Chaos in Cancer: Analyzing Network Morphology to Predict Tumor Angiogenesis using Chaos Theory

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Introduction

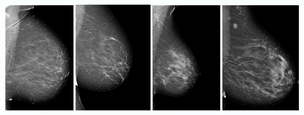
Human blood vessels build complex networks throughout the body estimated total length of 100,000 km, while all these networks are necessary for homeostasis, they can be exploited by various diseases. Tumor angiogenesis is the formation of blood vessels that provides the tumor with a supportive microenvironment rich in oxygen and nutrients required for cancer survival, malignancy, and metastasis.

The architecture of tumor vasculature is structurally and functionally chaotic and characterized by excessive branching and shunts. This makes it difficult to both anticipate tumor progression, for prognosis, and deliver treatment, due to poor perfusion. Existing models struggle with bias from vasculature abnormalities, capturing the dynamic patterns in growth rate, and addressing angiogenesis from a multilevel pertinence to the proteomic, genetic, and pathological sphere. Challenges with existing angiogenesis predictor models are:

- Bias from vasculature abnormalities
- Capturing the dynamic patterns in growth rate
- Addressing angiogenesis from a multilevel pertinence to the proteomic, genetic, and pathological sphere

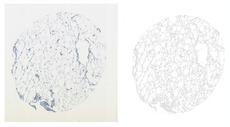
Can a computational network reconstruction of tumor angiogenesis mechanisms using coupled morphological, genomic, and physiological parameters when applied to chaos theory determine the predictability of tumor angiogenesis?

Materials

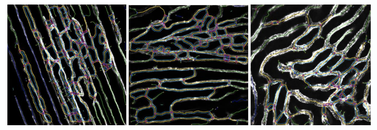


The King Abdulaziz University Breast Cancer Mammogram Dataset labeled into BIRADS catergories was used (right).

Steps in Imaging Preprocessing	
Challenges	**Solutions**
(1) Lack of contrast	Image channels transformed to grayscale
(2) Inconsistent lighting discrepancies	Homomorphic filter employing Fast Fourier Transformation
(3) Thin and faint veins	Edge segmentation using a Gaussian Filter $\sigma = 2$
(4) Irrelevant noise	Adaptive thresholding created using Gaussian Blur
(5) Skeletonization	Reduce binary objects to 1 pixel wide presentations, a method described by Zhang, 1984

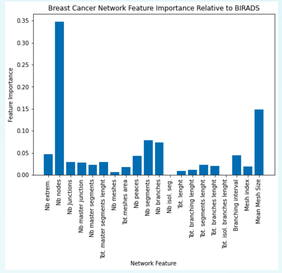


Skeletonization

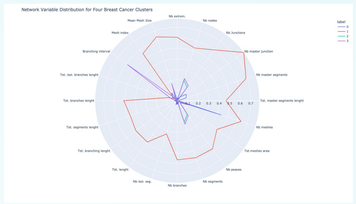


Bifurcation

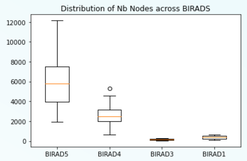
Methodology



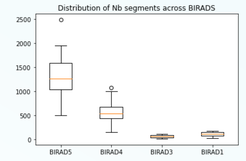
Exploratory data analysis employing AI and ML were leveraged to uncover general tendencies of biological networks and distinguish angiogenesis from healthy vasculature. First was network feature importance (left) to understand the extent of causation between certain variables on the magnitude of cancer.



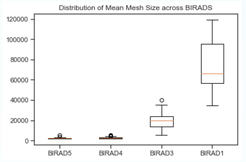
Topological features, network properties, and concepts behind graph theory through K-means clustering were described in a novel polar coordinate graph.



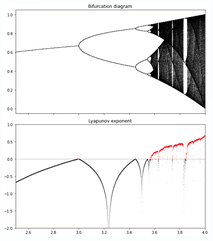
Positive nonlinear relationship between nodes and BIRADS. Inferred result caused by vascular sprouting and extending filopodial for increased permeability, perfusion, diffusion, and surface area.



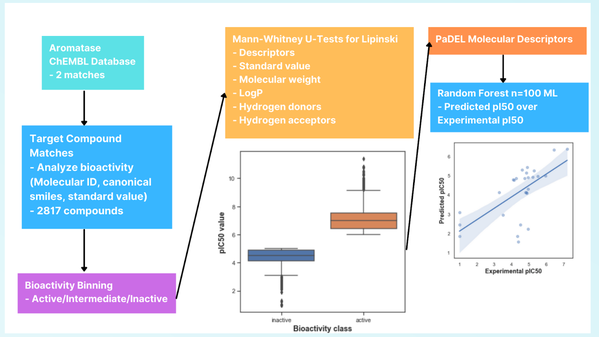
Positive nonlinear relationship can describe the connectivity of a graph as a scale-free network. Cancerous networks demonstrate a high degree of preferential attachment due to interplaying tumor microenvironment chemicals.



Negative nonlinear relationship between mean mesh and BIRADS. Inferred to result from endothelium loops that promote pericytes to enable more blood to circulate through adhesion molecules.



The bifurcation diagram splits at every occurrence of which the Lyapunov exponent reaches the origin. For a three axis phase space, there will be three λ consisting of the Lyapunov Characteristic Exponents set. Chaotic behavior ensues after the Lyapunov reaches the origin three times, and becomes positive.



Protein Targeting and Molecular Docking with Statistical Tests were performed using a target enzyme aromatase through a pipeline starting with the ChEMBL database, to identify drug targets, to predict IC50 standard values for drug compounds (above).

$$\dot{x} = \frac{dx}{dt} = \sigma(y - x),$$

$$\dot{y} = \frac{dy}{dt} = x(p - z) - y$$

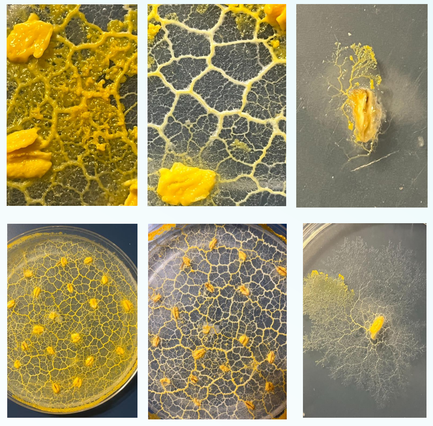
$$\dot{z} = \frac{dz}{dt} = xy - \beta z$$

The Lorenz attractor equation was implemented to conceptualize tumor vascularization on a three-axis phase space. Its constants were manipulated to represent the MinMax normalization of the three more significant network variables.

α = sigma representing Prandtl number
p = rho representing the Rayleigh number divided by the critical Rayleigh number
β = beta represents a geometric factor

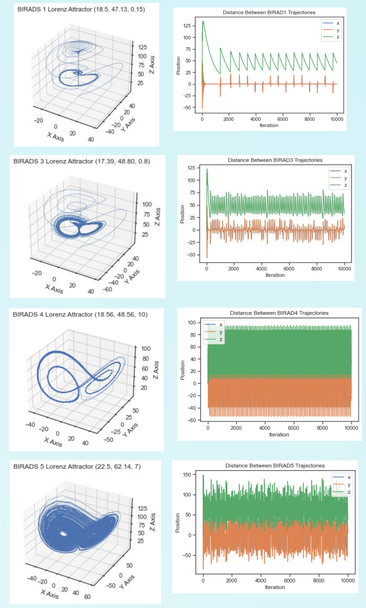
α = var x_1 highest feature importance
p = var x_2 second-highest feature importance
β = var x_3 third-highest feature important

Derivative calculations of the current point using the Fourth-order Runge-Kutta integrator were used to estimate the subsequent point of the ordinary differential equation in a 'time-step' fashion. Finally, the Lyapunov characteristic exponents, the fractal dimension, and the bifurcation diagram were used to determine a system's measure of chaos.



In vitro validation with P. polycephalum was conducted to culture the slime mold in adverse (1% salt), neutral (normal agar), and generative (1% sugar) agar plats to simulate biological network morphogenesis in various "tumor microenvironments"

Results



Based on the signs of the Lyapunov exponents, the fractal dimension of the BIRADS 1 network is a stable fixed point, and this can be visualized, as all perturbations (represented as spirals) eventually reach 0. The same can be done for BIRADS 3 and 4 but now demonstrating more loosely wound and continuous spirals. Then in BIRADS 5 where there is the greatest probability of cancer, there is a positive Lyapunov exponent.

This study provides the first preliminary evidence which suggests that tumor angiogenesis is chaotic, and thus concepts relating to chaos theory can be applied to determine what underlying chaotic patterns are yet to be explored in angiogenesis

Conclusion

It was found that angiogenesis breast cancer vasculature exhibited a higher Lyapunov exponent than in nontumorous vasculature, confirming the hypothesis that angiogenesis architecture can be modeled by deterministic chaos. Vasculatures with a higher number of nodes, segments, and smaller mean mesh size were the most chaotic due to vascular sprouting and variation in vascular density and permeability, and tip cells formed by sprouting filopodia toward proangiogenic signal sources, and the interplay of pericytes and the endothelial wall, respectively. Furthermore, a model predicting the drug potency of aromatase target compounds with an r^2 value of 0.512 was designed and the in vitro experiments of P. polycephalum confirmed and compelled for further investigation of how the tumor microenvironment impacts the morphology of angiogenesis. Potential applications and next steps include:

- Clinical Diagnosis
- Bridging Biochemical and Mathematical Research
- Novel Drug Discovery
- Integration into imaging hardware