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Nonlinear Systems Biology and Design: Surface Design

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Abstract

The intent of this project is to jointly investigate fundamental processes in living systems, their potential application in the novel design of responsive surfaces and spatial structures, and their applicability in cell biological research. Through the investigation of organotypic biological systems designed to recapitulate breast tissue homeostasis and changes associated with the development of cancer, parallel models work to unfold the parametric logic of these biological and responsive membrane and scaffold structures, potentially revealing their deep interior logics. At the design level, the result is an abstract surface architecture capable of responding dynamically to both environmental context, and to deeper interior programmed and non-programmed systems. At the biological level, this result is a more comprehensive understanding as to how proximal changes in tissue surface architecture may affect cell and tissue behavior at more distal sites.

1 Introduction

In "Nonlinear Systems Biology and Design: Surface Design", we argue that through analyses of "tissues" created within specialized 3-D designer microenvironments, that architects and cell biologists alike are afforded with new ways of thinking about synthetic and natural design assemblages through an understanding of dynamic feedback or reciprocity in context, albeit normal or pathological. The custom-designed digital tools used to interrogate and analyze the biological design problems at hand inform new designs for surface architectures, membrane structures, and building systems in architecture, and provide new ways of visualizing and representing complex, multi-dimensional biological data. Here, our process favors abstraction over biomimicry (i.e.

imitation of biological form).

One such project, researched by Wei Wang (PennDesign M.Arch. 2009 candidate), Misako Murata (PennDesign M.Arch. 2008, L.Arp 2009 candidate), Austin McInerny L.Arp. (University of Pennsylvania) Benjamin Vincent, Ph.D. (University of Dundee) and Agne Taraseviciute, Ph.D. (IME & University of Colorado), under the direction of Jenny E. Sabin and Dr. Peter Lloyd Jones, seeks to quantify and spatialize human breast cell and tissue contour information through the design of its surface architecture in spherical and elliptical space. Overall, the project looks at the role of personal shape change as it relates to changes in surface design. Here, the study of relationships found within the closed and open structure of tissues comprised of human mammary epithelial cells gives rise to an abstract understanding of form as it relates to a dynamic boundary condition, reflected by alterations in cell signaling, gene expression and tissue mechanics. Through the use of digital and physical algorithms, geometric abstraction gives rise to the formation of dynamic spatial structures capable of shape shifting in context.

2 Surface Design

Cell biologists and architects share similar concerns, including the question as to how form is generated and lost during development and with disease. At a fundamental level, architects and cell biologists have historically shared and borrowed from each others' shared theory, process and analysis of large information sets. In their differing approaches to the generation and systemic analyses of form, novel imaging techniques have inspired qualitative and quantitative modes of spatial-data visualization. With increasing amounts of visual data now being generated, however, there is a growing demand in science and architecture for more sophisticated computational tools that are capable of generating, extracting and analyzing specific temporo-spatial relationships.

These parallels are perhaps best reflected in the relationships that have emerged between our respective fields. Models borrowed from architects--such as tensegrity structures and geometric structures, all of which exist in nature, -have led to radical new insights into how living systems, including cells, tissues and whole organisms are assembled and function. Key to our research, this exchange has led to a new understanding as to how the tissue microenvironment surrounding cells, made up predominantly of the extracellular matrix (ECM), influences cell surfaces, its interior structure and function, including the genome itself. Similarly, models borrowed from biology, particularly regarding self-organization and the emergence of complex, non-linear global systems from simple local rules of organization, have led to the generation of new forms and structural organizations in architectural design. Examples such as these demonstrate how attentive architectural and scientific practices can be to each other--particularly within architecture and biology, which are constantly reinventing and questioning themselves in a manner that is similar to the historic avant gardes, or in the face of new technologies.

Referring to nature for design inspiration has held a long-standing tradition in architecture, industrial design and structural engineering. In 1933, Buckminster Fuller

designed a car modeled after a simple aerodynamic shape. His dymaxion automobile took advantage of one well-recognized form found in nature: the raindrop. Fuller understood that air resistance increases in ratio to velocity squared. Here, the study of nature and its principles for design, plays a key role in the success of Fuller's model. Fuller is not merely mimicking the shape of the raindrop, he is learning from the raindrop through a careful study of its chemical, physical and morphological properties thus giving rise to new ideas regarding form, function and structure.

Architects and structural engineers have historically looked to nature to design and build better shell and spatial structures. Cable nets have been inspired by the high strength-to-weight ratio of the spider web; pneumatic structures after soap bubbles; vaults after shells and eggs composed of hard and curved materials; and geodesics after radiolarian. The structural designer, Robert Le Ricolais, studied the tension networks inherent to radiolarian in order to understand the dynamic properties and qualities of closed and open "skeletal" structures. Le Ricolais professed that he had 'found no better discipline in this unpredictable problem of form than to observe the prodigies created by nature.' (Le Ricolais 1973). Particularly interesting is his observation that in nature, the art of structure and form is where to place holes, 'all different in dimension and in distribution.' (Le Ricolais 1973). This discovery lead to Le Ricolais' impossible desire to build with holes, to generate structures of 'zero weight and infinite span.' This seemingly contradictory statement shows us that in nature, we frequently find form that globally is extremely strong, yet is locally fragile. Le Ricolais argues for a higher level of (bio)synthesis. Why would we convert radiolarian structures into buildings? He exclaims, "Why should the Radiolarian help us to make money?" (Le Ricolais 1973). Robert Le Ricolais worked to unfold and eventually discover more intelligent translations and deeper relationships between architecture and science. Similarly, contemporary biology teaches the architect that context and dynamics count, leading to new models for building systems, structure, form and matter.

2.1 Architectural Biology: Context and Dynamics

The fashionable ideology of ultra-Darwinism, which reduces organisms to little more than machines for the replication of DNA, is gradually being replaced by a more holistic viewpoint, in which cell behavior is considered to depend upon complex interactions that occur within and between cells, as well as with their micro- and macro-environment through time and space. By placing the cell, tissue or organism, rather than just the genome at the center of life, a different perspective on the construction and dynamics of organismal architecture is beginning to emerge. And in this sense, the extracellular matrix plays a key role.

The idea that cells within tissues function as integrated architectural units that include their surrounding microenvironment was elegantly described by the developmental and cell biologist Paul Weiss in 1945…."the living units enmeshed in [the microenvironment—which includes the extracellular matrix (ECM)] …..bind them to the substratum. It thus confers upon what otherwise would be isolated units, the character of

a coherent tissue". (Weiss 1945). Scientific descendents who have developed this type of model include Mina Bissell, who has refined this idea to suggest that a state of "Dynamic Reciprocity" exists between cells and their immediate microenvironment: "A dynamic reciprocity exists between the extracellular matrix on the one hand and the cytoskeleton [which supports translation of messenger RNA into protein] and the nuclear matrix [which associates with chromatin, the site of transcription of genes into messenger RNA] on the other hand. The extracellular matrix is postulated to exert physical and chemical influences on the geometry and the biochemistry of the cells via transmembrane receptors so as to alter the pattern of gene expression by changing the association of cytoskeleton with the mRNA and the interaction of chromatin with the nuclear matrix. This, in turn would affect the extracellular matrix, which would affect the cell..."], (Bissell 1982) and so on (Fig 1).

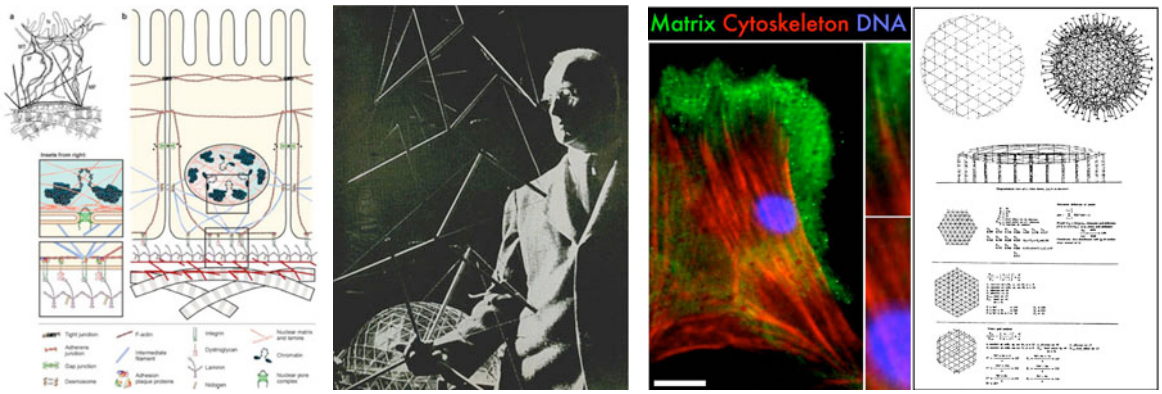


Fig 1. Bisell's model of Dynamic Reciprocity (left). Fig 2. Buckminster Fuller with tensegrity structures. Fig 3. Cells can be viewed as "hard-wired" networks of molecular struts, which extend from the extracellular space to the DNA via the cytoskeleton (middle right). At the physical level, this model is remarkably similar to Le Ricolais' Trihex network structures (far right).

What is the evidence that cell and tissue architecture, specified by the microenvironment, forms part of a dynamic chemico-physical loop that signals to cells and their cargo genomes and back again? Mostly inspired by the works of Buckminster Fuller and Kenneth Snelson, tensegrity has been successfully transposed from architecture and sculpture to cell biology (Fig 2). Tensegrity or as Fuller coined, 'Tension + Integrity = Tensegrity', is a categorical term used to describe a structural, material system defined by tensional integrity. It refers to structures that exhibit continuous self-tensioning through a balanced array of discrete tension and compression members. Significantly, as early as 1935 in his article entitled "Le Toles Composees et leurs applications aux constructions metaliques legeres", Le Ricolais imagined a rapport of relationships in opposition, leading to the conclusion that there is a correlation between a mechanical principle and a geometric pattern. (Nelson et al, 2006.). As with models of architectural tensegrity, tension in cellular tensegrity is continuously transmitted across all structures within the cell so that tension in one of the members, results in increased tension in members

throughout the structure. How does this relationship relate to environmental influences on gene expression and cell behavior? Inside cells, a network of filaments extend throughout the cell exerting tension. In turn, this structure is linked to the extracellular matrix and to the nucleus via filaments that comprise the nuclear matrix. Thus, the cell can be viewed as a "hard-wired" parametric network of molecular struts, which extend from the extracellular space to the DNA via the cytoskeleton (Fig 3). If the cell and nucleus are physically connected by tensile filaments and not solely by a fluid cytoplasm, then chemical or physical stimulation of receptors [which interact with the matrix] at the cell surface should produce immediate structural changes deep inside the cell. Indeed, both actual and simulation models of tensegrity reveal how mechanical forces applied to the cell surface lead to realignment of cytoskeletal fibers/filaments and structures within the nucleus (where the genome is located). What is more, soluble biochemical reactions are known to take place on the solid-state cytoskeletal fiber bundles, indicating that changing extracellular matrix-dependent cytoskeletal geometry can modulate signaling to and from the genome. At the physical level, this model is remarkably similar to Le Ricolais' Trihex network structures, and to his Funicular Polygon of Revolution system, which is described by "connectivity of the compression system, and the chain action of the tension cables, acting as bundles of fibers" (Fig 3).

3 New Models

Novel insights arising from collaborations between architects and biologists give rise to formerly unseen models for research, education and development in architectural and industrial design, biomedicine, nanotechnology, structural engineering and software development. These new models are informed by the study of code in context. Here, sets of relationships are defined by a blueprint of instructions or algorithms that are then altered and informed through program and especially environment, at all scales. Contemporary examples include the transformable and deployable structures developed by Chuck Hoberman. These retractable roofs, chairs, tents, wall elements and even toys and medical tools, are capable of transforming at multiple scales, adapting to diverse environments with varied functions through the use of highly adaptable 3-D scissor mechanisms. Hoberman Associates' work is based upon the fundamental idea that a designed object can transform the way a natural organism does. Hoberman argues that while the smooth transformation of size and shape is ubiquitous in the natural world, it is rare among man-made objects.

Or, perhaps we might learn from and possibly challenge the theoretical and deterministic work of Karl Chu who exclaims that the future of architecture and design is in genetic engineering, biotechnology and universal computing. He argues that for the very first time, we are able to "think of a new kind of xenoarchitecture: an information labyrinth or, better still, a universal matrix that is self-generating and self-organizing with its own autonomy and will to being." Chu references rule-based systems such as cellular automata, a discrete model invented by John Conway in Conway's Game of Life and now championed by the scientist and inventor, Stephen Wolfram. This deterministic

modeling system places code at the center of life and is studied in computation and theoretical biology. It consists of a regular grid of cells with a finite number of states such as on and off. Each cell state is determined by a nearest neighbor relationship and is configured by an initial starting set of rules. Chu offers up the challenging notion that we may very well be growing buildings through the design and mutation of code in the near future!

In contrast to Chu's autonomous and deterministic approach, the structural engineer, Cecil Balmond, and the Advanced Geometry Unit at ARUP London explores the use of mathematical, physical-geometric and natural algorithms in relationship to an active "datascape". Their proposed addition to the Victoria and Albert Museum's contemporary wing-in collaboration with Daniel Libeskind, features an interlocking natural spiral structure and an external tiled façade generated from a mathematical model called the Fibonacci Sequence that forms fractal and branching figures. This mathematical mosaic moves from ornament to structure and back again. This example shows how part-to-whole relationships drive assembly where the resultant geometric figure emerges through contextual understanding. Mutations in the generative code and the environment both intersect and interact to alter the blueprint or algorithm (literal and genomic) and new understandings emerge. What is it like to inhabit such a model? It demands a willingness to surrender to a process, to let loose a simple set of instructions, and to see how they are made intelligent and functional through mutations of transformation, feedback and context. It is a slight of hand moment where an intelligent architecture is clarified and we are allowed to enter.

3.1 IME-PennDesign LabStudio: Ongoing research between PennDesign, Pathology and Laboratory Medicine & the IME

The aforementioned dialogues and processes have already been initiated via a LabStudio initiated in Spring 2007 by Peter Lloyd Jones and Jenny E. Sabin, conducted at the Institute for Medicine and Engineering*, the School of Design and the Nonlinear Systems Organization at the University of Pennsylvania**. The LabStudio is comprised of architecture graduate students from PennDesign and graduate students and post-doctoral fellows at the Institute for Medicine and Engineering. To begin to explore models in complex physical material systems and shell and spatial structures, we have used the human mammary gland as a model system.

3.2 The Mammary Gland as an Architectural Model of Structural Connectivity

The physiologic function of the normal adult mammary gland is to produce milk upon demand, and to cease this process following weaning. Accordingly, the mammary gland must expand, differentiate and then regress in response to its global and local environment. Indeed, at puberty, a rudimentary duct or tube made from epithelial cells transforms into a fractal, tree-like structure, and with pregnancy, the structure of the mammary gland dramatically changes once more. In this instance, a specialized surface

membrane structure, made of ECM proteins is produced, and this matrix interacts with adjacent cells, and multiple soluble factors including lactogenic hormones, to promote a massive expansion of the ductal tree. Following birth, milk must be secreted from the ductal cells into a central hollow luminal space; creation of this space occurs via a cellular suicide program within a sub-population of ductal cells that no longer remain in contact with the extracellular matrix. Thus, by controlling cell growth, differentiation and survival, the ECM gives rise to boundaries and space, resulting in extraordinary overall form.Fig.4 This dependence on the ECM environment for normal breast structure and function explains why isolated mammary epithelial cells cultivated on hard, 2-D, chemically-inert, surfaces fail to differentiate, even though they possess the appropriate genes that allow them to do this (Fig 4). When cultivated within a 3-D extracellular matrix, however, ductal cells undergo a normal morphogenetic process. In contrast, with cancer, the integrity and quality of the ECM changes, resulting in inappropriate growth responses to this modified matrix environment. Collectively, these and other events lead to the loss of normal tissue architecture, a cardinal feature, and in fact a driving force in breast cancer. Clearly, modeling the behavior of tissues in 3-D represents an important step in understanding their behavior in development and disease.

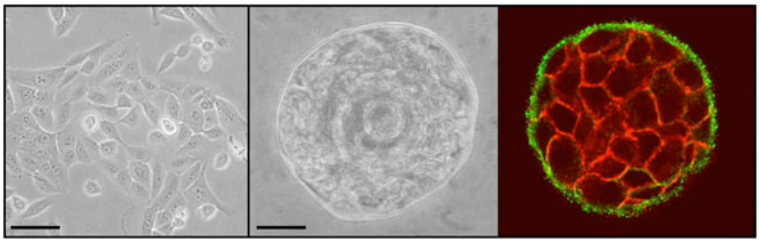


Fig 4. This dependence on the extracellular matrix environment for normal breast structure and function explains why isolated mammary epithelial cells cultivated on hard, 2-D, chemically-inert, surfaces fail to achieve a normal form, even though they possess the appropriate genes that should enable them to do this (Fig.4 left panel). When cultivated within a compliant, 3-D extracellular matrix "fabric" within a tissue culture dish, however, ductal cells can be induced to undergo a normal morphogenetic process (Fig.4 middle and right panels)

One of the crucial lessons arising from the above example is that in order for the model to reproduce relevant characteristics of the system being studied, the model has to share similar complexities and constraints of the original system. The design of these constraints, based on logic, intuition and experience, becomes the nuanced role of the scientist. To approach this, we are studying the interaction of human mammary epithelial cells with the ECM components, laminin and tenascin-C. Normal cells rest on a layer of laminin, whereas the cells surrounding breast cells produce tenascin-C. Importantly, we have shown that tenascin-C not only alters 3-D tissue architecture, but that it may actively promote the formation of structures and functions associated with breast cancer, including an ability to induce the expression of cancer-associated genes (i.e. oncogenes). To reach this conclusion, our studies made use of a complex 3-D in vitro model of breast

morphogenesis in which normal cells are cultured within a laminin-enriched gel-like matrix, either with or without the presence of exogenously added tenascin-C protein (Fig 5). Tenascin-C was included in the mix because this protein is produced in ever increasing quantities around putative and actual breast cancer cells. At the experimental level, whereas control cells formed polarized aggregated structures-designated acini-that to a large extent mimic normal breast tissue structure, complete with a continuous basement membrane and a central lumen (resulting from programmed, site-specific, cell suicide), exposure to TN-C provokes selective loss of the basement membrane and increased epithelial cell growth. To further determine the magnitude and to reveal more detail regarding these changes, we developed an imaging algorithm to generate 3-D renditions of mammary acini, which were then used to assess and quantify acinar topography and volume (Fig 5). Although TN-C increased acinar surface roughness, it had no effect on acinar volume. Based on these results, we hypothesized and thereafter showed that TN-C promotes epithelial cell proliferation within the luminal space. This finding is important, because luminal space filling is a feature of certain forms of breast cancer.

It is likely, however, that additional information regarding the relationships between mammary epithelial cells within acini and their ECM environment probably exists within our model system, yet the current tools and approaches have hampered this trajectory. Thus, finding these new relationships will likely rely upon other techniques. Moreover, abstraction of mammary acini structures is difficult using conventional cell biological computational tools. To resolve this, we have initiated a project to investigate new concepts and techniques that allow further examination of part-to-whole relationships in the normal mammary epithelium, and in one that is exposed to tenascin-C. It is hoped that these investigations will lead to novel scientific hypotheses and architectural designs.

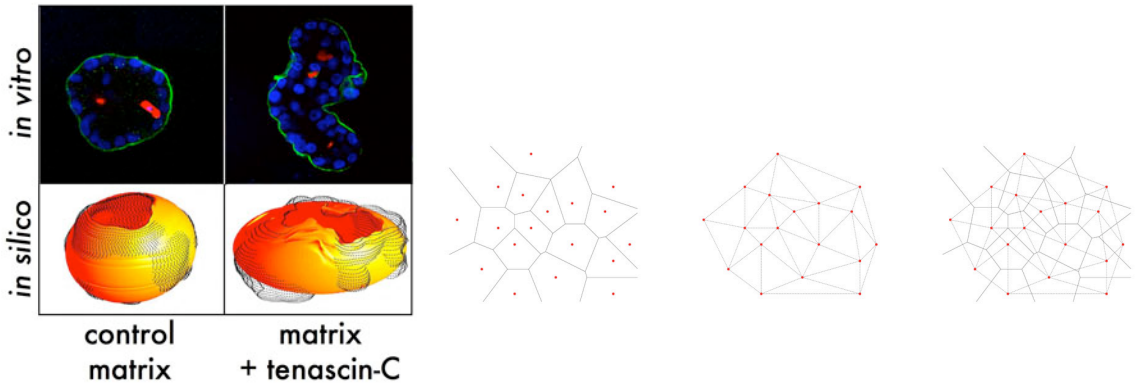


Fig 5. Importantly, our studies make use of a complex 3-D model of breast morphogenesis and cancer in which cells are cultured in a 3-D gel matrix, either with or without the presence of tenascin-C protein. Fig 6. The Delaunay triangulation is the dual structure of the Voronoi diagram.

3.3 New Concepts & Techniques: Surface Design

Overall, the surface design project seeks to quantify and spatialize mammary epithelial tissue contour information through the design of its surface architecture in spherical and elliptical space. Here, the study of relationships found within the closed and open structure of in vitro generated tissues gives rise to an abstract understanding of form as it relates to dynamic boundary conditions and biomechanics. The project entails the reconstruction and mapping of the mammary epithelium from a sequence of 2D images into abstractions that describe the interior composition of individual acini. Via this approach, the architect is afforded new insights into the shifting relationships between surface structure and deeper interior structural concerns. This in turn, may contribute to novel designs of shell and spatial structures that are not only responsive at the level of their surface structure, but also at their deep interior structural cores.

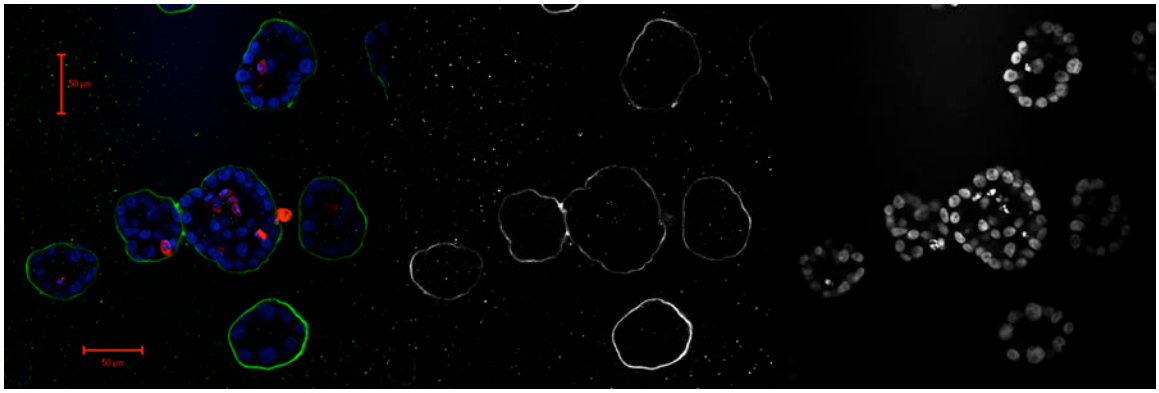
In this surface design project, we are working with physical and digital algorithms in three different trajectories. The first makes use of digital algorithms: Delaunay Tessellation and the Voronoi diagram. A second trajectory incorporates deployable structures as a testing ground for programmatic information gleaned from the biological model of the study. In the third study, apoptosis, or a programmed cell death, is considered as a modeling system for studying the formation and maintenance of luminal space in the normal human mammary gland.

4. Surface Design 1: Geometric Duals and Space-filling Polyhedra

The Delaunay Tessellation is a dual tessellation of the Voronoi diagram. A Voronoi diagram is a geometric structure that represents proximity information about a set of points or objects. Given a set of sites or objects, the plane is partitioned by assigning to each point its nearest site. The points, whose nearest site is not unique, form the Voronoi diagram. That is, the points on the Voronoi diagram are equidistant to two or more sites. The Delaunay triangulation of a point set is a collection of edges satisfying an "empty circle" property: for each edge we can find a circle containing the edge's endpoints but not containing any other points. The Delaunay triangulation is the dual structure of the Voronoi diagram. By dual, we mean to draw a line segment between two Voronoi vertices if their Voronoi polygons have a common edge, or in more mathematical terminology: there is a natural bisection between the two, which reverses the face inclusions. The circumcircle of a Delaunay triangle is called a Delaunay circle (Fig 6). This is not all that dissimilar to Le Ricolais' investigations into bimorphism, or the combination of a form with its dual. The planar image of a 3-D structure can be found by graphically representing the forces in its members, once the reactions at boundaries have been determined. This planar image is a structure's dual.

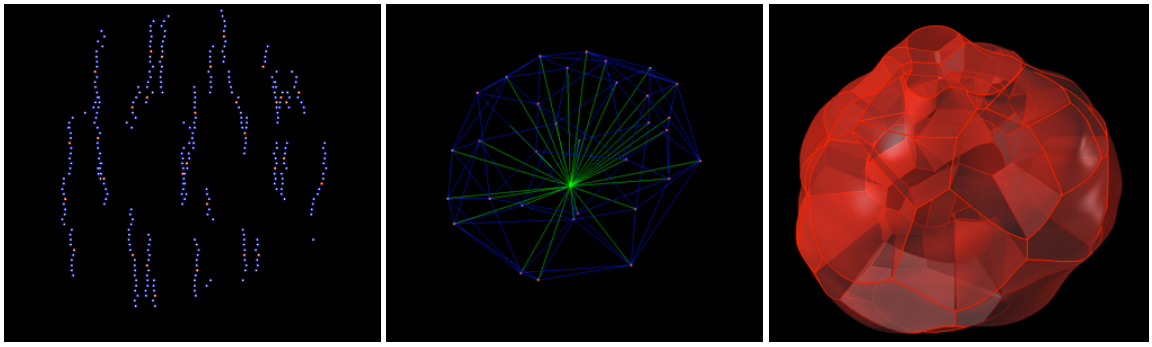
Early modeling investigations for the first trajectory include the analysis of several image Z-stacks derived via confocal microscopy. The first series of 63 images show how cells are distributed in space based on relationships between an external surface of the acini, .i.e. the basement membrane (shown in green), the nuclei (in blue) which houses the

nucleus and the majority of the genome, and the formation of an internal luminal void (Fig 7).



Figs 7,8,9. The first series of 63 images show how cells are stacked and distributed based on relationships between an external membrane called a basement membrane (shown in green) and the formation of an internal luminal void. Color channels are used to select pixel-based information from the original image sections.

The blue dots represent the location of the nuclei, while the red lines indicate the boundaries between neighboring cells. The geometrical centroid of each nucleus is used as reference points to regenerate the structure into a 3D parametric mesh model. The basement membrane (green) and the boundary of the inner void are traced in a 3D modeling program. Color channels are used to select pixel-based information from the original image sections (Figs 8,9). This pixel-based data is refined and sharpened through a series of filters that make adjustments in lightness, contrast and noise. The processing of pixel-based data enables a more accurate description of the location of the centroid of each nuclei and a clearer definition of the boundary condition.



Figs 10-12. The individual sections of traced points are synthesized by linear stacking with a deviation of 1 micrometer. The blue mesh is based on the Delaunay algorithm. This mesh structure models the linear connectivity within acini. The red mesh models geometric information filtered by the Voronoi algorithm.

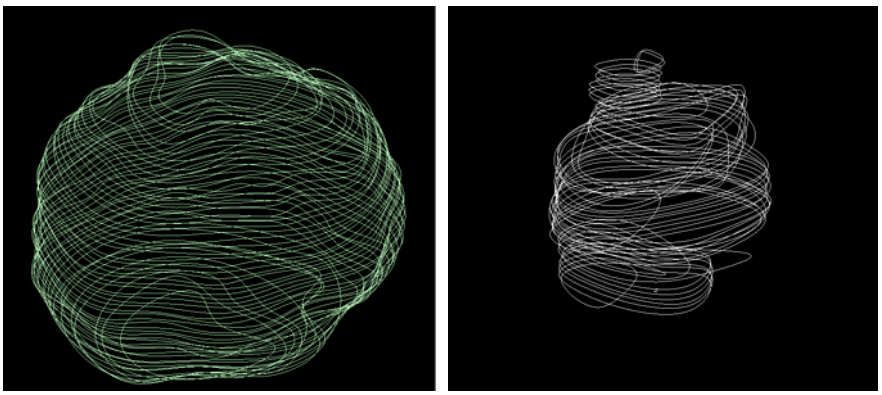
All 63 sections are mapped and reconstructed, using both the Delaunay and Voronoi meshes. The individual sections of traced points and curves are synthesized by linear

stacking with a deviation of 1 micrometer (Fig 10). The blue mesh is based on the Delaunay algorithm (Fig 11). This structure models the linear connectivity within acini. Connections are made between acini through shortest path or nearest neighbor information. The red mesh model depicts geometric information filtered by the Voronoi algorithm (Fig 12). This filter visualizes moments of equilibrium found at boundaries under variable pressures. A third algorithm is used which is based on the same geometric filter called the Voronoi Diagram, but this final step uses a 3D Voronoi Diagram. This allows for the modeling of the 3D space and structure of equal balanced boundaries between point sets. The algorithm follows the same logic as the 2D Voronoi, but nearest neighbor paths shift from straight-line connections to equal distant planes. The red enclosure models the boundaries of cells within the tissue.

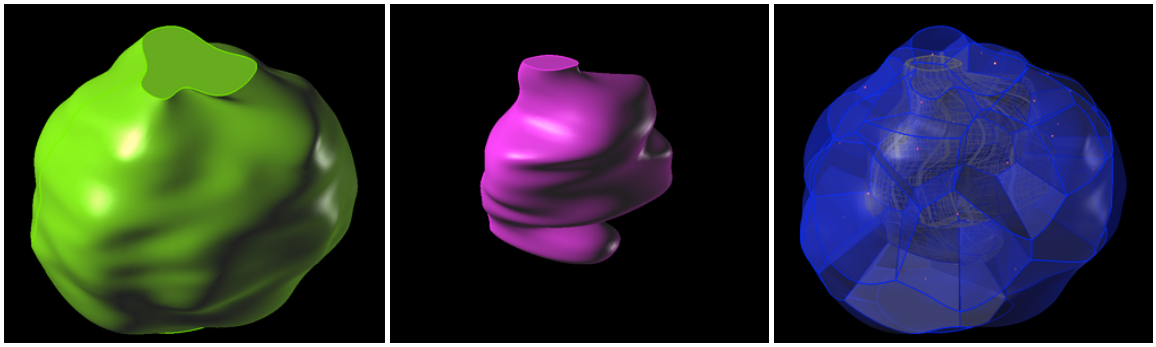
Within the aforementioned system, we are interested in how the Delaunay and Voronoi filters may aid in the modeling and description of the acinar formation, in terms of minimized energy and dynamics. Here, parametric relationships describe the distribution of forces throughout the structure. For example, a tension deferential exerted upon the external surface tells us about the logic and formation of interior structures. This in turn, provides new insight into the novel design of abstract shell and spatial structures composed of complex surfaces with dynamic interior structures. Subtle adjustments made to interior structures adjust membrane behavior and performance and *vice versa*.

4.1 Methods 1

In the more advanced modeling stages, the exterior basement membrane and the inner luminal void are reconstructed in 3D digital space from the data abstracted from the confocal image stacks (Figs 13,14). A single layer of smooth nurbs-based surface is generated from the contours traced from the original images (Figs 15,16). It should be noted that the basement membrane does not actually look like this, rather it is amorphous, but these tools allow us to precisely map the position of the basement membrane.



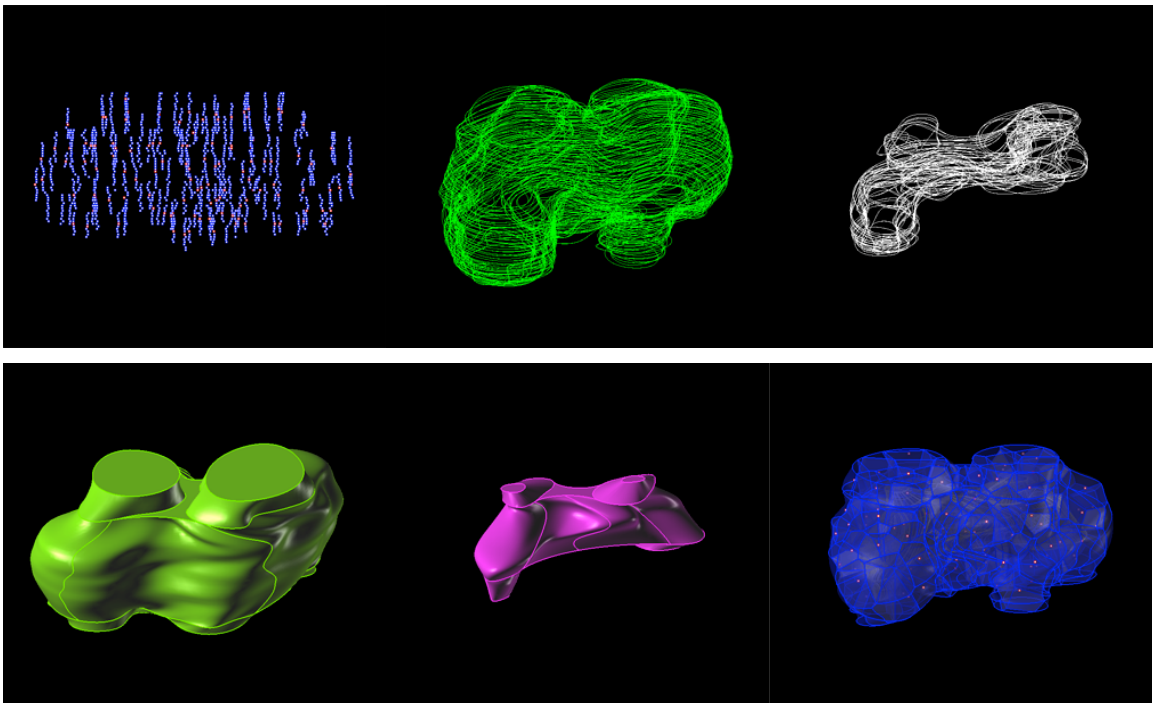
Figs 13,14. The next step is to "reconstruct" the surface of the exterior basement membrane (left) and the inner luminal void (right).



Figs 15,16. A single layer of smooth nurbs-based surface is generated from the contours traced from the original images. Fig.17 The third step is to utilize the centroid as a resource, the basement membrane and inner surface as boundaries or limits and to build a crystal-shaped cellular structure to abstract formation of acini. The logic of locating and forming the boundary for neighboring cells is again based on the 3-D Voronoi diagram, within which a flat surface is generated in an equal distant position from neighboring points.

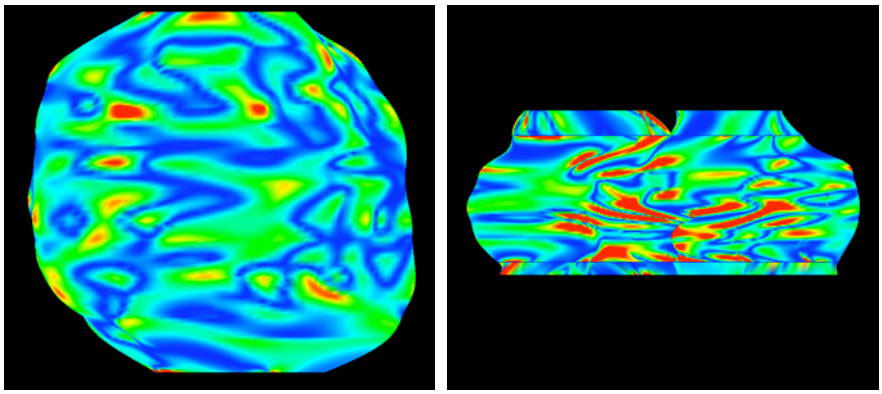
The third step is to utilize the centroid of the acinus as another reference point or resource, the basement membrane and inner surface as boundaries or limits, and to build a crystal-shaped cellular and spatial structure to abstract and better understand the structure of acini. The logic of locating the boundary for neighboring cells is again based on the 3D Voronoi diagram, within which a flat surface is generated in an equal distant position from neighboring points. The crystal structure encloses certain points and is the result of a series of calculations based on distance and point-to-point orientation. A single local crystal module is the result of the synthesis of global behavior across the entire structure (Fig 17). The logic that drives the behavior of the surface boundaries activate, limit and control the formation of both individual units and the entire shell structure.

In order to gain more information about the formation of the "crystalline" and spatial structural forms, their surface structures and their parametric relationships, two experimental conditions were modeled and compared—case 1 is a normal control, as described above, whereas case 2 represents acini exposed to both laminin and tenascin-C (i.e,. an ECM microenvironment that recapitulates the tumor microenvironment) as described below (Figs 18-23).



Figs 18-23. Case 2 with TN-C. Fig.18 stacked nuclei points (upper left), Fig.19 stacked contours generated from exterior points (upper middle), Fig 20. stacked contours generated from interior points (upper right), Fig 21. exterior smooth surface (lower left), Fig 22. interior smooth surface (lower middle), Fig 23. Voronoi mesh structure, nuclei and interior structure (lower right).

The first comparison focused on surface roughness, which increases in acinar cultures exposed to TN-C. Surface roughness is calculated by the slope of the tangent plane on specific points on the surface. The range of roughness is visualized through a color spectrum. Red indicates roughness and blue indicates a smoother surface. In the case of the control models, the surfaces are relatively smooth whereas the inclusion of TN-C increases the amount and degree of surface roughness (Figs 24,25).

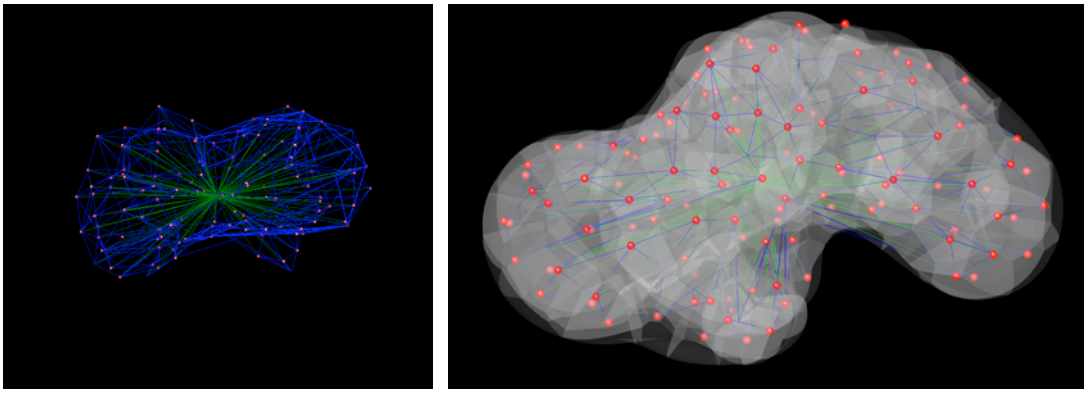


Figs 24, 25. The first comparison is focused on surface roughness, which we know

increases in breast cells treated with TN-C. Surface roughness is calculated by the slope of the tangent plane on specific points on the surface. The range of roughness is visualized through a color spectrum. Red indicates roughness and blue indicates flatness. Control (middle diagram) and TN-C treated (right).

The second comparison examines distance, packing behavior and connectivity between neighboring nuclei, features that are routinely assessed by cancer biologists when evaluating the extent of deviation from a normal mode of behavior. A 3D Delaunay system that is projected to the outer basement membrane surface is used to frame the local connectivity, and the distances between neighboring nuclei can be measured.

The third comparison focuses upon "surface tension". In terms of structure, the tension of a certain position is determined by the combination of its area and radius. Tension increases as area and radii increase. The distance represents the radius from the centroid of the acini to the centroid of the nucleus. The area is determined by how much of the basement membrane is occupied by an individual cell. Based upon observation, the tension in the controlled case is relatively evenly distributed, while in the diseased scenario, the tension shifts dramatically. Collectively, these findings may be relevant to breast tumorigenesis in which loss of basement membrane continuity, cell packing, and changes in tensional homeostasis in response to alterations in the ECM and gene expression are known to play a central role (Figs 26,27). Further, all three studies allow us to envisage potential parallel models where such environmentally impacted crystalline structures may take on new constraints within an architectural context, and at different length scales.



Figs 26, 27. The third comparison is focused on surface tension. In terms of structure, the tension of a certain position is determined by the combination of its' area and radius. Tension increases as area and radii increase. The distance represents the radius from the centroid of the acini to the centroid of the nucleus.

4 Surface Design 2: Adherens junctions as a mechanism to reveal novel forms of structural deployability

In the second trajectory of the surface design project, deployable structures are

incorporated as a testing ground to better study junctions between cell surfaces. Deployable structures are composed of three key elements: structure, mechanisms and the programming of such mechanisms. In our case, the information programmed and transmitted through the specified mechanisms comes directly from the biological model being studied.

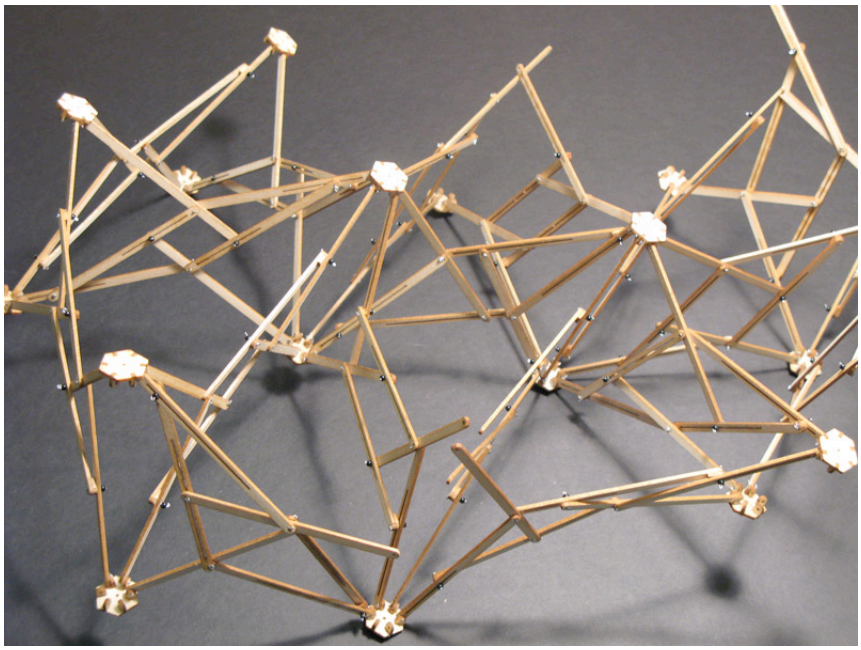
Adherens junctions are specialized forms of adhesive contacts important for tissue organization in developing and adult organisms, including construction and maintenance of the normal, adult mammary epithelium. Cadherins, a major component of adherens junctions, form protein complexes with cytoplasmic proteins that convert the binding capacity of the extracellular domain into stable cell adhesion between adjacent cells and their surrounding extracellular matrix. The extracellular and intracellular domains of cadherins provide cytoskeletal anchorage between cells, coupling cytoskeletal force generation to strongly adhere sites on the cell surface and the regulation of intracellular signaling events. With breast cancer, however, the stability of these junctions is compromised. In fact, loss of cadherin-based junctions has been shown to contribute to tumor formation. Mechanistically, this relies upon the release of cadherin-associated molecules into the cell interior, where their function is transformed to one that regulates the expression of genes in the nucleus that transform normal cell behavior into an aberrant form. Since tenascin-C affects cell-cell junctions at the level of actin cytoskeleton, we aimed- at the design level- to use this understanding in order to understand how this structural and functional cellular component changes between adjacent cells in control and tenascin-C treated 3D organotypic normal, mammary epithelial cell cultures with the hope that these studies might reveal novel modes of structural deployability.

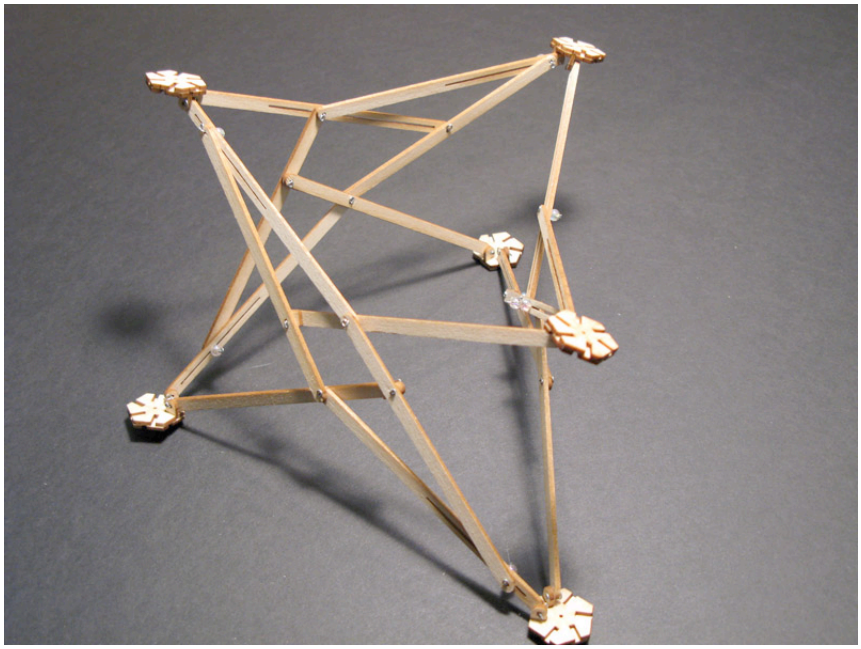
Methods 2

Filopodia are thin projections from a cell's cyctoplasmic edge containing actin filaments. Central to cell-to-cell adhesion, recent research has found that at coincident membrane sites, filopodia reach and penetrate into adjacent cells linking them together. Over time, this causes the actin cytoskeleton to remodel. Adherens proteins are expressed on epithelial cells near the apex of the surface showing basal lateral polarity. In our investigation, one hypothesis deals with the degradation of the basal lateral polarity in TN-C treated cells. Alternations in actin dynamics in response to changes in a surface con\dition are highly complex and rely upon super-imposition of solid state and soluble scaffolds and signaling hubs..(will explain in more detail), and so for this project, certain interactions are hypothesized based on available data for analysis. Nevertheless, this research has resulted in new ways to define possible variables that could be manipulated, abstracted and tested in novel deployable structures.

To further reveal the relationships between cell-basement membrane connections and cell-cell interactions that emanate from changes in the former, points of intersection where the cells touch the basement membrane, were extracted and abstracted to visualize the spatial relationships between these points of contact. When applying the deployable

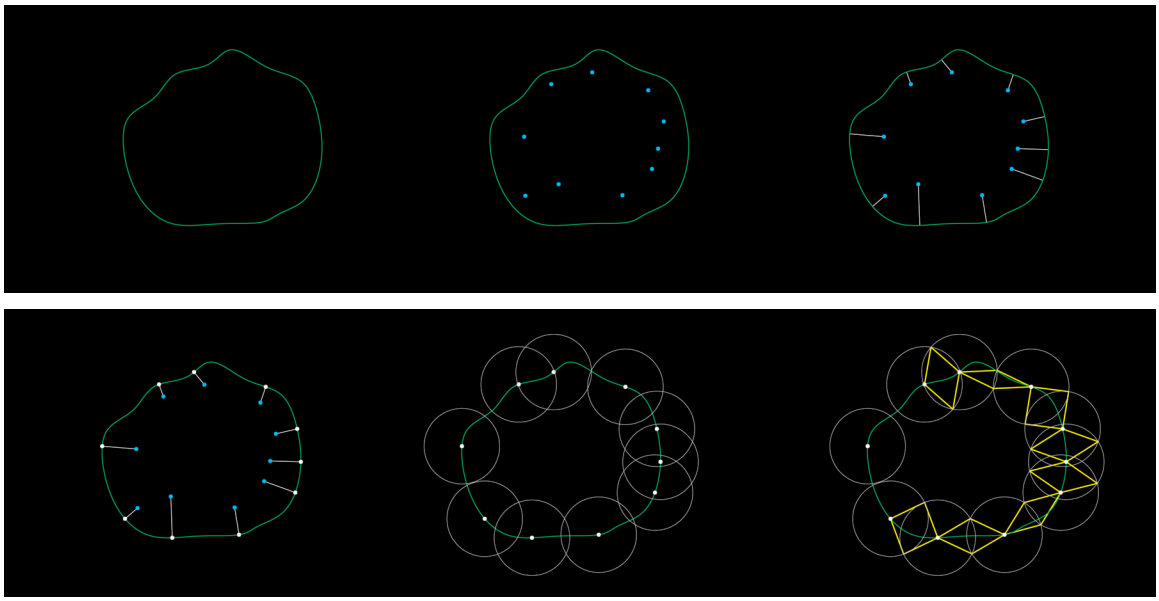
structure model, the varying range, quality and duration of each deployable performance varies within the normal and diseased contexts. Further, by programming common 2D and 3D scissor mechanisms with this biological information, we are able to generate dynamic and differentiated deployable structures. Here, the geometry of the structure transforms from a strictly abstract and predictable state to one that acquires variability and novel response mechanisms to shifts in environmental input. Below are two images of the described deployable structures (Figs 28,29).





Figs 28, 29. Deployable structures. Study models by Misako Murata.

The packing density in a typical 2D deployable structure may be changed either at the level of the distribution of points within the model being studied, or via manipulating the length of the lines connecting neighboring points. Both parameters contribute to the formation and duration of a deployable connection, but they also reference different packing performances. In order to calculate the effective range of both parameters and the length of the basement membrane contour, we built these connection models for every acini section. The diagrams below outline this process (Figs 30,31). Here, subtle adjustments to the exterior "basement membrane" change the degree and extent of each local deployment thus affecting the overall global behavior of the deployable structure.

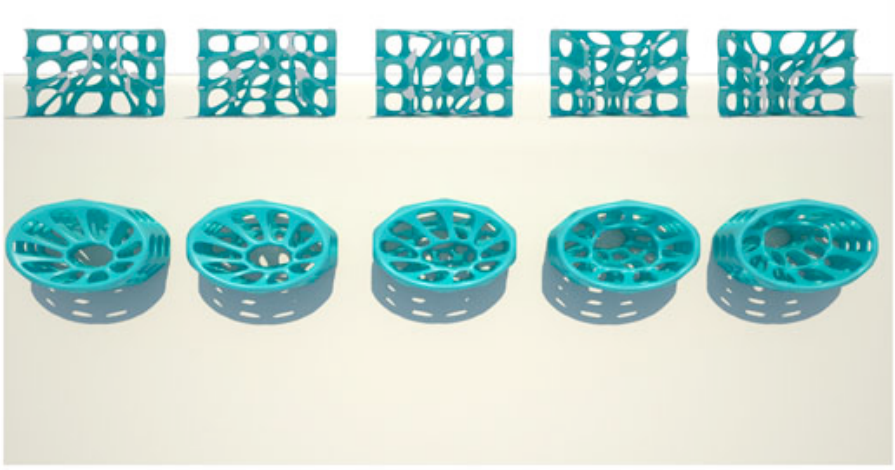


Figs 30, 31. Programming of the 2D and 3D mechanisms with information from the model of study: the human mammary gland.

The final stage of this study involved the scalable reconstruction of the embedded biological behavior in deployable systems (described above) to a building and pavilion prototype. The rapid manufacturing of a skin structure composed of water-jet cut aluminum flaps is married with the intricate design and fabrication of steel struts and mechanisms composed of hinges and pins. Information gained from studying geometry and matter at the cell and tissue level is embedded in the final assembled prototype alongside architectural constraints dealing with issues of scale, material, thickness and fabrication. The final prototype deploys locally and along nonlinear paths leading to a differential and local experience at an architectural scale (Figs 32,33,34).

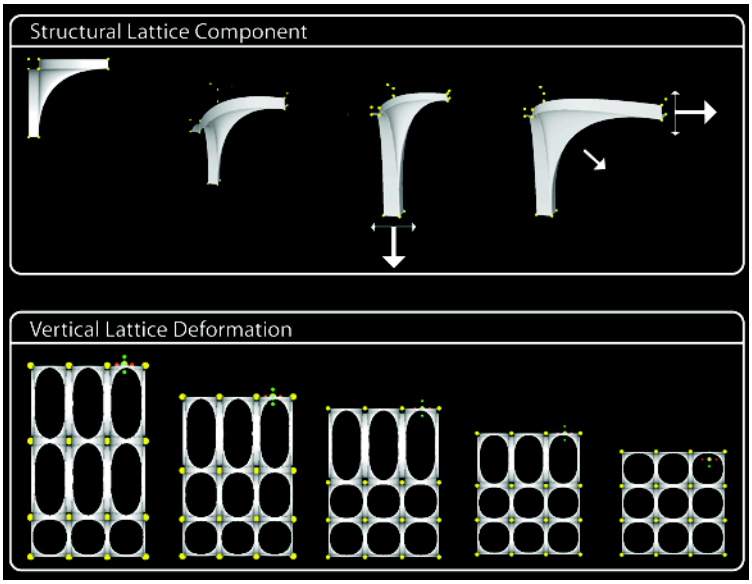
5 Surface Design 3: Apoptosis or programmed cell death as an architectural modeling system

The third and final project makes use of parametric and associative design methods to derive a modeling system from elements observed in a cellular apoptotic process. This system works by adjusting distance relationships between points, creating polygons with varying surface areas. Balance exists within the system to control the range in which the overall surface area and volume are able to change (Fig 35).



Normal human mammary epithelial cells (MCF-10A) cultured within a reconstituted extracellular matrix (ECM) form multi-cellular 3-D polarized acini, complete with a central lumen. These cells are enveloped by a continuous endogenous basement membrane. Apoptosis, or a programmed cell death, plays a crucial role in the formation and maintenance of luminal space in the mammary gland. The process of apoptosis begins when the cell's loss of contact to the basement membrane. This disconnect initiates the process of cell suicide. Upon proliferation of new cells within the layer of epithelial cell lining, others are forced off the ECM, beginning the process of cell death. Healthy cells develop during gestation until the layer of epithelial cells reach a level of stasis in which there is no more cell death or proliferation. In the cancerous condition, proliferation of cells proceeds without the process of apoptosis, eventually filling the luminal cavity. This developmental process was studied to understand the relationships between proliferation and the role of apoptosis in normal human mammary gland health.

The first translation of the digital model to physical form resulted in the discovery of structural relevance at the seams created along the lines of collapse. The re-association of the parametric equation from a 2D surface to a 3D volume developed what could be a material and structural system that could deploy and adapt to specific spatial requirements. The relationship between the ECM and the layer of epithelial cells manifests in a double-layered model of gradual difference responding to the luminal remodeling process, which occurs in conjunction with apoptosis (Fig 36).



6 Conclusion

How might the aforementioned modeling investigations enable new understandings in how a surface structure may respond dynamically to its environment and in turn be tuned by its deep interior structure through feedback mechanisms? Associative and parametric software packages are enabling architects and now cell biologists to model architectural and structural relationships inclusive of environmental, material and physical parameters. Never before have architects so readily been able to shorten the path between designs drawing to fabricated output. In fact, the act of drawing is arguably a modeling exercise in and of itself where fabrication and construction instructions become output. What was once seemingly impossible is now radicalizing our cityscapes worldwide. However, with these technological breakthroughs also comes a high degree of sameness. Furthermore, current generative modeling tools enable designers to model and visualize natural forms quite readily. Unfortunately, this ease frequently favors direct formal translation of natural and biological shapes and forms for architectural purposes as opposed to designing with a deeper understanding of the parametric relationships at hand. As Le Ricolais asked, why would we convert radiolarian structures into buildings? Le Ricolais claimed that nature is our greatest teacher in dealing with the problem of form. By immersing oneself in biological design problems, such as those described above, and abstracting these biological relationships into code-driven parametric and associative models, it is possible to gain new insights into how nature deals with dynamics, environment and feedback within cell and tissue structures. Certainly, we do not aim to generate a form or design a building after a cellular structure, but perhaps architects might learn from these biological models such that architecture acquires ‘tissueness’ or ‘cellness’ and is not merely ‘cell- or tissue-like’. We believe the tools produced and designed throughout this process will find potent alternative applications in architecture. The abstract models described in this paper offer up novel approaches and methods for

the design and fabrication of macro-scale shell, spatial and deployable structures capable of shape shifting in alternative and scalable contexts.

Based upon our investigations, we posit that any future investigation between architecture and biology should require a consideration of models that capture and cultivate the dynamic reciprocity of the less obvious organic systems of architecture and the more obvious living complexities of biological systems. To address this, we ask whether architecture can take a cue from biology in matching the complexity of its generative design models to the very dynamic features of the living environment and organic milieu in which the architecture is a part, or, perhaps even attempt to build models which do more than merely problem solve structural difficulties, and explore the intricacies and organizational capacities of the diverse physical material systems from which it is constructed. Only then will we begin to move towards a more dynamic and volumetric model where surface architecture acquires connectivity, performance and time as embedded features. The collective result, as depicted in the examples explained this paper, is the formation of visionary shell and spatial structures. Here, the abstract surface architecture becomes volumetric and responds dynamically to both environment (context) and to deeper interior systems.

7 Results

Since the first Annual Nonlinear Systems Organization (NSO) meeting in 2005, we have actively initiated research collaborations and teaching between the IME, the NLSO, and other associated faculty in the Department of Architecture at PennDesign. Our research collaborations and teaching have extended to and have included faculty and practitioners at the School of Medicine UPenn, School of Engineering and Applied Science UPenn, School of Arts and Sciences UPenn, the Architectural Association, Arup Advanced Geometry Unit, Bentley Systems, KPF Advanced Modeling Groups, Foster and Partners Smart Modeling Group and Black Box SOM.

Together with Peter Davies, Detlef Mertins and Cecil Balmond Jenny Sabin and Peter Jones have publicly discussed or exhibited (together and separately) our new ideas and collaborations at the MAK Center in Los Angeles, The Slought Foundation in Philadelphia, the second annual NSO meeting on Architecture Bits and the third annual NSO meeting on Nonlinear Fabrication hosted at PennDesign in Philadelphia, The Esther Klein Gallery at the University City Science Center, the Institute for Contemporary Art in Philadelphia, the NYC Design Computation Group (a group comprised of architects and structural engineers considered to be at the cutting edge in computational design), the IASS International Symposium, "Shell and Spatial Structures: Structural Architecture - Towards the future, looking to the Past," Venice, Italy, Cambridge University U.K., the Smart Geometry Conference 2008 in Munich, the exhibition FIBER at the F.U.E.L Collection featuring Sabin, Jones and Beesley with PennDesign graduate students, the College of Physicians in Philadelphia and at the Annual Pathology conference in Toronto, Canada.

These presentations have all showcased our new collaborations. As such, we are collectively extending our research findings and philosophy to a broad audience. For the most part, these meetings and exhibits have allowed us to feature new research findings that stem from a 2007 and 2008 Summer LabStudio sessions (co-directed by Sabin and Jones), which were based in the Jones lab at the IME and design studios at PennDesign (LabStudio couples architects with scientists within the research lab setting) and our 2007 and 2008 fall elective: Nonlinear Biosynthesis. This new, research intensive elective, co-taught by Sabin and Jones, involving 14 Architectural Graduate students (ARCH745) continues to explore directions through research at the IME and within the School of Design. This core elective now titled, Nonlinear Systems Biology and Design, has been recently voted into the permanent graduate architecture curriculum at PennDesign. Sabin and Jones are also actively working on an upcoming 2009 monograph entitled "LabBook" by Sabin & Jones, which will outline the beginnings of this highly productive collaboration that aims to exchange ideas and design tools from architecture and biomedicine for the analysis of form and function at multiple length and time scales.

Other publications related to our research have also been generated in architectural journals, including 306090 (Princeton Press), The MAK Foundation Gen(H)ome catalog (LA), 10+1, a Peer-reviewed paper, "Nonlinear Biosynthesis, Visionary Shell and Spatial Structures," published and presented at the IASS International Symposium, "Shell and Spatial Structures: Structural Architecture - Towards the future, looking to the Past," Venice, Italy and VIA (a Penn-based design journal). A paper to be submitted to the Journal of Pathology is being prepared. "Nonlinear Systems Biology and Design" was published by ACADIA 2008: Silicon + Skin, Biological Processes and Computation and our work was featured at the conference, Architectural Geometry 2008, Vienna.

We have not yet sought seed funding to support these initiatives, either at the SOM or the SOD, but hope that this possibility will arise. For the most part, support has been achieved via an existing R-01 (PI: Jones), a Bentley Systems grant (via the NSO), an ITMAT-IME Post-doctoral fellowship, an American Institute of Architects 2008 Upjohn Research Grant (to Sabin & Jones) ($18,000) and most recently, a Research Facilities Development Grant through the Vice Provost for Research at the University of Pennsylvania (to Sabin and Jones) ($170,000). Jones was recently elected to the Architecture faculty at PennDesign, and is the 2007-08 NSO Fellow. In 2007, Jenny Sabin was invited to become a member of the IME, and is the first PennDesign faculty member to achieve this.

8 Next Steps

Our research will continue to focus upon the design of tools for application in both scientific and architectural projects. 3D printing technology and micro-fabrication techniques will infiltrate and inform our research over the next year. Next steps for research entail the following:

(a) Motility: This project investigates the role of the microenvironment in controlling cellular movement and the shifting geometries inherent to this movement. In short, diseased cells move differently from healthy cells and we seek to derive 4 dimensional motility signatures for these movements. This project will develop a metric for quantifying these differences in motility and thus enable a novel understanding of the space and structure of movement and change in architecture. Results from this research are currently informing novel material and fabrication studies at the nano, micro and macro scales.

(b) Networking/Branching Morphogenesis: The second project topic investigates part to whole relationships found during the generation of branching structures formed by interacting vascular cells. The study and quantification of this network will allow for a greater understanding of how the design of variable components give rise to structured networks. Results from this project are currently informing the design, assembly and installation of a large-scale architectural project at Siggraph 2009.

10 Participants

Directors & Instructors

Jenny E Sabin (M.Arch., (Hons), B.F.A. Ceramics (Hons), B.A. (Hons))

Peter Lloyd Jones (B.Sc. (Hons) in Molecular Biology; Ph.D. in Pathology)

Designers/Researchers

Andrew Lucia (M.ARCH)

Erica Savig (M.ARCH)

Scientists/Researchers

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Vanesa Karamanian (M.D.)

Shawn Sweeney (PhD)

Agne Taraseviciute (PhD)

Mathieu Tamby (PhD)

Jan Baranski, B.Sc.

Jae-Won Shin, B.Sc. (Hons)

PennDesign M.ARCH Graduate Students and LabStudio Summer Research Interns

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Jared Bledsoe

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AJ Chan

Young-Suk Choi

David Ettinger

Shuni Feng

Joshua Freese

Kenta Fukanashi

Pablo Kohan

Chris Lee

Jaeyoung Lee

Huishi Li

Lauren McCuaig

Austin Mcinerny

Kara B Medow

Misako Murata

Vahit Muskara

Chuck Nawoj

Jeffrey Nesbit

Jason Niebish

Andrew Ruggles

Kirsten Shinnamon

Allison Schue

Gillian Stoneback

Wei Wang

Shuo Zhang

11 Comments

"This research collaboration between the IME and NLSO puts into operation a renewed dialog between architecture and biology that has been gaining momentum in recent years and holds great potential for the co-evolution of both disciplines."

Detlef Mertins, former Chair, Department of Architecture, University of Pennsylvania

"The IME-LabStudio collaboration is a unique approach to 'Nature's design' of biological systems and their regulation by the local environment. It promotes the flow of new ideas across disciplines, identifying and developing biological principles directed to architecture and an understanding of design approaches in biomedicine and potentially personalized medicine. Facilitating these important interactions through the IME is an enormous pleasure."

Peter F. Davies, Director, Institute for Medicine & Engineering, Department of Pathology & Laboratory Medicine, University of Pennsylvania

The content for this project would not have been possible without the hard work and dedication of the following students, post-docs and fellows: Wei Wang (PennDesign M.Arch. 2009 candidate), Misako Murata (PennDesign M.Arch. 2008, L.Arp 2009 candidate), and Austin McInerny L.Arp. (University of Pennsylvania), Benjamin Vincent, Ph.D. (University of Dundee) and Agne Taraseviciute, Ph.D. (IME & University of Colorado)

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Appendix

* The Institute for Medicine and Engineering (IME): The mission of the Institute for Medicine and Engineering (IME) is to stimulate fundamental research at the interface between biomedicine and engineering/physical/computational sciences leading to innovative applications in biomedical research and clinical practice. The IME was created in 1996 by a mandate from the Trustees of the University to bring together the Schools of Medicine (SOM) and Engineering and Applied Science (SEAS) to pursue opportunities for collaborative research.

** The Non-Linear Systems Organization (NLSO): The NLSO is a research group, based at University of Pennsylvania School of Design directed by internationally renowned engineer and designer, Cecil Balmond. The NLSO mission is to explore ways in which architecture can demonstrate, test and apply insights and theories from mathematics and the sciences in the design of material structures across an open-ended range of scales, materials and design disciplines. By transferring theoretical scientific knowledge into the applied design arts, it seeks to expand the horizons of design and, at the same time, promote a broader appreciation of these theories by the general public. The work of the NLSO is experimental and treats the activity of design itself as a form of research. The NLSO seeks to produce new organizations of matter and life that possess extraordinary beauty, diversity and versatility. By exposing scientists and theorists to the opportunities of applied design, the NLSO also seeks to stimulate the further development of science.