# Quantifying Spatial Heterogeneity of Syncytial Cells using Alpha Shapes

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## Background

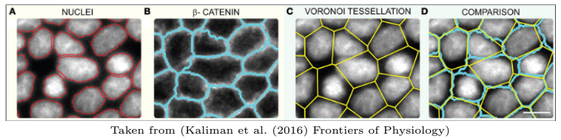
- Viruses are one of the main pathogens that cause illness as a response to infection.
- Some viruses form multi-nucleated cells due to viral protein expression on the surface of infected cells.
- These multi-nucleated cells are known as **syncytia**.
- Current models accurately represent the temporal increase in syncytia over time, but not the spatial effects syncytia have.
- We are interested in a quantitative measure that can represent these spatial components for the purpose of model validation.

## Cell-Cell Fusion Assay

- Cell fusion assays use a donor cells expressing the viral surface protein and acceptor cells expressing the cell receptor to observe fusion. This interaction is spatially dependent on the contact of a donor and acceptor cell.
- Using an Agent-Based Model (ABM), we can represent cell-cell fusion assays computationally. While having enough data to validate our ABM temporally, we do not have the information for spatial validation.
- Spatial heterogeneity is a measure of the density of syncytia in a space. Spatial heterogeneity can change between virus strains and time points. This measure will be used to validate our model off of experimental data.
- Our spatial heterogeneity measure will be based off of a topological framework.

## Spatial Heterogeneity

- We will calculate our spatial heterogeneity values using topology and graph theory.
- We will be using persistent simplicial homology to be able to investigate our voids in our data set.
- An important factor is the many targets of syncytia forming viruses are epithelial cells.
- It has been found that epithelial cell boundaries can be represented by Voronoi diagrams when plotting our nuclei of unfused cells as nodes.



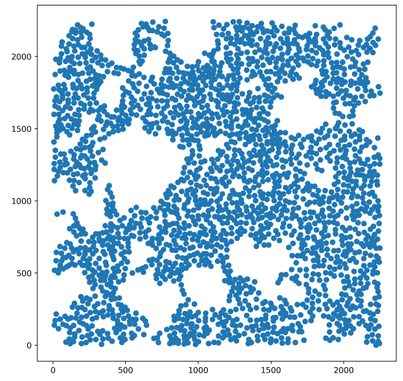

Taken from (Kaliman et al. (2016) Frontiers of Physiology)

## Methodology-Nodes

- We first start with a set of points, extracted from an virus mediated cell-cell fusion assay

$$A = \{a \in \mathcal{R}^2\}.$$

- These points are the nuclei of our unfused cells. We are interested in forming a graph of the nearest neighbors of all nodes.



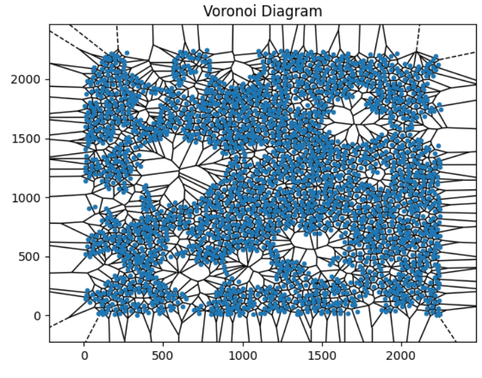

## Methodology-Voronoi Diagram

- We need to separate all points in space by their nearest node.
- Using the equation

$$V(a_k) = \{b \in B \mid d(b, a_k) \leq d(b, a_j) \text{ for all k} \neq \text{j}\}$$

we can define a Voronoi cell. In our equation $d(b, a_k)$ is our distances of our arbitrary point $(b)$ to our nearest node $(a_k)$.

- By putting all of our Voronoi cells together we can get a rough estimation of cell boundaries

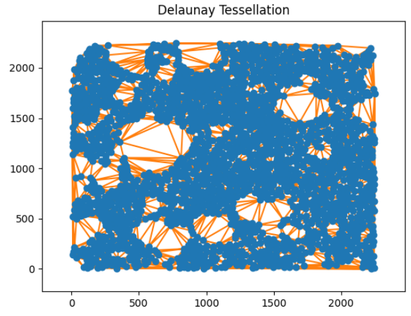



## Methodology-Delaunay Tessellation

- Using the Voronoi diagram, define the Delaunay tessellation as creating a 'line' anywhere there an intersection point of Voronoi cells

$$Del(A) = \{S \subseteq A \mid \bigcap_{a \in S} V_a \neq 0\}.$$

- The Delaunay tessellation have many different subsets containing different variations of combinations of lines
- We can filter through these using **alpha shape filtration**




## Methodology-Alpha Shape

- New definitions of our previous math is needed with applying this filtration.
- Using

$$B_{a_i}(r) = a_i + r_{del}\mathbf{B}^2.$$

to define our new allowed points to consider for Voronoi diagrams. Here $\mathbf{B}$ is the ball around our node, having a radius of $r_{del}$

- Now defining the filter Voronoi diagram as

$$\mathrm{R_{a_i}(r_{del}) = B_{a_i}(r_{del}) \bigcap V_{a_i}}$$

where $R_a$ is the new Voronoi diagram that is only composed of the points that fell within our radius.

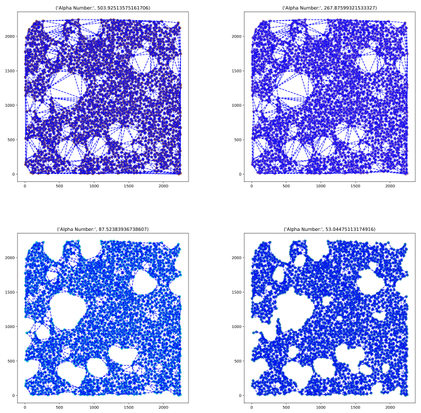
- Finally, the alpha shape can be defined as

$$\mathrm{Alpha(r_{del}) = \{S \subseteq A \mid \bigcap_{a \in S} R_a(r_{del}) \neq 0\}.}$$

Note that this equation looks very familiar to our Delaunay tessellation. This is due to our alpha shape being a subset of our Delaunay tessellation.

- The filtration value we are looking for is when our nearest neighbors do not cross any syncytia or voids, only connected to those cells that are adjacent to each other.

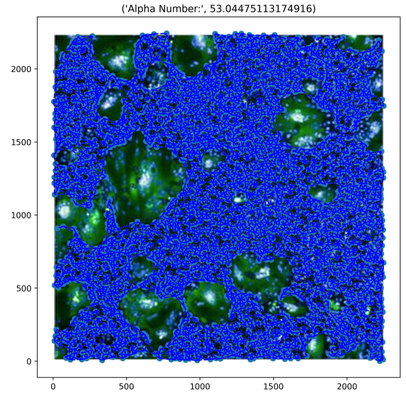
## Methodology-Alpha Shape cont.




- Here we can see our alpha filtration being applied to our data set. We can see our values of distances being filtered through.

## Conclusions/Future Plans

- The filtration has allowed us to define spatial heterogeneity off of our largest remaining distance value, our alpha number. We can then apply this algorithm to cells in space.
- We can also apply this to our computational model, allowing us to get a spatial heterogeneity measure for our model at different time steps.




- We want to implement this algorithm onto our ABM to validate it spatially.
- We can also apply this to our computational model, allowing us to get a spatial heterogeneity measure for our model at different time steps.