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The effect of report particle properties on lateral flow assays: A mathematical model

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ABSTRACT

Lateral flow assays (LFAs) have found widespread applications in biomedical fields, but improving their sensitivity remains challenging mainly due to the unclear convection-diffusion-reaction process. Therefore, we developed a 1D mathematical model to solve this process in LFAs. The model depicts the actual situation that one report particle may combine more than one target, which overcomes the deficiency of existing models where one report particle combines only one target. With this model, we studied the effect of report particle characteristics on LFAs, including binding site density, target analyte and report particle concentration. The model was qualitatively validated by reported experimental data and our designed experiments where the report particle with different accessible binding site (HIV-DP) densities is obtained by changing the ratio of HIV-DP and Dengue-DP in preparing AuNP-DP aggregates. The results indicate that a strong signal intensity can be obtained without consuming excess detector probe with the optimum binding site ($\mathbf{N}=30$). A maximum normalized target concentration of 120 is obtained to prevent the false-negative result, while a minimum normalized report particle concentration of 0.015 is recommended to produce a strong signal. The developed model would serve as a powerful tool for designing highly effective LFAs.

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1. Introduction

Lateral flow assays (LFAs) have shown promising applications in various fields, such as global and public health care [1] and environment monitoring [2], given their cost-effective, convenient, and rapid features. LFAs detect target analytes (*e.g.*, nucleic acid, protein, and cell) in samples through converting them into more easily detectable signals by using report particles with colored (*e.g.*, gold nanoparticles (AuNPs) [3]), luminescent (*e.g.*, upconversion nanoparticles (NPs) [4]), or magnetic (Fe_3O_4 NPs [5]) features. Specifically, the target analytes bind with report particles *via* bioreaction forming report particle–analyte complex, which flow *via* diffusion and convection through the test line as induced by the capillary force. The capture probes immobilized in the test line interact with the complex report particle–analytes and form a sandwich format complex (*e.g.*, capture probe–target–report particle). However, LFAs are generally developed empirically and associated with limitation of poor detection sensitivity, mainly due to the lack of understanding of the underlying mechanism of the convection–diffusion–reaction process in LFAs.

Generally, the report particle plays a significant role in the convection–diffusion–reaction process of LFA detection. To enhance detection sensitivity, significant experimental efforts have been put on assessing the effect of report particle characteristics on the LFA performance in the whole convection–diffusion–reaction process, including particle concentration, particle size, and the available binding sites to the target analyte [6]. For instance, the signal from up-converting phosphor particles first increases and then reaches a plateau with increasing particle concentration in detecting single-stranded nucleic acids using LFAs [7]. The detection limit

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increases with increasing report particle size, however a further increase in particle size has a detrimental effect on the detection limit [8]. Besides, particle size has an important contribution to signal intensity per particle and the maximum number of binding sites on the report particle surface [9]. Accordingly, composite report particles have been developed by coating NPs with chromogenic substance (*e.g.*, enzymes) [10] or linking NPs with other nanomaterials (*e.g.*, AuNP conjugate [11,12], Fe_2O_3 NPs [13], and silica nanorods [14]) to increase their size, binding site density, and signal intensity, which in turn improve the detection sensitivity of LFAs. In spite of these experimental advances, the underlying mechanism for the effect of the convection–diffusion–reaction processes on the performance of LFAs remains elusive.

To investigate the underlying mechanism, mathematical and numerical models have been adopted to evaluate the effects of crucial parameters (*e.g.*, concentrations of target analyte, report particle and capture probe) of LFAs. For instance, Qian and Bau introduced mathematical models based on the convection–diffusion–reaction equations to analyze LFAs with sandwich and competitive formats [15,16]. Zeng et al. proposed several algorithms (*e.g.*, extended Kalman filter (EKF) [17], hybrid EKF and the switching particle swarm optimization algorithm [18], particle filter approach [19], and particle swarm optimization method [20]) to simulate and improve the performance of sandwich-type LFAs. However, these existing models assume that one report particle only combines one analyte and neglect the structure of report particle to simplify the bioreactions in LFAs, which deviate from the actual condition where one report particle with numerous accessible binding sites may capture more than one target analyte [9]. Therefore, developing an effective mathematical model based on the real situation is necessary to reveal the effects of report particle with multi-binding sites on the detection result.

In this study, we developed a mathematical model based on the physical law of mass conservation to solve the 1D convection–diffusion–reaction process in LFAs. As the particle size determines the signal intensity, stability, flow characteristic and binding site density of AuNPs, the mathematical study is focused on studying the effects of binding site density and AuNP concentration, which play crucial roles on LFAs detections and can be validated by experiments qualitatively. The model was qualitatively validated by reported experimental data in literature and also our specially designed experiments where the report particles with different accessible binding site (HIV-DP) densities were obtained by changing the ratio of HIV-DP and Dengue-DP in preparing gold nanoparticle (AuNP)-DP aggregates. With this model, we investigated the relationship between report particle and target analyte concentrations, and the LFAs performance. The developed model would provide a physically intuitive illustration of the corresponding experimental results and could help optimize the design of highly sensitive LFAs.

2. Materials and methods

2.1. Experimental section

2.1.1. Preparation and modification of AuNPs

In the experiment, a nucleic acid of HIV is selected as the target analyte, and a part of its complementary base sequence is the available detector probe (HIV-DP) on AuNP surface. To keep the stability of AuNPs, an abundant detector probe is added to the AuNP solution fully coated on the AuNP surface, forming AuNP-DP aggregates. Therefore, a mixed solution of detector probes, including HIV-DP and Dengue-DP with different mixing proportions, is proposed to investigate the effect of report particle with multiple binding sites. The oligonucleotide sequence (Dengue-DP) doesn't participate in any chemical reactions (Table 1) and is only used to occupy the remainder binding sites on the AuNP surface and to adjust the mixing proportion of HIV-DP in the mixed solution of detector probes in preparing AuNP-DP aggregates.

To achieve different binding site densities, both HIV-DP and Dengue-DP are thiolated and mixed with different proportions to make a mixed detector probe solution. These mixed solutions of detector probes are added to the AuNP solution in different tubes to form AuNP-DPs aggregates with different proportions of HIV-DP. The preparation details are as follows. First, AuNPs with an average diameter of 13 ± 3 nm are prepared following the protocol from our previous study [11]. Subsequently, to activate the HIV-DP and to obtain a final concentration of 100 μM, 4 μL of 10 mM TCEP, 20 μL of 500 mM acetate buffer (pH 4.76), and 100 μL of ultrapure water are added to the HIV-DP, while 8 μL of 10 mM TCEP, 39 μL of 500 mM acetate buffer (pH 4.76), and 194 μL of ultrapure water are added to the Dengue-DP to activate the Dengue-DP and to obtain a final concentration of 100 μM. Using the HIV-DP and Dengue-DP, we prepare six mixed detector probe solutions with different HIV-DP/Dengue-DP ratios, namely, 10:0, 8:2, 6:4, 4:6, 2:8, and 10:0, respectively. The six solutions and 5 mL of the prepared AuNP solution are added to six tubes (labeled #1–#6) successively for preparing AuNP-DP conjugates with different binding sites as our previous study [11].

Although the quantitative binding site density is unsure, the different HIV-DP densities of the AuNP-DP conjugate increase with increasing proportions of HIV-DP in the mixed detector probe solutions. Therefore, six different binding site densities on the surface of AuNPs with the same particle size can be obtained by tuning the proportion of HIV-DP in the mixed detector probe solution. A typical proportion of HIV-DP/Dengue-DP (6:4) in the mixed detector probe solution is added to the AuNP solution for an ideal case (Fig. 1c). This figure implies that 60% of the HIV-DP binding sites on AuNP are available to capture the target HIV.

2.2. Mathematical model

2.2.1. Development of the model of the convection-diffusion-reaction process in LFAs

The LFA strip mainly comprises three pads (*e.g.*, immersing, detection, and absorption pads) and two lines (*e.g.*, test and control lines) (Fig. 1a). The specific target analyte (**A**) (*e.g.*, oligonucleotide sequence) exists in the sample, and the report particles (**P**) (*e.g.*, AuNPs) are encapsulated in the immersing pad near the side of detection pad. The capture probe (**R**) and the control probe (**C**) are immobilized in the test and control lines in sequence. The detail preparation process of LFA strip is shown in the Supplemental Information.

After the liquid sample with target analyte (**A**) is added to the sample pad, the sample flows to the conjugate pad as driven by capillary force. The report particles (**P**) are dissolved and migrate as fluid flows. In the detection pad, the report particle (**P**) can combine specifically with specific analyte (**A**) based on the complementary base-pairing reactions to form complex (**PA**). The **A** and **PA** further interact with the capture probes (**R**) to form complexes **RA** and **RPA** in the test line, where a red signal appears gradually with accumulation of complex **RPA** (Fig. 1bi). Meanwhile, the remaining report particles will be captured by the control probe (**C**) to form complex **CP** in the control line, where a red signal will also appear with accumulation of **CP**. Once the sample with a certain amount of target analytes is added to the sample pad, the test and control lines appears gradually, indicating a positive result (Fig. 1a). If the target analyte concentration is below the detection limit, only the control line works and the test line does not appear, indicating a negative result. If the control line does not appear, the device fails on account

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