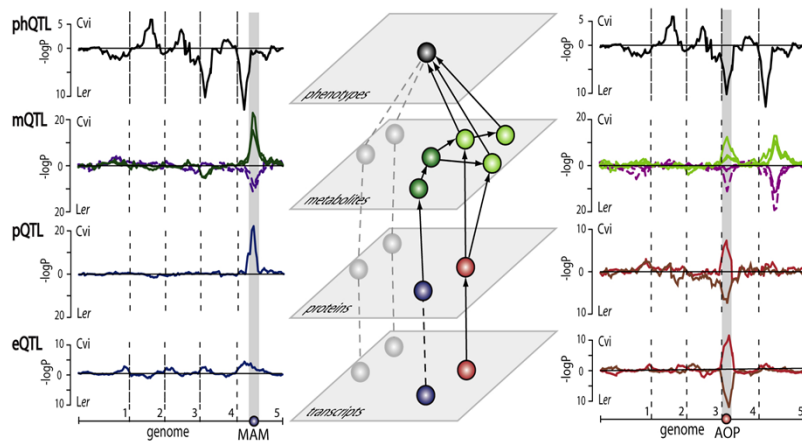


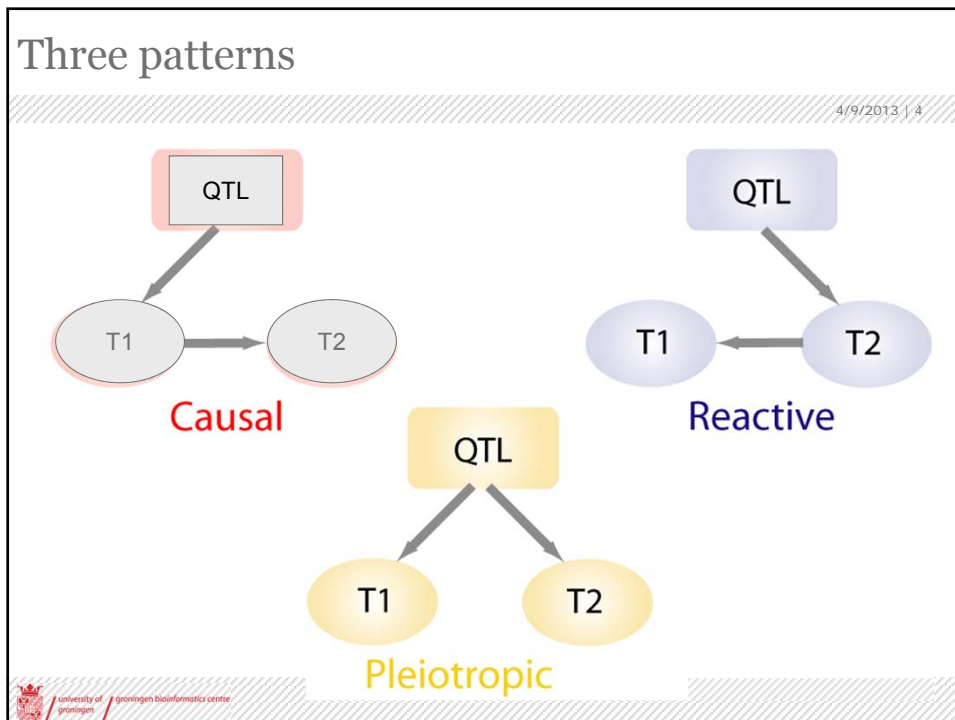
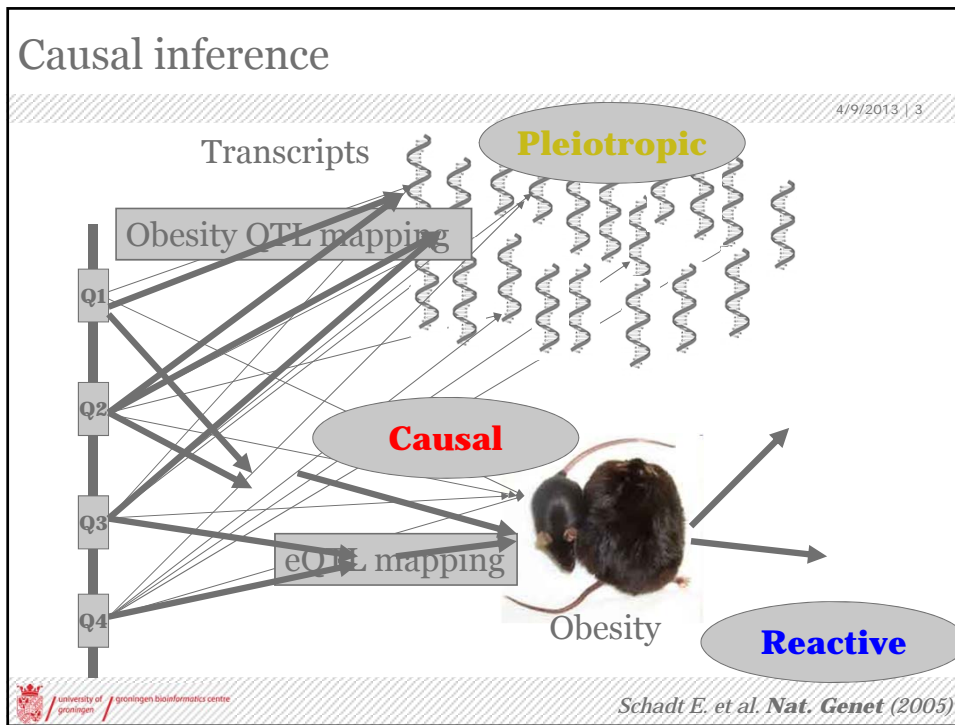
Causal inference with QTL data

- › Groningen Bioinformatics Centre
- › Yang Li

From genotype to (disease) phenotype:

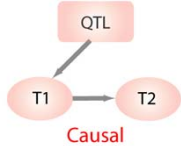
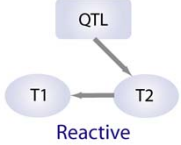
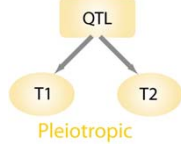


› How do we draw the arrows?



Is the QTL effect propagated from one trait to the other?

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Rules	$\text{corr}(Q, T1 T2)$	$\text{corr}(Q, T2 T1)$
 <p>Causal</p>	$\neq 0$	$== 0$
 <p>Reactive</p>	$== 0$	$\neq 0$
 <p>Pleiotropic</p>	$\neq 0$	$\neq 0$
Undecided	$== 0$	$== 0$

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Questions

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- › How **reliable** is the correlation method (false discovery rate)?
- › For which QTL **effect size** does the method work?
 - GWAS studies have reported QTL explaining <5% of the total variance
 - Typical eQTL explain under 30% of the mRNA variance
- › What is the effect of **measurement error/bias**?

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An analytical solution to causality inference allows rapid evaluation of different scenarios

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> Simple models:

$\begin{aligned} T_1 &= Q + e_1 \\ T_2 &= Q + e_2 \end{aligned}$	}	pleiotropic	$\begin{aligned} T_1 &= Q + e_1 \\ T_2 &= T_1 + e_2 = Q + e_1 + e_2 \end{aligned}$	}	causal
--	---	-------------	--	---	--------

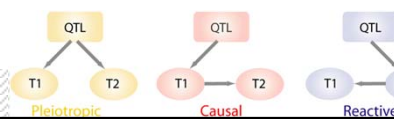
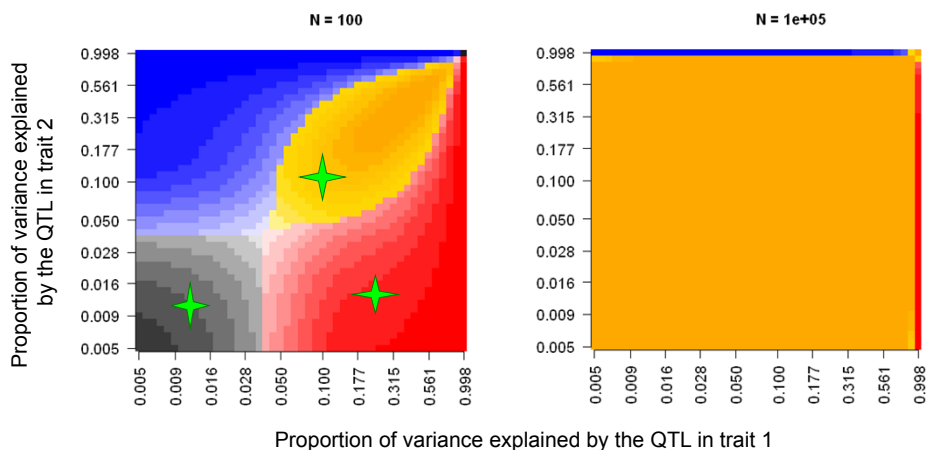
> Simulate? Better: derive *p*-values directly!

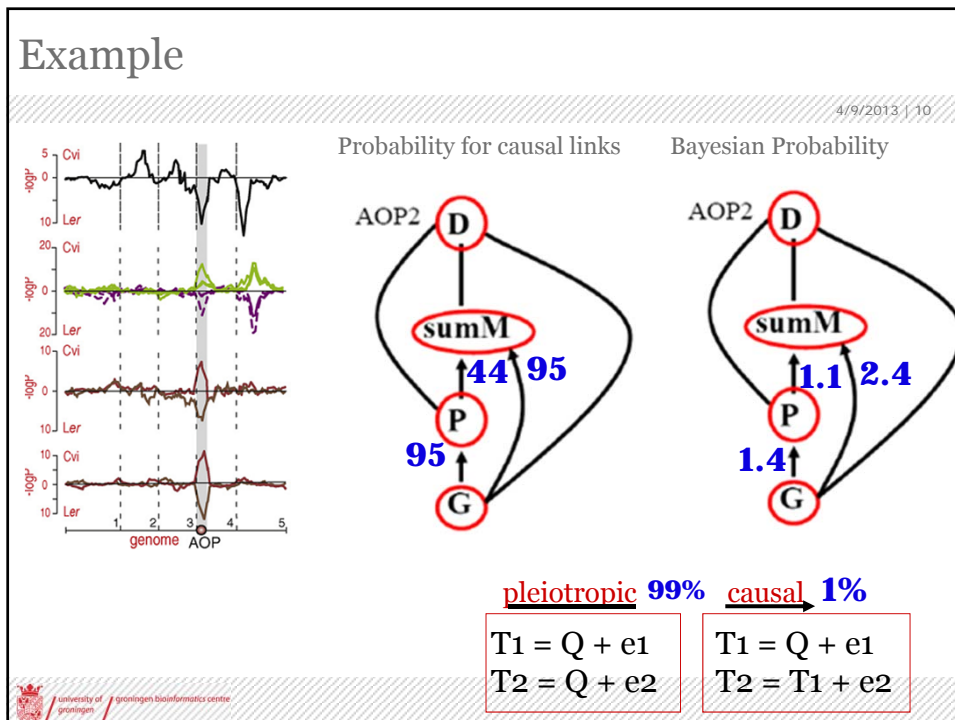
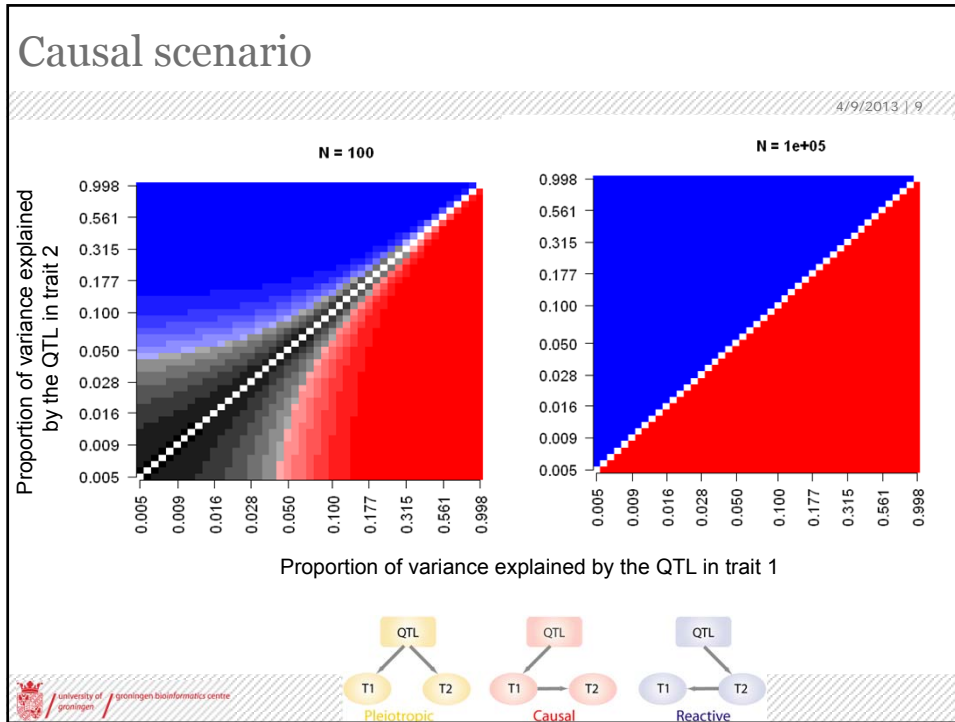
	Basic pleiotropic	Basic causal T1→T2
vt_1	$1+v_1$	$1+v_1$
vt_2	$1+v_2$	$1+v_1+v_2$
b_1	$1-v_2/vt_2$	$1-v_2/vt_2$
mq_1	$2v_2/vt_2$	$2v_2/vt_2$
vq_1	$v_1+v_2(v_2/vt_2-1)^2$	$v_2(v_2/vt_2-1)^2 + v_1(v_2/vt_2)^2$
b_2	$1-v_1/vt_1$	1
mq_2	$2v_1/vt_1$	0
vq_2	$v_2+v_1(v_1/vt_1-1)^2$	v_2
c_{12}	$v_1(v_1/vt_1-1)+v_2(v_2/vt_2-1)$	$v_2(v_2/vt_2-1)$

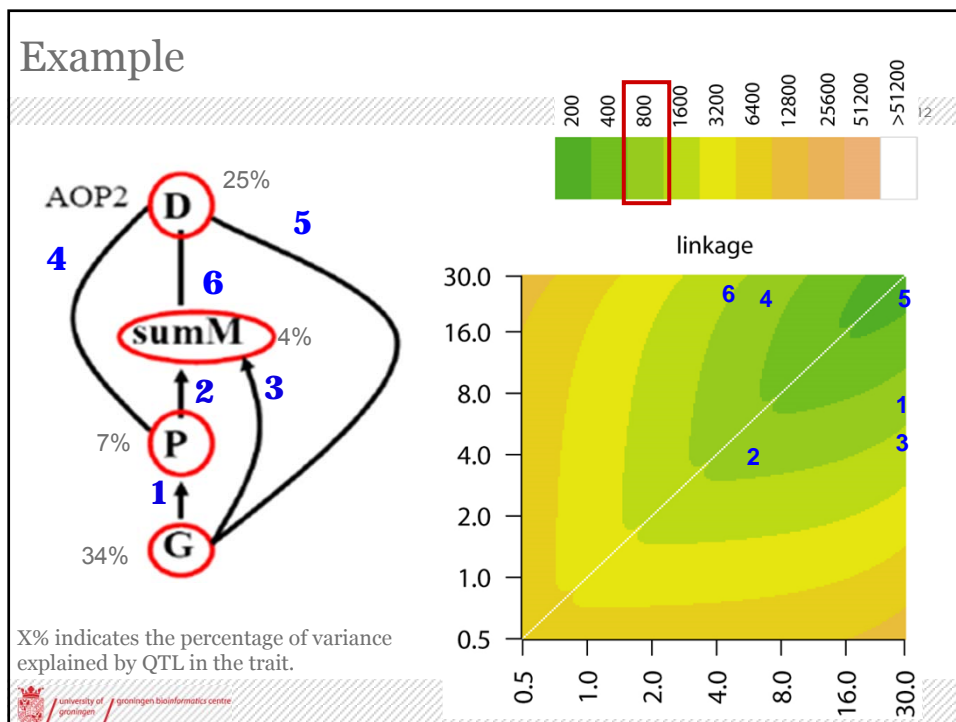
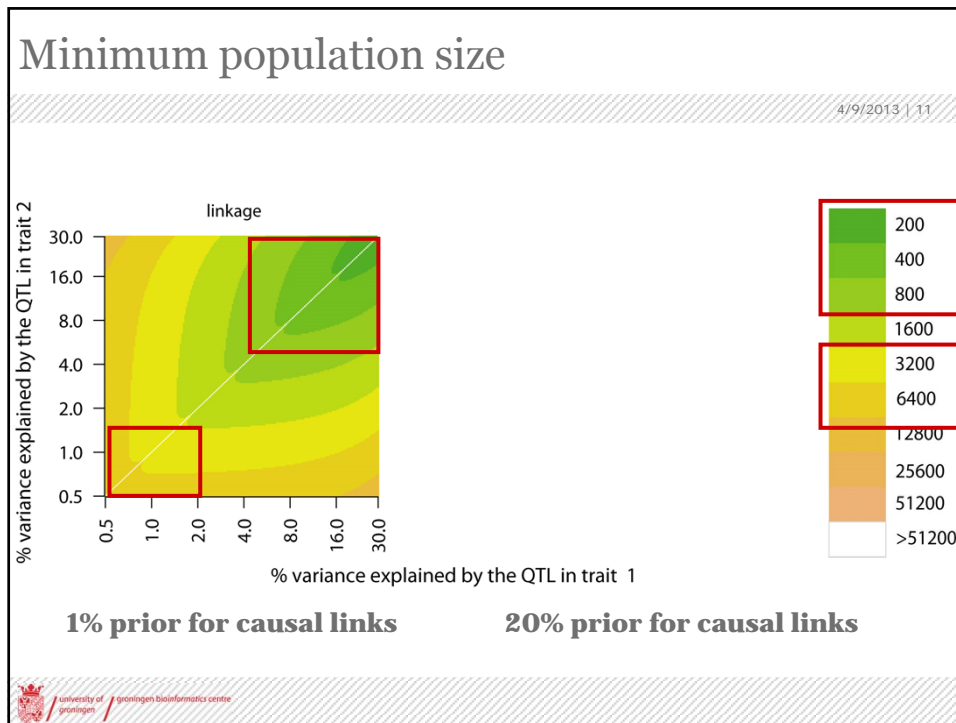


Pleiotropic scenario

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Measurement error complicates causality inference

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Triad with biological errors and measurement errors

(a)

$T1 = QTL + e_1$
 $T2 = QTL + e_2$

(b)

$T1 = QTL + e_1$
 $T2 = QTL + e_1 + e_2$

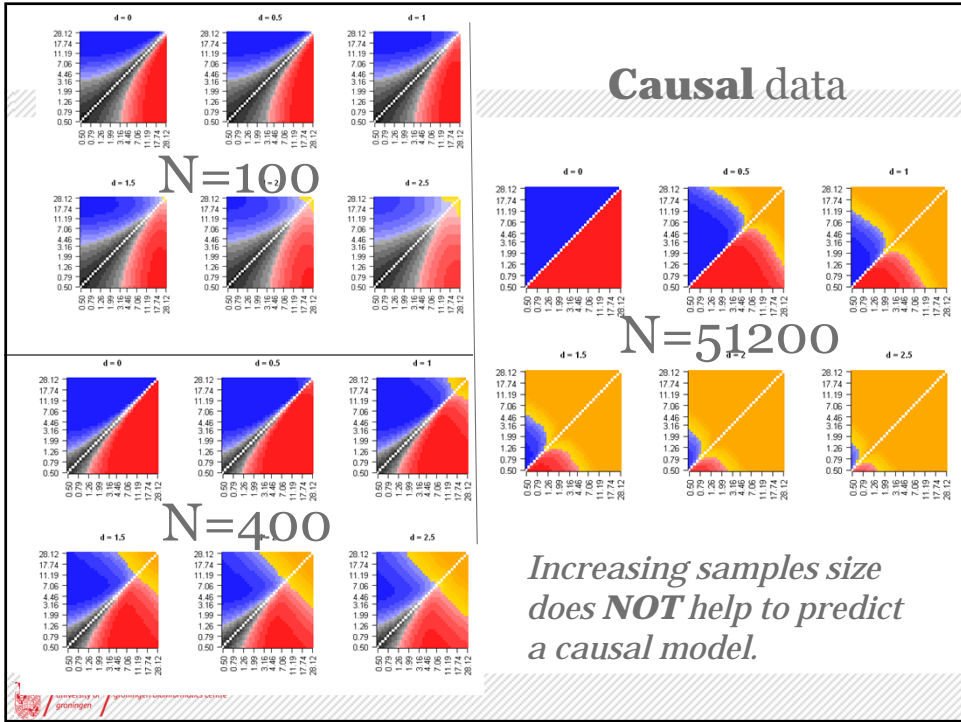
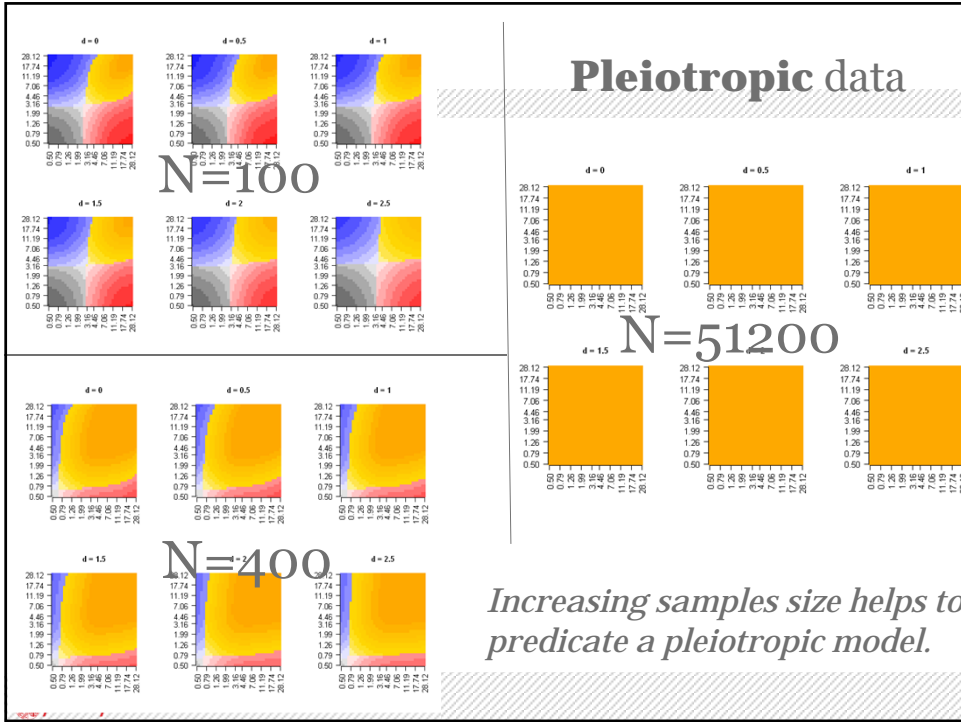
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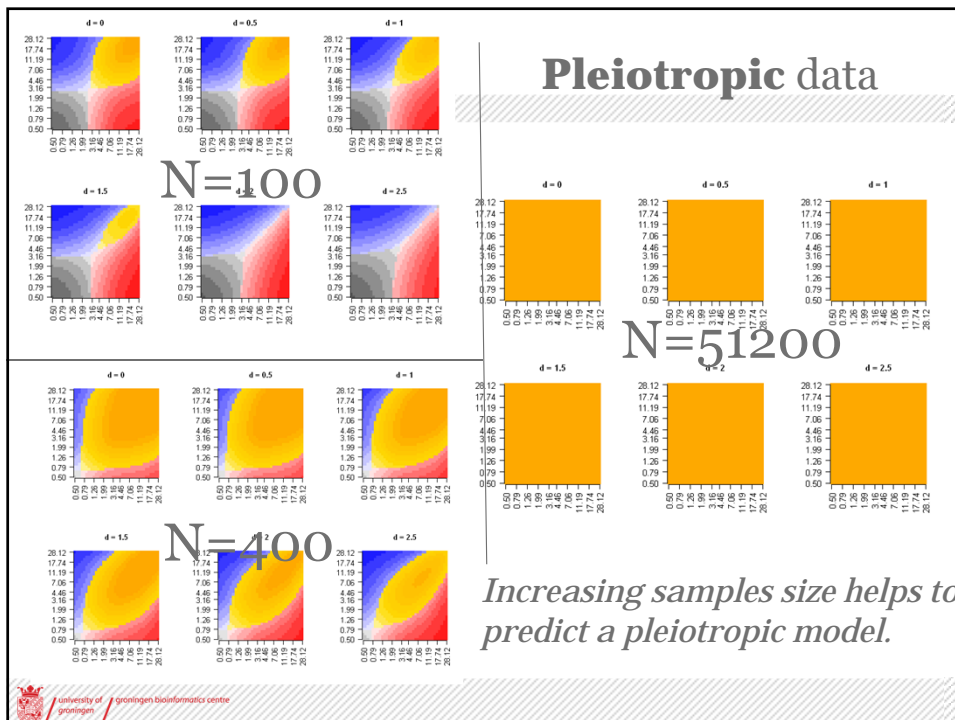
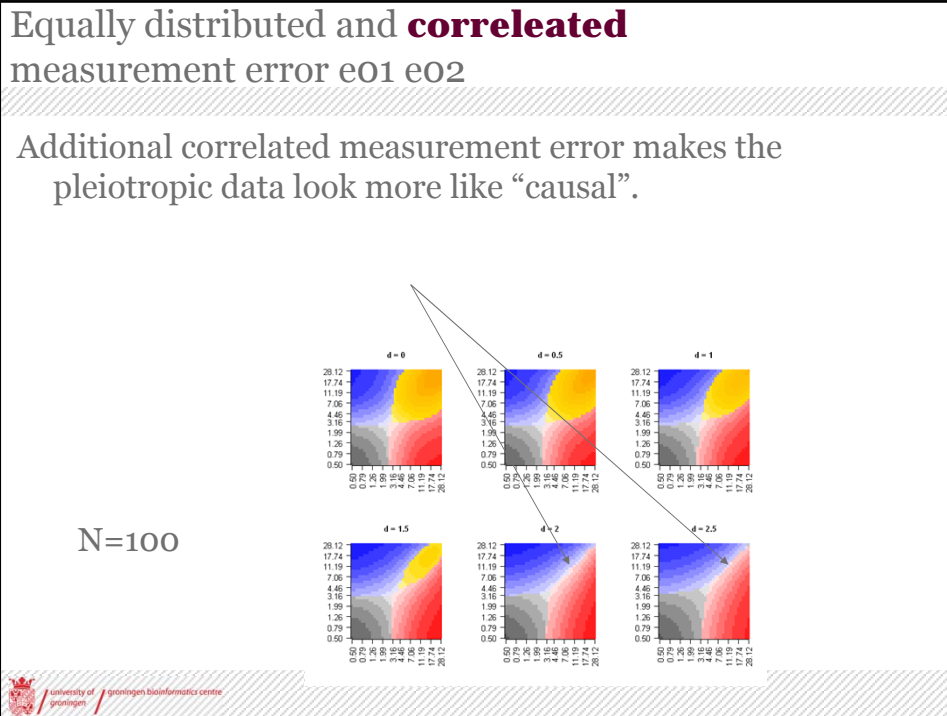
Equally distributed and **independent** measurement error e_{01} e_{02}

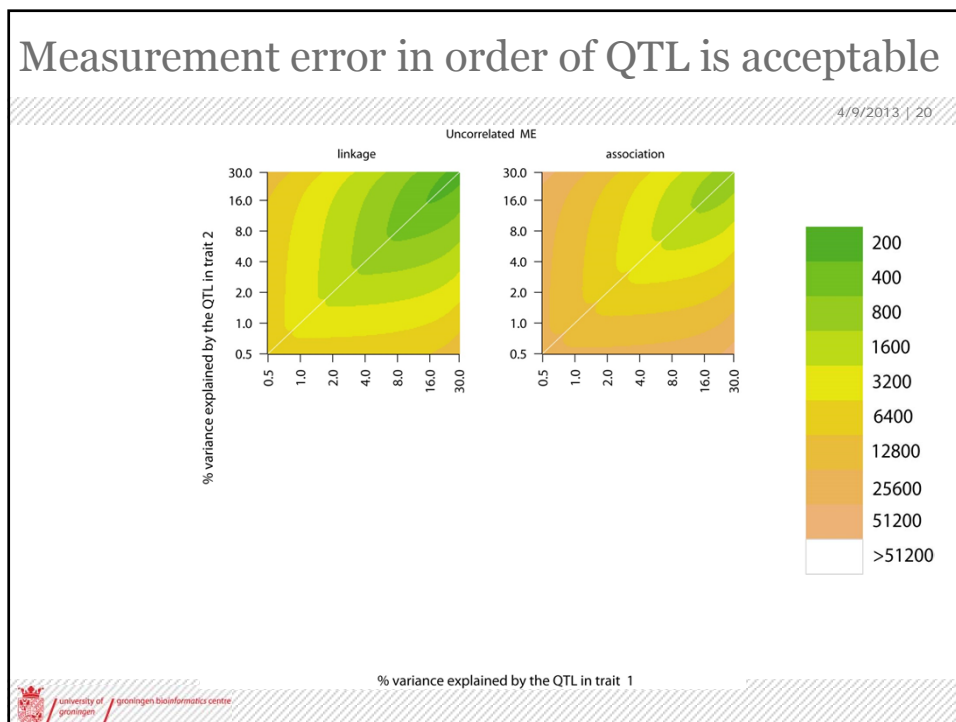
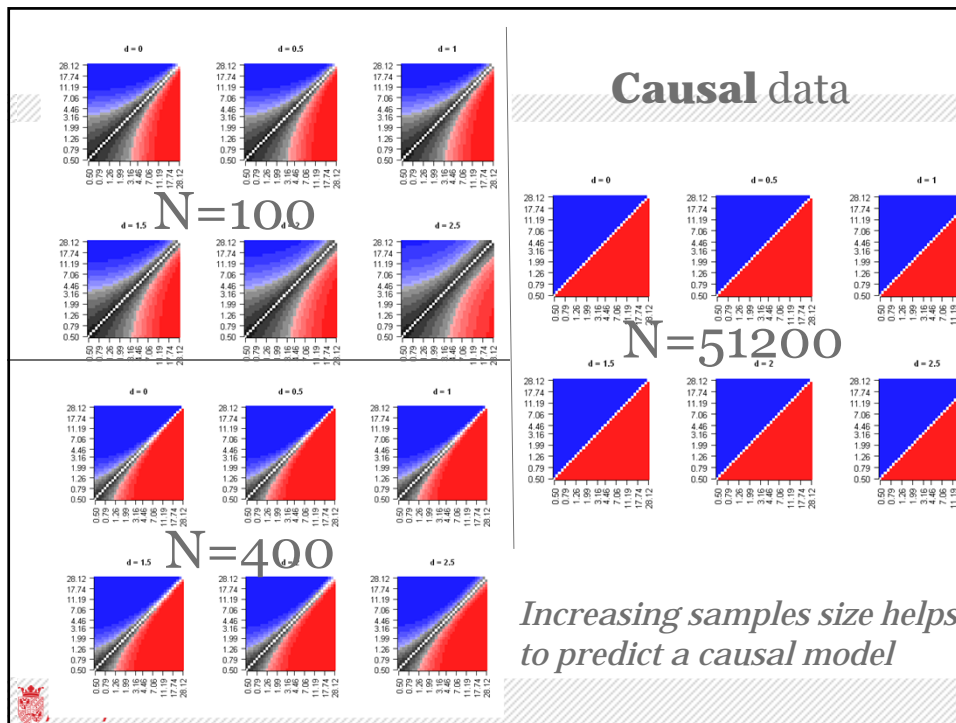
Additional independent measurement error makes the causal data look more like “pleiotropic”.

N=100

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Conclusions

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- › The correlation based causal inference is a promising strategy to prioritize network connections.
- › Clear dissection of trait variation will result in a better prediction of FDR for causality with sufficient amount of samples.
- › Accurate measurement and controlled correlations in the traits will make it possible to reconstruct reliable causal networks in systems genetics.

Acknowledgements

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