Magnetic manipulation and sensing of beads for bioapplications

Point-of-care diagnostics is predicted to revolutionize the way of healthcare and advance the field of personalized medicine. Point-of-care diagnostics opens the possibility of doing complex molecular biochemical analysis at the patient's home or at the doctor's office, instead of sending samples to a central laboratory. This will reduce the analysis time leading to earlier detections and easier disease monitoring, both of which are critical parameters for the efficacy of the applied treatment. So far, the commercially successful point-of-care devices have all been single purpose. However, much research have gone into making a customizable and multipurpose sensor platform, which could accelerate the number of practices.

This thesis investigates the role of magnetic beads as candidates for use in these new biosensing devices. Magnetic beads have stable properties and can be easily coated with biological recognition elements like proteins and DNA. Further, as all biological matter is none or weakly magnetic, magnetic beads are well suited for sample extraction and highly sensitive biodetection, where a low background level is needed. This thesis focuses on the use of magnetic beads in both molecular separation based on magnetophoresis and on biodetection based on magnetoresistive sensors.

Part I of this thesis explores magnetophoresis, both experimentally and theoretically. Experimentally, magnetophoresis was done on chips with stripes, two to ten microns in size and made of a permalloy based magnetic stack. The permalloy micro stripes created a spatially varying magnetic field, which in combination with a rotating external field was used to transport magnetic beads from stripe to stripe. Systematic measurements of the magnetophoresis properties on varying stripe geometries were performed. It was found that a symmetric geometry with equal stripe width and spacing was optimal, and that the stripe period should be twice the bead radius. Magnetophoretic bead velocities of 300 μm/s were measured, and selective separation based on differences in magnetophoretic mobility was hypothesized. However, the fabricated magnetophoresis systems had two major limitations. First, protein-coated magnetic beads had a tendency to stick to the surface, even though multiple surface blockings and modifications were tried. Second, as the systems are fabricated using a single UV lithography step, the stripe width has a minimum feature size of one micron, which limits the movable bead size to approximately one micron.

Parts II and III investigate magnetic bead detection using planar Hall effect bridge (PHEB) sensors. The PHEB sensor also uses a permalloy based magnetic tacks with anisotropic magnetoresistance. By combining four resistors in a Wheatstone bridge, the sensor output is shown to be proportional to low magnetic fields. In this thesis, the PHEB sensors are used for either detection of an external homogeneous magnetic field or for detection of magnetic beads that are magnetized by the sensor self-field. Multiple studies are made to optimize the bead detection using PHEB sensors. First, two new sensor designs are introduced: A parallel PHEB sensor, nominally only sensitive to self-field contributions and optimized for volume based relaxation measurements; a differential PHEB, which does on-chip reference measurements and is optimized for detecting small amounts of surface bound beads. The next study analyzes the thermal properties of the chip and setup. General methods for measuring or calculating the effective heat conductivity are given, along with a discussion on how to optimize this to facilitate the use of higher currents. The thesis then compares ring and diamond shaped PHEB sensors, both designs which have been argued to be superior. Theoretically, the diamond shaped sensors are more sensitive, but experimentally ring sensors are found to be less affected by the shape anisotropy. Diamond shaped sensors are thus only better for magnetic stacks with negligible shape anisotropy. Last, the inclusion of a copper layer in the magnetic stack was investigated. A six angstrom copper layer was found to double the signal from magnetic beads.

After studies of optimizing PHEB sensors, magnetic bead based bio-detection and bio-characterization were performed. PHEB sensors were used to detect magnetic beads tethered to the sensor surface through DNA-DNA interaction. By ramping the temperature on-chip DNA melting curves were measured, and conditions for differentiating mutant type and wild type DNA were identified. This method was also tried for studying of aptamer hybridization to magnetic beads coated with virus protein, a so-called magnetic artificial virus. Two aptamers from the literature were tried, but none of them showed any significant hybridization to the artificial virus.

Last Part IV performed a thorough theoretical analysis on how to measure a surface coverage of magnetic beads that are stochastically bound to the sensor surface and its surroundings. The field, from magnetic beads magnetized by an external field, varies with position and even changes sign. It is derived, how the signal will usually be dominated from magnetic beads outside of the sensor surface, as these are at a lower height relative to the sensor plane, and how magnetic beads on top of the sensor only decreases this signal. After having clarified the origin of the bead signal, a general framework for calculating the expected bead signal and its configurational fluctuations is described. This framework is used for analyzing three state-of-the-art sensors from the literature, and two of them are found to be limited by these statistical fluctuations.