Living in a World

of

Interactions

Kristel Van Steen, PhD² (*)

(*) WELBIO, GIGA-R Medical Genomics (BIO3), University of Liège, Belgium

Outline

• Motive

- Opportunity
 - -Data context
 - -Disease context
- Means
 - -MB-MDR
 - -GWAI protocol
- Take-home messages

MOTIVE

The complexity of complex diseases



(Weiss and Terwilliger 2000)

There are likely to be *many* susceptibility genes each with combinations of rare and common alleles and genotypes that impact disease susceptibility primarily through *non-linear* interactions with genetic and environmental factors (Moore 2008)

"Interactions" in humans come natural

- From an evolutionary biology perspective, for a phenotype to be buffered against the effects of mutations, it must have an underlying genetic architecture that is comprised of networks of genes that are redundant and robust.
- The existence of these networks creates dependencies among the genes in the network and is realized as gene-gene interactions or (*trans*-) epistasis.
- This suggests that epistasis is not only important in determining variation in natural and human populations, but should also be more widespread than initially thought (rather than being a limited phenomenon). (Moore et al. 2005)

Unexplained heritability

- The **statistical definition** for heritability defines it as the proportion of phenotypic variance attributable to genetic variance.
- The "sensical" definition defines it as the extent to which genetic individual differences contribute to individual differences in observed behavior (or phenotypic individual differences).
- The proportion of heritability explained by a set of variants is the ratio of (i) the heritability due to these variants (numerator), estimated directly from their observed effects, to (ii) the total heritability (denominator), inferred indirectly from population data.

(Maher 2008, Zuk et al. 2012)

Unexplained heritability

Explanation	Rationale	Comments
Overestimated heritability	These estimates are typically	Limiting pathway modeling
estimates	performed in the absence of	suggests that epistasis could
	gene-gene or gene-	account for missing
	environment interactions	heritability in complex
	(Young et al. 2014)	diseases (Zuk et al. 2012)
Rare genetic variants	Resequencing studies (e.g.,	Limited evidence for rare
	WES) could identify rare	variants of major effect in
	genetic determinants of large	complex diseases accounting
	effect size (Zuk et al. 2014)	for large amount of genetic
		variation – most rare variants
		analysis methods currently
		suffer from increased type I
		errors (Derkach et al. 2014)
Phenotypic and genetic	Most complex diseases are	Improvements in phenotyping
heterogeneity	like syndromes with multiple	of complex diseases will be
	potentially overlapping	required to understand
	disease subtypes	genetic architecture.

Explanation	Rationale	Comments
Interactions	Gene-gene and gene-	Limited <i>replicated</i> evidence
	environment interactions are	for statistical interactions in
	likely to be important for	complex diseases;
	complex diseases (Moore et	network-based approaches
	al 2005)	may be helpful (Hu et al.
	Roughly 80% of the currently	2011)
	missing heritability for	
	Crohn's disease could be due	
	to genetic interactions, if the	
	disease involves interaction	
	among three pathways (Zuk	
	et al. 2012)	

(adapted from Silverman et al. 2012)



(Hayden 2010) « Life is Complicated »)

A tale of ... multiple ... stories



Biological interactions

- Biological interactions are the effects that the organisms in a community have on one another. In the natural world no organism exists in absolute isolation, and thus every organism must interact with the environment and other organisms.
- An organism's interactions with its environment are fundamental to the survival of

that organism and the functioning of the ecosystem as a whole



(Elton 1968; Wikipedia)

Omics data as a starting point

- Roughly, omics data is a generic term that describes genome-scale data sets that emerge from high-throughput technologies
- These data describe virtually all biomolecules in a cell (e.g., proteins, metabolites)

(Joyce and Palsson 2006)



(courtesy figure Maggie Wang)

Gene-gene interactions (epistasis)

• Inference about gene-gene interactions using microarray data



(Prieto et al. 2008)

DNA-DNA interactions

 Two or more DNA variations may "interact" either directly to change transcription or translation levels, or indirectly by way of their protein product (to alter disease risk separate from their independent effects)



⁽Moore 2005)

Formal definition of epistasis

- The original definition (**driven by biology**) refers to a variant or allele at one locus preventing the variant at another locus from manifesting its effect (William Bateson 1861-1926).
- A later definition of epistasis (**driven by statistics**) is expressed in terms of deviations from a model of additive multiple effects (Ronald Fisher 1890-1962).



Correspondence between statistical and biological interactions

- Much discussion in the literature (primarily gene-gene):
 - Siemiatycki and Thomas (1981) Int J Epidemiol 10:383-387
 - Thompson (1991) J Clin Epidemiol 44:221-232
 - Phillips (1998) Genetics 149:1167-1171
 - Cordell (2002) Hum Molec Genet 11:2463-2468
 - McClay and van den Oord (2006) J Theor Biol 240:149-159
 - Phillips (2008) Nat Rev Genet 9:855-867
 - Clayton DG (2009) PLoS Genet 5(7): e1000540
 - Wang, Elston and Zhu (2010) Hum Hered 70:269-277
- Conclusions: 1) little direct correspondence (physical interactions) ;
 2) statistical interaction DOES imply joint involvement

(courtesy slide EUPancreas WG2 Training School, Antwerp, 2016)

Formal definition of gene-environment interactions

- Also gene-environment interactions can be defined in a statistical or a biological way.
- A **biological gene-environment** interaction occurs when one or more genetic and one or more environmental factors participate in the same causal mechanism in the same individual (Yang and Khoury 1997; Rothman et al. 2008)
- As with gene-gene interactions, a **statistical gene-environment** interaction does not imply any inference about a specific biological mode of action. It is based on modeling a sample of individuals.

Formal definition of epistasis

- In practice, when modeling or testing, it may only be possible to detect **effect modification** from real-life data and not **interaction**, or interaction but not effect modification.
- Whereas an interaction effect for "exposures" X_1 and X_2 relies on a symmetric role for both X_1 and X_2 , an effect modification relies on a conditioning argument (for instance on X_2) (VanderWeele 2009a)
- The distinction between both effect types is often concealed in regression analysis ... (Robins et al. 2000; North et al. 2005)

Portoroz, Slovenia 2016

Comparison between gene–gene and gene–environment issues

- Conceptually many similar issues in terms of definition and mathematical modelling.
- In practice, some clear differences emerge.
- For G x E:
 - We generally have to decide which environments to measure / test; these are typically only a few (often < 100)
 - Measurement error (lifestyle) and unknown confounding
 - Risk estimation, important for screening strategies and public health interventions

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Comparison between gene-gene and gene-environment issues

- For G x G
 - Assuming we have GWAS data, we have already measured the genetic factors of interest
 - Adequate error rates (except for newer sequencing technologies)
 - (Hundred) thousands of variants
 - Higher-order interactions may reflect the complex biological wiring of complex diseases (whereas G x E often restricts attention to pairwise interactions)

(courtesy slide EUPancreas WG2 Training School, Antwerp, 2016)

Looking for higher-order interactions



Edges represent small gene-gene interactions between SNPs.

Gray nodes and edges have weaker interactions.

Circle nodes represent SNPs that do not have a significant main effect. The diamond nodes represent significant main effect association.

The size of the node is proportional to the number of connections.

(McKinney et al 2012)

Some references

Published in final edited form as: *Hum Genet.* 2012 October ; 131(10): 1591–1613. doi:10.1007/s00439-012-1192-0.

Challenges and Opportunities in Genome-Wide Environmental Interaction (GWEI) studies

Hugues Aschard¹, Sharon Lutz^{2,*}, Bärbel Maus^{3,4,*}, Eric J. Duell⁵, Tasha Fingerlin², Nilanjan Chatterjee⁶, Peter Kraft^{1,7}, and Kristel Van Steen^{3,4}

Hum Genet (2014) 133:1343–1358 DOI 10.1007/s00439-014-1480-y

REVIEW PAPER

Practical aspects of genome-wide association interaction analysis

Elena S. Gusareva · Kristel Van Steen

OPPORTUNITY



Data context: Bioinformatics data availability

(Chen et al. 2012)



Addressing complexity in "complex diseases" - pancreatic cancer

"Because effective systemic therapy capable of controlling the aggressive pancreatic cancer biology is currently lacking, the need for a better understanding of detailed mechanisms underlying pancreatic cancer development and progression is **URGENT**"

(Xie and Xie 2015)

Examples of interactions in pancreatic cancer

Tumor-stromal interactions

- Treatments focusing on pancreatic cancer cells alone have failed to significantly improve patient outcome over many decades
- Research efforts have now moved to understanding the pathophysiology of the stromal reaction and its role in cancer progression



(Whatcott et al. 2014)

Gene-environment interactions

(Jansen et al. 2015)









Protein-protein interactions

A graph consisting of 2,080 shortest paths:

- The nodes on the inner circle (red nodes) represent 65 PC-related genes.
- The nodes on the outer circle (blue nodes) represent 69 shortest path genes.
- The numbers on the edges represent the weights of the edges.



(Yuan et al. 2015)

Gene-coexpression networks

(Anglani et al. 2014)



- Healthy condition on the left and disease-affected tissue on the right. Green links remain unchanged in the two phenotypes
- Red connections are loss from healthy to cancer network
- Blue edges are novel connections in the cancer tissue

Genetic-epigenetic mechanistic interactions (pancreatic islets)



(Olsson et al. 2014)

Gene-gene interactions using SNPs?

Wolpin BM (PMID: 25086665) ☑	2014-08-03	Nat Genet	Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer.	Pancreatic cancer	10	
	Initia desc	l sample ription	1,582 European ancest controls	ry cases, 5,203 E	uropean ances	try
	Initia (cou recru	l ancestry ntry of uitment)	6785 European (U.S., A Netherlands, Denmark, Greece, Italy, Spain)	Australia, France, Finland, Norway	Germany, , Sweden, U.K.,	
	Repl desc	ication sample ription	6,101 European ancest controls	ry cases, 9,194 E	uropean ances	try
	Repl (cou recru	ication ancestry ntry of uitment)	15295 European (Cana Netherlands, Denmark, Greece, Italy, Spain)	da, U.S., France, Finland, Norway,	, Germany, , Sweden, U.K.,	
	Platf	orm [SNPs ing QC]	Illumina [608202]			

GWAS Catalogue – "Pancreas Cancer"

(http://www.ebi.ac.uk/gwas/search?query=pancreas%20cancer#study)

Epistasis appearance versus detection

- Examples of DNA-DNA interactions from model organisms (Carlborg and Haley 2004):
 - Epistatic QTLs without individual effects have been found in various organisms, such as birds, mammals, Drosophila melanogaster and plants.
 - Other similar studies have reported only low levels of epistasis or no epistasis at all, despite being thorough and involving large sample sizes.
- Indicates the complexity with which multifactorial traits are regulated; no single mode of inheritance can be expected to be the rule in all populations and traits...

The only source of knowledge is experience (Albert Einstein)

Genome-wide association interaction analysis for Alzheimer's disease

Elena S. Gusareva^{1,2}, Minerva M. Carrasquillo³, Céline Bellenguez^{4,5,6}, Elise Cuyvers^{7,8}, Samuel Colon³, Neill R. Graff-Radford⁹, Ronald C. Petersen¹⁰, Dennis W. Dickson³, Jestinah M. Mahachie Johna^{1,2}, Kyrylo Bessonov^{1,2}, Christine Van Broeckhoven^{7,8}, The GERAD1 Consortium, Denise Harold¹¹, Julie Williams¹¹, Philippe Amouyel^{4,5,6}, Kristel Sleegers^{7,8}, Nilüfer Ertekin-Taner⁹, Jean-Charles Lambert^{4,5,6}, and Kristel Van Steen^{1,2}



(Gusareva et al. 2014)

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(Gusareva et al. 2014)

"This particular study in particular demonstrates an effective approach to elucidate the functional repercussions of epistasis"

(Ebbert et al. 2015)

MEANS

Although there is growing appreciation that attempting to map genetic interactions in humans may be a fruitful endeavor, there is no consensus as to the best strategy for their detection, particularly in the case of genome-wide association where the number of potential comparisons is enormous

(Evans et al. 2006)

One popular method singled out: (logistic) regression

- Most general saturated (9 parameter) genotype model allows all 9 penetrances to take different values
- Log odds is modelled in terms of a baseline effect (β_0), main effects of locus *G* (β_{G1} , β_{G2}), main effects of locus *H* (β_{H1} , β_{H2}), 4 interaction terms
- This corresponds in statistical analysis packages to coding X1, X2 (0,1,2) as a "factor"

		Locus H	
Locus G	2	1	0
2	$\beta_0 + \beta_{G2} + \beta_{H2} + \beta_{22}$	$\beta_0+\beta_{G2}+\beta_{H1}+\beta_{21}$	β_0 + β_{G2}
1	$\beta_0 + \beta_{G1} + \beta_{H2} + \frac{\beta_{12}}{\beta_{12}}$	β_0 + β_{G1} + β_{H1} + β 11	eta_0 + eta_{G1}
0	$\beta_0+\beta_{H2}$	eta_0 + eta_{H1}	eta_{0}

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One popular method singled out: (logistic) regression

• Alternatively, we can assume additive effects of each allele at each locus, leading to a single interaction term (instead of 4 before!)

		Locus H	
Locus G	2	1	0
2	$\beta_0 + 2\beta_G + 2\beta_H + 4\beta$	β_0 + 2 β_G + β_H + 2 β	β_0 + 2 β_G
1	$\beta_0 + \beta_G + 2\beta_H + 2\beta$	$\beta_0 + \beta_G + \beta_H + \beta$	β_0 + β_G
0	β_0 + 2 β_H	$\beta_0 + \beta_H$	eta_{0}

corresponding to the model (X1 and X2 coded as (0,1,2)):

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_G X_1 + \beta_H X_2 + \beta X_1 X_2$$

Concerns with (logistic) regression models

- There is no direct correspondence between the interaction effects and the underlying penetrance based models displaying some kind of epistasis effect (North et al. 2005) → interpretation and biological translation
- Standard regression techniques are hampered by inflated false positives, and diminished power caused by the presence of sparse data and multiple testing problems, even in small simulated data sets only including 10 SNPS (Vermeulen et al. 2007) → assessing significance
- Unknown confounders or wrong model assumptions: model misspecification → robust modeling

Investigating multi-locus correlations instead

- Test whether correlation is different in cases and controls via testing a "log OR" for association between two loci
- Examples :
 - Fast epistasis (PLINK)

	L	Locus H			Loci	us H
Locus G	2	1	0	Locus G	H_1	H_2
2	а	b	С	<i>G</i> ₁	A = 4a + 2b + 2d + e	B = 4c + 2b + 2f + e
1	d	е	f	G ₂	C = 4g + 2h + 2d + e	D = 4i + 2h + 2f + e
0	g	h	i			

See Ueki and Cordell (2012) for a correct variance estimation for the log(OR) (CASSI / PLINK 9.1)

- EPIBLASTER (Kam-Thong et al. 2011)

Model-Based Multifactor Dimensionality Reduction (MB-MDR)

Historical notes about MB-MDR

• Start: Multifactor Dimensionality Reduction by MD Ritchie et al (2001)



Which dimensions are reduced?

• The estimated degrees of freedom for MDR and LR using K=1, 2 and 3 factors (standard errors in parentheses). LR exact refers to the asymptotic exact degrees of freedom

	Number of Factors K			
Method	1	2	3	
MDR	1.9 (0.13)	5.6 (0.20)	17.4 (0.37)	
LR	2.1 (0.4)	8.0 (0.26)	26.8 (0.53)	
LR exact	2	8	26	

(Park and Hastie 2007)

Several MDR roads lead to Rome



Shift from prediction to association

- Model-Based MDR by Calle et al (2008a)
 - Rather, computation time is invested in optimal association tests to prioritize multilocus genotype combinations and in statistically valid permutation-based methods to assess joint statistical significance
 - Results of association tests are used to "label" multilocus genotype cells (for instance: increased / no evidence/ reduced risk, based on sign of "effect") and to "quantify" the multilocus signal wrt the trait of interest, "above and beyond lower order signals"

Global versus specific modeling

• Model-Based MDR by Calle et al (2008a,b)

SNP 40 x SNP 252 genotypes	Cases	Controls	OR	p-value	Category
c1 = (0,0)	88	77	1.01	0.9303	0
c2 = (0,1)	102	114	0.73	0.0562	L
c3 = (0,2)	38	34	0.98	1.0000	0
c4 = (1,0)	50	59	0.76	0.1229	0
c5 = (1,1)	96	37	2.68	0.0000	Н
c6 = (1,2)	18	28	0.55	0.0675	L
c7 = (2,0)	12	6	1.99	0.3399	0
c8 = (2,1)	14	18	0.67	0.3668	0
c9 = (2,2)	6	6	0.84	1.0000	0

Table 3. MB-MDR first step analysis for interaction between SNP 40

H: High risk; L: Low risk; 0: No evidence

and SNP 252 in the bladder cancer study



Fig. 1. Average Balanced Training accuracy (Acc) versus Average Balanced Predictive accuracy (Pred) for the 100 models with higher balanced training accuracy for the whole sample. First, second, third and forth order interactions are considered.



Model-Based Multifactor Dimensionality Reduction (MB-MDR)



MB-MDR

Summary of the steps involved in MB-MDR analysis:

- For every k variates (e.g., SNPs), Step 1 is a data organization step in which individuals are (naturally) allocated to k-dimensional (genotype) profiles.
- Step 2 labels individuals according to their profiles in multidimensional space and liberal association tests. Individuals with the same label are merged into a single group.
- Extreme groups are contrasted to each other via an association test, leading to a test value W_{max} for the selected k-tuple.
- The final k-models are selected in Step 3, using permutation-based significance assessments and adequate multiple testing control.

Power performance (absence/presence of genetic heterogeneity)

• Model-Based MDR by Cattaert et al. 2011



Comparative performance of 2-locus MB-MDR

• False positives

(example: pure epistasis scenario's; unpublished - 2010)



BOOST (dark blue) EpiCruncher optimal options (light blue) MB-MDR (green) PLINK epistasis (dark yellow) PLINK fast epistasis (light yellow) EPIBLASTER (red)

Comparative performance of 2-locus MB-MDR

• Power performance

Model R1, no GH Model R2, no GH Model R3, no GH Model R4, no GH Model R5, no GH Model R6, no GH 1.0 1.0 1.0 0.8 0.8 0.8 0.8 0.8 0.8 0.6 0.6 0.6 0.6 0.6 0.4 0.4 0.4 0.4 0.2 0.2 0.2 0.2 Model R1, GH both Model R2, GH both Model R3, GH both Model R4, GH both Model R5, GH both Model R6, GH both 1.0 1.0 1.0 -1.0 1.0 1.0 0.8 0.8 0.8 0.8 0.8 0.8 0.6 0.6 0.6 0.6 0.6 0.6 0.4 0.4 0.4 0.4 0.4 0.4 0.2 0.2 0.2 0.2 0.2 0.2

(example: pure epistasis scenario's; unpublished - 2010)

BOOST (dark blue)

EpiCruncher optimal options (light blue) MB-MDR (green) PLINK epistasis (dark yellow) PLINK fast epistasis (light yellow) EPIBLASTER (red)

Towards a GWAI Protocol

The BIO3 GWAI protocol



(Gusareva et al. 2014)

These critical steps are paramount to the *success* of GWAI studies

Prior biological information

- Some researchers incorporate prior biological "knowledge":
 - Allow for uncertainty involved in the data source entries
 - Acknowledge the complementary characteristics of each of the available data sources
 - Think about the "significance" of evidence scores
- The advantage is reduced data dimension and potentially saving costs
- The draw-back is to be restricted by the biological assumption: hypothesis-driven versus hypothesis generating analysis

Slight protocol changes may lead to huge differences in results



Slight protocol changes may lead to huge differences in results



• Bessonov K, Gusareva ES, Van Steen K (2015) A cautionary note on the impact of protocol changes for Genome-Wide Association SNP x SNP Interaction studies: an example on ankylosing spondylitis. Hum Genet accepted [non-robustness of GWAI analysis protocols]

Confounding by shared genetic ancestry

(MB-MDR and pair-specific genomic control – Van Lishout)



Multilocus Exposure

Disease Outcome

Replication

"Leaving aside for the moment **what replication means** or should mean in the context of GWAIS, even for the currently so-called replicated genetic interactions it is unclear to what extent **a false positive has been replicated** due to the adopted methodological strategy itself or whether the replication of epistasis is not solely attributed to main effects (such as HLA effects) not properly accounted for."



(Ritchie and Van Steen 2016)

MogPlot (Van Lishout)

Replication

"Genome-wide SNP genotyping platforms consist predominantly of **tagSNPs** from across the genome. Most of these SNPs are not causal and have no functional consequences. When two or more tagSNPs are combined in a genetic interaction model, is it reasonable to assume that the same combination of tagSNPs interacts in an independent dataset?"

(Ritchie and Van Steen 2016)



(Slide S Pineda – lab meeting 2014)

TAKE HOME MESSAGES



Learning from data (synthetic + real-life)

- Calle, M. L., Urrea, V., Vellalta, G., Malats, N. & Van Steen, K. (2008a) Model-Based Multifactor Dimensionality Reduction for detecting interactions in high-dimensional genomic data. Technical Report No. 24, Department of Systems Biology, Universitat de Vic, http://www.recercat.net/handle/2072/5001 [technical report, first mentioning MB-MDR]
- Calle M, Urrea V, Malats N, Van Steen K. (2008) Improving strategies for detecting genetic patterns of disease susceptibility in association studies Statistics in Medicine 27 (30): 6532-6546 [MB-MDR with Wald tests and MAF dependent empirical test distributions]
- Calle ML, Urrea V, Van Steen K (2010) mbmdr: an R package for exploring gene-gene interactions associated with binary or quantitative traits. Bioinformatics Applications Note 26 (17): 2198-2199 [first MB-MDR software tool, in R]
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- Cattaert T, Calle ML, Dudek SM, Mahachie John JM, Van Lishout F, Urrea V, Ritchie MD, Van Steen K (2010) Model-Based Multifactor Dimensionality Reduction for detecting epistasis in case-control data in the presence of noise (*invited paper*). Ann Hum Genet. 2011 Jan;75(1):78-89 [detailed study of C++ MB-MDR performance with binary traits]
- Mahachie John JM, Cattaert T, De Lobel L, Van Lishout F, Empain A, Van Steen K (2011) Comparison of genetic association strategies in the presence of rare alleles. BMC Proceedings, 5(Suppl 9):S32 [first explorations on C++ MB-MDR applied to rare variants]
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- Van Lishout F, Gadaleta F, Moore JH, Wehenkel L, Van Steen K (2015) gammaMAXT: a fast multiple-testing correction algorithm BioData Mining 8:36 [C++ MB-MDR made SUPER-fast]
- Fouladi R, Bessonov K, Van Lishout F, Van Steen K (2015) Model-Based Multifactor Dimensionality Reduction for Rare Variant Association Analysis. Human Heredity – accepted [aggregating based on similarity measures to deal with DNA-seq data]

Contact: f.vanlishout@ulg.ac.be (C++ MB-MDR software engineer)

Learning by data summary

• Backpack items on the road less travelled by, include:

Item	Our label
Speed controller	Gamma MaxT (Van Lishout et al.2015 – submitted)
Population/patient substructure or	MB-MDR for structured populations (Van
(cryptic) relatedness chart	Lishout et al. 2013 – poster ASHG,
	manuscript in preparation)
Correlated input features map	Component-based Path Modeling (PLS-PM;
	Esposito Vinzi @ ERCIM2014 short course)
Replication / Meta-analysis toolkit	Easier to do when units of analysis are at a
	higher level (such as genes instead of {SNPs,
	epigenetic markers, miRNAs,})
	(Gusareva et al. 2014 – GWAI protocol)

Thank You





"If we put our minds and resources together we will be able to improve things for all those suffering with this disease [pancreas cancer]. The EU has a prominent role to play"

(Françoise Grossetête, MEP)

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GIGA-R Medical Genomics - BIO3 Unit **University of Liège** Belgium



http://www.statgen.ulg.ac.be/ http://www.montefiore.ulg.ac.be/~kvansteen/ Google Scholar, Research Gate