Painless, needle-free, and continuous glucose monitoring sensors are needed to enhance the life quality of diabetic patients. To that extent, we propose a first-of-its-kind, highly sensitive, noninvasive continuous glycemic monitoring wearable multisensor system. The proposed sensors are validated on serum, animal tissues, and animal models of diabetes and in a clinical setting. The noninvasive measurement results during human trials reported high correlation (>0.9) between the system’s physical parameters and blood glucose levels, without any time lag. The accurate real-time responses of the sensors are attributed to their unique vasculature anatomy–inspired tunable electromagnetic topologies. These wearable apparels wirelessly sense hypo- to hyperglycemic variations with high fidelity. These components are designed to simultaneously target multiple body locations, which opens the door for the development of a closed-loop artificial pancreas.

INTRODUCTION
Diabetes is a chronic disease that affects more than 8.5% of the worldwide population (1). Monitoring the blood glucose levels (BGLs) on regular basis is necessary to manage diabetes progression (2). The glucometer, which is invasive, is the standard tool for monitoring glucose levels (GLs). This approach is painful and uncomfortable. Furthermore, it is not befitting to provide continuous glucose monitoring (CGM), often leading to missing some serious hyper- and hypoglycemic events that could occur between finger-prick measurements. To overcome this problem, minimally invasive technologies have been developed. However, the frequent use of these techniques causes discomfort and pain in addition to high socioeconomic burdens (3). Therefore, the development of an affordable noninvasive CGM device will be life changing for diabetic patients worldwide. Noninvasive glucose monitoring solutions have been introduced such as reverse iontophoresis (4), bioimpedance spectroscopy (6), infrared and ocular spectroscopy (7), and ultrasound (8). These technologies suffer from several difficulties. For instance, interstitial fluid GL measurements carry a serious time delay compared to the plasma GL (9). In addition, the stability, safety, and portability of the underlying technologies constitute their main challenges (10–12). In table S1, we present a list of recent common techniques available in literature along with the results obtained during clinical trials if available (Supplementary Text).

Nowadays, researchers are focusing on electromagnetism (EM) as a leading technology to achieve noninvasive and CGM. (13, 14). EM sensors are usually metallic devices designed for radiating or receiving EM waves. The properties of the reflected waves and the transmitted waves, in terms of scattering parameters or S parameters, are used and analyzed to determine the GLs. S parameters are defined as the input-output relationship between terminals of the EM sensors. More precisely, $S_{11}$ and $S_{22}$ represent the reflected waves at ports 1 and 2, respectively. $S_{21}$ and $S_{12}$ refer to the transmitted wave from port 1 to port 2 and vice versa.

Using EM sensors to monitor glucose variation is based on two important factors: (i) The dielectric properties of the medium under test (MUT) control the comportment of the EM waves in that medium, and (ii) the GL alters the dielectric properties of the blood. Therefore, when EM waves, out of an EM sensor, are transmitted to the body, the reflected and the transmitted waves are affected by the underlying tissues and carry valuable information of their properties (12). More precisely, the changes in the S parameters, in terms of magnitude and phase shifts, are associated with the glucose fluctuations in the MUT. By monitoring these variations, the BGLs are determined. EM-based technologies present several advantages. They enable the development of compact and miniaturized systems and can provide CGM while handling safety provisions.

A recent study shows that patch antennas (13) provide high sensitivity toward glucose variations. The study demonstrates a change in $S_{21}$ of 0.25 dB corresponding to a total of 55.6 mM ($\sim$1001.8 mg/dl) for serum-based experiments. When applied on human subjects in a controlled environment, the authors reported good correlation for 2 of the 10 participants. They attributed this to the system’s high sensitivity toward slight hand motion during measurements in controlled setups (13).

RESULTS
Concept and design of the proposed sensing system
Here, we introduce a first of a kind noninvasive wearable approach that relies on flexible sensors that can be aligned with body curvatures and adjust to small movements while focusing on the effective tailoring of EM waves to directly monitor the GL from blood (U.S. patent no. PCT/US2018/054627) (15). Therefore, a multisensor system that targets...
two different on-body locations and relies on multi-operating frequencies is proposed (Fig. 1).

The system is composed of two EM-based sensors: a multiband slot antenna and a multiband-reject filter (Fig. 1A). To achieve high sensitivity toward the glucose variations, different aspects are considered. First, the proposed sensors are designed to operate in the upper ultrahigh frequency (UHF) and lower microwave bands between 500 MHz and 3 GHz. This frequency range allows reaching the targeted veins and arteries, through the skin, muscle, and fat tissue layers (Fig. 1B) while maintaining good sensitivity (more details are provided in Supplementary Text). Second, the proposed structures mimic the vasculature anatomy (Fig. 1A). We verify that by concentrating the EM waves directly toward the blood network, we attain a higher sensitivity. In addition, the multiple slots result in a multiband response, which allows us to monitor the GL over a wide range of frequencies. We demonstrate later that this, in turn, improves the accuracy of GL estimation using multivariate regression modeling techniques. Moreover, the proposed antenna is designed when loaded with a human hand model. The operation of an antenna does not only depend on the physical dimensions of its structure but also depend on the permittivity of the MUT. Since, in our application, the antenna will radiate near the human body, which is considered a high-loss medium, a new design approach is adopted. This approach, named here as on-body matching, matches the antenna to the human body. As a result, the proposed antenna is designed to operate when loaded with a human hand model using ANSYS Electronics Desktop simulator. By matching the antenna to the human body, the reflections at air-skin boundary are reduced and more energy is transmitted into the body, allowing a more reliable analysis of the blood glucose variations. This technique overcomes traditional antenna designs that suffer from strong reflections of the incident waves when placed in contact with or near the human body, especially at the air-skin interface (16). Matching the antenna to the human body is of utmost importance to our application. As for the filter, its tuning feature is an important aspect, which adds another degree of freedom to the design, allowing further tailoring of the sensing system to better accommodate the specific individual characteristics.

As a proof of concept, our first prototype is designed to mimic the blood network at two different locations: the hand and the arm (Fig. 1D, left). The designed antenna is integrated as a part of a wearable glove, which monitors the BGL by sensing the hand’s vasculature network. The filter is incorporated as part of an arm-band (Fig. 1D, right). This diverse incorporation of the sensing components in multiple locations enables higher accuracy and faster responsiveness in tracking BGL. Several prototypes catered for both sensing locations are developed. Conceptual prototypes are tested on rigid substrates. A full flexible topology is then adopted to better fit the nature of the human body.

Both sensors are designed and simulated using ANSYS Electronics Desktop simulator (17). They are both composed of three layers. The top sensing layer comprises the slots; the middle layer is composed

![Fig. 1. Mimicking vasculature anatomy EM sensors.](image)
of the dielectric substrate, and the bottom layer contains the feeding line (Fig. 1C).

The antenna’s slots mimic parts of the deep palmar arch, the superficial palmar arch, the palmar digital arteries, and the dorsal metacarpal veins present in the hand (Fig. 1D, left). To achieve a multiband operation, these slots are excited by a spirally shaped 50-ohm feed line. This enables sensing BGL via wave interactions at a multitude of frequencies. The current surface distribution shows highly concentrated areas around the slots of the flexible antenna at different frequencies (Fig. 2A, top).

Note that the flexibility of the proposed system (Fig. 2, B and C) and its wearability are intended to enhance the sensor’s compatibility to expected body movements and adaptability to body surface. We evaluated the antenna’s performance in two different situations; first, we tested the antenna’s performance over curvatures of different bending diameters. The antenna maintained a stable performance for several configurations over planar or curved surfaces, as shown in Fig. 2B, with minimal difference between the flat and bended S11 response of the antenna. For this experiment, we used cylindrically shaped foam surfaces with curvatures of 10, 12, and 18 cm diameter, respectively. Second, the antenna is fixed inside a glove and separated from the skin surface by a flexible foam (with a thickness of 0.5 cm), allowing the antenna to move with the human body (Fig. 2C). Measurements with fingers open and closed (Fig. 2C, right) showed that the movements of the fingers do not affect the S11 parameters.

The tunable multiband-reject filter slots mimic the arm’s ulnar arteries (Fig. 1C, right). A tapered feeding topology on the bottom layer maximizes EM energy coupling to eight biologically inspired slots embedded in the top layer (Fig. 1D, right). The proposed filter is designed to resonate across 15 different microwave band frequencies between 1.5 and 2.7 GHz. The resonances are related to eight stop bands, which are separated by seven pass bands. The current surface distribution shows highly concentrated areas around the slots of the filter at different frequencies (Fig. 2A, bottom). To achieve tunability, a varactor diode SMV1705-079LF (18) reconfigures the operating frequencies. The varactor’s capacitance value is tuned from 31.5 to 5.2 pF, by varying the reverse voltage from 0 to 5 V.

In what follows, we study the solo performance of the proposed sensors while focusing on their sensing capabilities and GL estimation capabilities for different setup configurations. Afterward, both sensors are combined to better evaluate the performance of the proposed multisensing system.

During the development of EM-based sensors dedicated for biomedical use, one very important parameter to assure the safety of the proposed device is the specific absorption rate (SAR). The SAR is simulated using ANSYS Electronics Desktop simulator for both sensors when the hand and the arm models are placed above the sensors with a separation of 0.5 cm. The obtained values fulfill both the U.S. and the European Union guidelines for general public exposure (Supplementary Text and fig. S9B).
Performance validation: Response to glucose variation

Figure 3 (B and C) display the antenna’s and filter’s responses, respectively, in terms of $S$ parameters versus GL, which is measured using the experimental setups (Fig. 3A). In this experiment, we study the proposed sensor sensitivity toward glucose variations using fetal bovine serum (FBS)/glucose solutions. Because the normal BGL at fasting is less than 100 mg/dl and the BGL for diabetic patients is higher than 126 mg/dl (www.diabetes.org/diabetes-basics/diagnosis/), the glucose concentration is varied with small increments of 10 mg/dl to cover the hypo- to hyperglycemic range. The objective is to demonstrate the ability of the proposed sensors to detect very small glucose variations over the diabetic range.

During all conducted experiments, we collected the input complex reflection coefficients ($S_{11}$) from the antenna, the input complex reflection coefficients ($S_{11}$) from the filter, the forward complex transmission coefficients ($S_{21}$), and the output complex reflection coefficient.
coefficients ($S_{22}$) at different frequencies. The raw response of both sensors closely followed the curve of the reference GL measured by a commercial glucose meter [Accu-Chek from Roche (19)], achieving high correlation ($R > 0.9$). A correlation of $R = 0.98$ is obtained for the flexible antenna’s $S_{11}$ phase at 1.15 GHz (Fig. 3B, left), whereas an $R$ of 0.95 is achieved for the flexible filter’s $S_{11}$ phase at 1.575 GHz (Fig. 3C, left). These high correlation coefficient values indicate a strong relationship between the sensor’s response and GL. It is important to highlight that the antenna’s $S_{11}$ response remained stable over repeated experiments (Fig. 3F). We were able to identify multiple frequencies at which the physical parameters of the proposed sensor versus reference GLs remained stable in repeated experiments and demonstrated consistent behavior (Fig. 3F and fig.S9A).

**GL estimation**

For each sensor, the $S$ parameters (magnitude and phase) obtained at various frequencies, are normalized and then joined through a Gaussian process (GP) (20) regression model for GL estimation (Supplementary Text). To assess the accuracy of the proposed model and underlying system, we compare the mean estimated GL with the reference GL.

The standard error of prediction (SEP) (8) and mean absolute relative difference (MARD) (21) are used as performance criteria (Supplementary Text). Fig. 3 [B and C (right)] demonstrates that the noninvasively estimated GL obtained using the flexible antenna and filter, respectively, closely follow the trend of the reference GL. For the flexible antenna, SEP is found to be equal to 4.26 mg/dl for GL ranging between 0 to 70 mg/dl and 14.91 mg/dl for levels ranging above 180 mg/dl. We achieve a MARD of 3.09% for the flexible antenna and 7.3% for the flexible filter.

**Importance of the vasculature-inspired slots**

The importance of concentrating EM waves into the vessels’ network is demonstrated in the following two experiments using the rigid antenna and a vessel-like container: (i) The vessels of the container that are filled with FBS/glucose solution are aligned with and placed in parallel to the antenna’s slots. (ii) The container is rotated 180°, as shown in Fig. 3D, where the vessels are almost orthogonal to and, hence, not aligned with the antenna slots (only small sections of the antenna’s slots intersect with the vessels of the container).

In both cases, the same experimental setup parameters are used and the corresponding curves showing the $S_{11}$ responses versus the GL are compared. The actual GL are varied between 10 to 600 mg/dl, as measured by the invasive method, representing a total change of 590 mg/dl. The corresponding total change in the $S_{11}$ magnitude response for the highest correlated $S$ parameter is improved from 0.29 dB for the misaligned rotated position to 1.55 dB for the aligned or parallel position (Fig. 3E, left). Moreover, the total change in $S_{11}$’s phase response is improved from 1.04° for the rotated position to 10° for the parallel position (Fig. 3E, right), thus indicating enhanced sensitivity. By aligning the vessel’s network with the slots and concentrating the radiation on the vessels, the sensitivity of the antenna toward glucose variations is improved by more than fivefold in terms of the corresponding $S_{11}$ magnitude variation and 10-fold for the phase. To our knowledge, the research here represents the first direct demonstration of the importance of focusing the EM waves onto the vessels to increase the sensitivity of the proposed EM-based multiband sensor toward glucose variations.

It is important to highlight that we were able to obtain high correlation ($R > 0.95$) between the raw $S$ parameters and the GLs for both experiments. This high sensitivity is due to the concentration of the surface current around the slots and their extremities (Fig. 2A, bottom). This experiment was idealized to highlight the importance and the benefits of concentrating the EM waves on the vessels. In practical scenarios, the wearable nature of the design limits the room for misalignment. Moreover, the concentration of the surface current not only on the slots but also around them helps accommodate for any possible slight misalignment between the targeted vessels and the slots.

The proposed sensor showed more selectivity toward glucose variations than other interferent species including fructose (FRU), acetaminophen (AC), and oleic acid (OA) in concentrations that are much higher compared to physiological conditions (Supplementary Text). The difference in response is due to the difference in terms of dielectric properties between these interferents. In Fig. 3G, we successively added OC, AC, FRU, and glucose (50 mg/dl) to the same FBS solution. The $S_{11}$ parameters showed minimal to no shift when the interferents were added. In contrast, a notable shift of $S_{11}$ parameters is produced when the same amount of glucose is added to the solution, resulting in a correlation with the GLs of $R > 0.9$.

We next conducted ex vivo experiments on mammalian tissues, as displayed in fig. S1A. The effect of the ex vivo mammalian skin, fat, and muscle layers and that of the glucose variation on the response of the flexible antenna sensors is shown in fig. S1B.

The on-body matching characteristics are very clear when the antenna is loaded with rat tissues. This matching is well preserved and thus meets our design objectives. In this experiment, the volume of the FBS is reduced to one-half, allowing a more realistic setup. We observe excellent agreement between the sensors’ responses and the reference GL citing correlations of $R = 0.98$ for both the flexible antenna and filter, as shown in fig. S1 (B and C). The proposed sensors establish the following requirements: the ability (i) to detect small glycemic variations (10 mg/dl) over the hypo- to hyperglycemic range and (ii) to maintain a good sensitivity in the presence of a lossy medium (skin, fat, and muscle layers).

**In vivo experiments on animal models of diabetes**

In vivo experiments were performed on seven rats (female and male) to assess the proposed sensing system’s efficacy to detect BGL across living tissues. To take into consideration the coat color (white and black), we tested the system on two different rat strains, Sprague-Dawley and Long-Evans rats. As described in the Materials and Methods, the rats were divided as follows: Three female Long-Evans rats received intravenous streptozotocin injection (65 mg/kg) to render them diabetic. Diabetes was verified after 48 hours when the rat’s GLs are $>300$ mg/dl (two female and two male Sprague-Dawley rats). The Sprague-Dawley rats underwent intraperitoneal glucose tolerance test (IPPT), mimicking the oral glucose tolerance (OGTT) tests in humans, after overnight fasting to prove the capability of the proposed system to detect the increase and decrease of GLs over the hyper- to hypoglycemic levels. All rats received injection of insulin, during the experiment, to induce hypoglycemia. The raw $S$ parameters curves followed well the increase and decrease of BGL (Fig. 4, B and C) with a good correlation for both hypoglycemic and hyperglycemic ranges ($R = 0.89$ and $R = 0.97$). Another criterion for accuracy is the Clarke’s error grid (CEG) (22), which offers a means to measure the performance, taking into consideration the clinical relevance of the
Hanna et al., Sci. Adv. 2020; 6 : eaba5320     10 June 2020

We tested the antenna on 21 healthy volunteers, where each one underwent three separate OGTTs. The flexible and rigid antennas

We evaluate the proposed system on healthy subjects to demonstrate its ability to monitor the BGL in real-time settings during OGTTs. In addition, no statistical significance gender-based shift is observed (male, n = 30; female, n = 32), as shown in fig. S9 (C and D). This was performed on the antenna data collected from the 21 volunteers (including 10 male and 11 female) where each one was subject to three OGTTs. In addition, no statistical significance gender-based shift in the correlated frequencies is observed (male, n = 30; female, n = 32).

The filter-based sensor is tested on six healthy volunteers, who underwent two separate OGTTs (Fig. 5C). Figure 5D presents an example of the S parameters versus BGL for volunteer no. 3 during one OGTT. We notice that the filter’s response follows the reference BGL achieving high correlation (R = −0.94; Fig. 5B).

To estimate the GL, information obtained at various frequencies is used. The noninvasively estimated BGLs obtained by the GP model for a given OGTT (Fig. 5B) match well with the upward and downward trends of the reference BGL, achieving a MARD of 1.78% for this experiment.

The results show no delay between the two values. This indicates that our system is monitoring the BGL directly from the blood and can be attributed to the choice of the frequency range.

The sensing system achieves a MARD of 6.08 and 6.18% for the rigid and flexible antennas, respectively, across all volunteers (examples for the rigid antenna’s response and estimation are shown in figs. S2 and S3). These values show high accuracy and are comparable to those obtained by commercial self-monitoring systems. To prove repeatability, the CEG analysis (23) for all 63 OGTTs is shown in Fig. 5B. The mean estimated GLs fall 100% into the clinically acceptable zones (97.93% in zone A and 2.07% in zone B) for the flexible prototype. Moreover, 93.48% of the estimated values are within 15% error, 96.78% are within 20% error, 99.06% are within 30% error, and 99.65% are within 40% error. These percentages are obtained for a total of 1430 estimated points. The proposed system achieves very good matching between the estimated and reference GL, providing confidence in the potential of the proposed noninvasive antenna (additional examples for the flexible antenna’s response and estimation are shown in figs. S4 and S5).

To assess whether there is a sensitivity difference detected by the proposed sensor between male/female, we relied on unpaired Student’s t tests using the mean correlation (between the system’s parameters and BGL). No statistical significance differences due to gender or skin color were detected for both analyses, as shown in fig. S9E.

**Fig. 4. In vivo experiments on diabetic rats.** In vivo experiment on living animals covering the hypo- to hyperglycemic range. (A) The experimental setup. (B) Rigid filter’s response. Top: The rigid filter’s parameter response versus the actual BGL at 1.57 GHz, during one IPTT experiment. Bottom: The estimated GL versus the BGL for 10 randomly shuffled test/train datasets. (C) Rigid filter’s response. Top: The rigid filter’s parameter response versus the actual BGL at 1.95 GHz, for one streptozotocin-induced diabetic rat. Bottom: The estimated GL versus the BGL for 10 randomly shuffled test/train datasets. (D) CEG for the seven conducted experiments (the CEG shows the mean estimations each obtained from the 10 random repetitions).
During in vivo experiments, we did not study the effect of physical activities and different environmental conditions on the attained response. Future work will include these experiments on diabetic patients covering the full glycemic range.

One system with multiple sensors

To overcome the technical difficulties introduced by some environmental factors and to improve the sensitivity of the device, the antenna and the filter are joined into a multisensing system (Supplementary Text). The system is tested on six healthy volunteers during OGTTs while tuning the filter to cover different frequency bands using three different tuning voltages.

Figure 6 displays the antenna’s and the filter’s individual S parameters versus GL for one volunteer. For this volunteer, the filter’s third configuration provides the highest correlation between the S parameters and the GL. By combining the responses of both sensors and relying on the wrapper technique to select the most important features, we are able to reduce the MARD from 2.84% for the antenna alone to 0.91% for the combined system. The multisensing system reduces the impact of interfering factors in real-life condition such as surface temperature, humidity, and movement by monitoring the GL from two different locations.

We notice during the initial set of human trials that the response of the proposed sensors varied between patients (fig. S8). Hence, by monitoring the GL using both the antenna and the filter and by tuning the filter, we are able to tailor the proposed sensing system to better capture the specific individuals’ characteristics. Using the wrapper feature-selection technique, we are able to identify the most important features for each volunteer by analyzing their individual data that importantly improved the accuracy of the prediction.

This, in turn, helps us capture or identify the best combinations of features obtained from the different tunings of the filter and the antenna device. Figure S8 arrows are intended to indicate that each person may interact with each tuning differently; however, it emphasizes that the best set features obtained from the different sensors’ settings indeed provides the best predictions.

DISCUSSION

This is, to our knowledge, the first-of-its-kind, noninvasive, continuous, wearable, vasculature anatomy–inspired EM-based system for glycemic measurements. The multiband response of the proposed system results in an enhanced sensitivity. This sensitivity is also enhanced by the sensor’s structure, which mimics the vasculature anatomy. In addition, the multisensing system provides personalized monitoring of the GL based on a patient’s characteristics. The obtained results are highly encouraging, and our system presents a unique noninvasive solution that can be on par with Food and Drug Administration–approved systems.
Two prototypes of the proposed slot antenna and band-reject filter are designed on flexible and rigid substrate as main sensing elements for the noninvasive glucose monitoring system. Rogers RO3003 (23) substrate material of 0.5-mm thickness is used for the rigid antenna. However, the flexible antenna is designed by relying on polyethylene terephthalate (PET) substrate material of 136-μm thickness with a dielectric constant of 2.9 and a loss tangent of 0.00579. Each antenna’s slots are excited through EM coupling through a spiral feed line. They are designed to operate in the UHF and lower microwave frequency band ranges. The dimensions of the substrate and the integrated slots that mimic the blood network of the hand are optimized to operate with great matching at the desired frequencies of operation while being loaded by the human hand model. The width of the slots is optimized on the basis of the average diameters of the different blood vessel, which range between 1.2 and 2.8 mm (24), while the length of the slots are optimized to have multiple operational frequencies between 0.5 and 3 GHz. The hand ranges between 167.9 and 187.9 mm in terms of length and between 75.2 and 83.6 mm in terms of breadth for women and men, respectively (25). After optimization, the final dimensions of the flexible antenna are set to 70 mm by 80 mm. This size is optimized for integration in a wearable glove. The rigid antenna is fabricated using a computer numerical control milling machine. On the other hand, the flexible antenna is fabricated using inkjet printer together with the PET and silver nano-ink.

The proposed filter is composed of three layers including a feeding network, a dielectric substrate, and eight resonating slots. The slots, in this case, are inspired by the vasculature anatomy of a human anterior lower arm and mainly mimicking the ulnar arteries of the arm. The average diameter of the ulnar artery is found to be 2.4 ± 0.4 mm for the right arm and 2.3 ± 0.3 mm for the left one (26). Furthermore, the minimum diameters encountered for this artery are 1.3 and 1.5 mm for the right and left arms (26), respectively. After an optimization process, the width of the two set of slots is designed to be equal to 1.6 and 1.8 mm. For the feeding network, the implementation of a regular 50-ohm transmission line failed in producing an $S_{11}$ value close to the desired 0-dB level, especially for the higher frequency bands. To reach the targeted response, two alternative approaches are considered. The first approach is based on increasing the width of the transmission line from 1.9 to 3.4 mm. This is equivalent to decreasing the characteristic impedance of the feed line from 50 to 35 ohms. Using this topology, the feed line is...
able to cover all the slots, thus leading to better coupling and enhanced $S_{11}$ levels. The second proposed topology consists of implementing a rectangular resonator near the feed line. This resonator acts as a feeding relay between the line and the eight sensing slots. Using the tapered feeding topology, the proposed filter is printed on an RO3006 substrate with a thickness of 1.28 mm. The second topology is also considered to build a second prototype of the filter on a flexible RO3003 substrate with a thickness of 0.25 mm. The complete dimensions of the designs are 25 mm by 30 mm and 20 mm by 35 mm, respectively. To achieve tuning, an SMV1705-079LF (18) varactor diode is used to reconfigure the operating frequencies. The capacitance value of the varactor diode can be tuned from 31.5 to 5.2 pF by varying the reverse voltage from 0 to 5 V. Biassing the varactor diode requires the use of a 470-nH inductor and a 10-pF capacitor. The basic function of the inductor is to prevent the radio frequency signal from passing to the power supply, and the capacitor is used to prevent any dc shorting. All the electrical components are soldered on the upper substrate side to prevent any interference with the sensing area. The varactor diode and the capacitance are connected in parallel and this combination is placed between the internal and external metallic regions of one set of slots using two vias.

**Data processing and feature extraction**
Rather than focusing on a single frequency, our system monitors the $S$ parameter magnitude and phase at multiple frequencies over a range extending from 0.5 to 3 GHz. The recorded $S$ parameter magnitude and phase at each frequency represent two features. This results in a total of 42 device feature points for each reference GL for the antenna and 126 features for the filter. The datasets undergo several preprocessing steps. First, 10 $S$ parameter recordings at different frequencies are obtained for each reference measurement and averaged. Once the averaging is done, the features that correspond to magnitude values and phase values are normalized to a value between 0 and 1. These features are then used by the regression model to estimate the GLs. For regression model purposes and given the small size of the dataset, two feature selection techniques are explored: These are filter and wrapper, as discussed in the Supplementary Text.

**Regression modeling techniques**
Different regression models are evaluated. These include least absolute shrinkage and selection operator (27), partial least square (PLS) (28), locally weighted PLS (29), and GP (20) (Supplementary Text). In addition, two feature selection techniques are assessed: the filter and the wrapper methods. The estimations obtained by the GP regression model along with the wrapper feature selection are presented in this paper. GP has shown its ability to provide high performance when applied on small datasets. It is a probabilistic technique that provides both prediction and uncertainty information of the prediction. GP is based on “generating data located throughout some domain such that any finite subset of the range follows a multivariate Gaussian distribution.” In most of the cases, the mean of GP is assumed to be equal to zero. The sample points are related to one another using a covariance function $k(x, x_0)$. If the query $x_0$ is close to the sample points $x$, $k(x, x_0)$ approaches its maximum. Meaning that $f(x)$ is greatly correlated to $f(x_0)$. This effect renders the function smoothness by considering the similarity between the neighbors. When a new query $x_0$ requires estimation, the distant sample points will have a negligible effect because $k(x, x_0)$ approaches zero. This will provide better estimation accuracy, especially for low GLs (30). All the model data are trained using two-thirds of the dataset. The remaining one-third is used for testing. To compensate for the small size of datasets, this procedure is repeated 10 times by randomly dividing the data into training and testing sets.

**Serum-based experiments**
For the serum-based sensitivity experiments, FBS/glucose solutions are used. FBS is a liquid fraction of clotted blood harvested from bovine fetuses. It contains a large number of nutritional factors and growth factors along with small molecules like amino acids, sugars, lipids, and hormones. The initial GLs in FBS are usually less than 5 mg/dl (31). The FBS solution is filled inside a foam container with the same size of the sensor and a thickness of 0.5 cm, which is kept fixed during the whole experiment above the sensor. The container is covered with a thin nylon wrap to eliminate the absorption of the liquid by the foam throughout the experiment. An initial measurement using the Virtual Network Analyser (VNA) is taken at time zero. A small amount of glucose, which is equivalent to 10 mg/dl, is added to the FBS solution for each measurement. After the glucose addition, the FBS solution is mixed well and left for around 10 min to ensure the homogeneity of the solution. A reference GL is then taken using the Accu-Chek glucometer from Roche (19) simultaneously with 10 savings of the $S$ parameter magnitude and phase using a VNA. A total of 38 measurements are taken for the flexible antenna and 37 filter to cover GLs ranging from hypoglycemia to hyperglycemia.

**Selectivity tests**
OA (50 mg/dl), AC (50 mg/dl), FRU (50 mg/dl), and glucose (50 mg/dl) were added to the FBS solution in order twice, and the $S$ parameters were recored.

**Animal experimentation**
All animal procedures were conducted in accordance with the U.S. Public Health Service’s Policy on Humane Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee at the American University of Beirut.

**Ex vivo experiments**
Fresh abdominal unshaved rat skin, fat, and muscle are dissected. Then, they are cut into square pieces and preserved in phosphate-buffered saline (PBS) on ice. The different layers along with the PBS solution are placed inside a foam container above the sensors. A layer of FBS/glucose solution is then placed above the skin in a thin nylon container. Initial measurements using a VNA are taken at time zero. A small amount of glucose, equivalent to 100 mg/dl, is added to the FBS solution for each measurement. After the glucose addition, the FBS solution is well mixed and left for around 10 min to ensure the homogeneity of the solution. A reference GL is then taken using the invasive glucometer from Roche (19) simultaneously with 10 savings of the $S$ parameter magnitude and phase using a VNA. The same procedure is repeated for both antennas. A total of 14 measurements are taken for each sensor, both the flexible antenna and filter, to cover GLs ranging from 10 to 600 mg/dl.

**In vivo experiments on animal models of diabetes**
To assess the efficiency of our sensor to overcome the disparity between coat (skin) colors and genders, two strains of rats were
included (Sprague-Dawley and Long-Evans female rats) in this experiment. The rats were divided as follows: (i) three female Long-Evans rats, which received intravenous streptozotocin injection (65 mg/kg) to render them diabetic (diabetes was verified after 48 hours when the rat’s GLs are >300 mg/dl), (ii) two female Sprague-Dawley rats, and (iii) two male Sprague-Dawley rats.

During the experiments, rats are anesthetized using a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg) and injected in an intraperitoneal manner. After sedation is confirmed, the filter is fixed on the abdomen region of the Sprague-Dawley rats and on the neck of the Long-Evans rats (black coat). At time 0, the fasting GL is measured using both the filter and a commercial glucose meter. For streptozotocin-induced diabetic rats, after the first measurement, injection of insulin is given to reduce the GL until it reaches hypoglycemia. The Sprague-Dawley rats underwent an intraperitoneal glucose tolerance test where an intraperitoneal injection of glucose (2 mg/kg) is given immediately after the first measurement. A second injection of insulin is given to induce hypoglycemia around 15 min after the first injection. For all rats, the glucose variation is monitored every 5 min using the invasive glucometer and the proposed noninvasive technique for a total of 120 min.

**Human trials on healthy human controls**
A total of 33 volunteers (14 females and 19 males, 19 to 37 years of age) were recruited in this study. The International Review Board approved the experiments and all volunteers signed a consent form. Subjects were considered eligible for the study if they were between 18 and 70 years of age and able to provide informed consent. There were no restrictions on either race, sex, or ethnicity. Substance abuse, lactation, pregnancy, and being part of an interventional trial were the exclusive criteria. In the first phase of the study, only healthy subjects with hemoglobin A1c levels less than 6%, normal blood pressure, and no sign of dyslipidemia were recruited. Each volunteer participated in multiple separate modified OGTT experiments with one blood glucose measurement every 15 min. Ten minutes before sugar intake (75 g of sugar), the developed sensors were placed on the corresponding sensing locations and fixed for the entire OGTT 2-hour time span. Finger-stick glucose monitoring [Roche glucometer (19)] was also undergone for glucose fasting referencing. The timer was then started where the sugar intake time was controlled to be within 10 to 15 min. Afterward, finger-stick glucose monitoring was performed once every 15 min, and VNA savings were taken every 5 min. We relied on interpolation to populate the remaining reference glucose points over 5-min intervals. During the experiment, volunteers were kept indoors and asked to sit on a chair to limit their movements as much as possible.

**Statistics**
To assess whether there is a sensitivity difference captured by the proposed sensor between male and female and between skin colors, data were analyzed using GraphPad Prism software (32). For comparisons of the two groups, unpaired Student’s t test was used. A P value higher than 0.05 was considered statistically not significant.

**SUPPLEMENTARY MATERIALS**
Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/24/eaba5320/DC1

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Acknowledgments: We thank the American University of Beirut Animal Care Facility staff for help in taking care of the animals used in this manuscript. We thank the ATHENA Lab for assistance in the fabrication of the flexible antenna. Funding: This work was funded by the Lebanese National Council for Scientific Research Regular Research Grant for J.C., R.K., and A.A.E. and a UKLTH Research Grant for J.C., R.K., and A.A.E. Author contributions: J.C., R.K., and A.A.E. conceived, designed, and supervised the experiments described in the study. J.C. and Y.T. supervised the antenna, filter, and respective feeding networks’ designs. J.H. performed the antenna designs via simulations and measurements. M.B. performed the filter designs via simulations and measurements. A.H.R. supervised the antenna, filter design, and performance optimization. J.H. and M.B. realized the in vivo experiments and human trials on healthy human controls. A.A.E., J.H., M.B., and B.D. realized the ex vivo experiments. A.E. and J.H. executed the flexible antenna fabrication. F.A.A. and J.H. executed the rigid antenna fabrication. R.K. and J.H. realized the data analysis in terms of preprocessing, feature selection, and regression modeling. All authors reviewed the results, provided essential reviews of the manuscript, and approved the final version of the paper. Competing interests: J.C., R.K., A.E., J.H., A.R., and Y.T. are inventors on a pending patent related to this work (no. US20190388000A1, filed 26 June 2018). J.C., R.K., and A.E. are inventors on a pending patent related to this work filed (no. US20190104939A1, filed 5 October 2017). J.C., R.K., A.E., M.B., A.R., and Y.T. are inventors on a patent application related to this work (no. US: 62/811,760, filed 28 February 2019). The authors declare that they have no other competing interests. Data and materials availability: All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

Submitted 11 December 2019
Accepted 16 April 2020
Published 10 June 2020
10.1126/sciadv.aba5320

Citation: J. Hanna, M. Bteich, Y. Tawk, A. H. Ramadan, B. Dia, F. A. Asadallah, A. Eid, R. Kanj, J. Costantine, A. A. Eid, Noninvasive, wearable, and tunable electromagnetic multisensing system for continuous glucose monitoring, mimicking vasculature anatomy. Sci. Adv. 6, eaba5320 (2020).