Physics of respiration

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Maddalena Felici (Thèse Ecole polytechnique, 2003).

Benjamin Mauroy, Ecole normale supérieure, Cachan, France (Thèse ENS Cachan, 2004).

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Ewald R. Weibel, Department of Anatomy, University of Berne, CH.

Hiroko Kitaoka, Osaka University, Japan.

Thomas Similowski et Christian Straus, CHU Pitié-Salpétrière, Paris.

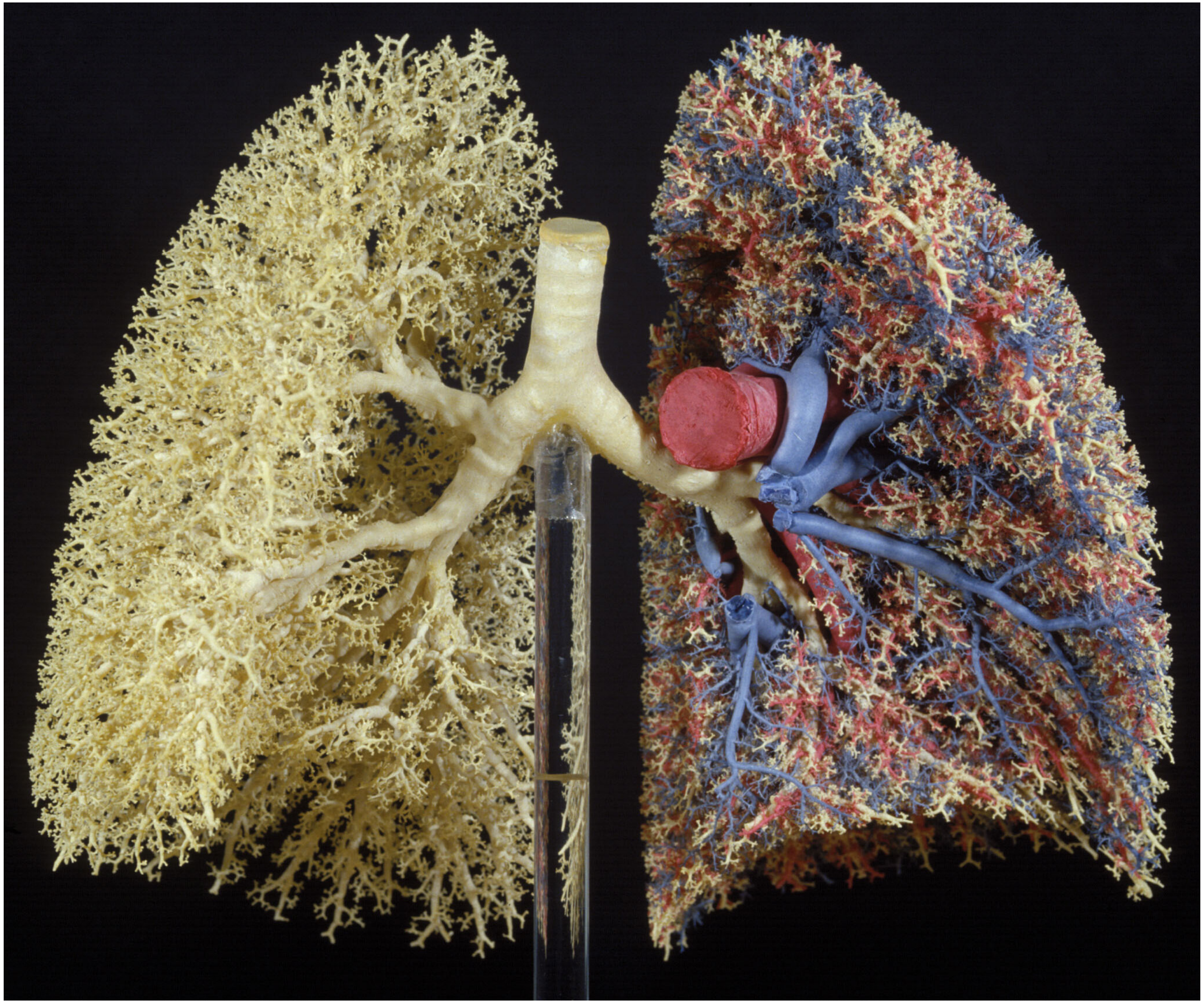
Question: do what extent physiological systems are "efficient" from a physical point of view ?

Old question with new recent developments:

West, G. B., Brown, J. H., and Enquist, B. J. Science, 1997.

Physical optimization is the cause of the value of the allometric exponents like 3/4 for the standard metabolic rate ???

Here we study the relation between the physical properties of the respiratory system and its geometry.



Cast of human lung - Weibel

Geometrical properties :

- 23 generations dichotomic tree

- Branches diameters decreases with generations.

- The total cross section of the tree increases with generation and the air velocity decreases.

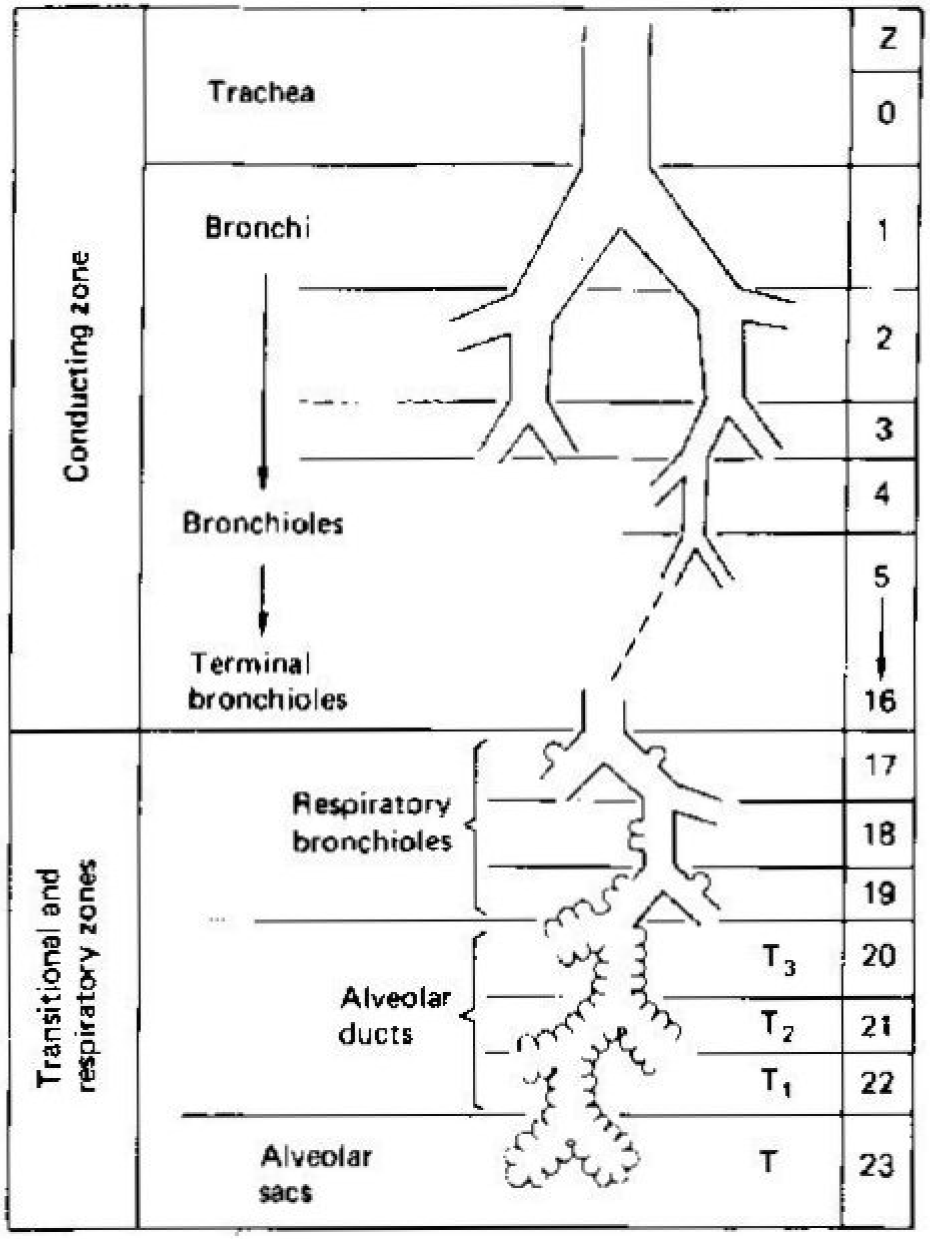
- The length over diameter ratio is of order 3 in the whole tree

The lung can be decomposed in a convective and a diffusive region :

The conductive region spreads from generations 0 to generation 16

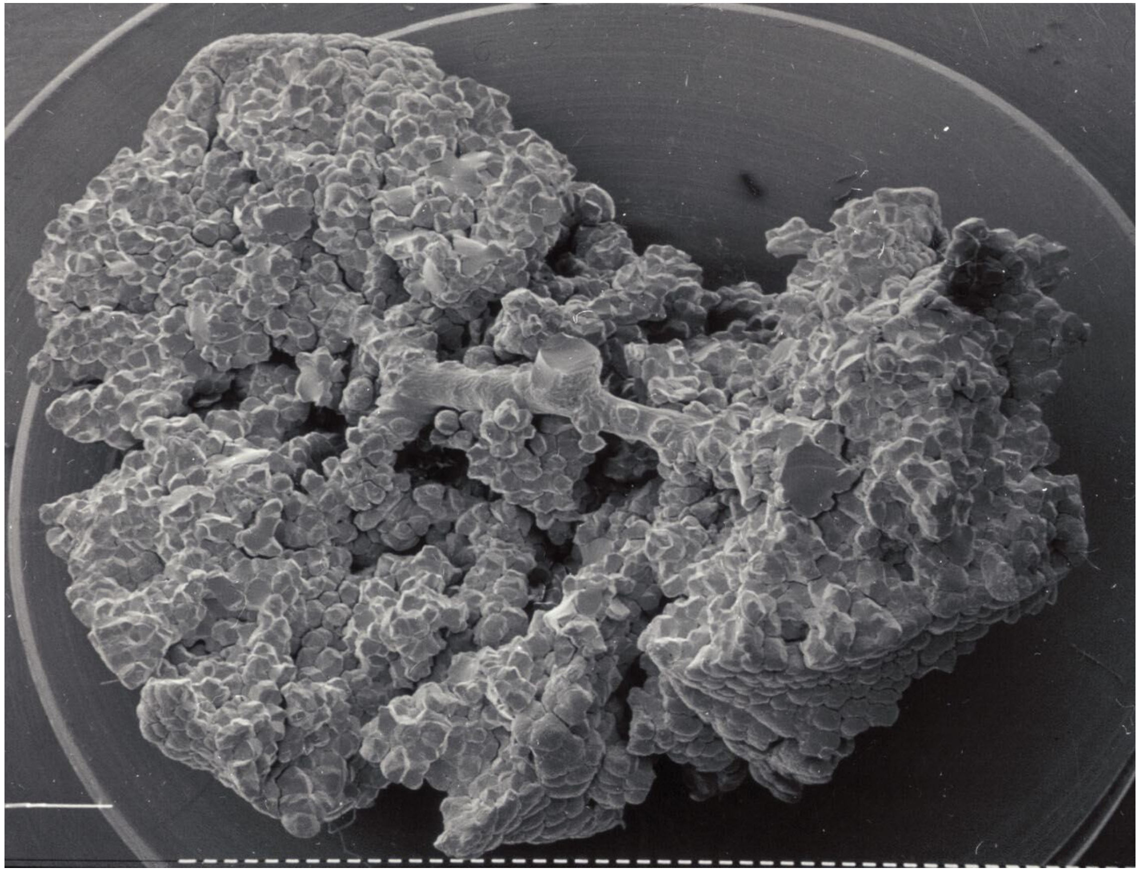
The deeper, diffusive region, (between generation 17 and 23) where air velocity becomes smaller than diffusion velocity and oxygen is absorbed in the alveoli. This takes place in the

acinus.



One acinus:

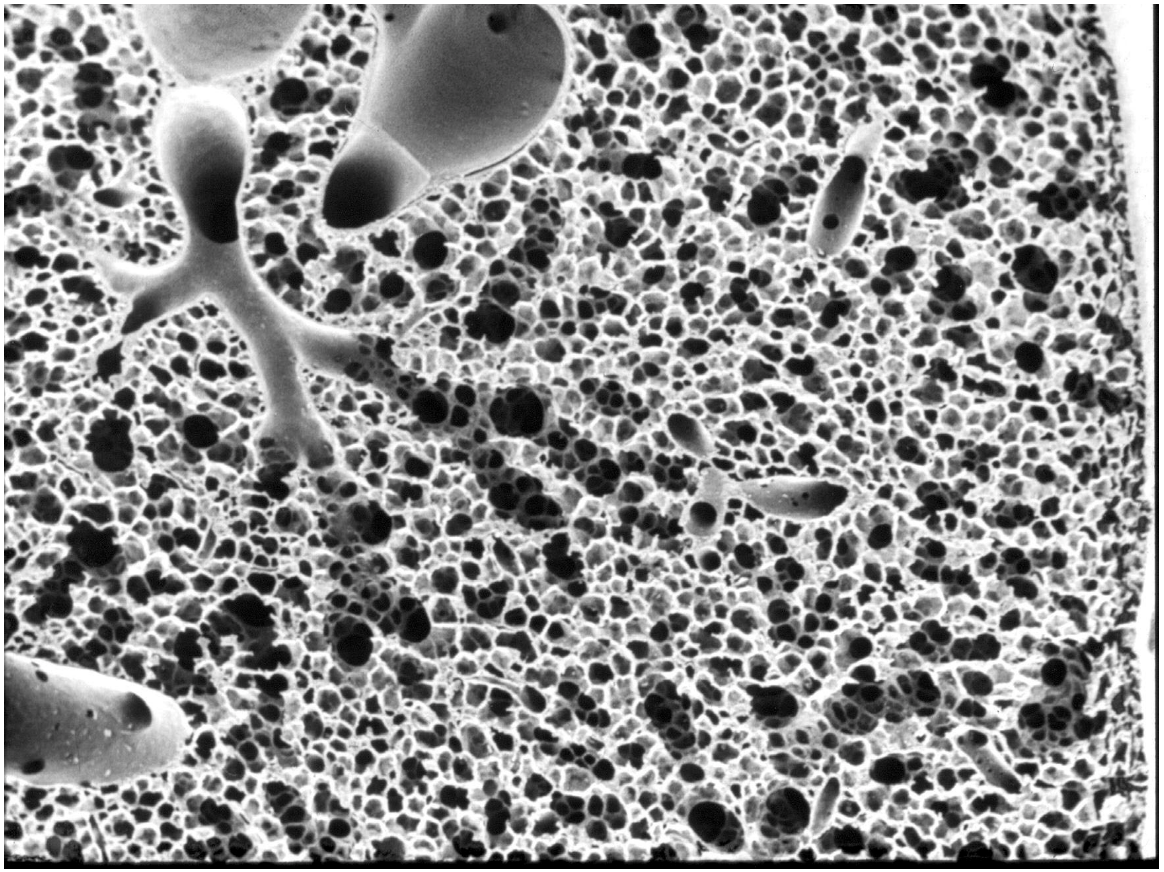
About
30 000
acini in the
human lung



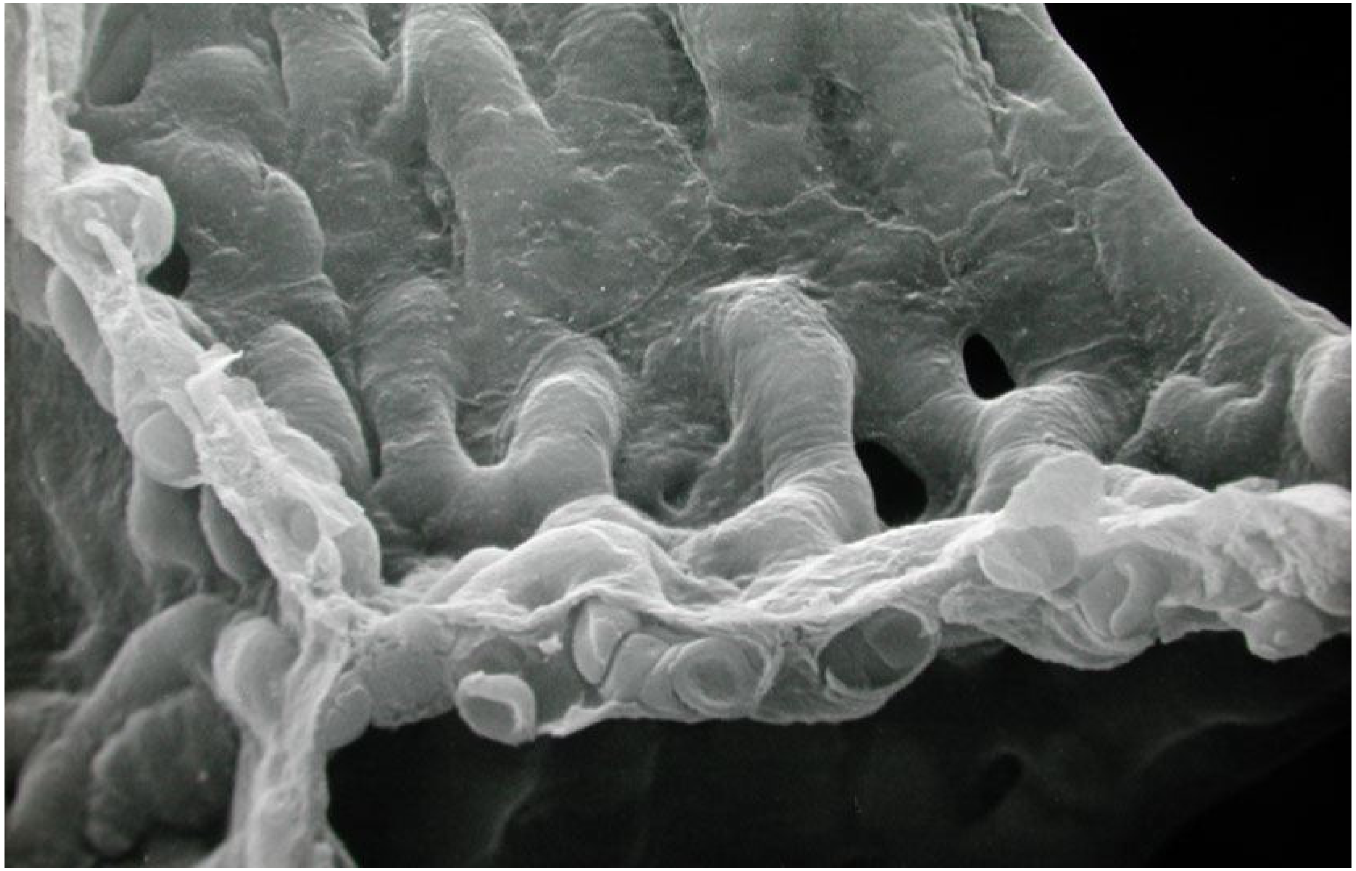
About
10 000
alveoli

$3.\ 10^8$ alveoli in the human lung

Planar cut of the acinus:



Alveolar membrane with capillaries and blood cells:



The motion of the diaphragm creates dilatation of the 2^{15} acini which act like little pumps

$\downarrow$

In the proximal bronchi: Navier-Stokes.

$$\begin{cases} \dfrac{\partial u}{\partial t} + (u.\nabla)u - \dfrac{\mu}{\rho}\Delta u + \dfrac{\nabla p}{\rho} = 0 \\ div(u) = 0 \end{cases}$$

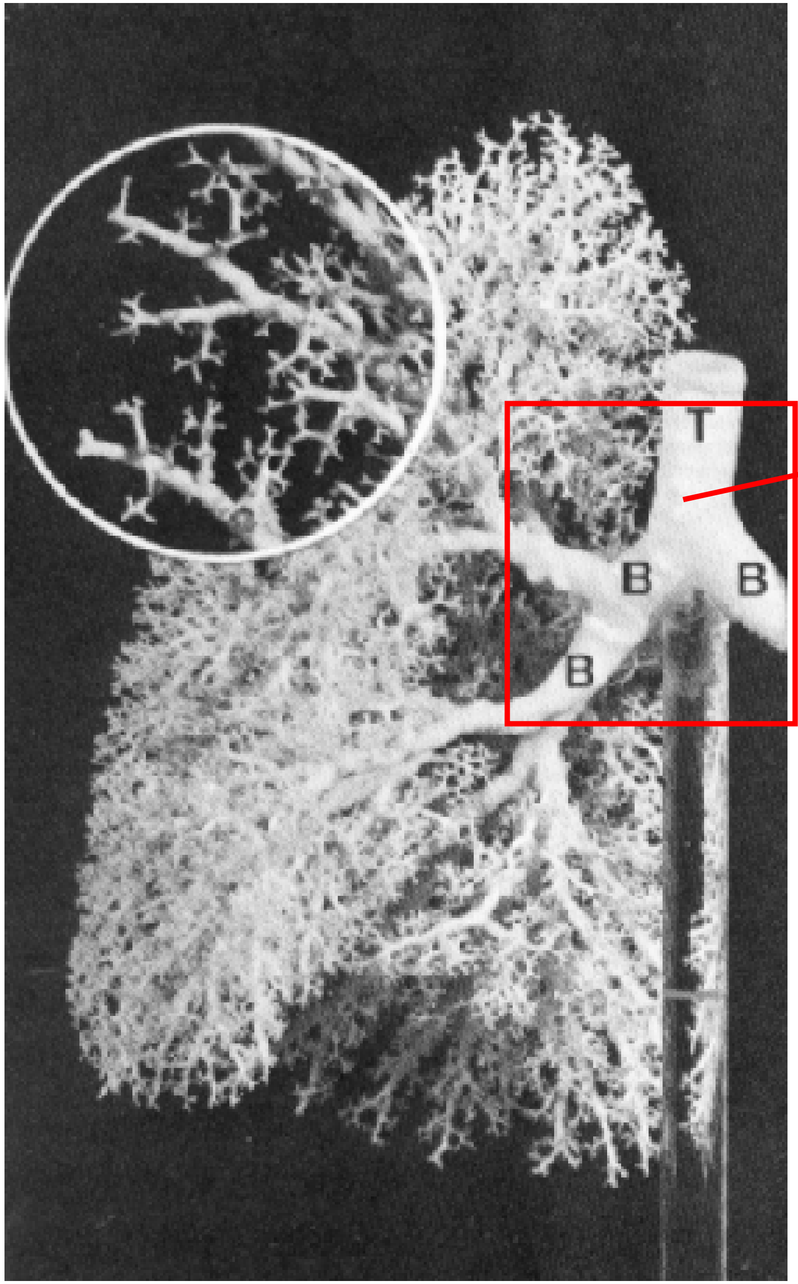
u(t,x) : air velocity

p(t,x) : air pressure

In the intermediate bronchial: Stokes flow

In the acini: diffusion equation

Upper Bronchial Tree Hydrodynamics:



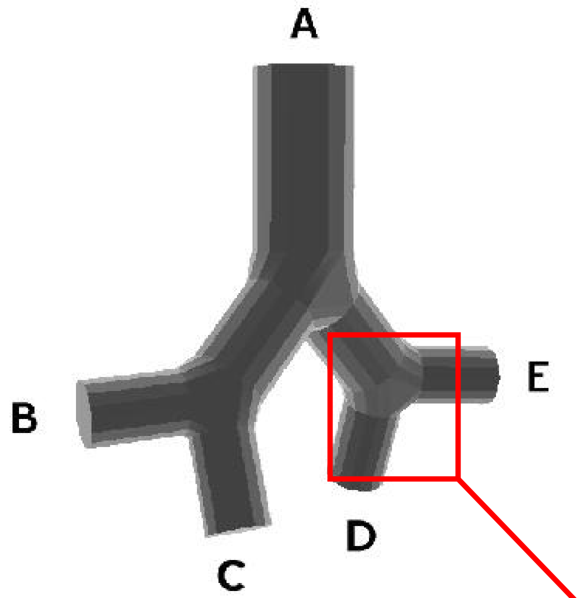
Trachea and bronchi

Generations 0 to 5

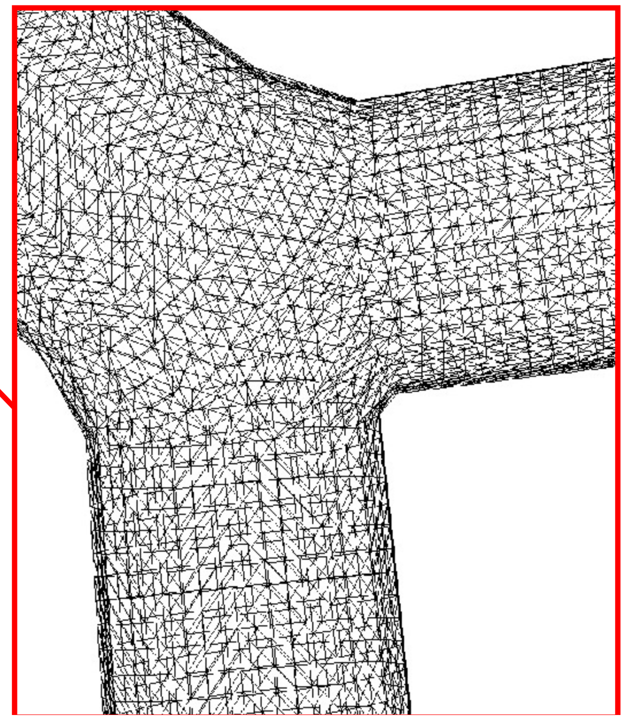
Inertial effects on the flow distribution in the upper bronchial tree

<u>First step:</u> steady-state solution, with steady-state boundary conditions.

Numerics: Finite elements method



The tree is symmetric and fills a symmetric volume

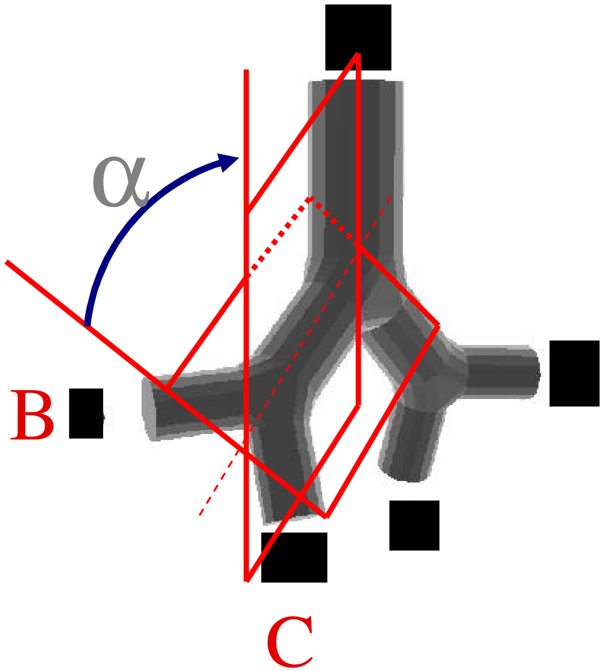


Tetraedric mesh with ~250000 elements

Softwares: SIMAIL (for the meshes), N3S (for Navier-Stokes equations), ENSIGHT (for visualisation). N3S uses finite elements method (Chorin-Temam), velocities are P2 and pressures are P1.

It is assumed that :

- the first generation diameter is 2 cm
- the diameters decreases with factor 0.79
- the angle between daughter branches is 90°
- the Reynolds number at inlet is 1200 (weak exercise)

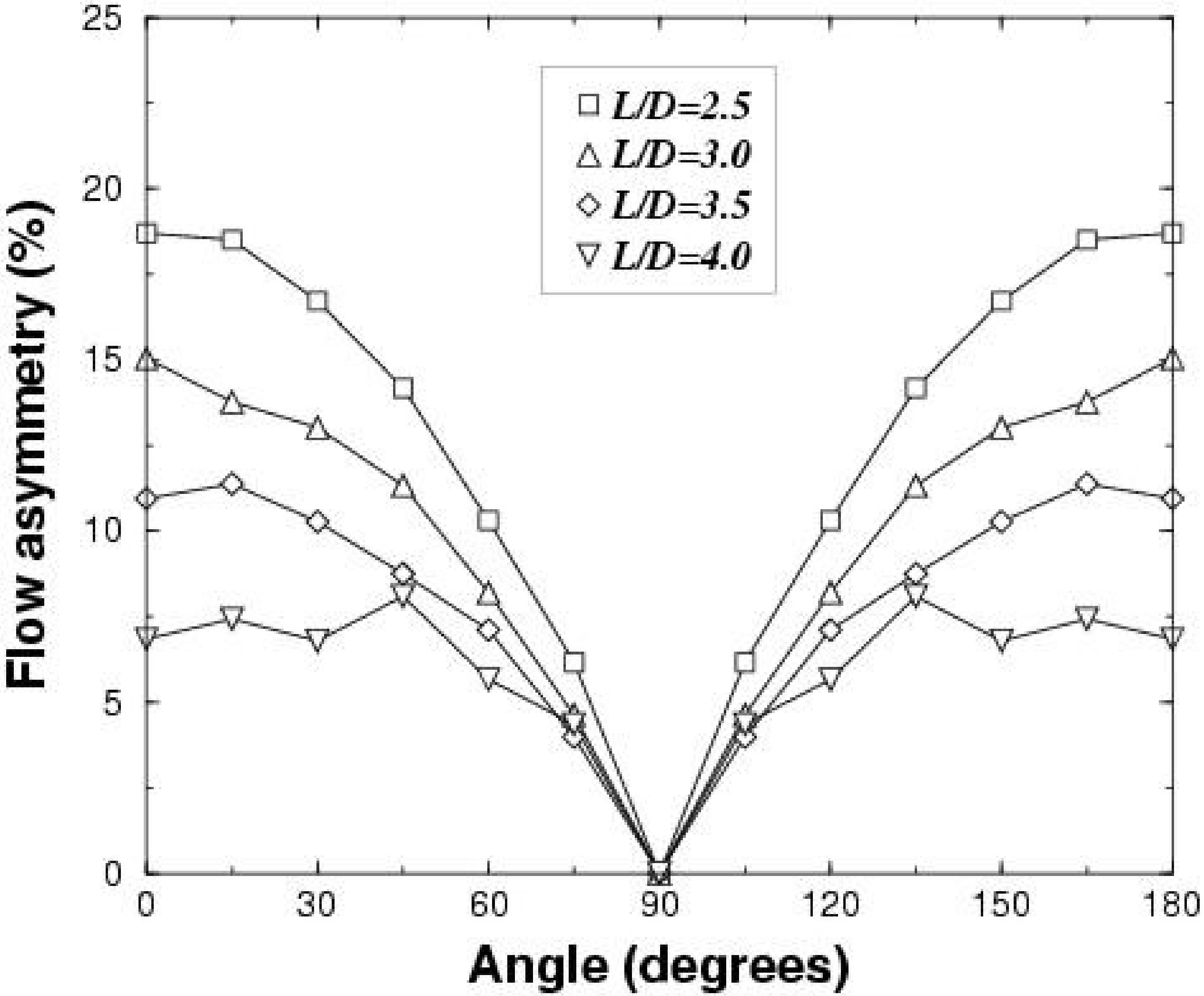


Parameters:

- L/D ratio (~ 3 in the lungs)
- Angle α of rotation between the two branching planes.

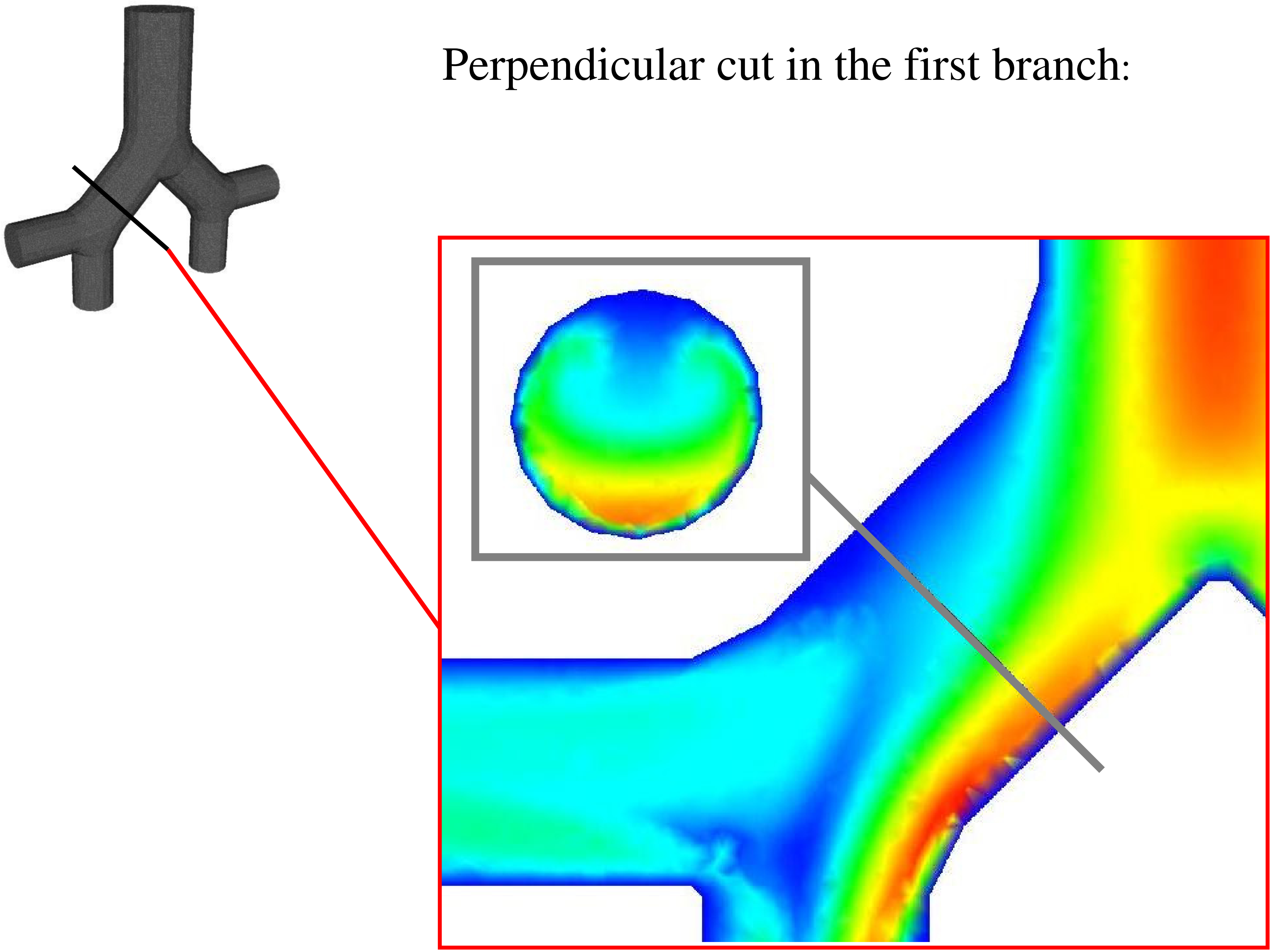
Flow asymmetry is defined by :

$$\boxed{\Sigma(\alpha, \frac{L}{D}) = \left| \frac{\Phi_B - \Phi_C}{\Phi_B + \Phi_C} \right|}$$



Flow asymmetry (%)
Angle (degrees)
L/D=2.5
L/D=3.0
L/D=3.5
L/D=4.0
0
5
10
15
20
25
0
30
60
90
120
150
180

Perpendicular cut in the first branch:

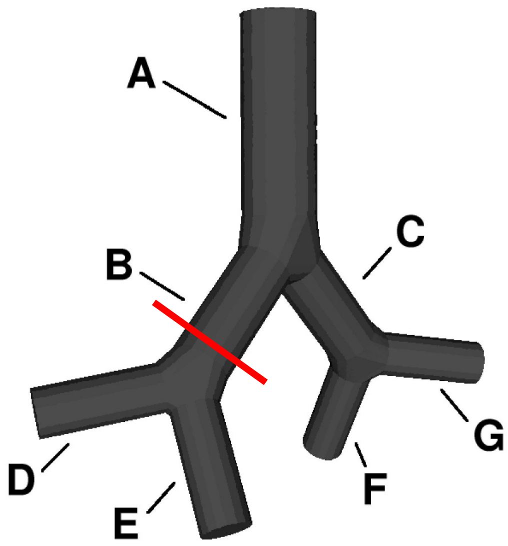


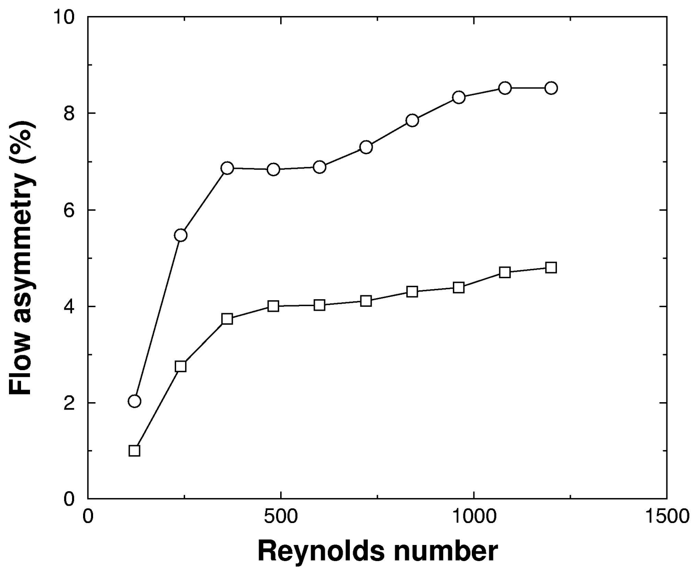
- Only the symmetic geometry spreads evenly the flow.

- A small variation of the angle triggers flow asymmetry.

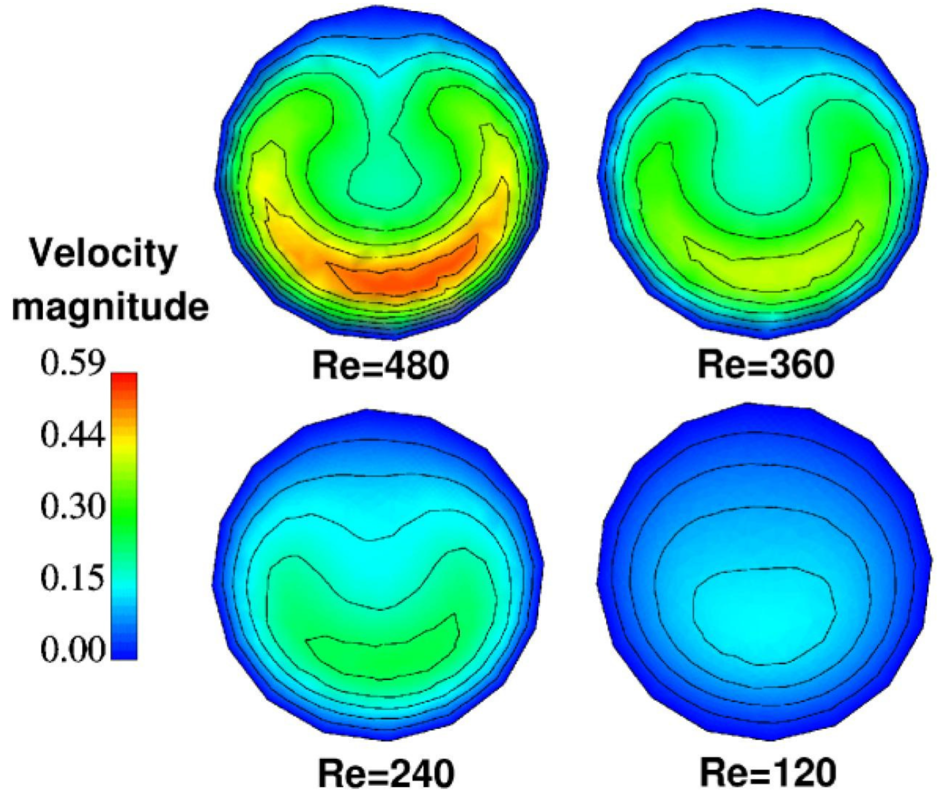
- If this spreads over generations, the distribution at the bottom of the tree will be multifractal : the tree cannot work in an homogenous way.

In the lung, the α values are close to 90° but this is subjected to physiological variability : hydrodynamics suggests the necessary existence of active flow regulation in order to obtain homogeneous flow distribution.





L/D = 3, α = 60° (circles) αα = 75° (squares)



The flow becomes Poiseuille for a Reynolds close to 60, this corresponds to the 6th generation in the lung at rest.

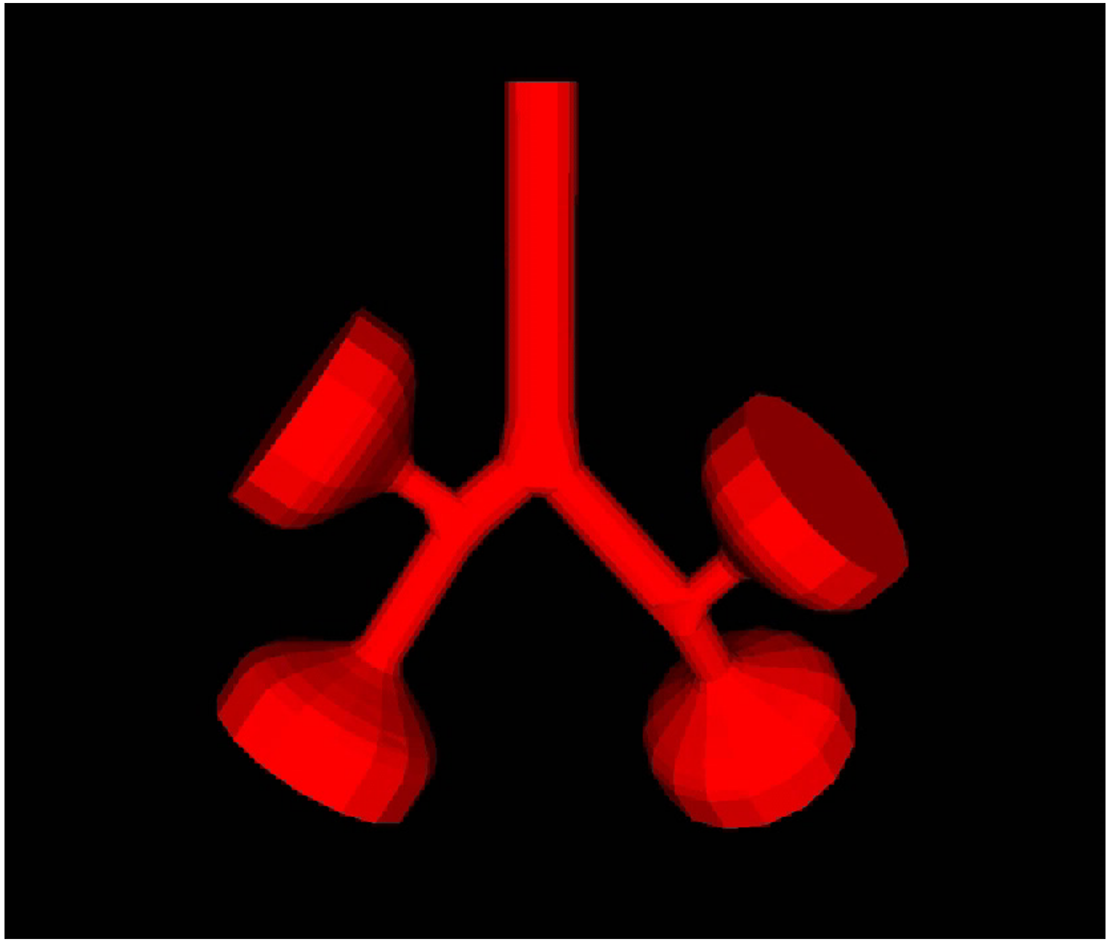
Conclusions

- Inertial effects play a role in airway flow distribution.
- The "physiological" value for L/D of order 3 appears as a physical compromise between the sensitivity to "angle mismatch" and viscous losses.
- Physiological regulation is necessary to permit homogeneous flow distribution.

- B. MAUROY, M. FILOCHE, J. S. ANDRADE, and B. SAPOVAL,
  Interplay between geometry and flow distribution in an airway tree,

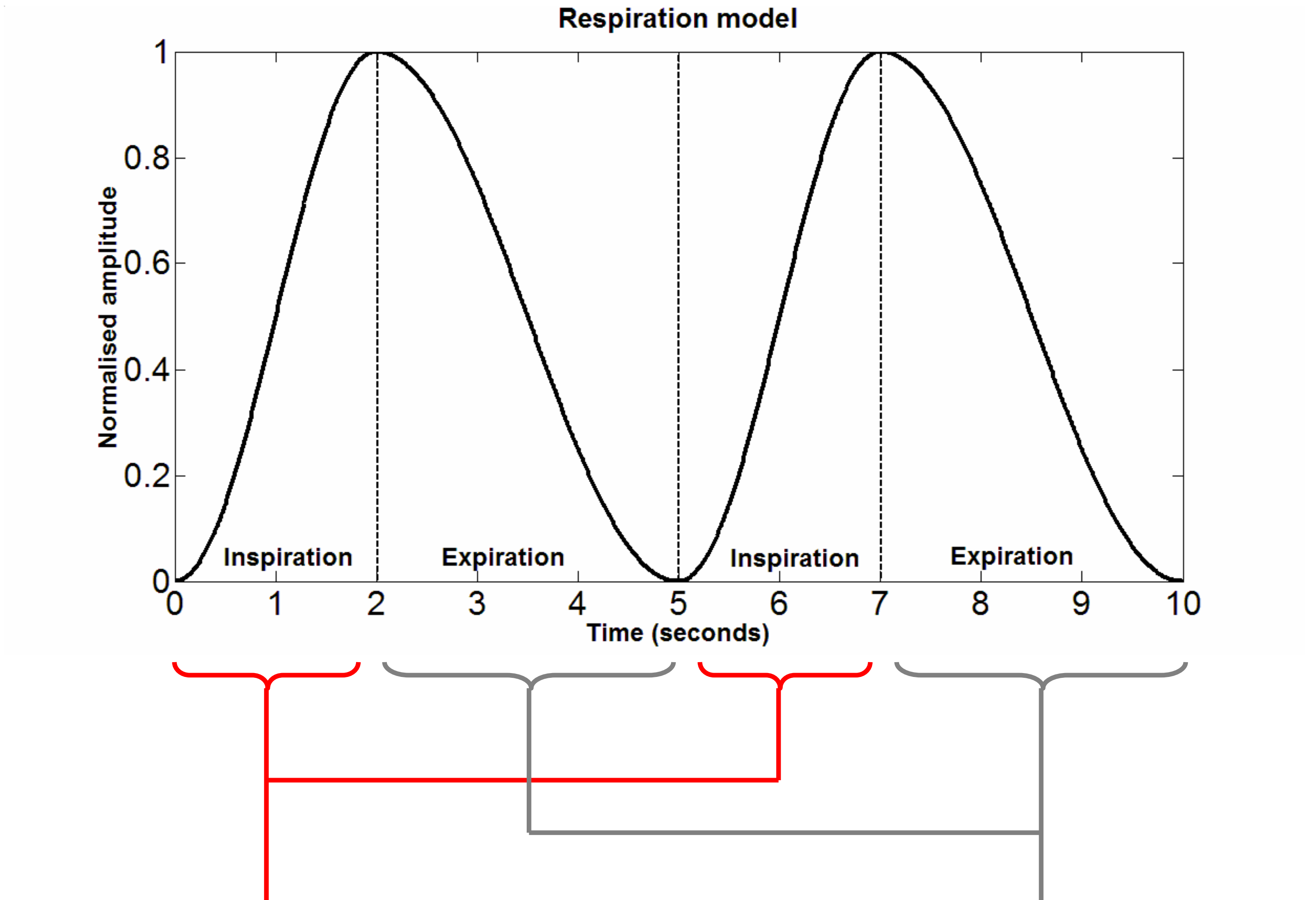
  Phys. Rev. Lett. 90, 148101-1-148101-4 (2003).

Hydrodynamical asymmetry between inspiration and expiration



H. Kitaoka, R. Takaki and B. Suki, ***Journal of Applied Physiology*** 87: 2207-2217, 1999.

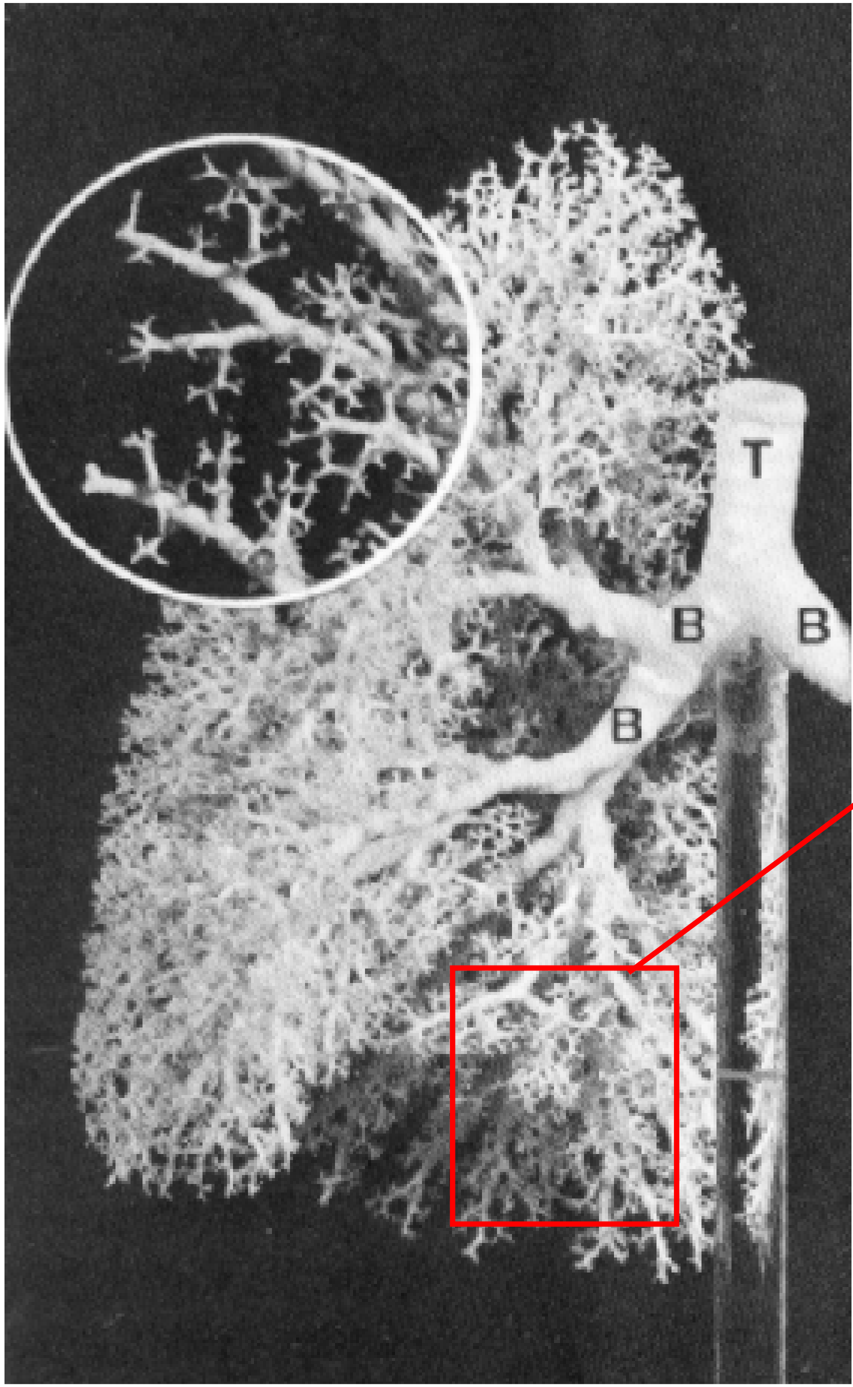
Respiratory cycle modelisation



Inspiration : 2 seconds

Expiration : 3 seconds

[redacted]



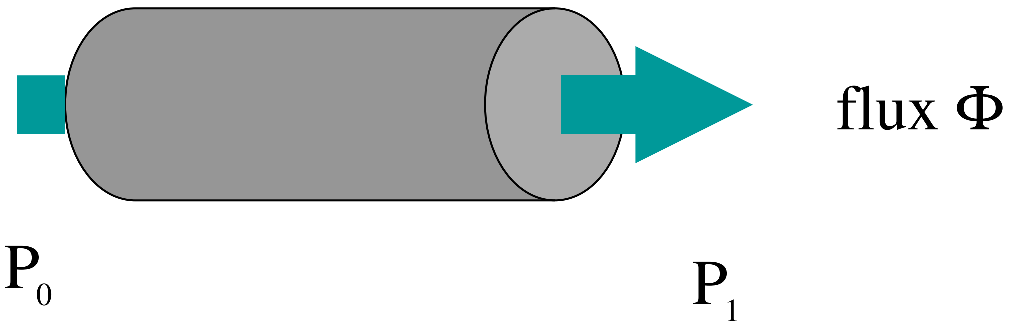
Hydrodynamics of the intermediate bronchial tree:

Bronchioles

- Generations 6 to 16
- Stokes regime where Poiseuille law can be used

Poiseuille regime corresponds to small fluid velocity.

(Jean Louis Marie Poiseuille, medical doctor, 1799-1869. He was interested in hemodynamics and made experiments with small tubes from which he founded hydrodynamics. He first used mercury for blood pressure measurement).

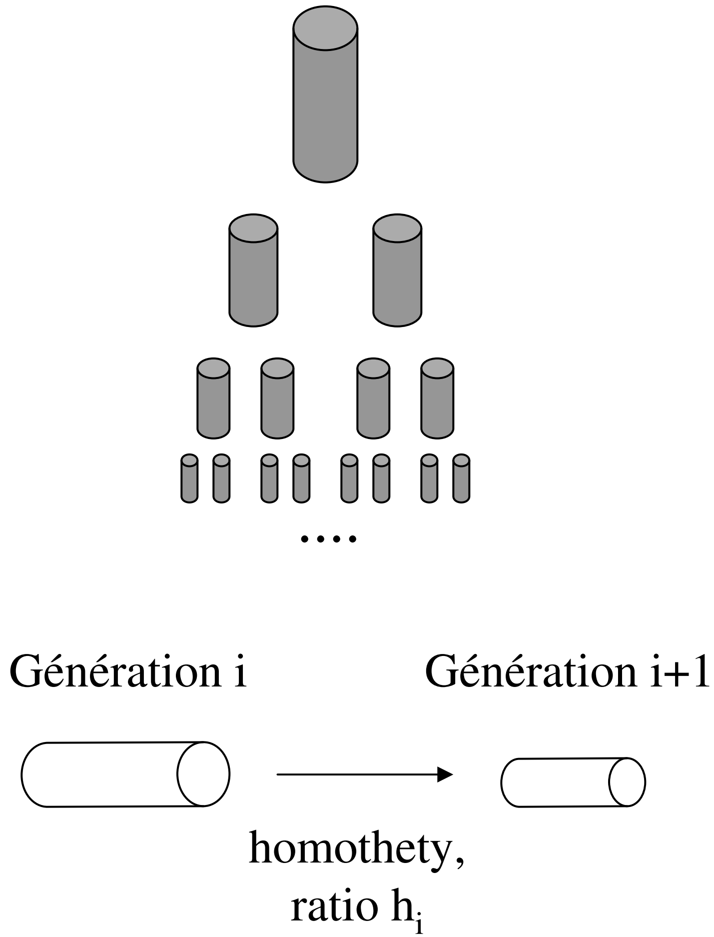


$$\boxed{P_0 - P_1 = R.\,\Phi}$$

$$\boxed{R = (\mu/2\pi)(L/D^4)}$$

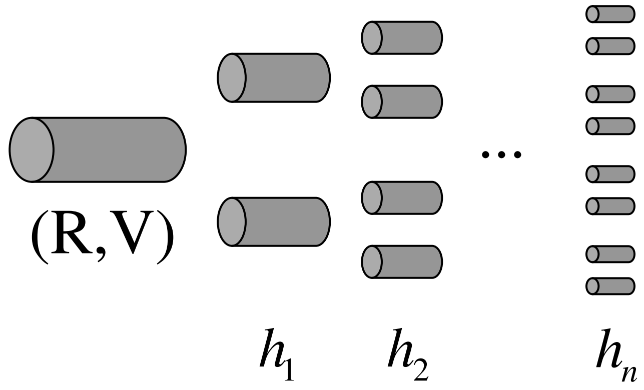
μ: fluid viscosity

(symmetry between inspiration and expiration)



....
Génération i
Génération i+1
homothety,
ratio h_i

Tree with *n+1* generations



The tree resistance can be written :

$$R_{eq} = R\left(1 + \frac{1}{2h_1^3} + \frac{1}{4h_1^3 h_2^3} + \ldots + \frac{1}{2^n h_1^3 \ldots h_n^3}\right)$$

Its total volume is :

$$V_{eq} = V\left(1 + 2h_1^3 + 4h_1^3 h_2^3 + \ldots + 2^n h_1^3 \ldots h_n^3\right)$$

We want to minimize R_{eq} with the constraint $V_{eq} \leq \Lambda$

There exists a Lagrange multiplicator such that : $\nabla R_{eq} = \lambda \nabla V_{eq}$

Hence : $\dfrac{\partial R_{eq}}{\partial h_i} = \lambda \dfrac{\partial V_{eq}}{\partial h_i} \quad \forall i = 1,\ldots,n$

After solving this system we obtain :

$h_1 = \left(\dfrac{\Lambda - V}{2nV} \right)^{\frac{1}{3}}$ and $h_i = \left(\dfrac{1}{2} \right)^{\frac{1}{3}}$ = 0.79… for i = 2,…,n

Hess (1914) Murray (1926)

The best bronchial tree:

The fractal dimension is $D_f = \ln 2/\ln h = 3$

$\Rightarrow$ space filling.

But its total volume $V_N = V_0\,[1 + \Sigma_1^N (2h^3)^p]$

or the total pressure drop $\Delta P_N = R_0\, \Phi\,[1 + \Sigma_1^N (2h^3)^{-p}]$

increases to infinity with N.

This increase is however *slower* for the value $h = 2^{-(1/3)}$ which can be considered as a critical value.

But, even for $h = 2^{-(1/3)}$ the sum diverges: it is ***not possible*** to obtain a non-zero flux from a finite pressure drop for an ***infinite*** tree.

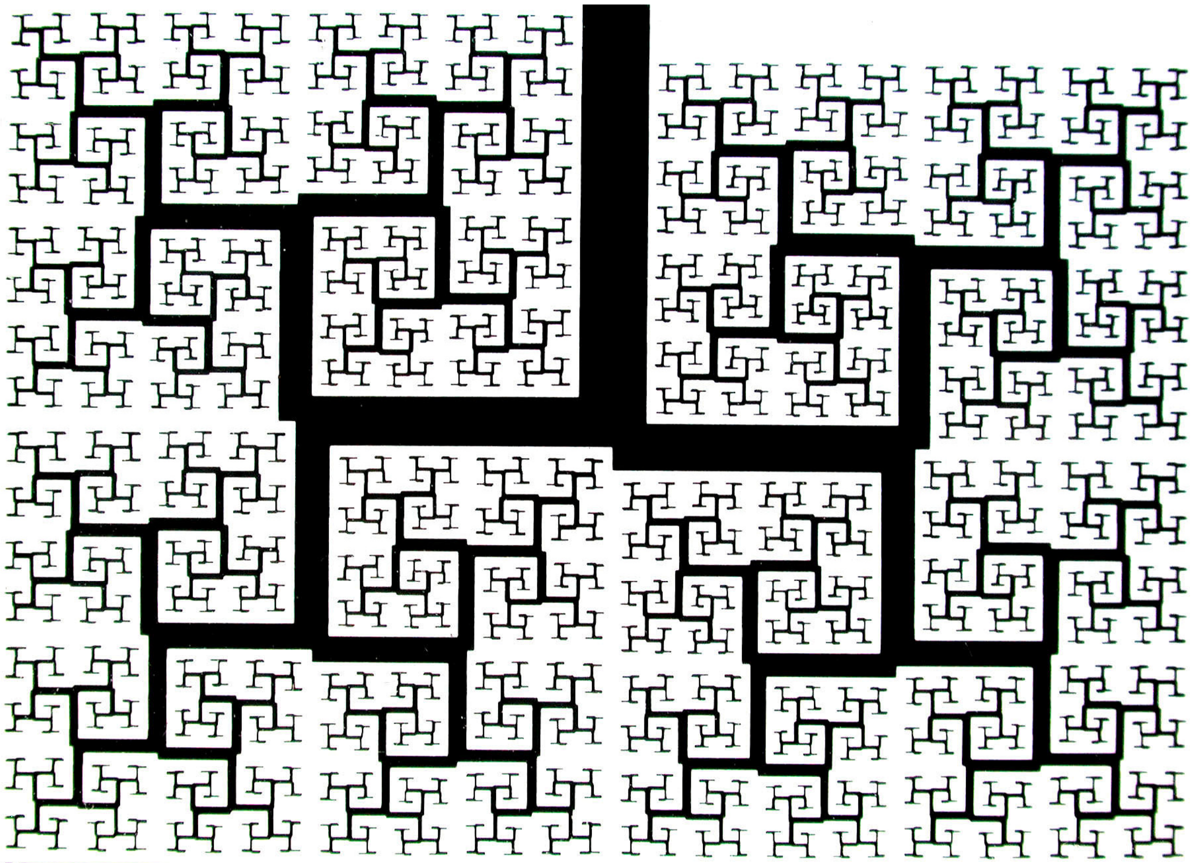
For large N, any $h < 2^{-(1/3)}$ creates an exponentially large resistance and $D_f < 3$.

For large N, any $h > 2^{-(1/3)}$ creates an exponentially large volume and $D_f > 3$.

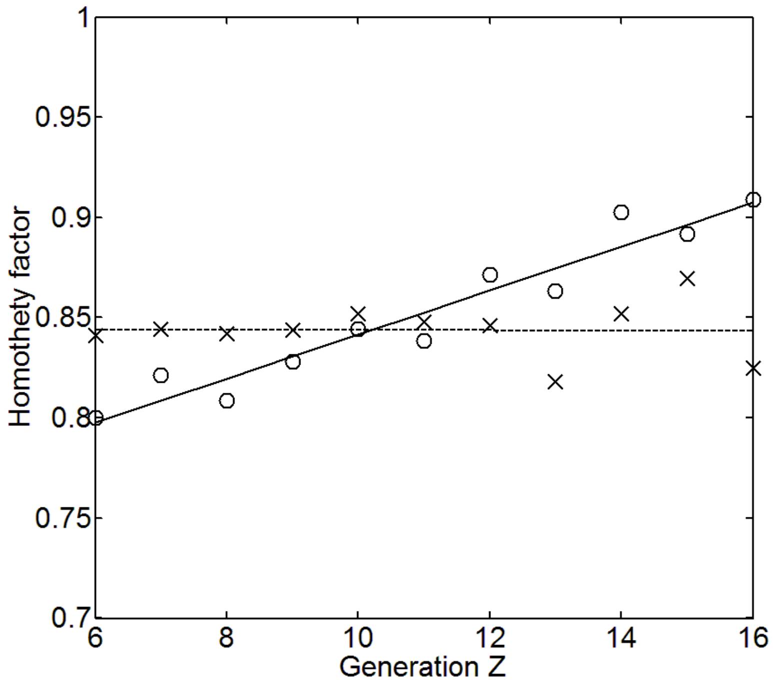
"MAMMALS CANNOT LIVE IN THE THERMODYNAMIC LIMIT"

B. Mauroy, M. Filoche, E. Weibel and B. Sapoval,
The best bronchial tree may be dangerous,
Nature, 677, 663_668 (2004).

The 'Mandelbrot tree' can be really space filling from a geometrical point of view but cannot work from a physical point of view.



What about the real lungs ?
Generation 6 to 16

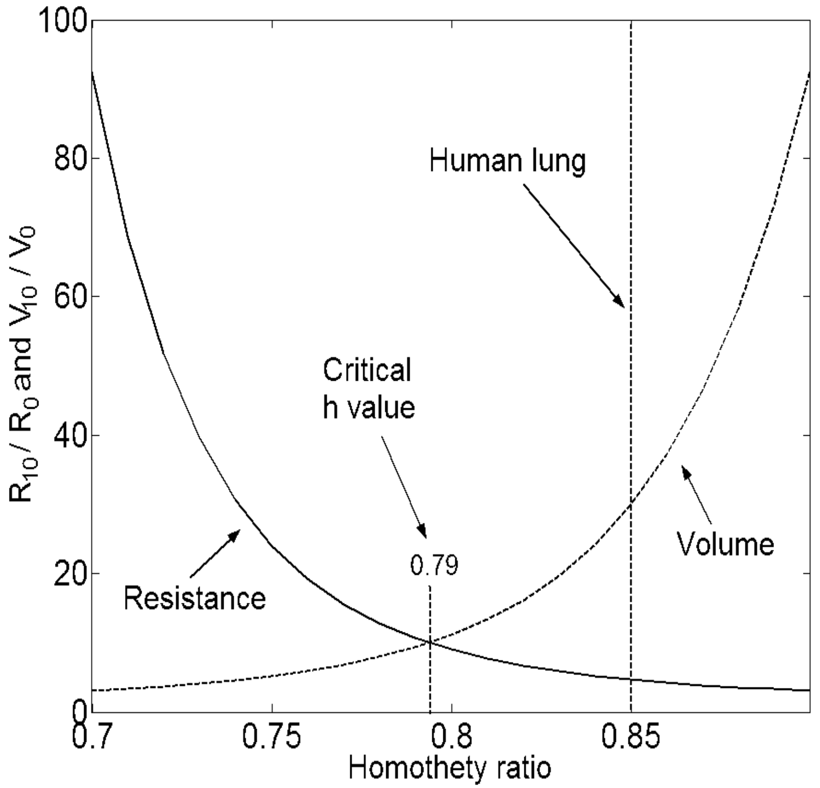


Real data of the human lung (Weibel), circles corresponds to diameters ratio and crosses to length ratio.

Diameters and lengths do no scale exactly in the same fashion.

In that sense the lung is (slightly) self-affine but on average $h = 0.85$ **not far from 0.79.**

For the finite tree that we consider (generation 6 to 16):



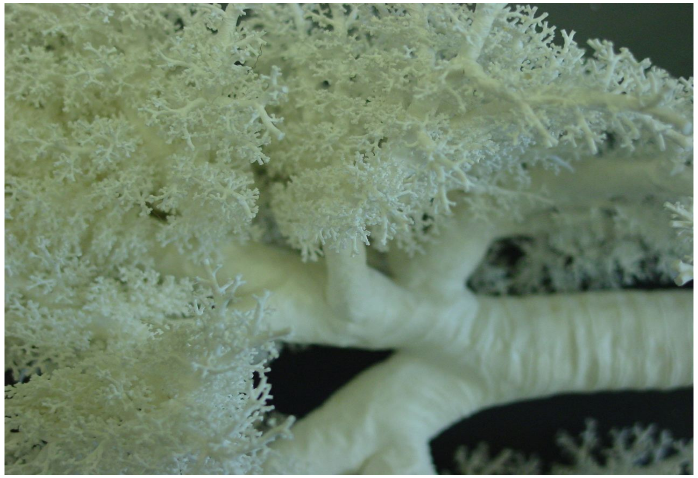
- Both the tree resistance and the tree volume are very sensitive to *h* variations around h = 0.79.

- Human bronchioles have a *somewhat* larger volume than optimality would require. The tree fractal dimension is larger than 3. This not very important as the bronchia occupy 3% of the lung volume.

The bronchiole tree structure is the same for all mammals:

Dog front

Cat front



Pig (zoom)

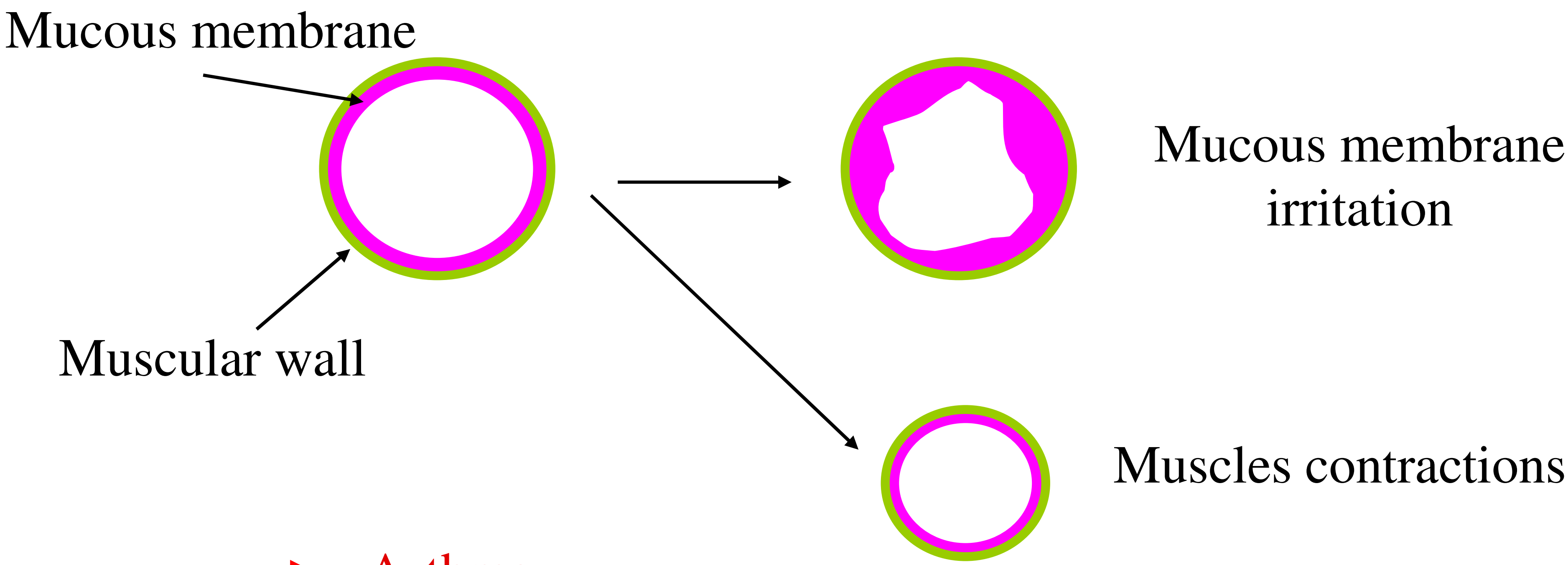
Camel back

Human lung has a *security margin* for the resistance, this authorizes geometrical variability which is always present in living systems.

There is however a strong sensitivity of the resistance to bronchia constriction.

Importance: a factor 2 in the air flux creates severe respiration pathology.

Pathological situations where the inner diameter of the bronchioles (not their lengths) is diminished.



→ Asthma,

Exercise induced broncho-spasm,

Bronchiolitis,

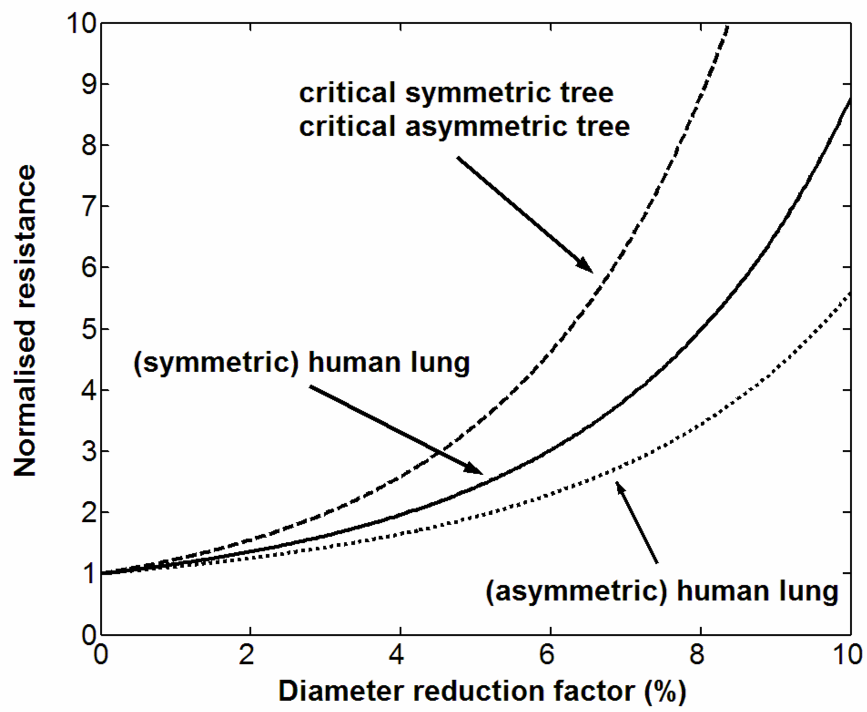
Allergenic reactions to pollen.

To modelise « more realistic » asthma, we assumed that diameters and lengths have different reduction factors : h_d and h_l.

During asthma, the diameter factor changes.

$$\Delta P_N = R_0 \Phi \left(1 + \sum_{p=1}^{N} \frac{1}{2^p} \left(\frac{h_l}{h_d^{\ 4}}\right)^p\right)$$

Another critical factor is obtained for h_d : 0.81 (it depends on $h_l \sim 0.85$ in human lung).



Specific conclusions

The tree structure of lung is close to the physical optimum but has a security margin to adapt its more important characteristic : its resistance.

From a strictly physical point of view, minor differences between individuals can induce considerable differences in respiratory performances.

The higher performances of athletes requires higher ventilation rates to ensure oxygen supply but this is not accompanied by a commensurate adjustment of lung structure. Higher flow rates must be achieved in the given bronchial tree so that its geometry becomes dominant.

There should then exists diameter regulation mechanisms but a more ***optimal*** (in fact more '***critical***') design of the airway tree is dangerous.

More generally:

Physical optimality of a tree is directly related to its fragility so it cannot be the *sole* commanding factor of evolution.

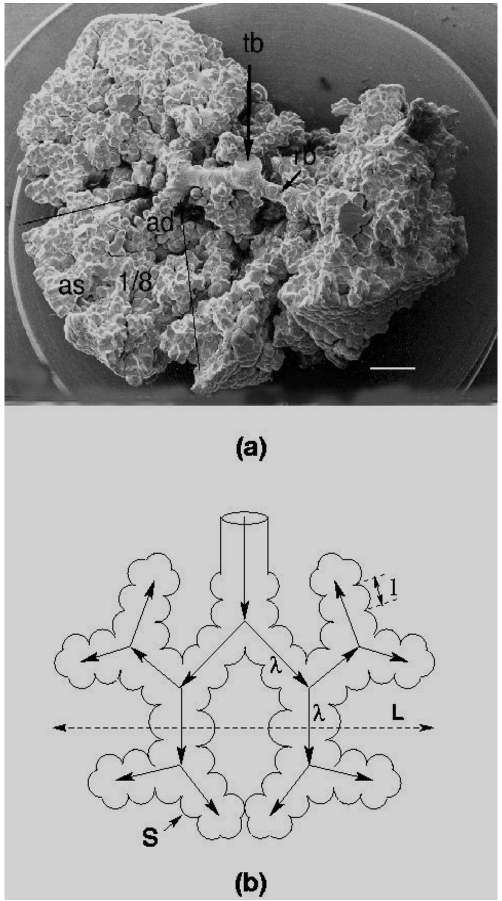
The possibility of regulation (adaptation) can be essential for survival … (Darwin).

3- Efficiency of the human pulmonary acinus:

the role of Laplacian (diffusional) screening effects.

Schematic acinar geometry

Dichotomous tree of alveolated ducts of length λ:



(a)

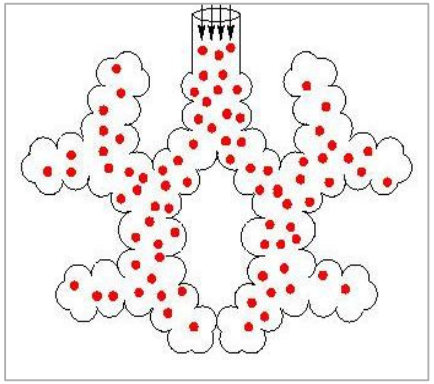
(b)

Questions addressed

- Diffusive transport

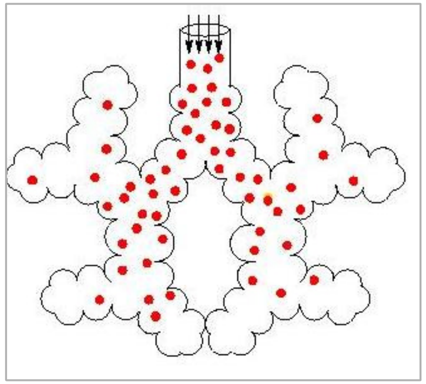
=> **Diffusion screening?**

Classical picture:



?

But?



- Complex morphology

⇒ **Is the structure of the acinus "optimal"?**

=> **What is the most efficient numerical model that captures the key features of the real acinus as a gas exchanger?**

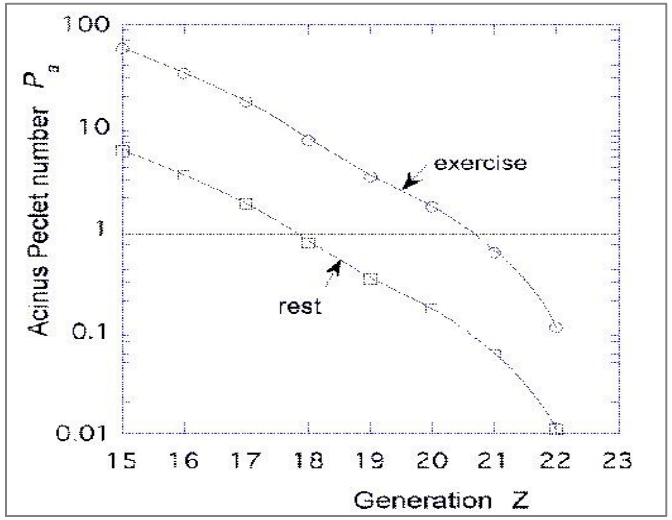
Mechanism for the oxygen transport through the lung: convection versus diffusion ?

At generation the air velocity is u(z) and
the distance to be crossed by diffusion is $(z_{max} - z)\lambda$.

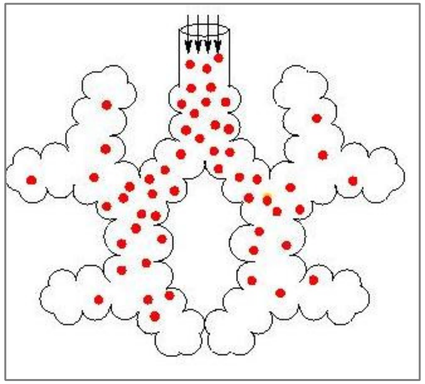
One defines acinus Peclet number: ratio of drift velocity to diffusion velocity

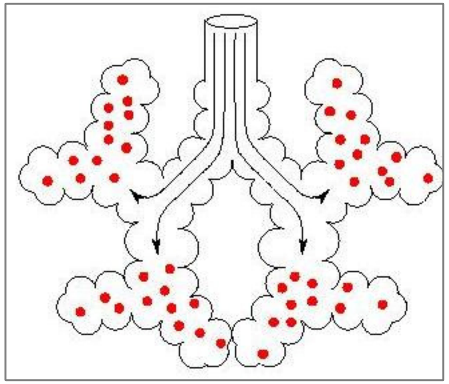
$$P_a = \frac{u(z)(z_{max} - z)\lambda}{D_{O_2,air}}$$

$P_a > 1$ transport by convection
$P_a < 1$ transport by diffusion



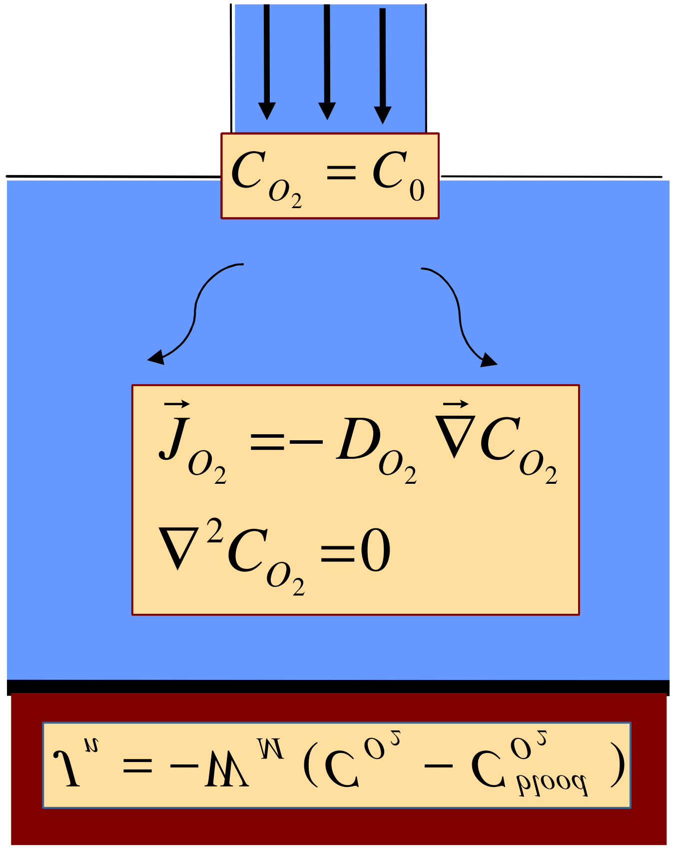
At rest





At exercice

The mathematical model



- At the subacinus entry:
  Diffusion source

- In the alveolar air:
  Steady diffusion obeys Fick's law

- At the air/blood interface:
  Membrane of permeability W_M

The real boundary condition:

$$J_{O_2} = J_n$$

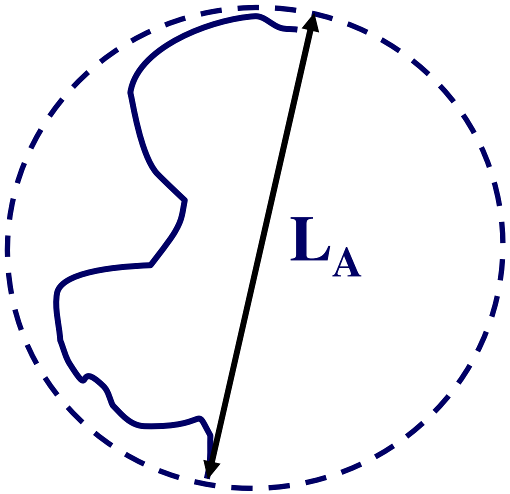
$$\frac{C_X}{\nabla_n C_X} = \frac{D_X}{W_{M,X}} = \Lambda_X$$

= Length

The role of the length Λ: unscreened perimeter length or exploration length:

- Conductance to **reach** a region of the surface:

$\mathbf{Y_{reach} \sim D\, L_A}$ (L_A: diameter of that region)



- Conductance to **cross** that region:

$\mathbf{Y_{cross} \sim W\, A}$ (A: area of the region)

- if $Y_{reach} > Y_{cross}$

$\Rightarrow$ the surface works uniformly.

- if $Y_{reach} < Y_{cross}$

=> less accessible regions are not reached and **there exists diffusion screening: the surface is partially passive.**

The crossover is obtained for:

$$Y_{reach} = Y_{cross} \Rightarrow A/L_A \approx \Lambda$$

What is the geometrical (here morphological) significance of the length $A/L_A = L_p$?

L_p is the perimeter of an "average planar cut" of the surface.

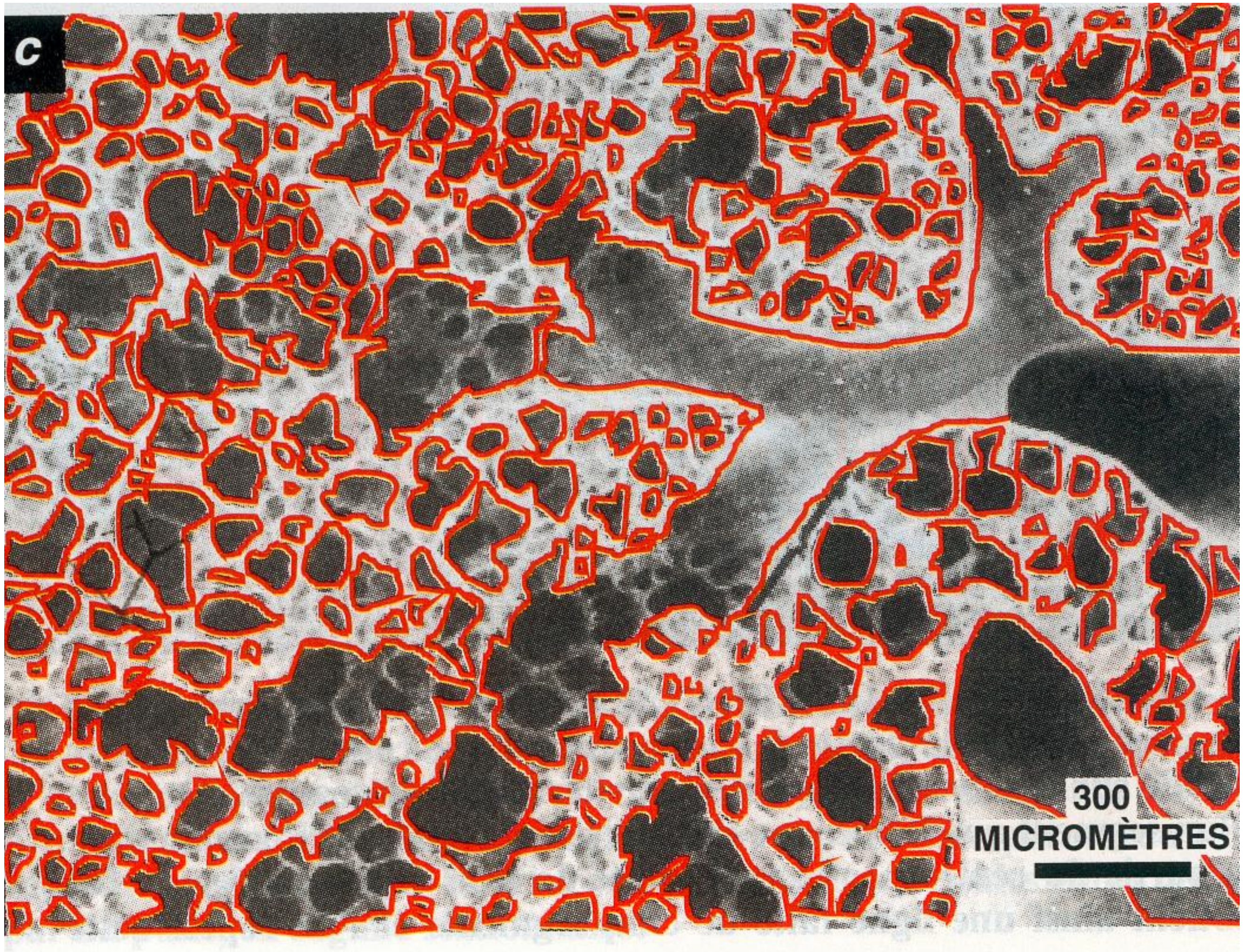
Examples:

Sphere: $A=4\pi R^2$; $L_A=2R$; $A/L_A=2\pi R$.

Cube: $A=6a^2$; $L_A \approx a$; $A/L_A \approx 6a$.

Self-similar fractal with dimension d: $A=l^2(L/l)^d$, $L_A=L$; $A/L_A= l(L/l)^{d-1}$. (Falconer)

Perimeter length of a planar cut of the acinus: total red length.



Permeability W_x of a gas X ?

W_x = (solubility of X).(diffusivity of X in water)/(membrane thickness)

For the human subacinus and oxygen:

$$\begin{cases} A = 8.63 \text{ cm}^2 \\ L = 0.29\text{cm} \end{cases} \Rightarrow L_P \approx 30 \text{ cm}$$

$$\begin{cases} D = 0.2 \text{ cm}^2 \text{ s}^{-1} \\ W = 0.79\ 10^{-2} \text{ cm s}^{-1} \end{cases} \Rightarrow \Lambda = 28 \text{ cm}$$

$$\boxed{\Lambda \approx L_P}\ !$$

B. Sapoval, Fractals in Biology and Medecine (1993).
B.Sapoval, M. Filoche, E.R. Weibel,
Smaller is better, but not too small: a physical scale for the mammalian acinus
Proc. Nat. Ac. Sc. **99**, 10411 (2002).

Other mammals:

	Mouse	Rat	Rabbit	Human
Acinus volume (10^{-3} cm^3)	0.41	1.70	3.40	23.4
Acinus surface (cm^2)	0.42	1.21	1.65	8.63
Acinus diameter (cm)	0.074	0.119	0.40	0.286
Acinus perimeter, L_p(cm)	5.6	10.2	11.0	30
Membrane thickness (μ. m)	0.60	0.75	1.0	1.1
Λ (cm)	15.2	18.9	25.3	27.8

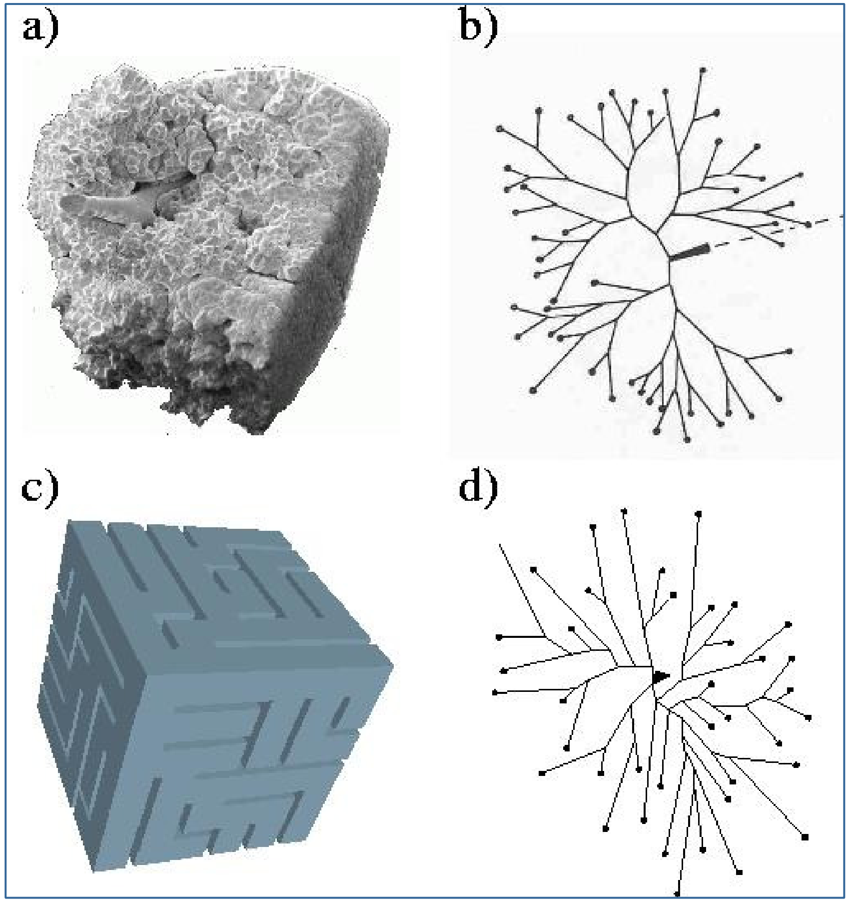
Numerical model of the human acinus

a) Cast of a real human subacinus

c) Kitaoka's model for a human subacinus

$L = 6\,\ell$

$\ell = 0.5$mm



b) Topological structure of a human subacinus

d) Topological structure of the geometry in c)

The acinus efficiency η:

→ **NUMBER WHICH MEASURES DIFFUSION SCREENING**

$$\eta_{O_2} = \frac{\text{Flux across the membrane}}{\text{Flux for infinite diffusivity}} = \frac{\int W\, P_{O_2}\, ds}{W\, P_0\, S_{ac}}$$

$$\Phi_p = \frac{V_p}{V_{ac}} \cdot \Phi_{ac}$$

$$\Phi_{ac} = \eta\, W\, P_0 S_{ac}$$

V_p lung volume

V_{ac} acinus volume

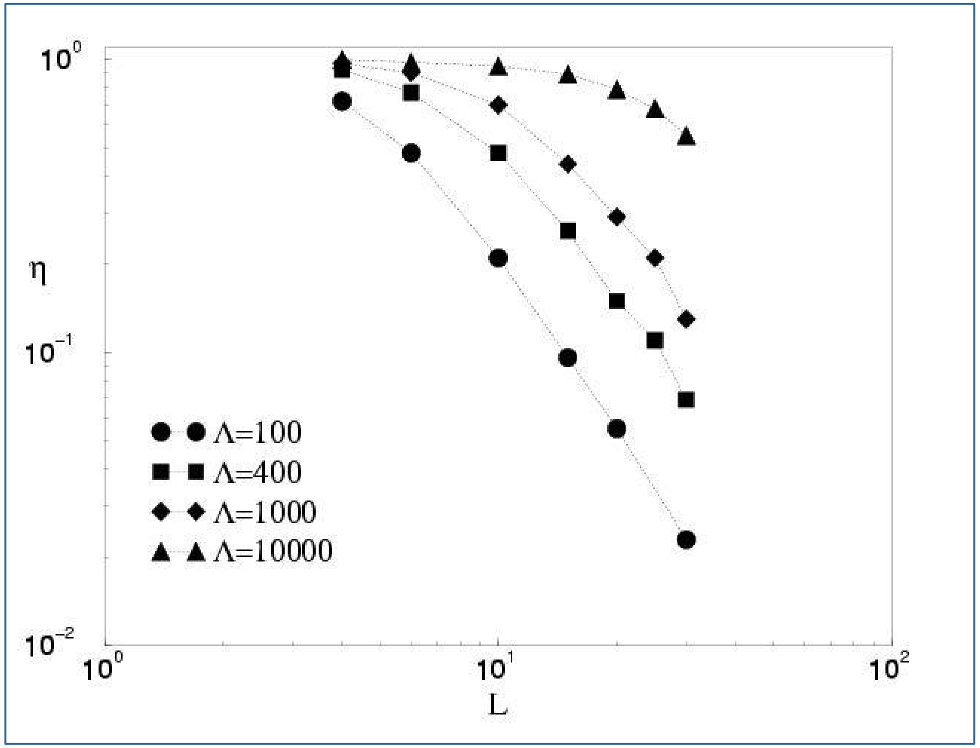
$$S_{ac} \propto V_{ac}$$

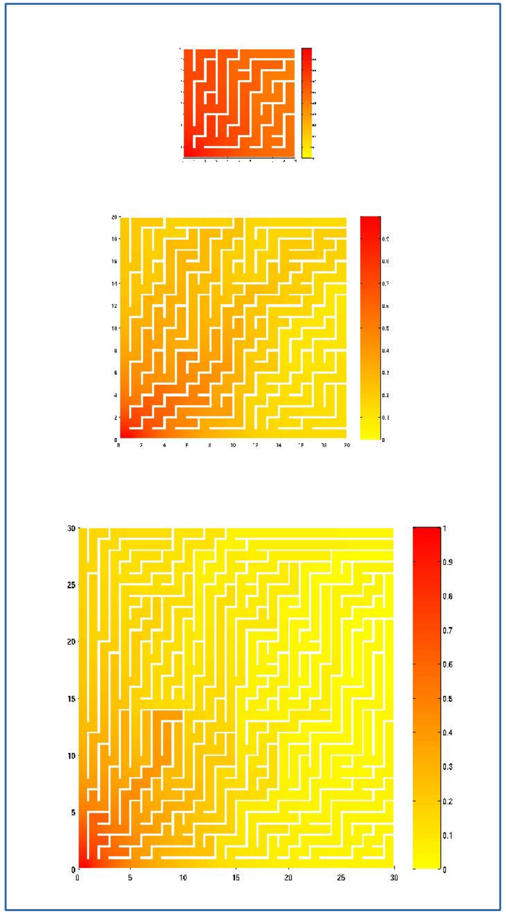
$$\Phi_{lung} \propto V_p\, W P_0 \cdot \eta$$

Why do we need so many subacini?

The efficiency decreases with the size

⇨ smaller acini are more efficient!

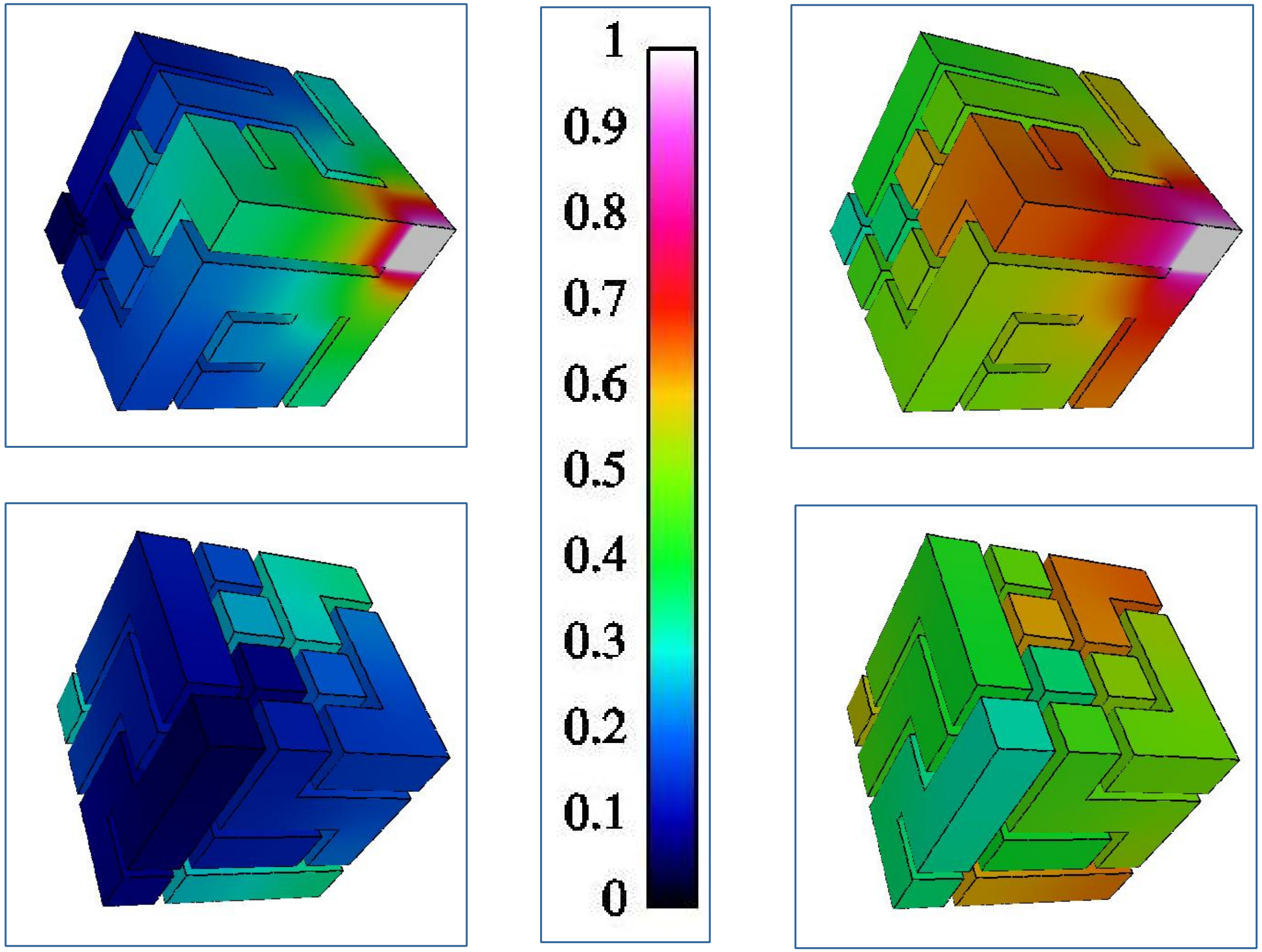




B.S., M. Filoche, E.R. Weibel, Proc. Nat. Ac. Sc. **99**, 10411 (2002).
M. Felici, M. Filoche, B. Sapoval, Journal of Applied Physiology, 84: 2010 (2003)

Direct 3D FEM computation

$\Lambda=32\ell$



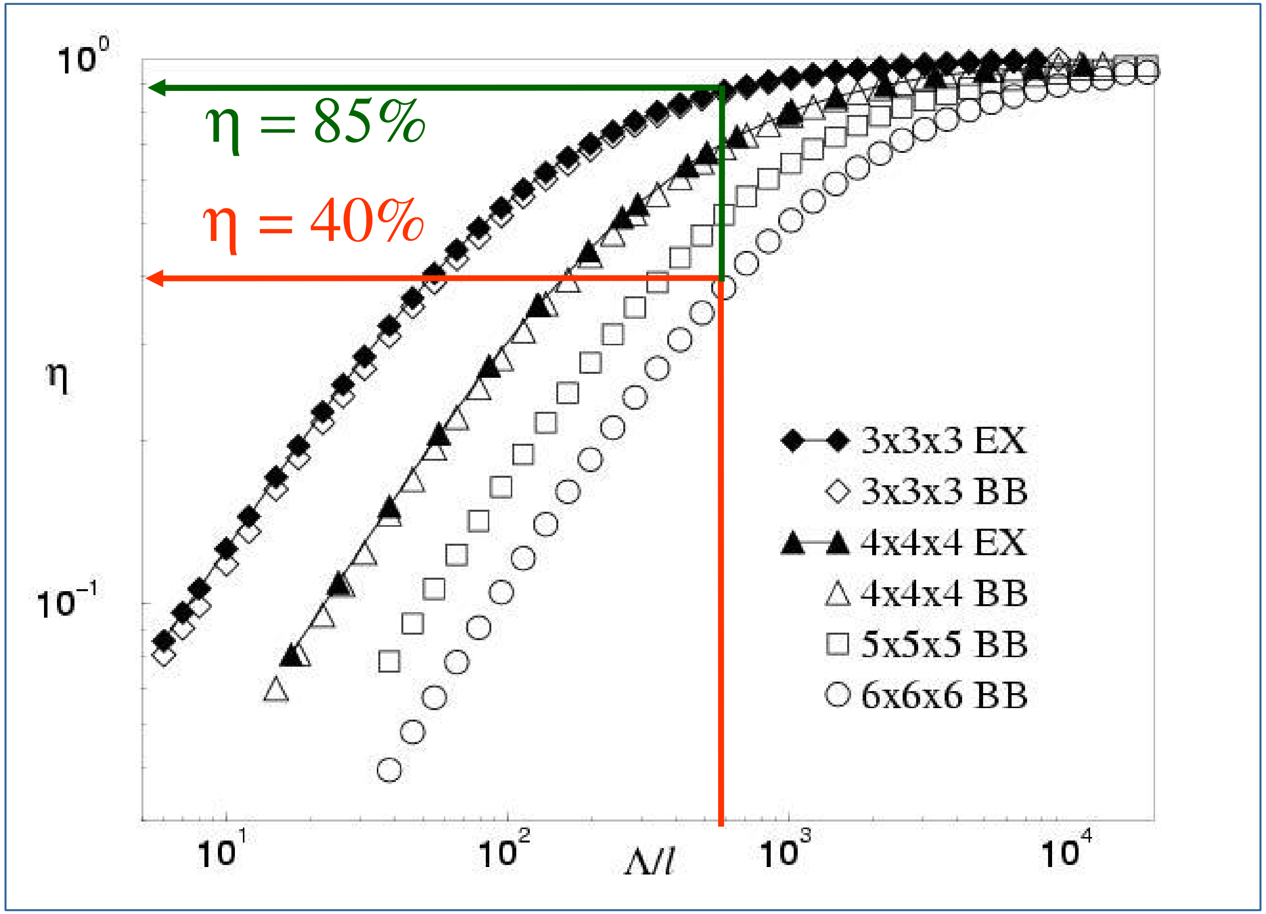
$\Lambda=256\ell$

Acinus efficiency

Human subacinus:
L=6ℓ ; Λ=600ℓ

At rest
η = 40%

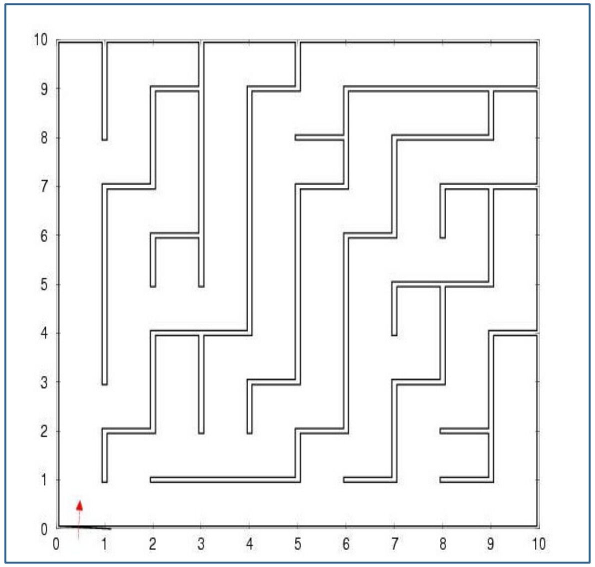
At exercice
η = 85%

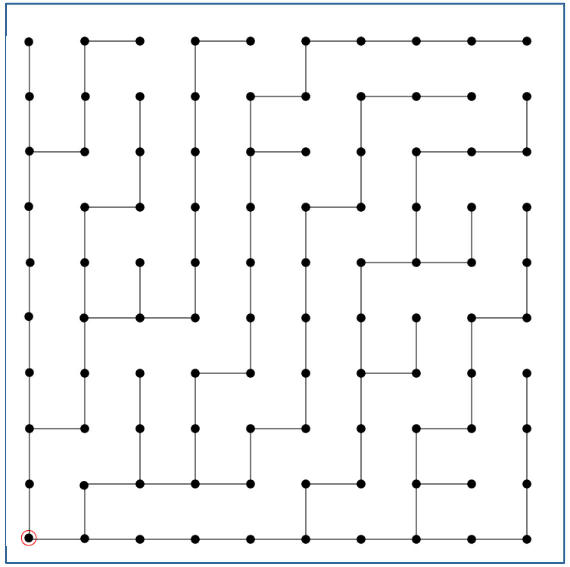


Renormalized random walk:

The coarse-grained approach

Volumic tree-like structure → Topological "skeleton" → Tree-like network





Random walk simulation on a lattice

Bulk diffusion: D ➡ Random walk on lattice: $D=a^2/2d\tau$

Membrane permeability: W ➡ Absorption probability σ:

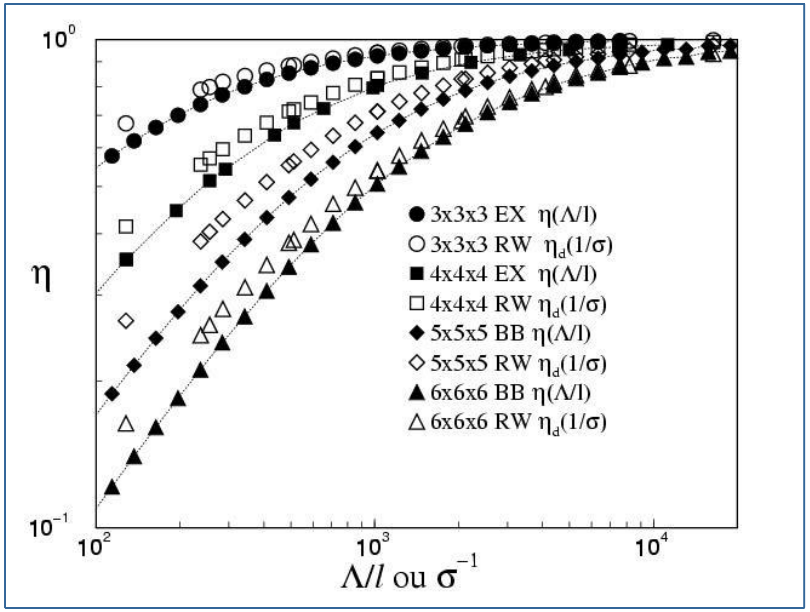
$W = a\,\sigma/2d\tau(1-\sigma)$ ➡ $\Lambda=a(1-\sigma)/\sigma \approx a/\sigma$

Concentration **C(x)** ➡ Mean occupation of the site i $\langle \mathbf{K_i} \rangle$

- On defines the efficiency by analogy between both models

$$\eta = \frac{\int \mathbf{WCdS}}{\mathbf{WC_0S}} \Rightarrow \eta = \frac{\sum_i \langle \mathbf{K}_i \rangle \mathbf{s}_i}{\langle \mathbf{K}_0 \rangle \sum_i \mathbf{s}_i}$$

Validation of the approach using Kitaoka's geometries

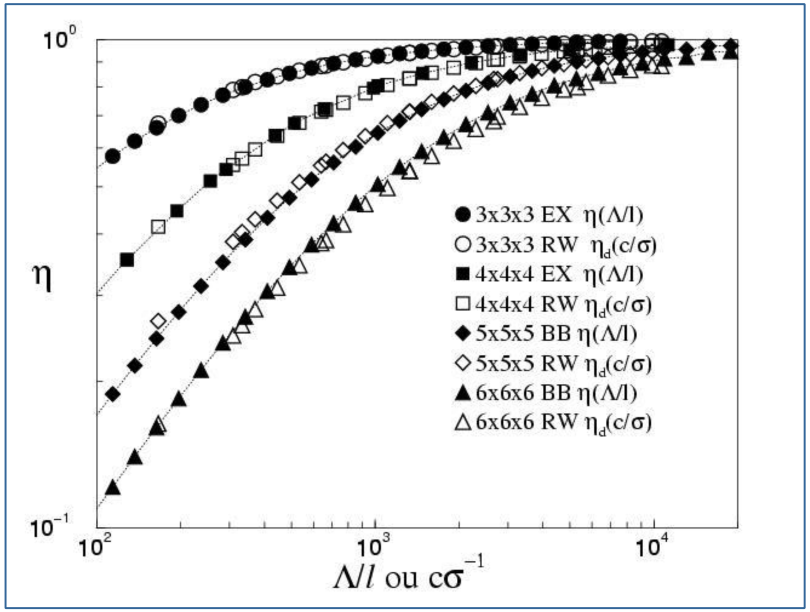


$a \rightarrow \ell$

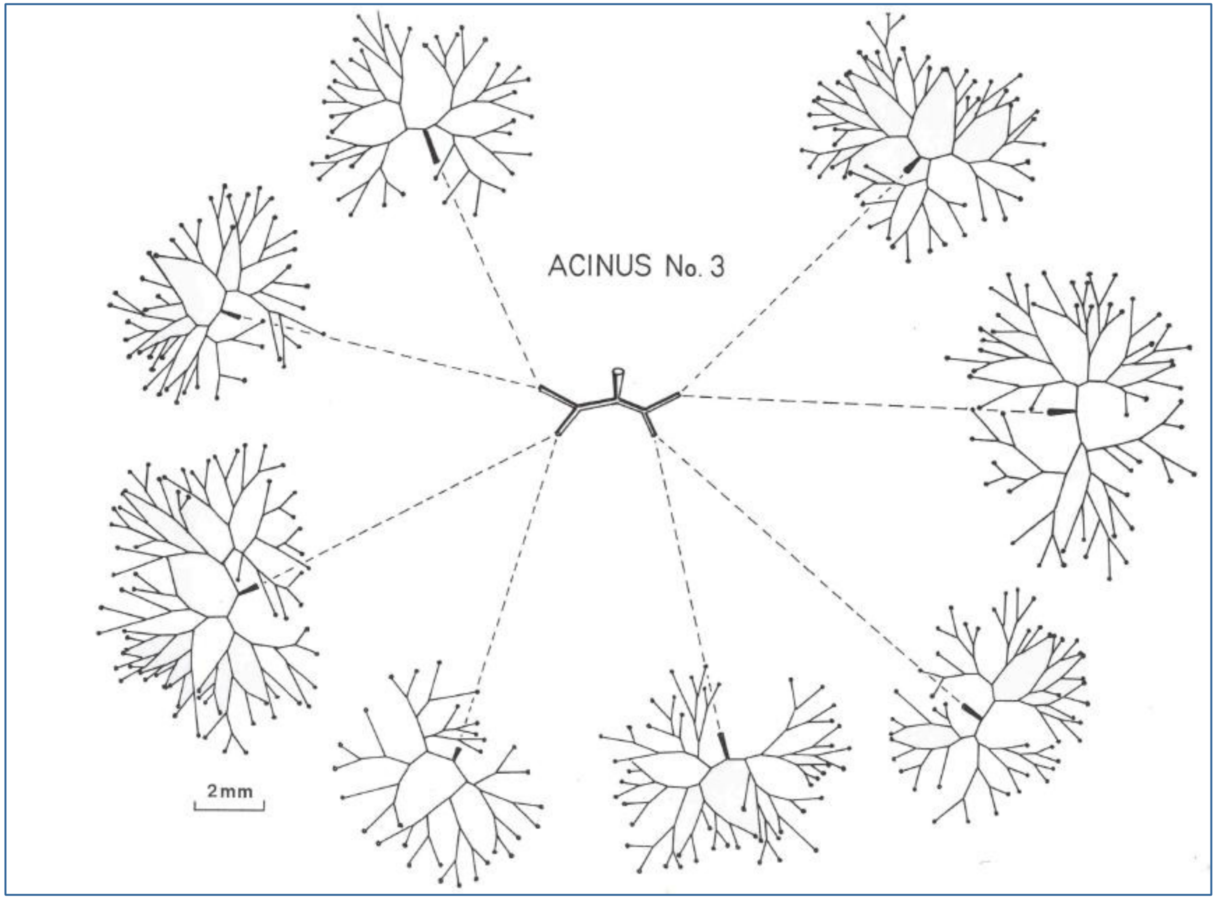
$n_i = 2d - s_i \quad ; \quad s_i = 1, \ldots, (2d-1)$

σ ? Λ/ℓ

$\Lambda/\ell \leftrightarrow c \cdot \sigma^{-1}$

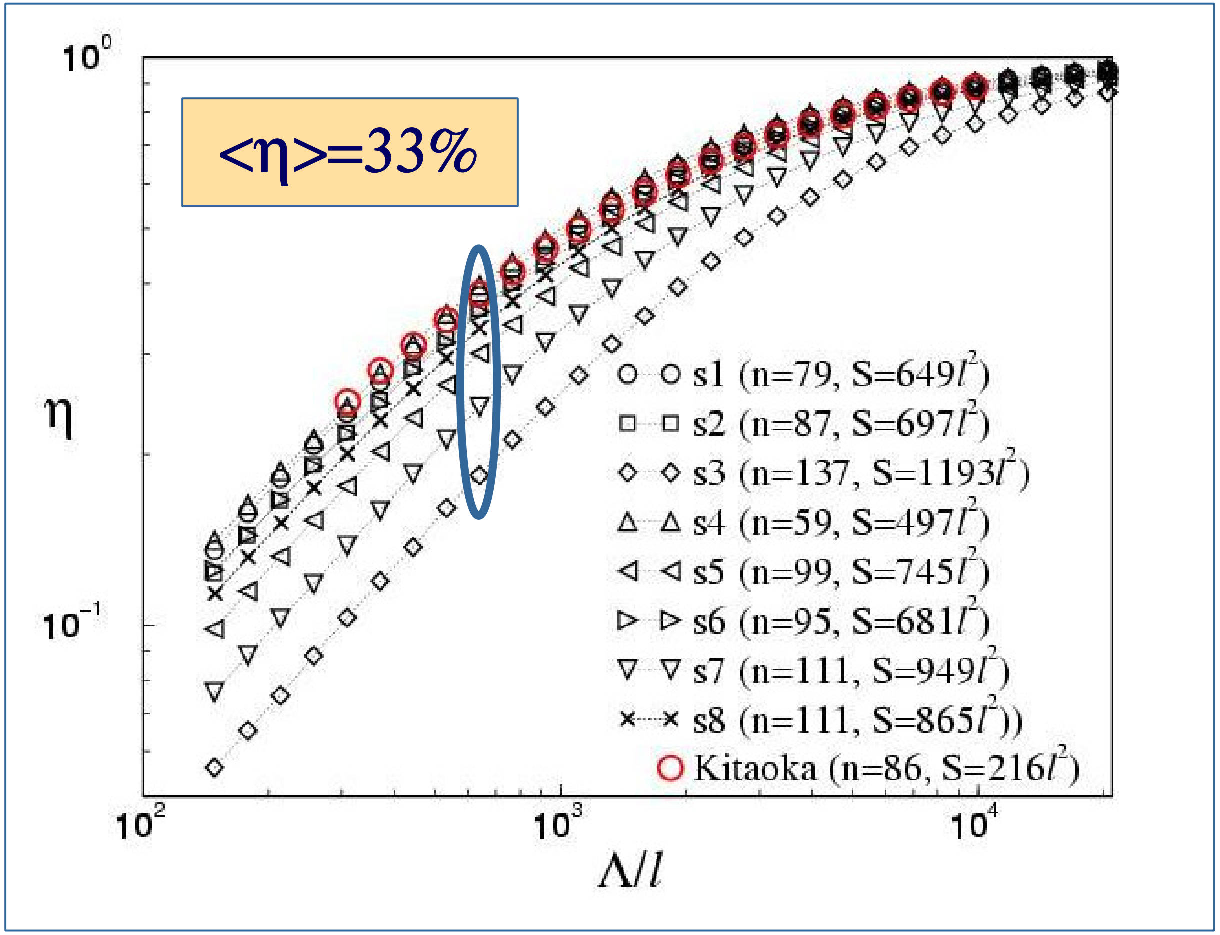


Random walks on the real morphometric trees.



B. Haefeli-Bleuer, E.R. Weibel, Anat. Rec. 220: 401 (1988)

Efficiency of real acini



M. Felici, M. Filoche, and B. Sapoval,
Renormalized Random Walk Study of Oxygen Absorption in the Human Lung,
Phys. Rev. Lett. 92,068101-1 (2004).

The acinus: also a CO_2 exchanger

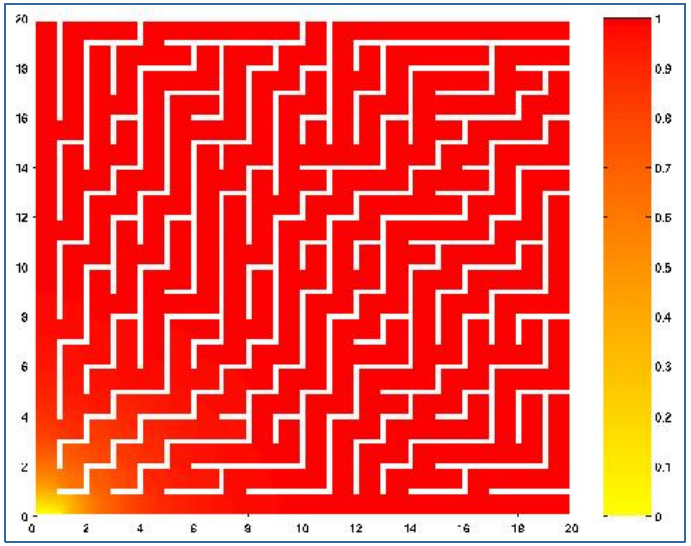
$$\mathbf{W}_{\mathbf{CO_2}} = \mathbf{20} \cdot \mathbf{W}_{\mathbf{O_2}}$$

$$\Rightarrow \Lambda_{\mathbf{CO_2}} = \frac{\mathbf{1}}{\mathbf{20}} \Lambda_{\mathbf{O_2}}$$

$$\Phi_{CO_2} = \eta_{CO_2} W_{CO_2} \left(P_{CO_2}^{blood} - P_{CO_2}^{entry} \right) S_{ac}$$

$$\Phi_{O_2} = \eta_{O_2} W_{O_2} \left(P_{O_2}^{blood} - P_{O_2}^{entry} \right) S_{ac}$$

2D map of CO_2 partial pressure



If the fluxes are equal:

$$P_{O_2}^{blood} = P_{O_2}^{entry} + \frac{\eta_{CO_2} W_{CO_2}}{\eta_{O_2} W_{O_2}} \left(P_{CO_2}^{entry} - P_{CO_2}^{blood} \right)$$

measured = 40 mmHg
computed = 38.5 mmHg

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PRL 92 (6), 060401–069901, 13 FEBRUARY 2004 (264 total pages)

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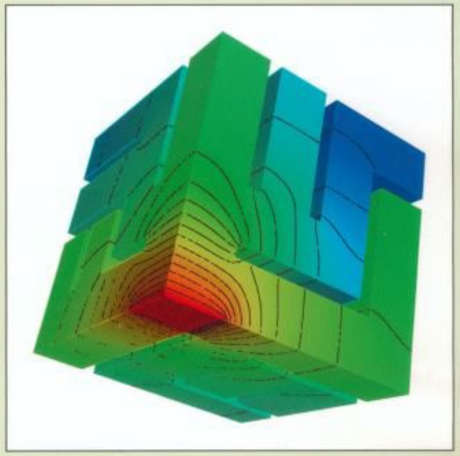

6

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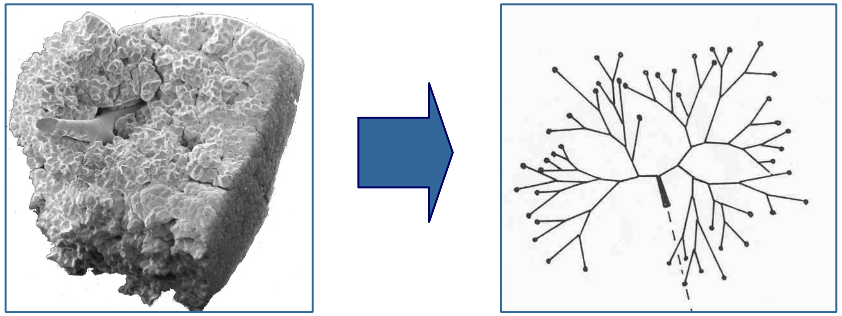
Physiological consequences

- Ventilation-perfusion matching
- Influence of physiological or structural modifications in several pathologies (pulmonary edema).
- New-borns acini are small: they are efficient: they cannot increase their efficiency. In case of exercize this creates cyanosis.
- Role of helium/oxygen mixture (Heliox). Paradox…

Conclusions

- The tree-like topology of the acinus determines its efficiency as a gas exchanger.



- The acinus does not work efficiently at rest(η = 30-40 %).
- It becomes efficient in exercise conditions (η = 90-100 %).
- The coarse-graining approach can be applied to compute the efficiency of real acini.
- The model explains the ratio between partial pressures differences in O_2 and CO_2 , and casts a new light on various physiological phenomena.