Modeling Aveolar Stability with Modified Duffing Equations

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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

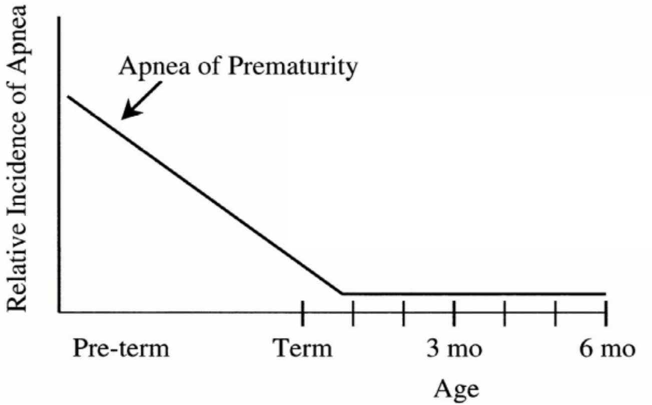
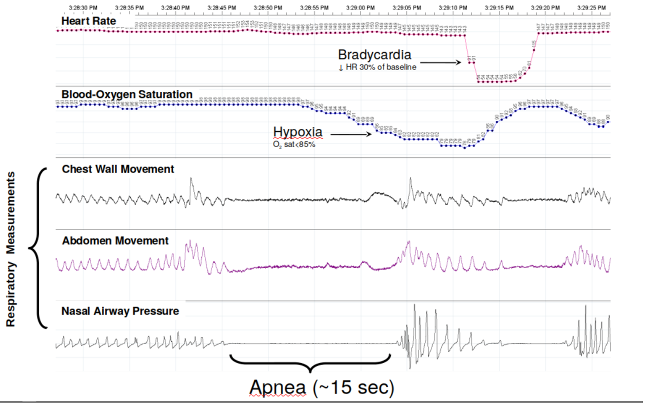
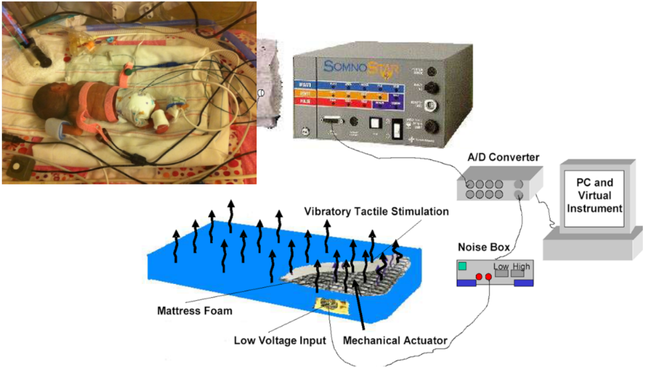


Figure: Martin RJ & Wilson CG (2012). Compr Physiol 2: 2923-31. DiFiore JM et al.(2010). Pediatr 157: 69-73.

Switching from rhythmic breathing to apneic state



Motivating Study



Mechanosensory Enhancement of Breathing

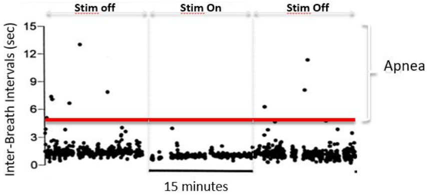


Figure: 10 preterm infants. Study Wt:1500 gm (1020-2175); PCA: 33.3 weeks (31.4-35.7) (Bloch-Salisbury E, Indic P, Bednarek F, Paydarfar D. J Appl Physiol. 2009 107(4): 1017-1027)

- 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

Reduction of Desaturation

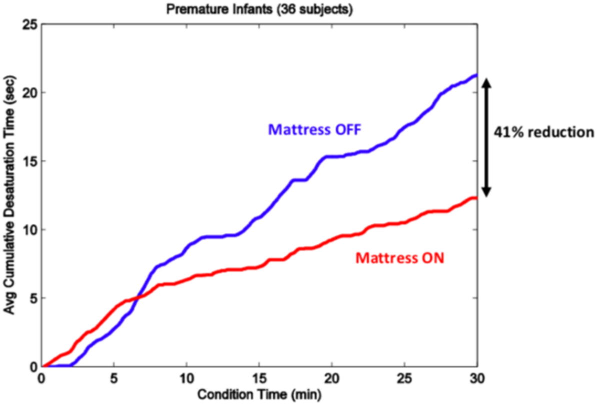


Figure: Average segments over 30 minutes of treatment (Gee AH, Temple C, Smith VC, Paydarfar D (in prep).)

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

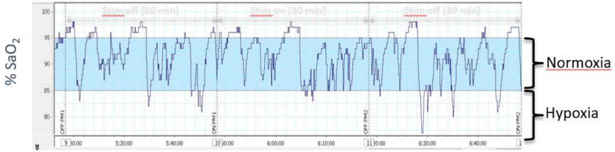
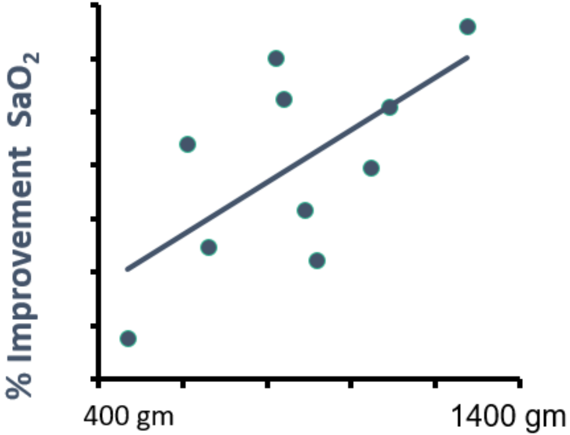


Figure: 10 preterm infants requiring mechanical ventilation. Study wt. 850 gm (470-1275); PCA 28.8 weeks (25-30); On ventilator for 16 days (2-35)

- 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



Reduction of Desaturation Time with Vent

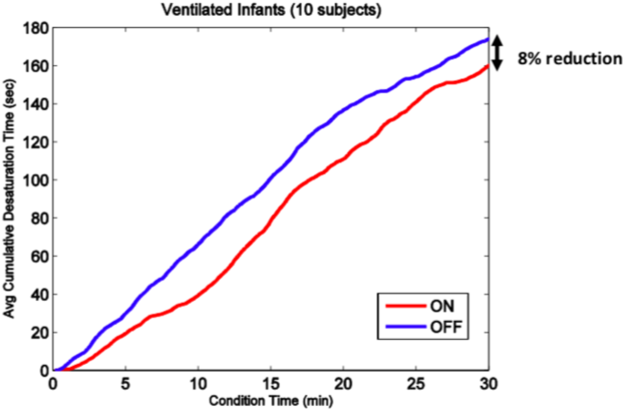


Figure: Average of Segments over 30 minutes of treatment (Gee AH, Temple C, Smith VC, Paydarfar D (in prep).)

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))

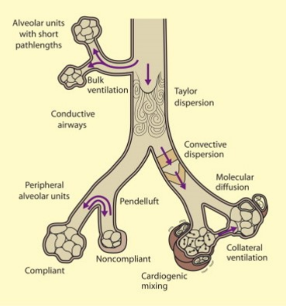


Figure: Wolf & Arnold. Paediatr Child Health. 2007 17(3):77-81

Focus on Decrease Atelectsis

We want to focus on the collapsing of the alveoli

Objective: To create a model of one bistable alveolus using a set of differential equations

Goals for the Model

- periodic forcing function is required for the system to oscillate
- prefer two state variables only
- system must be bistable
- the trapping region of the phaseless set bounds a fixed point and occupies a small region
- the ability to shift the system to the left and right
- Fixed point at $r = 0$

Expansion on objectives

Periodic forcing function:

- To model the opening and closing of the aveolus

Two state variables

- The state variables are the radius of the aveolus and velocity of the radius

Bistable system

- The system has to have an open and collapse state

Trapping region

- With added noise, the system must be able to switch between the open and collapsed states

Expansion on objectives cont.

Ability to shift the system left and right

- An aveolus on a ventilator might expand more then one that is breathing spontaneously

Fixed point at $r = 0$

- The collapsed state of the aveolus will occur when the radius is equal to zero

Original Duffing Equations

$$\ddot{r} + \beta r + \alpha r^3 + \delta \dot{r} = \gamma \cos(\omega t) \tag{1}$$

where

- δ: controls the amount of damping
- β: controls the linear stiffness
- α: controls the amount of non-linearity in the restoring force
- γ amplitude of the periodic driving force
- ω: angular frequency of the driving force

Modified Duffing Equations

$$\ddot{r} + \beta r + \alpha r^3 + (\delta - r)\dot{r} = \gamma \cos(\omega t) \tag{2}$$

where

- δ: controls the amount of damping
- β: controls the linear stiffness
- α: controls the amount of non-linearity in the restoring force
- γ amplitude of the periodic driving force
- ω: angular frequency of the driving force

Scaled Duffing Equations

$$\ddot{r} + \beta(r - \sqrt{\frac{\beta}{\alpha}}) + \alpha(r - \sqrt{\frac{\beta}{\alpha}})^3 + (2\sqrt{\frac{\beta}{\alpha}} - r)\dot{r} = \gamma \cos(\omega t) \quad (3)$$

- This assures there will be a stable fixed point at $r = 0$

Rewriting as a system of ODE

$$u' = v \tag{4}$$

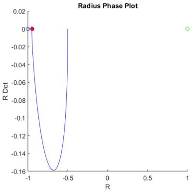
$$v' = \beta(u - \sqrt{\frac{\beta}{\alpha}}) - \alpha(u - \sqrt{\frac{\beta}{\alpha}})^3 - (2\sqrt{\frac{\beta}{\alpha}} - u)v + \gamma\cos(\omega t) \tag{5}$$

where

- $u = r$
- $v = r'$

Two fixed points

There are two fixed points, $r = 0$ and $r = 2\sqrt{\frac{\beta}{\alpha}}$



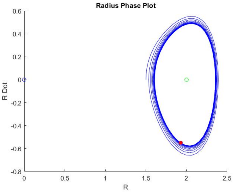
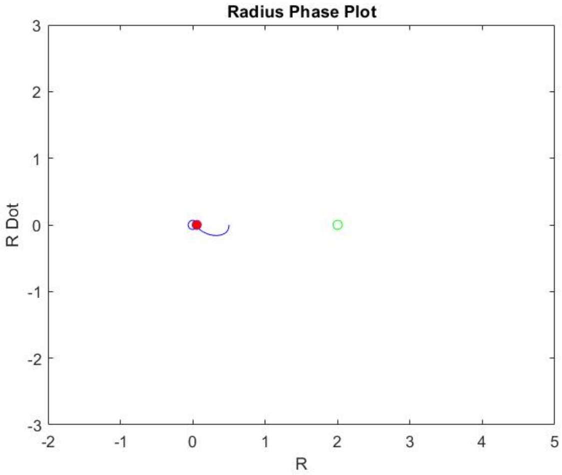
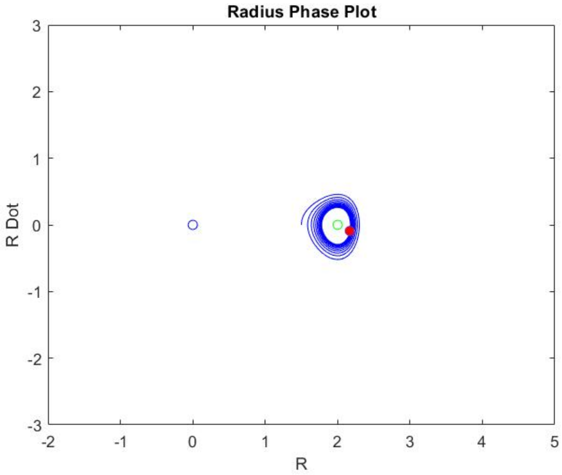


Figure: The phase plot for the right fixed point in the shifted modified duffing equations. Parameter values: $\beta = 1$, $\alpha = 1$, $\gamma = 0.1$, $\omega = 1$

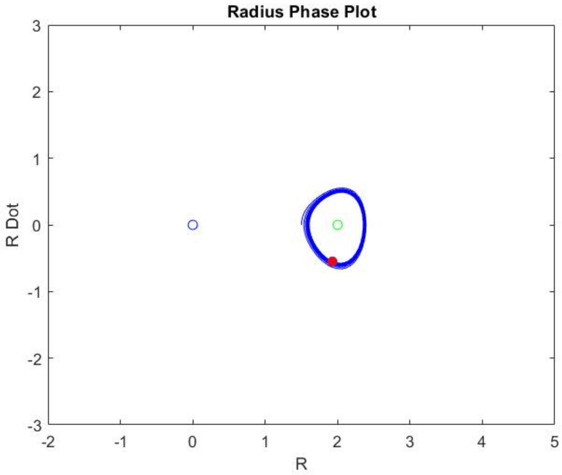
Closed State



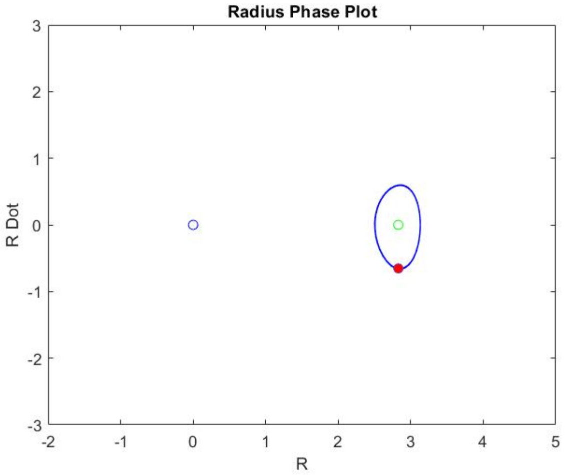
Open State with no forcing function



Open State with forcing function



Shifting the open state



Adding Noise to the Model

$$I(t) = \gamma \cos(\omega t) + A \cdot w \tag{6}$$

where w is a random number with a mean of 0

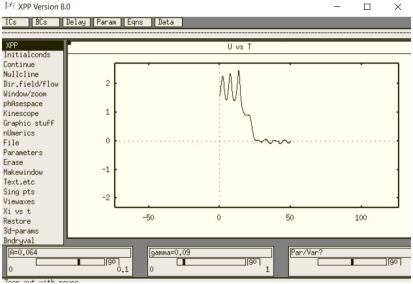


Figure: The U vs T from XPP with added noise. The limit cycle collapsed to the fixed point.

Goals of the Model

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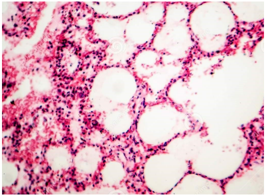
Considerations of the Model

- If the forcing functions amplitude is high enough, it does cause small oscillations at the 0 fixed point

Future Goals

1. Couple the model to include two or more alveoli
2. Include lung mechanic properties of the surrounding tissue



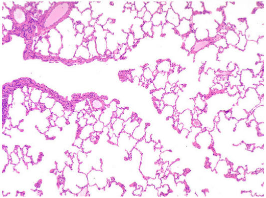


Figure: Microscopy of the aveoli (left) and bronchiole (right)

Ideas for Expansion