

INTERACTIONS

Examples and interpretations

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CENTRE FOR
FERTILITY AND HEALTH

MEANWHILE, IN BERGEN....



INTERACTIONS

The concept of “interaction” appears in numerous settings where a statistical analysis is used to throw light on complex biological systems

Loosely defined:

- One variable modifies the effect of another variable
- Thus, sometimes referred to as an “Effect modifications”
... but is that actually the same?

For instance:

- Smoking may be more dangerous to men than to women
- Vaccination may be more “useful” for older people than for younger
- A fetal gene might act differently depending on whether it is inherited from the mother or the father

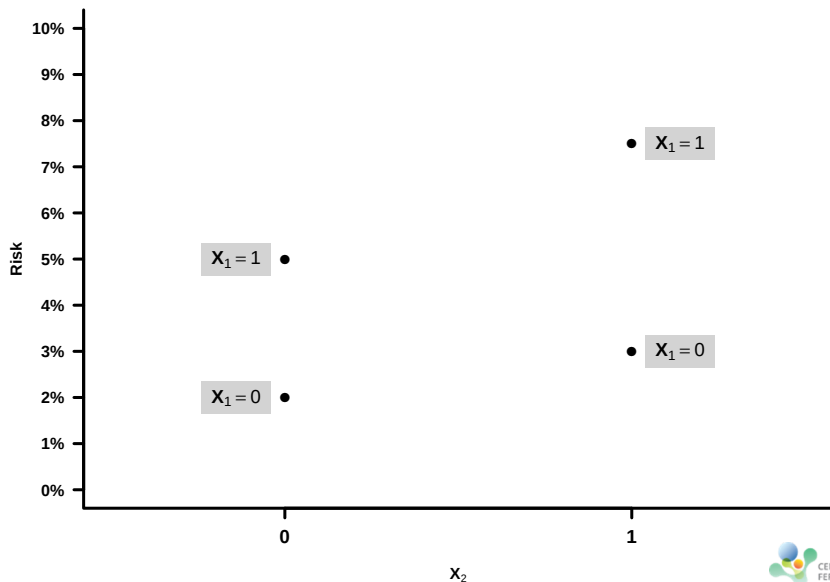
- Consider the effect of X_1 on Y
- Does the effect change over levels of another variable X_2 ?

Some questions:

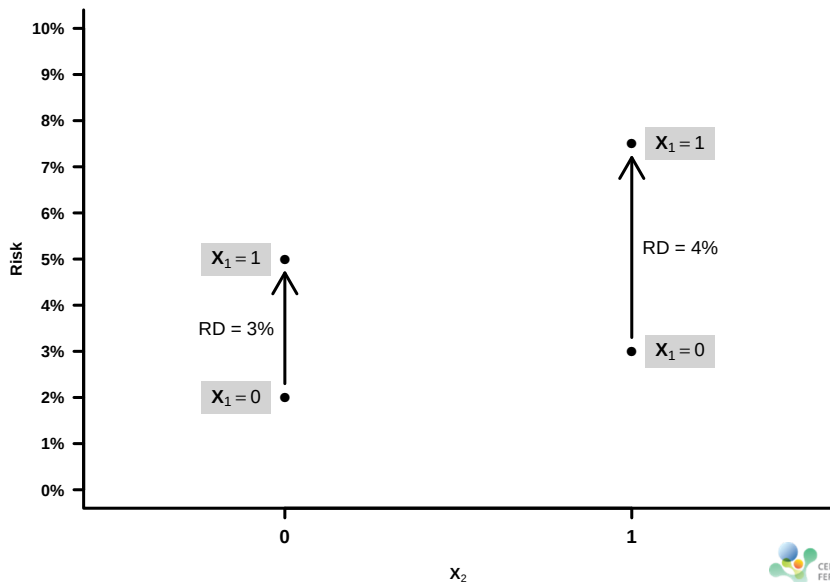
- What is the “correct” way of defining and measuring interactions?
- How does a statistical interaction reflect the underlying biological processes, for instance interactions at a molecular level?
- What are gene-gene (epistasis) and gene-environment interactions?
- How do interaction analyses increase the required sample size of a study?
- Are statisticians good at social interactions?

Avoiding the last question, we will see that the answers to the others are sometimes simple, sometimes complex.

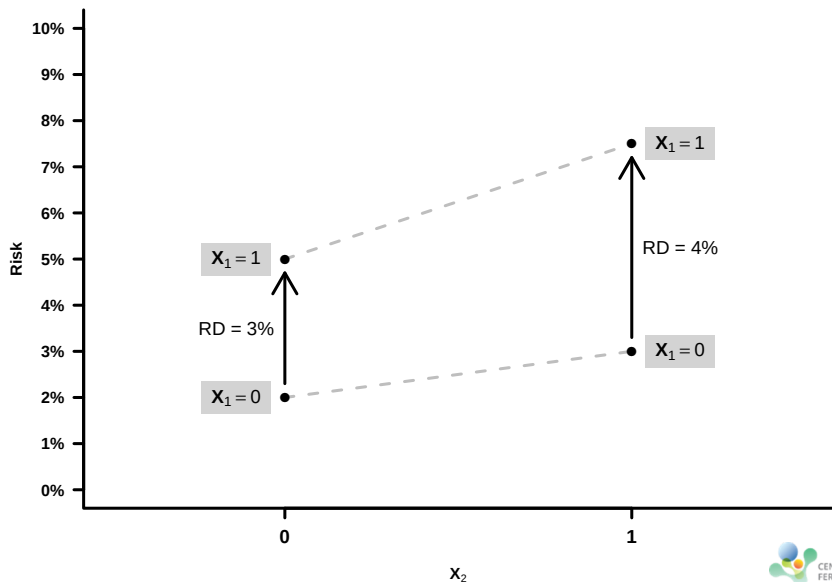
INTERACTIONS, RISK DIFFERENCE (RD)



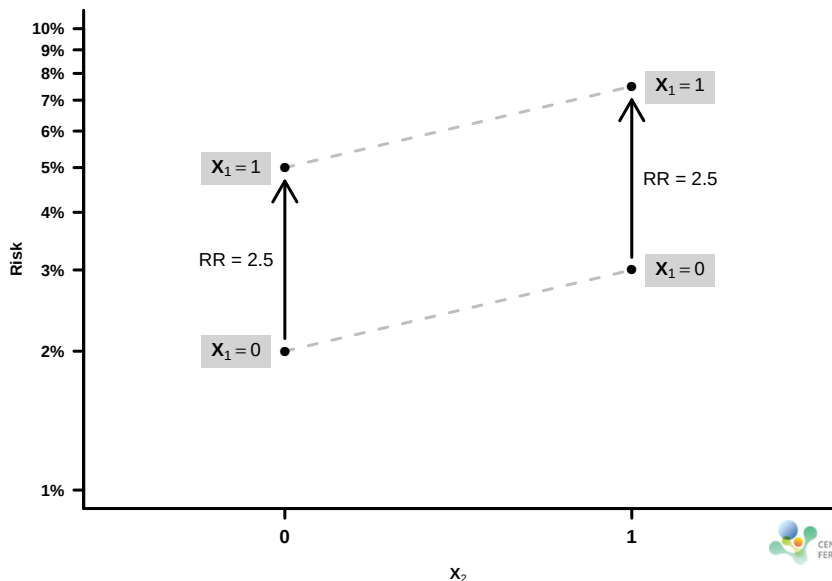
INTERACTIONS, RISK DIFFERENCE (RD)



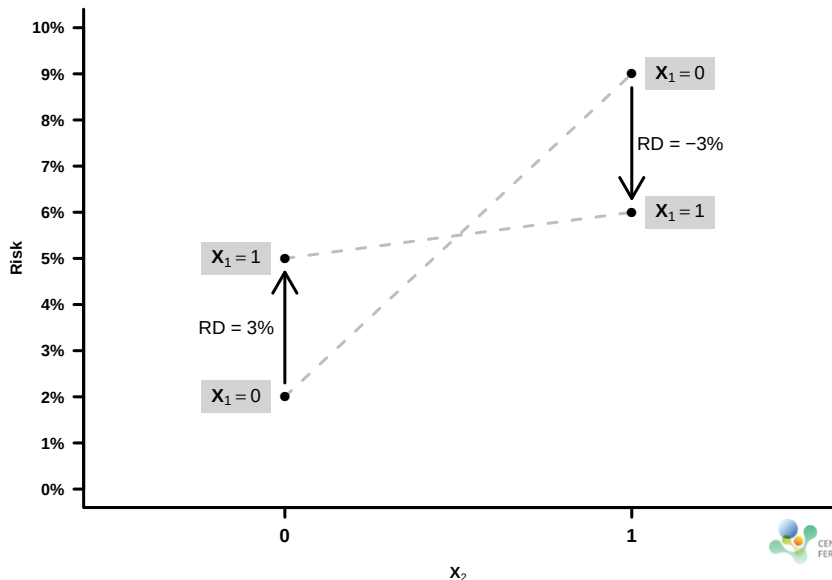
INTERACTIONS, RISK DIFFERENCE (RD)



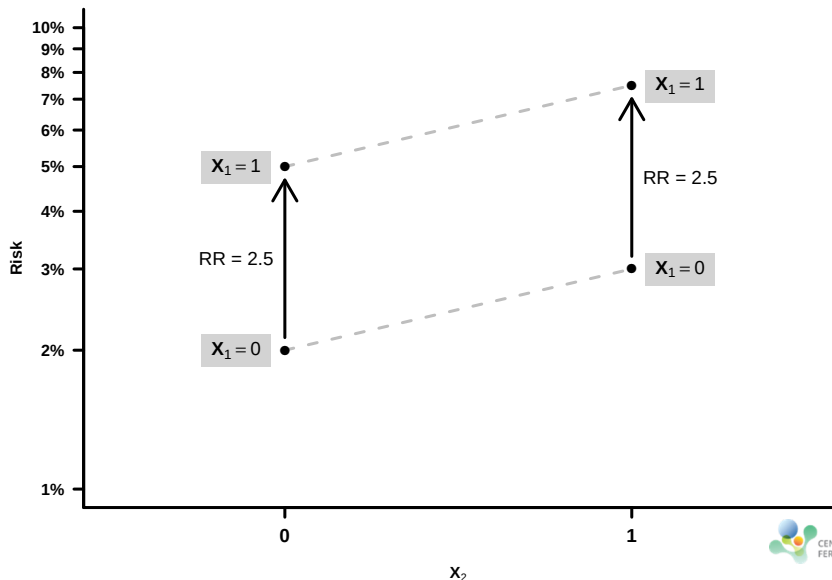
INTERACTIONS, RELATIVE RISK (RR), SCALE DEPENDENCE



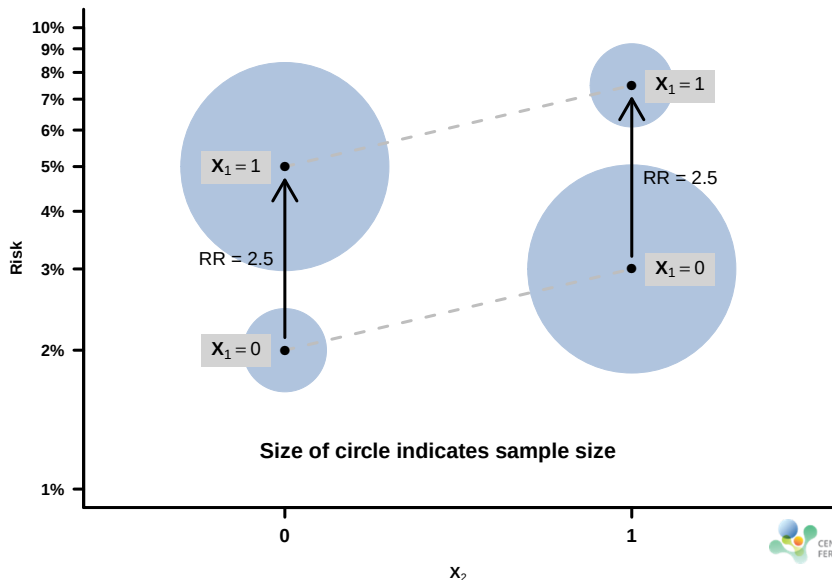
INTERACTIONS, QUALITATIVE



INTERACTIONS VERSUS CONFOUNDING



INTERACTIONS VERSUS CONFOUNDING



NOTE

If

- X_1 changes the effect of X_2 on Y

then **always**

- X_2 changes the effect of X_1 on Y

NOTE

If

- X_1 changes the effect of X_2 on Y

then **always**

- X_2 changes the effect of X_1 on Y

BUT if

- X_1 reverses the effect of X_2 on Y (i.e. “qualitative interaction”)

then it is **not necessarily** the case that

- X_2 reverses the effect of X_1 on Y

(Sigh...)

INTERACTIONS, BINOMIAL REGRESSION

- Logistic model (**logit** link):

$$\text{logit}(p) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \underbrace{\beta_3 x_1 \cdot x_2}_{\text{interaction}}$$

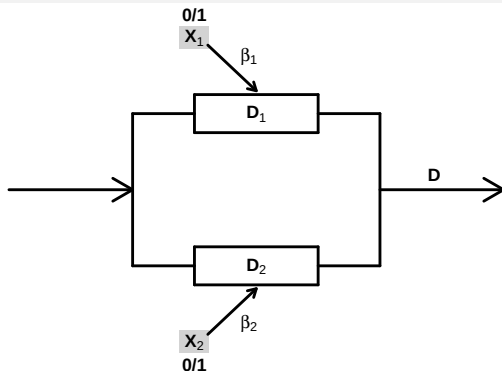
- Relative risk model (**log** link):

$$\log(p) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \underbrace{\beta_3 x_1 \cdot x_2}_{\text{interaction}}$$

- Additive model (**identity** link):

$$p = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \underbrace{\beta_3 x_1 \cdot x_2}_{\text{interaction}}$$

INTERACTION: HETEROGENEITY MODEL (INDEPENDENT ACTION)



$$P(D) = P(D_1 \cup D_2) = P(D_1) + P(D_2) - P(D_1 \cap D_2)$$

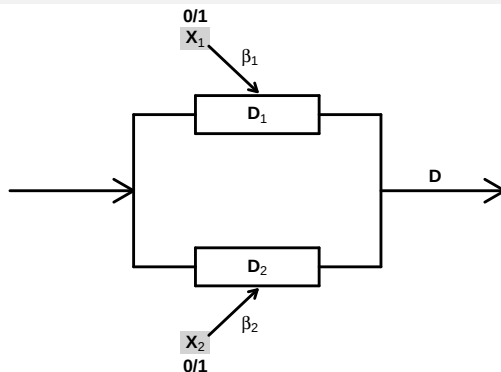
$$P(D_1) = \beta_1 X_1$$

$$P(D_2) = \beta_2 X_2$$

$$P(D) = \beta_1 X_1 + \beta_2 X_2 - \underbrace{\beta_1 \beta_2 X_1 \cdot X_2}_{\beta_3 = -\beta_1 \beta_2}$$

Interaction on an additive scale but components act independently!

INTERACTION: HETEROGENEITY MODEL (INDEPENDENT ACTION)

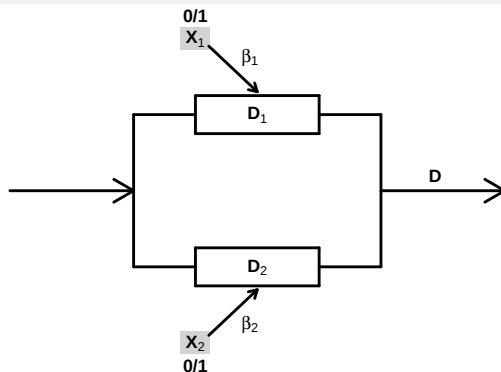


$$P(D) = P(D_1 \cup D_2) = P(D_1) + P(D_2) - P(D_1 \cap D_2)$$

Additive for $\log(1 - p)$

$$1 - P(D) = (1 - \beta_1 X_1)(1 - \beta_2 X_2)$$

INTERACTION: HETEROGENEITY MODEL (INDEPENDENT ACTION)

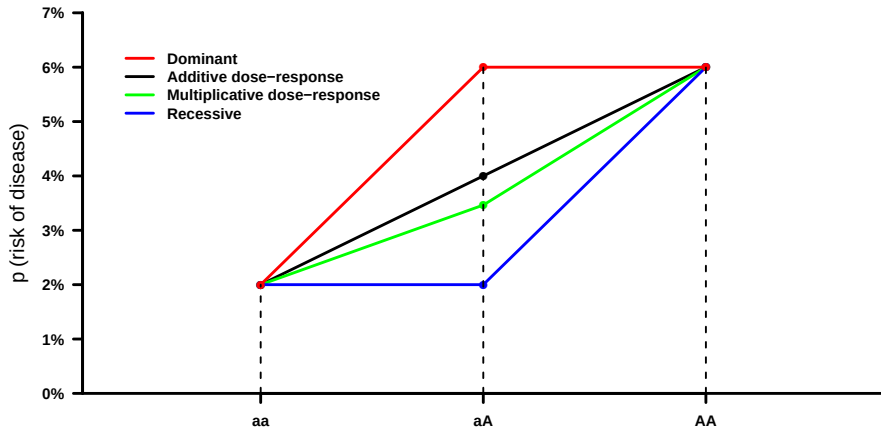


$$P(D) = P(D_1 \cup D_2) = P(D_1) + P(D_2) - P(D_1 \cap D_2)$$

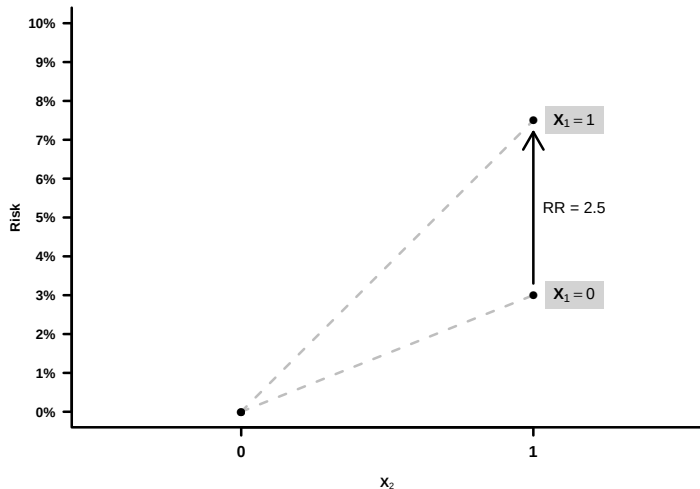
Multiple loci:

$$P(D) = P(D_1 \cup \dots \cup D_K) = 1 - \prod_i (1 - P(D_i)) = 1 - \prod_i (1 - \beta_i X_i)$$

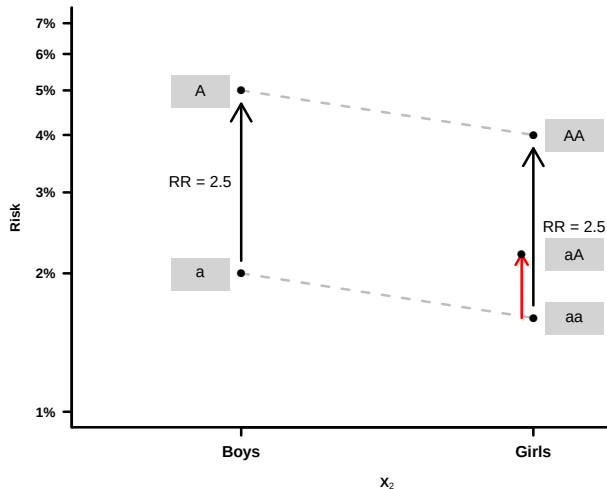
GENETIC INTERACTION MODELS: ALLELE INTERACTIONS



GENETIC INTERACTION MODELS: ONE NECESSARY LOCUS



GENETIC INTERACTION MODELS: X-INACTIVATION



MULTIPLICATIVE VERSUS ADDITIVE

Assume:

- Baseline risk 4%
- RD = 1% risk difference for both X_1 and X_2
- RR = 1.25 relative risk for both X_1 and X_2

Additive risk

		X_2	
		0	1
X_1	0	4%	$4\% + 1\% = 5\%$
	1	$4\% + 1\% = 5\%$	$4\% + 1\% + 1\% = 6\%$

Multiplicative risk

		X_2	
		0	1
X_1	0	4%	$4\% \cdot 1.25 = 5\%$
	1	$4\% \cdot 1.25 = 5\%$	$4\% \cdot 1.25 \cdot 1.25 = 6.25\%$

MULTIPLICATIVE VERSUS ADDITIVE

Assume:

- Baseline risk 4%
- $RR = 1.25$ relative risk for both X_1 and X_2
- $RD = 1\%$ risk difference for both X_1 and X_2

When $X_1 = 1$ and $X_2 = 1$:

ADDITIVE RISK

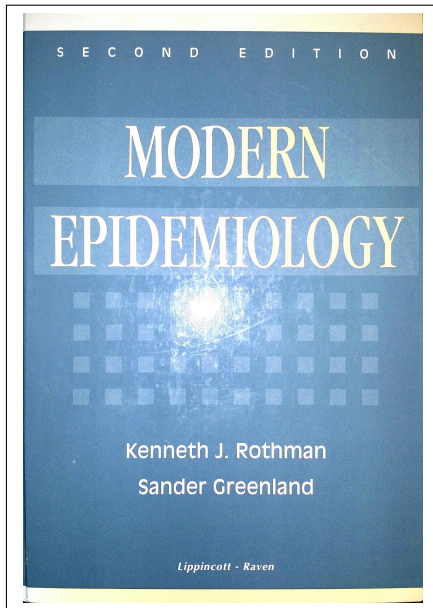
$$4\% + 1\% + 1\% = 4\% \cdot (1 + 0.25 + 0.25) = 6\%$$

MULTIPLICATIVE RISK

$$4\% \cdot (1 + 0.25) \cdot (1 + 0.25) = 4\% \cdot (1 + 0.25 + 0.25 + 0.0625) = 6.25\%$$

Difference is small when effect is “small” compared to baseline risk

Do “CANONICAL” INTERACTIONS EXIST?



INTERACTIONS: ALL COMBINATIONS

TABLE 18-2. Response types given four possible exposure combinations of two binary exposures

	Exposure combinations (type)				Description
	X = 1 Z = 1	X = 0 Z = 1	X = 1 Z = 0	X = 0 Z = 0	
1	1	1	1	1	No effects (doomed)
2*	1	1	1	0	Single plus joint causation by X = 1 and Z = 1
3*	1	1	0	1	Z = 1 blocks X = 1 effect (preventive antagonism)
4	1	1	0	0	X = 1 ineffective, Z = 1 causal
5*	1	0	1	1	X = 1 blocks Z = 1 effect (preventive antagonism)
6	1	0	1	0	X = 1 causal, Z = 1 ineffective
7*	1	0	0	1	Mutual blockage (preventive antagonism)
8*	1	0	0	0	X = 1 plus Z = 1 causal (causal synergism)
9*	0	1	1	1	X = 1 plus Z = 1 preventive (preventive synergism)
10*	0	1	1	0	Mutual blockage (causal antagonism)
11	0	1	0	1	X = 1 preventive, Z = 1 ineffective
12*	0	1	0	0	X = 1 blocks Z = 1 effect (causal antagonism)
13	0	0	1	1	X = 1 ineffective, Z = 1 preventive
14*	0	0	1	0	Z = 1 blocks X = 1 effect (causal antagonism)
15*	0	0	0	1	Single plus joint prevention by X = 1 and Z = 1
16	0	0	0	0	No effects (immune)

Name according to Miettinen (1982b) in parentheses

*Defined as interaction response type in present discussion

Exposures: X(0/1) and Z(0/1)

Response: 0/1

INTERACTIONS: STATISTICAL VERSUS “BIOLOGIC”??

According to Rothman & Greenland:

Statistical interaction

- Departure from additivity on any given scale

“Biologic” interaction

- Additivity on risk scale

	X = 1	X = 0	X = 1	X = 0	
	Z = 1	Z = 1	Z = 0	Z = 0	
2*	1	1	1	0	Single plus joint causation by X = 1 and Z = 1
3*	1	1	0	1	Z = 1 blocks X = 1 effect (preventive antagonism)

Example, 2* :

- Z is a fatal traffic accident
- X is heavy smoking
- Outcome is death

Dying in a traffic accident prevents death from smoking...

Is that “biologic interaction”??

INTERACTIONS: STATISTICAL VERSUS “BIOLOGIC”??

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“Biologic” interaction

- Additivity on risk scale

	X = 1	X = 0	X = 1	X = 0	
	Z = 1	Z = 1	Z = 0	Z = 0	
2*	1	1	1	0	Single plus joint causation by X = 1 and Z = 1
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Example, 2* :

- Z is a fatal traffic accident
- X is heavy smoking
- Outcome is death

Dying in a traffic accident prevents death from smoking...
Is that “biologic interaction”??



ACTUALLY ONLY 4 BASIC STRUCTURES POSSIBLE

0 = no outcome

1 = outcome

		Z	
		0	1
X	0	1	1
	1	1	1

		Z	
		0	1
X	0	0	1
	1	1	1

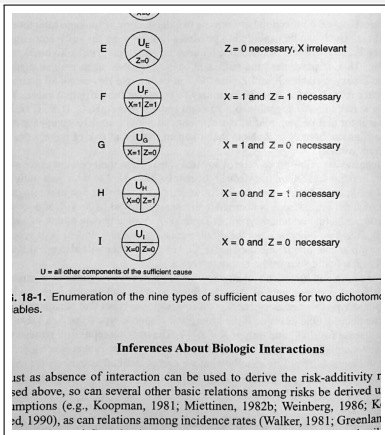
		Z	
		0	1
X	0	0	0
	1	1	1

		Z	
		0	1
X	0	0	1
	1	1	0

Non-interactions

Interactions

CAUSAL PIE (IN THE SKY)



*You will eat, bye and bye,
In that glorious land above the
sky;
Work and pray, live on hay,
You'll get pie in the sky when
you die*

"The Preacher and the Slave" by Joe Hill

A Complete Enumeration and Classification of Two-Locus Disease Models

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^bDepartment of Biomathematics, Max-Delbrück-Centrum, Berlin-Buch, Germany

Abstract

There are 512 two-locus, two-allele, two-phenotype, fully penetrant disease models. Using the permutation between two alleles, between two loci, and between being affected and unaffected, one model can be considered to be equivalent to another model under the corresponding permutation. These permutations greatly reduce the number of two-locus models in the analysis of complex diseases. This paper determines the number of nonredundant two-locus models (which can be 102, 100, 96, 51, 50, or 58, depending on which permutations are used, and depending on whether zero-locus and single-locus models are excluded). Whenever possible, these nonredundant two-locus models are classified by their

INTERACTIONS: WHO SAID IT WAS EASY?

property. Besides the familiar features of multiplicative models (logical AND), heterogeneity models (logical OR), and threshold models, new classifications are added or expanded: modifying-effect models, logical XOR models, interference and negative interference models (neither dominant nor recessive), conditionally dominant/recessive models, missing lethal genotype models, and highly symmetric models. The following aspects of two-locus models are studied: the marginal penetrance

INTERACTIONS: WHO SAID IT WAS EASY?

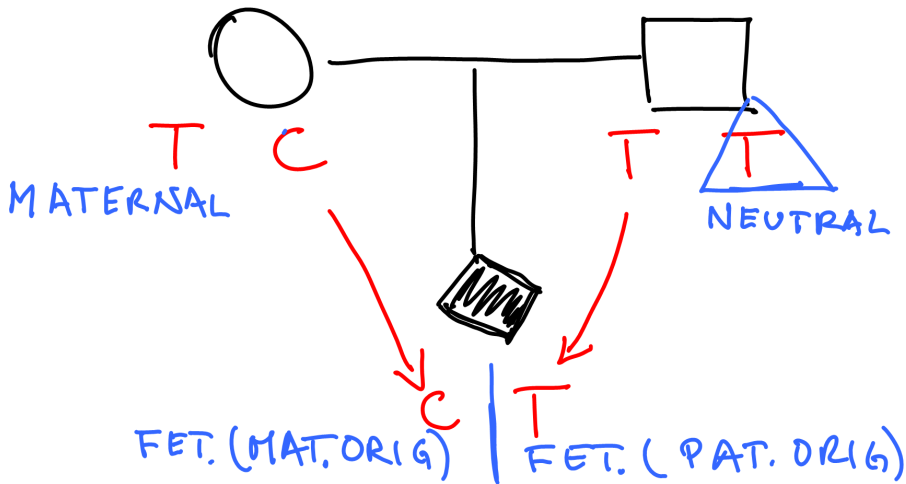
Example 1:

		Locus 2			
		bb	bB	BB	
Locus 1	aa	0	0	0	0 = no disease 1 = disease
	aA	0	0	0	
	AA	0	0	1	

Example 2:

		Locus 2			
		bb	bB	BB	
Locus 1	aa	0	1	1	0 = no disease 1 = disease
	aA	1	1	1	
	AA	1	1	1	

CASE TRIAD



PARENT-OF-ORIGIN EFFECTS

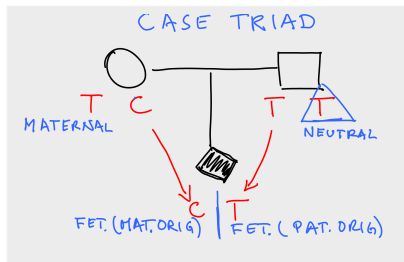
- **Parent-of-origin effect:**

Interaction between allele effect and parent-of-origin

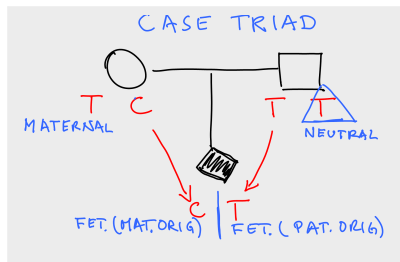
- **GxE:**

Further interaction with environment

Non-smokers



Smokers



HAPLIN

GENETIC ASSOCIATION ANALYSES IN R

HOME

FEATURES

INSTALLATION

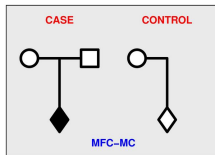
PUBLICATIONS

TEAM HAPLIN

HAPLIN

Genetic association analyses

Haplin is an open source R-package for analyzing case-parent triad data with or without independent controls, using candidate genes or GWAS data.



NEWS

Important installation note for Haplin 7.0.0!

Haplin 7.0.0 now on CRAN!

Haplin 7.0.0 now available!

Haplin temporarily archived!

Version 6.2.1 released!

NORBIS 2018 (FOR PARTICIPANTS)

Main course page

DOCUMENTATION

Haplin vignettes

Running Haplin

Data format

Designs

- Case-parent triads (trios)
- Case-mother dyads
- Case-parent triads with independent controls
- Case control

Effects

- Genetic effects
- Effects of fetal genes
- Parent-of-origin effects
- Effects of maternal genes

PARENT-OF-ORIGIN EFFECTS, CLEFT LIP/PALATE

RS2964137, KIAA0947

Test effect	Stratum	RR_{cm}	RR_{cf}	RR_{cm}/RR_{cf}
POO effects	S1	0.707	0.936	0.755 (0.505, 1.111)
	S2	0.707	0.936	0.755 (0.505, 1.111)
	S1/S2	1 (-)	1 (-)	1 (-)
GxE effects	S1	0.802	0.802	1 (-)
	S2	0.865	0.865	1 (-)
	S1/S2	0.928 (0.538, 1.603)	0.928 (0.538, 1.603)	1 (-)
POOxE effects	S1	0.533	1.170	0.456 (0.290, 0.705)
	S2	1.915	0.385	4.979 (2.137, 11.253)
	S1/S2	0.278 (0.135, 0.576)	3.038 (1.446, 6.345)	0.092 (0.036, 0.236)

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DOI: 10.1111/ahg.12224

ORIGINAL ARTICLE

WILEY **Annals of human genetics**

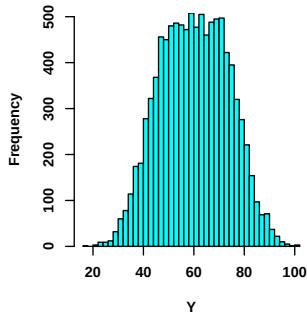
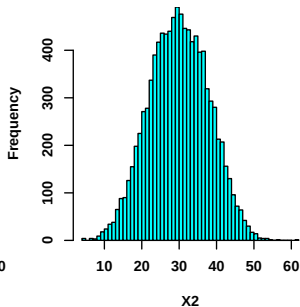
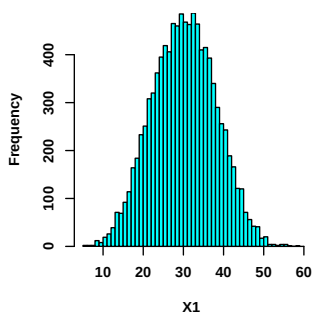
Parent-of-origin-environment interactions in case-parent triads with or without independent controls

Miriam Gjerdevik^{1,2} | Øystein A. Haaland¹  | Julia Romanowska^{1,3} | Rolv T. Lie^{1,4} |
 Astanand Jugessur^{1,2,5}  | Håkon K. Gjessing^{1,5} 



SURPRISE, SURPRISE(?)

Simulated data, $n = 10000$:

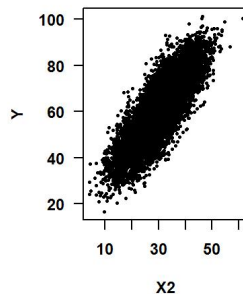
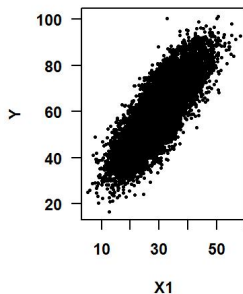
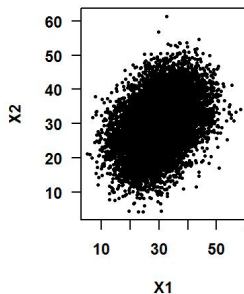


$$Y = X1 + X2 + \varepsilon$$

Data simulated without any interaction

(Cf. Prof. Magne Thoresen, UiO)

SURPRISE, SURPRISE(?)



Linear regression, including interaction:

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	-0.1128420	0.3990666	-0.283	0.777
X1	1.0038665	0.0135478	74.098	<2e-16 ***
X2	1.0037252	0.0135910	73.852	<2e-16 ***
I(X1 * X2)	-0.0001540	0.0004365	-0.353	0.724

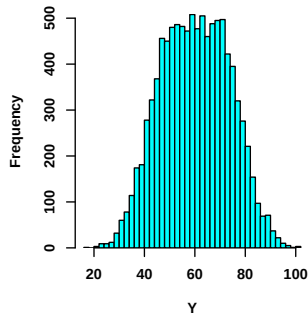
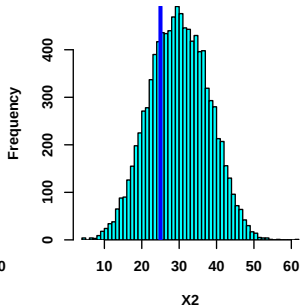
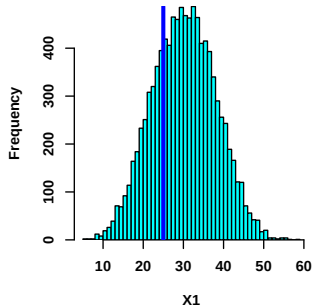
As expected, no sign of interaction

SURPRISE, SURPRISE(?)

Cut X1 and X2 at 25:

$$X1.cat = \begin{cases} 0 & \text{when } X1 < 25 \\ 1 & \text{when } X1 \geq 25 \end{cases}$$

$$X2.cat = \begin{cases} 0 & \text{when } X2 < 25 \\ 1 & \text{when } X2 \geq 25 \end{cases}$$



SURPRISE, SURPRISE(?)

New linear regression, using the two categorical variables:

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)	
(Intercept)	40.0916	0.2248	178.36	<2e-16	***
X1.cat	11.1076	0.3067	36.22	<2e-16	***
X2.cat	11.1162	0.3118	35.66	<2e-16	***
I(X1.cat * X2.cat)	6.5513	0.3897	16.81	<2e-16	***

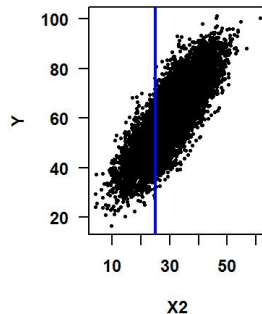
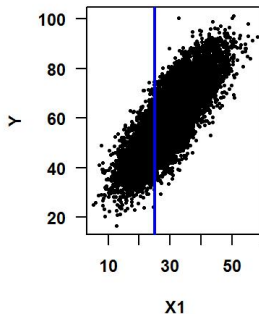
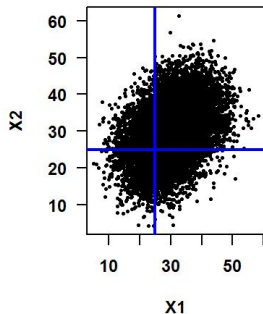
Rounded mean values of Y in categories of X1.cat and X2.cat:

		X2.cat	
		0	1
X1.cat	0	40	51
	1	51	69

		X2.cat	
		0	1
X1.cat	0	40	40 + 11
	1	40 + 11	40 + 11 + 11 + 7

SURPRISE, SURPRISE(?)

		X2.cat	
		0	1
X1.cat	0	40	40 + 11
	1	40 + 11	40 + 11 + 11 + 7



CAUTION: INTERPRETATION OF MAIN EFFECTS!

$$Y = X1.cat + X2.cat + I(X1.cat * X2.cat)$$

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)	
(Intercept)	40.0916	0.2248	178.36	<2e-16	***
X1.cat	11.1076	0.3067	36.22	<2e-16	***
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I(X1.cat * X2.cat)	6.5513	0.3897	16.81	<2e-16	***

$$Y = X1.cat + X2.cat$$

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)	
(Intercept)	37.9119	0.1862	203.62	<2e-16	***
X1.cat	15.1658	0.1919	79.05	<2e-16	***
X2.cat	15.3095	0.1897	80.72	<2e-16	***



INTERACTIONS: ALTERNATIVE CODING

Two new variables:

$$X2.cat0 = (1 - X1.cat) * X2.cat$$

$$X2.cat1 = X1.cat * X2.cat$$

REGRESSION

$$Y = X1.cat + X2.cat0 + X2.cat1$$

INTERACTIONS: ALTERNATIVE CODING

Coefficients:

	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	40.0916	0.2248	178.36	<2e-16 ***
X1.cat	11.1076	0.3067	36.22	<2e-16 ***
X2.cat0	11.1162	0.3118	35.66	<2e-16 ***
X2.cat1	17.6675	0.2338	75.57	<2e-16 ***

		X2.cat	
		0	1
X1.cat	0	40	40 + 11
	1	40 + 11	40 + 11 + 11 + 7

Interpretation:

- X2.cat0 is the effect of X_2 when $X_1 = 0$
- X2.cat1 is the effect of X_2 when $X_1 = 1$