Exploring the applicability of machine learning based artificial intelligence in the analysis of cardiovascular imaging

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3 | HYBRID CARDIAC IMAGING: THE ROLE OF MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE

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Abstract

Machine learning currently represents the corner stone of modern artificial intelligence. The algorithms involved have rapidly permeated into medical sciences and have demonstrated the capacity to revolutionize data analysis through optimized variable exploration and integration as well as improved image processing and recognition. As such, cardiovascular hybrid imaging constitutes an open pathway for implementation in the form of view identification, structure segmentation, disease identification, functional parameter estimation and prognostic evaluation in is traditional forms in SPECT/CT, PET/CT and PET/MR. Further, an elastic view on the concept of hybridization in cardiovascular imaging offers the possibility to concatenate applications based on the combination of machine learning models, data types and imaging modalities. Current aims for these implementations include process automation and generation of clinical decision support systems tailored to the needs of daily clinical practice in the evaluation of cardiovascular disease at the individual level. The present chapter summarizes core concepts in modern machine learning-based AI, provides an overview of the recent advances in data processing, image analysis, result interpretation and emerging clinical implementations, and suggests the potential and future perspectives of machine learning analytics within the context of hybrid cardiovascular imaging.

Introduction

The concept of hybrid imaging has long lingered in the minds of cardiovascular and imaging physicians. The benefit of combining imaging modalities has been increasingly demonstrated as it enhances the diagnostic and prognostic value of individual techniques. This synergistic effect could be due to various anatomical features being detected between modalities, but more often complementary anatomical information helps in the evaluation of the imaging results at the functional and molecular levels. Hybrid imaging has become an increasingly popular concept in cardiac imaging in the last decades. Predominantly, hybrid imaging has been evaluated in the combination of myocardial perfusion data from single photon (SPECT) and positron-emission computed tomography (PET) with coronary artery anatomy from computed tomography (CT), and myocardial metabolism imaging with PET with tissue characterization through cardiac magnetic resonance (CMR). On the other hand, invasive imaging has evolved to deliver complex anatomical-functional mapping for arrhythmia detection and modern analysis in angiographic images is on its way to deliver functional parameters with increasing ease. Ultimately, it is expected that the expanding hybrid imaging gamut will provide high-quality information to improve clinical decision-making.

While the technical feasibility is established, the time and labor consumed in processing and interpretation of the vast and increasing volume of data remains the major challenge of this era. It is within this landscape that the implementation of modern machine learning (ML)-based artificial intelligence (AI) has gravitated towards medical image analysis. ML offers the possibility to explore, integrate, and analyze massive amounts of data through its complex nonlinear dependencies, which notably are generally not fully exploited by traditional statistical modeling. In this sense, (cardiovascular) imaging represents a logical target for such analytics, given the gauge of its information stream. *Figure 1* shows the number of publications indexed with the topics "Hybrid Cardiac Imaging" or "Machine Learning in Hybrid Imaging" in the last three decades in the literature database PubMed.

In the present chapter, we present core concepts in modern machine learning-based AI. Further, we discuss recent advances with respect to data processing, image analysis, result interpretation, and clinical decision support within the context of (hybrid) cardiovascular imaging through a selected body of scientific work. Finally, we summarize the applicability and the envisioned potential of machine learning-based AI in daily clinical practice.

Machine learning-based AI

Machine learning (ML) is a field in computer science which involves the generation of computer systems (algorithms) that are capable of iteratively learning by exploring and utilizing patterns within data to act specifically, without being explicitly programmed. This process of system adaptation in order to optimize the task at hand (e.g., classification or prediction) mimics biological learning. In contrast, AI refers to the application of such systems for with a practically orientated-tasks that commonly would require at least human-level intelligence (e.g., driving, playing Go or making a medical diagnosis).
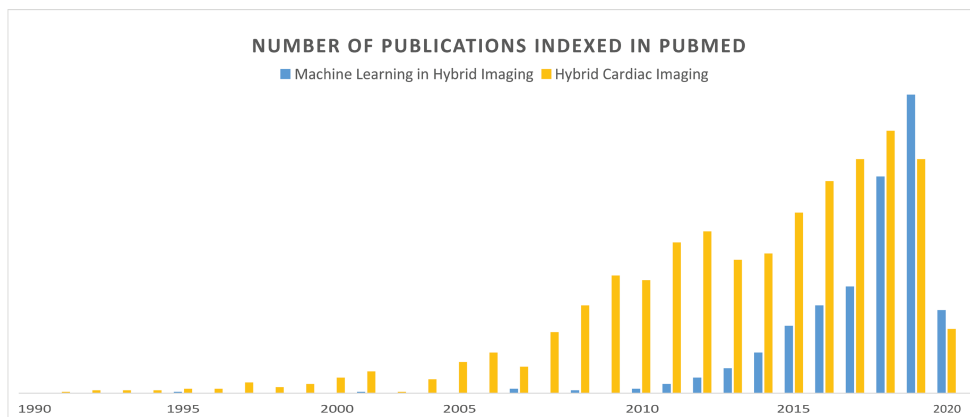
Figure 1. Number of publications per year found in Medline. Mesh Terms and Keywords "Hybrid Cardiac Imaging" (yellow) and "Machine Learning in Hybrid Imaging" (blue). Both topics have witnessed an increase in publications, but a more rapid growth has been seen in hybrid cardiac imaging.

Notably, neither of these terms are particularity new. In fact, the previous surfacing of AI into the common interest during the 80s and 90s became dampened by the limitations of its underlying algorithms, which depended on explicit programming (i.e., rule-based instead of learning-based). The original roots of ML and AI, as well as the concept of programmable learning, date to half a century ago and have only recently resurfaced their current new era is due to the convergence of three crucial forces, namely: large amounts of available data for robust-scale learning iterations, increasing computational power with parallel processors making the necessary operations time-feasible (i.e., Current graphic processing units or GPUs), and the innovation in the architecture and complexity of dedicated ML algorithms, thus the substrate, the engine and the fuel.

ML can be divided into three main types based on how the system "experience" is acquired: supervised learning, unsupervised learning and reinforcement learning. Supervised learning algorithms take a set of examples (training set) and asks the model to learn pick up the features that associated with specific labels in these examples. For instance, a classification model learns to predict skin cancer with images labelled by dermatologists[1]. In comparison, unsupervised learning algorithms do not restrict the learning trajectory with labels but instead ask the model to organize the data based on features crafted by the model itself, allowing it to identify patterns within the dataset. This approach may be particularly useful in exploring high dimensional data for complex patterns such as nonlinear relationships that may translate novel structures previously unknown and relevant to the task at hand without the constrains of a strictly defined output. This has demonstrated value in the clustering of genomic or radiomic features in cancer samples to reveal subtype characteristics[2,3]. Finally, reinforcement learning takes emphasis on learning through interaction within an environment. In the case of reinforcement, the model, often termed an agent, navigates in a specific environment and

performs self-initiated actions for which it is subsequently rewarded or penalized; with the aim to maximize the cumulative rewards the agent learns to solve the target task in the respective context (the predefined environment). Reinforcement learning is typically applied to tackle evolving problems, updated through interaction with environment, such as playing video or board games. In medical field reinforcement learning has been proposed to optimize therapeutic regimes which may be modified based on patient response[4,5].

There is a myriad of ML algorithms that can be employed depending on task complexity and intrinsic data characteristics such as dimensionality, operationalization nature and composition. *Figure 2* summarizes the discussed types of learning, exemplar algorithm (see description below) and their potential application sphere in (hybrid) cardiovascular imaging.

A distinctive commonality between ML algorithms is that they seek to minimize the error of the model expressed by some type of cost (or loss) function. Alternatively, this means that learning progresses through the optimization of a specified driving function (or set of them).
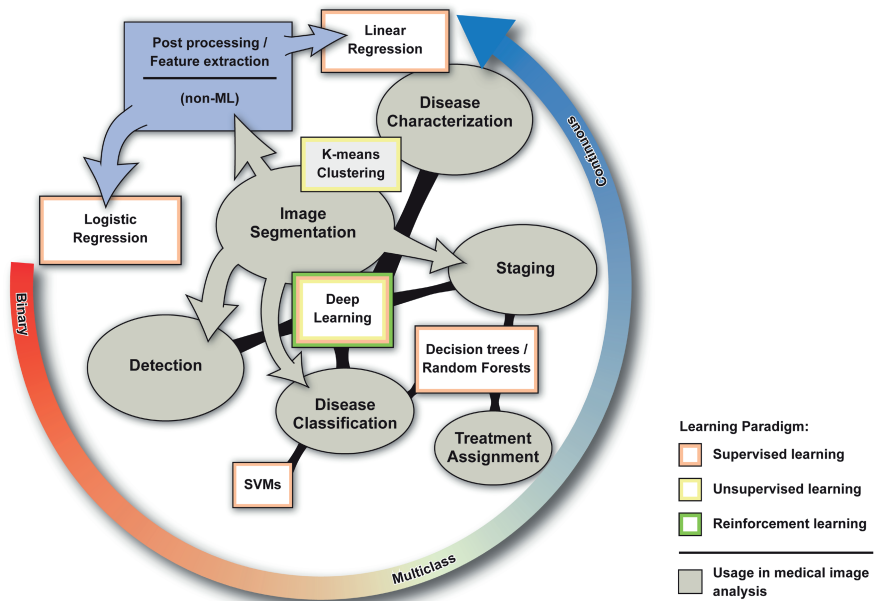
Figure 2. Overview of types of ML and their usages in Medical Imaging. A wide range of ML techniques are available, each serving a narrower or broader range of purposes in medical imaging and contingent upon type of input data. DL has a growing relevance in medical imaging processing. Segmentation represents a central task in this spectrum of DL applications, providing directly extractable automated measurements, but also functions as a first block to provide inputs for other DL-models in (hybrid) chains of models for disease classification, staging, characterization and detection of structural abnormalities.

Figure 3. Types of ML found in medical imaging explained. a) k-means clustering: each data point will be assigned to a cluster with the closest center in a pre-specified feature space such as anatomical characteristics of cardiovascular structures; **b)** random forest: features can be submitted for construction of decision trees to arrive at an ensembled model; **c)** SVM: an optimal hyperplane (black) that separate two classes is estimated, non-optimal 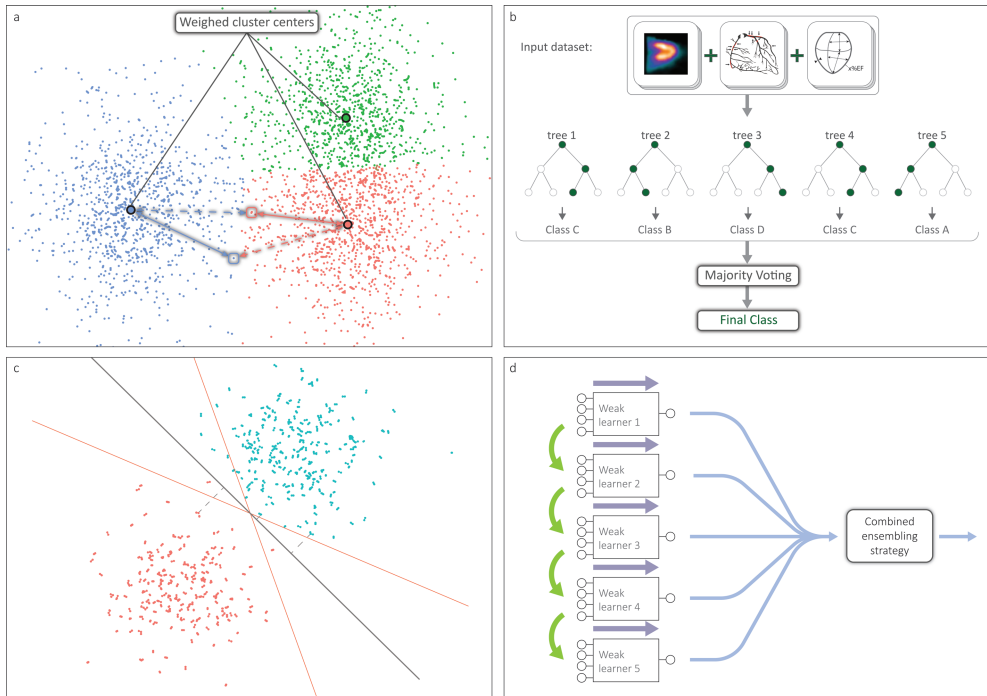hyperplanes shown in red; **d)** Ensembling: multiple so called 'weak learners', trained to solve the same problem, are combined into a weighed result combining the prediction of each learner to improve performance over individual ones. Different strategies can be chosen, e.g., in boosting, multiple learners are trained sequentially dependent on the previously built learner, while in bagging and stacking, multiple learners are trained in parallel and independently from each other. One strategy to combine the predictions can be averaging or voting.

Traditional modelling techniques seen in medical imaging analysis include linear and logistic regression (which notably also represent ML approaches by definition), decision trees and its ensemble version known as random forests, support vector machines (SVM), k-means clustering (*Figure 3*), and several types of deep neural networks (*vide infra*) (*Figure 4*).

The reason behind the popularity of linear and logistic regression in medical research is their arguable interpretability and ease-of-use and implementation. In the context of imaging analysis, regressions can be applied directly on raw data at the pixel/voxel level or performed on imaging-derived variables obtained from pre-processed data, with or without features from other data source (e.g., clinical or biochemical profile of the patient). However, a known drawback is that as the number of features surpasses a certain threshold (which approximates one per ten cases in a binary output distribution)

with respect to the sample size and balance (i.e., number of positive and negative cases to the outcome variable of interest), most features are expected to be non-informative. To exemplify such situation, consider that given the number of background pixels that take up much of a given image poses an unsurmountable difficulty when trying to find the best fitting linear model that allows for flexible interpretation and later generalization to a new input set (image). In such situation, one could consider opting for a regularized form of linear model, namely Ridge, Lasso and Elastic net regression. Both Ridge and Lasso regression shrink the coefficients of features by applying either an L1 or L2 norm (the cost function) while Elastic-net regression takes a combination of both penalty terms, finetuned based on the data at hand. Another ML technique known as boosting can be applied on classical statistical models to obtain an improved final model from multiple weaker models or *classifiers* (ensembling).

Decision trees as well as the ensemble of decision trees, termed random forest, are supervised learning methods used to build classifiers for typically discrete outcomes. As suggested in the name, decision trees resemble a flowchart with set of splits that can be used to determine the class label for each new incoming data point, step by step through the tree. The set of decision rules and respective position in the tree are selected and optimized using a labelled training set. The main advantage of decision tree is its interpretability as it mirrors the natural human decision-making process as in a differential diagnosis or clinical work-up. A random forest is an aggregate of multiple decision trees each built on random re-sampling of the training set. Alternatively boosting can also be applied to build an ensemble for greater performance.

Support vector machine (SVM) is another popular supervised learning method in which individual data points are first projected in a feature space based on their respective values for the selected features[6]; a hyperplane is then estimated to best separate members of different classes (typically two classes). In the context of medical imaging analysis, SVM may be used in disease diagnosis, staging and prognosis. It should be noted that performance of an SVM classifier depends substantially on the feature space, thus processing and pre-selection of radiomic features may be necessary.

K-means clustering belongs to the unsupervised learning paradigm. With a pre-selected number of clusters (k), every data point will be assigned a membership to one closest randomly initiated cluster center (mean of cluster) in k-means clustering; as the cluster centers get updated with new members, the computations are repeated until convergence (i.e., no change in membership for all data points). K-means clustering exemplifies a phenomenon we should not witness in individual development dependent-processes such as political affiliation. This algorithm can be used to organize pixels into groups (image segmentation) as well as organizing samples into groups such as disease subtypes. There are several features to note when applying this technique: as the choice of "k" – number of clusters will lead to a different result, an assumption on the structure of the dataset has to be made and sensitivity analyses of the resulting clusters' robustness,
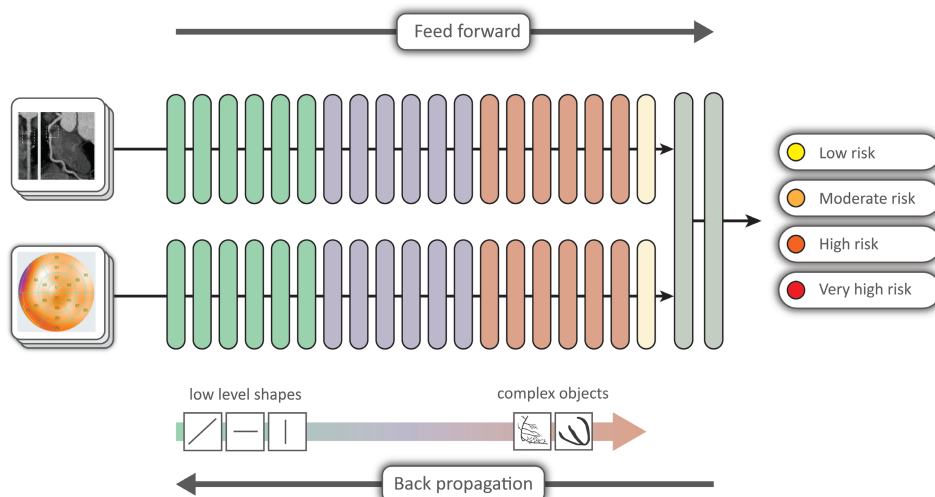
Figure 4. Schematic overview of a deep convolutional neural network. Images from various modalities submitted to the network in which spatial features on ascending levels of complexity will be learned by the network; the network then combines those features to achieve a defined task (e.g., classification of myocardial ischemia).

such as computing cluster silhouette, may be warranted.

Deep (convolutional and other types of) artificial neural networks, for which the term Deep Learning (DL) has recently been coined, are a subclass of ML which models that can be trained under every learning paradigm. A typical neural network is composed of layers of processing units (i.e., perceptrons, and consequently traditionally called multi-layer perceptrons) which mimic biological neurons. In these structures, each unit receives an input from units at a previous layer and react to cumulative signals by activation or lack thereof and emission of a signal towards neurons at the next layer (in a feedforward network). This emission was originally controlled by a nonlinear activation function such as a sigmoid function. Due to the limited range in the gradient of the sigmoid function which result in difficulty in optimization, it is in practice replaced by alternatives such as rectified linear units (ReLU), which output the positive cumulative input and zero otherwise, or a leaky version ReLU where a negative input would be assigned a small output. The units between two neighboring layers are connected and the strength of these connections (often called weights) is adjusted during training. With sufficient data to tune the weights, typically in the magnitude of millions, a DL model learns how to transform the data and automatically extract features to solve a specific (e.g., classification) task. Unlike typical linear/logistic regression models where solution of a single global minimum error (point of convergence) is possible (with mean square error as the cost function), DL models requires iterative optimization by gradient based methods towards one of many local error minima, which is deemed sufficient as set out by the trainer of the model[7]. In this regard, the learning scheme will also influence the learning outcome, whether a local

minimum (which minimum) can be reached, time required to reach the minima, etc. Parameters in this learning scheme are called hyperparameters and these also require tuning (often with a validation set) in the optimization process (*Figure 5*).

Optimization of a DL model is hence expensive in terms of both computational resources and time, which further scales with network complexity. As mentioned previously, technological advance in the form of GPUs has enabled relatively fast training of highly complex neural networks, and consequently DL has shown tremendous revolutionizing success in the field of computer vision since last decade. DL was shown to outperform other ML methods in image recognition. DL is now widely adapted in solving tasks in many different fields such as natural language processing, speech recognition and bioinformatics. As medical imaging analysis shares many tasks with computer vision including object detection, classification, image segmentation and enhancement, this field has seen an explosion in the use of DL. A selection of the body of reports available will be further discussed here.
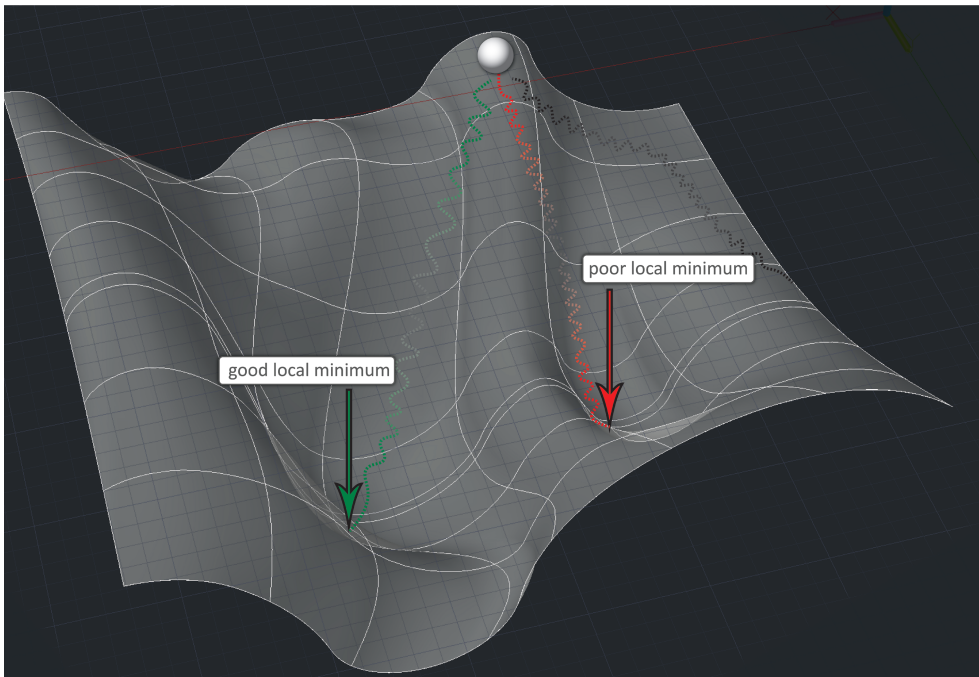

Figure 5. Optimization in DL with convergent to a better or worse local minimum. Learning process of DL involves iterative reduction of the loss function until a local minimum is arrived using gradient based algorithms. The hyperparameters in the learning scheme may have great impact on the learning trajectory, and consequently, on which local minimum is arrived to.

ML in cardiovascular imaging analysis

ML classification models have already been developed to automatically detect or differentiate between imaging views (axis). For example, Khamis et al. applied label consistent K- singular value decomposition, a discriminative learning dictionary technique[8]. This linear algebra method decomposes a complex matrix (such as a digital image) in multiple unitary matrices and a diagonal matrix that is uniquely determined by the complex matrix.

A typical example of modern ML techniques is the application of (convolutional) DL to improve time efficiency during image interpretation by humans. Zhang et al. demonstrated this approach for multiple tasks in automated processing of ultrasound images, including view detection, chamber segmentation and detection of hypertrophic cardiomyopathy (HCM), cardiac amyloid, and pulmonary arterial hypertension[9].

Another use for ML implemented in numerical data (I.e., echocardiography-derived structured data) is exemplified by Cikes et al. They proposed an unsupervised ML algorithm that integrates both clinical and complex echocardiographic data acquired in heart failure patients, which could be used for identification of patients that are likely to respond well to cardiac resynchronization therapy[10]. Inputs for the model are combined volumetric, strain and tissue-deformation sequences extracted from 2D echo imaging and a range of variables, extracted from patient demographics, clinical variables, laboratory measurement, use of medications and functional variables derived from ECG and echo. The algorithm uses a sequence of multiple kernel learning for dimensional reduction and k-means clustering for the eventual "phenogrouping" of patients. Cox proportional hazard analysis of the differences between left ventricular end-diastolic volume index before therapy and one year after treatment showed significantly differences between the groups.

A wide range of variation of in DL network architectures, such as ResNet[11,12], AlexNet[13] and DenseNet[14,15] have been implemented for medical imaging. However, a comparison of different architectures by Blaivas *et al.* has demonstrated that newer architectures that improve on different ML-model tasks in other fields, may not always show improved performance when applied in medical imaging[16]. In their research, different types of models were compared, when trained for classification of views in cardiac imaging. Even though hyperparameter-optimization details were not specified in this publication, (implying limitations in terms of reproducibility and verifiability common to most of the studies of the kind published in medical journals) this paper touches upon an important aspect of applying emerging novel algorithms within the space of medical imaging. With most of all medical images being constructed from tomographic image capturing and carrying a single grayscale brightness channel, medical images differ fundamentally from photorealistic images for which most network architectures have been developed. Medical images also display structures by local variations in brightness, thereby containing edges and surfaces, utilized by DL architectures. Contrarily, while image details may be

limited in channel count, 3D medical imaging techniques such as CT can substantially add to the tomographic nature of more basic imaging modalities. Data contained in 3D images exceed the information flow provided by the flattened 2D photographs produced by regular cameras and smartphones. It is therefore important to select an adequate architecture with correct characteristics for capturing the target region(s) of interest (for instance, specific cardiovascular sub-structures) and to thoughtfully adapt architectures to accommodate the tomographic nature of medical images. The greatest lesson drawn from this research is that eager advance in DL implementations should always be balanced with sensitive deliberation of their actual adequateness and related.

DL have also been used to classify image orientations[17], by dividing those into four classes according to 0-, 90-, 180- and 270-degree rotations. Albeit this application may only be useful in the extraordinary absence of image metadata, as produced by imaging modality instances, this research demonstrates that DL can distinguish between differently oriented examples of the same cardiac view, a complex task in traditional computer vision that may link to improvements in hybrid image fusion.

Another approach to time-efficiency improvement in data analysis is focusing on delineation of cardiac images, which may be quite labor-intensive as suggested by the fact that most cardiac images are ultimately never annotated if only manual delineation tools are available. Whether there is potential diagnostic gain to be sought is still an open matter.

Segmentation models have been developed for fully automatic delineation of cardiac chambers on CMR[18,19] and to derive secondary measurements during post-processing, such as cavity volume, tissue masse, wall- thickness and ejection fraction[20,21]. Most of these implementations are based on the U-NET architecture that was developed especially for segmentation of medical images[22]. Further variations on this architecture have been developed, such as V-NET[23] which improves on U-NET through implementation of residual functions, inspired by ResNet[24], or Ω-NET, which offers specific advantages in terms of improved segmentation and predictive power on multiple cardiac views within a single model, without prior knowledge about the presented view[19]. Segmentation optimization through ML has also been applied in coronary arteries and myocardium in CT angiography[25,26] and in measurement automation for intima-media thicknesses on carotid ultrasound images[27].

Liu et al. developed a 3D DL model for the detection of malignant tumors in pulmonary CT, using multiple slices to construct a spatial representation of a nodule, to be then classified for malignancy by the network. DL-based models like these have found their way to software applications with FDA clearance for use in the clinical setting**.**

Similar DL designs have been proposed for prediction of calcium scores. Wolterink et al. have reported on DL-predicted calcium scores from cardiac CT images, with a 0.944 (95 %CI [0.918, 0.962]) intra class correlation coefficient in comparison to traditional calcium

scoring[28]. A paired DL architecture was used, where one convolutional network accounted for extraction of voxels of interest (VOI) from the source CT-image and a second one was trained to predict the calcium score on the extracted VOI. Two different architectures consisting of 2.5D and 3D architectures were compared to assess volumetric cardiac structures, using triplane (axial, sagittal and coronal) inputs for the 2.5D CNN and 3D volumetric data as input for the 3D CNN architectures, showing a slightly better sensitivity of 0.72 over 0.71 for the 2.5D architecture. Further, improvement on either architecture was demonstrated by implementation of ensembles of CNNs with different input-sizes and dimensionalities.

Lessmann et al. proposed another combined CNN-architecture for calcium scoring, in this case on low-dose chest CT's that were initially acquired for cancer research[29]. In their proposal, the first of two CNN-models was not used for extraction of VOIs, but to perform preselection of smaller sub-regions that potentially contain calcified areas. A second CNN was then used to perform the calcium scoring on those preselected areas.

Notably, these advances in ML implementation on cardiovascular imaging have exclusively dealt in terms of single data sources/types for specific established tasks in daily imaging practice. And much in the same way that individual cardiac imaging techniques have been optimized and then introduced into the conceptual realm of hybrid imaging (*vide infra*), the ML horizon has arguably expanded into both the combination of algorithms applied in a single workflow and the combination of data sources (e.g., clinical and imaging) for task optimization to exploit the value of individual types of models. Expanding from basic segmentation for instance, Zreik et al. developed a "hybrid" solution for the prediction of myocardial ischemic lesions in CT angiographic imaging by subsequently implementing a convolutional neural network, an autoencoder and an SVM model[30].

While FFR is currently measured in an invasive procedure with the use of pressure wire and hyperemic stimulus, there has been research in estimating FFR from CTA image bypassing the invasive procedure. With coronary arteries and left ventricular mass segmented, a computational fluid dynamics (CFD) modeling-based estimation is possible. This process is however computationally expensive[31]. Consequently, with the aim to expedite assessment of CT-derived FFR, Itu et al. synthesized 12,000 artificial coronary trees and their corresponding FFR by combining the computational blood flow model with anatomical assumptions of the cardiovascular structure[32] reflected in 28 features and variations thereof used to train a DL model to predict FFR in independent new CT data. Result from a small set of data from real patients (n = 87) showed almost perfect correlation of DL estimated FFR and the reference FFR estimated using computational fluid dynamics, indicating successful knowledge transfer to the DL model. With the knowledge structured and stored in the network, estimation of CT-FFR resulted much faster than traditional CFD approaches computing FFR *de novo*. Nonetheless, while there was an 80-times compression in the estimation of FFR by DL model (2.4 ± 0.44 vs 196.3 ± 78.5 seconds) data preparation, i.e., generation of the coronary anatomical

model for features to be input to DL modelling, required 10-60 minutes and became a bottleneck that diminished the gained efficiency of that workflow. In this regard, Kumamaru et al. independently proposed a fully automated workflow in which the data preparation step would be replaced also by ML model. More specifically, they proposed a hybrid of 2D convolutional generative adversarial (cGAN), a 3D convolutional ladder and a fully connected neural network for automated estimation of minimum FFR[33]. Both (convolutional) autoencoders (CAE) and cGANs can be used to generate a desired image but they differ in the learning strategy: an autoencoder learns to convert the input to desired output with a set of mathematical operations fixed and stored in the trained network; while GAN learns to generate output that would appear to be as close as a real output that the competing discriminator network would not be able to differentiate it. One key philosophy in GANs is that the generator network must learn the underlying distribution of the data in order to perform well enough to "fool" the discriminator. The generative nature might allow GANs to potentially outperform autoencoder architectures which would be restricted by the provided training set. The authors argue their results improve on prior because their method utilizes input from coronary CT imaging, which seems to be more informational than the accumulated data from different myocardial views.

Notably the performance of the automatic workflow may not yet be comparable to simpler DL models which utilized radiomic features pre-engineered by experts[10,32,34]. summarizes the oriented tasks for which DL has the capacity to optimize workflows and performance.

ML in the current context hybrid imaging

Data pre-processing in hybrid imaging

Combining information from two different imaging sources, often not directly overlapping in space, time or dimensions is challenging. The ability to identify complex, nonlinear relations between data is bound to make ML a valuable tool to provide better image preparation, processing and data fusion in hybrid imaging.

Attenuation map generation

PET imaging requires attenuation correction (AC) for a reliable quantification of tracer activity. A photon attenuation map for this purpose can be generated by co-registered data from CT or CMR. In simultaneous PET/MR imaging, the MR imaging–based AC (MRAC) is currently generated through a segmentation-based method – with the use of ultrashort echo.

time (UTE) sequences the image is segmented into soft tissues groups or air for which specific coefficients are then assigned to construct the attenuation map. While some performance gain can be obtained through addition of bone information (atlas-based) to this method, ML has been recently implemented to this end. Liu et al. explored the

Table 1. Main tasks optimized through DL in cardiac imaging analysis.

Task	Description	Example usage in medical analysis
Object detection	Recognition of target objects and their location within an image	Cardiac structure identification and location
Semantic segmentation	Assignation of pixels/voxels in an 2D/3D image into a sensitive class	Segmentation of cardiovascular (sub)structures of interest for quantification and fusion
Classification	Class labelling for each data point based on the input image and its relation to the selected output	View classification in different imaging modalities Coronary artery calcium scoring Cardiovascular disease classification Differentiation of cardiovascular tissues Prognostic evaluation for adverse outcomes from aggregative imaging
Characterization	Feature extraction and pattern exploration from the datasets	Radiomic feature generation

utilization of DL for the construction of magnetic resonance-based AC maps[35]. With concurrent PET/CT data in addition to PET/MR data, they trained a fully convolutional autoencoder (CAE) network to generate a pseudo-CT image from MR image with the true CT image as reference. Thereon, PET images were comparatively reconstructed based on the true CT-based AC, the segmentation-based AC with MR, the atlas-based AC with MR and the AC based on pseudo-CT produced by DL. The DL model was trained on scans from 30 subjects and all methods were tested on a hold-out set of 10 subjects with the co-registered CT assigned as the reference. DL based AC resulted in the least construction error among all MR AC methods, while the segmentation-based method was outperformed by all the other methods.

Further, it has been suggested that DL may also be useful in scenarios where other methods are expected to have a suboptimal performance. For instance, in the absence of suitable references for the atlas-based method. This was explored in a study by Ladefoged et al. on a group of paediatric patients with cerebral tumours[36] since atlas-based AC was expected to perform poorly as it is based on adult subjects with normal anatomy for which sufficient age-matched paediatric references may not be available. Once again, a DL model was trained to generate a pseudo-CT image for AC which demonstrated better performance than the vendor-provided segmentation-based one, not only on the agreement with the reference AC (by co-registered CT) but also in the clinical metrics characterizing the brain tumours. These results hint the potential clinical benefit of optimizing a basic processing step in advanced imaging (AC) by means of powerful ML analytics such as DL.

Notably, the aforementioned studies were conducted on neurological imaging, while the same approach can be adapted for cardiovascular purposes. The transferability and relevance DL-based AC requires validation in the context of cardiac imaging. And a recent study by Shi et al. has explored the notion of directly generating attenuation maps for SPECT by encapsulating the complementary information across modalities gathered in cardiac SPECT/CT[37]. Taking the CT-based attenuation map as labels and SPECT scans (from photopeak window and scatter window), the authors trained two types of DL architectures, a fully CAE as well as GAN by addition of a competing discriminator network. In the current study by Shi et al., no significant difference was found between the autoencoder and GAN in generation of attenuation, i.e., SPECT reconstructed using AC from both architectures using both primary and scatter window inputs were consistent with the CT-based AC; but there was a substantial bias for the autoencoder architecture if only primary window input was supplied which might be related to a limited mapping capacity resulted from the reduced input space. Albeit the promising results in the study, it is important to note that these DL models are sensitive to training set such that biases created/existing in the training set could propagate to the model which was also evident in the current study – the slightly worse performance in female subjects might be attributed to a difference in sex ratio between the training set and test set and there exists indeed anatomical difference between sex. This suggested extensive finetuning

with local data to adapt to the target distribution will be required for such DL models to be useful in clinical practice.

Full-dose image estimation from low dose image

Generation of CT image with DL is not limited to AC for emission data. As image denoising using autoencoder is an extensively researched task in the field of computer vision, there is also an interest to transform low dose CT scan to high resolution image that would be equivalent to a high dose CT, as dose reduction generally lead to a higher signal-to-noise ratio. There is a clear benefit to patients if the high-resolution CT image could be constructed with lower exposure to radiation. In this regard, it is worthy to point out the potential incremental value of hybrid imaging for image reconstruction with the additional information collected. This was supported by a study by Xiang et al. who estimated normal dose PET image using low dose PET/MRI data[38]. In this study, the authors trained a relatively simple CNN composed of a stack of three blocks, each containing four convolutional layers (total depth = 12), on scans from 16 patients. Compared with training on low dose PET scan alone, training on both low dose PET and T1 image from MRI resulted in better estimation in all subjects, as assessed in leave-one-out cross validation. Often, DL based methods could be easily modified to accept images of different modalities offering an easy way to process data; additionally, the processing time of feedforward networks, the type of network commonly used in computer vision, is often very short. Notably, in the aforementioned study the DL model performed comparably with the state-of-art method for standard dose PET estimation but took only close to 2 seconds to process each sample and output the estimated PET image as opposed to the state-of-art method which took 1,008 seconds in average. In another study by Chen et al., multiple co-registered MR images were combined with a pseudo ultra-low-dose PET image to reconstruct the full dose image of the brain for amyloid plaque detection (ground truth); the ultra-low-dose images in this study were artificially created through sub-setting the events (100 fold) of the original full-dose image[39]. Again, a fully CAE architecture was used, and the model was trained on a dataset consisting of 32 patients under a 5-fold cross validation setup. Consistent with the previous study, image reconstructed using both MRI and ultra-low-dose PET scan showed the highest similarity to the original PET scan as measured by three typically used metrics (peak signal-to-noise ratio, root mean square error and structural similarity index measure) among submitting the ultra-low-dose PET scan alone for training and the scan without reconstruction. But perhaps more importantly, the reconstructed image using both MRI and ultra-low-dose PET scan offered higher agreement in clinical assessment with the original full-dose image by the same clinician; in particular almost all positive case (22/23 subjects) could be recovered from the reconstructed images using combined input as compared with 20/23 subjects from the reconstructions from PET scan alone. The results from this study showed improvement of the hybrid imaging protocol, in this case lower radiation exposure, may be optimized with the aid of ML.

ML in data integration and analysis in hybrid imaging

Medical images often require postprocessing and review by experts to ensure their diagnostic and prognostic role in clinical practice. At the same time, this need also convey a workload that scales with the number of incoming patients and the complexity of the modality. While expert revision is an important gatekeeper for the quality of the result, parts of the clinical workflow are very much suitable for automation. This allows on the one hand for more efficient use of time and human resources, while on the other it increases reproducibility due to potential interobserver differences.

Within current mainstream hybrid imaging, manual contour adjustment is often required for an accurate estimation of the perfusion values in SPECT/CT. Betancur et al. reported an ML model built with the aim to automate, for example, the localization of mitral valve plane (VP) during left ventricle segmentation[40]. In their study, a total of 22 plausible features, some derived from the scan while some describe clinical characteristics of the subject (sex), were considered and finally selected based on the ranking in information gain for the construction of an SVM model. Learning form the manual contours by two experts the model in general achieved higher correlations with the experts' VP localization in stress images (AC/non-AC) than rest image (AC/non-AC) (Person correlation 0.79-0.90 vs 0.66-0.80); Notably there was no significant difference regarding the diagnostic values- the SVM model achieved comparable performance in classification of obstructive stenosis with the two experts with a value of 0.8 in AUC by a 10-fold cross validation. This showed the potential of ML methods in condensing knowledge and experience from multiple experts, and they could be used to aid the clinical practice.

In PET/CT, the acquisition protocol for the CT component is often not optimized for estimation of calcium score. This implementation could avoid extra radiation if the calcium scoring is estimated directly from the CT images. Išgum et al. investigated such possibility in a cohort of 133 patients who underwent both myocardial perfusion PET/CT and calcium scoring dedicated CT[41]. After standard imaging processing steps to remove noise, features characterizing candidate calcified lesion describing shape, intensity and location of the lesion, were computed using the processed CT scans originally for attenuation correction (CT-AC) during PET/CT; an extremely randomized trees model (a decision tree based ensembling method) was then trained on these features to classify each lesion. To examine the model performance in a clinical context, patients were assigned in CVD risk category using the resulting Agatston scores. They reported a high correlation between calcium score manually estimated from CT-AC by expert and those from the automatic ML-based method (two-way mixed intraclass correlation coefficient :0.77 at rest and 0.83 at stress, by 10-fold cross validation) with larger disagreements in high calcium scores. Comparing with the reference manual scoring with CSCT, both manual and automatic scoring methods using CTAC underestimated and were statistically different from the reference, indicating the acquisition as the limiting difference. The differences in agreement between the manual and automatic methods were smaller in assignment of five CVD risk categories – both with over 80% of patients assigned to the correct category.

However, the random forest model struggled in patients with high Agatston score and tended to misclassify in the two highest risk groups. The higher variability might account the weaker performance of the extreme randomized trees model.

Cardiac MR is steadily becoming more present in cardiovascular imaging. It offers comprehensive imaging of the heart over the full cardiac cycle. More importantly, it allows for tissue and blood flow characterization. The latter makes hybrid imaging an appealing prospect in the cardiovascular realm. In hybrid PET/MR, anatomical information and myocardial tissue characteristics are used in to provide better assessment of PET imaging. Similar to PET/CT, ML techniques can significantly improve image acquisition and analysis in PET/MR. DL algorithms have mostly been applied to provide attenuation maps, in a way similar to the previously described methods for PET/CT. A smaller but interesting branch has focused on joint PET and CMR image reconstruction in order to reduce radiation dosages. Chen et al.[39] used a U-net architecture to synthesize a full dose PET image from its low dose priors. By considering the anatomical information of simultaneously acquired MR images, they showed net U-net was able to reconstruct images of similar quality to full dose PET acquisitions.

Another field of hybrid CMR is the combination of cardiac MR and invasive angiography (XMR). XMR allows for scar-guided atrial ablations[42], and radiation free assessment of complex hemodynamics in congenital heart diseases[43,44]. A main challenge of XMR is fast and reliable registration of catheter position or fluoroscopy imaging to the CMR images. Similar to the other image analysis problems, ML techniques can provide significant improvement of current workflows of image registration. Deep learning registration algorithms have been proposed to learn new similarity metrics for image registration[45,46] that can be used in conventional registration algorithms, or even perform full registration process through a DL architecture[47,48]. Implementation of such techniques for registration in XMR is likely to follow soon.

Emerging visualization techniques such as augmented-, merged- and virtual-reality that can arguably relate to an updated concept of hybrid imaging, offer the possibility to render information for clinical operators on a screen, a pair of glasses or a headset. Depending on the exact implementation, information may be presented in combination, or as an overlay of the environment the image information is viewed within. These advancements in visualization techniques may enhance the workflow and tools available in a clinical setting, e.g., in the catheterization lab, providing a 3D representation of the heart while performing an invasive procedure. The use of ML may be crucial to optimally use the data made available synchronously by multiple modalities, by rendering a mapped projection of the perfusion of the coronary arteries or a projection of the exact position of catheters on a real time, patient specific 3D rendering of the heart[49].

Notably, electroanatomic mapping (EAM) represents an area where developments in hybrid imaging, in its traditional sense, have continued parallelly to those in the cardiovascular imaging areas more logistically related to radiology. Three-dimensional

EAM systems have become the cornerstone for safe and efficient ablation of complex tachyarrhythmias. Briefly, parting from a reference electric signal (i.e., QRS), electrograms obtained at a specific site are stored and the activation time is defined, then the activation time is then compared point by point with a reference signal on the 3D geometry of the chamber of interest allowing a projection of its activation mode. Further, voltage maps can also be projected to display scar regions which in some cases correlates with arrhythmogenic substrate[43]. State-of-the-art software with increasing ML groundwork allows for integration of various imaging modalities such as CMR or CT in 3D reconstruction of ablation targets (*Figure 6a*). This technology can reduce the exposure of both patients and operators to ionizing radiation and improve clinical outcomes[50,51]. In the same regard, intracardiac echocardiography (ICE) can be applied and integrated for 3D reconstructions of complex structures such as a coronary cusps or papillary muscles, that often prove difficult ablation targets (*Figure 6b*). Based on corporate interests it remains relatively unknown to the scientific community how ML implementation has been incorporated or is to fuel consumer-grade EAM. Nevertheless, individual novel applications continue to develop rapidly. Undoubtedly, the mayor limitation for cardiac arrhythmia ablation is determining the location of its substrate. Proposed sites from rotors to drivers failed to provide a 100% efficacy in treatment even when all the potential sites are ablated. This opens the possibility for ML algorithm to accurately identify ablation target and maybe model mechanistic paths for recurrence. Mahnood et al, used spatiotemporal features extracted from electrograms to train a Kera's based DL for organized spatial sites identification, which displayed an accuracy of 95.2% to detect relevant ablation targets for atrial fibrillation with a sensitivity and specificity of 97.7% and 93.0% respectively[52]. For local abnormal ventricular activities (LAVA), Cabrera-Lozoya et al. used image features from delayed-enhanced CMR to describe local tissue heterogeneities then fed into a random forest classification framework with a five-fold nested cross-validation scheme in order to identify potential ablation targets. Based model feature augmentation was then carried out by applying a cell-specific cardiac electrophysiologic model as well as a tissue and electrogram recording models. This resulted in an algorithm with an overall accuracy of 98.9% across five patients with a LAVA-specificity of 99.4% and a LAVA-positive predictive value of 96.4%. Whether these models can generalize adequately to the larger population of patients in need for and that may benefit from ablation, is yet to be demonstrated[53].

Although ML has clearly taken decisive steps into the essential components of cardiovascular hybrid imaging through the optimization of data-preprocessing, image orientation, structural delineation, and functional quantification, the landscape of clinical implementation remains underdeveloped. ML optimization of hybrid image fusion or data integration are currently being explored. Integration of other data, such as clinical characteristics with advanced imaging (a novel look into what hybrid imaging can entail), may compensate for information loss such as lower image resolution resulted from reduced dosage of radioactive tracer or lower image resolution due to less optimal
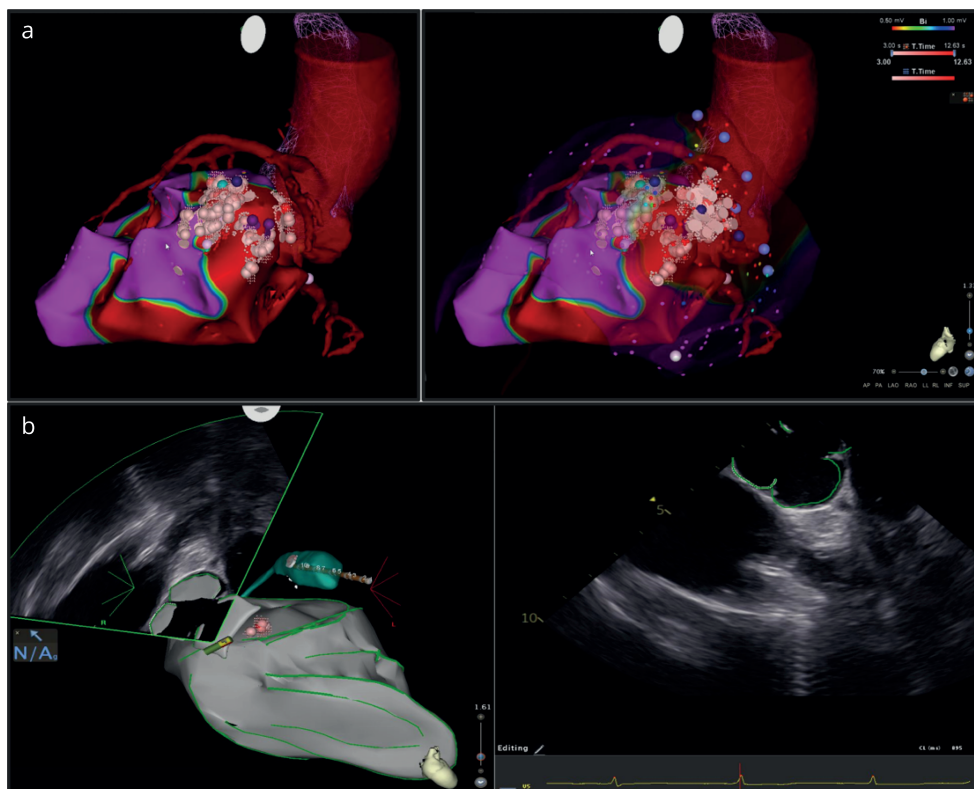
Figure 6. 3D Electroanatomical mapping system integration options. a) Left ventricle 3D CT/EAM reconstruction for endocardial/epicardial ablation of a ventricular tachycardia in a patient with Chagas disease. **b)** ICE reconstruction of coronary cusps for targeted radiofrequency ablation of persistent premature ventricular contractions. Performed with CARTOSOUND ® Module. Images provided by Dr. Santiago Nava, Electrophysiology Department, National Institute of Cardiology, Mexico City.

acquisition protocol. For example, radiomic features extracted from the CT scans in CT/PET scan may be submitted to the ML model along with demographics such as age, sex and cardiovascular risk factors like type 2 diabetes, hypertension and presence of dyslipidaemia to determine if patient would be likely to suffer from myocardial ischemia. In a retrospective study by Juarez-Orozco et al. aiming to refine prognostic value of hybrid PET/CT, CTA outputs were combined with clinical variables in a LogitBoost model (a boosting algorithm which combines weaker logistic regression predicters into a final model) to determine if a patient had suffered ischemia and would undergo early revascularization respectively[54]. In a cohort of around a thousand patients with low and intermediate risk of CAD, they observed models taking expert curated CTA variables outperformed models which directly took in raw CTA outputs in identifying patients who suffered from ischemia and eventually underwent early revascularization respectively; notably integration of clinical variables consistently improved the performance of all

models. The results demonstrated feasibility of ML in data integration which could expand to various sources, such as radiomics features from different modalities, clinical information and biochemical profiles.

It is likely that observational and retrospective evidence (based on big-data sets) will continue to gather while the necessary structures and trust in the performance of ML's novel analytics becomes increasingly present in the minds of cardiovascular scientists and physicians. Ultimately, it is expected that further prospective research will put the real-world performance of ML-derived to the test. In the next section, the envisioned paths of clinical implementation and the potential role of ML-based AI in the clinical reality of hybrid imaging will be discussed.

ML in decision-making and clinical-evaluation support

ML implementations in wearable biosensors has taken the spotlight in clinical implementation of AI as they offer the potential of large-scale screening for a vast range of both chronic and acute diseases. Recently, the Apple Heart Study provided evidence of an algorithm capable of detection of previously undiagnosed atrial fibrillation from pulse irregularity and variability[55]. However, the rate of detection triggers the question of cost-effectiveness viability. The potential of ML based algorithms to identify patterns from a constant string of data gathered by easily accessible portable technologies sparked an interest for advanced continuous monitoring. For example, Green et al. demonstrated that a multi-instance classifier could be used to identify patients with obstructive HCM from photoplethysmography tracings obtained by a wearable biosensor with an AUC of 0.99[56].

Within imaging, more explicit feature selection is expected to enhance the decision-support applicability of ML implementations. This is a clear need among clinicians even if especially scientifically oriented. Ease-of-use and interpretability, therefore, constitute paramount characteristics in every successfully ML-based AI implementation and should be further promoter in due time within hybrid cardiovascular imaging of any kind. Decision-support on diagnoses and treatment paths, and direct extraction/presentation of the most relevant related data could greatly enhance the way clinicians use the individual patient data to treat their patients.

Furthermore, with the potential to improve on diagnostic and prognostic probability estimation at the individual level, a clear niche for ML lies within the integral space of electronic health records and medical imaging systems. Decision support systems, patient-status alarm systems and workflow enhancements in the form of relevant content selection, speech recognition and on-the-go word predictions in text editors based on ML models are some examples already sparsely implemented. These tools may optimally use integrated data sources where available to the broadest extent and to extract the largest added value for patients.

Considering an inclusive take on the "hybrid" term, ML models have been developed

aggregating imaging and structured data as well as structured data integrated from different data sources including imaging-derived parameters. Whether the current concept of hybrid integration allows for such inclusions is yes to be argued. As an example, Juarez-Orozco et al. developed a model for the classification of myocardial ischemia and an increased risk of adverse cardiovascular events based on clinical and functional (imaging derived) variables using a boosting ensemble algorithm[57]. These hybridized modeling attempts have shown clear improvements over models based on single data sources, implying that aggregation of multi-source data into hybrid model adds diagnostic value to other single-source trained models. Therefore, the development of models that employ hybrid imaging data is viable and may be considered in a flexible understanding of hybrid imaging and modeling. This holds the potential to uncover yet untapped insights from high-dimensional cardiovascular hybrid imaging data, which are essentially not yet fully exploited.

Whether aiming to improve clinical workflow efficiency or patient outcomes with respect to diagnosis and allocation of treatment strategies, a rich source of information lies in the aggregation of data originating from multiple imaging modalities. This designates hybrid imaging as the ultimate area to harvest from these investments as portrayed over the recent years in ML in different individual imaging modalities.

The present chapter was written in the midst of the SARS-CoV-2 (COVID-19) pandemic, which has proven to pose a challenge for medical and populational sciences. These times have brought forward the systemic weaknesses that require attention to front expectable circumstances. For instance, delays in the development of PCR-based diagnostic tools have resulted counterproductive for the adequate detection of infected individuals at the individual level. In this regard, creation and deployment of ML-based AI systems that facilitate clinical- and image-based diagnostics tools can prove crucial to optimize detection and estimate prognosis. For example, Singh et al. developed a multi-objective differential evolution (MODE)-based DL model that applies chest CT images and provided good performance for classification of COVID-19 infected patients[55]. Further research into whether hybridization of these models and potential integration with other imagining modalities such as echocardiography can improve cardiac involvement in the disease and its relevance for the patient-based prognosis is warranted.

Future perspectives and challenges in ML-based AI for cardiovascular hybrid imaging

While studies discussed here suggest a promising path for the incorporation of ML into the common handlings of cardiovascular hybrid imaging, many have been performed on small datasets and hence should be viewed with a cautious optimism. There are still tasks in medical imaging analysis, such as motion correction, where ML is yet to achieve performance on par with the status quo. Moreover, there are and will continue to be cases in which ML may not provide a better solution than alternative, even more

traditional, analytics[32,33]. Rather, it is important to explore and identify the scenarios in which such implementations are bound to translate into clear benefits at the subject-, patient-, health professional- and population-level.

As presented in this chapter, DL can provide powerful tools for image acquisition, reconstruction and analysis in hybrid imaging. However, with the complexity of modelling correlations, the interpretability and accuracy of the models is suffering. Criteria on which decisions are made cannot readily be extracted from the models, and small nearly imperceptible perturbations in data can lead to significant errors in predictions[58]. Especially in medical imaging, such unreliability can be dangerous. To allow integration of DL in medicine two main issues need to be addressed: 1) there needs to be a degree of model interpretability, and 2) models need to be quality-controlled by independent algorithms that do not rely on the input of the original task, but use indirect data (for example; model outputs or priors based on existing medical knowledge). Models interpretability is challenging, and still a largely unsolved problem. Clough et al. used a 'concept activation vector' technique to associate known medical concepts (such as low ejection fraction) to certain vectors in the latent space of a VAE based classifier[59]. This approach provides some degree of explanation to the models' decisions but does not allow to fully interpret decisions made in the model. Another approach is to raise awareness about potential mistakes of a DL model using prediction uncertainty metrics[60,61] or attention maps[62]. Apart from efforts to prevent errors in one network, providing a comprehensive pipeline for DL analysis that includes quality control measures independent of the main DL algorithm can provide a robust solution for application of DL in clinical practice. In recent work, Ruijsink et al. proposed a comprehensive cluster of algorithms for quality controlled CMR image analysis. Similar to conventional medical practice, this pipeline consisted of a pre-analysis image-quality check (a CNN based image classification and several hard-coded conventional clinical rules), a segmentation network and a quality check of the output (using SVM classification and hardcoded rules based on basic cardiac physiology). As shown by their work, using such a multilayer approach to medical analysis problems assures the levels of error detection/prevention needed for implementation of DL models in daily clinical practice. With growing initiatives for open-access and medical image repositories such as the Cancer Imaging Archive and UK biobank cohort, it will become increasingly possible to extensively test, validate and perhaps certify novel ML models with reference datasets that required before clinical deployment. It should be noted that data heterogeneity as well as veracity (incompleteness and inconsistency in record) may have huge impact on final performance of ML models in practice. While this issue may be mitigated by careful curation of a representative training dataset for calibration of the model, it should still be taken account when assessing the utility of ML for certain tasks in the actual clinical context. This is especially important in advanced hybrid imaging given the known nuances and disparities in deployment across medical centers and countries.

Conclusion

Machine learning constitutes the modern underpinning of AI. Its implementation is beginning to play a substantial role in accelerating solutions to technical and practical limitations currently constraining the full-blown use of hybrid cardiovascular imaging.

Process automation in crucial and often time-intensive data processing steps, such as quality control, image registration, segmentation and analysis for diagnostic and prognostic purposes are some of the areas in which ML has gained popularity based on results optimization. The evolving concept of hybrid imaging may prove adequate elasticity to contemplate not of complementarity and synergy between imaging modalities but also between data sources and even ML-based image analysis models. At this moment, full operational ML implementation in traditional cardiovascular hybrid imaging (SPECT/CT, PET/CT and PET/MR) are still lacking, but we find ourselves in the brink of an accelerated development of clinical applications that is contingent upon acceptance and comfort with these novel analytics. The development of interpretable, quality-controlled, robust and trustworthy ML-based models is essential to further optimize data processing, insight generation, clinical decision support in cardiovascular hybrid imaging. Thereon, the future is open.

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PART I

ARTIFICIAL INTELLIGENCE BASED AUTOMATION

IN

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING