Biomechanics of the Sensor–Tissue Interface—Effects of Motion, Pressure, and Design on Sensor Performance and the Foreign Body Response—Part I: Theoretical Framework

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Abstract

The importance of biomechanics in glucose sensor function has been largely overlooked. This article is the first part of a two-part review in which we look beyond commonly recognized chemical biocompatibility to explore the biomechanics of the sensor–tissue interface as an important aspect of continuous glucose sensor biocompatibility. Part I provides a theoretical framework to describe how biomechanical factors such as motion and pressure (typically micromotion and micropressure) give rise to interfacial stresses, which affect tissue physiology around a sensor and, in turn, impact sensor performance. Three main contributors to sensor motion and pressure are explored: applied forces, sensor design, and subject/patient considerations. We describe how acute forces can temporarily impact sensor signal and how chronic forces can alter the foreign body response and inflammation around an implanted sensor, and thus impact sensor performance. The importance of sensor design (e.g., size, shape, modulus, texture) and specific implant location on the tissue response are also explored. In Part II: Examples and Application (a sister publication), examples from the literature are reviewed, and the application of biomechanical concepts to sensor design are described. We believe that adding biomechanical strategies to the arsenal of material compositions, surface modifications, drug elution, and other chemical strategies will lead to improvements in sensor biocompatibility and performance.

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Introduction

It is well established that tight regulation of glucose reduces the risk of diabetes-related complications[1] and that availability of continuous monitoring data to patients improves outcomes.[2,3] However, despite 40+ years of research and development, there does not exist an accurate, long-term continuous glucose sensor to aid patients in maintaining euglycemia or to make the much-needed artificial pancreas a reality. The state-of-the-art is the percutaneous (PerQ) electrochemical sensor that continually monitors the glucose levels in the subcutaneous (SubQ) interstitium. These devices, while FDA-approved for patient use, are only indicated as adjunctive to self-monitoring blood glucose finger stick data. To realize the full potential of continuous glucose

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monitoring (CGM) and to improve patient adoption of these technologies, glucose sensors will need improved accuracy and ease of use. The accuracy limitations are not inherent in the sensors, as demonstrated by good *in vitro* sensor performance.[4–6] However, in the *in vivo* environment, sensor signals generally decline over time in an erratic, unpredictable fashion.[4,7–9] The primary culprit is the complex and dynamic foreign body response (FBR), which includes inflammation, biofouling, fibrosis, receding microvasculature, and a barrage of free radicals and degradative enzymes at the sensor–tissue interface.[10–12]

Historical Perspective

For years, the major focus of sensor development was to apply traditional engineering approaches, with little understanding of the biological interactions. Electronics were hermetically sealed, size exclusion membranes were added to control analyte fluxes and enzymes were stabilized. The realization that sensor surface chemistries direct the cellular interactions that dictate tissue response, which in turn dictate overall functionality of the sensor, led to extensive surface modification efforts. Various surface chemistries, coatings, and exterior membranes were developed to reduce protein fouling at the sensor surface.[13] Additionally an understanding emerged that surface microarchitecture independent of surface chemistry affects tissue response[14] and subsequently sensor functionality.[15–18] Application of coatings with specific pore sizes and microarchitechtural details have been shown to induce angiogenesis surrounding implanted sensors,[4,19,20] but so far, a porous or textured sensor coating has not led to practical clinical use. Efforts to overcome the deleterious effects of the FBR have focused on the use of active surface coatings[21] including the use of drugs to reduce inflammation and induce angiogenesis,[22–38] enzymatic scavengers,[39] gene transfer to induce neovascularization,[40] and stem cell attachment.[41] Few of these strategies have yielded significant improvements, and in some cases, have resulted in poorer sensor performance.[4,20] All of these studies involving both passive and active coatings have increased our understanding of the sensor–tissue interface, but there remain major gaps in our understanding of how to control and stabilize the biological environment surrounding the sensor to enable long-term CGM.

In light of these confounding results, we review one less-explored contributing factor to *in vivo* performance of glucose sensors: the biomechanics of the sensor–tissue interface. The presence of an implanted sensor imposes chronic mechanical disruption to tissue, and in response, the tissue remodels to accommodate the new loading conditions.[42] The way in which tissue remodels around sensors affects sensor function.[15] Furthermore, on a short time scale (quicker than tissue remodeling), forces acting on tissue surrounding the sensor may alter key physiological parameters such as blood flow and cell metabolism around the sensor. Also, rubbing or irritation may disrupt cell membranes releasing tissue factor and other proinflammatory agents. Variable stresses and loading conditions give rise to motion and pressure (typically micromotion and micropressure) and impact implanted sensor functionality. We propose that the surface chemistry view of sensor biocompatibility is only a portion of the story, and that mechanical forces imposed at the sensor–tissue interface also have a critical impact on the tissue reaction surrounding the sensor. Therefore, establishing a theoretical framework of how mechanical forces act on the sensor and surrounding tissue is warranted.

Percutaneous versus Fully Implantable Sensors

Before a discussion of mechanical forces, it is worth distinguishing first between PerQ and fully implantable sensors because they can vary greatly in their size, insertion/implantation procedures, operational life, and most importantly for this review, experience different mechanical forces once implanted in tissue. Percutaneous sensors that are commercially available are needle-type electrochemical sensors that penetrate the outer layers of skin. Sensing elements reside in the SubQ compartment where they are exposed to interstitial fluid from which they sense glucose. The electrochemical signal is electrically transduced to the externally worn transmitter that adheres to the outer layers of the skin. These indwelling devices are easily inserted and removed by the patient and are currently the only type of FDA-approved continuous glucose monitors.

Fully implantable sensors represent the class of sensors that are surgically implanted or injected into the body. They have not been marketed and most implantable sensors in development are intended for use in the SubQ space. Peritoneal and other implantation sites besides SubQ tissue are not considered in this review. SubQ sensors may vary greatly in size and componentry. Fully implantable SubQ sensors are typically much larger than the indwelling portion of PerQ sensors because they must incorporate all sensing, power, and telemetry components. They tend to be on the scale of several centimeters[32,43–47] although advancements in nanotechnology and microelectronics are enabling the development of miniaturized versions.[48,49] Important to note is the surgical implantation of SubQ sensors and the resulting settling period, which is the time it takes for tissue

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response to settle or stabilize after sensor implantation.[46] The larger the sensor, the more tissue damage occurs during implantation. Gilligan and Updike reported a settling period from days to months after implantation of their sensors in a SubQ pocket created through blunt dissection through a 1–3-cm incision.[43,44,46,50] However, once stabilized, SubQ sensors have been reported to have long-term sensing capabilities of several months and even beyond a year.[32,43,45,47,51] In our discussion of biomechanical influences on sensors performance, we describe various forces to which sensors may be exposed, including differential forces caused by PerQ versus SubQ sensor designs.

Wound Healing and Foreign Body Response

The very act of sensor implantation causes tissue injury and induces the wound healing response through a series of complex events.[52,53] The continued presence of the sensor disrupts the normal course of wound healing and elicits a FBR.[11,13] Immune cells attempt to engulf and digest the foreign body (sensor). A cascade of degradative substances (e.g., superoxides and free radicals) may be released in an attempt to break down the foreign body. If the foreign object is not small enough to be engulfed by macrophages or other phagocytozing cells (<5–20 μm), the body's natural response is to form foreign body giant cells and isolate the implanted device in a fibrous capsule to minimize its interaction with surrounding tissue.[11,13,54,55]

There is evidence to suggest the fibrotic capsule plays a role in mechanically stabilizing the foreign body. For example, Hori and colleagues found a positive correlation between the migration distances of implants and increased capsule thickness.[56] The thicker capsule was attributed to the constant friction between migrating implants and tissue. Numerous others have also reported that surface-textured implants (e.g., pillars, porous surfaces) exhibit a significantly thinner and less dense fibrous capsule.[56–60] The greatly increased surface area of these porous and pillared materials serves to reduce interfacial stresses at the tissue–implant interface by allowing the stresses to distribute over a much greater surface area.[58] Therefore, it is hypothesized that the body does not attempt to provide as much mechanical stabilization when forces are distributed, so capsules are thinner and less dense. PerQ devices are exposed to greater biomechanical forces compared to fully implantable SubQ devices. It has been shown that capsule thickness decreases over time for SubQ implants but remains constant for PerQ devices,[61] thus supporting the notion that encapsulation is the body's attempt to mechanical stabilize implants.

Finally, collagen, which is the primary constituent of the fibrous capsule, varies in type and amount depending on the mechanical stimuli or load on the tissue.[42] Here, we discuss mechanical forces and tissue–sensor biomechanics as important aspects of biocompatibility ultimately affecting the degree of the FBR to the sensor and its resultant performance.

Scope

This review (Part I—Theoretical Framework) explores biomechanical factors that affect percutaneous and fully implantable glucose sensors. Here, we focus on soft tissue biomechanics, particularly SubQ tissue, as this is the compartment most typical for sensor placement. Not discussed is the growing body of single cell biomechanics literature that attempts to relate forces on various cell types to regulation of cell function and structure, including cytoskeletal remodeling, cytokine release, proliferation, adhesion, and cell spreading.[62–79] For example, Ingber and colleagues[80,81] have described the transduction of force from the extracellular matrix to the cytoskeleton via transmembrane integrin receptors and assert that mechanical forces are critical cellular and developmental regulators. Although single cell biomechanics literature is certainly relevant, it is beyond the scope of this article, which takes a more macrocellular, tissue-level view. The sister paper (Part II—Examples and Applications) reviews specific examples from the literature that relate biomechanics to sensor performance and explores application of biomechanical concepts to sensor design.[82]

Biomechanics of the Sensor–Tissue Interface

The effects of mechanical stress at the tissue–implant interface have been recognized in the biomaterial literature.[42,83,84] We found the reviews of Hilborn (2007) and Sanders (1997) to be particularly helpful in our exploration of soft tissue biomechanics; however, transmission of both external and internal forces that generate motion and/or pressure at the sensor–tissue interface is a relatively unexplored and underappreciated aspect of sensor biocompatibility. These forces may be large and cause short-term modulation of sensor signal or be small in magnitude, cause no pain, and go completely unnoticed by the patient but still have an effect on the tissue environment surrounding the sensor and hence affect the sensor signal in the long term. A review of biomechanical forces affecting sensor performance suggests that even low magnitude forces such as micromotion can affect wound healing and FBR. **Figure 1**

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illustrates some of the contributors to motion and pressure at the implant–tissue interface and groups them into three main categories that are explored in this review: (1) applied forces, (2) sensor design, and (3) subject/species considerations.

Applied Forces (Generation and Transmission)

Motion and pressure arise from the application of various forces. These forces may act directly on the device, as in the case of a person or animal scratching or rubbing up against external sensor components, or indirectly, as occurs in the case of running and walking. Even breathing and pulsing of blood vessels have been shown to create cyclical sensor micromotion artifacts (with brain electrodes).[85] Although the forces that must be endured are likely more severe in animal models compared to humans, there are clearly many forces pertinent to marketed sensors during wear (e.g., rubbing of the beltline or other clothing, sleeping directly on the sensors, etc.). The magnitude, duration and transmission of each type of force can be quite different. **Figure 2** describes some of the relevant forces affecting glucose sensor performance, including normal (compressive and tensile), shear, and contractile forces.

Normal Forces (Compressive and Tensile)

The most apparent sources of device motion are external forces that act directly on the sensor itself. Tensile forces are expected more in certain implantation sites and in some animal models (e.g., tethered leads to rodents)[86] and compressive forces have been reported in large animal studies (e.g., in dogs, direct pressure over the skin led to a marked reduction in sensor output).[44] In human and animal use, the sleeping position may put direct compressive forces on the sensor, particularly if sensors are located over bony protuberances. Cases of anomalous sensor readings caused by compressive forces and specifically due to lying directly on the sensors are presented in Part II.[82]

Shear Forces

Shear conditions may arise in tissue surrounding sensors due to normal physiologic activities that can vary widely in shear rates (0.01 to 1 s^{-1})[87] and frequencies (e.g., 0.1 Hz during walking and 12 Hz during running).[88] The magnitude of shear forces on sensors in SubQ tissue has not, to our knowledge, been well characterized. Holt and colleagues submit that even at low magnitudes, shear loading is a highly destructive modality especially under the chronic conditions of an implanted sensor.[88] These chronic shear
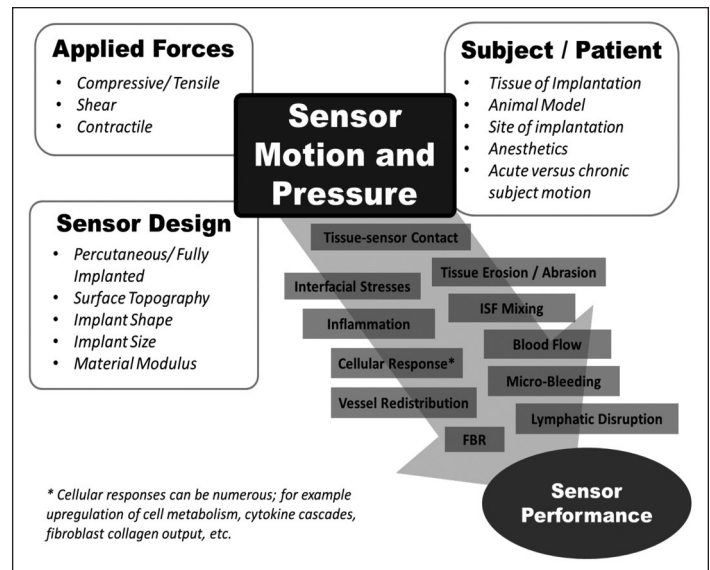

Figure 1. Applied forces, sensor design, and subject/patient consideration all contribute to sensor motion and pressure. Motion and pressure can affect sensor performance in a variety of ways. These biomechanical effects impact the tissue environment adjacent to the sensor in addition to chemical, electrical, magnetic, optical, or other possible effectors of the tissue response.
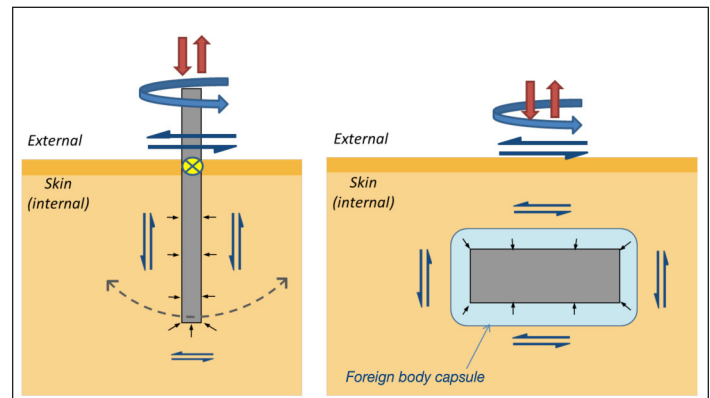

Figure 2. Schematic of applied forces acting on *in vivo* sensors. Examples of both external and internal forces generating motion and pressure on sensors relative to surrounding tissue for (a) percutaneous and (b) subcutaneous devices. **Normal forces** (red) include compressive and tensile forces that can arise from pushing or pulling on the external portion of the PerQ lead or device housing, or, in the case of a fully implanted SubQ sensor, an external force can be transmitted through the tissue to the implant. Common even in well-designed animal studies are attempts at scratching the sensor site and tugging the sensor leads, while human subjects are likely to experience tensile forces arising from snagging clothing and compressive forces from restrictive clothing and lying down on the sensor. **Shear forces** (blue) that act on PerQ and SubQ sensors include both transverse and torsional loadings. Shear stresses along the length of the sensor can also arise from pulling on the PerQ sensor. These forces may be acute (e.g., brushing across sensor while getting dressed) or repeated (e.g., walking, running). **Capsule or wound contracture (short black)** include wound contraction as the trauma of implantation is repaired. Contractile forces also arise from the constrictive fibrosis and contraction of the long-term foreign body capsule surrounding the device. The attachment of a PerQ device to the skin is represented by the yellow circle filled with an x and can serve as a fulcrum about which the implanted portion of a stiff sensor will rotate (dotted line) in response to an external shear force.

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forces in surrounding tissue give rise to micromotion of the sensor relative to surrounding tissue, and persistent interfacial stress has been related to the thickness of the foreign body capsule and the failure of PerQ devices.[59,89] Furthermore, continued local trauma arising from micromotion is evidenced by the necrosis of interfacial cells[42,90] despite traditional biocompatibility metrics of the materials (e.g., ISO 10993), and by the presence of microhemorrhages and edema in tissue surrounding implanted sensors.[32,91,92] Even after the initial implantation wound has completely healed, the force of the sensor against tissue seems to initiate bleeding in tissue around the sensor in some cases. Dr. Uli Klueh presented this information at the Diabetes Technology Meeting held in Bethesda, Maryland, November 11–13, 2010. In discussions with CGM users, one patient noted predictable bleeding at the site of the sensor during jogging. In this case, movement of the sensor relative to tissue appears to rewound the implantation site, causing microhemorrhages.

Contractile Forces

Quite different from the oscillatory shear stresses that give rise to micromotion are the inward normal, contractile forces. Contraction models (human fibroblasts cultured in three-dimensional collagen matrices), exhibited tension forces from 0.1 to 1 grams of force per million cells (approximately 1–10 nN/cell).[93] Stresses in this range (1–10 nN/cell contact) can cause remodeling of cell–cell contacts, cell extracellular matrix (ECM), and ECM.[42] Capsular contracture arising from constriction of the foreign body capsule has been reported to be strong enough to bend and fracture subcutaneously implanted polystyrene disks[94] and rupture breast implants.[95,96] Capsular contraction may not be relevant to available PerQ sensors but will become more relevant to sensor applications as the lifetime of fully implantable sensors is extended beyond 1-week implantation time.

Sensor Design Considerations

Various sensor design features are also important contributors to the way motion and pressure propagate to tissue surrounding the sensor and vice versa. The sensor size, shape, and material properties will affect the relative motion, intensity, and concentration of forces at the interface.

PerQ versus SubQ

The first design consideration is simply the type of sensor, an indwelling (PerQ) versus a fully implanted (SubQ) sensor. As described in the literature, the FBR to a PerQ implant is significantly different compared to a fully implanted device.[19,20,61] A PerQ device is subjected to direct external forces as well as the transmission of forces from various layers of skin. Data exhibiting the persistence of a foreign body capsule[61] support the notion that tissue remodels to adapt to the mechanical loading imparted by the implanted device.[42,84] Observed presence of fibrin was hypothesized to be the result of PerQ sensor movement,[97] which likely caused inflammation and/or direct microvascular damage, thereby increasing vascular permeability.

To minimize motion, various nonsensor PerQ devices (e.g., peritoneal dialysis ports) have been anchored to surrounding tissue. This has been achieved through first implanting meshes or porous flanges under the skin.[98–100] Once healed in place, the PerQ portion is inserted through the supporting mesh or flange. These approaches may require secondary surgery for device placement, and the new wound created during PerQ device injection could affect sensor performance if this long-term PerQ technique were applied to sensors.

Beyond the conduit for potential infection posed by PerQ sensors, the lifetime of PerQ devices may be limited by the micromotion and pressure exerted on the exterior of the device; forces propagate along the sensor and impact the cells and tissues at the sensor interface, thereby impacting sensor performance in an uncontrolled way. Conversely, a fully implanted SubQ sensor of (equivalent size and shape as the implanted PerQ portion) will experience less direct force, which likely leads to a relatively more stable sensing environment.[20,101] Certainly, researchers have shown considerably longer experimental data sets extending several months[32,43,44,46,47] and even beyond a year[51] with fully implanted sensors. However, one of the concerns with SubQ sensors is the longer settling period[43,44,46,50] required before the sensors track glucose, although this settling period is likely to be reduced as sensor miniaturization[48,49] enables microinjections and minimizes tissue damage.

Surface Topography

Surface microarchitecture (including microtopography, pillars, and porous coatings) is an area of abundant biomaterial research[14,58,60,102,103] and has been applied to glucose sensors.[4,19,20,43,50,104] It is known that materials of the exact same chemical composition can exhibit vastly different FBR depending on the surface microarchitecture.[14,17,102,103] These findings serve as direct evidence of biomechanical cues contributing (in addition to surface chemistry) to the tissue response. Ridges, fibers, or pores on the exterior of textured materials serve to

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increase surface area, and thus the force per unit area observed by an implant can be greatly reduced. Macrophages are not able to flatten on the surface of materials with certain pore or fiber size, and this likely changes their expression pattern to trigger an altered FBR. Picha and Drake found that surface pillars reduced interfacial shear by improving tissue integration and resulted in reduced fibrosis, improved vascularity, and improved overall tissue response (**Figure 3**).[58] Similarly, porous coatings have been shown to improve tissue integration and FBR.[14,17,102] One caveat to the use of porous coatings for PerQ soft-tissue sensors is that some researchers suggest that the tissue integration could

actually be detrimental, as external forces on the sensor are transmitted to the region occupied by the coating and beyond, a phenomenon that has been described as tearing the device from its implantation bed.[19,89]

Shape

The shape of sensors also greatly impacts the interfacial forces. Matlaga and colleagues[105] demonstrated the altered response to implants of different cross-sectional shapes and found that acute angles initiate a different tissue response. The regions of higher stress concentration at sharp angles elicit a denser encapsulation response (i.e., collagen density) compared to broad angles or flat edges.
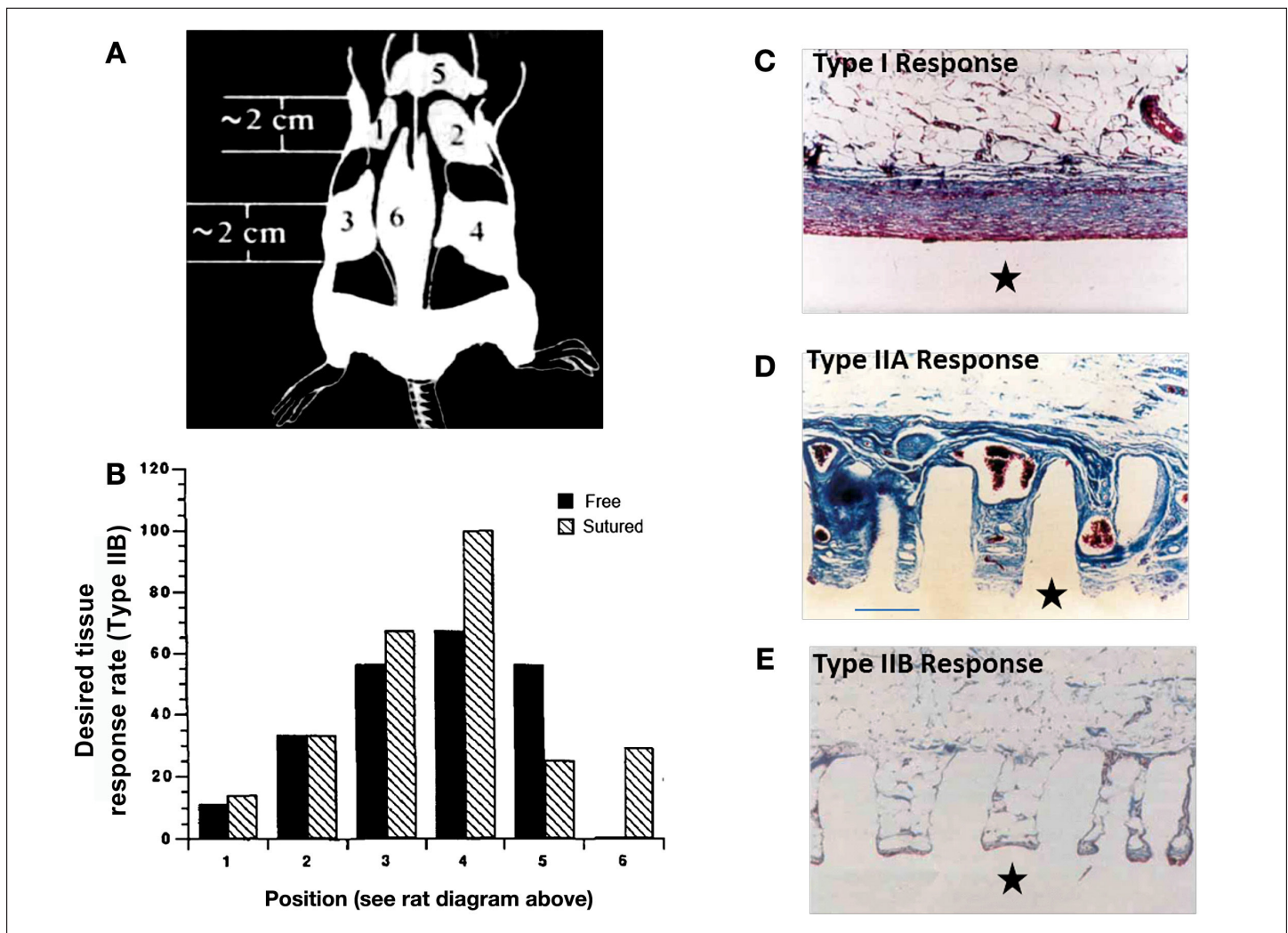

Figure 3. Even in the same compartment (SubQ), tissue response varies with site of implantation. **(A)** Solid and microtextured (100-μm-diameter pillars by 500 μm in height, spaced 200 μm center to center) silicone disks (★) were implanted into rat SubQ tissue in six different locations as illustrated. **(B)** The most favorable, Type IIB, response rate is plotted versus implantation site for free and sutured micropillared implants (4 weeks). A 100% type IIB response is observed for the sutured implant in the fatty tissue bed of site 4. No type IIB responses were noted for free implants in position 6, which is consistent with the authors' supposition that both microtexturing and reduced motion are as more likely to lead to a type IIB response. Trichrome stained, 100x. **(C)** A Type I response as measured for a flat (nontextured) implant, encapsulated by a highly aligned fibrous capsule. **(D)** A Type IIA response: dense collagen and large blood vessels (~100–200 μm) found in and around pillared surface material. **(E)** The optimal, Type IIB response with little to no capsule and capillaries in intimate contact with the pillar surface (too small to be imaged in this diagram). The varying tissue responses observed in **(D)** and **(E)** are dependent on the SubQ implantation site **(B)** as well as fixation to reduce motion. Figures adapted from Picha and colleages.[58]

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From the authors' personal experience, dense fibrous tissue found at the corners of rectangular-shaped implants is often purposefully neglected in FBR implant evaluations because it differs substantially from the reaction around the majority of the implant surface. However, from the perspective of sensor development, a complete understanding of the FBR may be necessary to help choose the optimal placement of electrodes or sensing components. Li and colleagues demonstrate that capsule thickness varies with time and position surrounding a rectangular-shaped SubQ implant (**Figure 4**).[106] Their work underscores the importance of not only the location of capsule measurements (corners versus nonangled surfaces) but also the implant orientation within the SubQ space.

Size

The smaller the sensor, the less tissue disruption created by the implantation procedure and by the continued presence of the sensor. Kvist and colleagues[107] demonstrated that using smaller insertion needles (compared 14, 18, and 21 gauge) significantly reduced insertion wound trauma (measured hemorrhage, inflammatory cells, and giant cells on day 3). In addition to reducing the short-term inflammatory response to the insertion wound, it is likely that miniaturization of sensors through advancements in nanotechnology and microelectromechanical systems will improve the long-term FBR.[108] In fact, it has already been shown that small-diameter implants exhibit less FBR and in some cases, surprisingly, appear to elude the host response all together (e.g., fibers <6 µm).[109]
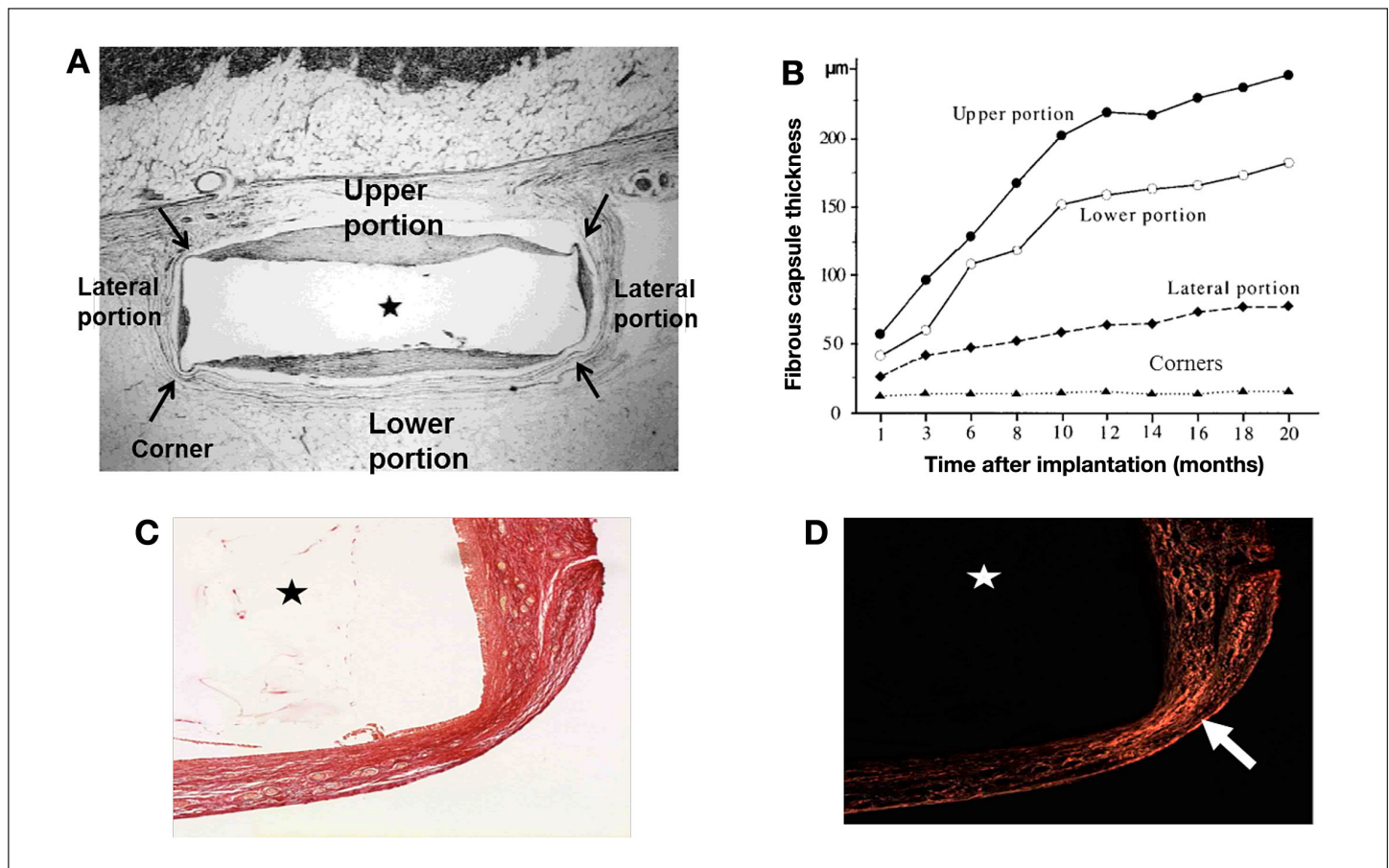

Figure 4. The foreign body capsule surrounding an implant varies (thickness and density) with position on the surface of the implant and time of residence in the body. **(A)** Foreign body capsule surrounding a hydroxyapatite disk (★) implanted subcutaneously into the interscapular region of rats. **(B)** Capsule thickness increases with time in all positions except for the corners (e.g., upper and lower capsule thicknesses increased 200% in the first 10 months and 20% per month thereafter, and lateral portion increased ~200% between months 1 and 20. Based on this data, it can be expected that sensing elements facing outward toward the skin versus inward will experience differential FBR. Furthermore, the plot clearly shows the time-dependent nature of the foreign body capsule.

In a different study, similarly shaped, pHEMA hydrogels (★) were implanted for four weeks in mice. **(C)** The implant region is visualized with picrosirius red stain under a light microscope. **(D)** Collagen density is estimated using circularly polarized light analysis of picrosirius red stained sections (4x magnification). Collagen density appears highest (brightest) in the regions of highest interfacial stress, including the corners (white arrow denotes high collagen density at one corner). Figures A and B adapted from Li and colleagues.[106] Figures C and D are unpublished data courtesy of Eric Sussman, University of Washington.

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Ward and colleagues[60] demonstrated that implants of varying thickness elicit different responses and that thinner implants exhibit thinner capsules. However, the orientation of the implant is critical and the thinnest dimension should be placed parallel to the surface of the skin to minimize extracellular matrix distortion in the vertical direction.[110] Sanders and colleagues[110] postulate that implant height (dimension perpendicular to the skin) is important because thicker implants substantially separate adjacent collagen fibers and create low-pressure void regions that require filling with new matrix. The presence of capsule was shown to be less dependent on the length of the implant (dimension parallel to skin), than implant height (dimension perpendicular to skin). The authors explain this observation is likely due to collagen fibers orienting principally in planes parallel with the skin surface, so there is less collagen disruption with sensor displacement parallel to the skin.[110]

Implant size was the likely contributor to the vastly different FBR observed around implants with the same microtopography and surface chemistry but very different thicknesses.[59,95,103,111] Campbell and von Recum found little fibrosis surrounding paper-thin, micro-textured implants of polyvinyl chloride/polyacrylonitride (PVC/PAN) and silicone-coated PVC/PAN. The authors concluded that a defined surface topography of 1 to 2 microns allowed direct fibroblast attachment and minimized connective tissue response. However, the paper-thin dimension was likely an underappreciated contributor to the reduced fibrosis they observed because the results were not replicated. In a similar study by den Braber[111] using thicker (1.45–2 mm) implants of the same material, there were no significant differences in capsule thickness for smooth and microgrooved silicone implants.

Another important aspect of sensor size is the settling period or time it takes for the sensor signal to stabilize after implantation. SubQ sensors that are small enough to be injected via syringe and reduce the wound created by surgical implantation are expected to settle more quickly. Available commercial PerQ sensors (approximately 200–500 μm in diameter) have a 2-hour wait time before sensor use, presumably to allow the immediate tissue response to settle (and also possibly for sensor wetting). Experimentally injected thin percutaneous fibers (100 μm) have been shown to have settling periods of only 3–6 minutes under anesthetized conditions.[112] Movement or normal activities would likely extend the settling time.

Material Modulus

Another sensor design challenge is the mismatch in mechanical properties of the device and skin, as this incongruity results in stress concentrations at the interface.[42,88,94,113,114] Sanders and colleagues[113] demonstrated that polyurethane implants, which had moduli two to three orders of magnitude lower than other plastics tested [polyester, polyethylene, poly(L-lactic acid)], exhibited significantly less foreign body capsule as compared to the more rigid materials. Similarly, a computational model of a brain electrode corroborated stress concentrations at the interface arising from modulus mismatch. Subbaroyan and colleagues[114] demonstrated significant differences in strain profiles and the shift in the high strain location for electrodes of different stiffness (**Figure 5**). Furthermore, the pressure exerted by the stiff electrode on surrounding tissue results in compression, expansion, and possibly tearing of the tissue,[114] and there exists a direct relationship between the electrode modulus and interfacial strain, which is hypothesized to contribute to the inflammatory response.[115] Therefore, to the extent that sensor electrode properties can be manipulated, the use of softer materials with material properties similar
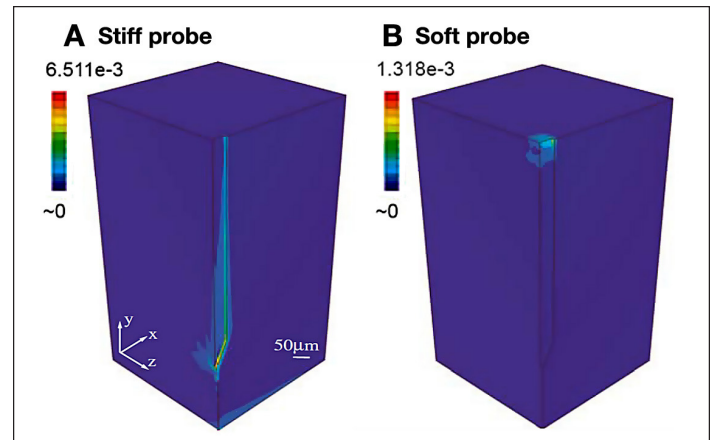

Figure 5. Finite element models demonstrate force transmission to the surrounding tissue depends on sensor modules. The strain profiles in the brain tissue resulting from a lateral displacement of 1 μm simulating a tangential tethering force on the electrode that would arise from rotational acceleration of an animal's head are plotted. The models demonstrate significant differences in strain profile in the brain tissues generated by a **(A)** stiff electrode (elastic modulus, E = 200 GPa) and **(B)** a hypothetical soft electrode (E = 6 MPa). The maximum principal strain for the stiff electrode is approximately five times greater than the maximum principal strain for the soft electrode (maximum values on color map scale at the top left of each simulation). Importantly, the region of high strain shifts from the stiff electrode tip **(A)** to the surface of the brain tissue **(B)**. The modulus of brain tissue is approximately 6 kPa (still 1,000 times lower than the hypothetical soft electrode material). These data demonstrate the significant shift in strain magnitude and location for electrodes of different material properties in a soft tissue. Figure adapted from Subbaroyan and colleagues.[114]

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to the implantation tissue could reduce interfacial strain and improve sensor biocompatibility.

Subject Considerations

Animal Model

The appropriate animal model for sensor and biomaterial implantation studies is a subject of some controversy. There is an expansive body of work performed in the rat (some examples in Part II, Table 1),[82] despite the fact that rodent skin has several anatomical and physiological differences from human skin. Even comparisons of the FBR among rodent models have yielded different results.[116] Commonly studied loose-skinned small mammals have dense fur, relatively thin epidermal and dermal layers, and a subepithelial layer with bundles of skeletal muscle fibers[117] that allow their hair to stand up on end. Profound differences between rats and humans in the FBR and flux of various metabolites in the interstitial fluid at the sensor–tissue interface have been demonstrated over 8 days of SubQ implantation.[118,119]

To relate the choice of animal models with physiological differences to biomechanical forces acting on the sensor–tissue interface, we consider several factors. First, the SubQ muscle layer that exists in furry animals will be a source of repetitive micromotion. Movement of the loose skin will generate greater shear forces on an implanted sensor compared to a tight skinned animal (e.g., pig, human), which may experience more compressive loading because of the tightness of their skin. Loose-skinned animals may also be more prone to implant migration. Grooming in animals with fur will likely produce more repetitive motion than pigs or humans. For these reasons, the micro- and macromotions will likely be greater in rodents and other haired animals (e.g., dogs). Undoubtedly, a comparative animal study is needed to elucidate FBR differences to implanted sensors over time in the SubQ tissue of various animals and compare these to human data to establish the most appropriate animal model.

The use of rodents is justified in many studies because of their low cost, easy handling, and approximation of human conditions such as diabetes and obesity by genetic modification.[119] One caveat to employing genetic modifications is that transgene expression has been demonstrated to change the tissue properties and composition of skin.[120] Nevertheless, Klueh and Kreutzer[86] have developed a mouse model, which has been validated to produce CGM sensor signals that approximate those observed in humans, though direct FBR comparison was not conducted. This CGM mouse model has enabled

exploration into the role of mast cells[8] and cytokines[121] through the use of knock-out mice, and this research would have been nearly impossible to achieve with more advanced animal models.

A common advanced sensor-testing model is porcine skin, which is structurally similar to human skin, having similar epidermal thickness (30–140 μm in pigs; 50–120 μm in humans) and ratios of dermis to epidermis thickness.[122–124] Human dermis thickness ranges from 1 mm on the face to 4 mm on the back[125,126] while pig dermis thickness can be up to twice as thick in some regions (6 mm),[127] but the dermis of young, 14–15 week-old pigs is thinner (~2 mm).[128] Pig skin has been reported to be similar to that of humans in the majority of anatomical and physiological aspects, including paucity of hair, skin thickness, pigmentation, and collagenous tissue framework,[122,129] and exhibit similar patterns of blood vessels.[117] Important to the study of biomechanics in tissue, is the fact that porcine skin contains dermal collagen and elastic content that is more similar to humans than other commonly used mammals.[130] Furthermore, experience of some researchers suggest that the collagenous capsule that forms around implants is of similar thickness in pigs and humans (personal correspondence with Dr. Andrew Marshall). Because of their large size, multiple sensors can be tested in a single pig and the implant-to-subject size ratio is comparable to that of human subjects. While porcine skin is compositionally and structurally similar to humans,[122] the skin of young pigs is mechanically most similar to humans, making it the preferred model in plastic surgery research.[131,132] Beyond biomechanical considerations, which support the porcine model, a direct comparison of CGM performance and FBR in humans and pigs as well as other animals would be helpful toward instilling confidence in the selection of animal models for sensor studies.

Tissue of Implantation

Skin is a complex, viscoelastic tissue composed of three layers: epidermis, dermis, and SubQ tissue, also sometimes referred to as the hypodermis. The mechanical properties of skin are dynamic and vary with age and skin region.[133] While skin is often treated as a homogeneous composite, the different layers of skin have distinct mechanical properties.[134] Holt and colleagues[88] demonstrated that whole skin exhibited rigidly elastic behavior as compared to the more viscous, fluid-like behavior of skin with the epidermis removed. A wide range of elastic modulus has been reported for the various skin layers, including the outer most layer of the epidermis, the stratum corneum (5–1000 MPa with decreasing hydration),[135] dermis

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(56–260 kPa),[133,136,137] and SubQ tissue (0.12–23 kPa).[136,138] Variation in modulus data arises from differing test methods (e.g., tensile, torsion, suction, indention), tissue sampling (*in vivo* versus *in vitro,* sample preparation, and storage), hydration, and the applied testing loads and strains. Also, depending on the tissue of implantation, the composition[140] and thickness[123,133,140–142] will vary.

As discussed earlier in the *Material Modulus* section, one strategy for reducing biomechanical forces is to design sensors to more closely match the modulus of the tissues in which they are implanted. This is an extraordinarily difficult materials challenge for PerQ sensors, because they will typically come into contact with all three layers of skin whose moduli can vary by four to five orders of magnitude. Fully implantable sensors are being developed for implantation into specific layers of the skin. For example, Clark and colleagues[143] are developing glucose-sensitive nanoparticles for injection into the epidermis, while McShane and Coté[144,145] are designing microparticles or smart tattoos for dermal injection. Other groups, such as Gough and colleagues[51] and Papadimitrakopoulos and Burgess[108] are designing sensors for the SubQ space. The biomechanics of the sensor–tissue interface in each of these compartments will vary greatly. To minimize biomechanical forces due to modulus mismatch, sensors intended for SubQ implantation need to be much softer than those injected into the stiffer epidermis layers.[88,146] Even without a perfect modulus match, implantation studies in adipose-rich tissues have exhibited a more benign FBR,[58,147] likely due to stress absorptive properties of fat. Of course, size constraints of the desire tissue compartment are important, that is to say, it would be difficult to place a 3-mm-thick sensor in a 1-mm-thick dermal layer. One must also consider the chemical and physiological properties of the tissue compartment.

Site of Implantation

The exact site of implantation for a given subject is not often carefully controlled and it is common to place multiple implants in a single subject during experimentation. Site-to-site variation with CGM has not been well characterized but has been reported.[148] In many experimental cases, biomaterial implants are rotated among the different locations in order to obfuscate site variations.[94,111] However, presented here is data that highlight the importance of the exact implant location within the SubQ compartment and demonstrate that varying sites (e.g., SubQ on the back in the scapular region versus SubQ on the back in the middorsal region) can confound experimental outcomes and should be

carefully controlled. From the authors' own experience, even the orientation of planar SubQ sensor electrodes (e.g., facing up toward the skin or down toward the muscle) can impact sensor performance (unpublished data). This may be expected based on the FBR data presented in **Figure 4** exhibiting a thicker capsule on skin-facing surface of the implant. We believe that some of these site-to-site differences may be due to differential biomechanical forces.

The data in **Figure 6** were collected from a study of porous, poly(2-hydroxyethyl methacrylate) (pHEMA) implanted into the SubQ tissue of mice.[149] **Figure 6** shows mean capsule thickness as a function of implantation site, scapular or middorsal. There was a significant difference in capsule thickness for the two implantation sites.[149] The large variation in capsule thickness between implantation sites was unanticipated and is presumed due to the different forces incurred at the scapular and middorsal sites. A thorough discussion of the variance requires a comprehensive evaluation of the site differences, including the measurement of forces (e.g., strain rates during ambulation, compressive forces of skin on the
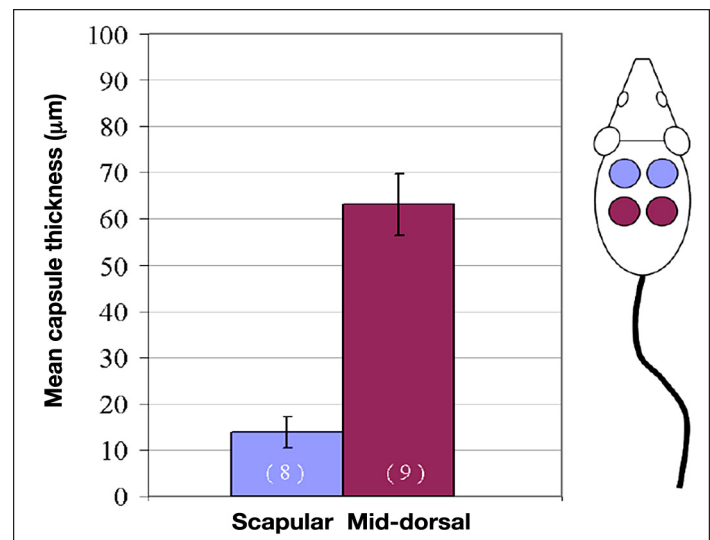

Figure 6. Implantation site is a primary determinant of capsule thickness surrounding implants placed in the same tissue compartment (SubQ). Four porous pHEMA disks (3.5 mm diameter and 1 mm thick) were implanted subcutaneously into the dorsum through one of two midline incisions. The implants were explanted after 4 weeks and stained with Masson's trichrome, a marker to visualize dense, oriented collagen capsule tissue. The mean capsule thickness is plotted as a function of implant site (scapular and middorsal). Even through all materials were implanted subcutaneously, the exact site of implantation within the subcutis significantly influenced the capsule thickness (error bars represent standard error of the mean). Differences in biomechanical forces at the two different locations are suspected to play a role in the differential capsule thickness. These data highlight the importance of choosing and controlling sensor implantation location in *in vivo* studies. Figure adapted from Marshall.[149]

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implant, and incidence of scratching at both sites) as well as physiologic variations in the SubQ tissue. The composition of the skin may also vary significantly with position.[58] The differences between sites underscore the importance of choosing and controlling a sensor implantation location.

Picha and colleagues[58] also observed site-to-site variation in tissue response (**Figure 3**). Smooth and micropillared silicone disks were rotated among six SubQ sites in a rat model (**Figure 3A**). Although the tissue response to the micropillared implants was more benign than to smooth implants, the response was found to be highly site-dependent (**Figure 3B**). The authors hypothesized that in areas of higher fatty content, the compliant, stress-absorbing fat reduced interfacial shear and led to a more benign FBR.[58] Site-dependent variation in vascularity around the implants was also observed. Importantly, the size and density of vasculature, for example, one capillary per fat cell in adipose tissue,[150] creates a very different glucose supply compared to the few large scattered macrovessels (**Figure 3D** compared to **3E**).

Anesthetics

Anesthetics, including isoflurane and halothane, have been reported to increase blood glucose concentrations, while pentobarbital was found to slightly decrease blood glucose levels.[151,152] In addition to chemical effects, there appear to be biomechanical differences between conscious and anesthetized animals due to reduced motion. Ward and colleagues[152] noted that fluctuations in sensor signals were markedly reduced in the anesthetized state as compared to the conscious state. While fluctuations in the conscious state could be due to electrochemical inter-ferants, they are most likely caused by local fluctuation of glucose, oxygen, or microvascular blood flow.[152] This finding highlights the need for a better understanding of the impact of anesthetics on skin physiology. Sensor developers should be aware that testing in anesthetized animals may not reflect physiological conditions of conscious animals, including motion artifacts.

Acute versus Chronic Subject Motion

Motion artifacts can also arise when acute forces temporarily impact sensor signal. It is hypothesized that applying direct pressure on the sensor and surrounding tissue can cause a temporary reduction of localized blood flow, thus perturbing sensor readings. This acute effect is often short-lived and sensor signal usually resolves once pressure is removed. As we describe in Part II of this review, a common cause of acute motion artifacts

is the subject lying or sleeping on the sensor. Chronic motion, however, affects the FBR to the sensor and can alter surrounding tissue. In this case, chronic motion often causes gradual signal loss and may require sensor recalibration.

Conclusions

While there are many important factors influencing sensor biocompatibility and affecting performance, we underscore the importance of device–tissue biomechanics. Motion (including micromotion) and pressure, as we have described, can affect the sequelae of the FBR and sensor performance. The contributors to motion and pressure include applied forces (normal, shear, contractile), sensor design (PerQ/SubQ, size, shape, surface topology, modulus), and various subject considerations (species, tissue compartment, exact site, anesthesia). The exact site of sensor implantation can greatly affect the FBR, and we emphasize the importance of controlling site variation in sensor studies. Of course, the biomechanics are just one of many elements that need to be considered in creating a sensor that will function in the biological environment. It will also be critical to perform comparative animal model studies to ensure that the tissue response and sensor performance are representative of human FBR and sensor data. Finite element models could provide a systematic way to evaluate the biomechanics of different sensor designs and aid in minimizing tissue–sensor interfacial stresses to improve FBR and sensor performance. The biomechanics (motion and pressure) of the device–tissue interface influence not only sensor performance but also have implications in the design and development of other long-term implantable devices in soft tissues.

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Sensor Performance and the Foreign Body Response—Part I: Theoretical Framework

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