Estimating Uncertainty in Neural Networks for Cardiac MRI Segmentation: A Benchmark Study

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Abstract—Objective: Convolutional neural networks (CNNs) have demonstrated promise in automated cardiac magnetic resonance image segmentation. However, when using CNNs in a large real-world dataset, it is important to quantify segmentation uncertainty and identify segmentations which could be problematic. In this work, we performed a systematic study of Bayesian and non-Bayesian methods for estimating uncertainty in segmentation neural networks. Methods: We evaluated Bayes by Backprop, Monte Carlo Dropout, Deep Ensembles, and Stochastic Segmentation Networks in terms of segmentation accuracy, probability calibration, uncertainty on out-of-distribution images, and segmentation quality control. Results: We observed that Deep Ensembles outperformed the other methods except for images with heavy noise and blurring distortions. We showed that Bayes by Backprop is more robust to noise distortions while Stochastic Segmentation Networks are more resistant to blurring distortions. For segmentation quality control, we showed that segmentation uncertainty is correlated with segmentation accuracy for all the methods. With the incorporation of uncertainty estimates, we were able to reduce the percentage of poor segmentation to 5% by flagging 31–48% of the most uncertain segmentations for manual review, substantially lower than random review without using neural network uncertainty (reviewing 75–78% of all images). Significance: Neural network uncertainty measures can help identify potentially inaccurate segmentations and alert users for manual review.

Index Terms—Cardiac MRI segmentation, segmentation quality control, Bayesian neural networks, uncertainty.

I. INTRODUCTION

CARDIAC magnetic resonance imaging (MRI) is the gold standard for evaluating cardiac function due to its excellent soft tissue contrast, high spatial and temporal resolution, and non-ionizing radiation [1]. Segmentation of cardiac structures such as the left ventricle cavity, left ventricle myocardium, and right ventricle cavity is required as a first step to quantify clinically relevant imaging biomarkers, such as the left ventricle ejection fraction and myocardial mass. Recently, convolutional neural networks (CNNs) have demonstrated promise for automatic cardiac MR image segmentation [2], [3] and may facilitate the development of efficient cardiac MR image processing pipelines for research and clinical use. However, when using a CNN in an automated image analysis pipeline, it is important to automatically identify which segmentations are problematic and require further manual inspection. This may improve workflow efficiency by focusing only on problematic cases, avoiding the review of all images and reducing errors in downstream analysis.

This problem has been referred to as segmentation quality control and is closely related to the task of anomaly detection or out-of-distribution detection [4]. While there are several approaches to this problem (e.g., using a dedicated quality
control module), in this work, we focus on the approach of using predictive uncertainty estimates of a segmentation model to solve this problem. The main idea here is that segmentation outputs with low uncertainty are likely correct while those with high uncertainty are likely problematic. While several studies have attempted to estimate CNN segmentation uncertainty, most of them used Monte Carlo (MC) Dropout or Deep Ensembles. However, there are some limitations associated with these methods, which motivates us to explore other algorithms. For example, when using a fixed dropout rate in MC Dropout, the model uncertainty does not decrease when training data is increased. This is potentially problematic since model uncertainty should approach zero in the limit of infinite training data [5]. For Deep Ensembles, it is not clear why this method generates well-calibrated uncertainty estimates. While Deep Ensembles was shown to learn diverse functions [6], recent work [7] has shown that ensemble diversity does not explain the improved uncertainty estimates on out-of-distribution data. In addition, in previous studies, evaluation of these algorithms was mostly limited to correlations between the predictive uncertainty and segmentation accuracy or metrics measuring how uncertainty can be used to improve segmentation [8], [9], [10]. There is a need to have a proper benchmark and metrics to evaluate uncertainty from different methods. In this work, we performed a systematic evaluation of several Bayesian and non-Bayesian approaches for uncertainty estimation. In particular, we evaluated Bayes by Backprop, MC Dropout, Deep Ensembles, and Stochastic Segmentation Networks based on segmentation accuracy, probability calibration, uncertainty on out-of-distribution datasets, and finally, we demonstrated the utility of these methods for segmentation quality control.

A. Uncertainty in Neural Networks

Uncertainty is usually classified into epistemic uncertainty or aleatoric uncertainty [11]. Epistemic or model uncertainty is uncertainty in model parameters due to a finite amount of data. In contrast, aleatoric or data-dependent uncertainty is uncertainty due to the data itself and cannot be reduced even with more data. This distinction can be useful when thinking about sources of uncertainty; however, it is difficult to distinguish these two types in practice. Instead, we can think about modelling uncertainties in neural networks by learning a distribution of neural network weights or by learning a distribution of neural network outputs for each individual input [11]. Uncertainty from both types of models can be used and compared for downstream tasks.

Bayesian neural networks (BNNs) provide a theoretical framework for generating well-calibrated uncertainty estimates [12]. In BNNs, we are interested in learning the posterior distribution of the neural network weights instead of a maximum likelihood or maximum-a-posteriori estimate. A challenge in learning BNNs is that integration over the posterior is intractable in high dimensional space. As such, inference techniques such as stochastic variational inference are commonly used as approximation. Examples include variational dropout [13], MC Dropout [14], Bayes by Backprop [15], multiplicative normalizing flows [16], and Flipout [17]. Non-Bayesian methods for estimating uncertainty in neural networks include bootstrapping [18], Deep Ensembles [19], and Resampling Uncertainty Estimation [20]. These methods estimate changes to the neural network when it is trained on different samples from the same training distribution. Note that in Bayesian methods, uncertainty is learned during training and is tightly coupled to the model structure. In non-Bayesian methods, uncertainty is learned during training or estimated after training. Another approach to uncertainty estimation is to directly learn a distribution of neural network outputs (and/or intermediate feature maps) instead of the weights. This is usually achieved by parameterizing the output distribution and learning the parameters during training as shown in [11].

B. Related Studies

The majority of investigations of BNNs used MC Dropout to approximate the posterior distribution of the weights and exploration of ways to evaluate the quality of uncertainty has been limited. Previous studies [8], [9], and [21] used MC Dropout for brain structure, brain tumour, and brain tumour cavity segmentation. These studies reported positive correlations between segmentation accuracy and uncertainty measures. Nair et al. [22] compared different uncertainty measures in brain lesion segmentation and showed that uncertainty measures can be used to improve lesion detection accuracy. Sander et al. [10] applied MC Dropout for cardiac MRI segmentation and showed that training a CNN using a Brier loss or cross-entropy loss produced well-calibrated pixel-wise segmentation uncertainty, and correcting uncertain pixels can improve segmentation results consistently. Devries et al. [23] used MC Dropout and non-Bayesian methods to generate skin lesion segmentation and segmentation uncertainty maps, which were then entered into another neural network to predict the Jaccard index of the segmentation. Hann et al. [24] estimated the quality of aortic MRI segmentation using an ensemble of neural networks and demonstrated improved segmentation accuracy with the use of these segmentation quality estimates. More recently, Jungo et al. [25] compared MC Dropout, Deep Ensembles, and auxiliary networks for predicting pixel-wise segmentation errors for two medical image segmentation tasks. In addition to segmentation probability calibration, they examined the overlap between segmentation uncertainty and errors, and the fraction of images which would benefit from uncertainty-guided segmentation correction. In a follow-up study [26], the authors compared different aggregation methods for uncertainty measures and their performance for segmentation failure detection. Similarly, Mehtash et al. [27] compared MC Dropout and Deep Ensembles for CNNs trained with different loss functions in terms of probability calibration and correlation between segmentation accuracy and uncertainty measures. However, these studies did not evaluate other Bayesian methods such as Bayes by Backprop and the performance of these methods on out-of-distribution datasets is unknown. Other methods such as Probabilistic U-net [28], PHISeg [29], and Stochastic Segmentation Networks [30] estimate uncertainty by directly predicting a distribution of neural network outputs. These methods have been applied to brain and lung tumour segmentation and have shown to produce diverse outputs matching inter-observer manual segmentation
variability. [31] presented a framework for segmentation quality control of cardiac T1 maps using the evidence lower bound scores from PHISeg and a separate quality control neural network. While this showed great sensitivity and specificity for detecting poor segmentations, it is not clear how other algorithms would compare with PHISeg for this task.

C. Contributions

In this work, we performed a systematic study of Bayesian and non-Bayesian neural networks for estimating uncertainty in the context of cardiac MRI segmentation. Our contributions are summarized as follows:

1) We compared MC Dropout and Deep Ensembles with Bayes by Backprop, which is a more theoretically justified algorithm for learning uncertainty in BNNs. We performed a comprehensive evaluation of these algorithms in terms of segmentation accuracy, probability calibration, uncertainty on out-of-distribution datasets, and segmentation quality control.

2) We evaluated MC Dropout, Deep Ensembles, Bayes by Backprop, and Stochastic Segmentation Networks on cardiac MRI datasets with various degrees of noise, blurring, and stretching distortions to mimic complex clinical scenarios and to investigate the relationships between image distortions and neural network uncertainty estimates. We showed that Bayes by Backprop is more robust to noise distortions while Stochastic Segmentation Networks are more resistant to blurring distortions.

3) We introduced a novel area-under-the-curve metric for quantifying algorithm performance on segmentation quality control. We showed that with the use of Deep Ensemble uncertainty estimates, 31–48% of the most uncertain segmentations need to be reviewed to reduce the percentage of poor segmentations to 5%, whereas ~80% of the results need to be reviewed when neural network uncertainty measures are not used.

We hope this work will serve as a benchmark for evaluating uncertainty in cardiac MRI segmentation and inspire further work on uncertainty estimation in medical image segmentation.

II. METHODS

A. Bayesian Neural Networks

Given a dataset of N images $X = \{x_i\}, i \in [1, N]$, and the corresponding manual segmentation $Y = \{y_i\}$ with $C$ classes, we fit a neural network parameterized by weights $w$ to perform segmentation. In BNNs, we are interested in learning the posterior distribution of the weights $p(w|X, Y)$, instead of a maximum likelihood or maximum-a-posteriori estimate. This posterior distribution represents uncertainty in the weights, which could be propagated to calculate uncertainty in the predictions [32]. In addition, BNNs have been shown to be able to improve the generalizability of neural networks [32].

A challenge in learning BNNs is that calculating the posterior is intractable due to the high dimensionality of the weights. Variational inference [33] is a scalable technique that aims to learn an approximate posterior distribution of the weights $q(w)$ by minimizing the Kullback-Leibler (KL) divergence between the approximate and true posterior. This is equivalent to maximizing the evidence lower bound as follows:

$$\arg\max_{q(w)} \mathbb{E}_{q(w)}[\log p(Y|X, w)] - \lambda \cdot KL[q(w)||p(w)], \quad (1)$$

where $\mathbb{E}_{q(w)}[\cdot]$ denotes expectation over the approximate posterior $q(w)$, $\log p(Y|X, w)$ is the log-likelihood of the training data with given weights $w$, $p(w)$ represents the prior distribution of $w$, and $KL[\cdot||\cdot]$ is the KL divergence between two probability distributions weighted by a hyperparameter $\lambda > 0$.

State-of-the-art segmentation neural networks such as the U-net formulate image segmentation as a pixel classification problem. For each pixel $x_{i,j}$ in image $x_i$, $i \in [1, N], j \in \Omega$, the neural network generates a prediction $\hat{y}_{i,j}$ with probability $p(\hat{y}_{i,j} = c), c \in [0, C - 1]$, through softmax activation of the features in the last layer. Assuming pixels are independent from each other, the log-likelihood of the training data in (1) is given by:

$$\log p(Y|X, w) = \sum_{i=1}^{N} \sum_{j \in \Omega} \sum_{c=0}^{C-1} \log p(\hat{y}_{i,j} = c)$$

where $y_{i,j}$ is the manual label for pixel $j$ in image $x_i$ and $[]$ is the indicator function. In this setting, the log-likelihood is also the negative cross entropy between the manual segmentation and algorithm prediction. The prediction $\hat{y}$ of a test image $x$ is generated by marginalizing out the weights of the neural network, i.e.,

$$p(\hat{y}|x) = \mathbb{E}_{q(w)}[p(\hat{y}|x, w)] \quad (2)$$

where $p(\hat{y}|x, w)$ denotes the prediction of an image $x$ given network weights $w$. In the following sections, we introduce methods for estimating an approximate posterior $q(w)$ for the weights of a BNN.

1) Bayes by Backprop: One way to parameterize the approximate posterior $q(w)$ is to use a fully factorized Gaussian. In a fully factorized Gaussian, each weight $w$ in $w$ is independent from others and follows its own Gaussian distribution with mean $\mu$ and standard deviation $\sigma$. To ensure $\sigma > 0$ and training stability, $\sigma$ is parameterized by a real number $\rho$, i.e., $\sigma = \text{softplus}(\rho) = \ln(1 + e^\rho)$. The prior distribution $p(w)$ is usually chosen as a fully factorized Gaussian with mean $\mu_{\text{prior}} I$ and covariance $\sigma_{\text{prior}} I$, i.e., $p(w) = \mathcal{N}(\mu_{\text{prior}} I, \sigma_{\text{prior}} I)$, where $I$ represents an identity matrix. Gradient updates can be performed using the “reparameterization trick”. The training procedure is known as Bayes by Backprop (BBB) [15] and is briefly described below:

1) For each weight $w$, sample $\epsilon \sim \mathcal{N}(0, 1)$ and set $w = \mu + \text{softplus}(\rho) \cdot \epsilon$.

2) Calculate the loss based on (1), i.e., $-\log p(Y|X, w) + \lambda \cdot KL[q(w)||\mathcal{N}(\mu_{\text{prior}} I, \sigma_{\text{prior}} I)]$.

3) Update $\mu$ and $\rho$ through gradient descent. After training, each weight $w$ can be sampled from $\mathcal{N}(\mu, \sigma)$, which is then used to generate the segmentation predictions following (2).
2) **MC Dropout**: MC Dropout (MCD) [14] is another commonly used method for learning BNNs because it is straightforward to implement and does not require additional parameters or weights. MCD can be interpreted as choosing the approximate posterior distribution $q(\mathbf{w})$ to be a mixture of two Gaussians with minimal variances, e.g., one at 0 and the other at the weight $w$. Dropout is applied during training and testing to sample weights from $q(\mathbf{w})$. In this method, the dropout rate is a hyperparameter chosen empirically based on a validation dataset. The dropout rate defines the amount of uncertainty in the weights and is fixed throughout network training and testing.

B. **Deep Ensembles**

In addition to BNNs, we characterized and evaluated uncertainty estimates using an ensemble of neural networks, i.e., Deep Ensembles [19]. Deep Ensembles consist of multiple neural networks trained using the same data (or different subsets of the same data) with different random initializations. Combing these models in an ensemble has been shown to produce well-calibrated probabilities in computer vision tasks and the variability between the model predictions can be used to calculate predictive uncertainty. This non-Bayesian method was inspired by the idea of bootstrapping, where stochasticity in the sampling of the training data and training algorithm define model uncertainty. This approach differs from Bayesian methods since it does not require approximation of the posterior distribution of the weights.

C. **Stochastic Segmentation Networks**

Another method for uncertainty estimation involves predicting a distribution over the neural network logits before transforming them into probabilities. Since standard segmentation neural networks output pixelwise logits, a simple method is to assume a Gaussian distribution of the logits and that each pixel is independent from others, i.e., for each image $x$, the neural network predicts logits $\eta \sim \mathcal{N}(\mu(x), \Sigma(x))$, where $\mu(x) \in \mathbb{R}^{\Omega \times C}$ is the mean logit and $\Sigma(x) \in \mathbb{R}^{\Omega \times C \times \Omega \times C}$ is a diagonal covariance matrix [11]. Stochastic Segmentation Networks (SSNs) [30] improved this method by using a low rank multivariate normal distribution on the pixelwise logits to model the dependencies between pixels in an image. In particular, SSNs use $\Sigma(x) = PP^T + D$, where $P \in \mathbb{R}^{\Omega \times C \times \Omega \times C}$ is a low rank matrix and $D \in \mathbb{R}^{\Omega \times C \times \Omega \times C}$ is a diagonal matrix.

D. **Algorithm Evaluation**

We evaluated the uncertainty estimation algorithms based on three aspects: (1) segmentation accuracy and probability calibration; (2) uncertainty on out-of-distribution datasets; and (3) application of uncertainty estimates for segmentation quality control. The purposes of these evaluations are as follows:

1) We show that BNNs can provide segmentation accuracies that are similar to or higher than plain or point estimate neural networks. In addition, predicted segmentation probabilities should be well-calibrated, i.e., a pixel with predicted probability of 60% belonging to the myocardium is 60% myocardium according to some ground truth. From a frequentist perspective, this means that out of all predictions with 60% probability, 60% of the predictions are correct.

2) We measure segmentation uncertainty on out-of-distribution data to validate that the uncertainty measures perform as expected, i.e., uncertainty should increase when test datasets substantially differ from training datasets.

3) We expect uncertainty measures to be useful in identifying problematic segmentations that require manual editing.

We used the following metrics for these evaluations:

1) **Segmentation Accuracy**: We calculated the algorithm segmentation accuracy using Dice similarity coefficient, average symmetric surface distance (ASSD), and Hausdorff distance (HD), as previously described [2].

2) **Probability Calibration**: These metrics measure how closely the neural network segmentation probabilities match the manual segmentation probabilities on a per-pixel basis.

Following the notation in Section II-A, let $\hat{y}_j$ and $y_j$ denote the prediction and manual label of pixel $j$ in a given image, $j \in \Omega$, respectively. We use $p(\hat{y}_j = c)$ to denote the average per-pixel probability from the samples of the neural network, i.e., $p(\hat{y}_j = c) = \mathbb{E}_{q(\mathbf{w})}[p(\hat{y}_j = c|\mathbf{w})]$. Negative log-likelihood (NLL) measures how well the learned model fits the observed (testing) data and is calculated as follows:

$$\text{NLL} = \sum_{j \in \Omega} \sum_{c=0}^{C-1} [y_j = c] \cdot \log p(\hat{y}_j = c).$$

Note that NLL is sensitive to tail probabilities; that is, a model that generates low probability for the correct class is heavily penalized.

Brier score (BS) [34] is a proper scoring rule used to measure probability calibration. It measures the mean squared error between the predicted and manual segmentation probabilities:

$$\text{BS} = \sum_{j \in \Omega} \sum_{c=0}^{C-1} [p(\hat{y}_j = c) - p(y_j = c)]^2.$$

A Brier score of 0 indicates that the model is perfectly calibrated.

3) **Predictive Uncertainty Measures**: Predictive uncertainty can be calculated from neural network predictions to indicate the degree of uncertainty of the outputs. This can be calculated per pixel or per structure/class.

   a) **Pixelwise Uncertainty Measures**: Pixelwise uncertainty measures are calculated per pixel and averaged across all pixels in an image if an image-level measure is required. In this work, we used multi-class predictive entropy and multi-class mutual information as suggested to be superior in [35]:

   - Multi-class Predictive Entropy measures the spread of probabilities across all the classes in the mean prediction, i.e.,
     $$\sum_{j \in \Omega} \sum_{c=0}^{C-1} [-p(\hat{y}_j = c) \log p(\hat{y}_j = c)].$$
   - Multi-class Mutual Information (MI) measures how different each sample is from the mean prediction and is
calculated as:
\[
\mathbb{E}_{q(w)} \left[ \sum_{c=0}^{C-1} \sum_{j=i} p(\hat{y}_j = c | w) \log p(\hat{y}_j = c | w) - \sum_{c=0}^{C-1} p(\hat{y}_j = c) \log p(\hat{y}_j = c) \right],
\]

where \(p(\hat{y}_j = c | w)\) denotes the prediction given a set of weights \(w\). MI is high if there are samples with both high and low confidence, and is low if all samples have low confidence or high confidence.

**b) Structural Uncertainty Measures:** We define two structural uncertainty measures, which quantify how different the prediction samples are for each structure in terms of Dice and ASSD.

- \(\text{Dice}_{\text{WithinSamples}}(\text{Dice}_{WS}) = \frac{1}{T} \sum_{i=1}^{T} \text{Dice}(\bar{S}, S_i)\)
- \(\text{ASSD}_{\text{WithinSamples}}(\text{ASSD}_{WS}) = \frac{1}{T} \sum_{i=1}^{T} \text{ASSD}(\bar{S}, S_i)\),

where \(\bar{S}\) is the mean of the \(T\) segmentation predictions \(S_i, i \in [1, T]\). We expect structural uncertainty measures to better align with common segmentation accuracy metrics because of their global image-level focus.

**E. Datasets**

1) **U.K. BioBank (UKBB):** The UKBB dataset [36] consists of 4845 healthy volunteers. For each subject, 2D cine cardiac MR images were acquired on a 1.5 T Siemens scanner using a bSSFP sequence under breath-hold conditions with ECG-gating (pixel size = 1.8–2.3 mm, slice thickness = 8 mm, number of slices = ~10, number of phases = ~50). Manual segmentation of the left ventricle blood pool (LV), left ventricle myocardium (Myo), and right ventricle (RV) was performed on the end-diastolic (ED) and end-systolic (ES) phases by one of eight observers followed by random checks by an expert to ensure segmentation quality and consistency. The dataset was randomly split into 4173, 103, and 569 subjects for training, validation, and testing, respectively. We have permission to use the UKBB dataset through U.K. Biobank’s generic RTB approval from the NHS North West REC.

2) **Automated Cardiac Diagnosis Challenge (ACDC):**

The ACDC dataset [3] consists of 100 patients with one of five conditions: normal, myocardial infarction, dilated cardiomyopathy, hypertrophic cardiomyopathy, and abnormal right ventricle. 2D cine MR images were acquired using a bSSFP sequence on a 1.5 T/3T Siemens scanner (pixel size = 0.7–1.9 mm, slice thickness = 5–10 mm, number of slices = 6–18, number of phases = 28–40). Manual segmentation was performed at ED and ES phases with approval by two experts. This dataset was used for testing only.

**F. Training Details**

We used a plain 2D U-net [37] for BBB, MCD, Deep Ensembles, and SSN. The plain U-net consisted of 10 layers with \(3 \times 3\) filters and 2 layers with \(1 \times 1\) convolutions followed by a softmax layer. The number of filters ranged from 32 to 512 from the top to the bottom layers.

For BBB, we experimented with different standard deviations of the prior distributions: \(\sigma_{\text{prior}} = 0.1\) or \(1.0\) and different weights for the KL term: \(\lambda = 0.1, 1.0, 10, 30\). These are commonly used hyperparameters in the literature [15], [38], [39]. For MCD, we added dropout on all layers or only on the middle layers of the U-net with different dropout rates: 0.5, 0.3, and 0.1. These settings effectively tuned the amount of uncertainty in the model. For both BBB and MCD, the final prediction was obtained by averaging the softmax probabilities of \(T = 50\) samples. For Deep Ensembles, we trained 10 plain U-net models separately using all the training data with different random initializations and averaged the softmax probabilities of the 10 models. For SSN, we used a rank of 10 for the multivariate normal distribution of the logits, as suggested in [30]. More training details can be found in Supplementary Material Section I.

**III. Experiments and Results**

To select the hyperparameters for each method, we chose the models with the lowest NLL on the validation dataset since NLL is directly related to segmentation accuracy and probability calibration. For BBB, \(\lambda = 10\) and \(\sigma_{\text{prior}} = 0.1\) achieved the best NLL on the validation dataset. For MCD, adding dropout in the middle layers with a dropout rate of 0.1 (MCD-0.1) performed the best. We also reported results for MC Dropout with a dropout rate of 0.5 in the middle layers (MCD-0.5), which is commonly used in the literature.

**A. Segmentation Accuracy and Probability Calibration**

As shown in Table I, Deep Ensembles performed the best in terms of segmentation accuracy and probability calibration. This was followed by BBB and MCD-0.1, which were comparable to the plain U-net. MCD-0.5 performed slightly worse than the other models. The differences of these methods compared to the plain U-net were small but mostly statistically significant except for some metrics between plain U-net and MCD-0.1 (Table I). These results indicate that Bayesian approaches or Deep Ensembles can yield similar, if not better, segmentation results compared to a plain U-net while providing uncertainty estimates at the same time. The tradeoff is that Deep Ensembles and BBB use more memory and computation time compared to a plain U-net.

Examples of predicted segmentation from all methods are shown in Supplementary Fig. S1.

**B. Uncertainty on Distorted Images**

In order to validate uncertainty measures as indicators of “out-of-distribution” datasets, we applied the trained models to carefully generated test images with various magnitudes of distortions, including:

- adding Rician noise, as found in MR images [40], with magnitudes ranging from 0.05 to 0.10 (on normalized images with intensities ranging from 0 to 1),


Table I

|                  | Dice ↑ | ASSD (mm) ↓ | HD (mm) ↓ | NLL ↓ | BS ↓ |
|------------------|--------|------------|----------|-------|------|
|                  | LV     | Myo        | RV       | LV    | Myo  | RV   |
|                  |        |            |          |       |      |      |
| Plain U-net      | .941(0.038) | .882(0.031) | .907(0.043) | 1.01(0.38) | 1.02(0.43) | 1.61(0.69) |
|                  |        |            |          |        |      |      |
| BBB              | .942(0.037)* | .883(0.030)* | .908(0.043)* | 1.00(0.36)* | 1.00(0.30)* | 1.60(0.70)* |
| MCD-3.1         | .941(0.037) | .882(0.030) | .907(0.043)* | 1.00(0.36)* | 1.01(0.31)† | 1.61(0.70)* |
| MCD-3.5         | .940(0.038)* | .879(0.030)* | .906(0.043)* | 1.00(0.38)* | 1.01(0.31)* | 1.60(0.69)* |
| Ensemble         | .943(0.037)* | .885(0.030)* | .909(0.043)* | .98(0.36)* | .98(0.29)* | 1.57(0.72)* |
| SSN             | .940(0.037)* | .882(0.030)† | .903(0.043)* | 1.03(0.39)* | 1.03(0.32)† | 1.65(0.67)* |

\* statistically different compared to the Plain U-net (Wilcoxon signed-rank test, p < 0.05, N = 1138 images).

\^ not statistically different compared to the Plain U-net (Wilcoxon signed-rank test, p > 0.05, N = 1138 images).

Fig. 1. Segmentation predictive entropy on images with increasing noise, blurring, and stretching. BBB showed the highest uncertainty on images with heavy noise (last two rows) while SSN showed the highest uncertainty on images with heavy blurring (last two rows); Deep Ensembles showed slightly higher uncertainty on images with heavy stretching compared to other methods. Reproduced with permission of U.K. Biobank ©.

- Gaussian blurring with a standard deviation of 1–4 pixels,
- deforming or stretching around LV, Myo, and RV.

Note that these distortions were not applied as part of data augmentation during training and these images were not seen by the neural networks. As such, we expected decreased segmentation accuracy and increased predictive uncertainty in images with greater magnitudes of distortions. Fig. 1 shows examples of distorted images.

1) Trends With Increasing Distortions: Fig. 2 and Supplementary Table S1 show that the segmentation accuracy decreased as the magnitude of the distortions (noise, Gaussian blur, stretch) was increased. This is expected since these types of distortions were not seen during training and increasing the magnitude of the distortions results in greater differences with the original training datasets.

In addition, we observed that the predictive uncertainty increased (i.e., higher predictive entropy, mutual information, ASSD_{WS}, and lower Dice_{WS}) with increasing magnitude of distortions but this decreased after a certain threshold, as shown in Fig. 2. This was the case for Deep Ensembles, BBB, MCD, and SSN on images with noise and blurring distortions but not with stretching. For example, for BBB, the median predictive entropy for images with slight, moderate, and large additional noise was $1.66 \times 10^{-2}$, $1.95 \times 10^{-2}$, and $1.23 \times 10^{-2}$, respectively. Similarly, the median ASSD_{WS} was 0.40, 3.40, and 0.71 mm for images with slight, moderate, and large amount of blurring, respectively (Supplementary Table S3). Fig. 1 and Supplementary Figs. S2–S4 show examples of segmentation predictions and uncertainty (predictive entropy, mutual information) for all the methods on images with increasing noise, blurring, and stretching.

While the increasing predictive uncertainty associated with increasing magnitude of distortions was expected, the decrease in predictive uncertainty after a threshold in cases of noise and blurring distortions is surprising. Specifically, for images that were highly distorted, all pixels were classified as background with low uncertainty (Fig. 1, bottom row). Although this seems correct when only given the labeling choices of background, LV, Myo, and RV, we argue that the distorted pixels are markedly different from the background pixels in the training images and therefore, should have high uncertainty nonetheless. This is a limitation of all the uncertainty models tested and may be improved using more expressive posteriors.

Another observation is that the uncertainty measures began to fail/decline when dramatic segmentation errors occurred, as shown in Fig. 2. This suggests that other heuristics or algorithms such as those presented in [41] can be used to complement the uncertainty measures when trying to detect inaccurate segmentations. For example, segmentation with a non-circular LV blood

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Fig. 2. Segmentation accuracy (ASSD LV), uncertainty measures (ASSD$_{WS}$ LV, entropy), and probability calibration (Brier score) on images with increasing magnitude of noise, blurring, and stretching using a plain U-net, U-net with BBB, MC Dropout, Deep Ensemble, and SSN.

pool or a blood volume $< 50$ mL is highly problematic and may indicate poor segmentation.

2) Comparison Between Deep Ensembles, BBB, MC Dropout, and SSN: In terms of segmentation accuracy and probability calibration, BBB was more robust to noise distortions compared to the other methods. Specifically, BBB showed higher Dice and lower ASSD for LV, lower NLL and BS on images with greater noise distortions (Fig. 1, rows 3–5 and Supplementary Tables S1 and S2, degree of distortion = 2, 3, 4). SSN showed higher segmentation accuracy in cases of greater blurring while Deep Ensembles showed higher segmentation accuracy with stretching distortions compared to the other methods (Fig. 2 and Supplementary Table S1, degree of distortion = 3, 4). In the greatest noise, blurring, and stretching distortions tested, BBB, SSN, and Deep Ensembles had statistically higher segmentation accuracy and probability calibration, respectively, when compared to other methods (Supplementary Tables S1 and S2).

C. Uncertainty on Dataset Shift

To further validate the uncertainty measures, we applied the models trained on the UKBB dataset to a distinctly different ACDC dataset. We expect decreased segmentation accuracy and increased predictive uncertainty on the ACDC test dataset compared to the UKBB test dataset, due to the presence of cardiac pathologies on the ACDC dataset and slightly different acquisition parameters.

As shown in Fig. 3, we observed decreased segmentation accuracy and increased predictive uncertainty compared to the UKBB test dataset. In terms of segmentation accuracy and probability calibration, the methods from the best to the worst are: Deep Ensembles, BBB, MCD-0.1, SSN, Plain U-net, and MCD-0.5, as shown in Fig. 3 and Supplementary Table S4. While most metrics are statistically different, some metrics between the following pairs are not statistically different: Deep Ensembles vs BBB, MCD-0.1 vs SSN, SSN vs Plain U-net, and Plain U-net vs MCD-0.5. Supplementary Table S5 shows detailed results of the pairwise significance tests.

D. Correlations Between Uncertainty and Segmentation Accuracy

To demonstrate the potential utility of uncertainty measures, we evaluated the Spearman rank correlation between uncertainty measures and segmentation accuracy. We used the rank correlation instead of linear correlation to reduce the effects of a potential non-linear relationship between the two quantities.

Supplementary Fig. S5 shows that the uncertainty measure with the strongest correlation with ASSD was ASSD$_{WS}$ (Spearman correlation between 0.58 and 0.69) in the case of training and testing on the UKBB dataset (UKBB $\rightarrow$ UKBB). This is
not surprising since the ASSD<sub>WS</sub> calculation was similar to ASSD. Similar observations were obtained for training on the UKBB dataset and testing on the ACDC dataset (UKBB → ACDC) although the correlations were slightly lower (Spearman correlation between 0.44 and 0.66). These correlations suggest that the ASSD<sub>WS</sub> uncertainty measure is useful in predicting the segmentation quality when manual segmentation is not available. Other uncertainty measures such as MI or Dice<sub>WS</sub> may correlate better with other segmentation quality metrics such as pixelwise accuracy or Dice (not explored in this work). They could also potentially be used as inputs to segmentation algorithms to improve segmentation performance.

Fig. 4 shows representative segmentation results, posterior prediction samples, and the structural uncertainty measures for RV. The images with poor segmentation (toward the right side) had greater uncertainty as measured by Dice<sub>WS</sub> and ASSD<sub>WS</sub>. Note that posterior prediction samples are not related to inter- or intra-observer variability but rather show what the network has learned from given data.

**E. Uncertainty for Segmentation Quality Control**

In this section, we explored the use of predictive uncertainty estimates to flag potentially problematic segmentations that require manual review. We view this task as a classification problem and we aim to use uncertainty measures to classify segmentations as either good or poor.

While the common segmentation accuracy metrics (Dice, ASSD, HD) may not always correlate with true segmentation quality [3], there are no good alternatives to quantify segmentation quality. Having experts to manually determine whether an automated segmentation is good or not for a large dataset is time consuming and adds observer noise. Instead, we used thresholds on segmentation accuracies to achieve this. Based on our experience and discussions with our clinical collaborators, we believe that contour or surface distance is more indicative of inaccurate segmentations. As such, for each method, the predicted segmentation was considered as poor when the ASSD between the prediction and manual segmentation is greater than the ASSD between manual observers. We used inter-observer ASSD of 1.17 mm for LV, 1.19 mm for Myo, and 1.88 mm for RV, based on a recent relatively large-scale study [2]. We then evaluated how well the ASSD<sub>WS</sub> uncertainty measure could identify potentially poor segmentation.

To utilize the ASSD<sub>WS</sub> uncertainty measure, a threshold can be set such that any segmentation with uncertainty above the threshold is flagged for manual review. This would hopefully result in a decreased number of poor segmentation in the dataset. Fig. 5 shows the fraction of images with poor segmentation remaining in the dataset and the fraction of images flagged for manual correction when the uncertainty thresholds were varied, i.e., (positives - true positives) vs (true positives + false positives), where positive represents poor segmentation. As we
decreased the uncertainty threshold (top left to bottom right in Fig. 5), we flagged more images for manual correction and the number of images with poor segmentation was decreased. The first point on the curves corresponds to a threshold where none of the images are reviewed while the last point indicates that all the images are reviewed. This is similar to a receiver operating curve with the consideration that the total number of positives or images with poor predicted segmentation is different for each method. This allows for comparison between all the uncertainty estimation methods. In particular, a curve that is closer to the bottom left corner or has smaller area under the curve (AUC) indicates that the algorithm provides better initial segmentation and/or its uncertainty is a good indicator of segmentation accuracy. Fig. 5 shows that all the methods performed similarly for detecting poor LV, Myo, and RV segmentation with Deep Ensembles having slightly lower AUC than the others.

The thresholds of the uncertainty measures for flagging images for manual review can be adjusted depending on the application. This approach provides a way to identify images to review and may result in substantial time savings. For example, using the ASSD<sub>WS</sub> uncertainty measure for the Deep Ensembles method, 48%, 38%, and 31% of the images required manual review in order to reduce the number of images with poor LV, Myo, or RV segmentation to 5% of the test dataset, respectively (Fig. 5). In contrast, without using uncertainty measures and assuming no other information about the images is used, approximately 75% of the images need to be reviewed to achieve this goal. Furthermore, using the ASSD<sub>WS</sub> uncertainty measure resulted in more time savings compared to using the slice position heuristic. For a dataset of 10,000 subjects each with 10 slices and manual segmentation of 30 seconds per structure per slice [2], using the ASSD<sub>WS</sub> uncertainty measure results in ~940 hours of time savings compared to reviewing the images randomly, and ~580 hours of time savings compared to using the slice position heuristic.

### IV. Discussion

#### A. BBB vs MC Dropout vs Deep Ensembles vs SSN

In this work, we evaluated and compared different Bayesian and non-Bayesian methods for estimating uncertainty in neural networks for cardiac MRI segmentation. Here, we discuss the similarities and differences about how uncertainty is learned in these methods, what was learned after training, and relate these differences to the quality of the predictive uncertainties on out-of-distribution images.

While uncertainty in neural network parameters is learned automatically in BBB, this can be tuned by changing the dropout rate in MCD. For the UKBB dataset, a small dropout rate of 0.1 in the middle layers performed better than the other MCD models in terms of segmentation accuracy and probability calibration. This is different from other studies which commonly used a dropout rate of 0.5 [38], [42] and may be because of the large amount of relatively uniform training data (i.e., images acquired following the same MR protocol in mainly healthy volunteers and labelled following the same guidelines). The dropout rate hyperparameters for MCD obtained through grid search correspond to the weight uncertainties learned by BBB to some extent. Fig. 6 shows that the standard deviation of the weights learned by BBB is lower in the early layers and higher in the middle layers of the U-net. This is similar to MCD with no dropout in the early layers and with dropout on the middle layers. Having greater dropout rate in middle layers is common in other studies [38].
Bayesian approaches and Deep Ensembles can be used to improve segmentation accuracy on slightly shifted datasets compared to the plain U-net (Supplementary Tables S4 and S5 show that there is a significant difference between the plain U-net and BBB/Deep Ensembles). While the segmentation accuracies on the ACDC test dataset using the models trained on UKBB dataset are lower than that obtained by training and testing on the ACDC dataset [3], the algorithms employed in this work may be combined with other techniques that are specifically designed to solve this problem, e.g., style augmentation or domain adversarial training [44], [45].

B. Pixelwise and Structural Uncertainty Measures

We introduced pixelwise and structural uncertainty measures to quantify the predictive uncertainty, and demonstrated the utility of these metrics for segmentation quality control. Both pixelwise and structural uncertainty measures can be used depending on the application. As the segmentation problem was formulated as pixel classification, pixelwise uncertainty measures are straightforward to obtain. These allow users to visualize which pixels and which areas are potentially problematic (Fig. 1). However, segmentation is often performed at the image-level slice by slice. Therefore, image-level uncertainty measures for determining problematic segmentation are also required. Accordingly, we showed that structural uncertainty measures were correlated with segmentation accuracy such as ASSD.

Other studies such as [35] evaluated uncertainty maps by comparing uncertainty and correctness at the per-pixel level. In contrast, we evaluated per-image uncertainty measures as a predictor of image-level segmentation quality, which is more reflective of the real-world scenario.

It is important to note that the predictive uncertainty measures reflect the neural network uncertainty, which is different from human uncertainty. An example is the image with heavy noise in the last row in Fig. 1. It is expected that human observers can manually segment this image with low observer variability; however, since this image is very different from the training data, the neural networks were not able to generate a reasonable segmentation and yielded high predictive entropy and mutual information for the entire cardiac structure.

C. Segmentation Quality Control

We showed that the uncertainty measures have moderate to good correlations with segmentation accuracy. This could have been negatively affected by manual segmentation noise. Framing segmentation quality control as a binary classification problem instead of evaluating the correlations or predicting the segmentation accuracy alleviates the issue of noise in manual segmentation. In this regard, we defined poor segmentation using a threshold on ASSD between the predicted and manual segmentation. This definition was adopted based on discussions with our clinical collaborators; however, it can be modified depending on the application. For example, other segmentation accuracy metrics such as Hausdorff distance or misclassification...
area can be used and the framework for evaluating uncertainty measures developed in this work may be applied directly.

Other studies of segmentation quality control include directly predicting segmentation accuracy or comparing the predicted segmentation to a reference database. Alba et al. [46] trained a random forest classifier to predict a binary label of correct or incorrect segmentation. The examples of correct segmentation were generated using the manual delineation while the incorrect segmentations were obtained by deforming or translating the manual segmentations. Robinson et al. [47] used a 3D residual network to directly predict the Dice of a segmentation from an image-segmentation pair. The network was trained and tested on a dataset created using a random forest segmentation algorithm. Ruijsink et al. [41] trained a CNN for detecting images with artefacts or incorrect planning and then excluded these from the segmentation pipeline. [41] and [48] also trained classification models to predict whether a segmentation is good or poor. These classifiers are agnostic to how the segmentation was generated. However, these approaches depend on training with expected segmentation failures, which may be challenging to incorporate during training. In contrast, our approach used uncertainty measures to detect poor segmentation and is more explainable without these issues. Instead of using a learning algorithm to determine segmentation quality, we used model uncertainty which emerges intrinsically during algorithm training. A slight limitation of our approach is that sampling during the testing phase required up to 50x more computation time compared to a single prediction but this may be accelerated through parallelization.

Additionally, some studies estimate the “similarity” of the test image and/or predicted segmentation with respect to the training data as a proxy for segmentation quality. For example, Gonzalez and Mukhopadhyay [49] used scores from a self-supervised task to detect out-of-distribution test images (which can then be assumed to have poor segmentation results). Galati and Zuluaga [50] trained a convolutional autoencoder to reconstruct segmentation maps. Then, the predicted segmentation is fed into the autoencoder and segmentation quality measures are calculated based on the predicted segmentation and reconstructed prediction. These generative modelling approaches represent a promising line of work and are quite different from the discriminative approaches used in this work. One advantage of [49] is that the algorithm does not require ground truth segmentation for training. However, in both approaches, the prediction of the segmentation itself is decoupled from the prediction of segmentation quality.

Finally, another approach for segmentation quality control is using a modified version of Reverse Classification Accuracy to predict the accuracy of an image-segmentation pair [51]. This approach requires a reference database with manual segmentation. Each reference image is registered to the test image and the associated manual segmentations are warped accordingly to generate potential segmentations of the test image. Segmentation quality is estimated by comparing the potential segmentations and algorithm segmentation. A limitation of this approach is that it requires long time to predict the segmentation quality, mainly due to the registration steps.

V. CONCLUSION

In this work, we compared Bayesian and non-Bayesian methods, namely BBB, MCD, Deep Ensembles, and SSN for segmentation accuracy, probability calibration, and uncertainty estimates in the context of cardiac MRI segmentation in cases of various distortions. We found that Deep Ensembles performed better in terms of segmentation accuracy and probability calibration on in-distribution and out-of-distribution datasets; BBB outperformed the other methods on images with noise distortions while SSN outperformed the others on images with blurring distortions. We showed that ASSDWS uncertainty measure was strongly correlated with the segmentation accuracy; using uncertainty measures can result in substantial time savings by reducing the number of images that needs manual review for segmentation quality control.

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