Lecture #6
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.

$$A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \qquad \underset{\text{Exchange time}}{1/\tau_{ex}} = \underset{\text{Exchange rate}}{k_{ex}} = k_A/k_b$$

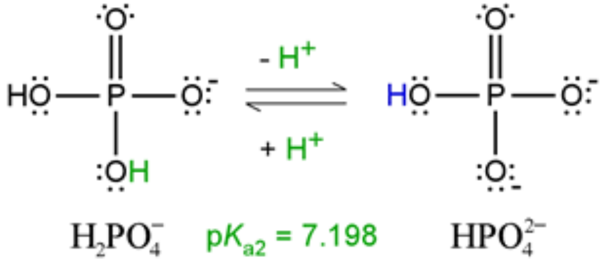
- We'll assume any transition from A to B is instantaneous, but happens at an average rate of $1/\tau_{ex}$.

Chemical Exchange Examples

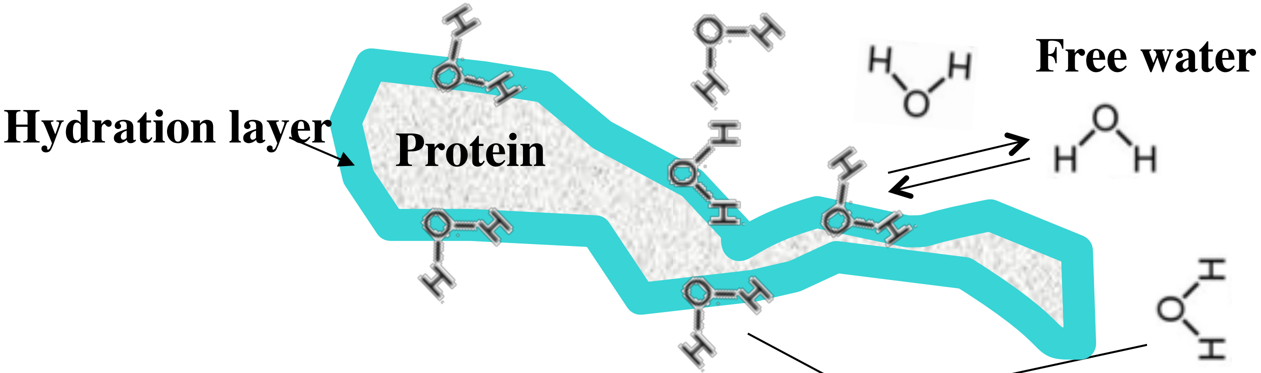
- Intramolecular: inorganic phosphate (^{31}P MRS)

$$H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H^+$$

Different chemical shifts



- Intramolecular: water and hydration layers

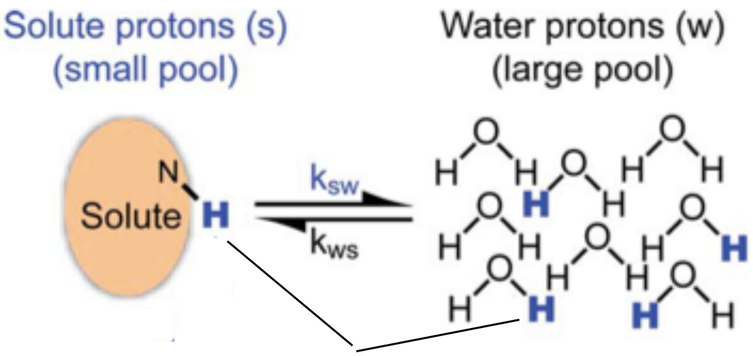

Hydration layer

Protein

Free water

Different correlation times

- Intermolecular: CEST


Solute protons (s)
(small pool)

Water protons (w)
(large pool)

Different chemical shifts

Chemical exchange and τ_c

- Chemical exchange → stochastic modulations → relaxation
- Exchange rates (μs to ms time scales) << 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 → If $1/\tau_e \gg \mathrm{J}$ then $G(\tau) = \langle \mathrm{J}(t)\mathrm{J}(t+\tau) \rangle = \mathrm{J}^2 e^{-|\tau|/\tau_e}$

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

The name for this particular effect is "scalar relaxation of the 1st kind".

In a few lectures, we'll see why J(ω) is probed at ω_I-ω_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…

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

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

Longitudinal Magnetization

Some interesting limiting cases…

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

Case 2: $T_{1B}^{-1} >> \tau_A^{-1}, \tau_B^{-1} >> T_{1A}^{-1} \Rightarrow \alpha_A \approx \tau_A^{-1},\ \alpha_B \approx T_{1B}^{-1}$

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.

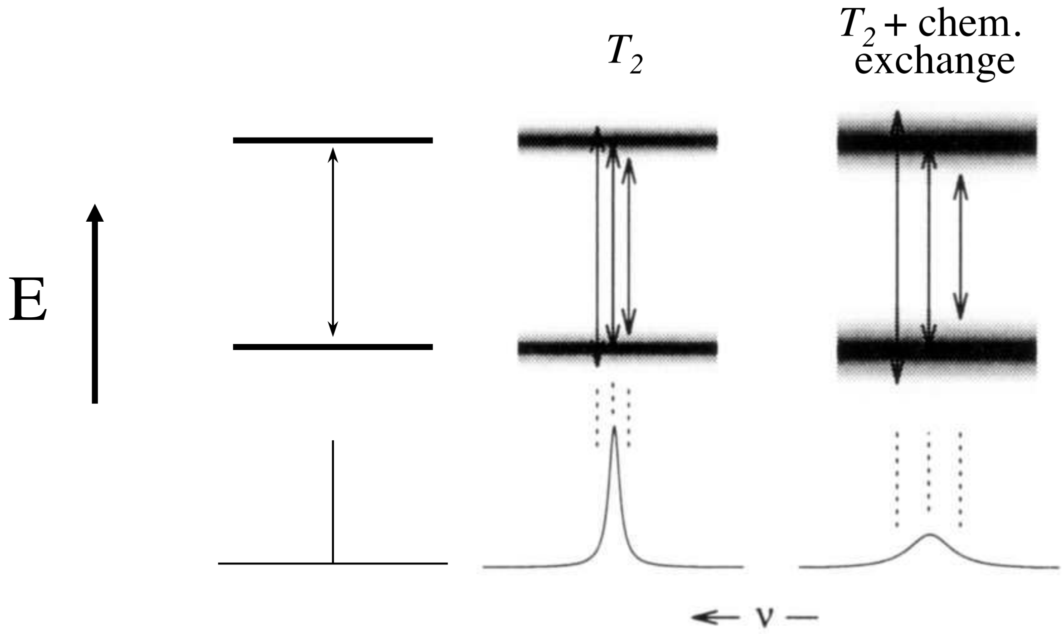
$$\alpha_A = \frac{1}{T_{1A}} + \frac{p_B}{p_A T_{1B} + p_B \tau_A}$$

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

$$\mathrm{A} \underset{k_B}{\overset{k_A}{\rightleftharpoons}} \mathrm{B}$$

- Modified Bloch equations with coupling:

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

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

(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…

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

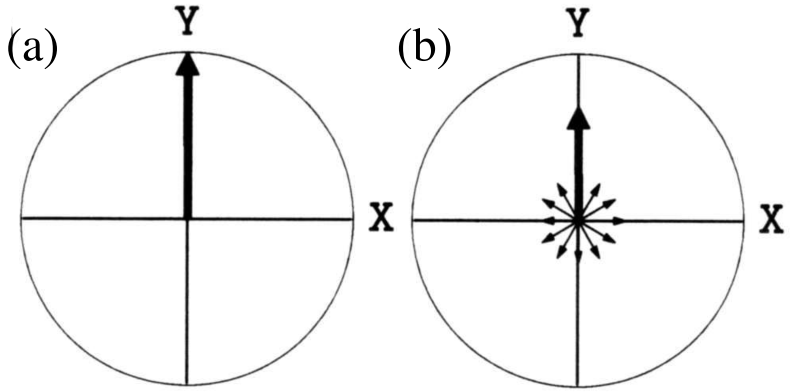
$$\text{and} \qquad \underline{\Omega} = \begin{pmatrix} i\Omega_A + 1/T_2^A & 0 \\ 0 & i\Omega_B + 1/T_2^B \end{pmatrix} \qquad \underline{k} = \begin{pmatrix} -k_A & k_B \\ k_A & -k_B \end{pmatrix}$$

- Solution:

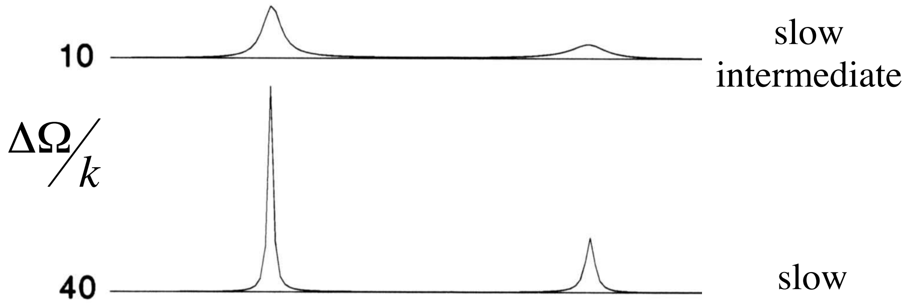
$$\vec{M}_{xy}(t) = e^{\underline{L}t}\vec{M}_{xy}(0)$$

Slow Intermediate Exchange

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



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*.

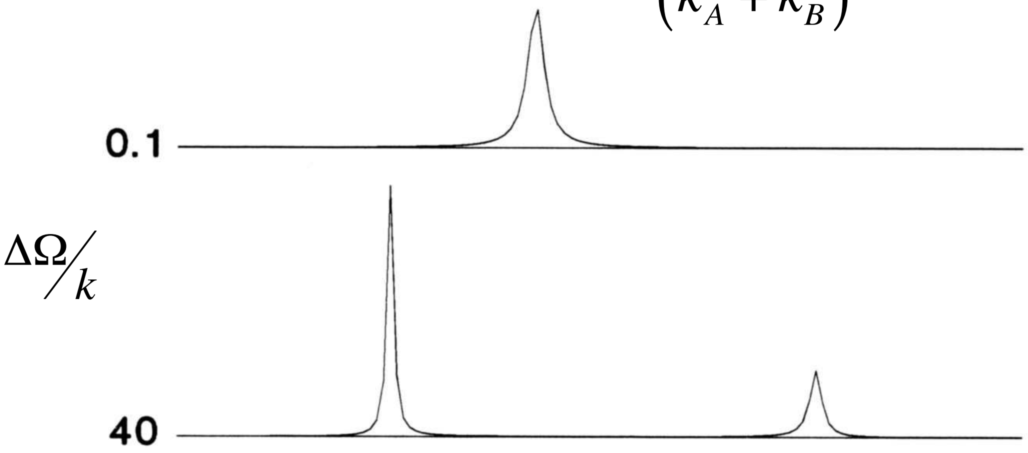
$$\frac{dM_{xy}^A}{dt} = -\left(i\Omega_A + 1/T_{2_{\text{app}}}^A\right)M_{xy}^A \quad \Longrightarrow \quad 1/T_{2_{\text{app}}}^A = 1/T_2^A + k_A$$

Fast Exchange

- Fast exchange: ⇨ $\left|\Omega_A - \Omega_B\right| << k_A, k_B$
- 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:

    $\overline{\Omega} = f_A \Omega_A + f_B \Omega_B$ 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*.

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



Detailed Calculations

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

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

yields (after considerable algebra):

Real part of spectrum

$$S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \boldsymbol{\tau}_{ex}^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\overline{\Omega} - \omega)^2 \boldsymbol{\tau}_{ex}^{-2}} M_0$$

where

$$\overline{\Omega} = f_A\Omega_A + f_B\Omega_B, \quad f_A + f_B = 1, \quad \frac{f_A}{f_B} = \frac{k_B}{k_A}, \quad \boldsymbol{\tau}_{ex} = \frac{1}{k_A + k_B}, \quad \frac{1}{\boldsymbol{\tau}_{ex}} = \frac{1}{\boldsymbol{\tau}_A} + \frac{1}{\boldsymbol{\tau}_B}$$

molar fractions of A and B

molar fractions related to reaction rates:

$$A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B$$

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 ω which correspond to spectral peaks

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

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

➡ peak visible under *slow exchange*

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

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

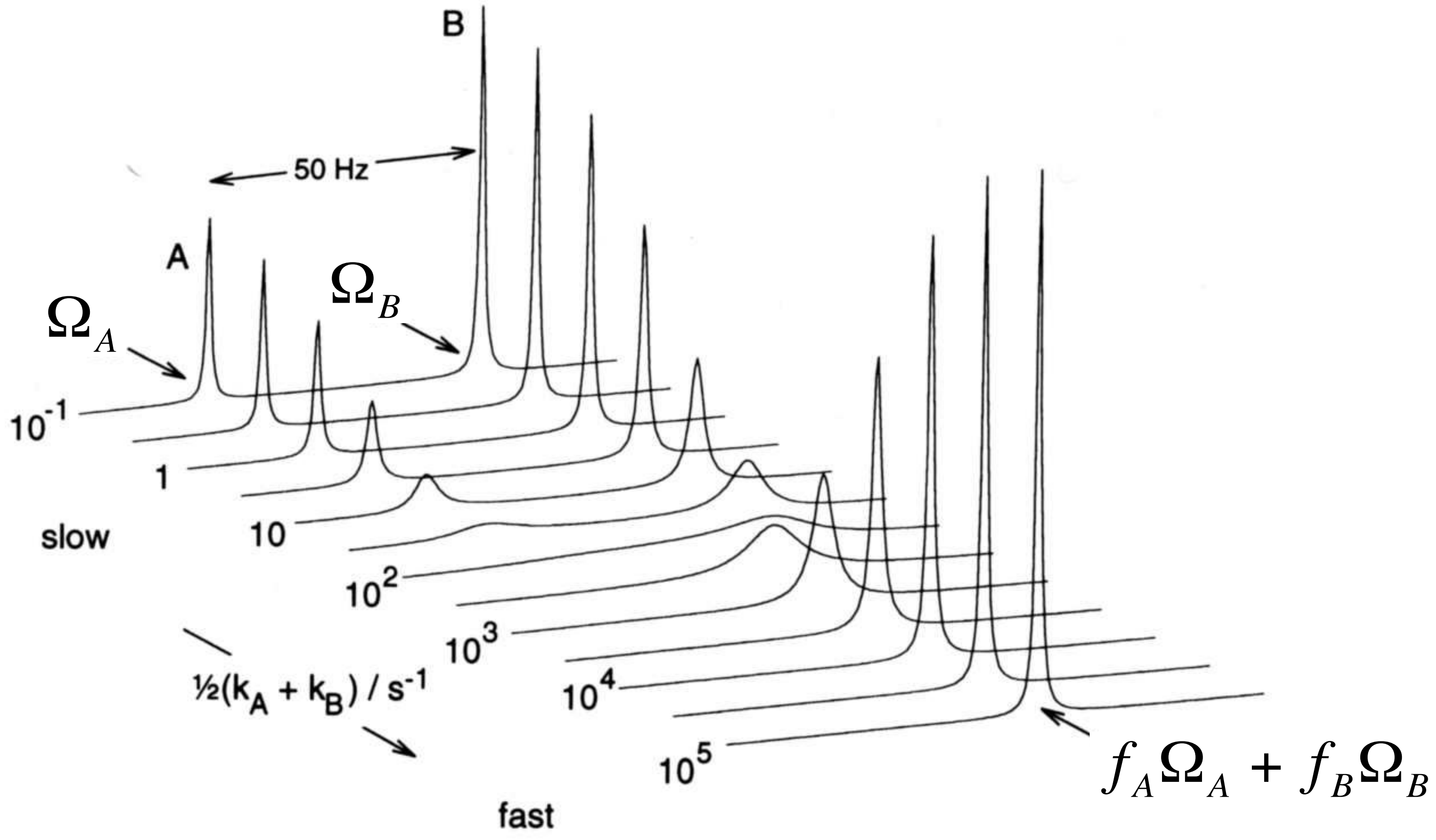
Lorentzian at $\bar{\Omega} = f_A \Omega_A + f_B \Omega_B$

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

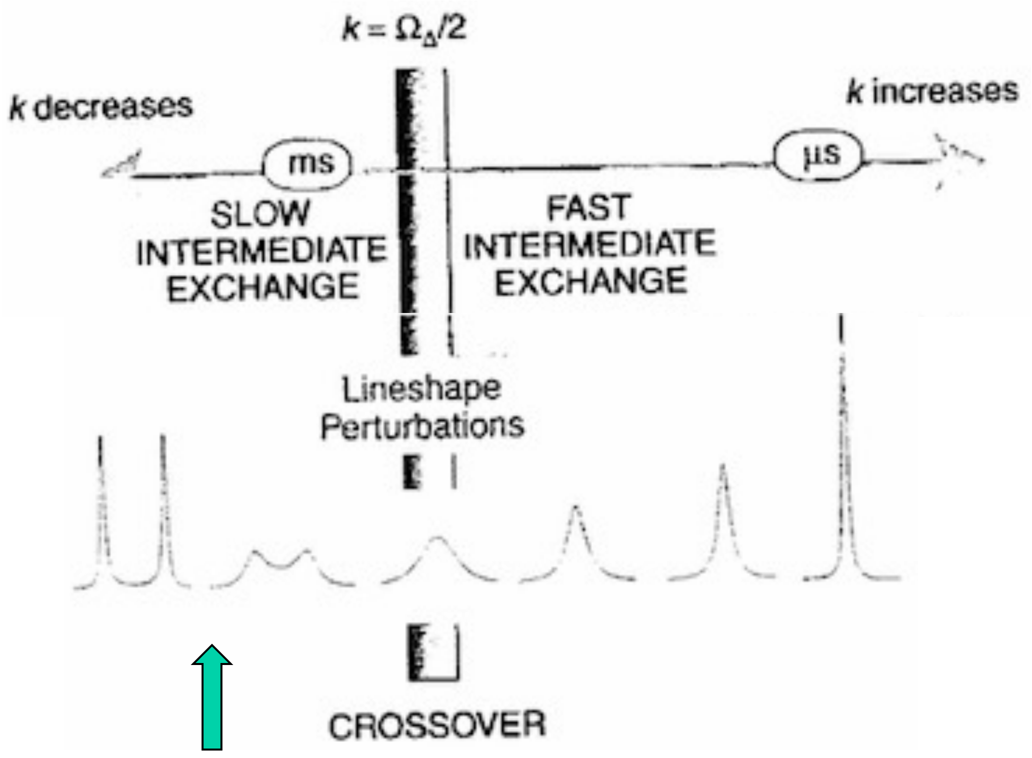
- $S(\omega) = \dfrac{f_A f_B (\Omega_A - \Omega_B)^2 \tau^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\overline{\Omega} - \omega)^2 \tau^{-2}} M_0$ …derived under assumptions that…

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

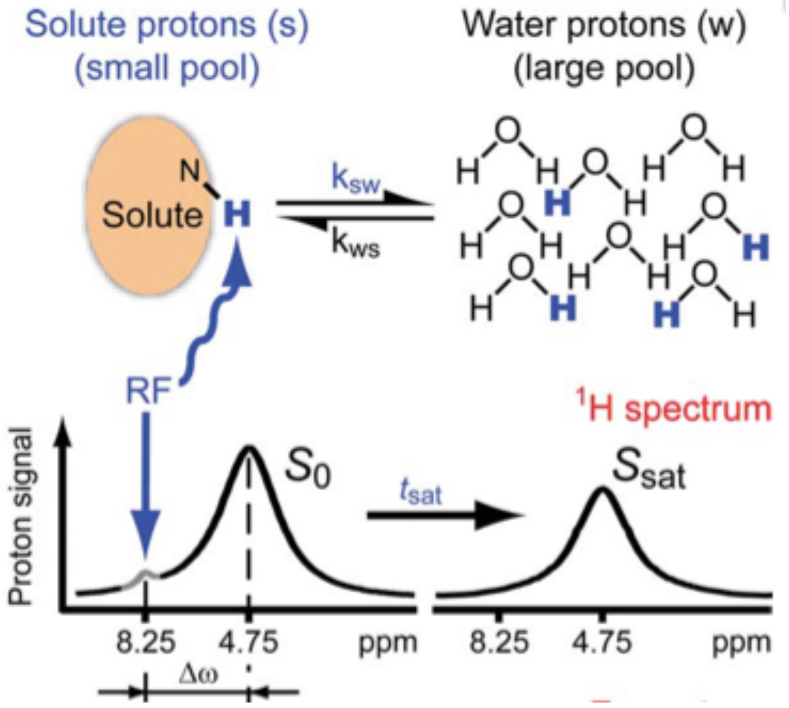
⇨ Not necessarily true for contrast agents.

- 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, τ_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)



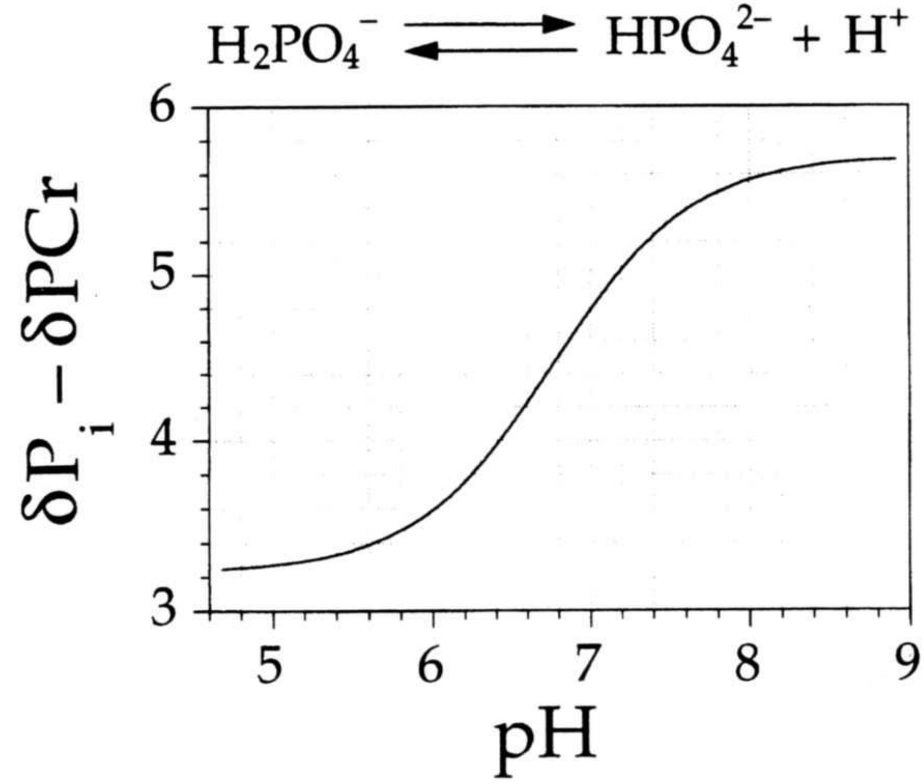
Example 3: Fast Exchange

- $\underset{\nwarrow \Omega_A = 3.2\text{ ppm}}{H_2PO_4^-} \rightleftharpoons \underset{\nwarrow \Omega_B = 5.7\text{ ppm}}{HPO_4^{2-}} + H^+$ (inorganic phosphate)
- Under fast exchange, the ^{31}P Pi peak will be at $\bar{\Omega} = f_A \Omega_A + f_B \Omega_B$
- Henderson-Hasselbach relationship

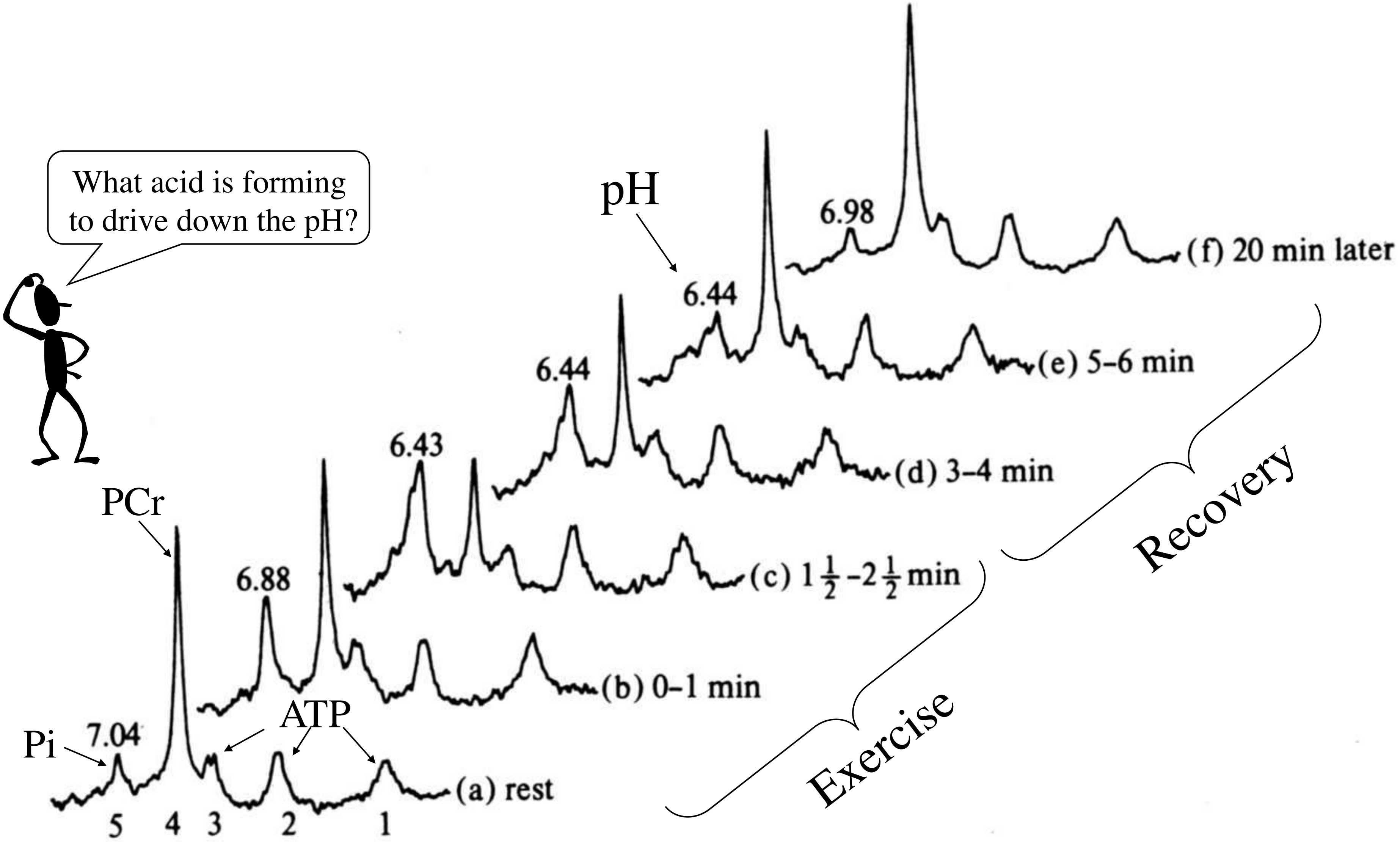
$$\mathrm{pH} = \mathrm{pK_A} + \log\left(\frac{f_A}{1 - f_A}\right)$$

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

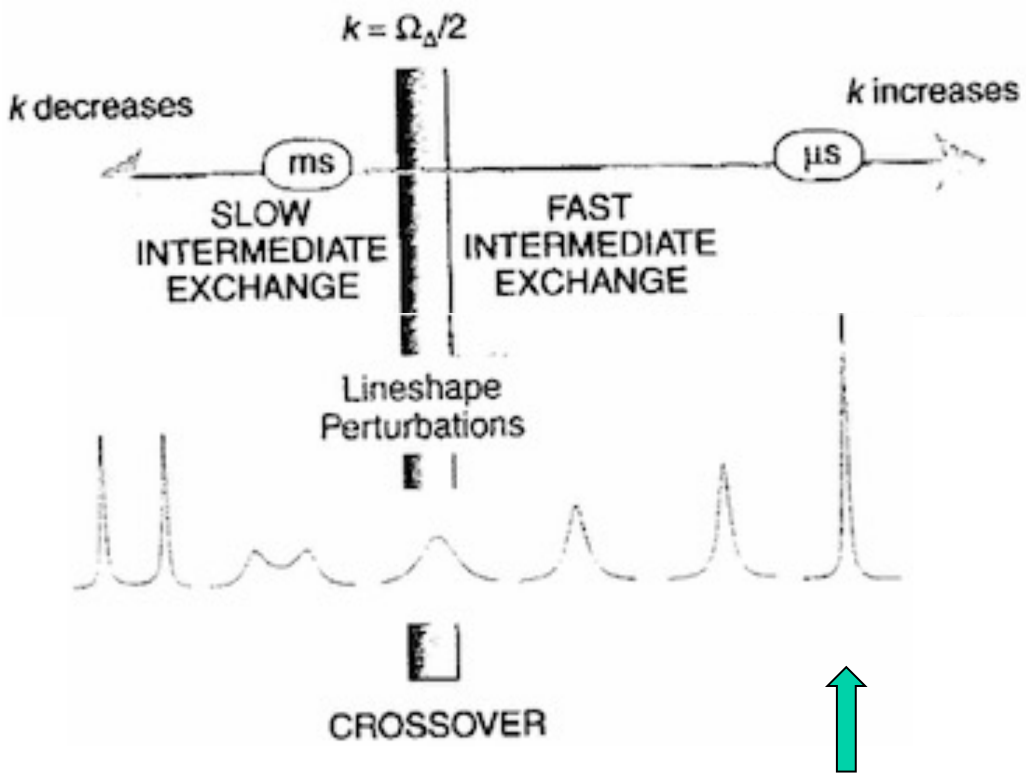
$$\mathrm{pH} = \mathrm{pK_A} + \log\left(\frac{\omega - \Omega_A}{\Omega_B - \omega}\right)$$



^{31}P Exercise Study



Example 4: Fast Exchange



Temperature mapping via water chemical shift

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

Temperature mapping with H_2O

- 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_2O

- 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 (ºC)	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/ºC.

What would we expect to see if the hydrogen-bonded and zero-bonded water were NOT in fast exchange?

Next Lecture: In vivo water