USING R TO INCORPORATE UNCERTAINTY IN DISCRETE EVENT SIMULATION MODELING: PROBLEMS AND SOLUTIONS.

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OUTLINE

1. Introduction – Previous experience
2. Conceptual model and main input parameters
3. Parameter uncertainty
4. Example

INTRODUCTION – PREVIOUS EXPERIENCE

- Working on Economic Evaluation based on DES modeling since 2008.

- Software:
  - Arena Rockwell for DES modeling
  - Stata for statistical analyses

- Main related publications:

Volume ** • Number ** • **
VALUE IN HEALTH

Budget Impact Analysis of Thrombolysis for Stroke in Spain: A Discrete Event Simulation Model

Javier Mar, MD,[1,2] Arantzazu Arrospide, BSc,[2] Mercè Comas, PhD[3,4]

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Arrospide et al. BMC Cancer (2016) 16:344
DOI 10.1186/s12885-016-2386-y
BMC Cancer

RESEARCH ARTICLE Open Access

Economic evaluation of the breast cancer screening programme in the Basque Country: retrospective cost-effectiveness and budget impact analysis

Arantzazu Arrospide[1,2,3*], Montserrat Rue[3,4], Nicolien T. van Ravesteyn[5], Merce Comas[3,6], Myriam Soto-Gordoa[1], Garbiñe Sarriugarte[7] and Javier Mar[1,2,3,8]

Arrospide et al. BMC Cancer (2018) 18:464
https://doi.org/10.1186/s12885-018-4362-1
BMC Cancer

RESEARCH ARTICLE Open Access

Cost-effectiveness and budget impact analyses of a colorectal cancer screening programme in a high adenoma prevalence scenario using MISCAN-Colon microsimulation model

Arantzazu Arrospide[1,2,3*], Isabel Idigoras[4], Javier Mar[1,2,3,5], Harry de Koning[6], Miriam van der Meulen[6], Myriam Soto-Gordoa[1,2,3], Jose Miguel Martinez-Llorente[7], Isabel Portillo[4], Eunate Arana-Arri[8], Oliver Ibarrondo[1] and Iris Lansdorp-Vogelaar[6]

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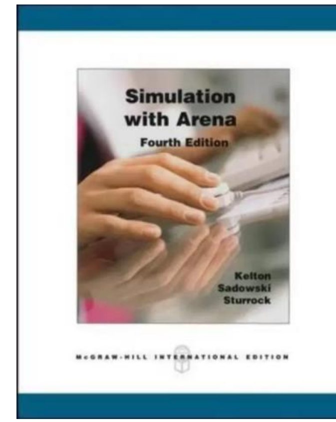
INTRODUCTION – PREVIOUS EXPERIENCE

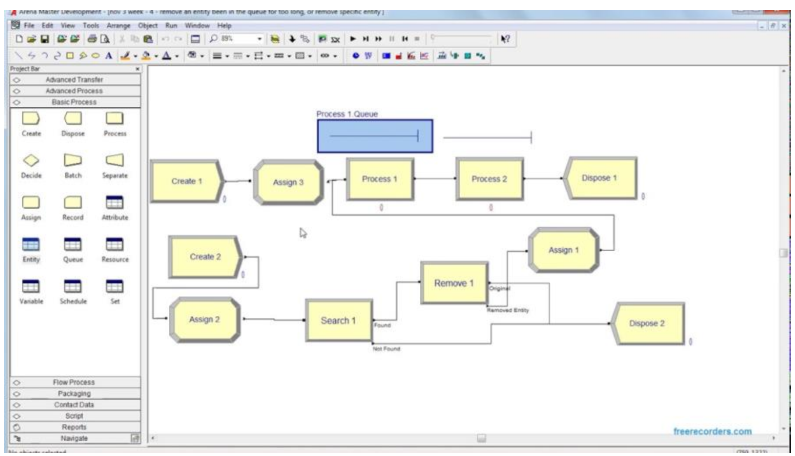
¿Why did we choose Arena Rockwell software for DES modeling?

- A colleague had previously worked with Arena.
- I had not used R before (neither for statistical analysis)

- It had a good tutorial book with examples

and a student demo version.





- The software has pre-specified modules, you only need to know which is the aim of each type of module and how to fulfill the parameters.

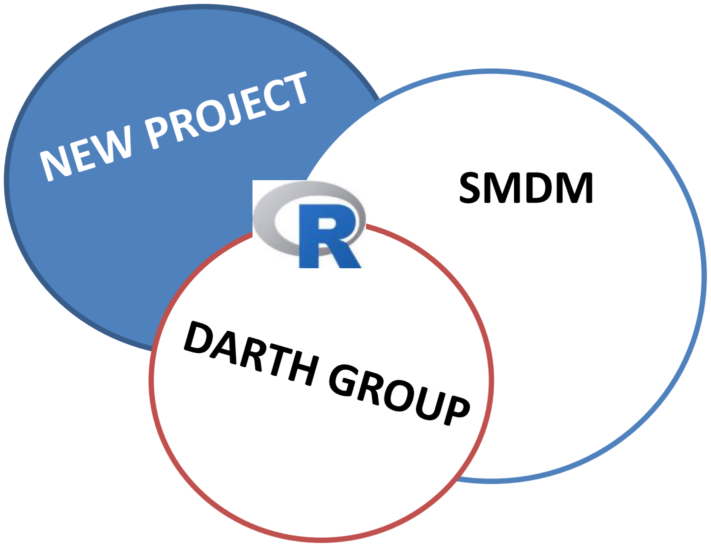
- Random number generators for different probability distributions.

INTRODUCTION – PREVIOUS EXPERIENCE

Difficulties using Arena Rockwell software for DES modeling

- ! Read data for parameter values.
- ! Incorporate parameter uncertainty in the model
- ! Write data for posterior analysis.

In 2016 **we changed our mind**:



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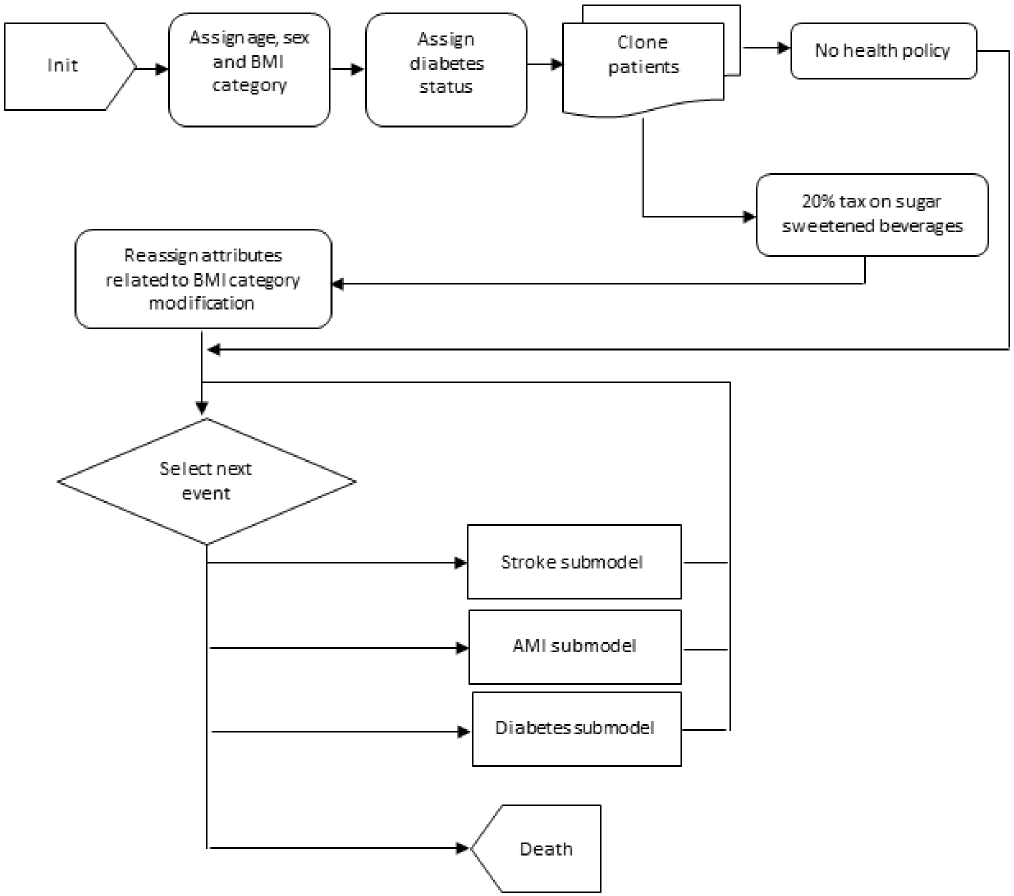
CONCEPTUAL MODEL AND INPUT PARAMETERS

NEW PROJECT

HEALTH AND ECONOMIC EFFECTS OF A SUGAR SWEETENED BEVERAGE TAX IN THE SPANISH POPULATION

Main Objective: The objective of this project is to analyze the impact on health and costs of two health policies aimed at reducing the consumption of salt and sugary drinks in the Spanish population by using discrete event simulation.



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CONCEPTUAL MODEL AND INPUT PARAMETERS

In order to reproduce the whole Spanish population:

Data set 1: National Statistics Centre. Alive population by age and sex.

- Sex: proportion of female population ~ Binomial distribution
- Birth date: Empirical distribution depending on Sex

Data set 2: National Health Survey 2011-2012.

- Social Status: depending on Sex and Age ~ Multinomial regression
- BMI category: depending on Sex, Age and Social Status ~ Multinomial regression

Based on previously published papers:

Impact of 20% tax	Overweight	-0.4%	Briggs et al. 2013
	Obesity	-1.3%	
All-cause mortality in obesity (Hazard ratio)	Normal weight	1.00	Flegal et al. 2013
	Overweight	0.92	
	Obesity	1.21	

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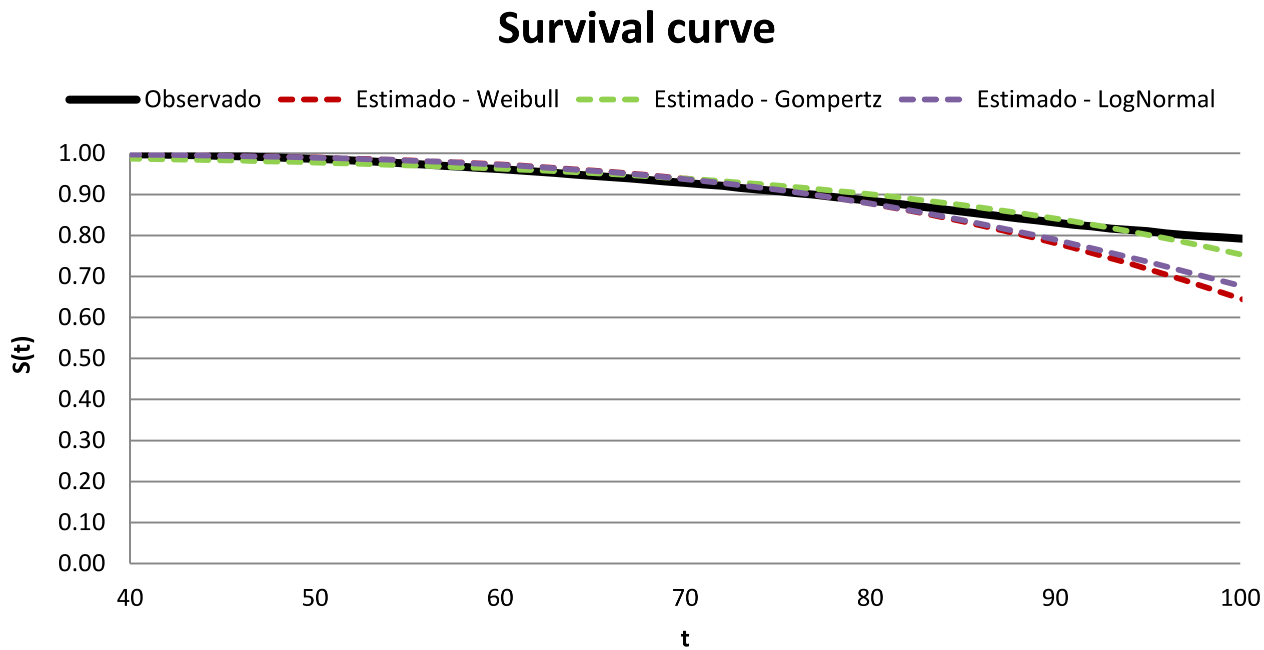
CONCEPTUAL MODEL AND INPUT PARAMETERS

Data set 3: National Statistics Centre. Mortality rates by age and sex.

Data set 4: Minimum Hospitalization Data Base (2009-2013).

- Stroke (ICD-9 430-438)
- Acute myocardial infarction (ICD-9 410)

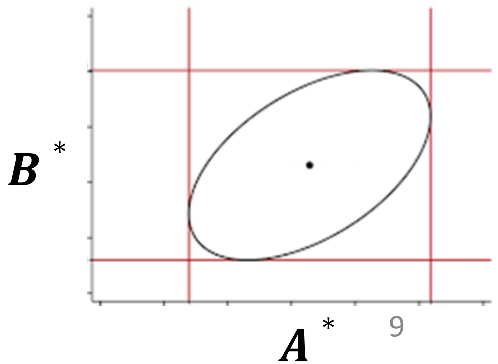
Classify first and successive events in 2013.



Gompertz

A = -9,1628

B = 0,0488



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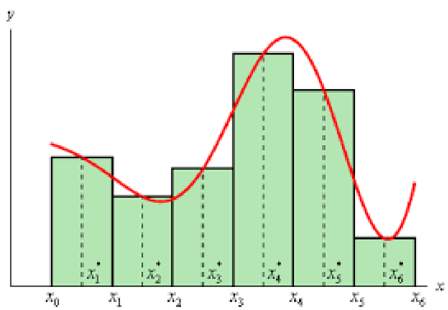
EXAMPLE - UTILITIES

In order to estimate quality-adjusted life years in our model:

Spanish Health Survey performed in 2012

- 21,007 adults
- EuroQol 5D-5L questionnaire: 63% in perfect health, mean = 0.91.



! Utilities ranged $(-\infty, 1]$

! High proportion of perfect health (utility equal to one)

- Two-part models ensure that estimated values will never adopt values higher than 1, while also allowing for negative mean utility values

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EXAMPLE - UTILITIES

The **two part model** is based on the decomposition of the mean utility value $u(x)$ as follows:

$$u(x) = p(x) \cdot 1 + (1 - p(x)) \cdot (1 - w(x))$$

First, a logistic regression model:

$$\log(\frac{p(x)}{1 - p(x)}) = \mathrm{Beta}_1 \cdot x$$

Second, the individuals not in perfect health are sub-selected and a generalized linear model (with log link if necessary) is applied to the disutilities $(\mathrm{i.e.}\, 1 - u(x))$.

$$\mathrm{link}(\mathrm{E}(w(x))) = \mathrm{link}(\mathrm{E}(1 - u(x))) = \mathrm{Beta}_2 \cdot x$$

and their correspondent variance-covariance matrixes $(\mathrm{V}_1, \mathrm{V}_2)$.

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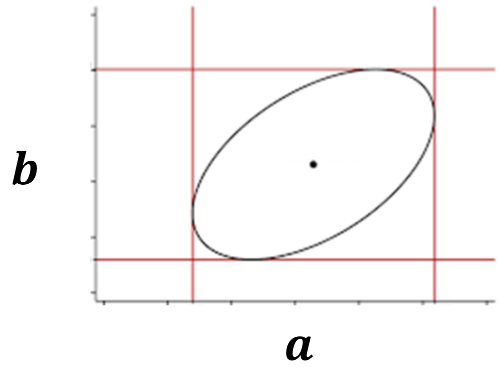
SECOND-ORDER UNCERTAINTY

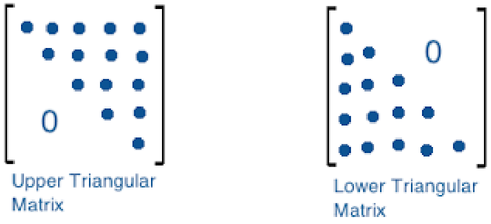
$$Y \sim a + b \cdot X$$



CHOLESKY DESCOMPOSITION

According to the methodology described in detail by Briggs et al., the Cholesky decomposition of the variance-covariance matrixes $(\mathrm{V}_1, \mathrm{V}_2)$ will yield the correspondent lower triangular matrixes $(\mathrm{T}_1, \mathrm{T}_2)$

$$\mathrm{V}_i = \mathrm{T}_i * \mathrm{T}_i{}', \text{ where } \mathrm{T}_i{}' \text{ is } \mathrm{T}_i \text{ transposed for } \mathrm{i} = 1, 2$$



SECOND-ORDER UNCERTAINTY

- Let it be $(\mathrm{Beta}_1, \mathrm{Beta}_2)$ the estimated coefficients vector and $(\mathrm{T}_1, \mathrm{T}_2)$ the triangular matrixes obtained by Cholesky descomposition of $(\mathrm{V}_1, \mathrm{V}_2)$.

- $(\mathrm{Z}_1, \mathrm{Z}_2)$ randomly generated vectors where each value follows a standard Normal distribution $(Z \sim N(0,1))$. Same length as $(\mathrm{Beta}_1, \mathrm{Beta}_2)$.

- New regression parameters $(\mathrm{Beta}_1^*, \mathrm{Beta}_2^*)$ were calculated as follows:

$$\mathrm{Beta}\ _1^* = \mathrm{Beta}_1 + (\mathrm{T}_1 * \mathrm{Z}_1)$$

$$\mathrm{Beta}\ _2^* = \mathrm{Beta}_2 + (\mathrm{T}_2 * \mathrm{Z}_2)$$

	STEP 1: LOGISTIC REGRESSION	Coefficient	Exp (Coef.)	95% CI	p-value
(P0)	Constant	1.02	2.78	(2.53, 3.05)	< 0.001
(P1)	Age	-0.04	0.96	(0.96, 0.97)	< 0.001
	Age ≤70 years	REF.	1.00		
(P2)	Age >70 years	0.77	2.16	(1.46, 3.22)	< 0.001
	Men	REF.	1.00		
(P3)	Women	-0.65	0.52	(0.49, 0.56)	< 0.001
	Low social status	REF.	1.00		
(P4)	Middle social status	0.38	1.46	(1.30, 1.64)	< 0.001
(P5)	High social status	0.52	1.68	(1.46, 1.92)	< 0.001
	BMI <25	REF.	1.00		
(P6)	BMI 25-30	-0.06	0.94	(0.84, 1.05)	0.268
(P7)	BMI > 30	-0.52	0.59	(0.52, 0.67)	< 0.001
(P8)	Age >70 years # Age	-0.03	0.97	(0.95, 0.98)	< 0.001
(P9)	Women # age	-0.01	0.99	(0.99, 1.00)	0.002
(P10)	BMI 25-30 # Middle social status	-0.18	0.84	(0.71, 0.99)	0.037
(P11)	BMI 25-30 # High social status	0.01	1.00	(0.82, 1.24)	0.962
(P12)	BMI >30 # Middle social status	-0.30	0.74	(0.61, 0.91)	0.005
(P13)	BMI >30 # High social status	0.13	1.14	(0.86, 1.51)	0.368

	STEP2: GLM	Coefficient	Exp (Coef.)	95% CI	p-value
(P0)	Constant	-1.74	0.18	(0.16, 0.19)	< 0.001
(P1)	Age	0.01	1.01	(1.01, 1.01)	< 0.001
	Age ≤70 years	REF.	1.00		
(P2)	Age > 70 years	-0.53	0.60	(0.50, 0.69)	< 0.001
	Men	REF.	1.00		
(P3)	Women	0.08	1.09	(1.03, 1.15)	0.004
	Low social status	REF.	1.00		
(P4)	Middle social status	-0.03	0.97	(0.89, 1.06)	0.483
(P5)	High social status	-0.18	0.84	(0.76, 0.92)	< 0.001
	BMI < 25	REF.	1.00		
(P6)	BMI 25-30	-0.01	0.99	(0.92, 1.06)	0.789
(P7)	BMI > 30	0.21	1.23	(1.15, 1.33)	< 0.001
(P8)	Age > 70 years # Age	0.02	1.02	(1.02, 1.03)	< 0.001
(P9)	Women # Age	0.00	1.00	(1.00, 1.01)	< 0.001
(P10)	BMI 25-30 # Middle social status	-0.06	0.95	(0.84, 1.06)	0.326
(P11)	BMI 25-30 # High social status	0.11	1.11	(0.97, 1.28)	0.136
(P12)	BMI >30 # Middle social status	-0.03	0.97	(0.85, 1.10)	0.629
(P13)	BMI >30 # High social status	0.17	1.19	(0.99, 1.43)	0.065

STEP 1	(P0)	(P1)	(P2)	(P3)	(P4)	(P5)	(P6)	(P7)	(P8)	(P9)	(P10)	(P11)	(P12)	(P13)
(P0)	0.0479	0.0001	0.0035	-0.0178	-0.0334	-0.0033	-0.0380	-0.0379	-0.0007	0.0002	0.0326	0.0319	0.0318	0.0329
(P1)		0.0018	0.0011	0.0056	0.0014	0.0001	-0.0021	-0.0025	-0.0013	-0.0013	-0.0015	-0.0007	-0.0025	-0.0018
(P2)			0.2021	-0.0006	-0.0001	-0.0001	-0.0027	-0.0033	-0.0070	-0.0001	-0.0001	0.0006	0.0003	0.0023
(P3)				0.0305	-0.0205	-0.0214	-0.0132	-0.0143	-0.0001	-0.0001	0.0210	0.0225	0.0224	0.0216
(P4)					0.0464	0.0010	0.0015	0.0011	-0.0003	0.0001	-0.0467	-0.0015	-0.0466	-0.0011
(P5)						0.0572	0.0010	0.0008	-0.0002	0.0001	-0.0002	-0.0575	-0.0001	-0.0572
(P6)							0.0401	0.0022	-0.0004	0.0001	-0.0038	-0.0380	-0.0003	0.0001
(P7)								0.0504	-0.0002	0.0001	0.0014	0.0012	-0.0493	-0.0491
(P8)									0.0017	-0.0008	-0.0074	-0.0063	-0.0057	-0.0064
(P9)										0.0014	-0.0043	-0.0043	-0.0044	-0.0505
(P10)											0.0462	0.0001	0.0001	0.0001
(P11)												0.0690	0.0001	0.0001
(P12)													0.0070	0.0001
(P13)														0.1164

STEP 2	(P0)	(P1)	(P2)	(P3)	(P4)	(P5)	(P6)	(P7)	(P8)	(P9)	(P10)	(P11)	(P12)	(P13)
(P0)	0.0333	-0.0002	0.0023	-0.0160	-0.0202	-0.0201	-0.0217	-0.0214	-0.0004	0.0004	0.0198	0.0192	0.0195	0.0198
(P1)		0.0014	-0.0001	0.0058	-0.0032	-0.0030	-0.0060	-0.0063	-0.0009	-0.0007	0.0033	0.0040	0.0025	0.0028
(P2)			0.0792	-0.0013	0.0001	-0.0006	-0.0030	-0.0042	-0.0025	0.0001	-0.0001	0.0032	0.0004	0.0040
(P3)				0.0225	-0.0139	-0.0151	-0.0101	-0.0110	0.0001	-0.0005	0.0136	0.0155	0.0148	0.0155
(P4)					0.0334	0.0012	0.0020	0.0019	-0.0001	-0.0001	-0.0337	-0.0015	-0.0335	-0.0014
(P5)						0.0460	0.0011	0.0010	-0.0001	-0.0001	-0.0002	-0.0461	-0.0001	-0.0461
(P6)							0.0251	0.0031	-0.0002	-0.0001	-0.0223	-0.0222	-0.0002	-0.0002
(P7)								0.0256	-0.0001	-0.0001	0.0022	0.0024	-0.0232	-0.0232
(P8)									0.0008	-0.0007	-0.0041	-0.0033	-0.0029	-0.0034
(P9)										0.0006	-0.0055	-0.0063	-0.0067	-0.0062
(P10)											0.0316	0.0001	0.0001	0.0001
(P11)												0.0496	0.0001	0.0001
(P12)													0.0364	-0.0001
(P13)														0.0665

EXAMPLE - UTILITIES

Thus, the parameters used to estimate mean utility values in the first simulation of our cost-effectiveness model were:

STEP 1

$$Beta_1 = (1.02, -0.04, 0.77, -0.65, 0.38, 0.52, -0.06, -0.52, -0.03, -0.01, -0.18, 0.01, -0.30, 0.13)$$

$$\mathrm{Z}_1 = (0.56, -0.45, 0.58, 0.17, 2.91, -0.63, 0.89, 1.02, 1.11, -1.02, -0.78, 0.30, -0.98, 0.59)$$

$$\mathrm{T}_1 * \mathrm{Z}_1 = (-0.15, 0.00, 0.10, -0.09, 0.22, -0.09, 0.06, 0.07, 0.01, 0.00, -0.04, 0.02, -0.07, 0.07)$$

$$\mathrm{Beta}_1^* = \mathrm{Beta}_1 + (\mathrm{T}_1 * \mathrm{Z}_1)$$

$$\mathrm{Beta}_1^* = (0.87, -0.04, 0.88, -0.73, 0.60, 0.43, -0.01, -0.45, -0.02, -0.00, -0.21, 0.03, -0.36, 0.20)$$

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EXAMPLE - UTILITIES

STEP 2

$$\text{Beta}_2 = (-1.74, 0.01, -0.53, 0.08, -0.03, -0.18, -0.01, 0.21, 0.02, 0.00, -0.06, 0.11, -0.03, 0.17)$$

$$Z_2 = (-0.97, 0.84, 0.21, -1.06, 0.01, -0.98, 1.21, -1.56, -0.10, 1.55, 0.78, 0.13, -0.34, 1.22)$$

$$T_2 * Z_2 = (0.05, 0.01, 0.03, 0.02, -0.02, -0.11, 0.00, -0.06, -0.01, -0.01, 0.02, 0.01, -0.01, 0.08)$$

$$\text{Beta}_2^* = \text{Beta}_2 + (T_2 * Z_2)$$

$$\text{Beta}_2^* = (-1.69, 0.01, -0.50, 0.10, -0.05, -0.29, -0.00, 0.15, 0.01, -0.00, -0.03, 0.11, -0.04, 0.25)$$

EXAMPLE - UTILITIES

Following the detailed procedure we will explain in the following example how to sample utility values for in each simulation of a cost-effectiveness analysis model:

Sex = Men

Age = 10 (60 years – 50 mean age)

Social status = High

Body mass index (BMI) < 25 (normal weight)

Models included also interactions between:

Sex and age

Social status and BMI

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EXAMPLE - UTILITIES

$$\text{Beta}_1^* = (0.87, -0.04, 0.88, -0.73, 0.60, 0.43, -0.01, -0.45, -0.02, -0.00, -0.21, 0.03, -0.36, 0.20)$$
$$\text{Beta}_2^* = (-1.69, 0.01, -0.50, 0.10, -0.05, -0.29, -0.00, 0.15, 0.01, -0.00, -0.03, 0.11, -0.04, 0.25)$$

Therefore, in the first step (Logistic regression):

$$ln\left(\frac{p(x)}{1-p(x)}\right) = \mathbf{0,87} - \mathbf{0.04} * (60-50) + \mathbf{0.43} = 0.90$$

$$p(x) = \frac{exp(0.90)}{1+exp(0.90)} = 0.7109$$

And in the second step (GLM, logartimic link):

$$ln(w(x)) = \mathbf{-1.69} + \mathbf{0.01}\,(60-50) - \mathbf{0.29} = -1.88$$

$$w(x) = exp(-1.88) = 0.1526$$

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EXAMPLE - UTILITIES

The estimated mean value using the two part regression analysis would be:

$$p(x) = 0.7109$$

$$w(x) = 0.1526$$

$$u(x) = p(x) \cdot 1 + \left(1 - p(x)\right) \cdot \left(1 - w(x)\right)$$
$$= 0.7109 + (1 - 0.7109) * (1 - 0.1526) = \mathbf{0.9559}$$

So, based on this regression model, **71.09%** of the selected subpopulation was assumed in perfect health, and the estimated mean utility value for those not in perfect health was **0.8474** (= 1- 0.1526).

EXAMPLE - UTILITIES

In fact, **using matrix operators in R it takes few code lines** to estimate individual characteristics adjusted utilities using the corresponding coefficients in each run.

$$\mathrm{T}_1 = \mathit{Chol}\,(\,\mathrm{V}_1\,);\quad \mathrm{T}_2 = \mathit{Chol}\,(\,\mathrm{V}_2\,);$$

$$\mathrm{Beta}_1^* = \mathrm{Beta}_1 + (\mathrm{T}_1 * \mathrm{Z}_1)$$

$$\mathrm{Beta}_2^* = \mathrm{Beta}_2 + (\mathrm{T}_2 * \mathrm{Z}_2)$$

$$p(\boldsymbol{x}) = \frac{exp(\mathrm{Beta}_1^* \cdot \boldsymbol{x})}{1 + exp(\mathrm{Beta}_1^* \cdot \boldsymbol{x})}$$

$$w(\boldsymbol{x}) = exp(\mathrm{Beta}_2^* \cdot \boldsymbol{x})$$

$$u(\boldsymbol{x}) = p(\boldsymbol{x}) \cdot 1 + \big(1 - p(\boldsymbol{x})\big) \cdot \big(1 - w(\boldsymbol{x})\big)$$

CONCLUSIONS

- Using the **same software** for:
  - Parameter estimation
  - Simulation run
  - Results analysis

  → allow **complex modelling**

- We work in **R code** that use data bases **without modifying the original source**.

- Using **matrix operators** to assign attributes reduce simulation time.

- **Collaborative work**, all methodological improvements can be public.

Thank you

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