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A magnetic immunization method based on magnetic nanomarkers under the DC bias fields

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Abstract

This paper investigates the effect of the SNR of the magnetic response harmonic signal on the sensitivity of biomolecular detection. A method is proposed for measuring the 2nd and 3rd harmonics of magnetic nanotags under a DC bias field, avoiding the influence of antimagnetic and paramagnetic substances around the magnetic nanotags, as well as the background magnetic field, on the 1st harmonic signal. Specific streptavidin-modified magnetic nanoparticles were used as measurement objects, and their binding to biotinylated polystyrene microspheres was measured by a prepared detection device to simulate the detection of specific biomolecules. Using the ratio of 2nd to 3rd harmonics, the limit of detection for polystyrene microspheres at least 40 amol in 100 uL (0.4 pM) was finally determined.

I. Introduction

The use of magnetic instead of optical immunolabelling of biomolecules such as viruses extends the lower limit of detection of immunoassays by avoiding optical background interference. Magnetic nanoparticles (MNP) are widely used in biosensing, targeted drug delivery, magnetic thermotherapy, immunoassays, etc. [1]. Superparamagnetic MNPs generate odd harmonics due to their non-linear response to alternating magnetic fields. The binding of surface-specific modified magnetic nanotags to the target changes the hydrodynamic size of the particles and thus affects the effective relaxation time. Rapid immunoassay based on magnetic nanotags can be achieved by measuring the attenuation of the effective relaxation time to each harmonic. The detection of a variety of biological targets such as HIN1 and novel coronaviruses has been achieved in seconds by magnetic nanoparticle spectroscopy (MPS) [2][3].

By reducing the concentration of magnetic nanomarkers the percentage of bound particles in the sample can be increased and thus lower concentrations of biomolecules can be measured [4]. However, as the concentration is reduced, the effect of the magnetic nanomarker's resistance to surrounding antimagnetic and paramagnetic materials and background magnetic field fluctuations will not be negligible. Moreover, the SNR of the system for magnetic signal measurement is limited by the fact that the concentration of the detected target still cannot exceed the pM magnitude. This paper presents a method for achieving 0.4 pM targets by measuring the ratio of the 2nd to 3rd harmonics ($R_{2nd/3rd}$) of magnetic nanomarkers under a DC bias field.

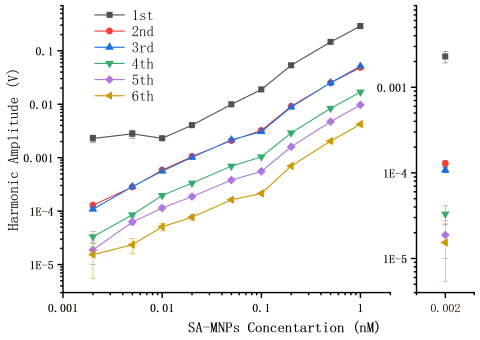

Figure 1: Measurement results of the 1rd-6th harmonics amplitudes vs. SA-MNP concentration curves.

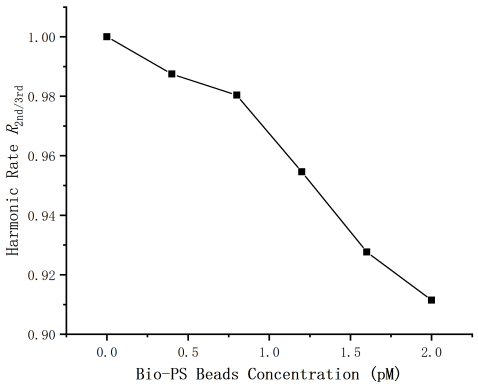

Figure 2: The ratio of the 2nd to 3rd harmonics vs. Bio-PS Beads concentration curves.

II. Material and methods

The magnetic nanomarkers chosen for this experiment were streptavidin-modified magnetic nanoparticles (SA-MNP), whose binding to biotinylated polystyrene microspheres (Bio-PS Beads) in suspension was measured to simulate biomolecular detection. SA-MNPs suspended in a matrix carrier solution exhibit relaxation, with effective relaxation times dominated by Brownian relaxation and varying with particle size [5], as in (1).

$$\tau_B = \frac{\pi \eta D_H^3}{2 k_B T}. \tag{1}$$

Where η is the viscosity coefficient of the base-loaded liquid and D_H is the hydrodynamic particle size of the magnetic nanotags. Mixing SA-MNPs with Bio-PS Beads increases the relaxation time as their specific binding causes aggregation of the monodisperse SA-MNPs leading to an increase in D_H. In the same concentration of SA-MNPs, the corresponding relaxation time increases the more the amount of Bio-PS Beads is added, causing a decay in the harmonic amplitude. By measuring the harmonic amplitude ratio at a specific frequency of the excitation magnetic field, factors such as the concentration and mass of SA-MNPs that are not relevant to the concentration of the biological target can be excluded, enabling magnetic immunoassay of biomolecules [6].

Considering the influence of the SNR of each harmonic on the sensitivity of biological target detection, it is proposed to detect the 2nd and 3rd harmonics with DC bias. Due to the DC bias field, the odd harmonics of the magnetisation response gradually decay and simultaneously produce even harmonics, with the 2nd harmonic having the largest SNR [7][8]. In addition, the 2nd harmonic amplitude is the least decayed by relaxation except for the 1st harmonic. In this paper, the sensitivity of biomolecule detection is enhanced by selecting a specific DC bias field to generate the appropriate 2nd and 3rd harmonics.

III. Results and discussion

This paper uses the developed MPS detection device to detect magnetic nanotags at different concentration gradients given a specific DC bias field, as shown in Fig. 1. It can be seen that as the concentration decreases, the 1st harmonic is severely disturbed by the background magnetic field at lower concentrations. In addition, the SNR of the 2nd and 3rd harmonics is the largest of all harmonics at the lowest concentrations with a total measurement time of about 1 s.

The SA-MNPs were divided into six groups and different concentrations of Bio-PS Beads were added. 100 uL of volume and a certain molar concentration of 50 pM of SA-MNPs was ensured. The $R_{2nd/3rd}$ of the Bio-PS Beads normalised to the different concentrations is shown in Fig. 2. It can be seen that as the concentration interval of the added polystyrene microspheres gradually increases at 0.4 pM, there is a clear trend of decay in $R_{2nd/3rd}$ and the concentration interval ratio of 0.4 pM can be clearly distinguished. Therefore, we believe that the limit of detection for biological targets can reach at least 0.4 pM by the ratio of 2nd to 3rd harmonics. Errors may be caused by the instability of the system or by the concentration of the sample.

IV. Conclusions

The method proposed in this paper for the detection of $R_{2nd/3rd}$ of magnetic markers using the mentioned MNP eventually achieves a lower limit of detection of 0.4 pM for Bio-PS Beads, promising a real-time, ultra-sensitive detection of biomolecules. Magnetic nanoparticles with greater saturation magnetisation intensity can provide higher sensitivity for the method proposed in this paper if the particle size is the same.

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Author's statement

Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

[1] A. P. Astalan, F. Ahrentorp, C. Johansson, K. Larsson, and A. Krozer, Biomolecular reactions studied using changes in Brownian rotation dynamics of magnetic particles, Biosens. Bioelectron., vol. 19, no. 8, pp. 945–951, 2004, doi: 10.1016/j.bios.2003.09.005.

[2] K. Wu et al., Magnetic Particle Spectroscopy for Detection of Influenza A Virus Subtype H1N1, ACS Appl. Mater. Interfaces, vol. 12, no. 12, pp. 13686–13697, 2020, doi: 10.1021/acsami.0c00815.

[3] J. Zhong, E. L. Rösch, T. Viereck, M. Schilling, and F. Ludwig, Toward Rapid and Sensitive Detection of SARS-CoV-2 with Functionalized Magnetic Nanoparticles, ACS Sensors, vol. 6, no. 3, pp. 976–984, 2021, doi: 10.1021/acssensors.0c02160.

[4] J. Zhong, K. J. Janssen, S. Draack, T. Viereck, M. Schilling, and F. Ludwig, Dependence of biomolecule detection on magnetic nanoparticle concentration, J. Magn. Magn. Mater., vol. 517, no. August 2020, p. 167408, 2021, doi: 10.1016/j.jmmm.2020.167408.

[5] P. Debye, Polar Molecules, New York: Chemical catalog company,1929:88

[6] K. Wu, J. Liu, D. Su, R. Saha, and J. P. Wang, Magnetic Nanoparticle Relaxation Dynamics-Based Magnetic Particle Spectroscopy for Rapid and Wash-Free Molecular Sensing, ACS Appl. Mater. Interfaces, vol. 11, no. 26, pp. 22979–22986, 2019,

[7] T. Yoshida, K. Ogawa, T. Tsubaki, N. B. Othman, and K. Enpuku, Detection of magnetic nanoparticles using the second-harmonic signal, IEEE Trans. Magn., vol. 47, no. 10, pp. 2863–2866, 2011,

[8] Y. Zhang, H. Murata, Y. Hatsukade, and S. Tanaka, Superparamagnetic nanoparticle detection using second harmonic of magnetization response, Rev. Sci. Instrum., vol. 84, no. 9, 2013.

