

IMSUT International Joint Usage/Research Center
International Project-completion Report (FY2022 ver.)

Date of submission: **Month / Date / Year**

Principal Investigator	Position, Institution: Associate Professor, Monash University
	Name: Jiangning Song
IMSUT Host Researcher	Division: Division of Health Medical Intelligence, Human Genome Center, IMSUT
	Name: Seiya Imoto
Project Title	Artificial intelligence-enabled cancer diagnosis, type classification and mutation prediction by leveraging deep learning and histopathology image analysis
Duration	From 04/01/2022 to 3/31/2023
Project Members	
Name	Position, Institution
Jiangning Song	Monash University, Biochemistry & Mol Biology
Seiya Imoto	Human Genome Center, IMSUT
Roger Daly	Monash University, Biochemistry & Mol Biology
David Thomas	Garvan Institute for Medical Research, Sydney
Rui Yamaguchi	Aichi Cancer Center Research Institute, Nagoya
Yaohong Zhang	Human Genome Center, IMSUT
Shuichi Kawano	The University of Electro-Communications
Tim Peng	Monash University/Biochemistry & Mol Biology
Yanan Wang	Monash University/Biochemistry & Mol Biology
Zhikang Wang	Monash University/Biochemistry & Mol Biology
Project-completion Report	

Supported by the FY2022 IMSUT International Joint Research Project fund, we have developed several new computational approaches for the histopathology image analysis and accordingly published two peer-reviewed papers. The major research findings and achievements include:

- 1) Development of a novel multiplex-detection-based multiple instance learning (MDMIL) to classify whole slide images (WSIs) for diagnostic pathology: The key challenge of multiple instance learning (MIL) on WSI classification is to discover the critical instances that trigger the bag label. Here, we propose a novel multiplex-detection-based multiple instance learning (MDMIL) which targets tumor heterogeneity by multiplex detection strategy and feature constraints among samples. Specifically, the internal query generated after the probability distribution analysis and the variational query optimized throughout the training process are utilized to detect potential instances in the form of internal and external assistance, respectively. The multiplex detection strategy significantly improves the instance-mining capacity of the deep neural network. Meanwhile, a memory-based contrastive loss is proposed to reach consistency on various phenotypes in the feature space. The novel network and loss function jointly achieve high robustness towards tumor heterogeneity. We conduct experiments on three computational pathology datasets. Benchmarking on the three datasets illustrates that our proposed MDMIL approach achieves superior performance over several existing state-of-the-art methods.
- 2) Development of PFresGo, an attention mechanism-based deep-learning approach for protein annotation: We have recently proposed a new approach, termed PFresGO, which is an attention mechanism-based deep-learning approach for protein annotation. It incorporates hierarchical structures in Gene Ontology (GO) graphs and advances in natural language processing algorithms for the functional annotation of proteins. It can also identify functionally important residues in protein sequences by assessing the distribution of attention weightings, which is directly interpretable and can be conversely applied to validate the predicted protein function at a residue level.

Research Results from the Project

<Publications>

1. Wang Z, Bi Y, Pan T, Wang X, Bain C, Bassed R, Imoto S, Yao J, Daly RJ, Song J. Targeting tumor heterogeneity: multiplex-detection-based multiple instance learning for whole slide image classification. *Bioinformatics*. 2023 Mar 1;39(3):btad114. doi: 10.1093/bioinformatics/btad114.
2. Pan T, Li C, Bi Y, Wang Z, Gasser RB, Purcell AW, Akutsu T, Webb GI, Imoto S*, Song J*. PFresGO: an attention mechanism-based deep-learning approach for protein annotation by integrating gene ontology inter-relationships. *Bioinformatics*. 2023 Mar 1;39(3):btad094. doi: 10.1093/bioinformatics/btad094.

<Patent Applications>

N.A.

Days of visits to IMSUT

Name	Position, Institution	Sex	Age	Visits to IMSUT (Days)
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Jiangning Song	Associate Professor, Monash University	Male	40 or older	From September 2 to September 10, 2022
Zhikang Wang	PhD student, Monash University	Male	35 or younger	From October 16 to October 31, 2022
Jing Xu	PhD student, Monash University	Female	35 or younger	January 29 to February 5, 2023
		Pull-down ▼	Pull-down ▼	
Name	Position, Institution	Sex	Age	Online Meetings (Days)
Jiangning Song	Associate Professor, Monash University	Male	40 or older	6 times of meetings and discussions with Prof. Imoto Seiya, A/Prof. Yaozhong Zhang, and Mr. Zhikang Wang. We discussed about the research plans and progress on our collaborative projects.
Zhikang Wang	PhD student, Monash University	Male	35 or younger	3 times of online meetings and discussions with Prof. Imoto Seiya, A/Prof. Yaozhong Zhang, A/Prof. Jiangning Song. We discussed about the research plans and progress on our collaborative projects.
Jing Xu	PhD student, Monash University	Female	35 or younger	2 times of online meetings and discussions with Prof. Imoto Seiya, A/Prof. Yaozhong Zhang, A/Prof. Jiangning Song. We discussed about the research plans and progress on our collaborative projects.

Name	Position, Institution	Sex	Age	Discussions via E-mail, Slack, etc. (Days)
Jiangning Song	Associate Professor, Monash University	Male	40 or older	Many times. We discussed about our research plans and progress on our collaborative projects.
Zhikang Wang	PhD student, Monash University	Male	35 or younger	2 times. We discussed about the research plan, potential medical image datasets and the visits to the Human Genome Center, University of Tokyo.
		Pull-down ▼	Pull-down ▼	
		Pull-down ▼	Pull-down ▼	

Usage of Facilities/Equipment			
Name of Facility	Equipment	Number of Use (Times)	Usage time (Hours)
FACS Core Laboratory	e.g.) FACS Aria (BD)	N/A	N/A
Medical Proteomics Laboratory	e.g.) Orbitrap QSTAR Elite	N/A	N/A
Imaging Core Laboratory	e.g.) Zeiss Multiphoton Microscopy (LSM710NLO)	N/A	N/A
Gene Manipulated Mouse Section	Creation and cryopreservation embryo of Knockout mouse	N/A	N/A
Human Genome Center	Supercomputer	10	200 hours
Amami Laboratory of Injurious Animals	Experimental lab	N/A	N/A
Other			
Usage of Scientific Resources			
Name of Scientific Resource			Number of Samples/Lines
Serum (BioBank Japan)			N/A

DNA (BioBank Japan)	N/A
Knockout mouse	N/A
Pathogenic bacteria	N/A
Other	
Usage of Database	
Name of Database	Number of Use (Times)