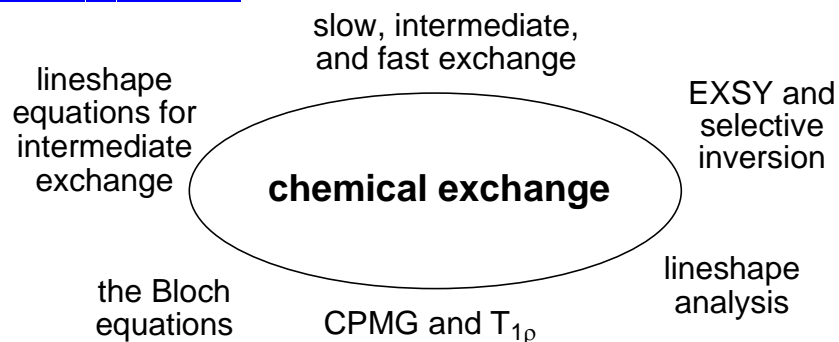# Chemical Exchange

Eugene E. Kwan

March 20, 2012.

$$v = \gamma B_1 M_z \frac{k(2\delta)^2}{(\delta - \omega)^2 (\delta + \omega)^2 + 4k^2\omega^2}$$

Scope of Lecture

slow, intermediate, and fast exchange

lineshape equations for intermediate exchange

chemical exchange

EXSY and selective inversion

the Bloch equations

CPMG and $T_{1\rho}$

lineshape analysis

Key References

1. The ABCs of FT-NMR Roberts, J.D. University Science Books, **2000**. (**Chapter 11**)

2. "Chemical Exchange." *Annual Reports on NMR Spec.* **2008**, *63*, 23-48. Also see *Prog. NMR Spec.* **2003**, *43*, 63-103.

3. Dynamic NMR Spectroscopy Sandsrom, J. Academic Press Inc., **1982**.

4. Applications of Dynamic NMR Spectroscopy to Organic Chemistry. Oki, M. in *Methods in Stereochemical Analysis*, Vol. 4. VCH, **1985**.

Key Questions

(1) What makes spectra look like this?
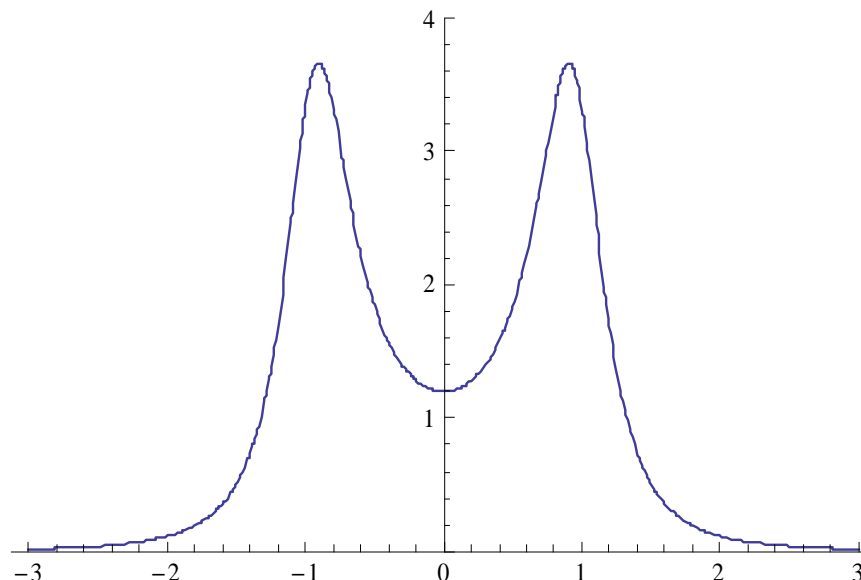
(2) What methods are available for probing exchange?

select one site

180   90
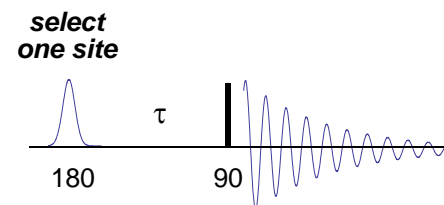
I thank Professor Alex Bain (McMaster) for a lot of useful material and advice for this lecture.

Goals

(1) What is chemical exchange, and how does it affect NMR spectra?

(2) How can the rate of exchange be measured? Why is this useful?

(3) What are the Bloch equations? How can the phenomenon of "coalescence" be described quantiatively?

We need some definitions:

A **site** is a particular chemical environment that gives rise to a certain Larmor frequency. For example, the *N*-methyl groups in DMF comprise two sites:
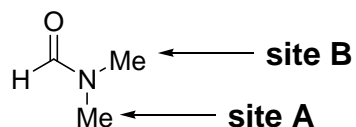
site B

site A

These methyl groups have very different chemical shifts, probably mostly due to the anisotropy of the carbonyl group. Amide bond rotation can take a methyl gruop from site A to site B. Any process that takes a given nucleus from one site to another is called **dynamic exchange**.

The classic sign of dynamic exchange is a dramatic change in lineshape as the temperature changes. At low temperatures, it is common to see two distinct chemical shifts, since the dynamic exchange process is slow. At high temperatures, the two signals merge into one signal ("coalescence"). At medium temperatures, the signals become very broad.

It is the **frequency separation between A and B** ($\Delta\omega$) that determines which regime is seen. Specifically:
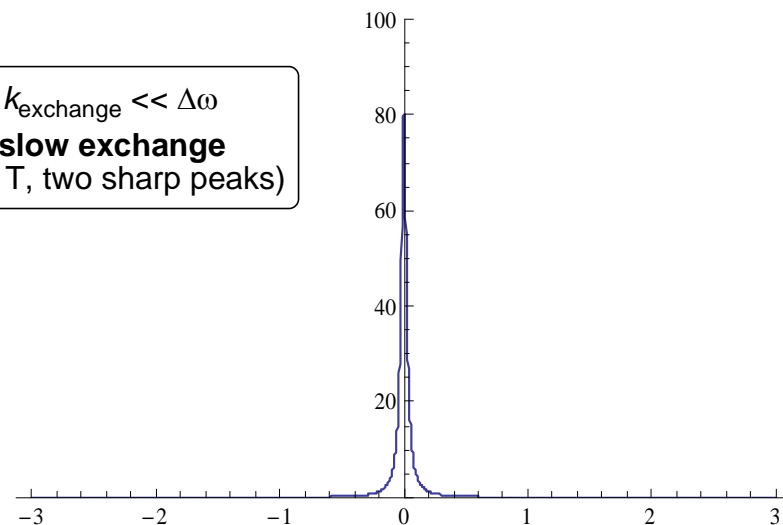
$k_{exchange} = \Delta\omega$

intermediate exchange
(coalescence)
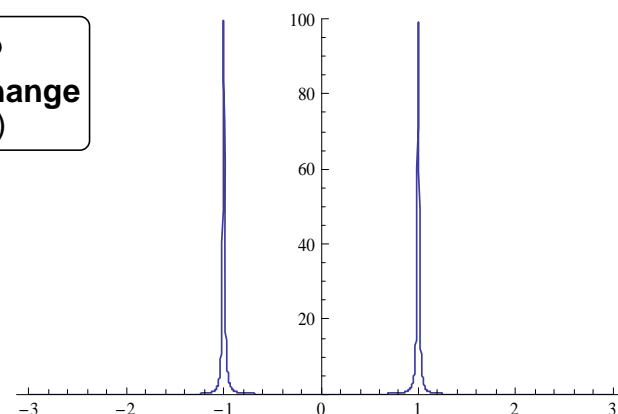
$k_{exchange} \gg \Delta\omega$

fast exchange
(high T, one broadened peak)
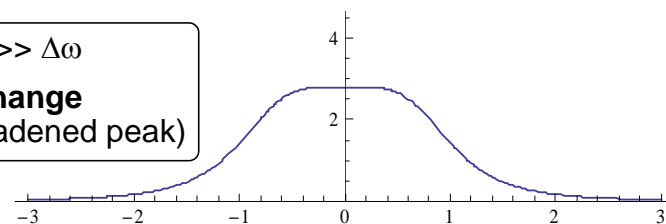
$k_{exchange} \ll \Delta\omega$

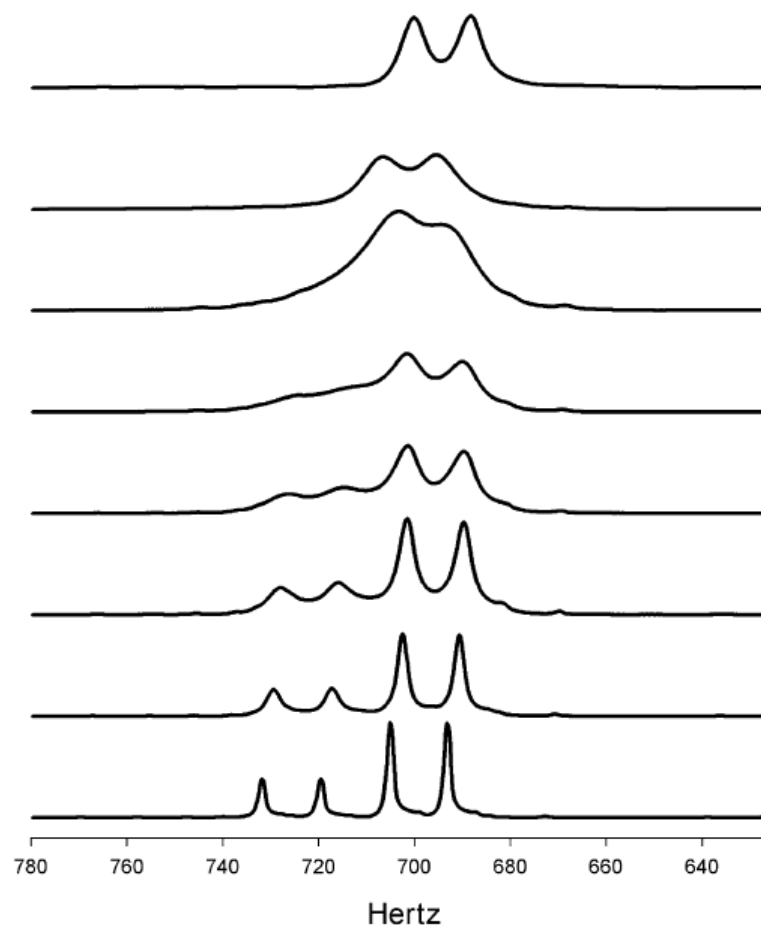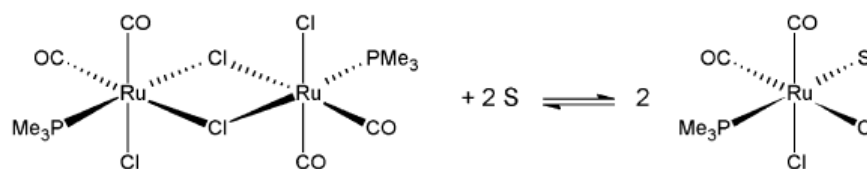**slow exchange**
(low T, two sharp peaks)

Hence, there is no unique NMR timescale. Note that $\Delta\omega$ is the rough timescale of a 1D experiment (relatively fast). 2D experiments such as EXSY have longer timesclaes related to their mixing time.

The appearance of spectra for systems where coupling is involved is more complicated (ref. 2):
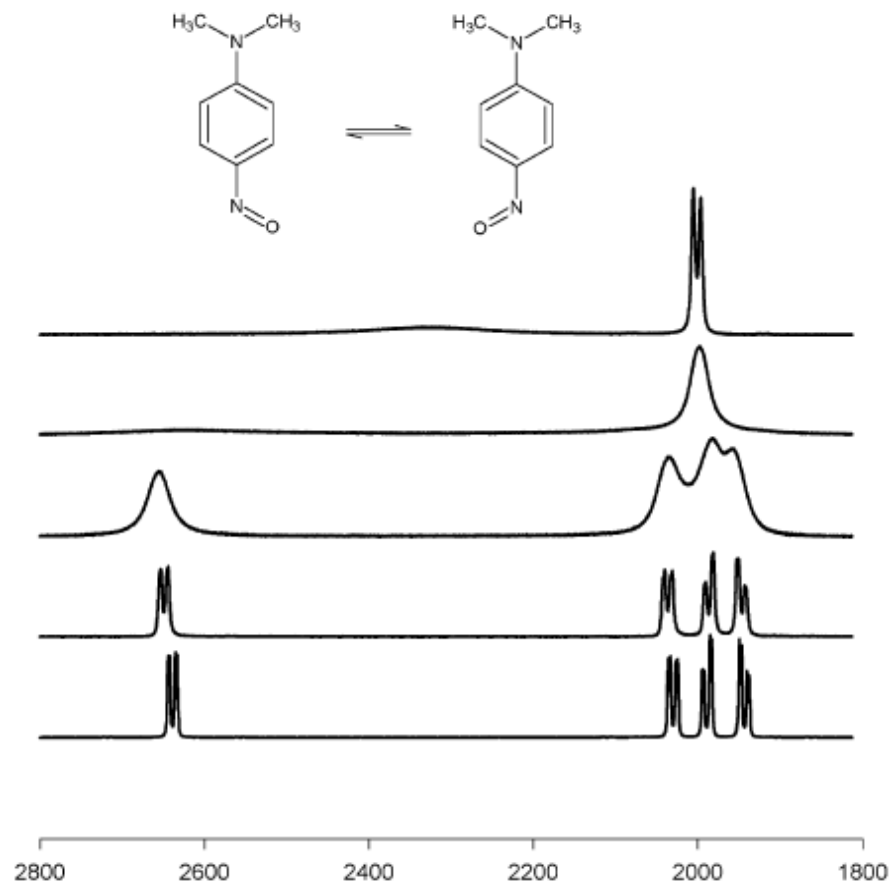
Exchange does *not* have to be a rotational barrier! *Any* process that moves a nucleus from one site to another will work. This is chemical exchange that reflects a monomer/dimer equilibrium (ref 2):

I now turn to the many different possible ways to measure exchange. For **slow exchange**, you have two basic options:

Slow Exchange Methods

(1) EXSY (Exchange Spectroscopy)

What: The same as the NOESY experiment. Yes, exactly the same. In NOESY, the 2D crosspeaks represent through-space magnetization transfer. In EXSY, magnetization is transfered via chemical exchange instead. For small molecules, this means that EXSY peaks will be **of opposite sign** to NOESY peaks.

Purpose: Good qualitative data. Identifies exchange interactions quickly and effectively. It should *not* be used to get quantitative data (Professor Bain's opinion, see his review articles).

Here are EXSY data for DMF (ref 2) (figures right):

(a) At short mixing times, the timescale of the experiment is short compared to the rate of exchange, so there are no crosspeaks (t_{mix} = 0.01 s)

(b) At long mixing times, the timescale of the experiment is on the order of the the exchange rate, so there are visible peaks of opposite phase.

Of note:

- If NOE and EXSY peaks overlap, there is the possibility they might cancel each other out. This is a serious problem.

- At long mixing times, relay effects can also produce negative peaks. See the lecture on the NOE.

- It may be difficult to distinguish between single- and multi-step transfers:
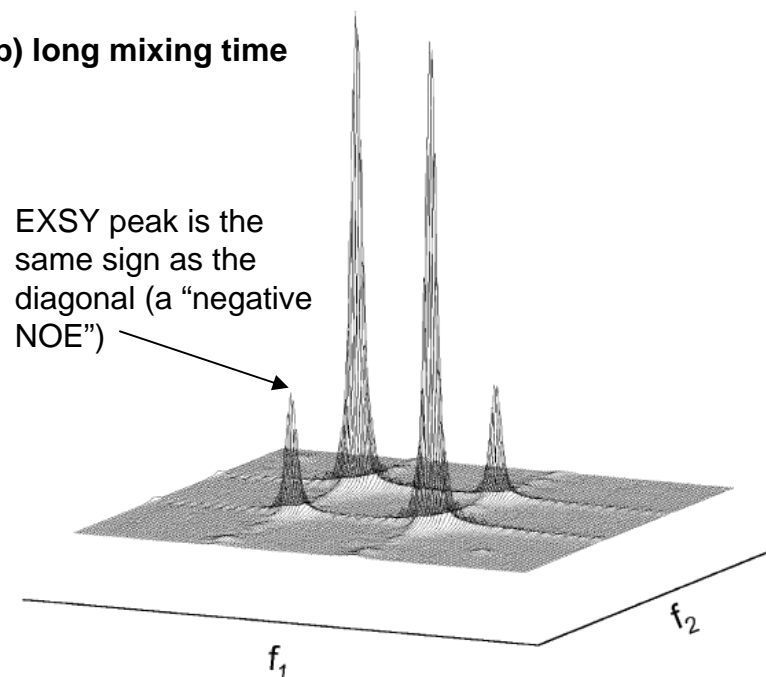
A ⟶ B ⟶ C
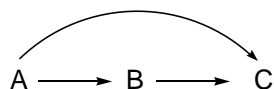
- Mixing times should be kept short to minimize confusion.

(a) short mixing time

f_1

f_2

(b) long mixing time

EXSY peak is the same sign as the diagonal (a "negative NOE")


f_1

f_2
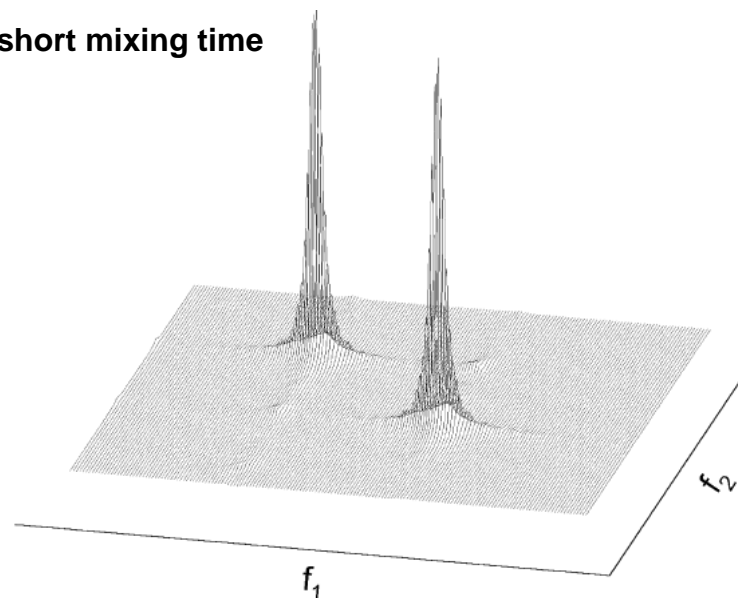
For two equally populated sites, the rate of exchange *k* is:

$$e^{-t_{mix}/2k} = \frac{1-r}{1+r}$$

where *r* is the ratio of the crosspeak volume to the diagonal peak volume. If one insists on performing fits of this nature, obtaining EXSY spectra for a series of mixing times and fitting the results is obligatory.

(2) Selective Inversion

What: This is very similar to the inversion-recovery experiment:

**select
one site**

180   90
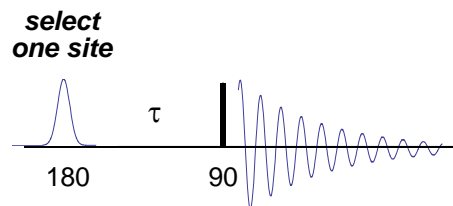
Purpose: Obtain quantitative data. This is more complicated to calibrate and set up than an EXSY, but produces much more reliable results.

To understand this, suppose we have a molecule with two sites, A and B. For the moment, let us assume that there is *no* chemical exchange. If A gets selectively inverted, then B will not be affected. A will merely return to equilibrium with time constant $T_{1,A}$:

magnetization of B
is unchanged

$+M_0$

z-magnetization   0

τ

A relaxes
$-M_0$ back to equilibrium
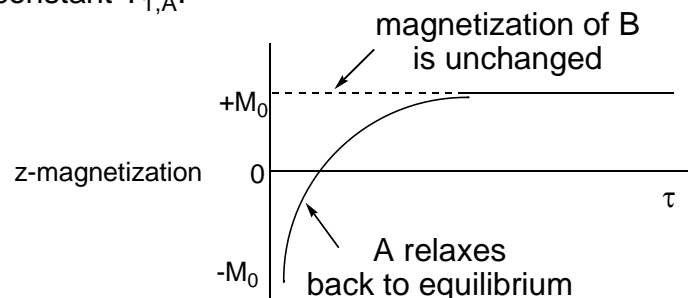
Of course, if I wait an infinite amount of time τ, then it is as if I never gave the first 180 pulse--everything will go back to eqm.

As a reminder, this is what happens to A from the vector perspective:
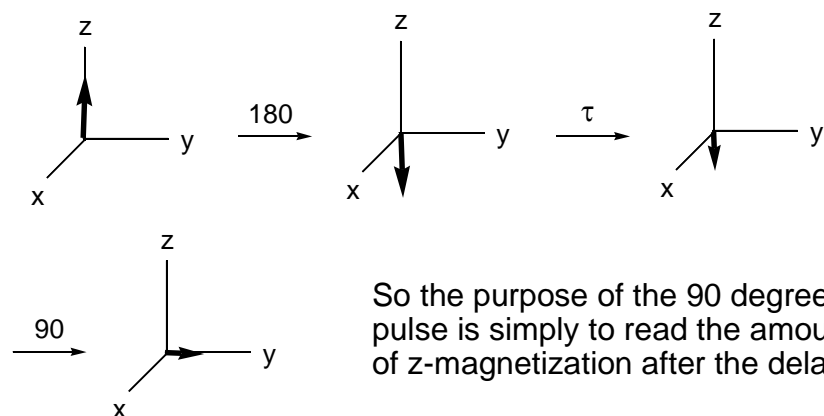

So the purpose of the 90 degree pulse is simply to read the amount of z-magnetization after the delay.

What if A and B *are* exchanging? The key idea is that a new way for A to relax appears. A can relax via the normal mechanisms inherent to its T_1, or an inverted nucleus of A can exchange over to site B. That means that site B will actually start getting inverted, even though it was never pulsed! At the same time, some relaxed site B nuclei will be converted to site A nuclei, so A will relax faster. The result of this is that A will recover faster than normal, while B will experience a transient dip. This process is called **saturation transfer**.

- The timescale of the experiment is ultimately limited by how fast A relaxes.

- Data can be fit quantiatively using Alex Bain's CIFIT program:
  http://www.chemistry.mcmaster.ca/bain/

- Temperatures should be carefully calibrated (ethylene glycol at higher temperatures, methanol at lower temperatures; these solvents have temperature-dependent hydrogen bonding.)

Here are selective inversion data showing the intensity as a function of delay time (between pulses, not between scans) for *N*,*N*-dimethylacetamide. The *N*-methyls are exchanging and perturbed, but the *C*-methyl is left alone:

transient dip

inverted peak
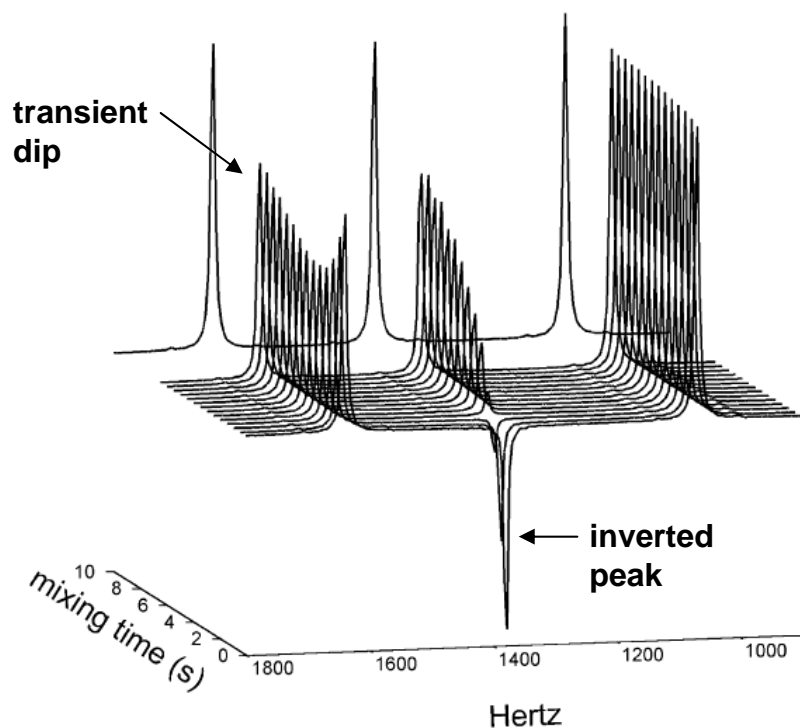
The data can be displayed in a more quantitative way as intensity vs. mixing time. Note that at different temperatures, the sites may change in frequency somewhat; this must be corrected for.

The selective inversion data are generally complemented with unselective inversion recovery data. One can think of the two experiments as operating under the same "rate laws" but different initial conditions. The unselective data preferentially probe the T_1 relaxation time; the selective data preferentially probe the rate of exchange. T

selective inversion

unselective inversion
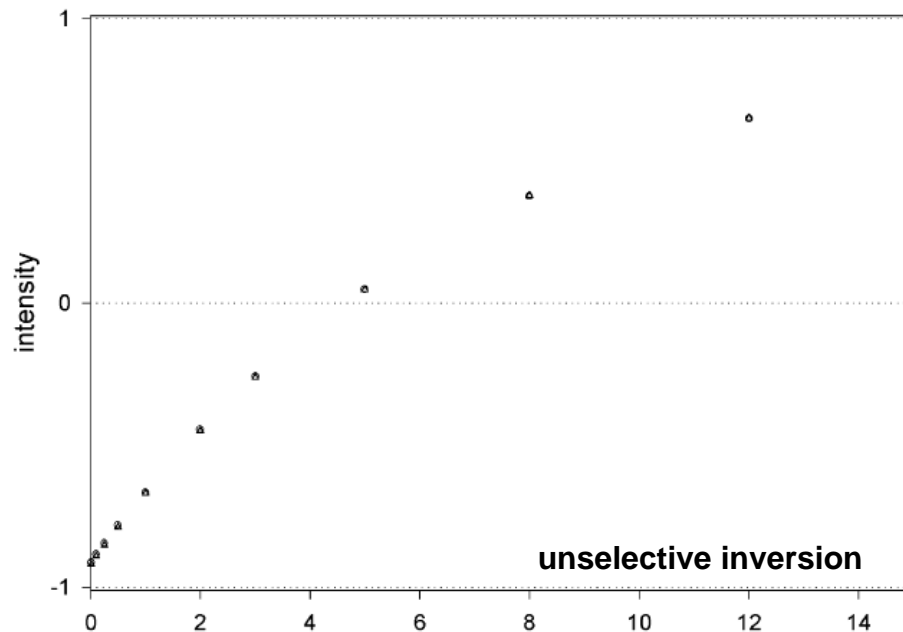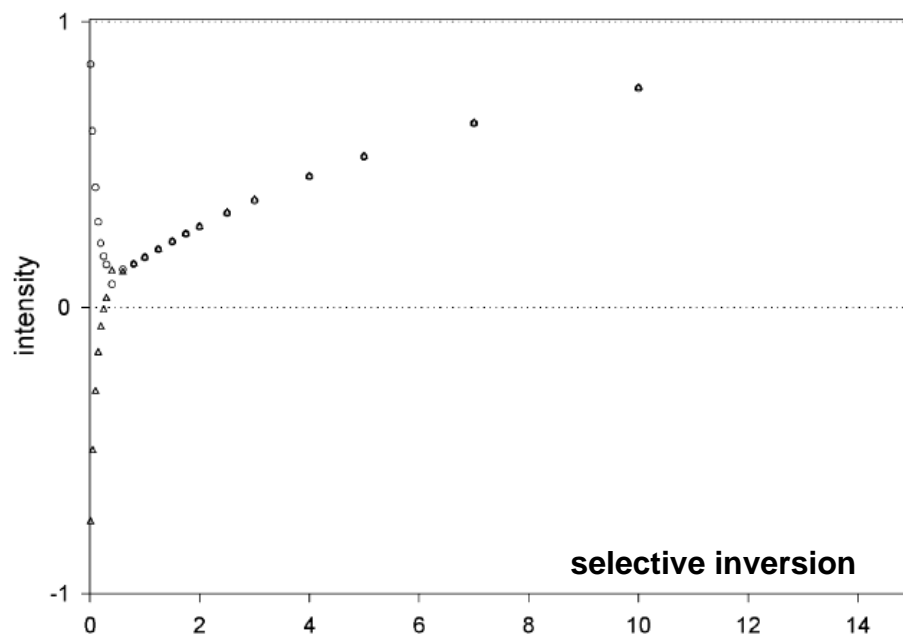
Intermediate Exchange

When the peaks are visibly coalescing, a **complete bandshape analysis** is called for. This means fitting the entire peak shape to a mathematical model of what it should look like, and then extracting rate parameters from the resulting coefficients. The treatment of arbitrary systems with coupling is complicated, but fortunately Alex Bain has devised the MEXICO program to do this in an automated way (*Mag. Reson. Chem.* **2001**, *39*, 122).

http://www.chemistry.mcmaster.ca/bain/exchange.html


data

fitted

residual

offset (Hz)
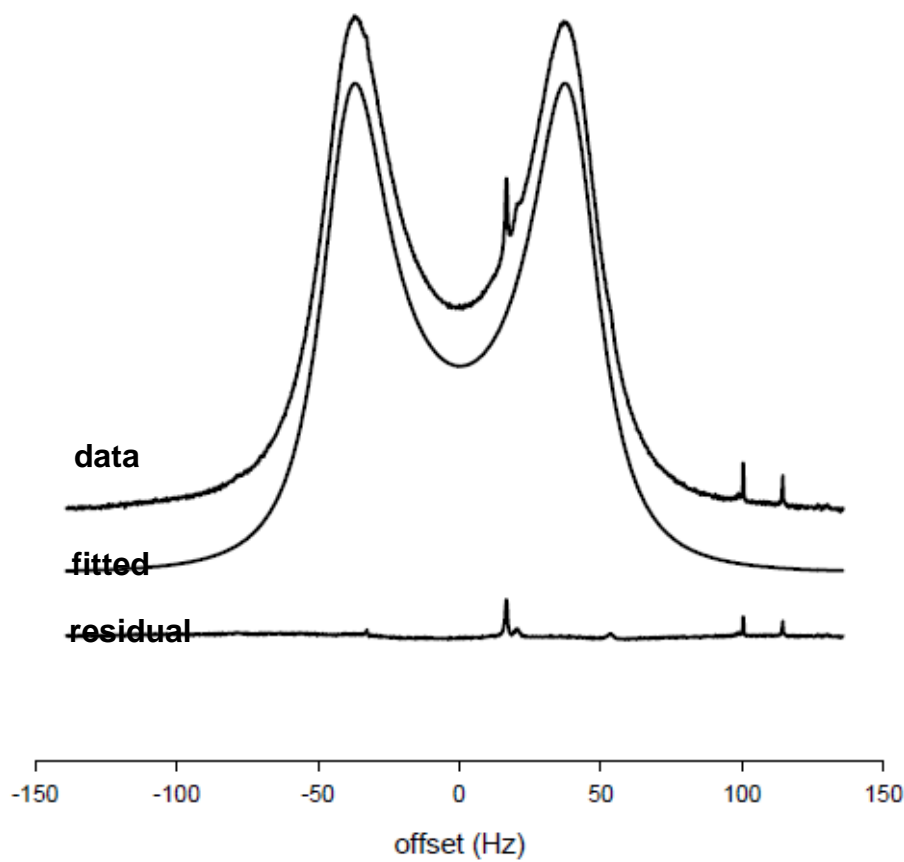
Fast Exchange

In fast exchange, the lines collapse to a single peak. What is odd is that the width of the line reflects the rate of exchange. As it turns out, exchange will broaden the peak, but by an amount that is comparable to the natural lindewidth. (In the extreme that exchange is infinitely fast, however, the exchange contribution will drop to zero.) Because of this, extracting the rate from the linewidth is not accurate. Practically, there are difficulties, since the shims tend to change significantly from temperature to temperature, which will affect the linewidth.

For a two equally populated sites with no *J*-coupling:

site A   site B
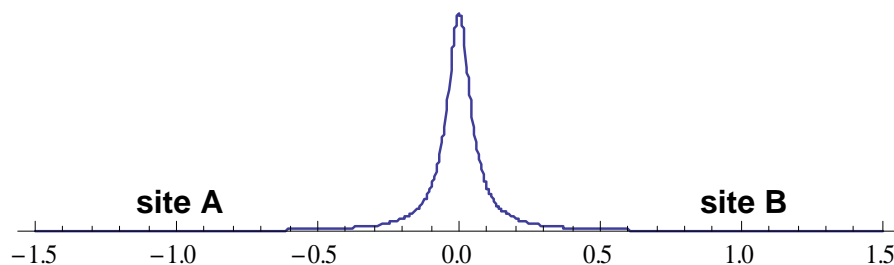
In this simulation, the sites are actually at +1 and -1 Hz, but average out to an offset of 0 Hz in the limit of fast exchange. (Note that exchange cannot affect the total *area* of the peaks, which is related to intrinsic population differences. However, exchangeable protons tend to under-integrate because their broadened signals disappear beneath the noise. This is also why very good shims are required for very good integrals.)

The linewidth in this case is given by:

$$\lambda = \frac{1}{T_2} + \frac{\delta^2}{2k}$$

where T_2 is the natural time constant, the two sites are at $+\delta$ and $-\delta$ Hz, and k is the rate of exchange.

Now exactly *why* the peaks are broader is a mysterious thing that I am ill equipped to explain. But overall, to measure the "extra" contribution to T_2, we need to remove the natural contribution from field inhomogeneity. But you already know how to do this--**CPMG** (Roberts, page 37):
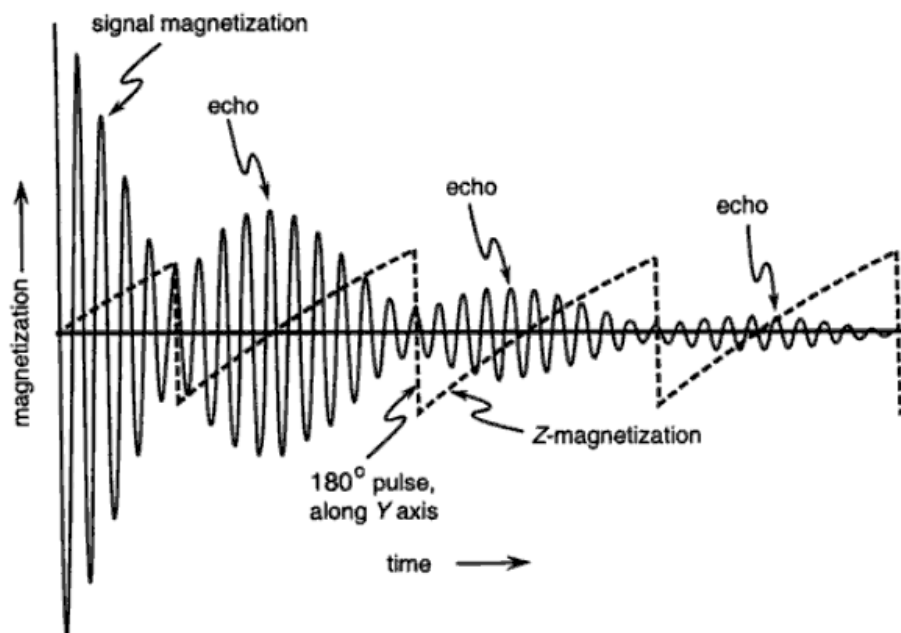
Fitting the envelope gives the intrinsic T_2 that will include a contribution from exchange; the rapid internal oscillations are due to T_2*. Now, in the experiment above, a fixed inter-echo delay was used. If the delay between echoes goes to zero, then what you have is a "spin-lock." If you use a spin-lock to measure exchange, you are performing a $T_{1\rho}$ experiment.

Alternatively, one can apply variable pulse spacings in CPMG. With slow pulsing, the timescale of the experiment is longer and exchange can be seen. If the pulsing is fast, then the timescale of the experiment is fast and exchange cannot be seen (ref 2):
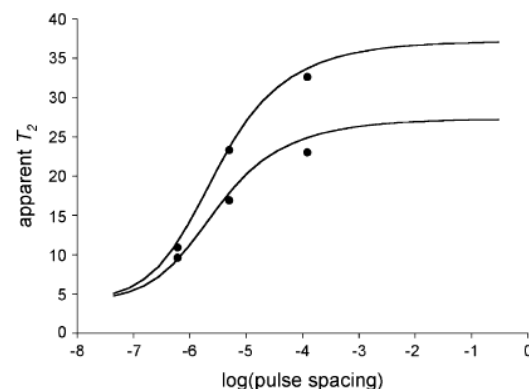
For the two equally populated sites case, we have:

$$\frac{1}{T_2} = \frac{1}{T_2{}^0} + k + \frac{1}{t_{CPMG}} \sinh^{-1} F$$

$$F = \frac{k}{\sqrt{k^2 - \delta^2}} \sinh\left(t_{CPMG} \frac{\sqrt{k^2 - \delta^2}}{2} \right)$$

The upper limit is instrumental in nature--if you try to go faster than about 1000 s^{-1}, you will simply fry the probe.

Applications

There are myraid uses that fill entire books like ref 4. Some examples:

- rotational barriers in biaryls
- ring flipping barriers
- nitrogen inversion
- ligand binding
- degenerate ligand exchange (e.g. Piers *JACS* **2007** *129* 1698; this looks at exchange in the metallocyclobutanes formed during metathesis reactions)

I now turn to a more rigorous treatment of intermediate exchange using the Bloch equations.

The Bloch Equations

The treatment I use here is adapted from Roberts, but will arrive at a slightly different result, since I have chosen to maintain the convention of CCW rotations in the course. In general, one has two choice for understanding NMR behavior:

(1) classical, macroscopic equations -- the Bloch equations
(2) quantum, miscroscopic equations -- the density matrix

The Bloch equations will not describe any scenarios with *J*-coupling, but will be sufficient for our purposes. Before I derive anything, it is useful to consider the difference between **continuous wave** and **Fourier transform** NMR.

In **CW NMR**, you send in one input frequency, and watch the sample absorb energy at resonance. The input frequency is always on, and the output signal is in the *frequency domain*. In **FT-NMR**, you send in every frequency at once by sending in a very short pulse, and then turn it off. Then you watch the *time domain* signal that comes out. Both produce equivalent results, but FT is much more practical. However, the classical derivation of the Bloch equations is for CW NMR, so I will stick to that here.
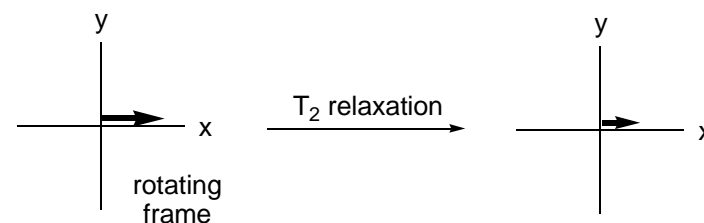
Recall the equations for relaxation:

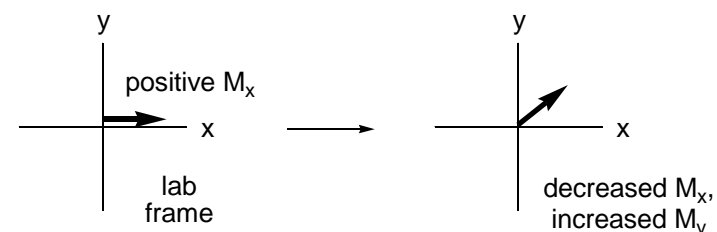$$\frac{dM_z}{dt} = \frac{M_{z,0} - M_z}{T_1} = \frac{M_0 - M_z}{T_1}$$

$$\frac{dM_{xy}}{dt} = \frac{-M_{xy}}{T_2}$$

Q: How do M_x and M_y change with time?

One way is T_2 relaxation:

rotating frame — T_2 relaxation

It can also change because of precession. M_x and M_y will simply "trade places":

positive M_x

lab frame
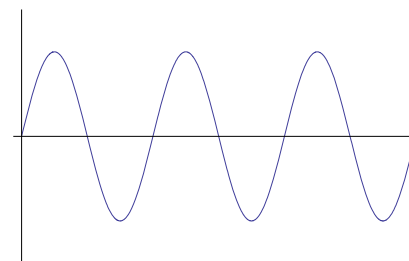
decreased M_x, increased M_y

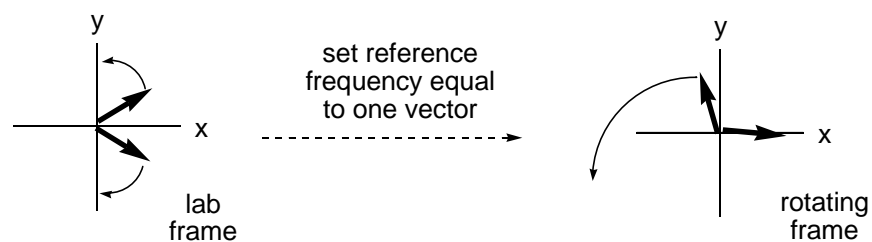The rate of precession depends on γB_0, the Larmor frequency:

$$\frac{dM_x}{dt} = \frac{-M_x}{T_2} - M_y \gamma B_0 \qquad \text{the faster precession is, the fast } M_x \text{ decreases}$$

$$\frac{dM_y}{dt} = \frac{-M_y}{T_2} + M_y \gamma B_0 \qquad \text{overall magnetization is conserved}$$

In CW NMR, there is an input RF field B_1:

This oscillating field can be considered the sum of two counterrotating vectors in the lab frame:
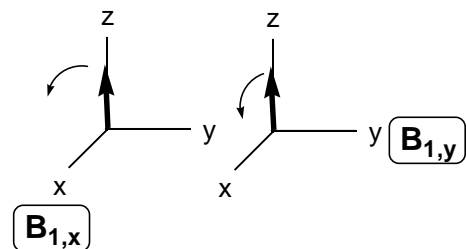
We can ignore one of the counterrotating vectors since it's far from resonance. We have:
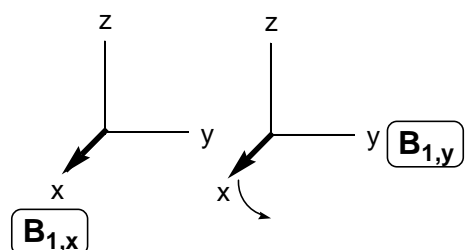
$$B_{1,x} = B_1 \cos(\omega t)$$

$$B_{1,y} = B_1 \sin(\omega t)$$

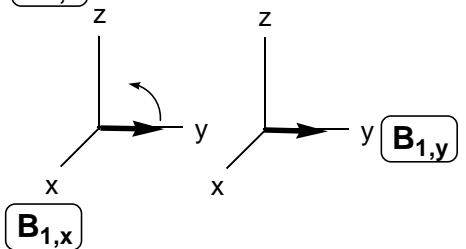What effect does B_1 have on M_x, M_y, and M_z? Assuming that pulses have a CCW effect:

$B_{1,x}$ will turn $+M_z$ into $-M_y$.

$B_{1,y}$ will turn $+M_z$ into $+M_x$.

$B_{1,x}$ will have no effect on $+M_x$.

$B_{1,y}$ will turn $+M_x$ into $-M_z$.

$B_{1,x}$ will turn $+M_y$ into $+M_z$.
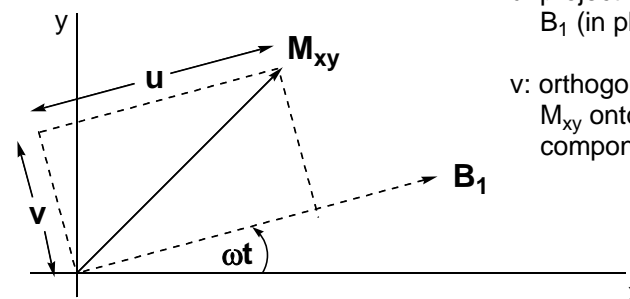
$B_{1,y}$ will have no effect on $+M_y$.

We can now update our equations (new terms underlined):

$$\frac{dM_z}{dt} = \frac{M_0 - M_z}{T_1} \underline{- M_y \gamma B_{1,x} + M_x \gamma B_{1,y}}$$

$$\frac{dM_x}{dt} = \frac{-M_x}{T_2} - M_y \gamma B_0 \underline{- M_z \gamma B_{1,y}}$$

$$\frac{dM_y}{dt} = \frac{-M_y}{T_2} + M_x \gamma B_0 \underline{+ M_z \gamma B_{1,x}}$$

All this is cast in the lab frame, but it is more convenient to be in the rotating frame, since the signals are usually detected in quadrature. Setting the reference frequency to the transmitter frequency:

u: projection of M_{xy} onto B_1 (in phase component)

v: orthogonal projection of M_{xy} onto B_1 (out of phase compononet)

Treating B_1 as a unit vector, we have:

$$M_{xy} = (M_x, M_y)$$

$$B_1 = (\cos \omega t, \sin \omega t)$$

For the projection *u*, recall the dot product:
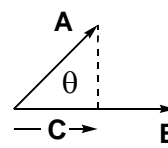
$$A \cdot B = |A||B|\cos\theta \qquad \text{definition of dot product}$$

$$|C| = |A|\cos\theta \qquad \text{definition of cosine}$$

$$|C| = \frac{|A||B|\cos\theta}{|B|} = \frac{A \cdot B}{|B|} \qquad \text{length of projection}$$

Therefore,

$$u = \left(M_x, M_y\right) \cdot \left(\cos \omega t, \sin \omega t\right)$$

$$u = M_x \cos \omega t + M_y \sin \omega t$$

To obtain the orthogonal projection, note that a vector orthogonal to (cos ωt, sin ωt) is (cos (ω+π/2)t, sin (ω+π/2)t) = (-sin ωt, cos ωt). Therefore,

$$u = M_x \cos \omega t + M_y \sin \omega t$$

$$v = -M_x \sin \omega t + M_y \cos \omega t$$

Apply this coordinate transformation:

$$u = M_x \cos \omega t + M_y \sin \omega t$$

$$\frac{du}{dt} = \frac{dM_x}{dt} \cos \omega t + M_x \omega \left(-\sin \omega t\right)$$

$$+ \frac{dM_y}{dt} \sin \omega t + M_y \omega \left(\cos \omega t\right)$$

$$\frac{du}{dt} = \left[\frac{-M_x}{T_2} - M_y \gamma B_0 - \cancel{M_z \gamma B_{1,y}}\right] \cos \omega t + \boxed{M_x \omega \left(-\sin \omega t\right)}$$

$$+ \left[\frac{-M_y}{T_2} + M_x \gamma B_0 + \cancel{M_z \gamma B_{1,x}}\right] \sin \omega t + \boxed{M_y \omega \left(\cos \omega t\right)}$$

ωv

Note that $B_{1,x} = B_1 \cos \omega t$ and $B_{1,y} = B_1 \sin \omega t$. This leads to cancellation. This simplifies to:

$$\frac{du}{dt} = \omega v + \left[-M_y \gamma B_0 \cos \omega t + M_x \gamma B_0 \sin \omega t\right]$$

$$- \frac{1}{T_2}\left[-M_x \cos \omega t - M_y \sin \omega t\right]$$

$$\frac{du}{dt} = \omega v + B_0 \gamma \left(-v\right) + \frac{u}{T_2}$$

$$\frac{du}{dt} = \left(\omega - \omega_0\right) v + \frac{u}{T_2}$$

(where $B_0\gamma = \omega_0$.) Similarly, one finds that:

$$\frac{dv}{dt} = \left(\omega - \omega_0\right) u + \frac{v}{T_2} + M_z \gamma B_1$$

$$\frac{dM_z}{dt} = \frac{M_0 - M_z}{T_1} - v \gamma B_1$$

These are the **Bloch equations**. Under **slow passage** conditions (i.e., very low power B_1),

$$\frac{du}{dt} = \frac{dv}{dt} = \frac{dM_z}{dt} = 0$$

We have:

$$\frac{du}{dt} = 0 = \left(\omega - \omega_0\right) v + \frac{u}{T_2}$$

$$u = \left(\omega_0 - \omega\right) v T_2$$

And:

$$\frac{dv}{dt} = 0 = \left(\omega - \omega_0\right) u + \frac{v}{T_2} + M_z \gamma B_1$$

$$v = T_2 \left[\left(\omega_0 - \omega\right) u - M_z \gamma B_1\right]$$

And:

$$M_z = M_0 - T_1 v \gamma B_1$$

One finds that:

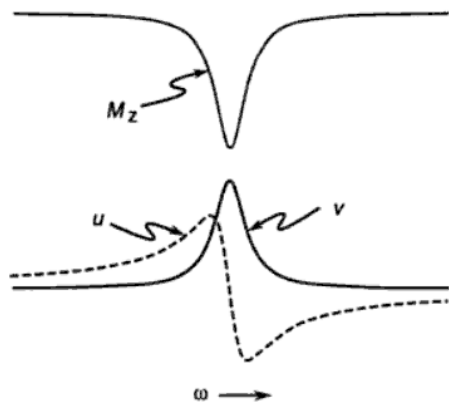$$M_z = \frac{M_0[1+(\omega_0-\omega)^2 T_2^2]}{1+(\omega_0-\omega)^2 T_2^2 + \gamma^2 B_1^2 T_1 T_2}$$

$$u = \frac{\gamma B_1 M_0 T_2}{1+(\omega_0-\omega)^2 T_2^2 + \gamma^2 B_1^2 T_1 T_2} \quad \textbf{dispersion Lorentzian}$$

$$v = \frac{\gamma B_1 (\omega_0-\omega) T_2^2 M_0}{1+(\omega_0-\omega)^2 T_2^2 + \gamma^2 B_1^2 T_1 T_2} \quad \textbf{absorption Lorentzian}$$

These are also the lineshapes that are observed in FT-NMR:

By convention, the time domain signal is formed as complex-valued combination of the real and imaginary channels:

$$M \equiv u + iv$$

$$\frac{dM}{dt} = \frac{du}{dt} + i\frac{dv}{dt}$$

$$\frac{dM}{dt} = (\omega-\omega_0)v + \frac{u}{T_2} + i\left[(\omega-\omega_0)u + \frac{v}{T_2} + M_z \gamma B_1\right]$$

$$\frac{dM}{dt} = -(\omega_0-\omega)v + \frac{1}{T_2}(u+iv) + iu(\omega_0-\omega) + iM_z\gamma B_1$$

$$\frac{dM}{dt} + (\omega_0-\omega)v - \frac{M}{T_2} - iu(\omega_0-\omega) = iM_z\gamma B_1$$

$$\frac{dM}{dt} + (\omega_0-\omega)(v-iu) - \frac{M}{T_2} = iM_z\gamma B_1$$

$$\boxed{\frac{dM}{dt} + i(\omega_0-\omega)M - \frac{M}{T_2} = iM_z\gamma B_1}$$

For two equally populated sites, an additional mechanism for magnetization transfer now exists, such that the Bloch equations become coupled:

$$\frac{dM_A}{dt} + i(\delta-\omega)M_A - \frac{M_A}{T_2} - kM_B + kM_A = iM_{z,A}\gamma B_1$$

$$\frac{dM_B}{dt} + i(-\delta-\omega)M_A - \frac{M_A}{T_2} - kM_A + kM_B = iM_{z,B}\gamma B_1$$

exchange terms

The solution of these with regular techniques is messy, so I will simply quote the result for two sites at $+\delta$ and $-\delta$ Hz. At steady state, and neglecting T_2 from inhomogeneity and other non-exchange sources, one finds that:

$$\boxed{v = \gamma B_1 M_z \frac{k(2\delta)^2}{(\delta-\omega)^2(\delta+\omega)^2 + 4k^2\omega^2}} \quad \textbf{exchange for two equally populated sites}$$

Unequal populations can also be handled, but it is messier. Note that *J*-coupling <u>cannot</u> be handled this way; you need the magic of the density matrix.