

Genome-based discovery of trait networks in dairy cattle

Sara Pegolo¹, Mehdi Momen², Gota Morota², Guilherme J. M. Rosa^{3,4}, Daniel Gianola^{3,5}, Giovanni Bittante¹ and Alessio Cecchinato¹

¹Department of Agronomy, Food Natural resources, Animals and Environment, University of Padua, Legnaro (PD), Italy

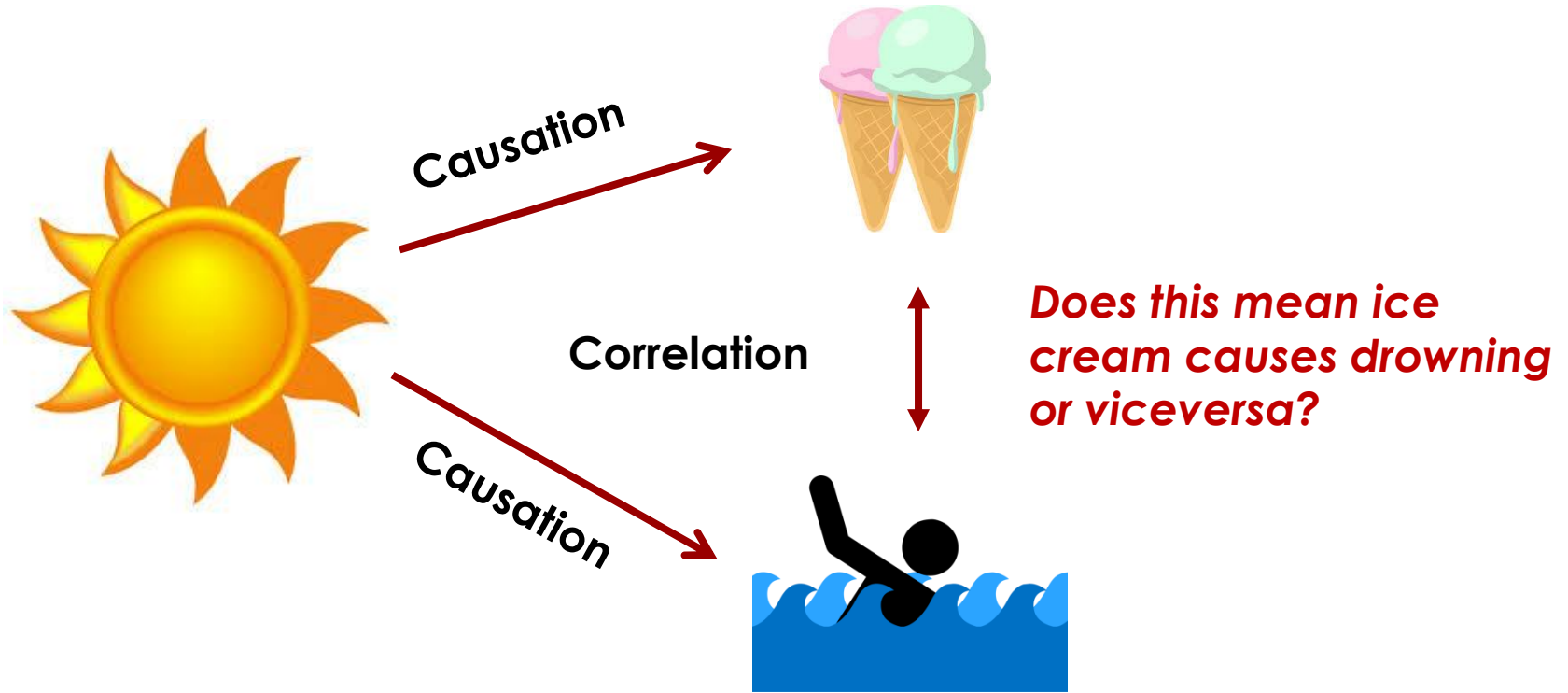
²Department of Animal and Poultry Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA

³Department of Animal Sciences, University of Wisconsin, Madison, WI, USA

⁴Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, USA

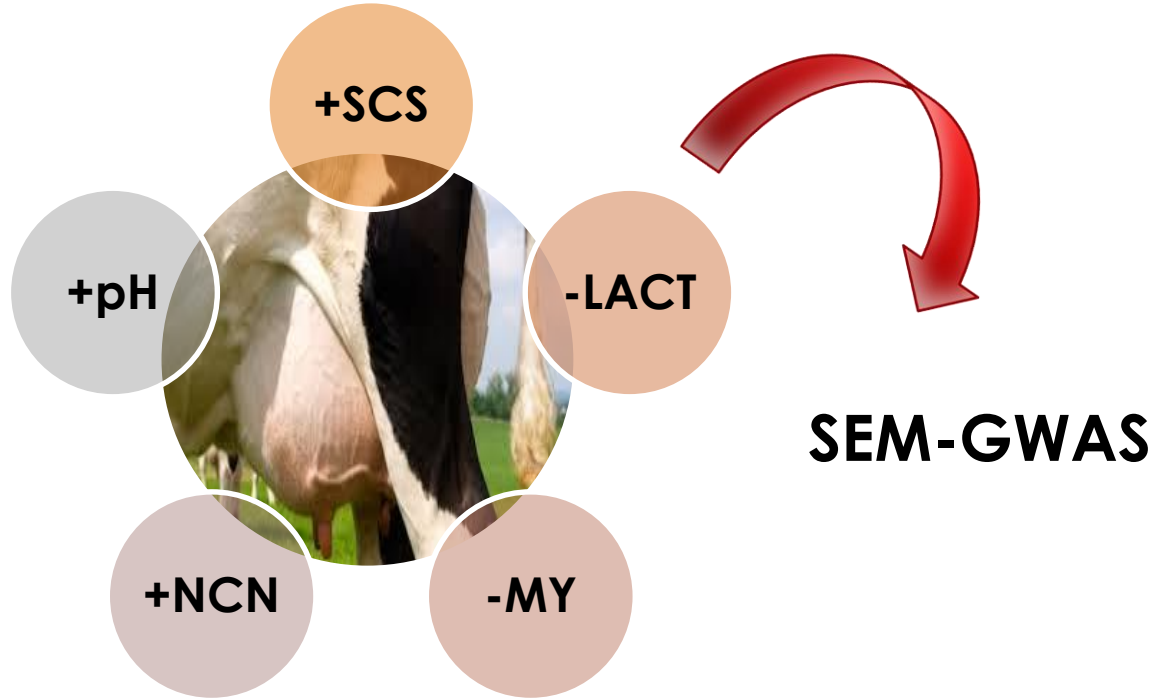
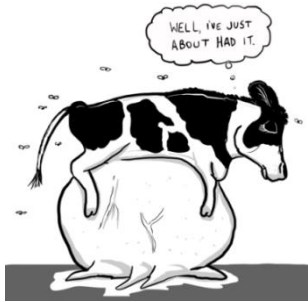
⁵Department of Dairy Science, University of Wisconsin, Madison, WI, USA

Correlation is not causation!





Causal relationships?



The approach

Phenotypes

Individual data from 990 Brown Swiss cows
(Cowability/Cowplus projects)



Genotypes

37,519 SNPs from Illumina Bovine SNP50

Bayesian multi-trait GBLUP VECTOR OF THE RESIDUALS

Bayesian networks

(Hill-Climbing algorithm, bnlearn R package)

Structural equations
SEM parameters

SEM-GWAS

Wombat «SNP Snappy»



MTM-GWAS

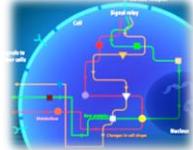
Wombat «SNP Snappy»

SNP

Path analyses

(right-sided hypergeometric test
with FDR<0.05, Cluego)

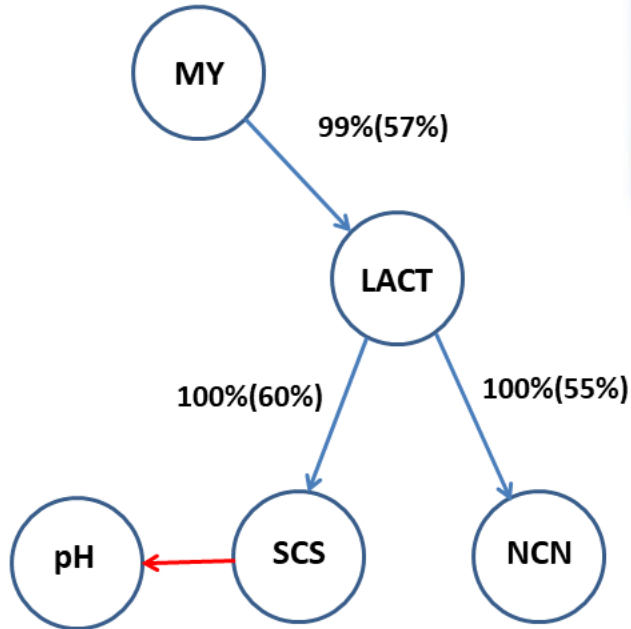
genes



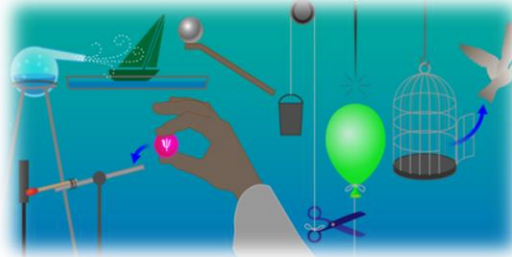
Effect decomposition for the significant SNP



From BNs to SEM parameters

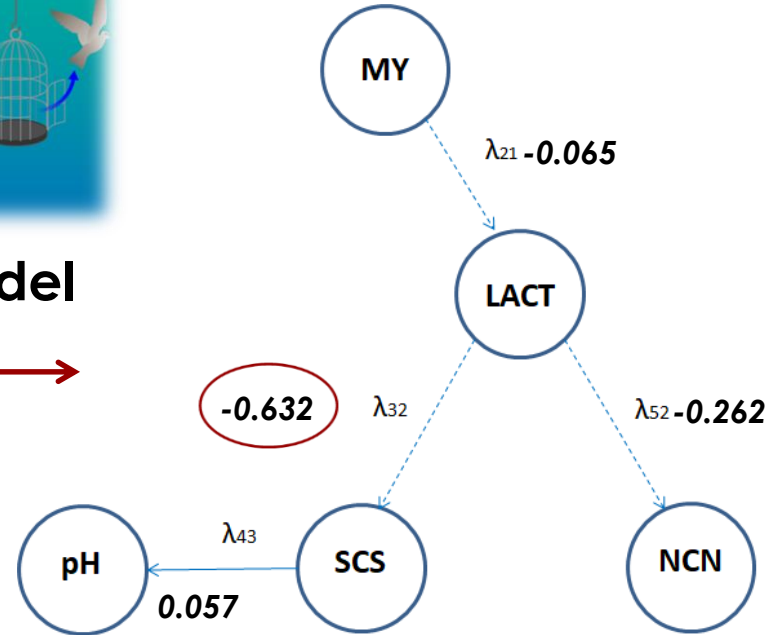


n=50,000 bootstrap samples



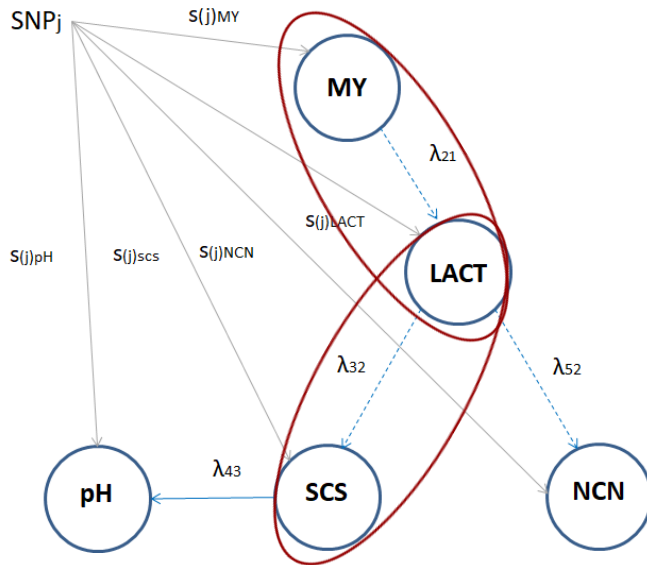
Recursive model (Wombat)

Structural
coefficients (λ)



$$\mathbf{y} = \underbrace{\Delta\mathbf{y}} + \mathbf{W}\mathbf{s} + \mathbf{X}\mathbf{b} + \mathbf{Z}\mathbf{g} + \mathbf{e}$$

Structural coefficients



SNP effect decomposition for SCS

$$\text{Direct}_{s_j \rightarrow y_{3SCS}} = s_j(y_{3SCS})$$

$$\text{Indirect(1)}_{s_j \rightarrow y_{3SCS}} = \lambda_{32} s_j(y_{2LACT})$$

$$\text{Indirect(2)}_{s_j \rightarrow y_{3SCS}} = \lambda_{32} \lambda_{21} s_j(y_{1MY})$$

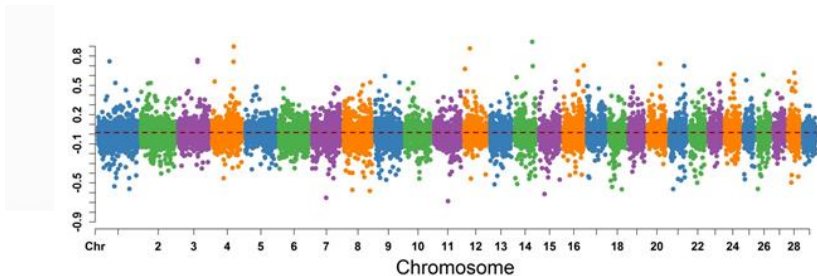


$$\begin{aligned} \text{Total}_{s_j \rightarrow y_{3SCS}} &= \text{Direct}_{s_j \rightarrow y_{3SCS}} + \text{Indirect(1)}_{s_j \rightarrow y_{3SCS}} + \text{Indirect(2)}_{s_j \rightarrow y_{3SCS}} \\ &= s_j(y_{3SCS}) + \lambda_{32} s_j(y_{2LACT}) + \lambda_{32} \lambda_{21} s_j(y_{1MY}) \end{aligned}$$

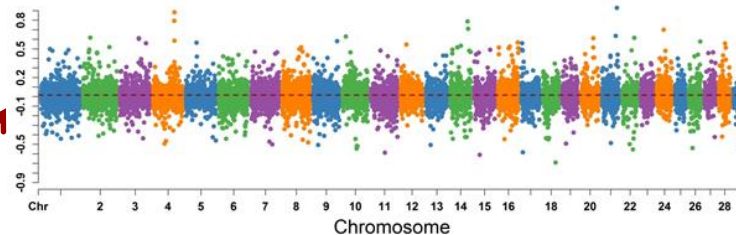
SEM GWAS - SNP effects

SCS

Total SNP effect

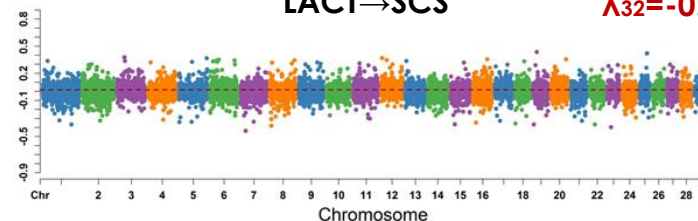


Direct SNP effect



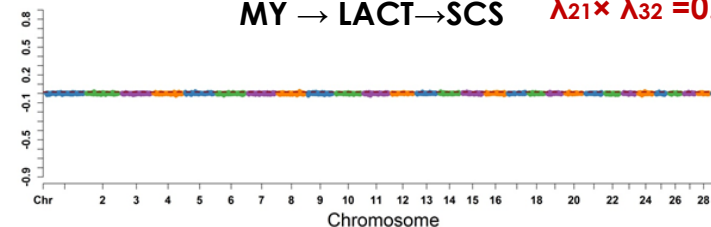
LACT → SCS

$\lambda_{32} = -0.632$



MY → LACT → SCS

$\lambda_{21} \times \lambda_{32} = 0.041$



Integration MTM-GWAS and SEM-GWAS

MTM-GWAS: significant SNP
($-\log_{10}P < 4.055$; Li and Ji, 2005)



SEM-GWAS: SNP effect
decomposition

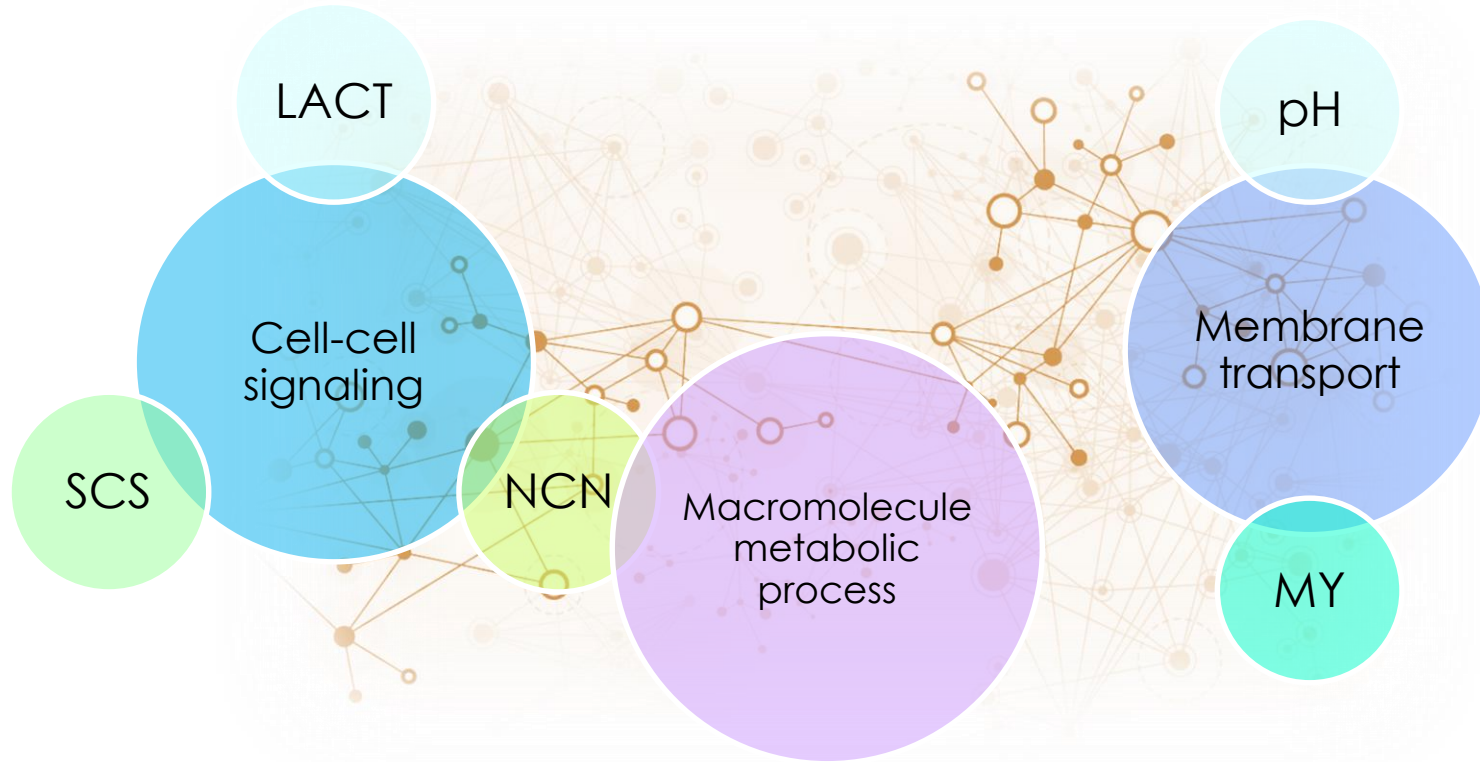


SNP	CHR	BP	$-\log_{10}P$	Direct effect	LACT→SCS	MY→LACT→SCS	Total effect
rs41569794	4	72532921	4.656	0.135	0.062	-0.003	0.194
rs110736919	4	76247713	4.494	0.171	0.028	-0.002	0.197
rs41615292	4	79930421	4.461	0.157	0.026	-0.001	0.182
rs110854438	4	76312755	4.377	0.173	0.020	-0.002	0.191
rs110811284	4	76377517	4.374	0.173	0.020	-0.002	0.191
rs110490432	13	5380158	4.054	0.158	0.040	<0.001	0.198

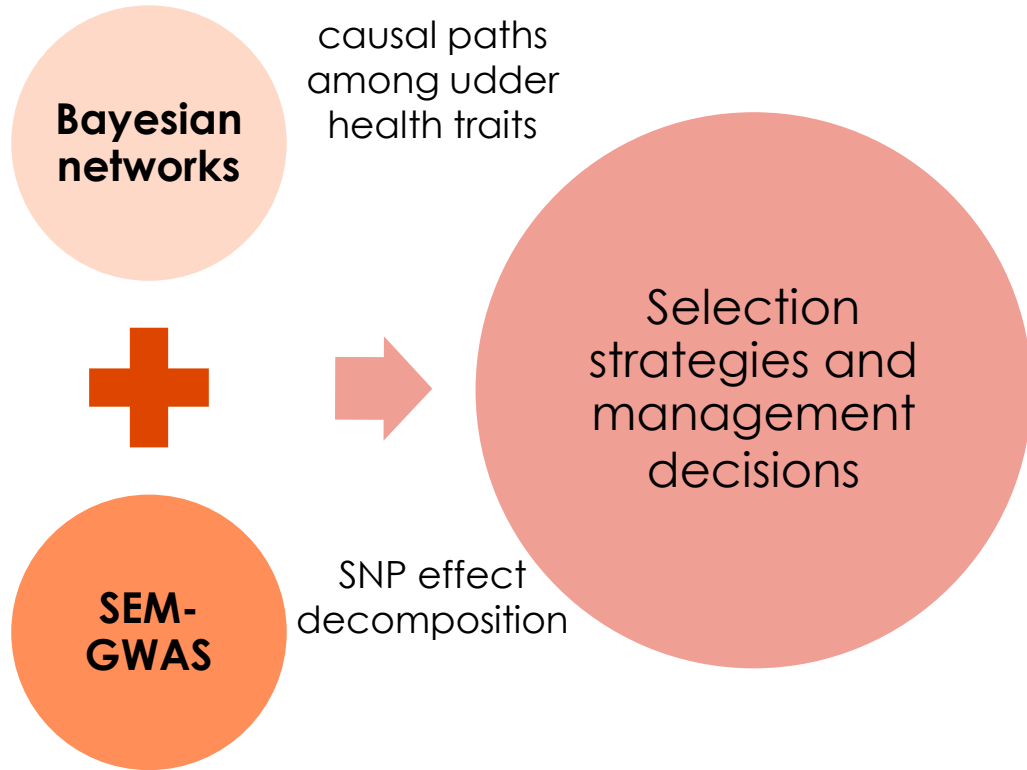


Inflammatory response
genes

Pathway analyses – Enriched terms



Conclusions & Challenges

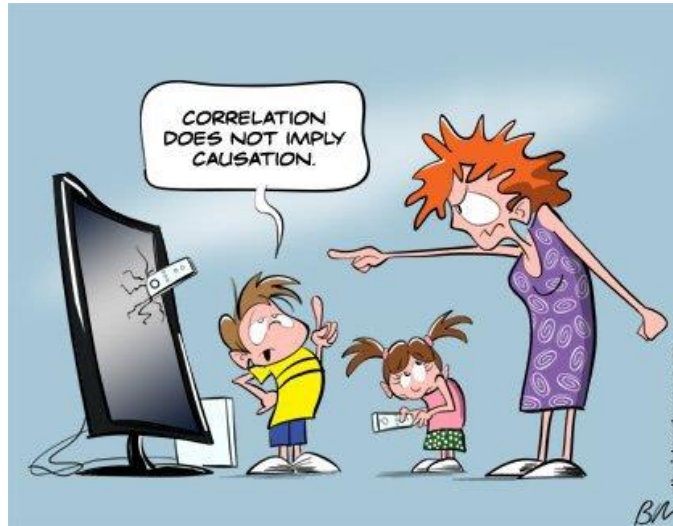


Complexity of multi-trait framework

But...

Hidden variables??





Thank you!



ANARB

Email: sara.pegolo@unipd.it