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Formulation of the excess absorption in infrared spectra by numerical decomposition for effective process monitoring

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ABSTRACT

Iterative optimization technology (IOT), a method that predicts the component composition from only the infrared (IR) spectra of the pure components and mixtures by using Beer's law, has been proposed to reduce the number of calibration samples for process analytical technology in the pharmaceutical industry. However, IOT cannot be applied to mixtures that have wavelength regions where Beer's law does not hold, such as liquid mixtures. The objective of this study is to apply IOT to liquid mixtures to realize a calibration-minimum method. We propose a novel calibration-minimum method that formulates spectral changes by polynomials of the mole fractions considering reasonable boundary conditions for online monitoring. The prediction ability of the proposed method was verified by three case studies: two binary mixtures and one ternary mixture. The model selection strategy, conditions for calibration, and estimation of missing pure component spectra are also discussed. This research represents a step towards advanced calibration-minimum methods.

1. Introduction

Process analytical technology (PAT) has been developed by the chemical and pharmaceutical industries to realize effective process development and control. One of goals of PAT is to monitor and control processes online to provide product quality assurance. To achieve this goal, a prediction model called a soft sensor is used to predict the target variables from input variables that are easy to measure online, particularly when the target variables are difficult to measure online. Soft sensors require many calibration samples to construct the model, but sample acquisition sometimes requires a lot of money and time. This drawback of soft sensors makes it difficult to switch products in continuous processes, even though such sensors are essential for continuous processes. Thus, it is important to develop a method to construct prediction models that requires only a couple of calibration samples.

For online control of the particle size, the concentrations of the pure components in a mixture are the target variables in crystallization processes. However, the concentrations are usually only measured offline by high-performance liquid chromatography (HPLC) (Shabir, 2003). Therefore, soft sensors are required for effective online concentration monitoring. Infrared (IR) spectra (Stuart, 2004) are usually used as an input for soft sensors using a calibration method such as partial least squares (Roggo et al., 2007) or indirect hard modeling (IHM) (Alsmeyer et al., 2004; Kriesten et al., 2008a, 2008b) because IR spectra contain physical chemical information. Before concentration estimation, a regression model is constructed between the IR spectra and the concentrations measured by HPLC. However, HPLC requires a lot of time and it is costly when using expensive materials. Thus, a model construction method for concentration prediction from IR spectra that uses only a couple of calibration samples is needed. The ideal number of calibration samples is two because two samples are always obtained from process tests.

Methods that require zero or only a couple of calibration samples are called calibration-free or calibration-minimum methods. One of established calibration-free method for IR spectroscopy is self-modeling curve resolution (SMCR) (Jiang et al., 2004; Jiang and Ozaki, 2002). SMCR aims to deconvolute mixture spectra into concentration profiles and pure-component spectra. SMCR consists of a group of calibration-free methods, for example, evolving factor analysis (Gampp et al., 1986; Maeder, 1987; Maeder and Zuberbuehler, 1986), window factor analysis (Malinowski, 1992), simple-to-use interactive self-modeling mixture analysis (Knorr and Futrell, 1979; Windig et al., 2005; Windig and Guilment, 1991), and multi-curve resolution with alternating least squares (Azzouz and Tauler, 2008; Garrido et al., 2008; Tauler, 1995). However, there is no SMCR method that accurately predicts concentrations because SMCR methods are not specialized for such a prediction. To predict concentrations using IR spectra with a small number of sets of calibrated concentrations, Muteki et al. (2013) proposed it-

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erative optimization technology (IOT) based on Beer's law. In principle, IOT can accurately predict concentrations with no calibration samples using the spectra of a mixture and the pure components. However, IOT is applicable to not all liquid mixtures because molecular interactions break Beer's law.

To overcome this limitation, two main approaches have been proposed. The first approach is to select wavelength regions where Beer's law holds. These wavelength regions are sometimes called linear regions because Beer's law expresses the linear relationship between the concentration and the absorbance. Kaneko et al. (2015) proposed IOT with genetic algorithm-based wavelength selection (GAWLS) to select the linear regions. However, GAWLS requires a lot of time for optimization by the genetic algorithm and does not give results that are interpretable. We have proposed a wavelength selection method that requires at least one set consisting of a spectrum and concentrations (Shibayama et al., 2016a) based on the excess absorption (e.g., Koga et al., 2009; Li et al., 2008; Sebe et al., 2012). This wavelength selection method, which is called wavelength selection based on excess absorption (WLSEA), uses the excess absorption that contains information about the noise and molecular interactions' effects. WLSEA selects wavelength regions where the excess absorbance is sufficiently small. Thus, WLSEA is faster than GAWLS and provides more reasonable results. However, such approaches involving wavelength selection are not applicable to more complicated systems than binary or ternary mixtures, because complicated mixtures may not have a linear wavelength region in their absorption spectra. To avoid this limitation of wavelength selection methods, another approach is required.

The second approach is to formulate the effects of molecular interactions on the IR spectra as a function of the concentration. Muteki et al. (2013) proposed nonlinear iterative optimization technology (NIOT) to trace spectral changes using a well-known nonlinear numerical transformation called the Box–Cox transformation (Box and Cox, 1964). However, wavelength selection in NIOT is performed by trial and error. Moreover, the nonlinear transformation is not relevant to the nonlinear relationship between the absorbances of the mixtures and the pure components, which corresponds to molecular interactions. To overcome this limitation of NIOT, we proposed iterative optimization technology with virtual molecular interaction spectra (IOT-VIS) (Shibayama et al., 2016b). IOT-VIS considers the nonlinear relationship as sum of Beer's-law mixture spectra and a function of the concentration. Although IOT-VIS shows good prediction ability for a binary mixture, the prediction accuracy of IOT-VIS strongly depends on the combination of the calibration samples. This limitation originates from the poor spectral model of IOT-VIS.

None of the previous predictive models consider the spectral changes caused by molecular interactions, that is, functions for the excess absorption. Molecular dynamics (MD) can be used to simulate the IR spectra of liquid mixtures considering the spectral changes caused by molecular interactions (e.g., Ueno et al., 2013). However, the simulated spectra are still different from the measured spectra because of, for example, baseline shifts, measurement noise, and unexpected peak shifts. To use MD calculation results for quantitative regression, correction methods are required. Because the correction is expected to need more training samples, a calibration-minimum method based on IOT-VIS that uses only a couple of real calibration samples is still desired by the chemical and pharmaceutical industry to realize model construction with a small number of training samples.

The spectra of some pure components cannot be obtained when the pure components are, for example, solid in the crystallization process or reaction intermediates in the reaction process. Some methods for estimation of pure component spectra have been proposed (Kriesten et al., 2008b), although their output only improves the prediction accuracy of IHM methods. Thus, a different method to estimate pure component spectra is required.

The objective of this research is to develop a calibration-minimum method for accurate online monitoring of pure-component concentrations. We propose an extension of IOT called iterative optimization technology with decomposed excess absorption spectra (IOT-DEAS) to realize better prediction accuracy than IOT-VIS and formulate the nonlinear relationship between the absorbances of the mixtures and the pure components. IOT-DEAS considers reasonable boundary conditions to improve the generalization ability. Generalization ability is ability of a model to be applied to wider variate samples. A model with high generalization ability, that is, interpolation ability is desired because prediction results of the model will be reliable. A novel method for estimation of pure component spectra for IOT-DEAS is also proposed.

The performance of the IOT-DEAS method was verified by three types of liquid mixtures and compared with that of established methods. The performances of IOT, NIOT, IOT-VIS, and IOT-DEAS were verified with the first mixture, while those of IOT-VIS and IOT-DEAS were verified with the second mixture. Finally, a method for estimation of pure component spectra and IOT-DEAS were applied to a ternary mixture.

2. Methods

In this section, we introduce the existing IOT-VIS and proposed IOT-DEAS methods. We propose practical model selection strategies because this is a major concern of the IOT-DEAS method. In addition, we propose an effective model selection strategy for multiple component systems and a method for estimation of pure component spectra.

2.1. Iterative optimization technology with virtual molecular interaction spectra

IOT-VIS is an extended IOT method (Shibayama et al., 2016b) that considers the effects of molecular interactions, such as hydrogen bonding, on IR spectra. IOT-VIS resolves the minimization problem (Eq. (A.1) in Appendix A) with the alternative spectral model

$$\boldsymbol{x}_{\mathrm{mix,calc}} = \sum_{i=1}^{c} r_i \boldsymbol{x}_{\mathrm{pure},i} + \sum_{i=1}^{c} r_i^{p_i} \boldsymbol{x}_{\mathrm{nonlin},i}, \tag{1}$$

where i, c, r_i, p_i, $\boldsymbol{x}_{\mathrm{pure},i}$, and $\boldsymbol{x}_{\mathrm{nonlin},i}$ are the index of the pure component, the number of pure components, the mole fraction of i, the power number for r_i, the pure spectrum vector of i, and the virtual molecular interaction spectrum attributed to r_i, respectively. $\boldsymbol{x}_{\mathrm{nonlin},i}$ $(i = 1, 2,\ldots, c)$ can be estimated from a small number of calibration samples, while p_i $(i = 1, 2,\ldots, c)$ is determined by an exhaustive search. Herein note that IOT-VIS consider approximately and equally the effects of molecular interactions with the polynomials. However, IOT-VIS can accurately predict concentrations with only a specific set of calibration samples, which means that IOT-VIS does not have generalization ability. This limitation is caused by the poor spectral model $\boldsymbol{x}_{\mathrm{mix,calc}}$. For example, $\boldsymbol{x}_{\mathrm{mix,calc}}$ in Eq. (1) does not match $\boldsymbol{x}_{\mathrm{pure},i}$.

2.2. Iterative optimization technology with decomposed excess absorption spectra

To overcome the limitation of IOT-VIS described in Section 2.1, we make the following assumption:

$$\begin{aligned} &\boldsymbol{x}_{\mathrm{mix}} - \sum_{i=1}^{c} r_i \boldsymbol{x}_{\mathrm{pure},i} = \boldsymbol{f}(\boldsymbol{r}) \\ &\text{such that} \\ &\boldsymbol{f}(r_i = 1) = 0 \ \ (i = 1, 2, \ldots, c), \end{aligned} \tag{2}$$