A COMPUTATIONAL MODEL OF BREAST DUCTS

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Abstract

Ductal Carcinoma represents almost 75% of breast cancer. In this specific type of cancer, malignant cells in the breast ducts invade the surrounding healthy tissue. Almost all researchers who are investigating microwave modality in the area of breast cancer detection employ oversimplified models of the internal structure of the breast. Use of engineered or biologically inaccurate models can render inaccurate results. Therefore, a mathematical biological model was implemented in this work aiming to bridge the gap between physiologists and engineers.

The results show that the proposed breast duct model has the capability of modeling the breast ducts of different kinds of women. The simulated breast ducts of older women have smaller breast ducts, leading to less dense breasts, which is in agreement with medical knowledge. Also, younger women have larger breast ducts leading to more dense breasts, which are consistent with the obtained results. The model was implemented computationally using the computer language C++ in both two and three dimensions. The potential impact of the research is to provide researchers with a greater understanding of the breast ducts as cancer treatment models evolve.

I. Introduction

There are current efforts that utilize simulated mammary gland models for theoretical research [1], [2]. To do this, it is necessary to recreate a mammary gland that is consistent biologically. Otherwise, research outcomes using simulated breast models will be inaccurate. Figure 1 shows a sample breast similar to one found in a paper [2] by a researcher using microwave methods to detect breast cancer. A simple look into the most basic anatomy books or websites shows that the model illustrated in Figure 1 is too much of an oversimplification. Random cylinders and spheres attempting to explain the complex morphology of the breast ducts is archaic.

Breast ducts employ branching morphogenesis during growth (see Figure 2). A single duct grows from the nipple for three weeks postpartum. Three to four weeks postpartum, the ovarian function begins, which leads to an increase in end bud elongation and branching. The end buds then extend and branch to form the breast ducts.

The ducts of the breast form by branching morphogenesis similar to the vasculature and lungs. There are models [3]

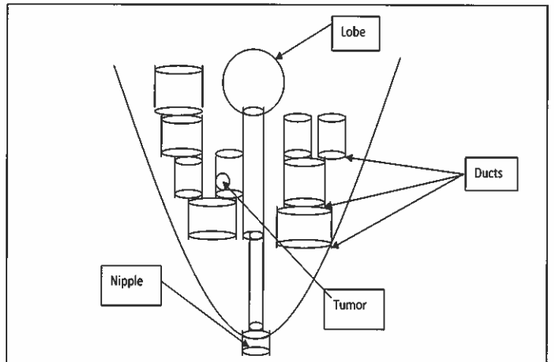

Figure 1: Engineered Breast Model

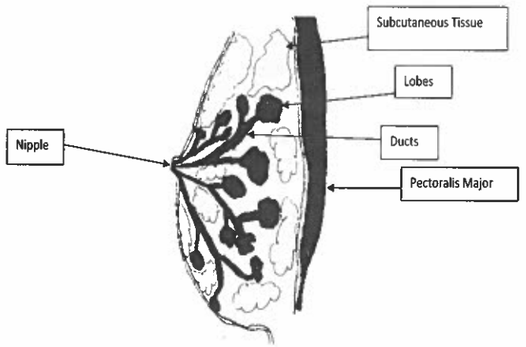

Figure 2: Sketch of Normal Breast Cross-Section

that describe this branching morphology, and it has been determined biologically that these structures can be modeled using a branching tree where a mother branch bifurcates into two or more smaller branches, resulting in a network spanning an entire cavity.

Unfortunately, the simplicity of this model is inhibiting, and its use will result in a biologically skewed breast duct model. In an extensive study [4], 72 breasts were excised for cancer and analyzed for the number of ducts. The researchers determined that the nipples contained 11 - 48 ducts with a median of 27 central ducts. Interestingly, this study found that "half of the breast was drained by three ducts and 75% by the largest six. Conversely, eight small duct systems together accounted for only 1.6% of breast volume" [4]. This finding establishes the heterogeneity of the breast duct system. Branching tree algorithms are inconsistent with actual breast ducts because they do not take into account how real breast ducts grow. They attempt to recreate the end-product by ignoring the means by which the breast ducts achieve the intricate patterns present.

However, there is present research [5] that takes into account biological mechanisms in modeling the breast ducts. This model functions on the basis that breast ducts elongate and bifurcate as a result of the extracellular matrix breaking down. There is an activator (matrix metalloproteinases) and an inhibitor (tissue inhibitors of metalloproteinases) present in this model, and these matrix metalloproteinases serve to break down the extracellular matrix, mainly the collagen and laminin. This model serves as the starting point for this study, which further developed a model that would more closely simulate the actual internal structure of the breast.

II. Methods

The model in this research was developed based on two activator-inhibitor reactions that have been experimentally established by researchers to occur naturally in the breast. The first reaction occurred between matrix metalloproteinases and tissue inhibitors of metalloprotenases. It was implemented in a previous model as illustrated in Figure 3 [5].

If the matrix metalloproteinases (MMP) reached a certain value at a point in the domain, then that point became a breast duct cell. If there was a breast duct cell at a certain point in the matrix, then that cell inhibited the proliferation of growth factors by inhibiting growth factor in that specific cell, which was then averaged over a Moore Neighborhood of three. However, growth factor was an activator of MMP. Therefore, if a point was a breast duct cell, it would eventually be inhibiting

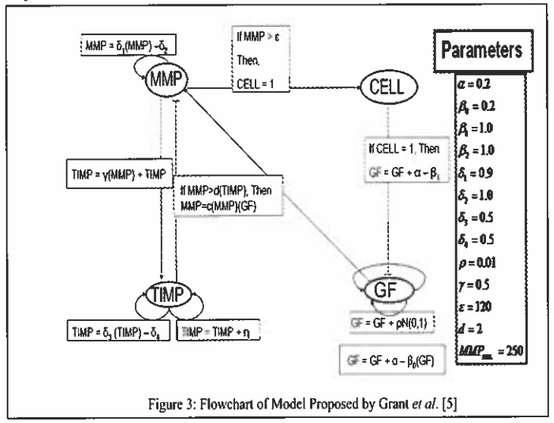

Figure 3: Flowchart of Model Proposed by Grant *et al.* [5]

MMP, which in turn inhibited the creation of new breast duct cells. This prevented anastamoses in the model. MMP also was an activator of tissue inhibitors of metalloprotenases (TIMP) which was an inhibitor of MMP. Thus, there was an element of feedback in the system. There was a random number between zero and one that was added to Growth Factor and allowed for variation in the system.

The second reaction occurred between growth factors and transforming growth factor – beta1 (TGF-β1). The work in [6] states, "Excellent evidence that TGF-β1 (Transforming Growth Factor) naturally inhibits this infilling, possibly by blocking hepatocyte growth factor synthesis." The fat pad can synthesize hepatocyte growth factor. Making use of this finding, an addition was made to the model proposed by Grant et al [5] shown in Figure 4. In the fat pad, growth factor was inhibited by transforming growth factor – beta one as proposed by Silberstein [6].

The motivation for this addition to the model came about in implementing a three-dimensional version. In the two-dimensional model, the duct cells tended to grow on boundaries of the available space as shown in Figure 5.

The breast duct cells congregating on the boundaries did not appear to be problematic in the two-dimensional model, but when the model was brought into three dimensions (Figure 6), it was apparent that an addition to the original model was needed. In the first attempt at a three-dimensional model, the parameters were restricted to a conical area with closed boundaries as originally proposed by Grant et al [5].

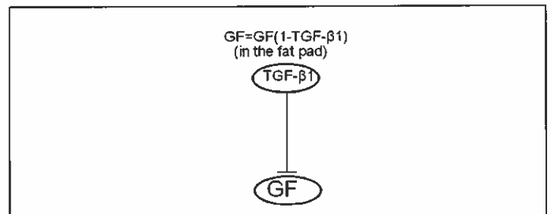

Figure 4: Addition to the Original Breast Duct Model

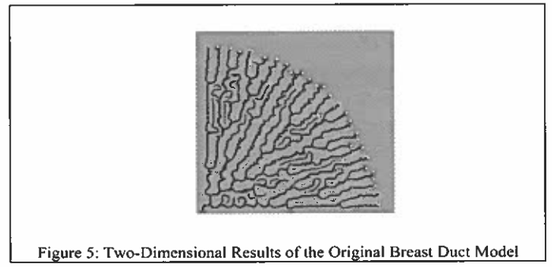

Figure 5: Two-Dimensional Results of the Original Breast Duct Model

III. Results

The first attempt at a three-dimensional model obviously conflicted with the requirement that the model be biologically accurate. It was then that the boundary conditions were determined to be problematic.

To understand why the boundary conditions were problematic, it is first necessary to understand the way in

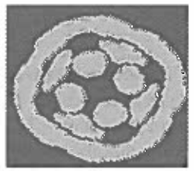

Figure 6: Cross-Section of Original Model in Three-Dimensions

which the activators and inhibitors travel in the simulation. The simulation can be considered as a complex cellular automaton. A cellular automaton is a method used to model biological structures as well as structures in other fields of study [7]. It is a discrete model, so a grid is established and each point in the grid is often considered a cell. These cells then interact with each other and other nutrients and proteins in the system to create a macroscopic order that mimics that found in-vivo.

In cellular automata, the cells in the grid can interact in two common ways. The first, which is employed in the breast duct model, is called the Moore neighborhood. Because it is actually used in the breast duct model, the Moore neighborhood is visited in greater detail while describing it. In a Moore neighborhood, a cell is averaged within a certain neighborhood or radius. All of the cells within the radius are added together and then that sum is divided by the total number of cells in the neighborhood. In Figure 7 (below), a Moore neighborhood is illustrated in a 10×10 grid with a cell denoted by "x". An average over all of the neighboring cells (dark pixels) and the cell itself is conducted. This is a two-dimensional example of a Moore neighborhood with radius=2.

The other most common neighborhood in cellular automata is the von Neumann neighborhood. Whereas the Moore neighborhood is the set of all cells that one could walk to if one could walk cardinal or ordinal directions, the von Neumann neighborhood is the set of cells one could travel to by only traversing cardinally. An example of a von Neumann neighborhood with a radius of two is shown in Figure 8 (above). The set of dark squares are those included in the

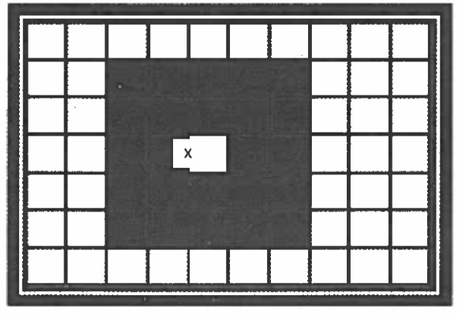

Figure 7: An example of a Moore's neighborhood

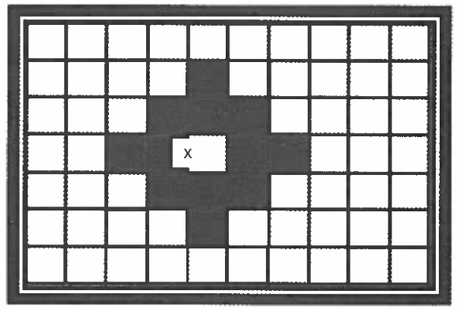

Figure 8: An example of a von Neumann neighborhood

neighborhood for the cell with an "x" in it.

The conical area in Figure 6 creates problems because the Moore neighborhood was being averaged over fewer cells at the edge of this conical boundary. Because it was being averaged over fewer cells, the levels of MMP tended to be higher. Thus, vast amounts of duct cells were being formed on the edge of the boundaries which led to a biologically inaccurate result.

Silberstein [6] provided biological insight into what inhibited the breast duct from growing at the edge of the fat pad. These findings were then implemented in the simulation. A fat pad was created in the simulation, and three breast duct system seeds, which were large amounts of MMP at different intervals in the simulation, were planted. The odd intervals were implemented in order to investigate the interactions between the duct systems at different intervals as shown in Figure 9.

Multiple breast duct systems were not implemented in previous work [5]. Only with the new boundary conditions would multiple breast duct systems result in a meaningful pattern, so the biological accuracy of the new configuration could be determined.

Figure 10 illustrates results from the three-dimensional breast duct model. The level of transforming growth factor

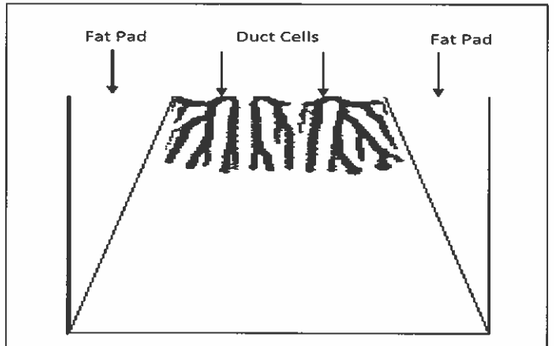

Figure 9: Improved Two-Dimensional Model

– beta one, which inhibits growth factor in the fat pad in the model, was increased from the two-dimensional model. Additionally, the Moore neighborhood for growth factor was increased from three to four. This was needed because the three-dimensional grid used was much larger, i.e. 300×300×300 pixels beginning at (0, 0, 0) and ending at (300, 300, 300) in the x, y, and z- directions, respectively. The two-dimensional model required 300×300 pixels beginning at (0, 0) and ending at (300, 300) in the x and y directions. Because of this change, growth factor could travel faster with lower levels in the entire grid.

IV. Conclusions

Relatively little is known about the breast ducts in three dimensions, mainly due to the way samples from the breast are collected to produce three-dimensional images of the breast [4]. The usual way the three-dimensional breast duct is imaged is by cutting thin slices of a breast and charting the progress of each duct. This method makes it difficult to compare observed

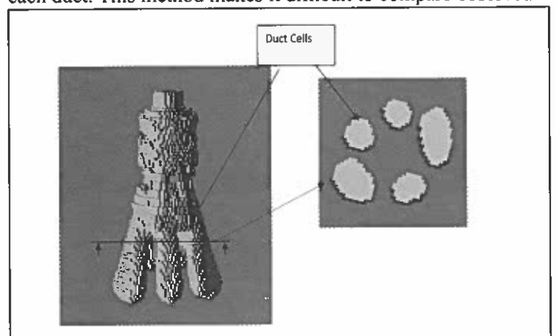

Figure 10: Improved Single Breast Duct Tree (Left) and Cross Section of Improved Single Breast Duct

in-vivo sample images with the model in this work.

However, a few key points can be made about the model proposed versus that found in nature. In Silberstein's paper [6], he notes how the breast ducts tend to trail off in nature while approaching the fat pad. This is consistent with the results of the current model, suggesting that it is qualitatively similar to that observed in nature.

Also, by changing different parameters in the model, it was fit to different women. For example, an older woman has smaller breast ducts and less dense breasts. In order to take this into account, the parameter "c" was lowered and a thinner breast duct was formed. Conversely, a younger woman's breast ducts are much thicker and the parameter "c" was increased. If a pregnant woman's ducts were being modeled, c would need to be even bigger. The next Figures (11 and 12) demonstrate this relationship in two examples.

Figure 11 illustrates six breast duct systems of an older woman whose breast ducts have began to shrink while Figure 12 is a simulation of a woman who is much younger and has much denser breasts. Both figures have six breast duct systems all starting in the same spots on the grid for both simulations. Also, both figures exhibit branching morphology with breast ducts ending at the fat pad. This is congruent with that seen in-vivo.

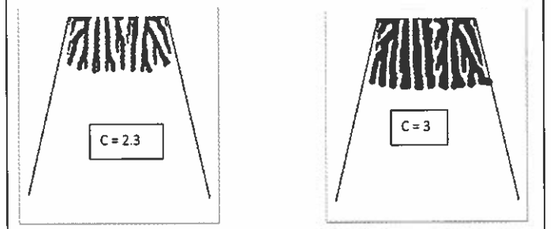

Figure 11: Breast Duct with C = 2.3

Figure 12: Breast Duct with C = 3.0

The three-dimensional results of the improved breast duct model (Figure 10) were similar to the two-dimensional results. The three-dimensional model results exhibited branching morphogenesis, which is consistent with medical knowledge. The cross-section in Figure 10 was not exactly symmetric due to the slight random element in the model. However, this was a simulation of one single breast duct system. If there were more in the simulation (like Figures 11 and 12), each separate breast duct system would be inhibiting the growth of others around it. This is because breast duct cells inhibit MMP in the cells around them. This inhibition would cause some breast ducts to flourish much less than others.

Additionally, the improved three-dimensional breast duct model no longer had breast duct cells congregating on the edges. This is apparent in the comparison of the cross sections in Figures 10 and 6. While Figure 6 had a ring surrounding the breast ducts, Figure 10 did not exhibit this characteristic. The improvement was due to the addition of the reaction between growth factors and transforming growth factor – beta1 (TGF-β1). Thus, the biological accuracy of the original model has been improved.

The ability to model the breast ducts in three dimensions will be a useful tool to researchers. Utilizing a biologically accurate breast duct model will render more accurate results and a greater understanding of the breast ducts.

Acknowledgments

This work is funded by the National Science Foundation Award Number ECS-0524042, the State Undergraduate Research Fellowship, NSF/IREE Award # ECS-0524042, and the University of Arkansas Honors College.

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Mentor Comments:

According to Professor Magda El-Shenawee, Jordan Greenlee has developed a model that more accurately represents breast ducts so that cancer detection can be improved in the future. She writes:

Jordan's major area of study is electrical engineering with major in mathematics. Jordan spent the spring semester of 2007 studying Mathematical Biology and other mathematics courses at the University of Dundee in Scotland.

Jordan has demonstrated a potential for mathematical biology research while he was working on modeling the breast. His project dealt with understanding, modeling and simulating the structures of breast ducts and blood vessels. His work is of extreme importance to the 3-year NSF funded ($250,000) project on breast cancer detection. The outcome of Jordan's research will significantly help the research group to understand the biology of the breast.

Almost all researchers who are investigating microwave modality for breast cancer detection model the breast from the engineering point of view, which is inaccurate. Therefore, a mathematical biology based model is needed to bridge the gap between physiologists and engineers. This is the motivation of Jordan's model and paper. His results show that the proposed model has the capability of modeling the breast ducts for young and old women. His results agree, in principle, with the published medical information. Jordan's research provides scientists with a greater understanding of the breast ducts and blood vessels.