

# On the response of a blood coagulation sensor

L. THEODORAKIS, E. PAPADOPOULOS, S. KATSARAGAKIS<sup>a</sup>, C. S. KARAGIANNI<sup>b</sup>, E. HRISTOFOROU<sup>c,d\*</sup>

*School of Mechanical Engineering, National Technical University of Athens, Zografou Campus, Athens, 15780, Greece*

<sup>a</sup>*Athens Medical School, University of Athens, Surgical Intensive Care Unit, 1<sup>st</sup> Department of Propaedeutic Surgery, Hippocratio Hospital, 114 Queen Sofia Ave, Athens, 11525, Greece*

<sup>b</sup>*School of Chemical Engineering, National Technical University of Athens, Zografou Campus, Athens, 15780, Greece*

<sup>c</sup>*School of Mining and Metallurgy Engineering, National Technical University of Athens, Zografou Campus, Athens, 15780, Greece*

<sup>d</sup>*Laboratory of Physical Metallurgy, School of Mining and Metallurgy Engineering, National Technical University of Athens, Zografou Campus, Athens 15780, Greece*

---

This paper focuses on results of a low cost magnetoelastic sensor able to measure coagulation time of fresh whole blood samples, using the properties of amorphous ribbons in an inductive arrangement. The results of the proposed sensing technique in terms of accuracy and repeatability are examined, thus proving the sensor's ability to monitor the in vitro viscosity changes that the liquid blood sample undergoes, while it transforms into a fibrin clot. The sensor response is fitted by an exponential function, allowing fast coagulation measurement based on the calculation of the exponential response parameters, thus reducing the time required for blood coagulation measurements.

(Received March 13, 2008; accepted May 5, 2008)

*Keywords:* Sensor, Blood coagulation, Magneto-classic properties

---

## 1. Introduction

Venous thromboembolism is one of the most common diseases related to coagulation disorders. The incidence of the disease exceeds 1 per 1,000 with over 200,000 new cases occurring annually in the United States. Thirty percent of patients die within thirty days of diagnosis, whereas one fifth suffers sudden death due to pulmonary embolism [1]. This disease requires long-term anticoagulation medical treatment.

There are also several other disorders (like atrial fibrillation) that require a similar treatment. Patients that are on anticoagulation therapy need to undergo several blood tests in order to individualize the dosing regiment and obtain optimal pharmacologic effect.

Several methodologies for coagulation measurement have been proposed. These rely on different blood properties and on changes of several of its physical parameters during the coagulation process. Piezoelectric crystal sensors have been used to determine the coagulation time in whole blood, containing anticoagulant [2]. Thromboelastography, a mechanical method for the examination of the blood plasma taken from the whole blood sample after centrifuging, has been developed [3]. Recently, coagulation sensors have been developed based on the magnetostrictive delay line technique [4]. Small devices for self monitoring of patients under oral anticoagulant therapy are already available in the market [5]. They offer quick and reliable coagulation

measurements through estimation of several time values, like ProThrombin time (PT), used for the characterization of blood samples.

In terms of accuracy and safety, the above mentioned methods, combined with the clinical blood tests have several advantages. However, inevitably, disadvantages do exist too, the most prominent of which being the cost of the equipment, the cost of the disposable and the electronics needed for the integration of the devices.

By exploiting the magnetoelastic properties of rapidly quenched, amorphous alloy ribbons (Amorphous Metallic Glasses-AMG), it is possible to evaluate the shift of the viscoelastic properties of blood under coagulation and obtain an easy-to-measure, time varying electric signal from them [6].

This paper presents the theoretical basis, and describes the design and development of a low cost magnetoelastic sensor that measures coagulation through the determination of the time needed for the liquid blood sample to transform into a fibrin clot. Experimental results on the response of the sensor are discussed in detail. Experiments show that the response of the sensor is exponential. Therefore, it will be shown that the time required for the coagulation measurement is reduced to the time required for the determination of the three parameters of the exponential function, within the accepted error limits.

## 2. The sensor

The operation of the developed sensor exploits the viscosity changes a blood sample undergoes during the coagulation process. This process is considered as a cascade of enzymoproteic reactions that can be triggered by several intrinsic as well as extrinsic factors. When a liquid blood sample transforms into a fibrin clot, the *in vitro* coagulation mechanism is terminated. The time between the initiation of the cascade and the total formation of the clot is called coagulation time ( $t_{coag}$ ), and has a characteristic value for different blood samples. Our aim was to build a sensor capable of determining the value of  $t_{coag}$  for different blood samples, allowing us to characterize it.

The major parts of the sensor are illustrated schematically in Fig. 1. As shown in this figure, the sensor is made of a secondary pickup coil, which is inserted in the primary coil. The secondary coil carries a bloodstain on a testing glass sited on an Amorphous Metallic Glass piece (AMG). A function generator supplies ac current to the primary coil. Consequently, the magnetic field generated in the primary coil magnetizes the amorphous magnetostrictive ribbon (AMG) causing it to vibrate. These vibrations become more prominent at a characteristic resonant frequency  $\omega_{res}$ , where the value of  $\omega_{res}$  depends on the physical properties of the AMG. The introduction of a blood sample undergoing coagulation onto the vibrating surface results in magnetic flux changes arising from magnetization changes,  $\Delta M$ . These changes can be detected by the voltage induced in the secondary or pick up coil. In other words, blood coagulates on the AMG and the mechanical resonance of this vibrating blood-coated material changes. Magnetoelastic properties of the material give the sensor the ability to detect the onset and the finalization of these changes, using the proposed coil configuration.

As far as the sensor operation is concerned, the AMG is modeled as a thin plate of thickness  $d$ , length  $L$ , and width  $W$ , see Fig. 2. Due to the thin plate assumption,  $d \ll L$ . The surface area  $A$  is given by  $W * L = A$ . For the needs of the model, width variations,  $\delta W$ , taking place during one vibration period are considered to be insignificant compared to the ones occurring in the longitudinal direction,  $\delta L$ , due to the longitudinal direction of the field applied by the primary coil and the secondary (pick up) coil geometry.

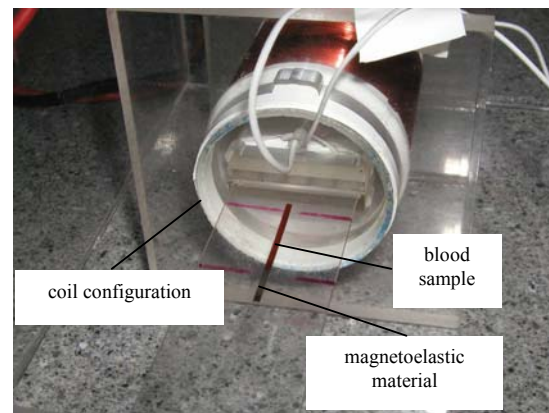
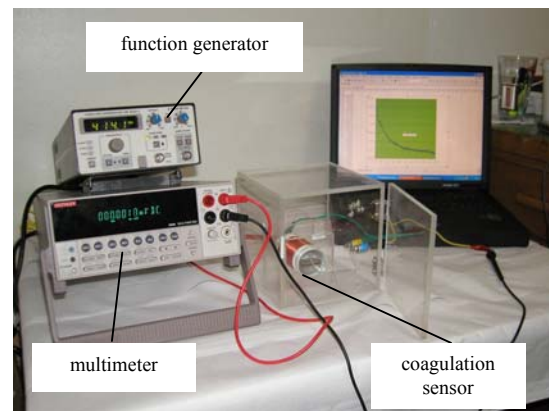
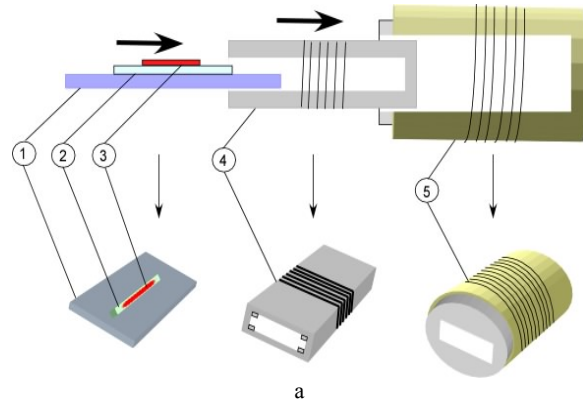


Fig. 1. The blood coagulation sensor. (a) Schematic representation of the sensor with its components (side view). The items illustrated are: 1. Testing glass 2. Amorphous Metallic Glass (AMG) 3. Blood sample 4. Secondary coil 5. Primary coil. (b) The complete laboratory setup and (c) the body of the magnetoelastic sensor.

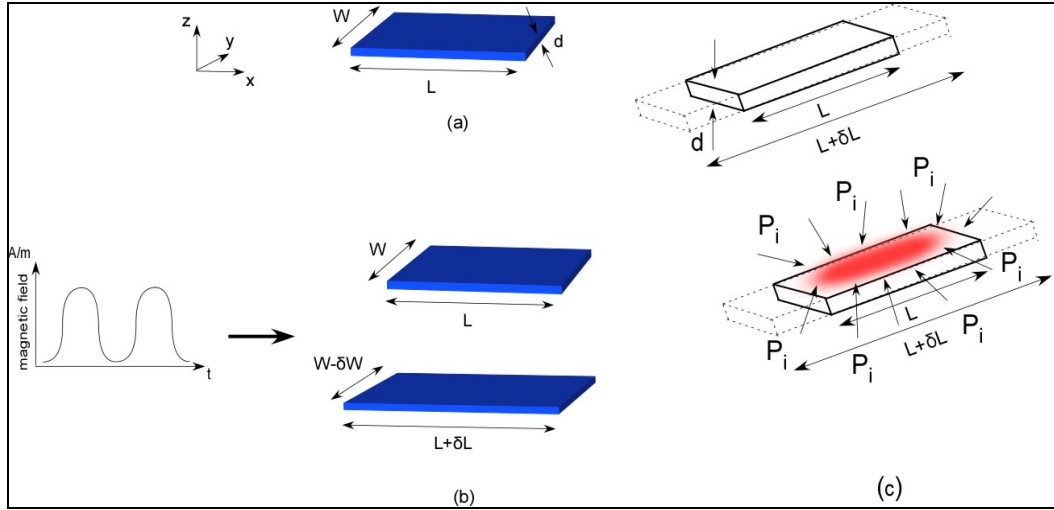


Fig. 2. (a) Model of the AMG (b) Vibration of the AMG due to applied magnetic field (c) Inhibition forces  $P_i$  from the coagulated blood sample undergoing viscosity changes  $\eta(t)$ . The forces in the model shown above are compressive in the case of the plate being extended.

The oscillation of the AMG is maximized when the frequency of the applied field is equal to its resonant frequency,  $\omega_{res}$ .

In the presence of an alternating magnetic field, the magnetoelastic properties of the AMG result in propagating elastic waves, deforming the material. In fact, the material's high magnetoelastic coupling allows efficient conversion between magnetic and elastic energies and vice versa.

The value of the resonant frequency  $\omega_{res}$  is [7]:

$$\omega_{res}^2 = \frac{E}{\rho_s(1-\sigma^2)} \frac{n^2\pi^2}{L^2} \Rightarrow \omega_{res} = \frac{n\pi}{L} \sqrt{\frac{E}{\rho_s(1-\sigma^2)}} \quad (1)$$

where  $E$  stands for the Young's modulus,  $\sigma$  for the Poisson's ratio  $\rho_s$  and  $L$  are the density and the length of the AMG respectively and  $n$  is an integer.

The vibration of the AMG is inhibited by the retraction of the blood sample and the resulting forces  $P_i$  during the formation of the clot, thus continuously reducing the initial resonant frequency of the AMG,  $\omega_{res}$ , into a new time-dependent value  $\omega'_{res}(t)$ . The amplitude of the forces produced is gradually increased due to the respective increase in blood viscosity  $\eta(t)$ , but it is stabilized shortly after the termination of the coagulation cascade.

Concerning the case of fresh whole blood undergoing coagulation, the resonant frequency shift  $\Delta\omega(t)$  is given again by [7]:

$$\Delta\omega(t) = \omega'_{res} - \omega_{res}(t) = -\frac{\sqrt{\pi\omega_{res}\eta(t)\rho_l}}{2\pi\rho_s d} \quad (2)$$

where  $\eta(t)$  is the time-dependent value of blood viscosity,  $\rho_l$  the density of liquid blood and  $d$  the thickness of the AMG.

The frequency effect during the formation of the clot, results in magnetization changes of the AMG, due to the inverse magnetostrictive effect (i.m.e.). These changes result in magnetic flux changes, which are responsible for the read-out signal.

The uniaxial forces applied on any positive magnetostrictive material such as the AMG, result in the reorientation of the magnetic moments of the material. The moments are oriented at an acute angle to the stress axis (Villari Effect). These reorientations also affect the total sum of the individual magnetic moments and therefore the total magnetization  $M_s$  of the AMG as illustrated in Fig. 3. In fact, this is the inverse magnetostrictive effect.

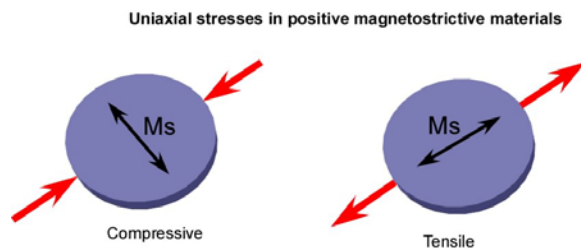


Fig. 3. Magnetization changes based on the Villari Effect.

The thin film of the blood sample under coagulation exerts the inhibition forces  $P_i$  on the magnetoelastic material and causes the above-mentioned reorientations. The direction of the forces is illustrated in Fig. 2, whereas their magnitude is initially  $P_{i0(i=1,2,..,n)}$  (initiation of the cascade), where  $n$  is the number of the individual force components. This magnitude has an initial value which is gradually reduced until it reaches the final value of  $P_{if(i=1,2,..,n)}$  (termination of the cascade). While the coagulation mechanism is still active, a magnitude response  $P_{i(t)}$  for each one of these forces should be considered. Taking into account only the uniaxial force components, their total sum is time-dependent:

$$\sum P = \sum P_{i(t)} \quad (3)$$

The total stress  $\sigma$  applied on the AMG surface  $A$  resulting from the aforementioned forces is:

$$\sigma(t) = \frac{\sum P_{i(t)}}{A} \quad (4)$$

Differentiation of Equation 4 with respect to time yields:

$$\frac{\partial \sigma}{\partial t} = \frac{1}{A} \frac{\partial \sum P_{i(t)}}{\partial t} \quad (5)$$

The magnetization changes resulting from the uniaxial stresses applied on the surface of the AMG during the formation of the clot in the anhysteretic magnetization case [8], can be mathematically described by:

$$\frac{\partial M}{\partial \sigma} = c \left( \frac{\partial M_{anhyst}}{\partial \sigma} - \frac{\partial M_{irr}}{\partial \sigma} \right) + \frac{\sigma}{E\xi} (M_{anhyst} - M_{irr}) \quad (6)$$

where  $M$  is the total magnetization,  $c$ ,  $\xi$  are constant numbers, and  $M_{anhyst}$ , and  $M_{irr}$  the anhysteretic and irreversible components respectively.

Finally, multiplication of Equations (5) and (6) results in the following total magnetization response:

$$\frac{\partial M}{\partial t} = \frac{1}{A} \frac{\partial \sum P_{i(t)}}{\partial t} \left[ c \left( \frac{\partial M_{anhyst}}{\partial \sigma} - \frac{\partial M_{irr}}{\partial \sigma} \right) + \frac{\sigma}{E\xi} (M_{anhyst} - M_{irr}) \right] \quad (7)$$

Magnetization changes described above in Equation (7), account for changes occurring in the time domain during the coagulation process, and they do not concern cyclic changes of the values during vibration periods of the AMG. They are detected by means of a time varying voltage  $V(t)$  across the secondary coil. Fig. 4 illustrates the expected  $V(t)$ .

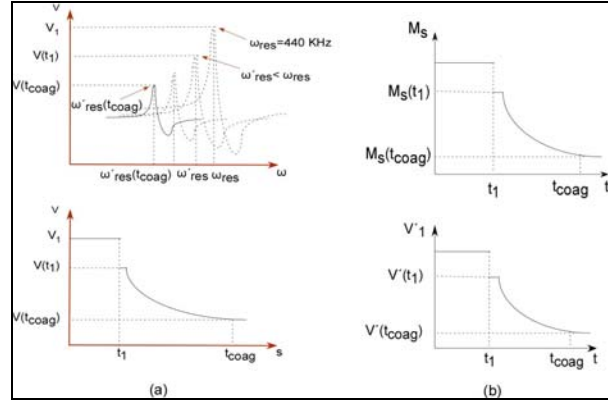


Fig. 4. (a) Frequency and (b) magnetization changes during clot formation.

The amplitude of the signal is initially reduced to the value  $V(t_1)$  immediately after the sample is applied on the surface of the AMG, due to the change in the mechanical boundary. Then, it continues to fall due to the inverse magnetostrictive effect, until the characteristic value  $V(t_{coag})$  is reached, where the blood is fully coagulated.

### 3. Experiments and discussion

The experimental set-up was realized as illustrated in Fig. 1. The transparent enclosure made from magnetic neutral material (plexiglass), was used to give the sensor a more compact form, and to make the sample deposition easier. A function generator was used to supply the double layer, 300-turn primary coil with ac voltage of 10V peak-to-peak. This coil is a 3 cm long cylinder, with a diameter of 4 cm. The pickup coil is a  $2,4 \times 6,6 \times 0,6$  cm rectangular coil, and the winding consists of 400 turns in a single layer. Insulated copper wire of 0.2 mm and 0.05 mm in diameter was used for the primary and the secondary coil respectively.

The material of the AMG is  $\text{Fe}_{63}\text{Co}_{17}\text{Si}_5\text{B}_{15}$ . The final product, after using the melt spinning process, is a strip 2 mm wide and approximately 20  $\mu\text{m}$  thick. The material was then annealed in 200  $^\circ\text{C}$  for  $\frac{1}{2}$  hour on Argon atmosphere to relieve residual stresses and thereby increase magnetic softness. For the needs of the experiments, several strips of 2 cm in length were cut. Further magnetic characterization of the material showed that the coercive field is closed to saturation (750 A/m) and uniformity of the magnetization loop around 10%. Saturation magnetostriction using field 1000 A/m, was  $\lambda_s = +10$  ppm, with its uniformity around 10%.

Anisotropy of the AMG is mainly shape induced, resulting to a longitudinal easy axis. Off-axis orientations of the domains magnetization vectors do exist too. Magnetic domains are preferably oriented along the ribbon axis, indicating this in-plane longitudinal anisotropy. Perpendicular anisotropies are typical of the as-annealed

state of positive magnetostrictive materials, when they are exposed at higher temperatures ( $T = 450\text{ }^{\circ}\text{C}$ ) [9].

The ac voltage frequency was 440 kHz, corresponding to the resonant frequency of the AMG. It is where the frequency of the mechanical vibration and the one of the alternating magnetic field become equal. Maximization of the signal coming from the pickup coil also shows that this is the frequency where the emitted flux changes become more prominent. Therefore, the sensitivity of the sensor is improved.

The only dc bias field present is the earth's magnetic field. Saturation characteristics of the material indicate that the sensor is operating at minor loop. The output of the sensor when blood is not yet loaded on the surface of the material is a sine wave of lower amplitude and the same frequency, compared with the wave supplied to the primary coil. Even when the maximum mechanical stress is applied on the AMG, the output of the sensor remains sinusoidal.

The multimeter measuring the rms values of the read-out signal across the pick-up coil,  $V(t)$ , was connected through a parallel port to a computer, storing individual voltage values every 1 s.

Fig. 5 illustrates the voltage response with respect to time  $t$  for different blood samples taken from a number of donors. All experimental data fit an exponential function of the form:

$$V(t) = ae^{-bt} + V_0 \quad (8)$$

where the coefficients  $a$  and  $b$  define the behavior of the response and consequently the coagulation profile of the blood sample under examination. This can be interpreted as a monotonic decrease in the rate by which liquid blood mass transforms into fully coagulated blood while the

cascade proceeds,  $\frac{\partial m_{coag}}{\partial t} < 0$ , where  $m_{coag}$  is the fully coagulated fraction of the entire mass of the sample and  $0 < t < t_{coag}$ . From Fig. 5 and Equation (8), it can be seen

that  $t_{coag}$  is roughly the time needed for the total retraction of the clot (fully coagulated samples), which corresponds to the moment after which the exponential term is no longer contributing to further reduction of the output signal.

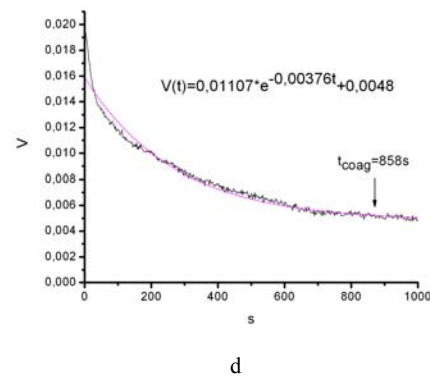
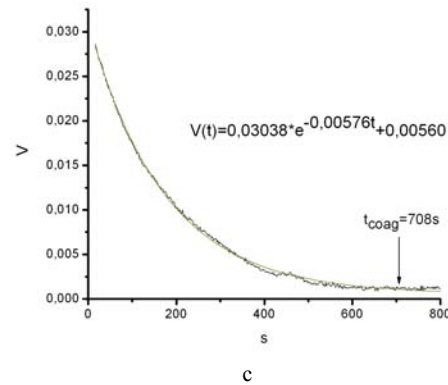
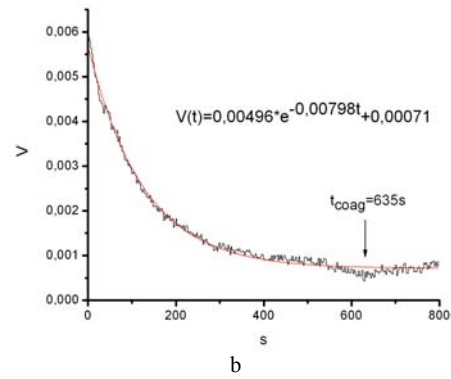
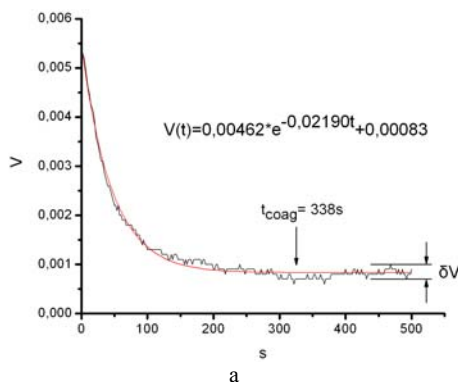


Fig. 5. Magnetoelastic inductive response for blood (a) sample 1:  $t_{coag} = 338s$  (b) sample 2:  $t_{coag} = 635s$  (c) sample 3:  $t_{coag} = 708s$  (d) sample 4:  $t_{coag} = 858s$ .

Practically, the determination of  $t_{coag}$  depends on the fluctuation  $\delta V$  of  $V(t)$  around  $V_0$ , see Fig. 5(a). Such fluctuation is mainly dependent on the sensitivity of the experiment. For a given experimental set-up,  $\delta V$  remains unchanged for all blood measurements. Taking into account that the acceptable fluctuation level of  $V(t)$  is  $\delta V$ , the critical time  $t_{coag}$  required for the coagulation of the blood sample, corresponds to the time after which,

$$\exists t_{coag} : |V(t_{coag}) - V_0| = \delta V \wedge |V(t) - V_0| \leq \delta V \forall t \geq t_{coag}$$

In other words,  $t_{coag}$  is the time at which  $|V(t) - V_0|$  becomes for the first time equal to  $\delta V$ , and after that time, it does not exceed it.

Thus, Equation (8) can be written as:

$$\delta V = ae^{-bt_{coag}} \Rightarrow \ln \frac{\delta V}{a} = -bt_{coag} \Rightarrow t_{coag} = \frac{1}{b} \ln \frac{a}{\delta V} \quad (9)$$

Equation (9) suggests that  $t_{coag}$  can be measured by using the following iterative algorithm: the set of the first three  $V(t)$  measurements is used to determine the coefficients of the fitting curve  $a|_1, b|_1, V_0|_1$ . The fluctuation between experimental and fitting data is  $u|_1$ , shown in Fig. 6(a). Upon acquisition of the fourth voltage measurement, the values of  $a|_1, b|_1, V_0|_1$  are corrected to values  $a|_2, b|_2, V_0|_2$  and  $u|_2$ , see Figure 6(b). The same procedure with consequent  $n$  measurements and estimations for the parameters is continued until  $V(t_n) - V_0 \leq \delta V$ , satisfying the requirement mentioned above. These values for parameters  $a$ ,  $b$  and  $V_0$  occurring immediately after the last set of measurements, are the ones used for the blood sample characterization.

From Fig. 5, it can be seen that  $\delta V \approx 200 \mu V$ . Measurement uncertainty and  $\delta V$  are strongly related, whereas proper shielding of the apparatus and signal filtering will achieve  $\delta V$  in the order of several  $\mu V$ . Then,

$$\ln \frac{a}{\delta V} \approx \ln(10^3) \cong 7$$

with sensitivity of the order of 0.1%. For  $\delta V$  of the order of nV, then,

$$\ln \frac{a}{\delta V} \approx \ln(10^6) \cong 14$$

presenting a sensitivity better than 1 ppm. Therefore, a commonly agreed level of measurement confidence may

result in the dependence of  $t_{coag}$  only on  $\frac{1}{b}$ . Coagulation

time  $t_{coag}$  is not so much dependent on the values of variable  $a$ , see Fig. 7(a), not affecting the output of the sensor in the time domain. On the other hand,  $b$  is strongly related to  $t_{coag}$ : as it can be seen in Fig. 7(b),

change in the amplitude of the coefficient  $b$  results in a change of  $t_{coag}$ . Taking into account that the coefficient  $a$  is measured in mV and  $\delta V$  is of the order of 0.1  $\mu V$ , when provided by a very precise measurement, it can be concluded that

$$\ln \frac{a}{\delta V} \approx 10$$

Thus, the time required for a blood coagulation measurement can be reduced down to the time required for a few sets of three voltage measurements at the ends of the secondary coil.

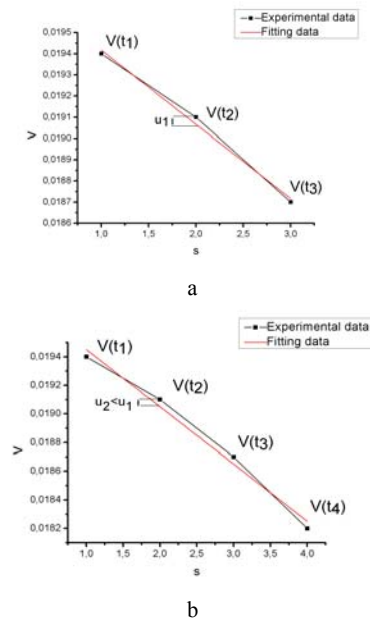


Fig. 6. (a) First set of three measurements for the initial estimation of the exponential parameters. (b) Acquiring the fourth experimental value, a new fitting curve is calculated, providing with corrected parameters. Data values have been taken from experiment shown in Fig. 5(d).

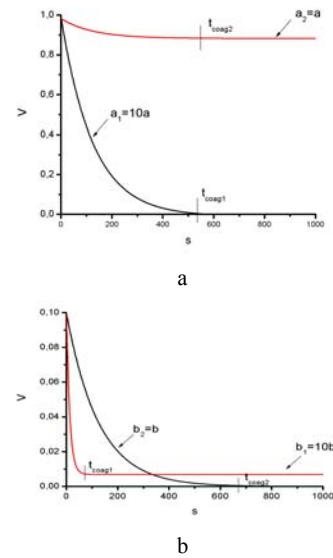


Fig. 7. (a) Coefficient  $a$  dependence on the estimation of coagulation time. Two different  $a$  values ( $a_1 = 10a_2$ ), with the same value of coefficient  $b$  result in a non-changing coagulation time, ( $t_{coag1} = t_{coag2}$ ) (b) Dependence of coefficient  $b$  on the estimation of coagulation time. Two different  $b$  values ( $b_1 = 10b_2$ ) result in different coagulation time estimations ( $t_{coag1} \neq t_{coag2}$ ), although coefficients  $a$  are equal.

From the metrological point of view, the value of  $\ln \frac{a}{\delta V}$  is clearly dependent on the calibration of the new sensor with respect to the instruments currently used for blood coagulation measurements. Considering such instruments as the primary standards and supposing that the blood coagulation time reference is  $t_{coag} |_R$ , then the value of  $\ln \frac{a}{\delta V}$  required for the near true value of the coagulation time  $t_{coag} |_{nv}$ , by using the presented sensor is given by:

$$\ln \frac{a}{\delta V} = b \cdot t_{coag} |_R = C \quad (10)$$

Such calibration procedure requires a number of blood tests to be certified. Therefore,  $t_{coag} |_{nv}$  is given by:

$$t_{coag} |_{nv} = \frac{C}{b} \quad (11)$$

Such an analysis could be correlated with a proper clinical protocol, i.e. calculation of the corresponding Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and Bleeding Time (BT) of the samples, based on the measurement of  $t_{coag}$  and the total coagulation profile provided by the sensor.

Abnormalities in the coagulation cascade of a blood sample will result in a relatively high or small  $b$  value compared with the respective value of a healthy sample, taken as reference. The difference between these two values can provide substantial information, concerning the type (hypercoagulation or hypocoagulation) and the severity of the abnormality. In fact, the referenced healthy sample may vary from person to person.

Table 1 illustrates values for coefficients  $a$  and  $b$ , as well as  $t_{coag}$  for each of the four samples, while dependence of  $t_{coag}$  on  $b$  is shown in Fig. 8.

Table 1. Calculated values of parameters  $a, b$  and of the estimated coagulation time  $t_{coag}$  corresponding to the data of Fig. 5.

Sample	$a$ ( $\times 10^{-3}$ ) (V)	$b$ ( $\times 10^{-3}$ ) (1/s)	$t_{coag}$ (s)
1	4.62	21.90	338
2	4.96	7.98	635
3	30.38	5.76	708
4	11.07	3.76	858

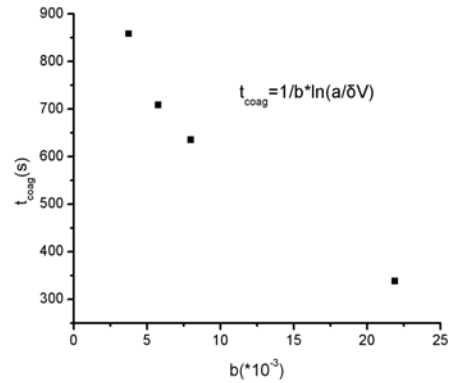


Fig. 8. Dependence of coefficient  $b$  on the estimated coagulation time  $t_{coag}$ . It can be seen that  $t_{coag} \approx \frac{1}{b}$ .

#### 4. Conclusions

The blood coagulation sensor showed acceptable sensitivity and accuracy in delivering the coagulation profiles for different samples. The profiles from the experimental data shown in Fig. 5 revealed satisfying agreement of the measured voltage values with the expected exponential responses.

The results are reproducible and can be used not only for the determination of the coagulation time, but also for future statistical analysis, in order to calibrate the sensor by using the accepted instruments for prothrombin time, activated partial thromboplastin time and sample bleeding time.

Advantages of the proposed sensor are related to the minimal volume of blood required, namely 2  $\mu$ l for every experiment.

The simplicity of the proposed setup combined with the low cost of the electronics needed are also vital, considering future industrial prospects of a small apparatus based on the technique. Under this view, small power consumption should also be noted. The magnetoelastic material is rather inexpensive, taking also into account that it could be cleaned up and used for more than one experiment.

#### References

- [1] John A. Heit, Marc D. Silverstein, David N. Mohr, Tanya M. Patterson, Christine M. Lohse, W. Michael O. Fallon, L. Joseph Melton III, The Epidemiology of Venous Thromboembolism in the Community, *Thrombosis and Haemostasis*, **86**, 452-463 (2001).
- [2] Tzong-Jih Cheng, Hsien-Chang Chang, Tsun-Mei Lin, *Biosensors & Bioelectronics* **13**, 147-156 (1998).
- [3] Connie L. Davis, Wayne L. Chandler, *J. Am. Soc. Nephrol.* **6**, 1250-1255 (1995).
- [4] E. Malariysi, L. Zoumpoulakis, J. Simitzis, P. Vassiliou, E. Hristoforou, *Journal of Magnetism and*

- Magnetic Materials **299**, 41-52 (2006).
- [5] [www.coaguchek.com](http://www.coaguchek.com)
- [6] Libby G. Puckett, Gary Barrett, Dimitris Kouzoudis, Craig Grimes, Leonidas G. Bachas, Biosensors and Bioelectronics **18**, 675-681 (2003).
- [7] Craig A. Grimes, Casey S. Mungle, Kefeng Zeng, Mahaveer K. Jain, William R. Dreschel, Maggie Paulose, Keat G. Ong, Wireless Magnetoelastic Sensors: A Critical Review, Sensors **2**(2), 294-313 (2002).
- [8] L. Kraus, F. Fendrych, P. Svec, J. Bydzovsky, M. Kollar, J. Optoelectron. Adv. Mater. **4**, 237-243 (2002).
- [9] F. Brinza, N. Sulitanu, J. Optoelectron. Adv. Mater. **7**, 1547-1551 (2005).

---

\*Corresponding author: [eh@metal.ntua.gr](mailto:eh@metal.ntua.gr)