

Interaction of exchange and differential relaxation in the saturation recovery behavior of the binary spin-bath model for magnetization transfer

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ABSTRACT

Most closed-form analytical solutions of the binary spin-bath are difficult to interpret in terms of underlying physics. The key notions are the presence of a kinetic and a thermal equilibrium and that the time course of saturation recovery under conditions of fast-exchange can be understood as conjoint relaxation and loss-less transfer. By introducing a suitable parameter it is shown how exchange and differential relaxation counteract each other: The amount of transferred saturation (transfer term) is altered and the kinetic equilibrium appears slightly disturbed (difference term). Although the factorization formally represents the general solution of saturation recovery in the binary spin-bath, this interpretation applies only to the case of fast exchange and slow relaxation. By calculating the set of parameters for a wide range of hypothetical values of R_{1m} , it was shown that the difference term is crucial to describe the transition to the slow-exchange limit. The transfer term vanishes as the two pools appear decoupled in this approximation.

INTRODUCTION

The ‘binary spin-bath’ (BSB) is a widely used model for NMR studies of two-site exchange processes. In the context of MR imaging (MRI), this phenomenological description of two pools of magnetization with linear exchange is commonly used to describe the mechanism of magnetization transfer (MT) contrast. Here, the two pools represent the observable bulk water and the ‘invisible’ rotationally restricted semi-solid macromolecules in biological tissues. Quantitative evaluation of MT in brain tissue has shown that the difference between the relaxation rates is much smaller than the sum of the exchange rates. This is the condition of the ‘fast exchange approximation’.

Recently, we presented a free-evolution model to describe the saturation created by periodic radio-frequency pulses (1,2). Contrary to other solutions of saturation recovery in analytically closed form, we introduced parameters that adopt a specific physical meaning under the condition of fast exchange. This provided insight into how the observed kinetic of saturation recovery is influenced by the saturation of macromolecules. Pursuing a more qualitative and less formalistic approach we elaborate the fast-exchange MT-model by starting from the asymptotic conditions of negligible relaxation and negligible difference in relaxation. This approach motivates a factorization of the evolution into relaxation and transfer, even for the general solution for the BSB. Since compartmental exchange is a basic mechanism of relaxation in tissue (3), this note places the theoretical framework into a wider context than MT applications. We elucidate specific issues of the BSB, like the kinetic equilibrium, the influence of differential relaxation, and the transition from conditions of rapid exchange to slow exchange (3,4).

THERMAL AND KINETIC EQUILIBRIUM

Before starting a general discussion of the binary spin-bath, one should draw a clear distinction between the *two* kinds of equilibrium involved: *thermal* (Boltzmann) and *kinetic* equilibrium. The spin densities of free water and macromolecules are the main determinants for both equilibria of the subsystems (or “pools”). The magnetizations in *thermal* equilibrium, M_f^0 and M_m^0 , are influenced by temperature and polarizing magnetic field B_0 determining the *absolute* size. They are restored by the intrinsic relaxation rates, R_{1f} and R_{1m} , which would be observed in the absence of exchange. The microscopic mechanisms determine the number of exchanging spin pairs during unit time. A formulation by a stochastic model is found in the classic account of Zimmerman and Brittin (4). The *kinetic* equilibrium is usually stated in terms of the equilibrium magnetizations,

$$dM_{\leftrightarrow}^0/dt = k_{fm}M_f^0 = k_{mf}M_m^0, \quad [1]$$

thus defining the first-order rate constants of transfer, k_{fm} and k_{mf} . Note that M_f^0 and M_m^0 , as well as k_{fm} and k_{mf} may be scaled arbitrarily without changing Eq. [1]. Like in kinetic theory, the kinetic equilibrium is characterized by a constant *proportion* between M_f^0 and M_m^0 (the pool size ratio, f), but not by the absolute size of magnetization and exchange rates. After disturbance of the system, the exchange mechanisms strive to re-establish kinetic equilibrium. Unlike thermal equilibrium, the kinetic equilibrium does *not* define a state of constant magnetization. The fact that the size is maintained by homeostasis in biological systems and that M_f^0 and M_m^0 represent *both* equilibria may explain why this distinction is rarely worked out in the context of MT.

The longitudinal part of the coupled Bloch (or McConnell) equations in the absence of RF irradiation is solved for the “saturation vector”:

$$\boldsymbol{\eta} = \begin{pmatrix} \eta_f \\ \eta_m \end{pmatrix} = \begin{pmatrix} 1 - M_f/M_f^0 \\ 1 - M_m/M_m^0 \end{pmatrix}. \quad [2]$$

This intuitively uncommon representation is used throughout the paper, because it provides the simplest form of a general solution for the time evolution of the coupled Bloch equations.

These are transformed to a homogeneous system of differential equations:

$$\frac{d}{dt} \begin{pmatrix} \eta_f \\ \eta_m \end{pmatrix} = \begin{pmatrix} -k_{fm} - R_{1f} & k_{fm} \\ k_{mf} & -k_{mf} - R_{1m} \end{pmatrix} \begin{pmatrix} \eta_f \\ \eta_m \end{pmatrix}. \quad [3]$$

A comprehensive treatment of the coupled Bloch equations is given in (5). In the notation of $\boldsymbol{\eta}$, the Boltzmann equilibrium refers to zero saturation, so longitudinal relaxation can be seen as decay of saturation. It is intuitively clear that equal saturation of the pools still satisfies the conditions of kinetic equilibrium:

$$\eta_f = \eta_m \Leftrightarrow \frac{M_f^o - M_f}{M_f^o} = \frac{M_m^o - M_m}{M_m^o} \Leftrightarrow \frac{M_m}{M_f} = \frac{M_m^o}{M_f^o} = f. \quad [4]$$

Consider now the recovery after complete saturation or inversion of the total system. Although the pools were still balanced with respect to exchange, differential relaxation of the pools will eventually disturb the kinetic equilibrium. The opposing effects of differential relaxation (disturbing the kinetic equilibrium) and exchange (establishing the kinetic equilibrium) are the key to understand the general behavior of the binary spin bath. Based on the distinction between relaxation and transfer we can step-by-step build up an understanding of the free evolution of the BSB following arbitrary saturation.

ABSENCE OF RELAXATION AND CONSERVATION OF MAGNETIZATION

In the asymptotic case of infinitely slow relaxation, the transfer of saturation occurs at a rate

$$R_T = k_{mf} + k_{fm}. \quad [5]$$

This can be shown by setting R_{1f} and R_{1m} to zero in Eq. [3]. The time evolution of $\boldsymbol{\eta}$ after an arbitrary initial saturation of the pools by δ_f and δ_m (which may have been created by a

selective radio-frequency pulse) is given by multiplication of a time-dependent 2x2 matrix, the transfer matrix \mathbf{T} :

$$\boldsymbol{\eta}(t) = \mathbf{T}(t) \begin{pmatrix} \delta_f \\ \delta_m \end{pmatrix} = \begin{pmatrix} 1 - F[1 - \exp(-R_T t)] & F[1 - \exp(-R_T t)] \\ (1 - F)[1 - \exp(-R_T t)] & 1 - (1 - F)[1 - \exp(-R_T t)] \end{pmatrix} \begin{pmatrix} \delta_f \\ \delta_m \end{pmatrix}. \quad [6]$$

F denotes the *fraction* of the macromolecular pool of the total magnetization in the BSB.

$$F = \frac{M_m^o}{M_f^o + M_m^o} = \frac{f}{1 + f}. \quad [7]$$

After the transfer is accomplished at $t > 5/R_T$, kinetic equilibrium is re-established at a common level of saturation that is given by the pool size weighted average:

$$\boldsymbol{\eta}(t > 5/R_T) = \begin{pmatrix} 1 - F & F \\ 1 - F & F \end{pmatrix} \begin{pmatrix} \delta_f \\ \delta_m \end{pmatrix} = \begin{pmatrix} (1 - F)\delta_f + F\delta_m \\ (1 - F)\delta_f + F\delta_m \end{pmatrix}. \quad [8]$$

This value corresponds to the fraction of the total magnetization that has been initially saturated, as expected for the kinetic equilibrium. For ideal MT ($\delta_m=1, \delta_f=0$), this is the macromolecular fraction (F); for inverse MT ($\delta_f=1, \delta_m=0$), this is the fraction of free water ($1-F$). This is a reasonable result, as the total magnetization must be conserved during transfer when there is no relaxation. However, the sum of the saturations is not conserved as each normalized by the pool size which are generally not equal. The terms with the $1 - \exp(-R_T t)$ time-dependence describe the transferred saturation. In the right column of \mathbf{T} (representing ideal MT), saturation is transferred from the macromolecules to water. The ratio of the corresponding amplitudes represents the pool size ratio as required by Eq. [3]

$$\frac{F}{1 - F} = f = \frac{M_m^o}{M_f^o} \quad [9]$$

The left column yields the inverse relationship for the case of inverse MT.

UNDISTURBED TRANSFER IN THE ABSENCE OF DIFFERENTIAL RELAXATION

When relaxation occurs at the same rate in both pools, the kinetic equilibrium remains undisturbed after equal saturation. The significance of the terms describing the time evolution of $\boldsymbol{\eta}$ can be established from this special case saturation recovery. It is usually written as a linear combination of exponentials decaying at rates of λ_R and λ_T . These are given by the negative eigenvalues of Eq. [3] (to render positive values of λ_R and λ_T). $R_{1m} = R_{1f} = R_1$ results in a simple factorization of the characteristic equation for

$$\lambda_R = R_1 \quad [10a]$$

and

$$\lambda_T = k_{fm} + k_{mf} + R_1 = R_T + R_1. \quad [10b]$$

When comparing Eqs. [5] and [10b], the occurrence of R_1 shows that λ_T may not be equated to the rate of transfer as claimed earlier (1). In fact, also the second exponential must have a contribution from R_1 , because the *whole* BSB is relaxing at this rate. This relation is concealed in the general solution (see Eq. [18] of (1)) because the expressions for λ_R and λ_T are more complicated. For the linear combination of $\exp(-\lambda_R t)$ and $\exp(-\lambda_T t)$ the unbiased term ‘evolution matrix’, $\mathbf{E}(t)$, is suggested. We have somewhat prematurely used the term ‘transfer matrix’ (1), while others have suggested ‘relaxation matrix’ (6). As a matter of fact, both terms are equally unsatisfactory, as the evolution comprises *both* transfer *and* relaxation. The evolution can be factorized into a scalar relaxation term and the actual transfer matrix, \mathbf{T} , of Eq. [8]:

$$\begin{aligned} \boldsymbol{\eta}(t) &= \mathbf{E}(t) \begin{pmatrix} \delta_f \\ \delta_m \end{pmatrix} = \exp(-R_1 t) \begin{pmatrix} 1 - F[1 - \exp(-R_T t)] & F[1 - \exp(-R_T t)] \\ (1 - F)[1 - \exp(-R_T t)] & 1 - (1 - F)[1 - \exp(-R_T t)] \end{pmatrix} \begin{pmatrix} \delta_f \\ \delta_m \end{pmatrix} \\ &= \exp(-R_1 t) \mathbf{T}(t) \begin{pmatrix} \delta_f \\ \delta_m \end{pmatrix} = \exp(-R_1 t) \boldsymbol{\delta}_{\text{app}}(t) \end{aligned} \quad [11]$$

The factorization of the free evolution matrix also motivates the use of a time-dependent ‘apparent saturation’, $\delta_{\text{app}}(t)$, to describe repetitive saturation (1,2,7). The apparent saturation

is simply the product of the transfer matrix during the repetition period, $\mathbf{T}(\text{PR})$, and the vector of initial saturations imposed by one RF pulse. The apparent saturation describes the transfer of saturation in the BSB by the rate of $\lambda_T - \lambda_R$ corrected for ongoing common relaxation by the rate of λ_R .

APPROXIMATION FOR FAST EXCHANGE

In the general solution one may identify similar terms as in the asymptotic case when there is no differential relaxation (1), so the evolution matrix of the BSB can be written as:

$$\mathbf{E}(t) = \exp(-\lambda_R t) \mathbf{T}(t) = \exp(-\lambda_R t) \begin{pmatrix} T_{ff} & T_{fm} \\ T_{mf} & T_{mm} \end{pmatrix} = \exp(-\lambda_R t) \begin{pmatrix} 1 - T[1 - \exp(-\Delta\lambda t)] & (T - D)[1 - \exp(-\Delta\lambda t)] \\ (1 - T)\frac{T}{T - D}[1 - \exp(-\Delta\lambda t)] & 1 - (1 - T)[1 - \exp(-\Delta\lambda t)] \end{pmatrix}. \quad [12]$$

With the general expressions for the four parameters, Eq. [13] represents the free evolution for arbitrary parameters of the BSB. Quantitative MT studies on brain tissue (8) have shown that the BSB model is characterized by conditions of fast exchange:

$$-1 \ll \varepsilon = (R_{1m} - R_{1f}) / (k_{fm} + k_{mf}) \ll 1 \quad [13]$$

The dimensionless parameter, ε , describing the ‘differential relaxation’ during the exchange time $1/R_T$, will be used in the next section. Under conditions of fast exchange, thermal equilibrium is restored in both pools simultaneously at a rate of

$$\lambda_R \rightleftharpoons (1 - F) R_{1f} + F R_{1m} = R_1, \quad [14]$$

showing the weighted average that is characteristic for conditions of fast exchange. Transfer takes place at a rate of

$$\Delta\lambda = \lambda_T - \lambda_R \rightleftharpoons k_{fm} + k_{mf} + (1 - 2F) (R_{1m} - R_{1f}) = R_T. \quad [15]$$

and not at λ_T as stated earlier (1). The amplitudes are given by the ‘transfer term’

$$T = \frac{k_{fm} + R_{1f} - \lambda_R}{\lambda_T - \lambda_R} \approx \frac{k_{fm} + F (R_{1f} - R_{1f})}{R_T}. \quad [16]$$

and the ‘difference term’

$$D = \frac{R_{1f} - \lambda_R}{\lambda_T - \lambda_R} \approx \frac{F(R_{1f} - R_{1m})}{R_T} \quad [17]$$

The sign of D is an arbitrary convention. In the context of MT, D is negligible because both the macromolecular fraction and the difference in relaxation are small. In order to illustrate the closeness of the conditions in tissue to the asymptotic case, Fig. 1 shows the time dependence of the transfer matrix \mathbf{T} . It was calculated for white matter (WM) at 1.5 Tesla for the same parameters of bovine WM (8) as used previously (1). Again, the elements in the right matrix column describe the case of “ideal MT” after selective saturation of the macromolecules (bottom curves T_{fm} , T_{mm}); the elements in the right matrix column the saturation transfer after selective saturation of the free water (“inverse MT”, top curves T_{ff} , T_{mf}). Convergence onto a constant plateau indicates kinetic equilibrium because these curves appear corrected for ongoing relaxation by R_1 when compared to Fig 1a in (1).

Fig. 1

The slight mismatch of T_{ff} and T_{mf} in kinetic equilibrium is the result of differential relaxation and will be discussed below. It was not seen for the dashed curve calculated for the asymptotic case of $R_{1m} = R_{1f}$.

DISTURBANCE OF TRANSFER BY DIFFERENTIAL RELAXATION

Using the small parameter of differential relaxation (Eq. [13]) to replace F , the relaxation rate can be rewritten as

$$R_1 = R_{1f} + F (R_{1m} - R_{1f}) = R_{1f} + k_{fm} \varepsilon \quad [18a]$$

or

$$R_1 = R_{1m} - (1-F) (R_{1m} - R_{1f}) = R_{1m} - k_{mf} \varepsilon \quad [18b]$$

One sees that the difference between the observed rate R_1 and the intrinsic relaxation rates R_{1m} and R_{1f} is due to the small disturbance by ε , which is conveyed by exchange.

Identical disturbance terms appear in

$$R_T = k_{fm} + k_{mf} + (1-2F)(R_{1m}-R_{1f}) = k_{fm} + k_{mf} + (k_{mf} - k_{fm}) \varepsilon = k_{fm}(1-\varepsilon) + k_{mf}(1+\varepsilon). \quad [19]$$

Thus, the exchange rate to the pool m k_{fm} is decreased if this pool relaxes faster, while more magnetization flows off to pool f, which is lagging behind in relaxation. Note that in the hypothetical combination of fast exchange and relaxation being much faster than exchange, the observed transfer rate would be much slower than the observed relaxation rate, reflecting that the kinetic equilibrium is mainly restored by relaxation to the thermal equilibrium. After a lengthy conversion, the transfer term can be written as

$$T \rightleftharpoons k_{fm}(1-\varepsilon) / [k_{fm}(1-\varepsilon) + k_{mf}(1+\varepsilon)], \quad [20]$$

By comparing the definition of F in Eq. [7] to Eq. [20] one sees that T may be interpreted as effective pool size in the presence of differential relaxation. The difference term applies to the case of ideal MT. It accounts for the mismatch between the observed level of *free* water saturation and the kinetic equilibrium expected for T . This explains why D is the difference between bulk water relaxation, R_{1f} , and the observed relaxation, λ_R , during the transfer time, $1/\Delta\lambda$ (Eq. [17] of (1)). Here, we write

$$D = T - k_{fm}/\Delta\lambda \rightleftharpoons -\varepsilon k_{fm} / [k_{fm}(1-\varepsilon) + k_{mf}(1+\varepsilon)] \rightleftharpoons -F \varepsilon, \quad [21]$$

In the special case of $\varepsilon = 0$, one gets $T = F$ and $D = 0$.

To discuss the effect of differential saturation, let's consider that macromolecules relax slower than the free water ($\varepsilon < 0$ like in our example: $R_{1m} = 1 \text{ s}^{-1}$ vs. $R_{1f} = 1.36 \text{ s}^{-1}$). Naturally, the average relaxation is slowed down when compared to free water. The average relaxation rate R_1 is of course slower than R_{1m} . For the case of ideal MT, this entails a smaller loss of macromolecular saturation than expected for conservation of magnetization and average relaxation. Thus, the macromolecule saturation (given by T_{mm}) in the disturbed kinetic equilibrium (given by T) is higher than F . On the other hand, the saturation transferred to the free water, $T-D$, is slightly lower than T , since the free water relaxes a bit faster than the average, indicating that D becomes positive.

A similar reasoning can be performed for the cases of increasing R_{1m} ($\epsilon > 0$) and inverse MT. The dependence of T , D , λ_R on R_{1m} is shown in Fig. 2. The values representing Fig. 1 are found for $R_{1m} = 1\text{s}^{-1}$ on the left margin. The difference term is small and changes its sign at $R_{1f} = R_{1m}$. T decreases clearly with increasing R_{1m} when compared to the estimate of F (dashed line) even though λ_R still obeys the fast exchange law for $R_{1m} < 10\text{ s}^{-1}$.

Fig. 2

The components of the transfer matrix are affected differently by ϵ . This may be illustrated by the approximation $R_{1m} = R_{1f}$ for bovine WM shown as dashed curve in Fig. 1. A significant deviation exceeding the linewidth of the plot was observed only for T_{mf} (inverse MT). This is due to the small relative size of the macromolecular pool: First, the difference between macromolecular and observed relaxation is proportional to $(1-F)$ and thus larger than for bulk water. Second, the equilibrium level of saturation for inverse MT higher than for MT. In T_{mf} the mismatch is proportional to $(1-F)^2$ because these effects multiply.

D has been introduced as a correction term for the saturation transferred to the visible pool by ideal MT, where the macromolecules are saturated. The mismatch is proportional to F^2 , so D may be neglected in the context MT where usually a small fraction of the total system is saturated (1).

FINDING T AND D FOR THE OTHER POOL

The definition of transfer and difference term in (1) was motivated by the asymmetry of the MT model, where the macromolecular pool is small and unobservable. It is equally valid to define T^* and D^* for the macromolecular pool. Due to the symmetry of the coupled Bloch equations, this can be achieved by swapping the subscripts 'f' and 'm'. The relationship with T and D is straightforward for the transfer term, where $1-T$ is simply substituted by T^* :

$$T^* \approx k_{mf}(1+\epsilon) / [k_{fm}(1-\epsilon) + k_{mf}(1+\epsilon)]. \quad [22]$$

The difference term is found by replacing $(1-T) T / (T-D)$ by T^*-D^* in T_{mf} .

$$D^* = (1-T) - \frac{(1-T)T}{T-D} = -D \frac{1-T}{T-D}. \quad [23]$$

This is the deviation of T_{mf} from the approximate kinetic equilibrium seen in Figure 1.

$$D^* = T^* - k_{mf}/\Delta\lambda \approx \varepsilon k_{mf} / [k_{fm}(1-\varepsilon) + k_{mf}(1+\varepsilon)] = -D/f \approx (1-F) \varepsilon, \quad [24]$$

This shows that D^* is much larger than D , the deviation of T_{fm} . This is again due to the scaling of the saturations. The change in sign occurs because one pool relaxes faster than λ_R and the other slower.

A common problem of MT is that R_{1m} cannot be measured experimentally from steady state conditions (7). If differential relaxation is small, its influence in free evolution can be parameterized by

$$\mathbf{E}(t) = \exp(-(R_{1f} + k_{fm}\varepsilon)t) \begin{pmatrix} 1 - \frac{k_{fm}(1-\varepsilon)}{R_T} [1 - \exp(-R_T t)] & \frac{k_{fm}}{R_T} [1 - \exp(-R_T t)] \\ \frac{k_{mf}}{R_T} [1 - \exp(-R_T t)] & 1 - \frac{k_{mf}(1+\varepsilon)}{R_T} [1 - \exp(-R_T t)] \end{pmatrix} [25]$$

This was derived by replacing R_1 , T and D . R_T still appears in the denominator and exponentials for the sake of abbreviation.

TRANSITION FROM FAST TO SLOW EXCHANGE

We explained above, how transfer tries to restore an imbalance between the pools and how differential saturation disturbs the kinetic equilibrium. The assignment of relaxation and transfer loses its meaning, when differential relaxation can no longer be regarded as small. For illustration, the dependence of λ_R , T , and D was calculated for a wide range of hypothetical relaxation rates of the macromolecular pool, R_{1m} (Fig. 2). All other parameters are the same as in Fig. 1.

For values up to 10 s^{-1} , the apparent relaxation rate λ_R increases according to the fast exchange approximation (Eq. [14], dotted curve). This increase is however limited. As R_{1m} increases the fraction of free water that relaxes via the transfer to macromolecules increase.

This channel is limited by the forward transfer rate. For large values ($R_{1m} > 1000 \text{ s}^{-1}$), λ_R approaches a constant maximum in the well-known “slow-exchange” approximation (3,4) yielding $\lambda_R = R_{1f} + k_{fm}$. This approximation is derived by applying

$$(k_{fm} + k_{mf}) / |R_{1m} - R_{1f}| \ll 1 \quad [26]$$

in a similar way as in Eq. [34] of (1). In the slow-exchange regime, the kinetic equilibrium can no longer be attained by transfer because one pool relaxes rapidly back to thermal equilibrium, here by $\lambda_T = R_{1m} + k_{mf}$. The observed rates of free evolution have become pool-specific and account for relaxation and flow-off to the other pool. Remember that in this example the exchange rates are actually still the same while only one relaxation rate was increased until it accounts for major part of relaxation of the whole system. Since relaxation via one pool prevails, the transfer term T describing the transferred amount of saturation to establish the kinetic equilibrium (T) is negligible. D is given by the amplitude of T_{fm} :

$$-D \approx k_{fm} / \Delta\lambda \approx k_{fm} / (k_{mf} + R_{1m}) \quad [27]$$

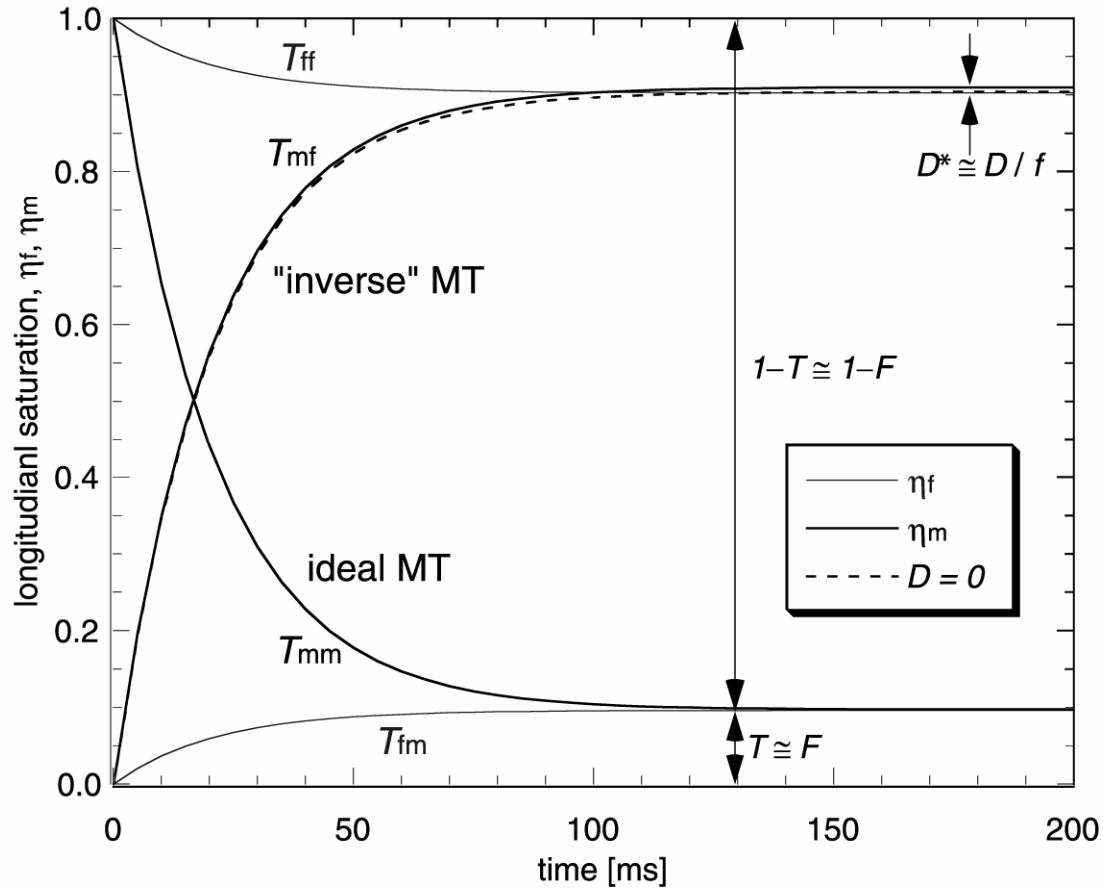
In the case of slow exchange D accounts for the amount of saturation transferred during the relaxation time of the macromolecular pool, which decreases with R_{1m} . The factorization of the evolution matrix (Eq. [12]) is no longer useful. Over the intermediate regime describing the transition from the fast to slow exchange, the exponential components can neither be assigned to relaxation or transfer (fast exchange) or a specific pool (slow exchange). The transfer term decreases to zero, while the difference term bridges the intermediate regime: It increases towards a maximum at the center of the transition, but is still considerably different from zero even where λ_R already nicely follows the approximations of fast and slow exchange.

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Figure 1:

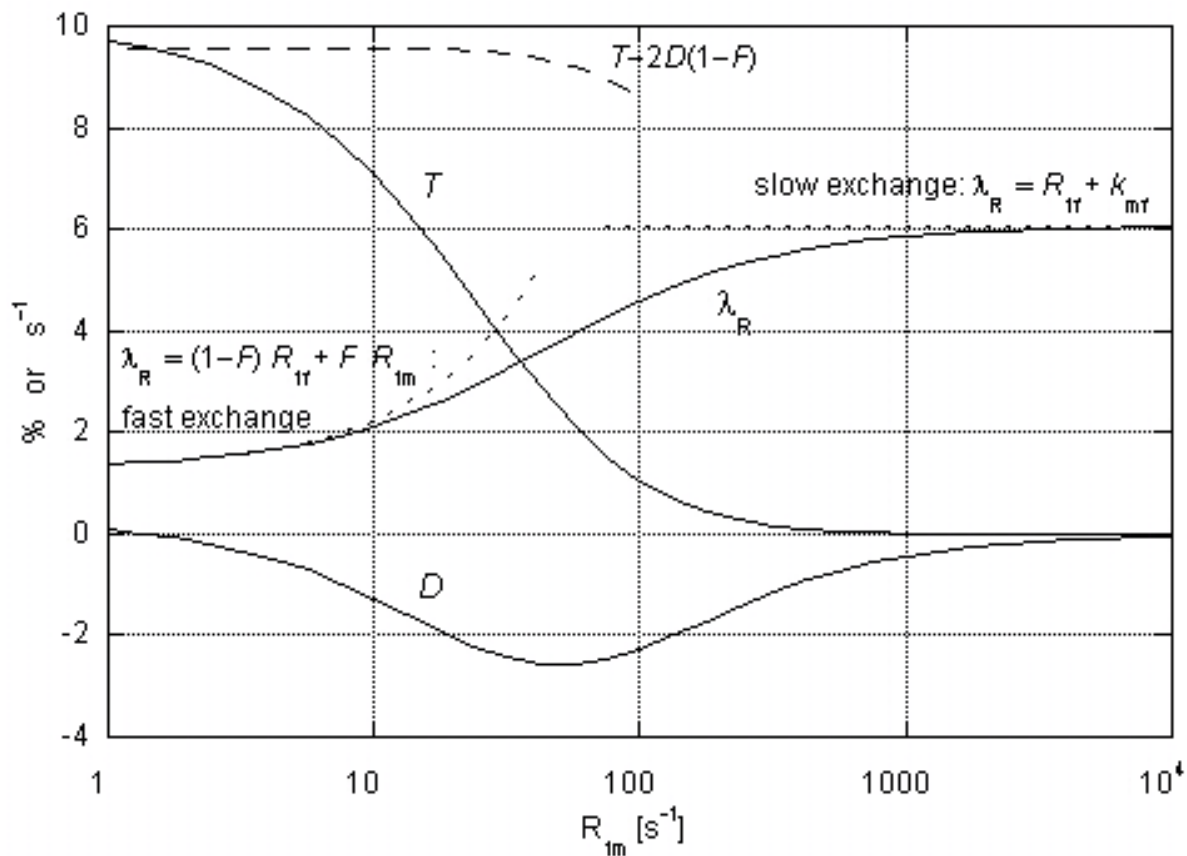
Time dependence of the re-defined transfer matrix (Eq. [12])



Solid lines represent saturation of macromolecules (ideal MT), thin lines the saturation of water (inverse MT). Convergence onto a level of constant saturation indicates the kinetic equilibrium. The mismatch between T_{mm} and T_{fm} due to differential relaxation is not resolved. Calculated with parameters determined experimentally on bovine white matter (8). The dashed line indicates the approximation of T_{mf} for equal relaxation ($R_{1m} = R_{1f}$). Deviations from the other curves did not exceed the line width of the plot.

Figure 2:

Transition between the limits of fast exchange and the slow exchange



The dotted lines indicate the approximations of λ_R for fast and slow exchange. The dashed line indicates an equivalent of F in the fast exchange case. All parameters as in Fig. 1