KU LEUVEN

FACULTEIT ECONOMIE EN BEDRIJFSWETENSCHAPPEN

# Identification of important contributions in diagnostic medical imaging

Identificatie van belangrijke contributies in diagnostische medische beeldvorming

Ir. Sven Van Hove
s0190440

**Masterproef aangeboden tot het behalen van de graad**

Master in het Management

**Promotor:** Prof. Dr. R. Veugelers
**Werkleider:** D. Verhoeven

**Academiejaar** 2013-2014

# Identification of important contributions in diagnostic medical imaging

Identificatie van belangrijke contributies in diagnostische medische beeldvorming

Sven Van Hove, Dennis Verhoeven, Reinhilde Veugelers

Managerial Economics, Strategy and Innovation (MSI)
Faculteit Economie en Bedrijfswetenschappen
KU Leuven

**Abstract**

Radical innovations have the power to disrupt whole technological fields, and are often seen as a key factor in long term growth. Therefore it is critical to identify early on how radical an innovation is. In this thesis, we performed a manual assessment of five interesting innovations in the field of diagnostic medical imaging: digital radiography, electron beam computed tomography, magnetic resonance imaging, 18F-FDG tracers in nuclear medicine and the application of computer aided detection and diagnosis in mammography. The assessment was performed based on a framework proposed by [VBV14]. This framework contains three dimensions: novelty of knowledge origins, novelty of functionality and technological impact. The resulting scores turned out lower than expected, so we looked into possible causes. In the future these scores can be compared against the outcome of an automatic assessment based on patent indicators. Conclusions drawn from this comparison could be used to optimize the framework.

**Keywords:** important technological inventions, radical innovation, diagnostic medical imaging, manual assessment, patent indicators.

# Contents

Chapter 1

# Introduction

## 1.1 Identification of important contributions in a technological field or industry

In the search for value creation on both the micro- and the macroeconomic scale, technological innovation has long been considered a very important factor. Some would argue that it is a key factor in long term growth [AAVL13]. This innovation comes in many forms, from a simple evolution of the previous state of the art to a veritable revolution that causes a paradigm shift. To that end, a lot of research has already been done to clarify what such a revolution or radical innovation is, and how we can quantify it [Art07, DB05, VBV14]. With this information, researchers hope to one day predict with high accuracy how much of a breakthrough an idea will be, even before it enters the market.

### 1.1.1 Innovation framework

In this text, we will work with the framework proposed by [VBV14]. This article proposes both technological and economical dimensions on which to rank innovation. We will focus on the three technological dimensions: new knowledge origins, new functionality and impact. Each of these will be explained in the following paragraphs.

#### Novelty in knowledge origins

The first two dimensions look at the underlying technology of an invention. In particular, the first dimension is concerned with the knowledge origins. For an innovation to work

as intended, a number of problems usually have to be solved first. The various sources of knowledge used to solve these problems are appropriately called knowledge origins. Non-disruptive innovations typically draw from the same knowledge origins compared to related technologies. On the other hand, radical innovations often use knowledge from an entirely different origin. Furthermore, we can distinguish scientific from technological origins.

#### Novelty in functionality

Besides knowledge origins, novelty in functionality is another dimension based on the underlying technology. That is, radical inventions often use new (combinations of) components and principles compared to previous related innovations.

#### Impact

The third dimension proposed is impact on future technological development. While technology mostly evolves along a relatively straightforward path, disruptive innovations often offer a whole new way of thinking - a paradigm shift. If successful, future innovations are likely to continue down that new path. In other words, the more the innovation under scrutiny impacts future developments, the more likely it is to be a radical innovation. Impact can be direct or indirect, and can be very broad (i.e., affecting other fields than its own).

#### Assessment methodology

To perform a manual assessment of a certain innovation, some standard questions related to these three dimensions need to be answered with a score. Those scores should be substantiated by the relevant literature or - if possible - by an expert in the field. The complete assessment sheet can be found in Appendix A.

### 1.1.2 Patent indicators

The framework not only defines the relevant dimensions and manual assessment methods, but also proposes similar patent indicators. Patents provide a rich source of data because they not only refer to the inventing entity, but also offer plenty of forward and backward citations that can be analysed. These allow us to find the true origin of a new technique, and estimate the impact a patent had on future research. On top of that, advanced computer algorithms can use them as a source for data mining and big data techniques. This allows us to automate part of the process, and gain new insights at the same time. One limitation of the patent database we work with, is that it only contains reliable data from 1980 onwards. Because of this, we will constrain ourselves to assessing inventions in that specific time span.

## 1.2 Goal of this thesis

In this thesis we will perform a manual assessment of a certain technological field based on the framework explained above. The field of choice is diagnostic medical imaging. This was chosen because it sits nicely on the intersection between biomedical engineering and computer science, two domains the author is fairly familiar with.

Before we can dive into that, chapter 2 introduces us to diagnostic medical imaging. Various imaging modalities, such as CT and MRI scanners will be discussed at length. Once we have a basic understanding of the most important techniques, chapter 3 will guide us through the actual assessment of some interesting breakthroughs in the field.

Future research will compare the results of this thesis with the outcome of an automated assessment based on patent indicators. This will provide the required feedback for and validation of the proposed framework and patent indicators.

Chapter 2

# Introduction to diagnostic medical imaging

## 2.1 Introduction

In this chapter, we provide an overview of diagnostic medical imaging and its history. Medical imaging is a field in medicine concerned with creating visual representations of a body for the purpose of clinical analysis. Although medical imaging is sometimes used for non-diagnostic purposes, we will only concern ourselves with diagnostic medical imaging. This subbranch has the goal to facilitate diagnosis of medical conditions without the need for invasive procedures. Over the past fifty years, this discipline has matured significantly, it has become indispensable in the modern age medical setting [Doi06].

The most important aspect of diagnostic medical imaging is image production, but various other aspects are involved. Image processing, image display, image recording, image transmission and image storage are all related. Modern day Picture Archiving and Communication Systems (PACS) provide all these features. Once the image has been captured and processed, it can be presented to a radiologist for diagnosis. In recent years, scientists have focused on augmenting the physician's diagnostic ability with various Computer Aided Diagnosis (CAD) schemes. For example, algorithms based on machine learning are able to autonomously detect lung nodules with ever increasing accuracy [vGAIdH+10]. Although some systems aim to make physicians redundant in the long term, most experts agree that software should augment them rather than replace them entirely [Doi07].

In the next sections, we will discuss the history, technical background and recent advancements of the most important imaging modalities.

## 2.2 Radiography

Radiography is the simplest form of medical imaging based on X-rays. These rays can travel through solid objects, but attenuate depending on the materials they meet along their path. For example, when passing through a human hand, the attenuation is stronger when passing through bones rather than through soft tissue. The image can be recorded (in negative) on ordinary photographic paper and processed in darkrooms. Figure 2.1 shows am example.

Figure 2.1: X-ray image of a human hand. In this negative image, bones are lighter because fewer X-rays managed to get through them.

### 2.2.1 History

Radiography builds on the work of Wilhelm Konrad Röntgen, a German physicist who produced and detected X-rays for the first time on November 8, 1895. These X-rays (X for unknown) had the remarkable property of being attenuated at different rates when passing through various materials. For example, bone strongly attenuates the X-rays while soft tissue does much less so. Röntgen also discovered that the radiation can be

captured on a photographic plate, just like regular light. He presented his findings in his paper "On a new kind or rays" [Roe96]. This discovery earned him the Nobel Prize in Physics in 1901.

Only two weeks after his discovery he produced the first X-ray photo of his wife's hand, after which she reportedly exclaimed: "I have seen my death!". Just a couple of months later, X-rays were already being used in a clinical setting on patients.

Note that during this time, not much was known about ionizing radiation or radioactivity. Only a year after the discovery of X-rays did Henri Becquerel discover radioactivity. Well known scientists such as Ernest Rutherford and Pierre & Marie Curie performed several more years worth of research before realizing the true danger of prolonged exposure to this type of radiation.

### 2.2.2 Technical background

To better understand the internal workings of imaging devices, we present a simplified mathematical and physical background based on the book of prof. Suetens[Sue09]. X-rays are simply a form of electromagnetic waves consisting of photons with a wavelength $\lambda$ on the order of Angstrøms ($10^{-10}$m). The corresponding frequency $f$ places these rays firmly in the ionizing part of the spectrum - that is, they can cause cancer. Figure 2.2 shows a schematic overview of the whole spectrum. The energy of such a wave can be calculated with the following formula, where $c$ is the speed of light and $h$ is Planck's constant.

$$E = hf = \frac{hc}{\lambda}. \tag{2.1}$$

X-rays are generated in an X-ray tube, a vacuum tube consisting of a cathode and an anode. Current flowing through the cathode releases electrons, which are accelerated toward the anode by an applied voltage. Once the electrons hit the anode, they release part of their energy in the form of X-ray photons. Thus, the two most important settings of an X-ray scan are the applied current multiplied by the exposure time (mA $\cdot$ s) and the applied voltage (keV).

The attenuation of X-rays through materials can easily be modeled using an attenuation coefficient $\mu$. The beam intensity when passed through a homogeneous material of depth $d$ is given by:

$$I_{out} = I_{in} \cdot \exp(-\mu d). \tag{2.2}$$

This formula can of course easily be extended to include heterogeneous materials and variable attenuation coefficients.

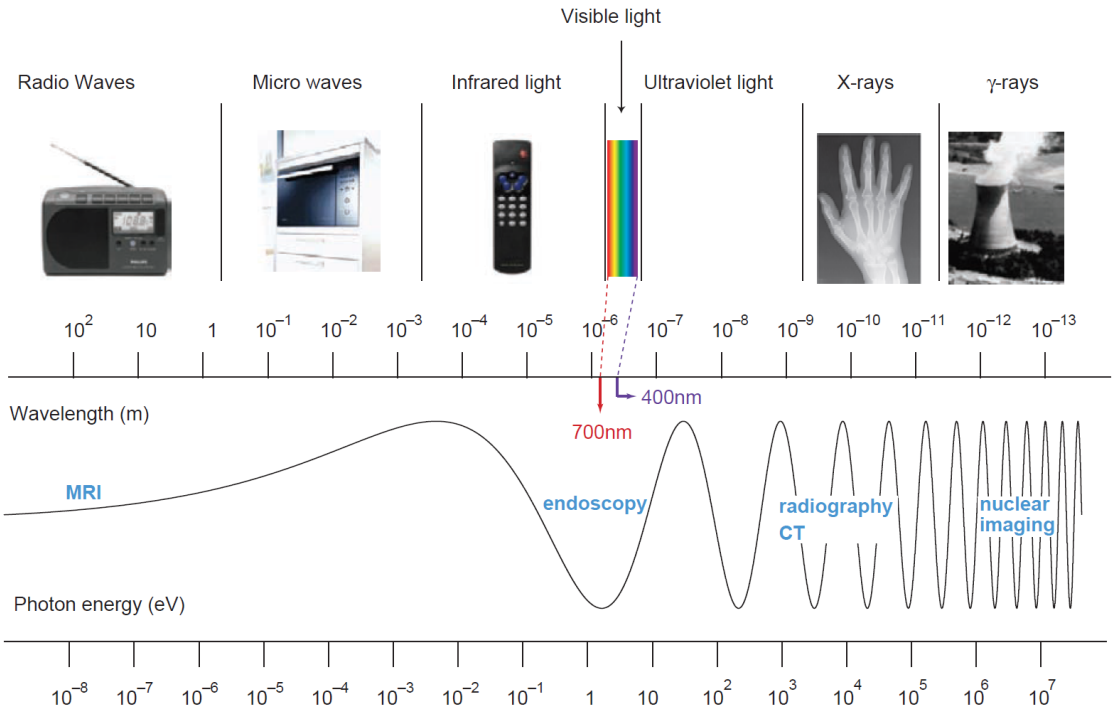


Figure 2.2: The electromagnetic spectrum. [Sue09]

To capture X-rays, a detector is needed. Traditionally, a screen-film detector was used. The familiar photographic film alone is very inefficient at capturing X-rays: only about 2% of all photons are absorbed. Because X-rays are ionizing, the applied dose cannot simply be increased to improve the image quality. Instead, an intensifier screen is used in front of the film. This screen contains heavy chemical elements, whose electrons are excited by the incoming photons. When returning to their original state, these electrons emit visible light that can be captured more efficiently by the film, raising the absorption rate to about 50%.

Besides ordinary radiography, special classes such as fluoroscopy and mammography exist. Fluoroscopy generates time-lapse recordings instead of still images. With modern technology, tens of frames per second are achievable. Of course, each frame must be shot at a very low exposure rate to minimize patient risk. Mammography on the other hand produces images of the human breast. The challenge here is to generate very high resolution images, so that small masses can be seen.

### 2.2.3 Recent advancements

Relatively recently, X-ray systems have moved away from analogue detectors towards digital ones. Much like digital photographs, digital X-ray scans are far easier to store,

copy, post-process and share. On top of that, they typically have a much wider exposure range making them more tolerant to over- and underexposure. These detector systems use storage phosphors to temporarily hold the absorbed radiation instead of immediately releasing it in the form of photons. This phenomenon is caused by electron traps in the doped material. Later, this phosphor can be read out pixel-wise using an optical detector array and a laser that gives the electrons enough energy to escape their trap. The main obstacle for this paradigm shift was the large pixel size. Large pixels translate to lower resolution, which is turn leads to a loss of diagnostic value. Only by the time pixels could be as small as 0.1 mm did the medical world embrace digital detectors [Doi06].

Even newer devices use active matrix flat panel detectors. These detectors are able to produce near real time images. In comparison, storage phosphors and older technologies required minutes or more of processing time.

### A note on image quality

The quality of an image can be expressed in three dimensions: resolution, contrast and noise [Sue09].

Resolution is sometimes simply stated as the pixel density (dots per inch). However, this only provides an upper bound because in practise neighbouring pixels are often correlated. For example, due to the imperfect nature of the recording equipment, a single point can appear as blurred blob on the resulting image. This blob is called the Point Spread Function (PSF), and is a better measure for the actual image resolution. If the resolution is isotropic, the Line Spread Function (LSF) - measured in distinguishable line pairs per millimeter (lp/mm) - can also be used. Alternatively, the Optical Transfer Function (OTF, sometimes also called MTF) representing amplitude and phase shifts of a sinusoidal target can be used. In fact, this OTF is nothing more than the Fourier transform of the PSF or LSF.

Second, contrast is the intensity difference between neighbouring regions of the image. More formally, contrast at a given frequency is the amplitude component of the image at that frequency in the frequency domain (calculated using the Fourier transform). Contrast is dependent on the whole imaging process, but also on the size and shape of the objects in the image.

Third, noise is partly the result of interfering phenomena. Yet, it is also inherent to the electromagnetic radiation itself because the waves themselves are stochastic processes. An important measure is the Signal to Noise Ratio (SNR) or, more appropriately, the Contrast to Noise Ratio (CNR). Noise can be estimated by examining the result of an scan with no object present, a so-called flat-field image. Another measure for the amount of noise is the Wiener spectrum.

Another frequently used metric called the Detective Quantum Efficiency (DQE) can compare various technologies without being dependent on the object being imaged.

$$DQE(f) = \frac{SNR(f)^2_{out}}{SNR(f)^2_{in}} \tag{2.3}$$

In addition to these elements, sometimes artifacts appear on scans. The causes of these artificial image features vary widely depending on the image modality used and can also be caused by excessive post-processing.

### 2.2.4 Future expectations

Ever since CT scanners - and to a lesser extent MRI scanners - made their way into hospitals, they have taken over many of the tasks traditionally reserved for basic radiography. This declining trend is expected to continue in the foreseeable future.

## 2.3 X-ray computed tomography

One step up from basic radiography is computed (axial) tomography (CT, formerly CAT). The goal here is to create image slices of patients in the cross-sectional plane rather than the frontal plane (tomography is Greek for "slice writing"). To accomplish this, the X-ray source-detector pair is rotated around the patient. From this raw data, a so-called filtered back projection algorithm can reconstruct the whole cross section image. A computer is needed to make sense of the output, hence the *computed* in the name. Figure 2.3 shows an example of a chest CT scan and Figure 2.4 shows an actual scanner.

### 2.3.1 History

Before computed tomography became possible, some simpler techniques were already being used to obtain slices from inside the patient's body. These techniques were called (non-computed) tomography. One example is linear tomography, where source and detector move on parallel tracks, but in opposite directions, during the scanning process. This way, one section of the patient is always projected on the same spot of the detector, while the rest is averaged out. Obviously, these techniques where nowhere near as accurate as the CT scanners we know today.

In 1917, Johann Radon - an Austrian mathematician - presented the first algorithm to reconstruct a function from its projections: the Radon transform [Rad17].

After World War II, the development of computers gained momentum, but it would still take a long while before the "computed" in "computed tomography" became feasible. In

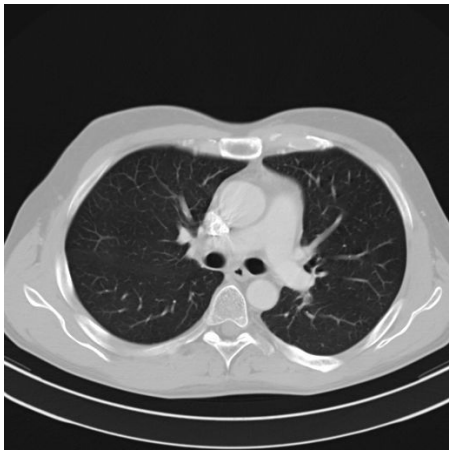

Figure 2.3: Example of a thoracic CT scan. The heart is clearly visible in the center. Bones (ribs, sternum, spine) are also easy to spot in the periphery. The large black area represents the lungs filled with air.

the 1960's, the South African Allan McLeod Cormack continued working on the mathematics invented by Radon [Kal06]. A decade later, in 1972, the first operational brain CT scanner (the EMI scanner) was designed by Godfrey Hounsfield, an Englishman. A scan took about 5 minutes, after which a computer performed calculation for up to 150 minutes. The final output was a 80px × 80px image. Cormack and Hounsfield shared the 1979 Nobel Prize in Physiology or Medicine for their work related to CT scans [Kal11].

### 2.3.2 Technical background

Just like radiographs, CT scanners are based on X-ray technology. They also require a source and a detector, but this time they can rotate along the patient. For every rotation angle $\theta$, we obtain an intensity profile $I_\theta(r)$ along the axis $r$ perpendicular to the incoming X-rays (with uniform incoming intensity $I_0$). The family of functions $I_\theta$ can be transformed into an attenuation profile $p(r,\theta) = -\ln \frac{I_\theta(r)}{I_0}$ (often called a sinogram). This $p(r,\theta)$ is called the Radon transform of the attenuation distribution $\mu(x,y)$ in the slice plane.

$$p(r,\theta) = \mathscr{R}\{\mu(x,y)\} \tag{2.4}$$

In short, the projections $p$ is what we can measure (or at least sample at fixed intervals) and the attenuation distribution $\mu$ is what we are interested in. The mathematics required to go from the latter to the former are pretty straightforward, but the reverse is more complicated. The inverse Radon transform $\mu = \mathscr{R}^{-1}(p)$ is needed.


Figure 2.4: A CT scanner made by Philips. The patient takes place on the table and slowly slides through the toroid wherein the rotating X-ray source-detector pair is embedded.

We will not go into details, but the solution lies in the projection theorem. This theorem states that the 2D Fourier transform $M(k_x, k_y)$ of $\mu(x, y)$ is equal to the 1D Fourier transform $P(k, \theta)$ of $p(r, \theta)$ (save for a simple polar coordinate transformation).

$$\mathscr{F}_{1D}\{p(r,\theta)\} = P(k,\theta) = M(k\cos\theta, k\sin\theta) = \mathscr{F}_{2D}\{\mu(x,u)\} \tag{2.5}$$

Because the inverse Fourier transform is well understood, we have a solution to our problem. Simply calculate $P$ from $p$ as explained above, and then apply the inverse 2D Fourier transform to obtain $\mu$. By using the polar version of the Fourier transform, we can reduce artifacts. This approach is called filtered back projection [Sue09].

After all the calculations are performed, we typically acquire a 512px $\times$ 512px scan. The values of the pixels in a CT scan are referred to as the CT numbers and are expressed

in Hounsfield Units (HU). They are calculated using the fomula below, where $\mu$ is again the attenuation coefficient.

$$\text{CT number} = \frac{\mu - \mu_{H_2O}}{\mu_{H_2O}} \cdot 1000 \tag{2.6}$$

From this, it becomes obvious that the CT number of air (with $\mu = 0$) is -1000 HU and that the CT number of water is 0 HU. Bones on the other hand have a very high attenuation coefficient and thus have a CT number in the thousands. Soft tissue lies somewhere in between.

### 2.3.3 Recent advancements

The previous section assumed parallel X-ray beams. However, newer generation scanners often employ cone-shaped beams. The procedure outlined above can reconstruct a single slice by rotating around the subject by 180 degrees at a time (a circular CT). On the other hand, modern CT scanners often spiral around the patient while he moves through the toroid (a helical CT) to speed up the process and thus decrease the exposure. Another useful trick is to capture multiple slices at once by using multiple detector arrays. Until recently, manufacturers were in a so-called *slice wars* to offer the most detector arrays. Needless to say, all this substantially complicates the mathematics required to perform a back projection, but it is feasible and daily used in hospitals around the world.

Another point of interest today is the combination of successive CT slices to generate a 3D model of the patient. Because of advancements in computer technology and algorithms, we can now post-process this 3D model to automatically segment the organs and other structures. This can for example help physicians plan their actions before and during complex surgery.

### 2.3.4 Future expectations

Because CT scanners still require relatively high doses of radiation, this is not an ideal solution. MRI scanners offer a safer alternative, but the large magnetic fields produced make them impossible to use on patients with ferromagnetic implants. Another advantage over MRI is the superior sub-millimeter resolution that only CT scanners can offer. These are only some of the reasons why they will not be replaced anytime soon. Future research will attempt to make CT scanners even faster and allow them to produce clearer (i.e., higher contrast) images with lower doses.

## 2.4 Magnetic resonance imaging

While the previous imaging modalities were based on X-rays, Magnetic Resonance Imaging (MRI) is based on magnetic fields. It is sometimes also referred to as Nuclear Magnetic Resonance (NMR) in professional circles. However, the general public has a certain aversion to the world "nuclear", so MRI is more common. Instead of measuring the electromagnetic attenuation properties of various tissue types as in CT scanners, we measure certain magnetic properties of the tissue. These magnetic properties mainly depend on the molecular composition of the material, for example on the amount of $H^+$ ions present (the proton density). These electromagnetic waves are non-ionizing, meaning they cannot cause cancer due to prolonged exposure. The goal is the same: imaging slices of a patient's body. While technically an MRI scanner can generate slices in any orientation without even moving the patient, CT-like cross sectional slices are still used predominantly. Figure 2.5 shows a picture of an MRI scanner.


Figure 2.5: A Phlips MRI scanner. The patient takes place on the bed and is moved inside the toroid, but is not moved again during the procedure.

### 2.4.1 History

During the late 1960's, researcher in Aberdeen worked on the predecessor of the modern MRI scanner [Mal06]. Their goal was to distinguish between malignant tumors and normal tissue without using ionizing radiation. Instead of measuring the magnetic properties of the nuclei, they initially focused on electrons. This proved to be a dead end, and by early 1970 the group moved on to NMR as we know it today. They realized that tumors have a longer $T_1$ time (see below), and concentrated on that instead.

Meanwhile in the USA, chemist Paul Lauterbur proposed a way to create images from NMR studies by using multiple field gradients to encode the position of each measurement [L$^+$73]. Another important contribution came from Peter Mansfield (now Sir), an English physicist. In 1974, he showed how to select spins from a specific slice and patented a method to selectively excite and define a slice across a sample. Lauterbur and Mansfield shared the 2003 Nobel Prize in Physiology or Medicine for their work on NMR.

From 1978 on, multiple research groups started presenting images generated by prototype MRI scanners. However, only in the early 1980's was the technology ready for clinical and diagnostic use. By 1983, major multinational corporations started producing commercial MRI machines.

### 2.4.2 Technical background

Unfortunately, the fundamental concepts that make MRI scanners work go beyond classical physics, and instead requires special relativity, quantum mechanics and quantum electrodynamics. Clearly, this is way beyond the scope of this text. We will present a simplified version of the core principles based on [Sue09] instead.

MRI scanners influence and measure the magnetic properties of atom nuclei in the patient's tissue. During typical studies $H^+$ ions (i.e., protons) are used because of their abundance in the human body, although alternatives exist (e.g., $^{13}_{6}$C or $^{17}_{8}$O).

When the scanner is operational, a large magnetic field $\vec{B_0} = (0, 0, B_0)$ (in the order of a couple Telsa) is induced along the patient's length using a big electromagnetic coil. By supercooling the coil, the resistance drops and power consumption can be reduced significantly.

The magnetic field $\vec{B_0}$ influences the magnetic moments $\vec{\mu_i}$ of the nuclei, causing them to precess around the z-axis with precession frequency $\omega_0 = f(B_0)$. Associated with the external magnetic field and the individuel magnetic moments is the potential energy $E$. Quantum mechanics states that for protons, this energy can only have two values, the so-called spin up ($E_\uparrow$, lowest) and spin down ($E_\downarrow$, highest) state. In these states, the $\vec{\mu_i}$ point respectively upwards ($\mu_{iz} > 0$) and downwards ($\mu_{iz} < 0$), although transverse

components are still present. Most protons will be in the lowest energy state, but they can be flipped by absorbing a photon with the appropriate amount of energy $\Delta E = E_{\downarrow} - E_{\uparrow}$. This holds when the photon has a specific Larmor frequency $\omega_{RF}$, which happens to be equal to $\omega_0$. In a 1.0T magnetic field, the Larmor frequency for hydrogen is 42.6 MHz, a radio-frequency (RF) wave.

Of course, we are more interested in macroscopic voxels (3D pixels) than in the individual nuclei. Fortunately, the net magnetization vector of each voxel is simply the sum of all individual magnetic moments: $\vec{M_0} = \sum_i \vec{\mu_i}$. The magnitude of this vector roughly represents the proton density in the voxel. In dynamic equilibrium, $\vec{M_0}$ points in the same direction as $\vec{B_0}$ because there are more nuclei in the spin up state and the individual transverse components cancel each other out. To summarize: the large magnetic field make sure the net magnetization vectors of all voxels are aligned.

Unfortunately, due to technical reasons we can only measure the transverse component of $\vec{M}$. As a solution, we will disturb the dynamic equilibrium with a resonating RF pulse, causing more protons to flip to the spin down state. This RF wave has a magnetic component $\vec{B_1} = (B_1, 0, 0)$. Following the same logic as above, $\vec{B_1}$ causes $\vec{M}$ to precess around it. With the appropriate timing, $\vec{M}$ can be flipped over an angle $\alpha$ of either 90 or 180 degrees.

After the pulse, the system returns to dynamic equilibrium during a process called relaxation. We can distinguish between two effects. First, spin-spin relaxation is responsible for the disappearance of the transverse component of the net magnetization vector due to loss of phase coherence (increase in entropy while energy stays constant). This process can easily be approximated by a first order model with a time constant $T_2$, called the spin-spin relaxation time.

$$M_{tr}(t) = M_0 \sin(\alpha) \exp\left(\frac{-t}{T_2}\right) \tag{2.7}$$

Different tissue types have different inherent $T_2$ times, which we will exploit later.

Second, spin-lattice relaxation is responsible for regenerating the longitudinal component of $\vec{M}$. Similarly, this process can be linked to a $T_1$ relaxation time. $T_1$ is also a tissue property, and is always larger than $T_2$.

$$M_l(t) = M_0 \cos(\alpha) \exp\left(\frac{-t}{T_1}\right) + M_0 \left(1 - \exp\left(\frac{-t}{T_1}\right)\right) \tag{2.8}$$

Using a quadrature detector in the xy-plane, we get the following reading after one 90 degree pulse:

$$s(t) = M_{tr}(t) = M_0 \exp\left(\frac{-t}{T_2}\right) \tag{2.9}$$

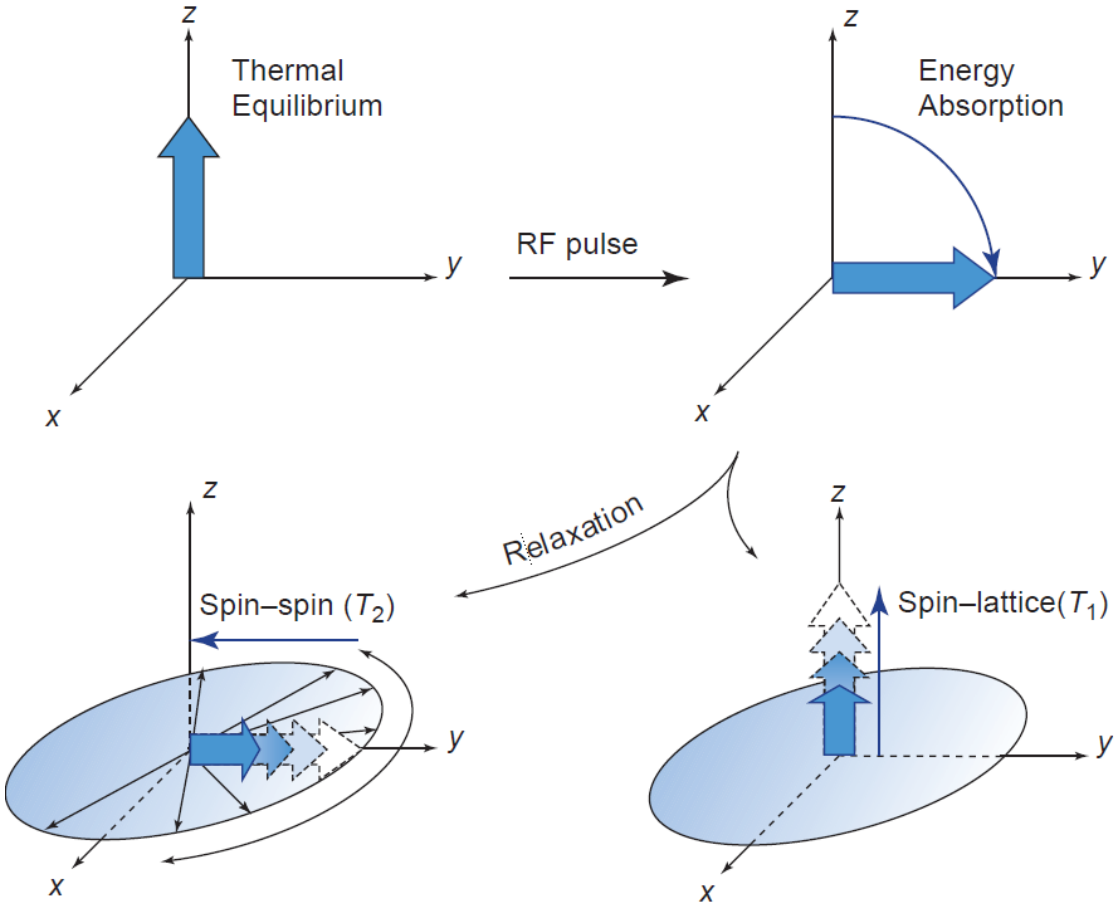


Figure 2.6: Schematic overview of relaxation after a 90 degree pulse. [Sue09]

To also measure $T_1$, we have to repeat the 90 degree pulse after repetition time TR:

$$s(t) = M_0 \left(1 - \exp\left(\frac{-TR}{T_1}\right)\right) \exp\left(\frac{-t}{T_2}\right) \tag{2.10}$$

Notice how the 90 degree pulse conveniently eliminates the sine and cosine factors.

Clearly the result is not just the proton density $M_0$, but involves other factors as well. This is not necessarily a problem as the $T_1$ and $T_2$ factors can increase the discriminative power of the scanner. If a short $TR$ is chosen, the image is said to be $T_1$ weighted because long $TR$ times cause the $T_1$ factor to diminish. If on the other hand a long $TE$ (echo time = moment of measurement) is chosen, the image is said to be $T_2$ weighted. Indeed, a short $TE$ time decreases the $T_2$ factor. By combining a long $TR$ with a short $TE$, we have a relatively pure proton density image. Remember that $TR$ and $TE$ can be chosen by the operator, while $T_1$ and $T_2$ are tissue dependent.

The attentive reader will have noticed that there is no spatial information encoded in this signal yet. Using this approach we could only measure the combined effects of all relaxations, which is useless. To solve this, we superimpose additional gradients $\vec{G}_{x/y/z}$ (in the order of milliTesla/meter) onto $\vec{B}_0$. This in turn affects the Larmor frequency. The exact details are far from trivial and will be omitted, but involve the 3D k-space. After the signal has been sampled everywhere in the region of interest in the k-space, a simple inverse Fourier transformation yields the image we are looking for.

Using two 90 degree pulses is just one of the many possible pulse sequences used in modern MRI scanners. Other examples include the spin-echo (SE) sequence and the gradient echo (GE) sequence. Each sequence has advantages and disadvantages with respect to discrimination of certain tissue types. The radiologist is responsible for making the proper choice.

### 2.4.3 Recent advancements

A lot of spin-off technologies based on MRI are in use. For example, Magnetic Resonance Angiography (MRA) generates images of arteries to detect pathologies such as stenosis (narrowing) or aneurysms (dilations). To make this work the patient can be injected with a paramagnetic contrast material. Alternatively, the scanner can detect anomalies in the measurements due to movement of the blood, and amplify those.

Similarly, Magnetic Resonance Spectroscopy (MRS) measures the levels of various metabolites in human tissue, while functional MRI (fMRI) visualizes brain activity based on local oxygen levels. The underlying principle is that oxygen-rich blood contains oxyhemoglobin, which is diamagnetic, while oxygen-poor blood containing deoxyhemoglobin is paramagnetic. Likewise, diffusion and perfusion can be measured.

### 2.4.4 Future expectations

MRI scanners today are still far less ubiquitous than CT scanners, and only make up a few percent of the worldwide radiographic examinations [Ind13]. However, because of the various advantages over other modalities - mostly the fact that it is not dependent on ionizing radiation - usage is expected to rise steadily in the future. MRI will never completely replace CT because it cannot properly image hydrogen-poor structures such as bone and air.

On top of that, future research will most likely improve the functional aspect (e.g. measuring blood flow) of MRI. This can be done by experimenting with nuclei other than hydrogen, by using new contrast agents and using novel pulse sequences. In addition - similar to CT scanners - research will try to increase the contrast and lower the acquisition times even further.

## 2.5 Nuclear medicine imaging

While the previous imaging modalities mostly focused on obtaining static images of the patient, nuclear medicine imaging concentrates on so-called functional imaging: visualizing some kind of dynamic process (e.g. drug metabolism) in the human body. CT or MRI scanners also have this capability by exploiting certain side effects of their underlying phenomena, but the Signal to Noise Ratio (SNR) is always significantly lower.

Diagnostic nuclear medicine imaging works by tracking radioactive isotopes (tracers) as they move through the body. A distinction can be made between two kinds of radiopharmaceuticals. One type is simply meant to spread through the body, and is expected to have some default, static distribution after a sufficient amount of time has passed. Contrast agents used in CT and MRI scans fit this description rather well. Physicians can compare the actual distribution with the expected distribution, and take the differences into account when coming up with a diagnosis. The other type of radiopharmaceuticals is used in nuclear medicine, and is more dynamic. Here, we are not interested in some static distribution, but in specific movements of the tracer over time. These movements are intended to be correlated with some kind of biochemical or physiological process in the human body. Unlike with the former type, the latter type does not require high quality images to be effective. Rather, the fidelity of the tracer used is paramount [TK98].

In the early days hospitals needed their own cyclotron to produce these tracers, which significantly slowed adoption. Nowadays various companies deliver the needed tracers daily to hospitals around the world [MK06]. Other variants of nuclear medicine are used in the oncology departments to fight cancer, but we will not go deeper into that.

Two main scanner types fall under nuclear medicine imaging: Positron Emission Tomography (PET) and Single Photon Emission Computer Tomography (SPECT). The exact difference will be explained later on in the technical background section. Figure 2.7 shows an example of a PET scanner.

### 2.5.1 History

The history of nuclear medicine begins with the work of German physicist Hans Geiger, a student of Ernest Rutherford, and his 1908 invention: the Geiger counter. This device can detect ionizing radiation by exploiting the fact that these rays can make an inert gas (e.g. Argon) conduct electricity. Using this rudimentary device, researchers could form a rough picture of the radioactive activity in a patient's body [Jas06, GW28].

Meanwhile, Paul Direc, an English theoretical physicist, laid the theoretical foundation for what would later be known as a positron.[Dir30]. Around the same time, Frédéric Joliot and Irène Curie (daughter of Pierre and Marie Curie) dicovered artificial radioactivity [JC34].

Figure 2.7: A PET scanner made by Siemens. The opening is completely surrounded by detectors, so there are no moving parts inside.

A significant breakthrough came with the invention of the Anger camera (or gamma camera) in 1957 by Hal Anger, an American engineer and physicist. This camera was able to detect incoming radiation from a whole organ at once, improving the spatial resolution dramatically. The technique he used was based on scintillator crystals [Ang58].

From there, several researchers such as Crandall, Cassen, Kuhl and Edwards built upon the work to create true scanner systems throughout the late 1960's and early 1970's. The first systems were SPECT scanners to make images in just one plane, and later on CT-like scanners that could calculate cross sections were invented.

Research concerning PET scanners was performed at about the same time as SPECT scanners. Scientists soon realised their advantage, but adoption took much longer in comparison [MK06]. G. Brownell and his group were the first to build a working dual planar PET scanner [BBW$^+$69]. Only since 1990 have PET scanners seen significant clinical usage [WJ98].

### 2.5.2 Technical background

Before we explain how PET and SPECT scanners work, we will quickly refresh some important radioactive decay modes.

The first is positron emission, also called $\beta^+$ decay. Positrons ($e^+$) are the anti-particles of electrons ($e^-$). During this decay, a proton ($p^+$) inside an atom is essentially transformed into a neutron (n) and a positron.

$$p^+ \rightarrow n + e^+ \tag{2.11}$$

$${}^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + e^+ \tag{2.12}$$

In the next couple of picoseconds, the positron will fly into a electron and annihilate. The mass of the two particles is is converted into pure energy in the form of two photons ($\gamma$). Using Einstein's famous equation $E = mc^2$, we can calculate that each photon carries 511 keV of energy. They fly away in opposite directions.

This physical phenomenon forms the basis of Positron Emission Tomography (PET). A typical element used during such studies is $^{18}$F, which has a half-life of about 110 minutes. It almost exclusively decays by positron emission and yields stable $^{18}$O [Sue09]. The radioactive element is typically coupled to another molecule to facilitate uptake and transport in the body. One commonly used molecule is Fluorodeoxyglucose (FDG), which binds to fluorine-18 and is used to visualize glucose metabolism.

The fact that two photons are emitted in opposite directions is very convenient. If both happen to be detected, we immediately know their projection line. (Remember that in CT scanners the projection line is known a priori and is fixed between source and detector.)

The opposite operation is also possible: $\beta^-$ decay by electron emission. Here, a neutron is converted into a proton and an electron.

$$n \rightarrow p^+ + e^- \tag{2.13}$$

$${}^{A}_{Z}X \rightarrow {}^{A}_{Z+1}Y + e^- \tag{2.14}$$

In certain cases, the resulting Y atom is in a metastable state ($^{Am}$Y). This means the atom will later decay further into a more stable nuclear configuration, releasing one or more photons in the process. This is much more interesting diagnostic-wise, because unlike electrons, photons don't damage the tissue they pass through during emission. A

common metastable element used is $^{99m}$Tc, generated after decay of $^{99}$Mo and further decaying into $^{99}$Tc (half-life of six hours) by emitting a single photon of 140 keV.

$\beta^-$ decay is mainly used in SPECT scanners. Because only one photon is emitted, we cannot immediately tell where it came from when it is detected. To solve this, a mechanical collimator - a thick lead plate with holes in it - is used to absorb all photons that do not approximately fly perpendicular to it. Knowing this, we can estimate the projection line of the photons we managed to detect after they passed through the plate. Sadly, this technique forces us to make a trade-off between spatial resolution (using smaller holes) and sensitivity (letting more photons through using bigger holes). This is a serious disadvantage compared to PET, in turn making SPECT less future-proof.

Note that these photons form electromagnetic waves, and their frequencies are equal to or higher than those of the X-rays in earlier sections. This means that they obey the same physical laws, and thus they also attenuate when passing through tissue. However, in this context we refer to the radiation as $\gamma$-rays instead.

When the photons are detected and the projection lines are calculated, we have two options. Either we are satisfied with planar imaging to get a result similar to basic radiography. In this case all depth information is lost, and the pixels simply give information about the photon emission activity on their entire projection line, combined with the attenuation properties of tissue on that line. Sometimes a SPECT scanner is simply called a gamma camera in this configuration, although the distinction is mostly theoretical. The other option is to use a slightly adapted filtered back projection algorithm to compute CT-like slices. Obviously this requires the detectors to rotate about the patient just like in a CT scanner.

The detectors used here differ significantly from those used with X-rays. Not only are there far fewer photons to be detected in the first place, but the acquisition time is also much longer. Photomultiplier Tubes (PMT) combined with NaI(Tl) scintillator crystals and, more recently, photo diodes are popular detectors for use in SPECT scanners today. PET scanners on the other hand use materials such as Bismuth Germanate (BGO) and Lutetium Oxyorthosilicate (LSO) in their detector scintillators.

### 2.5.3 Recent advancements

Due to the strong attenuation of the photons, filtered back projection produces significant artifacts in the final image. The images are still diagnostically relevant, but better methods are available. Iterative reconstruction based on Bayesian statistics or maximum likelihood calculations are becoming more popular [Sue09].

Another advancement, the Time-of-Flight (TOF) PET scanner, estimates the source location of the photon along the projection line by measuring the difference in arrival time between the two photons. This only works reliably if the difference is smaller than 1ns, which in turn requires very advanced measuring equipment.

While most researchers focus on nuclear medicine alone, others seek their fortune in hybrid scanners. For example, combining CT or MRI with PET or SPECT scanners significantly improves the specificity compared to their stand-alone versions. Especially the PET/CT combination is popular in clinical environments. In this case, the CT scanner can provide the attenuation correction needed for the PET scanner. One problem that has to be overcome is the long acquisition time needed for PET, and the mismatch it causes with CT scans due to patient movement. Image registration techniques can be helpful here, but are not straightforward. ...

### 2.5.4 Future expectations

As with all types of scanners, we expect steady technological advancements in the years and decades to come. However, in the case of nuclear medicine, experts expect most progress to be made on the tracer front. This will enable researcher to not only visualize biological processes on a macro level, but move to the molecular level. This way, advanced studies on gene regulation, radio immunotherapy etc. will become possible.

## 2.6 Computer-aided Detection and Diagnosis

This section on Computer-aided Detection and Diagnosis (CAD, not to be confused with Computer-aided Design) deals not with the image creation process, but with the subsequent processing. In this sense it is the odd one out.

CAD is one of the major research areas in diagnostic medical imaging [Doi07, Sue09]. CAD technologies help radiologists with the actual detection and diagnosis of pathologies in the image. Sometimes a further distinction is made between detection (CADe) and diagnosis (CADx). Either way, CAD does not attempt to replace physicians. You can think of it more as a second opinion. This is in contrast with Automated Computer Diagnosis (ACD) where the computer (supposedly) does all the work and no physician is needed anymore.

The rise of CAD is tied to the increased workload of radiologists. Decades ago, each radiological examination contained just a few images. Today, with multi-slice CT scans and full body MRI scans, a single examination can contain thousands of 2D images. Clearly, some form of automation would be more than welcome to reduce the radiologists' workload.

A (non-exhaustive) list of possible application of CAD include detection of vertebral fractures on radiographs, detection of microcalcifications on mammograms, detection of cranial aneurysms in MRA images and detection of lung nodules in CT scans [Doi07].

Note: in the following sections related to CAD, we assume that the reader is familiar with the basics of statistical binary classification theory. The most important concepts are True Positives (TP), False Positives (FP), True Negatives (TN), False Negatives (FN), accuracy, sensitivity and specificity.

### 2.6.1 History

Early in the 1980's, when large scale research on CAD began, the most common techniques fell under basic image processing. This is a branch of signal processing, applied to 2D signals (i.e., images). In the following years, a new field called Computer Vision formed around the subject.

To get a feel for such image processing techniques, consider a special filter to accentuate lung nodules, and another one to suppress them. Next, apply these two filters to the same image, and subtract the suppressed from the accentuated version. The result should then be a completely black image, save for the nodule-like structures in the image.

Early on, most research focused on ACD. It was not a success at first, because computers were not yet powerful enough, and advanced image processing algorithms were not yet available. The researchers had high hopes for the future, but unfortunately ACD never caught on. The algorithms' sensitivity and specificity simply did not match up to that of real physicians. That is why most researchers soon made the switch to CAD. To measure the performance of CAD systems, we do not only look at the outcome of the algorithm, but how this outcome combined with the physician's expertise can create synergy. Even if the sensitivity and specificity of the CAD algorithm are lower than that of the average physician, as long as the synergy is big enough, their combined use can trump that of the physician alone. This was proven for the first time in [CDV+90].

At the time, the most popular topics were related to cardiovascular diseases, lung cancer and breast cancer because of their high impact. This trend has largely continued, and even in recent year researchers still focus mostly on the latter two topics. [Doi07]

The first scanner with built-in CAD detection was approved by the U.S. Food and Drug Administration (FDA) in 1998.

### 2.6.2 Technical background

Contrary to the discussion of the previous imaging modalities, we will not go into the technical details of these techniques. There reason is simple: there are too many of them, and they all work in a very different way. The interested reader is invited to read a book on the subject such as [GW02].

Fortunately, most CAD systems follow a generic scheme, independent of the underlying technology [Suz12]. First of all, the organ of interest (e.g., the lungs) is segmented (I), and the rest of the image is discarded. Next, the object to be detected is somehow enhanced (II). The subtraction technique outlined above could work here. Then, these candidate objects have to be detected and segmented (III). After that, some kind of feature analysis is performed and the candidates are properly classified (IV). Most techniques will still have plenty of false positives at this point, so FP reduction is required (V). If simple detection was the goal, the remaining candidates are the end result of this scheme. Else, an extra diagnosis (characterization) step is required (VI).

### 2.6.3 Recent advancements

In the last two decades, more and more interest has been generated about the implementation of artificial intelligence (AI) and machine learning techniques in CAD. Examples of such techniques include Discriminant Analysis (DA), Artificial Neural Networks (ANN), Support Vector Machines (SVM) and decision tree models such as Random Forests (RF) [Suz12, vGAIdH+10]. The exact details of each method are out of scope for this text, but fortunately most can be treated as black boxes with highly similar in- and outputs.

Machine learning always works in two phases. The learning phase and the prediction phase. During the learning phase, a large number of class-annotated sample images are provided from which the algorithm can infer the differences between various classes. Examples of simple binary classes are tumors vs. non-tumors or malignant tumors vs. benign tumors. Once training has completed, an unannotated picture can be provided in the prediction phase. The algorithm will then predict - based on its internal model - to which class it belongs.

Of course it is possible to use a complete image, pixel by pixel, as input. However, this is computationally very expensive. Instead, features are typically calculated to describe a certain region of interest in an image. Simple features are the minimum, average and maximum intensity, but they can become arbitrarily complex.

### 2.6.4 Future expectations

[Doi07] sees future potential of CAD in combination with Picture Archiving and Communication Systems (PACS). Since the digital revolution, hospitals had to come up with a new way of storing and managing all this imaging data. PACS was the solution, and today every modern hospital has a PACS in one form or another. This means every hospital sits on piles of old and unused medical images. By combining CAD, AI techniques such as data mining and PACS, research could gain a serious momentum boost and unforeseen applications could pop up. Furthermore, integrating CAD as a PACS module would make it more accessible and promote adoption.

Aside from that, researchers will keep working on the underlying algorithms. This will hopefully bring steady improvements in performance.

Chapter 3

# Overview of radical inventions

## 3.1 Introduction

In this chapter, we perform the assessment of five inventions based on the framework described in chapter 1. Chapter 2 already described various breakthroughs in diagnostic medical imaging, but most of them predate 1980. Fortunately researchers in the field have come up with plenty of other innovations in the last thirty years, some of which will be detailed below. We included one invention per imaging modality described, plus one more related to computer aided detection and diagnosis (CAD).

For each innovation, a technological definition is provided wherein the purpose or goal is outlined, and the components plus their interactions are explained based on a thorough literature review. Next, the innovation is scored based on the assessment sheet in Appendix A.

## 3.2 Radiography invention: digital radiography

A quick Google search on "radiography breakthrough" suffices to show that digital radiography is the most significant invention for basic radiography in recent decades. As mentioned earlier in subsection 2.2.3, digital radiographs are much easier to store, copy, post-process and share compared to their analogue siblings. Additionally, unlike radiographic film there is no potential for over- or underexposure. Instead, the output can be rescaled as needed during post-processing. Some techniques also allow for a reduced exposure of the patient, minimizing the risk. The ubiquity of digital scanners these days prove that the advantages outclass the disadvantages. However, these disadvantages do exist. Analogue images have a very high inherent resolution, and by examining them

on a lightbox the contrast is unmatched by any kind of computer screen. In addition, because analogue systems do not use digital electronics, there is no electronic noise. Digital radiographs do not have necessarily to outclass their analogue counterparts on these fronts, but they have to achieve a minimum level to make sure their diagnostic value is not impaired.

### 3.2.1 Defining the technology

What makes radiography analogue or digital depends on kind of detector used. Other parts of the scanner such as the X-ray source do not have to be altered to make the transition. Furthermore, it is not one specific technology that makes this transition possible. Various components are needed, and for each of them there are some alternatives as well. On top of that, evolution in other fields such as digital electronics and computer machinery had to be advanced enough to take full advantage of the possibilities.

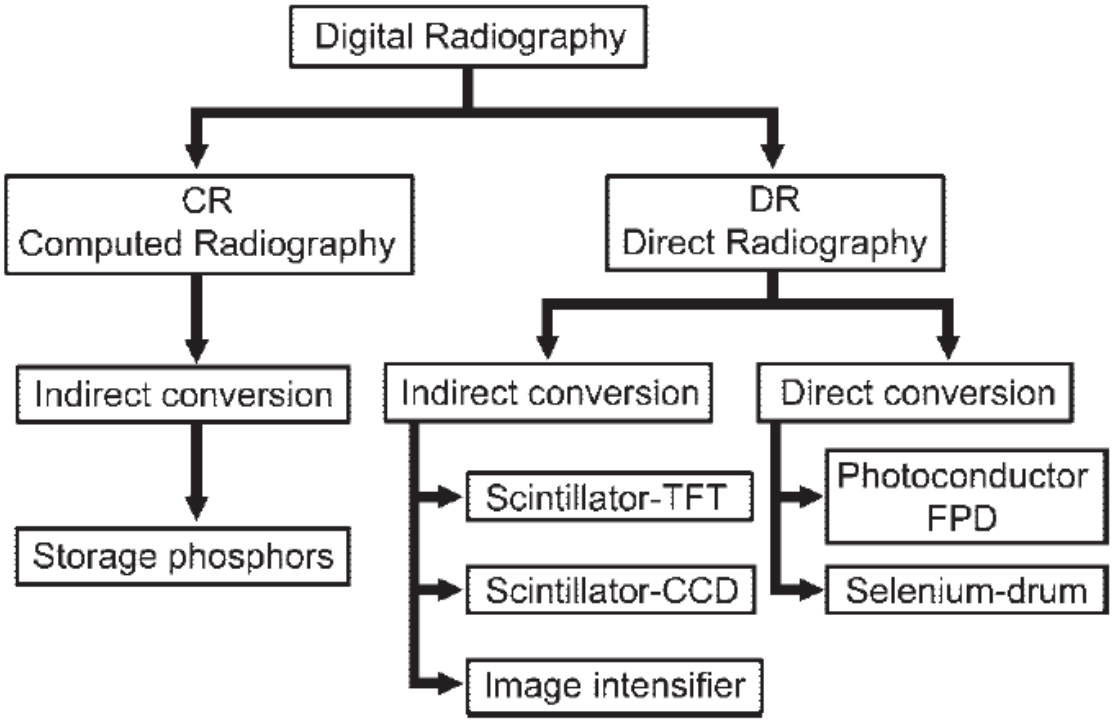


Figure 3.1: A systematic overview of various types of digital detectors. CCD = charge-coupled device, FPD = flat-panel detector, TFT = thin-film transistor. [KWW+07]

We first discuss the various types in greater detail using Figure 3.1. The first incarnation of digital radiography - called computed radiography (CR) - used storage phosphor to temporarily store the image information, and lasers to read out the values pixel by pixel

at a later stage [KWW+07]. Unfortunately, the physical properties of storage phosphors severely limited the resolution of the resulting image, reducing their diagnostic value. The technology underwent many iterations, as shown in Table 3.1.

| Year | Development |
|---|---|
| 1980 | Computed radiography (CR), storage phosphors |
| 1987 | Amorphous seleniumbased image plates |
| 1990 | Charge-coupled device (CCD) slot-scan direct radiography (DR) |
| 1994 | Selenium drum DR |
| 1995 | Amorphous siliconcesium iodide (scintillator) flat-panel detector |
| 1995 | Selenium-based flat-panel detector |
| 1997 | Gadolinium-based (scintillator) flat-panel detector |
| 2001 | Gadolinium-based (scintillator) portable flat-panel detector |
| 2001 | Dynamic flat-panel detector fluoroscopydigital subtraction angiography |

Table 3.1: Timetable of developments in digital radiography [KWW+07].

The alternative to computed radiography is direct radiography (DR). It comes in two forms, using either direct or indirect conversion. The direct form uses a photoconductor to convert the incident photons to electrical charges. Typical semiconductor materials used in photoconductors are amorphous Selenium (a-Se) and Gadolinium (Gd). In earlier versions the photons were projected onto a rotating drum and converted to electrical signals using an analog to digital converter (ADC). Newer versions however use a flat panel detector (FDP) where the ADC is swapped out for thin-film transistors (TFT, also used in LCD displays). These TFTs are made of amorphous Silicon (a-Si). Because the used materials have a very high intrinsic resolution, the final image resolution is only limited by the quality of the underlying detector array.

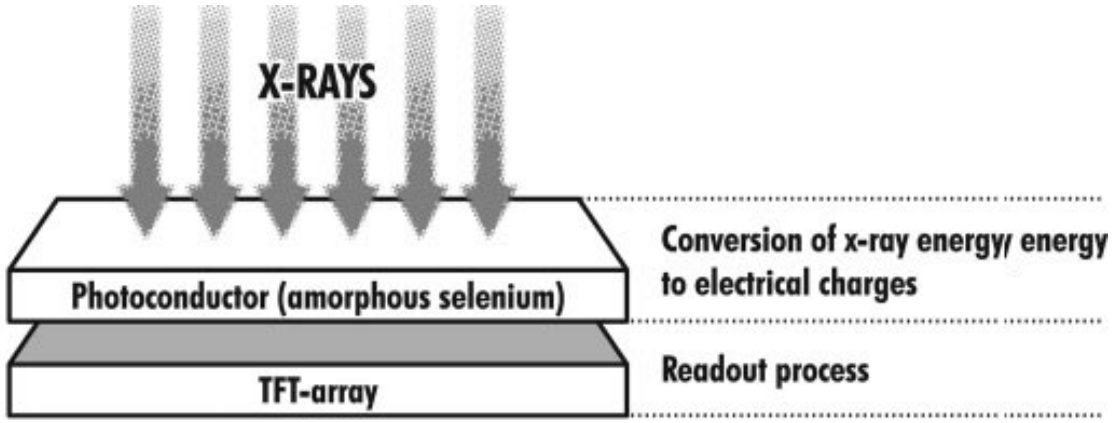


Figure 3.2: Components of a direct conversion flat panel detector. [KWW+07]

In indirect conversion DR, an extra element is added between the X-rays and the actual

detector. A common example is a scintillator plate that converts X-rays into visible light. Alternatively, an image intensifier (II) can be used to amplify the light output. This light can than be captured more easily by a charge-coupled device (CCD, also used in digital cameras) or a TFT. Because of the extra step, the point spread function (PSF) increases and the resolution suffers slightly.

A CCD chip is relatively small so it cannot under normal circumstances record a whole image at once. Two alternatives are possible. One uses a lens to focus the rays onto the smaller chip area, but this reduces the image quality. Another uses a small collimated fan-shaped beam combined with a moving CCD detector. This system performs comparable to FPDs. One drawback is that this elaborate setup is not very mobile.

Instead of a CCD, TFTs can also be used in a similar fashion as in direct conversion DR FPDs. Only this time a scintillator is added. These scintillators use either Cesium Iodide (CsI) or Gd-based crystals. Contrary to Gd, CsI crystals can be structured, improving the image quality. The trade-off is their brittleness, making them less portable. The visible light they emit is then captured by photo diodes and read out by a TFT array.

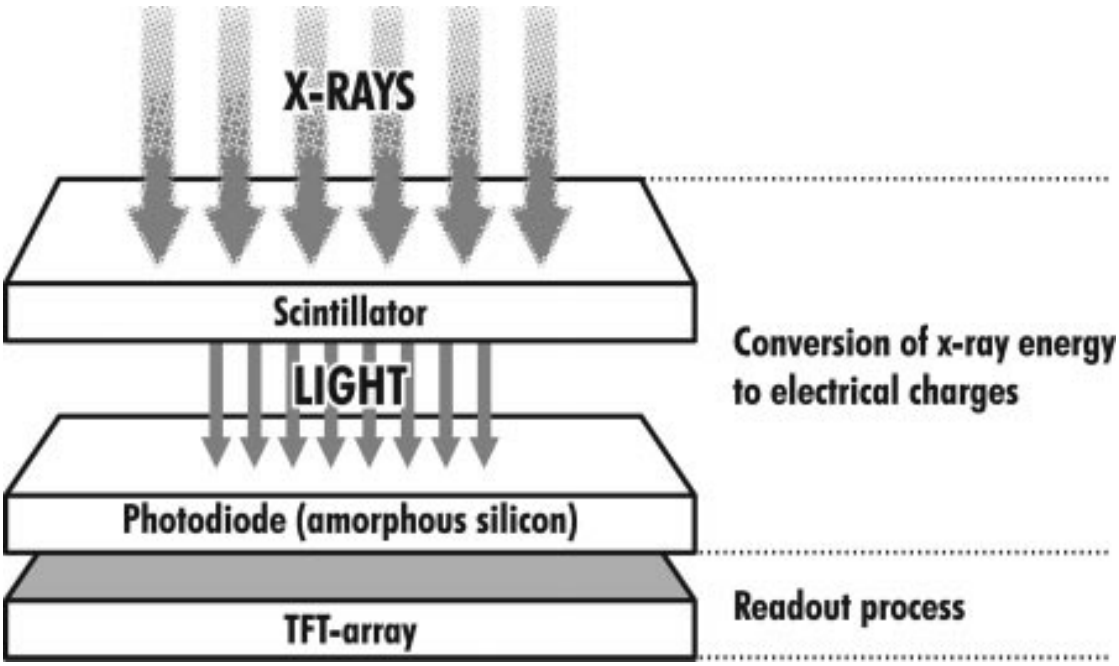


Figure 3.3: Components of an indirect conversion flat panel detector. [KWW+07]

For the actual assessment, we will focus on both direct and indirect FPDs.

### 3.2.2 Assessing novelty in functionality

Functionality-wise, we can distinguish between novelty in components and combinations thereof on the one hand, and novelty in natural effects exploited on the other hand.

#### Novelty in components

As explained above, digital radiography in general uses many of the same parts as analogue radiography. Only the detector is fundamentally different. Of course the real advantage of digitizing radiographs is what you can do with them afterwards. However, that is out of the scope of this text, and we will constrain ourselves to the hardware aspects for now.

The next question we ask ourselves is whether these new (combinations) of components were already used before. The answer is yes. For example CCDs were invented in 1969 at AT&T Bell Labs (patents: US3792322, US3796927) and first used in digital cameras by 1975 [ASA02]. On the other hand, the combination of a scintillator with CCDs to capture X-rays was not used before.

In the case of direct FPDs using TFTs, the results are similar. Engineers experimented with them as early as 1971 for use in display equipment [Kaw02]. To this day, they are almost exclusively used in LCD panels and in digital radiography. In conclusion, they were used before, but mostly in a field that is not closely related to medical imaging.

#### Novelty in natural effects exploited

Of course the primary natural effect exploited is that of the X-ray passing through tissue. This has not changed with digital radiography. On the other hand, the natural effects used in the digital detector are very distinct from those in classic photographic film. Where such films fall under the accomplishments of material science, modern digital recording equipment are made possible by advances in the electronic and semiconductor industry. Obviously these natural effects were exploited numerous times before by other digital equipment, but not equipment related to medical imaging.

#### Scores

In Table 3.2 we give an overview of the scores on the various topics.

| Novelty in functionality | |
|---|---|
| A. Novelty of components | B. Novelty in natural effects exploited |
| A1) 4 | B1) 8 |
| A2) 5 | B2) 5 |

Table 3.2: Novelty in functionality scores

### 3.2.3 Assessing novelty in knowledge origins

Regarding knowledge origins (KOs), we can make a distinction between scientific and technological origins. To find these KOs, we first provide a list of problems that had to be solved for digital radiography to become feasible.

The main purpose is to somehow intercept the X-rays and translate their intensities per pixel into a discrete values that can be processed by a computer. To do so, they X-rays must first be converted to electrical charges, which can then be interpreted as bits.

Problem 1: converting the X-ray intensities to bits

Problem 1.1: converting the X-rays to electrical charges

Solution 1.1a: direct conversion: use a photoconducting material (a-Se)

KO1: electromagnetism, semiconductors

Solution 1.1b: indirect conversion: use a scintillator (CsI) and photodiodes (a-Si)

KO2: electromagnetism, material science and semiconductors

Problem 1.2: converting the electrical charges to bits

Solution 1.2: use a TFT array

KO3: digital electronics (mostly transistors)

#### Scores

Electromagnetism falls under scientific origins. The use of electromagnetism knowledge in medical imaging is certainly nothing special, so it receives low scores.

The other origins fit better in the technological group. The use of digital electronics and all related disciplines makes digital radiography what it is. This warrants a high score, at least for the detector part. However, at the time of invention the digital electronics industry was booming and already widely in use in various other fields. In that regard it was only a matter of time before someone came up with the idea to combine digital electronics with radiography.

Table 3.3 shows the scores.

| Novelty in knowledge origins | |
|---|---|
| A. Novelty of scientific origins | B. Novelty of technological origins |
| A1) 2 | B1) 8 |
| A2) 2 | B2) 5 |

Table 3.3: Novelty in knowledge origins scores

### 3.2.4 Assessing technological impact

The last part of this digital radiography assessments looks into technological impact. Impact can be split into three parts: performance increase, technological accumulation and obsoleting previous technologies.

#### Performance increase

The goal of radiography is simply to make clear images that have a high diagnostic value. To that end, spatial resolution, contrast and noise as discussed in section 2.2.3 are all important. The aim of digital resolution was not necessarily to do better in this regard, because analogue images were already very detailed. If the quality is on par, we should consider ourselves happy.

As explained above, resolution was a problem with computer radiography using storage phosphors. However, the materials used in flat panel detectors all have a high inherent spatial resolution. Only the size of the underlying TFT array limits the final image resolution. Because analogue radiographs are not expressed in number of pixels, the performance comparison is complicated. However, tests performed by [Doi06] show that diagnostic value of analogue and digital images are almost on par as long as the pixels are about 0.1mm in size.

Contrast on the other hand is a serious problem for digital radiography. The deep blacks of photographic film combined with the strong light from a lightbox creates very high contrast. In comparison, radiologists now have to look at images on their computer screen in a dark room. On the other hand, digital radiography makes up for this defect by offering the possibility of post-processing where it is not only possible to zoom in spatially, but also on a certain intensity interval (using so-called grey-level transformations [Sue09]). This way, contrast can be increased in one intensity interval in exchange for lowering it in other intervals.

Noise-wise, the electronic circuits introduce additional electronic noise on top of the electromagnetic noise. Fortunately, modern electronics can minimize the former noise, as evident by our crisp digital photographs and big flat screens.

Other advances in performance include: lack of geometric distortion, no veiling glare, uniform response across the field of view [Doi06]. In addition, costs are reduces because

expensive photographic film is no longer needed, and time span is reduces because film development happens automatically and almost instantly.

It is difficult to assign a single score to this component because of the many issues at play. The image quality did not necessarily improve much, but this was not the goal. The real performance increase is due to indirect opportunities opened up by the digital image format. Therefore, in our opinion this still deserves a fairly high score.

### Technological accumulation

In this section we estimate the broadness, magnitude and novelty of the impact.

**Broadness of impact** The real breakthrough that made digital radiography possible was the advent of digital electronics. This breakthrough had a very broad impact on fields other than its own. Other fields looked directly at digital electronics, rather than digital radiography, for possible innovations. That is why this innovation does not score high on broadness of impact. It did however impact related fields such as CT and PET.

**Magnitude of impact** Although the broadness of impact was not big, and it mostly concentrated on highly related fields, the magnitude was considerable. In fact, computed tomography would not even be possible if it were not for the invention of digital detectors. The same goes (to a lesser extent) for detectors used in nuclear medicine imaging.

**Novelty of impact** The novelty of impact of digital radiography is very low because other technologies that never used digital electronics before, got their ideas from digital electronics in general, not specifically from digital radiography.

### Obsoleting previous technologies

The last aspect of impact assessment regards obsoleting previous technologies, i.e. analogue radiography. According to [Doi06] and [Sue09], this has indeed happened. Few radiology departments still stick with analogue systems because of their lower cost and extreme reliability, but most of the world has permanently moved on. Not only in radiography, but also in related disciplines such as CT and PET.

### Scores

Table 3.4 shows the scores.

| Technological impact | | |
|---|---|---|
| A. Performance increase | B. Tech. accumulation | Obsoleting previous tech. |
| A) 8 | B1 a) 3 — b) 1 | C) 10 |
| | B2 a) 8 — b) 7 | |
| | B3 a) 1 — b) 1 | |

Table 3.4: Technological impact scores

## 3.3 CT invention: Electron-beam CT

Our next assessment deals with an innovation related to computed tomography. In particular, we take a closer look at Electron-beam Computed Tomography (EBCT), also know as Ultrafast CT.

### 3.3.1 Defining the technology

Traditional CT scanners have an X-ray tube embedded in the toroid body. By mechanically rotating the tube along with the detector, projections from an arbitrary angle can be captured.

EBCT also needs to be able to capture projections from any angle, but takes another route. Remember that in a regular X-ray tube current flowing through the cathode releases electrons. The electrons are accelerated towards the anode by applying a voltage across the tube. When the electrons hit the anode at high speed, they release part of their energy as X-rays. The same principle is used in EBCT, except that the tube is physically split up in two dedicated parts. One is the cathode or electron gun and is placed along the patient's longitudinal axis. The other is the anode and is shaped in a semi-ring around the patient. Using magnetic fields, the electrons fired from the cathode are deflected onto this ring, where they produce X-rays that can be captured by a detector array as usual [Sue09]. Figure 3.4 illustrates this.

The main advantage of this setup is that the X-ray source rotation is no longer mechanical. This allows for faster sweeps, which in turn make it easier to image moving structures such as the heart. In traditional CT scanners, this movement would cause blurring in the final image, and thus a loss of diagnostic value. One very prominent EBCT application is the detection of calcifications from atherosclerosis in the coronal arteries (i.e., coronary artery disease) [BGB+96]. These are very close to the heart, and can move by about five times their own diameter every heartbeat.

More recently, these EBCT scanners have received strong competition from multislice helical CT scanners. The latter enjoy a widespread adoption and are also less costly (partly due to economies of scale and increased competition). However, their rotation speed still cannot match that of Ultrafast CT [CCIGJ+00]. In addition, this techniques

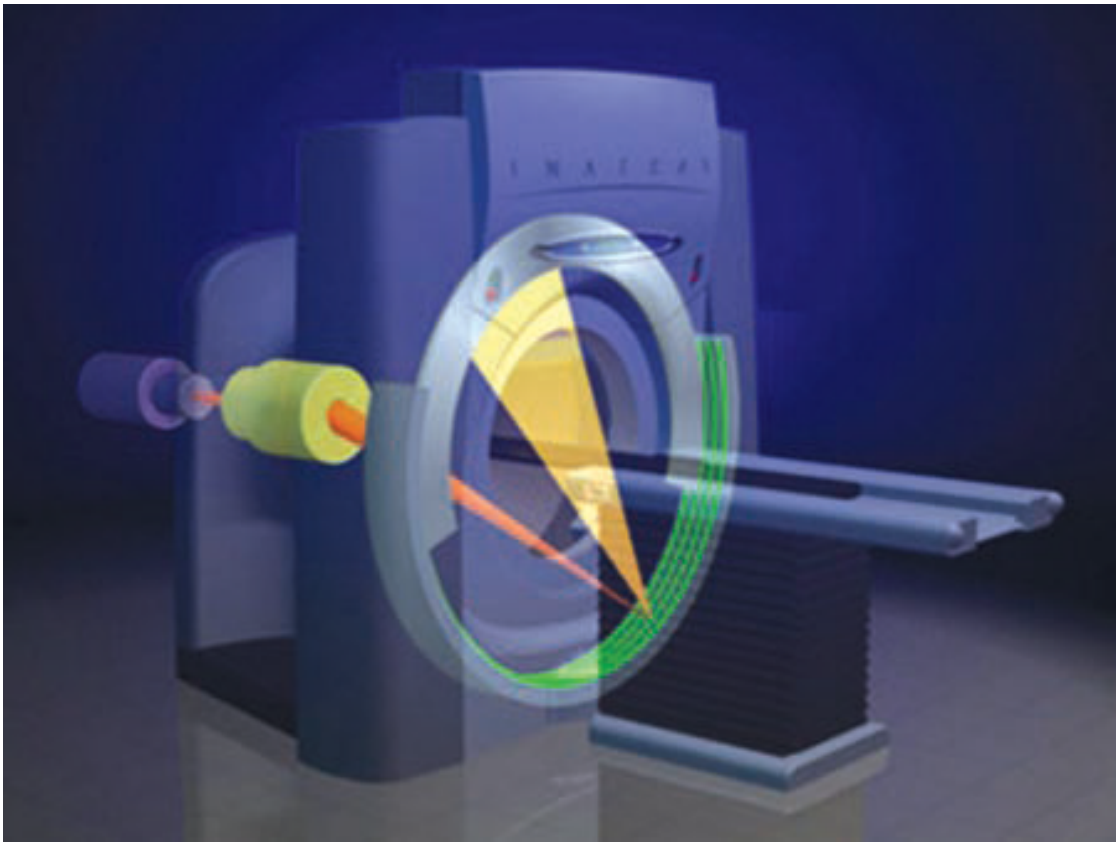

Figure 3.4: Rendering of an EBCT scanner's inner workings [Sue09].

requires a lower dose compared to traditional CT, and much lower than a CT angiography [HVS+03]. The latter is a common alternative for diagnosing coronary artery disease when an EBCT scanner is not available.

In conclusion, this technique is promising for non-invasive detection of coronary heart disease, but it has too many unsolved problems to replace general purpose CT scanners [OFB+06].

### 3.3.2 Assessing novelty in functionality

#### Novelty in components

As outlined above, the components are largely the same as in conventional CT scanners. Only their location is different. One additional component is the coil to generate the deflecting magnetic field. Such electromagnets were used before in imaging, particularly in MRI, but for a very different purpose.

#### Novelty in natural effects exploited

The same story applies for novelty in natural effects exploited: few new effects except bending of the electron beam using magnetic fields. The same principle was used much earlier in Cathode Ray Tube (CRT) monitors and televisions.

#### Scores

In Table 3.5 we give an overview of the scores on the various topics.

| Novelty in functionality | |
|---|---|
| A. Novelty of components | B. Novelty in natural effects exploited |
| A1) 3 | B1) 3 |
| A2) 5 | B2) 5 |

Table 3.5: Novelty in functionality scores

### 3.3.3 Assessing novelty in knowledge origins

Again, we look into the problems that had to be solved to find the knowledge origins. We only look at the problems that are different in comparison to a traditional CT scanner.

Problem 1: deflect the electron beam onto the anode ring.

Solution 1: use magnetic fields (electric field deflection only works for small angles)

KO1: electromagnetism, CRT monitors

Problem 1.1: overcoming Coulomb repulsion to obtain proper beam focus

Solution 1.1: leak nitrogen into vacuum chamber [Ret08]

KO2: charged particle optics

Problem 2: synchronise imaging with heart rhythm

Solution 2: use ECG equipment

KO3: biomedical sensors, signal processing

#### Scores

Electromagnetism, charged particle optics and signal processing can be considered scientific origins, while the others are technological in nature.

Note that using ECG equipment to synchronise imaging with the heart rhythm is not new. It was occasionally used before in various other imaging modalities [Sue09].

Table 3.6 shows the scores.

| Novelty in knowledge origins | |
|---|---|
| A. Novelty of scientific origins | B. Novelty of technological origins |
| A1) 4 | B1) 5 |
| A2) 1 | B2) 1 |

Table 3.6: Novelty in knowledge origins scores

### 3.3.4 Assessing technological impact

#### Performance increase

As outlined above, EBCT is very useful for mainly one thing: imaging the heart and its periphery. However, there are serious drawbacks that do not make it useful as a general purpose CT scanner. For example, due to the new geometry X-ray scatter cannot be reduced as effectively. This in turn generates extra artifacts on the resulting image. The electron gun also has limited power making it inadequate for higher dosage (i.e., higher contrast) studies [OFB+06].

#### Technological accumulation

Surprisingly, we were unable to identify any newer invention based on EBCT. Various other applications using electron beams were checked, such as electron microscopes and electron beam lithography, but none seem to be based on innovations in EBCT. This may be caused by the relative obscurity of EBCT outside of medical imaging fields.

#### Obsoleting previous technologies

EBCT has definitely not obsoleted previous technologies. Its application area is simply too narrow for many hospitals to warrant such an expensive purchase. Instead, older and cheaper but less effective methods are still used more often to diagnose coronary artery disease. Examples include a CT angiography, exercise stress tests but also invasive (catheter) examinations.

#### Scores

Table 3.7 shows the scores.

| Technological impact | | |
|---|---|---|
| A. Performance increase | B. Tech. accumulation | Obsoleting previous tech. |
| A) 5 | B) N/A | C) 2 |

Table 3.7: Technological impact scores

## 3.4 MRI invention

Normally we only consider inventions from 1980 onwards, but for this section we would like to make an exception. The invention of the MRI scanner itself was a veritable breakthrough, and still happened relatively close to 1980. Because we already had a close look at MRI in section 2.4, we will skip the technology definition and go straight to the assessment.

### 3.4.1 Assessing novelty in functionality

#### Novelty in components

The purpose of MRI scanners is largely the same as that of CT scanners: create cross-sectional images to look into patient's bodies without using invasive techniques. The essential components of CT are the X-ray source and the detector. With MRI, we again have a signal source and a signal detector. However, this time the source is a large electromagnet, and the detector is a quadrature detector.

Electromagnets are used in various other technologies to do the same thing: generate magnetic fields. Examples include motors, generators, transformers, relays and loudspeakers. In that sense the choice was not very special.

Similarly, quadrature detectors are used universally whenever signal demodulation is required [GH99]. Remember that MRI operates in the radio frequency range, so ordinary radio technology could be repurposed for use in these scanners.

In summary, these components were not used in medical imaging before the advent of MRI. Yet, once it was decided to exploit radio waves and magnetic fields, the choice of components was rather trivial.

#### Novelty in natural effects exploited

MRI has one thing in common with the other imaging modalities discussed: they all use electromagnetic radiation in one form or another. Nevertheless, the way this natural effect is exploited here is considerably different from other modalities. In radiography and CT, we measure the X-ray attenuation when traveling through the human body.

With nuclear medicine, we essentially detect photons emitted by radioactive materials. MRI on the other hand influences and measures the magnetic properties of tissues, in particular the proton density, the $T_1$ time or the $T_2$ time.

In a way, every researcher that ever worked on imaging based on magnetic fields contributed to the eventual creating of MRI. Of course some groups took a slightly different turn (e.g. measuring properties of electrons instead of protons), but their larger goal was the same. To our knowledge no one experimented with these specific magnetic properties for any other purposes.

**Scores**

In Table 3.8 we give an overview of the scores on the various topics.

| Novelty in functionality | |
|---|---|
| A. Novelty of components | B. Novelty in natural effects exploited |
| A1) 10 | B1) 8 |
| A2) 3 | B2) 8 |

Table 3.8: Novelty in functionality scores

### 3.4.2 Assessing novelty in knowledge origins

Once again, we start with a list of problems and corresponding solutions.

Problem 1: measure proton density in tissue

Problem 1.1: align net magnetization vectors

Solution 1.1: generate a large magnetic field

KO1: electromagnetism

Problem 1.1.1: increase field strength, lower power consumption

Solution 1.1.1: superconductivity by extreme cooling

KO2: physics (cryogenics), material science

Problem 1.2: measure magnetization vector

Solution 1.2a: disturb equilibrium with the appropriate pulse sequence

KO3: theory from electromagnetism, but to our knowledge never exploited before

Solution 1.2b: record relaxation phenomena using quadrature detector

KO4: analogue electronics, radio equipment

Problem 2: localize position using signal

Solution 2: apply a magnetic field gradient

KO5: electromagnetism, gradients recently used in [HPW+10, PFC+08], older: [BJ67].

#### Scores

None of these knowledge origins, except the usage of specific pulses, is out of the ordinary. Radio equipment is also a new technological origin, but its purpose in other inventions is very similar. That is why in Table 3.9 we give low scores except for this technological origin.

| Novelty in knowledge origins | |
|---|---|
| A. Novelty of scientific origins | B. Novelty of technological origins |
| A1) 2 | B1) 6 |
| A2) 2 | B2) 7 |

Table 3.9: Novelty in knowledge origins scores

### 3.4.3 Assessing technological impact

#### Performance increase

Although we have portrayed MRI as the successor to CT in the section above, this is not completely true. MRI allows us to visualize things we could not before with CT. For example, cancerous tissue is sometimes easier to spot on MRI scans. Whereas on CT scans the attenuation properties of both tissue types might be very similar, malignant tumors appear to exhibit a larger $T_1$ value than surrounding tissue [Mal06].

On the other hand, CT has the advantage when it comes to visualizing bone. Because it contains few free hydrogen atoms, it is very difficult to spot on an MRI scan. X-rays however are ideal for this type of diagnosis.

In conclusion, it is very difficult to unilaterally award the performance trophy to either side.

#### Technological accumulation

**Broadness of impact** MRI generated a lot of spin-off technologies, including Magnetic Resonance Angiography (MRA), Magnetic Resonance Spectroscopy (MRS) and functional MRI (fMRI). These are of course all part of the same imaging family, and we could not find any impact outside of this family in the literature. Perhaps mining through patents can show some interesting results.

**Magnitude of impact** Although the broadness is limited, the magnitude of impact is substantial. Especially for the direct spin-offs listed above, but also indirectly through the spin-offs of those spin-offs.

**Novelty of impact** As stated above, we only identified direct impact on its immediate spin-off technologies. The degree of novelty is thus very low.

#### Obsoleting previous technologies

As stated before in subsection 2.4.4, MRI has not replaced CT, but is expected to gain more traction in the future. For now, the two technologies are complimentary: each is better for a specific subcategory of diagnostic imaging.

#### Scores

Table 3.10 shows the final scores.

| Technological impact | | |
|---|---|---|
| A. Performance increase | B. Tech. accumulation | Obsoleting previous tech. |
| A) 5 | B1 a) 4 — b) 2 | C) 3 |
| | B2 a) 8 — b) 8 | |
| | B3 a) 1 — b) 1 | |

Table 3.10: Technological impact scores

## 3.5 Nuclear medicine invention: 18F-FDG tracers

In this assessment related to nuclear medicine we focus on something slightly unusual. Not a component or new technique used in the scanner, but on one of the popular tracers used during such examinations: $^{18}$F-FDG tracers.

### 3.5.1 Defining the technology

PET scanners work by detecting positrons formed by the decay of radioactive tracers, as explained in section 2.5. The most commonly used isotope is fluorine-18. It is very suited for PET because it almost exclusively emits positrons when decaying to oxygen-18. Its half life of 110 minutes gives it another attractive property.

However, the fluorine isotope is only responsible for the emission of positrons, it cannot be absorbed by or transported in the human body on its own. That is where 2-deoxy-2-fluoro-D-glucose or, more conveniently fluorodeoxyglucose (FDG), comes into play. One of its hydroxyl (-OH) groups can be replaced by fluorine-18. Because it is analogous to normal glucose, its uptake in the body is also similar. However, unlike normal glucose it cannot be completely metabolised as long as the fluorine isotope is present. Instead, it gets stuck in the cells until the fluorine decays into oxygen and it can form a hydroxyl group again.

When the tracer is injected into the body, a PET scanner can visualize its distribution throughout the various tissues. This way, physicians can monitor glucose metabolism and spot abnormalities or deviations. Those can be caused by tumors for example, which typically grow very fast and consequently need lots of energy. Brain activity can also be measured regionally because active parts of the brain tend to metabolise more glucose.

Synthesis of FDG is possible in a number of ways, but most are rather sophisticated.

### 3.5.2 Assessing novelty in functionality

#### Novelty in components

The F-FDG tracer is a composite made out of both FDG and fluorine-18. Earlier tracers also used FDG, but the isotopes were different. Carbon-14 was a popular choice [TK98]. The fluorine-18 seems to be exclusively used as a radioactive tracer. It is sometimes also combined with other molecules, for example to track dopamine instead of glucose [FGSM75, EHI06]. Another isotope (fluorine-19) is used as a contrast agent in MRI studies.

The first paper describing the synthesis of F-FDG already mentioned specific usage as a radiopharmaceutical [IWC$^+$78]. To our knowledge, it has not been used outside this context. Within this context however, it was used towards many different goals in biomedical research such as neuroscience and oncology.

#### Novelty in natural effects exploited

The tracer isotope exploits radioactive decay, more specifically positron emission decay. Considering PET works exclusively with positron emission decay, this is no special feat. However, what makes fluorine-18 special is that it hardly has any other decay mechanisms and that its half life has the ideal length for PET studies.

The second natural effect exploited is how the human body treats FDG very similar to normal glucose.

**Scores**

In Table 3.11 we give an overview of the scores on the various topics.

| Novelty in functionality | |
|---|---|
| A. Novelty of components | B. Novelty in natural effects exploited |
| A1) 6 | B1) 3 |
| A2) 2 | B2) 1 |

Table 3.11: Novelty in functionality scores

### 3.5.3 Assessing novelty in knowledge origins

To make F-FDG work, a number of problems had to be overcome.

Problem 1: find a tracer that emits positrons

Solution 1: the following isotopes are known to emit positrons: carbon-11, nitrogen-13, oxygen-15, fluorine-18, sodium-22, aluminium-26, potassium-40, and iodine-121

KO1: nuclear physics

Problem 1.1: find an isotope that easily combines with lots of molecules

Solution 1.1: carbon-11 and fluorine-18 [TK98]

KO2: biochemistry

Problem 1.2 find an isotope that has a suitable half life for PET studies

Solution 1.2 fluorine-18

KO3: nuclear physics

Problem 2: find a suitable transport molecule that mimics glucose

Solution 2: replace one hydroxyl group in normal glucose with an isotope

KO4: biochemistry, pharmacology

**Scores**

Table 3.12 shows the scores. Note that there are no technical knowledge origins. This is a consequence from the rather unique category of innovation radiopharmaceuticals belong to. The scientific knowledge origins on the other hand are rather straightforward for these kinds of applications.

| Novelty in knowledge origins | |
|---|---|
| A. Novelty of scientific origins | B. Novelty of technological origins |
| A1) 1 | B1) N/A |
| A2) 1 | B2) N/A |

Table 3.12: Novelty in knowledge origins scores

### 3.5.4 Assessing technological impact

#### Performance increase

Performance of positron emission tracers is difficult to quantify. Remember that in nuclear medicine the image quality is of secondary importance. More important is the fidelity of the tracer. It should properly visualize the biochemical and physiological processes, glucose metabolism in our case. Empirical tests confirmed that FDG is effectively processed in the same manner as normal glucose in the body, and that PET scans highlight regions where glucose metabolism is expected to be higher (brains, kidneys, tumors) [TK98]. Earlier incarnations such as $^{11}$C-glucose also achieved this. Unfortunately, because of the short half life of just 20 minutes, images had to be taken before the tracer had the chance to diffuse properly.

#### Technological accumulation

**Broadness of impact** The success of F-FDG inspired the production of several other tracers. One example is a tracer called F-fluoro-DOPA for studying dopamine utilization [TK98].

However, the biggest impact by far was on research in the fields of medicine and physiology. This tracer opened up lots of new possibilities, and application in oncology, neuroscience, virology etc. [MMS$^+$09, LOC$^+$09].

**Magnitude of impact** As stated before, the invention of FDG led to many spin-off tracers, and each of those tracers has multiple spin-offs itself. The magnitude of impact is thus significant.

**Novelty of impact** Fields such as virology could traditionally not make use of imaging modalities, because viruses are simply too small to be seen. However, FDG-related technologies in combination with PET scanners have allowed researchers to finally see what exactly goes on at this microscopic level [LOC$^+$09].

On the other hand, most of the impact was on fields that already made extensive use of imaging modalities, such as oncology or neuroscience.

**Obsoleting previous technologies**

These days PET and F-FDG are so intricately linked that it is hard to imagine a time before this tracer was used. Yet, research in this field is still ongoing and very active. Other biochemical processes obviously require different transport molecules, and not all of them are compatible with fluorine-18. That is why many other tracers are still in use today. But when it comes to visualizing glucose metabolism, F-FDG seems to be the gold standard for now [TK98].

**Scores**

Table 3.13 shows the scores.

| Technological impact | | |
|---|---|---|
| A. Performance increase | B. Tech. accumulation | Obsoleting previous tech. |
| A) 7 | B1 a) 7 — b) 3 | C) 8 |
| | B2 a) 7 — b) 6 | |
| | B3 a) 4 — b) 3 | |

Table 3.13: Technological impact scores

## 3.6 CAD invention: machine learning techniques for mammography

For this last assessment, we draw from the field of Computer-aided Detection and Diagnosis. For the rest of this section, we will focus on the usage of machine learning techniques for CADe in mammography. Breast cancer is one of the deadliest cancers among women today, but fortunately early detection significantly improves the chances of survival [TRX$^+$09]. To detect breast cancer, phycisians look for calcifications, masses and architectural distortions on high resolution radiographs (mammograms). Traditionally, every image is checked by at least two radiologists to increase sensitivity. This is known as the second reader principle. However, this approach effectively doubles the workload of the radiology department. Perhaps more than in any other medical field, CAD can help radiologists by acting as a surrogate second reader for mammograms. [WYB$^+$10].

One particular application where CAD has proven its worth, is in the detection of microcalcifications in mammograms. These are small calcium deposits of 0.05mm to 1mm in size that appear as bright white spots on the scan. They are known to appear in 30-50% of all breast cancer cases, and are thus an important indicator. Due to their

variable shape, brightness and size, they can be difficult to detect in the surrounding tissue [WYB+10].

Note that - unlike tangible inventions - software algorithms are not so straightforward to assess using the radical innovation framework. For example, algorithms typically do not exploit natural effects directly (but computers do). However, we will make an effort to make a meaningful assessment regardless.

### 3.6.1 Defining the technology

As explained in subsection 2.6.3, machine learning comprises a large group of methods and techniques. We are specifically interested in (binary) classifiers to determine whether a particular structure on a mammogram is suspicious enough. The exact nature of this classifier - whether it is a Support Vector Machine (SVM) or Random Forests (RF) or anything else - is of little interest for this assessment. We will simply look at them as one group with one goal.

When assessing this technology, we will compare it to earlier incarnations of CAD software without machine learning elements, and - where appropriate - with manual diagnosis by a physician.

### 3.6.2 Assessing novelty in functionality

Because we are dealing with software algorithms, we can only assess the novel functionality based on novelty in components, not on novelty in natural effects exploited.

#### Novelty in components

In subsection 2.6.2, we discussed the generic scheme that most CAD systems follow. Each of these steps can be considered a separate component in the algorithm. In our case, step III and IV are replaced by machine learning algorithms.

Of course these algorithms were used before in a variety of other applications, but not necessarily related to diagnostic medical imaging [LS95].

#### Scores

In Table 3.14 we give an overview of the scores on the various topics.

| Novelty in functionality | |
|---|---|
| A. Novelty of components | B. Novelty in natural effects exploited |
| A1) 5 | B1) N/A |
| A2) 4 | B2) N/A |

Table 3.14: Novelty in functionality scores

### 3.6.3 Assessing novelty in knowledge origins

As usual, we start by listing problems encountered during development of this invention, and present the proposed solution and its related knowledge origin. We again follow the five step detection scheme introduced before.

Problem 1: detect abnormalities in mammograms

Problem 1.1: segment the region of interest

Solution 1.1: trivial, the mammogram only contains the region of interest

Problem 1.2: enhance abnormalities

Solution 1.2: use traditional image processing and computer vision methods (e.g. convolution filters)

KO1: image processing

Problem 1.3: detect and segment abnormalities

Problem 1.3.1: detect abnormalities

Solution 1.3.1: use an appropriately trained machine learning classifier

KO2: statistics, artificial intelligence, machine learning

Problem 1.3.2: segment abnormalities

Solution 1.3.2: use traditional image processing and computer vision methods (e.g. region growing)

KO3: image processing

Problem 1.4: perform feature analysis and classification

Solution 1.4: use an appropriately trained machine learning classifier

KO4: statistics, artificial intelligence, machine learning

Problem 1.5: reduce false positives

Solution 1.5: use traditional false positive reduction methods

KO5: statistics, machine learning

#### Scores

Of the listed knowledge origins, we classify statistics as scientific, and the rest as technological.

Statistics forms the fundamental basis for almost all machine learning algorithms. Some more primitive image processing techniques also explicitly use statistical theory, but most do not. The radiologists that perform a manual diagnosis use their advanced human visual system instead of relying on statistics.

Of the technological knowledge origins, machine learning is by definition the only new element compared to earlier methods.

| Novelty in knowledge origins | |
|---|---|
| A. Novelty of scientific origins | B. Novelty of technological origins |
| A1) 6 | B1) 3 |
| A2) 1 | B2) 5 |

Table 3.15: Novelty in knowledge origins scores

### 3.6.4 Assessing technological impact

#### Performance increase

Already in 1990, [CDV+90] proved using observer studies that radiologists' performance in detecting microcalcifications could increase when using CAD systems, even if the number of false positives at the time were still fairly high. The review article [Doi07] looked into various large scale studies regarding CAD in mammography, and found that all of them reported an increase in detection performance compared to pre-CAD diagnosis. Remember that performance is this context is the combined performance of physician plus computer, not computer alone. It should be mentioned that other studies found no performance gain, or even a performance decrease [FTC+07], but they seem to be in the minority. They particularly lament the high number of false positives, claiming that these cause more unnecessary examinations and consequently an increase in medical insurance expenditures.

#### Technological accumulation

false positive reduction

**Broadness of impact** Machine learning is generally application-agnostic and thus a very versatile technique used in a variety of fields, from the financial world over social networks to medical applications. In fact, CAD was fairly late to jump on the machine learning bandwagon [WYB+10]. Nonetheless, a lot of related research is performed by biomedical scientists. This research is often generic enough in nature to potentially be applied to other fields again. Unfortunately, researchers outside of the medical field tend to ignore medical journals in favor of their own field-specific alternatives. This severely degrades the possible cross-pollination across fields, and in turn the broadness of impact. This is evident by the lack of medical literature citations from outside the field.

**Magnitude of impact** Globally speaking, the medical field only accounts for a relatively small slice of all machine learning research. Consequently, most breakthroughs will originate elsewhere, negatively impacting the magnitude of direct and indirect impact of CAD on unrelated applications.

**Novelty of impact** Due to the versatility of machine learning, there is a lot of potential for novelty of impact. But again, because of invisible walls surrounding the medical field, we could not locate specific applications that drew from biomedical machine learning research.

#### Obsoleting previous technologies

Within three years of FDA approval, about 10% of of U.S. facilities switched to CAD technology[1]. CAD technology using machine learning has not yet obsoleted conventional mammography diagnosis, although performance definitely increases when employed. Some physicians are simply reluctant to rely on technology for performing their diagnosis. This will require a change in mindset, which is a long-term endeavor. On top of that, these systems imply an additional cost on top of the already expensive imaging equipment. Perhaps integrating them as modules in PACS as suggested by [Doi07] will speed up their adoption. Because of these reasons, researchers believe it is only a matter of time before such methods are used globally.

#### Scores

Table 3.16 shows the scores.

[1] `http://www.nih.gov/news/pr/apr2007/nci-04b.htm`

| Technological impact | | |
|---|---|---|
| A. Performance increase | B. Tech. accumulation | Obsoleting previous tech. |
| A) 7 | B1 a) 3 — b) 5 | C) 4 |
| | B2 a) 3 — b) 2 | |
| | B3 a) 3 — b) 2 | |

Table 3.16: Technological impact scores

## 3.7 Conclusion

In this chapter, we presented the results of the assessment of various innovations related to diagnostic medical imaging. We tried to be as varied as possible in the selection of innovations. Not only did they all stem from a different field, but their scope and type also varied. For example, we tried a high-level assessment of MRI as a whole, but also assessment of a whole class of algorithms and a very specific radiopharmaceutical compound. In our newfound experience, the assessment framework seems to work best on rather low-level, yet tangible innovations. Nonetheless, it showed considerable flexibility when applied to concepts it was perhaps never intended for.

Truthfully, we are slightly disappointed by the seemingly low scores of these important innovations. We explore some reasons for this in the following paragraphs.

We have tried to make this assessment as detailed as possible. However, medical imaging is a very complex matter, and even our introduction in chapter 2 - much like many a review paper - just barely scratch the surface of all underlying methods and technologies. These details only become apparent when hands-on work is performed by scientists and researchers in the field. For example, a little known fact is that the anode in an X-ray tube gets hot during operation, lowering performance. A simple solution is to make it spin to cool it down. Such details will only be described in the most detailed literature and of course in patent applications. We fear that this discrepancy in level of detail will significantly hamper comparison with the automated patent analysis.

The way the framework is built also seems to favor automatic patent based analysis over manual assessment. The questions on the assessment sheet map nicely to data that can be extracted from patents. On the other hand, manually finding an answer to these questions without looking at patent data has proven to be challenging at times. The granularity of the scores presents another problem. It is very difficult to explain the difference between, say, a 5 and a 6. In that regard we would propose a rescaled score chart with scores from 1 to 5. The alternative is to improve the existing score chart with a more detailed description of how to quantify the small differences in score.

In addition, the 1980 limit made it significantly more difficult to go back to the real breakthrough invention, the so-called seed. For example, FDG in nuclear medicine was certainly a breakthrough but it would have been more interesting to go back further and

see who first managed to bring nuclear physics together with biochemistry and truly invent radiopharmacology. The fact that many imaging-related inventions spend a very long time in the research phase, taking decades before entering the market, does not help in this regard either. On the other hand, due to the ex-post nature of some assessment questions (i.e., impact), very recent innovations cannot be mapped either.

One final aspect we noticed, is that medical imaging research seems to "stay in the family" - so to speak. One imaging modality builds on top of another modality's body of knowledge, but the technology hardly seems to diffuse into other fields. One possible explanation is that biomedical researchers have plenty of very specific medicine-related journals to choose from for publishing, so they don't branch out. They do not interact much with journals that have similar content but focus on another sector. From personal experience, this is very apparent in the image processing literature. For example, one can browse image processing journals from IEEE in vain trying to find a solution for a generic non-medical problem. Meanwhile, medical researchers might have come up with such a solution years ago, applied it to medicine and published it in a medical image processing journal. Clearly, many disciplines could learn from research in the biomedical sector.

Chapter 4

# Conclusion

The centerpiece of this thesis is radical innovation. Such innovations have regularly been seen in the past, and seem to be a key factor in the long term growth of firms or even entire regions. It follows that identifying such radical innovations early is critical. Chapter 1 introduced the reader to a framework based on three dimensions that does just this. These three dimensions are novelty in knowledge origins, novelty in functionality and technological impact. Innovations that score high on all three components are very likely to be radical. In addition, the framework proposes patent indicators to automatically score innovations using complex computer algorithms.

In this text however, we restricted ourselves to a thorough manual assessment of a few innovations in the field of diagnostic medical imaging. To that end, we presented a short introduction to this field in chapter 2. In particular, we discussed the history, technical background, recent advancements and future expectations of four imaging modalities: radiography, computer tomography, magnetic resonance imaging and nuclear medicine imaging. We also briefly discussed computer aided detection and diagnosis.

Once we had a basic understanding of the field, chapter 3 provided us with a deeper understanding of some more recent innovations in the field. For each innovation, scores were given based on the assessment sheet in the appendix. These innovations include digital radiography, electron beam computed tomography, magnetic resonance imaging, fluorodeoxyglucose tracers and modern computer aided detection and diagnosis techniques. The scores turned out lower than expected, and we listed a few possible reasons for this.

This work can serve as a basis to validate and further refine the radical innovation framework. By comparing the results of this manual assessment with the outcome of an automatic assessment based on patent indicators, potential discrepancies and flaws in the framework can hopefully be found and alleviated.

# Bibliography


[AAVL13] Sam Arts, Francesco Paolo Appio, and Bart Van Looy. Inventions shaping technological trajectories: do existing patent indicators provide a comprehensive picture? *Scientometrics*, 97(2):397–419, 2013.

[Ang58] Hal O Anger. Scintillation camera. *Review of scientific instruments*, 29(1):27–33, 1958.

[Art07] W Brian Arthur. The structure of invention. *Research Policy*, 36(2):274–287, 2007.

[ASA02] S Abdallah, B Saleh, and AK Aboulsoud. A general overview of solid state imaging sensors types. In *Photonics and Its Application at Egyptian Engineering Faculties and Institutes, 2002. Third Workshop on*, pages 1–10. IEEE, 2002.

[BBW+69] GL Brownell, CA Burnham, S Wilensky, S Aronow, H Kazemi, and D Strieder. New developments in positron scintigraphy and the application of cyclotron-produced positron emitters. In *Medical Radioisotope Scintigraphy. VI Proceedings of a Symposium on Medical Radioisotope Scintigraphy*, 1969.

[BGB+96] Matthew J Budoff, Demetrios Georgiou, Alan Brody, Arthur S Agatston, John Kennedy, Christopher Wolfkiel, William Stanford, Paul Shields, Roger J Lewis, Warren R Janowitz, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease a multicenter study. *Circulation*, 93(5):898–904, 1996.

[BJ67] William E Byrd Jr. Potential applications of magnetic gradients to marine geophysics. Technical report, DTIC Document, 1967.

[CCIGJ+00] J Jeffrey Carr, John R Crouse III, David C Goff Jr, Ralph B D'Agostino Jr, Neil P Peterson, and Gregory L Burke. Evaluation of

subsecond gated helical ct for quantification of coronary artery calcium and comparison with electron beam ct. *American Journal of Roentgenology*, 174(4):915–921, 2000.

[CDV+90] Heang-Ping Chan, Kunio Doi, CARL J VYBRONY, Robert A Schmidt, Charles E Metz, Kwok Leung Lam, Toshihiro Ogura, Yuzheng Wu, and Heber MacMahon. Improvement in radiologists' detection of clustered microcalcifications on mammograms: The potential of computer-aided diagnosis. *Investigative radiology*, 25(10):1102–1110, 1990.

[DB05] Kristina B Dahlin and Dean M Behrens. When is an invention really radical?: Defining and measuring technological radicalness. *Research Policy*, 34(5):717–737, 2005.

[Dir30] Paul AM Dirac. A theory of electrons and protons. *Proceedings of the Royal Society of London. Series A, Containing papers of a mathematical and physical character*, pages 360–365, 1930.

[Doi06] Kunio Doi. Diagnostic imaging over the last 50 years: research and development in medical imaging science and technology. *Physics in medicine and biology*, 51(13):R5, 2006.

[Doi07] Kunio Doi. Computer-aided diagnosis in medical imaging: historical review, current status and future potential. *Computerized medical imaging and graphics*, 31(4-5):198–211, 2007.

[EHI06] Philip H Elsinga, Kentaro Hatano, and Kiichi Ishiwata. Pet tracers for imaging of the dopaminergic system. *Current medicinal chemistry*, 13(18):2139–2153, 2006.

[FGSM75] G Firnau, ES Garnett, TL Sourkes, and K Missala. [18 f] fluoro-dopa: A unique gamma emitting substrate for dopa decarboxylase. *Cellular and Molecular Life Sciences*, 31(11):1254–1255, 1975.

[FTC+07] Joshua J Fenton, Stephen H Taplin, Patricia A Carney, Linn Abraham, Edward A Sickles, Carl D'Orsi, Eric A Berns, Gary Cutter, R Edward Hendrick, William E Barlow, et al. Influence of computer-aided detection on performance of screening mammography. *New England Journal of Medicine*, 356(14):1399–1409, 2007.

[GH99] Li Gengying and Xie Haibin. Digital quadrature detection in nuclear magnetic resonance spectroscopy. *Review of scientific instruments*, 70(2):1511–1513, 1999.

[GW28] H Geiger and M Walther. The electron counting tube. *Physik Zeitschrift*, 29:839–841, 1928.

[GW02] Rafael C Gonzalez and Richard E Woods. Digital image processing, 2002.

[HPW+10] Zheyong Huang, Ning Pei, Yanyan Wang, Xinxing Xie, Aijun Sun, Li Shen, Shuning Zhang, Xuebo Liu, Yunzeng Zou, Juying Qian, and Junbo Ge. Deep magnetic capture of magnetically loaded cells for spatially targeted therapeutics. *Biomaterials*, 31(8):2130 – 2140, 2010.

[HVS+03] Peter Hunold, Florian M Vogt, Axel Schmermund, Jorg F Debatin, Gert Kerkhoff, Thomas Budde, Raimund Erbel, Klaus Ewen, and Jorg Barkhausen. Radiation exposure during cardiac ct: Effective doses at multi–detector row ct and electron-beam ct 1. *Radiology*, 226(1):145–152, 2003.

[Ind13] OECD Indicators. Health at a glance, 2013.

[IWC+78] T Ido, C-N Wan, V Casella, JS Fowler, AP Wolf, M Reivich, and DE Kuhl. Labeled 2-deoxy-d-glucose analogs. 18f-labeled 2-deoxy-2-fluoro-d-glucose, 2-deoxy-2-fluoro-d-mannose and 14c-2-deoxy-2-fluoro-d-glucose. *Journal of Labelled Compounds and Radiopharmaceuticals*, 14(2):175–183, 1978.

[Jas06] Ronald Jack Jaszczak. The early years of single photon emission computed tomography (spect): an anthology of selected reminiscences. *Physics in Medicine and Biology*, 51(13):R99, 2006.

[JC34] Frédéric Joliot and Irène Curie. Artificial production of a new kind of radio-element. *Nature*, 133(3354):201–202, 1934.

[Kal06] Willi A Kalender. X-ray computed tomography. *Physics in Medicine and Biology*, 51(13):R29, 2006.

[Kal11] Willi A Kalender. *Computed tomography: fundamentals, system technology, image quality, applications*. John Wiley & Sons, 2011.

[Kaw02] Hirohisa Kawamoto. The history of liquid-crystal displays. *Proceedings of the IEEE*, 90(4):460–500, 2002.

[KWW+07] Markus Korner, Christof H Weber, Stefan Wirth, Klaus-Jurgen Pfeifer, Maximilian F Reiser, and Marcus Treitl. Advances in digital radiography: Physical principles and system overview 1. *Radiographics*, 27(3):675–686, 2007.

[L+73] Paul C Lauterbur et al. Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature*, 242(5394):190–191, 1973.

[LOC+09] Giovanni Lucignani, Eva Orunesu, Miriam Cesari, Katia Marzo, Michela Pacei, Giulia Bechi, Andrea Gori, Sabrina Gaito, Mario Clerici, and Arturo Chiti. Fdg-pet imaging in hiv-infected subjects: relation with

therapy and immunovirological variables. *European journal of nuclear medicine and molecular imaging*, 36(4):640–647, 2009.

[LS95] Pat Langley and Herbert A Simon. Applications of machine learning and rule induction. *Communications of the ACM*, 38(11):54–64, 1995.

[Mal06] John R Mallard. Magnetic resonance imagingthe aberdeen perspective on developments in the early years. *Physics in Medicine and Biology*, 51(13):R45, 2006.

[MK06] Gerd Muehllehner and Joel S Karp. Positron emission tomography. *Physics in Medicine and Biology*, 51(13):R117, 2006.

[MMS+09] L Mosconi, R Mistur, R Switalski, M Brys, L Glodzik, K Rich, E Pirraglia, W Tsui, S De Santi, and MJ De Leon. Declining brain glucose metabolism in normal individuals with a maternal history of alzheimer disease. *Neurology*, 72(6):513–520, 2009.

[OFB+06] Bernd M Ohnesorge, Thomas G Flohr, Christoph R Becker, Andreas Knez, and Maximilian F Reiser. *Multi-slice and dual-source CT in cardiac imaging: Principles-protocols-indications-outlook*. Springer, 2006.

[PFC+08] Boris Polyak, Ilia Fishbein, Michael Chorny, Ivan Alferiev, Darryl Williams, Ben Yellen, Gary Friedman, and Robert J Levy. High field gradient targeting of magnetic nanoparticle-loaded endothelial cells to the surfaces of steel stents. *Proceedings of the National Academy of Sciences*, 105(2):698–703, 2008.

[Rad17] Johann Radon. Uber die bestimmung von funktionen durch ihre integralwerte langs gewissez mannigfaltigheiten, ber. *Verh. Sachs. Akad. Wiss. Leipzig, Math. Phys. Klass*, 69, 1917.

[Ret08] Michael Retsky. Electron beam computed tomography: challenges and opportunities. *Physics Procedia*, 1(1):149–154, 2008.

[Roe96] W.C. Roentgen. On a new kind or rays. *Journal of the Franklin Institute*, 141(3):183 – 191, 1896.

[Sue09] Paul Suetens. *Fundamentals of medical imaging*. Cambridge University Press, 2009.

[Suz12] Kenji Suzuki. A review of computer-aided diagnosis in thoracic and colonic imaging. *Quantitative imaging in medicine and surgery*, 2(3):163, 2012.

[TK98] Timothy J Tewson and Kenneth A Krohn. Pet radiopharmaceuticals: state-of-the-art and future prospects. In *Seminars in nuclear medicine*, volume 28, pages 221–234. Elsevier, 1998.

[TRX+09] Jinshan Tang, Rangaraj M Rangayyan, Jun Xu, Issam El Naqa, and Yongyi Yang. Computer-aided detection and diagnosis of breast cancer with mammography: recent advances. *Information Technology in Biomedicine, IEEE Transactions on*, 13(2):236–251, 2009.

[VBV14] Dennis Verhoeven, Jurriën Bakker, and Reinhilde Veugelers. Identifying ex ante characteristics of radical inventions through patent-based indicators. *FEB Research Report-MSI_1319*, 2014.

[vGAIdH+10] Bram van Ginneken, Samuel G Armato III, Bartjan de Hoop, Saskia van Amelsvoort-van de Vorst, Thomas Duindam, Meindert Niemeijer, Keelin Murphy, Arnold Schilham, Alessandra Retico, Maria Evelina Fantacci, et al. Comparing and combining algorithms for computer-aided detection of pulmonary nodules in computed tomography scans: the anode09 study. *Medical image analysis*, 14(6):707–722, 2010.

[WJ98] Henry N Wagner Jr. A brief history of positron emission tomography (pet). In *Seminars in nuclear medicine*, volume 28, pages 213–220. Elsevier, 1998.

[WYB+10] Miles N Wernick, Yongyi Yang, Jovan G Brankov, Grigori Yourganov, and Stephen C Strother. Machine learning in medical imaging. *Signal Processing Magazine, IEEE*, 27(4):25–38, 2010.

# Appendix A

# Assessment sheet



| Novelty in Functionality | Novelty in Knowledge Origins | Technological Impact |
|---|---|---|
| **A. Novelty of components** | **A. Novelty of scientific origins** | **A. Performance increase** |
| *A1. Given a certain purpose, to what extent does the technology embody different (combinations of) components compared to previous technologies with the same purpose?*<br>1) None of its (combination of) components are different<br>10) All of its (combinations of) components are different<br>*A2. Concerning the new (combinations of) components identified in A1:*<br>1) They were used before to serve purposes related to the purpose of the invention at hand<br>5) They were used before, but only to serve purposes unrelated to the purpose at hand<br>10) They were never used in any technology before | *A1. Given its purpose, to what extent are the scientific origins of the technology different compared to the scientific origins of technologies with the same purpose?*<br>1) None of the scientific origins are different<br>10) All of the scientific origins are different<br>*A2. Concerning the new scientific origins identified in A1:*<br>1) They were used before to serve purposes related to the purpose of the invention at hand<br>5) They were used before, but only to serve purposes unrelated to the purpose at hand<br>10) They were never used in any technology before | *To what extent was the goal set out to be served by the invention accomplished better compared to state-of-the-art practices at the moment of the invention?*<br>1) It had no overall performance increase<br>5) It made possible significant improvements compared to current practice, but still a number of significant problems are not assessed<br>10) It represented a major leap in performance and the goal set out is served completely thanks to the invention |
| **B. Novelty in natural effects exploited** | **B. Novelty of technological origins** | **B. Technological accumulation** |
| *B1. Given a certain purpose, to what extent does the technology embody different natural effects (guiding the selection of the combination of components) compared to previous technologies with the same purpose?*<br>1) None of its natural effects exploited are different<br>10) All of its natural effects exploited are different<br><br>*B2. Concerning the natural effects to serve the purpose of the invention identified in (B1):*<br>1) They were used before to serve purposes related to the purpose of the invention at hand<br>5) They were used before, but only to serve purposes unrelated to the purpose at hand<br>10) They were never used in any technology before | *B1. Given its purpose, to what extent are the technological origins of the technology different compared to the scientific origins of technologies with the same purpose?*<br>1) None of the technological origins are different<br>10) All of the technological origins are different<br><br>*B2. Concerning the new technological origins identified in (B1):*<br>1) They were used before to serve purposes related to the purpose of the invention at hand<br>5) They were used before, but only to serve purposes unrelated to the purpose at hand<br>10) They were never used in any technology before | *B1. Broadness of impact*<br>B1a. To what extent did the technology have an impact on technologies that serve purposes different to the technology at hand?<br>B1b. Concerning the technologies on which impact was identified in B1a:<br>1) They serve purposes very much related to the purpose of the invention at hand<br>10) They serve purposes entirely unrelated to the purpose at hand<br>*B2. Magnitude of (in)direct impact*<br>B2a. Given the scope of the impact, to what extent was it directly used by a multitude of inventions in the future?<br>B2b. Given the scope of the impact, to what extent were its (combination of) components used indirectly by a multitude of inventions in the future?<br>*B3. Novelty of impact*<br>B3a. To what extent did the technology have impact on technologies that have never before built on the technologies with the purpose of the focal invention?<br>B3b. Considering the novel impact identified above, to what extent did it pertain to technologies serving purposes unrelated to the purpose of the technology at hand? |
| | | **C. Obsoleting previous technologies** |
| | | *To what extent were the technologies previously used to serve the purpose of the invention made obsolete by the invention at hand?*<br>1) No previous technology was made obsolete<br>10) All previous technology were made obsolete |

Appendix B

# International Patent Classification codes

This section contains a list of relevant patent categories in relation to diagnostic medical imaging. The categories are identified using their International Patent Classification (IPC) codes. A complete reference of all IPC codes can be found at `http://web2.wipo.int/ipcpub`.

**A61B 1/005** Flexible endoscopes

**A61B 5/05** Measuring for diagnosis by means of electric currents or magnetic fields

**A61B 6/00** Apparatus for radiation diagnosis, e.g. combined with radiation therapy equipment

**A61B 6/03** Computerised tomographs

**A61B 8/00** Diagnosis using ultrasonic, sonic or infrasonic waves

**G01N 23/00** Investigating or analysing materials by the use of wave or particle radiation

**G01R 33/00** Arrangements or instruments for measuring magnetic variables

**G01T 1/36** Measuring spectral distribution of X-rays or of nuclear radiation

**G01T 1/161** Applications in the field of nuclear medicine, e.g. in vivo counting

**G02B 23/24** Instruments for viewing the inside of hollow bodies, e.g. fibrescopes

**G03B 42/02** using X-rays

**G06T** IMAGE DATA PROCESSING OR GENERATION, IN GENERAL

**H01J 35/00** X-ray tubes

**H05G** X-RAY TECHNIQUE

**FACULTY OF BUSINESS AND ECONOMICS**
Naamsestraat 69 bus 3500
3000 LEUVEN, BELGIË
tel. + 32 16 32 66 12
fax + 32 16 32 67 91
info@econ.kuleuven.be
www.econ.kuleuven.be