Label-free optical digital histology.

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The golden standard for tissue histopathology is hematoxylin and eosin (H&E) staining of thin tissue slices. It is based on lengthy and costly procedures. It is applied *ex vivo*, hindering longitudinal studies. The use of label-free optical microscopy *in vivo* can overcome these limitations. I will discuss two complementary applications of the near and middle infrared radiation micro-spectroscopy on biological tissues. In a first approach, we developed an implantable micro-structured device for the non-linear label-free optical microscopy assessment of the immune reaction to an implanted biomaterial. The device is implanted in living animals and used for in vivo imaging as shown for chicken embryos and for mice. The H&E histological analysis of the tissue sections is compared to label-free *in vivo* non-linear excitation imaging to build a cell atlas. Machine learning and AI methods help in quantifying the number and type of cells recruited in the tissue. In a second approach, we exploit photo-thermal imaging, bringing it to cellular resolution. We adopt an image-inversion method, that iteratively compares the detected temperature profile with the theoretical prediction formulated according to the 3D heat equation in the presence of laser-light illumination and thermo-camera based detection. In this way, the spatial distribution of the sample photo-thermal absorbers is reconstructed a posteriori via gradient-descent optimization as the one yielding the best match between computed and experimental images. Ex vivo analyses on murin and human tissues indicate that one can reach less than 5-µm spatial resolution opening the path to an alternative label-free analysis of tissue histology.

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