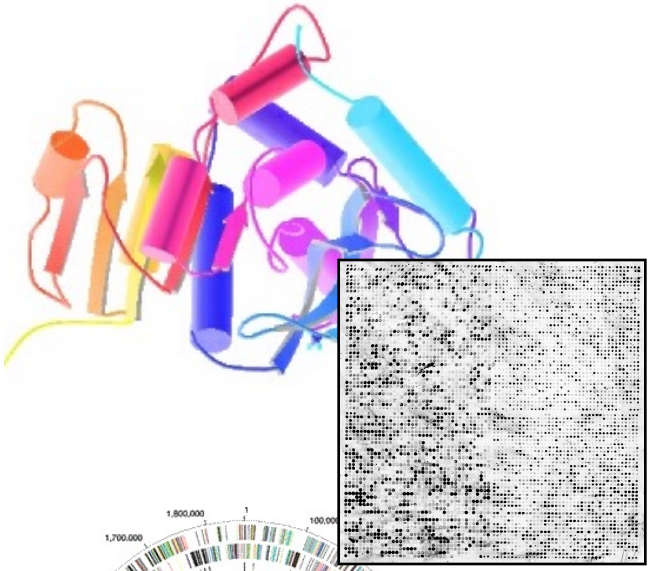
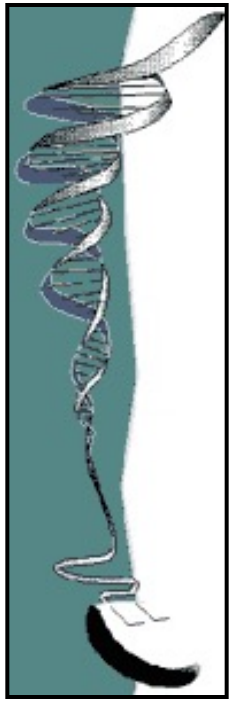
Biomed. Data Science:

Unsupervised Datamining D: SVD Extensions





Mark Gerstein, Yale University

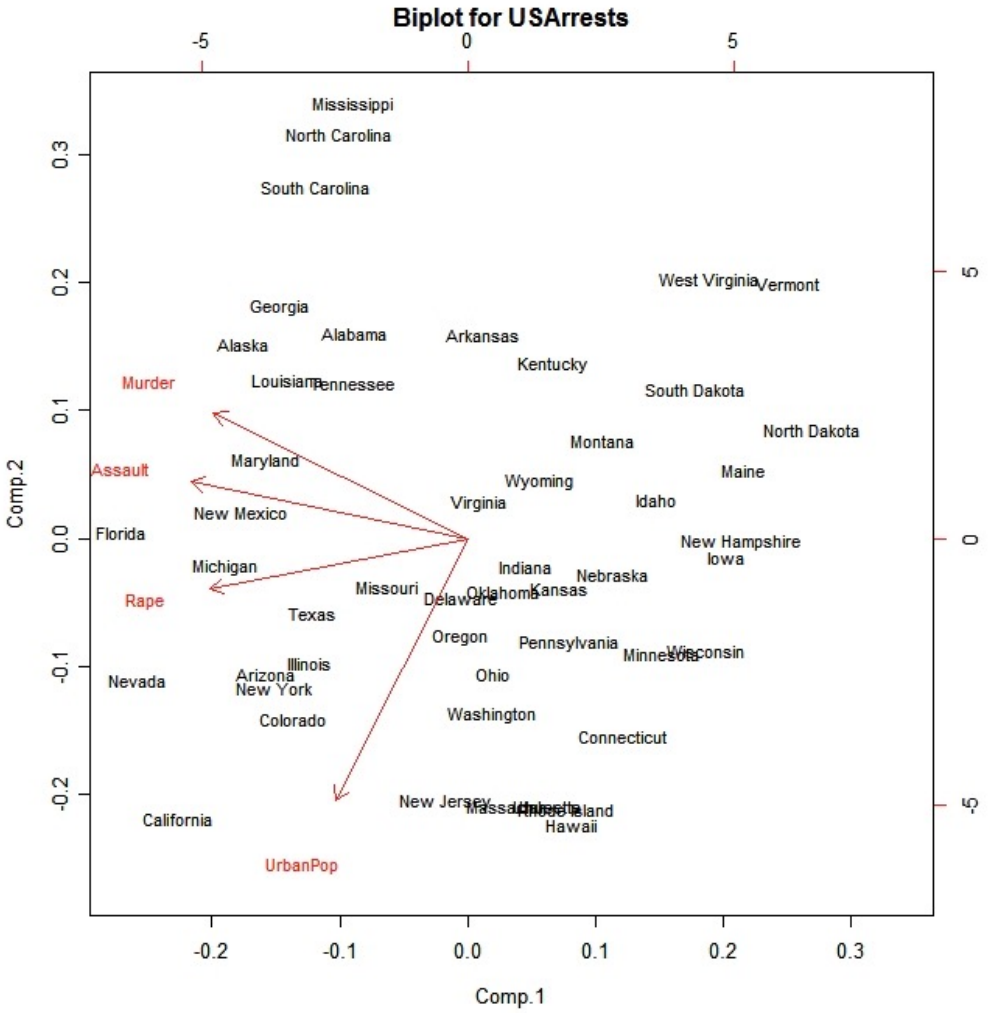
gersteinlab.org/courses/452

(last edit in spring ’21, pack #9d, final)

Unsupervised Mining

Biplot

Introduction



- A biplot is a low-dimensional (usually 2D) representation of a data matrix **A**.
  - A point for each of the *m* observation vectors (rows of **A**)
  - A line (or arrow) for each of the *n* variables (columns of **A**)

PCA

TFs: a, b, c...

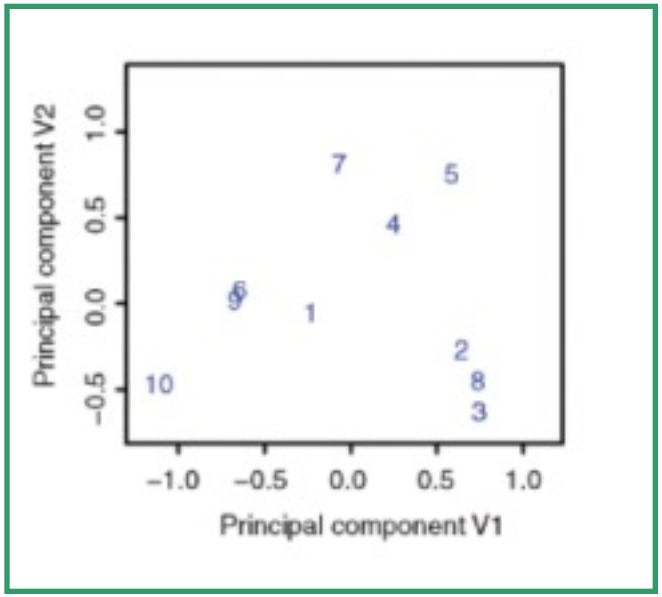
Genomic Sites: 1,2,3...

A

	a	b	c
1	21	16	28
2	14	18	25
3	14	17	22
4	14	19	33
5	17	23	28
6	20	14	34
7	22	21	30
8	15	18	22
9	18	13	36
10	24	10	32

	a	b	c
a	1.00	-0.44	0.48
b	-0.44	1.00	-0.40
c	0.48	-0.40	1.00

A^TA (TF-TF corr.)

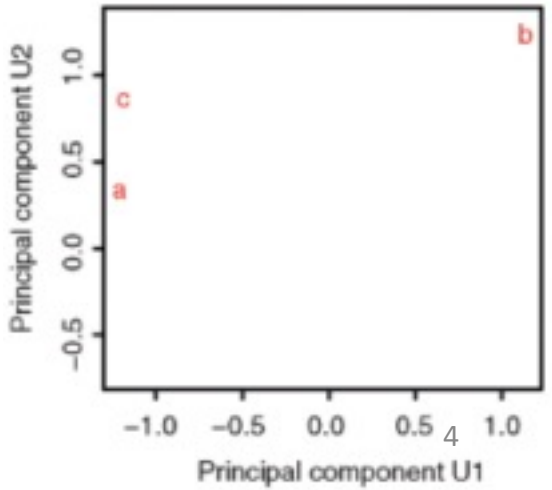


A^T

	1	2	3	4	5	6	7	8	9	10
a	21	14	14	14	17	20	22	15	18	24
b	16	18	17	19	23	14	21	18	13	10
c	28	25	22	33	28	34	30	22	36	32

	1	2	3	4	5	6	7	8	9	10
1	1.00	0.70	0.69	0.77	0.54	0.99	0.95	0.65	0.98	0.97
2	0.70	1.00	1.00	0.99	0.98	0.79	0.89	1.00	0.84	0.50
3	0.69	1.00	1.00	0.99	0.98	0.78	0.89	1.00	0.83	0.49
4	0.77	0.99	0.99	1.00	0.95	0.85	0.94	0.98	0.89	0.59
5	0.54	0.98	0.98	0.95	1.00	0.64	0.78	0.99	0.71	0.31
6	0.99	0.79	0.78	0.85	0.64	1.00	0.98	0.74	1.00	0.93
7	0.95	0.89	0.89	0.94	0.78	0.98	1.00	0.86	0.99	0.84
8	0.65	1.00	1.00	0.98	0.99	0.74	0.86	1.00	0.80	0.43
9	0.98	0.84	0.83	0.89	0.71	1.00	0.99	0.80	1.00	0.89
10	0.97	0.50	0.49	0.59	0.31	0.93	0.84	0.43	0.89	1.00

AA^T (site-site correlation)



Biplot to Show Overall Relationship of TFs & Sites

TFs: a, b, c...

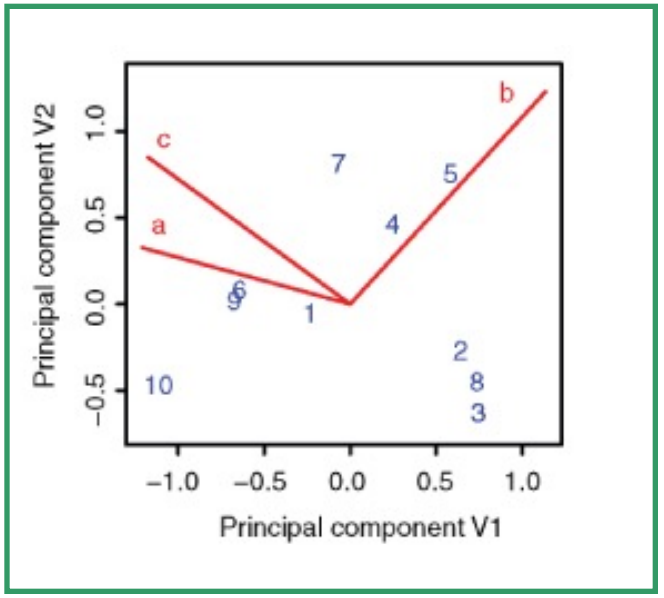
Genomic Sites: 1,2,3...

$A=USV^T$

	a	b	c
1	21	16	28
2	14	18	25
3	14	17	22
4	14	19	33
5	17	23	28
6	20	14	34
7	22	21	30
8	15	18	22
9	18	13	36
10	24	10	32

	a	b	c
a	1.00	-0.44	0.48
b	-0.44	1.00	-0.40
c	0.48	-0.40	1.00

A^TA (TF-TF corr.)

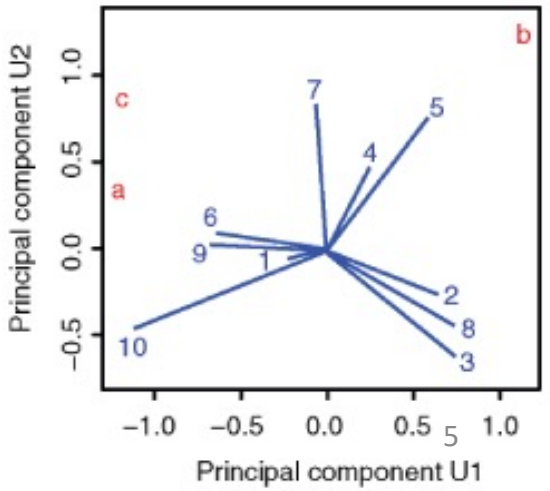


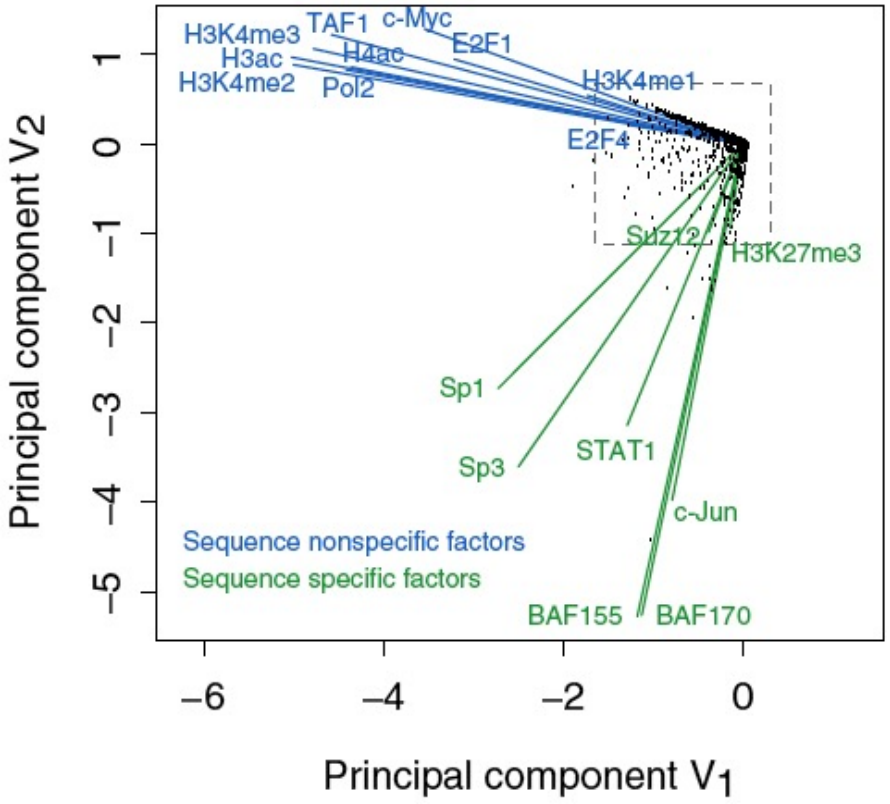
A^T

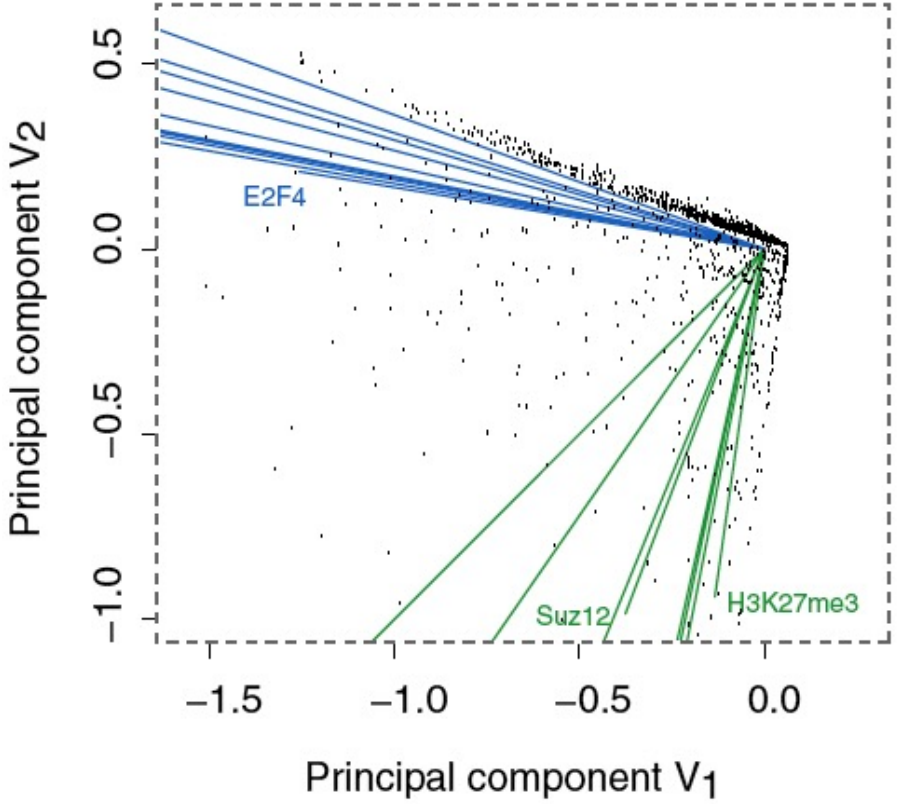
	1	2	3	4	5	6	7	8	9	10
a	21	14	14	14	17	20	22	15	18	24
b	16	18	17	19	23	14	21	18	13	10
c	28	25	22	33	28	34	30	22	36	32

	1	2	3	4	5	6	7	8	9	10
1	1.00	0.70	0.69	0.77	0.54	0.99	0.95	0.65	0.98	0.97
2	0.70	1.00	1.00	0.99	0.98	0.79	0.89	1.00	0.84	0.50
3	0.69	1.00	1.00	0.99	0.98	0.78	0.89	1.00	0.83	0.49
4	0.77	0.99	0.99	1.00	0.95	0.85	0.94	0.98	0.89	0.59
5	0.54	0.98	0.98	0.95	1.00	0.64	0.78	0.99	0.71	0.31
6	0.99	0.79	0.78	0.85	0.64	1.00	0.98	0.74	1.00	0.93
7	0.95	0.89	0.89	0.94	0.78	0.98	1.00	0.86	0.99	0.84
8	0.65	1.00	1.00	0.98	0.99	0.74	0.86	1.00	0.80	0.43
9	0.98	0.84	0.83	0.89	0.71	1.00	0.99	0.80	1.00	0.89
10	0.97	0.50	0.49	0.59	0.31	0.93	0.84	0.43	0.89	1.00

AA^T (site-site correlation)



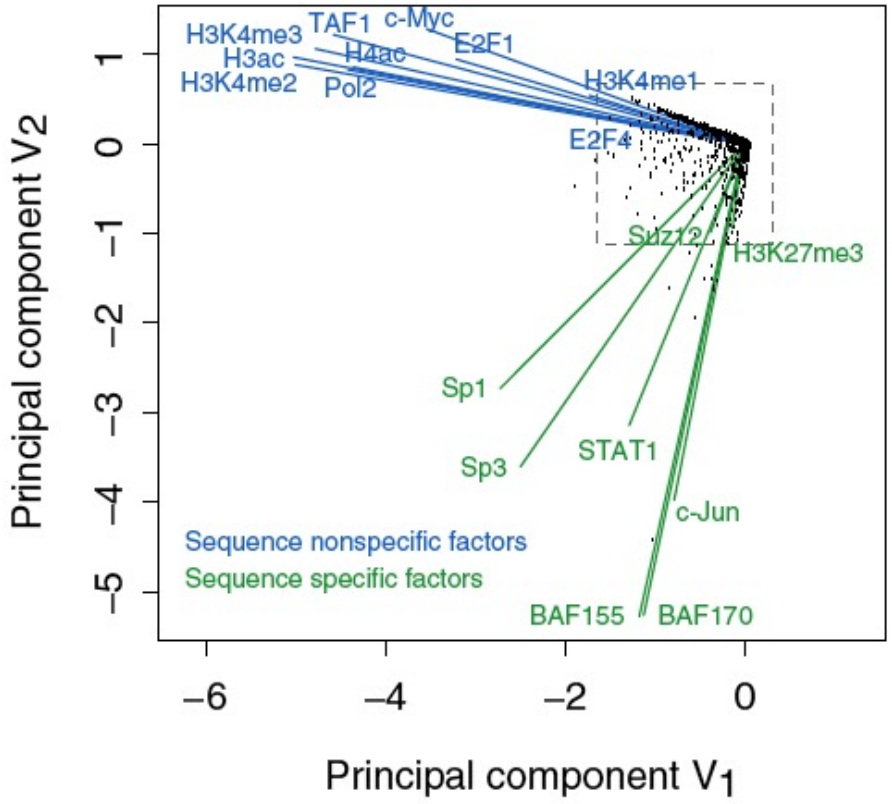


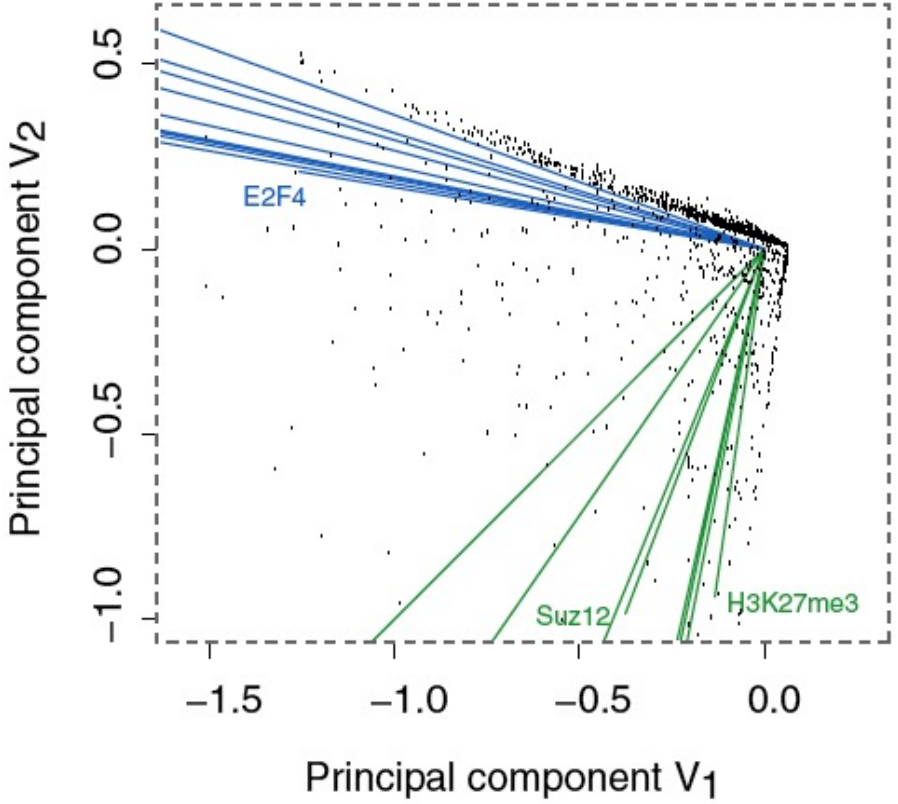


Results of Biplot

- Pilot ENCODE (1% genome): 5996 10 kb genomic bins (adding all hits) + 105 TF experiments → biplot
- Angle between TF vectors shows relation b/w factors
- Closeness of points gives clustering of "sites"
- Projection of site onto vector gives degree to which site is assoc. with a particular factor

Zhang et al. (2007) Gen. Res.





Results of Biplot

- Biplot groups TFs into sequence-specific and sequence-nonspecific clusters.
  - c-Myc may behave more like a sequence-nonspecific TF.
  - H3K27me3 functions in a transcriptional regulatory process in a rather sequence-specific manner.
- Genomic Bins are associated with different TFs and in this fashion each bin is "annotated" by closest TF cluster

Zhang et al. (2007) Gen. Res.

Unsupervised Mining

RCA

What is RCA?

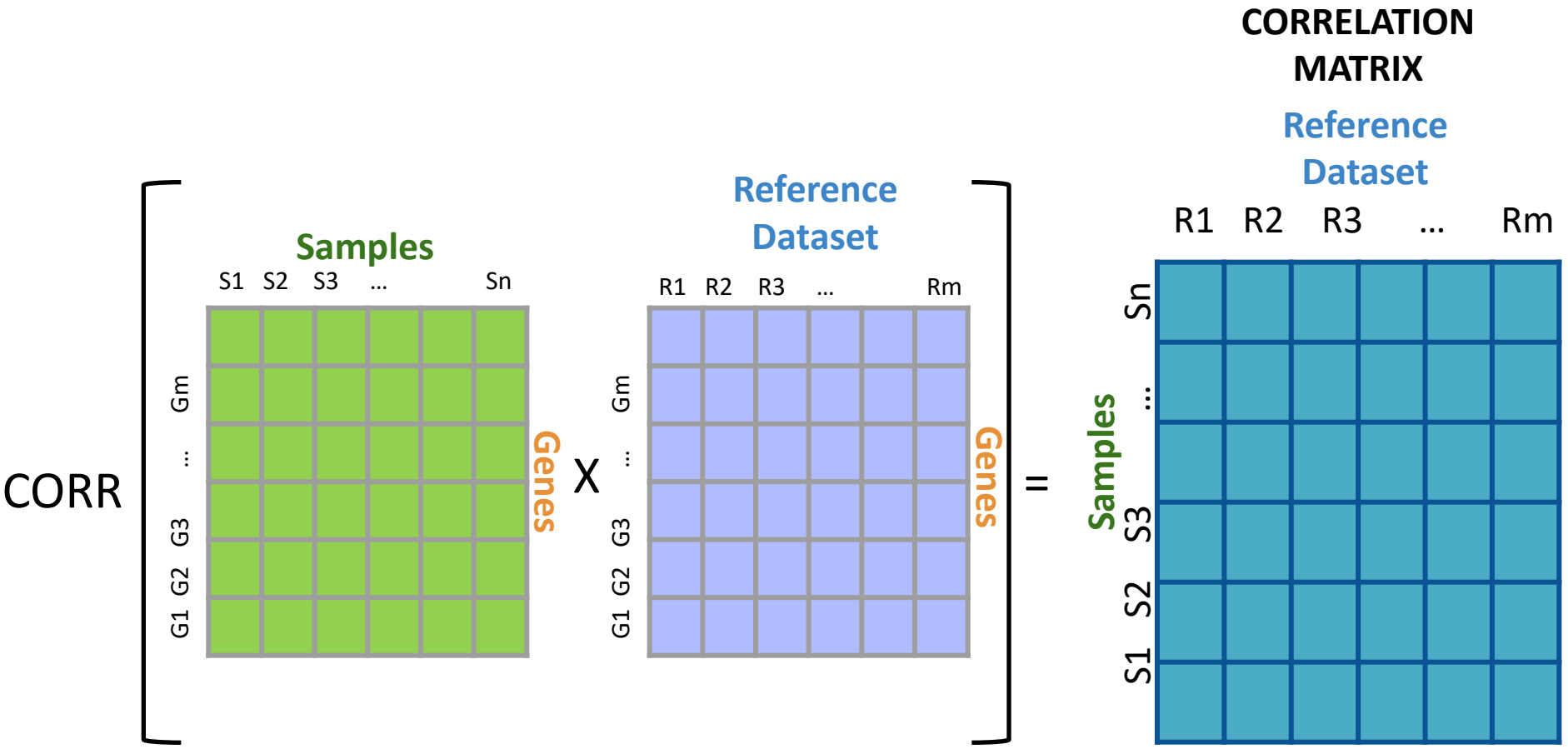
- RCA stands for **Reference** Component Analysis

- RCA is an algorithm that expands the standard PCA to address noisy data:
  - Batch effect
  - Low signal to noise datasets

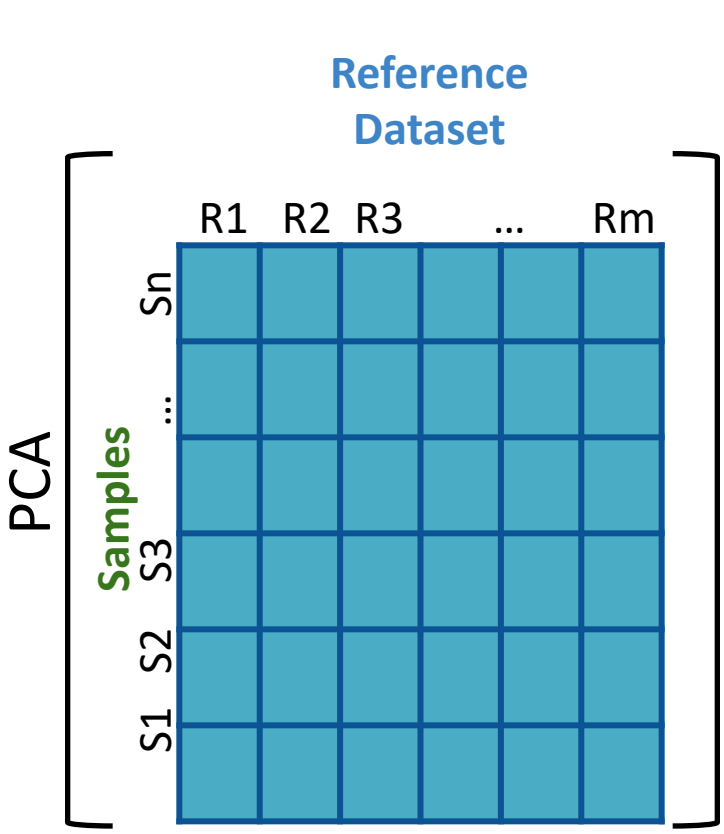
- It is still an unsupervised clustering method but, RCA adds external information to address noisy data:
  - Instead of projecting the original data into new axis
  - It first correlates the original data to a reference panel
  - And then, performs PCA on the correlations

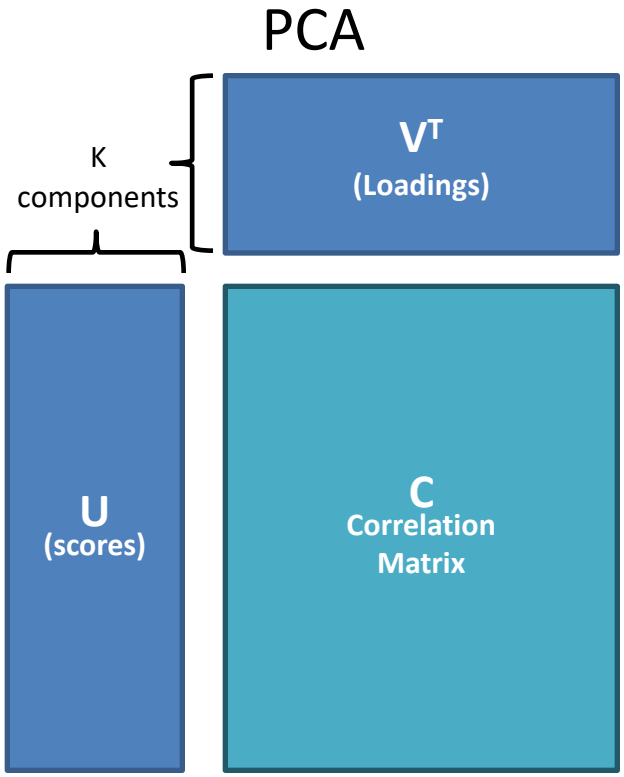
- In single-cell or bulk RNA-seq

Projection to external dataset

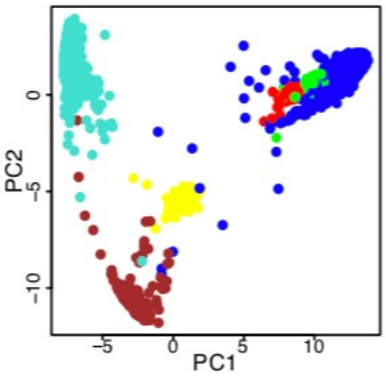


PCA on correlation matrix

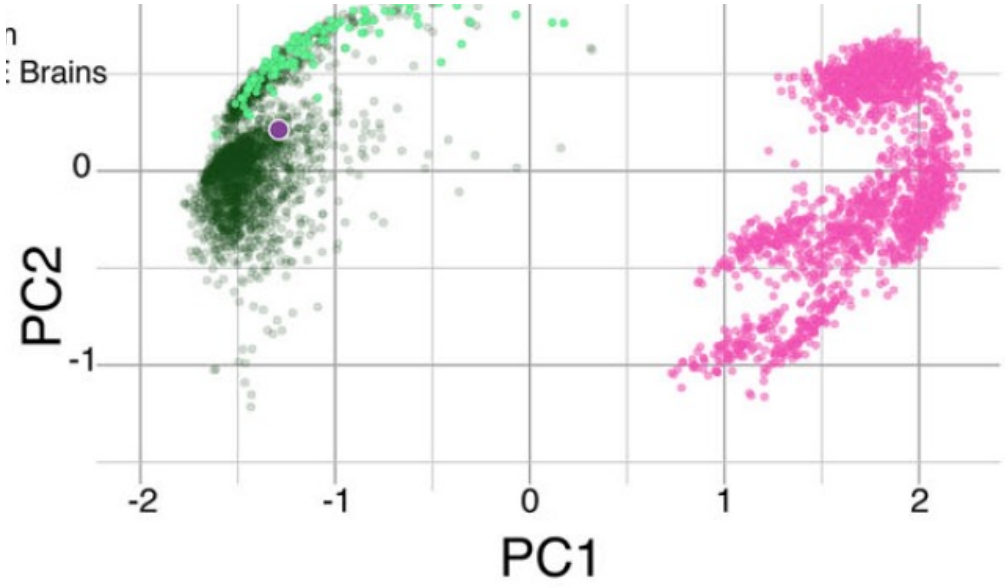




$C = U * V^T$



Placing
Brain expression data from psychencode in context of all other Body Tissues (expression from GTEx)



[Wang et al. (‘18) Science]

Unsupervised Mining

CCA

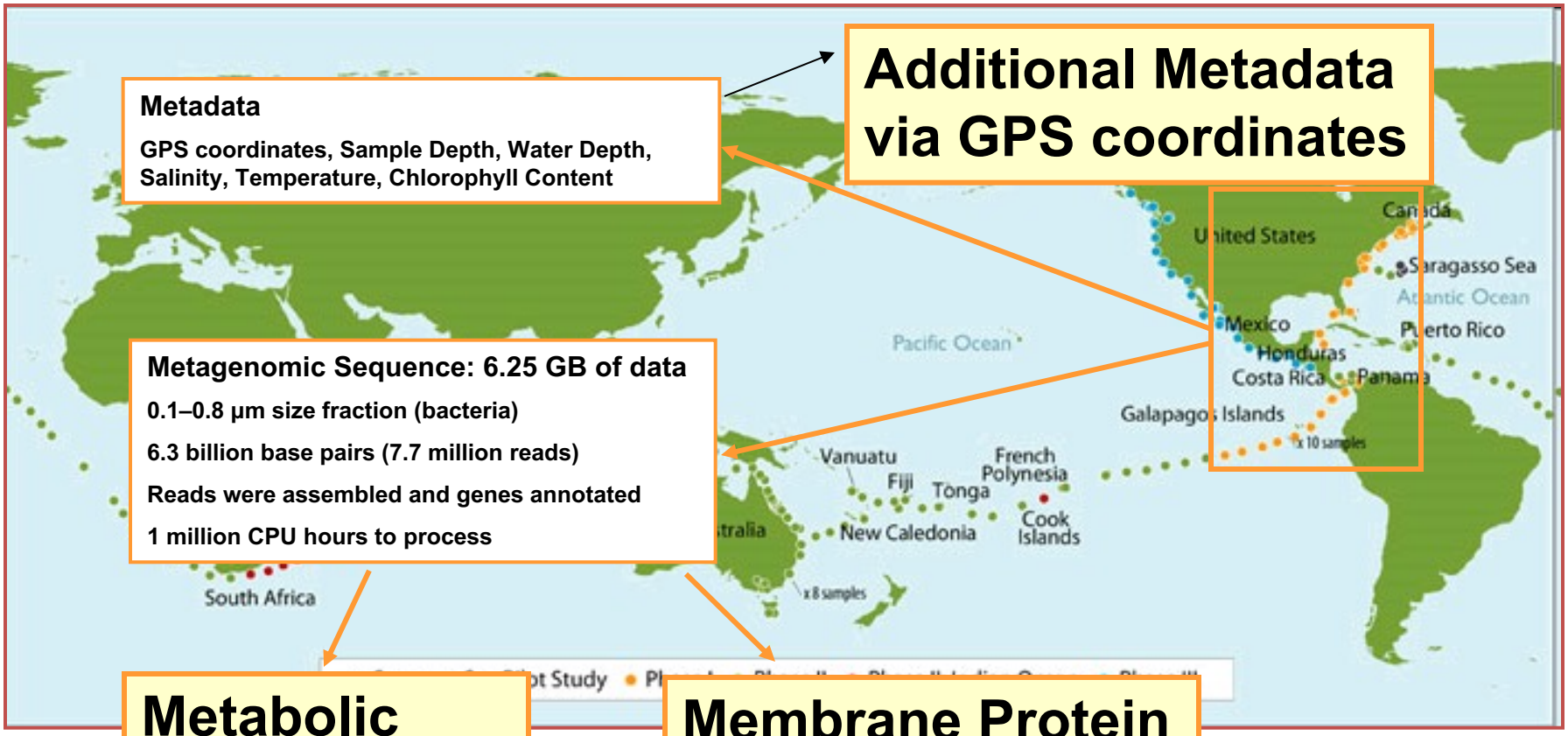
Sorcerer II Global Ocean Survey

***Sorcerer II* journey August 2003- January 2006**

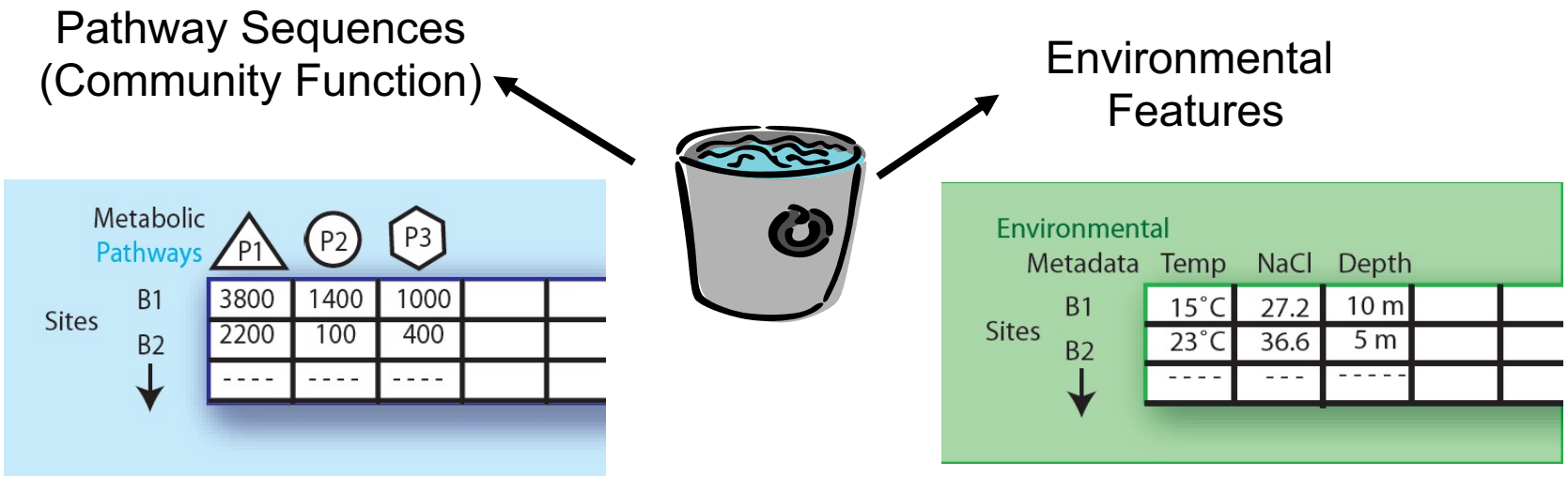
Sample approximately every 200 miles

Rusch, et al., *PLOS Biology* 2007

Sorcerer II Global Ocean Survey



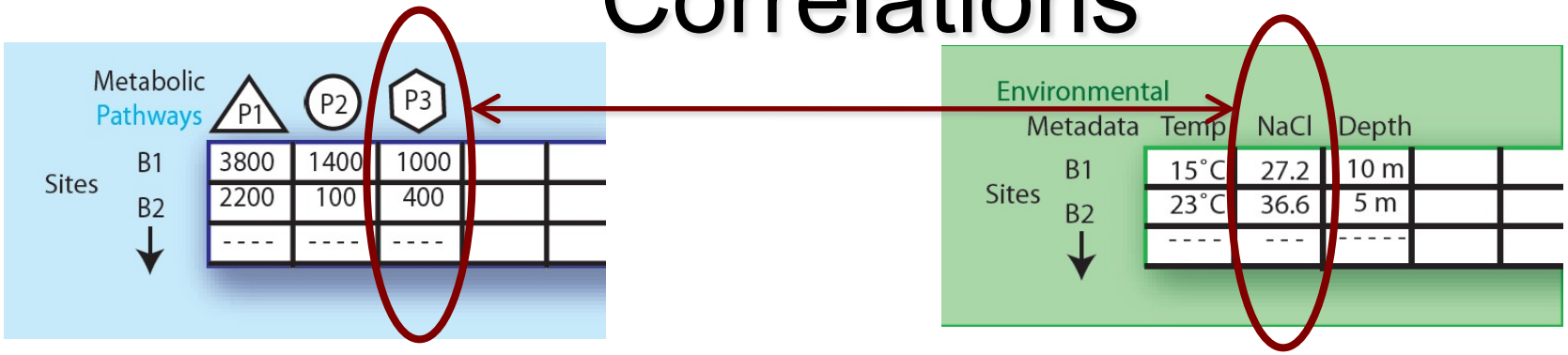
Rusch, et al., *PLOS Biology* 2007

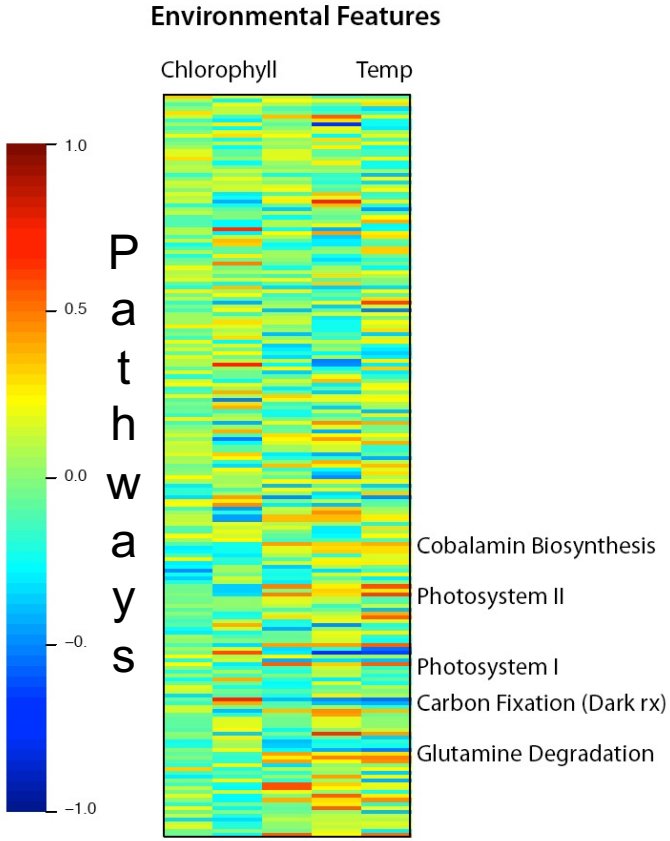


Expressing data as matrices indexed by site, env. var., and pathway usage

[Rusch et. al., (2007) PLOS Biology;
Gianoulis et al., PNAS (in press, 2009]

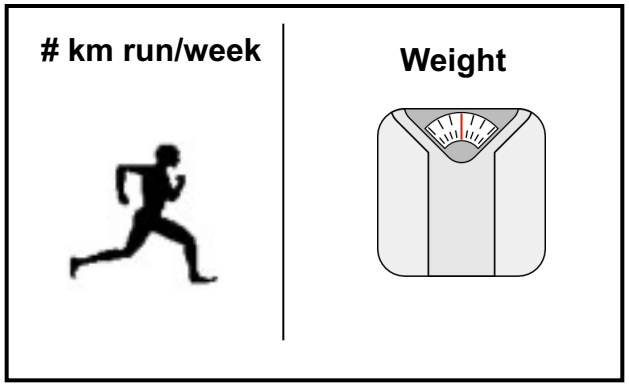
Simple Relationships: Pairwise Correlations

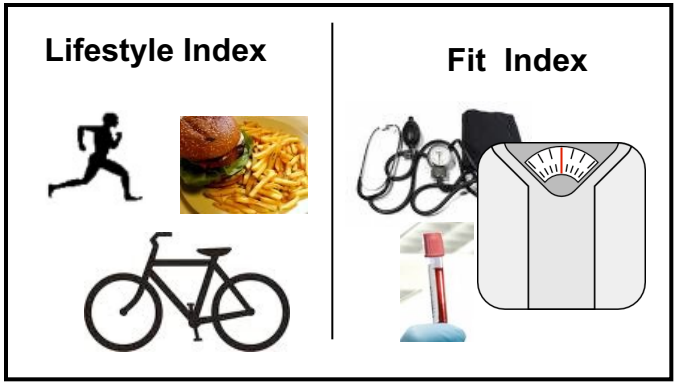




[Gianoulis et al., PNAS (in press, 2009)]

Canonical Correlation Analysis: Simultaneous weighting

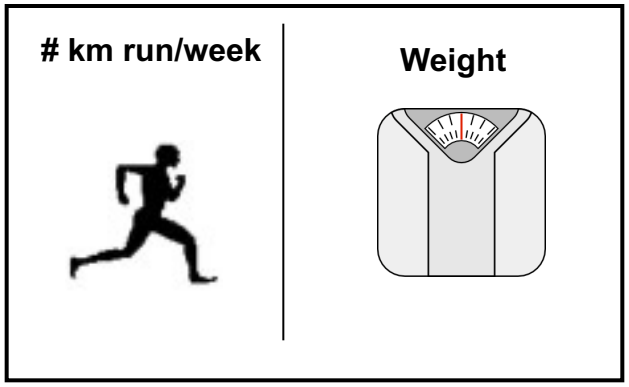


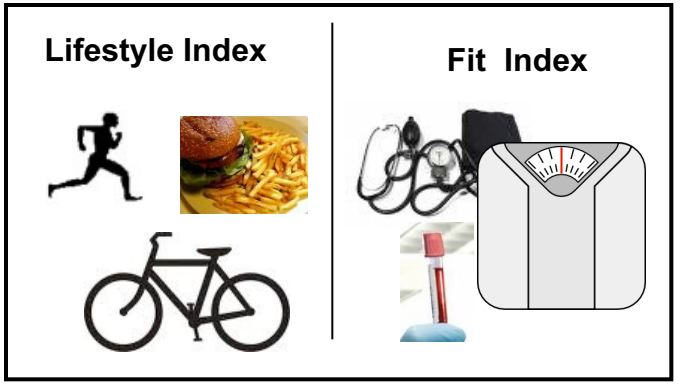


Lifestyle Index = a  +b  + c 

Fit Index = a  + b  +c 

Canonical Correlation Analysis: Simultaneous weighting



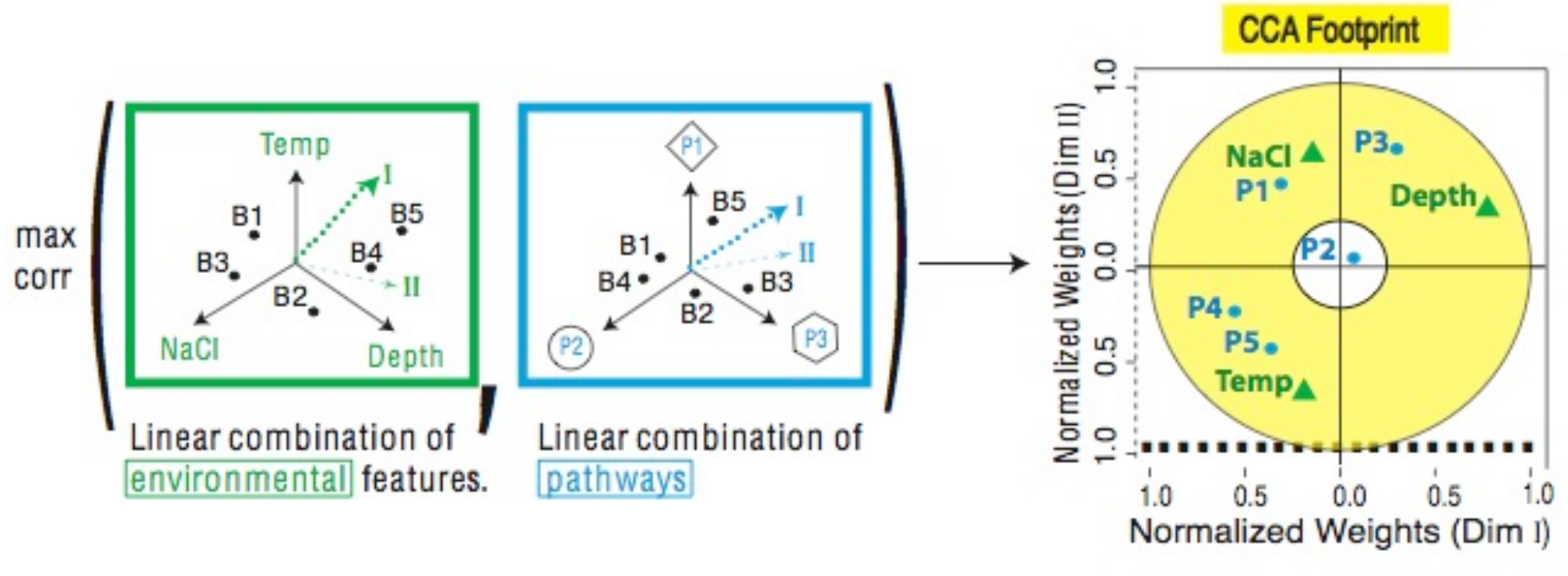


Life

Fit

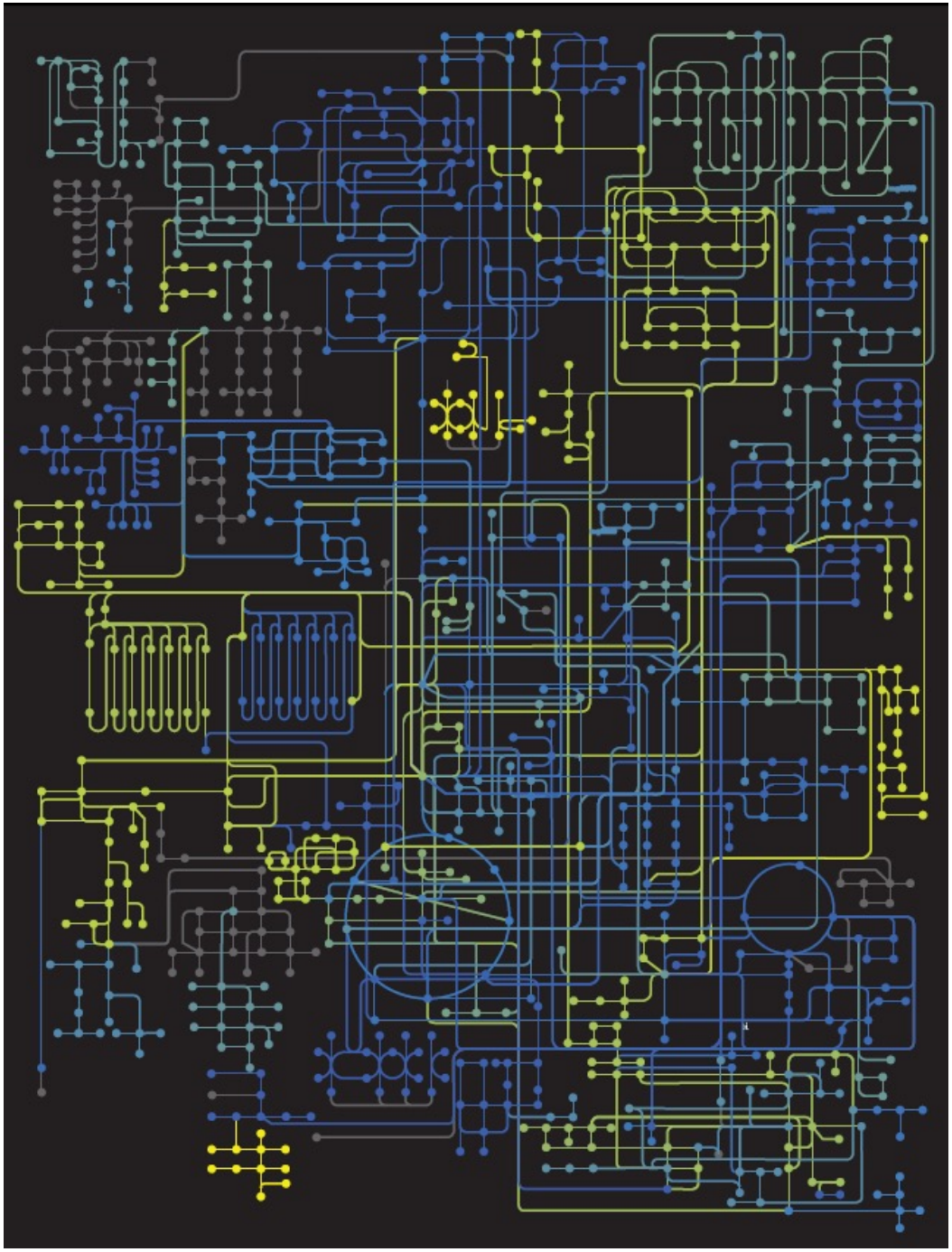
Environmental Features	Metabolic Pathways/ Protein Families
Temp etc	Photosynthesis etc
Chlorophyll	Lipid Metabolism

CCA: Finding Variables with Large Projections in "Correlation Circle"

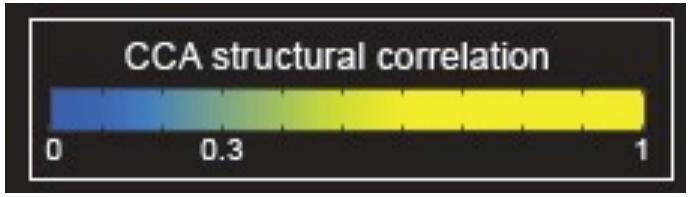


The goal of this technique is to interpret cross-variance matrices
We do this by defining a change of basis.

Gianoulis et al., PNAS 2009

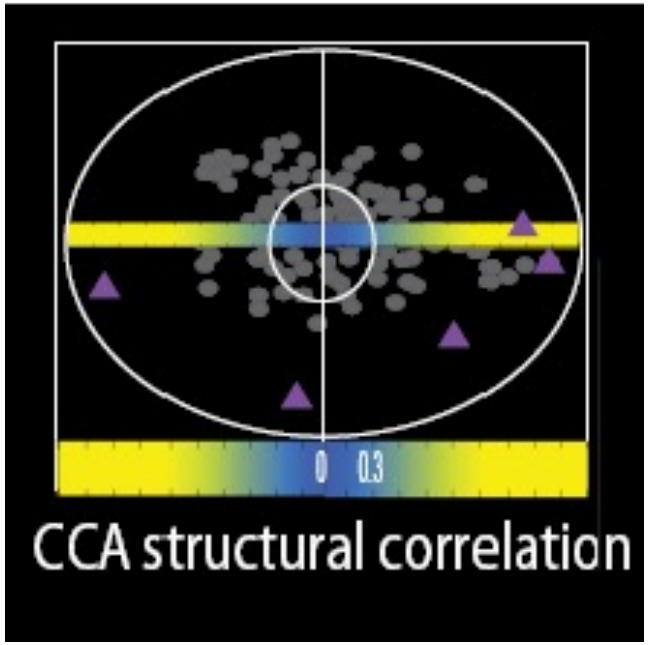


Strength of Pathway co-variation with environment



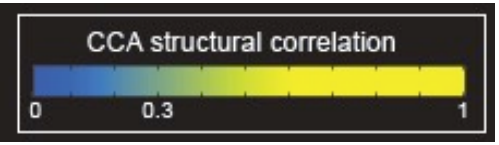
Environmentally invariant

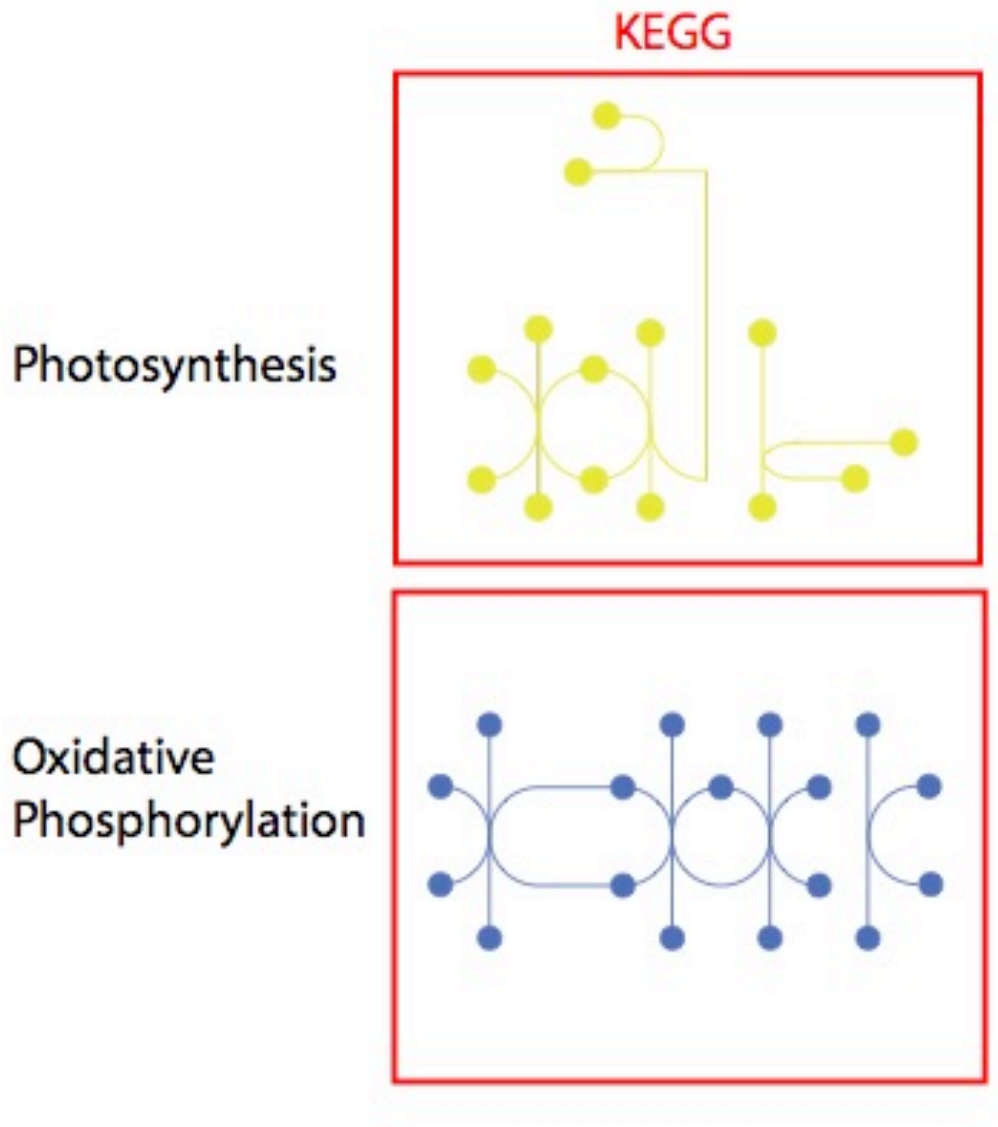
Environmentally variant



Gianoulis et al., *PNAS* 2009

Conclusion #1: energy conversion strategy, temp and depth





Gianoulis et al., *PNAS* 2009