# Alveolar Stability in Premature Infants

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March 18, 2020

# Impact

- 500,000 premature infants born annually in US
- Majority of those have pauses in breathing (apnea)
- Apnea can be life threatening
- Has both acute and life long consequences
- Average cost NICU stay $3k-$10k US per day
- Total market for medical treatment of prematurity is $26B US annually
- Care in developing nations is difficult

# Apnea of Prematurity

- One in 9 live births is preterm ($<$37 wks)
- Over 70% of preterm infants experience apnea of prematurity (AOP)
- AOP is associated with acute multi-organ failure and long term complications including retinopathy, developmental delay, and neuropsychiatric disorders

# Apnea in Prematurity

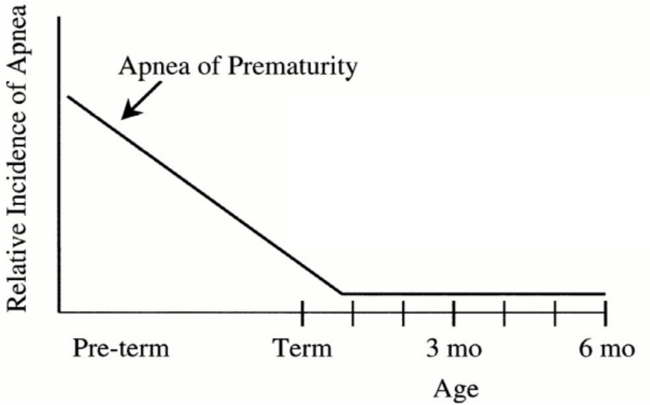
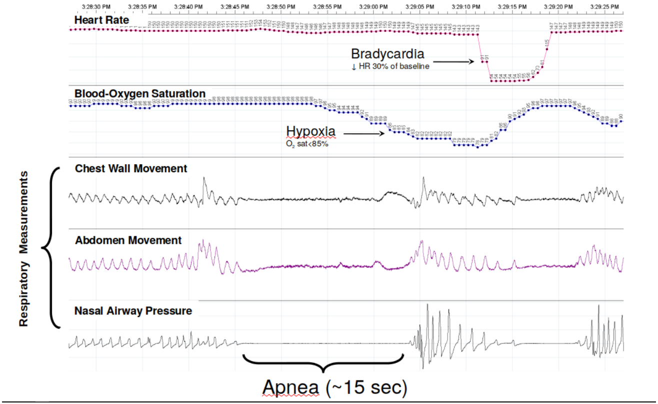
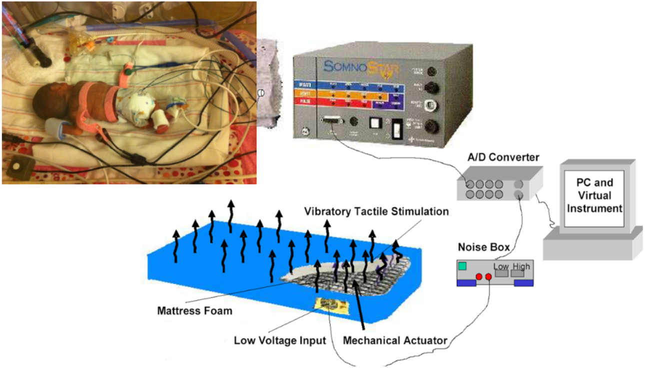



Figure: Martin RJ & Wilson CG (2012). Compr Physiol 2: 2923-31. DiFiore JM et al.(2010). Pediatr 157: 69-73.

# Switching from rhythmic breathing to apneic state



# Motivating Study



# Mechanosensory Enhancement of Breathing

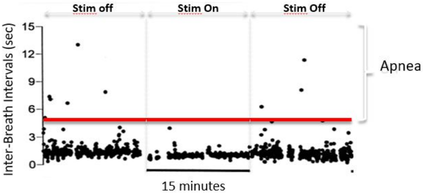



Figure: 10 preterm infants. Study Wt:1500 gm (1020-2175); PCA: 33.3 weeks (31.4-35.7) (Bloch-Salisbury E, Indic P, Bednarek F, Paydarfar D. J Appl Physiol. 2009 107(4): 1017-1027)

- 50% decrease incidence of apnea ($p=0.001$)
- 50 % decreased variance of inter-breath intervals ($p=0.001$)
- 70% decreased duration of hypoxia ($p=0.02$)
- No effect on infant sleep

# A Focus on Mechanically Ventilated Infants

Despite artificial ventilation administration, these infants suffer from severe episodes of hypoxia.

**Does Stochastic mechanical stimulation of the thorax improve pulmonary $O_2$ uptake?**

# Improving Oxygenation

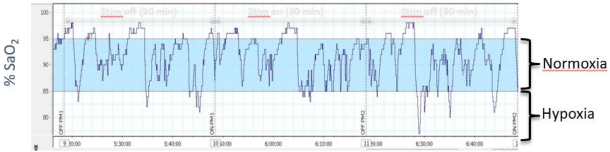
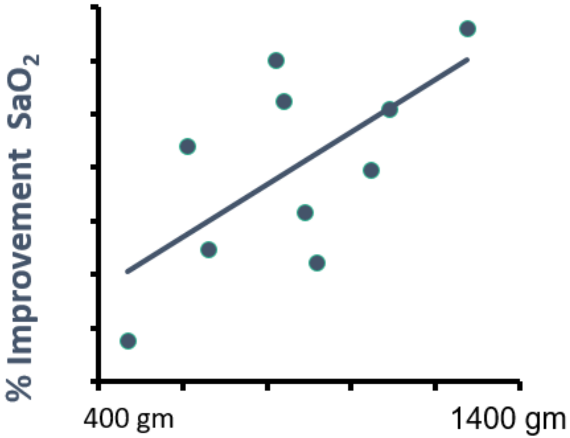



Figure: 10 preterm infants requiring mechanical ventilation. Study wt. 850 gm (470-1275); PCA 28.8 weeks (25-30); On ventilator for 16 days (2-35)

- 30% decreased duration of hypoxia (p=0.04)
- 20 % decrease variance in $SaO_2$ (p=0.025)
- Improvements correlated in infant weight
- No change in ariway pressure, exhaled $CO_2$, inspired $O_2$

# Oxygen Improvement Corresponding to Weight



# How does stochastic resonance improve pulmonary $O_2$ uptake?

- Increase gas mixing (Ventre & Arnold. (2004))
- Decrease Atelectasis (Suki et al. (1994))
- Increase surfactant (Arold et al. (2003))
- Increase Mucociliary function (King et al. (1983))

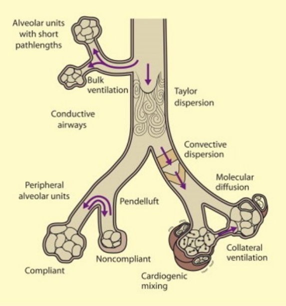
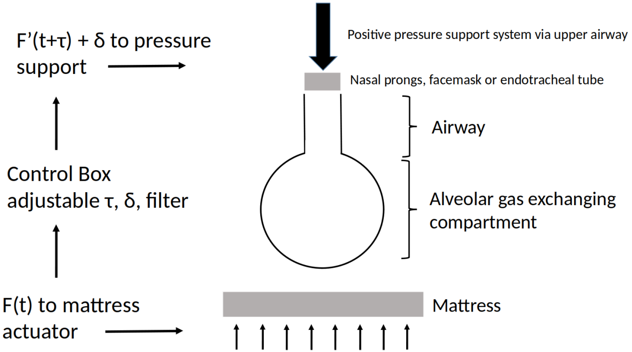



Figure: Wolf & Arnold. Paediatr Child Health. 2007 17(3):77-81

# Diagram


F’(t+τ) + δ to pressure support
Positive pressure support system via upper airway
Nasal prongs, facemask or endotracheal tube
Airway
Control Box
adjustable τ, δ, filter
Alveolar gas exchanging compartment
F(t) to mattress actuator
Mattress

# Objective

**To study the effects of tactile and pressure stimulus on the stability of alveoli through modelling and numerical simulations**

# Lung Models

- Avalanche Model
- Network Model

# Avalanche Model

**Experimental Results**

- Preformed experiments on isolated dog lungs
- The terminal airway resistance ($R_t$) was measured
- Characteristic of $R_t$ displayed power law distributions
    - Relative Jumps: $\alpha_e = 1.8 \pm .2$
    - Time Intervals: $\beta_e = 2.5 \pm .2$

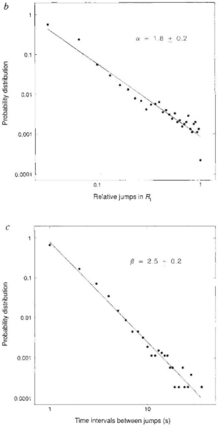



Figure: [4]

# Avalanche Model

**Computational Model**

- Assumed an airway threshold
- Airways terminated at alveoli, which are equal sized spheres
- Characteristics of $R_t$
  - Relative Jumps: $\alpha_c = 1.7 \pm .2$
  - Time Intervals: $\beta_c = 2.5 \pm .2$

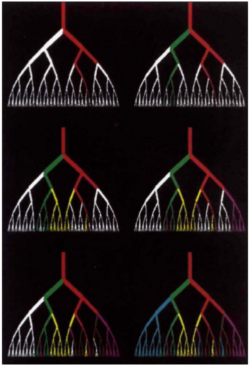


Figure: [4]

# Avalanche Model: Summary

- Validated threshold assumption
- Studied the pressure effects on opening of airways
- The opening of terminal alveoli is affected by the magnitude and time of ventilation

# Network Model

**Goal:** Expand a single terminal airway model to study the clustered constriction of airways

- There are two stable states:
  - The airway is nearly closed
  - The airway is kept open by tethering forces
- Clusters form when smooth muscle activation reaches a critical level
- Areas of poor ventilation are inversely affected by breathing volume

# Model Diagram

**Variables**

- $\dot{V}$: flow of breathing gases
- $P$: Pressure
- $R$: Resistance
- Resistance is a function of airway lenght, radius, and has viscosity

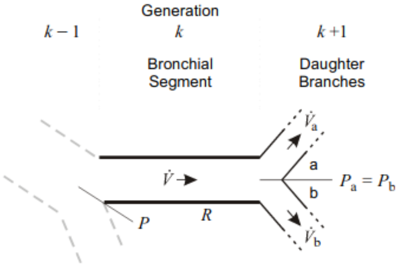



Figure: [5]

$$\dot{V}(t,k,i) = \dot{V}(t,k+1,i(a)) + \dot{V}(t,k+1,i(b)) \qquad (1)$$

## Model Diagram

The pressure difference is given by:

$$\underbrace{P(t,k,i)}_{\text{Pressure at gen k}} = \underbrace{R(z,k,i)}_{\text{Resistance}}\underbrace{\dot{V}(t,k,i)}_{\text{flow}} + \underbrace{P(t,k+1.i(a))}_{\text{Pressure at daughter branch}} \quad (2)$$

- R increases during bronchoconstriction due to a decrease in radius
- The radius (r) is calculated using a nonlinear model

$$r(z,k,i) = f(V(t,k,i), P(t,k,i), \tau_r) \quad (3)$$

where $\tau_r$ is the smooth muscle activation

# Introduction of Asymmetry

- Expanded the network model to include an asymmetric model of human lungs
- Asymmetric tree had more pronounced ventilation bifurcation
- The ventilation defects were more persistent in their locations in the asymmetric lung

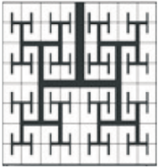


Figure: [2]

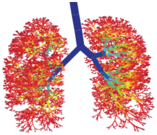


Figure: [2]

# Network Model Summary

- Constriction of the upper airways led to patchiness in ventilation
- Small perturbations in airway wall thickness were used in symmetric tree to break symmetry
- Did not consider the effects of gravity
- Did not include alveolus in the model

# Alveolar Models

- Single static alveolar
- Interdependence of static alveolar

# Single Alveolar Model

**Goal:**

- To study the structure and stability of alveoli
- Pressure-volume studies were preformed on intact lungs (including adult, child, premature infant, and rat lungs)
- Attempted to "quantify" stability

# Quantification of Characteristics

- Expansion Index

$$\underbrace{(V_{FR} - V_D)}_{\text{Function Residual Volume}} \quad / \underbrace{(V_{Max} - V_D)}_{\text{Maximum volume}} \tag{4}$$

- Stability Index:

$$S = \underbrace{2(\gamma_{max} - \gamma_{min})}_{\text{Change in tension}} / \underbrace{(\gamma_{max} + \gamma_{min})}_{\text{Average tension}} \tag{5}$$

# Normal Human Lung

- High film forming activity
- Change in surface tension: 33 dynes/cm
- Average surface tension: 20.5 dynes/cm

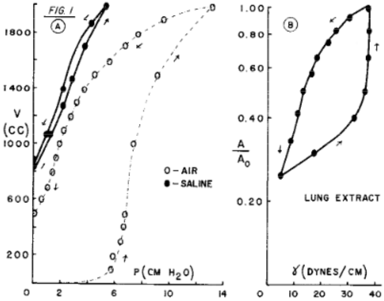



Figure: Pressure - volume curve for a normal human lung[1]

# Premature Infant Lung

- Less air was retained on deflation
- low film forming activity
- Change in surface tension: 24 dynes/cm
- Average surface tension: 30 dynes/cm

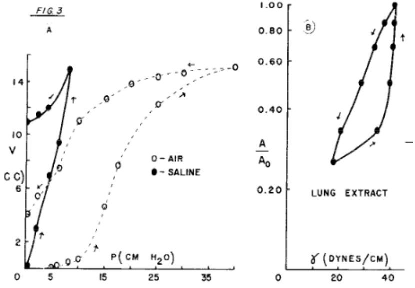



Figure: Pressure- volume curve for a premature infant [1]

# Constraint for Stability

$$R_{min} = \frac{8\gamma - 4A\frac{d\gamma}{dA}}{3P} \qquad (6)$$

$$P_{min} = \frac{8\gamma - 4A\frac{d\gamma}{dA}}{3R} \qquad (7)$$

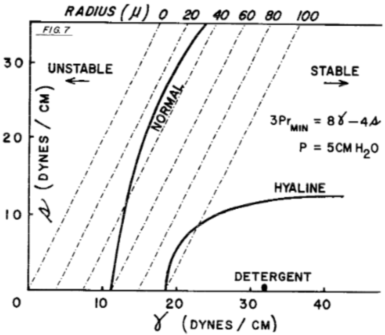



Figure: [1]

# Assumptions

- Modeled alveoli as hemispheres
- Only included one size of alveolus
- Only considered time-independent cases
- Does not include interdependence of alveolar

# Interaction between alveoli

- Used a simple sphere model
- Studied the stability of 2-15 alveoli
- Stability was classified as equal pressures
- Alveoli can coexist at both equilvalent and different volumes

# Stability of Two Alveoli

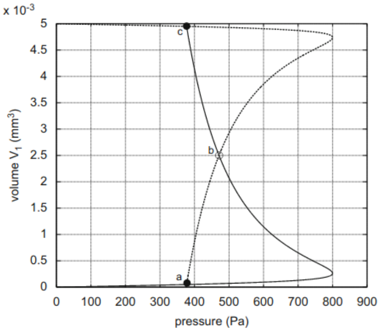



Figure: The PV curve of two connected alveoli. The shaded circles are stable states and the open circle is an unstable state. [3]

# Stability of up to 15 Alveoli

**Table 1**
Number of open alveoli against the pressure range in the different simulations (compare Figs. 4–7).

| Pressure range in Pa | 2 standard alveoli | 15 standard alveoli | 1 standard+1 alveolus with high surface tension | 1 standard+1 stiff alveolus |
|---|---|---|---|---|
| 0–300 | 0 | 0 | 0 | 0 |
| 300–390 | 0, 1 or 2 | 0–15 (different size possible) | 0 or 1 (standard) | 0 or 1 (standard) |
| 390–700 | 0, 1 or 2 | 0–x or 15 (x depends on pressure, see Fig. 5) | 0 or 1 (standard) | 0, 1 or 2 |
| 700–800 | 0, 1 or 2 | 0–15 (identical size) | 0 or 1 (standard) | 0, 1 or 2 |
| 800–1100 | 2 | 15 | 1 (standard) | 2 |
| 1100–2880 | 2 | 15 | 1 (standard) or 2 | 2 |
| > 2880 | 2 | 15 | 2 | 2 |

Figure: Number of open alveoli at different pressures [3]

# Summary of Alveoli Models

- Both models are static
- These models do not consider the complex geometry
- Show the stable/unstable states of alveoli
- Do not consider the larger airway structures

## Comparison

- Avalanche model has one alveolus at terminal airway
- The alveoli models use pressure
- The aveoli models are static
- The lung models do not consider alveoli and vice versa

# Ideas for Extension

1. Find/create a dynamic bistable alveoli model
2. Test external pressure and vibration stimulus
3. Expand to include a group of alveoli
4. Connect alveoli model to network model to study air flow through entire lung
5. Test stability against external stimulus
6. Optmize stimulus

# Resources


- John A Clements et al. "Pulmonary surface tension and alveolar stability". In: *Journal of applied physiology* 16.3 (1961), pp. 444–450.
- Del Leary et al. "Effects of airway tree asymmetry on the emergence and spatial persistence of ventilation defects". In: *Journal of Applied Physiology* 117.4 (2014), pp. 353–362.
- Kerstin Schirrmann et al. "Theoretical modeling of the interaction between alveoli during inflation and deflation in normal and diseased lungs". In: *Journal of biomechanics* 43.6 (2010), pp. 1202–1207.
- Béla Suki et al. "Avalanches and power-law behaviour in lung inflation". In: *Nature* 368.6472 (1994), pp. 615–618.
- Jose G Venegas et al. "Self-organized patchiness in asthma as a prelude to catastrophic shifts". In: *Nature* 434.7034 (2005), pp. 777–782.