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Magnetic particle spectroscopy based biosensing platform for nucleic acids detection

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Abstract

Reliable nucleic acid assays are essential for modern laboratory diagnostics. Due to the complex and numerous steps involved, polymerase chain reaction, the current gold standard in nucleic acid detection, is not suitable for point-of-care (POC) diagnostics. Assays based on magnetic nanoparticles (MNPs) and magnetic particle spectroscopy (MPS) are wash- and enzyme-free and combine signal amplification with a benchtop device, thus fulfilling all the requirements to close this gap. Our nucleic acids biosensing platform enables the specific detection of DNA in concentrations of less than 27 pM as well as the enzyme-free detection of viral RNA in combination with a highly sensitive MPS device with cost-effective technology.

I. Introduction

Fast and reliable detection methods of pathogens are essential in laboratory diagnostics. Polymerase chain reaction (PCR) as a leading technique for nucleic acid detection requires well-equipped laboratories and sophisticated equipment as well as enzymatic reactions making this method unsuitable for POC diagnostics in everyday clinical practice. Biosensing platforms based on MNPs promise to advance towards POC testing. The platform we developed to address these issues utilizes magnetic assays that are wash-free and enable enzyme-free signal amplification [1]. The samples are evaluated using a custom-built MPS device, which combines high sensitivity with cost-effective technology [2].

II. Material and methods

The magnetic relaxation dynamics of MNPs are very sensitive to the molecular interaction between the MNPs and the nucleic acids. Target nucleic acids in a sample can be detected by measuring its magnetization response. Our declustering-based assays offer higher specificity than clustering-based assays due to their nonspecific clustering, caused by e.g. electrostatic interactions. The readout of the assays is performed by MPS. MPS is a method to evaluate the dynamic properties of MNPs, with the harmonic ratio of the magnitudes from the fifth to the third harmonic commonly being used to detect binding events, as it is independent of the MNP concentration. Using the harmonics also eliminates the para- or diamagnetic sample background allowing the measurement signal to be specifically attributed to the MNPs.

II.I. Magnetic signal Amplification Circuit

The basic principle of our magnetic signal amplification circuit (MAC) is illustrated in Fig. 1.

Responsive magnetic clusters (RMCs) constructed from Brownian dominated MNPs, are disassembled via toehold-mediated strand displacement (TMSD) reac-

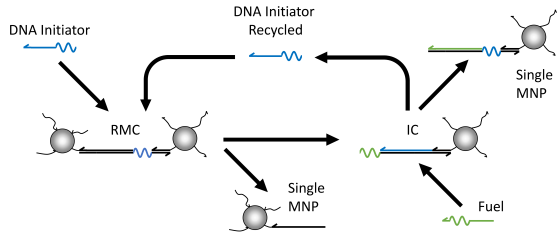

Figure 1: Schematic design of the MAC.

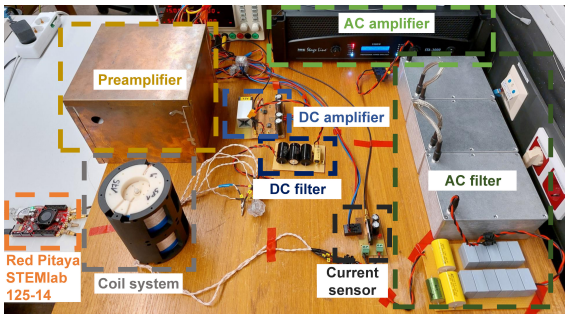

Figure 2: Table-top design of the next generation ImmunoMPS device.

tions, which are highly specific to the appropriate target nucleic acid sequence. The circuit starts with the DNA initiator binding to the RMC and releasing a single MNP from the intermediate complex (IC). A fuel DNA attaches to the IC and releases the DNA initiator, enabling its use in another TMSD based declustering. This chain reaction enables the cyclic disintegration of the RMCs, which changes the magnetic signal caused by low target concentrations and increases the amplitudes of the harmonics in the MPS [1].

II.II. Hardware

The new generation of our ImmunoMPS device for table-top operation is shown in Fig. 2. It operates with an excitation frequency of around 2 kHz at a magnetic field strength of 15 mT/μ_0. In addition to the coil system capable of generating an extra adjustable DC offset field (ADOF) in parallel to the AC field, the device consists of a low-noise preamplifier, DC and AC power amplifiers and corresponding filter structures to increase the spectral purity of the excitation signal. The decoupling of the DC and AC paths is achieved by doubling and antiserial interconnection of the coils. Furthermore, the system is customized for self-produced, Brownian relaxing cobalt-iron-zinc (CFZ) particles, which will replace the currently used BNF-S 80 nm particles from micromod GmbH.

The use of the ADOF offers the possibility of further increasing the sensitivity of the measuring system by selecting an operating point with a harmonic ratio more sensitive to binding events in the future [3].

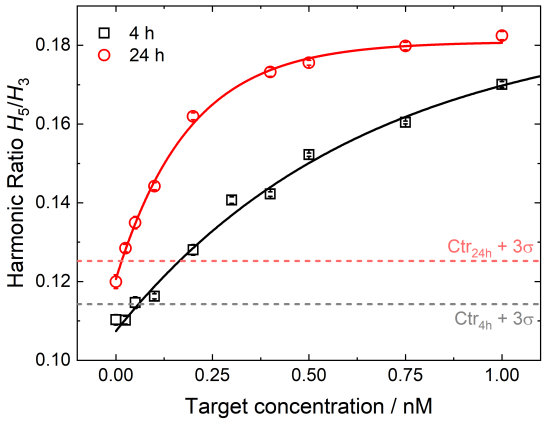

Figure 3: Detection limit for the improved MAC approach based on the harmonic ratio of the fifth to the thirrd harmonic measured with the predecessor immunoMPS [2].

III. Results and discussion

With our MAC approach, a detection limit of 27 pM DNA strands has already been demonstrated after 24 h of incubation. At the same time, this concept was employed in the wash- and enzyme-free detection of viral RNA amounts that corresponds to a Ct value of 26 in PCR [1]. Further development of our nucleic acids biosensing platform, however, yielded even better results are possible, as Fig. 3 illustrates. DNA concentrations of only 58.5 pM can be detected after only 4 h of incubation, whereas a limit of detection of 15 pM is reached after 24 h This is because the processes are diffusion-based and the chain reaction therefore needs time to take place.

IV. Conclusion and outlook

Our biosensing platform consisting of the MAC assays and the optimized MPS system is a powerful instrument for magnetically detecting small amounts of DNA or RNA. In the next step, the MPS measuring components will be installed in a housing, the ADOF tested and the DNA circuit further optimized to get closer to the field of POC testing.

Acknowledgments

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Author's statement

Authors state no conflict of interest. Informed consent has been obtained from all individuals included in this study.

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