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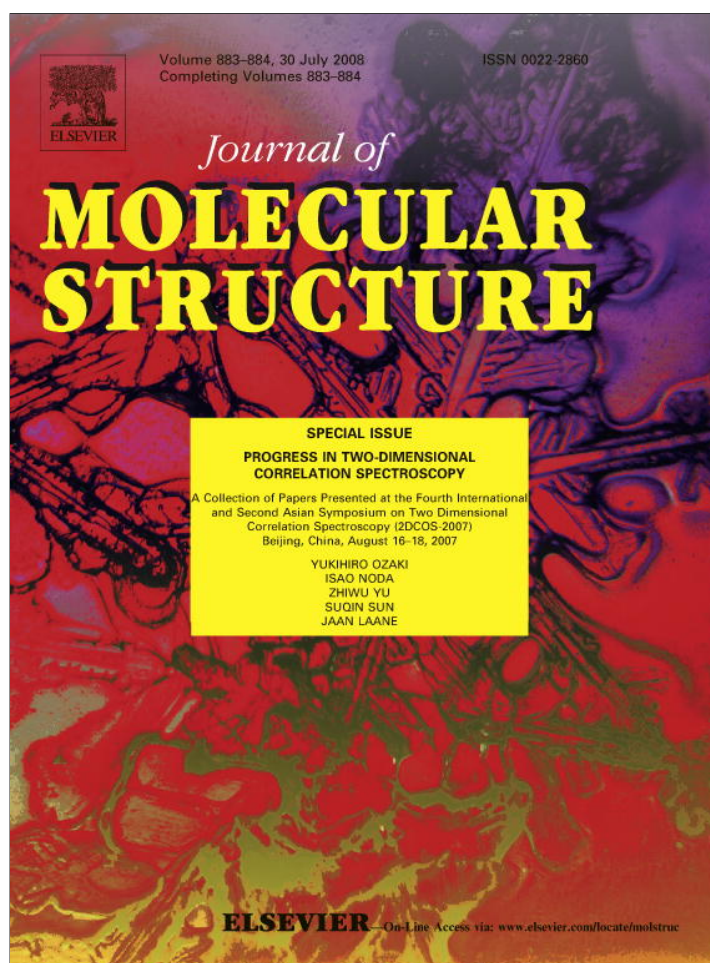University of Delaware
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Modified orthogonal sample design scheme to probe intermolecular interactions

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Abstract

In our previous work, we proposed an approach called orthogonal sample design (OSD) scheme, which was successful in eliminating interfering cross peaks in 2D synchronous spectrum. As a result, intermolecular interactions, which cause a deviation from the Beer–Lambert law, can be manifested in the form of the appearance of cross peaks in 2D synchronous spectra. However, the complex relationship between the deviation term and the intensity of the cross peak sometimes makes it possible that no cross peak appears even if an intermolecular interaction actually occurs in the system. In this paper, we propose a modified OSD approach based on a new concentration series, which can be applied on two-dimensional (2D) synchronous spectroscopy. The new approach greatly simplifies the relationship between the intensity of the synchronous cross peak and the deviation terms caused by intermolecular interactions. Accordingly, a protocol is proposed to check whether the absence of cross peaks in 2D synchronous spectra is indeed caused by the absence of intermolecular interactions or not. Therefore, a solid and unambiguous relationship between of the cross peak in 2D synchronous spectrum and intermolecular interaction can be established. That is to say, the appearance of cross peaks reflects genuine intermolecular interactions, while the disappearance of cross peak means no intermolecular interactions.
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Keywords: Orthogonal sample design scheme; 2D correlation analysis; Synchronous spectrum; Cross peaks; Intermolecular interaction

1. Introduction

Intermolecular interactions lie at the centre of many physical, chemical, and biological processes and have attracted extensive research interests. Two-dimensional (2D) correlation spectroscopy provides a new avenue to study intermolecular interactions, since the cross peaks in 2D synchronous spectra can be used to characterize intermolecular interactions [1–36]. Two-dimensional correlation spectroscopy, first proposed by Noda in the 1980s [1,2], is a powerful tool for the analysis of multivariable data based on spectral intensity variations induced by an external perturbation. The technique has been applied in a variety of research field over the past two decades [3–36]. One of the attractive features in this analysis is that the appearance of a synchronous cross peak provides the potential for characterizing the existence of intermolecular interactions. However, interfering cross peaks due to other sources of synchronicity, such as concentration variations of solutes, also arise even if there is no intermolecular interaction. As a result, the presence of cross peaks in a conventional 2D synchronous spectrum alone may not be used as a reliable criterion to judge if intermolecular interaction actually occurs or not.

In our previous work, we carried out a mathematical analysis on the generation of a cross peak in a 2D synchronous spectrum when variable concentration is used as a

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perturbation [36]. This work led to the development of the so-called orthogonal sample design (OSD) scheme for constructing 2D synchronous spectra specifically aimed at probing intermolecular interactions. Experimental results demonstrated that this approach is successful in eliminating interfering cross peaks from the simple concentration effect so that cross peaks that reflect only real intermolecular interactions can be obtained. Further theoretical analysis, however, points to the fact that there still remains a problem: intermolecular interactions under some special cases may fortuitously produce a cross peak with zero intensity in 2D synchronous spectrum. The absence of the cross peak may lead to a misleading result for the understanding of the physical–chemical nature of the molecular system. In this paper, we propose a modified OSD approach to solve the above problem.

2. Theory

A solution containing two solutes P and Q, whose characteristic peaks are located, respectively, at spectral coordinates x and y, was studied again as a model system. Just as in our previous work [36], varying concentrations were used as an external perturbation. The relationship between the perturbation and dynamic data becomes simple and can be expressed mathematically in a straightforward manner. This approach provides an opportunity to tailor the dynamic data by designing a suitable concentration series so as to extract useful spectral information selectively from 2D synchronous spectra. A series of 1D spectra ($i = 1, 2, \ldots, m$) with various concentrations of P and Q are recorded, so that the corresponding 2D spectrum can be constructed.

According to the algorithm proposed by Noda [4], the 2D synchronous correlation intensity $\Phi(x, y)$ can be acquired as following equation:

$$\Phi(x, y) = \frac{1}{m-1} \sum_{i=1}^{m} \tilde{A}^i(x) \tilde{A}^i(y) \tag{1}$$

Based on our previous work, intermolecular interaction is manifested as a deviation from the Beer–Lambert law. The intensity of the cross peak in the 2D synchronous spectra can be regarded as a sum of two parts as shown in the following equation,

$$\Phi(x, y) = N(x, y) + M(x, y) \tag{2}$$

$N(x, y)$ and $M(x, y)$ are given by

$$N(x, y) = \frac{\varepsilon_P(x) \varepsilon_Q(y) L^2}{m-1} \vec{\tilde{C}}_P \cdot \vec{\tilde{C}}_Q \tag{3}$$

and

$$M(x, y) = -\frac{1}{m-1} \left[\varepsilon_P(x) L \vec{\tilde{C}}_P \cdot \vec{\tilde{\delta}}_Q(y) \right.$$
$$\left. + \varepsilon_Q(y) L \vec{\tilde{C}}_Q \cdot \vec{\tilde{\delta}}_P(x) - \vec{\tilde{\delta}}_P(x) \cdot \vec{\tilde{\delta}}_Q(y) \right] \tag{4}$$

where L is the path-length of the solution; $\varepsilon_P(x)$ and $\varepsilon_Q(y)$ are the molar absorptivity of P and Q at x and y;

$\vec{\tilde{C}}_P$, $\vec{\tilde{C}}_Q$ are vectors of dynamic concentrations of P and Q and given by the following equation

$$\vec{\tilde{C}}_P = \left\{ \tilde{C}_P^1, \tilde{C}_P^2, \ldots, \tilde{C}_P^m \right\}$$
$$\vec{\tilde{C}}_Q = \left\{ \tilde{C}_Q^1, \tilde{C}_Q^2, \ldots, \tilde{C}_Q^m \right\} \tag{5}$$

$\vec{\tilde{\delta}}_P(x)$, $\vec{\tilde{\delta}}_Q(y)$ are the deviation terms that is related to the intermolecular interactions and given by the following equation

$$\vec{\tilde{\delta}}_P = \{ \tilde{\delta}_P^1, \tilde{\delta}_P^2, \ldots, \tilde{\delta}_P^m \}$$
$$\vec{\tilde{\delta}}_Q = \{ \tilde{\delta}_Q^1, \tilde{\delta}_Q^2, \ldots, \tilde{\delta}_Q^m \} \tag{6}$$

$N(x, y)$ is an interfering term reflecting only the concentration effect and has nothing to do with intermolecular interaction. If the 2D synchronous spectrum was constructed using variable concentrations of the solutes as perturbation without a specific experimental design or control, $N(x, y)$ is usually nonzero. Consequently, a simple logical relationship between the occurrence of cross peak in 2D synchronous spectra and existence of intermolecular interaction in the system is broken. That is to say, cross peaks may appear in a chemical system where there is no evidence of the existence of intermolecular interactions. Furthermore, it is also possible that $N(x, y)$ may fortuitously cancel the contribution of $M(x, y)$, so that no cross peak appear even if intermolecular interactions do exist in the system.

In our previous OSD paper [36], we adopted a strategy to make the dynamic concentration vector of P be orthogonal to that of Q so that $N(x, y)$ can be removed by the dot product defined according to Eq. (3).

Consequently, the intensity of a cross peak becomes equal to $M(x, y)$ which contains terms, $\tilde{\delta}_P(x)$ and $\tilde{\delta}_Q(y)$, that reflect intermolecular interaction in the form of the deviation from the Beer–Lambert law. If no interaction occurs, $\tilde{\delta}_P^i(x)$ and $\tilde{\delta}_Q^i(y)$ are zero and $M(x, y)$ also becomes zero.

Based on this approach, we have partially restored the unambiguous relationship between the presence of cross peaks and intermolecular interactions. That is, if a cross peak appears in 2D synchronous spectrum, we can safely say that intermolecular interaction causing the deviation from the Beer–Lambert law must occur in the system.

However, there still remains an unsolved problem. In our previous works, each 2D synchronous spectrum is constructed from four 1D spectra corresponding to four solutions, where the example set of acceptable concentrations of P and Q are listed in Table 1. For each of the four solutions, the values of $\tilde{\delta}_P^i(x)$ and $\tilde{\delta}_Q^i(y)$ are unique. Therefore, the intensity of the cross peak is related to eight δ terms. According to Eq. (4), it is sometimes possible that the value of $M(x, y)$ actually becomes zero even if none of the eight δ terms is zero. Therefore, we cannot safely say that there is

Table 1
Initial concentrations of P and Q in the simulated system[a]

Solution	P	Q
1	$5C_P^0$	$6C_Q^0$
2	$4C_P^0$	$7C_Q^0$
3	$3C_P^0$	$6C_Q^0$
4	$4C_P^0$	$5C_Q^0$

[a] C_P^0 and C_Q^0 are, respectively, the unit concentrations for P and Q.

no intermolecular interaction when no cross peak appears in 2D synchronous spectrum.

This problem stems from the complexity of $M(x,y)$, where we have very limited knowledge concerning the physical–chemical nature of the eight δ terms. A simplification on the δ terms is necessary to reflect the nature of the interactions in a straightforward manner.

However, this is a challenging task. In many cases, the values of δ terms are too subtle to be measured accurately. Additionally, the δ term may undergo a significant change upon the variation of concentration of the solutes. Because of the limited *a priori* understanding of the physical–chemical nature, the behavior of the δ terms is hard to be predicted.

When the species P or Q alone is present in the solution, $\delta_P^i(x)$ and $\delta_Q^i(y)$ should become zero, since no intermolecular interaction occurs. This physical constraint provides us a feasible route to simplify the expression of the intensity of the cross peak as a function of δ term. Hence a modified form of OSD with new concentration series (Table 2) has been proposed here.

The new concentration series possess the following features: (1) Only three 1D spectra rather than four 1D spectra are used to generate a 2D synchronous spectrum so as to simplify $M(x,y)$. (2) Among the three solutions, two of them are solutions containing Q only. As a result, only two δ terms are related to the intensity of the cross peak. (3) The resultant dynamic concentration and δ term are summarized in Table 3. Interestingly, $\tilde{C}_Q$ is orthogonal to

Table 2
New concentration series and deviation terms for modified OSD method[a]

	C_P^i	C_Q^i	$\delta_P^i(x)$	$\delta_Q^i(y)$
1#	$3C_P^0$	$2C_Q^0$	δ_P	δ_Q
2#	0	$3C_Q^0$	0	0
3#	0	C_Q^0	0	0

[a] C_P^0 and C_Q^0 are, respectively, the unit concentrations for P and Q.

Table 3
Dynamic concentrations of P and Q and the resultant dynamic deviation terms in the modified OSD experiments[a]

	$\tilde{C}_P^i$	$\tilde{C}_Q^i$	$\tilde{\delta}_P^i(x)$	$\tilde{\delta}_Q^i(y)$
1#	$2C_P^0$	0	$2\delta_P/3$	$2\delta_Q/3$
2#	$-C_P^0$	C_Q^0	$-\delta_P/3$	$-\delta_Q/3$
3#	$-C_P^0$	$-C_Q^0$	$-\delta_P/3$	$-\delta_Q/3$

[a] C_P^0 and C_Q^0 are, respectively, the unit concentrations for P and Q.

$\vec{\delta}_P(x)$, thus the dot product between them is removed in Eq. (4).

Finally, Eq. (7) was obtained as below:

$$\Phi(x,y) = -\varepsilon_P(x)\delta_Q C_P^0 L + \frac{\delta_P \delta_Q}{3} \tag{7}$$

The correlation intensity of a synchronous cross peak in Eq. (7) can still take the value of zero. The disappearance of the cross peak intensity may be caused by two possible reasons:

(1) The intensity of the cross peak happen to be zero because of a special combination of the variables in Eq. (7). According to Eq. (7), the intensity of the cross peak can be regarded as a linear function of the path-length L. That is to say, the intensity of the cross peak may happen to be zero for one specific path-length. It cannot be zero again if the path-length changes while other variables in Eq. (7) remain invariant. Thus, in this case, if we constructed another 2D synchronous spectrum by using a set of cuvettes with a different path-length, the intensity of the cross peak cannot be zero again.
(2) No intermolecular interactions occur in the system.

In this case, the intensity of the cross peaks remains always zero even if cuvettes with different path-lengths are used.

Thus, a protocol was designed to check whether an intermolecular interaction occurs or not when no cross peak appears in a 2D synchronous spectrum. The procedure is as follows:

(1) Prepare a set of solutions where the initial concentrations of the two solutes are set to the condition listed in Table 2.
(2) Use the set of solutions to recorded two spectral data sets of 1D spectra by using two cuvettes with different path-lengths.
(3) Generate two 2D synchronous spectra by using the above two data sets of 1D spectra. If the cross peak appear on either one of the two 2D synchronous spectra, we can say that an intermolecular interaction exists in the system. Or conversely, we say no intermolecular interactions occur, if no cross peak can be observed in the two 2D synchronous spectra.

In order to demonstrate that the above protocol is actually applicable in a real molecular system, we revisit a sys-

Table 4
Concentration series of NdCl₃/PrCl₃ solutions for modified OSD method

	C_{NdCl_3} (mol/dm^{-3})	C_{PrCl_3} (mol/dm^{-3})
1#	0.04	0.04
2#	0	0.06
3#	0	0.02

tem of aqueous solution of PrCl$_3$/NdCl$_3$, which was claimed to have no evidence of intermolecular interaction between Pr^{3+} and Nd^{3+}.

3. Experimental

3.1. Materials

Nd$_2$O$_3$ and Pr$_4$O$_{11}$ with purity of 99.99% were purchased from Shanghai Yuelong Chemical Factory.

The initial concentrations of the aqueous solutions of PrCl$_3$/NdCl$_3$ are listed in Table 4.

3.2. Instrument

The UV–vis spectra were recorded on a Varian Cary 1E UV–vis spectrophotometer, and the spectra were measured at a scanning rate of 60 nm/min.

3.3. Programming

The 2D synchronous spectra were calculated based on the algorithm by Noda [4] using the software of MATLAB (The Math Works Inc.).

4. Results and discussion

Both Nd^{3+} and Pr^{3+} are characterized by using their f–f transition bands in UV–vis spectra (Fig. 1). The main characteristic peaks of Nd^{3+} are found at 352, 520, and 573 nm, while those of Pr^{3+} occur at 442, 467, 480, and 588 nm.

The 2D mixed solutions synchronous spectrum of NdCl$_3$/PrCl$_3$ system obtained by using the modified orthogonal dynamic concentration series is shown in Fig. 2a and b. The two figures correspond to different path-length: 1 cm and 1 mm. Cross peaks for Nd^{3+}–Pr^{3+} do not occur in either one of the two 2D synchronous spectra constructed by using cuvettes of different
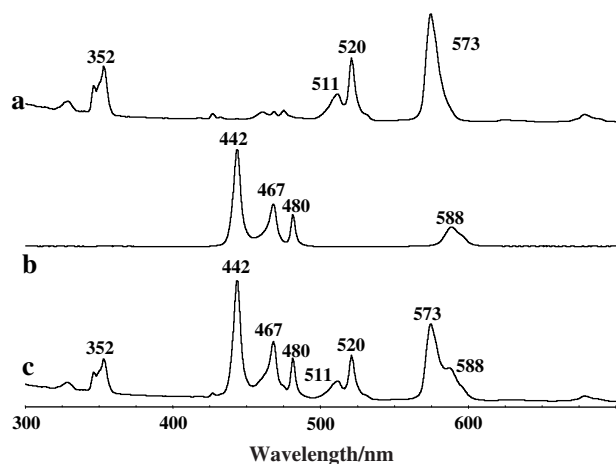
Fig. 1. UV–vis spectra of NdCl$_3$ (a), PrCl$_3$ (b) and NdCl$_3$/PrCl$_3$ mixture (c) in aqueous solutions.
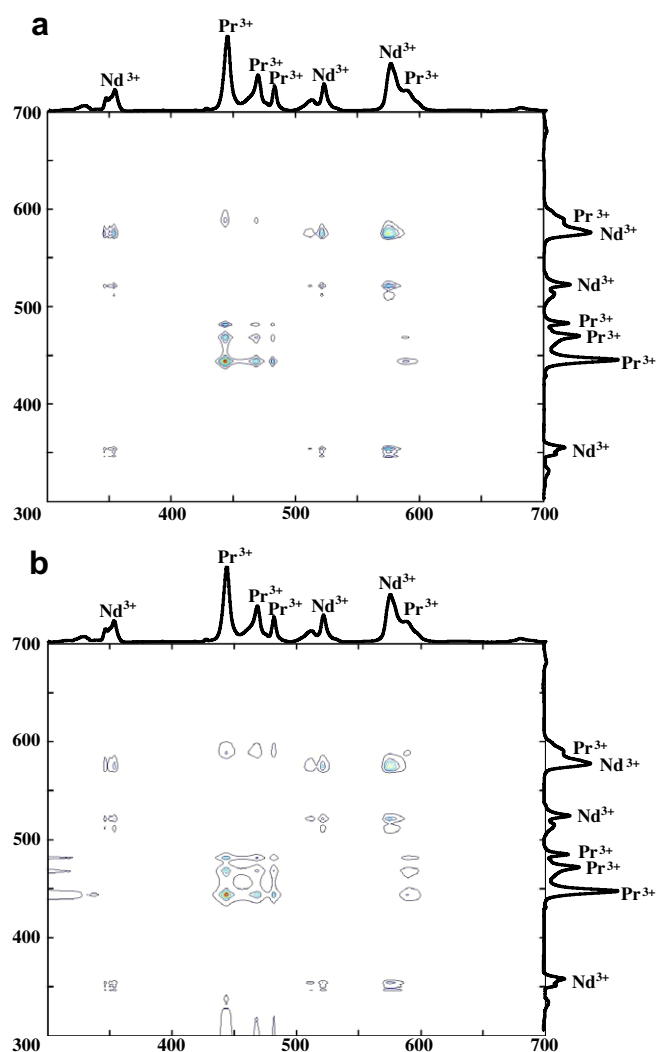
Fig. 2. (a) 2D synchronous spectrum of NdCl$_3$/PrCl$_3$ system using improved orthogonal dynamic concentration series listed in Table 4 (path-length $L = 1$ cm). (b) 2D synchronous spectrum of NdCl$_3$/PrCl$_3$ system using improved orthogonal dynamic concentration series listed in Table 4 (path-length $L = 1$ mm).

path-lengths. Thus we can say, the present result obtained by using the modified OSD approach confirms our previous results that no intermolecular interaction is observed between Pr^{3+} and Nd^{3+} when f–f transition band is used as a probe.

5. Conclusion

In this paper, we introduce a modified OSD approach based on a concentration series which can be applied on two-dimensional (2D) synchronous spectroscopy. The new approach greatly simplifies the relationship between the intensity of the cross peak in a 2D synchronous spectrum and the corresponding deviation term caused by intermolecular interactions. Based on this development, a protocol is proposed to check whether the absence of cross peaks in a 2D synchronous spectrum is truly caused by the

absence of intermolecular interactions or not. Therefore, a solid and unambiguous relationship between of the cross peak in 2D synchronous spectrum and intermolecular interaction can be established. That is to say, the appearance of cross peaks reflects genuine intermolecular interactions, while the disappearance of cross peak means no intermolecular interactions.

Another important perspective from this work is that it is easier to place some physical significance to the intensity of the cross peak. It is possible to have several series of spectral measurements from same set of solutions using cuvettes with different path-lengths, then we can extrapolate the result to where $L = 0$ according to Eq. (7). The resultant cross peak is just from purely excess terms, free from the influence of experimental condition, such as specific dynamic concentration used in the experiments. Further work is being performed.

Acknowledgments

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