UNIVERSITÉ DE NICE-SOPHIA ANTIPOLIS

Dossier de candidature pour
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La viscosité: un architecte pour le système respiratoire ?

Viscosity: an architect for the respiratory system?

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The most exciting phrase to hear in science,
the one that heralds the most discoveries,
is not "Eureka!" (I found it!) but "That's funny..."

Isaac Asimov

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Acknowledgements

I was told that acknowledgements were the section the most read in HDR manuscript. This put really a lot of pressure on my shoulders...

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Chapter 1

Introduction

1.1 Disclaimer

I see my job as an applied mathematician as using mathematics as a tool for the study of the surrounding world, biology for me. Thus my primary objectives are to give some answers to questions related to biology and not to study related mathematical aspects. So my research aims at explaining the respiratory system functioning and its evolution, and you will not find theorems in the usual form in this manuscript[1], even though many a result could have been written in a such way. However, I think the usual presentation of mathematical results is not an easy journey for readers from other disciplines, thus I chose to present them in a more "story telling" way. Of course, all this is a personal choice that can be discussed again and again, and I hope no one will be offended. Also, I am fully aware there are many ways to do applied mathematics, and all of them have their role to play in an equal way.

I wanted this manuscript to be personal and to describe the mood in which I do my work as a scientist... well, in the good days at least. So I tried to use this manuscript as a way to ban for a while the usual, though most often essential, sternness of scientific papers.

1.2 Running away

Figure 1.1: Rahan chased by a saber-tooth tiger, probably to the disappointment of the tiger (Rahan is a french comic book, the first episode was published in 1973 by Hachette edition).

When I think about human evolution, I often get the picture of a guy running away from some angry hungry predator, not unlike a saber-tooth tiger[2]. I was probably unconsciously inspired by

[1] Actually there are a few, can you find them?

[2] In fact, saber-tooth tiger (Smilodon) might not have been so much in chasing prey for a long time but more in jumping from nowhere, give a death blow and wait [37, 67].

the french comic character *Rahan* (see figure 1.1). Then the same question always pops up: will this guy escape the tiger? I have no worries for Rahan himself though, since more than a dozen episodes follow the first one. Anyway, apart from Rahan, I guess tigers are better runners that humans, so this is probably a rhetorical question if the guy is alone. But if he is not, then the tiger will be satisfied with one prey and this is were natural selection in human begins.

The success of the escape depends on many factors of course, but one of them will interest us more particularly: will the respiratory system be able to put up with the extra supply in oxygen needed by muscles and organs? Everything else being equal, if your respiratory system is a bit more efficient than the one of, say, Rahan[3], then you might have better chance to escape, and thus globally improve your success as an organism in a dangerous environment. Consequently, the efficiency of the respiratory system can be crucial for survival.

Of course the selection we speak about occurs in exercise regime, and the race with the tiger hints why the ability to undergo an exercise regime may have been selected by evolution. But it is not clear whether this means that all selection has occurred in that close-to-the-physiological-limits regime[4]. Of course, there may have been other activities in rest regime with less permanent fate, which affected human evolution and respiratory system in particular. To be able to supply basal metabolism with oxygen in an efficient way allows to spare energy for other means, such as reproduction.

An important feature of the respiratory system is that it uses fluids to transport oxygen: air in the lung and blood in the blood network. The circulation of air and blood has an energetic cost due to the physical property called viscosity, which is related to the friction inside the fluid. This energetic cost is the core of my work and I ask the question on how it may have influenced the evolution of the respiratory system.

1.3 A short bibliography

To my disappointment, I am not the first to study the role of viscosity on transport network efficiency. I give here a small, not exhaustive, bibliography of some of the literature I encountered in my work.

In 1926, Murray proposed the first law[5] for the optimal design of blood vessels, based on a trade-off between the power needed to make blood circulate in the vessel and the metabolic power needed to maintain blood. The law is formulated using Poiseuille's regime in cylindrical vessels, and the optimal configuration corresponds to the blood flow rate being proportional to the cube power of the radius of the blood vessel. The well known corollary for a bifurcation states that the cube radius of the parent vessel equals the sum of the cube radii of the daughter vessels [74]. In the seventies, Zamir extended this law to account for bifurcation angles [114] and expressed Murray's law in term of wall shear stress being constant independently on the vessel size [115]. While blood arterial macrocirculation checks Murray's law, this is not the case for microcirculation, where wall shear stress is decreasing with the sizes of the vessels. Different hypotheses were developed to explain the shifts to Murray's law observed with microcirculation, for example by adding smooth muscles energy costs [98]. In 2005, Alarcón et al [2] used semi-empirical laws from Pries et al [82] and showed that wall shear stress behavior in microcirculation can be explained by phase separation effects in small blood vessels. Phase separation effects make blood viscosity become a non monotonous function of vessel radius: the Fåhræus - Lindvquist effect [32, 33, 82, 83].

Similar researches about the lung were more recent [43, 93], in particular with the work of E.R. Weibel [107, 108] and B.J. West [110]. The links between the physics in the lung, its geometry and its efficiency were studied by the team with B. Sapoval and E.R. Weibel [25, 28, 29, 30, 57, 62, 63, 90]. A few other groups are also working on this topic, see for example [46, 51, 52]. Some interesting developments about fluid dynamics theory in lung models were performed by mathematicians and most particularly B. Maury and C. Grandmont [4, 39, 56, 96]. Studies on ventilation in

[3] You are probably an athlete and will participate to the next olympic games.
[4] See conclusion of section 8.3 for an example of close-to-the-physiological-limits.
[5] Actually, he developed the pioneer work of Hess [41].

anatomical lung models brought important insights on structure-function relationships [42, 48, 55], in particular the work of the team of M. Tawhai [100, 101, 102, 103].

Thus, the initial formulation of the cost by Murray has been extensively used and improved. It gave rise to general theories about biological networks design [7, 8, 36, 111, 112]. For example West and his colleagues propose scenarios based on fluid viscous dissipation that ought to explain allometric laws found in mammals[6] [111] or in plants [112]. Other more controversial theories have also emerged such as the optimal design theory [7].

1.4 Manuscript structure

I will start scientific work in chapter 2 by describing the concepts needed to understand the problems I intend to study. Then in chapter 3, I will explain what are the conditions for evolution to be able to select a tree structure under the hypothesis that evolution is driven by viscous costs. In chapter 4, I propose to discuss lung development and try to understand how evolution may have effectively selected some tracheobronchial tree features. Biological structures development is often submitted to a noise, as shown by our scenario from chapter 4, thus I propose in chapter 5, to study how evolution may account for this noise in the selection of an optimal strategy, with tracheobronchial tree as an application. In chapter 6, I want you to see that such fundamental work can find some practical application in the medical world. In that chapter I present two applications, one mostly about chronic obstructive pulmonary disease (COPD) diagnostic and the second about chest physiotherapy. The following chapters are dedicated to blood network efficiency relatively to its viscous dissipation. Chapter 7 develops how features of the mid level arterial network such as its fractal nature and the red blood cells concentration in blood can be deduced from an energetic cost involving viscosity. Finally, in chapter 8, we make the same study as in the previous chapter, but for capillaries where the physical phenomena are different. We show that even though the red blood cells concentration in capillaries is smaller than in large circulation, it remains optimal for a cost which is the same as in large circulation, except that it accounts for a different physics in the capillaries. In this chapter, we also studied some problems related to oxygen transfer toward the red blood cells. Chapter 9 concludes this manuscript.

The one before last chapter is a lexicon that describes a few of the technical terms used in the text. It is not really intended to be read, but only to be referred to if needed. The last chapter, chapter 10, is a summary of this manuscript in french with an integral translation of the introduction and of the conclusion.

All these studies without exception are based on mathematical and/or numerical tools applied to respiratory system modeling. These tools are based on partial differential equations theory, optimization theory, dynamical systems, population dynamics, numerical analysis or scientific computation. These tools are sometimes based on the literature and sometimes specifically developed for the problem studied. Thus most of the chapter begin by a description of the models and tools used for the problem studied in the chapter. Each chapter ends with a description of the collaborations and with the abstracts of the papers (published, in preprint or in preparation) on the chapter topic.

[6] Amazing power-law relationships between a physiological quantity and the mass (or size) of an animal. Typical quantities are the total number of heart beats during life, the basal metabolism, the oxygen consumption rate, etc.

Chapter 2

A brief summary of the concepts and theories involved in my research

2.1 Oxygen in the respiratory system

> *"I rarely use oxygen myself, sir. It promotes rust."*, Robby the robot, in the movie *Forbidden Planet* (MGM, 1956).

If you were a cell, you would use ATP[1] molecules as a source of energy. You would have two ways to produce and store ATP: the anaerobic and aerobic pathways. The anaerobic pathway, well named *glycolysis*, produces lactates, water and two ATP for each glucose molecule it can get a hand on. Good enough... Except that lactates actually still contain a lot of energy and alter blood pH, which is not good. In contrast, the aerobic pathway uses an oxidation process in the mitochondria that is able to produce thirty-six molecules of ATP from one molecule of glucose! Pretty efficient... Also its waste products are water and carbon dioxide: these are easily dealt with in the organism [107].

If you are a sensible, well educated cell, you will want to use the aerobic pathway as much as possible ... and you may even ask why bother with the anaerobic pathway? Any passing by athlete would then explain that the major drawback of the aerobic pathway is that it definitely needs oxygen, and oxygen you may lack... In which case you would then be happy to fall back on anaerobic pathway to go on with whatever energy demanding task you were performing. Moreover, some simple cells, like red blood cells, are outrageously stuck with just the anaerobic pathway.

So you will want to use oxygen, but oxygen is a resource that is present in ambient air and ambient air is obviously outside the body (luckily for us living beings, because there are many other not so friendly things in air that we want to keep at bay[2]). So to make things work smoothly, we have a built-in organ whose task, among others, is to remove oxygen from air and to bring it to our cells: the respiratory system. Fortunately for us respiratory system researchers, this organ is not simple and it is quite a job to study its many aspects. The organ divides into sub-organs with different physiologies involving different physical laws, making the system look like a mess to the padawan[3]. But these different parts fit nicely together and are finely tuned in such a way that the organ is quite efficient.

Oxygen quietly resides in the ambient air, until some passing by, absent-minded mammal inspires. Then an amount of air, with its oxygen molecules inhabitants, is sucked into the mammal lung. Then oxygen discovers that the lung is a tree structure with a trunk (the trachea) which

[1] it develops into the comely *adenosine triphosphate*

[2] pollutants, bacteria, viruses, Justin Bieber's music, etc.

[3] if you really need it: Jedi's apprentice in *Star Wars* movies (really?!)

divides into two smaller airways, and that each of these airways divide again into two smaller airways and so on. These divisions go on for about twenty-two times. Airways which accounts for the same number of bifurcations from the trunk belong to the same generation. Our friendly amount of air, with its oxygen hitchhikers, travels and spreads smoothly into the lung, its speed becoming smaller and smaller as it goes deeper into the lung. When it reaches about the seventeenth generation, the end of the well named tracheobronchial tree, its velocity has become really small: convective transport of oxygen with air is at an end. Fortunately, like the ninja, oxygen has many ways to move and one of them is diffusion. Oxygen diffuses because of the specific lung structures it is now meeting. From the seventeenth generations to the end, the airways form what is called the acini. Airways' walls in the acini are covered with alveoli. Alveoli look like bubbles and their walls consist in capillary beds where blood flows. The whole surface formed by the alveoli walls is the exchange surface between alveolar gas ($\sim$ air) and blood, it is about a hundred square meters in humans. Blood in the lungs is poorly oxygenated and, seen from the blood point of view, oxygen concentration near the acini openings looks like Eiffel Tower during a summer day. And because blood is flowing and air regularly renewed, the gradient in oxygen concentration is maintained. Since diffusion's motor is Brownian motion, it tends to homogenize concentrations [4] [5] and a flow of oxygen is maintained into the acinus, towards blood in alveoli walls. Once oxygen reaches the alveolo-capillary membrane, it dissolves into the membrane, diffuses to the plasma and go on its diffusive motion towards the red blood cells. Red blood cells (or erythrocytes) are disk-shaped cells that consist in a bilipidic membrane enclosing a cytosol that is highly concentrated with hemoglobin. Red blood cells are very deformable and take the shape of a parachute whenever they enter a vessel whose diameter is on the same size order, typically a capillary. Red blood cells account normally for about forty percent of blood. Once oxygen has been captured by the red blood cells in the pulmonary capillaries, it travels comfortably inside the red blood cells into the confluent pulmonary venous network, then through the heart left ventricle and finally it enters the arterial systemic circulation that feeds the organs. Oxygen is then unloaded by a process that is the inverse to that of its loading, it enters the cells and is mainly consumed into the mitochondria to produce ATP and thus store chemical energy. Red blood cells maintain a low inner oxygen concentration by fixing in real-time incoming oxygen molecules on its hemoglobin molecules, thus hiding them from the sagacity of diffusion. A map depicting oxygen journey is plotted on figure 2.1.

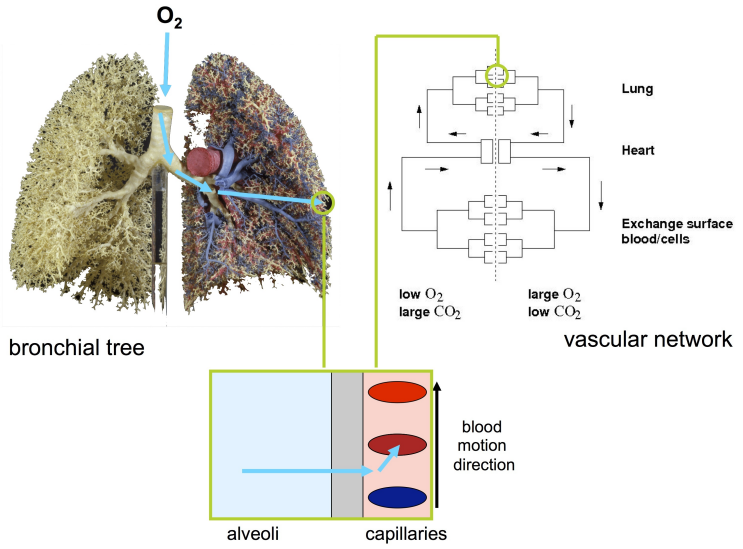


Figure 2.1: Oxygen's adventures (lung cast by E.R. Weibel, Bern).

[4] As discussed with colleagues in front of a bruscetta: if you take two identical, connected compartments, one with a high number of particles and one with a low number of particles, then each particle has one chance over two to reach the other compartment, which means that half the particles of each compartment will reach the other, thus homogenizing the concentrations. This does not work with olives on bruscetta.

[5] Restaurant choosing has the opposite behavior: most people will often chose the crowded one, even if it stands nearby an empty one, thus unstably crowding the first one even more, ultimately reaching a Dirac distribution (probably for good gastro-intestinal reasons).

2.2 The importance of being viscous

As you may have noticed, oxygen uses moving fluids as transportation systems: it starts its journeys within air and "jumps", in a graceful diffusive motion, into blood as soon as air transportation has brought it far enough. In lung or in blood networks, the fluids are flowing inside tube-like structures that bifurcate regularly.

The thing with fluids in cylinders, or at least with those we are looking at here, is that when they are viscous, they are clinging to the walls and stop moving as soon as you stop pushing them through. For a fluid, being viscous means that it is submitted to friction and, by definition, friction opposes any relative motion by converting motion energy into heat. A consequence is that friction wants the fluid to move everywhere with the same velocity. But in a tube, there is a wall and the wall is unmoving, so the fluid near the wall will stubbornly remain unmoving, because of friction and of wall rugosity. Consequently, a viscous fluid in a tube will want to stop, unless you continue to push it through the tube tirelessly, which is lung muscles and heart are doing all days long in many animals, including mammals. Whatever the way you push the fluid inside the tube, the fluid near the wall will not move. This unmoving layer will slow down the upper layer which will in turn slow down slightly less the next layer and so on, thus creating layers of fluid which are moving at different velocities: friction lurks everywhere! And the thinner the tube, the more friction you get.

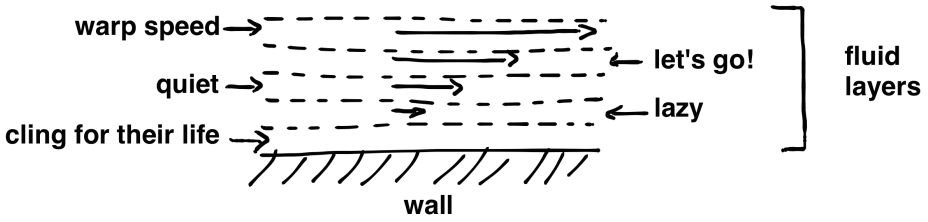


Figure 2.2: Fluid layers race: viscosity and wall rugosity make the layers near the wall slower.

Flows in straws.

Who never ordered a fancy drink and discover dreadfully it had to be drank with a straw so thin even light has trouble to go through[6]? Drinking through such a straw always ends up with people making funny faces[7]. Fortunately, fluid mechanics and the work of J.L.M. Poiseuille in the nineteenth century [97] make us able to quantify the power needed to keep the fluid in motion within the straw[8]. This power actually compensates viscous dissipation, i.e. the power converted to heat by friction. Let us assume our drink is incompressible, isotropic and Newtonian. Incompressible means that the volume of the fluid cannot change, luckily for us. Isotropic Newtonian means that the viscous constraints τ inside the fluid are proportional to the gradients of the velocity u, $\tau = \mu \times (\nabla u + {}^t\nabla u)$, with μ the (dynamic) viscosity, a constant and intrinsic property of the fluid; in other words, whatever the difference in velocity between two layers of fluid, the heat dissipated is always proportional to that difference. Typical Newtonian fluids are water or air; blood is not a Newtonian fluid although it can be approximated by a

Figure 2.3: Viscosity (added to gravity here) can make sipping through a straw a difficult business (photo credit: Saul Loeb/AFP/Getty Images).

[6] and undoubtedly this drink is dressed up with a small colorful paper umbrella.

[7] I always wondered if this was some kind of private conspiracy from some bartenders secret society.

[8] By saying this, we neglect gravity. This is reasonable only if the straw is tight enough, in which case viscosity effects overcome gravity effects. Typically the power needed to drink water with a straw whose diameter is smaller than 2-3 millimeters is dominated by viscous effects at normal drinking rates.

Newtonian fluid under certain conditions. Anyway, we will talk about blood later (who drinks blood anyway?[9]).

For such isotropic Newtonian incompressible fluids, the hydrodynamic resistance $\mathcal{R}$ of the tube relates the power we need to compensate with our jaws muscles - and the level of deformation of our jaws, see figure 2.3 - to the geometry of the straw and the viscosity μ of the fluid. If l is the straw length and r its radius, the power $\mathcal{P}$ needed to make a fluid flow F go through the tube can be deduced from Poiseuille's law[10] [79]:

$$\mathcal{P} = \mathcal{R}F^2 \quad \text{with} \quad \mathcal{R} = \frac{8\mu l}{\pi r^4} \tag{2.1}$$

The power $\mathcal{P}$ depends on the radius in $1/r^4$: a straw twice times tighter needs sixteen times the power... The conclusive philosophy is thus to never ever accept a thin straw.

From straws to oxygen transport.

What applies to straws can be extended to bronchi or blood vessels, which also belong, with some approximations[11], to the happy family of cylinders. We saw earlier that making fluid go through cylinders costs energy, the exact amount of energy depending on the cylinders' geometry and most particularly on their radii. Lung and blood network can be seen as cascades of cylinders: oxygen transport implies an energy cost due to viscous dissipation in those structures. Interestingly, oxygen transport is used to bring oxygen to the cell to produce energy for the metabolism, but this transport costs energy itself: the balance between oxygen gain and oxygen cost has to be positive in order for the transport system to have any efficiency. But how can efficiency emerge? This is a difficult question and, luckily, we have the privilege to live after Charles R. Darwin [21] and Alfred R. Wallace [106] who gave us the answer in the mid nineteenth century, when they discovered evolution and natural selection.

2.3 Evolution.

> *"For animals, the entire universe has been neatly divided into things to (a) mate with, (b) eat, (c) run away from, and (d) rocks"*, Equal Rites, Terry Pratchett.

Natural selection and mutations

Evolution is the transformation along the generations of heritable characteristics in a population. Evolution is influenced by several forces [26]. We will focus most particularly on two of these forces: natural selection [21], which is the origin of environment adaptation, and genetic variations (typically mutations) [26]. In a simple way, natural selection is the dynamical system consisting in the interactions between the organisms in their ressource limited environment. Individuals with an advantage in resource exploitation reproduce more efficiently. Thus, their relative number in the population increases and they leave less resources to the individuals which have not this advantage. Typically, such an advantage is gained through a genetic mutation that shifts the phenotypes of the individual and of its offsprings. This phenomenon forms the basis of natural selection, and it is based on surprisingly simple mathematical concepts.

The trouble with tribbles.[12]

Although imaginary, tribbles make a very good example to illustrate evolutionary dynamics. Tribbles are an imaginary alien species from Star Trek[13] which have two main characteristics: they are able to reproduce very quickly, and they are cute (fluffy balls that purr, see figure 2.4A). According to Mr Spock, the high reproduction rate is a consequence of the high predation they

[9] Vampires, but they are not as dangerous for humanity as their diet fellows the mosquitos.

[10] or the "never get laughed at again by a bartender formula"

[11] Bronchi and blood vessels are depressingly not perfect cylinders, but they can be approximated as such.

[12] If you are interested in evolution and in the weird paths evolution has taken, you must read the excellent book *The selfish gene* by Richard Dawkins [22]

[13] Tribbles first appear in episode 44 *The trouble with tribbles*, in Star Trek The Original Series, 1967.

suffer on their home-world, planet Iota Geminorum IV[14]. And indeed, a high reproduction rate is a frequent strategy of our earthly insects that also suffer high predation - typically mosquitos. Tribbles are thus submitted to a strong selective pressure on their reproductive rate, and indeed they do have a relatively large uterus that can accommodate many fetuses at once, see figure 2.4B. Let us assume the tribbles have a reproducing rate $r_x > 0$ (one tribble gives birth to a

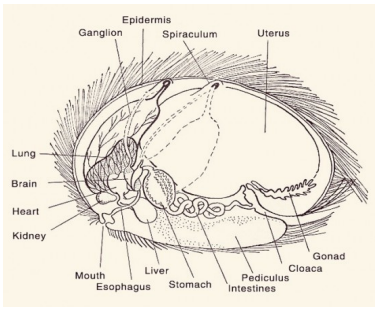
A  B 

Figure 2.4: A: a tribble is an imaginary animal from the Star Trek series which has a high reproducing rate. B: tribble anatomy, notice the large uterus at the origin of their high reproductive rate, image from *Star Fleet Medical Reference Manual* [78].

mean of r_x tribbles at each time unit) and that a mutation occurs and improves the capacity of a tribble to reproduce more with a rate r_y, larger than r_x. But as all living organisms, tribbles live in a resource limited environment which can support only K tribbles. In that case the effective reproductive ratio will be weighted by the resources left in the environment: $(1-(x+y)/K)$, where x is the number of "normal" tribbles and y the number of "mutants" tribbles. The tribbles suffer predation and they disappear at a rate $p > 0$[14]. This dynamic is reflected by the following equations:

$$\begin{cases} \dfrac{dx}{dt} = r_x(1-\dfrac{x+y}{K})\ x - p\ x \\ \dfrac{dy}{dt} = r_y(1-\dfrac{x+y}{K})\ y - p\ y \\ x(0) = N \ \text{ (the number of tribbles when the mutation occurs)} \\ y(0) = 1 \ \text{ (one tribble gets the mutation at time } t=0) \end{cases} \tag{2.2}$$

The mathematics of these equations are very classical and doing a stability study [75], we have the following results:

Lemma. *The tribbles do not go extinct, i.e.* $\lim_{t\to+\infty} x(t) > 0$ *or* $\lim_{t\to+\infty} y(t) > 0$ *if and only if* $r_y/p > 1$ *(more tribbles are born than eaten). If they do not extinct, then* $\lim_{t\to\infty} x(t) = 0$ *and* $\lim_{t\to\infty} y(t) = k\left(1-\frac{p}{r_y}\right)$*, i.e. only the mutant tribbles will remain at the end.*

Mutant tribbles invade the environment because they have an advantage in the exploitation of their environment: for the same resource quantities they are able to get more offspring. Because the resources are limited, their relative number increases regularly with time until they fill the environment. Actually the ratio between predation and reproduction rates p/r is very important and represents a cost: the higher its value, the lower the tribbles population. If this cost is larger than 1 then tribbles population goes extinct. If this ratio is decreased by any mutation, then the mutants will invade the population. Thus if predation p is high, birth rate r must also be high for the population to be maintained. You now get an idea on why Captain Kirk and his crew went into trouble when some tribbles found their way into grain storage where they could eat at will

[14]and according to Dr McCoy, they are pregnant before they are even born. Actually, this behavior does exist in the real world in some insects, such as aphids [47].

[14]In a more ineluctable way, p can be called the mortality rate.

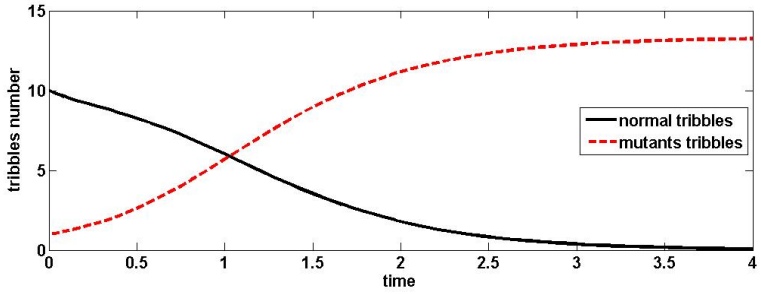


Figure 2.5: Mutants tribbles have an improved reproducing rate: they invade the environment and replace their cousins with lower reproducing rate.

with no predators...

Energetic costs.

We defined a cost from the ratio of the predation rate over the birth rate: p/r. The number of individuals in the tribbles population without predation would be k, but predation removes a number kp/r individuals from the population. Consequently, if the cost is distributed evenly to all individuals, then each tribble pays a price p/r, lost to predation. This cost corresponds to a direct loss of energy spent in reproduction. In the preceding paragraph, we saw that if a tribble got a mutation that makes the cost lower, for example by increasing the birth ratio r, then its offspring will eventually invade the tribble population.

Figure 2.6: Tribbles: the cost p/r as a function of the litter size. The optimal value is about 11 (already pregnant) tribbles per litter.

An organism can alter its ways to interact with the environment through what is called a trait. In biology, a trait is a characteristic of an organism. The energy cost we defined for the tribbles will be affected by several traits that will alter either the birth rate r or the predation rate p. Let us focus on the birth rate of tribbles, and on the following trait: the litter size of a tribble (number of offsprings). It seems obvious that the larger the litter size, the larger the birth rate[15], and increasing the litter size can be achieved by increasing the uterus size of the tribble, see figure 2.4B. However, if the uterus is too large, then the size and mobility of the tribble are altered and predation is increased. Thus the cost is a convex function of litter size, see figure 2.6.

Consequently, the level of adaptation to environment of a trait can be represented with a cost that measures directly or indirectly an amount of energy allocated to the trait. Evolution will select phenotypes with costs smaller and smaller, ultimately selecting the phenotype with the lowest cost [26]. Notice that another measure of adaptation is often used: the fitness that measures the number of mature offspring produced over the lifetime of an individual. While evolution minimizes costs, it maximizes fitness.

[15]Litter size can be larger if offsprings are smaller, in which case their survival may be lower [49]; for tribbles however, we will assume that offsprings size remains the same.

2.4 The trouble with costs functions.

"Your assumptions are your windows on the world. Scrub them off every once in a while, or the light won't come in.", Isaac Asimov.

In the previous section, we had enough fluffy animals for years[16], but with their reluctant help, we were able to connect evolution with the notion of costs. Evolution adapts traits expression to minimize the related costs, which arise from the interactions between the organism and its environment. In a more general way, any energetic cost is related to traits and faces evolution that may affect these traits in order to spare energy, in the limit of physiologically compatible step by step changes[17].

Let us go back to the respiratory system, we saw that viscosity implies an energetic costs for oxygen transport due to viscous dissipation. With the example of straws, we also saw that the amount of viscous dissipation is dependent on the geometry of the transport network. Consequently, traits related to respiratory system geometry may have been submitted to selection and affected in such a way viscous dissipation is not too high or even minimized. This brings us to the first of the two core hypotheses I made about evolution. This first hypothesis allows us to search for the phenotypes that minimize the costs. Typically, we will search for geometries that minimize viscous dissipation in the respiratory system.

Hypothesis 1. *Evolution convergence.*
We assume that the quantities we are studying have reached a stationary state for evolution (convergence): we consider that today's organisms configuration related to the respiratory system minimizes the costs on which they have been selected.

The second hypothesis is related to the environment dynamics. You probably recall that evolution of an organism is linked to its interaction with its environment and environment may change during the process of evolution, thus altering its trajectories. For the respiratory system which is an organ embedded in an organism, environment has a wide meaning, since it includes also the other organs with which it interacts.

Hypothesis 2. *Environment stability.*
We assume that the environmental quantities affecting the respiratory system did not change much, thus allowing us to approximate the environment with today's environment and to assume the dynamic came only from the respiratory system.

Although seemingly strong, these two hypotheses are globally compatible with the theory of *punctuated equilibria* in evolution [38] which suggests that the evolution process is quick relatively to environment changes. Even with those hypotheses, (at least) two main reasons make it almost impossible to build the real costs from biological data. The first one is that traits are most of the time intrinsically tangled together[18] and the change in the expression of one trait may change the expression of other traits and thus affect various energy costs. The second reason is that we can only observe the adapted organisms, since they are the ones that remain, leaving us with one single point to draw our cost function... scarcely enough to build a curve or, worst, a n-dimensional surface. Fortunately, modeling is our way out of these apparent dead-ends. Indeed, modeling allows to mimic traits that never existed or that do not exist any longer. With a model, we can estimate the costs of such ghost traits and compare them to the cost of the traits that have been selected. My goals were thus to build costs that include enough information to remain pertinent, while keeping the complexity in a minimal state. When such configuration is possible, then we may be able to understand the underlying mechanisms involved in the adaptive process. Consequently, one of the challenges I met in my research was to build pertinent approximations of cost functions for the respiratory system. And this is where we need the process called modeling.

[16] My cat disagrees with this statement.

[17] e.g. as a vertebrate, you can have either wings or front legs; this structural constraint may be a consequence of living matter whirls in the embryo (how cool is that?), see the impressive work of Vincent Fleury [27].

[18] Try to put many (many) earphones in a bag for a few days: the accomplishments of DNA and evolution are something infinitely more wicked.

2.5 Modeling

> *"Things that try to look like things often do look more like things than things. Well known fact. But I don't hold with encouraging in it!"*, Granny Wheatherwax in Wyrd Sisters, Terry Pratchett.

Miss Wheatherwax is a witch from the Ramtops, a far far away region in Terry Pratchett's Discworld. As a witch, she is known, respected and, let us face it, quite feared for her stern common knowledge. What she meant by this saying is that we often picture a thing differently as the thing itself. Specific features are being put forth while others are put back or not even accounted for, in a way that seems unrelated to the real features of the thing. Such behavior, if made consciously and scientifically, meets the modeling process: some features of the object we want to model play an important role in the phenomenon we are studying, while others are only influencing details of that phenomenon. This repartition is obviously very dependent on the phenomenon studied. We can put this in perspective through examples from the respiratory system modeling. If you plan to study the fluid mechanics of air inside the lungs, then you can neglect the molecular exchanges between air and blood: these exchanges have little influence on the mechanical properties of air inside the bronchial tree. On the contrary, if you study the oxygen flow through the exchange surface, you can probably neglect the air flow in the tracheobronchial tree, since oxygen concentration near the exchange surface can be considered unchanging (under certain conditions).

Our goal is to approximate the energetic costs that may have affected the evolution of the respiratory system. This goal drives the modeling process. The first step is to extract from the biology and physiology of the organ the traits involving potential largest energetic costs (e.g. for tribbles such traits were hinted by Mr. Spock: the reproductive and predation rates). Generally, such traits are linked together through one or several structural parameters we want to optimize (e.g. the tribbles size). These parameters can control the geometry, the physics, the mechanics or the chemistry affecting the organ; moreover they can be constrained by the organ function. Actually, constraints are more specific to organs because as a subpart of an organism, they fulfill a function for this organism. It constrains the parameters range into domains compatible with the function: typically oxygen flow rate in the respiratory system is constrained (i.e. blood flow rate in arterial network or air flow rate in the lung). The links between parameters and traits are made through the modeling of the organ, involving several physical or/and chemical processes. The optimal parameters determine the optimal phenotypes corresponding to the identified traits. The optimal configuration is then a compromise between the traits, it is called a *trade-off* in evolutionary ecology.

My scientific approach was to develop models with minimal complexity that are able to predict behaviors compatible with the respiratory system physiology. These predictions are either qualitative, like the upholding of a tree structure by evolution, or quantitative, like the prediction of red blood cells concentration in blood. By using minimal complexity, we keep a reasonable understanding of the behavior of the interacting phenomena, and clearly extract the core phenomena that drives the mean behavior of the system.

An example with mammals lung.

The air flow in mammal tracheobronchial tree implies an energetic cost because of viscosity, this energetic cost is measured with an hydrodynamic resistance of the tree, built from the resistance of each airways, see section 2.2 about straws. Hydrodynamic resistance is the first trait. Metabolic function of the lung is to bring oxygen to blood through the exchange surface. The exchange surface lies in the lung and thus shares lung volume with the tracheobronchial tree. Under the hypothesis that lung volume is constrained, the larger the tracheobronchial tree is, the smaller the exchange surface is, and thus the fewer oxygen molecules are transferred in blood. This reflects a cost, through the reduction in oxygen flow for the metabolism. Thus, the second trait would be the volume of the tracheobronchial tree. Both traits are related through a structural parameter of the lung: the bronchi sizes. Thus the optimization process is made on bronchi sizes and we showed

that the optimal configuration corresponds to a tracheobronchial tree whose bronchi sizes decrease after each bifurcation with a size ratio of $2^{-1/3} \sim 0.79$ [57, 63]. This ratio, often represented by the letter h, is called the tree reduction factor.

2.6 Where are we going from here?

In this chapter, I described how the different knowledges about respiratory system, viscous fluids, evolution and modeling assemble together to form a theoretical framework for my research. This framework fits a recent wider theory introduced by George C. Williams and Randolph M. Nesse in early 90's known as *Darwinian medicine* or *evolutionary medicine*. This theory aims at understanding health and diseases through the eyes of evolution, see for example [113] or the excellent book *Why we get sick?* [76].

The mammal respiratory system is a complex multi-scale system whose scales range from the centimeter (large bronchi or blood vessels diameters) down to a few microns (red blood cells, blood capillaries), covering all intermediate sizes. The physical and chemical processes driving the system thus depend on the scale: air and blood fluid mechanics (high or low Reynolds number, i.e. with or without inertia); tissue mechanics; convection, diffusion and chemistry of oxygen and hemoglobin. I have studied more specifically sub-organs of the respiratory system where dissipation is the strongest: the tracheobronchial tree, that conducts ambient air and thus its oxygen toward the exchange surface; the systemic arterial network in which oxygen is transported by blood to the organs; and the exchange surface itself in which oxygen crosses the alveoli-capillary membrane and reach the red blood cells and the hemoglobin.

All the questions we raise about respiratory system are formulated as if viscous dissipation were the main driver of evolution. We will see that with this sole hypothesis, we are able to draw interesting predictions, often compatible with the actual physiology. We will begin with a first simple, but central question: why has a tree structure been selected by evolution? There are obvious reasons, like a tree is handy for distributing a product on a large surface. While this is true, we show that such an assertion can be reformulated like this: the tree structure has to be stable for the dynamic process evolution. This is the topic we will study in chapter 3. Once we know the tree structure is stable for evolution, we will focus in chapter 4 on how a tree structure can develop in mammals, with a specific focus on tracheobronchial tree. We will also show how this development process can select a tree that would be efficient in adults. As a collateral effect, the development scenario we propose induces biological noises that interfere with the achievement of an efficient tree. The role of (environmental) noise on optimal strategy is actually a general process. We show in chapter 5, through a model for Mountford's cliff-edge theory [73], that environmental noise can be a selective pressure for evolution and by thus alter the optimal strategies. This theory is then applied for the tracheobronchial tree. The next chapter, chapter 6, describes two applications linked to the previous results on tracheobronchial tree properties, one about COPD and one about chest physiotherapy. The last two chapters are dedicated to blood arterial network and its adaptation to viscous dissipation, chapter 7 focuses on the blood arterial tree network itself, while chapter 8 focuses on the pulmonary capillaries. Each of these questions brings forth the development of a specific model, based on mathematical tools, either from the literature or specifically developed for the study.

Chapter 3

Tree structures selection by evolution.

The best way to distribute a product from a source to a volume is to use a tree structure, this is common knowledge and I am pretty sure even Miss Wheatherwax[1] is aware of that. Many biological systems indeed rely on tree structures to capture external products, from the tree (the real one, the plant), the lung, the blood network, jelly fish circulations, etc. Tree structures are per se dissipative and induce an energetic cost due to that dissipation. Consequently, to be maintained by evolution, such a cost must be outweighed by a gain, which is most probably linked to the organ function.

3.1 Minimizing dissipation in a tree, stability.

The alveoli form the air/blood exchange surface of the lung. They are connected to ambient air via the tracheobronchial tree. The size of the exchange surface, a hundred square-meters, ensures an oxygen flow in blood that is compatible with the metabolism. One of the functions of the tracheobronchial tree is to convey air, and thus oxygen, from the outside environment to the acini. As a first approximation, the tracheobronchial tree can be described with a dyadic tree with a cascade of sixteen successive bifurcations (i.e. seventeen generations), see figure 3.1.

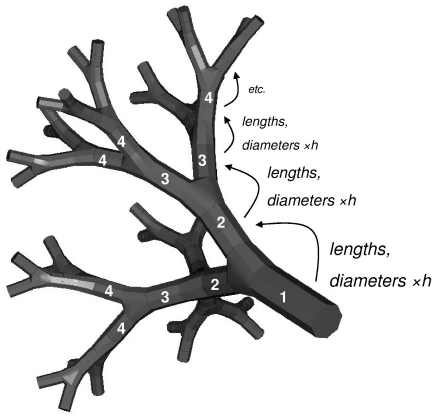


Figure 3.1: Artistic view of the typical tree model we use in this chapter. The quantity h measure the decrease in size of the branches after each bifurcation.

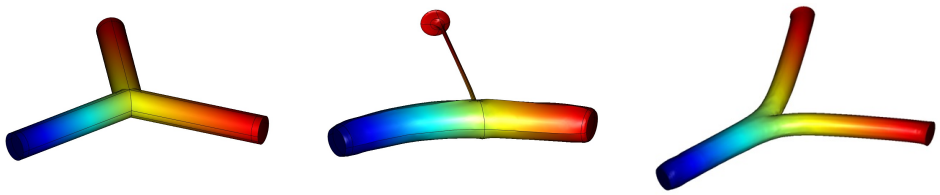
Similarly, the arterial system forms a transport structure between heart and blood microcirculation. Blood microcirculation is an exchange surface with tissues. Although very different in details, see section 7, the arterial system is also a tree structure in which a fluid is flowing.

The flow of a viscous fluid in a tree dissipates energy as heat, eventually stopping all fluid motion. Thus, the energy loss has to be compensated for the fluid to stay in motion. As we already explained in our straws section 2.2, dissipation is highly dependent on the sizes of the branches, which raises the question: how does dissipation interfere with the selection of a tree structure and some of its properties? Our goal was to give some answers to this question and we studied the behavior of a tree geometry made with successive

[1] the most serious witch from the Ramtops, see section 2.5

bifurcations and crossed by a Newtonian fluid. The tree branches were assumed cylindrical and the volume of the tree bounded. We modeled the function of the organ as a constraint on the fluid flow in the tree. Next, we determined the optimal configuration that minimizes the viscous dissipation of the fluid flow.

3.2 Stability of the tree as an optimal geometry structure.



A B C

Figure 3.2: A: initial configuration of the bifurcation before optimization; inlet is the left tube, outlets are upper and right tubes. Total fluid flow and volume of the bifurcation are given. The colors correspond to the local relative amplitude of deformation needed to reduce dissipation (shape gradient). B: optimal configuration if pressures constraints are applied at outlets. C: optimal configuration if fluid flow constraints are applied at outlets.

We studied mathematically the optimization process using a discrete framework, i.e. with a number of parameters that is finite (the unknowns are the branch diameters). We used low regime hypothesis to model air fluid mechanics (Poiseuille's regime) [23, 65]. Natural boundary conditions for the tree leaves are either to impose the flow in the leaves[2] or to impose the pressures on leaves outlets[3]. Our work shows that the tree structure is optimal for two configurations: when the air flow through the leaves of the tree are constrained (and non zero); or when the pressures on leaves outlets are all exactly identical. However, if there is at least two different pressures on the leaves then the optimal tree is degenerated: it becomes a simple tube. This shows instantly that any disturbance on pressures on leaves when all are identical drives irremediably the optimal configuration towards a tube: identical pressures on leaves outlets is unstable. With shape optimization tools, we studied numerically these phenomena in a continuous frame, i.e. with an infinite number of parameters (the entire tree wall is unknown). Our codes were developed using Comsol Multiphysics and FreeFem++ [23, 84]. Our simulations showed that these results were still true for two and three-dimensional trees with two generations (bifurcations) in which flows an incompressible fluid in laminar regime (checking Stokes or Navier-Stokes equations). With these numerical calculations, we were able to determine exactly the shape of an optimal bifurcation in 2D and 3D.

For the tracheobronchial tree, the stresses applied to the leaves of the tree are the result of a complex process of active regulation that combines the effects of respiratory muscles, the mechanical response of the tissue and the effects of the smooth muscles, which stand on the walls of the small airways (the role of smooth muscles remains unclear [5, 56]). Actually, it is not clear whether the system is controlled by the flow rates, the pressures or other conditions that would combine both. However, the conclusions from the previous paragraph applied to the lung allow us to propose, within the limits of our modeling assumptions, that to maintain the tree structure of the lung along evolution, the regulation system has to constrain in some way the amount of air flowing through the small airways. Indeed, for the tree structure to have been selected with pressure constraints on the leaves, our results indicate that these pressures must be regulated in such a way that they are perfectly identical. However, the fact that the configuration is both unstable and submitted to variability - see section 5 - makes an evolutionary

[2]Dirichlet conditions for the fluid

[3]Neumann conditions for the fluid, i.e. we apply a force per unit area to the fluid

cost appear: if descendants are unable to maintain identical pressures, then the evolution of the tracheobronchial tree for these descendants will tend to select geometries more and more tubular that could eventually not irrigate correctly the exchange surface: this branch of descendants would probably become extinct. Consequently, at equal maximum dissipation, a stable optimal configuration is more likely to be selected than an unstable configuration: evolution will always bring straying descendant back to the configuration compatible with the physiology. Moreover, one could imagine that any "mistake" on the bronchial geometry that makes it deviate from the optimal configuration could be offset by an active flow control in the small bronchi, for example by the smooth muscles [5]. Consequently, flow regulation is compulsory in a tree-like structure where natural selection occurs mostly on minimizing dissipation.

3.3 Structure of the optimal tree.

The models we have developed are more general than those based on symmetric bifurcation trees like in [63] because they do not assume anything about the relative size of the branches in a bifurcation. They allow to work with a tree that feeds an exchange surface unevenly distributed in space. The optimal configuration corresponds to a tree whose branches have a volume proportional to the ratio between the fluid flow rate in the branch and the total fluid flow rate in the tree. The air flow in one branch is used to irrigate the exchange surface of the downstream branch, and one can assume that this rate is proportional to the exchange surface area irrigated downstream of this branch, at least for the healthy lung [107]. Given the fact that the exchange surface fills the volume of the lung, its surface is approximately proportional to the volume it occupies. Thus, our studies indicate that the size of the branch has to be proportional to the lung volume it irrigates, which is consistent with the physiology [107]. If identical flow conditions apply to all the leaves of the tree, we find that the optimal configuration is a tree with symmetric bifurcations, which is it space-filling (with fractal dimension 3), and whose properties are comparable to lung physiology from about the fifth generation until about the seventeenth.

3.4 Conclusion.

All these results show that the tracheobronchial tree tends to minimize the criterion of viscous dissipation, indicating that this criterion has probably played a role in its evolution. Comparisons of our prediction with lung's data [102] shows there exists a small systematic deviation from the optimal predicted by our models. This shift makes the tracheobronchial tree a little too big. In the next chapters, we propose a scenario that could explain, at least partially, this shift. Although our results have been obtained for a Newtonian fluid, these results are likely to apply to large arterial network, where blood can be considered Newtonian.

3.5 Historical background.

The results of this chapter are based on two mathematics papers published in 2008 and 2011. The 2008 one was the result of my collaboration with Nicolas Meunier (MAP5, Université Paris Descartes) [65]:

Abstract 1. Optimal Poiseuille flow in a finite elastic dyadic tree [65]
In this paper we construct a model to describe some aspects of the deformation of the central region of the human lung considered as a continuous elastically deformable medium. To achieve this purpose, we study the interaction between the pipes composing the tree and the fluid that goes through it. We use a quasi-static approximation to determine the deformed radius of each branch. Then, we solve a constrained minimization problem, so as to minimize the viscous (dissipated) energy in the tree. The key feature of our approach is the use of a fixed point theorem in order to find the optimal flow associated to a deformed tree. We also give some numerical results with

interesting consequences on human lung deformation during expiration, particularly concerning the localization of the equal pressure point (EPP).

Beyond the results about the existence of an optimal tree in the deformed configuration, this paper developed the set of mathematical tools proposed earlier in [39], most particularly the mathematical properties of the resistance matrix associated to a tree structure in which a low regime Newtonian fluid is flowing. Another important result of this paper is that the distribution of fluid that has the minimal dissipation inside a tree has the same pressure at each tree root outlets, whatever the sizes of the branches.

The 2011 paper is a collaboration with Yannick Privat (LJLL, Université Pierre et Marie Curie) and Xavier Dubois de la Sablonnière (Supelec, Gif-sur-Yvette). This work extends further the mathematical tools developed in the 2008 paper and introduces new mathematical tools based on optimization theory. Moreover, an entire section of this paper deals with shape optimization theory based on Yannick Privat's work during his PhD thesis [84].

Abstract 2. Shape minimization of the dissipated energy in dyadic trees [23]
In this paper, we study the role of boundary conditions on the optimal shape of a dyadic tree in which flows a Newtonian fluid. Our optimization problem consists in finding the shape of the tree that minimizes the viscous energy dissipated by the fluid with a constrained volume, under the assumption that the total flow of the fluid is conserved throughout the structure. These hypotheses model situations where a fluid is transported from a source towards a 3D domain into which the transport network also spans. Such situations could be encountered in organs like for instance the lungs and the vascular networks. Two fluid regimes are studied: (i) low flow regime (Poiseuille) in trees with an arbitrary number of generations using a matricial approach and (ii) non linear flow regime (Navier-Stokes, moderate regime with a Reynolds number 100) in trees of two generations using shape derivatives in an augmented Lagrangian algorithm coupled with a 2D/3D finite elements code to solve Navier-Stokes equations. It relies on the study of a finite dimensional optimization problem in the case (i) and on a standard shape optimization problem in the case (ii). We show that the behaviours of both regimes are very similar and that the optimal shape is highly dependent on the boundary conditions of the fluid applied at the leaves of the tree.

In this last paper, we studied how the optimal geometry of a rigid tree is affected by viscous dissipation when the volume of the tree and the fluid flow inside the tree are constrained. We showed that a tree structure can be optimal only if a fluid flow is constrained into the leaves of the tree. This highlights the role of the function of the tree-like organs. Indeed, if only the total fluid flow in the tree is constrained, then the optimal structure is almost always a simple tube.

Chapter 4

Development of the tracheobronchial tree.

The scenario we propose in the previous section to justify the selection of the geometry of the tracheobronchial tree takes into account cost and functional constraints that are related to the amount of oxygen that is transmitted to the blood. We considered the organ in its final adult state, regardless of the fact that he went through a stage of development. Development can have important consequences, especially on the geometry of the tree, which would be difficult to interpret outside the context of development.

The most cited recent scenario for lung development [68] is based on an architectural algorithm hard-coded in the genome and based on elementary processes. However this scenario remains unsatisfactory: it relies on non identified genes that control branching modes in a cryptic way, it is partially not compatible with data (repeated errors) and thus is assumed to be regulated, and finally it needs a huge amount of information encoded in the genome. The scenario we propose in this section, inspired by [104], represents a new paradigm on bronchial tree development and, more generally, on the role of physics in development. Our scenario is based on a simple property of diffusion, related to Saffman-Taylor instability [87]. It requires very few genetics, thus being very parsimonious and is compatible with most of the experiments and data[1].

We derive from our scenario several consequences concerning the geometrical properties of the tracheobronchial tree and related to its efficiency with dissipation. This scenario is based on typical chemical pathways that are very similar to other branched organs such as kidney or salivary glands, thus our scenario is actually general and can be applied to any of those.

4.1 Modeling of the development of the tracheobronchial tree.

The biochemistry involved in the tracheobronchial tree development is complex and accounts for many biochemical species. Almost all of these species play a subtle role on the shape, number and fine organization of the bronchi [14] but without actually altering the overall properties of the tracheobronchial tree: being a self-avoiding tree. Roughly, only the FGF10 protein (FGF = fibroblast growth factor) seems to "contain" the branching pattern information. The usual role of this protein is to induce cell proliferation and thus tissue growth. Experiments have shown that cells respond to the flow of FGF10 they receive. Moreover, without FGF10 the tree can no longer form [14]. We can model the distribution of FGF10 during lung development as the result of a process of steady diffusion. In this diffusion model, the outer wall of the organ is the source of FGF10, which is consumed by the epithelial cells on the bronchial tree wall. Steady state diffusion can be used because the diffusion rate of FGF10 is much larger than the tissue

[1] I guess Guillaume d'Ockham would have been proud of our scenario.

growth rate. The concentration of FGF10 protein in the tissue is then the solution of a Laplace equation with Dirichlet boundary conditions at the edges. Bronchi cells respond to the local FGF10 concentration gradient (the flux is proportional to the gradient). The gradient is stronger where the curvature of the bronchi wall is larger (tip effect) and/or where the distance to the source of FGF10 is small. The consequence is then that the bronchi wall is unstable: a cell located on a small protrusion of the wall receives a slightly larger flow of FGF10 than its neighbors and thus proliferate slightly faster, thus the protrusion is amplified, becomes bigger and bigger and eventually becomes a tube. Because it is growing, the tube also becomes prone to irregularities on its tip, which gives rise to a bifurcation. The typical bronchus size at which those irregularities appear depends on the mechanical properties of its wall, and most particularly on its surface tension. Given the time scales, tissue growth is dominated by viscous effects. The tissue can therefore be seen as a viscous fluid whose mass increases gradually as the cells proliferate in the tissue. This proliferation is also a function of the local flow of FGF10.

We have studied this model in 2D [16, 18] and 3D [19]. Our study is based on an high-end numerical method based on homogeneous remeshings and smoothings of surfaces that deform in space (FreeFem ++ GMSH, [3, 99]). The diffusion of FGF10 proteins interacts with the geometry of the two surfaces formed by the bronchi wall and the organ wall. From these mere interactions, a dyadic self-avoiding tree emerges in a robust way. Figure 4.1 shows side by side 3D reconstructions of the lung of mouse embryos by Pierre Blanc (A) [9] and a realization of our model (B) [19]. The statistics of the geometric properties of the trees built with our model are very similar to those of the adult lung as shown on figure 4.3 and 4.4. For example, we studied the distribution of the branching asymmetry factor, which represents the size ratio between two branches stemming from a bifurcation. The distribution of the asymmetry factor is close to that of the adult lung, see figure 4.4. Adult lung's data come from Raabe and collaborators data set [86]. The average asymmetry ratio predicted by our model is about 0.8, which is in accordance with lung data [102]. Our

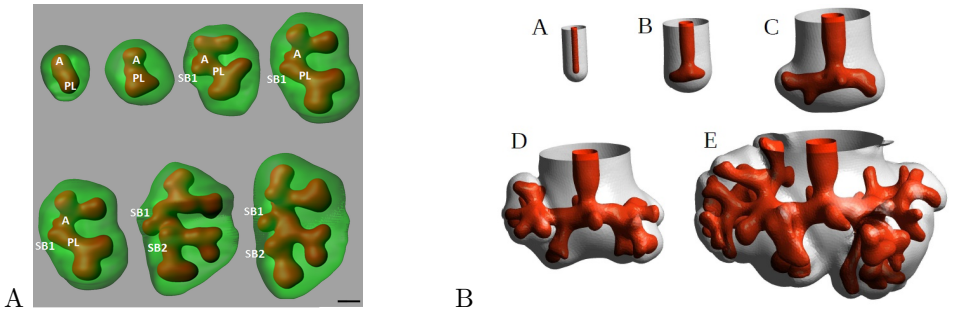


Figure 4.1: A: Series of reconstruction of right cranial lobe of mouse embryo lung between embryonic days 11 and 12, scale bar 100 μm, adapted from [9]. B: Typical tree resulting from our growth model.

scenario has a few corollaries. First, the many other proteins involved in lung development, or at least a part of them, are used to finely tune the bronchi characteristics. For example they can play a role on their geometry: by regulating the growth response of cells to FGF10 flux, or by affecting bronchi maturation during development, typically cells differentiation (to smooth muscles cells). Next, this model easily relates adult lung geometric properties with lung development parameters and in the next section, we will show how our scenario can explain two of them: the multi-scale structure of the tracheobronchial tree and the branching asymmetry in bifurcations.

4.2 Emergence of core properties of the tracheobronchial tree

In our scenario for the development of the tracheobronchial tree, we have neglected the fact that the embryo grows globally. In our previous model, the sizes of the branches do not depend on

the tree generation. Neglecting the overall growth allows us to work with smaller geometries and improves the performance of the numerical simulations. The global growth implies however a decrease in the size of the bronchi at bifurcations, simply because the older branches have had more time to grow than the younger ones. We proposed that global growth is the mechanism from which the tracheobronchial tree scaling law emerges. The process which triggers the branching is based on the emergence of a disturbance on the tip of the branches. The process related to the emergence is mechanical instability of the wall, and it is subject to inherent variability, for example on the size of the initial disturbance, or its time of emergence. This variability involves mechanically a difference in size between the two branches stemming from a bifurcation, and thus an asymmetry. The overall degree of asymmetry in the tree is then a direct consequence of the noise affecting the branching process.

Emergence of a multi-scaled structure.

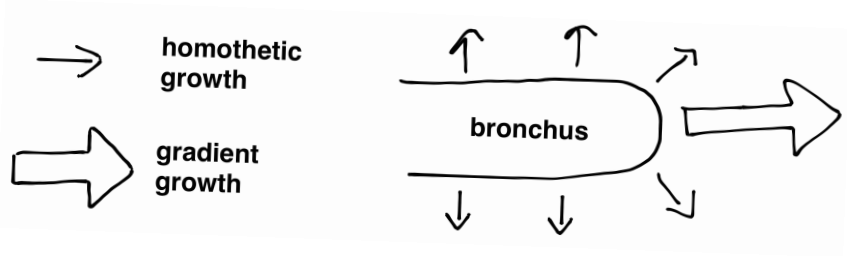


Figure 4.2: Growth decomposition into an overall of the organ (homothetic growth) and a growth due to FGF10 flow (gradient growth).

Once we have added to the lung development the global growth for the embryo, the growth of a bronchus is the result of two complementary growth processes. One is related to the flow of FGF10 as in the model we proposed in the preceding section, and one is due to the embryo overall growth. Let us assume first that the growth related to FGF10 flow, denoted V, is roughly constant throughout the formation of the bronchus. Let us assume next that the overall growth is homothetic, i.e. the velocity at which the size of the embryo is increasing is proportional to the size of the embryo with a proportionality constant k. Notice that this hypothesis is compatible with early stage of the embryo development, but when the embryo becomes older the proportionality constant k becomes time dependent, see e.g. [17] (case of chicken embryo). Under these assumptions, the diameter D and the length L of a bronchus vary in time according to the equations:

$$\frac{dD}{dt}(t) = kD(t) \tag{4.1}$$

$$\frac{dL}{dt}(t) = V + kL(t) \tag{4.2}$$

Let us call D_P the diameter of the perturbations when they emerge on the tip of a branch. Their length is then zero. Consequently, the diameter and length of a branch checks the following equation: $D(t) = D_P e^{kt}$ and $L(t) = \frac{V}{k}\left(e^{kt} - 1\right)$ ($t = 0$ corresponds to their emergence time). Now if T_p is the mean time for the perturbation to appear on a new branch tip, then the ratio between the diameter of a branch over the diameter of its parent branch is time independent, it corresponds exactly to the tree reduction factor h:

$$h = e^{kT_p} \tag{4.3}$$

The length over diameter ratio of a branch is growing as long as the branch also grows. Once the branch starts bifurcating, then the growth due to the flow of FGF10 becomes negligible relatively to the the overall growth: a diffusive screening effect [89] for FGF10 flow occurs between the two stemming branches and the mother branch. Thus, its growth becomes homothetic only ($V \approx 0$),

and as a consequence the ratio of length over diameter remains constant:

$$\frac{L(T_p)}{D(T_p)} = \frac{V}{D_p k}\left(1 - e^{-kT_p}\right) \tag{4.4}$$

Consequently, the tree reduction factor h and the length over diameter ratio depend on parameters related to the instability: the mean growth velocity related to FGF10 flow, the initial size of the perturbations D_p and the time needed for a perturbation to grow into a branch that itself suffers perturbations T_p. Because the length over diameter ratio is constant, the tree reduction factor h represents not only the diameter reduction factor at bifurcations, but also the length reduction factor at bifurcations. Hence, this growth process leads to a multi-scaled fractal structure with dimension $d = -\ln(2)/\ln(h)$ [57].

It is then easy to imagine that, through the numerous pathways involved in lung development [14], evolution may have altered the different parameters V (response to FGF10 flow), D_p (perturbations initial size, related to the mechanical properties of epithelial membrane - like surface tension) and T_p (time for perturbation to appear) in order for the adult lung to reach an efficient geometry.

Emergence of asymmetric bifurcations.

The asymmetry factor between two daughter branches stemming from the same bifurcation is computed with the daughter branches diameters D_{f_1} and D_{f_2}:

$$a = \frac{\min(D_{f_1}, D_{f_2})}{\max(D_{f_1}, D_{f_2})} \leqslant 1$$

The emergence of the branches is a consequence of a physical instability and the diameters of two branches stemming from a bifurcation are subjected to a noise. The two quantities D_{f_1}, D_{f_2} and a from the previous equality can be viewed as random variables. The probability distribution of diameters can be estimated from realizations of these random variables. These realizations are obtained either from lung data [18, 86] or from simulations of our model for lung development [18]. Examples of these realizations are shown on figure 4.3. From the distribution profiles on figure

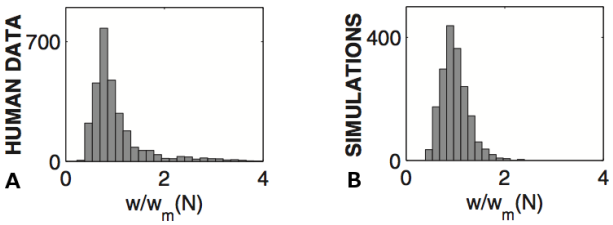


Figure 4.3: Relative branch size distributions from [18]) - normalized by their corresponding mother branch. A: lung data from Raabe (1976) [86]. B: model data [18].

4.3, we can -roughly- approximate the distributions with gaussian normal distributions $\mathcal{N}(D, \sigma^2)$[2], for the overrated sake of simplification. Moreover, we consider as a first approximation that these processes are independent. Then we can easily estimate the probability distribution of the variable a, see figure 4.5A. The average asymmetry factor is directly correlated with the standard deviation of the diameters distribution, see figure 4.5B[3]. To achieve an asymmetry similar to that of the lung, i.e. ~ 0.8 [102], the diameters relative standard deviation has to be about 20 %.

[2] i.e. with mean D and standard deviation σ, it is always refreshing to use pretty symbols such as $\mathcal{N}$.

[3] A Taylor series of the expectation (i.e. mean) of a, denoted $E(a)$, can be computed. If the standard deviation σ is small relatively to the mean diameter D, then $E(a) = 1 - \frac{2}{\sqrt{\pi}}\frac{\sigma}{D} + O\left(\left(\frac{\sigma}{D}\right)^2\right)$. This fancy development is however not really useful on the range we are interested in, and, although I admit it reluctantly, a crude approximation with $E(a) \approx 1 - \frac{\sigma}{D}$ is better for our purpose, see figure 4.5B.

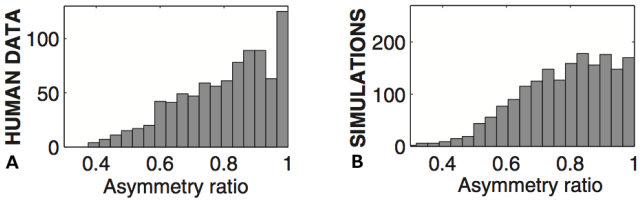


Figure 4.4: Asymmetry factor a distribution. A: lung data from Raabe (1976) [86], the high peak for $a = 1$ is an artifact due to the measures precision, it should redistribute on the bars to its left. B: model data [18].

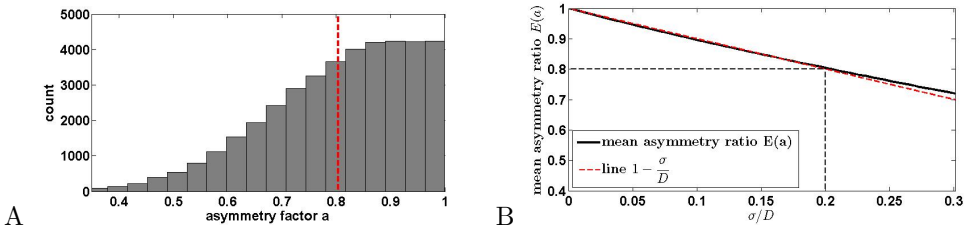


Figure 4.5: A: a realization ($n = 40000$) of the asymmetry ratio with the hypothesis that diameters are independent gaussian distribution. The dashed line locates the mean value computed from measurements. B: mean asymmetry ratio as a function of the standard deviation of the gaussian distribution, which mimics the diameter distribution.

We showed through dedicated numerical simulations that the asymmetry ratio is dependent on the quantity of space available in the vicinity of the emerging bifurcation [18]. The smaller the space, the lower the asymmetry. We observed in our model that the space-filling property of the tree is dependent on the growth response of cells to FGF10 flow. Thus evolution may have affected asymmetric ratio through the growth response.

4.3 Conclusion.

Our scenario for the development of the tracheobronchial tree during embryogenesis brings many interesting insights on the adult lung's structure. In particular, our scenario shows that airways sizes distribution may be strongly affected by the developmental stage since we found many similarities between the distributions predicted by our model and the adult distributions. We saw that such a mechanism for lung development induces a variability in the airways sizes that can be expressed as a noise. This noise has both local and global effects: it affects the size of each individual branches and by thus perturbs the distribution of air throughout the tree. This local aspect has been studied by Magali Florens, a PhD student of Bernard Sapoval (Ecole Polytechnique laboratory PMC [28, 29, 30]). The noise has also an effect on the overall performance of the tracheobronchial tree by affecting the average tree reduction factor h and thus potentially improving the risk of missing the optimal geometry during development [63].

Noise is also the cause for bifurcations to exhibit an asymmetry. This is fully compatible with physiology, since tree asymmetry has been observed in data [18, 86, 102]. Magali Florens also showed that asymmetry may be associated with a better ventilation of the acini as long as the asymmetry remains smaller than a critical threshold which happens to be an asymmetry ratio close to 0.8 [28, 30].

These new results on the interplay between lung geometry and function make it possible to better model the selection process of lung geometry, which is the subject developed in the next chapter. It required however to include the role of noise into the natural selection process itself

and to see how it could affect the optimal strategies. This is why we developed first a general study of the role of environmental variability on the strategies selected by evolution. Then, we applied this theory to a model of the lung whose tree reduction factor is submitted to an unpredictable variability and whose bifurcations are asymmetric.

4.4 Historical background.

In 2009, a PhD student, Raphaël Clément, came in my office to dicuss many difficult questions about lung, growth instabilities and conformal mappings. The topic of his PhD thesis, advised by Stéphane Douady, was the physics of lung's development. At this time, I had carefully ignored the subject of lung development: the small bit of literature I had read about showed lung development to me as an impossible chaos of intricate chemical pathways and I thought only mere luck (and the precious help of evolution) was able to bring these pathways to work out something that looks like a (efficient) lung. But the ideas of Raphaël and Stéphane were that lung's shape may be self-regulated with a simple physical phenomenon, based on the interaction of a geometry with a diffusive process, in the spirit of the Saffman-Taylor instability. This brought order in the chaos of my mental image of lung development and this is how everything started. After he finished his PhD thesis, Raphaël came as a post-doc in my new laboratory in Nice, in particular to improve the model of lung development.

Our first paper summarized the results, the model and a 2D numerical method developed by Raphaël during his PhD thesis. This paper is in collaboration with Raphaël Clément (now in IBDM, Université de Marseille), Stéphane Douady (MSC, Université Paris Diderot), Pierre Blanc and Vincent Sapin (R2D2, CHU Clermont-Ferrand, Université d'Auvergne).

Abstract 3. Shape self-regulation in lung morphogenesis [16]
The arborescent architecture of mammalian conductive airways results from the repeated branching of lung endoderm into surrounding mesoderm. Subsequent lung's striking geometrical features have long raised the question of developmental mechanisms involved in morphogenesis. Many molecular actors have been identified, and several studies demonstrated the central role of Fgf10 and Shh in growth and branching. However, the actual branching mechanism and the way branching events are organized at the organ scale to achieve a self-avoiding tree remain to be understood through a model compatible with evidenced signaling. In this paper we show that the mere diffusion of FGF10 from distal mesenchyme involves differential epithelial proliferation that spontaneously leads to branching. Modeling FGF10 diffusion from sub-mesothelial mesenchyme where Fgf10 is known to be expressed and computing epithelial and mesenchymal growth in a coupled manner, we found that the resulting laplacian dynamics precisely accounts for the patterning of FGF10-induced genes, and that it spontaneously involves differential proliferation leading to a self-avoiding and space-filling tree, through mechanisms that we detail. The tree's fine morphological features depend on the epithelial growth response to FGF10, underlain by the lung's complex regulatory network. Notably, our results suggest that no branching information has to be encoded and that no master routine is required to organize branching events at the organ scale. Despite its simplicity, this model identifies key mechanisms of lung development, from branching to organ-scale organization, and could prove relevant to the development of other branched organs relying on similar pathways.

The second paper aims at comparing lung's data with the model predictions. A new, most efficient, numerical model has been specifically developed using FreeFem++ along with specific analysis tools to extract data from the simulations. This second paper is a collaboration with Raphaël Clément (IBDM, Université de Marseille) and Stéphane Douady (MSC, Université Paris Diderot).

Abstract 4. Branching geometry induced by lung self-regulated growth [18]
Branching morphogenesis is a widely spread phenomenon in nature. In organogenesis, it results from the inhomogeneous growth of the epithelial sheet, leading to its repeated branching into surrounding mesoderm. Lung morphogenesis is an emblematic example of tree-like organogenesis

common to most mammals. The core signalling network is well identified, notably the Fgf10/Shh couple, required to initiate and maintain branching. In a previous study, we showed that the restriction by SHH of Fgf10 expression domain to distal mesenchyme spontaneously induces differential epithelial proliferation leading to branching. A simple Laplacian model qualitatively reproduced FGF10 dynamics in the mesenchyme and the spontaneous self-avoiding branching morphogenesis. However, early lung geometry has several striking features that remain to be addressed. In this paper, we investigate, through simulations and data analysis, if the FGF10-diffusion scenario accounts for the following aspects of lung morphology: size dispersion, asymmetry of branching events, and distal epithelium-mesothelium equilibrium. We report that they emerge spontaneously in the model, and that most of the underlying mechanisms can be understood as dynamical interactions between gradients and shape. This suggests that specific regulation may not be required for the emergence of these striking geometrical features.

The third paper proposes a much more realistic model, that support in a better way our scenario. This last paper counteracts some ardent comments: the model is now 3D and accounts for the volumetric growth of the lung tissue. This last paper is a collaboration with Raphaël Clément (IBDM, Université de Marseille).

Abstract 5. An archetypal mechanism for branching organogenesis [19]
Branched structures are ubiquitous in nature, both in living and non-living systems. While the functional benefits of branching organogenesis are straightforward, the developmental mechanisms leading to the repeated branching of epithelia in surrounding mesoderm remain unclear. Both molecular and physical aspects of growth control seem to play a critical role in shape emergence and maintenance. On the molecular side, the existence of a gradient of growth-promoting ligand between epithelial tips and distal mesenchyme seems to be common to branched organs. On the physical side, the branching process seems to require a mechanism of real-time adaptation to local geometry, as suggested by the self-avoiding nature of branching events. In this paper, we investigate the outcomes of a general three-dimensional growth model, in which epithelial growth is implemented as a function of ligand income, while the mesenchyme is considered as a proliferating viscous medium. Our results suggest that the existence of a gradient of growth-promoting ligand between distal and proximal mesenchyme implies a growth instability of the epithelial sheet, resulting in spontaneous self-avoiding branching morphogenesis. While the general nature of the model prevents one from fitting the development of specific organs, it suggests that few ingredients are actually required to achieve branching organogenesis.

Chapter 5

Robustness and natural selection : cliff-edge theory

Even in a globally stable environment, environmental conditions faced by two organisms during their development can never be identical. This phenomenon has led to the emergence of different phenotypes for individuals with the same genotype. From the perspective of the organisms these differences are unpredictable and therefore involve an environmental noise. Because of the randomness inherent to the noise, natural selection cannot develop any dedicated mechanism related to the sources of this noise. However, we shall see that this unpredictable variability may play a role as an evolutive force and alter globally the selection of optimal strategies in order to make them more robust to an eventual noise. Then, we propose that this evolutionary force may have played a role in the selection of the tracheobronchial tree and may explain, at least partially, the small shift between the data and the predictions of the model developed in chapter 3.

5.1 Cliff-edge theory

In this chapter, we will use fitnesses instead of costs[1]. Where the costs have to be minimized, fitnesses represent gains and thus have to be maximized. A minimal cost corresponds to a maximal fitness. A simple definition for fitness would be the number of offsprings that reach maturity. With such a definition for fitness, the cost would be the number of offsprings that are produced, but that do not reach maturity[2] (easily converted into an energetic cost). Fitness functions are built from trade-offs between several traits, and they have generally no reasons to have symmetry properties around their maximum. Thus, any shift near the fitness maximum may affect fitness in a way that depends on the direction of the shift. In the context where the genotype corresponds to an optimal strategy, any random disturbance in the development of a genotype into a phenotype can potentially shift the phenotype toward the less favorable direction. Consequently, a non negligible

Figure 5.1: Illustrating cliff-edge theory with sheeps: the closer you are to the drop, the better is the grass. Drawing credits: http://www.teambuildingwithsheep.co.uk/to-follow-or-not-to-follow/.

[1] Apart from the enjoyment of tangling the readers' minds, I use fitness in this chapter because ecologists are used to use fitness, and this chapter is definitely some evolutionary ecology. To me, costs seem more straightforward when dealing with energy, like we do for the respiratory system.

[2] making ecologists incurable optimists: they view things from the bright side.



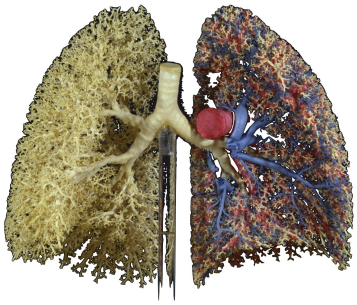


Figure 5.2: The unexpected fellowship for testing cliff-edge effects: the guinea pig's litter size (Mountford data), the wing patch size of male damsel fly *C. Splendens* and the scaling factor of the tracheobronchial tree (cast from E.R. Weibel, Berne).

part of the offspring may get a lower fitness than the other part whose phenotype is shifted in the other direction, less disadvantageous. It comes then naturally that a better strategy would be to step back from the disadvantageous direction, so that it becomes out of the range of the noise. Although this strategy would be less advantageous than being exactly on the maximal fitness, the resulting fitness pay-offs would be better knowing noise is present[3]. The amplitude of the step would obviously be correlated with the amplitude of the noise. This phenomenon is known as the *cliff-edge theory*, it has been shown experimentally in 1968 by Mountford [73] with guinea pigs. Surprisingly, this theory is very rarely used in the literature although it can play an important role on optimal strategies. We were the first to propose a mathematical model that explains the dynamics of its effects.

5.2 Cliff-edge theory

We have developed a model of population dynamics with limited resources that accounts for the role of an environment related noise on evolution. The trait distributions in the population as a function of time solve the resulting equations, which are non-linear integro-differential equations[4]. Our model mimics the natural selection in the framework where a genotype g expresses into a distribution $q \to G(q,g)$ of phenotypes because of the noise. Typically, $G(.,g)$ is a gaussian function centered on g. Each phenotype q has its specific reproductive rate $r(q)$ and predation rate $p(q)$[5]. Under those conditions, the fitness of a phenotype q is $r(q)/p(q)$. Any asymmetry around the maximum of this function implies mechanically that the best strategy is not anymore the maximum of the phenotype fitness. We define the genotype fitness which is the result of the convolution of the phenotype fitness with the phenotypes distribution:

$$F(g) = \int_q \frac{r(q)}{p(q)} G(q,g) dq \tag{5.1}$$

The genotype fitness replace the phenotype fitness when variability occurs, it has the exact same properties relatively to population behavior:

Theorem. *If $F(g) \leqslant 1$, there is only one stationary non-negative solution to the cliff-edge problem which is 0 for all phenotypes q (extinct population).*

If $F(g) > 1$, there are two possible non-negative stationary solutions to the cliff-edge problem which are 0 for all phenotype q (extinct population) and, $\frac{G(q,g)}{p(q)} \left(\int_q \frac{G(l,g)}{p(l)} dl \right)^{-1} \left(1 - \frac{1}{F(g)} \right)$ for

[3]Several throwing games, like darts, are based on this principle: high scores regions are small and close to low score regions. What would the strategy of an average sober player be? Probably to reach for the medium sized regions that give medium scores and staying away from the low -and thus high- score regions.

[4]i.e. a differential equation with integrals; In our case, the derivatives are on time only and integrals are on trait only.

[5]which, we recall, can be also wearing the dire name of *mortality rate*.

all phenotype q (population at equilibrium). The last case is characterized by a total population $1 - 1/F(q)$.

Moreover, when competition between two genotypes occur, as in section 2.3, the genotype that invades the environment is the one with the largest genotype function value. Hence, the best strategy becomes the maximum of the genotype fitness, as stated in the following theorem:

Theorem. *The population with genotype g_1 invades the population of genotype g_2 if and only if $F(g_1) > F(g_2)$ and $F(g_1) > 1$.*

The optimal genotype is then shifted away from the largest slope of the phenotype fitness. An example is plotted on figure 5.3.

Existence, unicity, asymptotic behavior and all the properties we just referred to are demonstrated in [59] and a numerical method is also proposed and tested. In [105], we applied this model to three examples, see figure 5.2: litter size in the guinea pig using historical data Mountford; the wing patch size of the damsel fly *Calopteryx Splendens*[6]; and a symmetric model for the tracheobronchial tree. Using inverse methods and data from the literature, our model is able to predict the "quantity" of variability experienced by the biological system being studied.

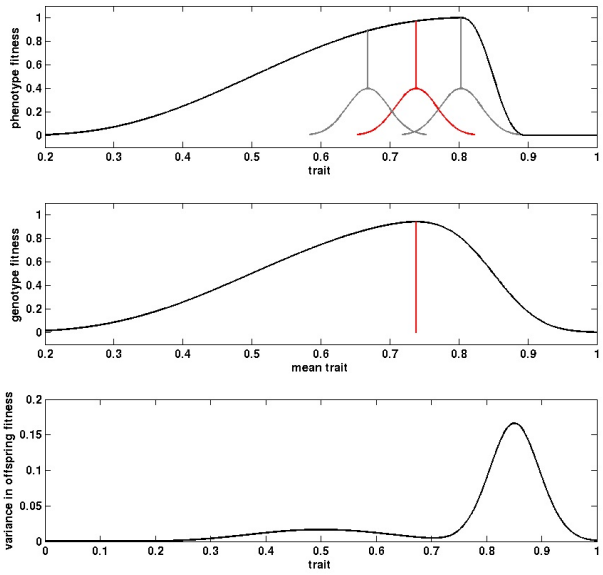


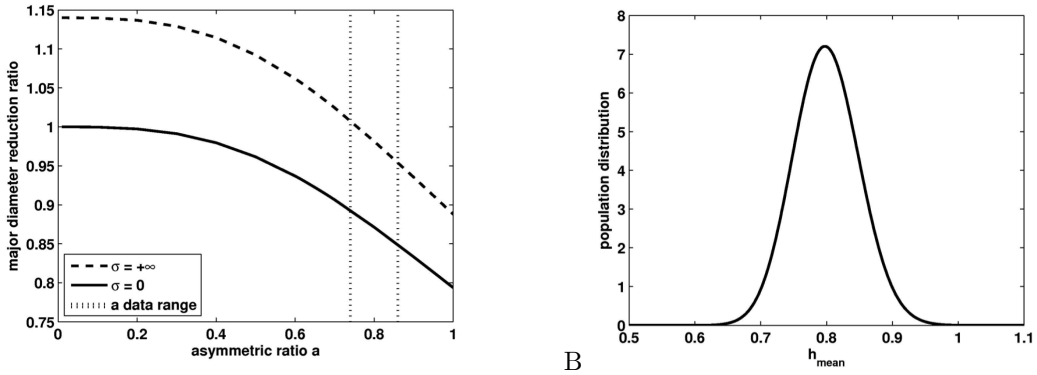
Figure 5.3: Up: phenotype fitness, asymmetric around the optimal. Middle: genotype fitness, whose maximum is shifted away from the "cliff" of phenotype fitness. Down: the best strategy selects the genotype whose phenotypic expression has the smallest possible variance.

5.3 Application to the tracheobronchial tree.

The tracheobronchial tree model discussed in chapter 3 was amended to reflect the asymmetry of bifurcations [60]. The model is based on the trade-off between the volume of the tracheobronchial tree, which has to be the smallest possible to maximize the air/blood exchange surface, and the hydrodynamic resistance of the tree, which is smaller with wider bronchi. The optimal geometry has a tree reduction factor of $h = 1/(1+a)^{\frac{1}{3}}$ where a is the asymmetry ratio between the two branches stemming from a bifurcation ($a = 1$ for symmetric bifurcations, measurements showed that $a \sim 0.8$ in the lung [102].

The resulting fitness function is asymmetric around the optimal geometry and decreases faster when the volume of the tracheobronchial tree decreases. By applying our model for cliff-edge theory, and by assuming that the whole shift between the maximum fitness and the data is induced by the cliff-edge phenomenon, we have determined the variance of the environmental noise affecting the lung, represented by the bounded region on figure 5.4A. With these predictions, we were able to build an estimation for the distribution of the trait "lung geometry" in the population, see figure 5.4B. This distribution is consistent with physiology for the asymmetric case only: this shows that although asymmetry is probably a direct consequence of lung development as we propose in chapter 4, it might play an important role on the pulmonary function [60], thus meeting the conclusion of Magali Florens [28, 30]. Our results also show that an environmental noise affecting lung geometry necessarily implies that a significant proportion of the population has a suboptimal

[6] Our work included field experiments and data collection mostly in Sweden.



A B

Figure 5.4: A: Optimal major tree reduction factor as a function of the variance σ of the noise. The major tree reduction factor is the factor computed with the largest of the two branches in an asymmetric bifurcation, the minor tree reduction factor is obtained by multiplying the major reduction factor by the asymmetry ratio a. Data on a range gives the optimal tree reduction factor in the bounded area on the figure. B: Prediction of the distribution of the mean tree reduction factor in the population, while many individuals are close to the optimal value, an important ratio has a suboptimal lung.

lung. This result might be part of the explanation for the prevalence of chronic lung diseases in modern human population, such as asthma [60][7].

5.4 Historical background

Our study on cliff-edge theory is a collaboration with Erik Svensson (EXEB, Lund University, Sweden), E. Vercken (INRA Sophia Antipolis, France) and Maren Wellenreuther (Department of Biology, Lund University, Sweden). These results brought out two papers, one published in PlosOne in 2012, and one that will be soon submitted about the mathematics of the model equations. The paper from 2012 describes the model and develops three of its applications [105]: the first one deals with the guinea pigs litter size, using data from the cliff-edge theory pioneer M.D. Mountford [73]; the second one is about the size of a black patch on the wings of damselflies *C. Splendens*[8]; the third one is, unexpectedly, a tracheobronchial tree model with symmetrical branching.

Abstract 6. Don't Fall Off the Adaptation Cliff: When Asymmetrical Fitness Selects for Suboptimal Traits [105]

The cliff-edge hypothesis introduces the counterintuitive idea that the trait value associated with the maximum of an asymmetrical fitness function is not necessarily the value that is selected for if the trait shows variability in its phenotypic expression. We develop a model of population dynamics to show that, in such a system, the evolutionary stable strategy depends on both the shape of the fitness function around its maximum and the amount of phenotypic variance. The model provides quantitative predictions of the expected trait value distribution and provides an alternative quantity that should be maximized ("genotype fitness") instead of the classical fitness function ("phenotype fitness"). We test the model's predictions on three examples: (1) litter size in guinea pigs, (2) sexual selection in damselflies, and (3) the geometry of the human lung. In all three cases, the model's predictions give a closer match to empirical data than traditional optimization theory models. Our model can be extended to most ecological situations, and the evolutionary conditions for its application are expected to be common in nature.

[7] Many other extrinsic factors come into play, like pollutants, dusts, etc. The prevalence of these pathologies comes probably from the interaction between all these factors.

[8] I participated to a field session during summer 2007 in Sweden. This is where I saw the fattest spiders ever. I caught one inadvertently in my net ... brrr

The mathematical results were straightforward for my collaborators, but not for me since the model equations are non-linear integro-differential equations. Thus I decided to put demonstrations on the properties of these equations. This lead to the writing of a second paper based on the mathematics of cliff-edge equations. It is still in preprint version [59].

Abstract 7. On the positive solutions of the cliff-edge equation [59]
In biology, a genotype expresses into a phenotype through development. If a noise is affecting the developmental process, it may play a role on the selection by evolution of the optimal genotype: this is the cliff-edge theory, initially described with laboratory guinea pigs by Mountford in 1968. Evolution tends to maximize the fitness function which reflects the success of an individual into adapting to its environment. When the fitness function is not symmetrical near its maximum and when a noise is affecting development, the optimal genotype becomes not only correlated with the noise, but also to the way the fitness function is behaving in the vicinity of the maximum. The optimal genotype shifts away from the maximal fitness value, toward the side where the absolute value of the slope is lower. The larger the amplitude of the noise is, the higher the optimal genotype shifts away from the maximal fitness value. We do a mathematical analysis of a model for cliff-edge theory developed by Vercken et al (PlosOne, 2012). This model gives rise to non linear integro-differential equations on the distribution of phenotypes in a population. Two cases are studied: one single genotype and two competing genotypes. We study the existence, unicity and asymptotic behaviors for large time of the solutions. We prove why and how the alternative fitness function proposed by Vercken et al (PlosOne 2012), a convolution of a distribution kernel with the regular fitness, enables to find the optimal strategy. Finally, we develop a numerical method to approximate the dynamics of the convergence toward the limit when the time goes to infinity.

Once we got a better understanding of the cliff-edge effects, I published a paper in collaboration with Plamen Bokov, at this time a PhD student of Patrice Flaud[9] in my ex-laboratory MSC (Université Paris Diderot). We studied how cliff-edge effect may have altered the selection of the tracheobronchial tree by evolution. This study is based on an asymmetric model of the bronchial tree.

Abstract 8. The influence of variability on the optimal shape of an airway tree branching asymmetrically [60]
The asymmetry of the bronchial tree has been reported on numerous occasions, and bronchi in the lung bifurcate most of the time into a major and a minor daughter. Asymmetry is most probably bound to play a role on the hydrodynamic resistance and volume occupation of the bronchial tree. Thus, in this work, we search for an optimal asymmetric airway tree crossed by Poiseuille flow that would be a good candidate to model the distal conductive part of the lung. The geometry is controlled by major and minor diameter reduction factors that depend on the generation. We show that the optimal asymmetric tree has diameter reduction factors that are adimensional from the second level of bifurcation and that they are highly dependent on the asymmetric ratio that defines the relative sizes of the major and minor branches in a bifurcation. This optimization also gives access to a cost function whose particularity is to be asymmetric around its minimum. Thus, the cliff-edge hypothesis predicts that if the system suffers variability, then the best tree is shifted from the optimal. We apply a recent theoretical model of cliff-edge in order to measure the role of variability on the determination of the best asymmetric tree. Then, we compare our results with lung data of the literature. In particular, we are able to quantify the variability needed to fit the data and to give hypothesis that could explain, at least partially, the shift found between the optimal tree and the measures in the case of asymmetric bronchial trees. Finally, our model predicts that, even if the population is adapted at best, there always exist individuals whose bronchial trees are associated with larger costs comparatively to the average and who ought to be more sensitive to geometrical remodeling.

[9]Sorry again, Patrice, for having vampirized so much precious time out of Plamen.

Chapter 6

Medical applications

The previous results indicate that the interaction between dissipation, geometry and function were important features on the tracheobronchial tree efficiency and may well have been amongst the core drivers of evolution of the tracheobronchial tree. The natural next step is then to search for implications that our results may have about diagnostic or treatments of pulmonary pathologies. I identified two ways to do this: 1/ to test if our concepts can be converted into tools that may help to diagnose specific lung pathologies; 2/ to adapt to specific medical problems the models and tools originally developed for fundamental research.

In this chapter I will illustrate both approaches. The first one deals mainly with chronic obstructive pulmonary disease (COPD), a disease frequent in smokers that affects most particularly the hydrodynamic resistance of the lung. It aims at using the tree reduction factor in diagnostics. The second one deals with the modeling of chest physiotherapy and we extended lung models of the previous sections to fit the needs of chest physiotherapists.

6.1 Role of the tree reduction factor on pathologic bronchi remodeling

This work is the result of my collaboration with three lung specialists from Hôpital Européen Georges Pompidou (Paris): Plamen Bokov, Christophe Delclaux and Bruno Mahut. Plamen has also the title of physicist, since at the time the work described in this section was made, he was doing the crazy thing to run in parallel his PhD in physics and his training as a physician[1].

Our goal was to understand how the geometrical parameters we defined for the previous models, and in particular the tree reduction factor, can play a role on chronic lung diseases that alter the airways lumen area. The two core typical diseases aimed by this study are chronic obstructive pulmonary disease (COPD) and asthma. These pathologies may be linked or amplified by permanent or temporary structural "defects" in the geometry of the lung. Therefore, they should be more frequent in individuals whose geometry is "non-optimal" in the sense defined in the previous sections. Chronic obstructive pulmonary disease (COPD) is a disease induced by chronic irritation of the airways, typically by poor air quality. COPD is frequent in smokers. Airways walls answer irritation by inducing a chronic inflammatory response which narrows the airways and increases mucus production. As a consequence, the hydrodynamic resistance of the lung is increased, and breathing difficulties occurs. Asthma is a pathology associated to an hyper-responsiveness of the airways triggered by environmental stimuli (pollutants, exercise, etc.). Asthma induces recurrent episodes of wheezing, breathing difficulty and coughs with various seriousness. Asthma remains poorly understood, probably because the term asthma encompasses range of diseases whose symptoms are similar, see e.g. [13].

We computed an appealing semi-analytical formula to estimate the hydrodynamic resistance

[1] As you have guessed, he succeeded in both.

of patients lung as a function of the size of the trachea (length L_0 and trachea D_0) and of an estimate of the reduction factor h.

$$R = \frac{128\mu L_0}{\pi D_0^4} \sum_{n=0}^{19} \left(\frac{1 + (h^{3.8}/90)(Re_0/(2h)^n}{(2h^3)^n} \right) \tag{6.1}$$

This formula accounts for the bifurcations asymmetry and for air inertial effects occurring in the first generations of the lung, μ is air viscosity ($\sim 1.8\,10^{-5}\ Pa.s$) and Re_0 is the Reynolds number at the entrance of the trachea[2]. Formula (6.1) is based on numerical simulations, and validated through specific measures in patients to determine their trachea diameter, and to estimate the reduction factor (scanner), and the pulmonary hydrodynamic resistance (plethysmography). The numerical calculations solved Navier-Stokes stationary equations in 3D in idealized tree geometries of five generations where we made the Reynolds number vary. By this technique, we were able to mimic lung subtrees at different depths. These subtrees were then assembled to compute an overall hydrodynamic resistance [11].

Pulmonary diseases with bronchial remodeling, like COPD or asthma, induce an increase in peripheral (deep) airway hydrodynamic resistance. This is confirmed by the data collected from patients with COPD and by the semi-analytical formula. Indeed, a fairly good agreement was observed between the predictions of formula (6.1) and patients measurements, see figure 6.1. This suggests that bronchi remodeling by COPD tends to reduce the tree reduction factor of the lung. This reduction implies a relative increase of resistance larger in the peripheral airways, which is consistent with the observations [10, 11, 12].

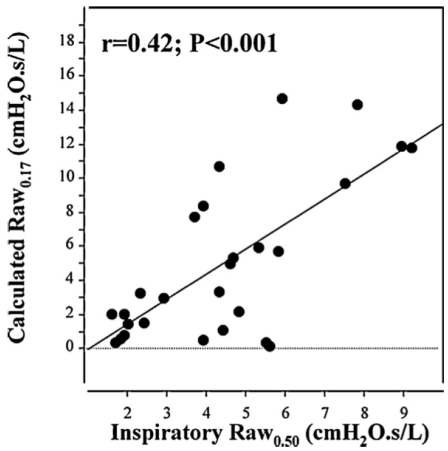


Figure 6.1: Relationship between measured and calculated lung hydrodynamic resistance. Airway resistance was measured using body plethysmography in smokers with and without COPD, while airway resistance was calculated using the measured values of tracheal sizes and h obtained in the same patients, and our semi-analytic formula.

6.2 Modeling chest physiotherapy

Pulmonary secretions (or pulmonary mucus) capture pollutants, whether chemical or biological. The natural movement of secretions toward the proximal part of the lung (trachea, large bronchi) removes these pollutants from the lung. The motion of secretions comes from two main mechanisms: the beating of cilia embedded in the epithelial cells and cough. However, these mechanisms are not mature in children and can be altered by age or by diseases, such as cystic fibrosis, bronchiolitis, asthma, chronic obstructive pulmonary disease (COPD), etc. Mucus stagnation in the lungs increases the risk of infection or bronchial obstruction. Chest physiotherapy is then used to assist secretions expectoration.

Chest physiotherapy is based on manipulations on chest wall that induces air flows in the airways. Through its motion in the airways, air induces physical constraints on the secretions, which can result in their motion. Apart from this qualitative concept, chest physiotherapy is a discipline which is surprisingly based on empirical knowledge mostly. The manipulations seems effective but the internal mechanisms that come into play are either unknown or unproven scientifically. Many techniques exist, their definition and the permission to use them is decided country per country in consensus conferences. Thus, the pool of available manipulations can differ depending

[2]The Reynolds number measures the "amount" of inertia.

on the country. This disparity is a direct consequence of the difficulty in comparing manipulations efficiency [53], and it opened the way to controversies, not only on the techniques [80] but also on chest physiotherapy itself [6]. Thus, chest physiotherapy needs now to be supported by a strong scientific background to be able to overcome its today's controversies. This is how Christian Fausser[3] and Dominique Pelca explained to Patrice Flaud, Jacques Merckx and me in 2009 the difficulties they meet in practicing chest physiotherapy as active members in their community.

The problem we were faced with was very complex and we decided to add secretions behavior to simple symmetric models of tracheobronchial tree. We decided to go on with the simplified axisymmetric framework for airways, where air flow in airways is fully developed, and we assumed that secretions layers stand on the airway walls only and had constant thickness all along the airway. The core behavior of the secretions can be represented with a Bingham fluid: either the shear constraints they suffer are too small, and they are solid, or the shear constraints are higher than a threshold and they become liquid and flow like a viscous fluid. Shear constraints are applied by the air flows inside the airways and the air flows are affected by both the way the chest is manipulated and the tree structure of the lung. We developed successively two models for chest physiotherapy, the first used rigid airways [61] and the second used deformable airways with quasi-static dynamics [1, 50, 64]. The bi-fluid models and the bronchi deformation lead to the solving of one non linear ordinary differential equation for each bronchus. Because we chose a lung model with symmetric bifurcations, the problem actually simplifies into twenty-three differential equations, one per generation. They are coupled together through the tree structure and through flow conservation in bifurcations. We developed dedicated numerical methods and implemented them in C++. They allows to solve the different variables of the system and to study how the secretions motion is affected by the threshold effect, the tree structure and the model parameters.

6.2.1 Rigid airways [61]

In the case of a tree with rigid airways, we showed the existence of a maximal asymptotic distribution for secretions in the tree. Depending on the air flow amplitude, on the initial secretions distribution in the tree and on the localization of the airway in the tree, the asymptotic distribution corresponds to a maximal mucus thickness in that airway. In the case where the lung model follows a scaling law with a tree reduction factor h, then we prove that the maximal asymptotic distribution for secretions forms a tree embedded in the lung model, and this second tree also follows a scaling law with a tree reduction factor equal to $(h/2)^{\frac{1}{4}}$. Our results also supports that a minimal air flow at mouth level is needed to be able to reach a constraint in airways high enough to overcome the secretion, and this minimal air flow increased all along the duration of a manipulation.

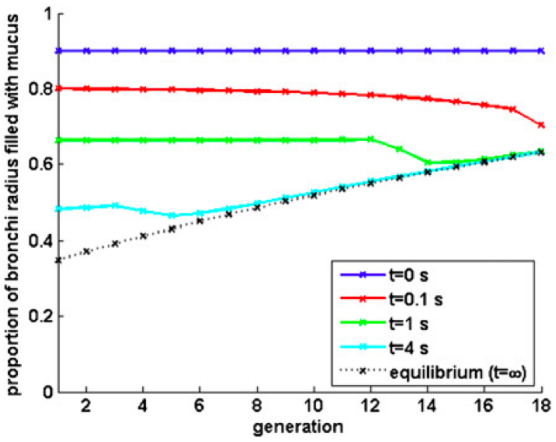


Figure 6.2: Evolution of the mucus layers in the tree for a mean velocity at mouth level of $50m.s^{-1}$. Airflow is the most effective during the initial seconds. The deepest bronchi empty quicker than the others because they have less daughter branches and thus they receive less mucus from the bottom of the tree. Maximal asymptotic distribution is plotted in black.

According to our physiotherapists collaborators, one of the major flaws in the preceding model with rigid airways is ... the

[3] A master in the art of mimicking the delightful noise of secretions going out during chest physiotherapy.

rigid airways[4]. It happens that I met Barrett Mitchell, the CEO of the startup RespInnovation[5] who was interested in understanding why the device he developed in his company was so efficient and comfortable relatively to other similar devices on the market. His device applies high frequency oscillations on the chest that are transmitted to the airways and induces mucus motions.

6.2.2 Deformable airways [64]

With so much pressure, in a way of speaking, we added to our model quasi-static airways deformations using data from literature [1, 50, 64]. We built a model whose input is the amount of pressure on the chest and whose output is air and mucus motion and airways deformations. The resulting dynamics is complex but it may be tamed with an dimensional number that represents an instantaneous efficiency measure of a manipulation. This number is a measure of the mean ratio in the tree between the shear forces in the airways over the shear threshold of the secretions, we called it the Shrek number, see figure 6.3:

Figure 6.3: The colorful troll character Shrek from Dreamworks animation *Shrek* (2001). For Shrek, mucus is the main material to build everyday objects.

$$Sh = \frac{R\Phi_a}{12N\sigma_0} \tag{6.2}$$

with R the lung hydrodynamic resistance (including the decrease due to secretions in the airways), Φ_a the air flow at mouth level, N the number of generations of the lungs and σ_0 the shear threshold for secretions. Shrek number expression can be reformulated in order to better understand how it is affected by the pressure applied on the chest: $Sh = C_L R\Delta P/(12N\sigma_0\Delta t)$ with C_L the lung compliance, ΔP the pressure jump on the chest and Δt the raising time of the pressure. The Shrek number of a chest physiotherapy manipulation is the time averaged Shrek number over the manipulation duration. The higher the Shrek number is, the greater is the efficiency of the manipulation.

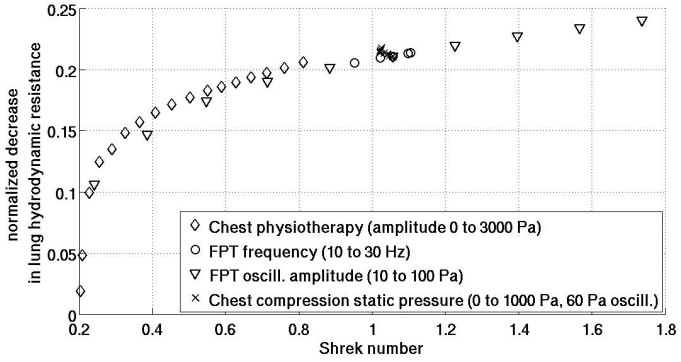


Figure 6.4: Relative reduction of lung hydrodynamic resistance after 200 seconds of manipulation (model predictions) as a function of the time averaged Shrek number.

As an example of application for the Shrek number, we plotted on figure 6.4 an example of typical results of our model. The plot represents the decrease of the lung relative hydrodynamic resistance[6] as a function of the time averaged Shrek number. Initial secretion distribution mimics an excess of secretions in lung generations six to ten, with about 40% of air lumen area obstructed

[4]Although they avoid at all cost bronchi constrictions in their manipulations, our schizophrenic physiotherapists collaborators were very eager to be able to simulate bronchi constriction.

[5]RespInnovation SAS, 611 Chemin de l'Adrech, 83440 Seillans, France.

[6]Again we are confronted to the perfidious influence of geometry/viscosity interaction on lung function.

by the secretions. Manipulations duration is 200 seconds. The figure represents the effects of different techniques simulated with our model: 1/ Chest physiotherapy with different chest pressures; 2/ FPT[7] oscillations frequency variation; 3/ FPT oscillations amplitude variation; 4/ Chest compression[8] static pressure variation. In this configuration, normal ventilation has a Shrek number of about 0.2 and quasi no effect on the lung hydrodynamic resistance in term of chest physiotherapy. When manipulations reach a Shrek number higher than 0.6, then their efficiency becomes roughly proportional to the Shrek number, indicating that the same secretions are motioned and that the increase in Shrek number is directly converted into secretion velocity. For Shrek number smaller than 0.6 then some secretions are not affected by the air flow and efficiency of the manipulation may not be optimal. Lower chest constraints may sometimes be more fitted to the health status of a patient, and Shrek number has the potential to inform the practitioner of how much efficiency is lost.

These first analyses are encouraging, but serious validation and practical measurement setups would be needed in the future to check whether the Shrek number really represents a reliable first tool able to evaluate the efficiency of chest physiotherapy techniques. Similarly, we plan to develop an index that would measure the patient comfort during the manipulations.

6.3 Abstracts

The first abstract deals with the work about homothety ratio and how it might be use for diagnostics.

Abstract 9. Homothety ratio of airway diameters and site of airway resistance in healthy and COPD subjects [11]
Our objective was to evaluate whether a decrease in the homothety ratio (h: diameter of child/parent bronchus, constant over generations) explains the shift in airway resistance toward periphery in chronic obstructive pulmonary disease (COPD). Using a validated computational model of fluid motion, we determined that reduced values of h (¡0.76) were associated with a shift in resistance toward periphery. The calculated luminal diameters of terminal bronchioles using normal h (0.80-0.85) or reduced h (0.70-0.75) fitted well with measured micro-CT values obtained by McDonough et al. (N. Engl. J. Med., 2011; 365:1567-75) in control and COPD patients, respectively. A semi-analytic formula of resistance using tracheal dimensions and h was developed, and using experimental data (tracheal area and h from patients [Bokov et al., Respir. Physiol. Neurobiol., 2010; 173:1-10]), we verified the agreement between measured and calculated resistance (r=0.42). In conclusion, the remodeling process of COPD may reduce h and explain the shift in resistance toward lung periphery.

The two following abstracts deal with chest physiotherapy modeling. The first is about the rigid airways model and the second about the deformable airways model.

Abstract 10. Toward the modeling of mucus draining from the human lung: role of the geometry of the airway tree [61]
Mucociliary clearance and cough are the two main natural mucus draining methods in the bronchial tree. If they are affected by a pathology, they can become insufficient or even ineffective, then therapeutic draining of mucus plays a critical role to keep mucus levels in the lungs acceptable. The manipulations of physical therapists are known to be very efficient clinically but they are mostly empirical since the biophysical mechanisms involved in these manipulations have never been studied. We develop in this work a model of mucus clearance in idealized rigid human bronchial trees and focus our study on the interaction between (1) tree geometry, (2) mucus physical properties and (3) amplitude of flow rate in the tree. The mucus is considered as a Bingham fluid (gel-like)

[7]FPT = focused pulse technology implemented in the mechanical chest physiotherapy device developed by RespInnovation.
[8]Mechanical technique that consists in applying a static constant pressure on the thorax in addition to a smaller oscillating pressure.

which is moved upward in the tree thanks to its viscous interaction with air flow. Our studies point out the important roles played both by the geometry and by the physical properties of mucus (yield stress and viscosity). More particularly, the yield stress has to be overcome to make mucus flow. Air flow rate and yield stress determine the maximal possible mucus thickness in each branch of the tree at equilibrium. This forms a specific distribution of mucus in the tree whose characteristics are strongly related to the multi-scaled structure of the tree. The behavior of any mucus distribution is then dependent on this distribution. Finally, our results indicate that increasing air flow rates ought to be more efficient to drain mucus out of the bronchial tree while minimizing patient discomfort.

Abstract 11. Toward the modeling of mucus draining from human lung : role of airways deformation on air-mucus interaction [64]
Chest physiotherapy is used to help secretions to get out of the lung whenever stagnation occurs. Although commonly used, little is known about the inner mechanisms of chest physiotherapy. Controversies about its use are coming out regularly [53]. Thus chest physiotherapy now needs strong scientific validation.

In this paper, we setup a quasi-static numerical model of chest physiotherapy based on thorax and lung physiology and on their respective biophysics. We assumed the lung to be a deformable symmetric bifurcating tree with 23 *generations and axisymmetric bronchi (cylinders). Static data from the literature [1, 50] are used to build a model that relates lung deformation to the pressure drop between the chest wall and the inner bronchi pressures, which are time dependent and generation dependent. We assumed the dynamics of the air and secretions to be at low regime and axisymmetric and the secretions to be a Bingham fluid. Secretion motion is the consequence of the shear constraints apply by the air flow. The input of the model is the pressure on the chest wall at each time, and the output is the bronchi geometry and the air and secretion flow properties (velocities, pressures).*

In the limit of our model, we mimicked manual and mechanical techniques of chest physiotherapy. we show that for secretions to move, air flow has to be high enough to overcome secretion resistance to motion. Moreover, the higher the pressure or the quicker it is applied, the higher is the air flow and thus the mobilization of secretions. We propose that in order to optimize patient comfort while effectively moving secretions, the pressure should always be kept slightly above the threshold. Lung hydrodynamic resistance is affected by the manipulation thus improving ventilation even if secretions are not going out of the lungs. We also observed that secretions might be pushed deeper in the lungs. Finally, we propose an adimensional number that depends on lung properties and that allows to measure the efficiency of a manipulation: the Shrek number. We tested its predictions with the idealized manipulation we made with our model and were able to relate the efficiency of the techniques to the value of the Shrek number. We believe this number may have the potential to be used as an indicator of the efficiency of a manipulation.

Chapter 7

Blood arterial network

Once inside the red blood cells, oxygen is transported with blood in the pulmonary venous system, through the heart and reaches the different organs via the systemic arterial network. Both veinous and arterial networks are tree structures. Blood motion in arterial network is primarily induced by heart contractions, thus making viscous effects critical for efficient blood circulation in arterial network. Tonicity of arterial blood vessels is high and makes them more liable to be modeled with rigid tubes than veinous blood vessels which are softer. Dissipation in veinous network is about three times smaller than in arterial network. Muscles contractions in veins surrounding tissue plays an important role on blood motion, and to avoid possible backward flow induced by this mechanism, veins also carry valves [77]. Consequently, we will focus our study on the part of blood circulation where dissipation likely plays a main role in its selection by evolution: arterial network.

7.1 Blood flows in straws

Figure 7.1: HBO teaser poster for the vampire TV show *True Blood* (cropped)[1].

Arterial network is a tree structure and each of its branch is a blood vessel. Blood vessels diameters decrease steadily with generations. From a mechanical point of view (rheology), the blood consists in plasma, a Newtonian fluid somewhat more viscous than water, and red blood cells. Blood is rheo-fluidifying: when blood internal shear forces are low, red blood cells assemble into

[1]The show pictures a fantasy modern world where vampires used to live - and feed - hidden, up to a day when a company managed to develop a synthetic blood, judiciously named *Tru Blood*. The events take place at the transition period when vampires are revealed to the world and depict how humans and vampires communities are dealing with each others (mostly: badly). The cropped part of the teaser poster says: "Friends don't let friends drink friends".

complex structures (rolls, rolls assemblies) which increases blood viscosity; when blood internal shear forces are large, the red blood cells structures break up to become isolated erythrocytes, and blood viscosity of low. Blood viscosity is not constant and blood is called a non-Newtonian fluid. Interestingly, the physiological proportion of red cells in blood varies little for most mammals, it is generally around 0.4 [107]. Since the non-Newtonian behavior is caused by some red blood cells dynamics, red blood cells proportion plays an important role on blood viscosity and consequently on the dissipation it generates for its motion. The higher the concentration of red blood cells, the greater the ability of blood to carry oxygen is, since red blood cells are the main oxygen vectors in blood. The volume fraction of red blood cells in blood is called the hematocrit.

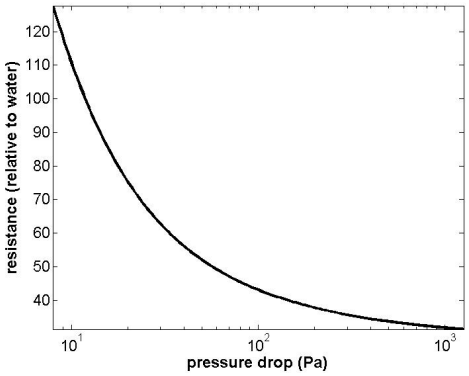


Figure 7.2: At the beginning, the vampire drinking blood through a straw will have to overcome about 120 times the resistance he would have to overcome with water. Then as the pressure drop applied by the vampire increases, blood velocity in the straw also increases and the resistance to overcome decreases down to about 30 times that for water: blood is rheofluidifying.

Let us go back shortly to straws and drinks, and focus to a vampire drinking *tru blood*, see figure 7.1. Let us also assume this vampire has the bad taste or luck to drink the bottle with a thin straw[2] so we can neglect again gravity effects. What would happen? Because the blood in the bottle is unmoving, its viscosity is high and the vampire would need to suck the blood up with mighty strength. Vampires are known to have unnatural strength, so that may do it. If not, I would advise the vampire to shake the bottle first and to start drinking quickly afterward. Now, assuming the vampire is drinking, then the blood flow in the straw would vary non linearly with the pressure drop the vampire applies on the straw to drink. The higher the pressure drop, the relatively more blood the vampire will get, up to some point where red blood cells are isolated and blood viscosity minimal. If the straw is really thin[3] with a diameter smaller than about 600 microns, then a phase separation effect would occur in the straw and a layer of plasma will lubricate the blood flow in the straw, for the delight of the vampire, in the limit that such a thin straw would anyway be hard to drink from, about ten thousands times harder than a normal straw with 5 millimeters diameter, see equation (2.1). This phase separation effect is called the Fåhræus effect [33].

The thirsty but well-mannered vampire from our previous paragraph helped us to show that blood flow has the following properties : 1/ red blood cells volume fraction in blood affects blood viscosity; 2/ blood inner shear constraints, which are correlated with blood flow amplitude, affect blood viscosity; 3/ Phase separation effects in small tubes make the flow dependent on the absolute dimension of the tube diameter.

We search for optimal geometries and red blood cell volume fractions that minimize a cost including blood viscous dissipation and blood maintenance costs. Our work on this topic was inspired by the pioneering work of Murray [74] and by other studies in his wake, such as [2, 114]. In the next section, section 7.2, we give some details about the hypotheses for our model. In section 7.3, we extend Murray's law to blood with the hypothesis that it is fully shear dependent and we include Fåhræus effect in the story. In section 7.4, we investigate how the preceding results and phenomena affect dissipation in rigid tree structures that mimic blood arterial network. Actually, we work in subtrees of the arterial network where inertial effects and pressure waves can reasonably be neglected, i.e. below the sixth generation at rest regime, and where continuous representations for blood remain satisfactory, i.e. for blood vessels with a minimum diameter of about 50 microns. In the next chapter 8, we study a similar problem in capillaries and optimize the red blood cells

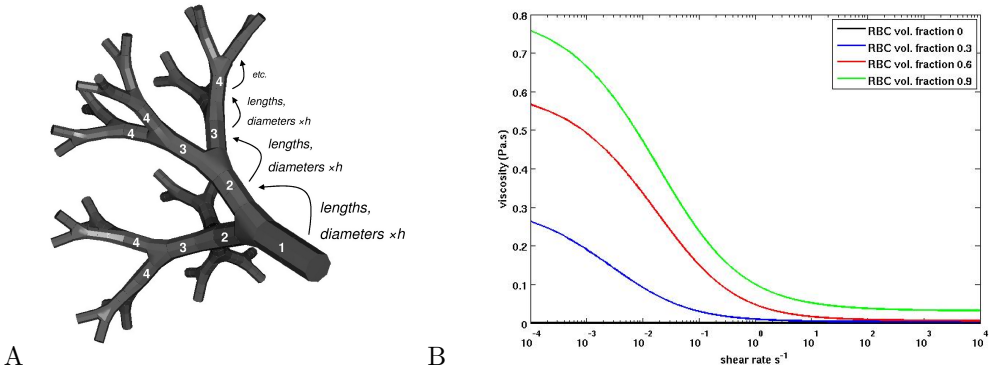
[2]Anyway, are vampire teeth even compatible with straws? Thus, I think we should keep our approach purely academical.

[3]Assuming the bartender has what it takes to make fun of a vampire.

volume fraction in a model of pulmonary capillary.

7.2 Minimal cost for the arterial network: hypotheses

The main difficulty comes from the coupling of a complex geometry with a complex fluid. Concerning the geometry, we work with simple geometric model, which we happen to know well by now: a rigid tree with cylindrical branches and symmetric divisions. Divisions can be either bifurcations with two branches stemming from one bigger branch, or n-furcations with n branches stemming from one bigger branch. The size of the tree branches is decreasing at each division with the tree reduction factor $h < 1$, see figure 7.3A. Such a "minimal" geometry forms a reasonable first approximation because it contains the core structural properties of the arterial system. Concerning



A B

Figure 7.3: A: The arterial network is modeled with a tree whose branches undergo repeated divisions into n smaller branches (here $n = 2$). The branches size is decreasing at each bifurcation: diameter and lengths of the branches are multiplied by the tree reduction factor $h < 1$. B: Dependence of viscosity on shear rate $\dot{\gamma}$ for different values of hematocrits.

fluid mechanics, blood velocity is assumed axisymmetric in the vessel axis and independent of the axial position in the vessel (developed profile). To model Fåhræus effect in the small branches, we assume that a plasma only layer stands on the branches wall. The plasma layer thickness is calculated with a semi-empirical formula from the literature [82]. Blood viscosity outside the plasma layer is calculated with Quémada's model [85] for viscosity. This model relates local blood viscosity with local red blood cells volume fraction H and local shear rate $\dot{\gamma}$ which represents the variation of the blood velocity along the radius of the vessel, see figure 7.3B:

$$\mu(\dot{\gamma}, H) = \mu_p \left(1 - \frac{H}{H_\infty}\right)^{-2} \left(\frac{1 + k(|\dot{\gamma}|)}{\chi(H) + k(|\dot{\gamma}|)}\right)^2 \tag{7.1}$$

To fulfill the function of oxygen transport, the network must be able to provide a suitable amount of oxygen to the downstream organs. Therefore, this defines a constraint to our optimization problem: the flow of oxygen transported by the system, which is proportional to the flow of red blood cells. Then the total energy cost spent by the arterial network for fulfilling this function is the sum of the viscous dissipation related to the blood flow in the network with the maintenance costs for the red blood cells (repairing, renewal). The two traits associated with these energy costs are the hydrodynamic resistance for blood dissipation in the network, and the volume of blood for the maintenance of red blood cells. The volume of blood actually corresponds to the volume of the network. These two traits are linked by two parameters: the tree reduction factor, which sets the vessel diameters, and the volume fraction of red blood cells. Both parameters induce a trade-off on total power dissipation,

- *For a given concentration of red blood cells*: if the vessel diameters are large, then the viscous dissipation is small. However the volume of blood is high and therefore the cost of red blood

cells maintenance is *large*. If the vessel diameters are small, then the viscous dissipation is *large* and the maintenance cost is small.

- *For given vessel diameters*: if the concentration of red blood cells is small, then the blood must flow more quickly to provide sufficient oxygen flow to the organ, which induces a *large dissipation*. However the maintenance cost is small. If the red blood cell concentration is large, then blood viscosity is high and dissipation is potentially *large*. Also the maintenance cost is *large*.

Such blood flow constraint and cost have been first introduced by Murray in 1926 in the case of a Newtonian fluid [74]. Murray demonstrates that to minimize the cost in a cylindrical tube, the fluid flow rate has to be proportional to the cube of the tube radius. This induces that the optimal shear rate is independent on the amplitude of the flow rate or the radius of the tube.

7.3 Murray's law extension to shear thinning/thickening fluids[4][66]

We extended Murray's law to Quémada's fluids; since our study is based on the fact that the dependence of viscosity on fluid mechanics is a monotonous function of the shear rate only, our results also holds for any other similar fluid. In a cylindrical tube, we showed that the mean shear rate drives the behavior of the effective viscosity of the tube and thus of the power dissipated in the flow. The consequence is that Murray's optimization principle in a cylindrical tube brings an universal optimal mean shear rate that does not depend on the flow amplitude or on the size of the tube. In the case of Quémada's law mimicking blood behavior, we found that this optimal mean shear rate is $\langle\dot{\gamma}\rangle^*_{noF} = 12.47\ s^{-1}$. This value is in accordance with arterial macrocirculation data where the mean shear rates in the successive vessels remain almost constant at about 10 s^{-1}. This optimal value is the smallest possible mean shear rate that allows viscosity to remain in its lowest plateau, see figure 7.3B. Applied to a fractal tree whose branches divide into n identical smaller branches, we found that the optimal scaling factor remains the same one as for a Newtonian fluid, i.e. $n^{-1/3}$.

However, if the tube diameter is small enough, the stubborn phase separation effect -Fåhræus effect- occurs and a plasma only layer appears near the wall of the tube, thus making the effective viscosity depend not anymore on the mean shear rate only, but also on r. Consequently, we derived a new optimal configuration from Murray's optimization principle in a tube, which formulates into a decreasing function relating the optimal mean shear rate in a tube and the radius of the tube $r \rightarrow \langle\dot{\gamma}\rangle^*_F(r)$. For large r, the function coincides with the optimal mean shear rate without Fåhræus effect. The function behavior highlights the fact that Fåhræus effect induces a lubrication phenomena into the tube. The case of Quémada's fluid mimicking blood is plotted on figure 7.4. We also derived the optimal configuration of a fractal tree when Fåhræus effect occurs. We showed that the optimal scaling factors become dependent on the generation index i, on the size of the root of the tree and on the function $r \rightarrow \langle\dot{\gamma}\rangle^*_F(r)$, i.e. $nh^3_{i,*}\langle\dot{\gamma}\rangle^*_F(h_{i,*}r_{i,*}) =$

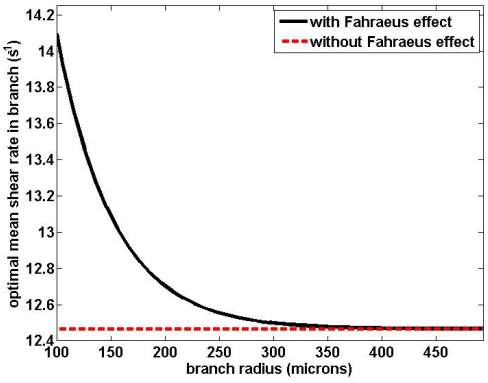


Figure 7.4: In black, the optimal mean shear rate in a branch as a function of the radius of the branch with Fåhræus effect (function $r \rightarrow \langle\dot{\gamma}\rangle^*_{noF}(r)$ in text), in red dotted line, the optimal mean shear rate without Fåhræus effect. Blood case: $H_D = 0.45$ and a volumetric energetic consumption rate for blood of 77.8 $J.m^{-3}.s^{-1}$ [2, 98].

[4] As of matter of fact, this includes blood, which is a shear thinning fluid.

$\langle\dot{\gamma}\rangle_F^*(r_{i,*})$. Optimal configuration of the fractal tree allows tighter branches when Fåhræus effect occurs and induces a drop in mean shear stresses along the tree, which has been reported in the literature for blood arterial microcirculation [82].

7.4 Optimizing hematocrit and geometry for the optimal feed of an organ [71]

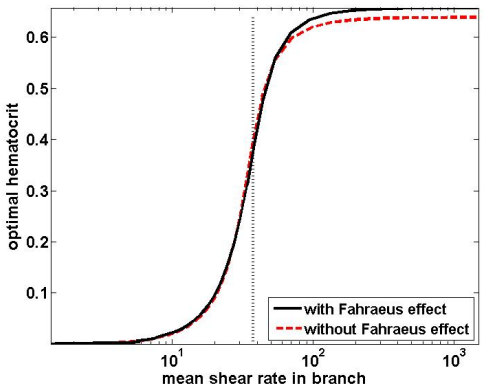


Figure 7.5: Hematocrit value that minimizes the cost function in the case of a single branch as a function of the mean shear rate in the vessel.

We assume now that we have a dichotomous tree ($n = 2$) that supplies an organ with oxygen. The tree carries oxygen from its root (the source) to the organ small microcirculation. To avoid inertial effects and pressure waves, the root of the tree corresponds to a blood vessel whose diameter is 5 millimeters, i.e. it belongs to something like the sixth generation of the arterial network. We assume the diameters of the tree leaves to be fixed at about 50 microns. As a consequence, the number of generations of the tree depends on the tree reduction factor h [69, 71]. We also took into account Fåhræus effect. At first we studied the optimal configuration in a single vessel. We found again that the mean shear rate in the vessel controlled the minimal cost hematocrit value, see figure 7.5[5]. Concerning the minimal cost hematocrit, we showed that its value when optimized in the whole tree, is a compromise between the values in each generation, see figure 7.6A.

Next, we searched the tree reduction factor and hematocrit values that minimize the cost and compared them to physiology. Given our assumptions, we are studying a nonlinear constrained optimization problem with piecewise regular application (discontinuities arise because the number of generations depends on the geometrical parameter and creates jumps in the cost). We addressed this problem through numerical simulations based on a set of theoretical results detailed in [66, 69]. The optimal network predicted by the model is close to the physiology, the model predicts a minimal cost hematocrit of 0.43 [6] and a tree reduction factor of about 0.79, see figure 7.6B. As for the tracheobronchial tree, these results suggest that the cost, and therefore the dissipation related to blood circulation in the arterial network, may have played a role on its selection. To support this hypothesis, we highlighted the model's predictions with properties of the cardiovascular system in altitude populations (Andes and Tibet). The cost built into this model also allowed us to mimic the energetic consequences (i.e. heart overloading) of doping, hypoxia (lack of oxygen in the blood) or polycythemia (increased proportion of red blood cells) [71].

Finally, from a physical point of view, we showed that the mean shear rate in a fractal tree follows a scaling law correlated with that of the tree. The optimal geometry predicted by our model is a direct consequence of this phenomenon.

[5] We use the terminology *minimal cost hematocrit* in order to avoid the confusion with the regular meaning of *optimal hematocrit*, which is a medical term that defines the hematocrit needed by a patient at a given time and status [40]. I would like to thank whoever our mysterious referee was for raising this tricky point.

[6] i.e. 43%... I was really sorry not to find the value 42, which is the "Answer to The Ultimate Question of Life, the Universe, and Everything" in Douglas Adams novel *The Hitchhiker's Guide to the Galaxy*, where, unfortunately, nobody knows the question to that answer.

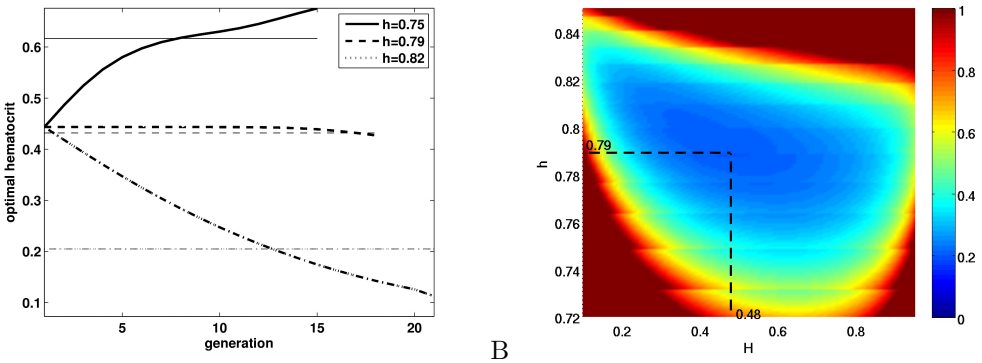


Figure 7.6: A: Minimal cost hematocrit computed in each branch (thick lines) and compared with the minimal cost hematocrit for the whole tree (horizontal thin lines). B: Energy cost landscape to irrigate the idealized organ (in $J.s^{-1}$). X-axis is the hematocrit H and Y-axis the homothety ratio h. The minimum is reached for $H = 0.43$ and $h = 0.79$.

7.5 Historical background

As I joined the Matière and Systèmes Complexes laboratory (Université Paris Diderot - Paris 7) in 2005, I met many interesting people who were working on blood circulation. I was intrigued because the fluids I had dealt with before were Newtonian and pretty affable[7]. The mathematics and dynamics I faced suddenly modeling blood were surprising and complex[8]. Definitely, I had no real intuition on the links between the equations and the physical phenomena. So I did what I thought was best: 1/ discussing with patient colleagues: Philippe Dantan and Patrice Flaud, mostly; 2/ performing scientific computations of the offensive equations. I also asked for fundings and went lucky: I got a funding for a PhD thesis from the CNRS and gave the job to Baptiste Moreau, a young applied mathematician.

The research described in this chapter are part or are extensions of the work of Baptiste Moreau during his PhD thesis [69], advised by Philippe and me between 2008 and 2012.

Abstract 12. Murray's law revisited with Quémada's fluids and fractal trees [66]
In 1926, Murray proposed the first law for the optimal design of blood vessels. He minimized the power dissipation arising from the trade-off between fluid circulation and blood maintenance. The law, based on a constant fluid viscosity, states that in the optimal configuration the fluid flow rate inside the vessel is proportional to the cube of the vessel radius, implying that wall shear stress is not dependent on the vessel radius. Murray's law has been found to be true in blood macrocirculation, but not in microcirculation. In 2005, Alarcón et al took into account the non monotonous dependence of viscosity on vessel radius - Fåhræus - Lindqvist effect - due to phase separation effect of blood. They were able to predict correctly the behavior of wall shear stresses in microcirculation. One last crucial step remains however: to account for the dependence of blood viscosity on shear rates. In this work, we investigate how viscosity dependence on shear rate affects Murray's law. We extended Murray's optimal design to the whole range of Quémada's fluids, that models pseudo-plastic fluids such as blood. Our study shows that Murray's original law is not restricted to Newtonian fluids, it is actually universal for all Quémada's fluid as long as there is no phase separation effect. When phase separation effect occurs, then we derive an extended version of Murray's law. Our analyses are very general and apply to most of fluids with shear dependent rheology. Finally, we study how these extended laws affect the optimal geometries of fractal trees to mimic an idealized arterial network.

[7] Well, not always... They can be affable indeed, but only at low Reynolds numbers.

[8] A bit later, I figured out that there were things far more terrible than blood-like fluids, things probably hidden in the dark under someone's bed: viscoelastic fluids, biological tissues and dreadful granular media.

Abstract 13. Functional optimization of an idealized mid-level arterial network [71]
One of the main function of the arterial blood network is to supply blood to the organs, either to bring oxygen (systemic network) or to capture oxygen (pulmonary network). By the process of evolution, the characteristics of this network are likely to have been selected to be efficient while fulfilling its function. In this work, we focus on the role of fluid dissipation in the arterial network and study wether dissipation may have played a role on the selection of arterial network characteristics by evolution. We consider an idealized organ with a given oxygen need. We assume this ideal organ is fed by a blood flow across a dichotomous tree whose vessels' sizes are decreasing regularly at each bifurcation by a factor h called the tree reduction factor. In the spirit of the optimal design proposed by Murray in 1926, we build an energetic cost based on blood dissipation in the tree and on blood maintenance, thus exhibiting a trade-off between tree hydrodynamic resistance and tree volume. We search for the scaling law and the red blood cell volume fraction that minimize the cost while fulfilling the organ needs in oxygen. Our model is based on developed non inertial fluid dynamics in cylindrical vessels, and covers a arteries whose diameters range from 5 *mm to* 50 *microns (thus our model does not account for large macrocirculation and for small microcirculation). We use Quémada's law to accounts for the non-Newtonian behavior of blood. The maintenance energetic cost is built from literature, and based on both the active red blood cells upkeep and on the red blood cells renewing costs. Finally, we account the Fåhræus phase separation effect by using a semi-empirical law from Pries et al (2008), and by assuming the smaller vessels exhibit a red blood cells depleted layer near the vessels walls.*

We first show that the mean shear rates in the vessels follow a scaling law related to the multiscale property of the tree network, and that this scaling law drives the behavior of the minimal cost hematocrit in the tree. Feeding relevant data from the literature to our model, it is able to predict a minimal cost hematocrit value of about 0.43 *and a tree reduction factor of close to* $h = 0.79$*. Our model predictions are in agreement with the physiology of most of the arterial network: the value of the cost for the arterial network is thus likely to be near the optimal. This indicates that dissipation in the medium sized arteries may have played an important role on the evolution of its geometry and of its hematocrit value. Interestingly, viscous dissipation is high, if not higher, in the small microcirculation. Thus our study suggests that the physiological hematocrit value may also be optimal for small microcirculation. We will study this aspect in future work in order to have a global understanding of the physiological hematocrit value.*

Chapter 8

Air/blood exchange surface

Oxygen is convected by air down to the sixteenth or seventeenth generation of the lung. Then it enters the acinus where, at some point, diffusion becomes the main driving force for oxygen displacement. The exact position in the acinus where diffusion becomes predominant on convection depends on the regime of ventilation[1]. The diffusion of oxygen in the acini was thoroughly studied by the team of Bernard Sapoval (Laboratoire PMC, Ecole Polytechnique), for example in the PhD theses of Maddalena Felici [25] and Aurélie Foucquier [31]. Once in the cells, the oxygen in alveolar gas dissolves into the alveolar-capillary membrane (less than one micron thick) and diffuses to the blood, in small vessels called capillaries. Capillaries diameters are of the order of ten microns and mean capillaries length is one millimeter. The pulmonary capillary structure is complex, they are

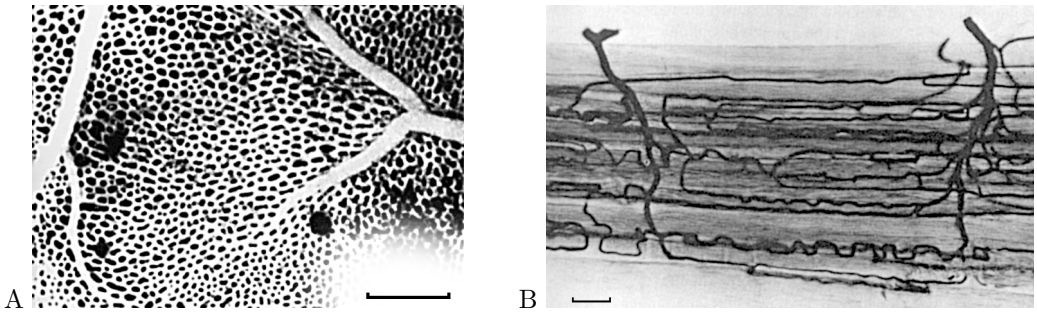


Figure 8.1: Capillaries, scale markers: 100 μm. A: pulmonary capillaries forms a capillary bed [54], mean length of a capillary path is about 1 mm. B: muscle capillaries are neatly aligned with muscle fibers [107], .

interconnected and form a two-dimensional structure called the capillary bed, see figure 8.1A[2]. The oxygen then diffuses into the red blood cells and is captured by hemoglobin. As the size of blood vessels decreases, the physical phenomena related to the biphasic nature of the blood, such as the Fåhræus effect [32, 33, 71] or the presence of the protein glycocalyx on capillary walls [92] imply a decrease in hematocrit, which can drop to 0.1 in the smallest capillaries [69].

As in chapter 7, we aim to understand some properties of blood inside the capillaries and we will focus most particularly on the red blood cell volume fraction in the capillaries, which is smaller than in the large circulation because of phase separation effects such as Fåhræus effect. We will use the same cost than in chapter 7: a Murray's like energetic cost [74] based on fluid viscous dissipation and red blood cell maintenance. As before, the capillaries are considered constrained by their function, which is represented by a fixed oxygen flow inside the capillary. The viscous

[1] Exercise regime if you are running away from a saber-tooth tiger; rest regime if you are having a drink with your vampire friend - unless the vampire is not *exactly* a friend.

[2] Systemic capillaries that feed the organs are structurally different, see for example muscles capillaries on figure 8.1B.

dissipation part of the cost is however more tricky to compute at this scale, where the size of the red blood cells is similar to the diameter of the capillary. Hence, we cannot anymore reach detailed data about oxygen transfers and blood circulation with a continuous model. We had to setup a numerical model of fluid-structure interaction between plasma and red blood cells in cylinders, which represent capillary geometries. Notice that cylinders can mimic either a muscle capillary or the environment encountered by a red blood cell as it goes through the capillary bed[3]. However, we could not hope to perform numerical simulations of red blood cells inside a capillary. Actually, the aspect ratio between capillary length and diameter is too large (about 100) and the number of red blood cells to high (about 1500 in a single 1 mm long capillary at physiological hematocrit). Thus we proposed a method specifically developed for this purpose which allows to follow one red blood cell belonging to a train of periodic red blood cells in a capillary: the camera method, which is the topic of section 8.1. The camera method is actually most general and, under some conditions, can be extended to the tracking of a particle in a network [70].

With the camera method, we can build a full model of periodic trains of red blood cells-like particles in a cylinder, based on different submodels for the alveolus, the alveolo-capillary membrane, the capillary, the red blood cell and the hemoglobin. The alveolus and the alveo-capillary membrane are incorporated into the model using boundary conditions on the cylinder wall. The model for oxygen and hemoglobin chemical interactions comes from the literature [20].

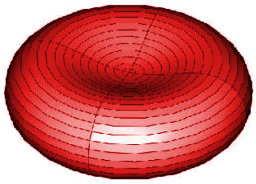
A  B 

Figure 8.2: Notice the nice similarity between the geometry of a real red blood cell (A) (photo from [24]) and of our model for red blood cell[4].

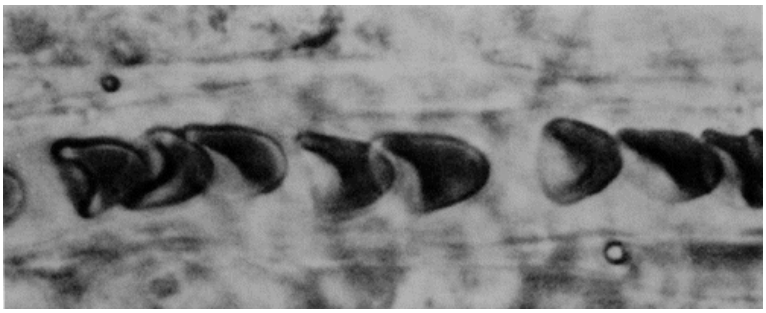


Figure 8.3: Red blood cells in a capillary from [94]. The diameter of the capillary is so small they have to deform into a parachute shape to be able to go through.

Red blood cells are shaped as a disk with a depression in the middle of the disk on each side, see figure 8.2. They are about eight microns in diameter and two to three microns thick. They are highly deformable. As the size of the red blood cells is of the order of the capillaries average diameter, red blood cells deform when they enter capillaries and they take the shape of a parachute [94] as on figure 8.3. To reach correct energetic cost estimations and to get detailed information about oxygen transfers, we had to build a numerical model that accounts for realistic geometries of

[3]In which case the cylinder is not exactly a capillary but rather represents a pathway.

[4]Granny Wheatherwax, from section 2.5, would probably agree with me saying that our model may well look more like a red blood cell than the red blood cell on the photo itself.

red blood cells. Hence, we have developed a numerical method for calculating the deformation of a periodic train of red blood cells in a capillary: the camera method (2D, 2D-axi, 3D) [58, 69, 70].

8.1 The camera method

The camera method is a fluid-structure interaction method, based on a fictitious domain approach coupled with a co-rotational formulation [88] for the mechanics equations of the structure. The idea is to perform the numerical simulation on a neighborhood $\mathcal{N}$ of the particle (the camera frame, see figure 8.4) and to make the mesh turn and move with the particles velocities in order to avoid at most mesh distortion[5]. The rotation angles and the translations are computed with the the co-rotational method. The wall of the network is defined by a penalty method on the fluid velocity.

The most difficult part is to determine the conditions to apply on the boundary of the neighborhood $\mathcal{N}$ where it meets the fluid. There are different ways to apply boundary conditions.

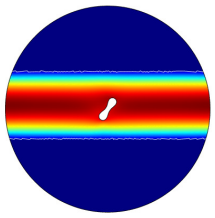


Figure 8.4: Example of camera method in 2D: the camera frame with the particle in the center.

- In the case of a train of red blood cells, then periodic boundary conditions for the fluid velocity can be used. The flow inside the neighborhood of the particle can be constrained using a Lagrange multiplier.
- This is more complex when only one particle travels the network. First we need the condition that the fluid flow rate in any piece of the network is fixed. This is typically true if the network exhibits no loop and if only Dirichlet boundary conditions apply at the inlets and outlets of the network. In that case, some specific mathematical results apply. Mathematical analysis of spatial decay estimates of velocity profiles for steady and non steady Stokes equations have been made in the past [34, 35, 95]. The results state that any input velocity profiles in semi-infinite tubes[6] converges exponentially fast along the tube axis to the Poiseuille's profile. Hence, any perturbation made by the particle on the fluid velocity decays exponentially fast along the tube axis, thus the error made by neglecting the parts outside the neighborhood can be controlled by the size of the particle neighborhood. So where the boundary of the neighborhood meets the network, one can apply an approximated velocity corresponding the velocity the fluid would have in the absence of the particle[7].

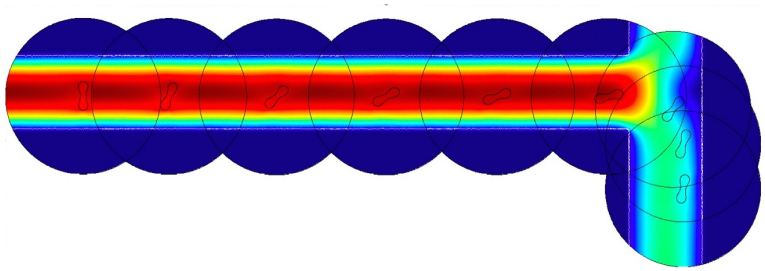
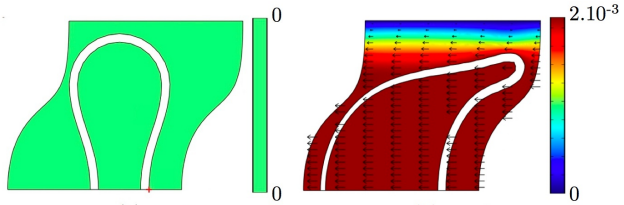


Figure 8.5: Example of camera method in 2D, camera and particle trajectory.

[5] If the particle is rigid, the mesh will not distort at all; if the particle deforms, then only fundamentals of the deformation will be felt by the mesh (i.e. no translations and no rotations will affect the mesh); in both cases, this is a big improvement in term of mesh deformation relatively to classical ALE method [44, 45]

[6] If you look for the exit in a semi-infinite tube, you had better to choose well your walking direction. Do not bother if the tube is infinite.

[7] Far easier to compute without that annoying particle, either analytically or numerically.



(a) $t = 0$ s (h) $t = 3$ s

Figure 8.6: Example of camera method for a periodic train of red blood cells (2D axisymmetry). Left: initial state. Right: steady deformed state.

We implemented the camera method using finite elements in the finite elements toolbox Comsol Multiphysics[8]. [70]. The system consists in the modified fluid-structure interaction equations, and one equation for each possible translation and rotation. The system is non linear and is solved using a modified Newton method embedded in Comsol. Example of simulations are plotted on figure 8.5 and 8.6.

8.2 Minimal cost in capillaries

First, we have shown that the energy stored in the membrane of the red blood cells when they are in parachute shape was negligible compared to plasma viscous dissipation in the capillary. When the oxygen flow through the capillary is given, the power dissipated by the plasma decreases with red blood cell concentration [72], however the power for red blood cells maintenance cost increases with their concentration. Hence, as in chapter 7, we are faced with a trade-off which leads to an optimal value for the volume fraction of red blood cells at a given oxygen flow rate. As an example, consider the case of a capillary with a diameter of eight microns, then our model predicts its minimal cost hematocrit to be reached for an hematocrit of about 0.26, see figure 8.7. This value is consistent with physiological data [69, 72, 82].

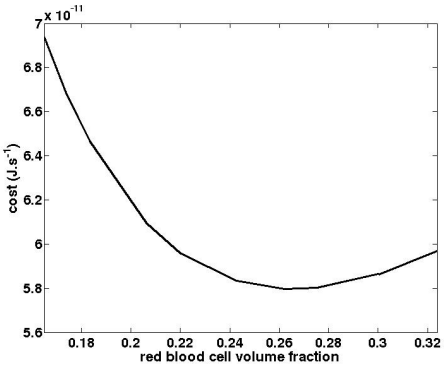


Figure 8.7: Power dissipation in the capillary as a function of the red blood cell volume fraction (capillary diameter is 8 microns).

The physiological value of hematocrit in capillary is close to the value that minimizes the cost we propose. Hence, the fact that hematocrit in the capillaries is smaller than hematocrit in the larger circulation is beneficial for the metabolism. This result brings up a new important question relative to capillaries design: has evolution something to do with the phase separation effects? Phase separation effects are either physical, like Fåhræus effect, or biological, like the layer of glycocalyx macromolecules [91]. If the answer to the previous question is yes, then it opens some interesting perspectives about our understanding of pathologies affecting the capillaries, typically like diabetes. A deeper investigation of those phenomena may thus be of strong interest in the future.

8.3 Oxygen capture by red blood cells

Oxygen and Hemoglobin chemical reactions are computed in a second step. They are described by a nonlinear model of reaction kinetics from the literature [20]. The model consists in ten different chemical species. It leads to good quantitative prediction of hemoglobin behavior, such as its

[8] http://www.comsol.com

saturation curve, which represents the proportion of hemoglobin oxygen sites filled as a function of blood partial pressure in oxygen [107]. A typical simulation of the time-dependent capture of oxygen by hemoglobin is plotted on figure 8.9.

A red blood cell remains approximately one second into the capillary at rest regime, and about half a second in exercise regime. Our model predicts that a red blood cell is saturated with oxygen in approximately half a second. Within the assumptions of our model, the red blood cells capture of oxygen is robust at rest regime.

It is therefore able to compensate for malfunctions that slow down oxygen uptake by red blood cells, such as the thickening of the alveolar-capillary membrane[9]. On the contrary, exercise regime is not robust because the red blood cell remains in the capillary about half a second, i.e. exactly the time needed for its saturation. As consequence, a dysfunction in the exchange system lay be more easily diagnosed in exercise regime[10]. On figure 8.8, we mimicked an alveolar edema (water in the alveoli), which implies a thickening of the alveolo-capillary membrane: at rest, the system can compensate (robustness) up to a point, when blood oxygenation starts to fall.

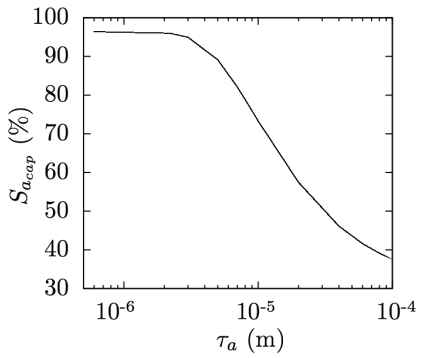


Figure 8.8: Saturation of hemoglobin in the capillary as a function of the alveoli-capillary membrane thickness [69].

8.4 Historical background

These topics were mostly studied in the framework of Baptiste Moreau PhD thesis in MSC (Université Paris Diderot - Paris 7) with Philippe Dantan and Patrice Flaud. A master student was also involved in 2012, Hassane Mbyas Saroukou.

Abstract 14. Following red blood cells in a pulmonary capillary [58]
The red blood cells or erythrocytes are biconcave shaped cells and consist mostly in a membrane delimiting a cytosol with a high concentration in hemoglobin. This membrane is highly deformable and allows the cells to go through narrow passages like the capillaries which diameters can be much smaller than red blood cells one. They carry oxygen thanks to hemoglobin, a complex molecule that have very high affinity for oxygen. The capacity of erythrocytes to load and unload oxygen is thus a determinant factor in their efficacy. In this paper, we will focus on the pulmonary capillary where red blood cells capture oxygen. In order to numerically study the behavior of red blood cells along a whole capillary, we propose a camera method that consists in working in a reference frame that follows the red blood cells. More precisely, the domain of study is reduced to a neighborhood of the red blood cells and moves along at erythrocytes mean velocity. This method avoids too large mesh deformation. Our goal is to understand how erythrocytes geometrical changes along the capillary can affect its capacity to capture oxygen.

The first part of this document presents the model chosen for the red blood cells along with the numerical method used to determine and follow their shapes along the capillary. The membrane of the red blood cell is complex and has been modelled by an hyper-elastic approach coming from [16]. This camera method is then validated and confronted with a standard Arbitrary Lagrangian Eulerian (ALE) method in which the displacements of the red blood cells are correlated with the deformation of an initial mesh of the whole capillary with red blood cells at start positions. Some geometrical properties of the red blood cells observed in our simulations are then studied and discussed. The second part of this paper deals with the modeling of oxygen and hemoglobin chemistry in the geometries obtained in the first part. We have implemented a full complex hemoglobin behavior with allosteric states inspired from [20].

[9] Lung edema: the membrane is thickened by water.

[10] At the decisive moment, it may come as a surprise that running away from the incoming, hungry and pretty big saber-tooth tiger turns out to be slightly more tricky than expected.

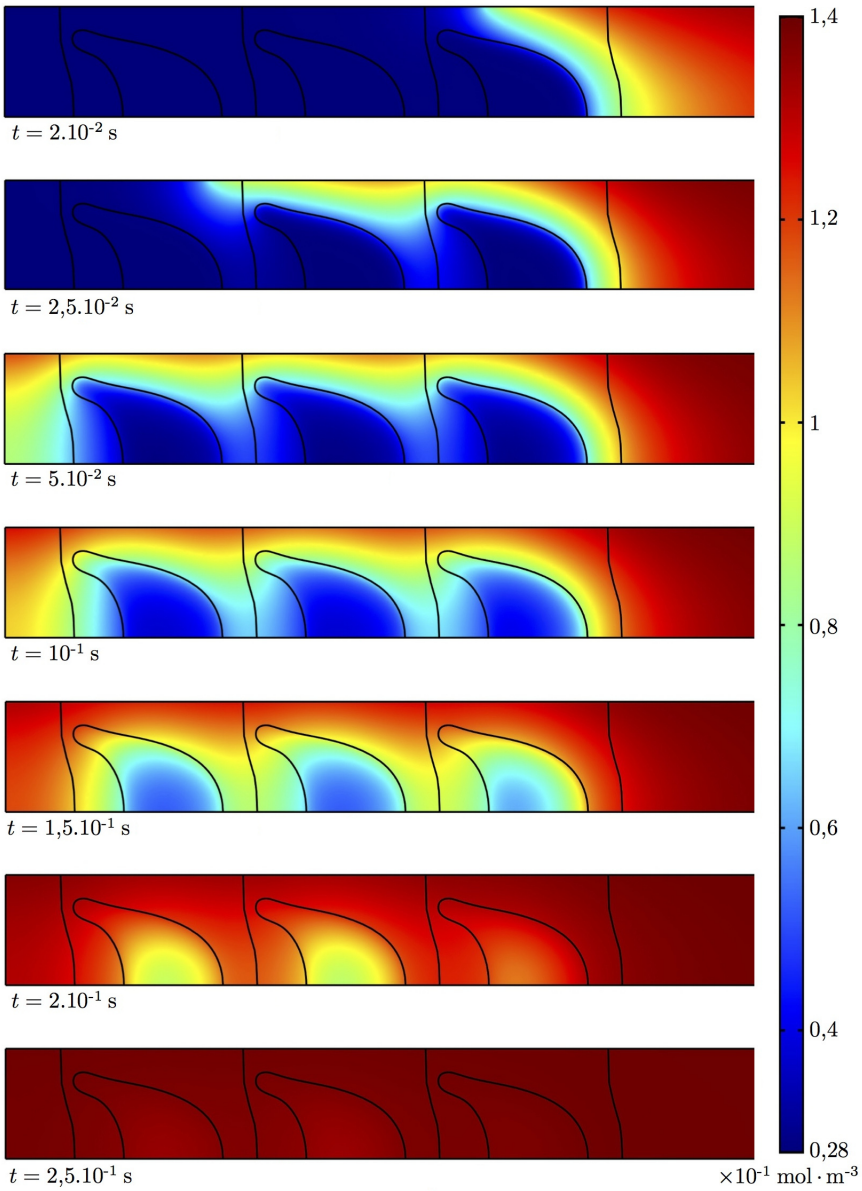


Figure 8.9: Oxygen diffusion in the capillary and capture by hemoglobin into the red blood cells [69].

Abstract 15. The camera method, or how to track numerically a deformable particle moving in a fluid network [70]
The goal of this work is to follow the displacement and possible deformation of a free particle in a fluid flow in 2D axi-symmetry, 2D or 3D using the classical finite elements method without the usual drawbacks finite elements bring for fluid-structure interaction, i.e. huge numerical problems and strong mesh distortions. Working with finite elements is a choice motivated by the fact that finite elements are well known by a large majority of researchers and are easy to manipulate. The method we describe in this paper, called the camera method, is well adapted to the study of a single particle in a network and most particularly when the study focuses on the particle behaviour. The camera method is based on two principles: 1/ the fluid structure interaction problem is restricted to a neighbourhood of the particle, thus reducing drastically the number of degrees of freedom of the problem; 2/ the neighbourhood mesh moves and rotates with the particle, thus avoiding most of the mesh distortions that occur in a standard ALE method. In this article, we present the camera method and the conditions under which it can be used. Then we apply it to several examples from the literature in 2D axi-symmetry, 2D and 3D.

Abstract 16. Optimal red blood cells concentration in an idealized capillary [72]
*In 1926, Murray proposed the first law for the optimal design of blood vessels assuming blood is Newtonian. He minimized the power dissipation arising from the trade-off between fluid circulation and blood maintenance. This law has then be extended to non-Newtonian fluid [2, 66]. Interestingly Murray's cost can also be used to optimize red blood cells volume fraction in blood (hematocrit). A preceding study has shown that in the mid-level arterial circulation the optimization of a cost similar to that of Murray lead to a minimal cost hematocrit compatible with the physiology (*0.43*) [71].*

In this work, we propose to search for the optimal value of hematocrit in a capillary. Phase separation effects in the microcirculation induce a reduction of hematocrit in the capillaries. We consider a model for blood capillary based on a periodic train of red blood cells. The hematocrit can be controlled either by varying the diameter of the capillary or the distance between two red blood cells. We used a numerical approach based on a specific periodic fluid-structure interaction method that follows one capillary slice with only one red blood cell and its close neighborhood, the camera method [58, 70]. Then we compute a cost similar to that of Murray.

Our results show first that the energy stored in the red blood cells membrane is negligible to the viscous energy dissipated by the plasma. Second, we observe that the difference in the physical processes involved in blood circulation between capillaries and mid-level arterial circulation implies that the minimal cost hematocrit in the capillaries is smaller than in the large circulation, in accordance with the physiology. As an example, for a capillary with 8 *microns diameter, the minimal cost hematocrit is about* 0.26*. The physiological value of hematocrit in capillary is close to the value that minimizes the cost we propose. Hence, the fact that hematocrit in the capillaries is smaller than hematocrit in the larger circulation is beneficial for the metabolism. This result brings up a new important question relative to capillaries design: has evolution something to do with the phase separation effects?*

Chapter 9

Conclusion.

All the results presented in this work come from modeling processes based on somewhat strong hypotheses. Although these hypotheses are based on physiology and biology, they imply necessarily a certain amount of simplification of the real phenomena. Hence the conclusions we draw from these researches should be highlighted in the limit of their hypotheses in order to keep track of the limitations of the models. The results they predict are however very encouraging since they often agree with observations, indicating that the assumptions we used are likely to be relevant to the objects we study. This means that the models we developed may likely account for processes whose influence is strong relatively to others that we chose to overlook.

This framework in mind, we can freely discuss our results. Our work indicates that the tree structures of mammals which carry oxygen, either through the air or blood, tend to be adapted to energy costs accounting for fluids viscous dissipation. It is also interesting to notice that for evolution to select a tree structure that minimizes dissipation, a regulation of the distal (at leaves) fluid flow seems necessary. Interestingly, this conclusion is fully compatible with the physiology of both lung and arterial network. With respect to blood, our results indicate that red blood cells concentration may also be selected to take this dissipation into account. It is therefore likely that dissipation played a role in the selection of the characteristics of these organs. With respect to the tracheobronchial tree, we were able to propose a simple scenario that explains how evolution can effectively affect the bronchial tree geometry during development and thus select a structure that dissipates the least possible. For example, evolution can alter the chemical pathways involved in the growth response of cells to FGF10 flow. Finally, we showed that, in general and more specifically in the case of the tracheobronchial tree, biological variability may affect evolution and alter the optimal strategy. This phenomena may explain the existence of security margins which prevent the appearance of disadvantageous phenotypes.

Another aspect discussed in our work is the connection between the lung and the arterial network through the exchange surface. Our results suggest that the transit time of red blood cells is adapted to exercise regime. In this regime, the oxygen exchange seems finely tuned and our studies indicate that a red blood cell spends the minimal amount of time in the capillary to be fully loaded in oxygen. However, while optimal, such an adjustment mechanically implies that exercise regime is not robust to a perturbation of the system. On the contrary, rest regime is very robust. As for the arterial system, our studies indicate that red blood cells concentration may also be adapted to minimize dissipation, although it is smaller than in large circulation. This raises an exciting question about the role evolution may have played on the phase separation effects, which cause the decrease of red blood cells concentration in small blood vessels and capillaries.

More generally, my research shows that physics can play a key role on the selection of biological systems by evolution. In our work, physics allowed to propose parsimonious scenarios whose mechanisms are well-defined. This demonstrates that modeling work based on the physiology of a biological object, on its function into a metabolism [109] and on relevant physico-chemical processes allows to construct evolutionary scenarios compatible with observations. Last and not least, my work shows the important role played by mathematics as a strong, sometimes almost silent, background for all the studies we made, either theoretical or numerical.

Lexicon

Acinus: this is the part of the lung where exchanges with blood take place. Acini correspond to approximately the six deepest generations of the lung. Oxygen moves into the acinus with air convection up to a point where diffusion becomes predominant. There is an acinus at each leaves of the tracheobronchial tree, for a total of about three hundred thousand acini in the human lung. Their size is about 3 mm and the diameter of the ducts inside the acini is about half a millimeter [107].

Alveolus: they are the unit of the exchange surface, their walls forms the air/blood exchange surface. They are shaped like bubbles and stand on the walls of the acini airways. Their typical diameter is about half a millimeter. There is about five hundreds millions alveoli in a human lung and they represent about 90 % of its volume [107].

Dissipation (viscous): in a purely viscous fluid, it is the energy dissipated as heat by the friction of fluid adjacent layers with different speeds. Dissipation must be counterbalanced to maintain the fluid flow, otherwise it will stop.

Exchange surface: this is the surface that separates blood and alveolar gas in the lung. The exchange surface is located in the acini, at the end of the tracheobronchial tree. It is folded in the lung volume so as to be "space-filling". The exchange surface forms the walls of the alveoli and blood is flowing inside it, its thickness is about a few microns.

Fitness: the fitness of an individual is the number of its offsprings that reach sexual maturity. Natural selection advantages individuals with the largest fitness.

Generation: the lung is (approximately) a dichotomous tree structure, i.e. each bronchus divides into two smaller bronchi that themselves divides in two and so on. The largest bronchus is called the trachea and forms traditionally the generation with the index zero. Starting from the trachea, each bifurcation increments by one the index of the generation. The lung and has about twenty-three generations of branches, i.e. about four millions branches.

Genotype : the genotype is the information coded in a gene.

Hematocrit / red blood cells volume fraction: in this manuscript, I consider that hematocrit is the red blood cells volume fraction in blood. Its value is about 0.4 in most mammals blood, except in the microcirculation. In microcirculation, the vessels have a diameter with the same order of magnitude than the red blood cells, and physical phenomena related to the biphasic nature of blood induce a decrease in hematocrit. Notice that I use the term hematocrit indifferently with the term red blood cells volume fraction, however it is important to know that the traditional hematocrit used in biomedicine is an approximation of the red blood cells volume fraction, because of the way it is measured.

Hydrodynamic resistance: the physical quantity obtained by dividing the pressure drop between the inlet and the outlet of a structure with the fluid flow rate going through this structure. It

represents the constraint (i.e. force per unit area) required to circulate a unit flow rate throughout the structure.

Phenotype: this is a characteristic of an individual associated to a specific genotype. Two individuals with the same genotype can have two different phenotypes if their living environmental conditions are different (which is quasi always the case).

Reynolds number: the Reynolds number measures the relative influence of inertia forces on viscous forces. Larger than 1, the inertial effects (nonlinearities in the fluid) dominate and they dominate all the more than the Reynolds number is larger than 1. Smaller than 1, the viscous effects dominate and if it is small enough the Navier-Stokes equations can be approximated with the Stokes linear equations (for example in the Stokes and Poiseuille regimes). At rest regime, air mechanics in the lung can be approximated with linear regime from the fifth or sixth generation [62].

Shear stress / shear rate: the shear stress is a constraint in a material that is induced by parallel displacement of two successive layers with different velocities. For example, if both hands are rubbed on each other, they are subjected to shear stresses. The shear rate is the velocity variation in the direction perpendicular to the flow.

Stress: force per unit area, for example a pressure (unit: Pascal or Newton per square meter).

Symmetric tree: in a symmetric tree, the daughter branches in a bifurcation or n-furcation are all the same. It implies that all the branches in a same generation are identical.

Tracheobronchial tree: this is the purely convective part of the lung. Within, oxygen is transported with air and there is no exchange with blood. The tracheobronchial tree corresponds to the sixteen or seventeen first generations of the bronchial tree.
Trade-off: If an advantageous configuration of a trait is associated with a disadvantageous configuration for another trait and vice-versa, then evolution tends to select a compromise between these two traits that is called a trade-off.

Trait: this is a characteristics of an organism, such as eye color or size.

Tree: in this document, a tree is a structure starting from a branch, the root, that divides into n smaller branches, each of which divides in turn into n smaller branches and so on for N times. The consecutive structure is then a tree with $N + 1$ generations, and any path between the root and one of the smaller branch meet the same number of divisions. Such a tree has $n^{N+1} - 1$ branches and n^N leaves. Most of the time we use $n = 2$ (dichotomic or dyadic tree).

Tree leaves: the branches in a tree that belongs to the deepest generation of the tree.

Tree reduction factor: the tree reduction factor is the size ratio between daughter branches and their mother branch in a bifurcation or in a n-furcation.

Tree root: the tree root is the first generation of a tree, for the lung that would be the trachea.

Viscosity: viscosity is a physical quantity that measures the resistance of a fluid to flow. For a Newtonian fluid such as air, viscosity is constant, to a non-Newtonian fluid like blood, it depends on the local physical properties of the fluid. Viscosity physical phenomena is related to the friction occurring inside the fluid.

Chapter 10

Résumé en français

10.1 Introduction

10.1.1 Disclaimer

En tant que mathématicien appliqué, je vois les mathématiques plutôt comme un ensemble très riche d'outils qui me permettent d'étudier le monde qui nous entoure, et en ce qui me concerne plus particulièrement, la biologie. Ainsi, mon objectif principal est de donner des réponses à des questions en rapport avec la biologie et pas vraiment d'en étudier les problèmes mathématiques liés, à moins bien sûr que cela n'ait un intérêt pour l'objet étudié lui-même. Mes travaux de recherche visent à comprendre le fonctionnement et l'évolution du système respiratoire et il y a peu de théorèmes dans mes résultats, du moins pas sous leur forme habituelle[1], alors même qu'un certain nombre d'entre eux aurait pu être formulé sous cette forme. Je pense en effet que les usages de présentation des mathématiciens restent cryptiques pour les lecteurs des autres disciplines, et par conséquent j'ai choisi un format qui a plutôt tendance à raconter les choses. Bien entendu, tous ces choix sont personnels et pourraient sans doute être discutés encore et encore, j'espère juste ne froisser personne. Je suis aussi pleinement conscient qu'il y a de nombreuses façons de faire des mathématiques appliquées et que toutes ont leur rôle à jouer.

J'ai souhaité que ce manuscrit soit avant tout personnel et qu'il décrive l'humeur dans laquelle je fais mes travaux de recherche ... du moins les bons jours. Ainsi, j'ai essayé d'utiliser ce support comme un moyen de repousser pour une fois les canons habituels d'écriture des articles scientifiques en utilisant un ton plus léger.

10.1.2 Courage, fuyons !

Quand je pense à l'évolution humaine, je vois souvent un homme s'enfuir devant un prédateur affamé, typiquement un tigre à dents de sabre[2]. J'étais probablement inconsciemment influencé par la bande-dessinée *Rahan* (voir figure 10.1). Dans tous les cas, une même question me taraude à chaque fois : est-ce que cet homme va s'en sortir ? Pour Rahan, je n'ai pas d'inquiétude, vu le nombre d'épisodes de la série. Néanmoins, à l'exception de Rahan, les tigres à dents de sabre avaient probablement l'avantage dans une course poursuite et la question est purement rhétorique, du moins si l'homme est seul. S'il n'est pas seul, en revanche, le tigre se satisfera probablement d'une seule proie : c'est là que la sélection naturelle se met à jouer son rôle.

Bien-entendu, le fait d'échapper au tigre dépend de nombreux facteurs, dont un va nous intéresser plus particulièrement : est-ce que le système respiratoire va être en capacité de fournir suffisamment d'oxygène pour les muscles et les organes ? Si toutes choses sont égales par ailleurs,

[1] En fait, il y en a quelques-uns à trouver dans mon texte !

[2] En fait, les tigres à dents de sabre, ou Smilodon, avaient plutôt une stratégie basée sur la surprise : bondir sur leur proie depuis une cachette, lui porter un coup mortel et attendre [37, 67].

Figure 10.1: Rahan poursuivi par un tigre à dents de sabre (Rahan est une bande-dessinée française, dont le premier épisode a été publié en 1973 aux éditions Hachette).

si votre système respiratoire est plus efficace que celui de Rahan par exemple[3], alors vous aurez de meilleures chances de vous en sortir, ce qui, en fait, augmente globalement votre réussite en tant qu'organisme dans un environnement hostile. On voit donc que l'efficacité du système respiratoire peut être cruciale pour la survie.

Bien-sûr, la sélection dont on parle a lieu en régime d'exercice, et on voit ainsi pourquoi le fait d'avoir un régime métabolique d'exercice peut avoir été sélectionné par l'évolution. Mais on ne peut cependant pas conclure que toute la sélection a eu lieu en ce régime "limite" d'exercice[4]. Bien-entendu, il a pu y avoir d'autres activités moins fatales en régime de repos qui on affecté l'évolution du système respiratoire, comme par exemple d'être capable de soutenir un métabolisme basal. Soutenir ce métabolisme basal de façon optimale permet ensuite de libérer de l'énergie pour d'autres activités fondamentales, comme la reproduction par exemple.

Un aspect important du système respiratoire est que l'oxygène est transporté par des fluides : l'air dans les poumons et le sang dans le réseau sanguin. La circulation de l'air et du sang a un coût énergétique lié à une propriété physique des fluides : la viscosité. La viscosité mesure en fait la friction interne à un fluide. Ce coût énergétique est le cœur de mes travaux, et je pose la question de comment il a pu avoir influencé la sélection du système respiratoire.

10.1.3 Une courte bibliographie

A mon grand regret, je ne suis pas le premier à avoir étudié le rôle de la viscosité sur l'efficacité du transport dans un réseau. Je donne ici une bibliographie résumée, non exhaustive, des travaux que j'ai pu rencontrer au cours de mes recherches.

En 1926, Murray a proposé la première loi qui décrivait le design optimal des vaisseaux sanguins[5], en se basant sur un compromis entre la puissance nécessaire pour faire circuler un fluide dans le vaisseau et la puissance nécessaire à la maintenance du sang. La loi est formulée en régime de Poiseuille dans un vaisseau cylindrique et la configuration optimale correspond à un flux de sang proportionnel au cube du rayon du vaisseau. Le corollaire bien connu est qu'une bifurcation est optimale si la somme des cubes des rayons des branches-filles égale le cube du rayon de la branche-mère [74]. Dans les années soixante-dix, Zamir a étendu la loi de Murray pour tenir compte des angles des bifurcations [114] et il a exprimé la loi de Murray en terme de contraintes de cisaillement aux parois constantes, indépendamment de la taille des vaisseaux [115]. Bien que la loi de Murray soit vérifiée dans la grande circulation sanguine, ce n'est pas le cas pour la microcirculation, ou les contraintes de cisaillement à la paroi décroissent avec la taille des vaisseaux. Plusieurs hypothèses ont été développées pour expliquer cette différence de comportement, par exemple en prenant en compte un coût métabolique lié aux muscles lisses sur la paroi des vaisseaux [98]. En 2005, Alarcón et al [2] ont utilisé des lois semi-empiriques publiées par Pries et al [82] et

[3] Auquel cas vous êtes probablement un athlète de haut niveau et les prochains jeux olympiques sont pour vous.
[4] Voir les conclusions de la partie 8.3 pour un exemple de ces "limites".
[5] En fait, il a développé les travaux de Hess [41].

montré que le comportement des contraintes de cisaillement aux parois dans la microcirculation pouvaient être expliquées par des effets de séparation de phase du sang, lesquelles n'apparaissent que dans les petits vaisseaux. Ces effets impliquent que la viscosité est une fonction non-monotone du rayon : l'effet Fåhræus - Lindvquist [32, 33, 82, 83].

Concernant le poumon, le sujet est plus récent [43, 93], en particulier avec les travaux d'E.R. Weibel [107, 108] et B.J. West [110]. Les liens entre la physique, la géométrie et l'efficacité des poumons ont été étudié par l'équipe de B. Sapoval et E.R. Weibel [25, 28, 29, 30, 57, 62, 63, 90]. Quelques autres groupes ont aussi travaillé sur ce sujet, voir par exemple [46, 51, 52]. Des développements intéressants sur la théorie de la mécanique des fluides dans les poumons ont été réalisés par des mathématiciens et plus particulièrement B. Maury et C. Grandmont [4, 39, 46, 51, 52, 56]. Des études sur la ventilation dans des modèles anatomiques du poumon ont donné lieu à des résultats important sur les liens structure-fonction [42, 48, 55], et en particulier les travaux de l'équipe de M. Tawhai [100, 101, 102, 103].

Ainsi, la formulation initiale du coût par Murray a été utilisée et améliorée régulièrement depuis sa découverte. Cela a donné naissance à des théories plus générales sur le design des réseaux biologiques [7, 8, 36, 111, 112]. Par exemple, West et ses collègues ont proposé un scénario basé sur la dissipation visqueuse des fluides qui vise à expliquer les lois allostériques observées chez les mammifères[6] [111] ou les plantes. D'autres théories, plus controversées, ont aussi vu le jour, comme la théorie du design optimal [7].

10.1.4 Structure du manuscrit

Dans le chapitre 2, je décris les concepts dont on a besoin pour comprendre le problème que j'étudie dans la suite. Le chapitre suivant 3, je montre sous quelles conditions, l'évolution peut sélectionner une structure d'arbre sous l'hypothèse que les coûts visqueux sont ceux qui dominent pour l'évolution. Dans le chapitre 4, je parle du développement des poumons et propose des scénarios pour comprendre comment l'évolution a pu effectivement sélectionner certaines propriétés de la géométrie du poumon. Le développement des structures biologiques est souvent soumis à un bruit, comme le montre notre scénario du chapitre 4, et je propose dans le chapitre 5 d'étudier comment ce bruit a pu affecter la sélection des stratégies optimales par l'évolution, et j'applique les résultats trouvés à l'arbre trachéobronchique. Dans le chapitre 6, j'illustre le fait que ces travaux fondamentaux peuvent avoir des applications pratiques dans le monde médical. Dans ce chapitre, je présente deux applications, la première sur le diagnostique de la bronchopneumopathie obstructive (BPCO), le second sur la kinésithérapie respiratoire. Les chapitres suivants sont dédiés à l'étude de l'efficacité du réseau sanguin pour la dissipation visqueuse. Le chapitre 7 décrit comment des propriétés d'une partie du réseau artériel sanguin, comme sa nature fractale ou sa concentration en globules rouges peuvent être la conséquence d'un coût impliquant la viscosité. Finalement, dans le chapitre 8, nous faisons une étude similaire à celle du chapitre précédent mais pour les capillaires, les plus petits vaisseaux sanguins, où la physique y est différente. Bien que la concentration des globules rouges dans les capillaires est plus petite que dans les gros vaisseaux, elle reste optimale pour le même coût calculé en tenant compte de la nouvelle physique qui affectent les capillaires. Dans ce dernier chapitre, nous parlerons aussi de questions en relation avec la capture de l'oxygène par l'hémoglobine. Le chapitre 9 conclut ce manuscrit.

L'avant-dernier chapitre est un lexique qui décrit quelques un des termes techniques utilisés dans le texte. Il n'est pas vraiment fait pour être lu, mais seulement pour s'y référer si besoin. Le dernier chapitre (celui-ci) est un résumé en français du texte anglais avec une traduction intégrale de l'introduction et de la conclusion.

Tous ces travaux sont basés sur des outils mathématiques et/ou numériques appliqués à la modélisation du système respiratoire. Ces outils s'appuient sur la théorie des équations aux dérivées partielles, de l'optimisation, des systèmes dynamiques, de la dynamique des populations, de l'analyse numérique et du calcul scientifique. Ils proviennent soit de la littérature ou de

[6] Ce sont des lois de puissances surprenantes qui relient des quantités physiologiques à la masse (ou taille) des animaux, par exemple le nombre total de battements de cœur dans une vie, le métabolisme basal, la quantité d'oxygène consommée par seconde, etc.

développements spécifiques pour un problème précis. Ainsi, la plupart des chapitres commence par une courte description du modèle et des outils utilisés. Chacun des chapitres se termine par une description de mes collaborations pour le sujet traité et par la liste des abstracts des articles (publiés, preprints ou en préparation) en lien avec le chapitre.

10.2 Le système respiratoire

Chez les mammifères, l'oxygène est au cœur du métabolisme aérobie des cellules, bien plus performant que le métabolisme anaérobie. Le métabolisme est capable d'utiliser l'oxygène de l'air ambiant grâce à un système de transport et de capture complexe : le système respiratoire.

Parcours de l'oxygène. L'oxygène est capturé par le poumon, organe arborescent d'environ vingt-trois générations. Depuis la bouche, l'oxygène est transporté par l'arbre trachéobronchique qui forme environ les dix-sept premières générations du poumon. Il atteint ensuite les acini qui forment les six dernières générations du poumons et qui contiennent les alvéoles. Les alvéoles sont de petites "bulles" dont les parois sont formées d'un lit capillaire dans lequel le sang s'écoule. L'ensemble de ces lits capillaires forme la surface d'échange alvéolo-capillaire entre l'air et le sang, de l'ordre d'une centaine de mètre-carrés chez l'humain. A cet endroit, l'oxygène traverse la membrane séparant l'air et le sang et se dissout dans le plasma sanguin pour ensuite atteindre les globules rouges. Ces derniers contiennent une grande concentration d'hémoglobine, une molécule qui a une grande affinité avec l'oxygène. La réaction de l'hémoglobine avec l'oxygène implique un gradient de concentration d'oxygène pour la diffusion entre l'alvéole et le plasma et entre le plasma et l'intérieur du globule rouge. Ainsi par diffusion, l'oxygène entre dans le globule rouge et est capturé par l'hémoglobine. Le globule rouge est une cellule formée d'une membrane bilipidique et d'un cytosol principalement constitué d'hémoglobine. Il est hautement déformable et prend une forme de parachute quand il pénètre dans les capillaires. Une fois l'oxygène capturé par les globules rouges, il est emporté avec ces derniers dans le réseau sanguin, lui aussi arborescent. Il traverse d'abord le réseau veineux pulmonaire, puis le cœur et enfin entre dans le réseau artériel systémique qui irrigue les organes. L'oxygène est alors déchargé des globules rouges au niveau des capillaires systémiques par un phénomène inverse de celui de sa capture dans les capillaires pulmonaires. Il traverse ensuite la membrane des cellules et est consommé au niveau des mitochondries pour produire de l'adénosine triphosphate (ATP), molécule qui permet de stocker l'énergie sous forme chimique.

Dans mes travaux, j'ai cherché à comprendre comment les coûts énergétiques liés à la circulation de fluides dans des géométries complexes ont pu modeler certaines caractéristiques du système respiratoire à travers sa sélection par l'évolution. La viscosité des fluides induit en effet une dissipation d'énergie sous forme de chaleur liée au frottement des couches de fluide entre elles. Cette énergie doit être compensée pour maintenir le fluide en écoulement et peut être directement imputée au métabolisme. La quantité d'énergie dissipée est fortement dépendante de la géométrie dans lequel le fluide s'écoule. Mes collaborateurs et moi avons donc étudié les conséquences de ce phénomène physique sur la sélection naturelle de certaines caractéristiques du système respiratoire.

Évolution. L'évolution est la transformation au cours des générations des caractéristiques héritables d'une population. Plusieurs forces agissent de concert sur l'évolution [26]. Nous nous focaliserons plus particulièrement sur les effets de deux de ces forces : la sélection naturelle [21], à l'origine de l'adaptation à l'environnement, et les variations génétiques (typiquement les mutations) [26]. De façon simple, on peut représenter la sélection naturelle comme le système dynamique formé par les organismes et leur environnement dans lequel les ressources sont limitées. Les individus qui ont un avantage dans l'exploitation de leur environnement se reproduisent plus efficacement. En devenant progressivement plus nombreux, ils remplacent petit à petit les individus qui n'ont pas cet avantage. Typiquement, un avantage est acquis par l'intermédiaire d'une variation génétique qui modifie le phénotype de l'individu et de ses descendants. En se focalisant sur un trait biologique (une caractéristique) précis d'un organisme, le degré d'adaptation de ce trait à l'environnement

peut être modélisé sous la forme d'un coût, qui mesure directement ou indirectement une dépense énergétique liée à ce trait (on peut aussi utiliser la *fitness* qui représente le nombre de descendants matures). Prenons un exemple avec deux phénotypes (réalisations) d'un même trait en compétition. Les individus associés au phénotype qui nécessite plus d'énergie passeront plus de temps à chercher de la nourriture pour compenser ce besoin supplémentaire d'énergie, ce qui peut par exemple augmenter leur taux de prédation et diminuer le temps qu'ils allouent à la reproduction. Globalement, ces derniers individus auront moins de descendants que ceux disposant de l'autre phénotype, ce qui implique, compte-tenu de la limitation des ressources dans l'environnement, que leur nombre tendra à diminuer au cours du temps pour finalement atteindre zéro, c'est à dire l'extinction. Ainsi, l'évolution tend à converger vers des phénotypes qui minimisent les coûts (ou maximisent la fitness) [26].

Nous ferons deux hypothèses simplificatrices importantes. D'abord nous supposerons que l'environnement est inchangé depuis suffisamment longtemps pour que le paysage des paramètres que nous explorons ne soit pas affecté par une dynamique autre que celle de l'organisme. Ensuite, nous supposerons que les processus de sélection induits par l'évolution ont convergé, au moins pour les paramètres que nous étudions. Ces hypothèses sous-entendent donc que les organismes que nous pouvons observer aujourd'hui dans la nature sont dans une configuration qui minimisent les coûts sur lesquels ils ont été sélectionnés. Il est donc difficile, voire impossible, de reconstruire ces coûts à partir de données biologiques. Le rôle de la modélisation prend alors tout son sens, car elle permet de mimer les coûts liés à des traits qui n'existent pas ou qui n'existent plus. Il faut cependant choisir soigneusement les hypothèses de travail si on veut étudier la sélection d'un organe car c'est l'organisme dans son ensemble qui est sélectionné et pas l'organe isolé.

Ainsi, une partie du challenge lié à ce type de travaux réside dans le fait de construire une approximation de la fonction de coût qui intègre suffisamment d'informations pour rester pertinente, tout en étant suffisamment minimaliste pour permettre une compréhension des mécanismes sous-jacents.

Approximation des coûts évolutifs. Pour construire l'approximation de ces coûts, on commence par identifier, grâce à la biologie et à la physiologie de l'organe, les traits biologiques qui impliquent potentiellement les plus grands coûts énergétiques associés à l'organe étudié. En général, ces traits sont reliés entre eux par un ou plusieurs paramètres structurels (typiquement géométriques, mécaniques ou chimiques) dont nous chercherons des valeurs optimales. Les relations entre les paramètres et les traits sélectionnés sont déterminées par la modélisation mathématique de l'organe qui fait intervenir un certain nombre de processus physico-chimiques. Les paramètres optimaux détermineront alors les phénotypes optimaux des traits identifiés (la situation de compromis ainsi obtenue est appelée un *trade-off* en écologie évolutive). Les coûts que nous regardons sont construits à partir la physique et de la fonction de l'organe dans le métabolisme. Cette dernière est souvent représentée par une contrainte sur un des traits (d'égalité ou d'inégalité) dans le processus d'optimisation.

Prenons par exemple le poumon des mammifères. L'écoulement de l'air dans la géométrie arborescente de l'arbre trachéobronchique induit une dépense énergétique liée à sa résistance hydrodynamique, c'est le premier trait identifié. La fonction métabolique du poumon est d'apporter l'oxygène au sang par l'intermédiaire de sa surface d'échange. Cette surface d'échange partage le volume du poumon avec l'arbre trachéobronchique. Ainsi si on considère le volume du poumon fixé, plus l'arbre trachéobronchique a un gros volume, moins la surface d'échange et donc la quantité d'oxygène capturée sont grandes. Cela induit un coût énergétique compte-tenu du fait que l'oxygène participe à générer l'énergie du métabolisme. On voit donc apparaître un second trait : le volume de l'arbre trachéobronchique. Les deux traits identifiés ici sont liés entre eux par un paramètre structurel du poumon qui sera le sujet de l'optimisation : la taille des bronches. On peut ainsi montrer que la configuration optimale correspond à un arbre dont les bronches sont de plus en plus petites quand on s'enfonce dans l'arbre, les changements de taille se font au niveau des bifurcations de l'arbre par une homothétie de rapport $\left(\frac{1}{2}\right)^{\frac{1}{3}}$ [57, 63]. Dans la suite, ce rapport sera aussi appelé facteur de réduction de l'arbre.

Le système respiratoire est un système complexe multi-échelle, couvrant une gamme de tailles allant du centimètre (diamètres des grosses bronches ou des gros vaisseaux sanguins), jusqu'à quelques microns (globules rouges, capillaires sanguins), en passant par toutes les échelles intermédiaires. Les processus physico-chimiques qui entrent en jeu dépendent des échelles : la mécanique de l'air et du sang (à haut et bas nombre de Reynolds); la mécanique des tissus; la convection, la diffusion et la chimie de l'oxygène et de l'hémoglobine. Mes travaux, focalisés sur le transport de l'oxygène et sur le rôle de la dissipation des fluides impliqués dans le système respiratoire couvrent ces différentes échelles. Nous nous sommes intéressés aux organes où la dissipation est la plus forte et où elle a donc le plus de chance d'avoir joué un rôle sur leur sélection par l'évolution : l'arbre trachéobronchique, qui conduit l'air ambiant et donc l'oxygène qu'il contient vers la surface d'échange, traité dans la section 10.3; le réseau artériel systémique dans lequel l'oxygène est transporté par le sang jusqu'aux organes, traité dans la section 10.4; et la surface d'échange au niveau de laquelle l'oxygène est capturé par les globules rouges, traité dans la section 10.5.

10.3 L'arbre trachéobronchique

10.3.1 Géométrie arborescente optimale[7].

Les acini forment la surface d'échange air/sang du poumon et sont connectés à l'air ambiant par l'intermédiaire de l'arbre trachéobronchique. La taille de la surface d'échange, une centaine de mètre-carrés, garantit un débit d'oxygène vers le sang compatible avec le métabolisme. Une des fonctions de l'arbre trachéobronchique est de transporter l'air, et donc l'oxygène, depuis le milieu extérieur jusqu'aux acini. En première approximation, l'arbre trachéobronchique est un arbre dyadique enchaînant seize bifurcations successives (dix-sept générations). Faire s'écouler de l'air dans cet arbre implique une dépense énergétique liée à la viscosité de l'air qui dissipe de l'énergie sous forme de chaleur. Cette dissipation doit être compensée pour que le fluide reste en mouvement, on parle de dissipation visqueuse. Cette dissipation dépend fortement des tailles des branches, ce qui pose la question suivante : dans quelle mesure la dissipation a-t-elle joué un rôle sur la sélection de l'arbre trachéobronchique ? Pour donner des éléments de réponse à cette question, nous avons développé un modèle de l'arbre trachéobronchique basé sur une géométrie arborescente formée d'une succession de bifurcations et traversée par un fluide Newtonien. Ses branches sont supposées cylindriques et le volume de l'arbre est borné. Nous avons modélisé la fonction de l'organe sous la forme d'une contrainte du débit total de fluide dans l'arbre. Ensuite, nous avons déterminé la configuration optimale qui minimise la dissipation visqueuse de l'écoulement dans un arbre. Enfin, nous avons comparé à la physiologie de l'organe.

Stabilité de la géométrie arborescente en tant que structure optimale. Nous avons étudié mathématiquement ces processus d'optimisation dans un cadre discret (le nombre de paramètres est fini : un diamètre inconnu par branche) en supposant une circulation de l'air à bas régime (Poiseuille) [23, 65]. Cette étude a montré qu'il fallait contraindre l'air à circuler à travers les feuilles de l'arbre pour obtenir une structure optimale arborescente. Si les pressions aux feuilles sont contraintes (conditions de Neumann pour le fluide, c'est à dire que l'on applique une force par unité de surface au fluide), nos travaux montrent qu'une configuration optimale arborescente serait instable relativement à une perturbation de ces pressions. La structure arborescente est conservée dans la configuration optimale seulement si toutes les pressions des feuilles sont exactement identiques. Si au moins deux pressions diffèrent alors l'arbre optimal est dégénéré : c'est en un simple tube. Si les débits d'air dans les feuilles sont contraintes (conditions de Dirichlet pour le fluide), alors la structure d'arbre est stable relativement à une perturbation de ces débits et la dissipation minimale est identique à celle du cas où les pressions sont contraintes. Grâce à des outils

[7]Ces travaux sont le résultat de collaborations avec N. Meunier (MAP5, Université Paris 5) [65], Y. Privat (LJLL, Université Paris 6) et X. Dubois De La Sablonnière (Supélec) [23].

d'optimisation de forme, nous avons fait une étude numérique de ces phénomènes dans un cadre continu (le nombre de paramètres est infini : l'ensemble de la paroi de l'arbre est une inconnue, nos codes sont développés en Comsol Multiphysics et FreeFem++ [23, 84]. Nos simulations ont montré que ces résultats étaient toujours vrais pour des arbres bi et tridimensionnels de deux générations (bifurcations) traversés par un fluide incompressible en régime laminaire (équations de Stokes et de Navier-Stokes). Ces calculs numériques nous ont ainsi permis de déterminer précisément les géométries bi- et tridimensionnelle optimales d'une bifurcation.

Dans le cas l'arbre trachéobronchique, les contraintes appliquées aux feuilles de l'arbre sont le résultat d'un processus de régulation active complexe mêlant l'action des muscles ventilatoires, la réponse mécanique des tissus et l'action des muscles lisses qui tapissent les parois des petites bronches (le rôle de ces derniers est d'ailleurs mal connu [5, 56]). En pratique, il n'est pas clair si le système est contrôlé par les débits, les pressions ou bien des conditions qui mixeraient les deux. Les résultats détaillés dans le paragraphe précédent appliqués au poumon nous permettent cependant de proposer, dans la limite de nos hypothèses de modélisation, que pour maintenir la structure arborescente du poumon au cours de l'évolution, le système de régulation doit contraindre d'une façon ou d'une autre la quantité d'air qui circule dans les petites bronches. En effet, pour que la structure d'arbre puisse avoir été sélectionnée avec des contraintes de pression aux feuilles de l'arbre, nos résultats indiquent que ces pressions doivent être régulées à l'identique. Or un coût évolutif lié à l'instabilité de cette configuration et à la variabilité des systèmes biologiques - voir section 10.3.3 - apparaît : si des descendants ne sont pas capables de maintenir ces pressions identiques, alors l'évolution de l'arbre trachéobronchique de cette branche d'individus tendrait à sélectionner des géométries de plus en plus tubulaires qui ne pourraient plus à terme irriguer correctement la surface d'échange. Cette branche de descendants serait donc vouée à s'éteindre. A dissipation optimale égale, une configuration optimale stable aura plus de chance d'être sélectionnée qu'une configuration instable car l'évolution y ramènera sans cesse les descendants même s'ils s'en écartent. En revanche, lorsque les débits aux feuilles sont régulés, la configuration optimale est stable, donc la sélection ramènerait tout écart chez les descendants vers l'optimal. De plus, on pourrait imaginer que chez un individu, toute "erreur" sur la géométrie bronchique qui l'écarterait de la configuration optimale pourrait être compensée par une régulation active des débits dans les petites bronches, par exemple par les muscles lisses [5].

Structure de l'arbre optimal. Les modèles que nous avons développés sont plus généraux que ceux basés sur les arbres à bifurcations symétriques [63] car ils ne présupposent pas la forme des bifurcations. Ils permettent de travailler avec un arbre qui irrigue une surface d'échange répartie de façon non homogène dans l'espace. La configuration optimale correspond à un arbre dont les branches ont un volume proportionnel au ratio entre le débit de fluide dans la branche et le débit de fluide total dans l'arbre. Le débit d'air dans une branche sert à irriguer la surface d'échange en aval de la branche, et on peut supposer que ce débit est proportionnel à la surface d'échange à irriguer en aval de cette branche, du moins dans le poumon sain [107]. Compte-tenu du fait que la surface d'échange remplit le volume pulmonaire, sa surface est proportionnelle au volume qu'elle occupe. Ainsi, nos travaux indiquent que la taille de la branche doit être proportionnelle au volume pulmonaire irrigué, ce qui est compatible avec la physiologie [107]. Si on applique des conditions de débit identiques à toutes les feuilles de l'arbre, on retrouve comme configuration optimale pour l'arbre trachéobronchique un arbre à bifurcation symétrique, *space-filling* (dimension fractale de 3), dont les propriétés sont comparables à la physiologie du poumon à partir environ de la cinquième génération et jusqu'à environ la dix-septième.

Tous ces résultats montrent que l'arbre trachéobronchique tend à minimiser le critère de dissipation visqueuse, ce qui indique que ce critère a probablement joué un rôle dans l'évolution de l'arbre trachéobronchique. On observe cependant dans les données [102] un petit écart systématique à l'optimal indiquant que l'arbre trachéobronchique est un petit peu trop gros. Nous proposerons dans les parties qui suivent un scénario pour expliquer cet écart. Les travaux présentés dans cette partie ont été publiés dans [23, 84] et dans [65] où une partie de ces résultats a été étendue au cas d'arbres à bronches déformables.

10.3.2 Développement de l'arbre trachéobronchique[8].

Le scénario que nous proposons dans la partie précédente pour expliquer la géométrie de l'arbre trachéobronchique tient compte de coûts et de contraintes fonctionnelles qui sont liées à la quantité d'oxygène qui est transmise au sang. Nous avons considéré l'organe dans son état adulte sans tenir compte du fait qu'il est passé par une étape développementale. Cette étape peut avoir des conséquences, en particulier sur la géométrie de l'arbre, qui seraient difficilement interprétables en dehors du contexte du développement. Dans cette partie, nous allons donc proposer un scénario pour le développement de l'arbre trachéobronchique s'inspirant de [104]. Le moteur principal de notre scénario est une instabilité physique similaire à l'instabilité de Saffman-Taylor [87]. Nous en déduisons un certain nombre de conséquences sur les propriétés géométriques de l'arbre trachéobronchique. En pratique, ce scénario est général et peut s'appliquer à plusieurs types d'organes branchés comme le rein ou les glandes salivaires.

Modélisation du développement de l'arbre trachéobronchique. La biochimie de développement de l'arbre trachéobronchique est complexe et implique de nombreuses espèces biochimiques. Presque toutes ces espèces jouent un rôle subtil sur la forme, le nombre et l'organisation fine des bronches [14] mais sans vraiment altérer globalement la structure arborescente et auto-évitante de l'arbre trachéobronchique. Grossièrement, seule la protéine FGF10 (FGF = fibroblast growth factor) semble "contenir" l'information de branchement. Le rôle habituel de cette protéine est de provoquer la prolifération cellulaire et donc la croissance des tissus. Des expériences ont montré que les cellules réagissent au flux de FGF10 qu'elles reçoivent et qu'en l'absence de cette protéine l'arbre ne se forme plus [14]. On peut modéliser la distribution de FGF10 dans le poumon en développement par un phénomène de diffusion stationnaire depuis la paroi externe de l'organe où on considère qu'elle est produite jusqu'à la paroi des bronches où elle est consommée. On peut travailler en régime stationnaire car la vitesse de diffusion est beaucoup plus grande que la vitesse de croissance des tissus. La concentration de la protéine FGF10 dans le tissu est donc la solution d'une équation de Laplace avec conditions de Dirichlet aux bords. Les cellules des bronches répondent au gradient local de la concentration en FGF10 (le flux est proportionnel au gradient). Or le gradient est d'autant plus fort que la courbure de la paroi des bronches est forte (effet de pointe) et que la distance à la source de FGF10 est petite. Ainsi, la paroi des bronches est instable : une cellule présente sur une petite excroissance de la paroi reçoit un peu plus de flux de FGF10 que ses voisines et donc prolifère un peu plus rapidement, amplifiant ainsi l'excroissance qui, à terme, prend une forme tubulaire. En grossissant, le tube devient lui aussi sujet à des irrégularités sur son extrémité, ce qui donne naissance à une bifurcation. La taille typique de la bronche à partir de laquelle des irrégularités apparaissent sur son extrémité dépend des propriétés mécaniques de sa paroi, en particulier de sa tension de surface. Compte-tenu des échelles de temps, la croissance du tissu est dominée par les effets visqueux. Le tissu peut donc être vu comme un fluide visqueux dont la masse augmente au fur et à mesure que les cellules prolifèrent dans le tissu. Cette prolifération est elle aussi une fonction du flux de FGF10 local.

Résultats. Nous avons étudié ce modèle en 2D [16, 18] et en 3D [19] par une approche numérique qui s'appuie sur des remaillages et lissages homogènes de surfaces qui se déforment dans l'espace (FreeFem++, GMSH, [3, 99]). Nous avons ainsi montré que la simple diffusion de la protéine FGF10 et son interaction avec la géométrie faisait émerger de façon robuste un arbre dyadique. La statistique des propriétés géométriques des arbres ainsi construits est très proche de celle du poumon. Par exemple, notre modèle prédit une asymétrie moyenne des branchements de l'ordre de 0.8 (rapport entre les tailles de deux bronches issues d'une même bifurcation), cette valeur correspond à celle mesurée dans le poumon [102]. Le scénario de développement des organes branchés que nous proposons permet aussi d'expliquer comment une structure arborescente peut se développer en adoptant une géométrie multi-échelle, comme celle de l'arbre trachéobronchique

[8] Ces travaux sont le résultat de collaborations avec R. Clément (IBDM, Université de Marseille), S. Douady (MSC, Université Paris 7), P. Blanc et V. Sapin (R2D2, CHU Clermont-Ferrand, Université d'Auvergne) [15, 16, 18, 19].

(voir la section précédente). Par exemple, le changement de taille des bronches dans une bifurcation, qui définit le comportement quasi-fractal du poumon, est corrélé à la vitesse de croissance globale de l'organisme et au temps nécessaire pour que l'extrémité d'une bronche se déstabilise. Grâce à ce modèle, on est donc capable de relier des paramètres géométriques du poumon adulte avec des paramètres liés à son développement. Dans notre scénario, nous proposons que le rôle de certaines des autres protéines intervenant dans la morphogenèse des bronches est de contrôler plus finement les caractéristiques des bronches, telles que leur géométrie, en régulant la réponse en croissance des cellules au flux de FGF10 ou encore leur maturation au cours du développement (typiquement leur différentiation).

Parmi toutes les conséquences que ce scénario peut avoir sur la forme adulte du poumon, nous allons nous attacher à deux en particulier : le bruit géométrique et l'asymétrie des bifurcations. Ce processus de développement induit un bruit géométrique, à la fois sur la taille des branches individuelles mais aussi sur le facteur de réduction moyen de l'arbre final. Le bruit individuel a été étudié par l'équipe de Bernard Sapoval (Ecole Polytechnique, laboratoire PMC [28]). De notre côté, nous avons étudié les conséquences d'un bruit sur le facteur de réduction moyen en développant une étude générale du rôle de la variabilité environnementale sur les stratégies optimales sélectionnées par l'évolution, détaillée dans la prochaine partie. Nous avons appliqué cette théorie à un modèle de poumon qui tient compte, sous la forme d'une contrainte géométrique, de l'asymétrie des bronches observée dans les données et conséquence structurelle du scénario de développement de l'arbre trachéobronchique que nous proposons.

10.3.3 Robustesse et sélection naturelle : la théorie du *cliff-edge*.

Même dans un environnement globalement stable, les conditions environnementales rencontrées par deux organismes lors de leur développement ne sont qu'exceptionnellement identiques. Ce phénomène est à l'origine de l'émergence de phénotypes différents pour des individus ayant pourtant les mêmes génotypes. Du point de vue des organismes ces différences peuvent être imprévisibles et donc impliquer un bruit sur le développement de leur génotype en un phénotype. C'est ce caractère imprévisible qui empêche la sélection par l'évolution de processus mécanistiques dédiés qui contreraient un à un les désavantages potentiellement liés à ce type de variabilité environnementale. Nous allons cependant voir que cette variabilité imprévisible peut jouer un rôle en tant que force évolutive et altérer globalement la sélection de stratégies optimales par l'évolution en les rendant plus robustes vis à vis de ce bruit. Nous proposons ensuite l'hypothèse que cette force évolutive a joué un rôle dans la sélection de l'arbre trachéobronchique et qu'elle peut expliquer, au moins partiellement, le petit décalage entre les données et les prédictions du modèle développé dans la partie précédente.

La théorie du cliff-edge[9]**.** La fonction de fitness issue d'un compromis entre plusieurs traits n'a pas, en général, de raison d'avoir des propriétés de symétrie autour de son maximum. Ainsi, un décalage autour du maximum modifie la fitness d'une façon qui dépend de la direction de ce décalage. Dans le cadre d'un génotype associé à une stratégie optimale, toute perturbation aléatoire dans le développement peut potentiellement induire un décalage du phénotype dans la direction la moins favorable. Étant donné qu'on peut lier la fitness à la réussite moyenne des descendants, on voit donc qu'en cas de perturbations répétées et imprévisibles, une meilleure stratégie serait de sélectionner non plus le maximum de la fitness, mais une valeur décalée dans la direction la moins défavorable. L'amplitude du décalage serait alors corrélée à l'amplitude de la perturbation. C'est la théorie du *cliff-edge* (bord de falaise) montrée expérimentalement chez les cochons d'Inde par Mountford en 1968 [73]. Cette théorie n'est toutefois reprise que très rarement dans la littérature et aucun modèle n'a été développé pour mieux comprendre son fonctionnement.

Nous avons donc modélisé le rôle d'un bruit lié à l'environnement sur la sélection naturelle par l'intermédiaire d'une équation de dynamique de population (integro-différentielle, non linéaire).

[9] Ces travaux sont le résultat de collaborations avec E. Svensson (EXEB, Université de Lund, Suède), E. Vercken (INRA Sophia Antipolis), M. Wellenreuther (Department of Biology, Université de Lund, Suède) [105].

Notre modèle mime la sélection naturelle en ressources limitées dans le cas où un génotype s'exprime non plus en un unique phénotype mais en une distribution de phénotypes. Nous avons alors montré que si la sélection naturelle agit sur une fonction de fitness asymétrique autour de l'optimal, l'existence d'un bruit implique que la meilleure stratégie n'est plus celle qui consiste à maximiser la fitness mais celle qui consiste à maximiser la fitness convolée avec le bruit. Ces résultats ont été démontrés dans [59] et appliqués à deux exemples issus du monde biologique [105] : la taille de portée chez le cochon d'Inde à partir des données historiques de Mountford, et la taille du patch sur l'aile de la demoiselle *C. Splendens* (expériences et résultats originaux). En utilisant une approche par méthodes inverses, on peut prédire, à partir de ce modèle et des mesures de la littérature, la "quantité" de variabilité subie par le système biologique que l'on étudie.

Application à l'arbre trachéobronchique[10]. Le modèle d'arbre trachéobronchique développé plus haut, section 10.3.1, a été modifié pour tenir compte de l'asymétrie des bifurcations [60]. Il met en opposition le volume de l'arbre trachéobronchique, qui doit être le plus petit possible pour maximiser l'espace de la surface d'échange entre l'air et le sang, et la dissipation qui est d'autant plus grande que le volume de l'arbre est petit. La géométrie optimale s'exprime par une diminution de la taille des bronches (facteur de réduction) selon un ratio $1/(1+a)^{\frac{1}{3}}$ avec a le rapport de taille entre les deux branches filles issues d'une bifurcation ($a = 1$ dans le cas de bifurcations symétriques, les mesures donnent $a \sim 0.8$ pour le poumon).

La fonction de fitness obtenue est asymétrique autour de la géométrie optimale et chute plus vite quand le volume de l'arbre trachéobronchique diminue. En appliquant le modèle de cliff-edge que nous avons développé, et en supposant que tout le décalage que nous observons entre le maximum de la fitness et les données est induit par le phénomène de cliff-edge, nous avons pu déterminer une variance pour le bruit environnemental et construire une prédiction de la distribution du trait "géométrie du poumon" dans la population. Cette distribution n'est compatible avec la physiologie que pour le cas asymétrique, ce qui montre que cette contrainte, probablement une conséquence du développement du poumon (voir section 10.3.2), joue un rôle important sur la fonction pulmonaire [28, 60]. Nous avons pu montrer que l'existence d'un bruit environnemental affectant la géométrie du poumon implique forcément qu'une proportion non négligeable des individus dispose d'un poumon non optimal pour la fitness que nous avons définie. Nous avons mis ce résultat en parallèle à la prévalence importante dans nos populations des maladies pulmonaires chroniques telles que l'asthme [60].

10.3.4 Applications médicales

Les modèles de l'arbre trachéobronchique que nous avons développés et les résultats que nous avons pu en tirer ont inspiré des travaux à orientation plus médicale. Ces travaux visent à intégrer de nouveaux aspects liés à la biophysique du poumon dans la compréhension des pathologies pulmonaire, de leurs diagnostiques et de leurs traitements.

Rôle du facteur de réduction du calibre des bronches dans le remodelage bronchique pathologique[11].

Nous avons voulu comprendre dans quelle mesure les paramètres géométriques que nous avons définis pour les modèles précédents, et en particulier le facteur de réduction, jouaient un rôle dans les pathologies pulmonaires chroniques telles que la broncho-pneumopathie chronique obstructive (BPCO) ou l'asthme. Ces pathologies semblent liées à des défauts structurels de la géométrie du poumon (permanents et/ou passagers) et devraient donc être plus fréquents chez des individus dont la géométrie est "non optimale" au sens où nous l'avons défini dans la section précédente.

[10] Ces travaux sont le résultat d'une collaboration avec P. Bokov (MSC, Université Paris 7 / Assistance Publique - Hôpitaux de Paris) [60]

[11] Ces travaux sont le résultat de collaborations avec P. Bokov (MSC, Université Paris 7 / Assistance Publique - Hôpitaux de Paris), C. Delclaux, B. Mahut (Service de Physiologie, Hôpital Européen Georges Pompidou, Université Paris 5) [11, 12]

Nous avons développé une formule semi-empirique qui permet d'estimer la résistance hydrodynamique du poumon de patients en fonction de la taille de leur trachée et d'une estimation de leur facteur de réduction des bronches qui tient compte de l'asymétrie des bifurcations et des effets inertiels de l'air dans les premières générations de bronches. Cette formule s'appuie sur des simulations numériques et a été validée grâce à des mesures chez des patients développées spécifiquement pour ces travaux (taille de la trachée, estimation facteur de réduction des bronches à partir de scanners pulmonaires et résistance pulmonaire par pléthysmographie). Les calculs que nous avons effectués sont des simulations numériques des équations de Navier-Stokes stationnaires (3D) dans des géométries arborescentes de cinq générations. Dans ces simulations, nous avons fait varier le nombre de Reynolds, qui mesure le rôle de l'inertie, pour mimer des sous-arbres à différentes profondeurs du poumon. Nous avons ensuite assemblé ces sous-arbres pour calculer une résistance hydrodynamique globale [11].

Les maladies impliquant un remodelage des bronches, typiquement une diminution de leur section (BPCO, asthme, etc.), vont de pair avec une augmentation de la résistance des voies aériennes périphériques (profondes). Fréquemment, les maladies pulmonaires chroniques comme la BPCO ou l'asthme induisent un remodelage des bronches qui se traduit par une diminution de leurs sections. La formule semi-empirique que nous avons développée et les données récoltées sur des patients atteints de BPCO indiquent que le remodelage lié à la BPCO tend à réduire le facteur de réduction des bronches. Cette diminution implique une augmentation relative plus grande de la résistance pulmonaire périphérique (bronches profondes), ce qui est compatible avec les observations [10, 11, 12].

Modélisation de la kinésithérapie respiratoire[12].

La kinésithérapie respiratoire. Les sécrétions pulmonaires (ou mucus pulmonaire) capturent les polluants extérieurs, qu'ils soient chimiques ou biologiques, et le mouvement naturel des sécrétions vers la partie proximale du poumon (trachée, grosses bronches) évacue ces polluants hors du poumon. Le mouvement des sécrétions est du à deux principaux mécanismes : le battement de cils ancrés dans des cellules de l'épithélium et la toux. Cependant ces mécanismes ne sont pas matures chez les enfants et peuvent être altérés par l'âge ou des pathologies comme la mucoviscidose, la bronchiolite, l'asthme, la broncho-pneumopathie chronique obstructive (BPCO), etc. La stagnation du mucus dans les poumons augmente les risques d'infection ou d'obstruction des bronches. La kinésithérapie respiratoire est alors utilisée pour aider à l'expectoration de ces sécrétions. S'appuyant sur des manipulations au niveau de la paroi du thorax, la kinésithérapie respiratoire est une discipline qui, étonnamment, se base sur des connaissances majoritairement empiriques. Les manipulations sont efficaces mais les mécanismes internes qui entrent en jeu restent soit inconnus soit non prouvés scientifiquement. De nombreuses techniques existent, leur définition et l'autorisation de les utiliser ou pas sont décidées pays par pays lors de conférences de consensus. Ainsi, les manipulations autorisées peuvent être différentes selon les pays, conséquence directe de la difficulté à comparer leurs efficacités [53]. Cette situation a mené aujourd'hui à l'émergence de controverses non seulement sur les techniques [80] mais aussi sur la kinésithérapie respiratoire elle-même [6]. Ainsi, la kinésithérapie respiratoire a désormais besoin d'être soutenue par un cadre scientifique solide.

Modélisation. Nous avons donc intégré à notre modèle d'arbre trachéobronchique le comportement des sécrétions bronchiques. Nous nous sommes placés dans un cadre simplifié où, dans chaque bronche, l'écoulement de l'air est complètement développé et où les sécrétions recouvrent la paroi de façon axi-symétrique et homogène le long de la bronche. Les sécrétions sont modélisées par un fluide à seuil qui ne commence à s'écouler que si les contraintes de cisaillement internes sont suffisamment fortes (fluide de Bingham). Ainsi, à basse contraintes, les sécrétions se comportent comme un solide, et au-delà d'une contrainte seuil, elle s'écoulent comme un fluide visqueux.

[12]Ces travaux sont le résultat de collaborations avec C. Fausser (CHU Bicêtre), P. Flaud (MSC, Université Paris 7), J. Merckx (MSC, Université Paris 7 / retraité de l'hôpital Necker), D. Pelca (réseau ARB Île de France) et la startup RespInnovation (Sophia Antipolis) [61, 64].

Dans les bronches, pendant la toux ou les sessions de kinésithérapie, les contraintes agissant sur les sécrétions proviennent des flux d'air induits. Nous avons développé successivement deux modèles de poumon à bifurcations symétriques : le premier avec des bronches rigides [61], et le deuxième avec des bronches déformables [64] (quasi-statique à partir des données de [1, 50]). Le modèle bi-fluides et le comportement des bronches conduisent à la résolution d'une équation différentielle non linéaire par bronche. En pratique, étant donné que l'arbre est à bifurcations symétriques, cela correspond à vingt-trois équations différentielles, une par génération, qui sont couplées entre elles par la structure d'arbre. Nous avons étudié numériquement comment la structure d'arbre interagit avec l'effet seuil, non linéaire, des sécrétions.

Résultats. Dans le cas d'un arbre à bronches rigides, nous avons observé une distribution asymptotique en temps du mucus qui suit une loi d'échelle corrélée à celle de l'arbre trachéobronchique. De manière générale, nous avons mis en évidence le fait que les écoulements à bas débit avaient peu de chance de mettre le mucus en mouvement et ce même si le poumon est à bas volume, avec des bronches comprimées. Enfin, notre modèle indique que l'application de pressions oscillantes à hautes fréquences ($\sim 20\ Hz$) est efficace pour déplacer les sécrétions, et plus particulièrement s'il est fait à volume de ventilation normale (cadre d'un contrat avec la société RespInnovation[13]).

10.4 Le réseau artériel[14].

Réseau artériel. Une fois capturé par les globules rouges, l'oxygène est transporté par le sang dans le réseau veineux pulmonaire, traverse le cœur et rejoint les différents organes en empruntant une structure arborescente formée de vaisseaux sanguins dont le diamètre diminue régulièrement avec les générations : le réseau artériel systémique. Du point de vue de son comportement mécanique (sa rhéologie), le sang est principalement constitué de plasma, un fluide Newtonien un peu plus visqueux que l'eau, et de globules rouges. On dit que le sang est rhéo-fluidifiant : quand les forces de cisaillement internes au fluide sont faibles, les globules rouges forment des structures complexes (rouleaux, assemblages de rouleaux) qui augmentent la viscosité du sang; quand ces forces sont grandes alors ces structures se disloquent (globules rouges isolés) et la viscosité du sang est réduite. La proportion physiologique des globules rouges dans le sang varie peu chez la plupart des mammifères, et est en général de l'ordre de 0.4 [107]. Compte-tenu du fait que la dynamique des globules rouges est à l'origine des propriétés non-Newtoniennes du sang, cette proportion joue un rôle important sur la viscosité du sang et donc sur la dissipation qu'il génère lors de sa circulation. Plus la concentration des globules rouges est grande plus la capacité du sang à transporter l'oxygène sera grande, les globules rouges étant les principaux vecteurs de l'oxygène. La fraction volumique en globules rouges dans le sang est appelée l'hématocrite.

Modélisation. La difficulté provient du couplage entre une géométrie complexe (structure arborescente multi-échelle déformable) et un fluide complexe (non-Newtonien). Nous allons donc travailler avec un modèle géométrique relativement simple : un arbre dichotomique rigide à bifurcations symétriques. Nous supposons que cet arbre fournit en oxygène un organe qui se situe à son aval, il transporte donc l'oxygène depuis une source (la racine de l'arbre) jusqu'au réseau capillaire de l'organe. Ainsi la taille des feuilles de l'arbre est fixée à celle des gros capillaires (lesquels ne sont pas inclus dans le modèle). Cette dernière hypothèse implique le nombre de générations de l'arbre n'est pas fixé a priori. Comme on néglige les effets fluides non linéaires, la racine de l'arbre correspond à un vaisseau de la sixième génération environ. Ce type de géométrie "minimale" forme une première approximation raisonnable car elle contient les propriétés structurelles importantes pour le réseau artériel.

Pour remplir la fonction de transport de l'oxygène sur laquelle nous travaillons, le réseau doit être capable de fournir une quantité d'oxygène adaptée aux besoins de l'organe qu'il irrigue en

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aval. On peut donc définir une contrainte pour notre futur problème d'optimisation qui est le débit d'oxygène fourni par ce réseau. Le coût énergétique total du fonctionnement de l'arbre artériel est la somme de la dissipation visqueuse, liée à la circulation du sang dans le réseau, et de la maintenance des globules rouges (réparation, renouvellement). Les deux traits associés à ces dépenses énergétiques élevées sont la résistance hydrodynamique et le volume de sang (qui correspond en fait au volume du réseau). Ces deux traits sont liés par deux paramètres : le facteur de réduction des branches aux bifurcations, qui fixe les diamètres des vaisseaux, et la fraction volumique en globules rouges. Le comportement de ces deux traits permet d'envisager l'existence de compromis sur ces deux paramètres.
Pour une concentration de globules rouges donnée : si les diamètres des vaisseaux sont grands, alors la dissipation visqueuse est réduite mais le volume du sang est grand et donc le coût lié à la maintenance des globules rouges est *grand*. Si les diamètres des vaisseaux sont petits, alors la dissipation visqueuse est *grande* et le coût de maintenance est petit.
Pour des diamètres de vaisseaux donnés : si la concentration en globules rouges est faible, alors le sang doit circuler plus vite pour fournir le débit en oxygène nécessaire à l'organe, ce qui induit une plus *grande* dissipation, en revanche le coût de maintenance est faible. Si la concentration en globules rouges est forte, alors la viscosité du sang est forte et donc la dissipation est potentiellement *grande*; de même le coût de maintenance est *grand*.

Résultats. La modélisation du réseau artériel que nous proposons mène donc à la construction d'un coût énergétique lié au fonctionnement du réseau artériel [69]. Pour savoir si ce coût a potentiellement joué un rôle sur la sélection par l'évolution des propriétés du réseau, nous avons cherché la configuration des paramètres qui minimise ce coût et nous l'avons comparée à la physiologie. Compte-tenu des hypothèses, ce problème est un problème d'optimisation non-linéaire sous contrainte d'une application régulière par morceaux (des discontinuités apparaissent car le nombre de générations dépend du paramètre géométrique et crée des sauts du coût). Nous avons choisi une approche numérique pour traiter ce problème. Le réseau optimal prédit par le modèle est proche de la physiologie avec un hématocrite de 0.43 et un facteur de réduction de la taille des vaisseaux à chaque bifurcation de l'ordre de 0.79. Comme pour l'arbre trachéobronchique, ces résultats indiquent que ce coût, et donc la dissipation liée l'écoulement du sang dans le réseau, ont probablement joué un rôle dans sa sélection. Pour soutenir cette hypothèse, nous avons mis en relief les prédictions du modèle avec les propriétés du système cardiovasculaire des populations d'altitude (Andes et Tibet). Le coût construit dans ce modèle nous a aussi permis de mimer les conséquences énergétiques (donc la surcharge du coeur) liées au dopage, aux pathologies liées à l'hypoxie (manque d'oxygène dans le sang) ou induisant une polyglobulie (augmentation de la proportion de globules rouges dans le sang) [71].

Enfin, d'un point de vue plus physique, ces travaux nous ont aussi permis de mettre en évidence que le cisaillement interne à un fluide dans un arbre suit une loi d'échelle corrélée à celle de l'arbre. La géométrie optimale du réseau artériel que nous prédisons avec le modèle développé dans cette partie est une conséquence de ce phénomène.

10.5 La surface d'échange air/sang [15].

L'oxygène au niveau de la surface d'échange. L'oxygène est transporté avec l'air par convection jusqu'à la seizième ou dix-septième génération et entre ensuite dans l'acinus où la diffusion commence à représenter un moteur non négligeable du déplacement de l'oxygène. La position exacte dans l'acinus où la diffusion devient prédominante sur la convection dépend du régime ventilatoire. La diffusion de l'oxygène dans l'acinus a été étudiée par l'équipe de Bernard Sapoval (Laboratoire PMC, Ecole Polytechnique), par exemple dans les thèses de M. Felici [25] et A. Foucquier [31]. Une fois arrivé dans les alvéoles, l'oxygène du gaz alvéolaire se dissout dans

[15] Ces travaux sont le résultat de collaborations avec P. Dantan (MSC, Université Paris 7), P. Flaud (MSC, Université Paris 7), B. Moreau (MSC, Université Paris 7), H. Mbyas Saroukou (LJAD, Université de Nice) [58, 69, 70, 72].

la membrane alvéolo-capillaire (épaisseur inférieure à un micron) et diffuse vers le sang, dans des petits vaisseaux appelés les capillaires dont les diamètres sont de l'ordre de dix microns et la longueur de l'ordre du millimètre. La structure des capillaires pulmonaires est complexe, ils sont très interconnectés entre eux et forment une structure bidimensionnelle appelée lit capillaire. L'oxygène diffuse ensuite vers les globules rouges, puis est fixé par l'hémoglobine. A mesure que la taille des vaisseaux sanguins diminuent, des phénomènes physiques liés au caractère diphasique du sang, comme par exemple l'effet Fåhræus [71] ou encore la présence de la protéine glycocalyx sur la paroi des capillaires [92], impliquent une diminution de l'hématocrite qui peut descendre jusqu'à 0.1 dans les plus petits capillaires [69]. A partir de tous ces phénomènes, nous avons développé un modèle pour améliorer notre compréhension de ce système et de sa sélection. Nous avons donc étudié le rôle de la fraction volumique en globules rouges dans les capillaires sur l'efficacité énergétique du transport de l'oxygène.

Modélisation. Nous avons construit un modèle de ce système qui agrège des sous-modèles des objets suivants : l'alvéole, la membrane alveolo-capillaire, le capillaire, le globule rouge et l'hémoglobine. Nous avons utilisé une structure cylindrique axi-symétrique pour modéliser l'environnement rencontré par le globule rouge quand il traverse le lit capillaire. Cette structure cylindrique ne représente pas exactement un vaisseau mais plutôt un chemin "type". Par abus de langage et pour simplifier la terminologie, nous continuerons dans la suite à parler de "capillaire" pour nommer ce chemin type cylindrique. L'alvéole et la membrane alvéolo-capillaire sont intégrées au modèle grâce à une condition au bord sur la paroi du capillaire.

Les globules rouges au repos ont une forme de disque creusé en leur centre de chaque côté, ils font environ huit microns de diamètre et deux ou trois microns d'épaisseur, ils sont très déformables. Comme les capillaires sont des vaisseaux dont le diamètre moyen est de l'ordre de celui des globules rouges, ceux-ci se déforment en y entrant et prennent une forme de parachute. Pour pouvoir modéliser correctement les échanges, il a fallu travailler avec des géométries réalistes des globules rouges. Nous avons donc mis en place une méthode numérique permettant de calculer la déformation d'un train de globules rouges périodique dans un capillaire : la méthode de caméra (2D, 2D-axi, 3D) [58, 70]. Cette méthode est une méthode d'interaction fluide-structure. Elle est basée sur une approche de domaine fictif couplée avec une écriture co-rotationnelle des équations de la mécanique [88]. Cette méthode se justifie mathématiquement par les travaux de Galdi et Song [34, 35, 95] qui montrent que le profil des vitesses sur la section d'un tube semi-infini converge exponentiellement vite le long de l'axe du tube.

Les réactions de l'hémoglobine avec l'oxygène sont calculées dans un deuxième temps. Elles sont modélisées à l'aide d'un modèle non linéaire de cinétique chimique issu de la littérature [20]. Ce modèle comporte dix espèces chimiques différentes et prédit bien les comportements globaux de l'hémoglobine, tels que la courbe de saturation de l'hémoglobine en fonction de la pression partielle en oxygène dans le sang.

Ce modèle a été étudié numériquement avec une approche par éléments finis (toolbox Comsol Multiphysics) [70]. Les équations d'interaction fluide-structure sont résolues par une méthode ALE, de façon implicite (méthode de Newton). La partie domaine fictif est traitée par une méthode de pénalisation.

Résultats. Nous avons montré que l'énergie stockée dans la déformation de la membrane des globules rouges était négligeable par rapport à l'énergie dissipée par le plasma dans les capillaires. A débit d'oxygène à travers le capillaire donné, l'énergie dissipée par le plasma décroît [72] avec la concentration en globules rouges, en revanche la maintenance liées aux globules rouges croît avec leur concentration. Le bilan nous permet donc de calculer, comme dans la partie précédente, une valeur optimale de la fraction volumique en globules rouges (hématocrite), toujours en contraignant le débit d'oxygène qui sort des capillaires. Ainsi, en prenant par exemple des capillaires d'un diamètre de huit microns, la valeur de l'hématocrite optimale calculée est de l'ordre de 0.26. Cette valeur est compatible avec les données physiologiques [69, 72]. Nos résultats indiquent donc que l'hématocrite dans les capillaires tend à minimiser le coût que nous proposons. La diminution de l'hématocrite dans les capillaires relativement au reste du réseau sanguin est donc bénéfique au

métabolisme en ce sens qu'elle compense la forte dissipation visqueuse dans les capillaires due à leurs petits diamètres. En extrapolant un peu, on peut imaginer que l'évolution ait pu favoriser les effets purement physiques qui réduisent la concentration en globules rouges dans les capillaires, comme l'effet Fåhræus , voire les amplifier en développant des mécanismes spécifiques comme de paver la paroi des capillaires avec des macromolécules de glycocalyx [81, 92].

Du point de vue de la capture de l'oxygène, un globule rouge reste environ une seconde dans le capillaire en régime de repos et une demi-seconde en régime d'exercice. Notre modèle prédit qu'il est saturé en oxygène en une demi-seconde environ. Dans la limite des hypothèses de notre modèle, on voit ainsi qu'en régime de repos, le système apparait robuste. Il est donc capable de compenser des phénomènes qui pourraient ralentir la capture de l'oxygène par le globule rouge, tels que l'épaississement de la membrane alvéolo-capillaire (oedème pulmonaire). En revanche, le régime d'exercice n'est pas robuste car le globule rouge est dans le capillaire juste le temps suffisant pour être saturé. Ainsi, un dysfonctionnement du système d'échange peut plus facilement être diagnostiqué en régime d'exercice.

10.6 Conclusion

Tous les résultats que nous présentons dans ces travaux sont issus de processus de modélisation dans lesquels des hypothèses fortes ont été faites. Ces hypothèses s'appuient sur la physiologie et la biologie des objets étudiés, cependant elles impliquent forcément une simplification des processus impliqués. Ainsi les conclusions que nous tirons de ces recherches doivent être mises en relief avec ces hypothèses pour ne pas perdre de vue les limitations des modèles utilisés. Les résultats obtenus sont cependant très encourageants étant donné leur compatibilité avec les observations, ce qui indique que les hypothèses que nous avons retenues sont probablement pertinentes avec les objets que nous étudions et que les modèles développés tiennent compte de processus dont l'influence est forte relativement à d'autres que nous avons pu négliger.

Une fois ce cadre bien posé, nous pouvons discuter de l'interprétation de nos résultats. Nos travaux indiquent que les structures arborescentes des mammifères qui transportent l'oxygène, que ce soit par l'intermédiaire de l'air ou du sang, tendent à être adaptées aux coûts énergétiques liés à la dissipation visqueuse de ces fluides. Il est aussi intéressant de voir que pour que l'évolution puisse sélectionner une structure arborescente minimisant la dissipation, une régulation des débits de fluide aux feuilles de l'arbre semble nécessaire, ce qui est compatible avec la physiologie du poumon et du réseau sanguin. Dans le cas du sang, nos résultats indiquent que la concentration des globules rouges pourrait aussi être sélectionnée de façon à tenir compte de cette dissipation. Il est donc probable que la dissipation a joué un rôle sur la sélection des caractéristiques de ces organes. Concernant l'arbre trachéobronchique, nous avons même pu proposer un scénario simple pour expliquer comment l'évolution peut agir sur l'arbre bronchique et sélectionner une structure qui dissipe le moins possible, par exemple en altérant la réponse en croissance des cellules au flux de FGF10. Enfin, nous avons montré que, de manière générale et dans le cas de l'arbre trachéobronchique en particulier, la variabilité biologique peut jouer un rôle sur la stratégie optimale et ainsi expliquer l'existence d'une marge de sécurité qui permet d'éviter l'apparition de phénotypes trop défavorisés.

Un autre aspect que nous avons abordé est la connexion entre le réseau bronchique et le réseau artériel pulmonaire à travers la surface d'échange. Nos résultats suggèrent que la durée de transit des globules rouges est adaptée au régime d'exercice. Ainsi, dans ce régime, les échanges d'oxygène semblent finement ajustés entre le transport aérien de l'oxygène et le transport sanguin. Cet ajustement implique cependant une perte de robustesse du régime d'exercice en cas de perturbation du système, qui disparaît en régime de repos. De la même façon que dans le réseau artériel, notre modélisation indique que la concentration en globules rouges dans les capillaires, plus faible que dans le reste du réseau, est elle aussi probablement adaptée pour minimiser la dissipation dans les capillaires, qui correspond à la partie du réseau sanguin où la dissipation est la plus forte.

D'une manière plus générale, nos travaux montrent le rôle fondamental que peuvent jouer les phénomènes physiques sur la sélection d'un système biologique par l'évolution. Dans notre cas,

la physique a permis de proposer des scénarios parcimonieux avec des mécanismes bien identifiés. On voit ainsi que des travaux de modélisation s'appuyant sur la physiologie de l'objet biologique, sur sa fonction dans le métabolisme qui l'abrite [109] et sur les phénomènes physico-chimiques pertinents permettent de construire des scénarios évolutifs compatibles avec les observations.

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Viscosity: an architect for the respiratory system?

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The mammals respiratory system characteristics have been selected because they bring benefits other characteristics do not. At first approximation, such benefices can be estimated through the minimization of energetic costs relatively to one or several of these characteristics. The cost is the consequence of a complex interaction between many phenomena, amongst which physiology, organ development, its inner physics and chemistry, and its surrounding environment. My work aims at building idealized cost functions which, I hypothesized, represent approximations of the real cost optimized by evolution. To build and study these cost functions, I use mathematical modeling processes often based on dedicated mathematical and numerical tools. The costs we propose try to retain only the core phenomena involved in the organ functioning. Then I compare the model predictions with physiology and discuss its validity. I applied this approach to different organs of the respiratory system where the role of viscous dissipation of fluids on the selection of their characteristics may have been the strongest.

The cost function we built for the tracheobronchial tree is based on the trade-off between lung's hydrodynamic resistance and the size of the lung's exchange surface. We showed that a tree structure associated to such a cost is stable for a dynamic process such as evolution only if the air flows in the bottom of the tree are regulated. We proposed an original and parsimonious model for tracheobronchial tree development based on a physical instability. The predictions of this model are in agreement with most of the experiments in the literature. We were able to relate the geometrical parameters of the adult lungs with parameters of our development model. We showed that biological noise during lung's development may have influenced the selection of the geometry of the tracheobronchial tree by shifting its multi-scaled geometry to branches slightly wider than the theoretical optimal and by implying asymmetric branching. The role of biological noise on tracheobronchial tree selection is an archetypal example of a more general framework we developed about the role of biological noise on evolution. Cliff-edge theory states that biological noise can be viewed as an evolutionary mechanism. We proposed and validated a general population dynamics model that includes cliff-edge effects and explains its mechanisms.

Our models and results for the tracheobronchial tree were also used in the frame of two medical applications. The first, based on patients data, aimed at testing whether variations at patient level of the multi-scale geometry may be correlated with chronic obstructive pulmonary disease (COPD). The second medical application aimed at understanding the underlying biophysics involved in chest physiotherapy and at arising a scientific background to a discipline that is, as of today, mostly empirical.

Another important organ involved in the respiratory system that uses a fluid to transport oxygen is blood network, and more specifically arterial network, where most of the system pressure drop occurs. Arterial system couples a multi-scaled tree structure with a non-Newtonian rheofluidifying fluid (blood), submitted to phase separation effects in small vessels (Fåhræus effect). We proposed that both the multi-scale property of arterial network geometry and the red blood cells fraction in blood (hematocrit) may have been selected through a trade-off inspired from Murray's original optimization principle. The cost we propose is based on fluid dissipation, metabolic energetic cost of blood and a given total oxygen flow in the tree. We showed that the dissipation is mostly driven by branches mean shear rates which checks a scaling law related to that of the tree. The multi-scaled geometry of arterial network and blood hematocrit are close to the minimal configuration for the cost we propose, thus indicating it may have played a role on the selection of blood arterial network properties.

In capillaries, the red blood cells fraction in blood is smaller than in the large circulation because of a phase separation effects on plasma and red blood cells. Thus, we modeled by numerical means the flow and deformation of a periodic train of red blood cells in a capillary using a dedicated numerical method - the camera method. Using the same cost function than for the arterial network, we predicted that the typical concentration of red blood cells in the capillaries also optimized the same cost in capillaries. With our numerical model, we also studied the oxygen transfer through the alveolo-capillary membrane and its capture by the red blood cells in the pulmonary capillaries.

My work brought out scenarios that explain how viscous dissipation of biological fluids may have played a role on the selection of some mammals respiratory system characteristics, and most particularly of its geometries. These scenarios are however based on simplification hypotheses which must be accounted for when confronted with the real objects. Nevertheless, the predictions made by the different models studied are consistent with physiology, which indicates that the models probably capture main behaviors. My research also highlights that the inherent fluctuations arising from organ's development may affect the adult organ function and consequently the organ selection. Finally, some of the models and concepts developed in my work expanded into medical applications.