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Versatile and inexpensive Hall-Effect force sensor for mechanical characterization of soft biological materials

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Abstract

Mismatch of hierarchical structure and mechanical properties between tissue-engineered implants and native tissue may result in signal cues that negatively impact repair and remodeling. With bottom-up tissue engineering approaches, designing tissue components with proper microscale mechanical properties is crucial to achieve necessary macroscale properties in the final implant. However, characterizing microscale mechanical properties is challenging, and current methods do not provide the versatility and sensitivity required to measure these fragile, soft biological materials. Here, we developed a novel, highly sensitive Hall-Effect based force sensor that is capable of measuring mechanical properties of biological materials over wide force ranges (μN to N), allowing its use at all steps in layer-by-layer fabrication of engineered tissues. The force sensor design can be easily customized to measure specific force ranges, while remaining easy to fabricate using inexpensive, commercial materials. Although we used the force sensor to characterize mechanics of single-layer cell sheets and silk fibers, the design can be easily adapted for different applications spanning larger force ranges ($> \text{N}$). This platform is thus a novel, versatile, and practical tool for mechanically characterizing biological and biomimetic materials.

Keywords

Force sensor; Cell sheet mechanics; Hall-Effect; Silk fiber mechanics

1. Introduction

In tissue engineering, matching host tissue mechanical properties is vital to avoid compliance mismatch that negatively impacts repair and remodeling (Langer and Vacanti, 1993). This requires an understanding of micro and macro-structural properties of native and engineered tissue, e.g. force measurements spanning multiple orders of magnitude (Butler et

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Conflict of interest statement

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al., 2000; Ingber et al., 2006). For example, cell sheet engineering builds three-dimensional tissues from monolayers of cells and associated extracellular matrix (ECM) (Williams et al., 2011; Yang et al., 2005). Although this technique has been successful in corneal (Nishida et al., 2004), myocardial (Masuda et al., 2008), and epidermal (Cerqueira et al., 2013) models, its full potential has not been explored: measurements of mechanical properties of individual tissue layers combined with computational studies could predict properties of more complex 3D tissue structures (Roberts et al., 2014). Employing such novel techniques would enable rational design of engineered tissue possessing requisite mechanical properties (Elbert, 2011; Nichol and Khademhosseini, 2009; Williams et al., 2009).

This approach requires a method to measure effects of small forces (< 1 mN) applied to individual cell/ECM sheets, comparing these results to effects of substantially larger forces (> 1 N) applied to multi-stacked cell sheet structures or tissue (Isenberg et al., 2012). Uniaxial and biaxial tensile testing provides physiologically relevant information useful in understanding *in vivo* mechanical properties (Harris et al., 2013). Most commercial sensors are only capable of measuring large forces (> 100 mN), whereas tissue engineering applications often require mechanical testing in force regimes spanning 0.01–100 mN. While more sensitive systems exist, their high cost can be a significant barrier. One inexpensive alternative to commercial force sensors involves optically measuring deflection of a compliant, cantilever beam, but requires post-processing of imaging data to extract force data (Harris et al., 2013).

To overcome these cost and performance limitations, we developed an inexpensive force sensor capable of measuring forces ranging from μN to N. The force sensor combines a cantilever beam, Hall-Effect magnetic field sensor, and magnets to measure force; sensor design is easily fabricated from commercial off-the-shelf components for less than \$50. To demonstrate applicability in tissue engineering, we show successful integration with a custom uniaxial tensile tester to measure mechanical properties of single-layer vascular smooth muscle cell (VSMC) sheets and silk fibers. Our force sensor design flexibility and low cost can also be applied to other applications.

2. Materials and methods

2.1. Force sensor materials

The magnetic yoke was constructed using $3/8'' \times 3/8'' \times 1/8''$ (width x length x thickness) rare earth N52 Neodymium magnets (K&J Magnetics, Pipersville, PA) with a residual magnetic induction of 1.48 mT. Magnetic shielding was constructed using 100 μm thick Interference-Shielding Nickel Foil (McMaster-Carr, Elmhurst, IL). Cantilevered beams were constructed using either brass (Alloy 260) or stainless steel (Alloy 304) (McMaster-Carr). The force sensor design uses an AKM EQ-730L Hall-Effect sensor (GMW Associates, San Carlos, CA) with a magnetic field sensitivity of 130 V/Tesla that achieves full voltage output (0–5 V) over magnetic field strengths ranging from -18 to 18 mT. The Hall-Effect sensor has a root mean square noise level of 1.6 mV.

2.2. Force sensor calibration

Each force sensor was calibrated by mounting the beams vertically, hanging and measuring sensor output voltage. Each calibration experiment was replicated multiple, independent times ($N=5$). Beam stiffness (mN/V) was determined by performing linear regression on calibration data using R (R Foundation for Statistical Computing, Vienna, Austria). Force range was estimated as beam stiffness (mN/V) multiplied by sensor voltage output range (5 V).

2.3. Biological material preparation and mechanical characterization

Bovine aortic vascular smooth muscle cells (VSMCs) (Coriell Cell Repositories, Camden, NJ) tested negative for mycoplasma and were cultured in low glucose Dulbecco's Modified Eagle Medium (Invitrogen, Grand Island, NY) supplemented with 10% fetal bovine serum (Hyclone, Logan, UT), 100 units/mL of penicillin, 100 $\mu\text{g/mL}$ streptomycin (Invitrogen), and 2 mM L-Glutamine (Invitrogen). Cells were seeded at a density of 55,000 cells/ cm^2 onto flat thermo-responsive PDMS substrates as previously published (Isenberg et al., 2012). After 4 days, culture medium was supplemented with 50 $\mu\text{g/mL}$ L-ascorbic acid (Sigma, St. Louis, MO) administered daily for 7 days. Vascular smooth muscle cell sheets were detached by incubating sheets at room temperature in phosphate-buffered saline (PBS; Invitrogen). Length and width of cell sheet strip samples were measured with calipers, and thickness was measured using an Axiovert S100 microscope (Karl Zeiss, Germany). Cell sheet strips were glued to mounts using cyanoacrylate adhesive (Loctite Instant-Bonding Adhesive, #414; Henkel Corporation, Westlake, OH) and then mounted in the tensile tester. Cell sheets were stretched to zero-strain state by stretching sheets until they began to bear load. During testing, cell sheets were imaged using a digital microscope (Aven Inc., Ann Arbor, MI) mounted above the test bath. Cell sheets were mechanically characterized by subjecting cell sheet strips to 3 pre-stress load cycles to 20% engineering strain before stretching to failure at a strain rate of 0.05/s. Failure stress and strain were measured, and Young's modulus was determined over the linear regime of the stress-strain curve.

Silk fibers were prepared as previously described (Kinahan et al., 2011) (See also Supplementary Materials & Methods).

3. Results

3.1. Force Sensor Design

The uniaxial tensile tester is comprised of three basic components: the test cell, linear actuator, and force sensor (Fig. 1). In the test cell, two ends of the sample are connected to a pair of mounts that attach the sample to the linear actuator and force sensor. The force sensor is composed of a cantilevered beam mounted within the test cell to allow direct connection to the biological sample (Fig. 2a). The beam extends beyond the sample attachment point and out of the aqueous bath where a Hall-Effect magnetic field sensor is mounted onto the end of the beam. By sampling different positions within the magnetic field created by a configuration of four magnets (magnetic yoke), the Hall-Effect sensor measures the cantilevered beam tip displacement, and resultant force measurements are collected (via DAQ board).

The optimal magnetic yoke configuration will produce a steep, linear magnetic field gradient to minimize beam deflection during mechanical testing, while also producing a stable magnetic field where misalignment between the Hall-Effect sensor and magnetic yoke causes minimal measurement error. Moreover, the magnetic field should be linear at small magnetic fields ($|B| < 18$ mT) to avoid sensor saturation. The optimal magnetic yoke configuration is shown in Fig. 2b. Adjacent magnets have magnetization vectors in opposite directions, and the two opposing Kittel domains are separated by a 1.25 mm gap. The optimal magnetic yoke design was built using four Neodymium rare-earth magnets (N52, 3/8" wide $\times$ 1/8" thick) with thin strips of magnetic shielding (100 μ m thick) covering either side of the Kittel domains. Magnetic field modeling results for the optimal configuration predict Hall-Effect sensor saturation everywhere within the magnetic yoke except near its center (Fig. 3a, b). Over displacements less than 50 μ m in the y-direction, the magnetic field (B_z) varies linearly from -18 to $+18$ mT, allowing full Hall-Effect sensor output (Fig. 3c.). Model implementation details and predictions for B_x and B_y (Fig. S1) can be found in the Supplementary Materials and Methods along with modeling results for magnetic yoke design variations (Fig. S2).

The sensor design uses a simple cantilevered to measure force (Fig. 2a). Elementary beam bending mechanics predict that beam tip displacement varies linearly with applied force as detailed by Equation 1 (see Supplementary Materials and Methods). By changing beam material and geometry (beam width, length, thickness, and loading point location), the sensor's force range can easily be customized. For example, for a given beam geometry, the sensor's force range spans several orders of magnitude by changing the position on the beam where the load is applied (Fig. 4b). When load is applied to the beam, the beam curves and the beam tip rotates. At maximum load, the Hall-Effect sensor rotates 0.001° toward the y-direction and correspondingly causes a nominal 0.0012% decrease in the magnetic field gradient (Fig. 4a). The actual beam shape shows no visible curvature and is plotted in the inset of Fig. 5a.

Using results from magnetic field modeling and beam bending analysis, we designed four force sensors to measure forces in different ranges using Equations 1 and 2 (see Supplementary Materials and Methods) to predict force sensor range. The experimental sensor calibration results (Fig. 4c; Table 1) show a highly linear ($R^2 > 0.997$) relationship between applied force and Hall-Effect sensor output (V) over multiple, independent calibration experiments ($N=5$).

3.2 Mechanical characterization of biological materials

Single-layer bovine VSMC sheets and silk fibers were mechanically characterized using the Hall-Effect based force sensor. The stress-strain behavior for the population of cell sheets ($N=8$) is shown in Fig. 5c. The population of cell sheets had a mean ($\pm$ s.d.) Young's modulus of 114.2 ± 33.5 kPa, a mean failure stress of 155.2 ± 98.2 kPa, and an engineering failure strain of 0.32 ± 0.10 . In addition to VSMC sheets, dry silk fibers were mechanically characterized. Mechanical behavior for the silk fiber population ($N=10$) shows significant variability (Fig. 5a). Typical silk fiber stress-strain behavior features an initial region where stress increases linearly with strain, and then the curve reaches an inflection point where

stiffness decreases (strain hardening behavior) and the silk fiber eventually fails. The silk fiber population had a mean Young's modulus of 59.8 ± 33.5 MPa within the initial linear regime of the stress-strain curve. The fibers failed at a mean engineering strain of 0.13 ± 0.06 and a corresponding mean engineering stress of 4.49 ± 3.19 MPa.

4. Discussion

Here, we present an accurate, inexpensive, and versatile biomechanical force sensor design capable of measuring mechanical properties of fragile tissue-engineered materials such as single-layer cell sheets and silk fibers. This sensor design can easily be customized and fabricated to measure multiple force ranges (μN to N). It is often difficult to estimate the magnitude of forces that tissue-engineered materials can withstand, making it difficult to justify purchasing expensive, commercial force sensors with limited range. For example, the force ranges required to mechanically characterize cell sheet-based tissue vary over several orders of magnitude depending upon culture conditions and tissue complexity. Therefore, it was ideal to design an inexpensive sensor where force range could easily be modified.

Mechanical characterization of regenerated silk fibroin (RSF) fiber mechanical measurements revealed stress-strain behavior similar to native fibers (Kinahan et al., 2011). Although RSF fiber's modulus was approximately two orders of magnitude smaller than native fibers, fibers failed at similar strains. Previous studies have shown that RSF fibers have fewer, less organized β -sheets than native fibers, which potentially explains differences in mechanical properties (Kinahan et al., 2011). Considering differences between native and RSF fiber stiffness, the force sensor design is ideal for this application because the sensor can easily be customized to measure both native and RSF fibers. Similarly, mechanical characterization of fragile, single-layer cell sheets showed stress-strain behavior typical of soft tissue. As the cell sheet is stretched to strains beyond its compliant region, the cell sheet stiffens dramatically before eventually failing. When compared to our previous work, VSMC cell sheets cultured for short durations (11 days) are 10x more compliant than cell sheets cultured for long durations (8–10 weeks), which have a modulus around 7 MPa (Isenberg et al., 2012).

As tissue engineering transitions into a quantitative field, it will become more important for researchers to have easy access to tools and techniques necessary for obtaining precise measurements. The Hall-Effect force sensor design possesses the sensitivity and versatility needed to characterize mechanical properties of soft materials ranging from 1 μN to 1 N . These qualities make the sensor ideal for characterizing both micro and macro-structure of engineered tissue, which becomes more powerful when integrated with computational models to predict tissue level properties (Roberts et al., 2014). The force sensor design presented here is an inexpensive, versatile tool that can easily be fabricated using commercial off-the-shelf materials and will help tissue engineers incorporate small force measurements into fundamental research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Uniaxial tensile tester schematic. The uniaxial tensile tester is composed of three sub-sections: the linear actuator that deforms the sample, the test cell, and the force sensor. The linear actuator stretches the sample during testing and connects to the biological sample through a mount in the test cell. The test cell consists of an aqueous bath to keep biological samples hydrated during testing. The samples are then connected to the Hall-Effect force sensor through a mount in the test cell.

Fig. 2.

Force sensor design. (a) The cantilevered beam consists of a flexible arm that bends when loaded. The Hall-Effect sensor is mounted on a rigid, aluminum mount attached to the bending beam. The Hall-Effect sensor resides within the magnetic yoke (not pictured) and moves in the y-direction as indicated by a red arrow (out of the page). The Side View of the force sensor from panel-a was taken from the perspective of the eye when the sensor is mounted in the uniaxial tensile tester. (b) The magnetic yoke consists of two sets of adjacent magnetic pairs (Kittel domain) separated by a gap. Magnetic shielding is mounted onto the backside of each of the two Kittel domains, and the Hall-Effect sensor resides within the gap of the magnetic yoke.

Fig. 3.

Computational prediction of the magnetic field (z-direction) produced by the optimal magnetic yoke configuration. (a) The Hall-Effect sensor moves in the y-direction (red arrows) and the sensor measures the z-component of the magnetic field. Magnets (brown) are shown with magnetization vectors corresponding to magnetic polarity. The white box highlights the region of interest (ROI). The magnetic shielding (grey) covers the outer regions. Dimensions are in mm. (b) Magnified plot of the z-component of the magnetic field within the ROI. The white line corresponds to the positions sampled for producing the magnetic field plot in panel-c. (c) The magnetic field (z-component) at the mid-plane between Kittel domains along the y-direction (white line from panel-b). The grey region corresponds to positions where the magnetic field does not saturate the Hall-Effect sensor.

Fig. 4.

Cantilever beam bending predictions and experimental force sensor calibration. (a) Cantilever beam angular deformation due to normal loading. The cantilever beam exhibits no visible curvature when subject to maximum load (inset). (b) Force sensor range can be controlled by the loading point location as predicted by Equation 2. (c) Experimental calibration results for two Hall-Effect force sensors (S127 & B254) with linear regression results ($N=5$, $\pm$ s.e.m.). Table 1 summarizes the calibration results and contains more details about sensor performance.

Fig. 5.

Mechanical characterization results using Hall-Effect force sensor design. (a) Engineering stress-strain behavior of RSF silk fibers (N=10) when stretched to failure. (b) Schematic of biological sample loading conditions. Samples are glued to mounts and then stretched along the long axis of the material. Cell sheet strips are glued to mounts and attached to the linear actuator (left) and the force sensor (right). (c) Engineering stress-strain behavior of vascular smooth muscle cell sheets stretched to failure after three pre-stress cycles to 20% strain (N=8).

Table 1

Hall-Effect force sensor calibration results.

Specification	S127	B254	B406	B635
Material	Steel	Brass	Brass	Brass
Thickness (mm)	0.127	0.254	0.406	0.635
Width (mm)	3.175	3.175	6.350	6.350
Force Range (mN)	0.450	1.650	13.966	39.11
Sensitivity (mN/V)	0.086	0.330	2.790	7.820
Resolution (μ N)	0.137	0.500	4.230	11.85
Linearity (R^2)	0.992	0.998	0.999	0.999
Predicted Force Range	0.466	1.640	13.46	51.36