Projet BIDASA ”Big DAta en SAnté”

Journées de restitution
MASTODONS’ 2017
Paris
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Nicolas SAVY

Institut de Mathématiques de Toulouse

Content of the talk

Context of BiDaSa Project

- Health data, is an **unusal Big Data**

- Because health components are diverse
  $\Longrightarrow$ "Big Data" is built from **various sources of information**:
  - clinical trials
  - medico-administrative databases
  - patients cohort
  - medical file
  - patients data (from connected devices for example)
  - social networks
  - ...

  $\Longrightarrow$ Components of the "definition" of "Big Data" are partially met
  Volume ($\pm$) - **V**elocity (-) - **V**ariety (+) - **V**eracity ($\pm$) - **V**alue (++)

  $\Longrightarrow$ To Exploit of these multitudes of databases ask questions
  - **Data chaining** to construct care path
  - **Data merging** to enlarge database
  - **Data Reuse**
  - ...

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In this context, **BiDaSa project** pays attention to

- **Axe 1: Data ReUse**
  The calibration of models for In Silico Clinical Trials
- **Axe 2: Data Merging**
  Recoding of variables

To do so, **the consortium** is composed of

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  - Thierry LANG (PU-PH)
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- **Institut de Recherche en Mathématiques de Rennes**
  - Valérie GARES (MCF)
  - Jérémy OMER (MCF)

Content of the talk

Axe 1: In Silico Clinical Trials

Make use of the **available knowledge** about

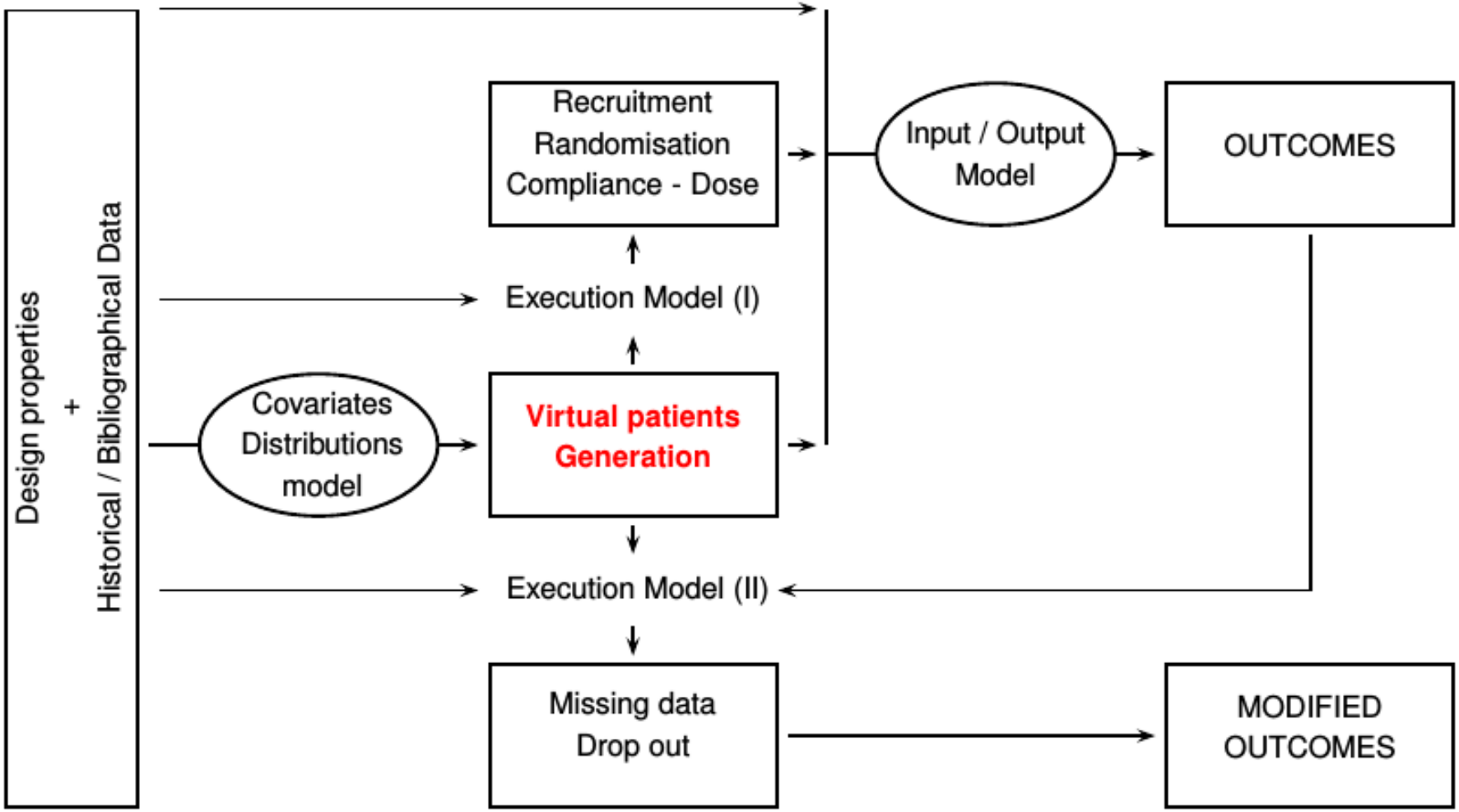
- drug
- patients
- disease progression
- clinical program

to investigate **in silico** aspects of the clinical study plan

- dose regimen
- study design
- patients population
- ...

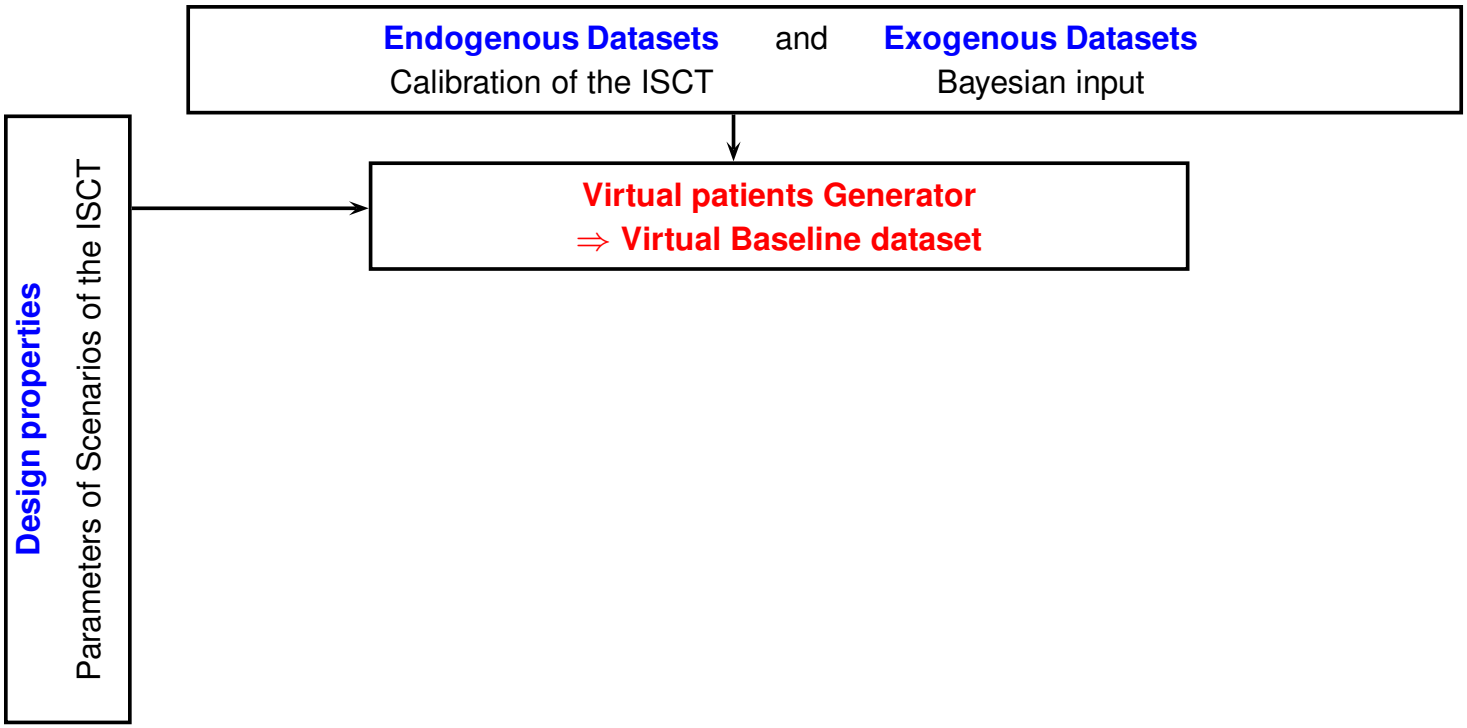
in order to make **rational, informed decision** with regards to **optimizing** the development plan of a new compound

Axe 1: In Silico Clinical Trials



Endogenous Datasets and **Exogenous Datasets**
Calibration of the ISCT | Bayesian input

Design properties
Parameters of Scenarios of the ISCT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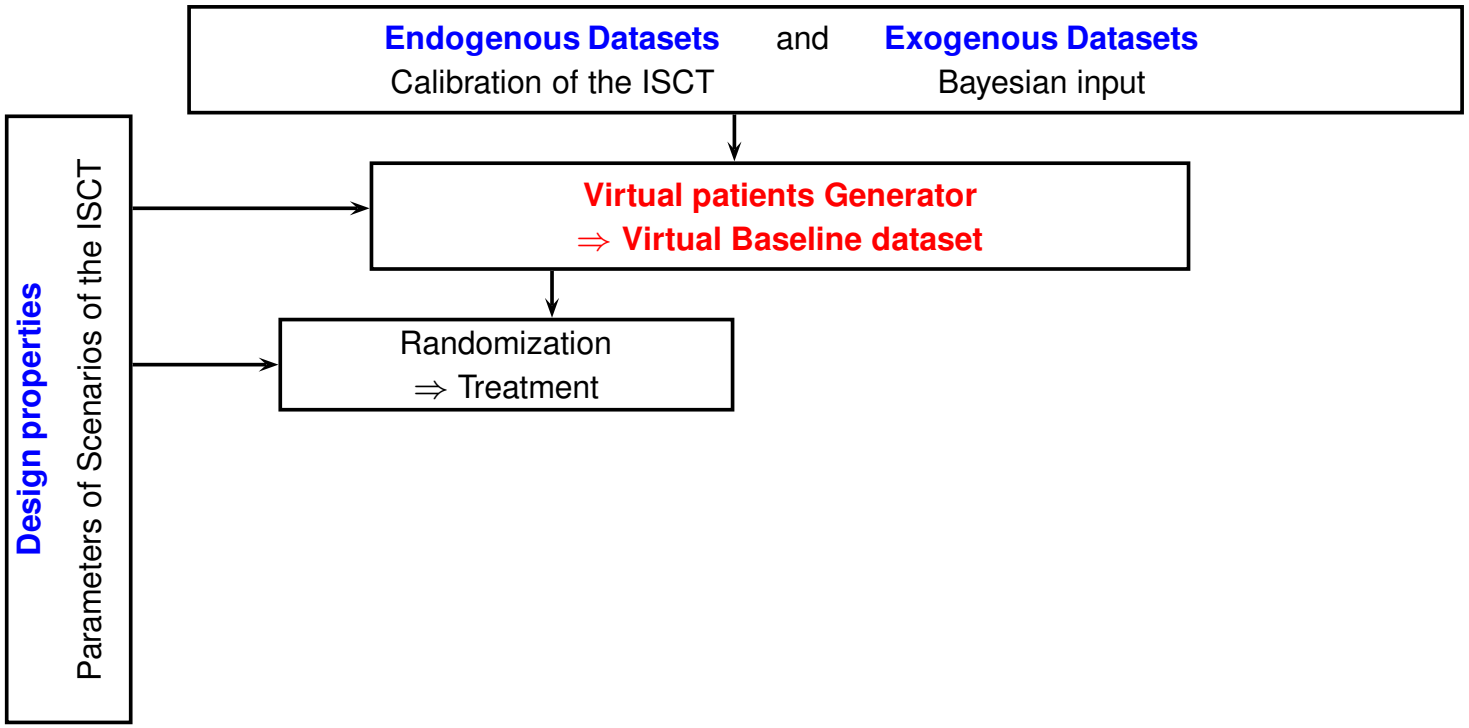
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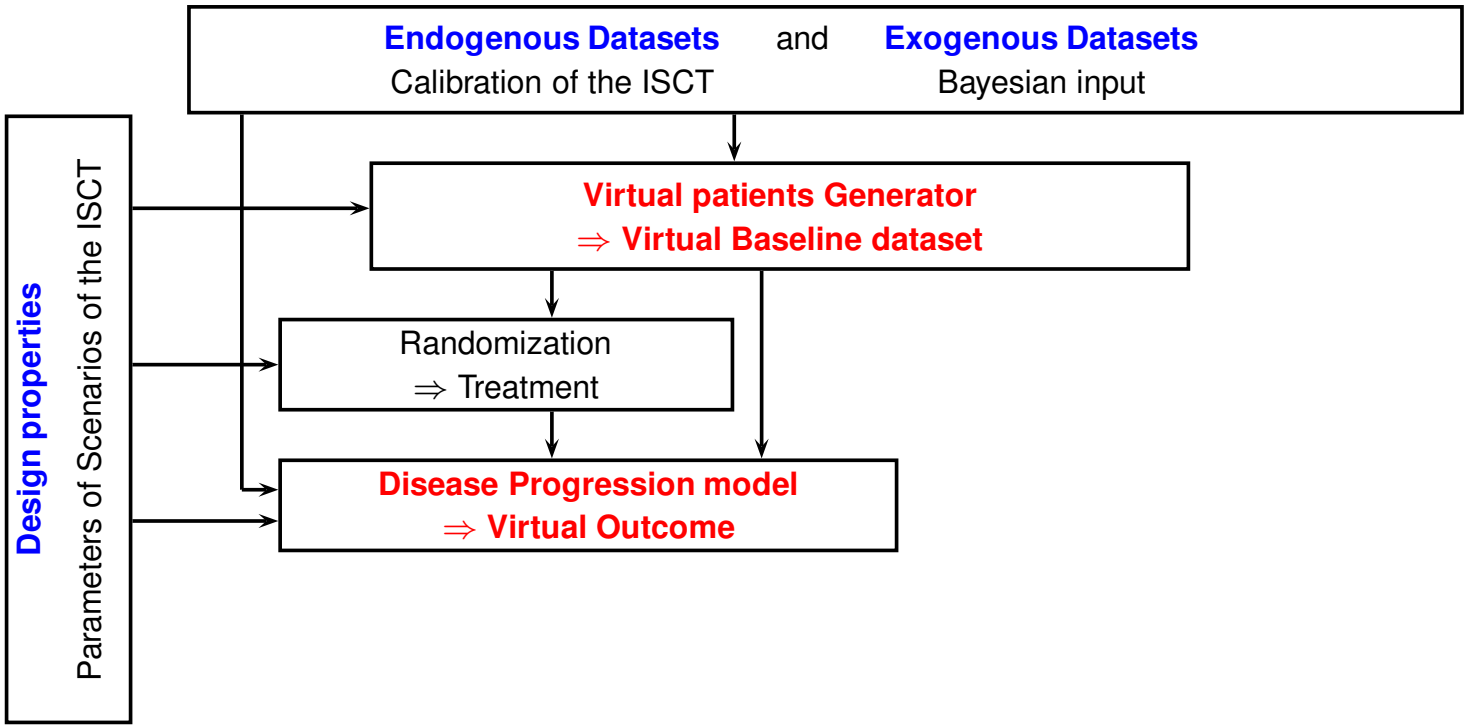
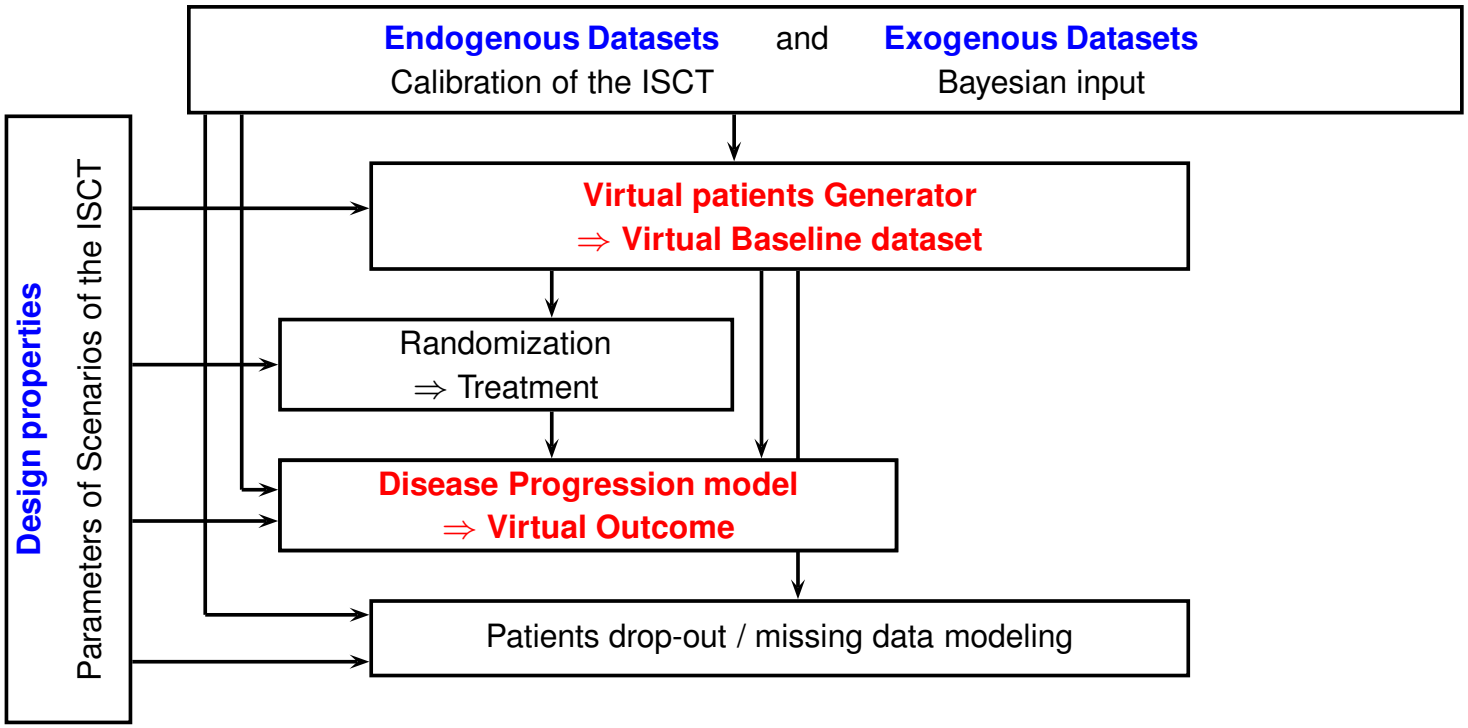
Axe 1: In Silico Clinical Trials

General Schema

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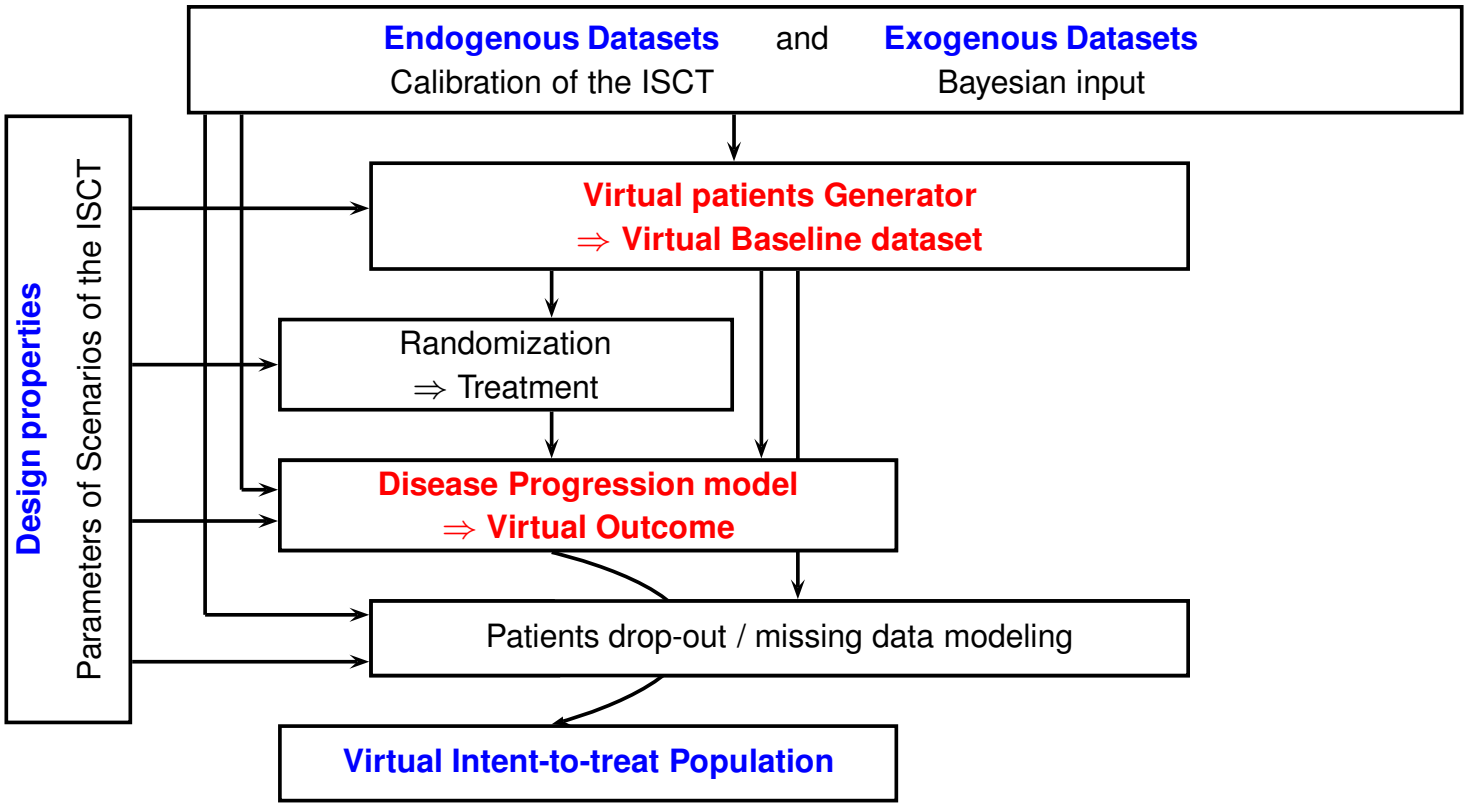
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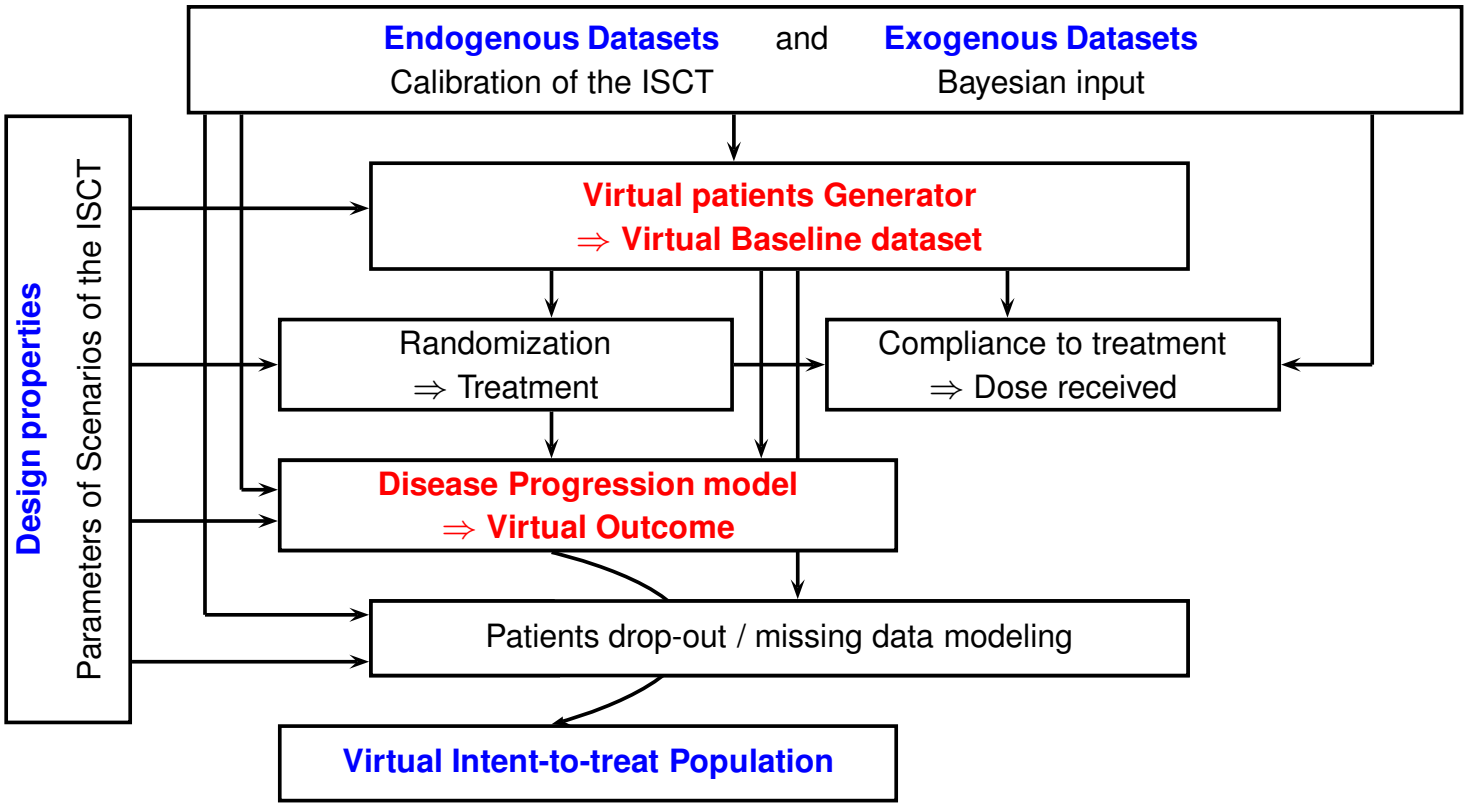
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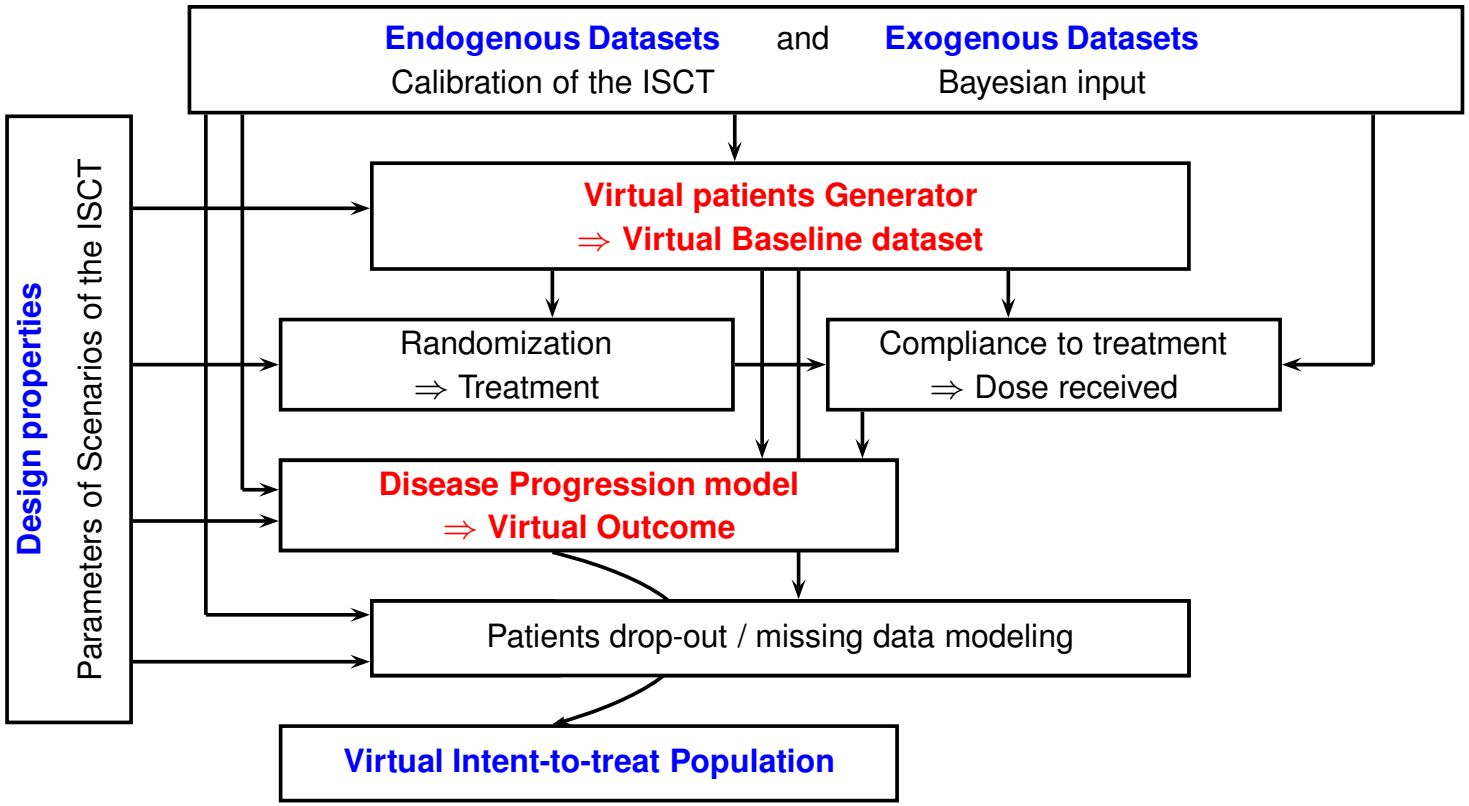
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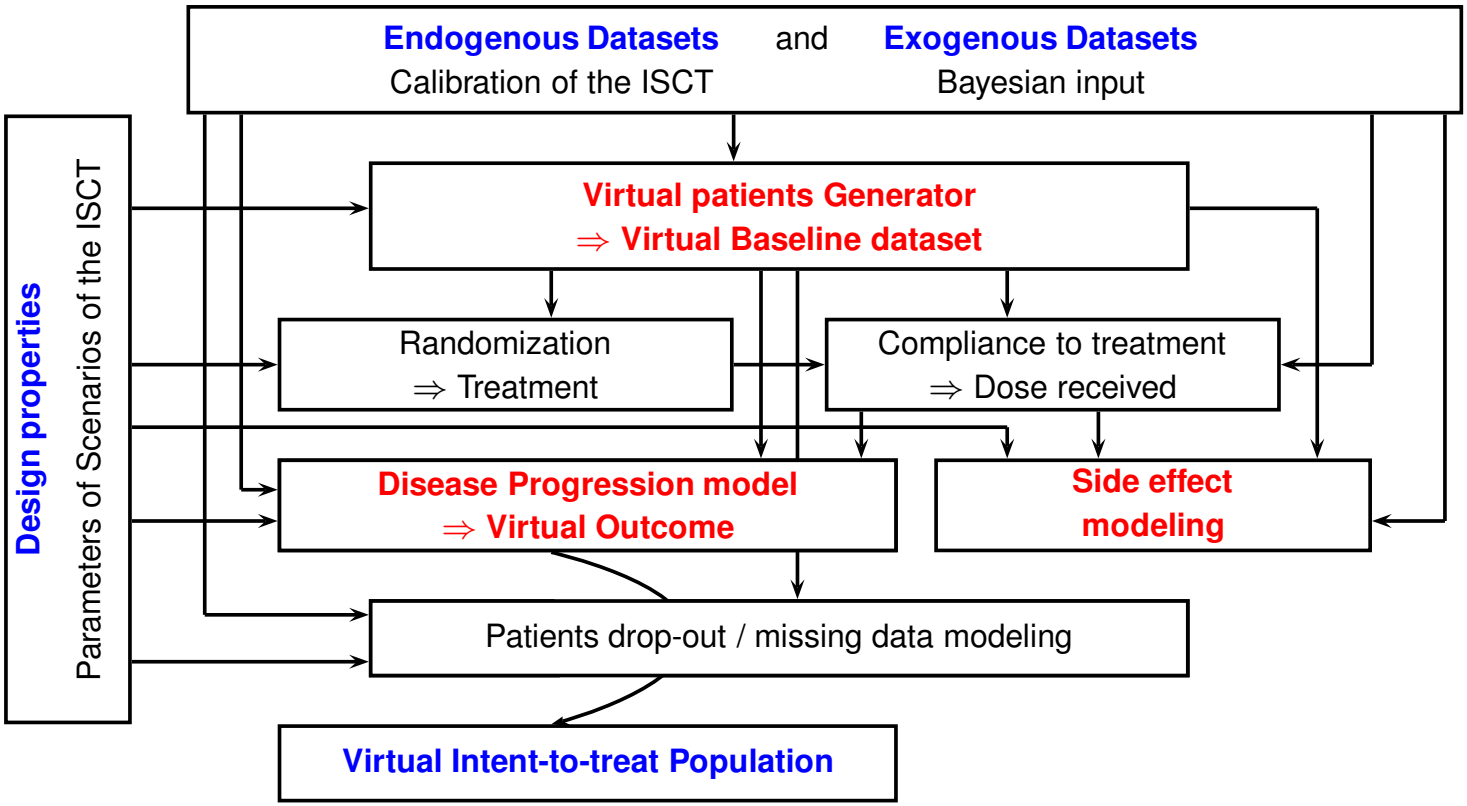
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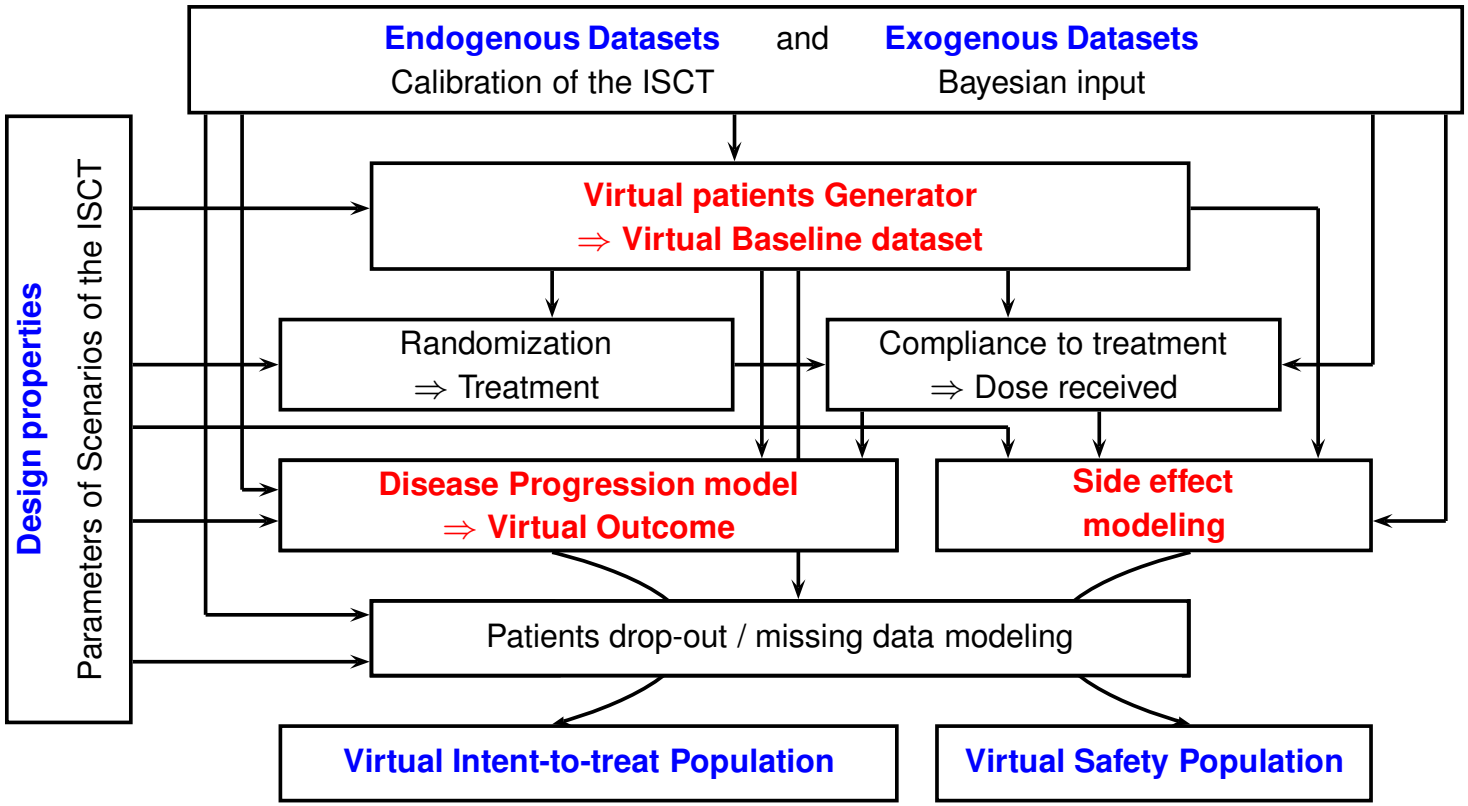
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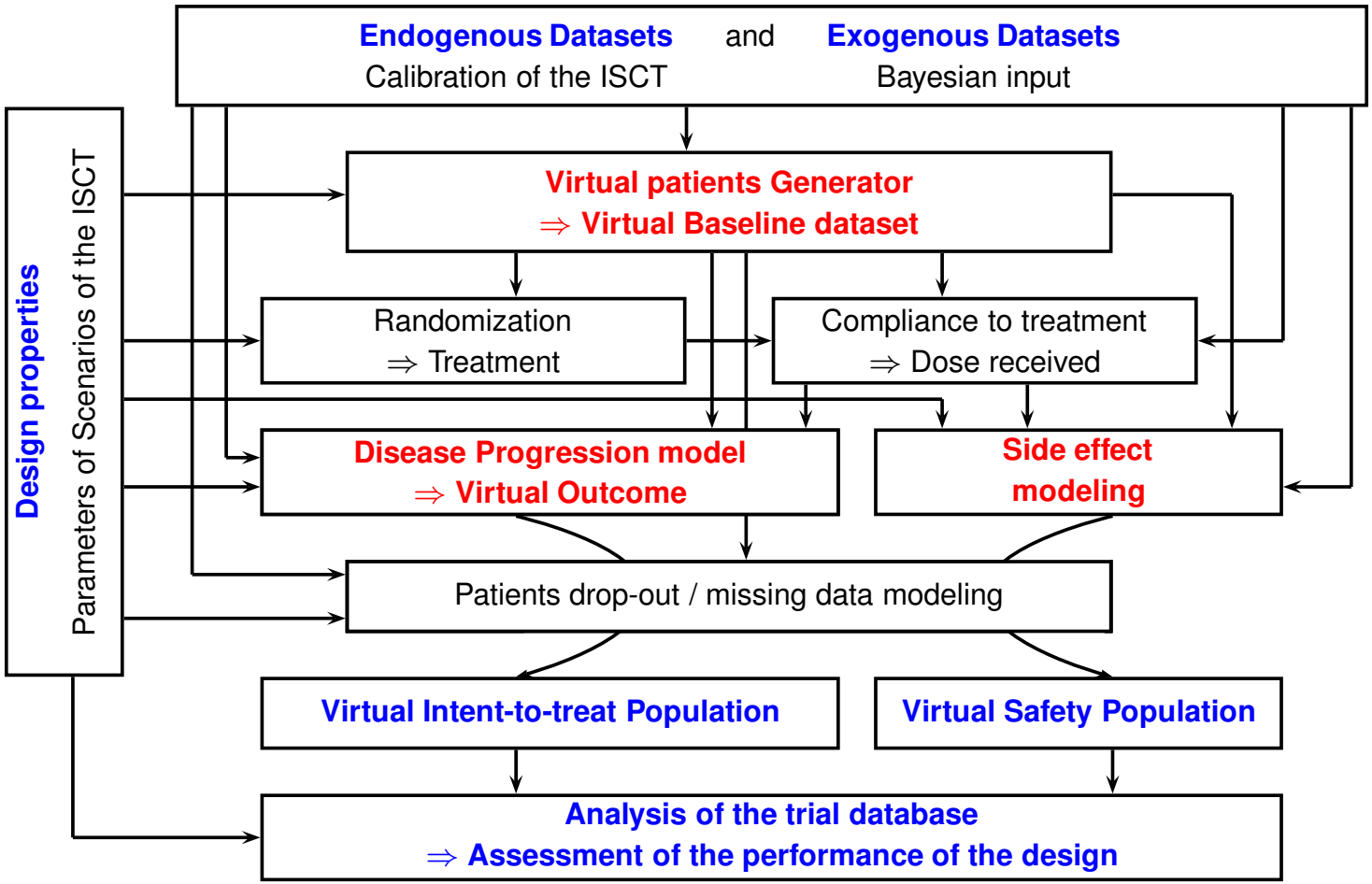
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Virtual Safety Population
Analysis of the trial database
⇒ Assessment of the performance of the design

- Problems related to **Monte Carlo simulation of multidimensional** random variable

- **Trade-off** between **details** of Virtual Patient and **complexity** of the model
- Have to account for **Correlation structure** between covariates
- Have to account for different types of covariates (Categorical / Quantitatives)
  - Different techniques exist: Discrete, Continuous, Copula ((Savy, 2017))

- Complexity depends on **number of covariates**
  - Issue for choosing variables
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    - **need huge datasets** (curse of dimensionality)
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  - **Parametric models** (Markov, Cox, linear, logistics,...)
    - Problem of database for parameters estimation
  - **Non-parametric models** (Machine learning)
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- Main difficulty comes from **Calibration / Learning** database
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Content of the talk

Variables recoding issue

Database A

	C_1	C_2	...	C_p	Y^A	Y^B
1					Observed	Unobserved
...						
...						
n_A						

Database B

	C_1	C_2	...	C_p	Y^A	Y^B
1					Unobserved	Observed
...						
...						
n_B						

- Y evaluated in both databases but not assessed on the same variable

Aim : Complete Y^A on database B and/or complete Y^B on database A

- Ideas
  - Missing data problem (MAR)
  - Latent variables models (class latent analysis, trait latent analysis)
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Optimal Transportation

Y^A Y^B

μ ν

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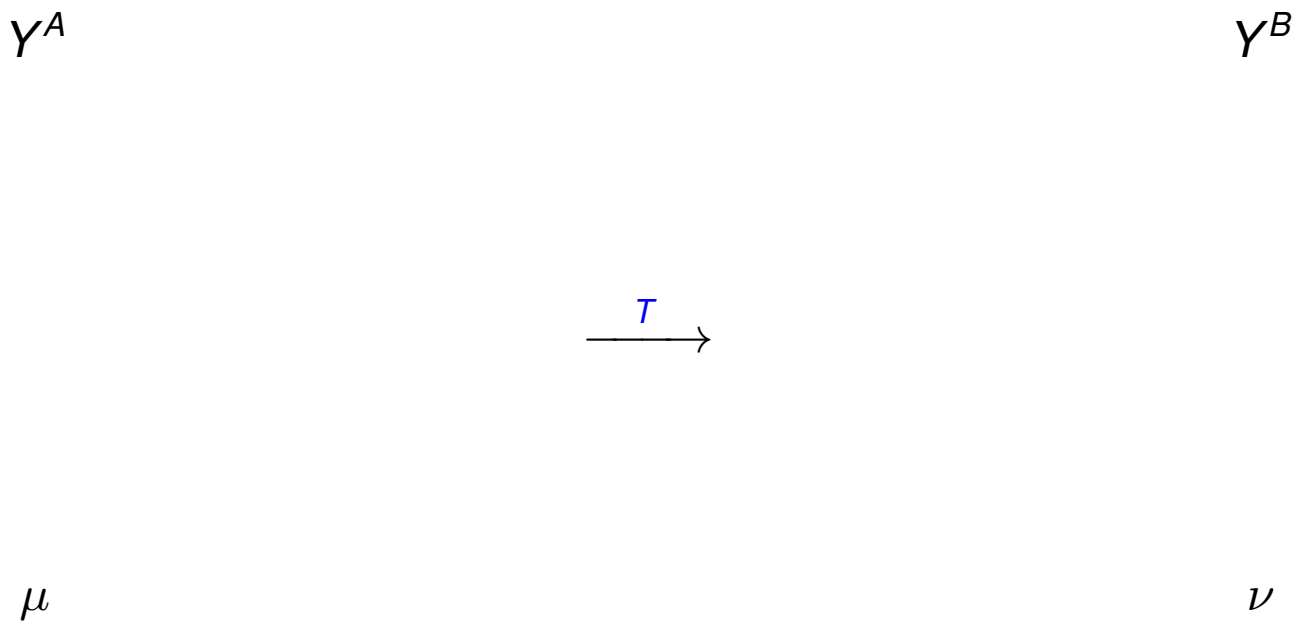

- T such that $\nu = T\mu$ is a **transportation map** from μ to ν

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- **Optimal transportation**
  - Let c a cost function measuring the displacement from y^A to y^B
  - Find a map T such that the average displacement is minimal

- $\mathbb{Y}^A$ and $\mathbb{Y}^B$: two Radon spaces
- $c : \mathbb{Y}^A \times \mathbb{Y}^B \longrightarrow [0, \infty]$ a Borel-measurable function given probability measures μ on $\mathbb{Y}^A$ and ν on $\mathbb{Y}^B$ (**cost function**)

- **Monge's formulation** (1781): Find a transport map $T : \mathbb{Y}^A \to \mathbb{Y}^B$ that realizes the infimum:

$$\left\{ \int_{\mathbb{Y}^A} c\left(y^A, T\left(y^A\right)\right) \mathrm{d}\mu\left(y^A\right) \;\middle|\; T(\mu) = \nu \right\},$$

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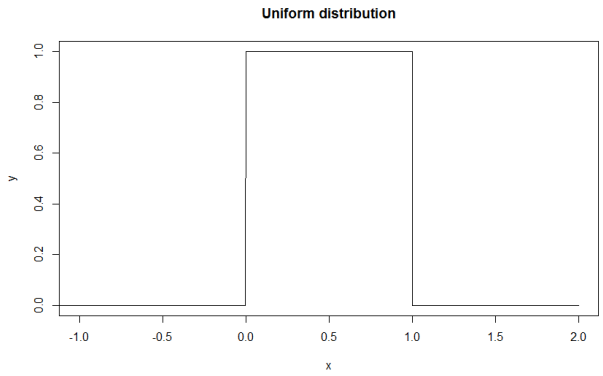
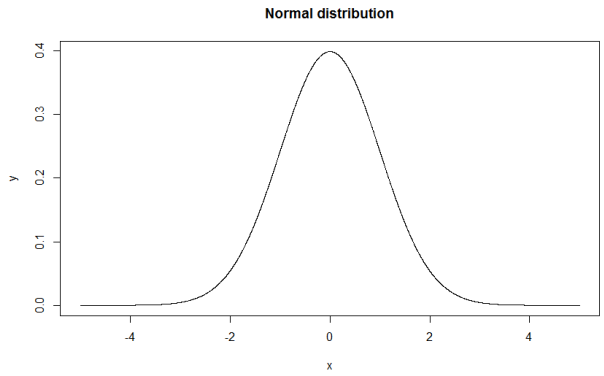
- **Continuous case**

$\mathcal{U}[0,1]$



$\mathcal{N}(0,1)$



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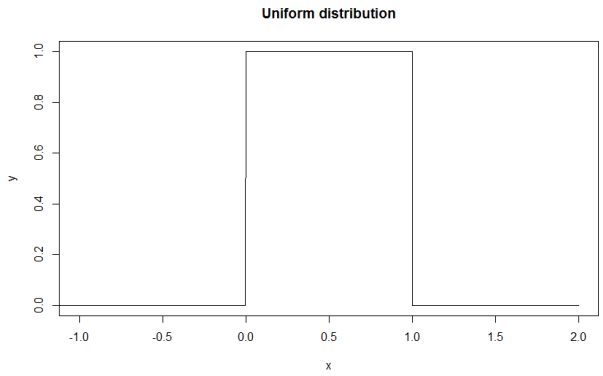

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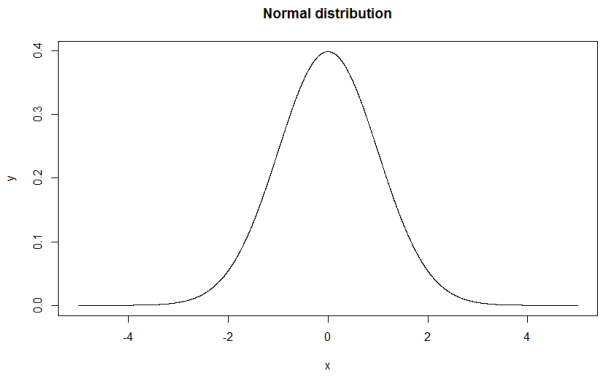

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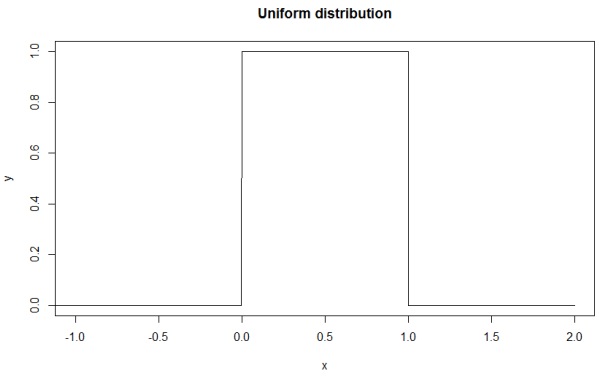

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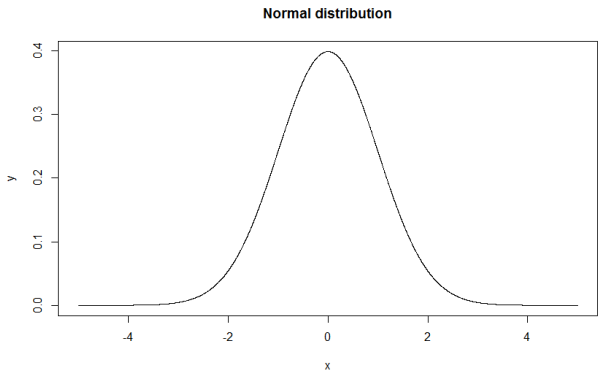

- The optimal transportation map **exists** and is **unique** if h is strictly convex with $c(x,y) = h(x-y)$

- **Discrete case: Hitchcock's problem (1941)**
  - Y^A the assessment of Y on database $D = A$
    - with distribution μ discrete with modalities $\{m_1^A, \ldots, m_R^A\}$
    - $a_r = \mathbb{P}(Y^A = m_r^A)$, $r = 1, \ldots, R$

$$\mu = \sum_{r=1}^{R} a_r \delta_{m_r^A}$$

  - Y^B the assessment of Y on database $D = B$
    - with distribution ν discrete with modalities $\{m_1^B, \ldots, m_S^B\}$
    - $b_s = \mathbb{P}(Y^B = m_s^B)$, $s = 1, \ldots, S$

$$\nu = \sum_{s=1}^{S} b_s \delta_{m_s^B}$$

  - $\mathbf{X} = (C_1, C_2, \ldots, C_p)$, covariates

The optimal joint distribution γ^{opt} of (Y^A, Y^B) is solution to the linear programming:

$$\gamma^{opt} \text{ minimizes } \gamma = \{\gamma_{r,s}, r = 1, \ldots, R, s = 1, \ldots, S\} \rightarrow \sum_{r=1}^{R} \sum_{s=1}^{S} \gamma_{r,s}\, c\,(p_r, q_s)\,,$$

under the following constraints

$$\begin{cases} \sum_{r=1}^{R} \gamma_{r,s} = \mu_s, \quad \forall s = 1, \ldots S \\ \sum_{s=1}^{S} \gamma_{r,s} = \nu_r, \quad \forall r = 1, \ldots R \\ \gamma_{r,s} \geq 0, \quad \forall r = 1, \ldots R, \forall s = 1, \ldots S. \end{cases}$$

with

$$\begin{aligned} c(p_r, q_s) &= \mathbb{E}\left[d\left(\bar{\mathbf{X}}, \bar{\bar{\mathbf{X}}}\right) | Y^A = p_r, Y^B = q_s\right] \quad \text{if } \mathbb{P}[Y^A = p_r, Y^B = q_s] \neq 0 \\ &= 0 \text{ otherwise} \end{aligned}$$

where $\bar{\mathbf{X}}$ and $\bar{\bar{\mathbf{X}}}$ are two independent copies of $\mathbf{X}$.

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γ^{opt} **is estimated by** $\hat{\gamma}^{opt}$ solution to the linear programming:

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under the following constraints

$$\begin{cases} \sum_{r=1}^{R} \gamma_{r,s} = (\hat{b}_{n_B})_s, \quad \forall s = 1, \ldots S \\ \sum_{s=1}^{S} \gamma_{r,s} = (\hat{a}_{n_A})_r, \quad \forall r = 1, \ldots R \\ \gamma_{r,s} \geq 0, \quad \forall r = 1, \ldots R, \forall s = 1, \ldots S \end{cases}$$

- The marginal distributions of Y^A and Y^B are estimated by

$$(\hat{a}_{n_A})_r = \frac{\text{card}\left\{\{i|\, Y_i^A = m_r^A\}\right\}}{n_A}, \qquad r = 1, \dots R,$$

$$(\hat{b}_{n_B})_s = \frac{\text{card}\left\{\{j|\, Y_j^B = m_s^B\}\right\}}{n_B}, \qquad s = 1, \dots S.$$

$\Rightarrow$ **Assumption 1 :** $\mathcal{L}(Y^A|D = A) = \mathcal{L}(Y^A|D = B)$

- The cost function is estimated by

$$\begin{aligned} \hat{c}_{n_A,n_B}(p_r, q_s) &= \frac{1}{\kappa_{r,s}} \sum_{i=1}^{n_A} \sum_{j=1}^{n_B} d(\mathbf{x}_i^A, \mathbf{x}_j^B)\, \mathbb{I}_{\left\{Y_i^A = p_r\ ,\ Y_j^B = q_s\right\}} \qquad \text{if } \kappa_{r,s} \neq 0 \\ &= 0 \text{ otherwise} \end{aligned}$$

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Example :

Consider Y^A is observed and Y^B unobserved.

		Variable Y^A			
		m_1^A	m_2^A	m_3^A	m_4^A
Variable Y^B	m_1^B				
	m_2^B				
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Consider Y^A is observed and Y^B unobserved.

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Variable Y^B	m_1^B	84	23	2	5
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Which are the 84 individuals encoded m_1^A that will be recoded m_1^B ?

Step 2 of OT algorithm: affectation

For each subject i of database A, a predicted value for $\hat{y}_i^B$ can be constructed by means of an **adapted nearest neighbor algorithm** accounting for the covariates with distance d.

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Among the 114 individuals encoded m_1^B will choose the 84 closest to the mean of individuals in modality m_1^A.

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Variable recoding - simulation studies

We consider 3 dependent covariates:

- C_1 categorical with 2 modalities
- C_2 categorical with 3 modalities
- C_3 quantitative normally distributed

Construct Y from these covariates and a normally distributed error term.

- Y^A is the discretization of Y by quartiles
- Y^B is the discretization of Y by tertiles

Remark

By construction, the coefficient R^2 **measuring the association between the covariates and the outcome** depends on the simulation parameters and is easy to control.

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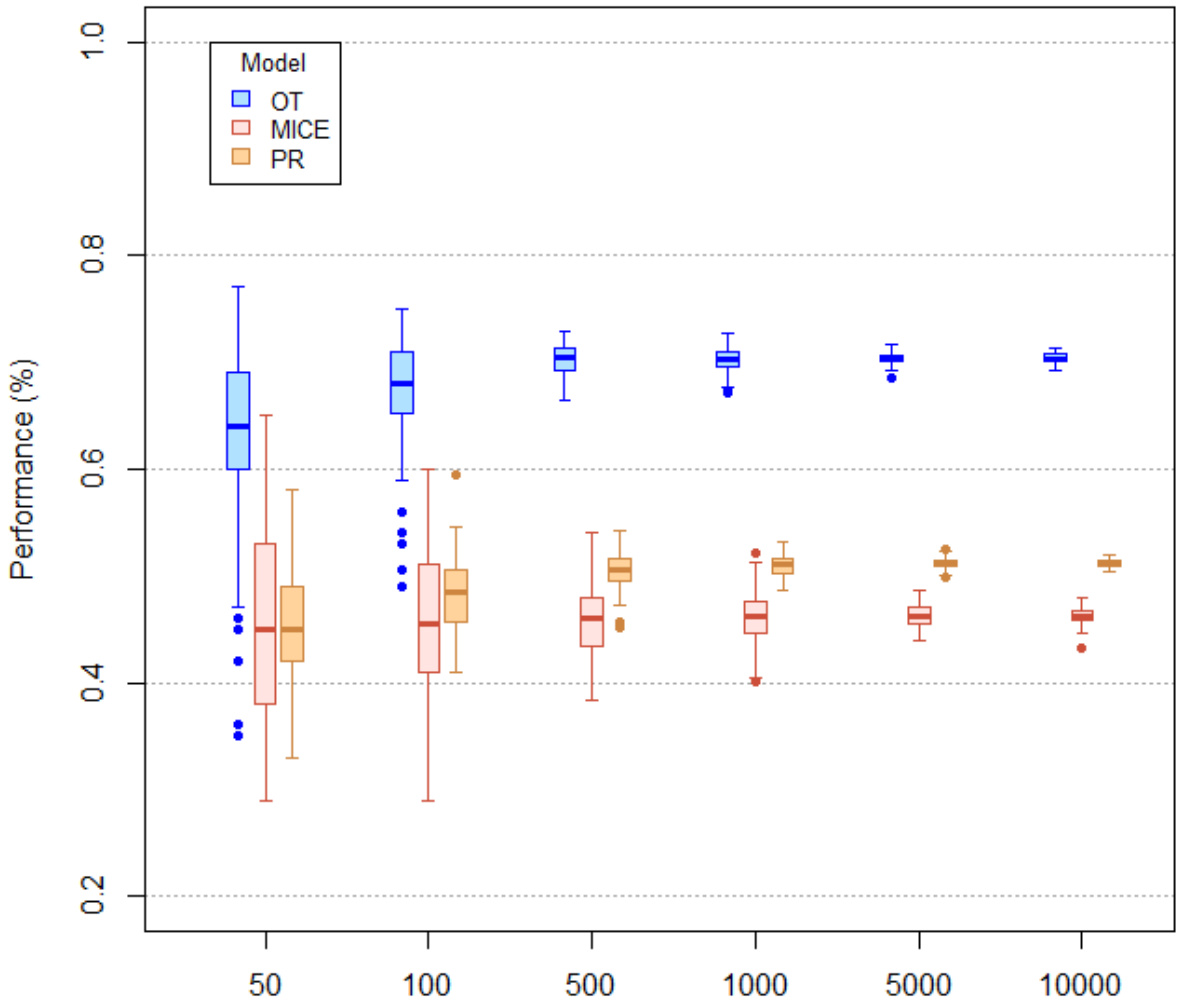
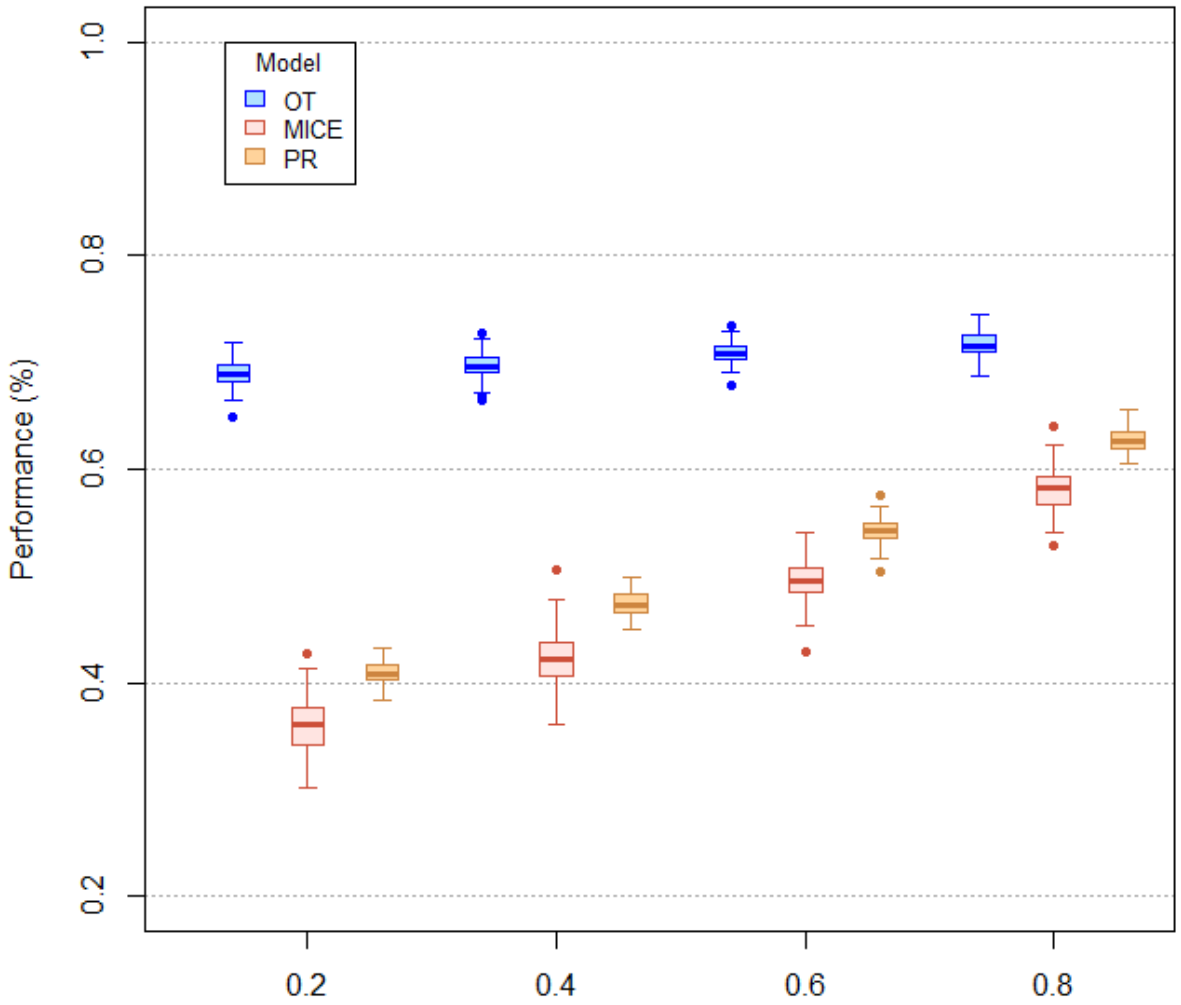
Variable recoding - simulation studies

$R^2 = 0.5$, n varies



Variable recoding - simulation studies

$n = 1000$, R^2 varies



Variable recoding - real life example

- NCDS (The National Child Development Study)
  - a continuing survey which follows the lives of over 17,000 people born in England, Scotland and Wales in a same week of the year 1958
  - collects specific information on many distinct fields
    - *physical and educational development, economic circumstances, employment, family life, health behaviour, well-being, social participation and attitudes*
  - 9 waves (0, 7, 11, 16, 22, 33, 42, 50 and 55 years old)

- **Outcome**: two measurements scales of the **social class** of the participants built from profession and collected at wave 5:
  - *Goldthorp social class'90 scale* (`GSS90`) : a scale in 11 categories
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- The initial database was randomly divided in two databases of the same size and we kept
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Variable recoding - real life example

Social class GSS90	Database *A*	Database *B*	Social class RGS91	Database *A*	Database *B*
Modalities	n (%)	n (%)	Modalities	n (%)	n (%)
Not applicable	116 (2.89)	85 (2.12)	Not applicable	129 (3.21)	102 (2.54)
I	646 (16.09)	697 (17.36)	I	201 (5.01)	207 (5.16)
II	761 (18.95)	702 (17.48)	II	1241 (30.91)	1214 (30.24)
IIIa	650 (16.19)	683 (17.01)	IIIN	930 (23.16)	982 (24.46)
IIIb	349 (8.69)	311 (7.75)	IIIM	736 (18.33)	765 (19.05)
IVa	13 (0.32)	12 (0.30)	IV	617 (15.37)	580 (14.45)
IVb	146 (3.64)	146 (3.64)	V	161 (4.01)	165 (4.11)
IVc	27 (0.67)	31 (0.77)			
V	161 (4.01)	182 (4.53)			
VI	426 (10.61)	435 (10.83)			
VIIa	699 (17.41)	705 (17.56)			
VIIb	21 (0.52)	26 (0.65)			

OT	MICE
63.5%	29.3%

Table: NCDS study. % of well classified subjects.

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Works in progress

- **Improvment** of OT-Algorithm by relaxation of hypotheses
  - ↬ V. Garès, J. Omer
    Recoding Variable with domain adaptation using optimal transport
    Submitted to Journal of American Statistician Association

- **Missing data** in covariates issue
  - ↬ G. Guernec, V. Garès, P. Saint-Pierre, B. Lepage, M. Kosorok, C. Diméglio and N. Savy
    - On the use of OT-algorithm when there are missing data in covariates. Application to clinical research
    - In preparation for Statistical Methods for Medical Research

- **Challenging** of OT algorithm by comparison with Machine Learning strategies
  - ↬ D. Vuillemenot, C. Diméglio, V. Garès, G. Guernec, B. Lepage, P. Muller, M. Kosorok, N. Savy and P. Saint-Pierre
    - Comparison of OT-algorithm and machine learning approach to merge databases. Application to clinical research.
    - In preparation for Computational Statistics & Data Analysis

- **Preparation** of a R packaqe

  - ↬ G. Guernec, V. Garès, P. Navaro, J. Omer, P. Saint-Pierre, N. Savy
    - OTRECOD: Using Optimal Transport theory in database fusion for recoding heterogeneous variables
    - Poster for UseR Conference, Toulouse, july 2019

Content of the talk

Project OT4DI

- Project **O**ptimal **T**ransportation for **D**ata **I**ntegration

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The consortium is:

- **Institut de Mathématiques de Toulouse**
  - Nicolas SAVY (MCF) - PI
  - Sébastien DEJEAN (IR)
  - Philippe SAINT-PIERRE (MCF)
  - **Jean-Michel Loubès (PR)**
- **Unité INSERM Epidémiologie Toulouse**
  - Grégory GUERNEC (IR)
- **Institut de Recherche en Mathématiques de Rennes**
  - Valérie GARES (MCF)
  - **Mounir Haddou (PR)**
- **University of North Carolina at Chapel Hill - USA**
  - **Michael Kosorok (PR)**
- **Mc Gill University - CAN**
  - **Erica Moodie (MCF)**

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