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Improved unsupervised physics-informed deep learning for intravoxel-incoherent motion modeling and evaluation in pancreatic cancer patients

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Abstract

Purpose: Earlier work showed that IVIM-NET$_{\text{orig}}$, an unsupervised physics-informed deep neural network, was faster and more accurate than other state-of-the-art intravoxel-incoherent motion (IVIM) fitting approaches to DWI. This study characterizes IVIM-NET$_{\text{orig}}$’s shortcomings and presents an optimized version: IVIM-NET$_{\text{optim}}$.

Method: In simulations (SNR=20), the accuracy, independence and consistency of IVIM-NET were evaluated for combinations of hyperparameters (fit $S_0$, constraints, network architecture, # hidden layers, dropout, batch normalization, learning rate), by calculating the normalized root-mean-square error (NRMSE), Spearman’s $\rho$, and the coefficient of variation (CV$_{\text{NET}}$), respectively. The best performing network, IVIM-NET$_{\text{optim}}$ was compared to least squares (LS) and a Bayesian approach at different SNRs. IVIM-NET$_{\text{optim}}$’s performance was evaluated in an independent dataset of twenty-three patients with pancreatic ductal adenocarcinoma (PDAC). Fourteen of the patients received no treatment between two repeated scan sessions and nine received chemoradiotherapy between the repeated sessions. Intersession within-subject standard deviations (wSD) and treatment-induced changes were assessed.

Results: In simulations, IVIM-NET$_{\text{optim}}$ outperformed IVIM-NET$_{\text{orig}}$ in accuracy (NRMSE($D$)=0.14 vs 0.17; NMRSE($f$)=0.26 vs 0.31; NMRSE($D^*$)=0.46 vs 0.49), independence ($\rho(D^*,f)$=0.32 vs 0.95) and consistency (CV$_{\text{NET}}$(D)=0.028 vs 0.185; CV$_{\text{NET}}$(f)=0.025 vs 0.078; CV$_{\text{NET}}$(D*)=0.075 vs 0.144). IVIM-NET$_{\text{optim}}$ showed superior performance to the LS and Bayesian approaches at SNRs<50. In vivo, IVIM-NET$_{\text{optim}}$ showed less noisy and more detailed parameter maps with lower wSD for $D$ and $f$ than the alternatives. In the treated cohort, IVIM-NET$_{\text{optim}}$ detected the most individual patients with significant parameter changes when compared to typical day-to-day variations.

Conclusion: IVIM-NET$_{\text{optim}}$ is recommended for accurate, informative and consistent IVIM fitting to DWI data.

Keywords: pancreatic cancer, deep neural network, diffusion-weighted magnetic resonance imaging, intravoxel incoherent motion, IVIM, unsupervised physics-informed deep learning
1. Introduction

The Intravoxel Incoherent Motion (IVIM) model (1) for diffusion-weighted imaging (DWI) shows great potential for estimating predictive and prognostic cancer imaging biomarkers (2–5). In the IVIM model, DWI signal is described by a bi-exponential decay, of which one component is attributed to conventional molecular diffusion and the other to the incoherent bulk motion of water molecules, typically credited to capillary blood flow. Hence, IVIM provides simultaneously information on diffusion ($D$ [mm$^2$/s]; diffusion coefficient), capillary microcirculation ($D^*$ [mm$^2$/s]; pseudo-diffusion coefficient) and the perfusion fraction ($f$ [%]) without the use of a contrast agent (6–8). However, despite IVIM’s great potential (2–5), it is rarely used clinically. Two major hurdles preventing routine clinical use of IVIM are its poor image quality and the long time to fit the data (9–11). Tackling these shortcomings will help towards wider use of IVIM (12).

Currently, IVIM is often fitted using the conventional least squares (LS) algorithm. However, more accurate alternative approaches have been suggested (9). Until recently, Bayesian algorithms for IVIM fitting to DWI (13) were most promising regarding inter-subject variability (9), precision, accuracy (14), and smooth parameter maps, suggesting less noise (15). Conversely, Bayesian approaches are substantially slower ($9 \times 10^{-2}$ seconds per voxel (11)) than the already slow LS approach ($8 \times 10^{-3}$ seconds per voxel (11)). Furthermore, Bayesian approaches may lead to biased perfusion estimates of the IVIM model under certain conditions (16).

Recently, a promising alternative for IVIM fitting was introduced: estimating IVIM parameters with deep neural networks (DNNs). Initially, Bertleff et al. (17) introduced a supervised DNN for IVIM parameter estimation, in which the network was trained on simulated data for which the underlying parameters were known. However, the strong assumption of simulated training and test data being identically distributed could limit the network’s performance in vivo, where noise behaves less ordered. We solved this shortcoming in earlier work (11), where we used unsupervised physics-informed deep neural networks (PI-DNNs) (18,19). PI-DNNs formulate a physics-informed-loss-function that finds learned parameters through an iterative process. In this case, the PI-DNN used consistency between the predicted signal from the IVIM model and the measured signal as a loss term in the DNN. This resulted in an unsupervised PI-DNN capable of training directly on patient data with no ground truth: IVIM-NET$_{\text{orig}}$. We demonstrated in both simulations and patient analysis that IVIM-NET$_{\text{orig}}$ is superior to the conventional LS approach and even performs (marginally) better than the Bayesian approach. Furthermore, IVIM-NET$_{\text{orig}}$’s fitting times were substantially lower ($4 \times 10^{-6}$ seconds per voxel (11)) than the LS and Bayesian approaches. However, that proof of principle IVIM-NET study did not explore many hyperparameters and focused on volunteer data.

In this work, we hypothesize that IVIM-NET$_{\text{orig}}$ can be further improved by exploring the architecture of the network, its training features and other hyperparameters. To show this, we characterized the
performance of IVIM-NET for different hyperparameter settings by assessing the accuracy, independence and consistency of the estimated IVIM parameters in simulated IVIM data. Finally, we compared the performance of our optimized IVIM-NET to LS and a Bayesian approach to IVIM fitting in patients with pancreatic ductal adenocarcinoma (PDAC) receiving neoadjuvant chemoradiotherapy (CRT), both in terms of test-retest reproducibility and sensitivity to treatment effects.

2. Methods

2.1 IVIM-NET

The code for all of our network implementations with some simple introductory examples in simulations and volunteer data are available on Github: https://github.com/oliverchampion/IVIMNET.

We initially implemented the original PI-DNN (IVIM-NETorig) (11) in Python 3.8 using PyTorch 0.4.1 (20). The input layer consisted of neurons that took the normalized DWI signal \( S(b)/S(b=0) \) as input, where \( S(b) \) is the measured signal at diffusion weighting \( b \) (b value). The input layer was followed by three fully connected hidden layers. Each hidden layer had a number of neurons equal to the number of measurements (b values and the number of repeated measures) and each neuron, in turn, contained an exponential linear unit activation function (21). The output layer of the network consisted of the three IVIM parameters (\( D, f, D^* \)). To enforce the output layer to predict these IVIM parameters, two steps were taken. First, the absolute activation function was taken of the neuron’s output \( X \) to constrain the predicted parameters, e.g. to compute \( D \):

\[
D = |X[1]| \quad [1].
\]

Second, a physics-based loss function was introduced that computed the mean squared error between the measured input signal, \( S(b) \), and the predicted IVIM signal \( S_{\text{net}}(b) \), which was obtained by inserting the predicted output parameters into the normalized IVIM model. Hence:

\[
L = \frac{1}{|B|} \sum_{b \in B} \left( \frac{S(b)}{S(b=0)} - S_{\text{net}}(b) \right)^2 \quad [2],
\]

with

\[
S_{\text{net}}(b) = f e^{-bD^*} + (1-f) e^{-bD} \quad [3],
\]

where \( B \) is the total number of image acquisitions (b values and repeated scans).

Next, we evaluated whether seven novel hyperparameters (Table 1; Figure 1) of IVIM-NET improved fitting results. First, instead of normalizing the input and predicted IVIM signals by \( S_0 \), we added \( S_0 \) as an additional output parameter, to allow the system to correct for noise in \( S(b=0) \). Second, to restrict parameter values to physiologically plausible ranges, scaled sigmoid activation functions instead of
absolute activation functions were used to constrain the predicted parameters of the output layer (Table 1), e.g. to compute $D$:

$$D = D_{\text{min}} + \text{sigmoid}(X[1]) \times (D_{\text{max}} - D_{\text{min}})$$

where $D_{\text{min}}$ and $D_{\text{max}}$ are the fit boundaries. Bound intervals were $D$: $-0.4 \times 10^{-3} - 5 \times 10^{-3}$ mm$^2$/s, $f$: -5–70%, $D^*,$ $5 \times 10^{-3} - 300 \times 10^{-3}$ mm$^2$/s, and $S0$: 0.7–1.3. The range was chosen broader than expected in vivo to compensate for the decreasing gradients at the asymptotes of the sigmoid function. Third, we varied the number of hidden layers between 1 and 9. Fourth, we used dropout regularisation (22) which randomly removes a set percentage of network-weights each iteration during training. Fifth, we used batch normalization (23) which normalizes the input by re-centering and re-scaling, and, consequently, preserves the representation ability of the network. Sixth, to reduce unwanted correlation between estimated parameter values, we implemented an alternative network architecture in which parameter values were predicted, in parallel, by independent sub-networks (Table 1; Figure 1). Furthermore, we evaluated different learning rates (LR) of the Adam optimizer (24), ranging from $1 \times 10^{-5}$ to $3 \times 10^{-2}$, and with constant $\beta=(0.9, 0.999)$.

In traditional deep learning, training and evaluation are done on separate datasets, but as this is an unsupervised DNN approach, training was done on the same data as evaluation. So, for simulations, these were simulated data, and in vivo, these were in vivo data. The data were split into two datasets, one containing 90% of the data used for training; and one containing 10% of the data used for validation. The validation set was used only to determine early stopping criteria. Early stopping occurred when the loss function did not improve over 10 consecutive training epochs. Given the large amount of training data and the limited number of network parameters, instead of feeding all the data at every epoch, we validated the network every 500 mini-batches. So, effectively the network saw $500 \times 128$ IVIM curves in between validations. Validation was done on the entire validation set.

### 2.2 Simulations: characterization and optimization

100,000 IVIM curves were simulated to investigate the effects of different hyperparameters on the accuracy, independence and consistency of the estimated IVIM parameters. DWI signals were simulated based on Eq. 3 with $S0 = 1$, 11 $b$ values ($b = 0, 5, 10, 20, 30, 40, 60, 150, 300, 500, \text{and } 700$ s/mm$^2$), and pseudorandom uniformly sampled values of $D$: $0.5 \times 10^{-3} - 3 \times 10^{-3}$ mm$^2$/s, $f$: 5–40%, and $D^*$: $10 \times 10^{-3} - 100 \times 10^{-3}$ mm$^2$/s. These ranges were slightly broader than typical values found in abdominal IVIM (25). Random Gaussian noise was added to the curves with predefined SNR levels (constant noise amplitude over $b$ values; SNR defined at $b = 0$).

Accuracy was assessed as the normalized root-mean-square error (NRMSE) between the ground truth parameter values and the estimated IVIM parameters.
Independence of the parameter estimates was assessed by the Spearman rank correlation coefficients ($\rho$) between $D$ and $D^*$; $\rho(D,D^*)$, $D$ and $f$; $\rho(D,f)$, and $D^*$ and $f$; $\rho(D^*,f)$. The absolute value of $\rho$ was taken, as both positive and negative deviations from zero are equally undesirable. Some networks always returned the same value for $D^*$, independent of the input data (Supporting Information Figure S1). For such cases, $\rho$ is technically undefined. As these cases are undesirable $\rho$ was set to 1.

As training a DNN is a stochastic process (random initialization, random dropout, random mini-batches), training on the same dataset usually results in different final network-weights, and consequently, different predictions on the same data. To assess the consistency of estimated parameter values, each network variant was trained 50 times on identical data, where each repeat had a new random initialization, dropout and mini-batch selection. The normalized coefficient of variation of the network over the repeated simulations ($CV_{NET}$) was taken as a measure of the consistency of each estimated parameter:

$$CV_{NET} = \frac{1}{\bar{x}_{true}} \sqrt{\frac{1}{n \times (m - 1)} \sum_{i=1}^{n} \sum_{j=1}^{m} (x_{i,j} - \bar{x}_{i})^2}$$  \hspace{1cm} [5],

where $\bar{x}_{true}$ is the mean value of the simulated IVIM parameter, $i=1,\ldots,n$ indicated the summation over the different decay curves with $n$ the number of simulated curves, $j=1,\ldots,m$ indicates the summation over the repeated neural network trainings with $m$ the number of repeated trainings, $x_{i,j}$ is the $j^{th}$ repeated prediction of the $i^{th}$ simulated decay curve, $\bar{x}_{i}$ is the mean over the repeated $m$ predictions of the $i^{th}$ simulated signal curve. As the LS and Bayesian approaches predict the same values for repeated fits to the same dataset, $CV_{NET}$ was zero for them.

As a result of the repeated training, we obtained 50 values for the NRMSEs and $\rho$’s. Therefore, the median and interquartile range were reported.

As a baseline for comparison, we evaluated the IVIM parameters $(D, f, D^*)$ in IVIM-NET$_{orig}$, the LS and Bayesian approaches. We used the Levenberg-Marquardt non-linear algorithm for the LS fit (26,27). For the Bayesian approach, we used the algorithm from previous work (11). For both the LS and Bayesian approaches $S0$ was included as a fit parameter. The Bayesian approach used a data-driven lognormal prior for $D$ and $D^*$, and a beta distribution for $f$ and $S0$. The prior distributions were determined empirically by fitting these distributions to the results from the LS approach on the same dataset. The maximum a posteriori probability was used as an estimate of the IVIM parameters. The LS and Bayesian approaches were performed with fit boundaries of $D$: $0 \times 10^{-3}$–$5 \times 10^{-3}$ mm$^2$/s, $f$: 0–70%, $D^*$: $5 \times 10^{-3}$–$300 \times 10^{-3}$ mm$^2$/s, and $S0$: 0.7–1.3.

After baseline characterization, IVIM-NET was optimized by testing various combinations of the hyperparameters (Table 1; Figure 1). Previous studies reported reliable SNR values of IVIM in the abdomen between 10 and 40 (28–31). So, to simulate reliable abdominal IVIM signals, an SNR of 20
was chosen for hyperparameter evaluation. We trained the network on the simulated signals using every combination of the following options: fitS0 parameters, absolute or sigmoid constraints, parallel network, dropout and batch normalization - while fixing the number of hidden layers to 3 (used in IVIM-NET<sub>orig</sub>, Table 1) and the LR to $1 \times 10^{-4}$. In an exploratory phase, we found that reducing the LR from $1 \times 10^{-3}$ (IVIM-NET<sub>orig</sub>) to $1 \times 10^{-4}$ was essential for obtaining networks with improvements in accuracy, independence and consistency. Based on these results, the best parameter combination was selected manually considering the combination of 1) NRMSE, 2) $\rho$ and 3) CV<sub>NET</sub>.

With the best options for the fitS0 parameters, constraints, parallel network, dropout and batch normalization, we tested the performance of the network as a function of the LR and number of hidden layers (Table 1). From those results, we finally selected the best performing optimized network: IVIM-NET<sub>optim</sub>.

IVIM-NET<sub>optim</sub>’s performance was characterized and compared to the LS approach, Bayesian approach and IVIM-NET<sub>orig</sub> for SNR values between 8 (low) and 100 (high). Furthermore, the performance of IVIM-NET<sub>orig</sub> and IVIM-NET<sub>optim</sub> were evaluated in two additional simulated datasets generated with other $b$-value distributions: 1) $b$ values from previous work (11,32): $b = 0, 10, 20, 60, 150, 300, 500,$ and 1000 s/mm<sup>2</sup>, and 2) $b$ values used in the in vivo data: $b = 0, 10, 20, 30, 40, 50, 75, 100, 150, 250, 400,$ and 600 sec/mm<sup>2</sup>.

### 2.3 Verification in patients with PDAC

To test how IVIM-NET<sub>optim</sub> performed in vivo two IVIM datasets of patients with PDAC were used: one to assess test-retest reproducibility, and one to see whether we can detect treatment effects. Both studies were approved by our local medical ethics committee and all patients gave written informed consent.

Both datasets (NCT01995240; NCT01989000) were published earlier (9,33,34). The first dataset consists of 14 patients with locally advanced or metastatic PDAC who underwent IVIM in two separate imaging sessions (average 4.5 days apart, range: 1–8 days) with no treatment in-between. The second dataset consisted of 9 PDAC patients with (borderline) resectable PDAC who received CRT as part of the PREOPANC study (35) where patients were scanned before and after CRT.

MRI data were acquired using a 3T MRI scanner (Ingenia, Philips, Best, The Netherlands). A respiratory triggered (navigator on liver dome) 2D multi-slice diffusion-weighted echo-planar imaging was used with parameters: TR > 2200 ms (depending on respiration speed), TE = 45 ms, flip angle = 90 deg, FOV = 432 x 108 mm<sup>2</sup>, acquisition matrix = 144 x 34, 18 slices, slice thickness = 3.7 mm and 12 $b$ values (directions): 0 (15), 10 (9), 20 (9), 30 (9), 40 (9), 50 (9), 75 (4), 100 (12), 150 (4), 250 (4), 400 (4) and 600 (16) mm<sup>2</sup>/s. Fat suppression was carried out with a gradient reversal during slice
selection and spectral presaturation with inversion recovery. Diffusion gradient times were 10.1 ms with a delay between diffusion gradients onset of 22.6 ms.

DWI images were co-registered to a reference volume consisting of a mean DWI image over all \( b \) values using deformable image registration in Elastix (36). A radiologist (10 years’ experience in abdominal radiology) and researcher (4 years’ experience in contouring pancreatic cancer) drew a region of interest (ROI) in the tumor in consensus. IVIM parameter maps of \( D, f \) and \( D^* \) were derived using the LS approach, Bayesian approach and IVIM-NET\(_{\text{optim}}\). Background voxels were removed automatically before fitting by removing voxels with \( S(b=0) < 0.5 \times \text{median}(S(b=0)) \). Fitting was done without averaging over the diffusion directions. IVIM-NET\(_{\text{optim}}\) was trained on all combined patient data. All computations were carried out on a single core of a conventional desktop computer (CPU: Intel Core i7-8700 CPU at 3.20 GHz). The average fitting time of each algorithm was recorded.

Further analysis was performed with the median parameter values from within the ROIs. To evaluate test-retest repeatability, intersession within-subject standard deviation (wSD) (37) was calculated for each IVIM parameter using the data from the patients with repeated baseline scans. Bland-Altman plots were plotted for patients from both cohorts. We calculated the 95% confidence intervals (95CI) from the patients with repeated scans at baseline (assuming zero offsets). In the cohort receiving treatment, we used a paired t-test to test whether parameters had significantly changed due to treatment within the cohort. Furthermore, patients from the treatment cohort were added to the Bland-Altman plots and individual patients who had changes exceeding the 95CI were considered to have significant changes in tumor microstructure (38).

3. Results

3.1 Simulations: characterization and optimization

The original network, IVIM-NET\(_{\text{orig}}\), showed substantially lower NRMSE for all estimated parameters than the LS and Bayesian approaches. However, IVIM-NET\(_{\text{orig}}\) had strong correlations between \( D^* \) and \( f \) (high \( \rho(D^*,f) \); Table 2 and Figure 2D) and had considerable CV\(_{\text{NET}}\). The NRMSE, \( \rho \) and CV\(_{\text{NET}}\) for all hyperparameter combinations are shown in the Supporting Information Figures S2–S7. From this data, we selected IVIM-NET\(_{\text{optim}}\) (Table 1) as optimal for IVIM-NET. IVIM-NET\(_{\text{optim}}\) resolved the high dependency between \( D^* \) and \( f \) found in IVIM-NET\(_{\text{orig}}\) (Table 2; Figure 2D, E) and substantially reduced the NRMSE and CV\(_{\text{NET}}\). Figure 3 illustrates the effect of changing a single option away from IVIM-NET\(_{\text{orig}}\) (left side) or away from the selected optimum (right side). It is clear that the reduced \( \rho(D^*,f) \) cannot be attributed to a single parameter, but was a result of the combination of the proposed changes. For IVIM-NET\(_{\text{orig}}\), enabling the additional fit parameter \( S_0 \), using sigmoid constraints and using the parallel network architecture all improved the NRMSE of all estimated IVIM parameters. Yet, the \( \rho(D^*,f) \) remains high for single deviations away from IVIM-
NET\textsubscript{orig} and the network’s consistency remains relatively poor (Figure 3). Single changes away from IVIM-NET\textsubscript{optim} can lead to marginally better NRMSE, lower \( \rho \) or lower CV\textsubscript{NET} (Figure 3), but only at a cost to the other two attributes. Supporting Information Figure S5–S7 show that the number of hidden layers did not have a substantial effect on the network’s performance, although generally, an increase in the number of hidden layers resulted in a higher \( \rho \), whereas a decrease resulted in higher NRMSE and CV\textsubscript{NET}. For the LR (Supporting Information Figure S5–S7), the order of magnitude was important as too high/low learning rates caused higher NRMSEs and less consistency.

Regardless of which \( b \)-value distribution was used, the abovementioned results hold and IVIM-NET\textsubscript{optim} outperformed IVIM-NET\textsubscript{orig} (Supporting Information Figure S8). Specifically, IVIM-NET\textsubscript{orig} showed high \( \rho(D^\ast,f) \) for every \( b \)-value distribution, while IVIM-NET\textsubscript{optim} had low \( \rho(D^\ast,f) \).

IVIM-NET\textsubscript{optim} was superior to the LS and Bayesian approaches for SNRs 8–50. Compared to IVIM-NET\textsubscript{orig}, IVIM-NET\textsubscript{optim} was associated with improved NRMSE for \( f \) and \( D \) at all SNRs (Figure 4). For \( D^\ast \), the networks performed similarly regarding NRMSE and CV\textsubscript{NET}, with IVIM-NET\textsubscript{optim} performing slightly better at SNRs > 20 and IVIM-NET\textsubscript{orig} for SNRs < 20. IVIM-NET\textsubscript{optim} had lower \( \rho(D^\ast,f) \) than IVIM-NET\textsubscript{orig} for all SNR levels.

### 3.2 Verification in patients with PDAC

The average interference fitting time per voxel of IVIM-NET\textsubscript{optim} after training was \( 3.0 \times 10^{-5} \) s per voxel, whereas the average fitting time per voxel of the LS approach was \( 4.2 \times 10^{-3} \) s and the Bayesian approach was \( 1.0 \times 10^{-1} \) s per voxel. The median training time for IVIM-NET\textsubscript{optim} (20 repeats) was 572 s with range 401–685 s.

An example of parameter maps computed with the LS approach, Bayesian approach and IVIM-NET\textsubscript{optim} of a PDAC patient before receiving CRT is presented in Figure 5. The parameter maps of IVIM-NET\textsubscript{optim} were less noisy and more detailed than those computed by the LS and Bayesian approaches.

In the test-retest cohort, IVIM-NET\textsubscript{optim} showed the lowest wSD for \( D \) and \( f \) (Table 3), while the Bayesian approach had the lowest wSD for \( D^\ast \). When averaging IVIM parameters for the repeated patient scans, IVIM-NET\textsubscript{optim} computed a higher \( D \), lower \( f \) and higher \( D^\ast \) than the LS and Bayesian approaches (Table 4). The repeated scans are visualized as black x’s in the Bland-Altman plots, together with their 95% CIs in Figure 6.

When taking into account the CRT patients as a whole, IVIM-NET\textsubscript{optim} found a significant \( (P < 0.05) \) increase in mean \( f \) after treatment, whereas the LS approach found a significant increase in \( D \) after treatment. Although non-significant, IVIM-NET\textsubscript{optim}’s P-value for \( D \) was 0.07.

Figure 6 shows the individual change in IVIM parameter values of patients receiving CRT compared to the 95CI of the test-retest. With 7 significant changes, IVIM-NET\textsubscript{optim} detected the most patients with significant parameter changes after CRT, with 4 individual patients with increased \( D \), 1 patient with
increased $f$ and 2 patients with changes in $D^*$. In comparison, the LS and Bayesian approaches detected only 2 and 4 significant parameter changes, respectively.

4. Discussion

This study is the first to show the potential clinical benefit of DNNs for IVIM fitting to DWI data in a patient cohort. We successfully developed and trained IVIM-NET\textsubscript{optim}, an unsupervised PI-DNN IVIM fitting approach to DWI that predicts accurate, independent and consistent IVIM parameters in simulations and in vivo, in patients with PDAC. IVIM-NET\textsubscript{optim} consisted of a parallel network architecture with 4 hidden layers, batch normalization, dropout of 10\%, sigmoid constraints and fitted $S_0$. Optimized training was performed using an Adam optimizer with a LR of $1 \times 10^{-4}$. In simulations, IVIM-NET\textsubscript{optim} outperformed the original version, IVIM-NET\textsubscript{orig}, by offering more accurate estimates of $D$, $f$ and $D^*$, with substantially less correlation between the estimated parameters $D^*$ and $f$ and more consistent parameter prediction. Furthermore, simulations demonstrated that IVIM-NET\textsubscript{optim} had substantially better accuracy than the conventional LS and state-of-the-art Bayesian approaches. Finally, in patients with PDAC, IVIM-NET\textsubscript{optim} also outperformed the alternatives. IVIM-NET\textsubscript{optim} showed the most detailed and least noisy parameter maps and a significant change in the perfusion fraction for the whole cohort receiving CRT. Furthermore, IVIM-NET\textsubscript{optim} was associated with the best test-retest repeatability (smallest wSD) for $D$ and $f$, which allowed it to detect the most patients with significant changes in all IVIM parameters after CRT.

IVIM-NET\textsubscript{optim} detected a significant positive trend in $f$ for the whole cohort of patients receiving CRT, whereas the LS approach found a significant positive trend in $D$. Conversely, IVIM-NET\textsubscript{optim} detected 4 patients with significant parameter increase for $D$, whereas the LS approach only detected 1 patient. Together with the fact that IVIM-NET\textsubscript{optim} detected an almost significant positive trend in $D$ for the whole cohort of patients receiving CRT, these findings strongly suggest IVIM-NET\textsubscript{optim} as a good alternative for IVIM fitting in PDAC patients. Findings from other studies support this increase in $D$ (39) and $f$ (40) during CRT in PDAC patients. In general, PDACs tend to have lower diffusion due to the impeded water movement of compressing cells (41). Furthermore, PDACs are typically hypoperfused, due to significant tumor sclerosis creating elevated interstitial pressure, which compresses tumor feeding vessels (40,42). Effective treatment leads to necrosis, which in turn leads to lower cell densities and reduced interstitial pressure, and consequently increased diffusion (43,44) perfusion (45). Not all patients demonstrated a significant change for both diffusion and perfusion parameters induced by treatment. Therefore, using IVIM to discriminate between individual treatment effects may be feasible in the future. As the treatment of these patients was part of induction therapy and patients received surgery directly after, overall survival cannot be attributed purely to the CRT effect. Hence, given the limited number of patients and the diluted treatment effect, we did not compare overall survival between patients that showed potential treatment effects and others.
Our previous work (34) showed that the LS approach to IVIM fitting was sensitive to individual treatment effects. However, high wSD was found which limited the study to detect individual treatment effects. Furthermore, this work (34) used denoised DWI b-images that substantially degraded image sharpness and tumor boundaries were harder to detect (e.g. compare figures from this work to example figures from (9)). Conversely, our present study demonstrates that DNNs can estimate parameter maps directly from the noisy data resulting in sharp high-quality IVIM parameter maps.

Although IVIM-NET showed consistently better results both in simulations and in vivo, IVIM-NET predicts different IVIM parameters in repeated training. This causes a new sort of variability that, until now, was not an issue in fitting parameter maps. There may be methods to mitigate this variability. First, when probing treatment response, we would advise using one network such that this additional effect is not different pre and post-treatment. Second, to reduce the variation, one could consider taking the median prediction from 10 repeated trainings instead. We did so in an exploratory study where we formed 5 groups of 10 networks and showed that the median of 10 networks was substantially more consistent, with \( CV_{NET} \) values of \( 7.6 \times 10^{-3} \), \( 6.3 \times 10^{-3} \) and \( 18.7 \times 10^{-3} \) for \( D, f \) and \( D^* \), respectively. Having a set of networks will also allow the user to estimate the variation on the predicted parameter. Finally, although we see this additional uncertainty, we would like to stress that it is secondary to the overall error of the LS approach, which is apparent from the fact that in the simulations, all 50 instances of IVIM-NET\(_{\text{opt}}\) had lower NRMSE than the LS approach.

IVIM-NET\(_{\text{opt}}\) was comparable or outperformed IVIM-NET\(_{\text{orig}}\) at SNRs 8–100 and superior to the LS and Bayesian approach for SNRs 8–50 (Figure 4). However, at extremely high SNR (SNR = 100; Figure 4), the LS approach outperformed IVIM-NET. The Levenberg-Marquardt algorithm for the LS function is an iterative function that finds a minimum of the squared difference. For a relatively smooth loss landscape and high SNR signal, the LS algorithm is designed to find the correct parameter estimates. However, at low SNR, the LS approach has trouble finding the correct parameters. This occurs either because the loss landscape is no longer smooth and hence it gets stuck in a local minimum, or, what we believe is more common, the noise has changed the signal such that the global optimum no longer is nearby the ground truth parameters. On the other hand, a DNN consists of a complex system that needs to encompass estimating the IVIM parameters for all voxels. It turns out that having been trained on all voxels enables better estimates for individual voxels at low SNR. We expect that DNNs focus on more consistent minima with parameter values that are more frequently observed. This might be similar to data-driven Bayesian fitting approaches (15,46). Conversely, our DNN seems to reach a maximum accuracy at high SNR. Potentially more complex DNNs that are optimized with simulations done at high SNR can comprise the subtle signal changes of the IVIM parameters at these SNRs. However, typical SNR values for IVIM data are < 50. Therefore, our findings suggest that using our DNN instead of the LS and Bayesian approaches for IVIM fitting to DWI-data would be beneficial in a clinical setting.
The choice of the hyperparameters for IVIM-NET\textsubscript{optim} was based on an optimal combination of accuracy, independence and consistency across all IVIM parameters. However, other hyperparameter options may be more appropriate when characterizing an individual IVIM parameter (e.g. when an observer is only interested in \( D \) and IVIM is barely used to correct for perfusion). Figures S1–S6 of the Supporting Information can help interested readers select the best network for their purposes.

The high dependency between \( D^* \) and \( f \) that appears in IVIM-NET\textsubscript{orig} could not be attributed to a single cause. Initially, we expected that this dependency originated in the fully connected shared hidden layers of the original network. Although \( \rho \) decreased when adding the ‘parallel network architecture’ to IVIM-NET\textsubscript{orig}, \( \rho \) remained substantial (Figure 3). These dependencies between estimated parameters are not per se specific to DNNs. For instance, similar dependencies between \( D^* \) and \( D \) or \( f \) were found in a different data-driven Bayesian fitting approach (9). For IVIM-NET\textsubscript{optim}, these dependencies were small at clinical SNR values and similar to those of the LS approach.

Although simulation studies in parameter estimation are extremely valuable as the underlying parameter values are known, they also come with limitations. One limitation is that the noise characterization of real data can be diverse and hard to model. For instance, DWI artifacts caused by motion are not considered in simulations and may affect the results of fitting the IVIM model (47). We are aware that Rician noise could be added to generate more realistic noise. However, to compare models, we believe that adding Rician noise and hence additional systematic errors, only complicates the comparison, as errors from the fit methods could cancel out errors induced by the Rician noise. We do not expect that adding Rician noise would have had a significant effect on our results, as we do not expect any of the fit approaches to deal differently with Rician noise. Hence, we employed Gaussian noise for a fairer and easier comparison between algorithms. Nonetheless, our in vivo results show that in the presence of real noise, IVIM-NET\textsubscript{optim} is superior to the alternatives. Another limitation is the underlying assumption that the IVIM model is complete and hence that data are perfectly bi-exponential. In reality, the IVIM model is a simplification and real data will be more complex.

5. Conclusion
We substantially improved the accuracy, independence and consistency of both diffusion and perfusion parameters from IVIM-NET by changing the network architecture and tuning hyperparameters. Our new IVIM-NET\textsubscript{optim} is considerably faster, and computes less noisy and more detailed parameter maps with substantially better test-retest repeatability for \( D \) and \( f \) than alternative state-of-the-art fitting methods. Furthermore, IVIM-NET\textsubscript{optim} was able to detect more individual patients with significant changes in the IVIM parameters throughout CRT. These results strongly suggest using IVIM-NET\textsubscript{optim} for detection of treatment response in individual patients. To stimulate wider clinical implementation of IVIM, we have shared IVIM-NET online and encourage our peers to test it.
6. **Bibliography**

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**Figures and Tables**

| Hyperparameter       | Values      | IVIM-NET\text{orig} | IVIM-NET\text{optim} |
|----------------------|-------------|----------------------|-----------------------|
| fitS0                | True, False | False                | True                  |
| Constraints          | Sigmoid, Absolute | Absolute            | Sigmoid               |
| Parallel networks    | True, False | False                | True                  |
| Number of hidden layers | 1, 2, 3, 4, 5, 6, 7, 8, 9 | 3                   | 4                     |
| Dropout regularisation | 0%, 10%, 20%, 30% | 0%                 | 10%                   |
| Batch normalization  | True, False | False                | True                  |
| Learning rate        | $1 \times 10^{-5}, 3 \times 10^{-5}, 1 \times 10^{-4}, 3 \times 10^{-4}, 1 \times 10^{-3}, 3 \times 10^{-3}, 1 \times 10^{-2}, 3 \times 10^{-2}$ | $1 \times 10^{-3}$ | $1 \times 10^{-4}$ |

Table 1: Hyperparameter settings for training IVIM-NET, including the settings for IVIM-NET\text{orig} and IVIM-NET\text{optim}. 
Table 2: Normalized root-mean-square error (NRMSE), Spearman rank correlation coefficient (ρ) and normalized coefficient of variation (CV_{NET}) of 50 repeated runs of the LS approach, Bayesian approach, IVIM-NET\textsubscript{orig} and IVIM-NET\textsubscript{optim} for all estimated IVIM parameters in simulations. Values of the DNNs: median (interquartile range).

|                           | Least Squares | Bayesian | IVIM-NET\textsubscript{orig} | IVIM-NET\textsubscript{optim} |
|---------------------------|---------------|----------|-------------------------------|-------------------------------|
| NRMSE $D$                 | 0.263         | 0.198    | 0.172 (0.158–0.237)           | 0.144 (0.143–0.147)           |
| NRMSE $f$                 | 0.570         | 0.351    | 0.312 (0.308–0.320)           | 0.260 (0.257–0.265)           |
| NRMSE $D^*$               | 1.169         | 0.710    | 0.489 (0.435–0.513)           | 0.456 (0.437–0.474)           |
| ρ($D, D^*$)               | 0.23          | 0.07     | 0.10 (0.05–0.15)              | 0.19 (0.182–0.205)            |
| ρ($D, f$)                 | 0.23          | 0.03     | 0.07 (0.03–0.10)              | 0.10 (0.09–0.12)              |
| ρ($D^*, f$)               | 0.23          | 0.14     | 0.95 (0.81–0.99)              | 0.32 (0.29–0.35)              |
| CV\textsubscript{NET} $D$ [× 10^{-2}] | 0             | 0        | 18.5                          | 2.8                           |
| CV\textsubscript{NET} $f$ [× 10^{-2}] | 0             | 0        | 7.2                           | 2.5                           |
| CV\textsubscript{NET} $D^*$ [× 10^{-2}] | 0             | 0        | 14.4                          | 7.5                           |
Table 3: Intersession within-subject standard deviation (wSD) of the IVIM parameters.

| wSD             | $D \times 10^3 \text{mm}^2/\text{s}$ | $f \%$ | $D^* \times 10^3 \text{mm}^2/\text{s}$ |
|-----------------|--------------------------------------|--------|---------------------------------------|
| Least squares   | 0.12                                 | 6.1    | 10                                    |
| Bayesian        | 0.09                                 | 5.0    | 5                                     |
| IVIM-NET$_{optm}$ | 0.07                               | 2.6    | 19                                    |
Table 4: Mean IVIM parameters in the test-retest cohort (top panel) and patients with treatment (bottom panel).

| Mean baseline          | $D \times 10^3$ mm$^2$/s | $f$ [%] | $D^* \times 10^3$ mm$^2$/s |
|------------------------|---------------------------|---------|-----------------------------|
| Least squares          | 1.33                      | 11.2    | 20                           |
| Bayesian               | 1.18                      | 16.3    | 7.4                          |
| IVIM-NET$\text{optm}$  | 1.47                      | 5.2     | 74                           |

| Mean treatment         | $D \times 10^3$ mm$^2$/s | $f$ [%] | $D^* \times 10^3$ mm$^2$/s |
|------------------------|---------------------------|---------|-----------------------------|
|                        | Pre           | Post    | Pre           | Post    | Pre          | Post          |
| Least squares          | 1.35          | 1.51    | 13.1          | 16.2    | 22           | 55            |
| Bayesian               | 1.21          | 1.32    | 18.2          | 22.2    | 8.5          | 19            |
| IVIM-NET$\text{optm}$  | 1.54          | 1.64    | **6.3**       | **9.6** | 93           | 94            |

*significant ($P < 0.05$) changes between pre and post-treatment, determined by a paired t-test, are printed bold.
Figure 1: Representation of the PI-DNN with different hyperparameter options (Table 1). In this example, the input signal, consisting of the measured DWI signal, is feedforwarded either through (A) a parallel network design where each parameter is predicted by a separate fully connected set of hidden layers or (B) the original single fully-connected network design. The blue circles indicate an example of randomly selected neurons for dropout. In this example, the output layer consists of four neurons with either absolute (Eq. 1) or sigmoid activation functions (Eq. 4) whose values correspond to the IVIM parameters. Subsequently, the network predicts the IVIM signal (Eq. 3) which is used to compute the loss function (Eq. 2). With the loss function, the network trains the PI-DNN to give good estimates of the IVIM parameters.
Figure 2: $D^*$ plotted against $f$ for (A) simulations, (B) Least squares, (C) Bayesian, (D) IVIM-NET$_{orig}$ and (E) IVIM-NET$_{optim}$. In all plots, the values of the simulations are presented in grey. The apparent patterns in the LS approach (many predictions at $D^* = 0.3$) and IVIM-NET$_{orig}$ (the line flips at $D^* = 0$) are a result of the fit constraints.
Figure 3: Normalized root-mean-square error (NRMSE; left), Spearman rank correlation coefficient ($\rho$; center) and normalized coefficient of variation ($\text{CV}_{\text{NET}}$; right) plots of the estimated IVIM parameters ($D$, $f$ and $D^*$) with a single parameter change for both IVIM-NET$_{orig}$ (orange) and IVIM-NET$_{optim}$ (green). Left of each plot shows the LS approach (blue) and Bayesian approach (brown).
Figure 4: Normalized root-mean-square error (NRMSE; left), Spearman rank correlation coefficient (ρ; center) and normalized coefficient of variation (CV_{NET}; right) plots of the estimated IVIM parameters (D, f and D') vs SNR for the LS (blue), Bayesian (brown), IVIM-NET_{orig} (orange) and IVIM-NET_{optim} (green) approaches to IVIM fitting. IVIM-NET_{optim} is comparable or outperforms IVIM-NET_{orig} for all SNRs. The LS and Bayesian approaches are superior at high SNRs.
Figure 5: IVIM parameter maps ($D$, $f$, $D^*$) of the LS, Bayesian and IVIM-NET$_{opt}$ approaches to IVIM fitting of a PDAC patient before receiving CRT. The red ROI represents the PDAC. The LS and Bayesian approaches appear noisy, whereas IVIM-NET$_{opt}$ shows less noisy and more detailed parameter maps.
Figure 6: Bland-Altman plots of the LS, Bayesian and IVIM-NET\textsubscript{optim} approaches to IVIM fitting showing the mean and difference ($\Delta$) between the intersession repeatability patients (black crosses) and the mean and $\Delta$ between pre and post-treatment patients (colored symbols) which represents the treatment effects. The dotted lines indicate the 95CI of the test-retest data. Colored measurements that exceed the 95CI were considered significant to treatment response.
Supporting Information

Figure S1: Plots of the estimated IVIM parameters where no Spearman rank correlation coefficient ($\rho$) can be determined and is set to a $\rho$ of 1.
Figure S2: Normalized root-mean-square error (NRMSE) plots of the estimated IVIM parameters ($D, f, D'$) that contain all hyperparameter combinations with a fixed learning rate set to $1 \times 10^{-4}$ and a fixed number of hidden layers set to 3 at an SNR of 20. For fair comparison, the LR was increased to $1 \times 10^{-4}$ in IVIM-NET$_{orig}$. Highlighted in green is the intermediate step of IVIM-NET$_{optim}$, which is IVIM-NET$_{optim}'$. Left of each plot shows the LS approach (blue), Bayesian approach (brown) and IVIM-NET$_{orig}$ (orange; LR = $1 \times 10^{-3}$).
Figure S3: Spearman rank correlation coefficient ($\rho$) plots of the estimated IVIM parameters ($D, f, D'$) that contain all hyperparameter combinations with a fixed learning rate set to $1 \times 10^{-4}$ and a fixed number of hidden layers set to 3 at an SNR of 20. For fair comparison, the LR was increased to $1 \times 10^{-4}$ in IVIM-NET$^{\text{orig}}$. Highlighted in green is the intermediate step of IVIM-NET$^{\text{opt}}$, which is IVIM-NET$^{\text{opt, orig}}$. Left of each plot shows the LS approach (blue), Bayesian approach (brown) and IVIM-NET$^{\text{orig}}$ (orange; LR = $1 \times 10^{-3}$).
Figure S4: Normalized Coefficient of variation (CV\textsubscript{NET}) plots of the estimated IVIM parameters ($D$, $f$, $D^*$) that contain all hyperparameter combinations with a fixed learning rate set to $1 \times 10^{-4}$ and a fixed number of hidden layers set to 3 at an SNR of 20. For fair comparison, the LR was increased to $1 \times 10^{-4}$ in IVIM-NET\textsubscript{orig}'. Highlighted in green is the intermediate step of IVIM-NET\textsubscript{optim}, which is IVIM-NET\textsubscript{optim}'. Left of each plot shows the LS approach (blue), Bayesian approach (brown) and IVIM-NET\textsubscript{orig} (orange; LR = $1 \times 10^{-3}$).
Figure S5: Normalized root-mean-square error (NRMSE) plots of the estimated IVIM parameters ($D, f, D^*$) of the second evaluation for different LR and number of hidden layers, with fixed hyperparameters of extra fitting parameter $S_0$, sigmoid activation functions, a parallel network architecture, 10% dropout and batch normalization, at an SNR of 20. Highlighted in green is IVIM-NET$_{optim}$. Left of each plot shows the LS approach (blue) and Bayesian approach (brown) and IVIM-NET$_{orig}$ (orange).
Figure S6: Spearman rank correlation coefficient plots of the estimated IVIM parameters \((D, f, D^*)\) of the second evaluation for different LR and number of hidden layers, with fixed hyperparameters of extra fitting parameter \(S_0\), sigmoid activation functions, a parallel network architecture, 10% dropout and batch normalization, at an SNR of 20. Highlighted in green is IVIM-NET\(\text{opt}_{\text{ms}}\). Left of each plot shows the LS approach (blue) and Bayesian approach (brown) and IVIM-NET\(\text{opt}_{\text{reg}}\) (orange).
Figure S7: Normalized coefficient of variation ($CV_{\text{NET}}$) plots of the estimated IVIM parameters ($D, f, D^*$) of the second evaluation for different LR and number of hidden layers, with fixed hyperparameters of extra fitting parameter $S0$, sigmoid activation functions, a parallel network architecture, 10% dropout and batch normalization, at an SNR of 20. Highlighted in green is IVIM-NET$_{\text{opt}}$. Left of each plot shows the LS approach (blue) and Bayesian approach (brown) and IVIM-NET$_{\text{orig}}$ (orange).
Figure S8: Normalized root-mean-square error (NRMSE; left), Spearman rank correlation coefficient ($\rho$; center) and normalized coefficient of variation ($CV_{\text{NET}}$; right) plots of the estimated IVIM parameters ($D$, $f$ and $D^*$) of both IVIM-NET$_{\text{orig}}$ (orange) and IVIM-NET$_{\text{optim}}$ (green) determined for different $b$ values. Distributions of $b$ values: Sim) $0, 5, 10, 20, 30, 40, 60, 150, 300, 500, \text{and } 700 \text{ s/mm}^2$; b1) $0, 10, 20, 60, 150, 300, 500, \text{and } 1000 \text{ s/mm}^2$; and b2) $0, 10, 20, 30, 40, 50, 75, 100, 150, 250, 400, \text{and } 600 \text{ sec/mm}^2$. 