Sometimes the digital Doctor should admit "I don't know"

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Digital technology is causing a sea-change in Medicine. In particular the meteoric rise of AI in general and deep learning in particular raises the possibility that doctors will be replaced computers (1). The father of deep learning, Geoff Hinton, said in 2017: "It's just completely obvious that in ten years deep learning is going to do better than Radiologists ... They should stop training radiologists now".

Sebastian thrun (1, 4), another authority in deep learning gives a more nuanced perspective, and argues that "... deep learning devices will not replace dermatologists and radiologists. They will augment professionals, offering the expertise and assistance". Artificial Intelligence (AI) and Intelligence Augmentation (IA) have been competing ideologies for decades. (see inset) Currently, AI is much more in Vogue IA. We present an argument that, in high risk domains, and in particular in medicine, IA is the better approach.

Artificial Intelligence and Intelligence Augmentation
The driving question of AI is: "are machines capable of behaving in a way that is indistinguishable by humans". Achieving this goal implies that humans can be replaced by machines.
Using computers to augment humans rather replace them is both tantalizing and utterly mundane. On the heady side, consider cyborgs whose anatomy is part human, part artificial and can with equal ease solve complex equations or write poetry. On the mundane side, ubiquitous technologies such as the smart phone and google search are ways in which our capabilities are augmented by computers.
The idea of using computers to augment or amplify human intelligence has a very long history. The acronyms AI (Artificial intelligence) and IA (Intelligence Amplification or Intelligence Augmentation) have both become popular in the early 1960's(2, 3). These days, the acronym AI is popular, while the acronym IA is not. However, Sebastian Thrun's statement indicates that the idea of Intelligence augmentation is still on some people's mind.

Our approach is based on the observation that the level of attention paid to a patient varies greatly. At the high end, a patient in surgery or in the Intensive Care Unit (ICU) has the full attention of several doctors and nurses. At the low end, a middle class elderly person living at home might be visited by a nurse once a week or even less.

Rather than using AI to replace doctors or nurses, we suggest that IA can free the staff from simple and repetitive tasks and allow them to devote their time to more complex decisions and to prsonal interaction with the patient.

Central to our approach is a quantification of prediction confidence. Such quantification is needed so that a patient monitor can sound an alarm when a patient is having a heart attack, but create only few false alarms. Similarly, it is needed when a diagnostics assistant can eliminate some diagnostic possibilities but not all of them.

We equate low prediction confidence with saying "I don't know" (IDK). The interaction between the IA agent and the doctor is based on this ability. When diagnosis is done by elimination, saying "I don't know" the agent can narrow the set of possible diagnosis without reducing it to a single diagnosis. It is then the doctor to decide how to proceed, whether to perform more tests, or whether to choose a treatment.

1. Ground truth, train and test error

In a highly cited paper in the journal Science (4) provides evidence supporting the claim that computers can diagnose skin cancer as well or better than board certified dermatologists (see insert).

Not surprisingly, each dermatologist gave a different diagnosis. As

Skin cancer diagnosis using Deep Neural Networks
One of the papers that provided evidence that deep neural networks might be able to outperform humans is the work of Esteva et al (4). They trained a Deep neural network to classify images of skin into three categories: benign, malignant and non-cancerous. The network was then tested, along with twenty five dermatologists on images which were labeled by a pathologist analysis

the goal was to to compare the performance of the DNN to that of the dermatologists they needed a independent source of ground truth. To that end they used the diagnosis of a biopsy as ground truth. It is arguable that this label is more accurate than the one given by the dermatologist, even though it too depends on the human judgement of the pathologist.

Leaving aside the question of the reliability of the pathologists. There is another, more fundamental problem with this experimental setup. The data in the experiment was retrospective, i.e. it was collected from the records of past patients for which both a skin image and a biopsy were available. Normally, patients get biopsied only if the dermatologist thinks there is a significant chance of **malignancy**. As a result, a retrospective study that is based on patients for whom a biopsy was taken is likely to over-represent malignant patients. Suppose an image-based classifier is trained using this data. If the classifier is applied to skin images of undiagnosed patients it is likely to over-diagnose them as melignant. In practice, the result would be that more patients thean necessary will be biopsied.

Arrhythmia detection using Deep Neural Networks
One of the papers that provided evidence that deep neural networks might be able to outperform humans is the work of Esteva et al (4). They trained a Deep neural network to classify electrocardiogram (ECG) into 12 rhythm classes. The network was then tested, along XXX. The neural network outperformed the human cardiologists. This result is impressive. This work is also based on a retrospective analysis. To predict the performance of the trained DNN XXX.

As we elaborate on in the next section, in medical usually not available, all that we have to go on are the opinions of human diagnosticians.

2. Uncertainty in medicine

Deep learning is a special case of supervised learning (see inset), sometimes called input-output learning (5, 6). Under this fomulation the only quantity of interest is the error on a held-out or test set.

Medical diagnostics cannot be described as an input-output mapping. This is evident studies of inter-rater agreement (see inset). In studies of this kind multiple doctors produce diagnostics based identical medical information.

When a new patient arrives at a clinique, all diagnostics are possible. After a series of tests and physical exams and talking with the patient, many possibilities are eliminated. In simple cases, this is enough for the doctor to confidently choose a treatment. In increasingly more complex cases, the doctor might ask for multiple tests and visits, refer the patient to a specialist, consult colleagues, journals and books etc. In most cases this process of narrowing

Supervised Learning and ground truth
Roughly speaking, machine learning (ML) can be divided into unsupervised learning and supervised learning. In both, the task of the learning algorith is transform a set of examples into a model. In unsupervised learning the examples are undifferentiated raw measurements. In supervised learning, which is the focus of this article, each example consists of an input and a label. Typically, the labels are provided by a human expert. These labels define the ground truth and the goal of the learning algorithm is to make predictions that diverge as little as possible from the ground truth.

will lead to a treatment plan. Ideally, followup visits and tests will confirm that the patient is recovering. In most cases, all that we can know about the patient is whether or not they recovered. This is a far cry from knowing what was their correct diagnostics when they first came in the door.

For the digital doctor to be effective, it should incorporate this notion of uncertainty. It needs to correctly classify the easiest cases and out "I don't know" on the hardest cases. Before describing how this might be achieved, lets consider some of the many sources of uncertainty in medical diagnostics.

Quantification of inter-rater agreement rate

A common measurement of inter-rater reliability (or intra-rater reliability) for categorical quantities is the Cohen's kappa coefficient, usually denoted as κ. Compared with the percent agreement calculation, it considers the possible agreement occurring by chance. Specifically, while the percent agreement, denoted as $0 \le a \le 1$ is defined as the percent agreement among raters, the Cohen's kappa is defined as the ratio of $a - c$ and $1 - c$, where $0 \le c \le 1$ is the agreement occurring byq chance. Clearly, the largest κ is 1, which means a complete agreement among raters, even under the possibility of agreement
totally by chance, that is, $c = a$, then κ is 0.
agreement by chance, then κ can be negative.
ded by Cohen (7) is that when $\kappa \le 0$, there is
0 as none to slight agreement, $0.2 < \kappa \le 0.40$
60 as moderate agreement, $0.6 < \kappa \le 0.80$ as
$< \kappa \le 1.00$ as perfect agreement. However,
ning of agreement might be different.

Uncertainty due to signal quality

Medical devices use a variety of bio-sensors that record, display and distribute different biometrics, ranging from vital signs such as heart rate, oxygen saturation, temperature and blood pressure, to high-frequency waveforms such as ECG, EEG, respiratory signal and arterial blood pressure. ~~suffer from variety of problems~~ usually suffer from artifacts and other signal quality problems, some of which depend on the patient. ~~Reducing these problem often requires~~ In some cases, these problems can be easily handled by a human expert. In some cases such as artifact removal of EEG is still an active research problem (8).

Patient monitors are bedside medical devices that monitor patients at risk, freeing the medical staff to attend to the patients that need care at the moment. However, Patient monitors suffer from signal quality issues and tend to generate false alarms at a high rate. These cause the medical staff to ignore the alarms, rendering them useless. This phenomenon, called alarm fatigue (or alarm overload) is a major problem in hospital care (9, 10).

Another common source of signal quality issue is how the sensor is placed. While there have been several standards, ranging from the well-known ECG systems (11) and international 10–20 EEG systems (12) to recently smart clothing system for telemedicine (13), it is not always possible to achieve a precise sensor placement for biomedical signal collection due to various reasons. This uncertainty might be tolerable for some clinical applications; for example, an imprecise ECG sensor placement might not impact the identification of some types of arrhythmia from the ECG signal, like atrial fibrillation. However, this uncertainty might cause troubles in other applications; for example, an imprecise placement of the deep brain stimulation lead inside subthalamic nucleus might downgrade the Parkinson disease treatment outcome.

Protocol limitation

Yoav : For readers that are not MD, we should explain what are protocols, how they are generated, and whether all or some of their functionality ca be taken over by a computer. Also, I would put "extrapolation error" in here According to NCI dictionaries, protocol means a detailed plan of a scientific or medical experiment, treatment, or procedure. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/protocol. In clinics, it is a document that guides decision making, including criteria regarding diagnosis, management, and treatment. It exists in different areas of healthcare with different formats. In a loose sense, it could be understood as an algorithm solving a given mathematics problem. However, unlike the relationship between an algorithm and a mathematics problem, a medical protocol might not cover every situation and provide all possible solutions, and have several limitations. The American Academy of Sleep Medicine (AASM) publishes criteria for manual sleep stage and sleep apnea annotation from the gold standard sleep study instrument, the polysomnogram (PSG). This annotation is based on manual analysis of biosignals recorded from the PSG (14, 15). The AASM is a protocol that has been extensively applied, with rigorous scientific support, and updated regularly according to latest evidences. A detail sleep profile is critical for sleep quality enhancement, or even medical condition improvement. However, it is well known that even with the well established protocol, the inter-rater agreement rate of sleep stage annotation among experienced experts, in terms of percentage of epoch-by-epoch agreement, is only about 76% over normal subjects and about 71% over subjects with sleep apnea, while the Cohen's kappa is 65% over normal subjects and about 59% over subjects with sleep apnea (16). Among many reasons, the one that is directly related to the intelligent system development is how the criteria are "described" in the protocol. For example, it is described in the protocol that if the delta wave occupies more than 20% of a given 30-second epoch of the electroencephalogram during sleep, that 30-second epoch is defined to be the N3 stage. 20% of a given 30-second epoch is 6 seconds. What about if the delta wave occupies 5.99-, or 6.01-seconds? What about if the delta wave sustains for 10 seconds, but it is divided into two consecutive 30-second epochs? When sitting on the "gray area" that is inherited from the protocol, sleep experts need to make a decision based on their experience or the information they have at hand, and this leads to medical uncertainties, and hence the inter-rater, or even intra-rater disagreement.

Another protocol limitation is the "extrapolation error"; that is, when we apply the developed protocol to the population different from the population that we collect the evidence for the protocol (17). Such extrapolation error usually comes from the variability among subjects. If such variability is big, it limits the development of a more quantitative protocol (18), and different protocols might be needed for different situations.

Medical uncertainty as manifest low inter-rater agreement consequence, can be found in many clinical problems (see blocks on ...) Besides the above-mentioned reasons, there are more. For example, in some situations, when the needed information is missing, it is challenging to make a differential diagnosis (27). Despite the variety of reasons, the key message here is that medical uncertainty is a non-negligible fact in medicine.

A direct consequence of the low

knowledge gap

Yoav : is this an example of uncertainty because of knowledge gap? Wouldn't it be better to use something better known such as Covid-19? Urodynamic studies provide the best bladder and sphincter functional data for urologists to decide how to treat patients at risk for renal damage (19). While it has been extensively studied and applied in clinics, the main issue that plagues this field of urodynamics is the lack of precise definition of a detrusor contraction or overactive contraction (19). The lack of a well defined definition is due to the lack of quantitative study from the pathophysiological perspective, so the definition is still based on "expert opinion". For example, usually an overactive contraction represents itself as a "bump" in the detrusor pressure signal. However, what is the breath and height of a bump should we call it an overactive contraction? How to distinguish a true overactive contraction from an artifact? While there have been several reference information, like abdominal pressure, that could help us identify artifacts, but it can only explain a small portion of them. Unsurprisingly, this fundamental issue has led to a significant inter-rater disagreement (18, 20).
Another example is the famous pandemic, COVID-19 (21). Back in Jan 2020, when it was first reported in China, nobody had a clue how it will generate damage to human body, not to mention how to treat a patient. All medical practices, ranging from diagnosis to treatment to vaccine were all made based on experience. For example, the quinine and remdesivir were considered potential

inter-rater agreement rate is that the trained intelligent system might be questionable. It is clear that such intelligent system is questionable and might raise concerns. Recently, various regulations in this regard have been proposed (28, 29).

Now, suppose we are able to eliminate all challenges from data calibration and validation issues, and we can provide as much information as possible to train the intelligence system. Even under this assumption, it is clear that the system still suffers from the protocol limitation or knowledge gap issues. Can such system be useful in clinics? To answer this question, we should not forget that physicians also follow the same protocol and have knowledge gaps. Depending on the clinical problems, and the experience of physicians under consideration, the agreement rate varies. Usually, intern doctors know the least, while a senior attending knows the most. It is natural that we trust a senior expert more, but it does not mean that we do not trust a junior intern doctor.

Managing uncertainty in medicine. Medical diagnosis is often uncertain or inconclusive. On the other hand, a doctor responsible for a patient's health has to make decisions in spite of this uncertainty. If the uncertainty presents a sufficiently small risk, the doctor can choose a treatment. Otherwise the doctor might consult other doctors, a medical journal or a book.

Inter-Rater agreement

A direct consequence of this low inter-rater agreement is a questionable trained "artificial intelligence". It is possible that we magically obtain a dataset that contains information that is sufficient for the decision making, while the information is too subtle so that it is not considered in the protocol, and we also magically obtain labels from a magical master that can see though all the information and provide the correct decision. However, by doing a simple math, we shall not count on such a magic and should come back to the protocol itself.

To better understand the process and the possible place of AI in it, we turn to the Kahaneman's (30) "Thinking Fast Thinking Slow" and to Vordermark book on medical decision making (31).

Medical diagnosis can be divided into two main types: recognition and elimination. Recognition is a fast mental process that is partially unconscious where the one correct diagnosis presents itself in the doctors mind. Sometimes the doctor is not able to explain their recognition in words, which hinders discussion and documentation. As recognition typically points to a single diagnosis, there is a danger that the recognized diagnosis will hide other possible diagnoses. Elimination, on the other hand, is a slow deliberate process which starts with all possible diagnoses and gradually eliminates unlikely ones based on patient history, examination and test results. As Elimination is deliberative, it is easier to discuss and document it.

In both recognition and elimination, past experience plays an important role. This experience is based on medical practice as well as knowledge learned from lectures or books.

IA can aid the doctor both in Recognition and in Elimination. On the Recognition side, an IA can sift through massive data and point the diagnostician to suspicious areas.

On the Elimination side, an IA system could help carefully and systematically eliminate diagnoses. This can help the doctor stay aware of possibilities that are not obvious, for differential diagnosis.

How to quantify IDK? We should discuss how to quantify the confidence, or certainty, a physician has when making a decision.

Clearly, experience leads to confidence. With more experience aggregated, diagnostic options that contradict the accumulated experience are eliminated, and hence more problems that need to be handled by the elimination process can be handled by the recognition process. However, facing our complicated human body, it is almost not possible for any single physician to aggregate all necessary experience to be confident about anything, so IDK is still an option. A practical and simple way to increase diagnostic certainty is to solicit the experience of a diverse group of doctors via discussion. If there is a clear majority for one diagnostic outcome, then the overall confidence in that diagnostics is high. While this voting procedure might guarantee the optimal outcome, it eliminates the uncertainty during the whole procedure. With this certain procedure, even if the outcome is negative, it can be traced back and accumulate evidence and experience.

> **Certainty and conditional probability**
> This certainty is very different from the the conditional probability of the disease given the diagnostic. The first is akin to saying: 95% of the dermatologists would give the same diagnostics. The second defines the probability that, if we had access to ground truth, then 95% of the patients that receive this diagnostics have the corresponding condition.

3. Uncertainty in Machine Learning

One can define "confidence" in machine learning. The definition follows a similar logic to the one used for human diagnosticians in the previous section. The yardstick by which we measure confidence of predicting a label is "how much do alternative labels contradict previous experience?". More formally, we ask how much do we need to change the training data so that it supports an alternative label.

- Bootstrap samples.
- Samples from different hospitals.
- Easy and hard cases.

4. Human decisions and Intelligence augmentation

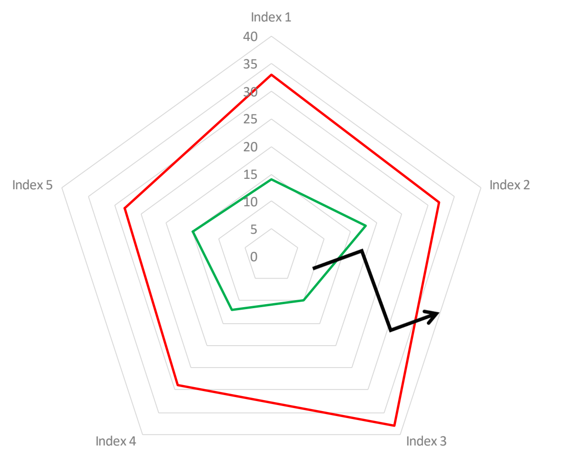
Computer has been an integral part of medical practice for decades. From electronic medical records (EMR) to medical instrumentation to billing, hospitals and cliniques cannot function without computers. By some measures computers can already make better diagnosis than human doctors. The question is not whether computer diagnostics will become part of medical practice, the question is how.

Some claim that human doctors and nurses are heading to extinction, following the fate of manufacturing jobs and bank cashiers. Our prediction is that computers will change the nature of medical work, but that it will increase, rather than decrease, the number of healthcare workers, especially in the care of chronic disease and aging, and exploring the nature of our complicated human body.

We believe computers can perform accurate diagnosis for cases where different doctors are likely to agree. In other cases that are in the diagnostic gray area, the computer will output "I don't know" and transfer the responsibility to the doctor. In most cases, the doctor cannot say "I don't know" because she is responsible for the patients health. On the other hand, resolving the diagnostic question is not her only choice. She can consult another doctor or the literature, ask for additional tests, or decide on a treatment based on available information. Deciding between these options requires much more than diagnostic information. It involves understanding the patient's emotional, mental and financial state, the patient's support system, the strengths and weaknesses of the hospital in which this is taking place etc. Such exploration and results will be fed back to the system to reduce the gray area, which is similar to training an intern doctor in the hospital.

Over time, computers will be able to take into consideration more and more of this complex information. However, for the foreseeable future, it is unlikely that computers will be given the responsibility to make medical decisions. Computers will take on much of the diagnostics and alarm tasks, improving the accuracy and timeliness of the doctors actions. Computers will output IDK in gray areas and will leave the decision making to the human doctor. Giving the computer the authority to make decisions currently done by human doctors will not only deprive the patient the human attention of the doctor, but also put patients in risk.

Some of the digitization of the medicine has come between patients and doctors. ~~The need to record all activities into the EMR system requires doctors to spend more time at the keyboard, reducing the amount of time of physical examination an discussion~~. **Hautieng :** I guess I know what you want to say, but to be safe, I'll do the edit here after we chat. We believe that IA can move medicine in the opposite direction, letting the computer make the common noncontroversial diagnostics and giving the patient more time to interact with the patient.



For IA technology to be widely adopted, the nurses and doctors that use them should experience an improvement in their practice with the IA system. Suppose that the display of the diagnostics computer uses a three color code to identify the pre-defined status. For example, green indicates a confident negative diagnostic, red corresponds to a confident positive diagnosis. Finally, yellow corresponds to IDK, meaning that the computer cannot confirm or reject the diagnostic outcome.

The thresholds which define the three ranges .... **Hautieng :** discuss.

We finish this section with a few application areas which seem ready for applications of IA.

- **Computer aided diagnostics for large-scale data**
  Medical imaging devices such at digital X-ray, CT, EMR and scanning microscope generate many gigabytes of data for each patient. Radiologists and pathologists spend their days analyzing these images to diagnose the patient. The large size and high resolution of the images on the one hand, and the time limitation on the analyst on the other imply that the analyst has to quickly narrow down the suspicious region, increase the chance of missing dangerous abonormalities.

  IA can help the pathologist by suggesting locations in the high resolution image that might contain cancer nodules ().

  directing her attention to the parts of the image that are

- **Adaptive Patient montors**

- **Dissemination of expertise** Computers, trained by experts, can help novices. Serves a function similar to score-cards.

  Teaching young diagnostics

5. Summary

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