

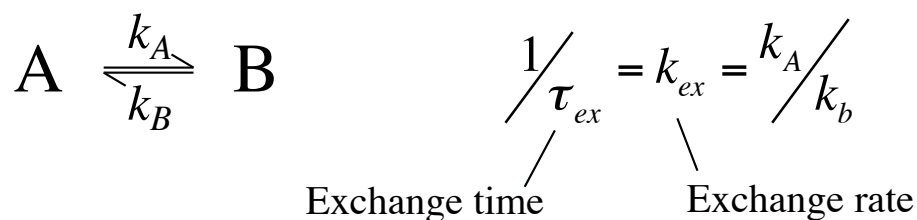
# Lecture #5

## Chemical Exchange

- Topics
  - Introduction
  - Effects on longitudinal magnetization
  - Effects on transverse magnetization
  - Examples
- Handouts and Reading assignments
  - Kowalewski, Chapter 13
  - Levitt, sections 15.5 and 15.6
  - van de Ven, sections 2.4, 2.5, and 6.1.2

# Chemical Exchange

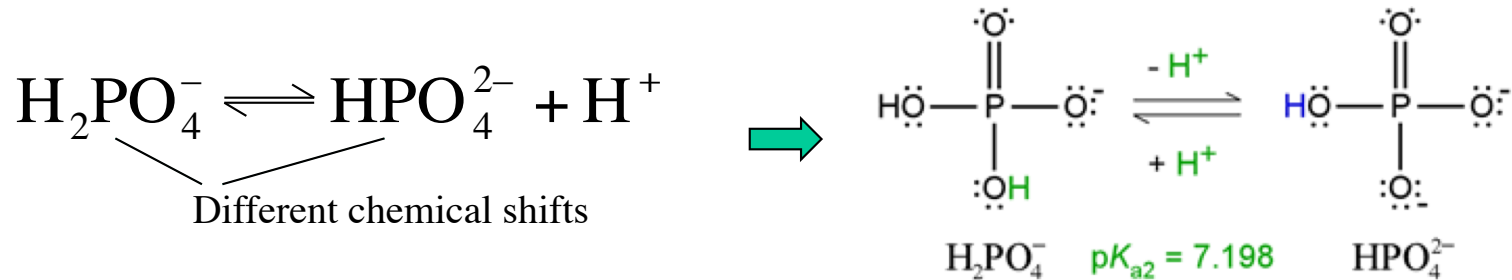
- Cross relaxation can lead to exchange of magnetization between coupled spins  $I$  and  $S$ .
- However, uncoupled spins can manifest themselves as an apparent coupled spin systems, if the spins are engaged in chemical exchange.
- Consider spins A and B on two molecules undergoing chemical exchange with rate constants  $k_A$  and  $k_B$  respectively.



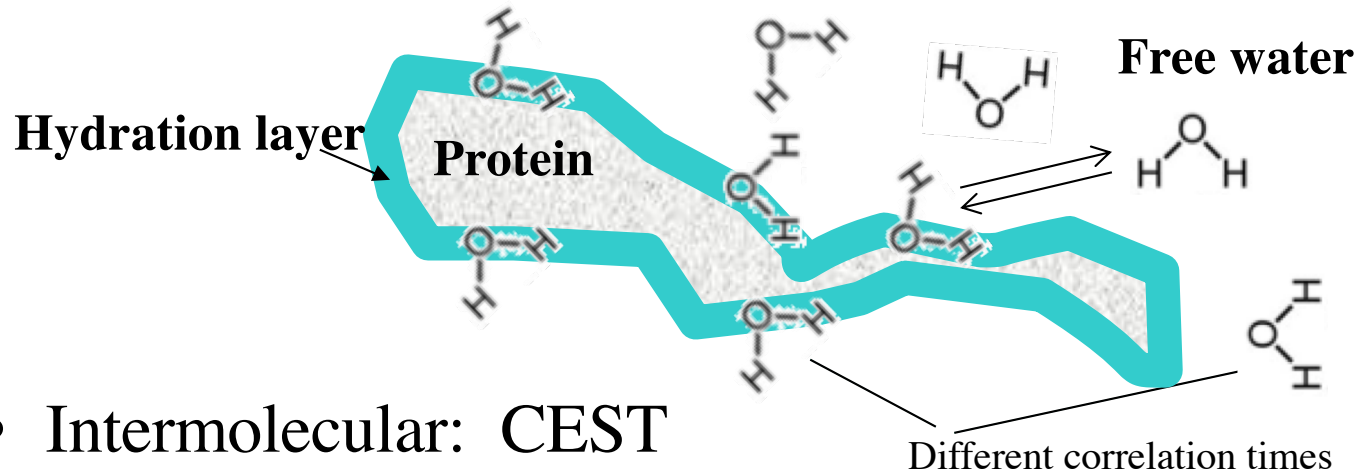
- We'll assume any transition from A to B is instantaneous, but happens at an average rate of  $1/\tau_{ex}$ .

# Chemical Exchange Examples

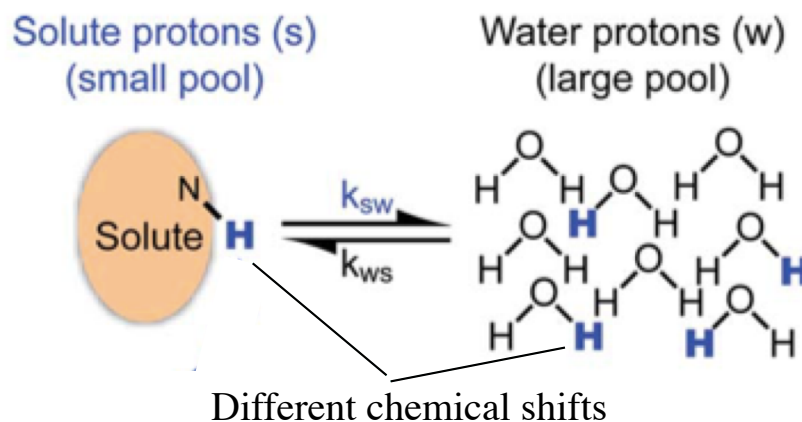
- Intramolecular: inorganic phosphate ( $^{31}\text{P}$  MRS)



- Intramolecular: water and hydration layers



- Intermolecular: CEST



# Chemical exchange and $\tau_c$

- Chemical exchange  $\longrightarrow$  stochastic modulations  $\longrightarrow$  relaxation
- Exchange rates ( $\mu\text{s}$  to  $\text{ms}$  time scales)  $\ll$  molecular tumbling
  - Too slow to effect anisotropic interactions such as CSA or dipole coupling
  - Can effect isotropic interactions such as chemical shift or J coupling
- Example: Let spins I and S be J coupled with the bond between them regularly broken by an exchange process.

J-coupling is modulated  $\longrightarrow$  If  $1/\tau_e \gg J$  then  $G(\tau) = \langle J(t)J(t+\tau) \rangle = J^2 e^{-|\tau|/\tau_e}$

$$\text{and } \frac{1}{T_{1,sc}} = \frac{(2\pi J)^2}{2} \frac{\tau_e}{1 + (\omega_I - \omega_S)\tau_e^2}$$

The name for this particular effect is “scalar relaxation of the 1<sup>st</sup> kind”.

In a few lectures, we’ll see why  $J(\omega)$  is probed at  $\omega_I - \omega_S$

Hence, the exchange time can look just like a rotational correlation time!

# Longitudinal Magnetization

- Chemical exchange can lead to the flow of longitudinal magnetization between sites.
- Bloch-McConnell equations

$$\frac{dM_z^A}{dt} = -\frac{M_z^A - M_{z,0}^A}{T_{1A}} - \frac{M_z^A}{\tau_A} + \frac{M_z^B}{\tau_B} \quad \text{and} \quad \frac{dM_z^B}{dt} = -\frac{M_z^B - M_{z,0}^B}{T_{1B}} - \frac{M_z^B}{\tau_B} + \frac{M_z^A}{\tau_A}$$

More compactly...

$$\frac{d}{dt} \begin{bmatrix} M_z^A \\ M_z^B \end{bmatrix} = - \begin{bmatrix} \alpha_A & \text{Cross relaxation} \\ -1/\tau_A & \alpha_B \end{bmatrix} \begin{bmatrix} M_z^A - M_{z,0}^A \\ M_z^B - M_{z,0}^B \end{bmatrix} \quad \text{with} \quad \begin{matrix} \alpha_A = \frac{1}{T_{1A}} + \frac{1}{\tau_A} \\ \alpha_B = \frac{1}{T_{1B}} + \frac{1}{\tau_B} \end{matrix}$$

Direct relaxation

Note, same form as the Solomon equations for dipolar coupling.

# Longitudinal Magnetization

Some interesting limiting cases...

Case 1: slow exchange  $\tau_A^{-1} + \tau_B^{-1} \ll T_{1A}^{-1} + T_{1B}^{-1} \Rightarrow \alpha_A \approx T_{1A}^{-1}, \alpha_B \approx T_{1B}^{-1}$

Case 2:  $T_{1B}^{-1} \gg \tau_A^{-1}, \tau_B^{-1} \gg T_{1A}^{-1} \Rightarrow \alpha_A \approx \tau_A^{-1}, \alpha_B \approx T_{1B}^{-1}$  Almost all relaxation at site B

Case 3: site B has very rapid relaxation and very small population, e.g. free water rapidly exchanging with a small pool of bound water.

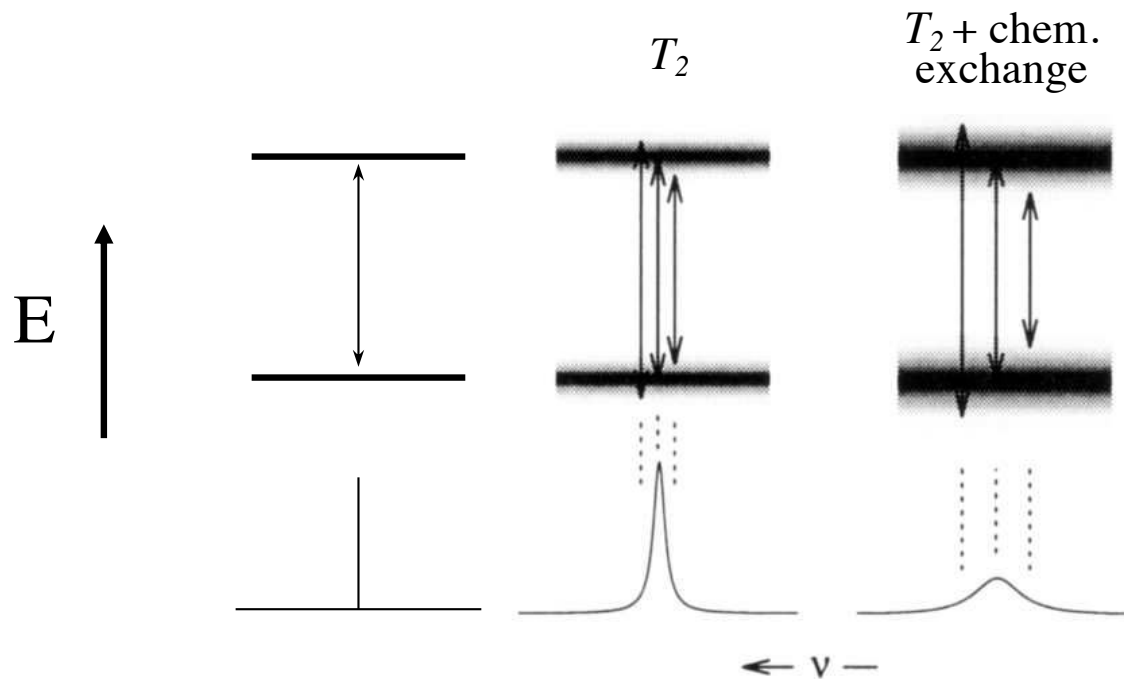
$$\alpha_A = \frac{1}{T_{1A}} + \frac{p_B}{p_A T_{1B} + p_B \tau_A}$$

$\setminus$  /  
 fractional  
 pool sizes

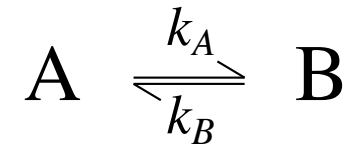
Important case for water  
in tissue as well as  
contrast agents

# Transverse Magnetization

- Chemical reactions can have profound effects on NMR linewidths, with the effects strongly dependent on the exchange rate.



# Lineshape Calculations



- Modified Bloch equations with coupling:

$$\frac{dM_x^A}{dt} = -\frac{1}{T_2^A} M_x^A + \cos(\Omega_A t) M_y^A - k_A M_x^A + k_B M_x^B$$

$$\frac{dM_y^A}{dt} = -\frac{1}{T_2^A} M_y^A - \sin(\Omega_A t) M_x^A - k_A M_y^A + k_B M_y^B$$

(analogous equations for the B spin)

Similar to the Bloch-McConnell equations, but now for transverse magnetization.

- Using  $M_{xy} = M_x + iM_y$ , compact notation for both A and B spins:

$$\frac{dM_{xy}^A}{dt} = -\left(i\Omega_A + 1/T_2^A\right) M_{xy}^A - k_A M_{xy}^A + k_B M_{xy}^B$$

$$\frac{dM_{xy}^B}{dt} = -\left(i\Omega_B + 1/T_2^B\right) M_{xy}^B - k_B M_{xy}^B + k_A M_{xy}^A$$



# Lineshape Calculations

- Rewriting...

$$\frac{d\vec{M}_{xy}}{dt} = \underline{L}\vec{M}_{xy} \quad \text{where} \quad \underline{L} = -\underline{\Omega} + \underline{k}$$

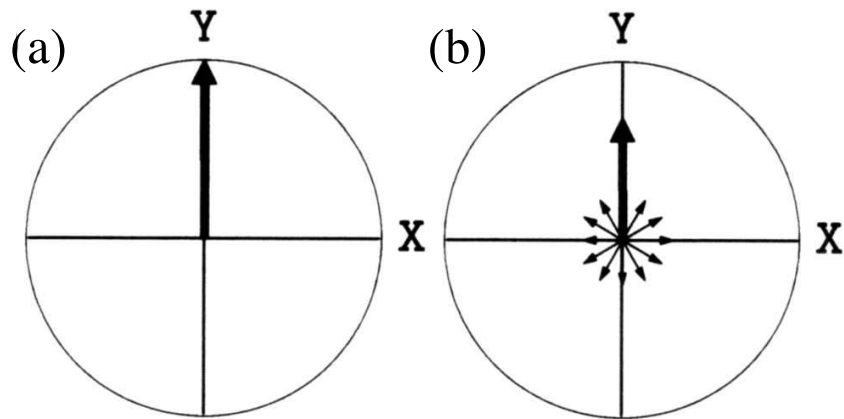
$$\text{and} \quad \underline{\Omega} = \begin{pmatrix} i\Omega_A + 1/T_2^A & 0 \\ 0 & i\Omega_B + 1/T_2^B \end{pmatrix} \quad \underline{k} = \begin{pmatrix} -k_A & k_B \\ k_A & -k_B \end{pmatrix}$$

- Solution:

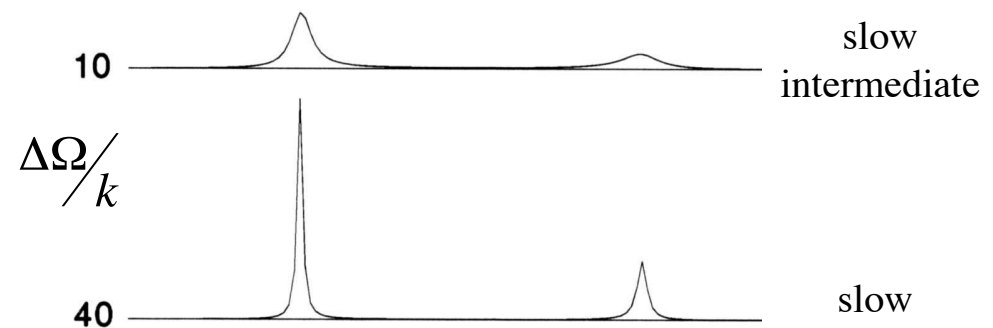
$$\vec{M}_{xy}(t) = e^{\underline{L}t} \vec{M}_{xy}(0)$$

# Slow Intermediate Exchange

- Before giving the general solution, let's look at two special cases.
- Spin A (similar for spin B)  $\Rightarrow$  Slow exchange:  $|\Omega_A - \Omega_B| \gg k_A, k_B$



$M_{xy}$  for species involved in slow exchange: (a)  $t=0$ , (b)  $t=T$



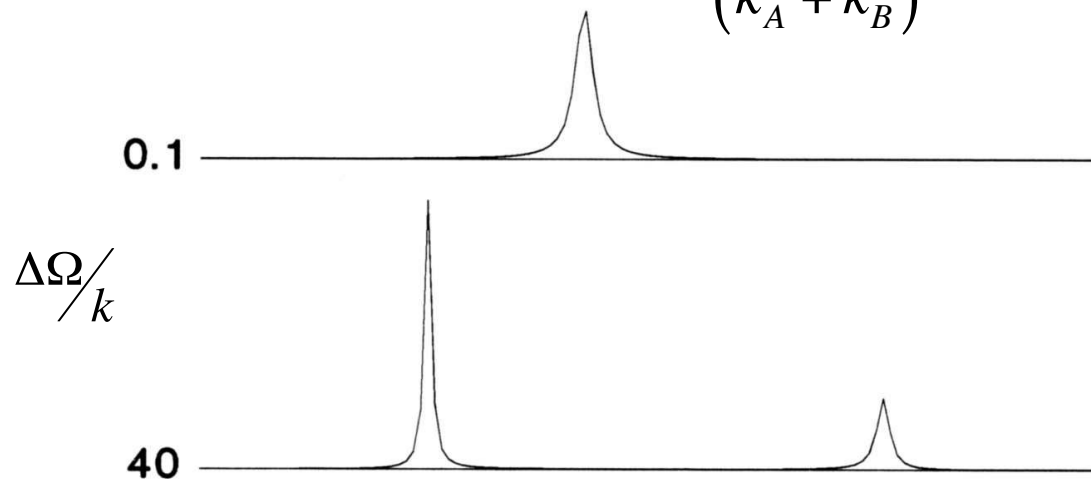
Linebroadening due to chemical exchange. As  $k_A$  increases lines get broader.

$$\frac{dM_{xy}^A}{dt} = -\left(i\Omega_A + 1/T_{2_{app}}^A\right)M_{xy}^A \quad \Rightarrow \quad 1/T_{2_{app}}^A = 1/T_2^A + k_A$$

# Fast Exchange

- Fast exchange:  $\rightarrow |\Omega_A - \Omega_B| \ll k_A, k_B$
- In many ways, the opposite of slow exchange.
  - Spins hop back and forth so fast that we observe a single resonance at the weighted average chemical shift:
 
$$\bar{\Omega} = f_A \Omega_A + f_B \Omega_B$$
 where  $f_A$  and  $f_B$  are the molar fractions of A and B
  - Linebroadening due to chemical exchange. As  $k_A$  and  $k_B$  increases line gets *sharper*.

$$1/T_{2_{app}} = 1/T_2 + \Delta\nu \quad \text{with} \quad \Delta\nu \propto \frac{\Delta\Omega^2}{(k_A + k_B)}$$



# Detailed Calculations

- Starting with  $\vec{M}_{xy}(t) = e^{Lt} \vec{M}_{xy}(0)$
- Taking the Fourier Transform and assuming that...

$$k_A \gg 1/T_2^A \text{ and } k_B \gg 1/T_2^B \text{ (i.e. chemical exchange is much faster than } T_2 \text{ relaxation)}$$

yields (after considerable algebra):

Real part of spectrum  $\rightarrow$

$$S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\bar{\Omega} - \omega)^2 \tau_{ex}^{-2}} M_0$$

where

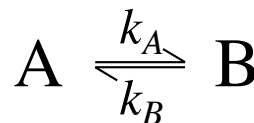
$$\bar{\Omega} = f_A \Omega_A + f_B \Omega_B, \quad f_A + f_B = 1, \quad \frac{f_A}{f_B} = \frac{k_B}{k_A}, \quad \tau_{ex} = \frac{1}{k_A + k_B}, \quad \frac{1}{\tau_{ex}} = \frac{1}{\tau_A} + \frac{1}{\tau_B}$$

$\swarrow \searrow$   
 molar fractions of A and B

$\swarrow$   
 molar fractions related to reaction rates:

$\swarrow$   
 measure of interconversion rate between A and B

$\tau_A = 1/k_A, \tau_B = 1/k_B$ :  
 lifetimes of A and B



# Detailed Calculations

$$S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\bar{\Omega} - \omega)^2 \tau_{ex}^{-2}} M_0$$

- Three values of  $\omega$  which correspond to spectral peaks

- $S(\omega \approx \Omega_A) = \frac{f_A \tau_A}{(\Omega_A - \omega)^2 + \tau_A^{-2}} M_0$ 

Lorentzian at  $\Omega_A$  with width  $1/\tau_A = k_A$ .  
If  $\tau_A$  is very short, peak very broad.

→ peak visible under *slow exchange*

- $S(\omega \approx \Omega_B)$ : analysis same as for A.

- $S(\omega \approx \bar{\Omega}) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}}{f_A^2 f_B^2 \tau_{ex}^2 (\Omega_A - \Omega_B)^4 + (\bar{\Omega} - \omega)^2} M_0$

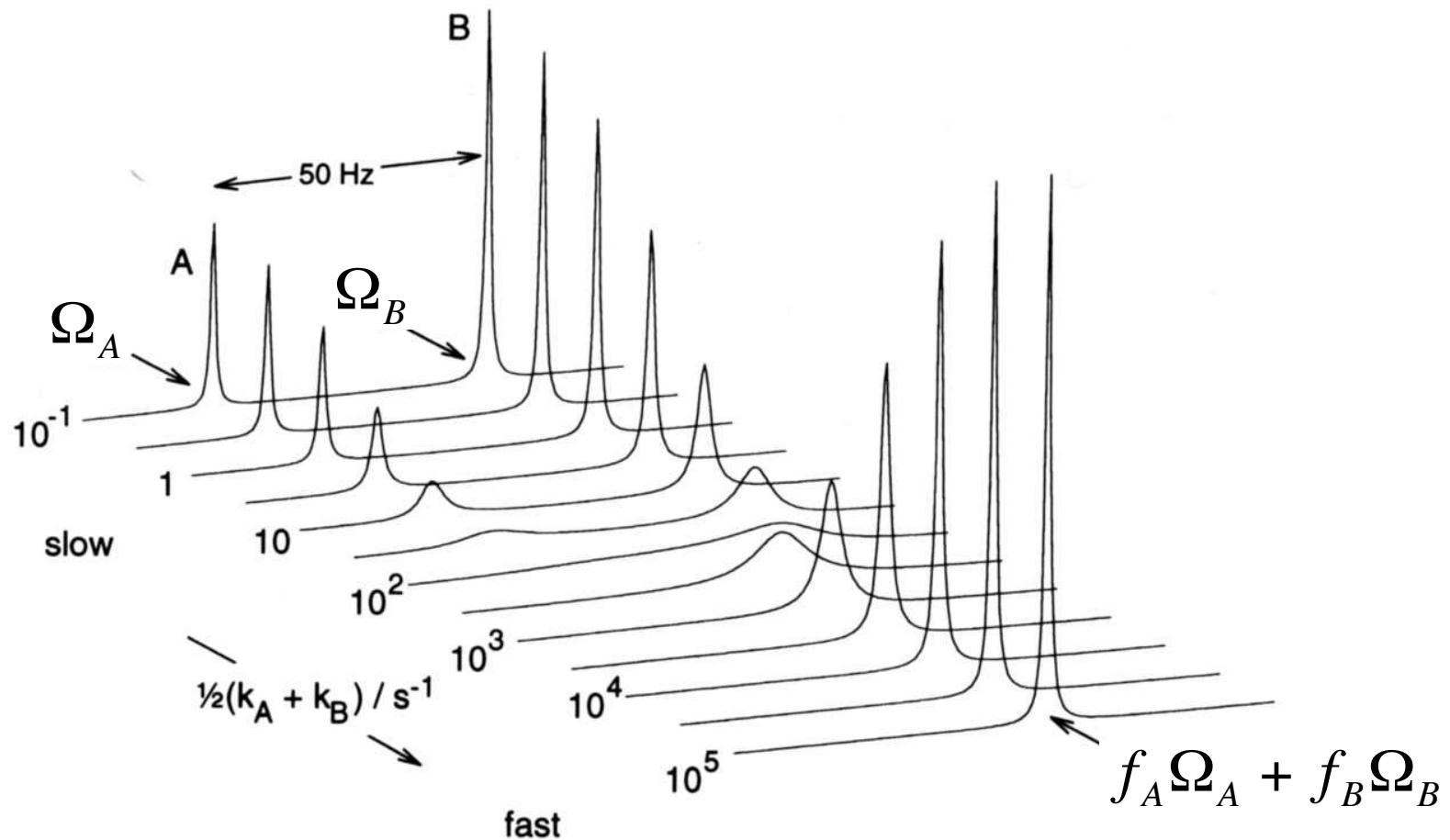
Lorentzian at  $\bar{\Omega} = f_A \Omega_A + f_B \Omega_B$  ← increases with  $\tau_{ex}$

Linewidth:  $\pi \Delta \nu = f_a f_b (\Omega_a - \Omega_b)^2 \tau_{ex}$

→ peak visible under *fast exchange*

# 2-Spin System with Chemical Exchange

$$S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\bar{\Omega} - \omega)^2 \tau_{ex}^{-2}} M_0$$



# Example 1: Fast Exchange

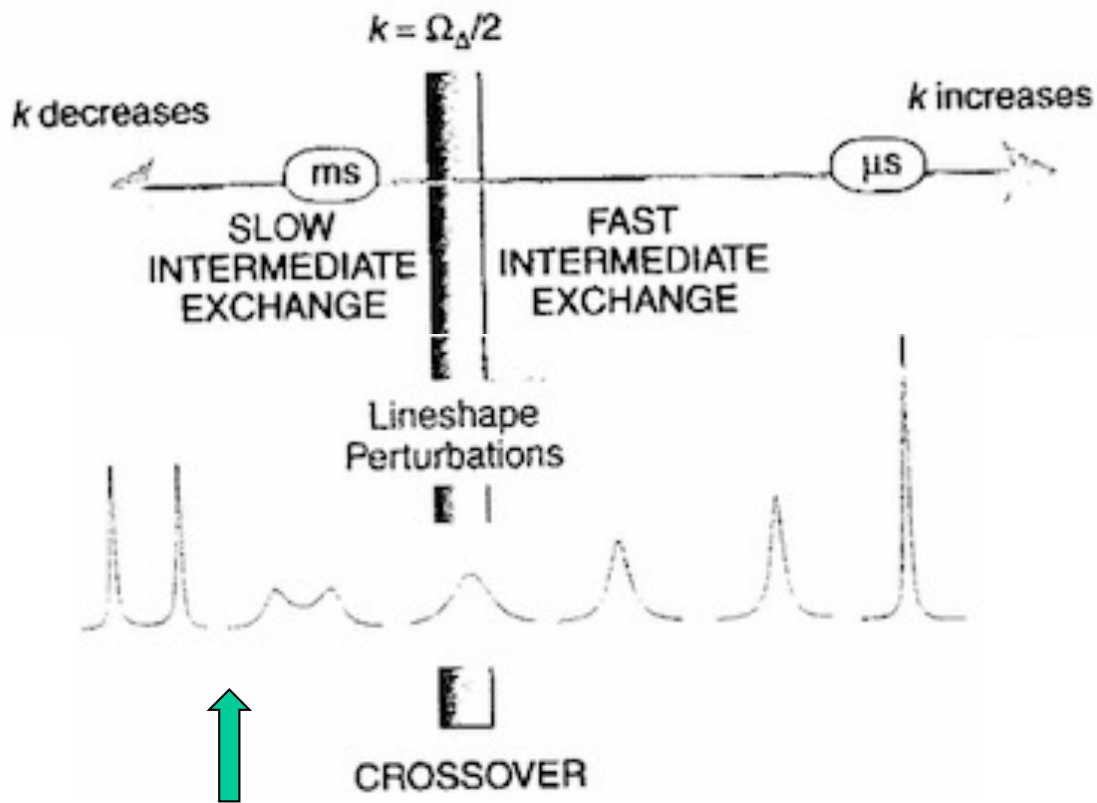
- $$S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\bar{\Omega} - \omega)^2 \tau^{-2}} M_0$$
 ...derived under assumptions that...

$k_A \gg 1/T_2^A$  and  $k_B \gg 1/T_2^B$  (i.e. chemical exchange much faster than  $T_2$ )

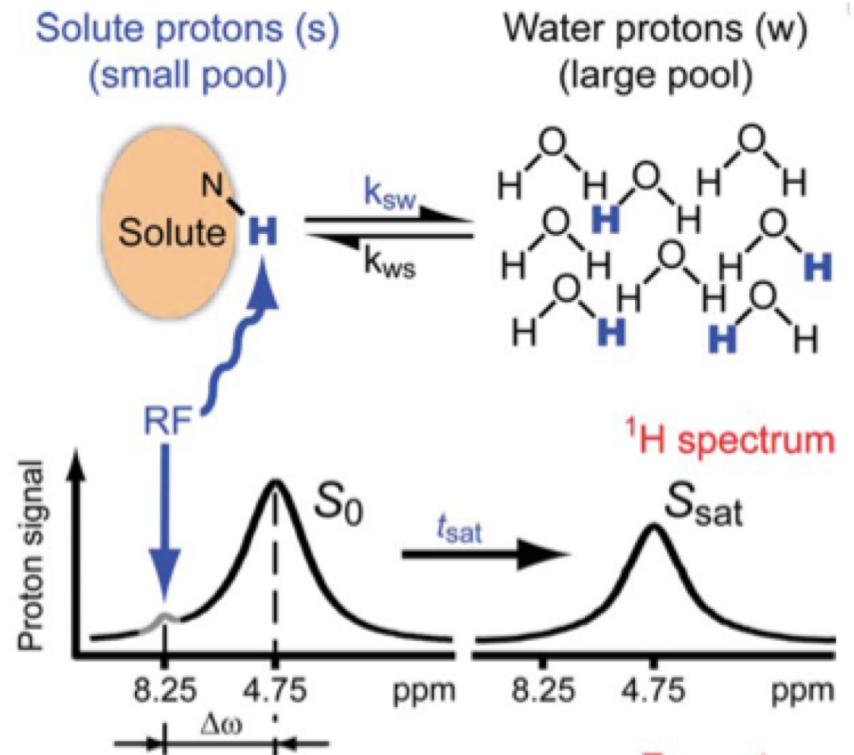
➡ Not necessarily true for contrast agents.

- Some parameters to consider.
  - Chemical shift difference between water when free and when coordinated with the agent/metal.
  - $T_2^B$  of water bound to the agent (typically dominated by the unpaired electron spin).
  - Lifetime,  $\tau_B$ , of the water in the coordination sphere of the contrast agent.
- To be discussed in detail later...

# Example 2: Intermediate Exchange



## Chemical exchange saturation transfer (CEST)





# Example 3: Fast Exchange

- $\text{H}_2\text{PO}_4^- \rightleftharpoons \text{HPO}_4^{2-} + \text{H}^+$  (inorganic phosphate)  
 $\Omega_A=3.2 \text{ ppm}$     $\Omega_B=5.7 \text{ ppm}$
- Under fast exchange, the  $^{31}\text{P}$  peak will be at  $\bar{\Omega} = f_A\Omega_A + f_B\Omega_B$
- Henderson-Hasselbach relationship

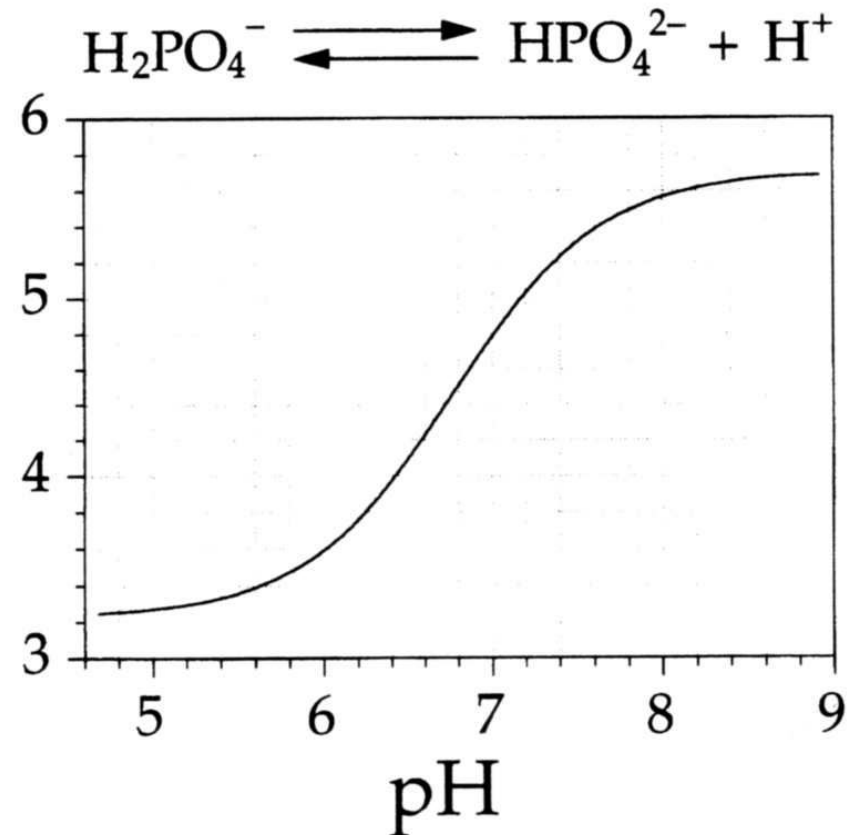
$$\text{pH} = \text{pK}_A + \log\left(\frac{f_A}{1 - f_A}\right)$$

- Combining the above and expressing things in terms of chemical shift yields ...

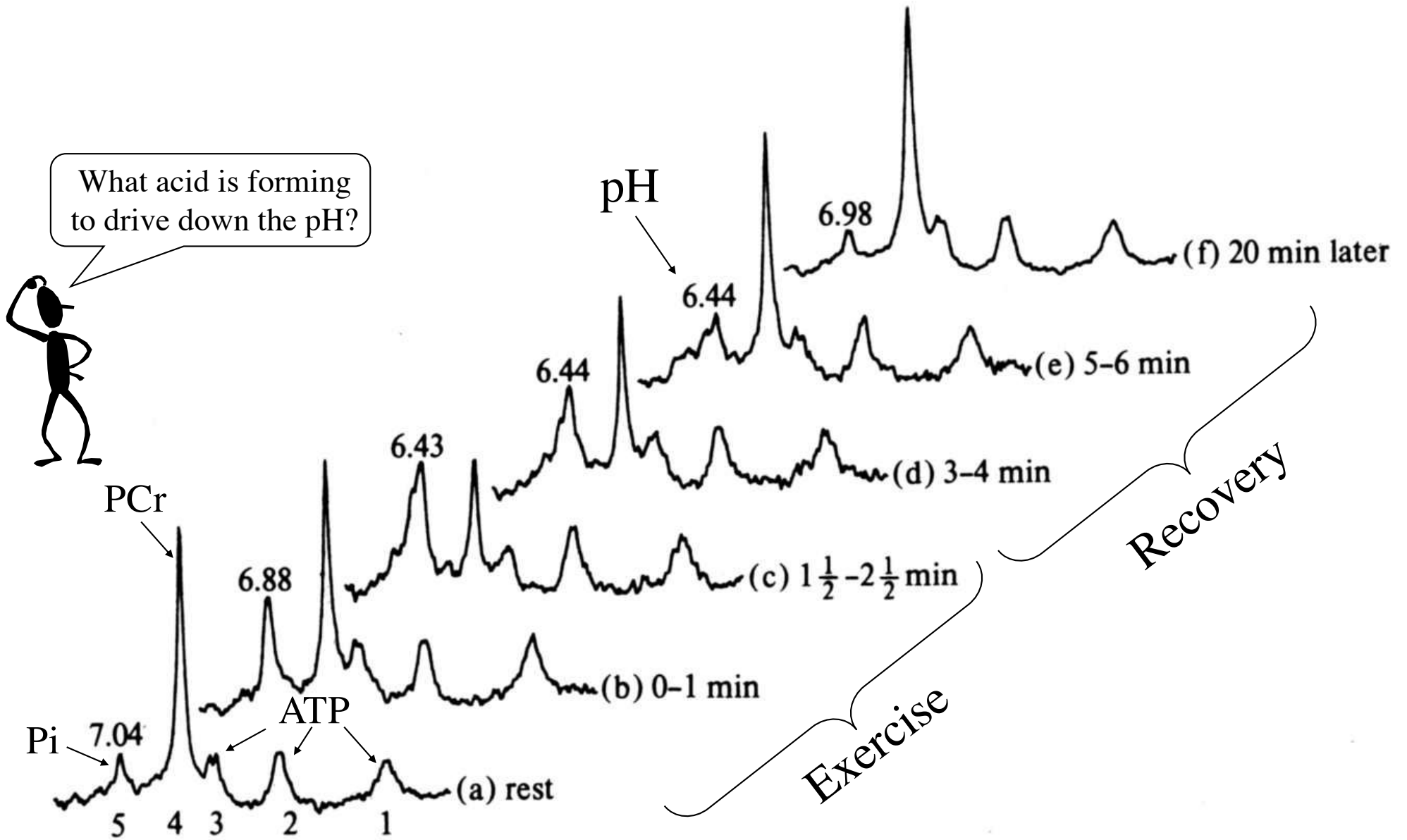
$$\text{pH} = \text{pK}_A + \log\left(\frac{\omega - \Omega_A}{\Omega_B - \omega}\right)$$



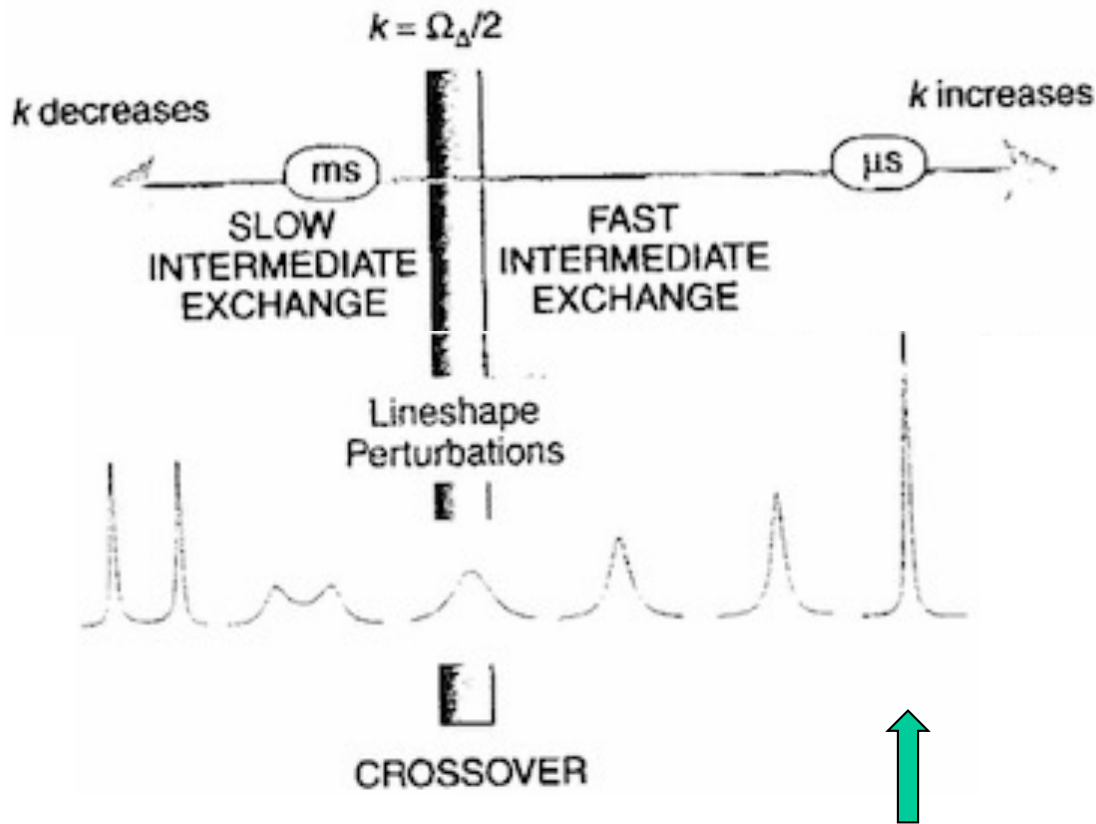
$$\delta\text{P}_i - \delta\text{PCr}$$



# $^{31}\text{P}$ Exercise Study



# Example 4: Fast Exchange



Temperature mapping via  
water chemical shift

The resonance frequency of the in vivo water  $^1\text{H}$  peak is known to shift with temperature at a rate of  $\sim 0.01\text{ppm}/^\circ\text{C}$ . This affect can be explained via a two-site exchange process.

# Temperature mapping with H<sub>2</sub>O

- The earliest reference I found was Hindman JC, “Proton Resonance Shift of Water in the Gas and Liquid States”, *J. Chemical Physics*, 44, 4583 (1966).
- Hydrogen bonds decrease the electron density at the involved proton site and hence lead to a positive frequency shift.
- Liquid water can be modeled as a mixture of two components: a hydrogen-bonded “ice-like” fraction and a non-hydrogen-bonded monomeric fraction.
- The chemical shifts for these two components, which are in fast exchange, are...

shielding constant for monomeric water,  $\sigma_w \cong -0.4 \times 10^{-6}$

shielding constant hydrogen-bonded water,  $\sigma_p \cong \sigma_w - 5.5 \times 10^{-6}$

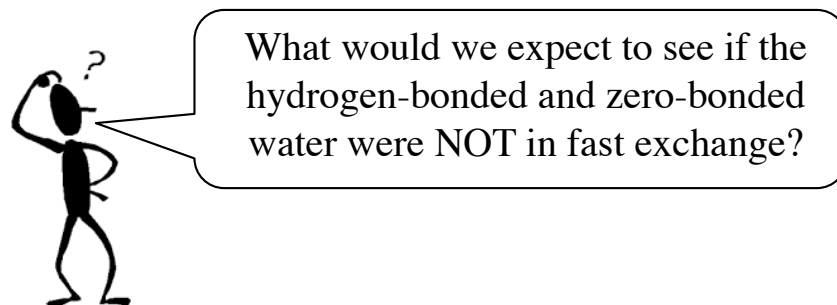
# Temperature mapping with H<sub>2</sub>O

- Under fast exchange, water chemical shift is  $\bar{\Omega} = f_A \Omega_A + f_B \Omega_B$
- Combining with the data provided below,

Table VI. Calculation of the fraction of zero-bonded water from thermal, dielectric, and chemical-shielding data.

Temp (°C)	Thermal	Shielding	Dielectric
0	(0.155)	(0.155)	0.16
25	0.19	0.21	0.19
50	0.22	0.26	0.22
75	0.25	0.31	0.25
100	0.29	0.35	0.29

yields a water proton frequency shift of  $\Delta \cong 0.008$  ppm/°C.



Next Lecture: In vivo water