\section{Introduction}
\paragraph{Background}
Segmentation of lesions is a task of separating lesions from other objects for medical-based imaging. This task requires a high-quality and large annotated training dataset, which normally requires medical experts to manually label them. However, this supervised method not only requires a large amount of human effort but also suffers from less generalizability to apply in atypical or unseen situations than unsupervised methods (1). Hence, an unsupervised approach can greatly help the segmentation task with limited labels.

To achieve better unsupervised segmentation performance, reinforcement learning (RL) can be introduced to enable an agent to learn the optimal behavior through maximizing reward. Among RL algorithms, Deep Q-learning (DQN) has demonstrated improved performance on radiological images and outperformed the supervised approach with a very small training set on image classification and segmentation problems (2).

\paragraph{Related Work}

Mask-Regional-CNN and U-net are the two most common CNN architectures used in medical segmentation problems. Among the top performers in the BraTS challenge, DeepMedic (3) is a two 11-layer 3D-CNN with residual connections to improve the performance. It has achieved a dice score of 0.89 for whole tumor segmentation tasks. Another 3D-Unet model (4) generated similar dice scores for whole tumor segmentation and tumor core segmentation tasks.

\section{Methods}
\paragraph{Dataset}

Our dataset comes from BraTS brain tumor segmentation 2016 and 2017 challenges. We used 60 images for training, 20 for validation, and 20 for testing. Our team implemented 2 different unsupervised methods to compare the results to a supervised approach.

\paragraph{Setup, Training and Evaluation}

The goal is to find the approach that achieves the best performance for medical image segmentation with limited labels.

We used a supervised 3D-Unet as a baseline model to compare performance with two unsupervised approaches, 3D-Unet-KMeans method and 3D-Clustering-CNN-DQN. Our hypothesis is that the supervised 3D-Unet would have the best performance overall, while unsupervised 3D-Clustering-CNN-DQN outperforms unsupervised 3D-Unet-KMeans.

For the unsupervised 3D-Unet KMeans, KMeans clustering was applied on the outputs of 3D-Unet to generate pseudo-labels, which are used to compute a dice loss for backpropagation to update weights.

For the 3D-Clustering-CNN-DQN, the pseudo-labels were generated by unsupervised 3D-Clustering-CNN and superpixel, where the CNN has 3 convolutional layers with 3x3x3 kernels, 1x1x1 padding, and 1x1x1 stride, and applied batch normalization after each layer with the final layer having output channel of 6. We selected the 60 masks as input for a DQN to predict the best cluster to serve as a lesion mask for the remaining test dataset.

The RL DQN-agent chooses the best mask from those 6 masks generated from the 3D-clustering-CNN. The agent is trained by sampling from the experience buffer, calculating the mean-square error between optimal Q-value and the current Q-value and backpropating the gradients. We evaluated the performance of the models by 1) segmentation accuracy: testing dice scores, 2) efficiency: total running time.

\section{Results}

\paragraph{Supervised 3D-Unet}

The model was trained for 50 epochs using the Adam optimizer and dice loss with learning rate=1. The model had the best performance in terms of segmentation accuracy and efficiency out of all experimenting models. The model successfully segmented the tumor from the rest of brain tissue.

\paragraph{Unsupervised KMeans 3D-Unet}

The model was trained for 50 epochs using the Adam optimizer and dice loss with learning rate=0.00005. The training and validation dice loss was the smallest across all models. Yet, the test dice score was the worst. Visualization of the pseudo-labels suggests that the model learned to segment the whole brain from the background, but could not detect the tumor in the brain.

\paragraph{Unsupervised 3D-clustering-CNN and Reinforcement Learning}

The superpixel uses nearest-neighbors with features of pixel intensity to generate cluster regions of images that are similar in color and close in distance. (3) We trained our 3D-clustering-CNN for 10 epochs using stochastic gradient descent, cross-entropy loss, and learning-rate=0.1. Pseudolabels were generated as masks based on the superpixels.

Creating table: https://www.tablesgenerator.com/latex_tables#

```
\begin{center}
\begin{tabular}{ |c|c|c|c| }
 \hline
  & \small3DUnet & \small3DUnet Kmean & \small3DCNN-RL\\
 \hline
 \small Accuracy & 0.65 & 0.10 & 0.80 \\
 \hline
 \small Efficiency & 24.89s & 51.67s & cell8  \\
 \hline
\end{tabular}
\end{center}
```

\section{Discussion}In addition, supervised method often suffers from overfitting problem, which potentially explains why 3D-clustering-CNN-RL did better than supervised U-net. Moreover, there is concern of biased dataset as we observed the first few training samples have much lower segmentation accuracy than the other training samples and testing samples. On the other hand, since the pseudo-labels generated by KMeans clustering are significantly influenced by the features of the raw input images, the model might not be optimized towards ground truths, which is the case we observed. During training, the unsupervised 3D-Unet KMeans had extremely low dice loss, suggesting that the model is optimized. Yet, it did not have a high dice score with respect to the ground truths, as the model segmented the whole brain from the background, which were more distinguishable by KMeans than the tumor in the brain.

\section{References}

\begin{enumerate}
\item Zeng, C., Gu, L., Liu, Z., Zhao, S. (2020, November). Review of Deep Learning Approaches for the segmentation of multiple sclerosis lesions on Brain MRI. Frontiers. DOI: 10.3389/fninf.2020.610967

\item Stember, J., Shalu H. (2020, December). Unsupervised deep clustering and reinforcement learning can accurately segment MRI brain tumors with very small training sets. https://doi.org/10.48550/arXiv.2012.13321

\item Kamnitsas, K., Ferrante, E., Parisot, S., Ledig, C., Nori, A. V., Criminisi, A., ... & Glocker, B. (2016, October). DeepMedic for brain tumor segmentation. In International workshop on Brainlesion: Glioma, multiple sclerosis, stroke and traumatic brain injuries (pp. 138-149). Springer, Cham.

\item Iftekharuddin, K. M., Jia, W., & Marsh, R. (2000, July). A fractal analysis approach to identification of tumor in brain MR images. In Proceedings of the 22nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Cat. No. 00CH37143) (Vol. 4, pp. 3064-3066). IEEE.

\item Ghaffari, M., Sowmya, A., & Oliver, R. (2019). Automated brain tumor segmentation using multimodal brain scans: a survey based on models submitted to the BraTS 2012–2018 challenges. IEEE reviews in biomedical engineering, 13, 156-168.

\end{enumerate}

\end{document}

Proposal Due: April 6th
Requirement: < 1 page, should be extended to the final project

Idea: under the medical segmentation topic and see differences in model performance by using annotated labels vs the one without labels based on unsupervised methods

1. Specify dataset: Medical Segmentation Decathlon

Objective: Finding which approach achieves the best performance for medical image segmentation with limited labels.

Hypothesis: Unsupervised learning followed by reinforcement learning most likely would give the best performance, while unsupervised learning combined with traditional architectures likely achieve the worst performance.

CS482/682 Final Project Proposal

Ting He, Victor Wu, Maxine Gong, Muchen Li

Background

Segmentation of lesions is a task of separating lesions from other objects for medical-based imaging. In this case, segmentation of lesions is clustering of parts of the image that belong to the same object class. Two basic methods include patch-wise segmentation and semantic-wise segmentation. Patch-wise segmentation takes a pixel as the center and then extracts a N x N classifier. This method could be relatively inefficient due to overlapping calculations from N x N patches since it randomly samples. Semantic-wise segmentation, meanwhile, will not have any redundant calculations from overlap. The input will instead be a very large patch or the entire MRI image itself, and semantic-wise segmentation feeds the input into a convolutional then deconvolutional layer to predict lesion mask. [7th paper citation] Finally,cascaded CNN architecture combines the patch-wise and semantic-wise architectures where the first CNN is used as input to the second CNN for classification. *Deep Learning for Brain MRI Segmentation* [insert ref 8 here] compiled literature pertaining to segmenting brain scans and all of the research they listed segmenting brain tumors used patch-wise CNN architecture. Semantic-wise segmentation seemed to have high accuracy from the limited data presented in their paper and cascaded CNN has potential to have both high accuracy and very high sensitivity as it combines patch-wise and semantic-wise CNN architecture. The next step is to move onto reinforcement learning after generating a model with selected segmentation CNN architecture.

Reinforcement learning is a machine learning technique that enables an agent to learn the optimal behavior through maximizing reward. Basic RL can be modeled as a Markov decision process which involves a set of environment and agent states, a set of actions of agent, transition probability and the reward function. Among RL algorithms, Q-learning is powerful to solve problems that can be represented by discrete spaces but it performs badly in very-large high-dimensional spaces. Deep Q-learning(QDN) is able to deal with continuous state spaces. Previous work[insert ref # here] has demonstrated that QDN is applicable to radiological images and outperformed the supervised approach with a very small training set on 2D image classification and segmentation problems. (https://doi.org/10.48550/arXiv.2012.13321, https://doi.org/10.48550/arXiv.2008.02708)

Related work and Dataset:

Our dataset comes from BraTS brain tumor segmentation 2016 (https://sites.google.com/site/braintumorsegmentation/home/brats_2016) and 2017 (https://www.med.upenn.edu/sbia/brats2017.html) challenges, which was first held in 2012 and has become almost an annual event after that. The datasets contain a large set of multimodal brain scans which came from T1-weighted MRI, T1-weighted MRI with contract, T2-weighted MRI, and Fluid-Attenuated Inversion Recovery MRI. The original task of events is to segment the brain images into 3 different locations, whole tumor, tumor core and enhancing tumor.

In the 2016 event, we have 200 training datasets and 191 test datasets. The annotations were generated from high-ranked models from previous competitions (BraTS 2012 and BraTS 2013) and then evaluated by experts. [insert first citation here] Among 18 submissions to the 2016 event, the top-performance algorithm was DeepMedic [insert the second citation here], which has two pathways with different specific scales, and each pathway has 11-layers 3D CNN with residual connections to improve the performance. The paper [second paper citation] stated that this architecture can increase the receptive field while keeping the computational cost low. After using 5-fold cross-validation, it achieved the performance of 0.89 for whole tumor, 0.76 for tumor core and 0.72 for enhancing tumor segmentation tasks based on the dice score. Another team applied U-net [insert the third paper] which generated similar dice scores for whole tumor segmentation and tumor core segmentation tasks but the performance of enhancing tumor only achieved 0.37.

Beginning from 2017, BraTS has provided a validation set with a size of 46, and the number of training datasets and test datasets increased a lot as well (285 and 146 correspondings). The datasets were labeled the same way as the event in 2016 with additional MRI scans from 19 institutions. [insert first citation]. We have more than 50 submission in 2017, and the majority of the models are variations of CNN. However, some scholars[insert first, 4th and 5th papers] pointed out that the performance of CNN methods highly depends on the choice of the loss function in terms of the imbalance dataset, and the choice of hyperparameters (learning rate, regularization method and dropout rate). The top 1 method for 2017 is Ensemble of Multiple Models and Architectures(EMMA) [insert 6th paper]. EMMA is an ensemble methods of 2 different DeepMedics, 2 fully convolutional network models, and 1 U-net, which achieved dice scores of 0.90(whole tumor), 0.82(core tumor) and 0.75(enhancing tumor).

Ref:

first : Ghaffari, M., Sowmya, A., & Oliver, R. (2019). Automated brain tumor segmentation using multimodal brain scans: a survey based on models submitted to the BraTS 2012–2018 challenges. *IEEE reviews in biomedical engineering*, *13*, 156-168.

Second: Kamnitsas, K., Ferrante, E., Parisot, S., Ledig, C., Nori, A. V., Criminisi, A., ... & Glocker, B. (2016, October). DeepMedic for brain tumor segmentation. In *International workshop on Brainlesion: Glioma, multiple sclerosis, stroke and traumatic brain injuries* (pp. 138-149). Springer, Cham.

Third: Iftekharuddin, K. M., Jia, W., & Marsh, R. (2000, July). A fractal analysis approach to identification of tumor in brain MR images. In *Proceedings of the 22nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Cat. No. 00CH37143)* (Vol. 4, pp. 3064-3066). IEEE.

4th: Shen, C., Roth, H. R., Oda, H., Oda, M., Hayashi, Y., Misawa, K., & Mori, K. (2018). On the influence of Dice loss function in multi-class organ segmentation of abdominal CT using 3D fully convolutional networks. *arXiv preprint arXiv:1801.05912*.

5th: Sudre, C. H., Li, W., Vercauteren, T., Ourselin, S., & Jorge Cardoso, M. (2017). Generalised dice overlap as a deep learning loss function for highly unbalanced segmentations. In *Deep learning in medical image analysis and multimodal learning for clinical decision support* (pp. 240-248). Springer, Cham.

6th:Kamnitsas, K., Bai, W., Ferrante, E., McDonagh, S., Sinclair, M., Pawlowski, N., ... & Glocker, B. (2017, September). Ensembles of multiple models and architectures for robust brain tumour segmentation. In *International MICCAI brainlesion workshop* (pp. 450-462). Springer, Cham.

7th: Zeng, C., Gu, L., Liu, Z., & Zhao, S. (2020, November). *Review of Deep Learning Approaches for the segmentation of multiple sclerosis lesions on Brain MRI*. Frontiers. Retrieved April 5, 2022, from https://www.frontiersin.org/articles/10.3389/fninf.2020.610967/full

8th: Akkus, Zeynettin & Galimzianova, Alfiia & Hoogi, Assaf & Rubin, Daniel & Erickson, Bradley. (2017). Deep Learning for Brain MRI Segmentation: State of the Art and Future Directions. Journal of digital imaging. 30. 10.1007/s10278-017-9983-4.

Method:

- Dataset part moved ahead

Preprocessing: https://github.com/richardbeare/mbwss using tools like mbwss to extract T1 MRI scans for human brains.

Setup: we are going to experiment with two architectures: 1. Unsupervised learning 3D-Unet. 2. Unsupervised learning 3DCNN followed by reinforcement learning.

Training: We will apply data augmentation to the training set to potentially increase the generalizability of our models.

For the first architecture, we would first construct a 3D U-net, which takes in MRI medical images as inputs. We will apply K-means clustering on the outputs from the model to generate pseudolabels, which are used to compute a dice loss and perform backpropagation to update weights. We will train the model for 200 epochs and apply early stopping.

For the second architecture, we first use an unsupervised clustering 3DCNN to generate masks. We will start with 5 layers with a filter size of 3*3*3. We will apply K-means clustering on the outputs from the model and backpropagate in the same way as described in the first architecture. After we trained the model, we will manually select the best masks generated from the model (by inspection and by comparing the masks to the ground truth), and feed them into a deep Q network (DQN) with 5 layers with a filter size of 3*3*3 that learns to predict the best cluster to serve as lesion mask. This unsupervised 3DCNN-DQN model will serve as our baseline model. In the next phase, we will tune the number of layers and filter size based on the performance of the model. We will try different combinations of layer numbers and filter sizes to identify the best combination for the 3DCNN-DQN.

Evaluation: We will evaluate the performance of both architectures based on efficiency, training loss, and test accuracy. In particular, we will measure the run time for training until convergence. We will compare the models' dice loss during training and dice scores on the testing sets.

3. Expected results

Tuesday, 1-2 pm, TA: xutong and ting
Final meeting, 6:30pm

Potential Tasks:

- Which architectures do we plan to use in segmentation? And how many do we plan to do?
- Which unsupervised methods?
- Which dataset do we want to use? (from the scope of medical zoo)
- How to train model fast? How to best utilize our own computer resources?
- What is our goal for the project? Finding the best-unsupervised methods which close to human annotation? or others?
- How to evaluate the results? Manually compare between human-labeled vs our generated one?
-

Background paper - MRI Segmentation of the Human Brain: Challenges, Methods, and Applications
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4402572/

(Maxine) Idea 1: unsupervised learning for segmentation task: Building a neural network (e.g. UNET), performing k-means clustering on the outputs to generate pseudolabels, then using the pseudolabels and outputs from the model for backpropagation to optimize the model. At the end of training, comparing the results generated from the model to the ground truth (labels). We can try a few different architectures to compare the performances.

This paper might be useful if you can't come up with ideas: https://arxiv.org/pdf/1812.07715.pdf

(Victor) Idea 2: using transformations including dilation and erosion to improve image contrast and reduce over-segmentation for image segment algorithms. We can use transforms to enchance image quality during training and marker classification to reduce noise and improve accuracy and sensitivity.
Supporting paper:
https://www.researchgate.net/publication/258389453_A_Novel_Model_of_Image_Segmentation_Based_on_Watershed_Algorithm /
https://www.frontiersin.org/articles/10.3389/fninf.2013.00032/full

(Muchen) Idea3: combining unsupervised deep learning clustering with reinforcement learning to segment brain lesions on MRI. Use unsupervised clustering to generate clusters that are candidate lesion masks. The user then selects the cluster that serves as the best mask. Then train a deep reinforcement learning (RL) deep Q network (DQN) in tandem with Q-learning to predict the best cluster to serve as lesion mask.
Supporting paper: Unsupervised deep clustering and reinforcement learning can accurately segment MRI brain tumors with very small training sets - https://arxiv.org/abs/2012.13321

(Ting) Idea 4: semi-supervised? The task is around exploring uncertainty measures in the context of glioma region segmentation, with resulting predictions that are: (1) confident when correct and (2) uncertain when incorrect of one or many of 3 labels (1) enhancing tumor, (2) tumore core, and (3) whole tumor

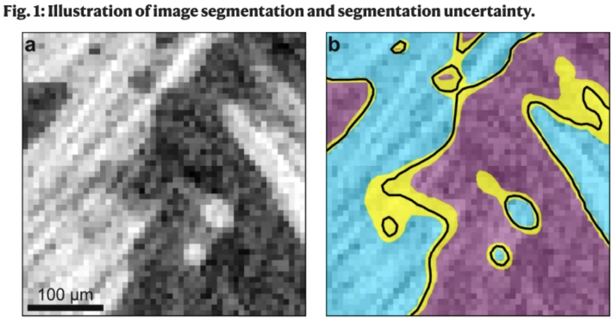
Dataset: In MICCAI [BraTs 2019 dataset] (task #3, quantification of uncertainty in segmentation), also similar tasks in MICCAI 2018 and 2020, etc

Background: 'Although the annotation would achieve a dice score over 0.9, the uncertainty still troubles. It might be also contradictory only to improve accuracy while ignoring this uncertainty. ' referred paper https://arxiv.org/pdf/2109.07045.pdf

Potential Methods: 2 big categories 1) uncertainty comes from each data point 2) uncertainty comes from model parameters; we have many probabilistic methods such as Bayesian NN and many ensemble methods in this area, I mainly found 2 papers interested with code. 1st paper:
https://arxiv.org/pdf/1907.03338.pdf
https://github.com/alainjungo/reliability-challenges-uncertainty
2nd paper: https://arxiv.org/abs/1906.04045
https://paperswithcode.com/paper/phiseg-capturing-uncertainty-in-medical-image

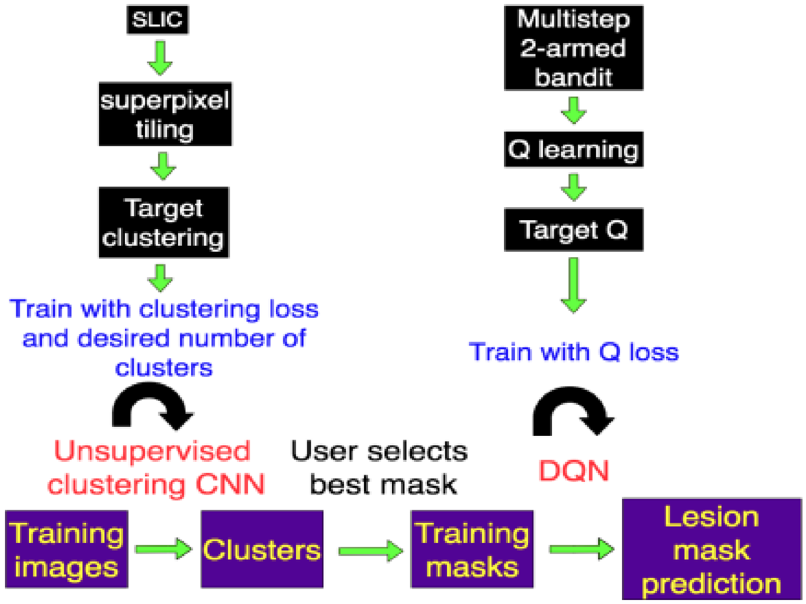
Visual representation of the question: https://www.nature.com/articles/s41467-021-25493-8

Fig. 1: Illustration of image segmentation and segmentation uncertainty.



A grayscale image (**a**) is segmented into white (blue region) and black (purple region) classes in (**b**), with black curves denoting one possible interface boundary between classes. The yellow region is a visual representation of the segmentation uncertainty that results from all possible image segmentations.

List of paper in uncertainty in medical image analysis:
https://github.com/JunMa11/MedUncertainty



Timeline

Final Report Due: May 4th

1. Download+Preprocessing+dataloader (2); how to use k-mean, unsupervised, etc (do research and plan for the next) (2) 3 days, due April 10
2. Baseline: Unsupervised clustering (k-mean)+ 3d-u net (2); unsupervised clustering CNN(2) ->Q learning(variation in cnn)(2) <= 2 week, due April 24
    a. Batch_size * label + h+w+d (expect input for k-mean/hirachical)
    b. Questions:
        i. Q learning: very little information in 3d
            1. Choices:
                a. 2-d
                b. 3-d
        ii. Too many parameters:
            1. Choices:
                a. Resize
                b. Pre-train model
                c. Simpler model
                d. Choose one modality (flair?) (yes)

New assignments: (Tuesday)

    c. 3d u net + unsupervised(k-mean, etc): xutong
    d. Unsupervised learning(k-mean, etc) + dice score: ting+muchen
    e. CNN(q -learning): victor
        i. 3d cnn+ deep q learning: https://arxiv.org/abs/1707.06783 (how about modality?)

Start with 3-d, if nothing work in 3-d q net, then change back to 2 d

3. tuning for step 2 (4) < 1 week, due May 1th
4. Write up & presentation, 3 days

Final report due: May 4th
Pitch & demo session: May 9th

Resource: 3dCNN-DQN-RNN: A deep reinforcement learning framework for semantic parsing of large-scale 3D point clouds

```
gpu_info = !nvidia-smi
gpu_info = '\n'.join(gpu_info)
if gpu_info.find('failed') >= 0:
  print('Not connected to a GPU')
else:
  print(gpu_info)
```

Resource:
A crash course on NumPy for images
https://scikit-image.org/docs/dev/user_guide/numpy_images.html?highlight=region
Convolution animations
https://github.com/vdumoulin/conv_arithmetic
Deep clustering paper
https://deepnotes.io/deep-clustering
Onboarding for practical machine learning research
https://suzyahyah.github.io/machine%20learning/2018/08/30/OnboardingML.html
Q learning
https://leonardoaraujosantos.gitbook.io/artificial-inteligence/artificial_intelligence/reinforcement_learning/qlearning_simple