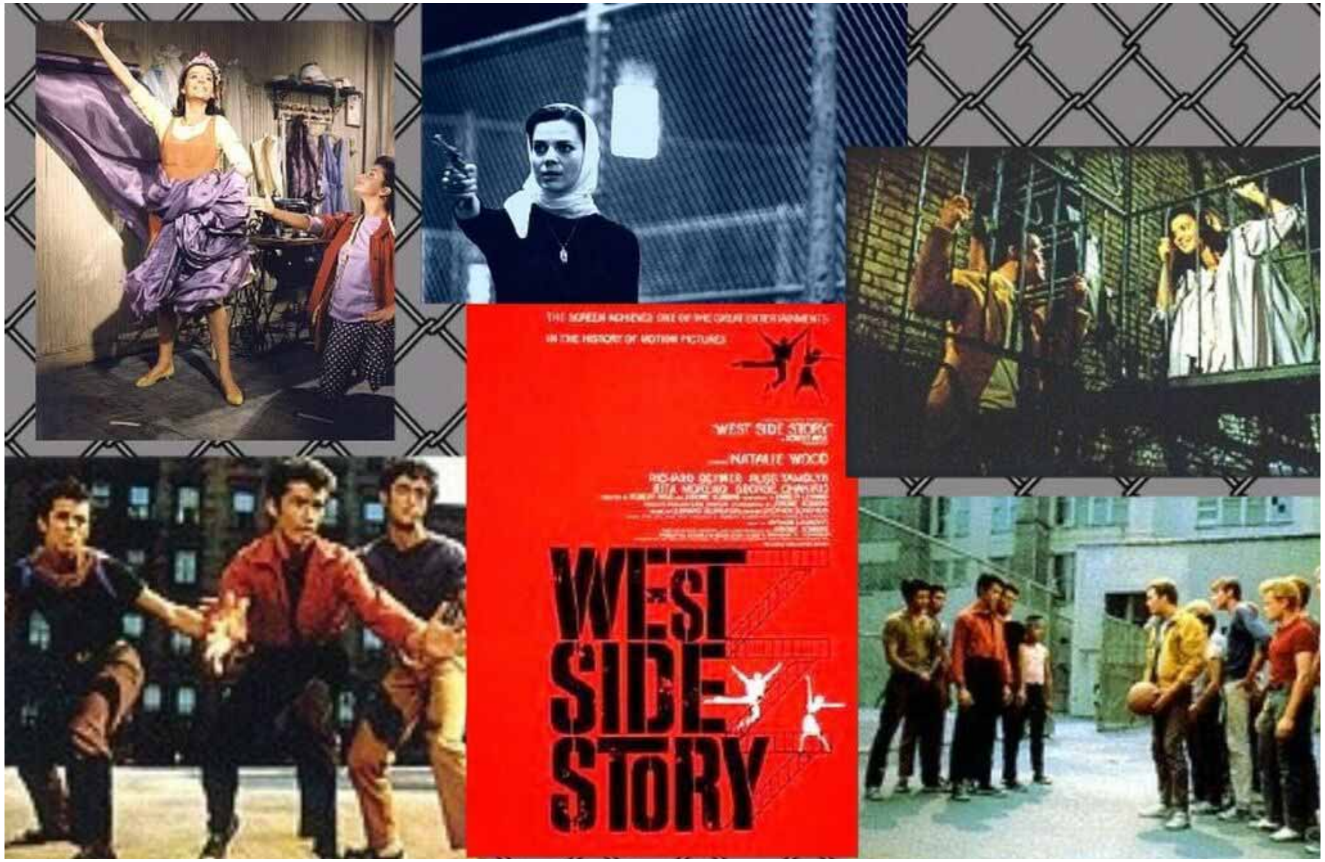
Electron Spin Resonance

Advanced MRI 第「亂」講
B91901010 電機四 油嘟嘟

West Side Story...



我買了今天晚上的票....希望可以來得及。

Outline

- Principle to NOE – Solomon Equation
- Imaging < PEDRI, FC-PEDRI
Pulsed ESR, CW-ESR, ESRI
- Other Applications – NOESY

Before we started

- 古人有云：前人種樹，後人乘涼。
- 俗話說的好：子孫不肖，富不過三代 XD
- 聯考物理成績—53.8。(目前沒問到任何聽到電機系的學生分數比我低)
- So........有說不清楚的地方，歡迎立刻發問。

電子也有spin

- 電子的 **γ** = -28.06GHz/T
- 計算一下吧，在1.5T之下：

  ω_{Nu}=63.87MHz、 ω_E=42.09GHz

  GSM 900MHz & 1800MHz
- 太高頻了，怎麼做影像？
- 如果能激發電子，然後讓它轉移到核身上那不就太棒了。

Outline

- Principle to NOE – Solomon Equation
- Imaging < PEDRI, FC-PEDRI / Pulsed ESR, CW-ESR, ESRI
- Other Applications – NOESY

Solomon Equation

- Physical Review Vol. 99 (1955)
- The relaxation of spin I is not only proportional to the states of the spin I itself.
- When existing other nearby spins, the states of those spins also have influence on I spin.

Solomon Equation (for 2 spins)

減少量正比於自己(I)的濃度差

$$\frac{d(I_Z - I_Z^0)}{dt} = -R_I \boxed{(I_Z - I_Z^0)} - \sigma_{IS} \boxed{(S_Z - S_Z^0)}$$

也跟S的濃度差有關係

R_I : self relaxation constant

σ_{IS} : cross relaxation constant

沒問題....那開始推導公式吧

Rev - Chemical Reaction

- Mono-direction & single step:

$$A \xrightarrow{k_1} B \qquad \frac{d[A]}{dt} = -\boxed{k_1[A]}$$

和自身濃度
成正比

PS 其最終會decay到0

- Bi-direction & single step:

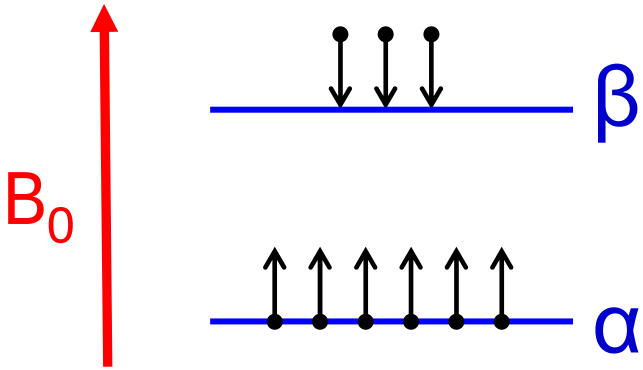
來自B的
補充量

$$A \xleftrightarrow{k_1, k_{-1}} B \qquad \frac{d[A]}{dt} = -k_1[A] + \boxed{k_{-1}[B]}$$

For one spin

- At thermal equilibrium:

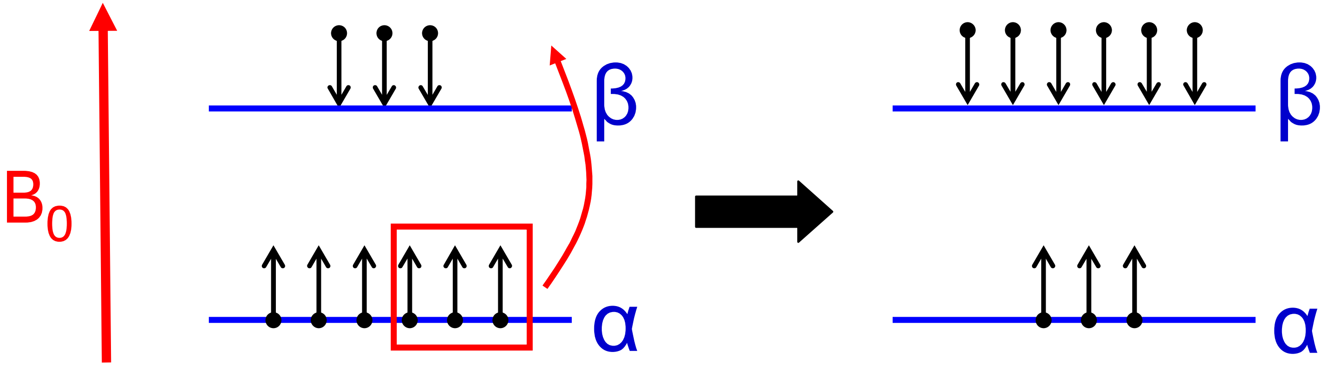
(i.e. Boltzmann distribution)



$$M_Z = A(N_\alpha - N_\beta) = 3A$$

For one spin (Cont.)

- When some excitation :

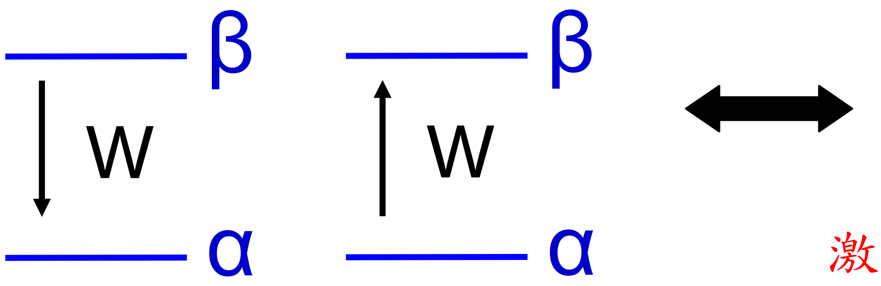


開始回復，α必須要回復到6個，β必須要減少到3個

$$M_Z = A(N_\alpha - N_\beta) = -3A$$

For one spin (Cont.)

- 電子躍遷的機率(W)是不受狀態的數量影響。



$$\alpha \xleftrightarrow{W,W} \beta$$

激發後的α和原本的差距，這才是要恢復的量。

The change rate of α is: $$\frac{dN_\alpha}{dt} = -W\boxed{(N_\alpha - N_\alpha^0)}+W(N_\beta - N_\beta^0)$$

The change rate of β is: $$\frac{dN_\beta}{dt} = +W(N_\alpha - N_\alpha^0)-W(N_\beta - N_\beta^0)$$

For one spin (Cont.)

$$M_Z = A(N_\alpha - N_\beta) \Rightarrow \frac{dM_Z}{dt} = A(\frac{dN_\alpha}{dt} - \frac{dN_\beta}{dt})$$

$$\left\{ \begin{aligned} \frac{dN_\alpha}{dt} &= -W(N_\alpha - N_\alpha^0) + W(N_\beta - N_\beta^0) \\ \frac{dN_\beta}{dt} &= +W(N_\alpha - N_\alpha^0) - W(N_\beta - N_\beta^0) \end{aligned} \right\}$$

太好了，直接帶入上式吧

$$\begin{aligned} \frac{dM_Z}{dt} &= A(\frac{dN_\alpha}{dt} - \frac{dN_\beta}{dt}) \\ &= A(-W(N_\alpha - N_\alpha^0) + W(N_\beta - N_\beta^0) - W(N_\alpha - N_\alpha^0) + W(N_\beta - N_\beta^0)) \\ &= -2AW((N_\alpha - N_\alpha^0) - (N_\beta - N_\beta^0)) \\ &= -2W(A\boxed{N_\alpha - N_\beta} - A\boxed{N_\alpha^0 - N_\beta^0}) \\ &= -2W(M_Z - M_Z^0) \end{aligned}$$

熱平衡時的磁場

現在的磁場

For one spin (Cont.)

- What does that remind you of?

$$\frac{dM_Z}{dt} = -2W(M_Z - M_Z^0) \quad \Longleftrightarrow \quad \frac{dM_Z}{dt} = -\frac{(M_Z - M_Z^0)}{T_1}$$

T_1=1/2W, spin lattice relaxation time

- 對於one spin而言，就是指數回復。
- 老師第一堂課說過：T_1會受到很多因素影響，都是來自W的改變。

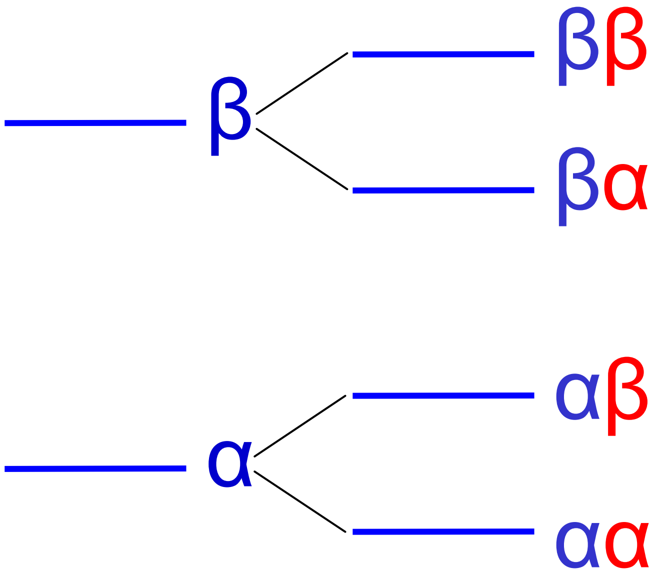
Two spins system (I & S)

- 若分子有兩個spins — 排列組合。
- 取名子 — 前面的是I、後面的是S。

S spin

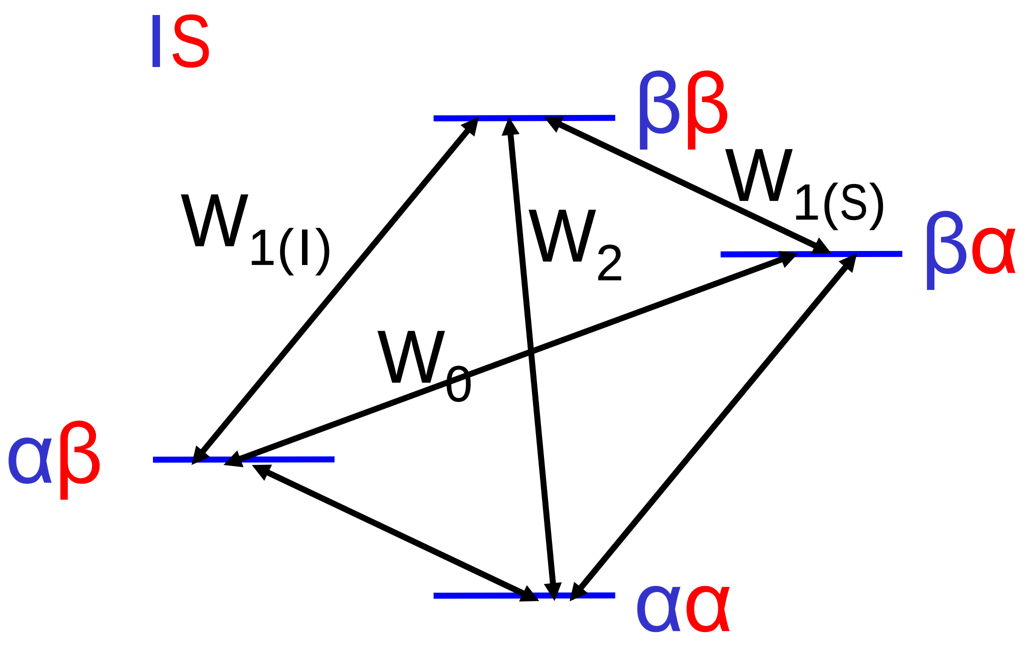
I spin

	α	β
α	αα	αβ
β	βα	ββ



Two spins system (Cont.)

- 有4種relaxation pathway。



W_0: $\Delta m = 0$

W_1: $\Delta m = 1$ or -1

W_2: $\Delta m = 2$ or -2

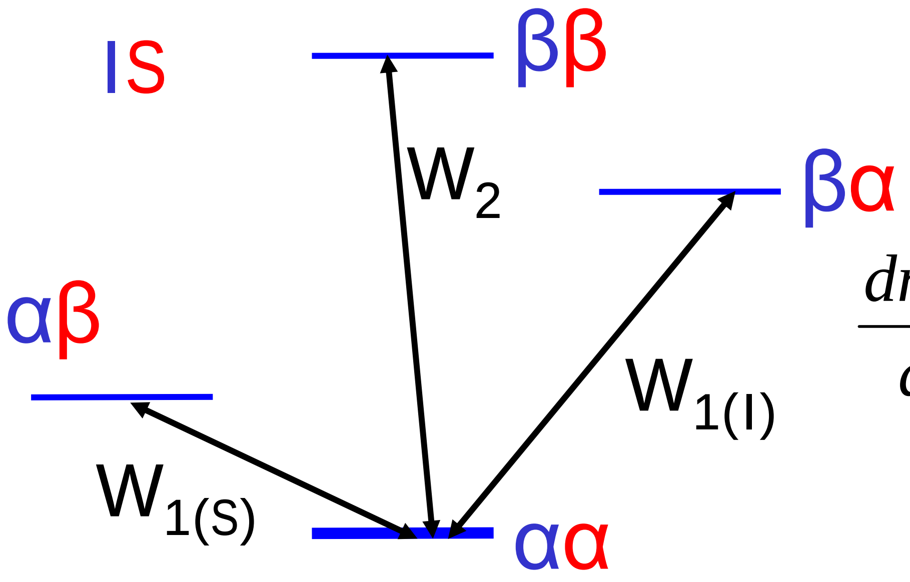
$\Delta m = \Delta m_s + \Delta m_I$

(總角動量變化量)

Selection Rule

- 一般而言，只有$\Delta m= 1 ,0, -1$才可以發生。
- Via dipole-dipole interaction, W_2 and W_0 is possible.
- What is dd interaction?(Later on)

Two spins system (Cont.)



The change rate of αα is:

變化率正比於從αα的量

$$\frac{dn_{\alpha\alpha}}{dt} = \boxed{-W_{1(S)}n_{\alpha\alpha} - W_{1(I)}n_{\alpha\alpha} - W_2 n_{\alpha\alpha}}$$

$$\boxed{+W_{1(S)}n_{\alpha\beta} + W_{1(I)}n_{\beta\alpha} + W_2 n_{\beta\beta}}$$

來自於其他state的補充

PS: $n_{\alpha\alpha} = (N_{\alpha\alpha} - N_{\alpha\alpha}^0)$ →數量差

Two spins system (Cont.)

$$\frac{dn_{\alpha\alpha}}{dt} = -W_{1(S)}n_{\alpha\alpha} - W_{1(I)}n_{\alpha\alpha} - W_2 n_{\alpha\alpha} + W_{1(S)}n_{\alpha\beta} + W_{1(I)}n_{\beta\alpha} + W_2 n_{\beta\beta}$$

$$\frac{dn_{\alpha\beta}}{dt} = -W_{1(S)}n_{\alpha\beta} - W_{1(I)}n_{\alpha\beta} - W_0 n_{\alpha\beta} + W_{1(S)}n_{\alpha\alpha} + W_{1(I)}n_{\beta\beta} + W_0 n_{\beta\alpha}$$

$$\frac{dn_{\beta\alpha}}{dt} = -W_{1(S)}n_{\beta\alpha} - W_{1(I)}n_{\beta\alpha} - W_0 n_{\alpha\beta} + W_{1(S)}n_{\beta\beta} + W_{1(I)}n_{\alpha\alpha} + W_0 n_{\alpha\beta}$$

$$\frac{dn_{\beta\beta}}{dt} = -W_{1(S)}n_{\beta\beta} - W_{1(I)}n_{\beta\beta} - W_0 n_{\beta\beta} + W_{1(S)}n_{\beta\alpha} + W_{1(I)}n_{\alpha\beta} + W_0 n_{\alpha\alpha}$$

革命尚未成功！

Solomon Equation (Revisit)

減少量正比於自己(I)的濃度差

$$\frac{d(I_Z - I_Z^0)}{dt} = -R_I \boxed{(I_Z - I_Z^0)} - \sigma_{IS} \boxed{(S_Z - S_Z^0)}$$

也跟S的濃度差有關係

R_I : self relaxation constant

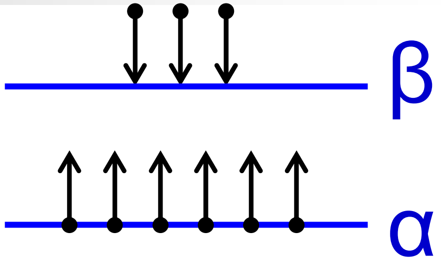
σ_{IS} : cross relaxation constant

什麼是I_z？什麼是S_z？還沒有提到啊？

Magnetization vector

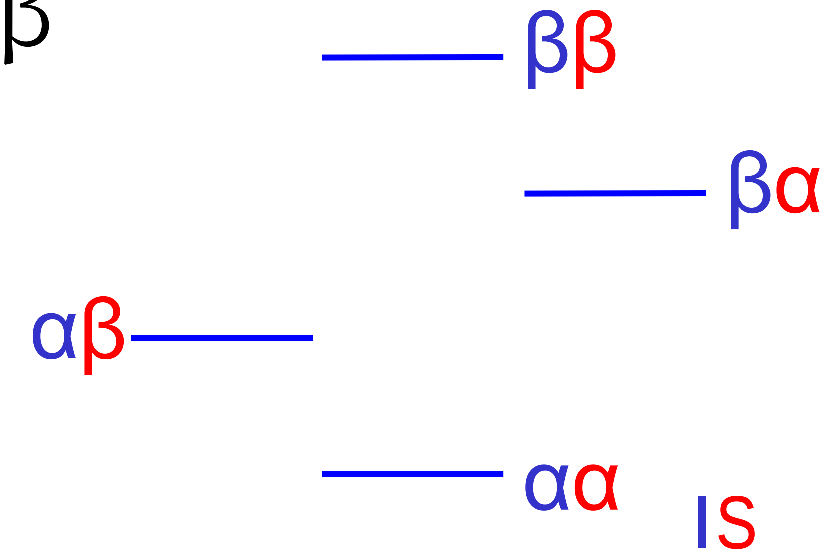
- 磁化向量 $M_Z = A(n_\alpha - n_\beta)$
- When 2 spins,

  M = total α - total β



$$i_Z = A(n_{\alpha\alpha} + n_{\alpha\beta} - n_{\beta\alpha} - n_{\beta\beta})$$

$$s_Z = A(n_{\alpha\alpha} + n_{\beta\alpha} - n_{\alpha\beta} - n_{\beta\beta})$$



PS 其實這是來自量子力學

最沒有技巧的時間到了

$$\frac{di_Z}{dt} = \frac{dn_{\alpha\alpha}}{dt} + \frac{dn_{\alpha\beta}}{dt} - \frac{dn_{\beta\alpha}}{dt} - \frac{dn_{\beta\beta}}{dt}$$

$$= \text{....加加減減好複雜....}$$

$$= 2(n_{\beta\beta} - n_{\alpha\alpha})(\mathrm{W}_{1(\mathrm{I})} + \mathrm{W}_2) + 2(n_{\beta\alpha} - n_{\alpha\beta})(\mathrm{W}_{1(\mathrm{I})} + \mathrm{W}_2)$$

$$= \text{....代換也很複雜....}$$

$$= -(i_Z + s_Z)(\mathrm{W}_{1(\mathrm{I})} + \mathrm{W}_2) - (i_Z - s_Z)(\mathrm{W}_{1(\mathrm{I})} + \mathrm{W}_0)$$

$$= -i_Z \boxed{(\mathrm{W}_0 + 2\mathrm{W}_{1(\mathrm{I})} + \mathrm{W}_2)} - s_Z \boxed{(\mathrm{W}_2 - \mathrm{W}_0)}$$

↑ R_I (self relaxation constant)

↑ σ_{IS} (cross relaxation constant)

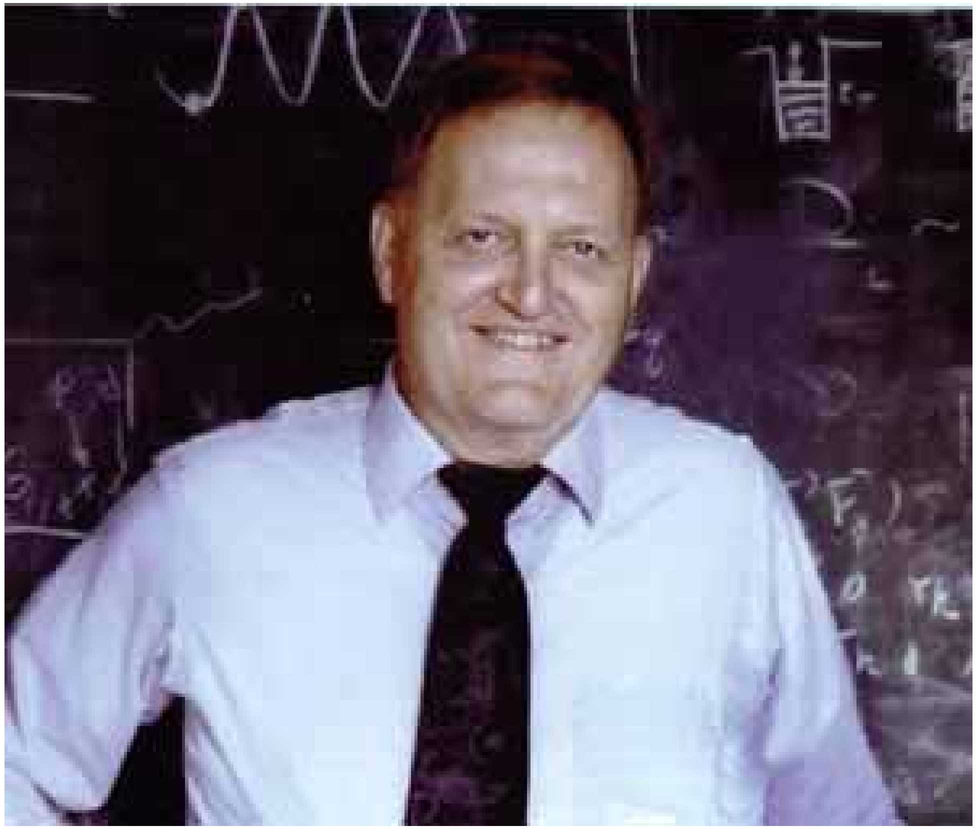
可喜可賀

都會影響變化率

$$\frac{d(I_Z - I_Z^0)}{dt} = -R_I(I_Z - I_Z^0) - \boxed{\sigma_{IS}(S_Z - S_Z^0)}$$

- In NMR ^{13}C-^{1}H, we saturate ^{1}H when observing ^{13}C.
- In PEDRI, we saturate electron spin to enhance ^{1}H.

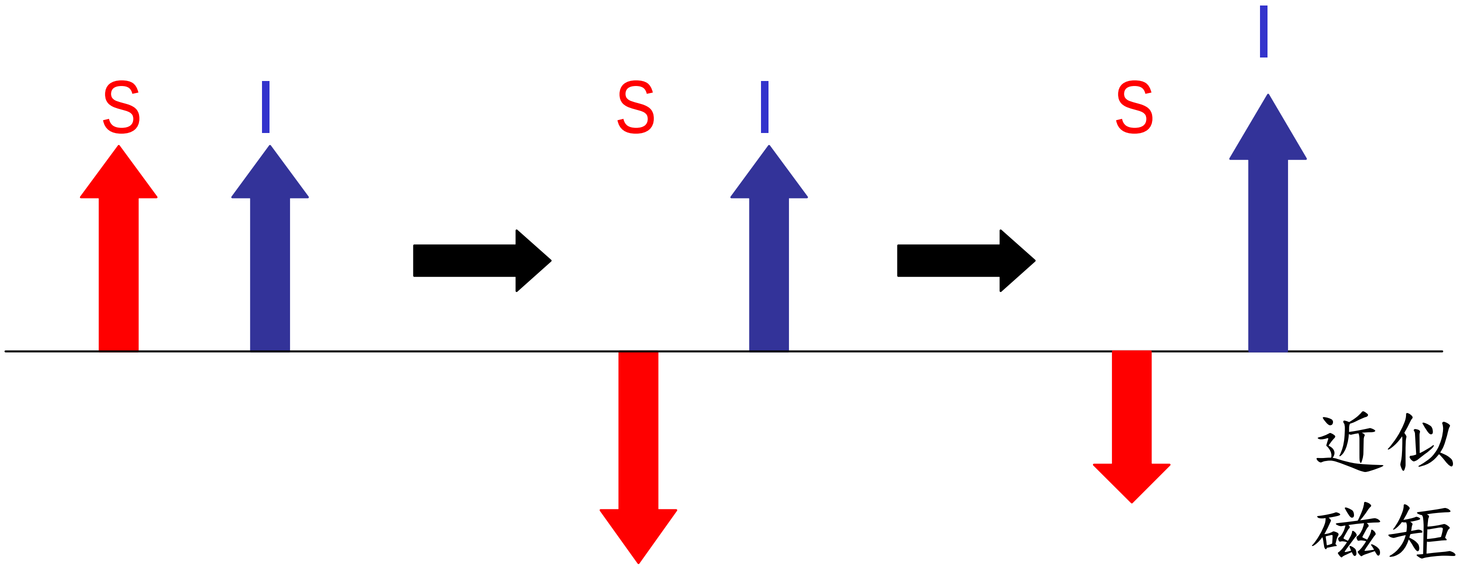
Nuclear Overhauser Effect



Professor Albert W. Overhauser (1925 ~)

Cross Relaxation Constant

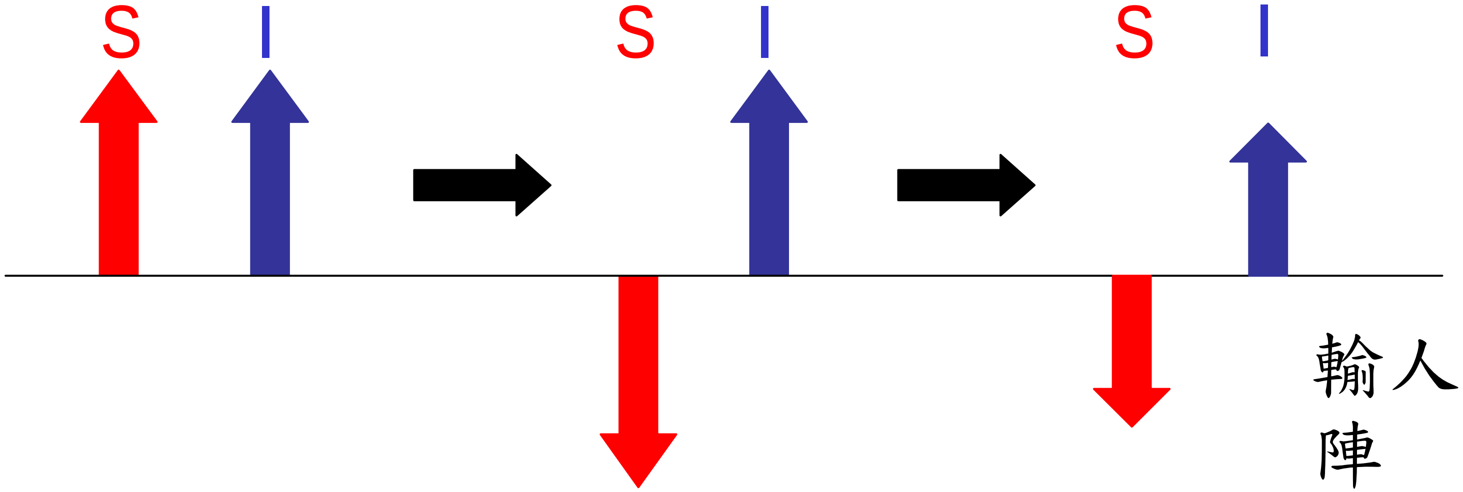
- 如果W_2 dominant, $\sigma_{IS}>0$
- $n_{\alpha\alpha}$會增加 — I_z會增加。 (positive NOE enhancement)



近似於總磁矩守恆

Cross Relaxation Constant

- 如果W_0 dominant, $\sigma_{IS}<0$
- $n_{\beta\alpha}$會增加 — I_z會減少。
  (negative NOE enhancement)

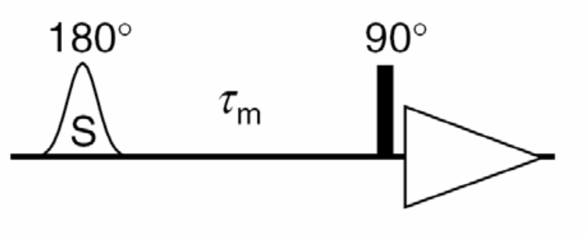


輸人不輸陣

結束了嗎？當然還沒有

Let's do some math

- IV: $I_z(0)=I_z^0$, $S_z(0)= -S_z^0$



$$\frac{d(I_Z-I_Z^0)}{dt}=-R_I(I_Z-I_Z^0)-\sigma_{IS}(S_Z-S_Z^0)$$

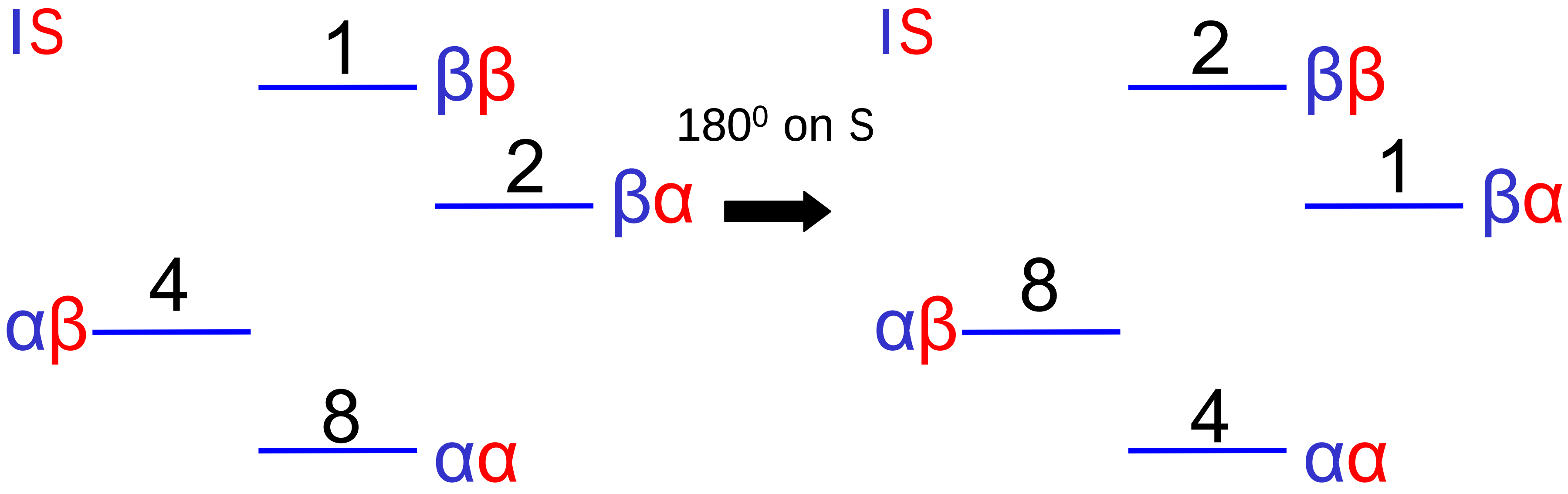
$$=-R_I(I_Z^0-I_Z^0)-\sigma_{IS}(-S_Z^0-S_Z^0)$$

$$=2\sigma_{IS}S_Z^0$$

- Case 1: S回復的很快 (i.e. τ_m太長)
→什麼改變都沒有。

Case 2:假設S spin不會回復…

- IV: $I_z(0)=I_z^0$, $S_z(0)= -S_z^0$



IS

1 ββ

2 βα

αβ 4

8 αα

180^0 on S

IS

2 ββ

1 βα

αβ 8

4 αα

$I_z=9$, $S_z=5$

$I_z=9$, $S_z=-5$

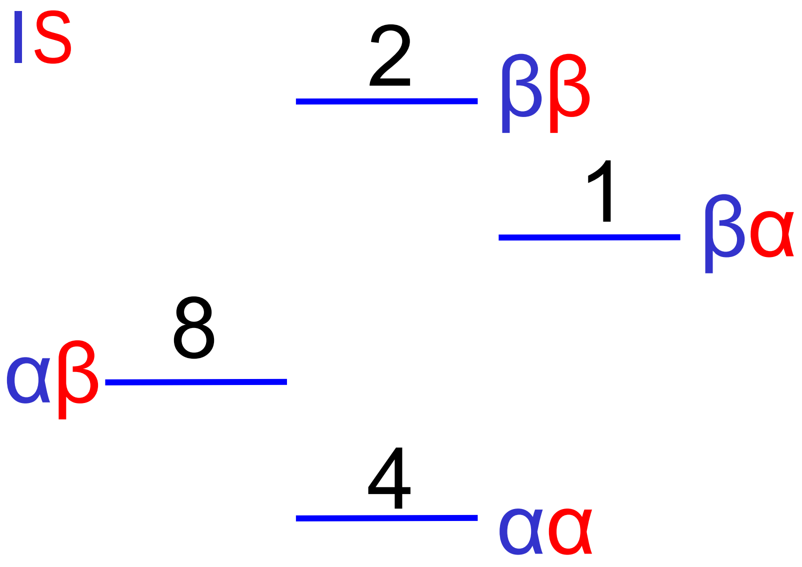
Case 2:假設W_{1s}很小...

- 計算I_Z的回復率:

$$\frac{d(I_Z - I_Z^0)}{dt} = 2\sigma_{IS} S_Z^0 = \boxed{10\sigma_{IS}} > 0$$

I_Z會隨時間增加

i.e. 就算沒有動到I_Z，也會讓其產生變化。



I_z=9, S_z=-5

於是I_Z就增加了

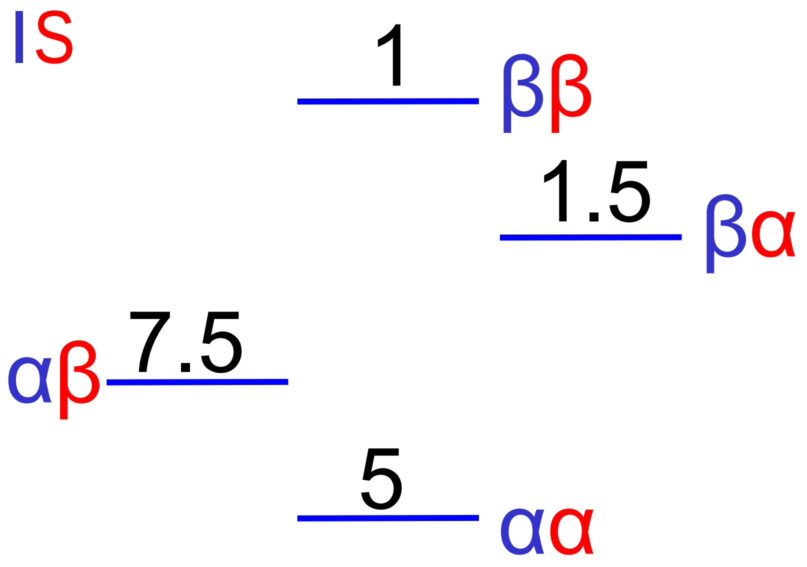
- 計算I_Z的回復率:

$$\frac{d(I_Z - I_Z^0)}{dt}$$

$$= -R_I(I_Z - I_Z^0) - \sigma_{IS}(S_Z - S_Z^0)$$

$$= -R_I(10-9) - \sigma_{IS}(-2-5)$$

$$= -R_I + 7\sigma_{IS} < 10\sigma_{IS}$$

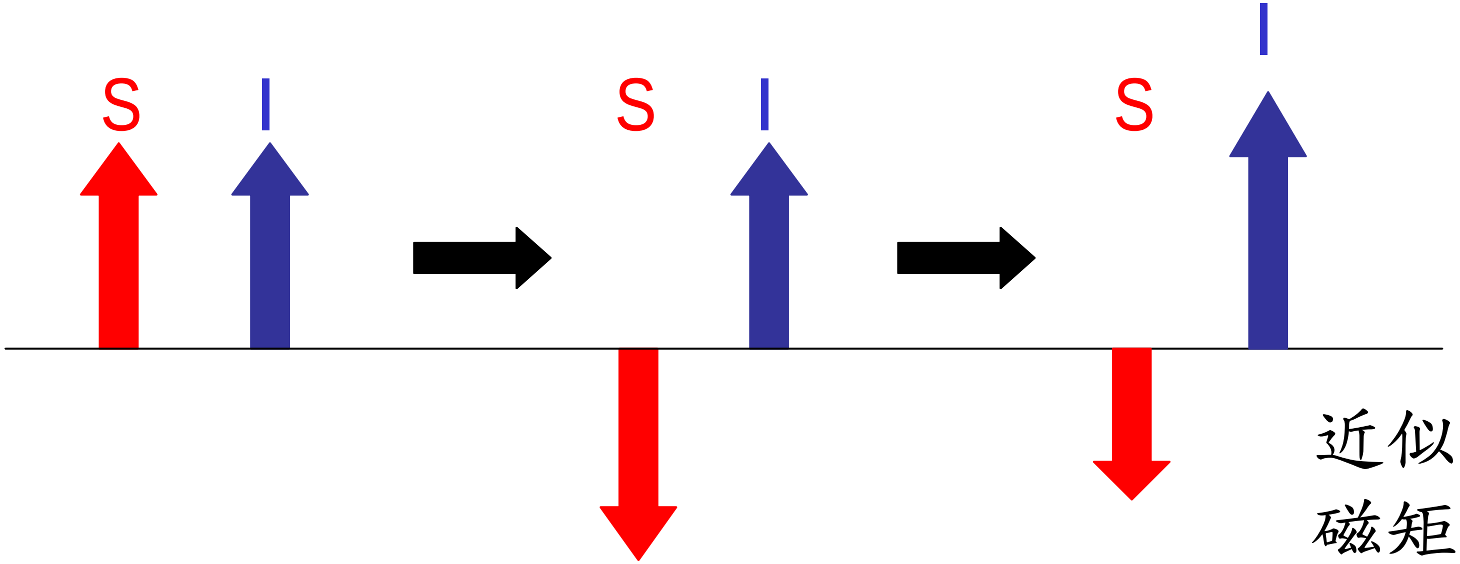


隨著I_Z的增加，變化率開始下降了

I_z=10, S_z=-2

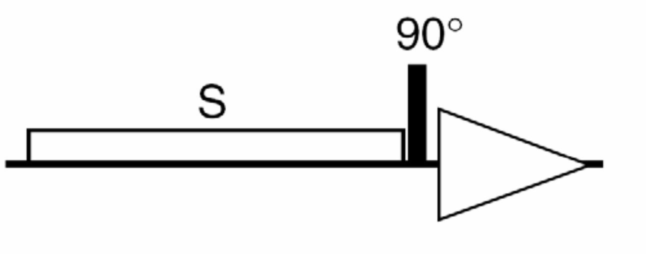
Cross Relaxation Con. (Revisit)

- 如果W_2 dominant, $\sigma_{IS}>0$
- $n_{\alpha\alpha}$會增加 — I_z會增加。
  (positive NOE enhancement)



近似於總
磁矩守恆

Saturation pulse



- 給SAT pulse，測量Steady State的情況。

$$\frac{d(I_Z - I_Z^0)}{dt}\Big|_{ss} = -R_I(I_Z - I_Z^0) - \sigma_{IS}(0 - S_Z^0) = 0$$

$$I_{Z,SS} = \frac{\sigma_{IS}}{R_I}(S_Z^0) + I_Z^0$$

Steady State Equation

Wehrli p.3

Def: NOE enhancement factor

$$\eta_{SS} = \frac{\Delta I_Z}{I_Z^0} = \frac{\sigma_{IS}}{R_I}\frac{S_Z^0}{I_Z^0}$$

NOE enhancement factor

- 不像？帶入前面定義的值就好啦！

R_I (self relaxation constant) = $W_2+2W_1+W_0$

σ_{IS} (cross relaxation constant) = W_2-W_0

$$\eta_{SS} = \frac{\Delta I_Z}{I_Z^0} = \frac{\sigma_{IS}}{R_I}\frac{S_Z^0}{I_Z^0} = \frac{W_2 - W_0}{W_2 + 2W_1 + W_0}\frac{S_Z^0}{I_Z^0}$$

還沒有完，接下來要找W！

Transition Rate

- W: Transition Rate，類似於化學反應的反應速率。
- 從一個狀態轉變到另外一個狀態的機率。

$$W_{ij} = M_{ij} \times J(\omega_{ij})$$

M_{ij} :molecular factor

$J(\omega_{ij})$: spectral density

- 這又是什麼鬼？ 找一個東西來比喻好了。

化學反應速率 k

- Mono-direction & single step:

$$A \xrightarrow{k_1} B \qquad \frac{d[A]}{dt} = -k_1[A]$$

- Arrhenius equation:

$$k = Ae^{-\frac{E_a}{kT}}$$

跟化學反應的
能量差有關係

比例常數，也就是M_{ij}

Transition Rate (Cont.)

- molecular factor M_{ij}
- Different relaxation mechanism

  β -> α : allowed transition

  β β -> α α : via dd relaxation
- Molecular geometry - distance

Relaxation mechanism

- Molecular factor 決定於relaxation方式。
- dd interaction : one create the field and one experience, reciprocally

$$M_{ij} \propto (\gamma_i^2 \gamma_j^2) \frac{1}{r_{ij}^6}$$

這是距離 請注意!!

Transition Rate (Cont.)

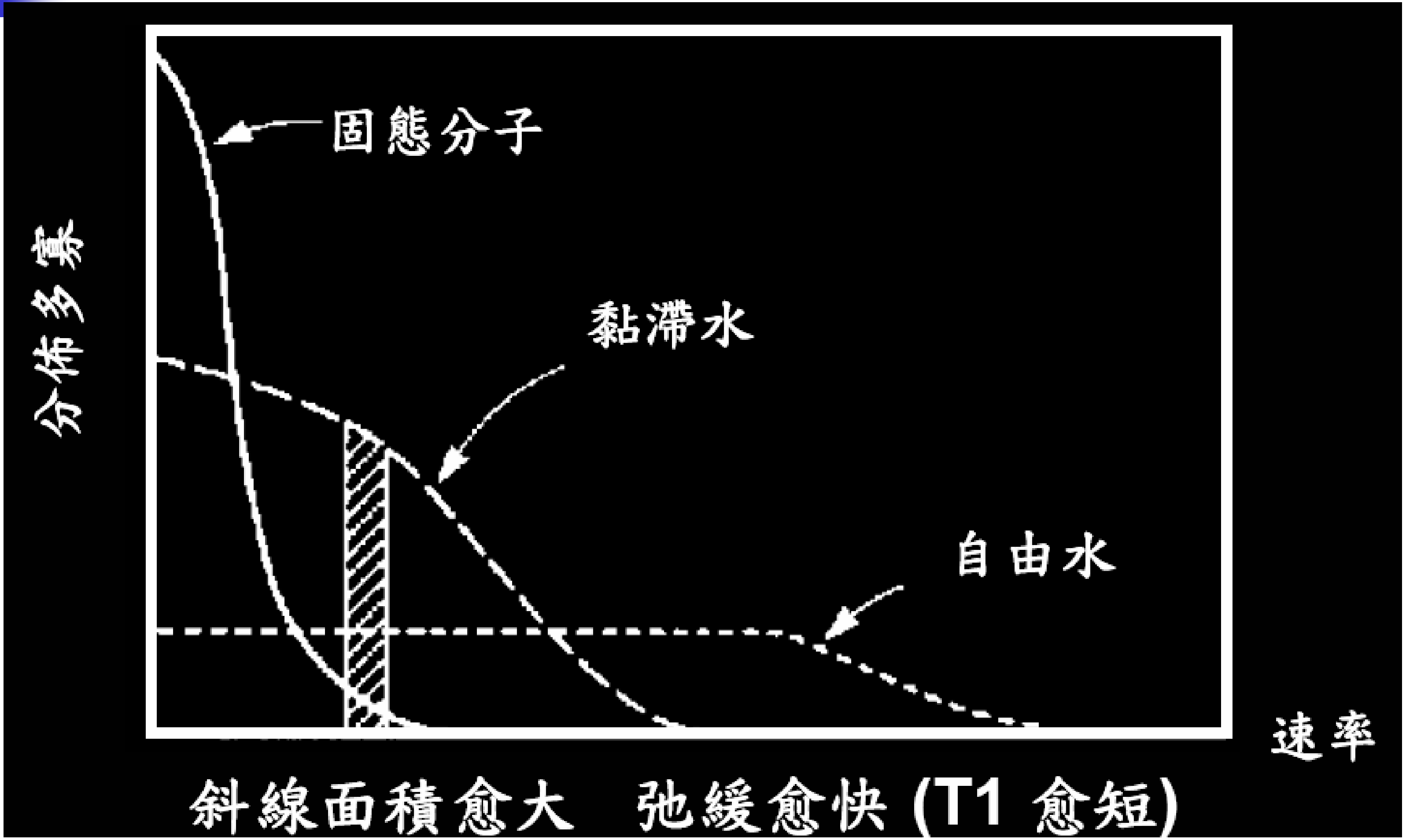
- Spectral density J(ω_{ij})
  amount of molecular motion at ω_{ij}
- 在spin特定頻率的運動 → 產生某個特定的電磁波 → 改變特定能階W

$$J(\omega_{ij}) \propto \frac{\tau_C}{1+\omega_I^2\tau_C^2}$$

τ_c: correlation time

- 似曾相識？

AMRI 第一講



斜線面積愈大　弛緩愈快 (T1 愈短)

終於，又到了代入的時間

$$W_{ij} = AM_{ij}J(\omega_{ij})$$

$$W_1(\omega_I) = A\times\gamma_I^2\gamma_S^2\frac{1}{r_{IS}^6}\times\frac{\tau_C}{1+\omega_I^2\tau_C^2}$$

Wehrli p3

$$\Rightarrow W_2(\omega_I+\omega_S) = B\times\gamma_I^2\gamma_S^2\frac{1}{r_{IS}^6}\times\frac{\tau_C}{1+(\omega_I+\omega_S)^2\tau_C^2}$$

$$W_0(\omega_I-\omega_S) = C\times\gamma_I^2\gamma_S^2\frac{1}{r_{IS}^6}\times\frac{\tau_C}{1+(\omega_I-\omega_S)^2\tau_C^2}$$

可喜可賀

- 全部代入，經過大亂鬥後：

$$\eta_{SS} = \frac{\sigma_{IS}}{R_I} = \frac{W_2 - W_0}{W_2 + 2W_1 + W_0} = \frac{\gamma_S}{2\gamma_I} = \frac{659}{2} = 330$$

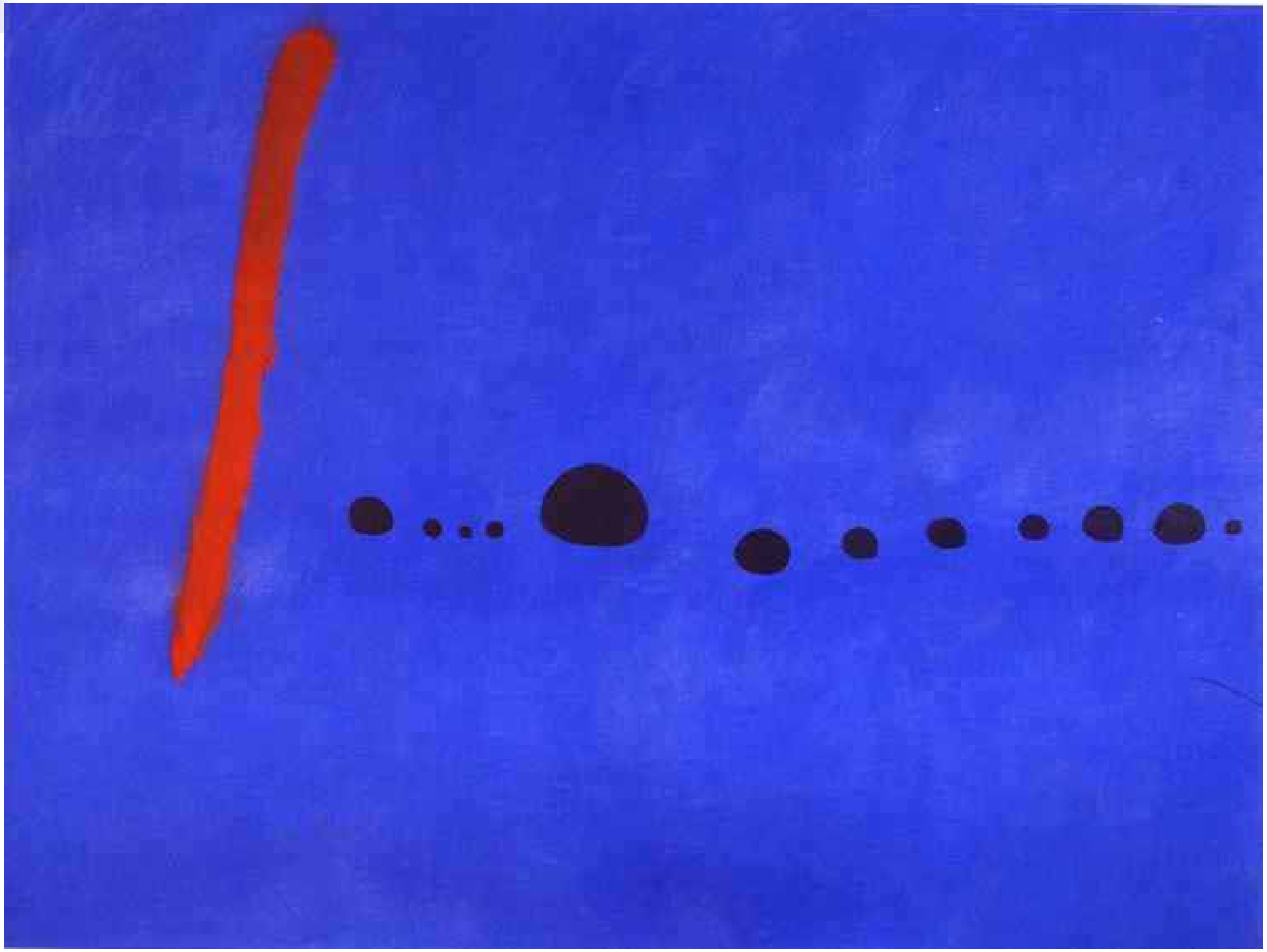
有330倍

- 有那麼好嗎？廣告過後告訴你。

猜猜看？

不要回來，馬上走開

誰的畫作



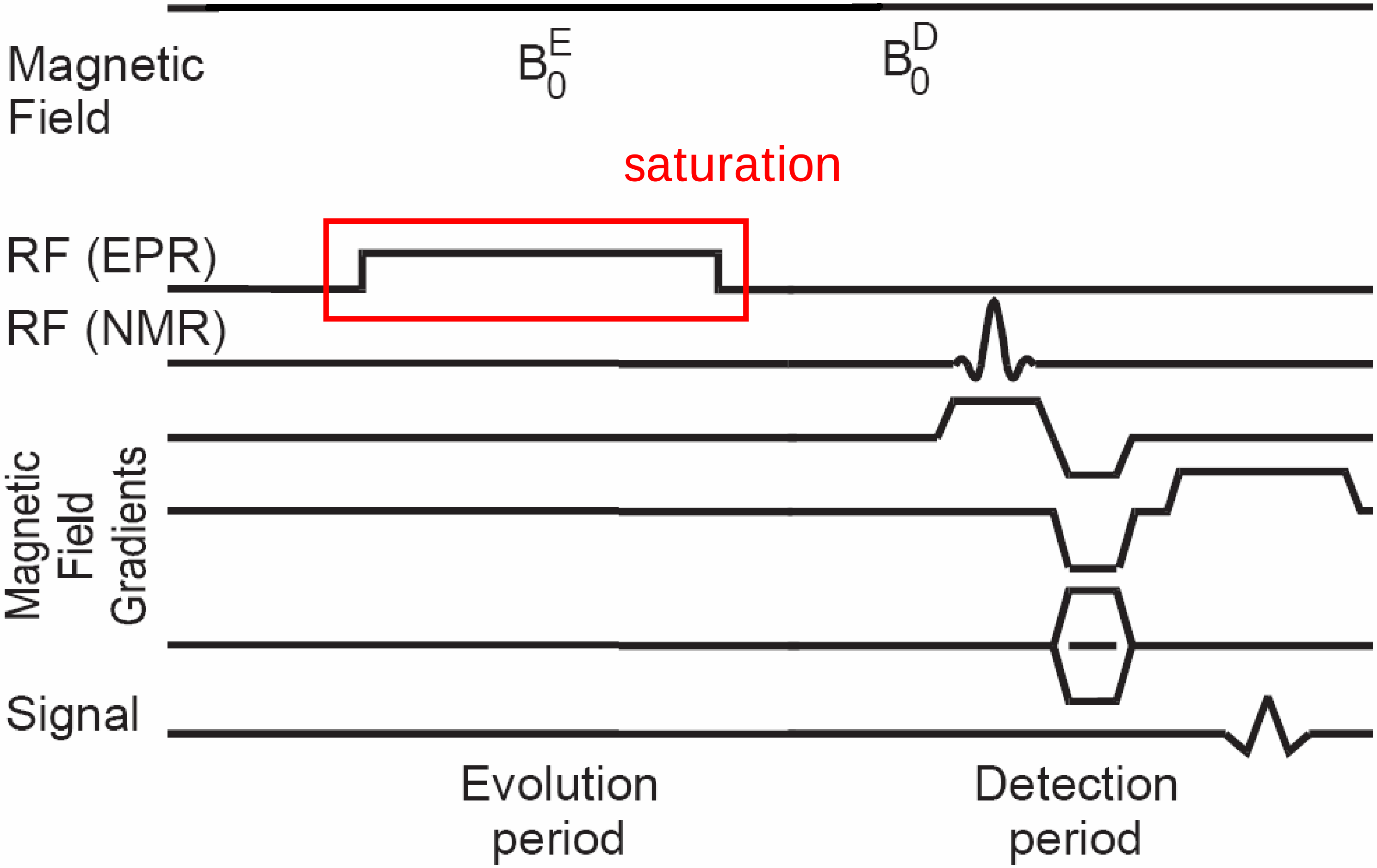
Outline

- Principle to NOE – Solomon Equation
- Imaging <
  - PEDRI, FC-PEDRI
  - Pulsed ESR, CW-ESR, ESRI
- Other Applications – NOESY

PEDRI / OMRI

- Proton Electron Double Resonance Imaging / Overhauser Effect MRI
- 先將電子spin飽和，在取^{1}H的影像。(聽說有330倍的SNR增強)
- 有哪麼容易嗎？

PEDRI


Magnetic Field
B_0^E
B_0^D
saturation
RF (EPR)
RF (NMR)
Magnetic Field Gradients
Signal
Evolution period
Detection period

Q1：relaxation time

- Electron spin T1約在0.1~1us。
- 所以無法達到完全saturate的狀態。

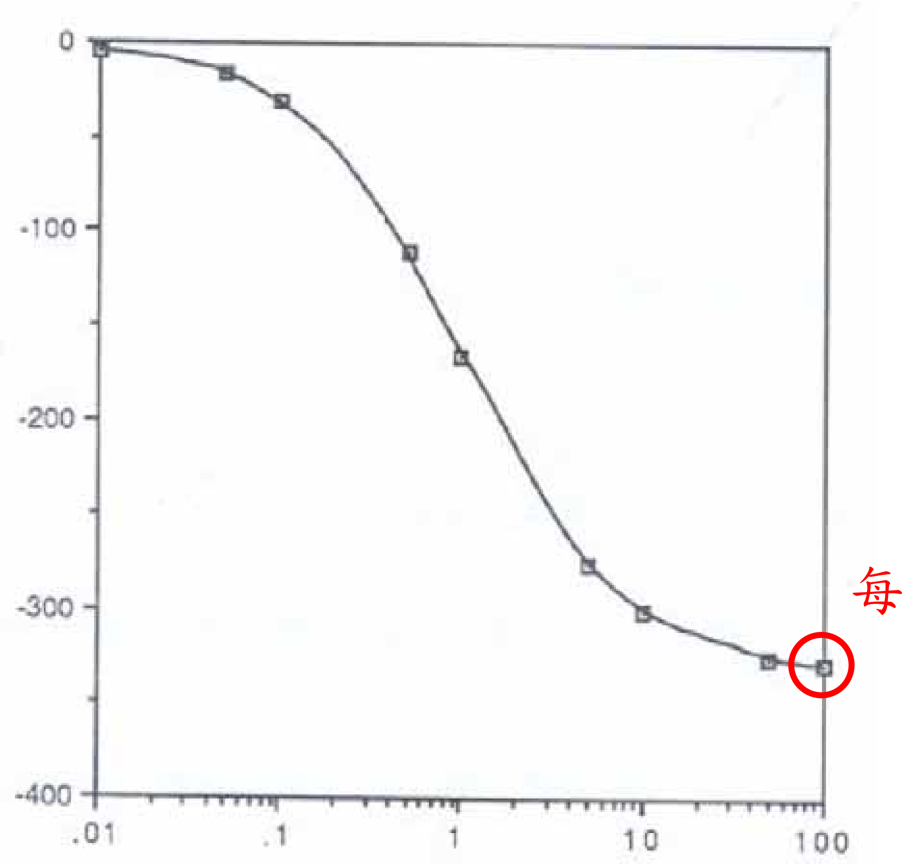
$$\eta = 1 - \frac{|\gamma_E|}{\gamma_H} \frac{f(s)}{f(s)+1}$$

← Wehrli p4

$$f(s) = \gamma_E^2 B_{1,ESR}^2 T_1 T_2$$

When complete saturation, f(s)>>1

NOE enhancement v.s. f(s)



Enhancement factor

每個點都是η

saturation factor f(s)

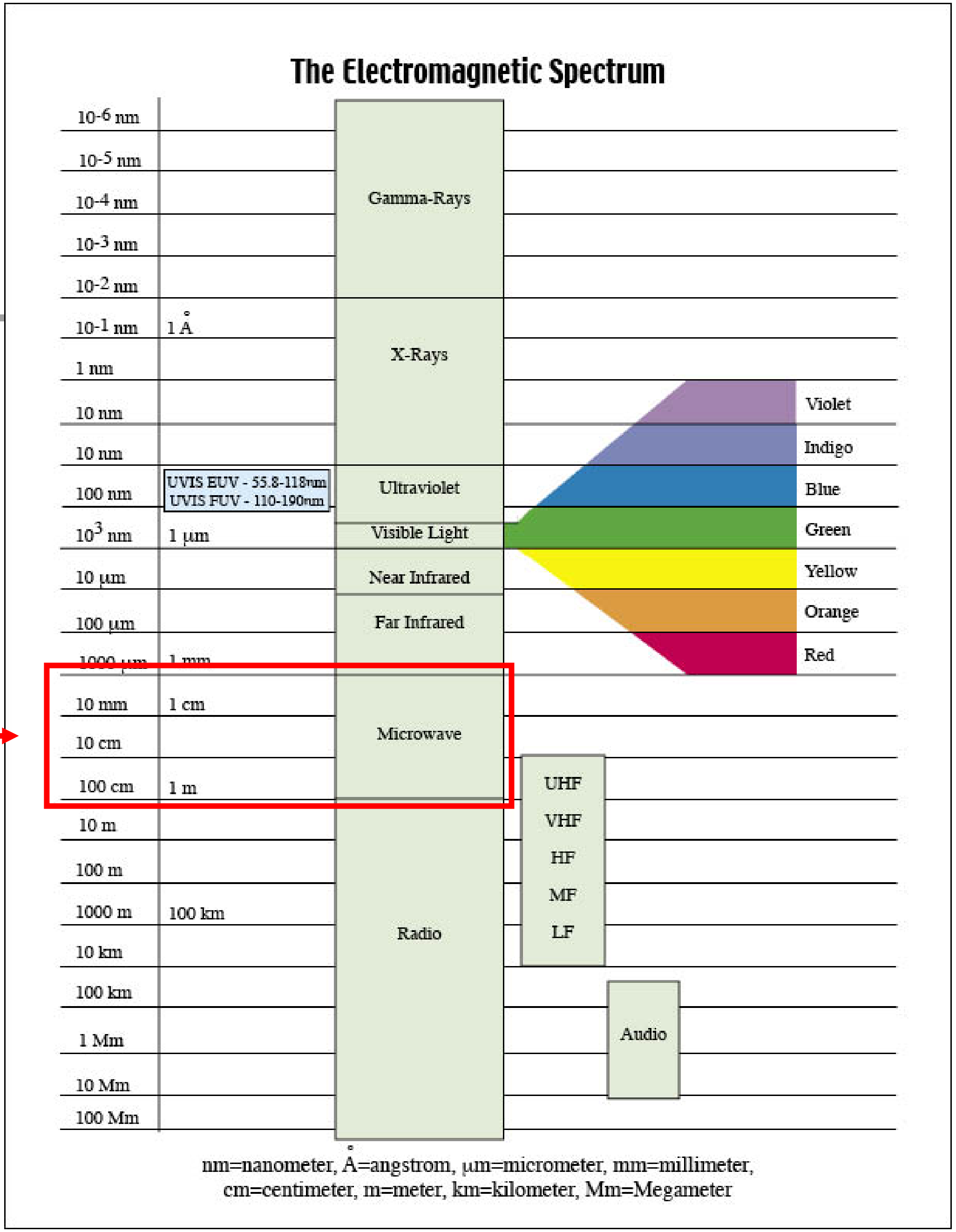
Q2：non-specific radiation

- Larmor frequency: $\omega = -\gamma B_0$
- 核的 γ = 42.58MHz/T
- 電子的 γ = $\bigcirc\!\!\!\!-$28.06GHz/T，約是核的 659倍。 請注意，是負的

- At 1.5T, ω_{Nu}=63.87MHz、 ω_E=42.09GHz
- At 0.35T, ω_E=$\underline{9.8GHz}$ 波長=0.03m(30cm)

EM Spectrum

MRI = 微波爐？ →



ESR的刺激時的主磁場勢必得更低.....

好吧，那就再低吧

- 減少主磁場同時減少SAR和SNR。
- P $\propto$ ν^2V
- SNR $\propto$ $B_0^{3/2}$
- 這樣不用玩了。使用ESR的目的本是希望增強多餘的信號，結果飽和完ESR，卻完收不到NMR信號。

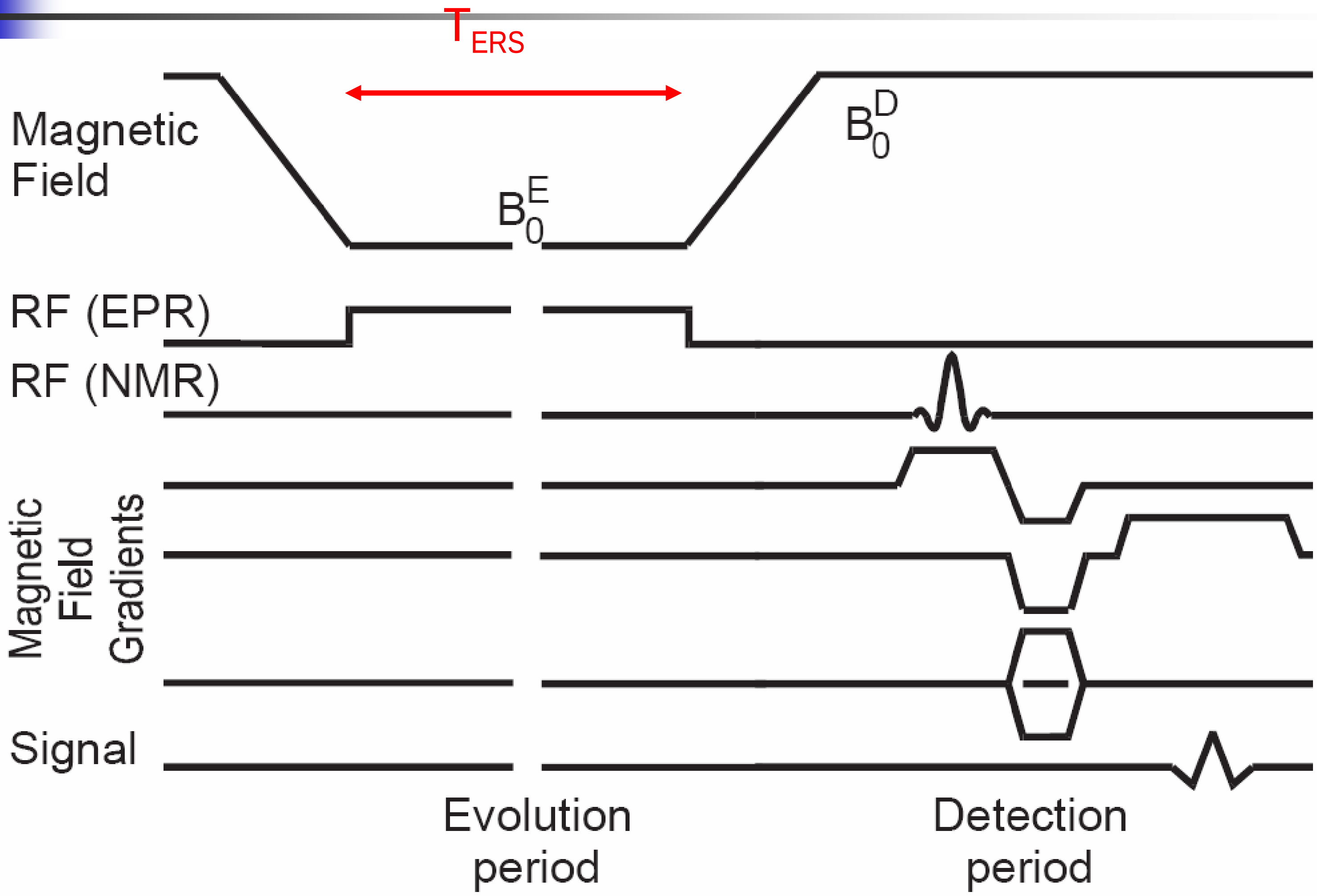
Field Cycle PEDRI

- 既然擔心收不到NMR信號，那就在取信號的時候把磁場升回去。
- 升太快，硬體要求高(i.e. MONEY)
- 升太慢，ESR效果就沒了
- 結果B_0^E=9mT, B_0^D=59mT (in 40ms)

Still some questions

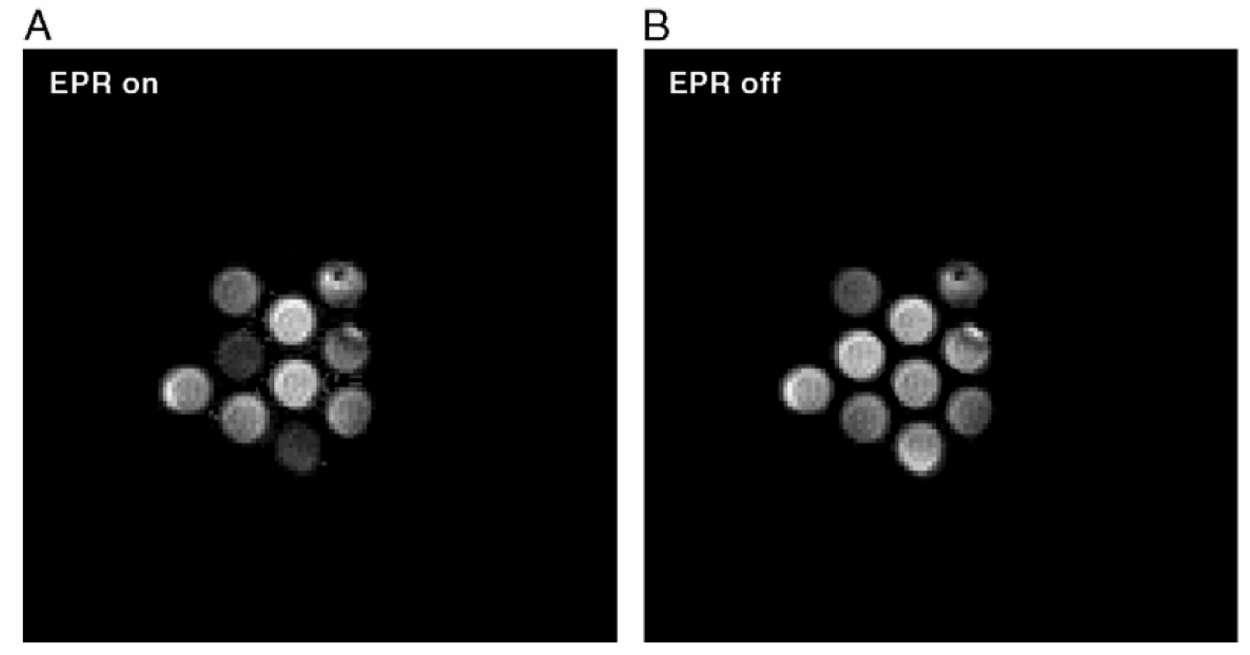
- Leakage : Relaxation is not entirely by electron-proton dd interaction.
- More than 2 spins : There is not only 2 spins in the system.(絕對有公式，要看嗎？)
- 東扣扣西扣扣 → 只剩下8倍的增強

FC-PEDRI


T_{ERS}
Magnetic Field
B_0^E
B_0^D
RF (EPR)
RF (NMR)
Magnetic Field Gradients
Signal
Evolution period
Detection period

FC PEDRI *in vitro* (2005)

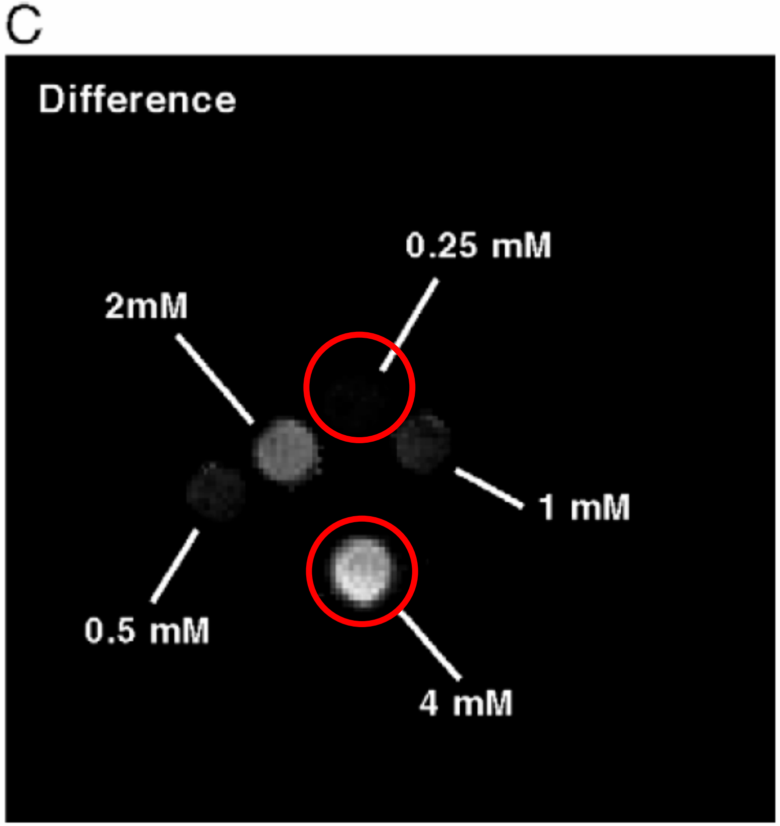
- B_0^E=5mT, B_0^D=450mT (in 40ms)



in vitro sample - $TEMPOL_{(aq)}$

FC PEDRI *in vitro* (2005)

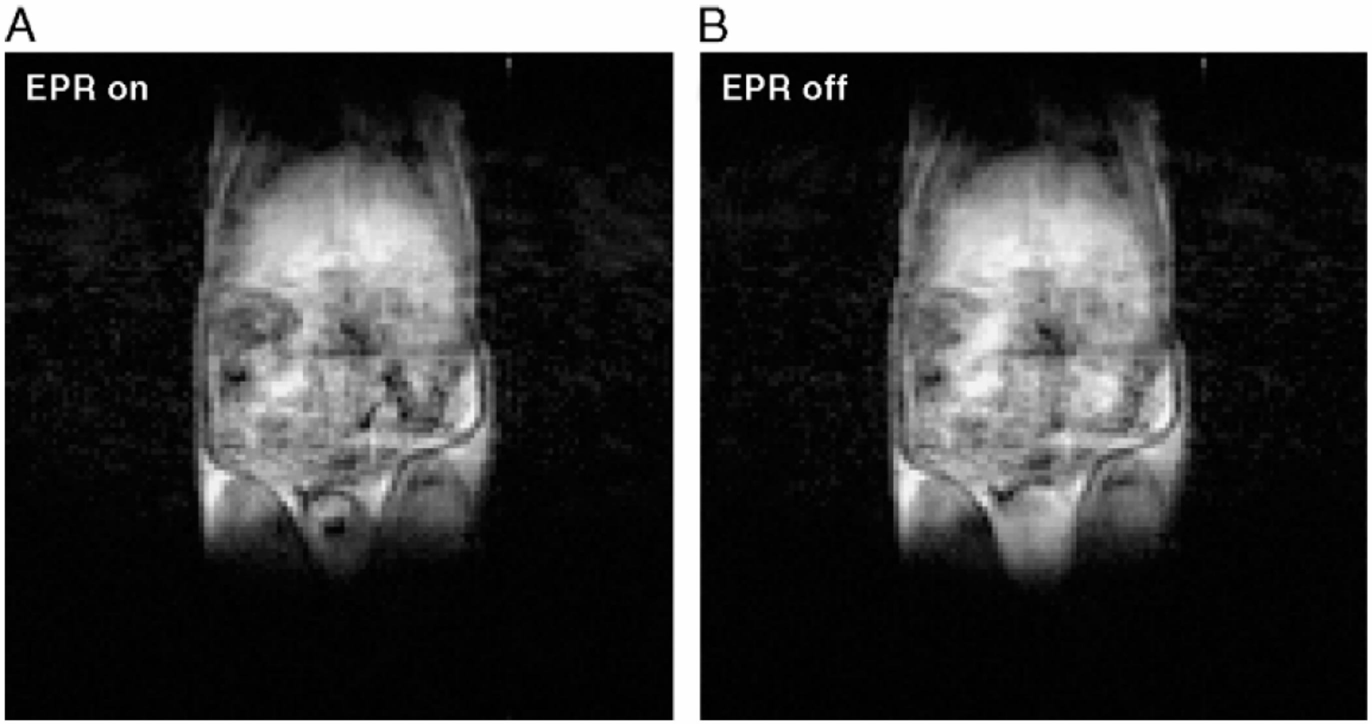
- 相減一下得到：
- 對於濃度越高的樣本，其影像相差越多。



in vitro sample - $TEMPOL_{(aq)}$

FC PEDRI *in vivo* (2005)

- Rats, 先麻醉後，再注射TAM。



slice = 30mm

128*128

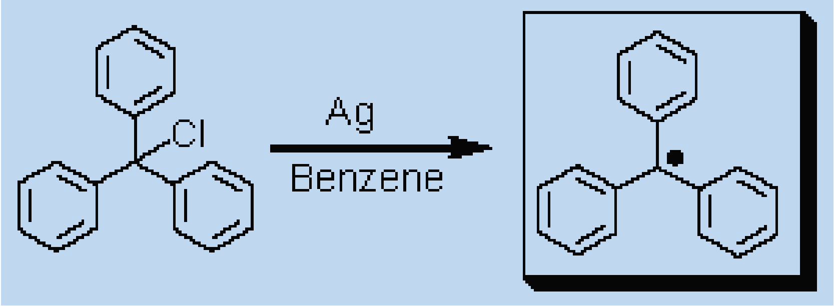
NEX = 1

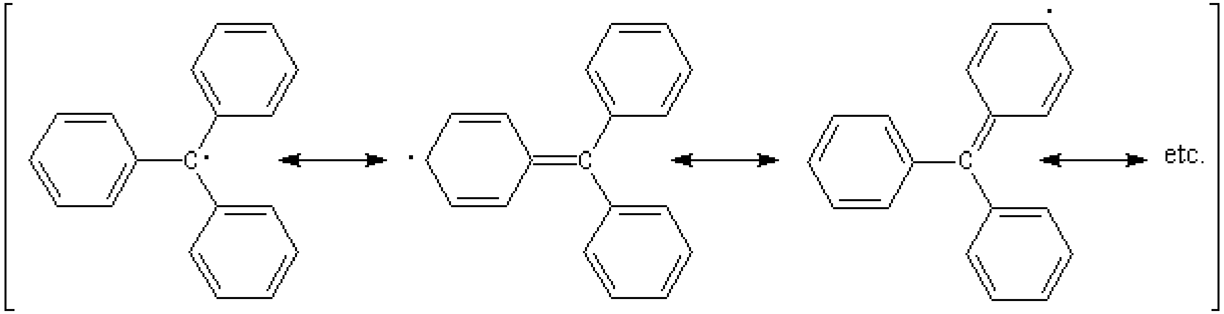
T_R = 1050ms

T_{ESR} = 400ms

Contrast Agent – TAM

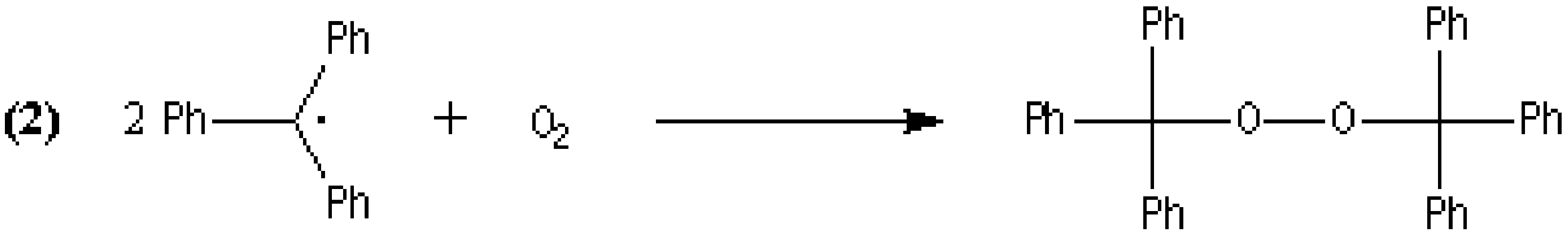
- Tri-aryl Methyl from Nycomed® (now in GE)
- Widely used in ESR





Contrast Agent – TAM (Cont.)

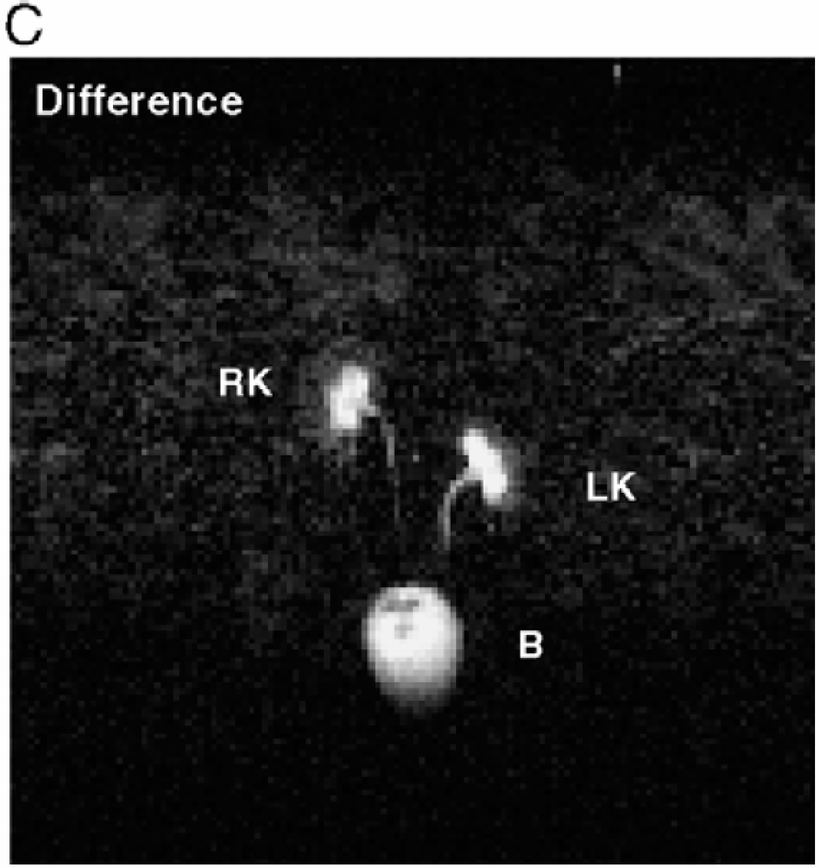
- It is an oxygen-sensitive radical.



- First concentrates in the kidneys, then in the bladder. Dissolved O_2 alters the electron relaxation times of TAM

FC PEDRI *in vivo* (2005)

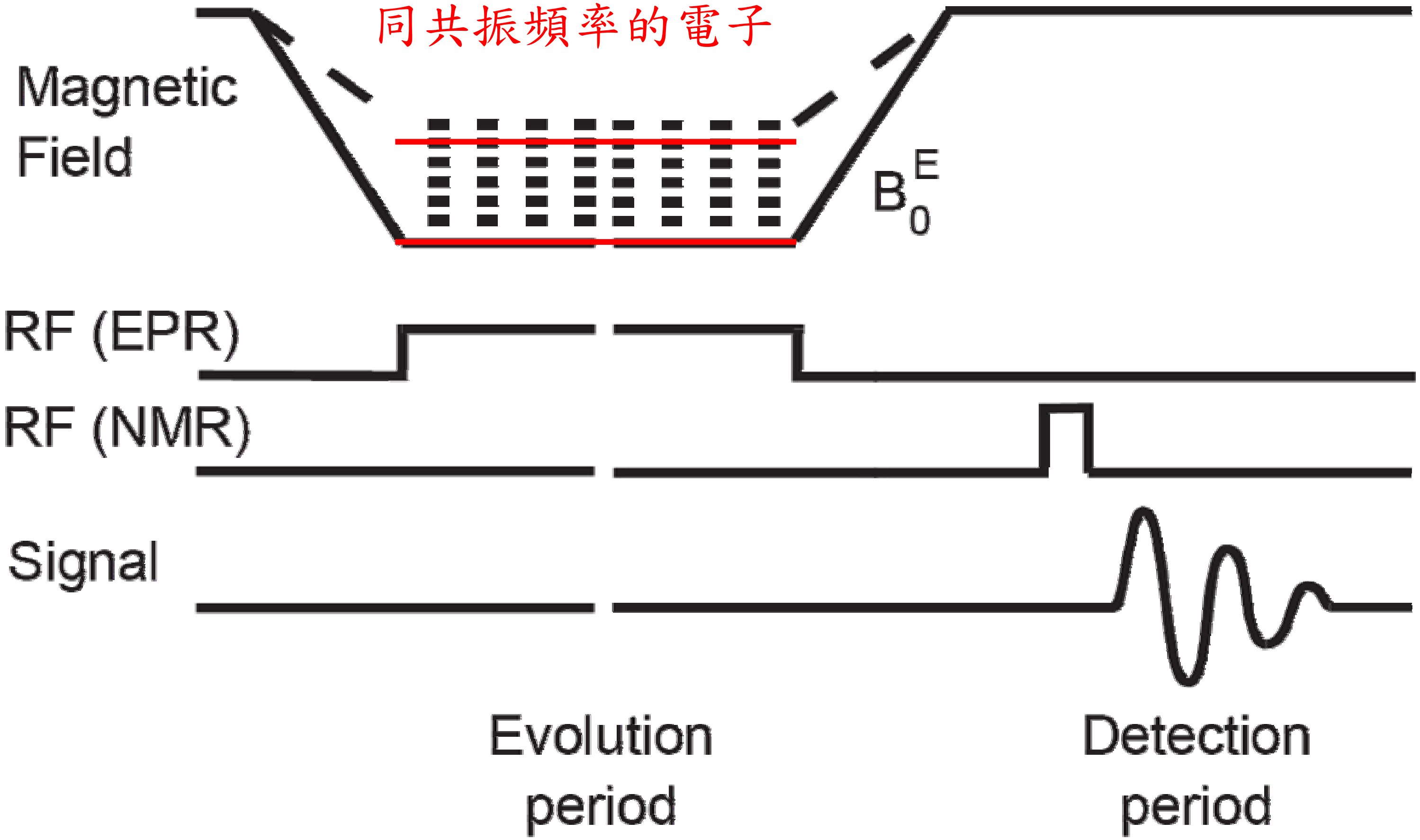
- 再相減吧。
- 腎臟還有膀胱相當明顯



FC-DNP spectroscopy

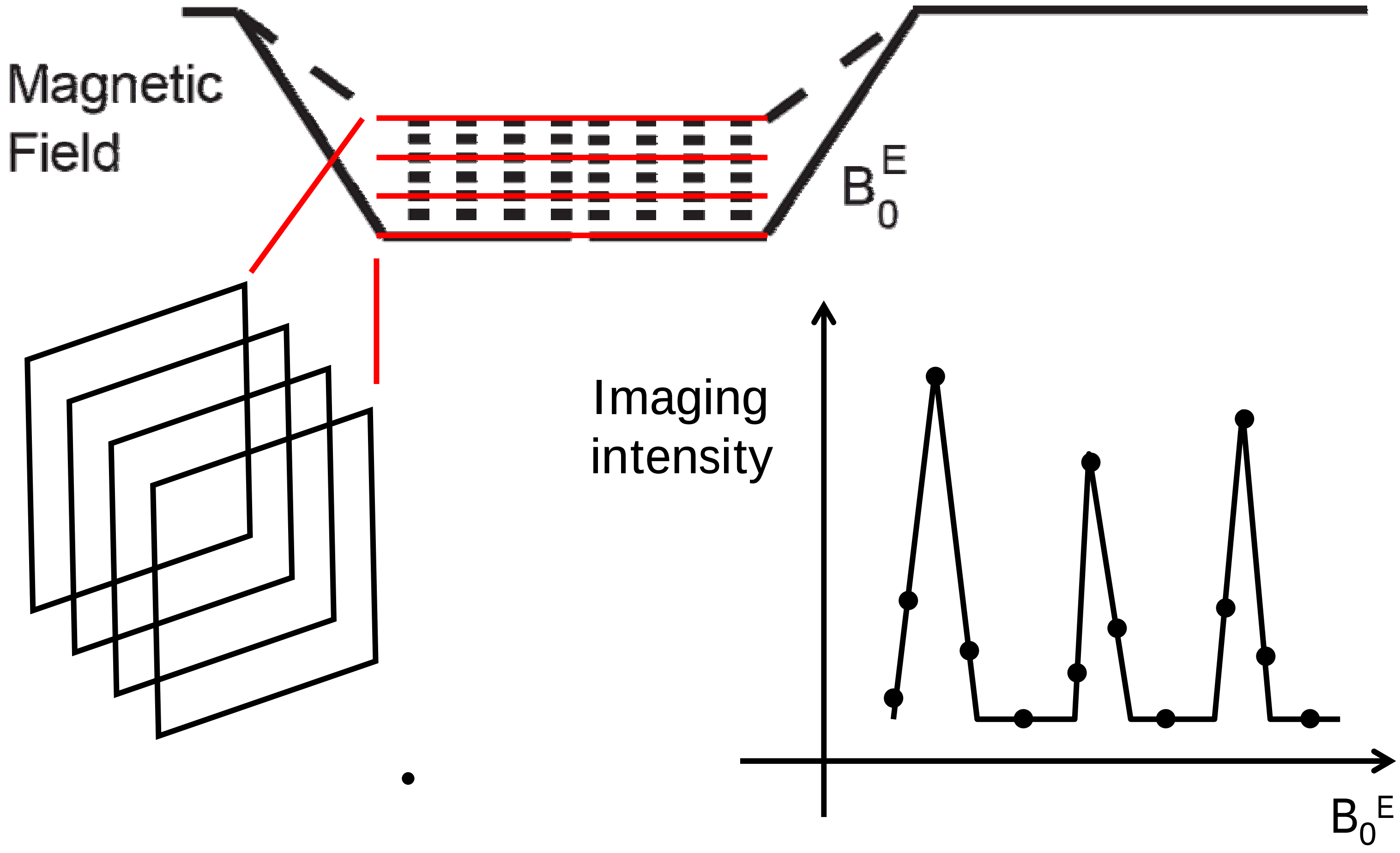
- Dynamic Nuclear Polarization
- 影像 + radical 的頻譜。
- 每次激發不同共振頻率的radicals。

FC-DNP spectroscopy



不同的B_E^0，SAT不同共振頻率的電子

FC-DNP spectroscopy (Cont.)



Outline

- Principle to NOE – Solomon Equation
- Imaging < PEDRI, FC-PEDRI / Pulsed ESR, CW-ESR, ESRI
- Other Applications – NOESY

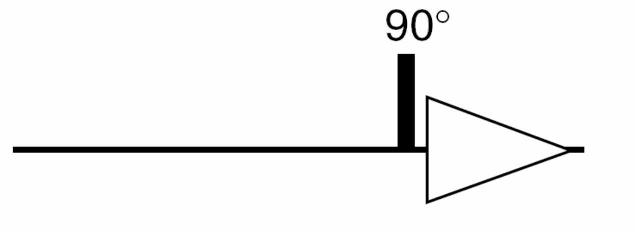
直接偵測Electron Spin

- 幹嘛要利用MRI間接取得radicals的比重影像，直接做不行嗎？

- 回憶我們的計算，在1.5T之下：
  ω_{Nu}=63.87MHz、 ω_{E}=42.09GHz
- 磁場太高？調低摟。

Pulsed ESR

- 跟最陽春的NMR相同：給一個excitation pulse，然後再接收FID。



- 也有Spin Echo
- 但是該有的問題也都有…

順便複習一下

- T1 Relaxation time (us等級)
- non-specific radiation (微波爐)
- dilemma of B_0 (SNR或SAR)
- Multi-spins model
- 當然不要忘記也有Contrast Agent

CW (Continuous Wave) ESR

- 復古風的NMR。
- sample放入，調到共振頻率上(50Ω)
- 持續給一個resonance RF pulse，然後慢慢增加主磁場，到$B_0=|\omega / \gamma|$時，RF就會被sample吸收。
- sample磁化率改變，阻抗改變—就可以偵測。

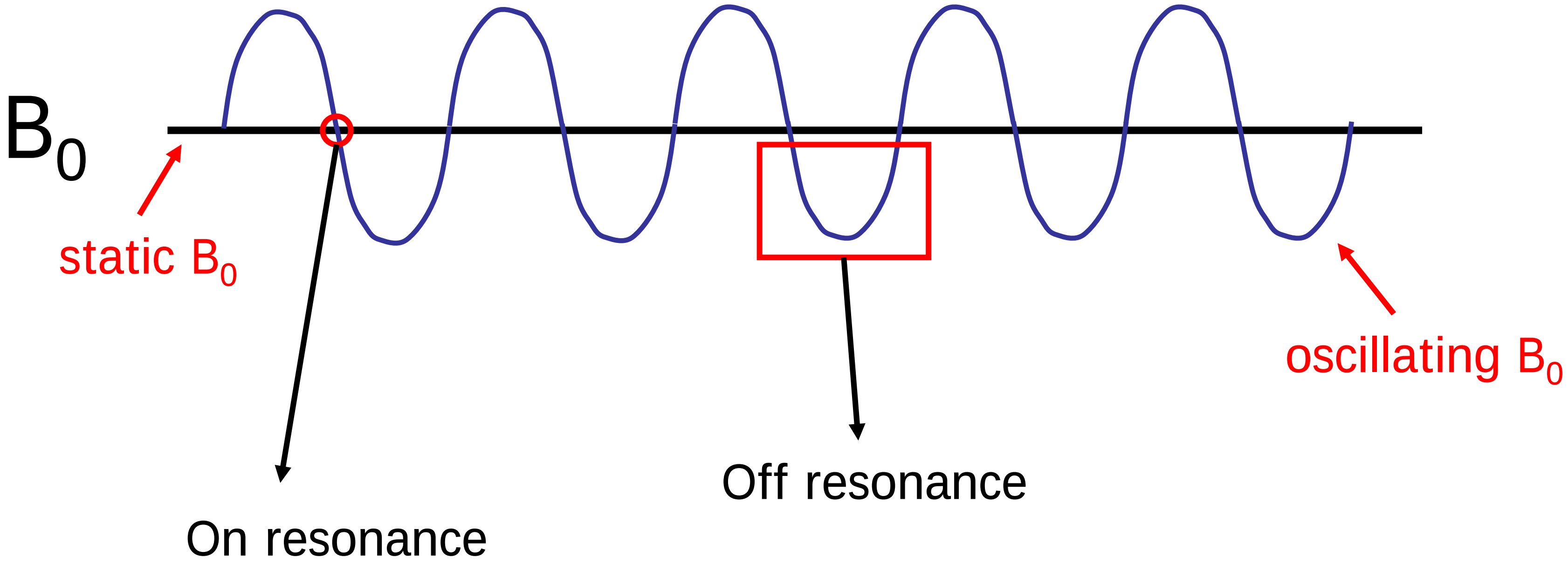
Q1: SNR有夠低

- Barely above noise level
- 在主磁場外，再加上一個oscillating magnetic field(@100kHz)
- 在resonance B_0附近時，電子就會以100kHz的頻率on and off resonance
- Lock-in amplifier (鎖相放大器)

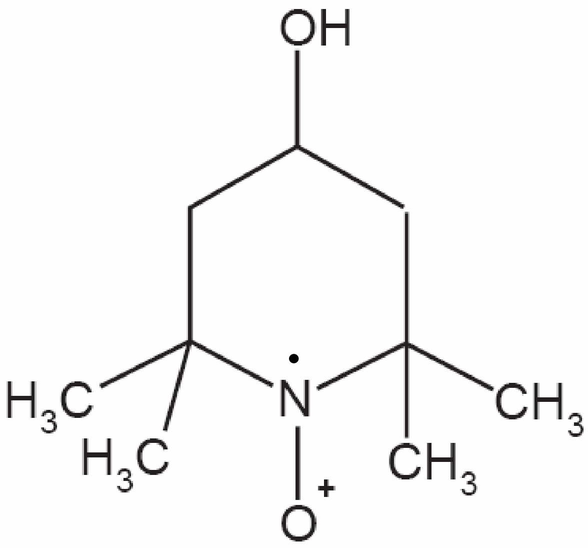
嘖嘖嘖!!

On and off resonance

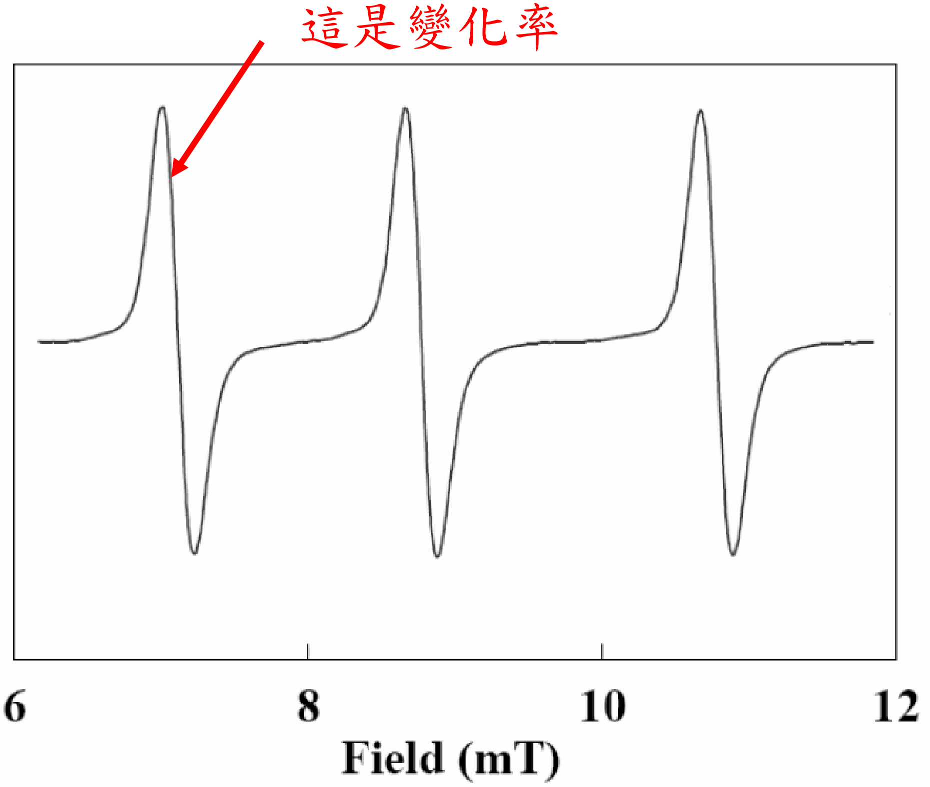
- 放大很多倍後，請假裝是一直線。



First derivatives spectrum



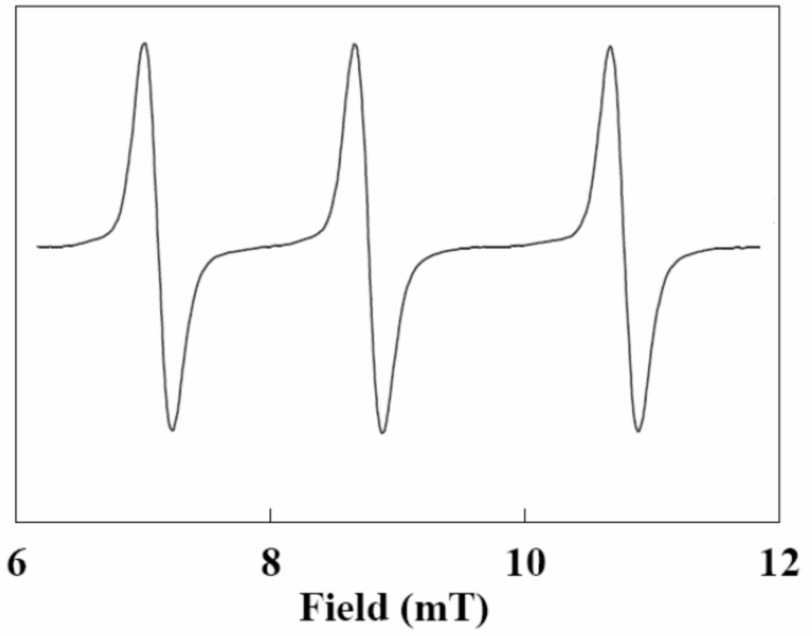
TEMPOL


這是變化率

260MHz CW ESR

Hyperfine Splitting

- 核影響電子
- 分成三條。
- 主要是因為N有 Spin = 1
- 會產生三種局部環境 1,0,-1



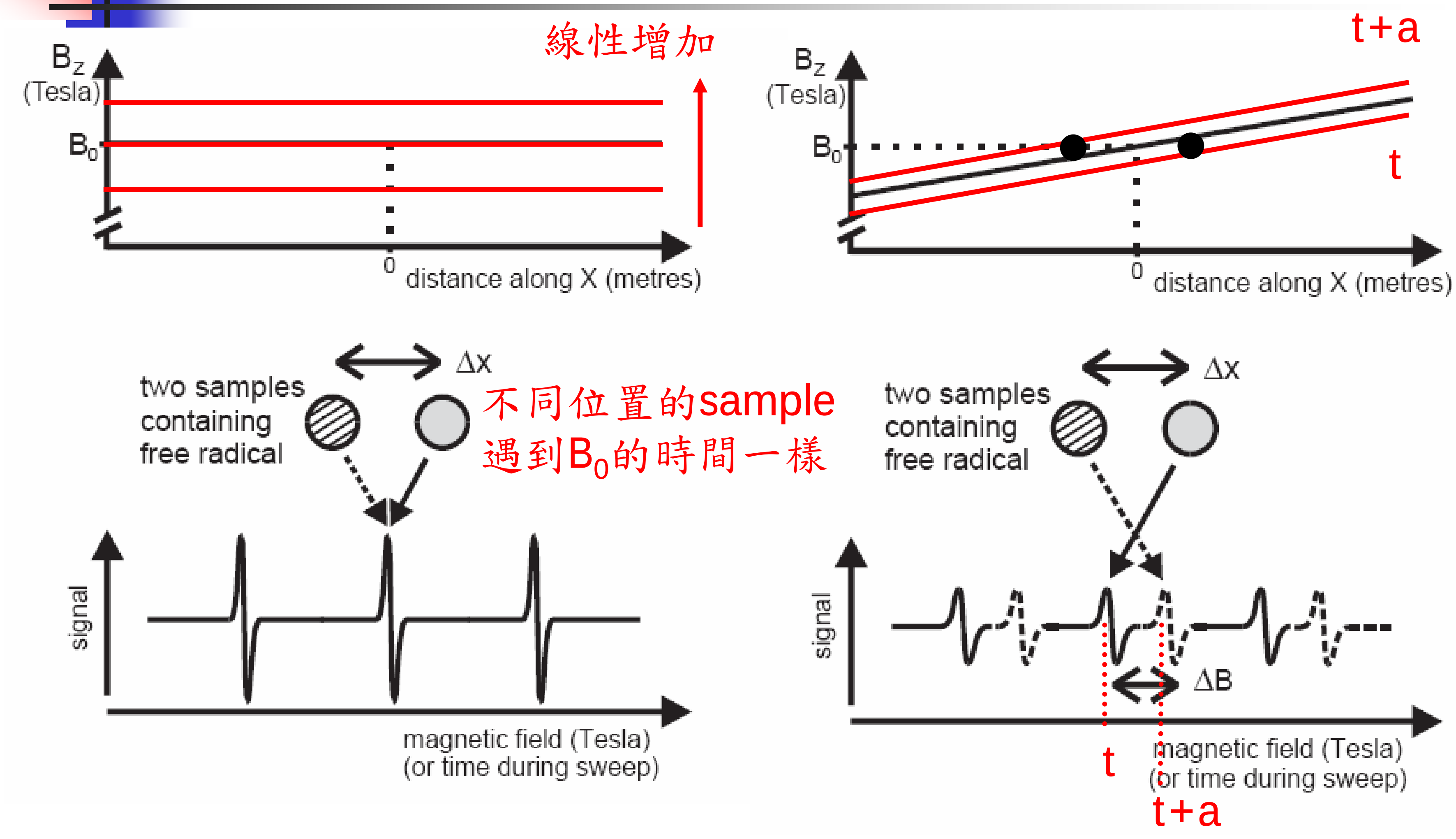
ESRI

- Unpaired electrons give ESR signal : free radicals & other paramagnetic molecules.
- ESRI – Distribution of them

MRI v.s. ESRI

- Nuclei v.s. Electrons
- Pulsed NMR v.s CW ESR
- k-space data v.s. projection-reconstruction method (like CT).

Projection-reconstruction



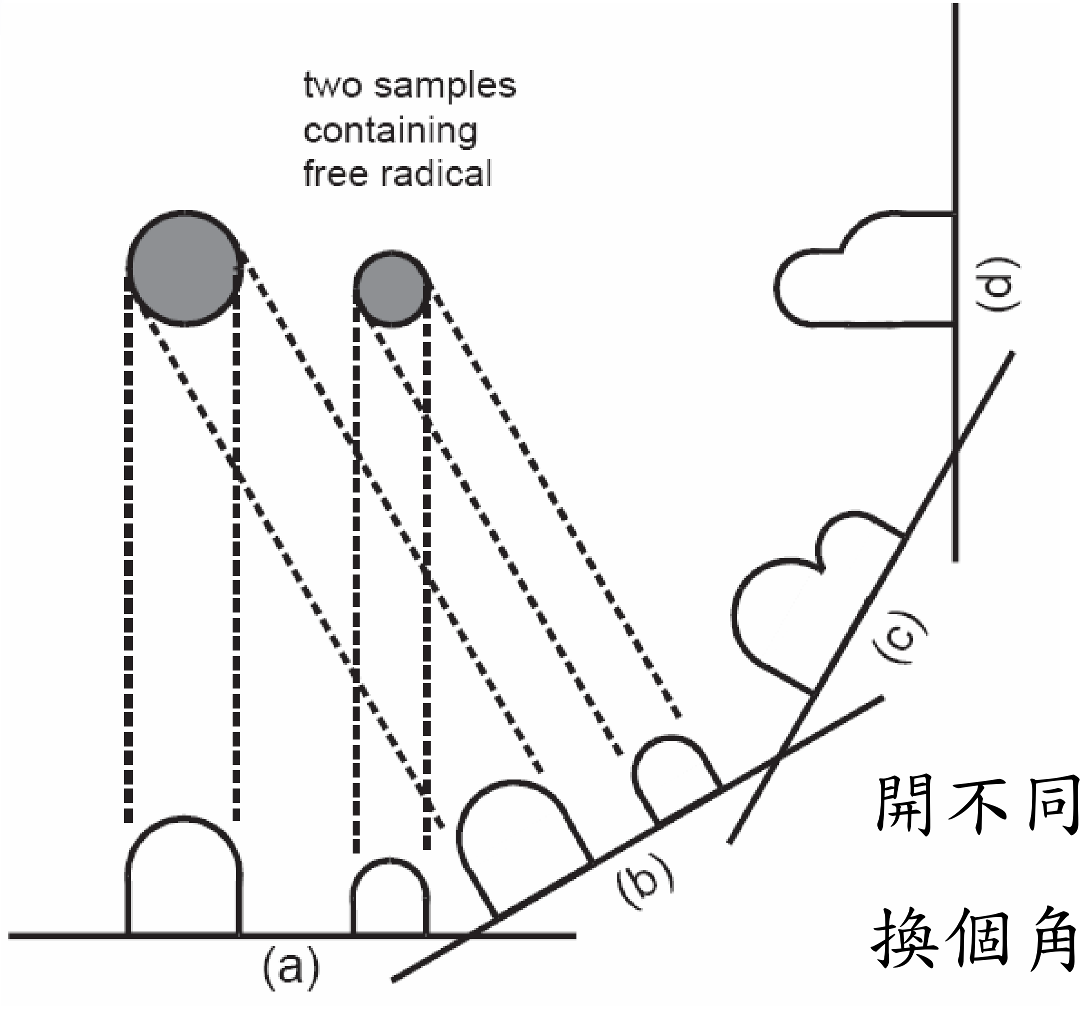
線性增加

不同位置的sample遇到B_0的時間一樣

Projection-reconstruction

- 如果 $B_x = G*x$
  x越大，就越早遇到resonance B_0
  x越小，就越晚遇到resonance B_0
- 空間上的分布 → 共振發生的早晚
- 該位置的ERS spin越多，該時間的信號越高。
- Inverse density projection

不同角度的投影



開不同方向的梯度，

換個角度，再來一次

Outline

- Principle to NOE – Solomon Equation
- Imaging <
  - PEDRI, FC-PEDRI
  - Pulsed ESR, CW-ESR, ESRI
- Other Applications – NOESY

NOESY

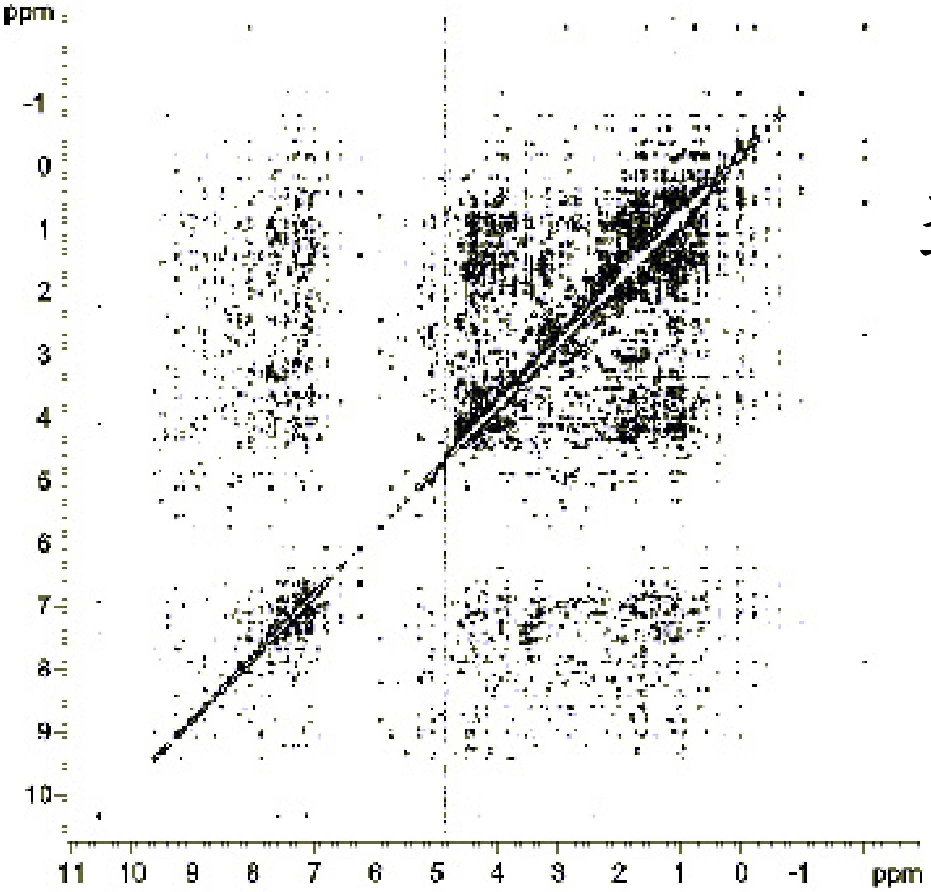
- Nuclear Overhauser Effect Spectroscopy，才是最重要的應用。
- dd interaction：molecular factor

$$M_{ij} \propto (\gamma_i^2 \gamma_j^2) \frac{1}{\boxed{r_{ij}^6}}$$

← 什麼！跟spin之間的距離有關？

- 利用cross relaxation constant 定位！

Structural Biology



達文西密碼！

以下是嘴炮時間 (茶)

- ESR Oximetry
- Trapping radicals metabolite
- Drug delivery

- 結合MRI與NOESY，活體蛋白質結構分析。XD

特別感謝

- 台下的學長姐還有老師，聽我鬼扯三小時。
- 台大物理系的好友—許文瑋同學
- 昨天被我抓去預講—程正傑學長
- 還有很多reference XD

Electron Spin Resonance

終於結束啦！

B91901010 電機四 油嘟嘟