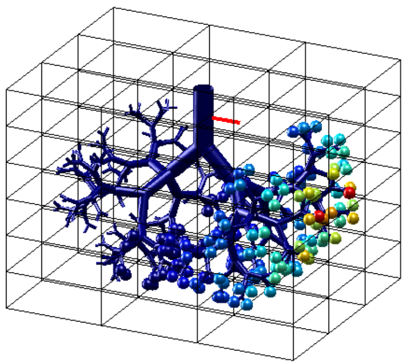
Gas and surfactant delivery into the lung airway system



Marcel Filoche

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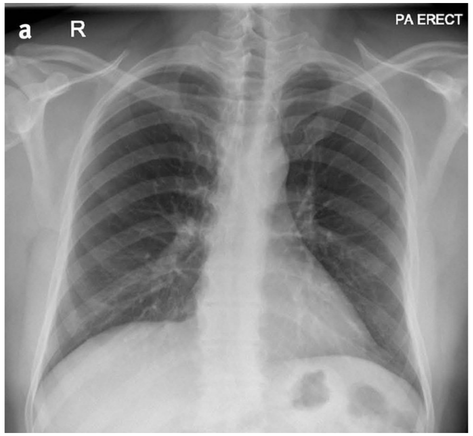
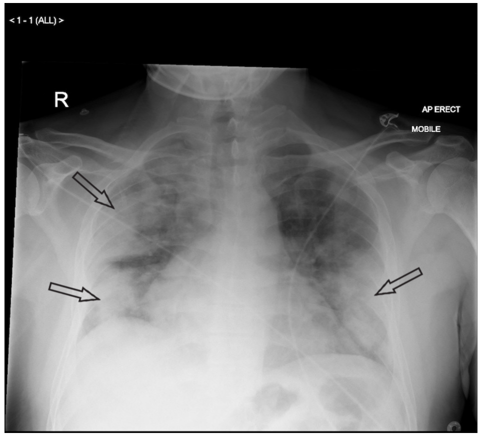
INSERM 955, Université Paris-Est Créteil

Multifractal Analysis and Self-Similarity, 26-30 June 2023, CIRM, Luminy

Covid-19 pandemic: about 7 million deaths worldwide

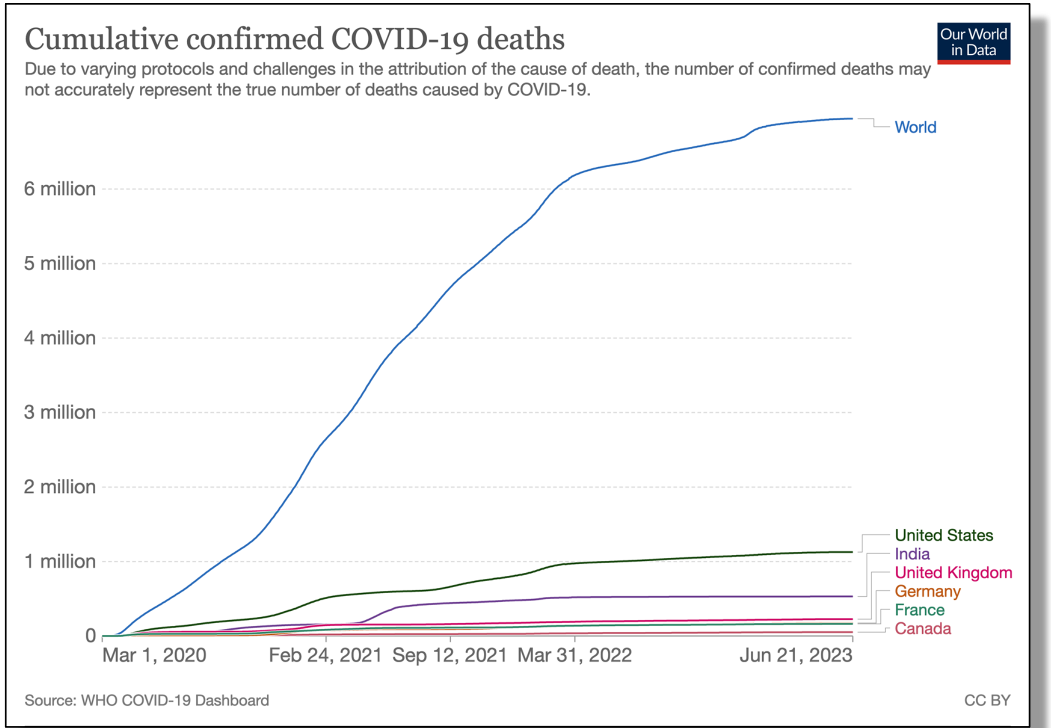


Normal posterior-anterior chest radiograph



severe covid-19 pneumonia

BMJ 2020;370:m2426



Joint work with

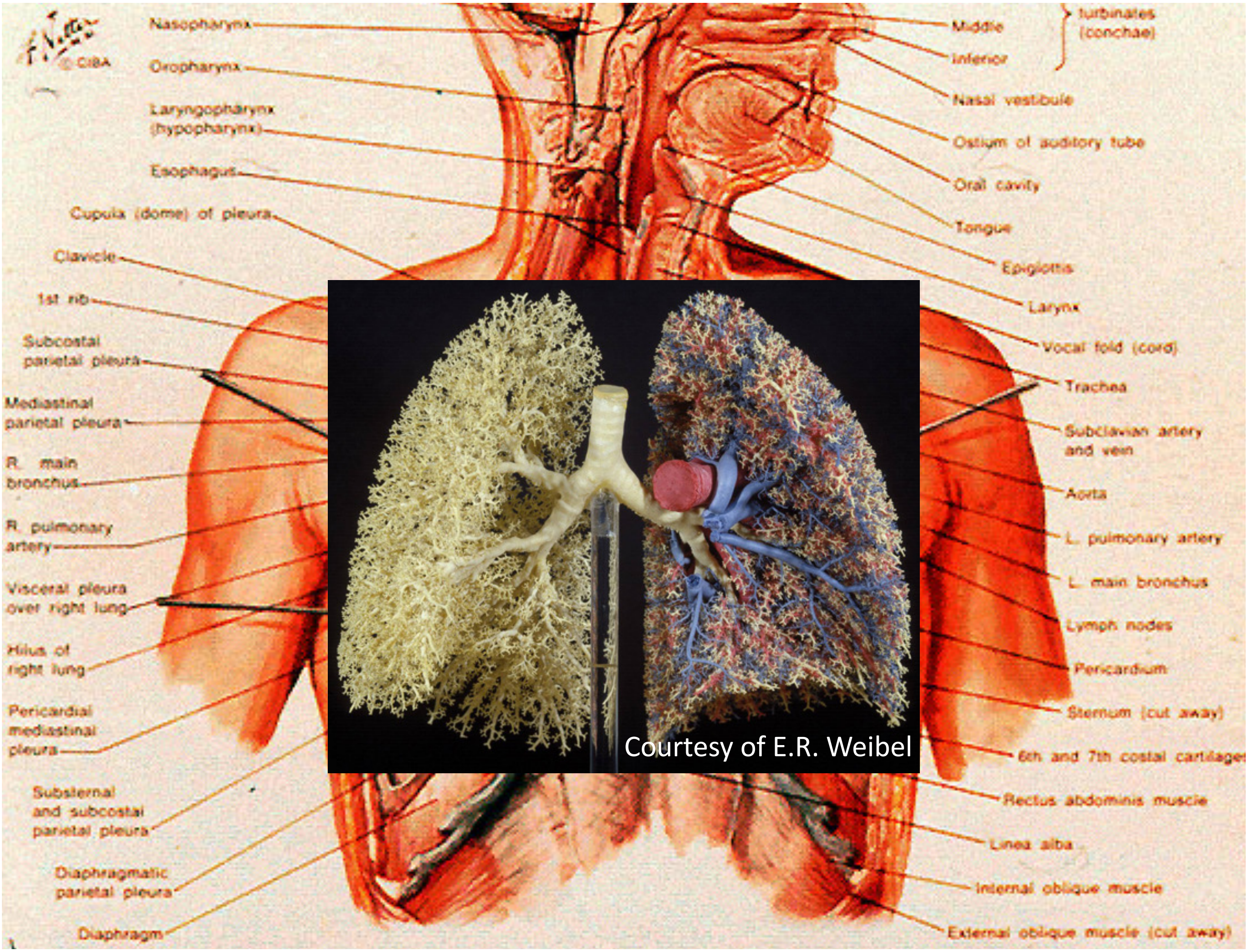
Gas transport

- **B. Sapoval, E. R. Weibel, D. Grebenkov, M. Felici** (Ecole polytechnique)
- **B. Mauroy, M. Florens** (ENS Cachan)
- **T. Similowski, C. Straus** (Hôpital de la Pitié-Salpêtrière)

Surfactant delivery

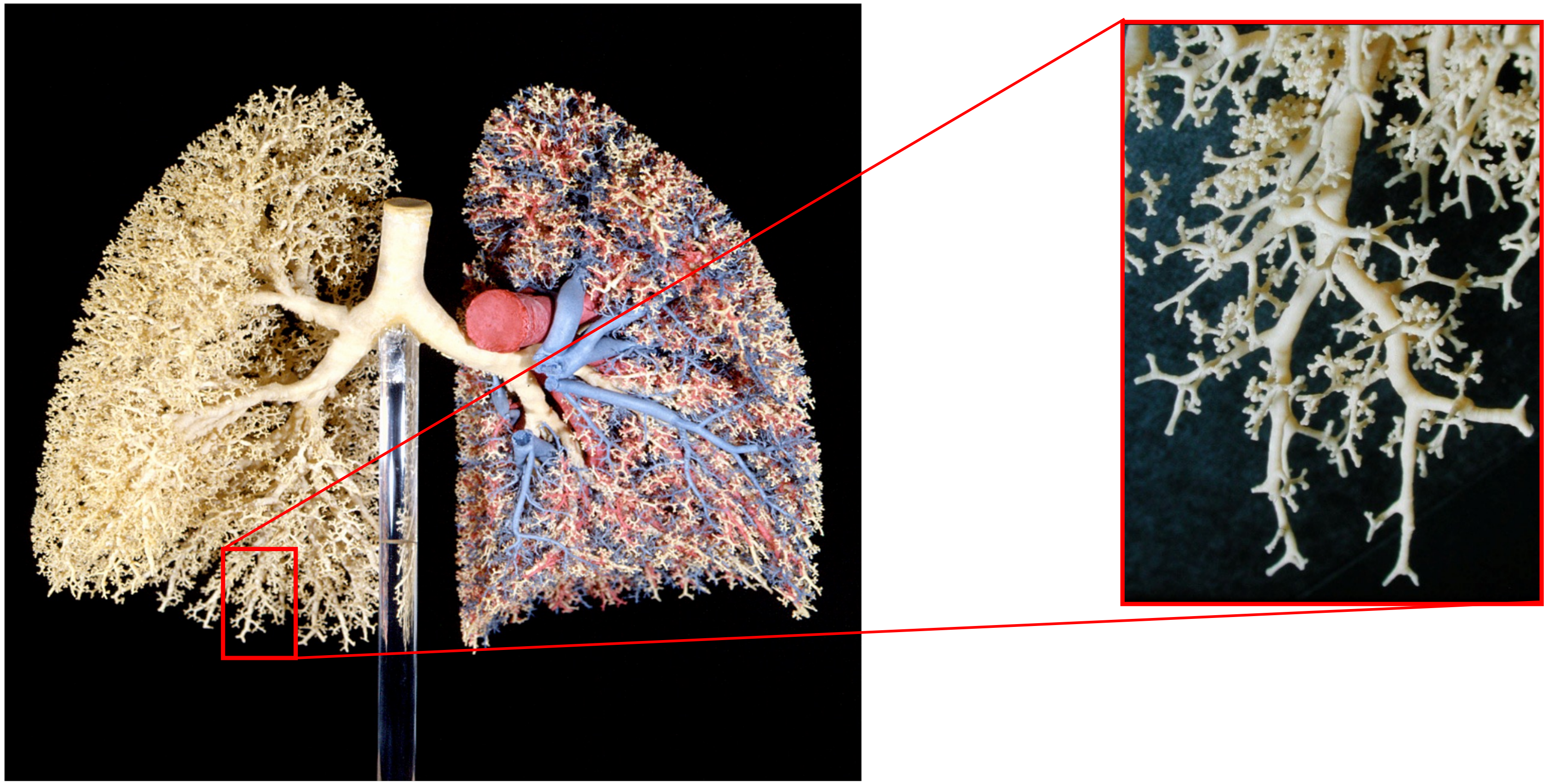
- **D. Isabey, B. Louis** (Institut Mondor de Recherche Biomédicale)
- **J. B. Grotberg, C.-F. Tai, S. Holcombe, K. Raghavendran** (University of Michigan)
- **D. F. Willson** (Virginia Commonwealth University)
- **R. H. Notter** (University of Rochester)
- **A. Kazemi** (Ecole polytechnique)
- **G. Nieman, L. Gatto** (SUNY Upstate Medical University)
- **C. Lenclud** (Hôpital de Mantes-la-Jolie)

The human respiratory tract

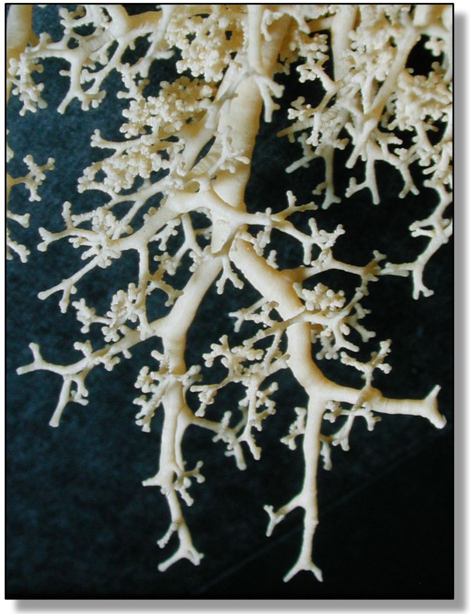


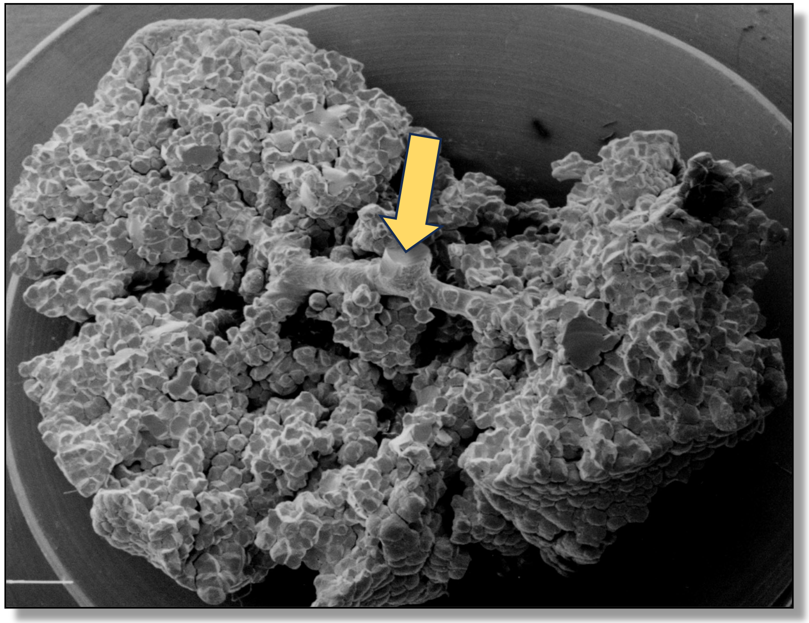
CIBA, Netter

The structure of the pulmonary airway system

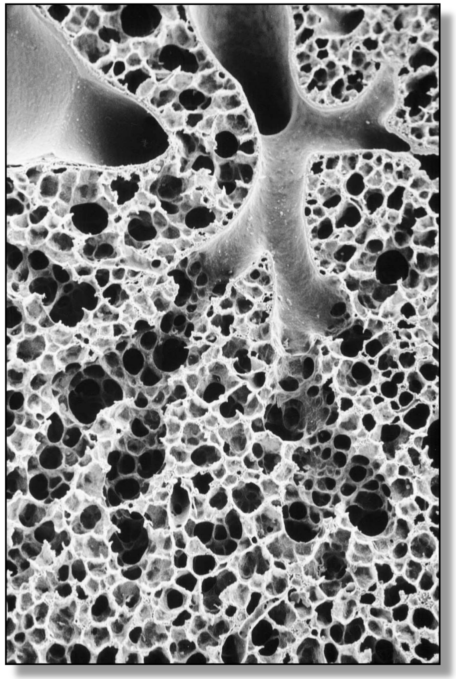


At the end of each of the 30,000 bronchioles, one acinus



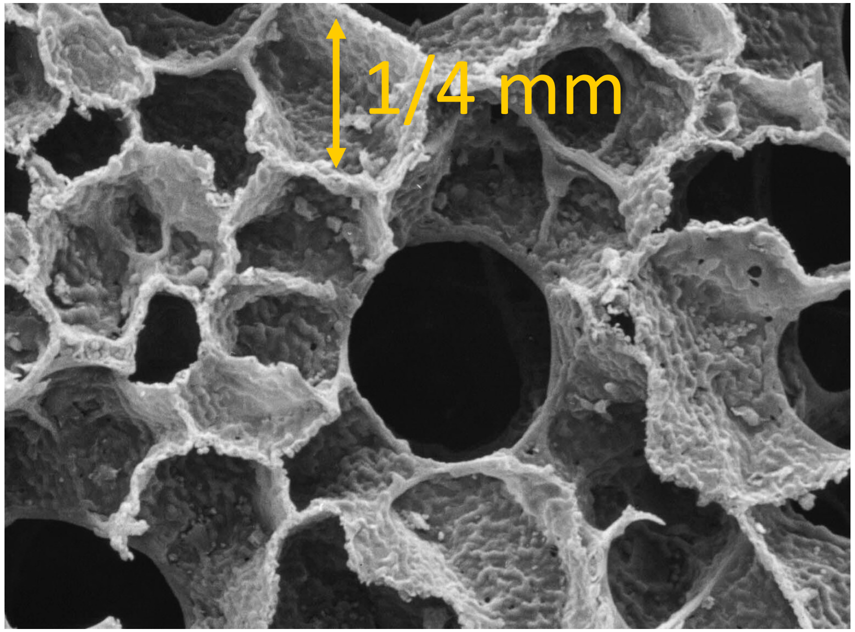


6 mm



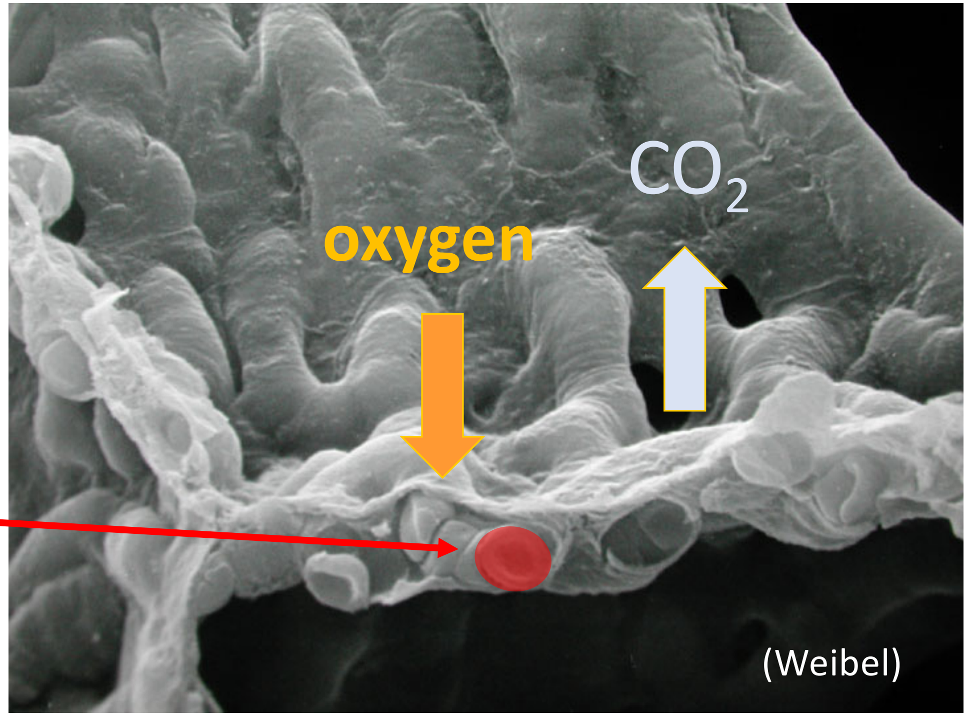
Section view

The alveolar region

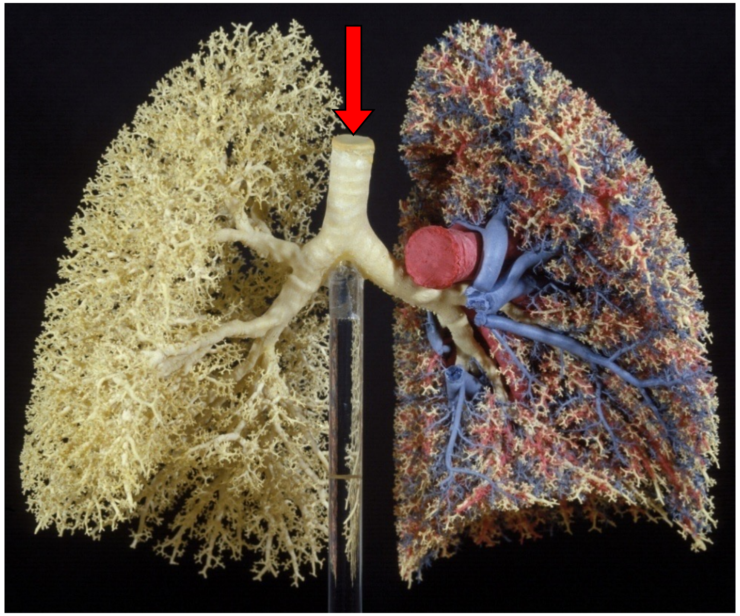


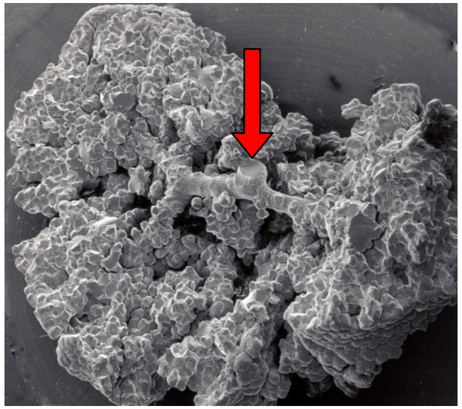
Pulmonary alveoli
(3-500 millions)

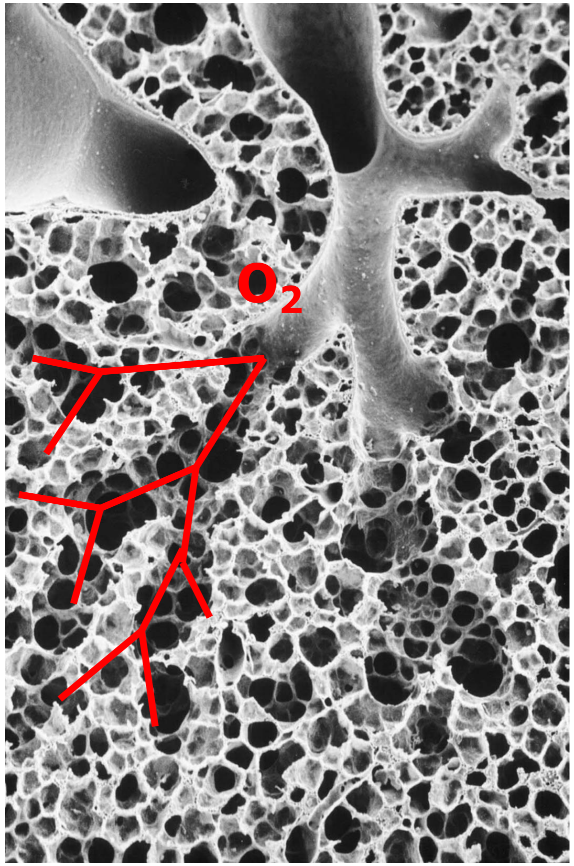
Red-blood cell



The journey of oxygen into the lung

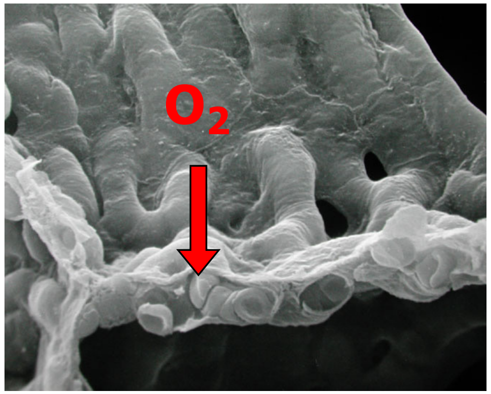


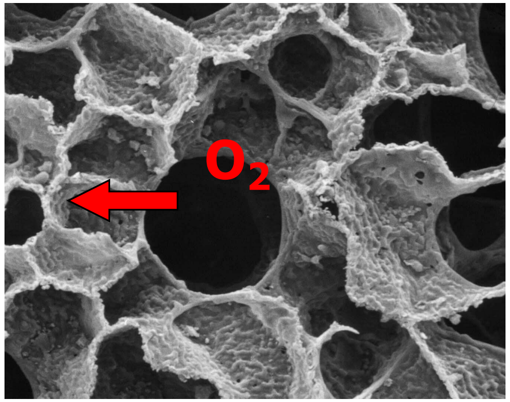




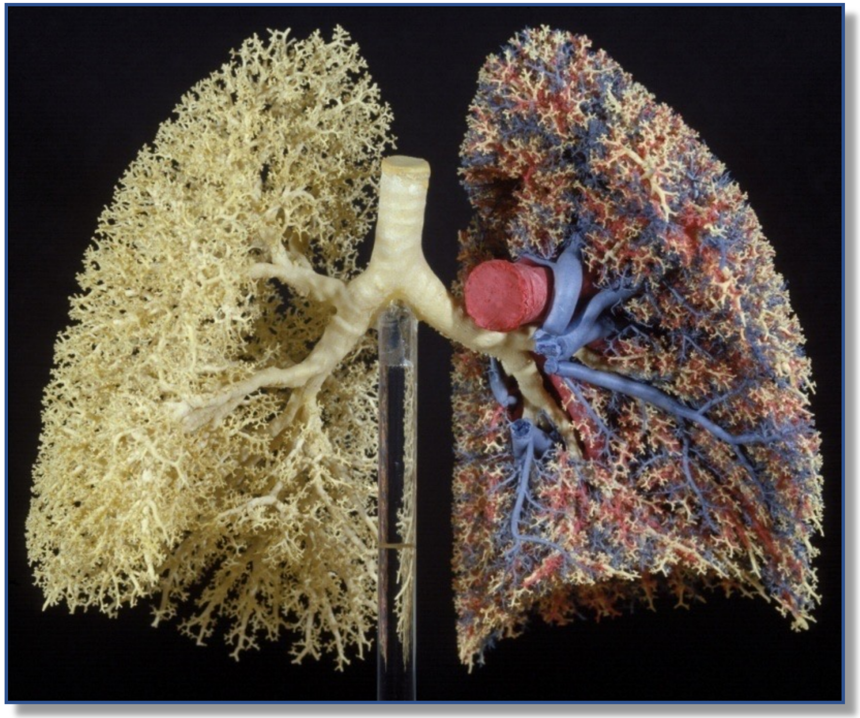
1 acinus ~ 8 generations
10-15,000 alveoli

Gas exchange





The bronchial tree feeds the alveolar exchange surface



Total alveolar surface in the human lung: ~100 m^2 !

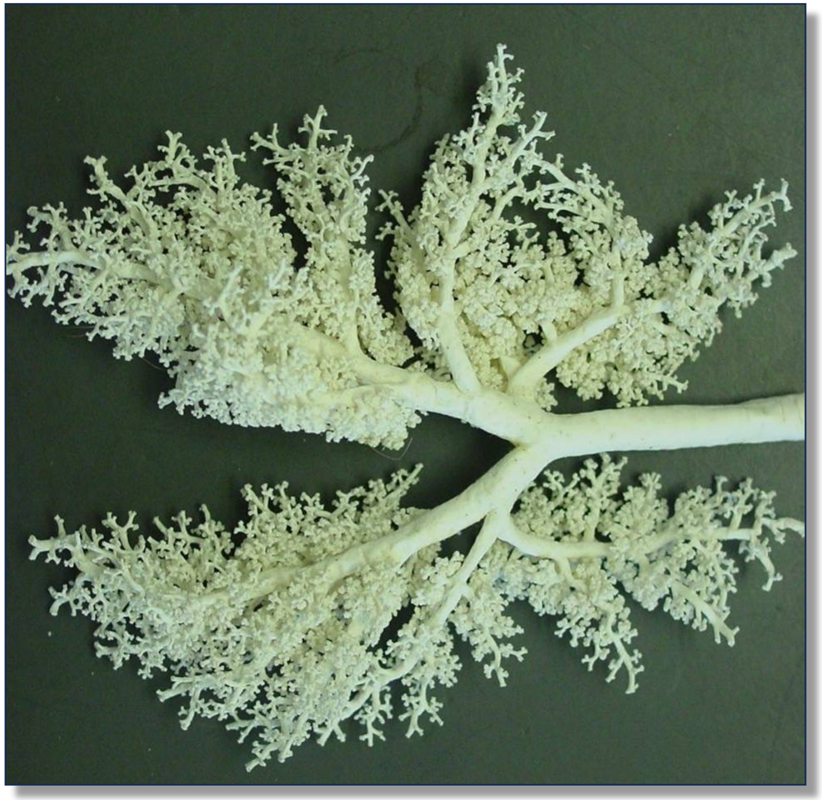
Mammalian lungs

Horse

Large dog

Cat lung

Cat front



Cat back

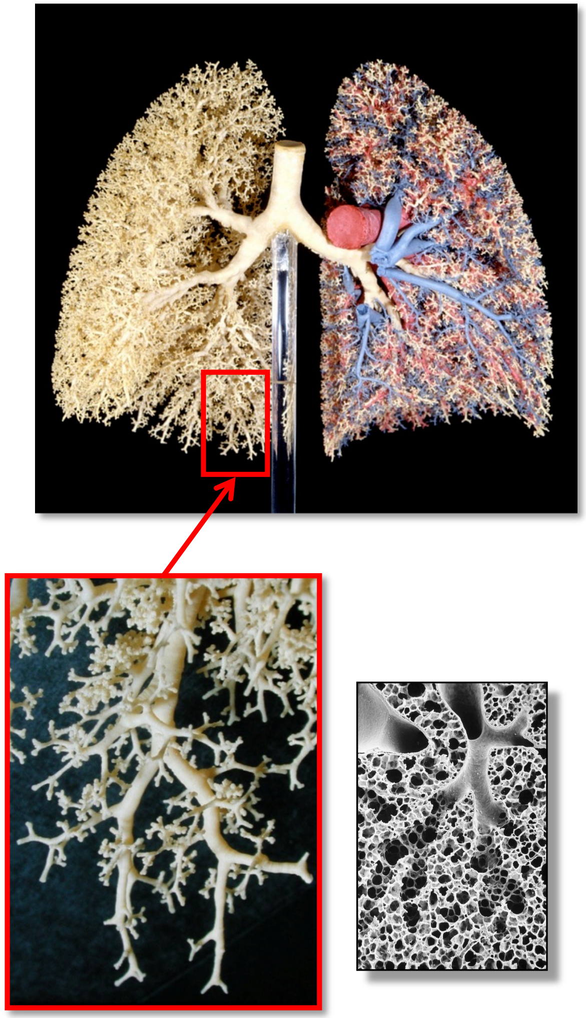
Pig lung

Pig front

Pig back

Pig zoom

Optimality of the pulmonary airway system?



What are the transport properties of this system?

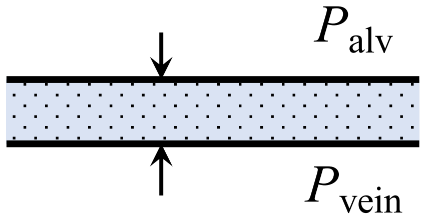
Why this shape and these dimensions?

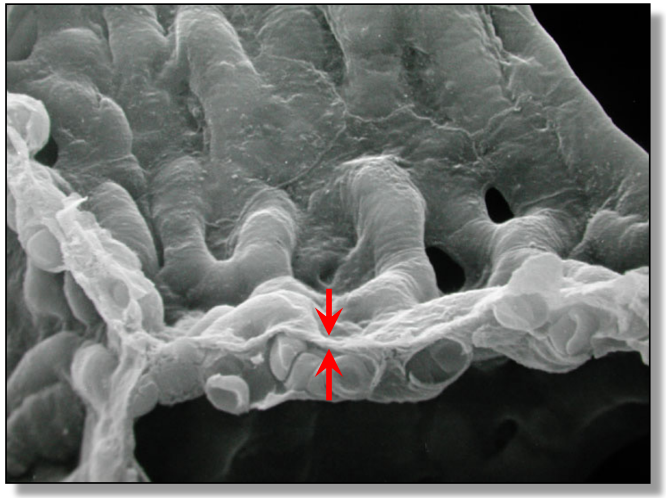
We observe the answer but…

what was the question?

Our needs in oxygen and the alveolo-capillar membrane

$$\boxed{\Phi = \frac{D}{\varepsilon} \times \beta\, \Delta P}$$





- D = diffusion constant of O_2 in water,
- ε = membrane thickness,
- β = Henry's constant,
- ΔP = O_2 partial pressure difference

$$\Phi = \frac{3.10^{-5}\,\text{cm}^2.\text{s}^{-1}}{1\,\mu\text{m}} \times 1{,}3.10^{-3}\,\text{mol.l}^{-1}.\text{atm}^{-1} \times \left(\frac{150-80}{760}\right)\text{atm}$$

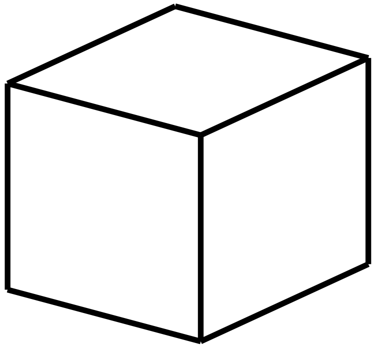
$$= \frac{3.10^{-5} \times 1{,}3.10^{-6}}{10^{-4} \times 10}\,\text{mol.cm}^{-2}.\text{s}^{-1} \approx \boxed{4.10^{-8}\,\text{mol.cm}^{-2}.\text{s}^{-1}}$$

$$V_{O_2,\max} \approx 40\ \text{ml.min}^{-1}.\text{Kg}^{-1}$$

$$\boxed{\frac{V_{O_2,\max} \times \dfrac{80}{60}}{\Phi \times 22{,}4.10^3} = \frac{40 \times 80}{60 \times 4.10^{-8} \times 22{,}4.10^3} \approx 60\ \text{m}^2\ !!}$$

Simple calculations

How to store 100 m^2 inside 10 L?



$$S \approx 6 \times (20\ \mathrm{cm})^2 = 0.24\ \mathrm{m}^2$$

$$\frac{100\ \mathrm{m}^2}{10\ \mathrm{L}} = \frac{1}{100\ \mu\mathrm{m}}$$

Air velocity of air from the trachea to the alveoli

Cross-section: from $3\ \mathrm{cm}^2$ to $100\ \mathrm{m}^2$: $\dfrac{100}{3(0.01)^2} \approx 300,000$

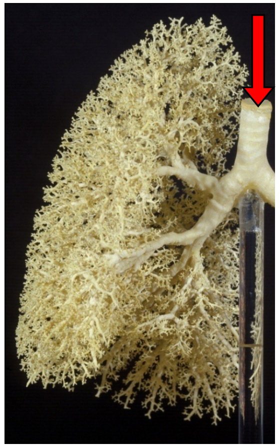
Air velocity: from $1\ \mathrm{m}\cdot\mathrm{s}^{-1}$ to $3.10^{-6}\ \mathrm{m}\cdot\mathrm{s}^{-1} = 3\ \mu\mathrm{m}\cdot\mathrm{s}^{-1}$

Limited time ⇒ diffusion of oxygen in air

Oxygen transfer in the lung

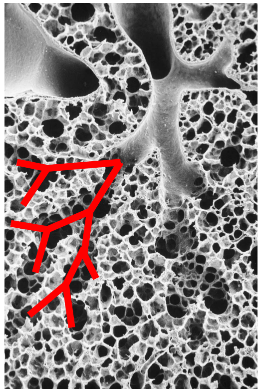
The journey of oxygen into the lung airway system

lung O_2



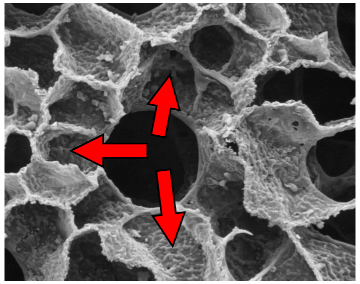
10 cm

acinus



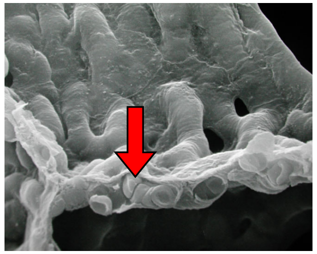
1 mm

alveolus



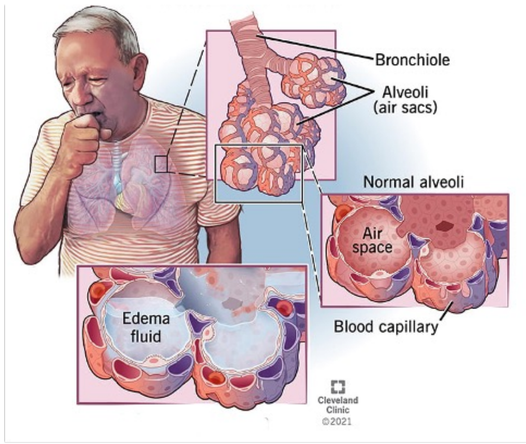
250 μm

alveolo-capillary membrane



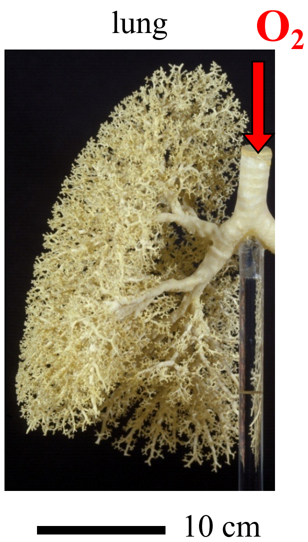
10 μm

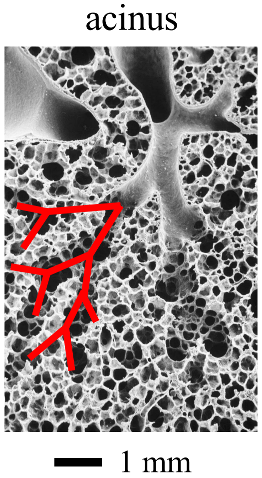
Pulmonary edema: fluids in the air space

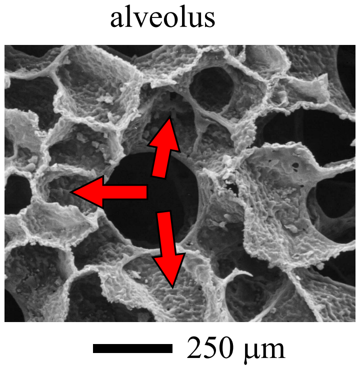


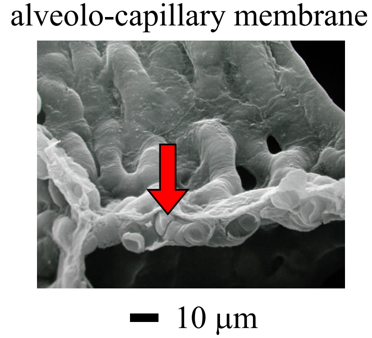
Oxygen transfer in the lung: a Robin boundary condition problem

The journey of oxygen into the lung airway system

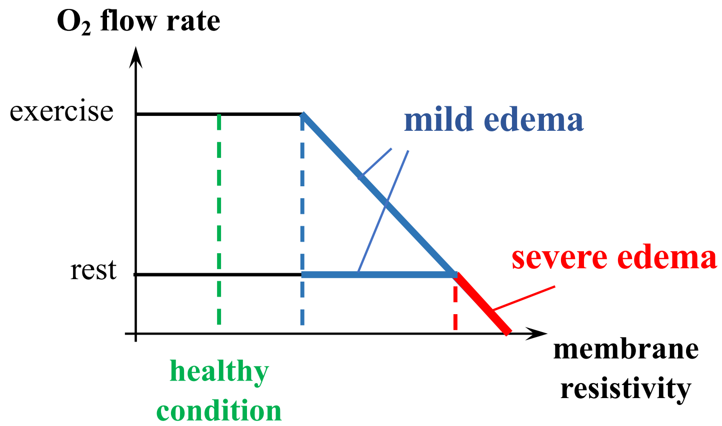


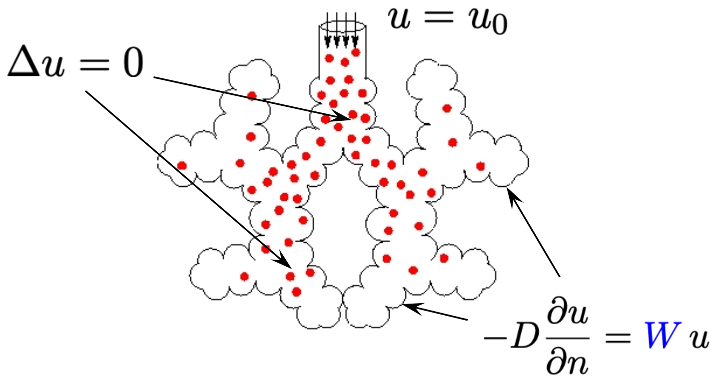






Oxygen diffusion inside the acinus

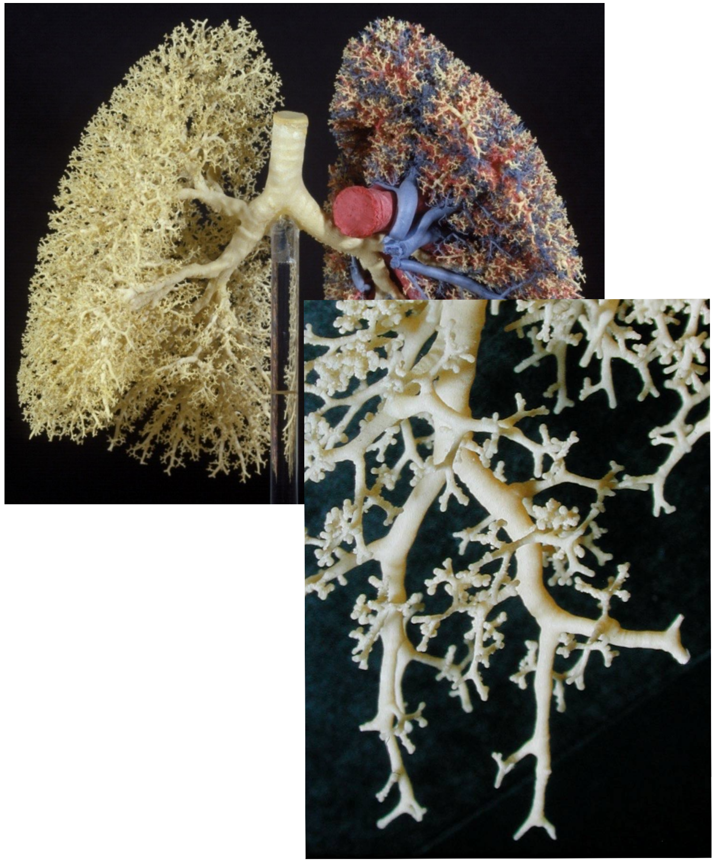


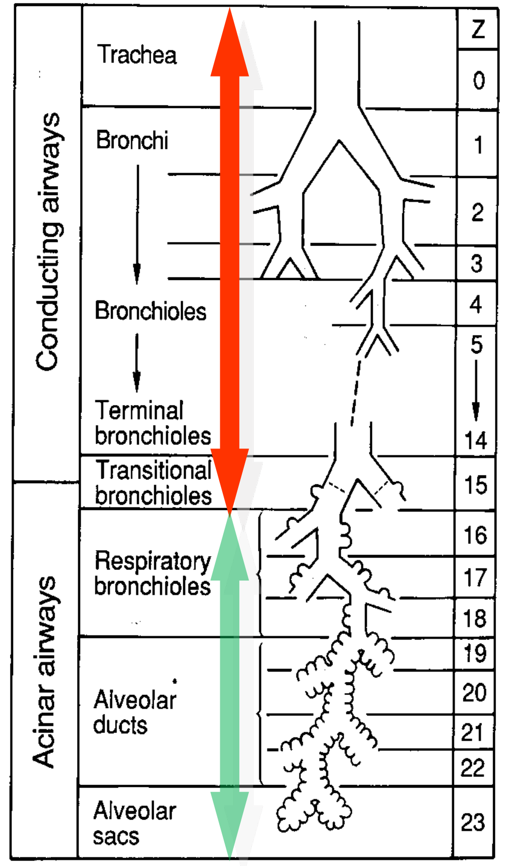


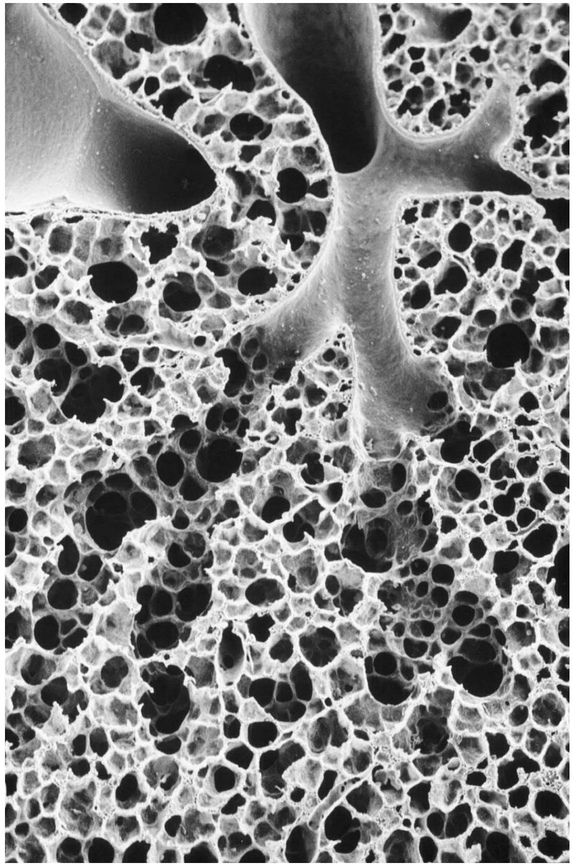
The conduction zone

Gen. 0 — 15, conduction

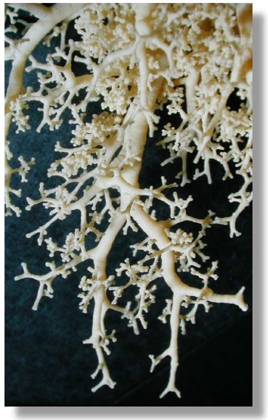
Gen. 16 — 23, respiration





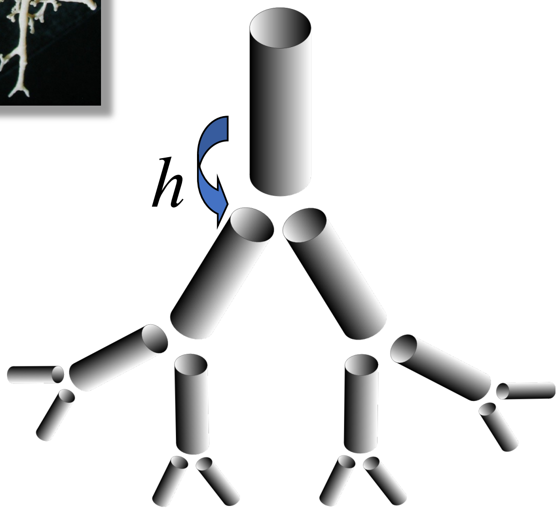


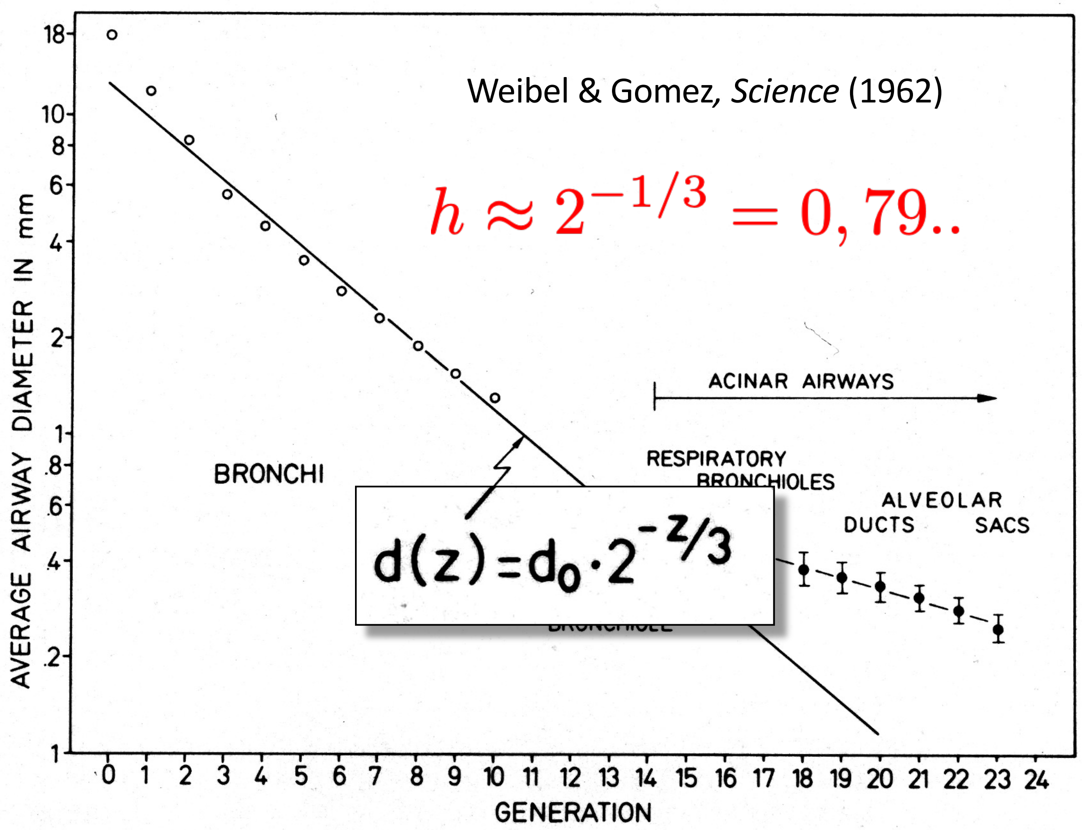
The bronchial geometry: a self-similar dichotomous tree



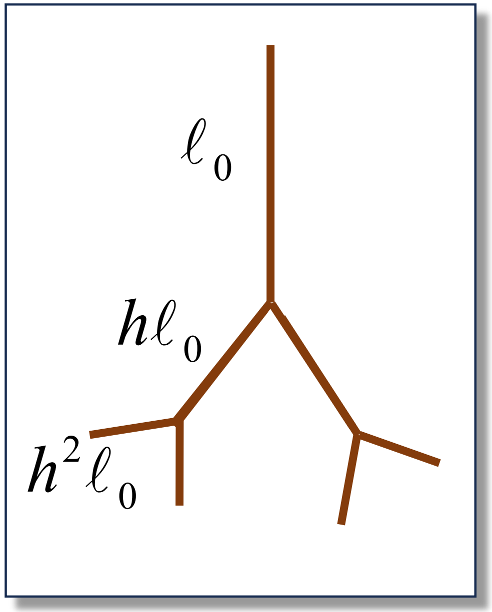
$$\boxed{D_n = h^n D_0}$$

$$\ln D_n = n \ln(h) + \ln(D_0)$$





The fractal dimension of the self-similar bronchial tree



$$L = \sum_{n=0}^{+\infty} 2^n \ell_n = \sum_{n=0}^{+\infty} 2^n h^n \ell_0 = \ell_0 \sum_{n=0}^{+\infty} (2h)^n$$

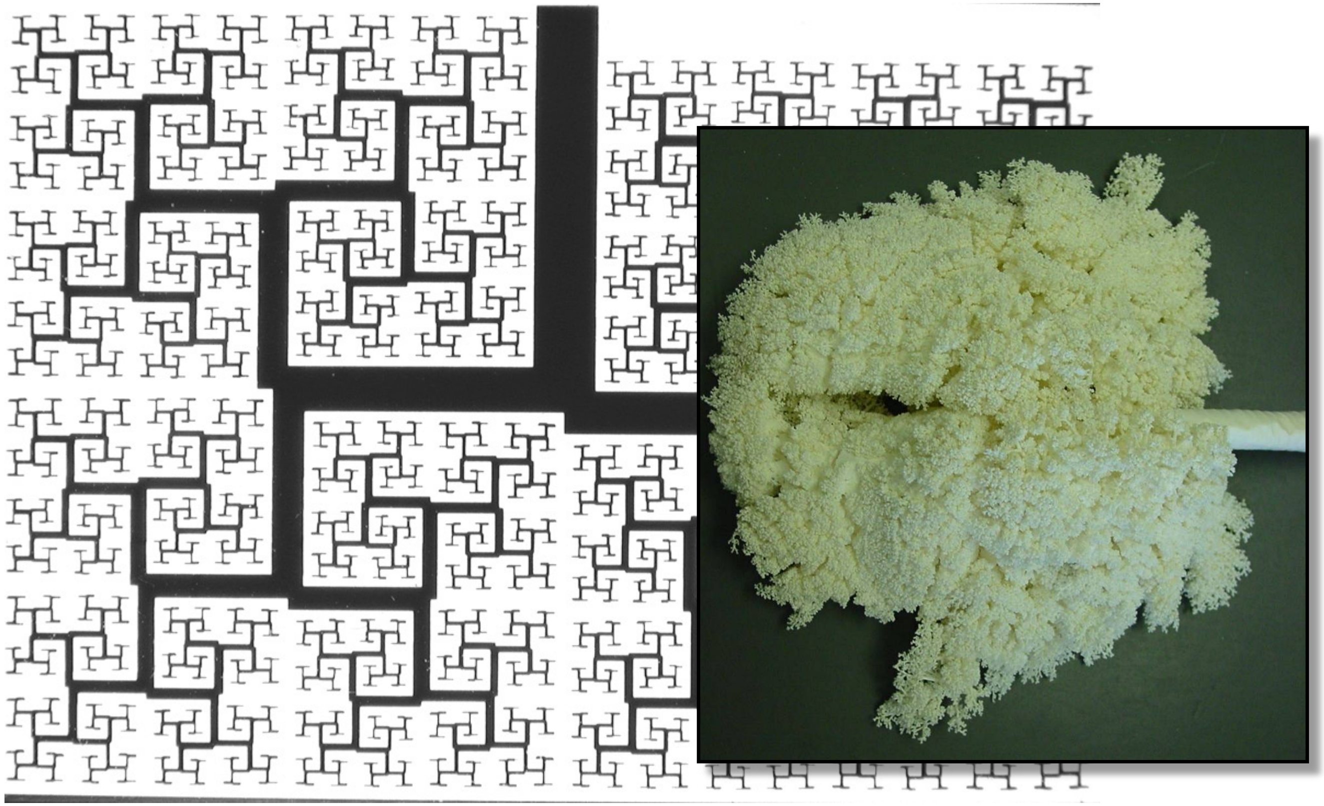
$$2 = \left(\frac{1}{h}\right)^D \qquad D = \frac{\ln(2)}{\ln\left(\frac{1}{h}\right)}$$

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

The bronchial tree is space-filling

The tracheobronchial geometry: the fractal model

From bronchi down to the terminal bronchioles



Benoit Mandelbrot 1977

Transport equations for incompressible flows

Navier-Stokes equation

$$\rho \left\{ \frac{\partial \vec{u}}{\partial t} + \left(\vec{u} \cdot \vec{\nabla} \right) \vec{u} \right\} = -\vec{\nabla} P + \eta \Delta \vec{u} + \vec{f}$$

Mass conservation

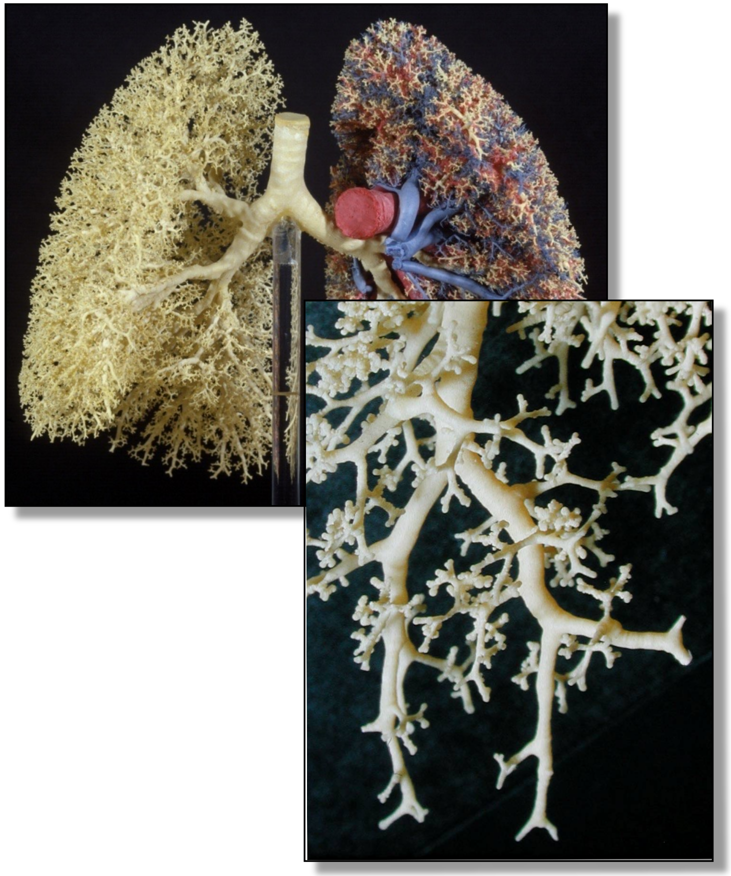
$$\operatorname{div} \vec{u} = 0$$

Reynolds number

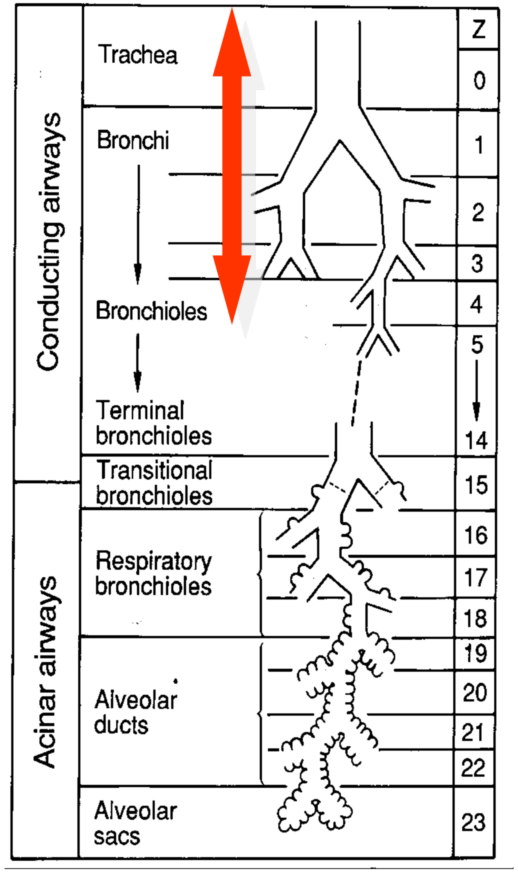
$$\boxed{\mathrm{Re} = \frac{\rho U L}{\eta}}$$

Convective inertial flow

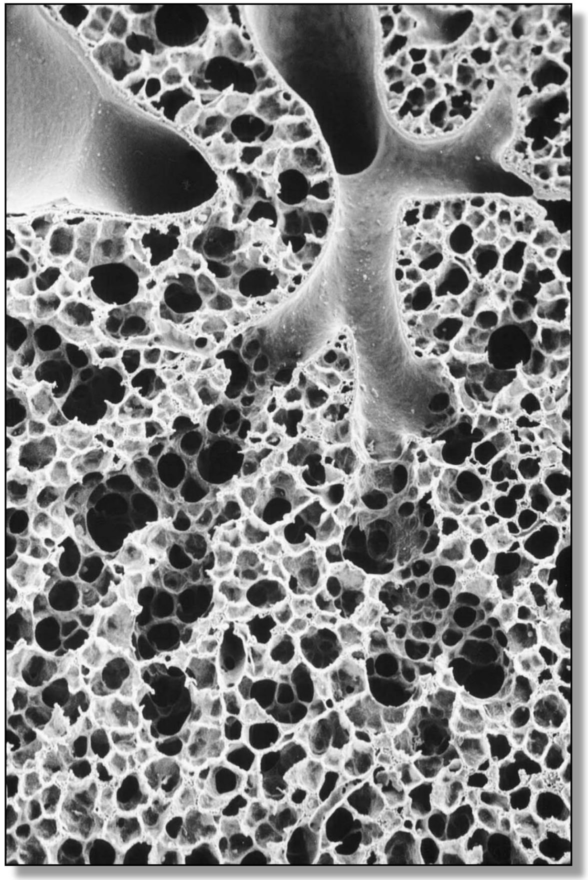
Gen. 0 — 15, conduction



Inertial flow

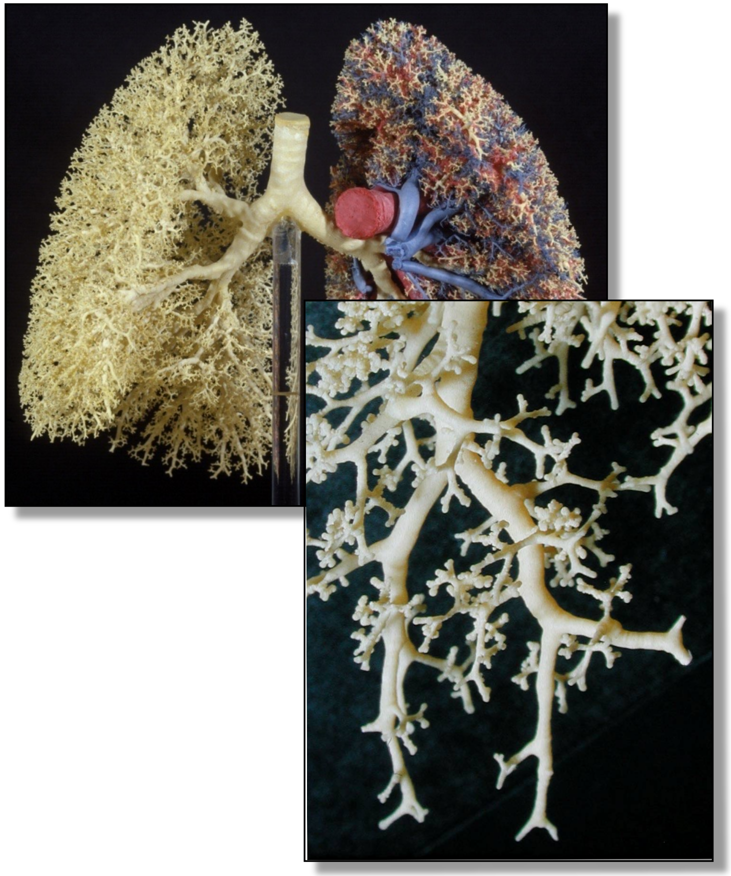


Gen. 16 — 23, respiration

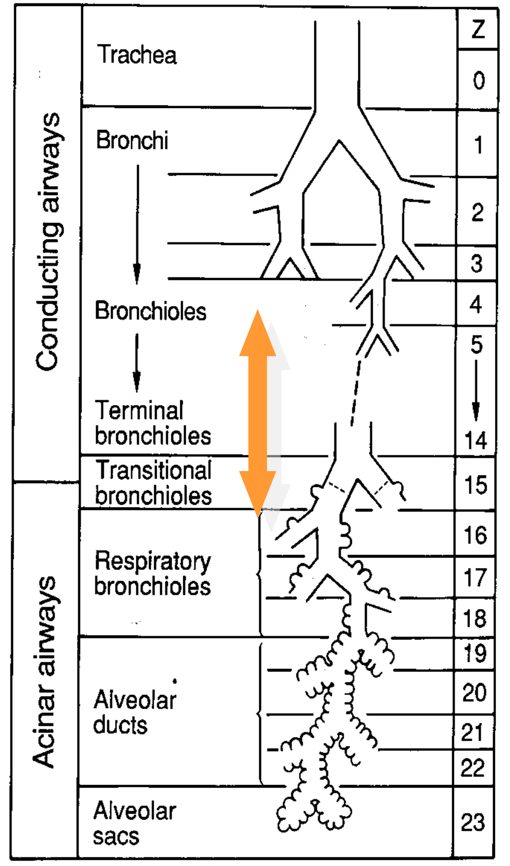


Non-inertial flow: the intermediate tree

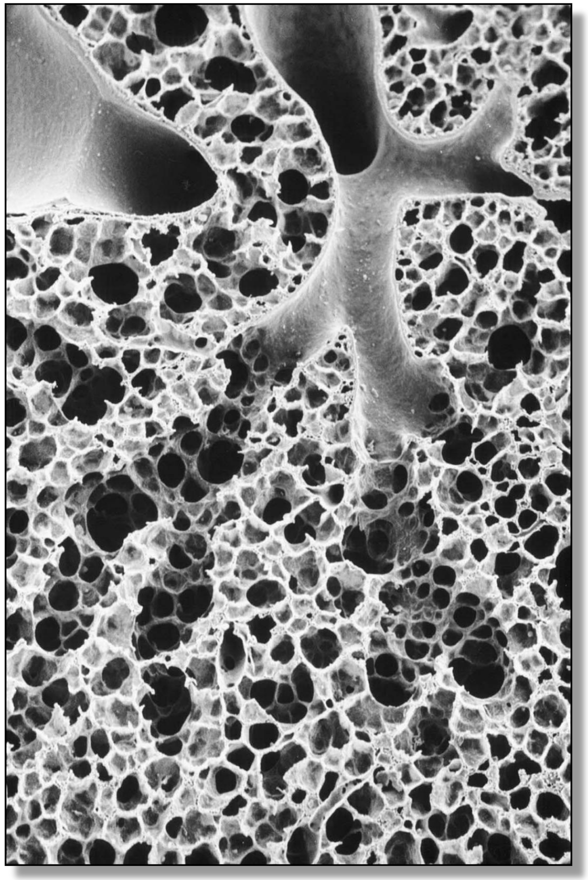
Gen. 0 — 15, conduction



Non-inertial flow



Gen. 16 — 23, respiration



Transport equations for incompressible flows

Navier-Stokes equation

$$\rho \left\{ \frac{\partial \vec{u}}{\partial t} + \left(\vec{u} \cdot \vec{\nabla} \right) \vec{u} \right\} = -\vec{\nabla} P + \eta \Delta \vec{u} + \vec{f}$$

Mass conservation

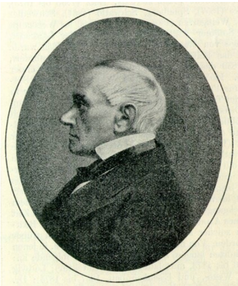
$$\mathrm{div}\, \vec{u} = 0$$

Reynolds number $\boxed{\mathrm{Re} = \dfrac{\rho U L}{\eta}}$

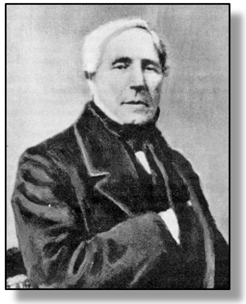
Non-inertial flow: the Stokes equation

$$-\vec{\nabla} P + \eta \Delta \vec{u} = 0$$

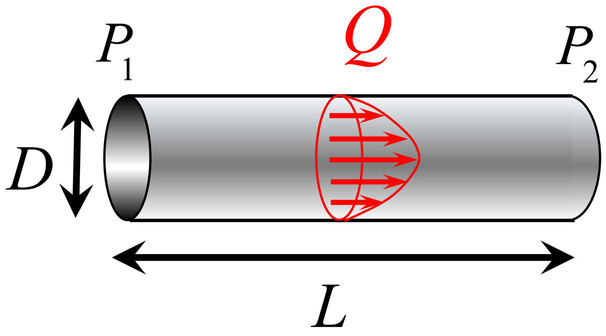
The Hagen-Poiseuille flow (steady-state, laminar)



Gotthilf Hagen
(1797 – 1884)



Jean Léonard Marie Poiseuille
(1797 – 1869)



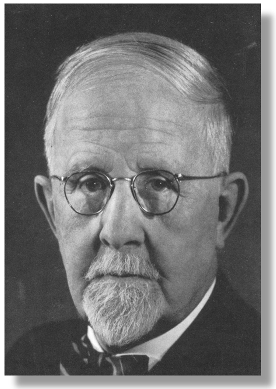
$$-\vec{\nabla} P + \eta \Delta \vec{u} = 0$$

$$Q = \frac{P_1 - P_2}{R_H} = \left(\frac{\pi}{128\eta} \frac{D^4}{L} \right) \left(P_1 - P_2 \right)$$

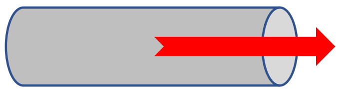
Airway resistance: $R_H = \frac{128\eta}{\pi} \frac{L}{D^4}$

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

The Murray-Hess law



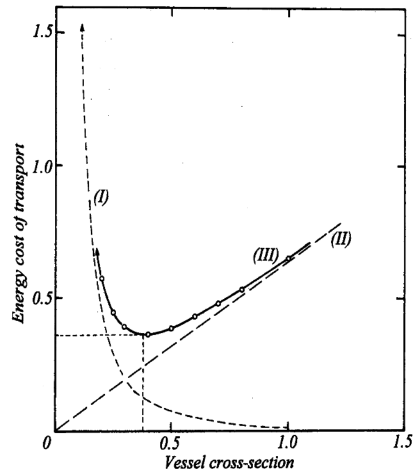
Walter Rudolf Hess

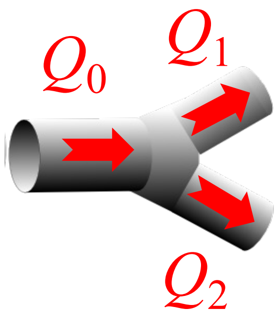


Minimizing the energetic consumption for a given flow rate Q

$$\varepsilon = \alpha V + R_H Q^2 = \alpha L D^2 + \beta \frac{L}{D^4} Q^2$$

$$0 = 2\alpha L D - 4\beta \frac{L}{D^5} Q^2 \qquad D^3 \propto Q \text{ !!}$$





One bifurcation

$$Q_0 = Q_1 + Q_2$$

Symmetrical

$$D_1 = D_2$$

$$\boxed{D_0^3 = D_1^3 + D_2^3}$$

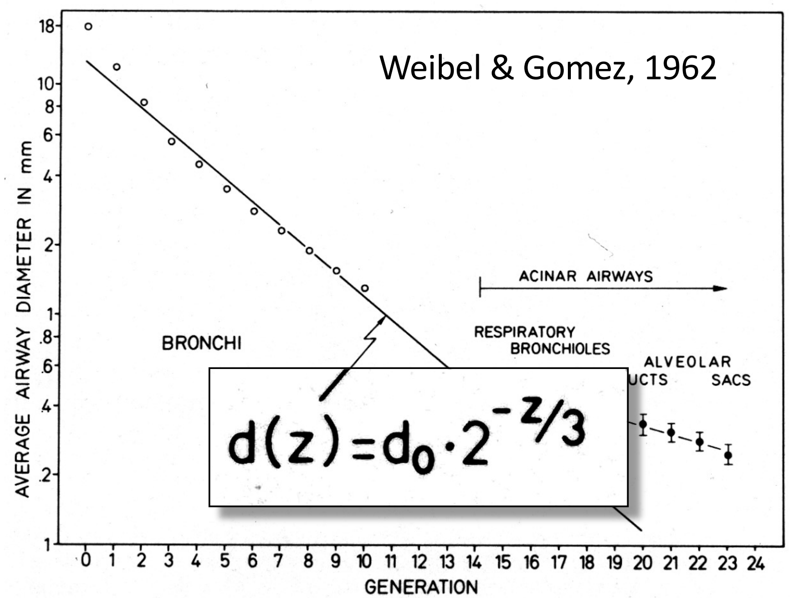
$$\boxed{h_c = \frac{D_1}{D_0} = 2^{-1/3} \approx 0.79}$$

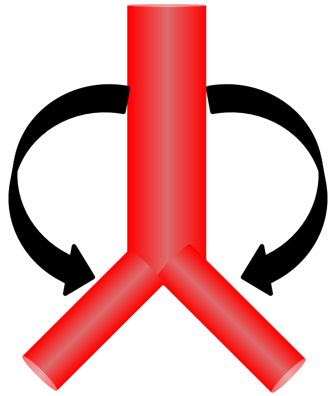
W.R.Hess, 1917 ; C.D. Murray, 1927; T.F. Sherman, 1981

Simplest model of the tracheobronchial tree

Weibel's symmetric model

- Cylindrical pipes
- Self-similarity: constant diameter ratio
- Dichotomous and symmetric branching



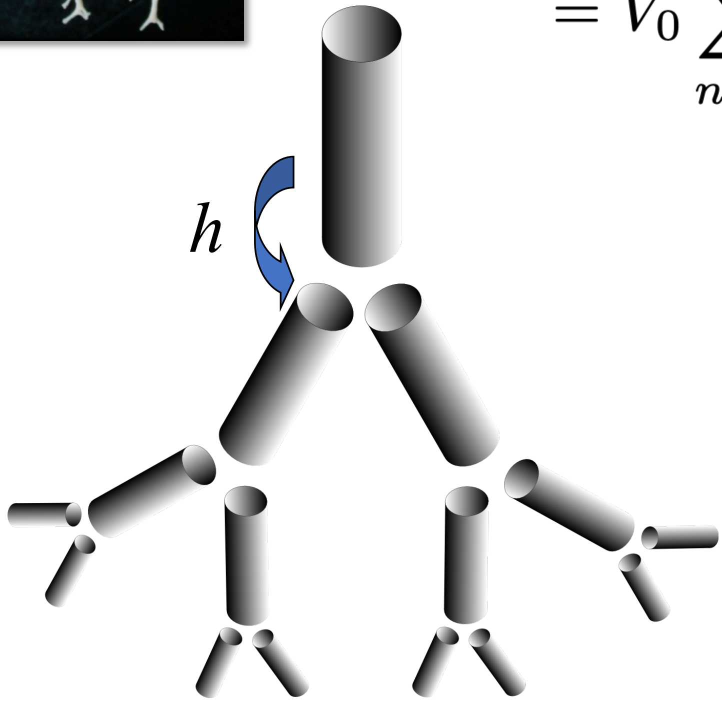


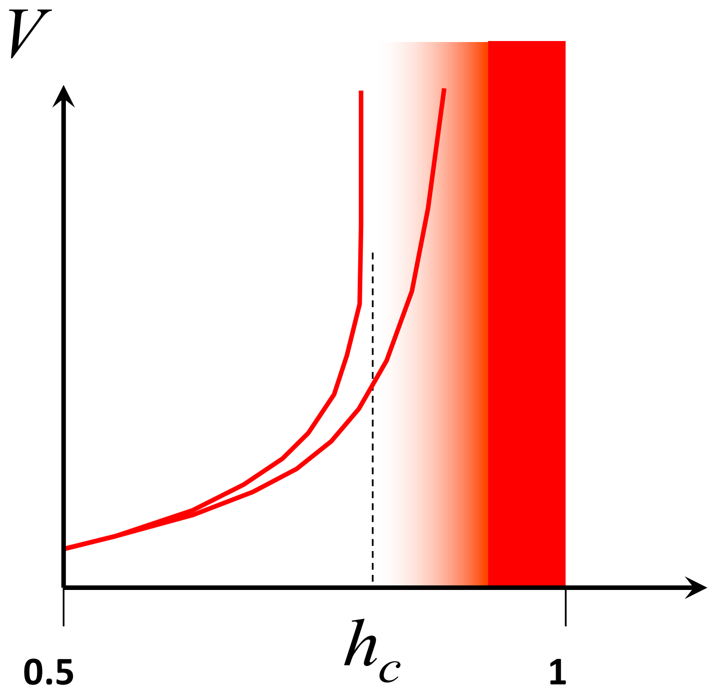
$$h_0 = \frac{D_{n+1}}{D_n}$$

The volume of the tracheobronchial tree: dead space volume

$$V = \sum_{n=0}^{+\infty} 2^n V_n = \sum_{n=0}^{+\infty} 2^n \frac{\pi}{4} D_n^2 L_n = \frac{\pi}{4} \sum_{n=0}^{+\infty} 2^n (h^2)^n D_0^2\, h^n L_0$$

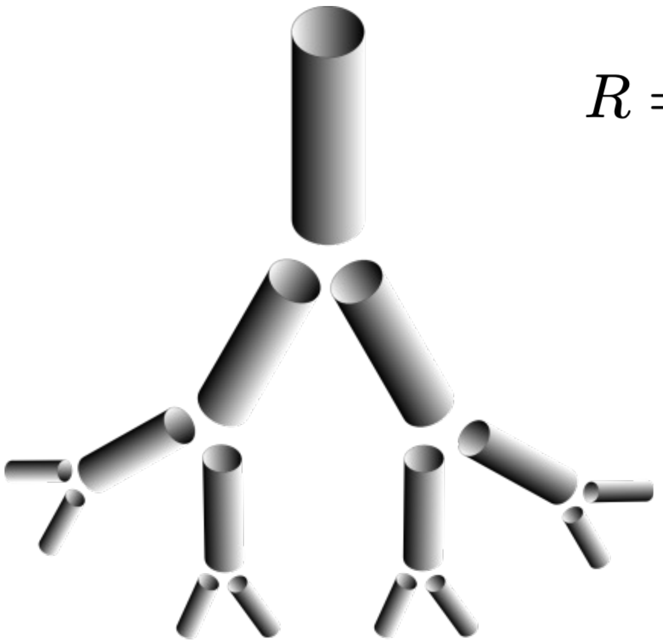
$$= V_0 \sum_{n=0}^{+\infty} (2h^3)^n$$



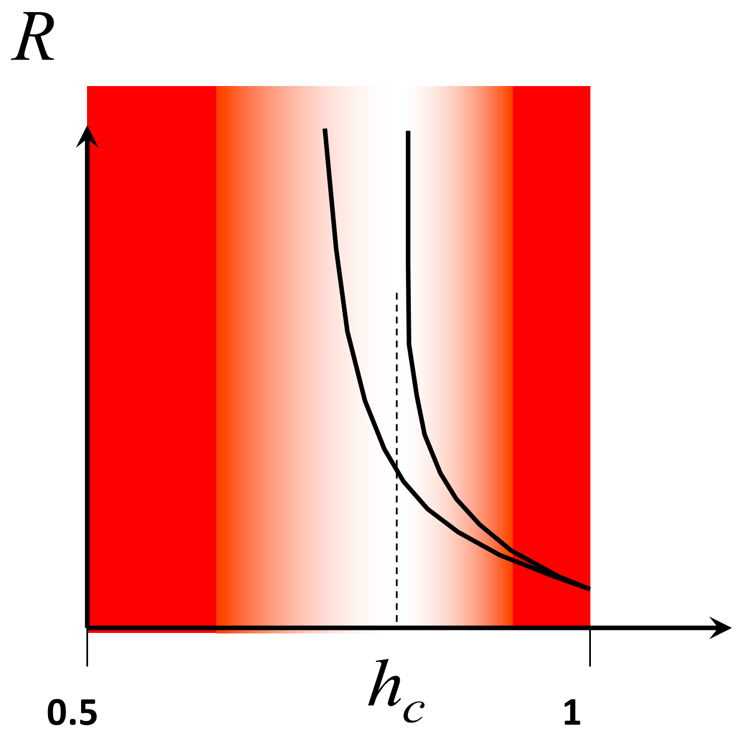


The total hydrodynamic resistance of the tree

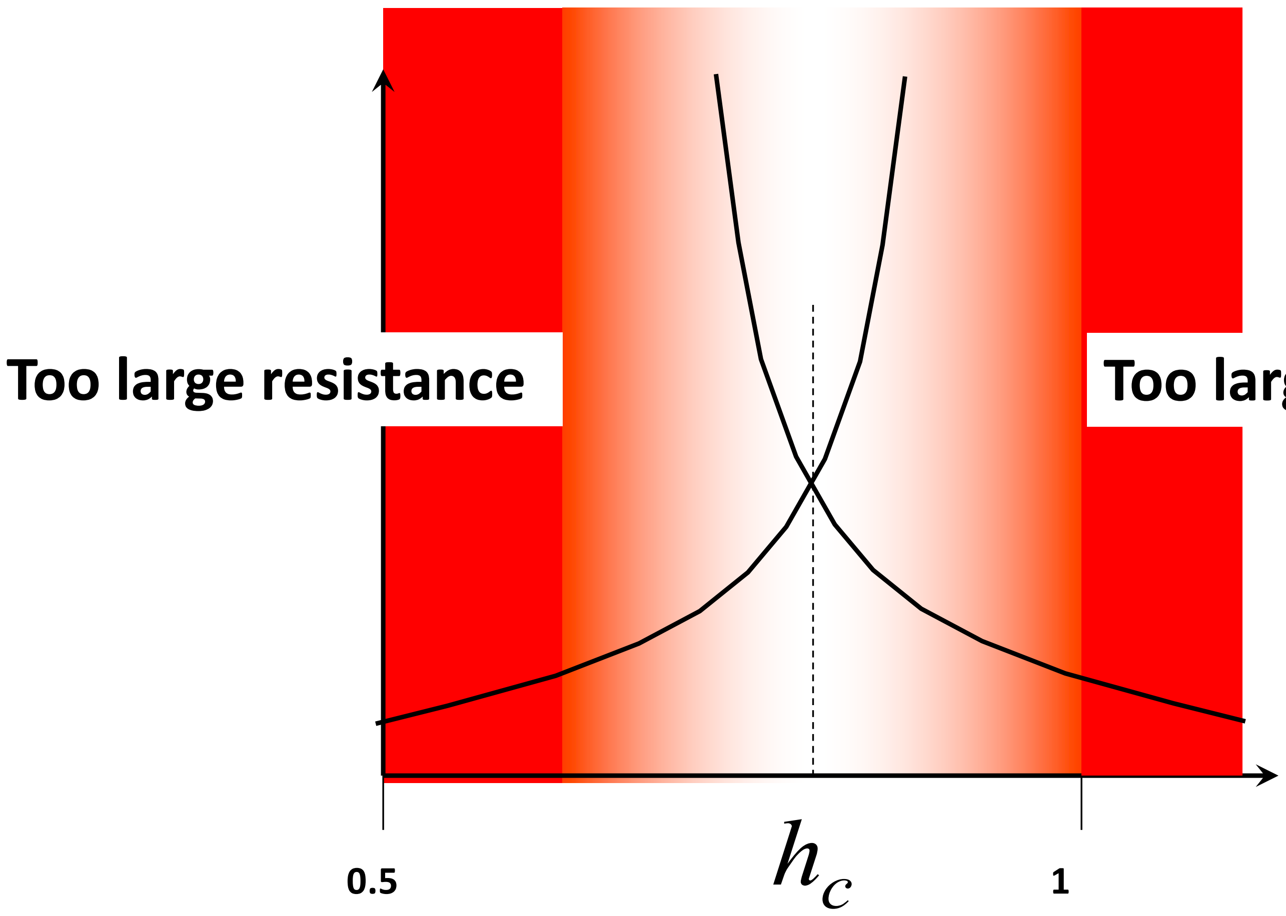
$$R = \sum_{n=0}^{+\infty} \frac{1}{2^n} R_n = \sum_{n=0}^{+\infty} \frac{1}{2^n} \alpha \frac{L_n}{D_n^4} = R_0 \sum_{n=0}^{+\infty} \frac{1}{(2h^3)^n}$$



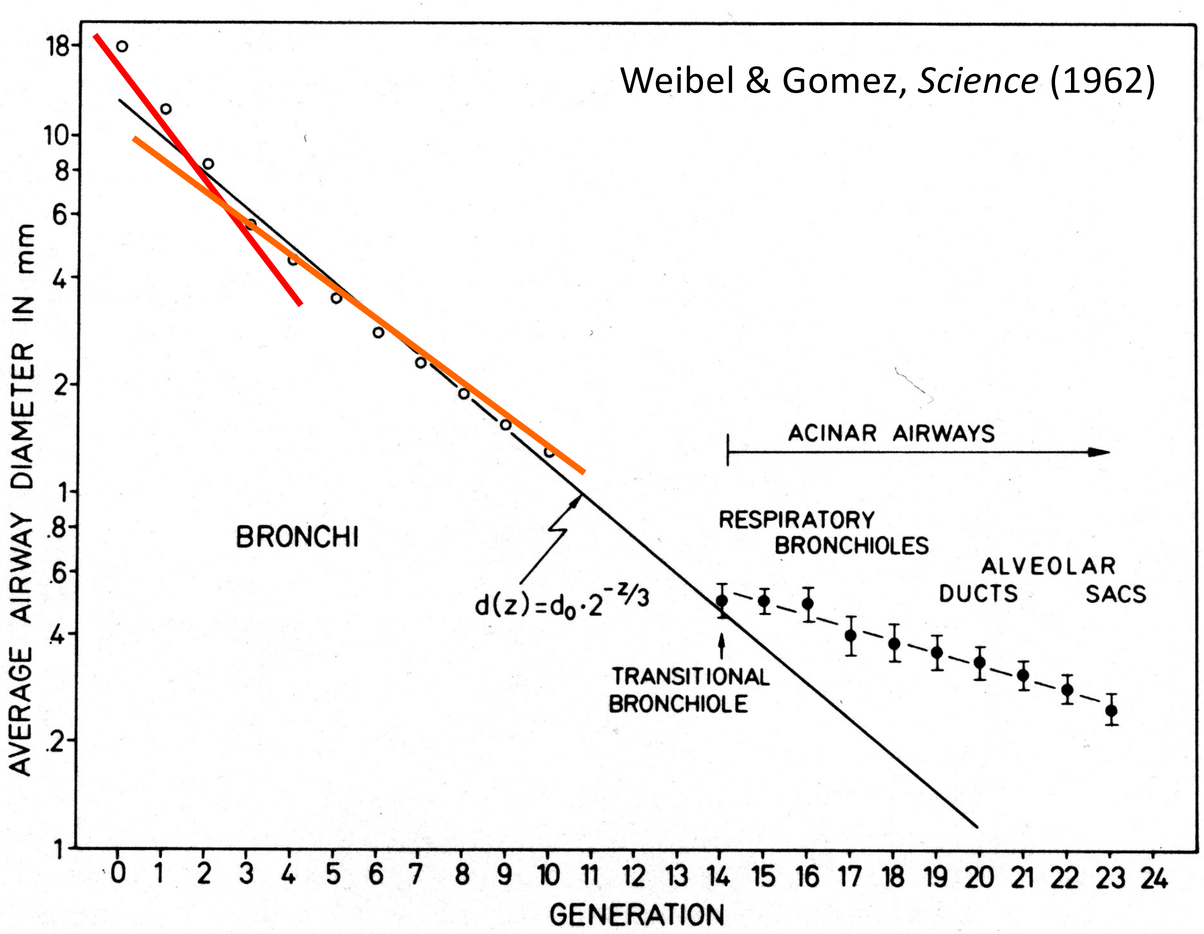
$$Q = \Delta P \left(\frac{\pi D^4}{128 \eta L} \right)$$



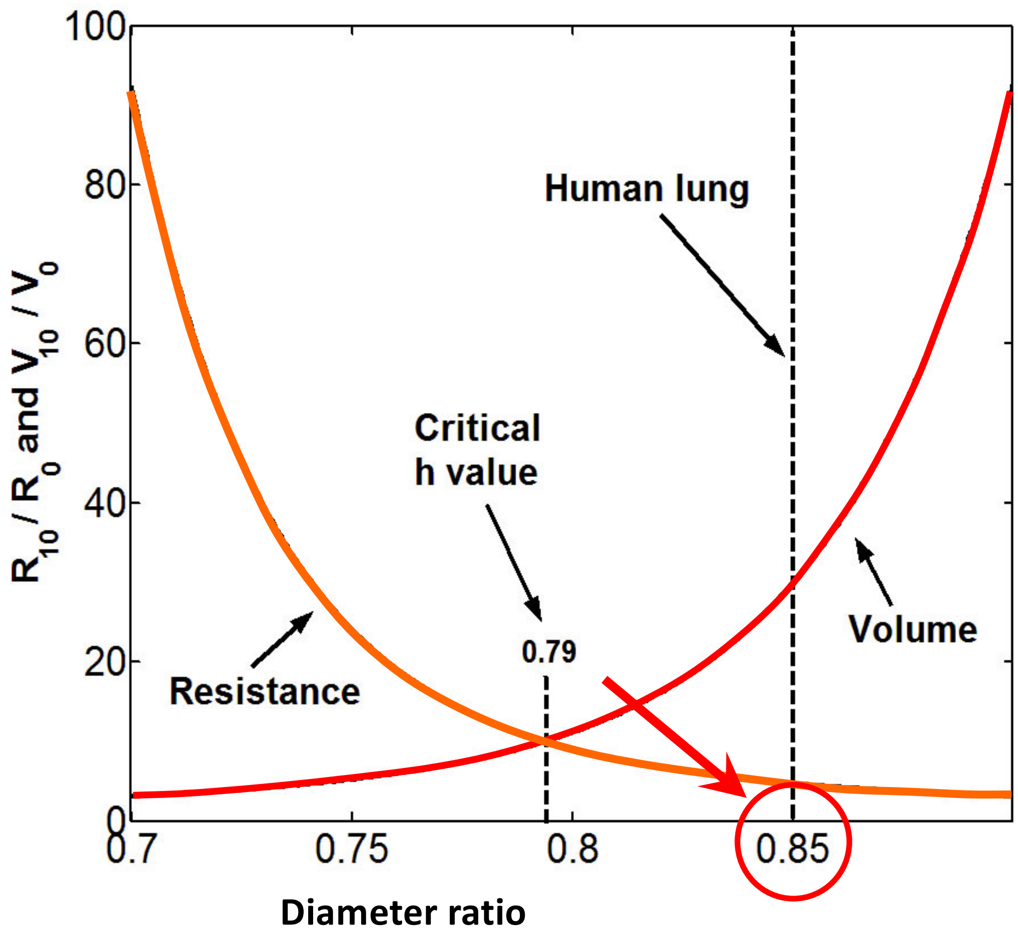
Fluidic distribution tree: a highly constrained system



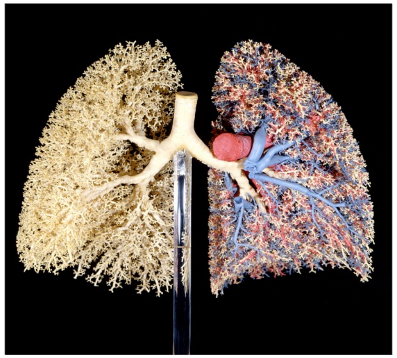
Actual scaling in the human bronchial tree



The lung is close to the optimal value of $h = 2^{-1/3}$



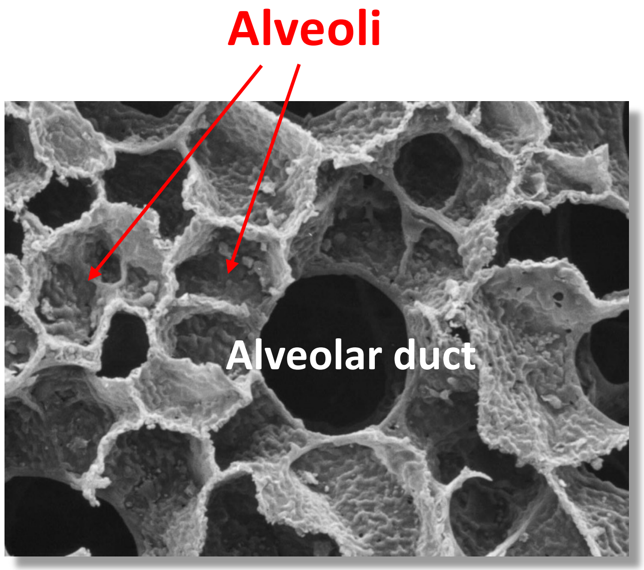
Mauroy, MF, Weibel, Sapoval, *Nature* (2004)



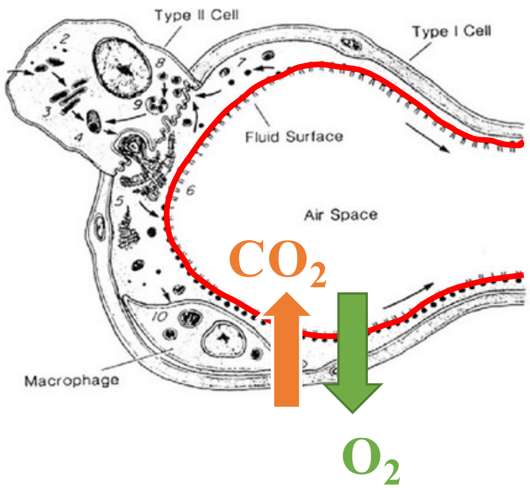
The fractal structure of the lung airway system is optimized for gas transport

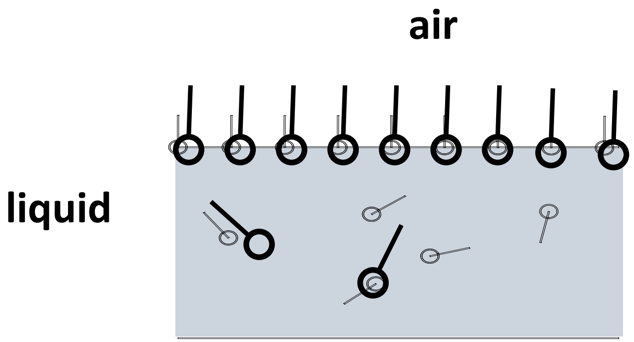
What about liquids?

Surfactant lining on the alveolar membrane



Surfactant is produced in Type II cells

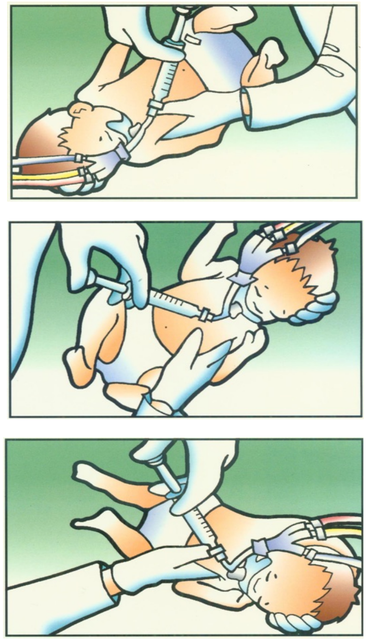




Surfactants at the interface
reduce surface tension

Neonatal Respiratory Distress Syndrome (NRDS)

- 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 births ~ **40,000 cases** annually in the US.

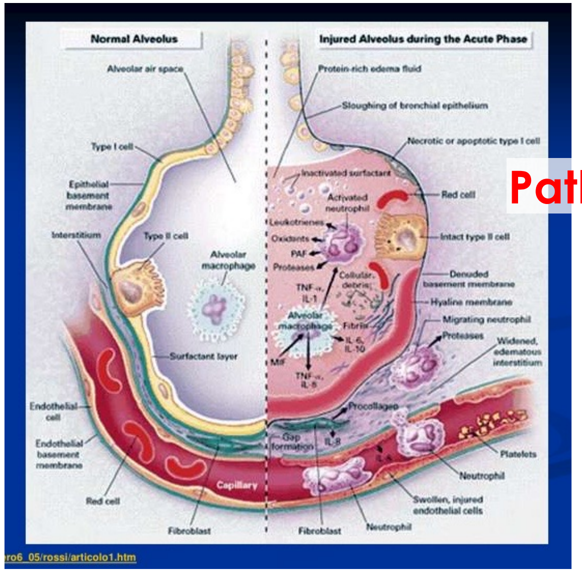


Surfactant Replacement Therapy (SRT)

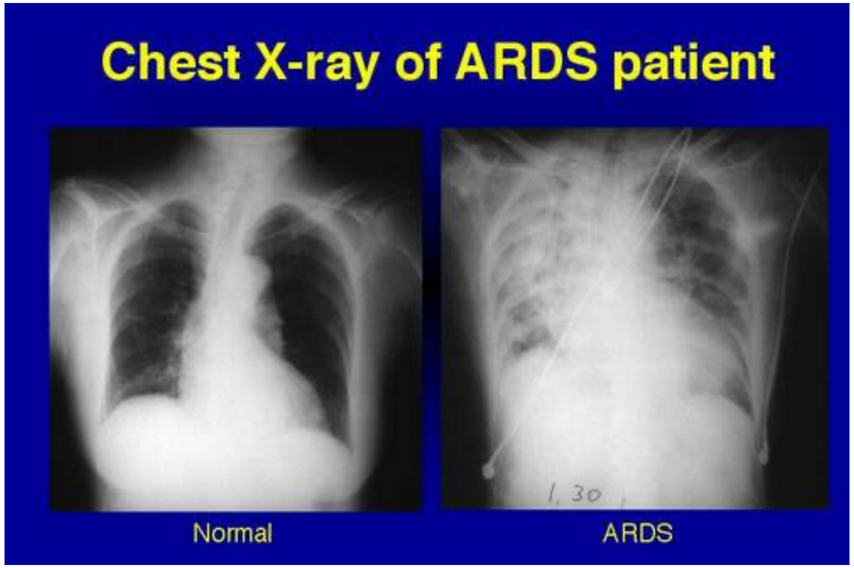
- Mortality dropped from **4,997 deaths** (1980) to **861** (2005)
- SRT played **a major role** in this decrease of mortality
- Survivors have still high incidence of bronchopulmonary dysplasia (BPD)

Acute Respiratory Distress Syndrome (ARDS)

Healthy



Pathological



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 with ARDS

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

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

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

Why this "failure" of SRT in adults?

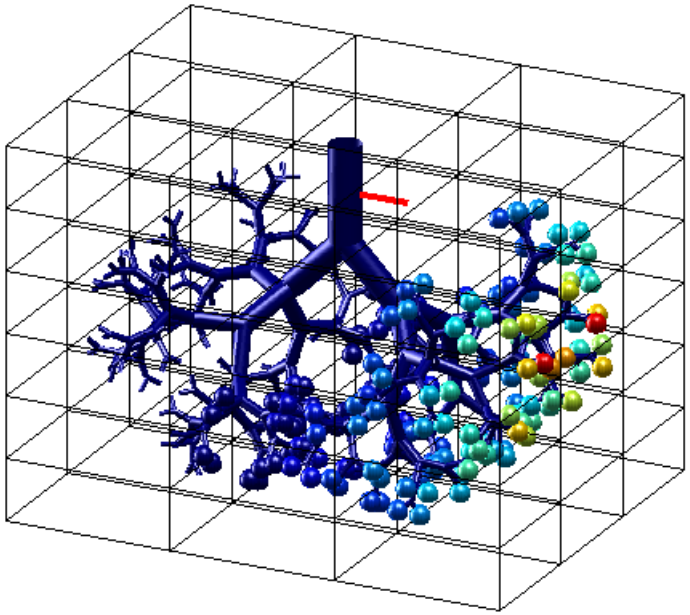
"Exogenous surfactant replacement in ARDS - One day, someday, or never?"

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.

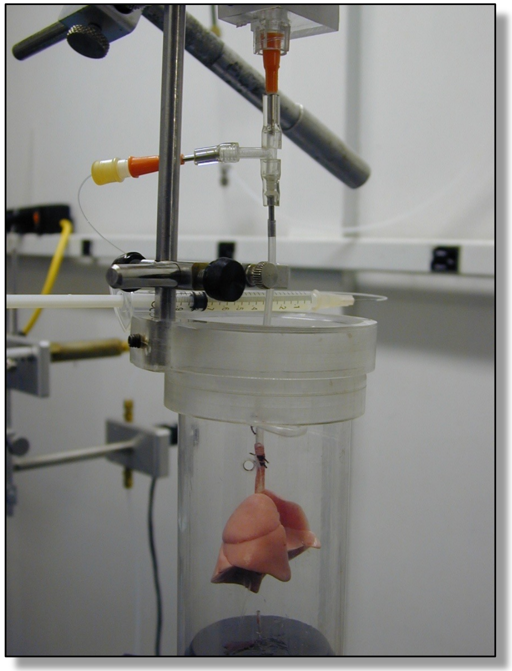
Modeling SRT

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



Surfactant instillation – lung close-up

- The excised lung is 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)

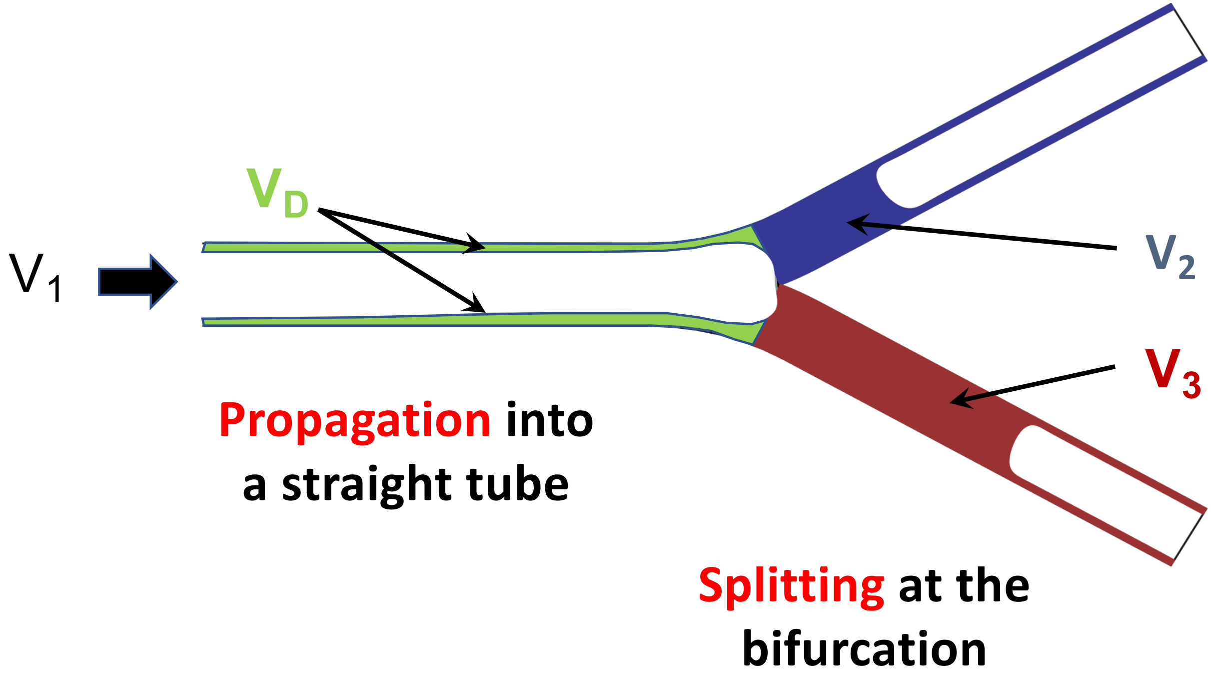
Experimental Conditions

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

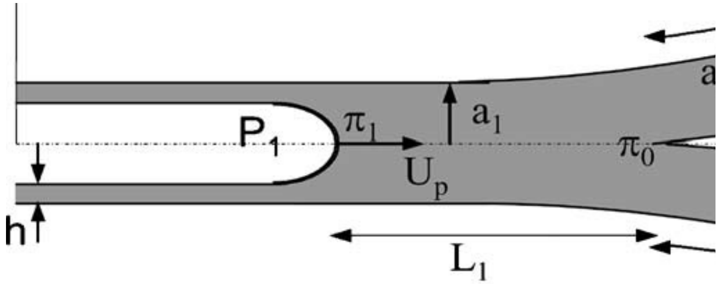
Propagation of a liquid plug into the tree

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

The process can be decomposed into two elementary steps:



Liquid deposition onto the airway walls



Capilllary number

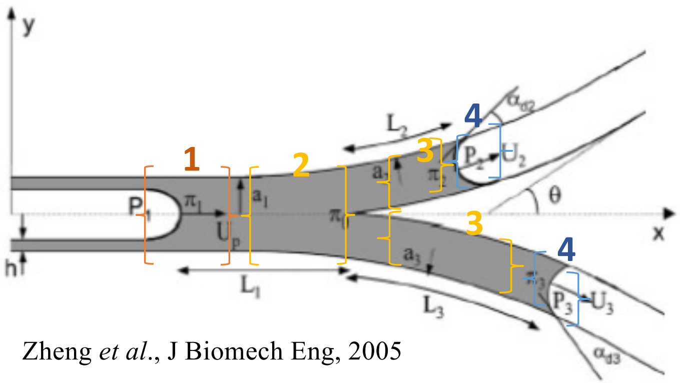
$$Ca = \frac{\mu U_P}{\sigma}$$

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

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

Larger flow rate ⇒ increased deposition

Computing the plug splitting at each bifurcation



Zheng *et al*., J Biomech Eng, 2005

a: tube radius
σ: liquid surface tension
μ: liquid viscosity
Q: flow rate
V: plug volume
ρ: liquid density
g: gravitational acceleration
i: 1, parent tube
i,j: 2,3, lower daughter and upper daughter tubes

- Pressure drop across the rear meniscus (Young-Laplace law).

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

- Pressure drop in the parent and daughter branches: viscous (Poiseuille) drop + hydrostatic pressure + kinetic term.

$$\pi_0 - \pi_i = \frac{8\mu L_i}{\pi a_i^4} Q_i + \rho g\left[\sin\theta_i \sin\varphi - \cos\theta_i \sin\gamma\right] L_i + \frac{1}{2}\rho\left(\frac{Q_j}{\pi a_j^2}\right)^2 - \frac{1}{2}\rho\left(\frac{Q_i}{\pi a_i^2}\right)^2$$

- Pressure drops across the front meniscus in daughters 2 and 3.

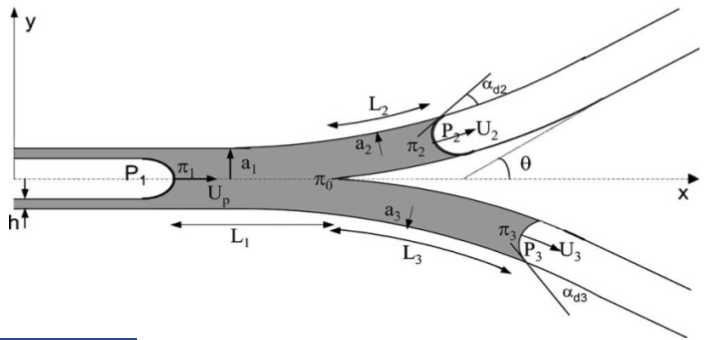
$$\pi_2 - P_2 = -\frac{2\sigma}{a_2}, \quad \pi_3 - P_3 = -\frac{2\sigma}{a_3}$$

Reducing the complexity

Navier-Stokes equation + mass conservation

$$\rho\left\{\frac{\partial\vec{u}}{\partial t}+\left(\vec{u}\cdot\vec{\nabla}\right)\vec{u}\right\}=-\vec{\nabla}P+\eta\Delta\vec{u}+\vec{f}$$

$$\operatorname{div}\vec{u}=0$$



Zheng *et al.*, J Biomech Eng 2005

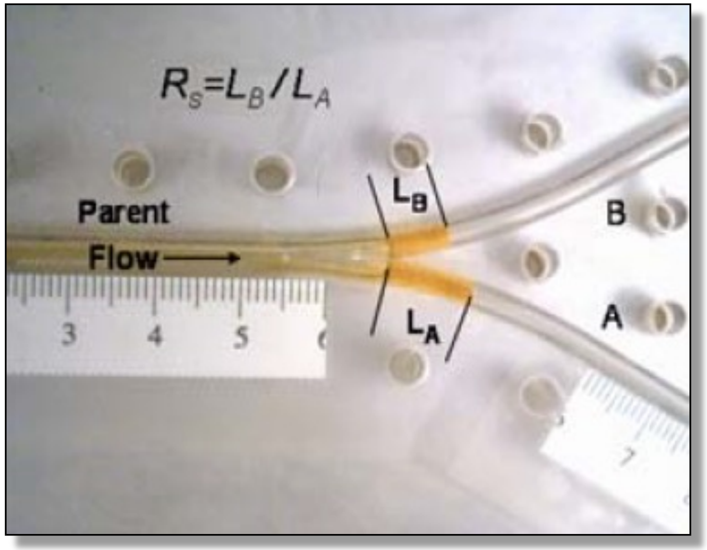
$$\left(\frac{8\mu\left(\pi a_1^2\frac{\sigma}{\mu}Ca\right)\alpha}{\pi a_2^4}-\frac{\sigma\,Bo}{a_1^2}\left(\sin\theta_2\sin\varphi+\cos\theta_2\sin\gamma\right)\right)\left(\frac{V_0-V_c}{\pi a_2^2}\right)\alpha-\frac{2\sigma}{a_2}$$

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

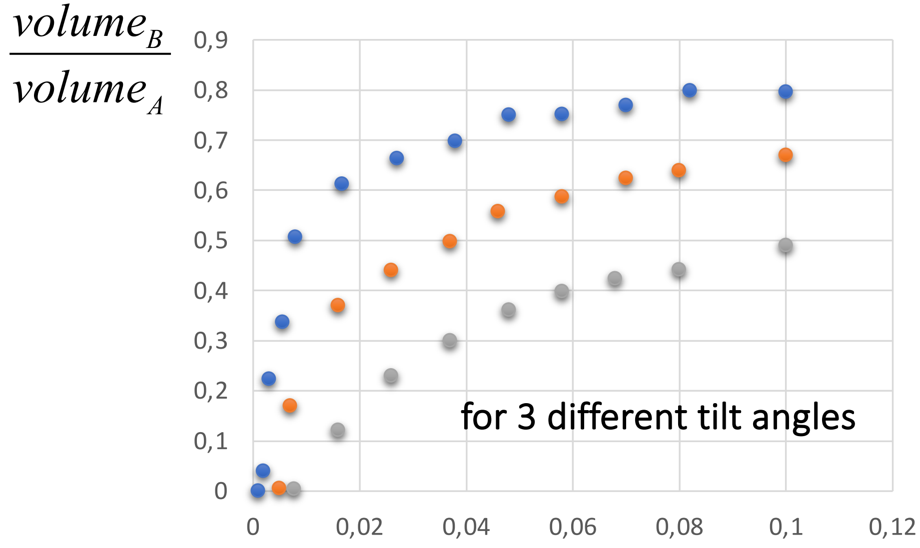
$$V_2=\alpha V_1$$

$$V_3=(1-\alpha)V_1$$

Plug splitting at a bifurcation



Zheng *et al.*, *J Biomech Eng* 2005



$$Ca = \frac{viscosity \times velocity}{surface\ tension}$$

The plug tends to follow gravity

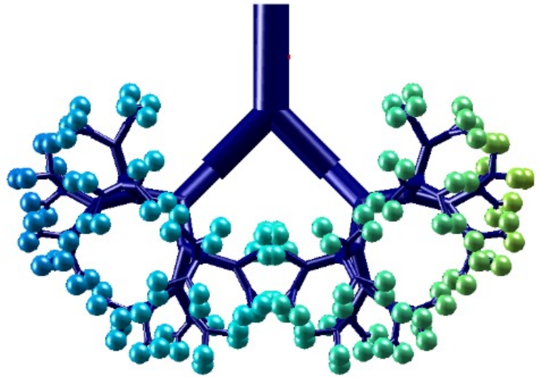
Larger flow rate ⇒ more homogeneous splitting

Schematic of the model

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

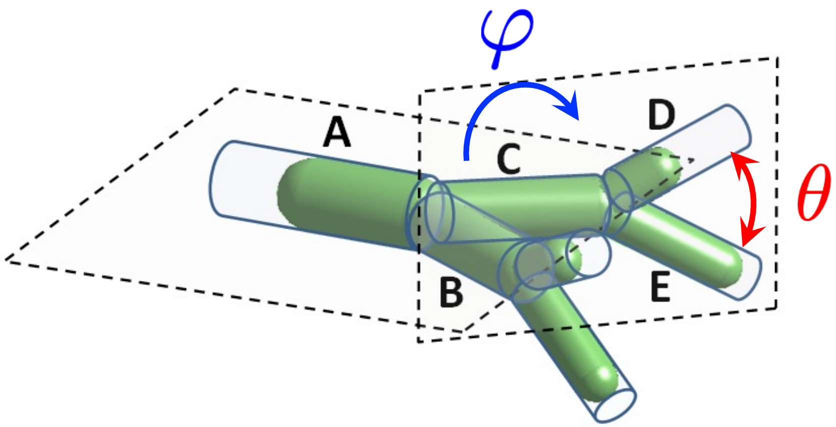
Delivery conditions

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

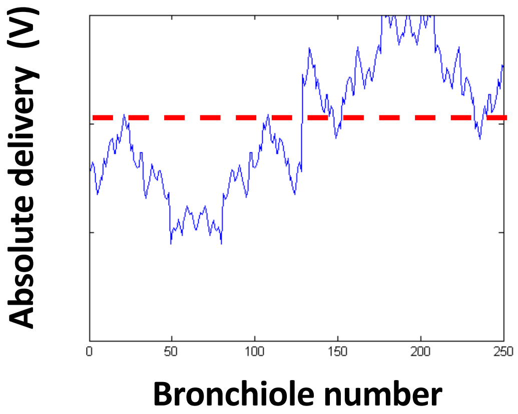


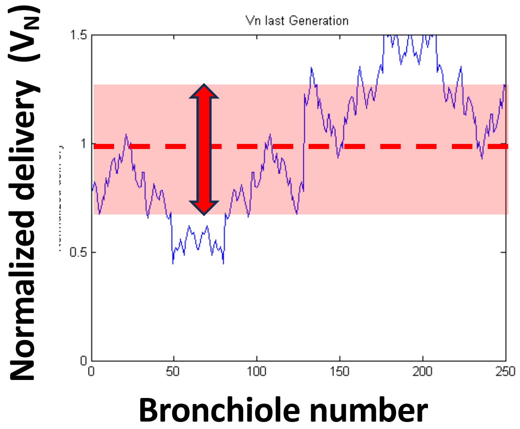
Geometrical model of the tracheobronchial tree

Each airway is characterized by	**Diameter**	$D_{n+1} = 2^{-1/3}\, D_n$
	Length	$L = 3D$
All bifurcations are coplanar and characterized by	**Rotation angle**	$\varphi = \dfrac{\pi}{2}$
	Branching angle	$\theta = \dfrac{\pi}{3}$



Characterizing the performance of the delivery





$$V_N(i) = \frac{V_i}{\langle V \rangle}$$

Efficiency (%) $$= 100 \sum_{i=1}^{N} \frac{V_i}{V_0}$$

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

Higher velocity → Higher homogeneity, Lower efficiency

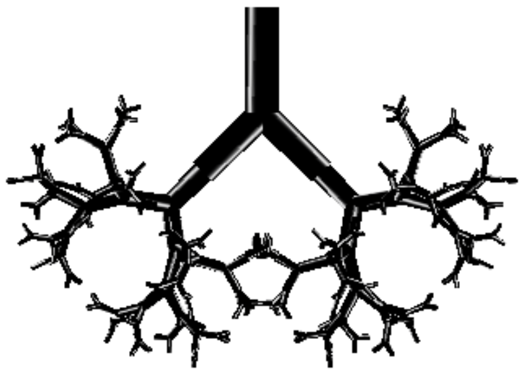
Fundamental dilemma

Test geometry

Surfactant properties

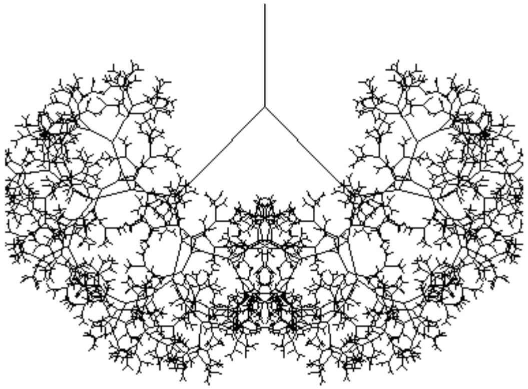
ρ = 1 g/cc, σ = 30 dynes/cm,
η = 30 cP (Infasurf, Survanta, Curosurf),
η = 3 cP (Exosurf)

2 lb Neonate



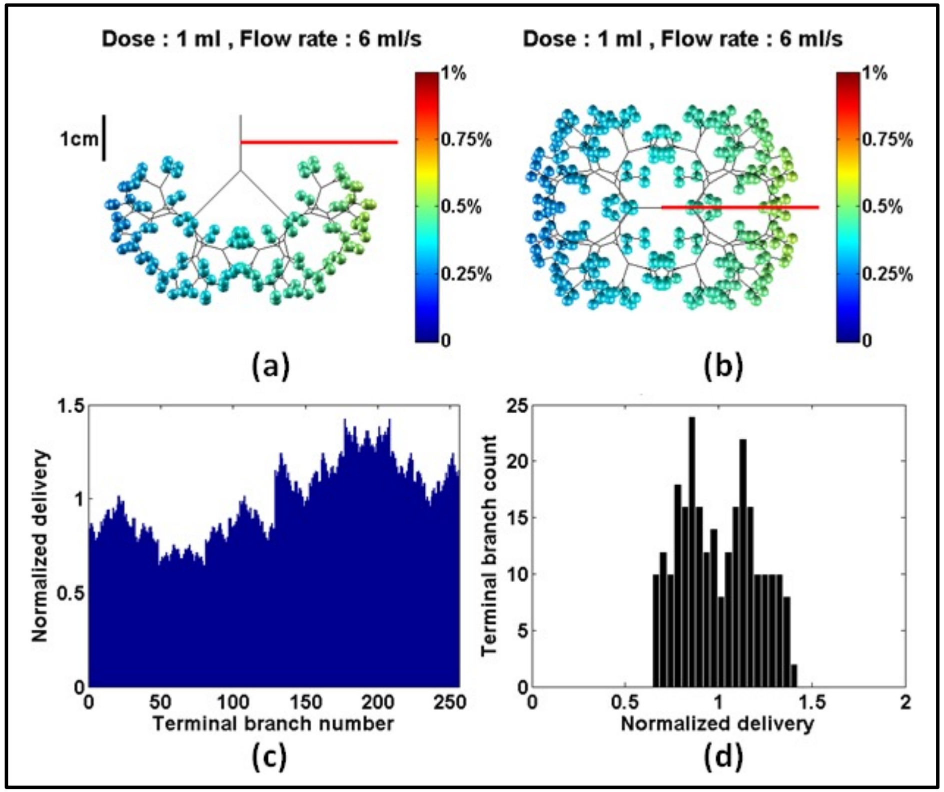
Weibel symmetric tree, branching angle = 90°, planar rotation angle = 90°,trachea diameter = 0.4 cm, terminal bronchiole diameter = 0.05 cm $\rightarrow$ **511 branches**, 256 leaves, 8 generations

Adult



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

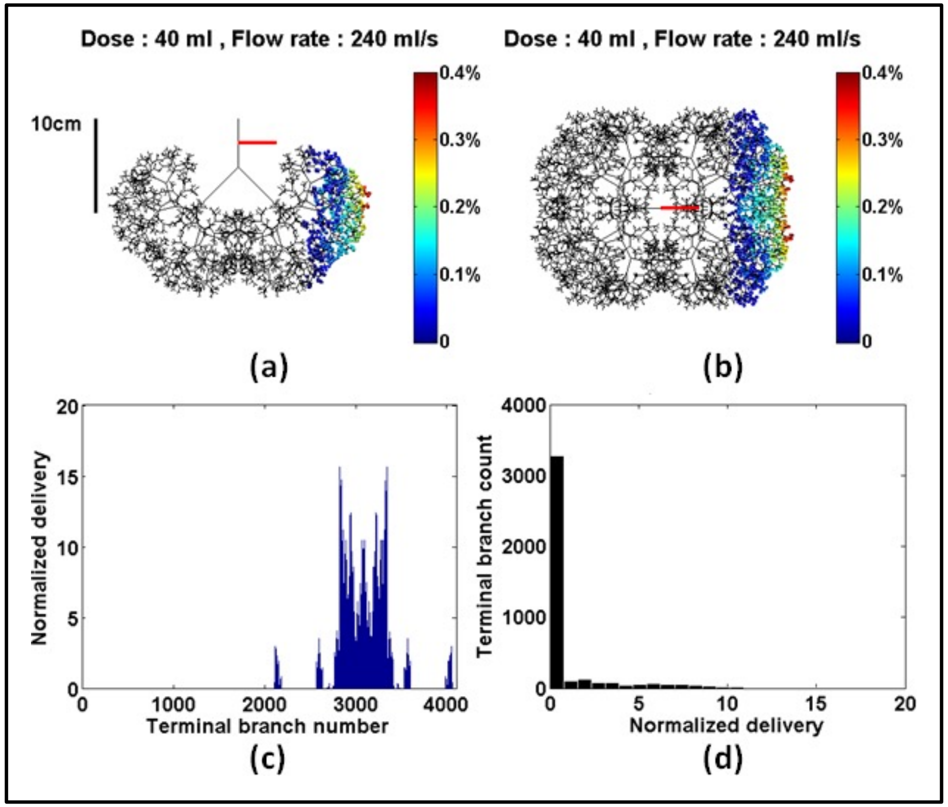
SRT in a 1 kg neonate



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

1 kg neonate in LLD, viscosity μ=30 cP, dose 1 ml, 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**.

SRT in a 70 kg adult



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

Grotberg *et al*., *AJRCCM* (2017)

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**.

SRT in adults with ARDS

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

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

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

SRT in adults with ARDS

Molecular dose (mg/kg) = Concentration (mg/ml) x **Dose volume (ml/kg)**

Gregory *et al.*, Am J Respir Crit Care Med, **1997**
Mortality: 18.8% SRT (n=43) vs 43.8% control (n=16)
Molecular Dose: **50 mg/kg** -100 mg/kg
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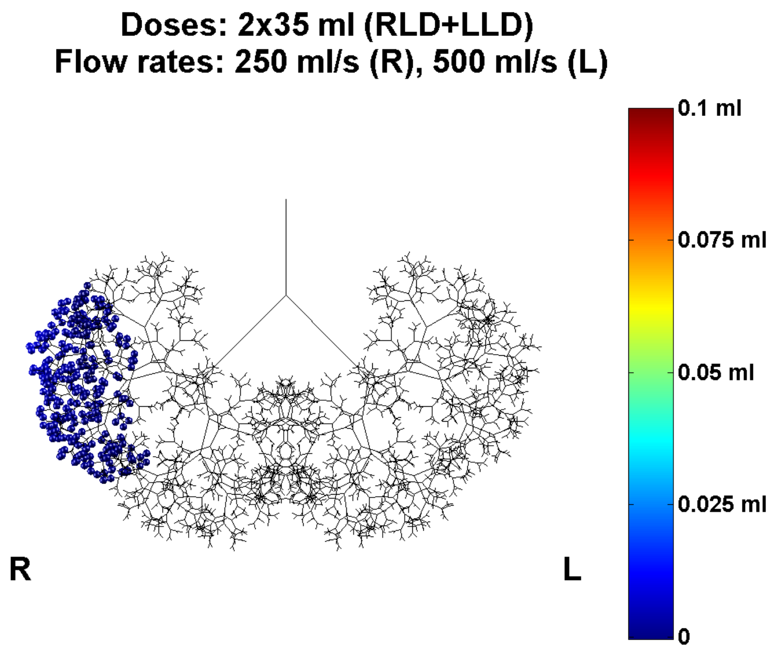
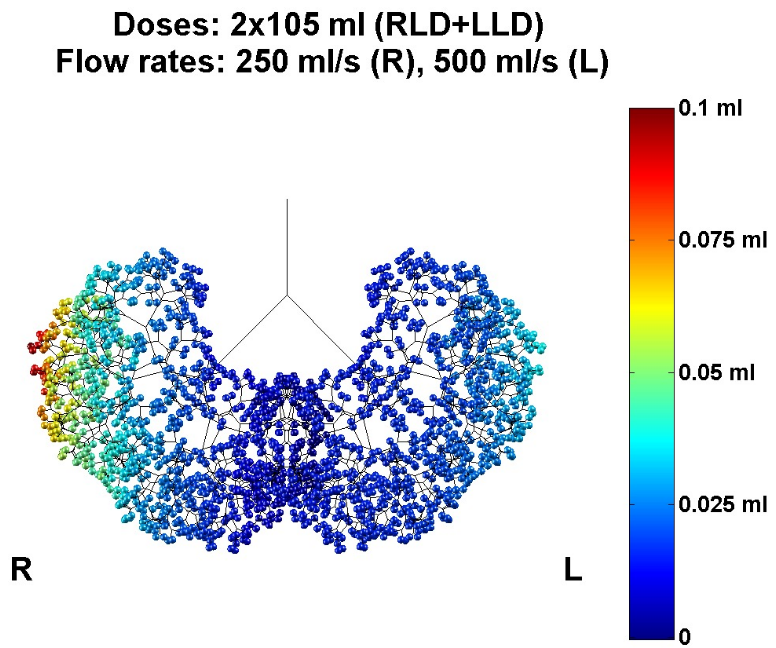
Addressing the medical community



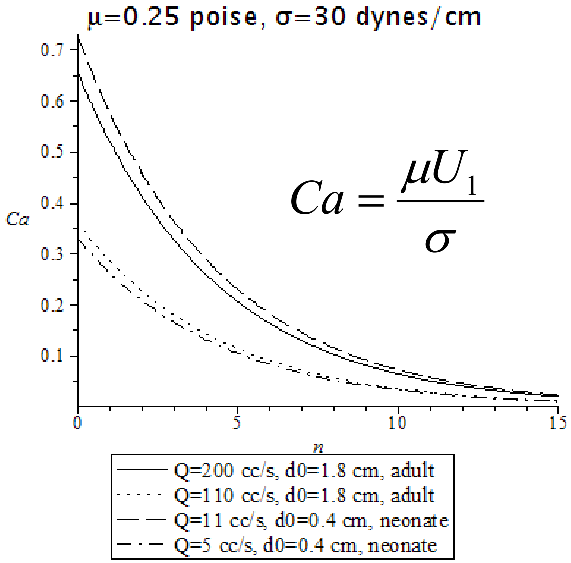


Grotberg et al., *Am. J. Respir. Crit. Care Med*. (2017)

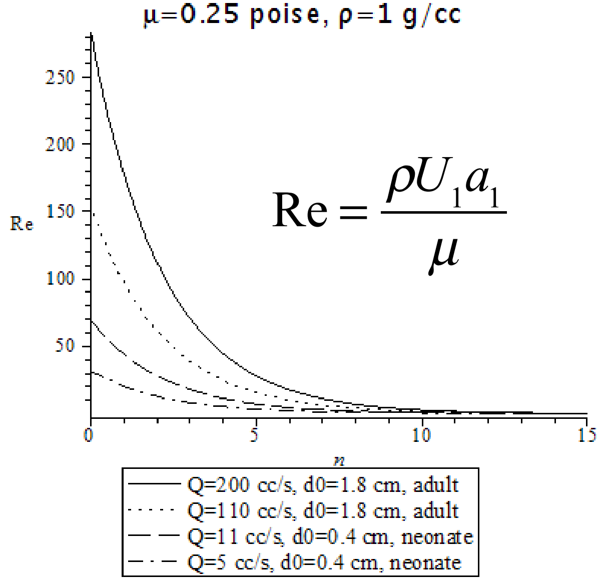
Parameter ranges of Ca, Re, and Bo

Neonates and adults vs. airway generation *n*

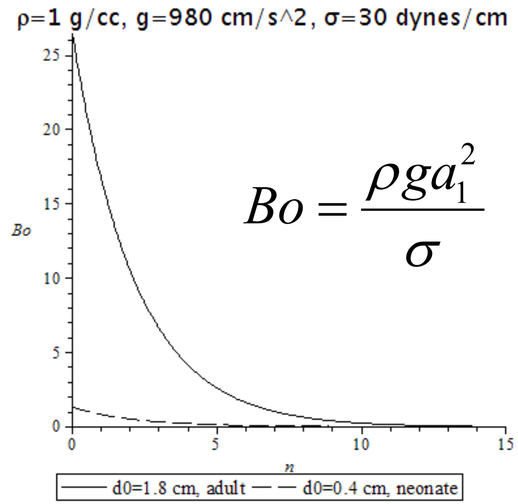
Capillary number



Reynolds number



Bond number



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

Order of magnitude difference for Bo between adults and neonates

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

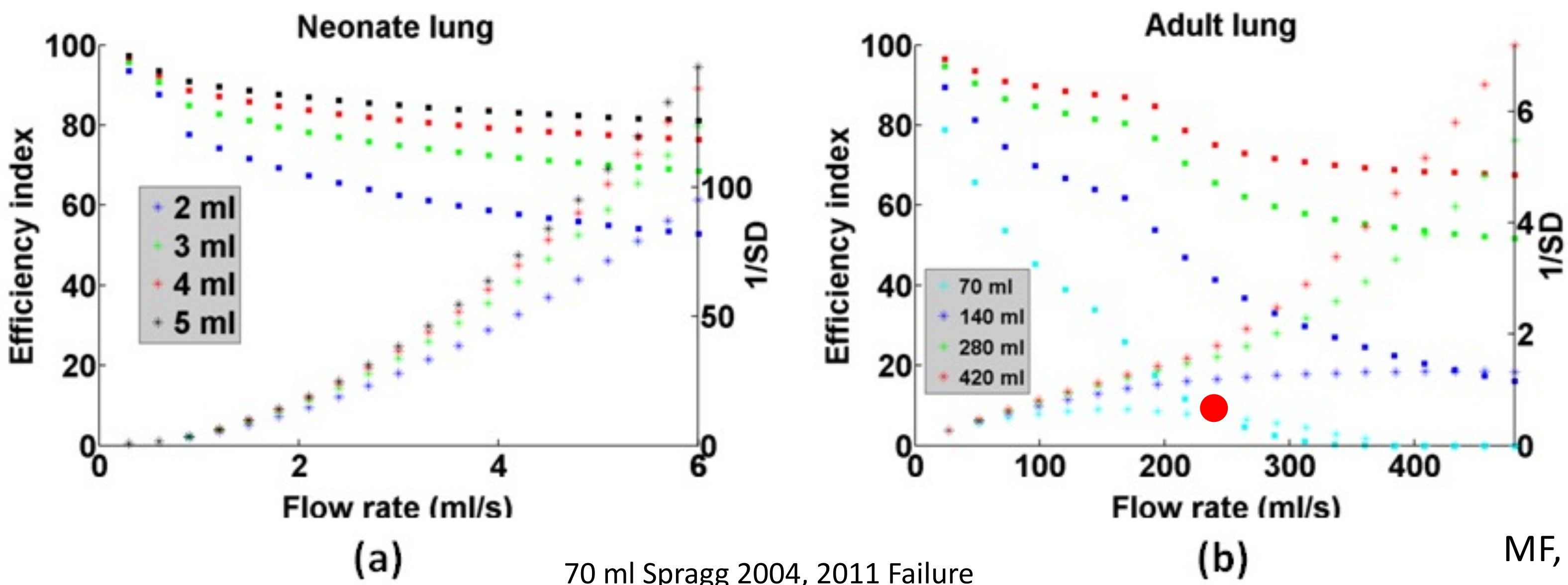
A fundamental misunderstanding?

- 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 homogeneity.
- The adult lung is **poorly mixed**, low homogeneity.
  - The absolute volume is “**critical**”
  - **Fixed cost** of airway coating

Physics and fluid mechanics send a new message

Efficiency vs. homogeneity

½ dose LLD, ½ dose RLD



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

MF, Tai, Grotberg, *PNAS* 2015

- Larger flow rate ⇒ less efficient (more surfactant left onto the airway walls)
- Larger flow rate ⇒ more homogeneous
- Homogeneity is one order of magnitude larger in the neonate

70 ml was the worst choice!!

Rat conducting airway model

Raabe-based
Morphometric measurements
Raabe *et al*., 1976, internal report

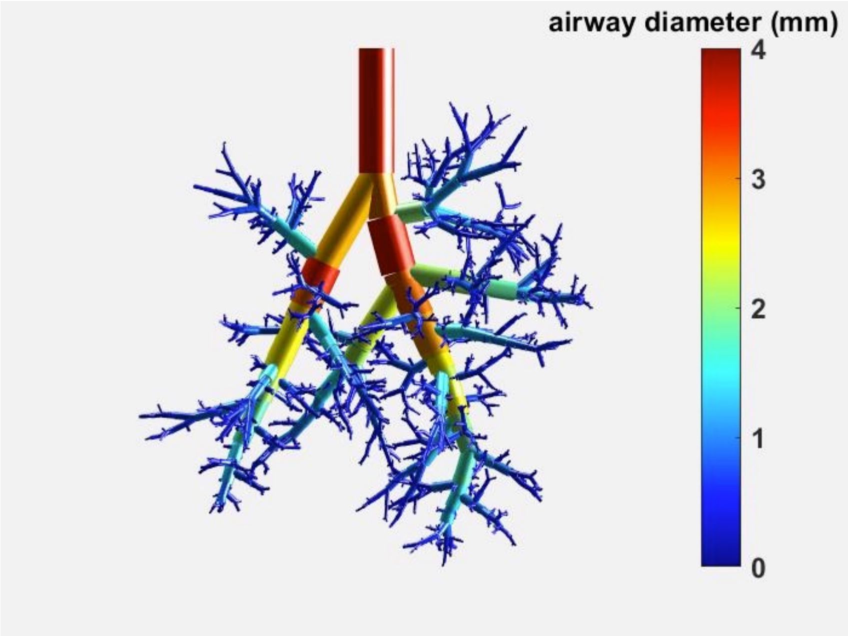
Asymmetric tree

Lengths

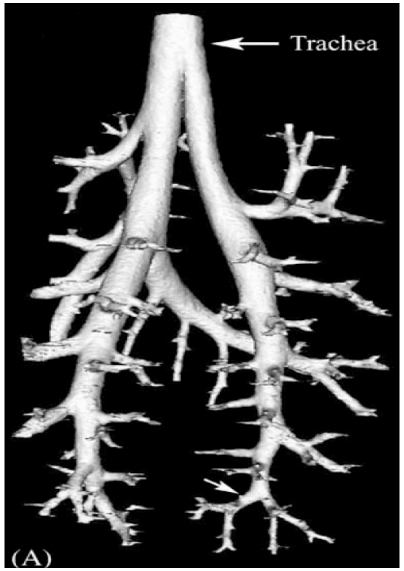
Diameters

Bifurcation angles

Rotation angles

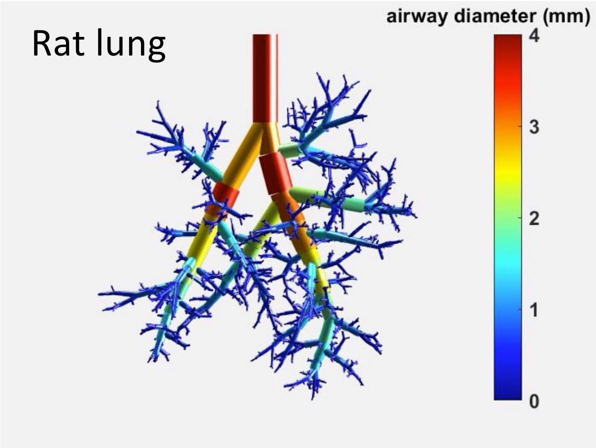


Kazemi *et al*., PLoS Comput Biol, 2019

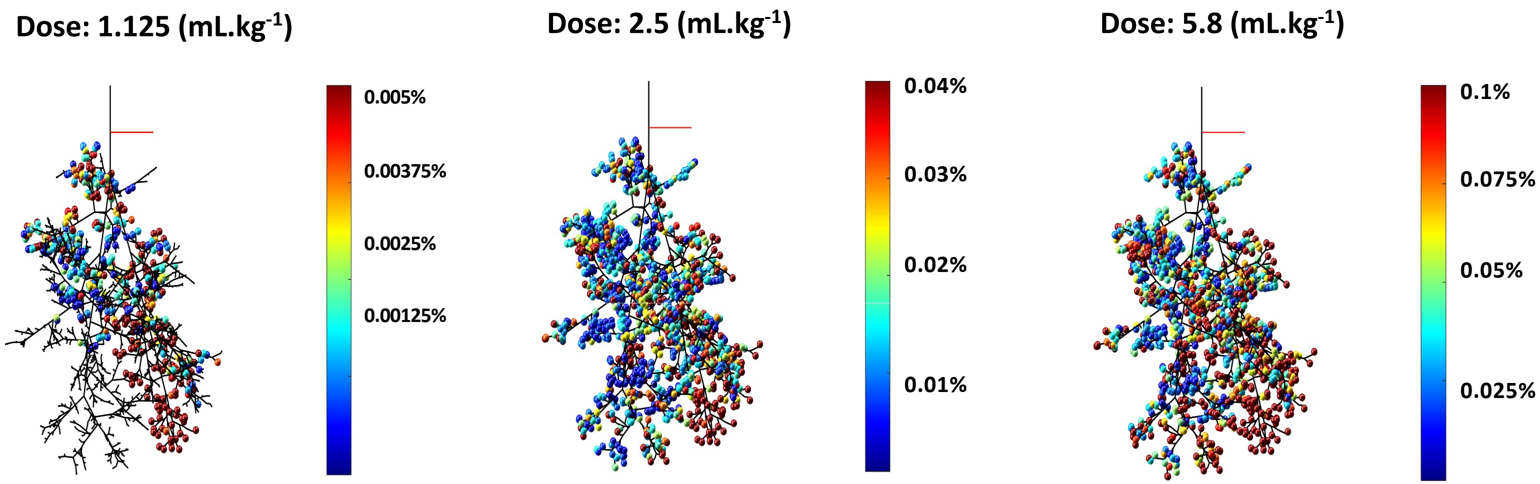


Sera *et al*., J Biomech, 2003

Testing the model on rats

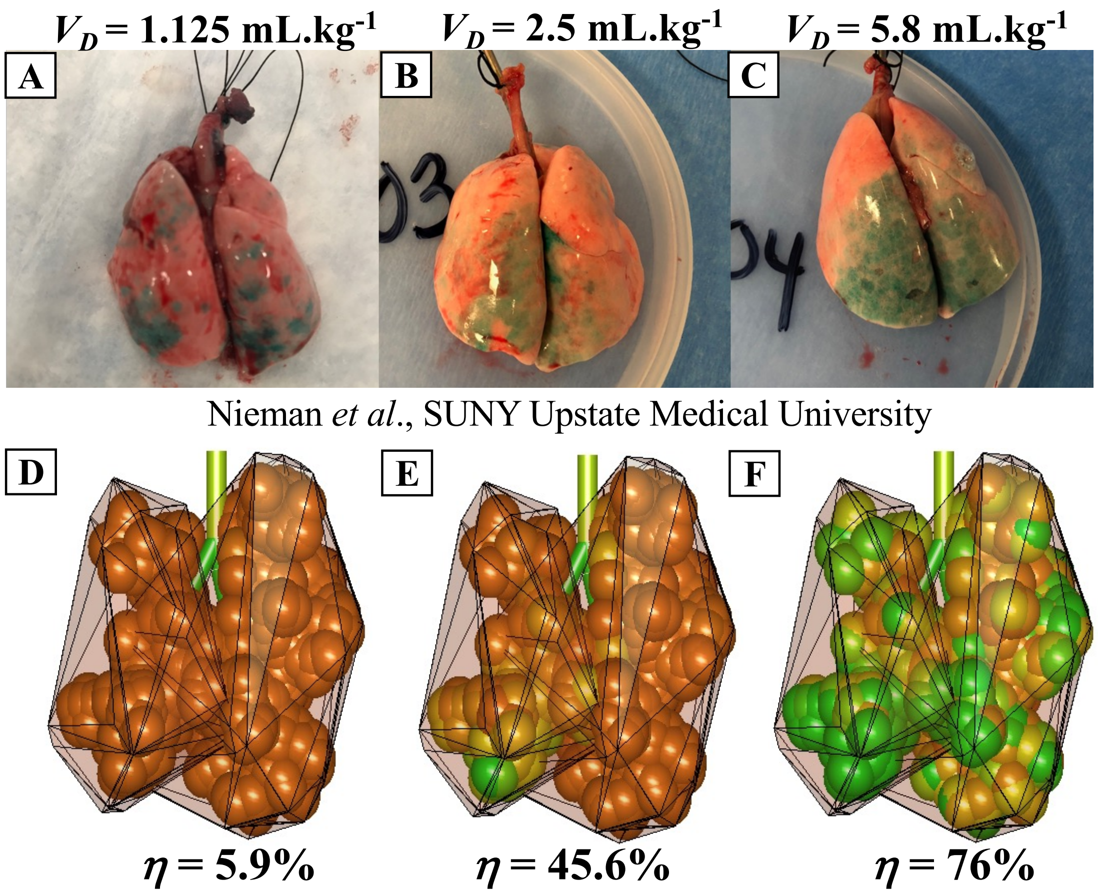


Virtual delivery



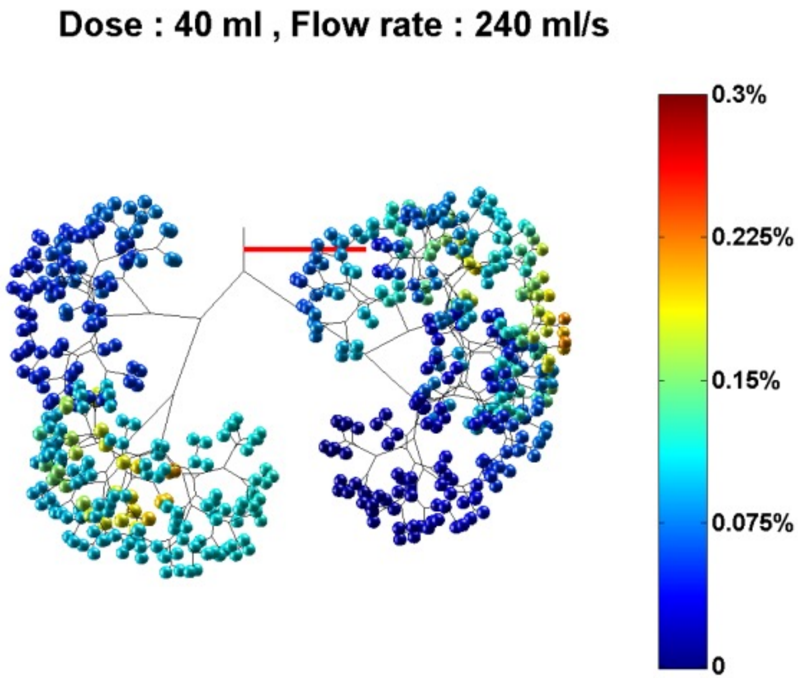
Kazemi *et al.*, *PLoS Comput Biol* 2019

Comparisons with surfactant delivery on rats

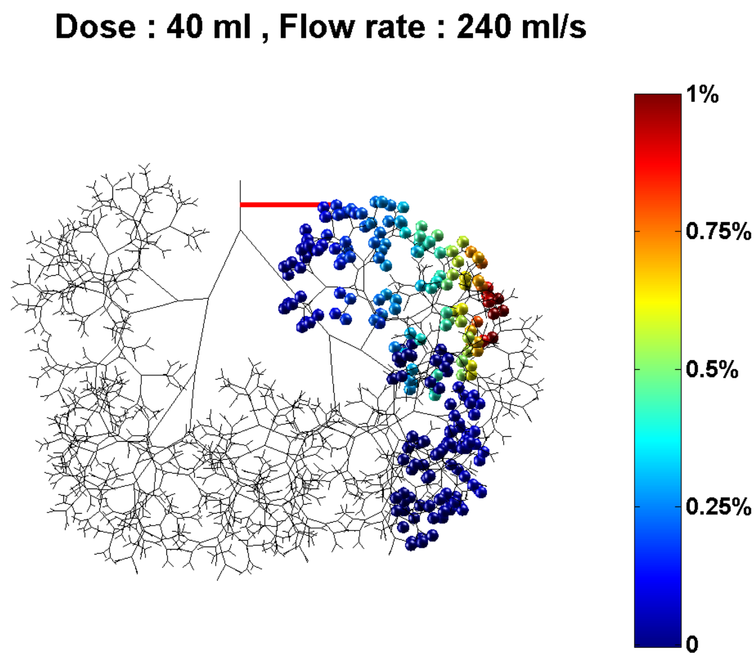


Kazemi *et al.*, *PLoS Comput Biol* 2019

Patient-specific SRT simulations: biomedical engineering



(a)



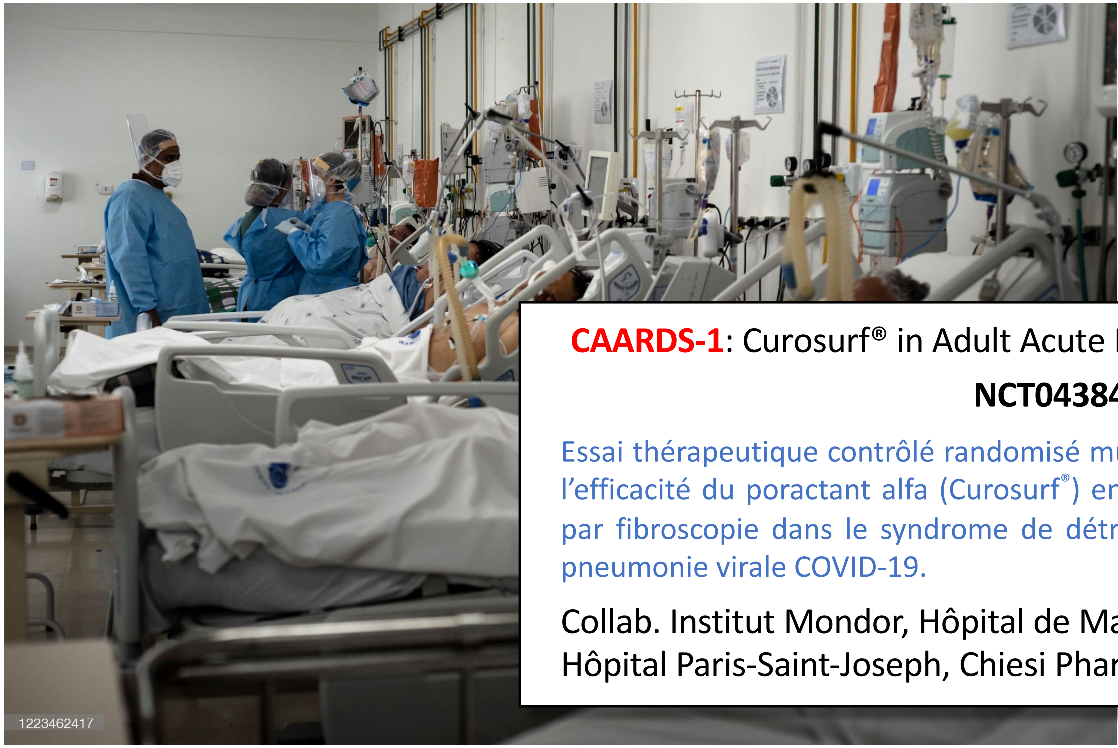
(b)

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).

The Covid-19 pandemic: clinical trial of surfactant delivery



CAARDS-1: Curosurf® in Adult Acute Respiratory Distress Syndrome – 1

NCT04384731

Essai thérapeutique contrôlé randomisé multicentrique de phase II visant à évaluer l'efficacité du poractant alfa (Curosurf®) en administration endobronchique dirigée par fibroscopie dans le syndrome de détresse respiratoire aiguë provoqué par la pneumonie virale COVID-19.

Collab. Institut Mondor, Hôpital de Mantes, CHI Poissy St-Germain-en-Laye, Hôpital Paris-Saint-Joseph, Chiesi Pharmaceuticals

What is the structure of the final distribution of surfactant?
Can it be optimized? Targeted?