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 – that is, both demonstrate *self-organized criticality* and *scale-free behavior***
  - **Systems with *self-organized criticality* have a critical point as an attractor**
  - ***Scale-free behavior* is a network with a degree distribution that follows a power-law asymptotically**

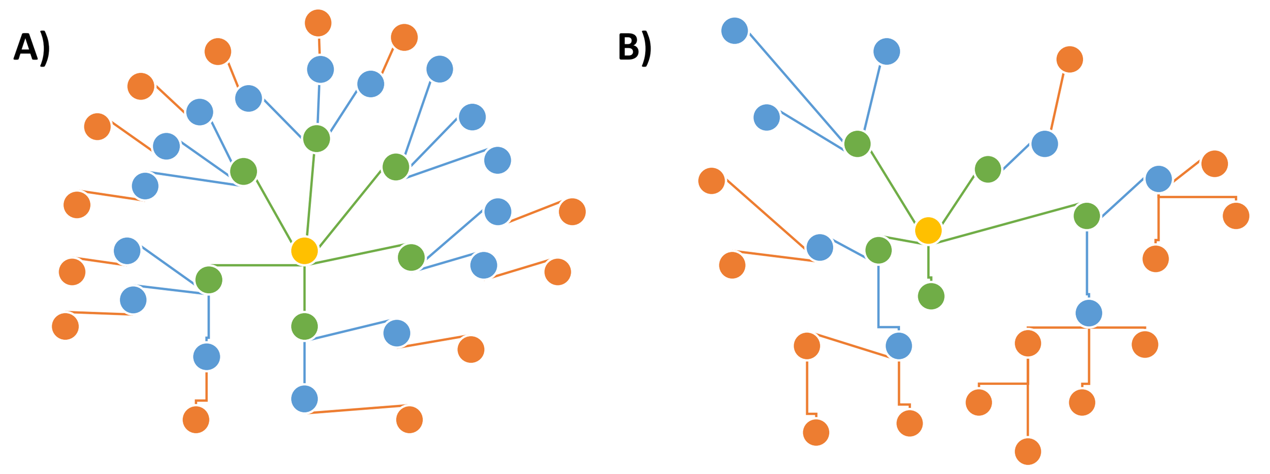


Figure 1. Representative graphs of a scale-free network (A) and a random network (B).

Model Derivation

These equations are inspired by Baiesi et al. 2004.

The probability distribution of injury in a given region can be described by:

$$P(m) \sim 10^{-bm}, \qquad (1)$$

where m is the size of a given injured region and $b = 1.7$ is the slope of the probability distribution. The parameter b was selected through a modified least-squares fitting, although the analysis is relatively insensitive to this parameter.

Thus, the average number of injured regions of size m within an interval Δm of m, occurring in an arbitrary area of radius r, is:

$$\bar{n} = C * r^{d_f} * \Delta m * 10^{-bm}, \qquad (2)$$

where C is a constant depending on susceptibility to injury and d_f is the fractal dimension. The fractal dimension is a ratio between the number of injured areas in a given region and its magnification factor (i.e., scale). This allows fractals to have non-integer dimensions, which extends the idea of topological dimension to more complex structures. The fractal dimension, d_f, was fitted through a box-counting algorithm for each slide preparation. Typical values of d_f range from 1.5 to 1.7.

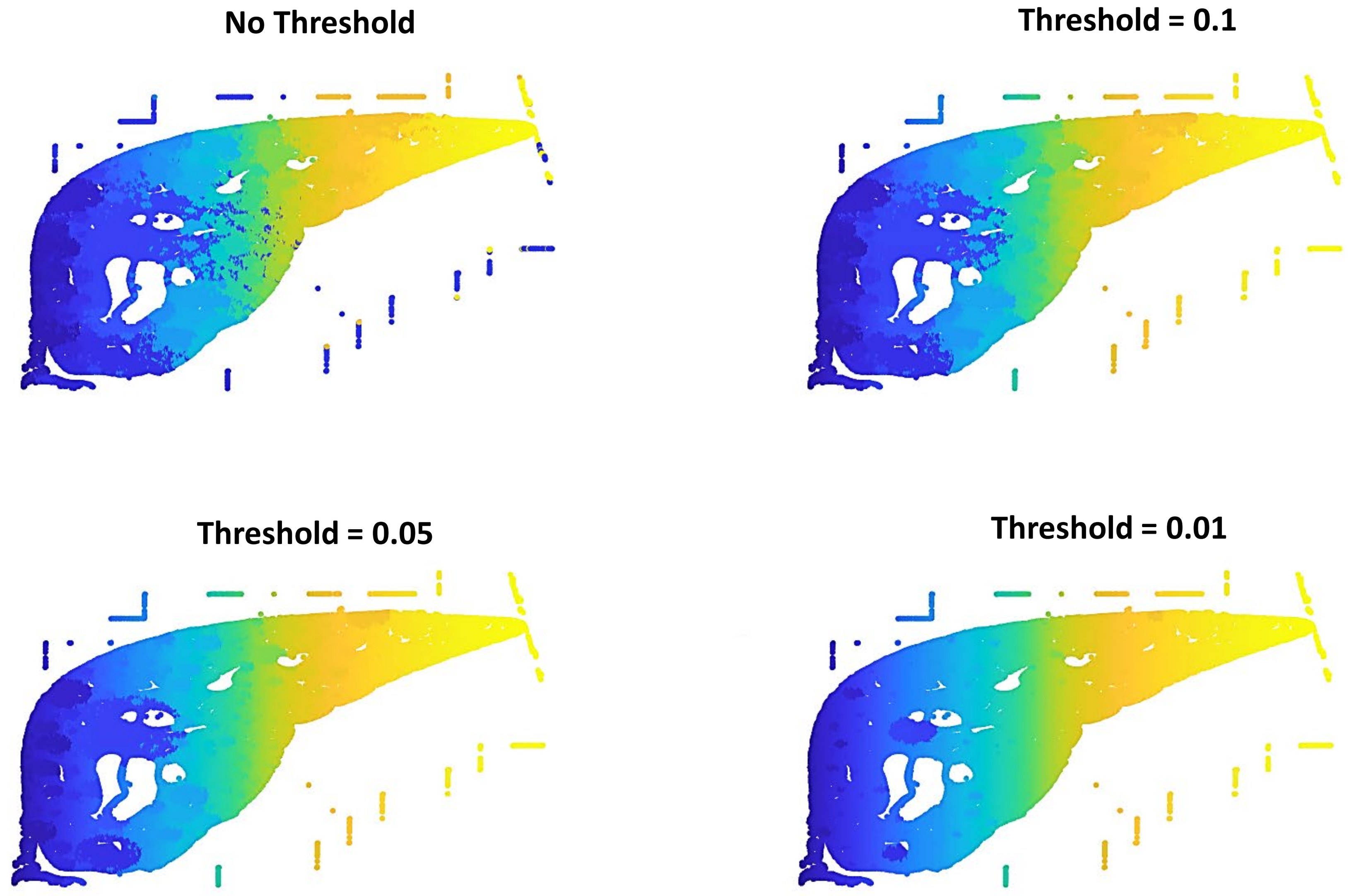
For two injured regions (i and j) separated by a distance r, the expected number of injured regions in a disk with radius r is:

$$\bar{n}_{ij} = C * r^{d_f} * \Delta m * 10^{-bm_i} \qquad (3)$$

The strength of the relationship between regions i and j relationship is inversely correlated to the value n_{ij}.

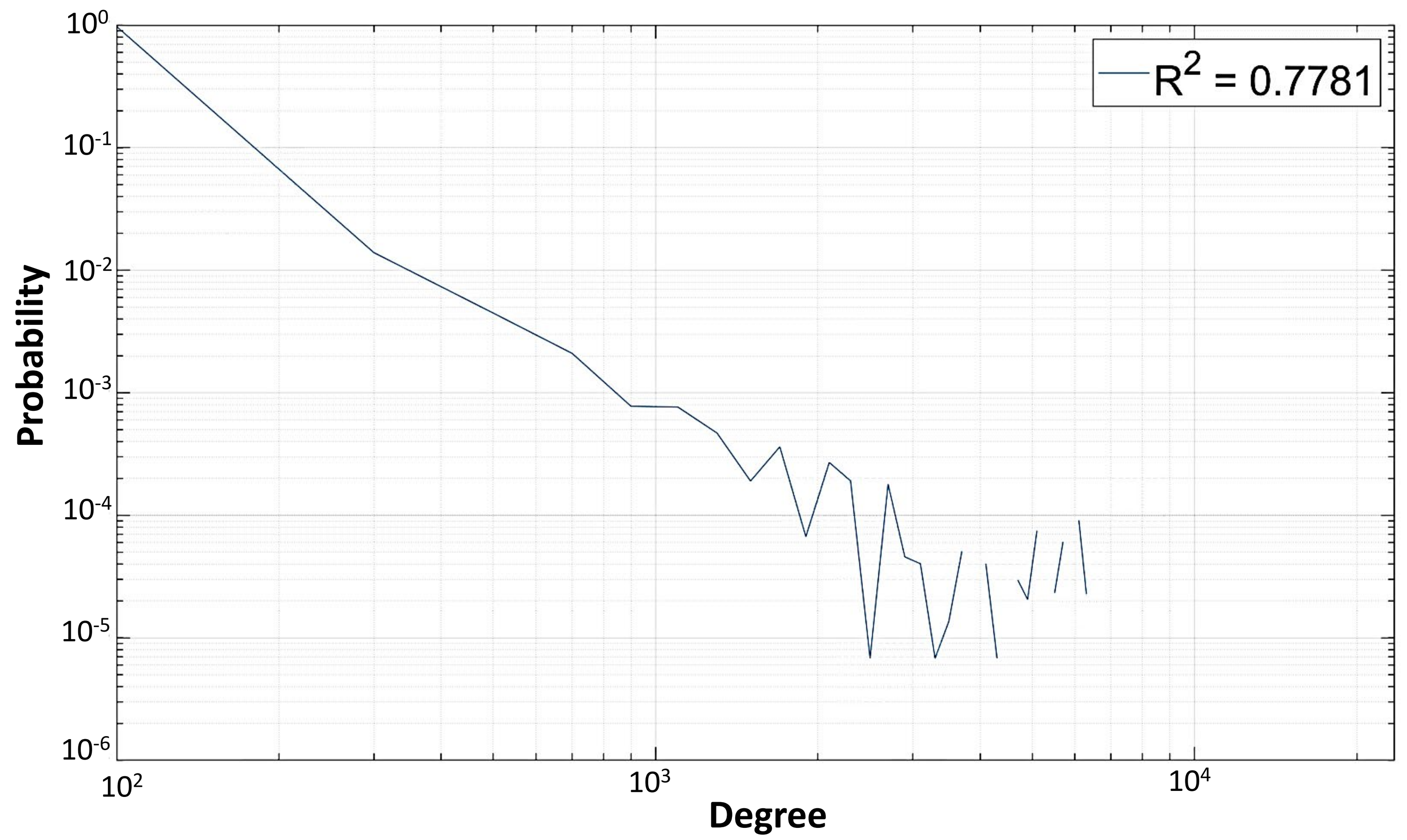
We create our network by linking injured regions i and j such that $\bar{n}_{ij}$ is minimized for each region j. That is, we select the region i that is most correlated to j for each j and link those two regions together. The rest of our analysis is conducted under this framework.

Results: Injury Clusters



- 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: Scale-Free Network



- Log-log plot of the *degree distribution* averaged over 12 lung lobe cross sections
- The degree of a node in the network is the number of connections it has to other nodes
- The degree distribution is the probability distribution of those degrees over the entire network
- This provides evidence of scale-free behavior, which is defined as a network whose degree distribution follows a power law

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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