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
Jonas BEAL
Le 15/09/2020

École doctorale n°515
Complexité du Vivant

Spécialité
Génomique

Composition du jury :

Test NOM Titre, Établissement	*Président*
Test NOM Titre, Établissement	*Rapporteur*
Test NOM Titre, Établissement	*Examinateur*
Test NOM Titre, Établissement	*Examinateur*
Emmanuel BARILLOT Institut Curie, INSERM, Mines ParisTech, PSL	*Directeur de thèse*
Aurélien LATOUCHE Institut Curie, Cnam	*Directeur de thèse*
Laurence CALZONE Institut Curie, INSERM, Mines ParisTech, PSL	*Co-encadrante de thèse*

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

Table **Page**

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] TRUE
##
## [[2]]
## [1] TRUE
##
## [[3]]
## [1] TRUE
```

```
##
## [[4]]
## [1] TRUE
##
## [[5]]
## [1] TRUE
##
## [[6]]
## [1] TRUE
##
## [[7]]
## [1] TRUE
```

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

1.1 What is a model?

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 1.2, while 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 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.

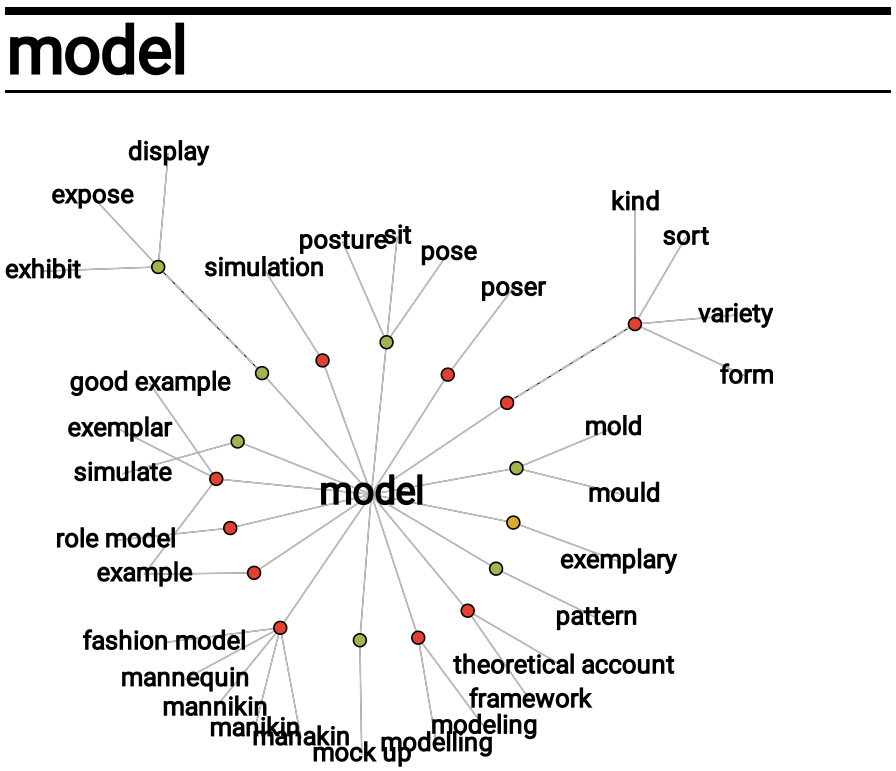


Figure 1.2: **Network visualization of *model* thesaurus entries.** Generated with the 'Visual Thesaurus' ressource

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

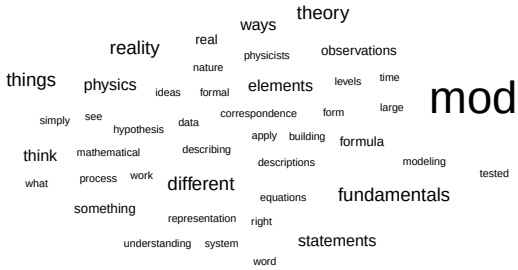


Figure 1.3: **Scientists talk about their models: words cloud.** Cloud of words summarizing the lexical fields used by scientists to talk about their models in dedicated interviews [Bailer-Jones, 2002].

Pubmed tree

Material/physical models (from orrery to drosophila) Formal/theoretical models

"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." https://www.nemenmanlab.org/~ilya/images/9/99/Rosenblueth-wiener-1945.pdf

Philosophy [Frigg and Hartmann, 2020]

Galilean idealization with reality distortion But even toy models for salient features

Historically physical models

Then mathematics as a language

Statistical models with a priori knowledge

In vivo, in vitro, in silico,

Mechanistic to explain observation –> epicycle Ptolémée

1.2 Statistical modeling

Within formal models -> 2 kinds

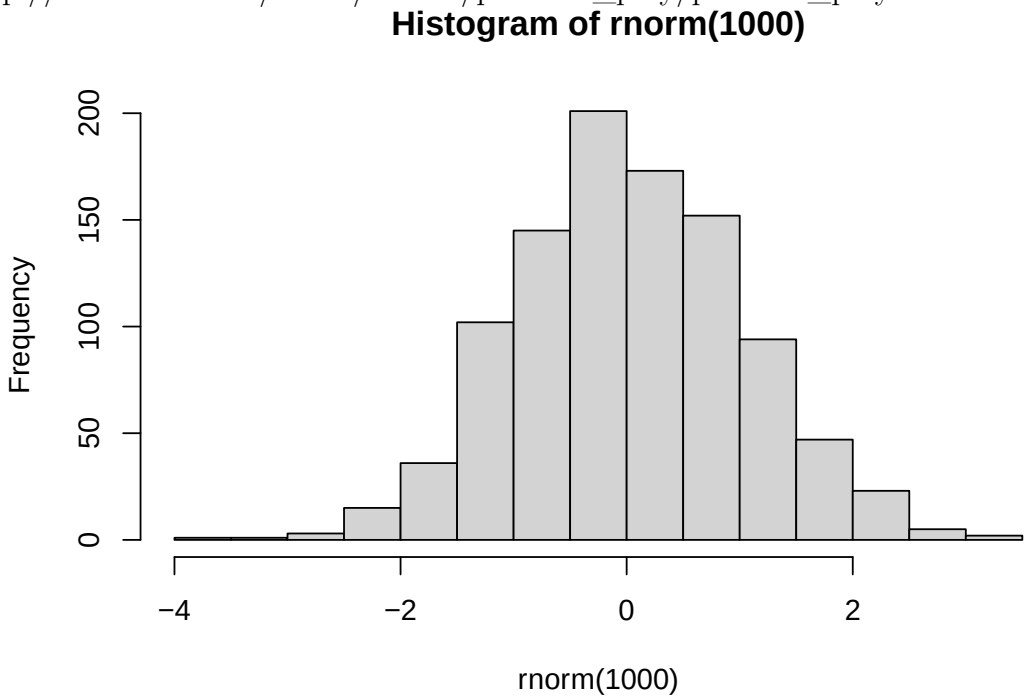
[Baker et al., 2018]

https://gosilico.com/technology/mechanistic-vs-statistical-models/

Mechanistic already answer the "how" –> causality inside Breiman –> Inside the box

https://theartofmodelling.wordpress.com/2012/02/19/mechanistic-models-what-is-the-value-of-understanding/

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



1.3 Mechanistic modeling

Chapter 2

What is cancer

This is a test

2.1 Abc

Bla bla

The LaTeX environment `tiny` is only generated for LaTeX output.

	mpg	cyl	disp	hp	drat	wt	qsec	vs	am	gear	carb
Mazda RX4	21.0	6	160.0	110	3.90	2.620	16.46	0	1	4	4
Mazda RX4 Wag	21.0	6	160.0	110	3.90	2.875	17.02	0	1	4	4
Datsun 710	22.8	4	108.0	93	3.85	2.320	18.61	1	1	4	1
Hornet 4 Drive	21.4	6	258.0	110	3.08	3.215	19.44	1	0	3	1
Hornet Sportabout	18.7	8	360.0	175	3.15	3.440	17.02	0	0	3	2
Valiant	18.1	6	225.0	105	2.76	3.460	20.22	1	0	3	1
Duster 360	14.3	8	360.0	245	3.21	3.570	15.84	0	0	3	4
Merc 240D	24.4	4	146.7	62	3.69	3.190	20.00	1	0	4	2
Merc 230	22.8	4	140.8	95	3.92	3.150	22.90	1	0	4	2
Merc 280	19.2	6	167.6	123	3.92	3.440	18.30	1	0	4	4
Merc 280C	17.8	6	167.6	123	3.92	3.440	18.90	1	0	4	4
Merc 450SE	16.4	8	275.8	180	3.07	4.070	17.40	0	0	3	3
Merc 450SL	17.3	8	275.8	180	3.07	3.730	17.60	0	0	3	3
Merc 450SLC	15.2	8	275.8	180	3.07	3.780	18.00	0	0	3	3
Cadillac Fleetwood	10.4	8	472.0	205	2.93	5.250	17.98	0	0	3	4
Lincoln Continental	10.4	8	460.0	215	3.00	5.424	17.82	0	0	3	4
Chrysler Imperial	14.7	8	440.0	230	3.23	5.345	17.42	0	0	3	4
Fiat 128	32.4	4	78.7	66	4.08	2.200	19.47	1	1	4	1
Honda Civic	30.4	4	75.7	52	4.93	1.615	18.52	1	1	4	2
Toyota Corolla	33.9	4	71.1	65	4.22	1.835	19.90	1	1	4	1
Toyota Corona	21.5	4	120.1	97	3.70	2.465	20.01	1	0	3	1
Dodge Challenger	15.5	8	318.0	150	2.76	3.520	16.87	0	0	3	2
AMC Javelin	15.2	8	304.0	150	3.15	3.435	17.30	0	0	3	2
Camaro Z28	13.3	8	350.0	245	3.73	3.840	15.41	0	0	3	4
Pontiac Firebird	19.2	8	400.0	175	3.08	3.845	17.05	0	0	3	2
Fiat X1-9	27.3	4	79.0	66	4.08	1.935	18.90	1	1	4	1
Porsche 914-2	26.0	4	120.3	91	4.43	2.140	16.70	0	1	5	2
Lotus Europa	30.4	4	95.1	113	3.77	1.513	16.90	1	1	5	2
Ford Pantera L	15.8	8	351.0	264	4.22	3.170	14.50	0	1	5	4
Ferrari Dino	19.7	6	145.0	175	3.62	2.770	15.50	0	1	5	6
Maserati Bora	15.0	8	301.0	335	3.54	3.570	14.60	0	1	5	8
Volvo 142E	21.4	4	121.0	109	4.11	2.780	18.60	1	1	4	2

By comparison, below is the table with the normal font size.

	mpg	cyl	disp	hp	drat	wt	qsec	vs	am	gear	carb
Mazda RX4	21.0	6	160.0	110	3.90	2.620	16.46	0	1	4	4
Mazda RX4 Wag	21.0	6	160.0	110	3.90	2.875	17.02	0	1	4	4
Datsun 710	22.8	4	108.0	93	3.85	2.320	18.61	1	1	4	1
Hornet 4 Drive	21.4	6	258.0	110	3.08	3.215	19.44	1	0	3	1
Hornet Sportabout	18.7	8	360.0	175	3.15	3.440	17.02	0	0	3	2
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Merc 230	22.8	4	140.8	95	3.92	3.150	22.90	1	0	4	2
Merc 280	19.2	6	167.6	123	3.92	3.440	18.30	1	0	4	4
Merc 280C	17.8	6	167.6	123	3.92	3.440	18.90	1	0	4	4
Merc 450SE	16.4	8	275.8	180	3.07	4.070	17.40	0	0	3	3
Merc 450SL	17.3	8	275.8	180	3.07	3.730	17.60	0	0	3	3
Merc 450SLC	15.2	8	275.8	180	3.07	3.780	18.00	0	0	3	3
Cadillac Fleetwood	10.4	8	472.0	205	2.93	5.250	17.98	0	0	3	4
Lincoln Continental	10.4	8	460.0	215	3.00	5.424	17.82	0	0	3	4
Chrysler Imperial	14.7	8	440.0	230	3.23	5.345	17.42	0	0	3	4
Fiat 128	32.4	4	78.7	66	4.08	2.200	19.47	1	1	4	1
Honda Civic	30.4	4	75.7	52	4.93	1.615	18.52	1	1	4	2
Toyota Corolla	33.9	4	71.1	65	4.22	1.835	19.90	1	1	4	1
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Dodge Challenger	15.5	8	318.0	150	2.76	3.520	16.87	0	0	3	2
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Maserati Bora	15.0	8	301.0	335	3.54	3.570	14.60	0	1	5	8
Volvo 142E	21.4	4	121.0	109	4.11	2.780	18.60	1	1	4	2

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

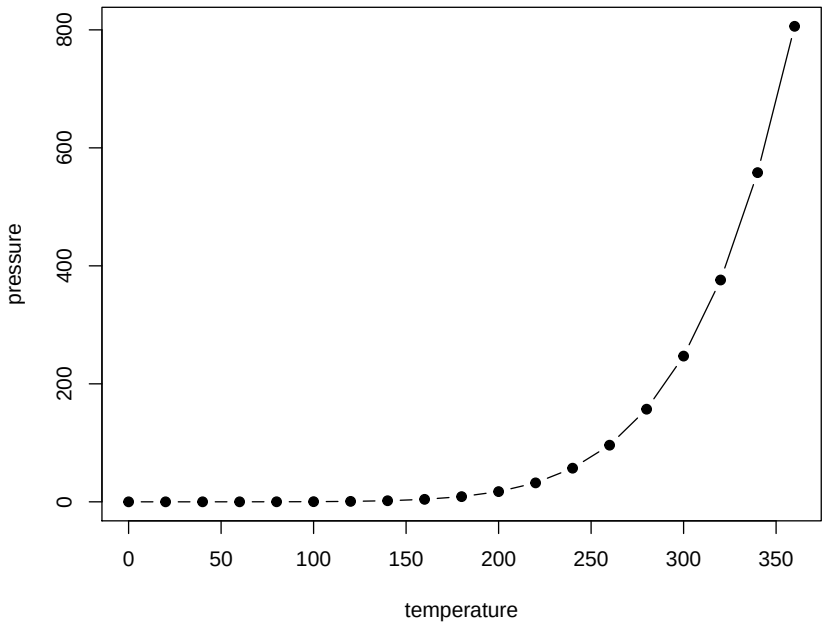

Figure 3.1: Here is a nice figure!

Figure 3.2: Example pic

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Ljubisa Miskovic, Jonas Béal, Michael Moret, and Vassily Hatzimanikatis. Uncertainty reduction in biochemical kinetic models: Enforcing desired model properties. *PLoS Computational Biology*, 2019. ISSN 15537358. doi: 10.1371/journal.pcbi.1007242. URL https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1007242.

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.