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FONDAZIONE
GHISLIERI

Progetto "Progressi in Biologia e Medicina"

22° corso di formazione avanzata

Artificial Intelligence
in Biologia e Medicina

8-10 maggio 2024

A cura di CarloAlberto Redi

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Prefazione

Negli ultimi anni l'intelligenza artificiale (AI) e le tecnologie ad essa collegate hanno compiuto un'accelerazione dirompente: addestrate sulla base di monumentali quantità di dati (sempre aggiornati all'ultimo minuto da letteratura scientifica, giornali, libri, blog, film, arte, etc) e grazie ad algoritmi di apprendimento automatico/elaborazione del linguaggio naturale sono state in grado di generare risposte su domande specifiche.

Il CRDU della Fondazione Ghislieri, per propria vocazione istituzionale, dedica il 22° corso di formazione avanzata ("AI in Biologia e Medicina") ad una dettagliata prospettiva del ruolo dell'AI nelle ricerche in Biologia e nelle relative applicazioni in Medicina.

Ingegneri delle macchine e sviluppatori di algoritmi introdurranno ai concetti di base così da permettere ai partecipanti una piena comprensione degli avanzamenti scientifici presentati nel corso delle giornate di studio senza tralasciare una necessaria riflessione filosofica ed etica: al termine delle giornate infatti i prof. Maurizio Ferraris, Marco Annoni e Giuseppe Remuzzi svolgeranno riflessioni per definire le condizioni al contorno dell'impiego di AI nella nostra vita di ricerca in laboratorio e ospedale.

Il corso intende porre in termini di riflessione critica il sempre più pervasivo utilizzo delle tecniche di AI: ad esempio, evidente il vantaggio per la previsione della struttura e delle proprietà di proteine complesse nella progettazione di nuovi farmaci, nella diagnostica per immagini, per la stadiazione tumorale, per la scoperta di nuovi biomarcatori, per la diagnosi e il trattamento precoce di malattie complesse, per la personalizzazione delle terapie ed altre risposte ottenute grazie all'analisi di grandi quantità di dati clinici. Ma va sempre considerato che ora la risposta diagnostica non è più basata su un albero di decisioni costruito su "semplici" inferenze logiche del tipo "if – then". È basata sulla costruzione di reti neurali i cui "neuroni" sono collegati da connessioni "pesate"; la rete neurale apprende dai dati forniti e regola il peso delle connessioni in base agli esempi forniti ed analizzati. E dunque in quali termini e con quale grado di probabilità è possibile accettare/validare l'esito diagnostico offerto dall'AI e tutte le risposte ottenute!? Non va dimenticato che sebbene AI "batta" l'umano in alcune operazioni (classificazione di immagini e *visual reasoning* tra tutte) ancora stenta rispetto all'umano in altre (competizione matematica ad alto livello e pianificazione gestionale tra tutte). Il progresso in AI avanza però in termini sorprendenti: pensiamo al lancio delle applicazioni da AlphaDev (per rendere più efficiente l'ordinamento degli algoritmi) o da GNoME (che in scienza dei materiali ne facilita la scoperta).

Ad oggi ci confrontiamo con un *pappagallo stocastico*... ma domani!?

Dobbiamo prepararci, ecco il 22° corso!

CarloAlberto Redi

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1

AI, il pappagallo stocastico… e la Biologia

CarloAlbertto Redi
Accademico dei Lincei, Presidente Comitato Etica Fondazione Umberto Veronesi,
Presidente del Comitato Scientifico del'area di Biologia e Medicina del Centro per la Ricerca e la Didattica Universitaria del Collegio Ghislieri; Dipartimento di Biologia e Biotecnologie Lazzaro Spallanzani, Università degli Studi di Pavia

Negli ultimi anni l'intelligenza artificiale (AI) e le tecnologie ad essa collegate hanno compiuto un'accelerazione dirompente: addestrate sulla base di monumentali quantità di dati (sempre aggiornati all'ultimo minuto da letteratura scientifica, giornali, libri, blog, film, arte, etc.) e grazie ad algoritmi di apprendimento automatico/elaborazione del linguaggio naturale sono state in grado di generare risposte su domande specifiche. È ora il momento per una riflessione sulle tante e rivoluzionarie ricadute dell'AI sul *mondo umano* (quello delle sue relazioni sociali e affettive, del lavoro, della produzione letteraria, degli effetti sull'economia, per non dire dell'indagine scientifica e delle ricadute in ambito sanitario e delle terapie e solo per citarne alcune senza dimenticare la possibilità di generare nostre immagini in contesti… esoterici!) e su quello del pianeta Terra (gestione risorse, controllo crisi ambientale, capacità predittive, pandemie, etc.).

Il CRDU della Fondazione Ghislieri, per propria vocazione istituzionale, dedica il 22° corso di formazione avanzata ("AI in Biologia e Medicina") ad una dettagliata prospettiva del ruolo dell'AI nelle ricerche in Biologia e nelle relative applicazioni in Medicina (scoperta di farmaci, diagnostica, stadiazione chemioterapica, etc). Non va infatti dimenticata la velocità di trasformazione delle app di AI divenuta travolgente senza che noi si sia in grado di conoscere come vengono costruite e allenate *per quale fine* mentre ne facciamo un uso sempre più frenetico (già nel febbraio 2023 sia Microsoft sia Google combinarono diversi chatbots con funzioni di ricerca… entrambi tentativi andati a vuoto, sia Bing Chat sia Bard… ma in continuo miglioramento; Bard ora è allenato da GEMINI (Google GPT-4)).

Ingegneri delle macchine e sviluppatori di algoritmi introdurranno ai concetti di base così da permettere ai partecipanti una piena comprensione degli avanzamenti scientifici presentati nel corso delle giornate di studio senza tralasciare una necessaria riflessione filosofica ed etica: al termine delle giornate infatti i prof. Maurizio Ferraris, Cinzia Caporale e Giuseppe Remuzzi svolgeranno riflessioni per definire le condizioni al contorno dell'impiego di AI nella nostra vita in laboratorio e ospedale. In particolare l'ultimo seminario richiamerà l'attenzione sul nostro comun denominatore, la scrittura di articoli scientifici. Grazie all'introduzione di agenti di AI il paradigma della scrittura di un articolo scientifico è totalmente cambiato. Il

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vantaggio più evidente è quello della raccolta dati (resa molto veloce) e della scrittura delle parti di un lavoro sperimentale ritenute “noiose” (M & M in primis) (resa ben più snella). Il rischio (svantaggio) è quello sia della creazione-invenzione di referenze bibliografiche apparentemente molto credibili sia della convincente scrittura a sostegno dei preconcetti degli autori. Ma è tutto lo spirito del corso a voler porre in termini di riflessione critica il nostro utilizzo delle tecniche di AI: ad esempio, evidente il vantaggio per la previsione della struttura e delle proprietà di proteine complesse nella progettazione di nuovi farmaci, nella diagnostica per immagini, per la stadiazione tumorale, per la scoperta di nuovi biomarcatori, per la diagnosi e il trattamento precoce di malattie complesse, per la personalizzazione delle terapie ed altre risposte ottenute grazie all’analisi di grandi quantità di dati clinici. Ma va sempre considerato che ora la risposta diagnostica non è più basata su un albero di decisioni costruito su “semplici” inferenze logiche del tipo “if – then”. È basata sulla costruzione di reti neurali i cui “neuroni” sono collegati da connessioni “pesate”; la rete neurale apprende dai dati forniti e regola il peso delle connessioni in base agli esempi forniti ed analizzati. E dunque in quali termini e con quale grado di probabilità è possibile accettare/validare l’esito diagnostico offerto dall’AI e tutte le risposte ottenute!?

Il dubbio deve essere sempre presente, ad oggi siamo dinnanzi ad un *pappagallo stocastico* che ci sta parlando sulla base dell’istruzione ricevuta!

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The Artificial Microscope. A microscope in the machine for an advanced perspective in biology and medicine

Alberto Diaspro

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Optical microscopy demonstrated an incredible power and ability in producing large data set originated from biological samples by light interrogation and tunable in terms of spatial at temporal resolution down to the nano- and pico- scale, respectively. Such a data set is the core for developing an artificial microscope aiming to transform a label-free interrogation of the sample into a molecular-rich fluorescence-based image. The intelligent artificial microscope is AI-guided through a computational core based on three modules based on a convolutional neural network (CNN) and a tensor independent component analysis (tICA) un-supervised machine learning within a supervised deep learning strategy having the ambitious target to create a robust virtual environment “to see “what we could not perceive before”. An interesting case study is related to understanding the visualisation of chromatin organisation.

A Microscope in the machine

Modern optical microscopes, from super-resolved fluorescence to label-free mechanisms of contrast, are powerful instruments able to produce images that are rich sources of molecular information towards an unprecedented insight into the morphological and functional properties of biological cells at the nanoscale. Super resolved fluorescence microscopy (19, incorporating photochemical parameters from brightness to lifetime, and non-linear approaches, like those associated with multi-photon excitation able to exploit intrinsic fluorescence and SHG/THG, is coupled to label-free polarisation methods like Mueller matrix microscopy (2), expanding the available data set. It is worth noting that today super-resolved fluorescence microscopy can provide 1Angstrom localization precision of fluorescent molecules at room temperature and an atmospheric pressure of fluorescent molecules (3, 4). So far, we are in the realm of multimodal optical microscopy boosted by artificial intelligence that makes intelligent the microscope (5). We aim to develop a microscope in the machine able to transform label-free imaging into molecular-rich images without the need to label the biological cells.

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The AI approach

Data generator

The first module of the AI architecture for the intelligent microscope has the dual purpose of predicting a fluorescence image from a label-free image, learning the specificity given by fluorescent proteins and improving the contrast of the label-free image, and it facilitates the acquisition of a multimodal dataset since multiple fluorescence images can be predicted and constructed from a single label-free image without the need to label the sample and deal with photobleaching and photodamage issues. The architecture is represented in Figure 1. It is a convolutional neural network in which the input is a label-free image while the output is a single fluorescence image. The first part of the network is an encoder that compresses the information and learns the features. In contrast, the second part is a decoder to reconstruct an image starting from the encoder representation. The case study is related to chromatin organization in the cell nucleus as function of potential cancer progression (6).

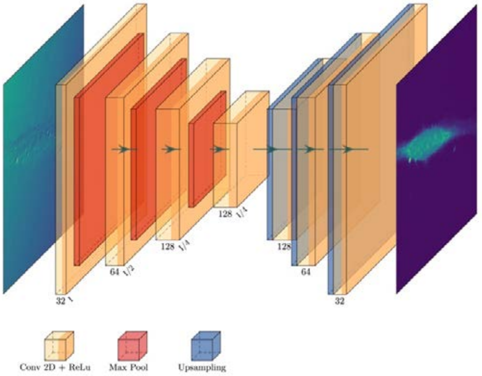

Fig. 1 - *Neural Network architecture. Credit: Lisa Cuneo, DiasproLab, IIT.* The example images for the training are acquired by means of a confocal microscope (Nikon A1r MP, Nikon) are HeLa cells nuclei stained with Hoechst 33342 for fluorescence and imaged by differential interference contrast (DIC) as label-free. Instruments, Yokohama, Japan). Training was preliminary carried out over 100 epochs, on 1700 images, with the MSE as a loss. An example of the prediction is shown in Figure 2.

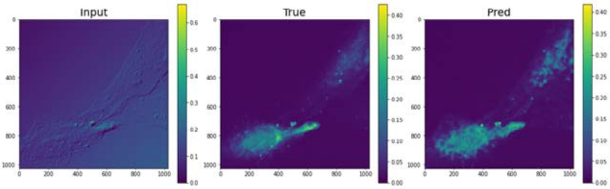

Fig. 2 - Example of prediction, the pixel size is 76.5nm. . Credit: Lisa Cuneo, DiasproLab, IIT.

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tICA

In general, the multimodal microscope produces a large amount of data coming from the different light-sample interactions that need to be structured. Therefore, the second module aims to merge data coming from different mechanisms of contrast (1, 2). The aim is to realise an approach able to automatically find patterns of related changes and discover common features across multiple modalities. We would like to infer the same spatial patterns across modalities from these features. In this way will be possible to fuse information across several contrast mechanisms. Mathematically, the problem of representation is finding a projection of the data distribution that leads to some sort of 'intrinsic' coordinate system in which the data structure is most apparent. The idea is to use Independent Component Analysis (ICA), a model for finding meaningful, spatially-independent components in an unsupervised setting, in a tensor way (7), in order to infer the same spatial patterns across modalities and therefore to fuse information. The multimodal data is modelled as a sum of components (Figure 3), each of which con be expressed as the tensor product of one spatial map ($n = 1,\ldots,voxel$), one subject-course ($r = 1,\ldots,R$) and one modality-course ($t = 1,\ldots,T$)

$$\boldsymbol{Y}_{n,t,r} = \textstyle\sum_{i=1}^{L} \boldsymbol{X}_{n,i} \boldsymbol{W}_{t,i} \boldsymbol{H}_{i,r} + \varepsilon_{n,t,r} \, (1)$$

where:

$\boldsymbol{X}_{n,i}$ are the spatial maps on n voxel for component i, each component i has a single spatial map for all modalities;

$\boldsymbol{W}_{t,i}$ are the modality weightings for component i in modality t, tells which modality t uses to look into a specific component (and so into a spatial maps);

$\boldsymbol{H}_{i,r}$ are the weights for component i in subject r, form a link between the different modalities, and it is the appropriate place to look in order to find out which modalities are driving a particular component;

$\varepsilon_{n,t,r}$ is the noise, i.e., everything can not be explained with the previous decomposition.

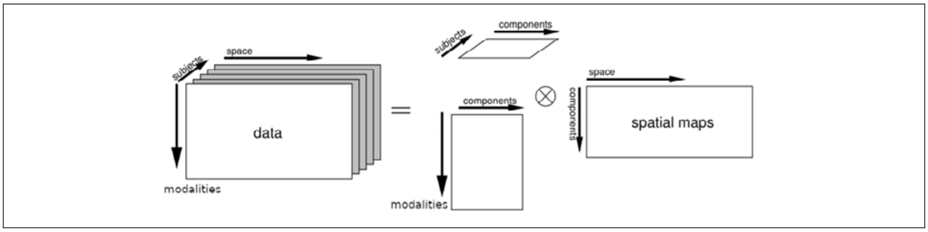

Fig. 3 - tensor ICA.

Fate prediction

The last module is responsible for leveraging the parameters obtained from tICA to predict in a supervised manner whether a cell, imaged through various different contrast methods, is healthy or diseased. The advantage of the use of the tICA is that it is easy to understand which mode is most responsible for the prediction for each sample.

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Conclusions

The artificial microscope aims to produce a new way of forming images in a “liquid” and tunable way (8) towards a better understanding structure and function relationships in biological cells. The ambitious target is to remove the need to use contrast agents when examining living cells with the perspective of performing real-time biopsies using label-free data. The growth of interest and the increased number of AI approaches (9) are encouraging and also suggest that this represents an important and challenging step for computational imaging at the molecular level. We are ready for a new expedition in the nanoworld towards applications in biology and medicine (10). The Artificial Microscope can provide investigation instruments for a new way of forming and using images of living systems.

Fig. 4 - A new instrument for forming new images. Credit: S.Spielberg, “The Fablemans” (2022).

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3

AI in medicine and biology: an introduction

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Artificial Intelligence (AI) refers to a diverse set of technologies that allow machines to display human-like capabilities such as reasoning, learning, planning and creativity. AI devices perceive their environment, deal with what they perceive, solve problems and act to achieve a specific goal. AI has a relatively long history, dating back to the 50s' (1, 2). Rather interestingly medicine has always been one of the areas of potential application, given the combination of interest for society and related conceptual challenges linked to diagnosis, prognosis, and therapy planning. In late '70s the raise of expert systems has coincided with the implementation of several prototypes for supporting diagnosis, such as Mycin (3), for assisting researchers with causal reasoning, such as ABEL (4), and finally for therapy planning, such as Oncocin (5). At the same time, some of the AI researchers were interested in scientific discovery and hypothesis formation. The project Dendral (6) was designed to support organic chemists in identifying unknown organic molecules, by mass spectra analysis and basic knowledge of chemistry. Also in Biology, early expert systems have been designed to support molecular biology experiments, such as MOLGEN (7). Early approaches suffered from several limitations related to the need to explicitly represent knowledge and reasoning mechanisms of human reasoning and the lack of computational resources (8). The most notable problem is the so-called "knowledge acquisition bottleneck": domain knowledge is costly to be elicited, and very hard to maintain over time. With the dusk of expert systems, there was the dawn of data science and machine learningI, an area of AI that deals with learning decision rules directly from data. Three concurrent factors enabled machine learning: first the exponential increase of available digital data, favored by the Internet and by the development of new experimental technologies, such as for example DNA microarrays and DNA-seq (9); second, the increase of computational power and storage capability; finally, the development of new algorithms, able to fully exploit the potentials of data arriving at an unprecedented pace and the corresponding increase in the speed of computation (10). It may be noted that a crucial factor has been the development of Graphical Processing Units (GPUs) (11), first exploited by the gaming industry.

The machine learning paradigm that took the lead is called "statistical learning". A target function dependent on a set of unknown parameters is "learned" from data by estimating the unknown parameters based on a set of available observations (training data). The more data are observed, the more complex functions can be learned. Traditionally, machine learning is classified in three different areas:

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1) Supervised learning. The target function describes the relationships of an outcome (output) variable with to some input data (features). An example is learning a rule to classify if a patient has signs of coronary disease from the analysis of a set of features derived from imaging and from clinical data. Each data point needs to be labeled with a ground truth (i.e. the true value of the outcome: the y^* of the function to be learned, $y=f(x)$), since the function is learned by observing the relationships between inputs and outputs.
2) Unsupervised learning. The target function is a criterion to find naturally occurring groups in unlabeled data. An example is to find clusters of patients with the same disease based on their molecular profile of a target tissue, say a biopsy, without knowing in advance what disease they actually have
3) Reinforcement learning. In this case the target function is a policy, i.e. a set of actions that an (artificial) agent should perform based on data that are dynamically collected by the agent through acting and receiving a corresponding reward. An example is given by a robot exploring an unknown space and receiving rewards or penalties during exploration, i.e. directions where movements are bringing the robot closer to the target and some others where movements are actually taking the robot farther away from the desired destination; the best strategy to move in the space is learned by interacting directly with the environment, in an iterative fashion, and improving the strategy, i.e. "learning", leveraging the feedback received (i.e. reward or penalty) at every step.

Machine learning has been strongly boosted by one of its subfields, called deep learning (12). Deep learning is based on computational architectures that repeatedly transform digital data, which can be structured data, images, or text, into a series of "latent" data sets by mathematical functions that are suited for a specific purpose, i.e. for example supervised learning. One of the most successful deep learning architectures is called "convolutional neural network", and it has been used to classify images or other data with intrinsic correlation structure (13). A lot of efforts have been devoted to analyzing textual content, by a set of methods called "natural language processing". Rather interestingly, deep learning architectures have been used also in this domain, with great results in the applications related to automated translation and text summarization. In 2017 a novel deep learning architecture, called transformer (14), based on a method known as "attention" has allowed to increase parallelization and enlarge the computational models used to process the data, making it feasible to learn functions with billions or even trillions of parameters and thus needing terabytes of data to be successfully trained. These models, and specifically those focusing on natural language, are called Large Language Models (LLMs). They are typically trained with a process called "semi-supervised learning" (15). Given for example a textual input, each token, i.e. words or its subparts, can be predicted given all the remaining words. This strategy is particularly effective for sequences (such as texts or aminoacidic series), but can be generalized to other types of data. LLMs, thanks to semi-supervised learning, model the joint probability distribution of all input elements, and can be thus used to generate items drawing them from the space of all input elements, according (i.e. sampling) to the underlying joint probability distribution. Popular tools, such as ChatGPT, are

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based on these types of models (16). In recent times, based on the LLM principles and the attention mechanism, several large models specialized on specific targets or domains have been proposed. They are called Foundation Models (FM) (17). The ambition of FMs is to support users in dealing with tasks related to their data (such as classification, regression, query answering, disease registry filling from textual notes, text summarization, …) almost without retraining the model or with very few data, respectively known as zero-shot and few-shot learning. FMs specialized in medicine, such as Meditron (18) from EPFL and Gatotron (19) from University of Florida, hold the promise to support many clinical tasks. Applications may include different goals ranging from descriptive to diagnostic, and from predictive to prescriptive. The snapshot of FDA approved AI-based medical devices released on October 2023 (20) shows that radiology is the field currently counting most of the registered AI-embedding medical device products. However, it can be easily forecasted that FMs will be soon included in tools to improve "productivity" in virtually any clinical setting.

Biology and Biotechnology are dealing with the flood of AI applications, too. The need of combining machine learning with knowledge accumulated in ontologies and knowledge repositories (such as Gene Ontology, String, Switch) (21) is pushing towards the implementation of novel strategies, such as graph neural networks (22, 23). In this area, the knowledge available on the domain is merged with data to hypothesize biological functions, forecast expected behaviors and plan novel experiments. A noteworthy implementation of attention and transformer architectures is represented by Alphafold (24), an AI system developed by Google DeepMind that predicts a protein's 3D structure from its amino acid sequence.

The complexity of LLMs and FMs has several potential drawbacks (17). First of all, these models are extremely expensive to be trained and quite expensive to be run. Clinicians and researchers need large computational facilities to fully exploit them. Moreover, only some LLMs are open source, while many of them require subscriptions. These has implications related to the concentration of knowledge (and power) in the hands of few providers and strong impact also from a sustainability viewpoint. Second, many models can be hardly "explained", both in terms of expected behavior, design principles and output interpretability (25). Finally, most part of the generative AI approaches still must be refined in order to guarantee the safety of the output. They require huge amounts of data that are difficult to collect and with a data quality that is not easy to be checked, let alone to be enforced.

For these reasons, EU has recently approved a regulation, known as AI act (26), which puts strong requirements to AI products requiring conformance checking and approval before being put on the European market. The main principle is related to the risk assessment of the final product and the fulfilling of requirements related to such risk classification. At the same time, many researchers are working on the definition of methods and tools to increase the trustworthiness of AI-based systems, following the guidelines on trustworthy AI published in 2019 (27). Such guidelines include checking explainability, reliability and fairness of AI tools.

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4

Robotics for the general surgeon

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When a procedure is called “robotic,” it does not indicate that a robot is really doing the work. Instead, it refers to surgical procedures in which doctors use robots to guide their actions. One or more robotic arms may be used in robotic surgical systems, which doctors can operate remotely and accurately from a console nearby. A laparoscope is attached to one of the robot arms. Small surgical tools may be carried in the other arms by the surgeons. The surgeon is able to see the tumor in three dimensions thanks to a computer screen. Each robotic arm is controlled by a joystick similar to that used in video games, which replicates the movements of the wrist and hand and provides dexterity.

In comparison to conventional laparoscopic or minimally invasive surgery, robotic devices are believed to have superior dexterity and range of motion. Surgeons may now operate on sections of the body that were previously inaccessible and get a better look at otherwise difficult-to-see areas. Minimally invasive operations often involve robots. Small incisions are used in these procedures, as the name suggests. Less discomfort, less bleeding, shorter hospital stays, and faster recovery periods are all common benefits of this approach.

Preoperative planning, surgical navigation, and surgical assistance may all be supported by a variety of computer-assisted surgical systems. An RAS device is a form of computer-aided surgical system that uses robots. A range of surgical procedures may be performed with RAS devices, which let the surgeon to employ computer and software technology to control and move surgical tools via one or more small incisions in the patient’s body (minimally invasive).

Some of the advantages of a RAS device may include its capacity to aid minimally invasive surgery and help with complicated tasks in restricted regions. In reality, the machine is not a robot since it cannot carry out surgery without direct human intervention.

In the right hands and with the right training, robotic surgery may be a safe and effective tool for completing specific surgeries. It is the goal of the FDA to ensure that devices are safe and effective for their intended use. Ensure manufacturers provide proper training for both new and seasoned users of RAS devices. Medical device training and education are not regulated or accredited by the FDA since they are not part of the agency’s purview. It is up to companies like pharmaceutical companies, doctors’ offices, and health care institutions to come up with and execute effective training programs. Specialty certification organizations and professional

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societies may also help to establish and fund training programs for its members' doctors of certain specialties.

In terms of medical technology, robotic surgery is nothing new. Many hospitals are still reluctant to use robots for patients because of the high expenses, human resources, and lack of competence required.

The future of robotic surgery, on the other hand, shows a quick growth towards precise and least invasive versions of fundamental surgery. Post-op infections and other problems linked with typical open procedures will also be less common in patients who have had minimally invasive surgery. Robotic surgery is expected to be combined with other cutting-edge technology in the future. Surgeons' job may be made easier with the aid of artificial intelligence in the medical industry.

Experts anticipate that the integration of AI and machine learning algorithms into robotic surgery will play a more prominent role in the future. These technologies can assist in real-time decision-making, improve surgical planning and enhance the precision of robotic procedures.

For example, surgical margins play a large part in achieving favorable ontological outcomes. Normally, surgeons rely on intraoperative frozen-section pathology to determine the status, which takes time and impedes operating room efficiency. But with machine learning and advancements in spectroscopy, surgeons could start providing real-time SM assessment.

Though we may look to the future, robotic surgery will not be able to take the position of human doctors anytime soon. Robotic systems, in their most basic, are here to augment human abilities and improve post-operative results.

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5

From Digital Models to Digital Twins: Scientific Machine Learning for Personalised Medicine

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Computational medicine represents a formidable generator of mathematical problems and numerical methods that enable a deeper understanding of human physiology and provide crucial support to physicians for more accurate diagnoses, optimized therapies, and patient-specific surgical interventions.

The inherent difficulties associated with the multiphysics and multiscale nature of the problems at hand, data uncertainty, inter- and intra-patient variability, and the curse of dimensionality, can be overcome thanks to the development of accurate, physics-based models empowered with data-driven artificial intelligence algorithms.

In this presentation, we will show how *the iHEART simulator*, an integrated model of the human heart function, enables us to achieve these objectives for the first time, and discuss its future developments. We will also discuss about the difference between digital models and (the far more challenging) digital twins.

From a more technical standpoint, the lecture will revolve around the phase of problem setting and problem solving. Problem setting is a critical precursor to problem solving. It involves the art of formulating the right problem statement.

The importance of this phase is underscored by the fact that without a well-defined problem, finding the right tools and techniques for problem solution becomes a cumbersome and often futile endeavour.

This transition from problem setting to problem solving is integral to the larger paradigm of knowledge development. While AI tools have made tremendous strides in recent years, they remain dependent on the foundation laid by human intelligence.

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6

Intelligenza Artificiale Generativa in Medicina

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L'applicazione dell'Intelligenza Artificiale in Medicina potrà avere un impatto tanto maggiore quanto sono prioritari i bisogni clinici dei pazienti che contribuirà a soddisfare.

In termini di sfide primarie per il miglioramento della salute e dell'aspettativa di vita degli individui, le malattie rare rappresentano un'emergenza sanitaria. Si tratta di patologie con un'incidenza di meno di 6 casi su 100.000 persone all'anno. Tuttavia, benché rare, il 25% dei pazienti con una diagnosi di tumore rientra in questa categoria, e ciascuna di queste patologie include una quota significativa di pazienti con bisogni assistenziali e terapeutici non soddisfatti. I tumori rari presentano limitazioni significative allo sviluppo di innovazioni cliniche come ampia eterogeneità clinica e biologica tra diversi pazienti, disponibilità limitata di dati e mancanza di evidenze cliniche robuste per le decisioni terapeutiche. C'è un urgente bisogno di definire nuove soluzioni per migliorare la diagnosi e la gestione dei pazienti. Per queste ragioni, lo studio dei tumori rari può essere considerato un prototipo in cui misurare l'impatto clinico di tecnologie basate sull'Intelligenza Artificiale (AI).

In Humanitas - dove da anni esiste un AI Center fortemente integrato con le attività cliniche dell'IRCCS Istituto Clinico Humanitas, con l'Ateneo internazionale Humanitas University e il Centro di Ricerca – adottiamo un approccio all'AI indirizzato da precise domande cliniche. Sono infatti le necessità dei pazienti e dei medici a guidare la realizzazione di strumenti e metodi innovativi di analisi dei dati. Gli strumenti di AI che nascono dalla collaborazione tra clinici, ricercatori, ingegneri e data scientist in Humanitas hanno due caratteristiche fondamentali: sono completamente spiegabili e intellegibili, ovvero tutte le figure coinvolte nel processo clinico decisionale e i pazienti hanno chiara visibilità delle motivazioni per cui, ad esempio, un algoritmo indica una prognosi in un paziente e su questa base suggerisce l'opportunità di una precisa scelta di trattamento; inoltre, sono validati in modo robusto su grandi numeri di pazienti, con percorsi ispirati ai criteri di validazione dei farmaci utilizzati da parte delle agenzie regolatorie. In sintesi, ogni algoritmo creato, per poter essere utilizzato in modo affidabile nel contesto clinico, deve dimostrare di essere robusto, utile e riproducibile. Lo scopo finale è fornire al medico un supporto concreto nelle decisioni cliniche, consentendogli di analizzare molte più informazioni rispetto a quelle disponibili fino a poco tempo fa, e che egli stesso potrebbe conoscere e gestire individualmente.

L'AI non è mai, dunque, un sostituto del medico, ma un aiuto per curare sempre

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meglio in un mondo molto complesso. Nell'epoca della genomica, infatti, tenere conto di tutti i fattori per prendere decisioni cliniche è una grande sfida. L'integrazione di tecnologie innovative rappresenta un percorso virtuoso verso un modello di Medicina personalizzata per tutti i pazienti che consenta una migliore sostenibilità del sistema sanitario.

Un altro aspetto fondamentale della ricerca in ambito AI è il perimetro etico, ovvero tutti i progetti e le iniziative devono agirea secondo gli standard di privacy e di qualità europei, che rappresentano la migliore risposta ai timori legati all'uso dell'AI.

Nell'ambito dei tumori rari, alcuni esempi di soluzioni basate sull'AI sviluppate per un uso clinico includono una piattaforma innovativa per la diagnosi e la prognosi dei tumori del sangue, basata sulla caratterizzazione genomica del singolo paziente; un algoritmo che assiste il medico nella fase di diagnosi, in particolare nell'interpretazione più precisa sospette lesioni tumorali; un sistema di supporto decisionale (Clinical Decision Support System) basato sul profilo genomico del paziente, che determina l'idoneità e il tempo ottimale per il trapianto di cellule staminali nelle malattie ematologiche rare.

Negli ultimi anni ha avuto uno sviluppo esplosivo un particolare tipo di AI, quella generativa (famosa soprattutto grazie allo sviluppo dei moderni chatbot, come ChatGPT), che mostra un'enorme potenzialità di applicazione anche in ambito sanitario. In Humanitas abbiamo sviluppato tecnologie di AI che consentono di generare "gemelli digitali": dati statisticamente identici a quelli reali di partenza (dati tabulari, testuali, di immagini o alfanumerici), però con un livello di privacy elevato perché non esistono nella realtà. I "gemelli digitali" contengono tutto il valore clinico e biologico dei pazienti reali e possono essere utilizzati per accelerare la Ricerca, ad esempio per ridurre i costi e i tempi di uno studio clinico, consentendo una più rapida validazione di un trattamento innovativo, soprattutto in ambiti di malattie rare o di particolare necessità terapeutica per i pazienti.

L'AI può essere un grande alleato nello sviluppo di programmi di Medicina personalizzata e di terapie innovative. È un alleato per i medici, che attraverso di essa possono disporre di uno strumento in grado di migliorare la qualità della propria attività, ed è un alleato dei pazienti come grande acceleratore del processo di innovazione nell'assistenza e nella cura. La validazione clinica degli strumenti, la trasparenza e l'interpretabilità dei risultati, oltre all'utilizzo della tecnologia secondo principi etici, rappresentano per la comunità scientifica e clinica la guida per uno sviluppo e un uso corretto dell'AI nel contesto sanitario.

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7

Intelligenza naturale e intelligenza artificiale

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Cercherò dunque di capire che cos’è l’intelligenza naturale attraverso il confronto con il suo presunto corrispettivo, l’intelligenza artificiale. Dico “presunto” perché, come vedremo, non c’è una vera continuità tra le due intelligenze (tanto per cominciare, quella artificiale non può davvero essere considerata una intelligenza), ma semplicemente una analogia.

Dopo aver cercato di dar forma alla intelligenza artificiale verrò alla intelligenza naturale, che riceve una fisionomia più netta proprio attraverso il confronto (e il contrasto) con l’intelligenza artificiale. L’idea di fondo è che la tecnologia possieda una funzione rivelativa, nella quale la protesi funge da amplificatore del naturale.

Conosciamo meglio le nostre dotazioni naturali quando le mettiamo in rapporto con dei supplementi artificiali che non necessariamente (anzi, quasi mai) ci assomigliano; leggere, scrivere e far di conto ci dicono molto su che cos’è l’intelligenza naturale, e non c’è nulla di sorprendente nel fatto che, per continuità o differenza, l’intelligenza artificiale risulti altamente rivelativa di quella naturale.

Questo però non avviene perché l’intelligenza artificiale non assomiglia a quella naturale. Malgrado l’uso di espressioni che richiamano una continuità (dallo stesso nome di “intelligenza” al ricorso alle reti *neurali*, all’uso di un vocabolario psicologico per descrivere il funzionamento dei computer), tra un computer e la mente c’è la stessa prossimità che tra la mano e la matita.

Ma come la matita rivela alcune possibilità della mano, così l’intelligenza artificiale fa emergere, per contrasto, i caratteri dell’intelligenza naturale che, come vedremo, si riassumono in due caratteri fondamentali: il fatto di essere una mente incarnata, cioè parte di un corpo, per un verso; e il fatto di essere una mente attrezzata, ossia sistematicamente collegata con supplementi tecnici (attrezzi, macchine, abitazioni, abiti…).

La nostra mente è, insieme, una mente incarnata (è parte di un corpo e ne emerge) e una mente attrezzata (si avvale sistematicamente di attrezzi e, più tardi, di macchine, sicché l’intelligenza artificiale è parte del destino della intelligenza naturale), il che significa che l’umano non sarà mai assimilabile a un meccanismo, che non ha un corpo, ma è per propria natura orientato verso la tecnica, che è definitoria della natura umana allo stesso titolo della componente organica.

Di lì verrò a una definizione dell’umano come “animale politecnico”, ossia come un organismo assimilabile a qualunque altro vivente, che però si distingue in quanto, diversamente da qualunque altro organismo, è sistematicamente collegato con dei meccanismi, dal fuoco alla ruota alla intelligenza artificiale.

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8

Artificial Intelligence in protein structure prediction and design

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At the molecular level, proteins are the key players in everything that happens in a living organism. Proteins perform structural functions by providing the skeleton of a cell, are used to send messages as hormones, perform chemical reactions of all kinds, for example to digest food and produce energy, generate movement, attack external organisms, regulate the homeostasis of a cell, just to name a few. Consequently, studying proteins means studying the basic functional blocks of life. Not surprisingly, a large number of genetic diseases are associated with protein mutations. But how do proteins accomplish their many tasks? They are polymers made up of a combination of 20 amino acids with lengths ranging from a few to thousands. These polymer chains can self-assemble into intricate 3D structures that are most often associated with protein function. However, a non-negligible fraction of proteins can perform a function without adopting a specific 3D structure. Proteins can perform their function alone or in combination with other proteins or molecules that regulate them (1).

From this brief introduction, it should be clear that knowing the structure of a protein is an important step in understanding its function. In addition, knowing how to determine structures may make it possible to design proteins that perform desired functions. The structure of a protein is, at least in principle, the result solely of its sequence of amino acids, in the same way that the meaning of a sentence should be deducible from the ordered list of letters (including spaces) that make it up, one needs to find the rules to get that meaning, that is, one needs to learn the language. This is the goal of protein structure prediction. Is not the whole story, that is, that protein structure prediction does not care about how the protein adopts this structure, that is, the sequence of events by which the polymer folds into it (2).

What is the structure of a protein? The structure of a protein is generally considered to be hierarchical. The sequence of 20 amino acids is reported as a sequence of 20 letters. Locally, the sequence can adopt a secondary structure, i.e. it can form helical turns, linear strands, or loops. These local elements can then associate with other elements to form what is called tertiary structure. The tertiary structure is usually the first layer in which protein function can emerge. When a protein combines more than one tertiary structure elements into more complex forms, we speak of super-tertiary structure, while when more than one protein combine, we speak of

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quaternary structure. As mentioned in the first paragraph, all of this goes together with amino acid sequences that lack any ordered structure. These intrinsically disordered regions or proteins can be part of proteins with structure or can be found as independent proteins (3).

The problem of protein structure prediction can then be seen either as a statistical learning problem, i.e., how to learn the pattern of amino acids and associate them with the resulting structure, or as a physicochemical problem, i.e., given the laws of physics and chemistry, how to use them to see the emergence of protein structure from sequence. In general, the first approach is the one that has been successful in addressing the problem. But what have been the key ingredients to determine a protein structure?

1) Patterns that associate the chemical properties of amino acids with local sequences where they are directly associated with secondary structure elements. These are not uniquely defined, but some trends are easy to recognize. Examples include (hydrophobic-hydrophobic-hydrophobic-polar)$_n$ for helices and (hydrophobic-polar)$_n$ for linear strands.
2) Comparison of structure and sequence allowed to postulate that protein structure is more conserved in evolution than protein sequence, and that consequently when two proteins have very similar sequences they are very likely to have the same structure.
3) Correlated mutations across species can be interpreted as a measure of spatial proximity in protein structure (coevolutionary analysis). This allows, in principle, to infer the structure of a protein from statistical analysis of sequence variation when many homologous sequences are available (2).

This, together with 50 years of high quality protein structure deposition in the Protein Data Bank (3), the 250 million protein sequences collected by UniProt (4), the increase in computing power of graphics cards, and technical developments in machine learning techniques, among others, have led to the development of AlphaFold2 (5), RosettaFold (6), and more recently RosettaFold All Atom (7), which represent the state of the art and probably the most important success of the application of artificial intelligence to science (8). But what about the inverse problem? Will it lead to a biotechnological revolution based on protein design (9)? Is artificial intelligence the future for a theoretical approach to biology (10)?

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9

Artificial Intelligence for Drug Discovery

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In this seminar, I will begin by outlining the intricate steps and processes involved in the discovery of small molecule drugs. Specifically, I will illustrate how computational methods play a pivotal role in supporting each stage of drug discovery, ranging from hit identification to lead generation and optimization.

Within this framework, I will delve into the transformative impact of artificial intelligence (AI) on these processes for the design and optimization of novel inhibitors. We will explore how AI serves as a powerful tool to expedite various aspects of small molecule design, including structure generation, enhancement of potency against the target, and optimization of drug-like properties.

Furthermore, I will present compelling case studies and representative examples to elucidate how AI-driven approaches are significantly accelerating computational efforts in the quest for discovering new drugs. These examples will underscore the tangible benefits and potential applications of integrating AI into drug discovery pipelines.

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10

The role of AI in the Pharma industry and in Medical Imaging

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Established in 1927, the Bracco Group is a key player in the field of diagnostic imaging, focusing on pioneering innovations to improve lives. Central to Bracco's mission is a strong commitment to research and development (R&D), aiming to create practical solutions rooted in human needs.

Bracco conducts its research activities across specialized centers worldwide located in Italy, Switzerland, US, UK, Germany and China. The current research programs of Bracco R&D in radiology revolve around the development of new contrast agents for medical imaging such as the recently marketed Gadopiclenol, a contrast agent for magnetic resonance with an unprecedented efficacy and safety profile. Another example is the BR55 contrast agent for contrast enhanced ultrasound imaging, a molecular imaging agent that targets angiogenesis offering unparalleled insights into disease progression. Moreover, again exploiting the ultrasound technology, Bracco is investigating the use of microbubbles for therapeutic applications promising new avenues for treatment. In nuclear medicine, Bracco with its affiliate company Blue Earth diagnostics, is working on the PSMA technology for prostate cancer diagnosis and treatment. Bracco has also programs in the medical device field including interventional cardiology and intraoperative diagnostics. In interventional diagnostics Bracco is creating an offer that combines state-of-the-art imaging technology with fluorescence targeted agents to empower surgical oncologists with unparalleled precision, revolutionizing tumor localization and resection. Process Innovation is another key area for Bracco R&D, by optimizing manufacturing processes and embracing sustainability, Bracco paves the way for a greener, more efficient future.

In summary, the activities of Bracco R&D include a variety of fields from drug discovery to manufacturing optimization and medical devices development. Consequently the range of applications of Artificial Intelligence (AI) in Bracco is very wide.

The branch of AI that everybody speaks about today is indeed Machine Learning (ML) that revolves around the concept of enabling machines to learn from data (training), identify patterns (learning), and make decisions about new data (inference or prediction). In the pharmaceutical industry ML is used for several tasks regarding both R&D and other business activities such as new drugs development,

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clinical trials optimization, supply chain optimization, manufacturing and quality control, predictive analytics for marketing and market access and personalized medicine (1, 2).

Bracco develops and sell contrast agents that are meant to enhance and create contrast in medical images to support the diagnosis and characterization of diseases. Because of that, Bracco is currently working to develop new products to support our customers, the Radiologists, in their daily work and to get the most out of contrast agents by applying ML to medical images.

The current revolution in AI revolves around the theory of representation. Representation in machine learning is pivotal as it pertains to how input data is represented for the algorithms to process effectively. Traditionally ML used features crafted based on domain knowledge, understanding of the problem, and insights about the data. In the domain of drug design, for example, molecular descriptors are used to provide ML a numerical representation of several aspects of molecules (3, 4). Another example of crafted features are those used for the analysis of biomedical images based on first and second-order statistics and on the analysis of images texture (5).

The current AI revolution has been started by a key idea that was firstly proposed in the field of computer vision based on Convolutional Neural Networks (CNN): learned representation. CNNs represent a significant milestone in the field of machine learning and computer vision, serving as one of the earliest examples of learned representation. CNNs are specifically designed to automatically learn hierarchical representations of data directly from images without the need for handcrafted features (6). CNNs marked the dawn of deep learning by enabling automated feature extraction from raw data, revolutionizing the field of AI. Since the dawn of deep learning the paradigm of AI has shifted from the idea of designing better features to the idea of designing AI systems with more *capacity* that informally represent the ability to learn a vast amount of patterns from data (7). The revolution of AI run rapidly since the introduction of CNN in the late '90 (8). In 2018 the proposal of a new AI architecture called *transformers* (9) paved the road for the current second revolution in AI leading to the development of Natural Language Processing (NLP) tools such as Generative Pre-trained Transformer (GPT). GPT-X models have been released year after year with an increasing number of parameters, raising the performance bar to an unprecedented level in the field of conversational AI, surpassing even the expectations of its creators. Transformers also revolutionized the field of bioinformatics, in fact, the *transformers* technology is at the base of Alphafold, a computer system that can predict 3D structure of proteins starting from their amino acids sequence (10), which value for drug development has still to be fully understood and exploited (11).

The emergence of deep learning centered around learned representation brings significant advancements, but also presents notable challenges. These include substantial data requirements compared to traditional techniques that are related to considerable costs of development and the opacity of black-box models leading to complex models validation. For instance, GPT-4, the latest iteration in the GPT chatbot series, boasts a staggering 1.7 trillion parameters, consuming approximately 6.8 ter-

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abytes of memory. To put this into perspective, in 1994, Bill Gates famously depicted himself standing atop a towering stack of paper, holding a compact disc containing an equivalent amount of information. Yet, the stack representing GPT-4’s memory usage would soar a remarkable 10,000 times higher. The huge data demand to train such a huge system led to high hardware and energy costs quantifiable in $100 million as stated by Sam Altman, the CEO of OpenAI. These statistics underscore the evolving landscape of AI research, posing challenges to the traditional role of academia (12). Academic laboratories often lack the necessary hardware and resources to engage in such research, rendering it unfeasible (13). This reality extends beyond NLP applications; the recent achievements of Alphafold by DeepMind (Google) in predicting protein folding, have been surely facilitated by the extensive resources provided by Google to the large team of engineers involved in the project (14).

Luckily enough, the use of ML is not limited to cutting-edge technology requiring such investment to be competitive. Simpler machine learning methods are successfully used in several applications for the pharmaceutical industry among which Quantitative Structure Activity Relationships (QSAR) is a notable example. QSAR objective is to establish mathematical models that correlate the chemical structure of molecules with their biological activity or other properties of interest (i.e. toxicity, efficacy and others). QSAR makes use of handcrafted features to describe molecular structure and simple models to model the relationship between this features and the property of interest. QSAR models, are not based on the learned representation paradigm and are far more transparent than those typical of deep learning but, despite that, they must be used carefully when used to predict the property of unknown molecules. ML models in fact learns patterns only from data that are presented during training and, at inference time, when a new molecule is presented to the model, the learned patterns are used to predict its properties. In turn, these properties are used to take decisions without any external information about the reliability of the prediction. In the QSAR field, the problem of assessing the reliability of a prediction about a new compound is called the Applicability Domain problem. The Application Domain is informally defined as “the response and chemical structure space in which the model makes predictions with a given reliability” (15). This problem of predictions reliability is particularly exacerbated when QSAR models are used for regulatory purposes (16).

The notion of the Application Domain may seem ambiguous, yet it underscores a fundamental issue well-recognized also in medical diagnosis. Diagnostic test performance is gauged by various parameters, with sensitivity and specificity being the most common. Sensitivity denotes the test’s ability to detect pathology, while specificity reflects its capacity to identify healthy individuals. The actual performance of a test depends on the real-world scenarios in which the test is applied. If a test that is biased towards labeling individuals as ’sick’ exhibiting high sensitivity but low specificity, may be considered optimal in some scenarios depending on the disease prevalence and on the clinical practice. These concepts extends to AI tools designed to work with radiological images. Diagnostic tools are developed using patient data from hospitals, necessitating multi-centric studies to mitigate biases associated with specific institutions. These studies typically involve one hospital for tool creation

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and validation (internal set), another for performance testing (external set), and prospective validation to address time-related data drift (prospective set). Ensuring that the test's performance is validated on a population representative of the target population and real worlds scenarios helps avoid hospital-related biases and temporal data drift.

AI tools in radiology often employ CNN-derived architectures, renowned for their efficacy but lacking transparency and explainability. While strides have been made in this regard, transparency remains a challenge. To provide a more accurate assessment of model performance, leading scientific works in AI for radiology advocate for comprehensive testing across internal, external, and prospective datasets (17).

Although AI systems may lack transparency, trust among radiologists has grown steadily. Recognizing AI's potential to relieve radiologists of repetitive tasks and maintain consistent performance throughout the day, the radiology community sees opportunities for improved patient care and more effective management of complex cases. Recent studies support the idea that integrating AI into radiology workflows can benefit patients, radiologists, and healthcare systems (18).

Examples from Bracco R&D

In the study titled "AIforCOVID: Predicting the clinical outcomes in patients with COVID-19 applying AI to chest-X-rays12. An Italian multicentre study." (19) researchers explore the use of artificial intelligence (AI) to predict clinical outcomes in COVID-19 patients based on chest X-rays (CXR) and clinical data. Given the strain on healthcare systems during the pandemic, effective triage methods are crucial. The study investigates three approaches: handcrafted features, hybrid models combining CNN-extracted features with clinical data, and end-to-end deep learning. The dataset comprises 820 COVID-19 patients from six Italian hospitals, including CXR images and clinical attributes. Promising results indicate that combining CXR features with clinical data can aid patient management and resource allocation. In conclusion, AI models leveraging CXR and clinical information hold potential for effective COVID-19 patient management.

"Amplifying the Effects of Contrast Agents on Magnetic Resonance Images Using a Deep Learning Method Trained on Synthetic Data" (20) discusses a novel approach to enhancing contrast in diagnostic magnetic resonance (MR) images using artificial intelligence (AI). The method involves training a neural network on synthetic data sets to predict image contrast at higher doses of contrast agents (CAs) than those typically used in clinical practice. By virtually doubling the CA dose, the network generates "virtual double-dose" images that improve lesion visibility and detection. The study validates this approach using preclinical and clinical data, demonstrating significant advantages in detecting small brain lesions. Overall, the technique holds promise for enhancing diagnostic power in MR imaging.

"Exploring the limitations of MR virtual contrast enhancement in gliomas and meningiomas: can AI replace GBCAs?" (21) investigates the potential of artificial intelligence (AI) to predict contrast enhancement in brain tumours from non-con-

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trast magnetic resonance imaging (MRI). Using a deep convolutional neural network (dCNN), the researchers trained the model to generate post-contrast images from pre-contrast images for gliomas and meningiomas. Results show a decline in performance with increasing glioma grade, while meningiomas posed significant challenges, especially in lesion detection. The study suggests that while AI-based virtual contrast methods show promise for no- or low-enhancing lesions, they are limited in tumours with higher contrast uptake.

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11

AI per la selezione di oociti competenti allo sviluppo

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L’infertilità viene definita come il mancato raggiungimento della gravidanza dopo 12 mesi o più di rapporti sessuali regolari non protetti mentre con sub fertilità si intende un ritardo nel raggiungimento della gravidanza. Entrambe le condizioni comportano significativi disagi sia personali che sociali.

Esistono numerosi fattori causativi di infertilità femminile ma, estremamente determinanti, risultano essere le alterazioni a carico degli ovociti antrali allo stadio di vescicola germinale (GV) che possono influenzare fortemente la bontà del gamete femminile stesso. Gli oociti antrali risiedono nei follicoli ovarici pre-ovulatori della maggior parte dei mammiferi costituendo la riserva ovarica iniziale, ma anche non rinnovabile, della donna. Si dividono in due popolazioni caratterizzate da una diversa configurazione assunta dalla eterocromatina (visualizzabile solo previa colorazione con un intercalante la doppia elica di DNA, ad es. DAPI) a livello nucleolare in oociti SN (Surrounded Nucleolus) e NSN (Not Surrounded Nucleolus). Questa differenza riflette la loro diversa capacità di supportare un prospettico sviluppo embrionale: mentre gli oociti SN (l’80% circa dell’intera popolazione antrale), in seguito a maturazione e fecondazione, sono potenzialmente in grado di dividersi sino a blastocisti, gli NSN, inspiegabilmente, si arrestano allo stadio di 4 cellule.

Tra le alterazioni sopra citate, la causa più comune di una scarsa qualità oocitaria è il naturale invecchiamento ma, nelle giovani donne, può dipendere anche da patologie come la sindrome dell’ovaio policistico, alterazioni dell’apparato riproduttivo, endometriosi, fibromi uterini, infezioni, disfunzioni ormonali, mutazioni genetiche e danni alla struttura del DNA. Non solo, fattori comportamentali, tra cui l’uso di tabacco, il consumo di alcol e droga, diete non equilibrate, disturbi alimentari ad esse associate, ansia, depressione, sedentarietà o esercizio fisico eccessivo possono avere un impatto fortemente negativo sulla fisiologia degli oociti (1-3). Queste condizioni possono indurre apoptosi delle cellule della granulosa dell’ovaio con conseguente riduzione dell’apporto di nutrienti e fattori essenziali per la maturazione degli oociti allo stadio di metafase II (4). Da qui la necessità, nei percorsi di fecondazione assistita, di isolare e maturare in vitro oociti immaturi allo stadio di GV. Poiché solo gli SN sono competenti allo sviluppo embrionale, si è reso necessario

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mettere a punto una metodica, non invasiva e basata su intelligenza artificiale (AI), per riconoscere i due tipi di oociti senza colorarne il nucleolo.

Utilizzando un pool di 183 immagini in DAPI e contrasto di fase è stato possibile istruire il software di AI a discriminare in modo corretto le due popolazioni di oociti antrali con una accuratezza pari al 90% (5). In particolare, è stato utilizzato il software di microscopia cellSensTM v3.2 di Olympus, che ha la capacità di addestrare modelli di AI usando reti neurali convoluzionali basate su l'architettura U-Net [6]. Grazie ad un programma commerciale per la creazione di contenuti grafici, sono state dipinte con due colori diversi le aree vicine al nucleolo di 116 immagini considerate di "addestramento" (in cui l'assegnazione in SN e NSN era stata precedentemente fatta utilizzando DAPI). In verde è stata colorata la regione nucleolare degli oociti SN e in rosso quella degli NSN. Il colore grigio è stato utilizzato per discriminare il background dell'immagine. Dopo aver addestrato il software a riconoscere le specifiche delle aree verdi e rosse, 12 immagini in contrasto di fase sono state usate per la convalida e 55 per testare il software in modalità *blind*. Il modello di AI così allenato è stato in grado di discriminare gli oociti di tipo SN e NSN producendo pixel di colore verde per gli oociti di tipo SN e rosso per gli NSN nella zona nucleolare con una alta affidabilità (Figura 1).

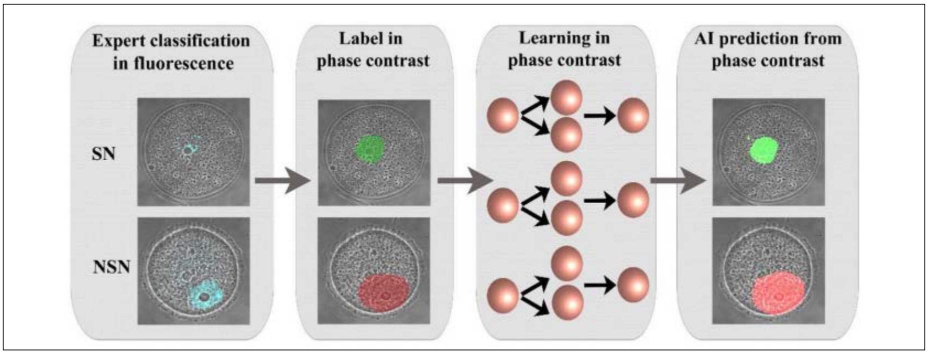

Fig. 1

I risultati riportati dimostrano che è possibile sviluppare un modello di intelligenza artificiale in grado di riconoscere i diversi tipi di oociti antrali avendo a disposizione solo un'immagine a contrasto di fase e senza utilizzare colorazioni invasive. Questa metodica può dunque essere utilizzata durante le procedure di fecondazione in vitro in cui le immagini di oociti e embrioni catturate dai più moderni incubatori multicamera possono essere impiegate dal software di AI per individuare i migliori gameti in grado di innalzare le rese di maturazione fecondazione di almeno il 30%.

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12

Fundamentals of Radiomics and Machine Learning in Medical Images

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Radiomics (1) applied to clinics, is a research field that aims to extract quantitative mathematical "features" from medical images, through one or more algorithms that make use of statistical and physical basic principles, and a subsequent analysis by means of artificial intelligence (AI) algorithms. The results can be used to improve and/or support a clinical decision, as well as to unravel disease characteristics that are difficult to be identified by simple human vision (2-4). These lectures have the purpose to present the basic principles of what is now known as full radiomic analysis process, that goes from features extraction (the original "Radiomics") until AI methods, e.g. Machine Learning (ML), Deep Learning (DL) and Neural Network (NN) approaches, which through a specific "model" correlate such features to the pathology characteristics, development and care (5-7). In particular, the analysis of Computed Tomography and Magnetic Resonance Imaging data sets will be presented (8, 9).

The main concepts involved in image acquisition, filtering and reconstruction, manual and semiautomated segmentation, class of features, features extraction, stability and robustness, data analysis and models adequate for clinical purposes, will be introduced; it is worth reminding that for each step, the underlying bio-medical, statistical and physical topics have, in principle, to be faced, with the objective of understanding the rationale of the whole data collection and analysis, thus i.e. moving to explainable-AI. The protocol and data interpretation will be presented for each step of the radiomic pathway, putting in evidence the currently unsolved problems, like e.g. low statistics, data filtering, independence of different features and feature classes, and so on. A special discussion will be addressed to correlate the features obtained in commercial codes (like e.g. shape, first, second and higher order ones, satisfying the IBSI standards) to skewness, kurtosis, texture features, wavelets, Laplacian transforms, and so on.

The influence of different imager apparatuses and their internal software codes will be, as well, shortly discussed, putting in evidence the role of the spatial resolution, the use of the contrast agents, the peak voltage, the X-ray tube current, and the convolution kernel (applied for image reconstruction). As one of the most relevant challenges, the problem of data harmonization among different centers, in terms of data collection and radiomic analysis, will be shortly introduced, and

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possible applications of ML/DL/NN to help and improve the whole automation process will be sketched. As a matter of fact, the use of ML algorithms is an interesting strategy to possibly overcome the limitations of pure radiomic features calculations, especially if the data sources (imagers) are more than one. Among these methods, NN are algorithms capable to approximate the non-linear relationship between the input data and the outputs, that the analytical functions cannot represent. Using such approaches, it is possible to implement and refine a ML model capable to predict, after a supervised or an unsupervised training procedure, the parameters associated with a specific input experimental fingerprint. Hence, NN can be applied to learn the tissue properties in a rapid and computationally efficient way. The radiomics quality score concept (3, 10) will be also finally presented.

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13

Opportunities and limitations of AI use in hematological diagnosis and therapy

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In the last few years, especially with the introduction of Large Language Models (LLM), there have been significant leaps in both the visibility and especially the usability of AI in this world. This is true, of course with specific prerequisites for patient and data protection, in medicine as well. Here, a very wide variety of projects are possible and could make a significant disruption: from diagnostics to specific therapy, precision medicine, to the writing of reports and also for integrated reports and letters. Also, in education and in research, there are very many possibilities for the application of AI.

For hematology, both the diagnostic areas, from phenotype to genotype to the genome, but especially the increasingly complex algorithms for therapy selection and recommendation, up to post-treatment monitoring (MRD) should be mentioned. Also, for any communication in medicine and any paperwork excellent opportunities are given (1-6).

It is time to rapidly polish all this, taking into account the necessary considerations, including the data protection regulations of the respective country and, for example, the AI Act of the EU, Use may be within the framework of various research projects/pilot trials, but also for any daily clinical application.

We, as hematologists and oncologists, are obligated, also in the interest of the best possible patient care, to promptly initiate, lead, and control the necessary steps and, ultimately, within this framework. We have to improve our knowledge and make our AI responsibility as doctors available to our patients and ourselves for daily use.

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14

AI in Biomedicina: profili bioetici e di etica della ricerca

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L'impiego crescente dell'intelligenza artificiale (IA) generativa nella biomedicina solleva una serie di interrogativi bioetici ed etici complessi, i quali richiedono un'analisi approfondita per comprendere appieno le implicazioni di questa tecnologia nell'ambito della ricerca scientifica e della pratica clinica. In tale contesto, il presente intervento sarà diviso in due parti.

La prima sarà dedicata a tracciare alcune recenti implicazioni dell'IA generativa per l'etica e soprattutto l'integrità della ricerca. Secondo le linee guida redatte dalla Commissione per l'Etica e l'Integrità nella Ricerca del CNR, per "Per integrità nella ricerca si intende l'insieme dei principi e dei valori etici, dei doveri deontologici e degli standard professionali sui quali si fonda una condotta responsabile e corretta da parte di chi svolge, finanzia o valuta la ricerca scientifica, nonché da parte delle istituzioni che la promuovono e la realizzano". L'integrità nella ricerca riguarda quindi la condotta di chi svolge o è coinvolto in attività di ricerca scientifica ampiamente intesa. Recentemente, la disponibilità di nuovi strumenti di IA generativa ha espanso in modo esponenziale la possibilità di generare nuove immagini, dati, testi e altri contenuti interamente fabbricati, falsificati o plagiati ben oltre quanto fosse possibile solo fino a pochi anni fa. Ne sono un esempio i recenti scandali che coinvolgono le cosiddette "Paper Mills", e cioè delle vere e proprie imprese o "cartiere" finalizzate a produrre rapidamente articoli e testi apparentemente scientifici ma privi di qualsiasi reale contenuto. Questo fenomeno, che era sempre stato solo marginale, rischia oggi di inquinare in modo grave e profondo la produzione di nuove conoscenze scientifiche, ponendo una sfida urgente non solo a tutta la comunità dei ricercatori ma anche alla società nel suo complesso.

Nella seconda parte di questo intervento, invece, saranno analizzate le conseguenze etiche di una particolare tipo di applicazione per l'intelligenza artificiale generativa in ambito clinico. Attualmente, il modello teorico di riferimento per le decisioni cliniche si basa principalmente sul consenso informato e sulla comprensione procedurale dell'autonomia del paziente. Tuttavia, i pazienti possono talvolta essere incapaci di decidere per sé in modo autonomo, sollevando la questione di come dovrebbero essere ricostruite le loro preferenze di trattamento in questi casi. Le direttive anticipate (DA, o DAT da "Disposizioni Anticipate di Trattamento") e

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le decisioni sostitutive (DS) sono strumenti comuni per determinare le preferenze del paziente in queste situazioni, ma entrambi sono problematici. Solo una piccola percentuale di pazienti redige le proprie DAT, mentre le DS spesso si basano su supposizioni poco informate e precarie da parte dei decisori sostitutivi designati. Inoltre, in ogni caso, le decisioni di trattamento sono spesso difficili a causa di pregiudizi cognitivi, scarsa conoscenza clinica, limitazioni cognitive e mancanza di preparazione etica. Per risolvere questi problemi, è stato recentemente proposto di sviluppare dei “Predictors of Personalized Patient Preference” (o P4s) utilizzando dei Large Language Models e altri modelli generativi di intelligenza artificiale. Combinando diversi metodi di addestramento, questi strumenti sono stati presentati come capaci di predire le preferenze dei pazienti in modo spesso più rispetto ai decisori surrogati - e forse anche i pazienti stessi. Nella seconda parte di questo intervento sarà quindi ricostruito il presente dibattito sull’etica dei P4s, mappando le diverse sfide pratiche, etiche e legali che lo sviluppo e l’implementazione di tali strumenti possono avere nell’ambito sanitario.

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Black-boxing the black box: AI and the new biomedicine

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This lecture will tackle the rising prominence of artificial intelligence in biomedical research and healthcare. Large language models and related methodologies are increasingly intersecting the most transformative development enabled by the molecular understanding of living processes, namely the digitization of life. Over the last decades, we have come to study, understand, frame and increasingly control virtually all layers of biological organization and function through what I have previously referred to as a digital epistemology. All the while, our social lives have also become nearly completely embedded in a digital matrix that pervades our daily lives, from their most inconspicuous facets to their most meaningful and overtly political acts. At this intersection of our digital worlds within and around us, the pursuit of understanding life and caring for it (ie. the backbone of the biomedical enterprise) is witnessing yet a further momentous turn with the advent of Artificial Intelligence. I will trace how developments in this area represent, in several ways, the peak of a process seeded from the very dawn of molecular biology, while also sketching the multiple ways in which AI is being increasingly framed – and in fact enabled – as a quantum leap that disrupts existing epistemic foundations and practices, experimental and social alike. Finally, the argumentative flow of the work presented in this lecture will invite a reflection on the possible reach of an emancipatory stance towards these developments, with special emphasis on the challenge of the so-called black-box components of AI and the perils, in turn, of black-boxing their silently growing impact.

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AI supporting medicine and research: History and applications of a revolution

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In recent years, Artificial Intelligence (AI) has increasingly become a transformative force in healthcare and medicine, offering the potential to improve diagnostic accuracy, disease and therapeutic monitoring, personalized treatments, and medical and pharmaceutical research (1-3).

By leveraging vast amounts of data and powerful computational algorithms, AI enables the automation of labor-intensive activities demanded to healthcare professionals, personalization of treatment approaches, and enhancement of the quality, efficiency, and equity of healthcare delivery worldwide (4, 5).

AI has a rich history intertwined with the evolution of medicine and the discoveries in the biological fields, dating back to its foundation in the 1950s. Early AI systems in healthcare were rule-based, relying on expert knowledge encoded into algorithms processing data in symbolic or logical form to assist with tasks such as diagnosis and decision-making. The MYCIN model, which was developed in the 1970s at Stanford University, was one of the earliest and most famous expert systems in medicine and was designed to assist physicians in diagnosing bacterial infections and selecting appropriate antibiotics (6).

In the 1980s and 1990s, advancements in machine learning algorithms paved the way for a new era of AI in medicine. Researchers began exploring techniques such as support vector machines and decision trees to analyze medical data and extract valuable insights. These approaches marked a significant departure from rule-based systems, allowing AI to learn from data and adapt its behavior over time.

The 21st century began with an exponential growth in AI applications across various healthcare domains. Breakthroughs in artificial neural networks and deep learning, a subset of machine learning, revolutionized medical imaging by enabling AI algorithms to analyze medical images with unprecedented accuracy. Radiology, pathology, and dermatology were among the first specialties to adopt AI-driven image analysis tools, demonstrating remarkable potential for improving diagnostic accuracy and efficiency (3).

Medical imaging is crucial in diagnosis and treatment planning across various medical specialties. However, interpreting medical images can be time-consuming and subjective, leading to variability in diagnostic accuracy among healthcare pro-

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viders. AI offers a solution to this challenge by assisting radiologists and other clinicians in image interpretation.

By leveraging large datasets of annotated images, AI systems can learn to recognize patterns indicative of disease in radiographic images, such as X-rays, CT scans, and MRIs, leading to fast and precise diagnoses.

In particular, AI techniques became a popular and extraordinary tool for performing the complex and time-consuming task of segmenting anatomical and pathological structures within medical images, which are required to precisely outline and quantify these potential biomarkers. The segmentation not only aids in diagnosis but also facilitates monitoring disease progression and response to treatment, making it invaluable for both clinical practice and research (7).

Similarly, AI has been deployed in pre-clinical research and pathology to assess tissue samples. AI algorithms can analyze microscopic images and detect subtle changes indicative of disease (8).

In dermatology, AI-powered image analysis tools can assist dermatologists in diagnosing skin conditions based on photographs of skin lesions. By comparing images against a database of known skin diseases, AI algorithms can provide clinicians with differential diagnoses and treatment recommendations, enhancing patient care and outcomes (9).

More recently, generative AI has been increasingly utilized in medicine, particularly in drug discovery and medical imaging. Generative AI techniques are used to create new molecules for drug discovery (10), for imaging tasks like reconstruction, segmentation, detection, classification, and cross-modality synthesis (11), and to improve the explainability of AI decisions.

Explainable AI (XAI) techniques in healthcare improve decision-making by revealing the mechanism behind deep learning model decisions and increasing interpretability (12).

In the study of DeGrave et al. (13) researchers combined the expertise of physicians with generative AI in auditing the inference processes of medical image classifiers. They used generative-AI-based synthesis to create counterfactual images, which are augmented images that answer the question, “What realistic alterations elicit a different prediction from the AI?”. These modifications were constrained to appear realistic so medical experts could interpret them. Following this approach, the researchers were able to identify and interpret the features that influenced the classifiers’ predictions, both in terms of medically relevant factors and potentially misleading attributes. This approach enables deeper understanding of the classification processes of the model and provides insights into the factors driving the decision-making. By examining the features and patterns the model identifies as necessary for making a prediction, clinicians can potentially gain new perspectives on the diagnostic process and uncover new subtle patterns in the images that may contribute significantly to the diagnosis.

In general, the vast majority of AI application in medicine so far are dealing with fast classifications, powerful data analysis and image processing. More recently generative AI has demonstrated the potential to obtain clinical decision-making (14). If this new technology will effectively enhance clinical decision making is now

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under evaluation. AI has the potential of simply providing support for clinical decisions but also of revolutionizing the future clinical practice.

However, the immense promise of AI also raises important ethical and regulatory considerations that must be carefully addressed. As AI technologies continue to evolve and become more pervasive in healthcare facilities, it is critical to prioritize patient privacy, data security, transparency, and equity [15].

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AI transforming Radiology: Interpretative and non-interpretative uses

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Radiology is indispensable in modern healthcare, concerning diagnosis and disease detection, treatment planning and guidance, monitoring, and follow-up in a wide range of medical pathological or physiological conditions.

Historically, radiology has always been a specialty of innovation. Through the years, radiology has been fearless in change and adaptation, embracing new technologies and recognized its potential, for example with the adoption of cross-sectional anatomic imaging with CT and MRI, with greater levels of detail in image interpretation.

Today, radiologists are in some ways the victims of their own success. Now we face large volumes of examinations, exponential increases in the number of images generated by each examination and the demand for 24/7 coverage. In an era of widespread physician burnout, this specialty is among the most affected. Artificial intelligence (AI) is emerging as an extremely powerful force in medicine and particularly in radiology.

With advanced computer algorithms and machine learning techniques, AI can help radiology in various tasks basically related to technical aspect (non-interpretative uses of AI) and to support diagnosis and radiological image interpretation (interpretative uses of AI).

Among the non-interpretative uses we find various applications mostly regarding improving image quality acting on images acquisition and preprocessing and optimize dose radiation and scanning time. Some others non-interpretative uses are workflow optimization through standard protocol systems, organizing patient’s worklist and prioritization, and on the report generation for decreasing report variability.

In the same way, among the other uses there are image recognition, detection and classification of lesions, with automated methods AI algorithms (for example for fractures detection or organs’ lesions characterization).

At last there are quantitative image analysis providing measurements and parameters, automated image segmentation and extraction of radiomic features, with the advantage of having the ability to detect some quantitative and reproducible biomarkers.

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Even though the Food and Drug Administration (FDA) has approved more than 200 commercial radiology AI products, there are some unresolved issues.

On one side, there are some various potential applications of AI in radiology education, personalized medicine, remote imaging and telemedicine, but on the other hand these systems present some conflicts and barriers.

Firstly the presence of the "black-box" nature, where some models developed by ML are complex and high dimensional, so it is difficult to explain them in simple terms; and especially after the approval of the so-called "AI act" by the European commission those limits will deeply affect AI in healthcare.

Last but not for importance, all the medical-legal aspects and the ethical issues: humans will always be responsible for the diagnosis, particularly if incorrect diagnosis is triggered by the AI?

In conclusion, there are many potential applications of AI in radiology that can improve the everyday practice. But at present, AI has a modest to moderate penetration in the clinical practice, where majority of research and commercial software focuses on diagnostic or interpretive applications.

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Lavori scientifici: Cosa sta cambiando? Un po’ per il COVID-19, un po’ per ChatGPT

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Il mondo della ricerca scientifica è in continua evoluzione e l’emergere di nuove sfide a livello globale o di tecnologie altamente rilevanti inducono una serie di trasformazioni significative, accelerando i ritmi e adattandosi a nuove sfide e opportunità. La crescita media delle pubblicazioni scientifiche è stimata essere del 4% all’anno, raddoppiando approssimativamente ogni 17 anni (1). Negli ultimi 4 anni, due fattori chiave hanno giocato un ruolo determinante in questo processo e nell’aumento dei tassi di pubblicazione: la pandemia di COVID-19 e l’emergere di tecnologie avanzate, come l’elaborazione del linguaggio naturale.

L’impatto del COVID-19

La pandemia di COVID-19 ha trasformato il modo in cui conduciamo e diffondiamo la ricerca scientifica. Questo cambiamento era evidente già nei primi mesi in cui il SARS-CoV-2 ha iniziato ad irrompere nelle nostre vite, come dimostra un’analisi di *Nature* (2). A dicembre 2020, circa il 4% della ricerca globale era dedicato al coronavirus (2). Le sottomissioni esclusivamente alle riviste Elsevier sono aumentate del 58% tra febbraio e maggio 2020 rispetto allo stesso periodo dell’anno precedente. Questo aumento è stato ancora più marcato per le pubblicazioni riguardanti la salute e la medicina, registrando un 92%. Tuttavia, l’incremento non si è limitato al COVID-19: nel corso del 2020 si è osservato un aumento generale del volume di articoli inviati alle riviste scientifiche su una vasta gamma di argomenti (3). Secondo un’analisi più recente di Cauchemez e colleghi, la pandemia di COVID-19 ha indotto un significativo aumento della ricerca in varie discipline delle scienze biomediche del 9%, approssimativamente, nelle pubblicazioni nelle scienze mediche e della salute tra il 2020 e il 2022 rispetto al volume previsto, con circa il 6% degli articoli in questo periodo che si concentrava su SARS-CoV-2 (4). Che questo sia imputabile direttamente al COVID-19, è emerso da un’interessante analisi in cui viene mostrato come l’Italia, uno dei primi paesi occidentali ad essere colpiti fortemente dalla pandemia, si sia posizionata come il quinto paese più produttivo in termini di pubblicazioni (5). Questo risultato è sorprendente poiché l’Italia non è mai stata classificata tra i primi cinque paesi editori prima della pandemia. Un pattern simile, anche se su scala più ridotta, si riscontra in altri paesi come il

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Brasile e Hong Kong: l'ampio e grave impatto della pandemia in questi paesi può spiegarlo (6).

Ma questo non riguarda solo il numero di pubblicazioni. Ad essere cambiato è anche il modo in cui gli articoli vengono disseminati. La pandemia ha alimentato un forte aumento della condivisione attraverso preprint – articoli pubblicati online prima della revisione paritaria – una pratica raramente vista nei tempi pre-pandemici. Secondo un'analisi di *Nature*, più di 30.000 degli articoli su COVID-19 pubblicati nel 2020 erano preprint, rappresentando tra il 17% e il 30% del totale dei documenti di ricerca su COVID-19 (2). Questo ha facilitato la circolazione di informazioni vitali prima che i dati fossero sottoposti a rigorosa revisione paritaria e scrutinio, garantendo l'integrità dei risultati scientifici. La necessità di velocità ha posto una considerevole pressione sui sistemi di revisione paritaria. I preprint correlati alla pandemia pubblicati nel primo trimestre del 2020 sono apparsi nelle riviste più rapidamente rispetto a quelli pubblicati in seguito (2). Le riviste si sono affrettate a pubblicare gli studi su COVID-19 per affrontare la crisi sanitaria. Ad esempio, *Nature* ha lanciato un invito aperto ai ricercatori con competenze pertinenti a revisionare gli articoli correlati al coronavirus in tempi brevi (7). Il risultato è stato che, mediamente, nel 2020 i lavori venivano pubblicati più velocemente (2). E una volta pubblicati, la maggior parte delle riviste ha adottato una cultura di accesso aperto per consentire la distribuzione ampia delle informazioni, accelerando non solo il ritmo delle scoperte ma anche alimentando uno spirito di progresso collettivo.

L'ascesa di ChatGPT

Se il COVID-19 ha scatenato un terremoto nel mondo delle pubblicazioni scientifiche nel 2020, l'emergere di tecnologie innovative quali l'intelligenza artificiale generativa rappresenta uno dei più importanti motori di cambiamento nuovo motore del cambiamento. In particolare, l'avvento di sistemi di "elaborazione del linguaggio naturale", comunemente abbreviata come LLM (dall'inglese Large Language Models) si sono imposti rapidamente come uno strumento per affrontare le sfide della comunicazione scientifica grazie alla loro capacità di generare testi coerenti e comprensibili. Per comprendere l'entità di questo cambiamento, basti sapere che ChatGPT – un sistema LLM rilasciato al pubblico nel novembre 2022 – è stato incluso nella lista dei 10 sviluppi chiave nella scienza pubblicata da *Nature* per il 2023 (8).

Quando *Nature* ha intervistato 1.600 ricercatori su quali fossero i principali benefici dell'intelligenza artificiale generativa per la scienza, la risposta più comune (30%) è stata che avrebbe aiutato i ricercatori non di madrelingua inglese a revisionare e correggere rapidamente i documenti, contribuendo a migliorarne chiarezza ed accuratezza, mentre circa il 15% ha dichiarato di averle utilizzate per aiutare a scrivere domande di finanziamento (9). In un sondaggio condotto dal Consiglio Europeo della Ricerca (ERC), il 75% dei più di 1.000 beneficiari di sovvenzioni ERC ha ritenuto che l'intelligenza artificiale generativa ridurrà le barriere linguistiche nella ricerca entro il 2030 (10).

Sebbene questi sistemi stiano rapidamente diventando strumenti comuni nei processi di ricerca quotidiana (11, 12) è importante ricordare che presentano diversi

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limiti. Gli attuali sistemi di linguaggio con trasferimento di conoscenza (LLM) utilizzano informazioni disponibili al momento dell'addestramento, il che può limitare la loro capacità di fornire dati aggiornati (13). Ciò rappresenta una sfida per la ricerca scientifica, che richiede accesso in tempo reale alle ultime scoperte. Inoltre, i LLM sono spesso addestrati su testi difficili da tracciare, sollevando preoccupazioni etiche riguardo alla violazione dei diritti d'autore e alla mancanza di citazioni adeguate (13). La mancanza di trasparenza delle fonti può portare a informazioni errate, mentre i LLM potrebbero non cogliere pienamente il significato o la rilevanza di ciò che generano, richiedendo ancora l'intervento umano per l'interpretazione corretta. L'uso diffuso dei LLM potrebbe favorire la produzione di articoli di bassa qualità e minacciare l'integrità della ricerca scientifica. Alcune case editrici hanno imposto limiti sull'uso dei LLM nelle pubblicazioni scientifiche, mentre altre hanno enfatizzato la necessità di trasparenza da parte degli autori riguardo all'uso di tali sistemi (13). Inoltre, è necessario affrontare le questioni etiche relative all'utilizzo di modelli linguistici per la generazione di contenuti scientifici. È importante che i modelli siano utilizzati in modo responsabile e trasparente, e che i contenuti generati siano sempre sottoposti a revisione da parte di esperti umani.

Sfide e opportunità

Il COVID-19 e ChatGPT hanno cambiato o stanno cambiando il mondo della ricerca scientifica in modi che sono ancora da esplorare completamente. Tuttavia, è chiaro che questi due fattori hanno il potenziale di rendere la scienza più accessibile, collaborativa e aperta a tutti ed è quindi importante essere consapevoli dei loro limiti al fine di adottare misure per mitigarli ed utilizzarli nel migliore dei modi possibile.

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