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Rapid and repetitive immunoassay with a surface acoustic wave device for monitoring of dust mite allergens

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ABSTRACT

In this work, we investigated a new approach to shorten a measurement time of house dust mite (HDM) allergens with a surface acoustic wave (SAW) immunosensor for improvement of continuity in monitoring of airborne HDM. It was achieved by employing differential method with which a slope of phase change was used as a sensor output instead of a phase shift that was used conventionally. Compared to the conventional method, measurement time of Group 1 HDM allergens of *Dermatophagoides farinae* (*Der f* 1) was shortened by 10 min from 30 min, while a sensitivity of SAW immunosensor was comparable (limit of detection of 20.1 ng/mL). 300 ng/mL *Der f* 1 was repeatedly measured ten times by the differential method, and it resulted in highly reproduced sensor output as represented by a coefficient of variation of 5.7%. In addition, due to smaller amount of bound detection antibodies on the sensor surface, decline of the baseline during the semi-continuous measurement that happened in the conventional method was not observed. Selectivity of the differential method was also investigated with four different common environmental allergens including *Der f* 1. No significant output was observed from the samples without *Der f* 1, and a high selectivity of the differential method with SAW immunosensor was validated. These results suggest that use of the differential method with SAW immunosensor would lead to advanced semi-continuous measurement with high continuity of airborne HDM allergens when it is incorporated with a monitoring system.

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1. Introduction

The prevalence of allergic diseases is rising and becomes a global public health issue. Environmental allergies are caused by such allergens as pollens and house dust mites (HDMs) which widely exist in living and working environments. Typical symptoms of environmental allergies are rhinitis and asthmatic attack [1–4] and there are about 300 million patients of the allergy-related asthma worldwide [3]. HDMs are sources of environmental allergens including *Dermatophagoides farinae* group 1 (*Der f* 1) and 2 (*Der f* 2), and *Dermatophagoides pteronyssinus* group 1 (*Der p* 1) and 2 (*Der p* 2) [5–7]. Group 1 and 2 are classified by origins of the proteins: group 1 is derived from mite bodies and group 2 is from digestive organs. Due to their strong allergenicity, the World Health Organization (WHO) set 20 ng/mL as a standard for sensitization and development of asthma [8–10]. Although main routes to develop HDM-related allergy diseases are inhalation and skin contact to airborne HDM allergens [11–13], HDMs are usually quantified from dust collected from a floor [6,12,14–16]. For prevention of the allergy diseases, it is important to follow fluctuation of airborne allergens in environments that is affected by many factors such as temperature, humidity and human activities [17,18] and to avoid exposure to them. Therefore, an on-site monitoring system that allows to continuously measure the airborne allergens in a living environment is expected to be useful for the prevention.

The monitoring system could be developed by combining two devices: an airborne allergen sampler that draws air containing

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airborne allergens, and a sensor that repeatedly measures the collected allergens [19–21]. In the system the allergens could be measured as follows: Firstly, airborne allergens are collected by the sampler in the gas phase; then, they are transported to the immunosensor in the liquid phase. After the measurement, the sensor is regenerated and another measurement is taken place. In future, these process could be fully automated. Although loss of the allergen sample at the gas-liquid interface is expected, the large number of measurements with a single sensor chip is more convenient for users because frequent exchange of the chip is not necessary; therefore the immunosensor should be in the liquid phase for long-term stability. In this work, we focused on the sensor for the monitoring system and HDM samples were measured in the liquid phase.

Conventionally enzyme-linked immunosorbent assay (ELISA) is widely used to measure the concentration of HDMs due to its high sensitivity [12,21,22]. Recently several researchers introduced alternative state of the art methods for the measurement. For example, Morris et al. developed a quartz crystal microbalance (QCM)-based immunosensor for monitoring of airborne cat allergens [23]. They demonstrated direct measurement of cat allergen from dust without separation. Shen et al. developed an electrochemical apatasensor for detection of HDM allergen. The sensor was comprised of nanostructured gold layer and employed impedimetric method for the measurement [24]. Huang et al. reported a method to enhance the signal in surface plasmon resonance (SPR)-based immunosensor for HDM allergen [25]. They utilized effective binding of an intact polyclonal antibody to the allergen for the signal amplification. In addition, several time-series studies of bioaerosols were also reported. Takahashi et al. demonstrated monitoring of airborne pollen allergens by SPR [26], and Tovey et al. introduced a device allowing to trace a personal HDM exposure over 24 h [22]. However, these above mentioned research focused more on a single detection or monitoring of relatively long-term change of allergens (e.g., at a time-interval of several hours to a month). There are few studies that concentrate on the concentration change at a short time interval, e.g., every couple of minutes, and relation between this fluctuation and impact on health. Therefore a sensor that allows rapid measurement of allergens is highly valuable.

Recently, we introduced a surface acoustic wave (SAW) immunosensor for the monitoring system that allowed repetitive measurement of *Der f* 1 [10]. A SAW sensor is superior in size of a whole system to a SPR sensor as is unambiguous from the application of SAW device in mobile phones, which is important when implementing the sensor into the monitoring system. In contrast, the SPR is usually more sensitive than the SAW. The SAW immunosensor was composed of a SAW device [27,28] and a highly stable ORLA85 protein monolayer. Due to high pH resistance of the protein monolayer [29–32], the sensor surface could be regenerated multiple times without significant degradation, and sensor output was highly reproduced in 10 repetitive measurements. Although duration of a single measurement was 30 min including the regeneration which is much shorter than that of ELISA, it is important to further improve continuity of measurement by shortening the measurement time so that the system enables to follow a much shorter-term fluctuation of airborne allergen concentration. Also a gradual decline of the baseline was observed during the repetitive measurement. It would deteriorate a reproducibility of the sensor output because this decline could be attributed to imperfection of the sensor surface regeneration; thus, there would be less binding sites for *Der f* 1. Therefore, in this work, we focused on advancing rapid measurement of HDM allergens with a stable baseline by employing differential method. A slope of phase change was used as a sensor output instead of a shift of the phase that was used conventionally. Since it was not necessary to wait until binding of detection antibodies was completed for the differential method, total measurement time was expected to be shortened. We also assessed a reproducibility of the output and selectivity of the differential method because these characteristics were as important as shortening of the measurement time to eventually apply it to the monitoring system.

2. Experimental

2.1. Reagents and chemicals

Ethanolamine and β-mercaptoethanol (BME) were purchased from Sigma-Aldrich. Sodium dodecyl sulfate (SDS), sodium acetate and acetic acid were from Wako. *Der f* 1, capture (cAb) and detection (dAb) antibodies for *Der f* 1 were from Indoor Biotechnologies. *Der f* 2 was bought from Seikagaku Bio Business. Japanese cedar (Cryptomeria japonica) pollen allergen (*Cry j* 1) was from Hayashibara Biochemical laboratories. Coarse extraction solutions of ragweed-pollen allergen (*Amb a* 1) was purchased from ITEA. A crosslinker, PEGylated bis(sulfosuccinimidyl)suberate ($BS(PEG)_5$), was from Thermo Fisher Scientific. Orla IgGBinder-G kit containing a mixed solution of protein G-fused Orla protein (ORLA85 protein) and 11-mercaptoundec-11-ylhexaethylene glycol (HS-C11-EG6, PEG-thiol), and tris(2-carboxyethyl)phosphine (TCEP) and Tris-HCl buffer solution (50 mM, pH 7.5) was from Orla Protein Technologies. Phosphate buffered saline (PBS) with Tween 20 (PBS-T) was prepared by adding Tween 20 (0.05% (v/v)) to PBS solution (10 mM phosphate buffer, 140 mM NaCl, 3 mM KCl, pH 7.4). Acetate buffered saline (ABS) was prepared by adding acetic acid solution (10 mM) to sodium acetate solution (10 mM) until pH reached a desired value. A mixture of ABS and Tween 20 (ABS-T, 0.05% (v/v) Tween in ABS) was prepared in the same way as PBS-T was prepared.

2.2. Preparation of the SAW immunosensor

A SAW chip was composed of input and output transducers, a delay line and a reflector. They were fabricated by depositing 90 nm thick gold on a cleaned 36Y-X quartz substrate, and then by conducting lift-off process. Shear horizontal (SH)-SAW was employed because it showed less attenuation into a liquid. SH-SAW was excited at the input transducer, and propagated on the delay-line to the reflector and back to the output transducer. The SAW immunosensor was prepared by modifying a surface of the delay-line with a self-assembled monolayer (SAM) of ORLA85 protein and PEG-thiol, then by immobilizing cAb on the modified surface (Fig. 1A) [10]. For the SAM formation on the delay-line, initially the surface was incubated with 1% (v/v) BME in ultrapure water for 5 min to render the surface hydrophilic and prevent non-specific hydrophobic adsorption of ORLA85 proteins [32]. Dithiols for anchoring of ORLA85 proteins onto the gold surface were formed by reducing disulphide bonds of the proteins. It was made by mixing the protein solution with TCEP solution (TCEP 150 mg/mL in Tris-HCl) and leaving the mixed for 30 min. Then the mixed solution was applied to the delay-line, and 10 min incubation was conducted to form the SAM. Non-covalently bound ORLA85 proteins and PEG-thiols were removed by washing the surface with 1% (w/v) SDS in ultrapure water. This process of the SAM formation was repeated twice to increase the surface density.

Preparation of the SAW immunosensor was completed by crosslinking cAb to ORLA85 protein (Fig. 1B). Firstly, 100 μg/mL cAb in a buffer solution at an optimum pH was added and left for 10 min to bind cAb to protein G of ORLA85. Then crosslinking reagent, 0.5 mM $BS(PEG)_5$ in PBS-T, was added and left for 10 min to crosslink between cAb and protein G through reaction

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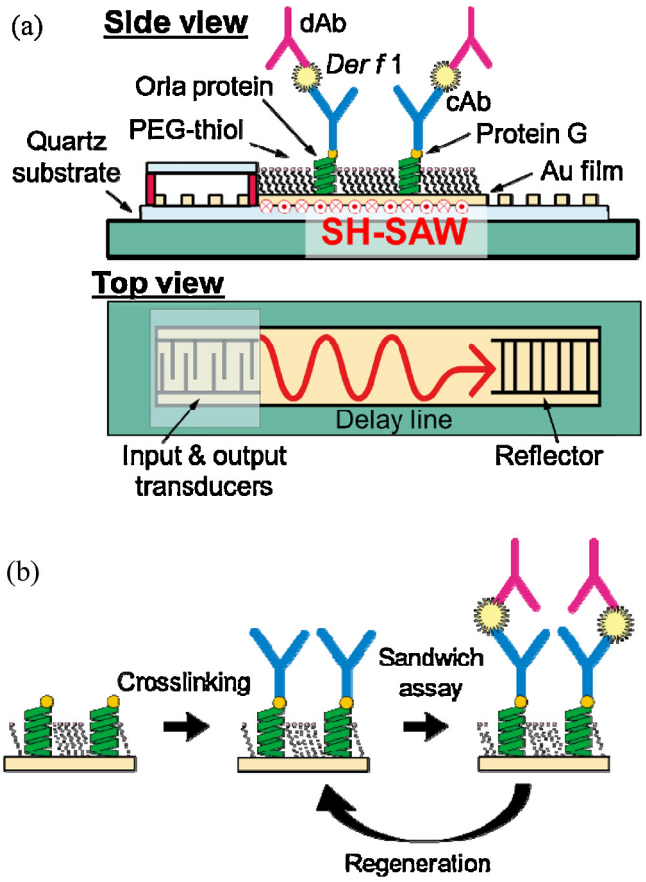


Fig. 1. (a) A schematic drawing of SAW immunosensor after binding of *Der f* 1 and dAb. SH-SAW propagates back and forth over a delay line. (b) Processes of cAb immobilization by crosslinking between cAb and protein G, and semi-continuous measurement of *Der f* 1. Shear horizontal-surface acoustic wave, SH-SAW; cAb, capture antibody; dAb, detection antibody.

of N-hydroxysuccinimide ester groups with lysine and N-terminal amino groups. Afterwards, 100 mM HCl and PBS-T were successively added to remove non-crosslinked cAbs from the surface. This process was repeated three times to increase immobilization rate (ratio of crosslinked cAb to bound cAb). Finally, 1 M ethanolamine pH 8.4 was added to passivate the unreacted active esters.

2.3. Rapid semi-continuous measurement of Der f 1

Semi-continuous measurement of *Der f* 1 was conducted with the prepared SAW immunosensor by repeating sandwich assay with *Der f* 1 and dAb, and surface regeneration by pH change (Fig. 1B). To shorten a measurement time and to advance continuity of the measurement, a slope of a phase change during dAb binding $\Delta P_{dAb}/\Delta t$ instead of a phase shift after dAb binding ΔP_{dAb} was used to determine the concentration of *Der f* 1. In the experiment, initially *Der f* 1 at a certain concertation in PBS-T was added and left for 10 min. After rinsing with PBS-T, 20 μg/mL dAb in PBS-T was added and left for 3 min. The slope $\Delta P_{dAb}/\Delta t$ was obtained by differentiating the phase change from dAb binding for 30 s by time. To assess the sensor performance in the rapid semi-continuous measurement, 300 ng/mL *Der f* 1 was repeatedly measured ten times using the differential method, and reproducibility of the sensor output in the measurement was evaluated.

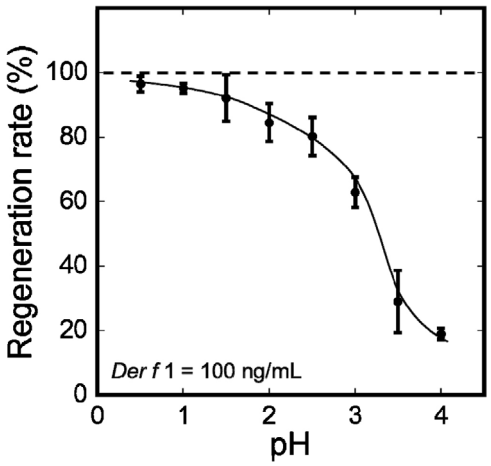


Fig. 2. Effects of pH of HCl solution on regeneration rate.

2.4. Selectivity of the SAW immunosensor in the rapid semi-continuous measurement

For assessment of the selectivity of the SAW immunosensor in the differential method, four common environmental allergens including *Der f* 1, *Der f* 2, *Cry j* 1 and *Amb a* 1, mixed solutions with (four allergens) and without (three allergens) *Der f* 1 were measured. Allergen concentration of each sample was 300 ng/mL in PBS-T, and the slopes of the phase changes during dAb binding $\Delta P_{dAb}/\Delta t$ were compared.

3. Results and discussion

3.1. Optimizations for sensor preparation and repetitive measurement

In cAb immobilization to the sensor surface, the binding condition of cAb to ORLA85 protein was optimized using different pH buffer solutions, ABS-T (pH 4.0–5.0) and PBS-T (pH 6.0–8.0), in which cAb molecules were diluted. The amount of the binding was evaluated from a phase shift from a baseline after 10 min biding of cAb (ΔP_{cAb}). It was found that the binding was maximized when using pH 6.0 PBS-T, and it was about 2.5-fold larger than that with pH 4.0 ABS-T (Fig. S1). This may be attributed to that acidic condition is optimum for binding of IgG molecules to protein G [33]. Therefore, pH 6.0 PBS-T was used for cAb binding in the subsequent experiments. In crosslinking, the immobilization rate ($\Delta a/\Delta b$) was increased from 77.3% to 98.0% while repeating the process three times (Fig. S2). This result suggested that 98.0% of affinity-bound cAb to protein G were successfully covalently bound and immobilized on the sensing area.

Optimum pH of HCl solution for regeneration was also investigated. HCl solutions with eight different pH (0.5–4.0) were used to assess the regeneration rate. The regeneration rate was defined as a ratio $\Delta P_{Re}/\Delta P_{dAb}$, where ΔP_{dAb} was a phase shift before regeneration from a baseline, and ΔP_{Re} was the shift between those before and after regeneration (see Fig. 3). Relation between the regeneration rate and the solution pH is summarized in Fig. 2. The rates were larger than 90% when using pH 0.5–1.5. The rate dramatically dropped above pH 3.0. The highest regeneration rate was observed when using pH 1.0; therefore, HCl solution with pH 1.0 was used for regeneration in semi-continuous measurement.

Fig. 3 shows a phase change during measurement of *Der f* 1. In conventional method using a phase shift ΔP_{dAb} as a sensor output, 10 min incubation for binding of dAb to *Der f* 1was required to obtain an adequate output. On the other hand, in the differential

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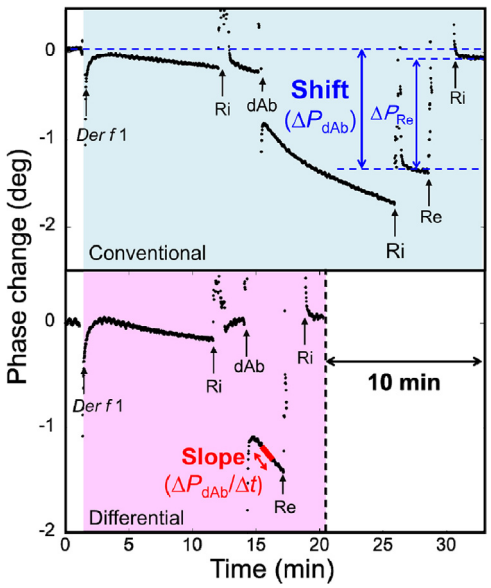


Fig. 3. Time courses of phase for the conventional method (upper) and the differential method (lower).

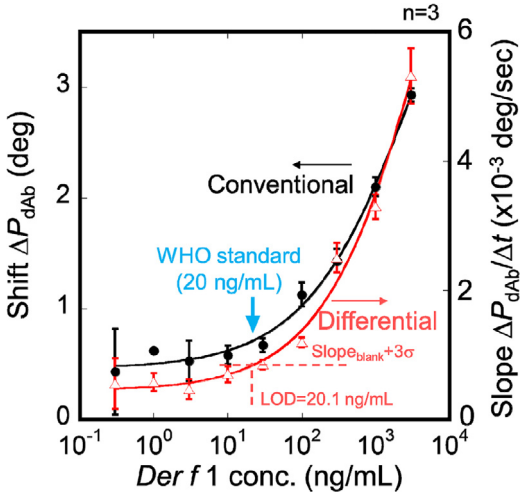


Fig. 4. Calibration curves of the conventional method (●) and the differential method (△) for *Der f* 1.

method, the incubation time was reduced to 3 min and the slope $\Delta P_{dAb}/\Delta t$ from 30 s was used as a sensor output. In addition, rinsing process after dAb binding was able to be skipped, and both non- and affinity-bound dAb was removed directly by HCl solution. This was because shortened incubation time lead to smaller amount of bound dAb, which made it easier to completely remove dAb and regenerate the sensor surface. As a result, the total measurement time was shortened by 10 min from the conventional measurement time of 30 min using the differentiation method. This further rapid measurement improved the continuity of immunoassays.

The sensor outputs obtained from both methods were compared by measuring various concentrations of *Der f* 1, and they were plotted in Fig. 4. The plots were fitted by the following equations for 0.3–3000 ng/mL with coefficient of correlations of 0.997 and 0.995, respectively:

$$\Delta P_{dAb}(\text{deg}) = A_1 + (B_1 - A_1)/\{1 + ([Derf1]/C_1)^{D1}\}, \quad (1)$$

$$\Delta P_{dAb}/\Delta t(\text{deg/sec}) = A_2 + (B_2 - A_2)/\{1 + ([Derf1]/C_2)^{D2}\}, \quad (2)$$

where $A_1 = 5.8$, $B_1 = 0.46, C_1 = 3940$ and $D_1 = -0.58$, and $A_2 = 1.3 \times 10^{-2}$, $B_2 = 4.5 \times 10^{-4}, C_2 = 7040$ and $D_2 = -0.60$ are the coefficients, and [*Der f* 1] is the concentration of applied *Der f* 1 in ng/mL. Limit of detection (LOD) was determined at the concentration where the mean slope of a blank sample $Slope_{blank}$ plus three times a standard deviation σ intersected the fitting curve. The LOD of the differential method was 20.1 ng/mL (0.80 nM), and the dynamic range was 100–3000 ng/mL. This LOD is comparable to other reported conventional and state of the art allergen detection methods such as electrochemical aptasensor (*Der p* 2, 16.47 ng/mL (1.2 nM)) [24], fiber-optic chemifluorescence sensor (*Der f* 1, 0.49 ng/mL (20 pM)) [20], ELISA (*Der f* 1, 0.58 ng/mL (23 pM)) [10], our previous SAW sensor (*Der f* 1, 6.1 ng/mL (0.24 nM)) [10], and SPR sensor (*Der f* 1, 13.7 ng/mL (0.55 nM)) [25]. Although ELISA and the fiber-optic sensor showed superior sensitivities to the differential method, the measurement time was notably shortened by the differential method (by about one order of magnitude), which was more important for the monitoring. Lower sensitivity than the previous SAW sensor might be attributed to a larger background of the blank sample. Conventionally the sensor output was a phase shift ΔP_{dAb} that was taken after rinsing of nonspecifically-bound dAb on the surface; thus only affnitiy-bound dAb contributed to the output. On the other hand, in the differential method the output was taken during the binding process; thus the output also contained the nonspecifically-bound dAb. This occurred even for a blank sample that had no *Der f* 1, and it resulted in a high background signal $Slope_{blank}$. However, considering that the standards for sensitization and acute attack of asthma are 20 ng/mL and 100 ng/mL, the differential method has a sufficient potential for implementation into the monitoring system with further optimizations.

Sensor performance using the differential method in semi-continuous measurement of *Der f* 1 was also evaluated. In experiments, 300 ng/mL *Der f* 1 was repeatedly measured ten times. Fig. 5A displays the phase changes for the entire measurement and relative slope $\Delta P_{dAb}/\Delta t$ at each measurement. Fig. 5B shows overlaid phase changes for the 1st, 5th, and 10th measurements. The phase changed with high reproducibility represented by a coefficient of variation (C.V.) of the slope $\Delta P_{dAb}/\Delta t$ of 5.7% for ten measurements. In addition, gradual decline of the baseline observed in previous work [10] in which the phase shift ΔP_{dAb} was used as a sensor output did not occur in this method. It was considered that the decline was attributed to imperfection of regeneration and residual molecules on the sensor surface; thus, there was less chance of the decline in the differential method with smaller amount of bound molecules. This result indicates that the SAW immunosensor holds a potential to measure the airborne allergens three times in an hour, keeping almost full binding sites on the surface.

3.2. Selectivity in rapid semi-continuous measurement

We examined the selectivity of SAW immunosensor employing the differential method with other three common environmental allergens: *Der f* 2, *Amb a* 1 and *Cry j* 1. 300 ng/mL sample solutions in PBS-T for each allergen, a mixture of three allergens (except *Der f* 1), and a mixture of the four (including *Der f* 1) were prepared. The slope $\Delta P_{dAb}/\Delta t$ for each sample was measured during dAb binding. The relative slopes were determined by dividing the slope of each sample by that of *Der f* 1 after subtracting it from the blank sample (no antigens). As summarized in Fig. 6, sensor output was observed only from the samples containing *Der f* 1. Especially no output from *Der f* 2 that has similar protein conformations to *Der f* 1 validates high selectivity of the differential method with SAW immunosensor [14,34–36].

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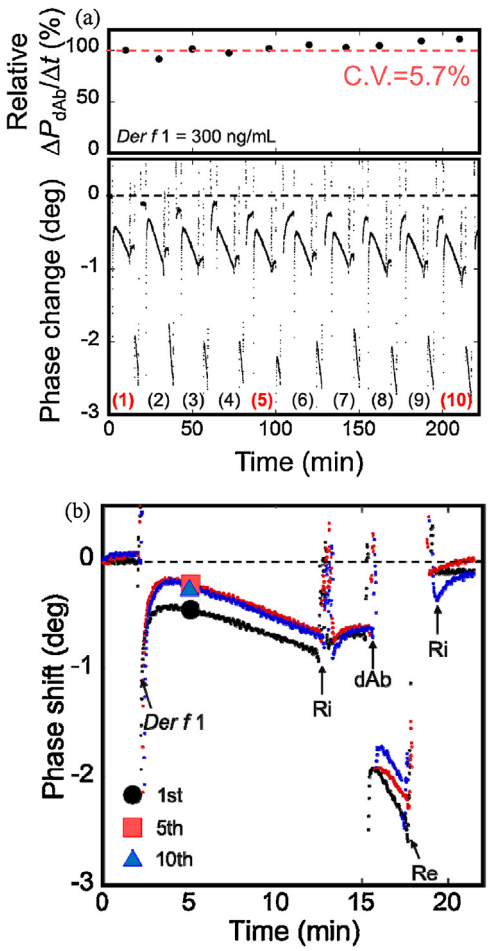


Fig. 5. (a) Phase change over ten repetitive measurements of *Der f* 1and output at each measurement. (b) the 1st (●), 5th (■) and 10th (▲) measurement picked up from (a).

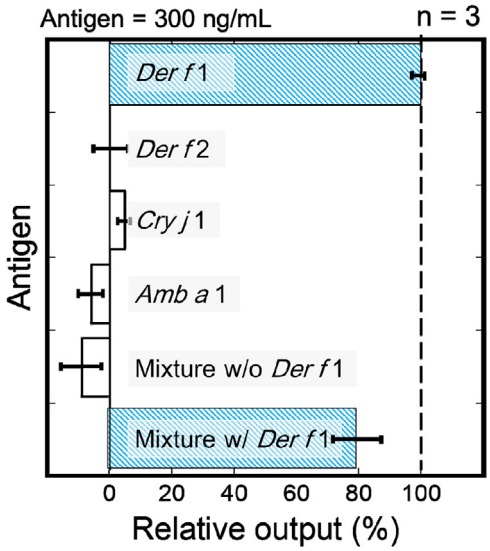


Fig. 6. Sensor responses to different allergens and a mixture of allergens. Hatched bars are the results from the samples containing *Der f* 1.

4. Conclusions

In this paper, we reported advanced rapid measurement using differential method for SAW immunosensor, and assessed the sensor performances. Employment of the differential method allowed us to shorten the measurement time by 10 min from the conventional (30 min) along with sufficient sensitivity (LOD of 20.1 ng/mL) and selectivity (no response to the other allergens including *Der f* 2). It also provided capability of repetitive measurement with high reproducibility and few residual molecules after regeneration, which could allow longer use of the sensor in the monitoring system. These results demonstrate that it is effective to employ the differential method to shorten the measurement time and to advance continuity of the measurement to follow short-time fluctuations of airborne HDM allergens. In future work, we intend to further advance the rapid measurement, eventually to develop SAW immunosensor allowing to measure HDM allergens directly without dAb.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.snb.2017.01.183.

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