

Deep learning-enabled, non-invasive virtual histology of skin using reflectance confocal microscopy

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250-word abstract

Conventional pathological diagnosis of skin tumors requires an invasive biopsy, followed by histological staining, which is cumbersome and time-consuming, frequently resulting in unnecessary biopsies and scars. Reflectance confocal microscopy (RCM) offers a biopsy-free solution to provide *in vivo* images of the skin structure with cellular-level resolution; however, analyzing RCM images requires specialized training since they are grayscale, lack nuclear features and have a low correlation with histology. Here, we present a deep learning-based virtual staining method to perform non-invasive virtual histology of the skin based on *in vivo*, label-free RCM images. Using RCM images of excised unstained tissue samples as inputs and RCM images of the

same tissue stained with acetic acid to generate nuclear contrast as ground truth, we trained a convolutional neural network under a generative adversarial scheme to rapidly transform *in vivo* RCM images of unstained skin into virtually-stained H&E-like microscopic images. This virtual histology framework revealed successful inference for various skin conditions, such as normal skin, basal cell carcinoma and melanocytic nevi with pigmented melanocytes, covering distinct skin layers, including epidermis, dermal-epidermal junction, and superficial dermis layers. Our virtual histology images also showed similar histological features compared to the standard histochemically-stained sections from the same excised tissue. We believe that this *in vivo* virtual staining of unstained skin using non-invasive RCM technologies can pave the way for faster and more accurate diagnosis of malignant skin neoplasms while reducing unnecessary skin biopsies.

100-word summary

Reflectance confocal microscopy (RCM) can provide *in vivo* images of the skin with cellular-level resolution; however, RCM images are grayscale, lack nuclear features and have a low correlation with histology. We present a deep learning-based virtual staining method to perform non-invasive virtual histology of the skin based on *in vivo*, label-free RCM images. This virtual histology framework revealed successful inference for various skin conditions, such as basal cell carcinoma, also covering distinct skin layers, including epidermis and dermal-epidermal junction. This method can pave the way for faster and more accurate diagnosis of malignant skin neoplasms while reducing unnecessary biopsies.

Keywords:

Optical biopsy, Confocal microscopy, Virtual staining, Skin cancer, Neural networks, Deep learning