Age-dependent Ventilator-Induced Lung Injury

Quintessa Hay[1], Christopher Grubb[2], Rebecca L. Heise[3], Sarah Minucci[1], Michael S. Valentine[3], Jennifer Van Mullekom[2], Angela M. Reynolds[1]

[1] Department of Mathematics & Applied Mathematics, Virginia Commonwealth University, Richmond, VA, USA.
[2] Department of Statistics, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA.
[3] Department of Biomedical Engineering, Virginia Commonwealth University, Richmond, VA, USA.

Motivation

Severe inflammation in the lungs can lead the Acute Respiratory Distress Syndrome and the need for mechanical ventilation (MV). While MV is often a life-saving intervention, prolonged use or misuse can cause Ventilator-Induced Lung Injury (VILI). Experimental data has also indicated an increased risk of VILI in elderly patients. This information combined with the increased demand of MV caused by the novel coronavirus Sars-CoV-2 stresses the need for further studies of VILI and age-dependent dynamics.

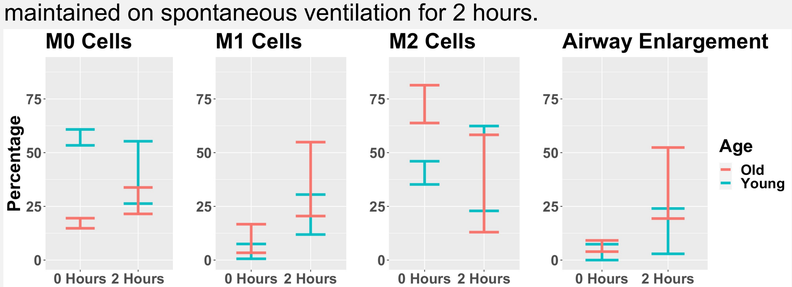
ODE Model

A previous model for VILI uses a system of ordinary differential equations tracking immune cell activation (including macrophage phenotype) and epithelial cell damage (Minucci et. al, 2021). The current model expands upon this previous model by including epithelial barrier breakdown leading to increased cytokines and immune cells in alveolar region.

$$\frac{dM_1}{dt} = \overbrace{M_0\left(\frac{k_{m0p}p^2}{x_{m0p}^2+p^2}\right)}^{\text{Differentiation to M1 via PIM}}\overbrace{\left(\frac{1}{1+\left(\frac{a}{a_\infty}\right)^2}\right)}^{\text{Inhibition by AIM}} - \overbrace{k_{man}(k_{anm1}ANM_1)}^{\text{M1 switch to M2 by phagocytosis}}\overbrace{\left(\frac{1}{1+\left(\frac{a}{a_\infty}\right)^2}\right)}^{\text{Inhibition by AIM}} + \overbrace{M_{1b}\frac{k_{ee}E_e^4}{x_{ee}^4+E_e^4}}^{\text{Leak into lung}} + \overbrace{k_{m1}M_{1b}}^{\text{Migration}} - \overbrace{\mu_{M_1}M_1}^{\text{Decay}}$$

Experimental Data

Young (2-3 mo) and old (20-25 mo) C57BL/6J wild-type mice were ventilated using a Scireq FlexiVent computer-driven small-animal ventilator. Mice were anesthetized, tracheotomized, and then ventilated for 5 minutes using a low pressure-controlled strategy. Mice were then ventilated for 2 hours using a high pressure-controlled mechanical ventilation (PCMV). Pulmonary function and tissue mechanics were measured and collected at baseline and every hour during the 2-hour high PCMV. A separate group of mice was anesthetized, tracheotomized, and maintained on spontaneous ventilation for 2 hours.



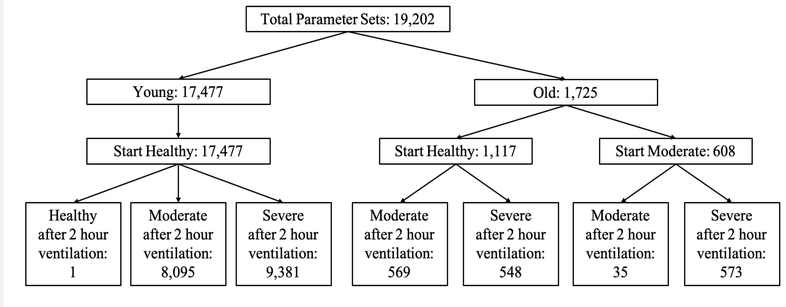
Methods

- Iterative parameter sampling with uniform distributions was used to determine plausible parameter sets that give rise to dynamics within the range of the experimental data associated with young or old mice
- Classification methods were used to determine indicators of age group and pre- and post-ventilation states:

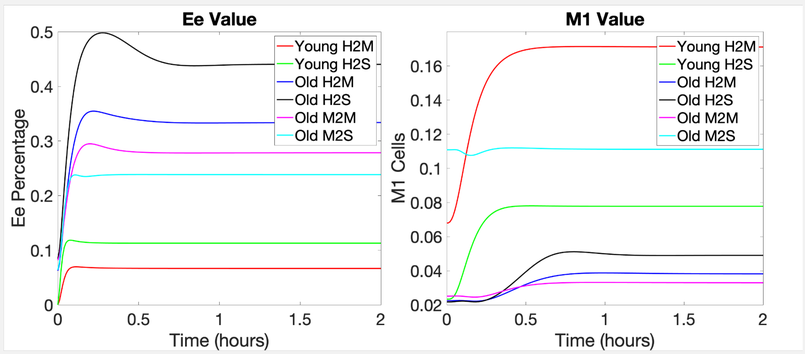
1. Healthy (healthy epithelial percentage > 90%)
2. Moderate (90% > healthy epithelial percentage > 50%)
3. Severe (healthy epithelial percentage < 50%)

Results

Plausible Parameter Set Breakdown

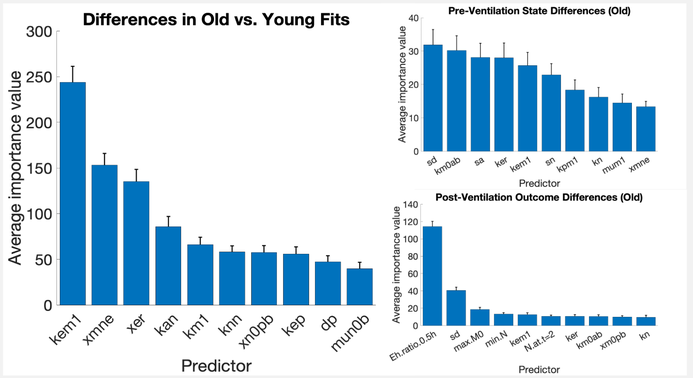


Sample Transients



Sample Transients: Ee (empty epithelial space), M1 (M1 phenotype macrophages). Young and old refer to the parameters sets that fit old or young experimental data. H2M refers to sets with a healthy starting state and moderate state after ventilation, H2S refers to sets with a healthy starting state and severe state after ventilation, M2M refers to sets with a moderate starting state and moderate state after ventilation, and M2S refers to sets with a moderate starting state and a severe state after ventilation.

Random Forest Results



Random Forest Results: s_d (parameter that describes the epithelial cell level damage caused by ventilation). k_{er} (repair of damaged epithelial cells), k_{m0ab} (differentiation of naïve macrophages to M2 macrophages in the blood), k_{em1} (damage to epithelial cells caused by M1 macrophages), and k_n (migration of activated neutrophils into the lung).

Discussion

- Our sampling methods produced a total of 19,202 plausible parameter sets with 17,477 fitting the young mouse data and 1,725 fitting the old mouse data.
- Old transients generally exhibited higher airway enlargement values compared with the young as well as increased M2 macrophage activation.
- State differences (healthy, moderate, or severe) showed high dependence on the parameter s_d. Other common parameters at 0 hours and 2 hours included k_{er}, k_{m0ab}, k_{em1}, and k_n.

Future Work

Future work would be to preform a formal sensitivity analysis on the parameters for the various groups of interest. This would be used to inform a model of an intervention on *in silico* transients to help improve the lung state during ventilation and post-ventilation. Analysis of important parameters in the old sets could also aid in modeling an improvement of pre-ventilation lung health that would likely have direct clinical relevance.

Acknowledgements

•Commonwealth Cyber Initiative Grant: Secure Smart Point-of-Care Sensors for Lung Health

•Minucci, S., Heise, R. L., Valentine, M. S., Kamga Gninzeko, F. J., & Reynolds, A. M. (2021). Mathematical modeling of ventilator-induced lung inflammation. Journal of theoretical biology, 526, 110738. https://doi.org/10.1016/j.jtbi.2021.110738