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# Data-driven machine learning: A new approach to process and utilize biomedical data

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## 1. An introduction to artificial intelligence and machine learning in healthcare

With the advancement of modern civilization, the need for improved basic amenities is bound to increase dramatically. Healthcare facilities are no exception. In the present scenario, when the world is ground to a halt by a pandemic of biblical proportions, the healthcare sector has come under pressure that has never been seen before. The sheer number of cases and patients that we are dealing with today has thrown an altogether new light on the necessity of new and improved medical practices and innovations that need to be made. Needless to say, medical practitioners, physicians, and all other healthcare sector employees are in dire need of all the help that can be mustered—human or artificial.

Artificial Intelligence, or AI, has revolutionized all the fields that it has touched. In general terms, AI can be defined as the simulation or modeling of intelligent, or even sentient behavior in a nonnatural entity (a machine), with negligible or minimal human intervention. It has the capacity to analyze complicated data, establish or deduce relationships between numerous variables in a given data set, and even predict the future course of the same. “Machine Learning” (ML), or “Deep Learning,” is nothing but the virtual counterpart of AI. It can be represented by mathematical algorithms which can “learn” to behave (or analyze and predict) when put in a training environment. The training is done as the algorithm “experiences” a given data set. Naturally, this feature of an AI-based system can be put into a diverse array of fascinating implementations in the field of medicine, where it can be pivotal in revolutionizing diagnosis, prognosis, and treatment, and can even be used to predict the odds of achieving success in individual cases. Thus, AI can

enhance the credibility of a diagnosis, reinforcing therapeutic decisions, enabling patient self-management and appropriate clinical interventions, and even predicting outcomes, which will in turn increase the overall efficiency of the treatment provided.

At present, the application of Machine Learning models in the processing of biomedical data, and for the development of predictive models, is rapidly gaining momentum. With the recent breakthroughs in the fields of healthcare and information technology, a convergence, which essentially redefines the relationships between the patients, doctors, and pharmaceutical firms, has been set into motion. As more and more researchers look toward big data for new breakthroughs in biomedical research, Machine Learning models are being explored extensively. Big data in biomedical research solely aims at the realization of the dreams of customizable, personalized healthcare tailored for the unique requirements of each patient, which will dramatically revolutionize healthcare services. The applications that these algorithms can be put to use may range from completely autonomous ones like diagnosis to nonautonomous assistive functions like the prediction of mortality in patients, so as to efficiently reallocate resources [1].

AI and Machine Learning based systems can prove to be instrumental in procuring, analyzing, and solving complex clinical problems with ease. AI and ML-based algorithms can be used to collect and analyze data from various other valuable sources like wearable gadgets, implants, and other forms of data from electronic health records. There are many examples of the successful use of AI and Machine Learning in the field of biomedicine, and many companies and start-ups are actively involved in the development of ML-based personal healthcare systems [2]. AI-based systems have recently been used to discover new therapeutic targets using self-driven protein–protein interaction algorithms [3], in the diagnosis of lung cancer tissue [4], for diagnosis and treatment in the field of neurology [5], and even in the field of surgery as early as in the year 1976 [6]. Furthermore, AI-based monitoring systems for medical conditions like diabetes are being approved by authorities like the US Food and Drug Administration (USFDA) [7].

## 1.1 Types of machine learning algorithms

All biomedical detection algorithms are fundamentally directed to extract biomarkers so as to form feature vectors, and then interpret them using a set of attributes called “classifiers.” On the basis of the type of learning pattern used by an algorithm, Machine Learning algorithms are of various types [8], which are as follows:

1. **Unsupervised algorithms**, which can find patterns among the recurring data sets. They are provided with both inputs and outputs at the time of training, and they “learn” by adjusting the weights of the inputs to match the output of the algorithm with the training output fed to the algorithm.
2. **Supervised algorithms**, which are mainly concerned with the classification of data and predicting trends based on previous examples encountered. In the training of these algorithms, only input data is fed. The algorithm develops its own answers using

techniques like clustering of input data, and using the same for the prediction of underlying trends.

3. **Semi-supervised algorithms**, wherein the training data is a mixture of both labeled and unlabeled data sets. The algorithm uses the labeled data sets to correct itself, while also learning the trends from the unlabeled data.
4. **Reinforcement learning algorithms**, which need to be “taught” to behave in a desired manner using a series of positive or negative feedback, without recommending any improvements for the incorrect results.
5. **Evolutionary learning algorithms**, which mimic the biological evolution by constantly learning and “evolving” as per the trends of the data that is fed to them. These algorithms, however, are more susceptible to biases and require regular checking.
6. **Deep learning algorithms**, which rely on a higher level of data abstraction and a comparatively larger number of analytical layers for their learning and improvement methods.

Fig. 1 shows the various kinds of ML algorithms. All of these algorithms require training prior to being implemented, and to implement them in actual clinical conditions, actual clinical data is required. This comes up as one of the prime hurdles in the development of these technologies and has been discussed further in the chapter. There are many popular models that are developed based on these types of algorithms, among which, Artificial Neural Networks (ANN), Fuzzy logic models, and Hybrid (also known as “Ensemble”) models [9] (which are combinations of more than one type of algorithms) are the most popular.

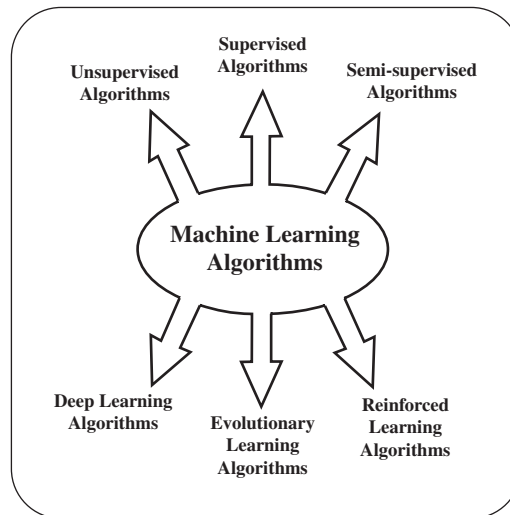


FIG. 1 Different types of machine learning algorithms.

ANNs are probably the most popular ML-based systems that are currently being used in biomedicine. They consist of a complex network of highly interconnected processing units, or “neurons,” that are able to process large amounts of complex data in parallel, or synergistically. Thus, ANNs can safely be considered to be puny replicas of a living brain, which can inherently analyze nonlinear data sets by reweighing and readjusting them, gaining a learning experience in the process. ANNs can be applied to almost all fields in biomedicine, including interpretation of data, analysis of images and waveforms, and even clinical prognosis and diagnosis, with fairly high accuracy and sensitivity. This has been explored in multiple studies, revealing various degrees of success in different cases [10,11]. In some cases, ANN models have even been known to surpass consultant surgeons in terms of prognosis [12]. Fig. 2 illustrates a schematic representation of an Artificial Neural Network.

Fuzzy logic based systems are a little more complex in their working, as they are grounded in the fact that “nothing is an absolute certainty.” Unlike conventional binary systems that discriminate completely between “true” and “false,” fuzzy logic works with intermediates, thus yielding more accurate results. Since there is an inherent heterogeneity in biomedical data, fuzzy logic is more suitable for medical applications. Fuzzy logic based systems have been known to work better with tumor marker profiles, resulting in accurate deductions and even predicting the chances of survival of patients [13]. Some algorithms have even been put to actual use for the administration of vasodilators and anesthetics in pre-surgical settings [14].

Some models are known to perform better in particular cases as compared to others. This, however, does not necessarily imply that a model is inferior [9]. All models, irrespective of build and functioning, follow a basic order of fundamental steps for their

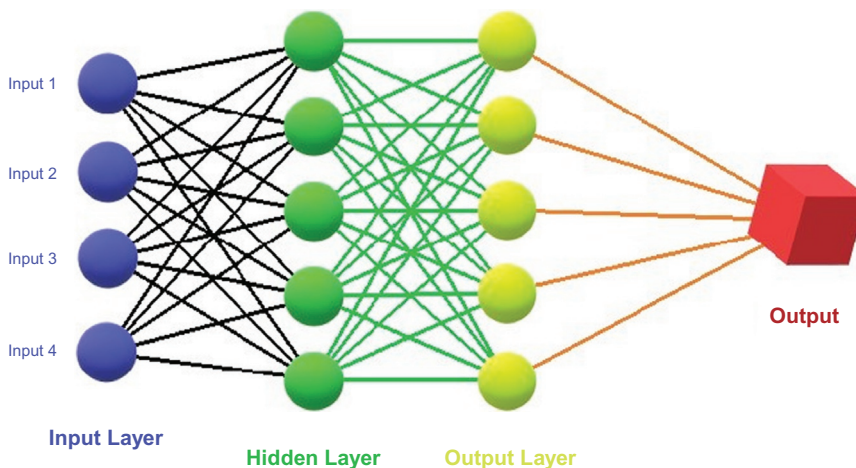


FIG. 2 Schematic representation of an artificial neural network.

functioning. These steps are meant to be followed in the training phase as well as the functional phase, and have been described as follows:

- 1. Collection of input data:** This step involves the use of various sensors (like infrared sensors, pulse meters, oxymeters, etc.) and input devices (cameras, etc.) for the collection of desired input data, which is to be analyzed by the algorithm. This is a crucial step, as any errors in collection may lead to inaccurate outputs. This is the reason why a higher sensitivity is desirable.
- 2. Preprocessing, enhancement, and quality check:** The collected data is subjected to preprocessing so as to enhance the quality. It is at this stage that improvisations are made for missing values; if possible, otherwise the data is rejected. Preprocessing is important for improving the quality of the data, so that feature selection can be correctly done.
- 3. Extraction of features:** Various algorithms (for example, the genetic algorithm, logistic regression, etc.) are used at this stage for the selection of relevant attributes, or “features,” for the diagnosis of the condition. In the training phase, this is when the classifiers are constructed, and the model “learns” to look for a specific data trend within the input values and constructs a database of information that will be used in the functioning phase. In the functional stage, however, this is the point where the model actually triangulates the attributes necessary for diagnosis.
- 4. Classification of data set using selected features:** The data set is now classified after the analysis of various criteria pertaining to the selected features. In this case, the data set may be classified into “healthy” or “diseased” categories, which may vary according to the particular case.
- 5. Generation of results:** The analyzed data is now displayed as a well-generated result, which can be used to assess the situation further. In cases like prediction of mortality or the suggestion of prognosis, the results may not be absolute, but an elaborate description of the same.

These steps may vary in different cases, for different models and purposes. However, the fundamental flow of data remains the same. [Figs. 3 and 4](#) illustrate the training and functioning of a generic ML-based model schematically.

The training of an Artificial Neural Network is based on the adjustment and readjustment of the “weights” of multiple input parameters and then comparing with a “global solution” (which is a theoretical output with the minimum errors or deviation from the actual output). This does not happen in a single run, which is why the phenomenon of “backpropagation” occurs. In backpropagation, the errors in the output are communicated in the reverse direction across the network, such that the weights are readjusted. The process is repeated till the global solution is achieved. This is very much like the tuning of a guitar, where the strings serve as input, the prongs as weights, and tightening or loosening these prongs is comparable to readjustment of weights. The value of the weights associated with a certain input value is a key factor in determining the strength of the connection between successive neurons in the respective neural pathway [15].

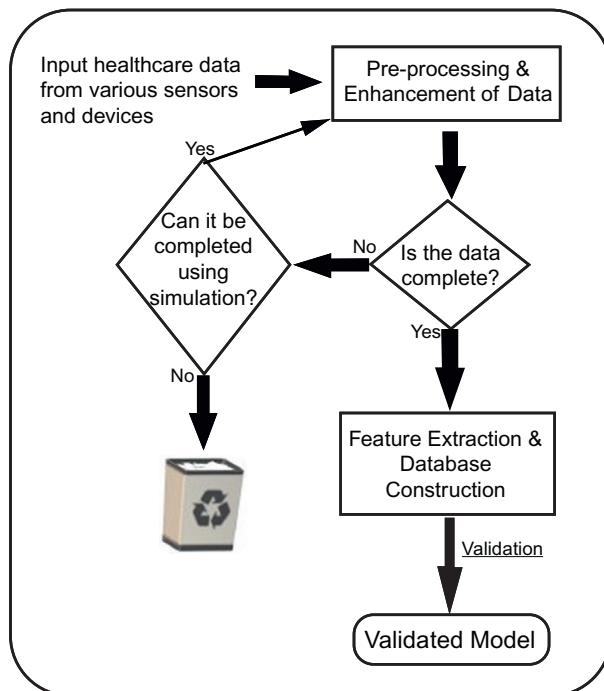


FIG. 3 Schematic representation of the steps involved in the training and validation of an ML model.

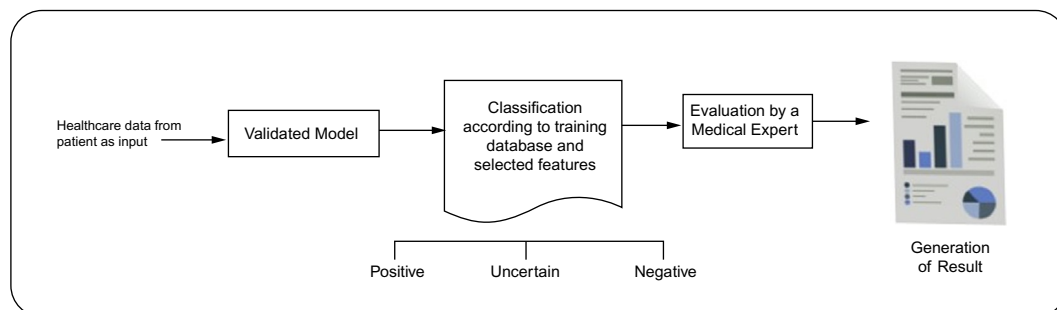


FIG. 4 Functioning of a validated machine learning model.

The rate at which the current processed solution of a model proceeds toward the global solution is called the “learning rate” of the model. Models with higher learning rates obviously train faster. However, it must be kept in mind that models with higher learning rates may prove to be problematic in the case of constantly learning algorithms, because they are more prone to biases as they learn the trends much faster.

It is needless to say that the complexity of Artificial Neural Networks is in no way comparable to that of the brain. However, a larger number of neurons and layers result in a

higher resolution of weight readjustment. This in turn means that the precision of an ANN is enhanced with an increase in the number of layers. Nevertheless, the number of neurons and layers is majorly dependent on the complexity of the data being analyzed. Therefore, it is imperative that an optimum number of neurons and layers be determined for a complex operation [15].

## 2. Challenges and roadblocks to be addressed

In today's scenario, healthcare services must not be centered on the traditional interactions between the patients and the caregivers alone. In addition, large organizations and cycles must also be included. Therefore, it is only natural to desire a system that evolves constantly, learning from its own previous experiences, applying the same so as to regularly improve the overall process. Not only this, the system must record the dynamics of each and every patient, analyzing the effects of the treatments and medications administered [16].

Thus, it can be said that ML-based systems fulfill all the prerequisites for being the ideal upgrade to biomedical research. ML-based systems certainly show promise of high accuracy and viability owing to the recent availability of biomedical data. However, there are a lot of issues that need to be addressed before the full potential of this technology can be harnessed. It goes unsaid that the basic ethical concerns that apply to other conventional clinical practices and biomedical research also apply to these techniques by extension [17]. Other issues may not be apparent to the researchers at first, but may arise later in the working of these models, making them even more difficult to eradicate. Furthermore, there are some unique ethical issues that are raised in the wake of the development of this technology [18–20], which have also been described in the forthcoming sections.

The absence of a systematic approach for examining the development of these algorithms makes the realization of these challenges a difficult task. Nevertheless, attempts have been made to extensively follow the course of proceeding, and the challenges encountered are described as follows:

### 2.1 Unreliability

As far as the potential of this technology is concerned, Machine Learning based tools are immensely promising additions to biomedical research. Artificial Neural Networks largely rely on the “layering” of their neurons for their computational capacity, learning, and decision-making skills. However, the same layering also makes them rather obscure and unclear for the investigators to understand. It is because of this reason, among others, that the full utility of this technology in actual clinical scenarios has been validated only to a limited extent [21]. There is already a prevalent trend of mistrust, owing to a growing preoccupation with medication and side effects among the patients, who have the full resources of the Internet at their beck and call, but lack a complete insight into the clinical practices.



Due to this obscurity surrounding this technology, it is often jestingly compared to “black magic” by some authors, who also say that it needs a lot of contradictory factors in harmony so as to function properly [22]. In the absence of the aforementioned harmony, there are increased chances of algorithms becoming prone to yielding false and even useless results when processing actual biomedical data. It is completely possible that the same algorithms may perform completely well with training data sets, a reason why such errors may often be overlooked, earning the “black box” reputation [23].

## 2.2 Choice of attributes and overfitting

It is a fact that biomedical engineering analyses involve a rather small population of subjects. Furthermore, the parameters that can be used to analyze these subjects are numerous. An algorithm processes data by developing a “classifier,” which is a set of parameters used to judge a data set and classify them. These classifiers are created by the algorithm in the training phase when the data set provided shows a predefined number of “events” (sick patients, in this case) that are to be recorded as “healthy” or “afflicted.” The classifiers hence produced are then used by the algorithm for the functions it is meant for, like diagnosis and prediction. Also, some studies have revealed that in order to obtain an acceptable predictive value from a classifier, at least 10 or more data points are required to adequately calibrate it to the desired resolution while in the training phase [24].

Given all these conditions, one may feel tempted to assign a large number of polynomials relative to the number of data points to be analyzed. This leads to the condition of “overfitting,” due to which the classifier would start learning the data, instead of capturing the underlying trends that actually define the event as “healthy” or “afflicted.” Overfitting is often the most common reason behind the loss of predictive value of most diagnostic algorithms as shown in Fig. 5.

One of the primary reasons for overfitting is the use of training data sets with a small number of samples. Because the sample count being very low as compared to the number of attributes, high dimensionality and other characteristics prove to be suicidal to the model, triggering overfitting [25]. It has been observed that the accuracy of predictive models may show dramatic variations during the validation and functioning phases, simply because the number of samples is below a critical threshold. Furthermore, going overboard with the sample count may increase the risk of biases along with overfitting [21]. In order to prevent overfitting, it is imperative that the parameters/polynomials being used are minimum relative to the data, and must obviously be relevant to the data being analyzed so as to capture the information to the fullest of their capacity. New methods to counter overfitting are being developed [26].

## 2.3 Circularity and insufficient validation

In order to gain the maximum predictive value from an algorithm, it is important that the pre-trained system is adequately validated by exposing it to a “test” data set. There are various techniques by which the validation of an algorithm can be conducted, like the hold-out method or the leave-one-out method. There are some techniques that merge

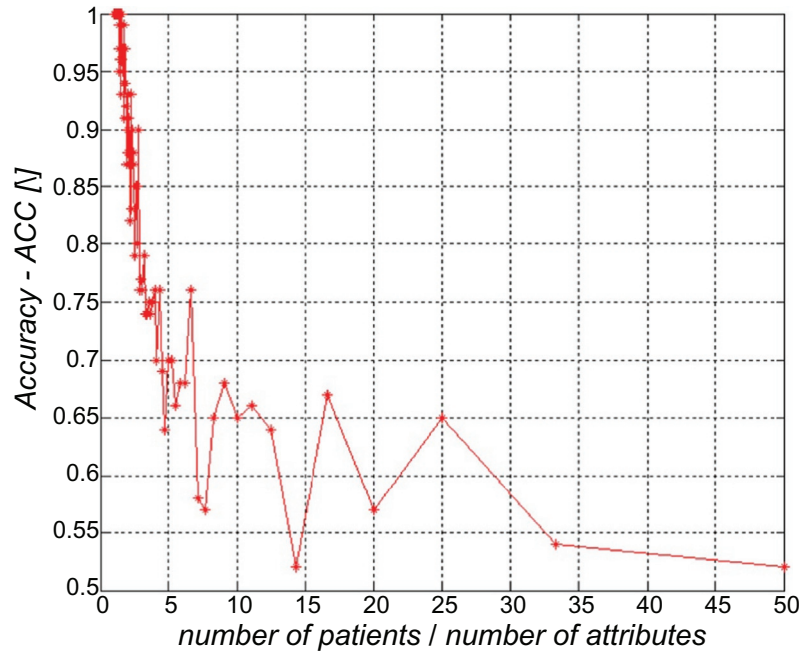


FIG. 5 Graphical representation of the decline in accuracy of a machine learning model due to overfitting.

the training and validation in the same step [27]. Since the basic, untrained ML-based algorithms are commercially available, it is rather easy for many investigators to apply and demonstrate their results by direct training and validation.

It must be ensured that the test set is completely independent of the data that is used in training, failing which the validation will be “circular,” as the algorithm is bound to perform well due to correlation between input data and the training data. Such validation is useless, leading to overly optimistic results. Most untrained researchers fail to pay sufficient attention to this aspect, leading to apparently “formidable” systems which, in reality, have inferior diagnostic or predictive values and are not credible or even usable [21].

It must be noted that biomedical data is not exactly black and white, as stated previously. This means that the diagnoses cannot be labeled definitively as correct or incorrect with respect to the data that is ideally considered to be the “Gold Standard” [28]. In this regard, the designer has to manage certain trade-offs so as to ensure accuracy. Furthermore, validation must be tailored to include not only standard data obtained from rigorous research in ideal conditions but also the data collected from general patient populations and actual clinical scenarios [17].

## 2.4 Data leakage

When known information or facts are used as unknown data, it leads to a condition called “data leakage” [29]. Data leakage may lead to overoptimistic performance of the

algorithms. Leakage may be outcome leakage, in which case the variables in the training set may include elements that can lead to direct outcomes. It may also be at the validation stage, wherein definitive data or “ground truths” used for validation of the algorithm may lead to apparently high-value results, which turn out to be not that well when applied to actual scenarios.

## 2.5 Lack of transparency

The conception of this technology has a direct impact on multiple parties, including the patients, doctors, pharmaceutical companies, computer scientists, engineers, entrepreneurs, and even the regulatory bodies concerned with the proper dispensing of healthcare services. With so many beneficiaries involved, the technology must be completely transparent and understandable to one and all. However, the “black box” like attributes [23], as mentioned previously, make these algorithms rather inscrutable to the clinicians, investors, patients, and sometimes even the investigators who developed them first-hand [17]. The obscurity in turn gives rise to doubts as to whether or not the algorithms will achieve the goals they are intended to achieve. This being the case, it becomes difficult for the stakeholders to decide if they want to throw in their support behind these algorithms. There have been ample evidence of ANN-based systems undergoing “catastrophic failures” and biases due to insufficient transparency [30]. Such non-explainable, autonomous, biased systems can pose a risk to the patients, raising the question about the accountability of the threat. It is thus very important to clearly state the extent of autonomy that an algorithm has in the very initial stages of development.

In order to overcome such issues, it must be ensured that the algorithms be auditable at all stages, keeping in mind the protection of the intellectual property of the researchers involved. The application must be very easy to dismantle, so that the working of the individual components may be understood with ease, and the results should be explainable, the architecture inspired from cognitive decision-making, and grounded in clinical evidence [17]. This will also yield the added advantage of easy debugging and fail-proofing of the algorithm.

## 2.6 Occurrence of Bias and distributional shifts

It has often been experienced in the course of the development of many algorithms that while in training, an algorithm may show a proclivity toward capturing certain trends related to the training data (like the age, sex, ethnicity, or medical history of a patient), which may or may not be directly relevant to the medical condition being diagnosed. The capturing of such irrelevant trends may lead to a perpetual bias in the diagnosis, which may even go unnoticed in the training and validation phases [31]. This tendency is heightened in algorithms with higher learning rates, as they are quick at learning, and may easily learn a wrong trend. The data used in training may sometimes not be diverse enough to cover different scenarios that the algorithm may encounter in an actual clinical scenario. Also, data differs from person to person, varying with age, health status,

or other factors. Furthermore, training data may be erroneous, noisy, or even incomplete, which further decreases the functionality and accuracy of the system. This can result in various inaccuracies, erroneous results, and even rather unpleasant occurrences of racial discrimination in the diagnosis of some cases [32].

It has been observed that the training of a system with clinical data alone may result in the perpetuation of such biases along with sub-optimal clinical practices, which defeats the purpose of enhancing the healthcare services provided. On the contrary, training of the algorithm solely with “ideal” research data results in a lack of valuable clinical insight and relevance, which is yet again counterproductive [33].

Biases may also occur due to the algorithm learning new trends when exposed to new clinical data that is different from the data sets encountered in the training and validation phases. It is thus very necessary to clarify whether an algorithm is “locked” (which means that it stops learning after the training and validation phases) or “constantly learning” (which means that the system continuously learns from the data that it encounters) in nature. Continuously learning systems, especially those with higher learning rates, are prone to a phenomenon called “distributional shift.” In this phenomenon, the algorithm learns the new trends according to the data that it encounters in clinical scenarios, resulting in a change in decision-making trends [34]. Distributional shifts may arise due to a certain class of data outnumbering the other, hence resulting in the “underlearning” of data trends that are less numerous. This may lead to the algorithms performing apparently well, but yielding erroneous results when data of minority type is encountered.

Also, the evaluation of the efficacy, safety, and equity of continuously learning algorithms is more tedious as compared to that of locked algorithms. In order to prevent loss of accuracy due to distributional shifts, periodic re-evaluation of accuracy is necessary, so that the benefits may be improved while simultaneously decreasing the harms. It must also be noted that biased data is completely natural, and in no way incorrect. However, its effect on the algorithm being trained is rather undesirable, and efforts must be taken to analyze data, followed by semi-supervised learning (using many unlabeled samples mixed with a few labeled samples for training) [35], so that biases are minimized.

Biasing of data may also occur due to training data or functions being different from the target data, and due to difference in the sensors or environments, which may or may not occur due to changes in trends as the algorithm learns. This can be removed by periodic re-evaluation and updates [36].

## 2.7 Data outsourcing and breach of privacy

For the training, validation, and overall development of a functional algorithm with acceptable sensitivity, accuracy, and a significantly high predictive value, voluminous quantities of original biomedical data are required. This data can be collected from various sources like live clinical sources, medical records of patients, electronic health records, various devices like smartphones and health-tracking wearable devices, IoT sensors, web-based information, and even social media [37]. As of now, medical records are

comparable to silos of wasted biomedical information, which cannot be adequately sourced due to various shortcomings in record-keeping [16]. Furthermore, a single specimen biomedical data can be as large as a few gigabytes, and is equally complex.

As of July 2020, there are about 7.8 billion people in the world, and out of them a large number of people do not have access to basic healthcare amenities. Since the health conditions, against which these algorithms are being developed, are quite rare, there is a shortage of good quality biomedical data for training. Furthermore, it is very common that the data collected may turn out to be incomplete due to improper handling or collection. A way of dealing with this missing data is excluding it from the training set (which is generally done if the reassembly is too tedious or expensive), but this can result in loss of precious data, which is already less.

The data needed must be captured in real time so as to ensure maximum efficiency. However, this extensive sourcing of data also involves some methods that may lie in the ethical gray areas related to data privacy and ownership [38], and may even be controversial, dwindling the boundaries of patient privacy and legal complexity. Issues related to stealing of data have recently been highlighted, adding to the vulnerability of biomedical data. In order to counter this, measures like differential privacy are being worked upon to yield detailed and informative results, without risking any breach in privacy [39].

Apart from these issues, there is a certain absence of computational infrastructure which is essential for the generation, maintenance, transfer, and analysis of large-scale biomedical data. The integration of these clinical data sets with other standard medical databases thus becomes a daunting task. Furthermore, issues related to the handling, storage, transfer, and security of data need to be addressed, and are not currently being paid the requisite attention by most investigators [40]. Certain groups have even proposed more reliable and secure healthcare information systems using a combination of various tools like masking encryption, granular access control, and end-point validation, among others [41]. Many novel applications are nowadays being developed to use cloud computing and big data based functional architectures [42].

Another challenge that hinders the efficient collection of data from IoT-based systems and wearable gadgets is the energy constraint. Despite IoT-based systems now being an integral part of personalized healthcare, the complexity and sensitive nature of clinical and lifestyle-related biomedical data simply cannot be ignored. This inherent complexity and sensitivity of biomedical data makes detection too computationally intensive, which means that energy constraints can turn out to be a limiting factor, which must be considered for efficient collection of real-time data [43]. The use of polynomial kernels has been explored by some groups as an alternative for low-energy collection and processing of biomedical data [44].

## 2.8 Other data-related challenges

Biomedical data is highly dimensional, heterogeneous, ambiguous, and sometimes incomplete. It may additionally be noisy, contaminated with artifacts, which altogether

gives rise to various complex issues [25,42,45]. In order to reduce noise and artifact contamination of data, novel acquisition tools and techniques like PCA and ICA have been used extensively [46]. Apart from these issues, there are still many diseases for which we do not have adequate information, and still need to be worked upon. Some diseases continually progress with time in a nondeterministic manner, due to which their attributes keep changing [23]. Currently available ML-based algorithms are not exactly equipped to evolve their diagnosis with these trends, and more novel solutions need to be developed to counter the same. Some investigators have suggested that upgrades in memory and attention mechanisms [47] are the next step in dealing with such time-dependent cases. For diseases where adequate knowledge is lacking, clinical expertise needs to be harnessed, so that expert knowledge may be incorporated into the learning mechanism of the models [23]. Complex data can be processed by adding as many attributes to the classifier as possible, without causing overfitting. Also, stacking of parallel processing units is known to increase the efficiency of the prediction system.

## 2.9 Accountability and responsibility

When investigators and stakeholders promote an algorithm for use in the actual biomedical scenario, it is expected that the system performs according to the cardinal features of safety, efficacy, and equity [17]. Even if the ML-based systems are made to yield superior results by eradicating all the issues, the results can never be perfect, and some or the other mistakes are bound to happen. In case of such an event, machine errors may be judged more severely as compared to the case when the same errors are committed by a human employee [48]. However, it must be remembered that the algorithm is a progeny of human thought, which also raises the ethical question of accountability—who is to be blamed in the event of an error, and how can the flaw be rectified? Furthermore, the decisions made by a human involve factors like instinct and emotion, which can yet not be simulated in an AI entity or a machine [37]. If these issues arise beyond a certain limit, the functionality of the algorithm can be compromised despite all efforts of debugging and validation.

It is due to all these challenges and issues that ML-based biomedical research and clinical practices are still not able to achieve their full potential. Some researchers have suggested that these challenges can be dealt with the help of the same tools that created them—ML-based algorithms for the elucidation and investigation of the results [36], which can produce a rationale for the predictions. Logical errors like confounding variables and causality also need to be addressed, so that the difference between the performances in the training and application phases can be reduced. It goes unsaid that the resolving of these issues will give rise to new challenges as well, which shows that the improvements and upgrades that are to be made are actually a constant work-in-progress. However, we must not forget that despite all the issues and hurdles in the realization of this technology, the advantages certainly outweigh the issues. This surely is the reason that makes it all worth the effort.

### 3. The need to address these issues

In order to overcome the issues faced by this technology in the current scenario, it is important to gain an understanding of the need for this technology, and the advantages that it has to offer. Machine Learning based biomedical tools are aimed toward the development and enhancement of biomedical services, which primarily involves clinical diagnostic algorithms and prediction algorithms, but there are also some other biomedical applications of supreme importance. The main reasons as to why we need this technology have been enlisted as follows:

- Machine Learning and deep learning models are the closest that we have gotten to autonomous decision-making by machines. This can prove to be of great assistance to the medical personnel and research investigators, they will increase work efficiency and improve quality of the services provided.
- Biomedical data is extremely complex and requires skilled personnel to process it, as in the case of clinical diagnosis [13]. In some cases like genetic data, data is almost impossible to process manually and requires complicated tools [36]. AI-based systems can not only be made to use these tools with ease but also yield more accurate and precise results that may sometimes even surpass those produced manually.
- ML-based algorithms, when used in synchrony with various sensors, smartphones, and health-monitoring devices, can be used for the development of fully customizable personal healthcare systems that can greatly simplify and improve healthcare practices [44].
- Well-calibrated prediction algorithms are essential for the efficient reallocation of resources. This is a crucial advantage as it ascertains the best use of resources, and the algorithms are improving by the day to make even more precise predictions. Predictive algorithms have great potential in both research [49] as well as clinical scenarios [50].

Given the advantages that ML-based systems have to offer, it would truly be a loss if we do not even attempt to rectify these issues. ML and deep learning algorithms are promising advancements in biomedical research, and attempts are already being made to improve them.

### 4. Recommendations and guidelines for the improvement of ML-based algorithms

Now that we have an understanding of the various challenges that are faced by AI- and ML-based algorithms, all that remains is to figure out definitive ways to remediate them. It must be understood that the task at hand is not a trivial one, and the altogether sensitivity and efficiency of the system has to be improved keeping in mind its relevance with respect to the patients it is meant to benefit. Needless to say, it is easier to nip these evils in the bud than to deal with them when they appear in the later stages when the

systems are actually supposed to work properly [21]. Extensive research have been conducted toward the said aim, and there has been a general agreement among experts as to the goals of the technology, along with the major hurdles and the ways to overcome them [22].

In addition to Machine Learning based models, deep learning methods are being used in combination with traditional Machine Learning systems for added efficiency [23]. Deep learning models can integrate complex heterogeneous data and process it with a great degree of success, owing to their hierarchical learning structure [23], and can greatly revolutionize biomedicine. Furthermore, the recent advancements that have been made in the development of low-cost, small computing devices and sensors mean that the various energy and sensitivity-related issues arising in smart wearable devices, health monitoring gadgets, and smartphones can be dealt with [37]. Some studies have already demonstrated the viability of kernel-energy trade-offs in wearable devices, furthering the cause of energy-efficient data collection even more [44].

It is safe to assume that if these recommendations are followed, it will result in an improvement in the application of ML-based systems in actual biomedical scenarios. However, attention must be paid to the need of constant improvements, so as to ensure the best application of the algorithms and predictive systems, which requires novel and innovative measures. Some of the possible improvements have been described as follows:

#### 4.1 Improvements related to data quality and quantity

The many data-related issues like low availability, lack of complete and balanced data, etc. are the main impediments in the training and validation of classifiers in almost all ML-based models and prediction algorithms. Since the data mining algorithms first need to procure the most relevant, effective, and robust attributes from the data available [23], issues with data quality and quantity cripple many algorithms in the most initial stages. Furthermore, lack of adequacy in correctly reporting data sources results in results that are hard to interpret [22].

Distributed human intelligence has been shown to be a rather simple and efficient solution for the low availability of data, with sufficiently comparable levels of accuracy [51]. This is done by tasking untrained, random individuals with the labeling and preprocessing of medical images that may otherwise require attention from skilled personnel, thus reducing their burden.

The use of ensemble methods and learning tools, which are a combination of more than one type of learning algorithm and data collection system, is now gaining momentum as an effective solution to imbalanced data [52]. Also, some studies have suggested the use of intuitive sampling techniques (like random undersampling, etc.), but they are not as efficient as other solutions and may lead to multiple new complications [25]. Other solutions, like cost-sensitive learning methods, have been shown to be rather superior when compared with such methods [53]. The generation of synthetic data has also been helpful in augmenting scarce data resources [54].



To tackle the issue of missing values, some have suggested the use of various common approaches like deletion of records or variables and mean/median/mode imputation [55] along with nearest k-neighbor imputation. Also, multiple imputation method has been shown to be an effective solution to reduce data-related bias in various fields of biomedical research [56]. Already, novel tools have been used in some biomolecular [57] and anatomical studies [58].

## 4.2 Data security enhancements

With the type and complexity of data involved in the operation of these systems, issues related to data handling, security, and privacy are bound to arise. However, the potential of various solutions is now being explored. Cloud computing has emerged to be the only model that allows the flexibility required in handling such sensitive data. It is the only technology that shows a potential rate of technological advancement to be greater than Moore's law, which is a limiting factor in many such cases [59]. In addition to this, the greatest benefit that entails with this system is the broad platform that it has to offer, which can be used for the development of new tools, sharing data, etc. Systems involving a combination of various techniques like activity monitoring, masking encryption, end-point validation, etc. have already been recommended as viable models for ensuring security and privacy of data [41]. There are certain corporate firms that are commercially offering such solutions for biomedical research purposes.

## 4.3 Calibration and eradication of biases

It is imperative that the developers and investigators try and incorporate the experts of the relevant field, so as to counter the lack of understanding related to the diseases that are to be investigated. Due to the temporality of the disease, care must also be taken that the attributes selected are relevant and as constant as they can be. Also, since only a limited number of attributes can be selected for building a classifier (so that overfitting can be prevented), various other training approaches like decision trees and weight elimination can be used [60]. It is also important that the entire process of building a classifier is taken seriously, as an integral part of the experiment [21].

Some experts also believe that once the presence and nature of biases in an algorithm have been identified and confirmed, ML-based algorithms can be used cyclically to identify and correct those biases without introducing any human biases, thus increasing "algorithmic fairness" [61]. However, this approach may not go as planned in case the assumptions considered initially are wrong, which will increase the risk of introducing even more biases in the algorithm instead of eradicating the ones that were previously present. Semi-supervised learning has instead been suggested as a promising approach in the prevention of biases in these systems. Also, periodic checks in continuously learning algorithms must be conducted regularly, so as to timely prevent the perpetuation of biases that may be introduced in the later functional phases [17].

## 4.4 Improving transportability

The problems related to the transportability of a diagnostic or predictive model, and the reproducibility of results, are supposedly the simplest to deal with. Care must be taken that the detailing of the types and exact model specifications of the various sensors and equipment used in the training and validation of the system are reported with accuracy. This can easily help avoid the errors which may arise due to difference in models and sensor specifications, and the subsequent differences in the work efficiency. After all, a newly developed and supposedly accurate model is effectively useless if it cannot be used by others [21]. Specifying these details can also help prospective operators tune the algorithm as per the availability of devices and sensors that are accessible to them.

## 4.5 Suggestions regarding ethical aspects

As is common knowledge, the technologies and systems in question have a significant impact on multiple parties, including the patients, the medical personnel, the investors, and even the authorities concerned with ensuring proper healthcare services. Thus, the ethical aspects of the technologies need to be improved upon. There are a lot of conceptual frameworks that have come up for the investigation of the ethical aspects of upcoming novel technologies, and also for estimating the values that are inherent in various designing approaches [62]. All these systems mainly identify the prime considerations out of a diverse and all-encompassing assortment of possibilities, leaving out the exceptions, but simultaneously leaving space for novel exceptional considerations to be discovered.

In order to analyze every ethical aspect of the system being developed and the impacts that it will have, it is important to have a complete and context-specific understanding. Thus, the investigation essentially has to be interdisciplinary, so that expertise from all the involved fields is put into the development and of the approach [17]. This would not only increase the transparency and trustworthiness but also aid us to better understand the obscurities of the techniques. At present, the need of the hour is to effectively “dismantle the black box,” aiding further improvements in not only ethical but also other aspects.

It is also important that “scouting” or exploratory investigations with inadequate validations must be avoided. The investigators and developers must clearly state the purpose of their research, so that there is no ambiguity in the functionality of the algorithms. In case of predictive models in general, and for those meant to be used in medical scenarios in particular, the algorithm must be sufficiently grounded in research and backed by ample analysis, so that the predictive value obtained is the maximum.

## 5. Applications in the present scenarios

With such immense potential, and in full awareness of the challenges and roadblocks in the current state of the technology, the application of ML-based models in various

scenarios relevant to diagnosis and healthcare services has been worked upon extensively, putting this technology to good use. Various techniques like spectroscopy, thermography, and even common ones like videography are being coupled with a diverse range of algorithms to make formidable ML models that are being put to use to enhance healthcare services. A few interesting examples have been briefly discussed herein.

A study performed by El-Daw et al. showed the use of ML techniques in the diagnosis of degenerative spondylolisthesis using photographic parameters like the shape of the pelvis and lumbar region [63]. This was based on various previous works, which showed that ML-based techniques can prove to be of use in describing posture-related anomalies and other relevant diagnoses [64,65]. They used the SMOTE (Synthetic Minority Over-sampling Technique) algorithm in this case, which showed a significant increase in accuracy, as compared to that recorded in traditional techniques [66]. Another group used a Hopfield Neural Network model with retinal images as diagnostic input for the detection of diabetic retinopathy [67]. Their model showed an accuracy of 99.25%, along with a specificity index of 0.99, which is higher than most conventional methods used for the same. Image inputs have also been used with Recurrent Convolutional Neural Network (RCNN) models to diagnose various gastrointestinal conditions with a fairly high accuracy of 99.13% [68]. Fig. 6 shows the detection of gastrointestinal ulcers using segmentation-based ML model. Various other studies have shown image input based models to be a viable addition to ease clinical diagnosis [69–71].

Infrared Thermography, which is a common technique used in the diagnosis of numerous medical conditions, is also being used to develop accurate testing models using ML-based systems. A rather detailed study showed that 68 such models are already being used for the diagnosis of various conditions like cancers, burns, diabetes, schizophrenia, and even the state of drunkenness, with varying degrees of sensitivity and accuracy [72]. Some studies, like the ones led by Schaefer et al. [73] and Hernandez-Contreras et al. [74], demonstrated significantly high levels of sensitivity and specificity.

Another study led by Banerjee et al. showed a detailed analysis of various ML-based models for risk prediction in heart failure, acute coronary syndromes, and atrial fibrillation [75], based on the abundance of previous research [76–78]. However, it was observed that most studies were geographically limited, and many of them had limitations in development due to a lack of standardization and definitive guidelines. This also reveals a shortage of routinely usable ML-based models for the management of cardiovascular diseases.

A certain study by Fan et al. [79] shows the comparison of six different ML-based models that are used in the diagnosis or prediction of Carotid Atherosclerosis by combining electronic health record data, like ultrasonography [80], with ML algorithms like Logistic Regression, Random Forest, Decision Trees, etc. The analysis revealed that Logistic Regression showed the highest predictive ability, which was also verified by tenfold cross-validation, whereas decision trees showed the poorest predictive performance. To be exact, Logistic Regression algorithm showed a predictive accuracy of 74.7%, which was found to be higher than the other tools that are traditionally being used in neurology [81].

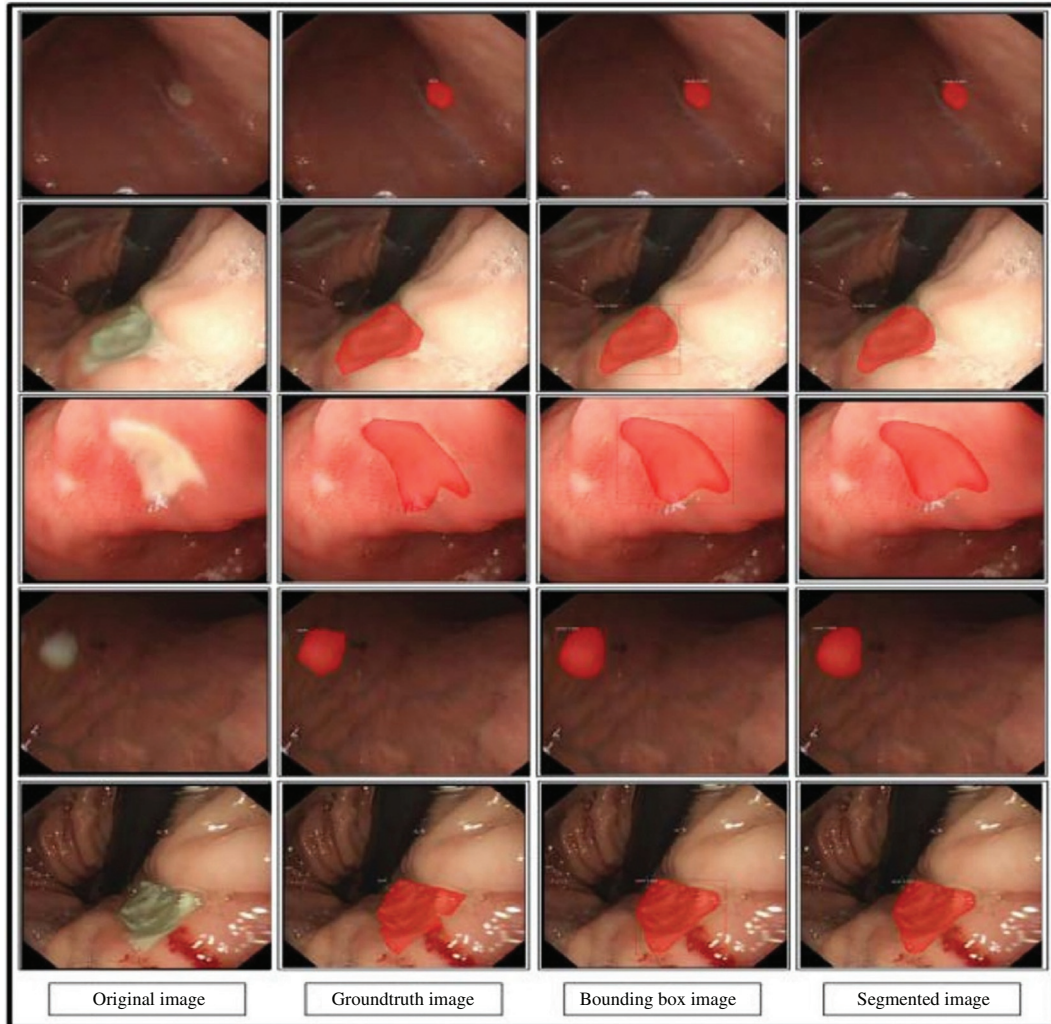


FIG. 6 Segmentation-based detection of gastric ulcers using a Machine Learning model.

In the case of Alzheimer's disease, highly effective diagnostic techniques can be developed using spectroscopy (for the analysis of cerebrospinal fluid compositions) and ML-based algorithms. These techniques can prove to be immensely useful, as preclinical intervention is the only hope of preventing the onset of the disease. A certain group very recently coupled near-infrared (NIR) Raman spectroscopy with classifiers made using Genetic Algorithm to develop a system for this purpose [82]. The resultant ML model achieved a remarkable 84% predictive accuracy in the diagnosis of Alzheimer's disease. Another group used Laser Induced Breakdown Spectroscopy (LIBS) with SelectKBest algorithm to develop a system for the detection of ovarian cancer, using spectroscopic data of

blood samples as input [83]. The model was developed using backpropagation neural networking and was validated using Chi-square test. The resultant model was fairly accurate, showing meager error rates of 1.9% for normal samples and 4.6% for cyst and cancer samples in ensemble. However, the model was not satisfactorily robust due to a shortage of training data.

There has been a dramatic rise in advancements in healthcare relevant to the current pandemic that the world is facing. Needless to say, AI and ML-based models have also been tried to ease the pressure faced by the medical practitioners worldwide. It is speculated that ML-based models may provide frontline workers with invaluable advantage, with the opportunity to reduce morbidity with more targeted and efficient treatments [84,85]. ADAM and Nesterov algorithms have been coupled with video cameras to analyze the behavioral parameters exhibited by patients and even recently vaccinated candidates to detect symptoms of Covid-19 infection [86]. However, the model showed some errors, probably due to overfitting and biasing of training samples, which stabilized as long as the input neurons were more numerous than the input parameters. This was further made difficult due to the increase in errors when the number of input neurons was increased. Regardless, the model showed fairly high accuracy, albeit with some discrimination, which can be increased with the increase in training data. This, however, may result in a decrease in accuracy.

Logistic Regression algorithm has been used in a lot of studies pertaining to Covid-19, which even includes a simulation of the spread of the virus in China [87]. Another model developed using Logistic Regression has been used for the prediction of mortality due to Covid-19 infection [50], and validation has been done using Chi-square test. The model predicted the death of patients with 100% accuracy, but showed a somewhat lesser 96% accuracy in predicting the survival chances.

It has also been observed that the severity of Covid-19 infection in adults has a direct and bidirectional relationship with the occurrence and severity of circulatory and cardiovascular diseases [88]. A study led by Ehwerhemuepha et al. demonstrated the usage of ensemble models in the prediction of Covid-19 severity among patients having cardiovascular diseases, and maybe even for the general population as well [89]. However, the study was limited demographically due to the availability of only local data (namely, white patients), which may have effects on the predictive accuracy of the model on a general scale. The most promising algorithms were found to be the Super Learner and Lasso Regression. Fig. 7 shows a schematic representation of a Super Learner algorithm. Despite the shortcomings of the model, it may prove to be advantageous while planning a treatment strategy in desperate times and has the potential to be life-saving.

## 6. Future prospects and conclusion

In conclusion, it can be stated that Artificial Intelligence based data research in the field of biomedical sciences is the next step in the series. Algorithms based on techniques like Machine Learning and even deep learning have been used in novel research-based areas

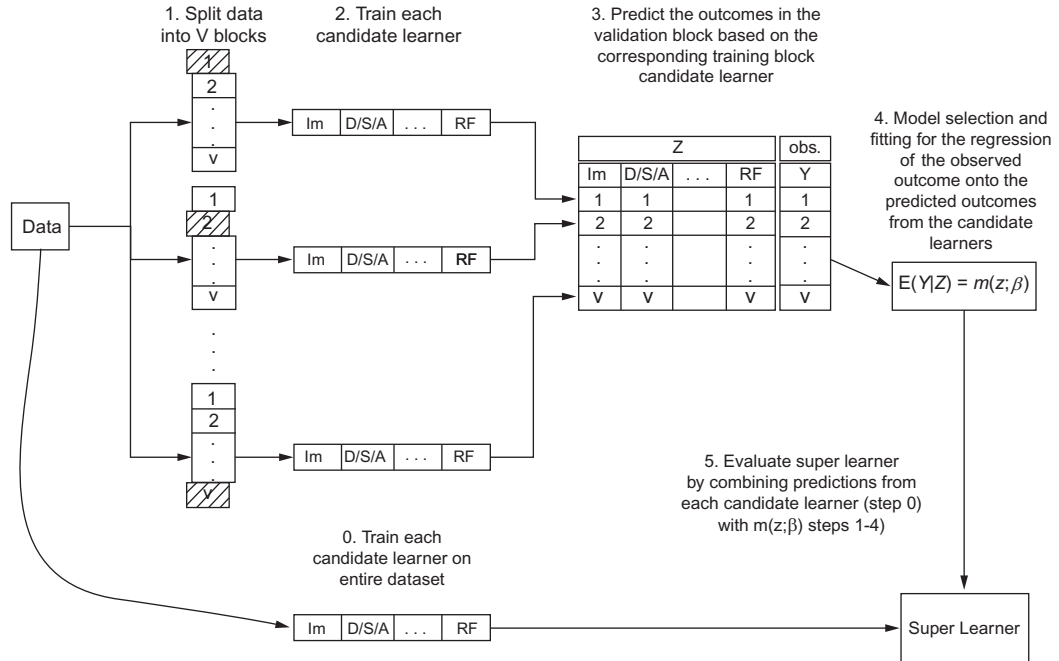


FIG. 7 Schematic representation of a super learner algorithm.

like nano-biotechnology [49], and in crucial and important domains like the healthcare sector, which has been explored in detail in the earlier sections. Machine Learning based techniques have the potential to completely revolutionize biomedicine and healthcare, but certain challenges, like data handling, security, unreliability of algorithms, and even a certain lack of transparency are making it difficult for this technology to achieve its full potential. In addition to these challenges, certain ethical issues have also come to the forefront, which need to be addressed so that more and more individuals can benefit from the same.

In order to deal with these challenges, it is imperative that a cross-disciplinary approach is adopted, so as to ensure a deep, contextual, and well-directed understanding of the problematic scenarios is achieved. Once that has been done, various plans and approaches need to be ascertained to ensure the overall improvement of the functionality and accuracy of these techniques. It can be said that ML-based algorithms have a lot to offer to biomedicine, in particular to the healthcare sector, but they also demand faith and attention in return—as more and more patients embrace this eventuality, the fundamental challenge of the shortage of data can be easily overcome, which will in turn herald new improvements in the technology.

It would be wrong to say that these technologies have not achieved any success in the scenarios that they have been implemented in. Patient data analyzed using these

algorithms has shown efficient detection and diagnosis, better response to healthcare services, accompanied by the increase in clinical efficiency and resource reallocation (especially in the case of predictive algorithms) [15,16]. Very recently, combinations of ML-based algorithms with deep learning and ensemble systems have been successfully implemented in the diagnosis and detection of various traditional diseases like cancer and Alzheimer's disease [63,72,75,79,82,83] and even in the case of Covid-19 [50,86,89], which has been ravaging the world. Some models have also been used to study pathogenesis and other aspects of cellular biology [36]. It is expected that with further improvements, more interactive tools such as caregiving “softbots” [90] and trainable “avatars” [91] can be developed for the diagnosis and treatment of complex psychological and psychosomatic disorders.

Thus, it can be said that with a proper understanding of the present situations, the various hurdles that bar the progress of these technologies can be easily overcome.

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