Journal of Pharmaceutical and Biomedical Analysis 55 (2011) 1239–1244

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Can odors of TCM be captured by electronic nose? The novel quality control method for *musk* by electronic nose coupled with chemometrics

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ARTICLE INFO

Article history:
Received 5 October 2010
Received in revised form 28 February 2011
Accepted 11 March 2011
Available online 17 March 2011

Keywords:
Musk
Electronic nose
Chemometrics
Principal component analysis
Quality control

ABSTRACT

Musk is a precious and wide applied material in traditional Chinese medicine, also, an important material for the perfume industry all over the world. To establish a rapid, cost-effective and relatively objective assessment for the quality of *musk*, different *musk* samples, including authentic, fake and adulterate, were collected. A oxide sensor based electronic nose (E-nose) was employed to measure the *musk* samples, the E-nose generated data were analyzed by principal component analysis (PCA), the responses of 18 sensors of E-nose were evaluated by loading analysis. Results showed that a rapid evaluation of complex response of the samples could be obtained, in combination with PCA and the perception level of the E-nose was given better results in the recognition values of the *musk* aroma. The authentic, fake and adulterate *musk* could be distinguished by E-nose coupled with PCA, sensor 2, 3, 5, 12, 15 and 17 were found to be able to better discriminate between *musk* samples, confirming the potential application of an electronic instrument coupled with chemometrics for a rapid and on-line quality control for the traditional medicines.

1. Introduction

Musk (Shexiang in Chinese), the glandular secretion of male musk deer, including *Moschus berezovskii Flerov*, *Moschus sifanicus Przewalski*, or *Moschus moschiferus Linnaeus*, is a kind of rare Chinese medicinal material, as well as an important material in perfumery industry over the world. As a major Chinese herbal material, *musk* was firstly recorded in *Shen Nong Ben Cao Jing* (*The Herbal Classic of the Divine Plowman*) in about 2700 BC and has been used with a history. Now it is officially listed in Chinese Pharmacopoeia as *Moschus*, recognized as a important medicinal material with many pharmacological activities, including resuscitation, activating blood to promote menstruation, detumescence and analgesia [1]. In fact, *musk* has been applied widely in about 10% Chinese commonly used formulated products.

Musk is one of the most valuable of all animal scents, even more expensive than gold [2]. Owing to its expense and wide applications, steep population declines have resulted from overexploitation, *musk* is in short supply all over the world [3–5]. This fact leads to a phenomenon of adulterate and fake goods on the market, especially in China. Up to now, researchers have developed many methods to identify *musk*, such as GC [6–8], MS [9] and HPLC [10], most of which were based on the special component-musone. However, due to the various adulteration statuses of *musk* and its products on the market, its very difficult to identify whether the *musk* is authentic or fake by only one component, not to speak the problem of estimating the grades of which.

The E-nose is one of the analytical devices used for detecting volatile compounds [11]. An array of broadly tuned chemical sensors, i.e. metal oxide sensors interacting with a broad range of chemicals with varying intensity were used to describe the odors of substances. Nowadays, positive applications of E-nose technology have been successfully applied in different fields, such as quality assessment of food products [12–16], medical diagnostics [17,18] as well as in the automobile industry [19]. The main purpose of E-nose application is to classify the quality grade of the materials [20–22]. Traditional drugs have some similar characteristics to food, as well as having some unique odors. As a result, the E-nose has gradually being applied in the quality assessment of Chinese

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0731-7085/$ – see front matter
doi:10.1016/j.jpba.2011.03.018

Table 1
Details of *musk* samples.

No.	Place	Origin	Sample name	Interpretation
S1	Beijing	China National Corporation of Traditional Medicine	A	Artificial
S2	Sichuan	Sichuan Institute of Raising *Musk*	N1	Nature
S3	Tibet	East Gate Weyerhaeuser Dispensary in Pingxiang City	N2	Commercial
S4	Tibet	A large prosperous pharmacy on the culture road in Pingxiang City	N3	Commercial
S5	Tibet	Tianshun Dispensary in Pingxiang City	N4	Commercial
S6	Tibet	Dongzhimen Hospital Pharmacy of Beijing	N5	Nature
S7	Unknown	Pharmaceutical and Biological Products in China	F1	Fake
S8	Hubei	Pharmaceutical and Biological Products in China	F2	Fake
S9	Sichuan	Pharmaceutical and Biological Products in China	F3	Fake

medicine [23–25]. As a non-invasive method, the E-nose thus has been appropriately used in the quality assessment of precious traditional Chinese medicines, such as *musk*.

For thousands of years, the aroma of *musk* has been the main test in determining the grade of *musk*, some subtle differences among the odors of *musk* might reflect different quality grades. According to its chemical characteristics, the employment of appropriate equipment to detect volatile compounds might also help in distinguishing the different quality grades of *musk*. Compared to those traditional methods, the main advantage of E-nose is that data normalization can perform odors assessment on a continuous basis with the characteristics of being non-invasive, fast, sensitive and requiring no pretreatment [26,27].

In this study, the electronic nose (αFOX-4000) was employed to analyze the multiple *musk* samples. The response values of the E-nose were recorded and analyzed by principal component analysis (PCA), which made possible the extraction of information based on the overall properties of the sample and thus perform a classification without the need for additional compositional data. In combination with PCA, the potential use of electronic nose may have great impact on a variety of applications including biological, clinical and environmental analysis.

2. Materials and methods

2.1. Experimental material

Artificial *musk* was purchased from China National Corporation of Traditional Medicine; natural *musk* was obtained from Sichuan Institute of Raising Musk Deer, Tibet, Jiangxi and other places; fake *musk* was provided by National Institute of Food and Drug Control in China. Details of the samples are illustrated in Table 1. Nos. S2 and S6 were identified as the dried secretions of forest musk deer *M. berezovskii Flerov* mature males sachets by Professor Xiaohe Xiao. Fake *musk* samples were verified by researcher Xinyue Xiao from National Institute of Food and Drug Control. The rest *musk* samples were bought from market. Distilled water was further purified by a Millipore Q-Plus system (Millipore, Bedford, MA, USA).

2.2. Electronic nose

αFOX-4000 consists of a sampling apparatus, a detector unit containing an array of sensors, air generator equipment, HS-100 autosampler and pattern recognition software (αSOFTV9.1) for data recording. The sensor array is composed of 18 metal oxide semiconductors (MOSs) chemical sensors divided into chambers as three types: T, P, and LY.

2.3. Experiment procedure

Experiments were performed on αFOX-4000. The *musk* samples were accurately weighed for 0.03 g and placed in 10 ml sealed headspace vials and loaded into the autosampler tray; then 1000 μl of headspace air was automatically injected into E-nose by a syringe and flow-injected into the carrier gas flow.

In the testing process, distilled water was used to adjust the carrier gas humidity. The synthetic dry air was pumped into the sensor chambers with a constant rate of 150 ml/min via an air transformer connected to a syringe during the measurement process. The injection volume was 1 ml, injection rate of 1 ml/s, the total syringe volume of 2.5 ml, while the syringe temperature was maintained at 35 °C. The time of acquisition parameters and the time between injections are respective 120 s and 600 s. Each sample was measured one time based on highly accurate repeatability. All other experiments were done without replication. The maximum response points automatically recorded for each 18 sensors were used as the E-nose response.

2.4. Statistical processing

There are many different patterns of recognition techniques available. Classical statistical methods, using a probability model were first developed and used in the field of applied mathematics, now called chemometrics. Several mathematical methods could be applied to the multi-component analysis of odors. A classification algorithm designed for a specific problem has to go through a preliminary training phase, in which it studies the patterns typical to the problem. During this phase, the algorithm is fed with samples whose classification is known in advance. When this phase is finished, the algorithm can be used to identify samples whose classification is not known. In some cases, it can also reject samples, thus determining that they do not belong to any of the classes it has 'seen'. PCA is a well known technique used for reducing the dimensionality of the data, calculating a number of compounds that best describe the differences between the samples and allow visualizing of cluster and outliers. This technique has been widely used for researchers to display the response of an E-nose to simple and complex odors and it provides qualitative information for E-nose pattern recognition file [28]. By employing PCA, the data set will be transformed into 2D or 3D coordinates. This is carried out through the data reduction that extracts the most important information from the database as a result. The results of training phase can be displayed in a two dimensional view. PCA is based on a linear project of multidimensional data into different coordinates based on maximum variance and minimum correlation [29]. Training pattern from measurements of similar samples will be located close to each other after transformation in advance. Hence, the graphical output can be used for determining the difference between groups and comparing this difference to the distribution of pattern within one group. In this study, combination of a specific E-nose device (αFOX-4000) based on an array of sensors and suitable chemometrics methods is the first time to classify *musk* according to different quality grades.

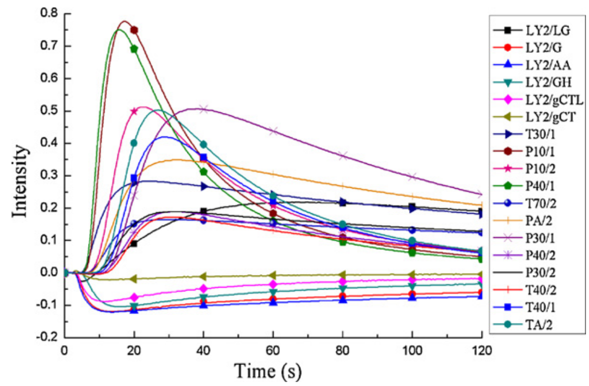

Fig. 1. A typical response of 18 sensors during the measurement of *musk* samples (N3).

3. Results

3.1. E-nose response to musk aroma

Fig. 1 shows the typical responses of sensors with *musk* samples. Each line represented the average signal variation of N3 *musk* sample respectively for one sensor of the 18 sensors. The curves represented the intensity of each sensor against time due to the electro-valve action when the volatiles reached the measurement chamber [30]. In the initial period, the intensity of each sensor was low, then increased continuously, and finally stabilized after a few seconds or minutes. The horizontal axis was the timeline, a total of 120 s; the vertical axis was the intensity of the response, each curve on behalf of a sensor in response to the changes within 120 s. In this study, the maximum response values of each sensor was extracted and analyzed individually. In this way, response values represented in different curves were explored and other response values with little significance were discarded.

3.2. Repeatability

The repeatability of the established method was evaluated of the sample N3, the samples were extracted and analyzed in six parallel tests. The relative standard deviation (RSD, $n = 6$) for repeatability was calculated and the results are shown in Fig. 2. The value of response of each sensor was expressed as means ± SD of six replicate measurements. The relative standard deviation values of 18 sensors response to N3 was less than 5%, attesting to a high repeatability of the response. The sensors did not exhibit a “memory” of prior exposure to the sample: re-freshing in air always brought the sensors back to approximately the same resistance. E-nose achieved better repeatability, sensitive, validity and stability of response singles. All other experiments were done without replication.

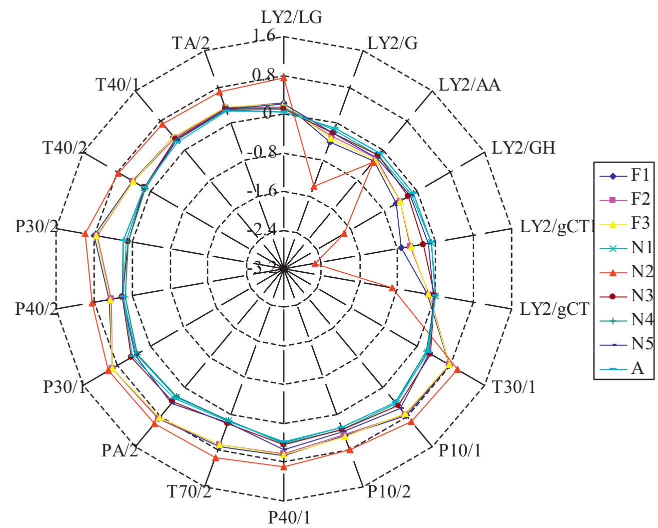

Fig. 3. Radar plots for nine samples of *musk*.

3.3. Effect of different quality grades

The influence of different quality grades in Table 1 on the responses of the E-nose for nine batches was analyzed by dynamic headspace methods. As it is illustrated in Fig. 3, the odors of *musk* samples did not show any obvious differences, indicating the composition of the samples in the performance being of the same odor. In comparison with others, N2 had an apparent difference from the results of the radar map and the bar chart of the fingerprint. It can be inferred that the sample N2 has higher values on the current pattern file, which might imply that this sample was apparently different from others. But the results showed that it's difficult to use a radar map to distinguish the quality of *musk* directly among these various kinds of samples, in view of the different nature of their individual characters.

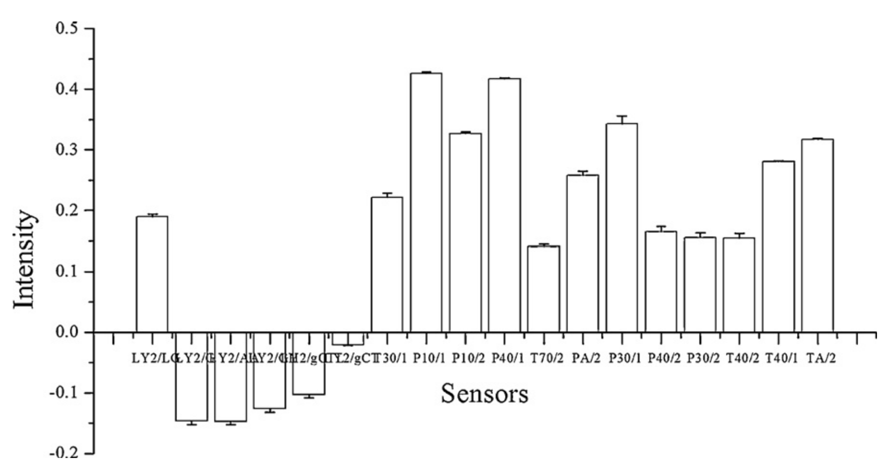

Fig. 2. Bar chart for the repeatability of the sample N3.

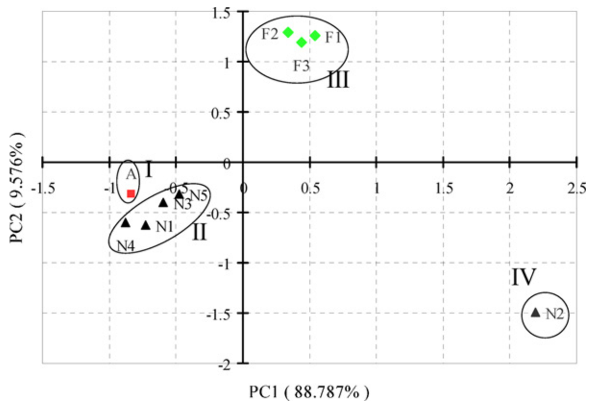

Fig. 4. PCA plots for *musk* samples (■ – artificial *musk* [A], ▲ – authentic *mus k* [N], ◆ – fake *musk* [F]).

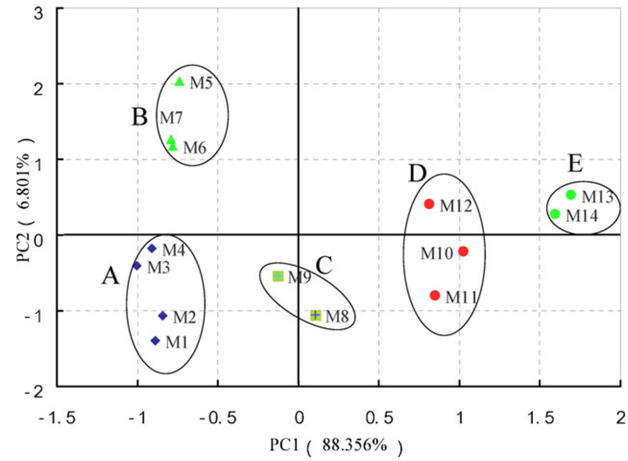

Fig. 5. PCA plots for *musk* samples by using vials with different quality proportions.

3.4. Discrimination of musk using principal component analysis (PCA)

3.4.1. PCA on discrimination the samples of authentic or fake musk

The data above showed that the chemical information was vitiated fiercely among different samples even between the two authentic *musk* samples, which lead to a complicated and ambiguous results in the assessment of *musk* quality. Principal component analysis, a linear combinatorial method, could reduce the complexity of the data-set and give a direct result; so it might be used in this analysis. The inherent structure of the dataset was preserved while its resulting variance is maximized [31]. PCA results in score plots always provide a visual evaluation of the similarity and dissimilarities that exist among the samples. From the visualization of the data in a reduced dimensional space by this method, the authentic and fake *musk* samples could be separated and discriminated. The original data obtained from the response values of 18 sensors which had been normalized and processed by statistic software of SPSS 16.0 (Chicago, USA) was performed by PCA depicted in Fig. 4. On the basis of eigenvalues >1, the processed data displayed the first principal component (PC1), which explains 88.787% of the total cumulative variance with value 98.363%. The second principal component (PC2) explains 5.54% of the cumulative variation.

The clear separation of authentic *musk* substitutes was observed in the 2D score plot of the first two PCs (Fig. 4), where each coordinate represented a sample, the substitutes and fake musk. From the scatter points, the 9 samples could be clustered into 4 groups, which were marked as group I–IV. The samples which clustered into one group were associated with similar quality grades. The distances among the groups reflected the discrepancy degree of those samples. It had to be noticed that the cluster corresponding to group IV (sample N2) appeared far from groups I and II, which was evident and consistent with the previous result as shown in the radar map. Samples F1, F2 and F3 (fake *musk*) in group III could also be discriminated from the artificial and natural samples. In addition, the cluster corresponding to group I appeared close to group II, but each sample was well separated, as summarized in Fig. 4.

3.4.2. PCA data in discriminating between the samples at different quality grades

The adulterates were not only easily discriminated from authentic *musk* samples based on the above analysis, but also showed a clear separation of different quality proportions of adulterated *musk*. Correspondingly, the response values of different sensors in electronic nose were identified by PCA. As it is summarized in Fig. 5, authentic and adulterated *musk* samples were measured in five concentrations, the total quality of single samples was 0.06 g. With the increasing proportion of authentic *musk*, the closer the load plot will approach to the field of authentic *musk* and vice versa. The plot could be readily divided into five groups: group A were samples of authentic *musk*, including samples M1–M4; group B were samples of adulterated *musk* with the proportion of 11:1, including samples M5–M7; group C and group D were also samples of adulterated *musk* with different proportions of 3:1 and 1:1, including samples M8, M9 and M10–M12. Group E were samples of fake *musk*, including samples M13 and M14. This fact showed that electronic technology could discriminate authentic and fake *musk* samples as well as varying degrees of adulteration rapidly and clearly. PCA had proven to be employed in classification of *musk* samples successfully.

3.5. Loading analysis

The loading plot in Fig. 6 shows the relationship between the variables and how much they influenced the system. The loading analysis might help to identify the importance of sensors responsible for discrimination in the current pattern file. It also showed the relative importance of the sensors in the analysis of *musk*. Single sensors might be switched off during analysis if they had a rather smaller influence on the identification process. Sensors with loading parameters near to zero for a particular principal component

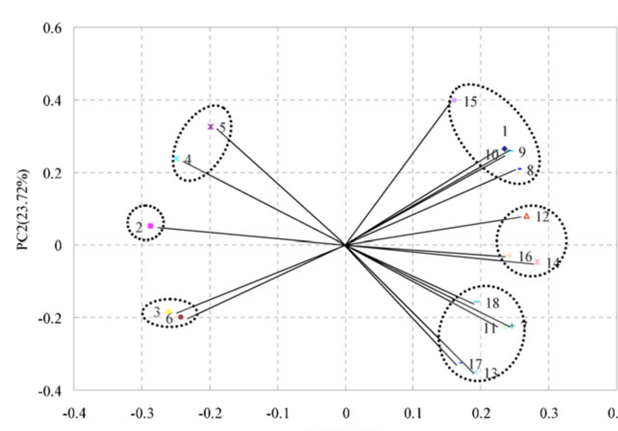

Fig. 6. Loading plot of all variables in the plane defined by the first two principal components. (1-LY2/LG,2-LY2/G,3-LY2/AA,4-LY2/GH,5-LY2/gCTL,6-LY2/gCT,7-T30/1,8-P10/1,9-P10/2,10-P40/1,11-T70/2,12-PA/2,13-P30/1,14-P40/2,15-P30/2,16-T40/2,17-T40/1, 18-TA/2).

have a low contribution to the total response of the array, whereas high values indicates a discriminating sensor.

The loading analysis performed well in the plot of the loading factors associated with PC1 and PC2 for *musk* is summarized in Fig. 6. It showed the relative importance of the sensors in the array. The sensors 2, 3, 12, 14 were dominant in the first principal component, while the sensors 5, 13, 15, 17 were dominant in the second principal component. There were some sensor groups that had almost equal loading parameters and were marked with a circle, and so it could be represented by just one sensor, respectively. Hence, a subset of a few sensors might be chosen to explain the variance. Sensors 2, 3, 5, 12, 15 and 17 in *musk* had the highest influence in the current pattern file, which represented a 90.74% variance of the total sensors.

In order to verify the ability of six sensors above, the responses of sensors 2, 3, 5, 12, 15 and 17 from nine *musk* samples (Table 1) were similar to the results in Fig. 4 and radar map. The use of six sensors is able to differentiate the samples successfully. So it is of great interest since a small subset of sensors is selected, this could be an advantage for the classification of new objects and optimize the number of the sensors in further.

4. Discussion and conclusion

As all *musk* deer species are categorized in the first class “key” species of wildlife protected by Chinese legislation in 2002, and are also listed in Appendix I by the CITE (Convention on International Trade in Endangered Species of Wild Fauna and Flora). It is well documented that most of the *musk* in the market place may be fake or adulterated. The aroma of *musk* is very complex and is a direct result of a great number of aromatic molecules that belong to different families such as ketones and terpenes. From a chemical point of view the differences are very subtle and their effects on the odors can only be appreciated by well trained people and other non-overall analysis methods. In this paper, it is the first time that electronic nose has been used to identify the precious traditional Chinese medicine *musk*.

Electronic noses, just like the human olfactory system, do not need to be specially designed to detect a particular volatile. In every case the electronic noses exhibited a better performance than the human sensory panel in the discrimination of aromas. The electronic nose can differentiate successfully the *musk* samples without prejudice, and has been demonstrated as a sensitive and non-invasive technology for differentiating between compounds. An interesting application is the determination of quality because it represents a means of reducing reliance on human judgment as well as saving time and costs. Generally, sensory analysis, based on microscopic identification, gas chromatography and chemical identification, is the most commonly used approach for classification and quality control of *musk*, because the electronic nose can detect compounds at concentrations that cannot be detected by any other method.

PCA had been proposed by Hotelling [32]. PCA is one of the most used classification procedures. The central idea of PCA is to reduce the dimensionality of a data set consisting of a large number of interrelated variables, while retaining as much as possible of the variation present in the data set. This is achieved by transforming to a new set of variables, the principal components (PCs), which are uncorrelated, and which are ordered so that the first few retain most of the variation present in all of the original variables [33]. It achieves a clear separation in all the cases by using PCA analysis. In combination with principal component data analysis, quick evaluation of complex response of the mixture can be obtained. In this study, the obtained results prove that the electronic nose can differ successfully the *musk* quality grades, and has demonstrated that electronic nose technology has excellent sensitivity and selectivity for differentiating *musk* on the basis of identification. The electronic nose was able to detect a clear difference in volatile odors on *musk* using PCA analysis. By the loading analysis, the relative importance of the sensors in the array was identified. Sensors 2, 3, 5, 12, 15 and 17 have the highest influence of identification in *musk*. This result could be used in further studies to optimize the number of sensors. Consequently, experiences of electronic nose technology can be used as a supporting technology for identification of odor identification in Chinese medicines.

In conclusion, the use of electronic nose in the identification of authentic and fake *musk* has been superior to the traditional methods adopted as well as having the advantages of being easy to use, reducing training time, quick, accurate, sensitive and requires no pretreatment as well as being non-invasive. Consequently, experience of electronic nose technology can be used as a supporting technology for identification of odors identification in Chinese medicines. It has not only discovered a novel path to assure the quality control of *musk*, but also expanded the application fields of electronic nose. It could be said electronic nose has contributed to the true modernization of Chinese traditional medicine not only in theory but also in practice as well.

Acknowledgements

This study was supported by grants from the Mega Project of Science Research for New Drug Development (No. 2009ZXJ09004-057, No. 2009ZX09502-022, No. 2009ZX10005-017) and National Natural Science Foundation of China (No. 81073043). We thank the reviewers for their critical comments on the manuscript.

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