Propagating Uncertainty Across Cascaded Medical Imaging Tasks For Improved Deep Learning Inference

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2 Montreal Neurological Institute, McGill University, Montreal, Canada
3 NeuroRx Research, Montreal, Canada

UNSURE 2019: **Un**certainty for **S**afe **U**tilization of Machine Lea**r**ning in M**e**dical Imaging

Introduction

- Medical Image analysis pipeline performs sequence of inference task before the task of interest

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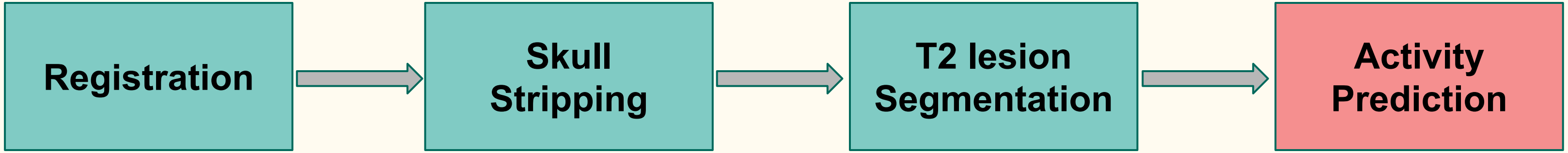
- Ex. Multiple Sclerosis (MS) disease activity prediction [1]



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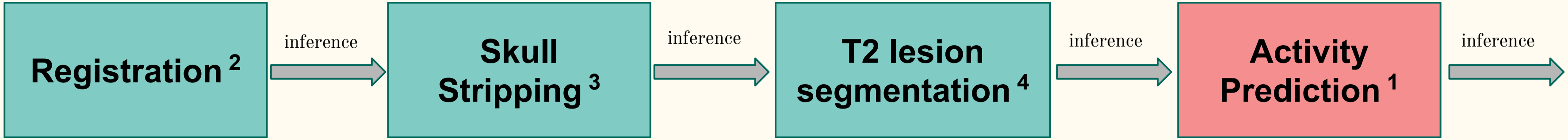

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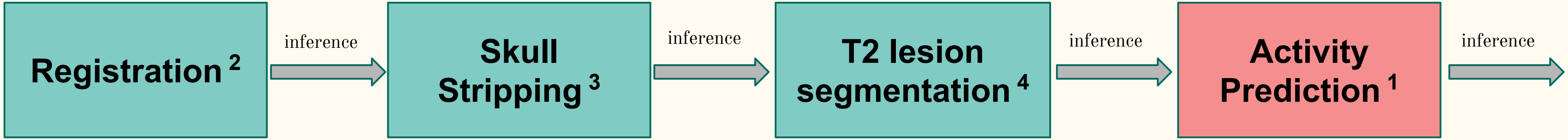

- Deep Learning based solutions provide only deterministic output
- Errors can accumulate over sequence of tasks
- This can hinder downstream task

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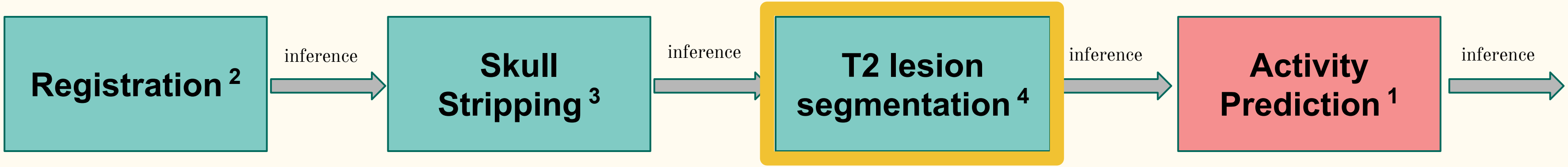

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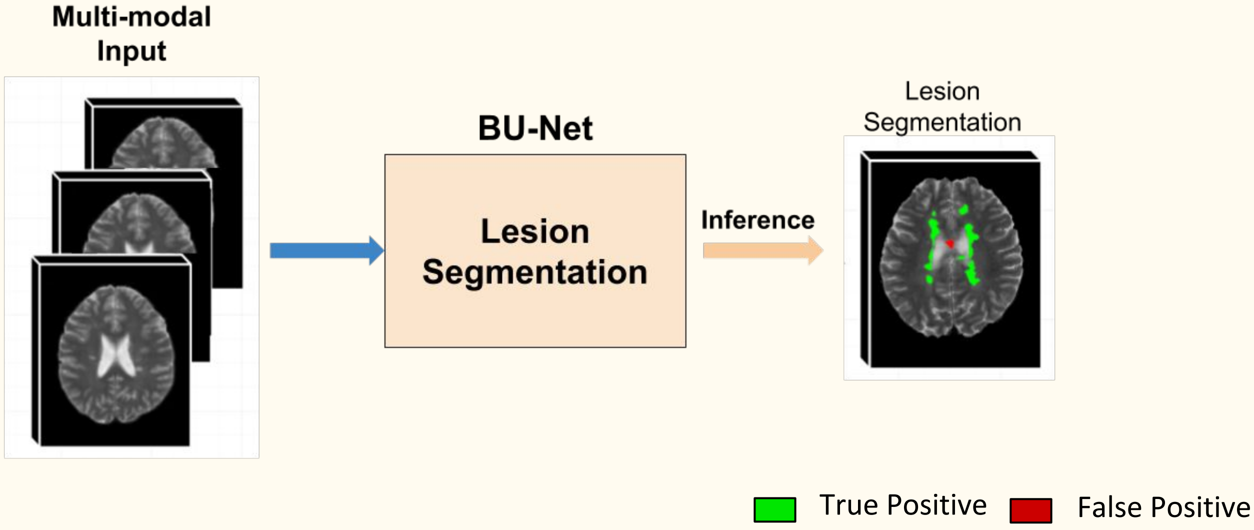
- MS T2 lesion segmentation using Bayesian U-Net (BU-Net) [4]



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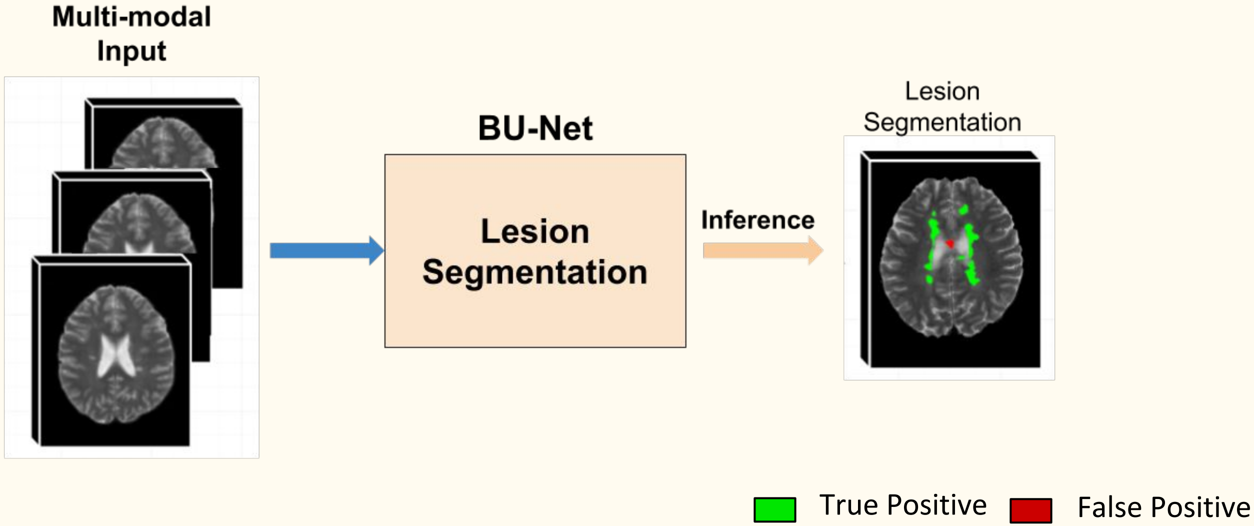
    - Uncertainty Estimation using Monte-Carlo Dropout (MC-Dropout) [5]



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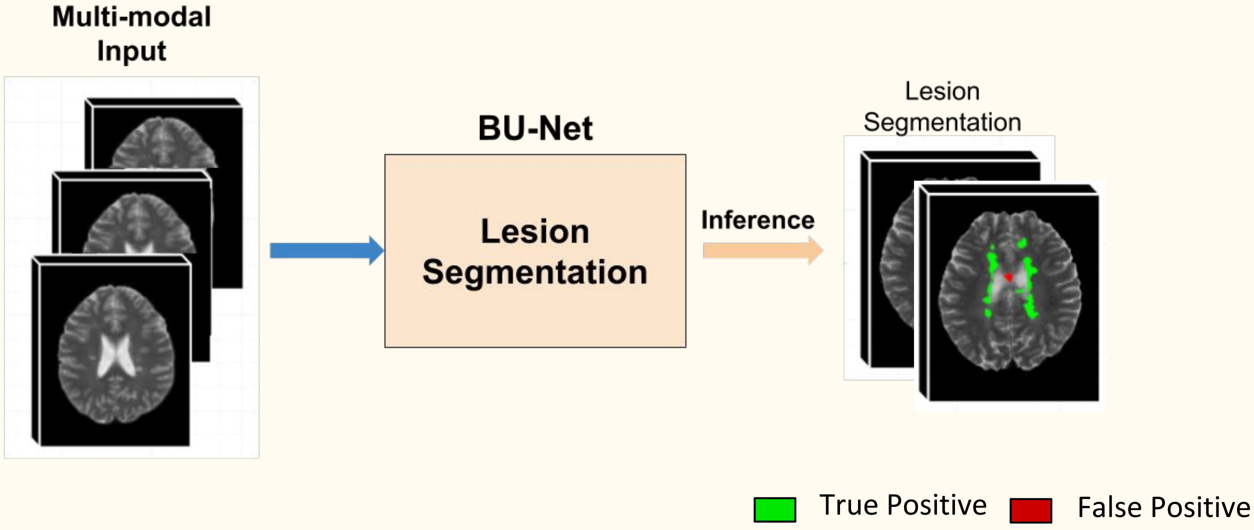

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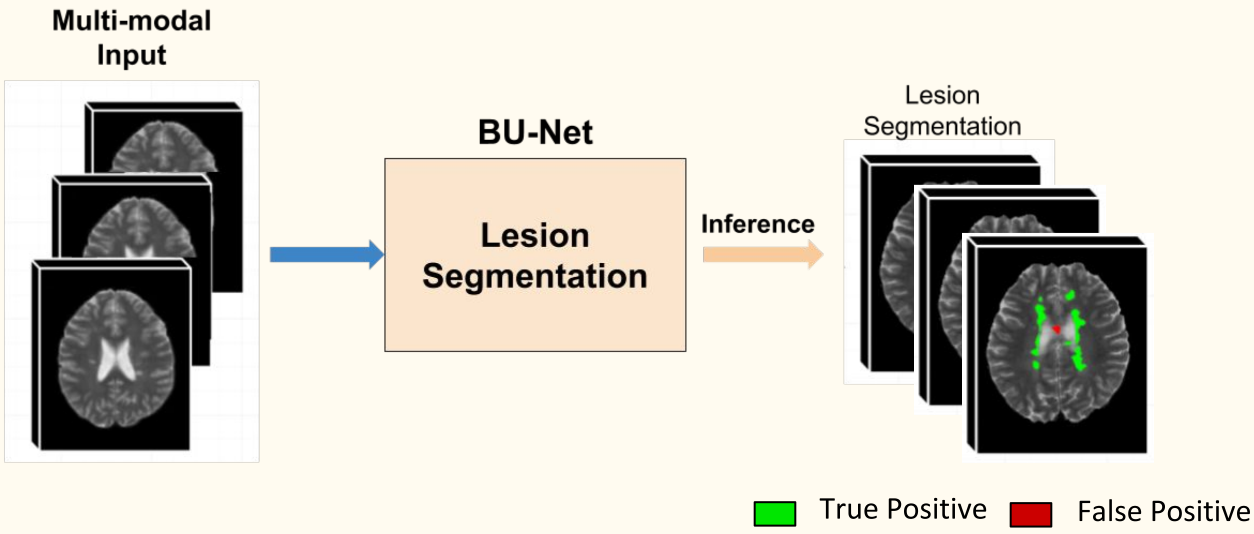

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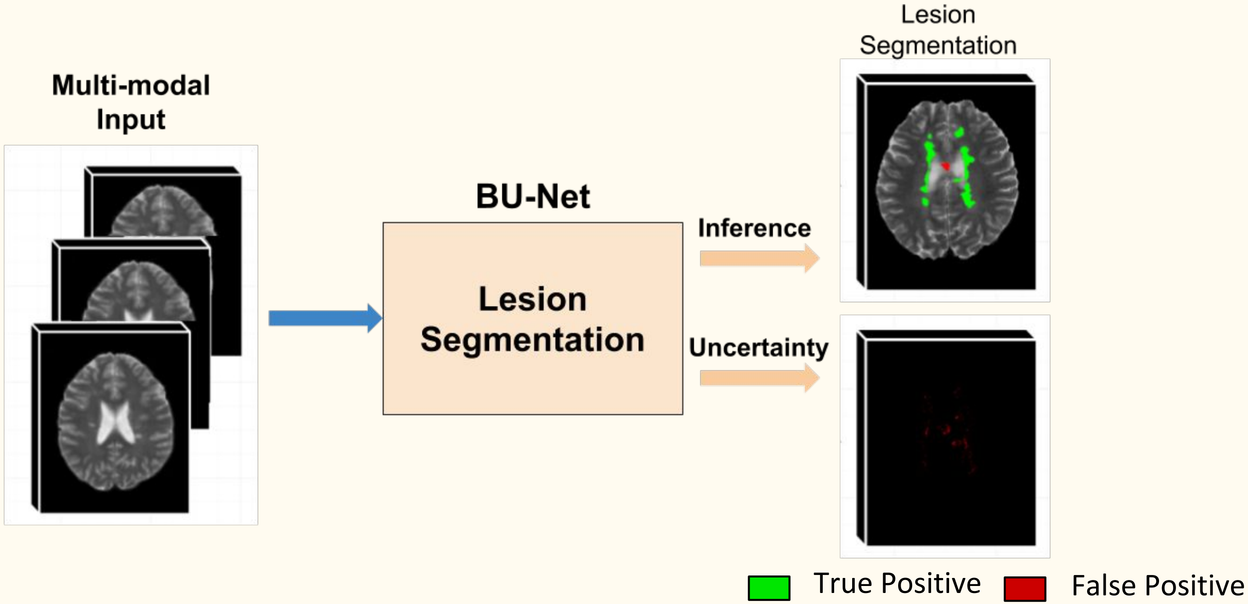

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Introduction

- Bayesian Deep Learning provides uncertainty estimation
  - Monte-Carlo (MC) Dropout [5]
  - Variational Dropout [6]
  - Probabilistic U-Net [7]
  - Deep Ensemble [8]
  - ...

[5] Gal and Ghahramani, “Dropout as a bayesian approximation: Representing model uncertainty in deep learning.”, ICML 2016.
[6] Kingma et al., “Variational dropout and the local reparameterization trick.”, NeurIPS 2015.
[7] Kohl et al., “A probabilistic u-net for segmentation of ambiguous images.”, NeurIPS 2018.
[8] Lakshminarayanan et al., “Simple and scalable predictive uncertainty estimation using deep ensembles.”, NeurIPS 2017.

Introduction

- Applied to different medical image analysis context contexts
  - MS T2 lesion segmentation and detection [4]
  - Lung cancer lesion segmentation [9]
  - Modality Synthesis [10]
  - dMRI Super-Resolution [11]
  - Brain structure segmentation [12]
  - MR registration [13]
  - Diabetic Ratinopathy Screening [14]
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  - MS T2 lesion segmentation and detection [4]
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  - Modality Synthesis [10]
  - dMRI Super-Resolution [11]
  - Brain structure segmentation [12]
  - MR registration [13]
  - Diabetic Ratinopathy Screening [14]
  - ...
- Papers report that
  - Areas where network is prone to error have higher uncertainty [10,11,13]
  - Improved performance when the network output is evaluated on its most certain predictions [4, 14]

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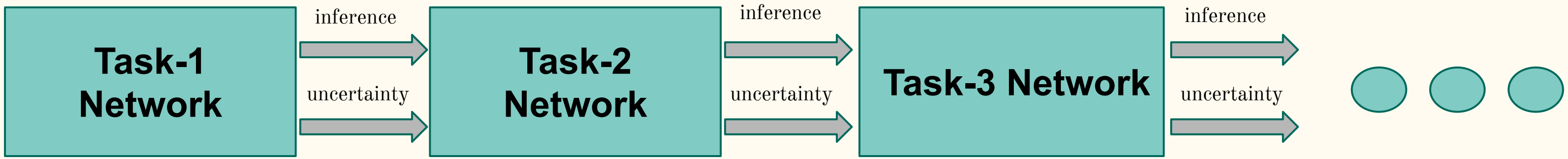
Can we use this uncertainty to improve downstream task?

Proposed Framework

- Leveraging Uncertainty for improved inference in cascaded medical image analysis task



Proposed Framework

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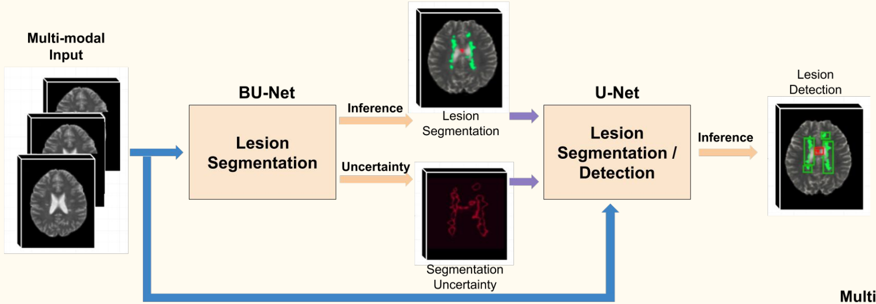
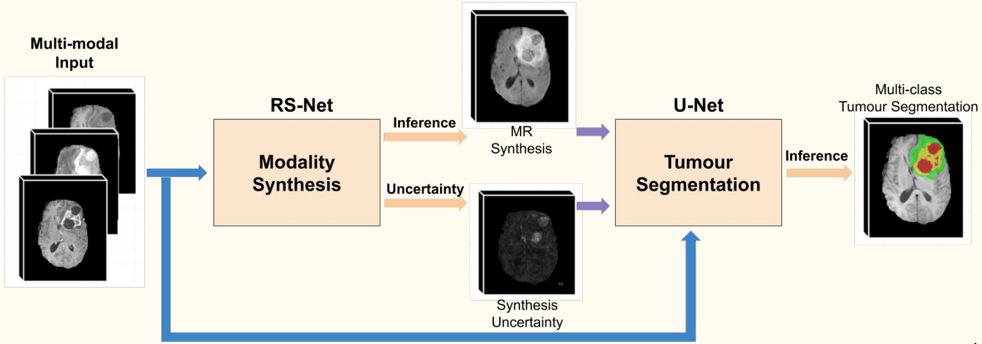


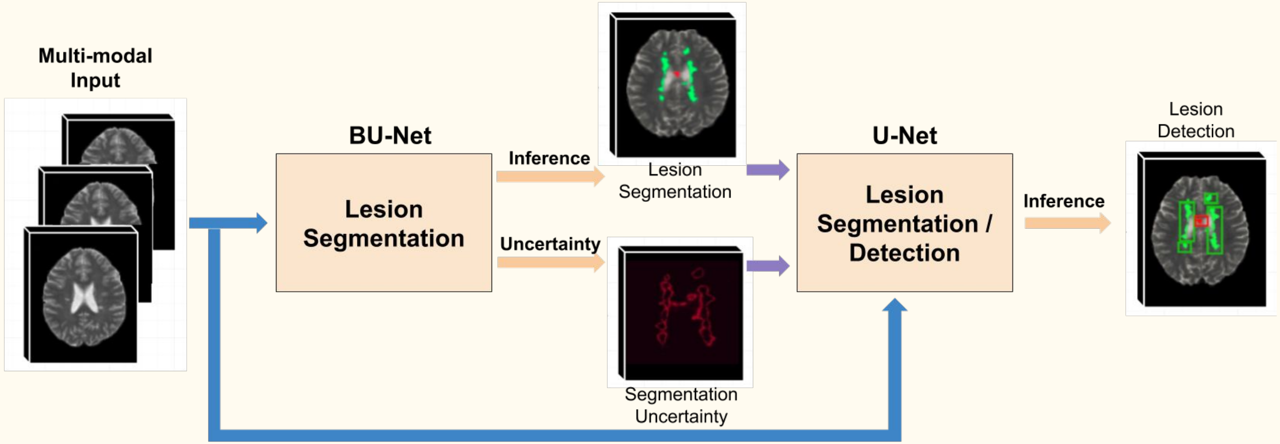
MS T2 lesion segmentation detection

Brain Tumour Segmentation



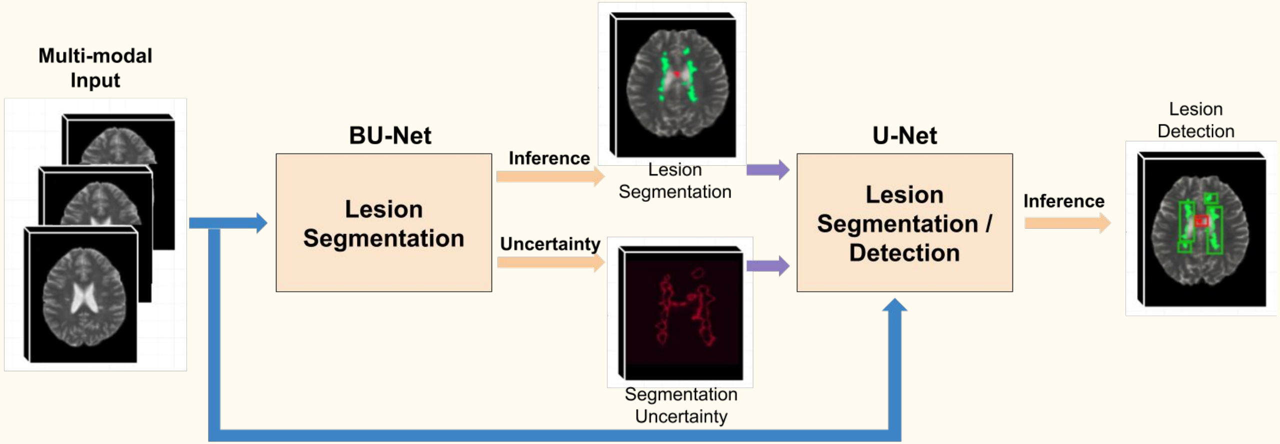
MS T2 Lesion Segmentation/Detection Pipeline

- **Task:** Accurate MS T2 lesion segmentation/detection



MS T2 Lesion Segmentation/Detection Pipeline

- **Task:** Accurate MS T2 lesion segmentation/detection
- **Task-1 Network:** Bayesian U-Net (BU-Net) [4] for lesion segmentation
- **Task-2 Network:** 3D U-Net [15] for segmentation
- MC-Dropout [5] to estimate uncertainty in BU-Net



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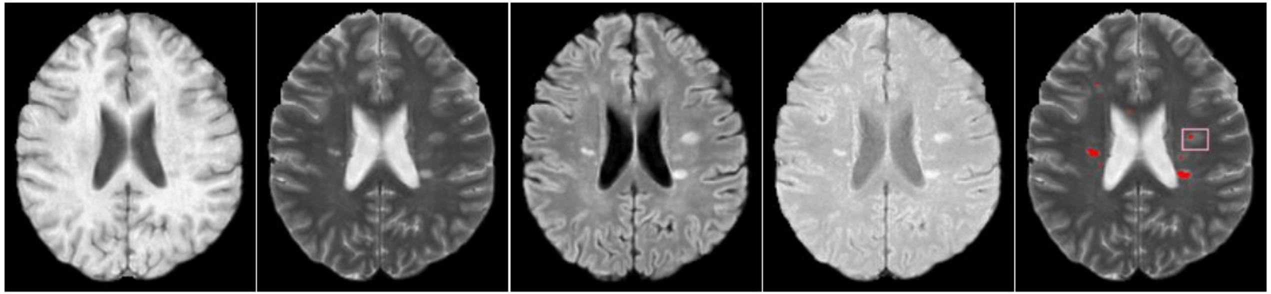
MS T2 Lesion Segmentation/Detection Pipeline

- **Dataset**
  - Proprietary multi-site, multi-scanner patient MRI from 2 clinical trials of patients with relapsing-remitting MS (RRMS)
  - 5800 multi-modal MRI (T1,T2, FLAIR, PD)
  - Expert T2 lesion labels
    - 40% of the available data used to train/validate BU-Net
    - 50% of the remaining to train 3D U-Net
    - 10% to test 3D U-Net



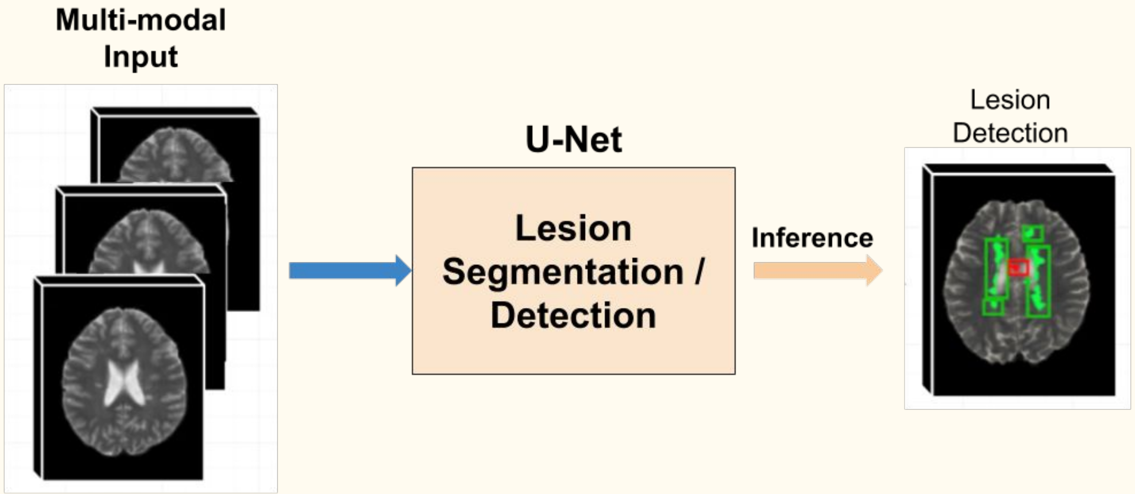
(a) T1w (b) T2w (c) FLAIR (d) PDW (e) Expert labels

MS T2 Lesion Segmentation/Detection Pipeline

- **Evaluation Metric**
  - Accurate detection of MS T2 lesion is of interest
  - Segmentation converted into lesion detection with connected component analysis
  - Lesions divided into 3 categories based on size.
    - Small (3-10 voxels) --- 40% of total lesions are small
    - Medium (11-50 voxels)
    - Large (50+ voxels)
  - Receiver operating characteristic (ROC) curves for each lesion size and for all lesions combined
    - Area under the curve (AUC) of ROC curve
    - True Positive Rate (TPR) at False detection rate (FDR) of 0.2

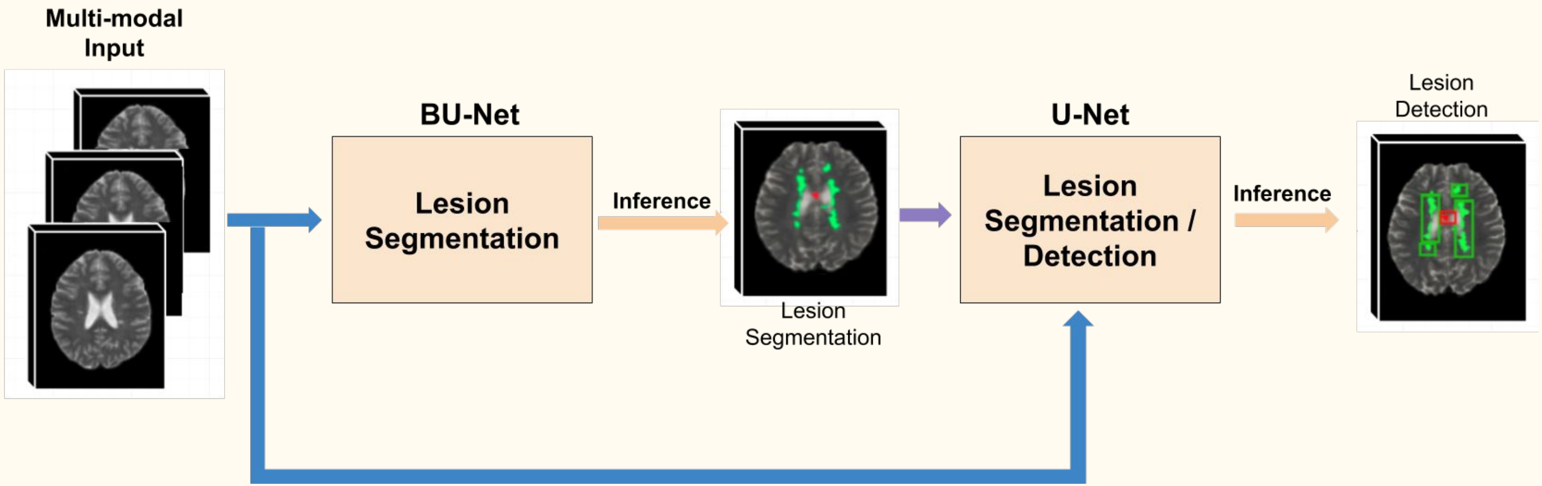
MS T2 Lesion Segmentation/Detection Pipeline

- **Baseline-1**
  - No Task-1 Network (BU-Net)



MS T2 Lesion Segmentation/Detection Pipeline

- **Baseline-2**
  - Only inference from Task-1 Network (BU-Net) is propagated to Task-2 Network (3D U-Net)



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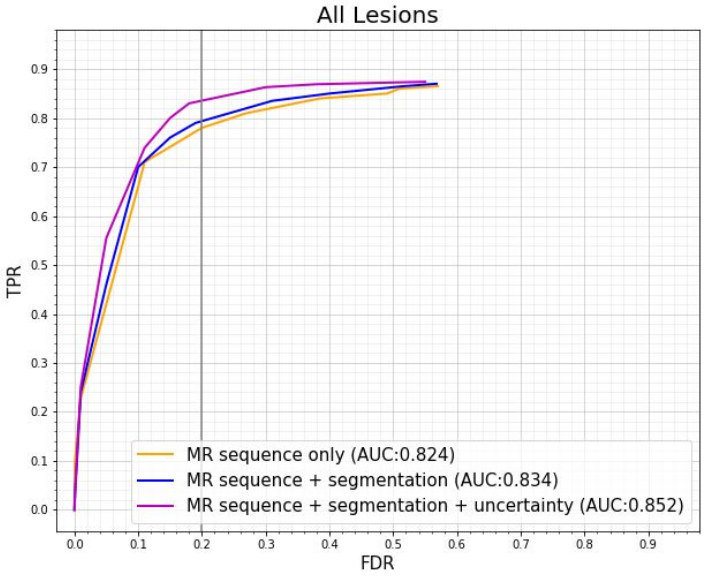
MS T2 Lesion Segmentation/Detection Pipeline

- **Quantitative Results**



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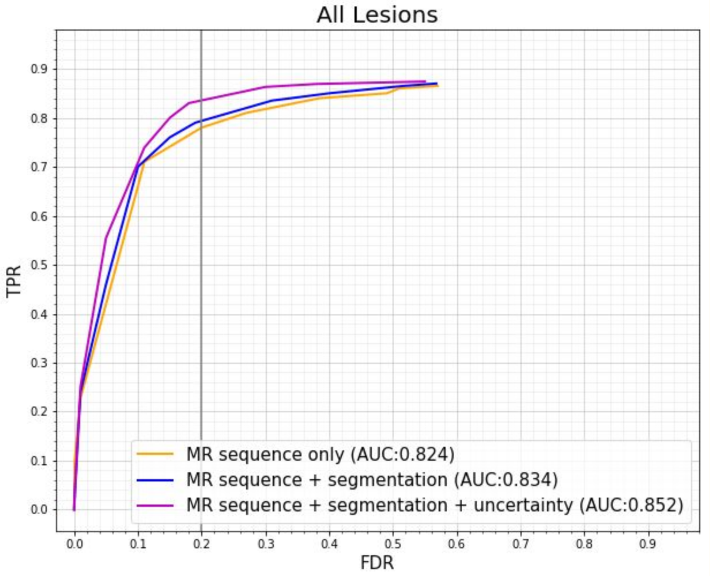
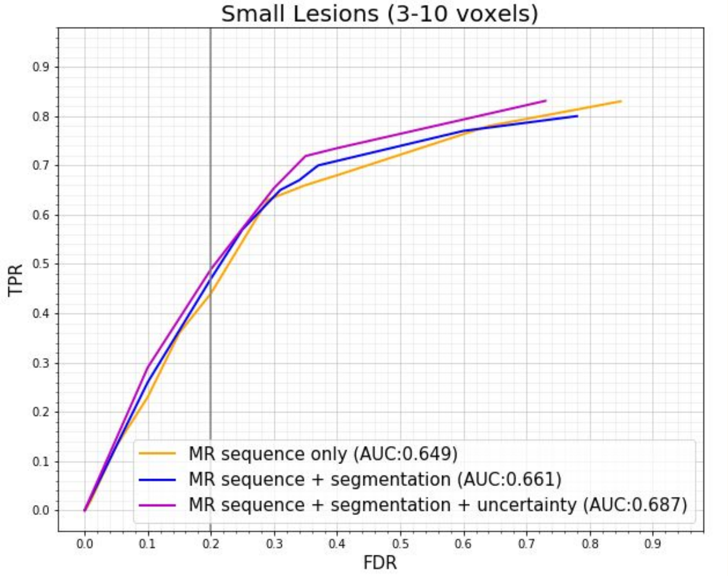
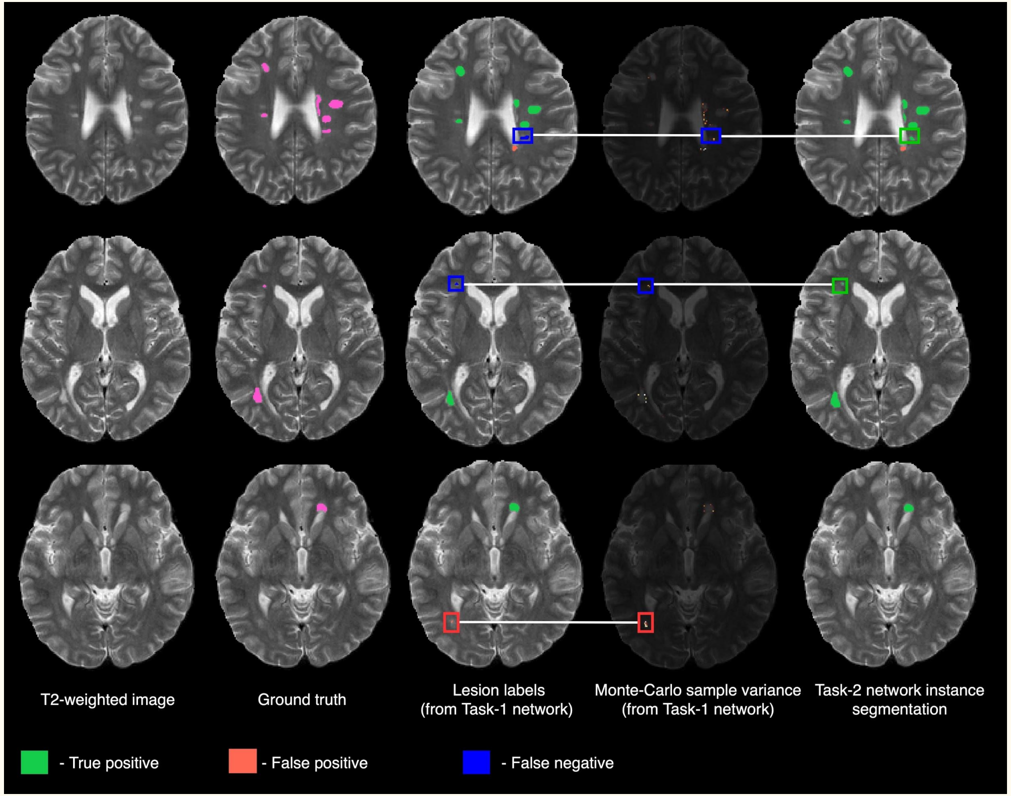




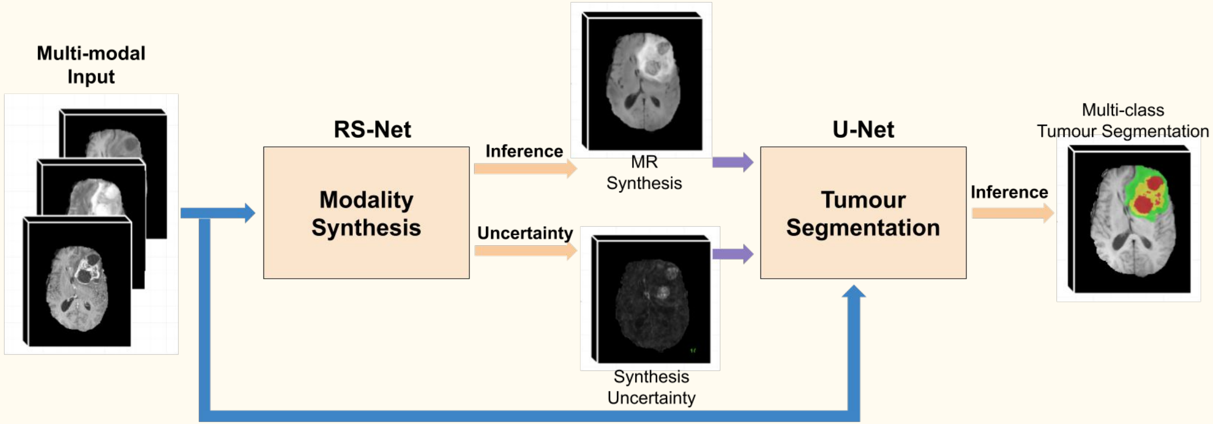
MS T2 Lesion Segmentation/Detection Pipeline

- Qualitative Results



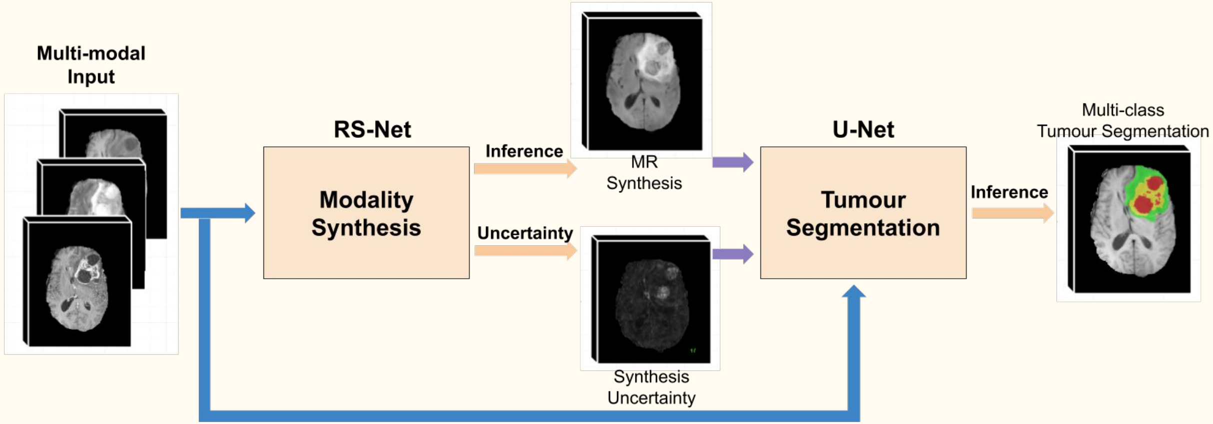
Brain Tumour Segmentation Pipeline

- **Task:** Accurate multi-class tumour segmentation in case of missing modality



Brain Tumour Segmentation Pipeline

- **Task:** Accurate multi-class tumour segmentation in case of missing modality
- **Task-1 Network:** Regression-Segmentation Network (RS-Net) [10] for modality synthesis
- **Task-2 Network:** 3D U-Net [15] for multi-class brain tumour segmentation
- MC-Dropout [5] to estimate uncertainty in RS-Net



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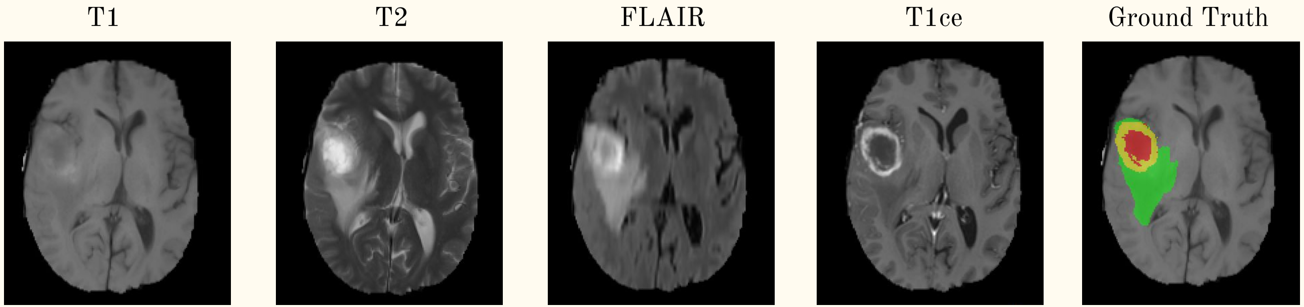
Brain Tumour Segmentation Pipeline

- **Dataset**
  - Brain Tumour Segmentation (BraTS) 2018 [16] challenge dataset
  - Multi-class tumour segmentation ground truth
    - Edema
    - Enhancing Tumour
    - Non-enhancing core
  - Multi-modal MRI (T1, T2, FLAIR, and T1ce)
    - BraTS 2018 Training set to train and validate RS-Net and 3D U-Net (285 patients)
    - BraTS 2018 Validation set (held-out) to test 3D U-Net (66 patients)



[16] S. Bakas, et al.: "Identifying the best machine learning algorithms for brain tumor segmentation, progression assessment, and overall survival prediction in the BRATS challenge", arXiv preprint arXiv:1811.02629 (2018)

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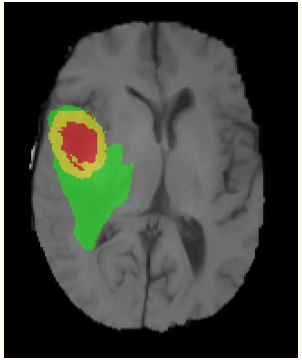
Brain Tumour Segmentation Pipeline

- **Evaluation Metric** [16]
  - Dice scores for three different tumour subtypes:
    - enhancing tumour (DE)
    - whole tumour (DT)
    - tumour core (DC)

$$Dice(G, P) = \frac{2|GP|}{|G| + |P|}$$

where |G| denotes the number of positive elements in the binary segmentation G and |GP| is the number of shared positive elements by G and P. Dice∈[0, 1]. A higher Dice value indicates a better segmentation performance.



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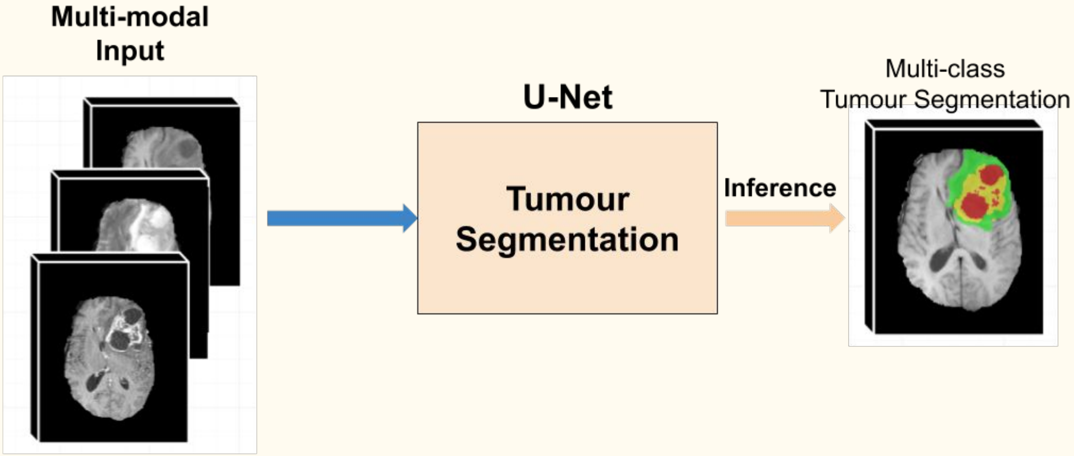
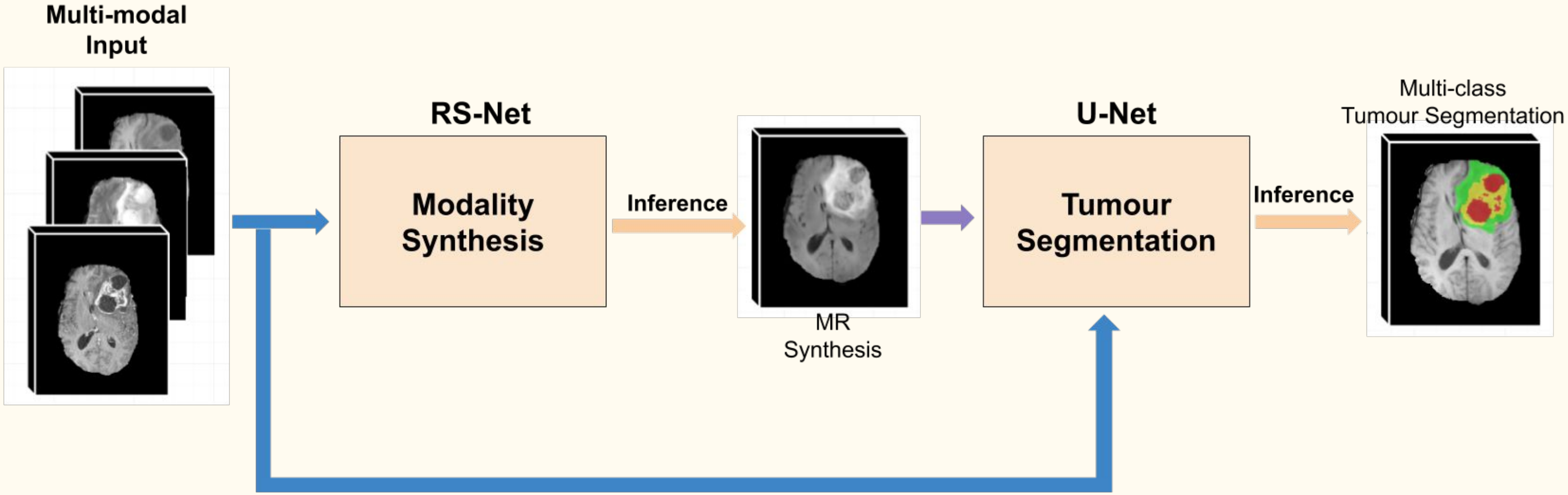
Brain Tumour Segmentation Pipeline

- **Baseline-1**
  - No Task-1 Network (RS-Net): No synthesis of missing modality



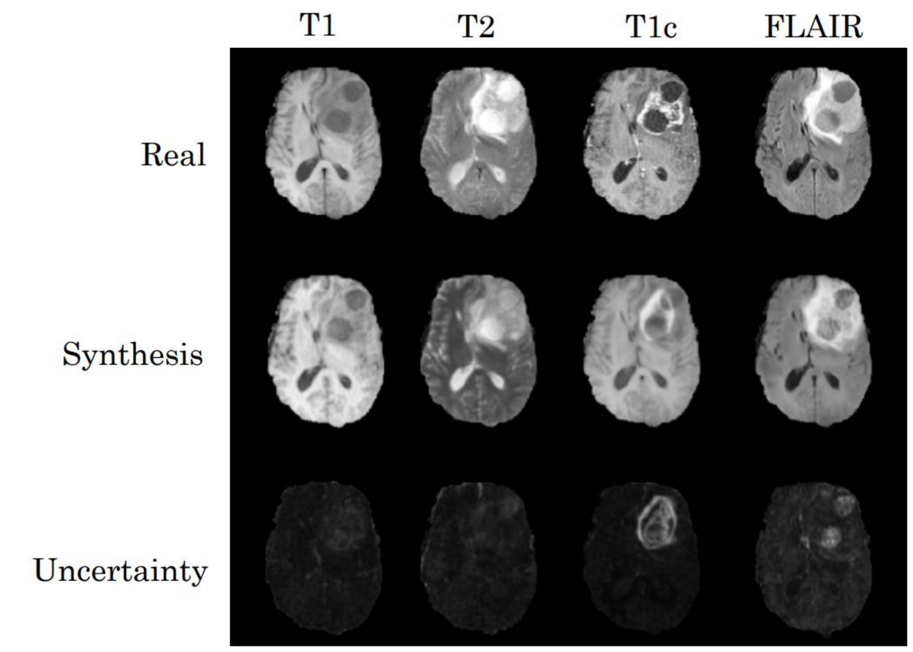
Brain Tumour Segmentation Pipeline

- **Baseline-2**
    - Only inference from Task-1 Network (RS-Net) is propagated to Task-2 Network (3D U-Net)



Brain Tumour Segmentation Pipeline

- **Uncertainty in Synthesis (RS-Net)** [10]



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Brain Tumour Segmentation Pipeline

- **Quantitative Results**

	T1ce synthesis		
	DT	DC	DE
real(3) sequences	87.17	50.25	26.89
real(3)+synthesized sequences	86.72	52.80	27.35
real(3)+synthesized+uncertainty	**88.20**	**57.29***	**32.86***

(*) indicates statistically significant ($p \leq 0.05$) differences between second and third row.

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Brain Tumour Segmentation Pipeline

- **Quantitative Results**

				FLAIR synthesis		
				DT	DC	DE
real(3) sequences				83.27	73.91	71.07
real(3)+synthesized sequences				84.56	76.72	72.89
real(3)+synthesized+uncertainty				**85.84***	**79.25***	**74.51***

(*) indicates statistically significant ($p \leq 0.05$) differences between second and third row.

Brain Tumour Segmentation Pipeline

- **Quantitative Results**

	T1ce synthesis			FLAIR synthesis		
	DT	DC	DE	DT	DC	DE
real(3) sequences	87.17	50.25	26.89	83.27	73.91	71.07
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real(3)+synthesized+uncertainty	**88.20**	**57.29***	**32.86***	**85.84***	**79.25***	**74.51***

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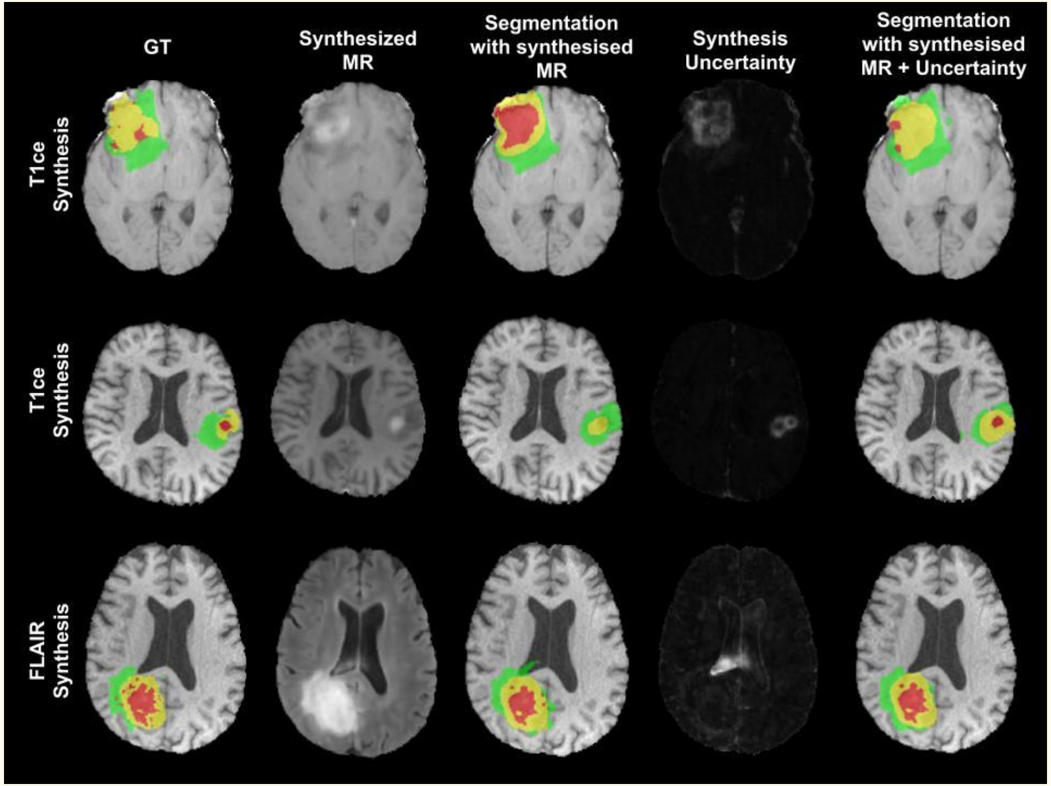
Brain Tumour Segmentation Pipeline

- Qualitative Results

Enhancing Tumour

Edema

Non Enhancing Core



Conclusion

- Proposed **a general deep learning framework** for the propagation of uncertainty across a sequence of inference tasks within a medical image analysis pipeline for improved inference
- **Evaluation on two different contexts** of MS T2 lesion segmentation/detection and Brain Tumour segmentation
- **2-10% improvement** for both tasks on their respected **quantitative** measures
- **Clearly visible qualitative improvement**
- **Future work** will explore how to properly develop **a complete end-to-end system** that includes uncertainty propagation across the inference modules

Thank you

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MS T2 Lesion Segmentation/Detection Pipeline

- **Implementation Details**
  - **Task-1 Network:** BU-Net [4]
  - **Task-1 Network uncertainty:** Variance of 10 MC samples [5]
  - **Task-2 Network:** 3D U-Net [15]
    - 3 resolution U-Net
    - Linear Upsampling
    - Leaky-ReLU non-linear activation [16]
    - Group Normalization [17]
    - Equally weighted Sorensen-Dice loss [18] and binary cross-entropy loss
  - 18 connected component to convert segmentation to detection

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[16] Maas et al., “Rectifier nonlinearities improve neural network acoustic models.”, ICML 2013.
[17] Wu and He., “Group normalization.”, In ECCV 2018.
[18] Milletari et al., “V-net: Fully convolutional neural networks for volumetric medical image segmentation.”, 3DV 2016

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Brain Tumour Segmentation

- **Implementation Details**
  - **Task-1 Network:** RS-Net [10]
  - **Task-1 Network uncertainty:** Variance of 20 MC samples [5]
  - **Task-2 Network:** 3D U-Net [15]
    - 4 resolution U-Net
    - Deconvolution [19]
    - ReLU non-linear activation [20]
    - Instance Normalization [21]
    - Weighted categorical cross-entropy loss

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[21] Ulyanov et al., “Instance normalization: The missing ingredient for fast stylization.”, arXiv preprint arXiv:1607.08022.