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Superparamagnetic nanoparticle-based viscosity test

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Hyperviscosity syndrome is triggered by high blood viscosity in the human body. This syndrome can result in retinopathy, vertigo, coma, and other unanticipated complications. Serum viscosity is one of the important factors affecting whole blood viscosity, which is regarded as an indicator of general health. In this letter, we propose and demonstrate a Brownian relaxation-based mixing frequency method to test human serum viscosity. This method uses excitatory and detection coils and Brownian relaxation-dominated superparamagnetic nanoparticles, which are sensitive to variables of the liquid environment such as viscosity and temperature. We collect the harmonic signals produced by magnetic nanoparticles and estimate the viscosity of unknown solutions by comparison to the calibration curves. An *in vitro* human serum viscosity test is performed in less than 1.5 min. [http://dx.doi.org/10.1063/1.4928057]

Human whole blood viscosity (WBV) is regarded as an indicator of general health. Several factors can affect WBV such as red blood cell aggregation, deformability, hematocrit level, protein concentration, and plasma viscosity. Hyperviscosity in blood occurs in several diseases such as cardiovascular diseases, leukemia, and hypergammaglobulinemia. Researchers have proposed a MicroElectroMechanical System (MEMS) for blood plasma and serum viscosity measurement.[1] Cakmak *et al.*[2] reported that their MEMS cantilever sensor could detect a viscosity range of 0.8–14.1 cp, which could be used for a human serum viscosity *in vitro* test. However, it is of great importance to find a cheaper and simpler way to test human blood/serum viscosities.

Brownian relaxation of superparamagnetic nanoparticles has been proposed and investigated for a variety of biosensing applications.[3–11] Brownian relaxation-dominated superparamagnetic nanoparticles are sensitive to characteristics of the suspension environment such as temperature,[7,8] hydrodynamic volume of magnetic nanoparticle (MNP),[3,6] and viscosity.[6] Rauwerdink and Weaver[12] reported that by applying one alternating magnetic field on MNPs in water and glycerol mixtures, they are able to distinguish viscosities ranging from 0.96 to 9.81 cp by monitoring harmonic angles. However, this harmonic angle based viscosity testing method has low sensitivity for viscosities higher than 3 cp. In this letter, we propose and demonstrate a Brownian relaxation-based human serum viscosity test using a mixing frequency method with superparamagnetic nanoparticles and a search coil detection system. We are able to distinguish viscosities from 0.99 to over 1000 cp by using the voltage drop percentage as a monitor.

A high frequency sinusoidal magnetic field and a low frequency sinusoidal magnetic field are applied to MNP suspensions simultaneously[4–6,10,11,13,14] in a search coil detection system. The high frequency magnetic field produces harmonic signals by mixing frequency with the low frequency field. This high frequency magnetic field is also responsible for modulating the harmonics in the high frequency region, which could significantly reduce the pink noise (1/f noise).[13] The low frequency magnetic field drives superparamagnetic nanoparticles into the nonlinear region as shown in Fig. 1.

In a fluid system, for non-spherical nanoparticles under non-equilibrium condition, such as an alternating magnetic field,[15] the orientation of nanoparticles is related to the rotational and translational relaxations.[16] In this letter, we use spherical nanoparticles, for which the orientation is only related to the translation relaxation. There exist two relaxation mechanisms for spherical MNPs under alternating magnetic fields: Brownian relaxation and Néel relaxation. Brownian relaxation is the physical rotation of magnetic nanoparticles in the solution. Néel relaxation is the magnetic dipole flipping inside a stationary particle.[4] Both relaxations contribute to the effective relaxation time of MNPs by

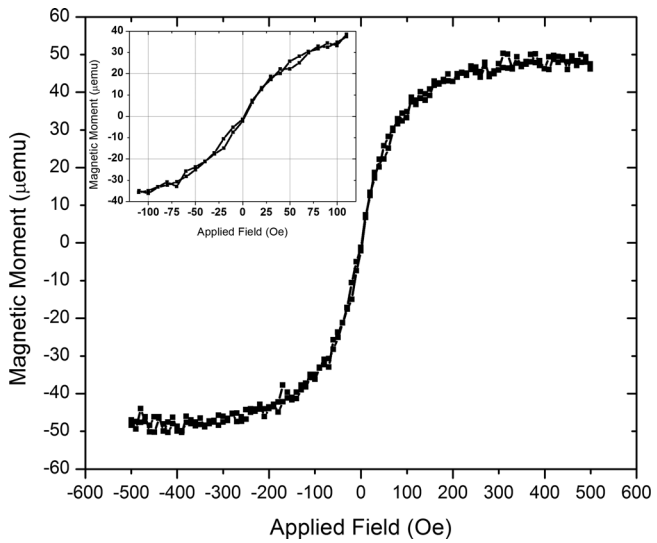

FIG. 1. Magnetization curve of iron oxide nanoparticle suspensions (SHP-25 from Ocean NanoTech) at 20 °C measured by a Vibrating Sample Magnetometer (VSM).

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$$\tau = \frac{\tau_B \times \tau_N}{\tau_B + \tau_N}. \quad (1)$$

SHP-series iron oxide magnetic nanoparticles produced by Ocean NanoTech are covered with 2 nm of oleic acid and 2 nm of a polymer coating. For this MNP solution, we assumed that the viscosity was 1 cp (in water), the uniaxial anisotropy constant was $K_u = 90\,000\,\text{ergs/cm}^3$, and T = 293 K. Simulated on Matlab, the Brownian, Néel, and effective relaxation time are dependent on the core size of MNPs plotted in Fig. 2.

For a core size larger than 20 nm, the effective relaxation time is determined by Brownian relaxation time

$$\tau = \tau_B = \frac{3\eta V_H}{k_B T}, \quad (2)$$

where η is the viscosity of MNP solution, V_H is the hydrodynamic volume of MNP, k_B is the Boltzmann constant, and T is the temperature of MNP solutions in Kelvins.

We used SHP-25 (iron oxide magnetic nanoparticles covered with carboxylic acid group, with an average core size of 25 nm) purchased from Ocean NanoTech. According to Fig. 2, the behavior of these MNPs is dominated by Brownian relaxation.

The MNP suspension is exposed to a mixture of high frequency and low frequency sinusoidal magnetic fields expressed as $H = A_L \cos(2\pi f_L t) + A_H \cos(2\pi f_H t)$. Magnetization of MNPs can be described by a static Langevin function[4,13]

$$\frac{M}{M_s} = L\left(\frac{m_0\mu_0 H}{k_B T}\right), \quad (3)$$

where M_s is the theoretical saturation magnetization of iron oxide nanoparticles, m_0 is the magnetic moment of each MNP, μ_0 is the vacuum permeability, and M is the magnetization of MNPs at a specific applied magnetic field H. Taylor expansion near zero magnetic field gives the 3rd $(f_H \pm 2f_L)$ and 5th $(f_H \pm 4f_L)$ harmonics[4,11,17]

$$\begin{aligned}\frac{M}{M_s} &= L\left(\frac{m_0\mu_0 H}{k_B T}\right) \\ &= \frac{1}{3}\left(\frac{m_0\mu_0}{k_B T}\right)H - \frac{1}{45}\left(\frac{m_0\mu_0}{k_B T}\right)^3 H^3 + \frac{2}{945}\left(\frac{m_0\mu_0}{k_B T}\right)^5 H^5 + \cdots \\ &= \cdots + \left[-\frac{1}{60}A_H A_L^2\left(\frac{m_0\mu_0}{k_B T}\right)^3 + \frac{1}{252}A_H^3 A_L^2\left(\frac{m_0\mu_0}{k_B T}\right)^5\right. \\ &\quad \left. + \frac{1}{378}A_H A_L^4\left(\frac{m_0\mu_0}{k_B T}\right)^5 + \cdots\right] \cdot \cos[2\pi(f_H \pm 2f_L)t] \\ &\quad + \left[\frac{1}{1512}A_H A_L^4\left(\frac{m_0\mu_0}{k_B T}\right)^5 + \cdots\right] \cdot \cos[2\pi(f_H \pm 4f_L)t] + \cdots\end{aligned} \quad (4)$$

The induced voltage V collected by a detection coil (Fig. 3) is

$$V \propto \frac{dM_0}{dt} \times V_M = \frac{dM}{dt} \times V_M \times \cos\phi \propto \omega \times M \times \cos\phi, \quad (5)$$

where the phase lag $\phi = \arctan(\omega\tau)$ is between the magnetization of MNP and the applied field, the magnetization amplitude of the MNP is $M_0 = M \times \cos\phi$, V_M is the magnetic core volume of MNP, and ω is the angular frequency.

The induced voltage V is a function of relaxation time τ (Eq. (2)). So we can use the induced voltage to distinguish liquids with different viscosities. First, we plot standard graphs corresponding to the specific type and volume of MNP samples according to experimental results. Signals from MNPs in glycerol and deionized (DI) water mixtures of different viscosities are collected and plotted on standard graphs. We can then test any liquid samples and collect the voltage signals. Finally, the collected data are inserted into the aforementioned standard graphs and the viscosity for the tested samples can be estimated.

In this experiment, high frequency and low frequency sinusoidal magnetic fields are produced by a Digital Acquisition card (DAQ, NI USB-6289, 18-Bit, 625 kS/s), which is controlled by the Labview software. Two instrument amplifiers amplify both sinusoidal signals. The low frequency excitatory coil with 1000 windings and an average diameter of 30 mm generates alternating magnetic field with

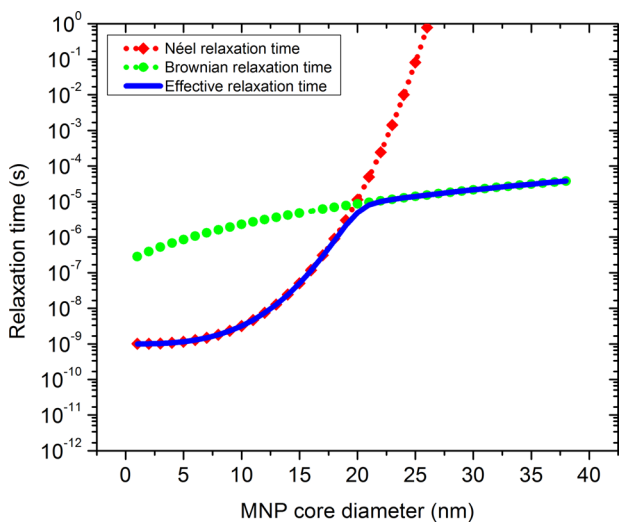

FIG. 2. Néel, Brownian, and total effective relaxation time as function of MNP core diameter, T = 293 K. Viscosity of the MNP solution is 1 cp.

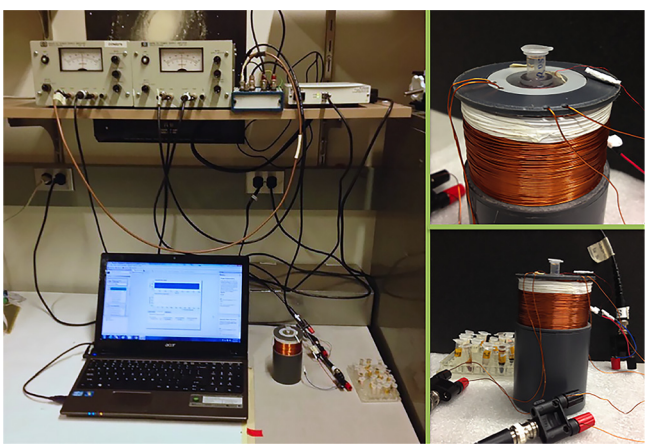

FIG. 3. Detection-coil based MNPs detection system experimental setup.

TABLE I. Viscosities of DI water and glycerol mixtures at 20 °C.

Mixture	Viscosity (cp)	Mixture	Viscosity (cp)
DI water	0.99	G2-1 W	22.99
G1-4 W	1.95	G3-1 W	44.78
G1-3 W	2.29	G4-1 W	136.58
G1-2 W	3.36	Glycerol	1087.43
G1-1 W	7.94		

TABLE II. Percentage voltage drop of the 3rd harmonic after adding mixtures with different viscosities at 20 °C.

Viscosity (cp)	$\Delta A\%$	Viscosity (cp)	$\Delta A\%$
0.99	18	22.99	61
1.95	38	44.78	63
2.29	42	136.58	70
3.36	50	1087.43	80
7.94	57		

amplitude of 100 Oe. The high frequency excitatory coil with 1000 windings and an average diameter of 20 mm generates alternating magnetic field with amplitude of 10 Oe. The copper wires for excitatory coils have diameter of 0.57 mm. A pair of differentially wound detection coils (800 clock-wise windings and 800 counter-clock-wise windings with an average diameter of 12 mm and a wire diameter of 0.14 mm) collects both voltage amplitude and phase signals generated by the MNPs. The overall length of the coil is 40 mm.

We mixed glycerol (purchased from Sigma-Aldrich, concentration ≥99%, density 1.25 g/ml) and DI water in different volume ratios (Table I). G1–4W means volume ratio of glycerol to DI water is 1 to 4. The rest are named in the same manner. These mixtures were sonicated for 2 h before being mixed evenly. Viscosities were tested by the AR-G2 rheometer (purchased from TA instruments) as standard values.

We prepared 50 μl SHP-25 iron oxide MNP solution and added 200 μl of glycerol-DI water mixture into the MNP solution. Signals were collected in real time before and after adding the mixtures so as to cancel out the noise induced by the unbalanced detection coil, white noise, and 1/f noise. We collected the noise floor for 20 s, after which 50 μl of MNP solution was added into the detection coil. The signal was collected for 30–50 s. Then 200 μl of mixed liquid was added to the MNP solution and the signal was collected for another 30–50 s. Three separate experiments were carried out for each mixture. The median was chosen from three tests. A high frequency field of 15 kHz and amplitude of 10 Oe accompanied with a low frequency field of 50 Hz and amplitude of 100 Oe were applied in this experiment.

By adding DI water and glycerol mixtures, MNPs experience a higher viscosity environment and the effective relaxation time τ increases, thus the phase lag increases, magnetization decreases, and the voltage signal decreased as a result.

As clearly shown in Fig. 4, the voltage signal of the 3rd harmonic drops to a different extent for different mixtures. Here, we define a new term as voltage change percentage $\Delta A\% = -\frac{A'-A}{A}$, where A' is the voltage of the 3rd harmonic after adding mixtures and A is the voltage before adding mixtures (Table II).

We plotted the voltage change percentage over viscosity in Fig. 5. Note that the corresponding viscosity on the x-axis is the viscosity of the glycerol-DI water mixture we added rather than the viscosity of the MNP solution. From Fig. 5, we can see that this method is more sensitive in viscosities ranging from 1 cp to 8 cp. The sensitivity is around 5.6% per cp. In contrast, the sensitivity is around 0.02% per cp for viscosities ranging from 8 cp to 1000 cp.

We noticed an 18% voltage drop when adding 200 μl of DI water into 50 μl of MNP suspension, despite the fact that the solution maintains the same viscosity. This is because, before we add the DI water solution, the MNPs mainly stay near the center of search coils. The magnetic field is at its maximum and keeps constant in the center of coil. After adding DI water, the volume increases to 250 μl and a small portion of MNPs reaches the edge of coil, where the magnetic

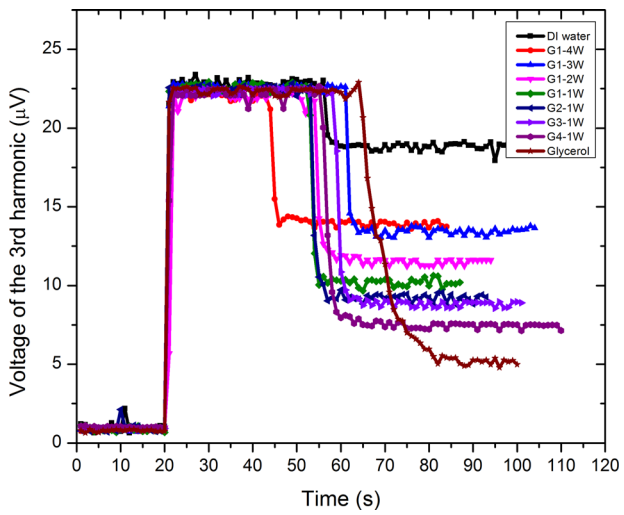

FIG. 4. The real-time voltage signal of the 3rd harmonic for MNPs in nine mixtures at 20 °C.

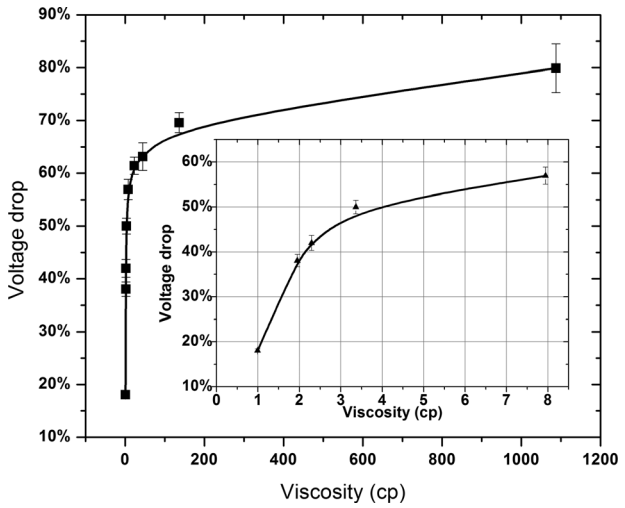

FIG. 5. Voltage drop in percentage vs. viscosity for MNPs in nine mixtures at 20 °C.

TABLE III. Percentage voltage drop on the male human serum type AB at 20 °C and 40 °C.

Voltage drop percentage	20 °C	40 °C
15 kHz	36.9%	41.4%
Estimated viscosity (cp)	1.8	2.2

field is smaller than at the center, and will therefore contribute less to the harmonic voltage.

A serum sample (male human serum type AB, purchased from Sigma-Aldrich) was tested. This product consists of hemoglobin $\leq$20 mg/dl and endotoxin $\leq$10 EU/ml. 50 μl of MNP suspensions and 200 μl of serum were heated in a 40 °C water bath for 30 min before being tested. Room temperature was 20 °C (Table III).

By inserting the voltage change percentage into the standard graph (Fig. 5), the viscosity of the male human serum type AB was estimated to be 2.2 cp at 40 °C and 1.8 cp at 20 °C. The standard viscosity value of male human serum type AB at 20 °C is 1.74 cp and 1.35 cp at 40 °C, as tested by the AR-G2 rheometer. The experimental serum viscosity tested from the search coil system agrees well at 20 °C; however, it failed to estimate the viscosity at 40 °C. This is attributed to the temperature and viscosity effects, which may affect harmonic signals induced from MNPs. To estimate the human serum viscosity at 40 °C, one may need to build up another standard chart like Fig. 5 with all the data points collected from mixtures at 40 °C.

In this letter, we proposed and demonstrated the feasibility of using a search coil detection system and MNPs to test human serum viscosity in real-time. Glycerol and DI water mixtures were used to simulate *in vitro* viscosity test processes. It was found that the measurement of the voltage change percentage of the 3rd harmonic works well for the *in vitro* viscosity test. We tested and plotted the standard graphs that could be used to estimate the viscosity of any unknown liquids. We also tested the viscosity of a male human serum type AB by inserting the collected data into standard graphs. The estimated viscosity of this serum is 2.2 cp at 40 °C and 1.8 cp at 20 °C, compared to the real value of 1.35 cp and 1.74 cp, respectively.

Compared to the MEMS method, our Brownian relaxation-based viscosity test method is less expensive and the setup is very simple. It needs only three coils (a high frequency coil, a low frequency coil, and a detection coil) and a DAQ as the main part of the system. Moreover, the testing process takes less than 1.5 min. We can then insert the data into standard graphs to estimate the viscosity.

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