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Chemometric analysis of luminescent quantum dots systems: Long way to go but first steps taken

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ABSTRACT

Due to diverse favorable physicochemical properties, luminescent quantum dots (QD) are widely used as labels or nanosensors for various analytical purposes. However, to the best of our knowledge there are not many reports applying chemometric approaches in nanoscience despite wide utilization of these methods in other research areas. The review addresses the usage of multivariate methods to resolve strongly overlapping signals for exploring different properties of QDs, as well as environmental characteristics. In particular, we discuss chemonetric applications for investigation of evolving luminescence signals of passive QD-based labels and active QD-based nanosensors, excitation-emission matrix (EEM) spectroscopic data and *in vivo* imaging of QD systems. Our review has shown that chemometrics plays an important role in the processing of luminescent nanoparticles signals and their role will definitely increase in the future.

Contents

1. Introduction

Due to distinctive properties of luminescent quantum dots (QD), such as small size (nanometer range), tunable optical and modifiable surface characteristics, high photostability and bright

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luminescence, these systems became advantageous for analytical purposes as labels and nanosensors. These useful QD features are also implemented in different optical systems based on various photophysical mechanisms [1–8]. Moreover, wide excitation and narrow emission bands provide possibilities for multiassay and multiimaging [9–11] as well as for ratiometric approaches for signal calibration [12,13].

However, higher resolution and broader possibilities provided by contemporary analytical methodology allows to solve new, more challenging and versatile problems. While QD are bright and small, their luminescence lifetime is much shorter than that of lanthanide-based luminophores with long-living emission and, therefore, ordinary Stocks luminescence does not provide advances of up-converting phosphors [14]. This makes it difficult to separate target signal(s) of QD luminescence from each other and from the emission of biological matrix. In this case modern statistical (chemometric) approaches would be advantageous to resolve target peak from matrix signal.

For a large variety of processes in biology, chemistry and medicine, where luminescent QD are used as labels, signal intensity depends on the number and type of QD in an analytical system [15–18]. To characterize these essential QD properties, 1D luminescence spectroscopy or emission-excitation matrix (EEM) fluorescence spectroscopy are commonly applied. One of the important advantages of certain QD types is narrow luminescence signals (half widths of about 30 nm), which can, however, overlap with spectral profiles of other QD types and/or matrix compounds. On the other side, QD spectra are not as broad as organic fluorophores emission, but significantly wider than NMR and IR signals, for which mathematical approaches for signal deconvolution are well developed and are widely applied [19–22]. Our literature search has shown that chemometric methods are rarely applied to nanoparticles with intermediate half width of their luminescence spectra.

On the other side, relative narrowness of luminescence peaks has the great impact on QD application in multiplexed assays, where their optical properties can simplify and expand diagnostic panels. The ability to excite multiple QDs with one excitation source and/or select a specific QD color greatly facilitates technical implementation of multiplexing. Similarly, narrow QD emission enables spectral encoding of different analyte signals rather than spatial encoding of different biomolecular probes [11,23]. This is complemented by the availability of Gaussian peak-fitting algorithms that can resolve overlapping QD luminescence profiles, although this is often unnecessary if only three or fewer spectrally resolved QD colors are present. This area gives a number of opportunities for application of advanced multivariate approaches for deconvolution of multiple unresolved peaks.

Good sensitivity of QD luminescence to environmental parameters makes nanosystems useful to detect analyte/analytes on the base of changing the distance between QD and quencher. This distance depends on the presence of target analyte/analytes [24–26] or changing the temperature [27], pH or other properties [28]. Active signal transduction is based on modulation of QD luminescence intensity, wavelength (characterized by 1D and 2D luminescence spectra) and lifetime rather than changing the number of QDs investigated. These changes are sometimes negligible and cannot be observed visually but rather have to be modelled using statistical tools.

The new area of QD application is their usage as distant environmental nanosensors for practical applications, where the parameters, such as pH or temperature cannot or can hardly be controlled by traditional techniques, for example, in bioimaging or biological labeling. Several pH sensors based on the phenomenon that pH of the medium critically affects luminescence properties of QD were developed [28–30]. However, overlapping QD luminescence response in such systems cannot be modeled using univariate approaches. Consequently, QD signals have to be isolated from the pH-induced spectral variations using multivariate statistics.

Thus, the current state of QDs application in analytical chemistry is characterized by broad application range both in terms of variability of matrices types and analytical tasks solved. However, the development of some promising methodologies (e.g., multiple analyte quantification or physical parameters modelling) is prevented by overlapping signals of multiple analytes and/or matrix background. Clearly, even more challenging is the evaluation of multidimensional data, such as the results of EEM fluorescence spectroscopy frequently used for observing the behavior of QD systems. Chemometric methods recently encountered in analytical practice can provide an opportunity to explore complex multicomponent systems containing QDs. The QD response is modeled on the basis of well-defined statistical equations and, therefore, hidden relationships in the matrix can be efficiently uncovered.

In this review we summarize available practical applications of different chemometric approaches for controlling QD properties via synthesis, purification and development of analytical systems (Fig. 1, Table 1). First, the common chemometric methods are reviewed and then their applications in nanoscience are discussed. The latter includes exploratory analysis of QD systems based on absorption and luminescence spectrometry or investigation of analytical systems where QDs are used as labels or sensors. Finally, the modeling of luminescence microscopic signals and i*n vivo* imaging profiles is reviewed.

2. Theory of chemometric methods used in nanoscience

2.1. Chemometric methods for one-dimensional responses modeling

The primary aim of chemometrics is to separate information from noise and to find the crucial patterns in the experimental data [19]. The central idea is to reduce the dimensionality of the data consisting of a large number of measured variables retaining as much useful information present in it as possible.

Most of the chemometric methods are based on the idea of latent variables (LVs). Initial (measured) variables can be combined and described by a fewer number of LVs, which describe the underlying structure of the data. Chemometric methods have found a lot of applications in signal processing, including but not restricted to spectroscopic, chromatographic and electrochemical methods [19–22,48]. The oldest and most common LV projection method is principal component analysis (PCA). PCA is based on transformation of the original data into a new set of a few orthogonal LVs (principal components, PCs), which describes most of the variation in the data. The first PC accounts for the maximal variation of data, while each successive PC does not correlate with the previous PCs and expresses as much of the remaining information as possible [49]. PCA is a helpful data visualization technique: since each object gets a score value on each PC, objects can be presented in score plots. Score plots can reveal patterns, trends and outliers in the data.

Another important tool for 1D multivariate modeling is evolving factor analysis (EFA). EFA was introduced as a chemometric method in 1985 by Gampp and Massart [50–52]. The fundamental idea of EFA is to follow the change or evolution of the rank of data matrix **X** as a function of the ordered variable. The EFA is based on evaluation of eigenvalues associated with all submatrices of the original data matrix built up by successively adding up all rows of the original data matrix. The calculations are performed in forward (starting with the first spectrum) and backward (starting with the last spectrum) directions. The presence of an eigenvalue from the pool of error eigenvalues in both directions indicates evolution or disappearance of a chemical species, respectively. EFA allows to estimate regions, or windows, where concentration of different compounds changes and, finally, provides information regarding the number of independent spectral components in the data set [50–52].