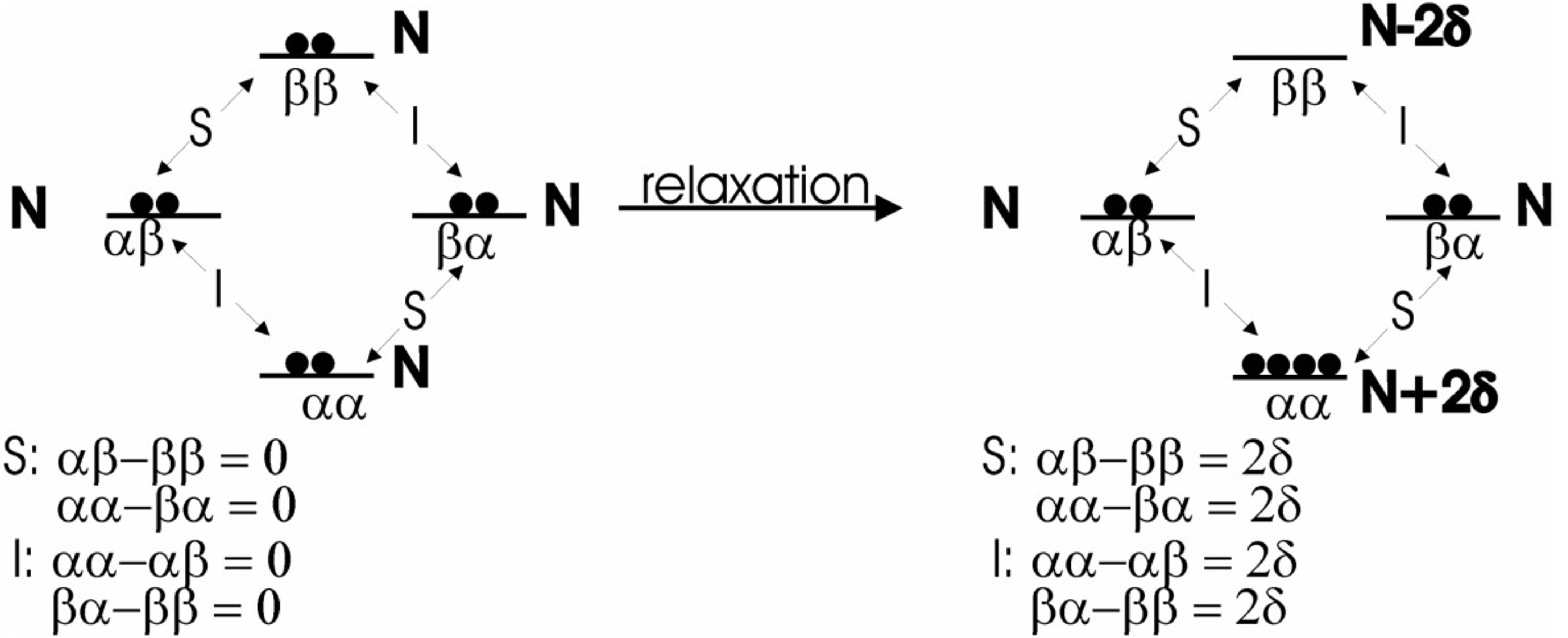
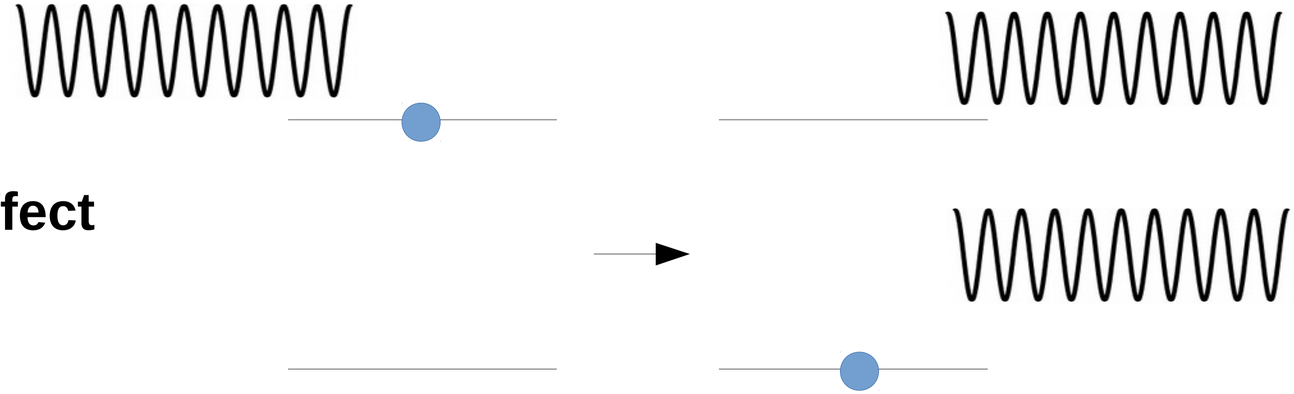


Just placed sample in magnetic field (“infinite“ spin temperature)

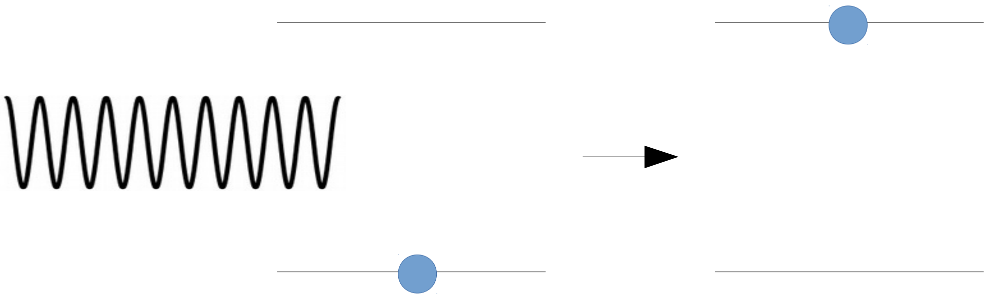
Sample at thermal equilibrium in magnetic field (relaxed)

Stimulated emission

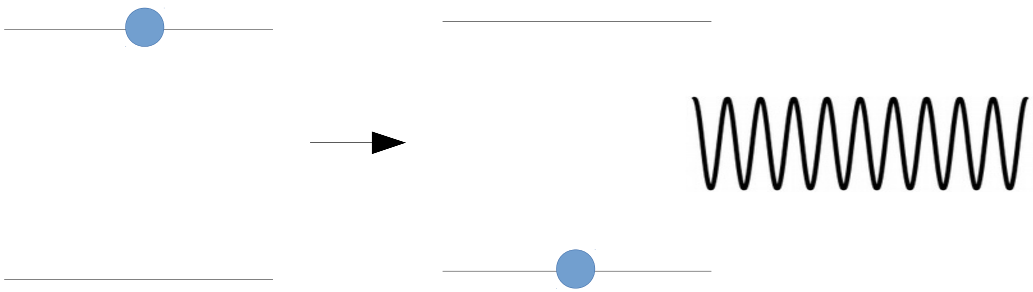


Photoelectric effect

Absorption



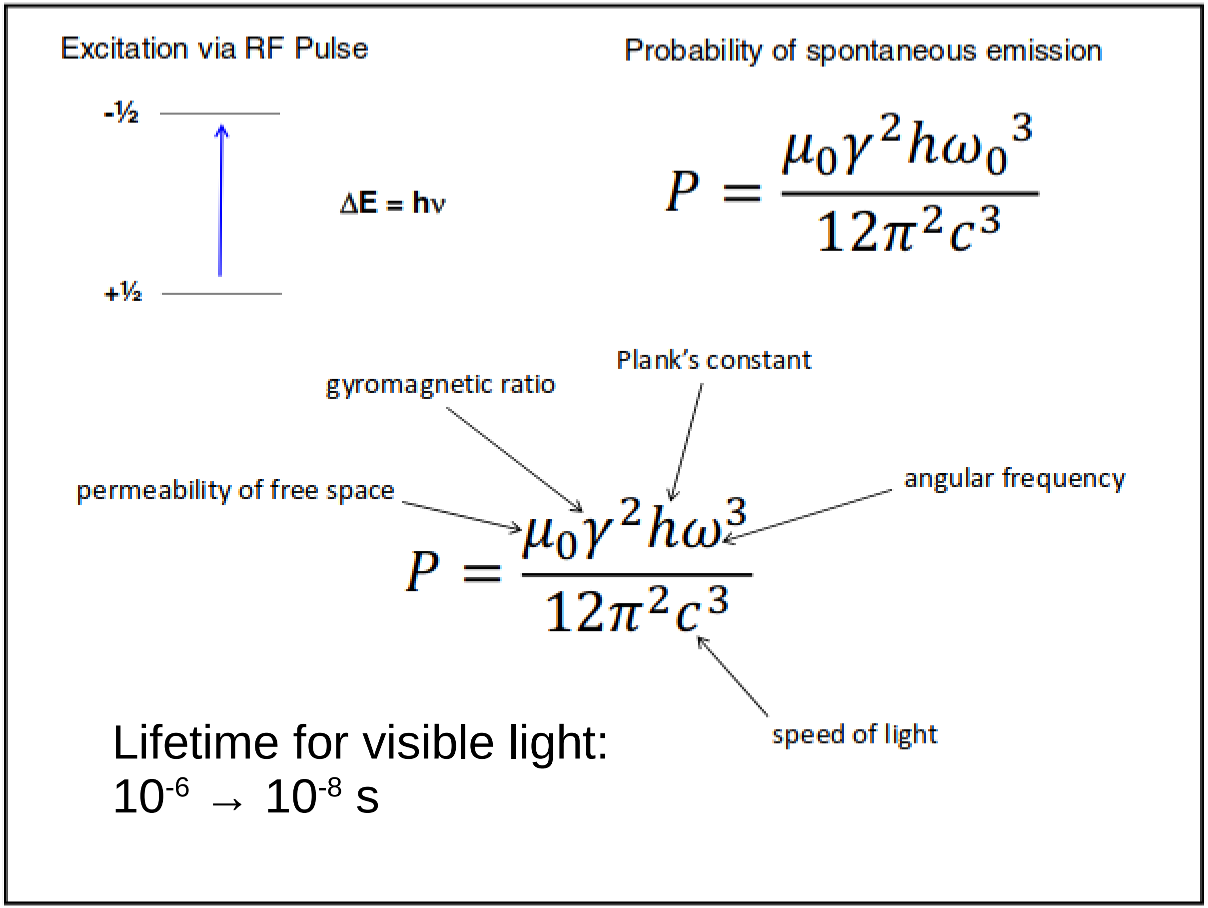
Spontaneous emission



Einstein, A. (1916). "Zur Quantentheorie der Strahlung". Mitteilungen der Physikalischen Gessellschaft Zürich. 18: 47–62.

“quantum theory of radiation”

Einstein coefficients: **spontaneous emission**



Excitation via RF Pulse

Probability of spontaneous emission

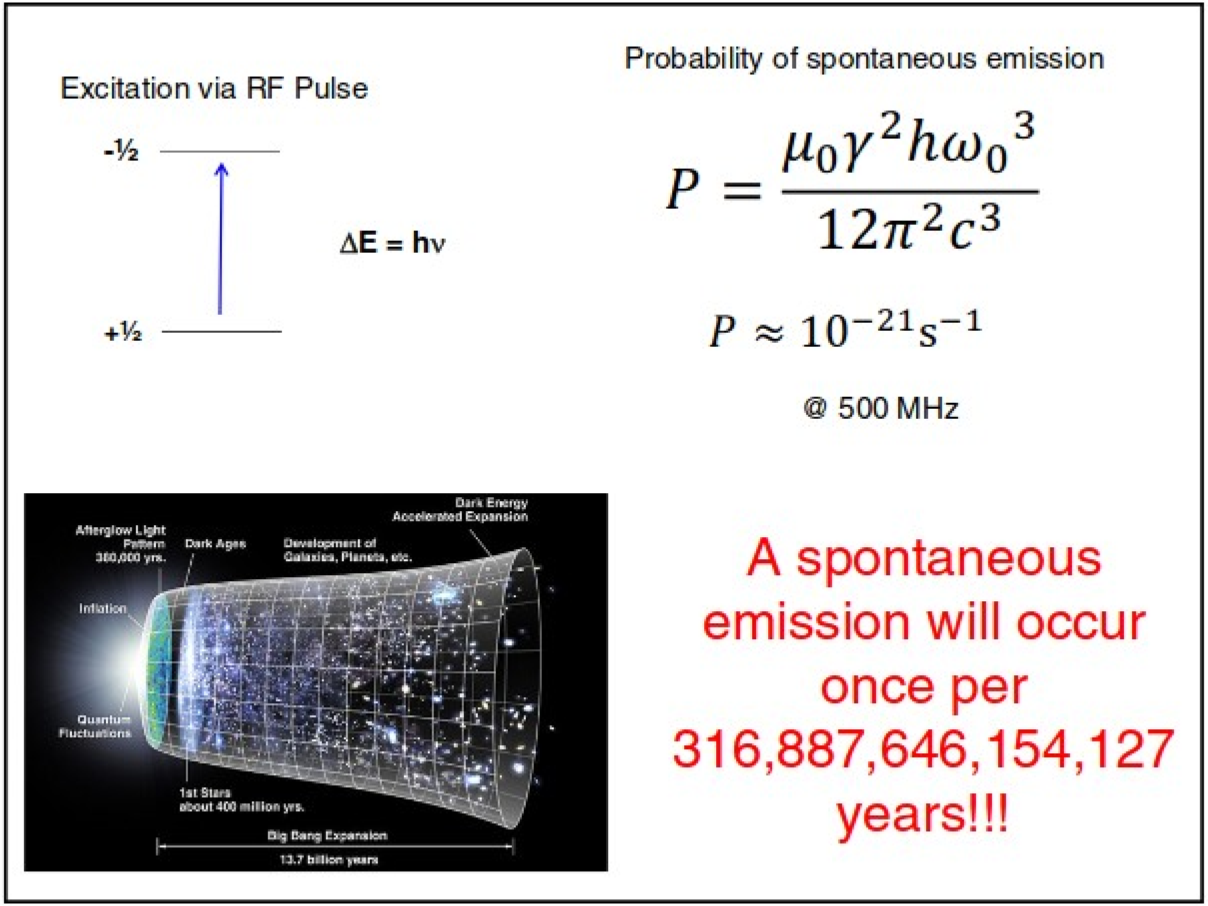
$$P = \frac{\mu_0 \gamma^2 h {\omega_0}^3}{12\pi^2 c^3}$$

$$P = \frac{\mu_0 \gamma^2 h \omega^3}{12\pi^2 c^3}$$

Lifetime for visible light:
$10^{-6} \rightarrow 10^{-8}$ s

Spontaneous emission does not occur in NMR. Only stimulated emission and absorption

600Mhz 6x10^-6 Kcal/mol
500 Thz (green light) ~53 kcal/mol



Excitation via RF Pulse

$\Delta E = h\nu$

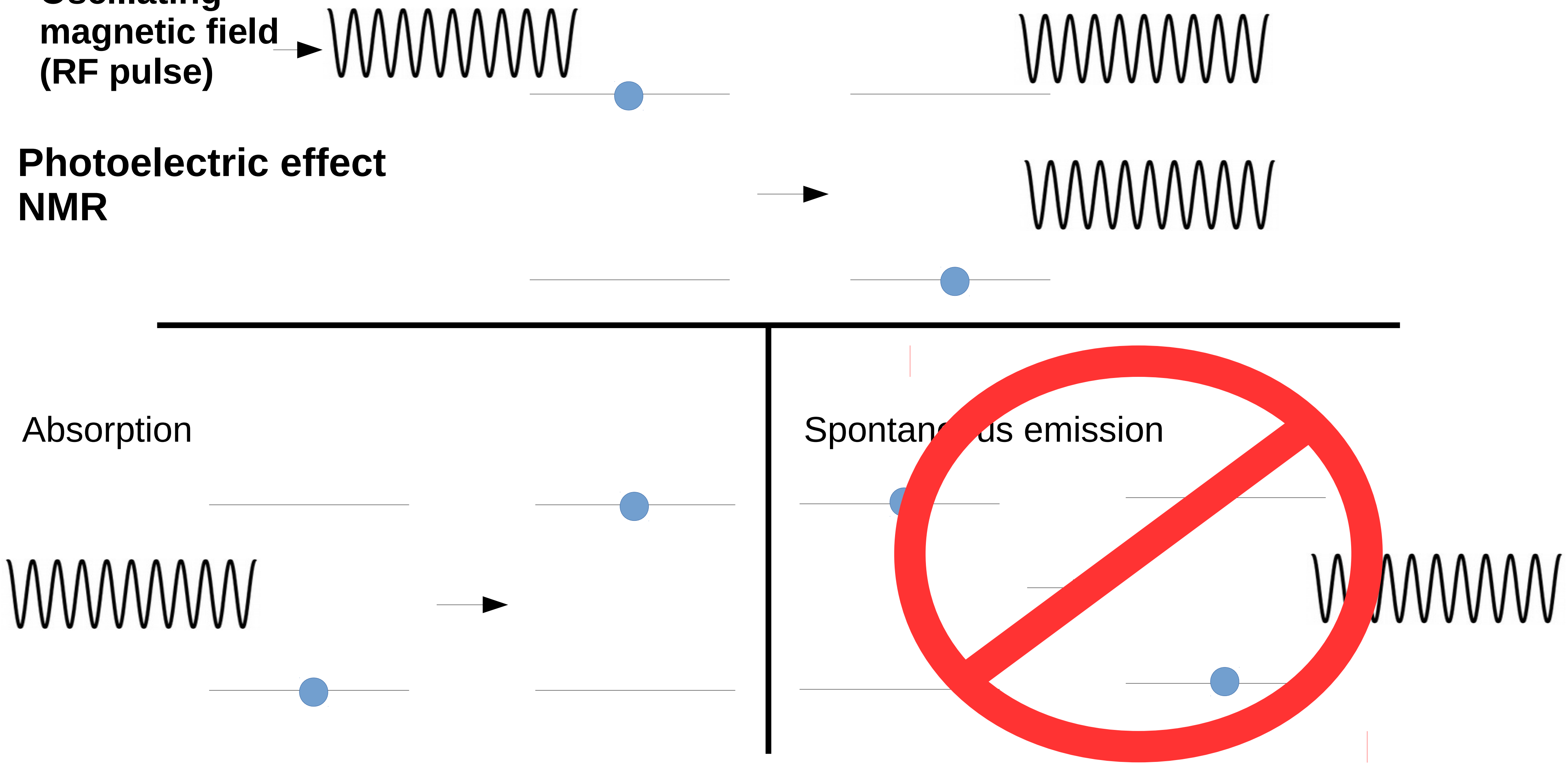
Probability of spontaneous emission

$$P = \frac{\mu_0 \gamma^2 h {\omega_0}^3}{12\pi^2 c^3}$$

$$P \approx 10^{-21} s^{-1}$$

@ 500 MHz

A spontaneous emission will occur once per 316,887,646,154,127 years!!!



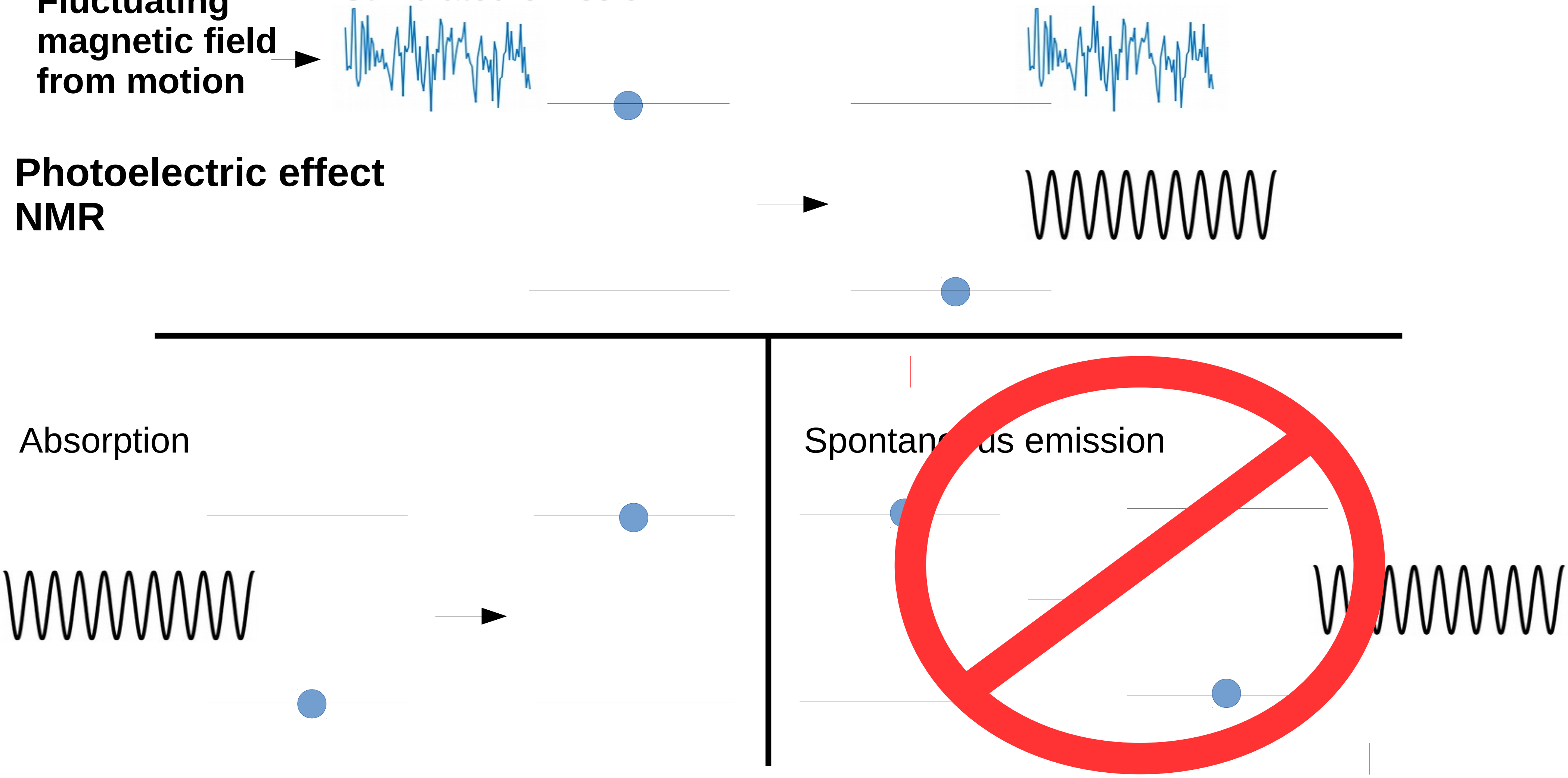
Stimulated emission

Oscillating magnetic field (RF pulse)

Photoelectric effect
NMR

Absorption

Spontaneous emission



Fluctuating magnetic field from motion

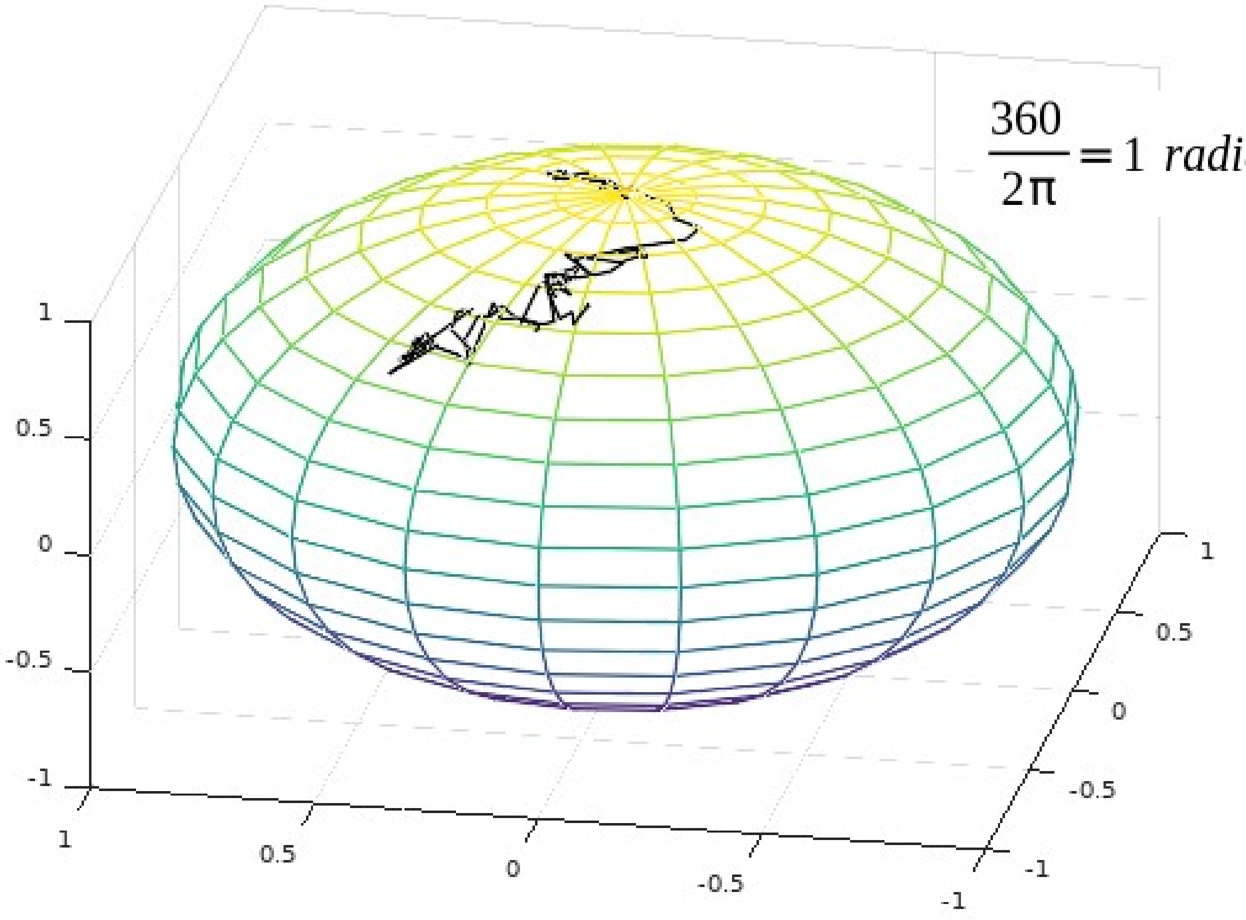
Stimulated emission

Photoelectric effect
NMR

Absorption

Spontan us emission

Rotational correlation time (τ_c) is the average time it takes for a molecule to rotate one radian.

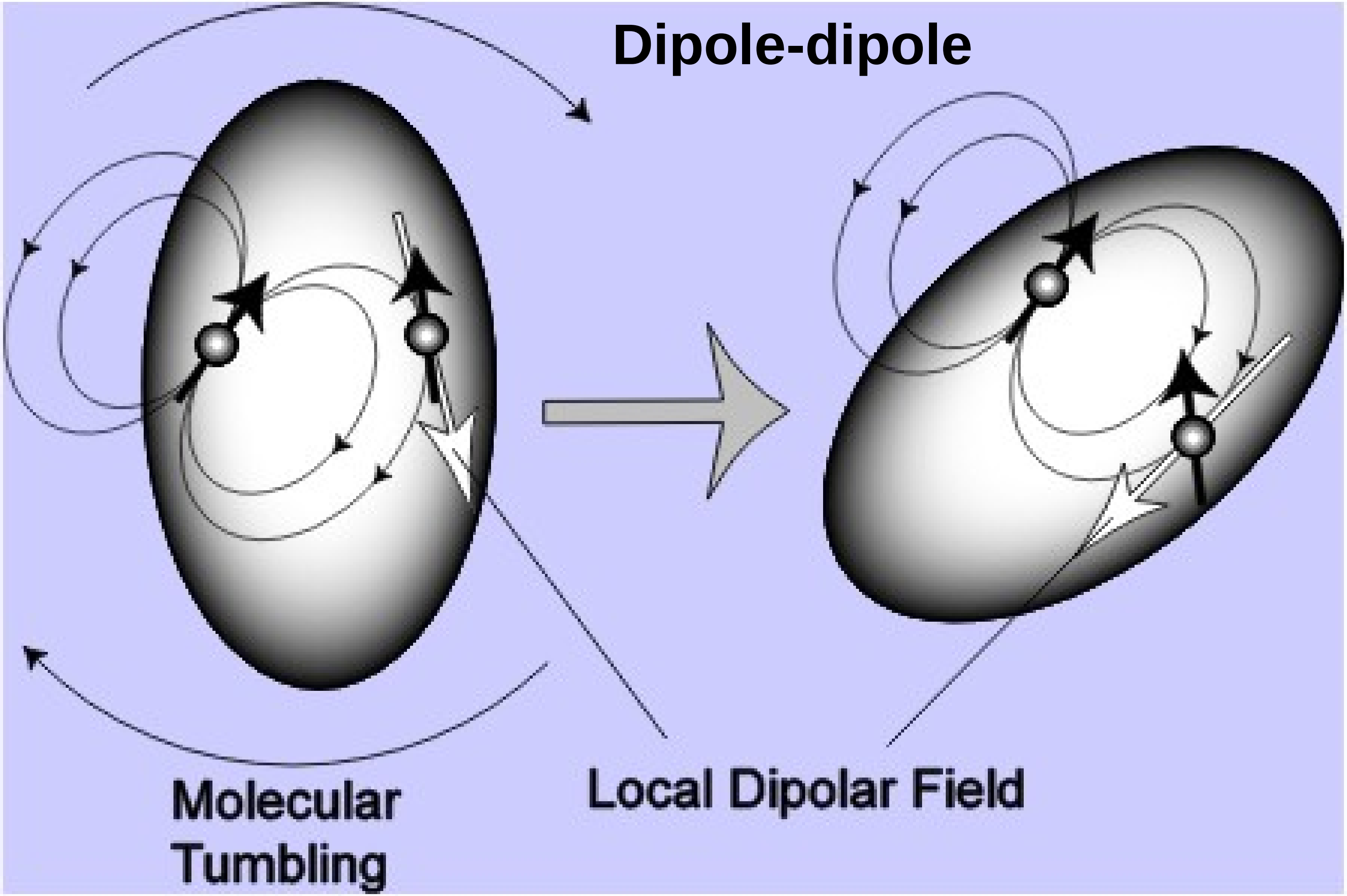


$$\frac{360}{2\pi} = 1 \ radian \simeq 57.3\,°$$

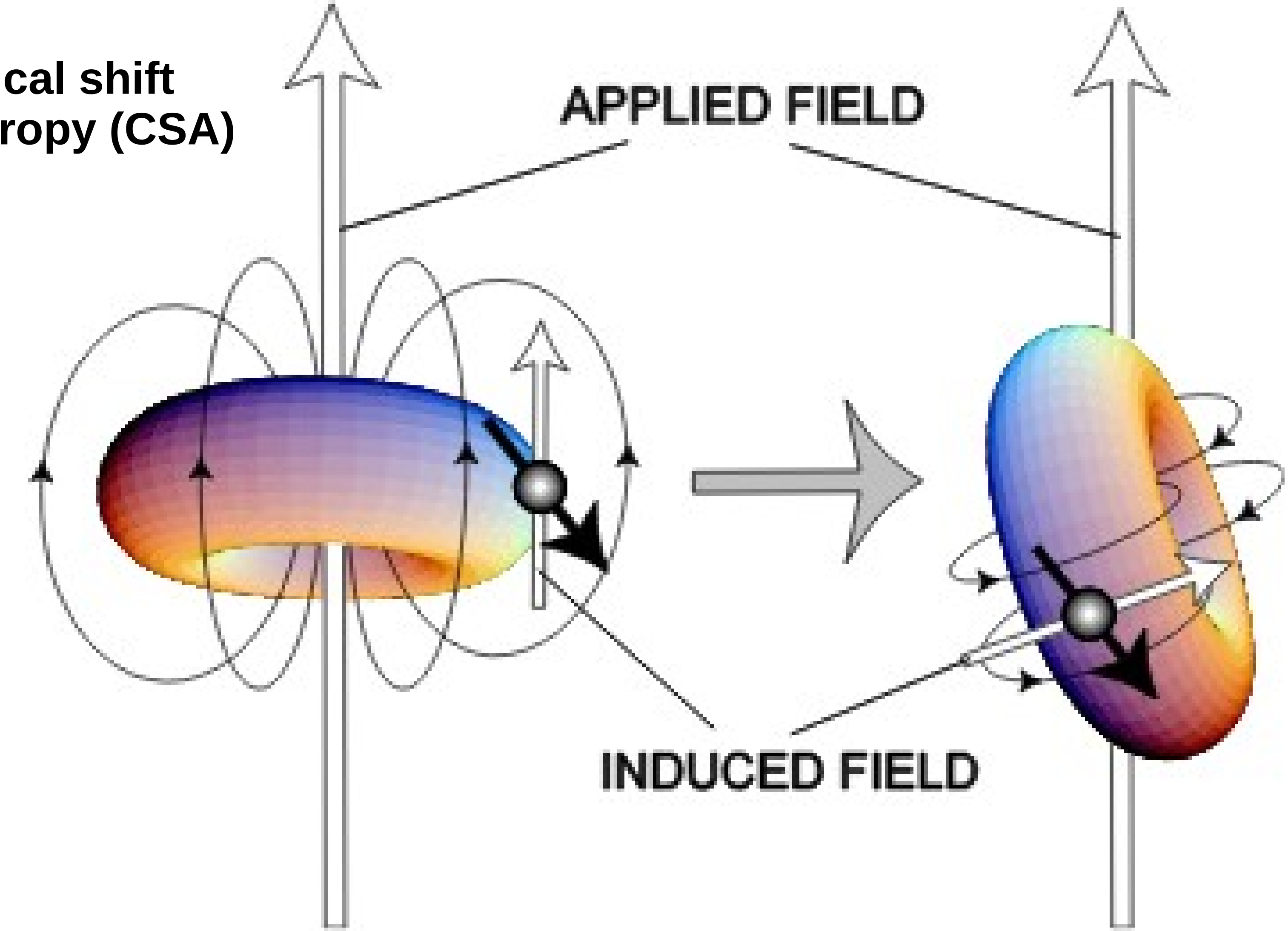
Relaxation mechanisms

- Dipole-dipole
  - interaction between magnetic dipoles
- Chemical shift anisotropy
  - non-spherical electron environment
- Quadrupolar
  - nuclei with spins > ½, oblong shape nucleus
- Scalar relaxation of the 1st kind
  - Chemical exchange
- Scalar relaxation of the 2nd kind
  - scalar coupling to quadrupolar nucleus
- Spin-rotation
  - changes in rotational angular momentum
  - usually only in small molecules in gas phase

Dipole-dipole

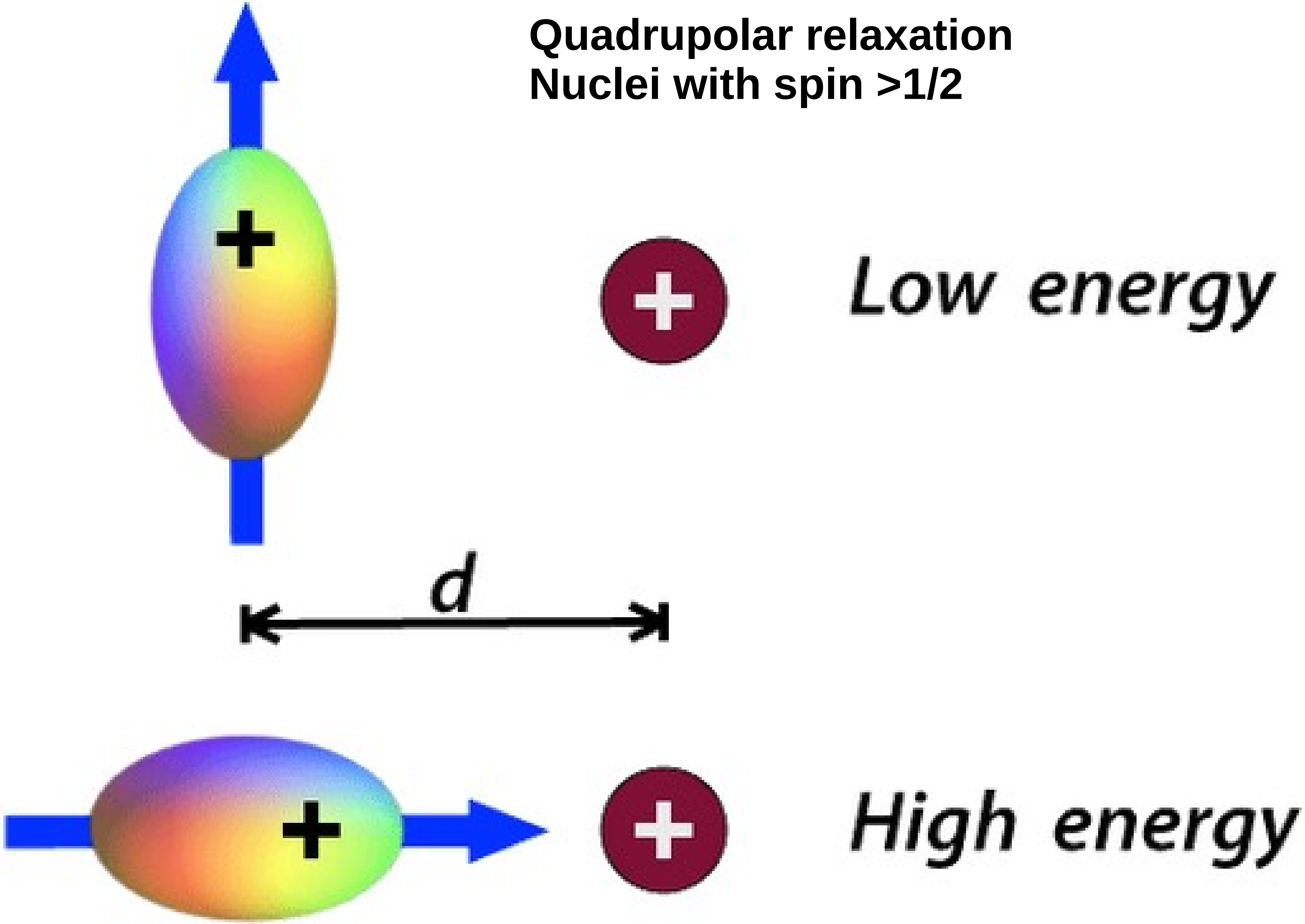


Chemical shift anisotropy (CSA)

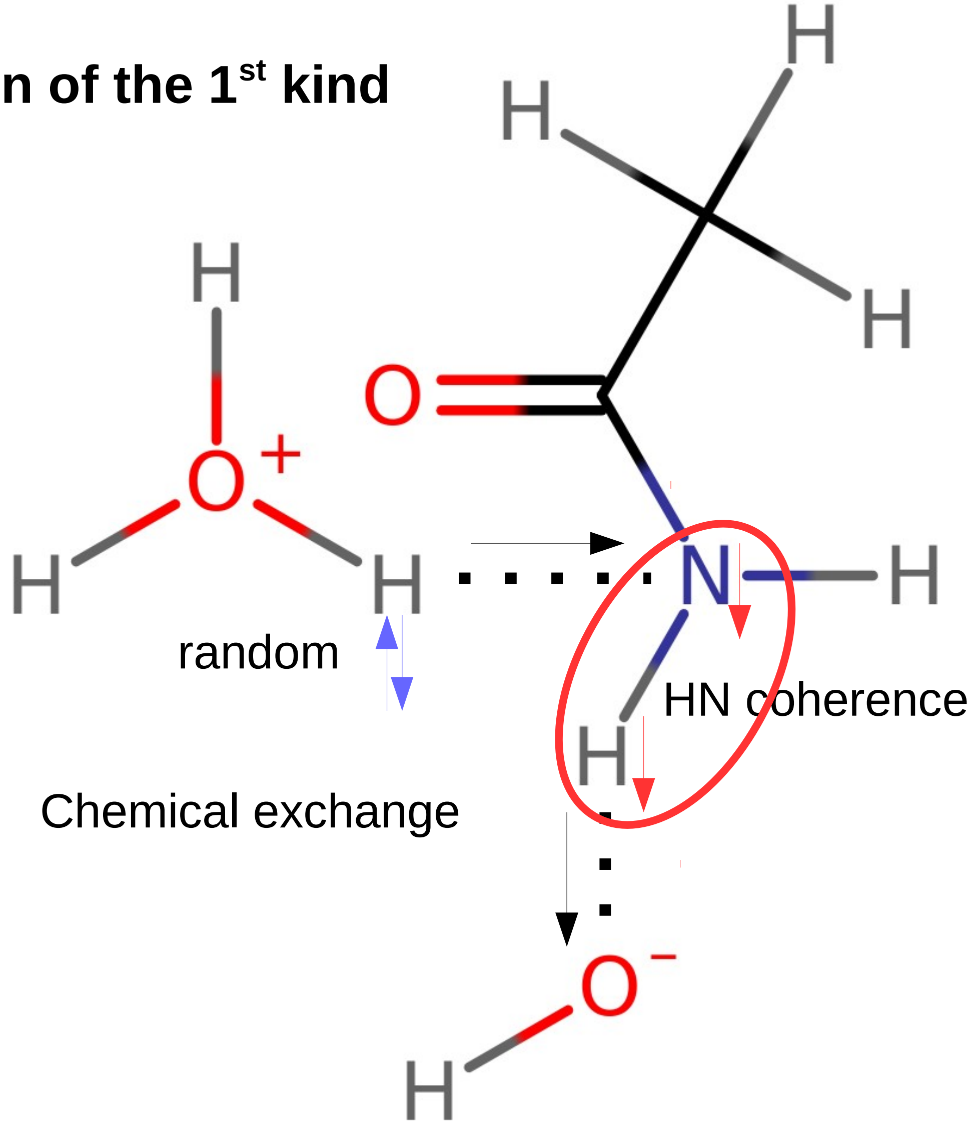


Quadrupolar relaxation

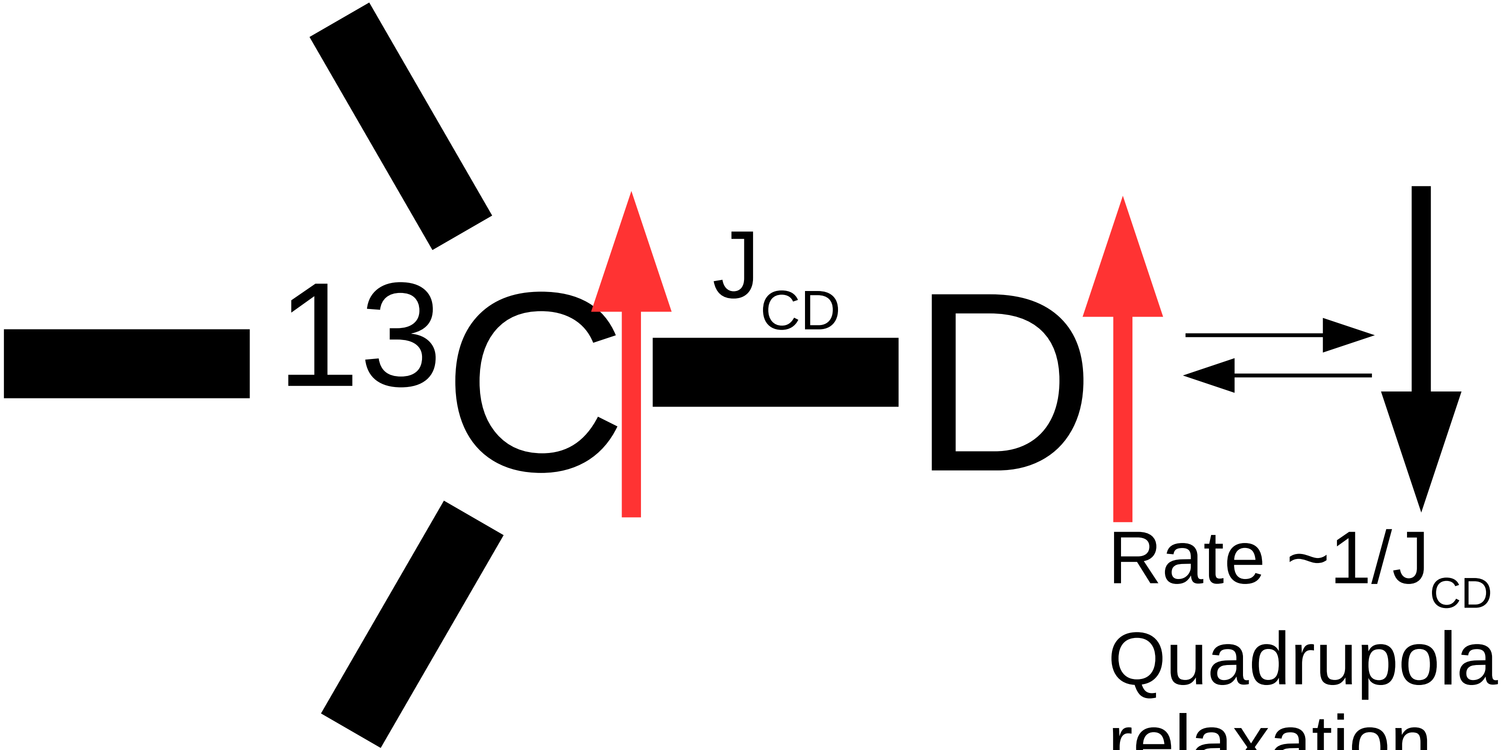
Nuclei with spin >1/2



Scalar relaxation of the 1st kind



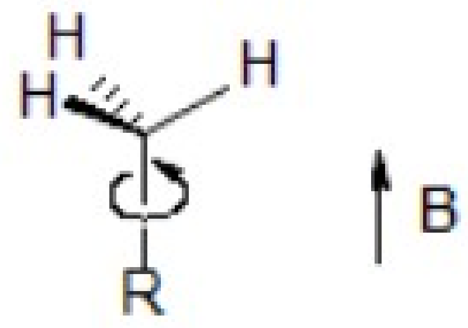
Scalar relaxation of the 2nd kind



Rate ~1/J_{CD}

Quadrupolar relaxation

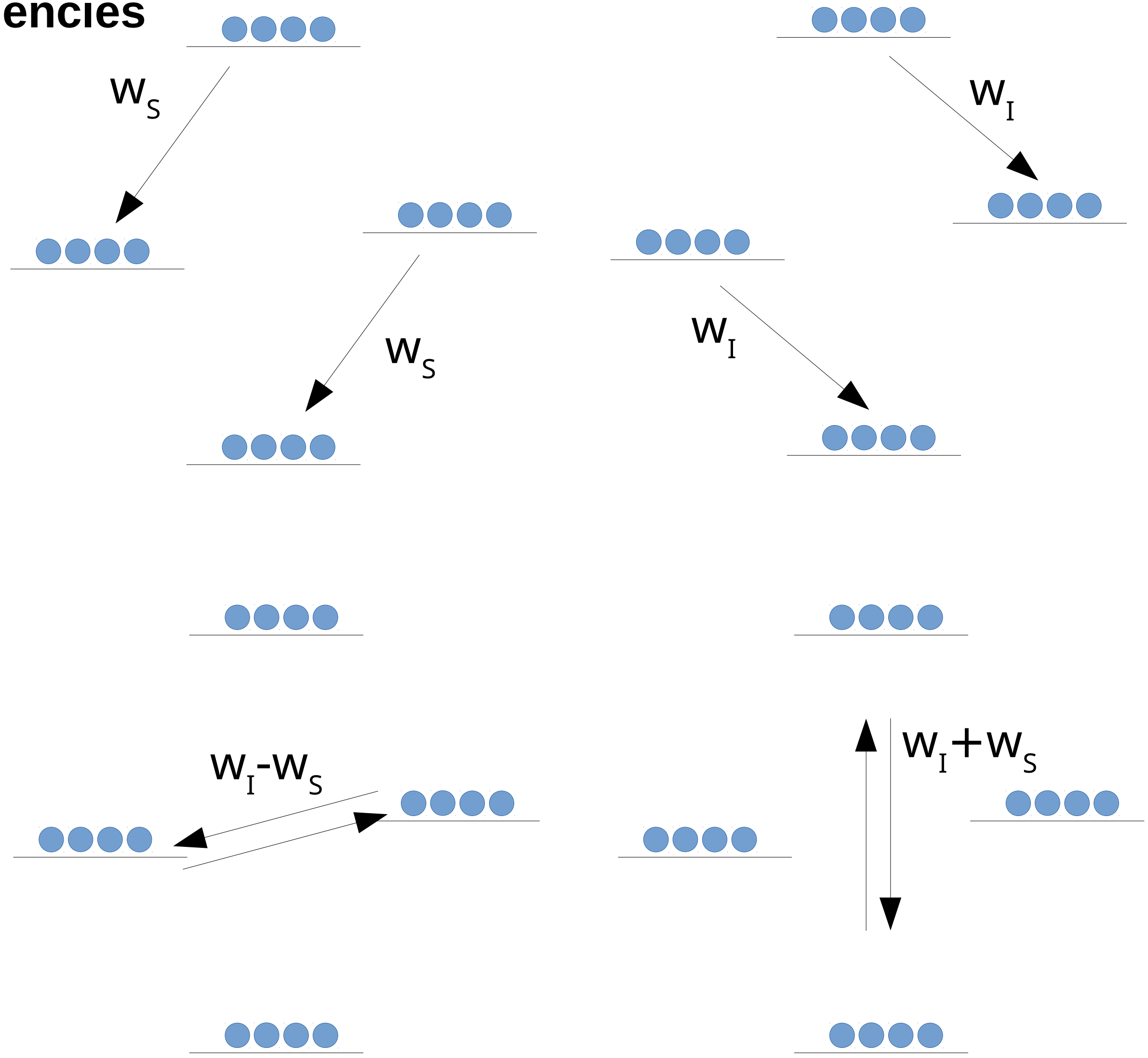
Spin-rotation relaxation



B changes as the rate of rotation changes

- Small molecules, or freely spinning portions of larger molecules without other efficient relaxation mechanisms.

Relaxation frequencies



$J(\omega_H)$

$J(\omega_N)$

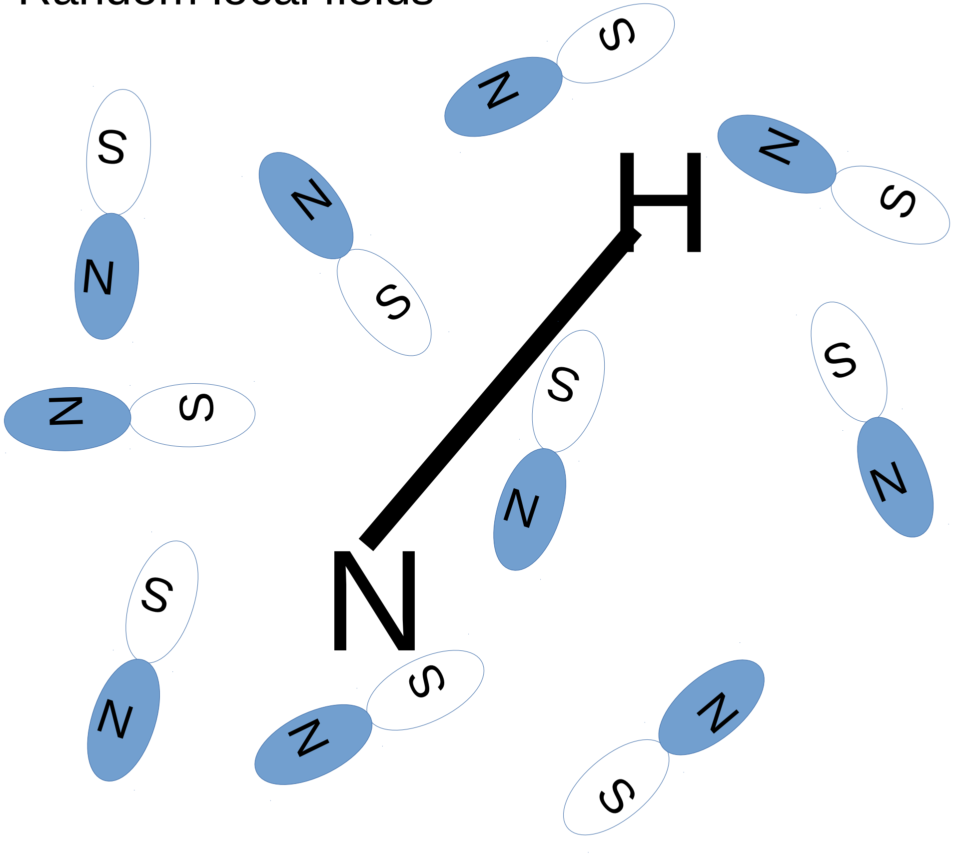
$J(\omega_H+\omega_N)$

$J(\omega_H-\omega_N)$

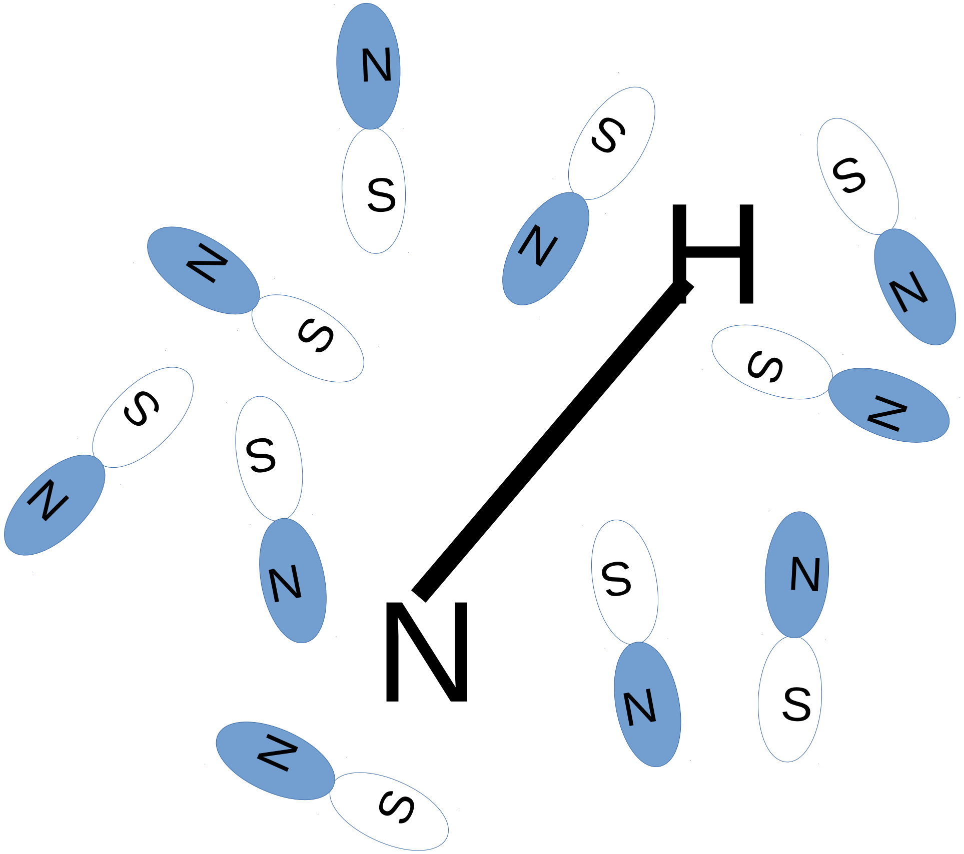
Zero frequency

$J(0)$

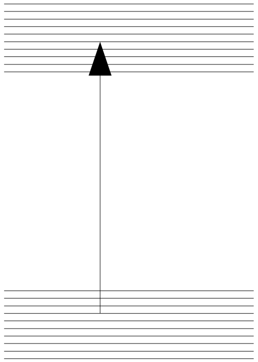
Random local fields



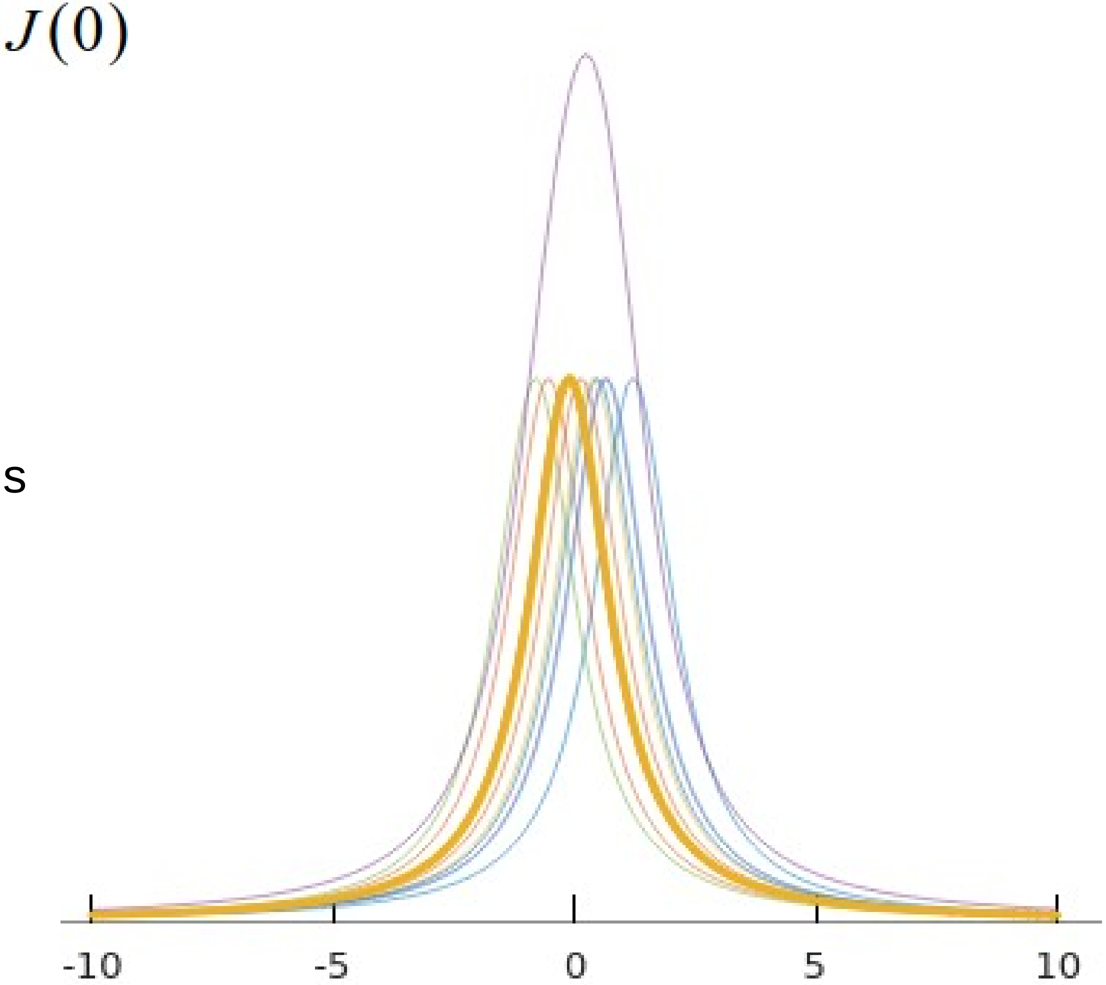
Molecule 1

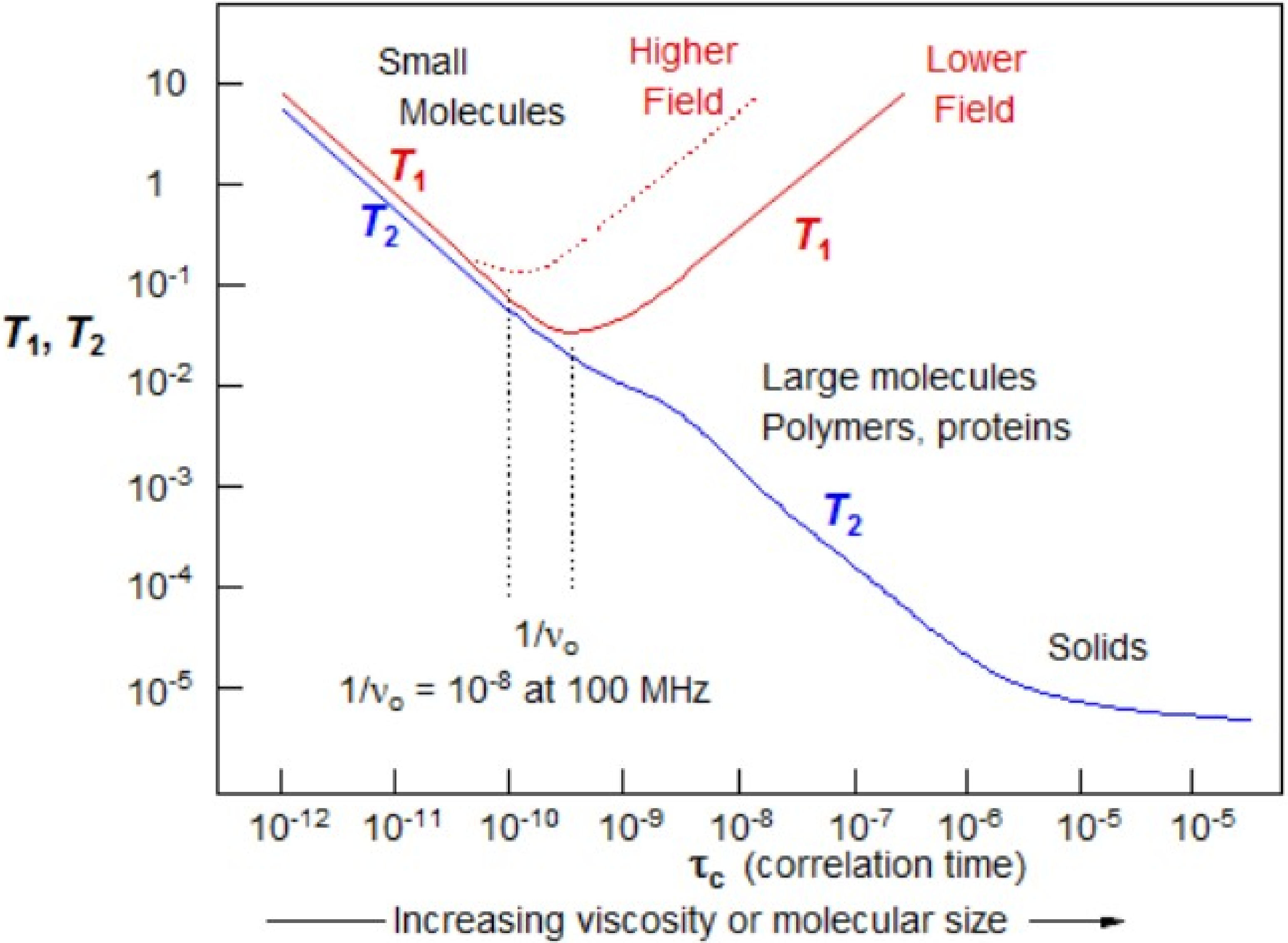


Molecule 2



Random local fields

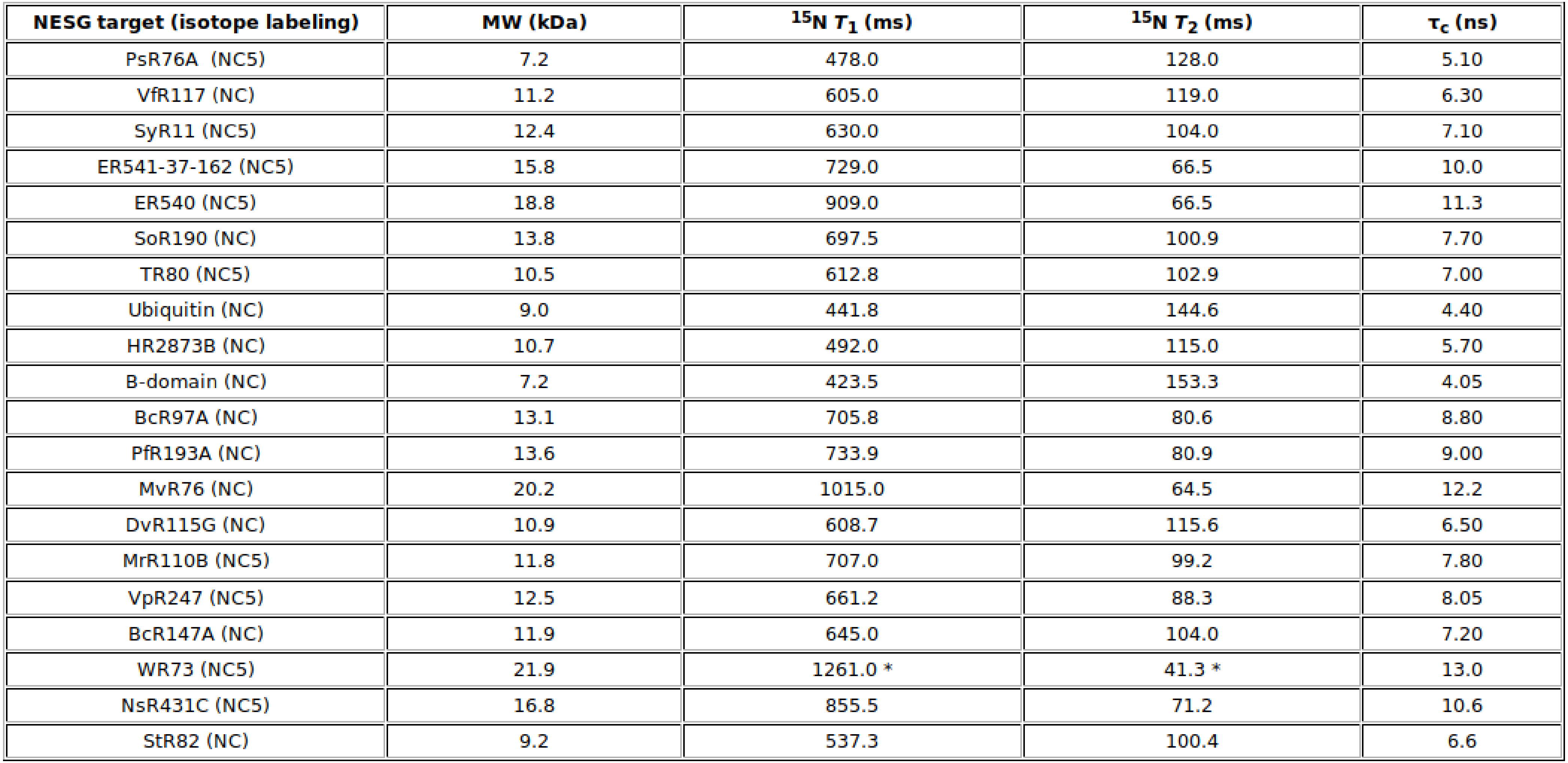




$$\tau_c = \frac{4\pi\eta r^3}{3kT},$$

Rough rule of thumb for spherical proteins:

T_c ~ MW(kDa)*0.6

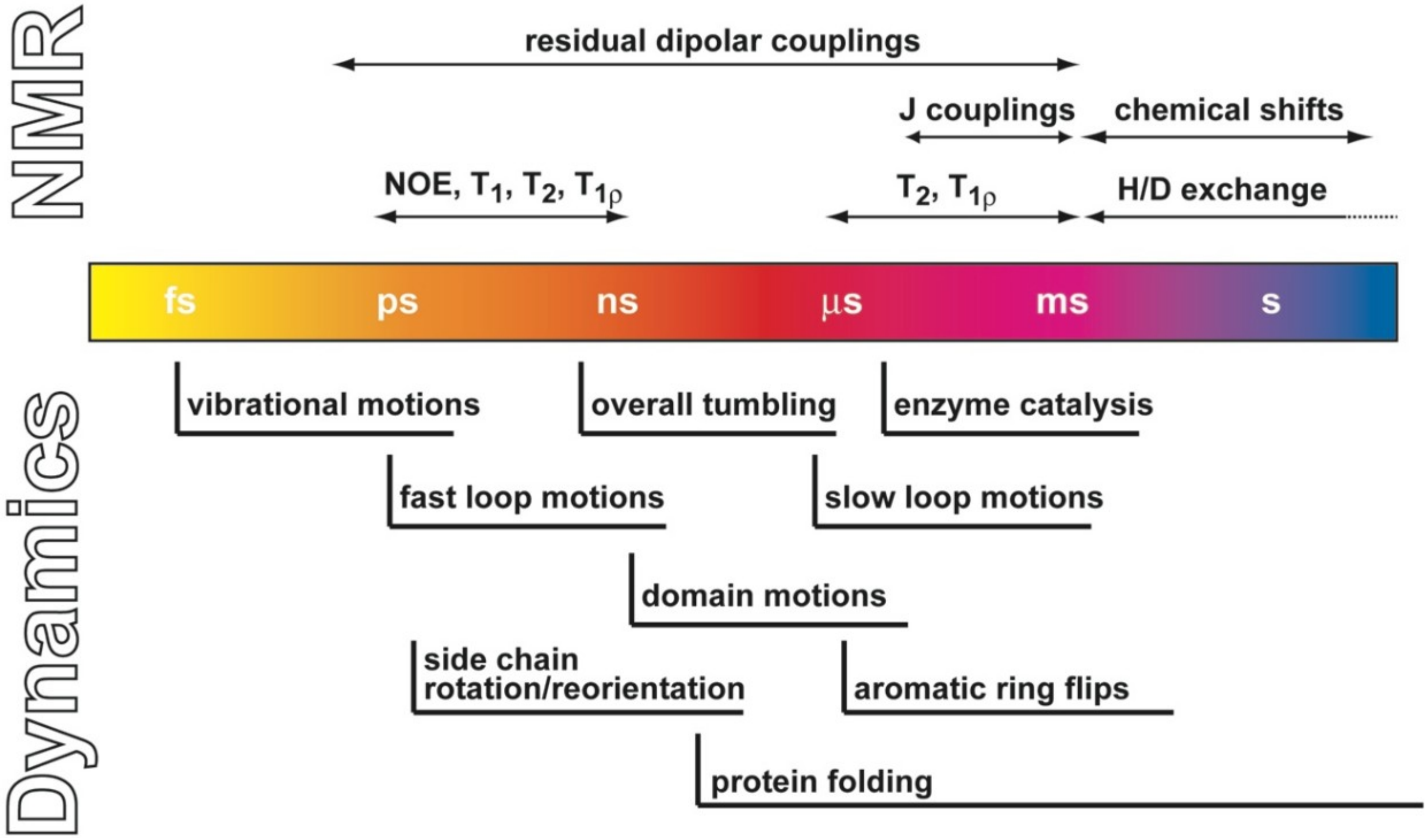


NESG target (isotope labeling)	MW (kDa)	^{15}N T_1 (ms)	^{15}N T_2 (ms)	τ_c (ns)
PsR76A (NC5)	7.2	478.0	128.0	5.10
VfR117 (NC)	11.2	605.0	119.0	6.30
SyR11 (NC5)	12.4	630.0	104.0	7.10
ER541-37-162 (NC5)	15.8	729.0	66.5	10.0
ER540 (NC5)	18.8	909.0	66.5	11.3
SoR190 (NC)	13.8	697.5	100.9	7.70
TR80 (NC5)	10.5	612.8	102.9	7.00
Ubiquitin (NC)	9.0	441.8	144.6	4.40
HR2873B (NC)	10.7	492.0	115.0	5.70
B-domain (NC)	7.2	423.5	153.3	4.05
BcR97A (NC)	13.1	705.8	80.6	8.80
PfR193A (NC)	13.6	733.9	80.9	9.00
MvR76 (NC)	20.2	1015.0	64.5	12.2
DvR115G (NC)	10.9	608.7	115.6	6.50
MrR110B (NC5)	11.8	707.0	99.2	7.80
VpR247 (NC5)	12.5	661.2	88.3	8.05
BcR147A (NC)	11.9	645.0	104.0	7.20
WR73 (NC5)	21.9	1261.0 *	41.3 *	13.0
NsR431C (NC5)	16.8	855.5	71.2	10.6
StR82 (NC)	9.2	537.3	100.4	6.6

Average t_c= 0.613*MW

NMR Spectroscopy

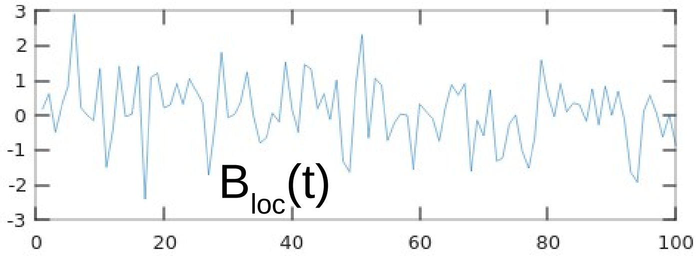
Protein dynamics

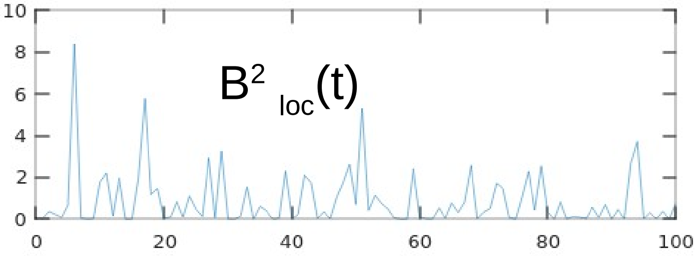


Stationary random function, $B_{loc}(t)$

$\langle B_{loc}(t)\rangle = 0$

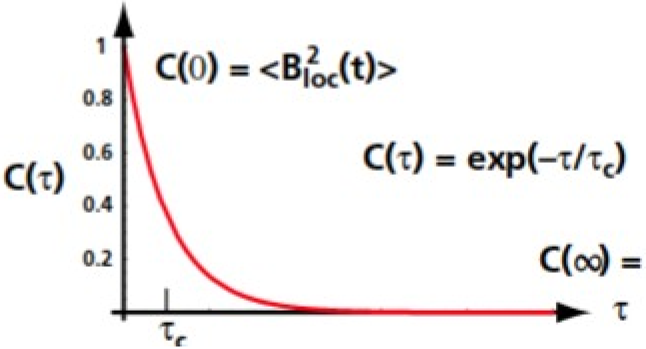
$\langle B^2_{loc}(t)\rangle \neq 0$





Time correlation function, $C(\tau)$

$$C(\tau) = \langle B_{loc}(t)B_{loc}(t+\tau)\rangle = \langle B_{loc}(0)B_{loc}(\tau)\rangle$$



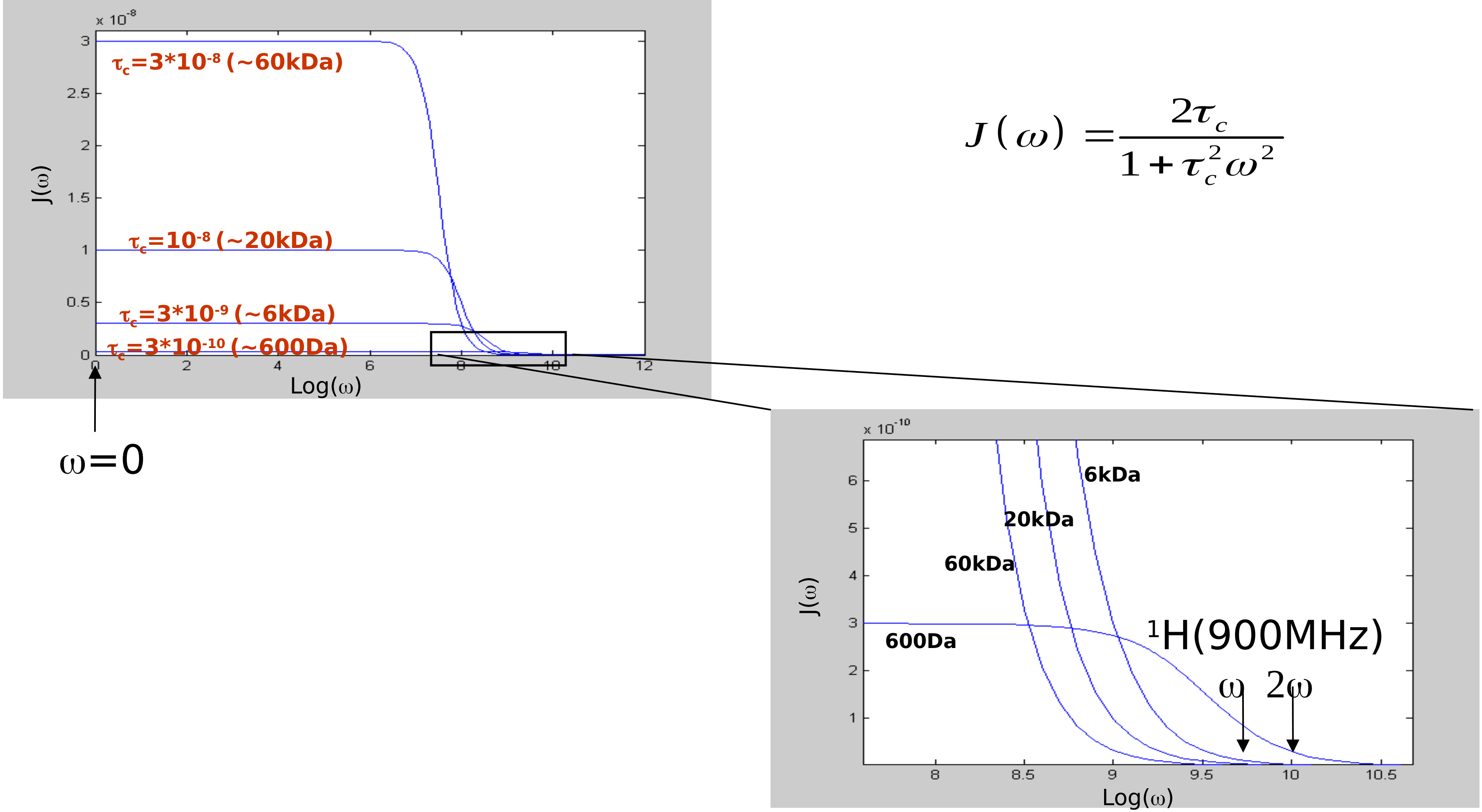
$C(0) = \langle B^2_{loc}(t)\rangle$

$C(\tau) = \exp(-\tau/\tau_c)$

$C(\infty) = \langle B_{loc}(t)\rangle^2 = 0$

Spectral densities

$$J(\omega) = \frac{2\tau_c}{1+\tau_c^2\omega^2}$$



Relaxation

Rate=Constants * ”mechanism” * correlation function

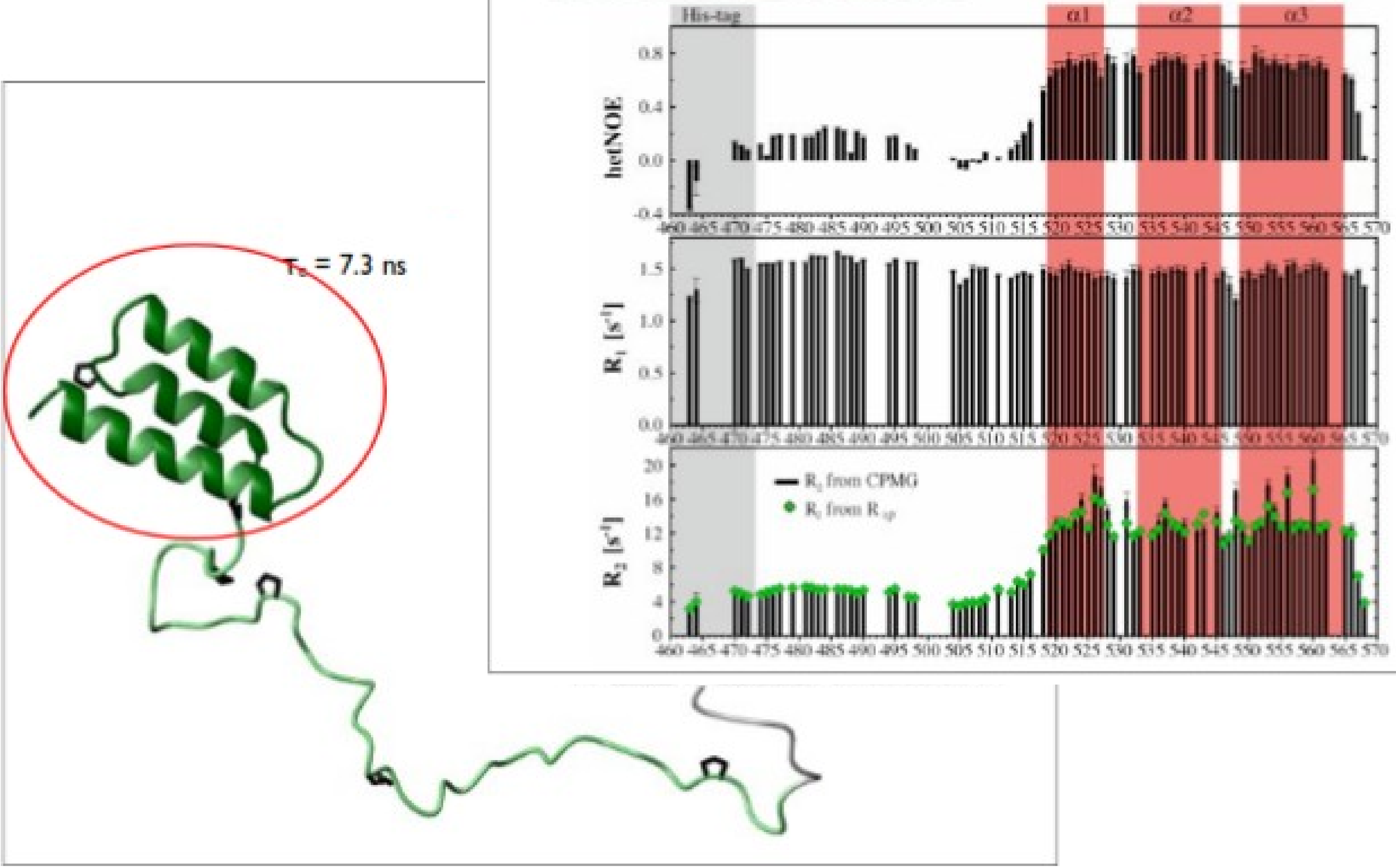
For pure Dipole-dipole:

$$R=\frac{\hbar^2\gamma_H^2\gamma_N^2}{4r_{HN}^6}*[J(\omega_H-\omega_N)+3J(\omega_N)+6J(\omega_H+\omega_N)]$$

$$J(\omega)=\frac{\tau_c}{1+\omega^2\tau_c^2}$$

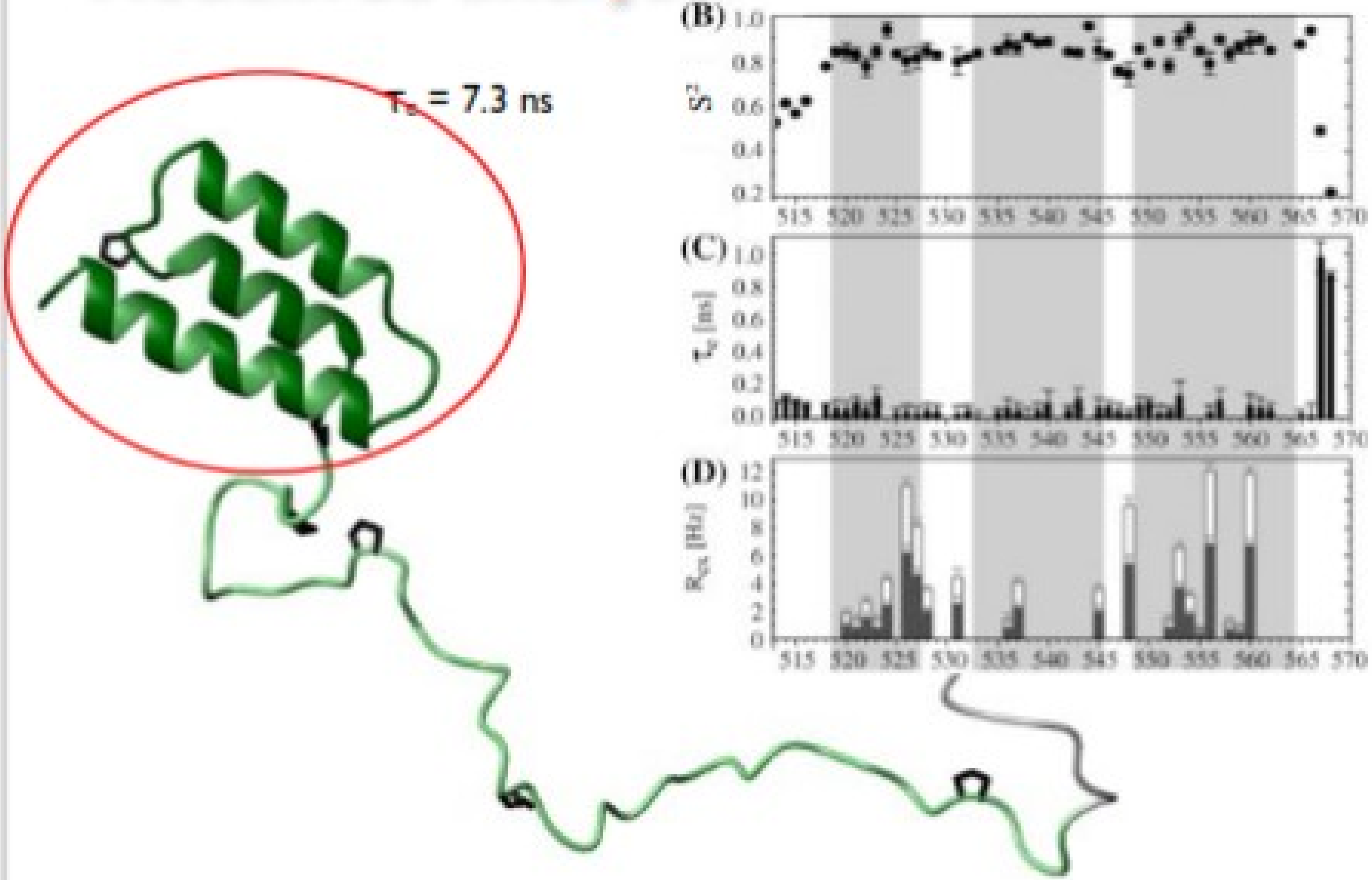
τ_c *is the correlation time*

Relaxation rates



Modelfree analysis

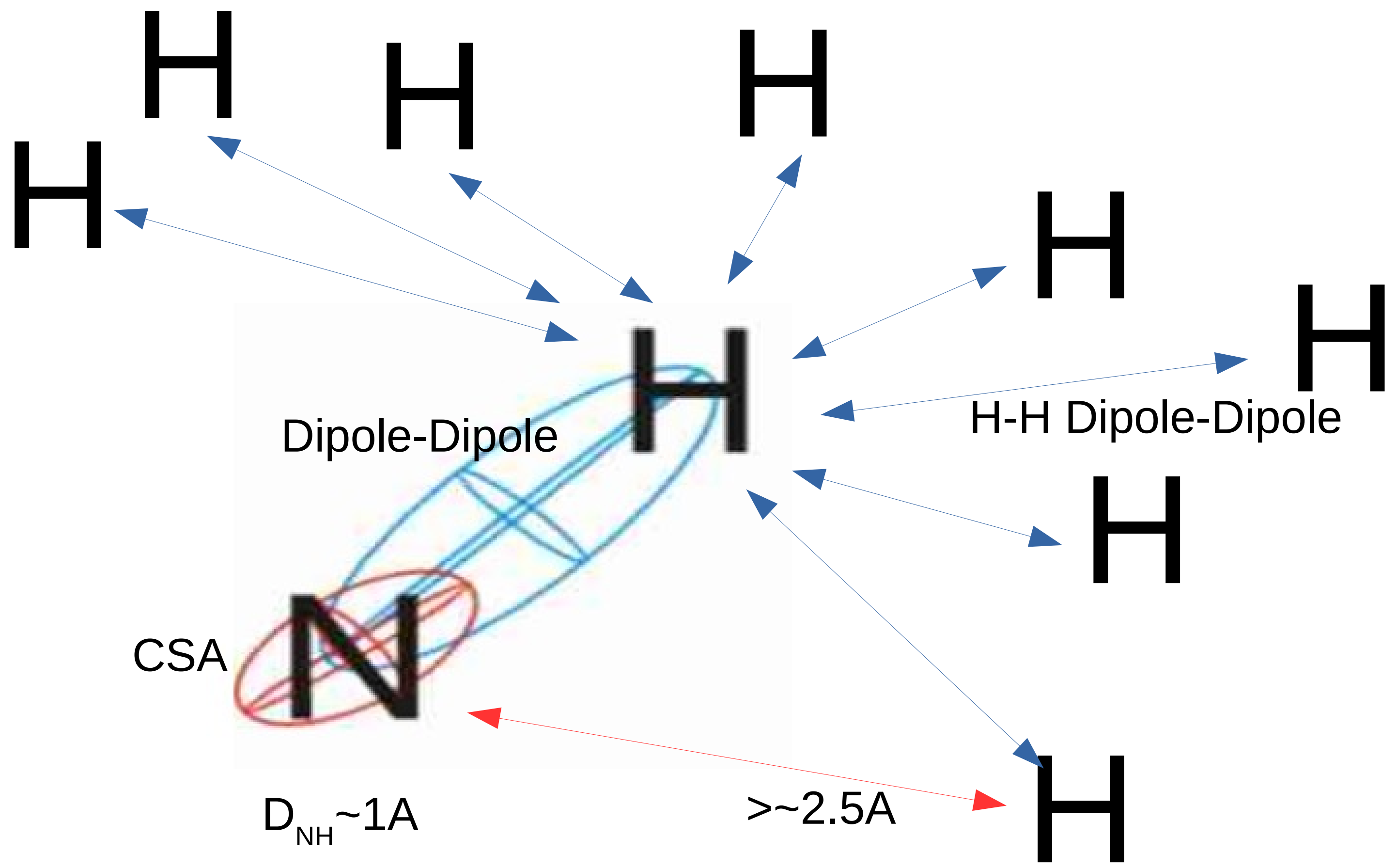
$$C_{\text{I}}(t) = \mathbf{S}^2 + (1 - \mathbf{S}^2)\, e^{-t/\tau_e}$$



More complex internal motion (e.g. 2 or more internal motions)

$$C_{\mathrm{I}}(t) = \mathbf{S}^2 + (1 - \mathbf{S}_f^2)\, e^{-t/\tau_f} + (\mathbf{S}_f^2 - \mathbf{S}^2)\, e^{-t/\tau_s}$$

Be Cautious: If τ_f if close to τ_s (within a order of magnitude or so), then the values may not be distinguishable due to noise



Dipole-Dipole

H-H Dipole-Dipole

CSA

D_{NH}~1A

>~2.5A

Non-bonded H contribution to N DD relaxation ~250 times smaller than direct bonded NH

Coherence order				
0	$\langle I_z \rangle$	$\langle S_z \rangle$	$\langle I_z S_z \rangle$	
1	$\langle I_x \rangle$	$\langle I_y \rangle$	$\langle S_x \rangle$	$\langle S_y \rangle$
1	$\langle I_z S_x \rangle$	$\langle I_z S_y \rangle$	$\langle I_x S_z \rangle$	$\langle I_y S_z \rangle$
0,2	$\langle I_x S_x \rangle$	$\langle I_x S_y \rangle$	$\langle I_y S_x \rangle$	$\langle I_y S_y \rangle$

HN relaxation depends on 5 frequencies

$$J(0)$$

$$J(\omega_H)$$

$$J(\omega_N)$$

$$J(\omega_H + \omega_N)$$

$$J(\omega_H - \omega_N)$$

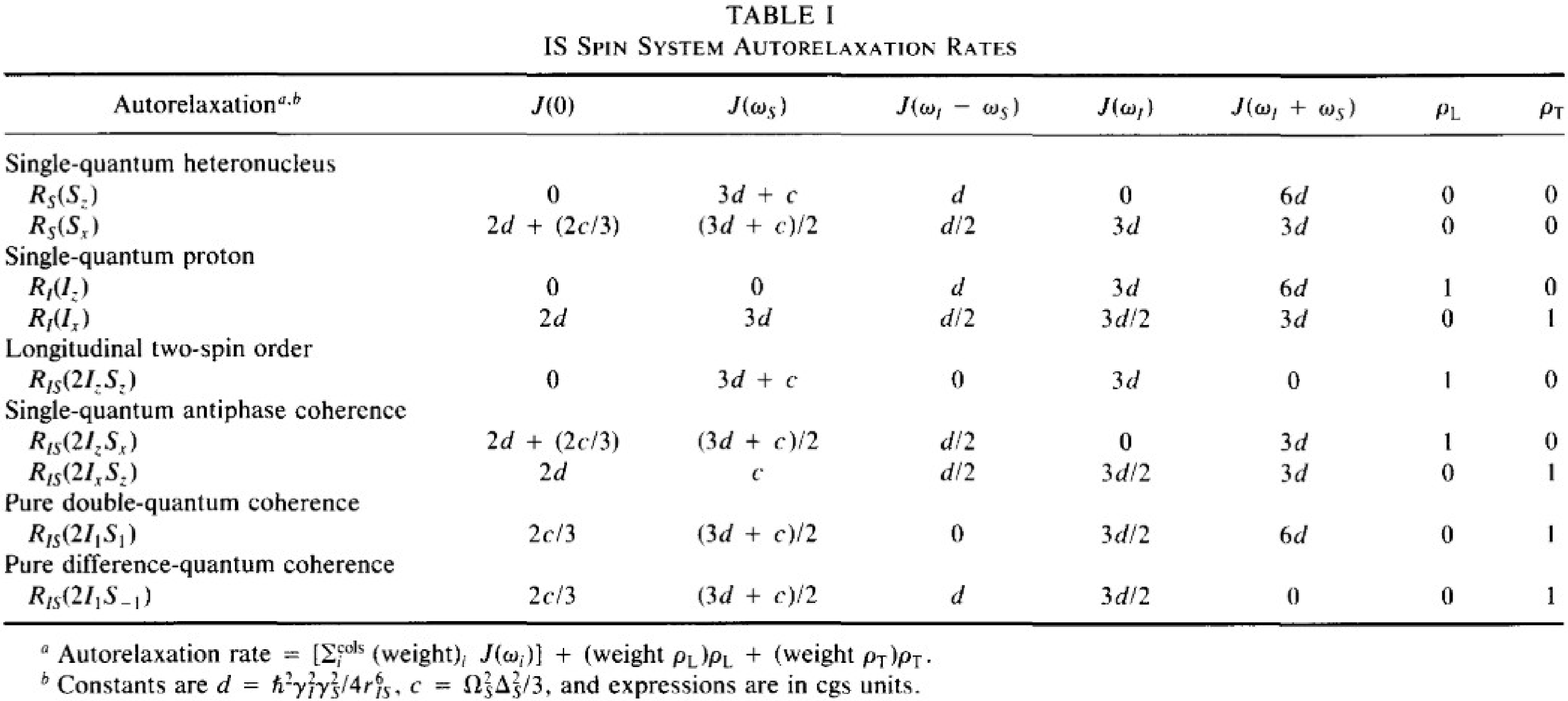


TABLE I
IS SPIN SYSTEM AUTORELAXATION RATES

Autorelaxation[a,b]	$J(0)$	$J(\omega_S)$	$J(\omega_I - \omega_S)$	$J(\omega_I)$	$J(\omega_I + \omega_S)$	ρ_L	ρ_T
Single-quantum heteronucleus							
$R_S(S_z)$	0	$3d + c$	d	0	$6d$	0	0
$R_S(S_x)$	$2d + (2c/3)$	$(3d + c)/2$	$d/2$	$3d$	$3d$	0	0
Single-quantum proton							
$R_I(I_z)$	0	0	d	$3d$	$6d$	1	0
$R_I(I_x)$	$2d$	$3d$	$d/2$	$3d/2$	$3d$	0	1
Longitudinal two-spin order							
$R_{IS}(2I_zS_z)$	0	$3d + c$	0	$3d$	0	1	0
Single-quantum antiphase coherence							
$R_{IS}(2I_zS_x)$	$2d + (2c/3)$	$(3d + c)/2$	$d/2$	0	$3d$	1	0
$R_{IS}(2I_xS_z)$	$2d$	c	$d/2$	$3d/2$	$3d$	0	1
Pure double-quantum coherence							
$R_{IS}(2I_1S_1)$	$2c/3$	$(3d + c)/2$	0	$3d/2$	$6d$	0	1
Pure difference-quantum coherence							
$R_{IS}(2I_1S_{-1})$	$2c/3$	$(3d + c)/2$	d	$3d/2$	0	0	1

[a] Autorelaxation rate = $[\Sigma_i^{\text{cols}} (\text{weight})_i \ J(\omega_i)] + (\text{weight } \rho_L)\rho_L + (\text{weight } \rho_T)\rho_T$.

[b] Constants are $d = \hbar^2\gamma_I^2\gamma_S^2/4r_{IS}^6$, $c = \Omega_S^2\Delta_S^2/3$, and expressions are in cgs units.

Peng, J. W., & Wagner, G. (1994). Nuclear Magnetic Resonance, Part C. Meth. Enzymol., 239(1987), 563–596. https://doi.org/10.1016/S0076-6879(94)39022-3

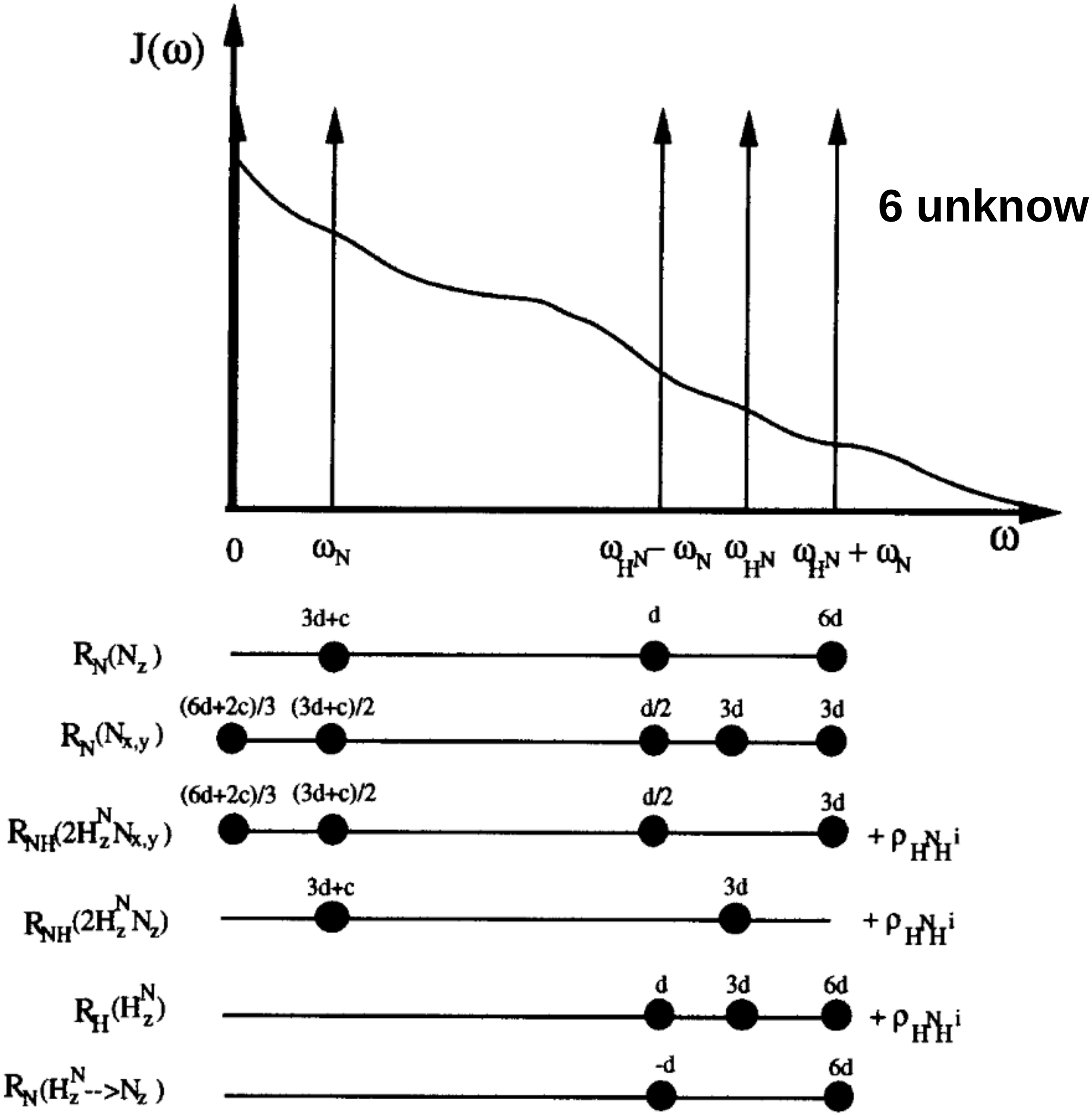
TABLE II
IS SPIN SYSTEM CROSS-RELAXATION RATES

Cross-relaxation[a,b]	$J(0)$	$J(\omega_S)$	$J(\omega_I - \omega_S)$	$J(\omega_I)$	$J(\omega_I + \omega_S)$	σ_{L}^{i}	σ_{T}^{i}
Heteronuclear dipolar cross-relaxation							
$R_S(I_z \leftrightarrow S_z)$	0	0	$-d$	0	$6d$	0	0
Proton longitudinal cross-relaxation (NOE)[c]							
$R_I(I_z \leftrightarrow A_z^i)$	0	0	0	0	0	1	0
Proton transverse cross-relaxation (ROE)[c]							
$R_I(I_x \leftrightarrow A_x^i)$	0	0	0	0	0	0	1
CSA–dipolar cross-correlated cross-relaxation							
$R_S(S_z \leftrightarrow 2I_zS_z)$	0	K	0	0	0	0	0
$R_S(S_x \leftrightarrow 2I_zS_x)$	$2K/3$	$K/2$	0	0	0	0	0

[a] Constants are $d = \hbar^2\gamma_I^2\gamma_S^2/4r_{IS}^6$, $c = \Omega_S^2\Delta_S^2/3$, and $K = \hbar\gamma_I\gamma_S\Omega_S\Delta_S\langle P_2(\cos\Phi)\rangle/r_{IS}^3$, and expressions are in cgs units.

[b] Cross-rate = $[\Sigma_i^{\mathrm{cols}}(\mathrm{weight})_i J(\omega_i)] + (\mathrm{weight}\ \sigma_{\mathrm{L}}^{i})\sigma_{\mathrm{L}}^{i} + (\mathrm{weight}\ \sigma_{\mathrm{T}}^{i})\sigma_{\mathrm{T}}^{i}$.

[c] $\sigma_{\mathrm{L}}^{i} = (\hbar^2\gamma_I^4/4r_{IA^i}^6)\{6J_{IA^i}(2\omega_I) - J_{IA^i}(0)\}$, $\sigma_{\mathrm{T}}^{i} = (\hbar^2\gamma_I^4/4r_{IA^i}^6)\{2J_{IA^i}(0) + 3J_{IA^i}(\omega_I)\}$.



6 unknowns

dipole-dipole

$$d = \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{r_{IS}^6}$$

Chemical shift anisotropy

$$c = \frac{\Delta\sigma^2 \omega_N^2}{3}$$

R1,R2,HetNOE
Used for model free

$$R_{\mathrm{N}}(N_z) = \frac{\gamma_{\mathrm{H^N}}^2 \gamma_{\mathrm{N}}^2 \hbar^2}{4 r_{\mathrm{NH^N}}^6} \{J(\omega_{\mathrm{H^N}} - \omega_{\mathrm{N}}) + 3J(\omega_{\mathrm{N}}) + 6J(\omega_{\mathrm{H^N}} + \omega_{\mathrm{N}})\} + \frac{\Delta^2 \omega_{\mathrm{N}}^2}{3} J(\omega_{\mathrm{N}})$$

$$R_{\mathrm{N}}(\mathrm{N}_{x,y}) = \frac{\gamma_{\mathrm{H^N}}^2 \gamma_{\mathrm{N}}^2 \hbar^2}{8 r_{\mathrm{NH^N}}^6} \{4J(0) + J(\omega_{\mathrm{H^N}} - \omega_{\mathrm{N}}) + 3J(\omega_{\mathrm{N}}) + 6J(\omega_{\mathrm{H^N}}) + 6J(\omega_{\mathrm{H^N}} + \omega_{\mathrm{N}})\} + \frac{\Delta^2 \omega_{\mathrm{N}}^2}{3} \left\{\frac{2}{3} J(0) + \frac{1}{2} \mathrm{J}(\omega_{\mathrm{N}})\right\}$$

$$R_{\mathrm{N}}(\mathrm{H}_z^{\mathrm{N}} \rightarrow \mathrm{N}_z) = \frac{\gamma_{\mathrm{H^N}}^2 \gamma_{\mathrm{N}}^2 \hbar^2}{4 r_{\mathrm{NH^N}}^6} \{6J(\omega_{\mathrm{H^N}} + \omega_{\mathrm{N}}) - J(\omega_{\mathrm{H^N}} - \omega_{\mathrm{N}})\}.$$

$$R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_z) = \frac{\gamma_{\mathrm{H^N}}^2\gamma_{\mathrm{N}}^2\hbar^2}{4r_{\mathrm{NH^N}}^6}\{3J(\omega_{\mathrm{N}}) + 3J(\omega_{\mathrm{H^N}})\} + \frac{\Delta^2\omega_{\mathrm{N}}^2}{3}J(\omega_{\mathrm{N}}) + \rho_{\mathrm{H^NH}^i}$$

$$\begin{aligned} R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_{x,y}) = {} & \frac{\gamma_{\mathrm{H^N}}^2\gamma_{\mathrm{N}}^2\hbar^2}{8r_{\mathrm{NH^N}}^6}\{4J(0) + J(\omega_{\mathrm{H^N}} - \omega_{\mathrm{N}}) \\ & + 3J(\omega_{\mathrm{N}}) + 6J(\omega_{\mathrm{H^N}} + \omega_{\mathrm{N}})\} + \frac{\Delta^2\omega_{\mathrm{N}}^2}{3}\left\{\frac{2}{3}J(0) + \frac{1}{2}J(\omega_{\mathrm{N}})\right\} + \rho_{\mathrm{H^NH}^i}, \end{aligned}$$

$$R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}}) = \frac{\gamma_{\mathrm{H^N}}^2\gamma_{\mathrm{N}}^2\hbar^2}{4r_{\mathrm{NH^N}}^6}\{J(\omega_{\mathrm{H^N}} - \omega_{\mathrm{N}}) + 3J(\omega_{\mathrm{H^N}}) + 6J(\omega_{\mathrm{H^N}} + \omega_{\mathrm{N}})\} + \rho_{\mathrm{H^NH}^i}$$

$$\begin{bmatrix} R_{\mathrm{N}}(\mathrm{N}_z) \\ R_{\mathrm{N}}(\mathrm{N}_{x,y}) \\ R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_{x,y}) \\ R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_z) \\ R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}}) \\ R_{\mathrm{N}}(\mathrm{H}_z^{\mathrm{N}} \rightarrow \mathrm{N}_z) \end{bmatrix} = \begin{bmatrix} 0 & d & 3d+c & 0 & 6d & 0 \\ \dfrac{6d+2c}{3} & \dfrac{d}{2} & \dfrac{3d+c}{2} & 3d & 3d & 0 \\ \dfrac{6d+2c}{3} & \dfrac{d}{2} & \dfrac{3d+c}{2} & 0 & 3d & 1 \\ 0 & 0 & 3d+c & 3d & 0 & 1 \\ 0 & d & 0 & 3d & 6d & 1 \\ 0 & -d & 0 & 0 & 6d & 0 \end{bmatrix} \begin{bmatrix} J(0) \\ J(\omega_{\mathrm{H}^{\mathrm{N}}} - \omega_{\mathrm{N}}) \\ J(\omega_{\mathrm{N}}) \\ J(\omega_{\mathrm{H}^{\mathrm{N}}}) \\ J(\omega_{\mathrm{H}^{\mathrm{N}}} + \omega_{\mathrm{N}}) \\ \rho_{\mathrm{H}^{\mathrm{N}}\mathrm{H}^{i}} \end{bmatrix}$$

$$\begin{aligned}J(0) = \frac{3}{4}\frac{1}{3d+c}\Big\{&-\frac{1}{2}R_{\mathrm{N}}(\mathrm{N}_z) + R_{\mathrm{N}}(\mathrm{N}_{x,y}) + R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_{x,y}) \\ &- \frac{1}{2}R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_z) - \frac{1}{2}R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}})\Big\}\end{aligned}$$

$$\begin{aligned}J(\omega_{\mathrm{H}^{\mathrm{N}}} - \omega_{\mathrm{N}}) = \frac{1}{4}\frac{1}{d}\{&R_{\mathrm{N}}(\mathrm{N}_z) - R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_z) \\ &+ R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}}) - 2R_{\mathrm{N}}(\mathrm{H}_z^{\mathrm{N}} \rightarrow \mathrm{N}_z)\}\end{aligned}$$

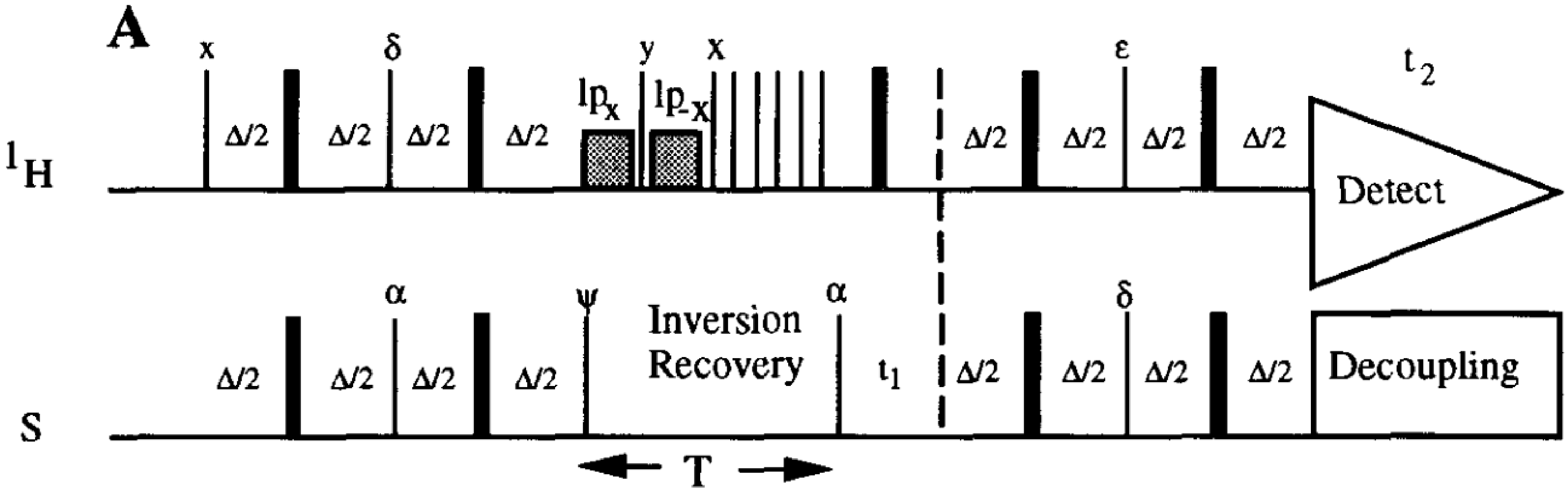
$$J(\omega_{\mathrm{N}}) = \frac{1}{2}\frac{1}{3d+c}\{R_{\mathrm{N}}(\mathrm{N}_z) + R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}N_z) - R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}})\}$$

$$\begin{aligned}J(\omega_{\mathrm{H}^{\mathrm{N}}}) = \frac{1}{12}\frac{1}{d}\{&-R_{\mathrm{N}}(\mathrm{N}_z) + 2R_{\mathrm{N}}(\mathrm{N}_{x,y}) - 2R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}N_{x,y}) \\ &+ R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_z) + R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}})\}\end{aligned}$$

$$\begin{aligned}J(\omega_{\mathrm{H}^{\mathrm{N}}} + \omega_{\mathrm{N}}) = \frac{1}{24}\frac{1}{d}\{&R_{\mathrm{N}}(\mathrm{N}_z) - R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}N_z) \\ &+ R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}}) + 2R_{\mathrm{N}}(\mathrm{H}_z^{\mathrm{N}} \rightarrow \mathrm{N}_z)\}.\end{aligned}$$

$$\begin{aligned}\rho_{\mathrm{H}^{\mathrm{N}}\mathrm{H}^i} = \{&-\tfrac{1}{4}R_{\mathrm{N}}(\mathrm{N}_z) - \tfrac{1}{2}R_{\mathrm{N}}(\mathrm{N}_{x,y}) + \tfrac{1}{2}R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_{x,y}) \\ &+ \tfrac{1}{4}R_{\mathrm{NH}}(2\mathrm{H}_z^{\mathrm{N}}\mathrm{N}_z) + \tfrac{1}{4}R_{\mathrm{H}}(\mathrm{H}_z^{\mathrm{N}})\}\end{aligned}$$

$R_N(N_z)$



$$\frac{d(S_z)}{dt} = -R_S(S_z)\left\langle\left\langle\left\langle S_z - S_z^0\right\rangle\right\rangle\right\rangle - R_{IS}(S_z \leftrightarrow I_z)\left\langle\left\langle I_z - I_z^0\right\rangle\right\rangle - R_{IS}(S_z \leftrightarrow 2I_zS_z)\left\langle 2I_zS_z\right\rangle$$

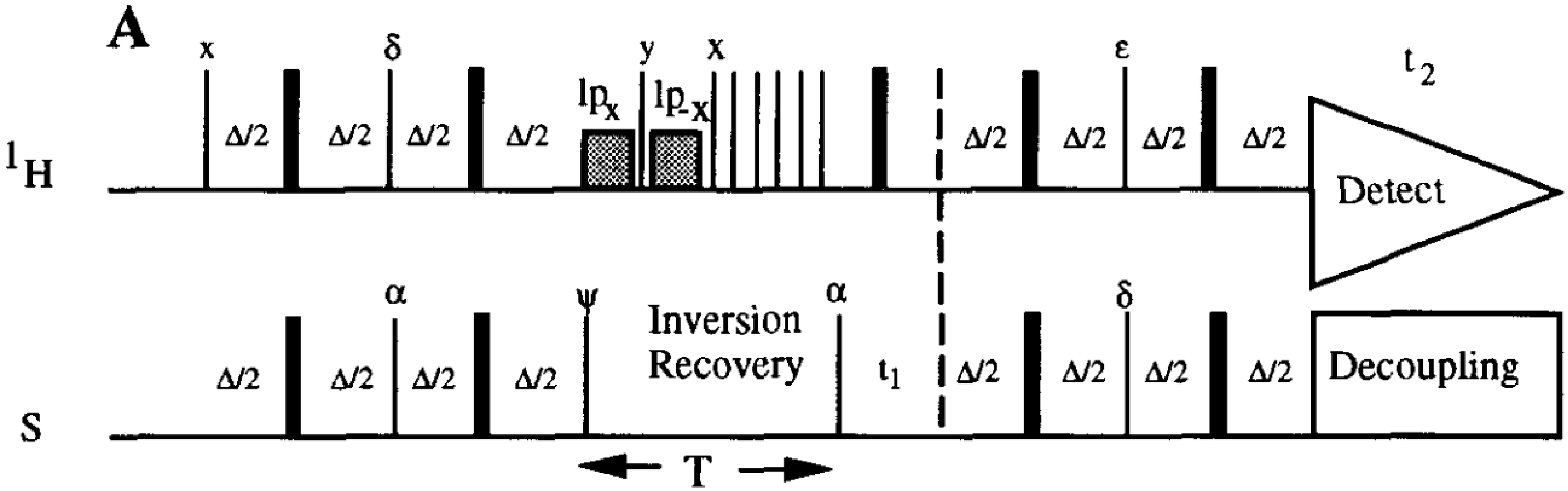
<5% $R_S(S_z)$

More serious

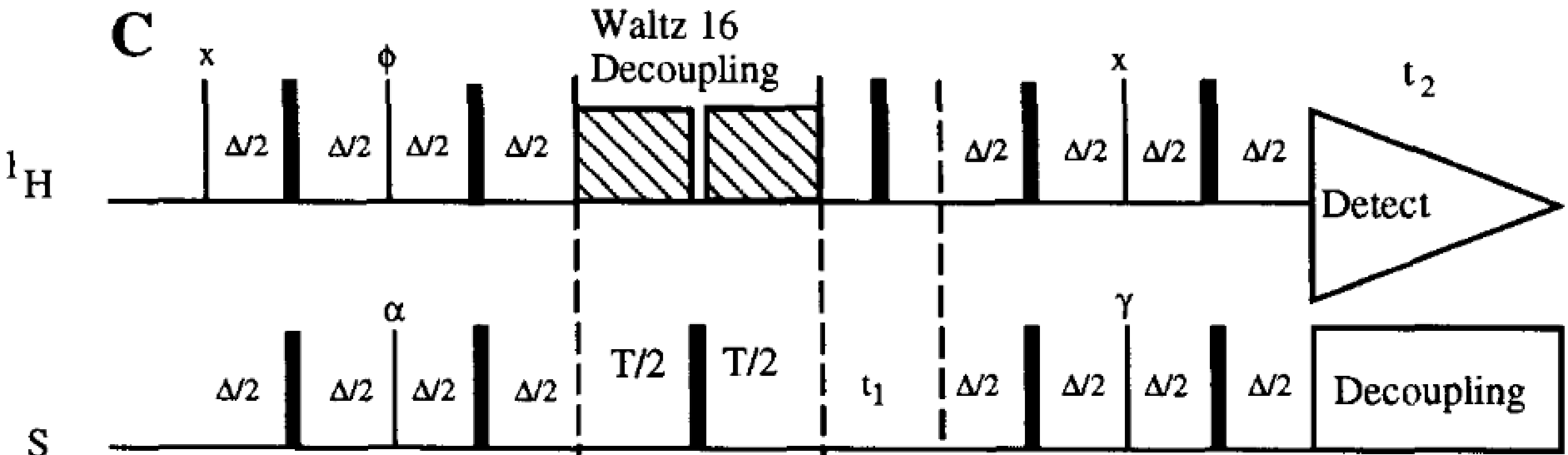
$(S_z \leftrightarrow I_z)$ – heteronuclear dipole–dipole cross relaxation

$(S_z \leftrightarrow 2I_zS_z)$– cross relaxation due to heteronuclear CSA–dipole cross correlation

$R_N(N_z)$

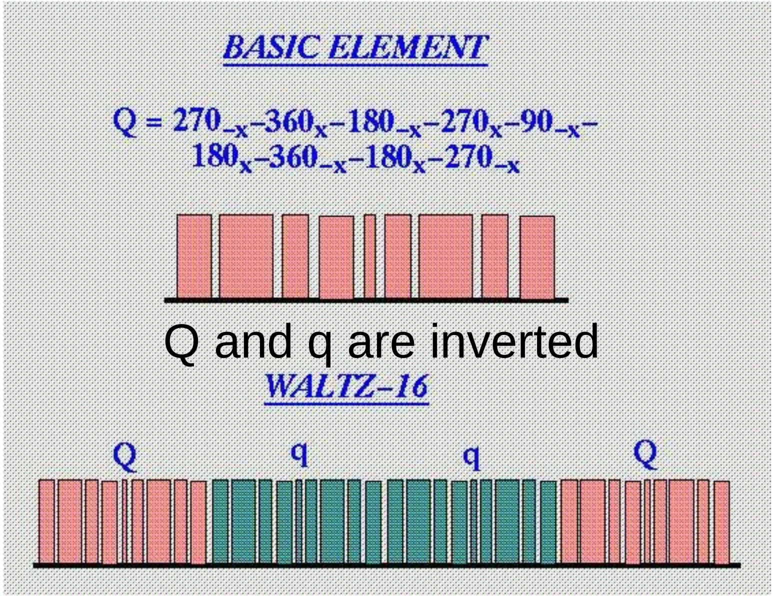


- Need to keep I_z and $2I_zS_z$ terms constant or zero.
- Initial saturation via 2 long pulses (double components of S_z remain equal and cross-correlation removed)
- Saturation maintained by pulse train of hard 90 pulses
  - could be achieved with proton broadband decoupling
- Saturation forces peak intensity to that of hetNOE



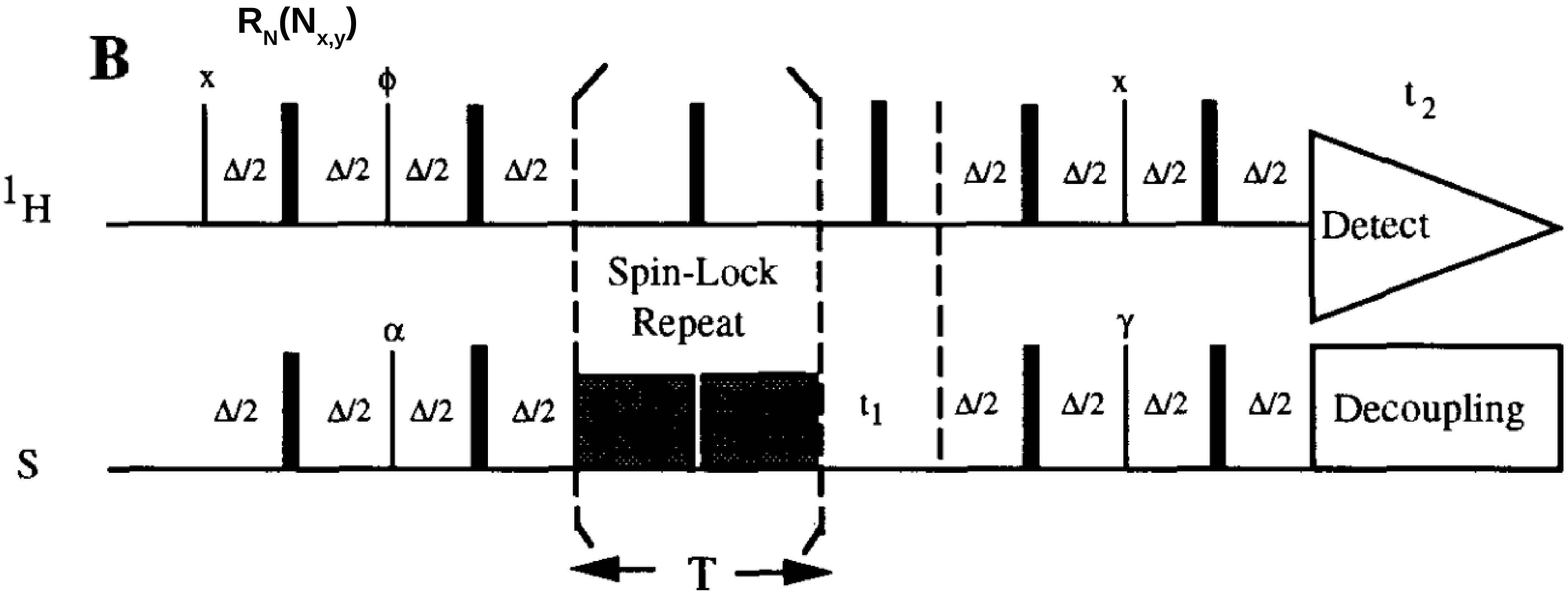
Alternative approach using ^{1}H decoupling

WALTZ→ 90_x-180_{-x}-270_x



$Q = 270_{-x}–360_x–180_{-x}–270_x–90_{-x}–180_x–360_{-x}–180_x–270_{-x}$

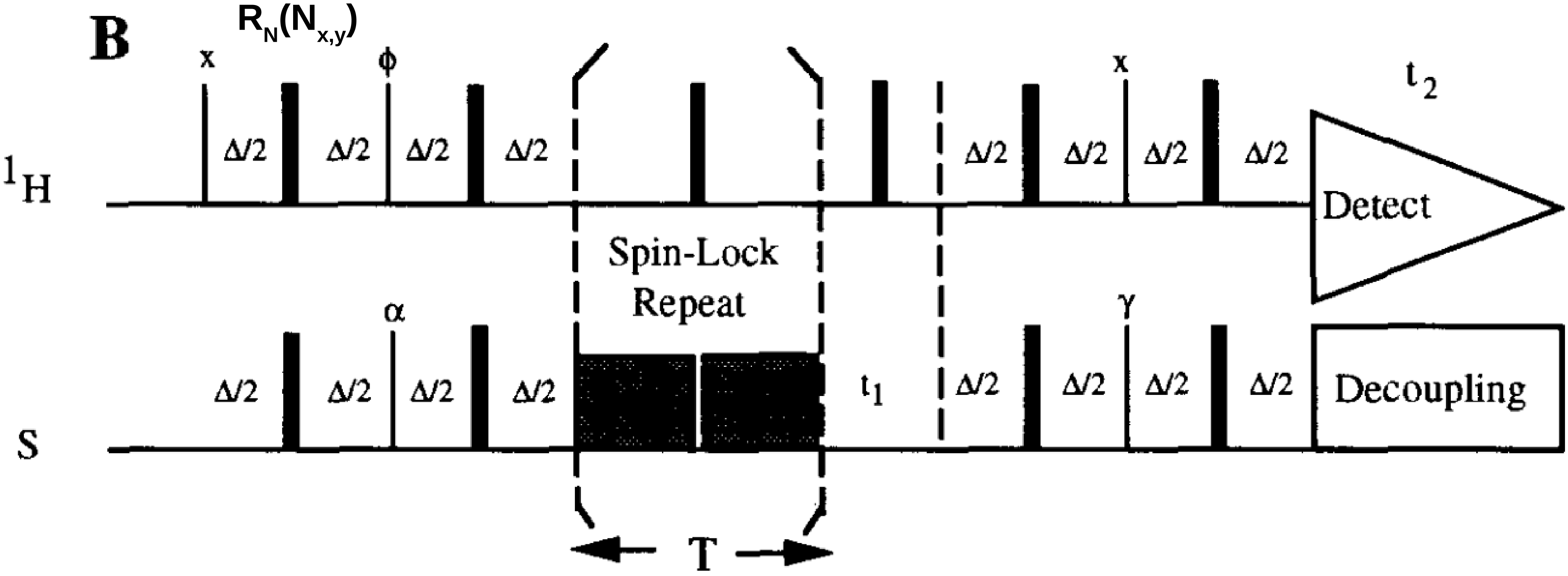
Q and q are inverted



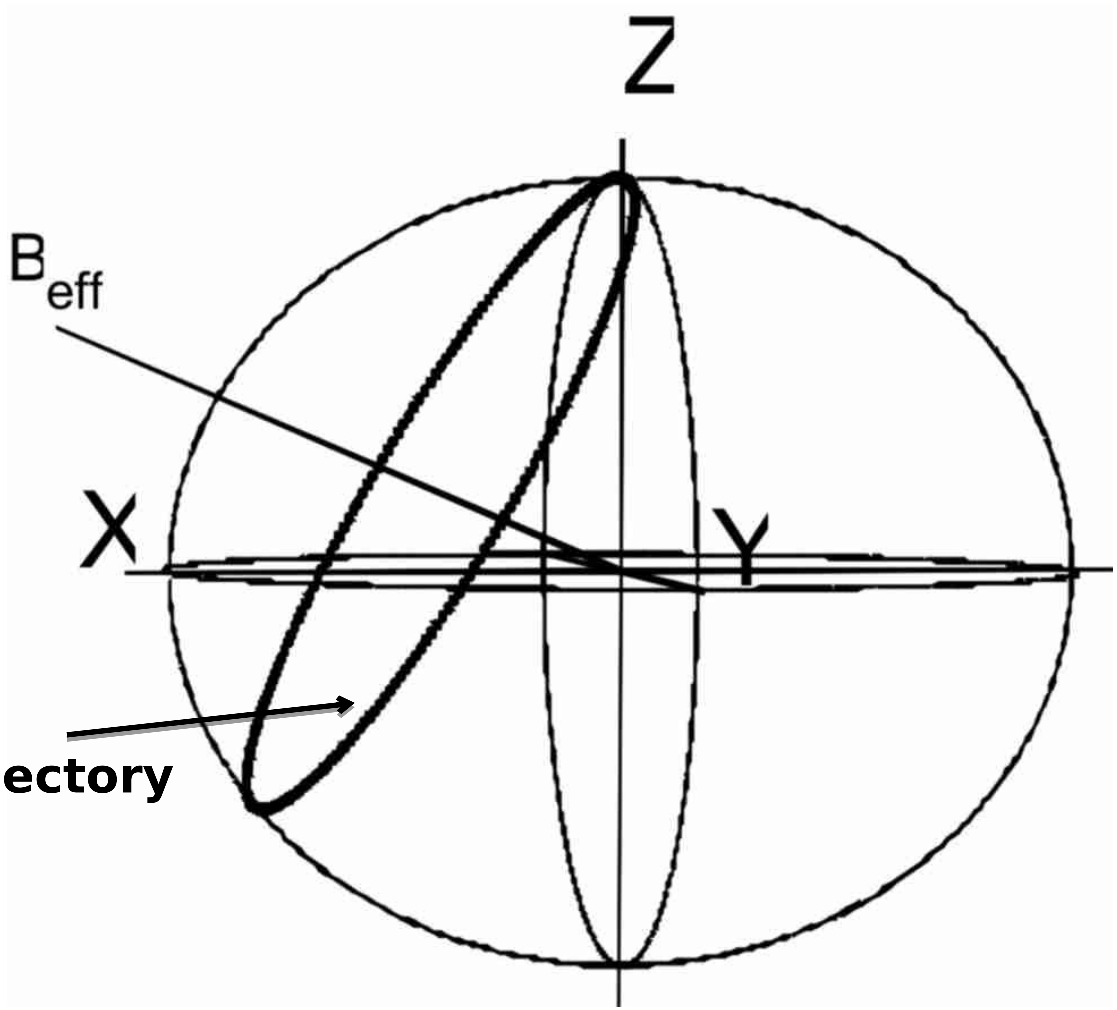
$$\frac{d(S_x)}{dt} = -R_S(S_x)\langle S_x\rangle - \pi J_{IS}\langle 2I_zS_y\rangle - R_{IS}(S_x \leftrightarrow 2I_zS_x)\langle 2I_zS_x\rangle$$

$\pi J_{IS}\langle 2I_zS_y\rangle$ − heteronuclear bond scalar coupling

$(S_x \leftrightarrow 2I_zS_x)\langle 2I_zS_x\rangle$ − cross relaxation due to heteronuclear CSA − dipole cross correlation

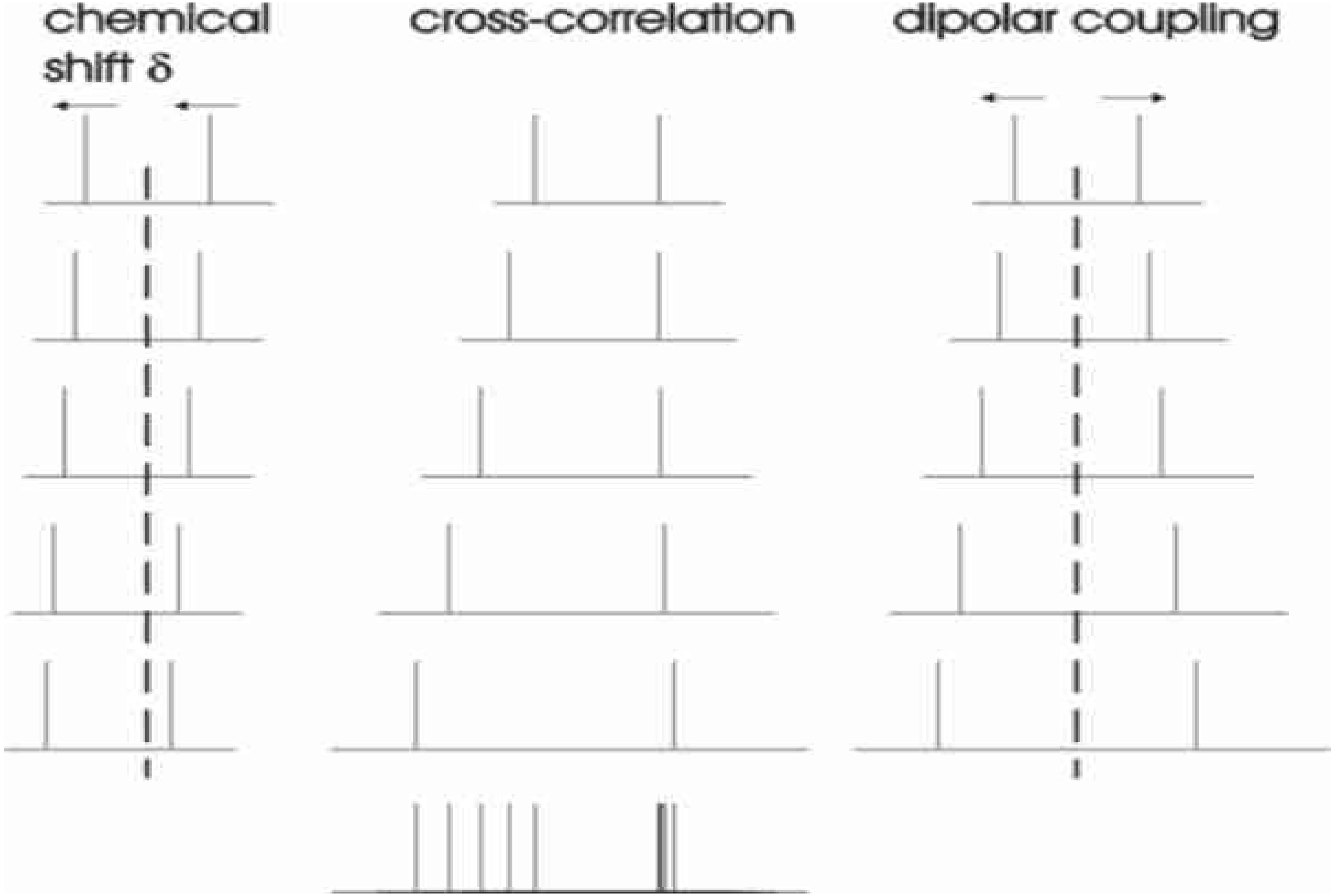


- Continuous wave spin lock along x axis effectively kills the J_{IS} term
    - CPMG could be used
- Cross-correlation due to CSA-DD is suppressed by inserting 180 proton pulses in spin lock
- Off resonance effects will effect the relaxation rate since the spin lock axis is tilted toward the Z axis as a function of off resonance



trajectory

Dipole-Dipole/CSA relaxation interference



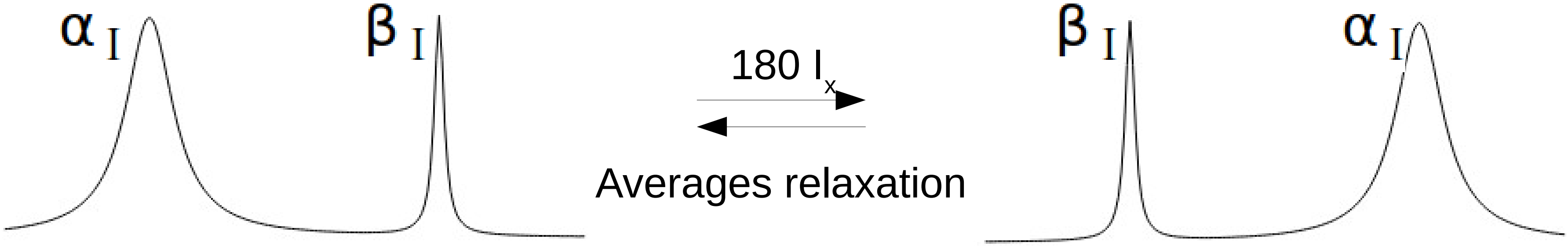
In relaxation, the interactions are squared averages.

For 2 relaxation interactions, A & B that have the same symmetry, the square contains cross terms.

$$R^{-1} \propto (A+B)^2 = A^2 + 2AB + B^2$$

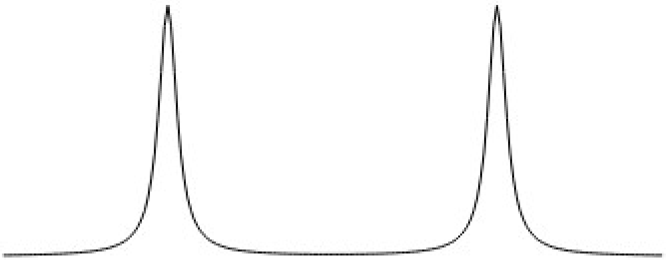
Relaxation interference

S relaxation due to cross-correlation

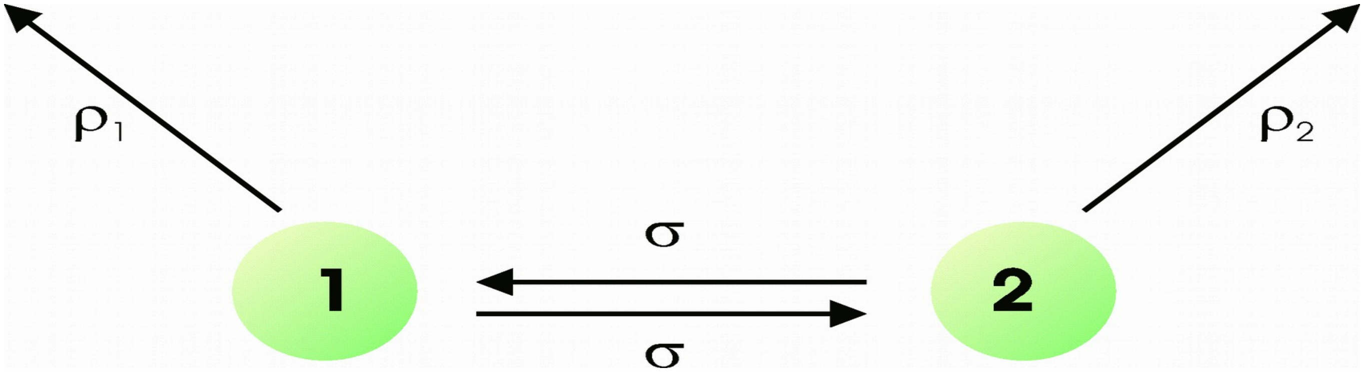


180 I_x

Averages relaxation



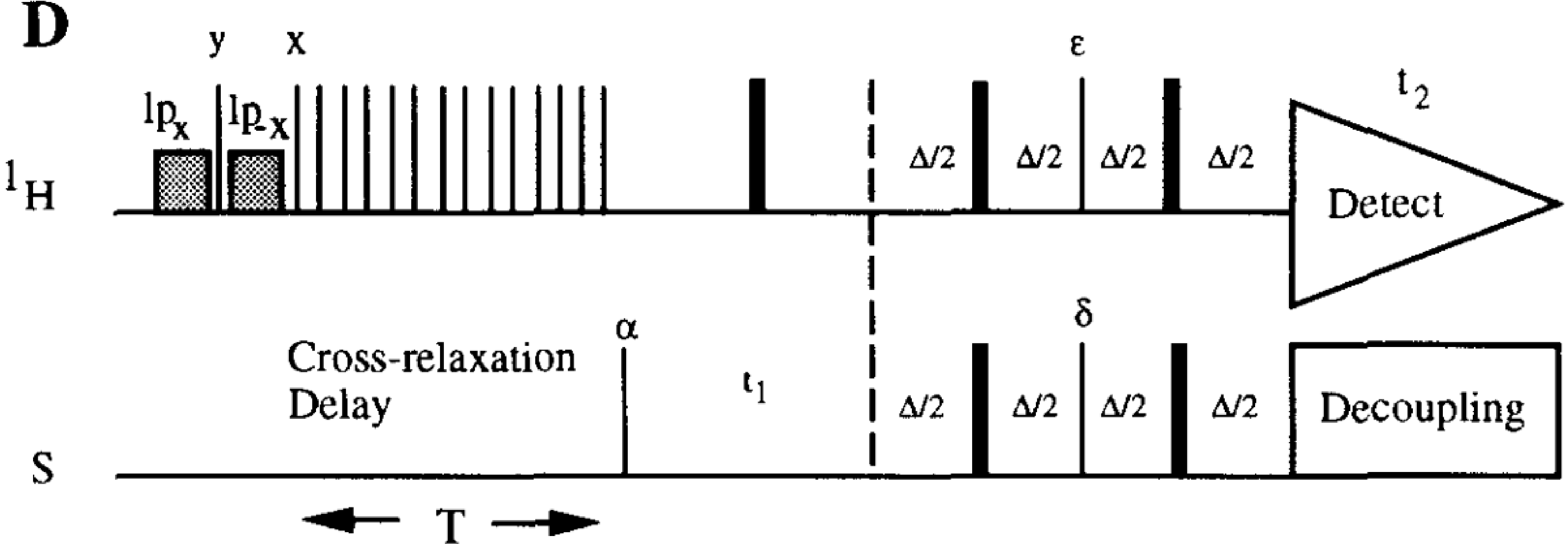
Heteronuclear NOE



$$\frac{dM_{1z}}{dt} = -\rho_1 \Delta M_{1z} - \sigma \Delta M_{2z}$$

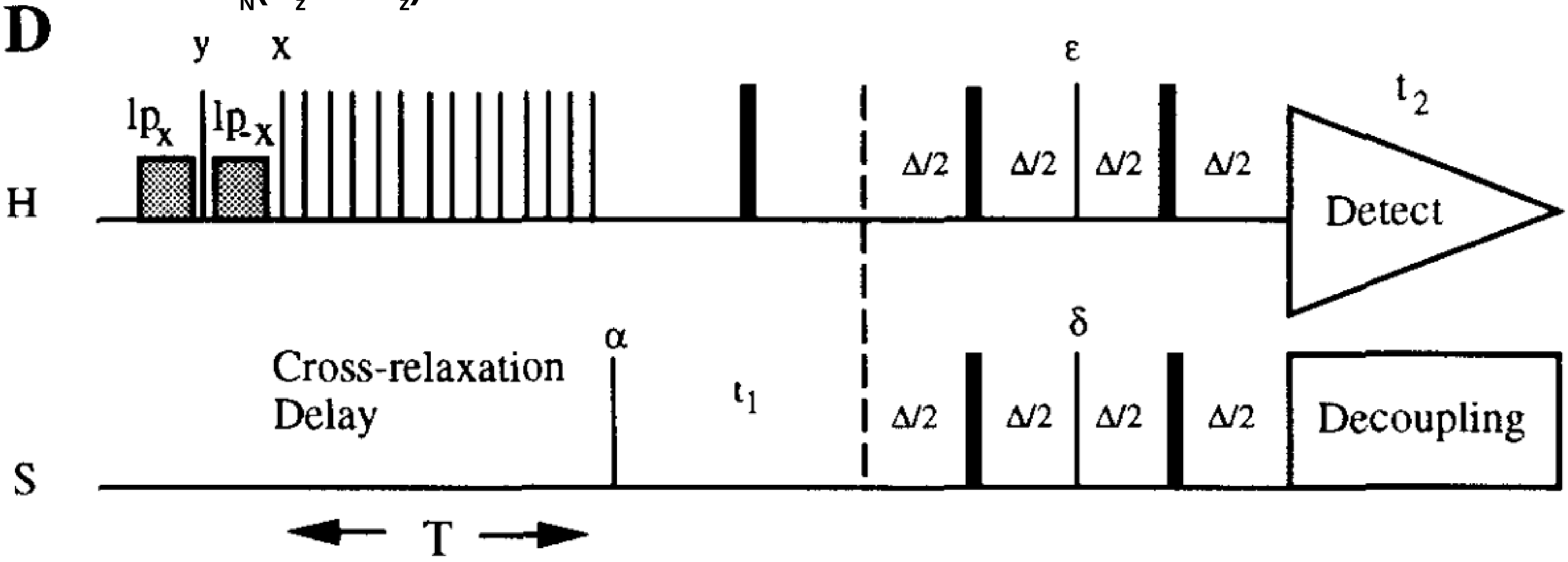
$$\frac{dM_{2z}}{dt} = -\sigma \Delta M_{1z} - \rho_2 \Delta M_{2z}$$

$R_N(H_z^N \rightarrow N_z)$



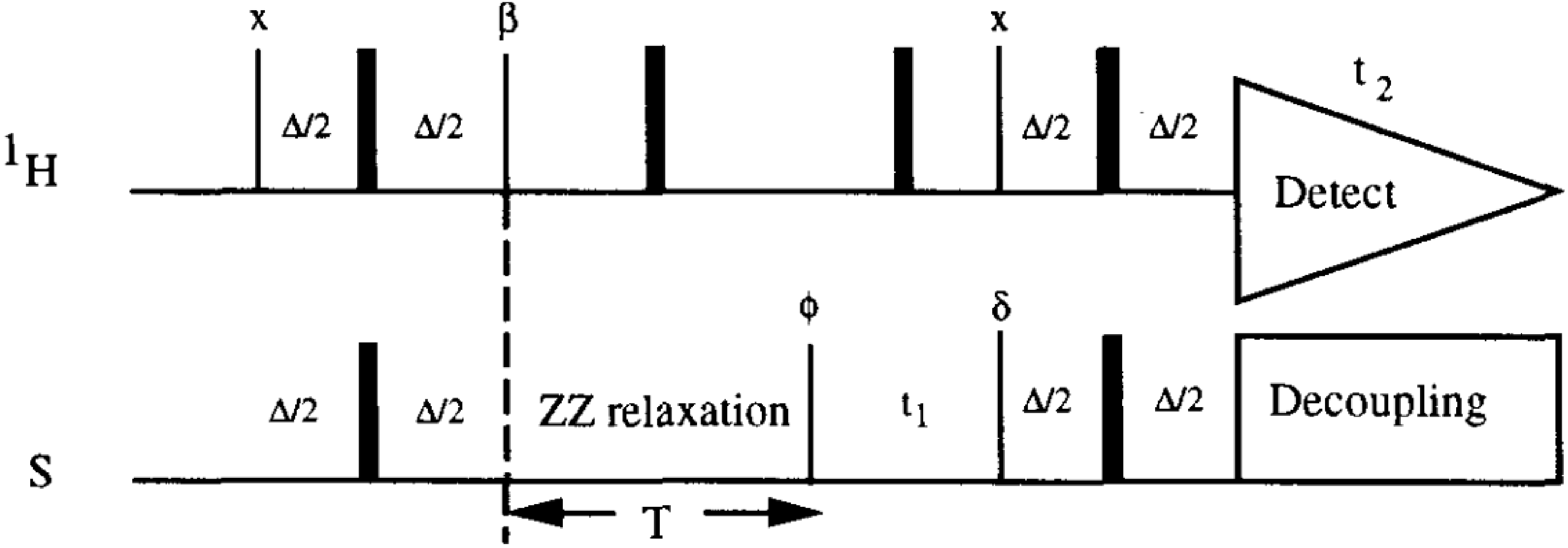
$$\eta = \frac{I_{sat} - I_{eq}}{I_{eq}} = \frac{\gamma_I}{\gamma_S}\,\frac{R_S(S_z \leftrightarrow I_z)}{R_S(S_z)}$$

$R_N(H_z^N \rightarrow N_z)$



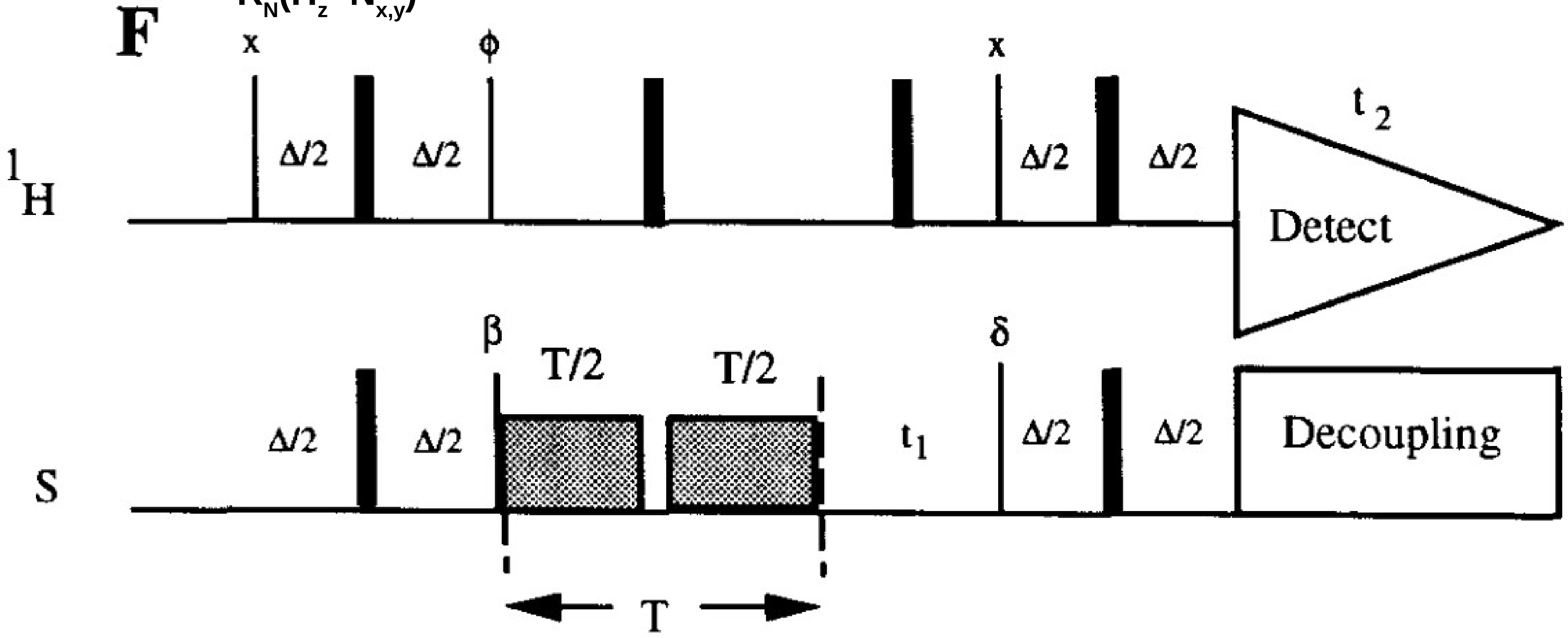
- I_{sat} with T = several seconds
- T_{eq} with T=0
- Solvent saturation can complicate this measurement- especially if relaxation delay too short
  - Amides remain partially saturated and underestimate the the equilibrium S_z
  - Relaxation delays rely on S spin polarization – longer relaxation delay required

E $R_N(H_z^N N_z)$

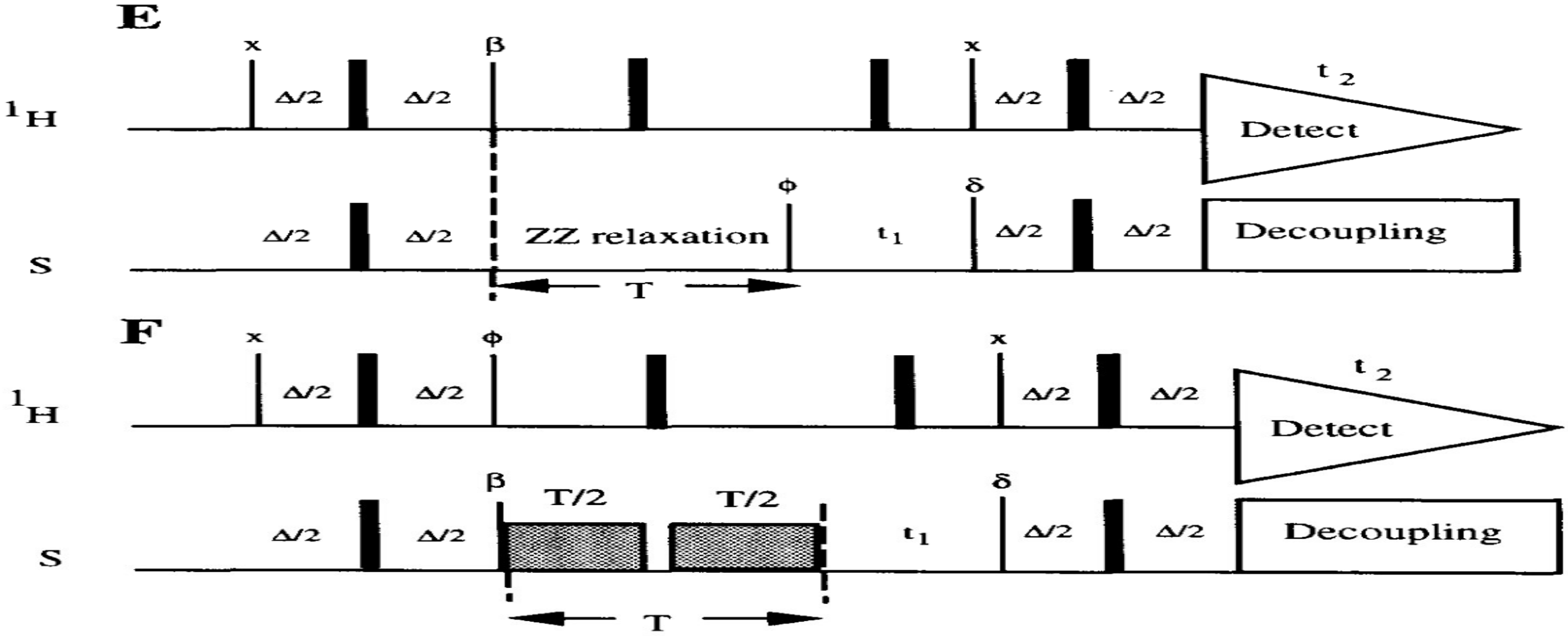


$$\frac{d(2I_zS_z)}{dt} = -R_{IS}(2I_zS_z)\left\langle 2I_zS_z \right\rangle - R_{IS}(2I_zS_z \leftrightarrow S_z)\left\langle S_z \right\rangle - \sum_i \sigma_L^i \left\langle 2A_z^1 S_z \right\rangle$$

$R_N(H_z^N N_{x,y})$

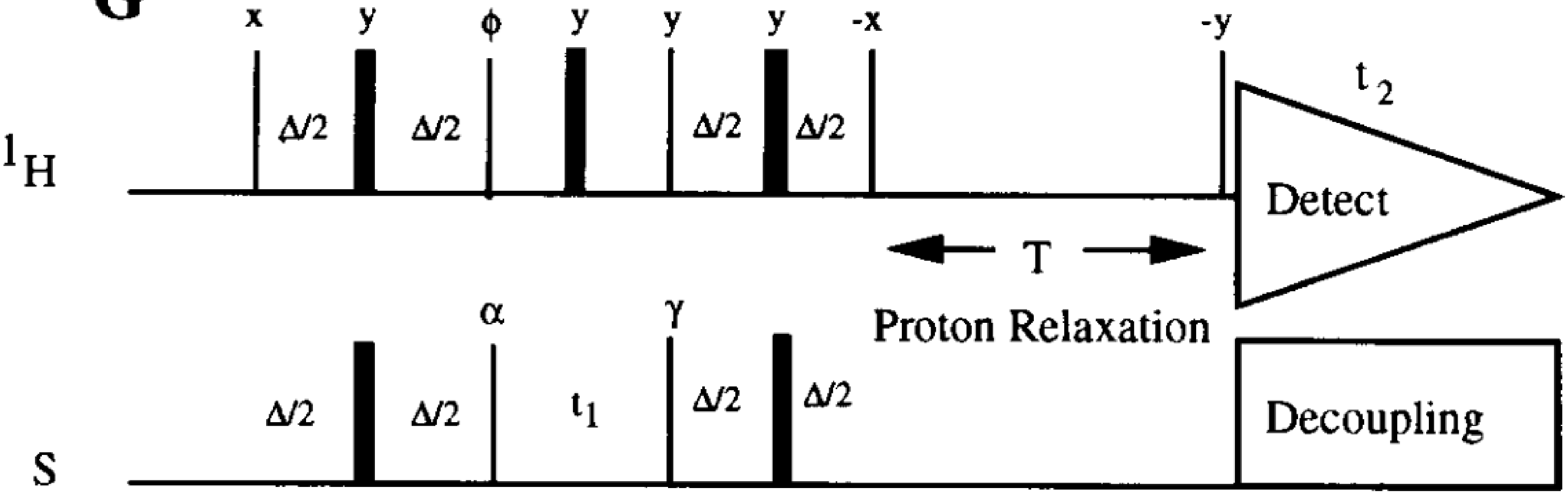


$$\frac{d(2I_zS_x)}{dt} = -R_{1S}(2I_zS_x)\left\langle 2I_zS_x \right\rangle - R_{IS}(2I_zS_x \leftrightarrow S_x)\left\langle S_x \right\rangle - \sum_i \sigma_L^i \left\langle 2A_z^1 S_x \right\rangle$$

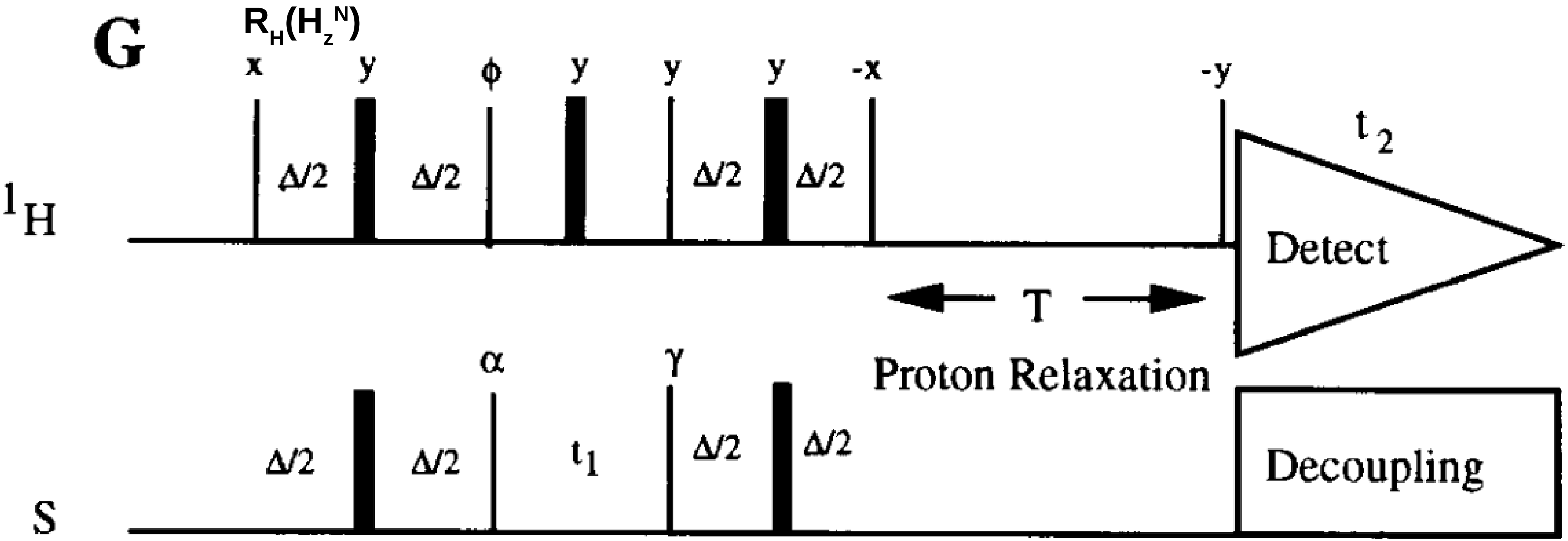


- Rates significantly faster than single operators (S_z, S_x) due to H relaxation
- Proton-proton cross relaxation couples the relaxation to with spins external to IS
  - Essentially driven by $J_{IAi}(0)$
- CSA-DD cross correlation causes cross-relaxation to the in-phase components (I_zS_z->S_x)
  - Generally these rates are significantly smaller than the antiphase rates

G $R_H(H_z^N)$



$$\frac{d\left(I_z - I_z^0\right)}{dt} = -R_I(I_z)\left\langle I_z - I_z^0\right\rangle - R_{IS}(I_z \leftrightarrow S_z)\left\langle S_z - S_z^0\right\rangle - \sum_i \sigma_L^i \left\langle A_z - A_z^0\right\rangle$$



- Proton I_z has a significant effect on the auto- and cross-relaxation rates of the anti-phase states
- Contains IS D-D interaction and many proton-proton D-D interactions
- Heteronuclear D-D relaxation is smaller than homonuclear D-D
- Reduce proton-proton DD cross relaxation
  - only S bound H inverted during relaxation (all non-bound H flipped to +z)
  - S bound H are inverted after S frequency labeling
  - Measure buildup in linear region (short times)

$$
\begin{aligned}
I_x S_x &= (I^+ + I^-) * (S^+ + S^-) \\
&= I^+ S^+ + I^+ S^- + I^- S^+ + I^- S^-
\end{aligned}
$$

Measurement of multiple quantum is an average of double and zero quantum relaxation
Proton-proton DD strong J(0) causes rapid decay
In general, difficult to measure