Olea Imagein

Big Bang Data

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Philippe Grenier, MD

Professor of Radiology
Pitié-Salpêtrière Hospital
Sorbonne University, Paris, France

Machine augmented diagnostics has become a reality. In the next years, radiology practice should change dramatically with the development of machine intelligence. Radiologists will not be replaced by computers. As radiologists, we should rather adapt our practice to this new model of machine augmented diagnostics. A medical futurist commentator said: “Radiologists should embrace Artificial Intelligence as those who use Artificial Intelligence will replace those who don’t”.

Artificial Intelligence (AI), Machine Learning (ML) and Deep Learning (DL) are terms now seen frequently, all of them referring to computer algorithms that change as they are exposed to more data. Artificial Intelligence includes computer performing tasks that require human intelligence, such as visual perception (reading images and decision making). Machine Learning is a type of AI in which algorithms are trained to perform tasks by learning patterns from data rather than by explicit programming. Deep Learning is a type of Machine Learning in which no feature engineering is used and in which the algorithms learn a composition of features that reflect a hierarchy of structures in the data. In other words, DL permits direct learning imaging data without object segmentation or feature extraction.

The number of publications on ML/DL developed for medical imaging applications has dramatically increased in the last 2 years. One of the first applications of ML/DL is screening detection. It will increase the accuracy of computer-aided diagnosis (CAD), potentially decreasing false positive results significantly and increasing CAD growth. Another objective of ML/DL in diagnostics is to classify diseases enabling quantitative characterization of local and diffuse disease. The ML/DL methods classify individual patients against huge reference database. They can also accurately track evolution of disease at individual level. By reducing error rates, ML/DL tools contribute to decreasing inter-observer variability, improving the global quality. Instead of replacing radiologists, the ML/DL techniques will likely assist radiologists in a variety of diagnostic tasks. They will undoubtedly work hand-in-hand with us.

Subsequent generation of AI algorithms will permit to analyze not only imaging findings but also electronic patient records and genomic data, to propose classifications and recommendations to radiologists to incorporate into their interpretation. Thus, the radiologists report will include structured recommendations based on findings of quantitative imaging phenotype that contains radiomics and other -omics correlations providing the future “precise radiology report”.

At the end of the day, AI algorithms used in diagnostic imaging will result in improved efficacy, accuracy and safety in our clinical practice. In the meantime, close collaboration between radiologists and computer scientists is the way-forward.

Enjoy your reading!

Artificial Intelligence

An Emotionless and Multiple Intelligence

The expression of Artificial Intelligence (AI) was officially born in 1956 at the Dartmouth College Conference, where John McCarthy defined the concept as "the science and engineering of making intelligent machines" [1]. Applications and interest in the specific field of medicine started in the early 70's [2], with a new rise observed in the past few years due to computer power increase and data availability.

Artificial Intelligence aims to mimic a part of human intelligence, by reproducing cognitive functions such as learning, understanding, perceiving or deciding. AI is not guided by a unified theory, it is instead composed of many different subfields (Figure 1), among them language translation, visual perception or modeling [3]. Therefore, the tasks performed by AI cover an extremely large scope, from pattern recognition and scene analysis to interactive problem formulation, through behavior adaptation based on previous experience or speech understanding.

Numerous tools derived from data science, statistics, mathematical optimization or neural networks techniques (see AI definitions p.30) are closely embedded to create different forms of Artificial Intelligence.

Applications in medicine

Supported by the Big Data input, AI methods have the potential to be applied in almost all fields of medicine. Based on neural networks, fuzzy logic, expert systems, game theory or genetic algorithms, the use of AI will expand in many different categories: decision-support tool for diagnosis, prediction of survival rate, tumors segmentation on MRI, analysis of mammographic micro-calcification, reduction of false-negative rate, image classification between healthy and abnormal, etc. [3]. AI will also boost discoveries in genetics and molecular medicine [1], and finally turn the patient's treatment from generic to personalized [4].

Radiologists and AI: friend or foe?

Artificial Intelligence brings both hopes and fears in radiology. On one side, it promises fascinating results and bright future through the improvement of the radiologist's work, making diagnosis easier and earlier for the patient. But on the other side, this field may be considered with uncertainty, with several questions: Will AI substitute to the radiologist by surpassing human analysis capabilities to the point of making the job obsolete? How to assess the reliability of the clinical outcome? In any case, AI will continue to grow and serve the development of health systems, finding novel answers to clinical problems, identifying the best treatments for the patients, personalizing the medical care. It is therefore important to get prepared, today, for the transformation taking place, tomorrow. Of course, to make the transition a success, one should understand how to create ethical standards: the next generation of computer-aided detection (CAD) software will have to observe the "privacy-by-design" practices enforced by regulatory bodies, a new engineering challenge. In the meantime, the repetitive and time consuming tasks will be automated, allowing significant time-saving for the radiologist, a time of great value which can be dedicated to the human and interventional part of the activity for tremendous healthcare benefits.

Sophie Campana Tremblay

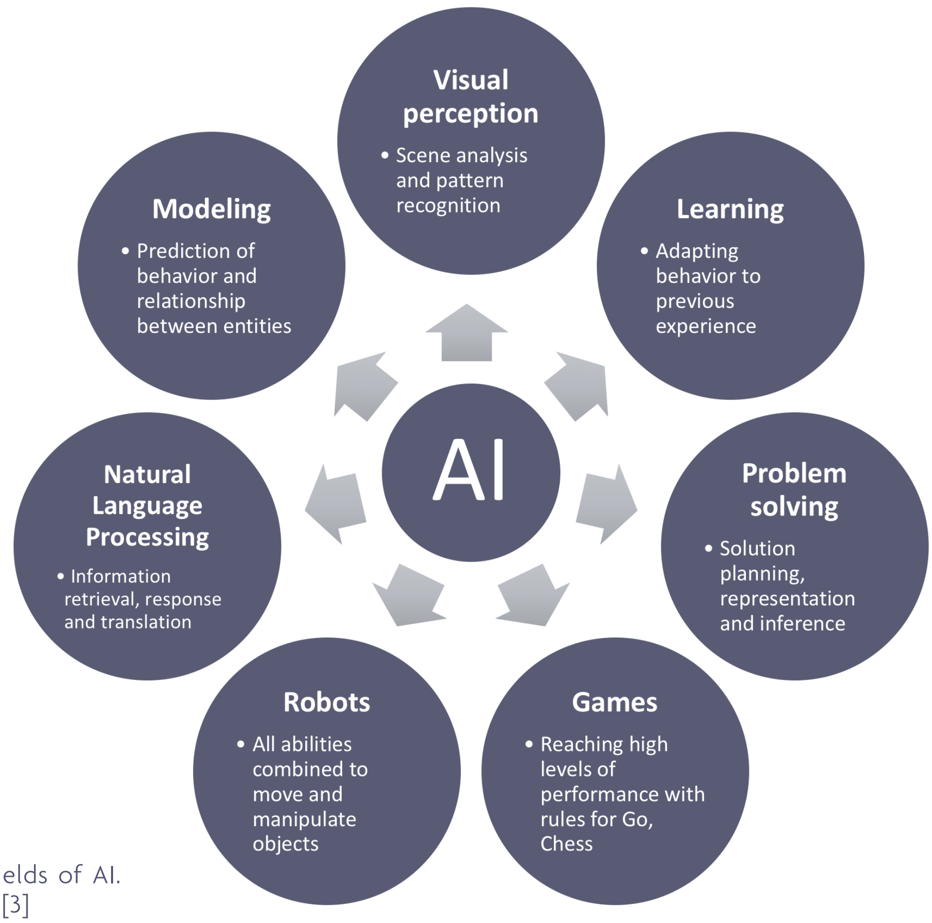

Figure 1: Subfields of AI. Adapted from [3]

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Artificial Intelligence

" (...) will influence, change and help in numerous processes in medicine "

Michael Forsting, MD
Professor and director of Radiology and Neuroradiology Departments; Chief Medical Officer of the IT Department; Dean of Research at the Faculty of Medicine, at Essen University Hospital, Germany.

Michael Forsting studied medicine at the RWTH Aachen University, Germany and at the University of Bern, Switzerland from 1980 to 1986. In 1997, he was appointed Professor of Neuroradiology at the University Hospital in Essen, Germany. Since 2003, he holds the Chair of Radiology and Neuroradiology. In February 2016, he was also appointed Medical Director of IT Department in the same hospital.

Michael Forsting is also co-organizer of the Emerging Technologies in Medicine (ETIM) Congress taking place at Essen University Hospital.

Olea Imagein: Artificial Intelligence (AI) or Deep Learning is new in medicine, either used for mining imaging data or for giving a hint in clinical analytics. Do you believe AI will open doors in radiology? When could this happen?

Michael Forsting: Artificial Intelligence is a kind of unsupervised learning algorithm, and we know from gaming like Chess, Go or even Poker, that these algorithms are really excellent in kind of pattern recognition. Therefore, it is definitely coming to radiology – it is actually already there, and not only to radiology. AI will go into pathology, into internal medicine, it will change and improve medicine, whatever we might think of that.

If we look back in the history of medicine, let's say 150 years ago, the physicians had to taste the urine of the patient to check whether or not there was diabetes. I assume these doctors were wrong in a certain number of patients! Over the past 30 years until now, we had a kind of industrialization of laboratory medicine; some people didn't like that but, at the end, laboratory medicine dramatically improved, becoming more reliable and cheaper. Nobody is really thinking that anything was wrong with this industrialization. The same will probably occur with AI in radiology and in pathology, not at 100%, but for all the boring all-day tasks.

O.I: Could you please briefly describe the different AI techniques currently foreseen to be used in clinical practice?

M.F: Those algorithms, the same that are applied for Go or for Chess, are mainly given by Google. There is nothing secret behind them anymore. The problem is not the algorithms – IT people are still improving them to make them faster – but the training. The algorithms are already there, many of them are freeware and we can just copy and paste them to start the training. But my message is the following: AI issue in medicine is not a question of different algorithms anymore, but exclusively a problem of valid data. We definitely need valid data to train the systems, and the difficulty is to get them with the question: who has these data? It is truly different from about 10 years ago, where at that time the algorithms were the problem; not anymore.

O.I: Among the numerous potential applications of AI – cancer screening, time-saving, computational modeling, early prediction of diseases, etc. – which would be most useful for clinical decision support and diagnostic improvement?

M.F: There are a couple of early applications for AI, one of them is screening. We do have mammography screening at Essen University Hospital; but one main problem is that it is difficult to get radiologists who really want to do that, because that's not really interesting. If we look worldwide, we have a shortage of radiologists, so we don't have really enough of them to do the work. If we consider screening programs — breast is one of them — imagine that we will probably have screening for lung cancers, to look for small nodules; it is a major application for Artificial Intelligence. As for the killer-number-two for men that is prostate cancer, I assume that AI will really help. In early stroke recognition on CT, Artificial Intelligence will clearly support radiologists in the detection of subtle minimal changes. Also, in Japan, the prevalence for intracranial aneurisms is 4%, and we can set screening programs to detect these aneurisms with AI.

> "... unlike the human brain, Artificial Intelligence systems will never forget anything"

That is the screening side, or the side of major diseases. But another application will concern rare diseases, because these diseases are not really rare, they are just not often overseen. If we train systems on rare diseases – and we did that for lung – we can guarantee that the system will recognize them; because, unlike the human brain, Artificial Intelligence systems will never forget anything. So, if we focus a system on rare diseases of the breast, the lung, the brain or whatever, we will really get support from AI systems.

These are the two main blocks of applications.

There will be two major problems with Artificial Intelligence. The first one is to define the normal state. If we look, for example, at the spine of people at different ages, we can see changes with increasing age. Unfortunately, these degenerative changes in the spine do not necessarily correlate with back pain, for instance. We will therefore have people with major diseases or degeneration of the spine, without any back pain in their history. The Artificial Intelligence systems will tell us: you exceed the 99% range of degeneration of the spine, even if you never had back pain, you will develop it. Therefore the definition of normal, and the correlation between normal or non-normal true specific with the clinical problems of the patient, is an important issue. Artificial Intelligence systems will maybe achieve this in 100 years, but that will be pretty difficult, at least at the beginning for the first two decades.

The second problem is that, in general, an image does not necessarily match one to one to a certain disease. We can have, for example, an image of the brain that looks pretty much the same in two or three or four different diseases. So, Artificial Intelligence will not replace radiologists to 100%, because we will still need a person that tries to match the clinical problem to the image.

O.I: What are the risks associated to AI in medicine?

M.F: I think that there is no risk; I always compare Artificial Intelligence to a hypermodern textbook, and there is no risk in using a textbook. If you get support from a system that is not a textbook but a digital kind of brain, then there is no risk. The risk is if you, as a radiologist, stop using your own brain: that might be a problem. You may have trained, better or worse systems, but that is the same with radiologists: sometimes you are facing a good radiologist and sometimes not.

O.I: Some people fear a substitution of the radiologists, what is your opinion?

M.F: As I pointed before, we encounter the general problem of not having enough physicians in the future for a more and more elderly population; that is already true in Japan, it will be true in Germany and it becomes true for even China and the US. So, we will have a shortage of physicians in general and of radiologists in particular. The purpose is to work with more patients and less physicians. As a specialist in neuroradiology, I did see so many epidural and subdural and dural and intracervical hematomas that, to be honest, I don't want to see them anymore. These algorithms will be able to recognize these diseases. At the end, maybe in 30 years, we will therefore probably need less radiologists than today; but again, that's the same thing as compared to laboratory medicine. Forty years ago, we had much more physicians specialized in laboratory medicine than today, but nobody is really missing them now. This is not a revolution, this is an evolution, and that always occurred in medicine. If the number of radiologists is reduced, that's fine and nobody should be afraid of that.

On the other side, we will still need radiologists for research, for example. Again, that's a nice comparison with laboratory medicine. All the routine things are done in an industrialized way nowadays in laboratory medicine. However, we do have a lot of research in microbiology or virology for example; there are many tests that have to be developed to become more sensitive, more specific. The same will come into radiology, therefore we will probably have more time for research on new imaging methods, like optical imaging, new metabolic approaches to different kind of diseases, more field strength in MRI or more speed in CT. We need more research in radiology and we will probably have a little more time to do it, because Artificial Intelligence will help us to get rid of really boring things.

O.I: Which barriers remain before a widespread adoption?

M.F: That is a difficult question. I think that the main problem could be barriers from regulations (see p.27). Everybody has the idea that Artificial Intelligence, from the beginning, is a medical product or a medical device. Therefore, we have regulations that will probably not help us, and hopefully we can avoid that. Again, it's like a textbook: there is no barrier for a textbook unless it is not well written or not usable. We should really consider AI during the next 10 years as a digital help, exactly similar to the help provided by a printed textbook, nothing else. I cannot imagine that there should be a barrier. If we see AI as a medical product or a medical device, then we will run into problems; we should really avoid that for the start up now, and we will see what the future brings.

O.I: According to you, which place will AI hold in the future?
Which new applications would you expect?

M.F: As I mentioned before, AI will not be something exclusively for radiology. It will come into pathology because pathology is more or less the same as radiology: looking at images and trying to identify certain patterns. But let's just focus on medicine, looking at the patient history, which should be the first diagnosis step. If a patient goes to a physician with pain in his left arm, and if the patient decides that he may have a heart problem, then he goes to the cardiologist; the cardiologist will clearly first try to rule out a coronary problem. If the patient goes first to a neurosurgeon, the surgeon will rule out a cervical disc problem. If the patient goes to an orthopedic surgeon, he will probably focus on the shoulders. If the patient goes to a vessel specialist, he will probably look at the vessels of the arm. What I mean is that usually, the physician thinks that the patient coming to him belongs in his discipline; it is an emotional problem. Artificial Intelligence does not have any emotions, and filling an AI questionnaire for the patient with a well-qualified nurse will clearly figure out what his or her main problem is. It could be composed of 10 or 15 questions, to guide the patient to the right physician.

Therefore, at the end, we will have AI in all parts of medicine, it will not stop in radiology or pathology. Everybody thinks that AI has something to do with digital, but radiology is already digital, so medicine can be digital as well. Artificial Intelligence will influence, change and help in numerous processes in medicine, with the advantage that the physician will have more time for the real problem of the patient.

Big Data

The concept of Big Data designates a mass of information, in the Petabytes range, beyond the human capability of analysis.

It was well defined by Gartner Research group using the 3 V's: Volume (number of data), Variety (type and source) and Velocity (reception throughput). Two other V's could be added for Veracity and Value.

Due to scales never reached so far, Big Data require cost-effective and innovative forms of processing that ultimately enable enhanced insight, decision-making or automation of many tasks [1].

Big Data are non-structured pieces of information coming from different sources, in such a quantity that we may not know how to store or analyze them.

From this extremely large quantity derives a very interesting hypothesis or property: statistically speaking, they can be considered not as a sample, but as a population. In other words, they contain all the information and the knowledge necessary to describe the population, leading to new analysis possibilities.

Data is the new oil

In the current context, data are wanted, because they are the basis on which both Data Mining and Deep Learning rely. Data Mining algorithms extract the relevant information from Big Data to show trends, build models or find correlations. In a similar way, neural networks need these data for training, before being part of Deep Learning applications.

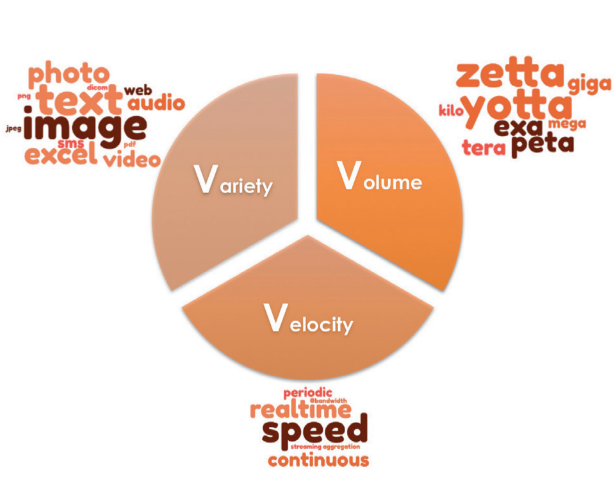

Figure 1: Big Data - Volume, Variety, Velocity

The potential of Big Data applications comes from its ability to merge and analyze data which are today stored into separate silos. Having access to patient history data, reports, images, even genomics, will bring much more opportunities than each one analyzed separately. This capability will change the way radiology is practiced and will allow scheduling of scans, creating patient-specific personalized scanning protocols, supporting the radiologist decision, making emergency reporting, etc. [2]. Clinicians will be able to customize the therapeutic approach by extracting significant insights; they will access relevant information much faster, compare their results to other patients with similar abnormalities, etc.

Big Data and radiology challenges

Although radiology is already digital, patient information is available in silos (PACS, VNAs, at different institutions, etc.). Therefore, a link has to be created for radiology to benefit from the Big Data approach. A more specific challenge, related to supervised training of neural networks, is the requirement of collecting thousands of carefully labelled images (contouring, classification, etc.), which is both labor intensive and costly.

Another challenge relates to the use of personal information. In healthcare, HIPAA (Health Insurance Portability and Accountability Act) compliance is mandatory. However, patient data protection laws are changing. For example, the European General Data Protection Regulation (GDPR) becoming effective May 2018, allows the usage of clinical data for sharing and research applications but under strict conditions. For more information on regulation for Big Data and Artificial Intelligence, please see p.27. Specific mechanisms must be implemented to collect those data; many research centers, just like American universities for example, organize themselves in clusters.

However, despite all these not-yet-fully-cleared issues, one thing is for sure: Big Data have great value because they will open the door to fulfilling an old dream: Personalized Medicine.

Brianna Bucciarelli

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A Brief History of Artificial Intelligence

Christophe Avare, PhD

FROM PERCEPTRON TO DEEP LEARNING

The past

Many different concepts lie behind the terms "Artificial Intelligence" (AI). Historically, AI was the hope to replicate the mechanisms of human thinking. All started in 1957, with the perceptron of Frank Rosenblatt at the Cornell Aeronautical Laboratory (Buffalo, NY, USA). Inspired by the cognitive theories of Friedrich Hayek and Donald Hebb, the perceptron was figuring a mono-layer neuron able to optimize its response by itself: supervised Machine Learning was born, or how to provide an expected output by adjusting a set of weights in order to minimize the error.

At that time, the human neuron individual behavior was just starting to be understood; the perceptron hence belongs to these neuro-mimetic or bio-inspired approaches tending to reproduce the biological mechanisms. This research was pursued through the decades, with all the material or software limitations related to the contemporary time. The main goal was to automate reasoning, to make deductions, only with a machine. Attempts were repeated in the 90's, especially via the Prolog language, but not with the expected results. Data were missing, computing power was too low. That was the period called "AI winter", characterized by disappointment, criticism and funding shrinking.

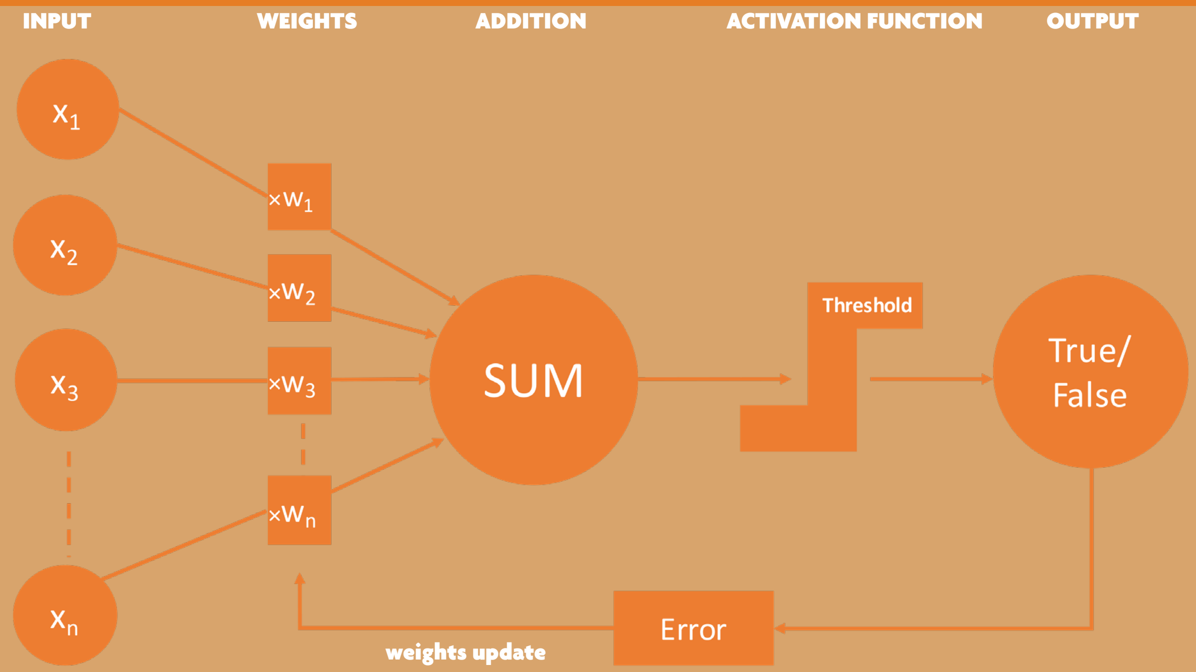

Figure 1: Schematic model of Rosenblatt's Perceptron.
Perceptron is a single layer neural network acting as a linear classifier: it delivers a binary response. All inputs xi are multiplied by their respective weights wi. The resulting weighted sum is passed through a step activation function with a given threshold to produce the output. Iterative steps next adjust the weights in order to minimize the error

Today

Renewal of interest gradually increased again until 2012, with the contribution of three key researchers who collaboratively improved the neural networks techniques to lay the basis of Deep Learning: Yann LeCun, Yoshua Bengio and Geoffrey Hinton. Training was optimized, accuracy raised to match human capabilities, making the method ready to be spread among many different fields outside computer vision, like text comprehension or translation. Therefore, if the theory of AI was established in the middle of the 20th century, 50 more years were needed to access the neural networks training techniques, the huge amount of data and the large computing capacities necessary to reach the numerous levels of abstraction of Deep Learning. With Deep Learning and the scaling possibilities, Machine Learning was moving a step closer to its initial goal: Artificial General Intelligence (AGI).

The future

Nevertheless, 2017 represents the top of the Hype Curve and a lot of practical applications are still to be discovered. But, whatever the impressive current achievements are, a key building block is still missing: human-like understanding and reasoning. AGI is not there yet, all the current AI techniques are some form of supervised learning that often requires millions of examples to achieve objects recognition in images, when a two-year old toddler can learn to recognize them from a couple of examples. The key difference here is how we generalize concepts and connect them in different semantic contexts, while the current practice is based on optimization methods, somewhat black-box like, that try to minimize the learning error on a given and focused task. Though useful for some use cases, this does not scale to tens of thousands of tasks, and we still need to design a system that can reason by itself and discover non pre-existing insights and patterns.

As an example, we were recently able to map the full connectome of a nematode worm containing about 300 neurons and a few thousand synapses. Integrated into a small Arduino-powered robot, it started to behave like the real worm: response to stimuli (avoid obstacles), search for light (food), etc. We know how to do that, but we do not know to scale to the 100 billion of neurons and 1000 trillion synapses found in a human brain. In the future we will have to overcome the scaling issue. "The closer the wall, the more we see of it"!

HOW TO GO FURTHER?

Obviously, software alone is not the answer. The next breakthrough will certainly involve new hardware, be it quantum computers or, more probably, new materials like memristors that can closely mimic neurons at the nano-scale and move towards what is called "neuromorphic computing" [1].

We are currently bound to a very generalist computing architecture, which is highly energy-inefficient: if we wanted to replicate a very small part of the brain today, we would need a full data center and 20 MW of power to run it, when our brain only needs 20 W. This gap illustrates that we have hardly started to understand the direction we must take: new materials, new way of thinking and creating software and, why not, no more coding but some form of "education".

Meanwhile, even the top AI researchers concede that we are in a kind of dead-end with the current techniques but many disruptive approaches are around the corner. For example, an about-to-be-published paper [2] suggests a way to generalize object pose (aka object orientation and position) in image recognition. This is an important feature compared to the current techniques in convolutional networks which are only invariant to translation. Applied to medical images, this opens the door to a much more robust recognition of an organ (crucial if generating a mask) or anatomical landmarks without requiring millions of examples and achieving clinically compatible robustness.

Another transitional evolution will be to consider all these neuron networks or Machine Learning models as focused tools, and introduce an expert system above them by using another approach like Multicriteria Decision Making (a subfield of AI associated to game theory) to get closer to real reasoning. This is a requirement if we want to use genomics or population-based statistics in the diagnostic process, in addition to image-based biomarkers. To do that, we need to capture human expert knowledge – possibly using an automated technique learning from books! Multidisciplinary research will be necessary to link all these aspects and generate true innovations.

We are at the very beginning of a new adventure, a new cycle has just started, the future will be neither AI as it is conceived today, nor some Skynet or "A(I)pocalypse": self-consciousness is decades away! The next important steps will be to find novel materials and methods to better generalize knowledge, new ways to become, in essence, more bio-mimetic.

LEARNING WITH EXAMPLES

Regarding database approaches, all the techniques based on supervised training need examples. In the early days, thousands or even millions of examples were necessary to reach the human scorings. From 2012, all this was significantly improved since the order of magnitude to learn efficiently is now thousands or even hundreds of examples. Nevertheless, gathering such large database remains an issue in the medical field, and quality is even more important than quantity. Remember: "garbage in, garbage out." With the current techniques, the increase in quality automatically goes through the increase of database size and quality, and obtaining the "ground truth" is still a manual – thus costly – operation.

WORKFLOW FOR AI INTEGRATION

In the medical imaging field, Deep Learning is essentially based on the famous neural networks. Their reliability depends on two main requirements: enough memory capacity to handle the calculations, and a proper training database adapted to the very specific images to be analyzed. It is also a fact that the nice applications in computer vision are not immediately transferable to medical images because they are 3D instead of 2D, anisotropic, generally fuzzy and noisy. Using those techniques will then require more than a simple adaptation. Regarding memory for example, 3D images cannot currently be digested at once, they must be fractionated into several parts; this complicates the training process.

There are no special technological problems to run in-house Deep Learning projects today, since everything is commoditized: the programs are widely available and easy to access via libraries. However, different steps must be controlled to integrate AI into a workflow. First, a specific type of expertise is mandatory to answer important questions: how to build a neural network? Which network family is the most interesting for the project? Second, the methodological steps of data processing must be well structured to correctly embed the small model in an application. Finally, upstream data must be available to train the system, in large quantity, and they are often difficult and time-consuming to collect.

Big Data are converted into training database, necessary for the neural networks to learn. Let's take the example of a set of medical images, injected for training a clinical process. After checking, a DICE similarity coefficient of 84% is reproducibly obtained, fine and suitable for diagnosis. But then, a new MR sequence appears in the protocols, which contains structural information different enough to make the DICE percentage collapse. This is not a software bug, nothing is wrong in there, you just need to acquire more data and re-train the whole system. Therefore, associated to AI, a necessary logistic process must be structured, to ensure a continuous update and improvement. This process must be included in the business model of AI companies, otherwise they cannot survive.

These three steps – neural nets expertise, embedding and data collection – are often much better achieved when the work is considered under a multidisciplinary angle.

WHAT ABOUT OLEA?

Today

In a sense, Artificial Intelligence algorithms are already present in Olea Medical® products, since one should not forget that most of the mathematical basis of AI are the same as the optimization techniques implemented, for example, in registration or motion correction. AI and many of its sub-fields use foundational mathematics like linear algebra, Machine Learning or non-linear optimization algorithms.

Tomorrow

It will be very interesting to guess where, in our clinical offer, AI can be introduced in the future – that will also be the tricky part. Three criteria need to be met. First, and contrary to what is often thought, AI is not an end but a mean, it should not necessarily be visible for the user. Think about understanding user habits and automatically configuring the software: once you remove this capability, using another software feels unintuitive, generating some friction or just being painful. Second, a fallback algorithm should always be available to replace AI in case it needs to be improved or further trained; ideally, all algorithms should be interchangeable, at least until the technology has been proven and accepted in the daily practice. The third criteria is about impact: using AI without impact is meaningless; real impacts deal with, for example, dividing post-processing times by 10, or getting significantly higher quality and robustness. In that context, if these three conditions are fulfilled, yes, we can think about including AI in our workflows, with maybe good surprises such as management of new sequences without additional coding…

Black Box syndrome

What is striking, from a mathematical point of view, is that all the algorithms used in Olea Sphere® software could be actually… learned. Deconvolution, for example, could probably be tuned and achieved with neural networks. But then, the problem is: how do we explain the procedure to a regulatory office? Why is this working? What mechanism is hidden behind the results? This black box aspect leads to many restrictions in the use of AI – at least today, where clinical evidence, validation tests and scientific studies are required for a commercially accepted product. But it started changing and we must be ready!

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2. Hinton et al. Matrix capsules with EM routing. ICLR 2018 (Vancouver, BC, Canada)

Christophe Avare, PhD
Research and Innovation Director
Olea Medical®

Roland Wiest, MD
Professor of advanced neuroimaging at the University of Bern, Switzerland; Director of the Support Center for Advanced Neuroimaging (SCAN); Vice Chair at the University Institute of Diagnostic and Interventional Neuroradiology.

Interview

Machine Learning

"A tremendous impact on healthcare systems due to the need of effective solutions to better quantify, "

Olea Imagein: Could you please introduce yourself to our readers?

Roland Wiest: I currently hold the position of a professor of advanced neuroimaging at the University of Bern, Switzerland, heading the Support Center for Advanced Neuroimaging (SCAN), and of the Deputy Chair at the Institute of Diagnostic and Interventional Neuroradiology. I received training in Neurology/Neurophysiology and Radiology/Neuroradiology in Munich and Augsburg, Germany and Bern, Switzerland. My main focus of research is the development, implementation and validation of automated image analysis tools into clinical practice.

Olea Imagein: What do you think about Machine Learning in healthcare?

R.W: Machine Learning has a tremendous impact on healthcare systems due to the need of effective solutions to better quantify, e.g. brain lesions, while using the most advanced medical image analysis technologies. Standardized quantitative reports have the potential to greatly improve and facilitate diagnosis and follow-up of patients with chronic and progressive disorders. In the context of drug development, they enable a standardized assessment of better paraclinical endpoints and response to therapy within clinical trials, ultimately assisting pharmaceutical industry in the identification of new drugs for diseases of the central nervous system. The social and economic burden of chronic diseases is very large – with more than 120 000 people affected in Switzerland solely by chronic neurological disorders – and likely to increase in an aging society like ours.

O.I: Your research team is developing applications using Machine Learning algorithms. Would you like to present us some of your projects?

R.W: Our team is jointly composed of experts in computer engineering, MR physicists, radiologists and clinical experts in neuromedicine. Together with our partners from biomedical engineering – Prof. Reyes, Medical Image Analysis, University of Bern – we introduced a fully automatic technique to segment multi-sequence images of glioblastoma patients. The technique is based on supervised Machine Learning and a novel hierarchical tissue compartmentalization strategy for tissue segmentation and regularization, which encodes and uses domain-knowledge about the different tumor compartments and the imaging process. The Machine Learning system yields a complete segmentation of tumor compartments (necrotic, active and edema regions), healthy tissues, as well as subcortical structures – useful for neurosurgery and radiation therapy. Based on these techniques, we developed a software tool called BraTumIA (Brain Tumor Image Analysis), which performs fully automatic brain tumor tissue segmentation in approximately five minutes.

For multiple sclerosis (MS) patients, our goal has been to implement a clinically applicable pipeline for automatic MS lesion analysis, where brain atrophy and lesion load for an individual patient are estimated and visualized within minutes after image acquisition. The classifier, based on a dense convolutional network architecture, segments an MS dataset (T1-weighted, T2-weighted and FLAIR imaging) in approximately three minutes, with results comparable to those obtained by manual segmentation.

> “... complete segmentation of tumor compartments (...) automatic MS lesion analysis (...) characterization of ischemic stroke brain lesions”

Recently, we have extended the Machine Learning technology for the characterization of ischemic stroke brain lesions, where structural and functional imaging is employed to train a Machine Learning system capable of identifying penumbra and infarct core in acute ischemic stroke patient images, as well as to predict the most probable outcome given a successful or unsuccessful mechanical thrombectomy intervention. Along with a patent of the innovation, we are currently clinically validating the software FASTER (Fully Automated Stroke Tissue Estimation using Random Forest Classifiers). FASTER provides the stroke neurologist and neuroradiologist with a quantification of the ischemic brain lesion as well as an estimation of tissue loss for a successful or unsuccessful mechanical thrombectomy.

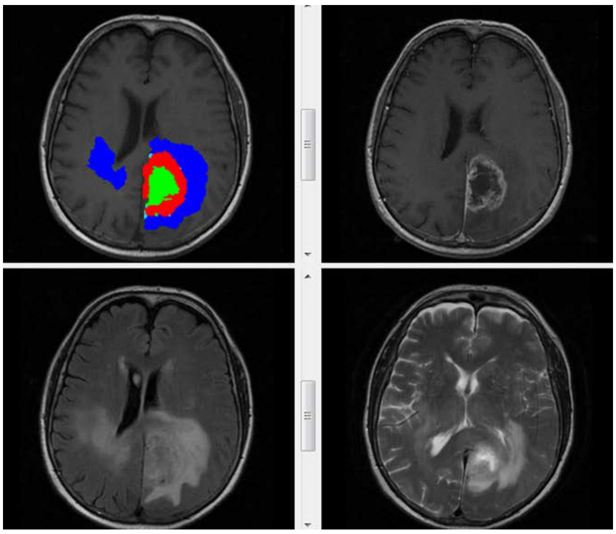


Figure 1: Automatic brain tumor tissue segmentation based on T1, T1 contrast, FLAIR and T2 series (green: necrotic; red: enhancing; blue: edema; light blue: non enhancing)

“… there is a need for standardized image acquisition and reconstruction to improve accuracy and robustness of Machine Learning approaches”

ML

MACHINE LEARNING

O.I: What are the challenges of Machine Learning and what are the risks when dealing with larger amounts and varieties of data?

R.W: Many approaches focus on particular clinical problems, omitting the development of a unified technology for brain lesions, which can handle the heterogeneity, required data compliance level and time-effectiveness of the clinical imaging workflow. Also, the main metrics for algorithmic development may sometimes lack robustness and applicability for a clinical workflow. Semi-automated approaches incorporate a clinical expert into the analysis, but are not suitable for a high-throughput analysis. This is critically important in an economically guided clinical setting where the demand of medical image interpretation and analysis is continuously growing, but manpower is restricted to carry out routine quantification in a manual or semi-manual manner. Time-effective solutions to correct computer-generated brain lesion quantification results are still lacking. Furthermore, there is a need for standardized image acquisition and reconstruction to improve accuracy and robustness of Machine Learning approaches.

> "... integrate radiomics (...) will be the challenge for the next generation of advanced Machine Learning methodologies"

There is also a lack of appropriate IT infrastructure to select, store, distribute and post-process images acquired in multi-institutional settings, and occurring within the clinical routine in order to minimize expert's workload and enable a sustainable and scalable data curation platform that can evolve with the clinical protocols.

Beyond quantitative lesion analysis, there is also a need to integrate radiomics into multi-dimensional modelling of patient characteristics and disease phenotypes. The latter will be the challenge for the next generation of advanced Machine Learning methodologies on enhancing interpretability of Machine Learning. We are currently working with international partners on an interface for Magnetic Resonance Fingerprinting (see p.45) exploiting modern Deep Learning technologies.

O.I: Do you think that Machine Learning will encourage multidisciplinarity?

R.W: Future work of the radiologists will face a close cooperation between engineers and imaging experts for our patients. Instead of developing algorithms based on limited sets of testing data at the Universities and/or companies and focusing only on the technical aspects, it is of utmost importance to bring the engineers to the patient and let them learn about the clinical needs, potential pitfalls and consequences their developments may have. We were among the early ones to have started such a cooperation on prediction of outcome in acute ischemic stroke at a time when engineers did not know much about stroke and we did not know much about automated image analysis. We have learned tremendously from each other and realized that it is very important to unite our research teams and to work together directly at the hospital. We are convinced that it will enable us to improve the technologies faster and tailor them to daily challenges that we meet in our clinical work with patients.

Deep Learning

“ The goal of a more personalized medicine, tailored to patient specific needs “

Dieter Hahn & Volker Daum
Co-founders of the medical software company Chimaera GmbH

Dieter Hahn studied Computer Sciences at the University of Erlangen-Nuremberg, Germany, and graduated in 2005 focusing on medical image processing. In 2009, he finished his doctoral thesis on statistical methods for medical image registration. In 2007, he co-founded the medical software company Chimaera GmbH. Since then, he is part of the general management. His major research interests include statistical methods in image processing, Deep Learning, and hardware acceleration.

Volker Daum obtained a degree in Computer Sciences at the University of Erlangen-Nuremberg, Germany. During his studies, he also spent a year abroad at the SCI Institute at the University of Utah, UT, USA. After working for one year at the Fraunhofer Institute for Integrated Circuits, he joined the University to pursue his doctoral degree, completed in 2011. In his thesis, he worked on non-rigid image registration and the usage of prior information in registration technology. He co-founded the medical software company Chimaera GmbH in 2007. He is part of the general management and his research focus is on non-rigid image registration, numerics and Deep Learning.

CHIMAERA

Olea Imagein: Could you please introduce yourself to our readers?

Dieter Hahn: My colleague and I both studied Computer Sciences at the University of Erlangen-Nuremberg, where we also worked together on different topics in medical image processing. When working with physicians and medical experts, we saw the challenges and opportunities in this field. So together with Dr. Marcus Prümmer and Prof. Joachim Hornegger, we co-founded the medical software company Chimaera GmbH.

Volker Daum: At Chimaera, we develop medical image processing software for various medical image processing tasks, such as registration, segmentation and Machine Learning. As a certified medical device manufacturer with ISO 13485 and FDA clearances, we offer service projects for business customers, as well as own application products. We are currently working on various challenges in non-rigid image registration, automatic segmentation, and also take part in interdisciplinary research projects. At the moment, we are using Deep Learning methods on multiple imaging modalities in a large research project funded by the German State and entirely focused on HCC (hepatocellular carcinoma).

O.I: Deep Learning is integrated into different tools you develop. How is it incorporated, in what form and for what purpose?

D.H: Before Deep Learning became this hot topic, we basically had to develop a new algorithm for each new task that was required, as the algorithms and their designs were usually so specific. Just to give you an example, segmenting a liver was requiring different algorithmic methods than segmenting bones or other organs, not to mention being able to use different MR sequences as input. Therefore, we had to spend quite some time adapting our algorithmic approaches to new tasks, which completely changed when we switched to Deep Learning.

V.D: At the time Deep Learning with Deep Neural Networks (DNNs) became popular again, which was roughly 2 or 3 years ago, we ran tests and comparisons on our data that we gathered already the years before. In short, we were quite amazed how good the results with DNNs turned. Since then, we use Deep Learning successfully for solving all kinds of automatic segmentation tasks in our software tools, which currently consist of various multi-modal organ presets like liver, kidneys and other soft tissues in the abdominal body region. Since last year, we also invested into our hardware infrastructure to be able to offer a complete Deep Learning service workflow for our customers. This covers the entire range from data retrieval and annotation, network design, fast training using high-end graphics cards and final integration into customer software. With this setup, we have successfully realized several customer projects on Deep Learning over the past year.

D.H: We are also integrating Deep Learning technologies into our own products, like our OEM libraries for automatic organ segmentation on multiple modalities. In addition, Deep Learning helps to improve our semi-automatic segmentation software and our image registration methods. Deep Learning methods are currently also being integrated into our own imaging toolkit that primarily targets clinical and preclinical research.

O.I: Could you explain the process of customization of a neural network? Why is this important, and how far can we go in this direction?

V.D: When we began using neural networks a few years ago, we did not start from scratch but reused existing network designs. Although these models were intended for something very different from medical imaging applications, we could nonetheless apply them to our tasks and benefit from existing optimization approaches and parameterizations back then.

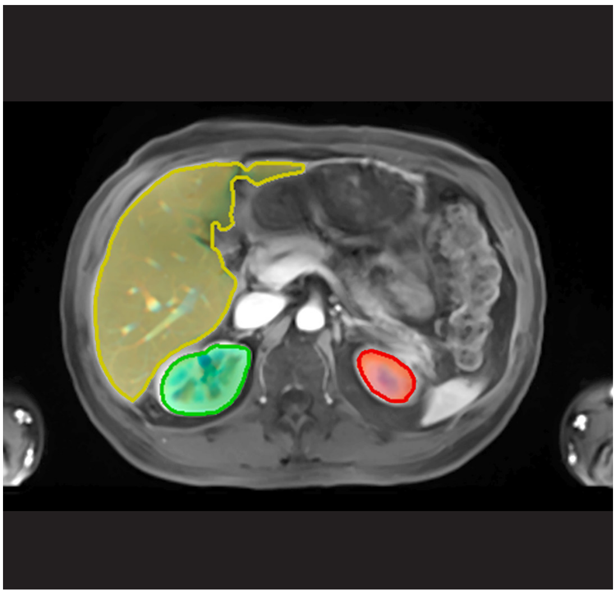


Figure 1: Automatic segmentation - DNN

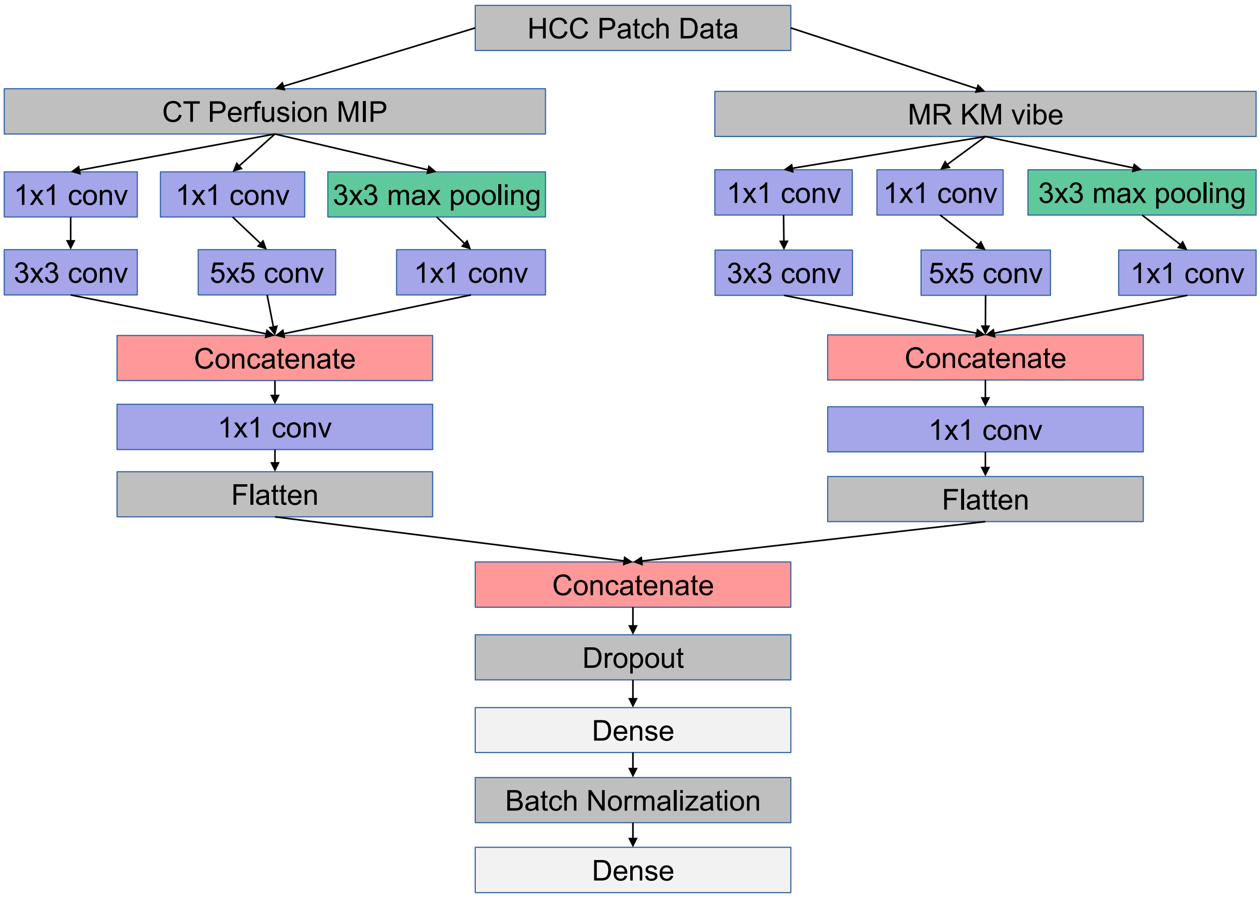


Figure 2: Custom Network Architecture

These technical issues are sometimes hard to come up with in the first place. In fact, we started by using neural networks that were originally designed for detecting vehicles and pedestrians. Over time, we gathered more and more experience by experimenting with the network design and the parameter optimization. Now, we are able to adapt the model design more specifically to the application at hand, which greatly improves the evaluation accuracy and overall quality of the results.

D.H: In my opinion, the most important aspects we have learned from our experiments with deep neural networks are how to identify basic building blocks of the network functionality and what sort of information they provide to the overall solution. Then a major goal for us is to achieve a good trade-off between the complexity of the network and the accuracy of the results. Our process of customization currently starts with arranging these basic network building blocks in a manner that we consider appropriate for the task. Then we try to figure out how to get a good initial parameterization and perform the model optimization. This is an iterative approach, where we modify the design and perform the optimization again to improve the evaluation results. In addition, we are currently investigating methods to automatically reduce the network size and number of parameters by combining several layers or by using more enhanced filters, while keeping the accuracy high. In my opinion, this seems to be important to somehow mitigate the effects of the curse of dimensionality, as the larger the parameter space, the larger the training sample size needs to be and the harder it is to find a good solution. Our first results show that we can often increase the accuracy by replacing parts of the network with a more condensed design and a reduced number of parameters.

V.D: The mentioned effects of the parameter reduction on the required number of training data is important, as in medical applications it is often quite difficult to get a large enough set of training data. On the hardware side, the reduction of space and parameters is a major factor when we are dealing with limited resources, like graphics memory. A customized network may very well fit onto a dedicated hardware or it can eventually run on a low-end graphics card, while its full blown general design may not. This can be a big factor for being accepted by a customer, as the available hardware is often already fixed when a new project is started.

O.I: Classification, detection, registration or segmentation are among the main AI applications in medical imaging. Which new task could be solved using Deep Learning in medicine?

D.H: You have probably mentioned the most popular applications, if it comes to Deep Learning. However, I can think of various regression tasks where Deep Learning could be quite beneficial, as well. In Machine Learning, we understand regression mainly as the estimation of a continuous response from given input data, compared to a discrete response in classification. To give you an example, we are currently involved in a research project on HCC patients and we are investigating whether we can estimate the likelihood for a patient to respond to a certain therapy from imaging data acquired at an early stage of the treatment. We apply Deep Learning for this task and use customized network models. Although these kinds of tasks are quite challenging, I expect to see more and more approaches like this applying Deep Learning in future. Another hot regression topic I currently think of is estimating attenuation maps in PET/MR hybrid scans with DNNs, especially when scanning body regions other than the human head.

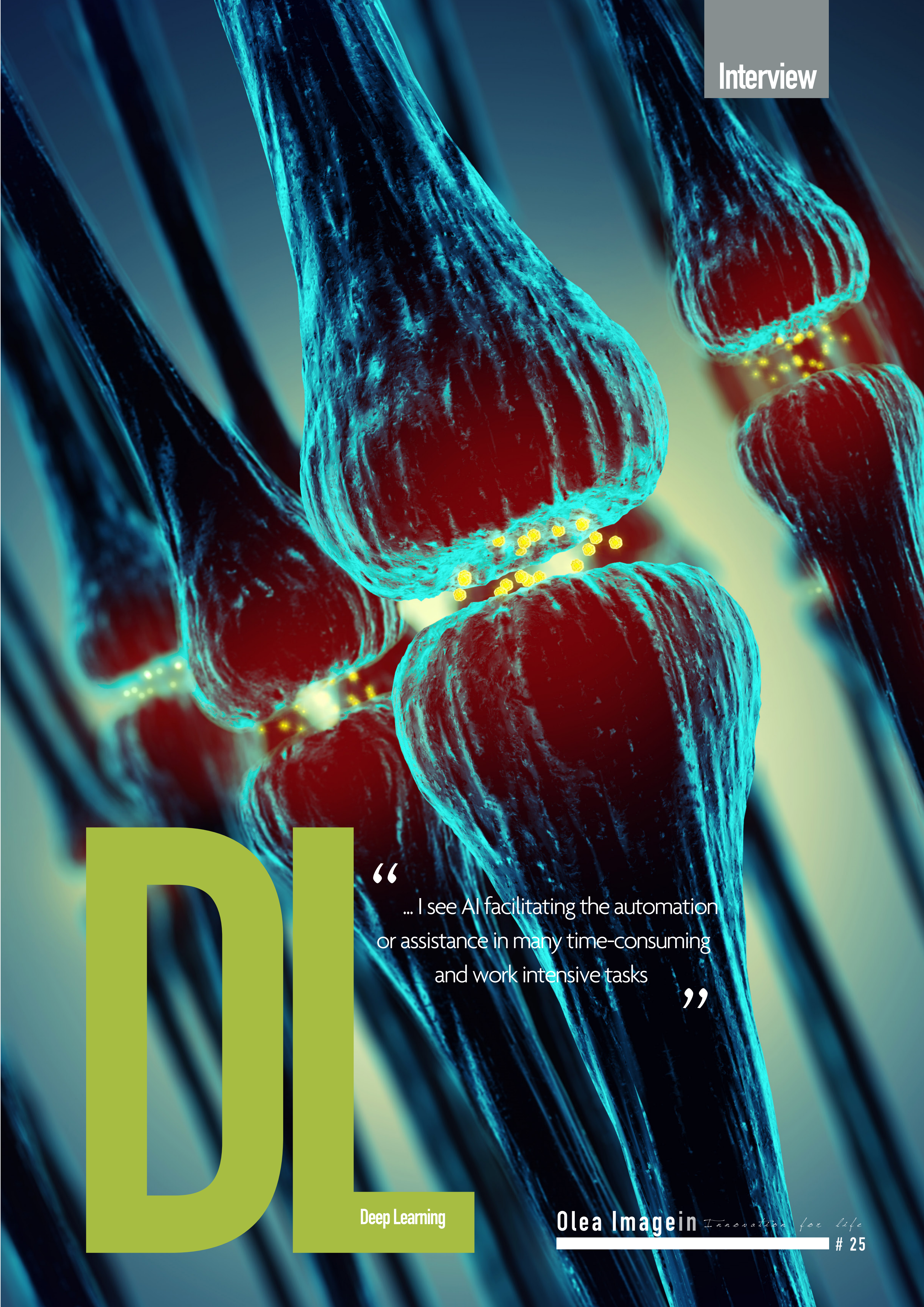
V.D: In previous issues of the Olea Imagein magazine, you have discussed aspects of introducing quantitative measurements from MR sequences. This is interesting also in terms of Deep Learning, as I can think of new types of derived sequences that are computed using DNNs that work on existing sequences as input. With DNNs, we can try, for example, to express dependencies and relationships between existing sequences and turn them into something new. For me, DNNs seem especially suitable for this, as by having a lot of varying training data as input, the models may become more and more invariant to several problems we always have to face in MR, like intensity inhomogeneity, partial volume effects or missing intensity standardization.

O.I: Which indicators reveal that Artificial Intelligence is a fast-growing field? How do the actors, such as Chimaera, adapt and adjust to this rapid evolution?

D.H: To me, one indication in the medical field is how this technology influences major academic and medical conferences, as well as journal contributions. Especially in the last year, I can hardly think of a big conference or medical exhibition on medical image processing that did not feature a dedicated workshop or exhibition on AI and Deep Learning. Major medical conferences were dominated by Deep Learning topics. Medical image processing, however, is only just one out of many technological areas where AI is currently being put into the spotlight. Consider the evolution of autonomous driving using Deep Learning, for example, which currently receives a lot of public attention and is certainly one of the driving forces behind the technology. At Chimaera, we noticed first indications of this evolution approximately three years ago, and this was when we discovered that the key to this technology probably lies within the data. Therefore, we started gathering training data for various applications, besides investigating how to keep up with the rapid development.

> “... the key to this technology probably lies within the data”

V.D: The key players driving AI technology as a whole are currently the big internet companies such as Google, Facebook or Amazon, which incidentally each develop and provide their own Deep Learning software framework. However, they benefit immensely from the fact that, at least in their respective fields, they have an abundance of data to work with and they do not have to adhere to very strict regulations for



DL

Deep Learning

“... I see AI facilitating the automation or assistance in many time-consuming and work intensive tasks” their software. In the medical field, acquiring significant amounts of data and generating the ground truth results needed for training a network is often a major challenge. It will, therefore, be beneficial to look into network designs that generalize well also for comparatively small amounts of training data sets.

> "... we have just seen the start of what might be possible using proper Deep Learning techniques"

A second major point, which is often a bit overlooked, is the necessity to facilitate the annotation of large numbers of medical data with the necessary ground truth information. To make this process as efficient as possible, we have, for instance, developed our own tools for semi-automatic segmentation that drastically reduced the time we need to produce manual ground truth segmentation of medical data in a larger scale. These tools are being currently also refined to become more and more intelligent along with the growing number of training sets.

O.I: How do you imagine the future of Deep Learning?

V.D: I would differentiate between two very different application types of AI in medical software. On the one side, I see AI facilitating the automation or assistance in many time-consuming and work intensive tasks, such as the automatic adjustment of presets, automatic organ segmentation, or computer aided tumor analysis, just to name a few examples. On the other side of the spectrum are more research-oriented developments that try to derive new medical information, that are currently not available from existing clinical data. This will certainly not be limited to imaging data but will encompass all kinds of medical and biological information. In therapy, this can help to predict the success of specific treatments, with the goal of a more personalized medicine, tailored to patient specific needs. In the diagnostic field it could enable a very early prediction of possible medical conditions from biomonitoring information collected through, for instance, health and fitness trackers.

D.H: In my opinion, we have just seen the start of what might be possible using proper Deep Learning techniques. For us, as a small and very specialized company, it already helped to provide more types of applications and services. Simply because we can apply the same Deep Learning techniques to solve different tasks. But besides all the success stories on Deep Learning seen so far, I think we should spend more effort on trying to better understand and control the core technology itself. To date, it seems to me that we are still lacking tools to gain more insight into what various parts of the networks actually do and how to influence certain aspects within the training. Trying to customize the networks to specific tasks certainly is a step in the right direction, but it still is only the beginning. Once we better understand this fascinating technology and how to control its complexity, I can imagine not only a more widespread use in clinical applications and workflows, but also a contribution to dispelling some of the fears and prejudices that physicians currently might be concerned with.

Artificial Intelligence Regulation

" This raises many questions for software able to evolve on their own, since it must be decided when the changes trigger the need for new validation, clearances or approvals "

Sylvain Fogola
Quality & Regulatory Affairs Director
Olea Medical ®

Olea Imagein: Artificial Intelligence is the buzzword on everyone's lips. Is it a new concept for International Organizations for Standardization?

Sylvain Fogola: We may have thought that it is. But Artificial Intelligence (AI) was already defined in the early 90's – at that time you were perhaps playing with your Super Nintendo®. AI definition given by ISO IEC 2383 was "branch of computer science devoted to developing data processing systems that perform functions normally associated with human intelligence, such as reasoning, learning and self-improvement".

O.I: Could you please clarify under which conditions a software is considered as a Medical Device?

S.F: First of all, the answer depends on the country we consider, since regulations may be different from one place to another – especially for software. So, let us focus on Europe and the US in this discussion.

A software can be developed for the purpose of being integrated into a physical Medical Device (MD) or as an independent Medical Device in its own right (standalone). In Europe, standalone software is considered as an MD since 2007. However, not all computer programs are regulated as MD... fortunately!

Indeed, a software is regulated as MD if it is intended to be used for medical purposes. For example, the EU Medical Devices Regulation (EU MDR 2017/745) and the 21st Century Cures Act in the US exclude software such as those for general purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes. In the US, the 21st Century Cures Act even excludes, with some restrictions, Clinical Decision Support (CDS) software.

O.I: How do the competent authorities regulate or will regulate software including Machine Learning algorithms?

S.F: As we said, in Europe and in the US, this is the software's intended use that really drives the level of regulation, whether the software includes Machine Learning features or not. No specific guidance related to the use of Machine Learning has been issued yet. The exclusion of some Clinical Decision Support software by the FDA may be an opportunity for some companies since Machine Learning can be extensively used in such software. However, don't go too fast... Some provisions allow the FDA to regulate some of that software based on their potential risks and severity of harm. On December 8th 2017, the FDA has already released new draft guidance documents for medical software and Clinical Decision Support software, in response to regulatory changes introduced by the 21st Century Cures Act.

O.I: Is there any medical imaging software already FDA-cleared based on Machine Learning technology?

S.F: As far as I know, today at least three software solutions including Machine Learning features are FDA-cleared. One company received FDA clearance in January 2017, for the first MR cardiac Zero-Footprint medical imaging analytics cloud software with Deep Learning – just after being CE-marked in December 2016. In this application, Machine Learning was successfully integrated to provide automated ventricle segmentations based on conventional cardiac MRI images; segmentations which are as accurate as those manually performed by experienced physicians. This software was classified as a class II device and got the clearance through premarket notification 510(k).

Another company got an FDA clearance in March 2017 for a device dedicated to Computer-Assisted Detection (CADe) of breast cancer using 3D tomosynthesis, built on Deep Learning technology. This software classified as a class III device received a Premarket Approval (PMA) from the FDA. Indeed, such CAD software which is intended to highlight areas of interest, even indicate the likelihood of the presence of a lesion or specify a disease type, is more stringently regulated because it presents greater risk.

But FDA's attitude towards CAD seems to be evolving. In July 2017, FDA decided to down-classify into class II (after a de novo classification request) a Computer-Assisted Diagnosis (CADx) software incorporating Machine and Deep Learning technologies for the evaluation of breast abnormalities – and they established a new generic product type. Based on features extracted from the images, the software characterizes the breast lesions and provides information to the user including similarity assessment to a robust database of abnormalities with clinically documented pathologies. Classifying this software in class II is really a strong encouragement to companies developing such software. Indeed, manufacturers of class III software must submit a huge enough PMA application that is typically based on extensive clinical trials, whereas manufacturers of class II software only need to demonstrate that their software is substantially equivalent to another one already on the market.

O.I: How do we validate image analysis software that employs Machine Learning?

S.F: There is a relatively well-established approach that consists in designing trials that compare analysis performed by the software with ground truth obtained from other techniques or experts. As of today, probably the best FDA guidance for software integrating Machine Learning is the 2012 guidance documents on CAD devices, that lists the information such as algorithm design, features, models, classifiers, data sets used to train and test the algorithm.

O.I: What are the specific concerns about Machine Learning algorithms?

S.F: For software that may contribute to serious injury to patients (safety class C according to IEC 62304), manufacturers shall document the detailed design and verification of the software units. The issue is that an algorithm employing AI (i.e. a software unit) can be seen as a "black box" for which we do not know exactly how the parameters of a neural network, for example, are set by the training phase. So, it may be trickier in this case to comply with these requirements.

Another concern is about the Machine Learning software that are referred to by the FDA as "adaptive systems" – which means that they may continue to evolve over time according to the data collected in the field, after going to the market. Even though really appealing for most developers, this is a challenge for competent authorities because changes to medical devices must be strictly controlled; and this raises many questions for software able to evolve on their own, since it must be decided when the changes trigger the need for new validation, clearances or approvals.

O.I: Are you optimistic about how competent authorities will welcome AI innovations in healthcare?

S.F: Yes, definitely. As often, the FDA is more reactive than European authorities. The FDA has already recognized new consensus standards for software that are not yet harmonized in Europe. Regarding AI and the even larger digital health field, the FDA is very responsive and seems to appreciate the value of innovations such as AI and how it may significantly improve healthcare. So, I think that the regulatory framework could be less seen as a burdensome pathway to approval but also as an opportunity to market innovative solutions with a good level of confidence in their performance and safety.

Some definitions

Artificial Intelligence

Ability for a computer to perform tasks commonly associated with human mind such as reasoning, generalizing, problem solving or learning.

Part of data science and statistics, AI is based on numerous different categories of tools: Bio-inspired algorithms (genetic, ant, swarm, etc.), Expert Systems, Fuzzy Logic, Machine Learning, etc.

Machine Learning

Ability for a computer to learn without being explicitly programmed.

Machine Learning can be supervised, with labeled data acting as teachers – example inputs and desired output; or unsupervised, using unlabeled data in order to find hidden patterns or create clusters among them.

Artificial Neuron

Mathematical function acting as a model of the biological neurons of brain.

An artificial neuron receives one or several inputs – by analogy to the postsynaptic potentials. These inputs are summed with separate weights and passed through a non-linear transfer function to produce an output – by analogy to the action potential transmitted along an axon.
Typical input are, for example, features describing an object in an image (texture, color, size, etc.).

Neural Network

Numerous artificial neurons organized in layers, so that the output of a group of neurons can be the input of another.

A neural network can be trained with labeled data thanks to the backpropagation of the error, defined as the difference between the effective output and the target. Starting with arbitrary weights, the error is distributed back through the network; repeatedly, the weights are adjusted and corrected so that the error is progressively minimized: this optimization feedback loop of the system is what is called "learning".

Deep Learning

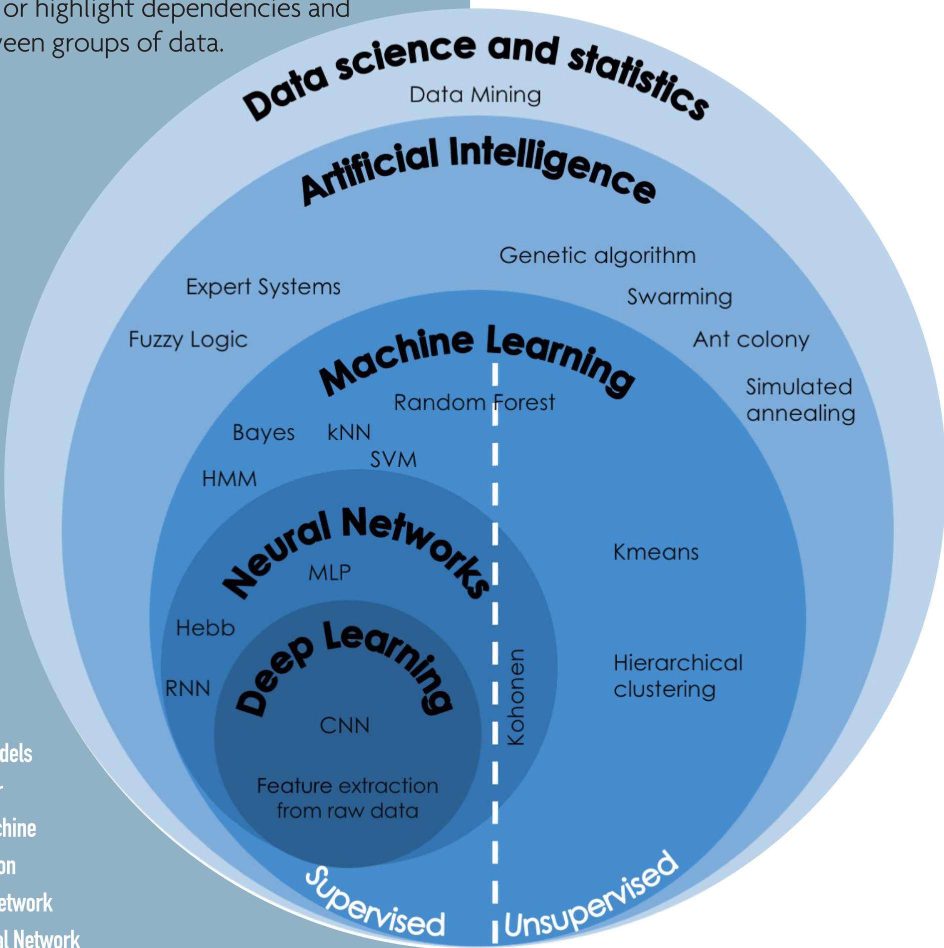
Broad family of Machine Learning methods using special types of neural networks, organized in multiple and hidden layers.

Deep Learning is based on broad families of neural networks – among them, CNN is the most famous – and presents a great advantage in terms of time-saving and accuracy: the input features are directly extracted by the neuronal units of the first layers, without explicit manual intervention on the training database. The deeper layers then learn from the features prepared upstream.

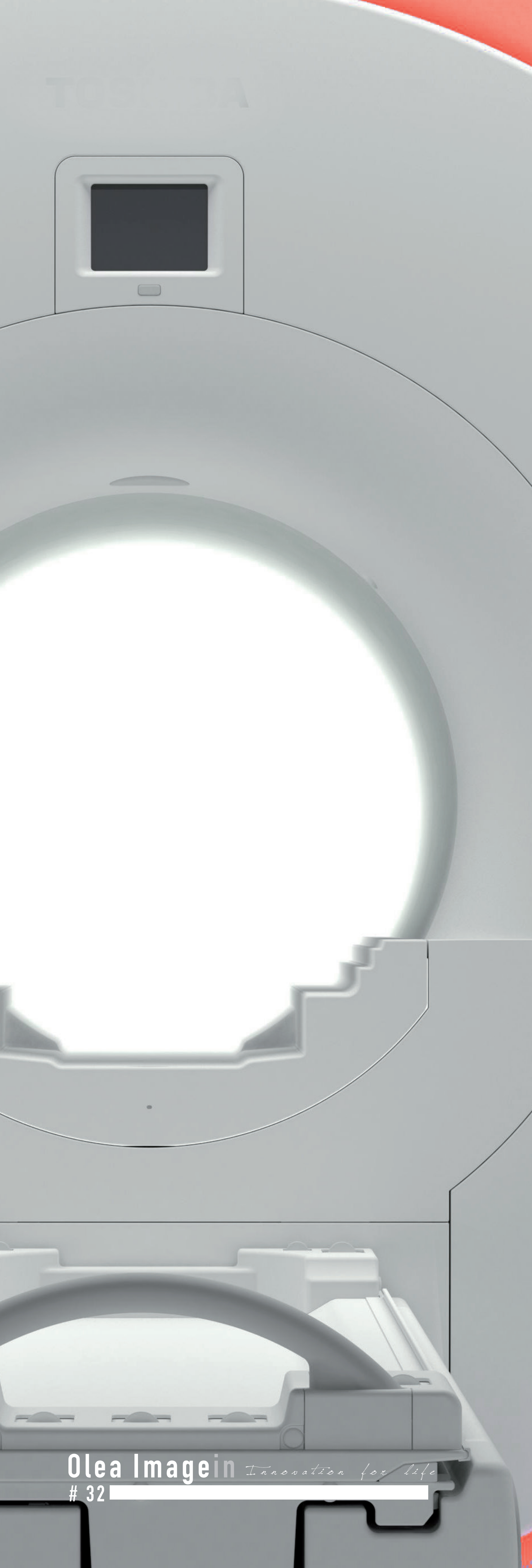
Data Mining

Interdisciplinary computing process aiming at highlighting patterns in large data sets, with methods mixing Statistics and Artificial Intelligence.

Data Mining can create clusters and categories, detect anomalies or highlight dependencies and associations between groups of data.



HMM: Hidden Markov Models
kNN: k-Nearest Neighbor
SVM: Support Vector Machine
MLP: Multilayer Perceptron
RNN: Recurrent Neural Network
CNN: Convolutional Neural Network



Aging Imageomics Study:

Looking at imaging, seeing health

Josep Puig, MD, PhD

The greatest demographic transformation in the history of humanity has taken place within the last 100 years. Improved survival has made it possible for the population to grow despite low birth rates. Increased life-expectancy is partly due to improved living conditions and healthcare, but the greatest impact is from government policies that promote health and primary prevention of disease. Indeed, to prevent disease, it is fundamental to focus on potential health risks for the population. To foster good health in the entire community, authorities need large volumes of reliable, accurate and comparable data about the impact of different risk factors. Health promotion and primary prevention are the most effective strategies to reduce morbidity and mortality and to delay the onset of chronic diseases associated with aging. Generally speaking, these strategies are based on the knowledge that many diseases develop over decades and that this process involves a long asymptomatic period during which specific actions can change the course of the disease.

Nowadays, the intensity of health promotion and primary prevention interventions is determined by classifying the risk of disease using different predictive models based on biomarkers. There are several of these models for classifying cardiovascular risk for example, such as the Framingham Risk Score – mainly used in the US, the Systemic COronary Risk Evaluation (SCORE) in Europe, or the Registre Gironí del Cor (ReGiCor) in the province of Girona. Nevertheless, these models may not be sufficiently accurate at classifying cardiometabolic risks; their shortcomings derive from the complex interaction of many components in the long period of "silent", subclinical development of most diseases. First, these algorithms are based on very prevalent risk factors, and this weakens their predictive power. Moreover, they do not take into account markers related to biopsychosocial factors, lifestyle, family history, vascular status, insulin-resistance, physical inactivity or obesity. Finally, many of the alterations in tissues occur gradually without causing symptoms in populations that are considered low risk. It is important to note that in some diseases, no symptoms are evident even after the disease has advanced considerably. These limitations underline the need for new noninvasive biomarkers that would enable the risk of disease to be classified and monitored earlier and more accurately.

MRI is accurate and reproducible; its versatility and ability to characterize organs and tissue is outstanding, including the detection of early changes in the human body that would be imperceptible with other techniques. Whole-body MRI is an efficient way to scan the entire human organism, allowing to extract precise information from targeted organs; it could be a useful tool for assessing asymptomatic individuals because of its high sensitivity and specificity in detecting morphological and functional alterations without inducing harmful effects. MRI biomarkers like those proposed in the project described below could be used to identify subclinical diseases and quantify the burden of morbidity from the different biopsychosocial risk factors. Over the past two decades, imaging has increasingly been implemented in population-based cohorts to obtain information on the assessment of subclinical disease burden, allowing for a more comprehensive assessment of development of disease states. This has resulted in improved

Figure 1: The mobile MRI scanner

understanding of complex disease processes, as well as identification of novel imaging biomarkers as a precursor for overt disease states.

'Aging Imageomics Study' is an ongoing prospective, longitudinal, observational study for the evaluation of the brain, vascular system, heart, liver, fat tissue and musculoskeletal system in 700 individuals aged 50 years and older by multimodal whole-body MRI. This project is developed by a large multidisciplinary research team and financed by the Government of Catalonia (Strategic Plan for Health Research and Innovation, PERIS 2016-2020). The subjects are the participants in the Madurez y Envejecimiento Saludable en Girona (MESGI50) study, whose objective is to compare the biologic, psychological and socioeconomic characteristics of the population aged 50 years and older in function of whether they live in a rural or urban setting in a representative sample from the province of Girona. The MESGI50 study uses the "Survey of Health, Aging and Retirement in Europe" (SHARE) project's field methodology and questionnaire, which include valid and reliable measures of various items – health-related (physical, emotional and cognitive health, use of healthcare resources), psychological (well-being, life satisfaction, beliefs), economic (line of work, retirement, savings, consumption), and social (social support, social and family network, intergenerational transfers). The ambitious objective of the 'Aging Imageomics Study' is to know more about the overall health of the population in order to improve it.

In biomedicine, terms ending in –omics refer to disciplines, technologies or research areas that encompass the totality of a biological system. The suffix –omics is added to a term to define a biological system, understood as an entire organism or a functional part

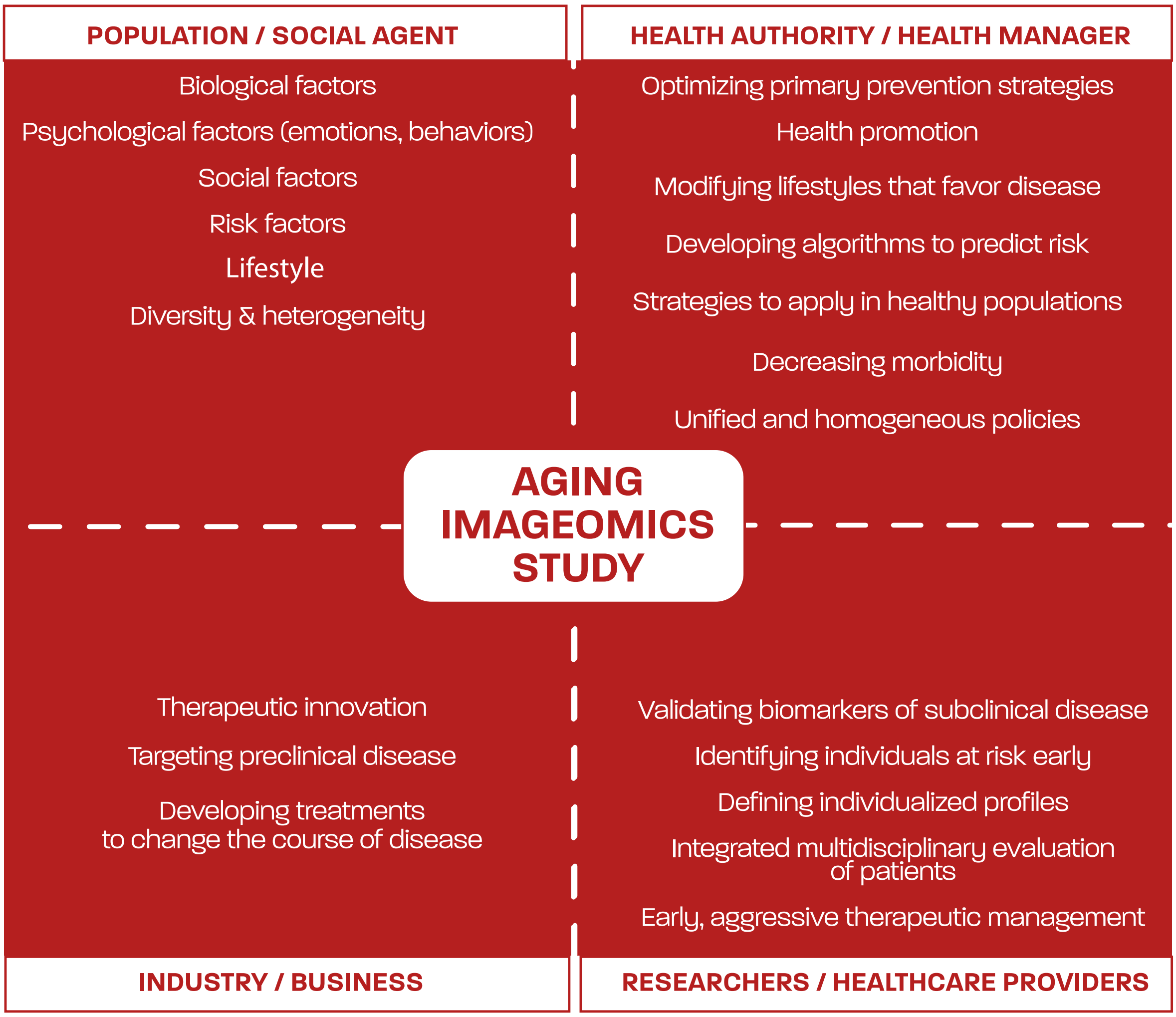


Figure 2: Why the 'Aging Imageomics Study' is interesting for society

of it. The –omics are important as disciplines in and of themselves, but also as new knowledge-based tools that allow to go deeper into more specific fields. The present project will make it possible to access a huge dataset of quantitative and qualitative imaging data of the human body from the age of 50 years; for this reason, the research team has coined the term 'Aging Imageomics'. In addition to correlating all the parameters related to the biopsychosocial and cardiometabolic profiles, this project will also determine the relationship between data from whole-body MRI and metabolomics (set of science and techniques for investigating the metabolic system at the molecular level) and gut microbiome (set of microorganisms normally found in the digestive tract). One of the challenges of this research is to integrate all this information in an individualized way to reach a better understanding of the physiological processes of the human body and to help describe the organism as a whole. The repository of MRI studies will help us to better understand the physiological processes associated with aging in the human body, as well as to model the aging of organs through a metabolic, structural and functional imaging atlas. All this information will be useful in developing advanced imaging biomarkers to identify biopsychosocial risks associated with aging and in generating new hypotheses for further studies. Identifying risk factors for health problems through advanced imaging biomarkers based on whole-body MRI could be a tool for stratifying subjects in the population who could benefit most from primary prevention. The project will allow us to determine the normal values for each of the many variables derived from the advanced whole-body MRI protocol.

All MRI examinations will be done on a mobile 1.5T scanner (Vantage Elan, Canon Medical Systems) installed in a truck (Figure 1), using a head coil and two body coils to cover the entire body, with a maximum gradient amplitude of 35mT/m-1. The acquisition protocol will include coronal T2-weighted short-tau inversion recovery (STIR) sequences of the whole body, sagittal T2-weighted turbo spin-echo (TSE) of the entire spine, short-axis 3D steady-state free precession (SSFP) sequences of the myocardium, 2D phase-contrast magnetic resonance angiography (MRA) of the aortic arch, coronal 4p Dixon method from the liver to the symphysis pubis, and diffusion tensor techniques, resting-state fMRI, R2* mapping, high resolution 3D T1-weighted and T2-weighted FLAIR sequences of the central nervous system. The complete whole-body MRI protocol will take about 40 minutes.

An estimation of the morbidity load derived from the various risk factors will be included, each of which can be modified by many different strategies; this will enable to obtain an overview of the relative role of the different risks for the health of the population as well as of individuals. Along these lines, in the future, imaging biomarkers based on whole-body MRI could be validated as tools to assess personalized risk, making it possible to reliably estimate and compare the morbidity load associated with one or more risk factors. The large amount of quantitative data available can make imaging biomarkers based on whole-body MRI useful for monitoring the effects of future primary prevention strategies. Finding a lesion in an asymptomatic patient results in more treatment options, better prognosis and lower treatment costs than finding the same lesion in later stages of disease. The impact and influence of the project will be important, as the results will be useful for the population, health authorities, public health officials, health researchers, health providers and health-related companies and industry (Figure 2), whose managers need solid tools to assess overall community health and apply plans and direct financial resources.

'Aging Imageomics Study' will enable to identify biomarkers of the risk of becoming ill and thus to stratify the population so that primary prevention strategies can be optimized with the final aim of reducing morbidity and mortality in the population.

Josep Puig, MD, PhD
Coordinator, Research Unit at Institute of Diagnostic Imaging (IDI) in Barcelona, Spain;
Girona Biomedical Research Institute (IDIBGI), Medical Imaging Group;
Department of Radiology,
University Hospital Dr Josep Trueta, Girona, Spain;
Associate Professor at the Faculty of Medicine, University of Girona, Spain.

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VR

Virtual Reality

Virtual, Augmented or Mixed Reality are not recent advanced visualization concepts. However, they are becoming hot topics and are deeply changing many fields, such as video games, education, military or healthcare.

Virtual Reality – A fully immersive experience

Virtual Reality (VR) appeared as early as the 1960s with the development of the Sensorama machine by Morton Heilig, a simulator providing the illusion of reality using a 3D motion picture with smell, stereo sound, vibrations of the seat and wind in the hair [1].

With VR, the user dives into a 3D-modelized virtual world full of motion and interaction possibilities, using sensory stimuli like sights or sounds. The needed devices are usually a head-mounted display, a stereo sound system, some head – or eye or body – motion tracking sensors and joysticks; but it can also be an entire room equipped with sensors and cameras, with large screens instead of walls.

VR applications in healthcare are numerous: from virtual medical images visualization to students' immersion in an entire virtual operating room where they can play a leading role, through stroke patients' motor recovery [2-4].

Augmented Reality – Adding value to real life

Augmented Reality (AR) emerged in the 1980's when Steve Mann invented the EyeTap, a device that is worn as glasses and allows the display of virtual information in front of the eyes of the user [5].

AR uses the real word to superimpose digital data – numbers, images, texts, in 2D or 3D – that the user can manipulate and interact with. The perceived reality is therefore augmented by this digital information, providing more details on the environment. AR needs head-mounted, glasses, smartphone, tablet or computer devices to be performed.

In the same way as VR, AR highly impacts applications such as diagnostic imaging, procedure training, image-guided intervention or interdisciplinary collaboration [6]. However, one of the advantages of the AR glasses could be that they are easier to wear in everyday life compared to the VR head-mounted displays.

Mixed Reality – Combining VR and AR

Mixed Reality (MR) was introduced in 1992 with the Virtual Fixtures platform developed by Louis Rosenberg at US Air Force Armstrong Labs, to enable human users to control robots in real-world environments [7].

MR, most recent but least known technology, combines the features of its elders. Instead of superimposing digital texts or images only, more sophisticated virtual items like living objects can be displayed with MR. In addition, it provides a greater amount of user interactions and brings flexibility by combining the best features of both VR and AR.

Advanced visualization offers tremendous potential to revolutionize the way information is displayed, manipulated and acquired in medicine. It creates new opportunities to teach and learn, and will especially impact radiology in both diagnostic and interventional imaging fields.

Brianna Bucciarelli

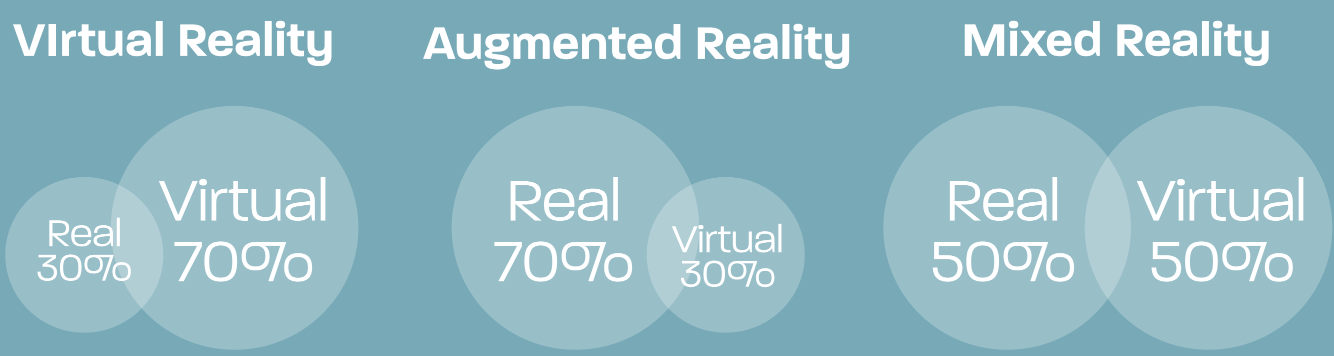

Figure 1: Virtual Reality (VR), Augmented Reality (AR) and Mixed Reality (MR) with the proportion of merging between virtual and real worlds

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Advanced Visualization

" There is no bigger 'big data' than simply waking up in the morning, opening your eyes and seeing the world around you "

Adam Davis, MD
Clinical Associate professor at New York University School of Medicine, and neuroradiologist at New York University Langone Medical Center (NYULMC) in New York, NY, USA. Director of Research and Collaboration of the Image Processing Labs in the Department of Radiology at NYULMC. Manager, Amalgamated Vision, LLC.

Adam Davis is a neuroradiologist specialized in cerebrovascular disease imaging including ischemic stroke, aneurysms and vascular malformations. He has nearly 2 decades experience in medical post-processing and expertise in CT imaging, particularly CT angiography, perfusion and dual energy technique. He is currently the Director of Research and Collaboration of the Image Processing Labs in the Department of Radiology at NYULMC and has special interests in data visualization, stereoscopy, volume rendering, user interface and display including Virtual, Augmented and Mixed Reality platforms. He is the manager of Amalgamated Vision, a technology company developing laser retinal display eyewear for AR, VR, MR and smart glasses applications.

Olea Imagein: Visualization technologies, including Virtual or Augmented Reality, enable the creation of real world objects from a computer.
How could medical imaging benefit from these technologies?

Adam Davis: I think medical imaging will be greatly impacted by these display technologies. As radiologists, we gather lots of data for our imaging studies, typically through MRI, CT or Ultrasound and we have spent the last several decades mainly concentrating on the acquisition, usually for better resolution, faster speed or larger volume. The medical community has spent time thinking about and developing post-processing, but within a very simple paradigm. We were always of the mindset that visualization (or understanding) and representation (or display) of data were similar, matched and straightforward concepts. However, visual understanding is more complicated. Perceiving data depends on many factors, not only the object and its display, but on the environment and how an individual interacts with it. Display needs to meet that deeper level of understanding.

I think of imaging studies as data sets in 3 dimensional space, not as 2D slices. There is a myriad of ways to learn about the inherent information it contains. How well we extract that data depends on the post-processing tools and display methods we use. Datasets were first shown, and to this day are basically still shown, in 2D formats; when 3D formats started to be used, it was done because people said “oh yes I understand more about what I am looking at”. But in the 20 years they have been in common usage we tended to neglect the underlying quality or the inherent nature of the volume datasets. That was a problem because this held us back in terms of what information we could extract from what we were looking at. We persisted with 2D imaging for nearly all diagnostic imaging interpretation. Volume rendering has always been simple and cartoonish, in part due to the computational burden of the algorithms and in part due to the low expectations of the interpreting physicians. So, many questions were neglected that needed to be asked to move it forward. How well delineated is the dataset that we are looking at? What is the conspicuity of the individual components? Do we understand complex morphology? Is relative spatial relationship between objects maintained and can it be readily understood? Does the lighting (luminescence) follow natural properties? What about the texture of the surfaces? These are all visual properties that we use in real life. Evolution designed us to use these properties as well as stereoscopy. The kinetics (the movement) are extremely important in understanding these

datasets and we ignored, or didn't look deeply into this facet for many years. So now that better reconstruction algorithms and display technologies are emerging, I think we will. How physicians visualize imaging data is now changing in a profound manner and even more importantly will be readily available to everyone.

All this will significantly impact medicine, because up until now I don't believe that we had a good visual appreciation of the data we collected. This is not only a problem in science and medicine, everybody is struggling to look at data in different ways. In the financial industries, reams of information are available and analysts want to know how to look deeper to find a trend for some market or investment product. Simpler ways to better evaluate large amounts of data are needed. In medicine for example, we acquire tremendous amounts of imaging data and we always end up dumbing it down for reading efficiency. We produce 0.4 mm primary CT reconstructions and convert them into 5 mm slices – so we throw much of that data out with volume averaging. We collect data over time, either through multiple studies on the same patient or by using temporal techniques like radial-VIBE or GRASP in MRI, or CT perfusion series. A Toshiba Aquilion Volume One acquires 320 slices over time so that one can see the dynamic body movement or watch the flow of contrast. All of these techniques are giving us huge amount of data that we tend to not use to its full potential.

O.I: Imaging studies as data; can you explain more?

A.D: I believe the best way to consider data is visually. People believe that it is from the statistical point of view, and for many scientists, that is a given. The statistical analysis is the final arbiter of truth or falsehood and everything in between in science. But data visualization is a more powerful paradigm, at least in my opinion. Given the proper graphical (design) representation and method of display, in a glance anyone can tell the importance of something by looking at it – an inherently deeper and more fundamental understanding of actual data than a statistical analysis. Big Data analysis has received a significant amount of attention. It is relegated to the aficionados of data science and mathematics. But I like to believe that there is no bigger 'big data' than simply waking up in the morning, opening your eyes and seeing the world around you. In terms of hard data this represents 10's of millions of bits of data per second from the retina, filtered and post-processed to much smaller amounts in clever and efficient ways by the visual pathway by the time it reaches the cortex. New evolving visualization technologies that present to us imaging data in a more natural, physiologic manner, closer to what evolution has intended us to look at, will greatly impact diagnostic and therapeutic medicine. We are on the verge of having a much better understanding of medical imaging data than we ever had before.

O.I: Do you believe Virtual Reality could become an important diagnostic tool for clinicians?

A.D: Absolutely. Visualization techniques – Virtual Reality (completely immersive self-contained environment), Augmented Reality (information or objects superimposed on your real environment), Mixed Reality (information or objects interacting with your environment) – will each impact medicine in different ways. An obvious example is education. There is much interest now in teaching anatomy with Virtual Reality techniques as opposed to using cadavers. I think the result will lie somewhere in the middle. Learning anatomy from a dead dry shrunken body is maybe not the best way to learn about normal living people but only looking at 2 dimensional textbook pictures or reading descriptions is not the best way either, because you are not getting your hands dirty – learning the reality of cadaveric relationships. Virtual Reality provides an experience somewhere in between. It is a great bridge, a profound method of learning that complements our traditional methods. Again, we need to have the right visualization techniques with high quality content and spatial understanding. Much of the power of these VR/AR/MR techniques is that we can present information in a stereoscopically interactive fashion.

Virtual Reality will impact medical practice in numerous ways; surgeons will be able to see a superimposed co-registered image on a patient as they are working – obviously it will help them with their surgical planning and provide a better understanding of the lesion they are looking at. Maybe it will enable them to see things that they may have not noticed before, particularly if temporal components are added – the beating of the heart, the movement of the lungs. Let's imagine that you are performing an endovascular or percutaneous interventional technique; instead of having two fluoroscopic planes to look at, sagittal and lateral views, you can have a superimposed, 3 dimensional and co-registered volume on that image. This gives you more information about where you are anatomically situated; so, perhaps you can do a more efficacious and less invasive procedure. These are things that we already have realized, and that people are already doing.

Virtual Reality will impact population health, not only doctors. It will affect the broader vista of healthcare: people learning about their diseases, people who are sick having their anxiety or pain reduced by using Virtual Reality relaxation techniques, people with psychological illnesses receiving remote psychotherapy. We know it is advantageous to actually be in a room with someone; "Skyping" by computer or "face timing" by phone your psychiatrist or your psychologist is good, but certainly not the same experience. So, if you have a Virtual Reality experience with them, you will maybe overcome many of the barriers, and have a more intimate and more efficacious therapy. It is important to remember that in addition to improved visualization, the psychological effect of Virtual or Mixed Reality is a very important aspect. People have termed it "presence". It is difficult to describe the feeling of realness but that feeling will certainly impact all of the things that people do for community and global health.

O.I: Could you provide examples of existing or future applications using these technologies, especially in the brain?

A.D: It is one thing to do a diffusion tensor imaging (DTI) and another thing to be able to visualize it stereoscopically in 3 dimensions for diagnostic or therapeutic purposes. Physicians have difficulty understanding the nuance of what they look at, because intertwined anatomy is visually too complicated to analyze even with a volume rendering on a 2D screen. Physicians are overwhelmed by the amount of data, so of course our response has been to dumb it down. However, when data is presented stereoscopically with movement or kinetics, the understanding is better. You can attend to detail and better ignore background. Surgeons are currently using DTI or functional MR techniques when they operate on a brain tumor; but it takes it to a whole new level when using Augmented Reality or stereotaxis. By providing an interactive real time superimposition of the eloquent areas of the brain in relationship to a mass or to a tumor, surgery can be planned in a more confident and safer manner. CT angiography viewed stereoscopically and interactively provides a much deeper understanding of complex anatomy – I use it myself routinely. There are more powerful algorithms, path tracing that produce 3D volume rendering, in a more "life-like" and "photo-realistic" appearance. The spatial relationships and surface detail of the anatomy – the imaging dataset – becomes more obvious and more accessible. These are powerful applications that exist right now. As the visualization gets better, and the content and the techniques improve, more applications will be developed.

O.I: Among diagnostic, preoperative planning, telemedicine or education areas, where do you think the visualization contribution will be the largest?

A.D: Hard to say. I think that the first impact for now will be education and then soon to follow, it will be pre-operative and surgical planning over the next 5 years. This is currently the main focus for most developers in the field and is going to evolve. Remote experience – being able to see and hear other people, to share experiences and collaborate even when geographically separated from each other – will ultimately be the biggest impact.

Remote applications or telemedicine will likely have an impact on world health. The presence of a remote expert in consultation during diagnosis or therapy, seeing and hearing what the local practitioner does, and guiding them through the visit or the procedure, will enable high quality health care to spread to areas that are in need. It will be a simple and cost effective solution to many of our geographic medical inequities. It will level the playing field in global healthcare. It will also disrupt medical economics.

Telemedicine, VR/AR/MR will be better able to disseminate information and educate people in a more powerful and more easily understood format. Medical knowledge and ultimately diagnostic and therapeutic capabilities will be equalized between wealthy industrialized nations and poorer nations; because we are going to be able to train doctors, nurses and other health professionals more easily in these countries. We are not going to need to disseminate experts as we do today, because lots of people with a more basic training in healthcare will be available to go into the community; when facing a difficult situation, they will be able to refer back to a more centralized point of expertise. With remote experience, a nurse practitioner, physician assistant, emergency provider will be able to be guided by a more experienced person who can help them. That kind of support and collaboration will impact global health because resources will be better utilized.

A surgeon can be guided while operating; let's say he or she is searching for an artery or is uncertain about the resection line within an organ. Using smart eyewear and video the surgeon can consult a trusted colleague, who can put an arrow in front of the surgeons' eyes or draw a line and say: "oh there it is!" Or a remote assistant can bring in imaging data for the surgeon to refer to that is viewable within their head mounted eye-wear. It is so powerful.

In addition to improving visualization techniques, Machine Learning will impact healthcare with automated diagnosis. An automated differential diagnosis and associated confidence levels for a particular diagnosis will fundamentally change the character of medical practice, particularly for visual diagnostic specialties like radiology. I believe that in the not-too-distant future, Machine Learning-based radiology assistants will reduce the need for radiologists in general and sub-specialists in particular. There was a popular discussion recently in the radiology community about this subject and a statement ensuring everyone that highly trained radiologists will always be needed. I am not so sure. I think humans with medical training will be needed and yes, some specialist physicians – but not in the way we practice today. Nurse practitioners or physician assistants in collaboration with Machine Learning visual diagnostic software, may perform diagnostic radiologic practice just as well as the general or sub-specialized radiologist, perhaps only occasionally needing human radiology experts for support on difficult cases. This won't be driven by medical societies; it will be driven by economics. Radiologic studies are increasing despite reimbursement controls contrary to what people previously believed. That is because there is pressure to see many patients and make a diagnosis quickly – radiologic studies provide that capability. But supporting a growing number of high cost reimbursements for high tech imaging and pricey radiologists to interpret these studies is unsustainable. Radiologic assistants (nurse practitioners or physician assistants) and Machine Learning solves this. Eventually the clinical subspecialist – the orthopedic surgeon, the neurosurgeon, the pulmonologist who receives the patient will make their own independent assessment of the imaging. That's how I see this unfolding.

Machine Learning, remote visualization, better content reconstruction and the ability to provide Virtual or Augmented Reality to enhance display or provide real time, interactive collaboration, will transform every health professional into an instant expert. The impact of this technology can be huge, but it depends on how we apply it. How easy it is to use, how expensive to acquire and maintain, how secure the information and most importantly how much we are willing to change.

O.I: What do you expect from these rapidly growing technologies?
Which impact do you believe they will have in the clinical practice?

A.D: For centuries, medicine was structured with the doctor as the central figure in making a diagnosis and administering therapy. The entire paradigm of medical care, health and wellness, is going to be completely altered by improving visualization, and by that I mean: Virtual, Augmented, Mixed Reality, smart glass data, remote experience… Putting all of these resources together will transform care by creating lots of experts on demand, more flexible and more specialized physicians (or their equivalent) who will be contacted by providers out in the community.

The economics of medicine are going to change. In a few years, there will be a very huge difference between doctors who use their hands and do procedures, versus those who don't. Those who don't, those who see patients and make a diagnosis with activities that require visual or cerebral work including reading imaging studies, are going to be – not eliminated – but significantly changed, through a combination of Machine Learning, improved display and remote experience. I think that the most in demand experts in a few decades will be those who actually work with their hands. I know this must sound crazy, but the manual labor of medicine is something that we cannot soon replicate. Maybe one-day robots will be able to do this; maybe someday these physicians will be replaced as well…

The organization of how we treat people at hospitals will be different. We are already seeing it today in busy large hospital systems. People will present with a chief complaint and depending on the general anatomic or functional area of interest, the emergency room nurse practitioner or physician assistant will order protocol sets of blood work, imaging and other diagnostic tests. These tests in combination with the Machine Learning-assisted emergency nurse practitioner, physician assistant, and/or radiology assistant will generate a differential diagnosis and then the patient will be discharged or admitted to the appropriate medical or surgical clinical service for further evaluation and treatment. The role of the radiologist, emergency room physician, and general practitioner will be obviated. This is the future of triage. Radiology has already become the specialty of triage. I think that much of our developing advanced visualization work done in radiology will then be geared entirely for the clinical specialists, like surgeons, because advanced visualization techniques will level the differences between novice and expert image interpreter. We won't need a radiologist to interpret the films – to see through the shadows of the x-ray – to translate the visual findings into meaningful results for the clinician – because the results will be that much more obvious. Volume acquisition imaging, advanced post-processing techniques, immersive/augmented displays and Machine Learning will bridge that gap. It will take data in space – and over time – and lay it out in an obvious graphical interface. Imaging now becomes the tool of the treating subspecialists who used to be thought of as the referrers. I think it is going to be a transformational moment in medicine.

Magnetic Resonance Fingerprinting is a new and completely different approach for rapid, simultaneous and flexible acquisition of quantitative data related to a specific tissue [1].

MR Fingerprinting:

Simultaneous and Quantitative imaging

From qualitative to quantitative

Unlike CT scan, MR signal is not quantitative by itself. The intensity provided by the images, more or less weighted according to specific choices of acquisition settings, remains relative: the diagnosis relies on a subjective comparison with the surrounding tissues.

Nonetheless, every part of tissue is characterized by typical MR properties: longitudinal T1 and transverse T2 relaxation times, proton density (PD), off-resonance frequency (f), etc. If quantified, these parameters can provide valuable information about the pathological condition of the analyzed region, since T1, T2 or PD vary together with the biological and physical changes within the tissue.

Several quantitative methods allow the computation of biomarkers, but these parameters are calculated one at a time, with a possible sensitivity to the environment. In this context, the novel MR Fingerprinting technique aims to answer the question: "How to extract all the quantitative information encapsulated in the MR signal, in a single acquisition, simultaneously?"

Random and Dictionary

Quantitative information are part of the MRI signal; they are combined with the acquisition settings (echo time TE, repetition time TR, flip angle FA, etc.) through the Bloch equations to create the voxel intensity [2].

MR conventional acquisitions are performed with fixed settings (TE, TR, FA, etc.). In order to separate the quantitative characteristics, the idea behind the MR Fingerprinting concept is to vary all the acquisition settings with time on a pseudo-random basis, so that different tissues have different signal evolution in time (Figure 1A).

The obtained images are not clinically meaningful, but a specific voxel of tissue with predefined quantitative characteristics will return a unique response, or fingerprint, according to its sensitivity to all the different settings. The next step is to compare this fingerprint, or sequence, with a pre-calculated dictionary (Figure 1B) and to detect the best match using a pattern recognition algorithm.

An adapted dictionary is designed using the Bloch equations or any other method; it is composed of thousands of different time courses simulated with different sets of quantitative parameters whose physiological ranges are well-known: example, from 200 to 5000 ms for T1 [3]. The approach is similar to matching a person's fingerprint to a database; but, instead of getting an identity, a set of quantitative characteristics is returned (Figure 1C).

Related to the concept of compressed-sensing, this young and promising technique may allow fast, robust, motion-insensitive and simultaneous quantitative MR acquisitions in the future [4-6]. Preclinical *in vivo* studies on heart, brain, liver, kidney, spleen, etc. are in progress [7-9].

Sophie Campana Tremblay

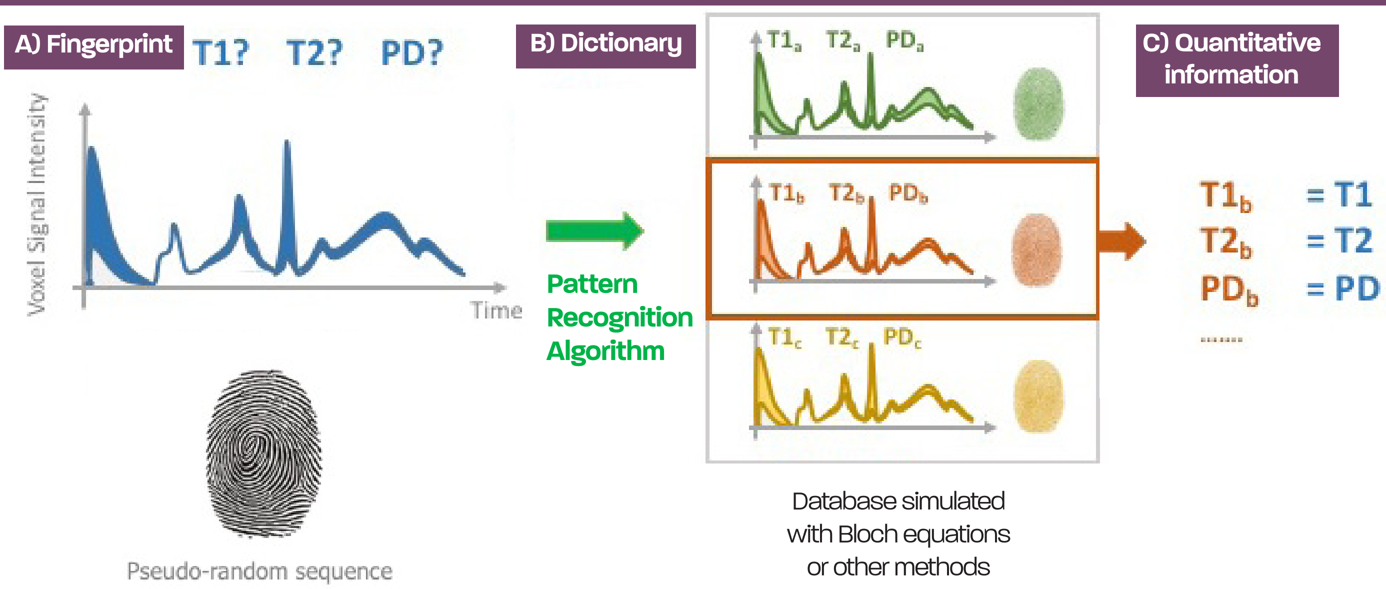

Figure 1: Fingerprinting principles effect. Adapted from [3]

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MR Fingerprinting

“ It is my hope that increasing reliance on quantitative approaches will lead to more certain, more uniform diagnosis ”

Vikas Gulani, MD, PhD
Associate Professor of Radiology, Case Western Reserve University (CWRU) School of Medicine; Director of MRI, University Hospitals (UH) Cleveland Medical Center, Cleveland, OH, USA.

Vikas Gulani is a radiologist in Cleveland, OH, USA and is affiliated with multiple hospitals in the area, including University Hospitals Bedford Medical Center and University Hospitals Cleveland Medical Center. He received his medical degree from University of Illinois College of Medicine and has been in practice since almost 20 years. His research interests include MR relaxometry, Perfusion MRI, Diffusion MRI, body MRI, image acquisition and reconstruction.

Olea Imagein: Your achievements in the development of Magnetic Resonance Fingerprinting (MRF) technique have raised the interest of the research and radiology community. Could you please share with our readers your motivations to select and develop this particular imaging process?

Vikas Gulani: The motivations behind this work really stretch a long way back, when I took a year away from my residency at the University of Michigan to be a post-doctoral researcher at the University of Würzburg in Germany. Even in medical school and residency, it struck me as amazing that we never clinically measure T1 and T2 and that we live in a world where signal intensity in MRI carries no absolute meaning. Coming from a rigorous MR background where I was taught to put a number on everything, this struck me as very odd in my clinical life. At the same time, the quantitative nature of CT really was powerful to see. If something measures 20 HU rather than 10, you can safely say that it is not simple fluid and need to think about what that means clinically. So, where is the Hounsfield Unit for MR? At the same time, Mark Griswold, who was also at University of Würzburg (incidentally we had also both been at the University of Illinois a few years back), was already exploring simultaneous T1 and T2 mapping using inversion-recovery balanced SSFP acquisitions. He was thinking deeply about T1 and T2 and how to get at measuring both of these characteristic times simultaneously. From his perspective, if you can measure something, why would you simply weigh images by these numbers? And what does it mean for an image to be T1 or T2 weighted? Thus we found each other's thinking on this topic convergent and started to work to solve the problem.

O.I: Could you describe the MRF method? What are the advantages and current limitations of this new MR technique?

V.G: The traditional approach to parameter mapping by MRI is to obtain several images that are differently weighted by that parameter, and then fit a curve through these images, usually an exponential. The problem is that in most cases, the information content is really high in the fast evolving portion of the curve, and there is very little information in the flat portion of the curve. The fast evolving part of the curve is very difficult to sample densely. The flat part of the curve is easy to sample, but is not helping you. Thus, not only do you need several full images, but the sampling process is not ideal for the measurement you are trying to make. Add to this the fact that, if you are interested in more than one parameter, you have to repeat the entire process, and the resultant maps are not going to be perfectly aligned.

In MRF, we tried to get around these limitations. We start with an acquisition where there should be sensitization to multiple interesting properties, so that we can map them simultaneously. Second, we let go off the goal of collecting high quality images at several points along a curve and fitting a simple exponential to them. Instead, we vary the scanner parameters such as TR, TE, flip angle, in a pseudo-random manner so that we do not ever live in the "flat" part of the curve that is low in information content. The "images" are highly under-sampled – very poor in any traditional metric of quality. This produces a signal evolution in each voxel that is dependent on the tissue properties we are interested in, which does

not look like any traditional curve that we are used to analyzing. The signal time course is also quite noisy due to the under-sampling, and the acquisition has to be designed so that the under-sampling artifacts are spatio-temporally incoherent, so we may be able to see through them. To our knowledge of the Bloch equations and the sequence (what was played out on the scanner), we can then construct a dictionary of all possible signal evolutions for a huge range of values of the properties we are interested in. The signal evolution in each voxel is matched to the best entry from the dictionary. The property values that went into creating that dictionary entry are assigned to that voxel, and repeating this process for the entire image matrix yields the maps we are interested in.

We have found thus far that this process is quite time-efficient and yields very reproducible maps of the properties of interest, perfectly registered to one another. These are the big advantages. A majority of the work so far has focused on T1 and T2 mapping, but we have started to explore simultaneous mapping of other properties – T1, T2, ADC; ASL derived perfusion properties; chemical exchange, etc. These latter experiments are more challenging. It is very early to say what the disadvantages are, because in many cases the experiments we are designing do not follow traditional MR intuition on these subjects. Exploring the huge acquisition space for this work is not an easy task and it will take work from us and many groups around the world to really sort out what are all the strengths and weaknesses of the technology.

> “... every biopsy is an imaging failure”

O.I: What would be the benefit for the patient and how could MRF methods improve or modify the clinical process?

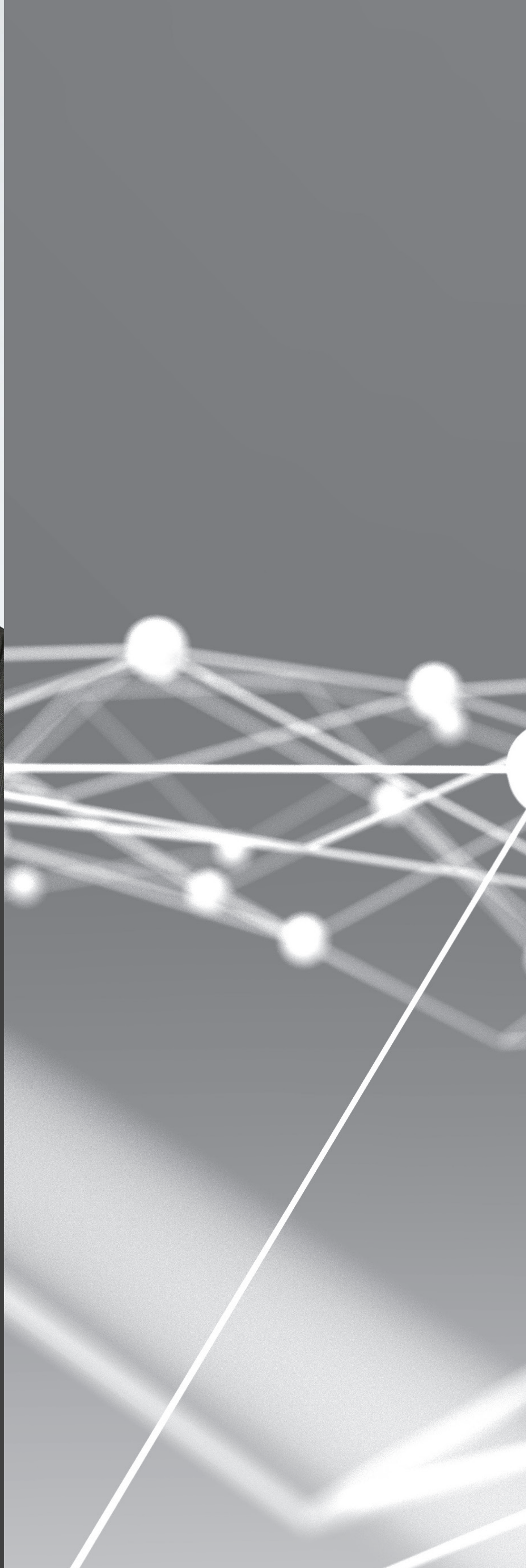
V.G: Right now the imaging process in MR is almost entirely qualitative, and anatomically based. The radiologist infers tissue characteristics by combining relative appearance of several tissues on weighted images, in his or her head. This leads to great variation in interpretation and certainty of interpretation, based on radiologist skill and comfort, acquisition quality, etc. It is my hope that increasing reliance on quantitative approaches will lead to more certain, more uniform diagnosis. Also the introduction of multiple quantitative measurements, along with available data from other sources such as blood tests, genetics, etc., could lead us to predictive models that allow accurate, objective and uniform diagnosis and follow-up of diseases. I am fond of saying that every biopsy is an imaging failure – if we have to rely on tiny amounts of tissue obtained in a highly invasive manner, and subsample that under a microscope for a true diagnosis, then we as imagers have left a lot to be desired. I cannot see the present status quo as being normal 30 years from now. A major step in countering this highly undesirable present setup in the future is to move towards quantitative, multidimensional and definitive tissue characterization. MRF is an important tool in that direction.

O.I: In your opinion, how many years from now for this new approach to become a part of routine clinical practice?

V.G: That is hard to say and is up to industry to some extent. I can see pathways that allow some initial implementations of the technology to become routinely available shortly – within a year or two. How fast it moves beyond that depends on the interplay between clever clinical use and technology development to solve challenging problems that need to be solved for clinical practicality and workflow.

O.I: Another method is yielding similar outcomes for T1, T2 and PD quantification: Synthetic MRI. What do you think about this technique compared to MRF?

V.G: Radiologists are not going to abandon the last 30-35 years of experience with weighted images and jump into quantitative imaging where normal, pathology, response to treatment, etc., still need to be fully defined. Thus presently qualitative imaging will persist and quantitative approaches add to the imaging process rather than replace the status quo. However, if one can generate clinical quality weighted images from T1 and T2 maps, then perhaps qualitative imaging is not needed and we can use the acquisition time for more accurate property mapping or save that time altogether. Thus Synthetic MRI is an important step in clinical adoption of quantitative imaging.



Nicolas Chapados, MSc, PhD
Co-founder & CSO of Element AI and Imagia; Co-founder of Chapados Couture Capital and ApSTAT Technologies Inc.

Nicolas Chapados holds an engineering degree from McGill University and a PhD in Computer Sciences from University of Montreal, Canada. While still writing his thesis and jointly with his advisor Yoshua Bengio, he co-founded ApSTAT Technologies in 2001, a Machine Learning technology transfer firm, to apply cutting-edge academic research ideas to areas such as insurance risk evaluation, supply chain planning, business forecasting, national defense and hedge fund management. From this work, he also co-founded spin-off companies: Imagia, to detect and quantify cancer early with AI analysis of medical images; Element AI, to help organizations plan and implement their AI transformation; and Chapados Couture Capital, a quantitative asset manager. He holds the Chartered Financial Analyst (CFA) designation.

Deep Learning Revolution

"Machine performance matches or exceeds humans on selected tasks"

DL

Deep Learning Revolution

O.I: Could you please introduce yourself to our readers?

Nicolas Chapados: I have a computer engineering degree from McGill University, Canada, and started my career in a corporate speech recognition research group within the now-defunct telecommunications equipment manufacturer Nortel. That gave me a taste of pattern recognition and Machine Learning (ML), and sparked my desire to pursue this in more depth. I went back to school to complete MSc and PhD studies in Machine Learning with Prof. Yoshua Bengio at University of Montreal. My research interests have been broad, and a recurring theme is time series modeling applied to several areas (e.g. finance, retail planning). Large portions of the motivation for research came from applications that I would come in contact with through a ML technology-transfer consultancy that I co-founded, along with Prof. Bengio and two of his then-students, in 2001. From this work emerged three startups, all headquartered in Montreal: Imagia, to apply cutting-edge Artificial Intelligence (AI) to the detection and diagnosis of cancer using medical images and other modalities; Element AI, to help large organizations plan and implement an AI transformation; and Chapados Couture Capital, a boutique asset management firm.

O.I: Over the recent years, you have become a recognized expert in Artificial Intelligence. What appealed to you in the idea of Machine Learning?

N.C: Machine Learning, and particularly Deep Learning, has become in the past decade the most successful path to AI. This is in large part due to the core ability of learning algorithms to absorb large amounts of data in order to carry out a task, with very little human specification of the minutiae of how to do so. In contrast, prior generations of rule-based AI systems would require extensive "knowledge engineering" to extract rules from human experts, a long and brittle process. Concurrently, we witnessed the extraordinary rise of enabling factors, such as cheap high-performance computing enabled by graphics processing units (GPUs) and the large amounts of data required to train ML models, being assembled by the "Big Data" initiatives within organizations. These, together, mean that we can now train ML models in many areas, ranging from image classification to game playing, where machine performance matches or exceeds humans on selected tasks. The appeal of ML, for me, was that after initially gaining expertise in "old-fashioned AI" and understanding how much work it could be to get a system to work poorly, ML made AI appear to become so easy!

> "... the ultimate hope is for AI to help make more accurate, more repeatable, and more cost-effective decisions at every step in a patient's journey"

O.I: After developing applications for Finance, you recently focused on applying these algorithms to healthcare. What encouraged you in that direction? What are your hopes for AI in the medical field? What benefits could it bring?

N.C: The startup I co-founded, Imagia, specializes in applying AI techniques to cancer detection and diagnosis. Around 2014, my co-founder and I were witnessing spectacular progress in Deep Learning techniques applied to computer vision — at the same time, a close family member of my co-founder was waging a very personal battle against cancer. Having both an entrepreneurial nature, and realizing that no modern AI technique was at that point applied clinically to cancer care, we decided to launch Imagia. Although we are far from that goal, the ultimate hope is for AI to help make more accurate, more repeatable, and more cost-effective decisions at every step in a patient's journey, from prevention and screening, to diagnosis, treatment planning and follow-up. An improvement to any of these steps can help drive better outcomes for patients, but improvements across all of them would mean a complete transformation of current healthcare practice.

O.I: In a TV show, a Deep Learning application you developed for the lung nodule detection was presented as more efficient than expert radiologists in case of subtle pathologies, but also as a potential predictor of the disease progression. Could you explain us how Deep Learning makes it possible?

N.C: In the case of solid tumors appearing on medical scans such as CTs and MRIs, Deep Learning captures imaging patterns that are related to the concept of radiomics, wherein subtle visual features such as shape appearance and texture heterogeneity are predictive of tumor characteristics, such as the presence of given mutations, or overall patient response to treatment and survival.

> “... the machine will amplify the radiologist’s abilities rather than squarely replace him or her”

Many of these features are too weak for the human eye to quantify reliably, but by putting together thousands of such features, trained across potentially millions of scans, a machine can produce a reliable model. That said, we firmly believe that the machine will amplify the radiologist’s abilities rather than squarely replace him or her: a model’s behavior remains limited to the extent of its training set, and still requires a radiologist to understand special conditions and exceptional cases.

O.I: Would you like to present us other applications?

N.C: In healthcare, Imagia is developing a real-time colon polyp characterization model that can be used within colonoscopy procedures. This model can visually inspect video frames that contain polyps, and immediately inform the gastroenterologist whether a given polyp appears to be benign or malignant with an accuracy that matches the best humans at that task.

O.I: What are the limitations? What is still missing?

N.C: A subject that has been a recent concern for the ML community is known as “adversarial examples”, which are specially-designed cases that are designed to fool the predictions made by a well-trained model. In the past year, this problem has attracted lots of research attention to enhance model robustness to these adversarial situations. More broadly, it remains a challenge to understand why a model behaved in one way rather than in another, as well as to convey to a user the operational boundaries in which the model can be expected to work well versus see its performance degrade – these “explainability” questions remain a fertile ground for applied research.

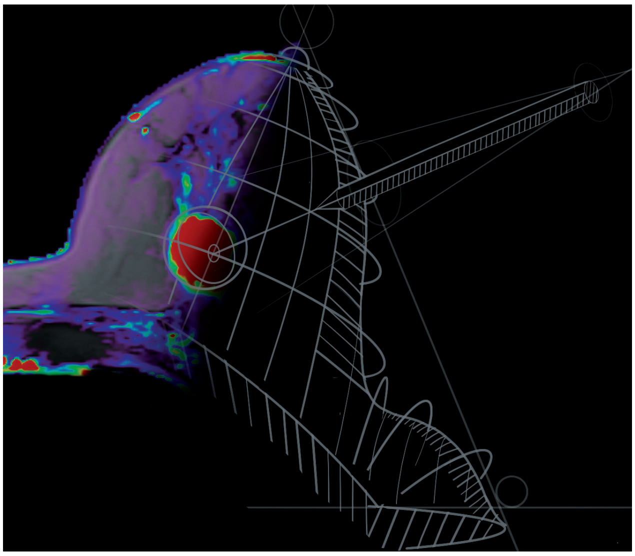
O.I: Could you tell us more about your mentors? How did your interaction with Pr. Yoshua Bengio change the course of your professional path?

N.C: A Yoshua is not just a mentor and business partner, but after more than 20 years of collaborating together, also a good friend. He truly is an inspiring force of nature, relentless in his pursuit of scientific understanding, but also seeing to its beneficial impacts on society. As an advisor, at least for me, he made the choice to trust my abilities as a student, along a wide freedom to explore crazy ideas – this means that many of those ideas would fail (because a student is not yet very good at filtering out bad ideas early), but it also means that I then learned to filter out bad ideas, and became a better researcher. This, along with his unrelenting support, set me on my current path, and I am immensely grateful not only for this, but for the improbable rise of a unique concentration of talent and the emergence of a diverse AI ecosystem in Montreal, in major part thanks to Yoshua’s leadership.

OleaImagein DIGEST: BREAST MRI

Breast cancer is the most commonly diagnosed cancer in women. In her lifetime, one in eight women (12%) will be diagnosed with breast cancer [1].

Breast MRI is a useful tool for the detection, characterization and assessment of local extent of the disease, evaluation of treatment response and guidance for biopsy and localization. MRI findings should be correlated with clinical history, physical examination, mammography results and any other prior breast imaging [2,3].



Investigators from Department of Radiology and College of Medicine at St. Mary's Hospital, Seoul, Korea, highlighted **associations of both perfusion parameters and ADC values with breast cancers histopathologic prognostic factors and immunohistochemical subtypes [4].**

This retrospective study was performed on 52 patients diagnosed with invasive ductal carcinoma, examined with a pre-operative MR protocol including T1-w, T1-postcontrast, T2-w, DCE and DWI sequences. Olea Sphere® was used for DCE post-processing. Perfusion parameters were computed with T1 mapping: Ktrans, Kep and Ve based on extended Tofts model, while AUC on the concentration time curve. A VOI was drawn on the whole tumor area for histogram analysis, and a ROI in the tumor at the highest Ktrans values. In parallel, ADC map was calculated; averaging over the whole tumor volume, histogram analysis and ROIs drawing at the lowest ADC value were performed. Finally, histopathologic information was collected, including axillary lymph node metastases, histologic grade, tumor size and biomarkers – ER, PR, Ki67, HER2 – characterizing tumor subtypes.

Three associations were found between some prognostic factors and the combination of perfusion and ADC parameters: median Ve was higher in PR positive tumors; AUC was higher in larger tumor sizes; ADC was positively correlated to HER2 status. Therefore, MR perfusion or ADC parameters could be used to predict the response to treatment in breast cancer patients, though a prospective study with a consistent design would be required in a large homogeneous tumor group to confirm these findings.

4. Lee HS, Kim SH, Kang BJ, Baek JE, Song BJ. Perfusion Parameters in Dynamic Contrast-enhanced MRI and Apparent Diffusion Coefficient Value in Diffusion-weighted MRI: Association with Prognostic Factors in Breast Cancer. Academic Radiology. 2016; 23(4):446-456.

Investigators from Department of Radiology and Research at Severance Hospital, Seoul, Korea, searched for associations between MR perfusion parameters and prognosis in triple-negative **breast cancer (TNBC): Ve, peak enhancement and tumor size were independent predictors of disease-specific survival outcome [5].**

Sixty-one patients with TNBC underwent breast MRI protocol – including T2-w, DWI and DCE, before surgical treatment and histologic analysis. DCE post-processing was achieved with Olea Sphere®. Kinetic parameters — signal enhancement ratio (SER) and peak enhancement (PE) — were computed using signal intensity time curve, and perfusion parameters — Ktrans, Kep and Ve — using extended Tofts model. Tumor segmentation was performed using a semi-automated region-growing segmentation method on the contrast-enhancing portion of the perfusion series, and was automatically propagated on all computed maps.

After undergoing definitive surgery, patients were followed up every 6 months (median total time = 46.1 months) to determine survival outcome: disease-free survival (DFS) – time between diagnosis and first evidence of recurrence or contralateral breast cancer; and disease-specific survival (DSS) – time between diagnosis and death from breast cancer.

Among the post-treatment measurements, larger tumor size at surgery and presence of axillary node metastasis were associated with both worse DFS and DSS. Among the pre-treatment measurements, larger MR tumor size was the only variable to be associated with worse DFS, while higher Ve, higher PE and larger MR tumor size were correlated with worse DSS. Perfusion and kinetic parameters may then have the potential to aid in evidence-based clinical decision support for patients with TNBC.

5. Park VY, Kim EK, Kim MJ, Yoon JH, Moon HJ. Perfusion Parameters on Breast Dynamic Contrast Enhanced MRI Are Associated With Disease-Specific Survival in Patients With Triple-Negative Breast Cancer. AJR Am J Roentgenol. 2017 Mar;208(3):687-694.

Investigators from Department of Radiology of Bernard and Irene Schwartz Center for Biomedical Imaging, and from Center for Advanced Imaging Innovation and Research, New York University School of Medicine, New York, USA, investigated the feasibility of using **simultaneous PET/MRI:** the combination of high **DCE-MRI** specificity and high FDG-PET sensitivity may **aid in the prediction of breast tumor aggressiveness and metastatic activity [6].**

The study was conducted on 12 newly-diagnosed breast cancer patients, who underwent breast and whole-body PET/MRI after a clinical PET/CT. DCE-parametric maps were computed in Olea Sphere® – Ktrans, Kep and Vp maps using the extended Tofts model, and AUC using concentration time curve. ROIs were drawn within the tumors on AUC superimposed on T1-postcontrast, and were automatically propagated on all computed maps. After co-registration between PET and MRI data, PET standard uptake values (SUV) were measured in the same ROIs chosen for DCE-MRI analysis, in addition to metabolic data (tumor volume and lesion glycolysis). Finally, prognostic factors from tumor pathology and immunohistochemistry were available for each patient, such as HER2, ER, PR and Ki67; and information regarding metastatic burden (none/local versus systemic/distant metastasis) was assessed from whole-body PET/MR and PET/CT scans, surgical pathology and biopsy results.

The authors reported several correlations: Kep was found statistically lower in the tumors of patients with systemic metastases compared to local disease; the metastatic burden correlated positively with Ktrans and SUV; Ki67 positive tumors had a statistically greater Ktrans compared to the negative ones; negative correlation could be highlighted between tumor volume and either Ktrans or Kep.

These findings may suggest possible clustering of patients by metastatic burden using a combination of Kep and tumor volume, and by Ki67 status using Ktrans and tumor volume. Studies on larger cohort may further demonstrate the utility of PET/MRI for breast tumor aggressiveness characterization.

6. Margolis NE, Moy L, Sigmund EE, Freed M, McKellop J, Melsaether AN, Kim SG. Assessment of Aggressiveness of Breast Cancer Using Simultaneous 18F-FDG-PET and DCE-MRI: Preliminary Observation. Clin Nucl Med. 2016 Aug;41(8):e355-61.

Additional resources:

- Togashi K. Diffusion in breast application. Olea Imagein, Issue#2, p.26.
- Jalaguier-Coudray A. The future of breast imaging. Olea Imagein, Issue#3, p.7.
- Le Bihan D. Signature index. Olea Imagein, Issue#4, p.7.

1. http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics
2. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA et al. ACR BIRADS ATLAS. Breast imaging reporting and data system. ACR American College of Radiology; 2013.
3. Mann RM, Kuhl CK, Kinkel K, Boetes C. Breast MRI: Guidelines from the European Society of Breast Imaging. Eur Radiol. 2008 Jul;18(7):1307–18.

Investigators from Università degli Studi di Milano, IRCCS Policlinico San Donato, Olea Medical and Vital Italian distributor, Italy, conducted a study on patients with invasive **breast cancer**, highlighting **correlations between DCE-derived parameters and pathological prognostic factors [7].**

DCE-MRI sequences, acquired in addition to T2-w and DWI on 25 patients with invasive breast cancer, were retrospectively reviewed by two independent radiologists. DCE perfusion parameters – TME, Peak, PE and Curve washout — were computed using Olea Sphere® software. Semi-automatic tumor volume segmentation was performed after subtracting pre-contrast and second contrast-enhanced phases. This volume was then propagated on DCE maps. Wash-in and wash-out types were also established. These results were compared with the histopathological findings of the patients after surgery.

Several significant correlations were revealed between DCE-MRI parameters and pathological prognosis: mean Peak with pathological tumor stage (pT); mean PE with HER2 overexpression and pT; percentage of voxels (fast or slow) PE with pT and axillary nodal stage (pN). In summary, DCE-MRI voxel-wise enhancement parameters in invasive breast cancers were shown to correlate with HER2, pT and pN.

7. Trimboli RM, Codari M, Khouri Chalouhi K, Ioan I, Lo Bue G, Ottini A, Casolino D, Carbonaro LA, Sardanelli F. Correlation between voxel-wise enhancement parameters on DCE-MRI and pathological prognostic factors in invasive breast cancers. Radiol Med. 2018 Feb;123(2):91-97.

Glossary

ER: estrogen receptor
PR: progesterone receptor
HER2: human epidermal growth factor receptor-2
Ki67: proliferation factor
DWI: diffusion-weighted imaging
ADC: apparent diffusion coefficient
DCE: dynamic contrast-enhanced
Ktrans: transfer constant between blood plasma and the interstitial space
Kep: transfer constant from the interstitial space to the blood plasma
Ve: interstitial space volume fraction
Vp: plasmatic volume fraction
AUC: area under the curve
TME: time to maximum enhancement – the time needed for the contrast agent to reach its maximum concentration
Peak: the maximal concentration of contrast agent over time
PE: Peak enhancement – percentage of increase of the initial up-slope of the signal intensity time curve
Curve washout: percentage of the down-slope of the signal intensity time curve
SER: signal enhancement ratio of the signal intensity time curve
Wash-in type: classification of the initial signal increase of the pixel intensity curve based on peak enhancement value (slow, medium, rapid)
Wash-out type: classification of the post initial signal course of the pixel intensity curve based on curve washout value (persistent, plateau, washout)
ROI: region of interest
VOI: volume of interest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56th Annual Meeting
Vancouver, Canada

June 16-21
International Society
for Magnetic Resonance in Medicine
(ISMRM)
26th Annual Meeting
Paris, France

October 12-15
Journées Françaises de Radiologie (JFR)
Paris, France

November 25-30
Radiological Society
of North America (RSNA)
Chicago, USA

Word scramble

C	O	E	Y	S	N	O	I	T	A	L	U	G	E	R
I	N	A	V	Z	W	C	K	N	V	L	C	N	V	F
N	B	I	G	D	A	T	A	H	C	Q	X	I	X	J
T	Q	U	U	Z	R	P	A	T	P	J	S	T	H	X
E	I	K	G	Y	T	O	G	K	F	S	X	N	W	A
L	T	Z	W	A	I	P	F	H	Q	B	Q	I	X	S
L	R	C	G	R	F	L	I	Y	M	B	C	R	J	N
I	V	L	N	I	I	N	M	R	E	K	W	P	Y	J
G	E	A	I	E	C	R	E	U	U	X	D	R	T	U
E	G	U	N	Z	I	R	C	W	S	H	C	E	J	U
N	R	T	R	H	A	U	F	F	G	S	B	G	E	O
C	E	R	A	M	L	P	K	Y	U	X	Y	N	T	P
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D	B	A	F	S	C	I	M	O	E	G	A	M	I	A

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- INTELLIGENCE
- MACHINE
- DEEP
- LEARNING
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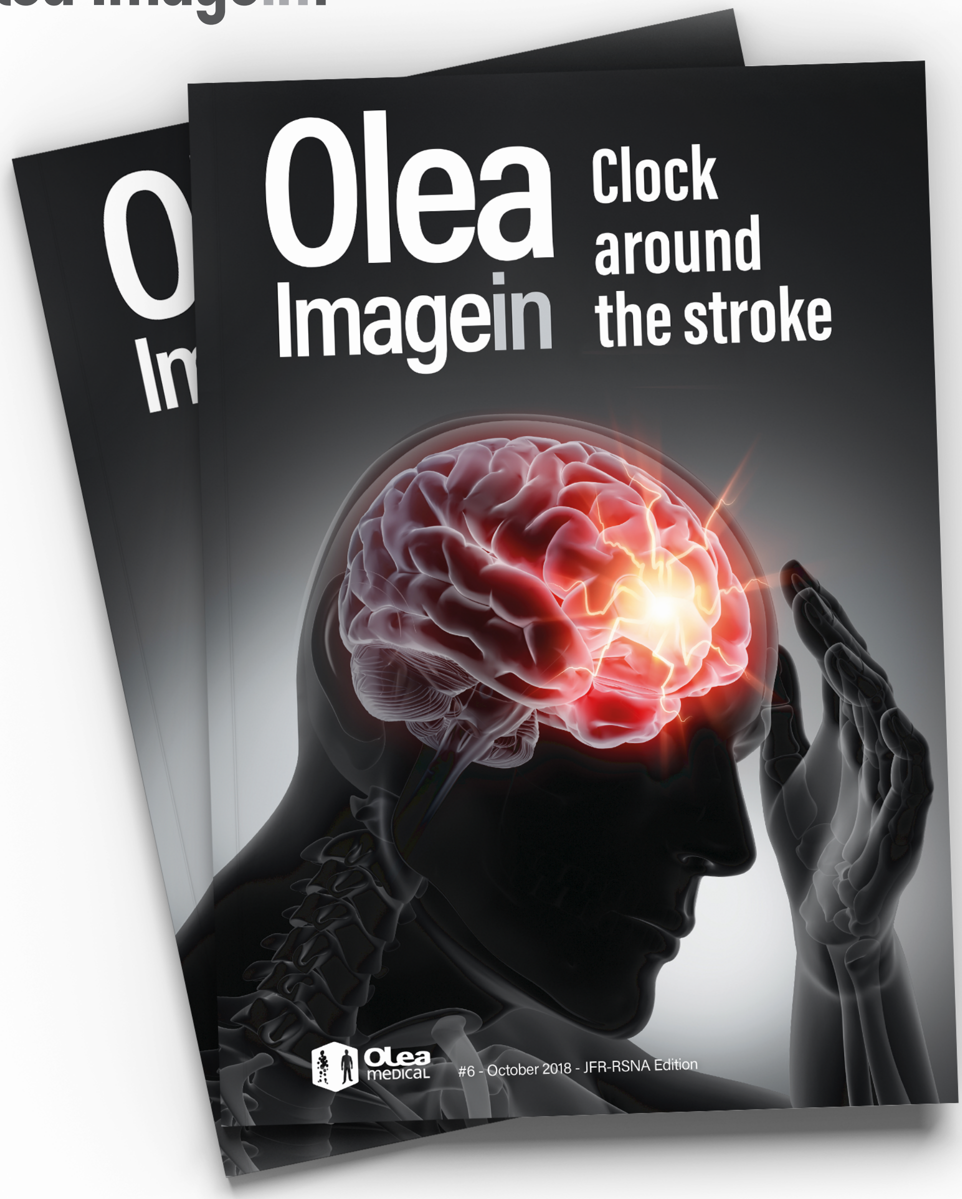

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