

A Patient-Specific *in silico* Model of Inflammation and Healing Tested in Acute Vocal Fold Injury

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Phonotrauma, a common vocal fold injury caused by phonation, is a complex process that involves both inflammation and healing. Phonotrauma results in substantial negative effects on quality of life in affected individuals. Statistics indicate that in teachers alone phonotrauma costs approximately \$2.5 billion annually to the U.S. economy [1]. Although phonotrauma is traditionally treated with voice rest, we have hypothesized that certain vocal fold mobilization approaches (“resonant voice”) exercises may result in better healing. Our recent studies suggest that the benefits of resonant voice exercise are both dose- and subject-specific.

Personalized, subject-specific medicine is a central goal of modern medicine. To approach this goal, the complexity of biological processes must be tamed. Agent-based computer models (ABMs) have been used to model the complex process of acute inflammation and wound healing in diverse settings [2]. We created an ABM that reproduced diverse trajectories of inflammatory mediators in human subjects’ vocal folds at early time points post-phonotrauma, and that was also capable of predicting the levels of these mediators at 24 h.

This ABM was developed using relevant literature on vocal fold injury as well as data from experimental measures of inflammatory cytokines in human laryngeal secretions [3,4,5]. The ABM includes cells (neutrophils, macrophages, fibroblasts), inflammatory cytokines (IL-1 β , TNF- α , TGF- β 1, IL-10), an extracellular matrix component (collagen), and a tissue damage function functionally analogous to alarm/ danger signals [6] that produces positive feedback to induce further inflammation [2]. We input the initial levels of IL-1 β , TNF- α , and IL-10 for three human subjects, added a phonotrauma event and then a 4-hr treatment event (voice rest, “resonant voice” exercise or spontaneous speech). We next calibrated the model using data from initial human cytokine levels in laryngeal fluid [4], both immediately after phonotrauma and following a 4-hr treatment. Due to the stochasticity of ABM, we performed ten runs of the ABM over five simulated days. The means and standard deviations of model variables were computed for subsequent analysis.

Figures 1-2 display both predicted and empirical mediator trajectories for each subject’s original treatment group. Figure 1 represents a single subject (Subject 3) who was experimentally involved in all three treatment modalities. Figure 2 represents data from three subjects who received spontaneous speech, voice rest and “resonant voice” treatments after vocal loading, respectively. In general, the ABM reproduced and predicted subject-specific cytokine trajectories as seen in our human data. A binomial test indicated that in 80% (12/15) of markers across subjects, the ABM predicted empirically obtained cytokine values—not used for model calibration—at 24 hr ($p < 0.05$).

Predicted levels of pro-inflammatory marker IL-1 β for spontaneous speech were significantly higher than for either voice rest or resonant voice conditions ($p < 0.05$, both comparisons). In contrast, levels of anti-inflammatory marker IL-10 for voice rest were significantly lower than for either resonant voice or spontaneous speech ($p < 0.05$, both comparisons). These results represent an early stage of translational application of ABM, which may have application to inflammation in other tissues.

Figure 1: Predictions of inflammatory and wound healing responses to acute phonotrauma in a single human subject (Subject 3) following spontaneous speech (Panels A-C), voice rest (Panels D-F) and resonant voice treatments (Panels G-I). Panels A, D and G are the predicted cytokine trajectories of IL-1 β . Panels B, E and H are the predicted cytokine trajectories of TNF- α . Panels C, F and I are the predicted cytokine trajectories of IL-10. Inflammatory marker concentrations are in pg/ml. The grey bars represent the mean of the simulated data, and the error bars represent standard deviations in the simulated data. The dark circles represent the input data of the first three time-points (baseline, post-loading, 4-hr post treatment), obtained from human laryngeal secretion data. The empty circles represent the validation data at the 24-hr time point from the human laryngeal secretion data. B: baseline; PL: post vocal loading; 4hrPRx: following a 4-hr treatment. Note that human validation data for Days 2-5 have not yet been generated.

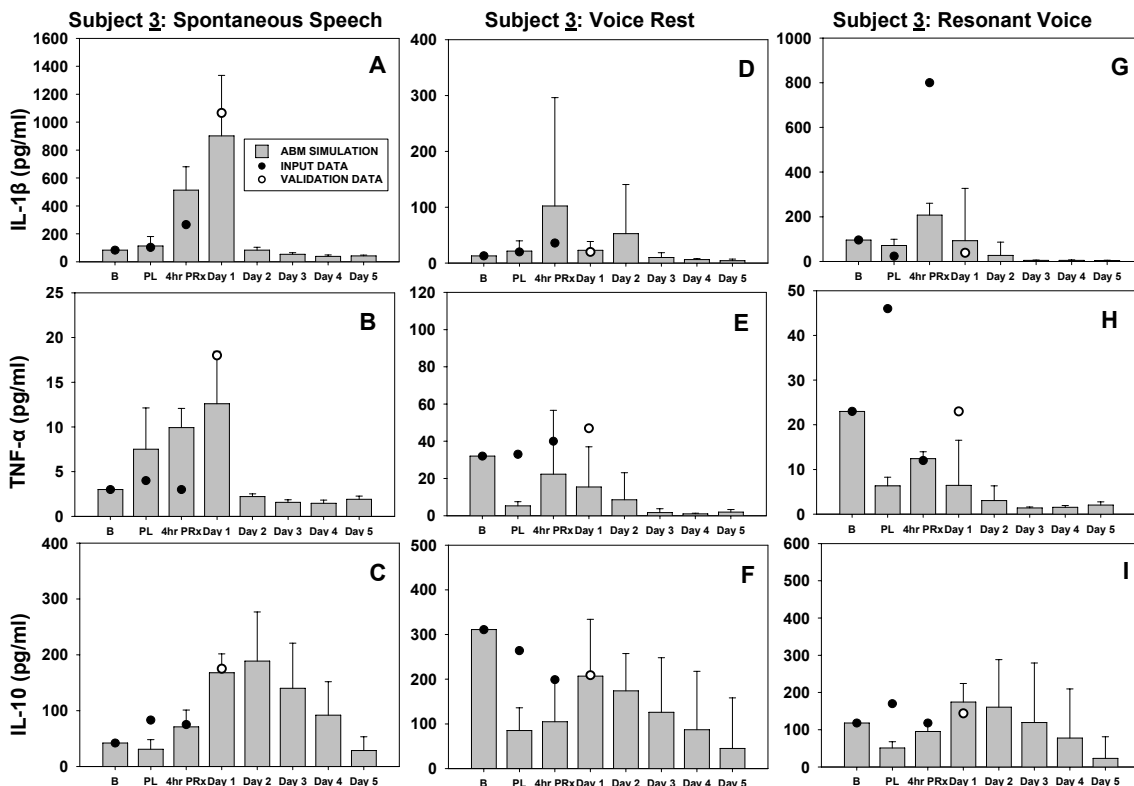
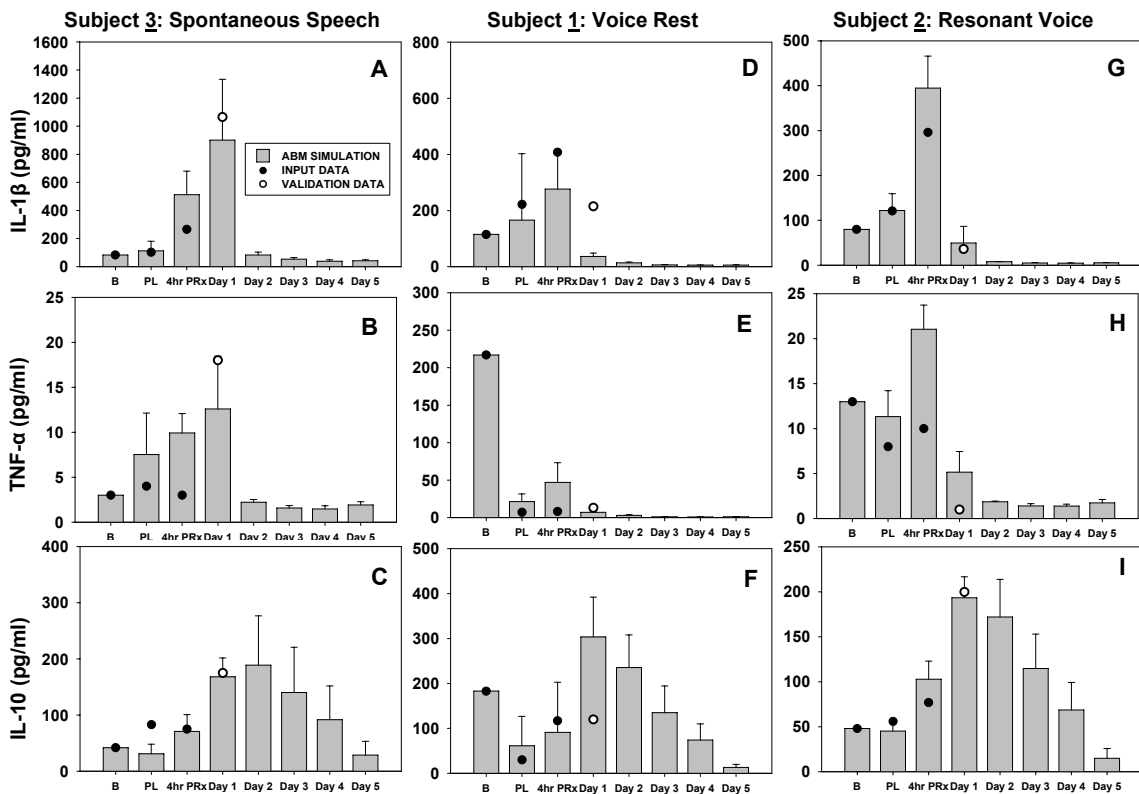


Figure 2: Predictions of inflammatory and wound healing responses to acute phonotrauma in three human subjects following spontaneous speech (Subject 3; Panels A-C), voice rest (Subject 1; Panels D-F) and resonant voice (Subject 2; Panels G-I). Panels A, D and G are the predicted cytokine trajectories of IL-1 β . Panels B, E and H are the predicted cytokine trajectories of TNF- α . Panels C, F and I are the predicted cytokine trajectories of IL-10. Inflammatory marker concentrations are in pg/ml. The grey bars represent the means from the simulated data, and the error bars represent the standard deviation from the simulated data. The dark circles represent the input data of the first three time-points (baseline, post-loading, 4-hr post treatment) from the human laryngeal secretion data. The empty circles represent the validation data at the 24-hr time point from the human laryngeal secretion data. B: baseline; PL: post vocal loading; 4hrPRx: following a 4-hr treatment. Note that validation data for Days 2-5 have not yet been generated.



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