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Non-destructive and wireless monitoring of biodegradable polymers

Timo Salpavaara^{a,†}, Aleksi Hänninen^{b,†,*}, Anni Antniemi^b, Jukka Leikkala^a, Minna Kellomäki^b

^aBioMediTech Institute and Faculty of Biomedical Sciences and Engineering, Sensor Technology and Biomeasurements Group, Tampere University of Technology, Korkeakoulunkatu 10, Tampere 33720, Finland

^bBioMediTech Institute and Faculty of Biomedical Sciences and Engineering, Biomaterials and Tissue Engineering Group, Tampere University of Technology, Korkeakoulunkatu 10, Tampere 33720, Finland

Abstract

A method for monitoring changes in biodegradable polymers during hydrolysis is proposed. This wireless and non-destructive method is based on inductively coupled passive resonance sensors embedded in the polymer shell. In this study, we prepared specimens using two poly(lactide-co-glycolide) copolymers possessing different degradation profiles. The copolymer embedded sensors were immersed in buffer solution and their resonance features were compared with periodically performed conventional polymer characterization methods. A clear difference was noticed in the wirelessly measured signals between the two tested copolymer materials. Also the reference methods showed clear differences between the degradation profiles of the copolymers. The wirelessly measured signals are likely to correlate to the structural changes in the materials during the hydrolysis. In the future, this technique could be used in the laboratory to provide easy-to-access *in situ* information about the polymers. Even the state of biodegradable polymer implants could be wirelessly monitored.

Keywords: Passive resonance sensor; biodegradable polymers; poly(lactide-co-glycolide); telemetry; wireless monitoring

* Corresponding author.

E-mail address: aleksi.hanninen@tut.fi (A.Hänninen)

† Equal contribution authors.

1 Introduction

Implants made of biodegradable polymers are used as temporary support structures in orthopedics and tissue engineering. For example, different types of bone fractures can be repaired with biodegradable fixation plates and screws. Ultimately, these polymers are cleared from the body via metabolic routes. This prevents the need for removal operations as well as chronic inflammatory responses associated with biostable implants. The degradation rate of the implant is affected by many factors, including the chemical structure and molecular weight of the polymer as well as the processing history, size and shape of the implant. Even if all these elements were carefully standardized, different enzymatic systems between individuals or different target tissues in a patient might lead to diverse degradation rates [1]. Therefore, there is a need for monitoring the degradation rate of the polymers to ensure the proper behavior of the implants.

There are many well-defined characterization techniques for polymer degradation which can be carried out in the laboratory. Gel permeation chromatography (GPC, also called size exclusion chromatography, SEC) for example separates the polymer chains based on their length and thus determines the molecular weight distribution of the polymer [2], which is the most important parameter for tracking polymer degradation [3]. Differential scanning calorimetry (DSC) is a commonly used thermoanalytical technique: by using modern DSC, several parameters related to polymer degradation such as crystallinity and glass transition temperature can be determined. Furthermore, the mechanical properties of the polymers can be analyzed by applying e.g. shear, flexural and tensile tests. In many applications it is crucial for the implants to retain their mechanical properties before starting to transfer the stress to the surrounding tissue by degrading [4].

A common drawback of all of the above-mentioned methods is that they are destructive to the sample [2]. Thus, they are discontinuous and require a set of parallel samples at each time point. Moreover, the methods are not applicable to *in vivo* measurements. Consequently, a wireless and non-destructive method for monitoring the degradation of poly(lactide-co-glycolide)s has been studied based on a fluorescent labeling technique [5]. However, the use of costly imaging methods and fluorescent markers might compromise the cost-effectiveness and safety of the method.

Inductively coupled passive resonance sensors with interdigital capacitive sensing elements have been previously used to detect changes in various materials and applications. Ong et al. tested it as a general way to monitor many environmental parameters like the temperature, humidity and complex permittivity of the surrounding material [6]. Applications for the method include the assessment of frying oil degradation [7] and water content in civil engineering materials [8]. Also an implantable sensor for tissue characterization has been proposed [9]. These types of sensors enable short range wireless measurements, which can be utilized in applications where the target to be measured is in a closed container or under the skin. Also the simple structure of the sensor is a benefit in *in vivo* applications, especially if the sensor should be fabricated from biodegradable materials.

A wireless online monitoring system capable of detecting day-to-day changes in biodegradable polymer materials could be used *in vitro* as an alternative to destructive and time consuming testing methods. Before using biodegradable sensor structures like presented in [10], we aim to acquire background information about the suitability of this measurement method for this application. Thus, we embedded inductively coupled passive resonance sensors into two biodegradable poly(lactide-co-glycolide)s with different degradation profiles to see if this kind of wireless measurement provides useful information about the degradation of these copolymers.

2 Materials and methods

The degradation of two copolymer materials in buffer solution was investigated for eight weeks. A reference degradation series was done using conventional polymer characterization methods. The other set of samples was wirelessly monitored utilizing inductively coupled passive resonance sensors embedded in the tested copolymers. The measured signals were then compared with the results of the reference series. The method is based on detecting changes in the relative permittivity of the material during hydrolysis by using interdigital capacitors. The capacitors were connected to RLC circuits whose characteristics were measured outside the container.

2.1. Resonance sensor

The resonance sensors used in this study were fabricated using a four-layer circuit board design. The 20 mm by 20 mm by 1.60 mm sized inductively coupled sensors (Fig. 1) comprised an interdigital capacitive sensing structure, a parallel-plate capacitor, and a coil. The operation principle of this sensor is similar to methods discussed in [6][9]. The measurable resonance characteristics of the sensor are modified by the permittivity and conductivity of the tested material. The geometry of the sensor was not optimized or studied in detail due to the different focus of this study.

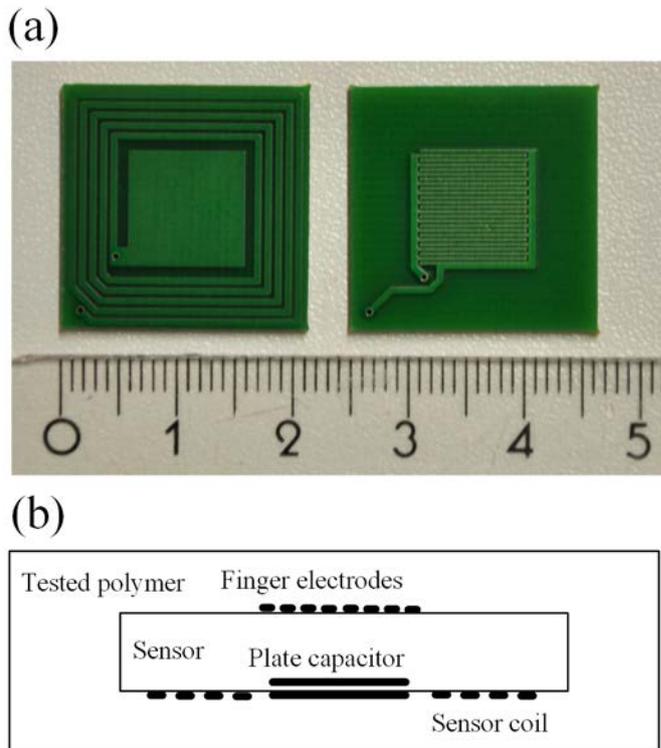


Fig. 1. (a) RLC resonance circuits with interdigital capacitive sensing elements were used to monitor biodegradable polymers. (b) The cross-section of the encapsulated sensor.

The total number of fingers in the capacitor was 24. The copper layer thickness was 35 μm . The fabrication process of the printed circuit board (PCB) included an electrically isolating solder resist layer (approximately 30 to 40 μm) on top of conductive areas.

Due to the noticed variation in the regular sensor series, four sensors were coated by polymerizing an approximately 14 μm thick layer of parylene C (Galxyl C, Galentis S.r.l., Marcon, Italy) onto them using a LabTop 3000 Parylene Deposition System (Para Tech, Aliso Viejo, California, USA) to increase the consistency of the measurements.

2.2. Sensor encapsulation and hydrolysis

Hydrolytically degradable poly(lactide-co-glycolide)s are commonly copolymerized from D,L-lactide or L,L-lactide together with glycolide [11]. Amorphous poly(L-lactide-co-glycolide) [80:20] (PLGA) and poly(DL-lactide-co-glycolide) [85:15] (PDLGA) were both obtained from Purac Biochem B.V. (Gorinchem, the Netherlands). The tested copolymer types were chosen based on their different degradation rates, as the presence of D-units into the poly(L-lactide) chain is known to increase the degradation rate [12]. Thus, the degradation of PDLGA was expected to be faster than that of PLGA.

After drying the materials in a vacuum chamber, copolymer sheets of 32 mm by 32 mm by 2 mm were compression molded from the raw material granules using a custom-made metallic mold. Seamless capsules were formed by placing one resonance sensor between two copolymer sheets and compression molding them into one piece (Fig. 1b). Two parylene

coated sensors per copolymer type were encapsulated. The full list of all the samples is presented in Table 1.

Table 1. A list of the samples.

Encapsulation copolymer	Resonance sensor	Number of samples	Sample codes
PLGA	Yes	10	PLGA 1-10
PDLGA	Yes	10	PDLGA 1-10
PLGA	Yes (parylene coated)	2	PLGA P1-P2
PDLGA	Yes (parylene coated)	2	PDLGA P1-P2
PLGA reference samples	No	12	PLGA R1-R12
PDLGA reference samples	No	12	PDLGA R1-R12

Samples were fixed 1 mm above the bottom of the container by using plastic 3D printed holders. The amount of Sørensen phosphate buffer per container was 100 ml. The buffer solution was prepared according to the “ISO 15814:1999(E): Implants for surgery – Copolymers and blends based on polylactide – In vitro degradation testing” standard and its pH was 7.46-7.49. All samples were held in an incubator at +37°C and the buffer solution was changed every other week. Similar hydrolysis procedure was applied for the reference samples.

2.3. Conventional polymer tests for reference

Compression molding was also used to produce the reference test samples from both copolymer types. The reference samples were tested at the time points of 0, 2, 4, 6 and 8 weeks. This time period was assumed to show differences between the copolymers and the number of the parallel samples remained moderate. The 0-week samples were tested dry, whereas the rest were tested wet after taking them out from the buffer solution.

Water absorption measurements were done by taking the samples from the buffer solution, rinsing them with distilled water, wiping gently with tissue paper and then weighing them using an analytical scale. Four samples per material were measured at each time point. The resulting wet weights were then compared with the dry weights, that were measured after drying the samples for three days under a fume hood and then one week in a vacuum chamber. The water absorption percentage was calculated using the equation: $water\ absorption\ (\%) = [(wet\ weight - dry\ weight) / dry\ weight] \times 100\%$.

Mechanical testing comprehended three-point bending tests (Instron 4411, Instron Ltd., High Wycombe, England) according to the “SFS-EN ISO 178 Plastics – Determination of flexural properties” standard at ambient conditions. Four parallel samples per time point per material were tested. The mean values and standard deviations of the flexural modulus were calculated in gigapascals (GPa).

The glass transition temperature (T_g) of the samples was measured utilizing differential scanning calorimetry (DSC) (Q1000, TA Instruments, New Castle, Delaware, USA) by analyzing two parallel samples per time point. The T_g corresponds to a reversible transit from a glassy state to a more viscous state. At lower molecular weights, the T_g of poly(lactide-co-

glycolide)s is a function of the molecular weight. A decrease in T_g indicates a decrease in molecular weight when at appropriate level, and thus T_g can be used to show the degradation of biodegradable polymers. Only amorphous polymers or the amorphous portions of semicrystalline polymers undergo the glass transition.

An automated Ubbelohde viscometer (LAUDA, Lauda-Königshofen, Germany) was used to assess the inherent viscosity (*i.v.*) of the copolymers, which is a viscometric measure of the molecular size utilizing the unit dl/g. After drying the samples, 20 ± 0.8 mg sized pieces were cut from the sample core and dissolved in 20 ml of chloroform overnight. The test was performed in ambient conditions and two parallel samples per time point were measured.

2.4. Resonance measurements

The resonance characteristics of the sensors were inductively measured by using a reader coil and custom-made reader device [13]. The illustration of the measurement arrangement is given in Fig. 2.

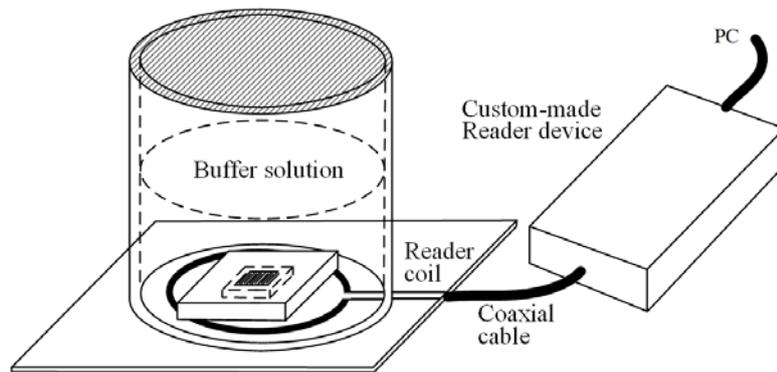


Fig. 2. The measurement of the resonance sensor in a buffer solution container by using an external reader coil and a custom-made reader device.

The reader device makes frequency sweeps and measures a phase shift against a reference channel. In this setup, the resonance circuit around the reader coil shows as a dip in the measured signal (Fig. 3a). The measurements in the lengthy test series were carried out during working days of the week at non-uniform intervals. Each test point consisted of the multiple frequency sweeps measured within 30 seconds at the sampling rate of one sweep per second. The frequency sweeps were first averaged and then the measured baseline of the reader coil was subtracted from the measurements.

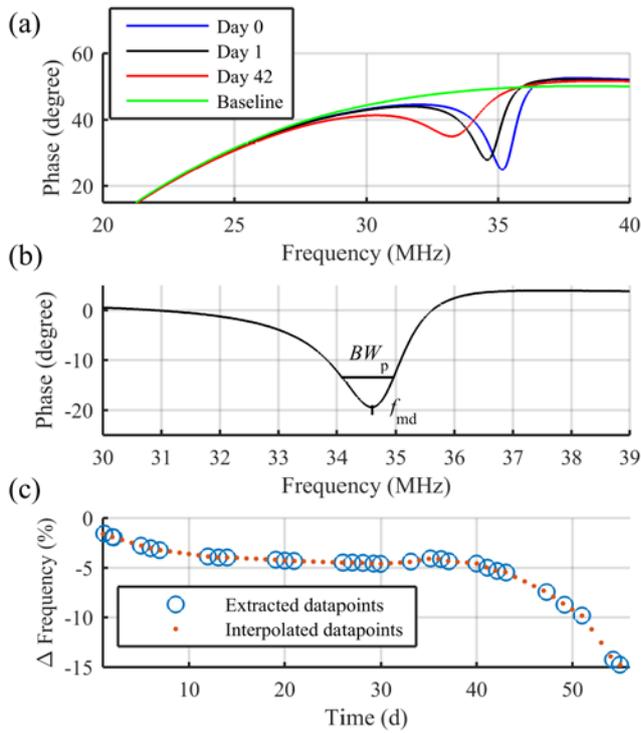


Fig. 3. (a) Examples of raw data measured at the beginning of the hydrolysis (Day 0), after one day, and after 42 days. The baseline of the measurement is also shown. (b) The features f_{md} and BW_p were extracted from the dip in the phase curve. (c) Illustration of interpolation of the data points.

Next, the resonance characteristics of the RLC circuit were extracted from the data. The feature extraction was done by modeling the measured dip by using a 3rd order polynomial regression model. The features f_{md} and BW_p used in the model, estimate the frequency and the width of the measured dip (Fig. 3b), respectively. The extraction process was similar to the method used in [14]. However, in this case, the measured phase signal was used instead of the measured gain signal because the form of the phase dip was more suitable for the feature extraction. Initially, all resonance circuits had slightly different resonance frequencies. Thus the phase changes were compared with the initial values at the beginning of the hydrolysis. The results of the inductively coupled measurements were given as a change in the features f_{md} and BW_p which are linked to the resonance frequency and losses of the RLC circuit. The average signal for each copolymer type was calculated after interpolating daily estimates for each sample (Fig. 3c).

3 Results

3.1. Conventional polymer characterization methods

The conventional polymer testing methods were used to get reference signals indicating the hydrolytic degradation of the tested copolymers. The changes in the flexural modulus, water

absorption percentage, inherent viscosity (*i.v.*) and glass transition temperature (T_g) of the biodegradable copolymers are shown in Fig. 4.

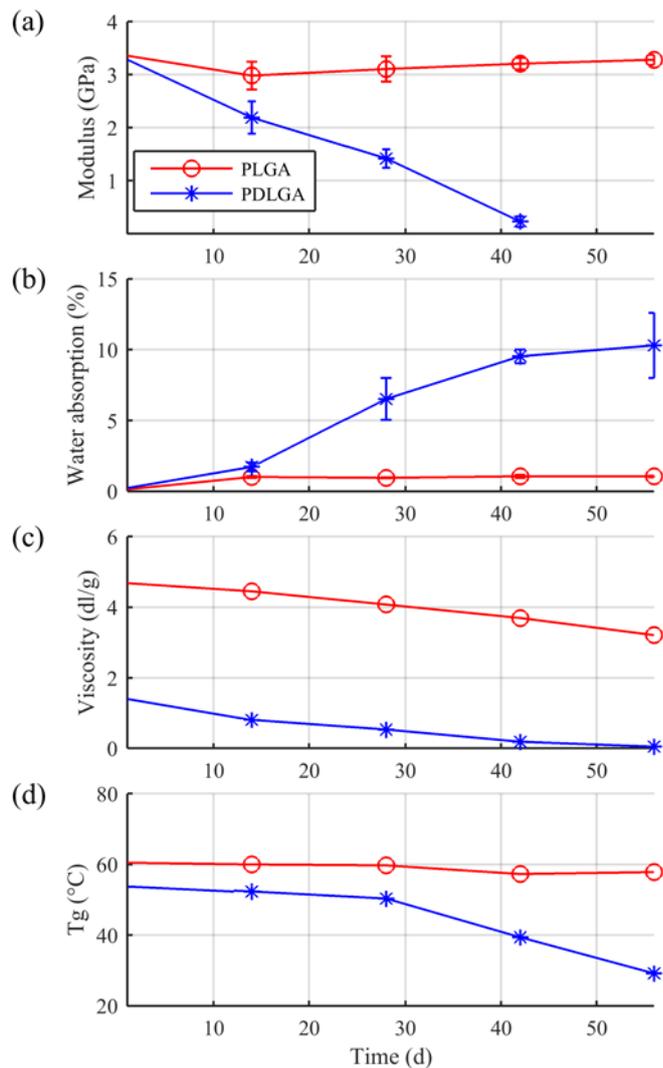


Fig. 4. Reference measurements indicating changes in the material properties of the copolymer samples. The two last graphs lack error bars, since only two parallel samples were measured in the *i.v.* and T_g tests.

After the second week follow-up, PLGA samples were saturated and did not absorb more water during the test period. PLGA also retained its mechanical properties (the flexural modulus indicates the stiffness of the material). However, the decreasing *i.v.* values indicated that the molecule chains were cleaved due to the presence of water. Also the *i.v.* values of PDLGA decreased throughout the test period. As the hydrolysis proceeded, the values decreased to such a low level, that drawing detailed conclusions becomes difficult. In addition, PDLGA lost its mechanical properties completely already after six weeks. The water absorption of PDLGA was noticed to increase rapidly after the second week follow-up. The T_g of PDLGA was detected to decrease sharply between the 4- and 6-week follow-ups, whereas this was not observed in the case of PLGA.

A visual illustration of the degradation of PDLGA and PLGA is presented in Fig. 5. The clear PDLGA copolymer turned into a white, opaque block soon after starting the hydrolysis. After a few weeks, it started to lose its original shape. The swelling phase occurred later, followed by bursting of the capsule, leaving only a thin copolymer film behind. On the contrary, the dimensions of the PLGA samples were hardly changed during eight weeks in buffer solution. Cracks were noticed in the PLGA samples after prolonged hydrolysis indicating the progress of degradation.

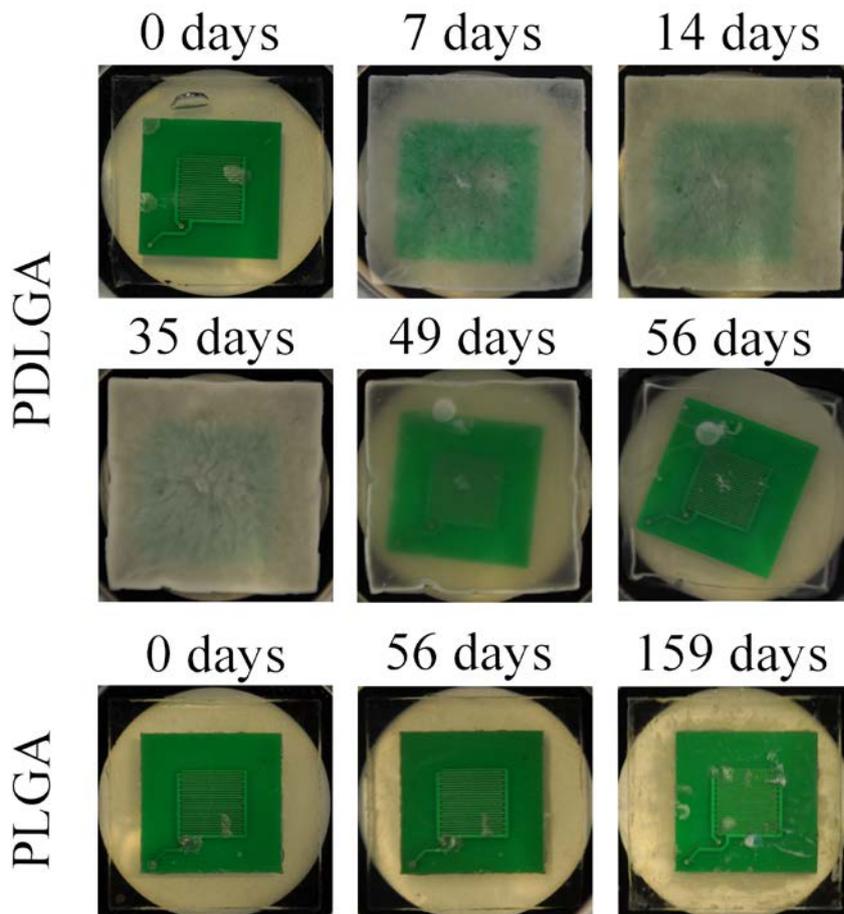


Fig. 5. A visual presentation of the copolymer capsule degradation at different time points, starting from the day when the buffer solution was added. The green sensor can be seen inside the capsules, which are held still with the black 3D printed holders. The last PLGA picture (159 days in buffer solution) is taken from a different sample than the two previous pictures.

3.2. Resonance measurements

The measured phase dip diminished as the hydrolysis progressed (Fig. 3a). The days when the signal from each individual sample was detectable are illustrated in Fig. 6. The resonance signal of the PDLGA samples faded to an undetectable level after most of the copolymer had dissolved after seven weeks. In general, the sensors in PLGA were detectable over 100 days. Three samples in PLGA samples were noticed to stop providing adequate resonance signals already after six weeks. These samples were excluded from the analysis.

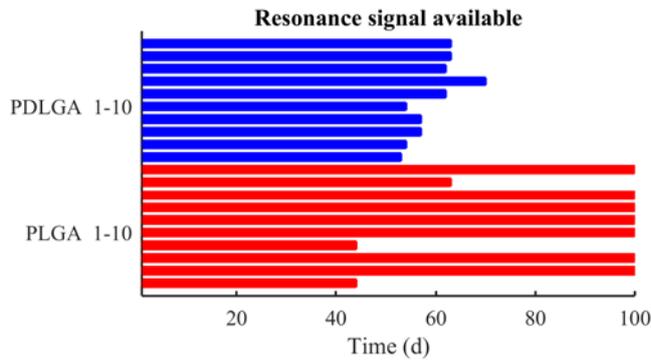


Fig. 6. A diagram showing the availability of the resonance signals of each individual PDLGA and PLGA encapsulated sensors.

The averages of the changes in the frequency (f_{md}) and bandwidth (BW_p) are presented in Fig. 7. In the case of PDLGA samples, a significant drop in the feature f_{md} was noticed after five weeks of hydrolysis. The signal from the PLGA samples showed only a minor drift. The feature BW_p of PDLGA samples had multiple phases: first, it increased for two weeks and then decreased until day 30. After that point, the feature began to increase again. The BW_p feature from the PLGA samples within this time scale was mainly an increasing drift.

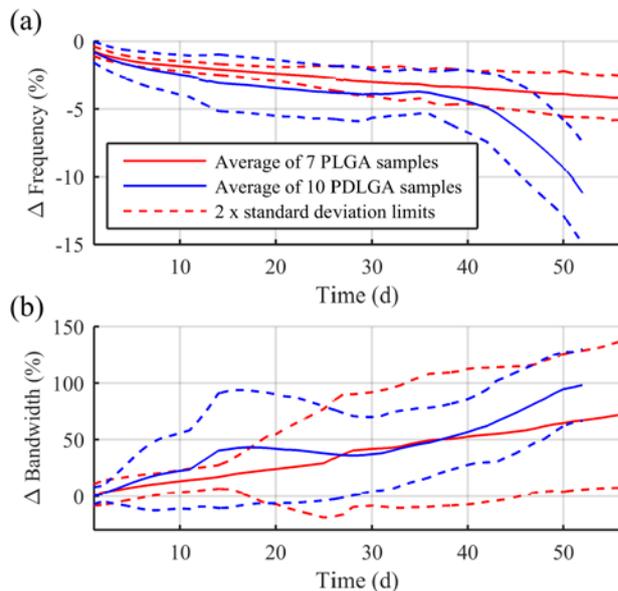


Fig. 7. The average of the changes in the feature f_{md} and (b) BW_p during the test period.

The changes in the features f_{md} and BW_p of the parylene coated samples are presented in Fig. 8. In addition, average signals of the non-coated sensors in PLGA and PDLGA are given to help comparison. In general, the changes of the signals were greater in the non-coated samples. The parylene coating was not noticed to affect the behaviour of the f_{md} feature in the PDLGA encapsulated sensors. The shift of the BW_p was greater in the case of non-coated

sensors. It was noticed that the transitions in the signals from all the sensors in PDLGA occurred simultaneously.

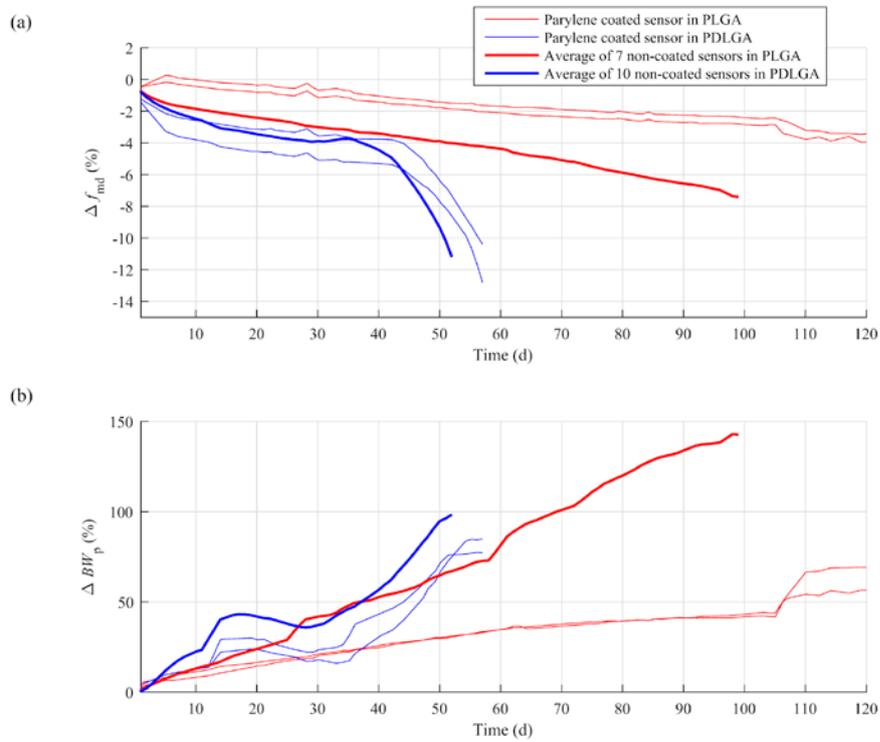


Fig. 8. The resonance features (f_{md} and BW_p) of two parallel parylene coated sensors encapsulated in PLGA and PDLGA. The averages of the non-coated sensors are presented for comparison.

Signals from the parylene coated sensors in PLGA were detectable at least 120 days. Both coated and non-coated sensors in PLGA showed a monotonic decreasing f_{md} and an increasing BW_p drift, which was steeper in the case of non-coated sensors. The parylene coated PLGA samples revealed a stepwise change in both f_{md} and BW_p around 110 days.

3.3. The effect of temperature

The effect of temperature on the extracted features was tested. This measurement was done using a PLGA sample that was kept in hydrolysis for 18 hours. Fig. 9 presents the change in the features f_{md} and BW_p as the temperature was varied. According to the measurements, the temperature sensitivity of the feature f_{md} was $-0.053\%/^{\circ}\text{C}$ and the temperature sensitivity of the feature BW_p was $0.22\%/^{\circ}\text{C}$.

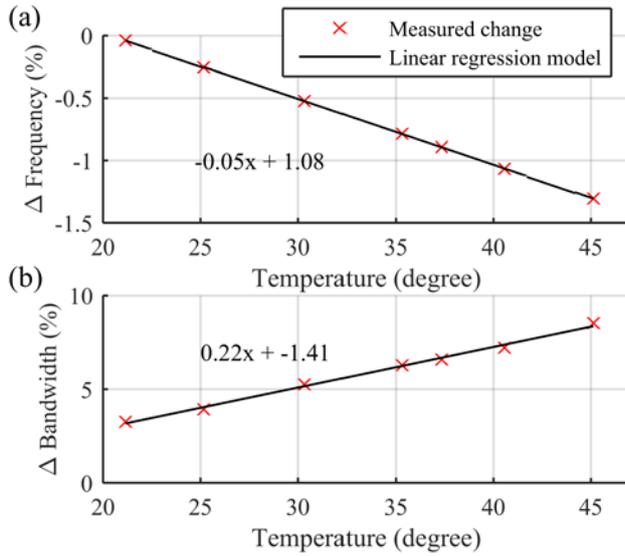


Fig. 9. The change of (a) resonance frequency (f_{md}) and (b) bandwidth (BW_p) as a function of temperature.

4 Discussion

We encapsulated resonance circuits with interdigital capacitive sensing elements in biodegradable PLGA and PDLGA copolymers and measured their response during the 8-week hydrolysis in buffer solution. The extracted resonance features (f_{md}) and (BW_p) were compared with the reference measurements that were performed using conventional polymer degradation characterization methods. According to the reference measurements, PLGA did not show any significant signs of degradation during eight weeks of hydrolysis. This expected result is consistent with the findings in the literature [15]. Respectively, the inductively measured resonance features from these samples showed only a slight drift. However, PDLGA was noticed to degrade almost completely in eight weeks. The feature f_{md} from the PDLGA encapsulated sensors showed a significant consistent decrease roughly after five weeks of follow-up. The behavior of the feature BW_p was not monotonic. The temperature dependency of the method was tested and it was not found to be a substantial error source.

Poly(lactide-co-glycolide)s used in this study degrade via bulk erosion [11]. These materials become saturated with water during the first few days in hydrolysis [1]. The water molecules start to cleave ester bonds, causing the molecular weight to decrease without any mass loss at this point. In some cases, the molecular weight keeps decreasing as the number of acidic chain ends becomes so large that their ability to catalyze the cleavage of polymer bonds becomes significant (autocatalysis). The mass loss starts when some of the polymer molecules reach a small enough size to become soluble in water. Typically, these low-molecular-weight components keep dissolving to the solution until the specimen has completely degraded. [11][1]

During the 8-week hydrolysis, our PDLGA samples degraded virtually completely and the inductively measured phase dip diminished to an undetectable level after seven weeks.

Previously, PDLGA [85:15] discs of 200-250 μm thickness have been estimated to degrade in 6-12 months [16]. We assume that the reason for fast degradation in our test was autocatalysis, which was an unintended but consistent result due to the thickness of our samples. Our PDLGA specimens were seen to soften and eventually turn into a viscous liquid with a harder outer shell. Similar autocatalytic behavior with thick samples has been reported and explained in [23]. As opposed to the PDLGA samples, no signs of autocatalysis were seen in the slower degrading PLGA samples during the test period.

There was an easily detectable drop in the f_{md} of PDLGA samples after five weeks. However, we interpret that the mechanical performance of the PDLGA samples was compromised already after four weeks in buffer solution. This indicates that tested feature cannot be used to predict the mechanical performance of PDLGA. In fact, the flexural modulus of PDLGA was lowered already after two weeks of hydrolysis. Part of this is explained by the fact, that the 0-week samples were tested dry: absorbed water acted as a plasticizer in polymers, thus reducing the modulus. The mechanical performance continued to drop significantly and at the 8-week time point the samples were already so deformed and soft that their testing was impossible.

On the other hand, the easily detectable f_{md} drop of PDLGA samples occurred within the same time frame than the decrease in the T_g values. Additionally, the opacity of PDLGA started to fade after approximately five weeks and the material turned to blurred but transparent substance as seen in Fig. 5. We suggest that the easily detectable change especially in f_{md} might result from the joint effect of the dissolution of the small copolymer degradation products and the following water absorption into the samples. We propose that the outer layer of the PDLGA sample acted as an osmotic membrane, which did not allow the permeation of salts.

Typically, the BW_p of PDLGA samples increased for two weeks, after which a decrease of 2-3 weeks was observed. Finally, the BW_p turned again into an upswing. The behavior of the feature BW_p may provide additional information about the degradation but definite conclusions cannot be drawn without more extensive studies. We speculate that such a behavior may be related to the outer layer of the specimen and changes in the distribution and size of the polymer chains.

In the consideration of the resonance measurements, the PLGA encapsulated sensors produced an initial frequency drop during the first few days in buffer solution. This drop is again expected to result from the penetration of water into the copolymer matrix. After that, a steadily decreasing f_{md} average was observed, whereas the BW_p average kept increasing. The signal from some sensor samples in PLGA was lost or significantly reduced during hydrolysis. This was probably due to the infiltration of buffer solution onto the interdigital capacitor (after drying the samples, the signals were recovered). We expect this infiltration to occur due to stress cracking, as clear cracks were seen in the PLGA samples. Especially in amorphous polymers, absorbed water can reduce the molecular anchoring of the polymer chains, causing accelerated cracking [1]. The cracking of the copolymer might partly explain the rather large deviation in inductively measured signals especially in the PLGA samples. It

is also critical, that the encapsulation process is reliable and the polymer material stays in contact with the sensor.

To test if the monitoring method could be made more consistent, a parylene coating covering the sensor was introduced. The slopes of the signals from the non-coated sensors in PLGA were steeper compared to the parylene coated sensors. Thus, the parylene coating was observed to decrease the sensitivity of the sensors resulting from the thicker isolating layer. However, the overall performance of the parylene coated sensors was similar to the non-coated ones. Accordingly, the parylene coating did not dominate the measurements. We presume that the parylene coated sensors give more consistent signals, which is more important than the slightly greater sensitivity of the non-coated sensors.

Both coated sensors in PLGA provided a detectable signal for at least 120 days. This prolonged measurement period revealed a change in both extracted features in both parallel samples around 110 days. For comparison, Alexis et al. noticed an increase in water absorption with their PLGA films around 100 days of hydrolysis, after which the mass loss started to slowly occur [15]. This suggests that the changes in the features might result from structural changes in the copolymers.

In comparison to the golden standard characterization methods, our approach provides means to observe changes in biodegradable polymers in a non-destructive, wireless manner. In practice, coating the sensors with parylene seemed to provide better results in terms of a longer measurement period and more consistent signals. However, a biodegradable alternative for parylene is needed for biodegradable applications. Ultimately, using for example bioactive glass as a circuit board material and biodegradable magnesium or zinc as conductors, an implantable completely bioresorbable sensor chip could be manufactured. This chip could then be embedded into compression or injection molded biodegradable implants to enable in vivo measurements.

The encapsulation methods of the sensors should be improved in the future studies. Based on this study, the suitability of the presented method on predicting the mechanical strength of the implants in general is still uncertain. Since polymer degradation and its effect on the complex permittivity are complicated processes, more studies are needed to investigate the parameters affecting the measurement and the resulting resonance features. For example, a test series where samples made from the same material are divided into sets of normal and accelerated degradation could be performed. More information about the effects of the buffer solution on the resonance features could be obtained by immersing one set of samples in buffer solution and another into distilled water. Furthermore, the presented monitoring method could be automated to make the measurement continuous.

5 Conclusions

Inductively coupled passive resonance sensors with interdigital capacitive sensing elements were used to monitor changes in two biodegradable poly(lactide-co-glycolide)s during an 8-week testing period. The inductively measured signals showed a clear difference between the tested materials, which was verified with the reference methods. However, the inductively

measured signals cannot be linked to any of the tested parameters without ambiguity. It was also noticed that the encapsulation process and coating of the sensors are critical for achieving consistent results. This has to be taken account when testing fully biodegradables sensors.

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