International Society of Therapeutic Ultrasound Annual Symposium 2023

Artifical Intelligence in Therapeutic Ultrasound

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Contents

What is AI?

Curve Fitting

The Turing award prize winner Judea Pearl said:

> » All the impressive achievements of deep learning amount to just curve fitting. «

This does not mean interpolating images in pixel space.

In practice, it often means interpolating on a learned approximation of the latent manifold of the data.

But what does this statement actually mean?

An accessible introduction can be found in Chapter 5 of "Deep Learning with Python" (Second Edition) by François Chollet [1].

We will briefly outline what an artificial neural network is and present a series of short examples of how they have been applied in therapeutic ultrasound.

What is AI?

Latent Space

The MNIST dataset contains over 60,000 black and white 28×28 images of the digits 0 to 9.

There are very few possible valid digits which can be generated from a random grid. If we linearly interpolate any two samples we will not get any thing meaningful either.

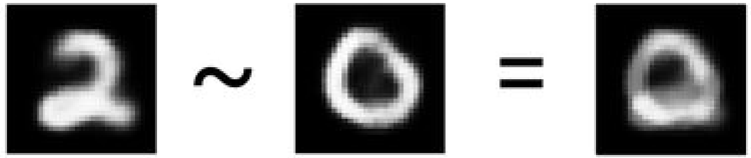


Figure 5.8 from [1], showing interpolation of images of digits

Valid digits occupy a tiny, microscopic subspace within the encoding space. This is called the latent space.

The valid digits don't just appear randomly – this would make reading the digits challenging!

What is AI?

Latent Space

The latent space is highly structured. So structured, in fact, that for many problems it can be considered to be continuous.

With the MNIST digits we can change from one set of digits to another and still be in the latent space.

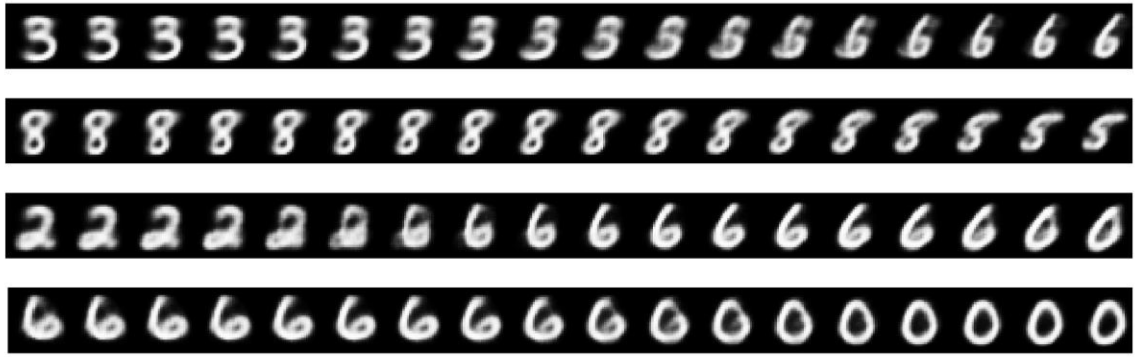


Figure 5.7 of [1] showing entries in latent space

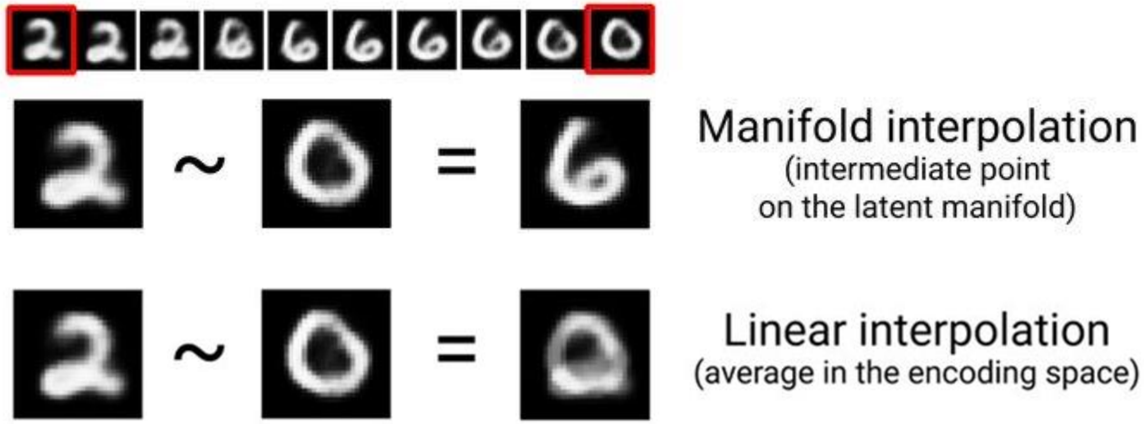


Figure 5.8 from [1]

What is AI?

Manifold Hypothesis

The fact that in many problems the latent space is a very small subspace which is continuous and structured is refered to as the manifold hypothesis.

This concept is central to understanding the nature of generalization in machine learning.

This states that for many problems, your samples lie on a low-dimensional manifold embedded in the original encoding space.

When you're dealing with data that lies on a manifold, you can use interpolation to generalize to samples you've never seen before.

You do this by using a small subset of the latent space to fit a curve that approximately matches the latent space.

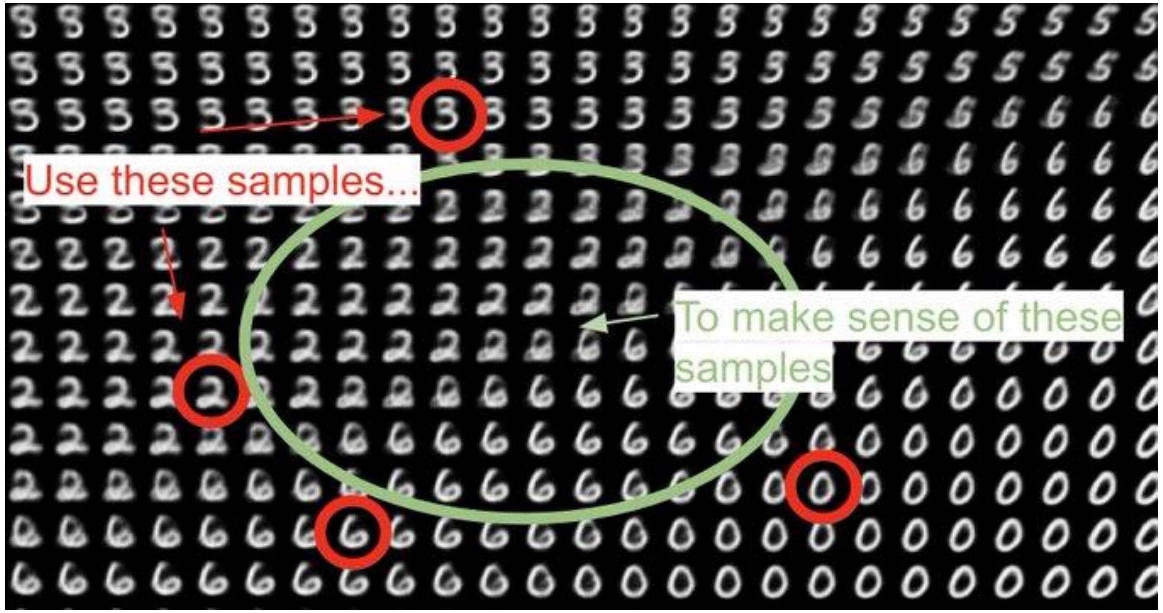


Image from @fchollet [here]

What is AI?

How do we generate these curves?

The quality of the approximation relies on the availability of a sufficiently dense sampling of the latent manifold.

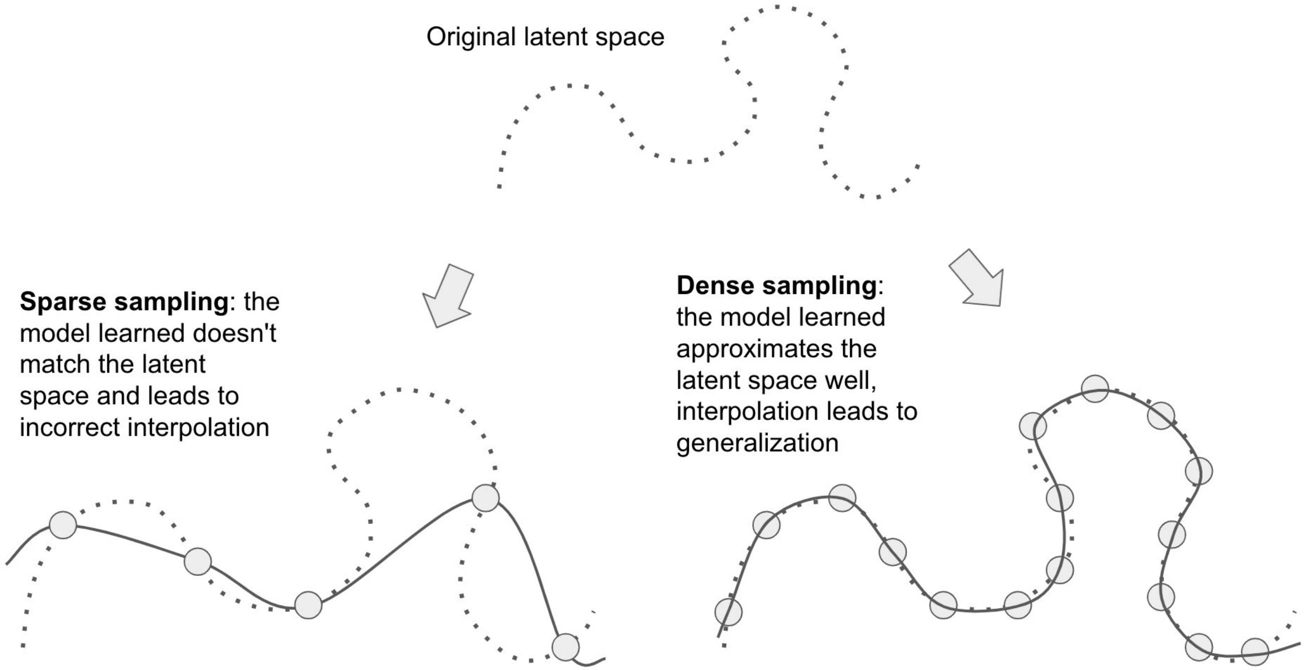


Figure 5.11 from [1]

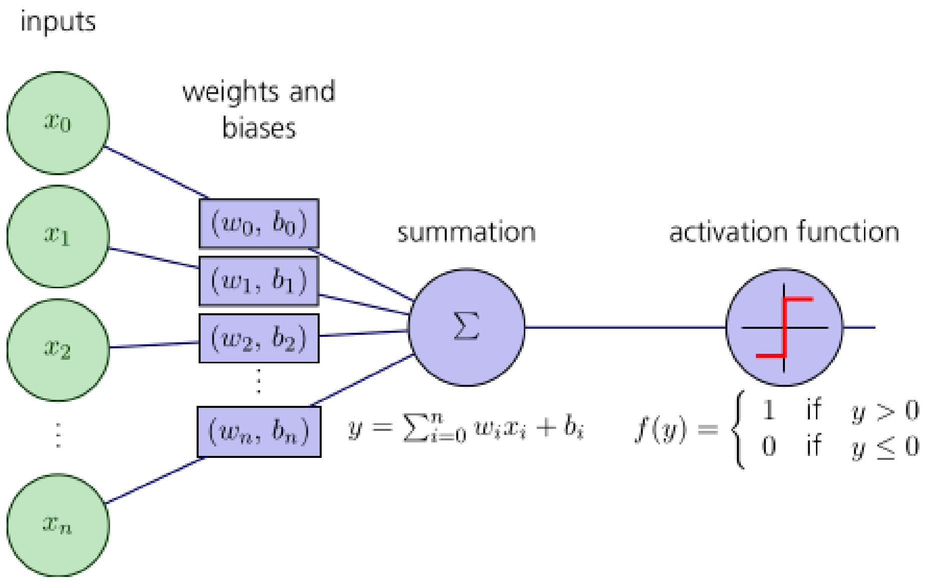
 20.04.2023

What is AI?
Perceptron

A perceptron is a single layer supervised neural network.

It was defined in as a simplified model of a biological neuron in 1943, consisting of:

1. An input set of labelled data
2. A set of weights and biases
3. A summation operator
4. An activation (or threshold) function providing the output

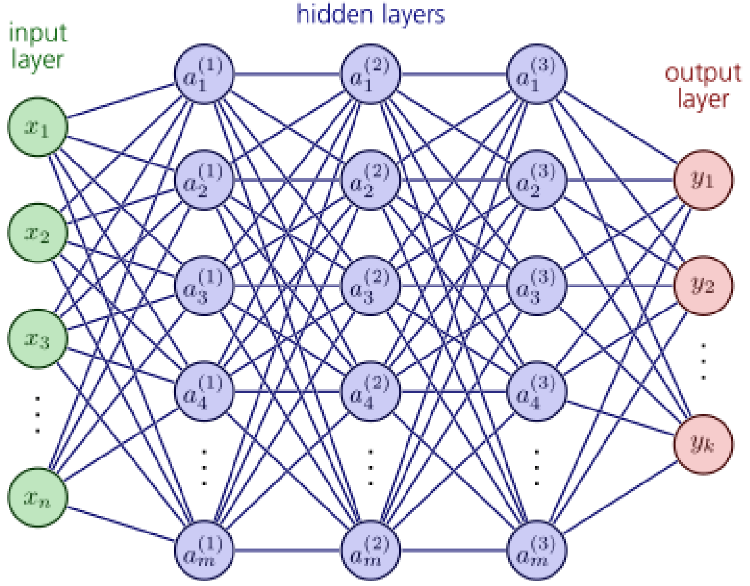


It is a binary classifier: this is given by the output of the activation function. The weights and the baises can be trained

What is AI?

Flavours

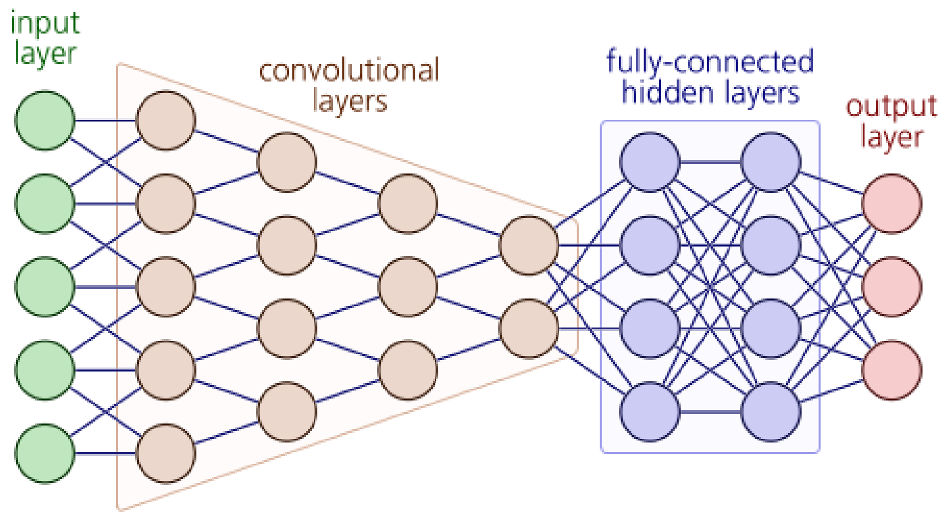
- From the perceptron, a multi-layer perceptron can be constructed, by inserting hidden layers between the input and output.
- An output layer can be constructed, rather than a single value.
- The Universal Approximation Theorem states that almost any continuous function can be approximated by at-least a one hidden layer based perceptron.
- Different layers and connections define different networks, which come in a variety of flavours. The operations at each node of the network may not just be multiplications by the weights and addition of biases. Different networks have different applications.
- Layer sizes can change through operations such as maxpooling or upsampling
- A network which has an input and output but multiple hidden layers is refered to a deep neural network.



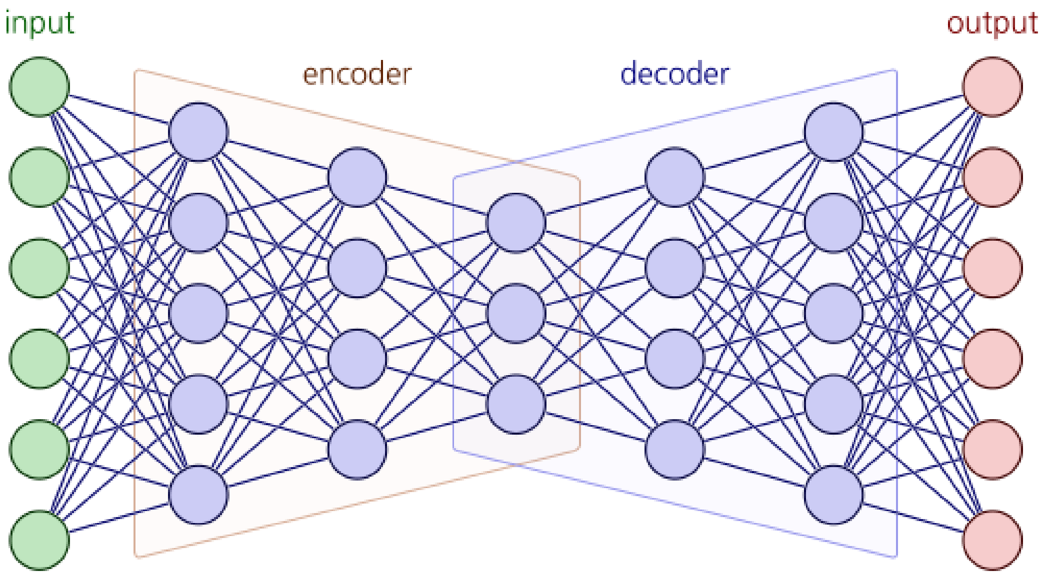
A fully-connected neural network

What is AI?

Flavours



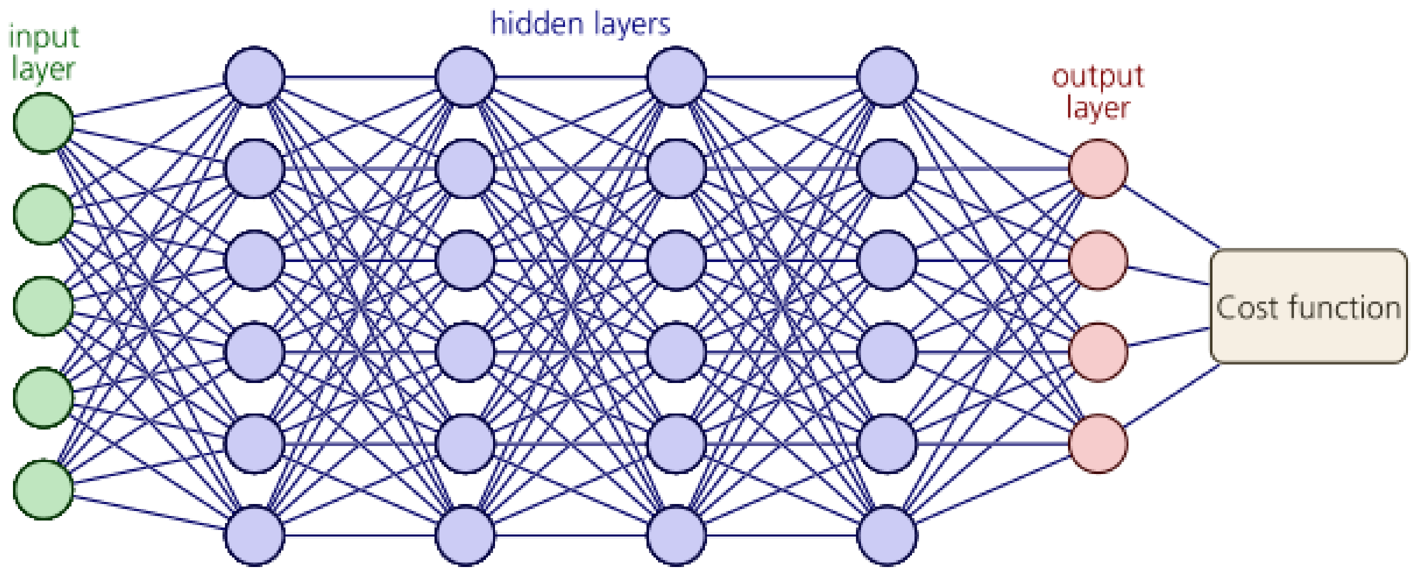
CNN: a convolutional neural network.



Autoencoder: auto- as input and output have the same shape and type.

What is AI?
Flavours

A network can be trained to minimize a cost (or loss) function, based on some measure of the difference between the output of the network and the labelled data from the training set.



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What is AI?

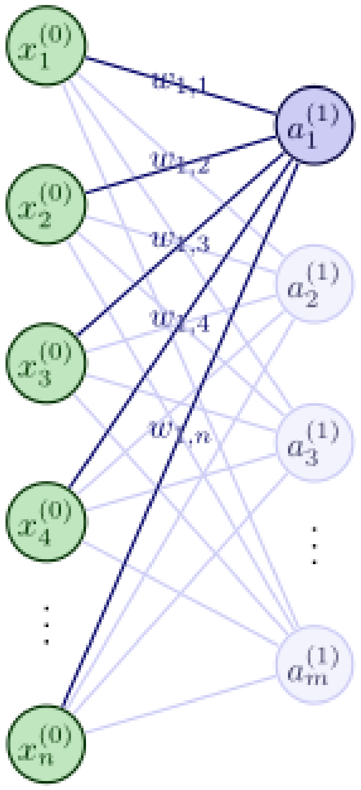
Forward Feed

From the input data, the values of each node of a hidden layer can be computed by propagating foward through the network.

The example shows, how given a set of weights and biases and an activation function, the value of a node in a hidden layer can be computed and how the values of all nodes in a hidden layer can be computed as a linear equation.

For large inputs the matrix-vector multiplication can be computational demanding. Fortunately graphical processing units (GPUs) can accelerate the compution.

Having computed one layer, the next can then be computed, until reaching the output layer.



$$= f\left(w_{1,0}a_0^{(0)} + w_{1,1}a_1^{(0)} + \ldots + w_{1,n}a_n^{(0)} + b_1^{(0)}\right)$$

$$= f\left(\sum_{i=1}^{n} w_{1,i}a_i^{(0)} + b_1^{(0)}\right)$$

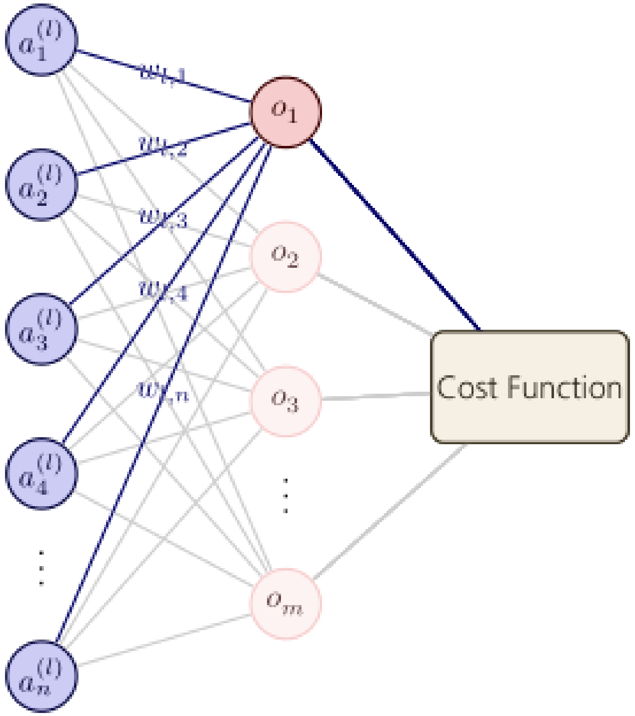
$$\begin{pmatrix} a_1^{(1)} \\ a_2^{(1)} \\ \vdots \\ a_m^{(1)} \end{pmatrix} = f\left(\begin{pmatrix} w_{1,0} & w_{1,1} & \cdots & w_{1,n} \\ w_{2,0} & w_{2,1} & \cdots & w_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ w_{m,0} & w_{m,1} & \cdots & w_{m,n} \end{pmatrix} \begin{pmatrix} x_1^{(0)} \\ x_2^{(0)} \\ \vdots \\ x_n^{(0)} \end{pmatrix} + \begin{pmatrix} b_1^{(0)} \\ b_2^{(0)} \\ \vdots \\ b_m^{(0)} \end{pmatrix}\right)$$

$$a^{(1)} = f\left(\underbrace{W^{(0)}x^{(0)} + b^{(0)}}_{\text{matrix-vector product}}\right)$$

What is AI?

Back Propagation

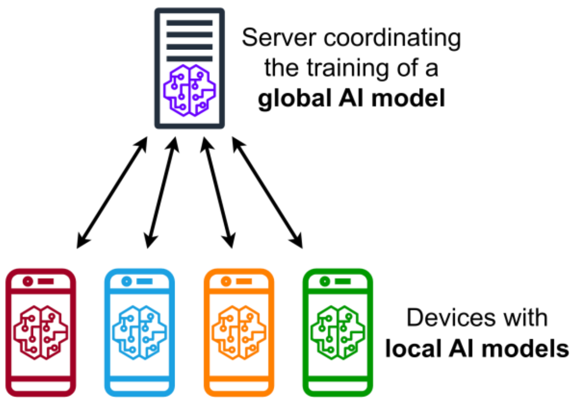
- This was a forward feed: the values of the weights can be computed by propagating forward through the network to the output layer. A cost function can then computed to give the error in the output
- The partial derivatives of the cost function can be computed with respect to each weight, which provide an estimation of the contribution of each weight to the error.
- The error can then be back propagated to the next layer to compute the partial derivate of the cost function with respect to this hidden layer, and so on.
- After computing all partial derivatives the network weights can updated to minimize a cost function. This is part of how the network is trained.
- There are many schemes to update, such as stochastic gradient descent and extensions such as Adam. These only need the partial derivative of the cost function with respect to the trainable parameters.

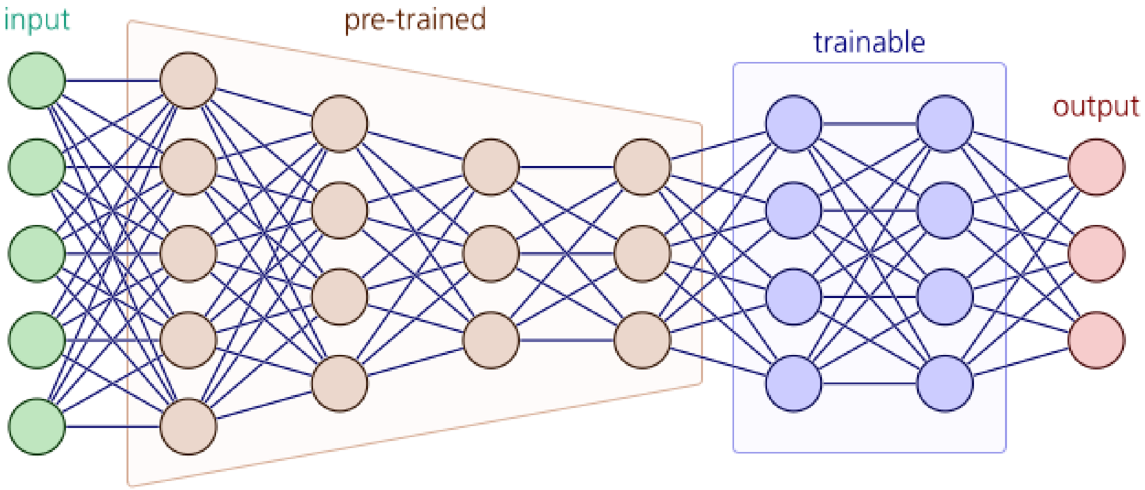


What is AI?

Other important concepts useful in the context of therapeutic ultrasound are:

- Federated learning: that trains an algorithm via multiple independent sessions, each using its own dataset. It seeks to address the problem of data governance and privacy by training algorithms collaboratively without exchanging the data itself.
- Transfer learning: refers to a machine learning concept which takes advantage of a pre-trained model or knowledge from a large dataset and applies to a different yet related scenario, usually with a much smaller dataset in the latter.





What is AI?
Getting started

What do you need to develop and build an AI model?

- A machine learning framework, such as:
  - JAX,
  - TensorFlow,
  - Keras or
  - PyTorch and so on ...
- Sufficient curated data to train a model
- At minimum, a graphical processing unit (GPU), ideally a GPU cluster or perhaps access to cloud computing for training, depending on volume of data

»

Will AI ever replace radiologists? I say the answer is no — but radiologists who use AI will replace radiologists who don't.«

Curtis Langlotz
Director of Center for AI in Medicine and Imaging, Stanford University
RSNA 2017

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Treatment Pipeline for Image-Guided Therapies

A typical pipeline for image-guided therapy may be:

Almost all stages of the pipeline have seen developments due to machine learning

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Segmentation and Registration

- This is perhaps the area in which AI techniques are the most established.
- Segmentation is often performed by a U-Net from Ronneberger et al. This is a convolutional neural network which takes as input an image and outputs a label for each pixel of the image.
- U-Net follows the classical autoencoder architecture: it contains two sub-structures: and encoder and a decoder. The encoder consists of a contracting path and the decoder an expansive path, which gives it the u-shaped architecture.
- The encoder structure follows the established process of convolutional and max pooling layers with the aim of decreasing the spatial information, while increasing the feature information.
- The expansive pathway then combines the feature and spatial information through a sequence of up-convolutions (i.e. transposed convolutions) and concatenations with high-resolution features from the contracting path.

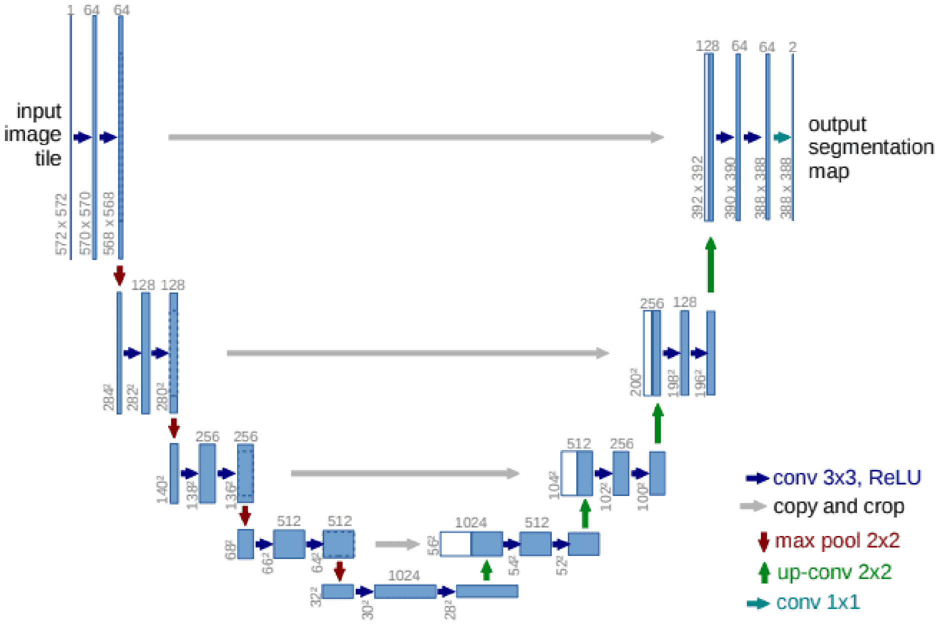

Figure 1 from Ronneberger et al showing architecture of U-Net

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Segmentation & Registration

- Registration can be considered in a similar manner as segmentation: typically registration uses a U-Net architecture and takes as input images and outputs a deformation field for each pixel of the image.
- This is a more challenging problem, as segmetation outputs an image whose pixels are labels which can be a small number of integers. Registration outputs an image whose pixels contain a vector of non-integer data.
- The deformation field may be rigid (i.e. a translation), affine (i.e. translation with rotation, shear, extension and compression) or non-rigid (i.e. nonlinear transformation)
- A loss function which compares a measure of the similarity of the output against the ground truth can then be trained.

Segmentation & Registration

- Haskins et al. used a U-net, with three rotation and three translation parameters to predict the deformation field to match ultrasound to MRI.
- The network was trained on a total 679 sets of data from the National Institute of Health (NIH) in T2w MR and reconstructed 3D transrectal ultrasound volumes from prostate cancer biopsy procedures.
- The network was trained by taking training image pairs that were registered manually by the medical expert who conducted the biopsy procedure and transforming the moving image using known rigid perturbations.

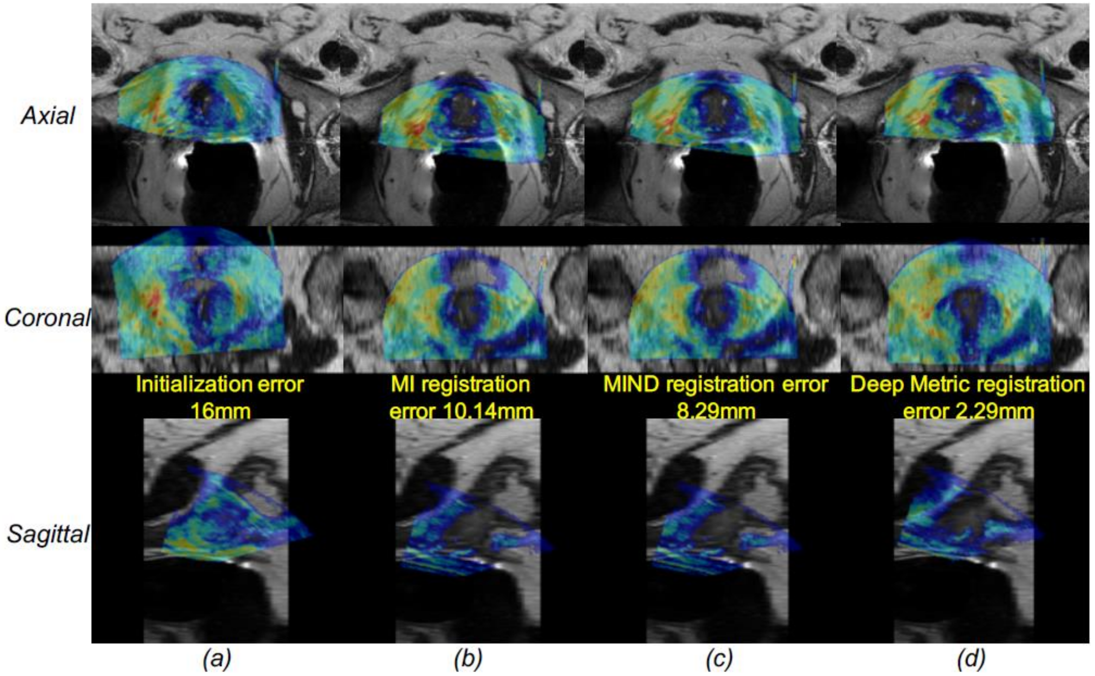

Fig. 4 Axial, coronal, and sagittal views of example registration results: (a) Initial alignment; (b) Registration performed by optimizing the mutual information (MI) using DINO; (c) Registration performed by optimizing the MIND similarity using DINO; (d) Registration performed by optimizing the learned metric using DINO.

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Thermal Monitoring

Using a network to regularize an underdetermined problem

Kim et al used the relative changes in the speed of sound acquired from ultrasound image to predict the relative change in temperature.

For the training of the network, thermal images are generated with a computational bioheat model of radio frequency ablation, and then converted to sound velocity images to obtain simulated time-of-flight datasets.

In this work, the network acts as a regularizer for an otherwise underdetermined problem.

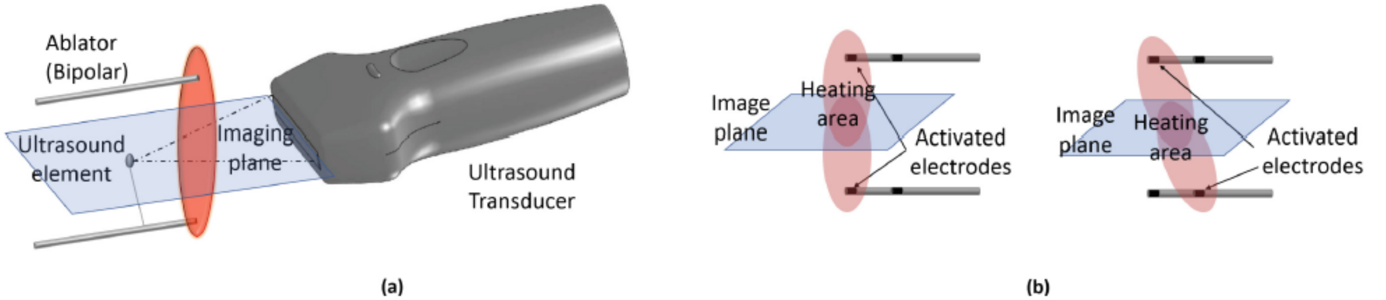


Fig. 1. (a) The ultrasound thermal monitoring setup. (b) Left: Horizontal ablation pattern. Right: Diagonal ablation pattern.

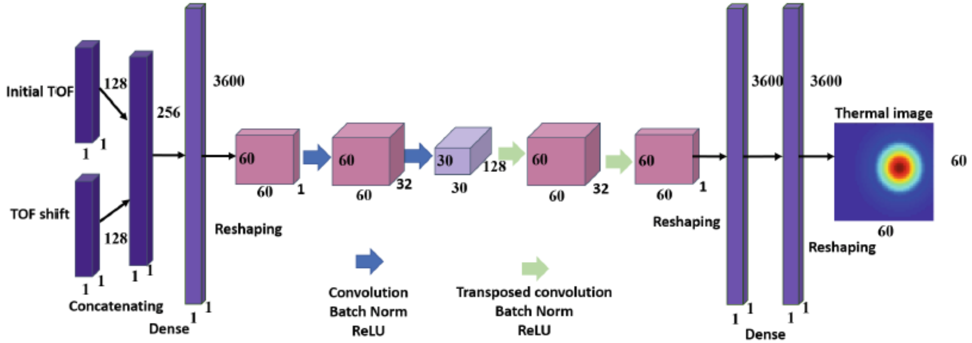


Fig. 2. Temperature image reconstruction network.

Images from Kim et al

Thermal Monitoring

Using a network for produce a similarity/distance measure

Byra et al trained a CNN, based on simulated RF data to predict scatterer density, which was correlated with temperature, to predict temperature rise from ultrasound heating.

Input data from RF data from heated was given to the network and its output was compared against the output of a reference value taken just before heating.

The model performed well against simulated data, but experimental data was more challenging.

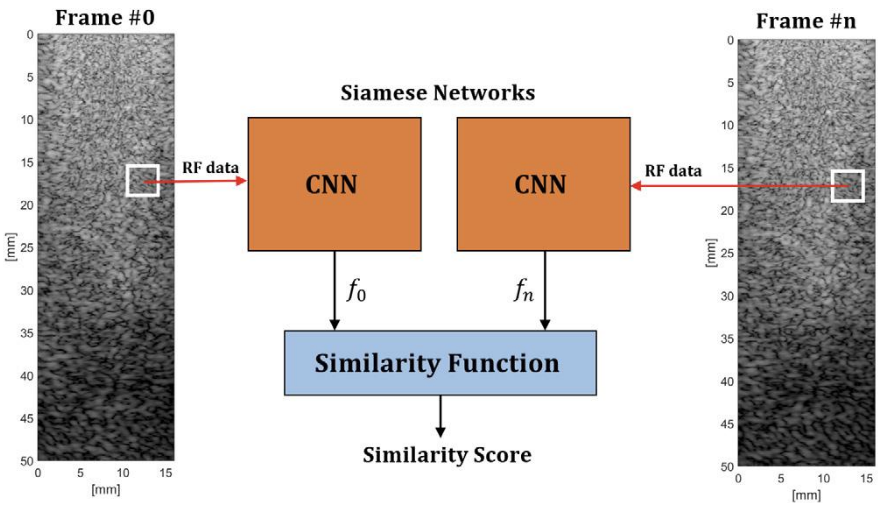


Figure 3 from Byra et al, showing pipeline to predict changes in scatterer density.

Thermal Monitoring

Strain-based: Clinical Training Data

Zhang et al used a deep CNN for the detection and monitoring of thermal lesions in microwave ablation (MWA).

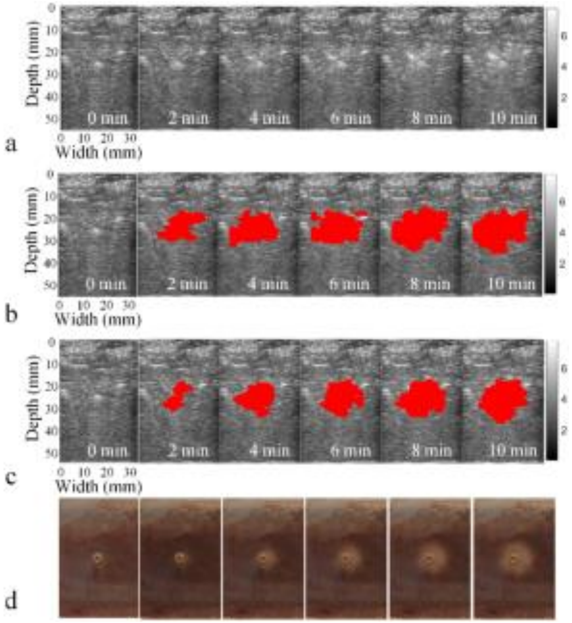


Figure 8 from Zhang et al: b-mode, AI ablation predictions and tissue section images

Freshly excised porcine livers were ablated using a clinical MWA system. During treatment, RF data were captured using a linear array imaging probe of an US scanner.

For training, gross-pathology images of tissue sections were used to label ultrasound RF data (after envelop detection) as ablated or not.

In total 1,640 ultrasound data matrices were acquired (approx. 82 ablation experiments)

The network could thus provide a binarized image of ablated regions, which could be compared against segmented data.

Dice score for ablation was 0.8688.

Figures 1 & 2 from Zhang et al

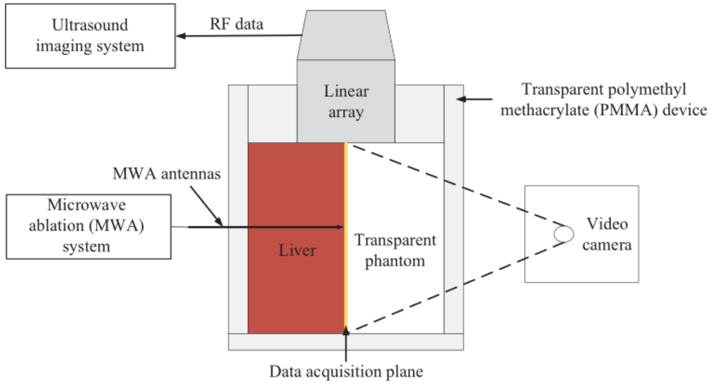
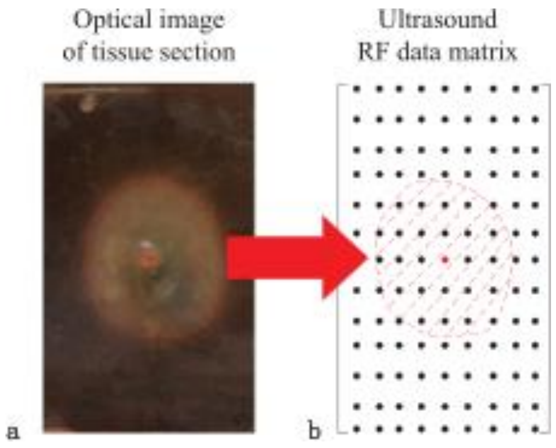


Fig. 2. Schematic of the experimental apparatus.



Cavitation Monitoring

Industrial Application

Cavitation can be a significant problem in many engineering applications, such as flow through a valve.

In a series of papers Sha et al. and coworkers developed a scheme to detect cavitation as well as cavitation intensity recognition.

They use labelled data from controlled experiments, taking a sliding window Fourier transform and extracted features. Other industrial applications have choosen features based on statistical properties of the data.

They are able to accurately classify the acoustic signatures of cavitation.

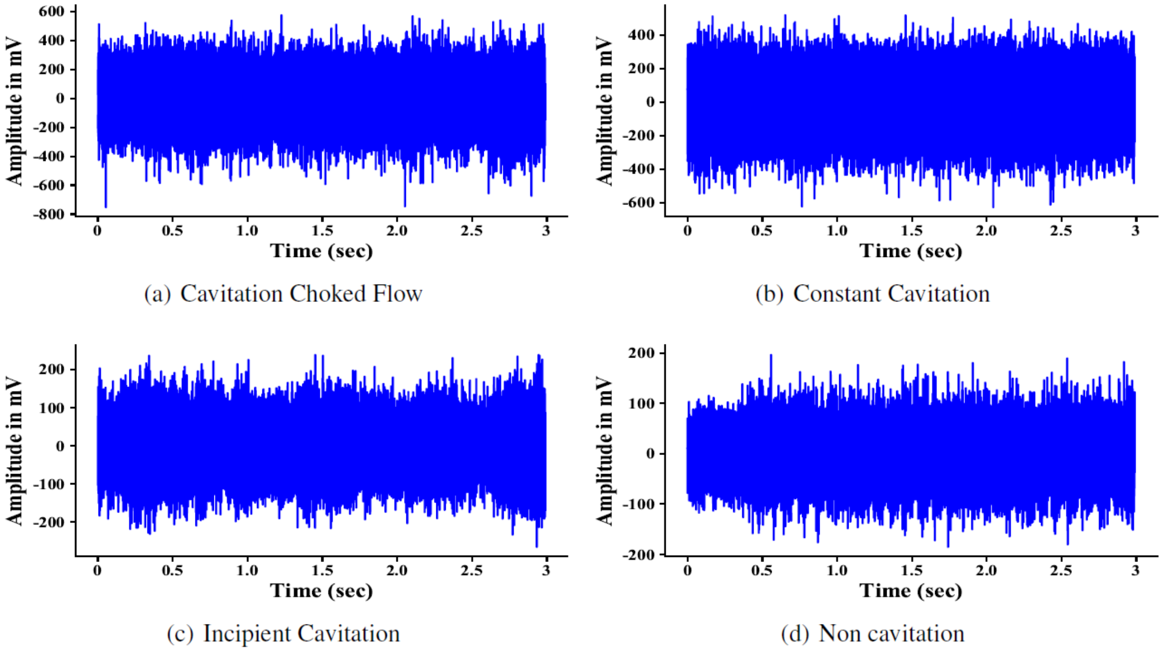


Figure 8 from Sha et al. : wave form data

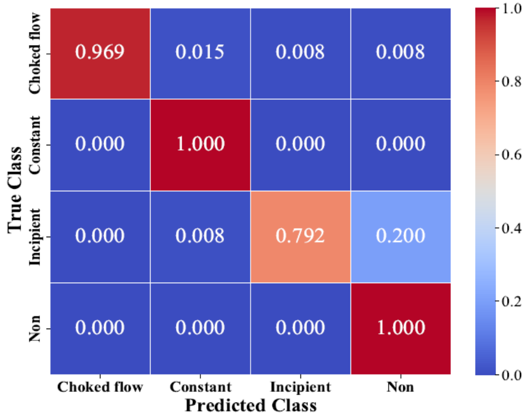


Figure 12 from Sha et al. showing confusion matrix

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Transfer Learning

In the context of radiotherapy, there are many useful applications of transfer learning:

- Khalifa et al. leveraged transfer learning to train a curative-intent VMAT radiotherapy treatment plan for prostate treatment based on MRI from an approved network trained on 99 sets of CT images.

- To overcome the lack of data in adrenal cancer, Wang et al. developed a transfer learning framework for adrenal SBRT planning that leverages knowledge in a pancreas SBRT planning model.

- Treatment plans generated by different practice styles to meet the national guidelines, in terms of plan quality, can end up with different spatial dose distributions. Also treatment planning systems and optimization algorithms introduce variations into clinical practice. Kandalan et al. used transfer learning to generate treatment plans based on different planning styles.

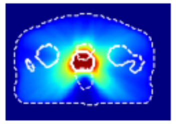
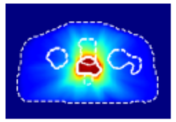
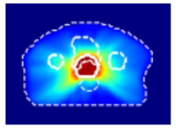
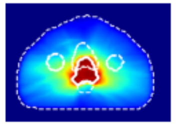
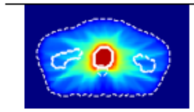
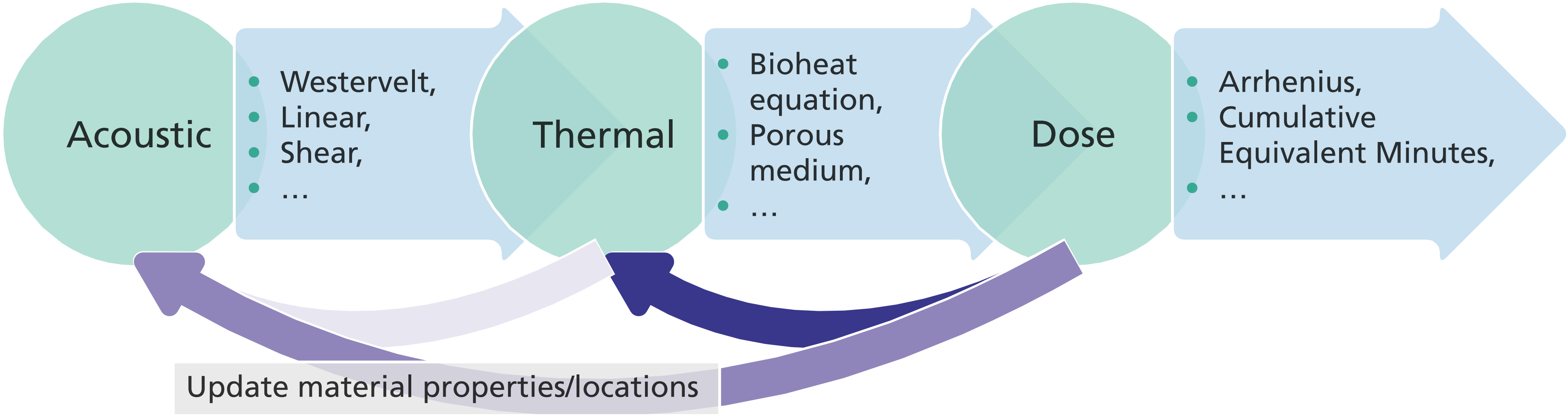
Dose Style	Name	Dataset	Training	Testing
	Source	118	108	10
	Internal-A	34	29	5
	Internal-B	16	14	2
	Internal-C	20	17	3
	External	60	20	40

Table 1: Patient datasets used for building the source model (Source) and for testing the model generalizability and then for adapting model (Internal-A, Internal-B, Internal-C, and External). First column shows a typical dose distribution of the planning style represented by each dataset.

Table from Kandalan et al.

Computational Pipeline

The simulation pipeline for thermal ablation typically involves solving three equations:



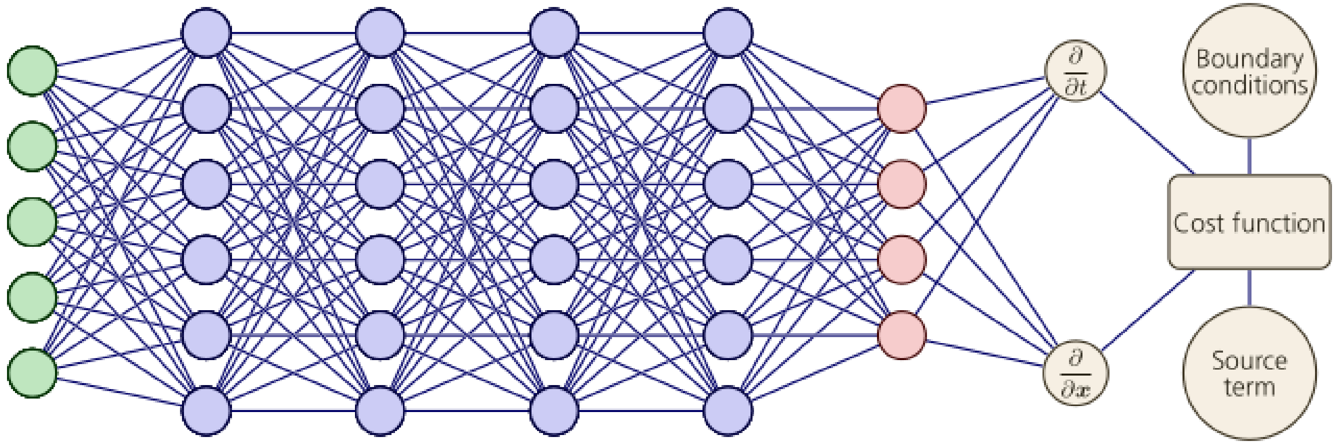
The first equation is an order of magnitude more computationally demanding than the second, which is, in turn more computationally demanding than the third. Accelerating the acoustic simulation would be a useful tool in treatment planning, especially in which multiple iterations of the acoustic field may be required to optimize the transducer settings.

Physics Informed Neural Networks (PINN)

The main idea is to enforce the neural network to generate an output which is the solution to a partial differential equation.

This can be expressed as a cost function (often called a loss function) which the network is trained to minimize.

Spatial and temporal derivatives may be applied to the output of the network, so that along with acoustic source, boundary conditions, a scalar cost function is defined which enforces the governing equation.



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Physics Informmed Neural Networks (PINN)

Helmnet

Stanziola et al created a network which could accurately predict linear acoustic fields in two-dimensional transcranial simulation:

- Training set with 9,000 sound speed distributions from skull phantoms and validation and test sets containing 1,000 distributions each.
- Training data with acoustic fields computed from a point source.
- The idealized skulls are randomly generated with a hollow convex structure with a constant thickness and constant speed of sound.
- Perfectly-matched layer boundary conditions applied in simulations

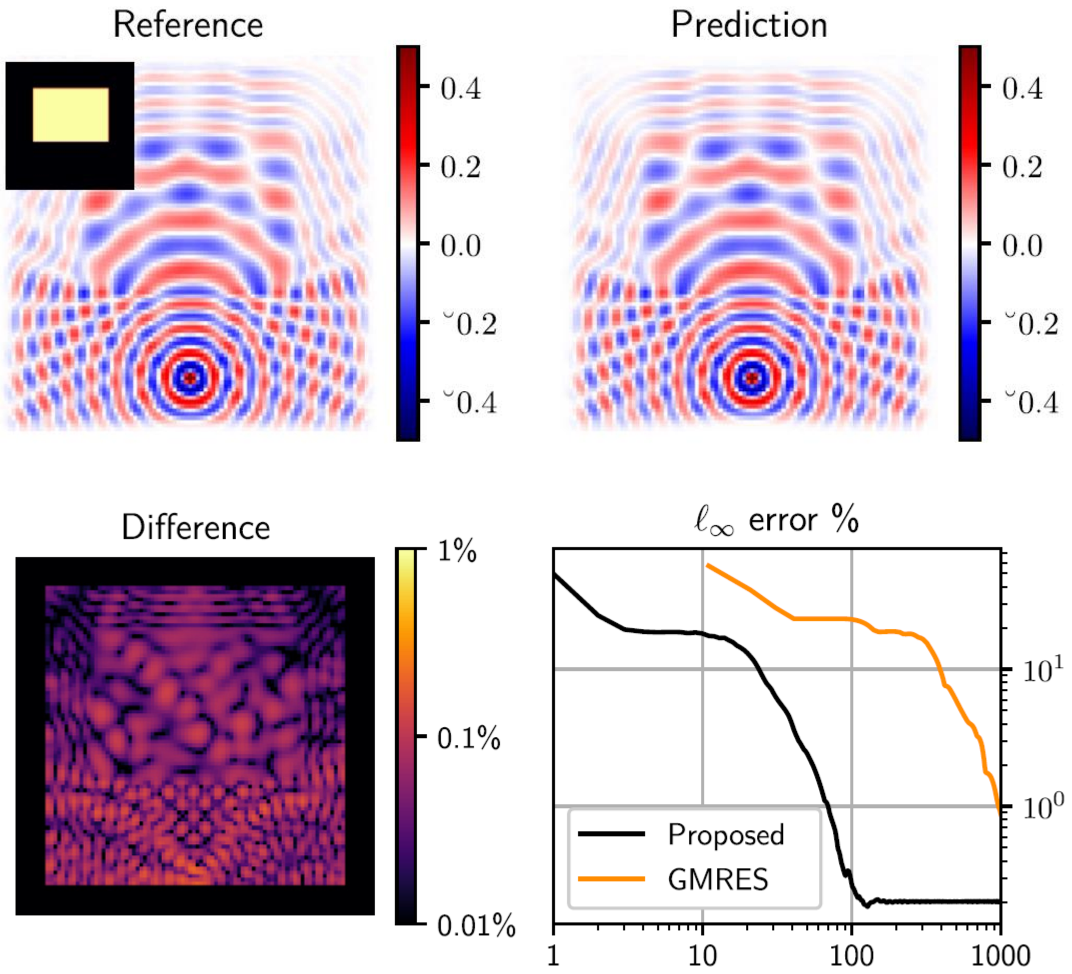


Figure 10 from Stanziola et al

Helmnet Solver

Learns Larger Domains

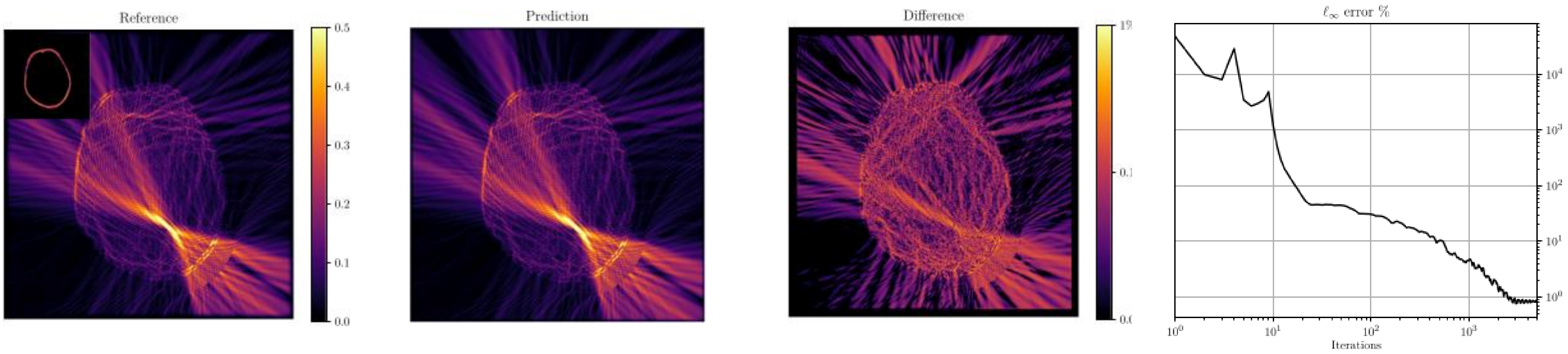


Figure 14 from [Stanziola et al](): generalised to larger domains: twice as large. Models field from different acoustic sources than trained on

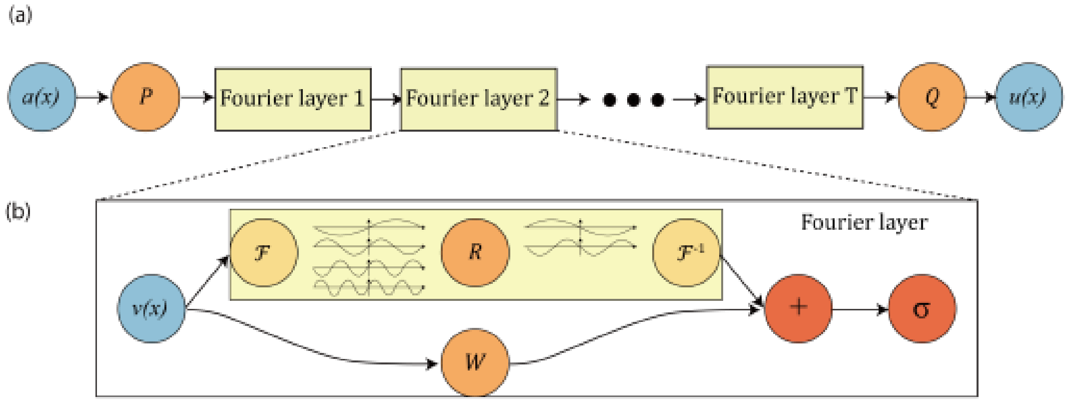
Fourier Neural Operators

- As mentioned, the computation units do not have to be linear operations. A recent development is to create a physics-informed neural network using a Fourier Neural Operator, presented by Li et al.

- This is mesh-independent, i.e. can be trained with data from different grid types.

- Can learn families of equations, rather than a single equation

- Features learned in the Fourier space are global by nature, representing patterns spanning the whole computational grid. Features learned in a standard CNN are local in nature and so represent patterns spanning over a small region.



(a) **The full architecture of neural operator**: start from input a. 1. Lift to a higher dimension channel space by a neural network P. 2. Apply four layers of integral operators and activation functions. 3. Project back to the target dimension by a neural network Q. Output u. **(b) Fourier layers**: Start from input v. On top: apply the Fourier transform $\mathcal{F}$; a linear transform R on the lower Fourier modes and filters out the higher modes; then apply the inverse Fourier transform $\mathcal{F}^{-1}$. On the bottom: apply a local linear transform W.

Figure 2: **top:** The architecture of the neural operators; **bottom:** Fourier layer.

- As such, Fourier networks out performs many other neural networks in terms as accuracy and generalisability.

Fourier Neural Operators

- Guan et al. trained a model using a Fourier Neural Operators for acoustic wave propagation in the context of photo-acoustics.
- Training on simulation data on 500 images of breast phantoms of 64×64 from linear simulations for 151 time steps
- Trained for approximately two days on a GPU, but network accurately predicts acoustic field 26 times quicker than simulation (although less for larger simulations)
- Model, from an initial source input, produces time domain images as output.

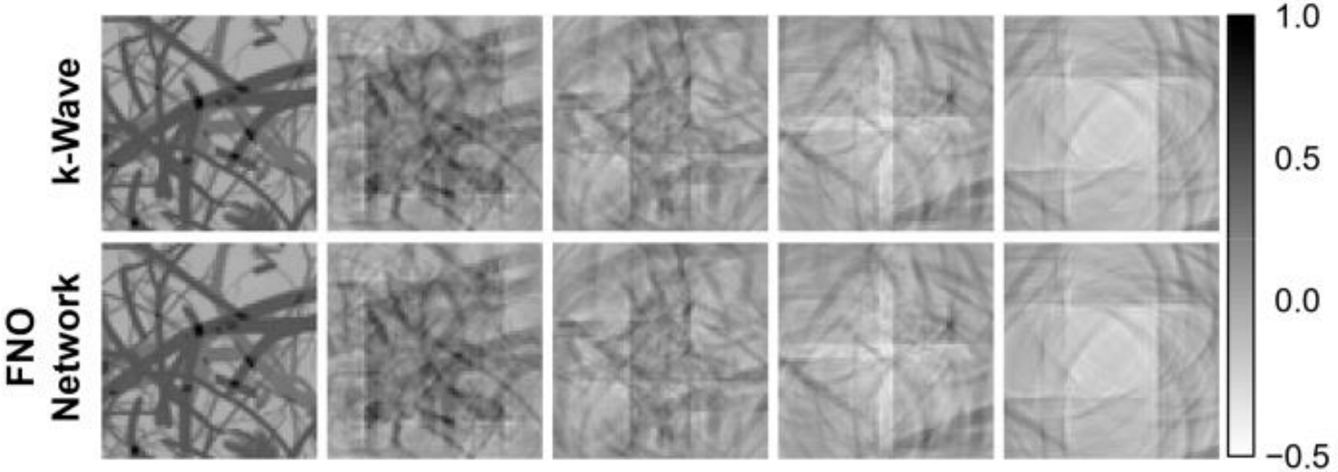


Figure 3. Visual comparison of the ground truth (**Top** Row) using k-Wave and the FNO network (**Bottom** Row) simulated photoacoustic wave propagation for an example vasculature image in a homogeneous medium at t = [1, 20, 40, 60, 80] time steps. The RMSE over all time steps was 3.8×10^{-3} for this example.

Data-driven Discovery of Partial Differential Equations

Physics informed neural networks provide a data-driven solution of a partial differential equation.

However, the multi-physics problem with coupled ultrasound, thermal and dosimetric fields may be simplified. How sure are we of the governing equation?

A possible scheme from Champion et al. is to investigate the data-driven discovery of partial differential equations to construct an equation which matchs the data.

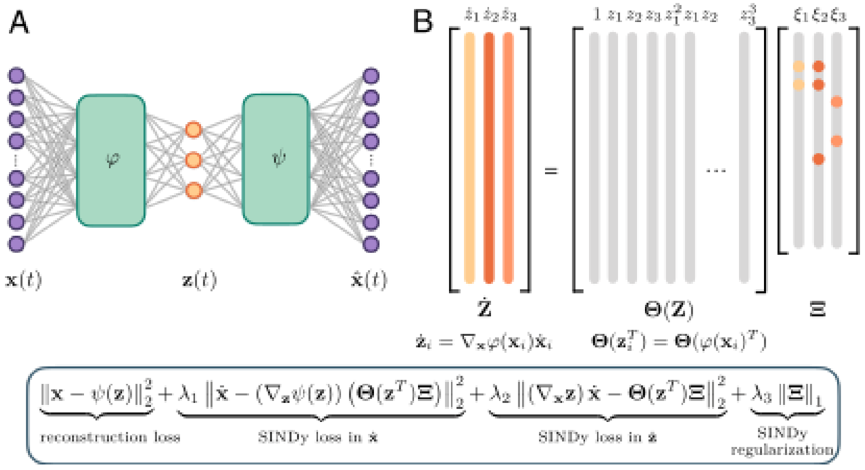


Figure 1 from Champion et al. showing network structure of scheme, pde that is generated and loss function.

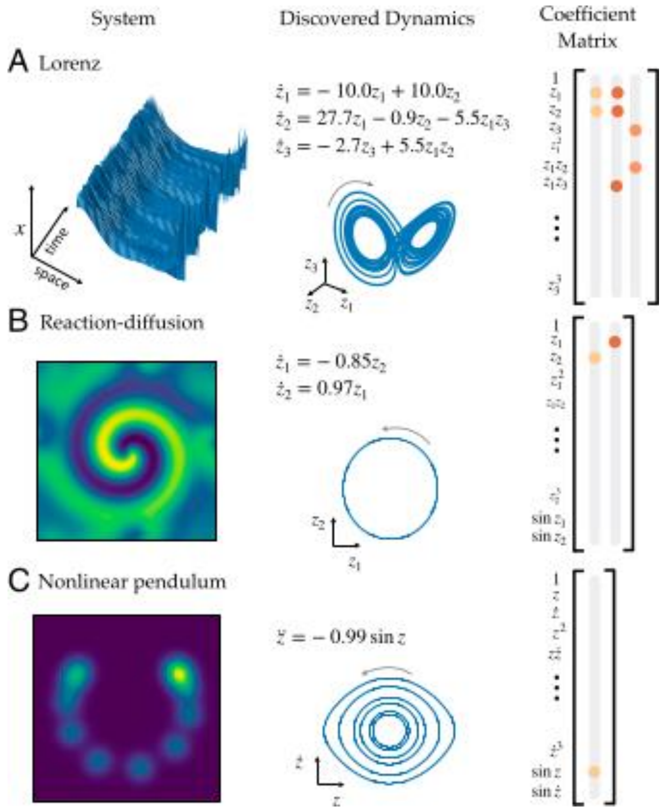


Figure 2 from Champion et al. discovered models

Treatment Prediction

Having derived and computed a computational model for treatment, assessment of treatment efficacy is important.

In the context of uterine fibroids, Soumi et al:

- 66 HIFU treatments on 89 fibroids
- 39 features extracted manually, 14 different filter-based selection methods (X^2, joint mutual information etc) used to rank most informative features
- Outcome was defined as non-perfused volume (NPV) ratio of less than 30%, 30–80% or greater than 80%
- Support vector classification used with RBF kernel to match features to outcome.

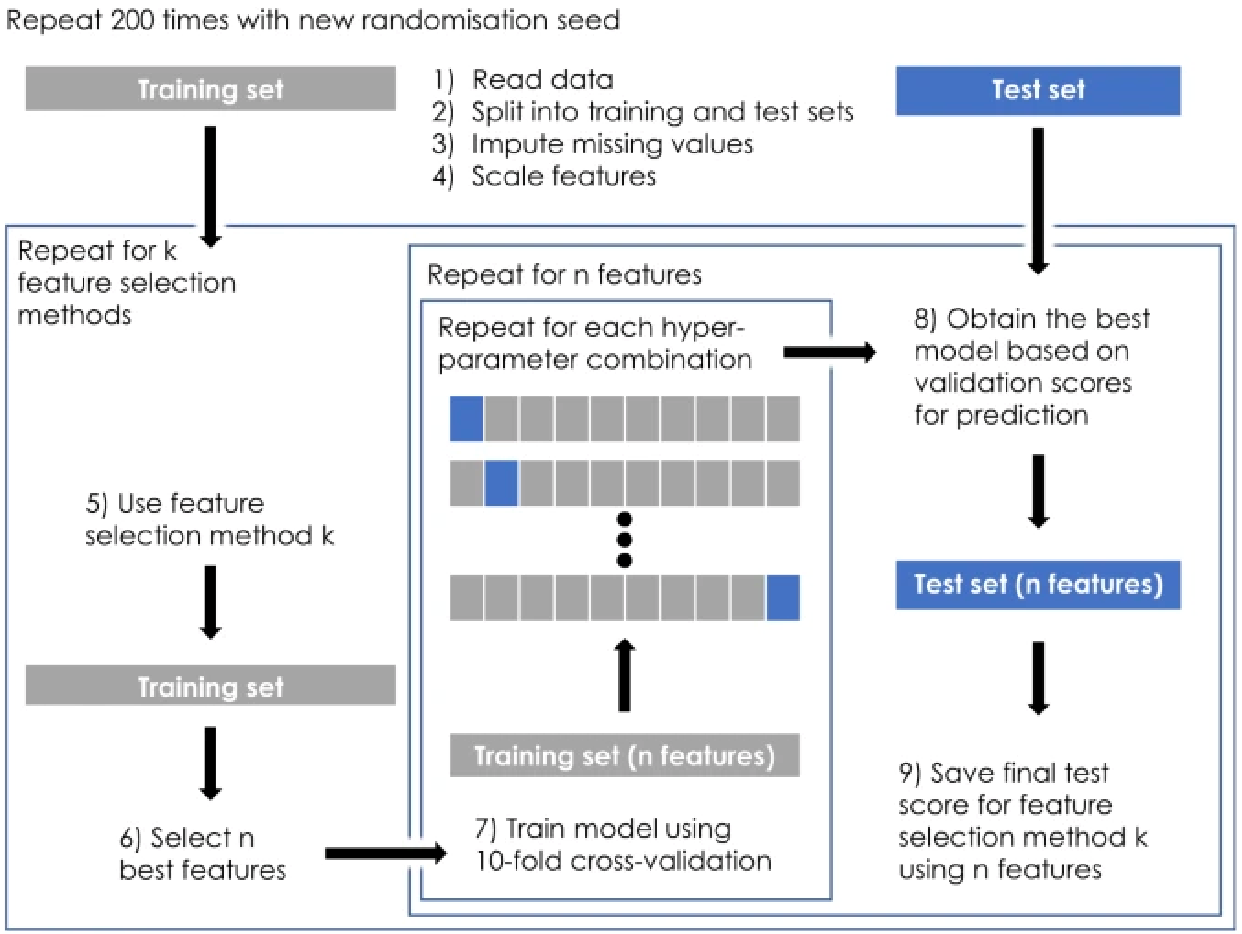


Figure 1 from Soumi et al showing data processing pipeline

Treatment Prediction

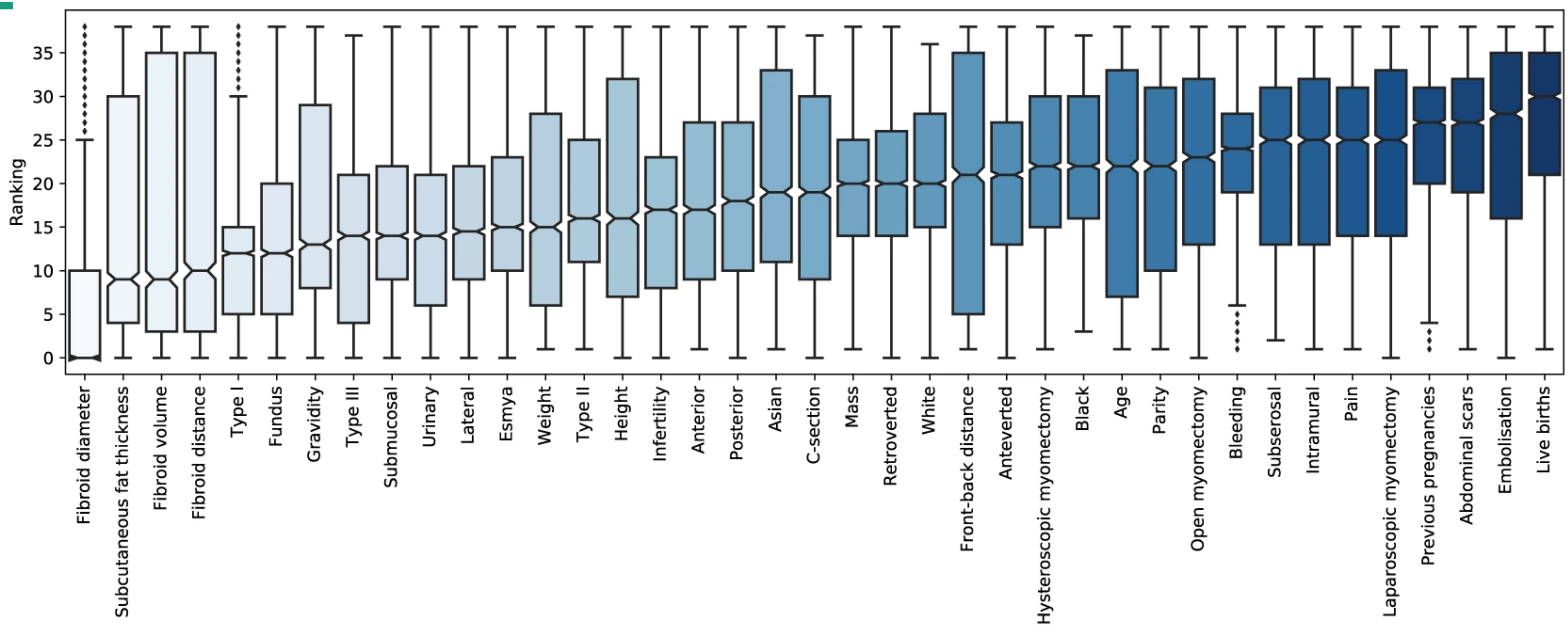


Figure 3 from Soumi et al. Boxplot showing the feature rankings (best to worst median values) from 14 different filter-based feature selection methods in classifying HIFU treatment outcome.

Treatment Prediction

The ten highest-ranking features given by their aggregate median value over all ranking types were:

1) fibroid diameter	2) subcutaneous fat layer thickness
3) fibroid volume	4) fibroid distance from the skin surface
5) Funaki type I	6) fundus location
7) gravidity	8) Funaki type III
9) submucosal fibroid type	10) urinary symptoms

Results may inform patient selection, but also treatment procedure: success delivery of treatment plan appears dependent on

- overcoming highly attenuating (2),
- long (4) propagation paths and
- steering to ablate large planned treatment volumes (1,3).

Recurrence Prediction

- On a longer time scale, in the context of curative intent radiotherapy for non-small cell lung cancer, a predictive model, similar to treatment prediction show previously, was developed by Hindocha et al to predict recurrence, recurrence-free survival and overall survival for patients two years after treatment
- A total of 657 patients from 5 hospitals were eligible for inclusion. Data pre-processing derived 34 features.
- Combinations of 8 feature reduction methods and 10 machine learning classification algorithms (including support vector classification) were compared, producing risk-stratification models for predicting recurrence, recurrence-free survival and overall survival
- Performance-status and TNM-stage are established prognostic factors. Logistic regression models were used to benchmark predictive models.
- Again, results were dependent on the classification algorithm.

Treatment Prediction

Wright et al trained a deep U-Net model using 95 contrast-free, treatment-day T1w (post-ablation), T2w (planning) and EPI thermometry MR images acquired during transurethral ultrasound ablation to predict synthetic contrast-enhanced images post treatment.

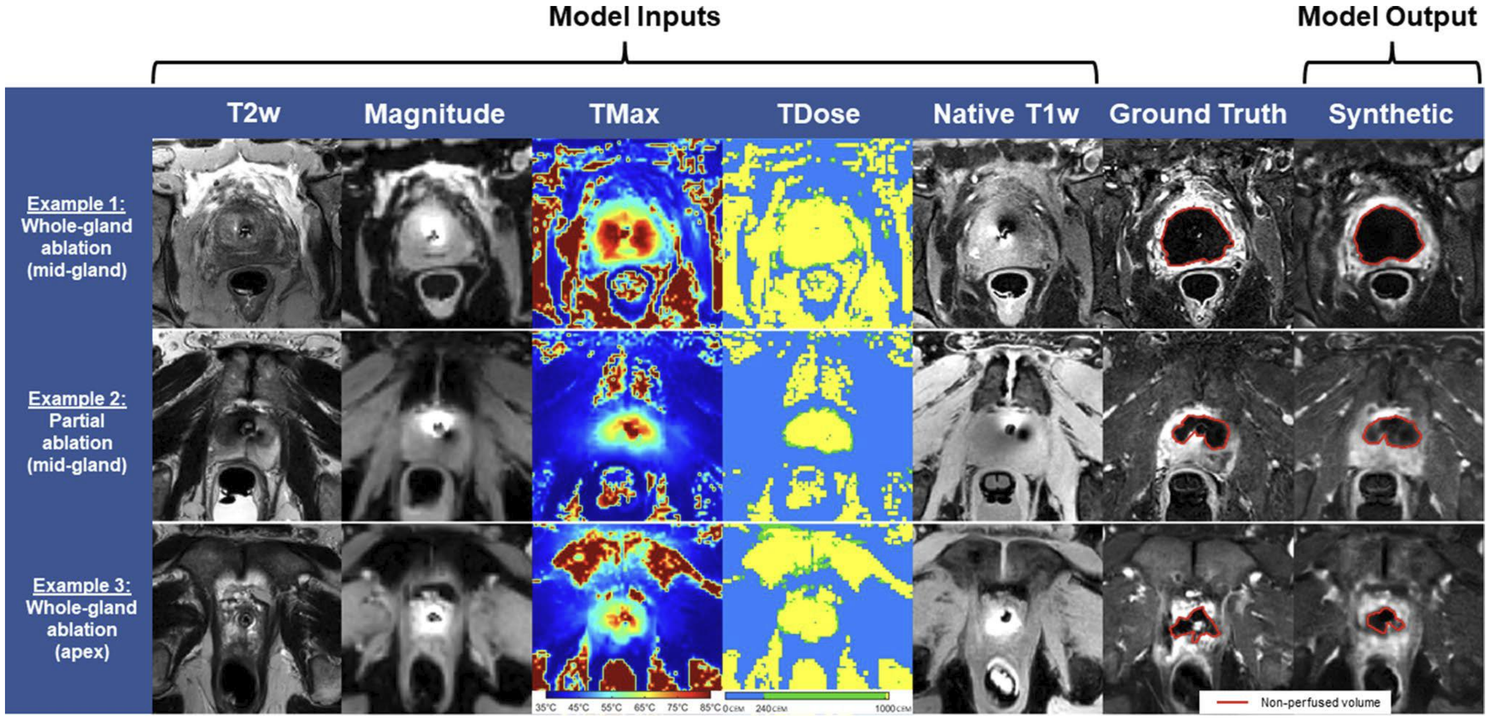


Figure 4 of Wright et al. In the first row, the Dice score was 94%, in the second row 88% and for the bottom row, for a whole-gland prostate ablation for a slice located near the prostate apex (where the measured prostate radius is smaller), the Dice score was 64% (Note as overlap is larger for larger objects, so smaller objects tend to have lower scores).

Contents

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Regulation & Future Opportunities

Software as a Medical Device

» The traditional paradigm of medical device regulation was **not designed** for adaptive AI/ML technologies, which have the potential to adapt and optimize device performance in real-time to continuously improve healthcare for patients.«

Proposed Regulatory Framework for Modifications to
Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device

As a product is used, new clinical data may be generated, which can help improve the model. Does the new model require resubmission? Not necessarily, if a

- SaMD Pre-Specifications (SPS) and an Algorithm Change Protocol (ACP) are supplied in any submission.

A set of guiding principles have been produced by regulators to aide model development with regulatory approval in mind.

Regulation & Future Opportunities

Best Practice Guide

Good Machine Learning Practice for Medical Device Development: Guiding Principles	
Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle	Good Software Engineering and Security Practices Are Implemented
Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population	Training Data Sets Are Independent of Test Sets
Selected Reference Datasets Are Based Upon Best Available Methods	Model Design Is Tailored to the Available Data and Reflects the Intended Use of the Device
Focus Is Placed on the Performance of the Human-AI Team	Testing Demonstrates Device Performance during Clinically Relevant Conditions
Users Are Provided Clear, Essential Information	Deployed Models Are Monitored for Performance and Re-training Risks are Managed

Regulation & Future Opportunities

Best Practice Guide: Implications?

- Clear need to have representative data, without bias which will reflect the treatment population: need to know where the training dataset was acquired, and record significant attributes which characterise the population.
- Tested extensively on clinically relevant data.
- The effects of updating model with data must be understood before being rolled-out.
- Model design is tailored to the available data: this can be interpreted as implying that a model to predict MRgFUS in the liver should ideally be trainined on MRgFUS data.

Regulation & Future Opportunities

Focused Ultrasound Foundation: Predicted Areas of Impact of AI

From the Focused Ultrasound Foundation website, areas of impact are:

Treatment Lifecycle:

- Patient Selection
- Treatment Planning
- Treatment Monitoring and Results Analysis

Indication/region:

- Neurological: Deep brain structures
- Neurological: Blood-brain barrier opening
- Urological: Prostate
- Gynaecological (potential sub-indications, e.g., uterine fibroids, etc.)
- Veterinary
- Emerging indications

FOCUSED ULTRASOUND FOUNDATION

Regulation & Future Opportunities

Focused Ultrasound Foundation Launches AI/ML Resources

- The Focused Ultrasound Foundation is setting up a FUS-ML Community of Practice to provide regular updates on the state of machine learning in focused ultrasound, developments and advances, and emerging opportunities within the field:

  https://www.fusfoundation.org/the-foundation/programs/join-our-fus-ml-community-of-practice/

- Also, the Focused Ultrasound Foundation has created the ML in FUS Community Forum, which is new tool reserved for academics, clinicians, practitioners, and researchers who are motivated to accelerate the field of machine learning in focused ultrasound:

  https://mlinfus.discourse.group/

- There are plenty of opportunities at the intersection of artificial intelligence and therapeutic ultrasound which will advance the field.

FOCUSED ULTRASOUND FOUNDATION

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Open Source Data Repositories

- REtroSpective Evaluation of Cerebral Tumors (RESECT): A clinical database of pre-operative MRI and intra-operative ultrasound in low-grade glioma surgeries: https://doi.org/10.1002/mp.12268
- Online database of clinical MR and ultrasound images of brain tumors (BITE) : https://doi.org/10.1118/1.4709600
- Synthetic data setused to train Helmholtz solver, helmnet: https://github.com/ucl-bug/helmnet

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Thank you for your attention

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