Biophysical Contribution to Tumor Progression and Incidence in Lung Cancer

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Introduction

- Early detection of lung cancer increases the 5-year survival rate of patients from 18.6% to 56%, however most cases are not diagnosed at an adequately early stage[1].
- Artificial Intelligence has been utilized on CT scans of patients' lungs for improved tumor detection[2,3].
- Mechanical stresses have been shown to affect tumor progression due to physical/biological interactions of cancer cells with the tumor microenvironment[4-7].
- It is hypothesized that augmenting CT images with biomechanically derived data will improve the performance of detection and classification of pulmonary nodules[8].

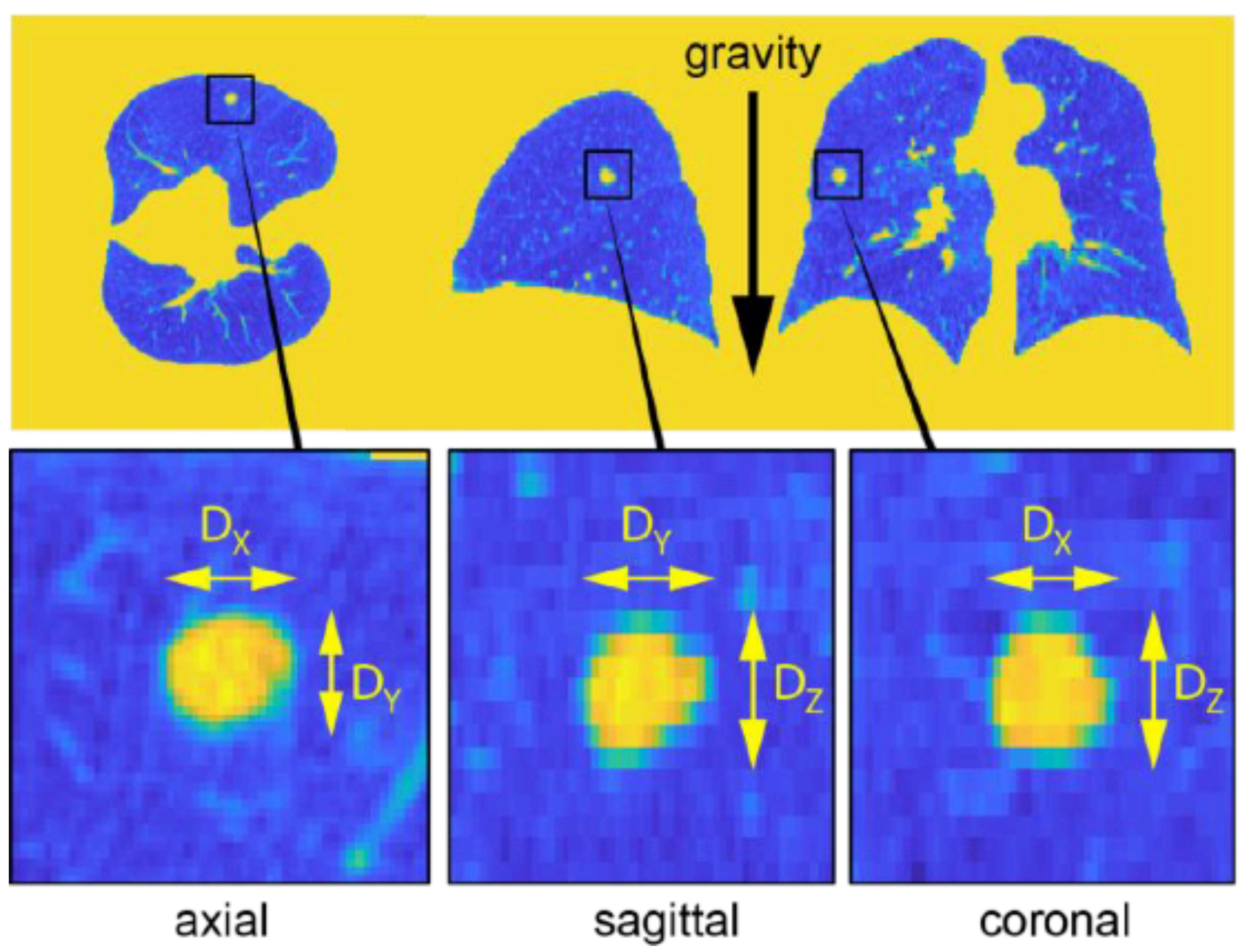

Figure 1: Representative tumor images from different CT perspectives. Tumor diameters are longer in D_Z direction compared to D_X and D_Y.

Materials & Methods

- CT scans (n ≈15,000) of lung cancer patients from the National Lung Screening Trial (NLST) were analyzed using MATLAB image processing functions[3].
- Horizontal and vertical diameters were calculated and then compared for each CT viewpoint for each tumor (Fig. 1).
- These directionality ratios were then aggregated and statistically compared (Fig. 2).
- Additionally, 1249 tumor locations from NLST's cancer cohort were normalized to a reference lung (Fig. 3) through 3D scaling and translation based on the lung boundaries and centroid.
- Spatial tumor incidence was measured by binning the normalized tumor locations into z-direction slices normalized by volume. All significance testing used Student's t-test.

Results and Discussion

- Tumor diameters are approximately 20% larger in the z-direction compared to the x- and y-directions (Fig. 2, n = 486). Tumors tend to grow faster in mechanically stressed regions, which is consistent with the hypothesis that gravitational tensile stresses cause directionality bias.
- Modelling normalized tumor locations (Fig. 3) reveals a significant correlation with z-location of tumors and number of tumors per volume (Fig. 4, n = 1249), with greater incidence in upper lungs. Gravity produces larger tensile stresses in the apex of the lung due to carrying a larger portion of the lung, thus the tumor incidence risk is consistent with the distribution of the gravity-induced mechanical forces.

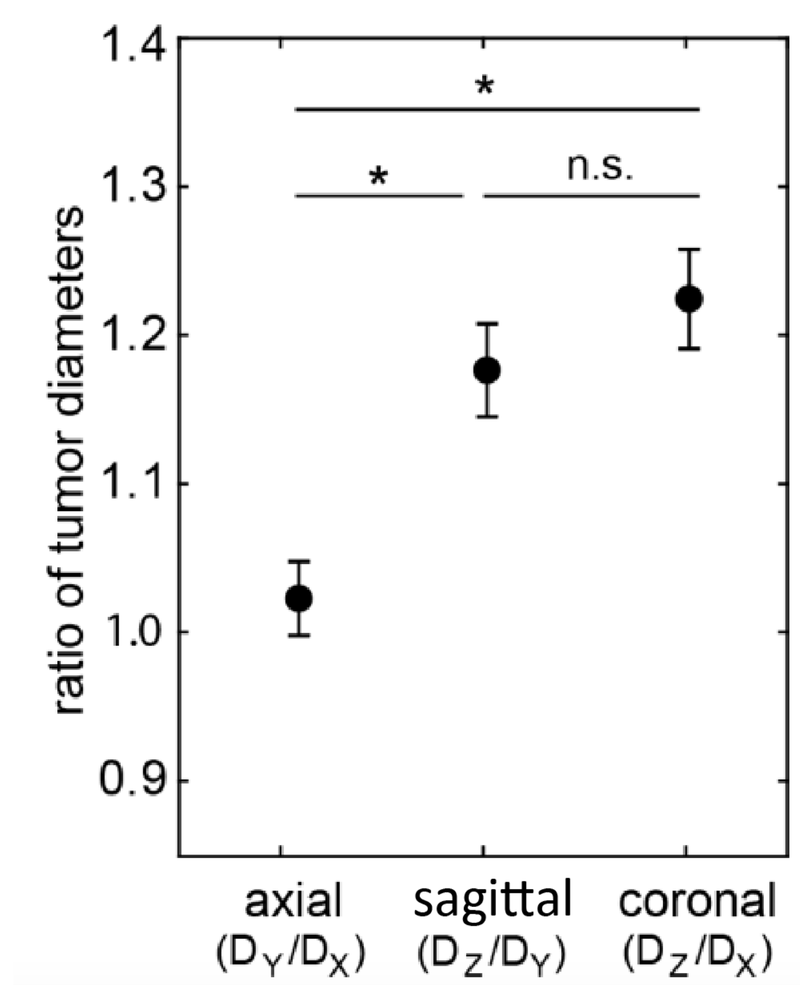

Figure 2: Ratios of tumor diameters for each CT perspective, shows growth preference of tumors in direction of gravity. *: p < 10^-5 (n = 486; mean +/- S.E.).

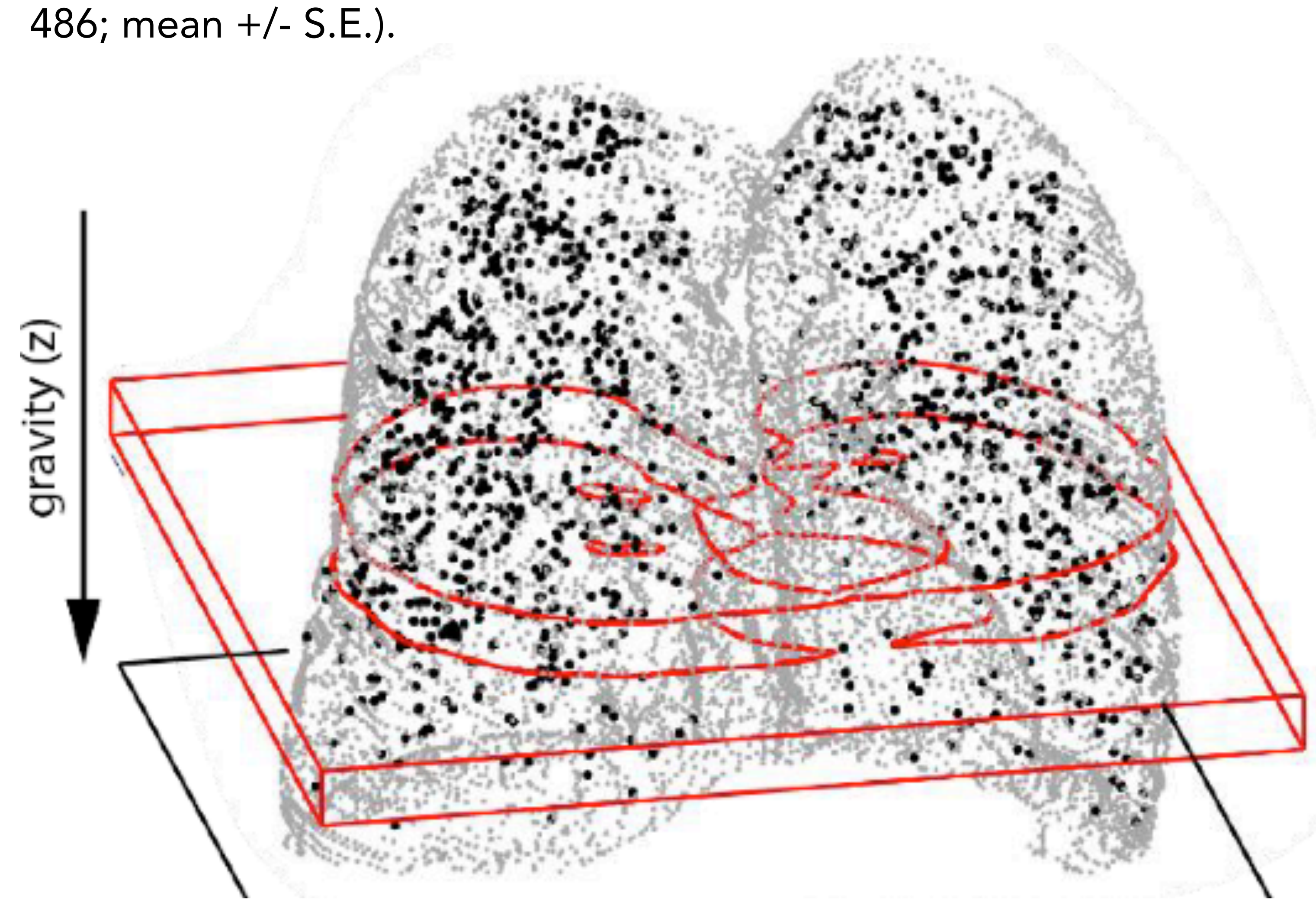

Figure 3: Spatial scatter plot of lung tumor locations (in black dots) normalized over reference lung volume (outer surface in gray dots).

Conclusions

- Gravitational tensile forces appear to have a biomechanical contribution to tumor growth with longer tumor diameters in the direction of gravity compared to orthogonal directions.
- Tumor incidence also appears to be affected by gravitational tensile forces, with the apex of the lung having greater normalized tumor density compared to lower regions.
- Augmenting existing pulmonary nodule detection/classification algorithms with biomechanical frameworks has the potential to enhance cancer prognostic/diagnostic model performance and improve patient outcomes.

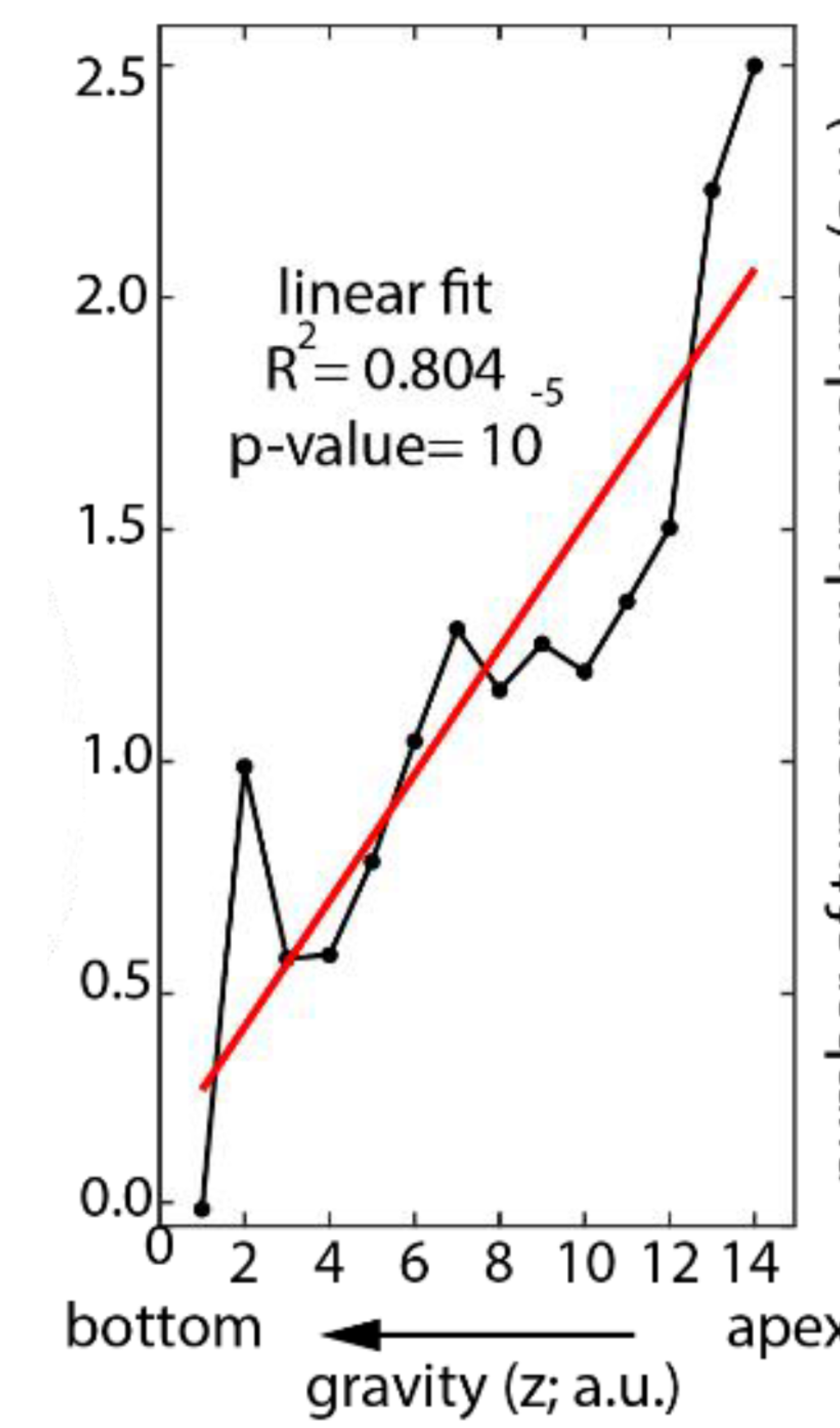

Figure 4: Normalized tumor incidence across all patients as a function of z-direction (gravity) normalized by volumetric units (a.u). A sample normalized slice is shown in red in Fig. 3. Spatial distribution of lung tumors strongly correlates with direction of gravity.

References

1. Knight, SB+ *Open Biol.* 2017; **2.** Topol, EJ+ *Nat Med.* 2019; **3.** Aberle D+ *NEJM. 2011;* **4.** Nia HT+ *Nat Biomed Eng.* 2016; **5.** Hassell, Bryan A+ *Cell Reports.* 2017; **6.** Jain, R.K.+ Annu Rev Biomed Eng, 2014; **7.** Northey, J.J.+ Cancer Discovery. 2017. **8.** Wason, JV+ *Bioinformation.* 2019