

A computationally efficient method for evaluating the gradient of 2D NOESY intensities

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SUMMARY

A computationally efficient method for calculating the derivative of NOE intensities with respect to any parameter is presented. This method is based on an integral expression representing the gradient. We will derive this expression from first principles using standard perturbation expansion techniques, and show it to be equivalent to an analytical expression [Yip, P. and Case, D.A. (1989) *J. Magn. Reson.*, **83**, 643] Implementation of this method in a refinement scheme (NOE-MD) is also briefly mentioned.

Until recently, 2D NOESY intensities have been used only in a qualitative way in structure determination (Wüthrich, 1986). Typically, distance bounds, estimated from a qualitative interpretation of the intensities, comprise part of the restraints for structural generation and refinement. While distance bounds are necessary for the initial generation of structures in metric matrix or simulated annealing methods, a refinement strategy employing distance bounds instead of the NOESY intensities is less than optimal. The drawbacks include the possibility of user bias in the distance estimates, the imprecision of the distance bounds and perhaps more significantly, the loss of information in replacing the NOEs by distance bounds as experimental restraints. For example, a distance bound only restricts the separation between the two protons in question, while the NOE intensity between these two protons contains additional information about their spin environment and dynamics. Thus, employing NOEs directly not only makes refinement more rigorous, but also can lead to more information concerning the molecule.

The growing number of works which use the NOE intensities in an automated fashion can be divided roughly into two categories: hybrid matrix based or gradient based. In hybrid-matrix based methods (Boelens et al., 1989; Nikonowicz et al., 1989; Borgias and James, 1990; Kim and Reid, 1992), a relaxation rate matrix is solved directly from a hybrid matrix of simulated and experimental NOE intensities. Distance bounds, deduced from this rate matrix, are then used as restraints for structural refinement by restrained molecular dynamics. This procedure is iterated until some convergence criteria are met.

In gradient-based methods, the gradient of the NOEs is incorporated into a molecular dynamics force field to help drive a structure toward better agreement with the experimental intensities. The gradient is calculated by using either an exact expression (Yip and Case, 1989; Nilges et al., 1991), an approximate expression (Bonvin et al., 1991), or numerical differentiation (Baleja et al., 1990). The gradient-based approaches are perhaps simpler in content and clearer in principles—they attempt to solve a gradient-driven optimization problem. However, the computation of the gradient of the NOEs, either using the exact expression or numerical differentiation, can be extremely time consuming. While avoiding the computational complexities of calculating the full gradient, the approach of Bonvin et al. (1991) could underestimate the effects of spin diffusion, because higher ordered terms in the Taylor series are neglected when computing the derivatives.

For refinement based on the gradient of NOEs to become more practicable and rigorous, a method of calculating the gradient both accurately and efficiently is needed. In this communication, we derive a new integral expression for the gradient of the NOEs. This expression is exact. Thus multi-spin effects are fully accounted for, without limitations on either mixing times or correlation times. Most importantly from a practical point of view, this expression can be evaluated efficiently by standard numerical techniques to give accurate results.

The 2D NOESY intensity matrix \mathbf{A} at a mixing time τ_m is given by the exponential of the relaxation rate matrix, \mathbf{R} (Macura and Ernst, 1980).

$$\mathbf{A}(\mathbf{R}) = \exp(-\mathbf{R}\tau_m). \quad (1)$$

The rate matrix is a function of the spectral densities J_0 , J_1 and J_2 (Solomon, 1955; Macura and Ernst, 1980; Tropp, 1980). The exact expression of the rate matrix will, of course, depend on the motional models used and will not concern us here. We are interested in a general expression for the partial derivative of the NOESY matrix \mathbf{A} with respect to any parameter (e.g. an atomic coordinate) on which the rate matrix depends. We denote the parameter by d . We would like to obtain $\delta A_{ij}/\delta d$. First of all, by the chain rule,

$$\frac{\partial A_{ij}}{\partial d} = \sum_{k,l} \frac{\partial A_{ij}}{\partial R_{kl}} \times \frac{\partial R_{kl}}{\partial d}. \quad (2)$$

The problem thus reduces to finding the derivatives of the rate matrix elements with respect to the parameter d , $\delta R_{kl}/\delta d$, and the derivatives of the NOE matrix elements with respect to the rate matrix elements, $\delta A_{ij}/\delta R_{kl}$. For most motional models, $\delta R_{kl}/\delta d$ is easily computable. For example, in the case of isotropic tumbling without internal mobility, the rate matrix is a simple function of all its parameters: the atomic coordinates, correlation time and spectrometer frequency. The model independent and technically challenging component of Eq. 2 is $\delta A_{ij}/\delta R_{kl}$. We start with the definition of the derivative:

$$\frac{\partial A_{ij}}{\partial R_{kl}} = \lim_{h \rightarrow 0} \frac{A(\mathbf{R} + \mathbf{D})_{ij} - A(\mathbf{R})_{ij}}{h}, \quad (3)$$

where \mathbf{R} denotes the rate matrix, \mathbf{D} is a matrix whose only nonvanishing component is h in the k -th row and l -th column, and $\mathbf{A}(\mathbf{R} + \mathbf{D})$ is $\exp(-(\mathbf{R} + \mathbf{D})\tau_m)$.

To obtain the derivative, one needs to calculate $\exp(-(\mathbf{R} + \mathbf{D})\tau_m)$ only to the first order in h as

higher ordered terms will vanish upon taking the limit. Treating \mathbf{D} as a perturbation of \mathbf{R} , we can easily obtain the first order expression by using the standard perturbation expansion techniques in quantum mechanics (for example, Schiff, 1955). More explicitly, the rate matrix \mathbf{R} , becomes the Hamiltonian, while τ_m plays the role of the imaginary time it . The NOE matrix \mathbf{A} can be identified as the evolution operator. \mathbf{D} then is the perturbation Hamiltonian. Such techniques have been used to obtain approximate expressions for the NOE matrix \mathbf{A} (Yip, 1989). Thus to first order in h ,

$$\mathbf{A}(\mathbf{R} + \mathbf{D})_{ij} = \mathbf{A}(\mathbf{R})_{ij} - h \int_0^{\tau_m} f(s) ds, \quad (4)$$

where the function $f(s)$ is simply a product of two components of the NOE matrix defined as follows,

$$f(s) = \exp(-\mathbf{R}(\tau_m - s))_{ik} \exp(-\mathbf{R}s)_{lj}. \quad (5)$$

Substituting Eq. 4 in Eq. 3, we finally obtain,

$$\frac{\partial A_{ij}}{\partial R_{kl}} = - \int_0^{\tau_m} f(s) ds. \quad (6)$$

More explicitly, we have, upon using Eq. 5,

$$\frac{\partial A_{ij}}{\partial R_{kl}} = - \int_0^{\tau_m} \exp(-\mathbf{R}(\tau_m - s))_{ik} \exp(-\mathbf{R}s)_{lj} ds. \quad (7)$$

Putting Eq. 7 into Eq. 2 will give us the derivative of the NOE matrix with respect to any parameter.

In the literature, an exact expression for the derivative using eigenvectors and eigenvalues has been proposed (Yip and Case, 1989):

$$\frac{\partial A_{ij}}{\partial R_{kl}} = \sum_{r,u} L_r L_{rk} L_{ul} L_{uj} (\exp(-\lambda_r \tau_m) - \exp(-\lambda_u \tau_m)) / (\lambda_r - \lambda_u), \quad (8)$$

where L_{ij} and λ_i are the eigenvectors and the eigenvalues matrix of \mathbf{R} , respectively.

$$\mathbf{R}_{ij} = \sum_k L_{ki} L_{kj} \lambda_k. \quad (9)$$

We can easily show that the two expressions for the derivatives are indeed equivalent. First, Eq. 9 implies that,

$$\exp(-\mathbf{R}s)_{ij} = \sum_k L_{ki} L_{kj} \exp(-\lambda_k s). \quad (10)$$

Using Eq. 10 in Eq. 7, we have,

$$\frac{\partial A_{ij}}{\partial R_{kl}} = - \sum_{r,u} L_r L_{rk} L_{ul} L_{uj} \times \int_0^{\tau_m} \exp(-\lambda_r(\tau_m - s)) \exp(-\lambda_u s) ds. \quad (11)$$

On carrying out the integral, we recover Eq. 8, thus establishing that Eq. 6 (or Eq. 7) is an exact

expression of the derivative. In addition to being exact, Eq. 6 also presents several significant practical advantages:

(i) *Computational efficiency.* The key is that the NOE matrix varies slowly and smoothly with time. For instance, build-up or diagonal curves obtained from our simulations can all be fitted extremely well by polynomials of order no higher than 6. The integrand in Eq. 6, $f(s)$, is a product of two components of the NOE matrix, and therefore a well-behaved function of the integrating variable s . Numerical integration techniques can thus be used effectively for accurate computation of the integral. For example, using a 10-point Simpson's rule or a 5-point Gaussian quadrature yields extremely accurate results (less than 0.5% error) to the integral. The computational load of evaluating $f(s)$ at 5–10 points is significantly smaller than that of Eq. 8, where multiple summations are required.

(ii) *Methodological flexibility.* Since the integrand does not involve diagonalization, any techniques that evaluate NOEs accurately and efficiently could be used to produce the derivatives. For example, one can use an approach based on the numerical integration of the Bloch's equation (Banks et al., 1989; Madrid et al., 1989), a Taylor series approach (Forster, 1991), a perturbation series approach (Yip, 1989) or even one employing diagonalization (Keepers and James, 1984). The crux is that once the NOEs have been evaluated, Eq. 6 could be used in a numerical integration scheme to produce the derivatives efficiently and accurately.

(iii) *Mathematical generality.* Again, since diagonalization is not required, Eq. 6 is still valid for cases where \mathbf{R} is not diagonalizable. For example, Eq. 1 can describe any first order rate process, for which the rate matrix might not be symmetric, hence not diagonalizable. In this case, Eq. 6 can still be used while Eq. 8 would not apply.

A NOE refinement code (NOE-MD) is being prototyped by incorporating Eq. 6 into the molecular dynamics routine DISCOVER. Preliminary results are quite promising. For example, for a crambin-sized molecule (~300 protons) with a cut-off distance of 6 Å, calculating 100 2D NOESY peaks and their gradients with respect to proton coordinates takes 0.6 s CPU on the IBM 560, and 2 s CPU on the Indigo R3000. This is significantly faster than a similar calculation done using the expression in Eq. 8 (Yip and Case, 1989), which took 9 s on the Cray XMP. In future publications, more details of the implementation will be presented.

Note added in proof

After submission of this article, Dr. T. Havel personally communicated to the author that his group is conducting work along similar lines and has submitted a manuscript to the Quarterly of Applied Mathematics.

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