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Detection of 28nm diameter superparamagnetic beads by magnetically-induced self-assembly with micrometer-sized magnetic beads: A new protocol for magnetically-labeled biosensing

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1. Introduction

Functionalized superparamagnetic beads show promise as magnetic-labels for monitoring biorecognition [1], where Hall effect and giant magnetoresistance devices are used to detect the magnetic beads, and thereby biomolecules attached to them [2–4]. This approach is a rapid, highly sensitive, and inexpensive method for point of care diagnosis of heart diseases, cancer and testing automobile drivers for the influence of illegal drugs [1]. Typically, the magnetic labels are 250 nm–3000 nm in diameter. However, in order to improve quantification and affinity to target-biomolecules, it is necessary to employ magnetic labels with sizes comparable to target molecules—typically less than 100 nm. In such cases, it is possible to accurately define the concentration of target molecules immobilized on the surface labels.

Here we report on combining a conventional optical microscope and magnetically induced self-assembly of micrometer-sized superparamagnetic beads to detect 28nm-diameter magnetic labels (‘targets’) immobilized on silicon substrates, over areas of several millimeters. The self-assembled structures formed by the magnetic interaction between the 28nm diameter target beads and micrometer superparamagnetic (‘columnar’) beads were easily visible under a conventional optical microscope, and our results are promising for sub-100nm magnetically-labeled biosensing. In contrast to magnetoresistive sensors, we demonstrated a simple procedure for directly detecting 28nm magnetic labels without complex peripheral experimental equipment. The capture of large micrometer sized beads by extremely small numbers of target 28nm-diameter magnetic-labels was clearly visible under an optical microscope even though the target beads were unobservable optically or detectable by magnetoresistive sensors.

2. Experimental

Fig. 1(a) shows the concept of our protocol, where the ‘target nanobeads’ are attached to probe molecules immobilized on substrates via biorecognition processes; (b) ‘columnar’ micrometer sized beads self-assemble onto the ‘target’ magnetic-labels due to the action of an external field; (c) optical observation of the substrate to confirm the self-assembled columnar-beads, and thereby the target biomolecules attached to magnetic-labels. In our experiments the 28nm-diameter targets were immobilized onto 8μm x 8μm arrays of gold surfaces, and self-assembly of 2.8μm superparamagnetic ‘columnar-beads’ induced by external magnetic fields.

The gold arrays were patterned by photolithography and on 5mm x 5mm silicon substrates. After liftoff, the substrate was dipped into an aqueous solution containing thiolated 28 nm-diameter superparamagnetic beads. The chemical affinity between the gold surface and thiolated 28nm beads resulted in the selective immobilization of the 28nm beads onto the gold surfaces.

The 28 nm magnetic beads were detected as follows: First, the substrate was positioned at the center of a 60 mm-diameter electromagnet coil. Next, the electromagnet coil with the substrate located at its center was placed under an optical microscope, and an aqueous solution containing micrometer sized superparamagnetic ‘columnar-beads’ was dropped onto its surface. The ‘columnar-beads’ were 2.8 μm diameter ‘Dynabeads’. After this, the electromagnetic coil was used to apply an external field of up to approximately 100 Oe. Finally, the self-assembly of the ‘columnar-beads’ onto the 28nm-diameter targets was monitored with the optical microscope.

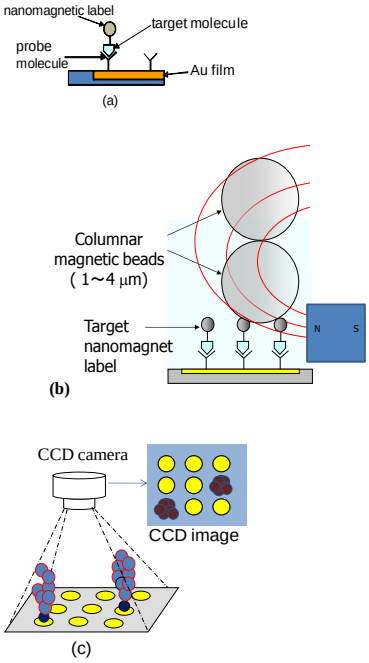

Fig. 1: Procedure for detection of magnetically labeled biomolecules. (a) Magnetically labeled biomolecules ('target nanobeads') are attached to probe molecules immobilized onto substrates via biorecognition processes; (b) 'Columnar' microbeads self-assemble onto 'target' nanomagnet beads. (c) Optical observation of the substrate reveals the self-assembled columnar micromagnetic beads confirming the presence of the target biomolecules attached to magnetic nanobead labels.

3. Results and Discussion

Fig. 2(a) is an optical image of an 8μm x 8μm array of gold squares immobilized with 28nm-diameter target beads prior to dropping the columnar-beads. Fig. 2(b) shows the sample surface after applying dropping an aqueous solution containing the 'columnar beads' and application of an external magnetic field. The 'columnar-beads' self-assembled within 30 seconds on regions immobilized with the 28nm target beads.

Removing the external magnetic field resulted in the 'columnar-beads' dissociating away from the 28nm target beads. This result showed that self-assembly was due to magnetic dipole-dipole interaction between the 28nm targets and the much larger micrometer sized 'columnar-beads'. The 'columnar beads' did not reassemble on the silicon dioxide areas between the gold arrays because the 28nm target beads did not exist in these regions. The average density of the 28nm diameter target beads on the gold square arrays was 106 beads/μm^2, and we estimate that this procedure enabled the detection of approximately 30 target beads.

We also explored the optimal conditions for producing greater than 90% self-assembly of 'columnar-beads' onto the 28nm targets, by changing magnetic field strength and concentration of 'columnar-beads'. We found that external magnetic fields of 37 Oe and 26 Oe were required for the self-assembly 2.8 μm and 1.0 μm 'columnar-beads', respectively.

Further experiments are underway to quantify the relationship between the minimum density of target beads required to self-assemble with 'columnar-beads' of differing sizes.

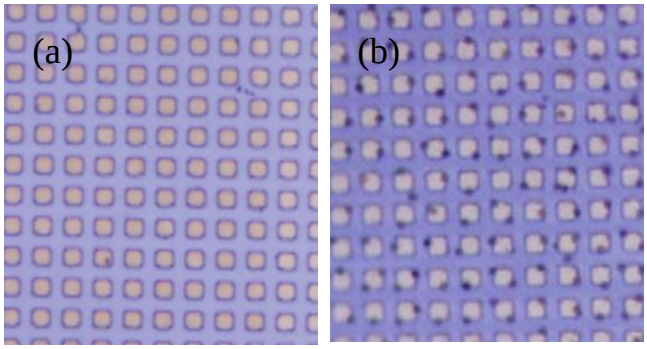

Fig. 2 (a): Before dropping an aqueous solution containing 2.8 μm diameter 'columnar-beads' onto gold arrays with 28nm-diameter beads immobilized to their surfaces; (b) magnetically induced self-assembly of 2.8 μm diameter 'columnar-beads' onto the 28nm targets.

4. Conclusions

We demonstrated the feasible of monitoring biorecognition by magnetically induced self-assembly of 2.8 μm diameter superparamagnetic 'columnar-beads' onto 28 nm diameter superparamagnetic target beads. Our experimental setup was simple and the procedure shows great potential for the rapid detection of extremely low concentrations of magnetically labeled biomolecules. Low concentrations of target beads of 28 nm in diameter—which are of comparable size to biomolecules—were detected by 'columnar-beads' in less than 30 s.

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