Research paper

Sensitive and rapid immunoassay for parathyroid hormone using magnetic particle labels and magnetic actuation

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A R T I C L E   I N F O

Article history:
Received 21 January 2008
Received in revised form 23 May 2008
Accepted 1 July 2008
Available online 25 July 2008

Keywords:
Magnetic particles
GMR
Actuation
Electromagnet
ELISA
Proteins

A B S T R A C T

A rapid method for the sensitive detection of proteins using actuated magnetic particle labels, which are measured with a giant magneto-resistive (GMR) biosensor, is described. The technique involves a 1-step sandwich immunoassay with no fluid replacement steps. The various assay binding reactions as well as the bound/free separation are entirely controlled by magnetic forces induced by electromagnets above and below the sensor chip. During the assay, particles conjugated with tracer antibodies are actuated through the sample for target capture, and rapidly brought to the sensor surface where they bind to immobilized capture antibodies. Weakly or unbound labels are removed with a magnetic force oriented away from the GMR sensor surface. For the measurement of parathyroid hormone (PTH), a detection limit in the 10 pM range is obtained with a total assay time of 15 min when 300 nm particles are used. The same sensitivity can be achieved in 5 min when 500 nm particles are used. If 500 nm particles are employed in a 15-minute assay, then 0.8 pM of PTH is detectable. The low sample volume, high analytical performance and high speed of the test coupled with the compact GMR biosensor make the system especially suitable for sensitive testing outside of laboratory environments.

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1. Introduction

The specific analytical determination of low concentrations of biological molecules such as proteins and nucleic acids requires at least one molecular recognition event. To facilitate the detection of the binding event, the reaction can be labelled with a signal generating moiety. For a given receptor–ligand combination, a number of strategies have been used to achieve ultra-high sensitivity, including high performance detectors (Armani et al., 2007; Zheng et al., 2005), label signal enhancement (Kerstens et al., 1995; Lyon et al., 1998; Seydack, 2005; Taton et al., 2000; Yu et al., 2006) and augmentation of the efficiency and specificity of the biological binding reactions (Gustafsdottir et al., 2005). Label signal improvements can be attained through the use of nanoparticle or microparticle labels which increase the overall signal generated per recognition event by several orders of magnitude (Lyon et al., 1998; Mulvaney et al., 2007; Seydack, 2005; Taton et al., 2000). For heterogeneous assays this comes however at the expense of the kinetics of the biological reactions as larger labels diffuse more slowly and are sterically hindered when binding to the bulk surface on which the detection is performed (Cummins et al., 2006).

In this work we demonstrate that one can overcome the disadvantages of employing larger particle labels (>100 nm) through the use of superparamagnetic particle labels (MP) in combination with a system of actuating electromagnets. This combination enables the control of particle motion through the reaction solution and the enhancement of particle binding at the sensor surface. Coupled with the appropriate assay format, magnetic particles under the influence of an actuating force can be also used to concentrate target and receptor
molecules at the sensor surface to improve the speed of the assay reaction. Of the recent reports of the detection of biological molecules with magnetic particle labels (Edelstein et al., 2000; Ferreira et al., 2006; Hsing et al., 2007; Morozov and Morozova, 2006; Mulvaney et al., 2007), a few describe the application of magnetic actuation to augment particle transport (Ferreira et al., 2006; Morozov and Morozova, 2006). However in these reports the benefits of magnetic particles for use in target and receptor molecule up-concentration are not realized. The magnetic particles are added separately in a second step only after the receptor–ligand reaction has occurred on the detection surface. Thus, the particles function primarily to label the presence of the desired species on the surface in the form of for example an immunosandwich (Fig. 1) or hybridized duplex DNA (Ferreira et al., 2005; Ferreira et al., 2006; Morozov and Morozova, 2006). In this report we describe a 1-step assay format in which the receptor molecule, in our case the tracer antibody of a parathyroid hormone (PTH) immunoassay, is directly coupled to the magnetic particle. This enables PTH molecules effectively to be captured from the solution due to the high local concentration of first antibodies on the particles (Soukka et al., 2001), and to be concentrated at the sensor surface where particle binding occurs. After binding to the sensor the particles are detected by a highly sensitive GMR sensor chip (Fig. 2b). The miniaturized chip is integrated in a disposable flow-cell cartridge (Nellissen et al., 2005) and placed under the influence of electromagnetic coils positioned above and below the chip. The device combined with the 1-step assay format is able to rapidly detect protein analytes in the sub-picomolar concentration range, without fluidic handling steps, and using a small sample volume.

Magnetic particles have been used extensively in bulk separation techniques as a carrier for the purification and up-concentration of macromolecules. In the molecular regime, magnetic particles provide a handle with which molecular interactions can be manipulated. By controlling the actuating magnetic field and gradient applied to the particle, the force pulling two bound molecules apart or bringing them together can precisely be tuned (Mak et al., 2006; Panhorst et al., 2005). With the development of sensors such as magneto-resistive (Freitas et al., 2007; Prins and Megens, 2007) and Hall sensors (Aytur et al., 2006) that can detect small magnetic fields, it is possible to extend the use of these particles to labelling by measuring the stray magnetic field generated from magnetized superparamagnetic particles. We have recently demonstrated a compact GMR sensor with integrated excitation wires for particle magnetization and a signal modulation scheme (Fig. 2a) (de Boer et al., 2007). The system is sensitive to a particle density of three 300 nm magnetic particles on a 1500 µm² chip surface. The sensor is based on a magnetic multilayer stack in which the electrical resistance changes in response to the presence of in-plane...
magnetic fields. Because of the high sensitivity of the device, it is possible to perform measurements on very small sample volumes. Our device is fitted with fluidic components that provide for a sample chamber volume of 1 µL. Since no excess fluid is required for mixing or washing, the total sample required is that necessary to fill the detection chamber. Magnetic detection technology has the additional advantage that biological samples are predominantly non-magnetic and thus do not contribute significantly to background signals. In contrast to several optical and electrical techniques where the properties of the sample add significantly to the background signal, magnetic detection can be potentially performed in untreated samples such as whole blood.

2. Materials and methods

Unless stated otherwise, materials were used as purchased without further purification. All reagents for the PTH assay (antibodies and assay buffers) can be purchased at Future Diagnostics BV, The Netherlands, as part of the PTH STAT Platform product line.

2.1. Preparation of the sensor surface

The sensor chip, approximately 2 mm² in area, comprised four GMR sensors on which an 80 nm layer of Au was sputtered. Details of the sensor, fluidics and reader can be found in our previous reports (de Boer et al., 2007; Nellissen et al., 2005). Before functionalization with antibodies, the Au layer was washed with ethanol and acetone (Sigma-Aldrich), dried in a N₂ stream and treated with UV-Ozone for 10 min to remove organic contaminants. Capture antibody (recognizing amino acids 39–84 on PTH) for PTH was immobilized on to the Au surface via physical adsorption by the application of a small droplet of anti-PTH capture antibody (0.9 µg in 1 µL phosphate buffered saline, PBS) for 1 h in a humid atmosphere. The sensors were washed with PBS (pH 7.4) and dried in a N₂ stream. Fluidic parts contained an inlet and outlet to a channel 1 cm in length and 1.6 mm in width. The fluidics parts were glued to the sensors (using a cyano-acrylate adhesive, Loctite 406 from Henkel) which were embedded in a moulded interconnect device with a 300 µm recess to form a chamber with a total volume of 1 µL. Thereafter the cartridge was blocked with a solution of 1 wt.% bovine serum albumin (BSA, Sigma) in PBS buffer for at least 1 h and stored at 4 °C until used.

2.2. Preparation of magnetic particle-antibody conjugate

Tracer anti-PTH antibodies (recognizing amino acids 1–35 on PTH) were covalently coupled to carboxylated superparamagnetic particles (Ademtech) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (Sigma-Aldrich) chemistry (Mayes, 2006). For the 300 nm and 500 nm diameter magnetic particles the coupling was performed with the suggested protocol from Ademtech. We summarize the procedure below for 300 nm particles:

Magnetic particles (300 µg) were washed and resuspended in 30 µL Activation buffer (Ademtech). 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 µg in 24 µL Activation buffer) was added and the mixture incubated for 10 min under shaking at 600 rpm and 40 °C. After addition of anti-PTH tracer antibody (15 µg), the beads were incubated for 2 h at 600 rpm and 37 °C. The supernatant was removed while attracting the particles to the vial wall with a magnet (Dynal) and BSA (15 µg, 0.05 wt.% in Activation buffer) was added to block the particles and the solution was further incubated for 30 min at 600 rpm and 37 °C. The particles were washed with Storage buffer using a magnet to collect particles at the vial wall and resuspended in 30 µL Storage buffer and stored at 4 °C until used.

2.3. Preparation of biotinylated sensor surfaces and assays with streptavidin coated particles

A mixture of PTH (Bachem GmbH) and biotinylated anti-PTH tracer antibody (1 µg/mL) in Assay buffer or whole blood diluted by 50% with the same buffer was injected into the cartridge containing capture antibody on the sensor surface. The mixture was allowed to react to form a biotinylated sensor surface for 1 h. After the incubation, the samples were washed with 100 µL of wash buffer (0.02 wt.% Tween 20 in PBS) or 50% whole blood. Thereafter, 60 µL of streptavidin coated 300 nm superparamagnetic particle (Ademtech) solution was injected into the cartridge at a flow rate of 190 µL/min using a syringe pump (Pump Pico II Plus, Harvard Apparatus). The particles were present either at a concentration of 0.1 wt.% in buffer (1:3 Assay buffer:Storage buffer) or in whole blood diluted by 50% with the same buffer. Although the chamber in which the sensor is embedded has a total volume of approximately 1 µL, an excess volume was required to fill the dead volume resulting from the tubing and fluidic connectors and to ensure the complete filling of the chamber without introducing air bubbles.

2.4. Magnetic particle chemiluminescence assay

Particles (25 µg) coated with anti-PTH tracer antibody were resuspended in Assay buffer and added to flat-bottomed 96 microtiter wellplates (high binding strip plate, Corning Inc.). Thereafter, 100 µL solutions with various PTH concentrations were added to these beads. After 1 hour incubation at room temperature and 180 rpm orbital shaking, 50 ng/well of anti-PTH capture Ab labelled with N-(4-Aminobutyl)-N-ethylisoluminol (ABEI, Sigma-Aldrich) was added. After 1 hour incubation at room temperature and 180 rpm, the beads were washed three times with 200 µL STAT-wash buffer using a magnet for 96-well plates (Retro-Quip, RetroTech). Finally, the microtiter plate, containing the beads, was loaded into the microplate luminometer (STAT platform, Future Diagnostics). Per well, 100 µL Activator 1 (luminol-enhancer solution, Future Diagnostics) and 100 µL Activator 2 (contains H₂O₂, Future Diagnostics) were injected and relative light units (RLU) were counted for 3 s. Experiments were performed in duplicate and error bars were calculated.

2.5. On-sensor chip1-step immunoassay

The cartridge was washed with 100 µL of wash buffer (0.02 wt.% Tween 20 in PBS). Antibody functionalized particles were diluted to 0.25 mg/mL in Assay buffer and sonicated on ice for 3 s (2 mm probe, 40% amplitude) using a VibraCell tip sonicator from Sonics. PTH was added to the beads (ratio 1:9) and 60 µL was injected into the cartridge at a
flow rate of 190 µL/min. Subsequently, attraction actuation towards the sensor surface was performed for 13 min (or 3 min for 500 nm MPs) with a magnetic field strength of $8 \times 10^4$ A/m and field gradient of $4 \times 10^7$ A/m$^2$ using an electromagnetic coil approximately 800 µm below the sensor surface. The electromagnetic coil consists of 360 copper windings around a 3 mm cobalt-iron alloy core. Unbound beads were removed by performing a magnetic wash at a field strength of $8 \times 10^4$ A/m and field gradient of approximately $4 \times 10^7$ A/m$^2$ away from the sensor surface for 2 min with a similar electromagnetic coil approximately 500 µm above the sensor. During the recording of each measurement point of the GMR signal, actuating coils were switched off. The GMR signal change was calculated with the formula $[(S_i - S_f)/S_i]$, wherein $S_i$ is the initial GMR signal before the addition of particles and $S_f$ is the final GMR signal after the magnetic “wash”. Measurements were taken over 3 to 4 different sensors on one GMR chip and error bars were calculated.

3. Results and discussions

The device is comprised of a silicon sensor chip measuring 1.4 mm by 1.4 mm in size on which four GMR sensors are defined, each by a single GMR strip with two integrated excitation wires (Fig. 2a). High frequency particle magnetization and signal modulation schemes for attaining high electronic signal to noise ratios have been described elsewhere (de Boer et al., 2007). Above and below the sensor chip are electromagnetic coils consisting of copper wound over 3 mm cobalt-iron magnet cores for actuating the particle labels. Fig. 2cd depicts the observed GMR signal after magnetic attraction and a magnetic bound/free separation step for the model reaction between streptavidin coated 300 nm magnetic particles on a biotinylated surface. The steep rise in observed signal in the first section is a consequence of the binding of magnetic particles, whose transport to the sensor surface is assisted by a magnetic field and field gradient (section A). Because the sensors are fabricated with a geometry such that they are most sensitive to particles within 3 µm of the surface (Fig. 2b), particles that do not bind contribute minimally to the signal as they are on average further away from the surface due to diffusion. As a result the slope measured for a binding surface is significantly higher than that of a non-binding surface. Particle labels that are weakly and non-specifically bound are then removed through the application of a magnetic force away from the surface (section B). The resulting signal change is proportional to the number of bound magnetic particles (de Boer et al., 2007). The use of magnetic fields is highly effective in enabling the binding reaction and washing process to occur controllably and rapidly.

With the GMR sensor it is possible to specifically detect bound magnetic particles in complex sample matrices such as full blood, saliva and milk. We observe that the background signal generated in the GMR sensor from a whole blood sample is indistinguishable from the signal arising from a protein rich assay buffer (data not shown). Fig. 3 displays various surface densities of streptavidin coated magnetic particles bound on biotinylated surfaces (generated from different concentrations of PTH in a whole blood or buffer sample). The particles can be detected with the same sensitivity in whole blood as in buffer. As a consequence sample pre-treatment is unnecessary for particle detection.

To demonstrate the performance of the biosensor and actuating system, a model sandwich immunoassay assay for the ligand PTH was chosen. PTH is a 10 kDa protein that acts to stimulate bone turnover and calcium resorption in the kidneys. Assays for PTH based on molecular recognition by specific, high affinity goat anti-PTH antibodies are used in clinical laboratories to diagnose parathyroid disorders (Wild, 2001). Tracer and capture antibodies were chosen that have been affinity purified to each recognize specific and different epitopes on the PTH molecule. In this way PTH can be used to bind magnetic particles to the sensor surface through an immunosandwich consisting of the tracer antibody, PTH and capture antibody. To convert the inorganic GMR surface to a biosensing surface, an 80 nm layer of Au was deposited by physical vapour deposition and a 4 nm layer of second anti-PTH antibodies was physically adsorbed onto the surface from solution (Coq et al., 2007). It is also possible to covalently couple anti-PTH antibodies to the Au substrate on the sensor through the use of carboxylated self-assembled monolayers of alkanethiols and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide activation (Lahiri et al., 1999). Because the anti-PTH antibodies are robust goat polyclonals, they can be immobilized using both methods to yield receptor surfaces with high activity. In the multistep assay format (Fig. 1), the concentration of PTH in solution determines the number of binding sites on the sensor surface. The reactions between PTH, the capture and biotinylated tracer antibodies are separated from the particle labelling reaction with a fluid replacement step which removes free PTH and tracer antibodies. In the 1-step assay format the tracer anti-PTH antibodies are directly attached to the magnetic particle and the concentration of PTH in solution determines the number of binding sites on the particle surface. Because the binding reactions of this assay are controlled by magnetic forces, no fluid replacement is required. To detect the amount of PTH in a solution, the sample is added with magnetic particles functionalized with antibodies to the GMR biosensor. Capture of the PTH target is enhanced by the high local concentration of the tracer antibodies on the particles. Since all antibodies on the particles recognize the same PTH epitope, particle–particle aggregation via PTH is prevented. The action of the actuation
field increases the speed at which the magnetic particles move through the sample fluid and consequently the efficiency of target capture. The target is then concentrated at the sensor surface by the application of an attracting force that brings the particle labels containing PTH rapidly towards the capture antibodies on the sensor surface. Fig. 4 depicts the signal resulting from magnetic particles bound to a sensor surface as a function of several concentrations of PTH in the presence and absence of an attracting magnetic force. The efficiency of target capture and binding to the sensor surface are reduced approximately 5-fold when diffusion and sedimentation are the only transport means. A magnetic field strength of $8 \times 10^4$ A/m and field gradient of $4 \times 10^7$ A/m$^2$ was applied, which did not vary substantially over the chamber height of approximately 300 µm. The field gradient was found to be optimal for enhancing assay speed without inducing the irreversible aggregation of particles and increasing non-specific binding. After the binding process a magnetic force in the direction away from the sensor surface was applied to remove free and weakly bound particles from the sensor surface (magnetic “wash”). The magnetic force used in the magnetic wash can be finely tuned such that particles bound to the sensor specifically through PTH molecules are not removed. For 300 nm particles magnetic fields and field gradients substantially greater than $8 \times 10^4$ A/m and $4 \times 10^7$ A/m$^2$, respectively cause a decrease in the specific signal without decreasing the signal from blank samples (0 pM PTH). Using vibrating sample magnetometry (VSM) a magnetic susceptibility per particle of $3 \times 10^{-20}$ m$^3$ and $4 \times 10^{-19}$ m$^3$ for 300 nm and 500 nm respectively, were measured. Based on these values and the applied field gradient, we calculate that forces slightly below 1 pN are exerted during the attraction and removal of particles. These forces are sufficient to remove excess and non-specifically bound particles from the surface but are below the typical forces required to break specific bonds (Mak et al., 2006). Particles that remain bound to the sensor surface are then magnetized and the stray magnetic field is detected by the GMR sensor.

In the 1-step assay, the probability that the label binds to the capture antibodies on the sensor surface is determined by the number of PTH molecules bound to the particle. The efficiency of target capture by the magnetic particle in turn is dependent upon the concentration of tracer antibodies immobilized on the particle surface (Soukka et al., 2001). By varying the concentration of first antibodies in the coating solution for magnetic particle-antibody conjugate preparation, it is possible to produce particles with a range of antibody coverages, as determined by a N-(4-Aminobutyl)-N-ethyl-isoluminol (ABEI) chemiluminescence immunoassay on the particle (Fig. 5a). In the chemiluminescence wellplate assay, the number of functional tracer antibodies coupled to the particle is measured semi-quantitatively by incubating the particles with PTH and then with ABEI-labelled capture antibodies. The signal generated from the ABEI is related to the amount of antibody coupled to the particle. It is found that for a given concentration of analyte, the particles with high antibody coverages yield the highest GMR sensor signal in the 1-step assay (Fig. 5b). In the chemiluminescence immunoassay, coating concentrations of 10 µg antibody/mg MP and 20 µg antibody/mg MP result in
similar signals, thus similar coverages of active antibodies on the particle. The GMR signal however, is more than 2-fold higher for a coating concentration of 20 µg antibody/mg MP than for 10 µg antibody/mg MP. The results suggest that at the higher coating concentration of 20 µg antibody/mg MP, the antibodies are more optimally oriented for binding the particle to the sensor surface through a PTH immunosandwich. The difference in sensitivity to the antibody orientation between the chemiluminescence bead assay and the GMR surface assay is to be expected as ABEI-labelled free antibody has more rotational and translational degrees of freedom than the capture antibody attached to the GMR sensor surface. For the given tracer antibody coverage on the particle there is an optimal magnetic particle concentration range for good assay performance. It was found that for 300 nm particles this optimal concentration was approximately 0.25 mg/mL. At this particle concentration, a sample volume of 1 µL results in less than one monolayer of magnetic particles over the entire sensor chip. If the magnetic particle concentration is high relative to the amount of PTH in solution, then the number of particles containing few or no PTH molecules is also high. For these particles, the probability that they can bind to the sensor surface is low. However if the particle concentration is low, then only a small amount of particles are available to bind resulting in low sensor signals, especially at high PTH concentrations and the dynamic range of the assay decreases.

A calibration function of the 1-step assay demonstrates that PTH concentrations in the 10 pM range are detectable with 300 nm magnetic particles (Fig. 6). A high dose hook effect is not observed for concentrations up to 4 nm, well above clinically relevant PTH values. In 1-step formats, high concentrations of analyte can result in capture binding sites on the surface being blocked and a low sensor signal being produced. It is possible to some extent prevent this high dose hook effect from occurring in the clinically relevant range and limiting the dynamic range by increasing the tracer antibody concentration. This can be achieved through either increasing the particle concentration or the concentration of antibody on the particle. For all concentrations, reaction of PTH with antibodies on the particle will dominate over the reaction of PTH with the sensor surface. This is a consequence of the fact that the concentration of tracer antibody is higher than that of the capture antibody due to the substantially higher surface area of the particles than the flat sensor surface.

Because the actuating field allows active transport especially with large particles, we can enhance the speed of transport as well as the sensitivity of detection by increasing the size of magnetic particle labels to 500 nm. Using these larger labels we are able to detect 0.8 pM of PTH in a total assay time of approximately 15 min (Fig. 7a). It is also possible to perform an assay using 500 nm particles with the same sensitivity as 300 nm particles but with a significantly shorter assay time. A 5-minute assay with 500 nm particles produces a comparable signal to a 15-minute assay with 300 nm particles. As a representative example the detection of 100 pM and 0 pM of PTH are shown in Fig. 7b. The GMR signal however at both particle sizes, is a sublinear function of the PTH concentration. In PTH assays employing 300 nm particles, a signal range of one decade is observed over a concentration range of two decades. We hypothesize this sublinearity at higher PTH concentrations (>100 pM) and thus significant surface densities of particles, to be a consequence of a combination of magnetic and steric

Fig. 6. Dose–response curve for PTH detection with the GMR sensor using 300 nm magnetic particles in the 1-step assay under magnetic actuation with a 15-minute total assay time. The hatched line depicts the signal of the blank (0 pM PTH) and the width of the line indicates 2 times the error in the blank measurement.

Fig. 7. a) A comparison of the performance of 300 nm and 500 nm magnetic particle labels for PTH detection with the GMR sensor using the 1-step assay under magnetic actuation in a 15-minute assay. The hatched line depicts the signal of the blank (0 pM PTH) for 500 nm magnetic particles and the width of the line indicates 2 times the error in the blank measurement. b) A comparison of the performance of 300 nm particles in a 15-minute 1-step assay detected with the GMR sensor with that of 500 nm particles in a 5-minute 1-step assay at 0 and 100 pM PTH.
hindrance effects. Magnetic hindrance results from the mutual repulsion of magnetized particles with out-of-plane magnetic dipoles. In the absence of magnetic detection or actuation it has been observed by others that the sublinear behaviour of the calibration function for assays using large particle labels is substantial. This is likely due to steric hindrance effects. For example, the calibration curve for assays using 2.8 μm magnetic particle labels reported by Mulvaney et al. (2007) shows only a 6-fold difference in signal over six orders of magnitude in target concentration. At low PTH concentrations (<100 pM), the sublinear behaviour is a consequence of the significant contribution of non-specifically bound particles. A certain degree of sublinearity in the calibration function is acceptable if the precision of the measurement is suitably high. When implementing increasingly larger particles it is necessary to consider the tradeoffs between on the one hand the enhanced signal and transport efficiency and on the other hand the increased particle aggregation, and departure from linearity in the calibration function. We find that using our current PTH assay buffer composition and magnetic field strengths, 1 μm magnetic particles result in significant irreversible aggregation and poor assay results are obtained. Using commercially available particles, 500 nm particles yield the highest sensitivity.

In conclusion, a compact biosensor system employing magnetic particle labels in a 1-step test has been demonstrated that is able to detect sub-picomolar concentrations of PTH in approximately 15 min. Using this assay format in which the tracer antibody is directly conjugated to the particle, it is possible to manipulate the process of target capture and label binding to the sensor surface with magnetic forces to speed up the assay and obtain high sensitivity. The 1-step test can be applied to other protein markers of disease and has the potential for high analytical performance testing outside centralized laboratories. Because the sample is exposed to the sensor simultaneously with antibody functionalized magnetic particles and no fluid replacement is necessary, the design of the disposable cartridge can be relatively simple, requiring only a chamber to contain the sample and sensor. In a potential product the functionalized particles can already be present in the cartridge in a dry form such that only the sample needs to be added. The robust technology consisting of a disposable chip-in-cartridge and compact reader is well suited for handheld diagnostics applications such as in the emergency department, ambulance, at the physician's office and at home. In future work we aim to apply our technique in the detection of other biological molecules such as small molecules and nucleic acids and perform tests in real patient samples.

Acknowledgments

We would like to acknowledge H. Vohs, J. Nieuwenhuis, P. van Lankvelt, H. van Zon and J. van Eemen for useful discussions and technical assistance. We would also like to acknowledge financial support from the Netherlands Ministry of Economic Affairs under the IS and Nanoprogrammes.

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