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Research Article

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Posted Date: March 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9014328/v1

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Additional Declarations: No competing interests reported.

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ABSTRACT

Rationale: Pulmonary emphysema is characterized by progressive extracellular matrix (ECM) degradation and loss of alveolar architecture. The nonlinear progression from stable disease to rapid deterioration remains poorly understood mechanistically. To increase understanding of this process, game theory principles were incorporated into a mathematical conceptualization of the emergence of uneven mechanical forces that are responsible for airspace enlargement.

Methods: We developed a mathematical framework integrating game theory and percolation theory to model emphysema progression as a cooperative network failure. Individual crosslinks between elastin and collagen fibers were modeled as players in an iterated prisoner's dilemma, where maintaining structural integrity (cooperation) competes against stress-induced failure (defection). Network connectivity was analyzed using three-dimensional percolation theory.

Results: The model demonstrates that tissue function L scales with the cooperation fraction c according to $L \propto (c - p_c)^{\beta}$, where p_c is the percolation threshold and β is the critical exponent for three-dimensional percolation. Near this threshold, small decreases in crosslink integrity produce disproportionately large functional losses. The cooperation-defection dynamics of game theory create positive feedback that accelerates alveolar wall failure. An additional feature of this conceptual approach is the stochastic variation in crosslink stability that provides a mathematically grounded rationale for individual differences in disease susceptibility and progression rates.

Conclusions: The game-theoretic framework explains the characteristic nonlinear progression, spatial heterogeneity of tissue destruction, and threshold behavior observed clinically. This model suggests that therapeutic interventions are most effective when they increase cooperation rates before the percolation threshold is approached.

Keywords: emphysema, game theory, percolation theory, extracellular matrix, crosslinking, COPD, network failure, prisoner's dilemma

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects over 300 million individuals worldwide and represents the third leading cause of death globally [1]. Pulmonary emphysema, the irreversible enlargement of airspaces distal to terminal bronchioles, constitutes a major pathological component of COPD [2]. Despite extensive research into the molecular mechanisms of emphysema, including protease-antiprotease imbalance, oxidative stress, and inflammatory cascades, the temporal pattern of disease progression remains mechanistically unclear [3, 4].

Clinical observations indicate nonlinearity in emphysema development. Patients may tolerate decades of smoking exposure with minimal functional decline, followed by sudden acceleration toward respiratory failure [5]. This pattern cannot be explained by simple linear accumulation of tissue damage. Furthermore, emphysema exhibits marked spatial heterogeneity, with large airspaces developing adjacent to relatively preserved parenchyma, suggesting complex underlying organizational principles [6].

The structural foundation of pulmonary architecture depends critically on the extracellular matrix (ECM), particularly the network of crosslinked elastin and collagen fibers that provide elastic recoil and prevent alveolar collapse [7]. Elastin crosslinks, primarily desmosine and isodesmosine, create a resilient three-dimensional network capable of withstanding the continuous mechanical forces associated with breathing [8]. Collagen crosslinking, mediated by lysyl oxidase and related enzymes, provides tensile strength and limits overexpansion [9]. This interconnected network functions through cooperative load-sharing, where mechanical stress is distributed across the entire structure, preventing localized failure.

We hypothesize that emphysema progression can be understood through the mathematical frameworks of game theory and percolation theory. In this conceptualization, individual molecular crosslinks face a fundamental dilemma analogous to the prisoner's dilemma in classical game theory, where maintaining structural integrity (cooperation) benefits the network but imposes local costs in stress-bearing, while failure (defection) provides immediate stress relief but imposes costs on neighboring elements [10].

The collective behavior of these crosslinks determines whether the tissue network maintains connectivity above a critical percolation threshold or fragments into disconnected clusters incapable of mechanical function [11]. This quantitative framework linking molecular crosslink decisions to tissue-level mechanical failure provides novel mechanistic insights into the nonlinear progression, spatial patterning, and individual variability characteristic of emphysema.

While this novel approach requires further experimental validation, previous studies from our laboratory involving elastin crosslink measurement in human postmortem lungs are consistent with a transition from cooperation to defection as airspace size increases [12]. This finding supports the validity of this conceptual approach and its potential applicability to the detection and treatment of pulmonary emphysema.

METHODS

Theoretical Framework

We modeled the alveolar ECM as a three-dimensional lattice where nodes represent junctions of elastin and collagen fibers, and edges represent molecular crosslinks between these fibers. Each crosslink was treated as an independent agent capable of two states: intact (cooperating, C) or broken (defecting, D).

Game-Theoretic Model

Following classical formulations of the prisoner's dilemma, we assigned payoff values to crosslink interactions with neighbors [10]. The payoff matrix is a phenomenological mapping of mechanical stress redistribution, based on existing game theory principles.

For mutual cooperation among crosslinking agents (C,C): Each receives R = 3

- Unilateral defection (D,C): Defector receives T = 5, cooperator receives S = 0
- Mutual defection (D,D): Each receives P = 1

These values satisfy T > R > P > S and 2R > T + S, defining the prisoner's dilemma structure.

The payoff matrix was translated into mechanical terms: cooperation corresponds to load-sharing with reduced failure probability, while defection corresponds to crosslink breakage that redistributes stress to neighbors. The stress amplification on a crosslink with n neighbors, of which k have defected, follows:

$$\frac{\sigma}{\sigma_0} = \frac{n}{n-k} \quad [1]$$

where σ_0 represents baseline stress under uniform load distribution. When a crosslink fails, its load must be redistributed to the remaining intact neighbors. If fewer neighbors remain, each must carry more load.

Percolation Analysis

Network connectivity was analyzed using standard percolation theory for three-dimensional lattices [11, 12]. The fraction of intact crosslinks is denoted c (cooperation rate), with defection rate d = 1 - c. The critical percolation threshold for a cubic lattice is $p_c \approx 0.249$ [13].

Network functionality L was modeled as proportional to the largest connected cluster size:

$$L(c) = \begin{cases} L_{\max}\,(c - p_c)^{\beta}, & c \geq p_c, \\ 0, & c < p_c, \end{cases} \quad [2]$$

where L_{max} is maximum lung function and $\beta \approx 0.41$ is the critical exponent for three-dimensional percolation [14]. Above the threshold, a spanning cluster exists and the lung continues to function. Below the threshold, the network fragments and the lung begins to fail.

While the true biological threshold may differ due to the nonuniform properties of actual alveolar networks, the qualitative behavior (critical transition) is applicable to a range of network topologies.

Dynamic Evolution

The temporal evolution of the cooperation fraction (c) follows:

$$\frac{\mathrm{d}c}{\mathrm{d}t} = -\gamma\, c(1-c)^2 \qquad [3]$$

Where:

only intact crosslinks (c) can fail
failures $(1-c)$ increase stress
stress amplification $(1-c)^2$ is superlinear
γ represents the rate of stress-induced defection.

Equation 3 captures positive feedback, where defections increase local stress, accelerating further defections. Near the threshold, losing 1% of crosslinks can cost far more than 1% of lung function.

Stochastic Variation

Individual variability was incorporated by treating c as a random variable with mean $\langle c \rangle$ and variance σc^2. The probability (P) of maintaining functional tissue is:

$$P_{\text{functional}} = P(c > p_c) = 1 - \Phi\left(\frac{p_c - \langle c \rangle}{\sigma_c}\right) \qquad [4]$$

Where,

σ_c is the standard deviation of crosslink stability
Φ is the cumulative normal distribution
p_c is the percolation threshold

Equation 4 gives the probability that a patient's tissue remains functional given variability in crosslink integrity. It helps explain why some smokers develop emphysema early while others do not. Larger σ_c indicates greater heterogeneity and earlier failure, and high-variance individuals fail sooner even with identical mean damage.

Cluster Size Distribution

The distribution of connected cluster sizes n_s near the percolation threshold follows [15]:

$$n_s(c) \propto s^{-\tau} \exp\left(-\frac{s}{s_\xi}\right) \quad [5]$$

Where,

n_s is number of clusters of size s
τ is the cluster size exponent (≈ 2.2) governing how many clusters of size s exist exactly at the critical threshold (p_c) in three-dimensional percolation
s_ξ is the characteristic cluster size
exp is the fundamental constant, e (approximately 2.718), used to express continuous growth or decay

And the characteristic cluster size s_ξ scales as:

$$s_\xi \propto (c - p_c)^{-\frac{1}{\sigma}} \quad [6]$$

with $\sigma \approx 0.45$ for three-dimensional systems [16].

As $c \to p_c$, $s_\xi \to \infty$

This produces lesions of all sizes (airspace heterogeneity), where small pockets of alveolar destruction coalesce into large, mechanically consequential regions.

RESULTS

The Prisoner's Dilemma in Molecular Crosslinking

The payoff structure for crosslink interactions creates a classic prisoner's dilemma at the molecular scale. Consider two adjacent crosslinks sharing mechanical load during respiratory cycling. If both maintain integrity (cooperate), they distribute stress equally, each experiencing moderate load with low failure probability (payoff R = 3). If one crosslink breaks while its neighbor remains intact, the defecting crosslink immediately experiences zero stress (payoff T = 5), while the cooperating crosslink must bear the full local load, drastically increasing its failure probability (payoff S = 0). If both fail, local tissue structure collapses, eliminating any residual function (payoff P = 1).

This payoff structure satisfies the defining inequality of the prisoner's dilemma: T > R > P > S (5 > 3 > 1 > 0), with the additional constraint 2R > T + S (6 > 5). Individual crosslinks experience selective pressure to defect despite cooperation yielding superior collective outcomes, a fundamental dilemma that drives network deterioration.

The mechanical basis for these payoffs emerges from load distribution physics. When a crosslink breaks, neighboring crosslinks must compensate by bearing additional stress. For a crosslink with n = 6 neighbors (typical in a cubic lattice approximation), the stress amplification from one neighbor defecting is $\sigma/\sigma_0 = 6/5 = 1.2$. With two neighbors failed, $\sigma/\sigma_0 = 6/4 = 1.5$. This positive feedback, where defections increase stress on remaining cooperators and make their defection more likely, drives the accelerating dynamics of emphysema progression.

Critical Transition at the Percolation Threshold

Network functionality exhibits a sharp transition at the percolation threshold $p_c \approx 0.249$ for three-dimensional lattices. Above p_c, a spanning cluster of intact crosslinks maintains tissue integrity and mechanical function. Below p_c, the network fragments into isolated clusters incapable of coordinated load bearing.

The derivative dL/dc provides crucial insight into disease progression rates:

$$\frac{dL}{dc} = L_{\max}\,\beta\,(c - p_c)^{\beta-1} \qquad [7]$$

Since $\beta \approx 0.41 < 1$, the exponent $\beta - 1 \approx -0.59$ is negative, causing the derivative to diverge as c approaches p_c from above. When cooperation fraction is 10% above threshold ($c = 0.35$, $\varepsilon = 0.1$), the functional loss rate is $dL/dc \approx 1.64 \cdot L_max$. This means losing just 1% of crosslinks reduces lung function by approximately 1.64%, a leverage effect that intensifies near the critical point.

Nonlinear Temporal Dynamics

The temporal evolution described by Equation 3 produces characteristic nonlinear progression. Starting from healthy tissue with $c_0 = 0.95$, cooperation fraction declines slowly initially, then accelerates as the feedback term $(1-c)^2$ increases. The trajectory shows three distinct phases:

1. Stable phase ($c > 0.6$): Slow decline with $dc/dt \approx -0.002\gamma$, corresponding to decades of stable lung function despite ongoing exposure
2. Transition phase ($0.3 < c < 0.6$): Accelerating decline with dc/dt increasing to -0.1γ, matching the clinical observation of progressive functional deterioration
3. Collapse phase (c approaching p_c): Rapid acceleration toward catastrophic failure

Previous studies from this laboratory support the concept of exponentially increasing mechanical failure as c reaches a critical threshold [12]. As shown in Figure 1, measurements of the release of the unique elastin crosslinks, desmosine and isodesmosine (DID), in postmortem human emphysematous lungs are consistent with a defection-induced abrupt loss of elastic fiber structural integrity as alveolar diameter exceeds 400 μm. Furthermore, a sigmoidal increase in lung tissue DID density preceded the marked release of crosslinks, consistent with initial attempts at cooperation which then transition to defection (Figure 2). The leveling off of DID density coincides with the exponential increase in the release of crosslinks, as predicted by the model.

Spatial Heterogeneity and Cystic Airspace Formation

The cluster size distribution (Equation 5) explains the characteristic spatial pattern of emphysema. At $c = 0.35$ (above threshold), one dominant cluster comprises >80% of intact crosslinks, with numerous small, isolated defects representing early emphysematous changes. At $c = 0.25$ (threshold), the distribution broadens significantly, with multiple medium-sized clusters corresponding to the development of cystic airspaces. At $c = 0.20$ (below threshold), no spanning cluster exists, only isolated islands of marginally functional tissue. The characteristic cluster size (s_ξ) diverges approaching p_c, resulting in emphysematous lesions that lack a characteristic size, as observed pathologically [6].

Stochastic Variation and Individual Susceptibility

Individual variation in emphysema susceptibility can be quantified through the stochastic model (Equation 5). Patients with low variance ($\sigma c^2 = 0.001$) exhibit sharp transitions, where tissue remains functional until $\langle c \rangle$ drops to approximately 0.26, then fails rapidly. High-variance patients ($\sigma c^2 = 0.01$) show gradual transitions, with substantial failure probability even when $\langle c \rangle = 0.35$.

This framework explains why genetic factors affecting crosslink formation or degradation significantly influence disease risk. Consider two individuals with identical smoking exposure reducing $\langle c \rangle$ from 0.95 to 0.30 over 20 years. Individual A has $\sigma_c = 0.03$ (tight distribution of crosslink stability), maintaining P(functional) > 0.95 until late in disease course. Individual B has $\sigma_c = 0.10$ (wide distribution), experiencing P(functional) < 0.5 even with $\langle c \rangle = 0.35$, manifesting symptomatic emphysema years earlier despite identical average tissue damage.

DISCUSSION

This paper develops a novel theoretical framework integrating game theory and percolation theory to explain emphysema progression as cooperative network failure. The key findings are: (1) individual crosslink failures constitute a molecular-scale prisoner's dilemma, where cooperation (maintaining integrity) is collectively optimal but individually costly under stress; (2) tissue function exhibits a critical transition at percolation threshold $p_c \approx 0.249$, below which network fragmentation eliminates mechanical competence; (3) the nonlinear dynamics, $dc/dt = -\gamma c(1-c)^2$, produce accelerating deterioration characteristic of clinical emphysema; (4) spatial heterogeneity and cystic airspace formation emerge naturally from critical cluster size distributions; and (5) stochastic variation in crosslink stability explains individual differences in disease susceptibility and progression.

The game-theoretic perspective reframes emphysema from a process of passive tissue destruction to an active failure of molecular cooperation. Each crosslink continuously "chooses" between maintaining structural integrity despite stress (cooperation) or yielding to local forces (defection). In healthy tissue, the payoff structure favors cooperation through effective load distribution, with stress shared among many crosslinks, keeping individual loads below failure

thresholds. As cumulative damage accumulates from proteases, oxidative stress, and mechanical fatigue, local stresses increase, altering the effective payoff matrix to favor defection.

This model explains several puzzling clinical observations. First, the long latency between initial exposure and symptomatic disease reflects the $_{\text{stable}}$ phase where c remains well above p_c. Decades of smoking may reduce c from 0.95 to 0.50 with minimal functional consequences because network connectivity remains robust. Second, the subsequent acceleration reflects proximity to the critical transition, where the derivative dL/dc diverges. Third, the irreversibility of emphysema follows from network topology: once the percolation threshold is crossed, no amount of crosslink repair can restore spanning connectivity without extensive structural regeneration.

The percolation framework offers advantages over continuum models. Continuum approaches treat tissue as homogeneous material with averaged properties, predicting smooth degradation as damage accumulates. In contrast, percolation theory predicts sharp transitions and scale-invariant cluster distributions, matching observed pathology more closely [18]. The characteristic fractal-like patterns of emphysematous destruction, with airspaces of all sizes lacking a dominant scale, emerge naturally from critical phenomena but cannot be explained by continuum models.

Game-theoretic modeling of biological systems has precedent in evolutionary biology [19, 20], immunology [21], and cancer [22], but has not previously been applied to tissue mechanics. The prisoner's dilemma framework is particularly appropriate for pulmonary emphysema because crosslink decisions affect neighbors through mechanical coupling, creating the externalities central to game-theoretic analysis. The model generates testable predictions with direct clinical relevance. It predicts that functional decline should accelerate as patients approach $FEV_1 \approx 25\%$ predicted, the approximate functional correlate of reaching the percolation threshold. Longitudinal pulmonary function data could test whether decline rates increase nonlinearly in this range.

The model also suggests that spatial heterogeneity of damage, quantifiable through CT density measurements or parametric response mapping, should correlate with proximity to the critical transition [23]. Patients with intermediate mean density but high variance may be closer to catastrophic failure than patients with similar means but low variance.

Therapeutic interventions should show maximum efficacy in early disease. Clinical trials of α_1-antitrypsin augmentation have shown modest benefits in unselected COPD populations, but the model predicts substantially larger effects in patients with $\langle c \rangle \approx 0.5\text{-}0.7$, before critical transition begins [24]. Stratifying trials by baseline tissue network integrity (assessed via novel imaging biomarkers) could identify optimal treatment windows.

Several simplifications in the current model warrant discussion. We employed a cubic lattice approximation for the ECM network, whereas actual alveolar architecture exhibits more complex geometry including pentagonal and hexagonal structures [25]. Future work should incorporate realistic network topologies derived from three-dimensional microscopy. Another limitation is the treatment all crosslinks as equivalent, ignoring the biochemical diversity of elastin and collagen crosslinks with differing mechanical properties and susceptibility to degradation [26].

Heterogeneous bond models could capture how specific crosslink types contribute differentially to network stability.

We also modeled static mechanical loads, whereas respiratory cycling imposes dynamic stress. Fatigue failure under cyclic loading may accelerate defection rates through ratcheting mechanisms [27]. Incorporating time-dependent mechanical properties would improve quantitative predictions.

Finally, biological repair processes, such as fibroblast-mediated matrix synthesis and crosslink formation, were omitted. Adding a cooperation restoration term dc(repair)/dt could model the competition between damage and repair that determines net progression rates. With regard to lung injury, we did not explicitly model inflammatory cells, proteases, or oxidative species, instead subsuming these effects into a phenomenological parameter involving the rate of stress-induced defection (γ). Mechanistic models coupling game-theoretic network dynamics to biochemical kinetics would provide deeper insights into therapeutic targets.

The framework developed here may apply beyond emphysema to other diseases characterized by progressive network failure. Osteoporosis involves trabecular bone network degradation with similar critical transitions [28]. Cerebral small vessel disease exhibits white matter network fragmentation [29]. Liver fibrosis progresses through architectural distortion of the sinusoidal network [30]. In each case, a cooperative structural network faces cumulative damage that may exhibit game-theoretic dynamics and percolation transitions.

More broadly, this work illustrates how concepts from statistical physics and game theory can illuminate biological processes. Living tissues are not passive materials but active networks of molecular agents making "decisions" based on local information. When these decisions involve externalities. with one element's choice affecting neighbors' payoffs, game theory provides a natural language for analysis.

Funding

No funding was involved in the preparation of the manuscript.

Competing Interests

The author has no conflicts of interest with regard to the material presented in the manuscript.

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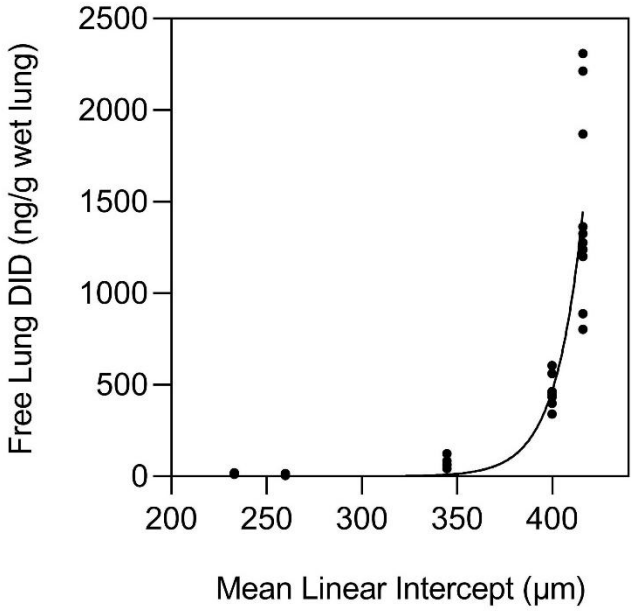


Figure 1: The levels of peptide-free desmosine and isodesmosine (DID) in human postmortem emphysematous lungs increase exponentially as alveolar diameter approaches 400 μm (measured by the mean linear intercept method). This finding reflects the sudden collapse of alveolar wall structural integrity as the cooperative crosslink fraction approaches a critical threshold and defection becomes the dominant process. Reprinted with permission [12].

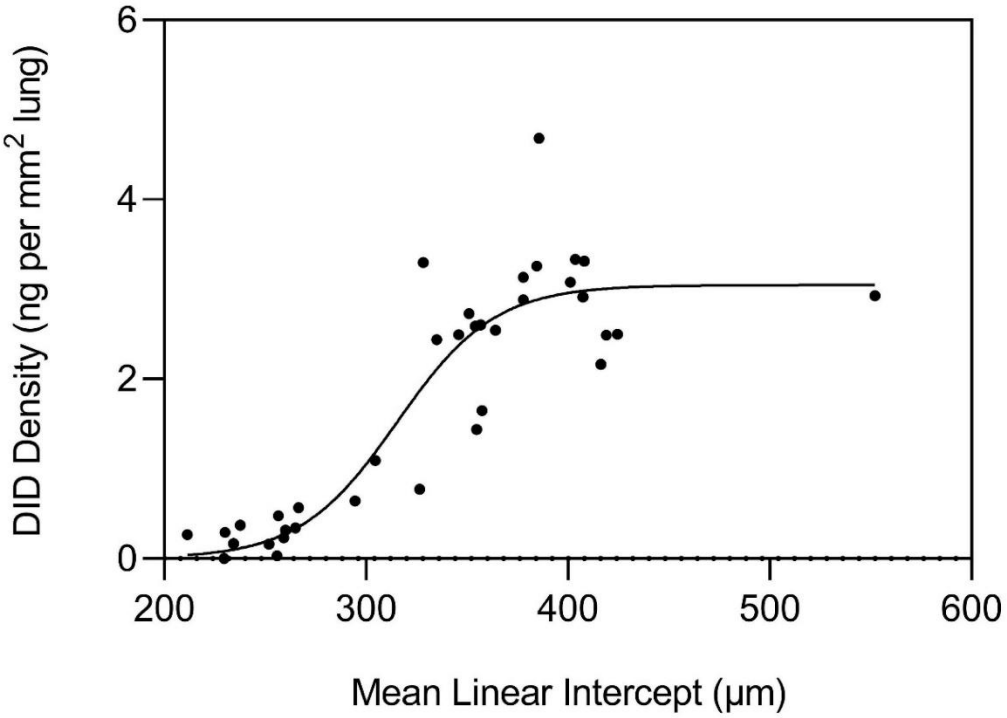


Figure 2: A sigmoidal increase in DID density was seen in human postmortem emphysematous lungs, consistent with a cooperative phase in crosslink formation followed by defection, as airspace size exceeds 400 μm. This transition coincides with the exponential increase in crosslink release from elastic fibers (Figure 1). Reprinted with permission (12).