Economy of organ form and function

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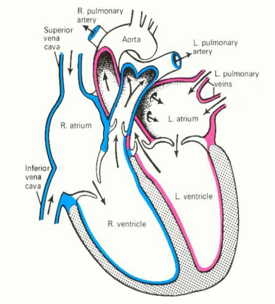
Table of contents

Organ morphogenesis

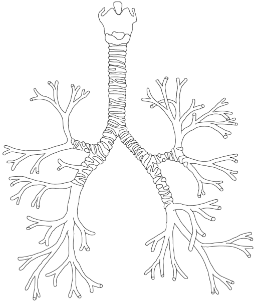
Constraints

Organ development in pluricellulars is submitted to constraints:

Function



Shape



Minimization of energy while satisfying the constraints

Optimization

The perfect organ does not exist. But the optimal can be reached.

Mathematical framework

- Cost function $\mathcal{E}$ dependent on one or several variables $x \in \mathbb{R}^n$
- One or several equality constraints: $c(x) = 0$, where $c : \mathbb{R}^n \to \mathbb{R}^m$
- Find an optimal value x^* that minimizes the function $\mathcal{E}(x)$ while $c(x^*) = 0$

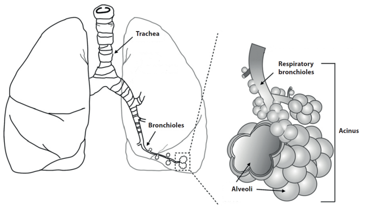
The example of the lung

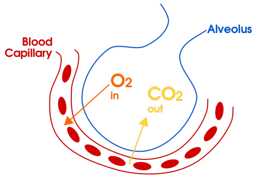
Problematics

- Role: connects O_2 and CO_2 in atmosphere with inner body
- Medium: gas transfer by diffusion through alveolar membrane
- Major constraints:
  - Diffusion: a surface process
  - Limited thoracic volume

Solution

Optimize (maximize) the surface/volume ratio!

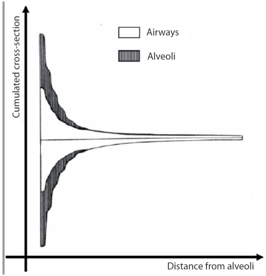


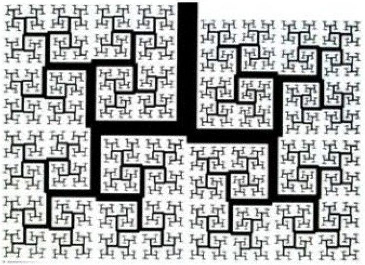


Lung morphometry

Characteristics necessary for a proper functioning of the lung

- Space-filling
- Self-avoiding

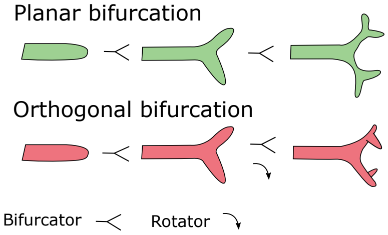




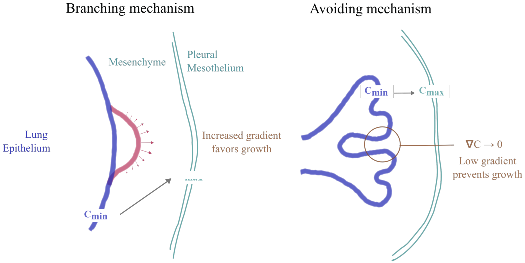
Lung morphogenesis

Two types of approaches

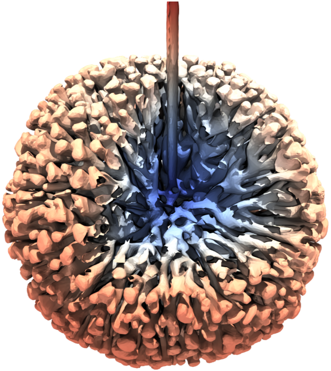
- Programmed morphogenesis
- Self-organized morphogenesis



Inspired by Metzger et al., 2008



Lung morphogenesis



Rendered image based on simulations from Clément et al., 2014

The lung as a model organ for optimization under constraints

Lung morphology

Bronchial tree

- Cascade of bifurcating airways with cylindrical shapes
- Around 17 generations
- Size of the airways decreases at each bifurcation

Acini

- Exchange surface with blood $(70 - 100\,\mathrm{m}^2)$
- Alveoli: bubble-like structure
- Around 6 generations

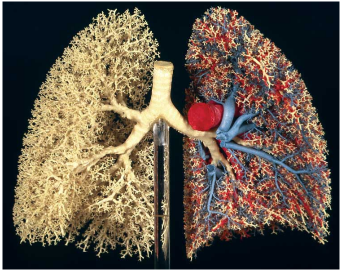


Figure: Cast of the human's lung made by E.R. Weibel

Modelling the human lung

Assumptions

- Symmetric dichotomic bifurcating tree.
- Branches are assumed to be cylindrical.
- Size of the bronchi of generation i:

$$l_{i+1} = l_i h \Rightarrow l_i = l_0 h^i,$$
$$r_{i+1} = r_i h \Rightarrow r_i = r_0 h^i,$$

- Homothetic ratio between generations.

$$h = \begin{cases} 2^{-1/3} \text{ in the bronchial tree,} \\ 1 \text{ in the acinus.} \end{cases}$$

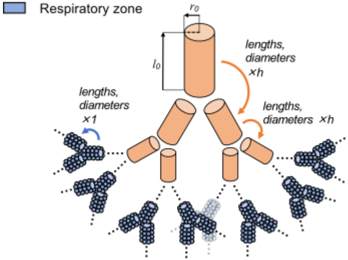


Figure: Illustration of the lung model

Diffusion process

Diffusion

- Passive process
- Balance the partial pressures between blood and the alveolar air

Limitations

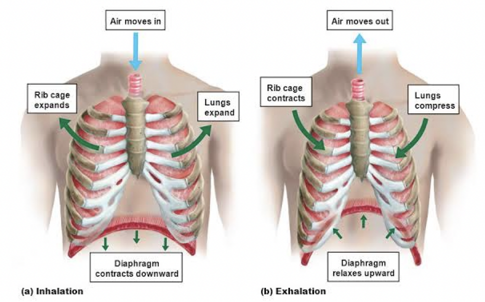
- Pathways from the ambient air to the respiratory zone are too long ($L_p \approx 30$ cm)
- Characteristic time to travel by diffusion:

$$t_p = \frac{L_p}{D} \approx 4500 \text{ s } = 1 \text{ hour and } 15 \text{ minutes !}$$

Convection process

Ventilation

- Dynamic process
- Air of the lung renewed
- Performed thanks to a set of muscles (ex. diaphragm)
- Two phases: inspiration and expiration



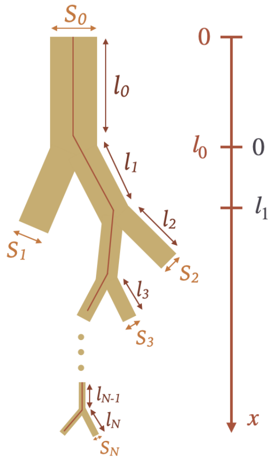
Modelling oxygen transport

Convection-diffusion-reaction equation in each airway

$$\frac{\partial P}{\partial t} - D\frac{\partial^2 P}{\partial x^2} + u(t)\frac{\partial P}{\partial x} = \beta\left(P_{\text{blood}} - P\right)$$

Link all generations by assuming:

- Continuity between generations
- Conservation of the quantity of oxygen



Numerical simulations

Inputs

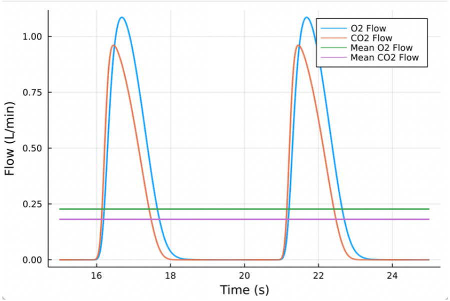
- Tidal volume
- Breathing frequency

Outputs

- O_2 flow to blood
- CO_2 flow to blood

$$\dot{V}_{O_2} = 230 \text{ mL} \cdot \text{min}^{-1}$$

$$\dot{V}_{CO_2} = 180 \text{ mL} \cdot \text{min}^{-1}$$

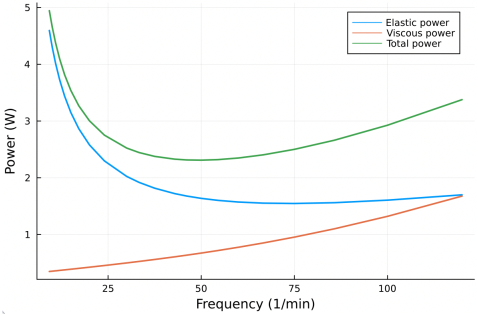


Power spent during ventilation

Action of the muscles on the lung:

- Deforms the tissues
- Displaces the air along the bronchial tree

$$\underbrace{\mathcal{P}_{\mathrm{m}}}_{\text{muscle power}} \simeq \underbrace{\mathcal{P}_{\mathrm{e}}}_{\text{elastic power}} + \underbrace{\mathcal{P}_{\mathrm{a}}}_{\text{air viscous dissipation}}$$



Power spent during ventilation

Viscous dissipation of air

- Characterized by the lung hydrodynamic resistance
  - Connects the airflow $\mathcal{F}$ to the air pressure p: $p = \mathcal{F}\mathcal{R}$
- Power dissipated

$$\mathcal{P}_{\mathrm{a}} = \mathcal{R}\mathcal{F}^2 = \frac{1}{4}\mathcal{R}(\pi f_b V_T)^2$$

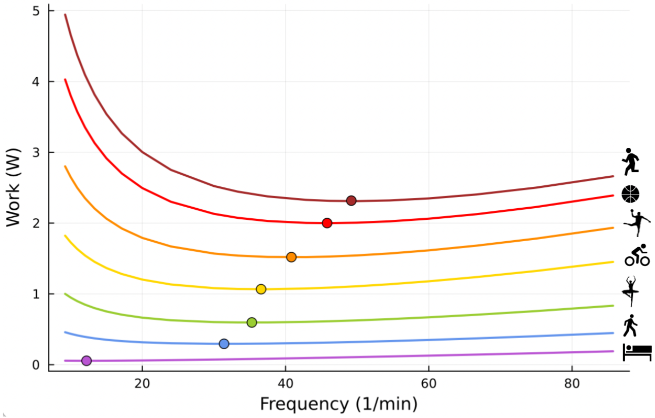
Elastic power

- Characterized by the compliance of the lung
  - Relates the force per unit of surface applied by the muscles to the volume change of the lung
- Elastic power

$$\mathcal{P}_{\mathrm{e}} = \frac{V_T^2 f_b}{2\mathcal{C}}$$

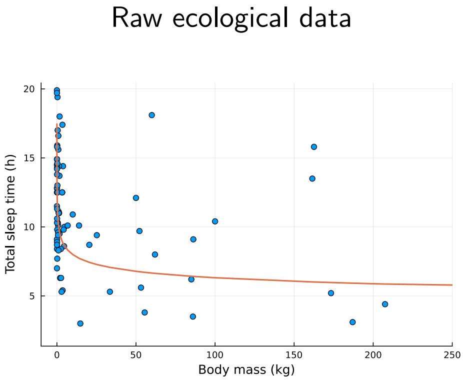
Optimal ventilation for humans

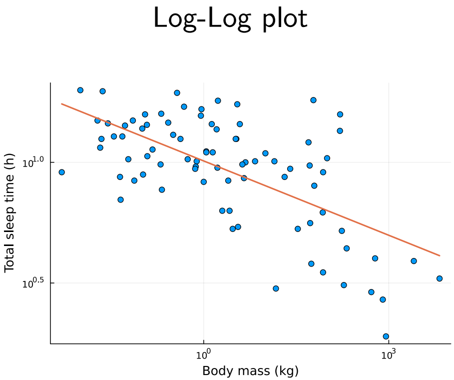
$$\min_{V_T, f_b} \mathcal{P}_\mathrm{e}(V_T, f_b) + \mathcal{P}_\mathrm{a}(V_T, f_b) \quad \text{s.t. } \dot{V}_{O_2}(V_T, f_b) = \dot{V}_{O_2}^{\mathrm{obs}}$$



Allometric scaling laws

Concept of allometry





$$t_s = 10.1\, M^{-0.103}$$

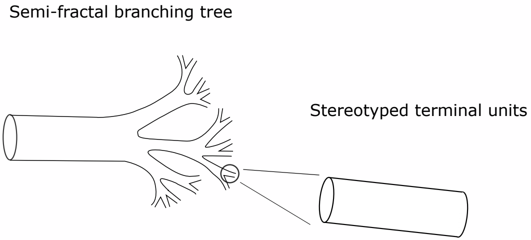
History of allometry

- 1897: Eugène Dubois described the relation between the brain's mass and the body's mass in mammals
$$b = c\,m^r$$
- 1907: Lapicque transformed Dubois' relation in a log-log dependency
- 1917: D'Arcy Thompson adopted the thesis that the living systems are submitted to the physical laws of nature
- 1936: Huxley and Tessier agreed for the terminology of allometry and the associated law
$$y = bx^\alpha$$

Mechanistic approach

WBE – Hypotheses (1997)

1. Transport of nutrients i.e., oxygen in a fractal-like branching tree
2. Fluid carrier incompressible
3. Total volume of the fluid proportional to body size
4. Size of the terminal units i.e., capillaries invariant or mass independent



Mechanistic approach

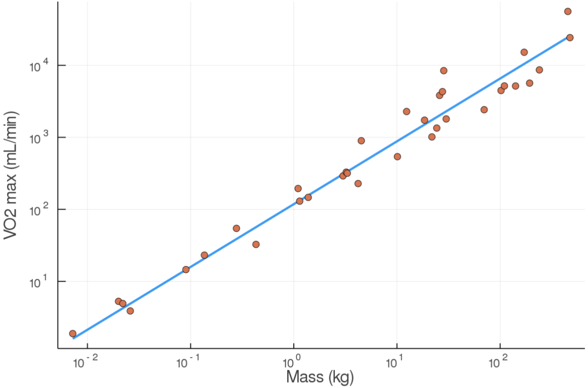
WBE – Model & Results

- General metabolic allometry follows a $\propto M^{\frac{3}{4}}$ relation
- Data-based allometric relations are retrieved from the model

Cardiovascular			Respiratory		
Variable	Exponent		Variable	Exponent	
	Observed	Predicted		Observed	Predicted
Aorta radius	0.36	$3/8 = 0.375$	Trachea radius	0.39	$3/8 = 0.375$
Blood volume	1.00	1.00	Lung volume	1.05	1.00
Circulation time	0.25	$1/4 = 0.25$	Respiratory frequency	-0.26	$-1/4 = -0.25$
Metabolic rate	0.75	$3/4 = 0.75$	Air velocity in trachea	0.02	0

Allometric laws in the respiratory system

- Mammals share morphological and functional properties dependent on the mass of the animal with allometric scaling laws
- Morphological differences amongst mammals affect the control of ventilation



Adaptation of the oxygen transport model

Shared characteristics

- Tree-like structure with bifurcating branches
- Decomposition into two parts: bronchial tree and acini

Adaptation of morphological parameters

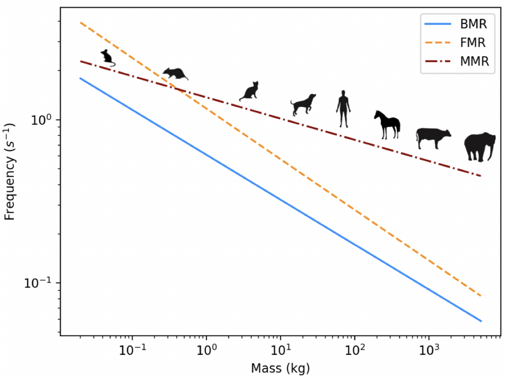
- Tracheal radius and length
- Radius and length of alveolar ducts
- Exchange surface

Oxygen transport

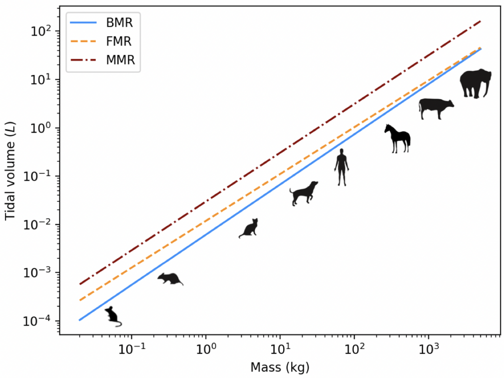
- Convection-diffusion-reaction equation
- Exchange β coefficient dependent on the mass of the mammal

Optimal ventilation for mammals

$$\min_{V_T, f_b} \mathcal{P}_\mathrm{e}(V_T, f_b) + \mathcal{P}_\mathrm{a}(V_T, f_b) \quad \text{s.t. } \dot{V}_{O_2}(V_T, f_b) = \dot{V}_{O_2}^{\mathrm{obs}}$$



(a) Frequency



(b) Tidal Volume

Allometric laws for ventilation

Allometric law:

$$Y = Y_0 M^{\alpha}$$

	f_b (pred)	f_b (obs)	V_T (pred)	V_T (obs)
BMR	-0.29	-0.26	1.05	1.04
FMR	-0.32	N.D	0.98	N.D.
MMR	-0.15	-0.14	1.04	N.D.

Table: Predicted and observed exponents α for the allometric scaling laws of breathing frequency f_b and tidal volume V_T at three different metabolic regimes.

Conclusion

Conclusion

- Principles of economy applied on larger living structures
- Constraints guide the development and the functioning of mammalian lung
- Allometric laws allow a deep understanding of the mechanisms of differential growth