From Physics to Biology and Medicine

李寬容
清華大學分子醫學研究所

學經歷

- **1974** 清華大學 化學系
- **1976-1981 University of Rochester**

  (Ph.D. in Physical Chemistry; NMR)
- **1981-1982 University of Pennsylvania** 醫學院

  (NIH Postdoctoral Fellow)
- **1982-1984** 成功大學生物系

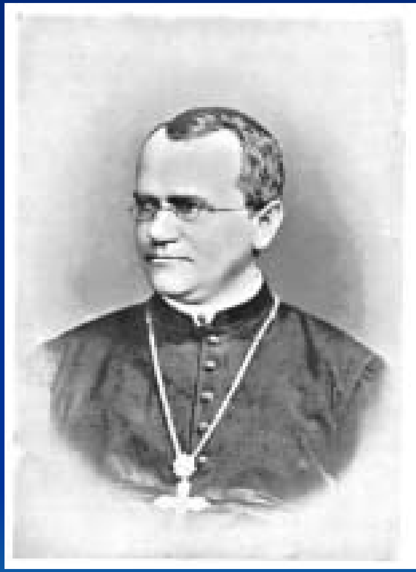
  (籌設成功大學醫學院**)**
- **1985-** 迄今 清華大學 **(**分子生物**,** 分子醫學**)**

上帝的數不清的謎語,
絕大部份靠物理學家來破解:
宇宙形成之謎, 太陽系形成之謎,
地球形成之謎,
演化之謎, 遺傳之謎
每一件都是物理學家練功的
偉大傑作.
沒有物理學家,
我們現在仍然靠打獵過日子.

今天 focus 的重點:

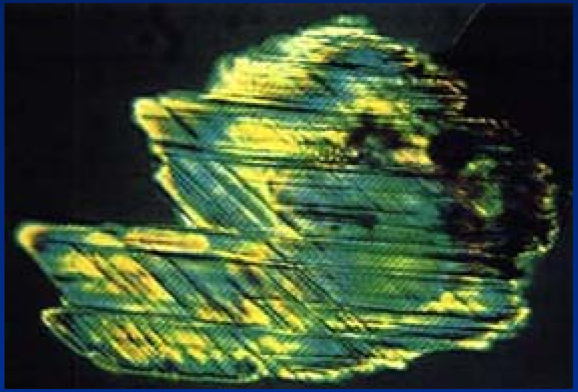
理論物理對醫學科學的偉大貢獻

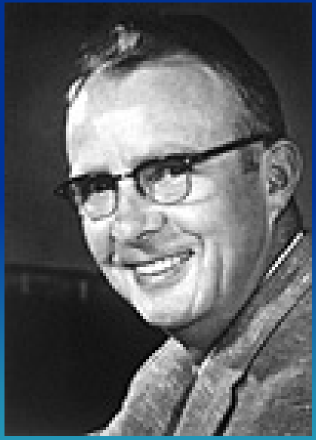
Gregor Mendel (1822-1884)
The Beginning of Biomathematics



Christian Doppler (1803-1853)

The extinction of dinosaurs

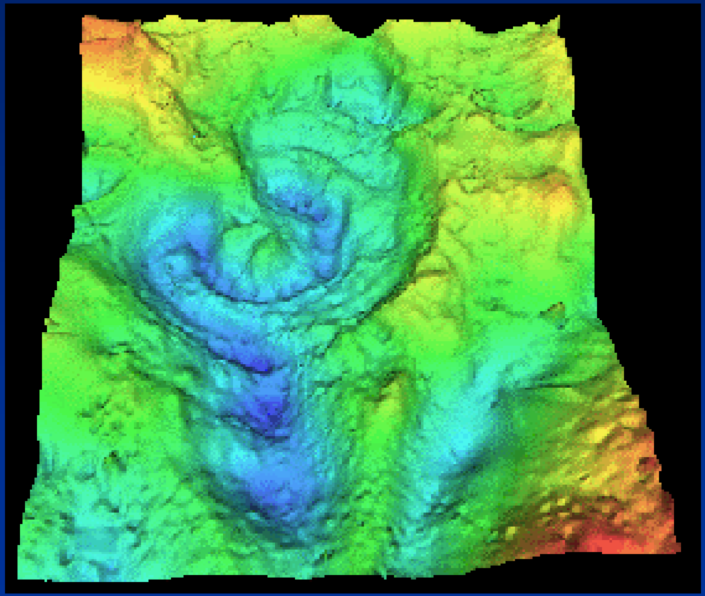




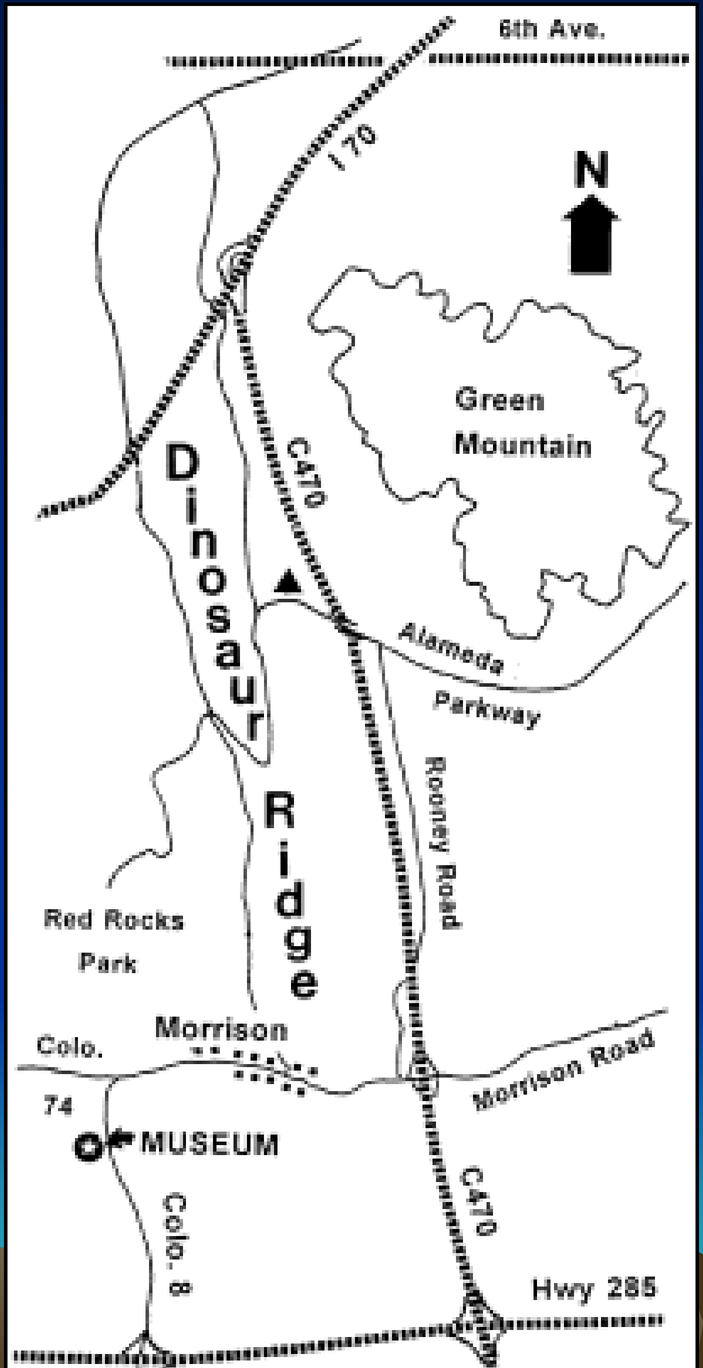
Luis Alvarez
Nobel Prize in
Physics 1968

The possible hit of meteorite 65 million years ago

The Yucatan Peninsula

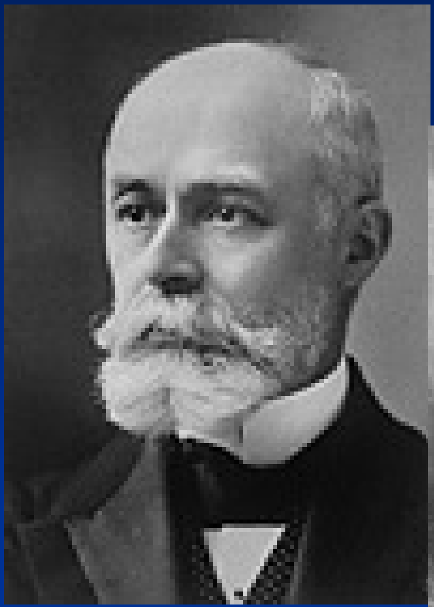


Chicxulub, Yucatan Peninsula, Mexico


6th Ave.
I 70
N
Green
Mountain
Dinosaur
Ridge
C470
Alameda
Parkway
Rooney Road
Red Rocks
Park
Morrison
Colo.
74
Morrison Road
MUSEUM
Colo. 8
C470
Hwy 285

Wilhelm Conrad Roentgen (1845-1923)

The Nobel Prize in Physics 1903
(The 2nd Nobel Prize in Chemistry 1911-Curie)



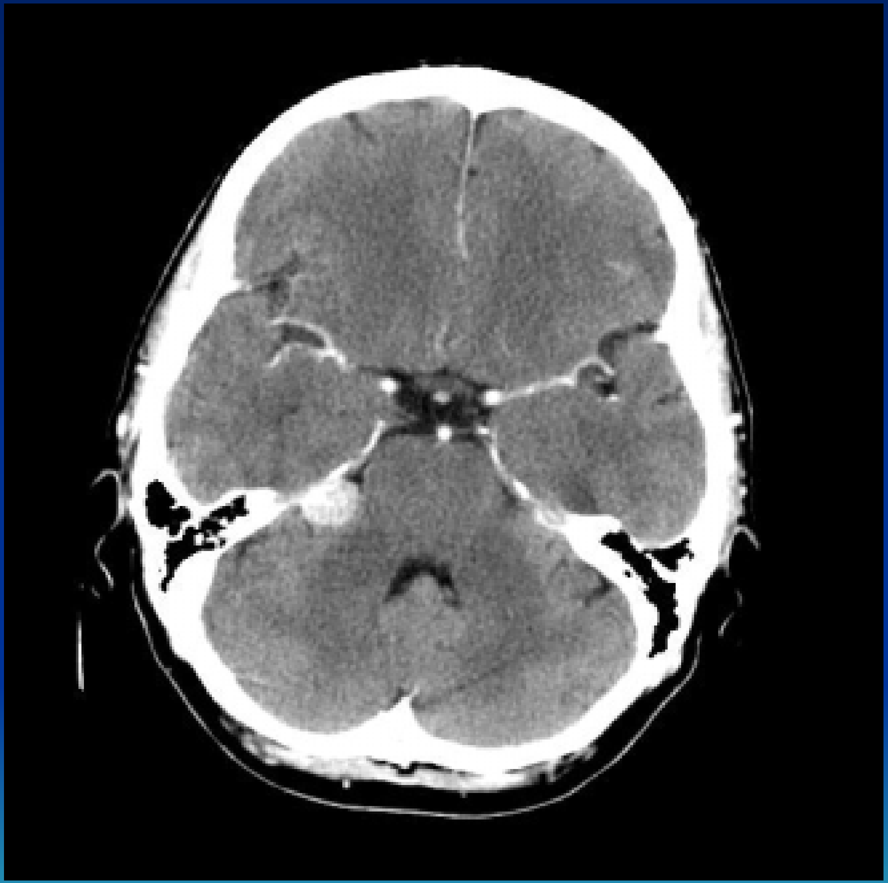

The Nobel Prize in Physiology or Medicine 1979 (Computer Assisted Tomography, CAT)

Allan M. Cormack
Tuft University, USA

Godfrey N. Hounsfield
EMI, England

Computer assisted tomography (CAT)

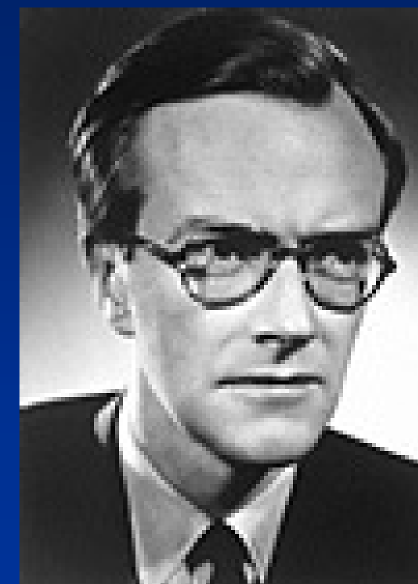
CAT images of brain and spine



The Nobel Prize in Physiology or Medicine 1962

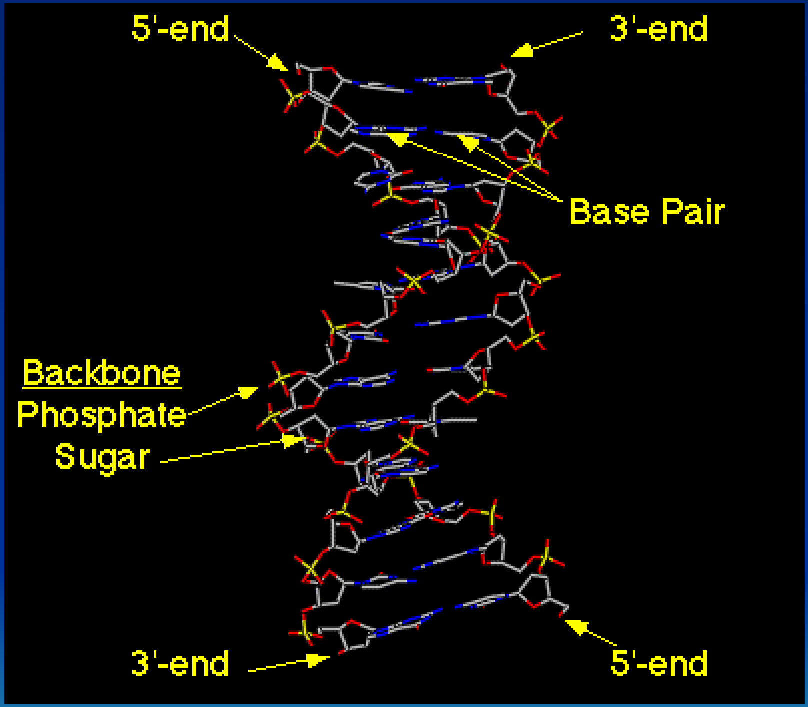
Francis Harry Compton Crick

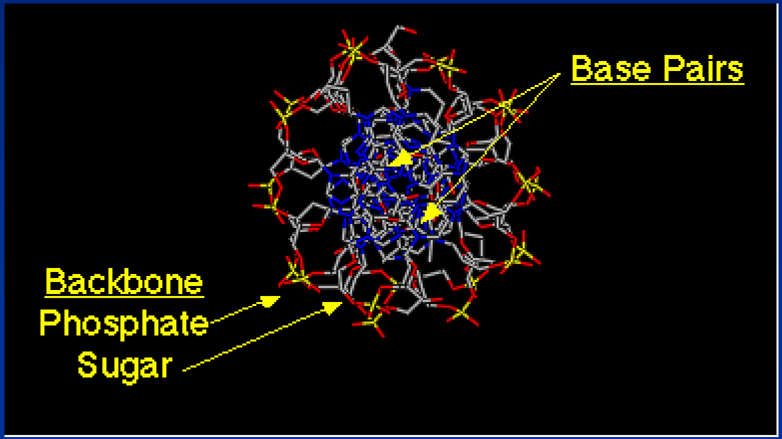
James Dewey Watson



Maurice Wilkins

DNA double helix

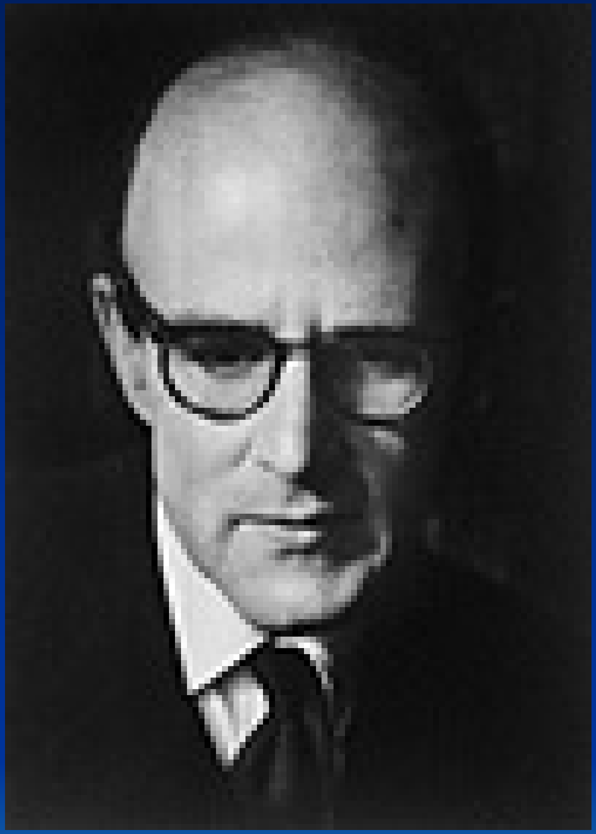


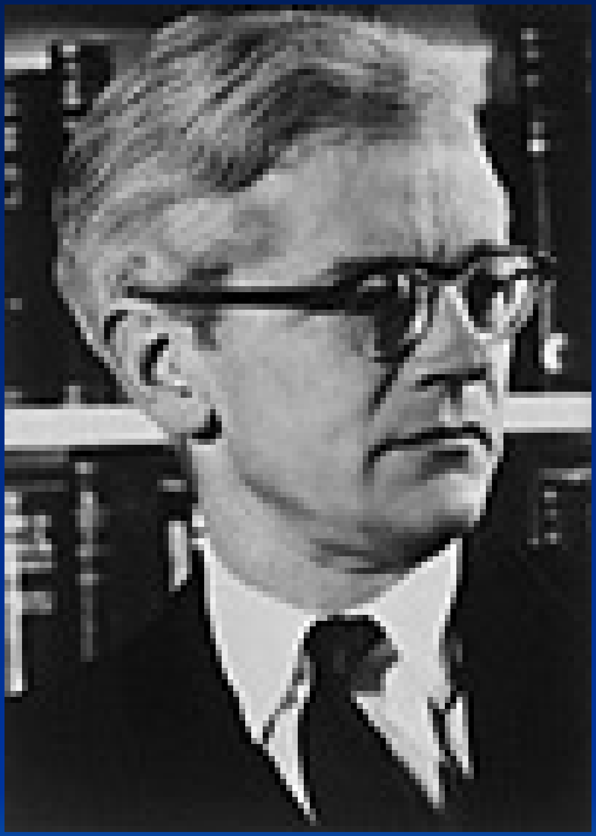


Side-view

Top-view)

The Nobel Prize in Chemistry 1962

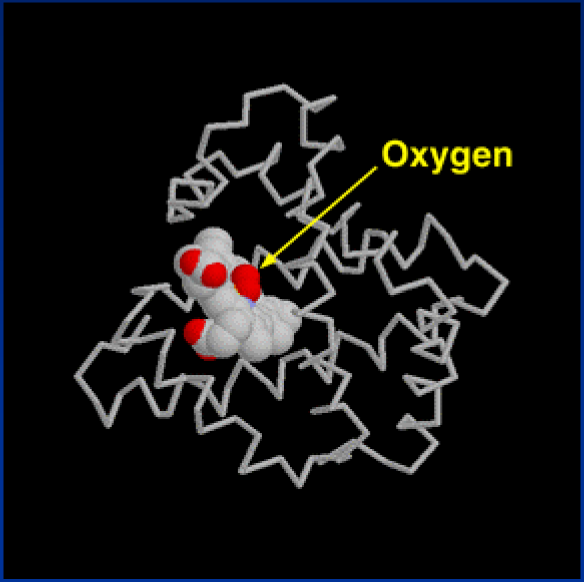


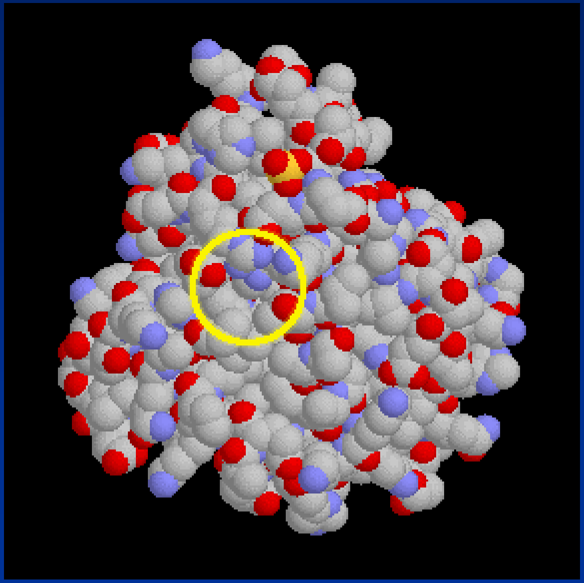


Max Ferdinand Perutz
(Hemoglobin)

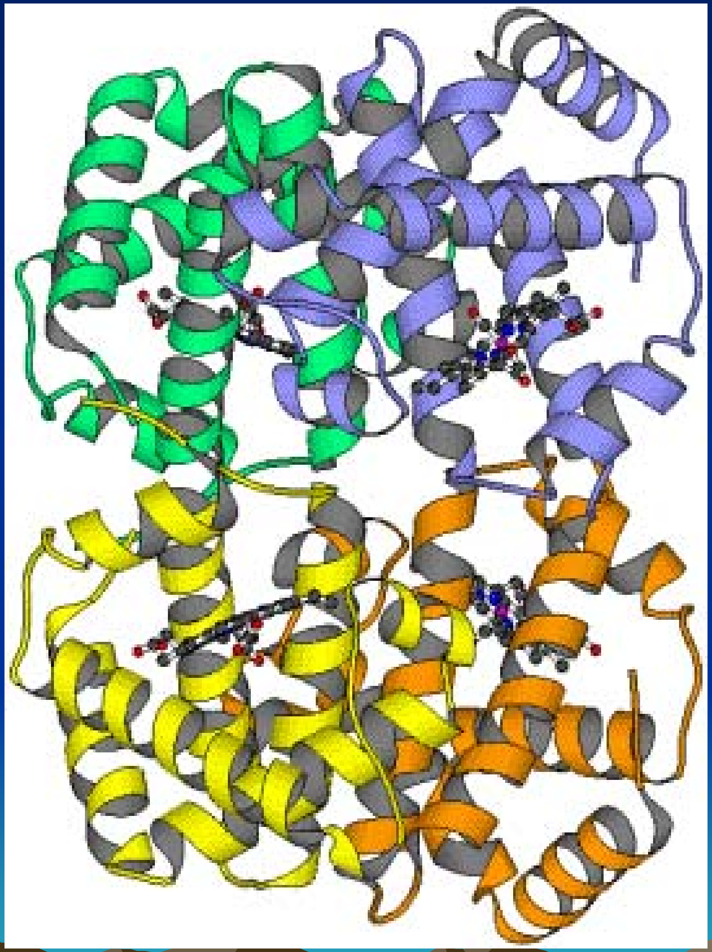
John Cowdery Kendrew
(Myoglobin)

John Kendrew's original myoglobin structure

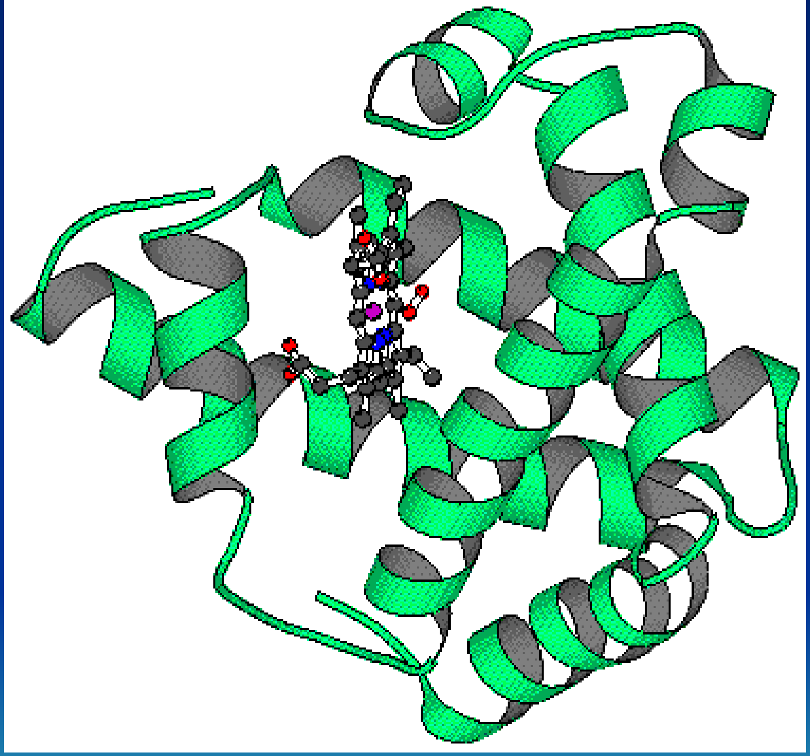




Hemoglobin and myoglobin



Hemoglobin



Myoglobin

物理學家的貢獻

- 180億年前宇宙形成之謎.
- 6500萬年前生物大滅絕之謎.
- 38億年來遺傳的定律.
- 38億年前地球自有生命以來的遺傳之謎.
- 解開血紅素的結構, 闡釋鐮刀型貧血的原因.

物理學家對生物及醫學的貢獻

- 發現了X-Ray.
- 發現了γ-Ray.
- 發明了CAT.
- 發明了MRI.

MRI
(Magnetic Resonance Imaging)
磁振造影

Press Release: The 2003 Nobel Prize in Physiology or Medicine

English
French
German
Swedish

6 October 2003

The Nobel Assembly at Karolinska Institutet has today decided to award The Nobel Prize in Physiology or Medicine for 2003 jointly to

Paul C Lauterbur and **Peter Mansfield**

for their discoveries concerning

"magnetic resonance imaging"

Nobel prize in Medicine or Physiology 2003

Paul C. Lauterbur

Peter Mansfield

Nobel Committee SUMMARY 1/3

- Imaging of human internal organs with exact and non-invasive methods is very important for medical diagnosis, treatment and follow-up. This year's Nobel Laureates in Physiology or Medicine have made seminal discoveries concerning the use of magnetic resonance to visualize different structures.

Nobel Committee SUMMARY 2/3

These discoveries have led to the development of modern magnetic resonance imaging, MRI, which represents a breakthrough in medical diagnostics and research.

Nobel Committee SUMMARY 3/3

Atomic nuclei in a strong magnetic field rotate with a frequency that is dependent on the strength of the magnetic field. Their energy can be increased if they absorb radio waves with the same frequency (resonance). When the atomic nuclei return to their previous energy level, radio waves are emitted. These discoveries were awarded the Nobel Prize in Physics in 1952.

Paul Lauterbur*

Paul Lauterbur (born 1929), Urbana, Illinois, USA, discovered the possibility to create a two-dimensional picture by introducing gradients in the magnetic field. By analysis of the characteristics of the emitted radio waves, he could determine their origin. This made it possible to build up two-dimensional pictures of structures that could not be visualized with other methods.

*From Nobel Committee

Peter Mansfield*

Peter Mansfield (born 1933), Nottingham, England, further developed the utilization of gradients in the magnetic field. He showed how the signals could be mathematically analyzed, which made it possible to develop a useful imaging technique. Mansfield also showed how extremely fast imaging could be achievable. This became technically possible within medicine a decade later.

*From Nobel Committee

Magnetic Resonance Imaging*

Magnetic resonance imaging, MRI, is now a routine method within medical diagnostics. Worldwide, more than 60 million investigations with MRI are performed each year, and the method is still in rapid development. MRI is often superior to other imaging techniques and has significantly improved diagnostics in many diseases. MRI has replaced several invasive modes of examination and thereby reduced the risk and discomfort for many patients.

*From Nobel Committee

Other NMR Nobel Prizes*

Several Nobel Prizes

The resonance phenomenon is governed by a simple relation between the strength of the magnetic field and the frequency of the radio waves. For every type of atomic nucleus with unpaired protons and/or neutrons, there is a mathematical constant by which it is possible to determine the wavelength as a function of the strength of the magnetic field. This phenomenon was demonstrated in 1946 for protons (the smallest of all atomic nuclei) by **Felix Bloch** and **Edward Mills Purcell**, USA. They were awarded the Nobel Prize in Physics in 1952.

*From Nobel Committee

Recent NMR Nobel Prizes* 1/2

In 1991, Richard Ernst, Switzerland, was awarded for his contributions to the development of the methodology of high resolution nuclear magnetic resonance spectroscopy.

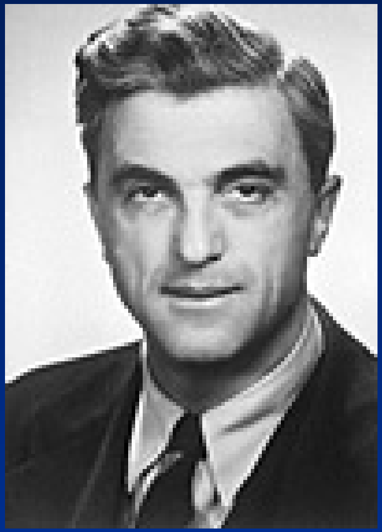
*From Nobel Committee

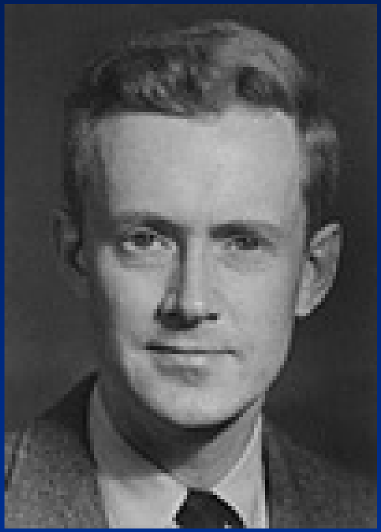
Recent NMR Nobel Prizes* 2/2

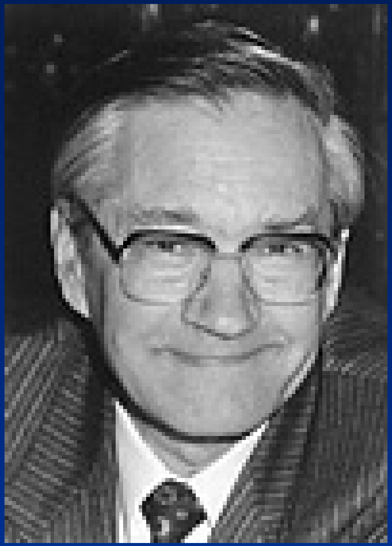
In 2002, Kurt Wüthrich, also from Switzerland, was awarded for his development of nuclear magnetic resonance spectroscopy for determination of the three-dimensional structure of biological macromolecules in solution.

* From Nobel Committee

永垂不朽的 NMR 千古英雄







Rapid development within medicine*

The medical use of magnetic resonance imaging has developed rapidly. The first MRI equipments in health were available at the beginning of the 1980s. In 2002, approximately 22 000 MRI cameras were in use worldwide, and more than 60 million MRI examinations were performed.

*From Nobel Committee

Areas of NMR application

- High resolution NMR (spectroscopy)

  Used for chemical analysis

- Solid state NMR (spectroscopy)

  Used for chemical and material/industrial analyses

- MR imaging (solid/semi-solid/liquid)

  Used for medical diagnosis

  - **MR imaging (Proton density, T1/T2 imaging)**
  - **MR angiography (血管攝影)**
  - **MR functional (功能攝影)**

Basic principle of NMR

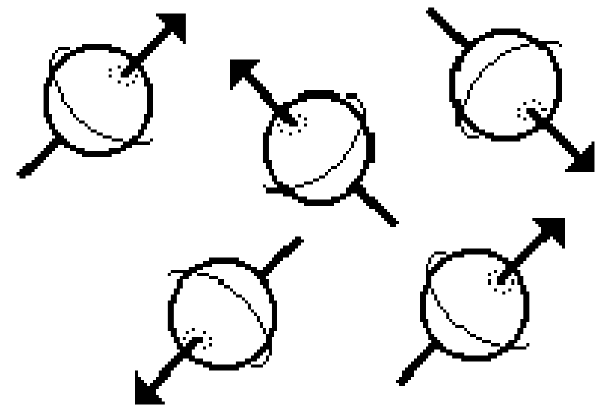


Figure 1
Randomly oriented
nuclear magnetic moments

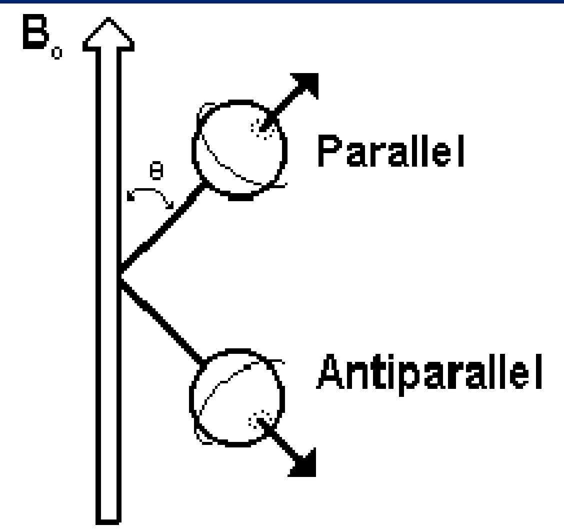


Figure 2
Nuclear magnetic moments
in the presence of an external field

α

β

Without external magnetic Field B_0

With external magnetic Field B_0

Nuclear Zeeman splitting

- The interaction energy between magnetic moment μ and external static magnetic field B_0 is:

  $E = -\mu \cdot B_0$

  The energy difference (Zeeman splitting) between α and β states is:

$$\Delta E_{Zeeman} = +\frac{1}{2}\gamma\hbar B_0 - \left[-\frac{1}{2}\gamma\hbar B_0\right] = \gamma\hbar B_0$$

B_0 and B_1 fields are absolutely necessary for observing NMR phenomenon

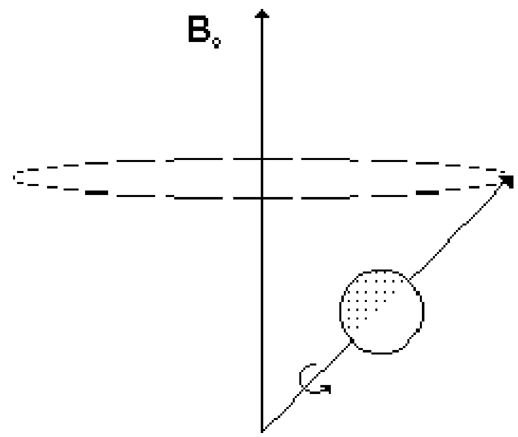


Figure 3
A spinning nucleus
precessing about B_0

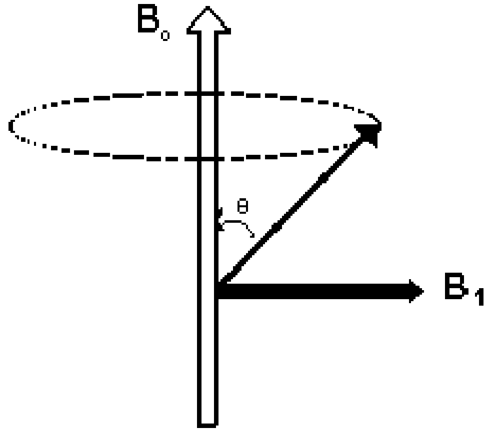


Figure 4

RF energy at the Larmor frequency acts as a second magnetic field. When the RF is on, the nuclei will precess about B_1

B_0 to generate bulk magnetic moment M

B_1 to generate $\alpha \rightarrow \beta$ nuclear transition

T_1 and T2 relaxations (Along z-axis and XY-plane)

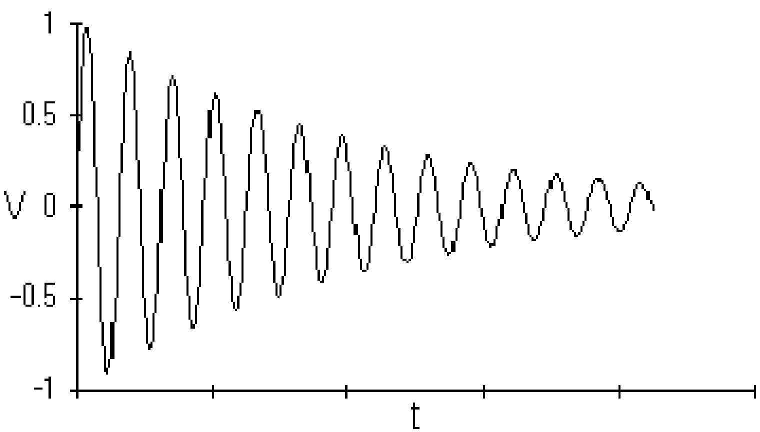
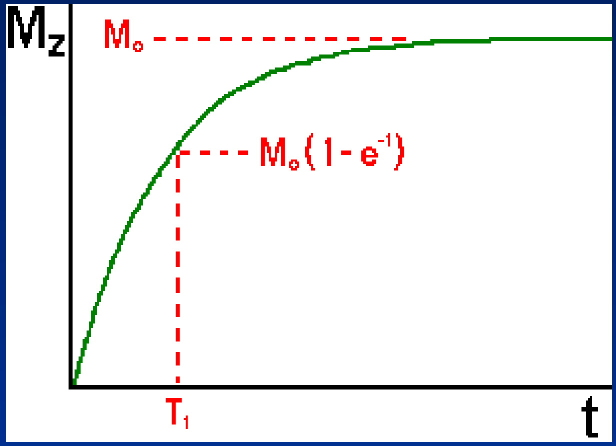
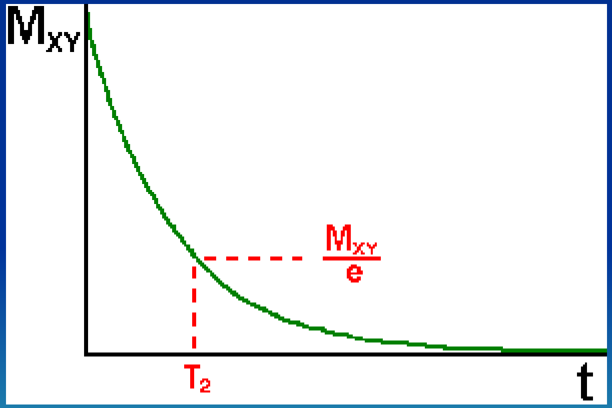


Figure 5
The voltage signal induced
in the receiver coil versus time.



T_1 relaxation



T_2 relaxation

Magnetization on the XY plane

The Bloch equations

$$\frac{dM_{x'}}{dt} = (\omega_o - \omega) M_{y'} - \frac{M_{x'}}{T_2}$$

$$\frac{dM_{y'}}{dt} = -(\omega_o - \omega) M_{x'} + 2\pi\gamma B_1 M_z - \frac{M_{y'}}{T_2}$$

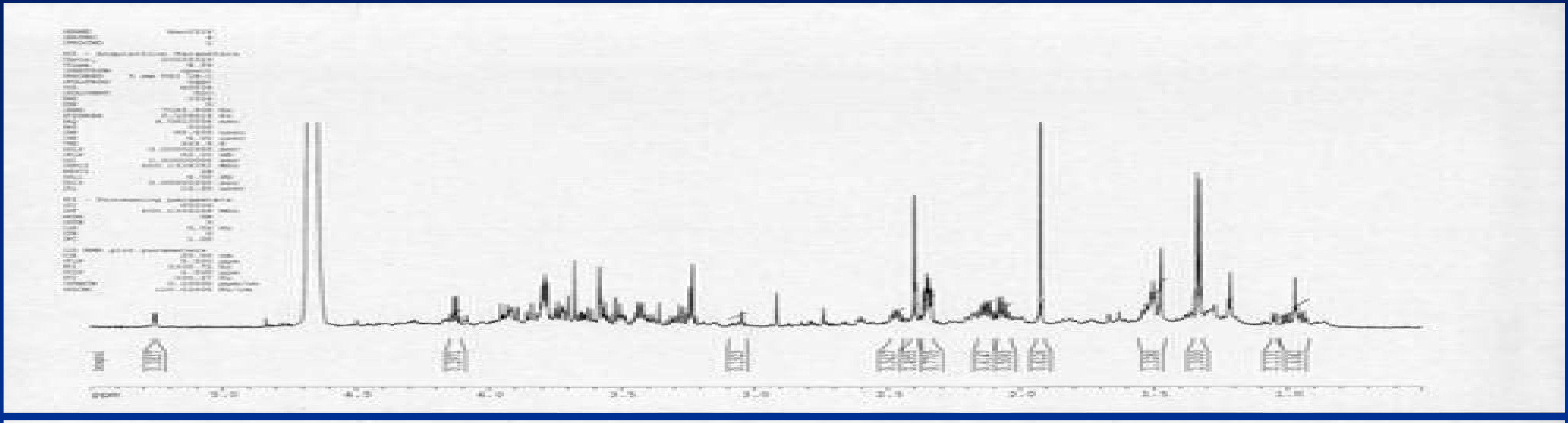
$$\frac{dM_z}{dt} = -2\pi\gamma B_1 M_{y'} - \frac{(M_z - M_{z_o})}{T_1}$$

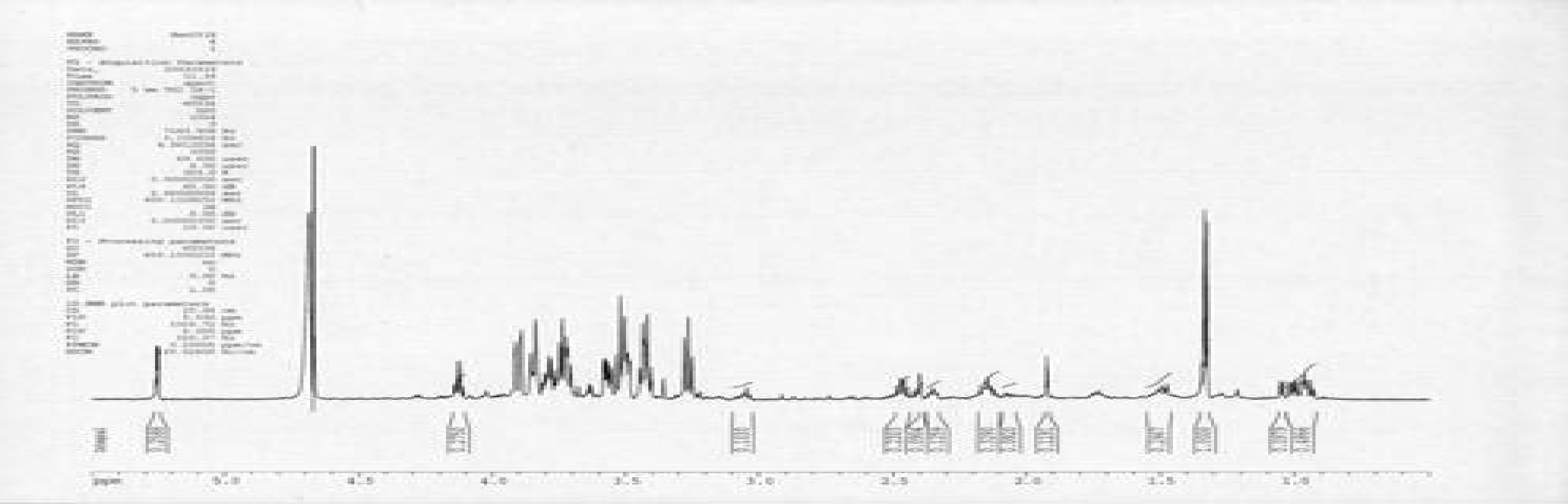
1D-NMR signal processing: 1D Fourier transform

$$\mathbf{f(w) = \int f(t)\, exp(-iwt)\, dt}$$

Time domain becomes frequency domain

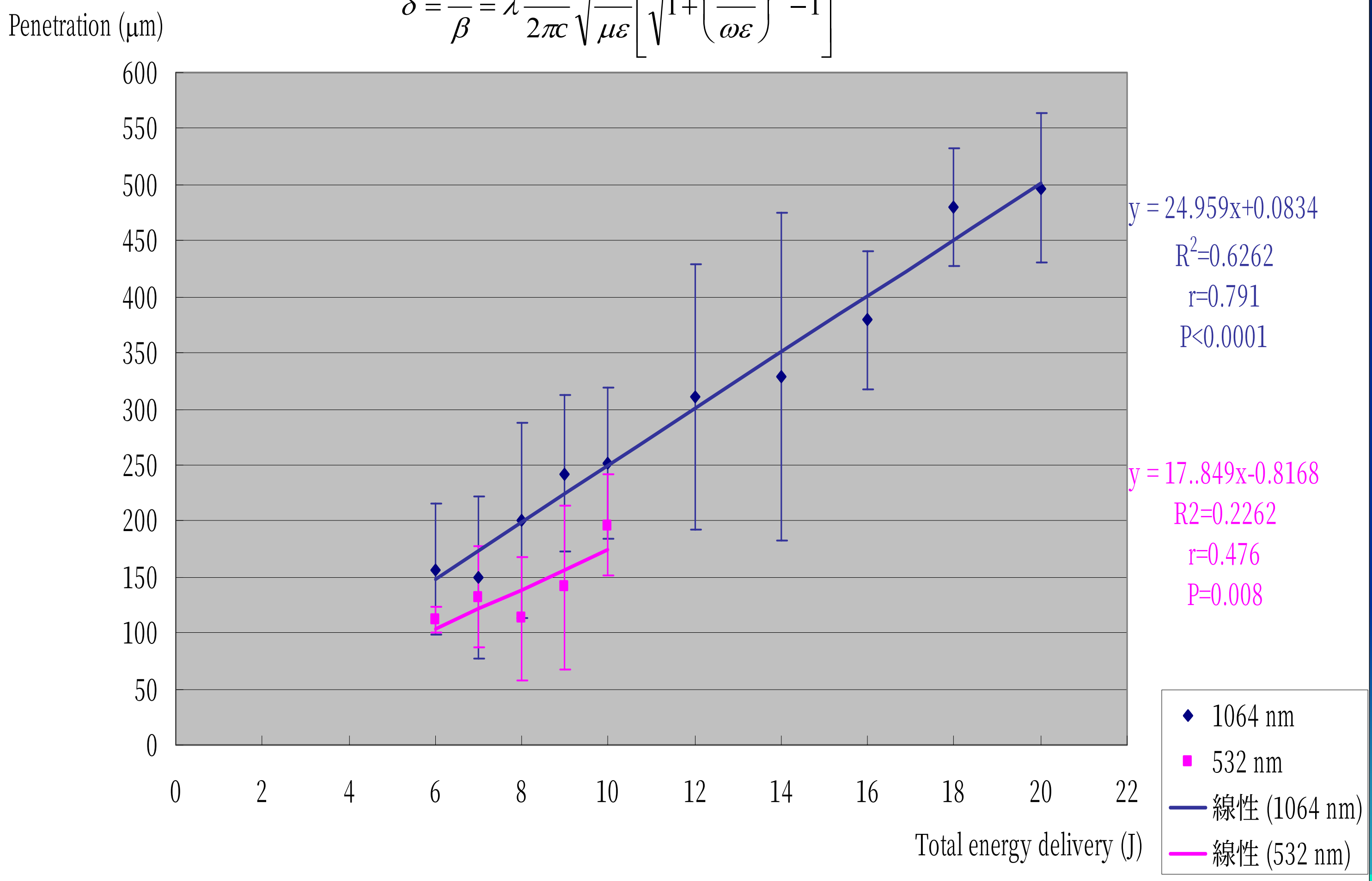
High resolution NMR spectroscopy





The Wave Equation for the Apparent Penetration of Laser into Epidermis

$$\delta = \frac{1}{\beta} = \lambda \frac{n}{2\pi c}\sqrt{\frac{2}{\mu\varepsilon}}\left[\sqrt{1+\left(\frac{\sigma}{\omega\varepsilon}\right)^2}-1\right]^{-\frac{1}{2}}$$



Magnetic field gradient

- How about if add a magnetic field gradient, G_x, along the x-axis, such that in z-axis,

$$B(x) = B_0 + G_x \cdot x$$

on a constant homogeneous magnetic field?

- Then, the absorption frequency $\omega(x)$ is a function of x.

Two more magnetic field gradients

- If another two field gradients are applied on y- and z-axis, respectively, then the NMR absorption frequency will be dependent on the localization (x, y, z).
- Thus, we need three orthogonal field gradient coils to generate a space-specific volume element. A set of n linearly independent gradients would do the same thing in n-dimensional space.