Magic Transport in Mammalian Respiration

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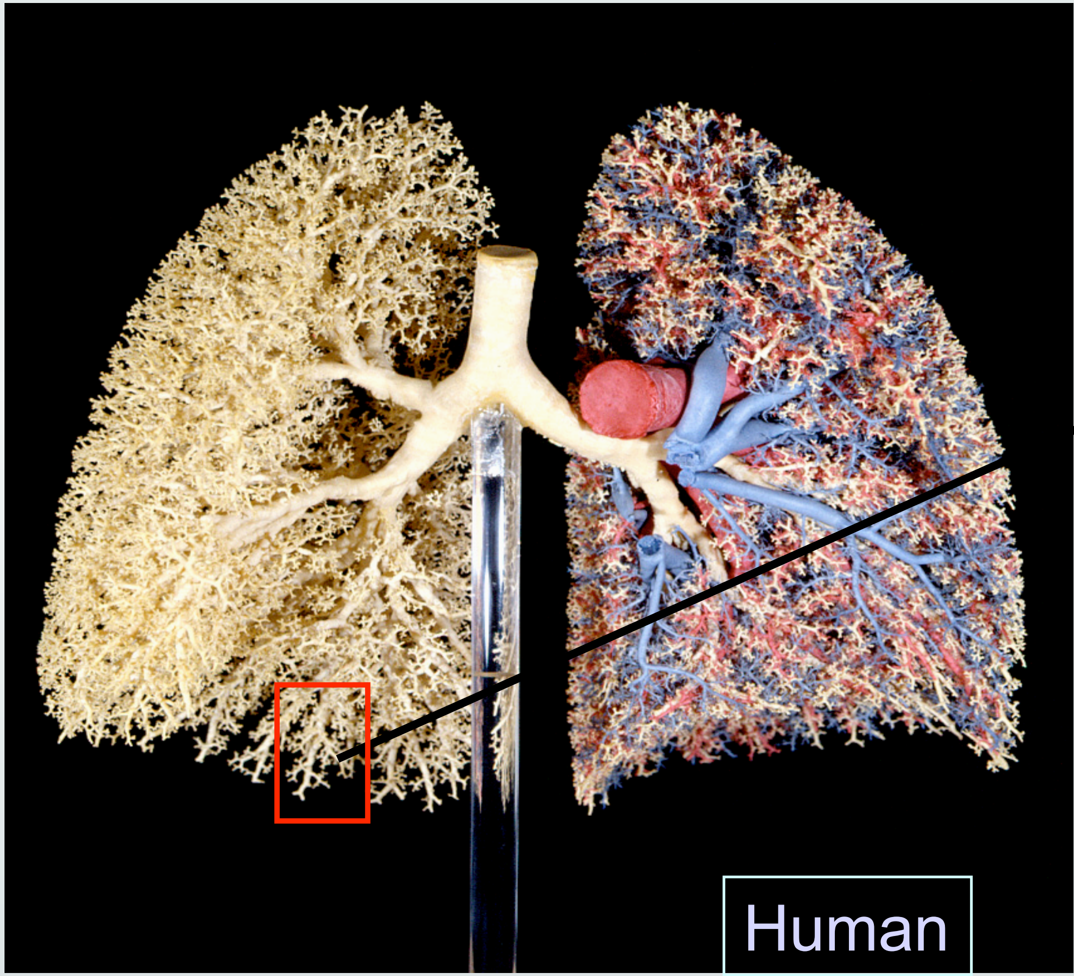
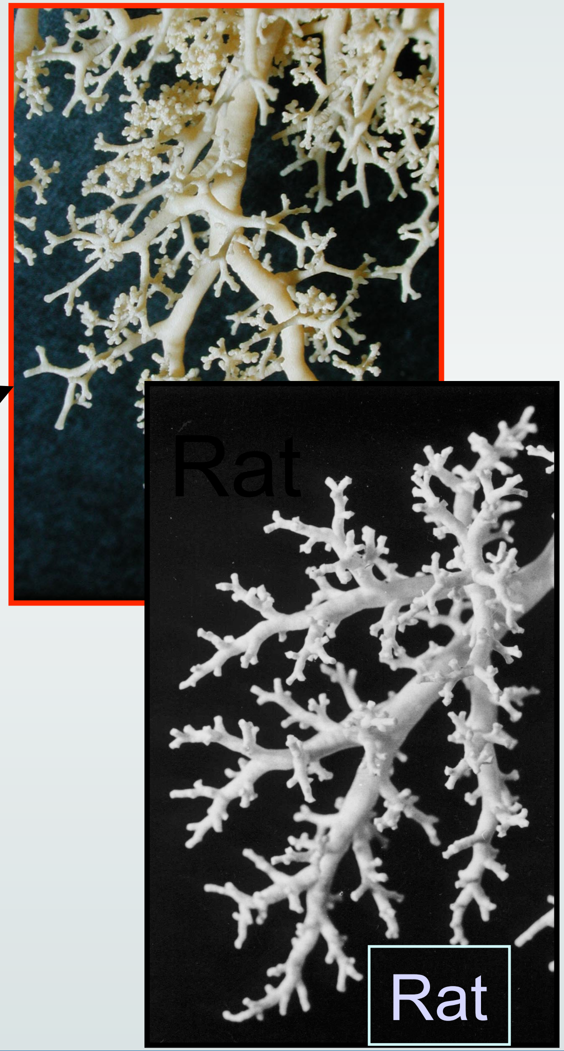
The respiration system of mammals is made of two successive tree structures.

The first structure is a purely conductive tree in which oxygen is transported with air and no oxygen is absorbed.

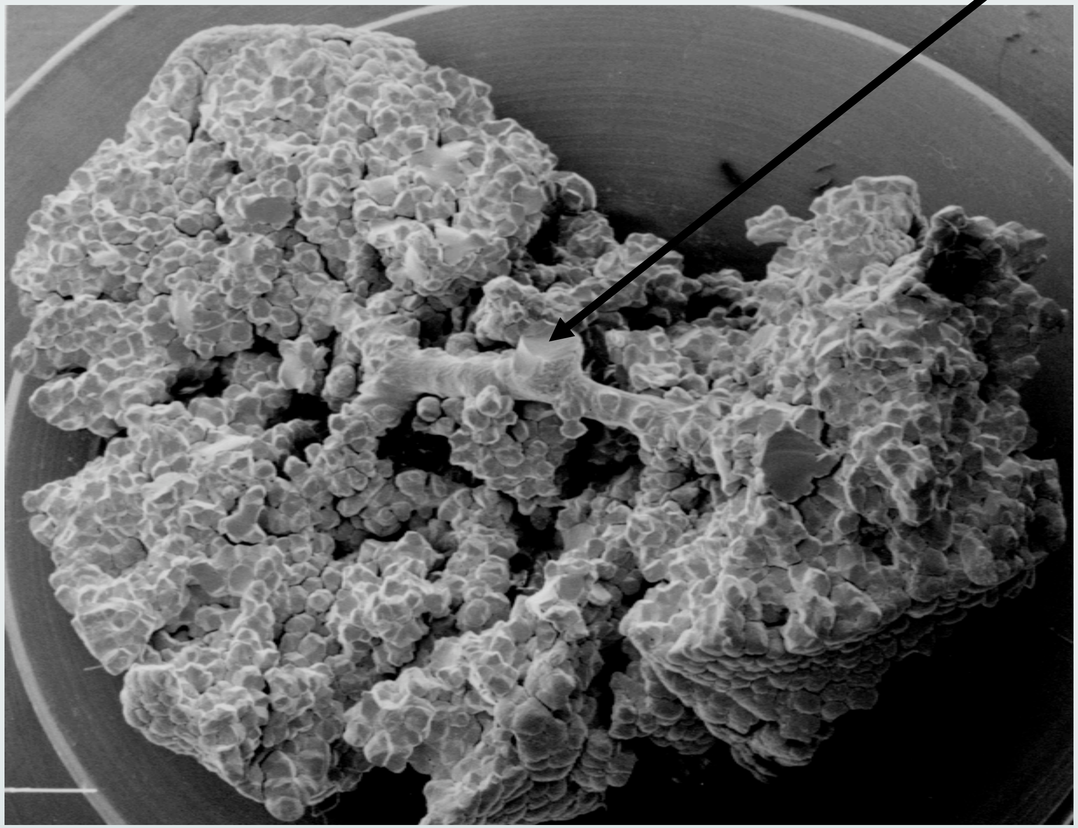
Conductive tree with 15 successive bifurcations: 2^{15} = 30,000 bronchioles?

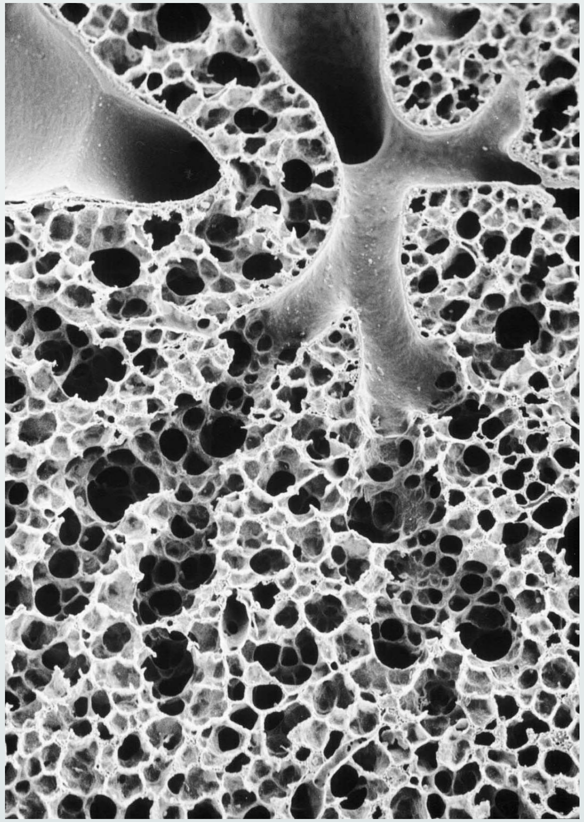


Cast of human lung - Weibel



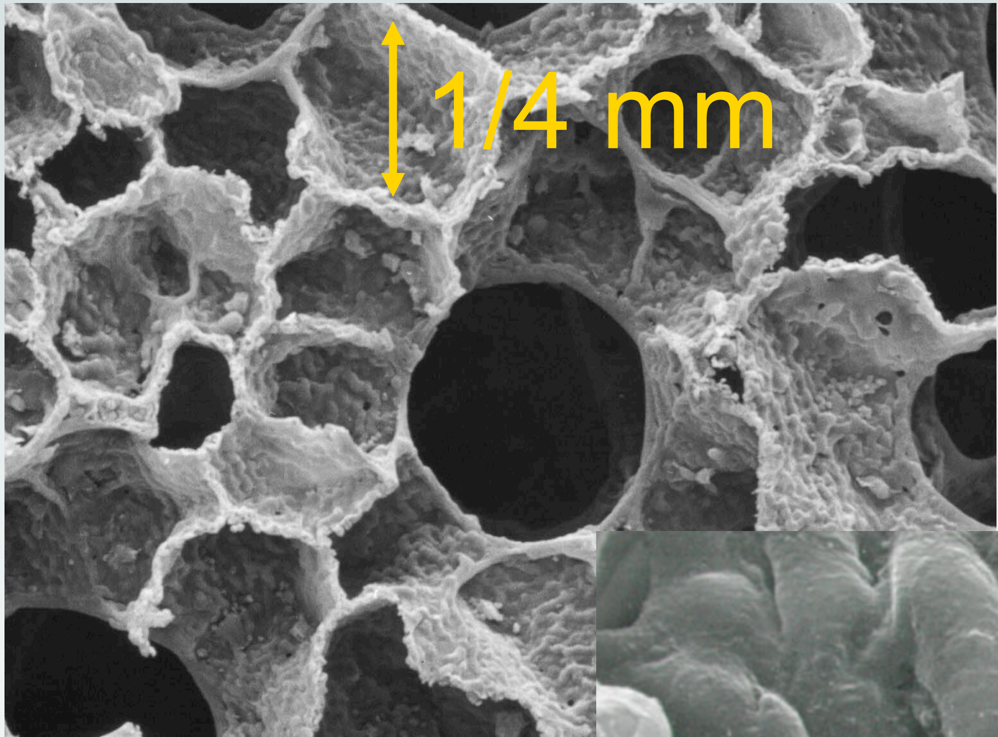
Each bronchiole is the opening of a diffusion-reaction tree of 8 generations in average: a pulmonary acinus

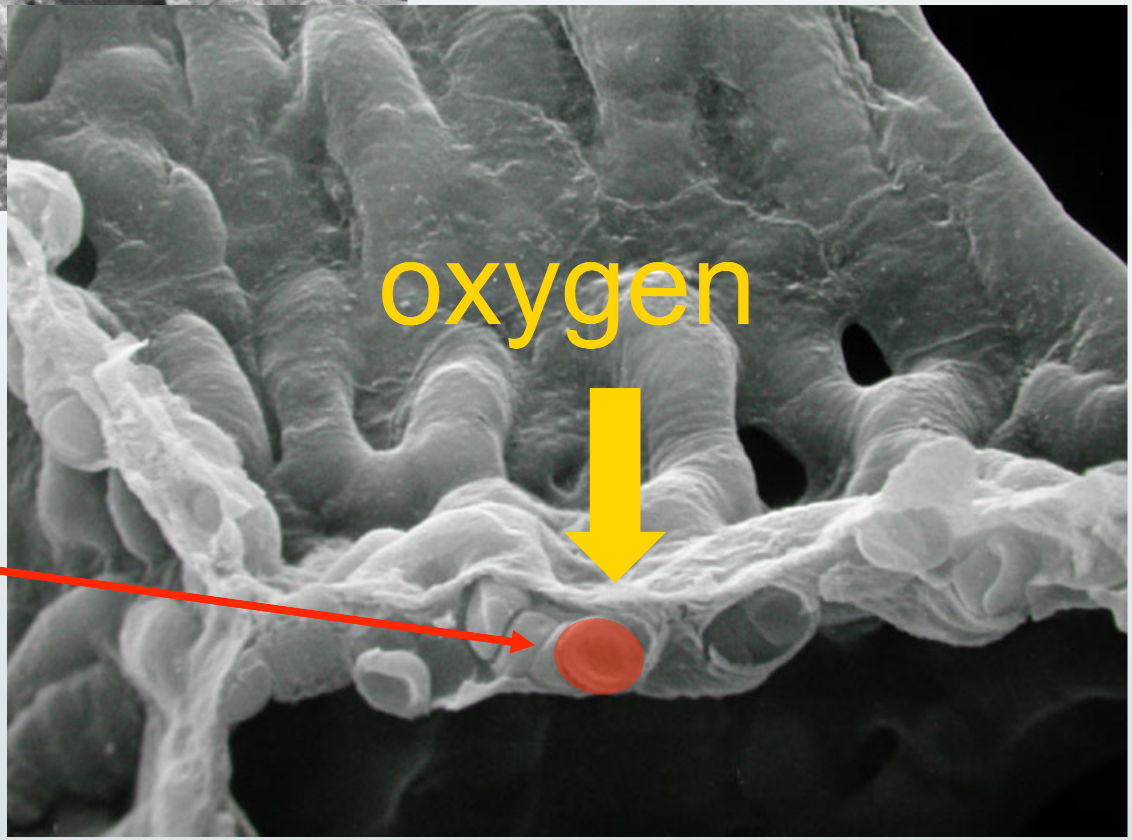




Cut of an acinus

pulmonary alveolae (300 millions)

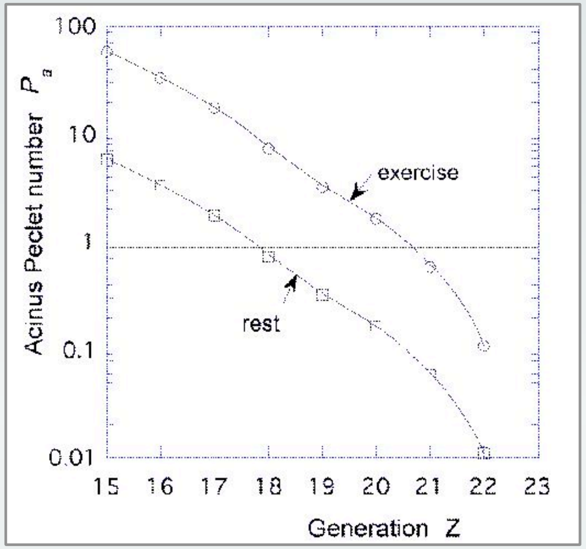




Convection/diffusion transition

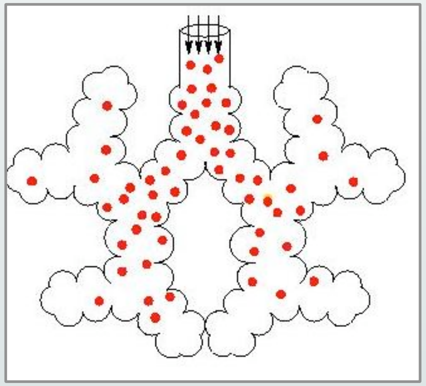
Acinus Peclet number:

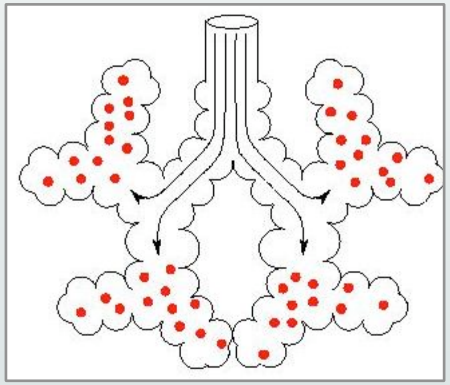
$$P_a(Z) = \frac{U(Z)(Z - Z_{max})\lambda}{D_{O2,air}}$$



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

At rest





At exercice

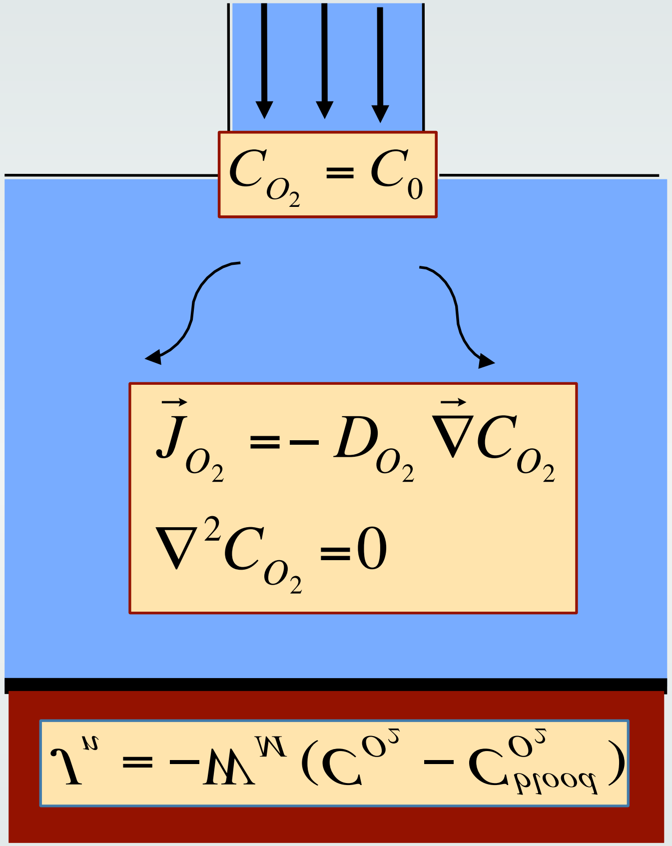
B.Sapoval, M. Filoche, E.R. Weibel, PNAS 99: 10411 (2002)

The mathematical frame

- 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

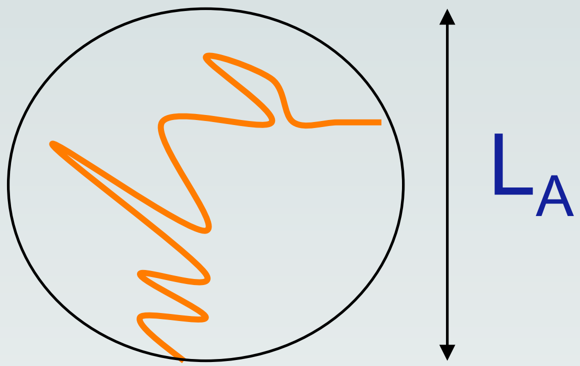


The real boundary condition::

$$J_{O_2} = J_n$$

Robin or Fourier BC: $$\frac{C_X}{\nabla_n C_X} = \frac{D_X}{W_{M,X}} = \Lambda_X = \text{Length}$$

Consider an irregular surface of area A and diameter L_A. How do we know if there is screening or not?



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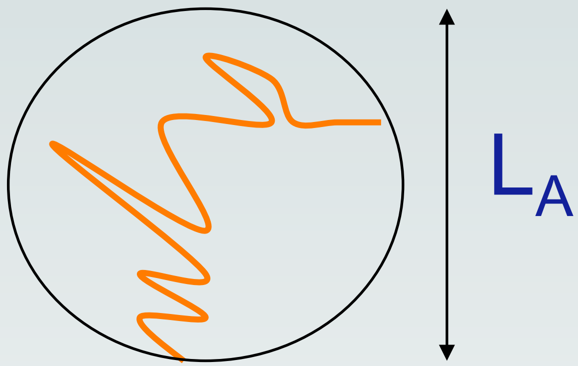

By comparing the conductance to reach the surface $Y_{reach} \sim D.L_A$ with the conductance to cross it $Y_{cross} \sim W.A$

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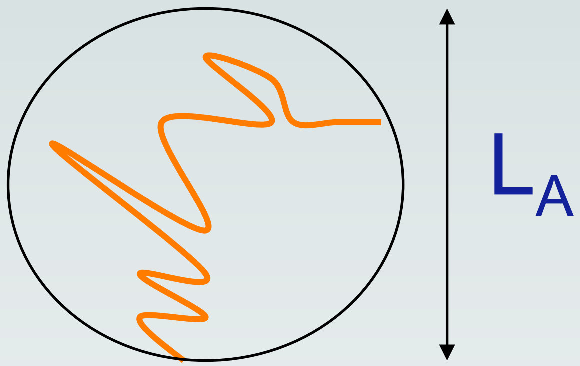
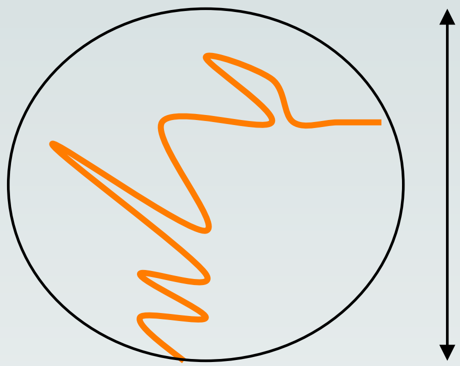


By comparing the conductance to reach the surface $Y_{reach} \sim D.L_A$ with the conductance to cross it $Y_{cross} \sim W.A$

- if $Y_{reach} > Y_{cross}$ the surface works uniformly
- if $Y_{reach} < Y_{cross}$ the less accessible regions are not reached,

transport is limited by diffusion, there is diffusion screening.

Consider an irregular surface of area A and diameter L_A. How do we know if there is screening or not?



By comparing the conductance to reach the surface $Y_{reach} \sim D.L_A$ with the conductance to cross it $Y_{cross} \sim W.A$

- if $Y_{reach} > Y_{cross}$ the surface works uniformly
- if $Y_{reach} < Y_{cross}$ the less accessible regions are not reached, there is strong diffusion screening.

crossover when:

$$Y_{reach} = Y_{cross}$$

$$\text{or } A/L_A \approx D/W = \Lambda$$

More generally this notion permits the comparison of bulk Laplacian and surface processes with morphology.

Λ is the ratio of the bulk transport coefficient to the surface transport coefficient

Here $\Lambda = D/W$

Heterogeneous catalysis: $\Lambda = D/R$ (reactivity)

Electrochemistry: Λ = (electrolyte conduct. / surface conduct.)

NMR relaxation: $\Lambda = D/W$ (spin permeability proportional to the surface spin relaxation rate)

Single phase porous flow Λ = hydraulic permeability/ surface permeability

Heat transport …

- if $A/L_A < \Lambda$ the surface works uniformly
- if $A/L_A > \Lambda$ the less accessible regions are not reached, there exists diffusion limitations

The crossover is obtained for:

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

So what is A/L_A???

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

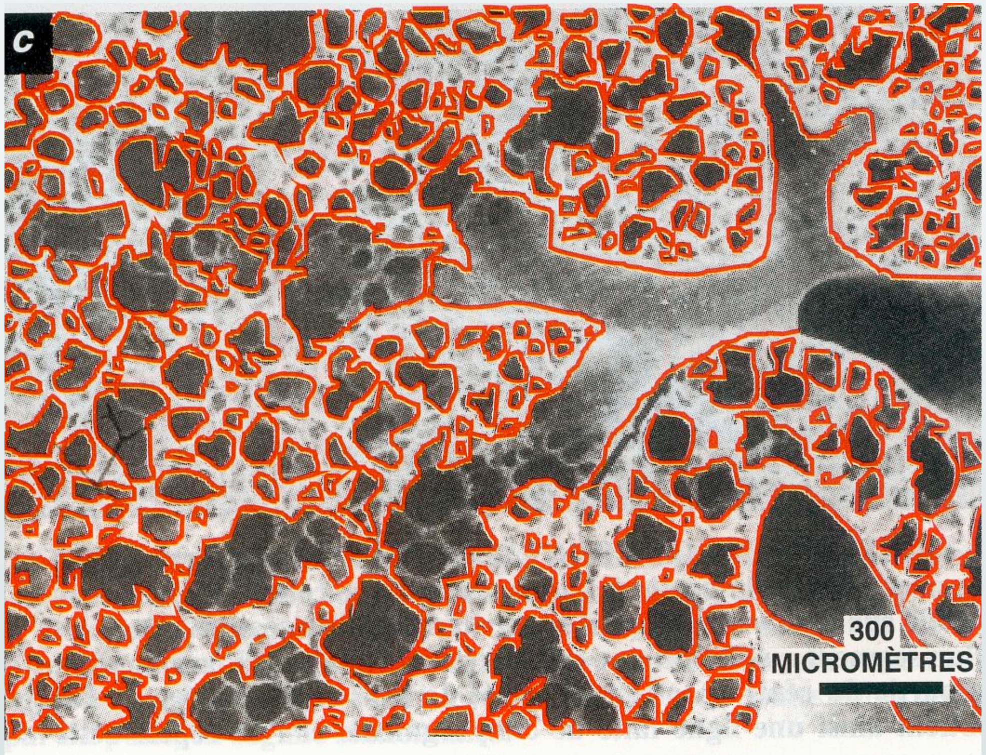
Cube: $A=6a^2$; $L_A \approx a$; $A/L_A \approx 6a$.

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

Experiment ...

For an irregular surface A/L_A is the total length of a planar cut.

In the acinus case: length the red curve. $A/L_A = L_p$



Permeability W_M for O_2?

W_M = (O_2 solubility).(O_2 diffusivity in water)/(membrane thickness)

For the human 1/8 sub-acinus and oxygen in air:

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

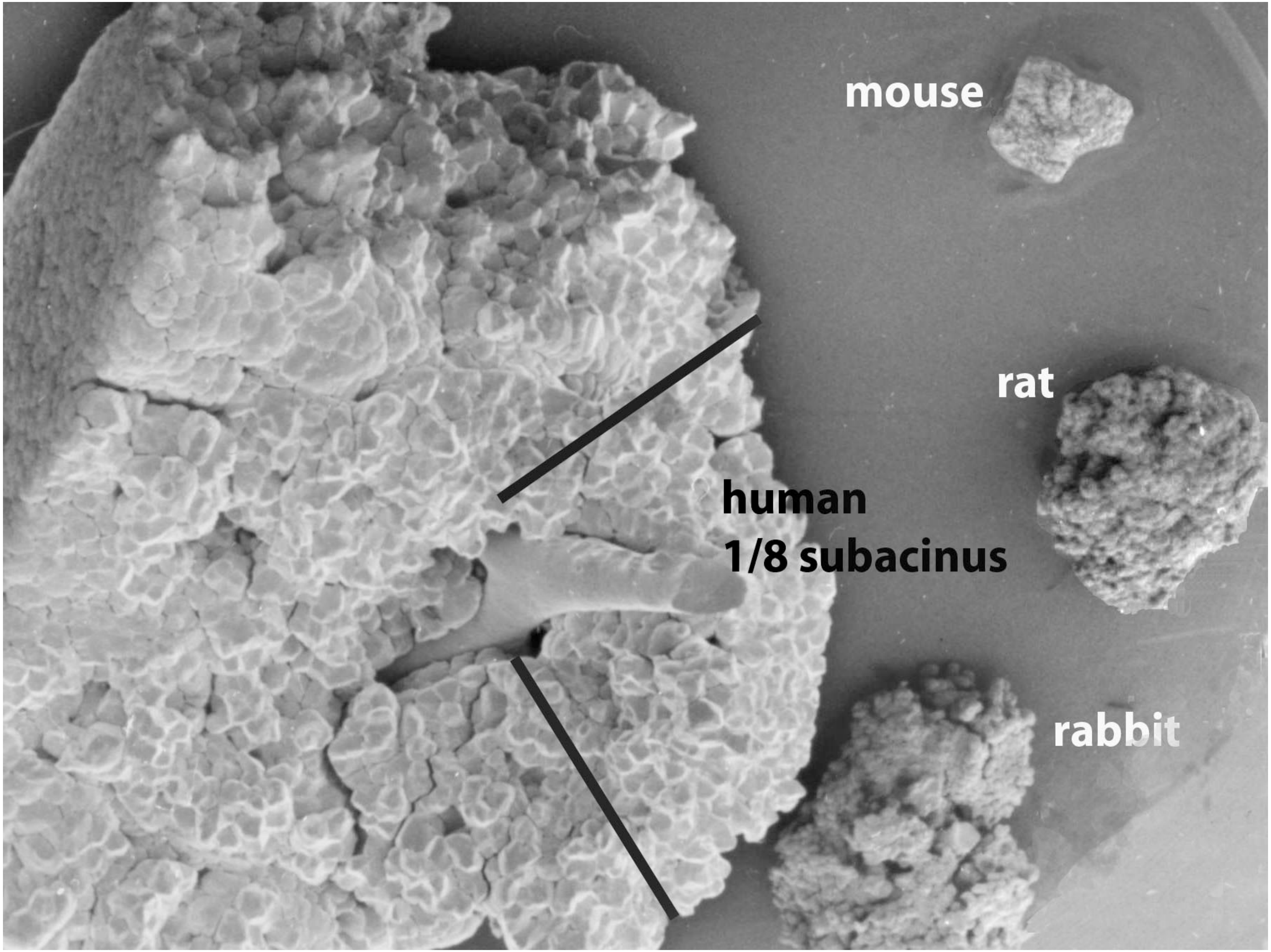
$$\begin{cases} D = 0.2 \text{ cm}^2 \text{ s}^{-1} \\ W_M = 0.79\ 10^{-2} \text{ cm s}^{-1} \end{cases} \Rightarrow \Lambda = 28 \text{ cm}$$

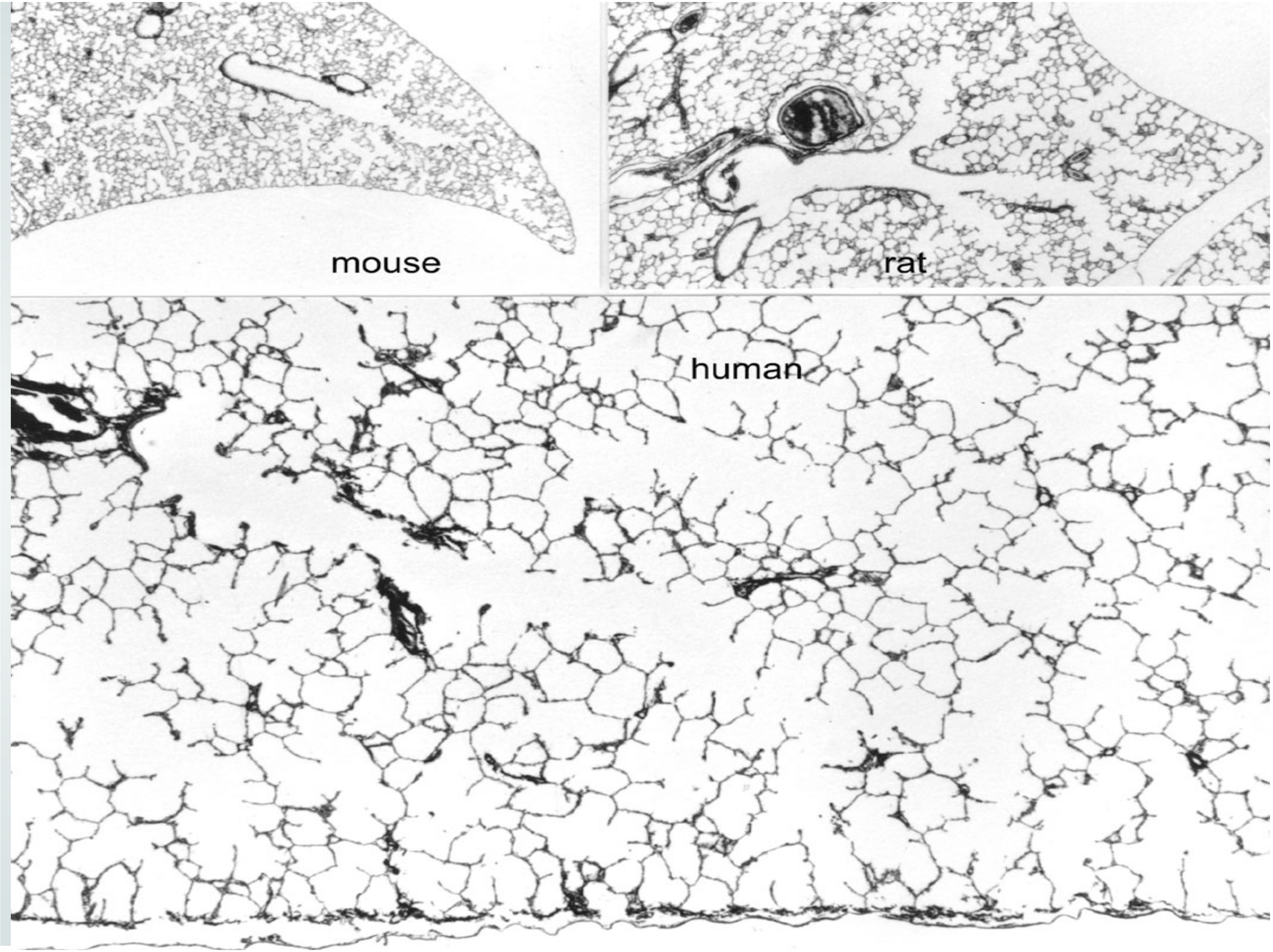
$\Lambda \approx L_P$!

This is true of 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

B. Sapoval, Proceedings of "Fractals in Biology and Medecine", Ascona, (1993).
B.Sapoval, M. Filoche, E.R. Weibel, Proc. Nat. Acad. Sc. 99: 10411 (2002).


mouse
rat
human
1/8 subacinus
rabbit


mouse
rat
human

THE FLUX Φ_X OF A GAS X :

$$\Phi_X \propto K \,.\, (\text{Acinar surface}) \,.\, W_X \,.\, \Delta P_X \,.\, \eta(\Lambda_X)$$

$\eta(\Lambda)$ IS THE ACINUS EFFICIENCY (≤ 1)

FOR O_2

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

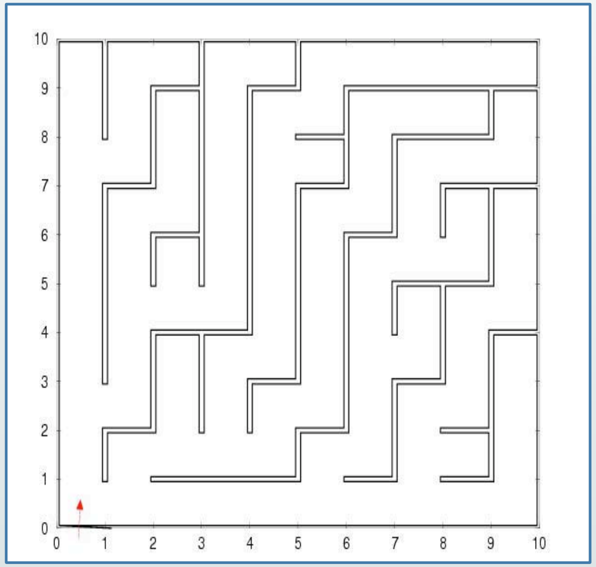
K= FUNCTION (O_2 BINDING, DYNAMICS OF THE RESPIRATORY CYCLE)

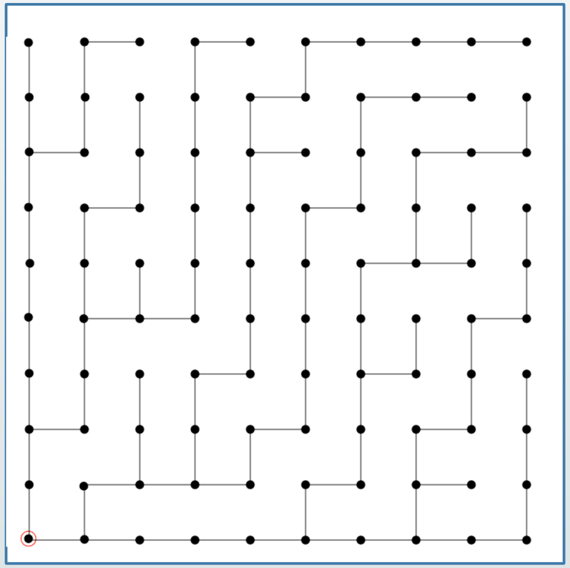
η ($\leq$ 1) measures the equivalent fraction of the surface which is active

Renormalized random walk:

The coarse-grained approach

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





Random walk simulation on the acinus real topology

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 $\langle K_i \rangle$

- On defines the efficiency by analogy between both models

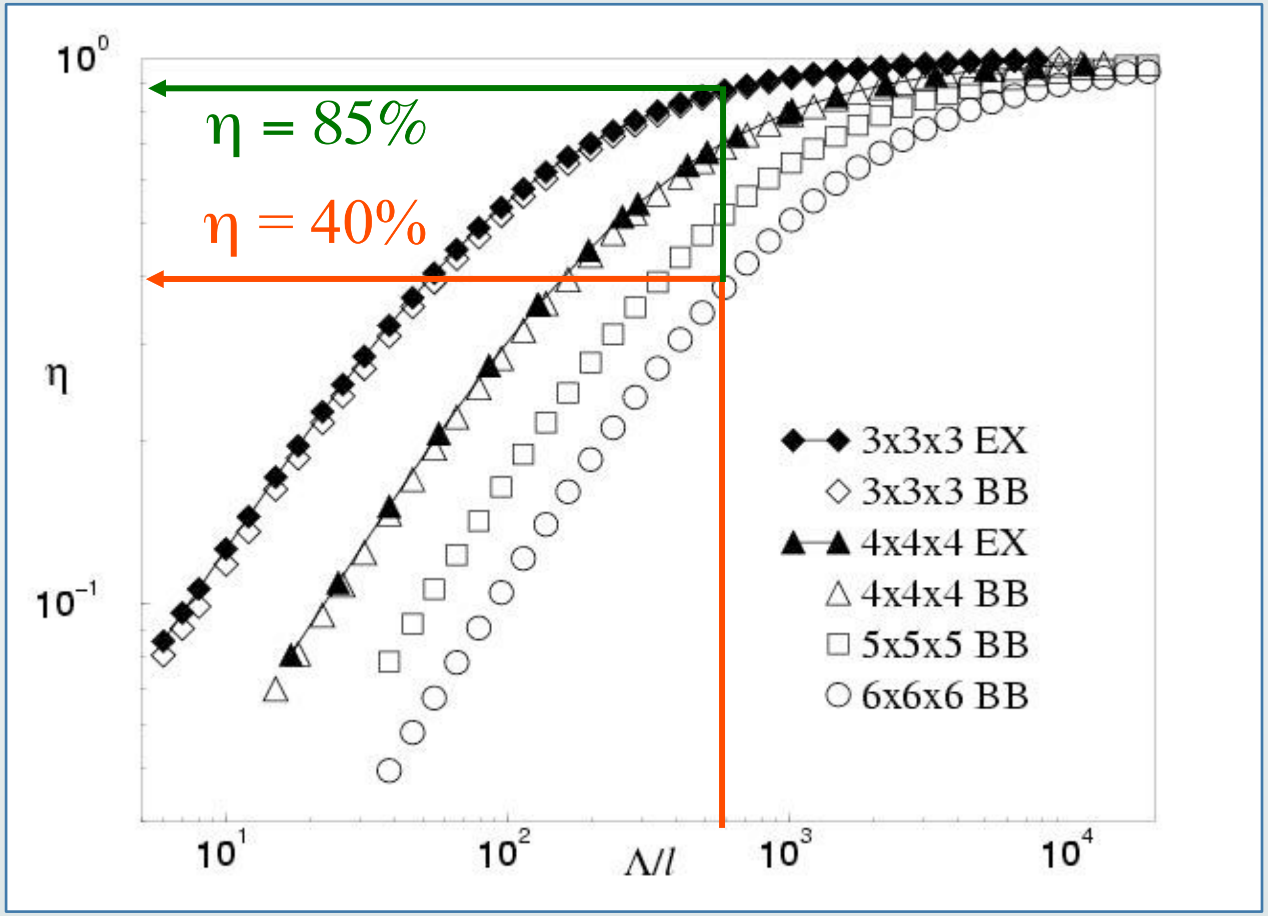
$$\eta = \frac{\int WCdS}{WC_0S} \Rightarrow \eta = \frac{\sum_i \langle K_i \rangle s_i}{\langle K_0 \rangle \sum_i s_i}$$

Acinus efficiency

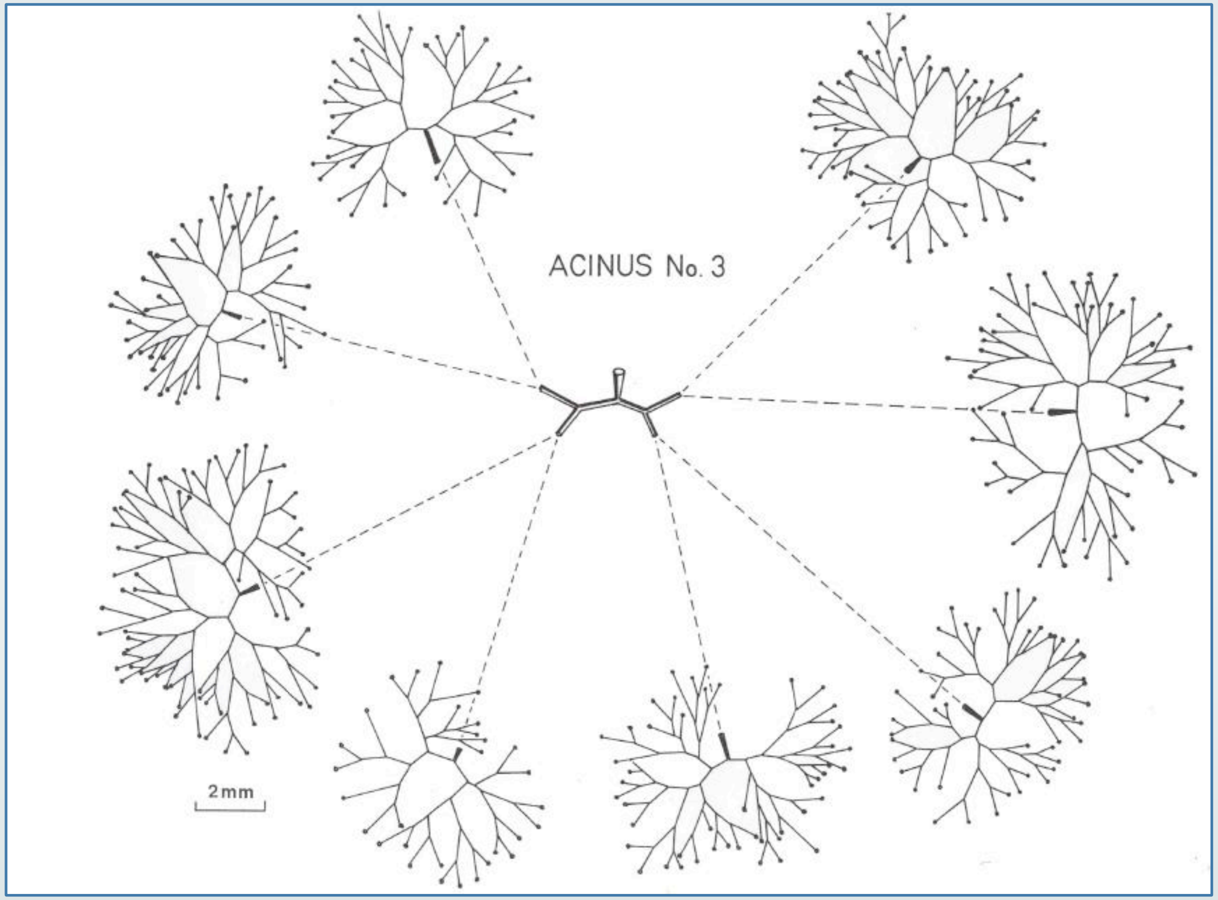
Human subacinus:
L=6ℓ ; Λ=600ℓ

At rest
η = 40%

At exercice
η = 85%

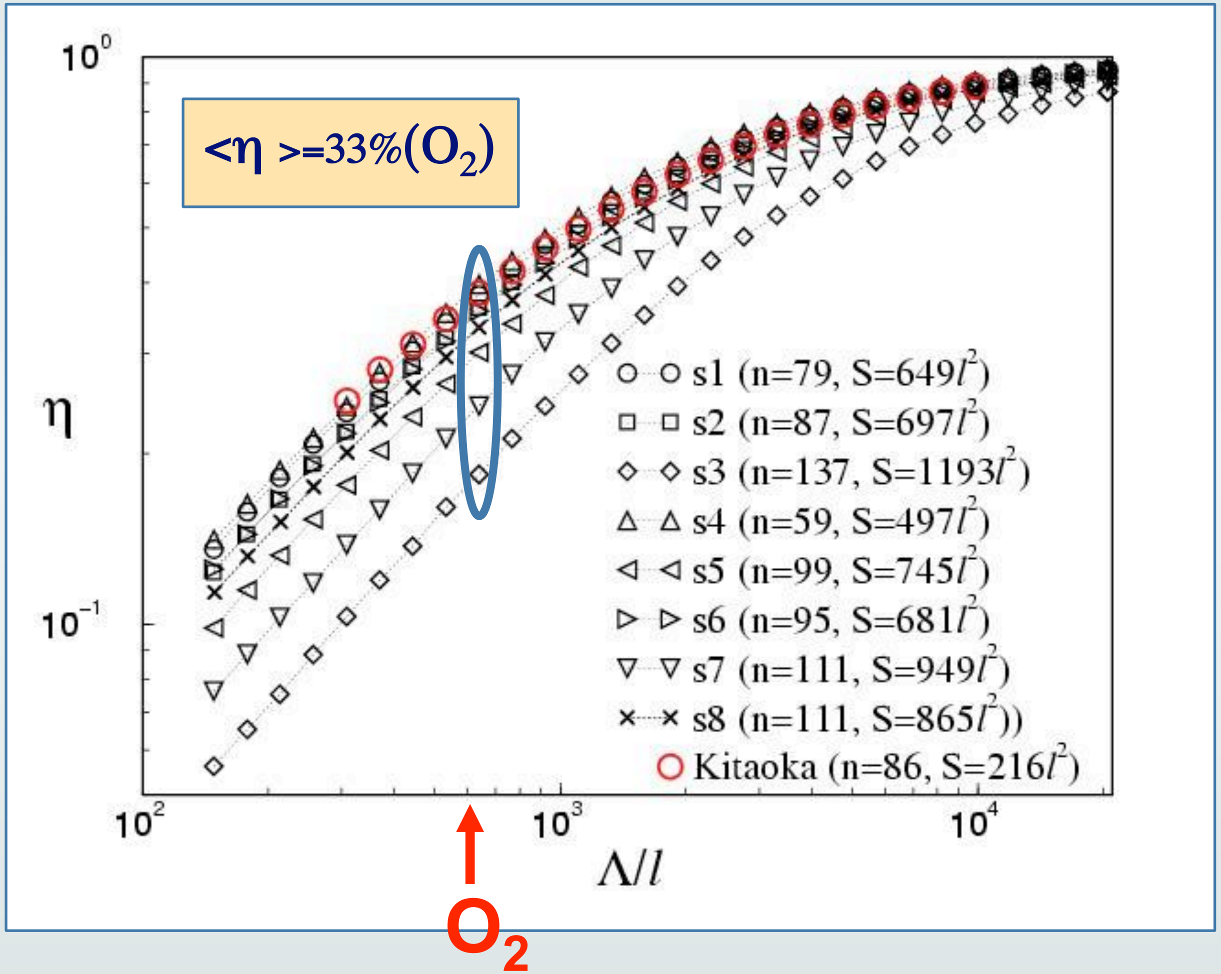


The efficiency can be computed form the morphometric data on 8 real sub-acini



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

Efficiency of real acini



At EXERCISE $<\eta(O_2)> = 85\%$

At rest the efficiency is 33%.

Not optimal from
the physical point of view

At maximum exercise the efficiency is 90%.

It is near optimality from
the physical point of view

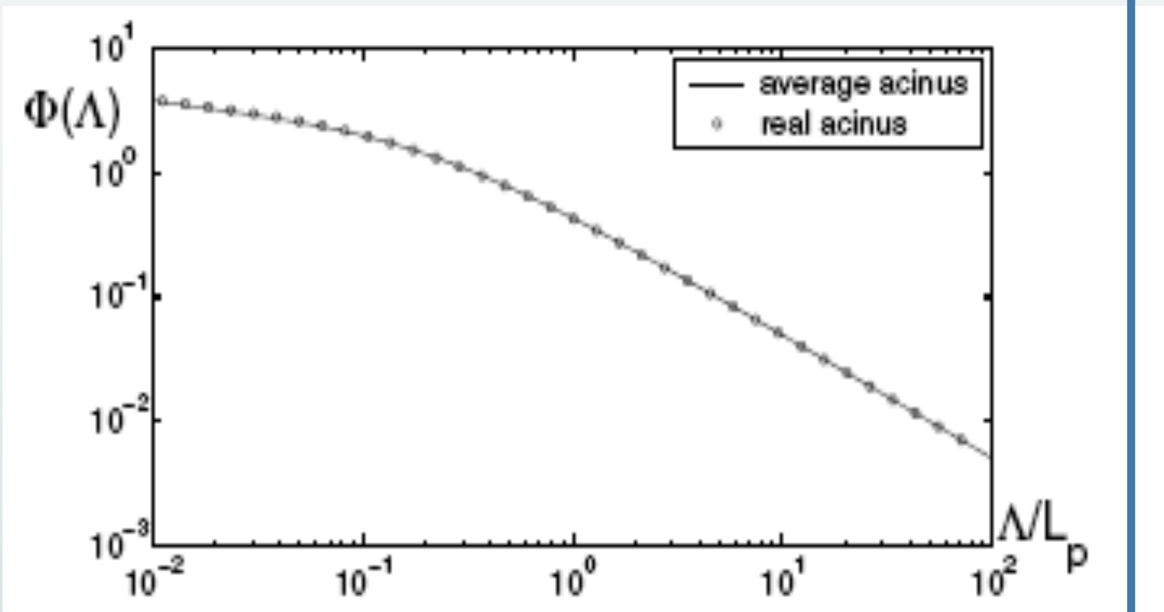
Does the randomness of the acinar tree really plays a role?

Comparison between the flux in an average symmetrized acinus and the real acinus of Haefeli-Bleuer and Weibel:

Exact analytical calculation of a finite tree:

No difference:

The symmetric dichotomic model of Weibel is sufficient



D. Grebenkov, M. Filoche, and B. Sapoval, Phys. Rev. Lett. 94, 050602-1 (2005)

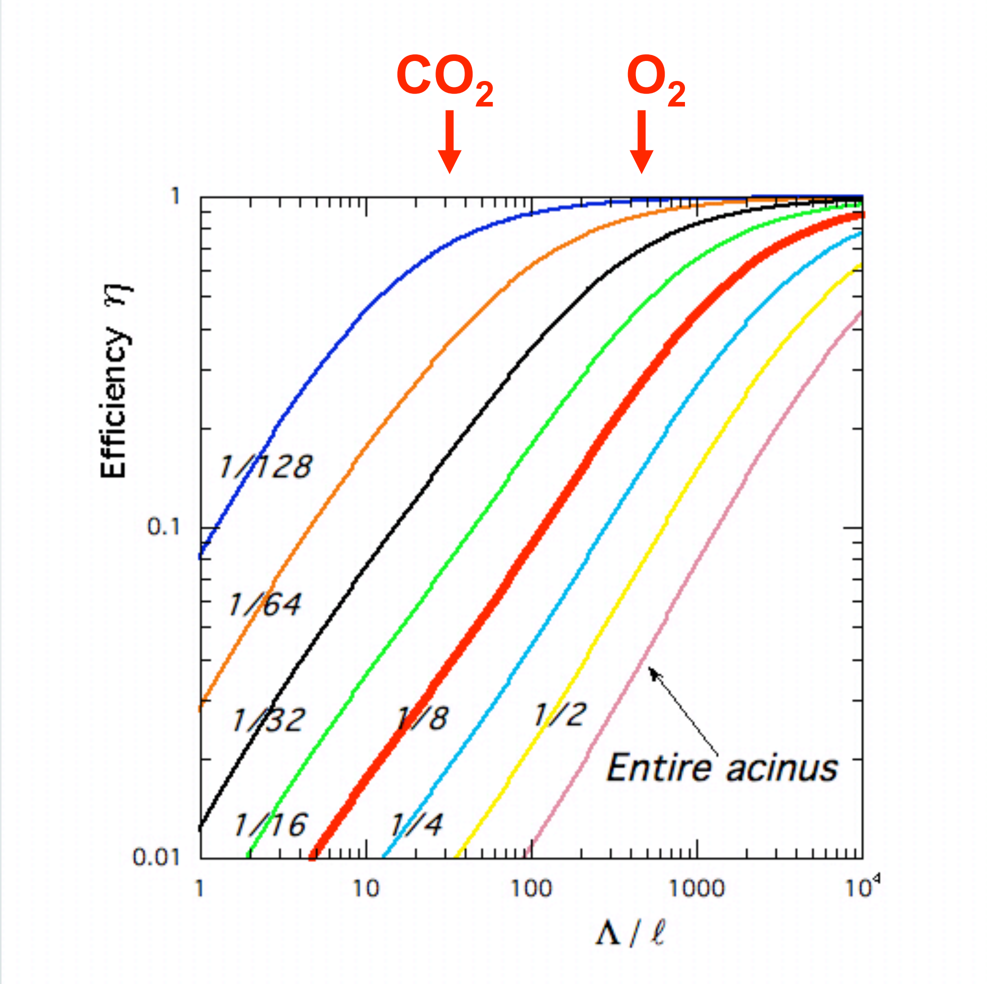
Dependance of the efficiency on the size of the diffusion cell

In the screening regime:

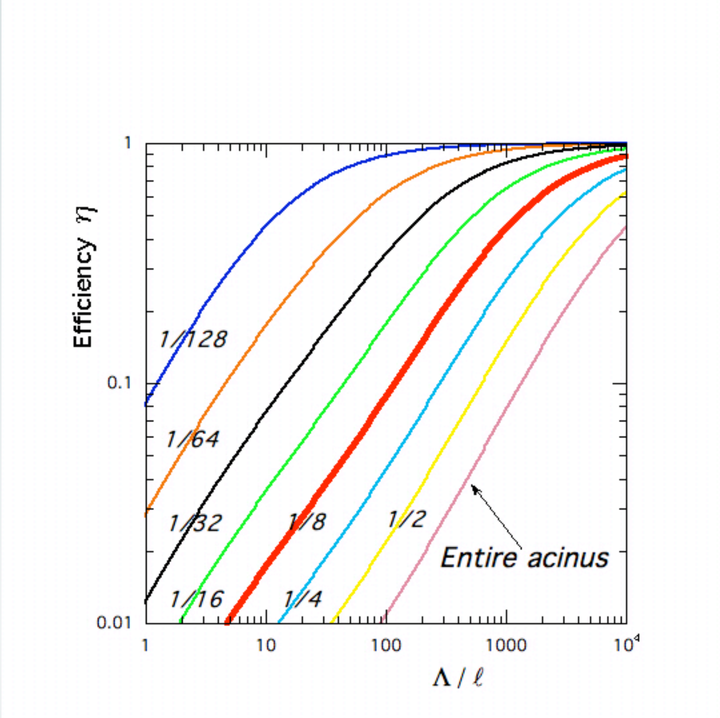
efficiency increases with

$\Lambda = D/W$

and decreases with the size of the diffusion cell



Here is the first magic of this diffusion reaction tree



- In the strong screening regime:

- The efficiency is inversely proportional to the size of the surface of the system

Pulmonary diseases: mild emphysema

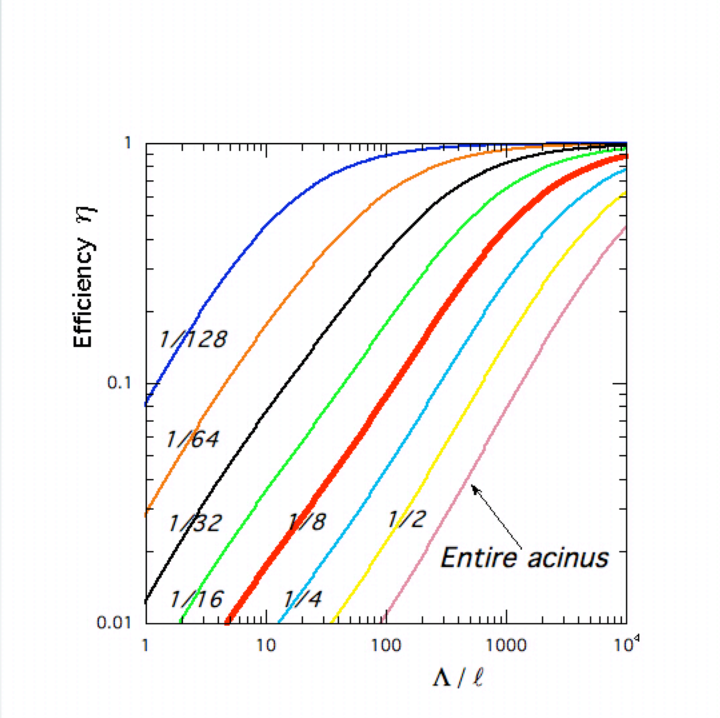
« considered as a loss of surface »

$$\Phi \propto K \,.\, (\text{Acinar surface}) \,.\, W \,.\, \Delta P \,.\, \eta(\Lambda)$$

may remain asymptomatic at rest

(same for O_2 and CO_2)

Here is the second magic of this diffusion reaction tree



- In the strong screening regime:

The efficiency is proportional to Λ i.e. inversely proportional to the permeability

Pulmonary diseases: edema

« considered as a deterioration of the membrane permeability »

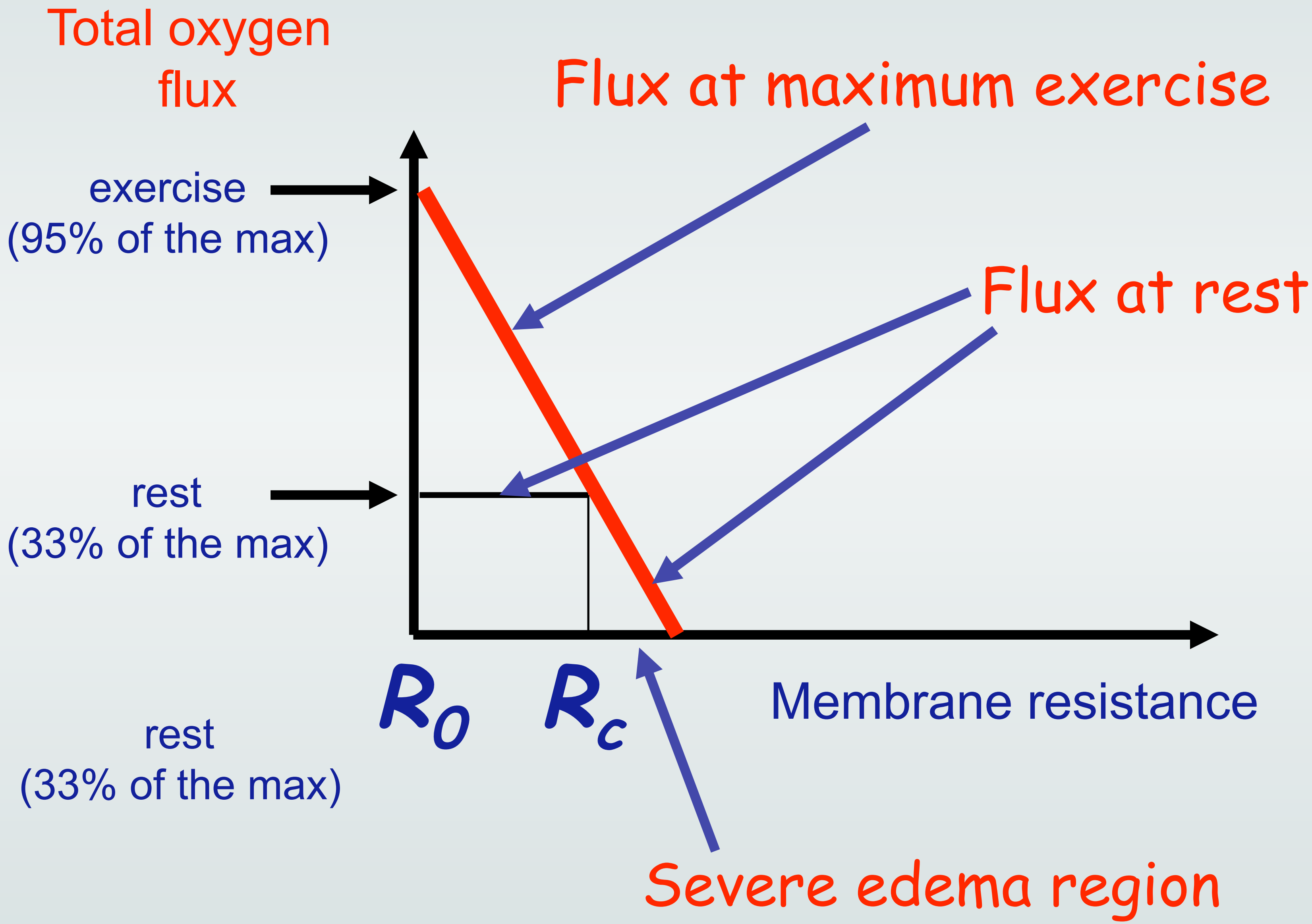
$$\Phi \propto K \,.\, (\text{Acinar surface}) \,.\, W \,.\, \Delta P \,.\, \eta(\Lambda)$$

W ↓ $\Lambda = D/W$ ↑ $\eta(\Lambda)$ ↑

independent of the permeability ! ! !

third magic

Pulmonary edema



Pulmonary diseases: mild COPD or asthma

« **Considered as a reduction of the diameter of the last bronchioles. If the acinus inflation is kept constant by muscular effort the entrance velocity U increases** »

The efficiency increases:
mild forms may remain asymptomatic.

At rest the efficiency is 33%.

Not optimal from
the physical point of view but robust!

At maximum exercise
the efficiency is 90%.

It is near optimality from
the physical point of view

but fragile!

•New-borns have small acini (Osborne et al., 1983): their efficiency is close to 1.

They cannot gain efficiency during “exercise” (crying) by breathing more rapidly: cyanosis.

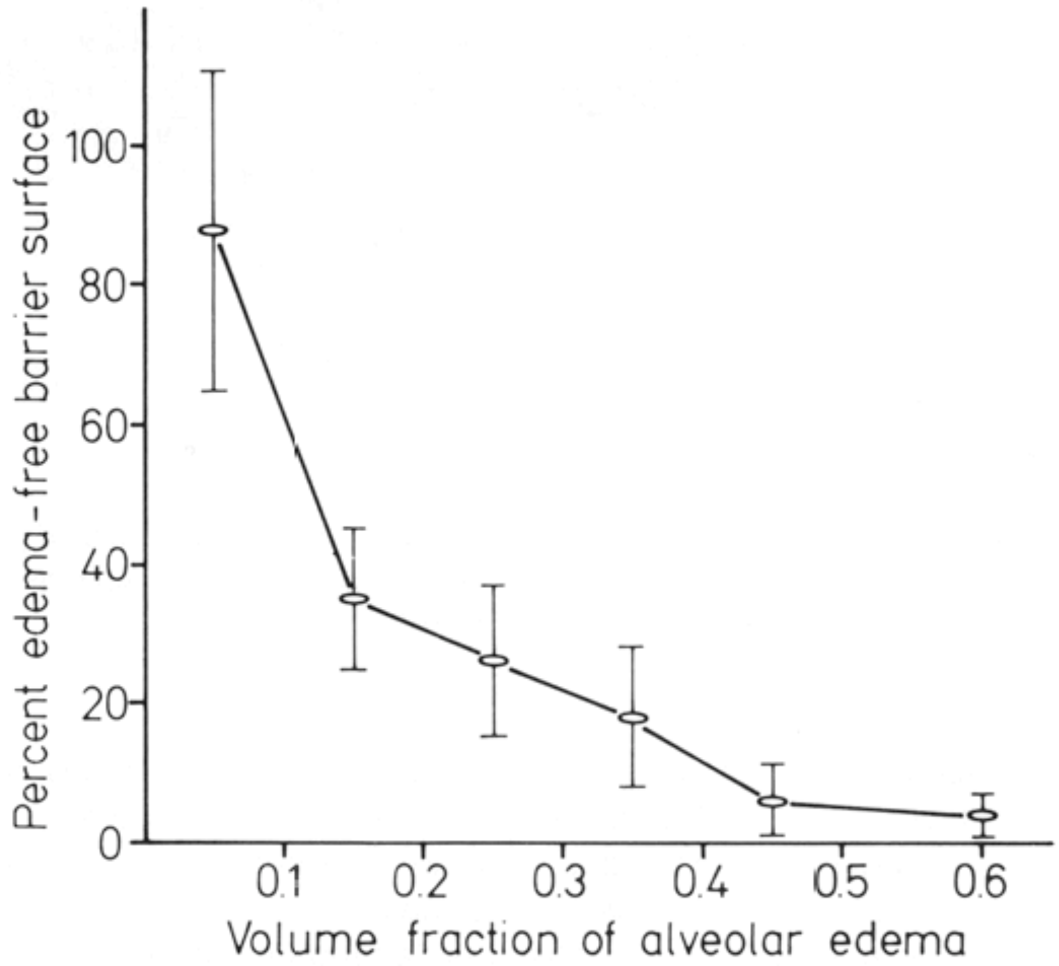
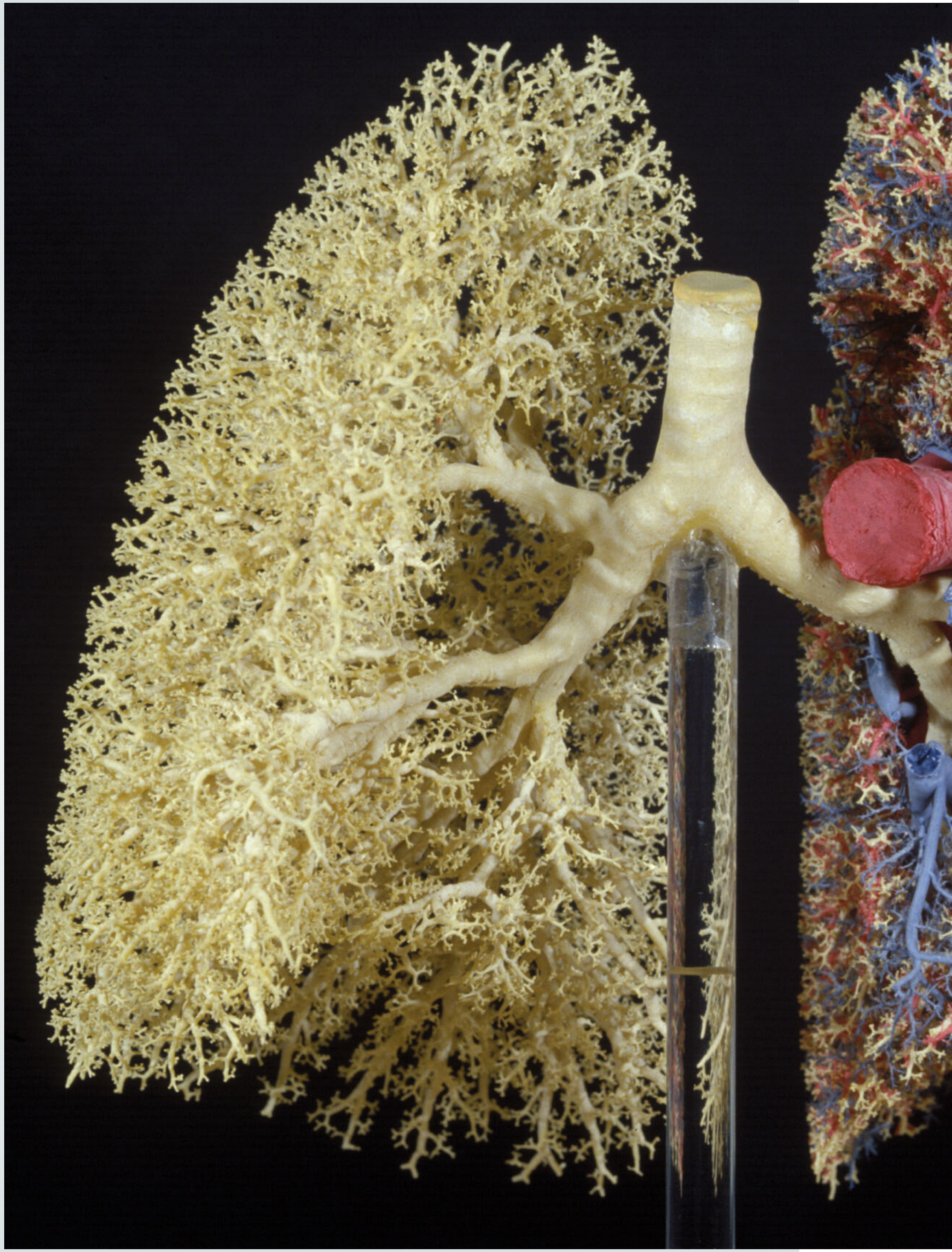


Figure 8. Decrease in free, that is, "dry," alveolar surface area with the increase in alveolar edema fluid.

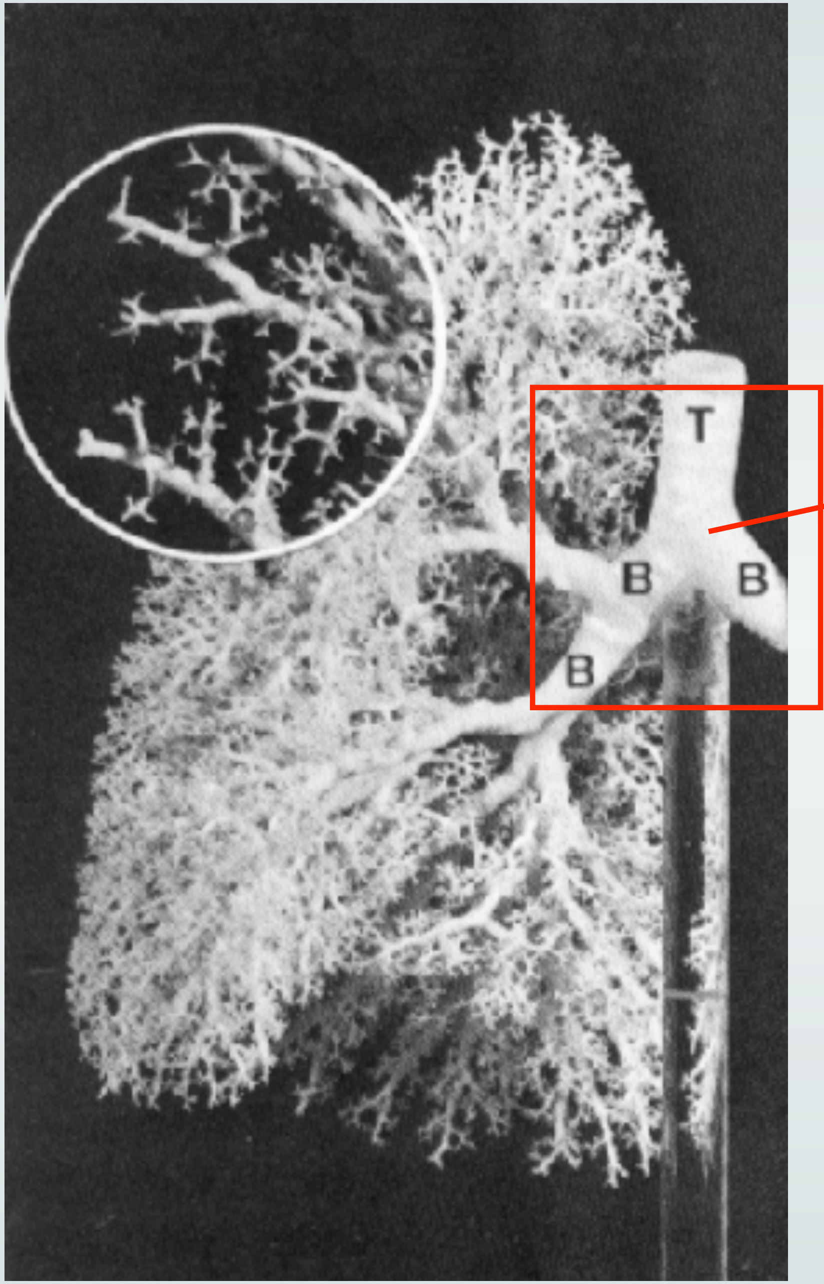
H. BACHOFEN, S. SCHÜRCH, R. P. MICHEL, and E. R. WEIBEL

Am Rev Respir Dis Vol 147. pp 989–996, 1993

A magic bronchial tree ?



Upper Bronchial Tree Hydrodynamics:

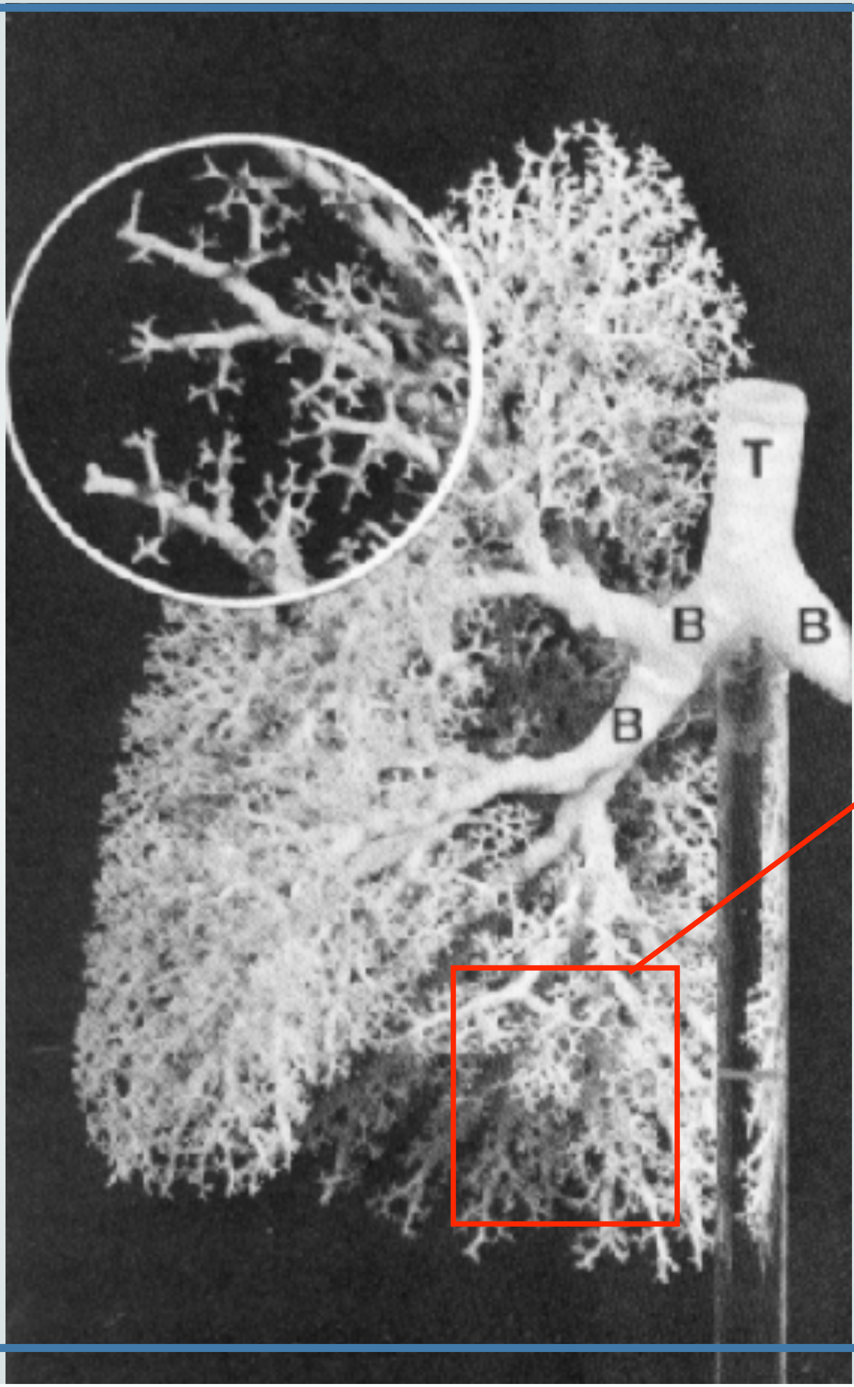


Trachea and bronchi

Generations 0 to 5

Inertial effects on the flow distribution in the upper bronchial tree

Hydrodynamics of the intermediate bronchial tree:



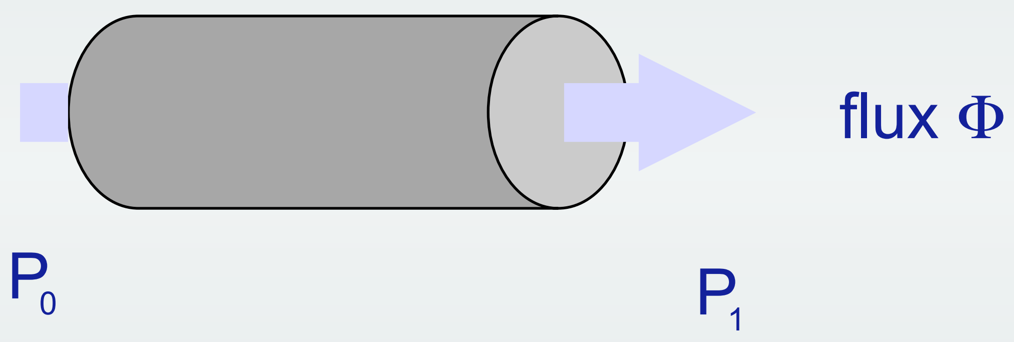
Bronchioles

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).



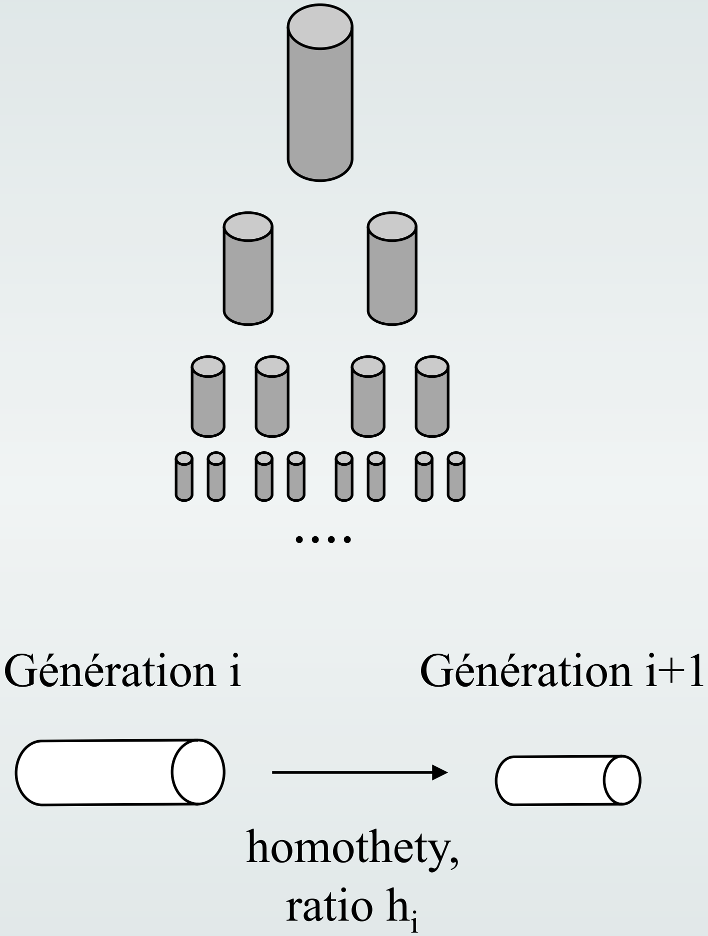
$$P_0 - P_1 = R.\,\Phi$$

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

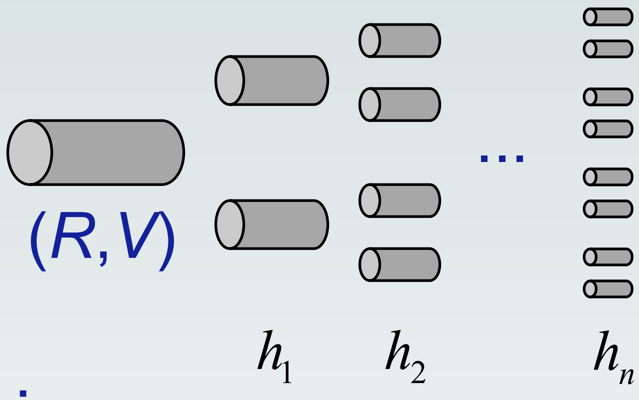
μ: fluid viscosity

(symmetry between inspiration and expiration)

Simple dichotomic tree



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 $V_{eq} \leq \Omega$

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 :

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

Hess (1914) Murray (1926): One single bifurcation for blood

The best bronchial tree:

The fractal dimension is

$$D_f = \ln 2/\ln(1/h) = 3$$

→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.

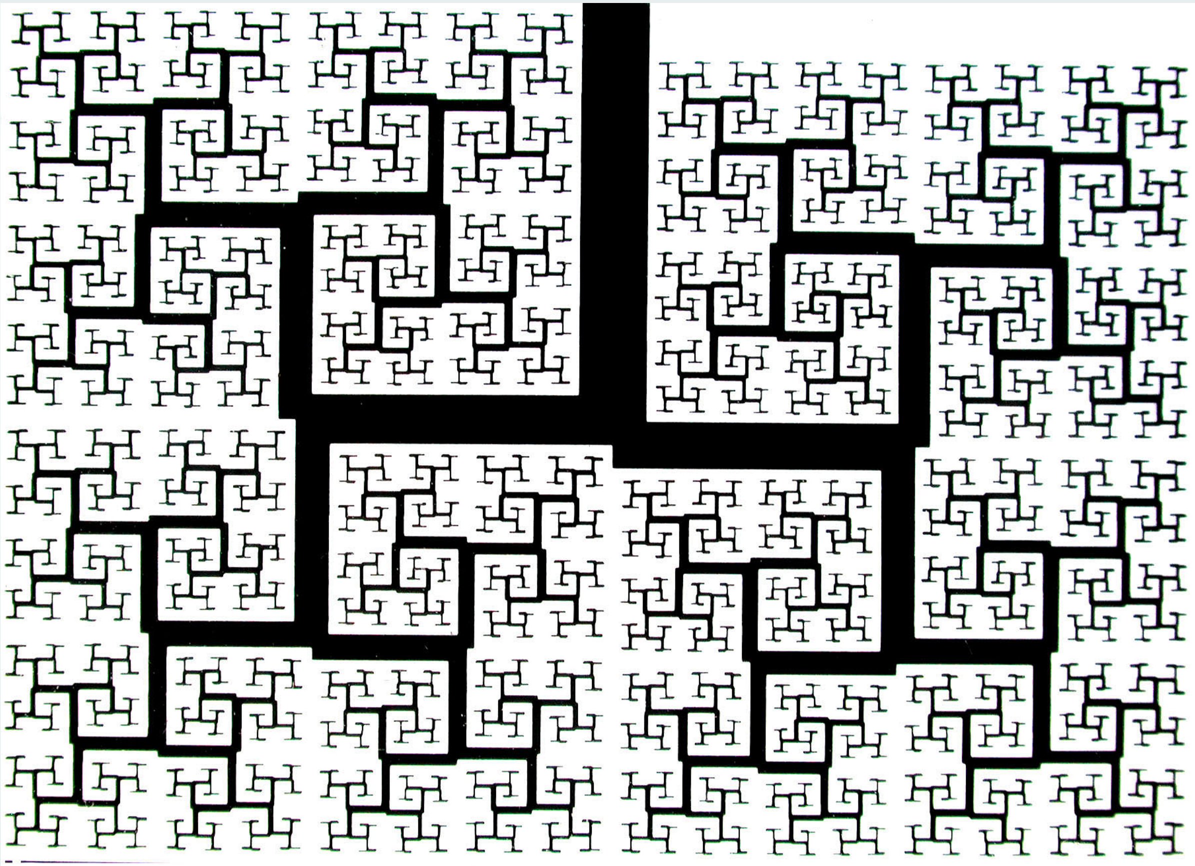
For large N, any $h < 2^{-(1/3)}$ creates an exponentially large resistance and $D_f < 3$.

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

"MAMMALS CANNOT LIVE IN THE THERMODYNAMIC LIMIT"

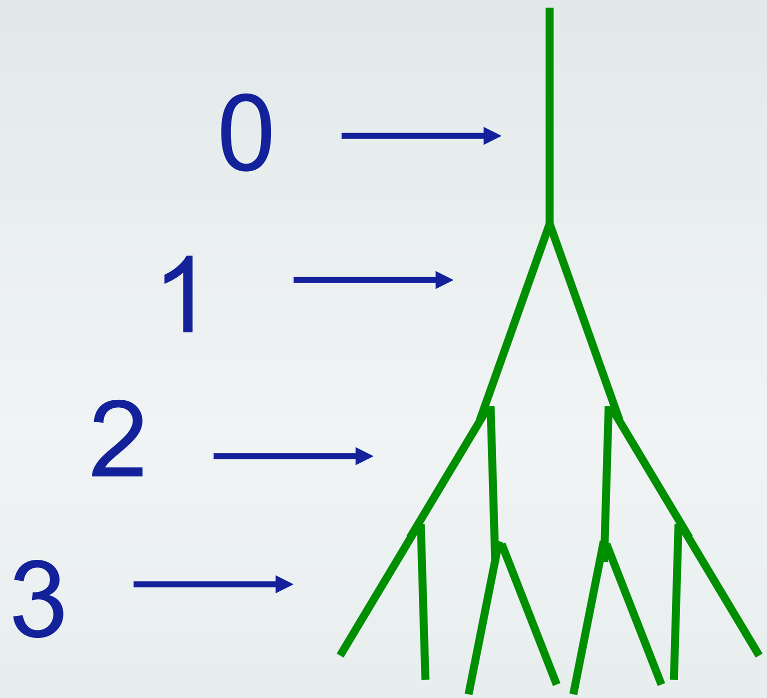
B. Mauroy, M. Filoche, E. Weibel and B. Sapoval,
The best bronchial tree may be dangerous,
Nature, 677, 663_668 (2004).

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



Where is the magic?

$R = L/D^4$

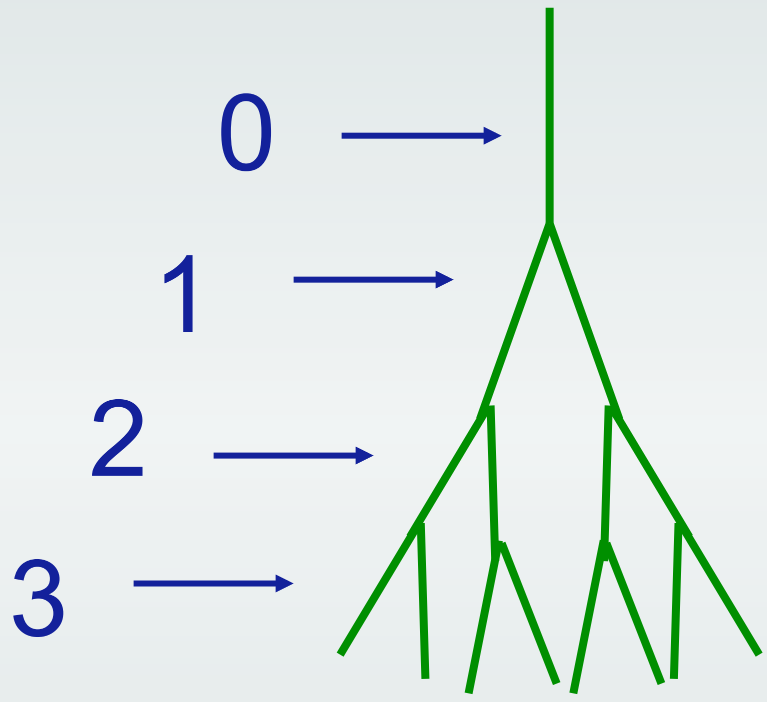


The resistance of the zones are the same

Where is the magic?

Time for the flow to cross a given generation

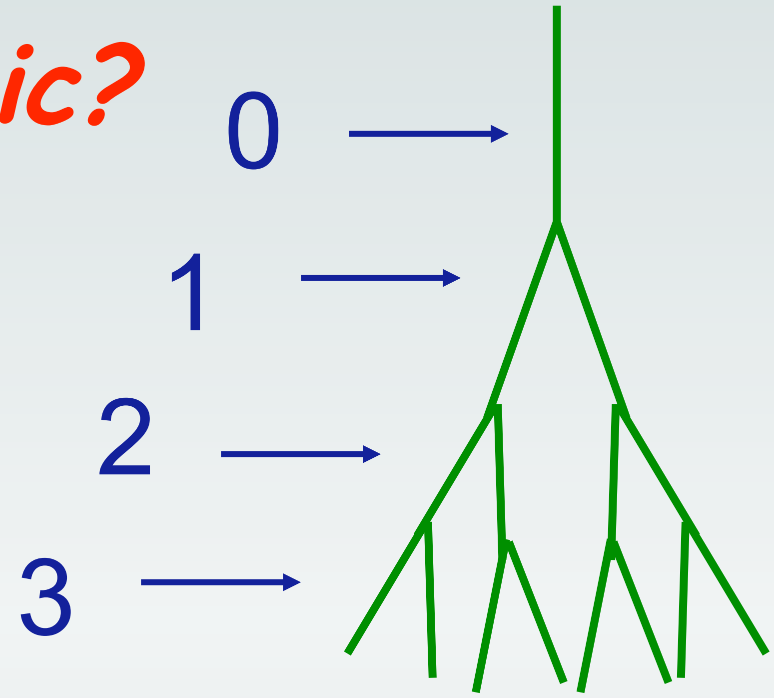
$t_0, t_1, t_2, t_{3,}\ldots$



Optimality: you want to minimize the transit time

$$T = t_0 + t_1 + t_2 + t_{3,}\ldots$$

Where is the magic?



Collage argument:
choose the smallest

$t_n = V_n/L_n,\ V_n=\Phi_n/S_n$

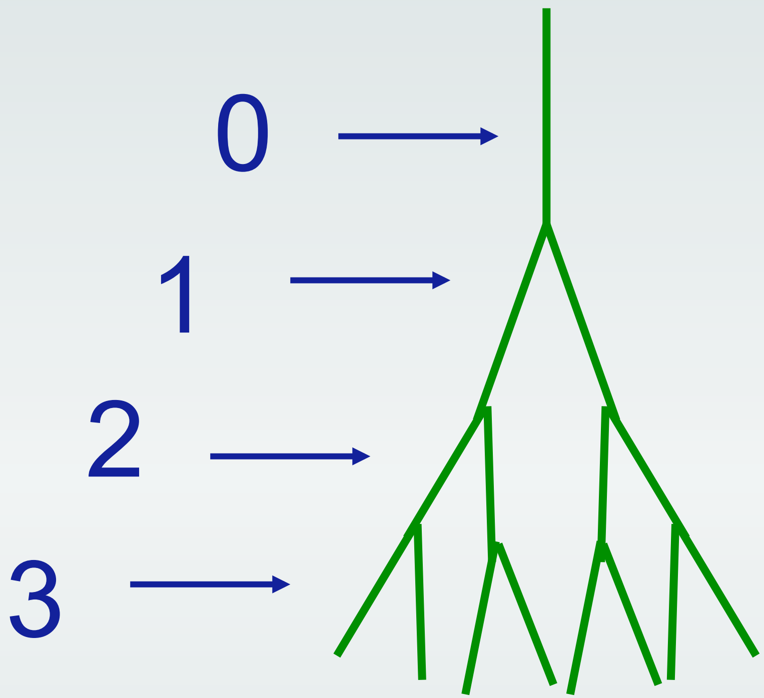
$t_{n+1} = V_{n+1}/L_{n+1},\ V_{n+1}=\Phi_{n+1}/S_{n+1}= \Phi_n/2S_{n+1}$

$t_n = t_{n+1} \longrightarrow L_{n+1} = L_n/2^{1/3}$

$h = 2^{-(1/3)}$ *is a magic number …*

1- It can be found from a purely cinematic argument (transit time)

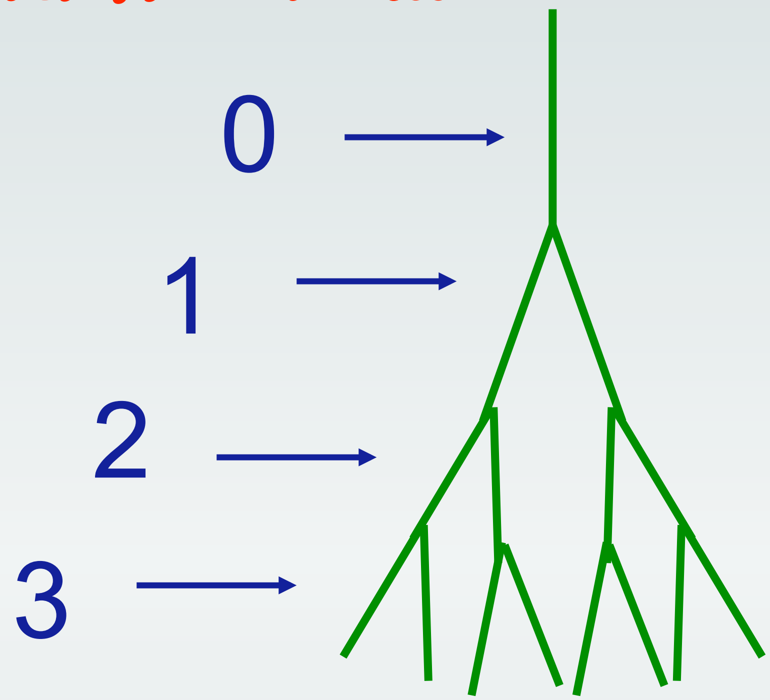
2- It can be found from a purely physical argument (Murray-Hess law)



$h = 2^{-(1/3)}$ is a magic number …

3- It can be found from a purely geometric argument: space filling

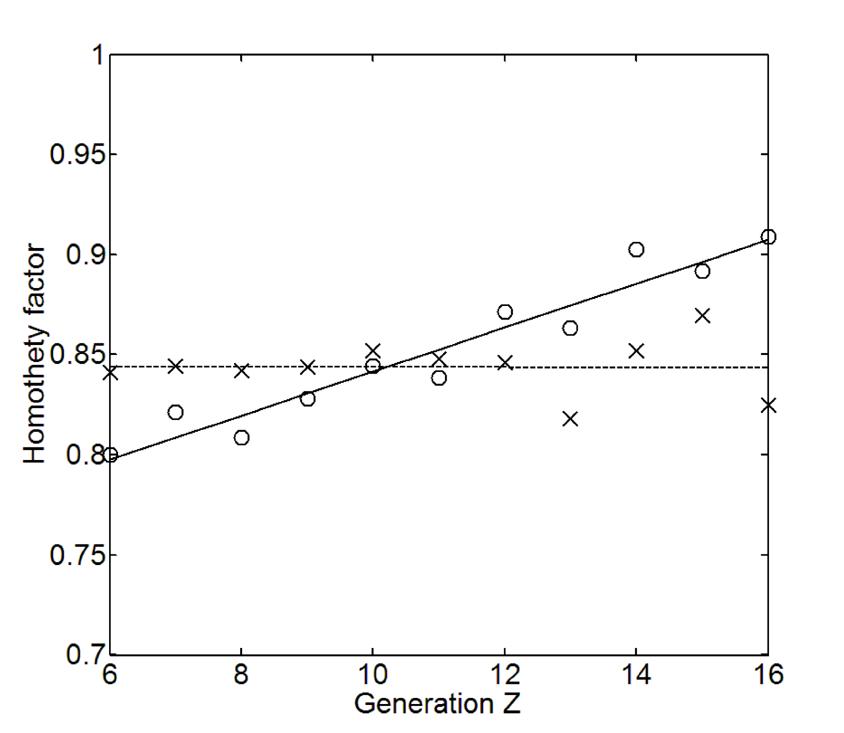
For a dichotomic tree:



$D_f = \ln 2 / \ln(1/h)$ ⟶ $h = 2^{(-1/D_f)}$

Point of view of evolution … several benefits

What about the real lungs ?
Generation 6 to 16



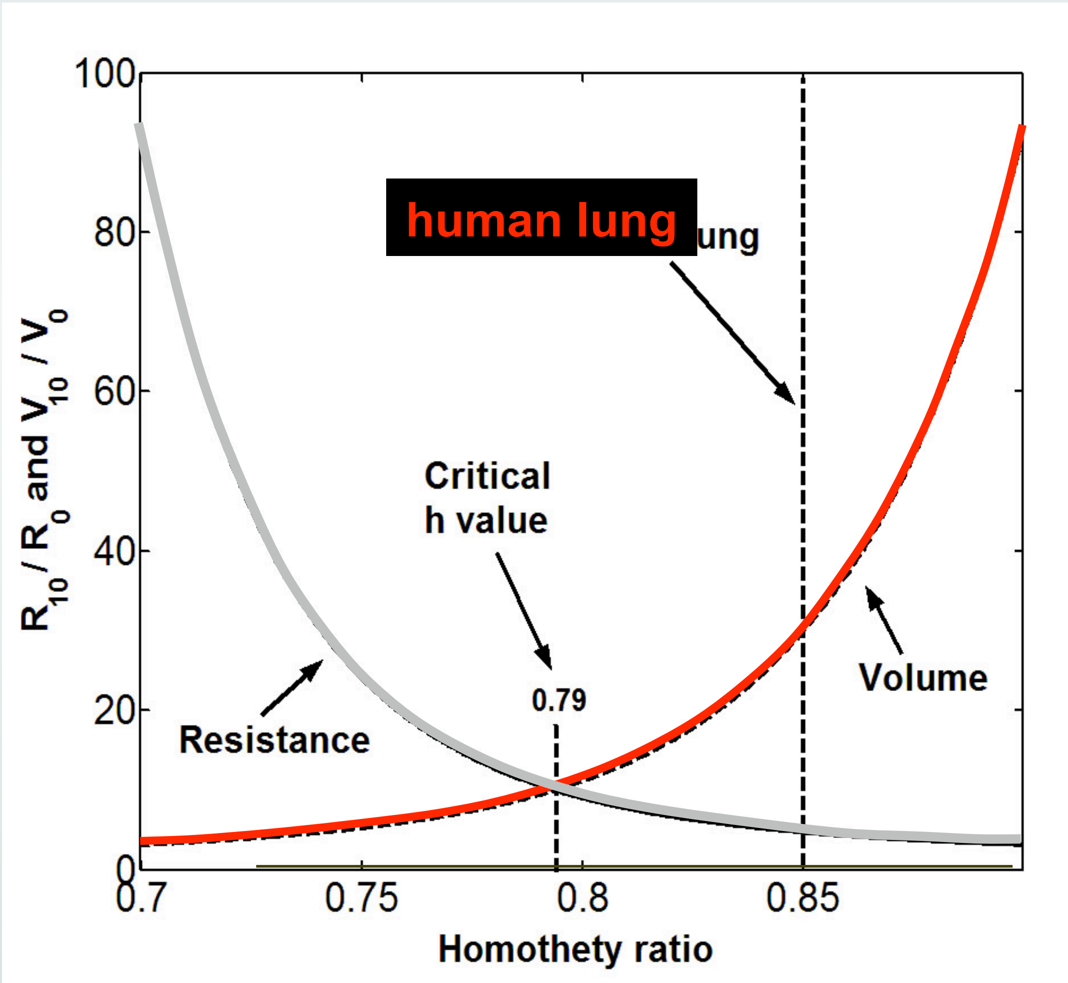
Real data of the human lung (Weibel), circles corresponds to diameters ratio and crosses to length ratio.

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.**

The « optimal » tree correspond to $h = (1/2)^{1/3} = O{,}79\ldots$

The human lung corresponds to 0,85

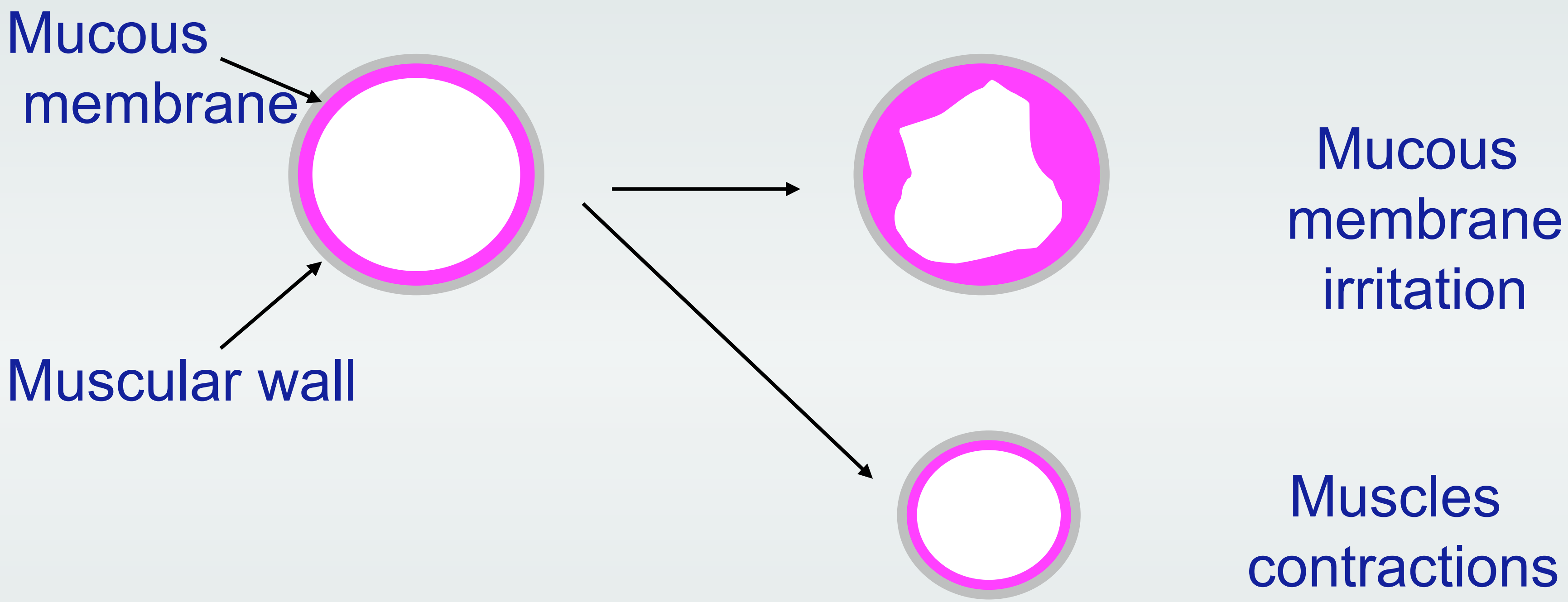


Human lung has a *security margin* for the resistance, this authorizes geometrical variability which is always present in living systems.

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

The best from the physical point of view are the most fragile: Athletes are the most fragile…

Anomalous transport: pathological situations where the bronchioles diameters are diminished.



- Asthma,
- Exercise induced broncho-spasm,
- Bronchiolitis,
- Allergenic reactions to pollen.

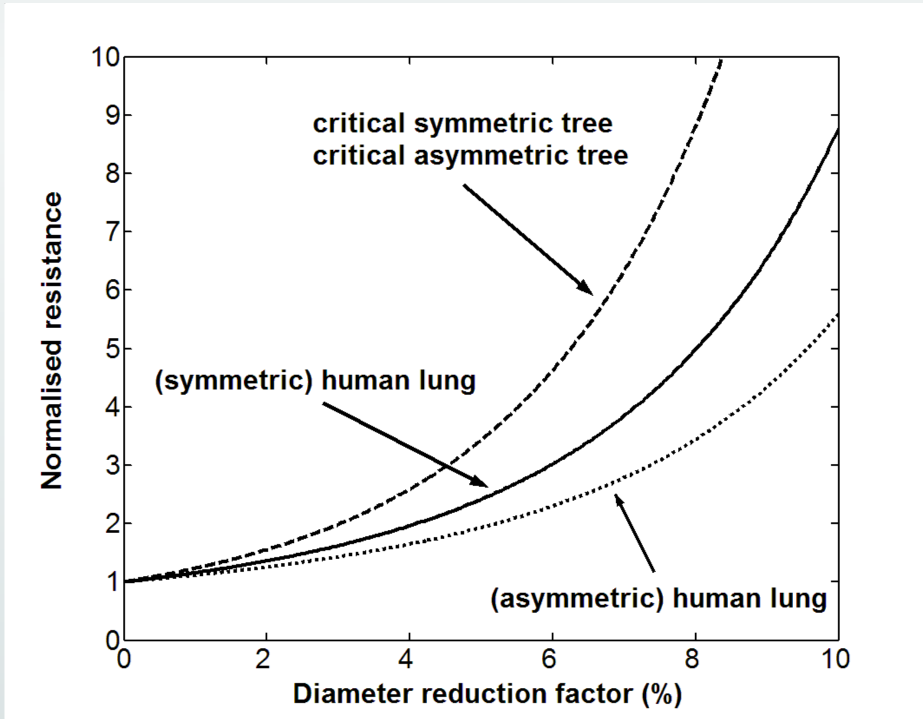
To model « more realistic » asthma, we assumed that diameters and lengths have different reduction factors :

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 ~ 0.85 in human lung).



Specific conclusions

The tree structure of the lung is close to physical optimality 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. (athletes)

The higher performances of athletes requires higher ventilation rates to ensure oxygen supply. Higher flow rates must be achieved in the given bronchial tree so that its geometry becomes dominant.

Athletes

Google: athlete asthma: 540,000

Google: sport asthma: 2,600,000

SUMMARY

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).

EVOLUTION ? ? ?

What came first between these three properties?

Energetic efficiency

Geometrical efficiency

Speed of delivery

A living organ must be fed by a space filling system: geometry came first.

Two types of space filling systems:

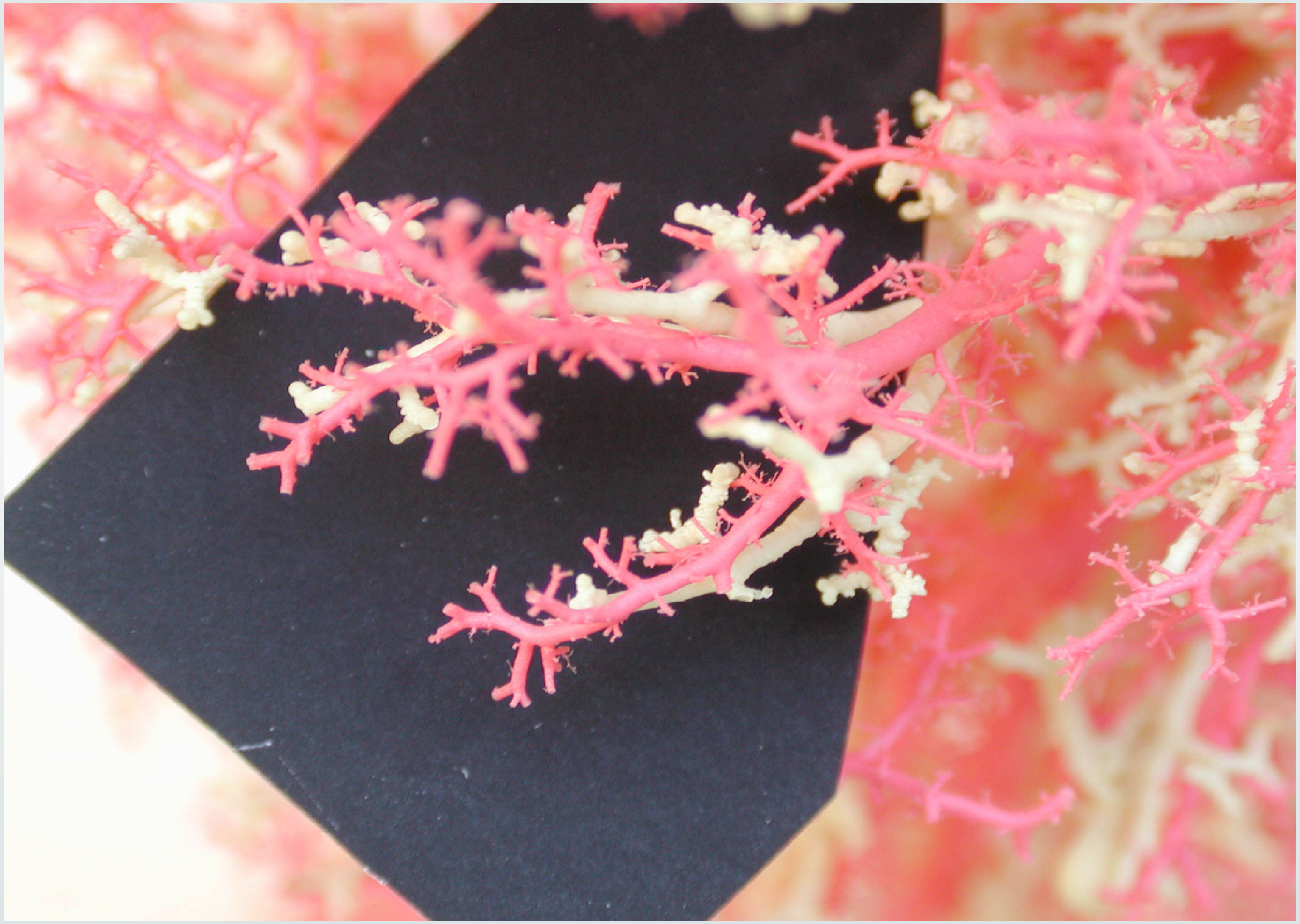
- lattice (may be disordered): streets
- tree

Life appeared in water: first animals were amphibious: viscous blood arterial tree.

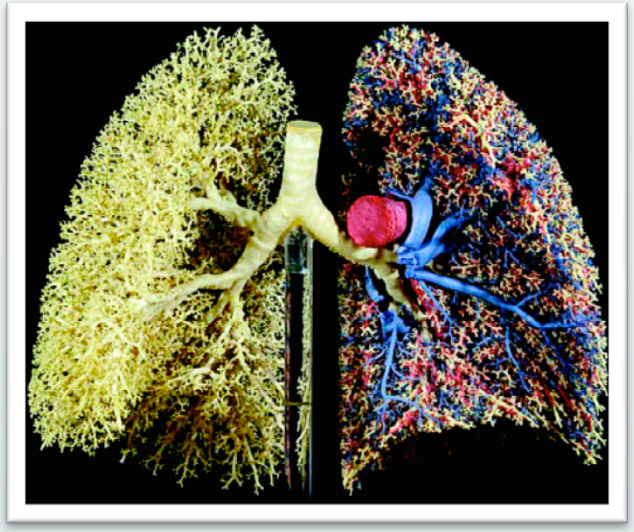
Fractal here means optimized by natural selection for viscous dissipation.

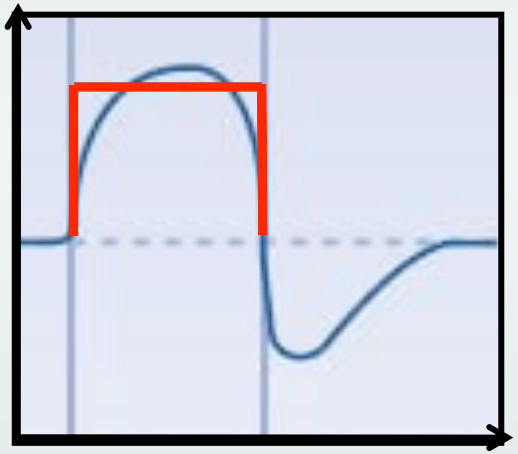
But, in fishes, the blood circulation is always in the same direction.

The magic is, that once optimized for dissipation, it is optimized for rapidity and mammalian cyclic respiration



Do we have time to breathe through an asymmetric tree? Which asymmetric tree?





Magali Florens

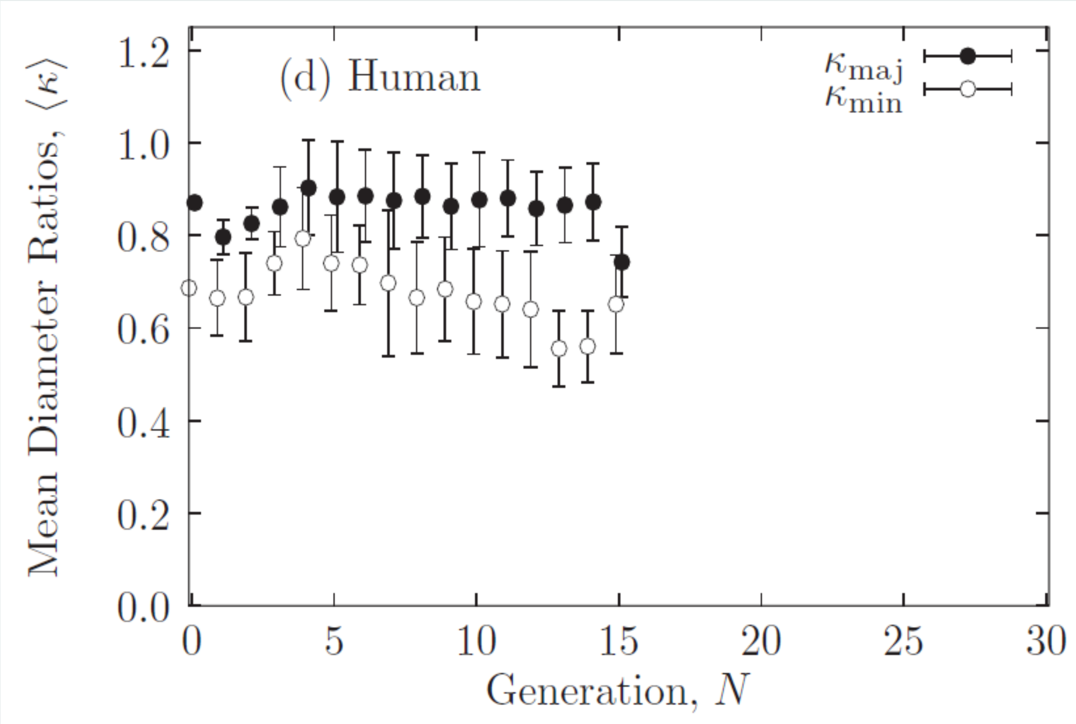
http://arxiv.org/abs/1005.1836

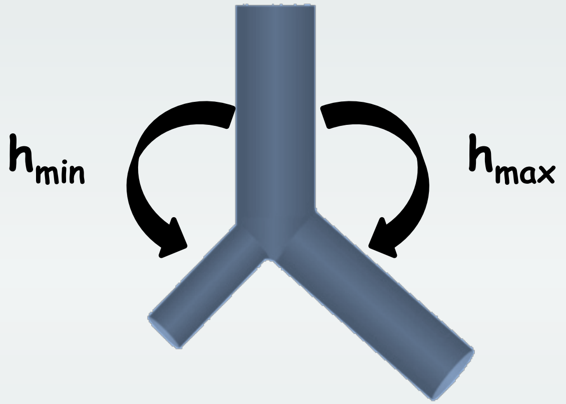
The real tree is asymetric

A unified geometrical model of the bronchial tree

- Morphometric data: **asymmetrical** branched structure

(Majumdar, Alencar,Buldyrev, Hantos, Lutchen, Stanley, Suki PRL 2005)





→Every airway splits into two branches of different length and diameter.

→ Different airway sizes at generation *g* :

$$h_{min} = h_{0,min}(1+\sigma X)$$
$$h_{max} = h_{0,max}(1-\sigma X)$$

X gaussian

σ

Geometrical model of the tracheobronchial tree

- Specific geometry of the proximal airways (L/D)

- Level of asymmetry: parameter α

$$(h_{0,max})^3 = (h_0)^3\,(1+\alpha)$$
$$(h_{0,min})^3 = (h_0)^3\,(1-\alpha)$$

TABLE I: Model parameters

Model	Scaling ratio for D	Ratio L/D [a]	DSV (mL)
Symmetric	$h_0 = 2^{-1/3}$	3.00	220
Asymmetric	$h_{0,min} = 0.68$ $h_{0,max} = 0.88$	3.00	213

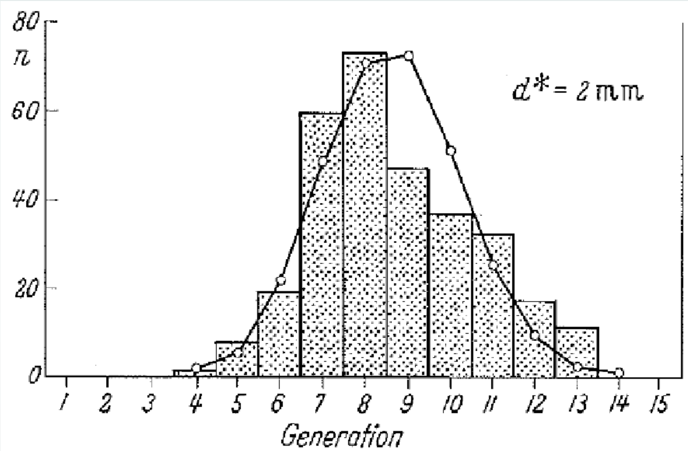
[a] D and L: diameter and length of the airway.

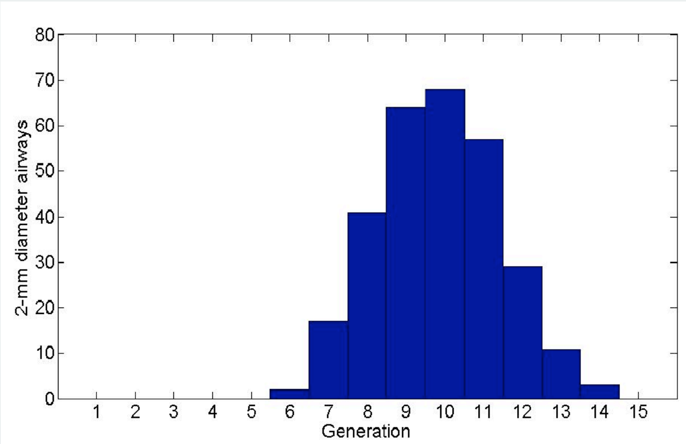
→ Measured systematic branching asymmetry in all airways (α = 36 %)

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

→ **The number of generations differs according the pathway in the tree: 10 to 23**

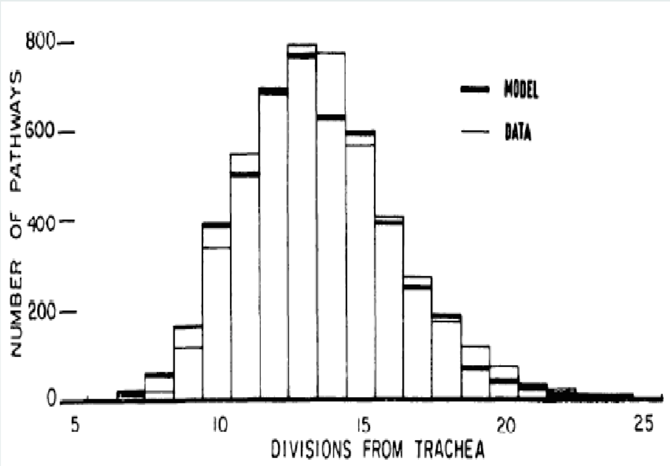
Comparison with anatomy

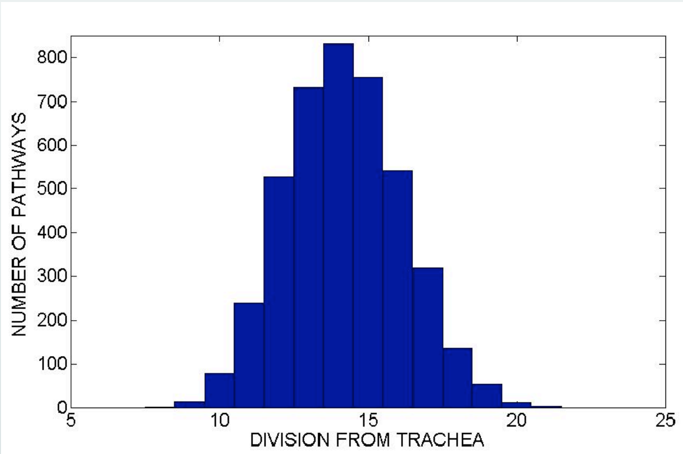




Weibel (1963) distribution of generations of bronchia with 2mm diameter

Comparison with anatomy



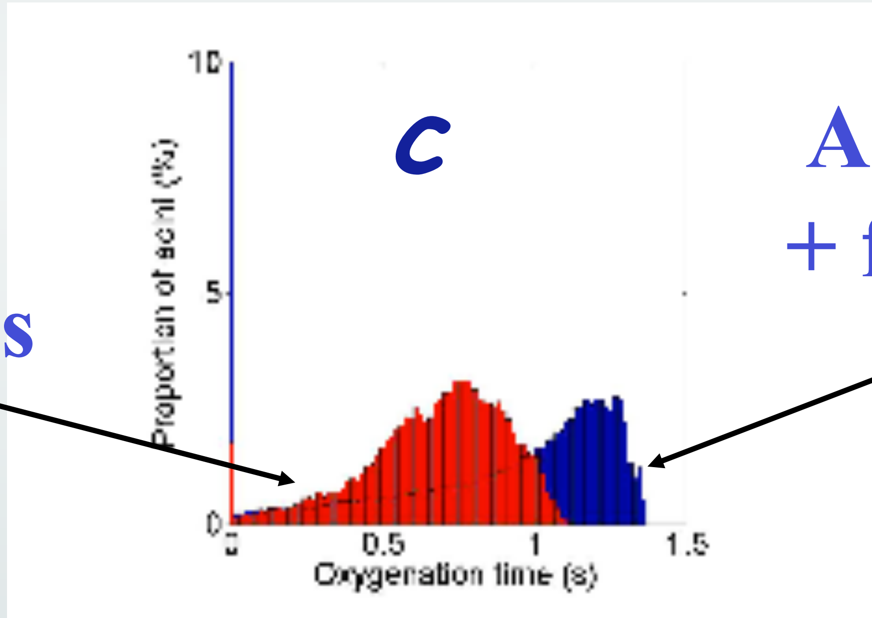


Horstfield (1971) distribution of generation of bronchia with 0.7 mm diameter

Time to breathe:

$$t_{oxygenation} = t_{insp.} - t_{extrathoracic} - t_{tracheobr.}$$

Symmetric
+ fluctuations

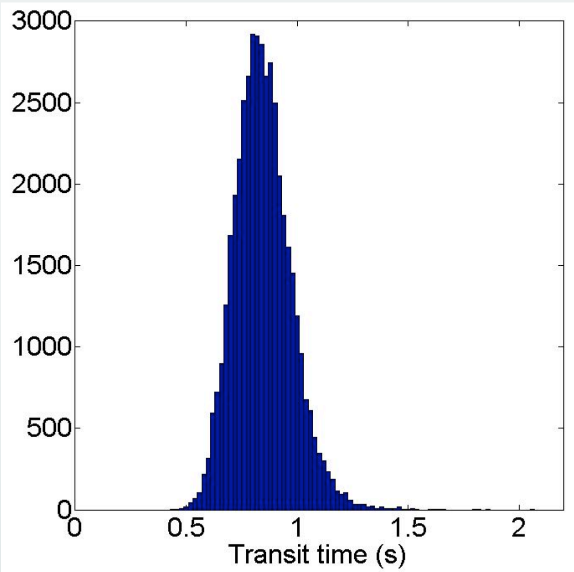


Asymmetric
+ fluctuations

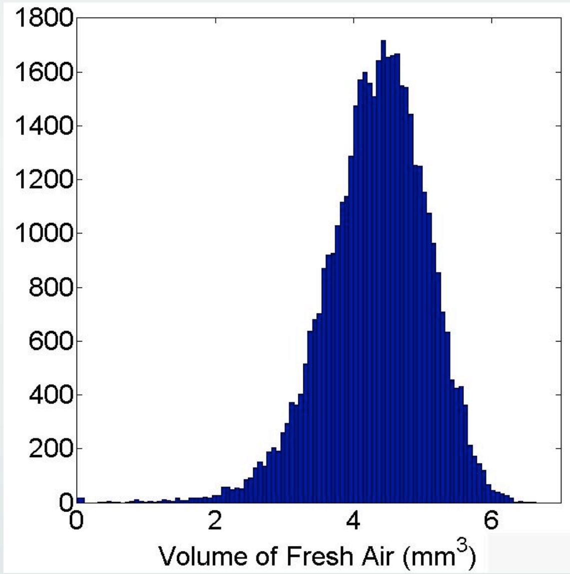
Model of ventilation

1- Air flow entering each acinus is assumed uniform and constant during inspiration.

2- Transit time from the entrance of the mouth to the entrance of the acinus.



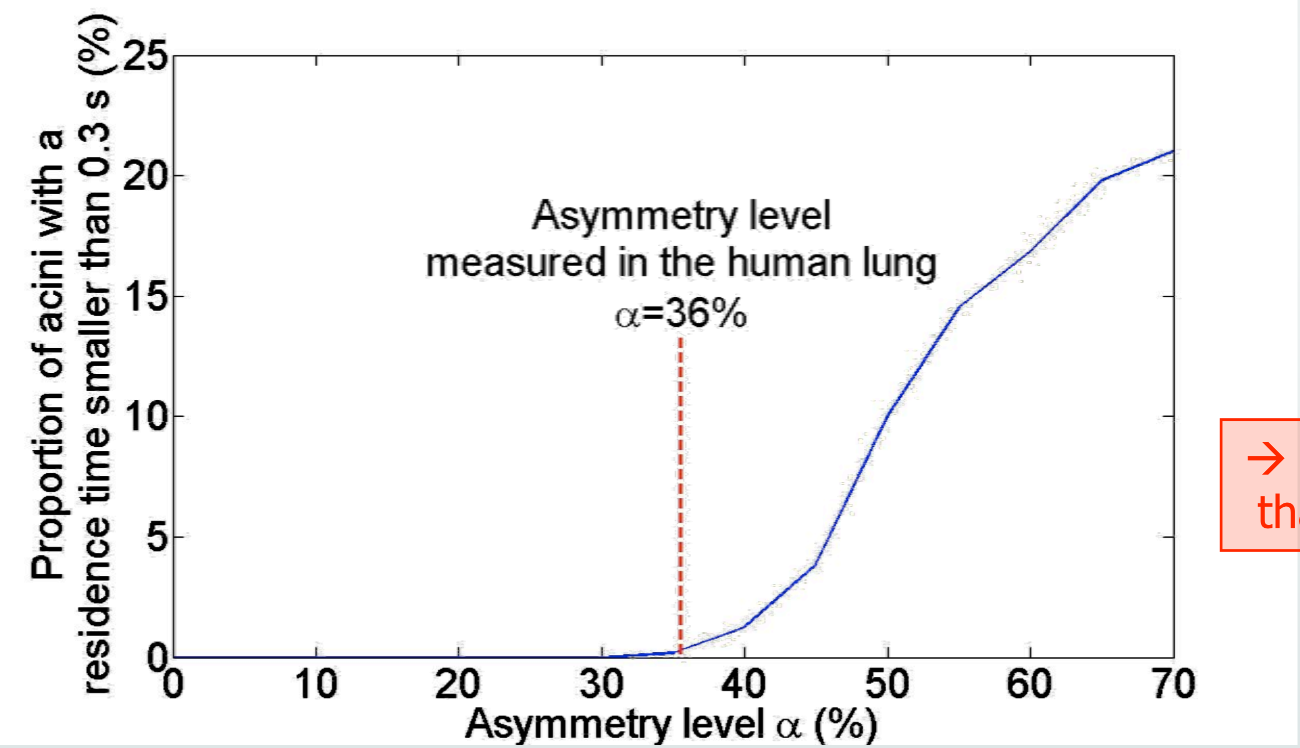
3- Volume of fresh air delivered to the acinus.



Which asymmetry

$$\begin{cases} h_{0,max}^3 = h_0^3\,(1+\alpha) \\ h_{0,min}^3 = h_0^3\,(1-\alpha) \end{cases}$$

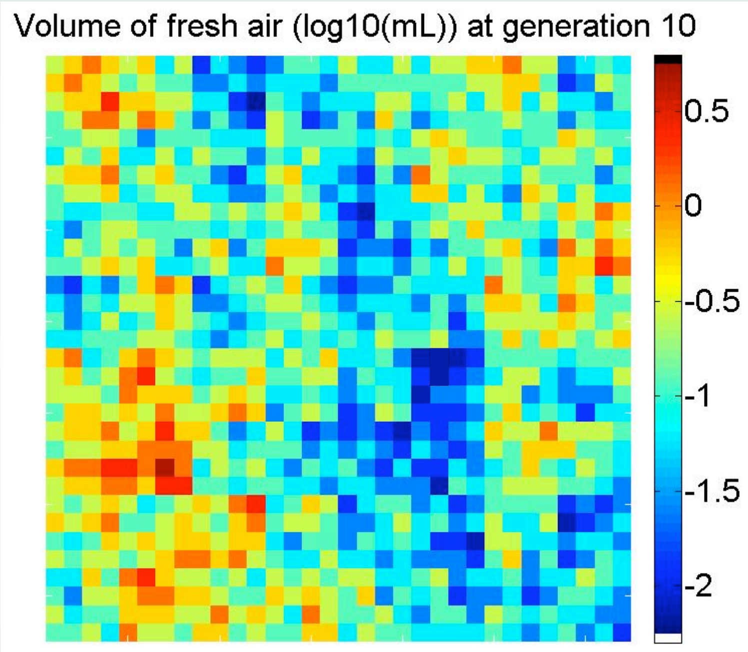
- All acini are ventilated during inspiration.
- Total ventilation (180 mL) is close to the average physiological data (220 mL).
- Proportion of acini with an oxygenation time smaller than 0.3 s (%)



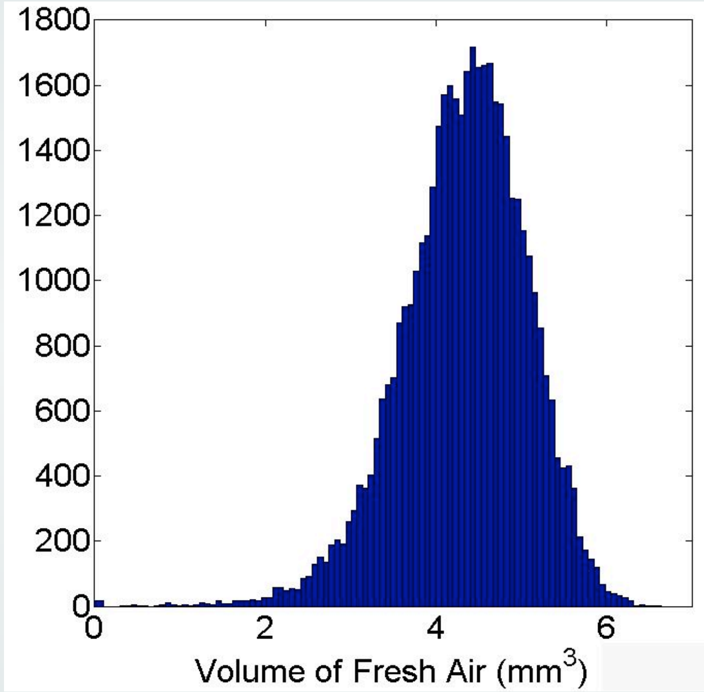
→ Maximal asymmetry level that allows to feed all acini

Heterogeneity of ventilation

- Volume of fresh air delivered by each airway at generation 10



- Volume of fresh air delivered to each acinus



→ **Conclusion: the ventilation heterogeneity is intrinsic of the lung structure.**

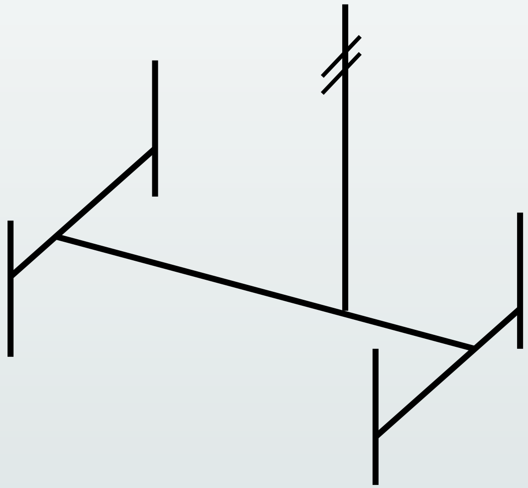
3D Representation of the tracheobronchial tree

❑ First level of 3D representation

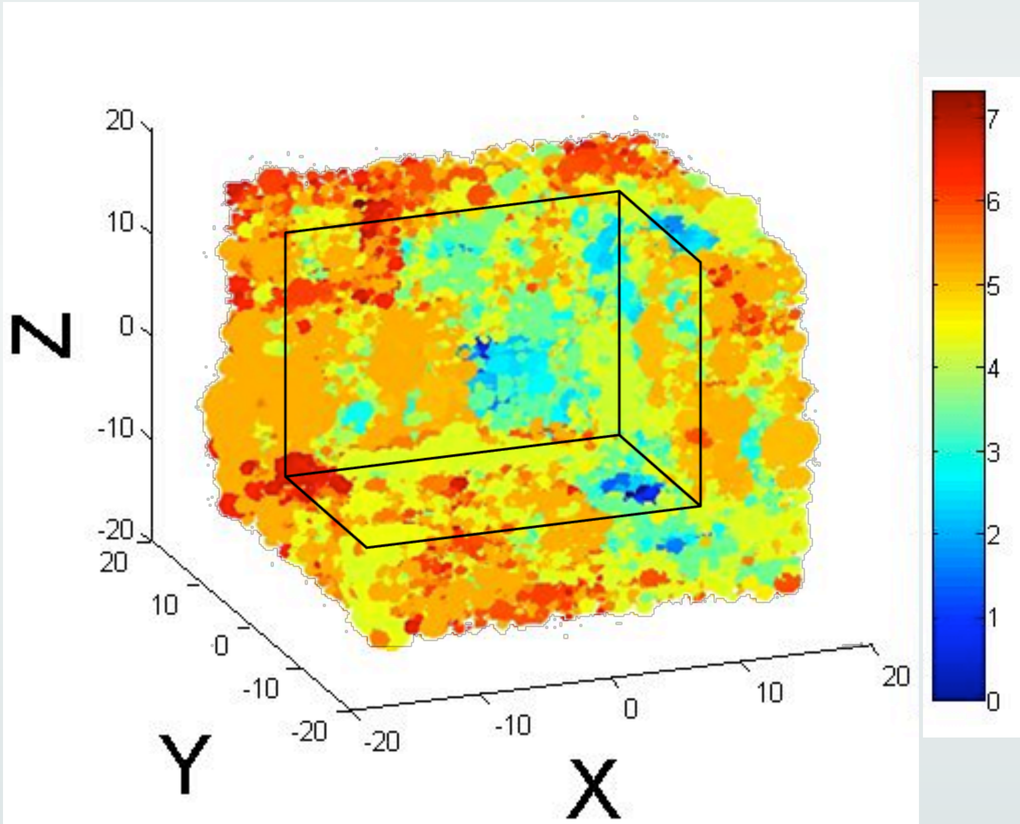
→ Asymmetric branching

→ Branching angle: 180°

→ Angle of rotation of the branching planes: 90°



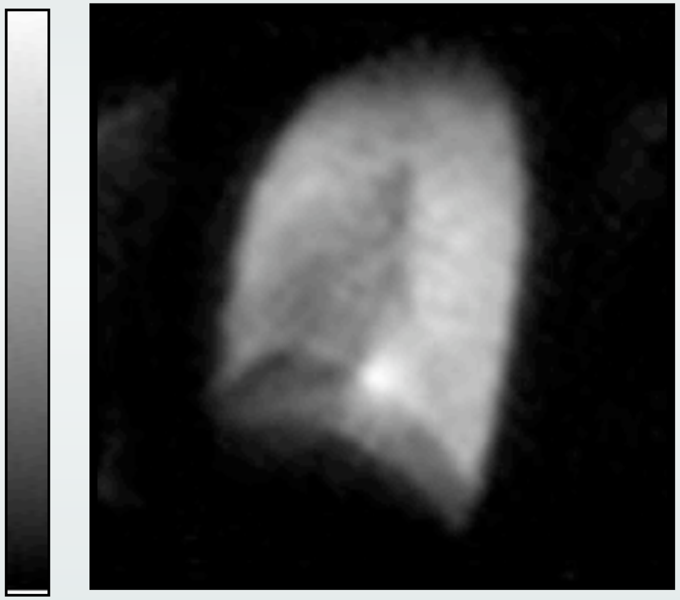
❑ 3D representation: volume of fresh air delivered by each terminal airway (mm^3)



Comparison: model & real lung images

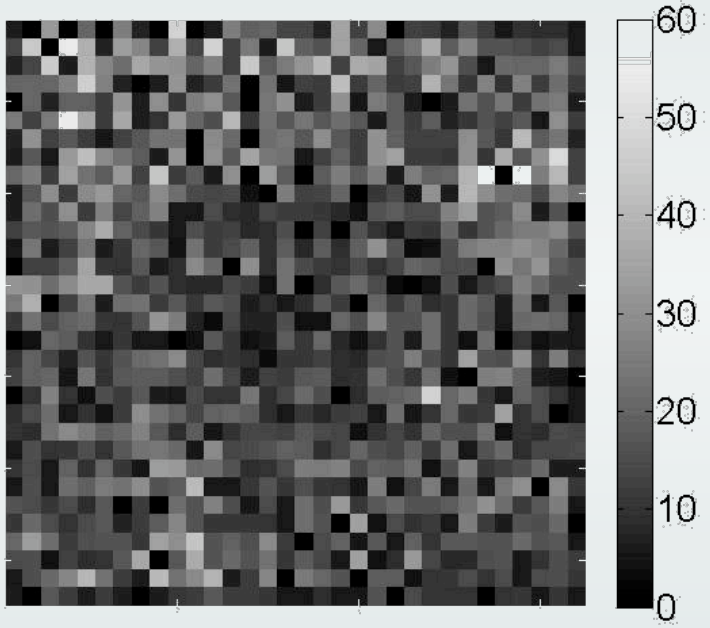
- Sagittal slice of the 3D representation

Distribution of polarized gas



(LKB, U2R2M, 1999)

Volume of polarized gas (mm^3)

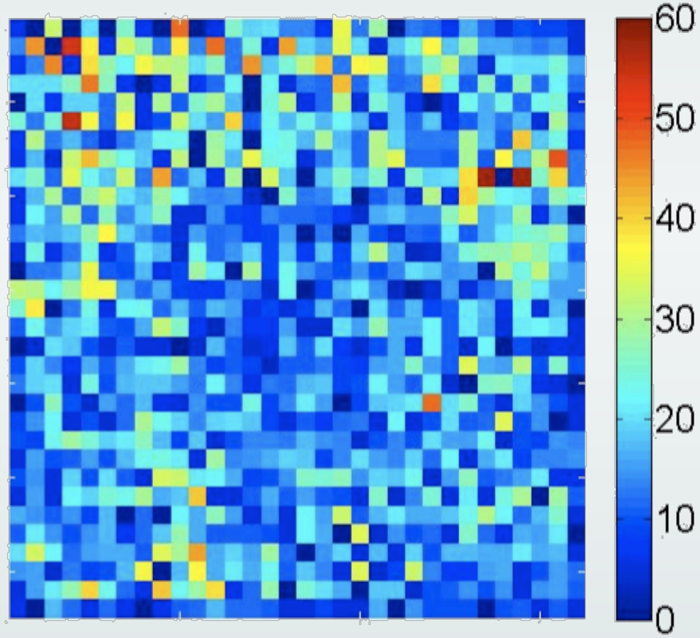


→ Similar level of heterogeneity of the gas distribution …

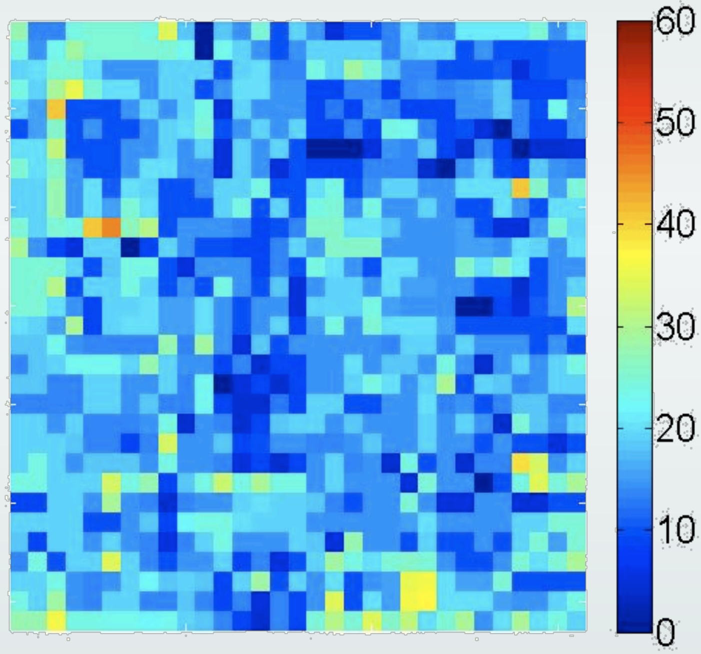
Comparison: level of asymmetry

- Volume of polarized gas (mm^3)

Asymmetric branching



Symmetric branching with **Gaussian noise** added to the geometrical structure



→ The level of heterogeneity of gas distribution increases with the level of branching asymmetry.

Conclusion

- The branching structure of the lung leads to an intrinsic heterogeneous distribution of the ventilation (fresh air or inhaled polarized gaz).

- Lung imaging: intrinsic noise