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A combined modeling and AI-driven optimization approach to enhance surfactant replacement therapy in adult lungs

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1. Introduction

Surfactant Replacement Therapy (SRT) is a life-saving treatment for neonatal respiratory distress syndrome (NRDS), a condition where surfactant deficiency causes alveolar collapse and respiratory failure. SRT has proven highly effective in preterm infants, but remains largely ineffective in adults, particularly in acute respiratory distress syndrome (ARDS), where current surfactant administration strategies fail to achieve sufficient alveolar delivery. Anatomical and physiological differences account for this discrepancy: adult bronchial trees are larger, which result in higher surfactant deposition on airway walls and decreased alveolar delivery. Despite advances in respiratory medicine, current protocols remain poorly suited to address the unique challenges of adult lung anatomy, highlighting the need for customized administration strategies.

2. Methods

To address these challenges, our study presents a computational framework that integrates an advanced mathematical model of surfactant delivery with machine learning (ML) techniques. The model follows a two-step propagation process: initially, a liquid plug spreads down the airway tube, coating the walls and flowing along the bronchial pathways. At each bifurcation, the plug splits, redistributing the surfactant throughout the bronchial tree in a recursive manner. This approach builds upon the foundational work of Filoche et al. 2015, incorporating asymptotic analyses where inertial and capillary forces dominate. By leveraging these principles, the model predicts surfactant delivery efficiency and homogeneity under a variety of conditions, ranging from neonatal to adult lung geometries. To systematically explore the impact of lung size and airway complexity, bronchial tree models of varying dimensions were generated, parameterized by tracheal diameter, and extended up to 15 generations. This allows for a comprehensive assessment of size and truncation effects. The model also accounts for clinically relevant parameters, including surfactant viscosity (with Curosurf as a reference), dose volumes, flow rates, and patient positioning. For optimization, we coupled this model with an in-house Deep Reinforcement Learning (DRL) algorithm. This AI-based approach enables thorough exploration of complex parameter spaces, as demonstrated by Hachem et al. 2021, which allows identifying robust administration protocols that adapt to variations in anatomy and fluid dynamics.

3. Results and discussion

Our findings reaffirm that, under classical administration conditions, the efficiency of surfactant delivery is significantly compromised in larger adult lungs due to excessive loss from airway coating, as initially reported in Kazemi et al. 2019. This results in poor alveolar deposition, reducing the therapeutic benefits of SRT in ARDS patients.

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We conducted extensive optimization runs under different constraints, evaluating both fixed-mixture conditions and free-mixture configurations to assess their respective impacts on delivery efficiency (Fig. 1).

Notably, our findings indicate that increasing the number of instillations does not necessarily enhance alveolar delivery. In fact, optimal surfactant distribution may be achieved by adjusting the instillation strategy; for example, delivering a fixed total dose in two aliquots instead of one or three can significantly improve alveolar deposition. This underscores the importance of not only optimizing total dosage but also fine-tuning delivery timing and distribution protocols to enhance therapeutic outcomes.

Our results demonstrate that combining detailed mathematical modeling with ML-based optimization can yield valuable insights into the fluid dynamics of SRT in larger lungs. As part of our ongoing efforts to refine this framework, we are now incorporating temporal dynamics into our simulations. By introducing time-dependent variables, we aim to design adaptive administration protocols that dynamically adjust in real time. These adaptive strategies leverage full actuation capabilities, allowing for modifications in patient positioning and real-time flow rate adjustments throughout the treatment. Such refinements maximize alveolar coating while simultaneously minimizing airway deposition, thereby improving overall delivery efficiency.

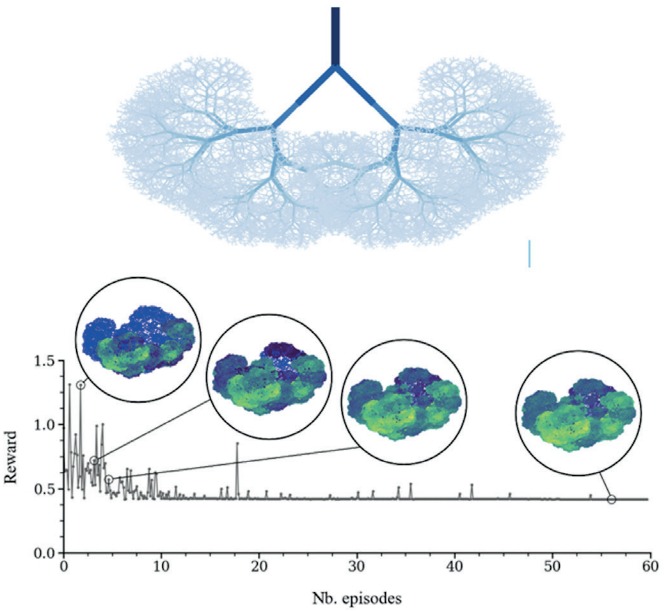

Figure 1. Top. Symmetric adult airway tree with 15 generations and 32,768 terminal branches. Airway narrowing is encoded by branch color and thickness.

Bottom. DRL optimization of surfactant delivery homogeneity by tuning instillation conditions and fluid rheology. The reward curve tracks progress over episodes (lower is better), with insets showing color-coded surfactant distributions at key stages of training.

Credit: G. Roncin

4. Conclusions

These advances are particularly significant given the limitations of traditional optimization methods in capturing the complex interplay of parameters governing surfactant delivery in large airways. In contrast, AI-driven strategies offer a powerful and individualized approach to protocol design. Our work marks a critical step toward personalized SRT, with potential impact on ARDS treatment and the extension of surfactant therapy beyond neonates.

To assess translational potential, experimental validation is underway in collaboration with clinical partners. The protocol will be tested in 3D-printed transparent airway models—ranging from simplified geometries with variable generation sizes to patient-specific anatomies—using programmable flow pumps and high-speed imaging to track fluid–air interface dynamics. These setups will enable direct comparison between standard clinical postures and DRL-optimized conditions under physiologically realistic flow scenarios.

Conflict of Interest Statement

None.

Contributor Roles

PM: Conceptualization, Methodology, Funding acquisition, Project administration, Supervision, Writing original draft; GR: Data curation, Formal analysis, Investigation, Validation, Visualization & editing; EH: Conceptualization, Funding acquisition, Resources, Supervision, Writing-review & editing.

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