Random-walk model of magnetic bead-based surface coverage immunoassays

M. Cornaglia, R. Trouillon, H.C. Tekin, T. Lehnert, and M.A.M. Gijs

Laboratory of Microsystems, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

We recently introduced a new kind of bead-based surface coverage immunoassay, based on the specific interaction between surface-bound “small” magnetic beads (1 µm in diameter) and a flow of “large” magnetic beads (3 µm in diameter), the latter ones carrying antigens (Ags) and being simultaneously used as detection labels. [1] While this immunoassay technique allows attaining extremely low limits of detection, down to the attomolar concentration range, the origin of this noteworthy performance remained unclear up to now. Furthermore, dose-response curves obtained with this assay, as well as with similar bead-based techniques, show a peculiar non-linear dependence on Ag concentration, which was so far unexplained.

In this work we introduce a comprehensive theoretical model finally allowing complete understanding of these unsolved issues. Our model is based on the concept of “magnetic bead-scanning”: in our assay, large magnetic beads, each one carrying down to single Ags, while transported by hydrodynamic forces, are subjected to sequential stochastic reorientations induced by magnetic dipolar interactions with substrate-bound small magnetic beads (Figure 1). We identify the “magnetic bead-scanning” as the main assay feature distinguishing our work from previously reported bead-based surface coverage assays. [2, 3] To describe and predict this phenomenon, our model encompasses a “random walk-based” description of the bead capture, in which the displacement of the contact point between an Ag-carrying large bead and the small magnetic bead pattern is modeled by stochastic moves over the surface of the moving particle, until this point coincides with the position of an Ag, thus resulting in the bead specific capture.

Our model elucidates the extremely low limit of detection attained with this kind of assay by carefully considering the probability of single immunocomplex formation, which is dramatically enhanced by the bead-scanning mechanism (Figure 2). The random walk-based modeling approach allows then explaining the exact behavior of the assay dose-response curves, for different ligand-receptor systems and over a wide range of Ag concentrations (Figure 3). Because of the pioneering nature of our model in explaining the principle of ultra-low sensitivity detection, we believe that the proposed model will represent a powerful tool for the design of novel magnetic bead-based immunoassays with unprecedented performance and limit of detection.

[1] H. C. Tekin, *et al.*, *Lab on a Chip* **2013**, *13*, 1053-1059,
[2] S. P. Mulvaney, *et al.*, *Biosensors & Bioelectronics* **2009**, *24*, 1109-1115
[3] V. N. Morozov, *et al.*, *Analytica Chimica Acta* **2006**, *564*, 40-52

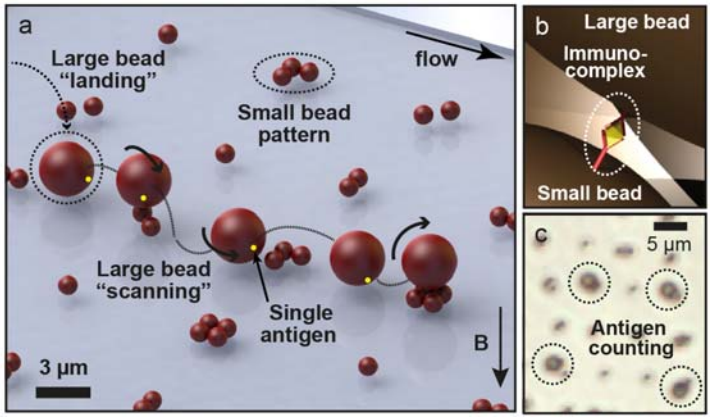

Figure 1. (a) Schematic representation of the principle of our magnetic bead-based assay. (b) Specific immunocomplex formation at the interface between a large and a small bead is responsible for the capture of large beads on the array. (c) Counting of the number of captured large particles provides the measure of the Ag-concentration in the sample under test.

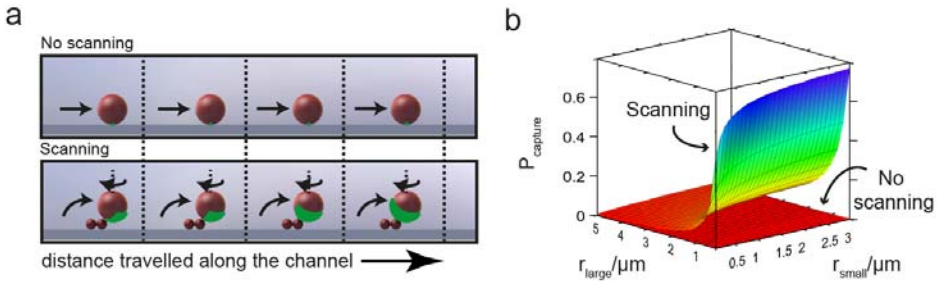

Figure 2. (a) In case of no bead-scanning, large magnetic beads slide over the substrate and probe it at one point, providing only a single chance for ligand-receptor binding. This is due to the pinning of the beads' magnetic moment imposed by the external magnetic field. Bead-scanning instead occurs when large beads move in presence of a magnetic field and the small bead array. In this case, the contact point describes a line on the surface of the large particle, increasing the chance for ligand-receptor encounter. Moreover, a different section of the large bead surface is explored at each interaction with a small bead group. (b) Probability of specific capture of single large beads ($P_{capture}$), as a function of the radii of the large and small beads.

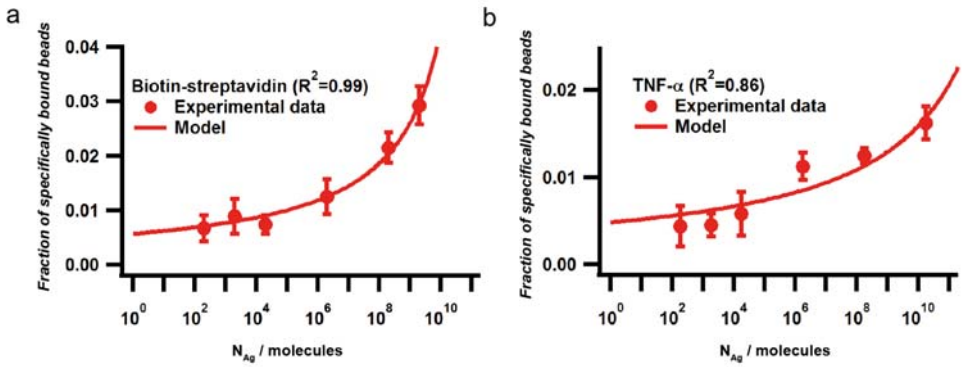

Figure 3. Experimental results of detection of (a) biotinylated anti-streptavidin and (b) TNF-α, spiked as Ag in 5 µL fetal bovine serum (FBS), as obtained from [1] and fitted according to our model predictions. The "random-walk" modeling approach explains the particular behavior of these experimental dose-response curves, for both ligand-receptor systems and over the whole range of analyzed concentrations.