Smart bone plates can monitor fracture healing

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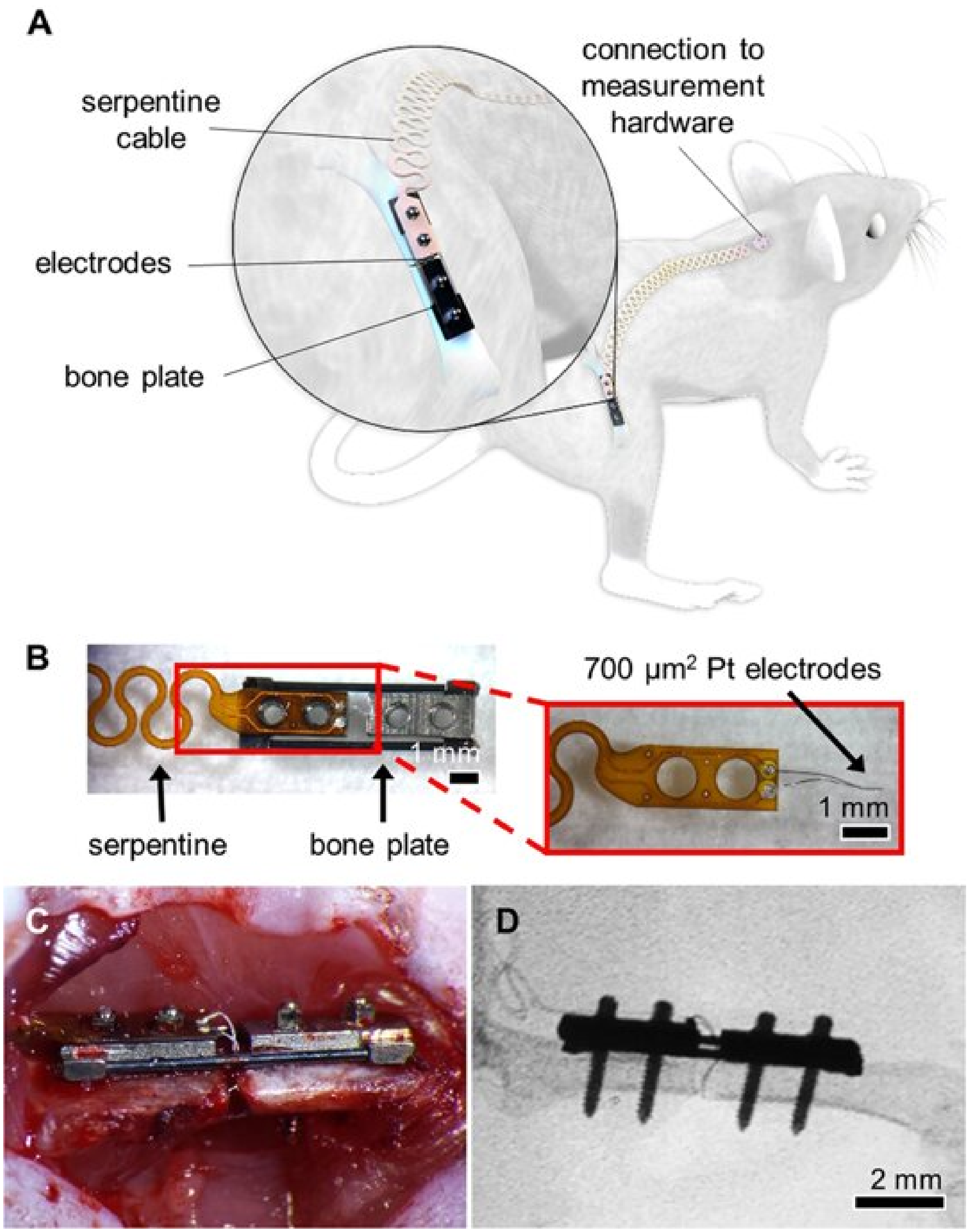
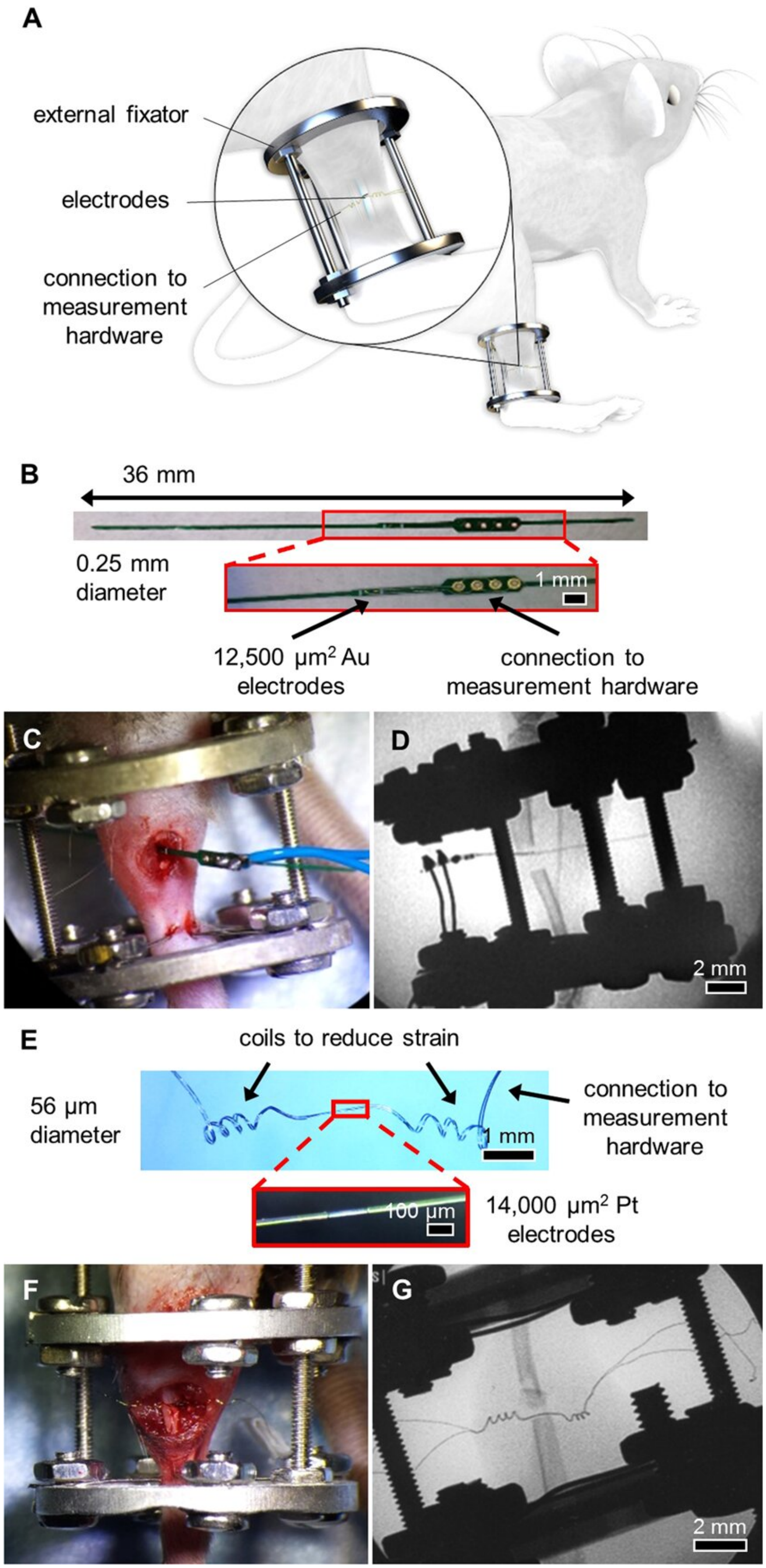


Experimental setup and sensor for a bone plate model. (A) System overview of sensor embedded in a mouse femur fracture, where the injury is stabilized with a bone plate. Image created by the Ella Maru Studio. (B) Sensors fabricated on a polyimide substrate with 700 µm2 platinum (Pt) electrodes spaced 0.5 mm apart. Sensors were affixed to the proximal half of the bone plate, with a long flexible cable extending off the proximal end. The serpentine pattern repeated for the length of the cable, ending in two vias that served as connectors linking the measurement hardware. (C) Photograph of open surgery performed to implant a bone plate and affixed sensor to stabilize a femur fracture. Surgical site was closed following sensor placement. (D) Fluoroscopy image of implanted Pt sensor in the fracture gap. Credit: *Scientific Reports*, doi: https://doi.org/10.1038/s41598-018-37784-0

Bone tissue engineering (BTE) is an evolving field at the intersection of materials science and bioengineering, focused on the development of bone substitute materials and diagnostic methods in orthopedics. At present, physicians rely on X-rays to assess fracture healing, which are more useful at the latter stages of bone repair. Accurately determining the process of bone fracture repair is a fundamental clinical requirement in orthopedics, but standard methods to assess fracture union remain to be developed.

In a recent study, Monica Lin and co-workers at the departments of Bioengineering and Orthopedics at the University of California, San Francisco (UCSF), used in vivo mouse fracture models to present primary evidence of microscale smart bone plate implants. These implants were able to monitor post-operative fracture healing with high sensitivity using electrical impedance spectroscopy (EIS) integrated to track the the healing tissue. The scientists fixed mouse long bone fractures with external fixtures and bone plates containing the sensor for the first time in an experimental study in the lab. The results are now published in *Scientific Reports*.

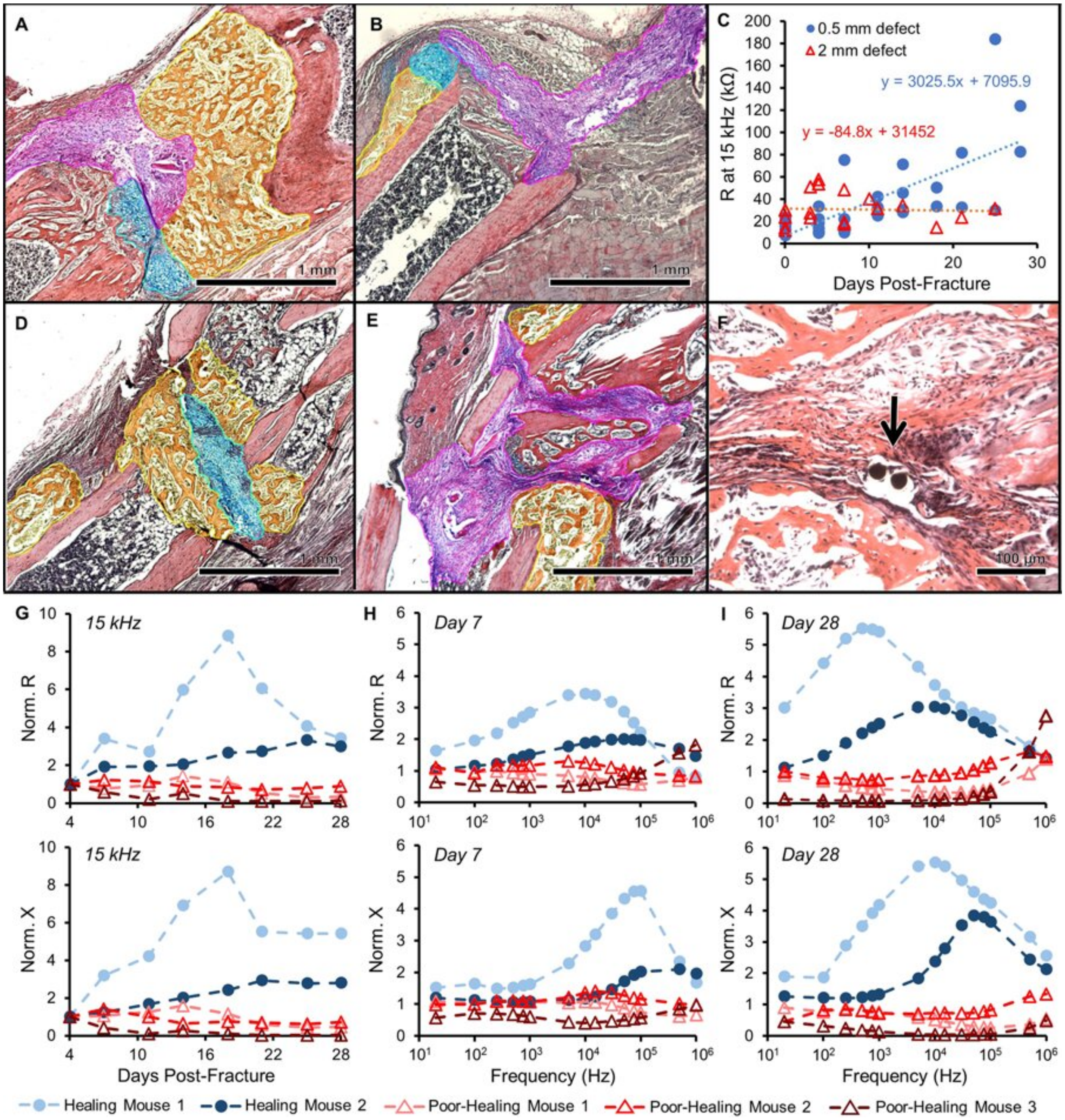
In the study, Lin et al. conducted EIS measurements across two microelectrodes in the fracture gap, to track longitudinal differences in mice with good versus poor healing. The scientists presented an equivalent circuit model combining the EIS data, to classify the states of fracture repair. Their measurements strongly correlated with standard qualitative X-ray microtomography (microCT) values, allowing the frequency-based technique to validate clinically relevant operating frequencies. The results indicated that EIS can be combined into existing clinical fracture management strategies such as bone plating. The process developed in the study can ultimately provide physicians quantitative information on the state of fracture repair in patients to guide clinical decision-making.


A
external fixator
electrodes
connection to measurement hardware
B
36 mm
0.25 mm diameter
1 mm
12,500 μm2 Au electrodes
connection to measurement hardware
C
D
2 mm
E
coils to reduce strain
56 μm diameter
1 mm
connection to measurement hardware
100 μm
14,000 μm2 Pt electrodes
F
G
2 mm

System overview and sensors for an external fixator model. (A) System overview of sensor embedded in a mouse tibia fracture, where the injury is stabilized with an external fixator. Image created by the Ella Maru Studio. (B) 0.25 mm diameter sensor fabricated on an FR4 substrate, with gold (Au) surface electrodes and large vias outside the leg to connect to measurement hardware. Sensors were implanted in externally-fixed mice tibias with 0.5 mm and 2 mm defects. (C) Photograph of open surgery performed to implant 0.25 mm sensor in the external fixator model. Surgical site was closed following sensor placement. (D) Fluoroscopy image of implanted 0.25 mm sensor in a 2 mm defect. (E) 56 µm diameter sensor assembled using platinum (Pt) wire, with recording sites exposed by a CO2 laser and coils added to provide strain relief. (F) Photograph of open surgery performed to implant 56 µm sensor in the external fixator model. Surgical site was closed following sensor placement. (G) Fluoroscopy image of implanted 56 µm sensor in a 0.5 mm defect. Credit: *Scientific Reports*, doi: https://doi.org/10.1038/s41598-018-37784-0

Musculoskeletal injuries including bone fractures are highly prevalent in the United States. Fracture treatment represents a significant burden on the U.S. healthcare system. To conduct accurate clinical decisions on fracture healing; it is imperative to determine how well a fracture is healing. Since a standard method to assess fracture union is still lacking, two of the most common methods at present include radiographic imaging and physical evaluation. While computed tomography (CT), dual X-ray absorptiometry (DEXA) and ultrasound can offer improved diagnostics, their clinical use is limited due to cost and the higher dose of radiation. As a result, patients rely on physical examinations by a physician, but the results are subjective and prone to imprecision. The biological process of fracture healing proceeds via two pathways; intramembranous (direct) and endochondral (indirect) ossification.

Early stages of fracture repair are not typically detected until the stage of bone mineralization. As a result, developing techniques to monitor fracture healing onset is an active area of academic research. Most studies have focused on mechanical feedback that correlates strain measurements to bone strength. In the present study, Lin et al. built on previous studies to use electrical techniques that can characterize fracture repair progression. The basis of their work was on the analogy that biological tissue can be electrically modeled as a combination of resistive and capacitive effects. The ion-rich intra- and extracellular matrices conduct charge as resistances, while the double-layered cell membranes can be modelled as capacitances or constant phase elements (CPE).



Impedance data distinguishes healing and poorly healing tibia fractures in an external fixator model. Histology sections in this image are stained with Hall's and Brunt's Quadruple (HBQ) stain and false-colored to aid interpretation of tissue composition. Blue = cartilage, yellow = trabecular bone, and purple = fibrous/amorphous tissue. Original red color = cortical bone, black/white area = bone marrow. (A) Representative histology section for an externally-fixed 0.5 mm defect at 14 days post-fracture; the fracture gap is clearly bridged by cartilage and new trabecular bone. (B) Representative histology section for an externally-fixed 2 mm critical-sized defect at 14 days post-fracture; the fracture gap is dominated by fibrous tissue. (C) Electrical resistance (R) at 15 kHz measured with a 250 µm sensor is plotted over days post-fracture for measurements taken in mice with 0.5 mm (N = 6) and 2 mm (N = 5) defects. Linear regression analyses determined that there is a significant positive relationship in mice with 0.5 mm defects (p