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Microneedle Array for Measuring Wound Generated Electric Fields

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Abstract— **A microneedle array has been fabricated and applied to the measurement of transdermal skin potentials in human subjects. Potential changes were recorded in the vicinity of superficial wounds, confirming the generation of a lateral electric field in human skin. The measured electric field decays with distance from the wound edge, and is directed towards the wound. The measurement of endogenous fields in skin is a prelude to the study of the therapeutic efficacy of applied electric fields to chronic non-healing wounds..**

I. IINTRODUCTION

Microfabrication not only enables the miniaturization of sensors and instruments, it also enables novel function and capability that is not accessible to the macro world. For biomedical applications, small size means less invasiveness, greater spatial resolution, and/or the ability to process miniscule sample volumes. A new, transdermal potential measuring instrument is presented here which utilizes tiny silicon microneedles to traverse the high impedance, stratum corneum of the skin and record both transdermal and intradermal potentials. This demonstration is preliminary to applying this or a similar device to examine the efficacy of applied electric fields in the treatment of chronic wounds and the evolution of a wound-healing, therapeutic device.

II. SKIN POTENTIAL

The presence of transepidermal skin potentials has been known for decades. In humans, this skin potential has been measured to be 20-50 mV [1]. These potentials are believed to be generated by the active basolateral pumping of sodium ions by the keratinocytes of the multilayered epidermis, resulting in an accumulation of sodium ions in the basal epidermis relative to the outer surface of the skin. When the epidermis is intact there is no current flow, but when the high resistance outer layer of the skin (stratum corneum) is wounded, a low resistance pathway for sodium ion leakage is generated, resulting in current flow and collapse of the transepidermal potential. The transdermal potentials fall to zero at the edge of the wound, resulting in a lateral electric field, which may play a role in wound healing, e.g. by affecting the transport of keratinocytes to the wound edge by galvanotaxis [2].In animal models, such as the cavy [3] and the newt [4], *in vivo* electric fields of 40-100 mV/mm have been measured in the vicinity of skin wounds. However, no definitive study of skin wound generated electric fields in humans has yet been performed.

In an effort to better understand and possibly affect wound healing by the application of electric fields [5], the measurement of transdermal potentials in the vicinity of skin wounds is underway. The microdevice presented here was specifically designed to measure wound generated skin potential variations in human subjects. An array of microneedles surround a wound site. The needles pierce the high resistance stratum corneum with minimal wounding and record potential at regularly spaced, radial distances from the wound edge, as defined by the electrode array sites. The measured values are then plotted to determine the lateral electric field.

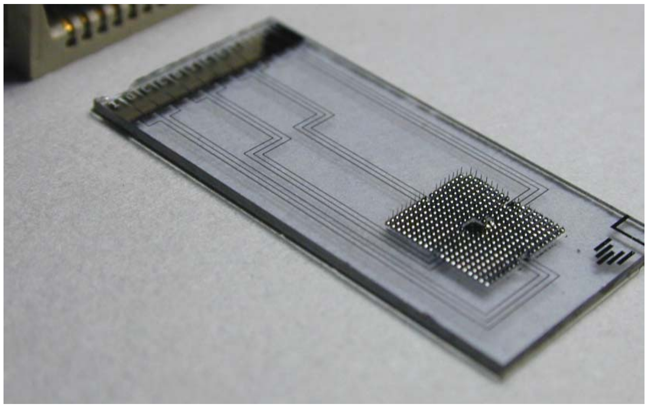

Figure 1 Photograph of a completed wound potential measuring device.

III. MICROFABRICATION OF ARRAY

A photograph of the completed transdermal potential recording chip is shown in Figure 1. The salient features of this device are a) an array of electrically isolated, silicon micromachined needles with metal coated tips, b) a supporting glass substrate with interfacing thin film metal electrodes and c) a laser wounding window at the center of the array.

The fabrication of this device is illustrated in Figure 2, showing cross-sections taken after specific steps in the

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process. In brief, the chip is fabricated by anodically bonding a micromachined silicon chip to a glass substrate which supports platinum metal traces. The anodic bonding step electrically connects the metal traces to the base of individual microneedles, creating a low resistance, platinum silicide (PtSi) contact to each. The silicon microneedles are shaped by a combination of deep reactive ion etching (DRIE), mechanical sawing with wafer dicing blade, and sharpening with a silicon isotropic etchant, HNA. During sharpening, the metal traces are protected by a silicon membrane which forms a connecting bridge between adjacent needles. After sharpening, photoresist is applied to the chip, coating the base of the device, but leaving the needle tips exposed. Platinum is then deposited by e-beam evaporation. The metal is lifted off by removal of the photoresist, leaving platinum on the needle tips and shanks. The bridging silicon membranes are then cut away with the dicing saw, and an insulating layer of silicon nitride is deposited by plasma enhanced chemical vapor deposition on all exposed surfaces. To remove the silicon nitride selectively from the needle tips, aluminum foil is pressed over the needle array so that only the needle tips poked through the foil. The silicon nitride on the exposed tips is then removed by reactive ion etching. This process produces electrically isolated microneedles with electrically conductive tips that are individually addressable.

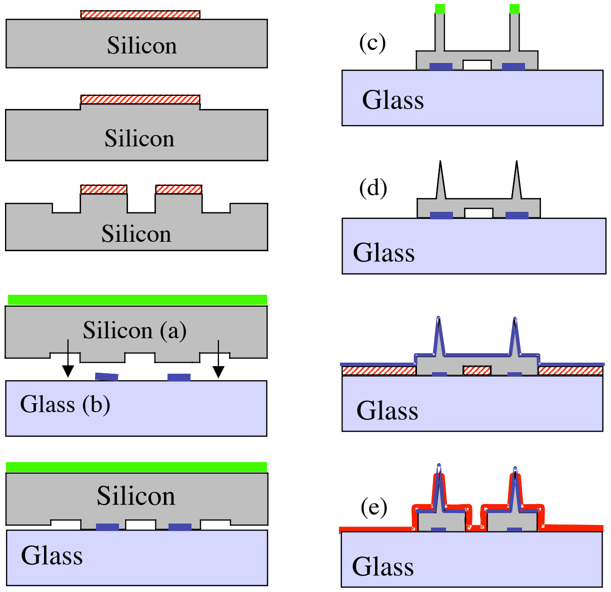

Figure 2. Microneedle array fabrication: micromachined silicon wafer (a) is anodically bonded to thin metal traces, supported by a glass substrate (b). Silicon columns are formed with a diamond tipped saw (c). After sharpening in HNA (d), the needles are coated with Pt and silicon nitride (e). The nitride is then selectively removed from the tips using an aluminum foil mask and reactive ion etching, to expose the Pt.

Although platinum metal does not provide an ohmic contact to biological tissue, the preferred Ag/AgCl tip coating would not survive the fabrication process nor the skin penetration. As a result, the absolute values of the recorded potentials at different Pt coated needle tips can be highly variable, as will be noted further on. However, potential changes that occur at a single electrode can be reliably and reproducibly measured. This was verified with measurements made between platinum electrodes immersed in saline and agarose gel.

A window, or absence of electrodes, is left at the center of the array to allow the controlled wounding of the skin by a dermatological, erbium laser (λ=2.9 μm) after placement of the microneedle array into the skin, thereby self-aligning the wound edge to the surrounding microneedles. The output power of the laser was 1.3 Joules with a pulse width of 250 ms. The laser generated wounds are intentionally superficial. They are not deep enough to enter the dermis and disrupt the superficial capillaries, thus there is no blood produced in the wound. The needles are so sharp (<10 μm radius) that the surrounding epithelial cells are only minimally damaged during penetration, as confirmed by imaging of the needle puncture wounds with a confocal *in vivo* microscope (Optiscan Stratum™).

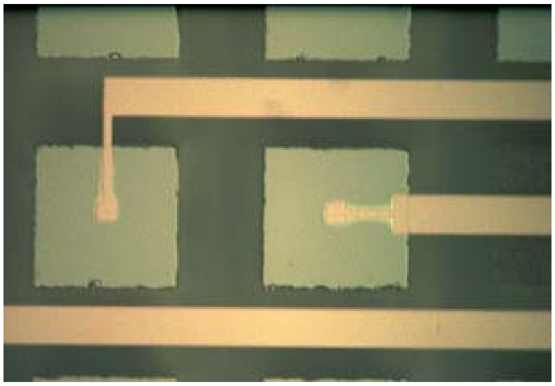

Figure 3. Photograph of Pt metal traces and contact to specific silicon microneedles, seen through the glass support.

In order for this device to be able to record wound generated, skin potential changes, the measuring electrodes must reside within 1 mm of the wound edge and have sufficiently small spacing (resolution) to reasonably map the generated electric field. Each array contains several hundred microneedles, of which only twelve are electrically addressed. Six, equally spaced, collinear electrodes extend radially outward, on either side of the wounding window. The spacing between adjacent electrodes is 300 μm. The connecting metal traces extend to the edge of the glass

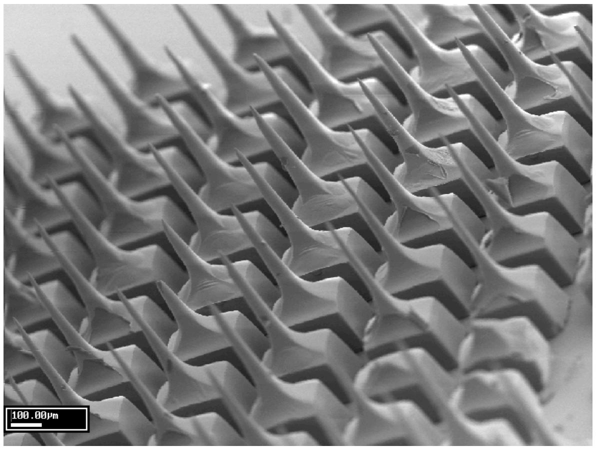

Figure 4. Scanning electron micrograph of the microneedle electrode array. The pitch of the electrodes is approximately 300 microns; the penetrating shank is approximately 200 microns in height.

support, where they terminate in large contact pads. Connections between the glass supported metal traces and the measurement circuitry are made with a spring loaded edge connector and ribbon cable (see Figure 1).

The piercing and recording electrode tips must also be fixed in depth below the skin surface so that they lie below the stratum corneum, but above the basement membrane, in order for the recordings to be reproducible and of the proper sign. The out-of-plane microneedle design fixes the maximum depth of penetration of the needles by the needle shank height. The microneedles have a shank height of 200 microns. Imaging with the Optiscan Stratum™ and fluoroscein dye was used to verify that the electrode tips lay between 100 and 150 μm beneath the skin surface.

The same microneedle array can be utilized for either stimulating or recording. Hence, in addition to wound potential recording, the same device may be used to apply potentials in an effort to promote wound healing, i.e. a smart bandage.

IV. MEASUREMENTS

In vivo measurements were made on five human subjects, aged 32 to 38 years of age, in accordance with an approved human subject testing protocol. An electrode array was applied to the wrist of each subject and held in place with tape. Measurements were taken every 1.5 seconds, using a custom preamplifier and an A/D converter. An Ag/AgCl surface EKG reference electrode was attached on the same forearm, four inches above the chip. Recordings were successfully obtained during laser wounding on all five test subjects. The absolute potential magnitudes varied from subject to subject and from electrode site to site, but all exhibited the same trend: potentials decreased after wounding with the largest change occurring at the electrode nearest the wound. The results shown in Figures 5-7 are from the same subject. The raw data (Figure 5) shows a dramatic potential reduction upon laser wounding that gradually increases again, but to a value less than before wounding. Potential values are measured at each electrode site just before and after wounding, when the potential versus time derivative approaches zero, to arrive at the wound generated potential change. Electrode 1 is closest to the wound edge, and electrode 6 is farthest. The measured change in potential is plotted in Figure 6.

The results confirm the existence of a variation in skin potential that is a maximum near the wound and a resulting transverse electric field directed towards the wound (more negative potential approaching the wound). The corresponding, lateral electric field magnitude is plotted in Figure 7. The measured electric fields were found to be comparable to those measured in animals, i.e. 40-100 mV/mm. This is the first known recording of skin wound generated electric fields in human subjects. Future studies are planned to measure wound generated fields surrounding both acute wounds and chronic wounds, and to determine if the application of electric fields can affect wound healing.

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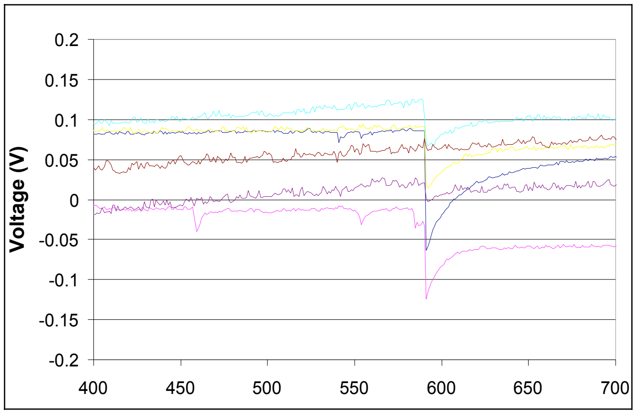

Figure 5. Potentials recorded at each of six electrodes, at positions of increasing radial distance from the wound edge. The x-axis units is data sample points, with one sample taken every 1.5 s. The rapid change in potential occurs when the laser is turned on (pulsed).

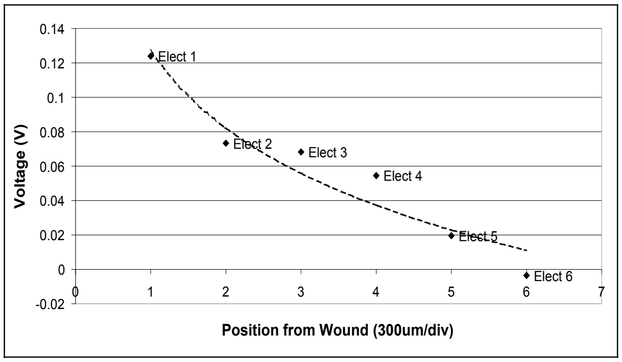

Figure 6. Difference in potential recorded before and after wounding at each of six electrodes.

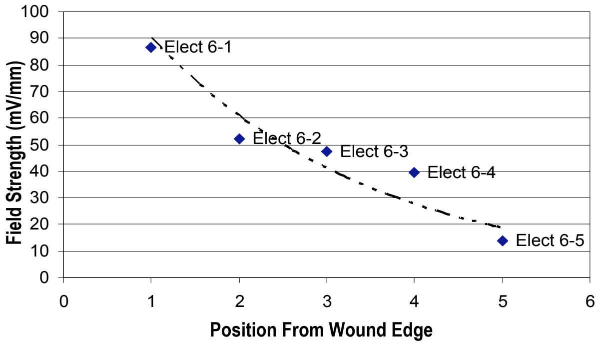

Figure 7. Lateral electric field calculated from electrode potential differences divided by their distance from the wound edge.