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Resolving nuclear magnetic resonance data of complex mixtures by three-way methods: Examples of chemical solutions and the human brain

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Abstract

Despite the use of hyphenated and/or high-resolution instruments in analytical spectroscopy, the resulting spectral data often represent mixtures of several components. When no reference data in the form of reference spectra or concentration profiles are available, self-modeling mixture analysis techniques can be utilized to obtain the spectra of the pure components and their concentration profiles. There are many different algorithms to resolve mixture spectra, and the mathematical procedures involved are not always simple. This paper will discuss some of the aspects and problems of self-modeling mixture analysis, with the focus on the three-way method and without going into the mathematical details. Practical examples will be shown of methods applied to nuclear magnetic resonance data. The techniques discussed can also be applied to magnetic resonance images and an example will be shown of the human brain.

Keywords: Generalized rank annihilation method (GRAM); Nuclear magnetic resonance (NMR); Magnetic resonance imaging (MRI); Exponential; Chemometrics; Diffusion ordered spectroscopy (DOSY); Pulsed gradient spin echo (PGSE)

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1. Introduction

1.1. Self-modeling mixture analysis

The goal of self-modeling mixture analysis is to resolve mixture data in terms of spectra of the pure components and their contributions ('concentrations') in the original spectra without using reference data.

In order to demonstrate the principles of self-modeling mixture analysis, a simulated mixture is created by combining the two spectra of pure components labeled in Fig. 1 as **spectrum 1** and **spectrum 2**. The first mixture spectrum, labeled as **mixture 1**, is created by taking a contribution of 1 part of **spectrum 1** and a contribution of 0.50 part of **spectrum 2** (these numbers are listed in the table in Fig. 1 on the first line in the columns under **spectrum 1** and **spectrum 2**). Similarly, **mixture 2** is created by taking a contribution of 1 part of **spectrum 1** and a contribution of 1 part of **spectrum 2**. **Mixture 3** is created by taking a contribution of 0.5 part of **spectrum 1** and a contribution of 1 part of **spectrum 2**.

The task of self-modeling mixture analysis is the following: given *only* **mixture 1, 2, and 3** calculate the pure spectra and their contributions.

A valid solution is, of course, **spectrum 1** and **spectrum 2** as the pure component spectra, with contributions as listed. However, another valid solution is **spectrum 3** and **spectrum 4** as pure component spectra with the contributions listed in the table in Fig. 1 (rows 1–3 of the columns under **spectrum 3** and **spectrum 4**). In fact, an infinite number of solutions are possible to resolve **mixture 1, 2, and 3** into pure component spectra and their contributions. The question now is how to find the right 'chemical' solution from the infinite number of 'mathematical' so-

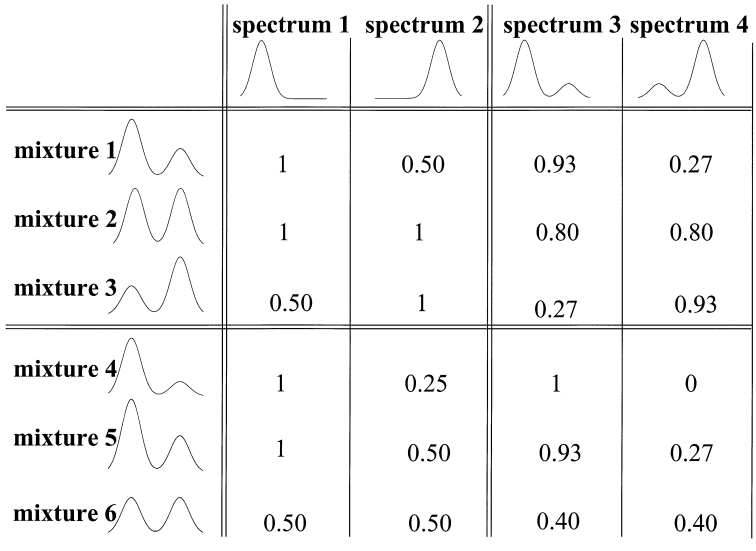

Fig. 1. Diagram representing the principle of self-modeling mixture analysis.

lutions. This is the subject of self-modeling mixture analysis. For overview and review articles see [1–4].

The methods used in the area of self-modeling mixture analysis to resolve mixtures are all based on the use of mathematical constraints. A widely used constraint is that spectra and their contributions should be positive. This alone is not enough to reach a single solution, as is demonstrated in Fig. 1 (both solutions are positive). An additional constraint may be that each pure component spectrum has only one peak. In this case the **spectrum 1** and **spectrum 2** solution would be found. Another constraint is the presence of a pure peak for every pure component spectrum. In other words, each pure component spectrum has a peak where all the other pure components do not have a peak. In this case, the **spectrum 1** and **spectrum 2** solution would be found again. Restrictions can also be applied to the contributions.

1.2. Self-modeling mixture analysis by the three-way method

Although the use of constraints is a powerful tool to resolve mixtures of unknown composition, the solution is only as valid as the constraint and is therefore not unique. However, it is possible to obtain a unique solution from *two* data sets, which have a proportional relationship [5–9]. In Fig. 1, a second mixture data set is presented as **mixture 4, 5, and 6**. This data set has a proportional relation with the data set presented by **mixture 1, 2, and 3**. The proportionality of two data sets means that the resolved spectra are identical, but the contributions for the components differ by a scale factor. The contributions of **spectrum 1** in the first mixture data set (1, 1, 0.5) is proportional to the contributions of **spectrum 1** in the second mixture data set (1, 1, 0.5) with a ratio between the contributions of one. The contributions of **spectrum 2** in the first mixture data set (0.5, 1, 1) are proportional to the contributions of **spectrum 2** in the second mixture data (0.25, 0.5, 0.5) set with a ratio of 2.

As with the first mixture data set, there are an infinite amount of solutions possible to resolve the second data set. However, if the two data sets have a proportional relation *only* the correct solution will show the proportionality. This is demonstrated in Fig. 1. The proper solution of the two mixtures with the pure **spectra 1 and 2** shows the proportionality, but the solution with pure component **spectra 3 and 4** does not show the proportional behavior of the resolved contributions. It can be proven mathematically that the proportionality is only preserved in one solution. As a consequence, when two proportional data sets are available, resolving them simultaneously with the restriction that the resolved contributions must be proportional, will lead to the correct solution. This problem can be solved as the generalized eigenproblem [7].

When a single spectral data set is analyzed, each spectrum is stored as a vector. A set of spectra are stored in a matrix, where each row represents a spectrum. A vector is a one-way array, and a matrix is a two-way array. When two spectral mixtures are analyzed, the data is present in two matrices that form a 'cube' of data and is called a three-way array. As a consequence, the methods to resolve several data sets simultaneously are called three-way methods [10].

Summarizing: a single mixture data set can be resolved in an infinite number of ways. Mathematical constraints can be used to approach the proper solution, but ambiguities will remain.

Two data sets with a proportional relationship can be stated as the generalized eigenvalue problem and the solution is unique.

In order to obtain two data sets with a proportional relationship, one needs, in general, two experiments: (a) one can analyze two samples with the required proportional relationship or (b) one can analyze one sample under two different conditions.

As an example of (a) one can think of the analysis of two samples with the same components, but different compositions by a method such as LC/UV (liquid chromatography/ultraviolet spectrometry) [11,12]. Generalized eigen analysis is often applied there for calibration purposes, using one sample with a known composition in combination with a sample with an unknown composition. The algorithm to perform this task is known as GRAM (generalized rank annihilation method) [8,9]. Problems arise because the resulting data is often not exactly proportional. This may be due to, for example, slight shifts in retention time in the case of chromatography. An example of (b) is fluorescence spectroscopy using different modulation frequencies, where successful applications have been reported [13].

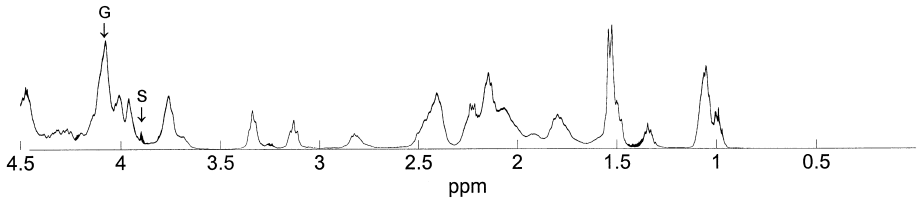

Fig. 2. Original spectra of the gelatin (10% w/w) and surfactant (0.2% w/w) mixtures. A 'typical' gelatin peak and surfactant peak are indicated by a 'G' and 'S', respectively.

1.3. Resolving mixture data with exponentially decaying contribution profiles

We recently developed a method to resolve a *single* data set with an exponential profile unambiguously solving the generalized eigenvalue problem [14,15]. Before discussing the mathematical principle of the procedure, we will first introduce the problem that led to our work.

Using nuclear magnetic resonance (NMR) spectroscopy, it is possible to generate a series of spectra of mixtures, where the contribution of each of the components decays with an exponential profile. This is the so-called pulsed gradient spin echo (PGSE) NMR experiment. The decay of the exponential is a function of the diffusion coefficient of the component. In Fig. 2 a series of overlaid spectra is shown with two components: 10% w/w gelatin and 0.2%

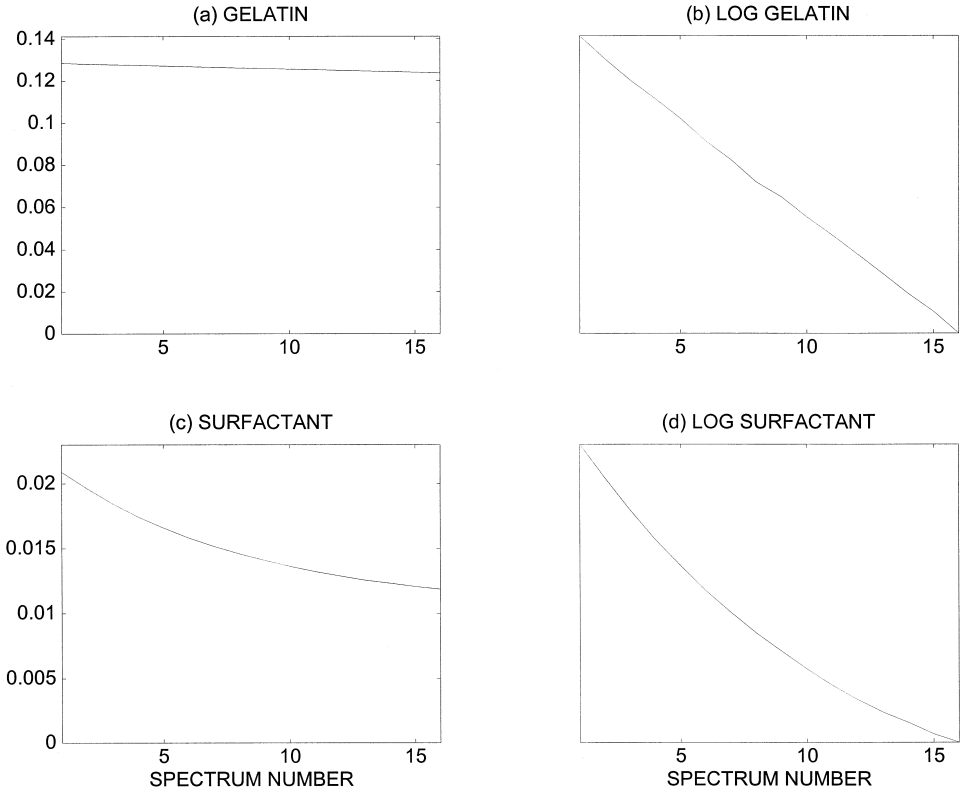

Fig. 3. Regular plot of the intensities of the (a) gelatin and (c) surfactant intensities and of the logarithm of the intensities of the (b) gelatin and (d) surfactant. Intensities were taken from the peaks indicated in Fig. 2.

w/w surfactant in water. Resonances downfield of 4.5 ppm (including water) have been excluded from the spectral region displayed. As can be seen in the overlay plot, the differences between the spectra are minimal. The spectrum is dominated by gelatin. A 'typical' gelatin and surfactant peak are indicated by arrows and plotted in Fig. 2. The peak used for the surfactant has a significant overlap with the gelatin.

In Fig. 3, intensities of the 'typical' gelatin and surfactant peaks are plotted on a linear scale and a logarithmic scale. Since exponential functions should be linear on a logarithmic scale, this is a convenient way to check whether profiles are exponential. The decay of the logarithmic plot of gelatin clearly shows an exponential behavior. The faster decaying surfactant, however, clearly shows a behavior that is not exponential; a significant deviation from a linear behavior can be observed in the logarithmic plot. This is due to a high overlap of the surfactant and the gelatin spectra.

The goal of an analysis such as described above is two-fold: (a) determination of diffusion coefficients and (b) resolve the mixture. For practical problems, appropriate reference spectra are generally not available for all the components, so that the contribution profiles cannot be determined. Even in cases where reference materials are available, the behavior in actual mixtures may be different because of physical or chemical changes such as the formation of micelles. Since the determination of the diffusion coefficient is a quantitative problem, self-modeling mixture analysis of this data set is of limited value, because of the ambiguities in the solution.

In order to obtain a unique solution, proportional data sets are required. At this point the exponential character of the decaying contributions appear to be the key to an unambiguous solution for this mixture problem. This will be demonstrated in Table 1. Under D, two exponential decays are listed. This is representative for the contribution profiles of a data set containing two components, such as the one under discussion. As a next step, D will be split in two (overlapping) parts. Under A, the first three rows of D are listed and under B the last three rows of D are listed. It can be seen now, that the first column under A is proportional to the first column under B, the only difference is a scale factor of 3. The second column under A is proportional to the second column under B, the difference is a scale factor of 2. This means that when a data set is available in which the components have contribution profiles of an exponential character, the data set can be split into two data sets with an proportional character, and can thus be resolved unambiguously! This application is called DECRA (direct exponential curve resolution algorithm), and has been applied successfully to NMR spectra [14,15] and magnetic resonance (MR) images [16,17].

Summarizing: a mixture data set in which the contribution profiles of the components are an exponential decay, can be split into two proportional data sets. The simultaneous resolution of the two data sets with the requirement to obtain a proportional solution will result into the resolution of the exponential decays.

2. Experimental

2.1. Instrumental analysis

The spectroscopy measurements were carried out on a Varian (Palo Alto, CA) Inova 400WB spectrometer operating at a ^{1}H frequency of 399.9 MHz and equipped with a standard pulsed field gradient (PFG) accessory. Three types of mixtures were analyzed. The first is a series of gelatin (deionized East-

Table 1
Model for data set D with exponential decays, and how it can be split into the proportional data sets A and B

D		A		B	
Component 1	Component 2	Component 1	Component 2	Component 1	Component 2
27	8	27	8	9	4
9	4	9	4	3	2
3	2	3	2	1	1
1	1				

man Gelatin, Peabody, MA) solutions containing a nonionic surfactant (di-C5-Glu, $(C_5H_{11})_2C[CH_2$-$NHCO(CHOH)_4CH_2OH]_2$, Eastman Kodak, UK). The solutions contain a fixed surfactant concentration of 0.2% w/w and a varied gelatin concentration ranging from 2 to 10% w/w. Samples were made with D_2O and experiments were performed at 45°C. The second mixture examined is a $CDCl_3$ solution of toluene (5 mg/ml) and dibutylphthalate (5 mg/ml). The third is a $CDCl_3$ solution of toluene (5 mg/ml) and tri-*p*-tolylphosphine (5 mg/ml). All deuterated compounds were obtained from Cambridge Isotope Laboratories, (Andover, MA) and others from Aldrich (Milwaukee, WI).

The PGSE NMR experiment was used to acquire the data. PGSE NMR is an established NMR method for obtaining diffusion coefficients of components in solution and involves the application of pulsed magnetic field gradients within a spin echo pulse sequence [18]. By varying the appropriate parameters in the experiment, one can establish an exponential relationship between the diffusion coefficient of the components in solution with the acquired signal. The signals from the faster moving components decay at a faster rate than the slower ones. The fact that this relationship is an exponential function is very important and plays a key role in the mathematical procedure for data analysis. Generally, 16 spectra are acquired to accommodate the range of exponential decays. Typical gradient strengths used were between 0 and 30 G/cm and typical pulse lengths were from 0.5 to 2 ms. Each spectra contained 8192 real data points.

MR images were acquired on a GE Signa, (GE Medical Systems, Milwaukee, WI) 1.5 T whole body imager employing a standard single-slice, single-echo, spin-echo pulse sequence [19] and a quadrature birdcage style RF head coil was used to acquire axial magnetic resonance images of the brain. The image

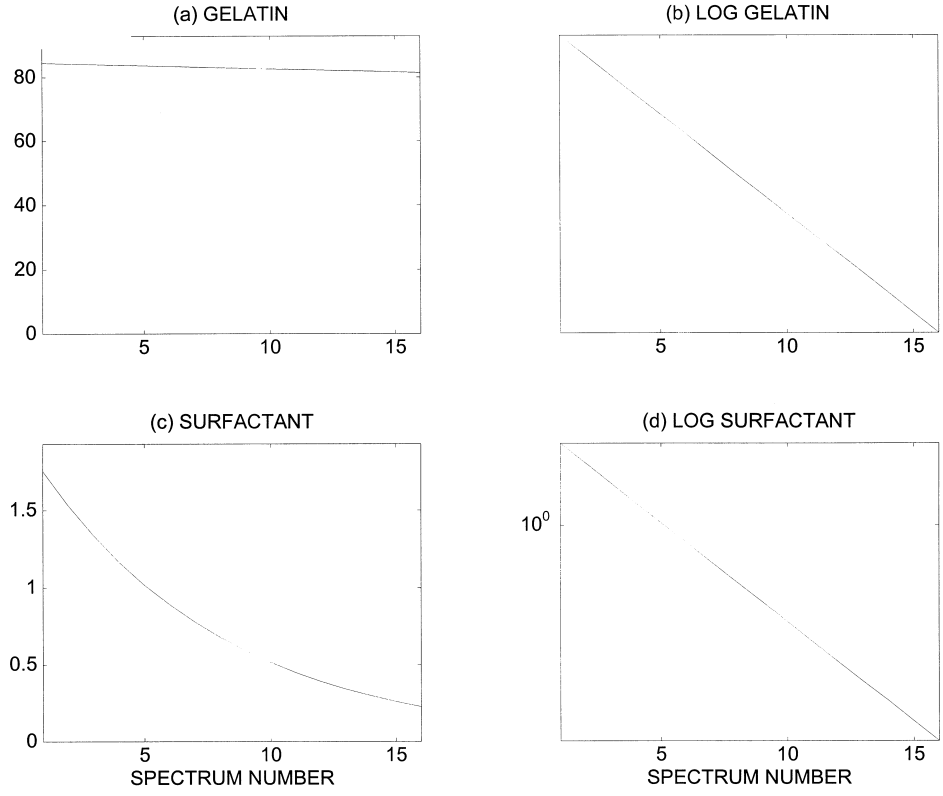

Fig. 4. Regular plot of the resolved contributions of (a) gelatin and (c) surfactant and of the logarithm of the resolved contributions of (b) gelatin and (d) surfactant.

plane passed through the head of the age 42 years, healthy male volunteer at the level of the lateral ventricles. A set of 14 images were acquired in which the echo time (TE) was varied between 15 and 210 ms in 15 ms steps and the repetition time (TR) was held constant at 1000 ms. This produced an effect similar to the one described above in the PGSE NMR experiment. Here, the relationship between TE and the signal of each individual component is an exponential that depends upon the component's spin–spin relaxation time (T_2). As the TE increases, the signal from each component decreases differentially depending on the magnitude of T_2. From a semi-log plot of signal versus TE, the T_2 for each component may be obtained. Each 24 cm field of view, 5 mm slice thickness image was acquired with 256 phase encoding steps to form a 256×256 pixel image. The motion of the volunteer was found to be minimal during the course of data collection, so no attempt was made to register the pixels within the series of correlated brain images.

2.2. Data analysis

For the data analysis MATLAB software (The MathWorks, Natich, MA) was used. The computer configuration is a 200 MHz Pentium Processor with 64 MB RAM. MATLAB functions used for processing the data are described elsewhere [16,17]. MATLAB code is given in Ref. [15].

Bi-exponential curve fitting is used for some of the data described in this paper. Kaleidagraph (Synergy Software, Reading, PA) was used for this purpose.

The DOSY (diffusion ordered spectroscopy) program is incorporated in Varian's VNMR software, which is written in C + + and runs on a SUN Sparc20 workstation.

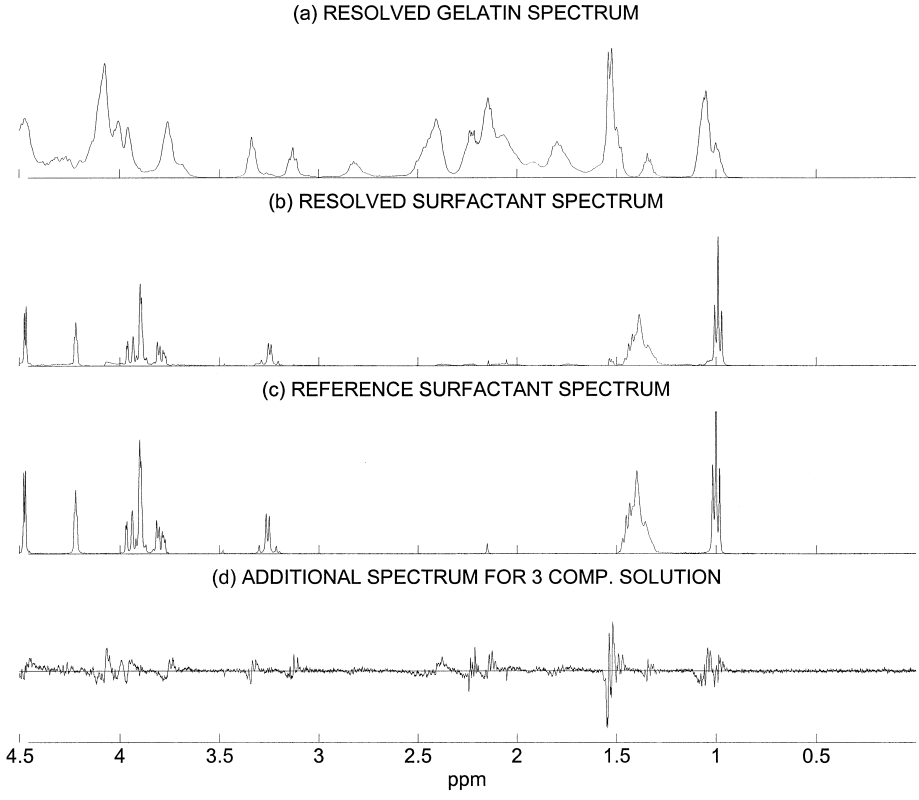

Fig. 5. Resolved spectra: (a) gelatin, (b) surfactant, (c) reference spectrum of surfactant and (d) the extra component resulting from a three-component resolution. The horizontal line represents a value of zero signal intensity.

3. Results and discussion

3.1. Application of DECRA to PGSE NMR data

In order to apply this approach to the data set shown in Fig. 2, we split the original file with 16 spectra into two files. The first file contains the spectra 1 to 15, the second file contains the spectra 2 to 16. Contribution profiles for both data sets result from the application of DECRA. In order to simplify the results, the overlapping parts of the contribution profiles (spectra 2 to 15) were averaged in order to create a single contribution profile for each component. As was shown before, the two overlapping parts are virtually identical [14–17]. The resulting contribution profiles are presented in Fig. 4. It is clear from the logarithmic plots that the extracted profiles are indeed exponential.

The resolved spectra are shown in Fig. 5. The resolved gelatin spectra looks very much like the original data, because it is the dominant component. The resolved surfactant spectrum shows high similarities with the reference spectrum of pure surfactant. Considering the minor contribution of the surfactant (the weight contribution of the surfactant is 2% of the weight contribution of gelatin, refer to Fig. 2), and the almost complete overlap of the pure components the results clearly show the feasibility of this technique to resolve spectral data with exponentially decaying contributions. When DECRA was applied to find three components, the additional spectrum in Fig. 5d was found. This 'spectrum' shows positive and negative intensities in the same range. This clearly shows that only two components are present in the mixture.

3.2. Comparison DECRA and exponential fitting

The next experiment involves establishing the relation between the concentration of gelatin and the diffusion coefficient of the surfactant. The diffusion coefficients were determined in a series of mixtures of gelatin and surfactant, where the gelatin concentration was varied for each mixture. The diffusion coefficients were determined in two ways. (a) A bi-exponential fitting procedure of integrated peak area between 0.75 and 1.25 ppm. This region contains signal from both gelatin and surfactant. (b) DECRA: the results of both techniques were plotted as a function of the concentration of the gelatin and shown in Fig. 6. Whereas the nonionic surfactant does not interact with the gelatin via electrostatic means, one expects a continuous relation. It is clear that the results of DECRA show a behavior that is continuous, while the results of the bilinear exponential fitting show a discontinuous behavior. A line is provided as a guide for the eye.

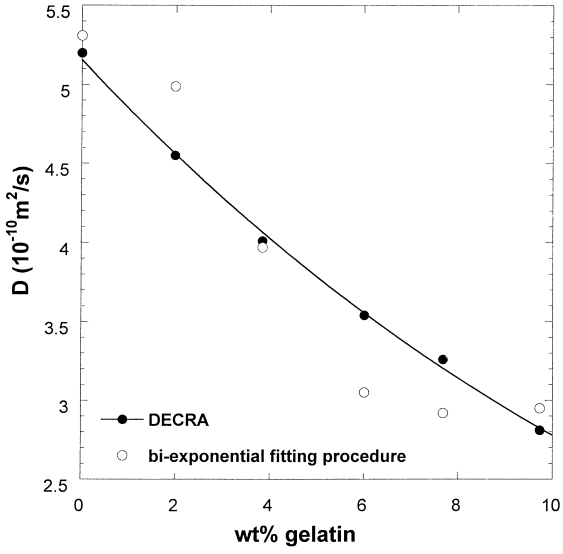

Fig. 6. Relation between gelatin concentration and diffusion coefficient as determined by DECRA and a bi-exponential fitting procedure.

3.3. Comparison between DOSY and DECRA

The next example shows the complimentary nature of DECRA with the DOSY (diffusion ordered spectroscopy) technique. In summary, DOSY calculates the diffusion coefficients for all the separate variables (ppm values), and displays them on a plot of the diffusion coefficient versus ppm. There are several methods for doing this and are described elsewhere [20]. The simplest approach is based on the assumption that each variable shows a single exponential decay [21]. In addition to this, a confidence interval is calculated and incorporated into the plot. An example of a DOSY plot is given in Fig. 7 for a series of spectra of a mixture of toluene and dibutylphthalate in $CDCL_3$. The diffusion spectrum in the DOSY plot in Fig. 7 clearly shows the pres-

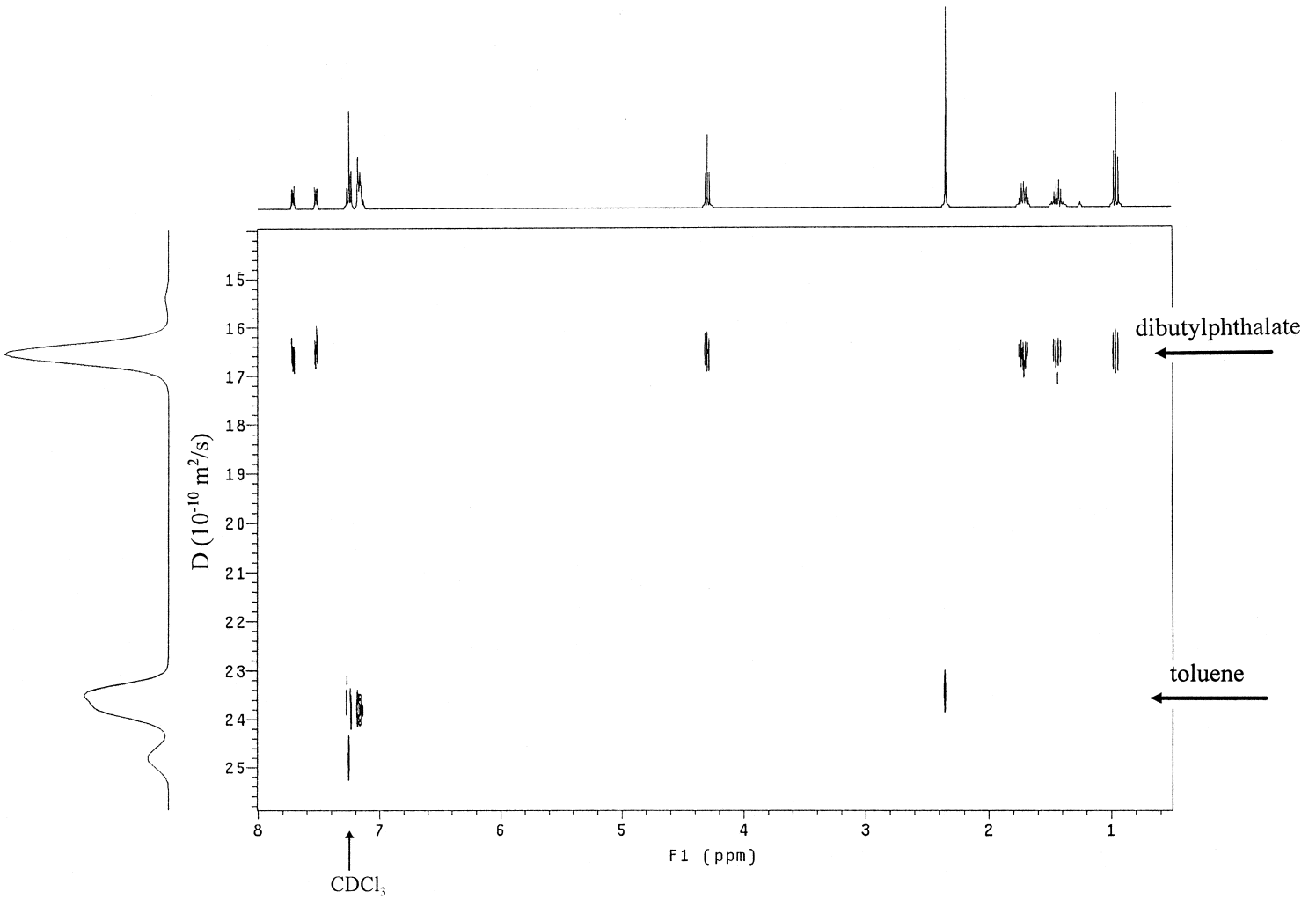

Fig. 7. DOSY plot for a mixture of toluene and dibutylphthalate in $CDCL_3$. The *x*-axis represents the spectral ppm scale and the *y*-axis is a measure for the diffusion coefficients. The spectrum at the top represents the mean spectrum of the data set. The so called diffusion spectrum along the *y*-axis represents the distribution of diffusion coefficients calculated. The three components are clearly separated.

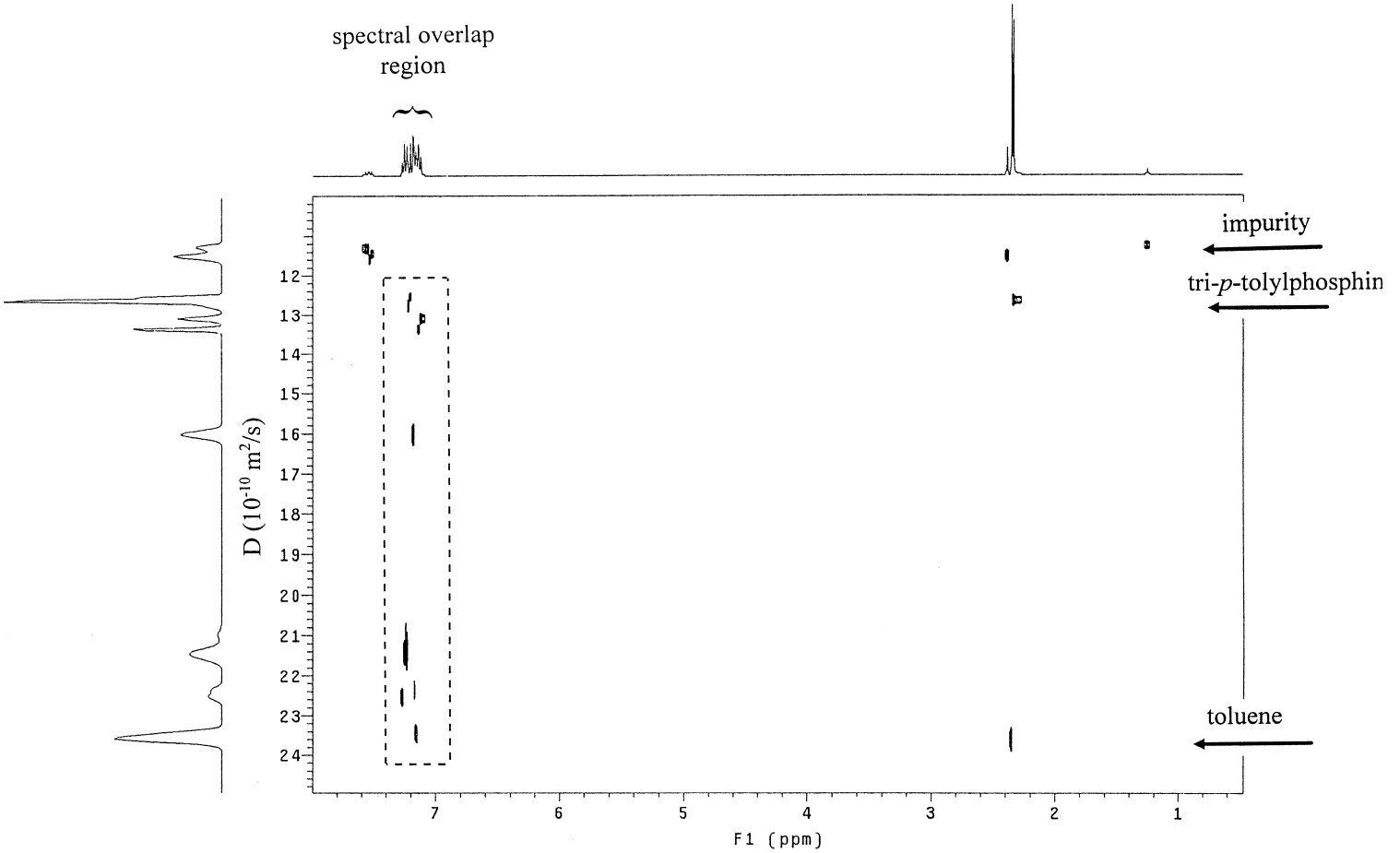

Fig. 8. DOSY plot for a mixture of tri-*p*-tolylphosphine and toluene in $CDCL_3$. This map is not able to separate the components, due to the overlapping spectral behavior. The hashed box represents the overlapped spectral region.

ence of three components: the peak at 16.5×10^{-10} m^2/s represents the pure peaks of dibutylphthalate and the peak at 23.6×10^{-10} m^2/s the pure peaks of toluene and $CDCL_3$ can be observed at 25.0×10^{-10} m^2/s.

As was shown above, DOSY works well for mixture spectra where the components are clearly separated (i.e., the assumption that each variable possess a single exponential value is valid). For mixtures where there are overlapping spectral areas, however, the DOSY plot seems to indicate more components than are really present. In order to demonstrate this, Fig. 8 shows a DOSY plot for a mixture of tri-*p*-tolylphosphine and toluene in $CDCL_3$. Arrows indicate the 'lines' with pure peaks of tri-*p*-tolylphosphine and toluene and an impurity of unknown composition which is present in the tri-*p*-tolylphosphine material. However, there is an area of spectral overlap indicated in the hashed box. It is obvious from this DOSY plot that it is impossible to determine the number of components in the mixture. High overlap is not a problem for DECRA, however. The spectral region in the hashed box was analyzed by DECRA, and the mixture could be resolved into two components (i.e., resolving it in more components resulted in noise spectra as in Fig. 4d). The resolved spectra and their and reference spectra are given in Fig. 9.

3.4. Application of DECRA to MR images of the human brain

The exponential behavior utilized to resolve the mixtures is certainly not limited to NMR diffusion experiments. In the area of magnetic resonance imaging (MRI) it is possible to create a series of MR images, where different structures in the brain have an intensity that decreases by an exponential decay related to the T_2 of that structure and DECRA has been

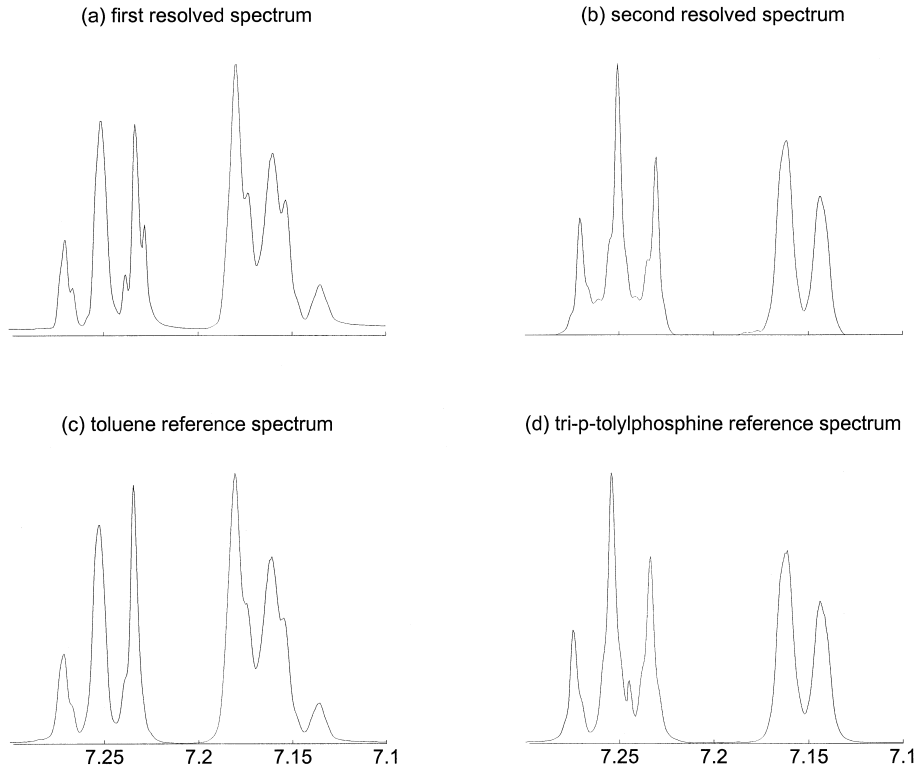

Fig. 9. The resolved spectra of the region indicated by the hashed box in Fig. 8: (a) represents the first resolved spectrum, compare with (c) reference spectrum of toluene; (b) represents the second resolved spectrum, compare with (d) reference spectrum of tri-*p*-tolylphosphine.

applied successfully [16,17]. As an example, three images out of a T_2 series of 14 images are shown in Fig. 10. These images show an exponentially decaying behavior that is different for different parts of the brain. The question now is if DECRA can be applied to these images. For spectral analysis, each spectrum is represented by an array, and a series of spectra forms a matrix. For the DECRA algorithm we use two matrices to resolve the mixture. For image analysis, however, each single image forms by itself a matrix, and a T_2 series of images forms a series of matrices. As a consequence, a direct application of the DECRA algorithm is not possible. There is a simple way around this problem, however. Each image matrix is reorganized in an array by taking the first row of the matrix, append the second row of the matrix, etc., and thus form an array representing the image. An image of 256×256 pixels forms an array of 65 536 elements. Once an image is represented as an array it is not different from the representation of spectra, and we can then apply DECRA to images. The resulting resolved 'spectra' need to be rearranged back into matrices again in order to obtain images, but this is a trivial procedure. The application of DECRA to the images represented in Fig. 10 resulted in three resolved images, which are shown in the same figure. The contribution profiles (not shown) are again of a clear exponential character. This shows that DECRA can be applied equally well to MR images. Again, the number of components was very clear, extracting

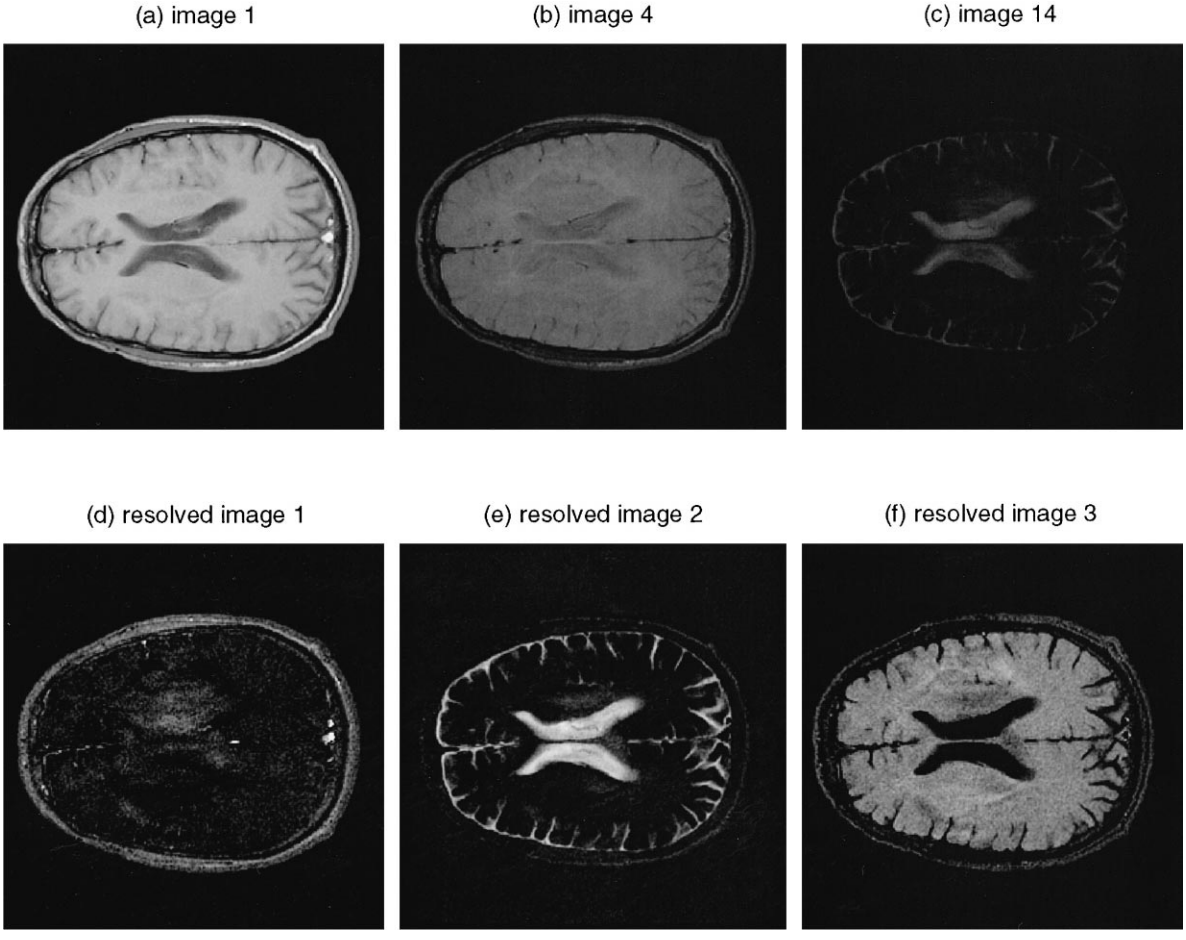

Fig. 10. The images (a), (b), (c) represent images of the original data set and clearly show the decaying behavior in the intensities. Images (d), (e) and (f) represent the resolved images.

more components resulted in images representing noise. Although one has to be careful with the interpretation of these resolved images in biological terms, the resolved images seem to represent the following features: the first resolved image is dominated by the tissues around the skull, the second resolved image is dominated by free water as indicated by the clear presence of the cerebro-spinal fluid, and the third image seems to be dominated by water within the brain tissue.

4. Conclusion

The examples discussed in this paper have demonstrated that the three-way method DECRA can be used as a tool for the analysis of PGSE NMR data. Furthermore, it could also be applied successfully to MR images. DECRA is applied as a routine tool at Eastman Kodak for chemical mixture analysis and to determine diffusion coefficients. DECRA can also be applied to other types of exponential by a simple transformation [16,17]. The high signal-to-noise data of NMR spectroscopy plays an important role in the success of these applications. Since an exponential is a common feature in nature, the application of DECRA in other areas can be expected.

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References

[1] W. Windig, Chemometrics Intell. Lab. Syst. 4 (1988) 201.
[2] J.C. Hamilton, P.J. Gemperline, J. Chemometrics 4 (1990) 1.
[3] W. Windig, Chemometrics Intell. Lab. Syst. 16 (1992) 1.
[4] W. Windig, Chemometrics Intell. Lab. Syst. 36 (1997) 3.
[5] M. Kubista, Chemometrics Intell. Lab. Syst. 7 (1990) 273.
[6] I. Scarminio, M. Kubista, Anal. Chem. 65 (1993) 409.
[7] K.S. Booksh, B.R. Kowalski, J. Chemometrics 8 (1994) 287.
[8] E. Sanchez, B.R. Kowalski, Anal. Chem. 58 (1988) 496.
[9] B. Wilson, E. Sanchez, B.R. Kowalski, J. Chemometrics 3 (1989) 493.
[10] A.K. Smilde, Chemometrics Intell. Lab. Syst. 15 (1992) 143.
[11] L.S. Ramos, E. Sanchez, B.R. Kowalski, J. Chrom. 385 (1987) 165.
[12] M. Josefson, L. Tekensbergs-Hjelte, J. Pharm. Biomed. Anal. 9 (1991) 643.
[13] D.S. Burdick, X.M. Tu, L.B. McGown, D.W. Millican, J. Chemometrics 4 (1990) 15.
[14] B. Antalek, W. Windig, J. Am. Chem. Soc. 118 (1996) 10331.
[15] W. Windig, B. Antalek, Chemometrics Intell. Lab. Syst. 37 (1997) 241.
[16] W. Windig, J.P. Hornak, B. Antalek, J. Magn. Reson. 132 (1998) 298.
[17] B. Antalek, J.P. Hornak, W. Windig, J. Magn. Reson. 132 (1998) 307.
[18] P. Stilbs, Prog. NMR Spectr. 19 (1987) 1.
[19] D.D. Stark, W.G. Bradley, Magnetic Resonance Imaging, 2nd edn. Mosby-Year Book, St. Louis, 1992.
[20] K.F. Morris, C.S. Johnson Jr., J. Am. Chem. Soc. 115 (1993) 4291.
[21] H. Barjat, G.A. Morris, S. Smart, A.G. Swanson, S.C.R. Williams, J. Magn. Res. B 108 (1995) 170–172.