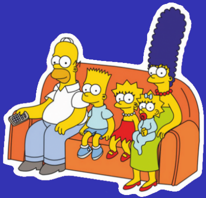
Bayesian Networks, Mendelian Genetics, and . . . the Simpsons



LPSM
LABORATOIRE DE PROBABILITÉS STATISTIQUE & MODÉLISATION

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May 5, 2020

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Blood Feud

In *“Blood Feud”* (S02E22):

- The rich Mr Burns badly needs O- blood for a transfusion
- Desesperate Mr Smithers asks nuclear power plant’s employees to give blood for the great man

Homer Simpson sees a golden opportunity:

- Mr Burns being immensely rich, he will probably reward the one who saves him
- Homer asks Marge about his own blood group, but he’s A+ (Homer: *“D’oh !”*)

What are the chances to find a O- blood donor in the Simpson family ?

The Blood Group/Rhesus system

Lisa asks Pr Frink about blood group genetics:

- ABO gene with three alleles: two codominant A, B, and one recessive O
  $$\Rightarrow p_O = 0.60, p_A = 0.30, p_B = 0.10$$
- RHD gene with two alleles: dominant D (positive Rh) and recessive d (negative Rh)
  $$\Rightarrow q_D = 0.60, q_d = 0.40$$
- This leads to a total of 8 blood phenotypes: A+, B+, AB+, O+, A-, B-, AB-, O-

With ABO/RHD independence we get:

RHD	ABO	OO 0.36	OA 0.36	OB 0.12	AA 0.09	AB 0.06	BB 0.01
DD	0.36	O+	A+	B+	A+	AB+	B+
Dd	0.48	O+	A+	B+	A+	AB+	B+
dd	0.16	O-	A-	B-	A-	AB-	B-

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With ABO/RHD independence we get:

Rh	group	O 0.36	A 0.45	B 0.13	AB 0.06
+	0.84	0.3024	0.378	0.1092	0.0504
-	0.16	0.0576	0.072	0.0208	0.0096

Nuclear Family

The problem to solve:

- **1**: Homer, **2**: Marge, **3**: Bart, **4**: Lisa, **5**: Maggie
- X_i (resp. Y_i) genotype (resp. phenotype) or ind. i
- we need to compute

$$\pi = \mathbb{P}(\exists i, Y_i = \text{O-} | Y_1 = \text{A+})$$

Model 1: independent genotypes:

$$\mathbb{P}(X, Y) = \prod_{i=1}^{5} \mathbb{P}(X_i)\mathbb{P}(Y_i|X_i)$$

- $\mathbb{P}(Y_1 = \text{O-}|Y_1 = \text{A+}) = 0$, for $i \neq 1$, $\mathbb{P}(Y_i = \text{O-}) = 0.0576$
- $\pi = 1 - (1 - 0.0576)^4 \simeq 0.2112$, easy, right !?

Lisa: *"But genotypes are not independent !"*

Homer: *"D'oh !"*

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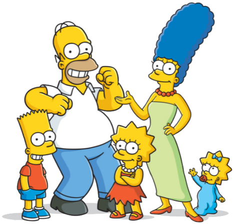
Model 2: Mendelian transmission of alleles:

$$\mathbb{P}(X, Y) = \mathbb{P}(X_1)\mathbb{P}(X_2) \prod_{i=3}^{5} \mathbb{P}(X_i | X_1, X_2) \times \prod_{i=1}^{5} \mathbb{P}(Y_i | X_i)$$

- $\mathbb{P}(X_1 = \text{OADd} |\ Y_1 = \text{A+}) = \frac{0.36}{0.36+0.09} \times \frac{0.48}{0.36+0.48} \simeq 0.4571$
- $\mathbb{P}(X_2 = \text{O}^{\text{A}}_{\text{B}}\text{Dd}) = 0.48 \times 0.48 = 0.2304$
- $\mathbb{P}(X_2 = \text{O}^{\text{A}}_{\text{B}}\text{dd}) = 0.48 \times 0.16 = 0.0768$
- $\mathbb{P}(X_2 = \text{OODd}) = 0.36 \times 0.48 = 0.1728$
- $\mathbb{P}(X_2 = \text{OOdd}) = 0.36 \times 0.16 = 0.0576$



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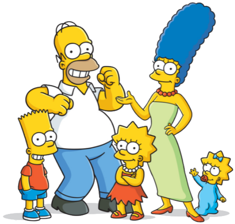
$\text{ev} = \{Y_1 = \text{A+}\}$ and N is the number of O- in the nuclear familly

- $\mathbb{P}(X_1 = \text{OADD}, \text{AADd}, \text{AADD} | \text{ev}) = 0.5429 \Rightarrow N \sim \mathcal{B}(1, 0.0567)$
- $\mathbb{P}(X_1 = \text{OADd}, X_2 \text{ not carrier} | \text{ev}) \simeq 0.2114 \Rightarrow N = 0$
- $\mathbb{P}(X_1 = \text{OADd}, X_2 = \text{O}^{\text{A}}_{\text{B}}\text{Dd} | \text{ev}) \simeq 0.1053 \Rightarrow N \sim \mathcal{B}(3, \frac{1}{16})$
- $\mathbb{P}(X_1 = \text{OADd}, X_2 = \text{O}^{\text{A}}_{\text{B}}\text{dd}, \text{OODd} | \text{ev}) \simeq 0.1141 \Rightarrow N \sim \mathcal{B}(3, \frac{1}{8})$
- $\mathbb{P}(X_1 = \text{OADd}, X_2 = \text{OOdd} | \text{ev}) \simeq 0.0263 \Rightarrow N \sim 1 + \mathcal{B}(3, \frac{1}{4})$

Nuclear Family



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$\text{ev} = \{Y_1 = \text{A+}\}$ and N is the number of O- in the nuclear familly

$$N | \text{ev} \sim 0.5429 \times \mathcal{B}(1, 0.0567) + 0.2114 \times \mathbf{1}_{N=0} + 0.1053 \times \mathcal{B}(3, 1/16) + 0.1141 \times \mathcal{B}(3, 1/8) + 0.0263 \times (1 + \mathcal{B}(3, 1/4))$$

$$\sum_{n \geqslant 0} \mathbb{P}(N = n | \text{ev}) z^n \simeq 0.8867 + 0.0920z + 0.0169z^2 + 0.0039z^3 + 0.0004z^4$$

$$\pi = 0.0920 + 0.0169 + 0.0039 + 0.0004 = 0.1132$$

What does it mean ?

Homer: *"So* $\pi = 0.1132$ *or whatever, is that good ?"*

- $\mathbb{P}$(at least one O-|Homer is A+) $= 11.32\%$
- $\mathbb{P}$(not any O-|Homer is A+) $= 88.68\%$

Homer: *"Huh ..."*

9 to 10 chances of <u>not</u> being able to help Mr Burns

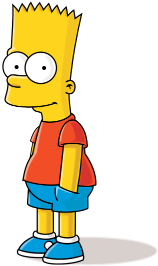
Homer: *"D'oh !"*

Frink: *"But I found a blood test in the criminal record of Bart . . . "*

Homer: *". . . and ?*

Frink: *"Bart is O- !!"*

Homer: *"Woohoo !"*



Weak-D Bart

- Frink: *"Alas, Bart has the weak-D phenotype. His blood might kill Mr Burns !"*
- RHD gene, 3 alleles: D, d, and w (weak-D, pseudo neg Rh)

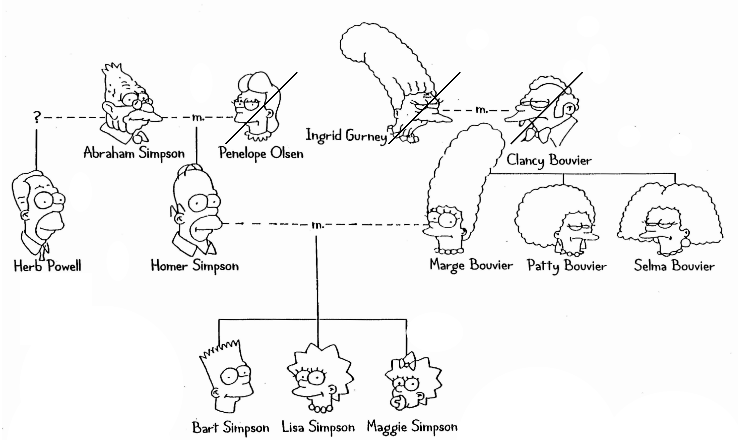
$$\Rightarrow q_{\mathrm{D}} = 0.60,\ q_{\mathrm{d}} = 0.39,\ q_{\mathrm{w}} = 0.01$$

- Only OOdd is compatible with Mr Burns !

RHD	ABO	OO	OA	OB	AA	AB	BB
		0.36	0.36	0.12	0.09	0.06	0.01
DD	0.3600	O+	A+	B+	A+	AB+	B+
Dd	0.4680	O+	A+	B+	A+	AB+	B+
Dw	0.0120	O+	A+	B+	A+	AB+	B+
dd	0.1521	O-	A-	B-	A-	AB-	B-
dw	0.0078	Ow	Aw	Bw	Aw	ABw	Bw
ww	0.0001	Ow	Aw	Bw	Aw	ABw	Bw

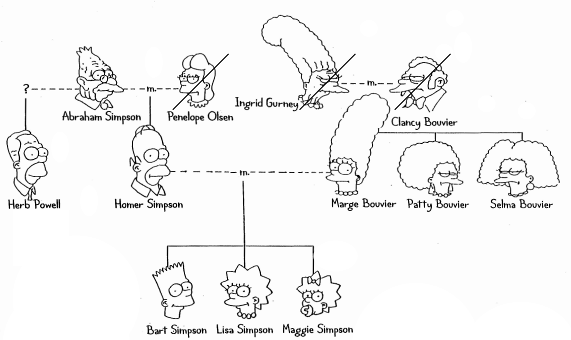
Lisa: *"We need to consider the extended Simpson family !"*

Simpsons' Pedigree and Bayesian Network



1: Herb's mother, **2**: Abraham, **3**: Penelope, **4**: Ingrid, **5**: Clancy, **6**: Herb, **7**: Homer, **8**: Marge, **9**: Patty, **10**: Selma, **11**: Bart, **12**: Lisa, **13**: Maggie

Simpsons' Pedigree and Bayesian Network



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6: Herb, **7**: Homer, **8**: Marge, **9**: Patty, **10**: Selma,
11: Bart, **12**: Lisa, **13**: Maggie

$$\mathbb{P}(X) = \mathbb{P}(X_1)\mathbb{P}(X_2)\mathbb{P}(X_3)\mathbb{P}(X_4)\mathbb{P}(X_5)$$
$$\mathbb{P}(X_6|\ X_{1,2})\mathbb{P}(X_7|\ X_{2,3})\mathbb{P}(X_8|\ X_{4,5})\mathbb{P}(X_9|\ X_{4,5})\mathbb{P}(X_{10}|\ X_{4,5})$$
$$\mathbb{P}(X_{11}|\ X_{7,8})\mathbb{P}(X_{12}|\ X_{7,8})\mathbb{P}(X_{13}|\ X_{7,8})$$

Simpsons' Pedigree and Bayesian Network

$$\mathbb{P}(X) = \mathbb{P}(X_1)\mathbb{P}(X_2)\mathbb{P}(X_3)\mathbb{P}(X_4)\mathbb{P}(X_5)$$
$$\mathbb{P}(X_6|\, X_{1,2})\mathbb{P}(X_7|\, X_{2,3})\mathbb{P}(X_8|\, X_{4,6})\mathbb{P}(X_9|\, X_{4,6})\mathbb{P}(X_{10}|\, X_{4,6})$$
$$\mathbb{P}(X_{11}|\, X_{7,8})\mathbb{P}(X_{12}|\, X_{7,8})\mathbb{P}(X_{13}|\, X_{7,8})$$

$$X_i \in \mathcal{G} = \{\mathrm{O}, \mathrm{A}, \mathrm{B}\}^2 \times \{\mathrm{D}, \mathrm{d}, \mathrm{w}\}^2 \quad |\mathcal{G}| = 3^2 \times 3^2 = 81$$

$$\mathrm{ev} = \{\text{Homer A+ and Bart Ow}\} \quad \mathbb{P}(X|\mathrm{ev}) = \frac{\mathbb{P}(X, \mathrm{ev})}{\sum_{X'} \mathbb{P}(X', \mathrm{ev})}$$

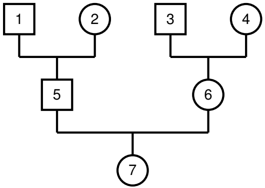
- $X = (X_1, X_2, \ldots, X_{13})$ is the family genotype
- in order to compute $\mathbb{P}(\mathrm{ev}) = \sum_{X'} \mathbb{P}(X', \mathrm{ev})$
- we *just* have to sum over 81^{13} configurations

$$\mathbf{81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176}$$

$\Rightarrow$ simply impossible !

Local computations in a simple pedigree

Idea: we consider a smaller (but similar) family, ev (evidence) still represents the available information.



- for *founders* $(1, 2, 3, 4)$ i:

$$\varphi_i(X_i) = \mathbb{P}(X_i \cap \text{ev})$$

- for *offsprings* $(5, 6, 7)$ k with parents i, j:

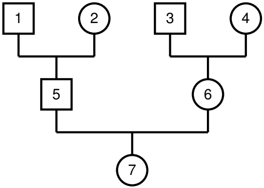
$$\varphi_j(X_i, X_j, X_k) = \mathbb{P}(X_k \cap \text{ev} | X_i, X_j)$$

$$\mathbb{P}(\text{ev}) = \sum_{X_1}\sum_{X_2}\sum_{X_3}\sum_{X_4}\sum_{X_5}\sum_{X_6}\sum_{X_7} \varphi_1(X_1)\varphi_2(X_2)\varphi_3(X_3)\varphi_4(X_4) \varphi_5(X_1, X_2, X_5)\varphi_6(X_3, X_4, X_6)\varphi_7(X_5, X_6, X_7)$$

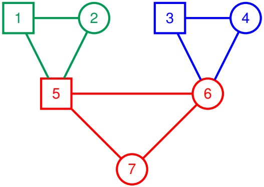
$\Rightarrow 81^7 = 22\,876\,792\,454\,961$ still too large !!

Local computations in a simple pedigree

Pedigree



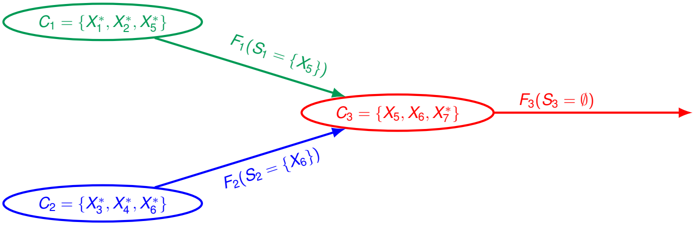
Clique decomposition



$$\mathbb{P}(\text{ev}) = \sum_{X_5}\sum_{X_6}\sum_{X_7}\left\{\left(\overbrace{\sum_{X_1}\sum_{X_2}\varphi_1(X_1)\varphi_2(X_2)\varphi_5(X_1,X_2,X_5)}^{F_1(X_5)}\right)\right.$$

$$\left.\left(\overbrace{\sum_{X_3}\sum_{X_4}\varphi_3(X_3)\varphi_4(X_4)\varphi_6(X_3,X_4,X_6)}^{F_2(X_6)}\right)\varphi_7(X_5,X_6,X_7)\right\}$$

Local computations in a simple pedigree



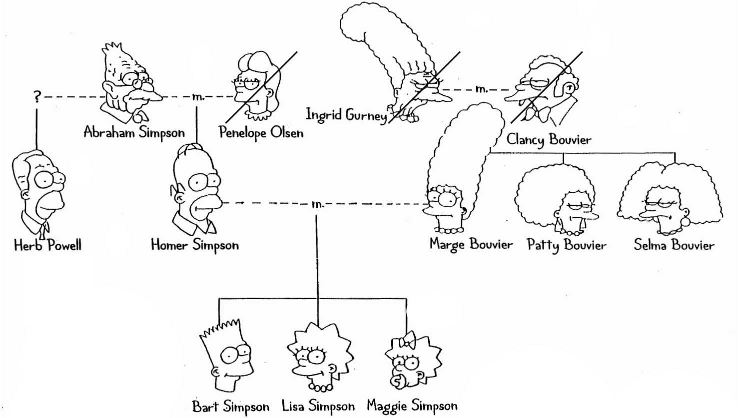
$$F_j(S_j) = \sum_{C_j \setminus S_j} \left(\prod_{i \in \mathrm{from}_j} F_i(S_i) \right) \times \prod_{X_u \in C_j{}^*} \varphi_u(X_{\mathrm{pa}_u}, X_u) \qquad F_3(\emptyset) = \mathbb{P}(\mathrm{ev})$$

Complexity:

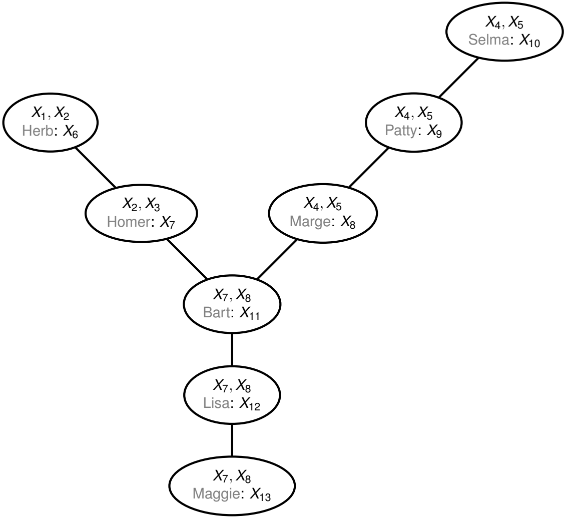
- from $81^7 = 22\,876\,792\,454\,961$
- to $3 \times 81^3 = 1\,594\,323$

Lisa: *“Much better !”* Homer: *“Woohoo !”*

Clique decomposition for the Simpsons

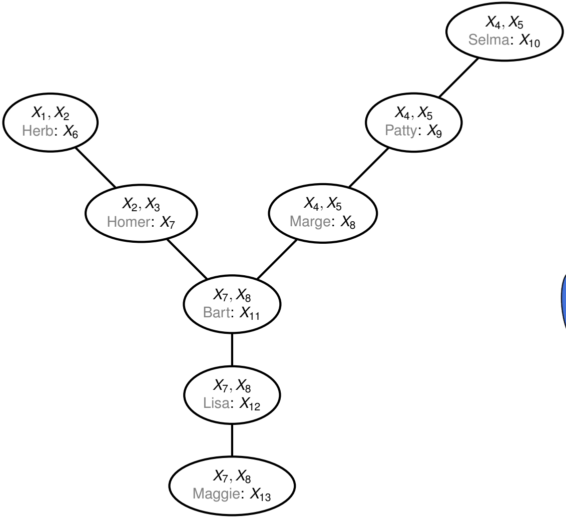


Clique decomposition for the Simpsons



- from $81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176$
- to $8 \times 81^3 = 4\,251\,528$

Clique decomposition for the Simpsons



- from $81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176$
- to $8 \times 81^3 = 4\,251\,528$

Posterior Distribution

After the sum-product algorithm we can combine forward/backward quantities with the potentials φ_i in order to derive:

- the marginal distribution $\mathbb{P}(C_j|\mathrm{ev})$ of each clique;
- the marginal distribution $\mathbb{P}(S_j|\mathrm{ev})$ of each separator;
- the full posterior $\mathbb{P}(X|\mathrm{ev})$ as a heterogenous Markov chain.

Introducing for all ind. i the *donor compatibility* random variable:

$$C_i = \mathbf{1}_{X_i=\text{OOdd}} = \begin{cases} 1 & \text{if } i \text{ compatible donor } \textit{i.e. } X_i = \text{OOdd} \\ 0 & \text{if } i \text{ not compatible donor } \textit{i.e. } X_i \neq \text{OOdd} \end{cases}$$

$$\mathbb{P}(C_i = 1|\mathrm{ev})$$

Herb's mum	Abraham	Penelope	Ingrid	Clancy
5.5%	2.4%	2.4%	16.2%	16.2%

Herb	Homer	Marge	Patty	Selma
3.8%	0.0%	13.5%	10.9%	10.9%

Bart	Lisa	Maggie
0.0%	1.5%	1.5%

Probability Generating Function

Idea: introduce a dummy variable z in the sum-product s.t.

$$\sum_{n \geqslant 0} \mathbb{P}(N = n, \mathrm{ev}) z^n = \sum_X \prod_i \varphi_i(X_{\mathrm{pa}_i}, X_i) z^{1_{X_i = \mathrm{OOdd}}}$$

complexity is just d times the previous one (d max degree).

$$\sum_{n \geqslant 0} \mathbb{P}(N = n | \mathrm{ev}) z^n = 0.528 + 0.282z + 0.0895z^2 + 0.0404z^3$$
$$+ 0.0329z^4 + 0.0250z^5 + 0.00189z^6 + 0.000148z^7 + 3.76 \times 10^{-7} z^8$$

$\mathbb{P}(C_i = 1 | \mathrm{ev})$

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5.5%	2.4%	2.4%	16.2%	16.2%

Herb	Homer	Marge	Patty	Selma
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$\mathbb{P}(C_i = 1 | N = 0, \mathrm{ev})$

Herb's mum	Abraham	Penelope	Ingrid	Clancy
0.0%	0.0%	0.0%	0.0%	0.0%

Herb	Homer	Marge	Patty	Selma
0.0%	0.0%	0.0%	0.0%	0.0%

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$$\mathbb{P}(C_i = 1 | N = 1, \mathrm{ev})$$

Herb's mum	Abraham	Penelope	Ingrid	Clancy
9.4%	5.4%	6.5%	28.3%	28.3%

Herb	Homer	Marge	Patty	Selma
5.8%	0.0%	11.8%	0.0%	0.0%

Bart	Lisa	Maggie
0.0%	2.3%	2.3%

Probability Generating Function

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$$\mathbb{P}(C_i = 1 | N = 2, \mathrm{ev})$$

Herb's mum	Abraham	Penelope	Ingrid	Clancy
18.6%	6.5%	4.5%	31.3%	31.3%

Herb	Homer	Marge	Patty	Selma
15.5%	0.0%	40.0%	19.8%	19.8%

Bart	Lisa	Maggie
0.0%	6.3%	6.3%

Probability Generating Function

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$$+ 0.0329z^4 + 0.0250z^5 + 0.00189z^6 + 0.000148z^7 + 3.76 \times 10^{-7} z^8$$

$$\mathbb{P}(C_i = 1 | N = 3, \mathrm{ev})$$

Herb's mum	Abraham	Penelope	Ingrid	Clancy
14.6%	6.0%	3.0%	33.2%	33.2%

Herb	Homer	Marge	Patty	Selma
11.8%	0.0%	27.9%	80.2%	80.2%

Bart	Lisa	Maggie
0.0%	4.9%	4.9%

Probability Generating Function

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$$\sum_{n \geqslant 0} \mathbb{P}(N = n | \mathrm{ev}) z^n = 0.528 + 0.282z + 0.0895z^2 + 0.0404z^3$$
$$+ 0.0329z^4 + 0.0250z^5 + 0.00189z^6 + 0.000148z^7 + 3.76 \times 10^{-7} z^8$$

$$\mathbb{P}(C_i = 1 | N = 4, \mathrm{ev})$$

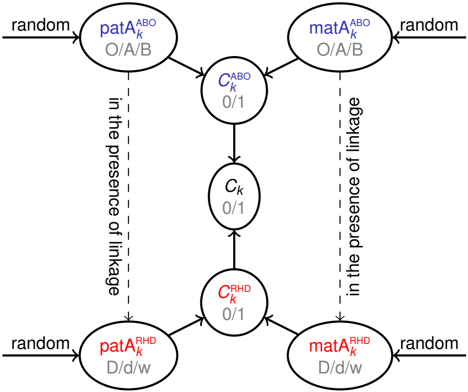
Herb's mum	Abraham	Penelope	Ingrid	Clancy
6.9%	2.1%	1.5%	48.2%	48.2%

Herb	Homer	Marge	Patty	Selma
4.8%	0.0%	86.5%	97.8%	97.8%

Bart	Lisa	Maggie
0.0%	3.2%	3.2%

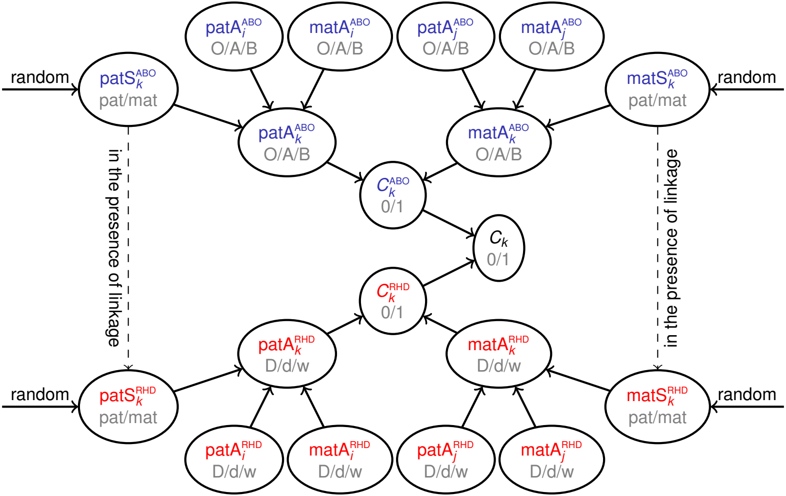
Extended Pedigree: Small Variables

For a *founder* i, instead of $X_i \in \mathcal{G}$ we have:



Extended Pedigree: Small Variables

For a *offspring k* (with father *i* and mother *j*),
instead of $X_k \in \mathcal{G} | X_i, X_j$ we have:



Extended Pedigree: Small Variables

Recall on complexity:

- naive $81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176$
- genotypes $8 \times 81^3 = 4\,251\,528$

Small variables with the three heuristics:

- min-neighbors: the smallest clique
  $\Rightarrow$ 61154 61649 89051
- min-fill: the clique with minimum fill-in
  $\Rightarrow$ 85205 92333 92360
- weighted min-fill: the clique with minimum weighted fill-in
  $\Rightarrow$ 57530 43841 43112

Epidemiological/Medical Applications

Many human diseases:

- Cancers:
  - Breast and Ovarian: *Institut Curie*
  - MSI Cancer and Lynch Syndrome: *Saint-Antoine*
  - Gliomas: *La Pitié-Salpêtrière*
- Rare Genetic Diseases:
  - Neuropathy Amyloid Hereditary: *Henri Mondor*
  - Pulmonary Arterial HT: *Marie Lannelongue*
  - Huntington Disease: *Hôpital Saint-Anne*
- Common Disease with Genetic Factors:
  - Alzheimer Disease: *CHU Rouen*
  - Diabetes, autism, cardio-vascular, obesity, . . .

And other applications: linkage analysis, genetic epidemiology, agronomy, recreative genetics, . . .

Aknowledgments

Funding:

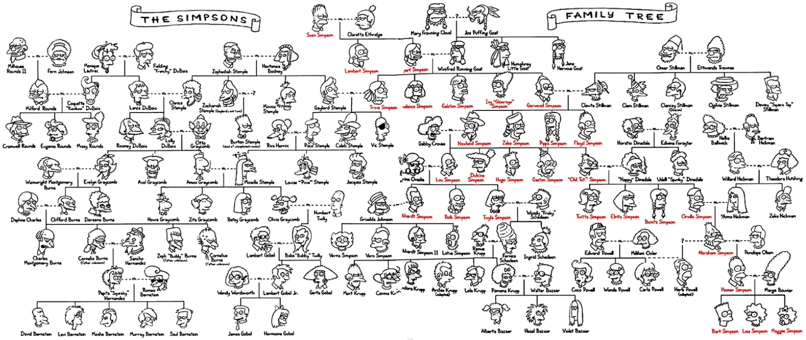
Institut de Recherche en Santé Publique
GIS-IReSP

LA LIGUE CONTRE LE CANCER

FRM FONDATION RECHERCHE MÉDICALE

and Special Thanks:

- Homer, Marge, Bart, Lisa, and Maggie Simpson
- Matt Groening


THE SIMPSONS
FAMILY TREE