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Artificial Intelligence and Infectious Disease Imaging

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The mass production of the graphics processing unit and the coronavirus disease 2019 (COVID-19) pandemic have provided the means and the motivation, respectively, for rapid developments in artificial intelligence (AI) and medical imaging techniques. This has led to new opportunities to improve patient care but also new challenges that must be overcome before these techniques are put into practice. In particular, early AI models reported high performances but failed to perform as well on new data. However, these mistakes motivated further innovation focused on developing models that were not only accurate but also stable and generalizable to new data. The recent developments in AI in response to the COVID-19 pandemic will reap future dividends by facilitating, expediting, and informing other medical AI applications and educating the broad academic audience on the topic. Furthermore, AI research on imaging animal models of infectious diseases offers a unique problem space that can fill in evidence gaps that exist in clinical infectious disease research. Here, we aim to provide a focused assessment of the AI techniques leveraged in the infectious disease imaging research space, highlight the unique challenges, and discuss burgeoning solutions.

Keywords. artificial intelligence; AI; imaging; infectious disease.

The global burden of the coronavirus disease 2019 (COVID-19) pandemic has led to an unprecedented acceleration of data science research focused on digital clinical data and medical imaging. Patients with COVID-19 develop a spectrum of lung abnormalities, ranging from ground-glass opacities and crazy paving (interlobular septal thickening) to lung consolidation leading to acute respiratory distress syndrome. In addition to radiography and computed tomography, acute and chronic cardiopulmonary manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may also be imaged with cardiac magnetic resonance (MR) imaging and ultrasonography. In the context of the rapidly changing pandemic, the data science community broadly applied emerging artificial intelligence (AI) tools toward quantitative and semiautomated measurement, classification, and interpretation of medical images. This commonly included fundamental models for deep-learning-based image segmentation and machine learning (ML) classification of disease.

Unfortunately, early fervor and broad speculation outpaced practical and validated deployment of impactful models that were generalizable and not overfit to a geographic area, demographic group, disease stage, or genetic variant. The number of research papers and models in this field grew quickly, and a growing need emerged to review and assess the current status and impact of efforts. AI tools have been proposed for assisting radiologist workflows in resource-challenged settings, optimizing triage, or quantifying disease severity. However, it is generally agreed in retrospect that reported model performances may be misrepresented and may not generalize to larger more diverse populations, disease settings, and geographies.

Although the application of AI methods to imaging patients with COVID-19 may prove important in the current pandemic, the major scientific impact of this acceleration and lessons learned may well be felt indirectly in future broader applications to other infectious diseases, each with their own disease phenotype. It is in this space that AI methods have been less successfully applied in the past. The common translational paradigm, from bench to preclinical model to the patient, does not always apply to the high-consequence infectious disease setting. Whereas the human outbreak setting informs epidemiology, transmission, infection dynamics, and early characterization of human disease, preclinical models are often required to interrogate pathophysiology, mechanisms of disease, and the early development of therapeutic countermeasures.

The application of AI methods to preclinical and clinical imaging shares some common features and challenges, though the unique properties and often varying goals present specific challenges that will be discussed in this review article. ML methods require high-quality training data sets and often need time-

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intensive and human resource–intensive manual definition of disease abnormalities or features in medical images. Preclinical modeling and imaging present a unique opportunity for rigorously controlled experiments, with preinfection baseline followed by serial imaging uniquely enabling longitudinal assessment of disease. This enables a focus on specific hypotheses and can restrict the influence of confounding factors.

SCOPE AND APPROACH

We aim to provide an overview and assessment of the AI techniques leveraged in the infectious disease imaging research space. We also aim to highlight the unique challenges of this research space as it applies to humans and animal models of disease. This review will focus on organ–scale imaging (eg, chest radiography, computed tomography [CT], MR imaging, and positron emission tomography [PET]) in the context of infectious disease research. Literature searches were conducted using PubMed and Google Scholar. with attention to both preclinical and clinical applications and models. Key terms used throughout the article are defined in Table 1.

Table 1. Definitions of Key Terms

Term	Definition
AI	Simulation of human intelligence in machines
Artificial neural networks	Algorithm inspired by biological neural networks in which interconnected neurons process information
Convolutional neural networks	Type of neural network that uses a series of learnable convolutional layers to distill spatial features from imaging data
Deep learning	A subset of ML, algorithms that use an artificial neural network to extract high-level features from data; these methods can be used to distill complex data types, such as images and text for predictive tasks
Labeled data	Data that include class labels; for example, if the task is to predict the fruit name (class label) given the color and shape, the labeled data would include the fruit name, color, and shape
Low/poor-quality labeled data	A labeled data set wherein the label is not accurate for some data points
ML	A subset of AI, algorithms that learn without explicit instructions
Model generalizability	The ability for a model to perform well on new data it has not been trained on
Partially labeled data	A data set that includes some combination of labeled and unlabeled data
Preclinical model	Nonhuman (typically animal) model of a disease in humans
Self-supervised learning	A type of ML in which the algorithm learns from unlabeled data to form representations; the representations can be used later to better complete a more useful downstream task
Supervised learning	A type of ML in which the algorithm learns from labeled data to produce the label for new data
Traditional/classic ML	A subset of ML, algorithms that learn from structured (tabular) data
Unlabeled data	Data that do not include class labels; for example, if the task is to predict the fruit name (class label) given the color and shape, the unlabeled data would include only the fruit color and shape
Weakly supervised or semi-supervised learning	A type of ML that falls between self-supervised and supervised learning, in which a small amount of labeled and a large amount of unlabeled data are used for model training

Abbreviations: AI, artificial intelligence; ML, machine learning.

EARLY APPLICATIONS OF AI IN INFECTIOUS DISEASE RESEARCH

One of the earliest attempts at a computer-based clinical decision support system for infectious diseases was MYCIN, which used >500 rules to determine the bacterial species responsible for an infection, provide a diagnosis, and recommend an antibody regimen [1]. However, it eventually became clear that the decision process clinicians make is far too complex to encode in explicitly defined rules. Furthermore, inputting a long series of answers to questions was not easily integrated into clinical practice [2]. ML has the potential to solve many of these issues by using large amounts of data to automatically derive a logic system for providing clinical decision support. Initial applications of AI to aid in clinical decision making on infectious diseases focused on structured and easily accessible types of medical data, including vital signs, laboratory measures, demographics, medical history, and physical examination data [2]. More complex (unstructured) data types, such as images, particularly 3-dimensional (3D) and time–series images, are difficult to quantify and thus require specialized AI methods to take full advantage of the wealth of information hidden within.

CURRENT AI APPROACHES FOR THE STUDY OF INFECTIOUS DISEASES USING IMAGING

As AI computer vision techniques have grown, so have their applications to infectious disease imaging. Imaging tasks that have been automated using AI have been directed toward 2 fundamental questions: “Where is it?” (segmentation) and “What is it?” (classification). Segmentation is the process of identifying the pixels in an image that correspond with a region of interest. Once an image is segmented, further analyses can be focused on specific organs or tissues. Manual segmentation of images is a time-consuming process, particularly for high-field-of-view and high-resolution 3D images commonly produced by modern medical imaging modalities, such as CT and MR imaging. Manual segmentation is even more time-consuming for modalities that image over time, such as functional MR imaging and PET. Therefore, the development of reliable automated segmentation methods is critical to advancing infectious disease imaging research and improving clinical practice.

With the advent of deep learning and enhanced computing resources, AI techniques have grown in popularity as an effective method to automatically segment images and have been applied across a wide range of infectious diseases. A probabilistic information method [3] was used to segment different regions of the whole brain to map abnormal subcortical brain morphometry in a human immunodeficiency virus (HIV) study [4]. A deep-learning-based method for tuberculosis detection and segmentation in chest radiographs was also used [5]. More recently, a deep-learning-based method was developed to segment the liver in CT images of animal models of Ebola and Marburg virus, Lassa virus, and Nipah virus infections [6]. In this study, Reza and colleagues [6] found that a feature pyramid network model could segment the liver from a CT scan with a dice score of 95%. During the COVID-19 pandemic, many automated lung lesions segmentation methods of CT scans and radiographs have been proposed, including the dual-branch combination network [7], semisupervised Inf-Net [8], slice-based 2-dimensional UNet [9], Dense-UNet [10], encoder-decoder-based attention network [11], dual-sampling attention network [12], and many similar convolutional neural network (CNN)–based methods [13].

In the context of infectious disease imaging, classification commonly involves predicting the infection status, disease severity or stage, or response to therapeutic intervention. Classification of images can be performed in segmented regions or directly on the original image. Traditional ML algorithms, such as logistic regression, support vector machine, k-nearest neighbors, naive Bayes, linear discriminant analysis, and tree-based algorithms, can be used to classify images, but the unstructured data must first be converted into a structured data format (ie, a table) through the calculation of descriptive features. Image features can be quantified using simple metrics, such as volume or mean intensity (eg, volume and mean intensity of a lesion). In addition, more complex metrics, such as radiomic [14] features, can be calculated to quantify shapes and textures found within the image.

Studies of SARS-CoV-2 [15–19] and other infectious lung diseases [20] have successfully deployed traditional ML algorithms for classifying images using radiomic features. AI approaches that have been applied to the imaging of infectious diseases have ranged in complexity from simple algorithms applied to structured data sets to the more complex deep-learning algorithms that excel in making predictions from unstructured data sets, including large imaging data sets. Deep-learning algorithms, such as CNNs, have been widely used in infectious disease research, including for the classification (ie, detection) of COVID-19, pneumonia, and pulmonary tuberculosis [21–23].

CNNs have proved useful in a diverse array of studies related to infectious disease research and medical imaging; however, the introduction of the vision transformer model, has had a great impact in these domains and seems to suggest a new era in deep learning [24,25]. This model has been shown to outperform CNN models and ensemble approaches trained on binary and multiclass scan data sets [26]. Similarly, a multitask vision transformer model was trained to perform both diagnostics and severity prediction of patients with COVID-19 [27]. When tasked with classifying radiographs as normal, COVID-19, or other infection, the model performed with areas under the curve of 0.932, 0.947, and 0.928; sensitivities of 83.4%, 88.4%, and 85.4%; and accuracies of 83.8%, 84.9%, and 86.9% on a set of 3 external data sets [26].

Challenge: Disease Specificity

Imaging techniques, such as CT and MR imaging, can produce high-resolution 3D images with intensities that relate to the atomic density of the tissue and the nuclear (usually hydrogen, used as a proxy for water) density within the tissue, respectively. Typically, viral infection either causes an inflammatory immune response (leading to an increase in tissue density) or causes cell death (leading to a reduction in tissue density). As a result, ML models have performed well when trained to detect infections from medical images in areas such as the lungs [28–30]. However, changes in tissue density (captured by CT, structural MR imaging, and ultrasonography), brain blood flow (captured by functional MR imaging), and metabolic activity (captured by $[^{18}F]$Fluorodeoxyglucose PET) are secondary effects of infection and thus not pathogen specific. As a result, AI models trained only on in vivo imaging modalities are limited in their potential performance as biomarkers of infectious disease progression. Of note, some PET tracers have been developed that aim to be bacteria specific, but they have been largely restricted to preclinical applications [31–34]. Building AI models that are trained on data that contain both physical and biological properties (eg, CT and blood biomarkers, or MR imaging and PET) would enable more specific models of disease that better generalize across the spectrum of infectious pathogens.

Challenge: Data Scarcity

AI models using medical images, particularly neural networks, are large and complex and thus require a large number of labeled samples to train adequately. This is a prominent challenge, particularly in the infectious disease imaging research space. Data scarcity is a function of multiple factors, including the prevalence of the disease, severity of the disease, duration of the disease, difficulty of the labeling task, prevalence of experts that can perform labeling, data-sharing hurdles, and privacy regulations. As a result, human data are more available for some diseases (eg, COVID-19), while in other diseases, data from animal models of disease are more available (eg, Ebola virus disease, Nipah virus disease, and Lassa fever). Methods such as self-supervised, semisupervised, and weakly supervised learning aim to provide robust models trained on unlabeled, partially labeled, or low-quality labeled data. Self-supervised learning, which has been used to pretrain a range of different attention models, has proved especially effective at leveraging unlabeled data toward significant improvements in model generalization and transfer learning [35].

Self-supervision, wherein a model learns a robust representation of a domain (eg, the English language), rather than task-specific information, has yielded significant improvements in model performance on complex downstream tasks involving small annotated data sets [36,37]. After the pretraining stage is complete, the models can be fine-tuned on the domain-specific data set, and the learned representation can be shifted slightly to facilitate performance on a complex task, while preserving the robust features learned from the large unlabeled training set [38–40] (Figure 1). Infectious disease researchers can deploy various self-supervision techniques to use the large quantities of unlabeled data sets (including those from other, related domains) that are often readily available. Both vision transformers and deep CNN models used for COVID-19 classification or detection are very often pretrained on large public data sets that include medical images as well as images from across many different categories (ie, ImageNet) [26,27,41–43]. Without this pretraining, the models would likely be overfitted to task-specific data sets owing to the scarcity of data.

In addition to algorithmic improvements to accomplish higher performance with less training data, some have turned their focus on improving the quality of the data used to train models. This approach, termed *data-centric AI,* focuses on using domain knowledge and systematic processes to remove poor-quality data points and design the input features to guide the model to be more robust and generalizable. DataPerf is a recently developed benchmark suite for ML data sets that aims to implement data-centric AI principles [44].

Challenge: Explainable AI

Most deep-learning models do not explain their predictions in a way that humans can understand [45]. For example, in CNNs, the convolutional layers are adjusted through the training process to deconstruct the image into relevant features. However, the trained weights of the convolutional layers are not organized into human-interpretable concepts (eg, shapes and textures) making the inner logic of the model unknown (Figure 2). Such black-box models may not be safe to use in high-stake applications, such as medical image diagnosis [46,47]. It has been demonstrated that current AI systems can easily be fooled: a small, carefully designed change in how inputs are presented to an AI system can completely change diagnostic performance (eg, from a benign to a malignant diagnostic decision when rotating the input image a few degrees or putting a small amount of noise into the image) [48].

Without the ability to understand the reasoning behind a radiological prediction, radiologists are unlikely to trust and adopt deep-learning models. This interpretability barrier is a critical challenge that AI researchers must overcome before these predictive models can be applied responsibly and adopted into clinical practice. Uninterpretable algorithms are still useful in some applications, such as the knowledge discovery process and the creation of baselines for performance comparison. However, uninterpretable AI models could have catastrophic consequences, such as severe impediments in therapy planning, intervention, and healthcare costs, [46,49,50].

It should be noted that there is no all-purpose definition for *explainability* or *interpretability* because the proper application of the concept is domain specific [47,51,52]. A large number of interpretable prediction studies exist in the literature [47,53–111], but most provide explanations that are not faithful to what the original model computes. As agreed by pioneers in the field of deep learning, including Rudin, G. Marcus, Schölkopf, Doshi-Velez, and several others [112–118], the currently available methods in the literature tend to present "interpretable" AI models in a misleading way such that the underlying mechanisms are not faithfully revealed.

Studies exploring how CNNs make predictions are typically done through post hoc interpretation techniques, but these do not provide a true (fully transparent) explanation. For instance, some studies remove parts of an image (pixels or regions) to determine their impact on the final prediction (called *perturbation-based* or *ablation-based* methods) [119–121]. These methods do not reflect built-in explainability, and their interpretations fail for several reasons. For instance, perturbation-based methods assume that the model trained on the ablated data set follows a similar process to the model trained on the full data set; however, deep-learning models are known to vary widely as a result of subtle changes in the training data set [48].

A second major group of post hoc interpretation techniques uses neuron activation maps to discover attention (eg, CAM and Grad-CAM) (called localization-based or attention-based methods) [122,123] or looks at the interpretability of individual neurons [56,124]. It has been shown that attention and gradient information are often uncorrelated, with many different attention maps yielding identical results, while others have shown that removing visually interpretable neurons versus uninterpretable ones had no measurable effect on network prediction accuracy [125]. Although Grad-CAM is becoming the de facto visualization method, it has been noted by several researchers that Grad-CAM is very sensitive to noise and is not a completely reliable technique. It has been shown that an alternative approach, based on information bottleneck attribution (IBA) [126], is far superior to the widely adopted Grad-CAM approach [123]. The study tested >1100 CT scans of patients with varying levels of COVID-19 severity and without dense annotations and found that IBA had minimal false-positive

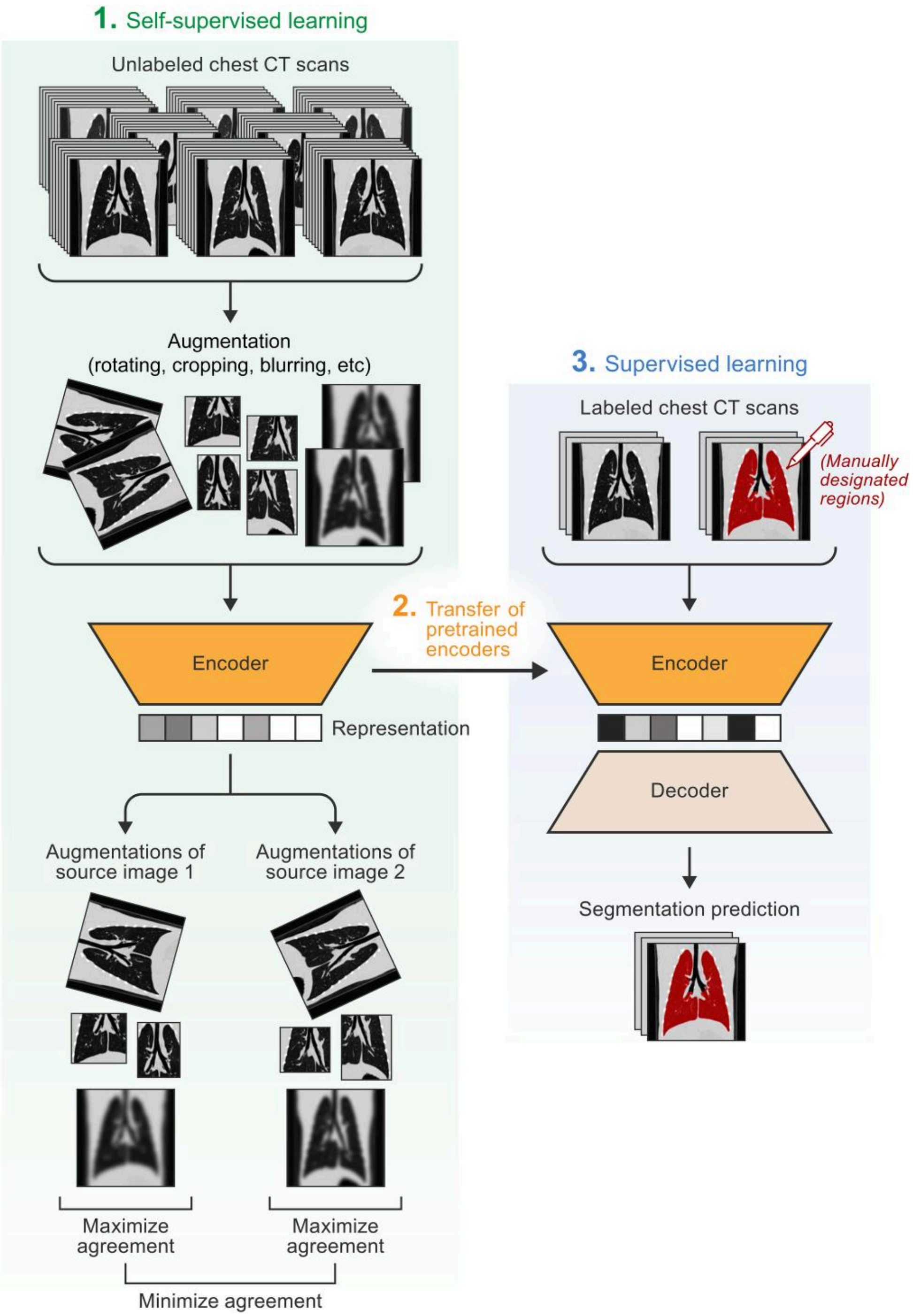
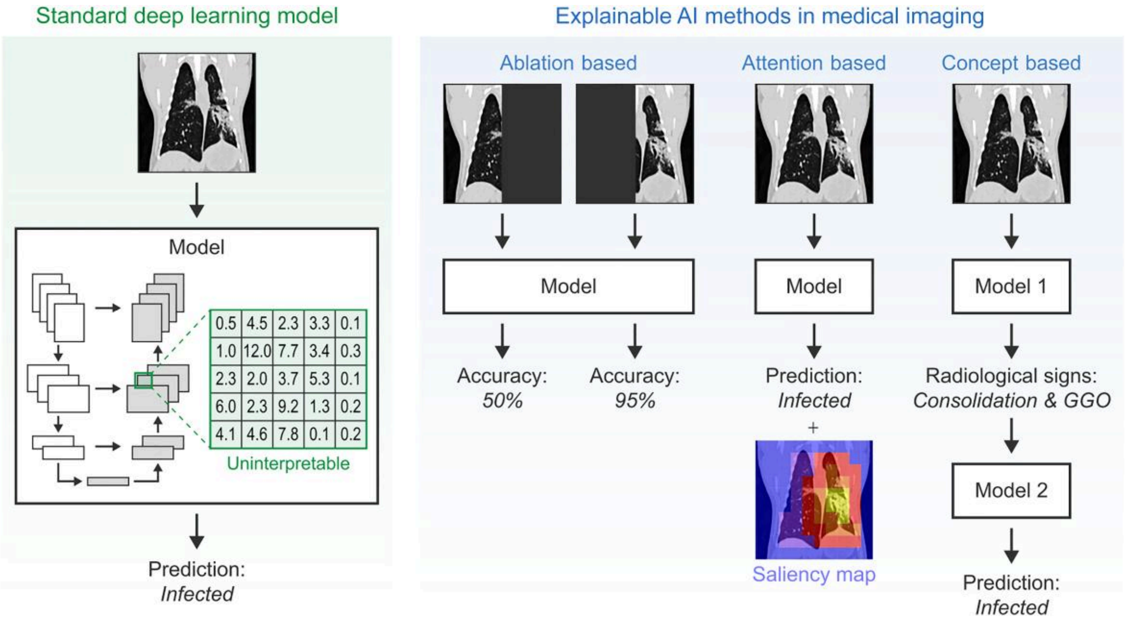


Figure 1. Self-supervised learning for medical image segmentation. The diagram describes an implementation of how unlabeled computed tomographic (CT) scans and self-supervised learning (specifically contrastive learning) can be used to enhance the performance of a supervised learning segmentation model. First, unlabeled scans are augmented using simple transformations, such as cropping, rotation, and blurring. These augmented scans are inputted into the self-supervised model, and the model is tasked with distinguishing augmented images that come from the same source image from augmented images that come from different images (ie, pretask). After training, the pretrained encoders can be transferred to a supervised learning model, which is given a small batch of labeled scans and tasked with producing the segmentation masks. Pretraining with a self-supervised learning task has been shown to enhance the performance of supervised learning models.

regions and was superior to Grad-CAM in >95% of the visual evaluations. Figure 3 shows the accurate localization of the IBA approach and failures of Grad-CAM.

In medical imaging of infectious diseases, many studies applied "explainable" models with varying levels of explainability. Methods such as Grad-CAM [123] and other direct gradient



0.5	4.5	2.3	3.3	0.1
1.0	12.0	7.7	3.4	0.3
2.3	2.0	3.7	5.3	0.1
6.0	2.3	9.2	1.3	0.2
4.1	4.6	7.8	0.1	0.2

Figure 2. Explainable artificial intelligence (AI) methods in medical imaging. Standard deep learning models are uninterpretable and therefore work as a "black box." Explainable AI methods, such as ablation-based, attention-based, and concept-based methods, provide clinicians and researchers with additional information about how the model forms its predictions. Abbreviation: GGO, ground-glass opacities.

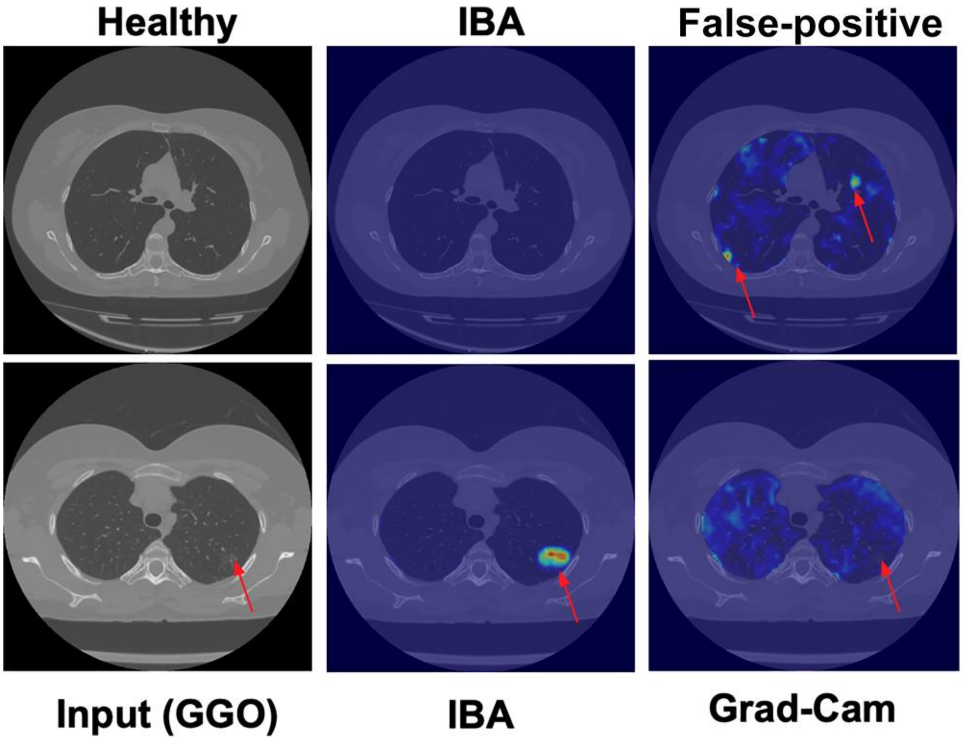


Figure 3. Grad-CAM compared with information bottleneck attribution (IBA) attention maps. Left, Computed tomographic (CT) scan with subtle ground-glass opacities (GGO) pattern. The proposed IBA shows the exact location of pathology without false-positives and precisely, while Grad-CAM fails. Arrows on the first row are pointing to areas within the image that are not true lesions but false positives predicted by Grad-Cam. Arrows on the bottom row point to true lesions not detected by Grad-Cam.

approaches have been applied to infectious disease imaging [127,128]. For example, one study developed a robust deep-learning model for COVID-19 detection/characterization on CT scans from a diverse multinational cohort [129]. The model achieved 92.4% accuracy in the validation set and 90.8% in the independent test set for the COVID-19 diagnosis. The Grad-CAM algorithm was used to highlight the pathological regions that the algorithm learns from. While the accuracy was high, the Grad-CAM saliency maps did not reveal intuitive attention trends.

Beyond commonly considered visual interpretation methods, some researchers have proposed improving the interpretability of deep-learning models by embedding radiographic interpretations (concept-based explainable AI). The idea is to learn the radiographic explanations of the object of interest (eg, pathological region) from radiologists and train the deep-learning architecture to learn these features in addition to the main outcome (eg, classification). For instance, the explainable capsule network (X-Caps) study [130] describes a novel multi-task capsule network providing radiographic explainability for prediction. Visual explanations (called “attributes”) are encoded as tasks and defined by radiologists using standard guidelines. For example, to detect infectious lung disease in a CT scan, the attributes may be set up as the existence of the following patterns: ground-glass opacities, consolidation, traction bronchiectasis, cysts, centrilobular nodules, reticulations, honeycombing, and subpleural lines.

Challenge: Spectrum Bias

The clinical utility of AI models is highly dependent on their ability to perform well across the spectrum of cases they are anticipated to analyze. AI researchers use techniques such as stratified cross-validation to ensure that the distribution of sub-classes in the testing set matches the training set. However, if the full data set does not replicate the range of cases in the population, then the calculated performance metrics may not represent the model’s performance on the population (termed spectrum bias). In clinical studies, spectrum bias may affect model performance on ethnic, age, or sex minorities. Spectrum bias can also occur as a result of recruiting methods and can lead to models biased toward those financially able to take time off to participate in a research study.

In preclinical research, much more control is maintained over animal demographics. However, differences in disease presentation across species can lead to another form of spectrum bias. In nonhuman primate models of SARS-CoV-2 infection, only a mild form of the disease has been replicated [131,132]. However, in crab-eating (cynomolgus) macaque models of Ebola virus disease, infection leads to death faster than that seen in humans (macaques, 5–8 days from exposure to death; humans, 4–10 days incubation period, followed by death at 6–16 days after onset of symptoms) [133,134]. Thus, animal models of infectious diseases sometimes overrepresent and sometimes underrepresent the disease’s pace and severity in humans. More work is needed to fine-tune these animal models to replicate human disease more accurately. In the meantime, AI researchers must keep this in mind while training their models on animal data for predictions on human data.

The primary method to improve the generalizability of a biased data set is to collect more data from the underrepresented group. If this is not an available option, other methods that have been developed to compensate for class imbalances may be applied. For example, designing the loss function to increase the penalty for incorrect predictions of the minority group draws the model’s “focus” to that group, potentially balancing performance across the minority and majority groups [135]. Other techniques involve inflating the weight of minority samples by reducing the number of majority samples (undersampling), creating duplicates of the minority samples (oversampling), and creating synthetic minority samples. In medical imaging, synthetic minority images can be created using generative adversarial neural networks, which have shown success in alleviating class imbalances [136]. In a study by Waheed and colleagues, it was found that COVID-19 detection in radiographs could be improved from 85% to 95% accuracy using generative adversarial neural networks [137].

UNIQUE GOALS AND CHALLENGES OF AI APPLICATIONS TO IMAGING ANIMAL MODELS OF INFECTIOUS DISEASES

Animal models of infectious diseases provide unique opportunities to study infectious diseases in a highly controlled environment typically not possible in the clinic, especially in most outbreak settings. With these opportunities also comes unique challenges in collecting and analyzing data in this field (Table 2). Ultimately, AI research on animal models of infectious diseases must be designed to build toward improving patient care, and thus goals must be carefully crafted to ensure this outcome.

Goals of AI Applications to Imaging Animal Models of Infectious Diseases

There are 3 main goals of AI in the research space of animal models of infectious disease imaging. One goal is to directly translate predictive models to humans. For diseases in which high-quality labeled data are more easily produced in animals than collected in humans (eg, rare and severe diseases); predictive models can be trained on animal models and applied in humans. However, this is challenging because the animal model of disease must replicate all key features of the disease in humans. An example of a model trained on animal data and likely to perform equally well on human data is deep learning for lung-lesion phenotyping in nonhuman primates. This is because lung lesion types (eg, ground-glass opacities, crazy-paving, and consolidation) are defined by common radiological

Table 2. Major Challenges for Humans and Animal Artificial Intelligence Infectious Disease Imaging Research and Corresponding Solutions

Challenges	Solutions	Animal Research	Human Research
Data scarcity	Self-supervised learning, semisupervised learning, and data-centric AI	X	X
Model interpretability	Explainable AI techniques	X	X
Disease specificity	Multimodal models	X	X
Spectrum bias	Improvement of recruiting methods and animal models, bias loss term, oversampling or undersampling, and synthetic data	X	X
Development of imaging tools	Additional funding for research	X	…
Control over environmental variables	Careful design of input features and explainable AI techniques	…	X
Cost per image	Additional funding for research	X	…
Privacy	Federated and swarm learning	…	X

Abbreviation: AI, artificial intelligence;

patterns and are not specific to anatomy, disease, or species [138].

The second major goal is to build biomarkers of disease progression for application in animal models. Such biomarkers could be used as a benchmark for assessing the effectiveness of emerging therapies. Imaging biomarkers (and AI-empowered imaging biomarkers) can be collected in vivo, enabling longitudinal studies and eliminating the need for serial sacrifice. Imaging biomarkers are well positioned to fill this role because all major imaging modalities (ie, CT, MR imaging, PET, and ultrasonography) quantify disease characteristics downstream of the initial infection. For example, imaging biomarkers of neurological impairment from HIV infection (termed HIV/neuroAIDS) have been developed using MR spectroscopy, diffusion tensor imaging, and functional MR imaging; these modalities measure changes in neurochemicals, brain tissue structure, and brain function, respectively. All of these measures do not detect HIV but instead detect a downstream consequence of HIV infection and can be correlated with clinical symptoms and signs. Imaging biomarkers bridge the gap between virus detection (too detached from symptoms) and symptom detection (too late in the disease process), thus filling an important role in therapy development.

The third major goal is to enhance our understanding of underlying disease mechanisms that are common between animal models of disease and the disease in humans. Particularly, models with high interpretability (eg, feature weights in logistic regression, feature importance in decision trees, and saliency maps in CNNs and graph-based data mining) provide information on the structure of predictive models and consequently a window into the system being modeled. Feature-importance measures have been used to determine the most important features in applications such as the prediction of COVID-19 disease progression [139], detection of influenza [140], and prediction of HIV therapy potency [141]. In a study examining the use of laboratory data for predicting the disease progression of COVID-19, feature importance was used to identify D-dimer, C-reactive protein, and age as the top 3 features used by the ML model [139]. Unlike linear statistical models, feature importance in a nonlinear ML model can highlight strong nonlinear relationships between features and the classification task. It should be noted that, although high feature importance suggests a relationship between a predictor and a classification task, there are no currently agreed-on conventions for determining how accurate a model must be and how important a feature must be to be considered “significant” (eg, the 95% confidence interval convention). Further work is needed in this area to maximize the knowledge gained from feature-importance calculations; until then, AI researchers must be cautious in their interpretation.

Challenges of AI Applications to Imaging Animal Models of Infectious Diseases

Animal imaging studies of infectious diseases with sample sizes typical of AI research are rare, primarily owing to the costs associated with such studies. In vivo modeling of highly infectious diseases imposes significant logistical and financial challenges. In a typical animal imaging experiment, specialized scanners (eg, high-field MR imaging, micro-CT, and small-animal PET) are needed to image the small organs found in rodent models of disease. Furthermore, infectious disease imaging requires specialized infrastructure to protect researchers during the scanning procedure [142]. To study highly infectious and high-consequence biological agents (eg, Marburg, Ebola, Lassa, Hendra, and Nipah viruses) entire facilities must be designed for maximum contaminant (biosafety level 4) conditions that encompass the animal care sections as well as imaging suites [143]. Although imaging animal models of infectious diseases is associated with a high cost per sample, experiments can be precisely designed to improve the value of each sample for training a predictive model.

A core tenet of the data-centric AI approach is that a predictive model trained on a small but well-designed data set may learn the generalizable predictive features better than a model trained on a large and noisy data set [44]. Finely tuned experimental parameters and highly controlled environmental factors can be used to create higher-quality training data compared to what is possible in humans. Parameters such as exposure dose and time from exposure can be precisely controlled in animal studies. Furthermore, preexposure data points and long-term follow-up data points are more easily collected in animal studies. Environmental factors, such as diet, physical activity, and comorbid conditions, vary widely in the human population but are easily standardized in animal studies. By keeping environmental factors consistent and using preexposure-corrected data, researchers can be more confident that high-performing predictive models are learning generalizable concepts and are not biased by confounding factors.

Image preprocessing, such as normalization, registration, and segmentation, can have an immense impact on the performance of a predictive model. Classic image-analysis techniques provide an opportunity for imaging scientists to leverage decades of previous research to minimize variability in imaging data unrelated to the infectious agent. Importantly, many of these techniques can significantly improve model performances without acquiring more data. Unfortunately, processing tools for animal images are less refined than those for human images. For example, brain researchers use registration tools to align brains across scans and control for slight differences in brain shape and size to focus predictive models on changes in intensity within common regions of the brain. While well-tuned for application in human imaging, the necessary templates and tools for preprocessing are not as developed for animal imaging, increasing the noise that predictive models must work around.

Unique Challenges of AI Applications to Imaging Infectious Diseases in Humans

Compared with animal models of infectious diseases, human imaging data are much noisier and more complicated by uncontrolled and confounding factors. These factors range across the full spectrum of human environmental and genetic variability, and each factor can modulate the response to infection directly or indirectly. Human data are also more often collected across multiple sites, introducing another layer of confounding factors. These confounders can distort model performance in ways that are not readily apparent. For example, it has been found that some imaging-based predictive models were detecting medical interventions in response to diseases [144,145] rather than biological markers of diseases. This can be particularly dangerous for clinical applications, as untreated patients with a disease are at the greatest risk for harm (compared with treated patients and those without disease). Great care must be taken to ensure that data fed into AI models do not contain features that have spurious correlations with the response variable. In addition, explainable AI techniques must become common practice to ensure that models are using appropriate features to form predictions.

CONCLUSIONS

Infectious disease imaging during the pandemic has proven a fertile ground for the development and application of classic ML, deep learning, and AI data science. AI tools have been used for both preclinical and clinical purposes but need to be fine-tuned. As AI researchers tackle increasingly complex problems, increasingly complex solutions have been developed. When patients' well-being is at stake, an equal, if not greater, effort must be dedicated to developing methods to ensure that new AI techniques are adequately generalizable, explainable, and unbiased. An AI roadway laid on the foundation of COVID-19 imaging and data acquisition attempts may facilitate subsequent passage toward robust and generalizable models. Certainly, the long-term impact on the data-science research community is broad.

Notes

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