Multi-Phase Cross-modal Learning for Noninvasive Gene Mutation Prediction in Hepatocellular Carcinoma

Jiapan Gu*1, Ziyuan Zhao*1, Zeng Zeng†1, Yuzhe Wang2, Zhengyiren Qiu2, Bharadwaj Veeravalli2
Brian Kim Poh Goh3, Glenn Kunnath Bonney4, Krishnakumar Madhavan4
Chan Wan Ying5, Lim Kheng Choon6, Thng Choon Hun5, and Pierce KH Chow7

Abstract—Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the fourth most common cause of cancer-related death worldwide. Understanding the underlying gene mutations in HCC provides great prognostic value for treatment planning and targeted therapy. Radiogenomics has revealed an association between non-invasive imaging features and molecular genomics. However, imaging feature identification is laborious and error-prone. In this paper, we propose an end-to-end deep learning framework for mutation prediction in APOB, COL11A1 and ATRX genes using multiphasic CT scans. Considering intra-tumour heterogeneity (ITH) in HCC, multi-region sampling technology is implemented to generate the dataset for experiments. Experimental results demonstrate the effectiveness of the proposed model.

Clinical relevance The proposed framework applied deep learning and multi-region sampling to predict gene mutations based on multi-phase 3D CT scans, achieving 75% average accuracy. The architecture can be implemented to provide clinical diagnostic and predictive oncology services.

I. INTRODUCTION

Liver cancer is one of the leading causes of cancer-related deaths in many parts of the world and one of the most common cancers among males in Singapore [1]. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer which is the sixth most common cancer in the world and the fourth leading cause of cancer mortality globally [2]. HCC is known to be a highly heterogeneous disease [3], especially in genetic level, which means the lack of consistency in the therapeutic outcome and thus may lead to the difficulty in clinic for designing targeted therapy and precision medicine. Recent studies have identified several mutations in genes associated with HCC. For instance, telomerase reverse transcriptase (TERT) promoter, TP53/p53 and CTNNB1/beta-catenin have been identified as the most commonly mutated genes in HCC [4].

In general, current methods of genome sequencing require liver biopsy and specialized equipment, which limit the routine usage. Besides, these invasive sampling methods are destructive, and can not provide multiple continuous snapshots. Many research work have demonstrated that different imaging features in computed tomography (CT) scans are correlated with the global gene expression of primary human liver cancer, e.g., Segal et al. used 28 features out of over 100 image features manually extracted from CT scans to reconstruct 78% of the gene expression patterns in HCC patients [5]. Such an integrated diagnostic approach between Radiology and Genomics is termed as “radiogenomics” [6].

However, the development of radiogenomics for HCC is critically impeded by the following challenges. First, Dynamic CT images are widely used in liver CT scanning. Multi-phase CT scans are divided into four phases, i.e., non-contrast (NC) phase, arterial (ART) phase, portal venous (PV) phase, and delay (DL) phase in Fig. 1. Varying object sizes, e.g., lesions and tumors make it difficult to obtain comprehensive information in dynamic multi-modal images. Second, there is intra-tumour heterogeneity (ITH) in HCC [7], which means gene mutations are different in different parts of tumors. This scenario makes machine learning approaches, especially convolutional neural network (CNN) very difficult to train for gene mutation prediction in HCC, as the input

Fig. 1. Illustration of the appearance of tumors in different phases. The appearance of the tumor and non-tumor (background) in NC and PV phase is similar. However, the appearance of the tumor and non-tumor is quite different in ART phase.
slices of the whole tumor with different gene mutations are assigned the same mutation label. Third, radiogenomics requires quantitative imaging features annotated by expert radiologists, which is laborious, time-consuming and suffers from high intra / inter-observer variance.

In this work, we propose a deep CNN framework to address the challenges of automatic gene mutation prediction in HCC. More specifically, a multi-stream CNN is applied for multi-phase cross-modal feature extraction followed by an aggregation layer to effectively fuse and utilize 4D information. Besides, some image traits (biomarkers) [8] identified by radiologists are aggregated as auxiliary information for decision making. Extensive experiments are implemented on the dataset collected from different hospitals in Singapore, in which, multi-region sampling is applied to avoid mismatch problems in ITH. Experimental results and analysis demonstrate the effectiveness of the proposed framework for mutation prediction in APOB, COL11A1, and ATRX genes, which is easily implemented to predict more gene mutations if sufficient data are provided.

II. RELATED WORK

A. Radiogenomics and AI

As a rapidly developing field, radiogenomics has shown potential value for diagnostic and therapeutic strategies. In the fields of radiomics and radiogenomics, high-throughput extraction of qualitative and quantitative imaging features from radiographs is required to obtain diagnostic, predictive, or prognostic information [9]. To explore the relationships between gene expression and imaging, Segal et al. [5] defined ‘units of distinctiveness’, termed as ‘traits’ from qualitative imaging features of liver cancer and reconstructed nearly 80% of the global gene expression profiles using 28 image traits. Aerts et al. [10] proposed a quantitative strategy for the correlation between CT images and genome data, which reflects great clinical significance. These contribute to the development of emerging technologies such as computer vision and deep learning in radiogenomics [11], [12]. The use of artificial intelligence (AI) for genomics and molecular profiling of cancers will be hugely beneficial as it is non-invasive and captures a comprehensive view of the tumor. However, most of the current radiogenomics analysis in liver cancer extracted image features from single-phase images which did not consider the changes of shapes and sizes of tumors across phases. Besides, merging multiphasic information remains a critical issue.

B. Multi-region Sampling

Genomic profiling methods behind most of the current radiogenomics analysis rely on single biopsy samples, which often reflects a part of the tumor. These methods significantly underestimate intratumoral genomic heterogeneity in cancers especially in HCC. A large proportion of HCC displays a clear geographic segregation where spatially closer sectors are genetically more similar [7]. Furthermore, this genetic heterogeneity in HCC influences the training process of CNNs. Slices with different mutations are put into networks with the same mutation label, which misleads the training process of networks. Zhai et al. [7] first carried out research on intra-tumour heterogeneity (ITH) in HCC using multi-region sampling. As shown in Fig. [2] first, tumor and sectors were annotated on the CT scans. Then a central slice is cut from the patient tumor, and a linear grid of tumor sectors is then harvested and examined for further multiomics analysis. The dataset used in this work adopted multi-region sampling.

III. METHODOLOGY

The proposed method for gene mutation prediction is illustrated in Fig. [3] which consists of three main components: (i) Multi-stream Feature Extraction, (ii) Feature Aggregation, and (iii) Auxiliary Embedding. First, the processed images from different phases are put into four deep CNN blocks separately for feature extraction; then a lightweight CNN is applied to fuse multi-stream information for further prediction [13]. For better prediction, biomarkers annotated by doctors are embedded into the network as auxiliary information to improve the prediction accuracy.

In multi-stream feature extraction, Residual Neural Network (ResNet) [14], [15] is implemented for deep feature extraction, in which some layers are skipped through shortcut connection to avoid the vanishing gradient problem. The 3D ResNet-18 pre-trained on ImageNet [16] is applied.

In feature aggregation, feature maps from four streams are combined by concatenation along the channel dimension, followed by a shallow network including one convolution layer (512, 1 × 1 × 1), one batch normalization layer, and one ReLU activation layer for dimensionality reduction in the channel dimension space.

Compared to using images only, some image traits (biomarkers) are embedded into the final fully connected

More details of multi-omics discovery platform PLANET are shown in: https://www.nccs.com.sg/research-innovation/research-programmes/disease-focus-liver
layer. These image traits are the characteristics described by radiologists, which can be regarded as indicators of physiologic and pathologic processes in response to various diagnostic or therapeutic procedures. In our experiments, nine kinds of biomarkers are annotated as binary variables by doctors, such as “presence of intra-tumoral vessels”. More details can be found in Fig. 5. These biomarkers are treated as a series of binary numbers followed by a fully connected layer with a size of 128. The output of the fully connected layer is combined with image features for further prediction. Binary cross-entropy is used as the loss function for the binary classification problem.

IV. EXPERIMENTS

A. Dataset and implementation

The dataset has been collected from multiple hospitals located in Singapore, which consists of 3D multiphasic CT scans, genomics information and biomarker sequences from 27 patients with the approval of the Institutional Review Board. Due to various sources of data, 14 patients with all four phases were considered in our experiments. The DNA sequencing was based on multi-region sampling, in which, gene mutations are different from different sectors of the tumor, therefore, our training samples are on the basis of the sector rather than patient. The ground truth mutation labels were extracted from the DNA sequencing, and the corresponding sectors were extracted from the patients’ CT scans. Because of various sizes of sectors, the sectors were padded with zeros to keep the same size in length and width, and five adjacent slices along z-axis based on the central slice of sector were cropped from volumetric images to probe the spatial information along the third dimension, see Fig. 4. Typically, HCC in different regions of the liver is clinically scored on the basis of their CT image features, such as size and margin. Therefore, nine biomarkers were annotated by radiologists based on CT scans.

Because of data imbalance in different gene mutations, prevalent mutated genes, i.e., APOB, COL11A1 and ATRX are considered in this study. Given that the mutations are not mutually exclusive, a separate model per mutation is used to alleviate the problem of data imbalance among mutations. We compare our model with single-stream CNN using single-phase CT scans, in which, ResNet-18 is trained on images from one of the four phases, e.g., Single Stream (ART phase). To explore the effectiveness of auxiliary embedding in the proposed architecture, the proposed model without biomarkers is also implemented, i.e., Proposed (without biomarkers). To validate the stability of the proposed model, leave-one-out cross validation (LOOCV) is performed, in which, each patient is excluded from the training set one at a time and then classified on the basis of the predictor built from the data for all the other patients.

| Methods                        | APOB  | COL11A1 | ATRX  |
|--------------------------------|-------|---------|-------|
| Single Stream (NC phase)       | 58.9% | 51.3%   | 60.1% |
| Single Stream (ART phase)      | 70.1% | 55.5%   | 57.5% |
| Single Stream (PV phase)       | 64.1% | 56.4%   | 68.1% |
| Single Stream (DL phase)       | 68.4% | 56.9%   | 64.5% |
| Proposed (without biomarkers)  | 77.3% | 67.7%   | 73.4% |
| Proposed                       | 76.7% | 71.7%   | 76.5% |
B. Results and discussion

Table I summarizes the results of all methods on the dataset. The proposed method outperforms all other methods in different gene mutations, which demonstrates the effectiveness of feature fusion cross phases. Besides, biomarkers can help to improve the accuracy of mutation prediction in COL11A1 and ATRX, which proves the feasibility of biomarkers in radiogenomics analysis.

To further explore the correlations among biomarkers and gene mutations, a correlation map is generated with the whole dataset, as shown in Fig. 5. We find that most of these biomarkers are correlated with gene mutations. Furthermore, some gene mutations are correlated with each other. We performed hierarchical clustering of the correlation map and found that some gene mutations are grouped into the same cluster, therefore, the complex relationships among gene mutations can be modeled using graph neural networks for prediction in the future [17].

![Correlation map and hierarchical clustering based on pairwise Pearson correlation coefficients of biomarkers and gene mutations. Some gene mutations are correlated (red) or anti-correlated (blue).](image)

V. CONCLUSIONS AND FUTURE WORK

In this work, we discuss the challenges and standard-of-care imaging technologies in HCC radiogenomics analysis. Considering the intra-tumour heterogeneity (ITH) in HCC, we propose a sector-based multi-stream cross-modal deep learning framework for mutation prediction in genes. Multiphasic CT scans are processed and extracted by multi-stream CNN followed by feature aggregation. Moreover, the biomarkers are embedded into the final layer for further prediction. Experimental results on the dataset show the effectiveness of the proposed framework on mutation prediction in APOB, COL11A1, and ATRX genes. However, our framework is extendable to more gene mutations with sufficient training data. The correlation between the gene mutations and biomarkers not only validate the predictive value of biomarkers, but also show the significant correlations among different gene mutations. In our future work, the relationships between gene mutations will be analyzed and considered as predictor variables.

REFERENCES

[1] “Liver Cancer Causes, Symptoms, Treatment,” https://www.healthhub.sg/a-z/diseases-and-conditions/60/livercancer, [Online; accessed 12-Apr-2020].
[2] Ju Dong Yang, Pierre Hainaut, Gregory J Gores, Amina Amadou, Amelie Plymouth, and Lewis R Roberts, “A global view of hepatocellular carcinoma: trends, risk, prevention and management,” Nature Reviews Gastroenterology & Hepatology, pp. 1–16, 2019.
[3] Tommaso A Dragani, “Risk of hcc: genetic heterogeneity and complex genetics,” Journal of hepatology, vol. 52, no. 2, pp. 252–257, 2010.
[4] Chinthalapally V Rao, Adam S Asch, and Hiroshi Y Yamada, “Frequently mutated genes/pathways and genomic instability as prevention targets in liver cancer,” Carcinogenesis, vol. 38, no. 1, pp. 2–11, 2016.
[5] Eran Segal, Claude B Sirlin, Clara Ooi, Adam S Adler, Jeremy Golubt, Xin Chen, Bryan K Chan, George R Malicu, Christopher T Barry, Howard Y Chang, et al., “Decoding global gene expression programs in liver cancer by noninvasive imaging,” Nature biotechnology, vol. 25, no. 6, pp. 675, 2007.
[6] Aaron M Rutman and Michael D Kuo, “Radiogenomics: creating a link between molecular diagnostics and diagnostic imaging,” European journal of radiology, vol. 70, no. 2, pp. 232–241, 2009.
[7] Weiwei Zhai, Tony Kiat-Hon Lim, Tong Zhang, Su-Ting Phang, Zeng Zhang, Peiyong Guan, Ming-Hwee Ng, Jia Qi Lim, Fei Yao, Zheng Li, et al., “The spatial organization of intra-tumour heterogeneity and evolutionary trajectories of metastases in hepatocellular carcinoma,” Nature communications, vol. 8, pp. 4565, 2017.
[8] Matthias Ocker, “Biomarkers for hepatocellular carcinoma: Whats new on the horizon?” World journal of gastroenterology, vol. 25, no. 35, pp. 3974, 2018.
[9] Virendra Kumar, Yuhua Gu, Satrajit Basu, Anders Berglund, Steven A Eschrich, Matthew B Schabath, Kenneth Forster, Hugo JW Aerts, Andre Dekker, David Fenstermacher, et al., “Radiomics: the process and the challenges,” Magnetic resonance imaging, vol. 30, no. 9, pp. 1234–1248, 2012.
[10] Hugo JW Aerts, Emmanuel Rios Velazquez, Ralph TH Leijenaar, Chintan Parmar, Patrick Grossmann, Sara Carvalho, Johan Bussink, René Monshouwer, Benjamin Haibe-Kains, Derek Rietveld, et al., “Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach,” Nature communications, vol. 5, pp. 4006, 2014.
[11] Shuai Li, Hongze Han, Dong Sui, Aimin Hao, and Hong Qin, “A novel radiogenomics framework for genomic and image feature correlation using deep learning,” in 2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM), IEEE, 2018, pp. 899–906.
[12] Nova F Smedley and William Hsu, “Using deep neural networks for radiogenomic analysis,” in 2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018), IEEE, 2018, pp. 1529–1533.
[13] Xulei Yang, Zeng Zeng, Sin G Teo, Li Wang, Vijay Chandrasekhar, and Steven Hoi, “Deep learning for practical image recognition: Case study on kaggle competitions,” in Proceedings of the 24th ACM SIGKDD International Conference on Knowledge Discovery & Data Mining, ACM, 2018, pp. 923–931.
[14] Kaiming He, Xiangyu Zhang, Shaoqing Ren, and Jian Sun, “Deep residual learning for image recognition,” in IEEE Int. Conf. on Computer Vision and Pattern Recognition, 2016, pp. 770–778.
[15] Ziyuan Zhao, Kerui Zhang, Xuejie Hao, Jing Tian, Matthew Chin Heng Chua, Li Chen, and Xin Xu, “Bira-net: Bilinear attention net for diabetic retinopathy grading,” in 2019 IEEE International Conference on Image Processing (ICIP), IEEE, 2019, pp. 1385–1389.
[16] Jia Deng, Wei Dong, Richard Socher, Li-Jia Li, Kai Li, and Li Fei-Fei, “Imagenet: A large-scale hierarchical image database,” in 2009 IEEE conference on computer vision and pattern recognition. Ieee, 2009, pp. 248–255.
[17] Chen Chen, Kenli Li, Sin G Teo, Xiaofeng Zou, Kang Wang, Jie Wang, and Zeng Zeng, “Gated residual recurrent graph neural networks for traffic prediction,” in Proceedings of the AAAI Conference on Artificial Intelligence, 2019, vol. 33, pp. 485–492.