# RINCKSIDE

ISSN 2364-3889

Volume 29, 2018


EMRF

THE ROUND TABLE
FOUNDATION

# RINCKSIDE

ISSN 2364-3889 • Volume 29, 2018

## CONTENTS



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# Mapping the biological world

Peter A. Rinck

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Relaxation and relaxation constants is a rather complicated topic, both to explain and to understand. There are two main relaxation constants important for MRI: T1 and T2.

T2* which is also often mentioned in this context is not a time constant, it is a capricious global parameter representing a fluctuant time or time range.

## An excursion into scientific history

This is not the place to go into the science of relaxation; a textbook is better suited for this [1]. Here I will just tell a bit about the history and background of relaxation times in biomedicine.

It all began in 1953 with Eric Odeblad. He was the first to describe relaxation times in biological systems. His first paper on the topic was entitled “Some preliminary observations on the proton magnetic resonance in biological samples” and published in Acta Radiologica Stockholm in early 1955 [2].

Odeblad had found that different tissues had distinct relaxation times, most likely due to water content but also to different bindings to lipids. Soon others joined in the new research field: Studies in blood, plasma and red blood cells, followed by T1- and T2-measurements of living frog muscle, the relaxation of water in living animals and in the arms of living humans.

Research groups in Brooklyn and in Baltimore got involved in the early 1970s. They measured relaxation times of excised normal and cancerous rat tissue, and the leader of the Brooklyn group stated that tumorous tissue had longer relaxation times than normal tissue and promoted these findings as the ultimate technology to screen for cancer [3].

However, already some months later the Baltimore group stated that independent verification on the same NMR instrument could not be provided; the results were not reproducible [4].

Later, the New York Times pointed out major discrepancies between what was claimed by the researchers from Brooklyn and what was actually accomplished, "discrepancies sufficient to make the author [Raymond Damadian] appear a fool if not a fraud." [5]

The summary of a paper published in 1975 – 42 years ago – by the group of Donald Hollis stated [6]:

> “The direct use of NMR T1 measurements for cancer diagnosis is clearly not feasible because of the lack of specificity … classification of tumors in this manner does not seem realistic.”

Shortly afterwards clinical MR imaging arrived and relaxation time measurements were considered very important during its first years. All machines were programmed to create true T1 and T2 images (T1- and T2-mapping), based on reliable and reproducible spin-echo (SE) and inversion-recovery (IR) sequences.

After absolute T1 and T2 values had been used unsuccessfully by researchers, combinations of T1 and T2, histogram techniques, and sophisticated three dimensional display techniques of factor representations were used. At that time, these approaches were called ‘electronic contrast agents’, today ‘fingerprinting’ or ‘biomarkers’.

However, soon it became clear that relaxation time values were not the claimed invaluable addition to diagnostics, and these applications were skipped in the early 1990s.

> “A spin-echo sequence with 24 echoes (Carr-Purcell-Meiboom-Gill sequence) was evaluated to determine the usefulness of magnetic resonance (MR) in detecting and typing brain tumors. ... T2 values calculated from an eight-point fit, however, did not allow discrimination of different tumors, nor did they allow differentiation between tumor, inflammatory tissue, and demyelination.” [7]

It was the time when the *Relaxation Times Blues* arrived [8], and Ian Young, one of the leading and influential scientists in MRI summed up the trials and errors in a short history of MRI as follows:

> "Sadly, the many attempts that were made to correlate pathology and relaxation behavior have yielded none of the precise numerical relationships that were hoped for in the early days of MRI, so that this line of investigation ... has now been abandoned." [9]

## A grant-creating perpetuum mobile?

It is rare that a method appears, disappears, and then re-appears again as is the case of tissue characterization based on relaxation time constants. Yet some years later these obsolete methods were dug out again, grants were given to answer questions which had been discarded 25 years earlier [10, 11]. New pulse sequences and algorithms were developed – researchers tried their luck again.

Still, there is no easily explainable causality nor any evidence of a straight connection between these numbers and a distinct pathology. There is no unique signature of distinct malignancies or other pathologies in tissue relaxation times, be it in ex vivo or in vivo measurements. Many people believe that numbers (or, more fashionable, data) are the truth but they do not understand how the numbers were acquired and what they stand for. Nature doesn't care about numbers. Believing in such postulations many years after they have been dismissed is a sign of scientific naiveté.

What's wrong in relaxation time mapping and applications: the precondition and presumption that a difficult biological structure such as a tissue or tissue changes in the human body can be quantified and qualified with NMR proton relaxation parameters.

Quantity and quality are being confused; it's so easy counting something – which doesn't mean that one can classify or characterize with numbers what one counts. The components and chemical and electrical processes in a tiny volume element, no matter how small it is, are far too complex and fickle to be expressed in bare figures. More so, on closer inspection, "objective" procedures, "objectively" defined range values as well as "objective" quality indicators for measurements often prove to be biased and interest-driven. There is no precise numerical fingerprinting based on relaxation constants in biomedicine.
It is helpful to once look into a microscope and to see how complex and complicated tissue structures are, both in normal and in pathological tissues – and in not-normal, but not (yet) pathological tissues.

In the end, it is not necessarily the errors or procedural "confounders" connected to the most elaborate and sophisticated data acquisition that make typing of normal and pathological tissues or grading of diseases impossible – but rather the complexity of tissue composition and the overlapping of relaxation time values of heterogeneous volume elements examined and processed into a single number or number range.

Nowadays lessons are rediscovered that became clear 25 years ago … and finally admitted, though diplomatically beating around the bush:

> "In conclusion, our question, whether native T1 mapping in cardiac MR imaging can differentiate between healthy and diffuse diseased myocardium, must be answered with 'yes' and 'no', since the native myocardial T1 relaxation time allows discriminating between groups of patients with certain diffuse myocardial pathologies and a group of healthy individuals, but does not allow differencing between healthy and diffuse diseased myocardium in individual subjects." [12]

Researchers also came to realize that novel methods for faster data acquisition deliver crude estimations but not accurate data. The higher the magnetic field, the larger seems to be the spread of T1 and T2 relaxation time estimations.

> "A vast extent of methods and sequences has been developed to calculate the T1 and T2 relaxation times of different tissues in diverse centers. Surprisingly, a wide range of values has been reported for similar tissues (e.g. T1 of white matter from 699 to 1735 ms and T2 of fat from 41 to 371 ms), and the true values that represent each specific tissue are still unclear, which have deterred their common use in clinical diagnostic imaging." [13]

## Exceptions from the rule

Few isolated cases allow tissue discrimination based on relaxation time alterations, but they are the exception. One needs massive changes of relaxation time constants, as well as large homogeneously altered

volumes to be able to use such data for diagnostic purposes. The data you get is not fake, it is not necessarily false, no, worse: it's half-true.

Does this mean that relaxation time maps cannot be used at all? Here are some insights into my own experiences: We started creating maps of relaxation constants and proton density as well as derivatives of these maps, called "synthetic images", in the early 1980s and presented the idea of synthetic MR images and simulating entire MR exams in the early 1980s at a conference in the United States. In 1994 we finally published the image simulation software MR Image Expert for teaching and research purposes. More than 12,000 copies of MR Image Expert were licensed since then.

The simulations were based on the three main contrast parameters in MRI: T1, T2, and proton density acquired with time-consuming, but precise data acquisitions and exact calculations – with "clean" basic pulse sequences: inversion recovery and spin echo. For a reliable T1 determination one needs between 15 and 30 IR measurements, for T2 we usually used 24 echoes of a SE echo train. They allowed the creation of outstandingly good simulations of MR images – but still simulations.

In general, from a scientific point of view, MR imaging is a crude and not very exact technology. Thus, in most cases, relaxation time mapping and derivatives of it – such as synthetic images – cannot be used to quantify exact tissue data (e.g., relaxation constants or proton density in tissues) since the calculated or estimated relaxation constants and proton density values are unreliable – and impracticable in diagnostic routine; they are not accurate and not conclusive.

The only way to exploit relaxation time values would be situations when the values change drastically under specific physiological or pathological circumstances. This can be the case before and after the application of an MR contrast agent. There are uses for such rough estimations.

An area of application of relaxation times measurements might be the follow-up of massive T1 changes after the injection of a targeted contrast agent, such as Mn-DPDP and the comparison of plain and contrast-enhanced tissue, e.g., in heart diseases. Here imprecise measurements might be of diagnostic value. However, such indications are limited because increasingly different and simpler MR techniques exist that may lead to the wanted result.

In one of the next columns I will try to discuss the non-scientific and non-medical reasons why these measurements returned and why they will stay with us for some time.

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Rinckside, ISSN 2364-3889

**Citation:** Rinck PA. Mapping the biological world. Rinckside 2018; 29,1. 1-3.

# Some side effects of the great gadolinium scare

Peter A. Rinck

This is a slightly different follow-up of the gadolinium scandal. I believe that I have put on the table in earlier columns and in our MR textbook all facts I know and feel publishable. [1] There are numerous publications about the topic containing "fake news," among them papers by certain authors that have to be digested *cum grano salis* as described earlier [2] because they try to whitewash themselves or make money.

Many feel competent enough to offer their humble opinion about gadolinium-based contrast agents (GBCA), not only radiologists and physicians of every shade and color, but also physicists and chemists, as well as want-to-be experts such as journalists and movie actors. Of particular interest may be the U.S.A., where lawyers mix up ethical and moral values with personal financial advantages.

They all incense fear and lead to confusion. Patients are increasingly becoming uneasy and worried. I am receiving letters like this one:

> "I am trying to find alternatives to gadolinium as I don't think the risk is worth it. Would the newer MRI machines with bigger magnets, more sensitive detectors, more computing power, and techniques to enhance the images, thinner slices, higher resolution, be good enough to detect a 3 mm to 4 mm in size or smaller acoustic neuroma tumor on the hearing nerve? How small of a tumor (mm) can a 3-Tesla MRI detect without gadolinium contrast?"

**For some time, there is a witch hunt going on ...**

For some time now, there has been a witch hunt going on in the U.S.A. against the Italian company Bracco and its contrast agent MultiHance (gadobenate, gadobenic acid), a compound superior to all of the competitors: far better relaxivity and higher contrast, enhancing both in the central nervous system and liver.

As I have already stated earlier:

> "Gadobenic acid (MultiHance) as well as gadoxetic acid (Primovist) are excreted by both the kidneys and the liver, although the percentage of liver excretion is far higher for gadoxetic acid. Still, MultiHance is the best-enhancing contrast agent on the market. As far as I am aware, there were no direct cases of nephrogenic systemic fibrosis with MultiHance, but there were a small number of 'confounding' cases with combinations of Omniscan. There is no scientific or statistically based reason to damn MultiHance and to promote Primovist for liver examinations, as the European Medicines Agency has now done." [3]

There is an increasing animosity against the European Medicines Agency (EMA) and their decisions; some companies say their precautionary measures are not based on facts and that the EMA used controversial "experts." There are also rumors about partial outside influence. I believe there has been a strong will from some to kill MultiHance.

Agencies such as the EMA and the U.S. Food and Drug Administration (FDA) differ in regulating the use of gadolinium-based contrast agents. The FDA's Medical Imaging Drugs Advisory Committee met on 8 September 2017 and finally stated:

> "To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. We have also received reports of adverse events involving multiple organ systems in patients with normal kidney function. A causal association between these adverse events and gadolinium retention could not be established." [4]

Among others, the committee invited the testimony of U.S. movie star Chuck Norris and his wife Gena, who suffers from rheumatoid arthritis. After three MRI examinations five years ago, Norris and his wife Gena claim that she now has "gadolinium depo-

sition disease" and, according to an article in the U.S. news magazine Newsweek, are suing for $10 million in damages, first and foremost directed at Bracco. [5]

According to reports, Gena Norris suffered from symptoms that include burning sensation in various parts of the body.

The term "gadolinium deposition disease" was introduced by Dr. Richard C. Semelka in 2016. [6] It's a syndrome whose symptoms are headache, cognitive disturbance, skin hyperpigmentation, and arthralgia – which according to the authors are clinical manifestations of presumed gadolinium toxicity in patients with normal renal function.

Semelka also proposed the application of Ca-DTPA and Zn-DTPA to reduce or eliminate gadolinium deposition disease symptoms. Meanwhile, a clinical study to prove this was suspended. [7] The idea is chemically sound – but the gadolinium has to be reachable and removable. If clustered as an insoluble phosphate deposit, it is rather unlikely that it will be caught and removed.

After at least 400 million doses of GBCAs have been injected into humans since the 1980s, there is no convincing evidence of systematic symptoms after recommended application, other than NSF in patients with impaired renal function. To repeat the statement of the FDA: "A causal association between these adverse events and gadolinium retention could not be established."

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Rinckside, ISSN 2364-3889

**Citation:** Rinck PA. Some side effects of the great gadolinium scare. Rinckside 2018; 29,2. 5-6.

# German newspapers and the gadolinium controversy

Peter A. Rinck

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During the last two months, radiologists in Germany and beyond have been confronted with several newspaper articles about MR contrast agents and their factual and imagined side effects.

For instance, the author of an article in the German daily *Die Welt* follows the old leitmotif of the yellow press that sensationalism sells: Bad news is good news. The author's attempt to pluck the readership's heartstrings is brilliant. The headline warns that "An MRI shot can be quite poisonous" and the article begins more like a crime novel:

> 'The contrast medium gadolinium has made nurse Georg Wehr ill – and he is not the only one … Two years ago Georg Wehr was still working as a nurse. Then a patient fell, he tried to catch her, injuring an intervertebral disc and his hip. Four MRI exams followed … Wehr received a gadolinium-containing contrast agent at each exam. "I wanted to get better and trusted the doctors," says Wehr. He has been unable to work since the accident – also because the gadolinium has made him ill. Pure gadolinium metal is very toxic …' [1]

The entire article casts a lurid light on clinical MRI, as did a similar article in the same newspaper discussed in an earlier column [2]. Unfortunately, after reading this article one is left in a state of confusion, not being able to distinguish which parts were important or how the described facts tie up. There is no detailed explanation in the paper. It just spreads uneasiness and fear.

I have written about science and the media last year – the arguments have not changed at all [3]. But a ray of sunshine in the gray mist is an article published by the *Frankfurter Allgemeine Zeitung (FAZ)* on the same topic. It sets an example and shows how the lay press can present difficult scientific or medical subjects.

The headline of the *FAZ* article is a little sensational, but the article itself is clean, well researched, and its language appropriate and understandable [4]. Although it's a rehash of the story of the nurse mentioned six weeks earlier in *Die Welt* and the Chuck Norris story told in my last column [5], it has a solid foundation and even gives fitting references. It also cites the remarks and recommendations of well-known experts in the field. It is balanced and fair, and readers can draw their own conclusions.

Good science reporting depends on an informed and conscious grasp of scientific methods and outcomes. In its absence, questionable judgments can create or perpetuate obscure scientific perspectives. Lack of knowledge and critical attention to even marginal aspects of research easily slant a story.

**Good science reporting depends on an informed and conscious grasp of scientific methods and outcomes.**

A good example is another article in *Die Welt*. It revived a topic I had focused on in a column some years ago. Its theme attracts readers like a cesspool attracts flies, because it's slightly voyeuristic: Publications from the University of Kiel in Germany claim that a simple functional MRI (fMRI) study can identify pedophiles with high accuracy. The authors stated: "The automatic classification of these [fMRI] patterns is a promising objective tool to clinically diagnose pedophilia."

The authors' claims are false and have to be actively countered as forcefully as possible. Years ago scientists demanded that the papers should be retracted [6]. However, now you can read a friendly and encouraging review in *Die Welt* [7].

If this newspaper article were one of the thousands, or tens of thousands, of meaningless scientific papers published in research journals, it would be less precarious. But the manipulation of public opinion by the lay press in matters scientific or on the physician-patient relationship is treacherous – as is ruminating wrong results the journalist has not understood. The question that occurs to me after reading such articles

is whether in some there is an underlying deeper motive than their simple, superficial contents hint.

This makes me think about an old and well-known tip for readers: not everything that is printed is true, but it might be food for thought.

And, by the way, this is not only a problem for German newspapers. Others happily mix fact and fiction in science and elsewhere.

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Rinckside, ISSN 2364-3889

**Citation:** Rinck PA. German newspapers and the gadolinium controversy. Rinckside 2018; 29,3. 7-8.

# The dilusion and demise of human expertise

Peter A. Rinck

Medical research and clinical practice are largely based on anecdotes, opinions of "authorities", "experts", "opinion makers" – and biased investigations. In spite of that, diagnostic imaging has experienced the introduction of many "revolutionary" technologies that have dramatically changed imaging practice over the past 40 years.

Yet, the diffusion of these novel technologies and their utilization has been guided by many methodologically inadequate and deficient reports that tended to exaggerate their performance, creating new "clinical" needs without proving that these needs really exist. Developers and initial evaluators systematically exaggerate the performance of novel technologies and – unconsciously – are carried away to interpreting results in ways that confirm their preconceived views.

A great number of diagnostic imaging methods and technologies silently disappeared again: Here today, gone tomorrow.

**Not many people in the exact sciences and medicine at universities encourage or practice critical thinking skills.**

A main cause of the trouble is the scientific innocence of many people involved in medical imaging (and medicine at large) as they read literature and listen to meeting presentations – as well as the deficiency of research scientists, among them medical physicists and engineers, lacking sufficient knowledge of bread-and-butter medicine.

More so, not many people in the exact sciences and medicine at universities encourage or practice critical thinking skills, because it produces neither research grants and third-party support nor career benefits. It's easier to follow the pack, and to have and keep your job and academic position.

Thus it is easily understandable that mere users of imaging technologies – radiologists, radiographers, cardiologists et al. – hardly ever go to the trouble of trying to deeply understand the complicated physical, chemical, physiological, and technical aspects of the machines and methodologies they are using.

Some 30 years ago, a well-known English radiologist, Dr. Ivan Moseley, wrote in a book review:

> "How much does the practicing neuroscientist need to know of the technical aspects of magnetic resonance imaging and spectroscopy? One can argue either way: the basic theory is relatively simple, and the phenomena it describes determine the appearances of the images, so it behooves the clinician to be familiar with them; or, beyond the simplest level, the people would be well advised to leave technical details to their specialist colleagues.
>
> "I incline to the latter view, not through arrogance, but because I regard these complex details as entirely analogous to the electronics of spectral analysis of the EEG, the methodology of S100 staining of the identification of CSF proteins: merely technical …" [1]

Neuroscience is the scientific study of the nervous system; a neuroradiologist isn't a neuroscientist, and here Moseley erred. However, as far as his statement is concerned, he was not alone. A large number of radiologists shy away from having to learn the detailed basics of new techniques, in particular such complex and challenging techniques as MRI. Still, many of them want to be scientists, performing scientific research. The system demands it, and in most cases only the quantity of publications counts. However, it doesn't create good radiologists – or any kind of physicians or scientists.

Moseley's "practicing neuroscientists" have mushroomed over the years, as the fiasco of functional MRI (fMRI) shows. Thousands of fMRI researchers fell prey to wishful thinking and published tens of thousands of papers whose validity is, at best, questionable. They performed applied research, but not scientific research; and they failed. It was research in

the hands of amateurs playing with MRI and fMRI, lacking the background in physics, chemistry, biology and physiology – and the scientific rigor necessary to work in a new field. They saw pictures with colorful enhancement of the brain and overnight became cognitive social neuroscientists. I have described the background in the latest edition of our magnetic resonance textbook. [2]

Hand-in-glove with these developments there is an increasing commercialization and a general change of mentality. Self-realization and self-affirmation today lies in the writing of congress abstracts and pseudo-scientific articles, websites and books. Although often vehemently denied, quantity is considered a merit, while quality comes in second and is often not even checked.

A typical example is the explosion of contributions to conferences; every year the number of submissions increases, more oral presentations, more posters. New categories are invented to attract more submissions – for example "My Thesis in 3 Minutes – MyT3" (this is no joke). No attendee of the mega-conferences can take in this excessive offer. It's no presentation of genuine or serious research, science or medical progress – it's show business.

Jeffrey R. Immelt, the then chairman of the board and CEO of General Electric, made a bright and lucid remark when delivering the New Horizons Lecture at the 2015 RSNA Annual Meeting:

> "We need to concentrate our efforts to deliver the type of innovation that will truly improve the health of millions of people around the world ... Innovation must deliver more than a new device; it must deliver real outcomes for our patients. In a time where high-tech is in high demand, it will be seemingly simple ideas such as a low-cost infant warmer that will become the true innovations of our time." [3]

Does this, basically, mean that the entire spectrum of gimmicks and apps companies exhibit and try to sell will be dropped and only proven useful products will be sold? I doubt it.

Copy and paste not only of text but also of other researchers' ideas has become easy; more people have quick access to all kind of information whose background, nature and reliability they do not understand and cannot measure. The academic mindset has turned into fast McDonalds-style science, an illusion that cherry-picked data is already a scientific result and data that challenges own data can be dismissed without further ado. Hard evidence, clear and proven results are ousted by assertions lacking scientific foundations. The ivory tower of yore has been replaced by blathering smartphone science and research bubbles, and inconsistent narratives are the "scientific" talk of the town.

The awe of, and respect for, outstanding scientists has disappeared and been supplanted by unreason and undigested misinformation.

I only describe what I see; I cannot offer a solution – which, in any case, would be rather unpopular. It has to be a political one to be made by politicians, outside medicine and the sciences. It would include changes in the structures and hacking orders of society, recognition of being excellent in the art of healing and caring, i.e. in the humane parts of medicine, and less kowtowing to titles, pompous notion, and pseudo-excellence.

However, as Santiago Ramón y Cajal, the Spanish neuroscientist who received the Nobel Prize in Physiology or Medicine in 1906, pointed out:

> "This lack of appreciation [of sincere medical research] is definitely shared by the average citizen, often including lawyers, writers, industrialists, and unfortunately even distinguished statesmen, whose initiatives can have serious consequences for the cultural development of their nation." [4]

We live it today.

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Rinckside, ISSN 2364-3889

**Citation:** Rinck PA. The dilusion and demise of human expertise. Rinckside 2018; 29,4. 9-10.

# Some reflections on artificial intelligence in medicine

Peter A. Rinck

The point of artificial intelligence is that it "learns" on its own and becomes an – or even the one and only – expert. However, artificial intelligence is not as simple an approach as it's sold today, and artificial intelligence or expert systems are not recent ideas – they come and go since the 1940s, or even since the 18th century with Maelzel's chess-playing automaton, The Turk.

The reliance on advanced scientific theories and modes of reasoning and the utilization of scientific methodology, specifically observation, can easily lead to tunnel vision or wrong conclusions as it's known from the 19th century "ratiocination".

In 1843, the English philosopher John Stuart Mill differentiated in his book "A System of Logic, Ratiocinative and Inductive" induction from ratiocination, and developed principles of inductive reasoning:

> "Reasoning, in the extended sense in which I use the term, and in which it is synonymous with Inference, is popularly said to be of two kinds: reasoning from particulars to generals, and reasoning from generals to particulars; the former being called Induction, the latter Ratiocination or Syllogism … The meaning intended by these expressions is, that Induction is inferring a proposition from propositions less general than itself, and Ratiocination is inferring a proposition from propositions equally or more general [1]."

Two years earlier, Edgar Allan Poe described the same approach in his short story "The Murder in the Rue Morgue":

> "But it is in matters beyond the limits of mere rule that the skill of the analyst is evinced. He makes, in silence, a host of observations and inferences. So, perhaps, do his companions; and the difference in the extent of the information obtained, lies not so much in the validity of the inference as in the quality of the observation. The necessary knowledge is that of what to observe [2]."

## A hundred years later

A little more than a hundred years later, in 1958, the New York Times reported in an article that ...

> "The Navy revealed the embryo of an electronic computer today that it expects will be able to walk, talk, see, write, reproduce itself and be conscious of its existence … The Navy said the Perceptron would be the first non-living mechanism 'capable of receiving, recognizing and identifying its surrounding without any human training or control.' The 'brain' is designed to remember images and information it has perceived itself … It is expected to be finished in about a year [3]."

It didn't work due to "technical limitations".

The most famous first medical application of AI was MYCIN, a program developed in the 1970s at Stanford University in California [4].

MYCIN, as Bruce G. Buchanan and Edward H. Shortliffe described it in a recapitulation of the project, was a software that embodied some intelligence and provided data on the extent to which intelligent behavior could be programmed.

The intention was to identify bacteria causing severe infections, such as bacteremia and meningitis, and to recommend antibiotics at the right dosage for a patient. As with other AI programs, its development was slow and not always in a forward direction.

It worked, but it also didn't, and was never used in practice – not only because computing power was insufficient, but rather for an inherent problem of AI: the knowledge of a human expert cannot be translated into digitizable rule bases.

Additionally, AI is not immune against human prejudice that always exists – wittingly or unwittingly. Such preconceptions cannot be filtered out because of AI's lack of a critical mind. Buchanan described this problem in a conclusion:

> "There are many 'soft' or ill-structured domains, including medical diagnosis, in which formal algorithmic methods do not exist. In diagnostic tasks there are several sources of uncertainty besides the heuristic rules themselves. There are so-called clinical algorithms in medicine, but they do not carry the guarantees of correctness that characterize mathematical or computational algorithms. They are decision flow charts in which heuristics have been built into a branching logic [5]."

### The flaws

AI is mindless, lacks consciousness and curiosity. These are fundamental flaws, distinguishing it from real intelligence. Although meant to be a "science" by its fathers, AI is not a real science; it's closer to computer gambling and tinkering than to creating a fundamentally reliable support system for highly specific tasks.

**Artificial intelligence is mindless. This is a fundamental flaw.**

Neural AI networks are good at – crudely – classifying pictures not only in radiology, meanwhile they encompass the entire spectrum of medical imaging, including for example nuclear medicine, dermatology, and microscopy. The are known for years as CAD, computer-assisted diagnosis.

A typical example is a recent paper by a dermatology group at Heidelberg University. They used deep learning neural networks for the detection of melanomas. The British newspaper *The Guardian* summarized the press release from Heidelberg with the headline: "Computer learns to detect skin cancer more accurately than doctors". The authors of the paper concluded: "Most dermatologists were outperformed by the neural networks. Irrespective of any physicians' experience, they may benefit from assistance by a neural networks' image classification [6]."

In an editorial accompanying the dermatology article in *Annals of Oncology*, the commentators were more careful and raised some additional concrete questions.

> "This is the catch; for challenging lesions where machine-assisted diagnosis would be most useful, the reliability is lowest." They also point out: "Whilst dermatology is a visual specialty, it is also a tactile one. Subtle melanomas may become more apparent with touch as they feel firm or look shiny when stretched [7]."

### Legal responsibility

Another main problem of AI is that the overwhelming majority of its users do not understand and cannot follow its black-box judgments and its reasoning to reach certain choices. Interestingly, there also are a number of reports that developers of AI software did not understand why their algorithms reach certain results and decisions; the algorithms are impenetrable.

Thus, the well-meant "right to an explanation" of decisions made by an AI expert system concerning a person, passed as a European law in the *General Data Protection Regulation (GDPR)*, can hardly be fulfilled because if even some creators are unable to find inherent flaws in their source code they won't be able to explain it to their "victims". I wonder what the legal consequences will be.

It is a principle of information technology that convenience and security are generally mutually exclusive. Once again the question arises whether the limits of what is ethically permissible are being shifted because something is technically possible. However, financial and career interest often override established values of the medical profession. More so, there are other interests in forcing the introduction of AI by groups and institutions owing no allegiance and acknowledging no responsibility to patients, doctors or the people in general.

At this point we are faced with another question – who is really responsible and accountable for the quality of the results? The radiologist, the hospital's administrator, the software engineer who wrote the source code, the company that sold the software? The companies will reject any responsibility, stating that the AI software was delivered free of defects. Even if the customer will get access to the source code, nobody will ever be able to prove that the algorithm has a flaw. You bought a pig in a poke – and are stuck with it.

### Understanding AI

There are other problems. In a recent overview of AI in AME the author stated:

> "The accuracy of these algorithms is dependent on two important factors: the type of algorithms used and also the acquisition parameters applied by the modality. If the algorithm is to be accurate, it is really important the acquisition parameters are standardized prior to application of the algorithm [8]."

This is a major dilemma of AI and deep learning. In many instances, the calculated parameter data are incorrect, as we have seen in "MR fingerprinting" and related methodologies. These values cannot be reliably reproduced, thus they shouldn't be used in a neural network [9]. Deep learning can lead to the description of complex relationships that might only exist because they are based on artifacts or wrong presumptions.

Simple tasks are easily solved by AI, multi-layered tasks are far more complicated to be worked out. During the last ten years, neural networks have shown promises. Still, AI doesn't mean an understanding, thinking, and comprehending computer, but programmed if-then ordered decisions. At the present stage, artificial intelligence is more real incompetence that easily can run wild and lose control than helpful support in diagnosis.

■ AI is also claimed to be objective. But there is no objectivity or neutrality in AI, its decisions are not necessarily knowledge based, but biased. More so, quantifying algorithms freeze a state of the past because they use old data.

Artificial imaging programs are useless if applied randomly without a well-defined and sharply delineated aim. Many approaches to explain results of AI are based on hypotheses which are still to be proved, and much research in this field is empirical and heuristic.

■ Still, AI will come on the market; it's business value is enormous. By the way: If AI should work, even limping and stuttering, other disciplines will take over radiology in those fields which they find attractive – because with fast AI results it's easy and makes money. Anyone can use it, from technologists to physicians in clinical disciplines. Radiologists are not needed for this.

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Rinckside, ISSN 2364-3889

**Citation:** Rinck PA. Some reflections on artificial intelligence in medicine. Or: Why radiology must take care when it comes to AI. Rinckside 2018; 29,5. 11-13.

# Will artificial intelligence increase costs of medical imaging?

Peter A. Rinck

At present, many attendees of conferences and courses see medicine and radiology through the lens of fanatic devotion to artificial intelligence. Its promoters promise earlier and more reliable diagnoses, fewer examinations and procedures to establish these diagnoses, less morbidity, perhaps even mortality, altogether a better outcome for the patients, and lower costs for the health care system.

Since it's the talk of the town, of scientific journals, newspapers, the internet, conference sessions, it must be good, or so the theory goes. The neighbor has it, let's get it too. And one can even play with it: men against machine, sometimes even on stage in front of a congress audience.

Nobody mentions that AI is seductive but an unsettled and immature technology that requires permanent updates.1 It will be a cash cow for developers and the industry, and add to the exploding costs of medical imaging: Nothing is stable, nothing is really reliable; there is permanent change that foils the stability and validity of radiological diagnostics.

AI software will never be a final product. The programs always need to be upgraded and updated. Much in radiology that is subsumed in artificial intelligence today had an earlier life going by another name.

Some years ago I cited Dr. Donald A. Berry from the M.D. Anderson Cancer Center in Houston, who summarized his experience with artificial intelligence in mammography. At that time AI was still called “CAD” in radiology, “computer-assisted diagnosis” (or “detection”) [1].

> "An argument for the use of CAD with film or digital mammograms is that it will get better over time. Fine. Researchers and device companies should work to make the software ever better. But this should happen in an experimental setting and not while exposing millions of women to a technology that may be more harmful than it is beneficial [2]."

## Pressures on radiologists

AI software is like coffee in capsules – expensive, but you never know what's really inside. However, there are social, economical, and political pressures to conform and to purchase certain digital devices. Radiologists are also considered consumers and told by others what is good for them.

Salespeople are already salivating over AI sales contracts. Many business models rely on artificial intelligence to facilitate tasks so much that we no longer want or can do without it.

**Salespeople are already salivating over AI sales contracts.**

Health care, the commercial part of medicine, avoids any accountability; new techniques and methods are introduced at random, praised to the skies enthusiastically, partly militantly by technocrats and paid experts.

The shelf life of many of the new fashions and products is approximately two years. That's at least the interval we were told by two representatives of COCIR, the European Trade Association representing the medical imaging industries, invited to a meeting on the future of radiology at WHO in Geneva some time ago.

Therefore, they said, outcome studies are irrelevant – all digital procedures or equipment you buy today will be hopelessly outdated in five years, after limited use. Still, they claim that these very same products will increase productivity, one of the central themes favored by commercial salespeople and hospital managers.

At the time of the introduction of x-ray CT, 45 years ago, the overall costs of medical imaging were between 1% and 3% of overall health care expenses; to-

day just the yearly worldwide sales of diagnostic and therapeutic imaging equipment amounts to 100 billion euro; the sales increase by 5% annually [3].

Artificial intelligence is a mix of the virtual digital world and the real world. Intellectually, it is a step backwards. It's a shift of knowledge and assessment of collected and processed data from the human brain to a black box digital system – and the blind reliance on the correctness of this system. But it doesn't provide a rational, independent opinion. It also creates an addictive dependence because people will tend to totally rely on it. Already voices are raised claiming that the use of AI will lead to de-skilling of the workforce. Immature and costly technologies shouldn't be used in medicine.

A recent Italian paper stresses that the processes of medical device decision-making are largely unpredictable and points out that there are major differences between Europa and the United States:

> "Generally, while in the U.S. AI the technology sector prospered in a permissionless innovation policy environment, in the EU decision-makers adopted a different policy for this revolutionary technological branch. Certainly, swifter approval of AI medical devices helps generate revenue for manufacturers, and physicians may benefit from having more tools at their disposal. But the final goal of bringing new devices to market should be to improve prevention, diagnosis, treatment, prognosis of diseases with a potential positive impact on patient outcome. Therefore, systems for approving new medical devices must provide pathways to market for important innovations while also ensuring that patients are adequately protected. To achieve these goals, the EU and the U.S. use different approaches [4]."

## The Canadian perspective

Arguably the best and most balanced review paper on AI in radiology was the white paper published by the Canadian Association of Radiologists in May 2018, considering the pros and cons of the introduction of AI in diagnostic imaging. It is worthwhile reading [5]. The authors are realistic and down-to-earth in terms of applications and development:

Practicing radiologists need to understand both the value, and the pitfalls, weaknesses, and potential errors that may occur when an AI product performs image analysis. While these algorithms are powerful, they are often brittle, and may give inappropriate answers when presented with images outside of their knowledge set ... an algorithm-evaluating brain CTs may work perfectly for long stretches, but then a new software upgrade to the CT occurs, or a new CT machine comes on-line, and all of a sudden, the algorithm produces faulty results.

AI is a mix of the virtual digital world and the real world. It's a shift of knowledge and assessment of collected and processed data from the human brain to a black box digital system – and the blind reliance on the correctness of this system. But it doesn't provide a rational, independent opinion. It also creates an addictive dependence because people will tend to totally rely on it. Already voices are raised claiming that the use of AI will lead to deskilling of the workforce.

As the Canadians remark:

> "Currently, there is no evidence in the literature that AI can replace radiologists in day-to-day clinical practice. However, there is evidence that AI can improve the performance of clinicians and that both clinicians and AI working together are better than either alone."

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Rinckside, ISSN 2364-3889

**Citation:** Rinck PA. Will artificial intelligence increase costs of medical imaging? Rinckside 2018; 29,6. 15-16.