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SPR imaging based electronic tongue *via* landscape images for complex mixture analysis

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ABSTRACT

Electronic noses/tongues (eN/eT) have emerged as promising alternatives for analysis of complex mixtures in the domain of food and beverage quality control. We have recently developed an electronic tongue by combining surface plasmon resonance imaging (SPRi) with an array of non-specific and cross-reactive receptors prepared by simply mixing two small molecules in varying and controlled proportions and allowing the mixtures to self-assemble on the SPRi prism surface. The obtained eT generated novel and unique 2D continuous evolution profiles (CEPs) and 3D continuous evolution landscapes (CELs) based on which the differentiation of complex mixtures such as red wine, beer and milk were successful. The preliminary experiments performed for monitoring the deterioration of UHT milk demonstrated its potential for quality control applications. Furthermore, the eT exhibited good repeatability and stability, capable of operating after a minimum storage period of 5 months.

1. Introduction

Quality control of food and beverages is extremely important for both industrial and personal concerns. Traditional methodologies (e.g., gas or liquid chromatography), though accurate and reliable, are often time-consuming and laborious to perform. Consequently, there has been an increase in demand for new technologies able to provide reliable, inexpensive and rapid analysis in such contexts. In this regard, electronic noses/tongues (eN/eT) have demonstrated their interest, particularly when a full component-by-component analysis is not really necessary, such as for comparisons against a standard, discrimination of subtle differences during the manufacturing process, or detection of changes in the products as a function of time or conditions. [1–4] The eN/eT are multisensor systems consisting of an array of nonspecific and low-selective sensors with cross-sensitivity to different species in complex mixtures and uses advanced mathematical procedures for signal processing based on pattern recognition and/or multivariate analysis.

As the most common technique, electrochemical detection has been explored in the eN/eT context and has proven its efficiency. [5–10] Other detection systems include mass sensors and optical sensors. A variety of mass sensors based on multichannel quartz crystal microbalance (QCM) [11,12] and surface acoustic wave (SAW) [13,14] are promising. Optical sensing approaches have also played a very important role in the development of eT/eN [15,16]. For analysis of complex mixtures various optical systems have been developed, including colorimetric sensor arrays using metalloporphyrin dyes, [17,18] or boronic acid based peptidic receptors coupled with indicator displacement assays; [19] fluorescence change assays using fluorescent polymers, [20] fluorescent dyes, [21,22] porphyrin derivatives, [23] or gold nanoparticles-fluorophore complexes [24,25]; chemiluminescence sensor array using catalytic nanoparticles; [26] and photonic color sensor using porous nanoparticles [27]. However, these optical approaches may be limited by irreversible responses or long recovery times due to the strong interaction between analytes and receptors and by short lifetimes of some dye-arrays due to fluorescence bleaching. In addition, monitoring the binding events in real-time is extremely difficult using these systems. Finally, in some cases, the diversity of the sensing materials is limited due to the complicated design and laborious synthesis required for preparation of a set of differential receptors. In this context, combinatorial approaches were developed through polymer chemistry that has greatly accelerated the development and optimization of sensing materials for eN/eT applications [28–30]. However, in these approaches the use of fluorescent probes were necessary. In recent years, we have developed an electronic tongue system using surface

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plasmon resonance imaging (SPRi) as a detection system [31] taking advantages of its capabilities of monitoring binding events in a label-free, real-time and high-throughput manner. [32]

SPR has become one of the primary methods for investigating and quatifying biomolecules and interactions. This technique is routinely used for development of various biochips in our laboratory. [33–37] Besides, "lock-and-key" based SPR biosensors have been widely used for detection of analytes related to food quality and safety [38]. However, to the best of our knowledge, we were the first to combine SPRi with an array of nonspecific and cross-reactive receptors (CRRs) for electronic tongue development. To prepare the CRR array, a combinatorial approach was proposed based on self-assembly of different combinations of building block (BBs) on the gold surface of a prism *via* thiol/gold or disulfide /gold bond. In this concept, BBs are small and easily accessible molecules with various physicochemical properties (hydrophilic, hydrophobic, neutral, charged, *etc.*). The self-assembled monolayers (SAMs) of BBs allow facile tuning of physicochemical properties of the obtained combinatorial cross-reactive receptors (CoCRRs) by varying BB proportions in the mixtures. In this way, an array of CoCRR with a high diversity can be rapidly generated, for example, 11 combinations can be prepared with only two BBs mixed in concentrations varying from 0 to 100% in 10% increments and 66 by adding a third BB. In the current study, we prepared 11-CoCRR array using only two BBs, which are disulfides with lactose (BB1) and sulfated lactose (BB2) at the terminal functional group. They are both hydrophilic but BB1 is neutral while BB2 is highly negatively charged. The objective is to demonstrate the feasability of the obtained electronic tongue for the analysis of complex mixtures, such as wine, beer, and milk, based on pattern recognition. In addition, some preliminary tests were performed for monitoring the deterioration of UHT milk to demonstrate the potency of the eT for applications in the domain of food and beverages.

2. Materials and methods

2.1. Reagents and materials

The detailed synthesis of BB1 and BB2 and their chemical structures were given elsewhere [31]. Protein lectin from *Erythrina cristagalli* (ECL), sodium chloride, sodium dihydrogen phosphate, HEPES, sodium dodecyl sulfate (SDS), Tween 20 and glycerol were purchased from Sigma-Aldrich. All of them were used as received. Ultrapure water (18.2 MΩ cm) produced by a Purelab classic system (Elga) was used for the preparation of HEPES and phosphate buffer solutions (PBS).

Three types of complex mixtures, wine, beer, and milk, were tested. They were bought from a local supermarket and included three French wines: Côtes du Rhône, Bordeaux and Bourgogne; three beers: Stella Artois (Belgium), Leffe (Belgium) and Pelforth-dark (France); ultrahigh temperature (UHT) pasteurized milk. All the containers were freshly opened before treatment for analysis. The different wines were filtered twice through a 0.2 μm syringe filter and then diluted to 1% (v/v) solutions in HEPES buffer (10 mM HEPES, 150 mM NaCl, 0.005% Tween 20, pH 7.4). Beers were degassed by filtration under vacuum through a 22 μm sintered glass filter, filtered through a 0.2 μm syringe filter and then diluted to 10% (v/v) in HEPES buffer. For the UHT milk, all the samples used in this study were from the same bottle. To study the deterioration of the UHT milk, immediately upon opening some undiluted aliquots were prepared in open tubes and stored in a 25 °C thermostat-controlled water bath (Polystat; Fisher Bioblock Scientific). Measurements were taken 1, 24, 48, and 72 h after exposing the sample to air. The rest of milk was left in the bottle and stored at 4 °C. Before use, all the milk samples were directly diluted to 0.125% (v/v) solution in HEPES buffer, without filtering or any other pretreatment. In this study, different dilutions in HEPES buffer for the three complex mixtures was used in order to obtain comparable SPRi signal intensity.

2.2. Preparation of the CoCRR array

The CoCRR array was constructed by spotting pure and mixed solutions of BB1 and BB2 onto the gold surface of a prism, which was provided by GenOptics (Horiba Scientific, Orsay, France). Forty-eight hours prior to spotting, the prism was treated by plasma (0.6 mbar, 75% Oxygen, 25% Argon, power 40 W, 3 min) with a Femto plasma cleaner (Diener Electronic, Germany). Eleven [BB1]/([BB1]+[BB2]) ratios (0, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100%) were prepared in PBS (50 mM NaH_2PO_4, 50 mM NaCl, 10% glycerol, pH 6.8) at a total concentration of 0.1 mM. Then droplets of 8 nL of these solutions were spotted using a non-contact piezoelectric spotter (Siliflow, France) with four duplicates for each ratio. The prism was then left overnight at room temperature for self assembly of the CoCRRs. In each spot the ratio of the two BBs anchored on the gold surface was assumed to be equal to the molar ratio in the parent solution [39]. Finally, the chip was rinsed thoroughly with ultrapure water and dried under a flow of argon.

2.3. Analysis of complex mixtures by SPRi

SPRi combines the strength of SPR to monitor label-free biomolecular interactions to the throughput of microarrays (multiplexing). A collimated, polarized and monochromatic light beam is sent towards the functionalized gold surface through the prism to illuminate the entire surface of the array. The reflected light intensity is monitored and collected by a CCD camera where each pixel maps into a specific location on the gold surface and provides the surface information about that spot on the surface. In this way, SPRi allows monitoring simultaneously binding events on all the spots of the array. Herein, SPRi measurements were performed at a fixed working angle chosen at the highest slope of the plasmon curves where the measured intensity change is proportional to the change in effective refractive index, which in turn is proportional to adsorbate coverage.

In the present study, sample sensing was performed at 25 °C with an SPRi apparatus (Horiba Scientific) placed in a temperature regulated incubator (Memmert, Germany) using a 10 μL PEEK flow cell with hexagonal configuration. Freshly filtered and degassed running buffer solution HEPES was introduced using a computer controlled syringe pump (Cavro XLP 6000, Cavro scientific instruments, USA) which was connected to a degassing system (Alltech, France). Samples (500 μL) were injected using a 6-port medium pressure injection valve (Upchurch Scientific, USA) at 100 μL/min flow rate. Under these conditions, it took about 2 min for the samples to arrive in the flow cell and it took about 7 min to complete each sample injection.

Prior to exposing any sample, NaCl solution (8.55 mM) was injected onto the array to verify the response of each CoCRR for calibration [40]. In addition, in this study, ECL at 200 nM was used as a standard to evaluate the functionality of the eT in terms of stability and repeatability. For this, it was systematically injected onto each 11-CoCRR array at the beginning, several times randomly in the middle and at the end of each set of analysis. For the complex mixtures, including three different brands of wines, three beers, and UHT milk, at least three replicated injections and measurements were performed in a random order for each sample. After each injection, the array was rinsed with running buffer for 8 min and then regenerated with 2% SDS (w/w) dissolved in ultrapure water.

Upon sample injection, molecular binding occurred, resulting in light-up of spots with different intensities, which was registered by an 8-bit CCD video camera at a fixed interval of time (0.2 s). With the help of imaging software SPR images were then converted to variations of reflectivity (expressed as R%) versus time, giving a series of kinetic binding curves, called sensorgrams. Based on sensorgrams, two types of recognition patterns were generated: 2D continuous evolution pattern (CEP) by plotting the variation of reflectivity (*R*%) versus BB1% evolution at a fixed time, and 3D continuous evolution landscape (CEL) by adding an axis describing the BB1% evolution in the standard sensorgrams. In this study, they were both used as recognition patterns for differentiation and identification of the complex mixtures.

2.4. Data processing for classification of complex mixtures

Principal Component Analysis (PCA) was used for classification purposes. It takes data in *n* dimensions and reorients the axes along which the data are represented. The axes are chosen such that PC1 contains the majority of the response variance from the data, PC2 is orthogonal to PC1 and contains the second most response variance, etc. This mathematical approach is extremely useful for convenient visualization by re-expressing the original data along a truncated number of principal components, thus elucidating in two dimensions the natural response clustering of higher-dimensional data. Herein, for classification of wine, beer and milk samples PCA was performed using the appropriate package within Mathematica 8.0 software with the experimental data of 33 complex mixture injections where 11 ratios of the BB were considered as independent variables.

3. Results and discussion

Prior to each set of analysis, NaCl solution was injected onto the 11-CoCRR array. The response of all the CoCRRs to NaCl was very similar with a variance of less than 5%. This demonstrates that the sensitivity of all the CoCRRs is almost the same, illustrating that the change on each CoCRR upon sample injection is related only to its affinity to the sample.

3.1. Differentiation and identification of complex mixtures by the electronic tongue based on 2D and 3D recognition patterns

Upon the injection of the complex mixtures, the resulting sensorgrams (not shown) revealed that the CoCRR array was sensitive and responded quite differently to all these three kinds of samples. For better illustration, Fig. 1 shows an example of CEL and CEP for each species. Clearly, CELs and CEPs of the three complex mixtures were very different from each other.

Notably, due to the combination of the CoCRRs–SPRi, the obtained eT was able to "taste" the complex mixtures as vivid images, such as 3D CELs. Comparing to the sets of uncorrelated discrete date used for pattern recognition by conventional eN/eT system, in CELs the signal of one CRR correlates with others and an abnormal signal arising from a defective one can be easily identified. Meanwhile, CEL provides valuable information on real-time adsorption and desorption kinetics, which renders such kind of response pattern unique and illustrates well the advantages of SPRi over other optical techniques.

As for CEPs, they offered a more direct way to evaluate the binding affinity between all the CoCRRs and each beverage species. The CEP of each beverage species shown in Fig. 1 corresponds to the cross section of the CEL at the 13th minute after sample injection, which is 6 min after the end of the injection phase. At this time, the intensity of signal on the CoCRRs for each beverage species is more related to the binding affinity rather than to changes of refractive index systematically induced by the complex mediums. Gratifyingly, the CEP of red wine (Bourgogne) reached a maximum for the CoCRR containing 100% BB1 and was completely different from the ones obtained for beer and milk, which displayed maximal signals at 100% BB2. Moreover, the intensity of signal upon injection of milk was much higher than those following injections of beer or wine. Remarkably, for the milk sample the intensity of signal on the CoCRRs rich in lactose BB1 was very low, probably due to the competition of lactose present in abundance in milk. In a word, both their CELs and CEPs showed remarkable differences between each other and could thus behave as "fingerprints" for rapid differentiation and identification of each species.

3.2. Classification of complex mixtures by the electronic tongue

The capability of the eT for classification of complex mixtures was then investigated using a larger number of samples, including three different brands of red wines (Côtes du Rhône, Bordeaux and Bourgogne) and beers (Stella Artois, Leffe and Pelforth-dark), as well as UHT milk. For easier visualization, the data based on CEPs obtained from SPRi experiment were analyzed by PCA to classify these samples in a 2D single plot. As shown in Fig. 2, triplicate measurements for each brand of wine and beer were plotted together with fifteen replicated measurements for the UHT milk sample. Excellent separation of the three species was obtained using the two principle component axes to represent 97% of the variance in the original data set. This attested to the significant degree of success in the discrimination of these real-world complex mixtures using this model eT system.

Interestingly, the observation of the large distribution of data points in the milk cluster could be attributed to the age of the milk in 15 samples. As mentioned before in this study all wine, beer and milk samples were injected onto the array in a random order. Therefore, the freshness of 15 milk samples at the moment they were analyzed was not the same; some were used in the first hour after opening the bottle, and some others were used after 24 h storage at 4 °C. These results demonstrated that the eT is sensitive to the minor changes in the complex mixtures. Therefore, it may have potential for quality control applications.

3.3. Exploration of potential applications of the electronic tongue for quality control

To explore this point, a set of preliminary experiments were conducted for monitoring the deterioration of UHT milk over time. Immediately upon opening, undiluted aliquots of milk samples were stored at 25 °C in an open tube and measurements were taken 1, 24, 48, and 72 h after exposing the sample to air. The resulting 3D CELs are shown in Fig. 3A.

The pattern generated by the milk after the 1st hour of storage was barely distinguishable from that obtained after 24 h but easily distinguishable from those collected in the 48th and 72nd hours. Interestingly, the array allowed imaging the changes in the complex milieu with increasing storage time. The signals of the CoCRRs rich in BB 2 increased for storage time up to 48 h, then decreased: the CoCRR containing 100% of BB 2 displayed 4% reflectivity after one hour of aging, 5.5% after 24 h and 11.8% after 48 h. Then, the signal decreased to 1.5% after 72 h of aging, which was even lower than that of fresh milk and was associated with casein precipitation in the spoiled milk. The PCA shown in Fig. 3B corroborates the visual examination of the CELs. There was no clear separation between the clusters representing patterns of the milk samples after one hour and 24 h storage probably due to lack of major changes between the two stages while excellent

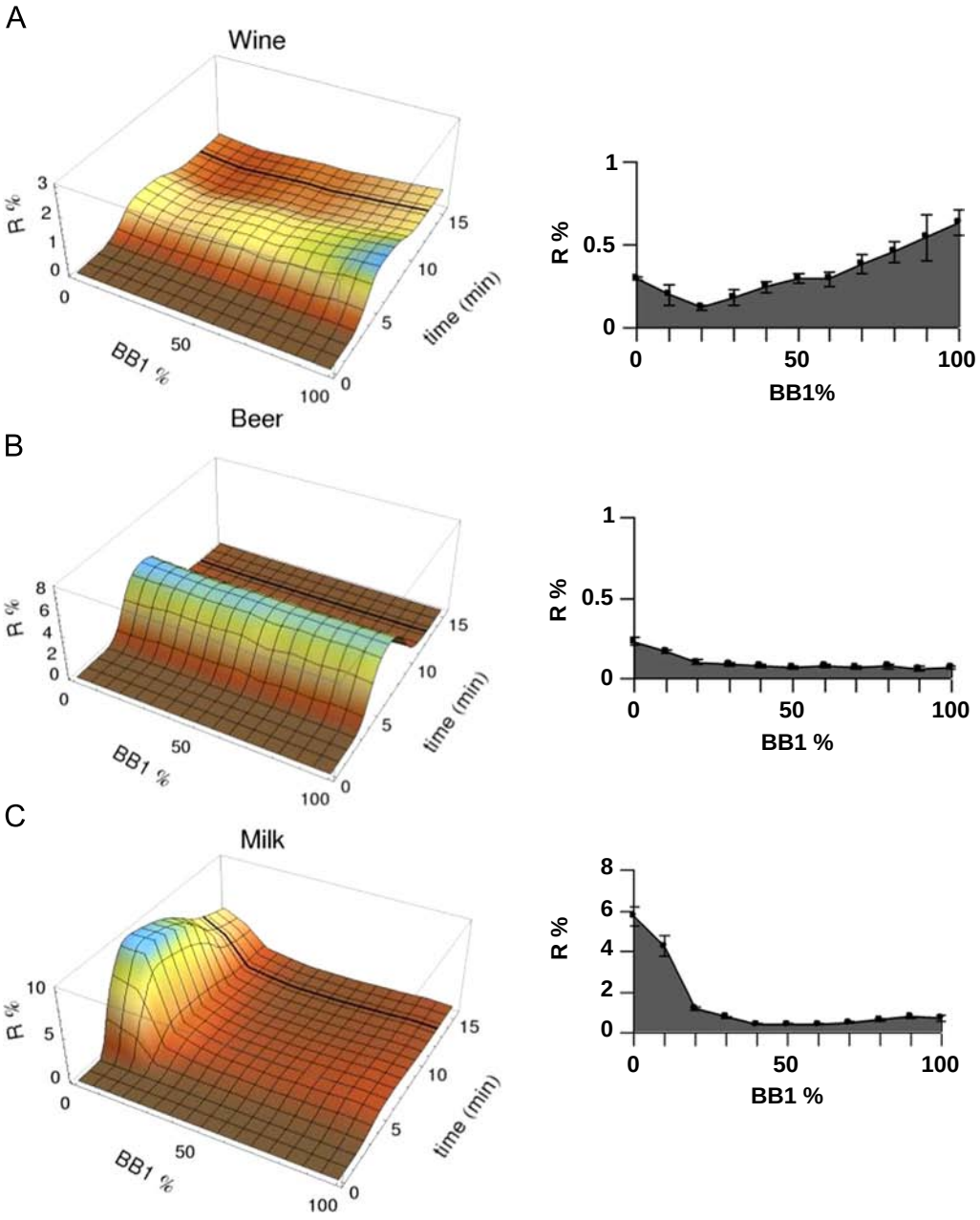

Fig. 1. Examples of 3D continuous evolution landscapes (CEL) and 2D continuous evolution profiles (CEP) at the 13th minute after sample injection generated by the 11-CoCRR array: A) red wine (Bourgogne), B) beer (Leffe) and C) UHT milk. Each error bar in 2D CEPs represents the standard deviation of four duplicates of the CoCRRs on the same array.

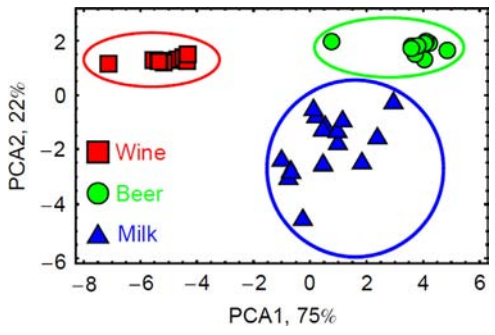

Fig. 2. PCA score plot using two principal components representing 97% of the variance from the original data for the classification of complex mixtures wine, beer, and milk.

discrimination was achieved between these samples and those stored for 48 and 72 h. These preliminary results showed that the CoCRRs–SPRi eT is sensitive to the changes associated with the deterioration of the milk and thus demonstrating the potential of such a system for quality control applications. It is noteworthy that the eN/eT approach does not give quantitative information about individual components so it is complementary to, rather than competitive with, traditional analysis methods.

3.4. Repeatability and stability of the electronic tongue

Evaluating repeatability and stability, two important features of any eN/eT system, is much more complicated for systems incorporating multidimensional sensor arrays than for devices based on single sensors. Herein, the repeatability was not evaluated for each

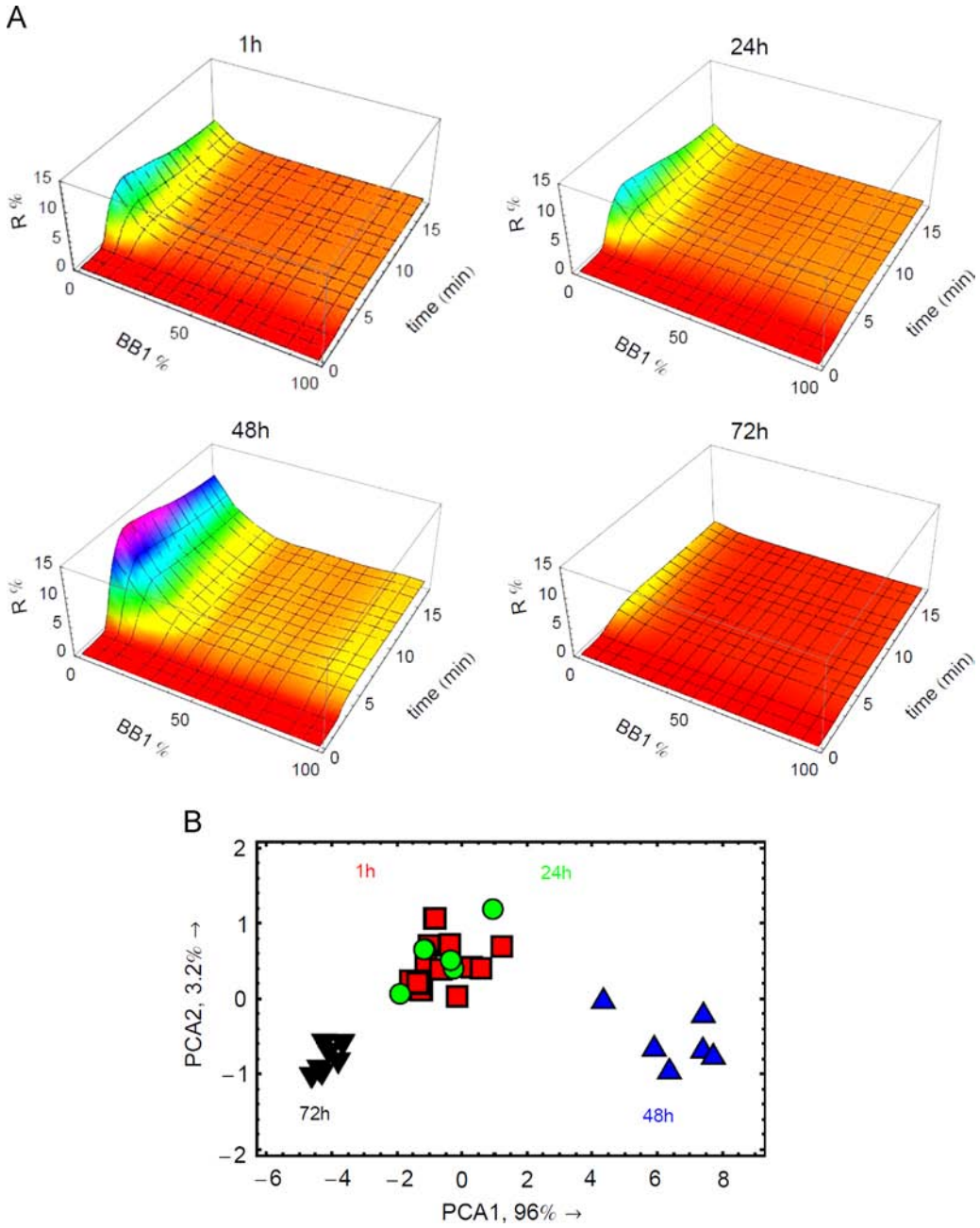

Fig. 3. A) 3D CEL of the milk in the 1st, 24th, 48th, and 72nd hour after opening. B) PCA score plot derived from the data obtained using these milk samples, each with at least six replicates. The two principal components represent 99.2% of the variance from the original data.

CoCRR individually but for the correlation between the overall 2D CEP patterns obtained with replicated measurements. The continuous evolution profiles must be evaluated holistically to provide an accurate assessment of repeatability since in our CoCRRs–SPRi eT design the relationship between each ratio and neighboring points is crucial to understand the agreement between two full patterns. The correlation coefficient C_{12} between two full patterns for experiments 1 and 2 was defined as follows,

$$C_{12} = \frac{\sum_{BB1\%} R_1(BB1\%)R_2(BB1\%)}{\sqrt{\sum_{BB1\%} R_1^2(BB1\%) \sum_{BB1\%} R_2^2(BB1\%)}}$$

with R_1(BB1%) referring to SPRi signals based on the CEP at the 13th minute for experiment 1 with various ratios in BB1%.

As mentioned previously, pure protein ECL (200 nM) whose CEP was well established in our previous work [31] was used for evaluating the repeatability and stability of the eT. It was systematically injected onto the 11-CoCRR array at the beginning, several times randomly in the middle and at the end of each set of analysis. In this study, a set of analysis consists of more than 50 sample injections for ECL and all complex mixtures/regeneration cycles. Based on experimental results, a correlation of $>99\%$ was obtained between any two full patterns of CEP for ECL. Remarkably, even for the complex mixture samples the coefficient C_{12} between the CEPs upon replicated injections is also $>99\%$. These results demonstrate both excellent measurement to measurement repeatability of the eT system and good stability under continuous use.

Furthermore, we have addressed the long-term stability of the eT upon storage by performing regular injections of the ECL

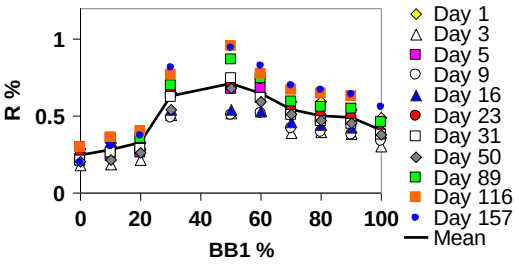

Fig. 4. CEPs of the reference ECL (200 nM) obtained by performing regular injections on a single 11-CoCRR array over a period of 5 months for evaluation of long-term stability of the electronic tongue upon storage at 4 °C. The profile in each color was obtained by averaging the signals of the four duplicates for all the CoCRRs. The black line is the average profile. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

solutions on a single 11-CoCRR array over a period of 5 months (day 1, 3, 5, 9, 16, 23, 31, 50, 89, 116 and 157). After each measurement, the array was regenerated with 2% SDS, thoroughly cleaned with ultrapure water, dried carefully under an argon gas flow, and then stored in a small closed bottle at 4 °C for reuse. As shown in Fig. 4, the CEP signal intensity increased slightly over time but there is no loss of signal, which means that the eT did not deteriorate. Meanwhile, the shape of all the CEPs was kept almost the same. The coefficient C_{12} between any two different full patterns is $>95\%$, which shows a good stability of our eT system upon prolonged storage. Taken together, these results confirmed that our eT system is very repeatable and stable.

4. Conclusions

In summary, an electronic tongue was constructed based on a combinatorial approach for preparation of the CoCRR array and the optical detection technique SPRi. Satisfyingly, the CoCRR array obtained by self-assembly of mixtures of only two small molecules in varying proportions had good cross-sensitivity to different species in complex mixtures such as wine, beer, and milk. The CoCRRs–SPRi eT was capable of generating unique 2D continuous evolution profiles and 3D continuous evolution landscapes behaving as "fingerprints" for identification and differentiation of these complex mixtures. Besides, the eT has proven effective for monitoring changes in the mixtures as a function of time, such as deterioration of UHT milk, demonstrating its potential as a complementary approach to classical chemical analysis for quality control applications. In addition to its ease of preparation, the eT demonstrated good repeatability and stability upon prolonged storage. In the near future, the performance of the CoCRRs–SPRi will be improved by the use of new BBs with complementary physicochemical properties to explore its potential in the analysis of complex mixtures in gas.

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