Real Time Blood Coagulation Sensor

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Introduction:

Non-compressible hemorrhage is the leading cause of potentially survivable deaths from combat injuries in Operation Iraqi Freedom. In trauma injuries, naturally produced coagulation proteins are quickly depleted, which can lead to hemorrhage-related death [1]. The blood coagulation process can be described as an enzymatic cascade, which is activated in two cases: i) immediately after the damage of any blood vessel as the intrinsic system, or ii) if blood contacts with foreign materials as an extrinsic system [2]. There are numerous methods of monitoring the coagulation process such as prothrombin time and activated thromboplastin time. Acoustic resonators such as the quartz crystal microbalance, which resonates in a pure thickness shear mode, shift their resonant frequency with proportion to the square root of the viscosity density product of the coagulating blood sample [3].

We report a method of measuring blood coagulation in real time, using microelectromechanical systems (MEMS)-based small-size, portable, and disposable devices. The devices utilize contour-mode acoustic waves to measure viscosity change in real time. The contour mode MEMS-based film bulk acoustic resonator (C-FBAR) has a suspended ring-shaped piezoelectric layer of aluminum nitride thin film, sandwiched between two metal electrodes. The C-FBAR is excited in its radial directions and has a low motional impedance when coupled with liquids, allowing the device to maintain a high quality factor (Q) in liquids, up to 189. The high Q offers high sensitivity to the viscosity change during the coagulation process.

Experimental Procedure:

To characterize the C-FBAR as a viscosity sensor, we measured the viscosity of several controlled aqueous glycerine solutions using the C-FBAR. These solutions have been characterized for their viscosity and density at room temperature [4]. As shown in Figure 1, the theoretical and the measured viscosity values are closely correlated in the range from 1 to 10 centipoises (cP). For the blood coagulation experiments, samples of citrated blood were prepared. Citrate prevents blood from coagulation, and calcium ions reverse the anti-coagulation process. The C-FBARs were placed on a probe station and were connected to a network analyzer (Agilent 5071C) to measure the one-port reflection coefficient ($S11$). The C-FBARs were first characterized in the air and consequently performed blood coagulation monitoring as follows: after the citrated blood samples restored to 20 °C, we added different amounts of $CaCO_3$ powder to the blood samples, gently agitated, and dispensed a droplet to the C-FBAR surface immediately using a micromanipulator. The micromanipulator allowed very precisely controlled 3-axis movements, so that the minute volumes of liquid could be dispensed onto the delicate suspended resonator safely. The resonant frequency was recorded in real time after the sample droplet was applied via a LabVIEW program.

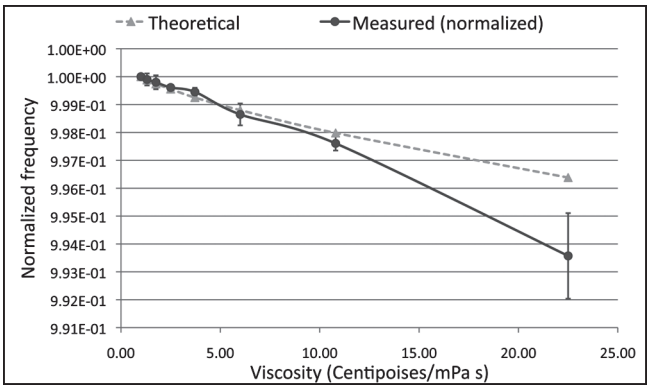

Figure 1: Desired range is 1-10 cP because blood coagulates occurs at 3-5 cP.

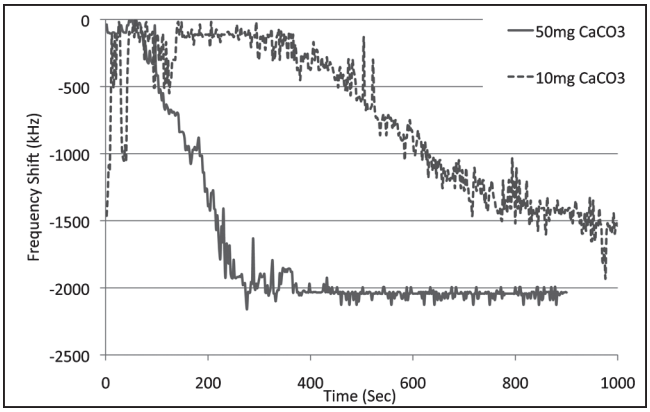

Figure 2: Real time frequency response of C-FBAR.

Results:

Figure 2 shows the real time frequency responses of the C-FBAR monitoring the blood coagulation process.

The addition of Ca^{2+} ions initiated the coagulation process, resulting in negative frequency shifts of the C-FBAR. Two different concentrations of $CaCO_3$-added blood samples were tested. The frequency was steady during the initial stage, where the enzymatic cascade occurred and no viscosity changes were observed, resulting in a plateau phase in the frequency response. Consequently, at the end of the coagulation cascade, thrombin as central-protein cleaved fibrinogen to fibrin. The fibrin monomers eventually polymerized into fibers. As a result of the build-up and growth of polymerization clusters, the viscosity of the liquid increased [5], which demonstrated a continuous decrease of the resonant frequency. When the fibrin creation ended, a steady state was reached with no further change of the resonant frequency, indicating a constant viscosity was reached. Higher Ca^{2+} concentrations expedited the coagulation process.

With 10 mg of $CaCO_3$ added to 0.5 mL citrated blood, the coagulation cascade completed at approximate six minutes and the creation of fibrin started. The fibrin formation ended and the final plateau phase began at around 14 min.

With 50 mg $CaCO_3$ in 0.5 mL citrated blood, the coagulation time was about two minutes and the fibrin creation ended before five minutes.

Conclusions:

By measuring resonant frequency shift we demonstrate that the MEMS-based C-FBAR can be used to monitor blood's coagulation in real time. The full coagulation time and the start and end of fibrin creation can be determined by monitoring the frequency shift in real time. The observation suggests that the C-FBAR has the potential to become a small-size, light-weight, low cost tool for medics in the field.

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