



A review of implantable biosensors for closed-loop glucose control and other drug delivery applications

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ABSTRACT

Closed-loop drug delivery promises autonomous control of pharmacotherapy through the continuous monitoring of biomarker levels. For decades, researchers have strived for portable closed-loop systems capable of treating ambulatory patients with chronic conditions such as diabetes mellitus. After years of development, the first of these systems have left the laboratory and entered commercial use. This long-awaited advance reflects recent development of chronically stable implantable biosensors able to accurately measure biomarker levels *in vivo*. This review discusses the role of implantable biosensors in closed-loop drug delivery applications, with the intent to provide a resource for engineers and researchers studying such systems. We provide an overview of common biosensor designs and review the principle challenges in implementing long indwelling sensors: namely device sensitivity, selectivity, and lifetime. This review examines novel advances in transducer design, biological interface, and material biocompatibility, with a focus on recent academic and commercial work which provide successful strategies to overcome perennial challenges. This review focuses primarily on the topics of closed-loop glucose control and continuous glucose monitoring biosensors, which make up the overwhelming majority of published research in this area. We conclude with an overview of recent advances in closed-loop systems targeting applications outside blood glucose management.

1. Introduction

Closed-loop drug delivery is a fully automated method for regulating pharmacotherapy using a self-controlled feedback system. A diagram of a theoretical system is presented in Fig. 1 highlighting the three principal components: (i) an *implanted biosensor* which monitors physiological condition, circulating drug concentration, or biomarker level; (ii) a *control system* which receives input from the sensor and provides medication dosing instructions; and (iii) a *drug delivery device* which provides pharmacotherapy with the goal of creating a measurable change in patient-condition as monitored by the sensor (closing the loop). Semi-closed-loop systems, which require some degree of user input, have been present in the practice of anesthesiology for years; a physiological sensor monitors breathing rate and/or blood gas concentrations, and continuously informs the anesthesiologist who oversees delivery of anesthesia (Miller and Gan, 2013). Bedside systems for temporary closed-loop delivery of insulin, featuring continuous blood glucose monitoring, were introduced in 1974 (Albisser et al., 1974) and commercialized in 1977 (Clemens et al., 1977). For decades, researchers have hypothesized a wearable or implantable system for treating chronic conditions - an idea borne out of continuous advances

in medical device miniaturization and automation. Consider a microscopic implantable sensor continuously monitoring chemical biomarkers, a pocket computer able to interpret the data and confidently make treatment decisions, and a personal drug-infusion pump able to precisely infuse the patient with medication. Such a system would offer more than convenience; it would fundamentally change how many conditions are treated. Medication could be maintained at precisely the required levels for optimal therapeutic effect over long durations. Closed-loop systems could respond immediately, or even preemptively, to sudden deterioration in condition. Perennial problems of patient adherence, physician error, and over- or under-medication could be almost entirely eliminated.

Several of the requisite technologies for such closed-loop control have reached maturation. The proliferation of smartphones has made powerful, ubiquitous computers a reality, and wearable drug-infusion pumps are commercially available for treatment of conditions such as type 1 *diabetes mellitus*. However, despite considerable interest and intensive effort, complete closed-loop systems have remained hypothetical, with the development of a viable and reliable sensor posing the largest obstacle.

This long abeyance appears to have ended. In recent years, a flurry

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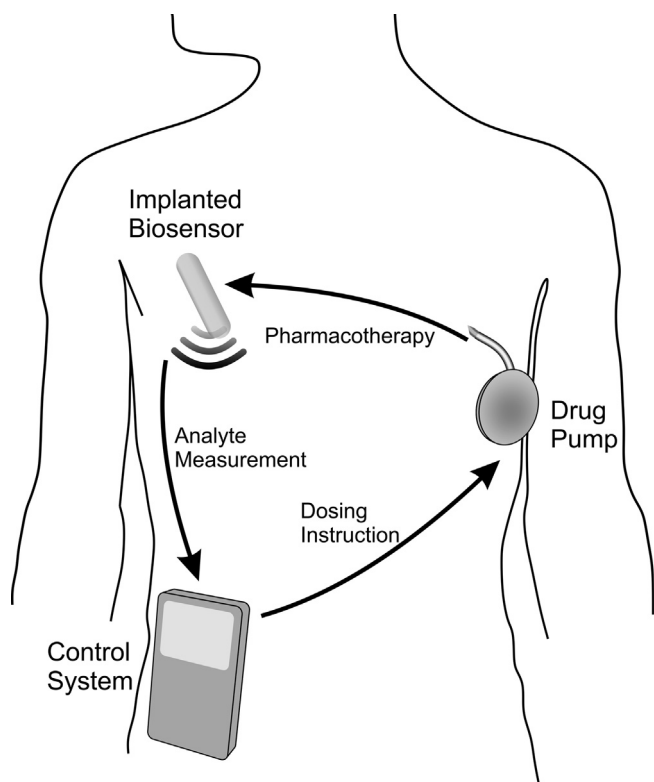


Fig. 1. Diagram of a closed-loop drug delivery system featuring the three major components: implanted biosensor, control system, and drug pump.

of clinical studies have explored *ad hoc* closed-loop systems comprising a mix of research and commercial devices (Bergental et al., 2016; Kovatchev et al., 2014; Kropff et al., 2015; Leelarathna et al., 2014; Renard et al., 2016; Tauschmann et al., 2016; Thabit et al., 2014; Thabit et al., 2015). Public and academic interest has soared, spurred by the Juveniles Diabetes Research Foundation's mission to develop a permanent closed-loop therapy for diabetes patients. News reports have emerged of inventive diabetes patients cobbling together home-brew semi-closed-loop systems for insulin control using commercial insulin pumps, glucose sensors, and personal microcomputers (Leigh, 2017; Mann, 2016). Finally, in 2017, the first purportedly closed-loop system received FDA approval. The MiniMed® 670G (Medtronic PLC., Dublin, Ireland) automatically modulates insulin delivery, albeit with limited user input still required, relying on an implantable glucose sensor to continuously measure blood sugar levels (FDA, 2016c). This sudden progress is a consequence of major advances in implantable biomedical technologies, and in particular, the development of a commercially available glucose biosensor implant. We believe further advances and proliferation of closed-loop drug delivery systems are impending, primarily as a consequence of further biosensor development.

Here we review the role of implantable biosensors for closed-loop drug delivery platforms. We examine the principle challenges facing biosensor development with a focus on the needs for long-indwelling devices, namely: sensitivity, selectivity, and lifetime. We examine and discuss results from the recent literature, with an emphasis on novel advances in transducer design, biological interface, and biocompatibility. Finally, we review the status of biosensor technology for current and future closed-loop drug delivery applications, with a primary focus on type 1 diabetes, which captivates the overwhelming majority of biosensor and closed-loop drug delivery system research.

2. Overview of a closed-loop drug delivery system

2.1. Implantable biosensor

A biosensor is a tool which detects the presence of a specific chemical or biological molecule and outputs a physical signal in proportion to the amount or concentration of the target. A biosensor relies on a biological component, sometimes called a biological recognition element, to identify, trap, or bind with the target analyte. The use of a biological component distinguishes biosensors from the broader field of chemical/biochemical sensors, and imparts high selectivity due to the specific biological interaction of the analyte and the recognition element. For implanted sensors, which are exposed to the truly vast number of proteins, metabolites, cells, and chemicals present in a physiological environment, this high selectivity is absolutely crucial for accurate operation. The archetypal biosensor has two basic components, the biological element which interacts with the target analyte, and the physical transducer which interacts with the biological element to convert the chemical interaction into a quantifiable signal. Biosensors can be broadly classified into two categories, differentiated by the type of biological component: bioaffinity sensors and biocatalytic or enzymatic sensors (Fig. 2).

A diagram of a generic bioaffinity sensor is presented in Fig. 2a. Bioaffinity sensors consist of a physical transducer coated with a thin functionalization layer of 'capture molecules', which bind selectively and typically irreversibly to target analytes. These capture molecules represent the biological recognition element of a bioaffinity sensor, and may be an immobilized film of antibodies, antigens, aptamers, or DNA/RNA segments. Detection of an analyte is encoded in a transduction signal, such as a measured change in mass, film thickness, charge, dielectric constant, or local-field potential due to the presence of the captured analyte, or the fluorescent signal from an accompanying fluorophore tag. These devices are incredibly selective and sensitive owing to the strong interaction between the biological component and the target, and comprise the core technology of powerful *ex vivo* immunosensors. However, due to typically short lifetimes *in vivo* and the slow response times (relative to the high temporal resolution needed for drug-delivery feedback), they are rarely used as implants and even less frequently in closed-loop research. Accordingly, we will discuss these devices sparingly in this review.

Enzymatic sensors use a biological enzyme to catalyze the reaction of the target into another species, and typically transduce the

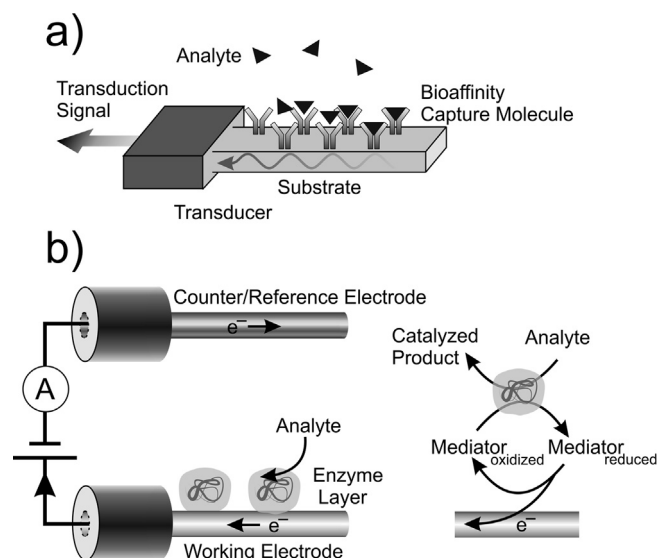


Fig. 2. Diagram of (a) generic bioaffinity-type biosensor and (b) generic enzyme-based amperometric biosensor.

accompanying production or consumption of a mediator, co-product, or substrate. Enzymatic sensors are selective, owing to the specific action of the biological enzyme and, unlike bioaffinity sensors, the biological element is unchanged after detection. As such, enzymatic biosensors can be used repeatedly and continuously, and make up the overwhelming majority of implantable biosensors. While both oxidase and dehydrogenase enzymes are commonly used in *ex vivo* biosensors, only oxidases are typically used *in vivo* as there is an available supply of O₂ to regenerate the enzyme. Though enzymatic sensors include those using fluorescent, plasmonic, and voltammetric transducers among others, by far the most common are amperometric designs. Notably, both the first biosensor (Clark and Lyons, 1962) and first implanted biosensor (Sternberg et al., 1989) were amperometric and enzymatic. A diagram of a common amperometric biocatalytic sensor is presented in Fig. 2b. The basic transducer comprises a set of electrodes held at a constant potential difference, with the working electrode coated in a layer of enzyme. Analytes at the enzyme layer undergo a catalyzed reaction and the enzyme is regenerated through the reduction of a mediator compound, which may be naturally present in the body or co-immobilized with the enzyme. The reduced mediator is electrochemically oxidized at the working electrode, resulting in an electric current (nA to μ A) proportional to the local concentration of the target analyte. Section 4.1.1 provides a more detailed examination of several common enzymatic sensor designs for the specific case of glucose biosensors. The success of these devices can be attributed to the simplicity of the design, the selectivity and stability of commercial enzymes, and the ease of integrating amperometric signals into electronic controllers.

In a closed-loop drug delivery system, the biosensor provides a continuous measurement of the target analyte, which may be a biomarker indicative of an adverse condition or a direct measure of circulating drug concentration. Measurements are collected intermittently and transmitted to the controller to inform rate of drug infusion. The sensor must respond sensitively, accurately, and quickly to small fluctuations in analyte concentration, and must be stable *in vivo* for chronic use. These challenges are addressed in greater detail in Section 3.

2.2. Control system

The control system serves as the intermediary between the biosensor and the drug delivery mechanism, translating the sensor output into instructions for pharmacological dosing. In practice, the control system is a personal computer, either a purpose-built unit or a laptop or smartphone running proprietary software. During operation, the control system converts the raw output of the biosensor to an estimate of analyte concentration using a pre-calibrated conversion factor, and modulates drug infusion in accordance with an algorithm. Control algorithms can vary greatly in complexity; in the simplest approach, the controller simply activates drug infusion when the biosensor response falls outside a preset window, and halts delivery when the response returns to a desired value. More sophisticated algorithms attempt to model the dynamics of the target biomarker and the action of the drug for precise therapeutic control. Researchers have proposed numerous control schemes (Bequette, 2005), though there have been few clinical studies providing head-to-head comparisons of performance. Among recently developed closed-loop systems model predictive control and proportional integral derivative control have emerged as popular choices. In general, control algorithms demand modest computational resources, regardless of specific design, and so choice of algorithm has little effect on the requirements for the physical control system.

The control system is typically worn or carried by the patient at all times, and therefore the form-factor has great significance for system reliability and patient adherence. The ideal control system is small, lightweight, and unobtrusive, with a long battery life and wireless capabilities to obviate the need for wired connections to the drug pump and biosensor. Smartphones are an appealing choice owing to their ubiquity and wireless features. Several studies of closed-loop glucose

delivery feature commercial smartphone control systems (Keith-Hynes et al., 2014; Kovatchev et al., 2014; Renard et al., 2016), and both Dexcom (San Diego, CA) and Abbott Laboratories (Lake Bluff, IL) offer implantable glucose biosensors with smartphone integration, using the Bluetooth and NFC protocols respectively (AirStrip Technologies, 2016; Dexcom, 2017). The MiniMed® 670G instead integrates the control system into the insulin pump, which is tethered to the patient by a catheter and communicates wirelessly with the implanted biosensor (Medtronic, 2017). This integrated approach removes the need for additional components, and reduces the risk that the control unit will become separated from the user. Despite the critical role of the control system, there is currently limited published research examining the effect of different designs on patient outcome.

2.3. Drug delivery mechanism

The typical administration mechanism is a personal drug infusion pump, a small, electronically controlled, mechanical pump which delivers pharmaceutical infusions to the user by way of a subcutaneous or intravascular catheter. Drug infusion pumps represent the most mature technology of the closed-loop drug delivery system. Modern devices feature low flow rates (< μ l/minute) achievable with high precision, small form-factors, battery power, and wireless control (Mossman, 2010). Commercial examples include portable and/or wearable insulin pumps for diabetics and continuous infusion pumps for at-home chemotherapy. Researchers have adapted several commercial insulin pumps for use in closed-loop control of blood glucose levels, demonstrating the systems as an effective platform for future closed-loop research. Many current devices already feature wireless, app-based control, and require no major adaptation for integration into closed-loop application. The majority of current closed-loop research features subcutaneous pumps due to the higher ease-of-use for patients, though they induce a time-lag for which the control system must compensate. Phelps (2011) provides a more expansive examination of current drug delivery technology.

3. Challenges in implantable biosensor design

3.1. Sensitivity

Sensitivity to the target analyte is the foremost requirement for biosensor design. An implantable biosensor must respond to changes in target analyte concentration at physiologically relevant values in the presence of interfering species and, for closed-loop applications, this response must be quantitative in order to properly titrate drug delivery. For the purposes of this review we define sensitivity as the change in sensor output for a given change in analyte concentration:

$$S = \frac{\partial f([a])}{\partial [a]} \approx \frac{f([a]) - f(0)}{[a]} \quad (1)$$

where f is the function describing sensor output to analyte a , and the approximation holds for biosensors with linear responses over the range of concentration of interest. Consequently the limit of detection (LOD), or minimum resolution, of the sensor can be defined as:

$$LOD = \frac{3\sigma}{S} \quad (2)$$

assuming a sensor which responds linearly with analyte concentration and a baseline noise characterized by a standard deviation σ . The LOD is the smallest change in concentration the sensor can confidently discriminate. Viable biosensors require a LOD below the smallest change in biomarker concentration of clinical relevance. This requirement is strongly dependent on application, as the physiological concentration of biomarkers can vary by several orders of magnitude between analytes. For example, in whole-blood metabolites such as glucose are present in millimolar concentrations (Psychogios et al., 2011), whereas

Table 1

Typical or representative range of glucose and L-lactate in various physiological fluids in healthy adults.

Medium	Concentration (mM)		References
	Glucose	L-Lactate	
Blood	4–7	0.5–2.2	Beaumont Laboratory (2017)
Tears	0.1–0.6	2–5	Berman (2013)
Sweat (heat induced)	0.1–4	5–20	Al-Tajer and Hadi (1994)
Saliva	0.01–0.2	0.1–2.5	Campbell (1965)
			Guilbault et al. (1995)
Cerebrospinal fluid	2.7–4.4	0.5–2.6	ARUP Laboratories (2017)

cytokines such as interleukin-6 are in pg/mL concentrations (Fernandez-Real et al., 2001). The requisite sensitivity is also dependent on medium. Table 1 presents concentrations of L-lactate and glucose, common biosensor targets, in several physiological fluids; note that concentration of both analytes varies discordantly by several orders of magnitude among various media. For example, a biosensor targeting L-lactate in sweat requires a much lower sensitivity than one targeting blood or saliva, whereas the sensitivity required to detect glucose in blood is lower than required for other media.

In the broader field of *ex vivo* devices, there are several examples of sensors with single molecule detection limits, but *in vivo* devices offer dramatically lower sensitivities owing to the challenges of translating such technologies to the physiological environment. Sensitive transducers may be overloaded by physical and chemical noise unless properly shielded from interference, and sensitive biological components can suffer instability and degradation under *in vivo* temperature and pH. The incorporation of nano-structures (e.g. nanotubes, nanoparticles) to increase effective surface area of a biosensor is a common approach to enhance sensitivity among *ex vivo* devices (Vaddiraju et al., 2010), however, there are few implantable devices using these materials owing to concerns of biocompatibility and toxicity.

The challenge then is not the design of a high resolution sensor, but maintaining high sensitivity while addressing simultaneous concerns of biocompatibility, lifetime, and accuracy. Researchers should be aware of these tradeoffs when designing new biosensors; for example, semipermeable membranes, commonly used to block interferents among *in vivo* devices (see Section 3.2), can limit diffusion of the analyte and decrease sensitivity. With these considerations in mind, the broad lessons from *ex vivo* design are still applicable: utilizing sensitive transducers, maximizing the surface area of the sensing site, increasing the coupling between biological component and transducer, and minimizing noise are all viable approaches for optimizing sensitivity.

3.2. Selectivity

Sensors intended for closed-loop drug delivery require exceptional selectivity against interfering species. More so than *ex vivo* devices, implanted sensors are exposed to a large number of possible interferents at a wide range of concentrations including a diverse array of exogenous substances present in medications. The risks of anomalous readings are severe, and represent the greatest public and regulatory fears regarding closed-loop systems. An automated drug delivery pump, responding to a false-positive from a confounded sensor, could deliver a harmful or even fatal bolus.

The need for highly selective detection of biomarkers motivates the use of the biosensors over physiological sensors or non-biological chemical sensors. The interactions between analytes and the biological component of biosensors is highly specific, and if necessary, selectivity can be tuned through choice of specific biological component. For example, glucose 2-oxidase is known to react with xylose and other carbohydrates, and so biosensors favor the more specific glucose 1-oxidase (Wilson and Turner, 1992). In general, the selectivity of the biological

Table 2

List of commonly tested interferents for amperometric enzyme-based sensors (FDA, 2006, 2010, 2013a).

Potential interferent
Acetaminophen
Ascorbic acid
Bilirubin
Cholesterol
Creatinine
Dopamine
Ephedrine
L-dopa
Methyl dopa
Gentisic acid
Glutathione
Ibuprofen
Tetracycline
Tolbutamide
Triglycerides
Urea
Uric acid

component is rarely a serious concern, but for the amperometric or voltammetric transducer there is a common problem with interference by other electroactive species. Many enzymatic biosensors, including those for detection of glucose, L-lactate, and L-glutamate, rely on the electrochemical detection of H₂O₂ produced from a biocatalytic reaction, and the high potential required to oxidize peroxide can oxidize interferents including ascorbic acid, L-cystine, uric acid and acetaminophen (the active ingredient in Tylenol), generating a false response (Barr, 2013). A complete list of commonly tested interferents is presented in Table 2. A large body of work has focused on minimizing interference from these species, with the most common approach entailing use of a permselective membrane or other semipermeable barrier to block interferents from reaching the electrode. Common examples of membrane materials include Nafion®, polyurethane, and cellulose acetate, and a focused review of this topic is provided by Kulkarni and Slaughter (2016). Though effective at improving selectivity, the use of these membranes can limit sensitivity, increase the time lag between physiological change and sensor response, and exacerbate biofouling. Other approaches involve reducing the electrochemical potential by either including catalase at the electrode site, or replacing peroxide with a mediator which oxidizes at a lower potential (e.g. ferrocene). These designs, however, have limited use for implantable biosensors owing to concerns over mediator leaching and toxicity (Chen et al., 2013; Wang, 2008). Some recent designs use a co-immobilized mediator to directly wire enzymes to the electrode, avoiding the issue entirely. TheraSense Inc. (Alameda, CA), now Abbott Diabetes Care, has built a wired-type enzymatic sensor incorporating an osmium-based mediator (Feldman et al., 2003) which forms the basis of their commercial glucose monitor, with demonstrated *in vivo* efficacy.

Selectivity remains an obstacle for the current generation of commercially available biosensor implants despite recent improvements. Among glucose sensors in particular, erroneous measurements due to acetaminophen continue to be observed in clinical trials (Basu et al., 2016; Maahs et al., 2015), and users of the MiniMed® 670G, a semi-closed loop system for glucose monitoring and insulin delivery, are warned about interference from xylose, acetaminophen, ascorbic acid, bilirubin, and uric acid (Medtronic, 2017).

3.3. Lifetime

Ideally an implanted biosensor would function indefinitely, providing accurate and reliable measurements for closed-loop drug delivery. In practice, biosensors have finite, and typically short, operating lifetime due to one of numerous mechanical, electrical, and/or biological failure modes (Fraser, 1997). Implanted biosensors have to

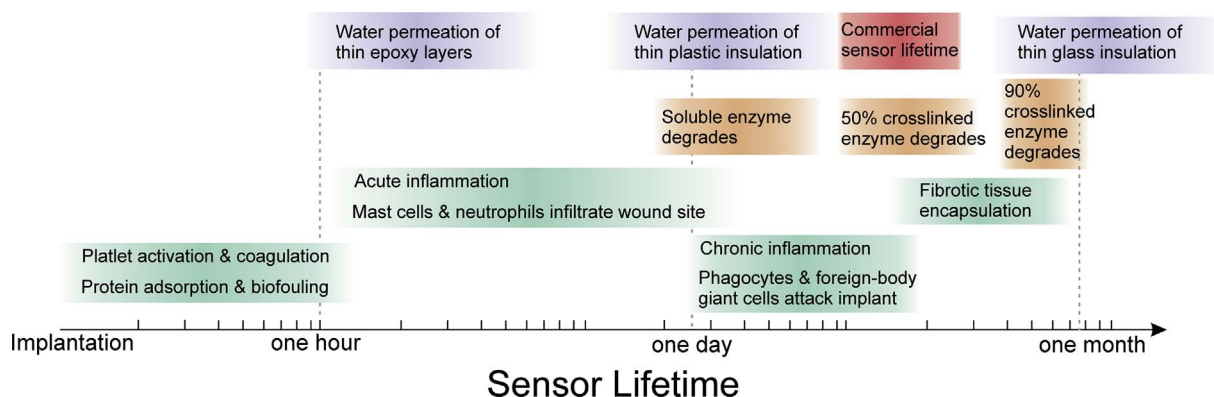


Fig. 3. Timeline of the events following implantation of a generic glucose biosensor (log-time scale). Estimates are drawn from the following references: (Anderson et al., 2008; Cunningham and Stenken, 2009; Gough and Bremer, 2000; Joung, 2013; Tse and Gough, 1987; Wang et al., 2015).

content with the additional challenges of *in vivo* conditions; the warm, saline environment can accelerate degradation of electrical components (Bowman and Meindl, 1986) and the physiological response of the host's immune system can impede or even destroy sensor function (Gilligan et al., 1994; Moatti-Sirat et al., 1992; Moussy and Harrison, 1994; Pickup et al., 1993; Rebrin et al., 1992; Thomé-Duret et al., 1996; Wisniewski and Reichert, 2000).

Fig. 3 depicts a hypothetical timeline for the life of a generic implanted sensor. Moisture intrusion of porous materials and the initial physiological response begin almost immediately. By the end of the first day, the body's acute inflammatory response is underway, and common biological recognition components suffer initial degradation. Over the course of several days, as part of a chronic inflammatory response, the immune system attempts to clear the foreign body. Cross-linked enzymes used for detection begin to degrade, and a fibrotic capsule forms around the implant. By the end of the first month, thin barrier layers, including plastics and glass, are subject to serious water permeation, threatening corrosion of metal components and electronics. The majority of devices presented in the available literature have effective *in vivo* lifetimes of a few days to a month. Of the commercially available examples, all of which are glucose biosensors, the recommended use is between 6 and 14 days depending on the model. Only a handful of reports describe successful multi-month trials in humans with a functioning biosensor (Dehennis et al., 2015; Gilligan et al., 2004; Lucisano et al., 2016).

The major obstacles to extended biosensor lifetime are (i) the foreign body response, (ii) degradation and consumption of the sensor's biological component and (iii) electrical and mechanical failure. Here we expand upon these challenges in greater detail.

3.3.1. Foreign body response and encapsulation

The foreign body response (FBR) describes the myriad biological reactions to the implantation and subsequent presence of a foreign entity. The typical sequence consists of an inflammatory response and a subsequent wound-healing response. Immediately following insertion, damaged tissue and vasculature release platelets and coagulants which agglomerate at the wound site, followed by protein adsorption onto the exterior of the biosensor. The acute inflammatory response is characterized by the infiltration of mast cells and neutrophils at the implant site, followed by a chronic inflammatory response wherein macrophages and foreign-body giant cells attempt to clear the device. At between 1 and 4 weeks, a fibrotic collagen capsule forms around the implant, typically rendering the sensor nonfunctional. For a thorough description of the underlying biomolecular processes comprising FBR, we refer the reader to several excellent reviews which focus on the topic in detail (Anderson et al., 2008; Cunningham and Stenken, 2009; Soto et al., 2016; Wang et al., 2015).

Long term, reliable function of implantable biosensors, as required

for closed-loop applications, therefore requires suppression or mitigation of the FBR. While there is no known method to permanently subvert the response, choice of material has a significant effect on the degree of the immune response. Though we caution against describing any material as universally biocompatible, certain materials including titanium (Hille, 1966; Laing, 1973; Steinemann, 1998), platinum (Agnew et al., 1986; Cowley and Woodward, 2011; Stensaas and Stensaas, 1978), certain glasses and ceramics (Clarke, 1992; Dokmeci et al., 1997; Hascup et al., 2013; Wilson et al., 1981; Wolfe and Boyde, 1992), and some specific formulations of polydimethylsiloxane (Colas and Curtis, 2004; Kalousdian et al., 1998; Quinn and Courtney, 1988), polyimide (Haggerty and Lusted, 1989; Lago et al., 2007; Richardson et al., 1993), Parylene (Hara et al., 2016; Loeb et al., 1977; Schmidt et al., 1988), and polymethylmethacrylate (King, 2013) have been used *in vivo* for extended periods of time with minimal response from the body (Scholten and Meng, 2015). A landmark study by Gough et al. (2010) demonstrates a rare example of a biosensor functioning for more than a year *in vivo* in porcine trials, and up to 180 days in human trials (Lucisano et al., 2016), with no fibrotic encapsulation, a feat the authors attribute to the use of alumina, titanium, and medical grade silicone in the sensor packaging, as well as the inclusion of peroxide catalase in their O₂ tension sensor design (see Section 3.3.2). For biosensors requiring a semipermeable exterior to allow analytes to reach the biological component, many incorporate hydrogels owing to their high porosity, biomimetic mechanical properties, and low rates of protein adhesion (Barone and Strano, 2006; Cummins et al., 2013; Sassolas et al., 2012). PHEMA (poly(hydroxyethyl methacrylate)) and PEG (poly(ethylene glycol))-based hydrogels have garnered particular attention, following several *in vivo* studies reporting reduced levels of fibrosis, and/or prolonged function of coated biosensors (Abraham et al., 2005; Quinn et al., 1997; Quinn et al., 1995; Yu et al., 2008). One notable example is the Senseonics Eversense® (Senseonics Holdings, Inc., Germantown, MD) continuous glucose monitor, an implantable glucose sensor based on a fluorophore-linked PHEMA hydrogel coating, reported to function for up to 3 months in human trials (Colvin and Jiang, 2013; Dehennis et al., 2015).

We also caution that that physical design parameters, including size, shape, and mechanical properties, play a role in mitigating, or exacerbating, the FBR. Results of biocompatibility testing across a broad spectrum of materials show that hard, sharp, and rough surfaces contribute to more severe inflammatory response, greater accumulation of macrophages at the sensor interface, and faster formation of thicker fibrotic capsules (Matlaga et al., 1976; Salthouse, 1984; Veisoh et al., 2015). A growing body of evidence indicates that the mechanical compliance of an implant plays a role in triggering FBR; studies of biosensor micromotion indicate that the stress of a rigid implant moving against soft tissue can induce damage and trigger additional inflammation (Helton et al., 2011; Hilborn and Bjursten, 2007). These

results have great consequence for the common percutaneous ‘needle-type’ design that dominates the field of implantable, electrochemical sensors. The choice of tethering the sensor to the skin may result in greater FBR, and functionally shorter lifetime, compared to fully implanted ‘free-moving’ sensors. Contrary to what one might assume, there is no strong dependence of implant size on the magnitude of FBR, at least for macroscale implants (major dimensions > 100 μm), though there may be a dependence on magnitude of insertion trauma (Veiseh et al., 2015; Wang et al., 2015). For microscale devices (major dimension < 100 μm), size appears to play a significant role. Sanders et al. (2000) describe the FBR to microscale polymer fibers decreasing with size, and abating entirely for structures < 6 μm diameter. This finding is in agreement with recent reports of flexible neural probes with sub-cellular dimension (< 15 μm width) exhibiting excellent chronic *in vivo* performance and encountering minimal scar tissue encapsulation (Luan et al., 2017; Patel et al., 2015; Schwerdt et al., 2017). With improvements in sensor miniaturization, soft, flexible, sub-cellular biosensors could be fabricated which avoid the FBR entirely, enabling the long indwelling sensors required for chronic closed-loop applications.

Other strategies to extend sensor lifetime include use of drugs to disrupt or mitigate FBR. This approach is commonly used for intravascular sensors, as device presence can trigger blood coagulation and thrombosis. For such devices, thin-coatings of anti-coagulants such as heparin, and NO releasing polymer coatings have been used successfully *in vivo* (Nagaoka et al., 1990; Wu et al., 2007; Yang et al., 1997). For subcutaneous and percutaneous biosensors, several *in vivo* tests have shown mitigated inflammation, thinner fibrotic encapsulation, and/or improved sensor lifetime through use of dexamethasone, (Klueh et al., 2007; Kozai et al., 2016; Vallejo-Heligon et al., 2016) the tyrosine-kinase inhibitor mastinib (Avula et al., 2016; Avula et al., 2013), and NO releasing coatings (Soto et al., 2014). The effects can be extended up to several weeks by incorporating drugs into slow dissolving polymer microspheres for time-delayed release (Gu et al., 2015; Hickey et al., 2002; Zolnik and Burgess, 2008), and recent work has explored the use of multidrug compartments for dosing strategies incorporating staggered release of multiple drugs (Morris et al., 2017). Dexamethasone loaded coatings in particular have emerged as a significant breakthrough in FBR mitigation for implantable biosensors. Glucose sensors with dexamethasone coatings have been tested under chronic *in vivo* conditions, showing significant improvements in sensor lifetime and sensitivity up to 21 days (Vallejo-Heligon et al., 2016; Vallejo-Heligon et al., 2014). More recently dexamethasone coatings have been incorporated into clinical studies for commercial efforts; the PRECISE study examined the Senseonics Eversense® glucose sensor over 180 days, and featured a silicone dexamethasone acetate collar to reduce chronic tissue inflammation (Kropff et al., 2017). Soto et al. (2016) provide a more thorough examination of the use of anti-inflammatory compounds for sensor biocompatibility.

An alternate approach entails the use of angiogenic growth factors to promote the formation of vascular tissue around an implant, tailoring the FBR as opposed to attempted mitigation (Ward, 2008). Vascular endothelial growth factor (VEGF) has been demonstrated to promote neovascularization during the encapsulation of an implant, permitting diffusion of analytes across the capsule, resulting in increased biosensor performance and lifetime (Klueh et al., 2005; Ward et al., 2003; Ward et al., 2004). VEGF can also be combined with dexamethasone in slow-release polymer-coatings to both minimize inflammation and promote vascular tissue simultaneously (Kastellorizios et al., 2015; Patil et al., 2007).

3.3.2. Degradation and/or consumption of biological components

The biological component of a biosensor has a limited, and typically short, lifetime under *in vivo* conditions. Biological receptors and enzymes can degrade gradually, fail catastrophically, or be consumed either by the host's immune response or under sensor operation. The

transient nature of biological materials drives chronic sensor drift, and ultimately limits the functional lifetime of implanted biosensors.

Bioaffinity sensors, those relying on biomolecular specific binding to antibodies, aptamers, or other receptor sites, are fundamentally consumptive by design. The bindings are specific yet irreversible; as available receptor sites are depleted, the sensor is gradually used up. This is the primary reason why affinity sensors are so rarely used in for implantable applications, despite being so commonly used for *ex vivo* devices. Implantable affinity sensors require weak, reversible bindings to analytes, which limits sensitivity and selectivity, or a means to periodically strip bound analytes. Such designs are uncommon, and typically affinity sensors are simply not pursued for chronic *in vivo* applications.

Enzymatic biosensors, where the biological component serves as a catalyst and not a receptor, are in principal non-consumptive, although some require a mediator which must be present in the environment at sufficient concentration (e.g. dissolved O_2 for typical glucose oxidase reaction), which can be depleted. These biosensors are still subject to the gradual deterioration of the enzyme protein. While many commercial enzymes are stable for months when stored under refrigeration or at room temperature for single-use *ex vivo* biosensors, under conditions of physiological temperature and pH they can denature, undergo conformational changes, or oxidize. For example, the glucose dehydrogenase enzyme GLD-PQQ, which is used in several blood glucose tests, has an *in vivo* lifetime of only a few hours to a few days (Okuda et al., 2004). Even ‘stable’ enzymes require chemical crosslinking and careful sensor design when intended for prolonged *in vivo* use. The soluble form of the glucose oxidase enzyme will persist in an *in vivo* environment for only a few days (Gough and Bremer, 2000; Valdes and Moussy, 2000), but exhibits a half-life of approximately 3 months following cross-linking with glutaraldehyde (Tse and Gough, 1987). During sensor operation, however, the enzyme tends to degrade much more quickly due to the action of H_2O_2 generated by the catalyzed reaction with glucose (Gough and Bremer, 2000; Harris et al., 2013). In practice, crosslinked glucose oxidase has an operational half-life of a few days to 1 week (Towe et al., 1996; Valdes and Moussy, 2000). Implantable biosensors typically circumvent this limitation by incorporating an excess of glucose oxidase and recalibrating multiple times a day to account for sensitivity drift. The O_2 tension-sensor design employed by Lucisano et al. (2016) incorporates an excess of immobilized catalase, to mitigate peroxide-induced oxidase inactivation. In this design, paired electrochemical oxygen sensors measure the consumption of ambient O_2 during the catalyzed oxidation of glucose, and immobilized catalase decomposes the produced peroxide. The authors attribute this design feature, in part, to the long-lifetime of their implanted devices. More recently, researchers have explored novel methods to immobilize enzymes as a means to increase stability, including incorporating enzymes into silica and titania based sol-gels, and binding enzymes to nanostructures such as carbon nanotubes and metal nanoparticles. To date, however, no strategy has yielded significantly improved *in vivo* stability. Reviews by Sassolas et al. (2012) and Harris et al. (2013) explore progress on these methods in greater detail.

3.3.3. Mechanical and electrical failure

Common mechanical failures are driven by chronic fatigue and stress: broken wires, worn components, and cracked casings. Common electrical failures are driven by gradual moisture intrusion: electrical shorts, corrosion, and component failure from ionic contamination. Relatively little discussion is awarded to these problems in much of the literature, as they are rarely concerns in acute proof-of-concept testing. Instead these issues manifest in chronic use (multi-day to multi-month), due to cumulative damage of natural tissue micro-motion, and prolonged exposure to the warm saline environment of the body.

Implantable sensors should be physically robust, with the expectation that devices will face continual, if low magnitude, strain and motion. Alternatively, devices can be made intentionally flexible, an

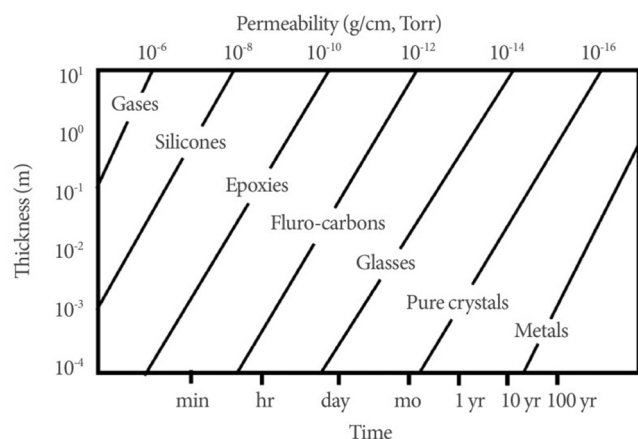


Fig. 4. Approximate material dependent permeability of water vapor as a function of material thickness. Reprinted from [Joung \(2013\)](#).

approach driving recent research into soft polymer-based biomedical devices ([Liao et al., 2015](#); [Scholten and Meng, 2015](#)). Wires, particularly those crossing the skin, are a potential weak-point, as natural micro-motion may induce fatigue failure. Electrical insulation should be selected for chronic exposure to physiological fluid at elevated (37 °C) temperatures. Polymers commonly used in the electronics and medical industries and typically considered water resistant (e.g. silicone, rubber, most organic polymers) can fail within a few days under these conditions. Even thin films of materials typically renowned for their barrier properties (e.g. Parylene C) can suffer moisture intrusion from prolonged *in vivo* exposure. [Fig. 4](#) depicts approximate time-to-failure for varied classes of materials at different thicknesses. Note that even relatively thick (mm) layers of common insulating materials (glass, polymers) are subject to significant moisture intrusion within a few days to weeks. While implantable sensors intended for acute application may survive with thin coatings of high-density organic or fluoro-carbon polymers, long-indwelling sensors may require hermetically sealed packaging of glass or metal.

4. Applications for closed-loop drug delivery

There are only a few fully-realized examples of closed-loop drug delivery systems, and only a few biosensor technologies mature enough to provide the continuous real time measurements required to develop such systems. The majority of current research has focused on the development of implantable glucose sensors for closed-loop control of insulin and blood sugar levels, while other applications remain in the early development stage or are entirely theoretical. Here we will describe the current state of implantable biosensors as used in, or with application for, chronic closed-loop drug delivery.

4.1. Continuous glucose monitoring

Glucose biosensors make up the overwhelming majority of biosensors in production, and continuous glucose monitors (CGM) make up the majority of implantable biosensors currently under study. CGMs are used to detect changes in blood glucose levels for guiding treatment (including insulin or glycogen infusion) for type 1 diabetes. Typical blood glucose levels range from 4 to 7 mM, with hypoglycemic symptoms appearing at levels below 4 mM and hyperglycemic symptoms appearing above 11 mM. Sub-millimolar resolution is desired for CGM applications, though this requirement rarely poses a major obstacle. Sensor accuracy remains the largest challenge facing CGM development, with reported values from implanted devices varying substantially from laboratory standards. Sensor accuracy is typically quantified as the mean absolute relative difference (MARD) between CGM measurement and blood glucose reference measurements. MARD

is calculated with [Eq. \(3\)](#), for a sample of N measurements, where $f_{\text{sensor}}(t_i)$ is the response of the sensor at timepoint t_i , and $f_{\text{ref}}(t_i)$ is the corresponding reference value.

$$\text{MARD} = \frac{1}{N} \sum_i \left| \frac{f_{\text{sensor}}(t_i) - f_{\text{ref}}(t_i)}{f_{\text{ref}}(t_i)} \right| \quad (3)$$

MARD values represent the variation in measurement between a sensor and a reference as averaged across a sample population, with low values suggesting an accurate sensor. High MARD values may be indicative of low selectivity, high noise, persistent bias, or other confounding factors, though the value itself may not convey how accurately a sensor tracks rates of change in analyte levels, or capture the likelihood of significant error. Commercial CGMs have reported MARD values ranging from just below 10% ([FDA, 2016a](#)) to over 25% ([FDA, 2007](#)), which are high compared to established self-monitoring blood glucose (SMBG) systems capable of MARD values below 5% ([Freckmann et al., 2015](#)).

Major sources of inaccuracy include transient decreases in sensitivity and sensor drift induced by FBR encapsulation and biofouling (see [Section 3.3.1](#)), presence of interferents (see [Section 3.2](#)), and the time lag between changes in blood glucose levels and corresponding changes in interstitial fluid ([Kovatchev et al., 2009](#); [Rebrin et al., 1999](#); [Steil et al., 2005](#); [Wentholt et al., 2007](#)). The latter is a major consequence of subcutaneous placement of CGM devices, and can be exacerbated by the often complicated diffusion dynamics between blood, interstitial fluid, and biosensor, which can confound sensor calibration and measurement ([Cengiz and Tamborlane, 2009](#)). Efforts to improve CGM accuracy is a major focus of continuing research; below we describe several avenues to improve accuracy through advances in biosensor design, but we note considerable efforts also focus on changes to the algorithms and software which filter and interpret CGM measurements ([Facchinetti, 2016](#); [Facchinetti et al., 2013](#); [Rebrin et al., 2010](#)).

CGMs may supplement (adjunctive use) or replace (non-adjunctive use) conventional SMBG measurements such as finger-stick tests. In typical use, CGMs report glucose measurements every few minutes to an external controller, which users can then forward to an insulin infusion pump. The majority of commercial devices to date have been approved only for adjunctive use, meaning treatment decisions must be accompanied by SMBG confirmation, and the few non-adjunctive devices available still require daily calibrations using the more reliable SMBG measurements. In recent years, trials of closed-loop drug delivery (insulin infusion) have been conducted using CGMs as the biosensor input, and commercial development of the first closed-loop systems is currently underway. For a comprehensive discussion of CGM biosensors, their design, operation and use, and their role in type 1 diabetes management, we refer the reader to the excellent text by ([Cunningham and Stenken, 2009](#)). In addition, several recent articles provide complementary reviews of critical topics: [Wang and Lee \(2015\)](#) provides a thorough description of the chemical mechanisms underlying several glucose biosensors, [Bruen et al. \(2017\)](#) reviews non-subcutaneous glucose biosensors, which are not emphasized here, and [Chen et al. \(2017\)](#) provides a detailed look at the state of the art in CGM technology.

4.1.1. Electrochemical glucose biosensors

The majority of glucose biosensors are enzymatic. The basic design consists of an immobilized film of glucose oxidase enzyme, serving as the biological recognition layer, and a set of electrodes (typically a Pt working electrode and Ag/AgCl reference), serving as the transducer. These devices have been reviewed extensively, and for a more thorough discussion of electrochemical glucose biosensors we direct the reader to reviews by [Wilson and Gifford \(2005\)](#), [Newman and Setford \(2006\)](#), [Wang \(2008\)](#), and [Vashist \(2013\)](#). There are four basic architectures commonly represented in the literature, all of which involve amperometric detection of the co-products consumed or generated during the

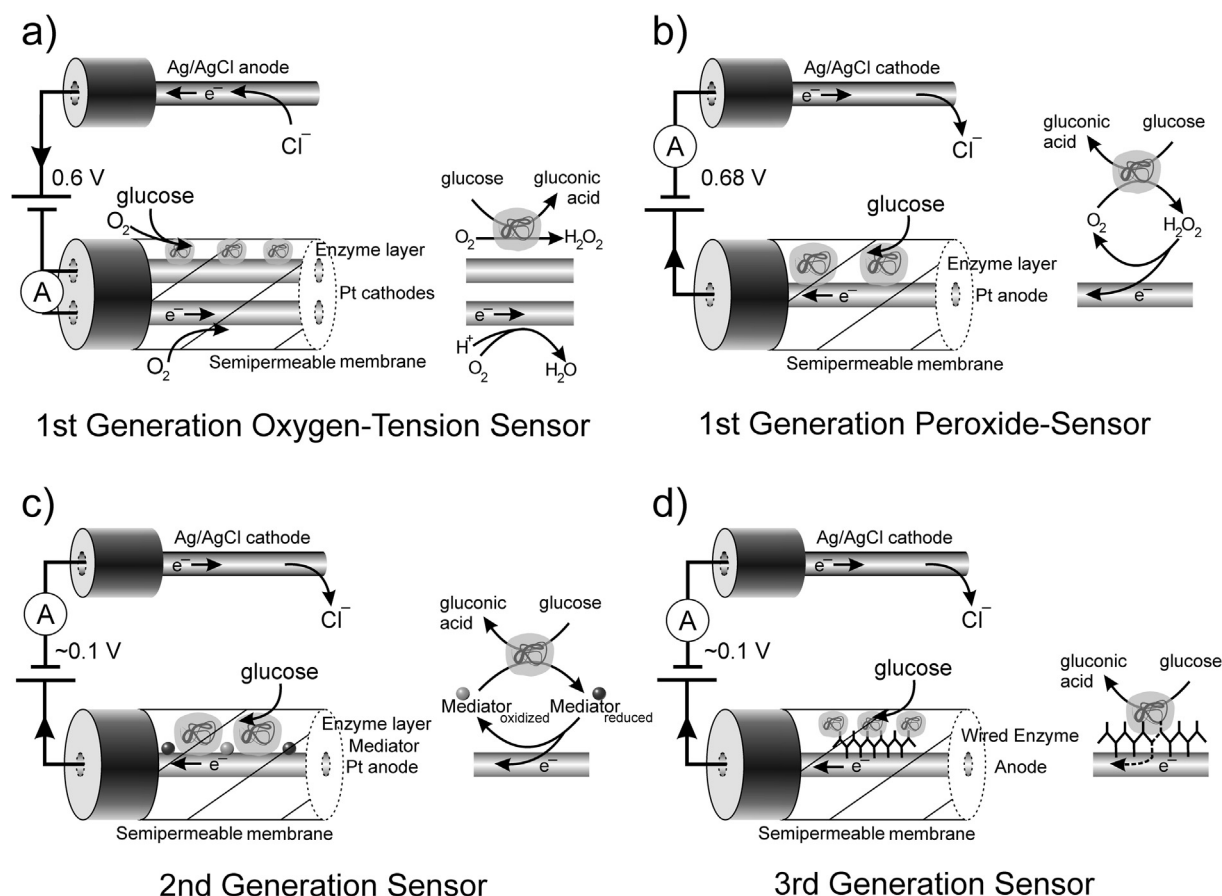


Fig. 5. Diagram of the four common designs for amperometric, enzyme-based biosensors: (a) First generation sensor measuring oxygen-tension, (b) second generation sensor measuring hydrogen peroxide, (c) second generation sensor with artificial mediator, (d) third generation sensor with directly wired enzyme.

oxidation of glucose to gluconic acid. Diagrams depicting the operation of each design are presented in Fig. 5.

First generation sensors rely on physiological O₂ as the electron acceptor, consuming O₂ during the catalyzed oxidation of glucose and producing H₂O₂. Fig. 5a depicts a first generation O₂-tension sensor; the design consists of two working cathodes enclosed in a semi-permeable membrane, with a one functionalized with immobilized glucose oxidase and a bare cathode serving as a control. Both working electrodes are held at a potential difference (~0.6 V) compared to a combined reference/counter anode. Ambient O₂ is electrochemically detected at both cathodes, and the measured signal is the difference in current between the electrodes. As the glucose oxidase reaction consumes ambient O₂, the difference in the flux of O₂ to the electrode surface is proportional to the rate of glucose oxidation.

Fig. 5b depicts a first generation peroxide sensor. These devices consist of a single working anode, coated with immobilized glucose oxidase, and a combined counter/reference electrode. Physiological glucose is oxidized at the enzyme to gluconic acid, resulting in the consumption of O₂ and production of H₂O₂. H₂O₂ is detected electrochemically at the anode surface, and the resulting current is measured as a signal of glucose concentration. This design is the most commonly used in research and industry, owing to its simplicity and extensive development history, and biosensors mimicking this approach with other enzymatically oxidizable biomarkers are ubiquitous. Though common, first generation sensors suffer from several inherent limitations, notably a reliance on local O₂, which can be consumed during operation or limited due to complications from the foreign body response (i.e. scar tissue encapsulation). The high over-potential required for the oxidation of H₂O₂ (approximately 0.7 mV) also promotes interference from other electroactive species (Barr, 2013). Common

strategies to mitigate this problem, including use of a permselective diffusion membranes to block interferents, can affect sensitivity and sensor lag by slowing diffusion of glucose to the sensor (see Section 3.2). Additionally, the action of H₂O₂ on the glucose oxidase enzyme greatly accelerates enzyme degradation, limiting overall lifetime (Gough and Bremer, 2000; Harris et al., 2013). These issues motivated the development of second and third generation glucose sensors.

Fig. 5c depicts a second generation sensor. The design is functionally similar to a first generation peroxide sensor, with the additional component of mediator compound co-immobilized with the enzyme layer. The mediator serves to replace the O₂/H₂O₂ redox pair; during typical operation the mediator is reduced as a consequence of the enzymatic oxidation of glucose, and then oxidized electrochemically by the anode. Popular examples of mediators include ferricyanide and ferrocene derivatives (Cass et al., 1984). Second generation sensors can operate at lower potentials, reducing risk of interference from electro-oxidizable compounds, and are not dependent on physiological O₂ concentration. While use of mediators is common in the design of *ex vivo* sensors, second generation glucose sensors have seen limited deployment for *in vivo* applications due to concerns of mediator stability and possible toxicity (Wang, 2008). Third generation sensors (Fig. 5d) directly “wire” the enzyme to the electrode, replacing the need for any intermediary, and allow electrons to transfer directly from the redox-center of an enzyme to the electrode (Bott, 2004; Feldman et al., 2003). These sensors largely ameliorate issues of mediator solubility, electroactive interference, and O₂ depletion. Though this approach is considerably less explored than the others, in part due to the difficulties associated with creating an efficient and biocompatible wiring element, an osmium-polymer based wired enzyme device has been successfully commercialized through the Abbott Freestyle® Navigator and

Freestyle® Libre lines of implantable glucose monitors (Distiller et al., 2016; Heller and Feldman, 2010).

The sensitivity of electrochemical CGMs can vary widely, but typically span the range of 1–10 nA/mM, with detection limits on the order of 0.1–1 mM. Sensor lifetime is typically limited by a combination of foreign body response and glucose oxidase instability to between a few days and a few weeks. The failure of devices is typically gradual. Due to diminishing quantities of active enzyme and increasing encapsulation by fibrotic tissue, the sensitivity of implanted devices decreases steadily over the course of its lifetime, requiring frequent (twice a day) calibrations using reference SMBG measurements.

The most common sensor geometry is a percutaneous needle, such that the electrodes can be inserted shallowly under the skin for measurement of interstitial glucose from subcutaneous tissue. This design avoids the complications associated with intravenous implantation, minimizes invasiveness, and allows users to easily implant the sensors at home. The success of the implantable glucose biosensor can in part be attributed to the versatility of this design, which is made possible by the strong correlation between interstitial and blood glucose values (Kulcu et al., 2003; Rebrin and Steil, 2000). The percutaneous design also allows for ancillary electronics to be attached to the outside of the body. A common packaging solution has the sensor connect to an external wireless transmitter, which can then transmit data to an external controller or smartphone that can display sensor readings or direct an infusion pump for closed-loop applications.

4.1.2. Fluorescent glucose biosensors

Fluorescent glucose biosensors were developed in parallel with electrochemical sensors, though they have yet to achieve the same level of clinical success or widespread use. The concept is simple and enticing: a substrate is loaded with a glucose-sensitive fluorophore, implanted subcutaneously, and the fluorescent signal is measured across the skin with an external device. In principle, a fluorescent sensor could function continuously for long periods of time without need for percutaneous wire connections, implanted batteries, or wireless telemetry. The majority of reports on such devices describe variations on the bioaffinity design first developed by Schultz and Sims (1979). In this approach, the protein concanavalin A serves as a bioaffinity receptor for glucose, glucose binds to concanavalin A, displacing a fluorescently tagged competing sugar (e.g. dextrose), which in turn modulates the total fluorescent signal of the assembly. An alternative approach by Barone et al. relies on catalysis by the glucose oxidase enzyme, and the near-infrared fluorescence of single-walled carbon nanotubes. Similar to electrochemical methods, glucose is oxidized by the enzyme, and the co-product H_2O_2 modulates the fluorescence, either by acting on the surface chemistry of the nanotubes (Barone et al., 2005) or changing the density of nanotube agglomerations (Barone and Strano, 2006; Barone et al., 2009). Despite considerable study, neither approach has led to a practical sensor for continuous glucose monitoring, let alone application to closed-loop systems. Major obstacles include risk of toxicity from concanavalin A (Ballerstadt et al., 2006) and/or nanostructures, limited lifetime due to fluorophore photo-bleaching, and difficulties achieving reliable responses.

In contrast, researchers exploring boronic-acid derived fluorescent hydrogels have made rapid strides towards a fully-functioning device. Boronic/diboronic acids are a well-established class of glucose-sensitive fluorophores, with demonstrated reversibility and high-sensitivity (Fang et al., 2004; Kawanishi et al., 2004). Hydrogel composites containing a boronic acid derived monomer, which fluoresces under near-UV light with exposure to glucose, have been successfully tested *in vivo* with microsphere and microfiber form-factors (Heo et al., 2011; Heo and Takeuchi, 2013; Shibata et al., 2010). In recent years, researchers have developed electronic implants built around this technology. Fig. 6 shows a diagrammatic example of such a device, which entails a wirelessly powered UV LED light source, with a glucose hydrogel coating. LED excitation stimulates the boronic-acid fluorescence in the

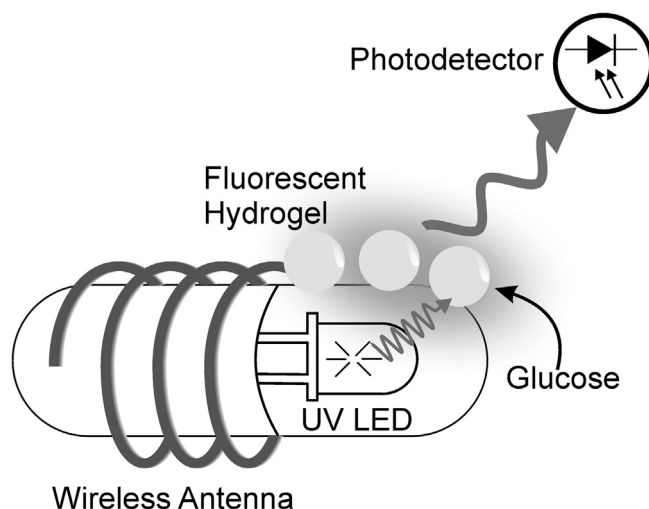


Fig. 6. Diagram of an implantable glucose sensor relying on a fluorescent glucose-sensitive hydrogel.

presence of physiological glucose, and the resulting emission is then measured by either an internal or external photodetector. Tokuda et al. have presented preliminary *in vitro* and *in vivo* results using such a design (Tokuda et al., 2016; Tokuda et al., 2014); successful detection and long sensor lifetimes are reported, but with sensor responses lagging significantly (> 10 min) behind blood glucose measurements. A similar device built under a commercial effort by Senseonics incorporates both a light source and detector (DeHennis et al., 2016; DeHennis et al., 2015). The Senseonics Eversense® comprises a LED, a photodiode, CMOS controller, and wireless antenna in a polymer capsule surrounded by a glucose-sensitive hydrogel. The fluorescent signal is both excited and recorded at the site of the implant, and a wireless signal is transmitted conveying the glucose concentration. The Eversense® has been tested in humans for up to 3 months, with reported MARD value of 11.1%, comparable to presently available continuous glucose monitors. The device is currently under application for regulatory approval for sale, and will likely be the first fluorescence-based device to market. The impressive sensor lifetime represents a significant advantage over current electrochemical designs, and the use of wireless electronics should enable easy integration with existing insulin infusion pumps for future closed-loop control. For a more focused review of boronic-acid based glucose sensors, including non-fluorescent designs, we direct the reader to recent work by Lacina et al. (2014).

4.1.3. Clinical trials demonstrating improved outcome with closed-loop control

Over the past decade, a series of clinical trials demonstrated the safety and efficacy of closed-loop insulin delivery for patients with type 1 diabetes relying on CGM measurements. These trials have grown in size and sophistication, reflecting refinements in technology and methodology and greater confidence in the safety of the closed-loop approach. The first published studies tested over-night control of closed-loop devices, relying on glucose measurements from commercially available subcutaneous glucose monitors, and laptop controllers to direct insulin infusion (Bruttomesso et al., 2009; Clarke et al., 2009; Hovorka et al., 2011; Steil et al., 2006). Investigators reported favorable performance of the closed-loop systems: comparable or lower rates of hypoglycemic events when compared to open-loop protocols, higher percentage of time spent within targeted blood glucose levels, and critically, few-to-no adverse events arising from the reliance on the closed-loop systems. These trials, however, excluded exercise or meals which pose the greatest challenge to glucose control.

The advent of smartphone software capable of managing the algorithmic control of insulin infusion enabled out-patient/at-home clinical

trials of increasingly longer duration (Kovatchev et al., 2014; Leelarathna et al., 2014; Thabit et al., 2014). Bergenstal et al. (2016) reported on the largest such trial to date, involving 124 out-patient participants (no control group) over a 3 month period. Participants relied on the closed-loop system night and day, providing daily calibrations and carbohydrate estimates for meal boluses, but otherwise allowed the system to regulate insulin doses automatically in response to an implanted CGM measurements. The authors reported no significant number of adverse incidents over the period, and a percent-time in recommended blood glucose range of 72.2% by study end, comparable to other closed-loop studies. A series of recent crossover studies have compared closed-loop systems to sensor-augmented-pump therapy, wherein patients rely on data from a CGM for self-administered insulin treatment (Kropff et al., 2015; Renard et al., 2016; Tauschmann et al., 2016; Thabit et al., 2015). The results indicate a slight advantage in closed-loop control over manual control, both for decreasing rates of hypoglycemic events and in increasing time spent in recommended blood glucose range. This outcome suggests the closed-loop approach offers fundamental advantages in maintaining glucose control, beyond that of patient convenience and adherence.

With several commercial actors currently developing closed-loop systems for market, there is a need for clinical studies with larger populations and larger study periods. In response, four large clinical trials are currently recruiting or underway, each of which will involve over 100 participants and lengthy trial periods (National Institutes of Health, 2017). Future work would ideally attempt controlled comparisons of sensor type or system design. In particular, there has been little work comparing model predictive control algorithms vs. proportional integrative derivative algorithms (Pinsker et al., 2016), and more clinical research might shed important light on effective differences.

4.1.4. Towards commercially available closed loop systems

Investment by private industry into implantable biosensors has focused almost solely on the development of CGM devices for the treatment of *diabetes mellitus*. The first commercially available incarnation, the MiniMed CGMS[®], was restricted for physician-use; the device was inserted under the patient's skin and retrieved after three days to download and analyze glucose levels retrospectively. In the years that followed, the technology and industry matured rapidly. Today three companies offer commercially available CGM sensors (Medtronic, Dexcom, and Abbott), all of which offer real-time monitoring of glucose levels and, to varying degrees, software integration with insulin pumps, SMBG devices, and smartphones. Current sensors are considered reliable for 6–7 days, with recent iterations of the FreeStyle[®] Libre (Abbott Laboratories) proven reliable for up to 14 days (Hoss et al., 2013).

The industry focus on CGM sensors can be traced to a confluence of financial and technical factors. The target market is very large: 30 million type 1 diabetics globally (WHO, 2016) that are familiar with at-home diagnostics and treatment from decades of using SMBG devices and manual insulin injections. The glucose oxidase amperometric sensor design underlying current commercial technology is simple, effective, and well-established. The ubiquity of SMBG devices provides a simple method for frequent calibration to compensate for sensor drift. These factors have minimized the technical obstacles in commercial CGM development, while providing sufficient impetus for the substantial investments necessary for regulatory trials.

Until recently, regulatory agencies have strictly limited the role of CGM sensors in informing treatment decisions (i.e. insulin delivery). The first several generations of commercial CGM devices were labeled only for adjunctive use, as a complement to SMBG devices (Castle and Jacobs, 2016; Edelman, 2017), and were used to discern changing trends in glucose levels, or to warn of impending hypoglycemia, but not to make definite determinations of glucose levels. These restrictions were predicated on the low accuracy of CGM sensors. The first commercial generation could err by as much as 20% in clinical comparisons with SMBG measurements, as measured by MARD value, and studies by

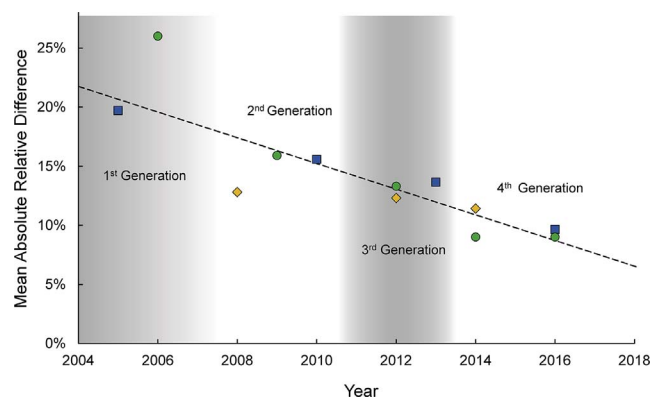


Fig. 7. Performance of selected CGM biosensors compared to blood glucose measurements, measured as mean absolute relative difference (MARD) between CGM values and those from comparator methods; Presented values are reported aggregate values from a disparate collection of academic studies, clinical trials for FDA approval, and manufacturer reports, under different experimental conditions, and as such cannot be considered a rigorous comparison of sensors or manufacturers. The data is presented here to demonstrate the broad trend of improving sensor accuracy as measured by MARD value. Dexcom (circles): STS[™] (FDA, 2007); SEVEN[®] (Zisser et al., 2009); SEVEN[®] Plus (Bailey et al., 2009); G4[®] (FDA, 2014); G4[®] with 505 Update (FDA, 2014); G5[®] (FDA, 2016a); Medtronic (squares): Guardian[®] RT (FDA, 2005); Paradigm Revel[™] (FDA, 2015); Enlite[®]: 530G system (FDA, 2013b); Guardian[®] 3: 670G system (FDA, 2016b); Abbott Laboratories (diamonds): Freestyle[®] Navigator (Weinstein et al., 2007); Freestyle[®] Navigator II (Vashist, 2013); Freestyle[®] Libre Flash (Bailey et al., 2015); Presented by manufacture in order of release.

Kovatchev et al. (2015) and Wilinska and Hovorka (2014) suggested use of sensors with errors greater than 10% could be responsible for increased rates of hypoglycemia.

Over the past ten years the accuracy of commercial sensors has continuously improved, a result of refinements in sensor design, system architecture, and software. This trend is visible in Fig. 7, which plots reported MARD values over four generations of commercial CGM releases. The most recent generation of CGMs have achieved a < 10% MARD value, clearing the final hurdle for non-adjunctive use. The FreeStyle[®] Libre Flash, built around an implantable subcutaneous biosensor, was approved in the European Union as a SMBG replacement under certain conditions in 2014 (Abbott Media Room, 2014), and approved in the United States for sale as the first CGM which does not require SMBG calibration (FDA News Release, 2017). In 2016, the Dexcom G5[®] became the first CGM system to receive non-adjunctive labeling in both the United States and European Union, though users are still required to calibrate the device twice a day with finger-sticks measurements, and must manually administer insulin doses. Finally, the FDA approved the MiniMed[®] 670G for sale in 2017 (FDA, 2016c). The system provides closed-loop control of basal glucose levels using a CGM sensor and wearable insulin pump. The device is formally identified as a hybrid-closed-loop system, as users are still required to manually deliver meal boluses, input information regarding diet and exercise, and calibrate the sensor to SMBG data 2–4 times per day (FDA, 2016b). These limitations notwithstanding, the MiniMed 670G[®] is the first consumer device capable of administering therapy in direct response to sensor readings, and as such, represents a tremendous step towards a fully closed-loop system.

Partnerships between Dexcom and Tandem Diabetes Care (Businesswire, 2016), Abbott and Bigfoot Biomedical (Pnewswire, 2017), and Senseonics and Roche (Businesswire, 2017b), have all announced efforts to create competing closed-loop systems with releases expected over the next two to three years. In the interim, several new commercial actors have declared intentions to release alternative closed-loop systems and CGM paradigms. Examples include: Inreda, which has completed early clinical trials with a bi-hormonal closed-loop system (Blauw et al., 2016), Verily Life Sciences, which is developing a CGM sensor embedded in a contact lens (Barrettino, 2017), and

Nemura Medical, which has announced development of a disposable, skin-mounted CGM (Businesswire, 2017a). There is also growing interest in the development of intraperitoneal CGM sensors, on the basis of improved glucose sensing kinetics (Burnett et al., 2014; Fougner et al., 2016), and the larger peritoneal space (Zisser et al., 2015). Huyett et al. (2016) have presented chronic performance of intraperitoneal CGM in animal models, and researchers from Trondheim University have declared exploration of a double intraperitoneal closed-loop system, featuring a linked intraperitoneal CGM and insulin pump (Stavdahl et al., 2016). The flurry of new attention is a positive for further advances in the field, though it is unclear how many of the many recently proposed ventures will successfully reach market.

4.2. Non-glucose biosensors: potential and future applications

Despite the recent advances in closed-loop insulin control using implantable glucose biosensors, there are currently no comparable systems targeting other analytes. There are, however, several promising avenues of implantable biosensor research with potential closed-loop applications. Here we describe several promising state-of-the-art research efforts.

4.2.1. Lactate

L-lactate (lactate) is a key metabolite and a predictive biomarker for conditions such as lactic acidosis, heart failure, hypoxia, hemorrhage, and shock (Kotani and Guiseppi-Elie, 2013; Rassaei et al., 2014). Typical blood plasma levels span 0.5–2.2 mM (ARUP Laboratories, 2017). Measurements of blood lactate concentration have clinical relevance, particularly for trauma patients; elevated lactate levels are associated with higher mortality rates (Nguyen et al., 2004), and a sudden spike in lactate concentrations may indicate impending circulatory failure (Bakker and De Lima, 2004). Continuous lactate measurement would provide a new strategy for monitoring intensive care patients. A continuous lactate monitor could trigger an alarm to notify physicians in the event of suddenly rising concentration, or even trigger an automated therapeutic intervention in a closed-loop emergency response system. The necessary sensor technology is largely established. Lactate biosensors are a mature technology in use for point-of-care blood measurements in trauma and sports medicine (Rathee et al., 2016). The most common design is an enzyme-based amperometric sensor, comprising a set of electrodes and an immobilized film of lactate oxidase; during operation the enzyme catalyzes the oxidation of L-lactate and the electrodes are used to electrochemically detect either the production of H_2O_2 or the consumption of ambient O_2 . Subcutaneous and intravenous lactate biosensors have been successfully demonstrated *in vivo* using needle-type designs remarkably similar to implantable glucose biosensors (Baker and Gough, 1995; Hu et al., 1993). Demonstrated devices exhibit sub-millimolar detection limits, rapid response times, and dynamic ranges exceeding the typical concentrations of interest (0.5–5 mM). Given the success of the underlying technology, the similarities to commercialized glucose-monitors, and the relevant medical application, lactate biosensors seem the obvious choice for the next long-indwelling closed-loop system.

However, to date there have been no clinical human trials with implantable lactate biosensors, let alone significant steps towards a closed-loop system. This is in part due to the difficulty correlating measurements of lactate in interstitial fluid with blood concentrations. Guiseppi-Elie (2011) and Rong et al. (2008) both observed discordance between subcutaneous lactate sensor measurements and conventional blood measurements, while Spehar-Deleze et al. (2012) reported no agreement between their subcutaneous lactate sensor and blood measurement controls. Long indwelling intravenous sensors remain too risky for chronic use due to possibility of thrombosis. More recently investigators have explored alternative approaches targeting sweat, tears, and saliva, using novel sensor packaging incorporated into epidermal bands (Imani et al., 2016), contact lenses (Thomas et al., 2012),

and mouth guards (Kim et al., 2014), respectively. These devices offer continuous monitoring without the invasiveness of fully-implanted sensors, though further *in vivo* studies are required to verify their accuracy and long-term stability.

4.2.2. Chemotherapeutics and anti-cancer medication

Chemotherapeutics and other anti-cancer drugs often have narrow windows of therapeutic concentrations, above which agents become toxic and below which they are rendered ineffective. Blood concentration of chemotherapeutics is considerably lower than metabolites such as glucose and L-lactate, with typical ranges between single nanomolar and single micromolar values. Optimizing drug concentration can be difficult due to pharmacodynamic dependence on patient mass, age, sex, body-surface area and genetics, and optimizing dosing regimen is further frustrated by the varying pharmacokinetic factors modulating the body's uptake, metabolism, and excretion of the drug. For decades, oncologists have experimented with pharmacokinetic-guided (PK-guided) dosing, using direct blood measurements of drug concentration to individually tailor dosage. Use of PK-guided dosing has proven effective for several common anti-cancer drugs (e.g. busulfan and fluorouracil) with evidence of improved outcomes and lower toxicity (Gao et al., 2012; Patel and Papachristos, 2015; Walko and McLeod, 2008). In principle, this approach can be expanded to create a closed-loop chemotherapy system. By monitoring *in vivo* drug concentrations in real-time, a feedback system can continuously adjust the rate of drug delivery, ensuring the patient receives a dosage that minimizes side-effects and toxicity while maximizing therapeutic effectiveness. A closed-loop approach is well suited for the many cancer treatments which require long sessions of intravenous delivery from automated infusion pumps, and may offer improved outcomes for several therapies, but to date, little work has been done in this area.

This is in part due to the lack of a generalizable physical or biological response to serve as a proxy for *in vivo* chemotherapeutic concentration. Drug concentrations must be measured directly, typically using laborious and slow analytical techniques (e.g. immunoassay or HPLC); the development of a closed-loop system first requires a biosensor capable of rapid measurements of circulating drug concentrations. Recent advances in electrochemical biosensors provide the most likely platform. Soh and co-authors recently presented an aptamer-based voltammetric biosensor that enabled the first demonstration of closed-loop control of doxorubicin in rabbits (Ferguson et al., 2013; Mage et al., 2017). The sensor is designed for *ex vivo* operation and requires catheterization of the patient for continuous blood flow, but the fundamental design is amenable to miniaturization and implantation with improvements in packaging. An implantable design has been demonstrated by Baj-Rossi et al. (2012); the device is a voltammetric biosensor which exploits isoforms of the cytochrome P450 enzyme for electrochemical detection of several chemotherapeutics. This biosensor has been incorporated into an implantable, wireless package, with preliminary work performed to examine the biocompatibility of the design (Baj-Rossi et al., 2014); however, the sensor has not yet been deployed in PK-guided dosing or closed-loop applications. The key innovation of these sensors is the rapid response times and the generalizability of the platform. In principle, these sensors could be adapted for detection of any small-molecule pharmaceutical for which an appropriate aptamer or enzyme isoform can be found.

Though there are no current examples of implantable biosensors used in closed-loop control of chemotherapy or other anti-cancer treatment, recent advances in biosensor development and recent trends in cancer treatment seem likely to converge on this technology. There is a growing focus within oncology on personalizing therapy, and a growing emphasis on minimizing toxicity. Successful trials of PK-guided dosing will motivate healthcare providers and patients to seek greater access to the practice, and a biosensor-based, closed-loop system eliminates many of the major technical hurdles, particularly the time and resources required for frequent bloodwork analysis. The

growing prevalence of at-home and even ambulatory infusion pumps for chemotherapy treatments echoes the history of diabetes treatment, which ultimately led to the convenience of implantable biosensors integrated with personal drug delivery devices.

4.2.3. Neurotransmitters

Implantable biosensors have application for real-time detection of neurotransmitters, and are of particular use for detecting non-electro-oxidizable species which cannot be detected using cyclic voltammetry (e.g. L-glutamate or acetylcholine) (Chandra et al., 2017). The typical biosensor design consists of a modified electrophysiological recording microelectrode with an immobilized matrix of an oxidoreductase enzyme coating an electrode recording site, enabling specific amperometric detection for species of interest. These neural biosensor probes exhibit sub-micromolar sensitivities, adequate for monitoring extracellular concentrations of neurotransmitters, and are primarily used in fundamental neuroscience and behavioral research.

In recent years, investigators studying neurotransmitter levels in response to therapeutic deep brain stimulation (DBS) have begun using neural biosensors for closed-loop control of neurotransmitter levels. In an early example, Behrend et al. (2009) demonstrated an ability to control *in vivo* L-glutamate levels using high frequency subthalamic stimulation in rats. L-glutamate was measured with a glutamate oxidase linked amperometric probe, and provided feedback for an empirically determined transfer function which modulated stimulation. L-glutamate levels were controlled dynamically *in vivo* for several hours. In subsequent work, several investigators created closed-loop DBS systems exploiting voltammetric detection of dopamine, serotonin, and adenosine using carbon fiber microelectrodes (Araujo et al., 2015; Bozorgzadeh et al., 2016; Grahn et al., 2014; Lee et al., 2017). These efforts have established the viability of closed-loop control over neurochemical levels, albeit with electrophysiological modulation (DBS) instead of pharmaceutical modulation (drug-delivery). With recent developments of neurochemical sensors integrating direct drug delivery capabilities (Gibson, 2011; Rohatgi et al., 2009), the potential for closed-loop drug delivery systems in the brain for modulation of psychological conditions is growing.

5. Outlook and future directions

The long-awaited arrival of closed-loop drug control is attributable to recent advances in biosensor technology, and continued development is predicated on further improvements in sensor lifetime and accuracy. Though the state-of-the-art represents tremendous innovation over past iterations, implantable biosensors remain short-lived, and less-reliable than the blood measurement standards which inform current pharmaceutical dosing. These shortcomings motivate a move away from the ubiquitous peroxide-detection schemes which dominate biosensor design, and incur persistent problems of interference and enzyme instability. The successful *in vivo* demonstration of long-indwelling fluorescence and wired-enzyme sensors for continuous glucose monitoring may forecast the future of this technology: mediator-free or non-enzymatic sensors featuring long lifetimes and a decreased reliance on *in situ* calibrations.

Looking forward, the ever-present problem of the foreign body response will likely remain a prominent obstacle for some time. Chronic inflammation and scar tissue formation poses both a major technical challenge and a critical regulatory concern, and efforts to subvert the immune response have succeeded only in delays and mitigation. Future work will likely incorporate those strategies that have demonstrated the greatest promise, including the use of biomimetic hydrogel coatings to reduce biofouling, and a move towards fully implantable devices and away from the common percutaneous needle designs. Advances in miniaturization, particularly for wireless antennas, will enable the development of smaller, untethered devices with longer lifetimes and reduced discomfort following implantation.

The next several years will witness rapid commercialization of closed-loop drug control, driven by a focus on diabetes therapy. We expect commercialization to spur a positive feedback in research efforts: market demand will fuel interest and funding for newer technologies, and commercial systems will provide a convenient platform for extended clinical studies on the therapeutic gains under closed-loop control. Successful adoption by patients and positive results from clinical and epidemiological study may lead to greater interest in closed-loop systems outside of the narrow purview of diabetes treatment.

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