Préparée à l'Institut Curie

THÈSE DE DOCTORAT

DE L'UNIVERSITÉ PSL

# From mechanistic modelling of cancer to clinical interpretation and impact evaluation


Soutenue par

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**Complexité du Vivant**

Spécialité

**Génomique**

Composition du jury :

| | |
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# Abstract

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**Key-words**:

# Résumé

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**Mots-clés**:

# Acknowledgements

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# Table of contents

# List of Tables

# List of Figures

# Part I

# Cells and their models

Chapter 1

# Scientific modeling: abstract the complexity

*"Ce qui est simple est toujours faux. Ce qui ne l'est pas est inutilisable."*
*Paul Valéry (Mauvaises pensées et autres, 1942)*

The notion of modeling is embedded in science, to the point that it has sometimes been used to define the very nature of scientific research. What is called a model can, however, correspond to very different realities which need to be defined before addressing the object of this thesis which will consist, if one wants to be mischievous, in analyzing models with other models. This semantic elucidation is all the more necessary as this thesis is interdisciplinary, suspended between systems biology and biostatistics. In order to convince the reader of the need for such a preamble, he is invited to ask a statistician and a systems biologist the question how they would define what a model is.

## 1.1 What is a model?

### 1.1.1 In your own words

A model is first of all an ambiguous object and a polysemous word. It therefore seems necessary to start with a semantic study. Among the many meanings and synonymous proposed by the dictionary (Figure 1.2), while

Figure 1.1: **A scientist and his model.** Joseph Wright of Derby, *A Philosopher Giving a Lecture at the Orrery (in which a lamp is put in place of the sun)*, c. 1763-65, oil on canvas, Derby Museums and Art Gallery

some definitions are more related to art, several find echoes in scientific practice. It is sometimes a question of the physical representation of an object, often on a reduced scale as in Figure 1.1, and sometimes of a theoretical description intended to facilitate the understanding of the way in which a system works [Collins, 2020]. It is even sometimes an ideal to be reached and therefore an ambitious prospect for an introduction.

The narrower perspective of the scientist does not reduce the completeness of the dictionary's description to an unambiguous object [Bailer-Jones, 2002]. In an attempt to approach these mult-faceted objects that are the models, Daniela Bailer-Jones interviewed different scientists and asked them the same question: what is a model? Across the different profiles and fields of study, the answers vary but some patterns begin to emerge (Figure 1.3). A model must capture the essence of the phenomenon being studied. Because it eludes, voluntarily or not, many details or complexity, it is by nature a simplification of the phenomenon. These limitations may restrict its validity to certain cases or suspend it to the fulfilment of some hypotheses. They are not necessarily predictive, but they must be able to generate new hypotheses, be tested and possibly questioned. Finally, and fundamen-

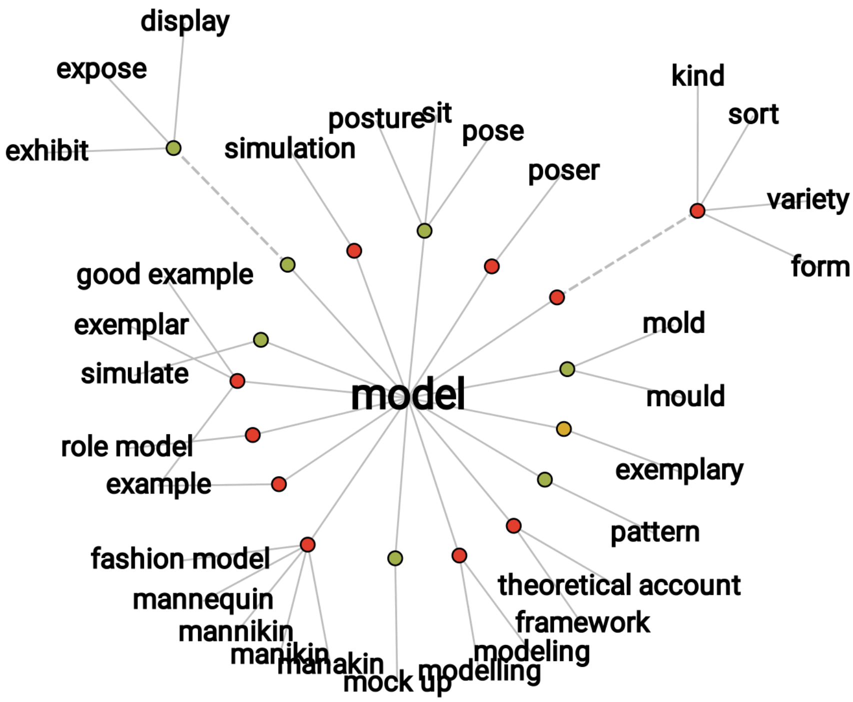


Figure 1.2: **Network visualization of *model* thesaurus entries.** Generated with the 'Visual Thesaurus' ressource

tally, they must provide insights about the object of study and contribute to its understanding.

These definitions circumscribe the *model* object, its use and its objectives, but they do not in any way describe its nature. And for good reason, because even if we agree on the described contours, the biodiversity of the models remains overwhelming for taxonomists:

> *Probing models, phenomenological models, computational models, developmental models, explanatory models, impoverished models, testing models, idealized models, theoretical models, scale models, heuristic models, caricature models, exploratory models, didactic models, fantasy models, minimal models, toy models, imaginary models, mathematical models, mechanistic models, substitute models, iconic models, formal models, analogue models, and instrumental models are but some of the notions that are used to categorize models.*
> [Frigg and Hartmann, 2020]

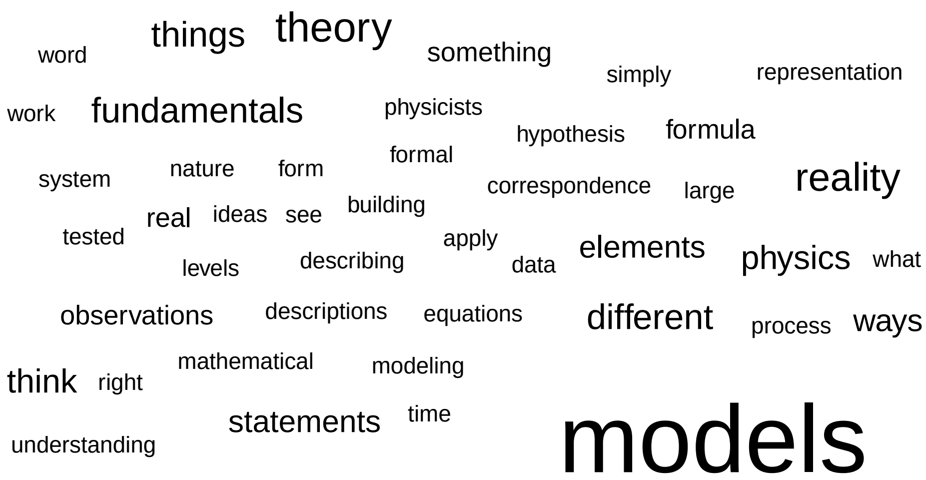


Figure 1.3: **Scientists talk about their models: words cloud.** Cloud of words summarizing the lexical fields used by scientists to talk about their models in dedicated interviews [Bailer-Jones, 2002].

### 1.1.2 Physical world and world of ideas

Without claiming to be exhaustive, we can make a first simple dichotomy between physical/material and formal/intellectual models [Rosenblueth and Wiener, 1945]. The former consist in replacing the object of study by another object, just as physical but nevertheless simpler or better known. These may be models involving a change of scale such as the simple miniature replica placed in a wind tunnel, or the metal double helix model used by Watson and Crick to visualize DNA. In all these cases the model allows to visualize the object of study (Figure 1.4 A and B) to manipulate it and play with it to better understand or explain, just like the scientist with his orrery (Figure 1.1). In the case of biology, we will think mainly of model organisms such as drosophila, zebrafish or mice, for example. We then benefit from the relative simplicity of their genomes, a shorter time scale or ethical differences, usually to elucidate mechanisms of interest in humans. Correspondence between the target system and its model can sometimes be more conceptual, such as that ones relying on mechanical–electrical analogies: a mechanical system (e.g. a spring-mass system) can sometimes be represented by an electric network (e.g. a RLC circuit).

The model is then no longer simply a mimetic replica but is based on an intellectual equivalence: we are gradually moving into the realm of formal models [Rosenblueth and Wiener, 1945]. These are of a more symbolic nature and they represent the original system with a set of logical or mathe-

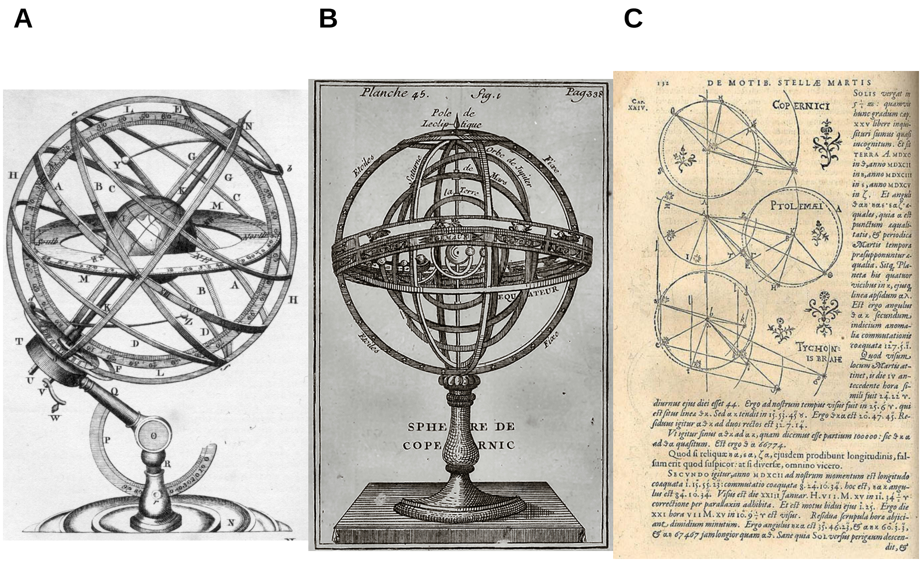


Figure 1.4: **Orrery, planets and models**. Physical models of planetary motion, either geocentric (Armillary sphere from *Plate LXXVII* in *Encyclopedia Britannica*, 1771) or heliocentric in panel B (Bion, 1751, catalogue Bnf) and some geometric representations by Johannes Kepler in panel C (in *Astronomia Nova*, 1609)

matical terms, describing the main driving forces or similar structural properties as geometrical models of planetary motions summarized by Kepler in Figure 1.4C. Historically these models have often been expressed by sets of mathematical equations or relationships. Increasingly, these have been implemented by computer. Despite their sometimes less analytical and more numerical nature, many so-called computational models could also belong to this category of formal models. There are then many formalisms, discrete or continuous, deterministic or stochastic, based on differential equations or Boolean algebra [Fowler et al., 1997]. Despite their more abstract nature, they offer similar scientific services: it is possible to play with their parameters, specifications or boundary conditions in order to better understand the phenomenon. One can also imagine these formal models from a different perspective, which starts from the data in a bottom-up approach instead of starting from the phenomenon in a top-down analysis. These models will then often be called statistical models or models of data[Frigg and Hartmann, 2020]. This distinction will be further clarified in section 1.2.

To summarize and continue a little longer with the astronomical metaphor, the study of a particularly complex system (the solar system) can be broken down into a variety of different models. Physical and mechanical models such as armillary spheres (1.4A and B), which make it possible to touch the object of study. Moreover, we can observe the evolution of models which, when confronted with data, have progressed from a geocentric to a heliocentric representation to get closer to the current state of knowledge. Sometimes, models with more formal representations are used to give substance to ideas and hypotheses (1.4C). One of the most conceptual forms is then the mathematical language and one can thus consider that the different models find their culmination in Kepler's equations about orbits, areas and periods that describe the elliptical motion of the planets. We refer to them today as Kepler's laws. The model has become a law and therefore a paragon of mathematical modeling [Wan, 2018].

### 1.1.3 Preview about cancer models

As we get closer to the subject of our study, and in order to illustrate these definitions more concretely, we can take an interest in the meaning of the word *model* in the context of cancer research. For this, we restrict our corpus to articles responding to the "cancer model" search in the Pubmed article database. Among these, we look at the occurrences of the word *model* and the sentences in which it is included. This cancer-related context of model is represented as a tree in Figure 1.5. Some of the distinctions already mentioned can be found here. The *mouse* and *xenograft* models, which will be discussed later in this thesis, represent some of the most common physical models in cancer studies. These are animal models in which the occurrence and mechanisms of cancer, usually induced by the experimenter, are studied. On the other hand, *prediction*, *prognostic* or *risk score* models refer to formal models and borrow from statistical language.

Another way to classify cancer models may be to group them into the following categories: *in vivo*, *in vitro* and *in silico*. The first two clearly belong to the physical models but one uses whole living organisms (a human tumour implanted in an immunodeficient mouse) and the other separates the living from its organism in order to place it in a controlled environment (tumour cells in growth medium in a Petri dish). **In the thesis, data from both *in vivo* and *in vitro* models will be used. However, unless otherwise stated, a model will always refer to a representation *in silico*.** This third category, however, contains a very wide variety of models [Deisboeck et al., 2009], to which we will come back in chapter @ref(computational_cancer). A final ambiguity about the nature of the formal models used in this thesis needs to be clarified beforehand.

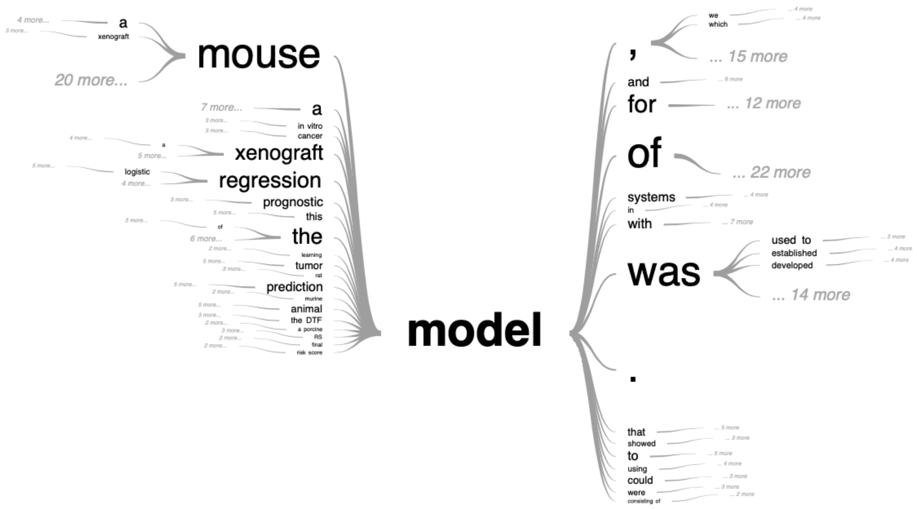


Figure 1.5: **Tree visualization of *model* semantic context in cancer-related literature** Generated with the 'PubTrees' tool by Ed Sperr, and based on most relevant PubMed entries for "cancer model" search.

## 1.2 Statistics or mechanistic

A rather frequent metaphor is to compare formal models to black boxes that take in input $X$ predictors, or independent variables, and output response variable(s) $Y$, also named dependent variables. The models then split into two categories (Figure 1.6) depending on the answer to the question: are you modeling the inside of the box or not?

### 1.2.1 The inside of the box

The purpose of this section is to present in a schematic, and therefore somewhat caricatural, manner the two competing formal modeling approaches that will be used in this thesis and that we will call mechanistic modeling and statistical modeling. Assuming the unambiguous nature of the predictors and outputs we can imagine that the natural process consists in defining the result Y from the inputs X according to a function of a completely unknown form (Figure 1.6A).

The first modeling approach, that we will call mechanistic, consists in building the box by imitating what we think is the process of data generation (Figure 1.6B). This integration of a priori knowledge can take different forms. In this thesis it will often come back to presupposing certain relations between entities according to what is known about their behaviour.

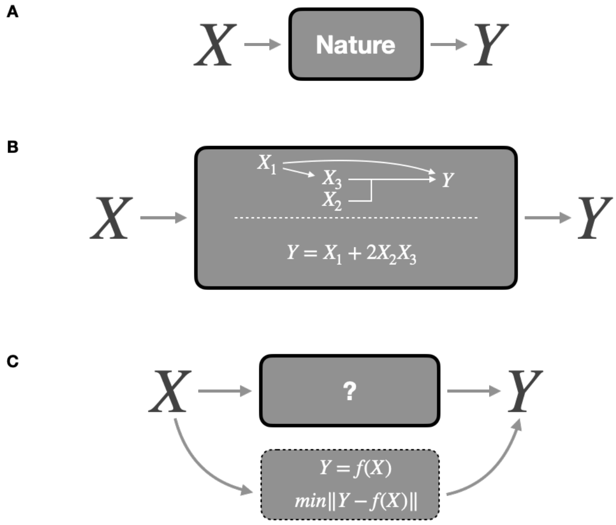


Figure 1.6: **Different modeling strategies.** (A) Data generation from predictors $X$ to response $Y$ in the natural phenomenon. (B) Mechanistic modeling defining mechanisms of data generation inside the box. (C) Statistical modeling finding the function $f$ that gives the best predictions (adapted from Breiman [2001b]).

$X_1$ which acts on $X_3$ may correspond to the action of one biological entity on another, supposedly unidirectional; just as the joint action of $X_2$ and $X_3$ may reflect a known synergy in the expression of genes or the action of proteins. Mathematically this is expressed here with a perfectly deterministic model defined a priori. All in all, in a purely mechanistic approach, the nature of the relations between entities should be linked to biological processes and the parameters in the model all have biological definitions in such a way that it could even be considered to measure them.

The second approach, often called statistical modeling or machine learning, does not necessarily seek to reproduce the natural process of data generation but to find the function allowing the best prediction of $Y$ from $X$ (Figure 1.6C). Pushed to the limit, they are "idealized version of the data we gain from immediate observation" [Frigg and Hartmann, 2020], thus providing a phenomenological description. The methods and algorithms used are then intended to be sufficiently flexible and to make the fewest possible assumptions about the relationships between variables or the distribution of data. Without listing them exhaustively, the approaches such as boosting [Bühlmann and Hothorn, 2007], support vector machines [Cortes and Vapnik, 1995] or random forests [Breiman, 2001a], which will sometimes be mentioned in this thesis, fall into this category which contains many others [Hastie et al., 2009].

Several discrepancies result from this difference in nature, some of which are summarized in the Table 1.1. In a somewhat schematic way, we can say that the mechanistic model first asks the question of *how* and then looks at the result for the output. The notion of causality is intrinsic to the definition of the model. Conversely, the statistical model first tries to approach the Y and then possibly analyses what can be deduced from it, regarding the importance of the variables or their relationships in a *post hoc* approach [Ishwaran, 2007, Manica et al. [2019]]. The causality is then not a by-product of the algorithm and must be evaluated according to dedicated frameworks [Hernán and Robins, 2020]. The greater flexibility of statistical methods makes it possible to better accept the heterogeneity of the variables, but this is generally done at the cost of a larger number of parameters and therefore requires more data. Moreover, we can contrast the inductive capability of statistical models able to use already generated data to identify patterns in it. Conversely, mechanistic models are more deductive in the sense that they can theoretically allow to extrapolate beyond the original data or knowledge used to build the model [Baker et al., 2018]. Finally, the most relevant way of assessing the value or adequacy of these models may be quite different. A statistical model is measured by its ability to predict output in a validation dataset different from the one used to train its parameters. The mechanistic model will also be evaluated on its capacity to approach the data but also to order, to give a meaning. If its pure predictive performance is generally inferior, how can the value of understanding be assessed? This question will be one of the threads of the dissertation.

Mechanistic and statistical models are not perfectly exclusive and rather form the two ends of a spectrum. The definitions and classification of some examples is therefore still partly personal and arbitrary. For instance, the example in 1.6B can be transformed into a model with a more ambiguous status:

$$logit(P[Y = 1]) = \beta_1 X_1 + \beta_{23} X_2 X_3$$

The logistic model shown in Figure 1.6B is deliberately ambiguous. It is a logistic model which it is therefore natural to define as a statistical model. The definition of the interaction between $X_2$ and $X_3$ denotes a mechanistic presupposition. The very choice of a logistic and therefore parametric model could result from a knowledge of the phenomenon even if in practice it is often a default choice for a binary output. Finally, the nature of the parameters $\beta_1$ and $\beta_{23}$ is likely to change the interpretation

Table 1.1: **Some pros and cons for mechanistic and statistical modeling** (adapted from Baker et al. [2018])

| Mechanistic modeling | Statistical modeling |
|---|---|
| **Definition** | |
| seeks to establish a mechanistic relationship between inputs and outputs | seeks to establish statistical relationships between inputs and outputs |
| **Pros and cons** | |
| presupposes and investigates causal links between the variables | looks for patterns and establishes correlations between variables |
| capable of handling small datasets | requires large datasets |
| once validated, can be used as a predictive tool in new situations possibly difficult to access through experimentation | can only make predictions that relate to patterns within the data supplied |
| difficult to accurately incorporate information from multiple space and time scales due to constrained specifications | can tackle problems with multiple space and time scales thanks to flexible specifications |
| evaluated on closeness to data and ability to make sense of it | evaluated based on predictive performance |

of the model. If they are deduced from the data and therefore optimized to fit Y as well as possible, one will think of a statistical model whose specification is nevertheless based on knowledge of the phenomenon. On the other hand, one could imagine that these parameters are taken from the literature, biochemical or other data. The model will then be more mechanistic. The boundary between these models is further blurred by the different possibilities of combining these approaches and making them complementary [Baker et al., 2018, Salvucci et al., 2019], we will come back to this later.

### 1.2.2 A tale of prey and predators

The following is a final general illustration of the concepts introduced with respect to statistical and mechanistic models through a famous and characteristic example: the Lotka-Volterra model of interactions between prey and predators. This model was thus, like many students, my first encounter with what could be called mathematical biology. A detailed description of their context and historical formulation can be found in original articles [Lotka, 1925, Volterra, 1926] or dedicated reviews [Knuuttila and Loettgers, 2017] that we summarize here.

The general objective is to understand the evolution of the populations of a species of prey and its predator, reasonably isolated from outside intervention. Here we will use Canada lynx (*Lynx canadensis*) and snowshow hare (*Lepus americanus*) populations for which an illustrative data set exists [Hewitt, 1917]. In fact, commercial records listing the quantities of furs sold by trappers to the Canadian Hudson Bay Company may represent a proxy for the populations of these two species. Denoting the population of lynx $L(t)$ and the population of hare $H(t)$ we can deinfe the following system of differential equations:

$$\frac{dH}{dt} = a_1 H - a_2 HT$$

$$\frac{dL}{dt} = -b_1 L + b_2 HL$$

with all coefficients $a_1, a_2, b_1, b_2 > 0$. $a_1 H$ represents the growth rate of the hare population (prey), i.e. the population grows in proportion to its own population. The main losses of hares are due to predation by lynx, as represented with a negative coefficient in the $-a_2 HT$ term. It is therefore assumed that a fixed percentage of prey-predator encounters will result in the death of the prey. Conversely, it is assumed that the growth of the lynx population depends primarily on the availability of food for all lynxes, summarized in the $b_2 HL$ term. In the absence of hares, the lynx population decreases exponentially, as denoted by the coefficient $-b_1 L$. It is thus noted that in the absence of predators, prey increases exponentially, while in the absence of prey, predators would decline in the same way.

Example with data, stat and mech for Lotka-Volterra https://mc-stan.org/users/documentation/case-studies/lotka-volterra-predator-prey.html http://www2.nau.edu/lrm22/lessons/predator_prey/predator_prey.html

[Flake, 1998] [Knuuttila and Loettgers, 2017]

## 1.3 Simplicity is the ultimate sophistication

To conclude this modeling introduction, it is important to highlight one of the most important points already introduced in a concise manner by Valéry at the beginning of this chapter. Whatever its nature, a model is a simplified representation of reality and by extension is always wrong to a certain extent. This is a generally well-accepted fact, but it is crucial to understand the implications for the modeller. This simplification is not a collateral effect but an intrinsic feature of any model:

> *No substantial part of the universe is so simple that it can be grasped and controlled without abstraction. Abstraction consists in replacing the part of the universe under consideration by a model of similar but simpler structure. Models, formal and intellectual on the one hand, or material on the other, are thus a central necessity of scientific procedure.*
> [Rosenblueth and Wiener, 1945]

Therefore, a model exists only because we are not able to deal directly with the phenomenon and simplification is a necessity to make it more tractable [Potochnik, 2017]. This simplification appeared many times in the studies of frictionless planes or theoretically isolated systems, in a totally deliberate strategy. However, this idealization can be viewed in several ways [weisberg2007three]. One of them, called Aristotelian or minimal idealization, is to eliminate all the properties of an object that we think are not relevant to the problem in question. This amounts to lying by omission or making assumptions of insignificance by focusing on key causal factors only [Frigg and Hartmann, 2020]. We therefore refer to the *a priori* idea that we have of the phenomenon. The other idealization, called Galilean, is to deliberately distort the theory to make it tractable as explicited by Galileo himself:

> *We are trying to investigate what would happen to moveables very diverse in weight, in a medium quite devoid of resistance, so that the whole difference of speed existing between these moveables would have to be referred to inequality of weight alone. ... Since we lack such a space, let us (instead) observe what happens in the thinnest and least resistant media, comparing this with what happens in others less thin and more resistant.*

This fairly pragmatic approach should make it possible to evolve iteratively, reducing distortions as and when possible. We will have the opportunity to come back to the idealizations made in the course of the cancer models but it is already possible to give some orientations. The experimenter who seeks to study cancer using cell lines or animal models is clearly part of Galileo's lineage. The mathematical or *in silico* modeler has a more balanced profile. The design of qualitative mechanistic models based on prior knowledge, which is the core of the second part of the thesis, is more akin to minimal idealization, which seeks to highlight the salient features of a system. This pragmatism consisting in creating computationnaly-tractable models is also quite widespread, particularly in highly dimensional statistical approaches.

Because of the complexity of the phenomena, simplification is therefore a necessity. The objective then should not necessarily be to make the model more complex, but to match its level of simplification with its assumptions and objectives. Faced with the temptation of the author of the model, or his reviewer, to always extend and complicate the model, it could be replied with Lewis Carrol words[1]:

> *"That's another thing we've learned from your Nation," said Mein Herr, "map-making. But we've carried it much further than you. What do you consider the largest map that would be really useful?"*
> *"About six inches to the mile."*
> *"Only six inches!" exclaimed Mein Herr. "We very soon got to six yards to the mile. Then we tried a hundred yards to the mile. And then came the grandest idea of all! We actually made a map of the country, on the scale of a mile to the mile!"*
> *"Have you used it much?" I enquired.*
> *"It has never been spread out, yet," said Mein Herr: "the farmers objected: they said it would cover the whole country, and shut out the sunlight! So we now use the country itself, as its own map, and I assure you it does nearly as well."*
> *Lewis Carroll,* Sylvie and Bruno* (1893)

[1]More concisely, in [Rosenblueth and Wiener, 1945], "best material model for a cat is another cat, or preferably the same cat."

CHAPTER 2

# Cancer as deregulation of complex machinery

*"All happy families are alike; each unhappy family is unhappy in its own way."*
*Leo Tolstoy (Anna Karenina, 1877)*

The notion of modeling is embedded in science, to the point that it has sometimes been used to define the very nature of scientific research.

## 2.1 Cancer from a distance: epidemiology and main figures

## 2.2 Basic molecular biology

## 2.3 High-throughput data and multi-omics

## 2.4 From genetic to network disease

CHAPTER 3

# Test part

This is a test

## 3.1 Abc

Bla bla ref Miskovic et al. [2019] and [Miskovic et al., 2019].

But in Béal et al. [2019] we have the Figure 3.1 as referenced in Chapter 3

```
par(mar = c(4, 4, .1, .1))
plot(pressure, type = 'b', pch = 19)
```

And an external figure 3.2

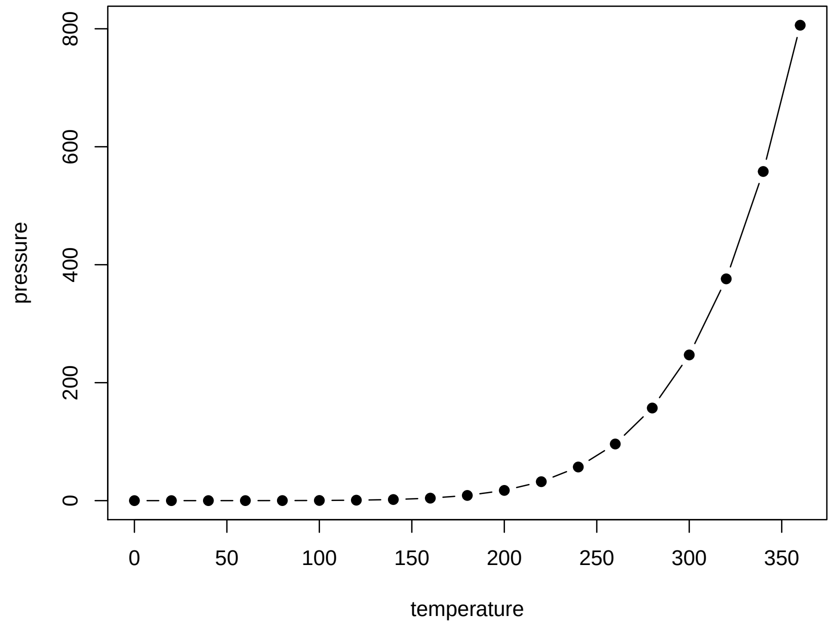


Figure 3.1: Here is a nice figure!



Figure 3.2: Example pic

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## RÉSUMÉ

Cuius acerbitati uxor grave accesserat incentivum, germanitate Augusti turgida supra modum, quam Hannibaliano regi fratris filio antehac Constantinus iunxerat pater, Megaera quaedam mortalis, inflammatrix saevientis adsidua, humani cruoris avida nihil mitius quam maritus; qui paulatim eruditiores facti processu temporis ad nocendum per clandestinos versutosque rumigerulos conpertis leviter addere quaedam male suetos falsa et placentia sibi discentes, adfectati regni vel artium nefandarum calumnias insontibus adfligebant.

## MOTS CLÉS

Caesar licentia post honoratis haec adhibens urbium honoratis nullum Caesar.

## ABSTRACT

Verum ad istam omnem orationem brevis est defensio. Nam quoad aetas M. Caeli dare potuit isti suspicioni locum, fuit primum ipsius pudore, deinde etiam patris diligentia disciplinaque munita. Qui ut huic virilem togam dedit nihil dicam hoc loco de me; tantum sit, quantum vos existimatis; hoc dicam, hunc a patre continuo ad me esse deductum; nemo hunc M. Caelium in illo aetatis flore vidit nisi aut cum patre aut mecum aut in M. Crassi castissima domo, cum artibus honestissimis erudiretur.

## KEYWORDS

Delatus delatus nominatus onere aut trahebatur quod tenus et bonorum.