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COMPLEXITY
& BIOSYSTEMS
University of Milan



F. Font-Clos, S. Zapperi, C.A.M. La Porta
NPJ Systems Biology & Applications 18, 2017
doi:10.1038/s41540-017-0018-z

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BioRxiv doi: <https://doi.org/10.1101/159186>

Pathway deregulation in obesity

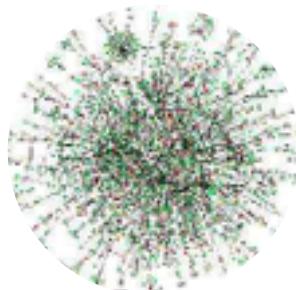
24 July 2015
—Como
ISINP

Caterina A. M. La Porta
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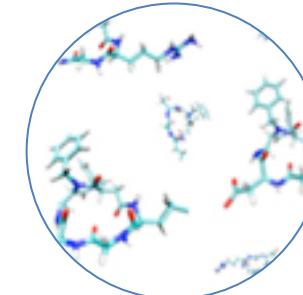
WWW.COMPLEXITY.UNIMI.IT

RESEARCH

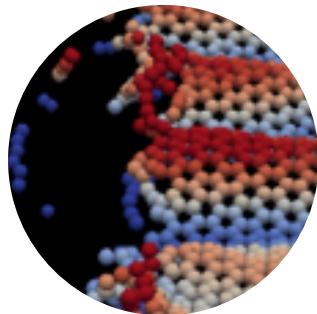
Complex
Networks
& Data science



Neurodegenerative
diseases



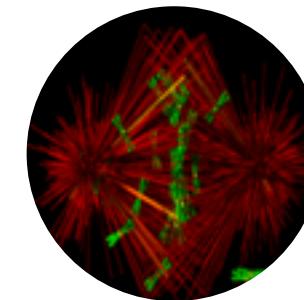
Protein/RNA
simulations



Disordered
materials

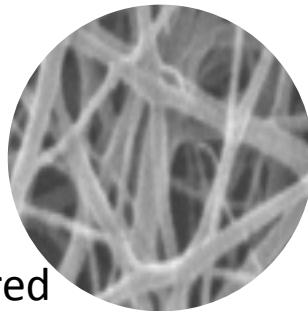
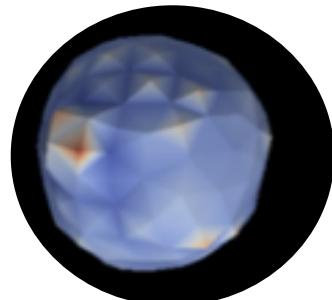


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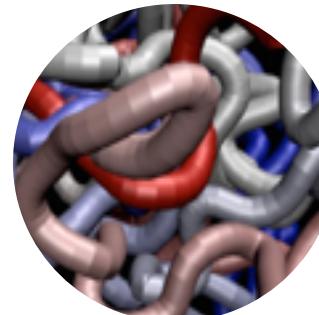


Cell division

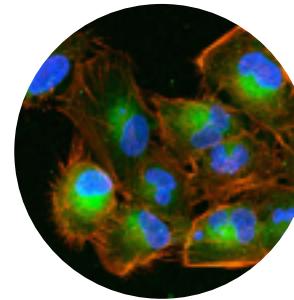
Cell
biomechanics



Bio-inspired
Materials (animals/plants)



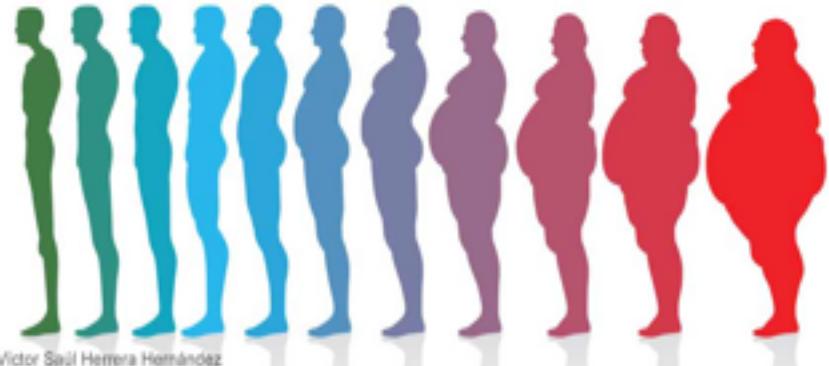
Chromatin



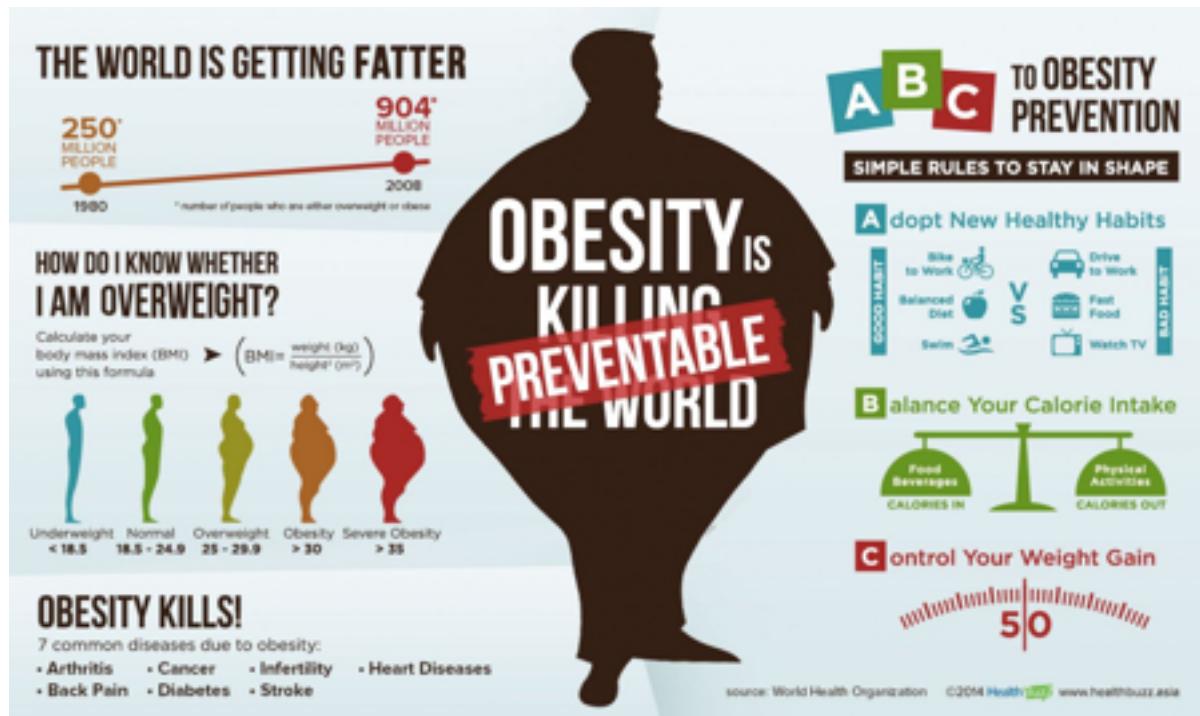
Cancer

OBESITY: WHY DO WE CARE?

OBESITY IS NOW A GLOBAL EPIDEMIC!



© iStock.com / Ernesto Victor Saul Herrera Hernandez



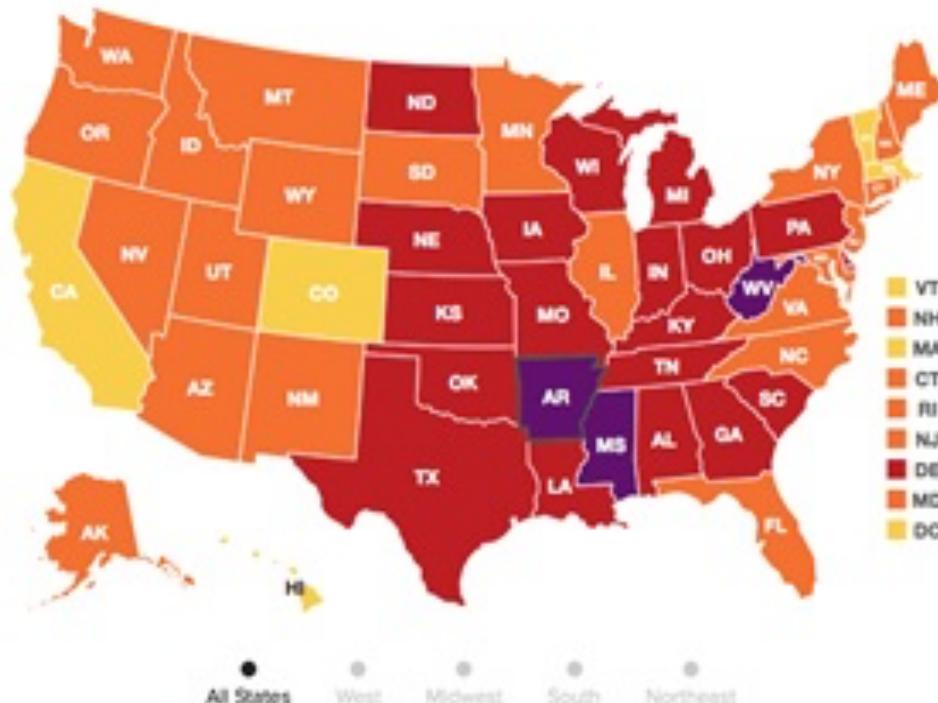
STATISTICS

Adult Obesity Rate by State, 2014

Select years with the slider to see historical data. Hover over states for more information. Click a state to lock the selection. Click again to unlock.

Percent of obese adults (Body Mass Index of 30+)

0 - 9.9% 10 - 14.9% 15 - 19.9% 20 - 24.9% 25 - 29.9% 30 - 34.9% 35%+



< 2005 - 2009

2010

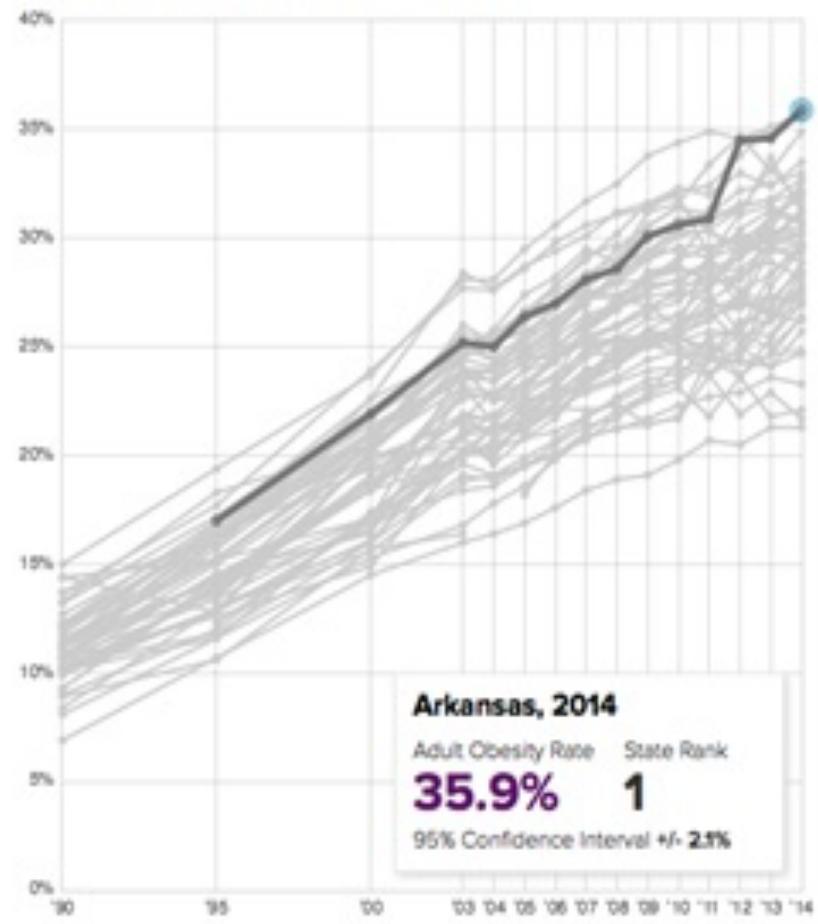
2011

2012

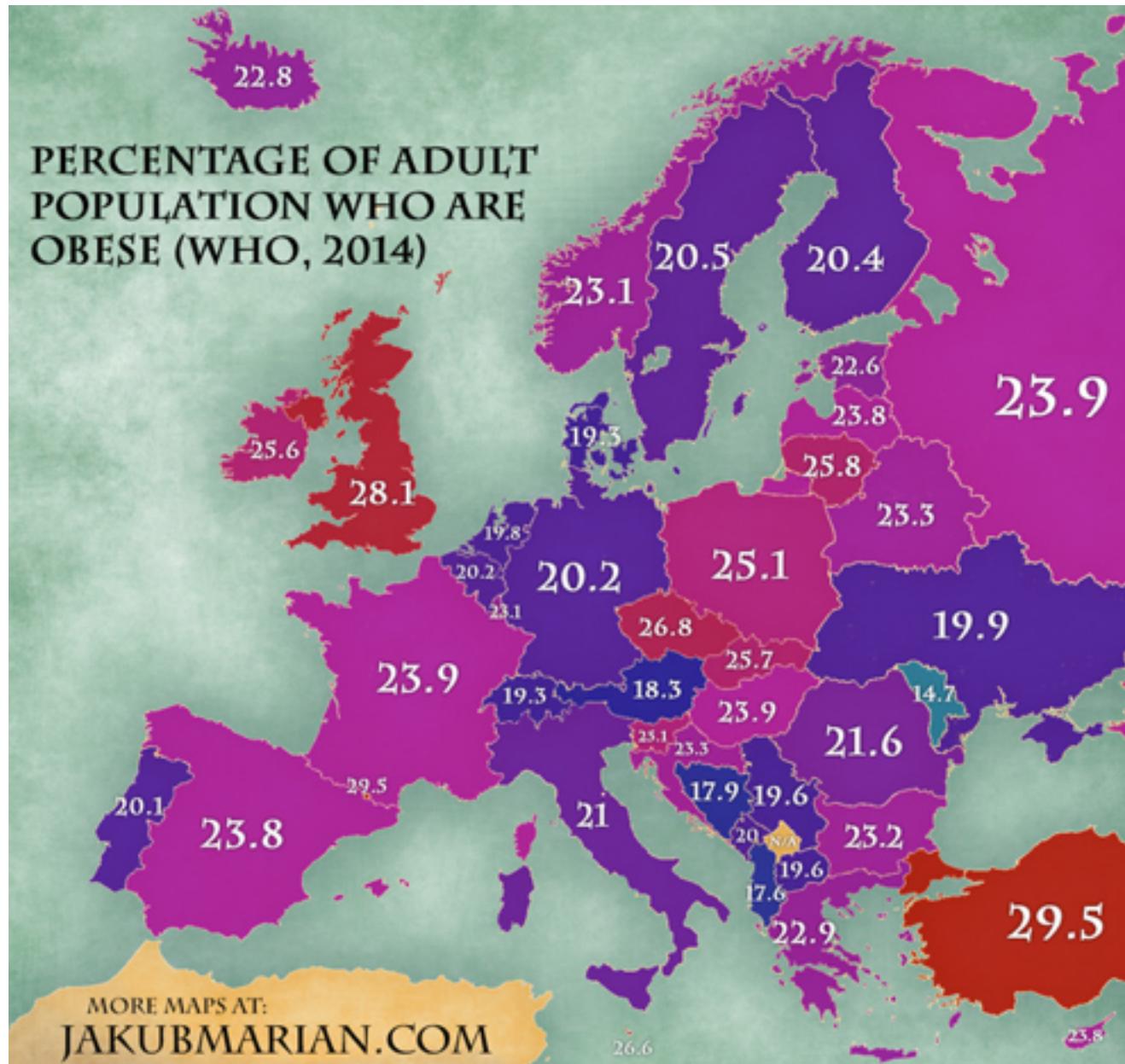
2013

2014

Adult obesity rates, 1990 to 2014



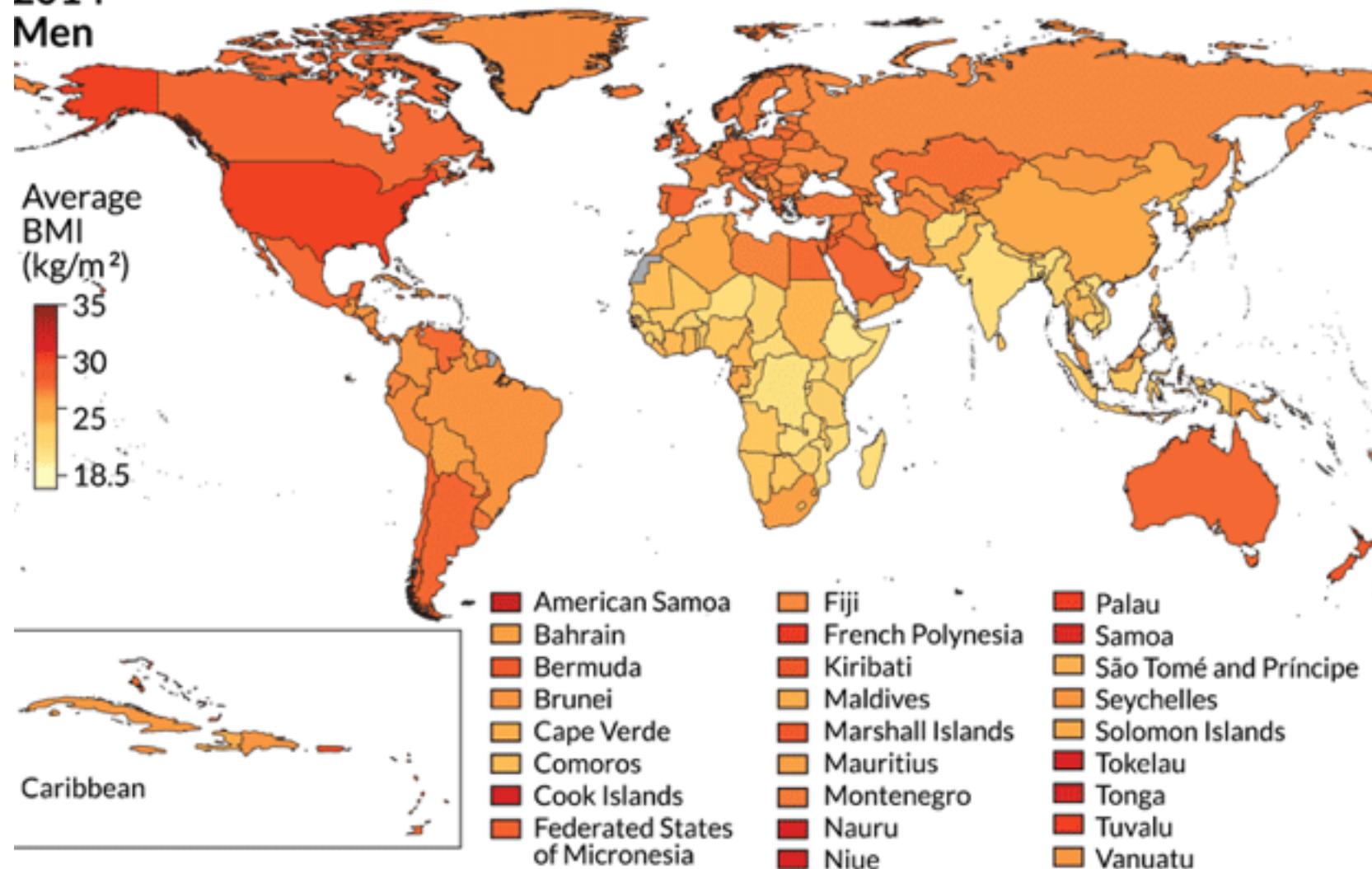
STATISTICS



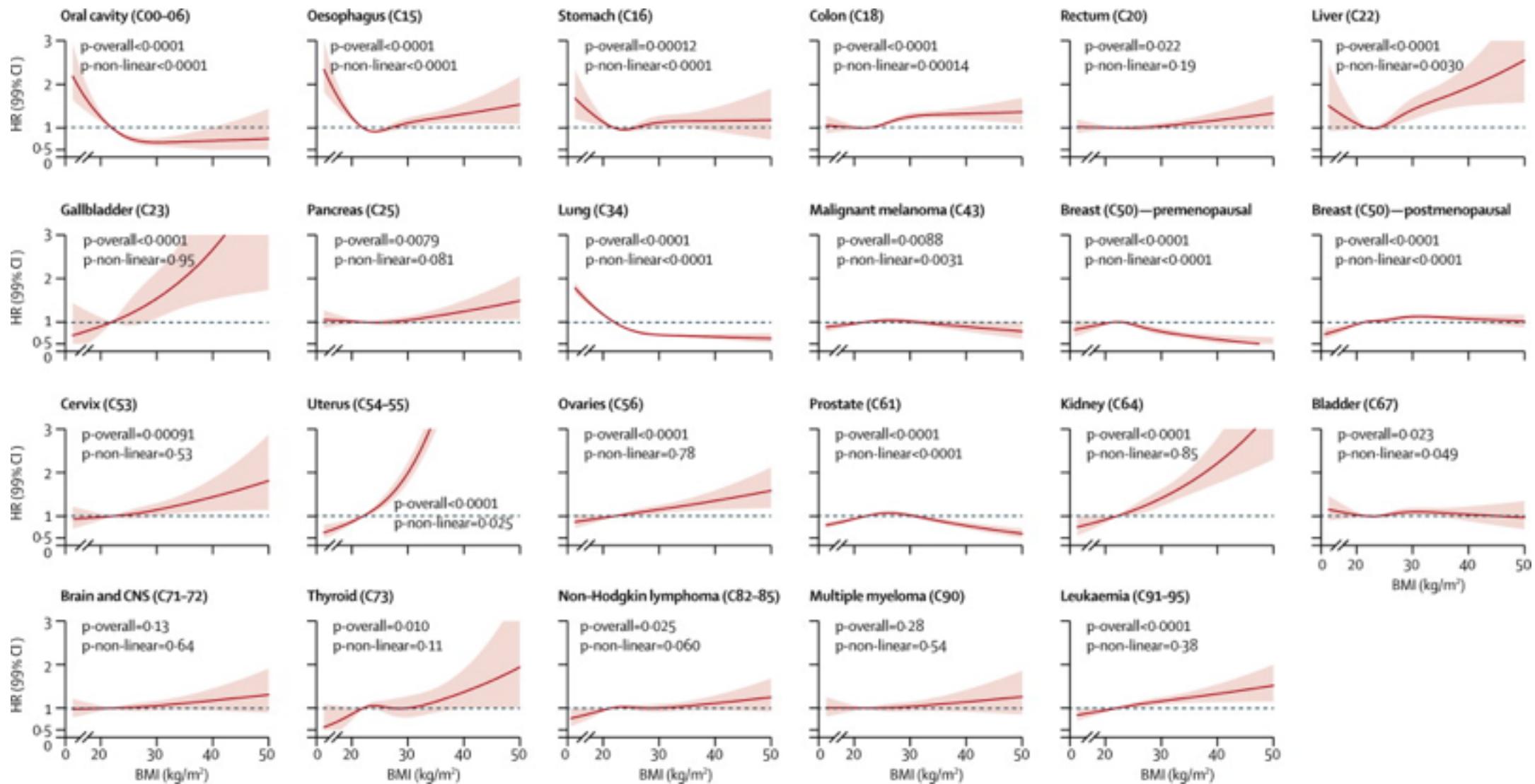
STATISTICS

2014

Men

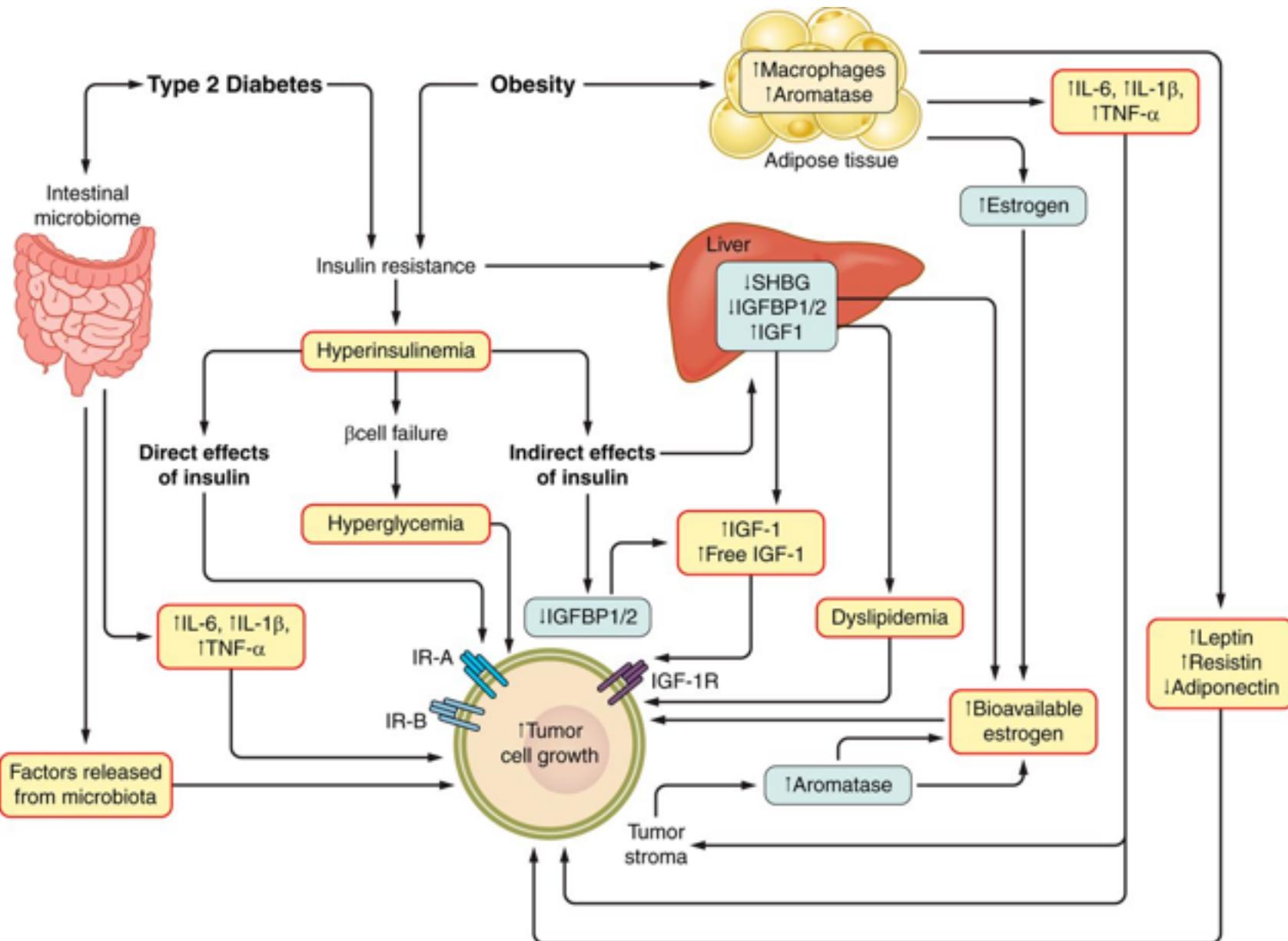


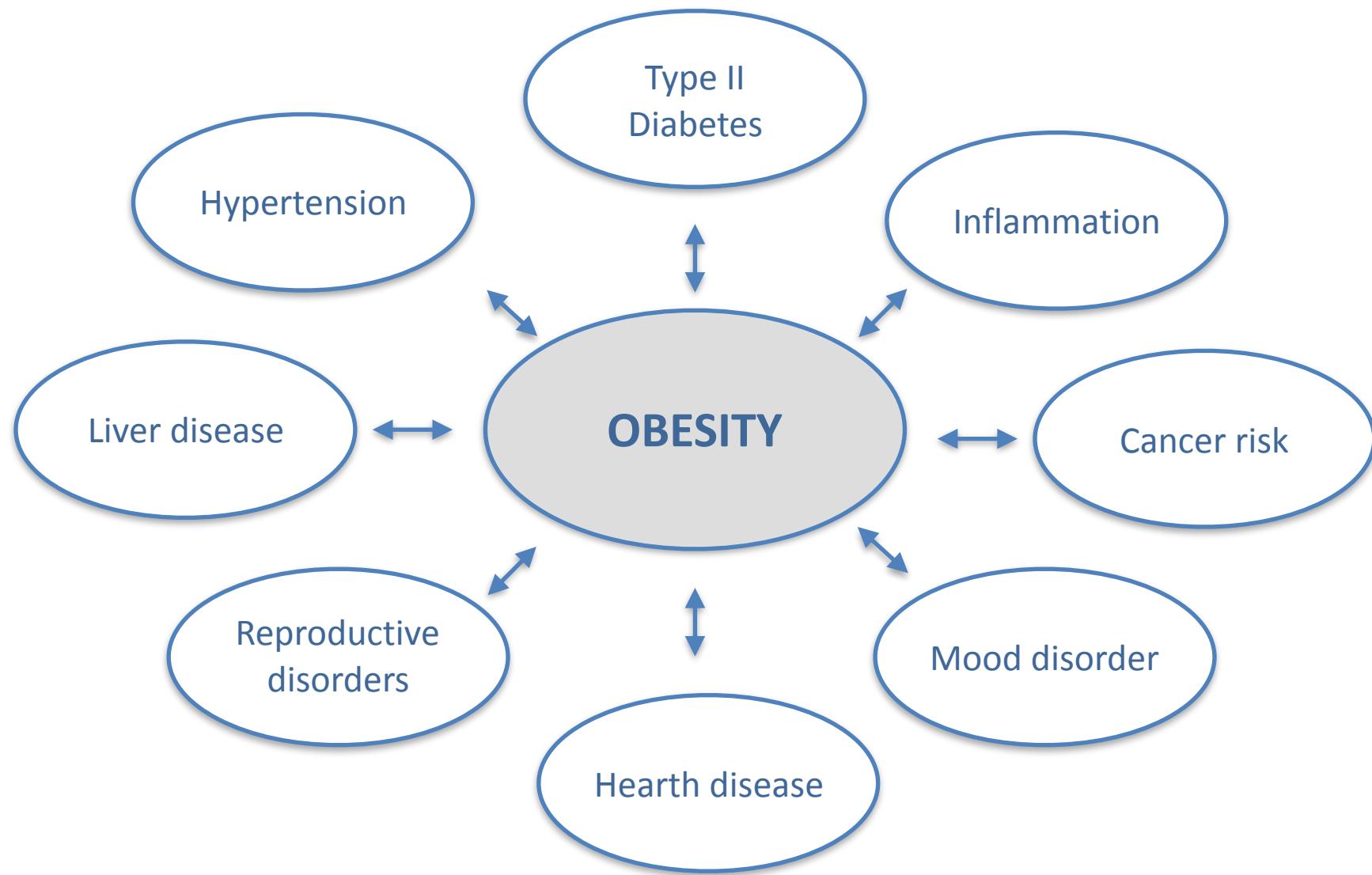
CORRELATIONS BETWEEN CANCER AND OBESITY



Body-mass index and risk of 22 specific cancers:
 a population-based cohort study of 5·24 million UK adults
 Bhaskaran, Krishnan et al. The Lancet , Volume 384 , Issue 9945 , 755 - 765

BIOCHEMICAL NETWORKS





GOAL

Transcriptomic data provides a picture of the alterations in regulatory and metabolic activities associated with obesity, but its interpretation is typically blurred by noise.

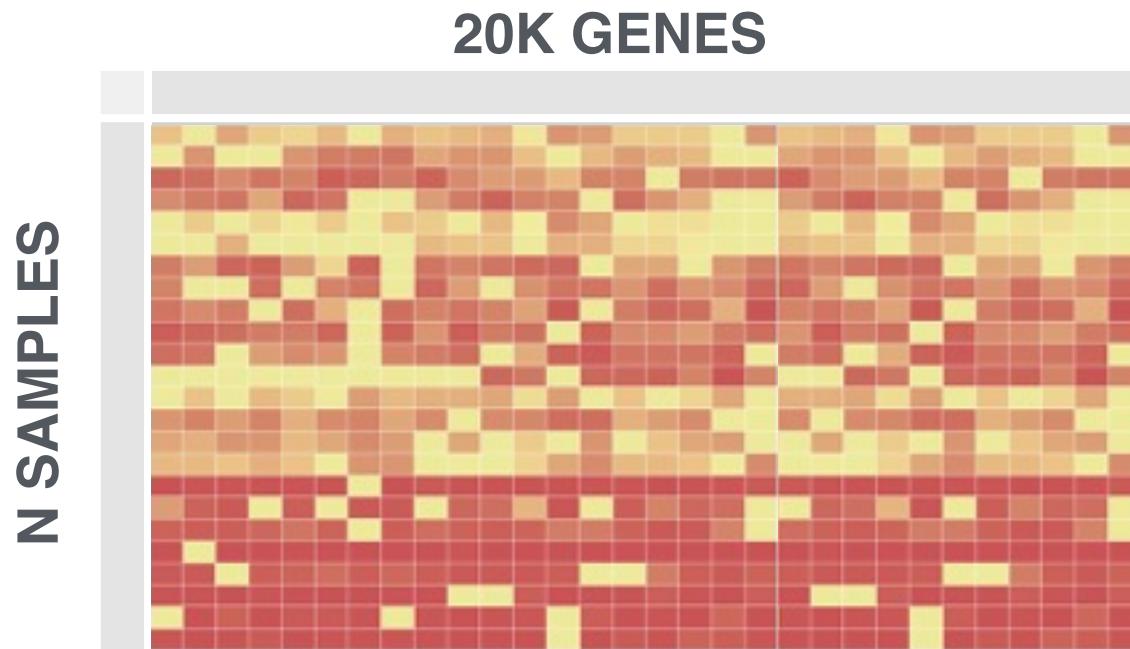
STRATEGY

collecting publicly available transcriptomic data from adipocytes and blood with obese and type 2 diabetes and lean subjects

collecting publicly available transcriptomic data from adipocytes of breast cancer patients with known BMI and cancer history

collecting publicly available transcriptomic data from adipocytes of twins subjects

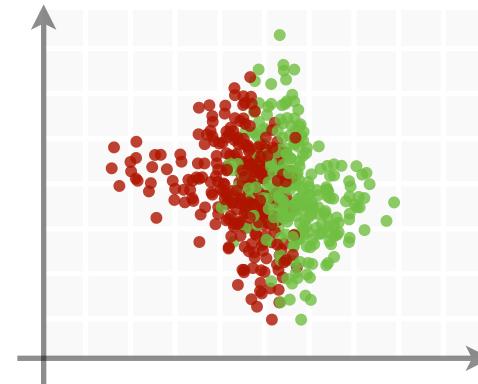
TRANSCRIPTOMICS: THE CURSE OF DIMENSIONALITY



#variables is much larger than **#samples**

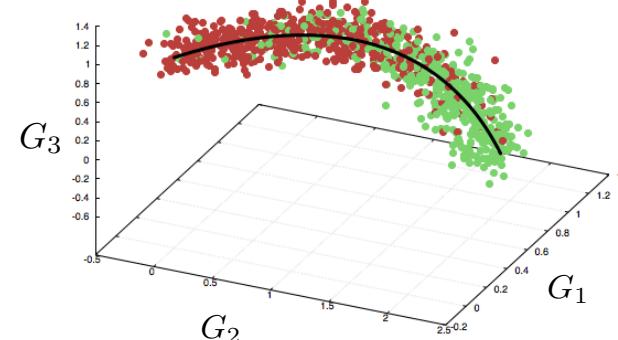
SOLUTIONS

increase **#samples**



Spectral method to
merge datasets and
remove batch effects

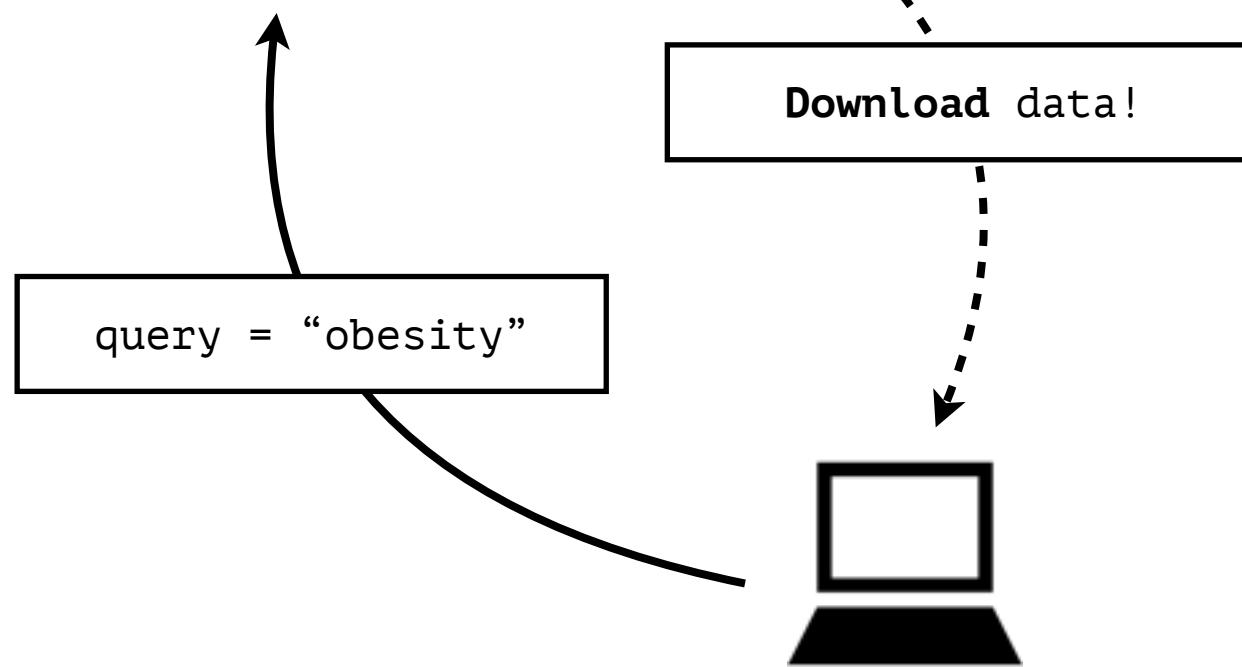
decrease **#variables**

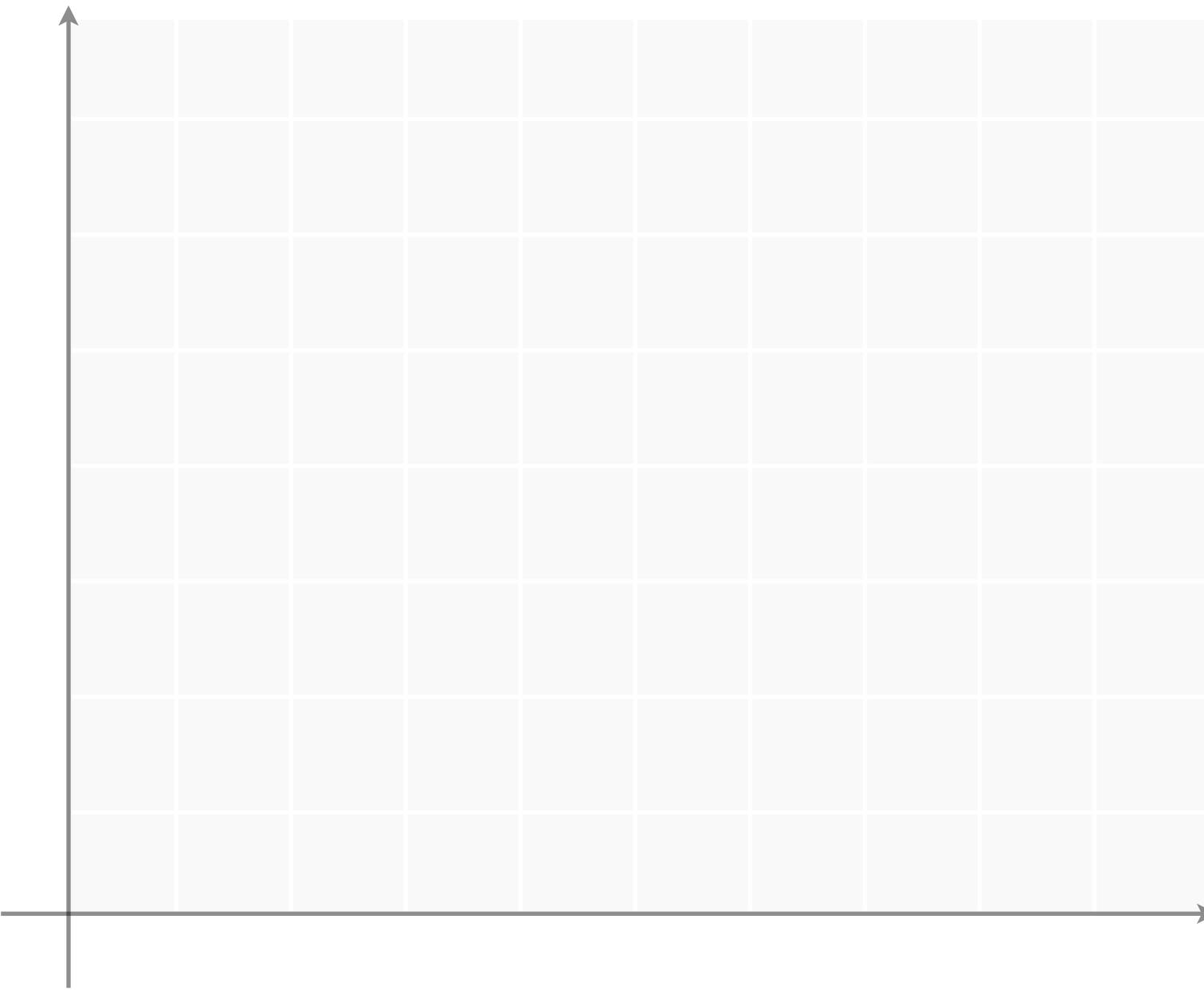


Nonlinear fitting to compute
pathway deregulation scores

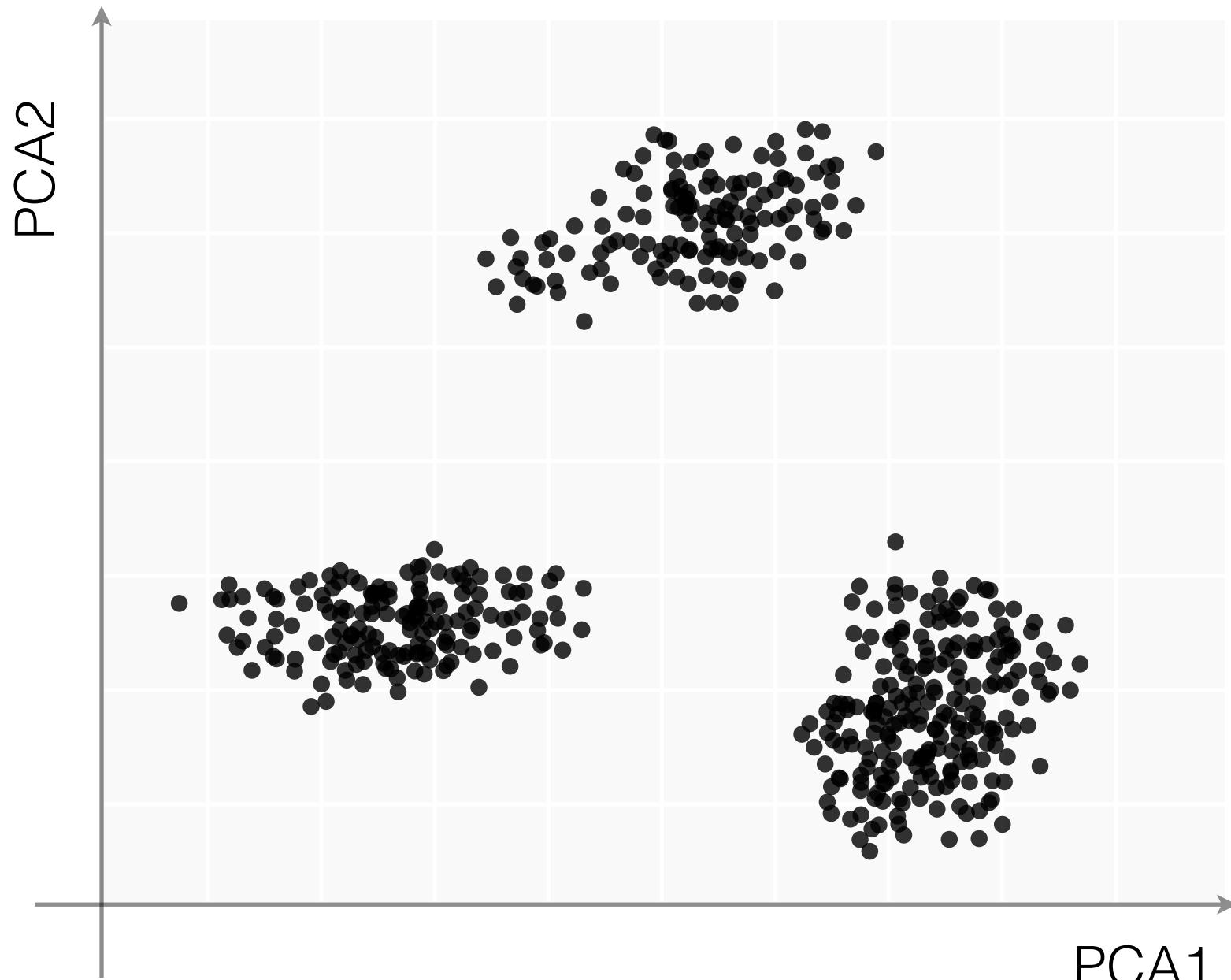


44.35 TB of archived data
~**2.1M** assays
~**68K** experiments

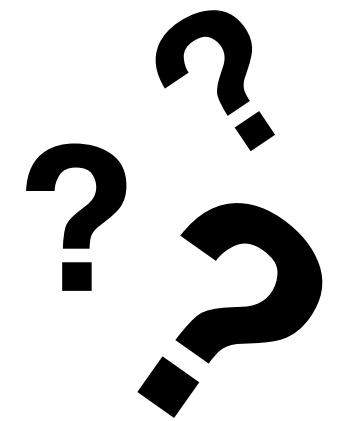




● HEALTHY
● DISEASE



GREEN CIRCLE: HEALTHY
RED CIRCLE: DISEASE

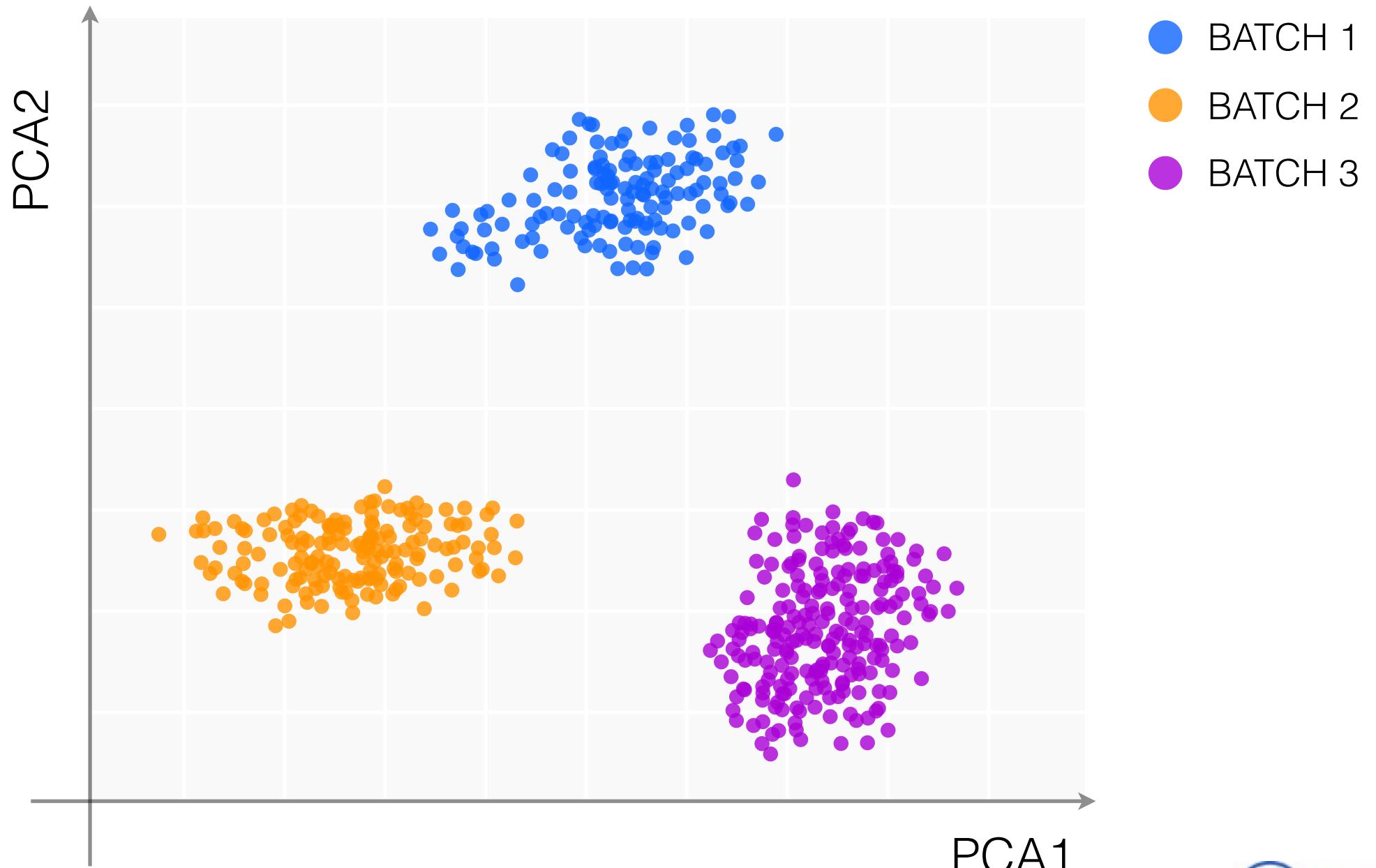


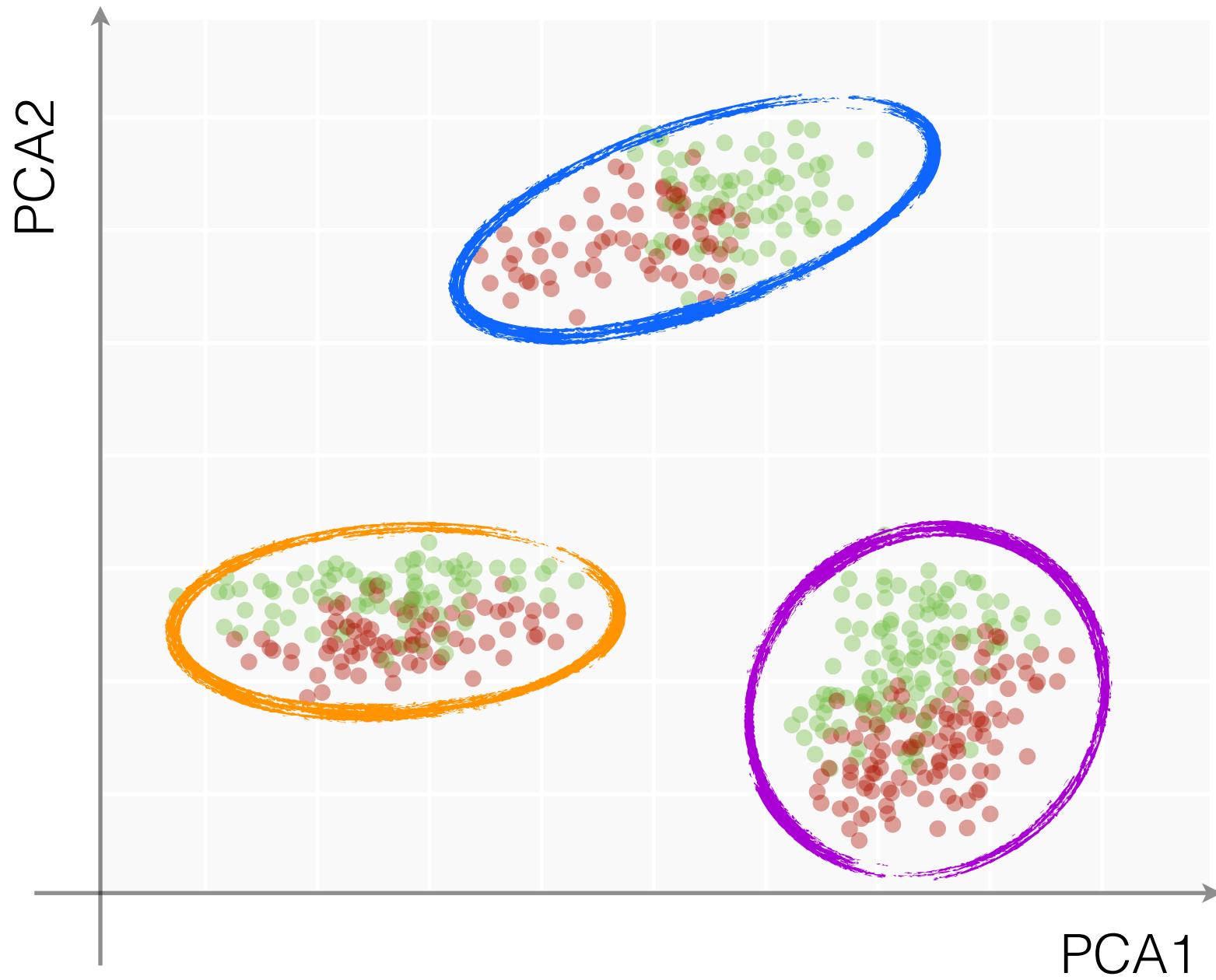
PCA1



● HEALTHY
● DISEASE

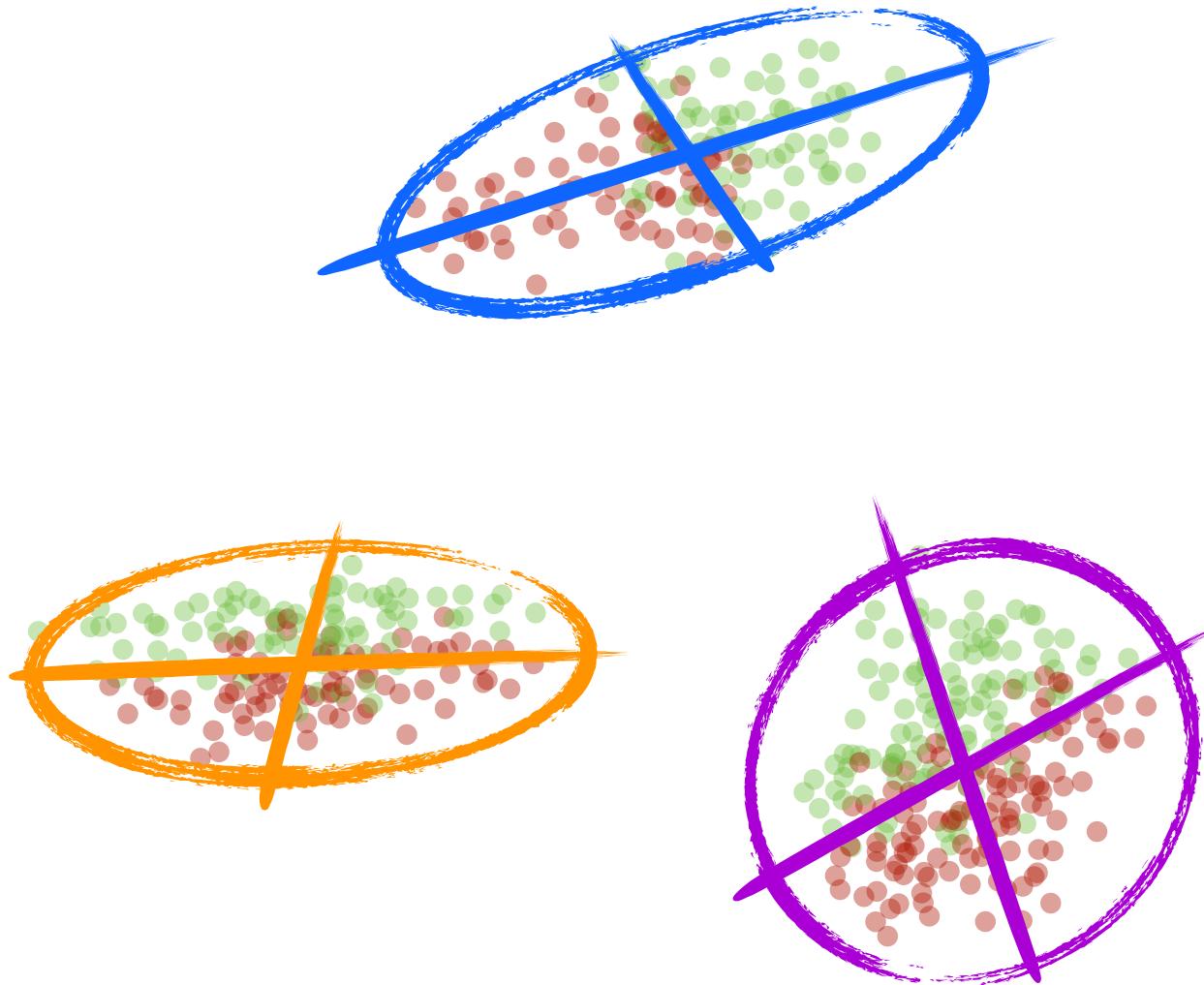
PCA1

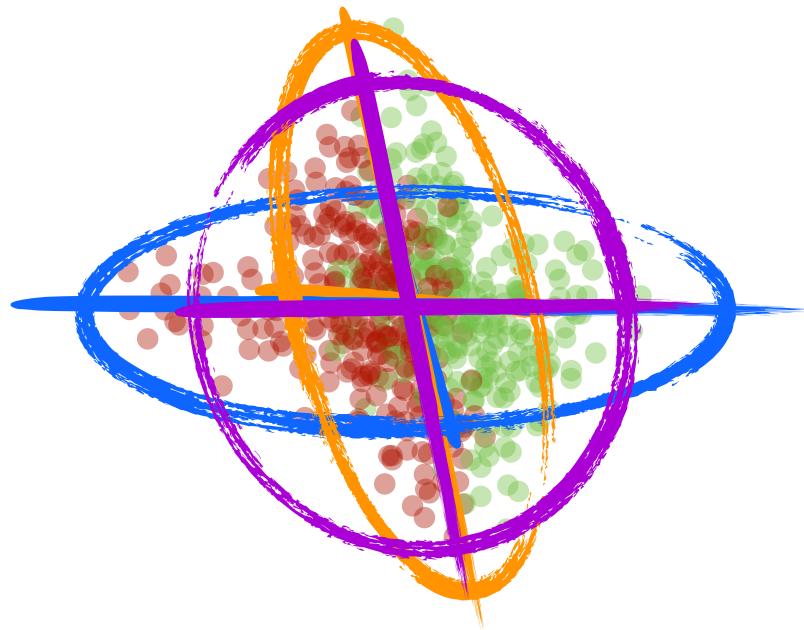


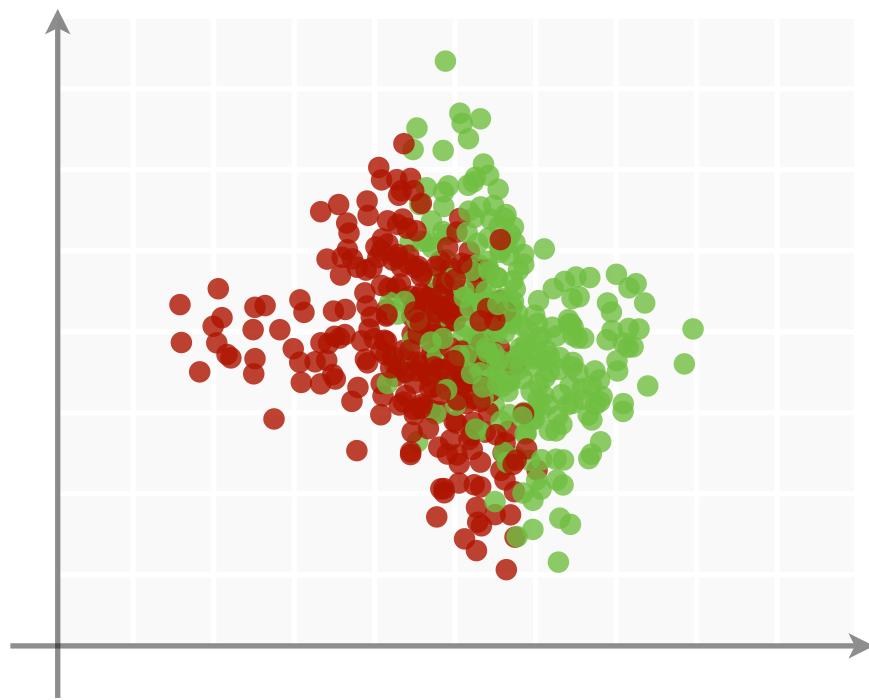


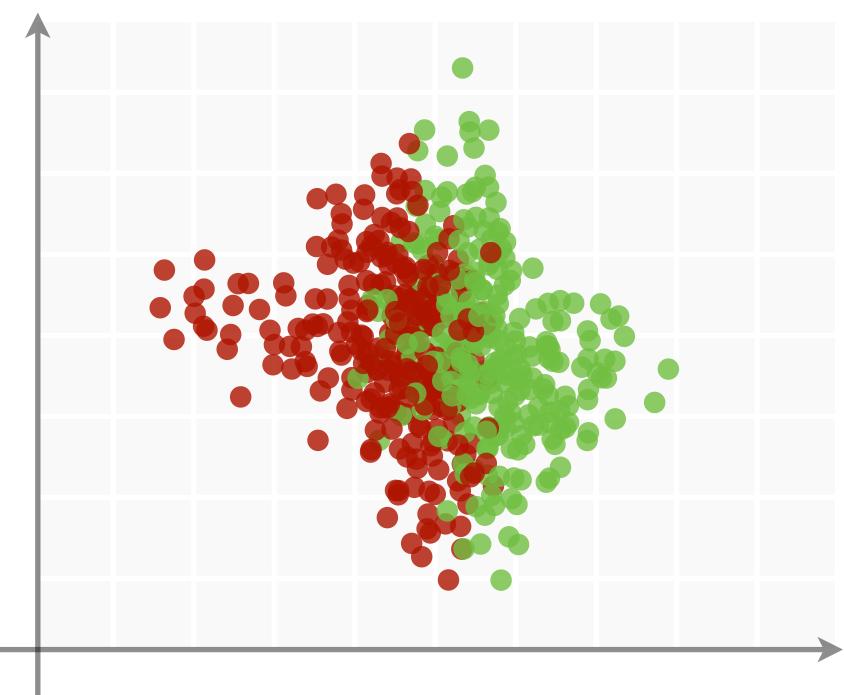
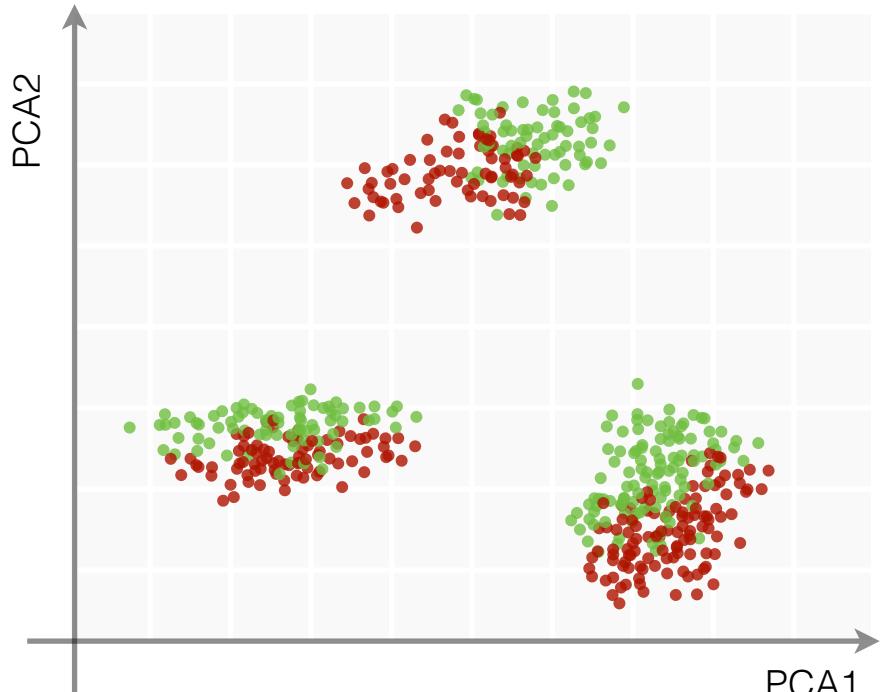
- HEALTHY
- DISEASE
- BATCH 1
- BATCH 2
- BATCH 3

PCA1





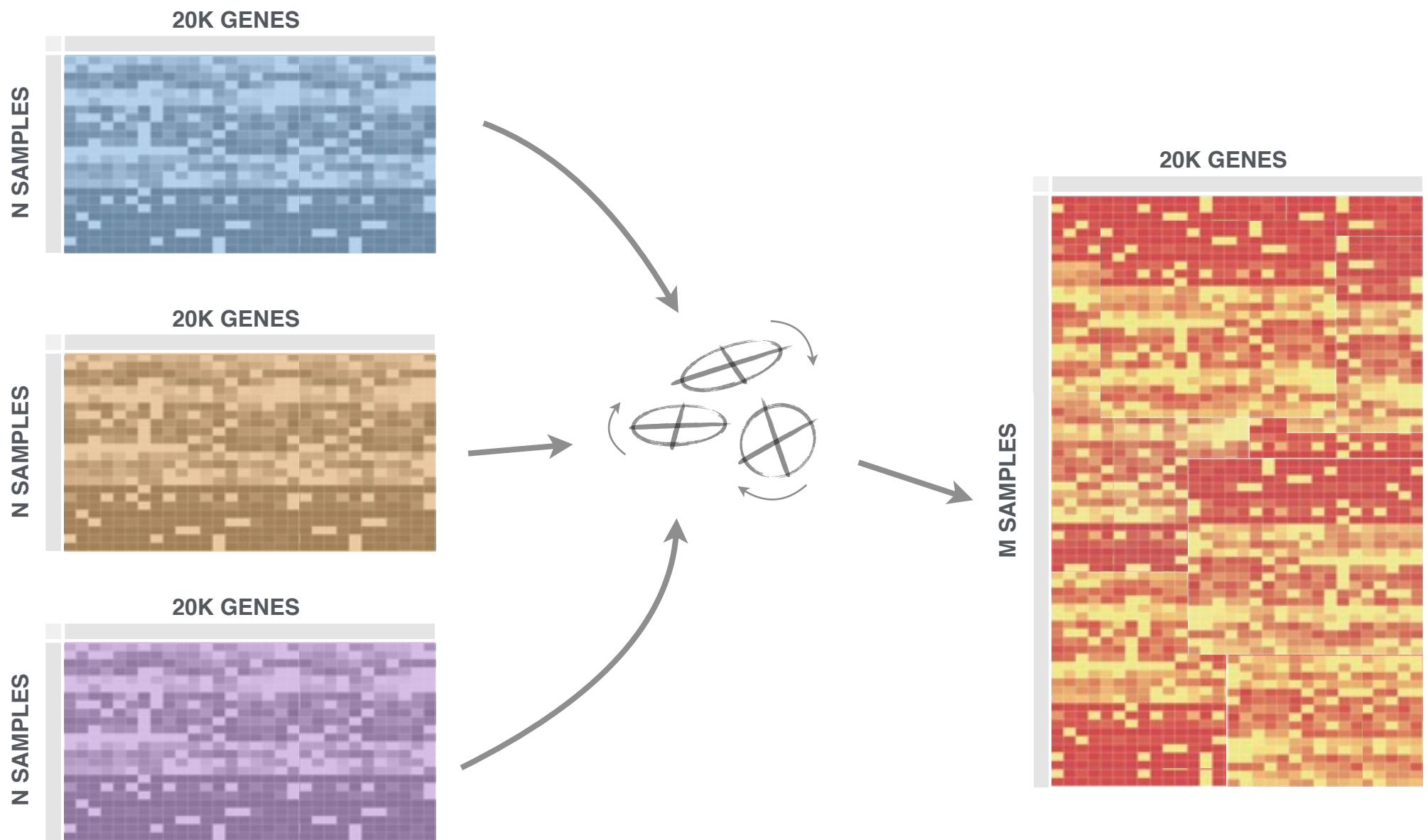




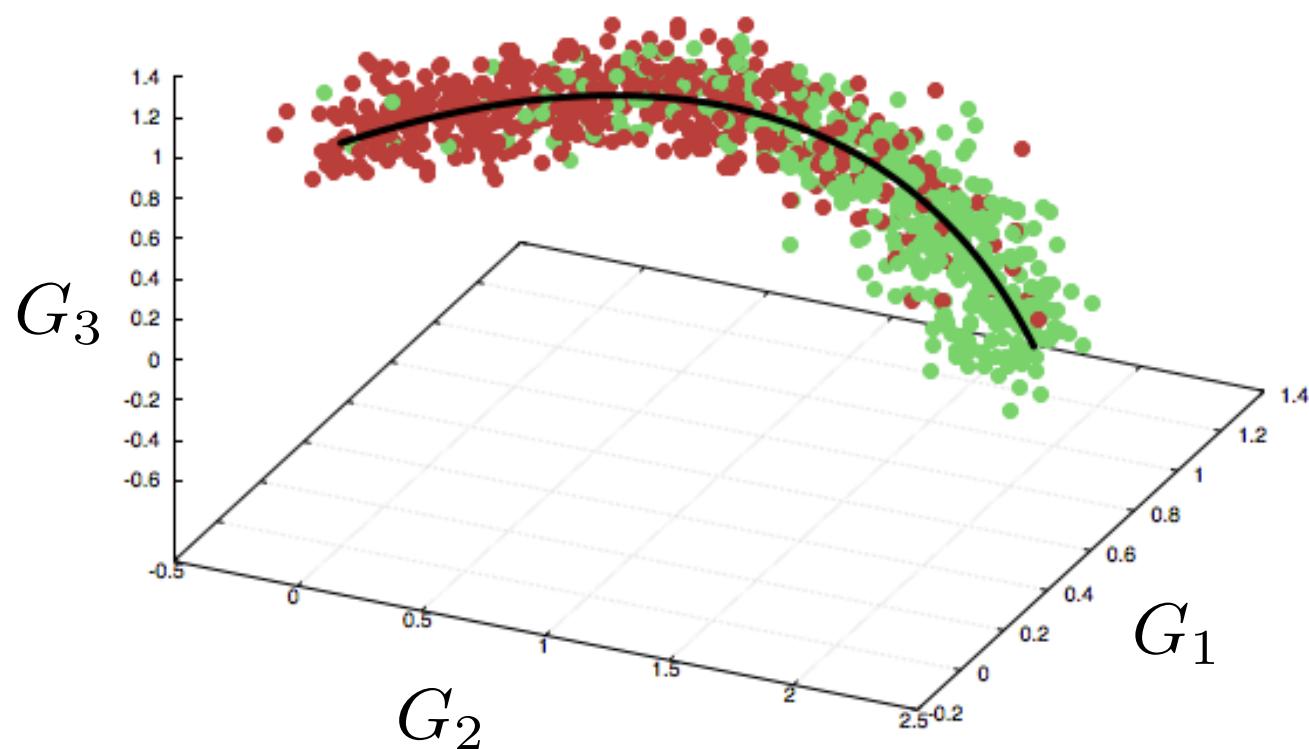
Spectral Method for **Batch Effects** Removal

- completely automatic
- allows integration of public datasets
- merged data provides new insights

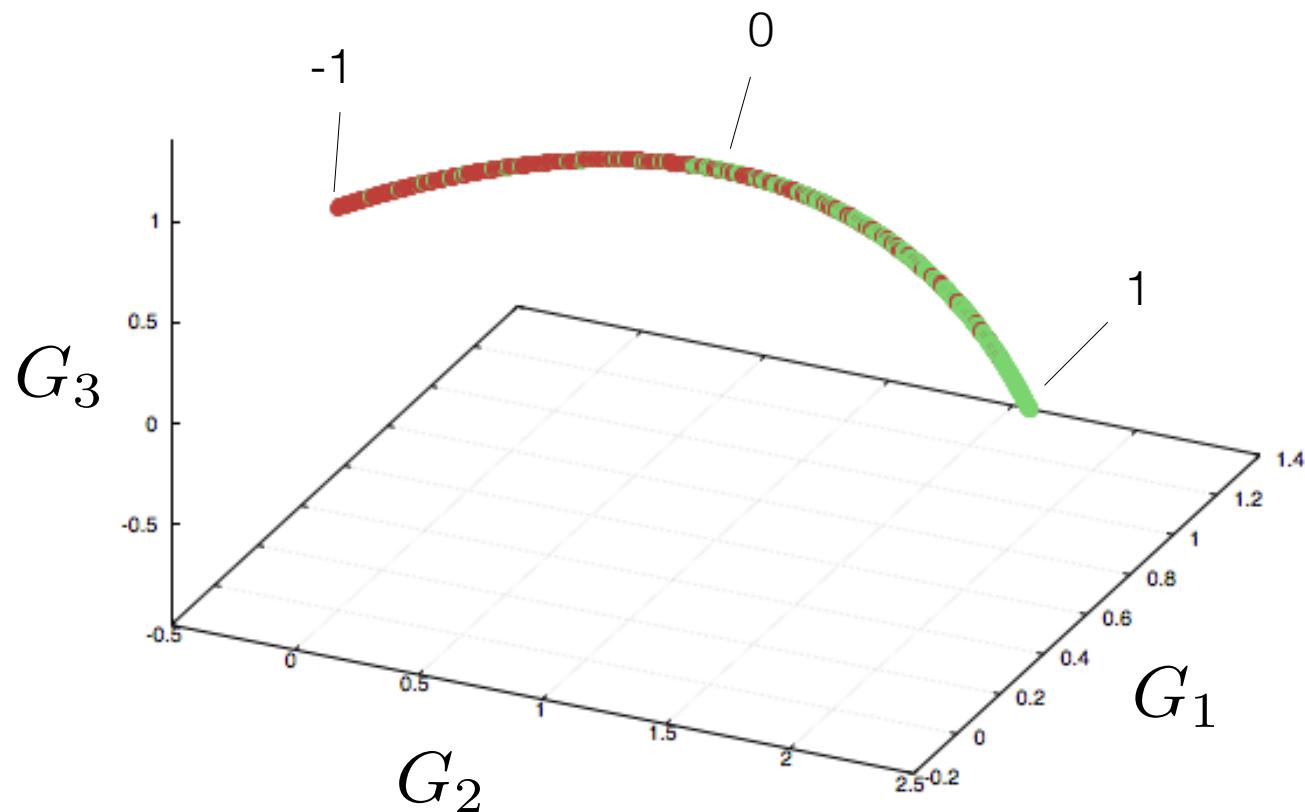
DATA MERGING



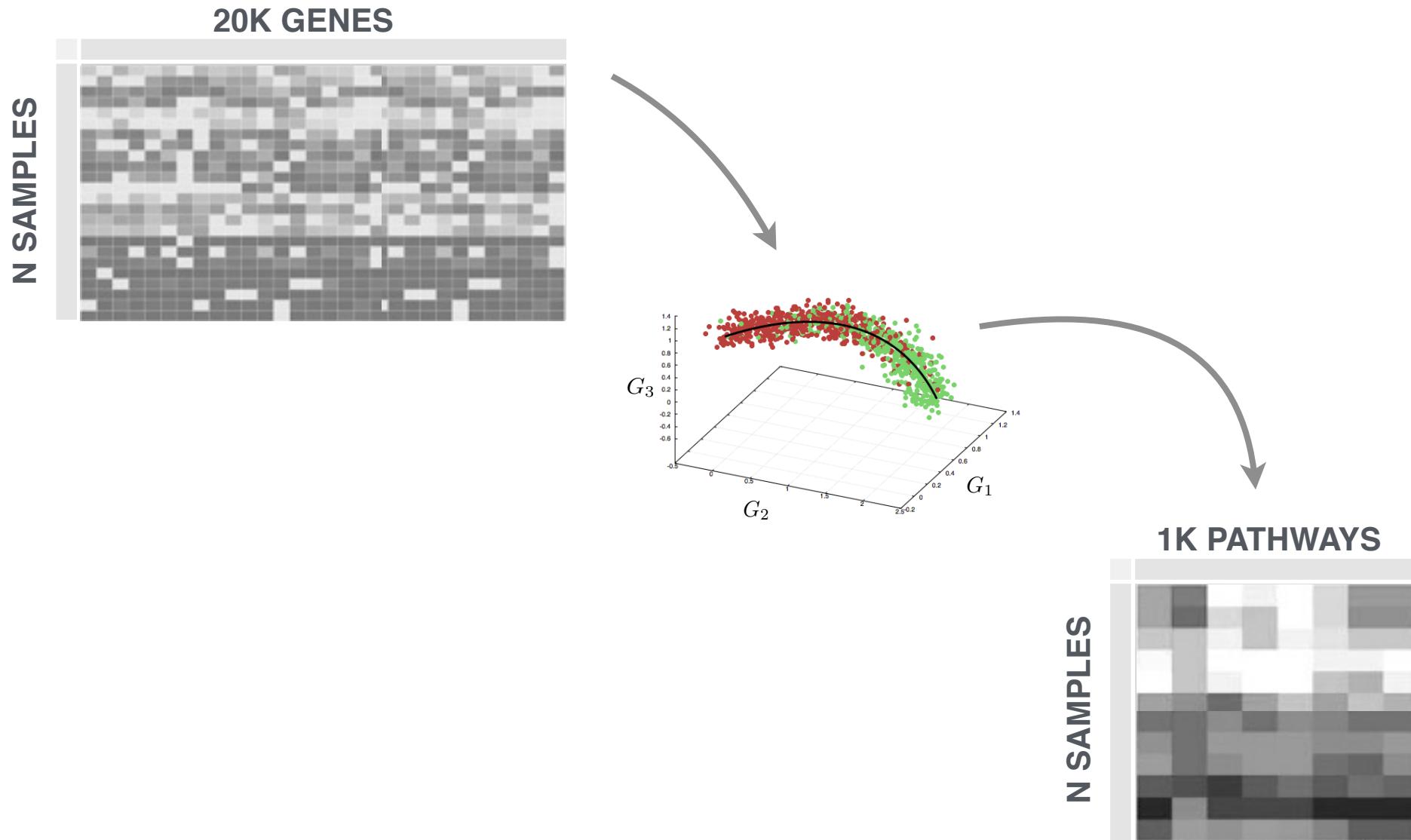
PATHWAY DEREGLULATION

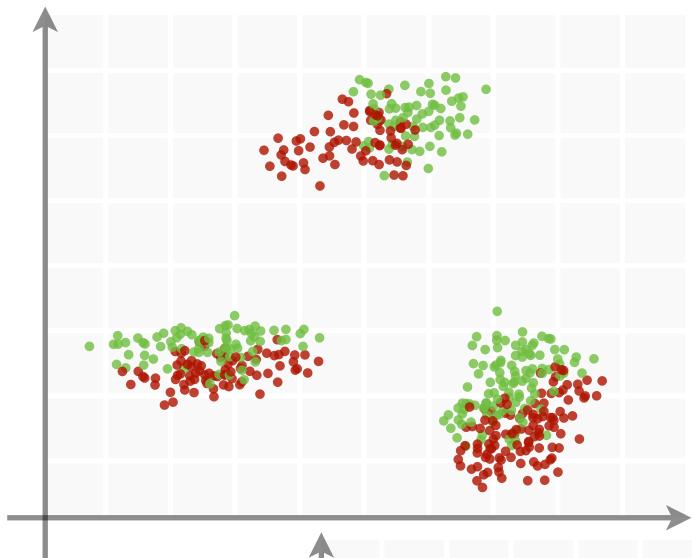


PATHWAY DEREGLULATION

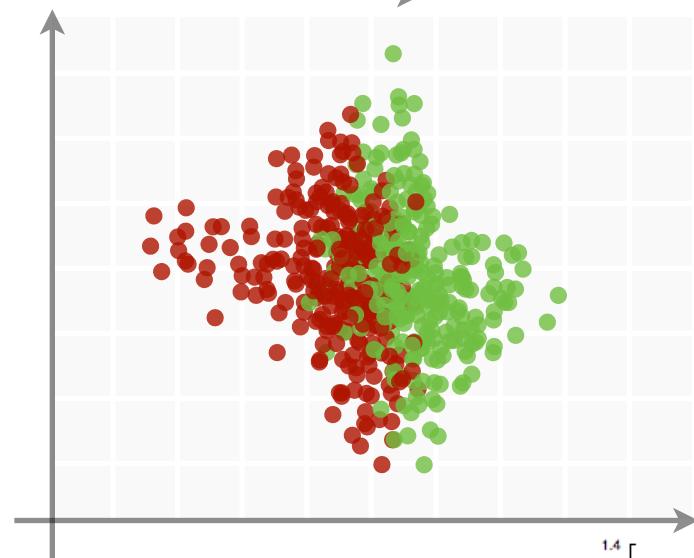


PATHWAY DEREGULATION

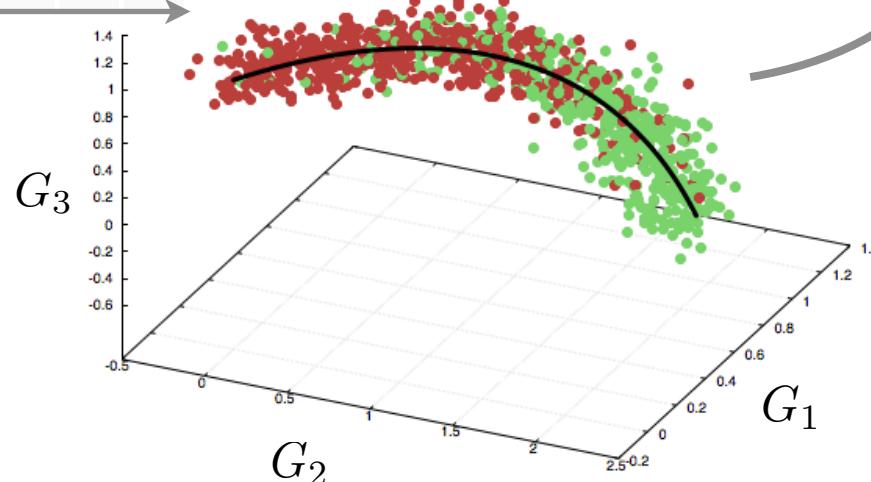




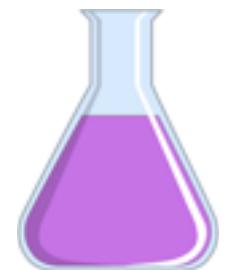
Merge lots
of data



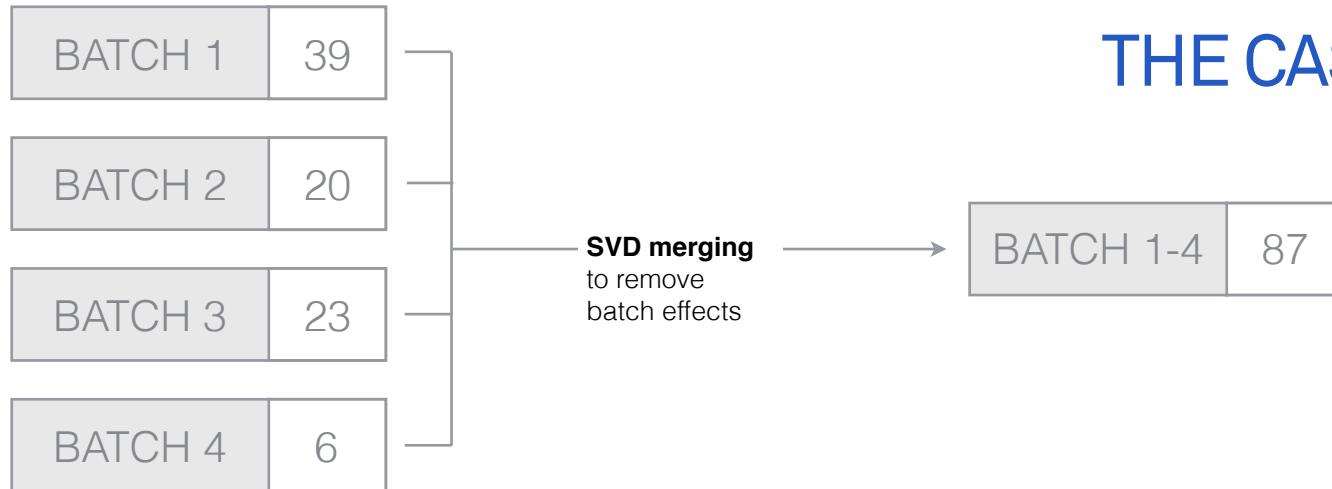
Find new
dereregulated
pathways



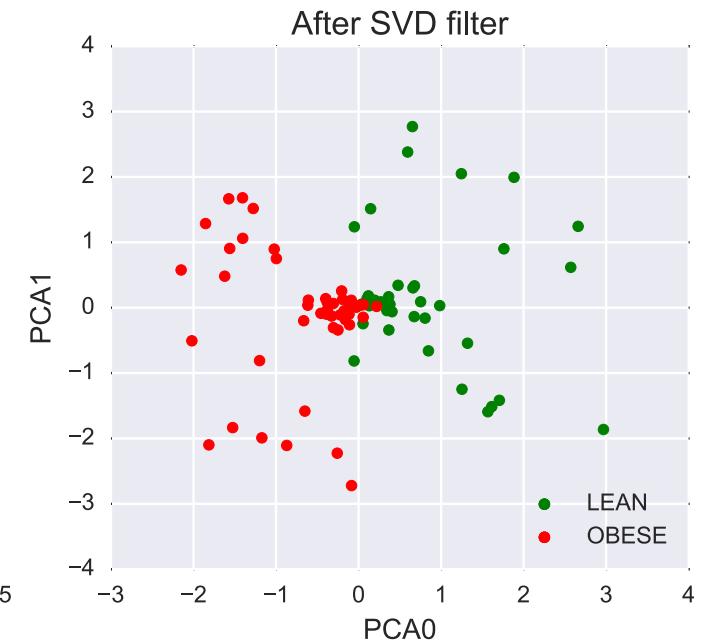
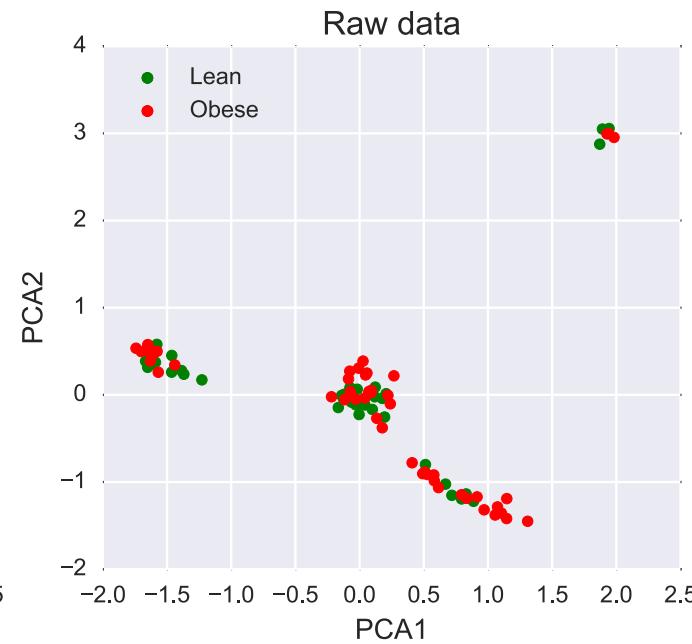
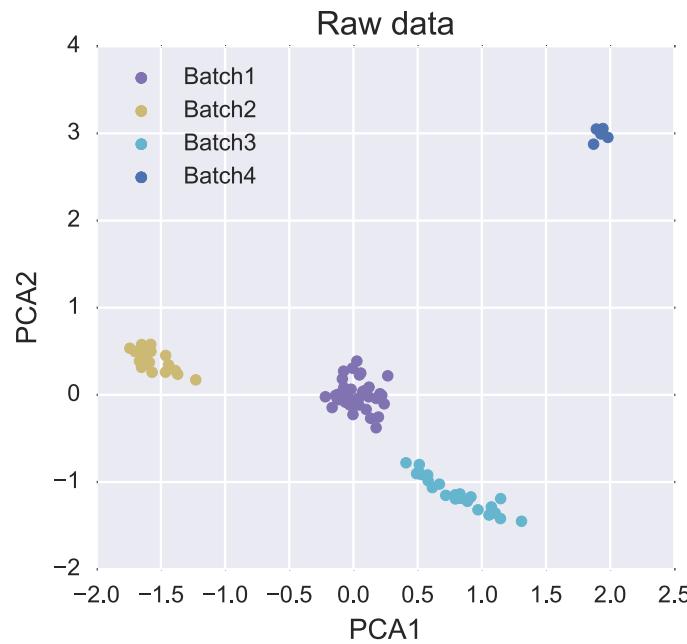
Validate
in the lab



THE CASE OF OBESITY



FILTERING THE DATA

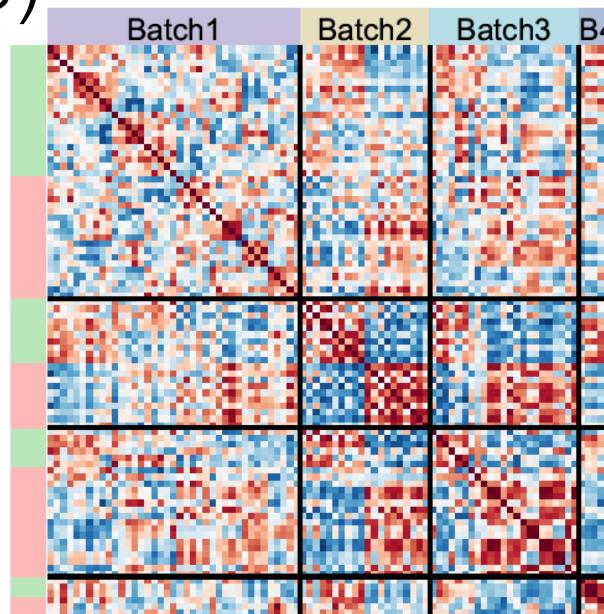


FILTERING THE DATA

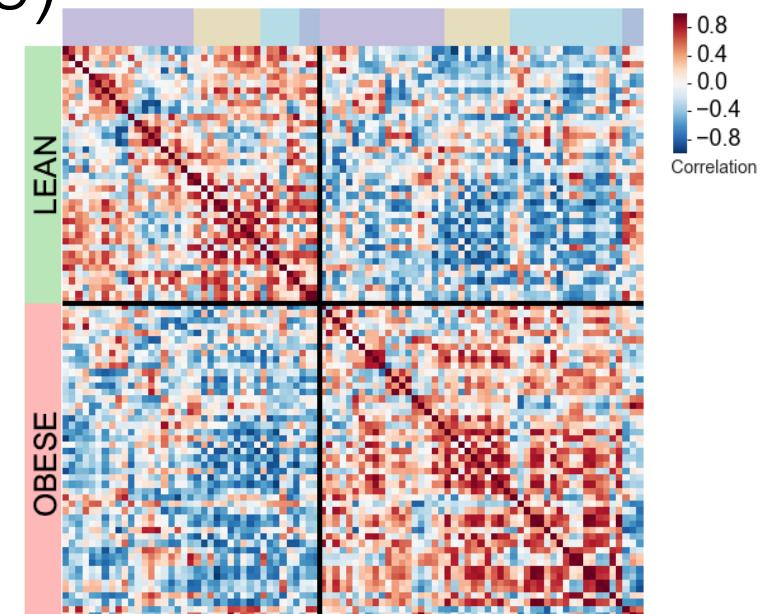
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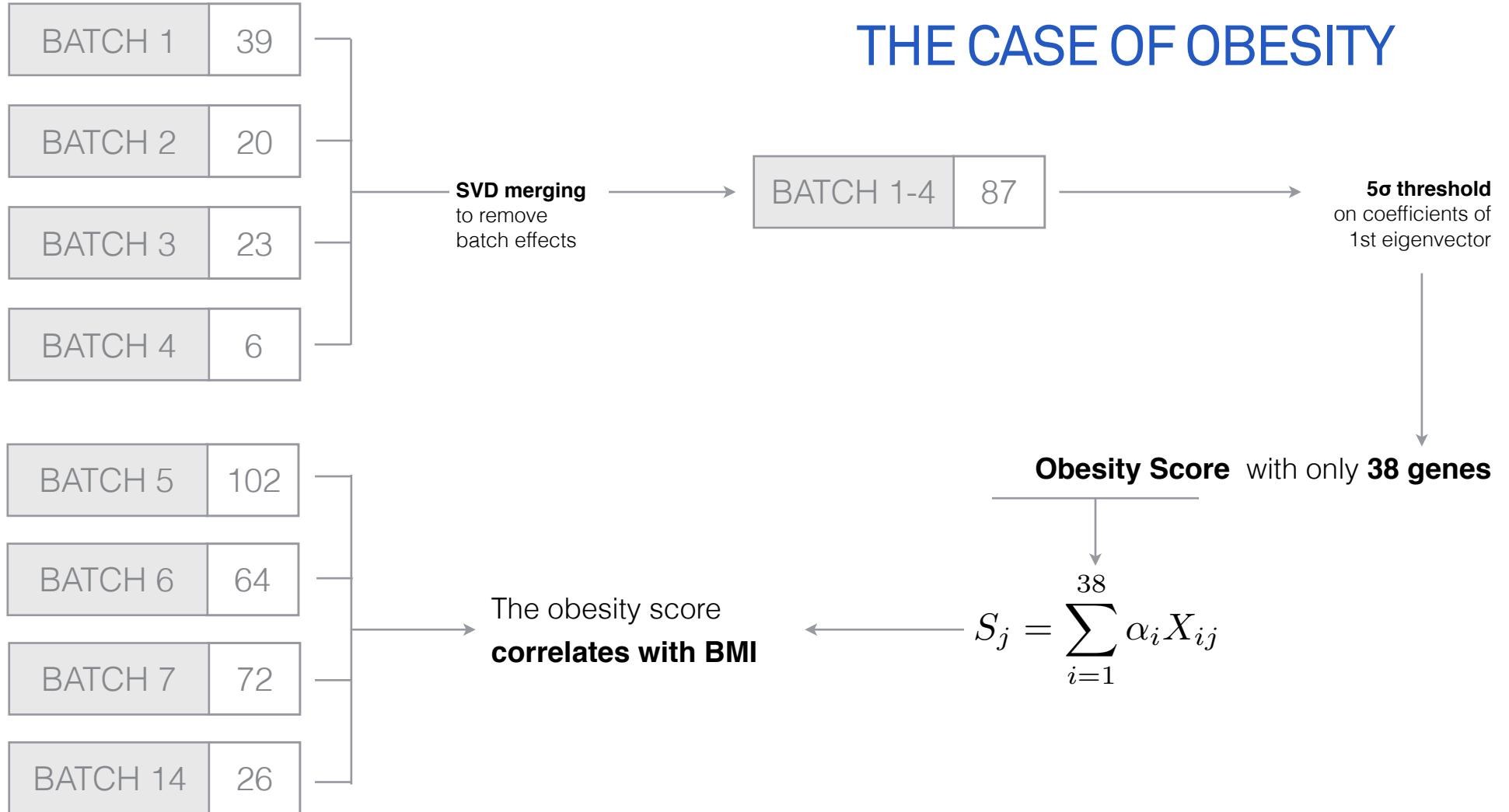
b)



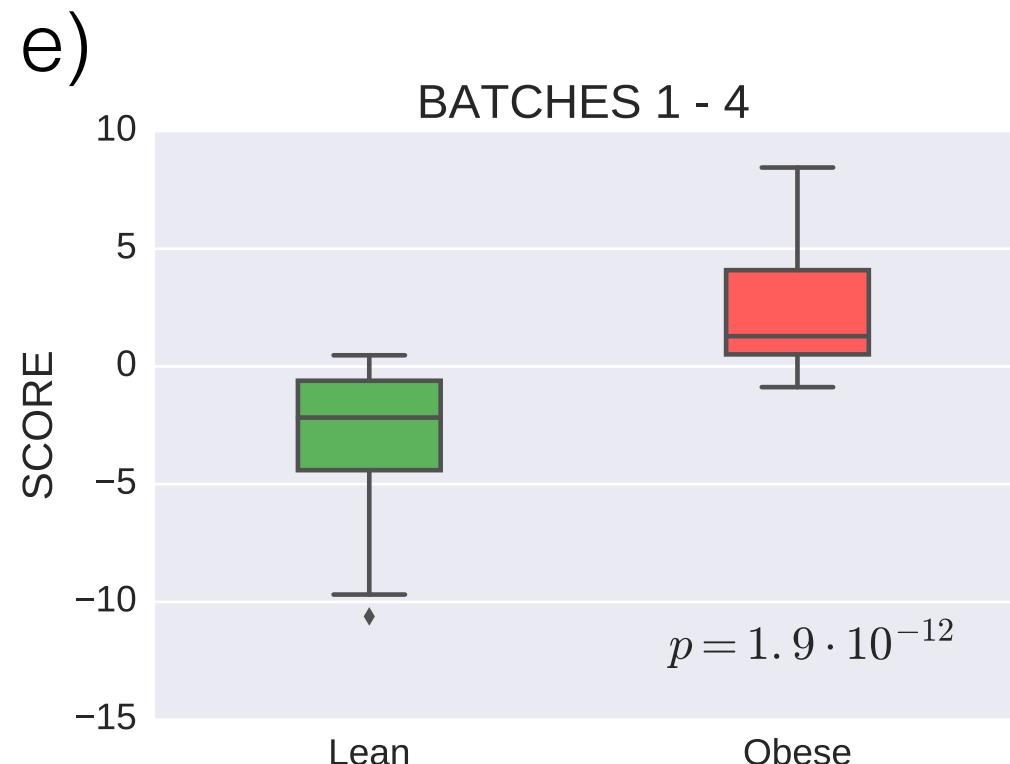
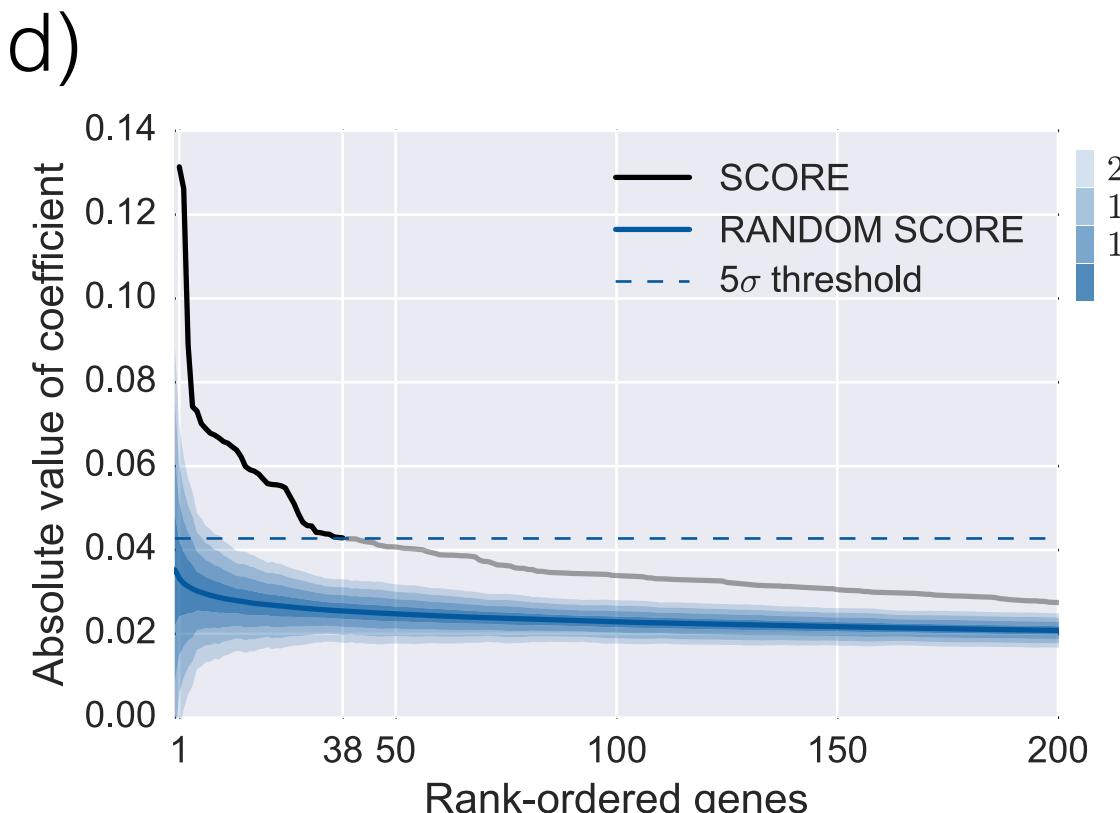
c)



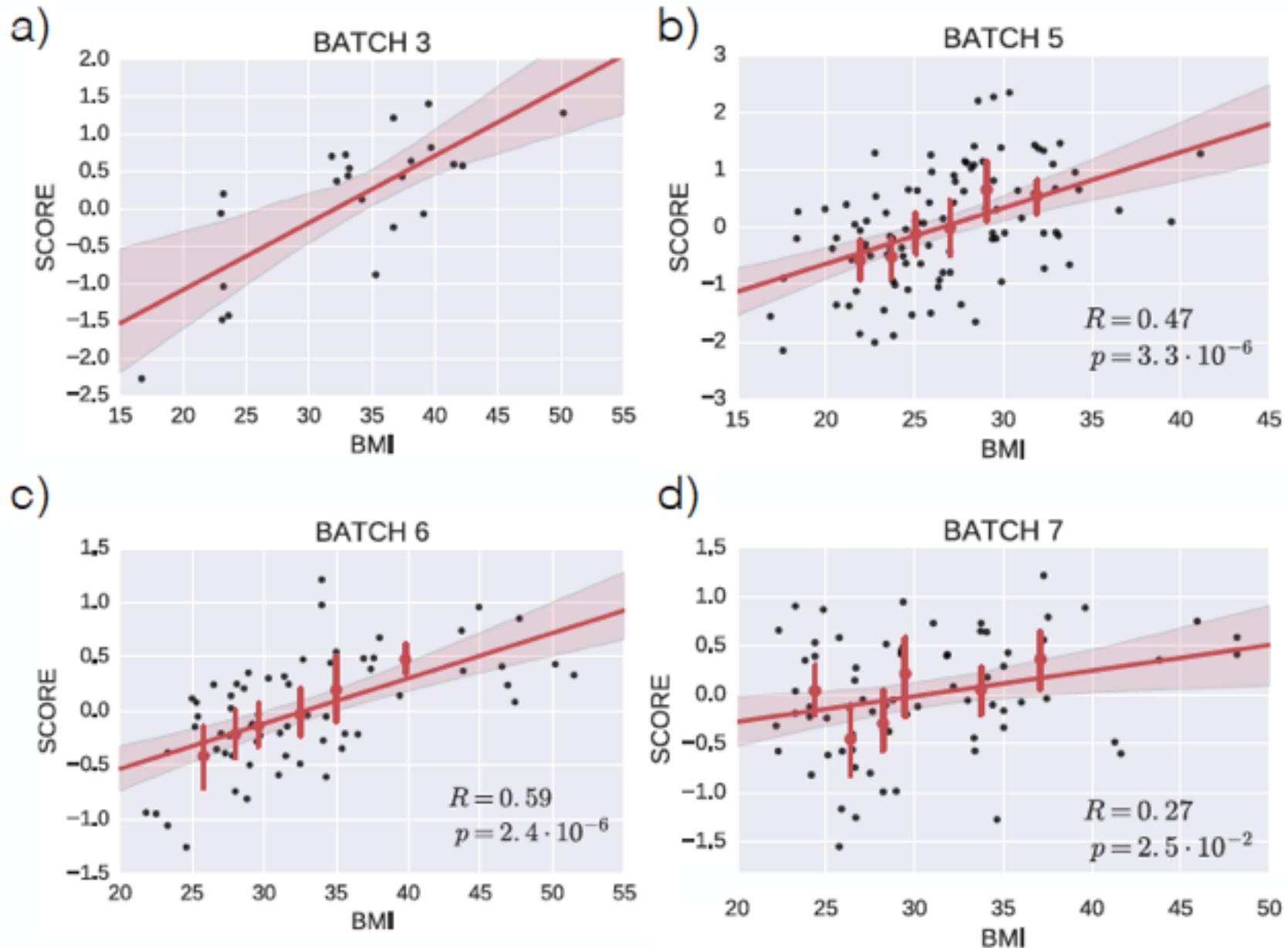
THE CASE OF OBESITY



THE OBESITY SCORE

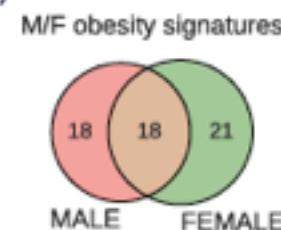


SCORE CORRELATES WITH BMI

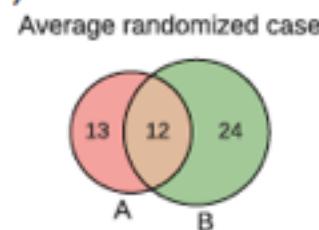


SCORE IS GENDER INDEPENDENT

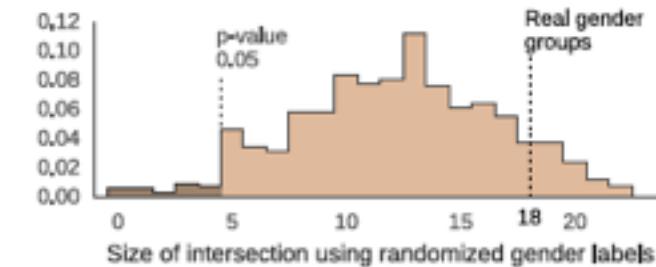
a)



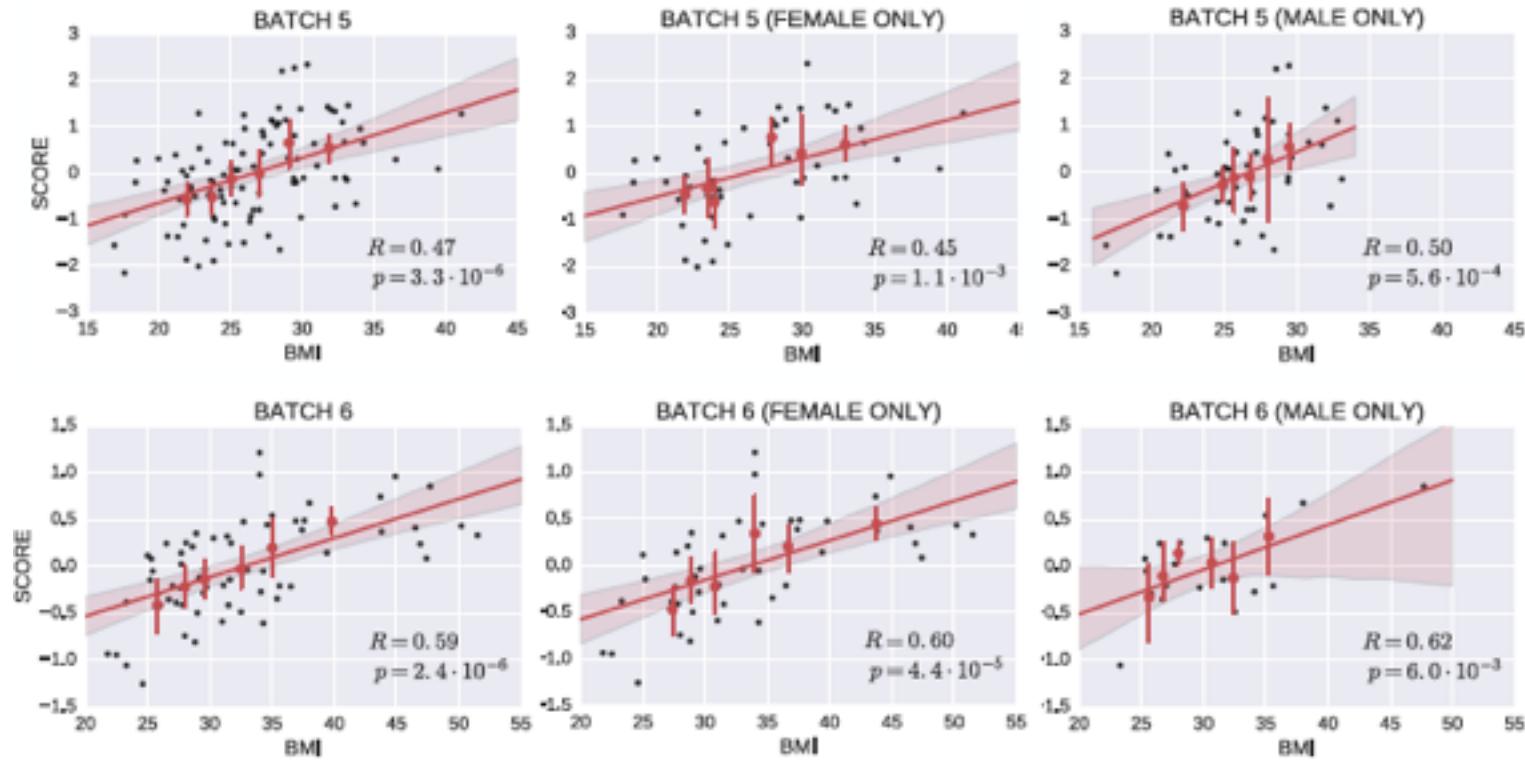
b)

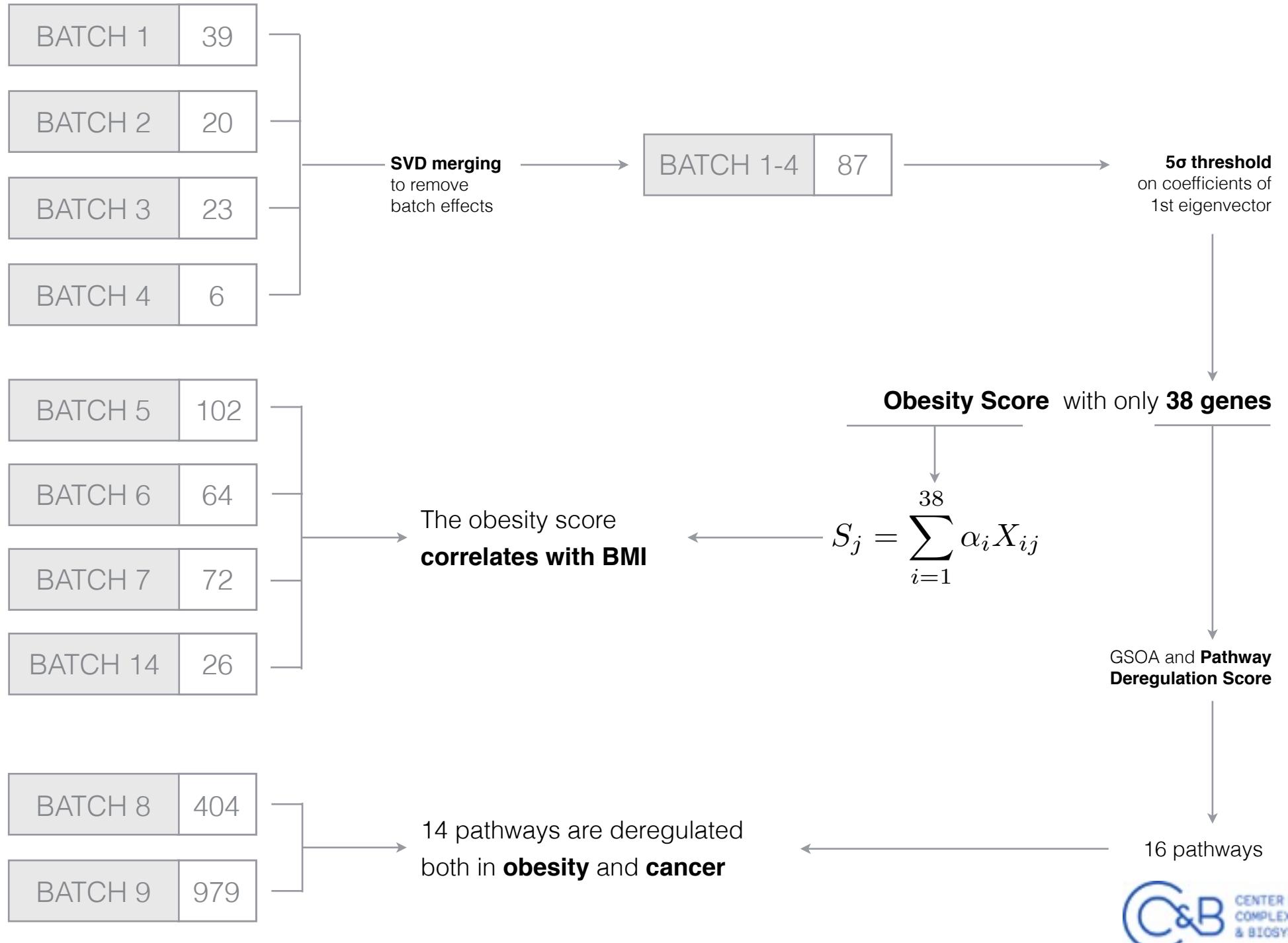


c)

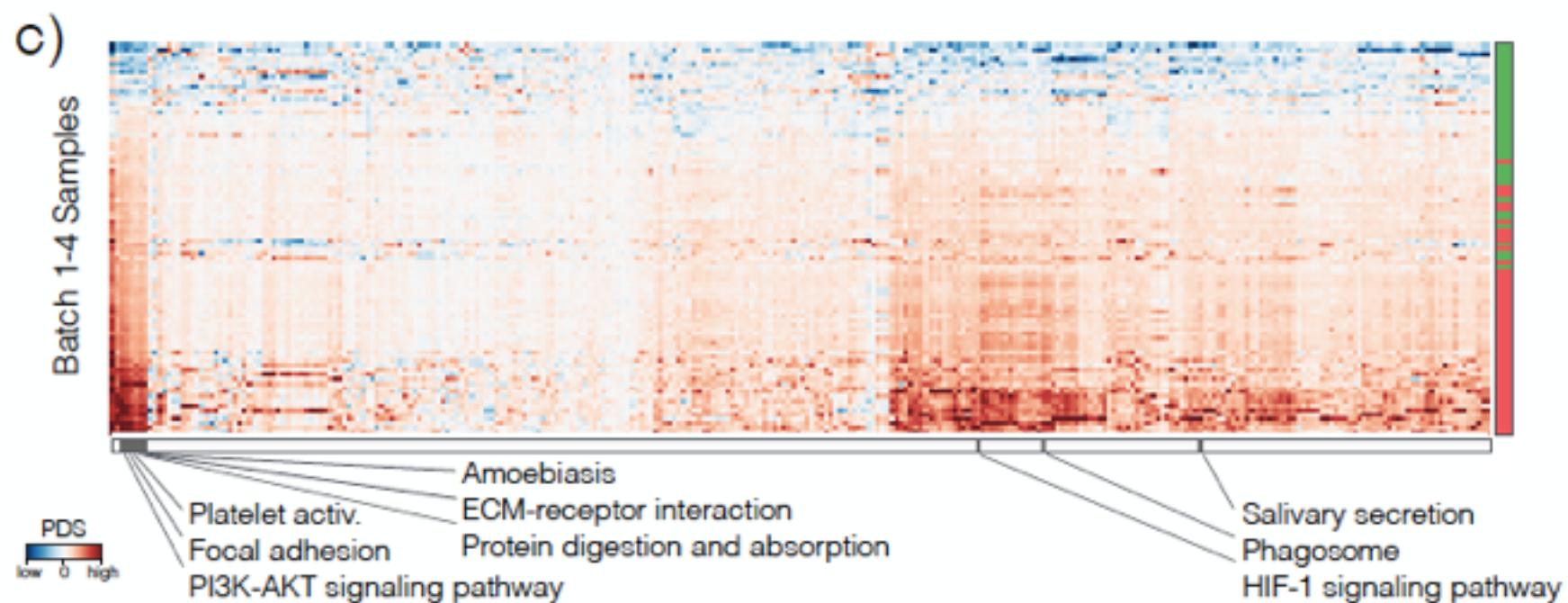
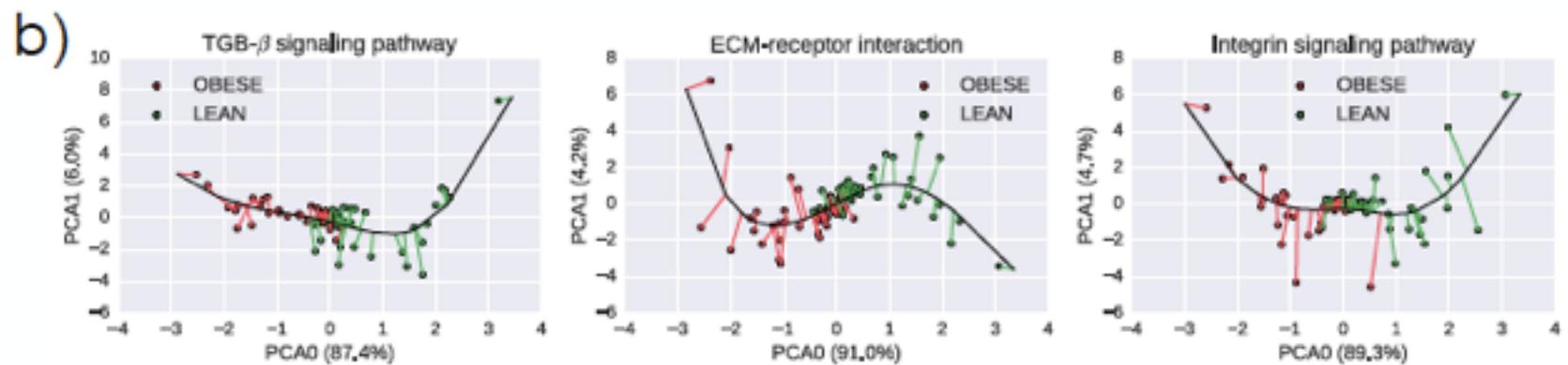


d)





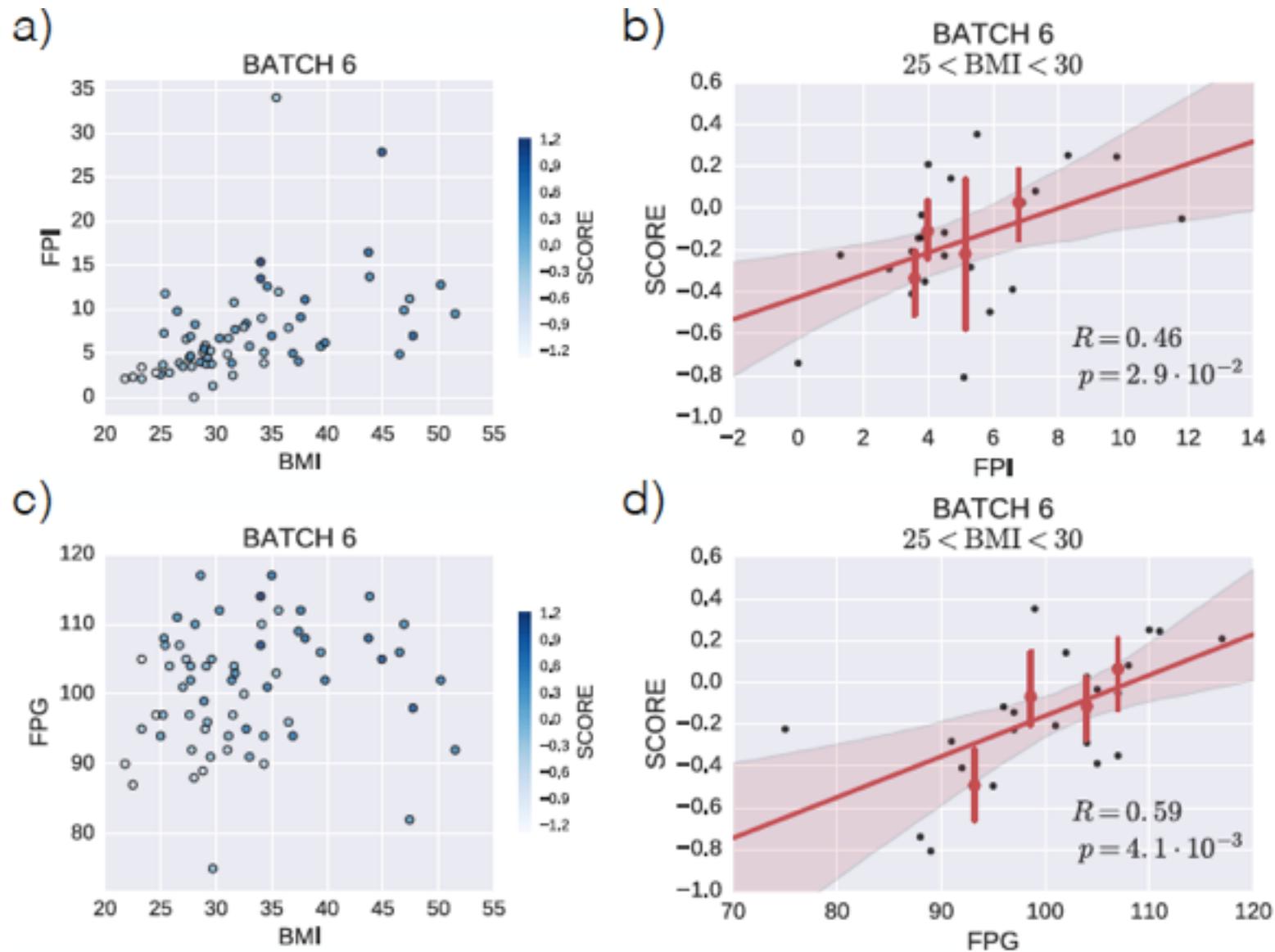
PATHWAY DEREGLULATION IN OBESITY



PATHWAY DEREGULATION IN OBESITY AND CANCER



OBESEITY SCORE AND TYPE II DIABETES

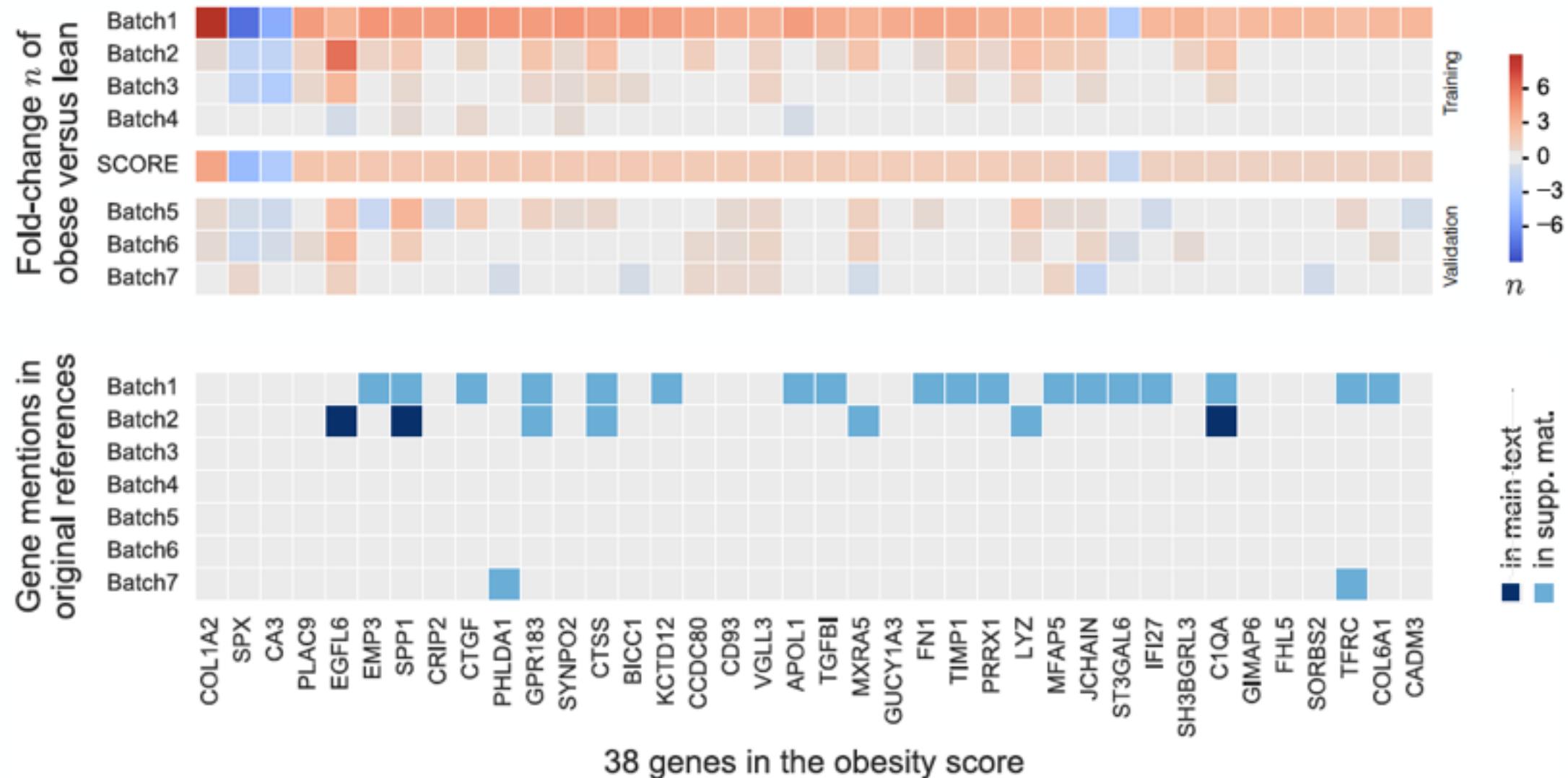


FPI: Fasting plasma insulin

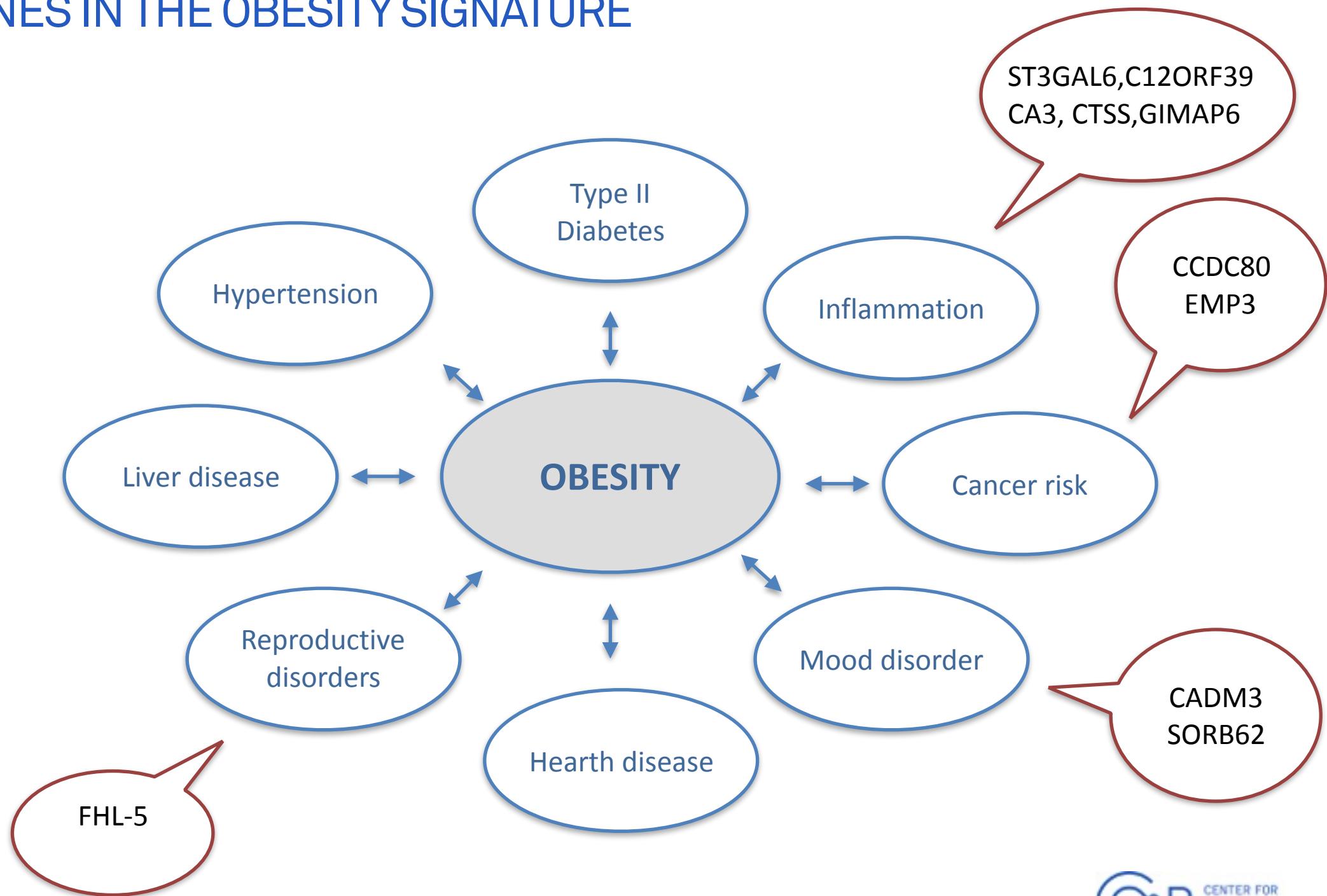
FPG: Fasting plasma glucose

GENES IN THE OBESITY SIGNATURE

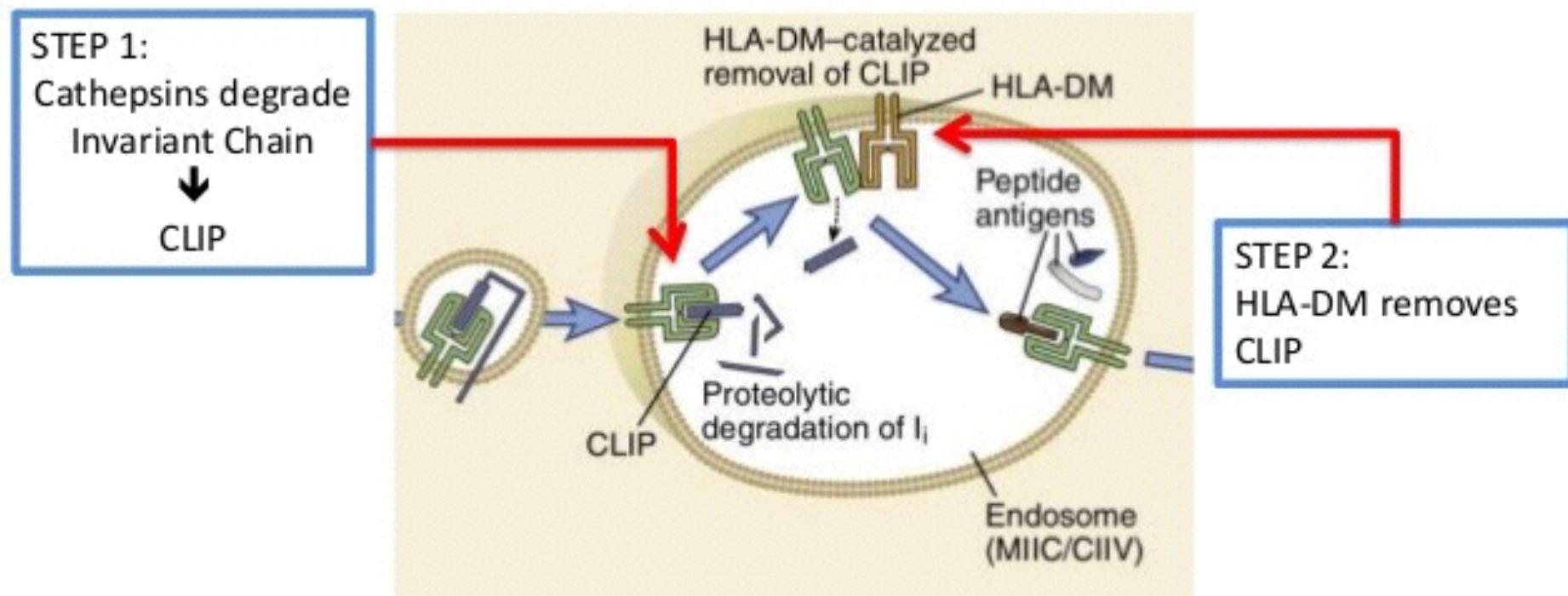
5σ significance (like Higgs boson!)



GENES IN THE OBESITY SIGNATURE



Class II MHC Pathway

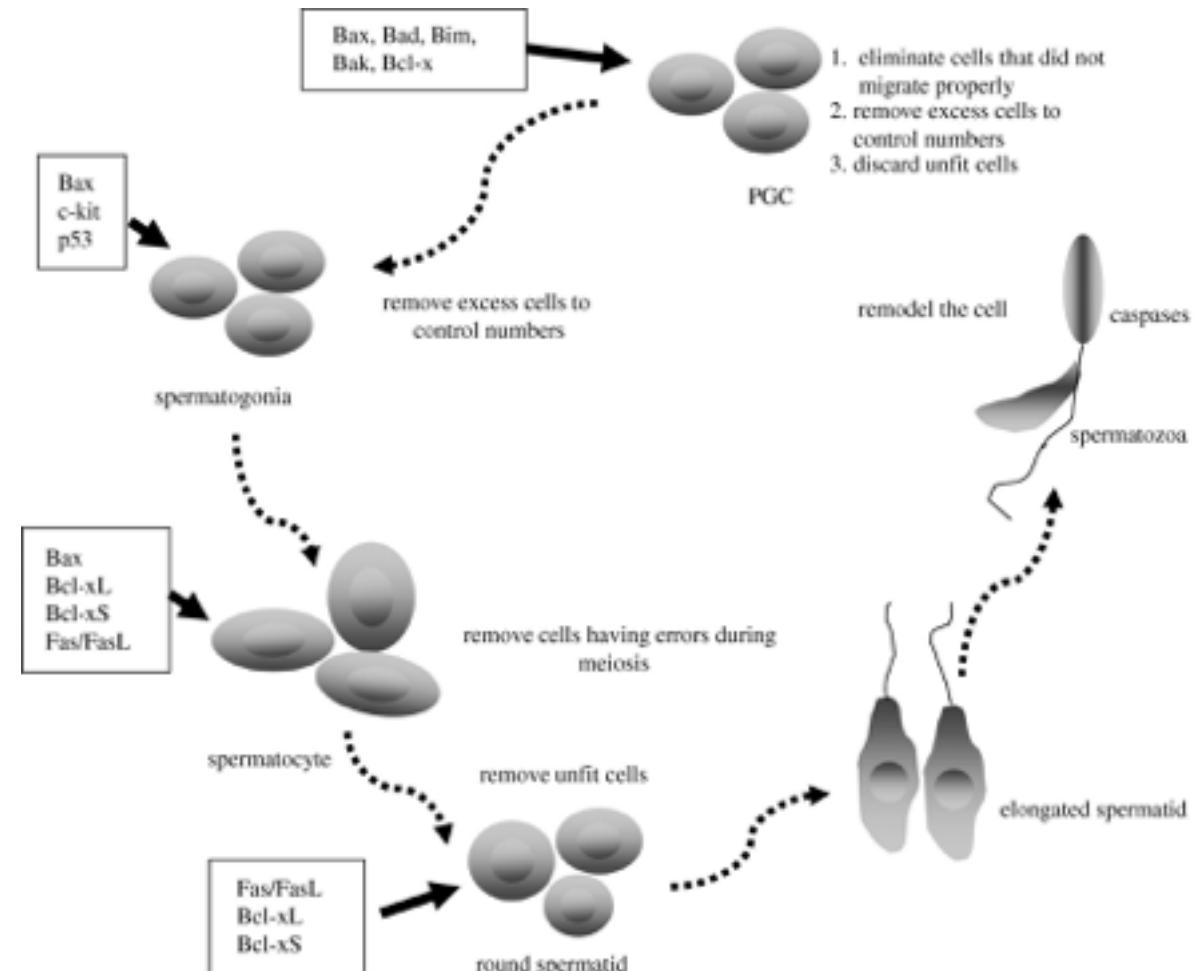
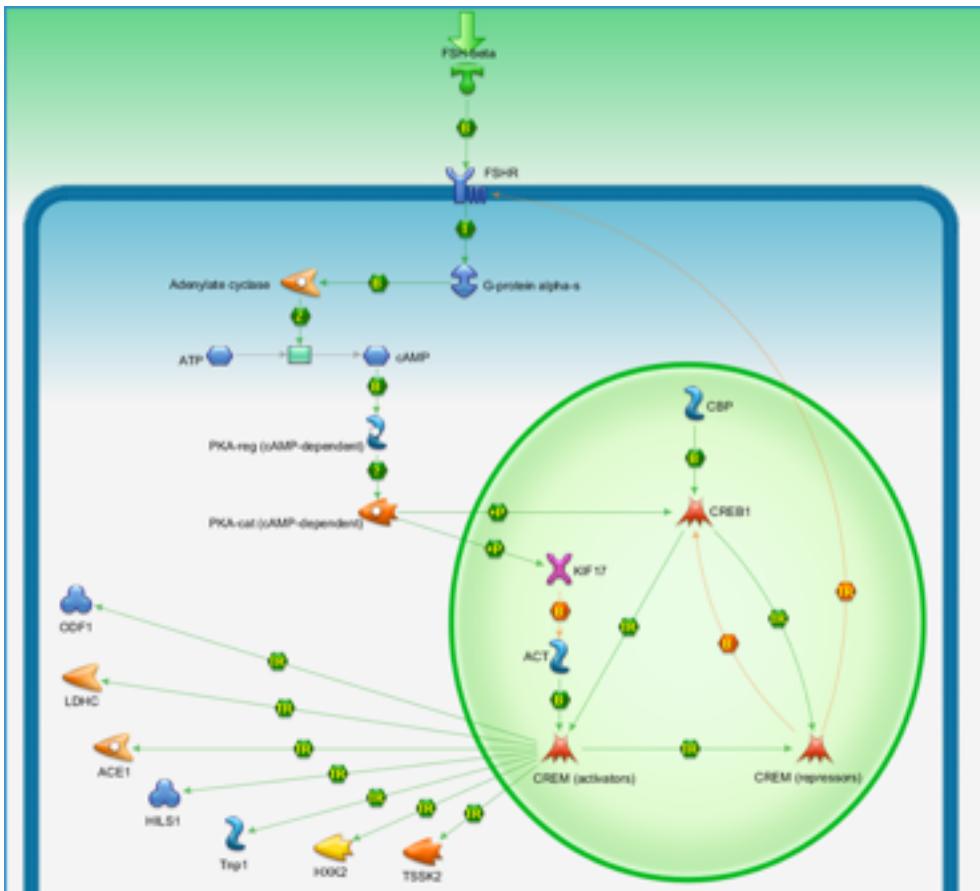


Cellular and Molecular Immunology 8th Ed. (2015) by Abbas et al.

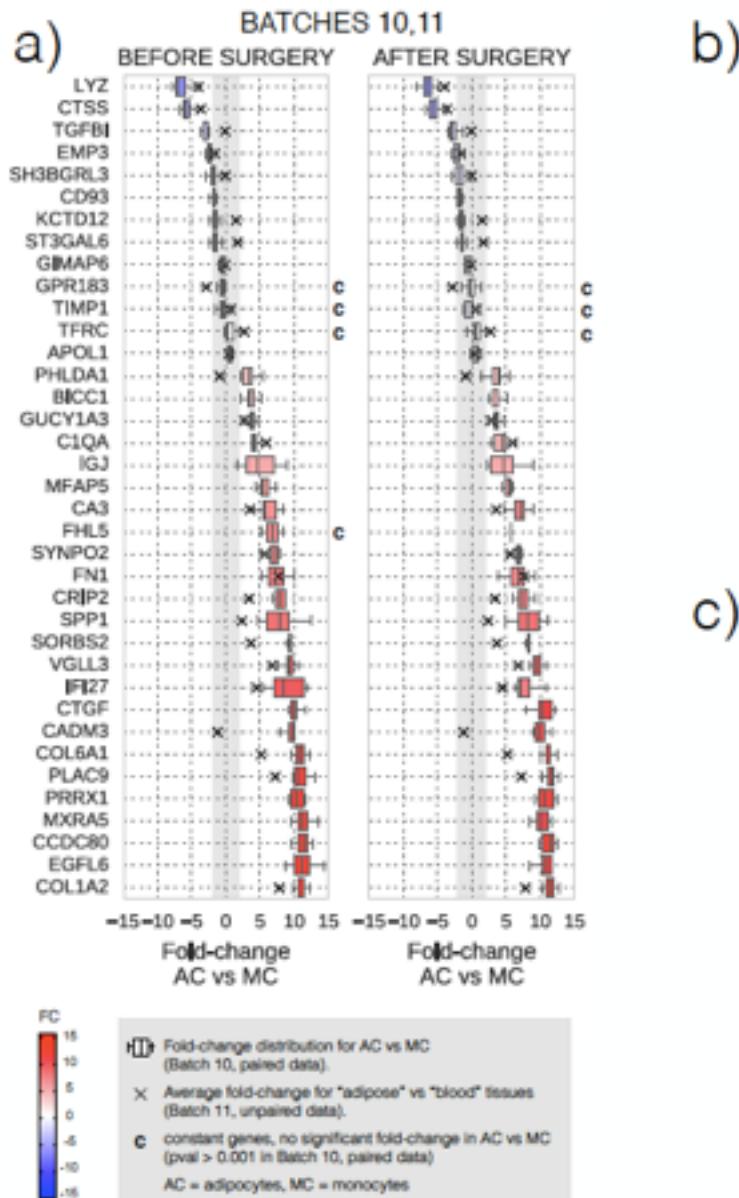
Cathepsins S circulating levels have been found to correlate with BMI and triglycerides

GENES IN THE OBESITY SIGNATURE: FERTILITY

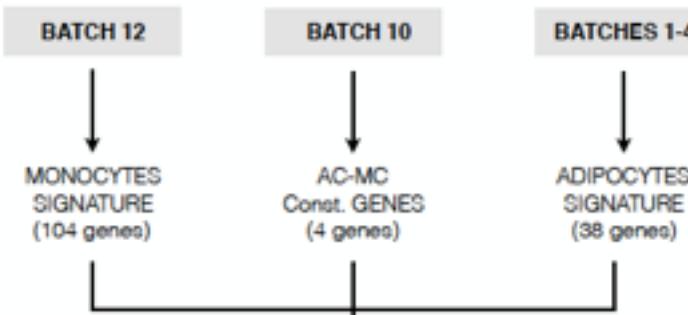
FHL5



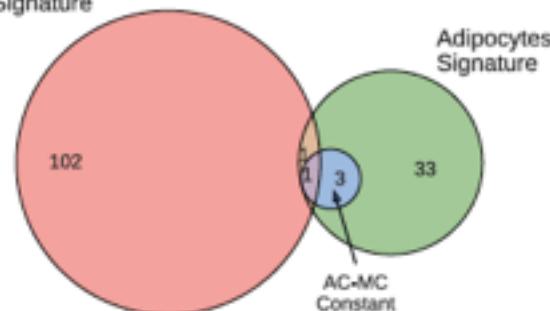
SIGNATURE IN MONOCYTES



b)



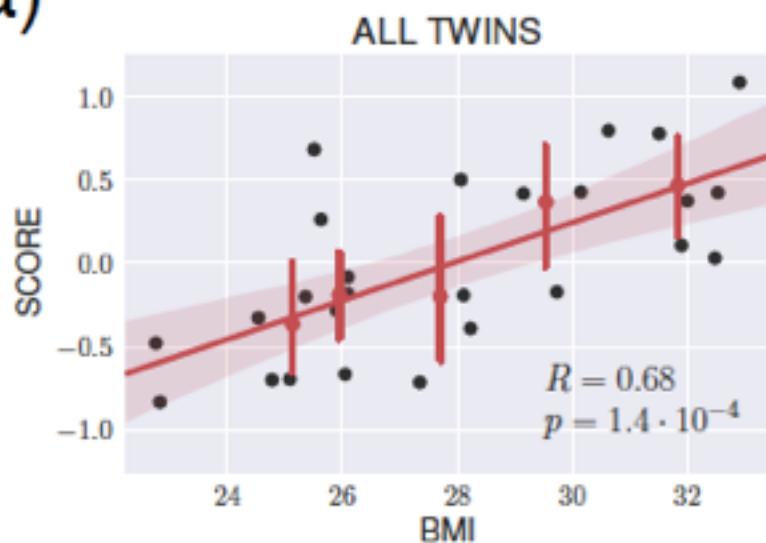
c)



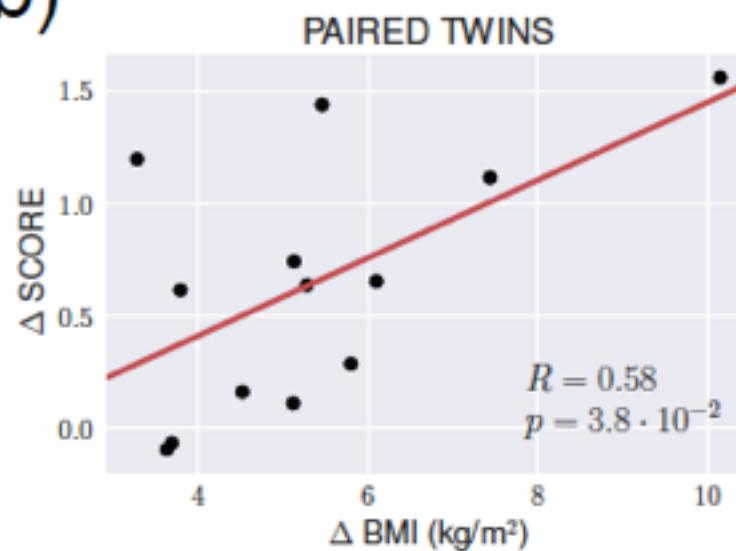
Obesity signatures
are tissue-dependent

IS OBESITY A GENETIC DISEASE?

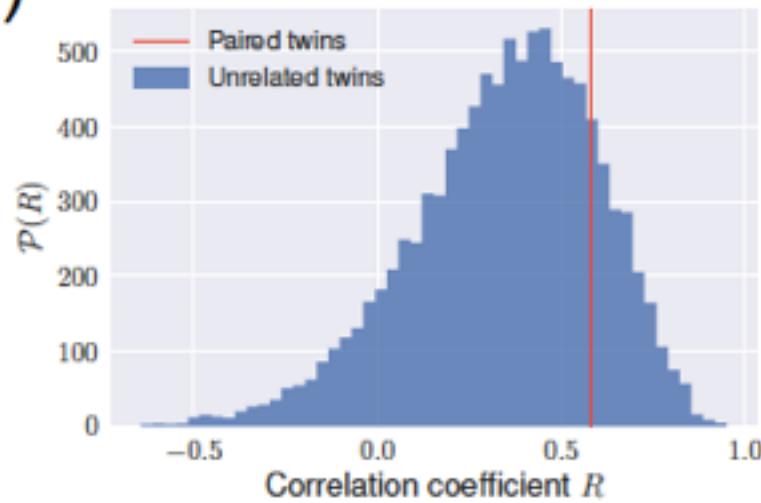
a)



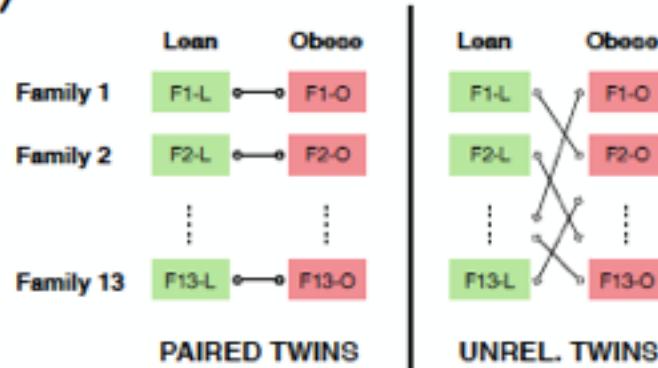
b)



c)



d)



CONCLUSIONS

Obesity is not a gender dependent disease

Genetic causes of obesity are extremely rare

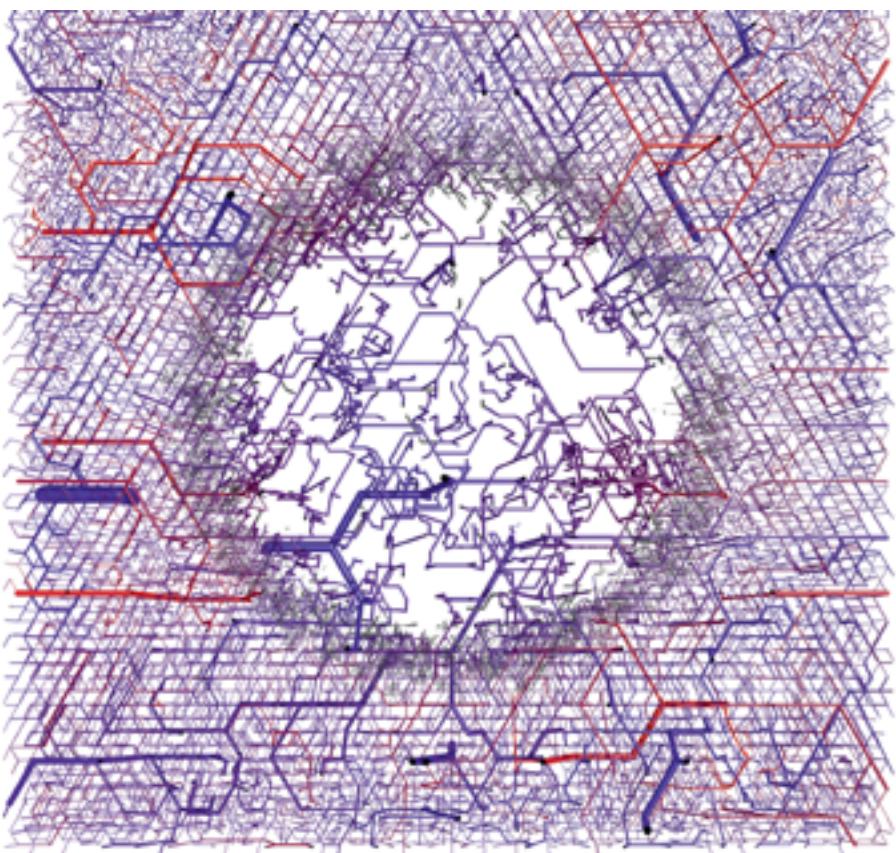
Gene expression data, once properly filtered, help identify a fingerprint of obesity.

Environment and lifestyle are the keys!

THE GROUP

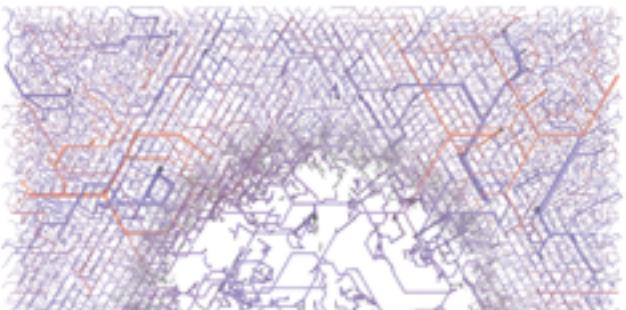


2016-2017



Caterina La Porta and Stefano Zapperi

The Physics of Cancer



Publisher: Cambridge University Press
Publication date: May 2017
ISBN: 9781316271759
DOI: [10.1017/9781316271759](https://doi.org/10.1017/9781316271759)

Thank you for your attention!