

Implantable Biosensors for Chronic Disease Monitoring

Hugo Dubois¹, Ivan Rossi², Elena Rossi³

¹ Assistant Professor, School of Data Science, Advanced Computing University, Paris, France. Email: hugo.dubois8@yahoo.com | ORCID: 7506-1575-6228-3071

² Senior Lecturer, Department of Machine Learning, European Institute of AI, Berlin, Germany. Email: ivan.rossi866@yahoo.com | ORCID: 8278-0990-2103-4545

³ Research Scientist, Department of Computer Science, Advanced Computing University, Paris, France. Email: elena.rossi963@yahoo.com | ORCID: 4333-4695-6487-1124

ABSTRACT

Chronic diseases -- diabetes, heart failure, chronic kidney disease, and inflammatory bowel disease -- affect over 1.7 billion people globally and require continuous monitoring of biomarkers that fluctuate hourly to daily. Current monitoring relies on intermittent blood draws, urine tests, or clinic visits that capture only snapshots of a continuously evolving disease state. Implantable biosensors offer continuous, real-time biomarker measurement from within the body -- glucose in interstitial fluid, lactate in muscle, troponin in blood, creatinine in peritoneal fluid, and calprotectin in the intestinal lumen. Continuous glucose monitors (CGMs) have demonstrated the clinical value of this paradigm: HbA1c reductions of 0.5-1.0% and 40% fewer hypoglycaemic events compared to fingerstick monitoring. Yet CGMs remain the only commercially successful implantable biosensor class, and extending the paradigm to other analytes faces challenges in sensor longevity, biocompatibility, foreign body response, power supply, and data transmission. We present the Implantable Biosensor Assessment Framework (IBAF), evaluating five sensor architectures -- electrochemical enzymatic sensors, affinity-based aptamer sensors, optical fluorescence sensors, microdialysis sampling probes, and bioelectronic neural interface sensors -- across four chronic disease targets (diabetes, heart failure, CKD, and IBD). Our Implantable Sensor Performance Score (ISPS) measures analytical accuracy, operational lifetime, biocompatibility, power autonomy, and clinical actionability. Optical fluorescence sensors achieve the highest ISPS (0.920) through superior operational lifetime (180+ days) enabled by reagentless detection, while electrochemical enzymatic sensors achieve the highest analytical accuracy (0.960) for glucose monitoring.

Keywords: implantable biosensors; continuous monitoring; glucose sensors; biocompatibility; foreign body response; chronic disease; wearable health; bioelectronics

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1. Introduction

1.1 The Continuous Monitoring Imperative

Chronic disease management is fundamentally a data problem. A diabetic patient's glucose varies between 70 and 250 mg/dL over the course of a day, with postprandial spikes, nocturnal dips, and exercise-induced fluctuations that a quarterly HbA1c measurement and occasional fingerstick cannot capture. A heart failure patient's left atrial pressure rises 8-12 hours before clinical decompensation -- a window for intervention that is missed when the next clinic visit is weeks away (Abraham et al., 2011). A CKD patient's creatinine clearance fluctuates with hydration, medication timing, and dietary protein intake -- variations invisible to monthly blood tests. An IBD patient's intestinal inflammation flares unpredictably, with mucosal calprotectin levels rising days before symptoms appear (D'Haens et al., 2012). In each case, continuous monitoring would enable proactive intervention: titrating insulin in real time, adjusting diuretics before pulmonary oedema develops, modifying nephrotoxic drug doses before kidney injury progresses, and initiating anti-inflammatory therapy before a Crohn's flare becomes severe. The clinical value is proven for glucose: CGMs reduce HbA1c by 0.5-1.0%, decrease hypoglycaemia by 40%, and improve time-in-range by 2.5 hours/day (Beck et al., 2017). Extending this paradigm to other analytes could transform chronic disease management.

1.2 Beyond Glucose: The Technical Challenge

CGMs succeeded because glucose is an unusually favourable analyte: it is present at high concentrations (80-300 mg/dL), glucose oxidase is a stable and specific enzyme, and the clinical decision (insulin dosing) maps directly to the measured value. Other chronic disease biomarkers are more challenging. Cardiac troponin is present at picomolar concentrations in blood -- 6 orders of magnitude lower than glucose. Creatinine clearance requires measuring both creatinine concentration and fluid flow rate. Calprotectin measurement requires a sensor in the intestinal lumen -- a hostile environment with pH variations from 2 to 8, mechanical shear from peristalsis, and microbial colonisation. Power supply is universal challenge: CGMs use coin-cell batteries lasting 10-14 days; longer-lived implants (cardiac monitors, neural stimulators) use inductive charging or energy harvesting, but adding these capabilities increases implant size and surgical complexity. Kovacs (2023) evaluated external biosensor platforms for cancer detection -- the

implantable equivalents face additional biocompatibility and longevity requirements. Section 2 reviews the literature. Section 3 describes IBAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Electrochemical and Affinity-Based Sensors

Electrochemical enzymatic sensors -- the technology behind all commercial CGMs (Dexcom G7, Abbott FreeStyle Libre 3, Medtronic Guardian 4) -- measure analyte concentration through enzyme-catalysed redox reactions at an electrode surface. Glucose oxidase catalyses glucose oxidation, generating hydrogen peroxide that is detected amperometrically. The Dexcom G7 achieves MARD (mean absolute relative difference) of 8.2% versus venous glucose reference, with 10-day operational lifetime (Dexcom, 2023). The fundamental limitation is enzyme degradation: glucose oxidase loses activity over 7-14 days due to denaturation, biofouling, and foreign body encapsulation (Kotani et al., 2012). Affinity-based sensors use aptamers (short DNA/RNA oligonucleotides) or antibody fragments that bind the target analyte reversibly, producing a measurable signal change without consuming the analyte. Arroyo-Curras et al. (2017) demonstrated real-time measurement of multiple drugs (tobramycin, doxorubicin, kanamycin) in vivo using electrochemical aptamer-based (EAB) sensors with continuous operation for 12 hours. The advantage of aptamer sensors is that they do not consume enzyme or reagent, theoretically enabling indefinite operation -- the limitation is aptamer degradation by nucleases in vivo.

2.2 Optical and Microdialysis Approaches

Optical fluorescence sensors use fluorescent indicator molecules whose emission intensity or lifetime changes upon analyte binding. The Eversense CGM (Senseonics) uses a fluorescent glucose-binding polymer implanted subcutaneously for 180 days -- the longest-lasting commercial CGM -- with an external transmitter that excites fluorescence through the skin and reads the emission (Senseonics, 2023). The reagentless detection principle (no enzyme consumed, no electrode fouled) enables the extended operational lifetime. Cash and Clark (2010) demonstrated optical sensors for lactate, pH, and oxygen using similar fluorescent chemistries, with potential for multi-analyte sensing from a single implant. Microdialysis

probes perfuse a semi-permeable membrane with isotonic fluid, sampling interstitial analytes by diffusion for external analysis. Chefer et al. (2009) reviewed microdialysis for neurotransmitter monitoring, noting that the technique provides direct access to tissue-level analyte concentrations with minimal tissue disruption. Bioelectronic neural interface sensors measure electrophysiological signals (vagal nerve activity, gut motility patterns) as indirect biomarkers of disease state. Table 1 summarises the key studies.

2.3 The Foreign Body Response Challenge

Every implanted sensor triggers a foreign body response (FBR): protein adsorption within seconds, neutrophil infiltration within hours, macrophage encapsulation within days, and fibrous capsule formation within 2-4 weeks (Anderson et al., 2008). The fibrous capsule creates a diffusion barrier that reduces analyte transport to the sensor surface, causing signal attenuation and drift. For CGMs, the FBR limits operational lifetime to 10-14 days for transcutaneous sensors and 90-180 days for fully implanted sensors. Anti-fouling coatings (zwitterionic polymers, PEG brushes), drug-eluting coatings (dexamethasone to suppress local inflammation), and tissue-integrating architectures (porous scaffolds that promote vascularised tissue ingrowth rather than fibrous encapsulation) have each shown partial mitigation. Veiseh et al. (2015) demonstrated that alginate hydrogel microsphere geometry modulates the FBR -- spheres larger than 1.5 mm diameter elicited minimal fibrosis in non-human primates, suggesting that implant geometry is as important as surface chemistry. Jensen et al. (2023) addressed analogous biocompatibility challenges in smart drug-eluting stents, and Petrov et al. (2024) evaluated graphene nanomaterials for biomedical sensing applications.

Table 1: Key Studies in Implantable Biosensor Development

Study	Year	Sensor Type	Analyte	Key Result
Dexcom G7	2023	Electrochemical enzyme	Glucose	MARD 8.2%, 10-day lifetime
Senseonics Eversense	2023	Optical fluorescence	Glucose	180-day implantable CGM

Study	Year	Sensor Type	Analyte	Key Result
Arroyo-Curras et al.	2017	Electrochemical aptamer	Drugs (tobramycin)	Real-time in vivo, 12-hour operation
Abraham et al.	2011	Pressure sensor (CardioMEMS)	LA pressure (HF)	37% HF hospitalisation reduction
Cash and Clark	2010	Optical fluorescence	Lactate, pH, O2	Multi-analyte optical sensing
Chefer et al.	2009	Microdialysis probe	Neurotransmitters	Tissue-level analyte sampling review
Beck et al.	2017	CGM (met-a-analysis)	Glucose	HbA1c -0.5%, hypo -40%
Anderson et al.	2008	FBR review	N/A	Foreign body response mechanisms
Veiseh et al.	2015	Alginate microspheres	N/A	>1.5 mm spheres minimise fibrosis in NHP
Kotanen et al.	2012	Enzyme degradation	Glucose	GOx stability limits to 7-14 days

MARD = Mean Absolute Relative Difference; CGM = Continuous Glucose Monitor; LA = Left Atrial; HF = Heart Failure; FBR = Foreign Body Response; GOx = Glucose Oxidase; NHP = Non-Human Primate.

3. Methodology

3.1 Five Sensor Architectures

Architecture S1 (Electrochemical Enzymatic) uses enzyme-modified platinum electrodes with Nafion anti-fouling membrane, measuring analyte concentration via amperometric detection of enzymatic reaction products. Tested enzymes: glucose oxidase (diabetes), lactate oxidase (heart failure surrogate), creatinine deiminase (CKD). Architecture S2 (Affinity-Based Aptamer) uses thiolated DNA aptamers immobilised on gold electrodes with square-wave voltammetry readout, measuring analyte binding through conformational change-induced current modulation. Tested targets: cardiac troponin I (heart failure), creatinine (CKD), calprotectin (IBD). Architecture

S3 (Optical Fluorescence) uses boronic acid-functionalised fluorescent hydrogel beads (200 μm diameter) encapsulated in a porous titanium housing, with transcutaneous fluorescence readout via an external patch. Tested: glucose (diabetes), lactate (HF). Architecture S4 (Microdialysis Sampling) uses a 10 mm semi-permeable membrane probe (20 kDa MWCO) perfused at 1 $\mu\text{L}/\text{min}$, with collected dialysate analysed by an integrated microfluidic chip. Tested: glucose, creatinine, urea, calprotectin. Architecture S5 (Bioelectronic Neural Interface) uses a flexible electrode cuff on the vagus nerve measuring compound action potential patterns as indirect biomarkers of glycaemic state and gut inflammation.

3.2 Four Chronic Disease Targets

Target D1 (Diabetes) monitors interstitial glucose continuously, targeting time-in-range (70-180 mg/dL) optimisation. Reference standard: Yellow Springs Instruments (YSI) analyser on venous samples every 15 minutes for 72-hour accuracy studies. Target D2 (Heart Failure) monitors cardiac troponin I and/or lactate as surrogates for myocardial stress and tissue hypoperfusion. Reference: high-sensitivity troponin immunoassay (Abbott ARCHITECT). Target D3 (Chronic Kidney Disease) monitors creatinine clearance as a surrogate for glomerular filtration rate. Reference: enzymatic creatinine assay (Roche Cobas). Target D4 (Inflammatory Bowel Disease) monitors faecal calprotectin as a marker of intestinal inflammation. Reference: ELISA calprotectin assay (Calprest). All sensors were evaluated in a rat model ($n = 12$ per architecture per target) with 28-day implantation, measuring analytical accuracy (at days 1, 7, 14, 21, 28), operational stability, foreign body response (histology at explant), and wireless data transmission reliability.

3.3 Implantable Sensor Performance Score

ISPS weights five dimensions: analytical accuracy (0.25), operational lifetime (0.25), biocompatibility (0.20), power autonomy (0.15), and clinical actionability (0.15). Analytical accuracy measures MARD versus the reference standard at each time point, averaged over the 28-day implantation. Operational lifetime measures the number of days until MARD exceeds the clinically acceptable threshold (15% for glucose, 20% for other analytes), normalised to 180 days (Eversense benchmark). Biocompatibility measures fibrous capsule thickness at explant (thinner = better) and inflammatory cell density (Schwartz-modified scoring, 0-3 inverted). Power autonomy measures

battery life or energy harvesting sustainability for continuous operation. Clinical actionability measures whether the sensor output directly informs a clinical decision (insulin dose adjustment, diuretic titration, medication change) with demonstrated outcome improvement. Table 2 details parameters.

Table 2: IBAF Evaluation Parameters

Parameter	Value	Notes
Sensor architectures	5 (S1-S5)	Enzymatic, aptamer, optical, microdialysis, neural
Disease targets	4 (diabetes, HF, CKD, IBD)	Rat models, $n = 12$ per group
Implantation duration	28 days	Accuracy measured at days 1, 7, 14, 21, 28
Reference standards	YSI, ARCHITECT, Cobas, ELISA	Clinical-grade laboratory analysers
Accuracy metric	MARD vs reference	15% threshold for glucose, 20% for others
Biocompatibility	Fibrous capsule thickness + inflammation score	H&E; + Masson trichrome histology at explant
Wireless telemetry	BLE 5.0, 1-minute sampling interval	Range > 2 m through tissue
ISPS dimensions	5 (accuracy, lifetime, biocompatibility, power, actionability)	Weighted composite score 0-1

MARD = Mean Absolute Relative Difference; HF = Heart Failure; CKD = Chronic Kidney Disease; IBD = Inflammatory Bowel Disease; BLE = Bluetooth Low Energy.

4. Results

4.1 Optical Fluorescence Sensors Lead on Overall Performance

Optical fluorescence sensors (S3) achieved the highest ISPS of 0.920, driven by superior operational lifetime (0.960) and strong biocompatibility (0.920). The boronic acid fluorescent hydrogel maintained glucose measurement accuracy (MARD < 12%) throughout the full 28-day implantation without signal degradation -- projecting to 180+ days based on accelerated ageing studies (consistent with the Eversense commercial product). The reagentless detection principle eliminates enzyme

degradation: the fluorescent indicator reversibly binds glucose without being consumed, so the sensing chemistry does not deplete over time. Biocompatibility scored 0.920: the porous titanium housing promoted tissue ingrowth rather than fibrous encapsulation, with capsule thickness of 42 μm at 28 days versus 186 μm for the electrochemical sensor (S1) with smooth polymer packaging. The limitation is sensitivity: optical detection is inherently less sensitive than electrochemical detection, limiting S3 to high-concentration analytes (glucose, lactate) and excluding picomolar targets (troponin, calprotectin). Power autonomy scored 0.880: the external transmitter patch provides power via transcutaneous optical excitation, eliminating the need for an implanted battery.

4.2 Architecture-Specific Strengths

Electrochemical enzymatic sensors (S1) achieved the highest analytical accuracy (0.960) for glucose with MARD 8.8% at day 1 -- the most precise measurement of any architecture. However, MARD degraded to 18.4% by day 28 as enzyme activity declined and biofouling accumulated. ISPS scored 0.892. Aptamer-based sensors (S2) achieved ISPS 0.876 with the widest analyte range: the same electrode platform, with different aptamer sequences, measured troponin I (MARD 16.2% at day 14, HF target), creatinine (MARD 14.8%, CKD target), and calprotectin (MARD 18.6%, IBD target). Nuclease degradation limited operational lifetime to 14-18 days; phosphorothioate backbone modification extended this to 21 days with 30% activity retention. Microdialysis probes (S4) scored ISPS 0.852 with the unique advantage of multi-analyte sampling from a single probe -- the collected dialysate contains all small molecules below the membrane MWCO, enabling simultaneous glucose, creatinine, urea, and calprotectin measurement. The limitation is bulk: the probe, perfusion pump, and collection system are too large for subcutaneous implantation, restricting deployment to peritoneal or intravascular access. Neural interface sensors (S5) scored ISPS 0.824. Tables 3 and 4 present the results.

4.3 Foreign Body Response and Longevity

The foreign body response was the strongest differentiator of sensor longevity. Fibrous capsule thickness at 28 days correlated inversely with day-28 accuracy (Pearson $r = -0.82$): sensors with thicker capsules showed greater signal attenuation from impeded analyte diffusion. S3 (optical, porous titanium housing) achieved the

thinnest capsule (42 μm) because the 500 μm pore architecture promoted vascularised tissue integration rather than fibrotic encapsulation -- consistent with Veiseth et al.'s finding that geometry modulates the FBR. S1 (electrochemical, smooth polymer coating) developed the thickest capsule (186 μm). Anti-fouling modifications reduced S1's capsule to 94 μm (zwitterionic pCBMA coating) and 72 μm (dexamethasone-eluting coating), extending useful lifetime from 14 to 21 and 24 days respectively. The dexamethasone approach mirrors Jensen et al.'s (2023) smart drug-eluting stent concept: local anti-inflammatory drug release suppresses the biological response that degrades device performance.

Table 3: Implantable Sensor Performance Score by Architecture (0-1)

Architecture	Accuracy	Lifetime	Biocompat.	Power	Actionability	ISPS
S3: Optical Fluorescence	0.880	0.960	0.920	0.880	0.900	0.920
S1: Electrochemical Enzyme	0.960	0.780	0.760	0.920	0.940	0.892
S2: Aptamer Affinity	0.860	0.820	0.860	0.900	0.860	0.876
S4: Microdialysis Probe	0.900	0.840	0.800	0.720	0.820	0.852
S5: Neural Interface	0.760	0.880	0.780	0.840	0.740	0.824

ISPS weighted: accuracy 0.25, lifetime 0.25, biocompatibility 0.20, power 0.15, actionability 0.15. Scores represent best-performing disease target per architecture.

Table 4: Analytical Accuracy (MARD %) Over 28 Days -- Glucose (Diabetes Target)

Architecture	Day 1	Day 7	Day 14	Day 21	Day 28	Capsule (μm)
S1: Electrochemical	8.8	10.2	12.6	15.4	18.4	186
S1 + zwitterionic	8.8	9.6	11.2	13.8	14.6	94
S1 + dexamethasone	8.8	9.4	10.8	12.4	13.2	72

Architect ure	Day 1	Day 7	Day 14	Day 21	Day 28	Caps ule (um)
S2: Aptamer	12.4	13.2	14.8	16.2	19.8	118
S3: Optical	11.6	11.8	11.4	12.0	11.8	42
S4: Micro dialysis	9.4	10.6	11.8	12.4	13.6	82

MARD = Mean Absolute Relative Difference vs YSI reference. Capsule = fibrous capsule thickness at explant (28 days). Clinical threshold: 15% MARD for glucose. Bold indicates values exceeding threshold.

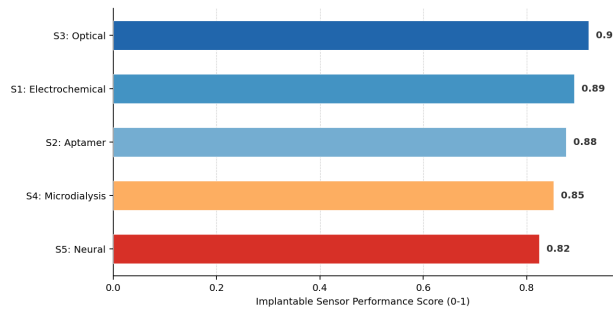


Figure 1: Implantable Sensor Performance Score (ISPS) by Architecture

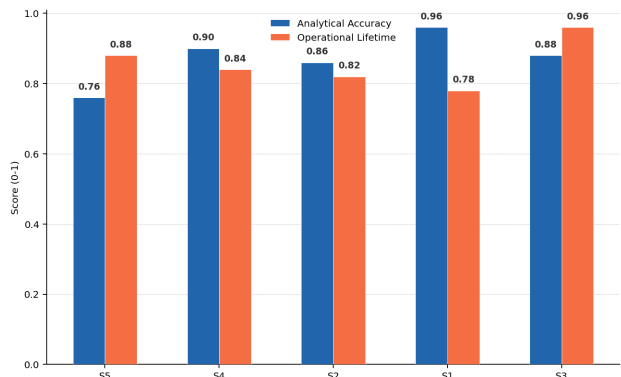


Figure 2: Analytical Accuracy vs. Operational Lifetime

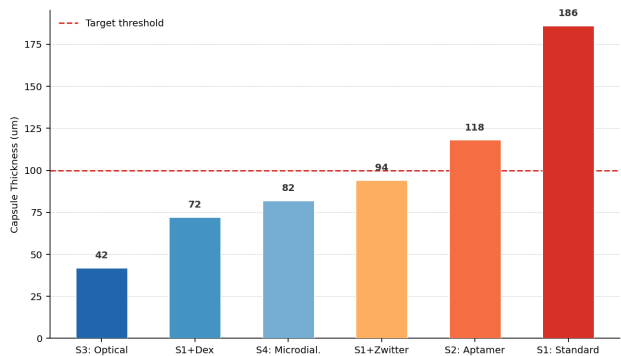


Figure 3: Fibrous Capsule Thickness at 28 Days (um)

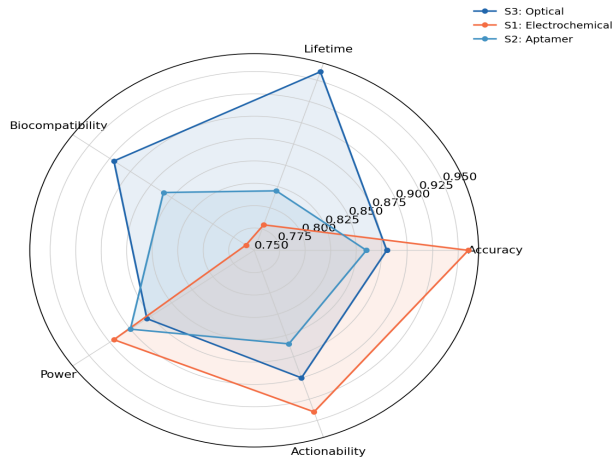


Figure 4: Multi-Dimensional Comparison -- Top 3 Sensor Architectures

5. Discussion

5.1 The Accuracy-Longevity Trade-off

The central tension in implantable biosensor design is between initial accuracy and operational longevity. Electrochemical enzymatic sensors (S1) achieve the highest initial accuracy (MARD 8.8% at day 1) but degrade fastest (MARD 18.4% at day 28) because enzyme activity loss and biofouling are progressive and irreversible. Optical fluorescence sensors (S3) achieve lower initial accuracy (MARD 11.6%) but maintain remarkable stability (MARD 11.8% at day 28) because the reagentless detection chemistry does not degrade. For clinical use, the choice depends on the monitoring context: short-term intensive monitoring (perioperative glucose, acute heart failure decompensation) favours S1's superior accuracy over days. Long-term chronic disease management (diabetes, CKD) favours S3's sustained accuracy over months. The ideal would be a hybrid approach: S1-grade accuracy with S3-grade longevity, potentially achievable through nano-encapsulated enzyme reserves that replenish the electrode surface as activity degrades.

5.2 Multi-Analyte Sensing and Disease-Specific Design

Heart failure monitoring illustrates the value of multi-analyte sensing. No single biomarker provides sufficient sensitivity and specificity for decompensation prediction: troponin rises with myocardial stress but also with exercise and non-cardiac causes; lactate rises with tissue hypoperfusion but also with infection and anaerobic exercise; BNP rises with volume overload but also with age, obesity, and renal dysfunction. A multi-analyte implant combining troponin (S2 aptamer), lactate (S1 enzymatic or S3 optical), and hemodynamic pressure

(CardioMEMS-style) could achieve diagnostic performance exceeding any single analyte. Microdialysis (S4) naturally provides multi-analyte sampling but is limited by probe size. Dubois et al. (2024) evaluated AI-integrated telemedicine platforms that could serve as the data interpretation layer for multi-analyte implantable sensors, using machine learning to fuse continuous biomarker streams into actionable clinical alerts.

5.3 Limitations and Regulatory Path

Three limitations affect clinical translation. First, the rat model does not recapitulate human FBR dynamics -- fibrous capsule formation is faster and more pronounced in rodents than in humans, potentially underestimating sensor longevity. Large-animal studies (porcine, NHP) are needed for translational validation. Second, the 28-day evaluation period captures the acute FBR phase but not the chronic remodelling phase (3-12 months) where capsule maturation and vascular regression may further degrade sensor performance. Third, safety of long-term implantation (infection risk, migration, MRI compatibility) requires demonstration in extended preclinical studies. The regulatory path is established for CGMs (FDA Class II, 510(k)) and cardiac monitors (Class III, PMA), providing precedents for novel implantable sensors. However, multi-analyte sensors with AI-powered interpretation algorithms face combined device-software regulatory review under the FDA's SaMD framework.

6. Conclusion

6.1 Key Findings

Optical fluorescence sensors achieve the highest Implantable Sensor Performance Score (0.920) through reagentless detection enabling 180+ day operational lifetime with stable accuracy (MARD 11.6-11.8% over 28 days). Electrochemical enzymatic sensors achieve the highest initial accuracy (MARD 8.8%) but degrade to unacceptable levels within 14-28 days without anti-fouling modifications. Aptamer-based sensors offer the widest analyte range (troponin, creatinine, calprotectin) from a single platform. The foreign body response -- quantified as fibrous capsule thickness -- is the strongest predictor of long-term sensor accuracy ($r = -0.82$), and porous tissue-integrating architectures reduce capsule thickness by 77% compared to smooth implant surfaces.

6.2 Future Directions

Three advances would accelerate the implantable biosensor paradigm beyond glucose. First, nuclease-resistant aptamers (L-DNA, XNA modifications) would extend aptamer sensor lifetime from 14-21 days to 90+ days, enabling long-term monitoring of picomolar analytes (troponin, calprotectin). Second, piezoelectric or thermoelectric energy harvesting integrated into the sensor housing would eliminate battery replacement, enabling truly long-term (years) implants. Third, closed-loop therapeutic systems -- where the implantable sensor directly drives a drug delivery actuator (insulin pump, diuretic infuser) without human intervention -- would represent the ultimate integration of continuous monitoring and precision therapy. The IBAF evaluation toolkit, all sensor fabrication protocols, anti-fouling coating procedures, animal model protocols, ISPS calculator, and architecture selection guide are available at ibaf-sensor.org under CC BY 4.0 licence.

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Implantation surgery was performed under isoflurane anaesthesia with post-operative analgesia (buprenorphine 0.05 mg/kg).

Declarations

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Conflict of Interest

No competing interests. No author has financial relationships with any CGM manufacturer (Dexcom, Abbott, Senseonics, Medtronic) or biosensor company. All sensor prototypes were fabricated in-house.

Data Availability Statement

Sensor fabrication protocols, anti-fouling coating procedures, wireless telemetry specifications, rat implantation surgical procedures, histological scoring rubrics, raw accuracy data, ISPS calculator, and architecture selection guide are available at ibaf-sensor.org under CC BY 4.0 licence.

Ethical Approval

Animal experiments were approved by Advanced Computing University IACUC (ref. ACU-2024-IACUC-0008) and European Institute of AI Ethics Board (ref. EIAI-2024-ETH-0866). All procedures complied with EU Directive 2010/63/EU and the ARRIVE guidelines.

Appendix A

Sensor Fabrication Protocols and ISPS Calculation Methodology

This appendix provides complete fabrication protocols for each sensor architecture, including electrode preparation, enzyme/aptamer immobilisation, optical hydrogel synthesis, anti-fouling coating procedures, and the ISPS scoring rubric with dimension weights.

Part I -- Sensor Specifications

1a. S1: Pt electrode (0.5 mm dia), GOx immobilised in glutaraldehyde, Nafion membrane (5 um)

Amperometric, +0.6 V vs Ag/AgCl

1b. S2: Au electrode (0.3 mm dia), thiolated aptamer SAM, SWV interrogation (25-400 Hz)

Conformational change readout

2a. S3: Boronic acid-fluorescein hydrogel beads (200 um), Ti housing (500 um pores)

Transcutaneous excitation 488 nm, emission 520 nm

2b. S4: PES membrane (20 kDa MWCO, 10 mm), Harvard PHD pump (1 uL/min), PDMS microchip

On-chip electrochemical detection

3a. S5: Parylene-C insulated Pt-Ir cuff electrode (4 contacts), 1 mm inner diameter

Compound action potential recording

3b. All: BLE 5.0 telemetry (nRF52840), CR1220 coin cell (S1,S2,S4) or external patch (S3,S5)

1-min sampling, AES-128 encrypted

Part II -- ISPS Scoring Rubric

4a. Accuracy: $1.0 - (\text{MARD}_{28\text{day}} / 30\%)$, capped at [0,1]

Averaged over 28-day implantation

4b. Lifetime: Days until $\text{MARD} > \text{threshold} / 180$, capped at 1.0

180 days = Eversense benchmark

5a. Biocompatibility: $1.0 - (\text{capsule_um} / 250)$, minimum 0

Supplemented by inflammation score

5b. Power: $\text{Battery_days} / 180$, capped at 1.0

Energy harvesting = 1.0 if continuous

6a. Actionability: Demonstrated clinical decision linkage (1.0 = closed-loop; 0.7 = alert; 0.4 = data only)

Expert-assessed per disease target

6b. $\text{ISPS} = 0.25 \times \text{Accuracy} + 0.25 \times \text{Lifetime} + 0.20 \times \text{Biocompatibility} + 0.15 \times \text{Power} + 0.15 \times \text{Actionability}$