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Computational growth model of breast microcalcification clusters in simulated mammographic environments

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ABSTRACT

Background: When screening for breast cancer, the radiological interpretation of mammograms is a difficult task, particularly when classifying precancerous growth such as microcalcifications (MCs). Biophysical modeling of benign vs. malignant growth of MCs in simulated mammographic backgrounds may improve characterization of these structures

Methods: A mathematical model based on crystal growth rules for calcium oxide (benign) and hydroxyapatite (malignant) was used in conjunction with simulated mammographic backgrounds, which were generated by fractional Brownian motion of varying roughness and quantified by the Hurst exponent to mimic tissue of varying density. Simulated MC clusters were compared by fractal dimension, average circularity of individual MCs, average number of MCs per cluster, and average cluster area.

Results: Benign and malignant clusters were distinguishable by average circularity, average number of MCs per cluster, and average cluster area with $p < 0.01$ across all Hurst exponent values considered. Clusters were distinguishable by fractal dimension with $p < 0.05$ in low Hurst exponent environments. As the Hurst exponent increased (tissue density increased) benign and malignant MCs became indistinguishable by fractal dimension.

Conclusions: The fractal dimension of MCs changes with breast tissue density, which suggests tissue environment plays a role in regulating MC growth. Benign and malignant MCs are distinguishable in all types of tissue by shape, size, and area, which is consistent with findings in the literature. These results may help to better understand the effects of the tissue environment on tumor progression, and improve classification of MCs in mammograms via computer-aided diagnosis.

1. Introduction

Breast cancer is the most common cancer worldwide according to the World Health Organization and the second leading cause of cancer-related death among women in the United States [1]. Cancer is easiest to treat when it is found in early stages of development. Mammograms are the most commonly used screening process for breast cancer, and are widely recognized to play a vital role in diagnosing the disease. However, the radiological interpretation of mammograms is a difficult task, especially since the mammographic appearance of normal tissue is highly variable. Modeling tumor and tumor precursor growth in mammographic backgrounds can provide insights into the structure of benign and malignant tumors, which may improve radiological interpretation in the future [2].

Microcalcifications (MCs) are small, often clustered deposits of calcium spread throughout breast tissue. Radiologists know that MCs, which appear as small white spots in mammograms, can be an indicator of cancer depending on their quantity, shape, and dispersion pattern [3–7]. The proposition that this dispersion is mathematical in nature and quantifiable through fractal measurements—specifically that malignant tumor growth may develop into fractal [8] patterns—is well accepted [9–13].

The fractal dimension, D, is a mathematical tool that has been used extensively in all sciences. While standard geometry is limited to the study of Euclidean objects such as smooth curves, circles, and cubes, fractal geometry can be seen as a generalization of Euclidean geometry. Objects exhibiting a geometrical structure that cannot be described with tools such as area, perimeter, and volume are naturally characterized via the fractal dimension.

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Classical Euclidean objects have an integer fractal dimension ($D=1$, 2, 3 respectively), while most (tree-like or filamentary) fractal objects have a non-integer fractal dimension [8].

Recently, using the 2D Wavelet-Transform Modulus Maxima (WTMM) method [14–18] to detect MCs in mammographic breast tissue, we characterized the fractal geometry of benign vs. malignant MC clusters using two separate 2D projected mammographic views of the same breast [13]. It was shown that 92% of malignant breast lesions studied (23 out of 25 cases) had a fractal architecture, while 88% of the benign lesions had a Euclidean (non-fractal) architecture (30 out of 34 cases). Furthermore, using a Bayesian analysis, it was shown with 95% credibility that the probability that fractal breast lesions were malignant was between 74% and 98%, and the probability that Euclidean breast lesions were benign was between 76% and 96%. These results supported the notion that the fractal structure of malignant tumors more likely were associated with invasive behavior in the surrounding tissue, compared to the non-invasive Euclidean structure of benign tumors [13].

In addition to the fractal dimension, we calculated the average circularity of a cluster, number of distinct MCs making up a given cluster, and total area of a MC cluster. Circularity of MCs is an accepted radiological criterion for discriminating between benign and malignant MCs [4–7]. Willekens et al. suggested that malignant clusters contain a greater number of distinct MCs than benign ones, but did not find statistical significance of this in their data [7]. Discriminating MCs via size was supported in 2D mammograms [19], but inconclusive in 3D micro-CT imaging [7]. While clear advantages of using 3D digital breast tomosynthesis (BT) over standard mammography have been unambiguously demonstrated in terms of improving the accuracy of detection as well as lowering the number of false-positives by up to 50% [20–23], recent work showed that 2D digital mammography outperformed BT for MC detection [24].

The main goal of this paper was to present a simple 2D model of MC cluster growth in simulated mammographic backgrounds and, in particular, to assess their fractal structure. The model proposed is in accordance with most tumor growth models [25–28], as the biophysical principles behind benign and malignant MCs are the origin of benign and malignant tumor growth, respectively. The malignant MC simulated the growth of the necrotic tumor core, where calcium ions and phospholipids of dying cells react [26,29]. The benign model simulated the buildup of calcium secretions in cysts and ducts [5,29,30]. Calcium oxide (CaO) crystals are associated exclusively with benign MCs, while hydroxyapatite (HA) crystals are associated with both benign and malignant MCs [29]. This paper examined the respective influences of mammographic backgrounds and crystal structure on MC growth by building strictly CaO or HA crystals in simulated tissue. It was expected that CaO would yield benign MCs in all simulated backgrounds, while HA would generate malignant MCs only in some backgrounds due to the occasional association of HA with benign calcifications [29]. HA growth should be more invasive than CaO growth due to its association with malignant MCs.

A secondary goal of this paper was to present an alternative way of generating breast tissue background. We did not attempt to develop truly realistic variable mammogram backgrounds, which are difficult and imperfect as correctly stated by Näppi et al. [27], nor did we base our model on breast anatomy, as presented in more recent work ([31] and the first eight references therein). Rather we proposed a model based on observational mammographic measurements of the breast tissue background via multifractal roughness analysis of density fluctuations [15]. Rough surfaces generated from 2D fractional Brownian motion provided empirical resemblance to mammographic backgrounds [15]. Fatty and dense breast tissues were simulated as needed by varying the Hurst exponent H, which dictated the roughness of the fractional Brownian process. Higher values of H ($0.55 < H < 0.75$), corresponding to persistent, long-range correlations, were associated with dense breast tissue, while lower values of H ($0.25 < H < 0.45$), corresponding to anti-persistent correlations, were associated with fatty breast tissue [15]. In this way we achieved quantifiably realistic background tissue and observed quantifiably realistic growth of MC clusters within breast tissue.

2. Proposed model

2.1. Background tissue generation

Rather than simulate background tissue using a recursive 2D midpoint displacement algorithm, which can create artificial ridges in otherwise smooth tissue [32], the background tissue was generated using fractional Brownian motion [14–16,33], which allowed fine control over the tissue roughness and did not create ridges.

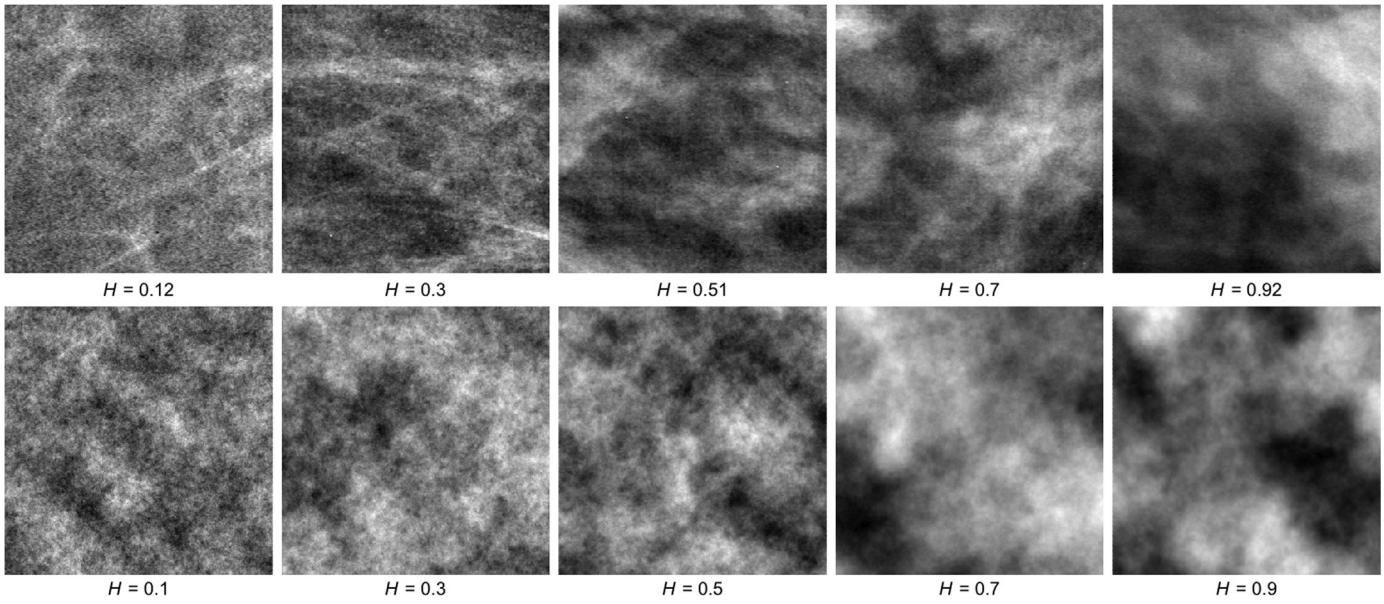

Fig. 1. Real (top) vs. generated (bottom) mammographic backgrounds at $H \approx 0.1$, 0.3, 0.5, 0.7, and 0.9. The top images were obtained from the Digital Database for Screening Mammography (DDSM) [55,56] and their roughness exponent, H, was estimated using the 2D WTMM method [13–18].