Integrating *Tara* Oceans data sets using Multiple Kernel Learning

Jérôme Mariette* and Nathalie Villa-Vialaneix

NETBIO 2017

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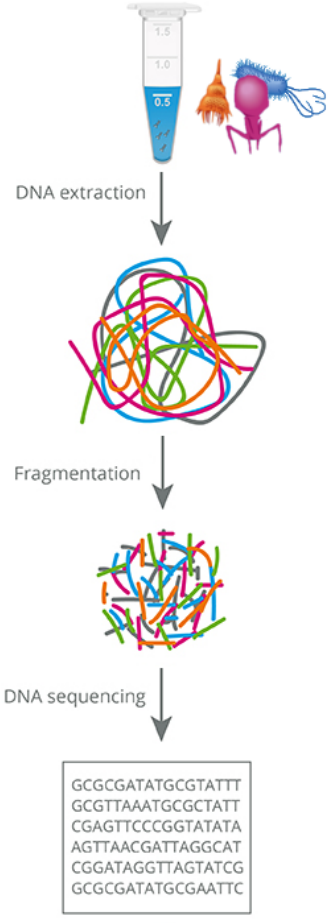
What are metagenomic data?



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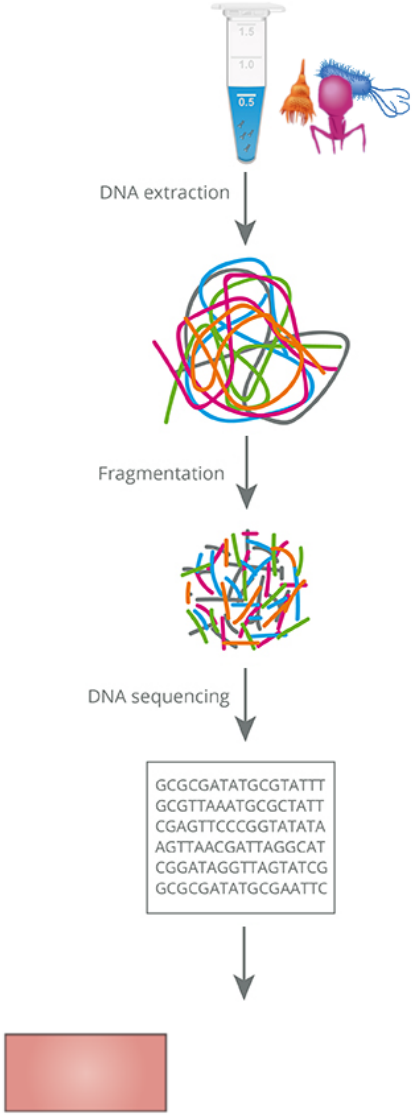

Heterogeneous types

- Abundance data: sparse $n \times p$-matrices with count data of samples in rows and descriptors (species, OTUs, KEGG groups, k-mer, ...) in columns.

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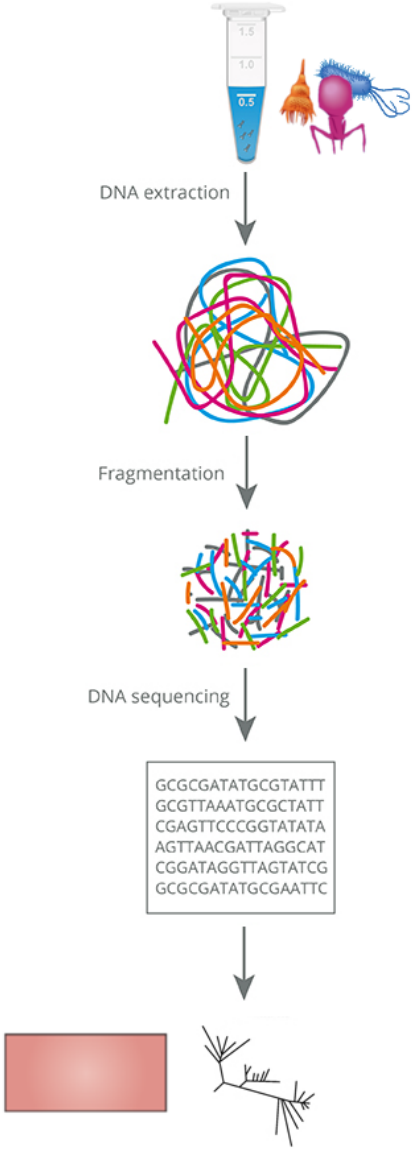

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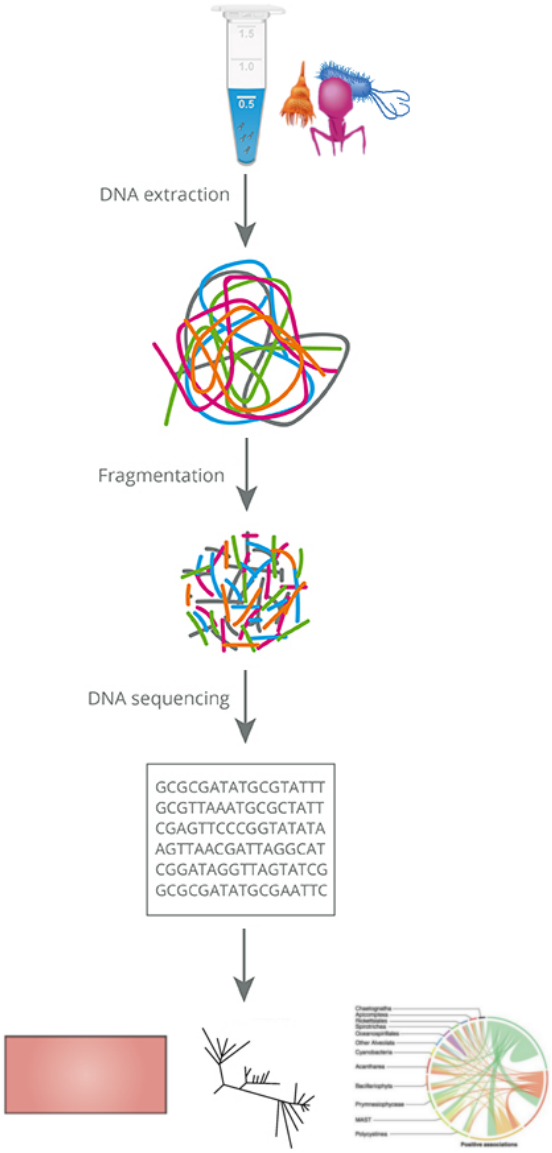

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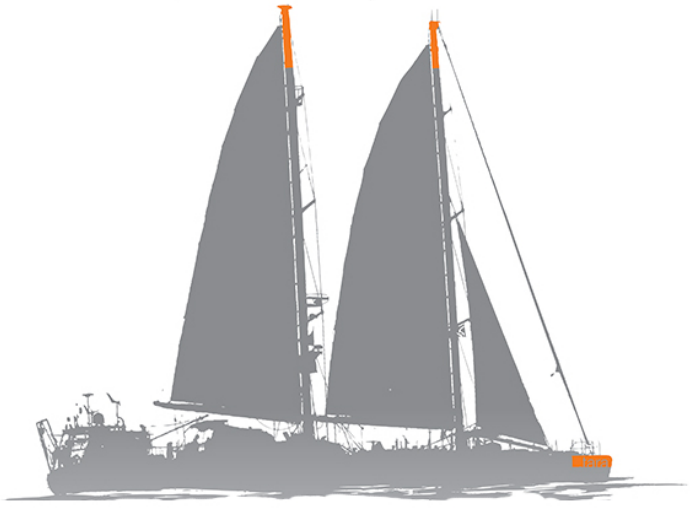
- Co-occurence graph: a p nodes graph.
- ...

TARA Oceans expedition



TARA OCEANS

EXPEDITIONS
www.taraexpeditions.org

The 2009-2013 expedition

- Co-directed by Étienne Bourgois and Éric Karsenti.
- 7,012 datasets collected from 35,000 samples of plankton and water (11,535 Gb of data).
- Study of plankton: bacteria, protists, metazoans and viruses representing more than 90% of the biomass in the ocean.

TARA Oceans expedition

Science (May 2015) - Studies on:

- eukaryotic plankton diversity [de Vargas et al., 2015],
- ocean viral communities [Brum et al., 2015],
- global plankton interactome [Lima-Mendez et al., 2015],
- global ocean microbiome [Sunagawa et al., 2015],
- ....

→ datasets from different types and different sources analyzed separately.

Background of this talk

Objectives

- Until now: many papers using many methods. No integrated analysis performed.
- What do the datasets reveal if integrated in a single analysis?
- Our purpose: develop a generic method to integrate phylogenetic, taxonomic and functional community composition to environmental factors.

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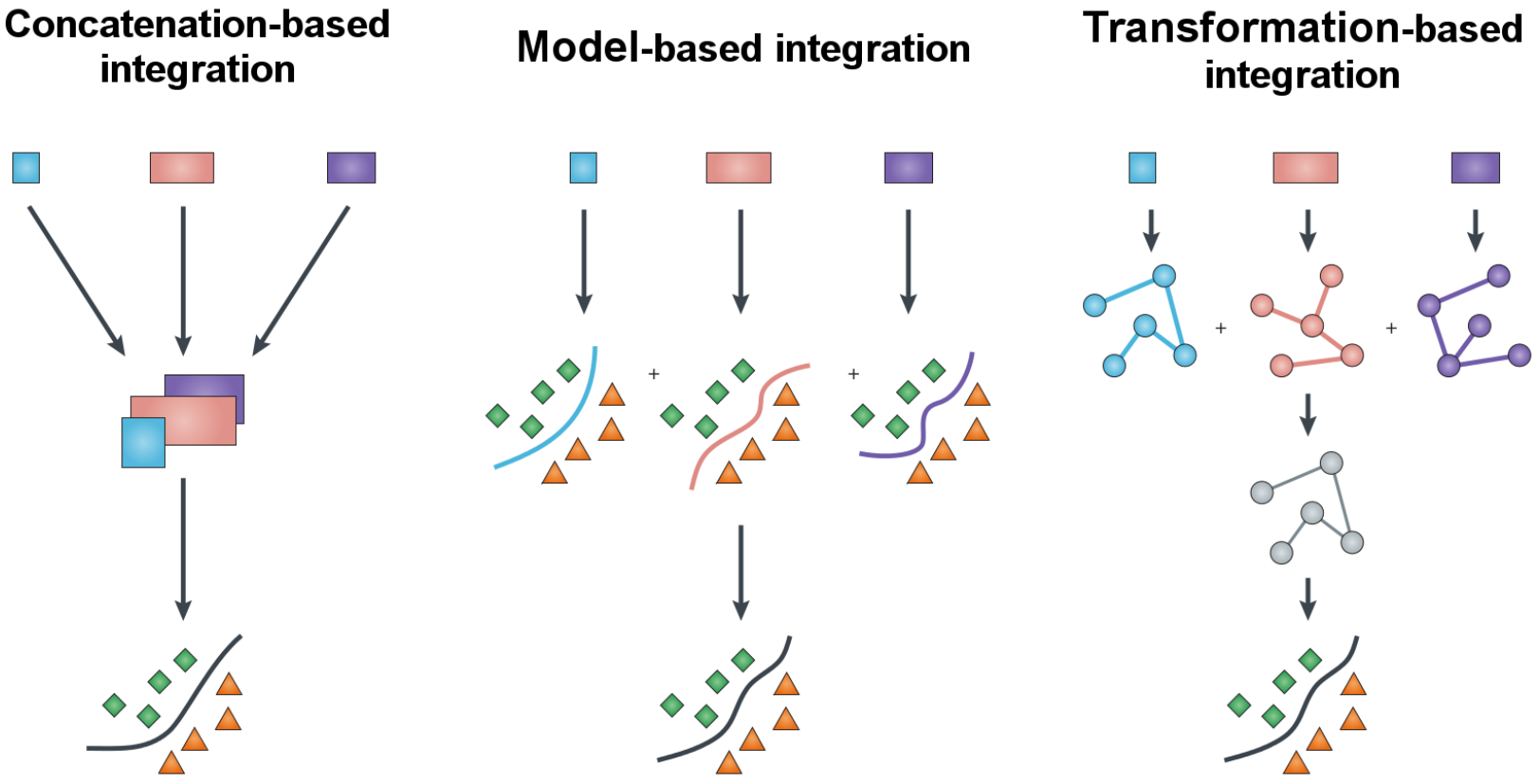
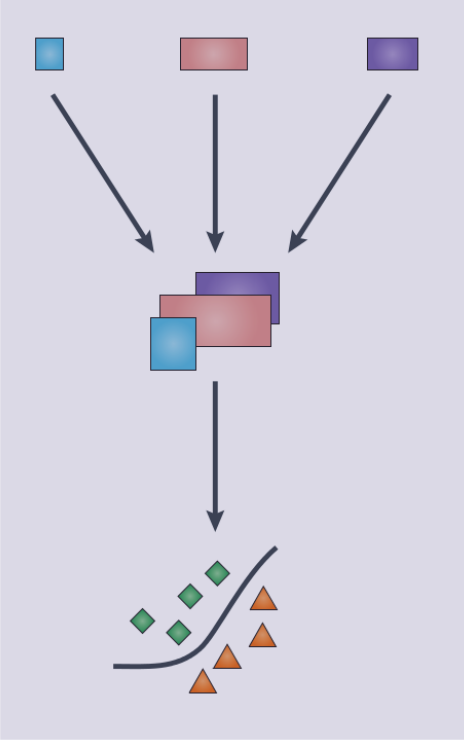


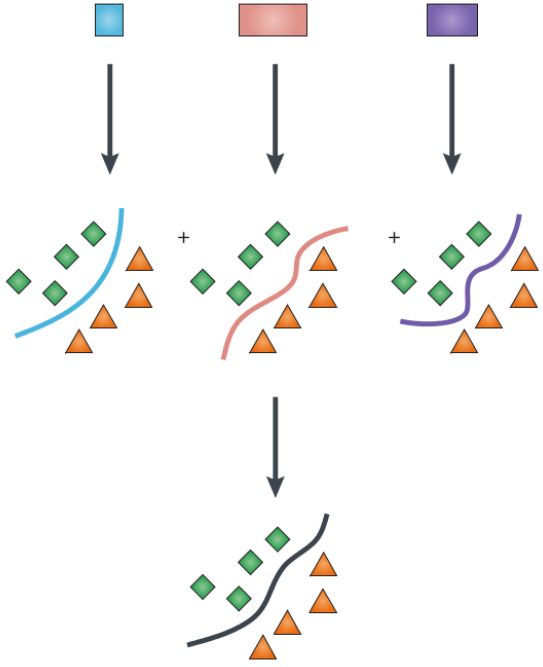
[Ritchie et al., 2015]

Integrating ’omics data

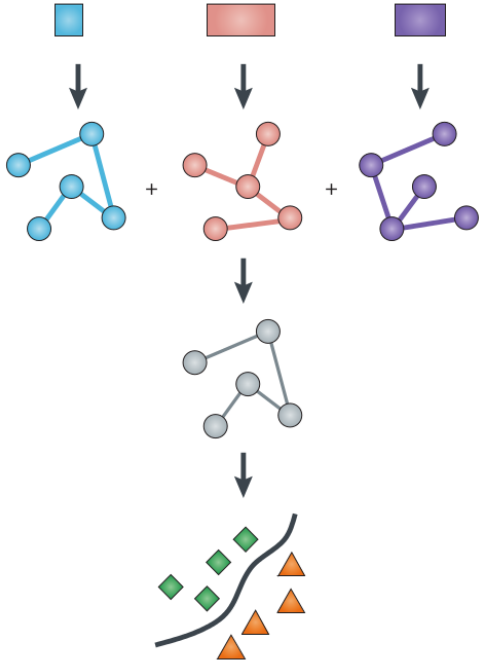
Concatenation-based integration



Model-based integration



Transformation-based integration



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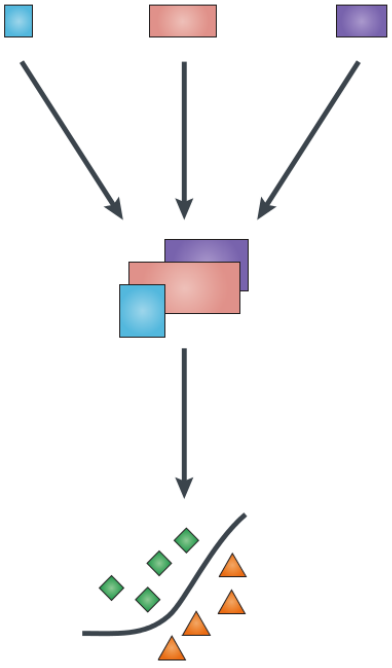

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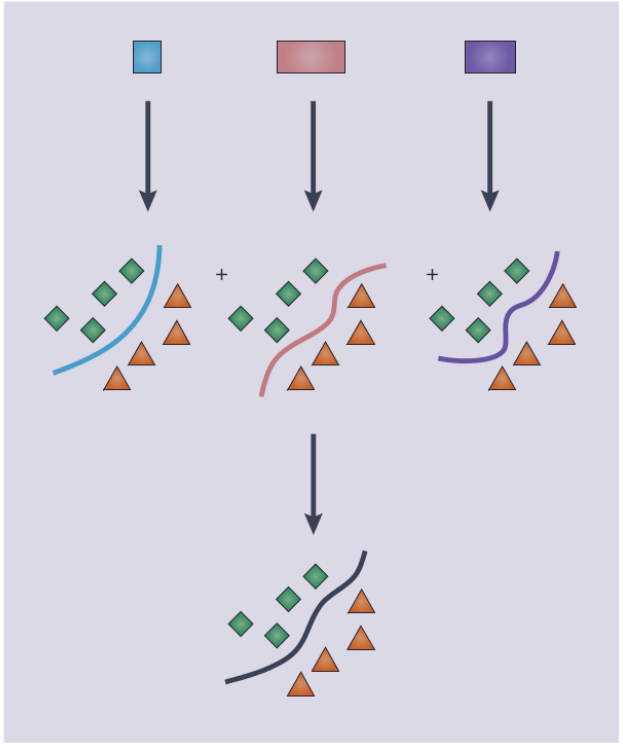

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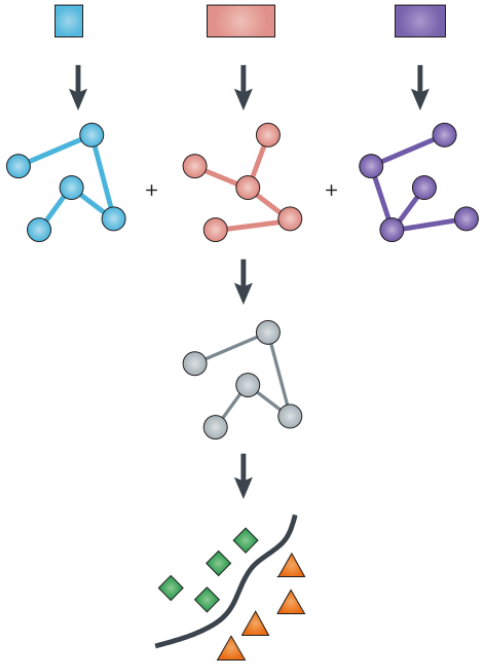

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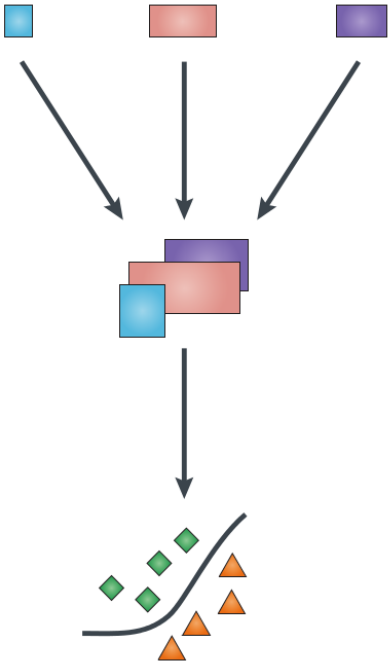

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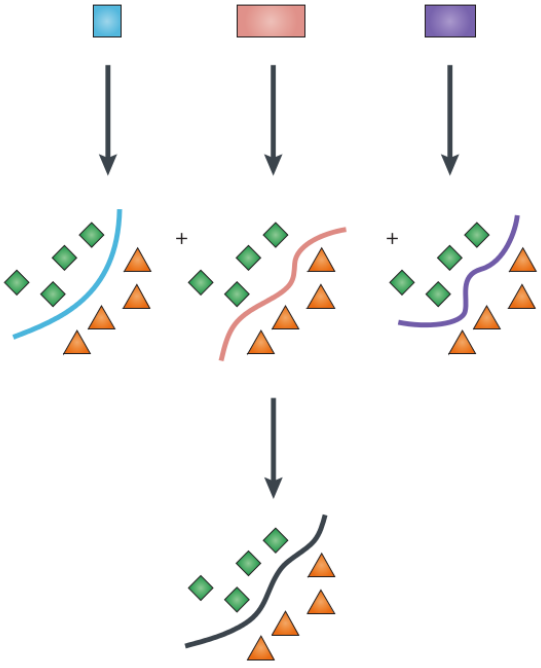

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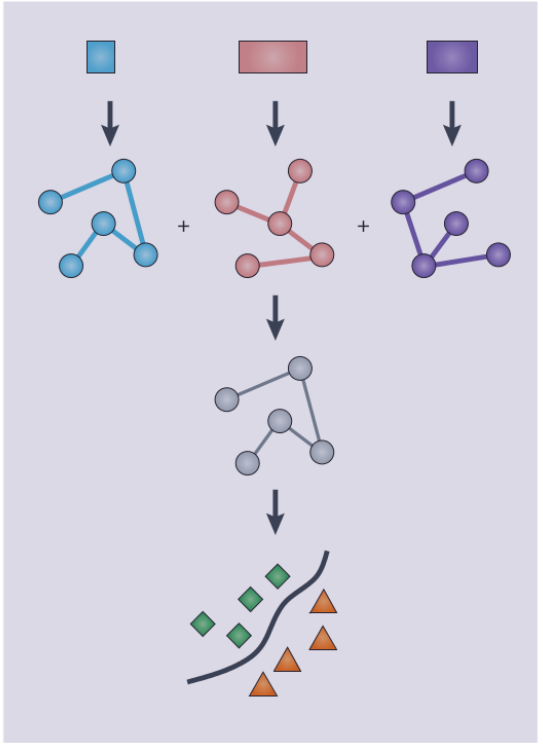

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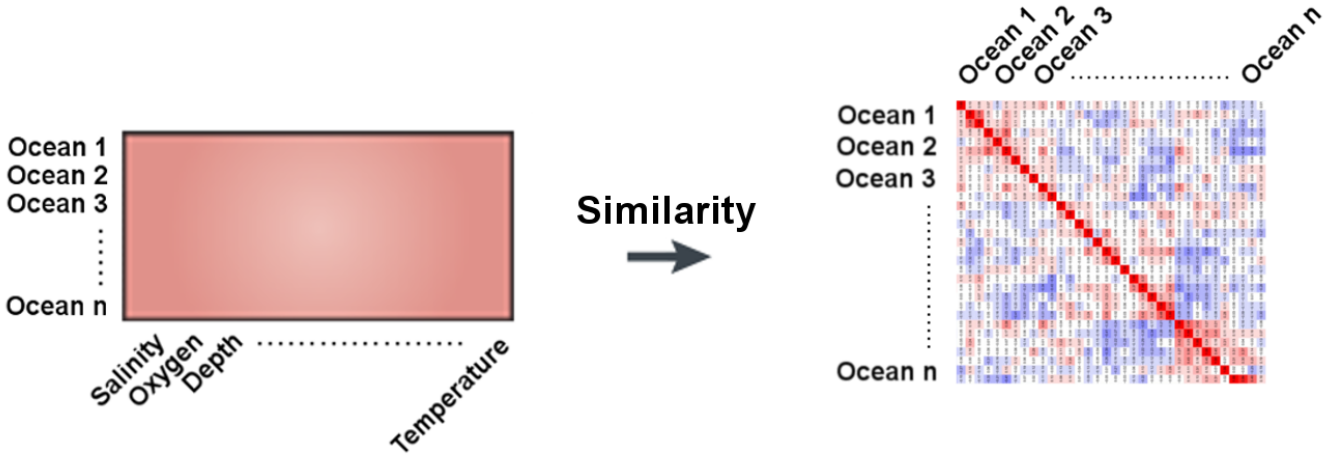
Integrating ’omics data using kernels



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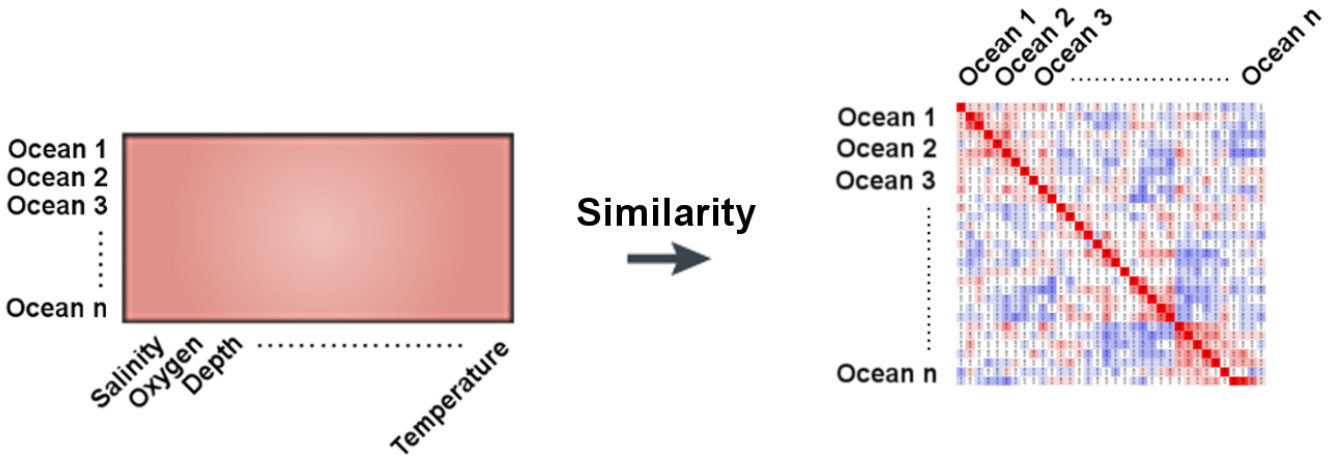

Desired mathematical properties for the similarity

Function $K : \mathcal{G} \times \mathcal{G} \to \mathbb{R}$ st: $K(x_i, x_j) = K(x_j, x_i)$ and $\forall m \in \mathbb{N}$, $\forall x_1, ..., x_m \in \mathcal{G}$, $\forall \alpha_1, ..., \alpha_m \in \mathbb{R}$, $\sum_{i,j=1}^{m} \alpha_i \alpha_j K(x_i, x_j) \geq 0$
In this case:

$$\exists (\mathcal{H}, \langle ., . \rangle), \phi : \mathcal{G} \to \mathcal{H} \text{ st: } K(x_i, x_j) = \langle \phi(x_i), \phi(x_j) \rangle$$

K can be viewed as a dot product for $\mathcal{G}$.

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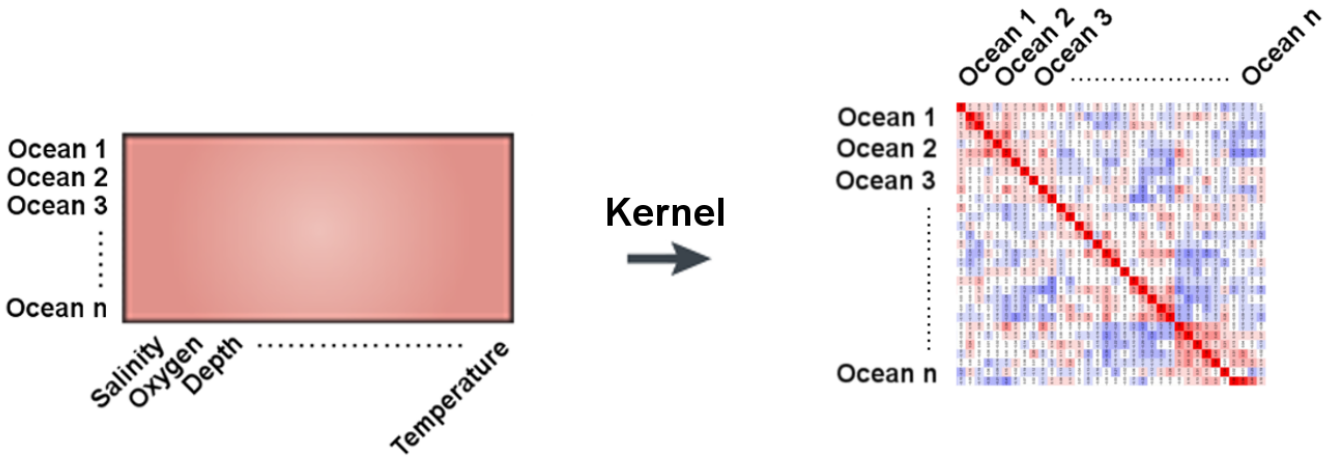

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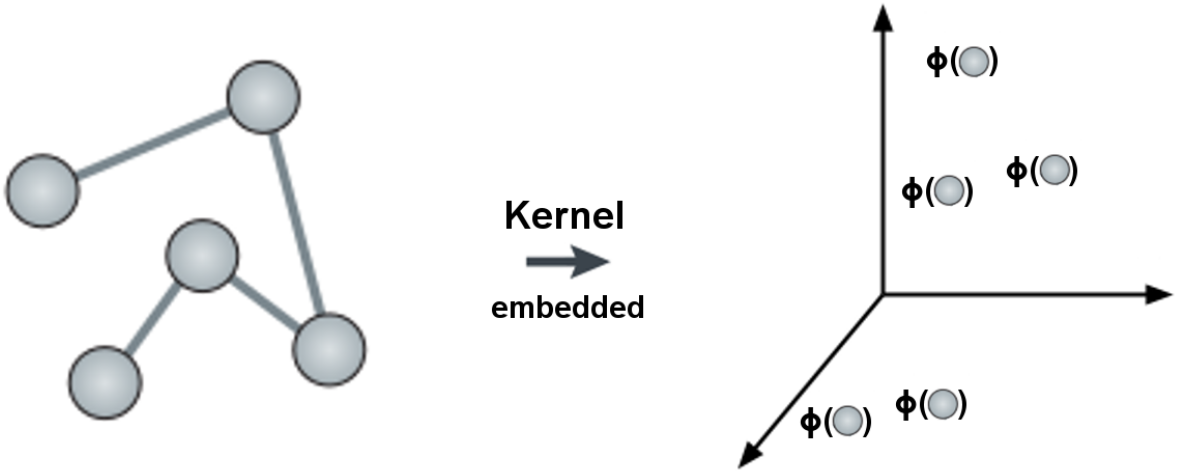

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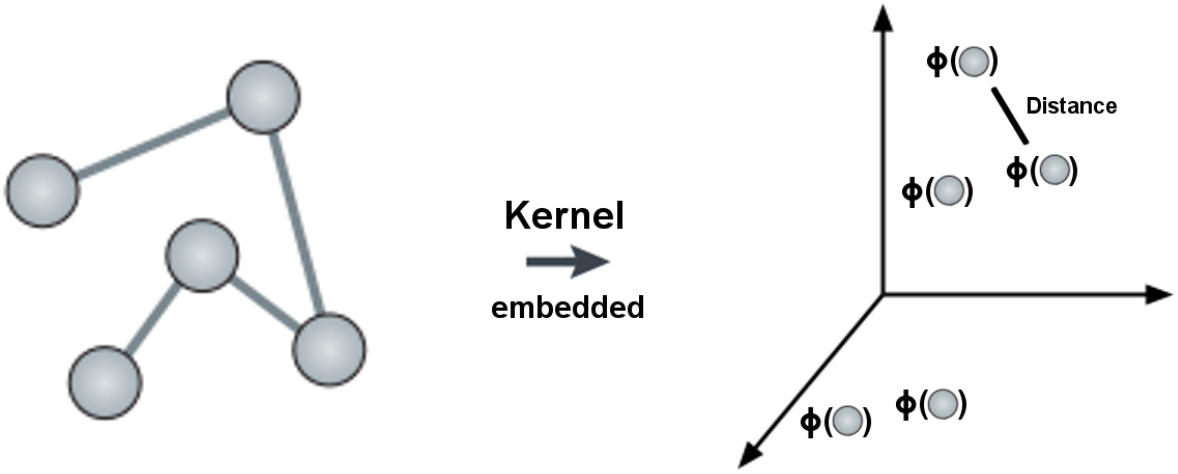

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From multiple kernels to an integrated kernel

How to combine M kernels?

- naive approach: $K^* = \frac{1}{M} \sum_m^M K^m$

From multiple kernels to an integrated kernel

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- naive approach: $K^* = \frac{1}{M} \sum_m^M K^m$
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- unsupervised framework but input space is $\mathbb{R}^d$ [Zhuang et al., 2011] $K^* = \sum_m^M \beta_m K^m$ with $\beta_m \geq 0$ and $\sum_m \beta_m = 1$ with β_m chosen so as to
  - minimize the distortion between all training data $\sum_{ij} K^*(x_i, x_j) \|x_i - x_j\|^2$;
  - AND minimize the approximation of the original data by the kernel embedding $\sum_i \left\| x_i - \sum_j K^*(x_i, x_j) x_j \right\|^2$.

:

From multiple kernels to an integrated kernel

Our proposal

- 2 UMKL frameworks which do not require data to have values in $\mathbb{R}^d$.
  - maximizing the average similarity between kernels (STATIS)
  - minimizing the distorsion with the topology of the data

From multiple kernels to an integrated kernel

Maximizing the average similarity between kernels (STATIS)

- STATIS: exploratory tools for multi-block datasets.

From multiple kernels to an integrated kernel

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- STATIS: exploratory tools for multi-block datasets.
- first step: compute a similarity matrix between kernels.

$$C_{mm'} = \frac{\langle K^m, K^{m'} \rangle_F}{\|K^m\|_F \|K^{m'}\|_F}.$$

From multiple kernels to an integrated kernel

Maximizing the average similarity between kernels (STATIS)

- STATIS: exploratory tools for multi-block datasets.
- first step: compute a similarity matrix between kernels.

$$C_{mm'} = \frac{\langle K^m, K^{m'} \rangle_F}{\|K^m\|_F \|K^{m'}\|_F}.$$

- second step:

$$\arg\max_{\beta} \sum_{m=1}^{M} \left\langle K^*(\beta), \frac{K^m}{\|K^m\|} \right\rangle = \arg\max_{\beta} \sum_{m,m'=1}^{M} \beta_m \beta_{m'} C_{mm'}.$$

From multiple kernels to an integrated kernel

A kernel preserving the original topology of the data

- From an idea similar to that of [Lin et al., 2010], find a kernel such that the local geometry of the data in the feature space is similar to that of the original data.

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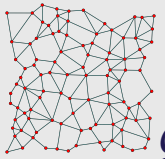
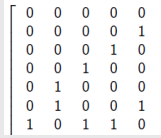
$K^m \longrightarrow$  $\mathcal{G}_k^m \longrightarrow$  A_k^m

$k-$nearest neighbors graph

adjacency matrix

$\Rightarrow W = \sum_m \mathbb{I}_{\{A_k^m > 0\}}$ or $W = \sum_m A_k^m$

From multiple kernels to an integrated kernel

A kernel preserving the original topology of the data

- From an idea similar to that of [Lin et al., 2010], find a kernel such that the local geometry of the data in the feature space is similar to that of the original data.

$$K^m \longrightarrow \underbrace{\mathcal{G}_k^m}_{k-\text{nearest neighbors graph}} \longrightarrow \underbrace{A_k^m}_{\text{adjacency matrix}}$$

$$\Rightarrow W = \sum_m \mathbb{I}_{\{A_k^m > 0\}} \text{ or } W = \sum_m A_k^m$$

-

$$\arg\min_{\beta} \sum_{i,j=1}^{n} W_{ij} \left\| \sum_{m=1}^{M} \beta_m \left(\begin{bmatrix} K_{i1}^m \\ \vdots \\ K_{in}^m \end{bmatrix} - \begin{bmatrix} K_{j1}^m \\ \vdots \\ K_{jn}^m \end{bmatrix} \right) \right\|^2 .$$

From multiple kernels to an integrated kernel

A kernel preserving the original topology of the data

- Sparse version with $\|\beta\|_1 = \sum_m \beta_m = 1 \Rightarrow$ standard QP problem with linear constrains (ex: package **quadprog** in R).

From multiple kernels to an integrated kernel

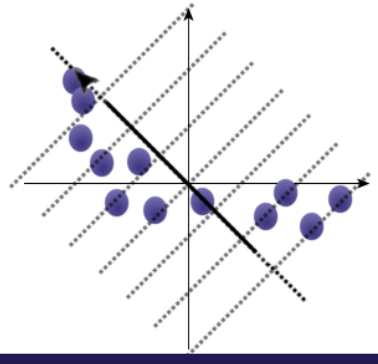
A kernel preserving the original topology of the data

- Sparse version with $\|\beta\|_1 = \sum_m \beta_m = 1 \Rightarrow$ standard QP problem with linear constrains (ex: package **quadprog** in R).
- Non sparse version with $\|\beta\|_2 = 1 \Rightarrow$ QPQC problem (hard to solve). Solved using Alternating Direction Method of Multipliers (ADMM [Boyd et al., 2011]).

Contents

K-PCA [Schölkopf et al., 1998]

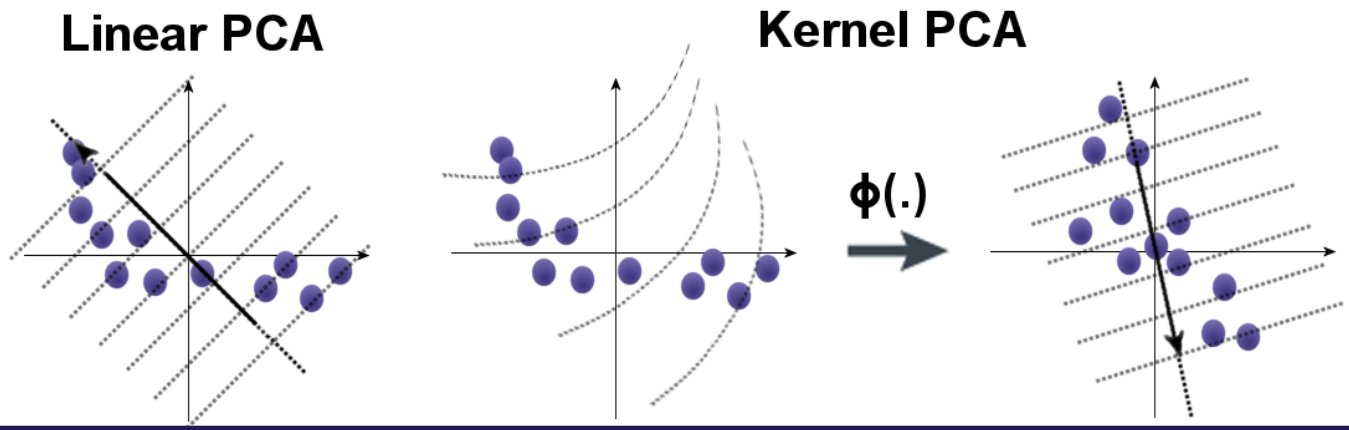
Linear PCA



Standard Principal Component Analysis (PCA)

- Projection of high dimensional dataset in a small dimensional space
- Designed so as to keep most of the data variability
- Axes interpretable from a variable and from an observation point of view (axes are linear combinations of the original variables)

K-PCA [Schölkopf et al., 1998]



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Kernel Principal Component Analysis (K-PCA)

- PCA in the feature space (corresponds to a non linear projection of the original data in the original space)
- No representation for the variables

K-PCA [Schölkopf et al., 1998]

How to interprete the axes ?

- few attempts in the literature to help understand the relations of KPCA with the original measures.
- [Reverter et al., 2014] add a representation of the variables to the plot: visualizing their influence over the results from derivative computations (datasets take values in $\mathbb{R}^d$).

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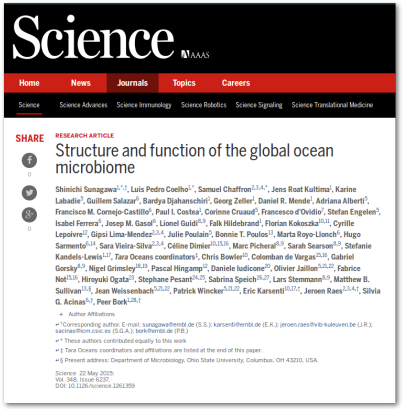
Our proposal

- generic approach that assesses the influence of variables.
- randomize a dataset variable and build a new kernel $\tilde{K^*}$.
- compute the Crone and Crosby distance [Crone and Crosby, 1995] between the K^* and $\tilde{K^*}$ K-PCA sub-spaces.

Contents

TARA Oceans datasets



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RESEARCH ARTICLE

Structure and function of the global ocean microbiome

Shinichi Sunagawa[1,*,†], Luis Pedro Coelho[1,*], Samuel Chaffron[2,3,4,*], Jens Roat Kultima[1], Karine Labadie[5], Guillem Salazar[6], Bardya Djahanschiri[1], Georg Zeller[1], Daniel R. Mende[1], Adriana Alberti[5], Francisco M. Cornejo-Castillo[6], Paul I. Costea[1], Corinne Cruaud[5], Francesco d'Ovidio[7], Stefan Engelen[5], Isabel Ferrera[6], Josep M. Gasol[6], Lionel Guidi[8,9], Falk Hildebrand[1], Florian Kokoszka[10,11], Cyrille Lepoivre[12], Gipsi Lima-Mendez[2,3,4], Julie Poulain[5], Bonnie T. Poulos[13], Marta Royo-Llonch[6], Hugo Sarmento[6,14], Sara Vieira-Silva[2,3,4], Céline Dimier[15,15,16], Marc Picheral[8,9], Sarah Searson[8,9], Stefanie Kandels-Lewis[1,17], *Tara* Oceans coordinators[1], Chris Bowler[15], Colomban de Vargas[15,18], Gabriel Gorsky[8,9], Nigel Grimsley[19,20], Pascal Hingamp[12], Daniele Iudicone[10], Olivier Jaillon[5,21,22], Fabrice Not[15,16], Hiroyuki Ogata[23], Stephane Pesant[24,25], Sabrina Speich[26,27], Lars Stemmann[8,9], Matthew B. Sullivan[13,], Jean Weissenbach[5,21,22], Patrick Wincker[5,21,22], Eric Karsenti[10,17,‡], Jeroen Raes[2,3,4,‡], Silvia G. Acinas[6,‡], Peer Bork[1,28,‡]

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↵* These authors contributed equally to this work

↵‡ *Tara* Oceans coordinators and affiliations are listed at the end of this paper.

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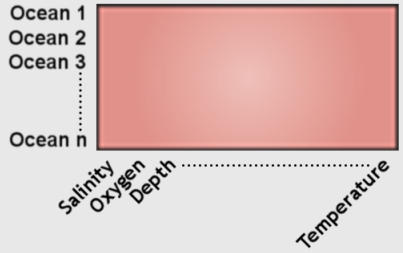
Vol. 348, Issue 6237.
DOI: 10.1126/science.1261359

[Sunagawa et al., 2015]



Datasets used

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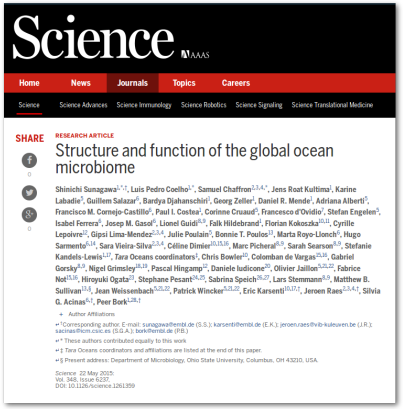
TARA Oceans datasets



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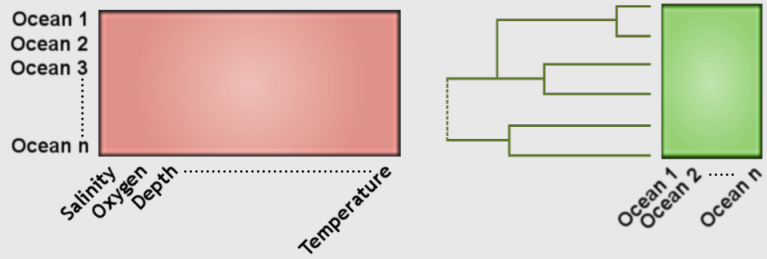

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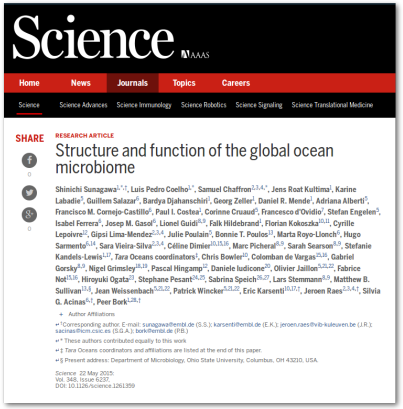
- bacteria phylogenomic tree: computed from $\sim$ 35,000 OTUs.

TARA Oceans datasets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RESEARCH ARTICLE

Structure and function of the global ocean microbiome

Shinichi Sunagawa[1,*,†], Luis Pedro Coelho[1,*], Samuel Chaffron[2,3,4,*], Jens Roat Kultima[1], Karine Labadie[5], Guillem Salazar[6], Bardya Djahanschiri[1], Georg Zeller[1], Daniel R. Mende[1], Adriana Alberti[5], Francisco M. Cornejo-Castillo[6], Paul I. Costea[1], Corinne Cruaud[5], Francesco d'Ovidio[7], Stefan Engelen[5], Isabel Ferrera[6], Josep M. Gasol[6], Lionel Guidi[8,9], Falk Hildebrand[1], Florian Kokoszka[10,11], Cyrille Lepoivre[12], Gipsi Lima-Mendez[2,3,4], Julie Poulain[5], Bonnie T. Poulos[13], Marta Royo-Llonch[6], Hugo Sarmento[6,14], Sara Vieira-Silva[2,3,4], Céline Dimier[15,15,16], Marc Picheral[8,9], Sarah Searson[8,9], Stefanie Kandels-Lewis[1,17], *Tara* Oceans coordinators[1], Chris Bowler[15], Colomban de Vargas[15,18], Gabriel Gorsky[8,9], Nigel Grimsley[19,20], Pascal Hingamp[12], Daniele Iudicone[10], Olivier Jaillon[5,21,22], Fabrice Not[15,16], Hiroyuki Ogata[12], Stephane Pesant[23,24], Sabrina Speich[25,17], Lars Stemmann[8,9], Matthew B. Sullivan[13,3], Jean Weissenbach[5,21,22], Patrick Wincker[5,21,22], Eric Karsenti[10,17,*], Jeroen Raes[2,3,4,*], Silvia G. Acinas[6,*], Peer Bork[1,26,*]

+ Author Affiliations

*Corresponding author. E-mail: sunagawa@embl.de (S.S.); karsenti@embl.de (E.K.); jeroen.raes@vib-kuleuven.be (J.R.); sacinas@icm.csic.es (S.G.A.); bork@embl.de (P.B.)

† These authors contributed equally to this work

‡ Tara Oceans coordinators and affiliations are listed at the end of this paper.

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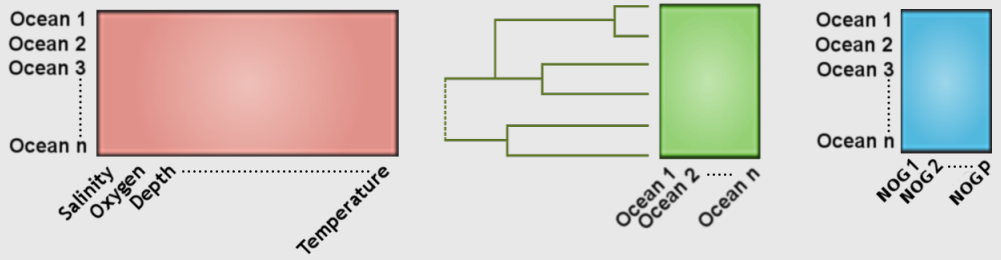
DOI: 10.1126/science.1261359

[Sunagawa et al., 2015]

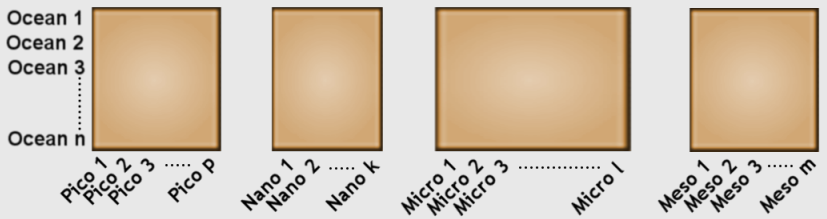


Datasets used

- environmental dataset: 22 numeric features (temperature, salinity, . . .).
- bacteria phylogenomic tree: computed from $\sim$ 35,000 OTUs.
- bacteria functional composition: $\sim$ 63,000 eggNOG gene families.

TARA Oceans datasets

[de Vargas et al., 2015]



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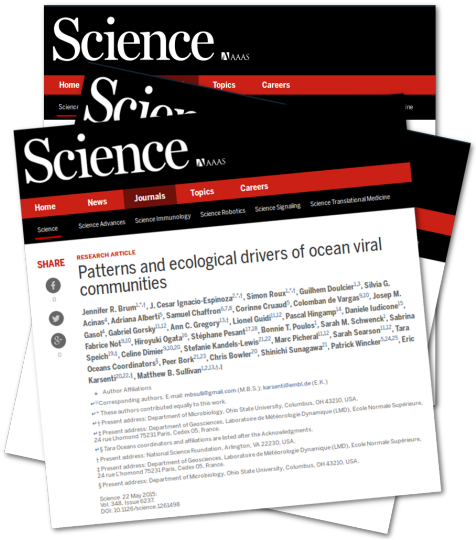
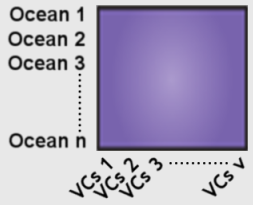
TARA Oceans datasets



[Brum et al., 2015]



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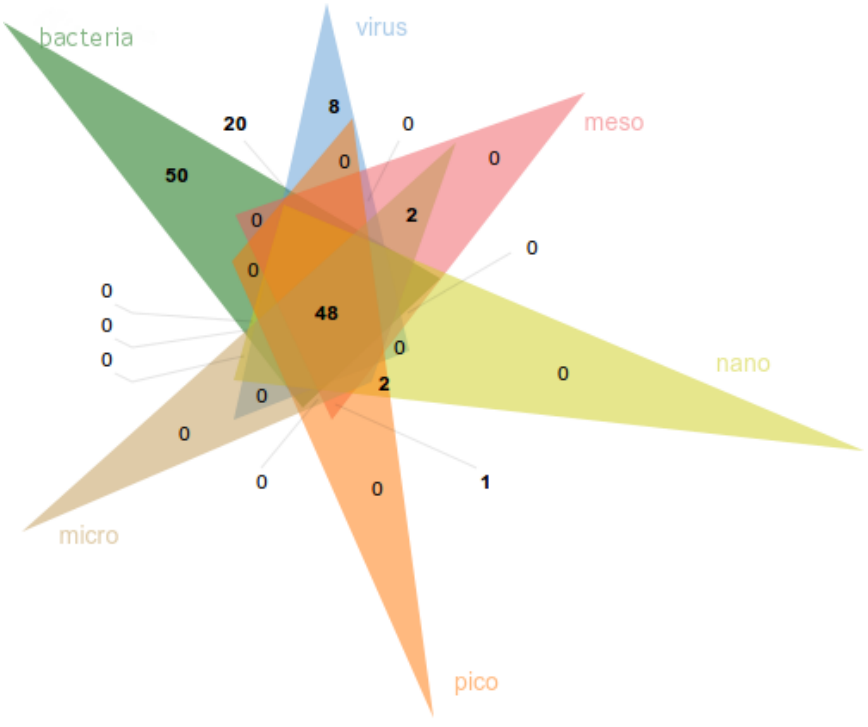
- virus composition: $\sim$ 867 virus clusters based on shared gene content.

TARA Oceans datasets



Common samples

- 48 samples,
- 2 depth layers: surface (SRF) and deep chlorophyll maximum (DCM),
- 31 different sampling stations.

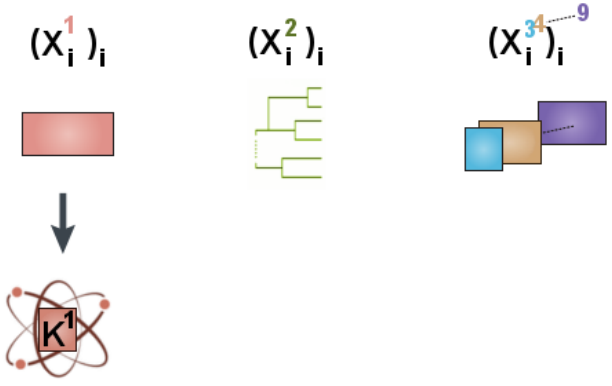
Integrating *TARA* Oceans datasets

M TARA Oceans datasets

$(x_i^m)_{i=1,\ldots,N,m=1,\ldots,M}$ measured on the same ocean samples $(1,\ldots,N)$ which take values in an arbitrary space $(\mathcal{X}^m)_m$:

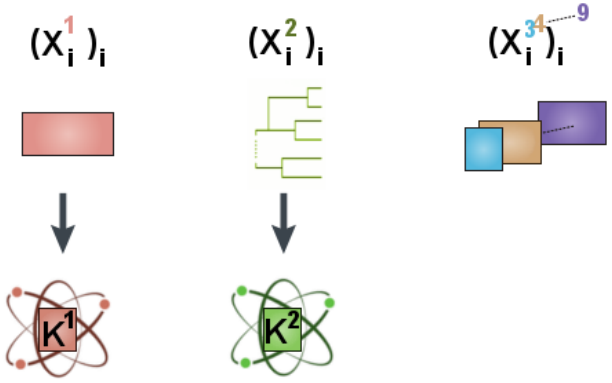
- phychem: environmental dataset,
- pro.phylo: prokaryote phylogenomic tree,
- pro.NOGs: prokaryote functional composition,
- euk.pina: eukaryote pico-nano-plankton composition,
- ...
- vir.VCs: virus composition.

Integrating *TARA* Oceans datasets



phychem (environmental dataset): standard euclidean distance, given by $K(x_i, x_j) = x_i^T x_j$.

Integrating *TARA* Oceans datasets

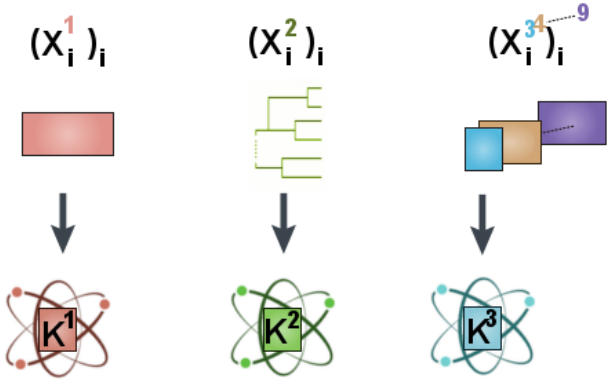


pro.phylo (prokarote phylogenomic tree): the weighted Unifrac distance, given by

$$d_{wUF}(A,B) = \frac{\sum_e l_e |p_e - q_e|}{\sum_e p_e + q_e},$$

l_e: length of branch e.
p_e: the fraction of community A below branch e.
q_e: the fraction of community B below branch e.

Integrating *TARA* Oceans datasets



All composition based datasets: pro.NOGs (bacteria functional composition), eukaryote composition (euk.pina, euk.nano, euk.micro, euk.meso) and vir.VCs (virus composition) calculated using the Bray-Curtis dissimilarity,

$$d_{BC}(A,B) = \frac{\sum_g |n_g^A - n_g^B|}{\sum_g n_g^A + n_g^B},$$

n_g^A: gene g abundances summarized at eggNOG gene families level in community A.
n_g^B: same for community B.

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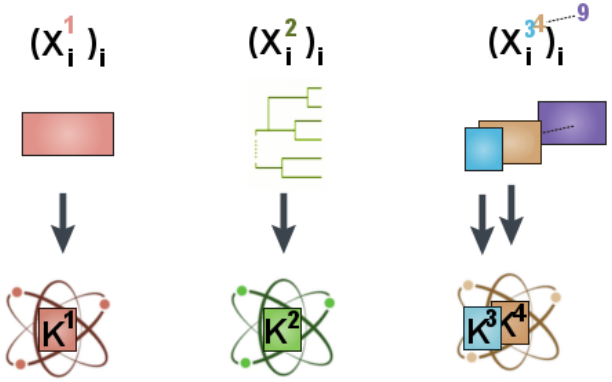

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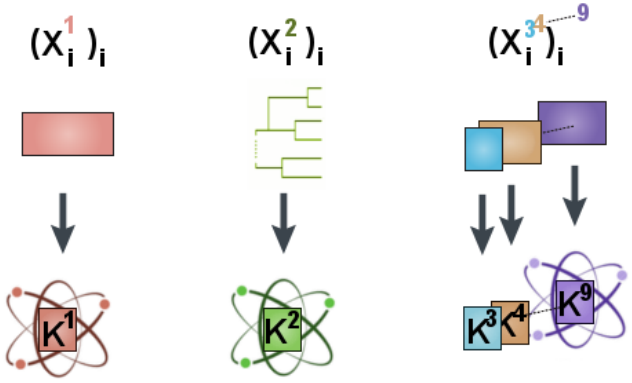

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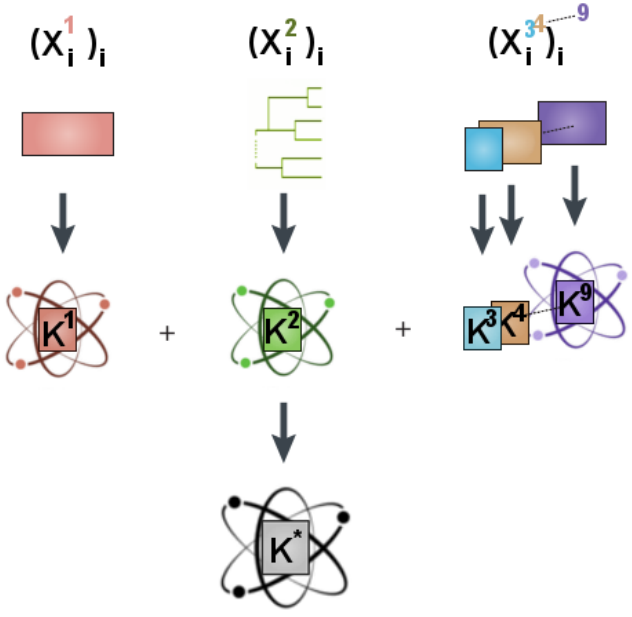
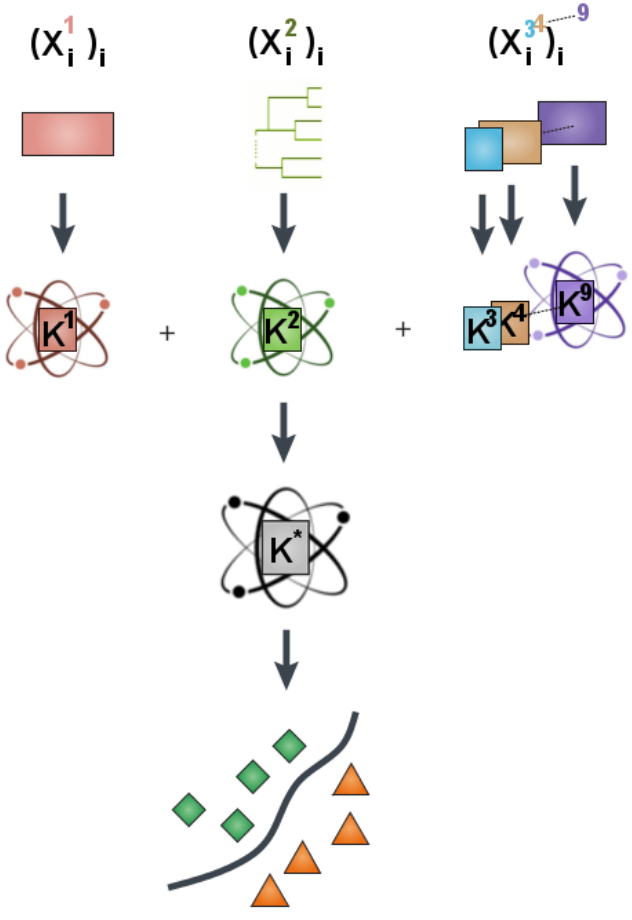


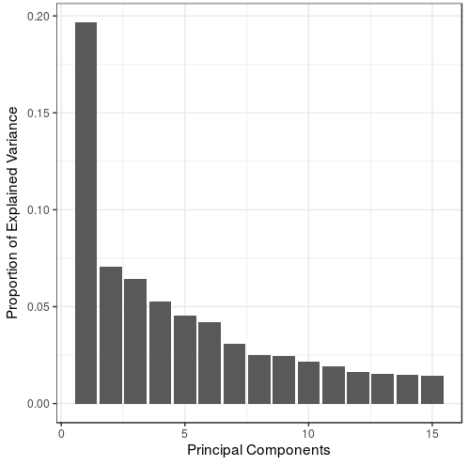
Combinaison of the M kernels to obtain K^*, a kernel preserving topology with L_2-norm constraint.

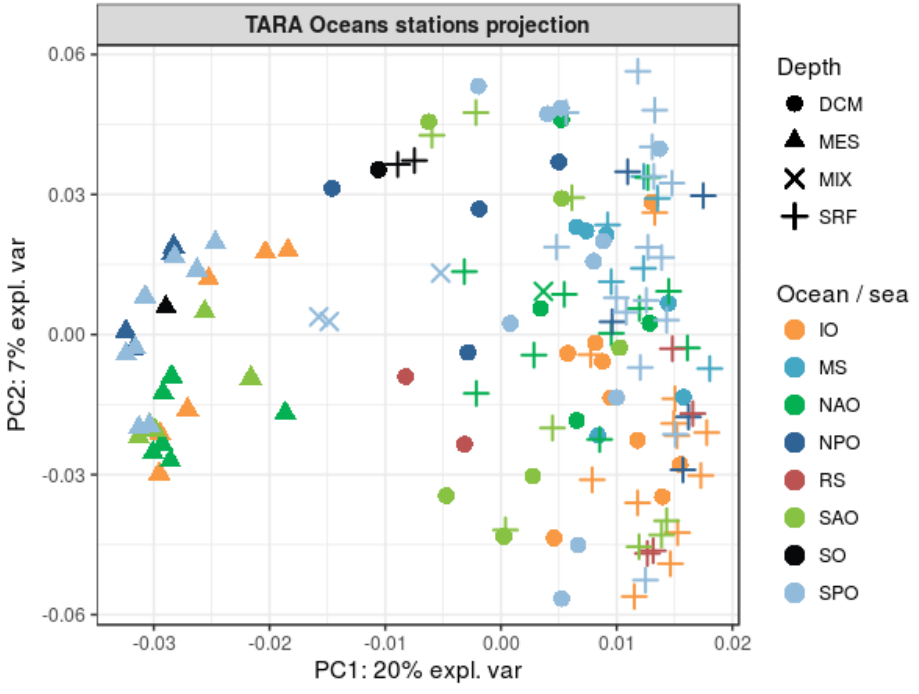
Integrating *TARA* Oceans datasets



Apply KPCA (could have been clustering, linear model, . . . , in the feature space).

Proof of concept on [Sunagawa et al., 2015]





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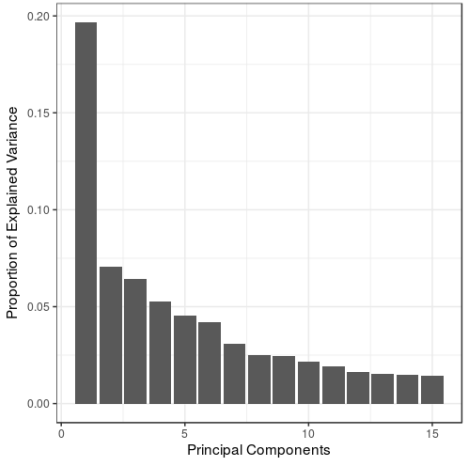

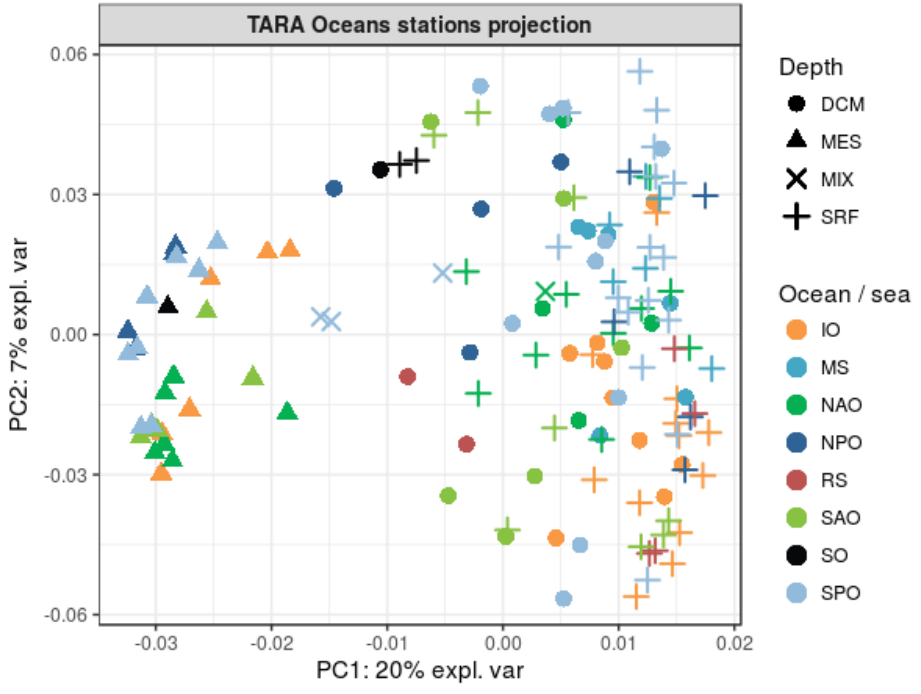

- samples are separated by their depth layer of origin, *i.e.*, SRF, DCM or MES, with stronger differences for MES samples.

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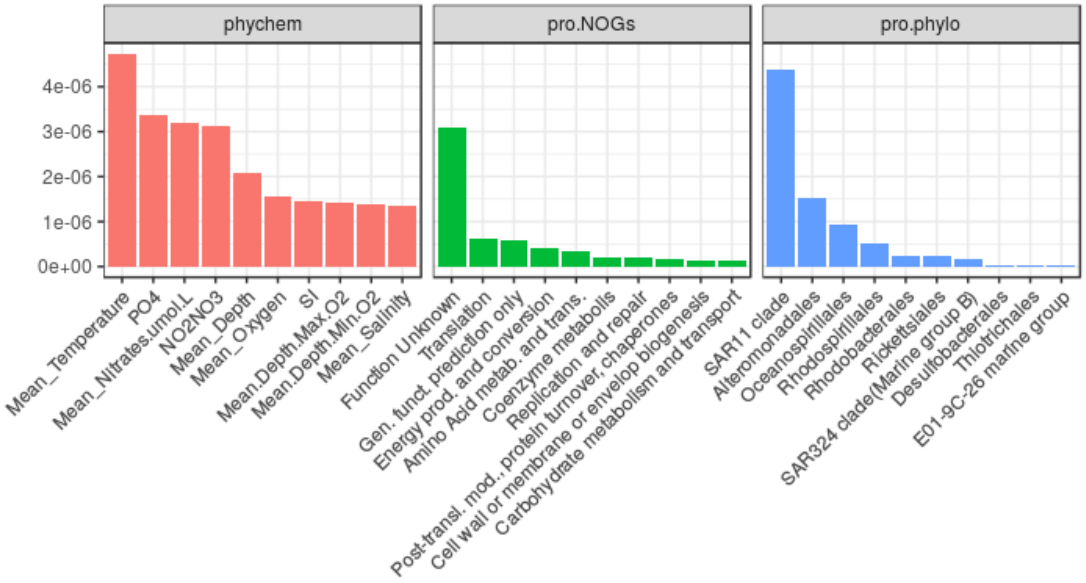

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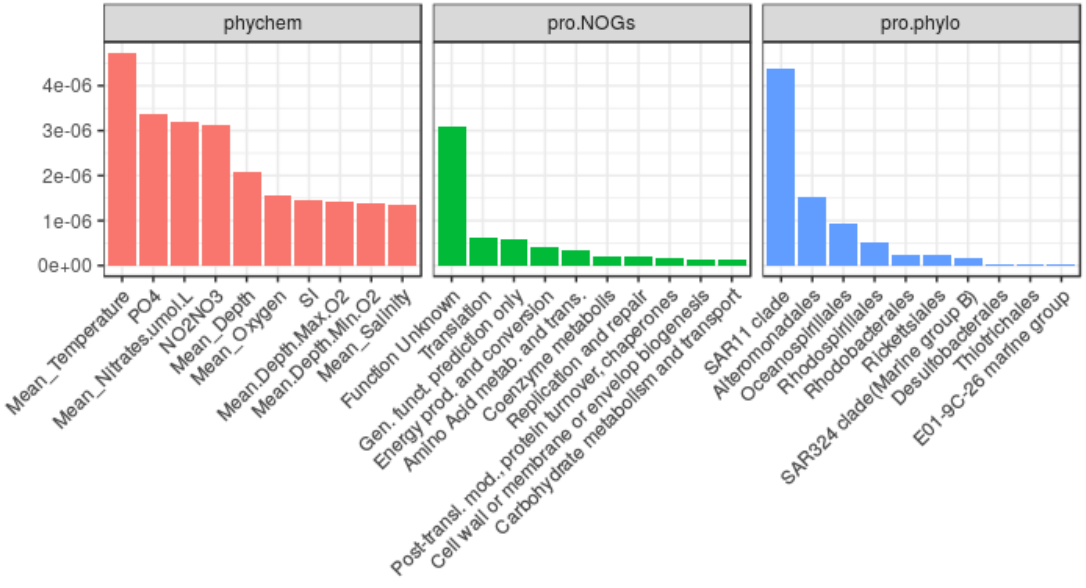

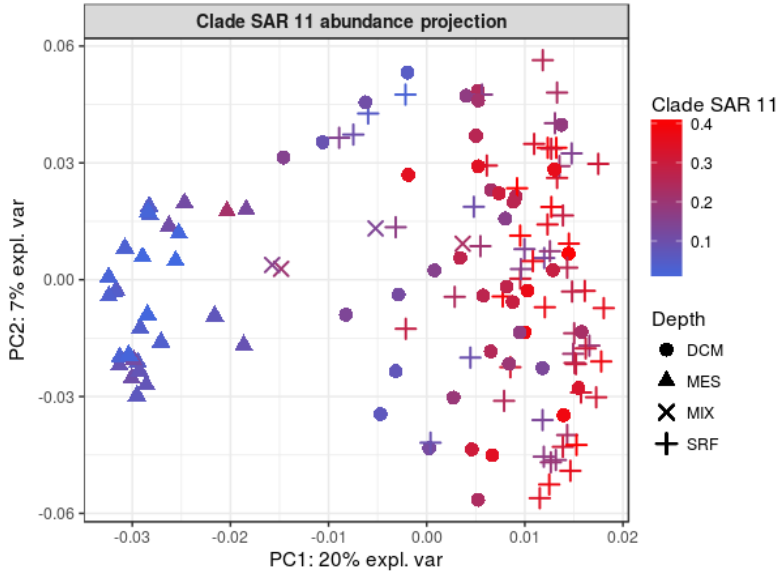

[Sunagawa et al., 2015]

- Proteobacteria (clade SAR11 (Alphaproteobacteria)) dominate the sampled areas.

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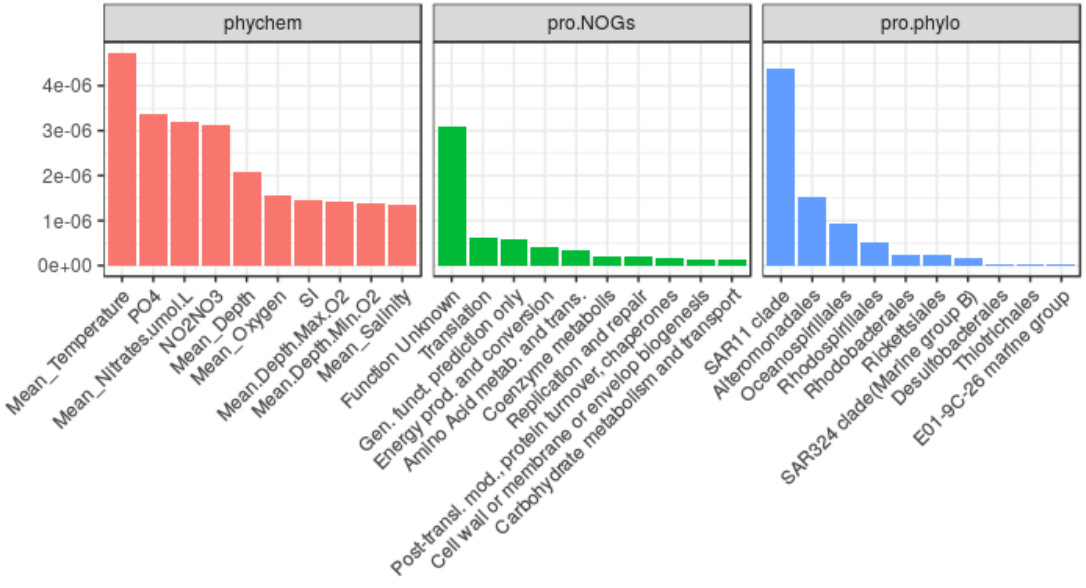
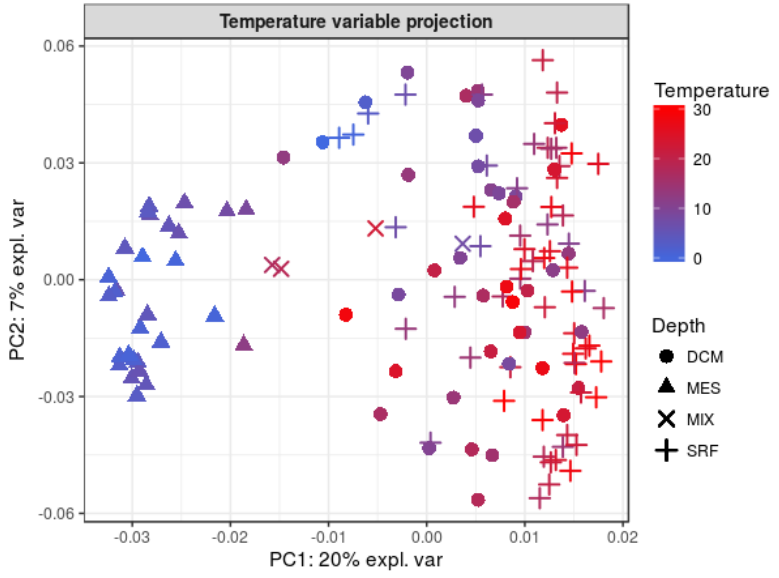
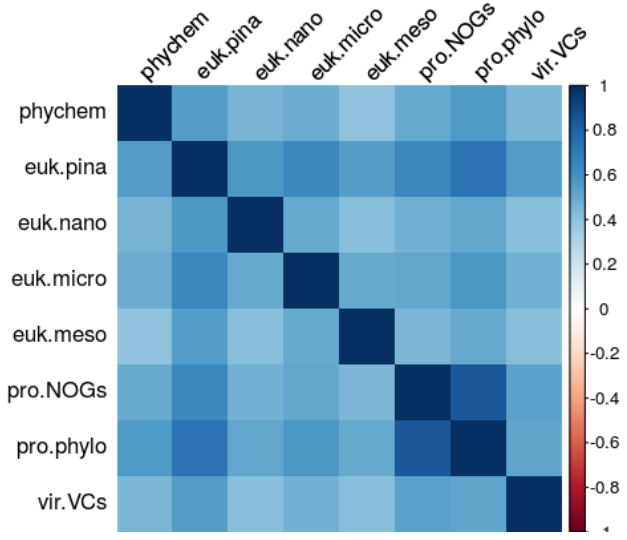




[Sunagawa et al., 2015]

- Proteobacteria (clade SAR11 (Alphaproteobacteria)) dominate the sampled areas.
- Vertical stratification mostly driven by temperature.

Integrating all *Tara* Oceans data sets



Similarities between kernels (STATIS)

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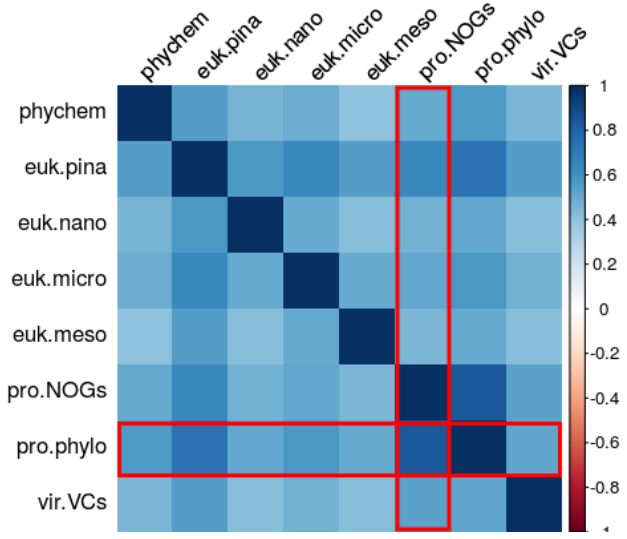

Similarities between kernels (STATIS)

- High similarities between prokaryote phylogenomic tree (pro.phylo) and prokaryote functional composition (pro.NOGs).

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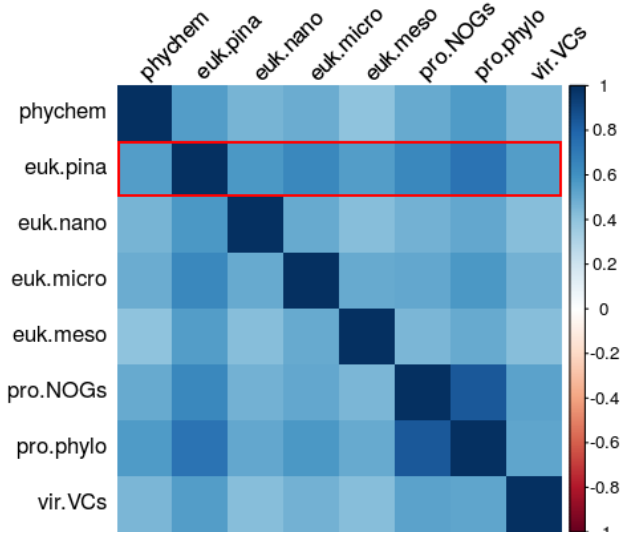
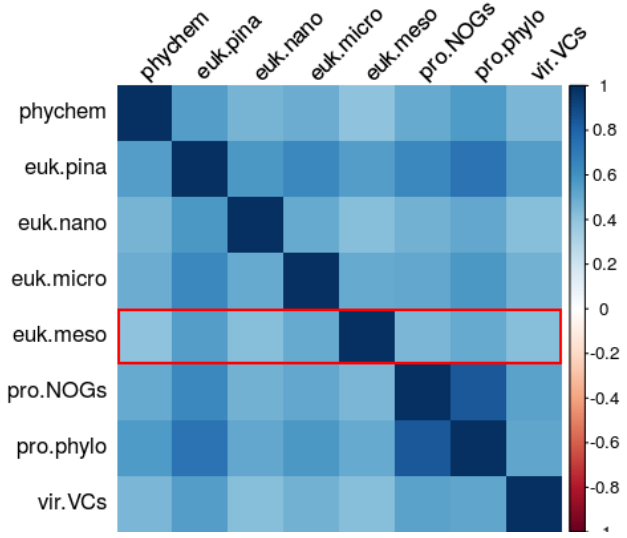


Similarities between kernels (STATIS)

- High similarities between prokaryote phylogenomic tree (pro.phylo) and prokaryote functional composition (pro.NOGs).
- High similarities between pico-nano-plankton (euk.pina) and other datasets: piconanoplankton communities are more homogeneous across the world's ocean ([de Vargas et al., 2015]).

Integrating all *Tara* Oceans data sets



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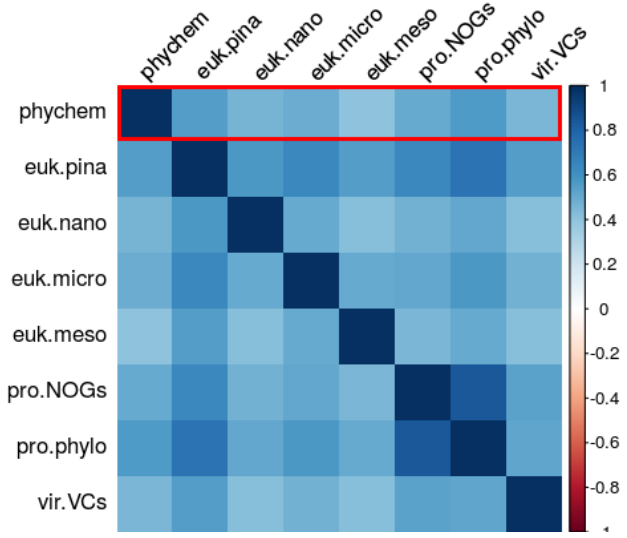

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- Strongest similarities between environmental variables and small organisms than largest ones ([de Vargas et al., 2015] and [Sunagawa et al., 2015]).

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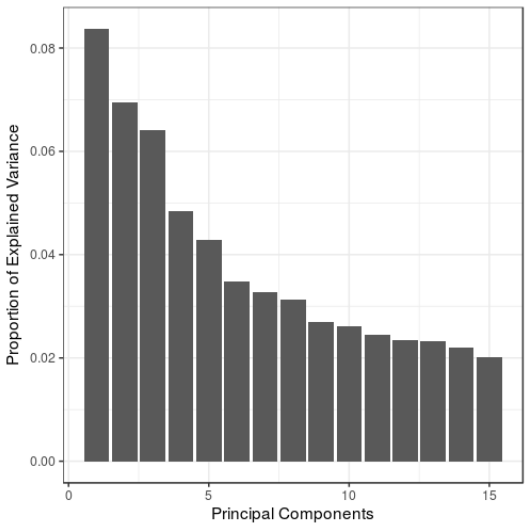

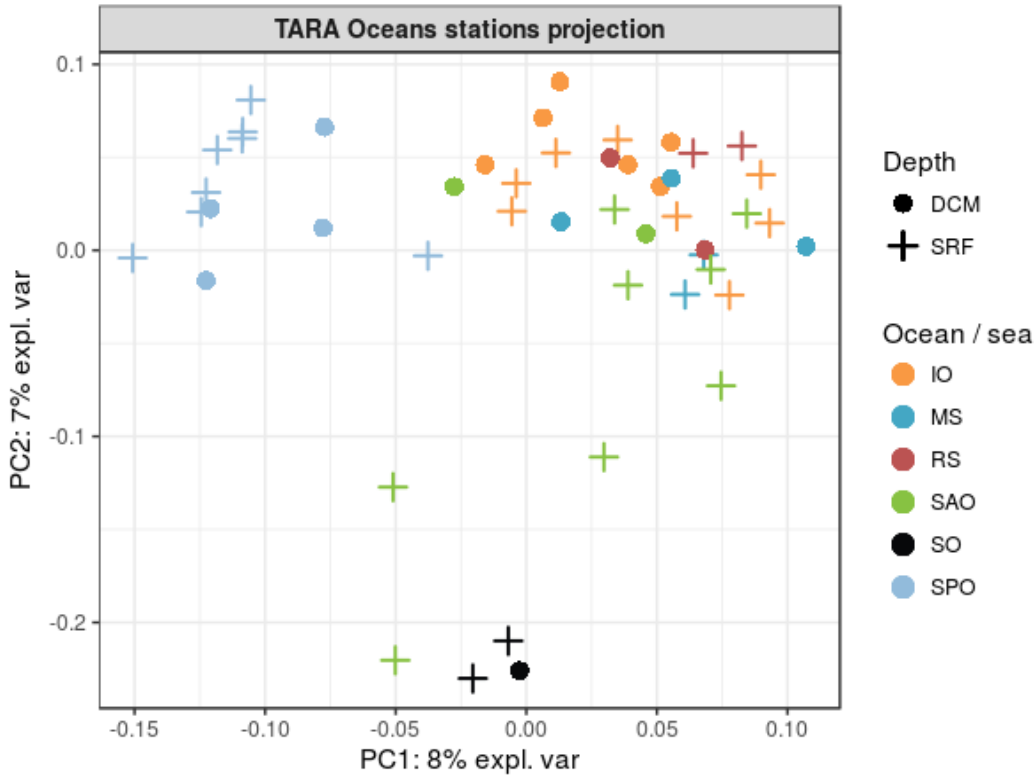

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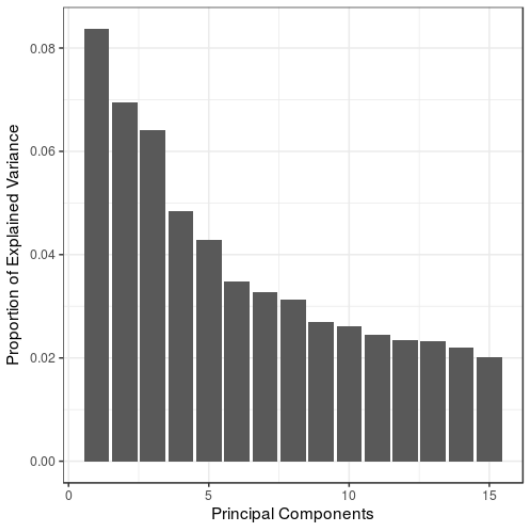

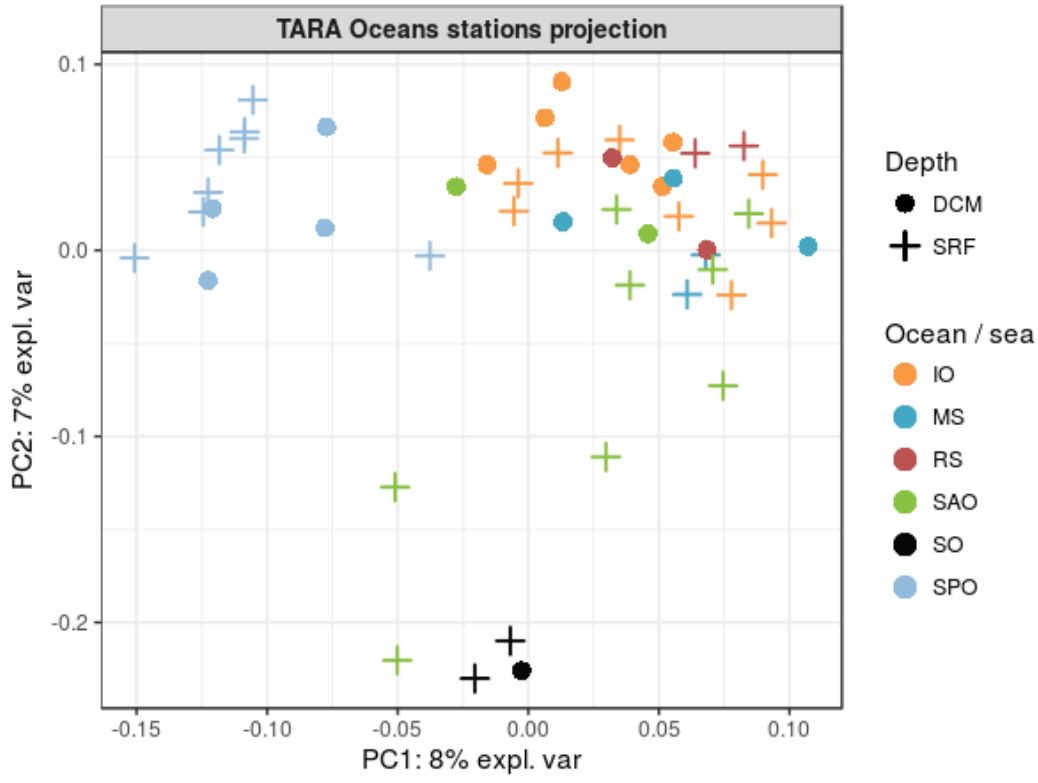

- no particular pattern in terms of depth layers but in terms of geography.

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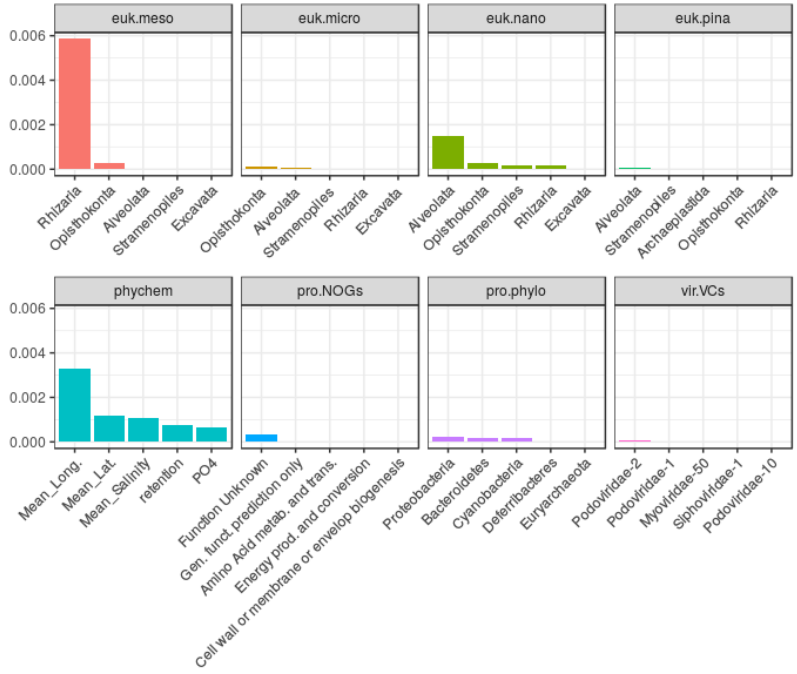

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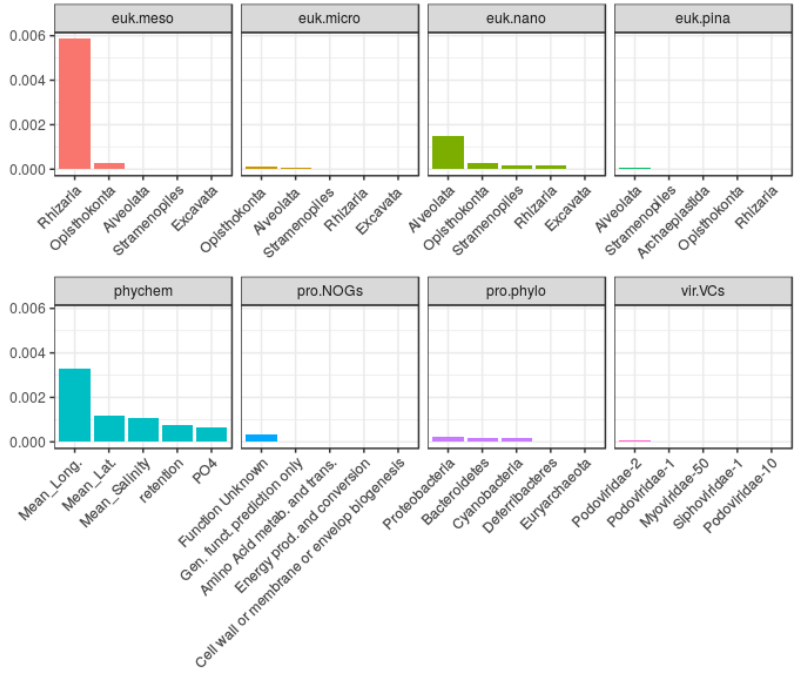
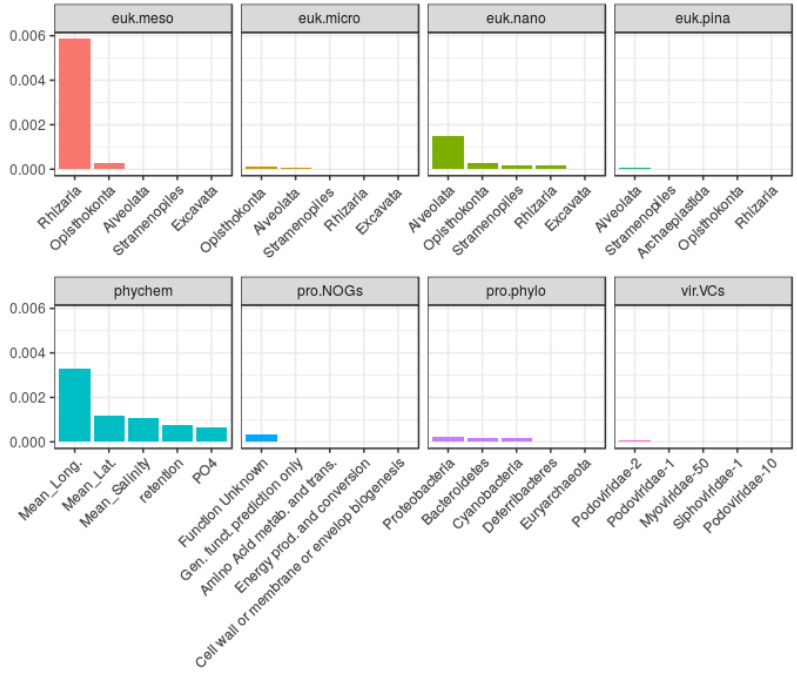
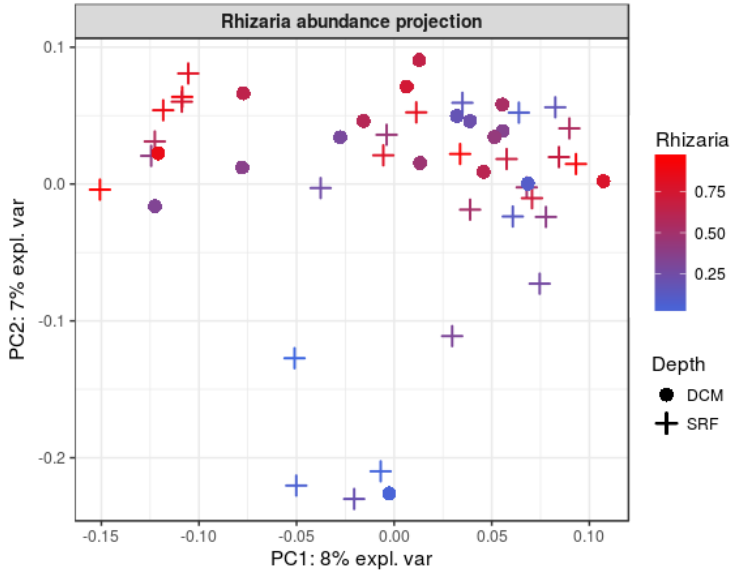


- Large size organisms are the most important: *Rhizaria* and *Alveolata* phyla.

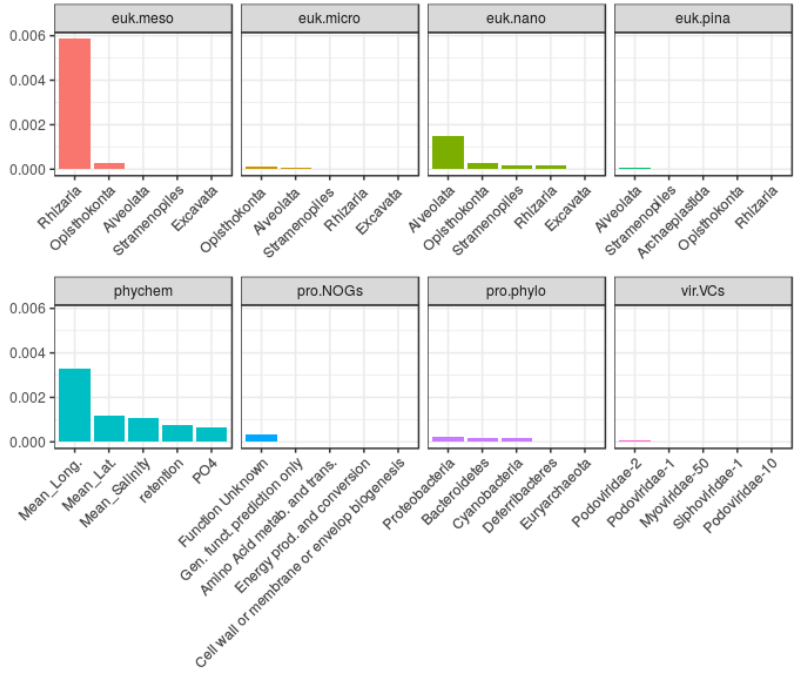
Integrating all *Tara* Oceans data sets

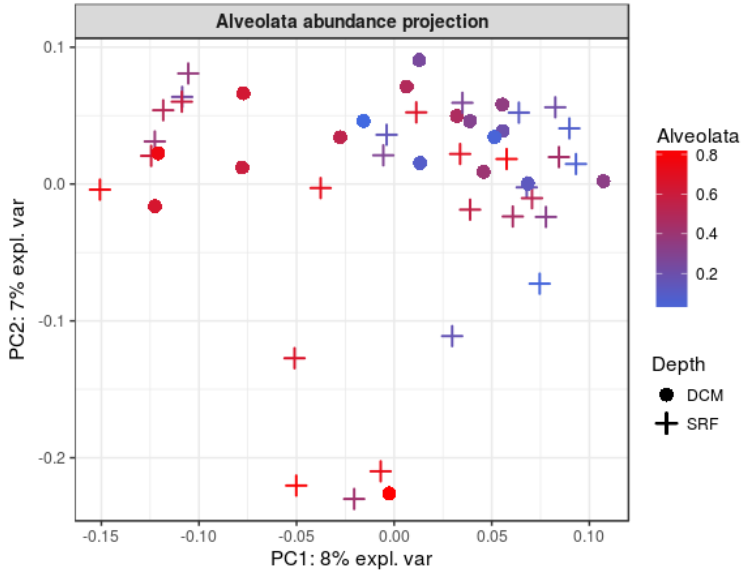




- Large size organisms are the most important: *Rhizaria* and *Alveolata* phyla.
- SO and SPO epipelagic waters mainly differ in terms of Rhizarians abundances

Integrating all *Tara* Oceans data sets





- Large size organisms are the most important: *Rhizaria* and *Alveolata* phyla.
- SO and SPO epipelagic waters mainly differ in terms of Rhizarians abundances
- both of them differ from the other studied waters in terms of alveolata abundances.

Conclusions & Perspectives

What did we do?

- Integrate taxonomic, functional and community composition with environmental factors
- Use a K-PCA to visualize the datasets in an integrated way and improved its interpretability by assessing the influence of input variables in a generic way.
- Learn the kernels weights using MKL algorithms in order to understand their respective importance/contribution

$\Rightarrow$ Give access to a fast insight of the different datasets within a single analysis

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Availability [Mariette and Villa-Vialaneix, 2017]

- Available in the R package **mixKernel**, released on CRAN.
- Fully compatible with the **mixOmics** package, coming with a tutorial describing the approach.

Thanks for your attention!

[Boyd et al., 2011] Boyd, S., Parikh, N., Chu, E., Peleato, B., and Eckstein, J. (2011).
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