Quantification of bone tissue heterogeneity and cell distribution patterns from digital histology: application to osteosarcoma

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Like most sarcomas with complex genomics [1], or more generally bone tissues, osteosarcoma is a type of tumors exhibiting a strong spatial heterogeneity of the micro-environment. This heterogeneity makes the diagnostic complex and can induce strong spatial variability in the response to treatments [2]. New research strategies are consequently needed to understand the impact of spatial heterogeneity on the diagnostic accuracy and on the treatment efficiency, and more generally to understand the links between tissue scale bone matrix structures and underlying biology occurring at the cell scale.

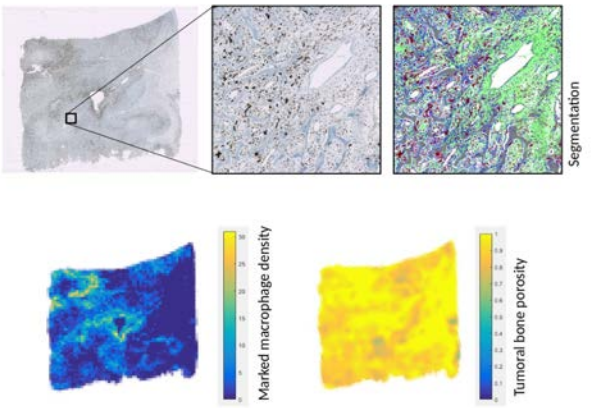

Figure 1 : **a)** Immunohistological section of a resection sample stained with CD68, **b)** zoom of the section, **c)** segmentation, **d)** marked cell density on macro-pixel with characteristic size evaluated with a semi-variogram and **e)** quatification of the 2D tissue porosity.

The aim of this interdisciplinary work is to obtain the quantification of correlations between clinical data, heterogeneity of bone tissues and mechanobiological parameters.
To this purpose, original numerical developments [3] were initiated in our group to study the intratumoral and healthy bone tissue heterogeneity from histological and immunohistological sections [4]. The code aimed at obtaining quantitative metrics of the cell population distribution (fig 1d), of the bone matrix micro-architecture (porosity, fig 1e) and of the transport properties (such as effective diffusivity). Because tissues exhibit naturally a complex spatial scales cascade, it can be modeled, at the tissue scale, as a three phases porous medium (fluid, solid, cell populations). Using methodologies related to porous media analysis [5], characteristic lengths were extracted and correlations of phenomena occurring cell and tissue scale examined. Further developments permitted the calculation of effective mechanical properties. The methodology used successive algorithms of machine learning for the histological image segmentation and a combination of iterative algorithms and filters for the correlation calculations. Results put forward the strength of this approach for the identification of new markers in the study of pathological bone tissues.

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