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A smart polymer hydrogel as a chemical sensor on biomedical implant

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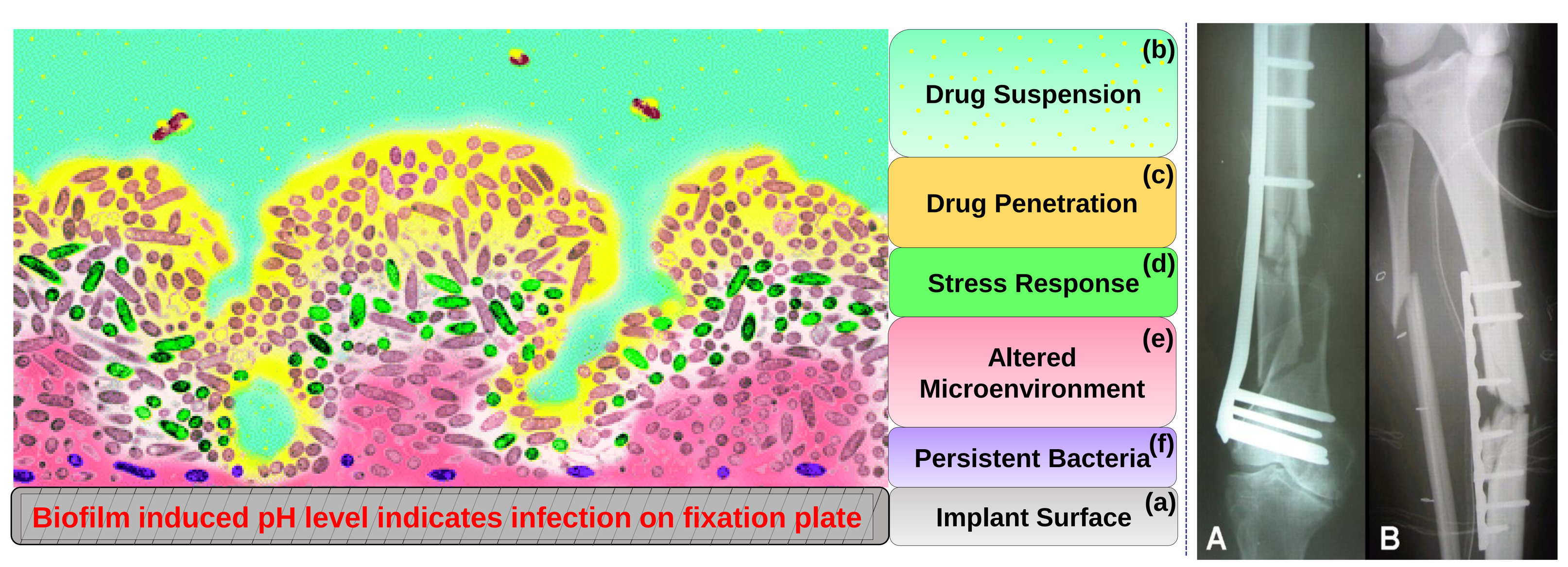
ABSTRACT

Orthopedic implants are manufactured to support on healing fractured bones. In United States, over 2 million fracture fixation devices, including intra-medullary nails, external fixation pins, plates, and screws, and over 600 thousands joint prostheses, are implanted in patients annually. While fairly common, these fixation surgeries (5%) sometimes lead to unavoidable infection, which only amplifies health care costs accumulated from the initial procedures. In most cases, bacterial biofilms acutely causes infection which is a major reason of medical device failure. In order to obtain proper infections detection around biomedical implants a non-invasive chemical sensor is required. In vivo detection of low pH around implant is an indication of bacterial infection. Therefore, the sensor, which can detect low and/or high pH in the target, needs to be coupled with the implant. In addition, it should be biocompatible and stable material. To address this issue we are building a smart implant sensor out of soft, wet hydrogels which would be highly acceptable and useful.

BIOFILM FORMATION ON IMPLANT SURFACES

Detection of infection on medical implant non-invasively caused by biofilm

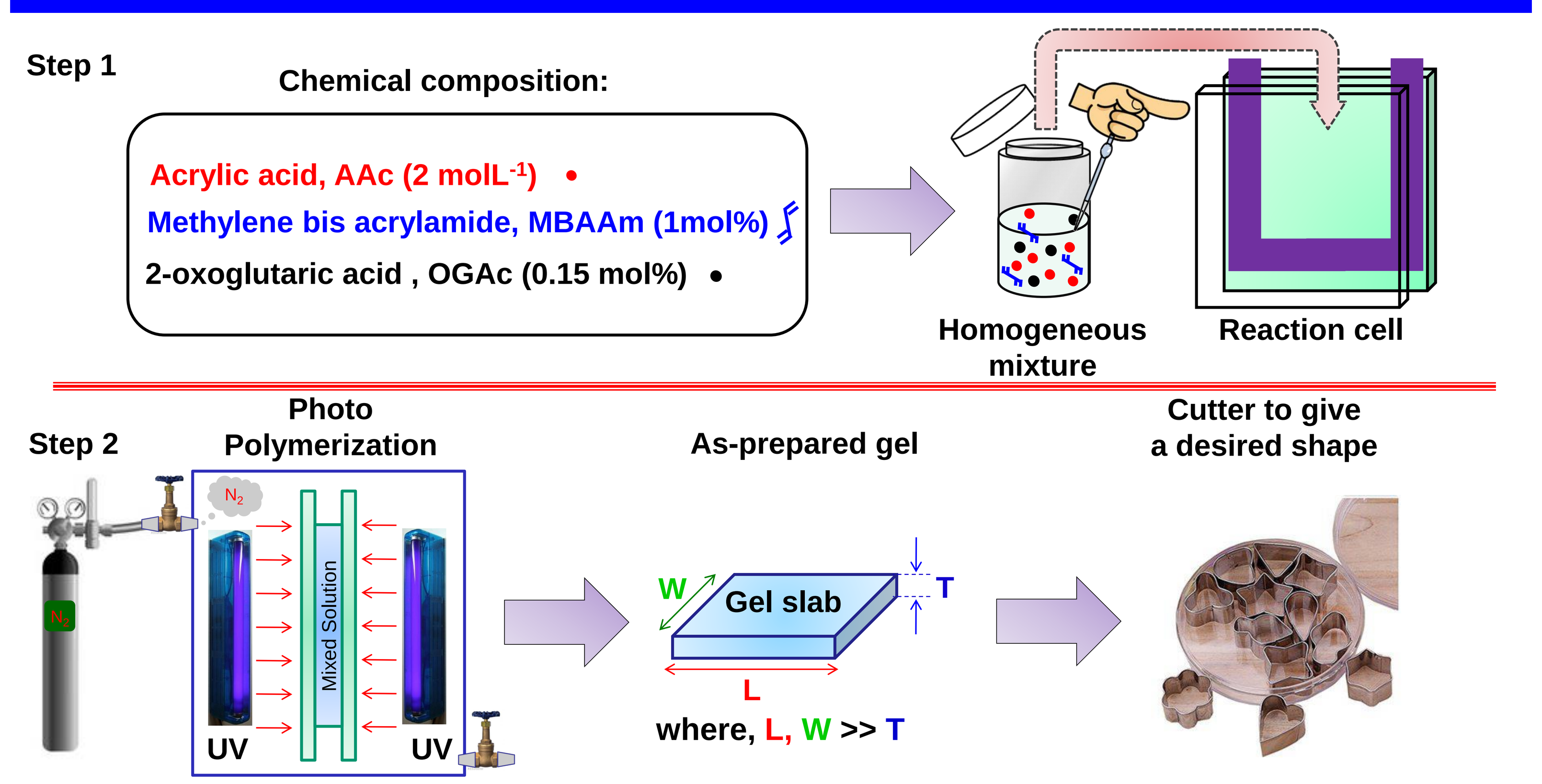


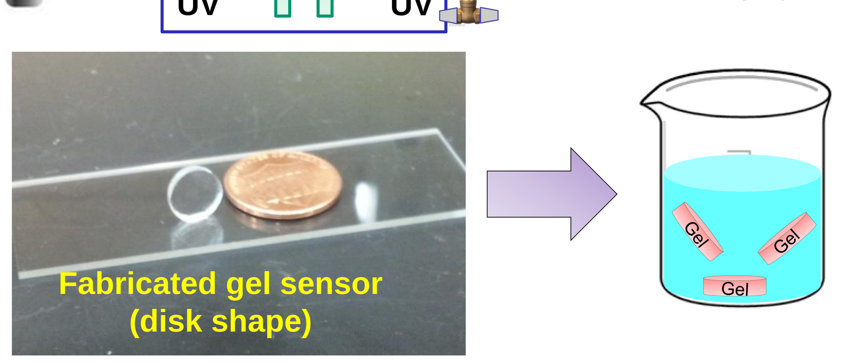
*Appl and Environ Microbiol, 72, **2006**, 2005*

*J Bone and Joint Surge, 89, **2007**, 2298*

Figure: *In left*, a biofilm cross-section attached with an implant surface at the bottom **(a)**, the aqueous phase containing antibiotic (AB) **(b)**, layers of the biofilm with penetrated drug **(c)**, zone of bacteria which are resistant to AB by differentiating their phenotype into protective state **(d)**, zones of nutrient depletion or waste product accumulation **(e)**, survived antagonized bacteria **(f)**. *In right*, locking plates are used for fixation of a distal femoral fracture **(A)** and a tibial shaft fracture **(B)**.

SENSOR FABRICATION





Hydrogel is synthesized in a glove box maintaining inert atmosphere by purging with pure Nitrogen. After successful fabrication, the gel-sensor, incubated in deionized (DI) water or in 1x phosphate buffer, is incorporated in fixation plate for pH response experiments.

PRIMITIVE OBSERVATION

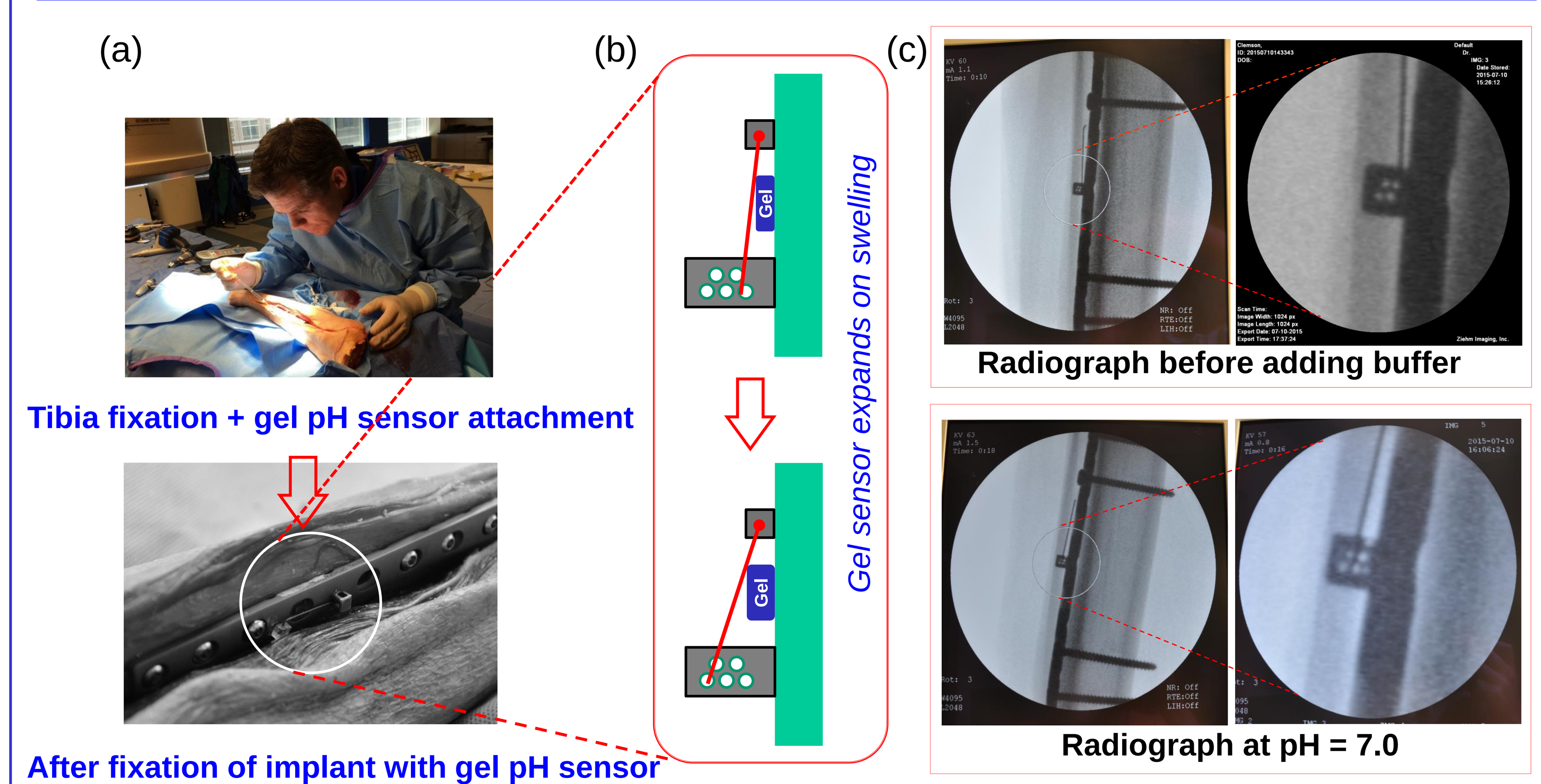
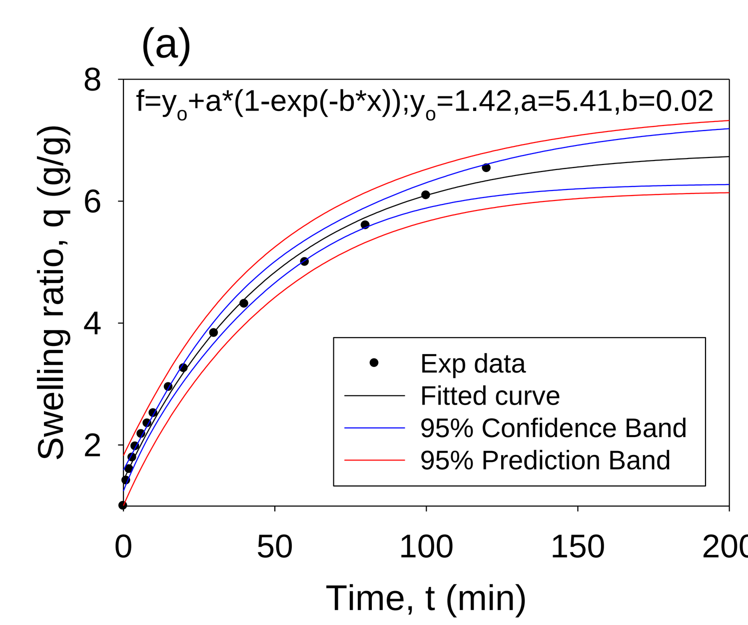


Figure: An orthopedic surgeon **(a)** (up) was fixing an implant on a cadaver tibia and afterwards attached the gel sensor in that implant. Investigation plan on the gel sensor placed in the fixation **(a)** (down) is presented by using a schematic diagram **(b)**. X-ray images enlarged in right side of **(c)** exhibits: clearly a tungsten dial adhered on the sensor reasonably displaced when expansion and contraction of the gel was occurred after adding buffers of high and low pH respectively.

CHARACTERIZATION OF THE SENSOR



(b)

	pH of the buffer		
Swelling ratio, q (g/g) of the gel sensor	2.0	7.0	12.0
	~ 5	~ 40	~ 60

Figure: Swelling kinetics measurement of the gel sensor film in deionized water **(a)**. This study helps to determine the swelling time constant which indicates the course of time required to almost reach an equilibrium state. Assumption of gel sensor response at different pH buffers by measuring swelling ratio (mass) at equilibrium state **(b)**.

Reversible response of the sensor gel at switching pH:

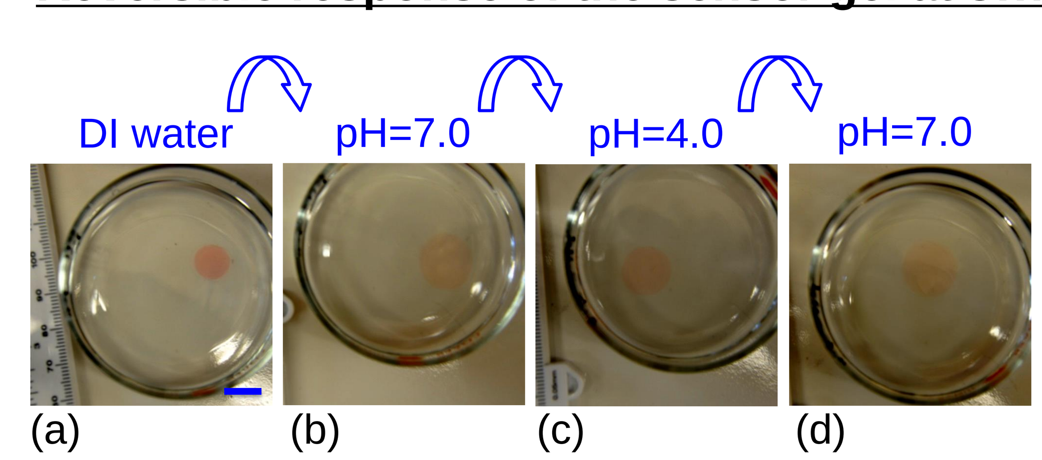
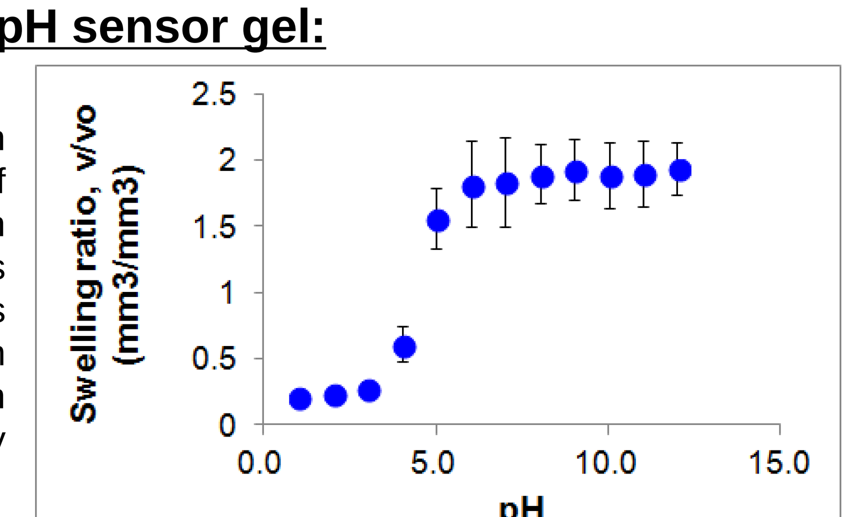


Figure: Reversible behavior of gel sensor film fully hydrated in deionized water **(a)** at switching pH buffer from 7 to 4, and later 4 to 7. The gel is expanded after exposure into pH buffer 7.0 because of swelling by the de-protonation of fixed COOH group in the network **(b)**, **(d)**. In the sink of pH buffer 4.0 the gel is contracted due to de-swelling by the resolving protonation into COO^- ions **(c)**. Scale bar is of 10 mm and is universal for the set.

Swelling ratio calibration curve of the pH sensor gel:

Figure: A calibration curve for the gel sensor based on the swelling ratio (volume) measurement . A piece of sensing hydrogel of ~ 7 mm in diameter and ~1 mm in thickness was incubated in standard pH buffers ranging from 1 to 12. After attaining equilibrium states the dimensions of the gel sensor were measured from the images taken in a digital camera. The calibration curve exhibits a sigmoidal shape which agrees very well with the reported pH responsive system.



SENSOR IMPLIMENTATIONS

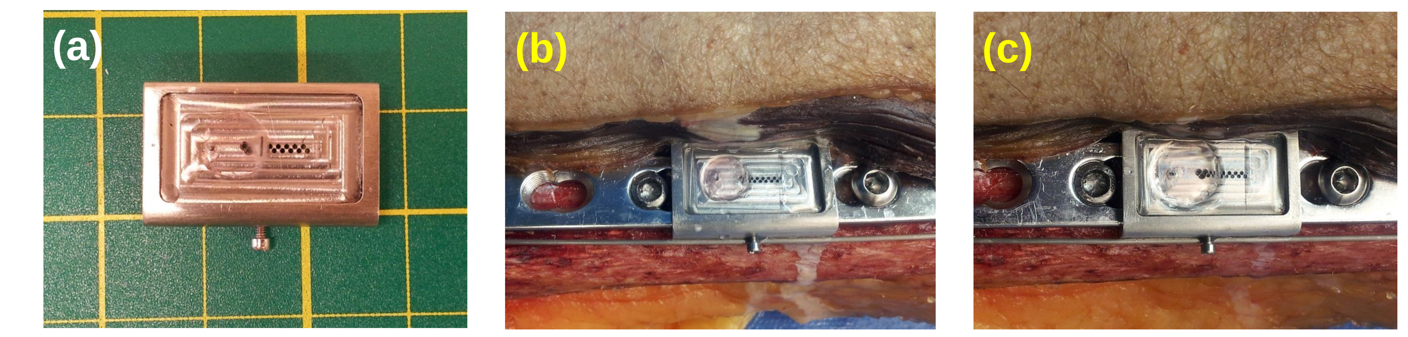
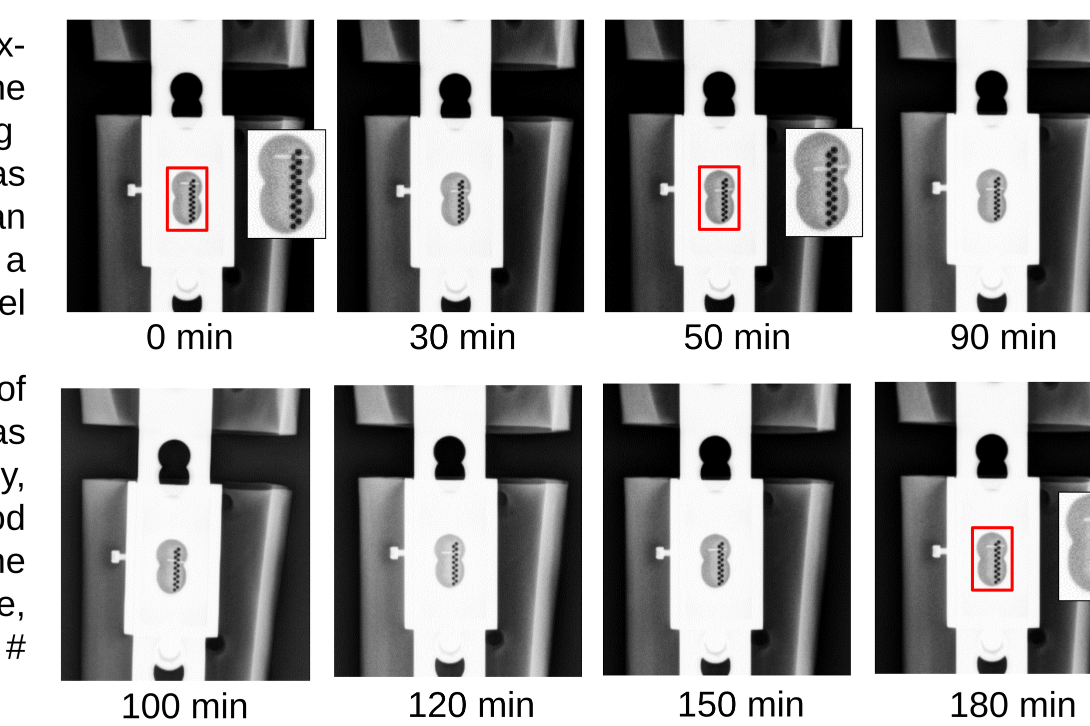


Figure: The gel sensor and a metallic base with reference holes each of 500 micron diameter made in two lines **(a)**. Spacing between holes is 200 micron. The gel sensor is hold in a built in pin of the metal base. A piece of length 2 mm tungsten rod is carefully attached on the edge of disk shaped gel sensor. The contraction and expansion of the gel sensor attached into a cadaver tibia implant after the administration of standard buffer solution of pH = 4.0 and 7.0 (**(b)**, **(c)**) respectively.

Figure: Time lapse x-ray images of the expanding-contracting gel sensor which was attached with an implant fixed on a cadaver tibia. The gel expanded/contracted when the buffer of pH=7.0 and 4.0 was added respectively, and the tungsten rod firmly adhered on the gel surface, therefore, moved into different # of reference holes.



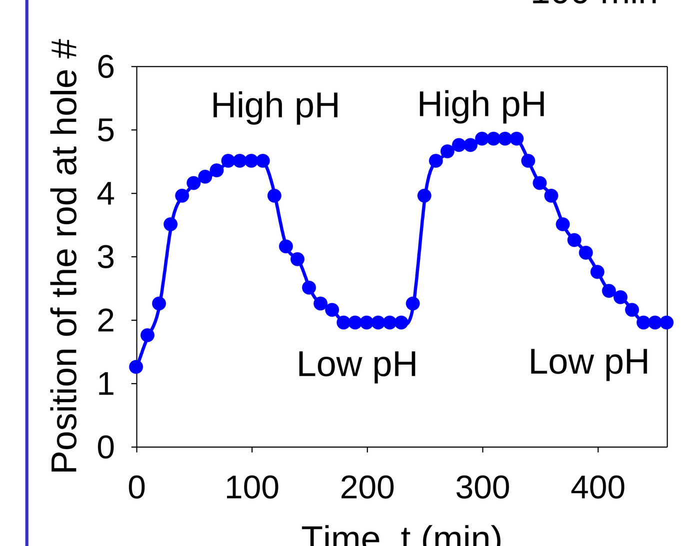


Figure: Displacement kinetics of the tungsten rod attached on the edge of the gel sensor placed on the cadaver tibia implant. At low pH (4.0) buffer application the position of the rod is around the reference hole # 2-3. When high pH (7.0) buffer was added the sensor started expanding and the rod was being moved to a greater # of holes until the sensor attained the steady state. Afterwards, when low pH (4.0) buffer was added the rod came back to the lesser # of reference holes because of contraction of the sensor. The sensor exhibited remarkable reversible behavior when the pH of the buffer was switched from low to high or, high to low.

CONCLUSION

We succeeded in designing an effective pH sensor for an orthopedic internal fixation plate using swelling induced macroscopic mechanical deformation (strain) in a polymer hydrogel. A covalently cross-liked polyelectrolyte network is fabricated to test as a pH sensor for orthopedic implant. After synthesis, the hydrogel sensor hydrated in deionized water (pH~5) was placed on the implant attached to a cadaver bone (tibia). When phosphate buffer (pH~ 7 or, 4) was applied, mass/volume of the gel increased/decreased remarkably due to swelling/de-swelling and macroscopic strain was induced, and, therefore, significant displacement of a tungsten dial/rod placed on the gel surface was clearly observed in radiographs. Through this work we invented a simple, robust sensor for implant which will detect bacterial infection non-invasively through tissue by applying plain radiography easily available in almost all hospitals.

FUTURE WORK

We need to fabricate gel-sensor with reduced dimensions so that response time will decrease. Also, mechanical property of the sensor film needs to improve for minimization the risk of handling. We will run experiment to check the sensor in animal models with infections. Miniaturized gels, responsive to implant infection with the exhibition of fast and macro scale anisotropic deformation is our dream goal for near future.

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