Weakly-supervised deep learning models in computational pathology

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eBioMedicine 2022;81: 104117
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.104117

Computational pathology is a burgeoning field which shows promise in increasing access to health care, particularly in resource-limited settings with a shortage of experienced pathologists.[1] Complementing advances in artificial intelligence (AI) methods in identifying patterns of disease, is the advent of publicly available haematoxylin and eosin (H&E)-stained whole slide datasets from the Cancer Genome Atlas (TCGA), and other consortia that have provided a basis on which AI models can be trained and tested.[2] AI simulates a human approach to problem-solving, utilising algorithms for visual perception, decision-making and learning while processing large datasets.[1] Deep learning models, a subdivision of AI, has greater advantages than traditional machine learning approaches, in that these multi-layered neural network algorithms are able to extract more discriminatory features for diagnostic purposes.[2,3] Two main approaches are employed, supervised and unsupervised or weakly supervised approaches. Supervised approaches rely on pathologists to manually identify multiple regions of interest on H&E slides that are then used to train the model. This is regarded as a more time-consuming, and computationally expensive approach that is dependent on large, gigapixel sized images or extensive pixel-level annotations.[2,4,5] To overcome these limitations, research is being undertaken in developing weakly-supervised approaches to deep learning where the slide is given a single annotation (label) with features from image patches or tiles being pooled under a multiple-instance learning framework (MIL). Thus with slide-level labelling if a slide is positive then one or all tiles must contain a tumour sample, whereas if a slide is negative all tiles must be tumour-free.[4,5]

A recent paper published in eBioMedicine, Brendel *et al.*,[4] using data accessible from The Cancer Genome Atlas (TCGA), presents a weakly supervised deep learning model that is capable of identifying key features on H&E stained slides to accurately estimate tumour purity. Tumour purity refers to the percentage of tumour cells over a range of regions of interest (ROI) in a tissue section enumerated by pathologists. Tumour purity estimates are not only reflective of the tumour microenvironment (TME), but may have clinical significance in prognosis and therapeutic response.[6,7] In addition to the challenges of inter-observer variability between pathologist scores, these scores have been found to correlate poorly with molecular tumour purity values generated from genomic and gene expression data.[6] These latter methodologies are themselves time-consuming and expensive that while enabling precision oncology nevertheless have limitations in their utility for traditional diagnostic methods. In this weakly-supervised approach, Brendel *et al.*, employed an attention based, multi-task, multiple-instance learning (MIL) model to learn weight features for ROIs within a slide as well as feature representation that can vie with pathologist-derived estimates of tumour purity, exceeding accuracy of previous supervised learning approaches.[4] With tumour purity associated with tumour type, the author's model could predict cancer type in both test and validation tests with 93% accuracy. However, misclassification of breast cancer and lung cancer were common.[4] While this may relate to the spatial distribution of the tissue, reducing noise and variability in generation of large datasets and ensuring robusticity of algorithms, is crucial to preventing false negatives and positives in real-life application.[4,8] The model derived by Brendel *et al.* additionally was able to permit visualisation of ROIs.[4] These spatial maps are necessary for downstream applications including sequencing or proteomics analysis from tissue sections for precision medicine or exploratory research that can assist in understanding the key cell types, including immune cell influence, in the TME that can describe tumour progression.[6] Moreover, as targeted therapies emerge confirming sufficient tumour purity for extraction for subsequent molecular testing is essential to preventing false negative results.[3] Model validation on formalin-fixed paraffin-wax embedded tissue sections,[6] the mainstay of resource-poor countries, is also required given concerns regarding model robustness when taking into account variance in preservation methods on tissue architecture and tissue processing. Nevertheless, by being able to accurately predict tumour purity, such models could assist in improving understanding tumour progression and clinical outcomes without sequencing, particularly in resource-limited settings. Computational pathology studies could be enhanced with greater access to and development of omics and histopathological databases that would permit further training of such models in cases of extreme low tumour purity,[4] with the incorporation of other laboratory

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2022.104067

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diagnostic information including tumour subtype to improve sensitivity and accuracy. By determining whether histopathological data could be used to infer omics information, a better understanding of the TME and tumour progression could ensue. Further testing in larger cohorts would better elucidate patient-patient variation as well as unearth potential population group variations that impact response to therapy and ultimately patient outcomes.

Contributors

TNA wrote this commissioned commentary.

Declaration of interests

The author declares no conflict of interest.

References

1 Cui M, Zhang DY. Artificial intelligence and computational pathology. *Lab Investig*. 2021;101:412–422.
2 Lee K, Lockhart JH, Xie M, et al. Deep learning of histopathology images at the single cell level. *Front Artif Intell*. 2021;4:1–14.
3 Sakamoto T, Furukawa T, Lami K, et al. A narrative review of digital pathology and artificial intelligence: focusing on lung cancer. *Transl Lung Cancer Res*. 2020;9:2255–2276.
4 Brendel M, Getseva V, Assaad M Al, Sigouros M, Sigaras A, Kane T. Articles weakly-supervised tumor purity prediction from frozen H & E stained slides. *eBioMedicine*. 2022;80:104067.
5 Campanella G, Hanna MG, Geneslaw L, et al. Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. *Nat Med*. 2019;25:1301–1309.
6 Oner MU, Chen J, Revkov E, et al. Obtaining spatially resolved tumor purity maps using deep multiple instance learning in a pan-cancer study. *Patterns*. 2022;3:100399.
7 Tran KA, Kondrashova O, Bradley A, Williams ED, Pearson JV, Waddell N. Deep learning in cancer diagnosis, prognosis and treatment selection. *Genome Med*. 2021;13:1–17.
8 Lu MY, Chen TY, Williamson DFK, et al. AI-based pathology predicts origins for cancers of unknown primary. *Nature*. 2021;594:106–110.