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Spin-diffusion approach for relaxation in bi-spaced periodic one-dimensional systems

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Abstract

A theoretical model for ^{1}H–^{1}H dipolar nuclear spin relaxation for a bi-spaced periodic one-dimensional array of spin 1/2 nuclei has been developed. A diffusion equation is formed for such a system by assuming nearest-neighbor interaction and isotropic random molecular reorientations. Under spin-diffusion conditions ($\omega\tau_c \gg 1$), this equation has been solved using Laplace transform for an infinite chain. The results are presented for the boundary conditions described for truncated driven Nuclear Overhauser effect experiments. The solution is further generalized by making the inter-spin spacing as a random variable with a Gaussian distribution.
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Keywords: Spin diffusion; Nuclear Overhauser effect; Relaxation

1. Introduction

The transfer of magnetization from one spin to another via inter-nuclear dipolar interaction acting as a relaxation mechanism in liquids is known as Nuclear Overhauser effect (NOE). While the heteronuclear NOE is used to enhance the signal of nuclei with low gyro-magnetic ratio (γ), the proton–proton NOE's are used to study the solution structures of organic and bio-molecules [1–3]. The observed polarization of a spin, while saturating a nearby spin, can show an increase (positive NOE) or decrease (negative NOE) depending on the relative signs and magnitudes of γ of the two nuclei and the time scale of the motional processes of the molecules. The homonuclear NOE for organic and small bio-molecules which reorient rapidly such that $\omega\tau_c \ll 1$ (where ω is the Larmor frequency and τ_c is the correlation time of the isotropic random motion), is positive, weak, and does not migrate to many spins. On the other hand, for large bio-molecules, where $\omega\tau_c \gg 1$, NOE is negative, large in magnitude, and migrates over long distances within the molecule. This limit is therefore often referred as "spin-diffusion" limit [4–6].

It has been shown by Krishnan et al. [7,8] that in the spin-diffusion limit, the migration of spin magnetization in an one-dimensional chain can be described by a diffusion equation. The assumption of equidistant one-dimensional chain is well suited for systems such as helical peptides and proteins, which are deuterated at all positions except labile amide protons. In such cases, $d_{N,N+1}$, the distance between adjacent amide protons (denoted in literature as $d_{NN}(i, i + 1)$), is short ($\sim$2.8 Å) [9] and shows pronounced sequential NOEs. However, in extended β sheet conformations of peptides and proteins in which the side chains are deuterated, the $NH_i - C_{i-1}^{\alpha}H$ distance (denoted as $d_{\alpha N}(i, i + 1)$) is of the order of 2.2 Å, while the $NH_i - C_i^{\alpha}H$ distance ($d_{N\alpha}(i, i)$) is about 2.8 Å and the inter-spin distance is bi-spaced periodic as shown in Fig. 1 [9]. This continues throughout the chain. Similar distance pattern exist in other secondary structures for

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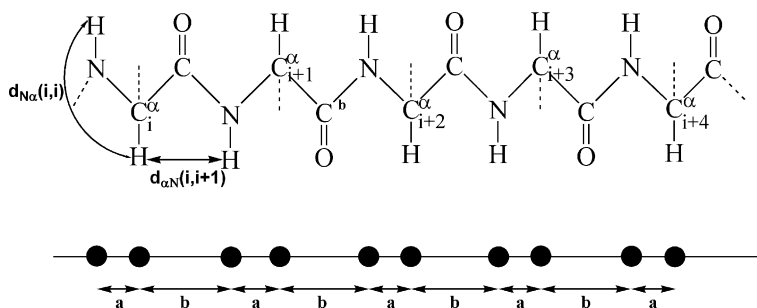 *E-mail address:* mrignayani@uni-duisburg.de (M. Kotecha).

Fig. 1. Schematic diagram of short sequential ^{1}H–^{1}H connectivity in polypeptide segment of secondary structures. In extended β sheet conformation the $NH_i - C_{i+1}^{\alpha}H$ distance ($d_{\alpha N}$) is of the order of 2.2 Å, while the $NH_i - C_i^{\alpha}H$ distance ($d_{N\alpha}$) is about 2.8 Å [9].

example alpha helical $d_{\alpha N}(i, i+1) = 3.5$ Å, $d_{N\alpha}(i,i) = 2.2$ to 2.8 Å depending on Φ. 3_{10} helical chain $d_{\alpha N}(i,i+1) = 3.4$ Å and $d_{N\alpha}(i,i) = 2.7$ Å [data from [9]]. Such a chain will be not linear but the migration of magnetization will be uni-directional (either forward or backward) and it can be considered as one-dimensional chain because all other leakage paths are blocked by the process of deuteration. Here, we are considering only intra-molecular NOE, ignoring inter-molecular NOEs. Also, in flexible polypeptide chains where most NOEs are quenched by motion, chain remains practically one-dimensional. In the present paper, we have therefore extended the one-dimensional equidistant model to bi-spaced periodic lattice model. The general rate equations for the spin populations have been formed and are solved for specific initial and boundary conditions for driven NOE experiment. For the future, we plan to extend current model to two- and three-dimensions to incorporate all NOE connectivities in protein conformations.

The distance measurement using NOE data and its modeling assumes fixed ^{1}H–^{1}H distances as taken by [7]. The real systems, such as proteins and nucleic acids in solution at ambient temperature, are not rigid. The interpretation of observed NOE for flexible system presents a difficult problem and needs to address theoretically [2]. In order to account for motional fluctuation of distance vector, the equidistance model of [7] is further extended for a one-dimensional stochastic chain having random inter-molecular distance with a Gaussian distribution.

It may be mentioned that Krishnan et al. [7] have shown that the migration of magnetization in a one-dimensional chain can be described by a second order diffusion equation only for driven NOE experiments in which the irradiated spin is assumed to be saturated for all times. It has been further shown by them that in experiments utilizing transient NOE, where the irradiated spin is selectively inverted at $t = 0$ and the migration of magnetization is monitored at other spins, higher order terms in the Taylor expansion are needed and the migration of magnetization can no longer be described by a second order "diffusion equation" [8]. In the following we therefore consider only the driven NOE experiment.

2. Spin-diffusion equation for bi-spaced lattice

A one-dimensional homo-nuclear chain of bi-spaced periodic lattice of spin 1/2 having dipolar coupling only is considered. It is assumed that each spin interacts with its nearest neighbor only. The spatial coordinates for these spins along one dimension have positions ... $x - 2b - a, x - b - a, x - b, x, x + a, x + a + b, x + 2a + b$ ... (Fig. 2). The population of the lower level of the spin at position x and time t is denoted by $n_+(x,t)$ and that of the upper level as $n_-(x,t)$ as shown in Fig. 2. The rate of change $n_+(x,t)$ can be written as

$$\frac{\partial n_+}{\partial t}(x,t)$$
$$= -n_+(x,t)W_{1a} - n_+(x,t)W_{1b} + n_-(x,t)W_{1a} + n_-(x,t)W_{1b}$$
$$- n_+(x,t)n_-(x+a,t)W_{0a} + n_-(x,t)n_+(x+a,t)W_{0a}$$
$$- n_+(x,t)n_-(x-b,t)W_{0b} + n_-(x,t)n_+(x-b,t)W_{0b}$$
$$- n_+(x,t)n_+(x+a,t)W_{2a} + n_-(x,t)n_-(x+a,t)W_{2a}$$
$$- n_+(x,t)n_+(x-b,t)W_{2b} + n_-(x,t)n_-(x-b,t)W_{2b}, \quad (1)$$

where W_{0r}, W_{1r}, and W_{2r} ($r = a, b$) are, respectively, the zero, single, and double quantum transition probabilities with inter-spin spacing as r for a pair of spin 1/2 homonuclear spin system and are given by [10,11]:

$$W_{0r} = \frac{1}{10} \frac{\gamma^4 \hbar^2}{r^6} \tau_c,$$

$$W_{1r} = \frac{3}{20} \frac{\gamma^4 \hbar^2}{r^6} \left\{ \frac{\tau_c}{1 + \omega_x^2 \tau_c^2} \right\},$$

$$W_{2r} = \frac{3}{5} \frac{\gamma^4 \hbar^2}{r^6} \left\{ \frac{\tau_c}{1 + 4\omega_x^2 \tau_c^2} \right\}, \quad (2)$$

with τ_c as the isotropic rotational correlation time. An expression similar to Eq. (1) can be written for $n_-(x,t)$. The magnetization would be proportional to $N(x,t) = [n_+(x,t) - n_-(x,t)]$. The rate of change of $N(x,t)$ is obtained as

$$\frac{\partial N(x,t)}{\partial t} = -2\rho N(x,t) - \sigma_a N(x+a,t) - \sigma_b N(x-b,t), \quad (3)$$
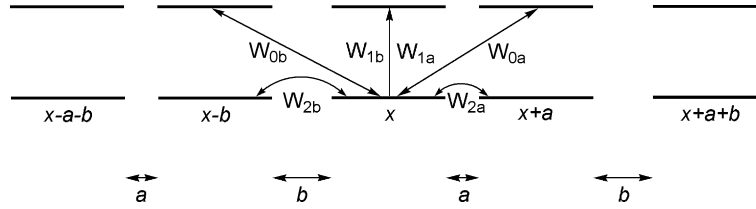
where

Fig. 2. Schematic energy level diagram of spins (I = 1/2) in a bi-spaced one-dimensional chain. W_{0a} (or W_{0b}) are the Mutual flip-flop term of the dipolar Hamiltonian, where spin at x goes up and spin at $x + a$ (or $x - b$) comes down. W_{2a} (or W_{2b}) is the double quantum transition probability which represent the simultaneous upward (or downward) flip of the pair of the spin. W_{1a} (or W_{1b}) is the single quantum transition probability and counted twice for each pair of spin.

$$\rho_a = 2W_{1a} + W_{0a} + W_{2a},$$

$$\rho_b = 2W_{1b} + W_{0b} + W_{2b},$$

$$\rho = \tfrac{1}{2}(\rho_a + \rho_b),$$

$$\sigma_a = W_{2a} - W_{0a},$$

$$\sigma_b = W_{2b} - W_{0b}.$$

Expanding $N(x + a, t)$ and $N(x - b, t)$ using Taylor series expansion about x gives,

$$N(x + a, t) = N(x, t) + \frac{a}{1!}\frac{\partial N(x, t)}{\partial x} + \frac{a^2}{2!}\frac{\partial^2 N(x, t)}{\partial x^2} + \cdots$$

$$N(x - b, t) = N(x, t) - \frac{b}{1!}\frac{\partial N(x, t)}{\partial x} + \frac{b^2}{2!}\frac{\partial^2 N(x, t)}{\partial x^2} + \cdots \quad (4)$$

Substituting Eq. (4) into Eq. (3) and retaining the terms up to second order yields,

$$\frac{\partial N}{\partial t}(x, t) = -2(\rho + \sigma)N(x, t) - \delta\frac{\partial N}{\partial x}(x, t) + D\frac{\partial^2 N}{\partial x^2}(x, t), \quad (5)$$

where

$$\sigma = \tfrac{1}{2}(\sigma_a + \sigma_b),$$

$$\rho = \tfrac{1}{2}(\rho_a + \rho_b),$$

$$\delta = a\sigma_a - b\sigma_b,$$

$$D = -\tfrac{1}{2}[a^2\sigma_a + b^2\sigma_b].$$

This diffusion equation is similar to the Eq. (7) of [7] for equidistant spins, except the additional term containing δ. δ represents difference between the migration of magnetization in opposite directions from each spin.

By using the substitution

$$N(x, t) = e^{-2(\rho + \sigma)t}\mu(x, t), \quad (6)$$

Eq. (5) reduces to

$$\frac{\partial\mu}{\partial t}(x, t) = -\delta\frac{\partial\mu}{\partial x}(x, t) + D\frac{\partial^2\mu}{\partial x^2}(x, t). \quad (7)$$

This equation would now be solved using suitable initial and boundary condition by method of Laplace transform [12,13]. Taking Laplace transform of Eq. (7) gives

$$D\frac{\partial^2 L}{\partial x^2}(x, s) - \delta\frac{\partial L}{\partial x}(x, s) - sL + \mu(x, 0) = 0, \quad (8)$$

where $L(x, s)$ is the Laplace variable of $\mu(x, t)$. The solution of this second order differential equation can be written as

$$L(x, s) = \frac{\mu(x, 0)}{s} + Ce^{-qx} + C'e^{q'x}, \quad (9)$$

where

$$q = \frac{-\delta + \sqrt{\delta^2 + 4sD}}{2D}, \quad q' = \frac{\delta + \sqrt{\delta^2 + 4sD}}{2D},$$

and C and C' are the constants to be determined from the boundary conditions. Since q' is always positive, C' should be zero due to boundness condition. Therefore, Eq. (9) is reduced to

$$L(x, s) = \frac{\mu(x, 0)}{s} + Ce^{-qx}. \quad (10)$$

3. Boundary condition for driven NOE

In the driven NOE experiment, a large rf saturates the selected spin and the migration of magnetization to the other spins is monitored as a function of time. Though not strictly valid, the irradiated spin is assumed to be saturated at all times. Substituting for the first boundary condition names the spin at $x = 0$ is assumed to be saturated at all times, yields

$$N(x, t) = -I_z^0 \quad \text{at } x = 0 \text{ for all } t.$$

Substituting this in Eq. (6) gives

$$\mu(0, t) = -I_z^0 e^{2(\rho + \sigma)t}. \quad (11)$$

Further substituting the second boundary condition that all spins at $x \neq 0$ are at thermal equilibrium at $t = 0$, gives

$$N(x, t) = 0 \quad \text{for } x \neq 0 \text{ at } t = 0,$$

we get

$$\mu(x, 0) = 0. \quad (12)$$

Also, it is assumed that the chain is infinite in length such that at $x = \infty$, the system remains in thermal equilibrium at all times, yielding

$$N_0(x, t) = 0 \quad \text{at } x = \infty \text{ for all } t$$

and

$$\mu(\infty, t) = 0 \tag{13}$$

Substituting boundary conditions (11)–(13), Eq. (10) can be written as

$$L(x, s) = -\frac{I_z^0}{s - 2(\rho + \sigma)} e^{-qx} \tag{14}$$

Eq. (14) is identical to Eq. (22) of [7] except the definition of q. For equidistant spins, $\delta = 0$, and the q becomes identical to [7]. Taking Inverse Laplace transform of Eq. (14), we get

$$
\begin{aligned}
&\mu(x,t) \\
&= -\frac{I_z^0}{2} \exp\left(\frac{\delta x}{2D}\right) \exp(\{2(\rho+\sigma)\}t) \\
&\times \left[\begin{array}{l} \exp\left(-\sqrt{\frac{\delta^2}{4D}+2(\rho+\sigma)}\frac{x}{\sqrt{D}}\right)\mathrm{erfc}\left(-\sqrt{\left(\frac{\delta^2}{4D}+2(\rho+\sigma)\right)t}+\frac{x}{2\sqrt{Dt}}\right) \\ +\exp\left(\sqrt{\frac{\delta^2}{4D}+2(\rho+\sigma)}\frac{x}{\sqrt{D}}\right)\mathrm{erfc}\left(\sqrt{\left(\frac{\delta^2}{4D}+2(\rho+\sigma)\right)t}+\frac{x}{2\sqrt{Dt}}\right) \end{array} \right],
\end{aligned}
\tag{15}
$$

where erfc is the complementary error function [14]. Substituting Eq. (15) into Eq. (6), the difference of population as a function of position and time is obtained as

$$
\begin{aligned}
N(x,t) &= -\frac{I_z^0}{2} \exp\left(\frac{\delta x}{2D}\right) \\
&\times \left[\begin{array}{l} \exp\left(-\sqrt{\frac{\delta^2}{4D}+2(\rho+\sigma)}\frac{x}{\sqrt{D}}\right)\mathrm{erfc}\left(-\sqrt{\left(\frac{\delta^2}{4D}+2(\rho+\sigma)\right)t}+\frac{x}{2\sqrt{Dt}}\right) \\ +\exp\left(\sqrt{\frac{\delta^2}{4D}+2(\rho+\sigma)}\frac{x}{\sqrt{D}}\right)\mathrm{erfc}\left(\sqrt{\left(\frac{\delta^2}{4D}+2(\rho+\sigma)\right)t}+\frac{x}{2\sqrt{Dt}}\right) \end{array} \right].
\end{aligned}
\tag{16}
$$

The transfer of magnetization for driven NOE case is proportional to $N(x,t)$ and can be calculated at different value of x, such as

$$
x = \begin{cases} \frac{n+1}{2}a + \frac{n-1}{2}b, & n \text{ odd} \\ \frac{n}{2}a + \frac{n}{2}b, & n \text{ even} \end{cases}.
$$

The variation of NOE obtained using $N(x,t)$ given by Eq. (16) is plotted in Figs. 3A and B for various values of x_n viz., $n = 1$ and 2 taking $\omega = 270$ MHz, $\omega\tau_c = 10$, $a = 2\text{Å}$ and $b/a = 0.8, 1.0, 1.2$. It is clear from these figures that NOE enhancement increases when the ratio b/a is less then 1 for each spin. This is obvious as the NOE is 6th power dependence of the inter-spin spacing, the spin which is close to the saturated spin will always get more NOE transfer and then it will dominate as compare to the spin which is comparatively far. Fig. 4 shows NOE (η) for different values of $\omega\tau_c$ for $b/a = 0.9$, 1.0, and 1.1. Again the enhancement is more for higher $\omega\tau_c$ (spin-diffusion limit) and for lower ratio of b/a as expected.

This type of physical situation, where the inter-spin spacing is not a constant but jumps to values 'a' and 'b' periodically as one moves along the chain, is found in extended β sheet structure in peptide [1,9], where the $NH_i - C_{i-1}^\alpha$ distance is of the order of 2.2 Å, while the $NH_i - C_{i+1}^\alpha$ is about 2.8 Å, as shown in Fig. 1, hence
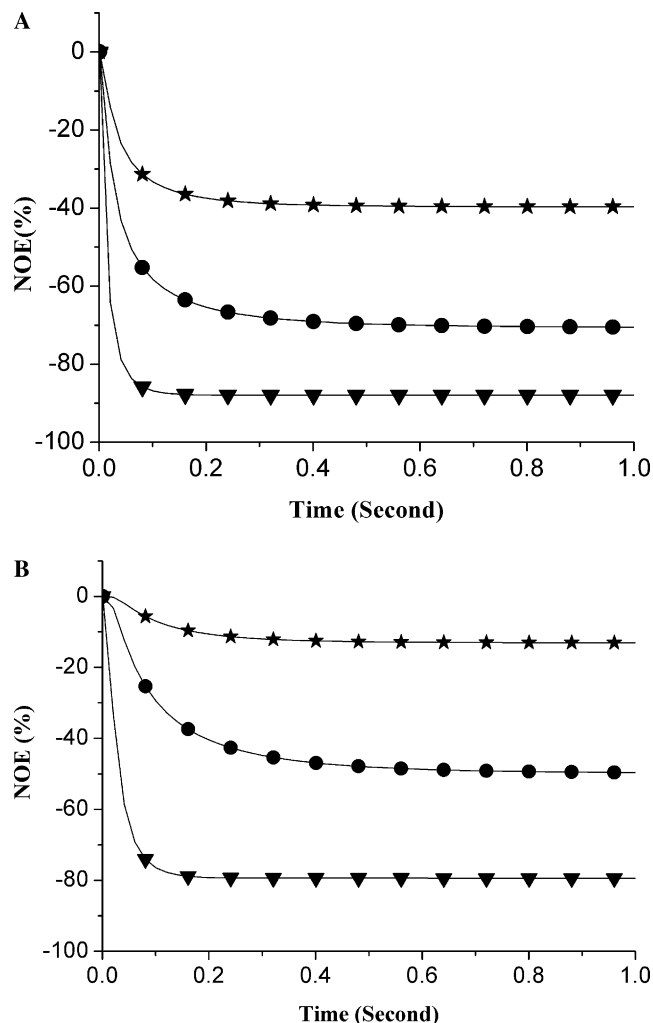
Fig. 3. (A) The plot of NOE (η) in driven NOE experiment for the spin at $x = a$ in the infinite chain for different ratio of b/a such as 0.8 (-▼-), 1.0 (-●-), 1.2 (-★-) as a function of time when the spin at $x = 0$ is assumed to be saturated for all time. The parameters used are $a = 2$ Å, $\omega = 270$ MHz, and $\omega\tau_c = 10$. (B) The plot of NOE (η) in driven NOE experiment for the spin at $x = a + b$ in the infinite chain for different ratio of b/a such as 0.8 (-▼-), 1.0 (-●-), 1.2 (-★-) as a function of time when the spin at $x = 0$ is assumed to be saturated for all time. The parameters used are $a = 2$ Å, $\omega = 270$ MHz, and $\omega\tau_c = 10$.

the magnetization travels in one dimension but the inter-spin distance is periodically bi-spaced. The NOE in such cases can be calculated using Eq. (16). When b is equal to a, the above results reduce to that presented earlier [7].

4. NOE for random inter-spin spacing

For a fixed inter-spin spacing a, the transfer of magnetization for driven NOE case is given by [7],

$$
N(x,t) = -\frac{I_z^0}{2} \left[\begin{array}{l} \exp\left\{-x\sqrt{\frac{2(\rho+\sigma)}{D}}\right\}\mathrm{erfc}\left\{\frac{x}{2\sqrt{Dt}}-\sqrt{2(\rho+\sigma)}\right\} \\ +\exp\left\{x\sqrt{\frac{2(\rho+\sigma)}{D}}\right\}\mathrm{erfc}\left\{\frac{x}{2\sqrt{Dt}}+\sqrt{2(\rho+\sigma)}\right\} \end{array} \right],
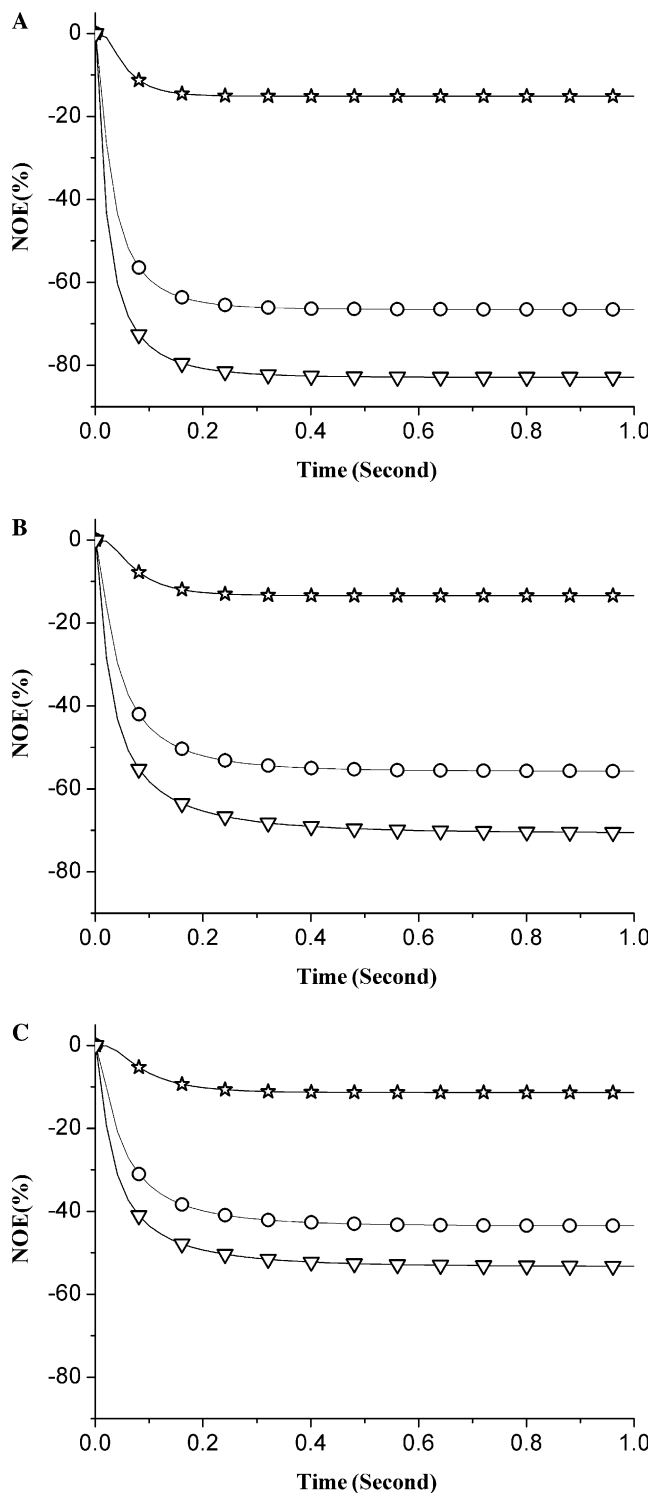\tag{17}
$$

Fig. 4. The time dependence of η in the driven NOE experiment for the spin at $x = a$ in infinite chain for correlation factors $\omega\tau_c = 2$ (-☆-), 6 (-○-), and 10 (-▽-) with $a = 2$ Å, $\omega = 270$ MHz for the different ratio of b/a (A) $b/a = 0.9$, (B) $b/a = 1.0$, and (C) $b/a = 1.1$.

where

$$D = \sigma a^2,$$

$$\rho = W_0 + 2W_1 + W_2,$$

$$\sigma = W_2 - W_0.$$

Here, W's are the transition probabilities given by Eq. (2). In what follows we present a treatment similar to that presented in the preceding sections, but where the inter-spin distances changes randomly. Let the inter-spin spacing a be a random variable distributed normally around the mean value a_0 with variance Δ^2 as shown in Fig. 5. Therefore, the probability that the inter-spin spacing be a is given by [14]

$$P(a) = \frac{1}{\sqrt{2\pi}\Delta} \exp\{-(a - a_0)^2/2\Delta^2\}. \qquad (18)$$

The expectation value of transition probabilities is now given by

$$\langle W_i(a) \rangle = W_i + \frac{21W_i}{a_0^2}\Delta^2. \qquad (19)$$

Similarly, the expectation value of the diffusion coefficient D is given by,

$$\langle D(a) \rangle = D\left[1 + 21\frac{a^2}{\Delta^2}\right] \qquad (20)$$

using Eqs. (19) and (20) in Eq. (17), we can obtain the transfer of NOE for random inter-spin spacing. That means we can still use Eq. (17), which gives NOE transfer for equidistant spin system with the expectation values of transition probabilities W's and diffusion coefficient. It has been plotted in Fig. 6 for different values of Δ. It is clear from figure that as we increase the deviation of inter-spin distance from its mean value, NOE enhancement is sharp and increased. This is well expected as when we choose the inter-spin spacing to be random, some spins are very near and some spins can be far, but as the NOE depends on the 6th power of the distance, those spins which are near will be dominating and show up in overall NOE enhancement whereas those spins which are far will not be effective and can be ignored.

5. Conclusion

Spin-diffusion equation for bi-spaced periodic lattice has been formed from the first principles and solved for driven NOE case. This type of situation is found in secondary structures such as extended β sheet structure in peptides. It has been shown that NOE process can be modeled by diffusive process even when chain is not equidistant and the NOE intensity will depend on the ratio of inter-spin spacing. Also, the solution is obtained and results are plotted for the case when the inter-spin spacing is a random variable with Gaussian distribution. It was found that if the distance vector is random, it will affect overall NOE intensity pattern and intensity will increased. These results are theoretical and may prompt experimentalist to verify these findings. Also, these equations can be used to optimize protein conformations from the experimental NOE data. For the future, we plan to extend these models for two- and three-dimensional cases which are realistic systems for protein.
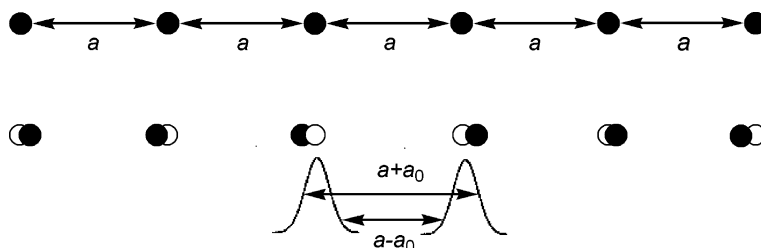
Fig. 5. Symbolic representation of random inter-spin spacing in infinite chain. It is assumed that the distribution is Gaussian with variance Δ^2.
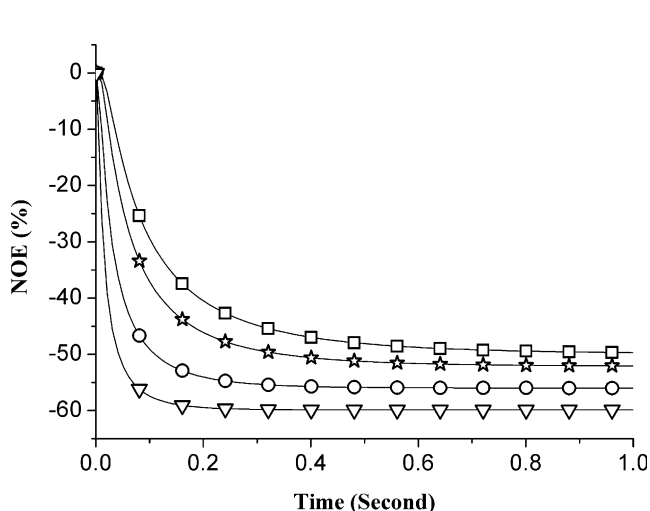

Fig. 6. The plot of NOE (η) for the infinite chain with random inter-spin spacing for the different value of $\Delta = 0.0$ (-□-), $0.1a_0$ (-☆-), $0.2a_0$ (-○-), and $0.3a_0$ (-▽-), where a_0 is the mean inter-spin spacing. Other parameter used are $x = 2a$, $a = 2$ Å, $\omega = 270$ MHz, and $\omega\tau_c = 10$.

Appendix A

For the purpose of optimizing protein conformation using NOE data, we present our theoretical result (Eq. (16)) in terms of NMR parameters which can be readily used by optimizing programs. The NOE intensity at any time at position x will be given by,

$$N(x,t) = -\frac{I_z^0}{2} \exp(A_1 x) \left[\begin{array}{l} \exp\left(-\sqrt{\frac{A_2}{D}}x\right) \mathrm{erfc}\left(-\sqrt{A_2}t + \frac{x}{2\sqrt{Dt}}\right) \\ + \exp\left(\sqrt{\frac{A_2}{D}}x\right) \mathrm{erfc}\left(\sqrt{A_2}t + \frac{x}{2\sqrt{Dt}}\right) \end{array} \right],$$

where

$$A_1 = \frac{1 - \left(\frac{b}{a}\right)^5}{b\left(1 + \left(\frac{b}{a}\right)^4\right)},$$

$$\frac{A_2}{D} = \frac{1}{b^2} \cdot \left[\frac{1 - \left(\frac{b}{a}\right)^5}{\left(1 + \left(\frac{b}{a}\right)^4\right)} \right]^2 - \frac{4}{b^2} \cdot \frac{W_1 + W_2}{W_2 - W_0} \cdot \frac{1 + \left(\frac{b}{a}\right)^6}{1 + \left(\frac{b}{a}\right)^4},$$

$$D = -\frac{1}{2}(W_2 - W_0)\left(\frac{1}{a^4} + \frac{1}{b^4}\right),$$

with

$$W_0 = \tfrac{1}{10}\gamma^4\hbar^2\tau_c,$$

$$W_1 = \frac{3}{20}\gamma^4\hbar^2\left\{\frac{\tau_c}{1 + \omega^2\tau_c^2}\right\},$$

$$W_2 = \frac{3}{5}\gamma^4\hbar^2\left\{\frac{\tau_c}{1 + 4\omega^2\tau_c^2}\right\}$$

and

$$x = \left\{ \begin{array}{ll} \frac{n+1}{2}a + \frac{n-1}{2}b, & n \text{ odd} \\ \frac{n}{2}a + \frac{n}{2}b, & n \text{ even} \end{array} \right\}.$$

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