

## 1.1 Non-invasive medical imaging techniques

In the last few decades, several non-invasive imaging techniques have been discovered which are capable of providing full 3-D information of an object. Earlier methods had either

- lost spatial information (e.g. standard X-rays, failing to discriminate between overlapping structures), or
- been highly invasive (for ex. 'serial-section microscopy', typically requiring the object to be frozen and then sliced up).

Important non-invasive imaging methods include

1. *Ultrasound*. Very high sound frequencies (several MHz) allow beams to remain very narrow. These beams are typically sent / received by a small transducer which is held in contact with the body. It can rapidly change the direction of the beam, making it 'sweep' an angular domain. Echoes from interfaces between different soft tissue types are recorded, with time delays corresponding to depths. The technique is used for a large number of organs, including fetal monitoring during pregnancy. The method is considered very safe, gives images in real-time, and the equipment is inexpensive. Strong sound absorption by bones somewhat limits its use, for ex. in brain studies.
2. *CT - Computerized Tomography*. A parallel sheet of X-rays is sent through the object, and recorded by a 1-D row of detectors. From the accumulated data when source and receiver (or object) are rotated  $180^\circ$ , cross-sectional images (Greek  $\tau\omega\mu\omega\sigma$  = slice) can be computed. In medical application, the resolution is normally about 0.3 mm. With the use of much more intense X-rays (which would destroy living tissues; such X-rays can be obtained from accelerators in the form of synchrotron radiation), resolutions around 0.001 mm (= 1  $\mu\text{m}$ ) are achieved. This is comparable to the best resolution that is possible with optical microscopes when used on sliced samples. Some drawbacks with medical use of X-ray tomography include possible tissue damage from ionization (X-ray absorption depends on the target's electron density), and low contrasts between different types of soft tissues (e.g. between malignant and healthy ones).

Mathematical tools needed for successful CT imaging were more than once discovered, not recognized for their potential, and then forgotten before successful experimental realizations (employing less effective algorithms) were achieved. For independent pioneering work in experimentally realizing CT and bringing it to medical use, the 1979 Nobel Prize in Physiology and Medicine was awarded jointly to G. Hounsfield and A.M. Cormack. The history of CT and other applications of it are described in more detail in Section 1.2.

3. *MRI - Magnetic Resonance Imaging* (earlier called NMR - Nuclear Magnetic Resonance). The object that is to be imaged is placed in a very strong, highly uniform magnetic field (e.g. inside a large superconducting magnet). Two different (relatively weak) magnetic gradients are introduced - one stationary and (orthogonal to it) one that is stepped in time. When subjected to accurately tuned high frequency radio pulses, many light atoms (with an odd number of nucleons, such as hydrogen) start to spin. While returning to a state of magnetic alignment, they re-radiate these waves. The frequency is proportional to the local magnetic field, i.e. it carries information about the positions of the different atoms. The numerical

techniques needed to create images are similar to those used in CT (with Fourier inversion nowadays preferred over back projection-type algorithms). Advantages of MRI over CT in medical applications include

- high contrast between many different soft tissues,
- possibility (although little used) to 'tune in' on different atoms with very distinct biological functions (e.g.  $^1\text{H}$ ,  $^{23}\text{Na}$ , and  $^{31}\text{P}$  resonate at 42.57, 11.26 and 17.24 MHz resp. in a field of 1 Tesla), and
- far safer radiation (the frequencies are about 11 orders of magnitude lower than those of X-rays - the associated electromagnetic quanta carry correspondingly less energy, and cannot alter molecules of living tissues). In spite of using wavelengths in the 5 - 25 meter range, 1-2 mm resolution is obtained.

Disadvantages compared to CT include slightly less resolution and higher cost of equipment. In practical usage, the big risk factor has turned out to be that inadvertently present metallic objects can become dangerous projectiles due to the extreme magnetic fields. Even minute amounts of iron can cause problems (e.g. the iron-based pigments in some tattoo inks can sometimes deny such patients access to MRI diagnostics).

The Nobel Prize in Physics for 1952 was awarded to E. Purcell and F. Bloch (at Harvard and Stanford Universities) for their discovery of the NMR phenomenon. The problem of obtaining spatial information from NMR data was considered already in the early 50's and solved (in different ways) in the mid-70's. Routine medical use began in the mid-80's. Technology improvements have reduced recording times from hours to, in some cases, 30-100 ms (when using echo-planar imaging (EPI) - a high-speed recording technique that permits a full image to be obtained in a single nuclear excitation cycle (as opposed to a few hundred cycles; c.f. Stehling et.al. (1991) ). The principles of MRI are summarized in Pykett (1982).

4. *PET - Positron Emission Tomography.* A radioactively labeled substance is injected and follows the blood stream, while emitting positrons. After traveling a very short distance, a positron will encounter an electron, and annihilate it. The energy gets transferred into two gamma rays that are sent off in nearly perfectly opposite directions of each other. When two detectors (out of a big array surrounding the body part - typically the head) detect signals at the same instant, the emission is assumed to have occurred along the straight line between them. This procedure generates data on the accumulated concentrations of the tracer substance along a large number of different lines through the body, thus allowing its distribution to be reconstructed through 3-D generalizations of the 2-D CT algorithms that are described in Sections 1.3 - 1.7.

When using radioactively labeled glucose, brain activities can be followed in 'real time', since the blood flow (and glucose usage) very quickly responds to areas of activity (however, EPI-type MRI, in connection with the use of contrast agents in the blood offer competition to PET in this field). Another usage is based on the fact that certain substances tend to concentrate in different tissues, e.g.  $\text{Cu}^{64}$  can be used to spot some brain abnormalities. Disadvantages include quite low resolution, very high cost, and possibly dangerous radiation levels (somewhat minimized by the use of radioisotopes with short half-times - however, this

requires the availability of a nearby accelerator).

Nobel prizes .... ???

The last two methods to be mentioned here are entirely non-invasive also as far as waves and radiation are concerned. However, their ability to provide true imaging is very limited. Both can record brain signals in cases when thousands of neighboring neurons fire in a synchronized manner.

5. *EEG - Electroencephalography*; electric potentials on the scalp are recorded at tens (or more) locations with time resolutions in milliseconds. The low spatial resolution and the mathematically ill-posed inversion problem makes the technique more important in studying general neural firing patterns (e.g. to diagnose epilepsy) than for imaging.
6. *MEG - Magnetoencephalography*; the very weak magnetic fields from neural activities are picked up outside the skull by SQUIDs (superconducting quantum interference devices), possibly the most sensitive recording devices of any kind:

Using low temperature (liquid helium cooled) superconductors, individual flux quanta can be recorded. This can in turn be utilized for a variety of measurement tasks, giving astounding precisions, e.g.

magnetic field	$10^{-15}\text{T}$	(=1 fT; femto-Tesla); signals from the brain reach about 10-100 fT (measured outside the skull); from the heart 50,000 fT; the earth's field is about $10^{11}\text{fT} = 10^{-4}\text{T}$ .
voltage	$10^{-14}\text{V}$	about 5 orders of magnitude better than semiconductor voltmeters,
motion	$10^{-18}\text{m}$	about 1/1,000 of the diameter of an atomic nucleus; 1/1,000,000 of the typical diameter of an atom.

'High temperature' (using liquid nitrogen at 77K) superconducting SQUIDs are much cheaper than liquid He-ones; however their ability to detect fields of around 25 fT is only barely sufficient for brain studies.

Although SQUIDs operate much faster than neurons, acceptable signal-to-noise ratios (when applied to brain imaging) require recording times in the tens of seconds. Already in 1853, it was shown by Helmholtz that the inversion problem (determining internal currents from external magnetic fields) was not uniquely solvable. As a consequence, additional data needs to be supplied. Possibilities to supply such when using MEG include

- simultaneous EEG-data for potentials (this offers the best signal when currents are orthogonal to the skull - the magnetically least visible case), and
- MRI-provided structural information. This will pinpoint folds in the cortex. As it happens, primary sensor areas tend to be located in such folds, with the consequence that the key currents become relatively parallel to the skull, i.e. well oriented for a good magnetic signal.

MEG is described in Hämäläinen (1993). Recently, one of the inventors of MEG (D. Cohen, MIT) has raised serious questions about the utility of the approach (Crease, 19??).