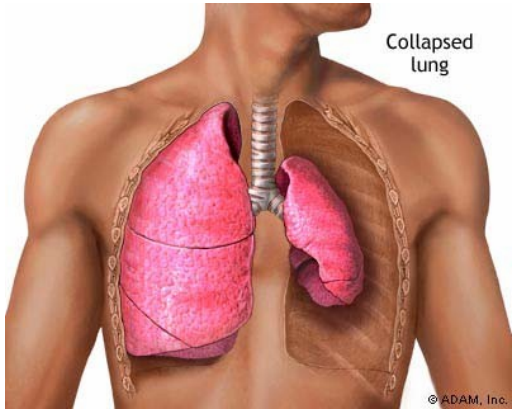
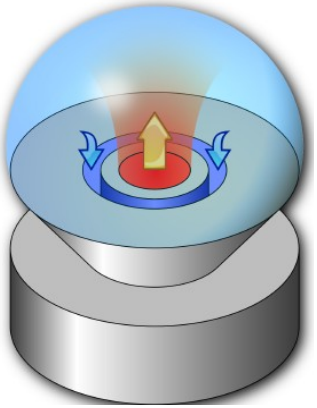
University of Toronto

Laboratory for Applied Surface Thermodynamics
Laboratory of Colloid and Formulation Engineering

predicting lung mechanics from dynamic surface tension evaluations of lung surfactants

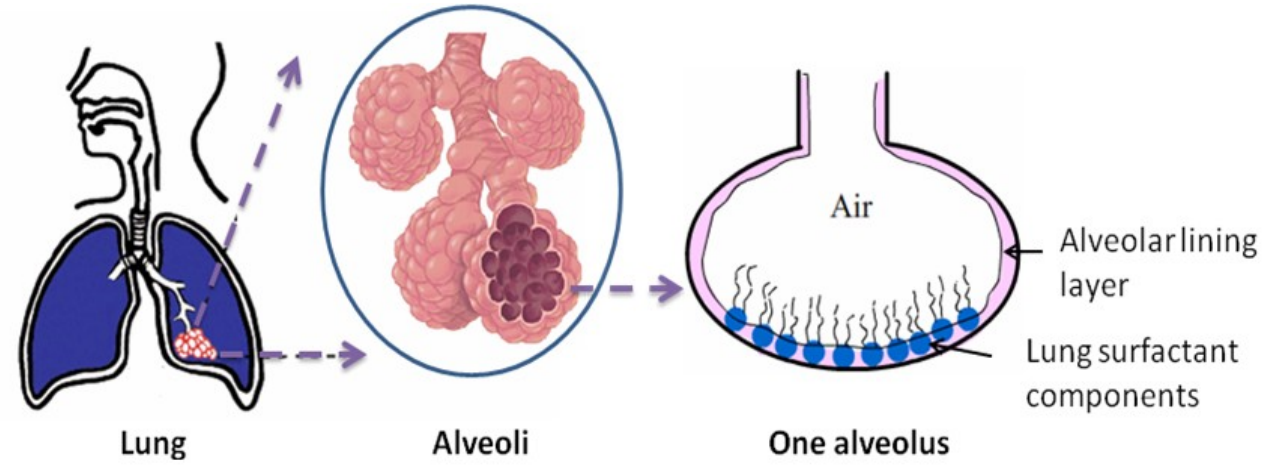


Edgar Acosta, Z. Policova, S. Saad , A. W. Neumann.



February 22, 2012
Workshop on Surfactant Driven Thin Film Flows
to be held at the Fields Institute

Lung Surfactants and Lung Physiology



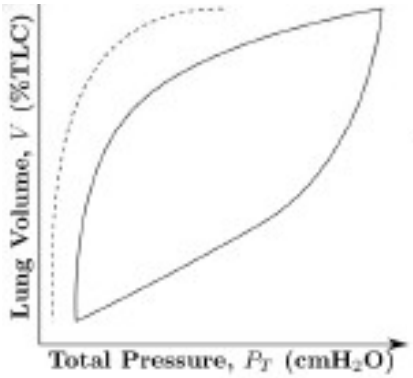
Upon compression (exhalation) the lung surfactants produce a near zero surface tension that reduce the pressure difference between the smaller alveoli and the airways

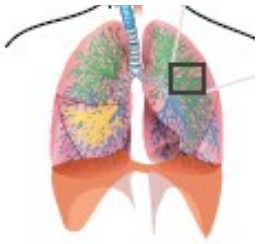
Laplace Pressure: $\Delta P \sim \gamma/R$ (R, radius of the alveolus)

The Engineering Approach

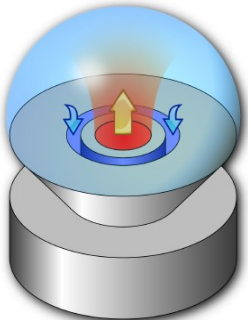
Surfactant chemistry and additives

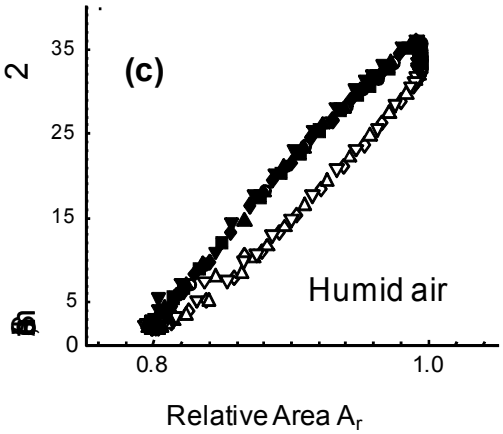
In vivo





In vitro

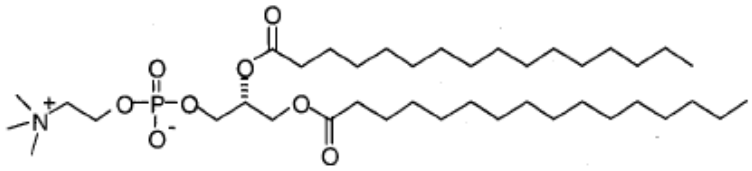




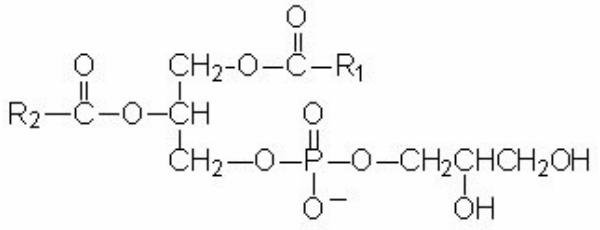
Surfactant and lung mechanics

Composition of lung surfactants

- Phospholipids ~ 85-90%
  - Mainly phostphatidyl cholines (zwitterionic), and particularly dipalmitoyl phosphatidyl cholines (DPPC) to give solid-like properties.



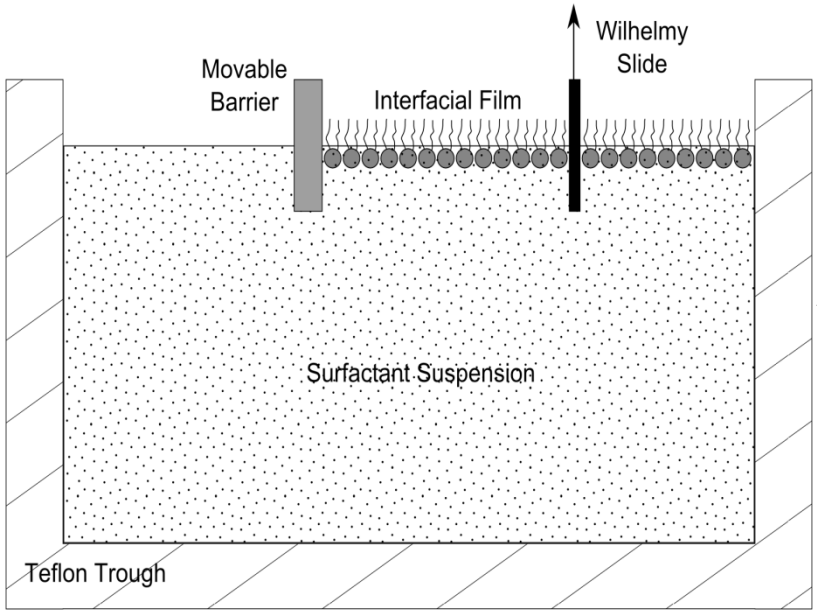
  - Phosphatidyl glycerols (anionic) that impart appropriate dynamic folding/unfolding properties to the surfactant film



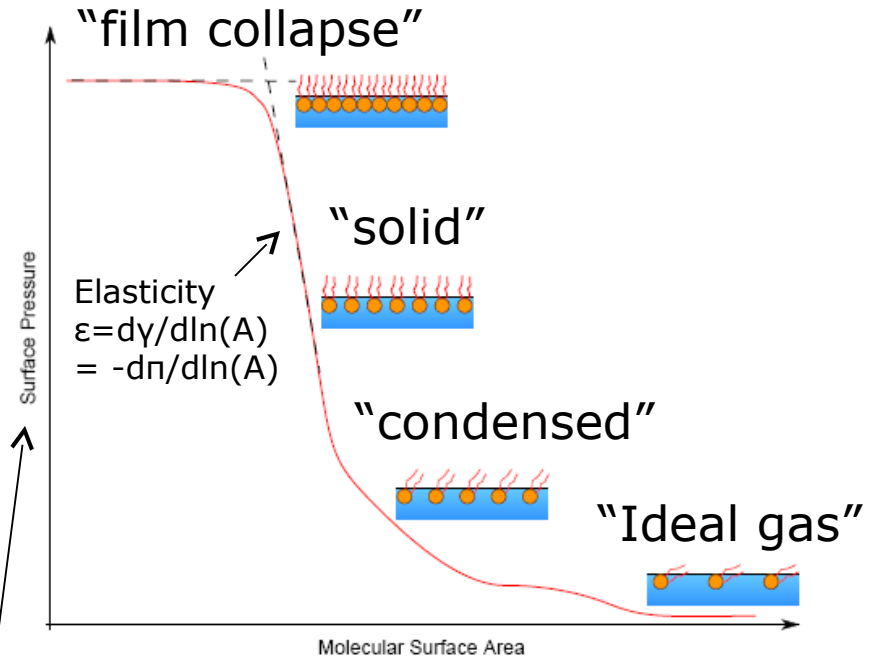
- Neutral Lipids ~ 1-5% (cholesterol)

- Proteins ~ 5-10%
  - Surfactant Proteins A and D => anionic, hydrophilic
  - Surfactant Proteins B and C => cationic, hydrophobic
  - Surfactant Protein B is essential

Surfactant Evaluation => Compression isotherms



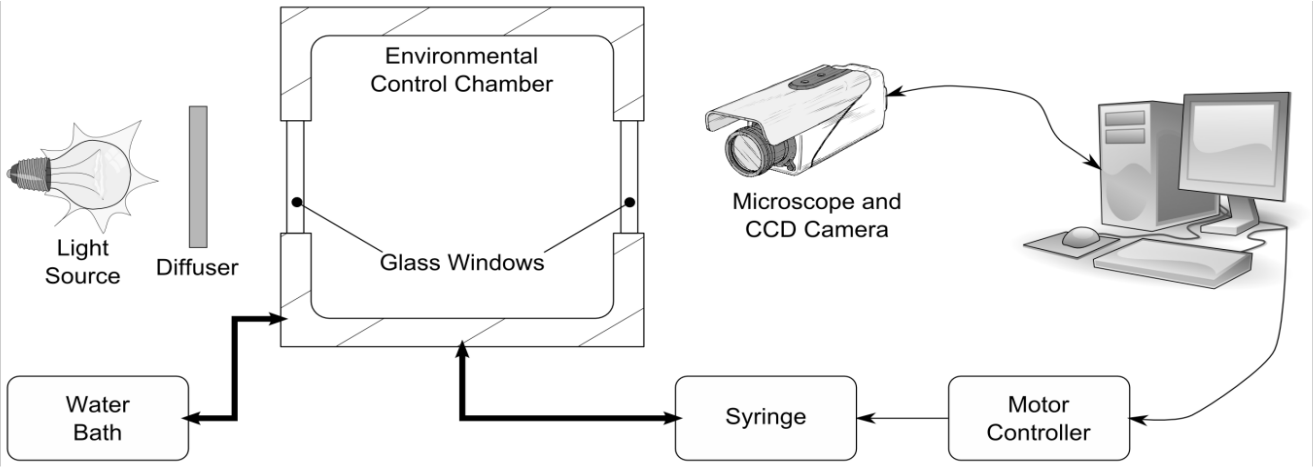
Wilhelmy Balance

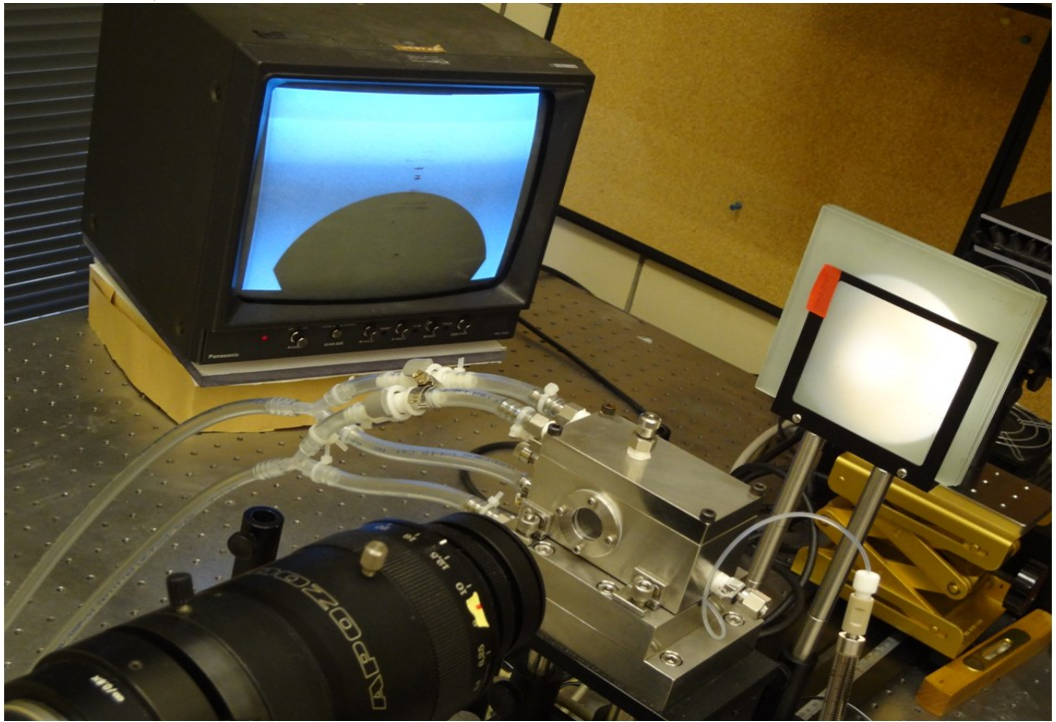


Molecular area = 1/surface concentration=$1/\Gamma$

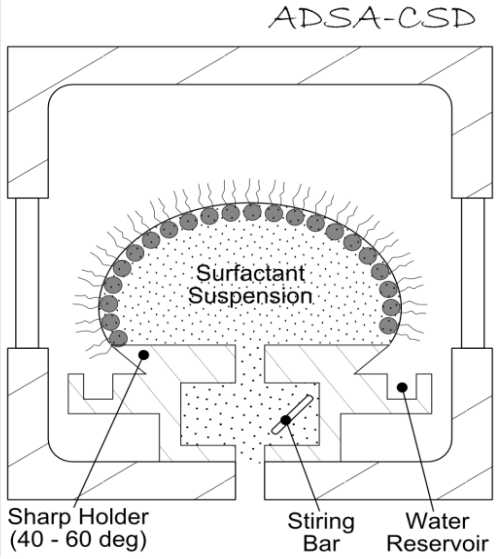
Surface pressure = surface tension of the pure liquid (γ_0)- surface tension (γ)

Evaluation of Surfactant Dynamics

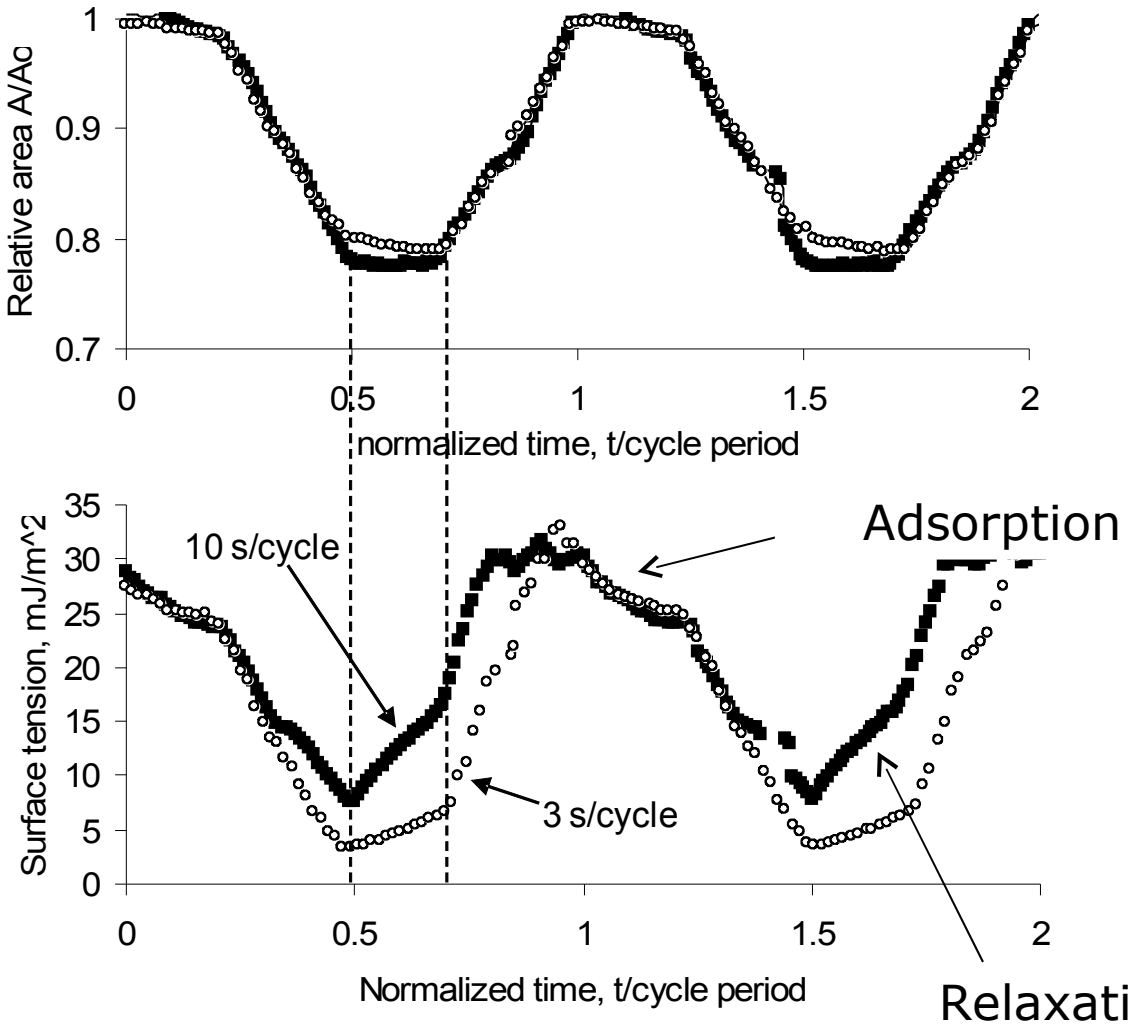




Constrain Sessile Drop



Dynamic Evaluation => adsorption and relaxation effects



Adsorption and relaxation effects depend on:

Compression dynamics

Environment

Surfactant composition

Compression Relaxation Model

$$\frac{d\gamma}{dt} = \begin{cases} \frac{d\gamma_1}{dt} + \frac{d\gamma_2}{dt} & \text{if } \gamma \geq \gamma_{min} \\ 0 & \text{if } \gamma \leq \gamma_{min} \end{cases}$$

where

$$\frac{d\gamma_1}{dt} = \begin{cases} k_a \left(\gamma_{eq} - \gamma\right) & \text{if } \gamma \geq \gamma_{eq} \\ k_r \left(\gamma_{eq} - \gamma\right) & \text{if } \gamma \leq \gamma_{eq} \end{cases}$$

$$\frac{d\gamma_2}{dt} = \begin{cases} \epsilon_c \left(\frac{1}{A}\frac{dA}{dt}\right) & \text{if } \frac{dA}{dt} \leq 0 \\ \epsilon_e \left(\frac{1}{A}\frac{dA}{dt}\right) & \text{if } \frac{dA}{dt} \geq 0 \end{cases}$$

γ_{eq} Equilibrium surface tension

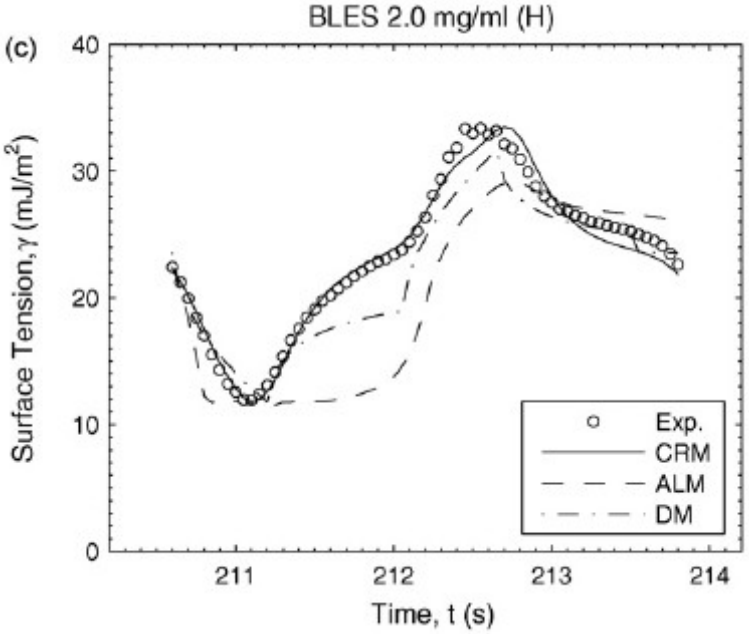
$\gamma_{min,c}$ Minimum surface tension at collapse

k_a, k_r First order adsorption and relaxation constants

ε_c, ε_e Elasticity during compression and expansion

Compression Relaxation Model

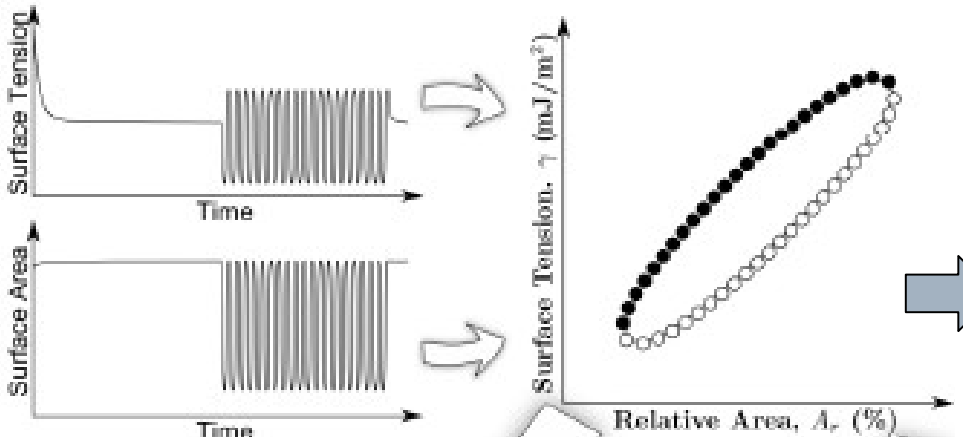
Typical fit of CRM model



Parameters for specific scenarios

Formulation	ε_c, mJ/m^2	ε_e, mJ/m^2	k_a, s^{-1}	k_r, s^{-1}	γ_{min}, mJ/m^2	γ_{eq}, mJ/m^2
BLES	120	130	2.5	0.0	2	22
BLES-albumin	72	78	1.5	2.5	20	25
Formulation	ε_c, mJ/m^2	ε_e, mJ/m^2	k_a, s^{-1}	k_r, s^{-1}	γ_{min}, mJ/m^2	γ_{eq}, mJ/m^2

CRM - Pressure-Volume Model

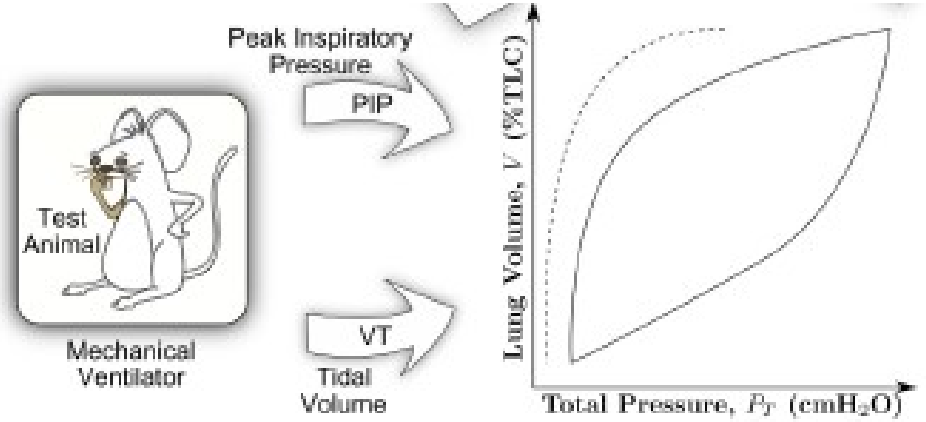


Ventilator waveform:
V=f(t)

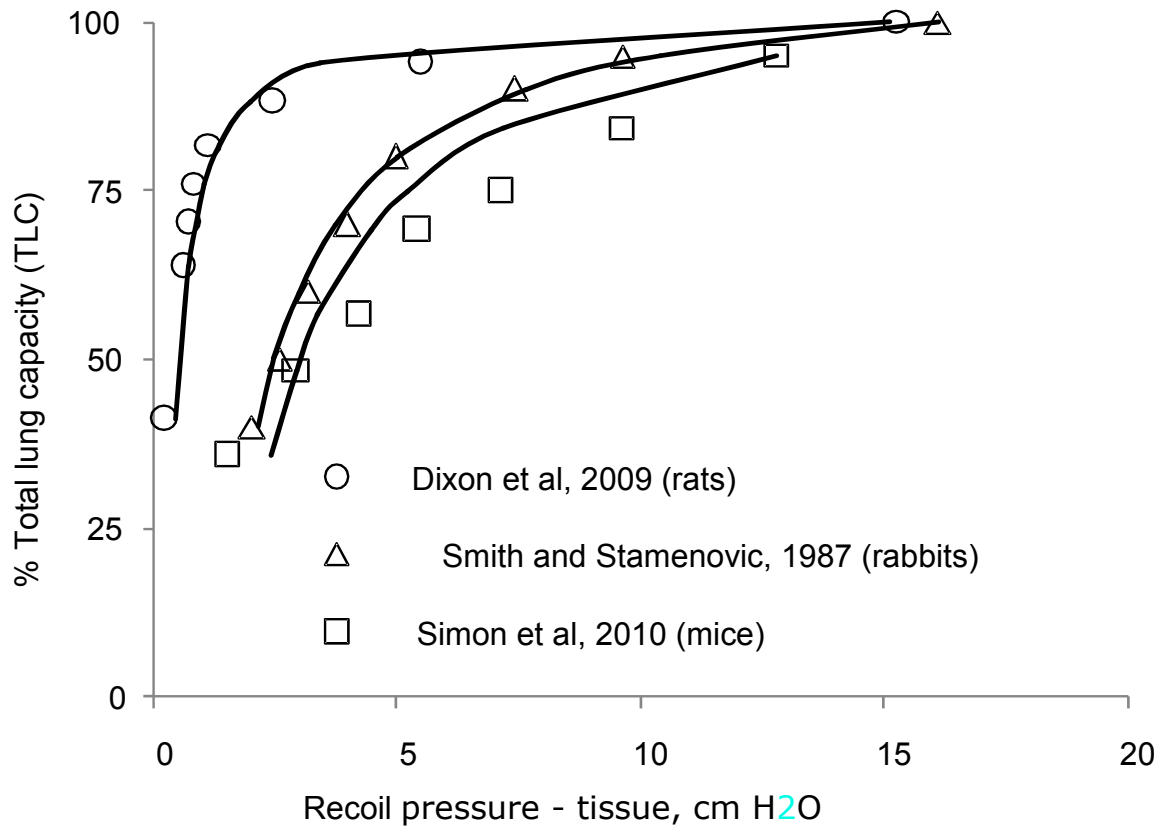
CRM parameters:
γ_{eq}, $\gamma_{min,c}$, k_a, k_r , ε_c, ε_e
γ =f(A, t)

Prokop et al. (1999)
A =f(V, γ)

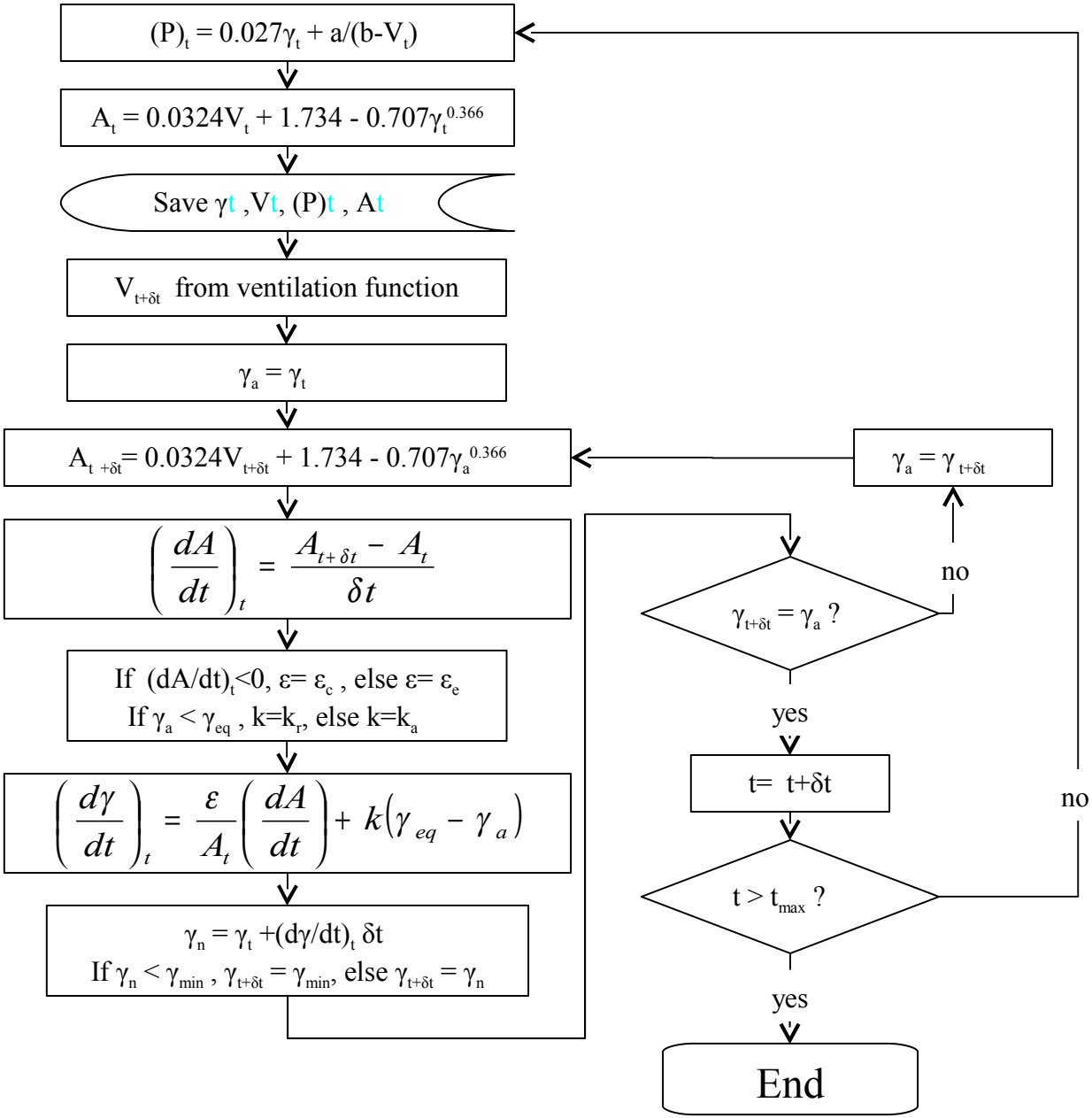
Smith et al. (1986)
$P = P_{tissue}(V) + P_{capillary}(\gamma)$



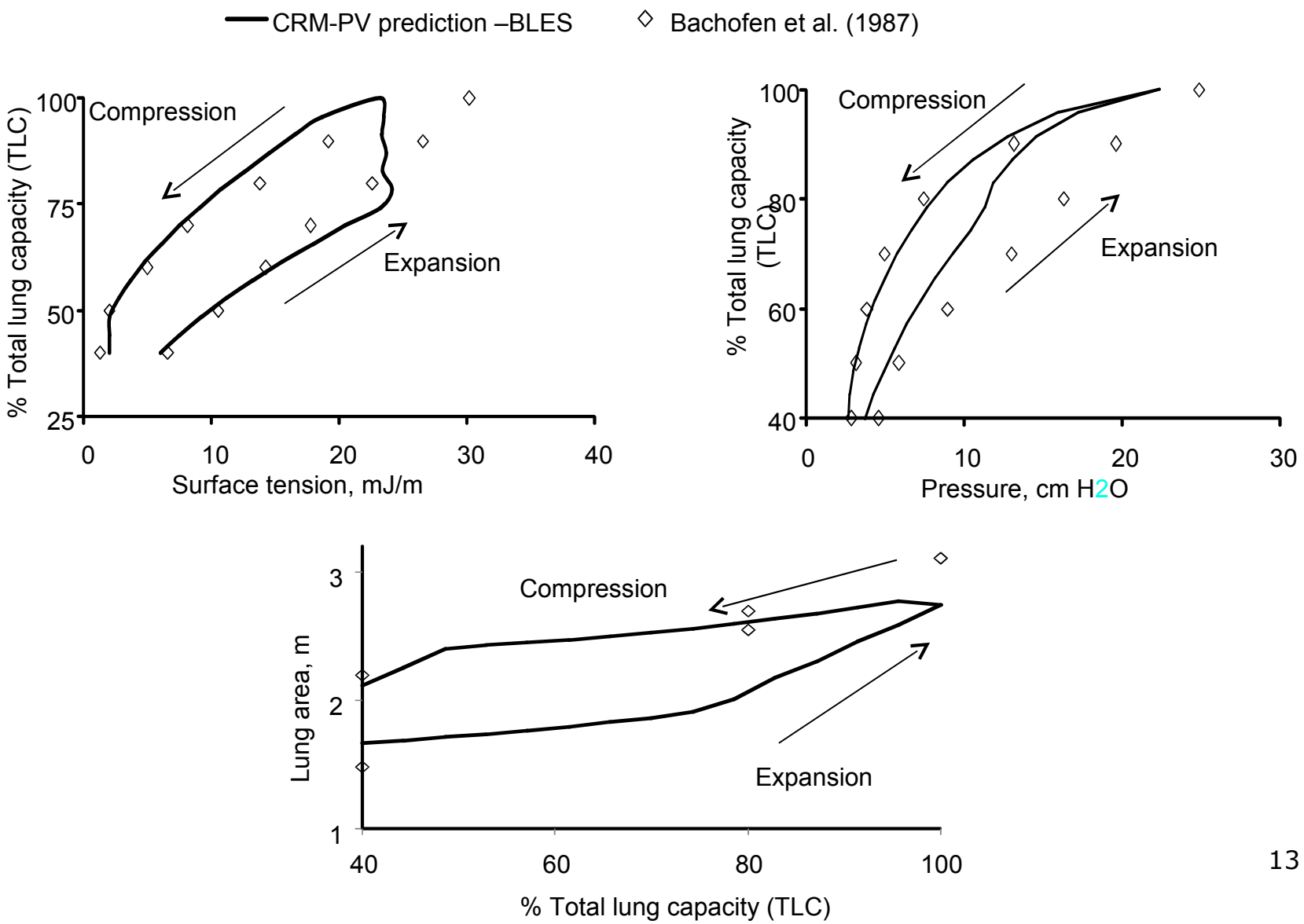
Tissue contribution to lung pressure



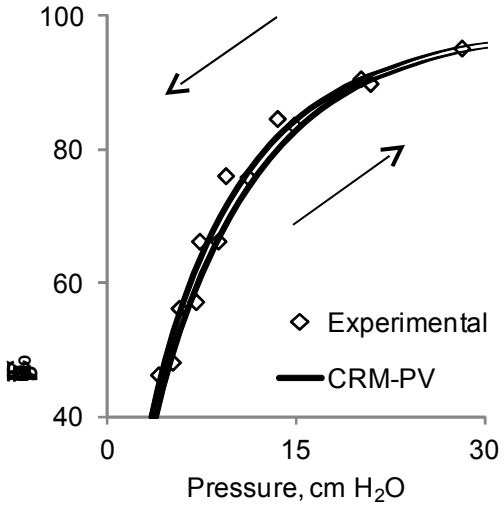
CRM-PV algorithm

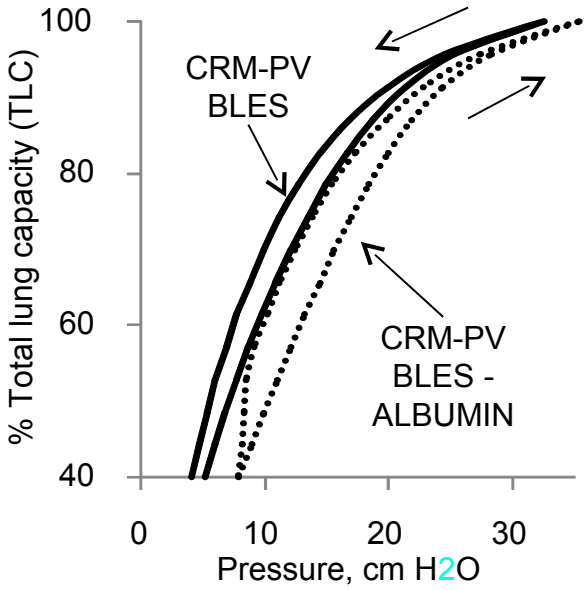


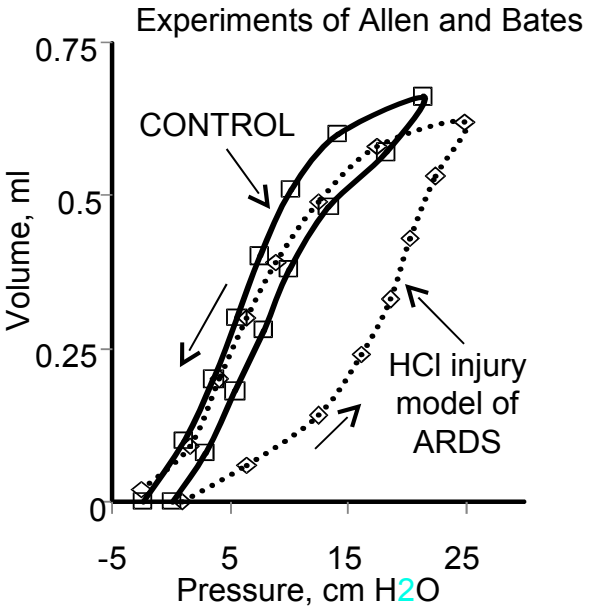
CRM – PV –rabbit model



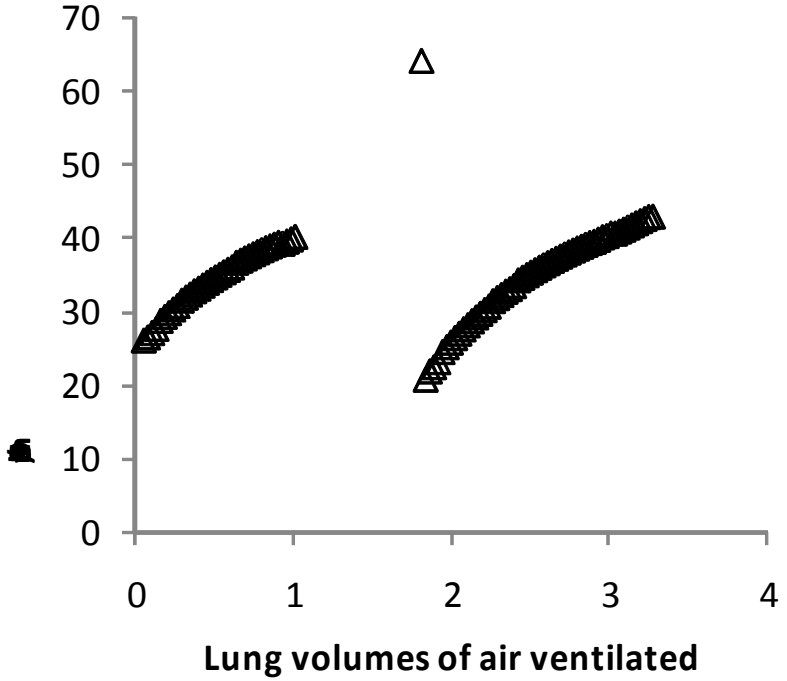
CRM – PV –mice model

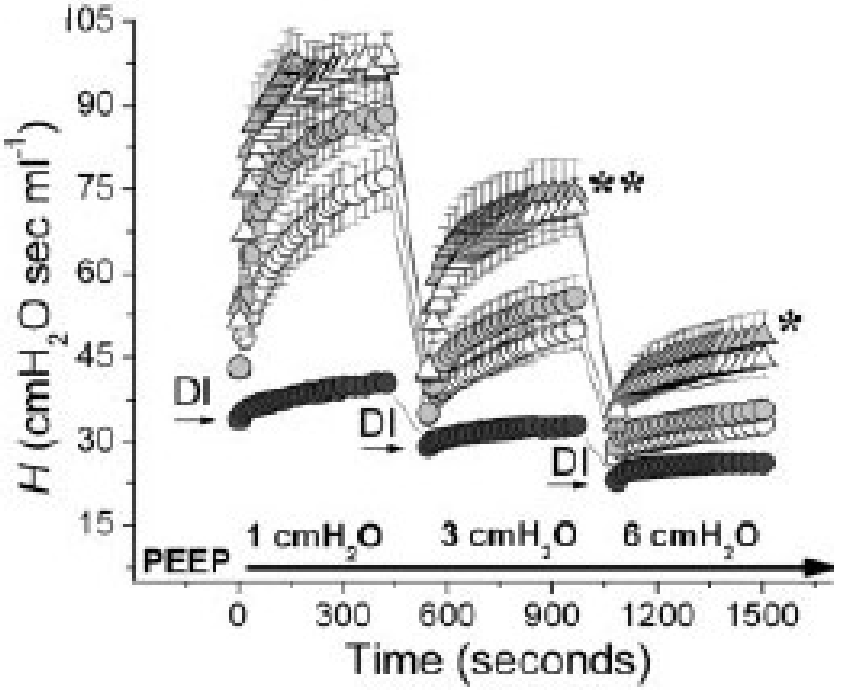






CRM – PV, dynamic properties





CRM-PV prediction of lung elastance (ΔP/ ΔV) – left – and experimental values –right - using variable ventilation

*** low minimum surface tension is not always important ***

Fast surfactant adsorption is essential

Conclusions

1 – *In vitro* – *in vivo* correlations are closer to reality => integrated approach to design surfactant therapies

2 – Much to be learned of the physics of surfactant membranes at the molecular scale

3 – A combination of strategies: surfactant additives, method of ventilation may be used in alternative therapies

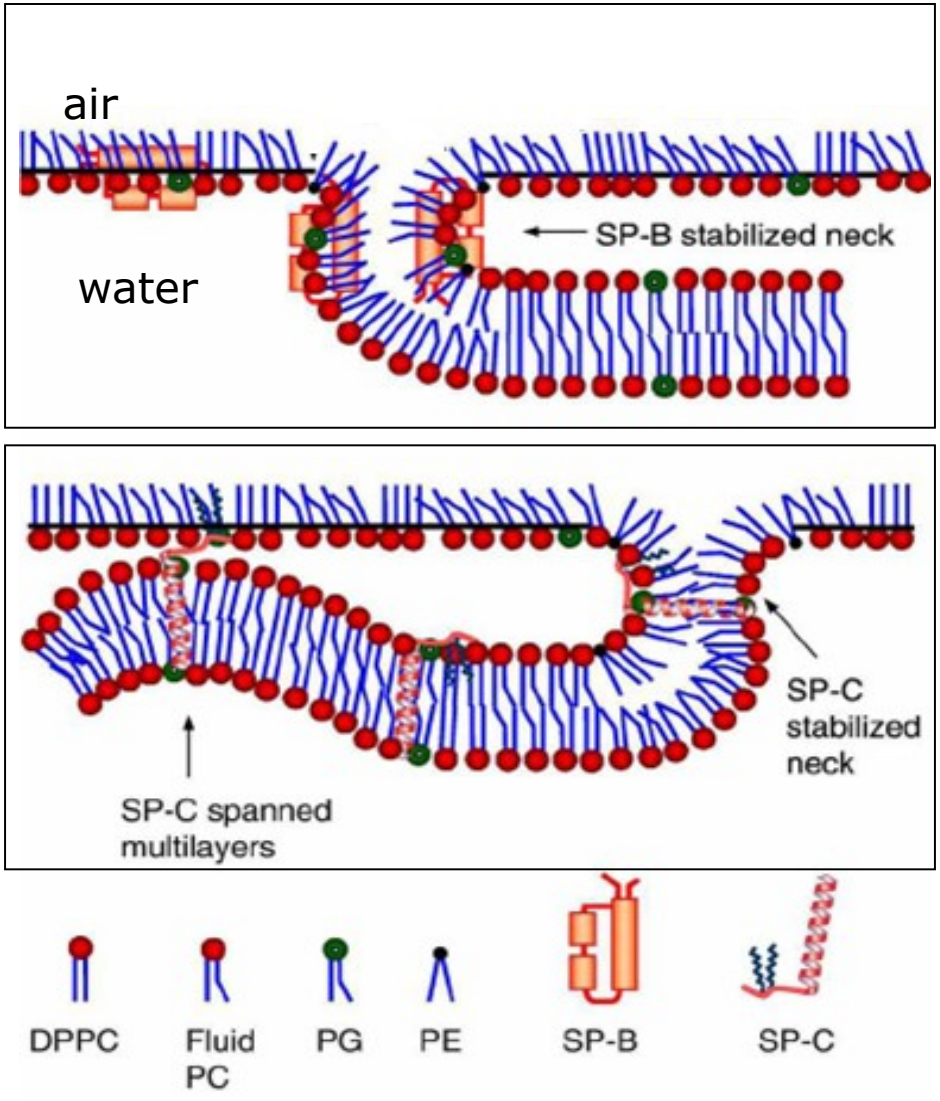
4 – Need to introduce flow-driven pressure drop

5 – Need to incorporate surfactant spreading

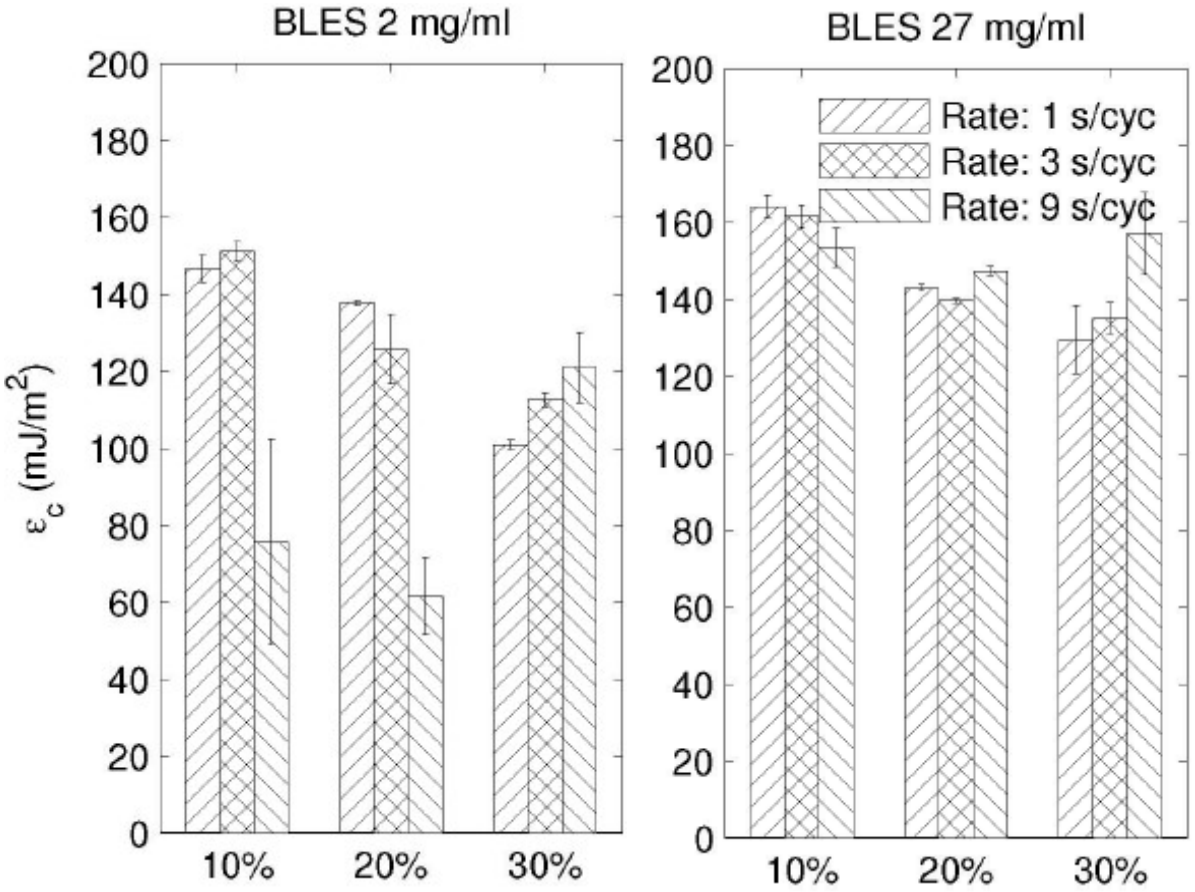
Acknowledgements

- *Canada Institute for Health Research (CIHR)*
- *BLES Biochemicals (London, Ontario)*

Surfactant membrane conformations



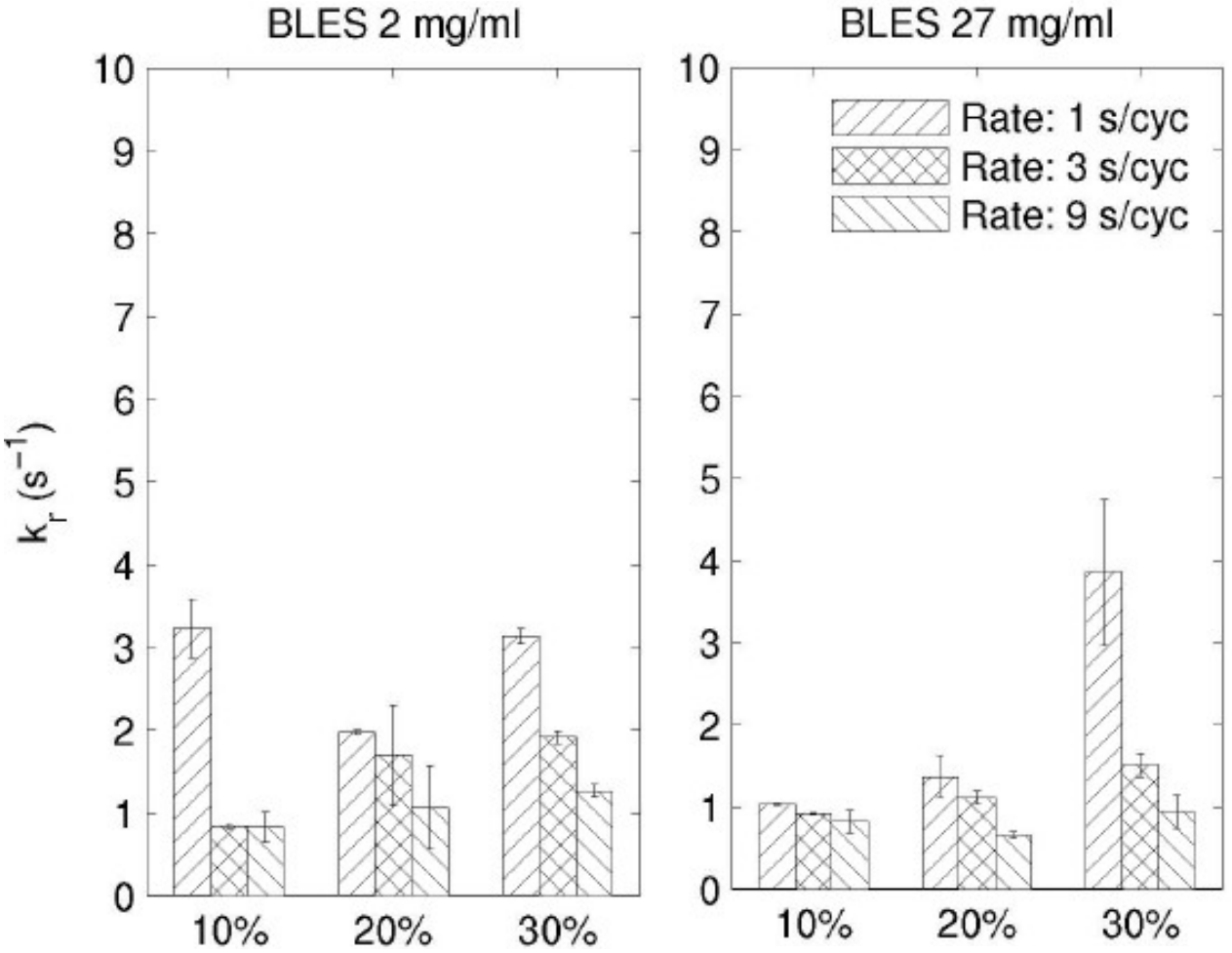
Compression Relaxation Model



% Area reduction (compression)

Elasticity slightly improves with surfactant concentration

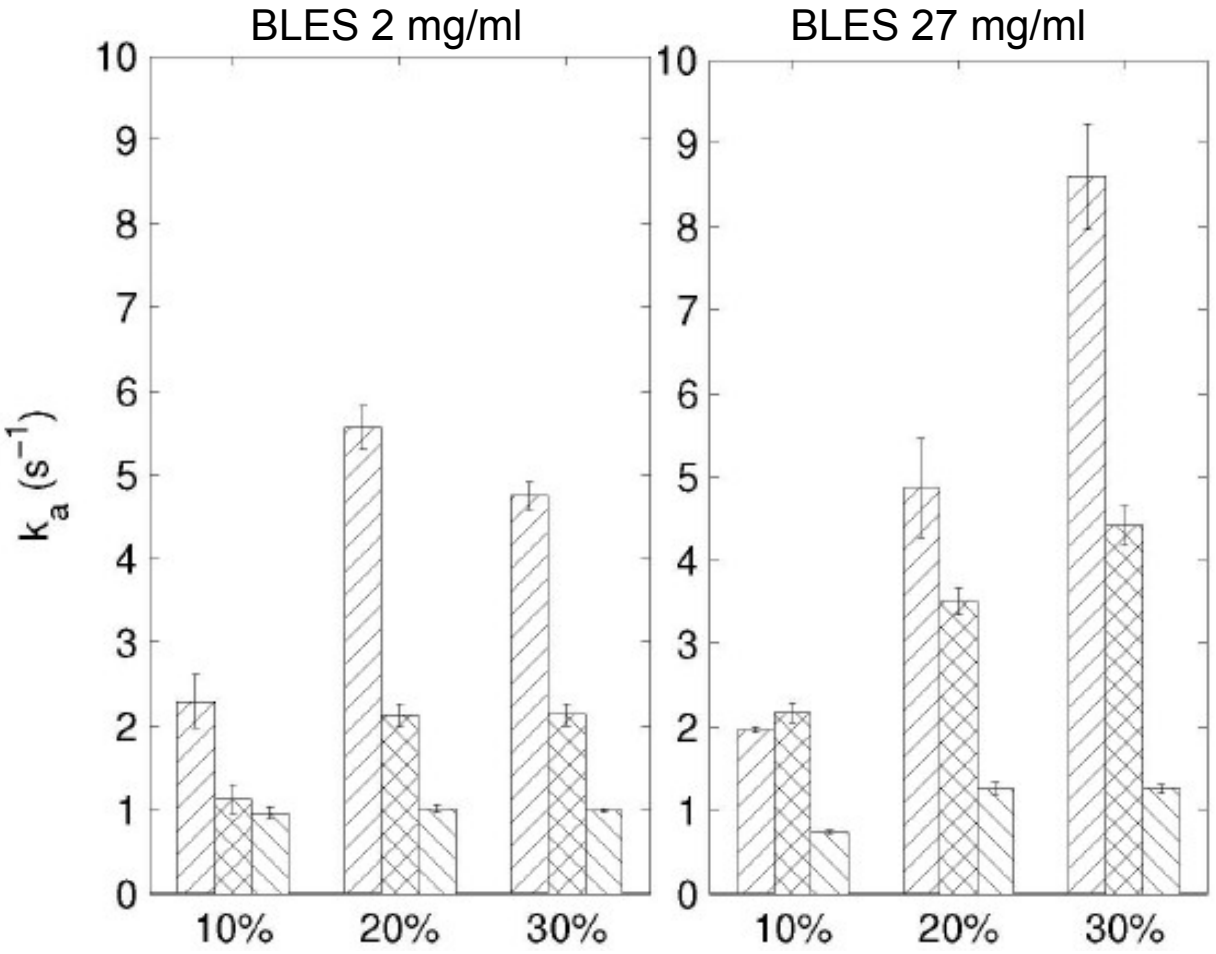
Compression Relaxation Model



% Area reduction (compression)

Relaxation constant is not a function of surfactant concentration

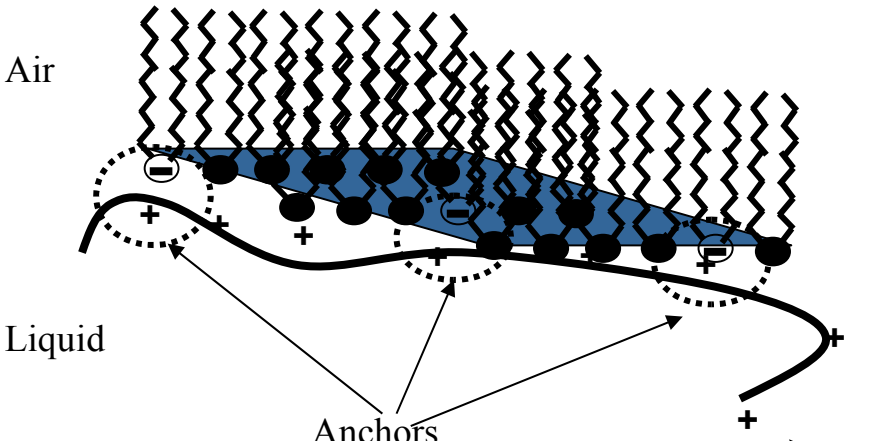
Compression Relaxation Model

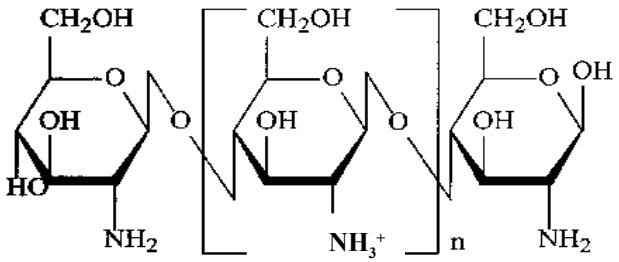


% Area reduction (compression)

Adsorption constant tends to increase with surfactant concentration

Cationic Surfactant Additives





Chitosan

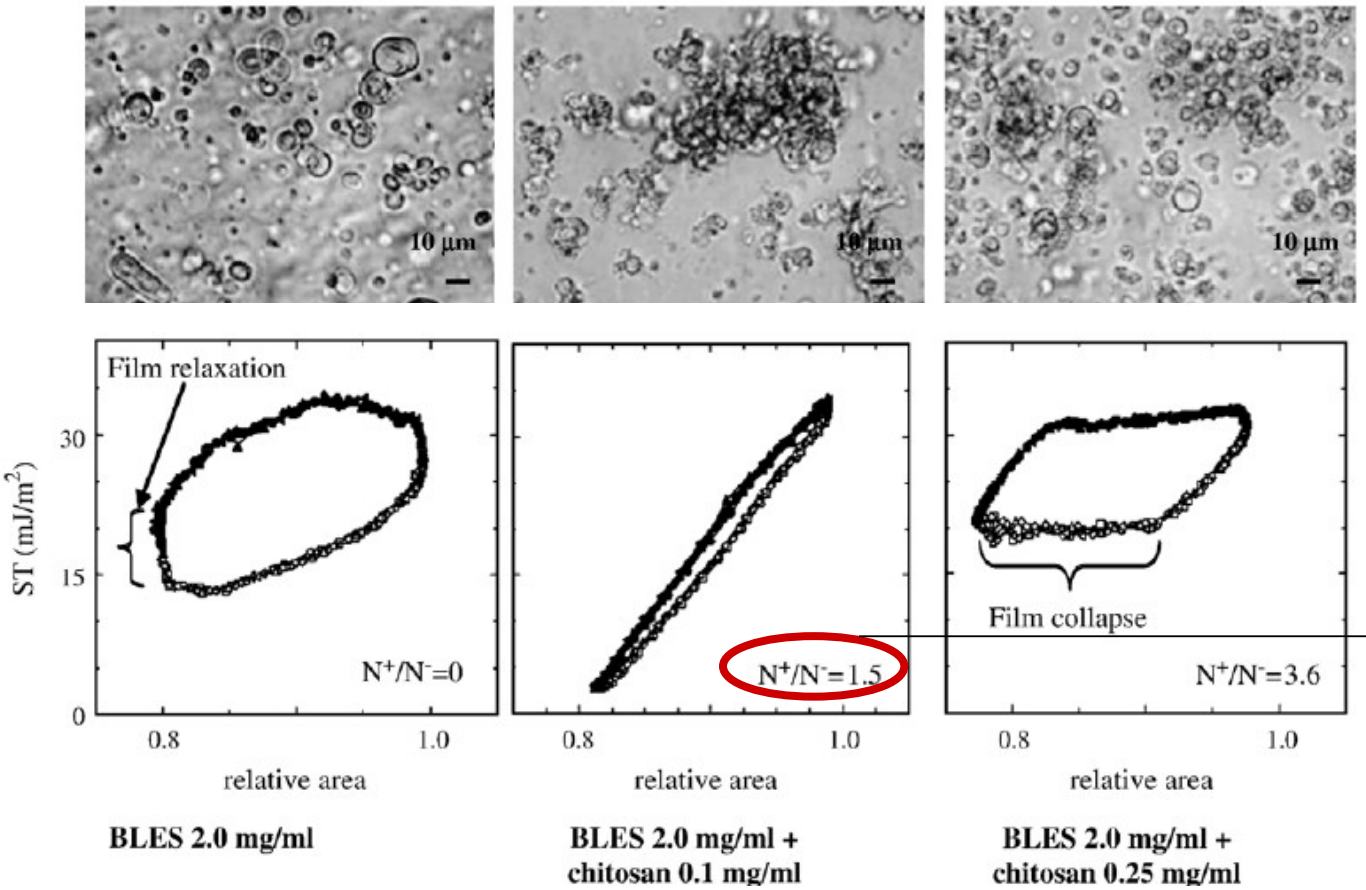
Reasoning:

Cationic additives can be use to induce flocculation and larger, more active, surfactant aggregates

SP-B, a cationic protein, is essential to life

The anionic headgroup of phosphatidyl glycerols seems to easily hydrate, weakening the surfactant film

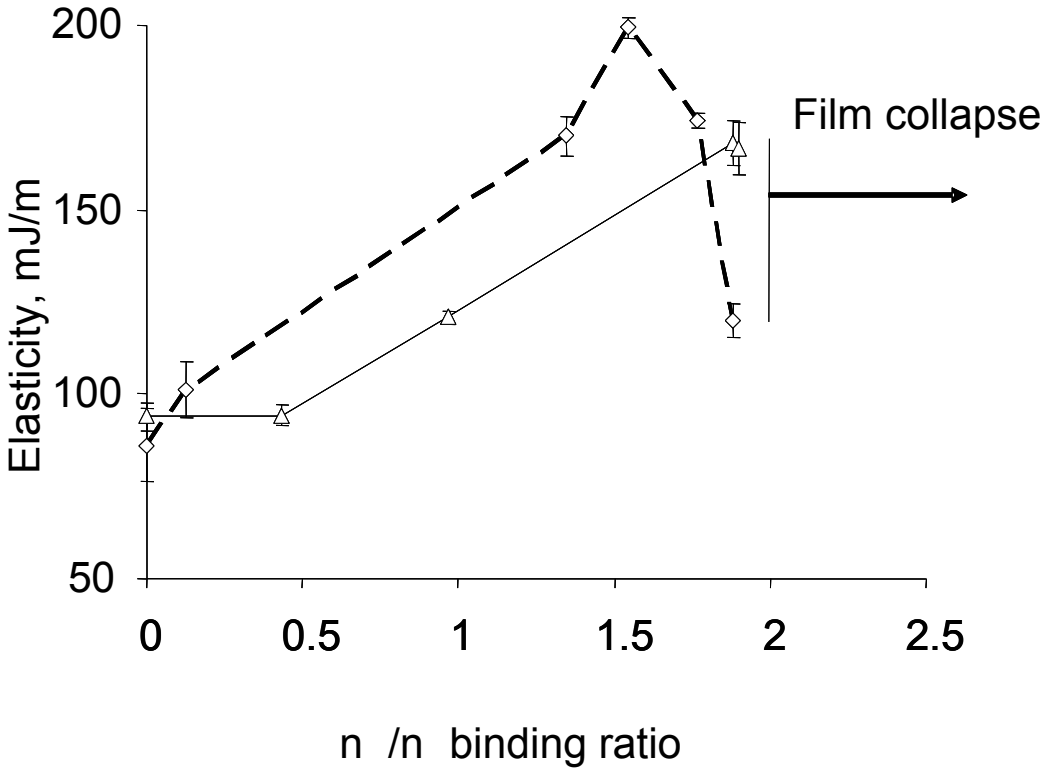
Effect of Chitosan on BLES



Optimal molar ratio of number of cationic groups in polymer to anionic groups in lipids

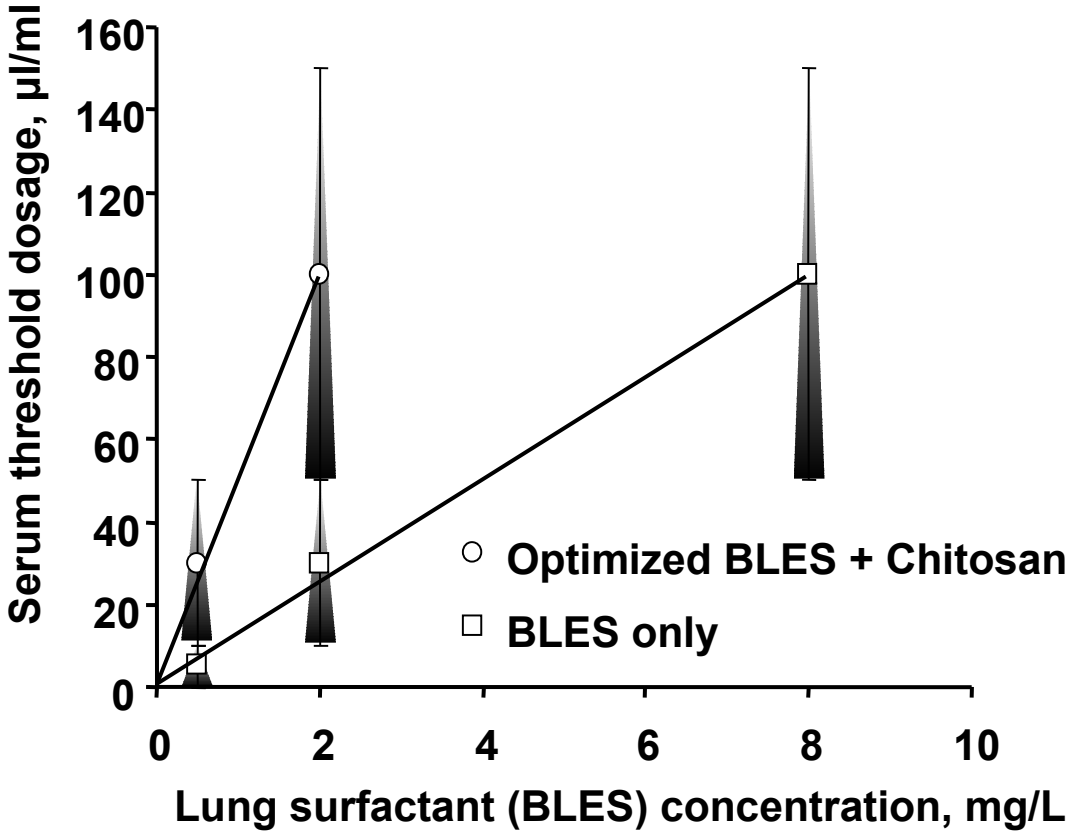
Addition of chitosan, up to a certain ratio, induce larger aggregates to form, also improving the surface activity

Effect of Chitosan on BLES



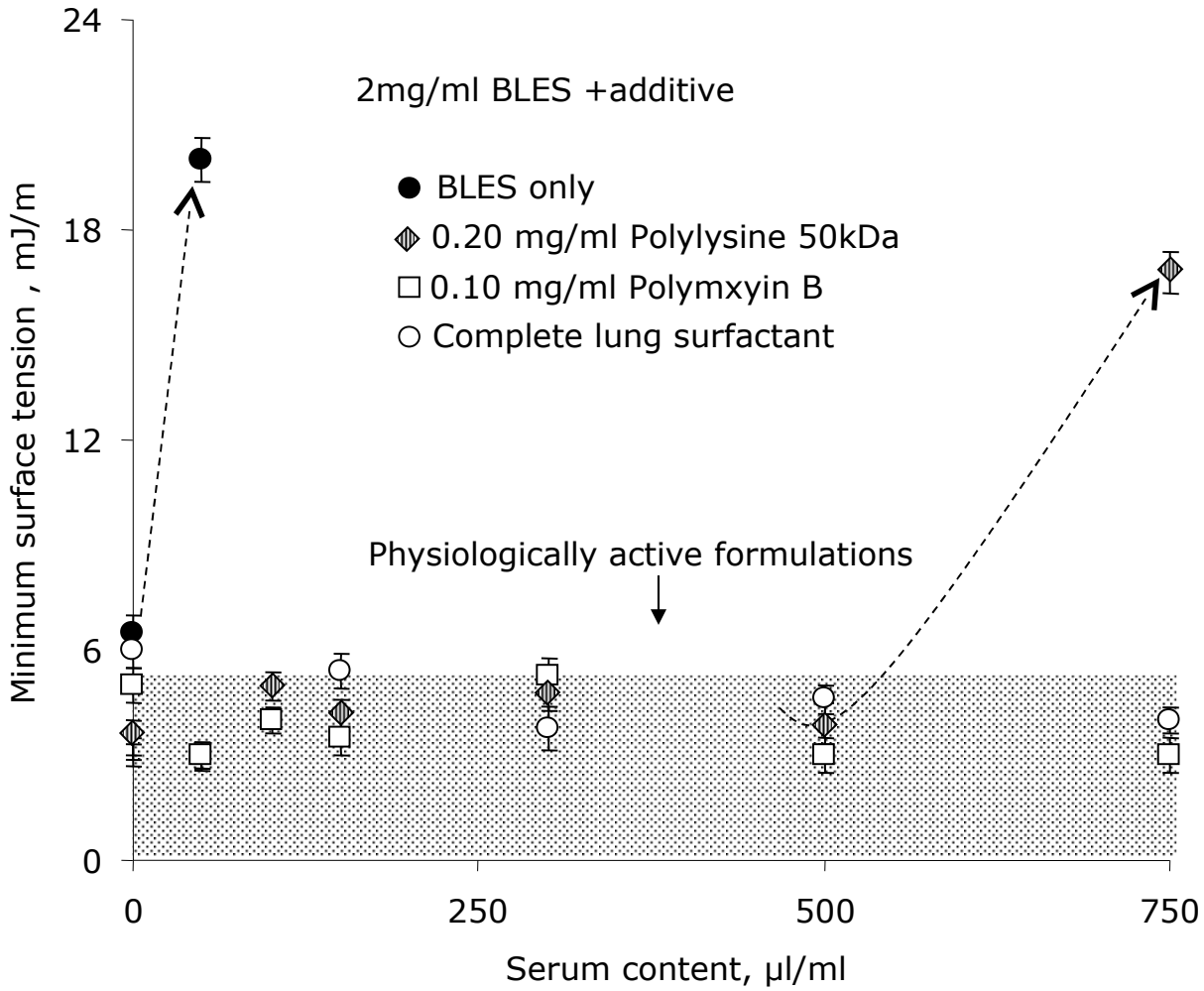
Cationic surfactant additives can improve the elasticity of exogenous surfactant and reduce the relaxation constant

Cationic additives may be the answer to ARDS



550 µl/ml serum simulates the high protein content in the lungs of ARDS patients. Even a high exogenous surfactant concentration ~ 27 mg/ml BLES would not work

Effect of cationic peptides



Polymyxin B