Computational methods for the characterization of the mechanical behaviour of healthy and tumour cells.

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Background Nowadays tumours are one of the principal causes of death in the world, more precisely the second one in Italy as in Europe. Tumour is caused by the uncontrolled growth and proliferation of mutated cells. Indeed, while healthy cells sense and respond to mechanical stimuli, by producing biochemical signals, in tumour cells these mechanisms are altered and biochemical signals are ignored. This results in an uncontrolled tumour cells proliferation and failure of the apoptosis process. Moreover, it has been seen that, when a healthy cell becomes a tumour one, a variation in its mechanical behaviour occurs, as well as in the mechanotransduction of signals that regulate cell's processes such as proliferation, migration and differentiation. Thence, biomechanical signals appear to play a key role in cells' life and behaviour.

Aim For the above-mentioned reasons, the main focuses of this Master thesis were: (i) to create a computational model and to characterize the mechanical behaviour of healthy and tumour cells in order to better understand the origin, the development and spread of cancer; (ii) to evaluate the contribution and the role of cell subcomponents in tumour mechanical processes; (iii) to pave the way for future computational models that will overcame the complexity of studying the neoplasms, in particular concerning the inter and intra tumour variability.

Material and Methods A three-dimensional finite element model of a cell was realized with the finite element software Abaqus Standard 2019 (Abaqus/CAE 2019, Dassault System). The model simulates a cell adherent to a substrate, composed of all those features that mainly contribute to the cell mechanics such as the cytoskeleton (composed of microfilaments and microtubules), cytoplasm, cell membrane and nucleus. The whole model was discretized by means of about 65000 hexahedral elements for cytoplasm and nucleus, about 23000 quadrilateral elements for cell membrane and 3000-line elements for the cytoskeleton, leading to about 330000 variables.
A continuum-tensegrity model was adopted to describe the behaviour of cells subcomponents. More precisely, cytoplasm, nucleus and cell membrane were defined as a homogeneous continuum material, while the cytoskeleton was modelled with a tensegrity structure, composed of compression and tension bearing elements that mimic the behaviour of microtubules and microfilaments, respectively. Viscoelastic properties were assigned to cell subcomponents, referring to values reported in the literature.
Two types of numerical simulations were realized: tensile tests and indentation tests. In tensile tests the cytoskeleton was firstly prestressed (first step), then tensile forces were applied at two opposite nodes of the plasma membrane (second step); in indentation tests (simulating Atomic Force Microscopy i.e., AFM indentation) an applied normal load phase (first step) was followed by a relaxation one (second step). In this latter, a hard sphere simulated the cantilever tip of the AFM, while approaching the cell.
Even if the model has the potential to hypothetically mimic all kinds of cells, this work primarily focused on chondrocytes (specialized cells present in the cartilage) and chondrosarcoma cells (malignant tumour cells that origin from chondrocytes), thanks to a larger availability of data in the literature with respect to other cells.

Results and Discussion The validity of the continuum-tensegrity choice for describing the cell was assessed by tensile tests. Consistently with data taken from literature, it was observed that at a linearly increase in stiffness (between 0% and 10%) corresponded to a non-linear increase in cell prestress. With indentation tests, it was realized a sensitivity analysis of the constitutive parameters of cell subcomponents, by comparing computational stress relaxation curves with Hertz model. These results showed the ability of the model to mimic the behaviour of an average human cell. It was also possible to observe the differences in mechanical behaviour between a healthy and a tumour cell. The outcomes suggested that the cytoskeleton plays a key role when a cell is tight from two opposite parts, while the cytoplasm mostly influences the cell response under compression. Furthermore, healthy cells appeared to be stiffer than tumour cells (Young's Modulus of chondrocytes were about two time higher than the chondrosarcoma cells'). This was assessed to be the effect of the increased cellular activity of tumour cells as reported in literature. These results could serve as a primarily step in the development of more accurate computational models for cell mechanics.