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Self-propelled affinity biosensors: Moving the receptor around the sample

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ABSTRACT

Self-propelled nanomotors offer considerable promise for developing novel biosensing protocols involving 'on-the-fly' recognition events. This article reviews recent advances in using catalytic nanomotors for bioaffinity sensing and for isolating target biomolecules and cells from complex biological samples. A variety of receptors, attached to self-propelled nanoscale motors, can thus move around the sample and, along with the generated microbubbles, lead to greatly enhanced fluid transport and accelerated recognition process. Such operation addresses the challenges imposed by the slow analyte transport in designing sensitive bioaffinity assays. The recognition element can be attached onto the motor surface or embedded in the motor material itself. Receptor-functionalized nanomotors based on different biomolecular interactions have thus been shown extremely useful for rapid target isolation from complex biological samples without preparatory and washing steps. Tubular microengine microtransporters, functionalized with antibody, ss-DNA, aptamer or lectin receptors, are particularly useful for direct detection and isolation of proteins, nucleic acids, proteins or cancer cells. Micromotors with 'built-in' recognition, exploiting the selective binding properties of the outer layer of such micronegines, can also be used. Greatly enhanced analyte–receptor interactions can also be achieved through the increased fluid transport associated with the movement of unmodified micromotors. The attractive features of the new motion-based bioaffinity sensing and separation protocols open up new opportunities for diverse biomedical, environmental and security applications.

1. Introduction

Locomotion of nanoscale objects through fluid environments is one of the most exciting fields of nanotechnology (Wang, 2013; Guix et al., 2014, Paxton et al., 2004; Ozin et al., 2005; Mei et al., 2008; Pumera, 2010). Recent efforts have led to the development of a wide range of nanomotors based on different propulsion mechanisms. These include chemically-powered motors that convert chemical energy into autonomous motion (Paxton et al., 2004; Mei et al., 2011; Sanchez et al., 2015; Solovev et al., 2009) and fuel-free motors that rely on variety of external stimuli, such as magnetic or ultrasound actuations (Peyer et al., 2013; Kagan et al., 2012). Such synthetic nano/microscale motors represent a major step towards the development of practical nanomachines. Advanced fabrication schemes used for creating such nanomachines can impart new functionalities and capabilities. These recent advances and new capabilities have opened up new sensing opportunities and bioanalytical applications. These involve not only new sensing applications in previously inaccessible microscale environments but primarily fundamentally new sensing approaches based on the motor movement.

This article reviews recent advances in using self-propelled nanomotors for bioaffinity sensing and for isolating target biomolecules and cells from complex body fluids. Bioffinity sensors, that exploit selective recognition of specific target species for triggering useful signals, represent a major class of modern biosensors (Cosnier, 2005; Wang, 2006; Merkoci, 2013). While low detection limits are required to facilitate early disease detection, such ultrasensitive detection remains a major challenge to bioaffinity assays in view of the ultrasmall sample volumes. Common bioaffinity sensors rely on placing the sample droplet over the receptor-modified transducer and measuring the extent of the analyte–receptor interaction following an incubation period under quiescent conditions. Such droplet-based bioassays thus rely solely on diffusion transport. Fundamental studies revealed that the detection limits for such bioaffinity assays reflect the analyte transport limitations, and not a signal transduction limitation (Sheehan and Whitman, 2005). Enhancing the mass transport by using convection, e.g., solution stirring, is often challenging for increasing the response of such microassays. Attempts in this direction have included acoustic streaming, air-driven bladders, or

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moving boundaries (Links, 2012; Adey et al., 2002; Morales-Narváez et al., 2014). Bioaffinity interactions are also widely used for separating and isolating biological targets from raw biological samples. Such isolation processes are extremely challenging owing to the complexity of body fluids and rely on laborious time-consuming procedures.

The motion-based biosensing strategy relies on the continuous movement receptor-modified microengines through such complex samples in connection to diverse 'on-the-fly' biomolecular interactions. Such movement of the receptor around a complex sample promotes its interaction with the target analytes and represents a fundamentally new paradigm in analytical chemistry. In particular, bubble-propelled catalytic micromotors, functionalized with different bioreceptors, described in this article, provide a new 'on-the-fly' approach for bioaffinity assays and for isolating target biomolecules from complex biological samples and transporting them to a clean environment for downstream analysis (Campuzano et al., 2011; Kagan et al., 2011; Restrepo-Pérez et al., 2014). Movement of the bioreceptor around the sample leads to a new approach for bioaffinity assays and bioseparations that addresses the limitations associated with the slow analyte transport under quiescent conditions used in such microassays (Fig. 1A). Unmodified self-propelled micromotors can also enhance greatly analyte–receptor interactions through the increased fluid transport and mixing associated with the motor movement and generated microbubbles tail (Orozco et al., 2014) (Fig. 1B). Such mixing induced by the micromotor motion can assist the transport of the target molecule within the sample solution toward an immobilized receptor (Morales-Narváez et al., 2014). Such motion-based sensing strategy thus holds considerable promise for diverse biosensing and biochip applications, involving a variety of self-propelled receptor-modified microtransporters and involving different biomolecular interactions. The motor-based 'capture-and-transport' approach leads also to effective isolation of biological targets of different scales from unprocessed biological samples.

The successful realization of the new motion-based bioaffinity sensing and separation concepts requires an optimal propulsion behavior and a large towing force of individual microtransporters in complex biological matrices along with control of their surface chemistry and directionality. We will thus discuss first the fabrication and operation of tubular microengines that are most commonly used in such motion-based biosensing and separation, followed by other practical considerations, novel sensing strategies, analytical performance and future prospects of these self-propelled biosensors.

2. Tubular microengine transporters

Among chemically-powered nanomotors, tubular microengines are particularly attractive for biosensing applications due to their efficient bubble-induced propulsion in relevant biological fluids containing hydrogen peroxide fuel (Mei et al., 2011, Sanchez et al., 2015). Bubble-propelled tubular microengines ('microrockets') have been developed to address the limitation of catalytic nanowire motors to low ionic-strength media. Such tubular microengines display high speed and power, along with a precise motion control and can be easily modified to impart new functionalities and capabilities. Tubular microengines have been commonly fabricated using standard photolithography or template electrosynthesis procedures (Mei et al., 2008; Gao et al., 2011). The resulting tubular microengines have an inner (catalytic) Pt surface, a diameter opening of 2–10 μm and are typically 5–100 μm long. The oxygen-bubble propulsion thrust of these tubular microengines is associated with the decomposition of the hydrogen peroxide fuel on the inner catalytic platinum surface. The conical shape of the microengine assists in the unidirectional bubble evolution, with small amounts of surfactant (e.g., 2% sodium cholate) are used to promote this bubble evolution and release. The movement of the micromotor can be controlled using external mechanisms, including magnetic or ultrasound fields, as well as temperature or light stimuli (Balasubramanian et al., 2009; Wang and Manesh, 2010; Restrepo-Pérez et al., 2014; Rao et al., 2015). For example, the incorporation of a magnetic layer (e.g., Ni) during the preparation process allows for a precise magnetic navigation of their movement within narrow microchip channels. Tubular microengines based on metals others than platinum have been developed recently. In particular, zinc-based microengines have been developed for efficient propulsion in acidic (stomach) media (Gao et al., 2012) and were recently used for the first operation of micromotors in living organisms (Gao et al. 2015).

An outer gold or polymeric layer can be used to functionalize the tubular microengines with different bioreceptors (using the surface chemistry described below). Such surface functionalization reduces the speed of these micromotors from ~500–1000 bl/s (body-lengths

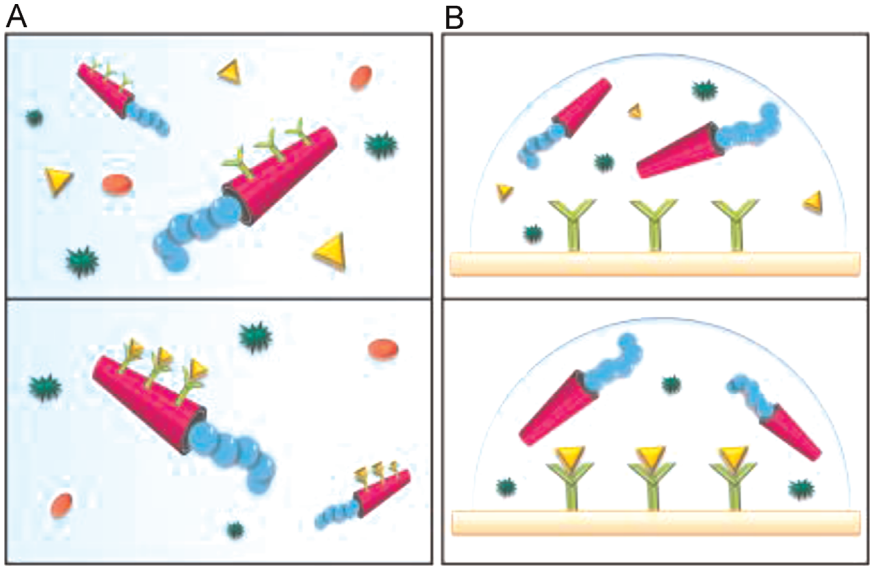

Fig. 1. Micromotor-based routes for enhancing bioaffinity sensing. (A) Movement of the bioreceptor-functionalized motor around a complex sample, and (B) the mixing and accelerated analyte–receptor interactions induced by the motion of unmodified micromotors.

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