

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

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## Abstract

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**Key-words:**



## Résumé

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### Mots-clés:



## Acknowledgements

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# **Part I**

## **Cells and their models**



C H A P T E R



## 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

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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 multi-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-

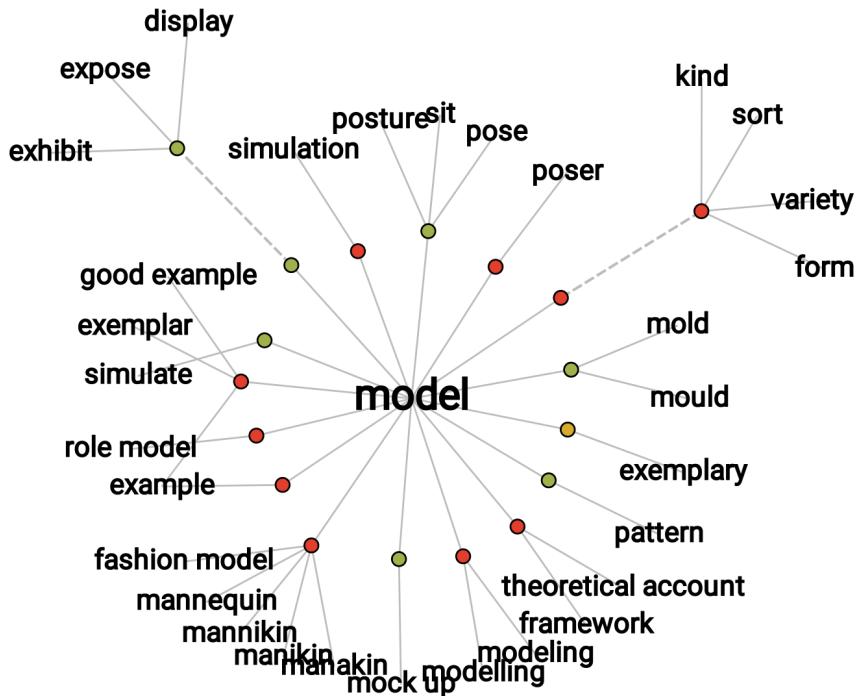


Figure 1.2: Network visualization of *model* thesaurus entries. Generated with the ‘Visual Thesaurus’ ressource

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]

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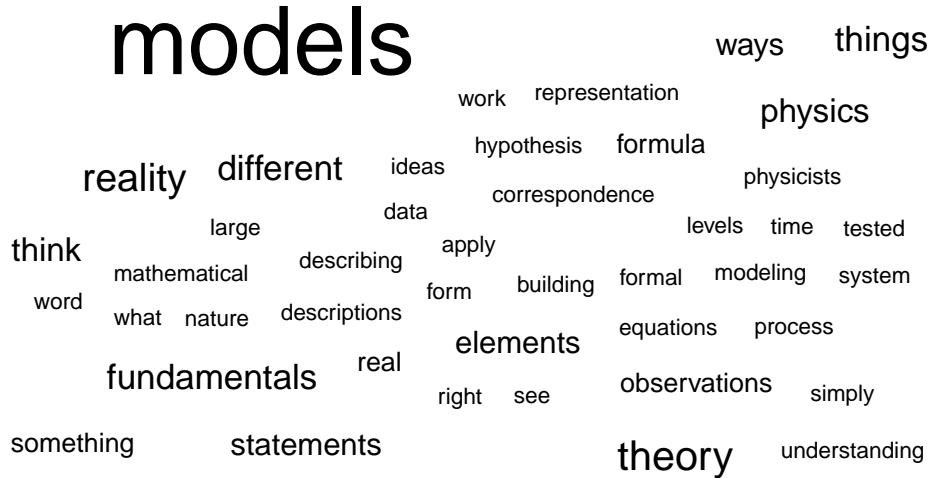


Figure 1.3: **Scientists talk about their models: words cloud.** Cloud of words summarizing the lexical fields used by scientists to talk about their models in dedicated interviews [Bailer-Jones, 2002].

### 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-

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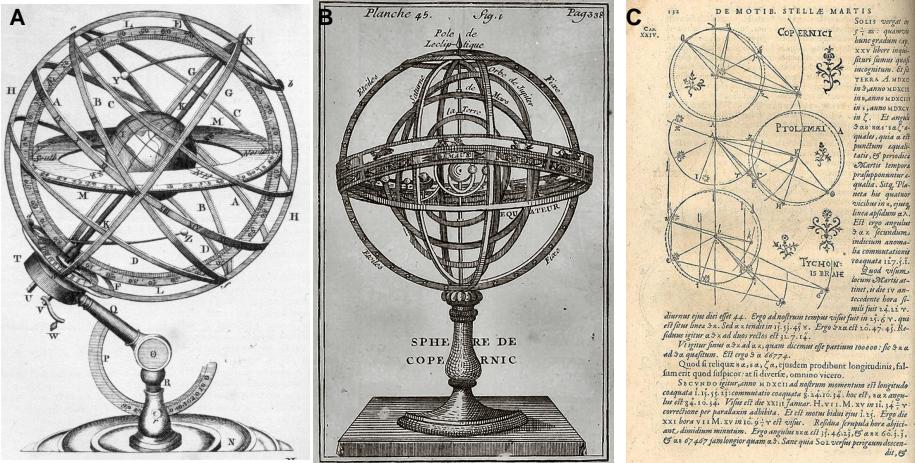


Figure 1.4: **Orrery, planets and models.** Physical models of planetary motion, either geocentric (Armillary sphere from *Plate LXXVII in Encyclopedia Britannica*, 1771) or heliocentric in panel B (Bion, 1751, catalogue Bnf) and some geometric representations by Johannes Kepler in panel C (in *Astronomia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

mathematical 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

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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.

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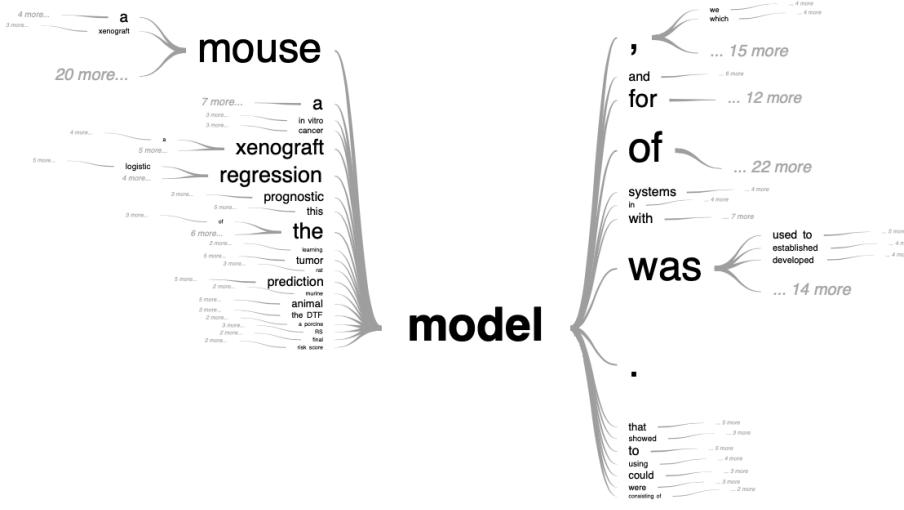


Figure 1.5: **Tree visualization of *model* semantic context in cancer-related literature** Generated with the ‘PubTrees’ tool by Ed Sperr, and based on most relevant PubMed entries for “cancer model” search.

## 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.

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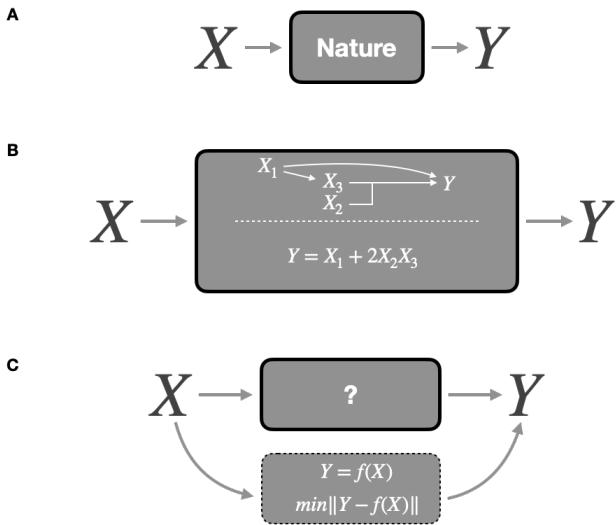


Figure 1.6: **Different modeling strategies.** (A) Data generation from predictors  $X$  to response  $Y$  in the natural phenomenon. (B) Mechanistic modeling defining mechanisms of data generation inside the box. (C) Statistical modeling finding the function  $f$  that gives the best predictions (adapted 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 directly. In some fields of literature these models are sometimes called mathematical models because they propose a mathematical translation of a phenomenon, which does not start from the data in a bottom-up approach but rather from a top-down theoretical framework. In this thesis we will adhere to the mechanistic model name, which is more transparent and less ambiguous compared to other approaches also based on mathematics, without necessarily the other characteristics described above.

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:

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

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

Mechanistic modeling	Statistical modeling
<b>Definition</b>	
Seeks to establish a mechanistic relationship between inputs and outputs	Seeks to establish statistical relationships between inputs and outputs
<b>Pros and cons</b>	
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

The logistic model shown in Figure 1.6B is deliberately ambiguous. It is a logistic model which is therefore naturally defined 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 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 and procedures 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, like many students, my first encounter with what could be called mathematical biology. The Italian mathematician Vito Volterra states this system for the first time studying the unexpected characteristics of fish populations in the Adriatic Sea after the First World War. Interestingly, Alfred Lotka, an American physicist deduced the exact same system independantly, starting from very generic process of redistribution of matter among the several components derived from law of mass action [Knuuttila and Loettgers, 2017]. A detailed description of their works and historical formulation can be found in original articles [Lotka, 1925, Volterra, 1926] or dedicated reviews [Knuuttila and Loettgers, 2017].

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 snowshoe 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 as represented in Figure 1.7A. Denoting the population of lynx  $L(t)$  and the population of hare  $H(t)$  it can be hypothesized that prey, in the absence of predators, would increase in population, while predators on their own would decline in the absence of preys. A prey/predator interaction term can then be added, which will positively impact predators and negatively impact prey. The system can then be formalized with the following differential equations with all coefficients  $a_1, a_2, b_1, b_2 > 0$ :

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

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

$a_1 H$  represents the growth rate of the hare population (prey), i.e. the population grows in proportion to the population itself according to usual birth modeling. 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

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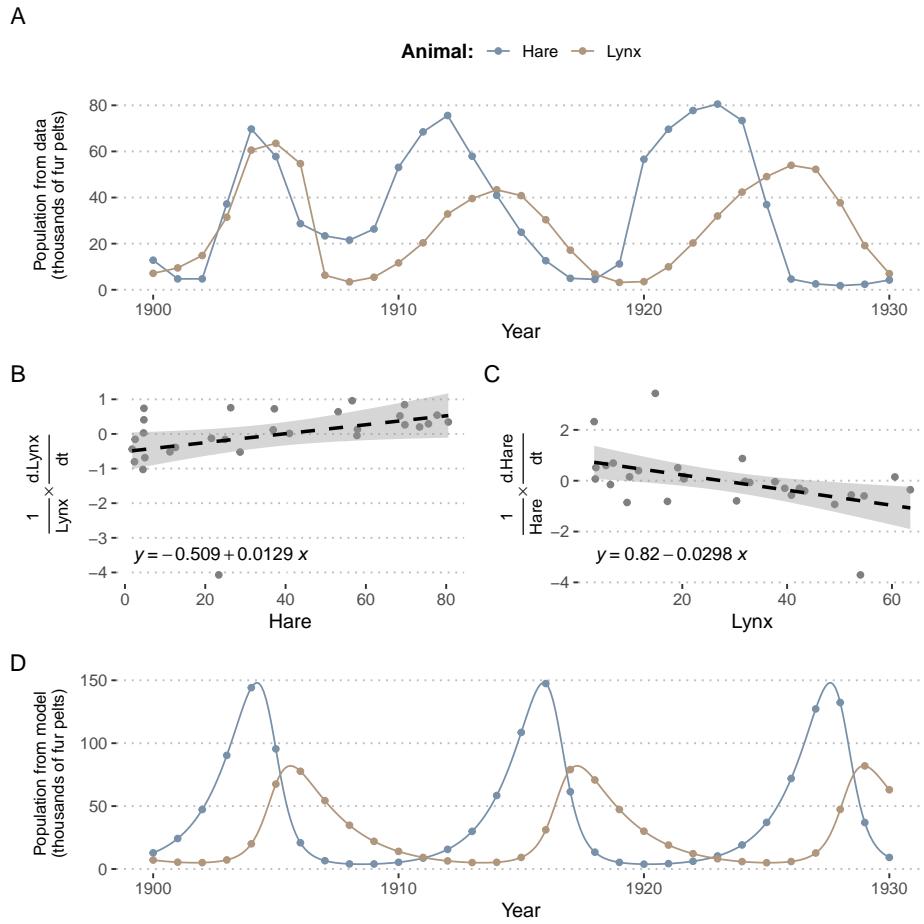


Figure 1.7: **Some analyses around Lotka-Volterra model of a prey-predator system.** (A) Evolution of lynx and hares populations based on Hudson Bay Company data about fur pelts. (B) and (C) Linear regression for estimation of parameters. (D) Evolution of lynx and hare populations as predicted by the model based on inferred parameters and initial conditions.

the lynx population depends primarily on the availability of food for all lynxes, summarized in the  $b_2HL$  term. In the absence of hares, the lynx population decreases, as denoted by the coefficient  $-b_1L$ . Here we find some of the important characteristics of a mechanistic model. The equations are based on a priori knowledge or assumptions about the structure of the problem and the parameters of the model can be interpreted.  $a_1$ , for example, could correspond to the frequency of litters among hares and the number of offspring per litter.

This being said, the structure of the model having been defined a priori,

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it remains to determine its parameters. Two options would theoretically be possible: to propose values based on the interpretation of the parameters and ecological knowledge, or to fit the model to the data in order to find the best parameters. For the sake of simplicity, and because this example has only a pedagogical value in this presentation, we propose to determine them roughly using the following Taylor-based approximation:

$$\frac{1}{y(t)} \frac{dy}{dt} \simeq \frac{1}{y(t)} \frac{y(t+1) - y(t-1)}{2}$$

By applying this approximation to the two equations of the differential system and plotting the corresponding linear regressions (Figures 1.7B and C), we can obtain an evaluation of the parameters such as  $a_1 = 0.82$ ,  $a_2 = 0.0298$ ,  $b_1 = 0.509$ ,  $b_2 = 0.0129$ . By matching the initial conditions to the data, the differential system can then be fully determined and solved numerically (Figures 1.7D). Comparison of data and modeling provides a good illustration of the virtues and weaknesses of a mechanistic model. Firstly, based on explicit and interpretable hypotheses, the model was able to recover the cyclical behaviour and dependencies between the two species: the increase in the lynx population always seems to be preceded by the increase in the hare population. However, the amplitude of the oscillations and their periods are not exactly those observed in the data. This may be related to approximations in the evaluation of parameters, random variation in the data or, of course, simplifications or errors in the structure of the model itself.

Besides, if one tries to carry out a statistical modeling of these data, it is very likely that it is possible to approach the curve of populations evolution much closer, especially for the hares. But should it be expressed simply as a function of time or should a joint modeling be proposed? The nature of the causal link between prey and predators will be extremely difficult to establish without strong hypotheses such as those of the mechanistic model. On the other hand, if populations in later years had to be predicted as accurately as possible, it is likely that a sufficiently well-trained statistical model would perform better. Finally, and this is a fundamental difference, the mechanical model makes it possible to test cases or hypotheses that go beyond the scope of the data. Quite simply, by playing with the variables or parameters of the model, we can predict the exponential decrease of predators in the absence of prey and the exponential growth of prey in the absence of prey. More generally, it is also possible to study analytically or numerically the bifurcation points of the system in order to determine the families of behaviours according to the relative values of the parameters [Flake, 1998]. It is not possible to infer these new or hypothet-

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ical behaviours directly from the data  $\mathbf{o}$  of the statistical model. This is theoretically possible on the basis of the mechanistic model, provided that it is sufficiently relevant and that its operating hypotheses cover the cases under investigation. Now that the value of mechanistic models has been illustrated in a fairly theoretical example, all that remains is to explore in the next chapters how they can be built and used in the context of cancer.

### 1.3 Simplicity is the ultimate sophistication

Before concluding 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 always 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 explicated by Galileo himself:

*We are trying to investigate what would happen to moveables very diverse in weight, in a medium quite devoid of resistance,*

### 1.3. SIMPLICITY IS THE ULTIMATE SOPHISTICATION

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*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. This could involve the addition of other species or human intervention into the Lotka-Volterra system described above. A three-species Lotka-Volterra model can however become chaotic [Flake, 1998], and therefore extremely difficult to use and interpret, thus underlining the importance of simplifying the model.

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<sup>1</sup>:

*“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.*

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<sup>1</sup>More concisely, in [Rosenblueth and Wiener, 1945], “best material model for a cat is another cat, or preferably the same cat.”

## CHAPTER 1. SCIENTIFIC MODELING: ABSTRACT THE COMPLEXITY

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*“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)

CHAPTER



## 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)*

**A**rmed with all these models, whether statistical or mechanistic, we are going to look at a particularly complex system that fully justifies their use: cancer. Since the first chapter recalled how important prior knowledge of the phenomenon under study is for designing models, whatever their nature, this chapter will briefly summarize some of the most important characteristics of this disease before returning to the models themselves in the next chapter. Without aiming for exhaustiveness, and after an epidemiological and statistical description, we will focus on the most useful information for the modeller, i.e. the underlying biological mechanisms and available data.

### 2.1 What is cancer?

Cancer can be described as a group of diseases characterized by uncontrolled cell divisions and growth which can spread to surrounding tissues. Descrip-

## CHAPTER 2. CANCER AS DEREGULATION OF COMPLEX MACHINERY

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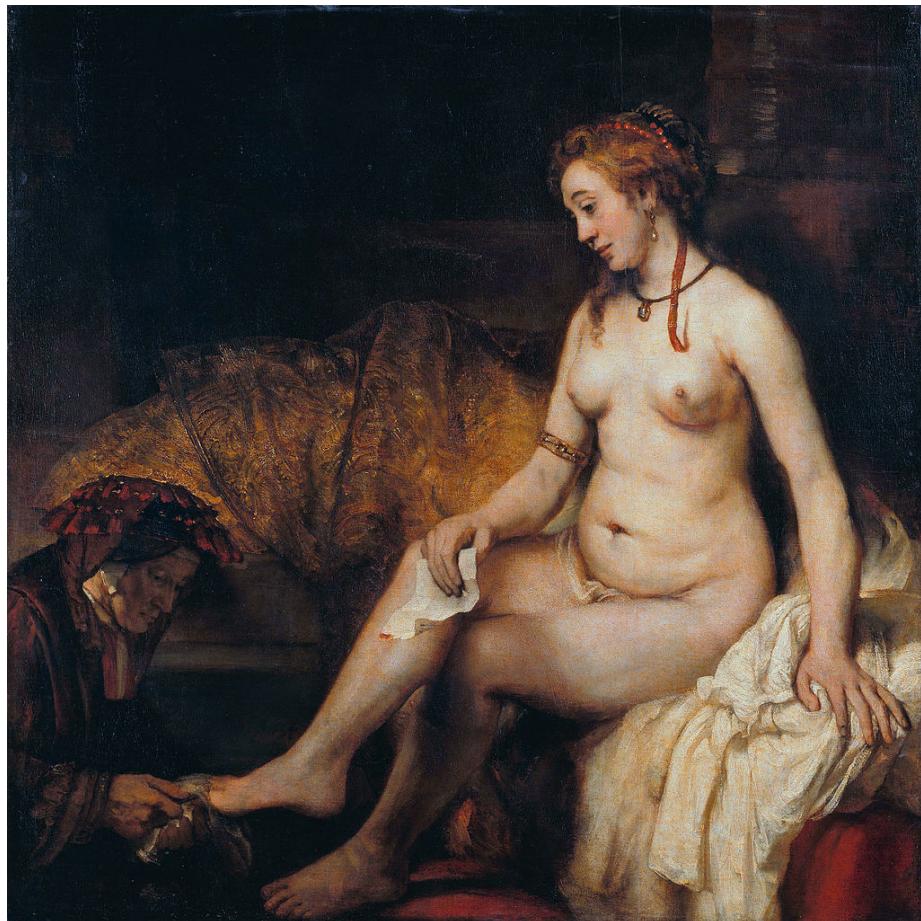


Figure 2.1: **Cancer is an old disease.** Rembrandt, *Bathsheba at Her Bath*, c. 1654, oil on canvas, Louvre Museum, Paris

tions of this disease, and essentially associated solid tumours, have been found as far back as ancient Egyptian documents, at least 1600 BC and we know from the first century A.D. with Aulus Celsus that it is better to remove the tumors and this as soon as possible [Hajdu, 2011a]. Progress will accelerate during the Renaissance with the renewed interest in medicine, and anatomy in particular, which will advance the knowledge of tumour pathology and surgery [Hajdu, 2011b]. The progress of anatomical knowledge has also left brilliant testimonies in the field of painting, which make the renown of the Renaissance today. The precision of these artists' traits has also allowed some retrospective medical analyses, some of them going so far as to identify the signs of a tumour in certain subjects [Bianucci et al., 2018]. Such is the bluish stain on the left breast of the Bathsheba painted

## 2.2. CANCER FROM A DISTANCE: EPIDEMIOLOGY AND MAIN FIGURES

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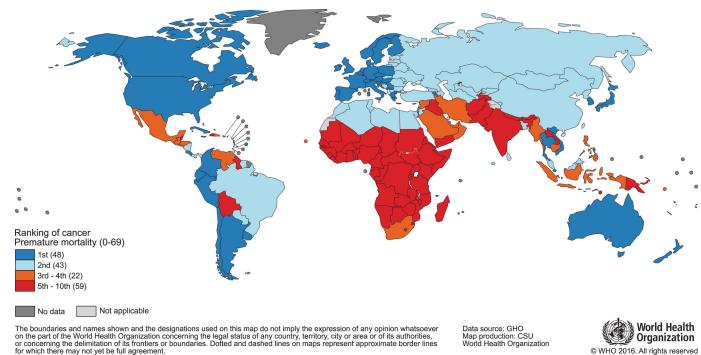
by Rembrandt (Figure 2.1) which has been subject to controversial interpretations, sometimes described as an example of “skin discolouration, distortion of symmetry with axillary fullness and peau d’orange” [Braithwaite and Shugg, 1983] and sometimes spared by photonic and computationnal analyses [Heijblom et al., 2014]. The mechanisms of the disease only began to be elucidated with the appearance of the microscope in the 19th century, which revealed its cellular origin [Hajdu, 2012a]. The classification and description of cancers is then gradually refined and the first non-surgical treatments appear with the discovery of ionising radiation by the Curies [Hajdu, 2012b]. The 20th century is then the century of understanding the causes of cancer [Hajdu and Darvishian, 2013, Hajdu and Vadmal, 2013]. Some environmental exposures are characterized as asbestos or tobacco. Finally, the biological mechanisms become clearer with the identification of tmour-causing viruses and especially with the discovery of DNA [Watson and Crick, 1953]. The foundations of our current understanding of cancer date back to this period, which marks the beginning of the molecular biology of cancer. It is this branch of biology that contains the bulk of the knowledge that will be used to build our mechanistic models, and it will be later detailed in Section 2.3.

One of the ways to read this brief history of cancer is to see that theoretical and clinical progress has not followed the same timeframes. The medical and clinical management of cancers initially progressed slowly but surely, and this in the absence of an understanding of the mechanisms of cancer. Conversely, the theoretical progress of the last century has not always led to parallel medical progress, except on certain specific points. The interaction between the two is therefore not always obvious. The transformation of fundamental knowledge into medical and clinical impact is therefore of particular importance. This is what is called *translational medicine*, the aim of which is to go from laboratory bench to bedside [Cohrs et al., 2015]. It is, modestly, in this perspective that the mechanistic models of cancer that will receive particular attention in this thesis are placed. Their objective is to integrate biological knowledge, or at least a synthesis this knowledge, in order to transform it into with a relevant clinical information.

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

Before going down to the molecular level, it is important to detail some figures and trends in the epidemiology of cancer today. Following the de-

## CHAPTER 2. CANCER AS DEREGULATION OF COMPLEX MACHINERY



**Figure 2.2: World map and national rankings of cancer as a cause of premature death.** Classification of cancer as a cause of death before the age of 70, based on data for the year 2015. Original Figure, data and methods from Bray et al. [2018].

scription in the previous section, cancer is first and foremost defined as a disease. Considered to be a unique disease, it caused 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 according to the Global Cancer Observatory affiliated to World Health Organization [Bray et al., 2018]. However, these aggregated data conceal disparities of various kinds. The first one is geographical. Indeed, mortality figures make cancer one of the leading causes of premature death in most countries of the world but its importance relative to other causes of death is even greater in the more developed countries (Figure 2.2). All in all, cancer is the first or second cause of premature death in almost 100 countries worldwide [Bray et al., 2018]. These differences call for careful consideration of the impact of population age structures and health-related covariates.

A second disparity lies in the different types of cancer. If we classify tumours solely according to their location, i.e. the organ affected first, we already obtain very wide differences. First of all, the incidence varies considerably (Figure 2.3A)). Cancers do not occur randomly anywhere in the body and certain environments or cell types appear to be more favourable [Tomasetti and Vogelstein, 2015]. Mortality is also highly variable but is not directly inferred from incidence. Not all types of cancer have the same prognosis (Figure 2.3A and B) and survival rates [Liu et al., 2018]. Although breast cancer is much more common than lung cancer, it causes fewer deaths because its prognosis is, on average, much better. The mechanisms at work in the emergence of cancer are therefore not necessarily the same as those that will govern its evolution or its response to treatment. And still on the response to treatment, Figure 2.3B highlights another disparity: not only

## 2.2. CANCER FROM A DISTANCE: EPIDEMIOLOGY AND MAIN FIGURES

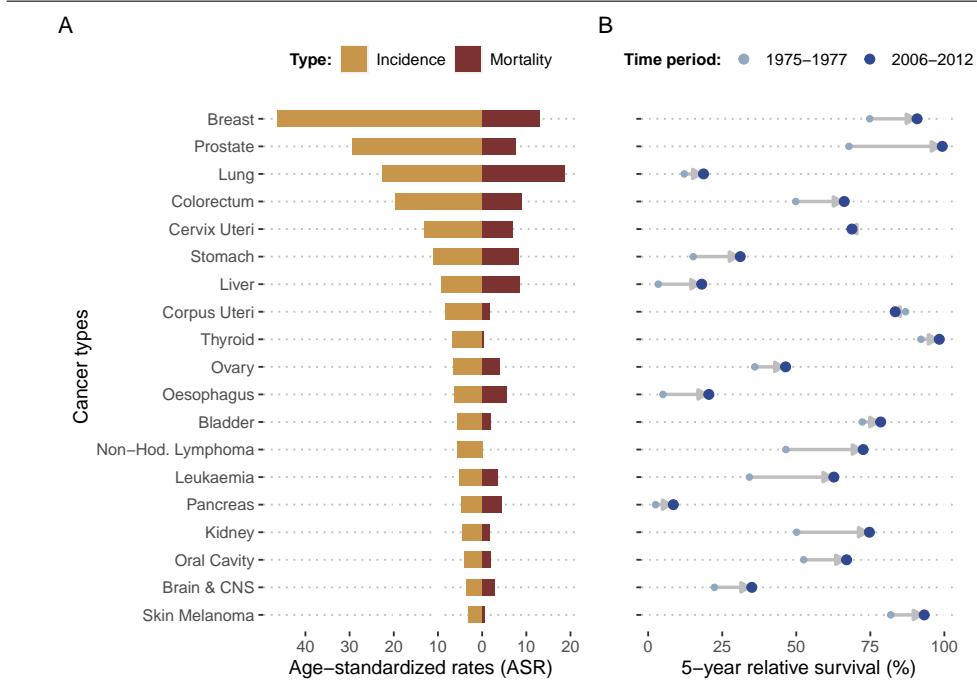


Figure 2.3: **Incidence, mortality and survival per cancer types.** (A) World incidence and mortality for the 19 most frequent cancer types in 2018, expressed age-standardized rates (adjusted age structure based on world population); data retrieved from Global Cancer Observatory. (B) Evolution of 5-years relative survival for the same cancer types based on US data from SEER registries in 1975-1977 and 2006-2012; data retrieved from Jemal et al. [2017].

are the survival prognosis associated with each cancer very different, but the evolution (and generally the improvement) of these prognoses has been very uneven over the last few decades. This means that theoretical and therapeutic advances have not been applied to all types of cancer with the same success. It is one more indication of the diversity of biological mechanisms at work, which make it impossible to find a panacea, and which, on the contrary, encourage us to carefully consider the particularities of each tumour, both to understand them and to treat them. Under a generic name and in spite of common characteristics, the cancers thus appear as extremely heterogeneous. And to understand the sources of this heterogeneity, it will be necessary to place ourselves on a much smaller scale.

## 2.3 Basic molecular biology and cancer

If it is not possible an ddesirable to summarize here the state of knowledge about the biology of cancer, we are going to give a very partial vision focused on the main elements used in this thesis, thus aiming to make it a self-sufficient document. The details necessary for a finer and more general understanding can be found in dedicated textbooks such as Alberts et al. [2007] and Weinberg [2013].

### 2.3.1 Central dogma and core principles

Some of the principles that govern biology can be described at the level of one of its simplest elements, the cell. Let us consider for the moment a perfectly healthy cell. It must ensure a certain number of functions necessary for its survival and, if necessary, for its division/reproduction. These functions are encoded in its genetic information in the form of DNA, which is *a priori* stable and shared by the different cells since it is defined at the level of the individual. Most biological functions, however, are not performed by DNA itself which remains in the nucleus of the cell. The DNA is thus transcribed into RNA, another nucleic acid which, in addition to performing some biological functions, becomes the support of the genetic information in the cell. The RNA is then itself translated into new molecules composed of long chains of amino acid residues and called proteins. They are the ones that execute most of the numerous cellular functions: DNA replication, physical structuring of the cell, molecule transport within the cell etc. A rather simplistic but fruitful way to understand this functioning is to consider it as a progressive transfer of biological information from DNA to proteins, which has sometimes been summarized as the central dogma of the molecular biology (2.4) first stated Francis Crick [Crick, 1970].

However, many changes would be necessary to clarify this scheme. The uni-directional nature was questioned early on. And above all, a large number of regulations interact with and disrupt this master plan. The genes are not always all transcribed, or at least not at variable intensities, interrupting or modulating the chain upstream. These switches in the transcript of genes can be proteins, called transcription factors. After a gene transcription, its expression can still be regulated at various stages. RNAs, too, can be degraded more or less rapidly. RNAs can be reshaped in their structure by a process called splicing, which varies the genetic information they carry. Finally, proteins are subject to all kinds of modifications referred to as post-translational, which can change the chemical nature of certain groups or modify the three-dimensional structure of the whole protein. For

## 2.3. BASIC MOLECULAR BIOLOGY AND CANCER

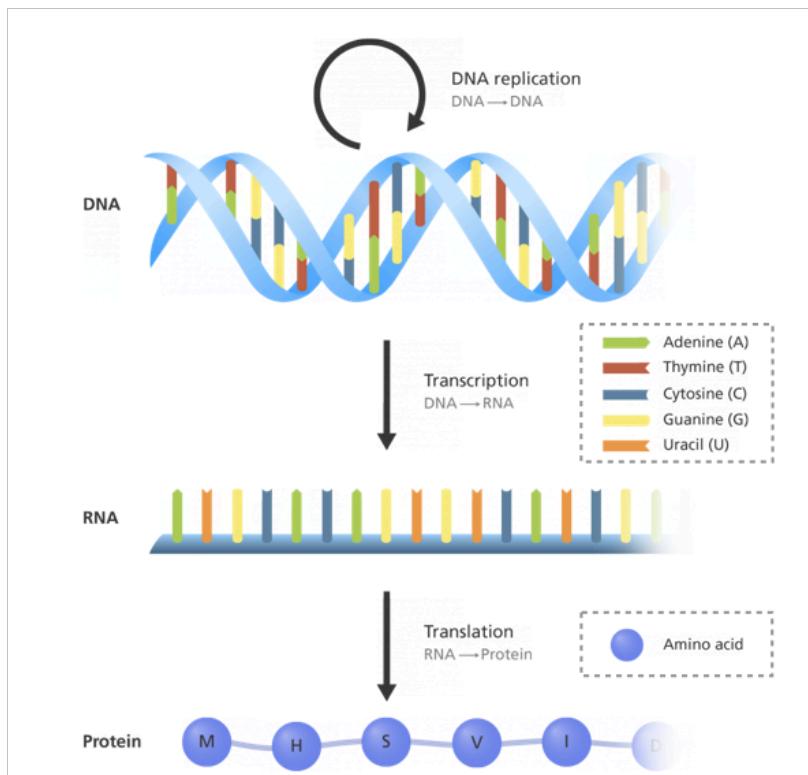


Figure 2.4: **Central dogma of molecular biology.** Schematic representation of the information flow within the cell, from DNA to proteins through RNA, more precisely described in this video (Image credit *Genome Research Limited*).

instance, some proteins perform their function only if a specific amino acid residue is phosphorylated. In addition, these modifications can be transmitted between proteins, further complicating the flow of information. All these possibilities of regulation play an absolutely essential role in the life of the cell by allowing it to adapt to different contexts and situations. From the same genetic material, a cell of the eye and a cell of the heart can thus perform different functions. In the same way, the same cell subjected to different stimuli at different times can provide different responses because these molecular stimuli induce a regulation of its programme. But these regulatory mechanisms can be corrupted.

## CHAPTER 2. CANCER AS DEREGLULATION OF COMPLEX MACHINERY

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### 2.3.2 A rogue machinery

With the above knowledge we can now return to the definition of cancer as an uncontrolled division of cells that can lead to the growth of a tumour that eventually spreads to the surrounding tissues. Therefore, this corresponds to normal processes, like cell division and reproduction, that are no longer regulated as they should be and are out of control. Experiments on different model organisms have gradually identified genetic mutations as a major source of these deregulations [Nowell, 1976, Reddy et al. [1982]] until cancer was clearly considered as a genetic disease making Renato Dulbecco, Nobel Laureate in Medicine for his work on oncoviruses, say:

*If we wish to learn more about cancer, we must now concentrate on the cellular genome.*

[Dulbecco, 1986].

However, cancer is not a Mendelian disease for which it would be sufficient to identify the one and only gene responsible for deregulation. Indeed, the cell has many protective mechanisms. For example, if a genetic mutation appears in the DNA, it has a very high chance of being repaired by dedicated mechanisms. And if it is not repaired, other mechanisms will take over to trigger the programmed death of the cell, called apoptosis, before it can proliferate wildly. So a cancer cell is probably a cell that has learned to resist this cell death. Similarly, in order to generate excessive growth, a cell will need to be able to replicate itself many, many times. However, there are pieces of sequences on chromosomes called telomeres that help to limit the number of times each cell can replicate. A cancer cell will therefore have to manage to bypass this protection. Thus we can schematically define the properties that must be acquired by the cancerous cells in order to truly deviate the machinery. In an influential article, these properties were summarized in six hallmarks (Figure 2.5) which are: resisting cell death, enabling replicative immortality, sustaining proliferative signaling, evading growth suppressors, activating invasion and inducing angiogenesis [Hanahan and Weinberg, 2000]. Two new ones were subsequently added in the light of advances in knowledge [Hanahan and Weinberg, 2011]: deregulating cancer energetics and avoiding immune destruction. The acquisition of these capacities generally requires genetic mutations and is therefore favoured by an underlying genome instability.

Each of these characteristics constitutes a research program in its own right. And for each one there are genetic alterations. These are tissue-specific or not, specific to a hallmark or common to several of them [Hanahan and Weinberg, 2000]. In any case, cancer can only result from different

## 2.4. THE NEW ERA OF GENOMICS

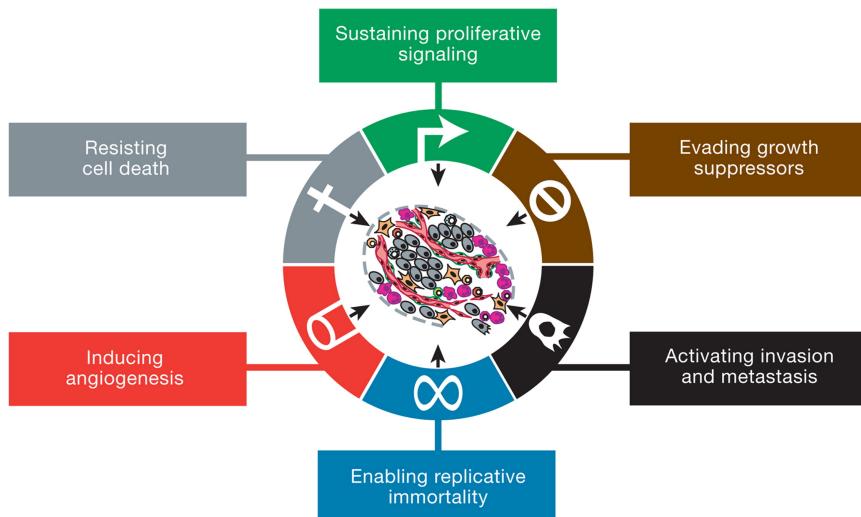


Figure 2.5: **Hallmarks of cancer.** The different biological capabilities acquired by cancer cells, as described in Hanahan and Weinberg [2000]. Reprinted from Hanahan and Weinberg [2011].

joint alterations that invalidate several protective mechanisms at the same time. This is often part of a multi-step process of hallmark acquisition that has been experimentally documented in some specific cases [Hahn et al., 1999] or more recently inferred from genome-wide data for human patients [Tomasetti et al., 2015]. In summary, it appears that in order to study the functioning of cancer cells it is necessary to look at several mechanisms and to be able to consider them not separately but together, in as many different patients as possible. This ambitious programme has been made possible by a technological revolution.

## 2.4 The new era of genomics

### 2.4.1 From sequencing to multi-omics data

In 2001, the first sequencing of the human genome symbolized the beginning of a new era, that of what will become high-throughput genomics [Lander et al., 2001, Venter et al., 2001]. From the end of the 20th century, biological data started to accumulate at an ever-increasing rate [Reuter et al., 2015], feeding and accelerating cancer research in particular [Stratton et al., 2009, Meyerson et al., 2010]. The ability to sequence the human genome as a whole, for an ever-increasing number of individuals, has enabled less

## CHAPTER 2. CANCER AS DEREGLULATION OF COMPLEX MACHINERY

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biased and more systematic studies of the causes of cancer [Lander, 2011]. The number of genes associated with cancer increased drastically and some very important genes such as BRAF or PIK3CA have been identified [Davies et al., 2002, Samuels et al., 2004]. Progress also extended to the gene expression data. Gene-expression arrays have made an important contribution by providing access to transcriptomic data (RNA), i.e. what has been transcribed from DNA and is therefore one step further in terms of biological information. This information has made it possible to further explore the differences between normal and tumour cells [Perou et al., 1999], or even to refine the classification of cancers, which until now has been done mainly according to the tumour site. Breast cancers are thus divided into subtypes with different combinations of molecular markers that facilitate the understanding of clinical behavior [Perou et al., 2000]. One step further, we also note the appearance of prognostic gene signatures such as gene expression patterns correlated with the survival of patients [Van't Veer et al., 2002]. This revolution was then extended to other types of data such as proteins (proteomics), reversible modifications of DNA or DNA-associated proteins (epigenomics), metabolites (metabolomics) and others, each representing a perspective that can complement the others to better understand biological mechanisms, particularly in the case of diseases [Hasin et al., 2017]. We have thus entered the era of multiomics data [Vucic et al., 2012].

### 2.4.2 State-of-the art of cancer data

With respect to cancer in particular, this wealth of data is particularly represented by a whole series of studies conducted by The Cancer Genome Atlas (TCGA) consortium started in 2008 [Network et al., 2008]. Cohorts of several hundred patients are thus sequenced over the years for different types of cancer [Network et al., 2012], resulting today in a total of 11,000 tumors from 33 of the most prevalent forms of cancer [Ding et al., 2018]. Figure 2.6 provides a partial but striking overview of the depth of data available under this program. We can see the frequencies of alterations of certain groups of genes for a list of cancer types, making it possible to visualize the disparities already anticipated in section 2.2 based on patient survival. There are indeed important differences between the organs but also between the different subtypes associated with the same organ. And this representation only corresponds to one layer of data, that of genetic alterations. It could be used for transcriptomic, epigenomic or proteomic data, thus giving rise to an incredibly complex photography.

However, the diversity of data available for cancer research extends far beyond this, both in terms of technology and type of data. This may

## 2.4. THE NEW ERA OF GENOMICS

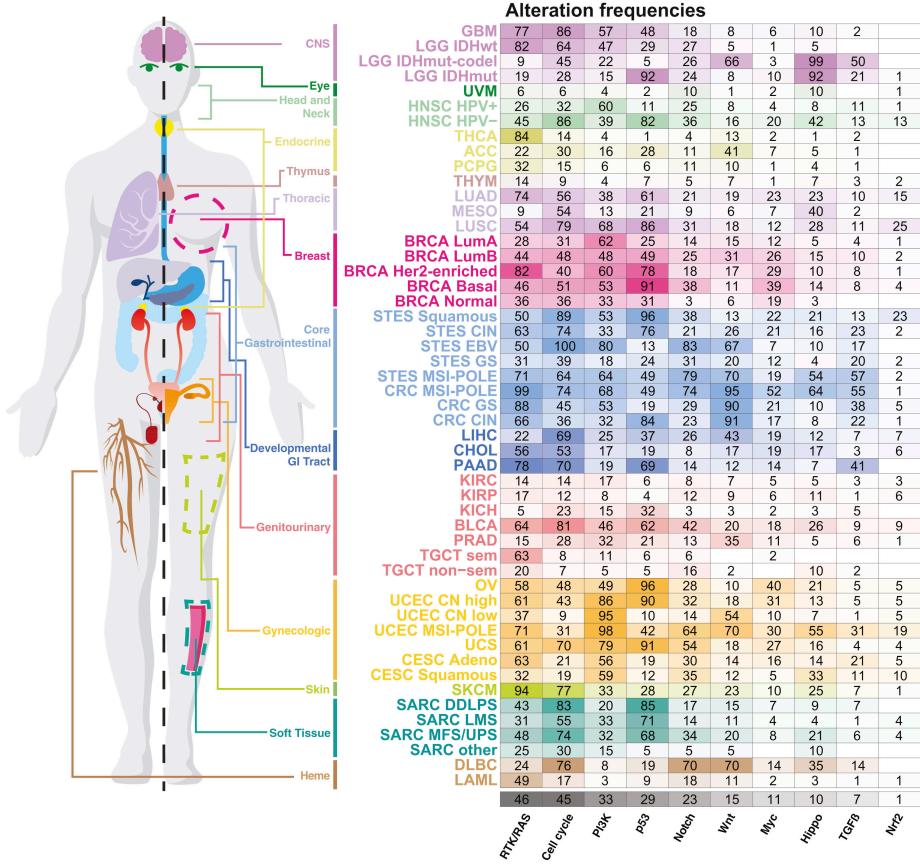


Figure 2.6: **Genetic alterations frequencies for cancer types from TCGA data.** Frequencies of alteration per pathway and tumour types as summarised in Pan-cancer analyses from TCGA data. Reprinted from Sanchez-Vega et al. [2018].

be data from model organisms such as mice or tumours of human origin but made more suitable for experimentation. In the latter category, it is crucial to mention the huge amount of data available on cell lines, extracted from human tumours and transformed to be studied in culture. It is then possible to go beyond descriptive data and vary the experimental conditions in order to study the responses of these cells to perturbations and to enrich our knowledge. It is therefore possible to know the response to more than 100 drugs of about 700 cell lines [Yang et al., 2012]. The richness of these data, coupled with the omic profiling of each cell line, enables to study the determinants of response to treatment with unprecedented scope [Iorio et al., 2016]. More recently, but following a similar logic, other types of

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inhibition screenings have been proposed based on a more specific technique called CRISPR-Cas9 [Behan et al., 2019]. The simplicity of the cell lines in relation to the original tumours makes all these studies possible but sometimes hinders the clinical application of the knowledge acquired. For this reason, other types of biological models have been developed, including patient-derived xenografts (PDX) which is an implant of human tumours in mice to maintain the existence of a certain tumour microenvironment [Hidalgo et al., 2014], while maintaining drug screening possibilities [Gao et al., 2015]. These two types of data, cell lines and PDX, have been used in this thesis, in addition to TCGA patient data, thus justifying the limitation of this presentation, which could otherwise be extended to other types of biological models. Similarly, other technologies are becoming increasingly important in the generation of cancer data, such as single-cell sequencing [Navin, 2015], but will not be used in this work.

## 2.5 Data and beyond: from genetic to network disease

All that remains to be done now is to make sense of all these data, to organize it, because understanding does not flow directly from the abundance of data and the ability to produce the data may have been outpaced by the ability to analyze it [Stadler et al., 2014]. A striking example is that of the prognostic signatures mentioned above. The many signatures or lists of genes proposed, even for the same cancer type, share relatively few genes, are difficult to interpret and their efficiency is sometimes poorly reproducible [Domany, 2014]. Even more surprisingly, most signatures composed of randomly selected genes were also found to be associated with patient survival [Venet et al., 2011]. One of the main avenues for improving the interpretability of the data is the integration of the prior knowledge we have of the phenomena, and in this case of cancer [Domany, 2014].

This *a priori* knowledge is in fact already present in Figure 2.6 since genetic alterations have been grouped in several categories called pathways. A pathway is group of biological entities, and associated chemical reactions, working together to control a specific cell function like apoptosis or cell division. The interest of these groupings maybe understood based on the description of hallmarks. Indeed, if the “aim” of a cancer cell is to inactivate each of the protective functions, then it is more relevant to think not by gene but by function. Inactivating only one of the genes associated with the function may be sufficient and it is no longer necessary to inactivate

## 2.5. DATA AND BEYOND: FROM GENETIC TO NETWORK DISEASE

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the others. Numerous alterations in a large number of genes result often in few key impaired pathways, like alterations of cell cycle or angiogenesis for instance [Jones et al., 2008]. It is therefore possible to improve the stability and interpretability of analyses by moving from the gene scale to the pathway scale [Drier et al., 2013]. More generally, the integration of biological knowledge often leads to improved performance in various cancer-related prediction tasks, either through the selection of variables or by taking into account the structure of the variables [Bilal et al. [2013]; ferranti2017value]. Increasingly, the biological variables are not interpreted separately but in relation to each other [Barabasi and Oltvai, 2004]. This is reflected in the emergence of more and more resources to summarize and represent signaling pathways and associated networks such as SIGNOR [Perfetto et al., 2016], OmniPath [Türei et al., 2016] or the Atlas of Cancer Signaling Network [Kuperstein et al., 2015]. Like other diseases, cancer then goes from a genetic disease to a network disease [Del Sol et al., 2010] and one can study how all kinds of genetic alterations affect the wiring of these networks [Pawson and Warner, 2007], and modify the cellular functions leading to the previously described cancer hallmarks as depicted schmatically in Figure 2.7. In short, the richness of the data did not make it less necessary to use *a priori* knowledge in order to make the analyses more interpretable and more robust.

The final step, to obtain one of the most complete and integrated visions of cancer biology, is then to integrate omics knowledge with knowledge about the structure of pathways to try to understand in detail how their combinations can lead to so many cancers that are both similar and different. An example of such a representation is given by mapping the TCGA data about genetic alterations, presented in Figure 2.6, on a representation of the different pathways showing not only their internal organization but also their cross-talk [Sanchez-Vega et al., 2018]. This representation is proposed in Figure 2.8 and is the most recent view of the kind of tools and data available to the modeller who wants to dissect more deeply the mechanisms at work.

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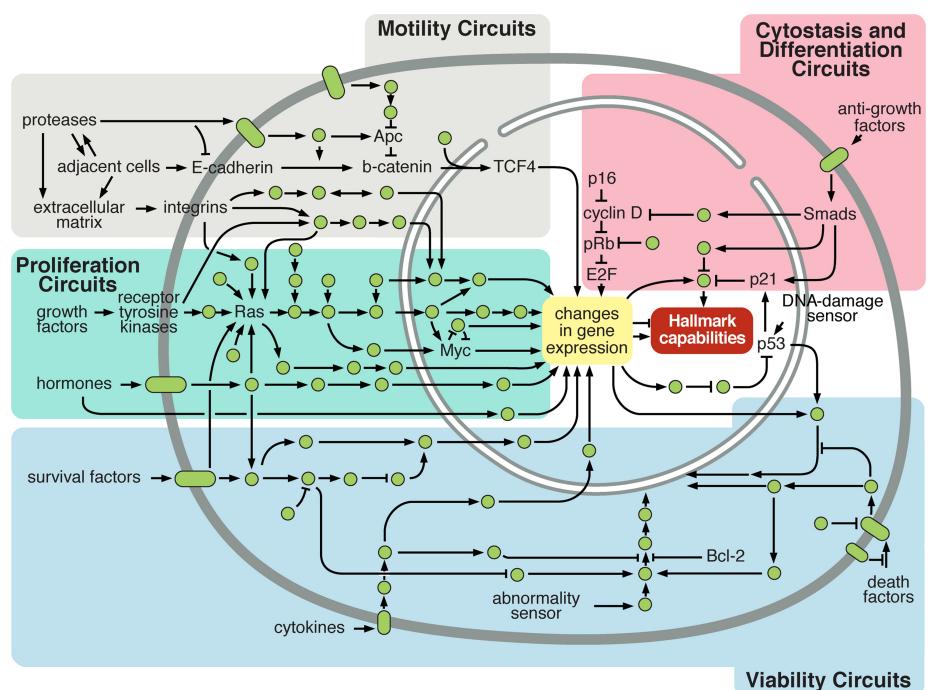


Figure 2.7: **Simplistic representation of cellular circuitry.** Normal cellular circuit sand sub-circuits (identified by colours) can be reprogrammed to regulate hallmark capabilities within cancer cells. Reprinted from Hanahan and Weinberg [2011].

## 2.5. DATA AND BEYOND: FROM GENETIC TO NETWORK DISEASE

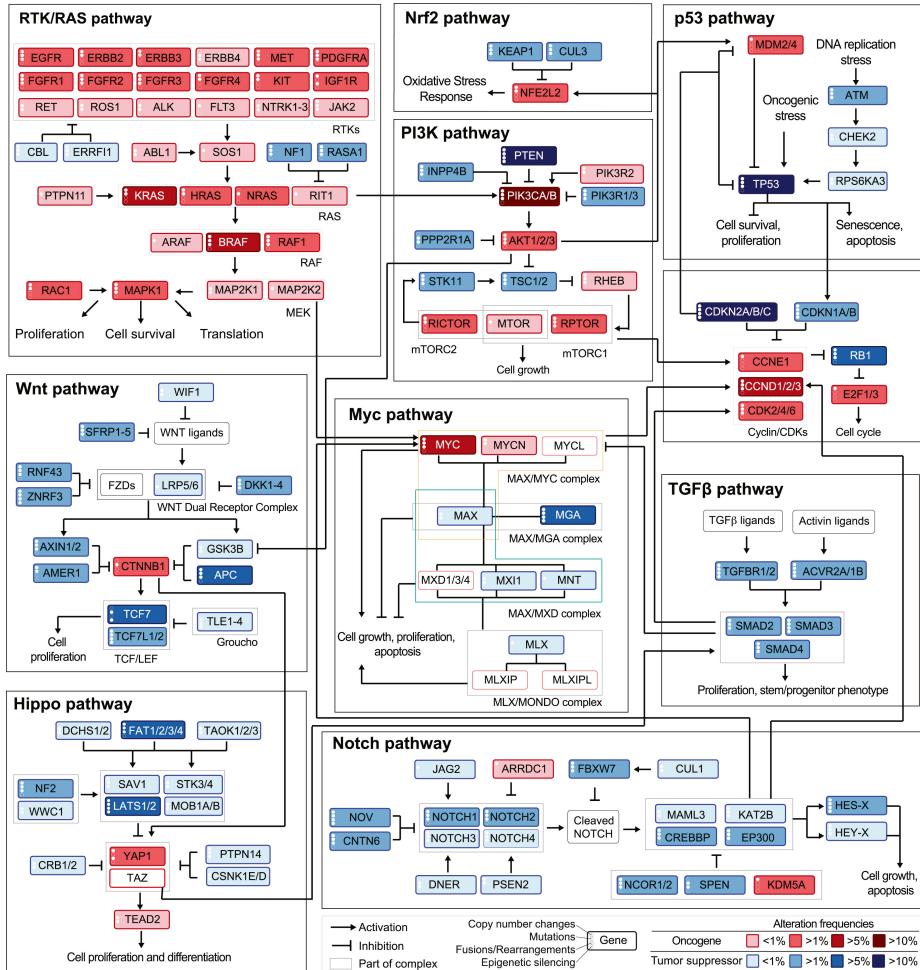


Figure 2.8: Genetic alterations frequencies from TCGA data mapped on a schematic signaling network. Frequencies of alteration per pathway and tumour types as summarised in Pan-cancer analyses from TCGA data. Reprinted from Sanchez-Vega et al. [2018].



## Mechanistic modeling of cancer: from complex disease to systems biology

*"How remarkable is life? The answer is: very. Those of us who deal in networks of chemical reactions know of nothing like it... How could a chemical sludge become a rose, even with billions of years to try."*

*George Whitesides*

The previous chapter identified the need to organize cancer knowledge and data. The integration of biological knowledge, particularly in the form of networks, is a first step in this direction. The deepening of knowledge, however, requires the ability to manipulate objects even more, to experiment, to dissect their behaviour in an infinite number of situations, such as the astronomer with his orrery or physicians with their old anatomical models (Figure 3.1). Is it then possible to create mechanistic models of cancer in the same way?

### 3.1 Introducing the diversity of mechanistic models of cancer

Modeling cancer is not a new idea. And the diversity of biological phenomena at work in cancer has given rise to an equally important diversity of

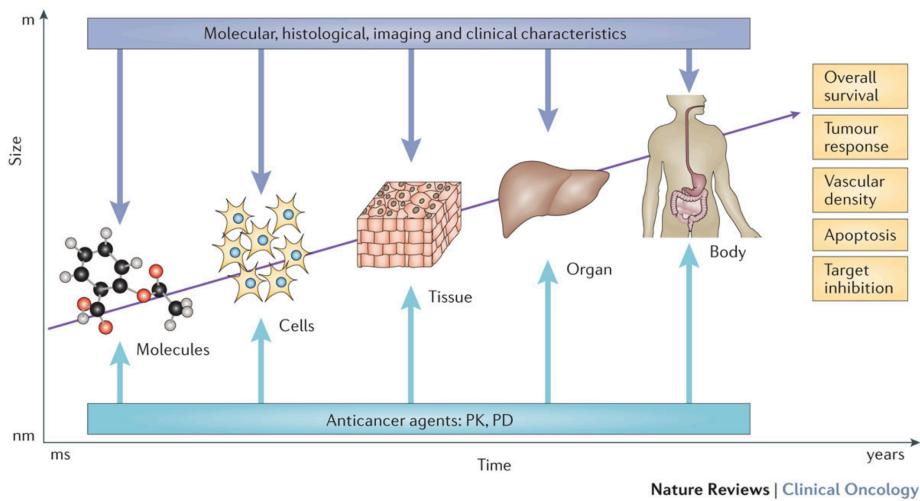


Figure 3.1: **Dissecting a biological phenomenon using a non-computational model.** Rembrandt, *The Anatomy Lesson of Dr Nicolaes Tulp*, 1634, oil on canvas, Mauritshuis museum, The Hague

models and formalisms, which we seek here to give a brief overview in order to better identify the specific models that we will focus on later. One way to order this diversity is to consider the scales of these models (Figure 3.2). Indeed, cancer can be read at different levels, from the molecular level of DNA and proteins, to the cellular level, to the level of tissues and the organism [Anderson and Quaranta, 2008]. Models have been proposed at all these scales, using different formalisms [Bellomo et al., 2008] and answering different questions.

Consistent with the evolution of knowledge and data, the early models were at the macroscopic level. While methods and terminologies may have changed, there are nevertheless traces of these models as early as the 1950s. We then speak rather of mathematical modeling with a meaning that is nevertheless intermediate between what we have defined as mechanistic models and statistical models [Byrne, 2010]. First, the initiation of tumorigenesis was theorized with biologically-supported mathematical expressions in order to make sense of cancer incidence statistics [Armitage and Doll, 1954, Knudson [1971]]. These models, however, remained relatively descriptive

### 3.1. INTRODUCING THE DIVERSITY OF MECHANISTIC MODELS OF CANCER



**Figure 3.2: The different scales of cancer modeling.** Cancer can be approached at different scales, from molecules to organs, using different data (dark blue), but often with the direct or indirect objective of contributing to the study of clinically interpretable phenomena (yellow boxes), in particular by studying the influence of anticancer agents (pale blue). Reprinted from Barbolosi et al. [2016].

in that they did not shed any particular light on the biological mechanisms involved and focused on gross characteristics of tumours. The integration of more advanced knowledge as well as the progressive refinement of mathematical formalisms has nevertheless allowed these models to proliferate while gaining in interpretability, with for instance mechanistic models of metastatic relapse [Nicolò et al., 2020]. Always on a macroscopic scale, the study of tumor growth has also been the playground of many mathematicians [Araujo and McElwain [2004]; byrne2010dissecting], even predicting invasion or response to surgical treatments using spatial modeling [Swanson et al., 2003]. This line of research is still quite active today and provides a mathematical basis for comparison with tumour experimental growth [Benzekry et al., 2014].

Taking it down a step further, it is also possible to model cancer at the cellular level, for example by looking at the clonal evolution of the cancer [Altrock et al., 2015]. The aim is then to understand the impact of the processes of mutation, selection, expansion and cohabitation of different populations of cells, at specific rates. The accumulation of a mutation in a population of cells can thus be studied [Bozic et al., 2010]. Modeling at the cellular level is well suited to the study of interactions between cells,

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between cancer cells and their environment or with the immune system. Similar to other kinds of studies of population dynamics, formalisms based on differential equations are quite common [Bellomo et al., 2008]; but there are many other methods such partial differential equations or agent-based modeling [Letort et al., 2019].

Finally, at an even smaller scale, it is possible to model the molecular networks at work in cells [Le Novere, 2015]. The aim is then to simulate mathematically how the different genes and molecules regulate each other, transmit information and, in the case of cancer, end up being deregulated [Calzone et al., 2010, Flobak et al., 2015]. These models will be the subject of the thesis and will therefore be defined more precisely and used to detail the concepts and tools of systems biology in the following sections. It can already be noted that while these models can integrate the most fundamental biological mechanisms of living organisms, one of the most burning questions is whether it is possible to link them to the larger scales that are clinically more interesting (tissues, organs etc.). Can these models tell us about the molecular nature of cancer? About patient survival? Their response to treatment? These questions apply to all of the above models, whatever their scales (Figure 3.2), but are more difficult to answer for models defined at molecular scale that are further from the clinical data of interest. The aim of this thesis is to provide potential answers to these questions. One of the ways of approaching these issues has been to propose multi-scale models, which are nevertheless very complex [Anderson and Quaranta, 2008, Powathil et al., 2015]. We will focus here on the use of models defined almost exclusively at the molecular scale, which is assumed to be prominent, to study what can be inferred on the larger scales.

## 3.2 Cell circuitry and the need for cancer systems biology

Most biological systems, and certainly cells, fall into the category of complex systems. These are systems made up of many interacting elements. While these systems can be found in many different scientific fields, the cell as a complex system is characterized by the diversity and multifunctionality of its constituent elements (genes, proteins, small molecules, enzymes), which nevertheless contribute to organized and *a priori* non-chaotic behaviour [Kitano, 2002]. Thus, the role of a protein such as the p53 tumour suppressor can only be understood by taking into account the interplay between its relationships with transcription factors and biochemical modifications of

### 3.2. CELL CIRCUITRY AND THE NEED FOR CANCER SYSTEMS BIOLOGY

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the molecule itself [Kitano, 2002]. In a cell, as in any complex system, the multiplication of components and interactions can make the response or behaviour of the system unexpected or unpredictable. Non-linear responses, such as abrupt changes in the state of a system, called critical transitions, can be observed in response to a moderate change in the signal [Trefois et al., 2015]. Generally speaking, it is possible to observe emergent behaviours, i.e. behaviours of the system as a whole that were not trivially deducible from the individual behaviours of its components. This has been documented, through experiments and simulations, in the study of cell signalling pathways and the resulting biological decisions [Bhalla and Iyengar, 1999, Helikar et al., 2008]. These considerations have thus given rise to system-level or holistic approaches that aim to integrate data and knowledge into more comprehensive representations, often called **systems biology**.

What is true for the cell in general is just as true for cancer in particular. Understanding the intertwining of signaling pathways is necessary to study their contributions to different cancer hallmarks, as shown in Figure 2.7. The concepts described above can thus be transposed to cancer systems biology [Hornberg et al., 2006, Kreeger and Lauffenburger, 2010, Barillot et al., 2012]. Indeed, it is often a question of understanding or predicting the impact of perturbations on cellular networks. Understanding how a single genetic mutation disrupts and reprograms networks, or even predicting the responses triggered by a drug on a presumably promising molecular target, makes little sense without integrated approaches. In addition, Cancers are characterized by the accumulation of numerous mutations and alterations over time that must be considered concomitantly. These points of view of biologists and modellers reinforce the observation already made in the previous chapter of cancer as a network disease, as a system disease (Figure 2.8).

Finally, to conclude this general presentation, it is important to understand that while small molecular network modeling is not recent, the rise and multiplication of wide range systems biology approaches is very much related to the production of biological data [De Jong, 2002]. The last few decades have seen the emergence of high-throughput data that have made it possible to identify and link hundreds of genes or proteins involved in cancer. Exploring the interaction and back and forth between these models and the data they use or predict is therefore of utmost importance. In addition, the now massive amount of data has also imposed mathematical or computational approaches as central to managing this profusion and more and more modeling approaches are focused on data integration or inference [Fröhlich et al., 2018, Bouhaddou et al., 2018]More generally, Figure 3.3

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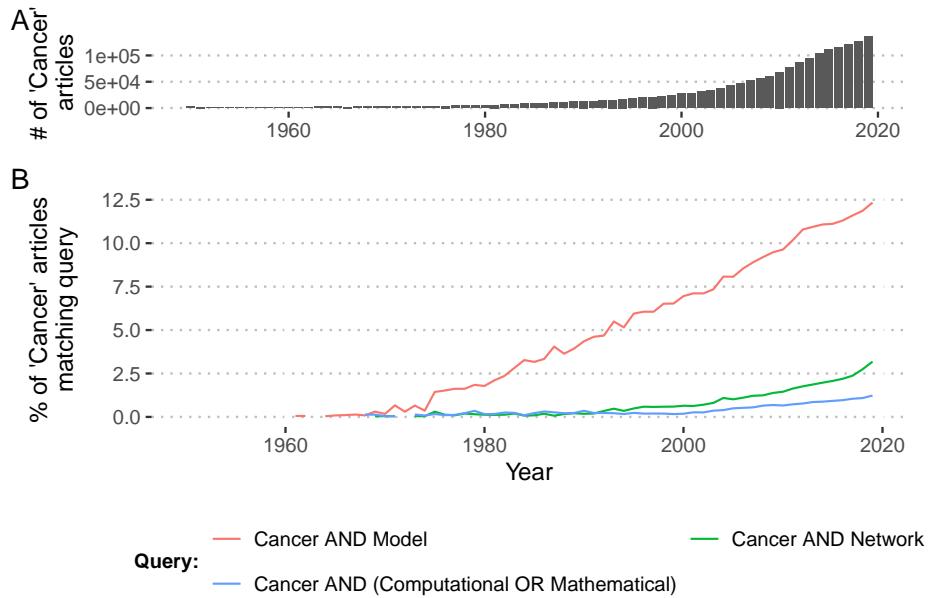


Figure 3.3: **PubMed trends in cancer studies.** (A) PubMed articles with the word *Cancer* in either title or abstract from 1950 to 2019. (B) Proportion of the *Cancer* articles with additional keywords expressed as PubMed logical queries.

shows that while the number of scientific articles devoted to cancer has increased drastically since the 1950s (panel A), the proportion of these same articles mentioning *models*, *networks* or *computational* approaches has also increased (panel B), illustrating a change in paradigms.

### 3.3 Mechanistic models of molecular signaling

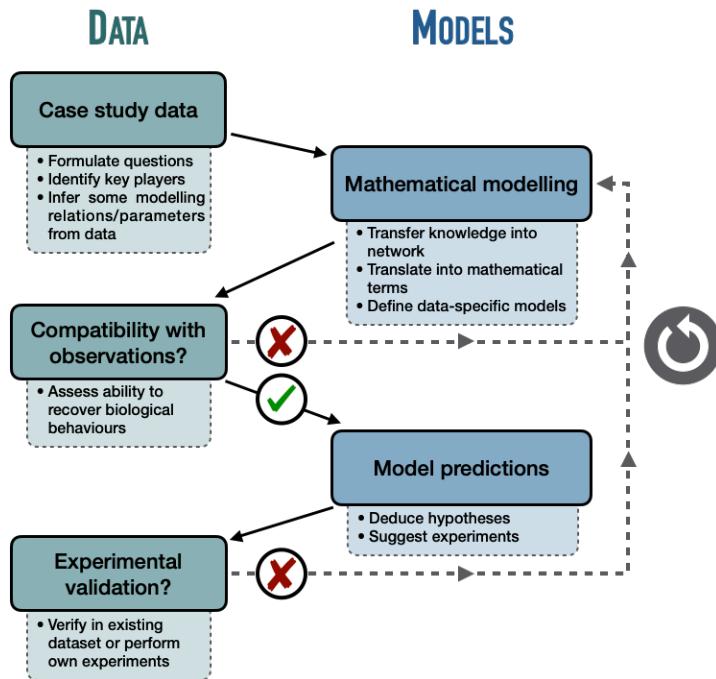
Once the context has been defined, both biologically and methodologically, it is possible to begin the exploration of the models that will constitute the core of this thesis: the **mechanistic models of molecular networks** and signaling pathways. Before describing and illustrating some of the existing mathematical formalisms, it is possible to describe the common fundamental elements of this family of approaches. The simplest is a network of undirected interaction between entities, which therefore only establishes relationships and not causal mechanisms.

### 3.3.1 Networks and data

The first step is to identify the relevant biological entities from a question or system of interest (e.g. tumor suppressor genes, signaling cascades of proteins) and then to model their interactions, the regulatory relationships that link them. At this stage the model can generally be represented by a network but this word can cover different realities [Le Novere, 2015]. The simplest network just represents undirected interactions between entities, which therefore only establishes relationships and not causal mechanisms. But modeling requires more precise definitions, in particular concerning the direction of the interaction (is it A that acts on B or the opposite) and its nature (type of chemical reaction, activation/inhibition etc.). This is usually summarized as activity flows (or influence diagrams) with activation and inhibition arrows as in Figure 2.7 or Figure 3.5A. These arrows emphasize the transformation of static networks into dynamic objects that can be manipulated and interpreted mechanistically. This work can be taken further by writing bipartite graphs, known as process descriptions, which explicitly show the different states of each variable (first type of nodes), depending on their phosphorylation state for instance, and the reactions that link them (second type of nodes) as in Figure 3.5B. A more precise description of these different representations and their meanings can be found in Le Novere [2015]. Once the network structure of the model has been defined, it is possible write the corresponding mathematical formalism and potentially to refine certain parameters. Finally, the model is often confronted with new data to check its consistency with the biological behaviour studied or possibly make new predictions.

However, all these steps are not linear and sequential, but rather iterative and cyclical. This modeling cycle, with back and forth to the data, is not specific to molecular network models, but it is possible to specify it in this case (Figure 3.4). The names of the key players involved in the question of interest are thus first extracted from adapted data or from the literature. A first mathematical translation of the relationships between the entities is then proposed before verifying the compatibility of this model with the observations, whether qualitative or quantitative. If the compatibility is not good, we come back to the definition or the parameterization of the model. If compatibility is correct, the model can be used to make new predictions or study phenomena that go beyond the initial data set. Ideally, these predictions will be tested afterwards. This cyclic approach with two successive checks is analogous to the use of validation and test data in the evaluation of most learning algorithms. This analogy can sometimes be masked by the qualitative nature of the predictions or by the lack of explicit fitting of the

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**Figure 3.4: Modeling a biological network: an iterative and cyclical process.** Reprinted from [Béal et al., 2020]. A different and simpler version of this cycle is described in [Le Novère, 2015].

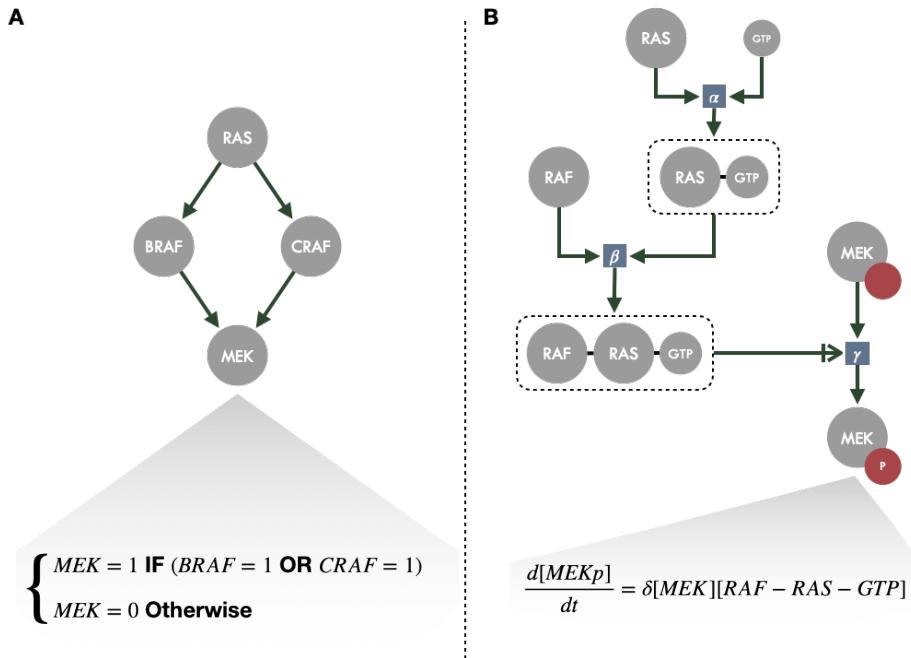
parameters.

### 3.3.2 Different formalisms for different applications

Beyond these similarities in the construction and representation of models, the precise mathematical formalism that underlies them varies according to the type of question and the data [De Jong, 2002]. For the sake of simplicity, and without exhaustiveness, we propose to divide into quantitative and qualitative formalisms which will be essentially illustrated respectively by **ordinary differential equation (ODE)** models and **logical (or Boolean) models** for which a graphical and schematic comparison is proposed in Figure 3.5.

One of the most frequent approaches is the use of chemical kinetics equations to construct ODE systems which are a fairly natural translation of the process description networks described in the previous section [Polynikis et al., 2009]. Each biological interaction is treated as a reaction governed by the law of mass action and, under certain hypotheses, as a differential equation; the set of reactions in the system then generates a set

### 3.3. MECHANISTIC MODELS OF MOLECULAR SIGNALING



**Figure 3.5: Schematic example of logical and ODE modeling around MAPK signaling.** (A) Activity flow diagram of a small part of MAPK signaling, each node representing a gene or protein, with an example of logical rule for MEK node for the corresponding logical model. (B) Process description of the same diagram with BRAF and CRAF merged in RAF for the sake of simplicity; each square representing a reaction and the correspondong rate; an example differential equation is provided for the phosphorylated (active) form of MEK.

of differential equations with coupled variables, in an analogous way to the Lotka Volterra system presented in section 1.2.2. Thus the variables generally represent quantities of molecular species, for example concentrations of RNA or proteins, and the stoichiometric coefficients and reaction rates are used to define the system parameters. Approximations are sometimes made to simplify the equations, for example by assuming that they can be written as Michaelis Menten's enzymatic reactions, which have a simple and well known behaviour. However, the theoretical accuracy of quantitative models has a cost since each differential equation requires parameters, such as reaction constants or initial conditions, to which the system is very sensitive [Le Novere, 2015]. The biochemical interpretation of the parameters sometimes allow to find their value in the literature, if the reactions are well characterized, even if possible variations in a given biological or

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physical context are often unknown. Since knowledge of the values of these parameters is often limited or even non-existent, it may require a very large volume of data (including time series) to fit the many missing parameters which can be difficult if the number of parameters is large [Villaverde and Banga, 2014]. However, recent work has demonstrated the feasibility and scalability of this type of inference with sufficiently rich data. [Fröhlich et al., 2018]

At the same time, more qualitative approaches to modeling biological networks have been proposed with discrete variables linked together by rules expressed as logical statements [Abou-Jaoudé et al., 2016]. These models are both more abstract since variables do not have a direct biological interpretation (e.g. concentration of a species) but are more versatile since they can unify different biological realities under the same formalism (e.g. activation of a gene or phosphorylation of a protein). The discrete nature of the variables can then be seen as an asymptotic case of the sigmoidal (e.g. Hill function) relationships often found in biology [Le Novère, 2015]. The step function thus obtained can keep a natural interpretation in the context of biological phenomena: genes activated or not, protein present or absent etc. Similarly, interactions between species are not quantified but are based on a qualitative statements (e.g. A will be active if B and C are active), drastically reducing the number of parameters. If the theoretical interest of this formalism to study biological mechanisms was proposed quite early [Kauffman, 1969, Thomas, 1973], many concrete applications have also been developed over the years, particularly in cancer research [Saez-Rodriguez et al., 2011, Remy et al., 2015]. This **logical formalism will constitute the core of the work presented in Part II**, where it will therefore be discussed in greater detail.

These two formalisms, which are among the most frequent for modelling biological networks, share many similarities, in particular the propensity to be built according to bottom-up strategies based on knowledge of the elementary parts of the model, i.e. biological entities and reactions. However, they differ in their implementation and objectives, one aiming at the most accurate representation possible, the other seeking to capture the essence of the system's dynamics in a parsimonious way (Table 3.1). The opposition is not irrevocable, as illustrated by the numerous hybrid formalisms that lie within the spectrum delimited by these two extremes such as fuzzy logic or discrete-time differential equations [Le Novère, 2015, Calzone et al., 2018]. To conclude, a comparison between the two approaches applied to the same problem is proposed by Calzone et al. [2018], studying the epithelial-mesenchymal transition (EMT, a biological process involved in cancer), to illustrate in concrete terms their complementarity.

### 3.4. FROM MECHANISTIC MODELS TO CLINICAL IMPACT?

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Table 3.1: **Features of quantitative and qualitative modeling applied to biological molecular networks** (adapted from Le Novere [2015])

Quantitative modeling	
Example formalism	Ordinary differential equation (ODE) models
Type of variables	Direct translation of biological quantities, usually continuous
Objective	Quantitatively accurate and temporal simulation of an experimental phenomenon
Advantages	Direct confrontation with experimental data; precise; linear representation of time
Drawbacks	Difficulty determining or fitting parameters

#### 3.3.3 Some examples of complex features

With the help of these models, both qualitative and quantitative, many complex behaviours have been identified. Benefiting from the knowledge accumulated in the study of dynamic systems, a whole zoo of patterns with complex and non-intuitive behaviours such as non-linearities have been highlighted [Tyson et al., 2003]. The MAPK pathway, coarsely described in Figure 3.5, and often simplified as a rather unidirectional cascade, shows switch or bistability behaviors generated by the complexity of its multiple phosphorylation sites [Markevich et al., 2004]. These models have also been put at the service of understanding cancer and the erroneous decision-making by cells resulting from impaired signaling pathways. Thus Tyson et al. [2011] summarize superbly well the complexity that can be hidden in the dynamics of smallest molecular networks as soon as they contain more than two entities and crossed regulations or feedback loops. Logical models have also made it possible to better dissect some complex phenomena at play in the cell such as emergent behaviours [Helikar et al., 2008] or mechanisms behind mutation patterns in cancer [Remy et al., 2015].

## 3.4 From mechanistic models to clinical impact?

Mechanistic models have therefore undeniably led to a better understanding of the complex molecular machinery of signalling pathways. But beyond the interest that this understanding represents, do these models also have a clinical utility? In other words, **are they of clinical or only scientific**

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**value?** Throughout this thesis, the clinical value of mechanical models will often be analyzed by analogy to that of biomarkers. Throughout this thesis, the clinical value of mechanical models will often be analyzed by analogy to that of biomarkers. Biomarkers are defined as measurable indicators of patient status or disease progression, such as prostate-specific antigen (PSA) for prostate cancer screening or BRCA1 mutation for breast cancer risk [Henry and Hayes, 2012]. [Oldenhuis et al., 2008]

### 3.4.1 Prognostic models

2 types of models 2 types of data, either prognosis (on patients) or response to treatment (validated on cell lines)

Khan logical pronostic [Khan et al., 2017] Logical treatment[Zañudo et al., 2017] Details Fey [Fey et al., 2015] First Prehn [Hector et al., 2012] [Salvucci et al., 2017] [Fröhlich et al., 2018] logic drugs [Knijnenburg et al., 2016]

Other formalisms for drugs [Jastrzebski et al., 2018] and activity flows for prognostic [Hidalgo et al., 2017]

plus machine learning [Salvucci et al., 2019]

## Test part

This is a test

### 4.1 Abc

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

But in Béal et al. [2019] we have the Figure 4.1 as referenced in Chapter 4

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

And an external figure 4.2

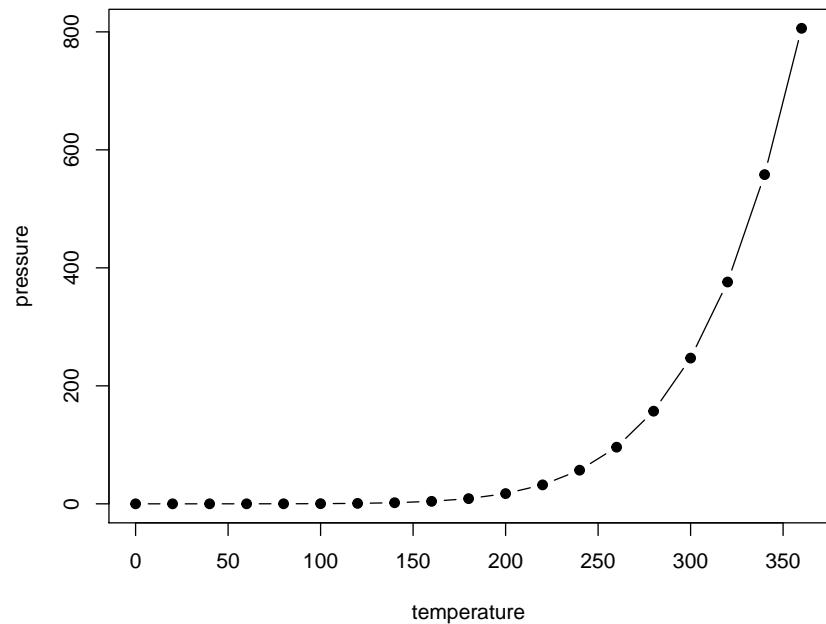


Figure 4.1: Here is a nice figure!



Figure 4.2: Example pic

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## RÉSUMÉ

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Cuius acerbitati uxor grave accesserat incentivum, germanitate Augusti turgida supra modum, quam Hannibaliano regi fratri filio antehac Constantinus iunxerat pater, Megaera quaedam mortal is, inflammatrix saeuentis adsidua, humani cruris 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

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Caesar licentia post honoratis haec adhibens urbium honoratis nullum Caesar.

## ABSTRACT

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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

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Delatus delatus nominatus onere aut trahebatur quod tenus et bonorum.