A Scale Free Model of Ventilation-Induced Lung Injury

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Rationale

- Mechanical ventilation is a necessary life-saving intervention for patients with acute respiratory distress syndrome (ARDS)
- Ventilation can also exacerbate ARDS and further propagate lung injury
- **Previous studies have found that lung injury is heterogeneous; however, our understanding of injury heterogeneity is incomplete.**
- **Improving on existing models of lung injury heterogeneity may facilitate development of more protective ventilation modalities**

Methods

- Mice were subjected to a two-hit injury model of pulmonary lavage and ventilator-induced lung injury
- Histological lung cross sections were prepared and whole slide images were recorded
- Areas of pulmonary edema and atelectasis – two markers of lung injury – were segmented with the machine learning software Ilastik
- **We conceptualized the dynamics governing lung injury as analogous to earthquakes using network model that assigns correlations between injury regions based on size and distance apart**
- **We found evidence of "injury hubs" and rich-get-richer behavior that govern injury progression**

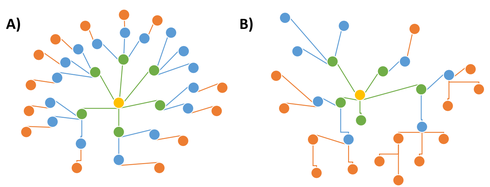

Figure 1. Representative graphs of a scale-free network (A) and a random network (B).

Segmentation Results

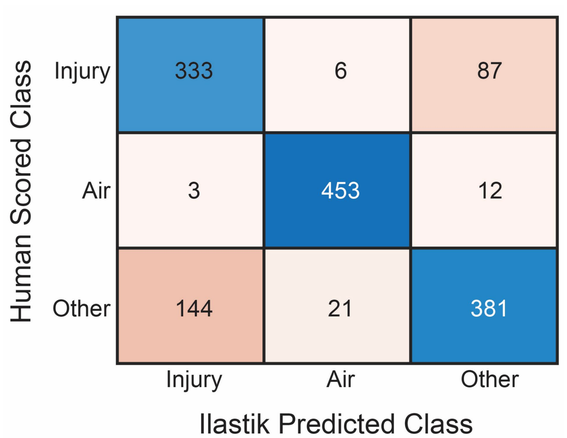

Figure 2. Confusion matrix of human classification versus automated pixel classification using Ilastik for the three pixel classes: 'Injury', 'Air', and 'Other'. Rows are human scores while columns are Ilastik scores. For each tissue section, twenty pixels from each class were manually scored.

- Ilastik demonstrated good sensitivity and specificity for pixel classification compared to human classification
- Injury pixels
  - Sensitivity: 78%
  - Specificity: 85%
- Air pixels
  - Sensitivity: 97%
  - Specificity: 97%
- Other pixels
  - Sensitivity: 69%
  - Specificity: 89%
- Overall accuracy: 81%

Results: Injury Clusters

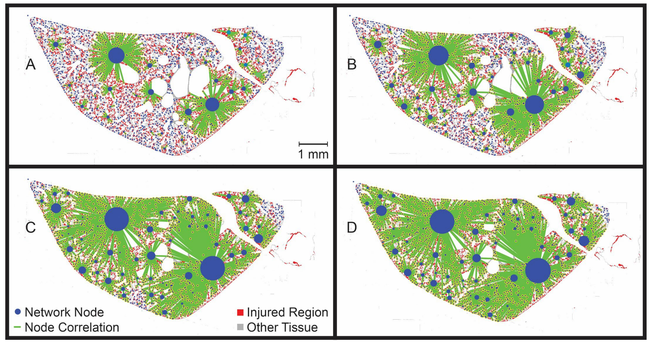

Figure 3. The strength of correlations between different injured areas are elucidated by varying the threshold n_c according to percentiles of n∗j∗nj* *. **(A)** has a threshold at the 25th percentile, **(B)** at the 50th percentile, **(C)** at the 75th percentile, and **(D)** at the 90th percentile. Injured pixels are red, while other tissue is grey. Nodes of the network, corresponding to discrete, injured regions, are denoted with a blue circle and green lines represent correlations between nodes in the network. The number of correlations that a given injured region receives is directly proportional to the size of the blue circle representing that injured region.

- Each injured region *j* is assigned a color according to the injured region *i* that *j* is connected to in the network
- Weaker correlations are eliminated according to the threshold assigned with smaller thresholds being more stringent
- This allows us to correlate and cluster regions of injury with varying levels of confidence and minimal visual clutter

Results: Secondary Injury Events

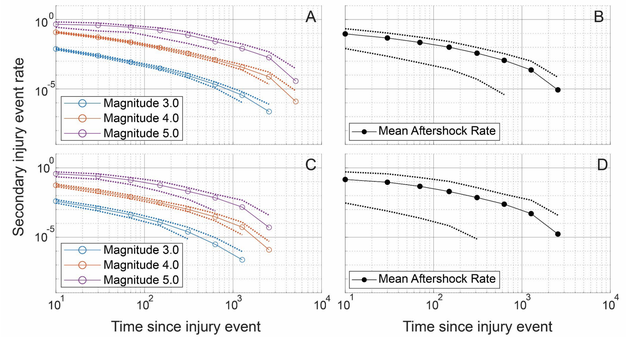

Figure 4. Simulated secondary injury event rates after a primary injury event are shown for randomly chosen CTRL **(A, B)** and LAV **(C, D)** sections. Simulated secondary injury event rates are shown separated by magnitude **(A, C)** and not separated by magnitude **(B, D)**. 95% confidence bands are plotted for each magnitude and for the aggregated magnitudes. Injury magnitudes (sizes) are shown in a $\log_{10}$ scale, analogous to the Richter scale, with a reference injury size of 1. Secondary injury event rates approximate power-law behavior with clear separation between secondary injury event rates at different magnitudes. Exponential binning is used to obtain approximately equal sample sizes in each time bin.

- Each injury event was randomly assigned a point in time and this process was repeated 100 times.
- Injuries were correlated using proximity across space and time as well as injury size.
- Injury event rates were plotted across time like aftershocks would be plotted after an earthquake.
- Pattern is similar to Omori's law from seismology.

Conclusions

- **Regional correlations of earthquakes have similarities with those governing acute and ventilator-induced lung injury**
- **Our model allows us to correlate regions of injury with minimal assumptions of the actual mechanism**
- **Our model is generalizable to a variety of injuries, allowing for inspection of subtle patterns of injury heterogeneity**

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- **I have no financial disclosures to report**