# CANCER INVASIVENESS IS DETERMINED BY CELL ADAPTABILITY TO CHANGES IN MICROENVIRONMENT MECHANICS

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## Introduction

Metastases are the leading cause of cancer-associated deaths. A key process in metastasis is cell invasiveness, which is driven and controlled by cancer cell interactions with their microenvironment. We have previously shown that invasive cancer cells forcefully push into and indent physiological-stiffness gels to cell-scale depths [1,2]. Notably, the percentage of indenting cells and their attained depths provide a clinically relevant prediction of invasiveness and the potential metastatic risk [2–4]. Cell-attained indentation depths are directly affected by changes in gel mechanics, which can in turn modulate the cells' mechanics and force application capacity, inducing complex, coordinated mechanobiological responses. As experimentally isolating the different contributions is impossible, we use finite element modeling to evaluate the roles of cell and gel mechanics on cancer-cell invasiveness.

## Methods

We extended our finite element model [5] to evaluate the roles of cell and gel mechanics on cancer-cell invasiveness. Cells were modelled as initially hemispherical, Neo-Hookean materials. The gel-substrate was modeled to match the elastic polyacrylamide gel used in experiments [2,6]. Cells apply forces at their perimeters and centers, respectively, pulling and pushing the gel surface; force balance (zero net force) is maintained.

## Results

Under constant, literature based, cell cytoplasm and nucleus mechanics and cell-applied force levels, increasing gel stiffness 1-50 kPa significantly reduced the attained indentation depth by >200%. The gel's Poisson ratio, however, reduced depths by up to 20% and only when the ratio was >0.4. In experiments, varying-invasiveness cancer cells, from lines of breast and pancreatic cancers, exhibited qualitatively different changes to indentation depth with gel-stiffness increase, e.g. large/small reduction or increase followed by reduction. We were able to accurately reproduce the experimental responses via coordinated changes in cell mechanics and applied force-levels, scaled based on published effects of gel-stiffness on cells.

## Conclusions

Our work shows that different cancer invasiveness and metastatic risk-levels most likely result from the varying capacities of cells to adapt their mechanobiology in response to changing microenvironments.

## References

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