Non linear transport of fluids into the tracheobronchial tree

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hermitage.VR

Joint work with

Ventilation

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- **B. Mauroy, M. Florens** (ENS Cachan)
- **E. R. Weibel** (University of Bern)
- **T. Similowski, C. Strauss** (Hôpital de la Pitié Salpêtrière)

Surfactant delivery

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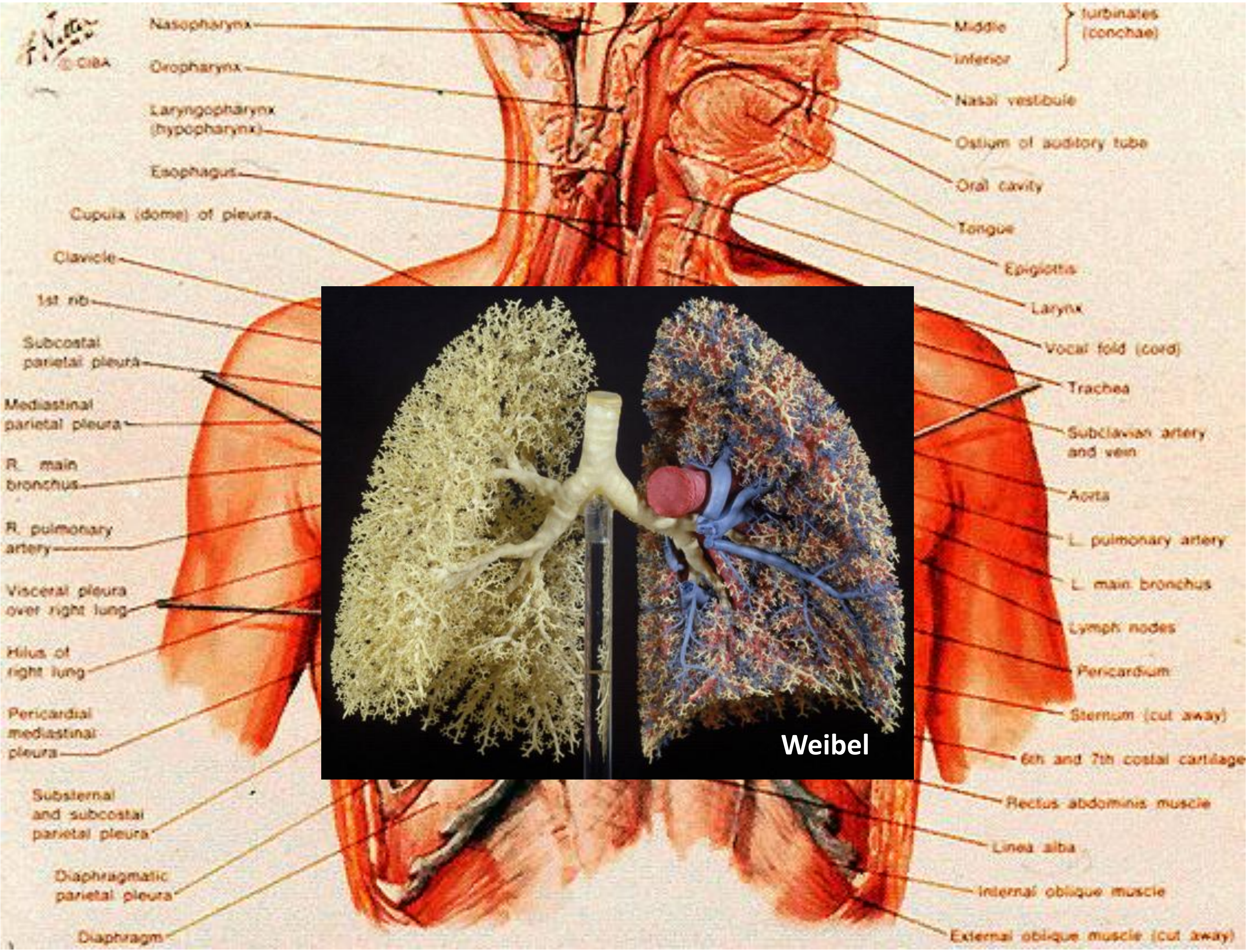
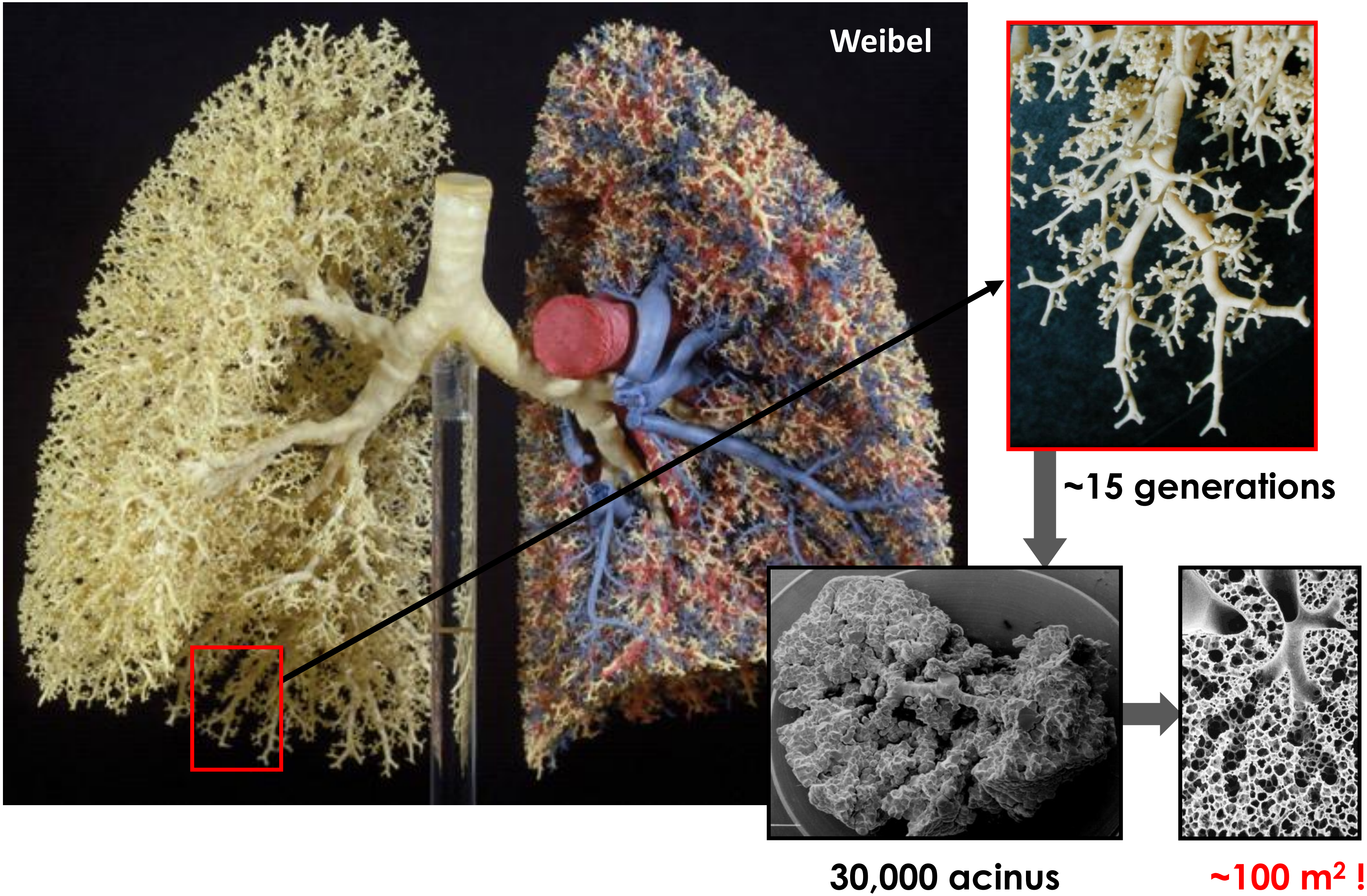
- **D. F. Willson (**Virginia Commonwealth University)
- **R. H. Notter** (University of Rochester)
- **A. Kazemi** (Ecole Polytechnique & Institut Mondor de Recherche Biomédicale)

The human respiratory system



CIBA, Netter

The human respiratory system

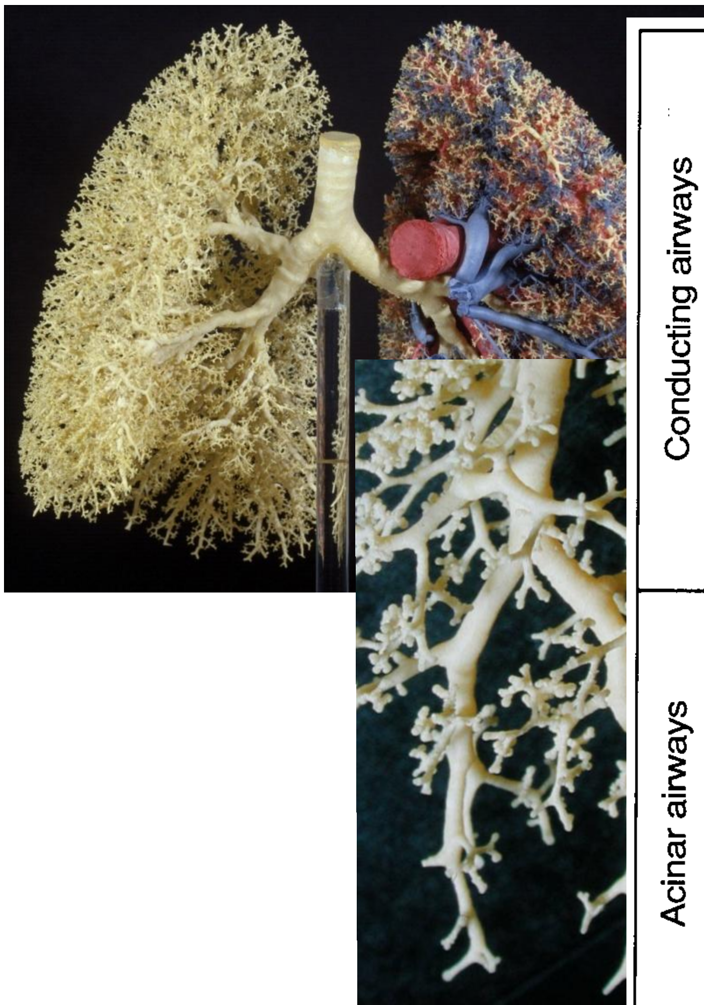


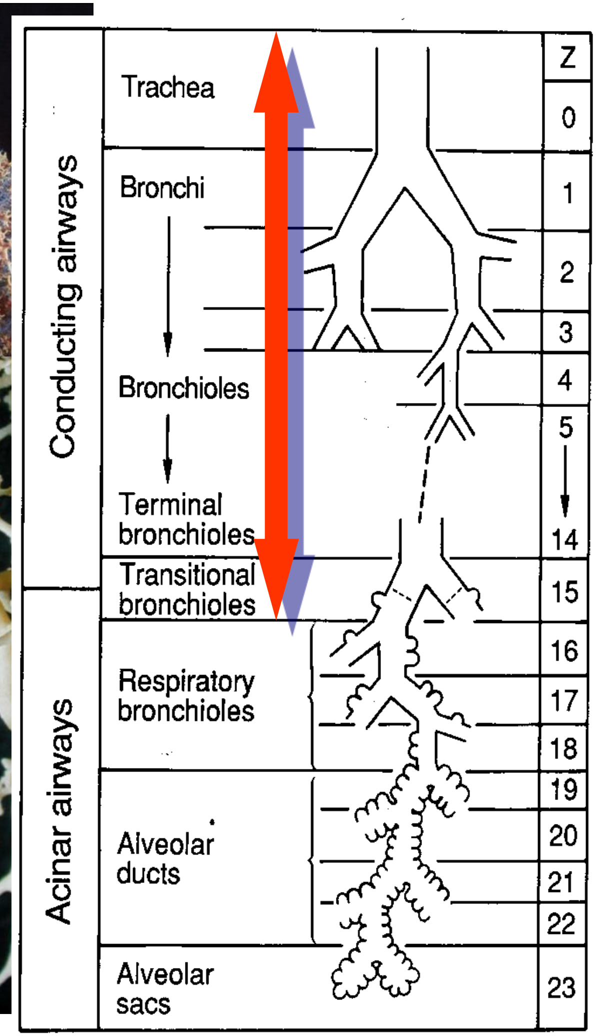
The pulmonary airway system

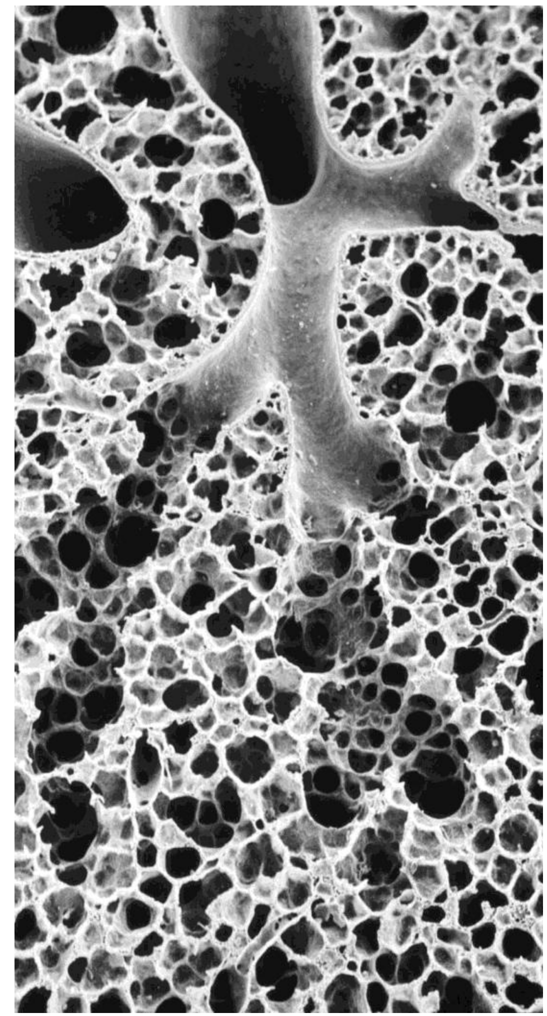
23 generations on average in the human lung

Gen. 0 — 15, conduction

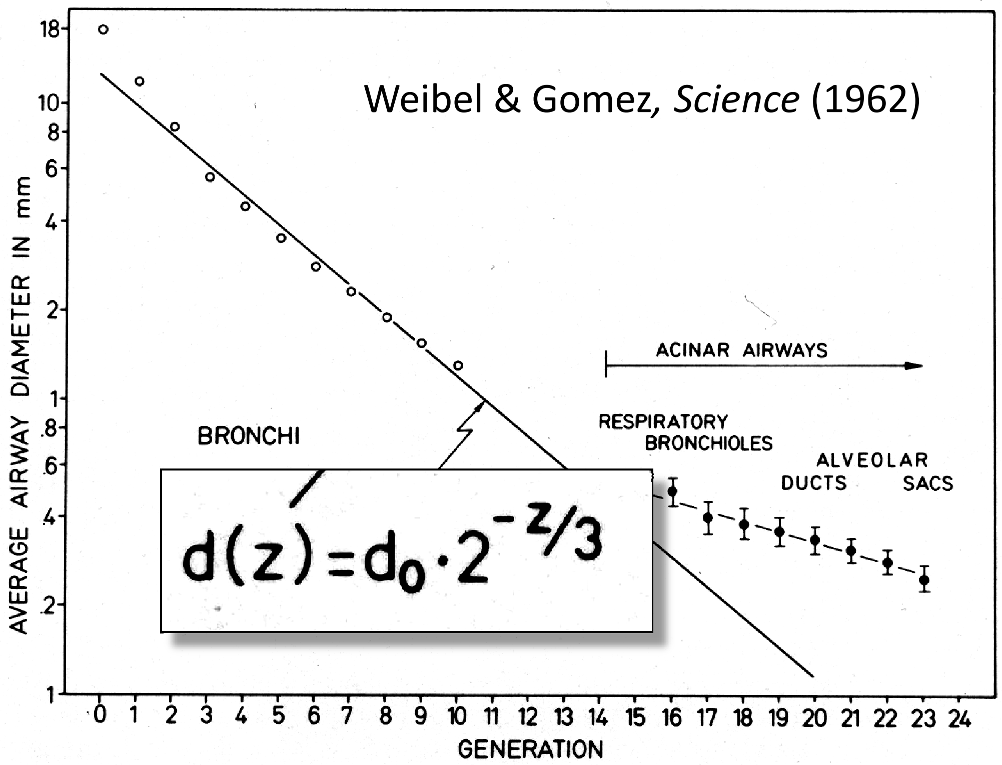
Gen. 16 — 23, respiration

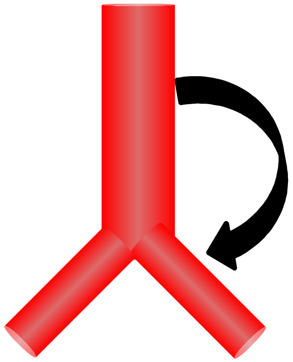






Scaling in the pulmonary airway system





$$h = \frac{D_{\text{daughter}}}{D_{\text{parent}}}$$

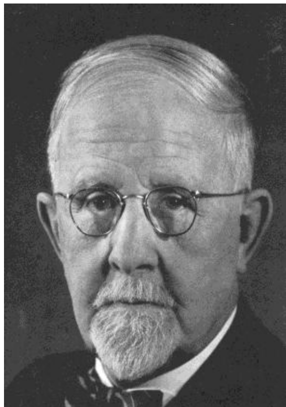
$$\boxed{D_n = D_0 h^n}$$

Weibel's symmetric model

- cylindrical tubes
- self-similarity: constant diameter ratio
- Dichotomous and symmetric branching

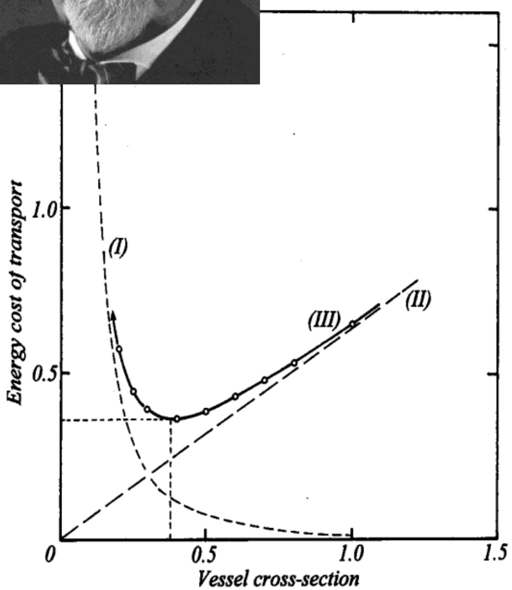
Murray-Hess law

How to minimize the energy cost for a given flow rate?



$$\varepsilon = \alpha V + R\,\phi^2 = \alpha\, LD^2 + \beta \frac{L}{D^4}\phi^2$$

$$0 = 2\alpha\, LD - 4\beta \frac{L}{D^5}\phi^2 \qquad \boxed{D^3 \propto \varphi\,!!}$$



At each bifurcation:

$$\phi_0 = \phi_1 + \phi_2 \Rightarrow \boxed{D_0^3 = D_1^3 + D_2^3}$$

$$\boxed{h_c = \frac{D_1}{D_0} = 2^{-1/3} \approx 0.79}$$

W.R.Hess, 1913 ; C.D. Murray, 1927; T.F. Sherman, 1981

[2] Borelli, G. A., *De motu animalium*, Rome, 1681.

[3] Thompson, D. W., "On Growth and Form," Camb. Univ. Press, 1917.

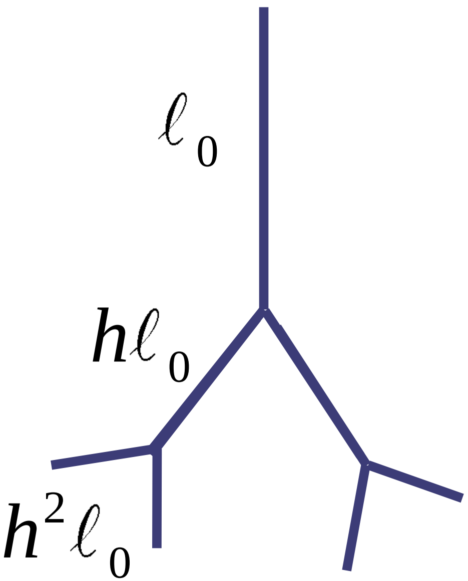
[4] Henderson, L. J., "The Order of Nature," Harvard Univ. Press, 2nd ed., 1925.

[5] Tschuewsky, J. A., *Pfluger's Arch.*, **97**, 1903 (210–288).

[6] Krogh, A., "The Anatomy and Physiology of the Capillaries," Yale Univ. Press, 1922.

Previous work on the economy of the circulation is to be found in the articles by W. R. Hess. (See especially, *Pfluger's Arch.*, **168**, 1917 (439–490). In this paper he deals with the compromise between resistance to flow and the volume of a vessel. He develops equations (which can be derived from those given in the present paper), but, failing to recognize the significance of his units, the dimensions of his constants, and particularly the fact that economy is a question of *work*, he misses what seems to be the essence of the problem. The fundamental equations given in the present paper cannot be derived from those of Hess.)

The fractal dimension of a tree



***h* < 0,5** $D = 1$

***h* > 0,5** **Infinite length**

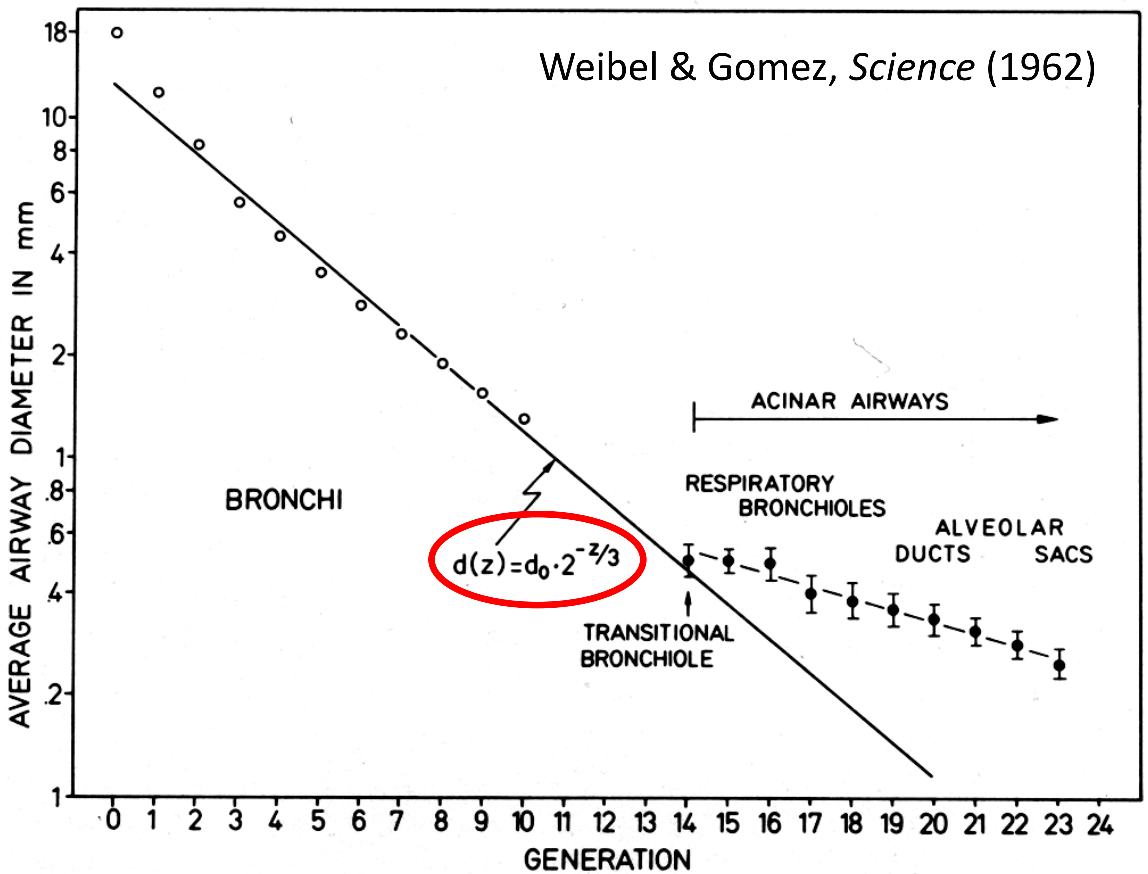
It requires 1 parent branch + 2 sub-trees (scaled by *h*) to recover the entire initial tree

$$2 + 1 \text{ branch} = \left(\frac{1}{h}\right)^D$$

$$2 = \left(\frac{1}{h}\right)^D$$

$$\boxed{D = \frac{\ln 2}{\ln\left(\frac{1}{h}\right)}}$$

The fractal dimension of the tracheobronchial tree



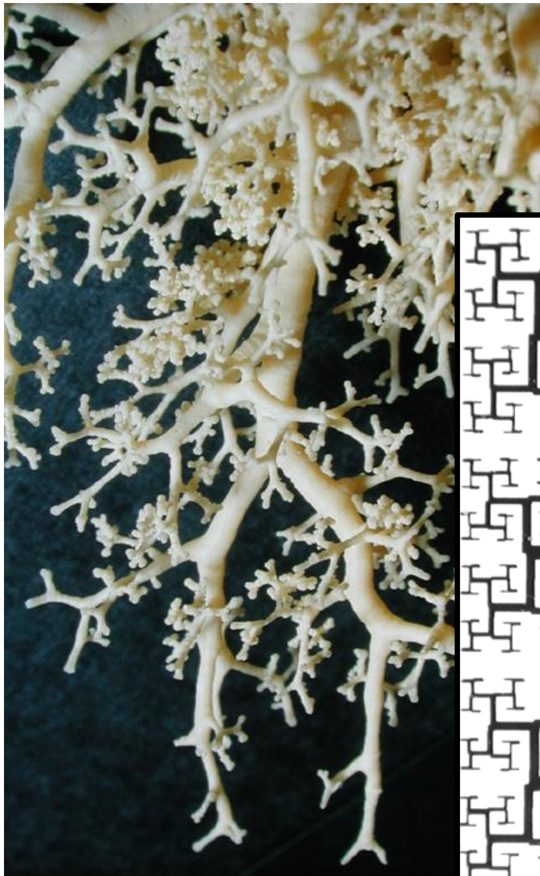
$$D(z) = D_0\left(2^{-1/3}\right)^z$$

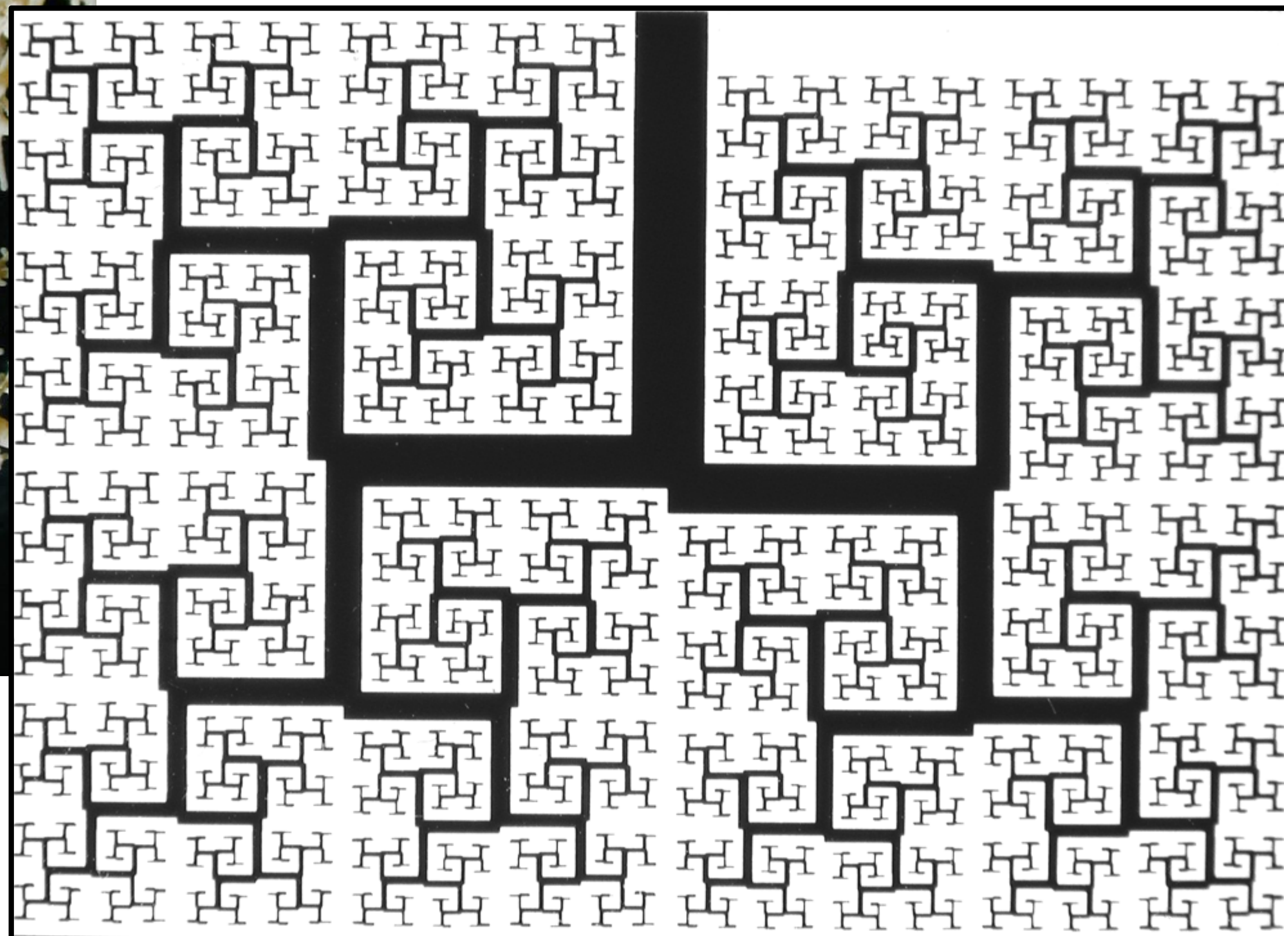
$$h = 2^{-1/3}$$

$$\boxed{D = \frac{\ln 2}{\ln\left(2^{1/3}\right)} = 3}$$

The bronchial tree is space-filling!

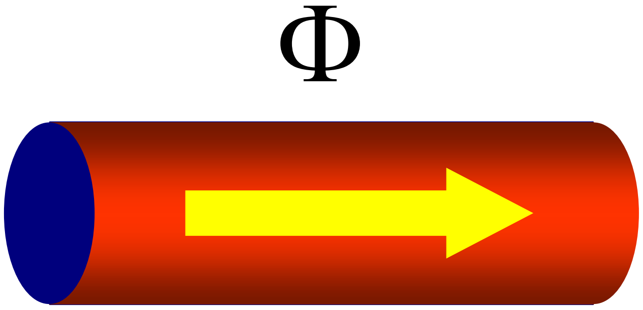
The fractal lung





Benoit Mandelbrot 1977

Poiseuille flow
(stationary, laminar)

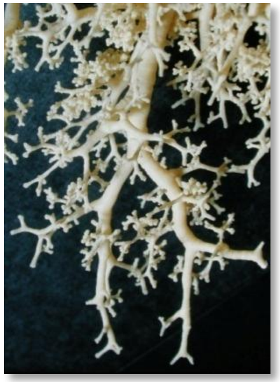


$$\Phi = \Delta P.\left(\frac{\pi D^4}{128\eta L}\right)$$

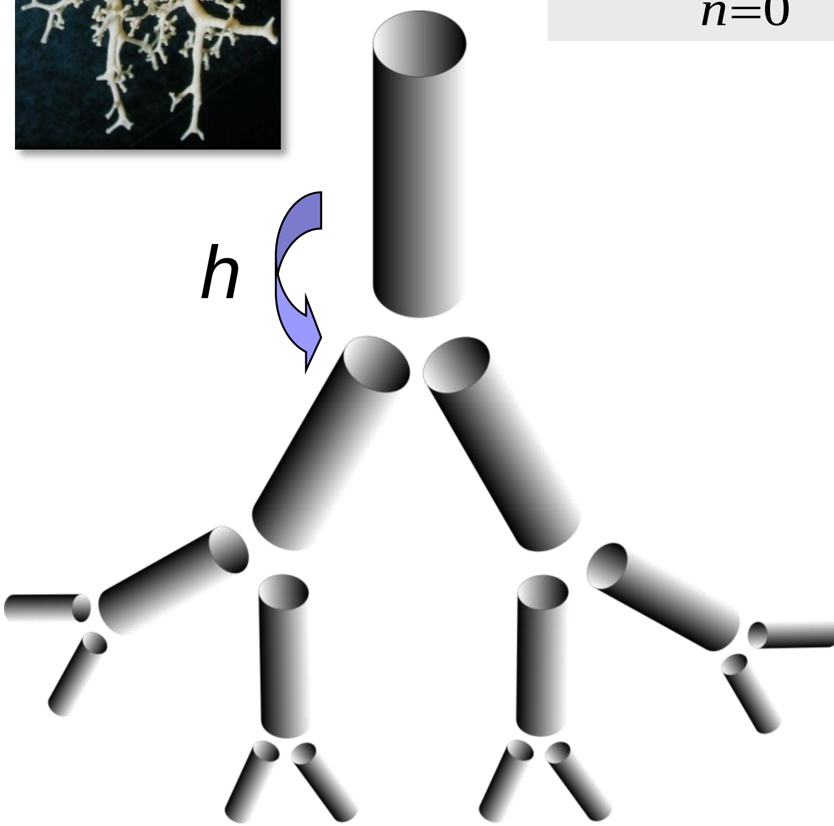
Airway resistance: $R = \frac{128\eta}{\pi}\frac{L}{D^4}$

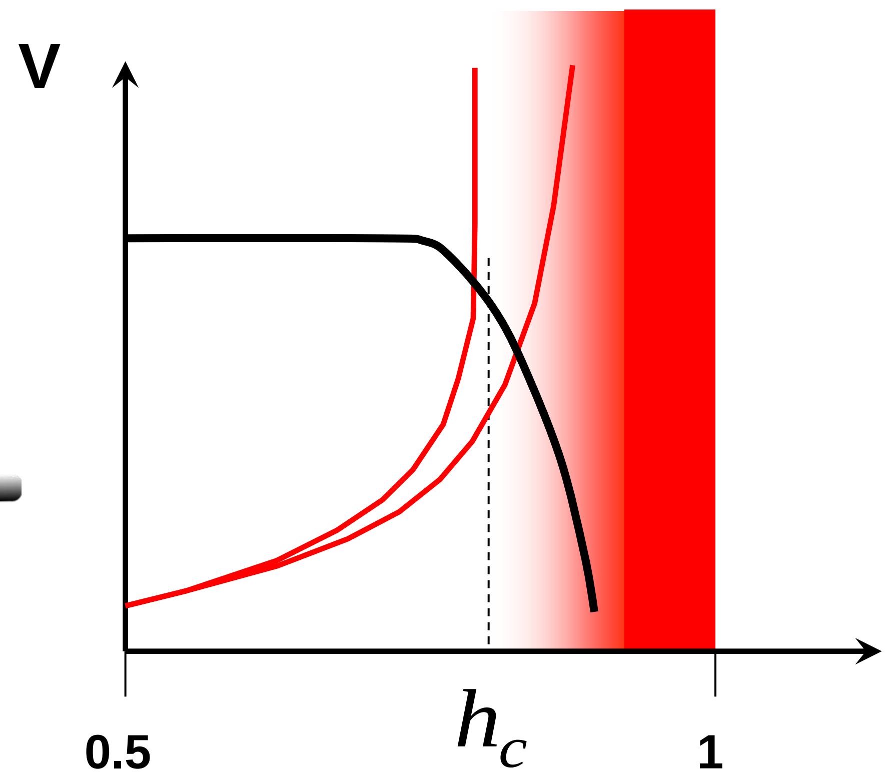
Airway volume: $V = \frac{\pi D^2}{4}L$

Dead space volume

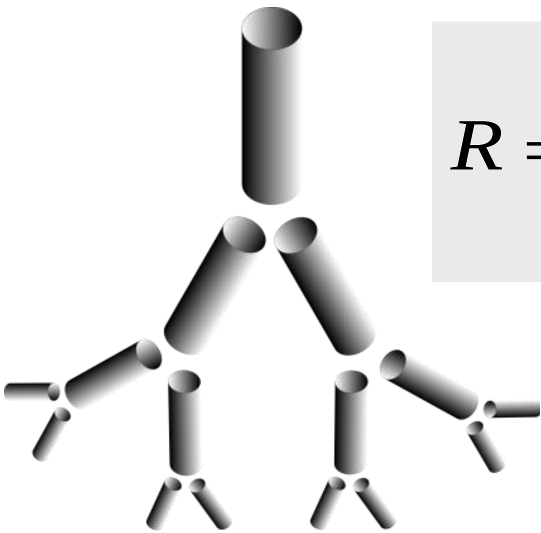


$$V = \sum_{n=0}^{N} 2^{n}\left(\frac{\pi D_n^{2}}{4} L_n\right) = V_0 \sum_{n=0}^{N} \left(2h^{3}\right)^{n}$$



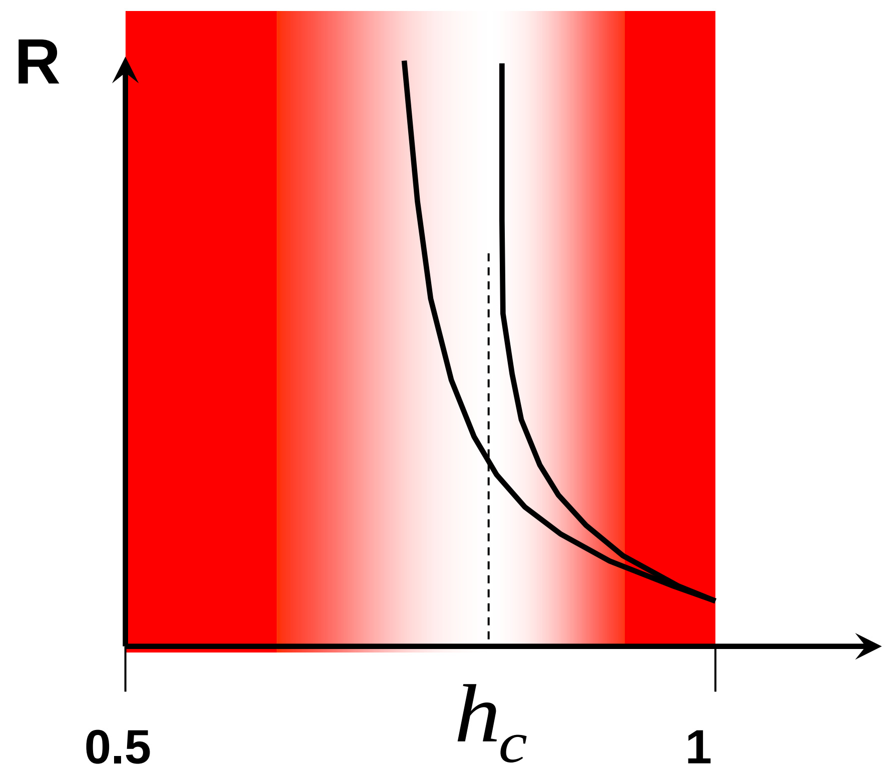


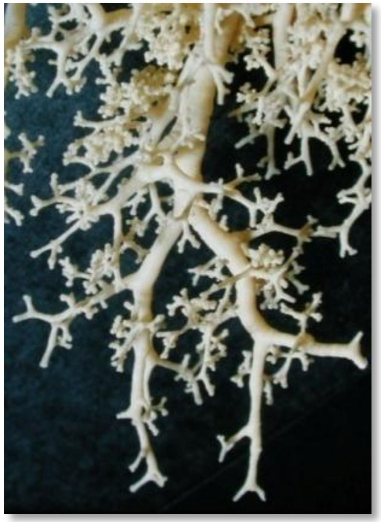
Total airway resistance



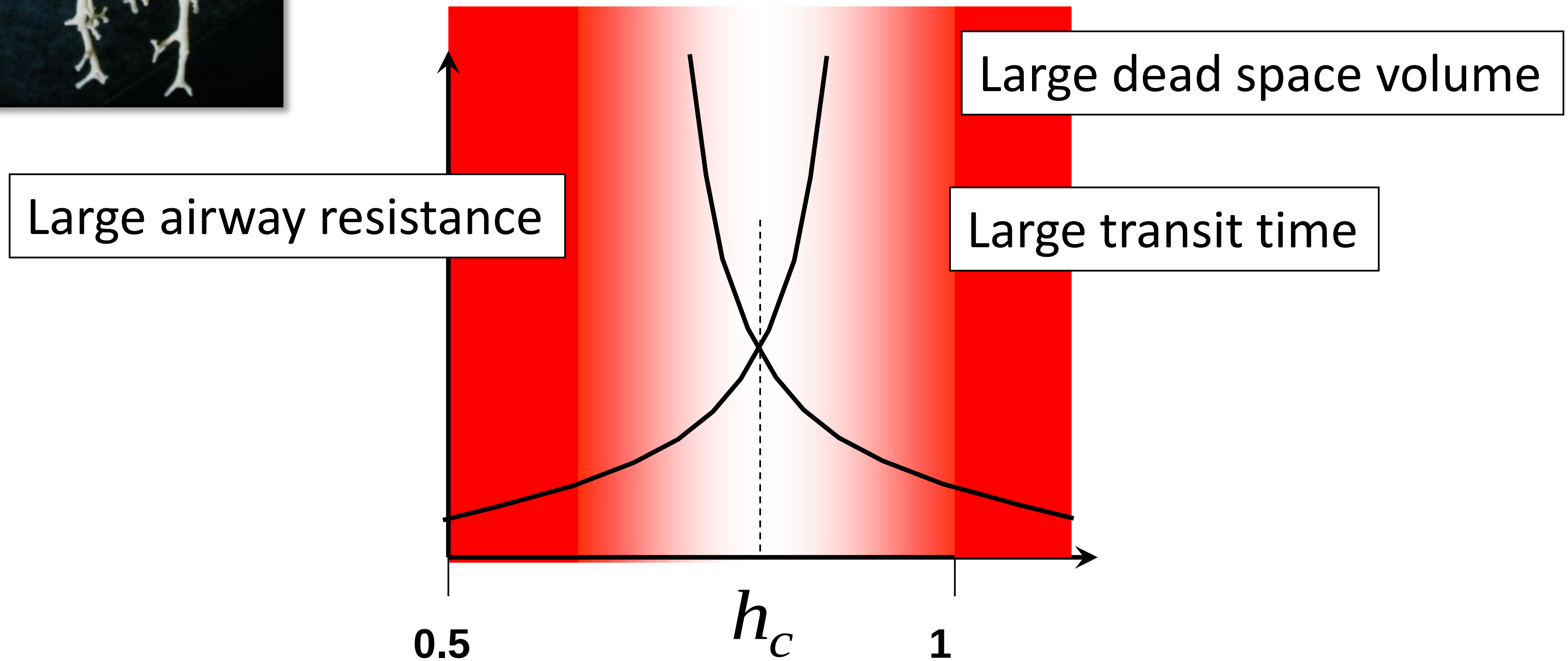
$$R = \frac{128\,\eta}{\pi}\sum_{n=0}^{N}\frac{1}{2^n}\left(\frac{L_n}{D_n^4}\right) = R_0\sum_{n=0}^{N}\frac{1}{\left(2h^3\right)^n}$$

$$\Phi = \Delta P.\left(\frac{\pi D^4}{128\,\eta L}\right)$$

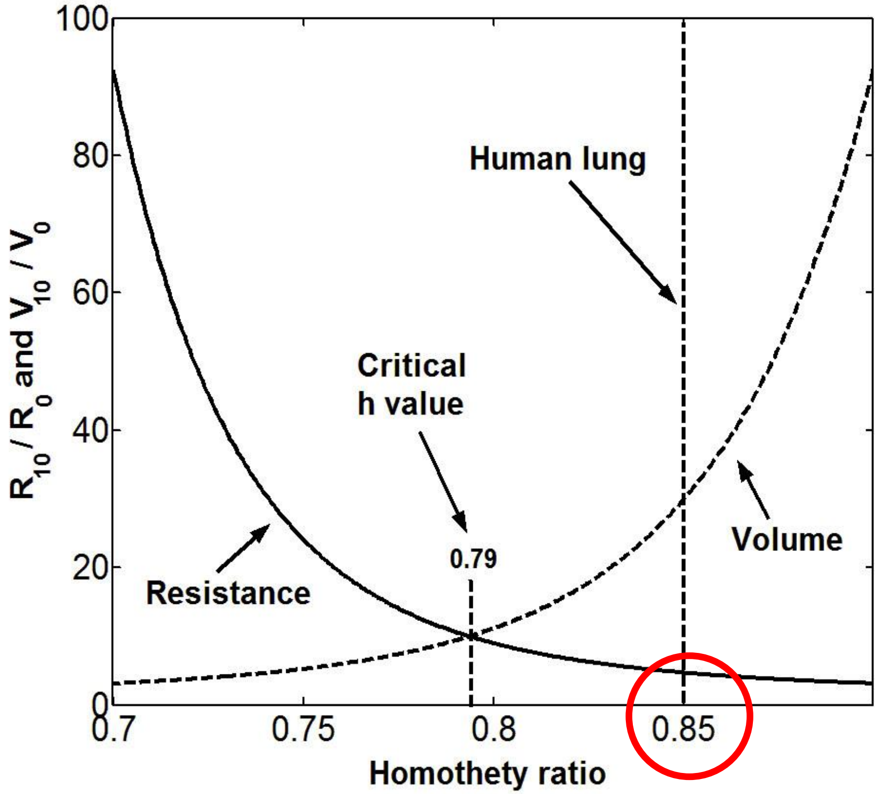




A highly constrained system

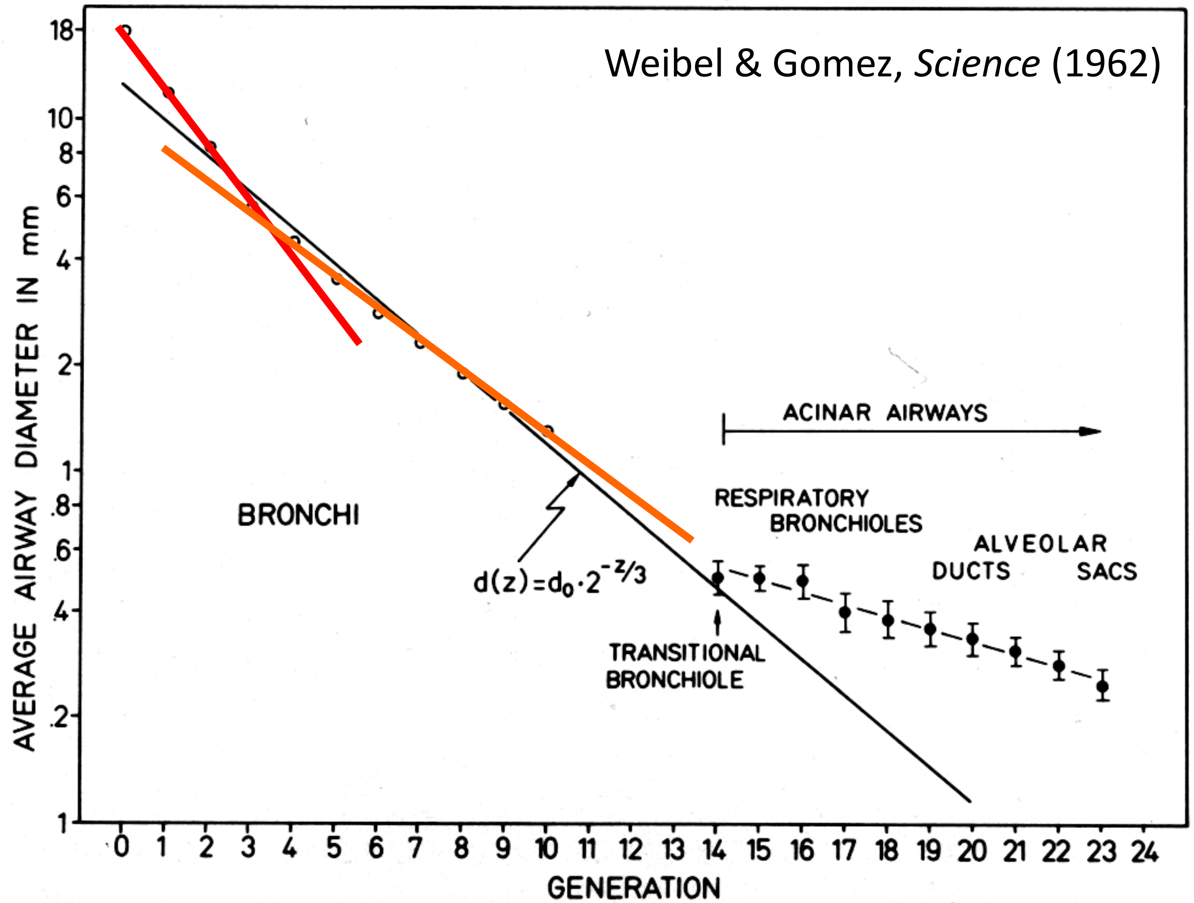


The optimal tree would correspond to h=$2^{-1/3}$, but…



Mauroy et al., *Nature* (2004)

Actual scaling in the tracheobronchial tree

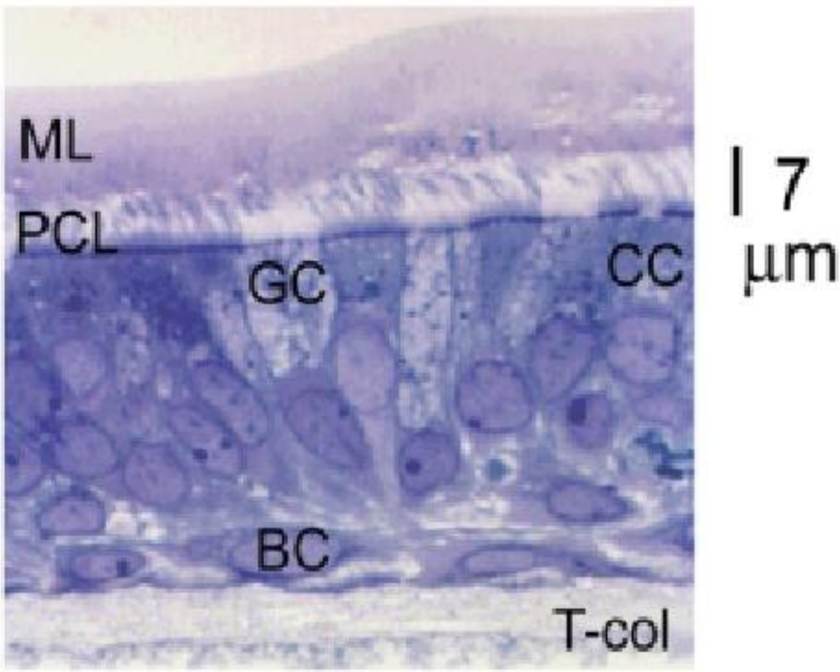


Surfactant delivery into the human lung

Non linear transport of fluids into the pulmonary airway system

Airway and alveolar liquid lining

Cultured human tracheobronchial airway epithelia



ML-mucus layer, PCL-periciliary layer, GC-goblet cell, CC-ciliated cell, BC-basal cell, T-col-semipermeable supports

Measurements of Airway Surface Liquid Height (Volume) by Confocal Microscopy

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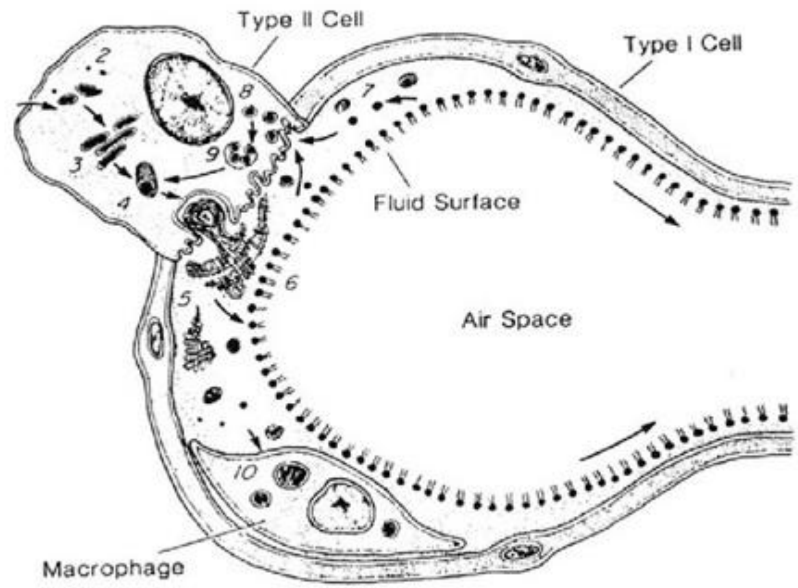
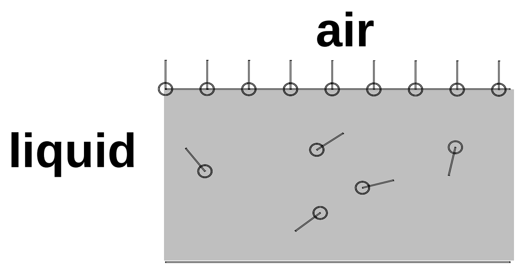
Alveolar liquid lining and surfactant system

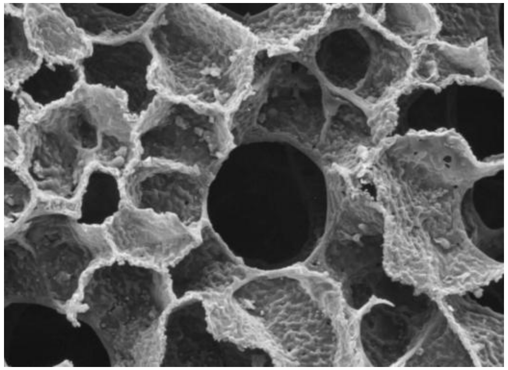


Surfactant made in Type II cells

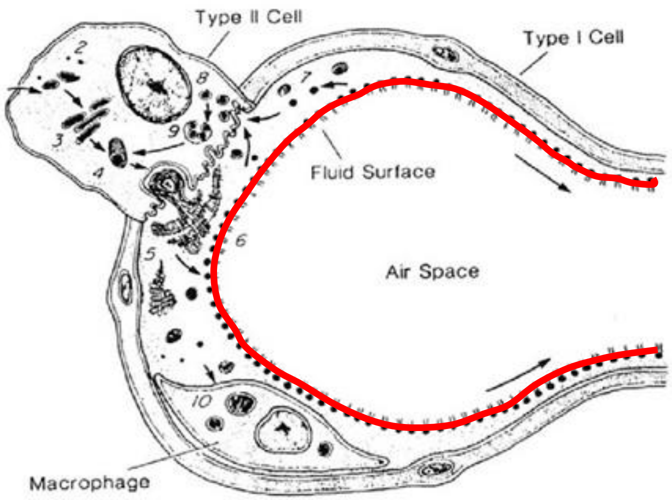
Surfactant effects on surface tension

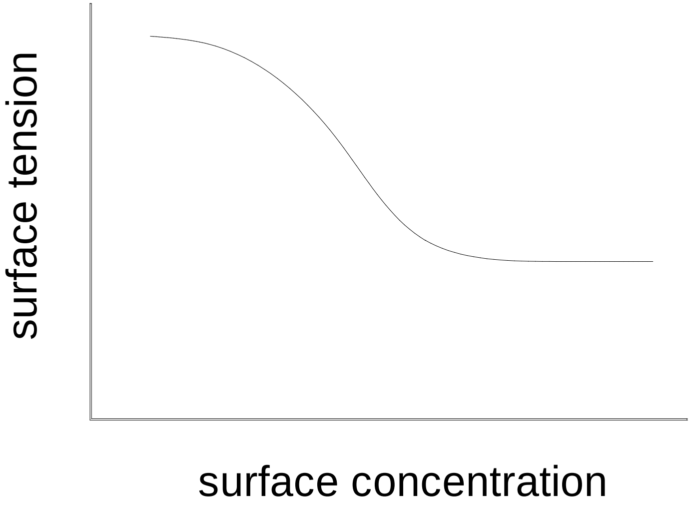
- Alveolar Type II cells produce surfactants





- Surfactant molecules (DPPC) are in the liquid lining bulk and interface





•Surfactants at the interface **reduce surface tension**

Air-cycled vs. Saline-cycled Lung

Saline-cycling → removes air-liquid interface, no surface tension

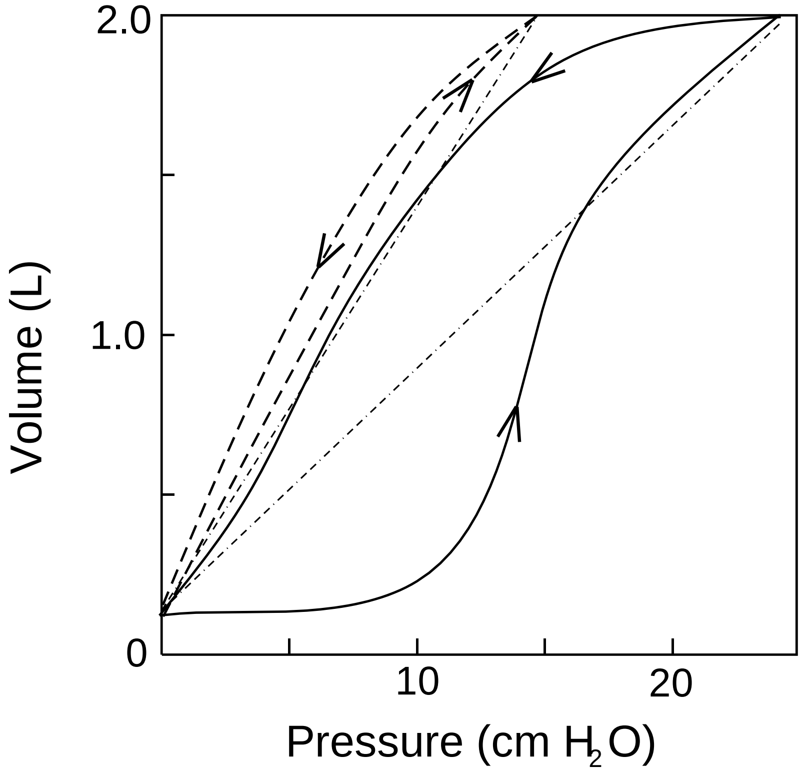
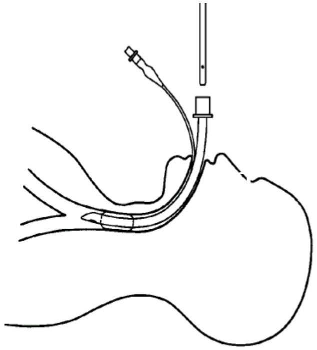


FIG. 5. Kurt von Neergaard (1887–1947). He made important studies of lung elasticity and flow resistance with Wirz. Independently he published a classic paper on surface forces in the lung. Like Wirz, von Neergaard spent only a relatively brief period in physiology and devoted his later life to clinical practice at the Institute of Physical Therapy in Zurich. (Courtesy of the National Library of Medicine.)

Air: less compliant, larger hysteresis
Saline: more compliant, smaller hysteresis

Neonatal Respiratory Distress Syndrome

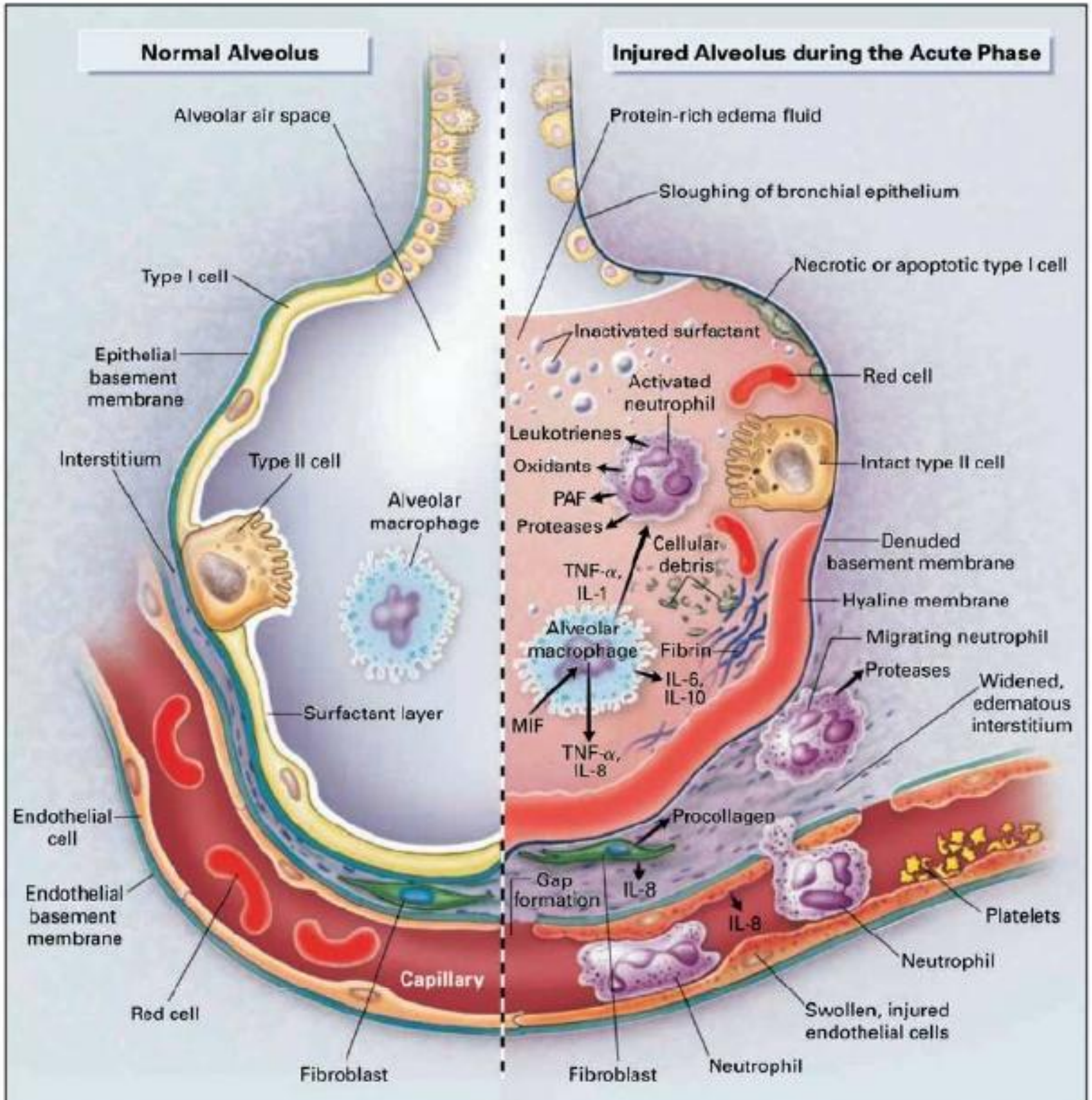
- Prematurely-born neonates have immature alveolar type II cells
- These type II cells **lack sufficient surfactant-producing capacity**
- Abnormally high surface tension reduces compliance
- Develop **Respiratory Distress Syndrome** (hyaline membrane dis.)
- ~ 1% of all birth ~ **40,000 cases** annually in the US



Surfactant Replacement Therapy (SRT)

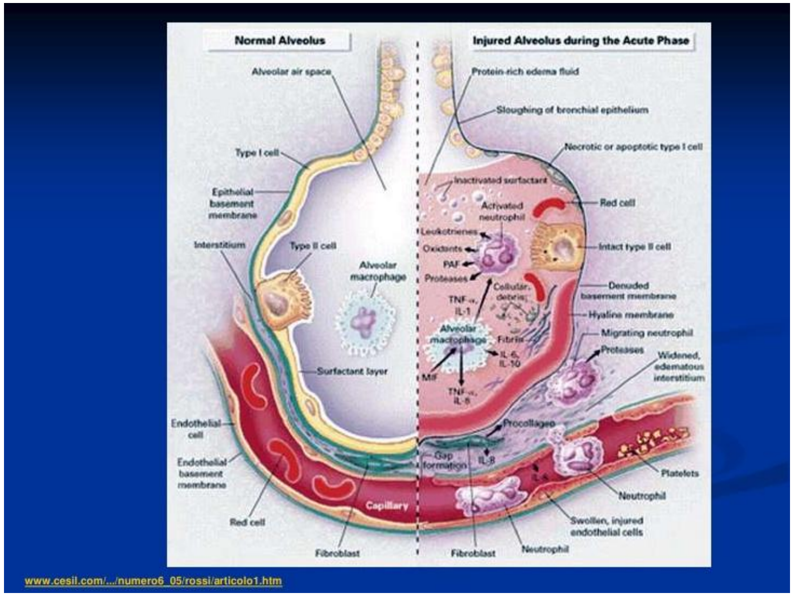
- Mortality dropped from **4,997 deaths** (1980) to **861** (2005)
- SRT played **a major role** in this decrease of mortality
- Survivors have still high incidence of bronchopulmonary dysplasia (BPD)

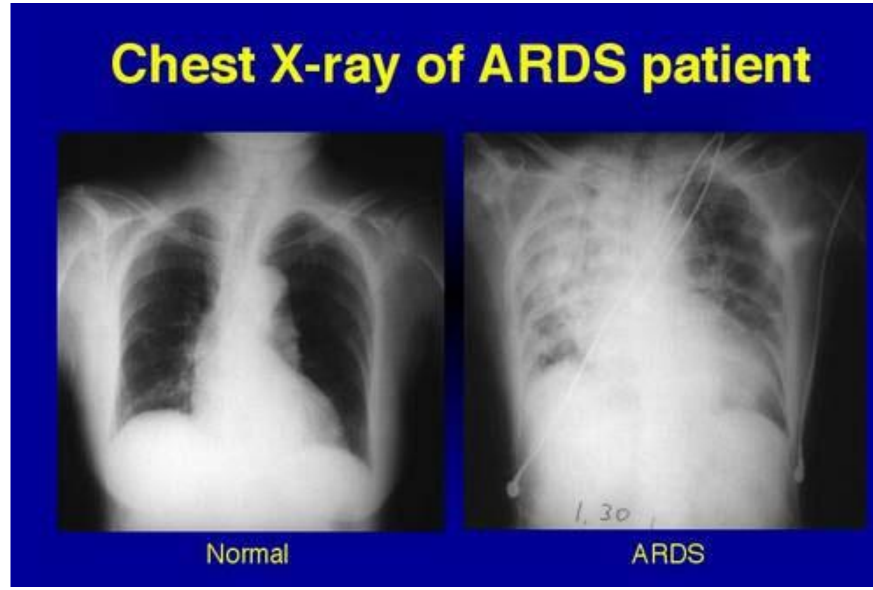
Acute Respiratory Distress Syndrome (ARDS)



Ware LB, *NEngl J Med* 2000;342:1334

Acute Respiratory Distress Syndrome (ARDS)





- Adults with Acute Respiratory Distress Syndrome have impaired surfactant function from lung injury.
  - Direct: aspiration, pneumonia, toxic inhalants
  - Indirect: trauma, shock, sepsis
  - **190,000 cases in US annually**
  - ~40% mortality or 75,000 deaths per year
  - **SRT is not working in adults, studies have been discontinued**

SRT in adults for ARDS

Gregory *et al*., *Am J Respir Crit Care Med.* **1997**
Dose Volume: **2 ml/kg-4 ml/kg** ~ 140/280 ml for 70 kg patient
Surfactant Concentration: 25 mg/ml
Molecular Dose: 50 mg/kg -100 mg/kg
Mortality: 18.8% SRT (n=43) vs 43.8% control (n=16)

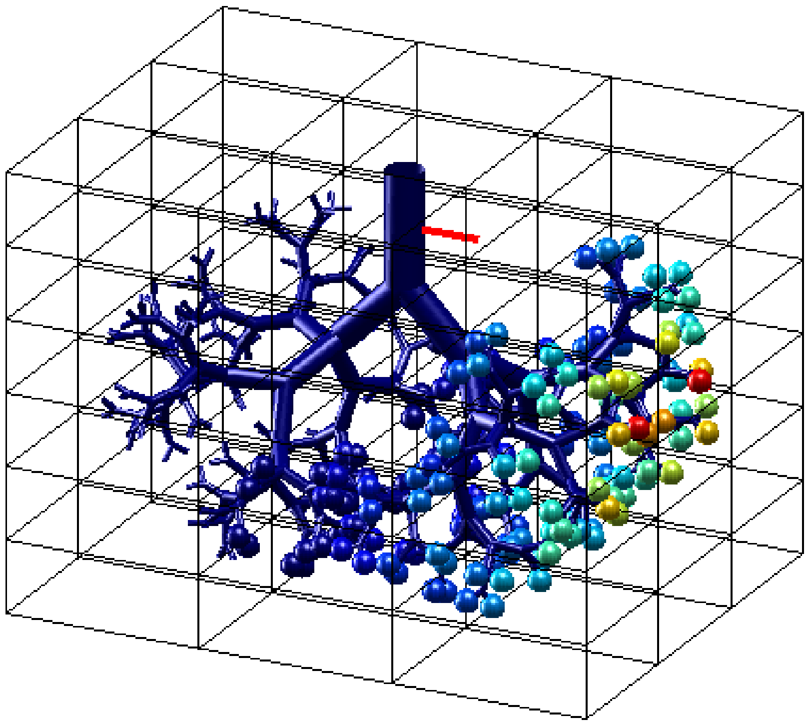
Lewis *et al.*, *Am J Respir Crit Care Med*. **1999**
Dose Volume: **4 ml/kg** (40 kg sheep)
Surfactant Concentration: 6.25 mg/ml, 25 mg/ml, 50 mg/ml
Molecular Dose: 25 mg/kg, 100 mg/kg, 200 mg/kg
Result: Improved oxygenation all concentrations, better for 25,50 mg/ml

Spragg *et al.*, *N Engl J Med.* **2004**
Dose Volume: **1ml/kg** ~ 70 ml for 70 kg patient
Surfactant Concentration: 50 mg/ml
Molecular Dose: 50 mg/kg
Mortality: no effect (n=224 SRT, n=224 control)

Spragg *et al.*, *Am J Respir Crit Care Med*. **2011**
Dose Volume: **1ml/kg** ~ 70 ml for 70 kg patient
Surfactant Concentration: 50 mg/ml
Molecular Dose: 50 mg/kg
Mortality: no effect (n=419 SRT, n=424 control)

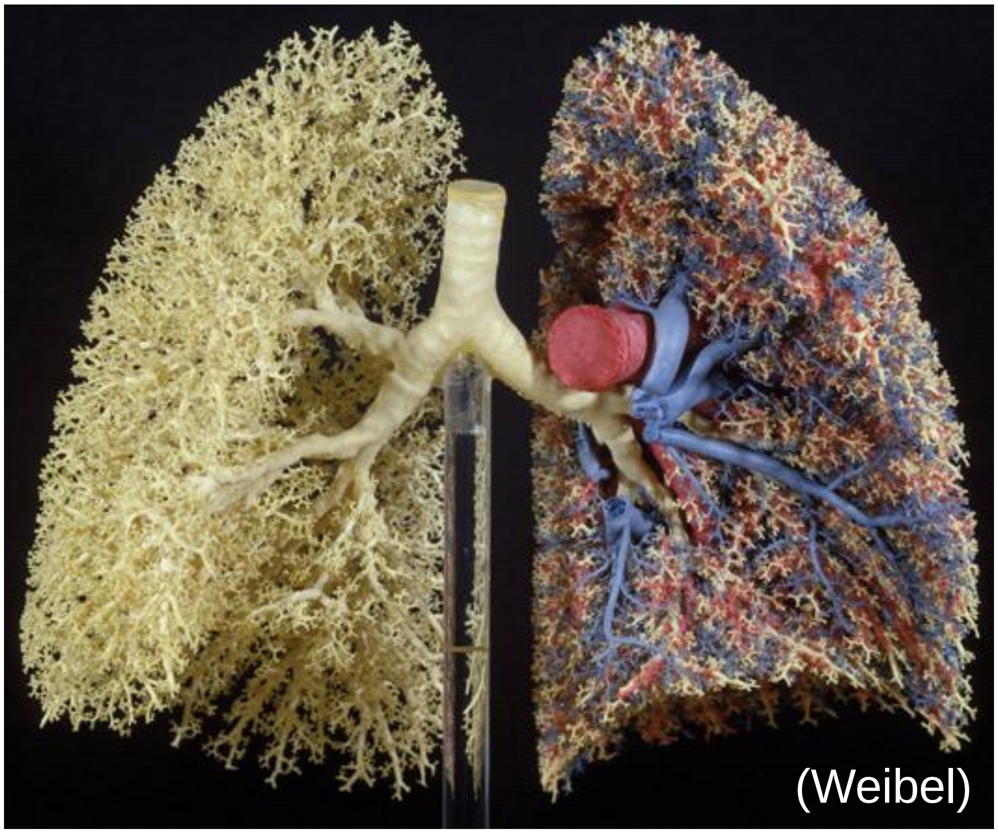
Aim

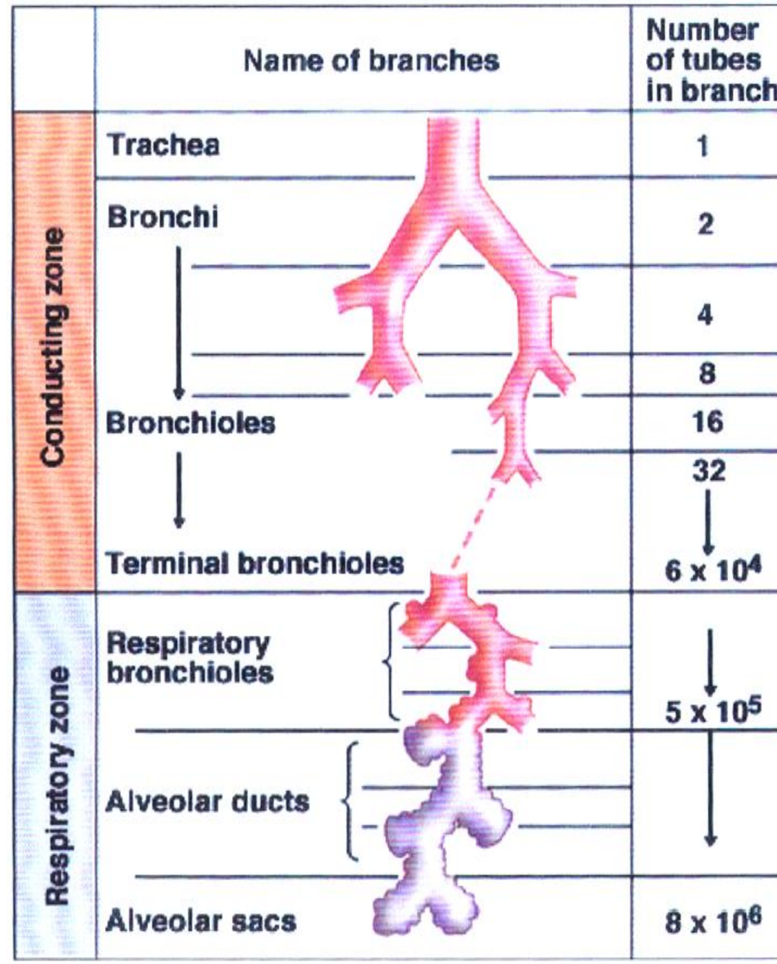
To develop a **3D mathematical and numerical model of the lung** for **predicting the final distribution of a liquid bolus** initially instilled into the trachea.



Modeling SRT

Computing plug propagation in the entire pulmonary airway tree?





Building a model of SRT

Geometrical model of the lung

Solve the fluid transport in the geometrical model

Delivery conditions

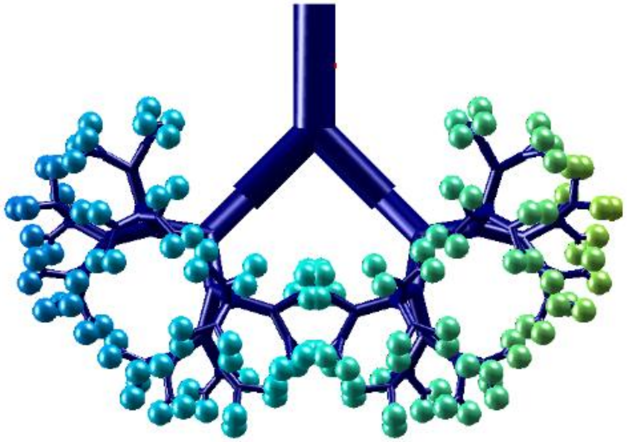
Surfactant properties	Density Viscosity Surface tension
patient	Position
Instillation	Flow rate Volume

Geometrical model of the tracheobronchial tree

Simplified pulmonary airway system (3D)

Instillation (surfactant)	→	**Delivery**
Trachea	→	**Bronchioles**

The entire airway system is described as
an assembly of straight tubes connected by bifurcations



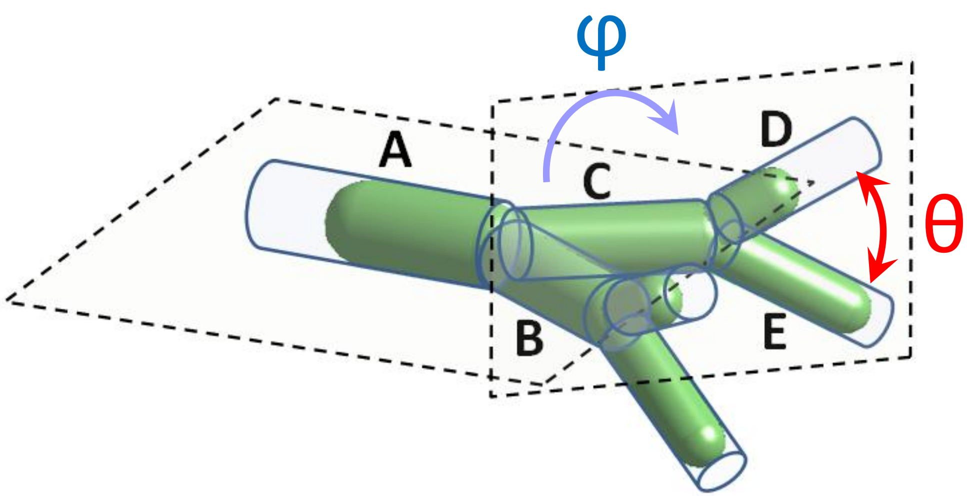
Geometrical model of the tracheobronchial tree

Each airway is parameterized by

- **Diameter** $\frac{D_{n+1}}{D_n} = 0.79$
- **Length** $L = 3D$

All bifurcations are coplanar and characterized by

- **Rotation angle** φ=90°
- **Branching angle** θ=60°



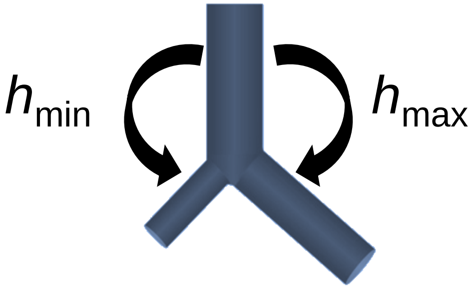
The geometrical model of the tracheobronchial tree

- **Specific geometry of the proximal airways**

  Small DSV, admissible transit time to acinar regions.

- **Self-similar & asymmetric intermediate TB tree**

  Small hydrodynamic resistance, airway size distribution.

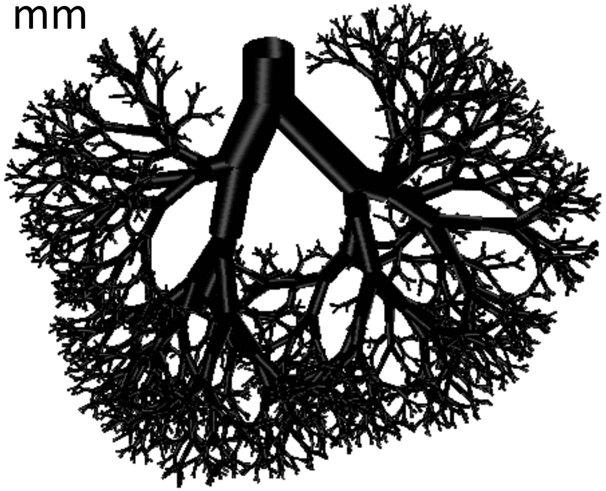


ratio L/D

- **Terminal airway**: diameter of the terminal bronchioles D = 0.5 mm

Generation	Scaling ratio h for D		Ratio L/D
	h_{max}	h_{min}	
1	0.87	0.69	3.07
2	0.80	0.67	1.75
3	0.83	0.67	1.43
4	0.86	0.74	1.85
5 - 23	0.87	0.67	3.00

Systematic branching asymmetry



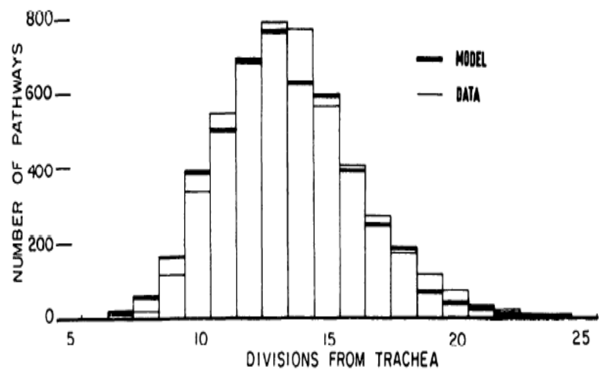
Florens et al.
J. Appl. Physiol., 2011

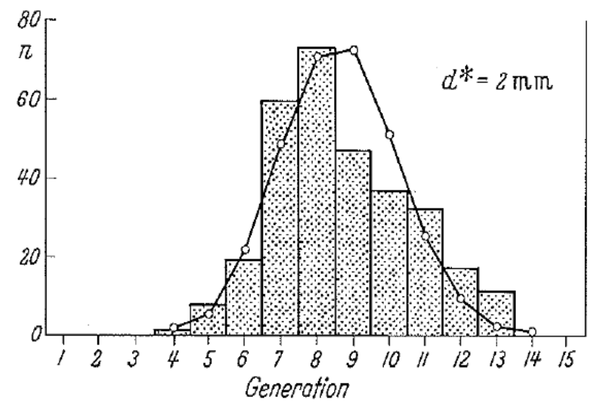
Size distributions in the lung airways

References

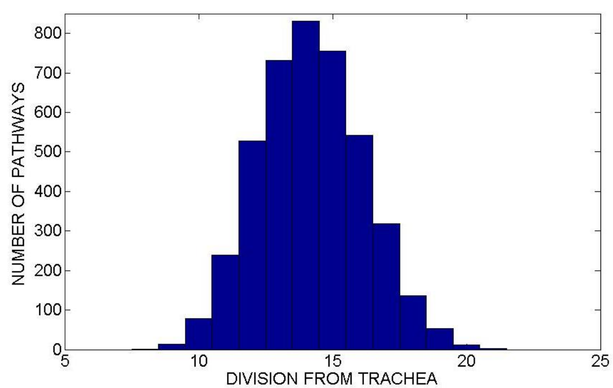
▪ Teminal airways:	$9 \le g \le 23$ & $\langle g \rangle \approx 15\text{-}16 \pm 2$	(15 ± 2-4)
▪ Acini:	≈ 23000	(30000: 15000 – 61000)
▪ Dead Space Vol:	153 mL	(150 – 170 mL)

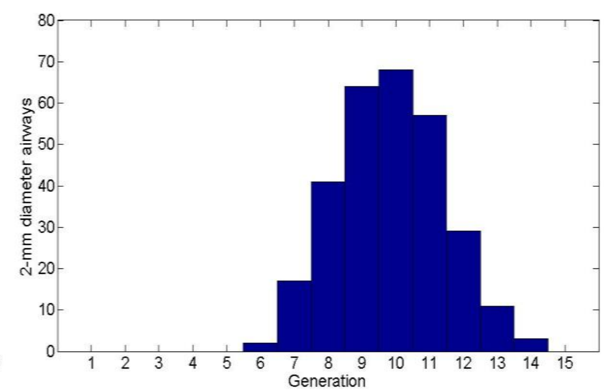
Horsfield,
J Appl Physiol
1971





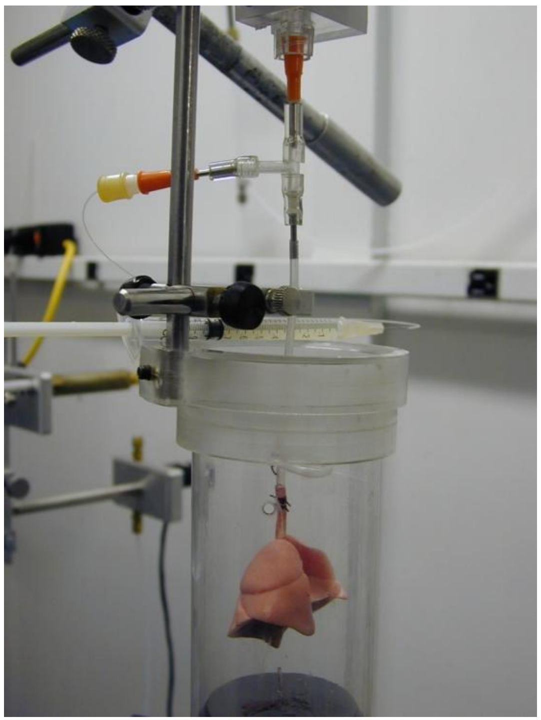
Weibel, 1963





Surfactant instillation – Lung Close-up

- **The excised lung suspended and ventilated from tracheal cannula.**
- **A small diameter tube attached to a syringe was inserted into the cannula (upper center of figure).**
- **A surfactant bolus was formed in the cannula by injecting 0.05 ml of surfactant through the small diameter tube.**



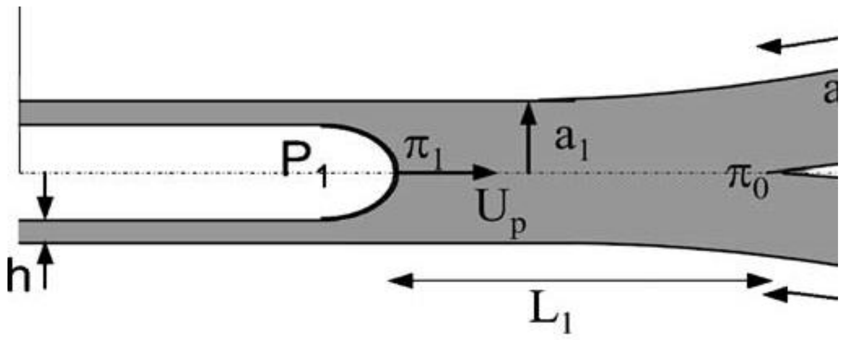
(Courtesy of Robert Molthen, Medical College of Wisconsin, Milwaukee, WI)

Cassidy et al., J. Appl. Physiol. 2001.
Anderson et al.,J. Appl. Physiol. 2004.

<u>Experimental Conditions</u>

- **Excised Rat Lung**
- **Lung Suspended Vertically**
- **Normal Bolus Volume**
- **Surfactant = Survanta**
- **Ventilation Rate - 60 br/min**

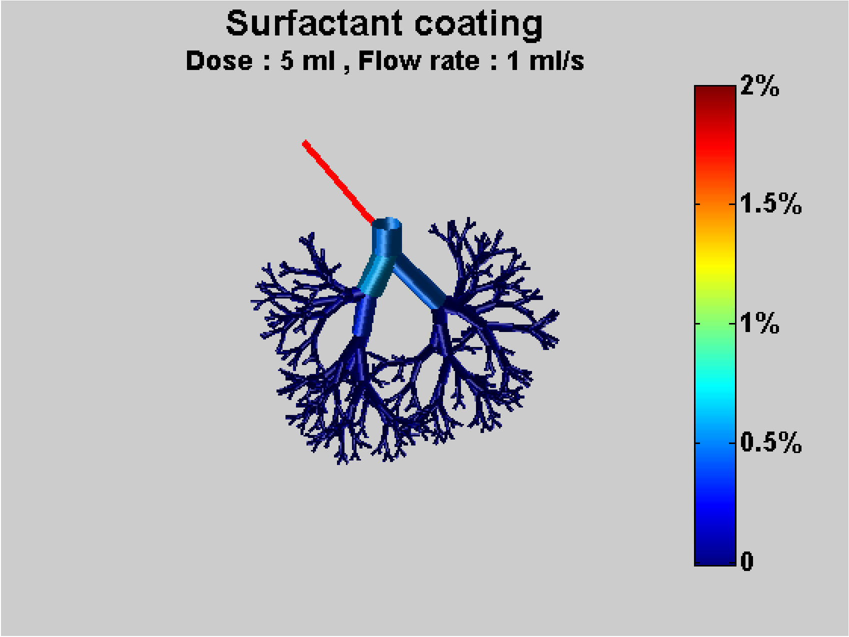
Surfactant deposition on the airway walls

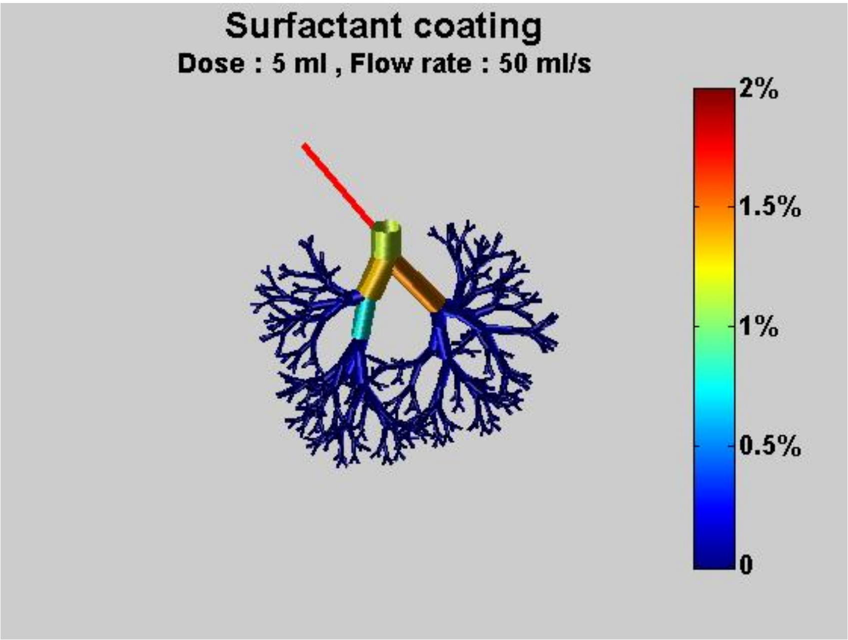


$$\boxed{\frac{h}{a_1} = 0.36\left(1 - e^{-2Ca^{0.523}}\right)}$$

$$Ca = \frac{\mu U_P}{\sigma}$$

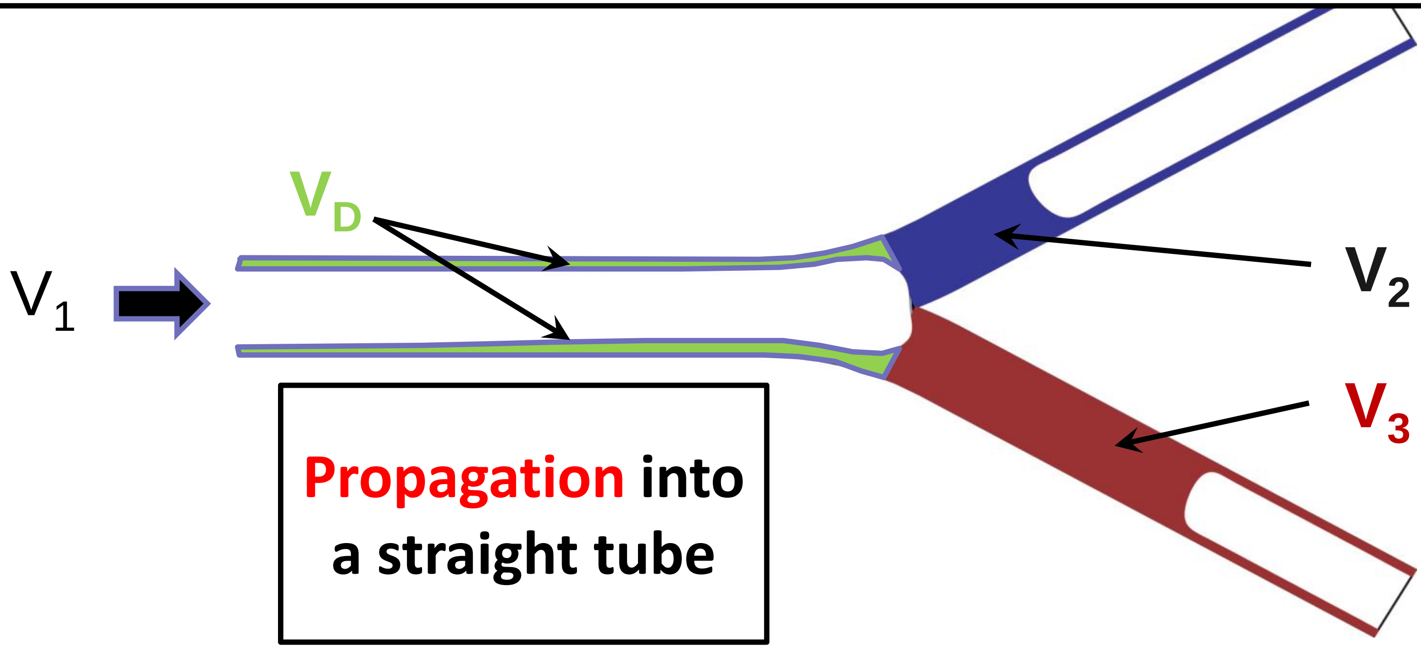
Halpern and Grotberg, *J. Fluid Mech*. (1992)
Halpern, Jensen, Grotberg *J. Appl. Physiol*. (1998)





Propagation of a plug in the tree

When the plug is instilled, it follows a succession of propagations in straight tubes and splitting at bifurcations



Propagation into a straight tube

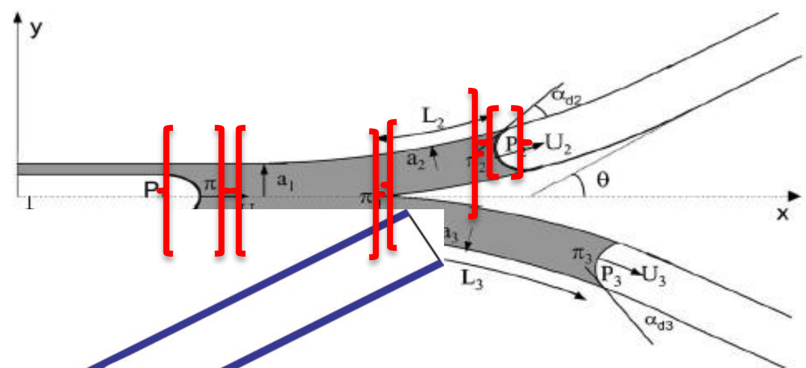
The process can be decomposed into two elementary steps:

Splitting at the bifurcation

Splitting ratio

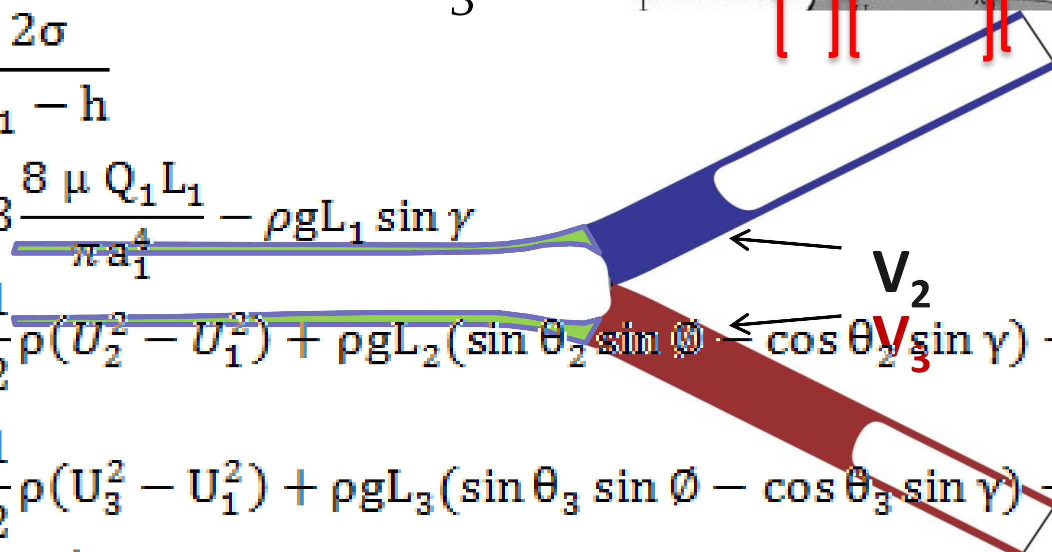
The splitting ratio is defined as the ratio of the volume of liquid entering the upper daughter, V_2 , to the volume of liquid entering the lower daughter, V_3

$$R_s = \frac{V_2}{V_3}$$



$$P_1 - \pi_1 = \frac{2\sigma}{a_1 - h}$$

$$\pi_1 - \pi_0 = \beta \frac{8\,\mu\,Q_1 L_1}{\pi a_1^4} - \rho g L_1 \sin\gamma$$



$$\pi_0 - \pi_2 = \frac{1}{2}\rho(U_2^2 - U_1^2) + \rho g L_2(\sin\theta_2 \sin\emptyset - \cos\theta_2 \sin\gamma) + \beta\frac{8\,\mu\,U_2 L_2}{a_2^2}$$

$$\pi_0 - \pi_3 = \frac{1}{2}\rho(U_3^2 - U_1^2) + \rho g L_3(\sin\theta_3 \sin\emptyset - \cos\theta_3 \sin\gamma) + \beta\frac{8\,\mu\,U_3 L_3}{a_3^2}$$

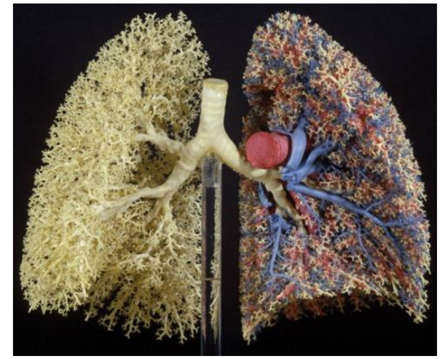
$$\pi_2 - P_2 = -\frac{2\sigma}{a_2}$$

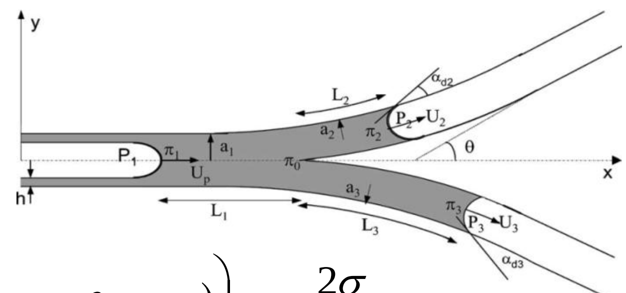
Reducing the complexity

Navier-Stokes equation + Mass conservation

$$\rho\frac{\partial\vec{u}}{\partial t}+\rho\,\vec{u}\cdot\vec{\nabla}\vec{u}-\mu\,\Delta\vec{u}+\vec{\nabla}P=\vec{f}$$

$$div(\vec{u})=0$$





$$P_1-P_a=(P_1-\pi_1)+(\pi_1-\pi_0)+(\pi_0-\pi_2)+(\pi_2-P_a)$$

$$=\frac{2\sigma}{a_1-h}+\left(\frac{8\mu Q_1}{\pi a_1^4}-\rho g\sin\gamma\right)L_1+\left(\frac{8\mu Q_2}{\pi a_2^4}-\rho g\left(\sin\theta_2\sin\varphi+\cos\theta_2\sin\gamma\right)\right)L_2-\frac{2\sigma}{a_2}$$

$$=\frac{2\sigma}{a_1-h}+\left(\frac{8\mu Q_1}{\pi a_1^4}-\rho g\sin\gamma\right)L_1+\left(\frac{8\mu Q_3}{\pi a_3^4}-\rho g\left(\sin\theta_3\sin\varphi+\cos\theta_3\sin\gamma\right)\right)L_2-\frac{2\sigma}{a_3}$$

$$V_2=\pi a_2^2L_2=\alpha(V_1-V_c)$$

$$V_3=\pi a_3^2L_3=(1-\alpha)(V_1-V_c)$$

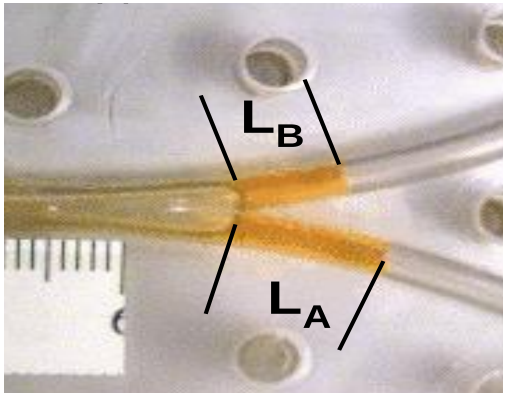
$$V_c=\pi\left(a_1^2-h^2\right)L_0$$

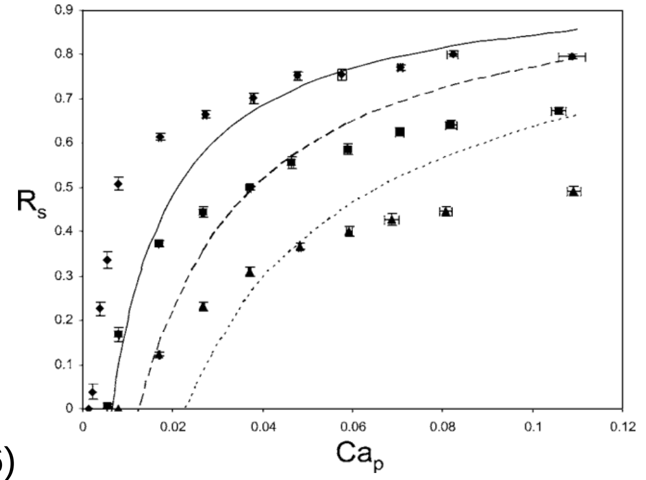
$$h/a_1=0.36\left(1-e^{-2Ca^{0.523}}\right)$$

$$\boxed{R_s=\frac{V_2}{V_3}=\frac{\alpha}{1-\alpha}}$$

Critical value of Ca for plug splitting in an asymmetric bifurcation

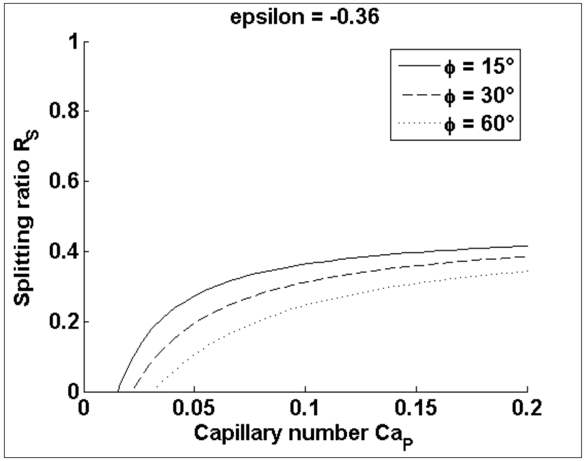
Symmetric

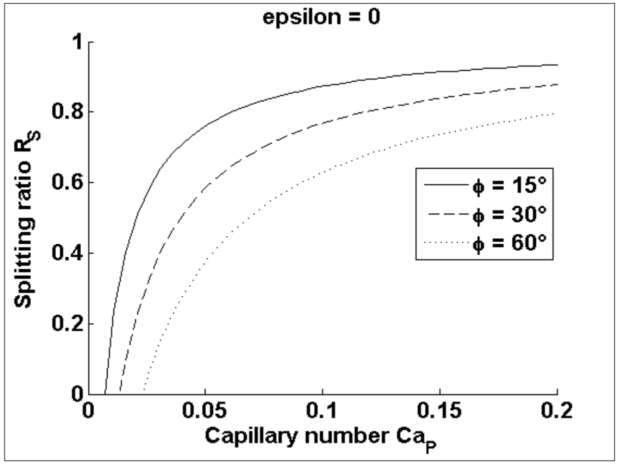


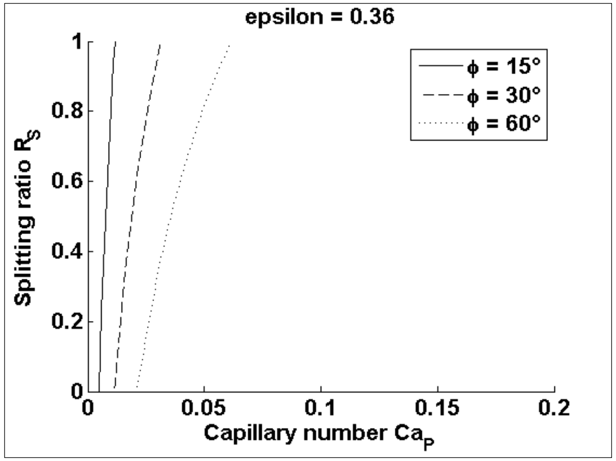


Zheng et al., *J Biomech Eng* (2005, 2006)

Asymmetric







Rate equations in asymmetric branching

$$\left(\frac{8\mu Q_2}{\pi a_2^4}-\rho g\left(\sin\theta_2\sin\varphi+\cos\theta_2\sin\gamma\right)\right)L_2-\frac{2\sigma}{a_2}=\left(\frac{8\mu Q_3}{\pi a_3^4}-\rho g\left(\sin\theta_3\sin\varphi+\cos\theta_3\sin\gamma\right)\right)L_3-\frac{2\sigma}{a_3}$$

Dimensionless numbers: $\boxed{Ca=\frac{\mu U_1}{\sigma}}$ $\boxed{Bo=\frac{\rho g a_1^2}{\sigma}}$

$$\left(\frac{8\mu\left(\pi a_1^2\frac{\sigma}{\mu}Ca\right)\alpha}{\pi a_2^4}-\frac{\sigma\,Bo}{a_1^2}\left(\sin\theta_2\sin\varphi+\cos\theta_2\sin\gamma\right)\right)\left(\frac{V_0-V_c}{\pi a_2^2}\right)\alpha-\frac{2\sigma}{a_2}$$

$$=\left(\frac{8\mu\left(\pi a_1^2\frac{\sigma}{\mu}Ca\right)(1-\alpha)}{\pi a_3^4}-\frac{\sigma\,Bo}{a_1^2}\left(\sin\theta_3\sin\varphi+\cos\theta_3\sin\gamma\right)\right)\left(\frac{V_0-V_c}{\pi a_3^2}\right)(1-\alpha)-\frac{2\sigma}{a_3}$$

$$\boxed{\left(\frac{\alpha}{h_2^6}-\frac{Bo}{8Ca}\frac{f_2}{h_2^2}\right)\alpha-\frac{2\pi a_1^3}{8Ca\left(V_0-V_c\right)h_2}=\left(\frac{(1-\alpha)}{h_3^6}-\frac{Bo}{8Ca}\frac{f_3}{h_3^2}\right)(1-\alpha)-\frac{2\pi a_1^3}{8Ca\left(V_0-V_c\right)h_3}}$$

SRT model

Geometrical model of the lung

Solve the fluid transport in the geometrical model

Delivery conditions

Surfactant properties	Density Viscosity Surface tension
patient	Position
Instillation	Flow rate Volume

Parameters

Surface Tension

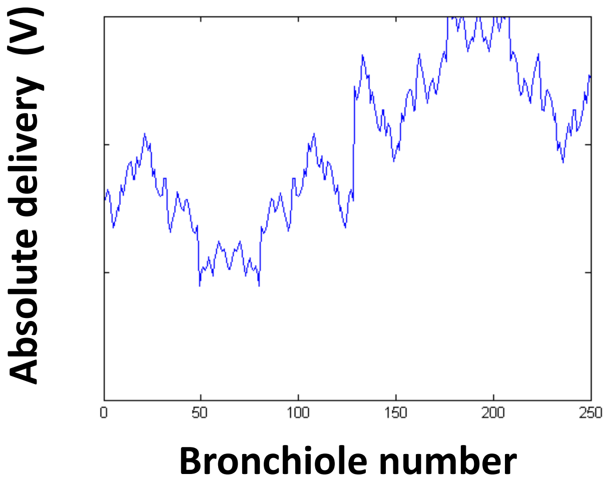
- From 30 to 50 dynes/cm
  σ = 30 dynes/cm
  Bernhard W*, et al. Am. J. Respir. Crit. Care Med.* , 2000

Viscosity

- μ = 30 cP
  - Survanta (bovine)
  - Infasurf (calf)
  - Curosurf (porcine)
- μ = 3 cP
  - Exosurf (synthetic)

King et al *Am. J. Physiol.-Lung Cell. Mol. Physiol.,* 2002
Lu et al *BBA-Biomembranes,* 2009

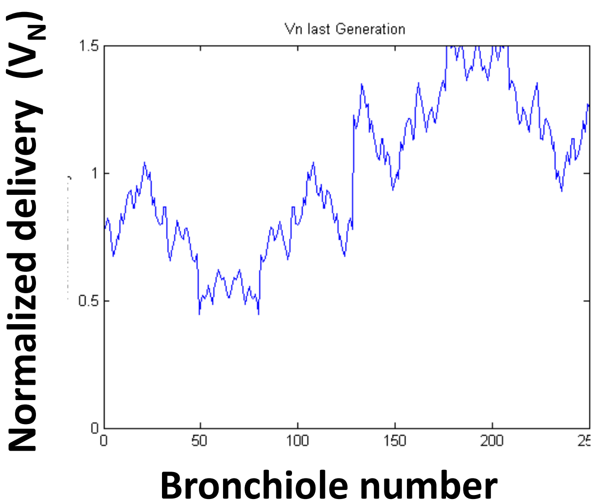
Distribution of surfactant at the end of the tree



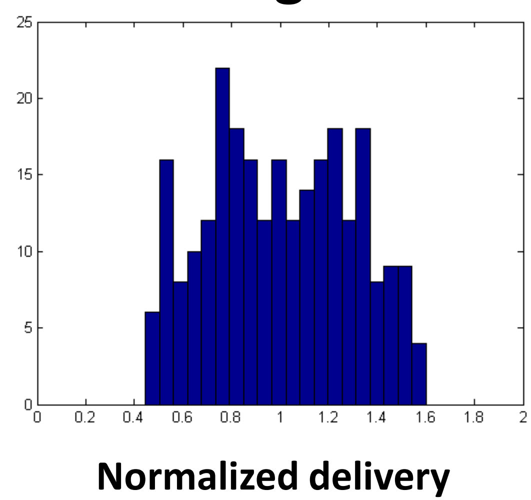
V_0: Initial volume of the plug

V_i: Volume reaching terminal airway *i*

Efficiency = $100 \times \sum_i \frac{V_i}{V_0}$



Histogram



$$V_N(i) = \frac{V_i}{\text{mean}(V_i)}$$

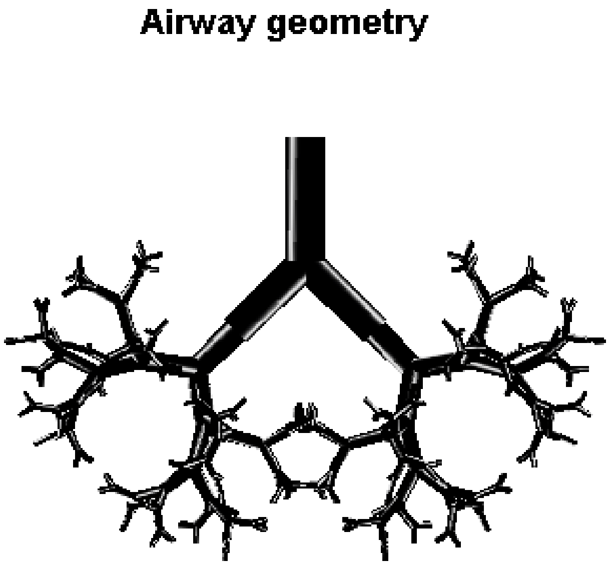
Homogeneity = $\frac{1}{SD(V_N)}$

Higher velocity → Higher homogeneity

Higher velocity → Lower efficiency

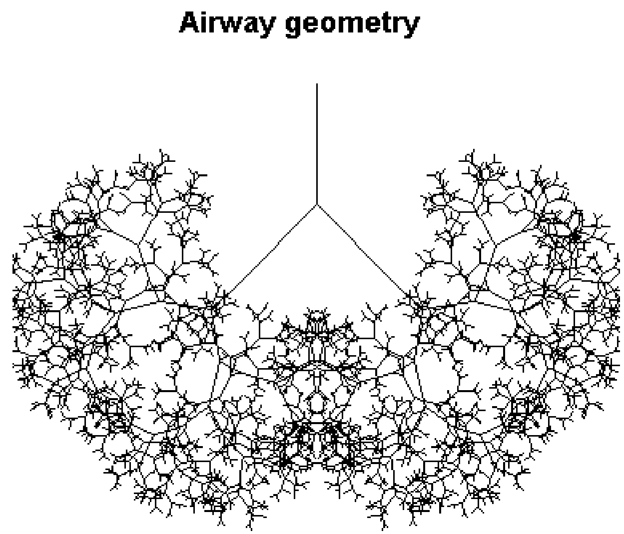
Fundamental dilemma

2 lb Neonate



Weibel symmetric tree, branching angle = 90°, planar rotation angle = 90°,trachea diameter = 0.4 cm, terminal bronchiole diameter = 0.05 cm → **511 branches**, 256 leaves, 8 generations

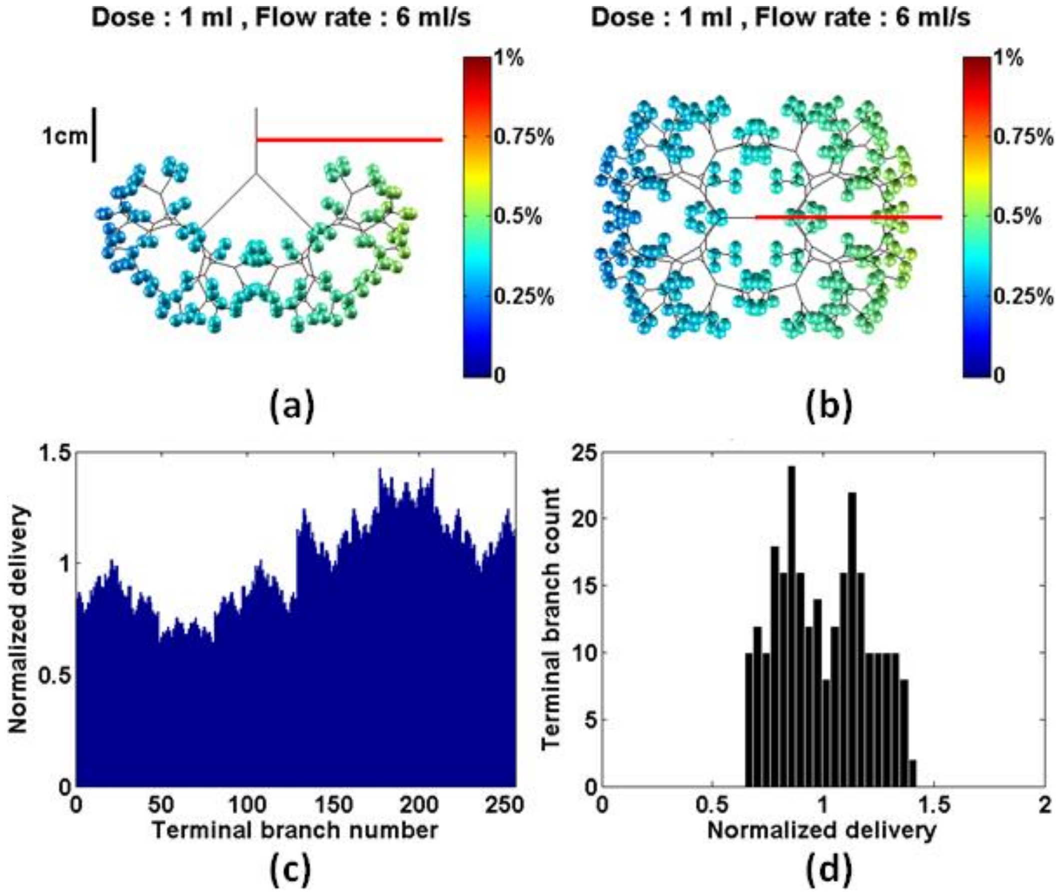
Adult



Weibel symmetric tree, branching angle = 90°, planar rotation angle = 90°, trachea diameter = 2 cm, terminal bronchiole diameter = 0.1 cm → **8191 branches**, 4096 leaves, 12 generations

Surfactant properties: ρ= 1 g/cc, σ= 30 dynes/cm,
μ= 30 cP (Infasurf, Survanta, Curosurf),
μ= 3 cP (Exosurf)

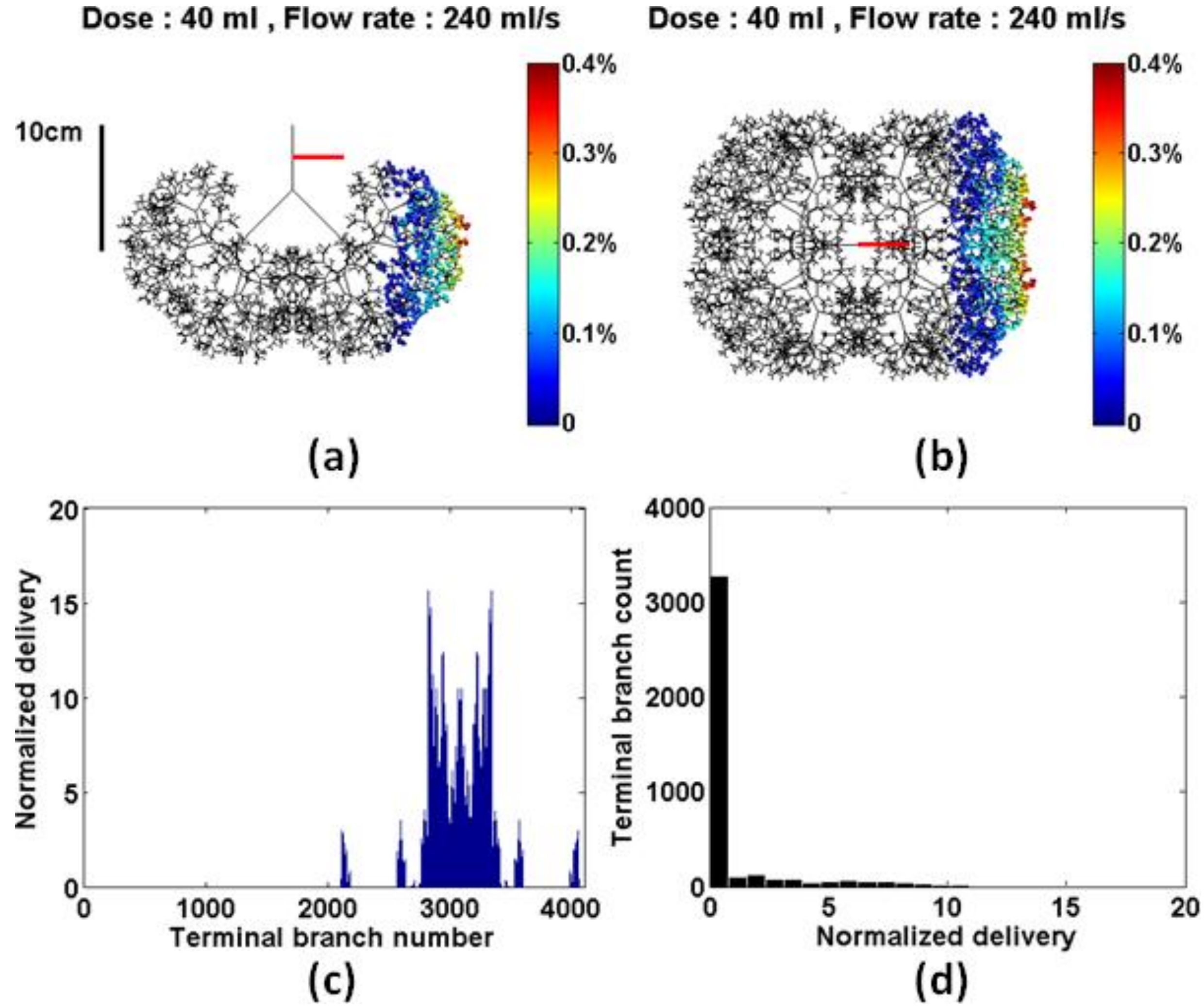
SRT 1 kg Neonate



1 kg neonate in LLD, viscosity μ=30 cP, dose 1ml, flow rate 6 ml/sec. **η=52.8%** (a) front view (b) top view of the 3D model with color coded amounts percentages in the acini (c) normalized delivery plotted vs i=1 to 256 acini (d) histogram showing **1/SD=4.9**.

MF, Tai, Grotberg, *PNAS* (2015)

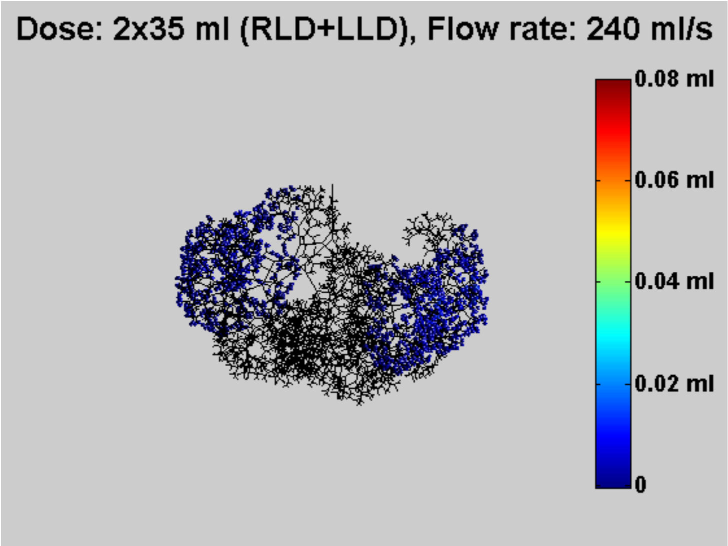
SRT 70 kg Adult

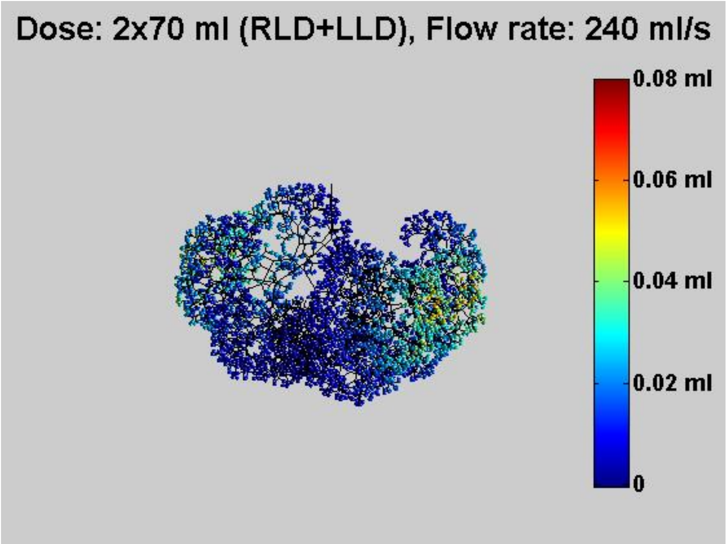


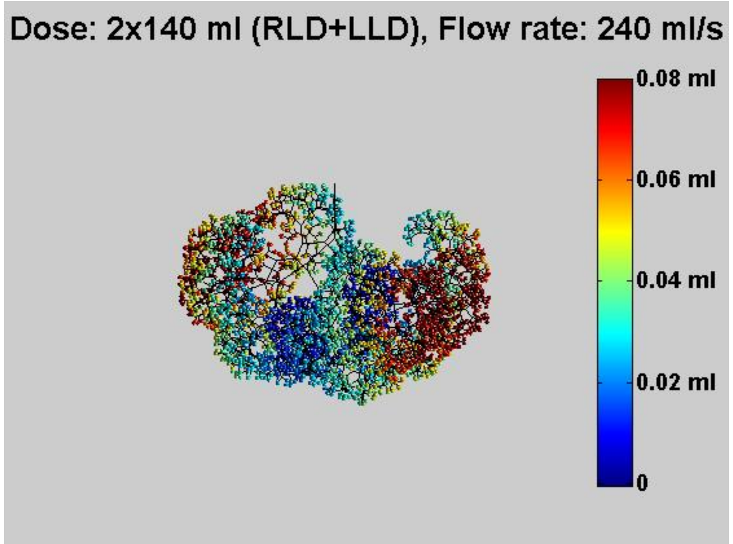
70 kg adult in LLD position, dose 40 ml, flow rate 240 ml/s, μ=30 cP, **η=13.0%**, (a) front view (b) top view (c) vs i=1 to 4096 (d) histogram showing **1/SD=0.41**.

MF, Tai, Grotberg, *PNAS* (2015)

Same geometry, same surfactant, 3 different volumes



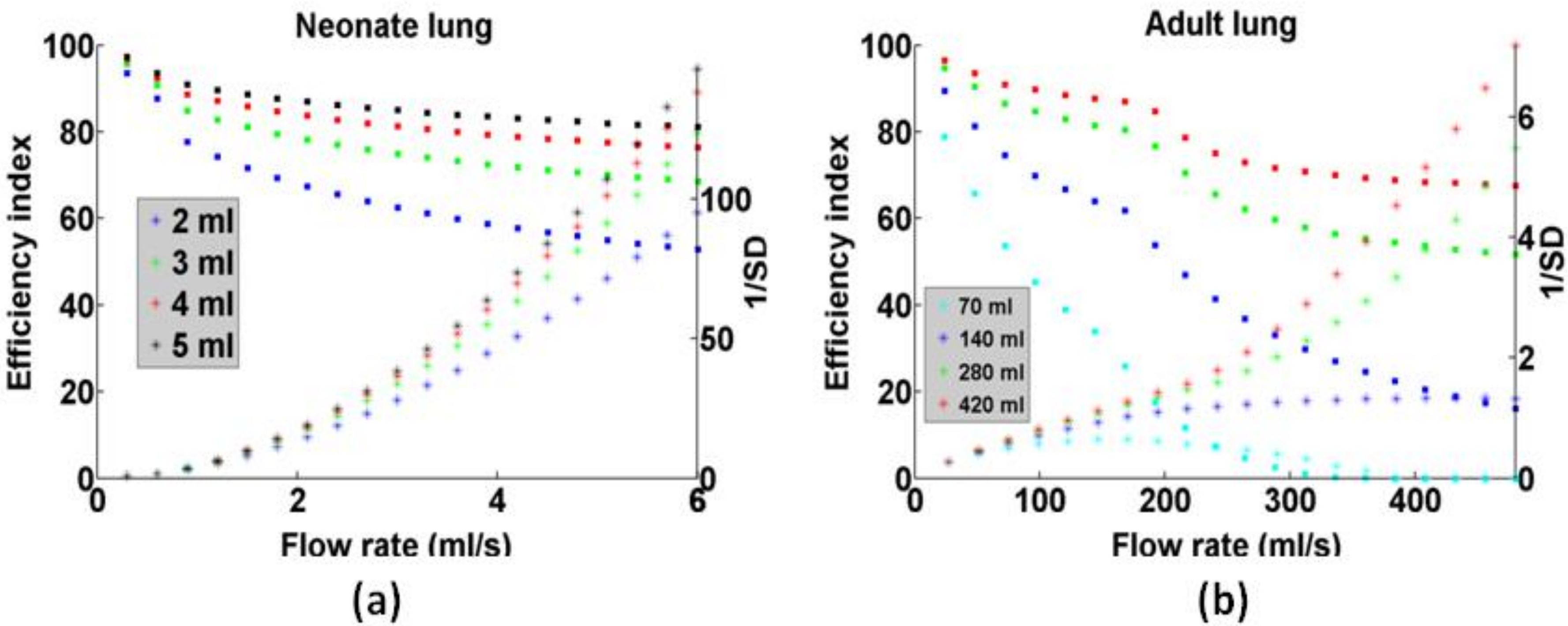




SRT Model Efficiency and Homogeneity

Dependence on Flow Rate, Dose Volume, Lung Size

½ dose volume LLD
½ dose volume RLD



MF, Tai, Grotberg, *PNAS* (2015)

SRT in adults for ARDS

Gregory et al, Am J Respir Crit Care Med. **1997**
Dose Volume: **2 ml/kg-4 ml/kg** ~ 140/280 ml for 70 kg patient
Surfactant Concentration: 25 mg/ml
Molecular Dose: 50 mg/kg -100 mg/kg
Mortality: 18.8% SRT (n=43) vs 43.8% control (n=16)

Lewis et al, Am J Respir Crit Care Med. **1999**
Dose Volume: **4 ml/kg** (40 kg sheep)
Surfactant Concentration: 6.25 mg/ml, 25 mg/ml, 50 mg/ml
Molecular Dose: 25 mg/kg, 100 mg/kg, 200 mg/kg
Result: Improved oxygenation all concentrations, better for 25,50 mg/ml

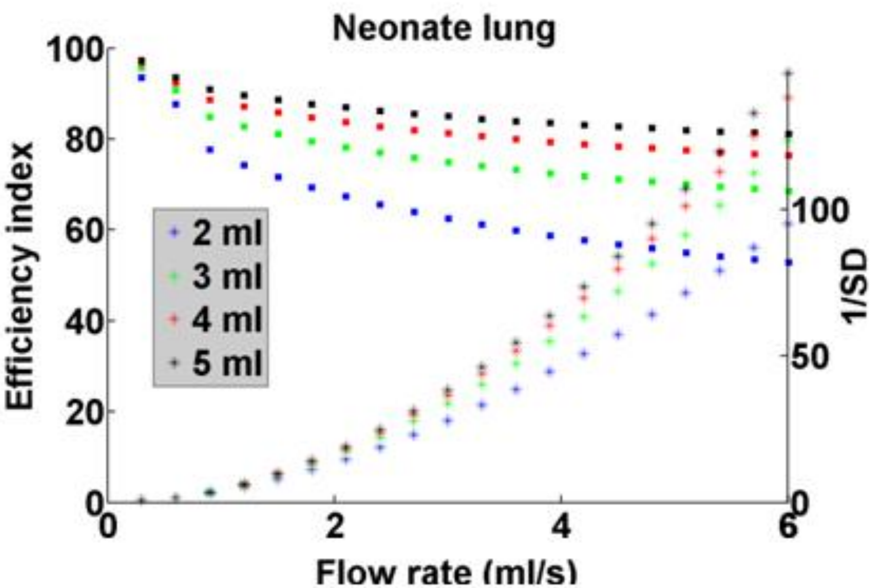
Spragg et al, N Engl J Med. **2004**
Dose Volume: **1 ml/kg** ~ **70 ml for 70 kg patient**
Surfactant Concentration: 50 mg/ml
Molecular Dose: 50 mg/kg
Mortality: no effect (n=224 SRT, n=224 control)

Spragg et al, Am J Respir Crit Care Med. **2011**
Dose Volume: **1 ml/kg** ~ **70 ml for 70 kg patient**
Surfactant Concentration: 50 mg/ml
Molecular Dose: 50 mg/kg
Mortality: no effect (n=419 SRT, n=424 control)

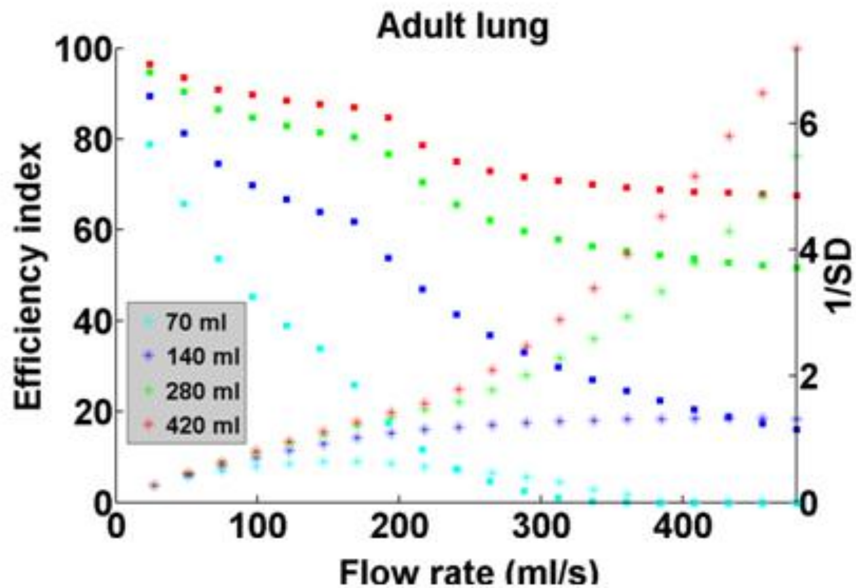
SRT Model Efficiency and Homogeneity

Dependence on Flow Rate, Dose Volume, Lung Size

½ dose volume LLD
½ dose volume RLD



(a)



(b)

70 ml Spragg 2004, 2011 **Failure**
140 ml/280 ml Gregory 1997 **Success**

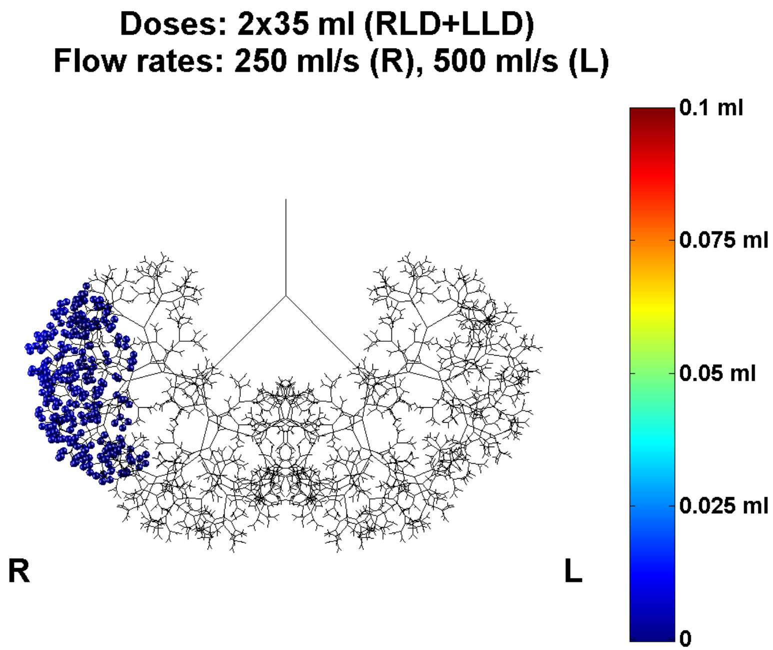
Flow rate **decreases** efficiency due to increasing R_D "coating cost"

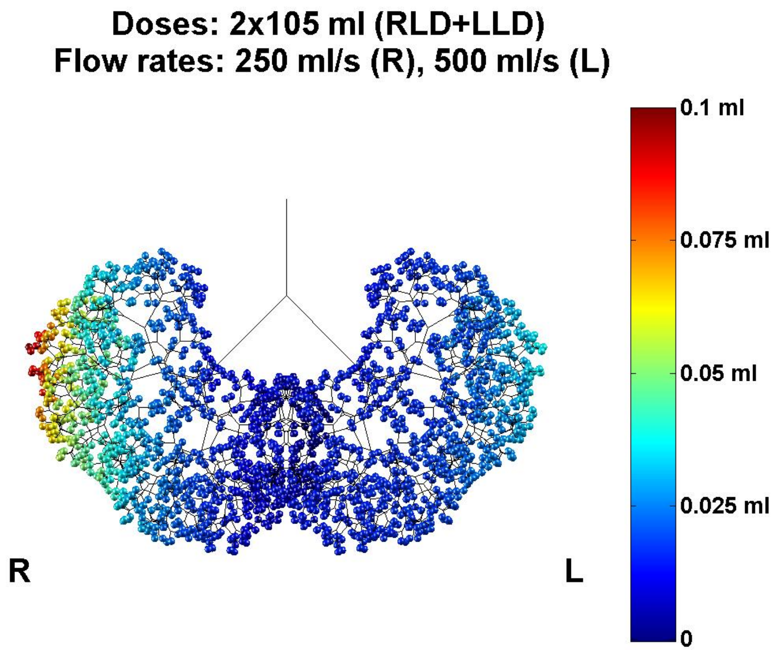
Flow rate mostly **increases** homogeneity due to increasing R_S toward unity

Neonatal homogeneity is an order of magnitude larger than adult

70 ml adult worst choice, local max, both η and 1/SD near zero from coating cost

Addressing the medical community





Grotberg et al., *Am. J. Respir. Crit. Care Med*. (2017)

Why this "failure" of SRT in adults?

"Exogenous surfactant replacement in ARDS - One day, someday, or never?" Baudouin SV. N Engl J Med. 2004

- Surfactant biochemistry is not working
- The surfactant does not reach the acinus
- The underlying ARDS injury is still active

Equations modeling the flow motion

Navier-Stokes/Continuity Equations

$$La\left(\frac{\partial \mathbf{u}}{\partial t}+\mathbf{u}\cdot\nabla\mathbf{u}\right)=\nabla^2\mathbf{u}-\nabla p-Bo\sin(\varphi)e_y$$

$$\nabla\cdot\mathbf{u}=0$$

Dimensionless Parameters:

Laplace #: $La=\frac{\rho\sigma h}{\mu}$

Bond #: $Bo=\frac{\rho g h^2}{\sigma}$

Capillary #: $Ca=\frac{Q\mu}{h\sigma}$

Dimensional Parameters:

u: fluid velocity

$\boldsymbol{e}_y$: vertical unit vector

h: parent channel height

Q: gas flow rate

p: fluid pressure

ρ: liquid density

μ: liquid viscosity

φ: roll angle

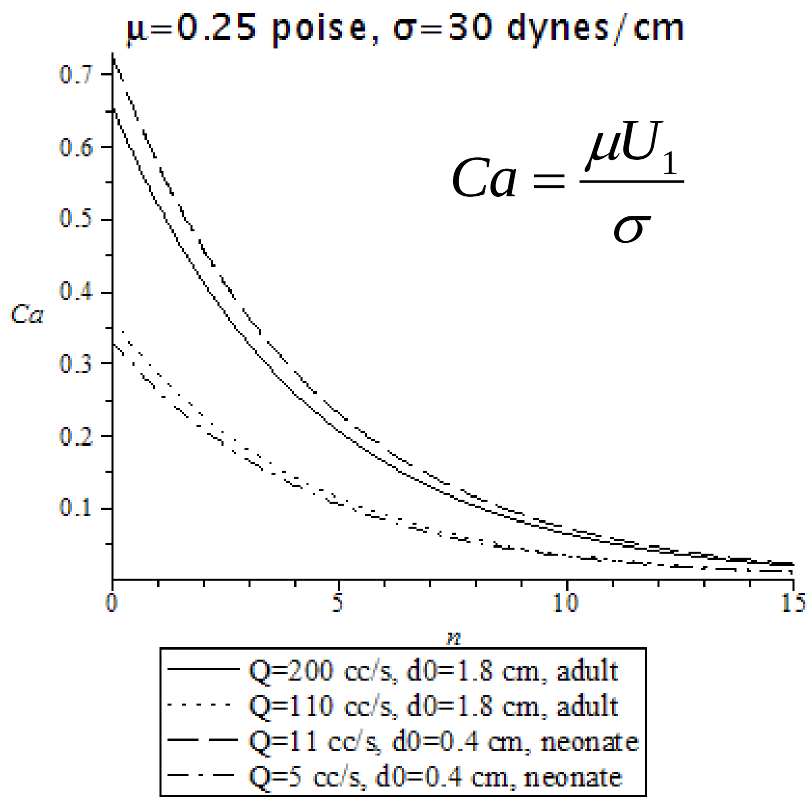
σ: surface tension

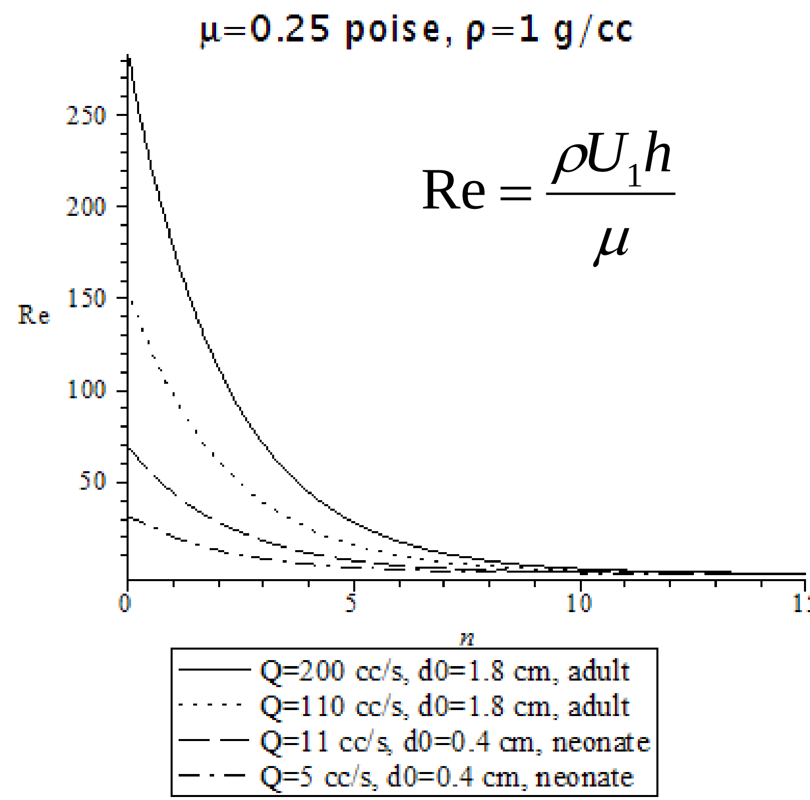
g: gravitational const

Assume Passive Gas Phase & *La* << 1 (Stokes Flow)

Parameter Ranges of Ca and Re

Neonates and Adults at **airway generation** ***n***

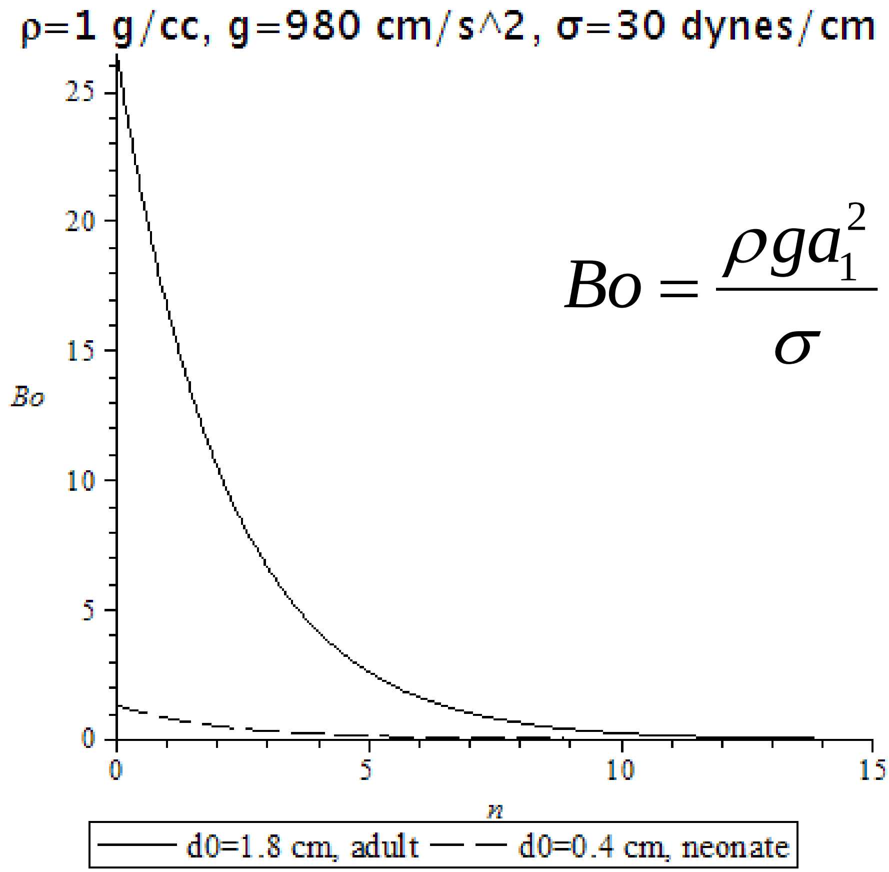




Ca, Re, **similar order of magnitude** for adults and neonates.

Parameter Range of Bo

Neonates and Adults at **airway generation** *n*

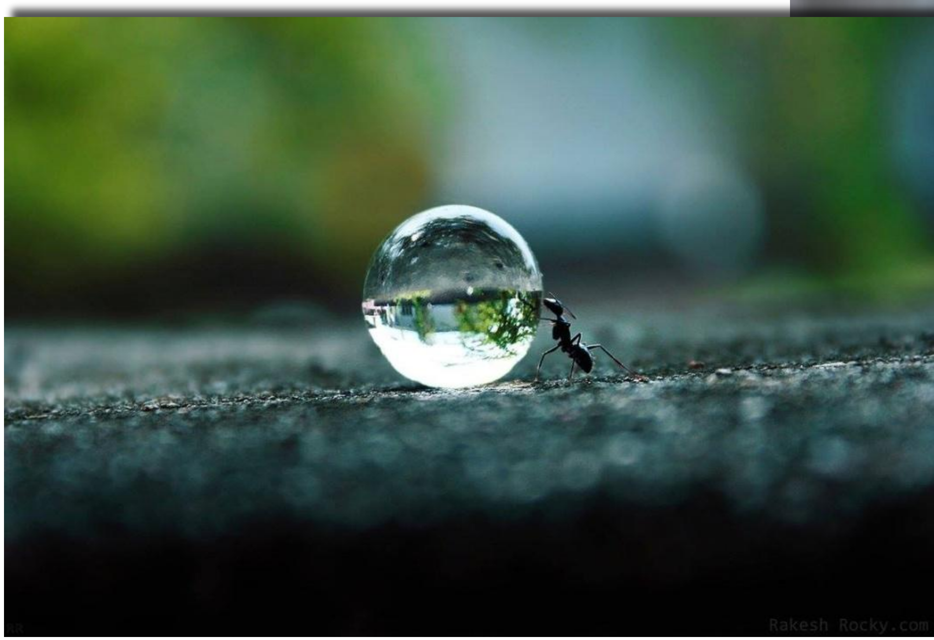


$$Bo = \frac{\rho g a_1^2}{\sigma}$$

Order of magnitude difference between adults and neonates

Scaling in Nature

Surface tension, gravity effects, and velocity do not scale identically!



A fundamental misunderstanding?

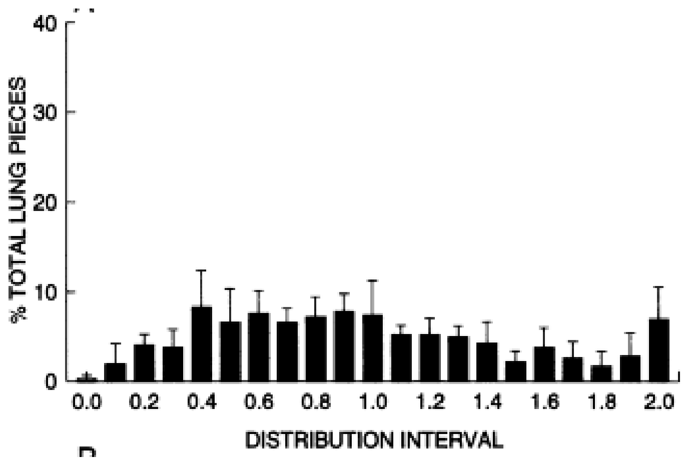
- Common concept in drug delivery assumes a "**well mixed compartment**"
- Double the concentration and halve the volume… should result in the same **clinical** result
- The neonate lung is **well mixed**, very high 1/SD
- The adult lung is **poorly mixed**, low 1/SD
  - The absolute volume is "**critical**"
  - **Fixed cost** of airway coating
- **Physics and fluid mechanics send a new message**

Surfactant delivery distribution in rabbit experiments

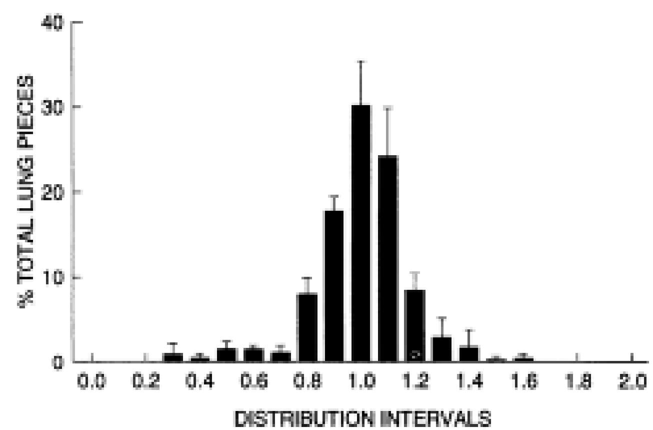
Measurement of surfactant distribution in living systems has been done in animal models by instilling surfactant mixtures with radio-tagged molecules. The lung or lobe is then frozen and sliced into many pieces, on the order of 50-200 depending on the study. The radioactivity or microsphere count of each slice is divided by its weight, giving a measure of the amount of surfactant delivered per unit weight. Then that value is divided by the average value of all of the slices, so a relative delivery ratio is achieved. If the surfactant were uniformly distributed, that ratio would be unity for all slices.

Distribution of instilled surfactant in rabbits per unit weight for

5 ml containing 200 mg surfactant
relatively heterogeneous distribution



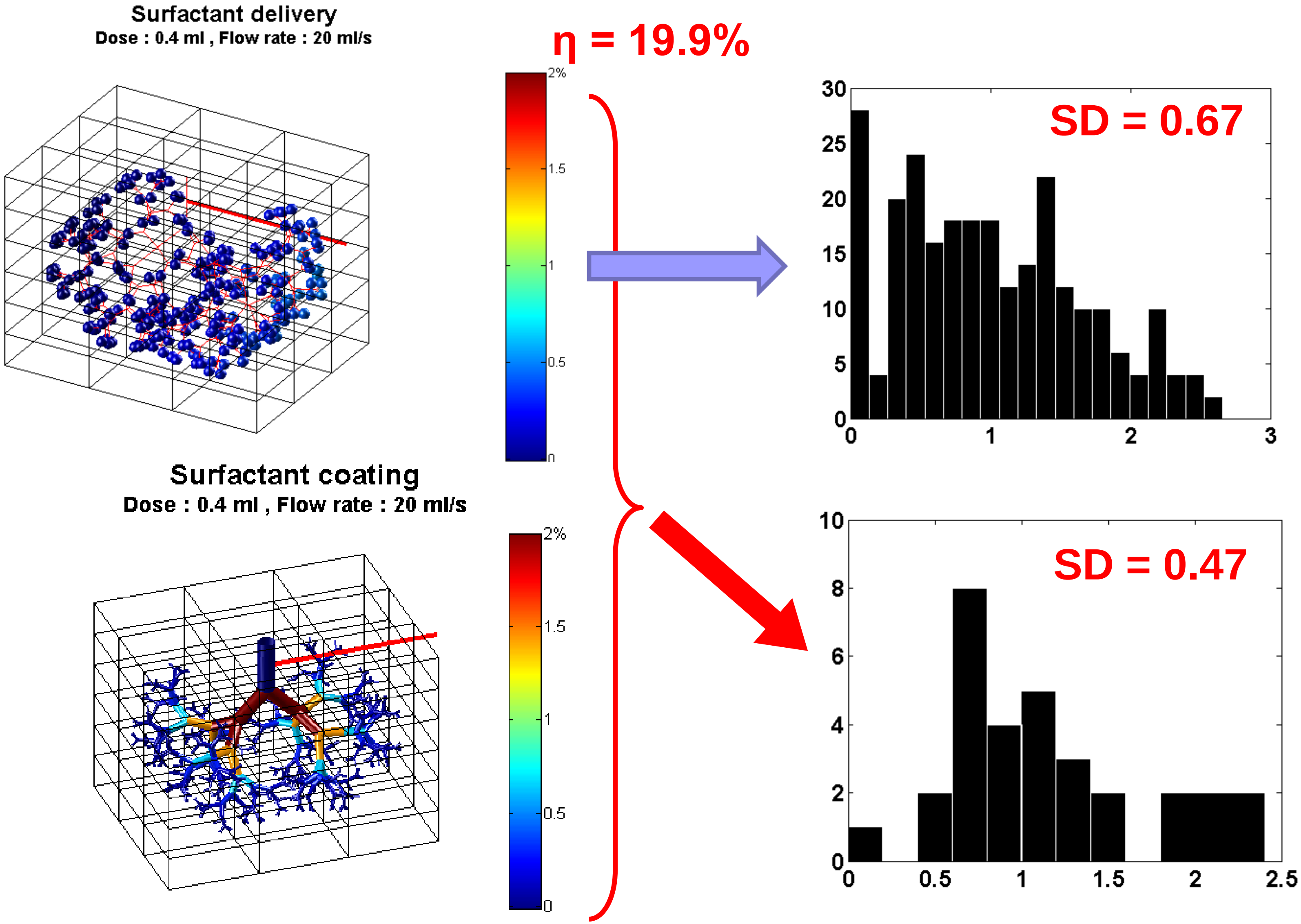
50 ml containing 50 mg surfactant
relatively homogeneous distribution.



Gilliard, Pappert, Spragg, J Appl Physiol 1995

Error sources in experimental slices

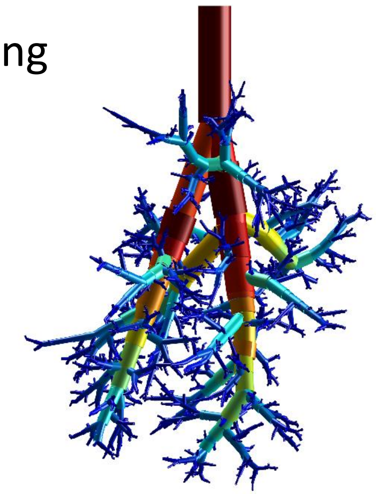
Neonate LLD Head Level, μ=3 cP



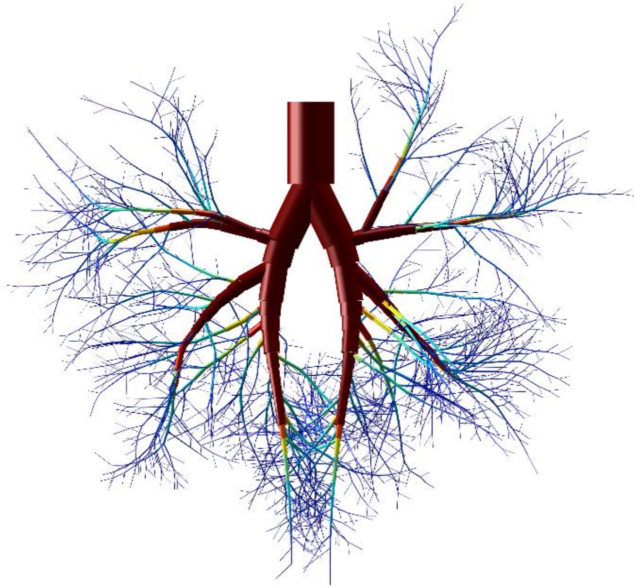
The future of SRT

Reliable animal models?

Rat lung

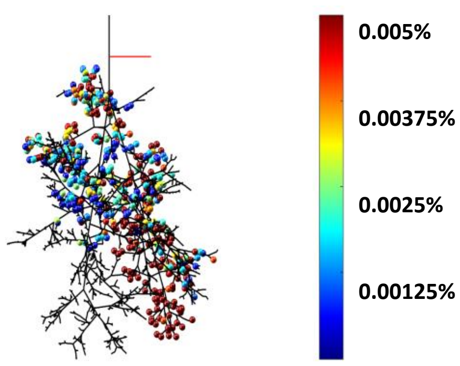


Pig lung

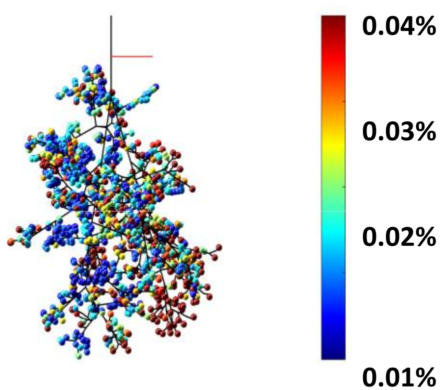


Virtual delivery

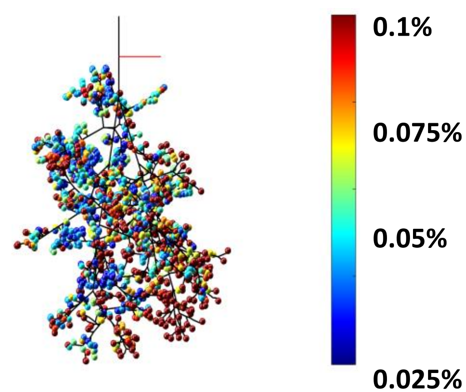
Dose: 1.125 (mL.kg^{-1})



Dose: 2.5 (mL.kg^{-1})



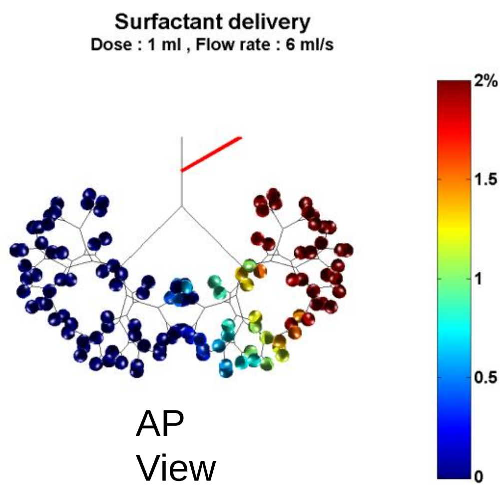
Dose: 5.8 (mL.kg^{-1})



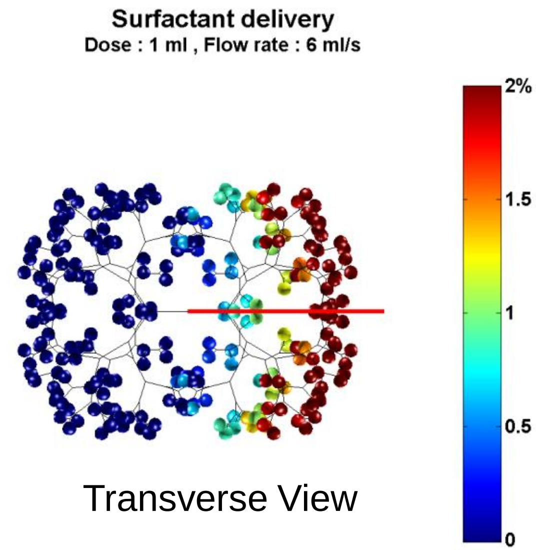
(Simulations by A. Kazemi)

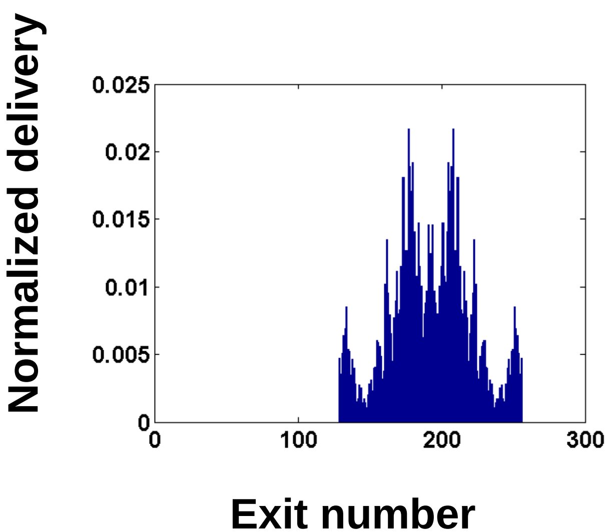
Playing with surfactant viscosity (Exosurf)

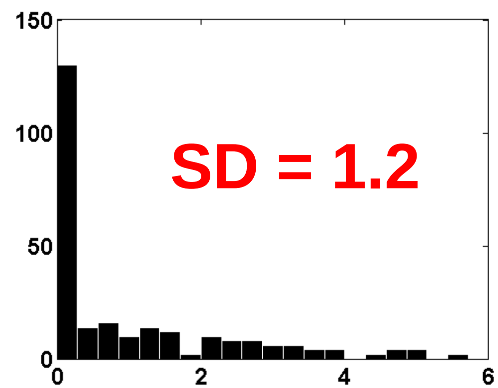
Case 2: Neonate LLD Head Down 30˚ μ= 3 cP



η = 90.6%



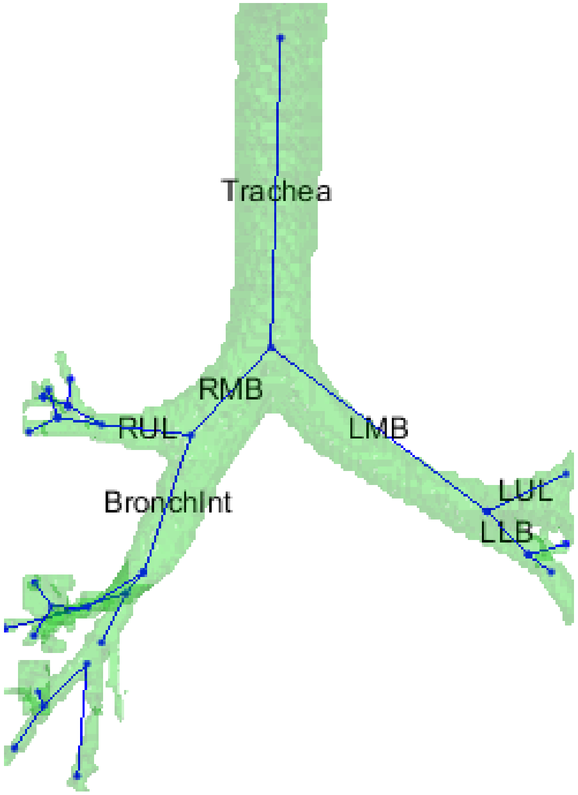




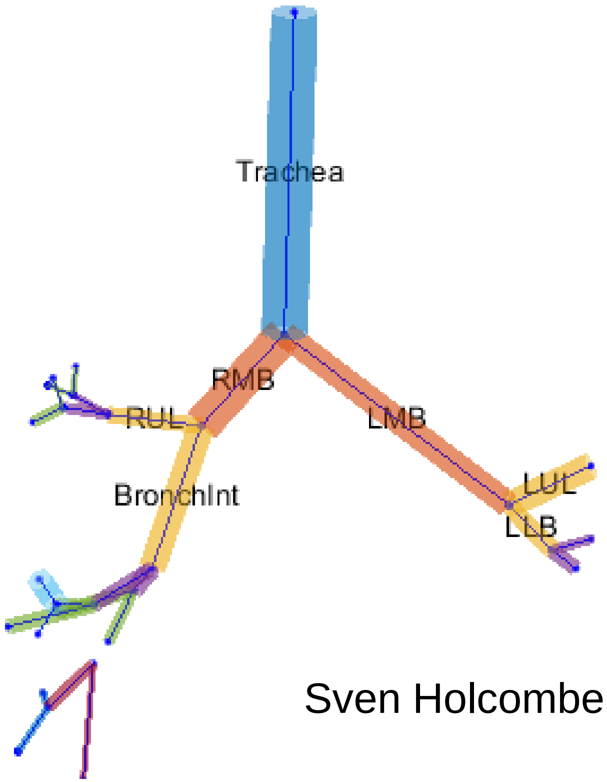
Acinar delivery histogram

η 2x Case 1 , SD 6x Case 1
Very inhomogeneous.
No delivery right lung.
Exosurf discontinued.
Biochemistry or delivery?

Patient-Specific SRT
CT Scan and Image Processing



(a)

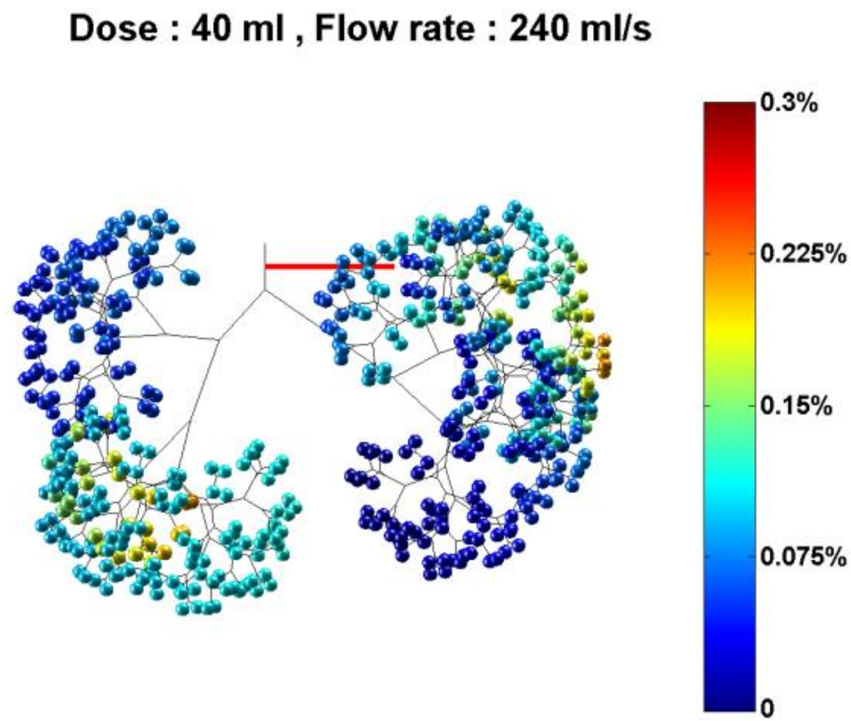


Sven Holcombe, 2015

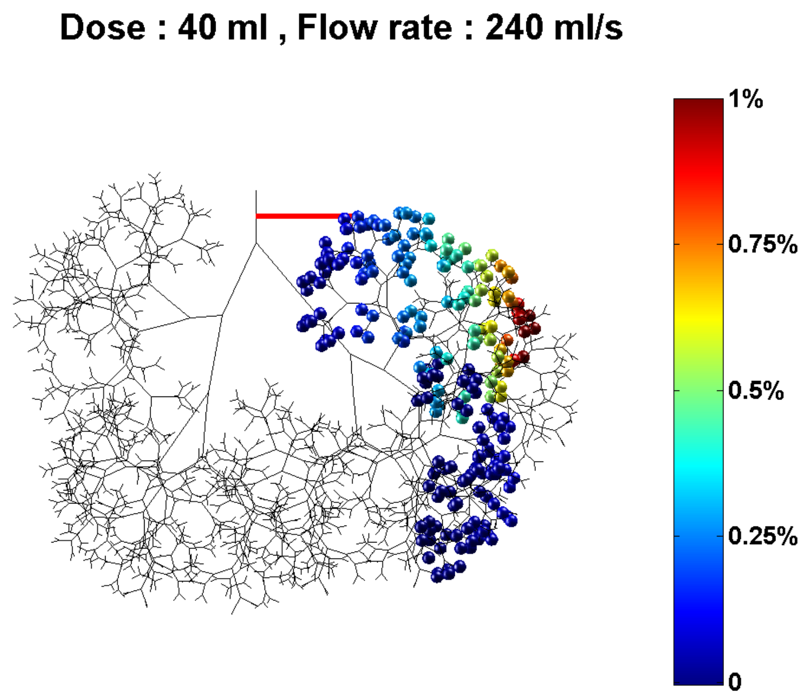
(b)

(a) 6 generation airway tree of a 67 y.o. female with normal lungs. (b) same airway tree with equivalent tubes and angles which are inputted to the SRT simulations.

Patient-specific SRT simulations



(a)



(b)

Numerical simulation of surfactant delivery in an airway tree based on

(a) 67 y.o. female patient data with tracheal diameter **1.4 cm**.

(b) Raabe data (1976) with tracheal diameter **2 cm** and similar planar rotation angles from (a).

Conclusions and perspectives

- First physico-mathematical model of SRT
- Computes efficiency and homogeneity down to the individual airway.
- Increasing Ca has **two opposite effects**: increases homogeneity, but reduces efficiency.
- Delivery in adults is facing simultaneous high values of the Bond number (inhomogeneous splitting) and of the capillary number (airway coating)
- Room for **Biomedical engineering of SRT**: to determine optimal volumes, orientations, flow rates
- Modify the physical properties of the surfactant (viscosity, density, surface tension)
- Animal models: **Large animals** (sheep, pig)
- Future: **patient specific delivery**