Detecting Microsatellite Instability (MSI) in Colorectal Cancer Tissues

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Overview

01
Background

02
Problem Statement

03
Cancer Tissue Images

04
Deep Learning Model

05
Limitations & Recommendations

06
Conclusion

01 Background

Colorectal Cancer

UPDATED MAR 22, 2023, 04:00 AM

According to the National Cancer Centre Singapore, colorectal cancer is the most commonly diagnosed cancer affecting men in Singapore, and the second most common for women.

The Straits Times

Treatment:

- Surgery
- Chemotherapy
- Radiation therapy
- Targeted therapy
- Immunotherapy

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Immunotherapy

A class of treatments that take advantage of a person's immune system to help kill cancer cells. [1]

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Microsatellite Instability (MSI)

Microsatellites: short, repeated sequences of DNA

Cancer cells with high MSI have a defect in the ability to correct mistakes when DNA is copied in the cell.

Found most often in colorectal cancer, gastric cancer, and endometrial cancer, but may also be found in other cancer types. [2]

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The criteria to be eligible for immunotherapy is the presence of high microsatellite instability (MSI) in cancer cells.

[1] https://www.cancerresearch.org/cancer-types/colorectal-cancer
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Dr Esmé Lee

Consultant Pathologist, Pathology Department, SGH

Primary responsibility
Diagnose diseases - analyse tissue & body fluids using various techniques
e.g. microscopy & immunohistochemistry

Pain point
Current long waiting times for screening tumours for high MSI

Concern
Many patients who could potentially benefit from immunotherapy might not be identified in time for this treatment

Goal
Hopes for quick detection tool as a preliminary analysis so that patients can be sent for additional (genetic or immunohistochemical)[1] tests to confirm presence of MSI in their tumour.

[1] https://ascopubs.org/doi/full/10.1200/PO.17.00084

Problem Statement

How might we develop a deep learning model that accurately classifies colorectal cancer tissues as microsatellite stable (MSS) or microsatellite instable (MSI) based on histopathological image data,

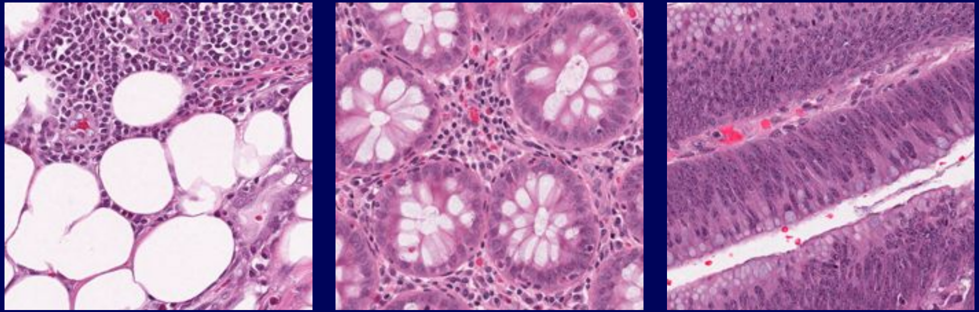
to screen patient suitability for immunotherapy treatment?

Trigger Warning

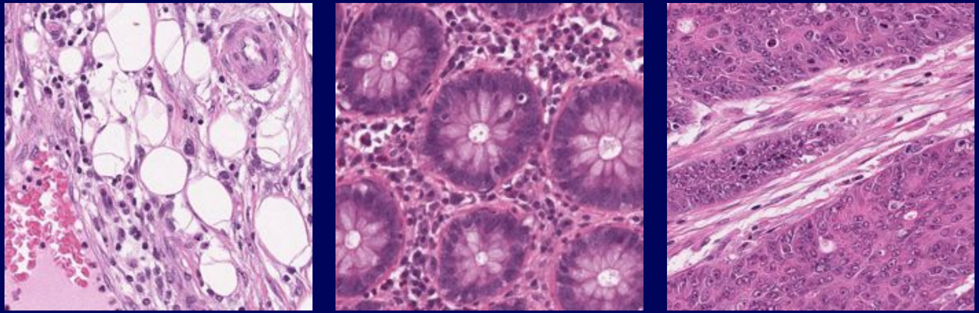
The following presents medically sensitive images of human tissue. For those who may find such imagery disturbing, please look away during the next few slides.

Histopathological Images

Microsatellite Stable (MSS)



Microsatellite Instable (MSI) / highly mutated (MSIMUT)



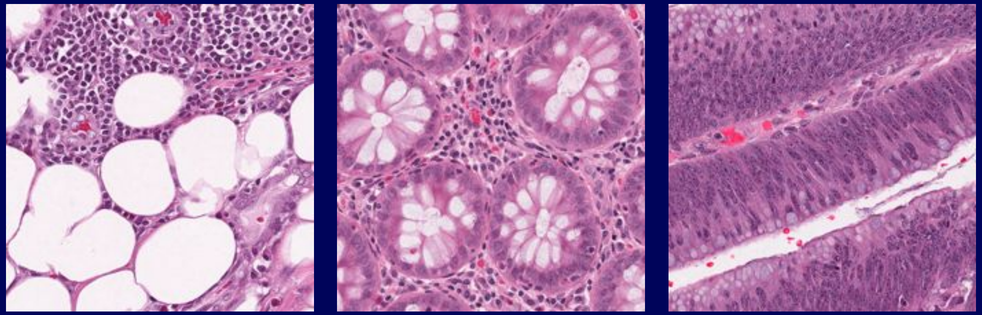
Histopathological Images

- All images are patches of colorectal cancer (tumor) tissues

- Grouped into two classes
  - MSS
  - MSIMUT

- 2000 images for the model to learn
- 2130 images to verify its accuracy

Microsatellite Stable (MSS)



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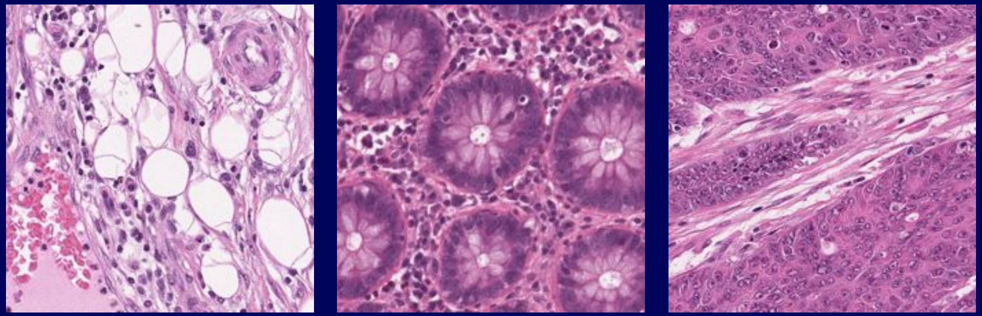


Pixel Values

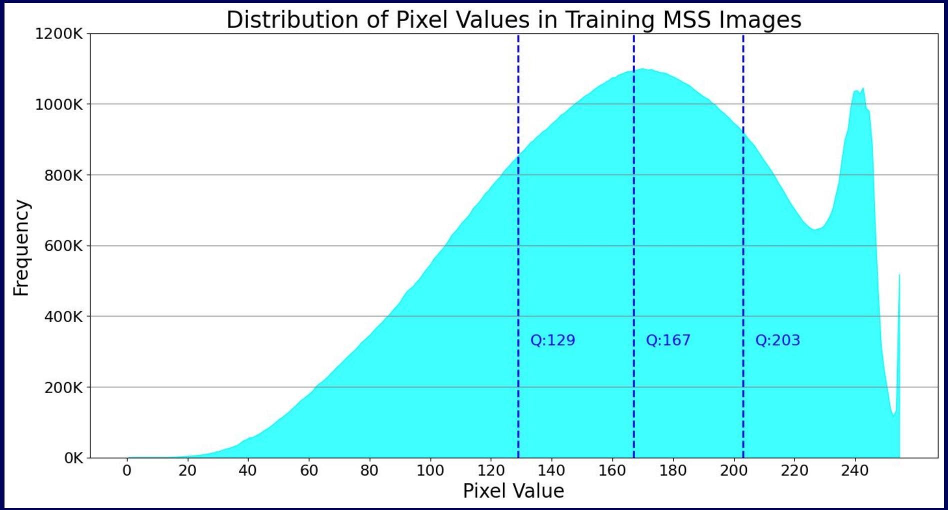
Comparison

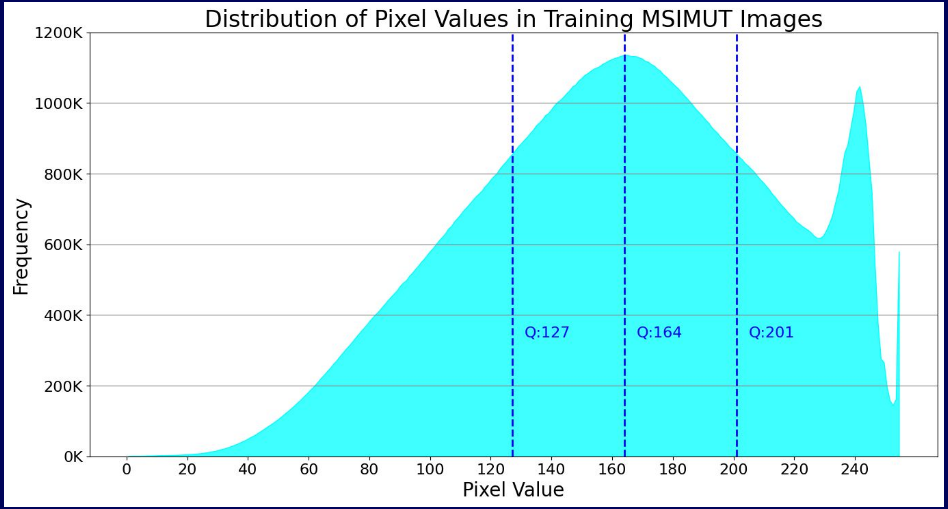
25th, 50th, 75th percentiles
- Similar pixel values

MSS slightly higher than MSIMUT
- MSS only slightly brighter than MSIMUT

Similar trend
- No significant difference in brightness between classes

Difficult to detect MSIMUT based on brightness





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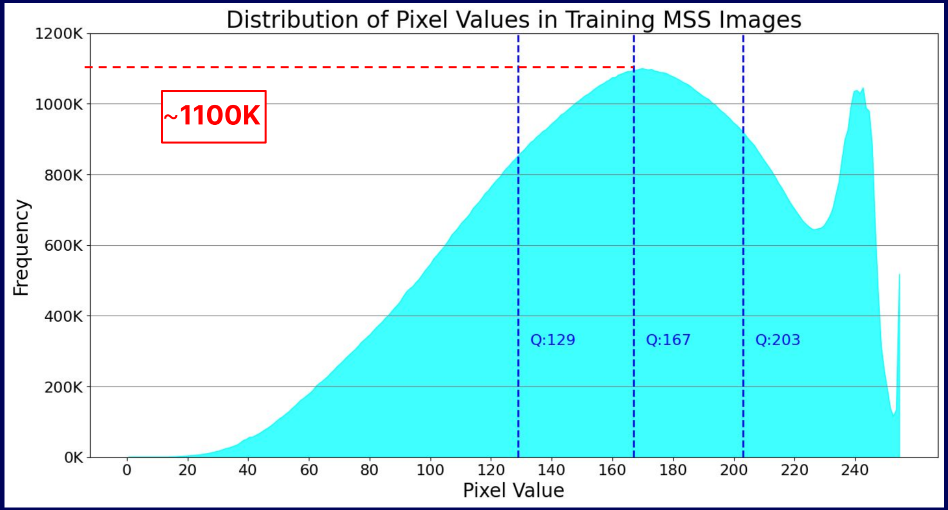
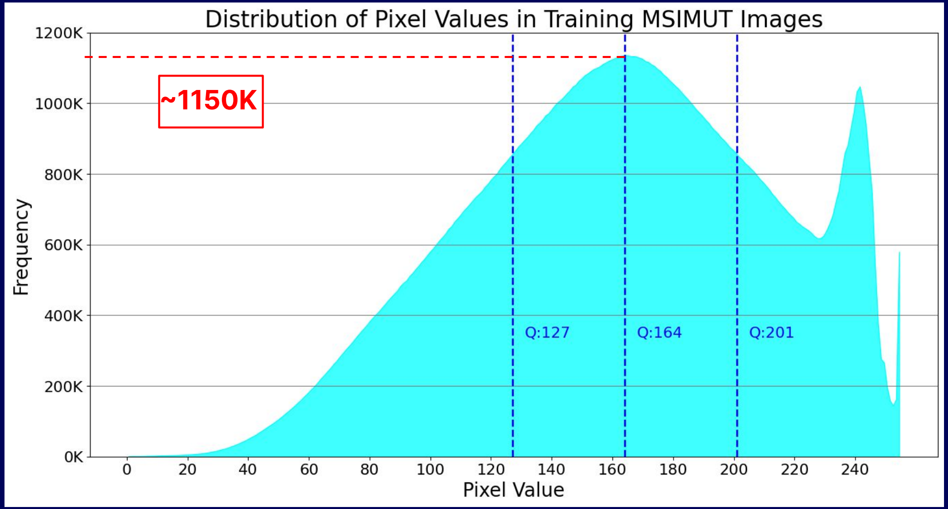
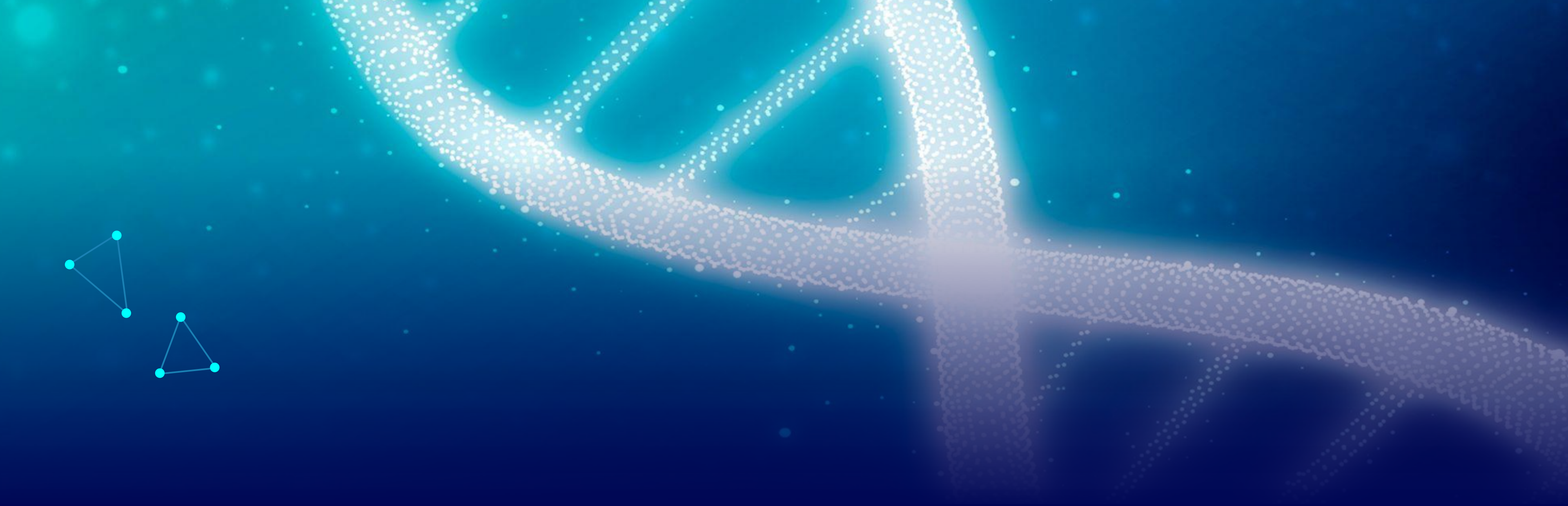
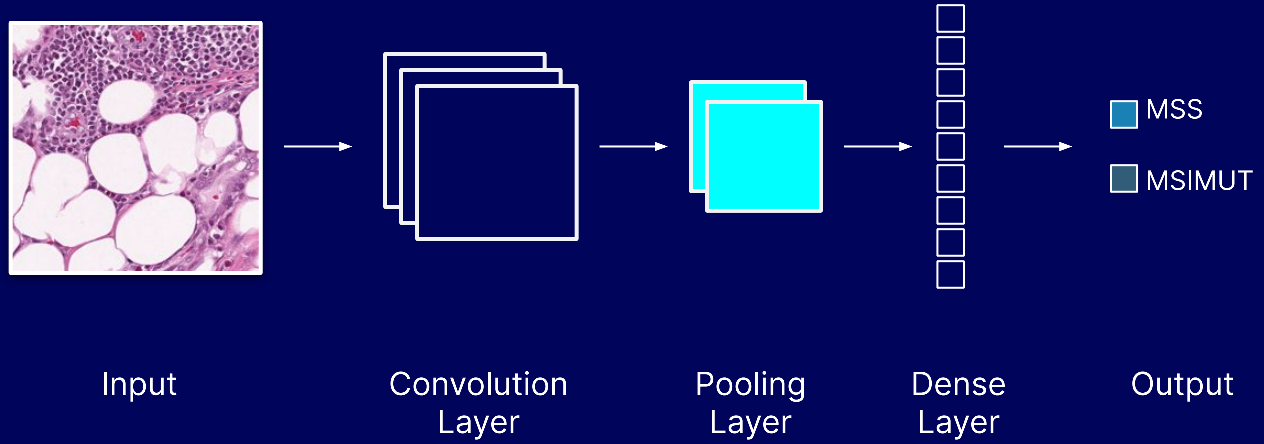






04 Deep Learning Model

Built Model


MSS
MSIMUT
Input
Convolution Layer
Pooling Layer
Dense Layer
Output

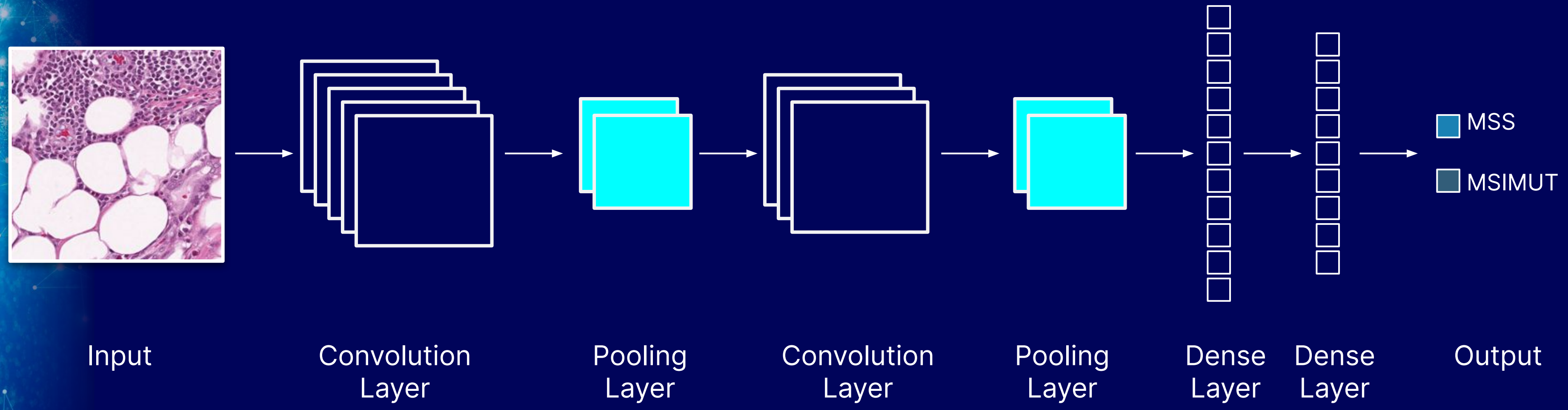
Built Model - Results

Metric	Result	Explanation
Accuracy	Inconsistent	The model either classifies all of the images as MSIMUT or classifies all of the images as MSS

Conclusion

This model is not conclusive, as its classification performance is likened to a 50:50 coin toss

EfficientNetV2M Model



EfficientNetV2M - Results

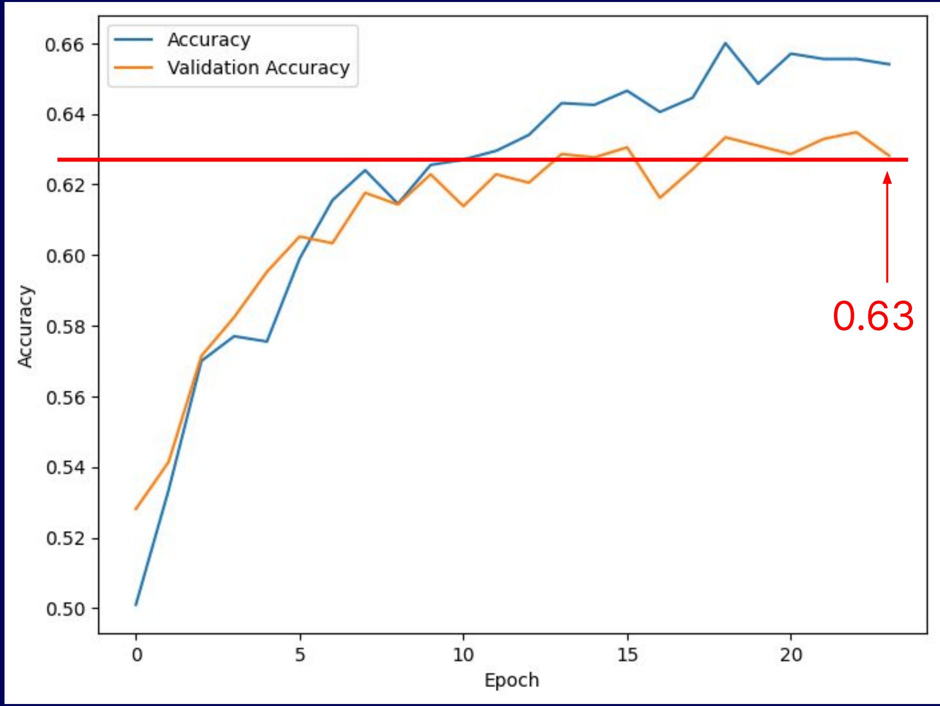
Metric	**Result** EfficientNetV2M	Explanation
Accuracy	61%	The model correctly classifies 61% of all the images

Conclusion

This model is more accurate than the earlier built model

EfficientNetV2M (tuned) - Results

Graph of Accuracy scores over epochs



EfficientNetV2M (tuned) - Results

Metric	**Result** EfficientNetV2M	**Result** EfficientNetV2M Tuned	**Explanation**
Accuracy	61%	63%	The model correctly classifies 63% of all the images

Conclusion

This model is more accurate than the untuned EfficientNetV2M model

Other Pre-Trained Models

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Models Evaluated:
ResNet50 & ResNet50V2

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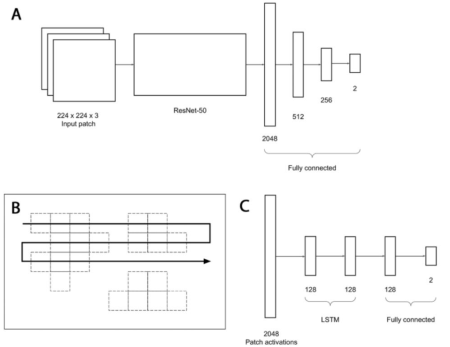
Convolutional neural network for feature extraction

The ResNet-50 architecture with an input size of 224 × 224 pixels was employed[36]. The ResNet-50 layers were then followed by the global average pooling layer, followed by two fully connected layers before terminating in two output nodes representing the FA and PT classes (Fig. 4A). Patch-level activation values from the global average pooling layer are intended to serve as representations of features learnt by the CNN model. The CNN model was first initialized with weights from the ImageNet database, and then further trained on the training data subset. The training subset was augmented with random vertical and horizontal image flips to make the model potentially more robust against variations in position and orientation.

Fig. 4: Details of convolutional neural network and recurrent neural network components.



A Architecture of convolutional neural network component. Numbers denote the dimensions of each layer. The global average pooling layer is shown in bold. **B** Row-wise arrangement of patch-level features that were fed into the recurrent neural network. Dashed lines denote valid patches generated from whole-slide image. **C** Architecture of recurrent neural network component. Numbers denote the dimensions of each layer. Patch activations were obtained from the global average pooling layer in the convolutional neural network component.

[1] Cheng, C.L., Md Nasir, N.D., Ng, G.J.Z. et al. Artificial intelligence modelling in differentiating core biopsies of fibroadenoma from phyllodes tumor. Lab Invest 102, 245–252 (2022). https://doi.org/10.1038/s41374-021-00689-0

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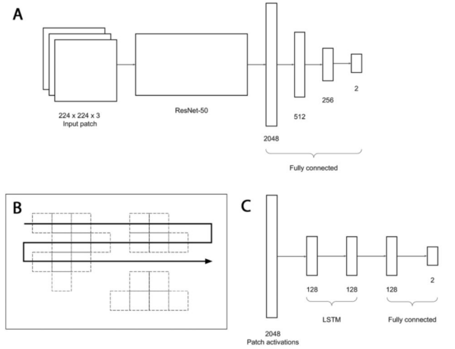

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Scalability Challenges:

- Migration to a cloud-based GPU platform, Google Colab, with expanded dataset
- Technical compatibility issues prevented reliable model deployment

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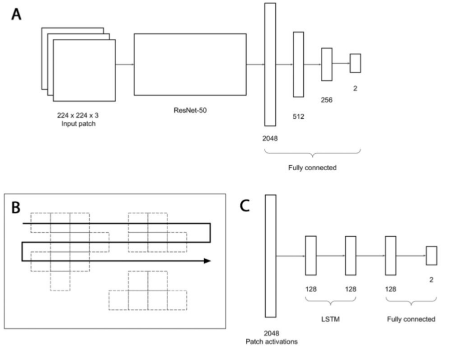

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Demo

Upload image here

Drag and drop files here

Limit 200MB per file • JPG, PNG, JPEG

Browse files

blk-YYWKICYFE...
86.6KB

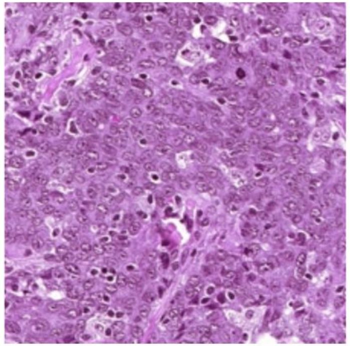
blk-YYPEEGMG...
110.5KB

blk-YYPDTKEGLT...
116.5KB

Showing page 1 of 4

Presence of Microsatellite Instability (MSI)

Image

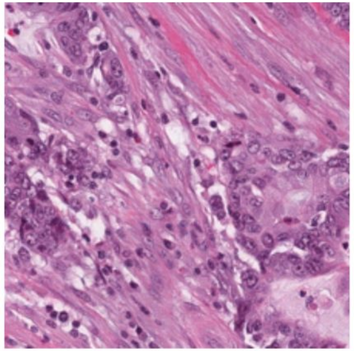


Uploaded Image : blk-YYPLFYPPMYCI-TCGA-AA-A01R-01Z-00-DX1.png

Prediction

Predicted Class : MSIMUT

Image

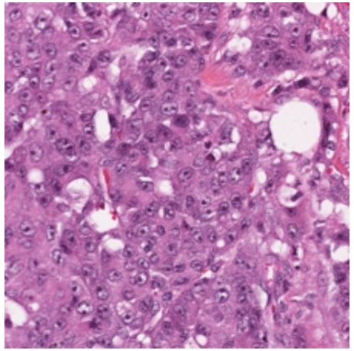


Uploaded Image : blk-YYQEKWYIESPP-TCGA-CM-5861-01Z-00-DX1.png

Prediction

Predicted Class : MSIMUT

Image



Uploaded Image : blk-YYQFGVNEYFWI-TCGA-5M-AAT6-01Z-00-DX1.png

Prediction

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05 Limitations & Recommendations

Limitations

Cost

Access to higher-end GPUs is costly, limiting the ability to train larger datasets on deeper neural networks.

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Technical Compatibility

Software/hardware compatibility issues arose when scaling from a CPU environment with a smaller dataset, to a GPU environment with a larger dataset, hindering the use of certain models (ResNet50, ResNet50V2).

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Time

Limited time prevented thorough troubleshooting on compatibility issues, and exploration of hyperparameter optimization potential.

Technical Compatibility

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Recommendations

Invest in Increased Computational Power

Access to lower-cost, high-end GPUs would allow for training larger datasets on more complex neural networks, potentially boosting performance.

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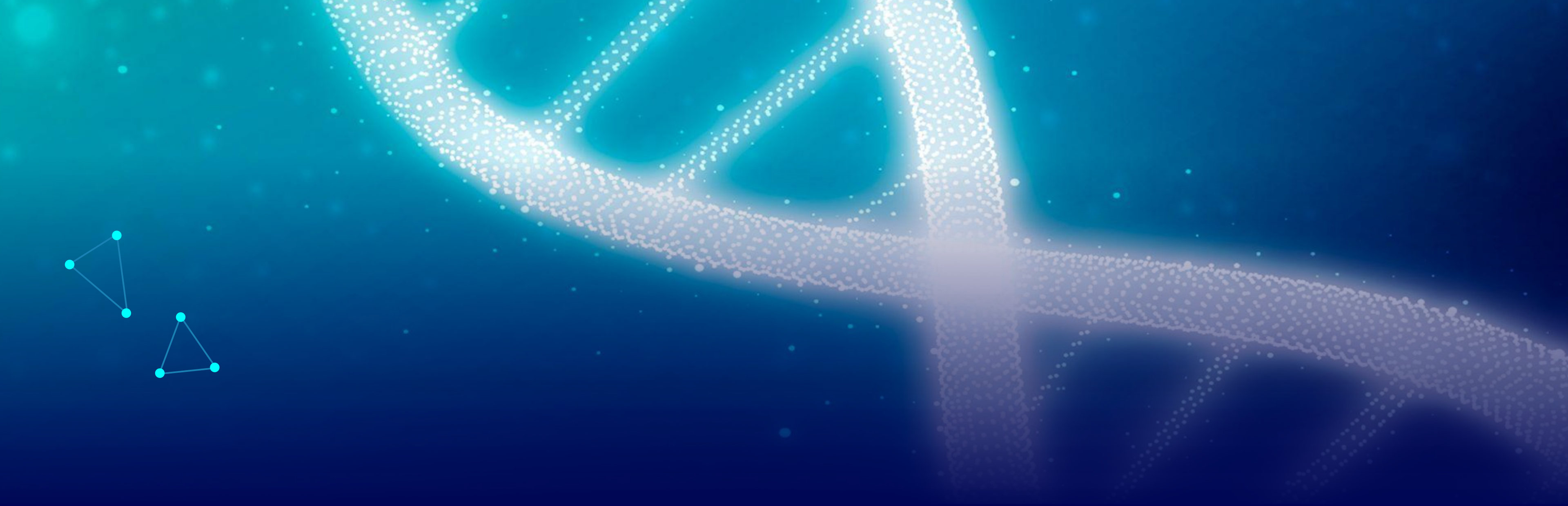
Time Allocation

Invest more time to address compatibility issues and thoroughly explore the potential of various hyperparameter combinations for optimal model performance.



06 Conclusion

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This work demonstrates the feasibility of a deep learning model for MSI detection based on histopathological images.

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This work demonstrates the feasibility of a deep learning model for MSI detection based on histopathological images.

- It is not intended to replace doctors.
- To provide doctors with a preliminary analysis to screen patients for suitability for immunotherapy treatment before they can be sent for additional tests to confirm the presence of MSI in their tumour(s).

Conclusion

Given additional time and resources for continued refinement, it has the potential to expand diagnostic capabilities to multiple cancer types.
E.g. gastric, breast, endometrial cancers

Potential to move into clinics to more efficiently tailor treatment strategies for patients.

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Visual MSI detection presents a challenge as visual distinctions are subtle and often imperceptible to the human eye, unlike a cat vs dog.

Differentiating MSI status is akin to detecting subtle radiographic findings, where even trained specialists may require additional diagnostic tools.

Thank You

linkedin.com/in/si-min-suen

github.com/s-simin

Appendix

MSI Testing

Duration

The test is batched and performed once every week

The test itself takes 3 working days to complete [1]

[1] https://www.kkh.com.sg/patient-care/areas-of-care/eLab-book/Pages/Microsatellite%20Instability%20-MSI-%20PCR%20Testing.aspx

MSI Testing

Microsatellite instability/ Mismatch Repair status[1]

A small number of bowel cancers have DNA changes called microsatellite instability or mismatch repair deficiency. Your doctor might check your bowel cancer for either of these changes.

Microsatellites are short, repeating arrangements (sequences) of DNA inside cells. Every time a cell divides, it makes new copies of these DNA sequences. Cells can correct any mistakes that happen in this process. Mismatch repair proteins identify and repair any mistakes made when cells make copies of DNA.

But if these mismatch repair processes are faulty, mistakes can happen when the cell divides causing changes in the new copies of DNA. Changes in the length of the new DNA sequence are called microsatellite instability. These changes can cause cells to grow abnormally.

Dependent on which test your doctor arranges they might describe your test results as:

- microsatellite stable (MSS) – this means they didn't see any instability
- microsatellite low (MSI low) – this means they saw a low level of instability
- microsatellite instability high (MSI high) – this means they saw a high level of instability
- mismatch repair deficient (MMRd) – this means that one, or more of the mismatch repair proteins aren't identified on testing
- mismatch repair proficient (MMRp) – this means that the MMR proteins are expressed normally

If a bowel cancer shows MMRd it is normally also MSI-high.

Your doctor can use the test results to help you decide whether to have further genetic tests. Further genetic tests can tell you whether there is an inherited cause for your bowel cancer.

[1] https://www.cancerresearchuk.org/about-cancer/bowel-cancer/getting-diagnosed/tests-on-your-bowel-cancer-cells

MSI Testing Methods

MSI is detected molecularly instead of visually [1]

Reliable Pan-Cancer Microsatellite Instability Assessment by Using Targeted Next-Generation Sequencing Data

JCO Precision Oncology

Volume 1

2017

‹ Previous Next ›

Introduction

Microsatellites are short, tandemly repeated DNA sequences of 1 to 6 bases scattered throughout the human genome. These sites are prone to DNA replication errors as a result of DNA polymerase slippage, which is effectively corrected through the mismatch repair (MMR) system. Deficiencies in MMR result in increased variation at genomic loci with mononucleotide repeats. Microsatellite instability (MSI) testing often is used to screen MMR protein status, and MSI polymerase chain reaction (PCR) and MMR immunohistochemistry (IHC) testing are particularly important for the clinical management of both colorectal cancer (CRC) and uterine endometrioid cancer (UEC). The National Comprehensive Cancer Network recommends MSI PCR/MMR IHC testing for all patients with CRC[1,2] and for patients with UEC at risk for Lynch syndrome.[1] MSI/MMR status has implications for prognosis,[3] screening for Lynch syndrome, and response to fluorouracil[3] and immune checkpoint inhibitor therapy.[4] Recently, the Food and Drug Administration granted pembrolizumab accelerated approval as the first drug approved for any solid tumor with a specific genetic feature (MSI-high [MSI-H] status) on the basis of new data that confirm its activity across 12 different cancer types, with complete responses observed in 21% of patients.[5]

[1] https://ascopubs.org/doi/full/10.1200/PO.17.00084

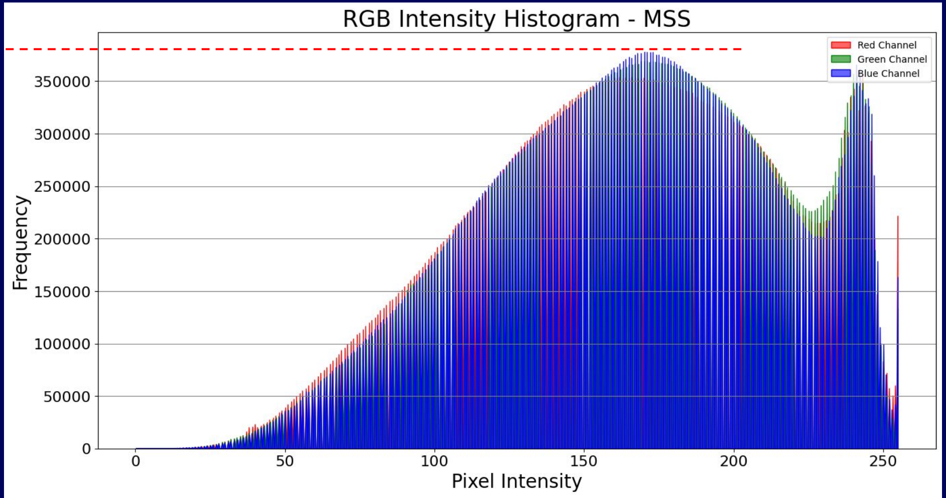
Pixel Values by RGB Channels

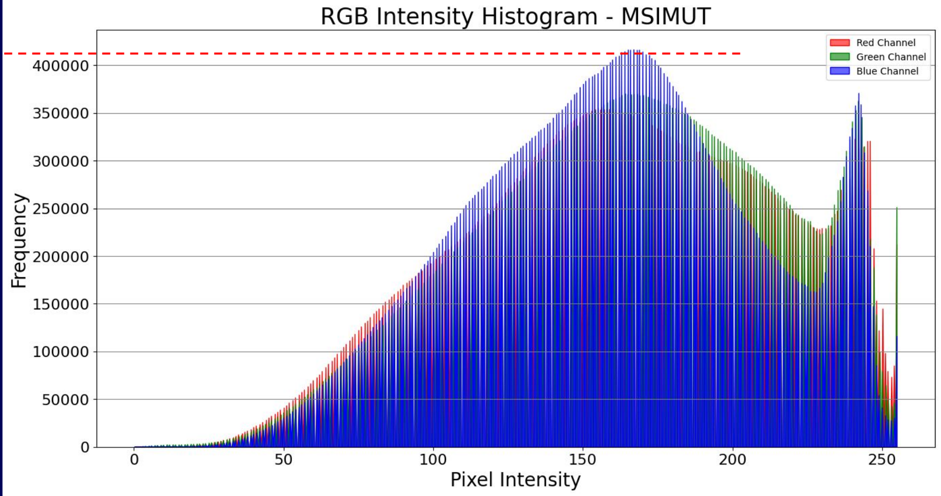
General observation:

- All 3 color channels have similar frequency of pixel values.
- Blue has the highest frequency of values around the median followed by green and lastly red.
- Distribution for MSS is more towards the right than for MSIMUT, indicating that values are slightly brighter for MSS images.
- MSIMUT images have higher frequency of pixel values in the median in the blue channel as compared to MSS images, which may imply that MSIMUT images have a slightly more bluish tint compared to MSS images.

Conclusion:

- Differences in pixel distribution between both classes are small
- No obvious differences can be detected by the naked eye.
- Therefore, turning to deep learning models allows us to uncover subtle patterns that may distinguish MSIMUT and MSS cancer tissues.

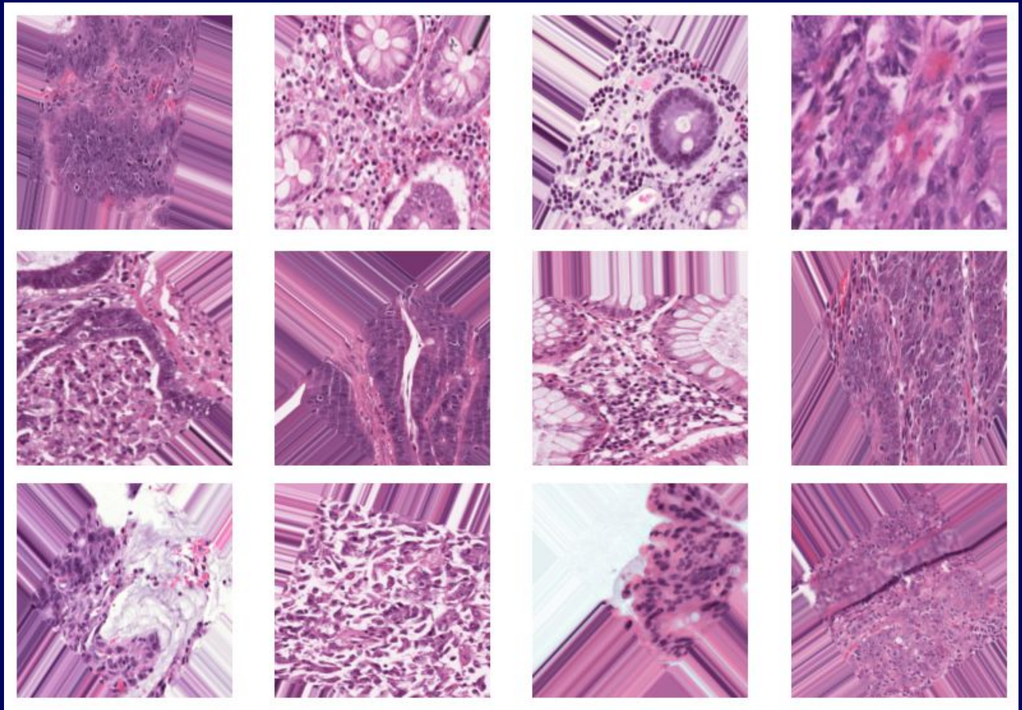




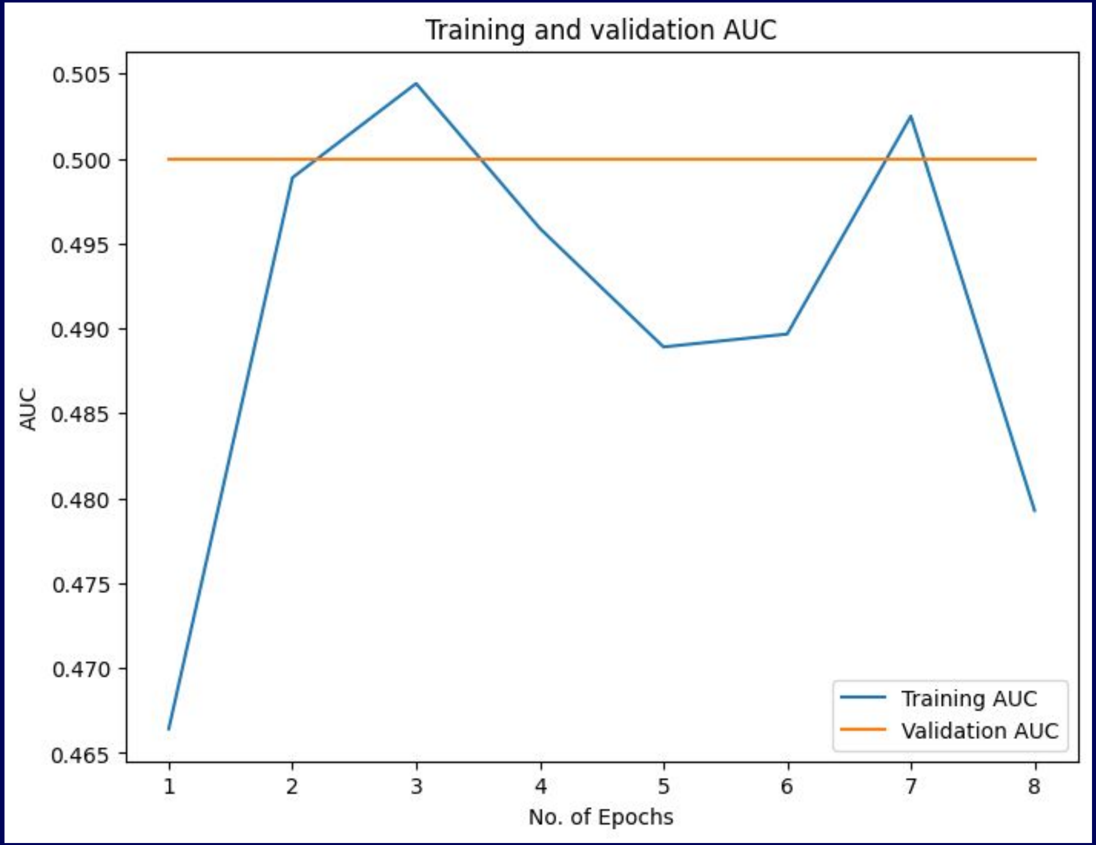
Augmented Images

The images were altered as follows:

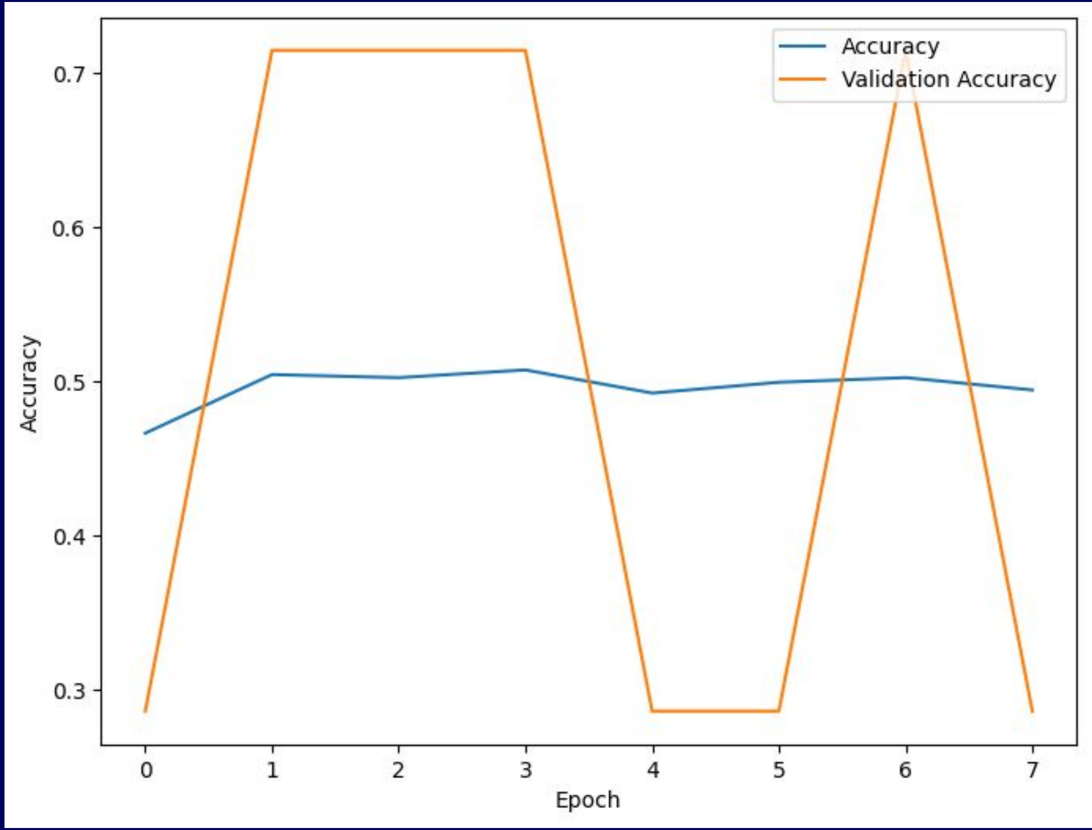
- Rotation: Randomly rotated up to 45 degrees in either clockwise or counterclockwise direction
- Horizontal Shift: Width randomly shifted by up to 20% in either direction
- Vertical Shift: Height randomly shifted by up to 20% in either direction
- Shearing: Sheared up to 20%
- Horizontal Flip: Flipped horizontally
- Zoom: Zooming into the images, up to 50% zoom



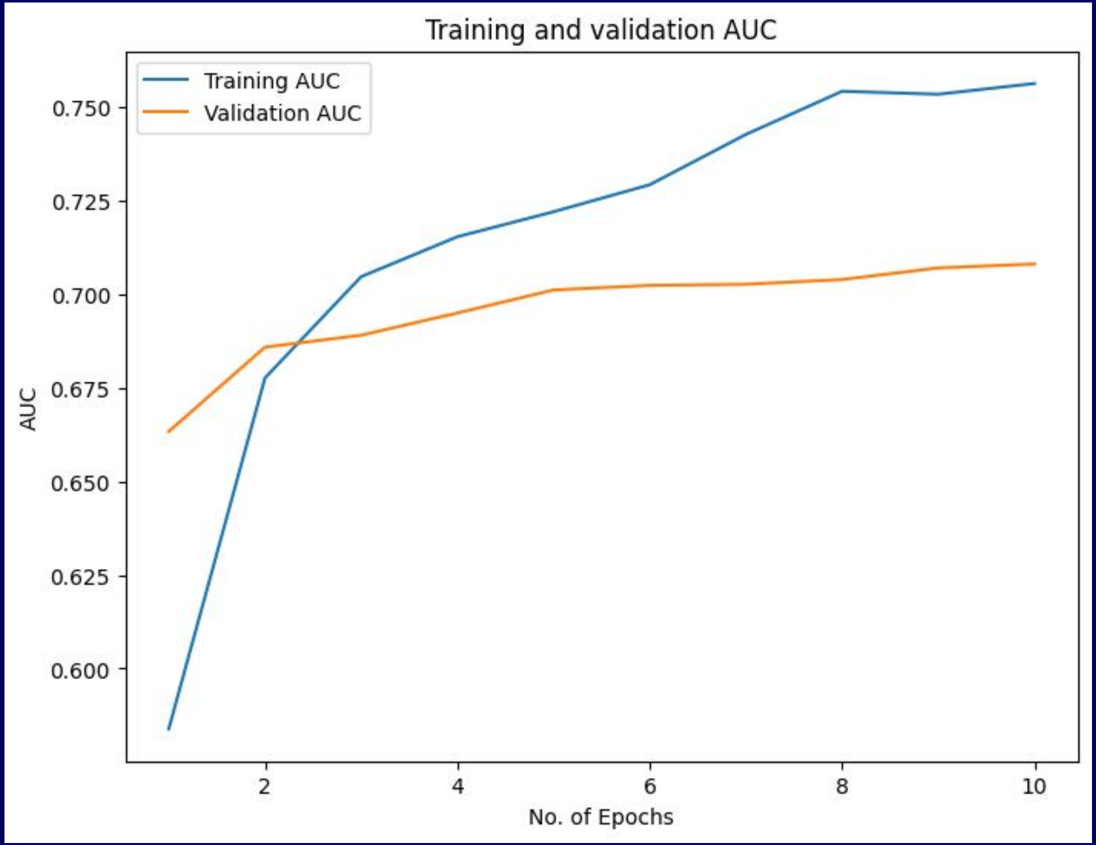
Created Model - AUC



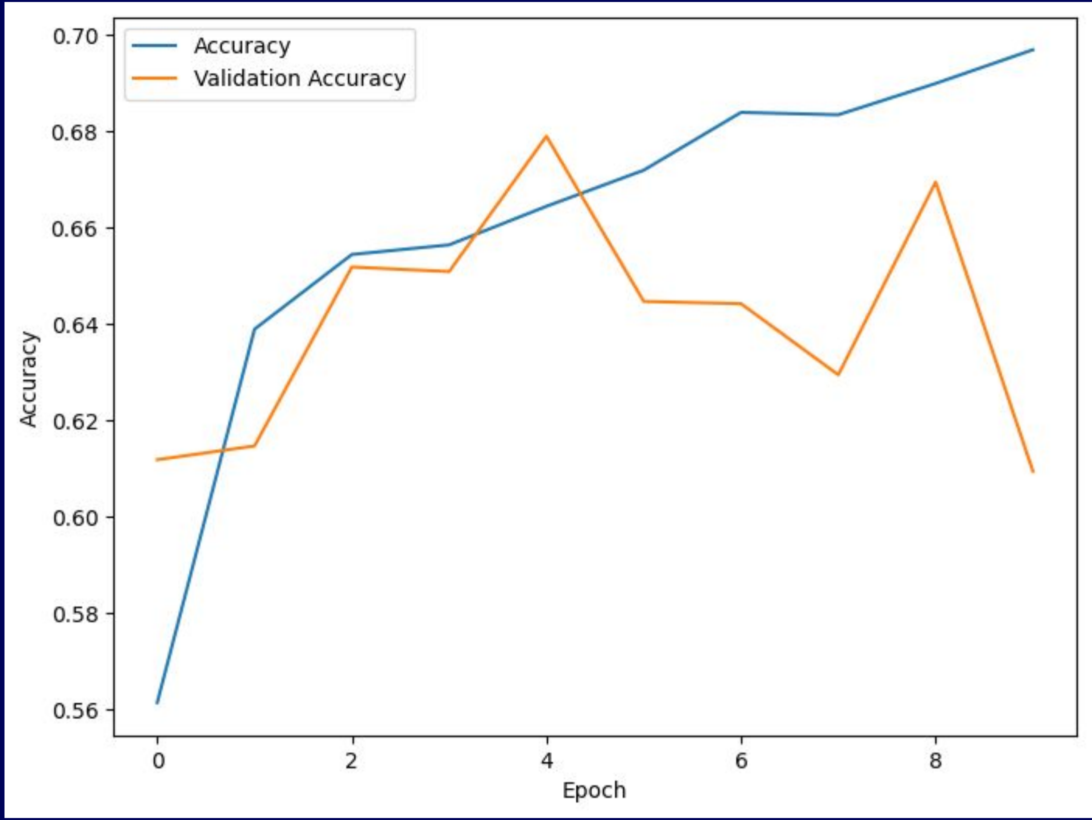
Created Model - Accuracy



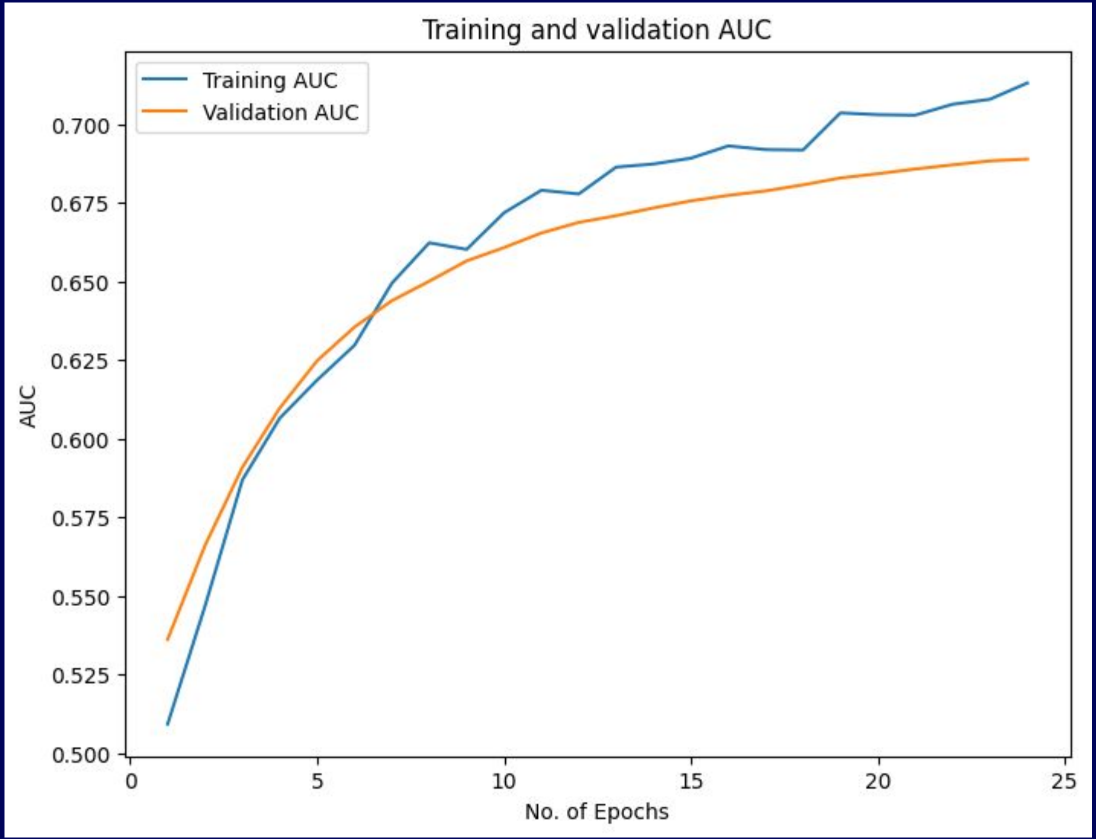
EfficientNetV2M - AUC



EfficientNetV2M - Accuracy



EfficientNetV2M (tuned) - AUC



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