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Numerical modeling of analyte diffusion and adsorption behavior in microparticle and nanoparticle based biosensors

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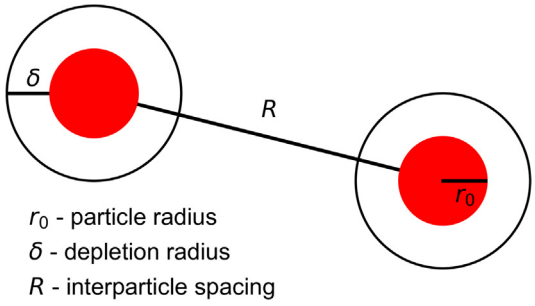
HIGHLIGHTS

- Colloidal assays possess large total surface areas and small diffusion distances.
- Spherical particles experience high analyte flux at reduced dimensional scales.
- Colloidal capture systems exhibit analyte capture of very dilute analyte.

GRAPHICAL ABSTRACT



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ABSTRACT

Increasingly medical diagnostic platforms rely upon the use of colloidal nanoparticles for the detection of biomolecules. Colloids offer greatly increased surface area to volume ratios and lack diffusion limitations that typically reduce reaction rates in assays employing planar surfaces. These characteristics are anticipated to improve the speed to answer as well as the total number of analytes that are captured in colloidal assay systems. This paper details a reaction-diffusion modeling approach to optimize colloidal affinity-based bioassays, with emphasis on the key figures of merit of projected sensitivities and time to answer over a broad range of conditions. The computational results illustrate the intuitive sense that colloidal sensing surfaces have improved kinetics as compared to solid supports, that the curvature of the spherical sensing surface probes a larger volume than a planar surface of the same area resulting in a larger diffusional driving force for reaction to the surface and equilibrium of bound analyte. The governing regime of particle systems skewed toward kinetically limited regimes and multiple configurations of particle diameter and concentration achieved equivalent analyte capture. Surface based sensor platforms have benefited from miniaturization of the capture area and particle capture systems provide a route to further surface miniaturization, as well as unique opportunities for the rapid analysis of dilute samples of particular interest for point-of-care (POC) diagnostics.

1. Introduction

The capture of target analyte by affinity-based biological recognition of surface immobilized probes forms the basis of a range of bioassays that detect antigens, antibodies, DNA fragments and small molecules for the purposes of clinical diagnostics and point-of-care (POC) applications (van Lierop et al., 2012; Granger et al., 2013; Choi et al., 2012; Tonga et al., 2014). The features of sensitivity, speed, portability and ease of use are the principal design criteria driving the next generation of laboratory diagnostics and POC assays (Holford et al., 2012). Improvements in assay speed and sensitivity have primarily been accomplished through

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the miniaturization of the capture surface, owing to the inverse relationship between analyte flux and capture feature size (Ekins and Chu, 1994; Mir-Simon et al., 2015). The reduction in capture area from dimensions of mm to dimensions of μm has greatly improved assay performance in terms speed and sensitivity through a greater proportion of the capture surface undergoing radial type analyte flux as well as the surface experiencing greater fractional occupancy of analyte. Further miniaturization below μm characteristic length scales may actually produce negative affects due to limits in signal transduction or from the system entering a kinetically limited regime (Ekins et al., 1998; Dandy et al., 2007). On capture surfaces of highly miniaturized dimensions, the number of bound capture probes able to occupy a finite area will be limited and the probability of a diffuse analyte encountering the capture surface is decreased, thereby increasing the time for a minimum detectable number of analytes to bind (Das et al., 2009; Dahlin, 2012; Hassibi et al., 2005).

Colloidal based assays have emerged as popular detection platforms, focused around signal transduction methods utilizing surface plasmon resonance, surface enhanced Raman spectroscopy (SERS) and particle aggregation, and provide unique characteristics at reduced length scales, including large total surface area and rapid kinetics (Neng et al., 2013; Zhang et al., 2012; Chon et al., 2011; Gong et al., 2007; Li and Rothberg, 2004; James and Driskell, 2013; Howes et al., 2014). In a microparticle assay, the sensitivity was improved six-fold compared with that of the standard surface based assay for the same length of incubation time, while an immunoassay for allergen detection reported the sensitivity of the nanoparticle based assay to be improved by an order of magnitude when compared to the assay as run in a microwell plate, along with the a reduced incubation time from five hours to 50 min (Jungell-Nortamo et al., 1988; Soderlund, 1990; Teste et al., 2011). The effects of curvature and size are attributable to these gains in assay performance. The curvature of a spherical capture surface increases the analyte flux and both the dimensional scale and Brownian motion of nanoparticles in solution cause the kinetics of the heterogeneous, surface based reactions on nanoparticle surfaces to approach the limits of homogeneous, solution based reaction kinetics (Bard and Faulkner, 1980; Nair and Alam, 2006). Additionally for planar surfaces the total capture area scales with the characteristic length of the sensor, but in microparticle or nanoparticle systems, surface area scales with the total number of particles in solution and results in large total capture areas on the order of 10^2–10^6 μm^2 for typical reaction conditions (Squires et al., 2008; Sheehan and Whitman, 2005). The introduction of convection for surface based capture systems has produced improvements in assay performance similar to those provided by colloids (Driskell et al., 2007; Hofmann et al., 2002). Microscale surfaces are able to benefit from increased analyte flux through convection because of the formation of an analyte depletion zone, though the improvements introduced by convection have been shown to only be marginal for nanosensors (Ekins et al., 1998; Dahlin, 2012; Sheehan and Whitman, 2005).

A substantial body of literature exists for the modeling of the convective, diffusive and adsorptive processes that occur in surface based assays, ranging from analytical models in the limiting case of a perfectly absorbing surface to full numerical analyses over a range of binding regimes. The results from such models, particularly the numerical methods, have provided insights into the behavior of the assay system, as well as the identification of relevant parameters and guidelines for the optimization of assay design (Squires et al., 2008; Hofmann et al., 2002; Hansen et al., 2012; Vijayendran et al., 1999; Levich, 1962; Skykes et al., 2014). Particle based assay platforms have already demonstrated promising performance characteristics, such as small reaction volumes, high levels of sensitivity and reaction times on the order of 1 h for largely unoptimized platforms (Levich, 1962; Skykes et al., 2014; Chon et al., 2009; Neng et al., 2010; Sha et al., 2008; Huynh et al., 2016). An analytical solution exists for the system of equations describing the diffusion of analyte to a freely diffusing sphere in an unstirred solution under a boundary condition of perfectly absorbing sphere, and this can provide initial estimates of how the spherical capture system would perform compared to planar capture surfaces (Sha et al., 2008). The analytical solution lacks the ability to estimate the fundamental figure of merit in assay design, that of the number of analytes which bind over a range of initial analyte concentrations and dissociation constants. A full numerical analysis of particle based reaction systems would provide insight into this key figure as well as the interplay of the variables specific to this emerging assay platform that can be utilized for the refinement and optimization of assay design.

In this paper, our aim is to identify the effects of the parameter space involving particle concentration, particle diameter, initial analyte concentration and dissociation constants on the number of analytes captured and the governing regime of the system through the use of a numerical reaction-diffusion model. The outcomes of the concentration profile as a function of space and time, analyte capture and interparticle spacing are used to understand system equilibrium and to derive quantitative descriptions of the system such as the Damköhler number (Da) and analyte depletion depth (δ). The results of the numerical model that are characteristic of previously published experimental conditions for nanoparticle assays are compared to other common assay platforms, such as microspots and nanowires, to understand how particle based sensing systems fit into the detection platform landscape. The case study of antibody-antigen binding presented here can easily be adopted for capture systems such as DNA hybridization, extending the relevancy of the model to other biomolecular recognition platforms (Seinfeld and Pandis, 1998). From the outcomes of the numerical model, we provide guidelines in the design and optimization of particle based assays, and hope to contribute to the understanding of the physical processes that occur in microparticle and nanoparticle systems to advance their applications in rapid diagnostics and POC settings.

2. Theory

The reaction-diffusion process, whereby a target analyte diffuses through the sample solution and undergoes reversible binding with an immobilized capture probe at a particle surface, was modeled by Fick's law expressed in a spherical geometry. Due to symmetry, the differential equation was dependent only on the radial spatial variable

$$\frac{\partial C}{\partial t} = D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) \tag{1}$$

and subjected to a Neumann boundary condition far from the particle surface,

$$\frac{\partial C}{\partial r} = \text{at } r0 = R \tag{2}$$

and a flux boundary condition at the particle surface,

$$\frac{\partial \Gamma}{\partial t} = D\frac{\partial C}{\partial r} \text{ as } r \to r_0 \tag{3}$$

with an initial condition of constant analyte

$$C = C_0 \text{for } r_0 < r \leqslant R \text{ at } t = 0 \tag{4}$$

The particle surfaces were modeled as being functionalized with antibodies that capture antigen from solution according to the first-order equilibrium expression