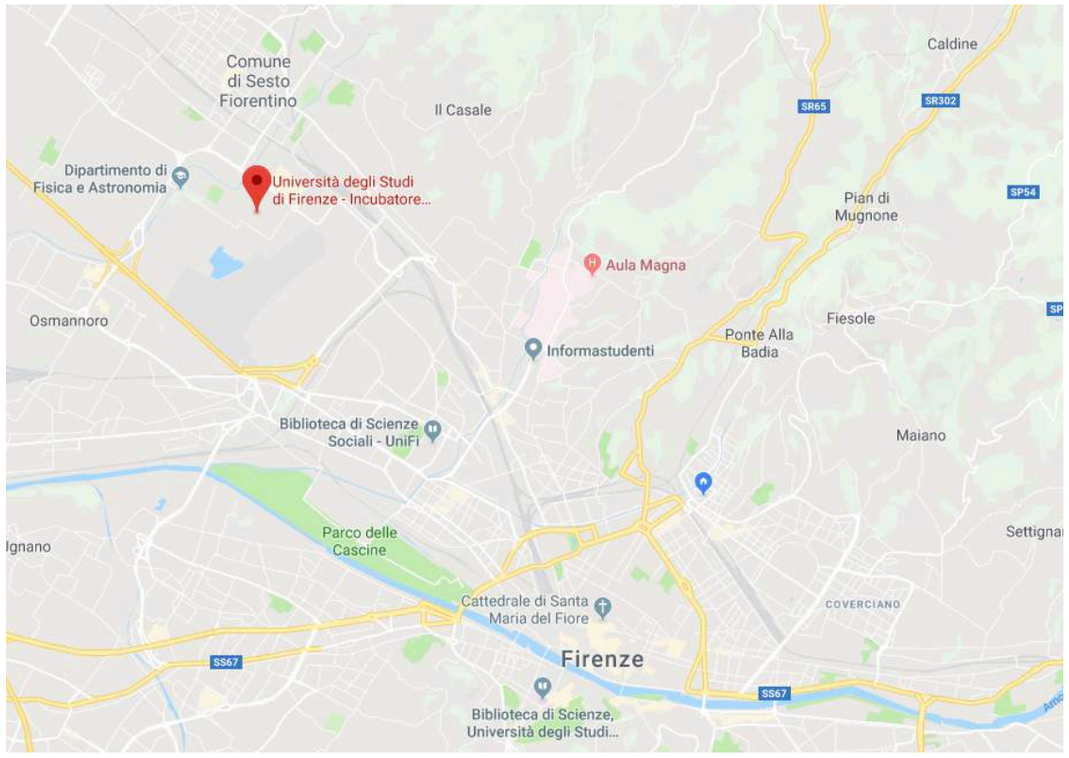
In-silico prediction of microbial assemblages

from metagenomics to community modelling

Giovanni Bacci - giovanni.bacci@unifi.it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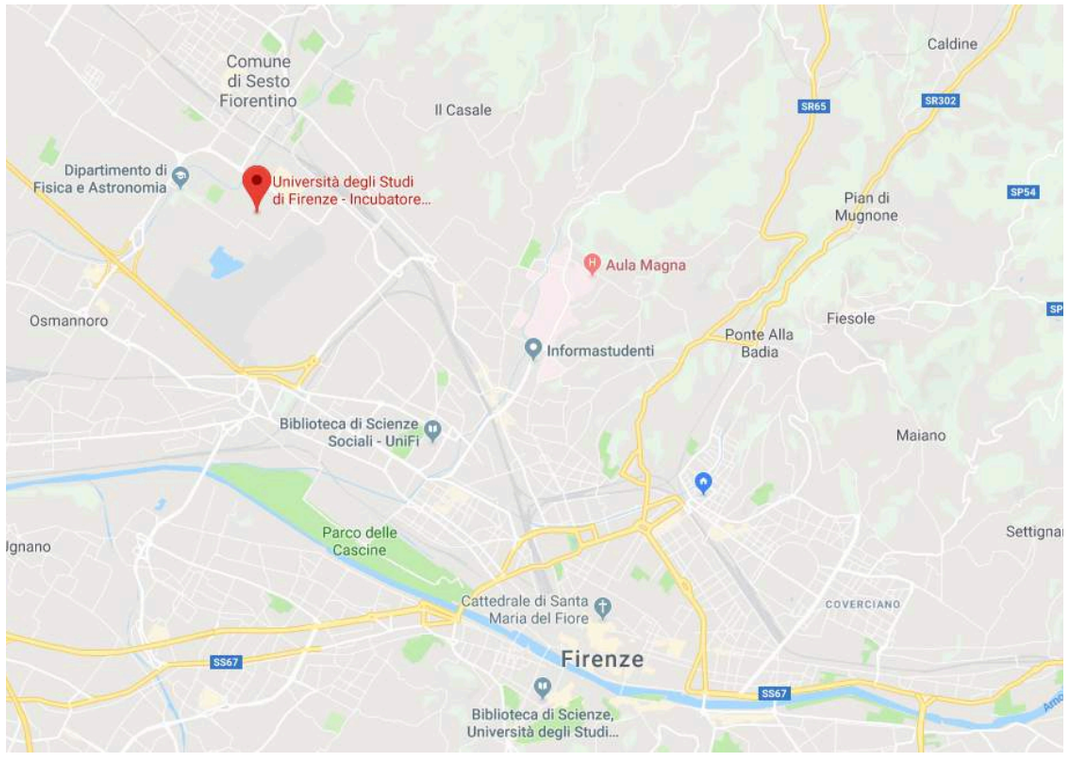
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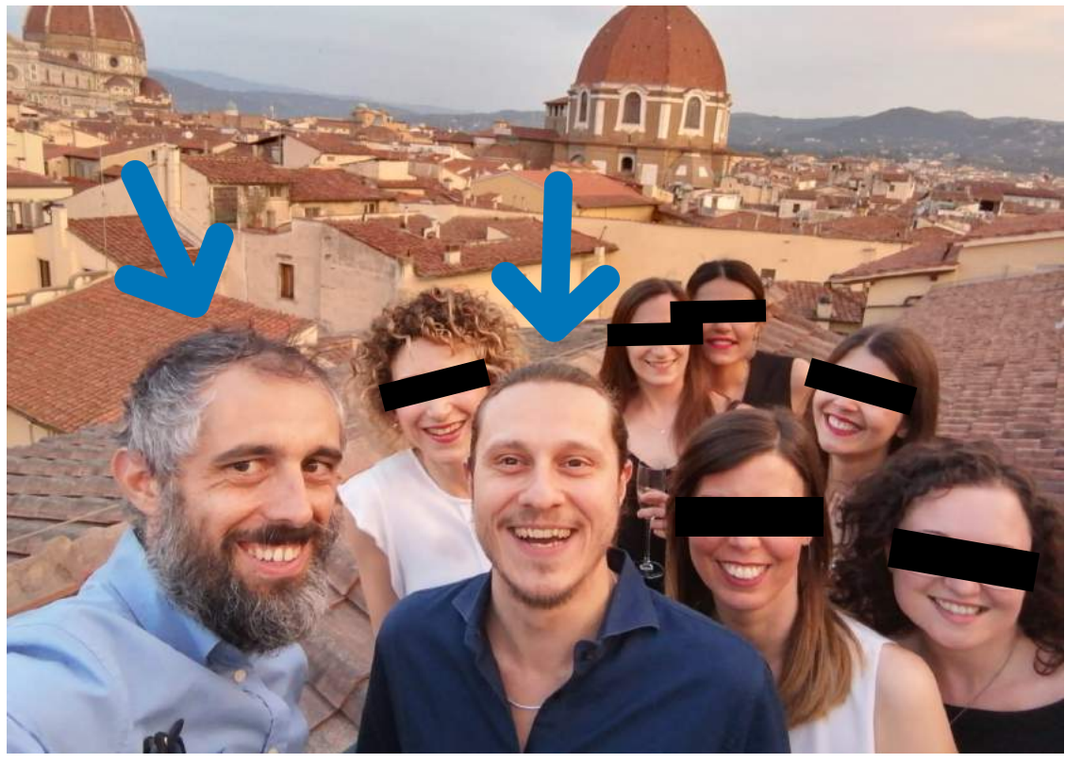
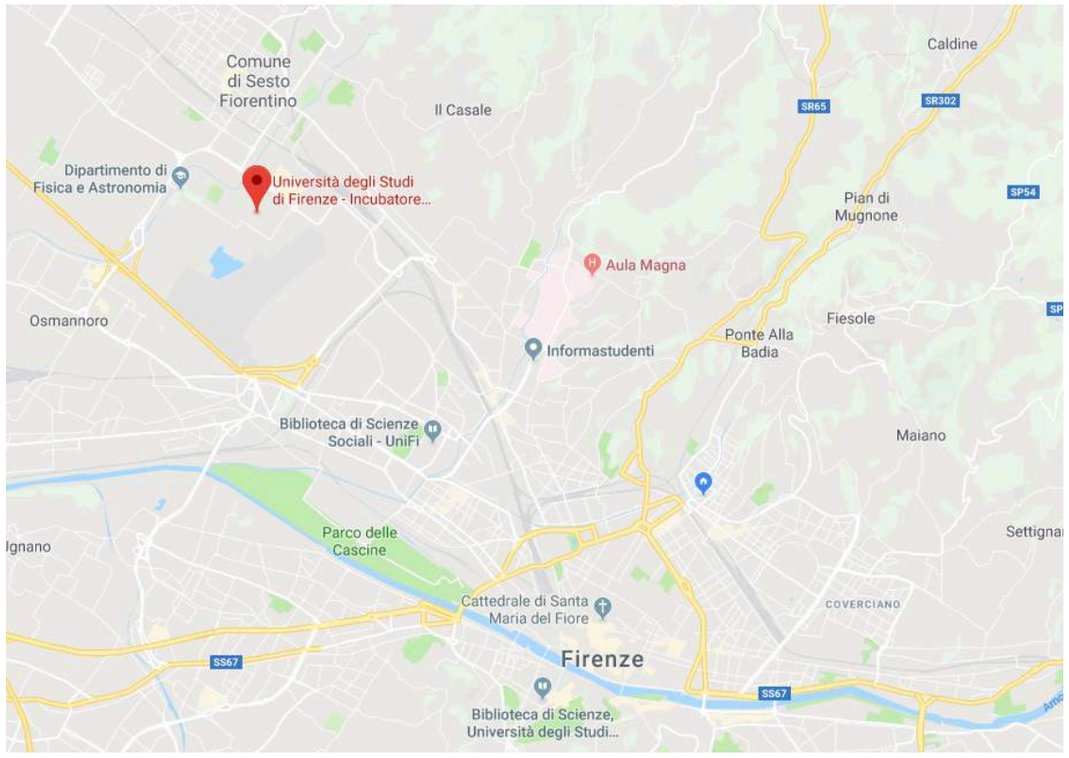
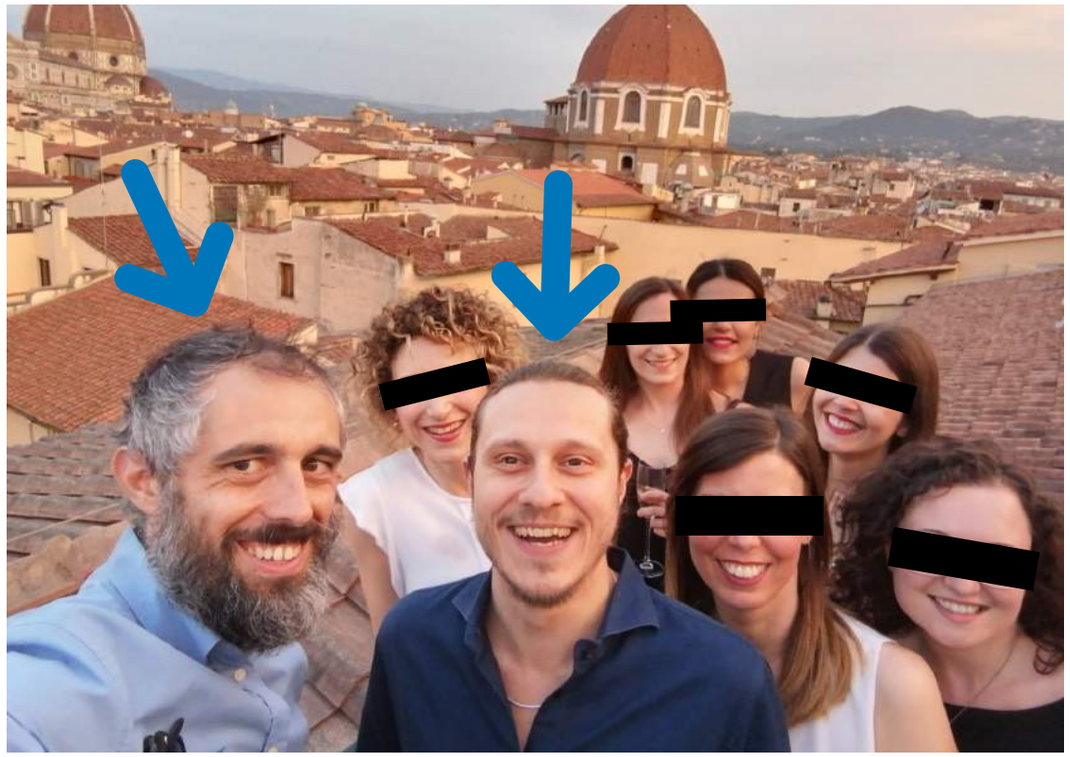


Florence
computational
biology group

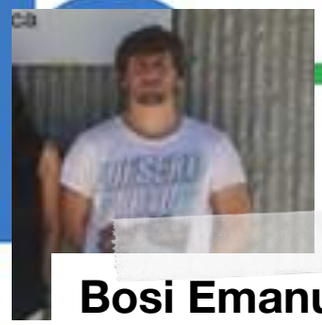
cmbg





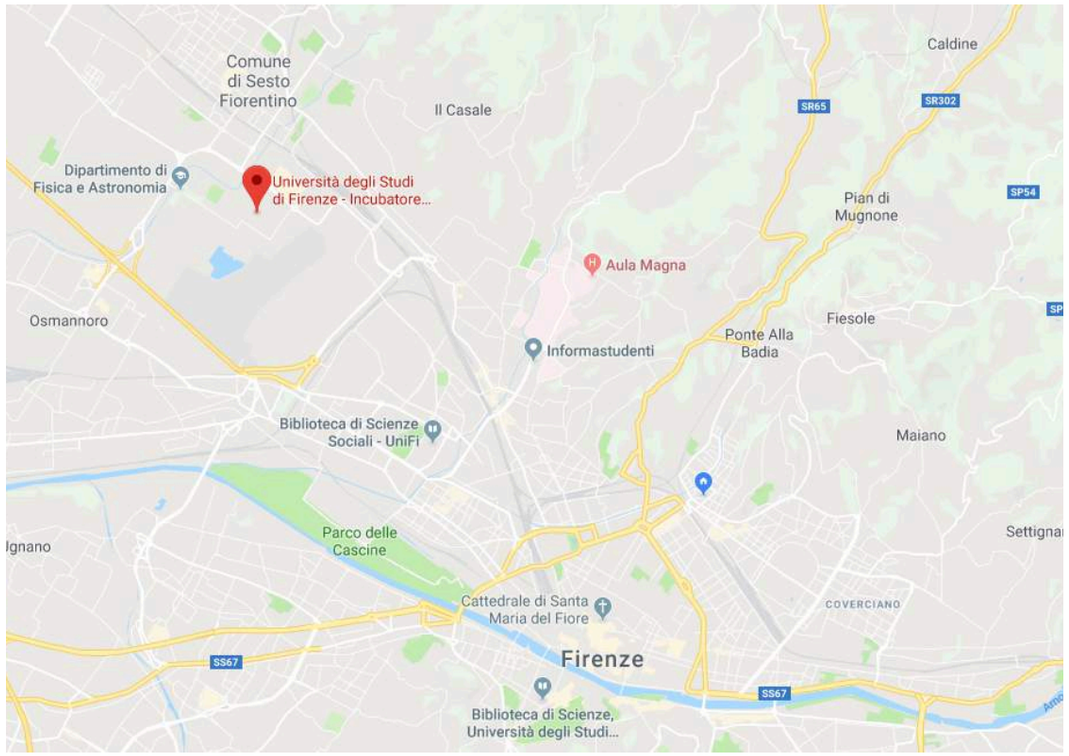
Luana Presta
University of Luxembourg

Florence computational biology group

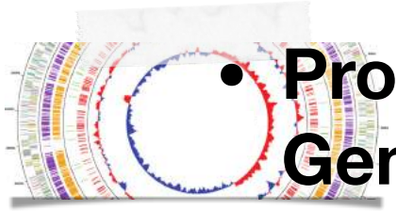


Bosi Emanuele
University of Pisa

Marco Galardini
Boston University

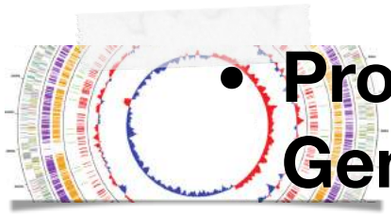


Research fields



- **Prokaryotic / Eukaryotic Genomics**

Research fields



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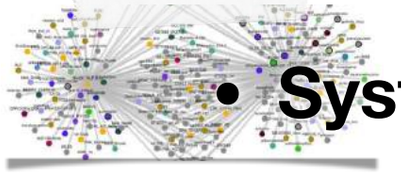
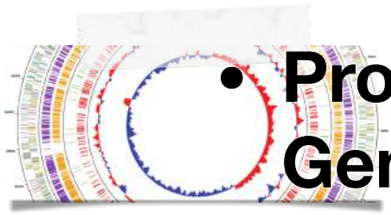


- **Systems Biology**

Research fields



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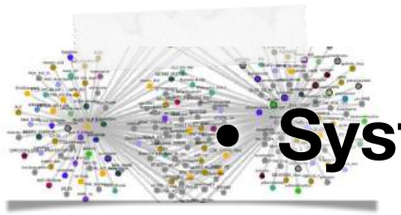

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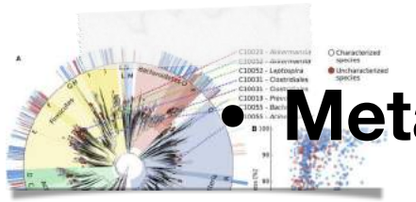
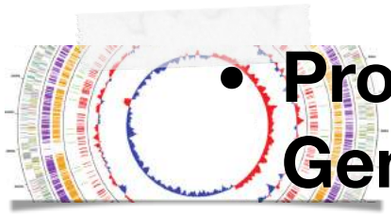


- **Metagenomics**

Research fields



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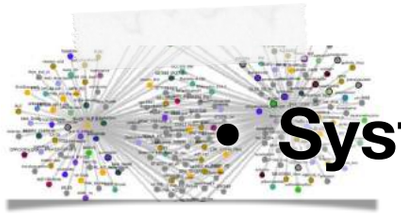

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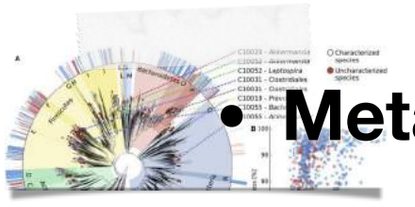

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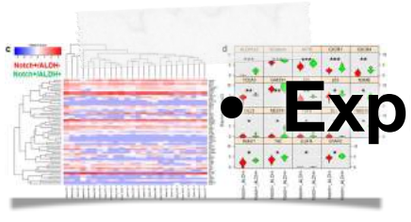
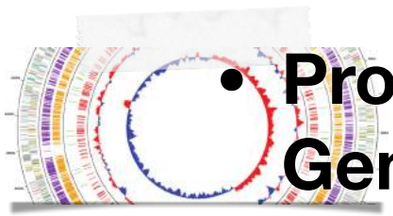


- **Expression data**

Research fields



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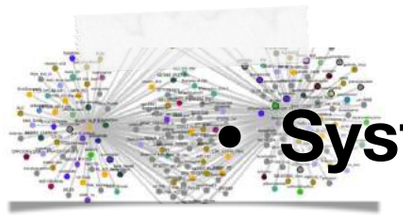

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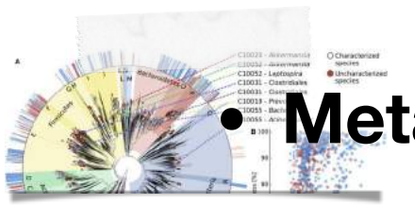
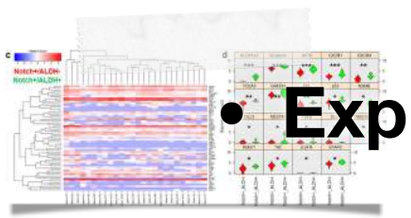


- **Metagenomics**



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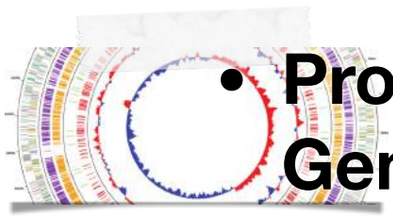

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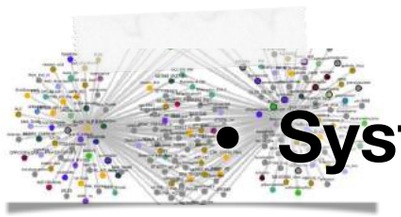

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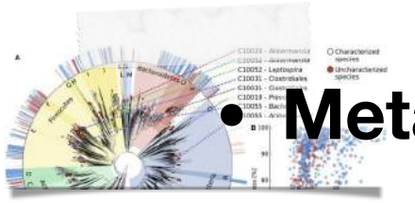

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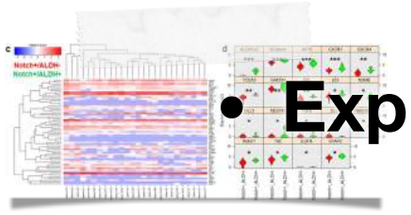
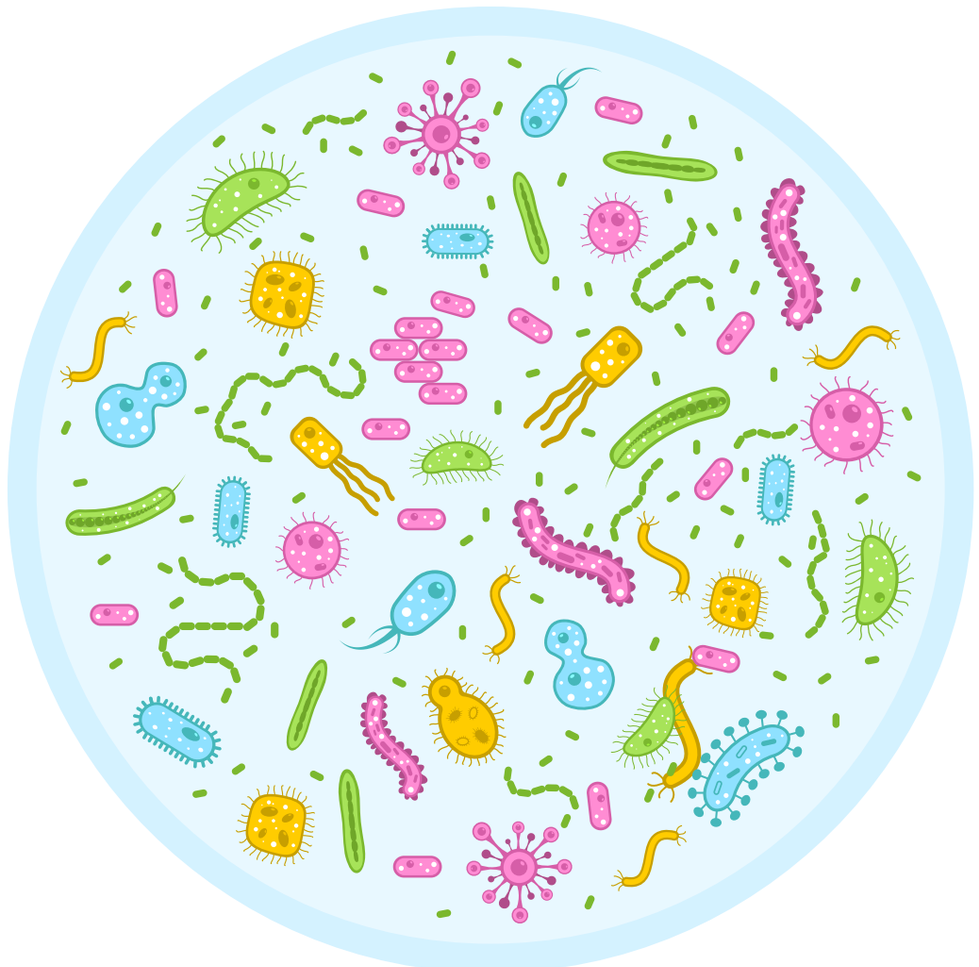
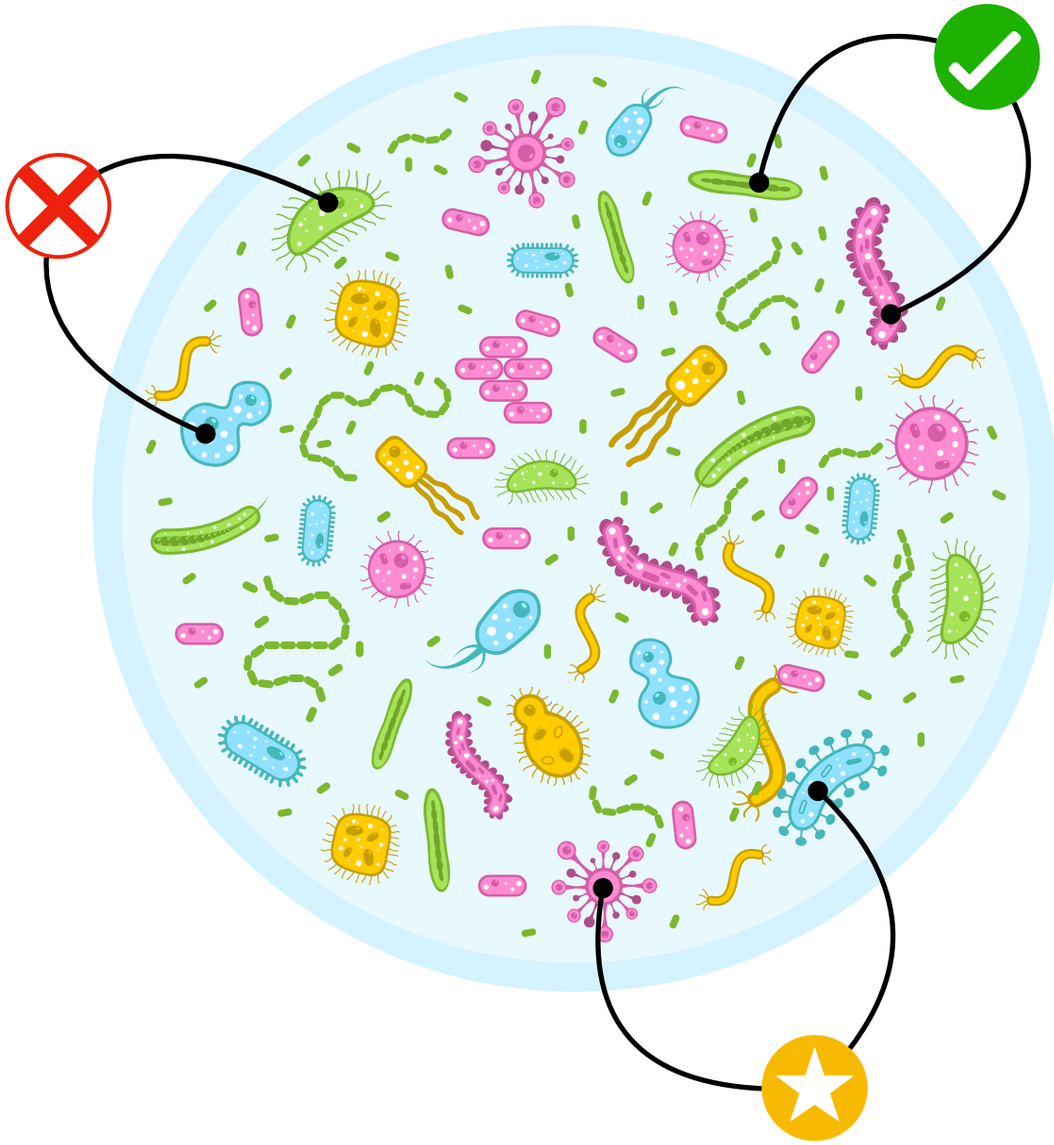


- **Expression data**

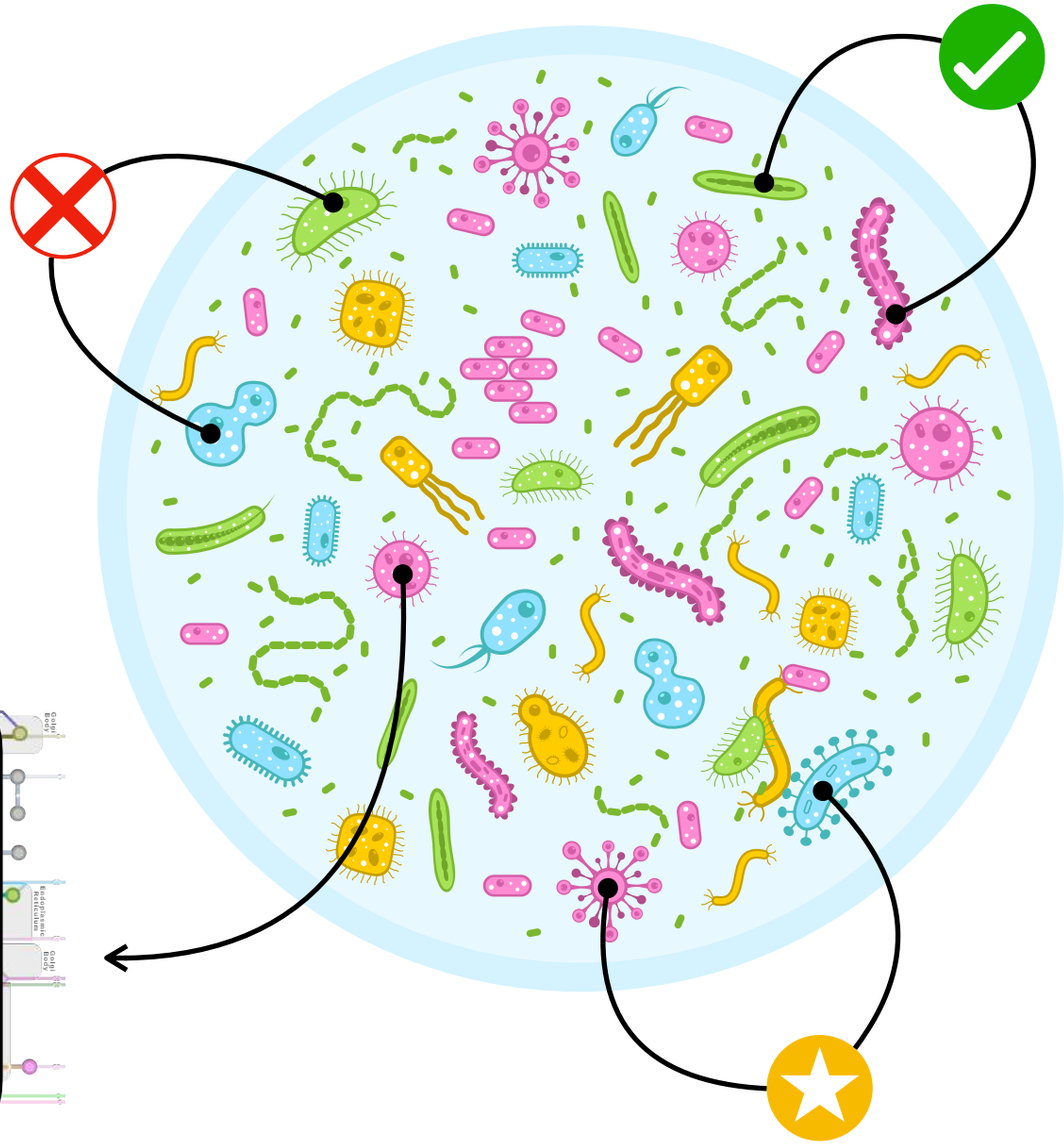
Bacterial roommates

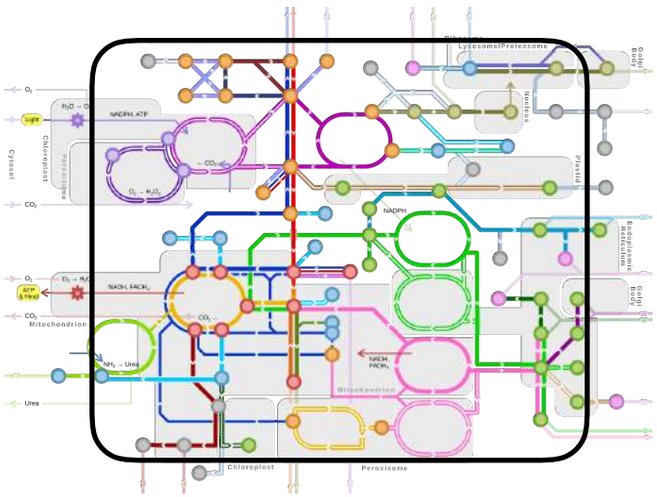


Bacterial roommates

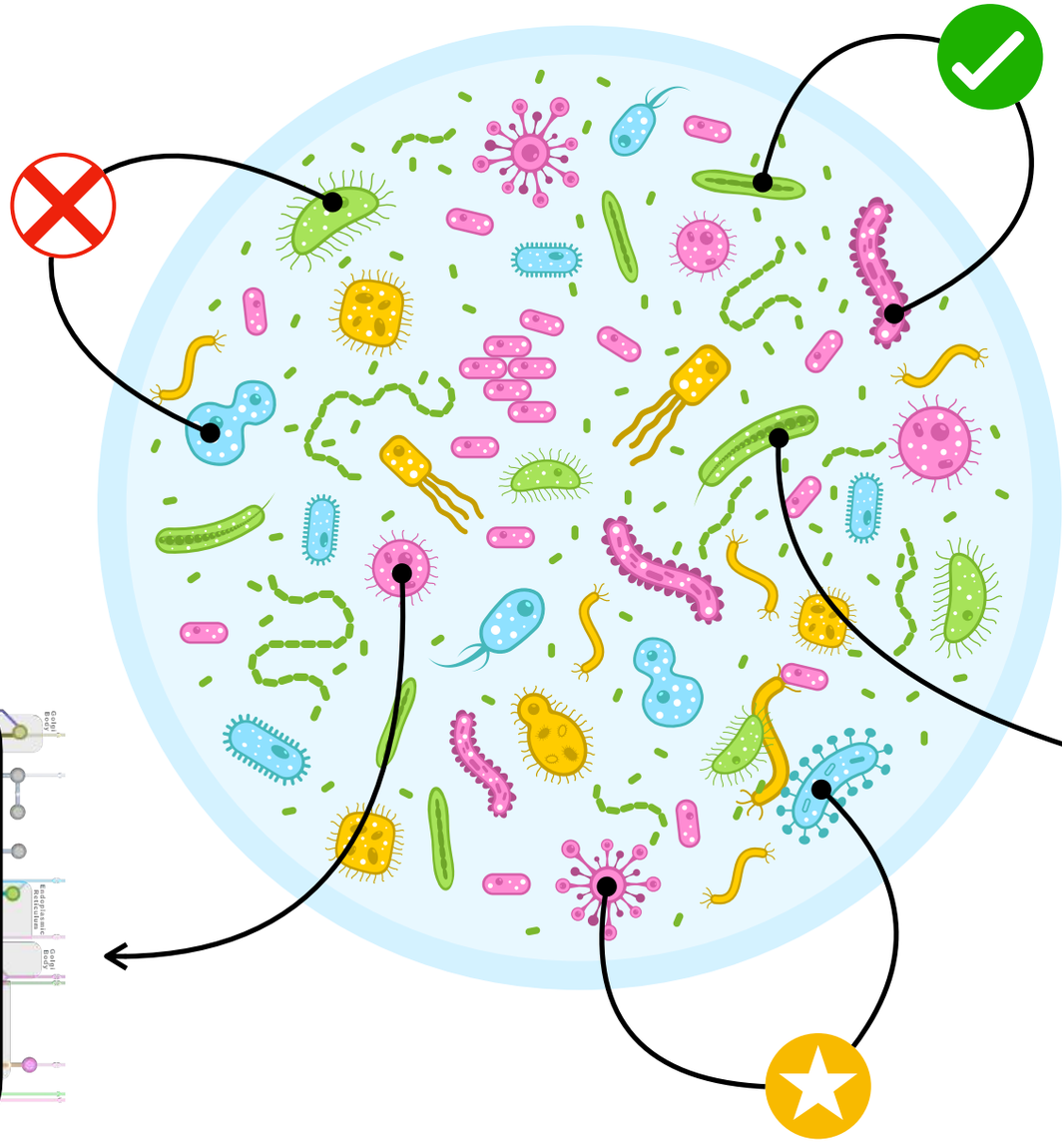


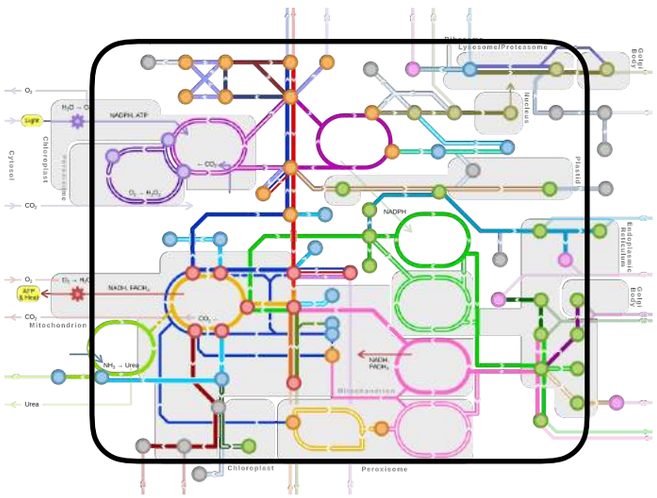
Bacterial roommates





Bacterial roommates





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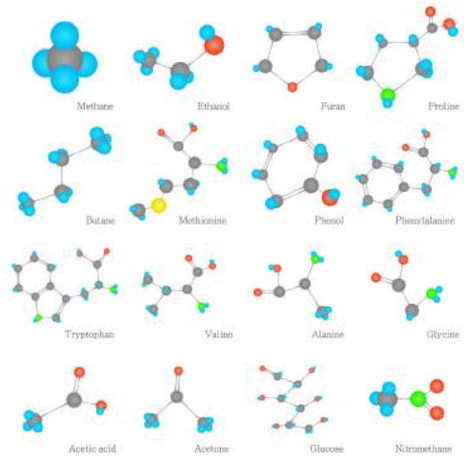

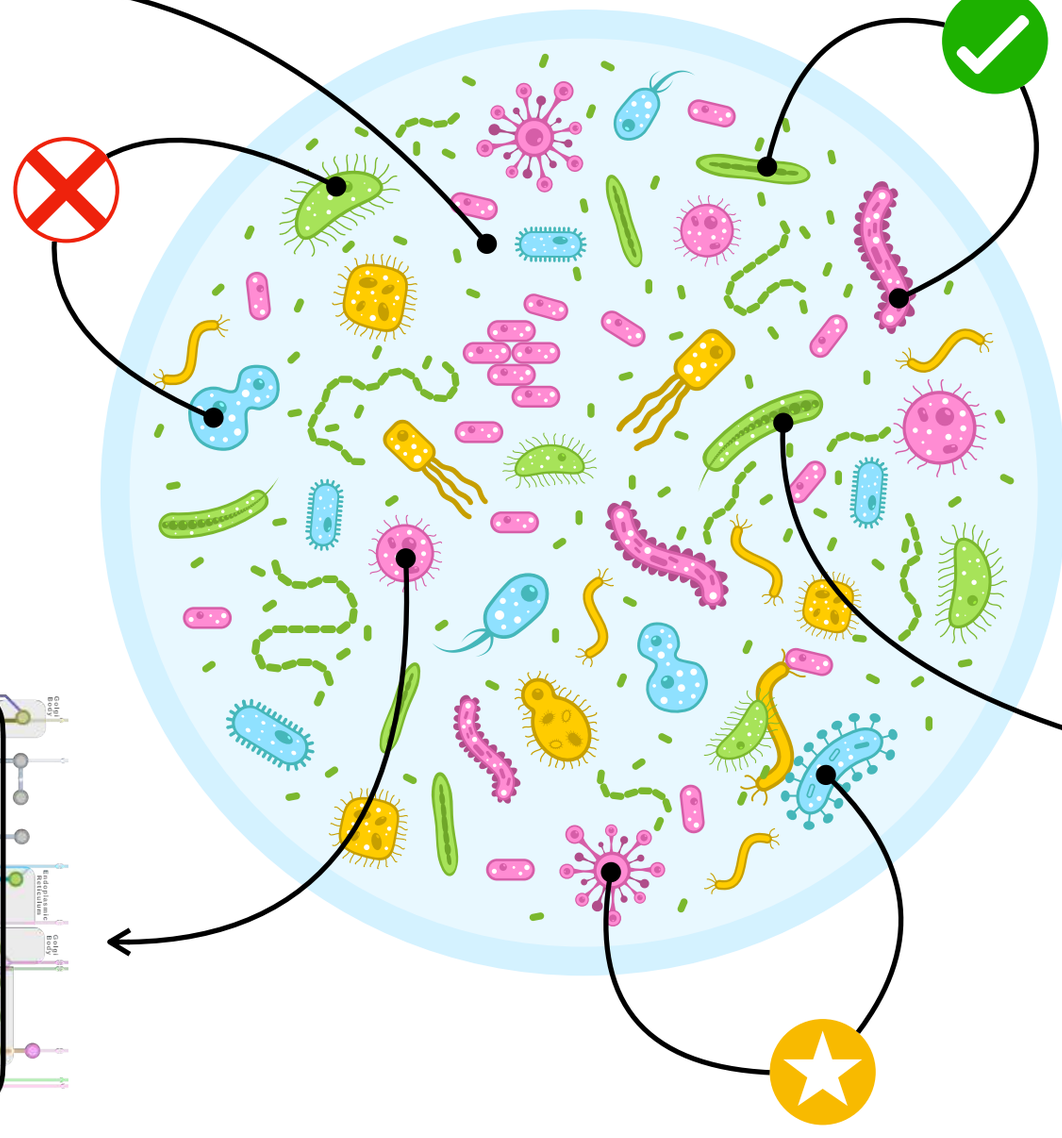

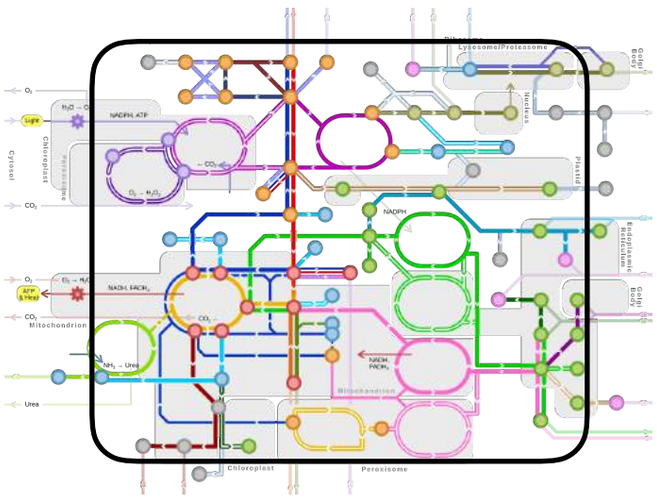

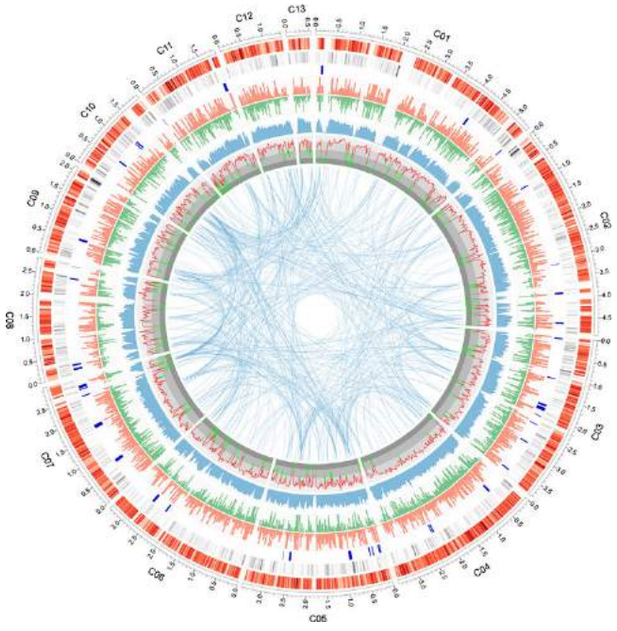

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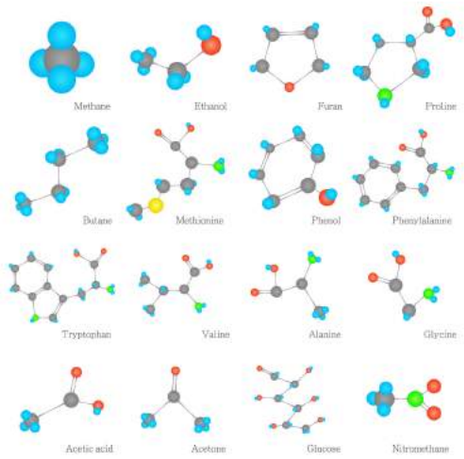

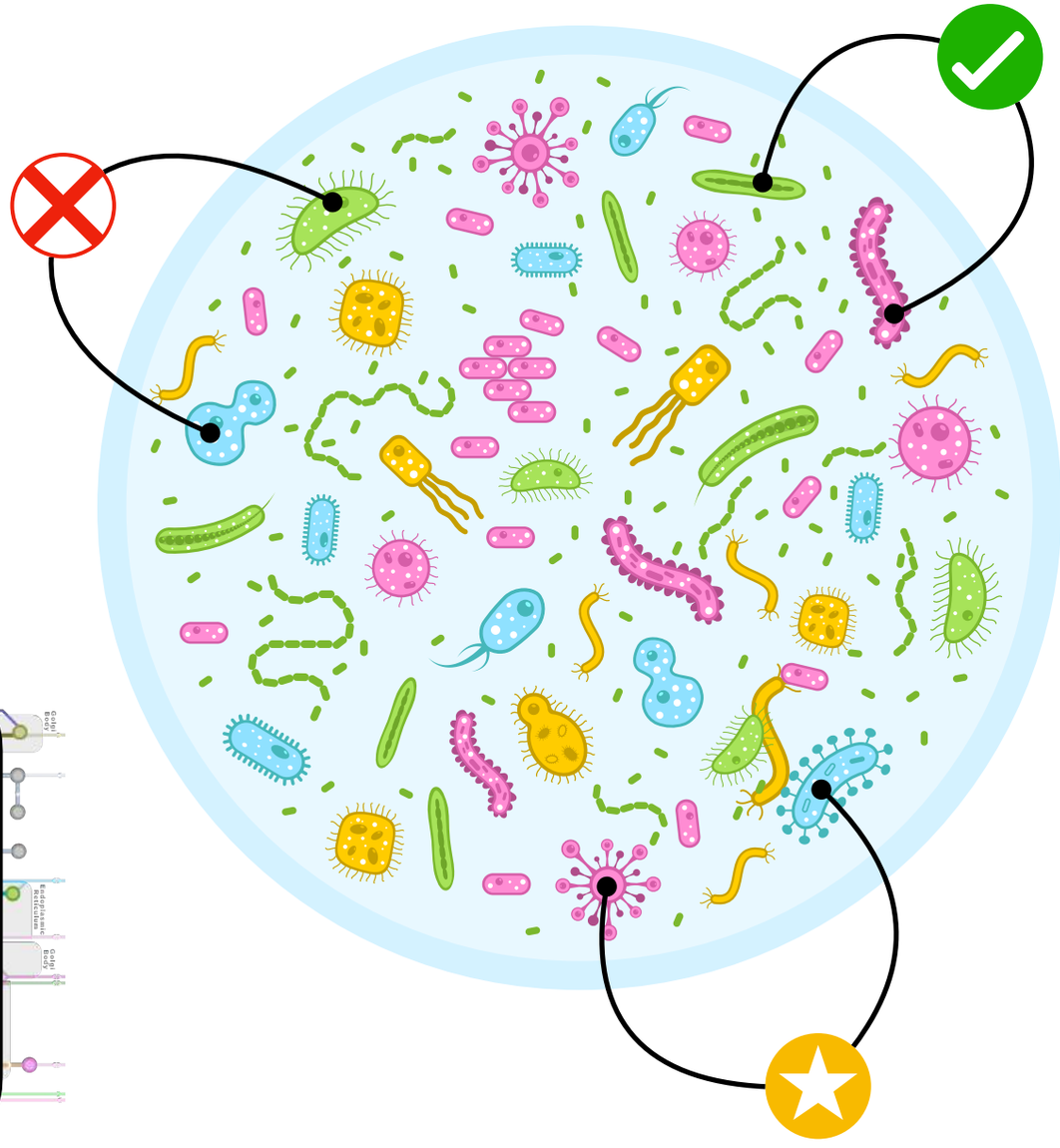

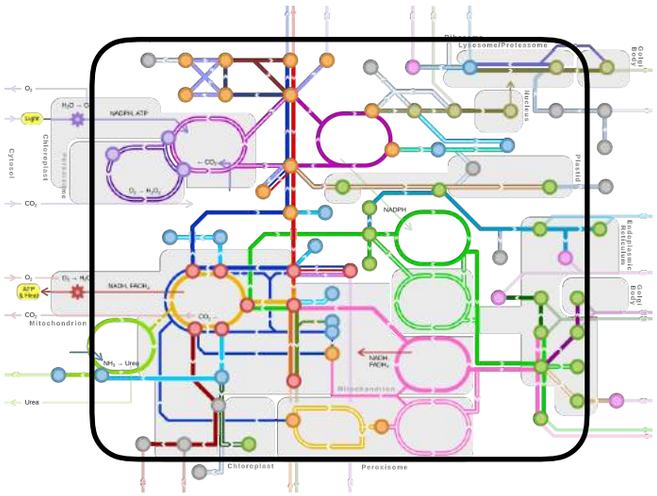

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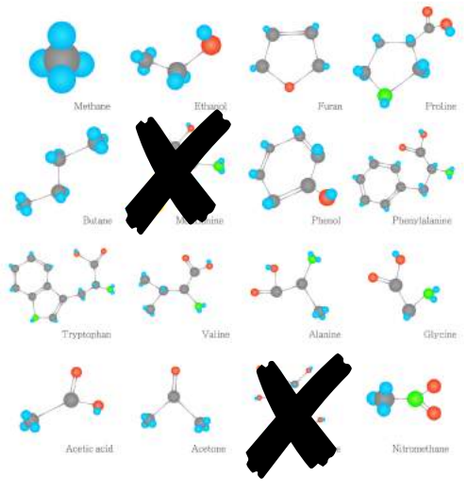

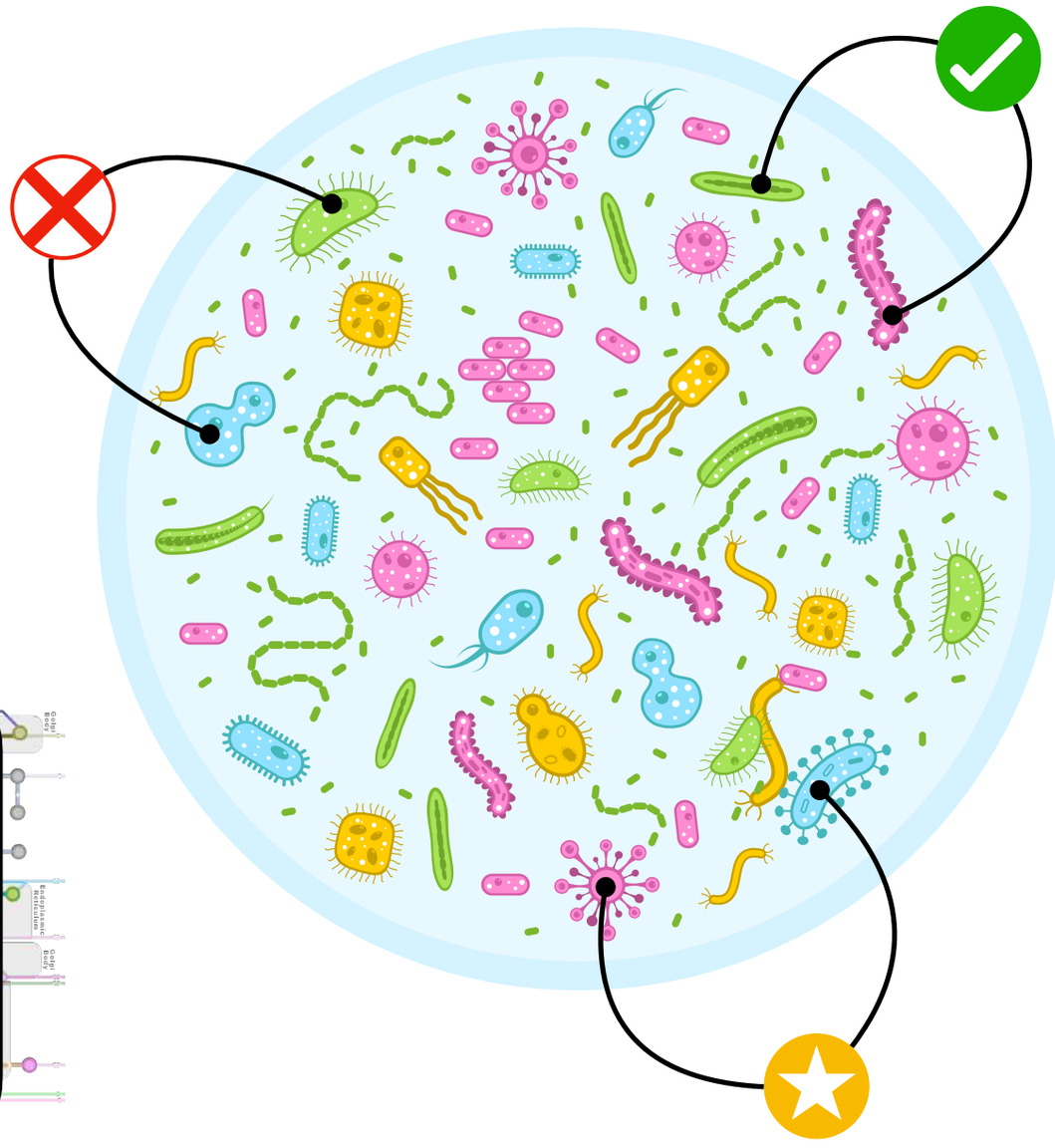

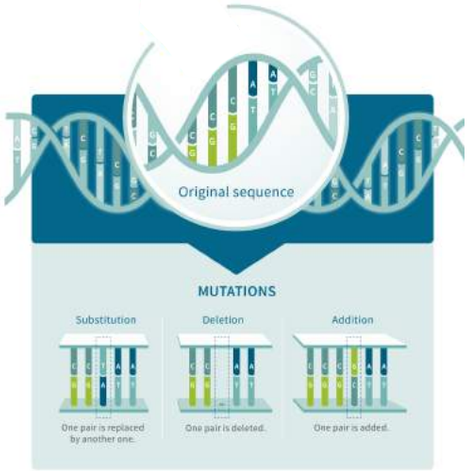

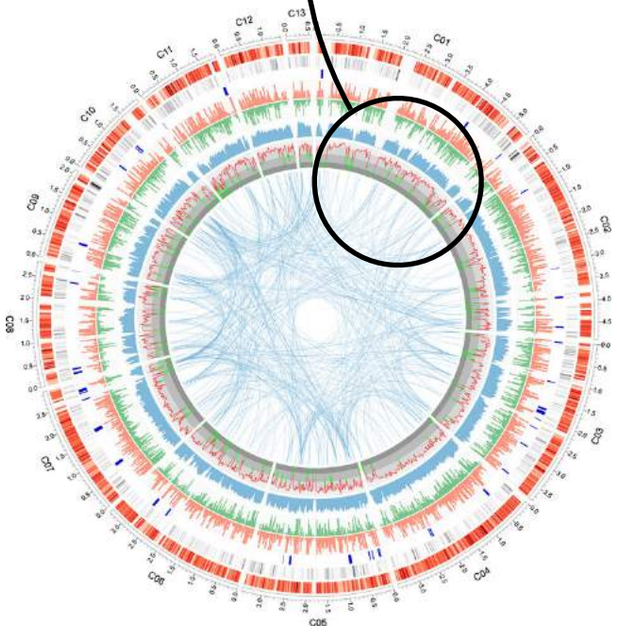

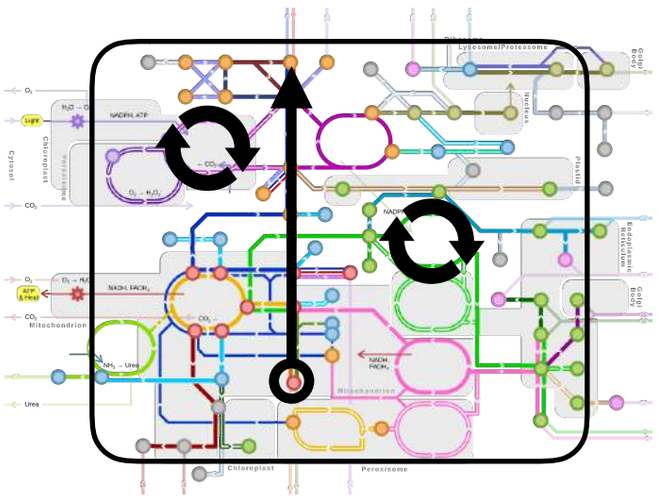

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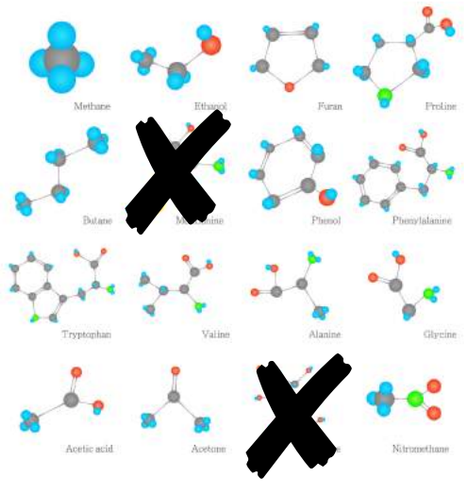
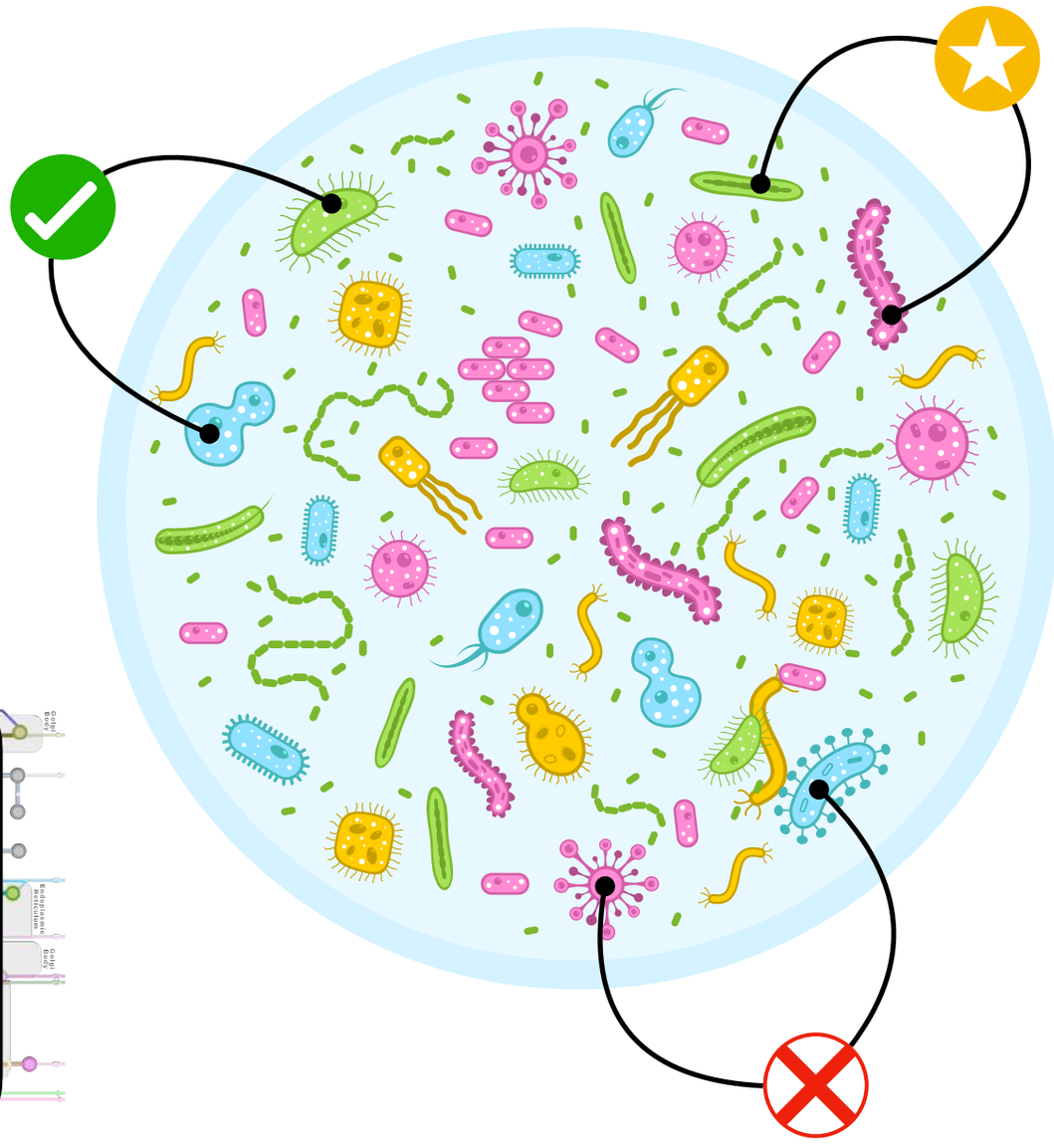
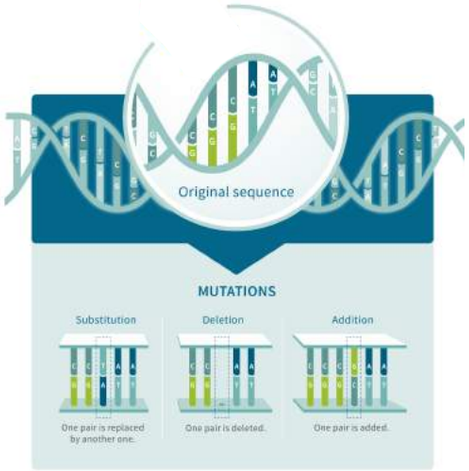
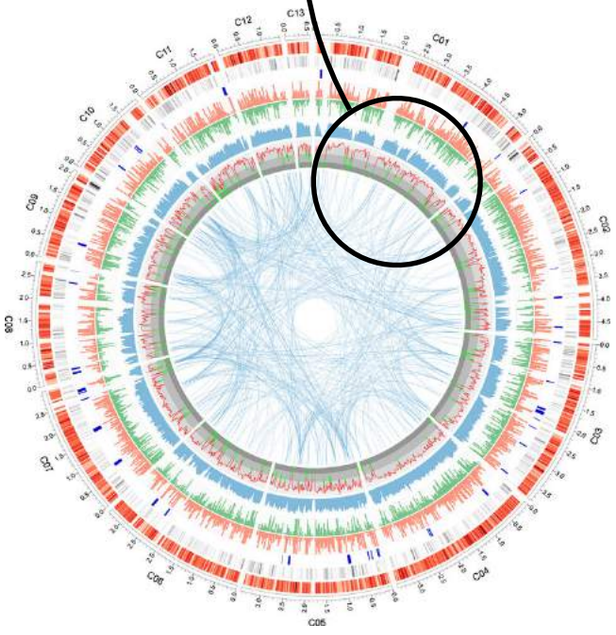
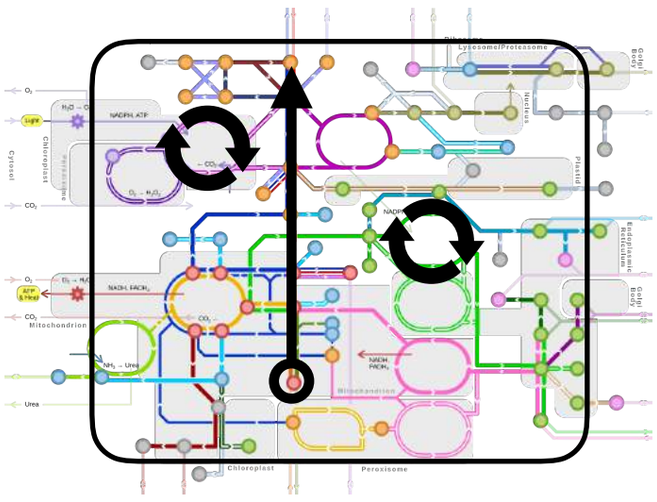








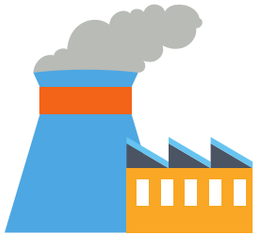


Microbes matter

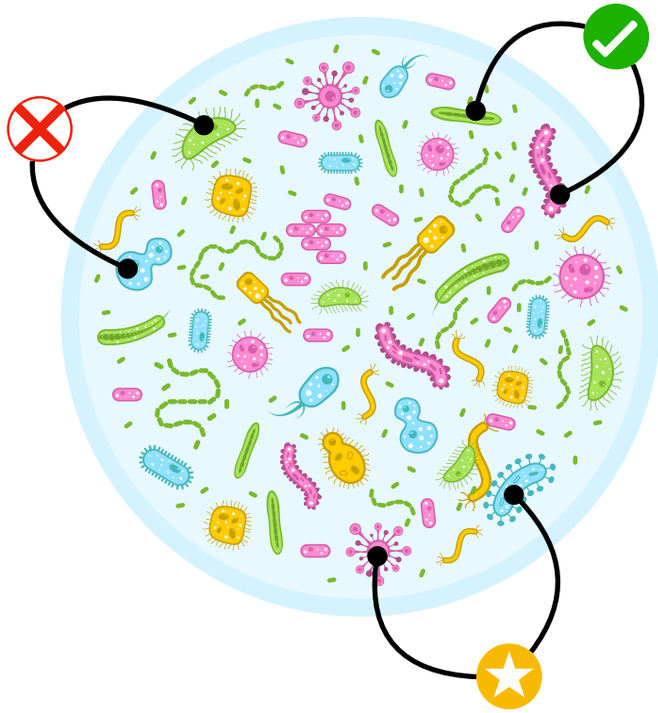
Microbes are a lot!
They are (almost) everywhere
They do a lot of things

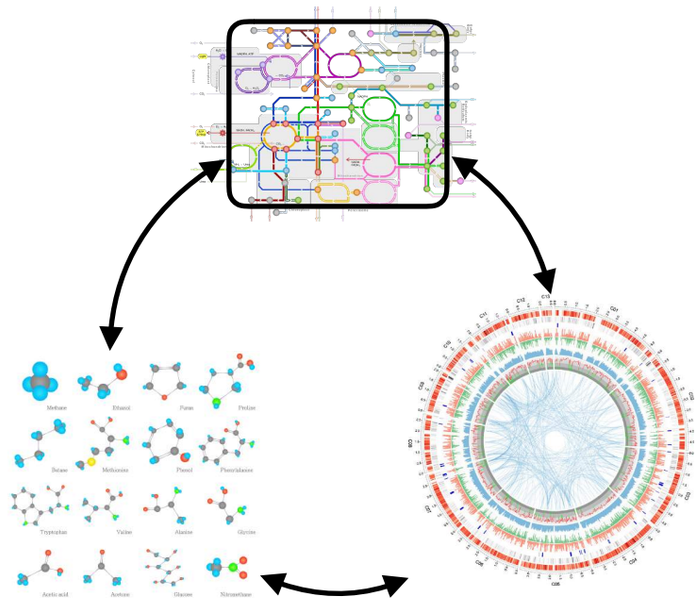
Biogeochemical cycles

Host genome integration
(Hologenome)

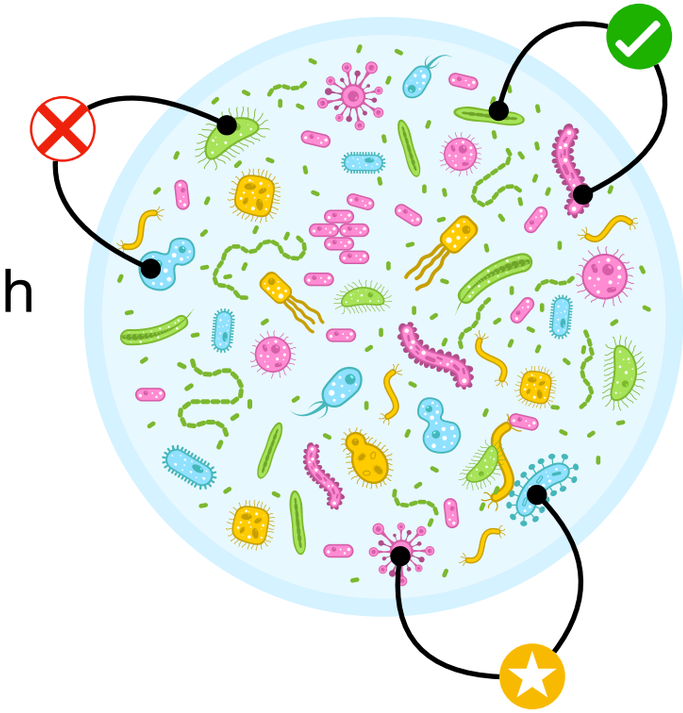


Useful compounds

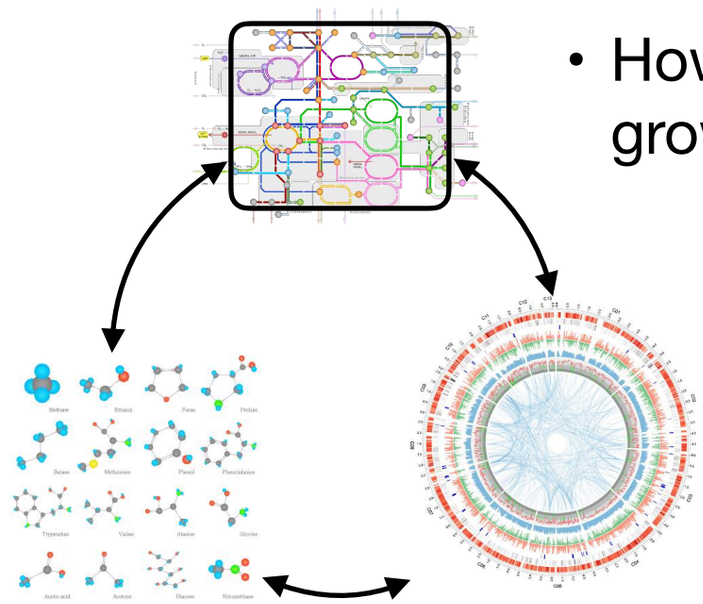



Methane
Ethanol
Furan
Proline
Butane
Methionine
Phenol
Phenylalanine
Tryptophan
Valine
Alanine
Glycine
Acetic acid
Acetone
Glucose
Nitromethane

- Who is there?
- How are they influencing each other?



- What are they doing?
- How fast are they growing?



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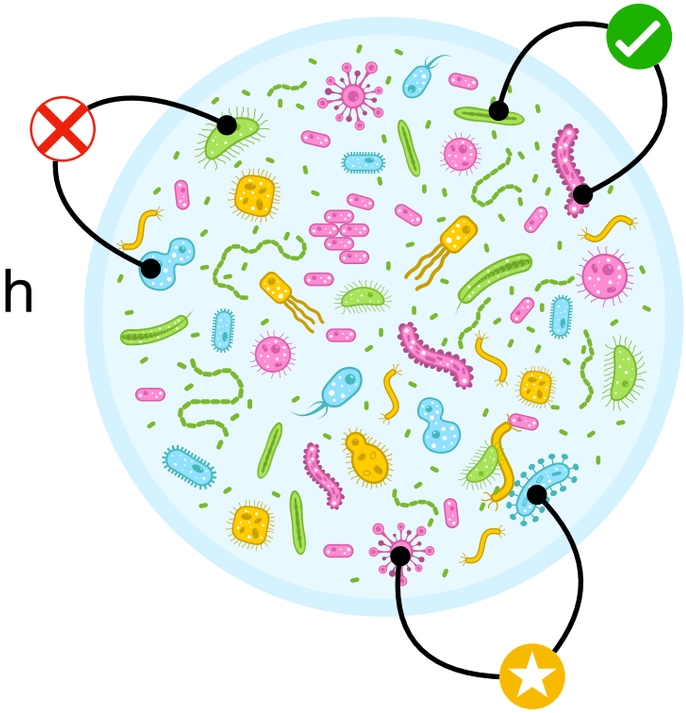

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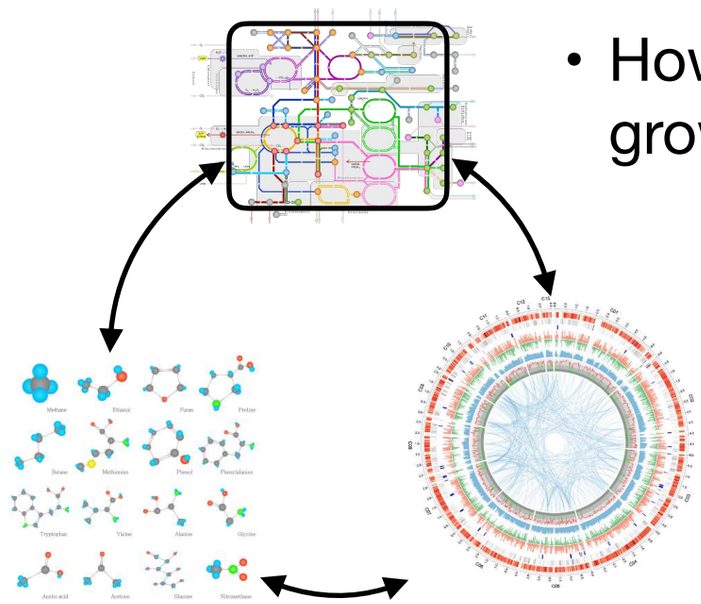
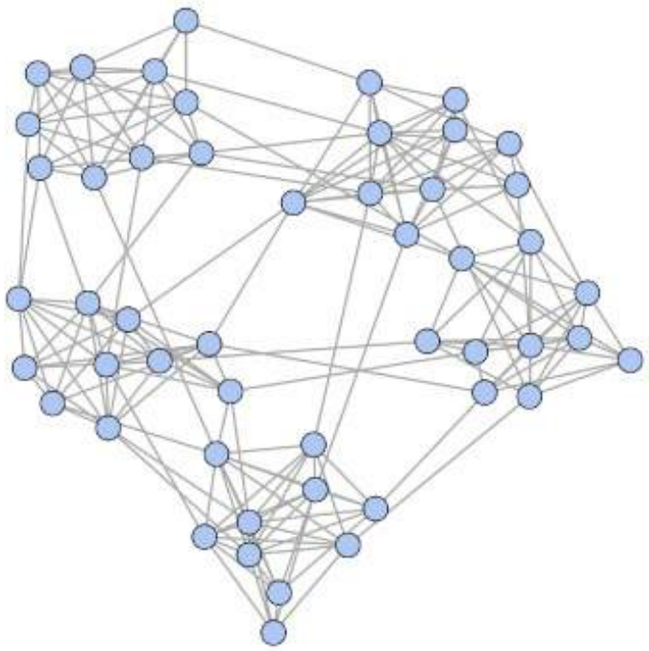
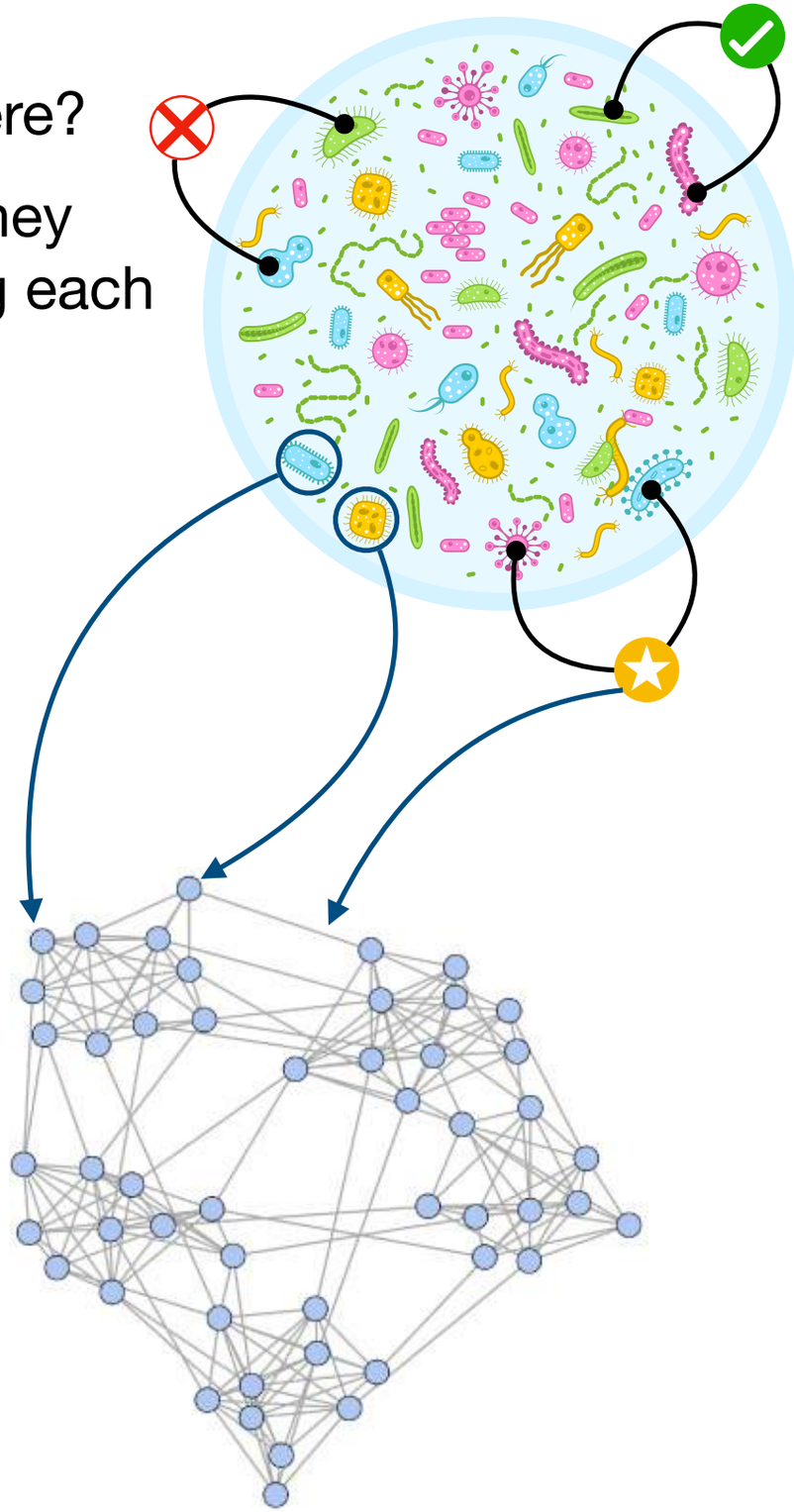
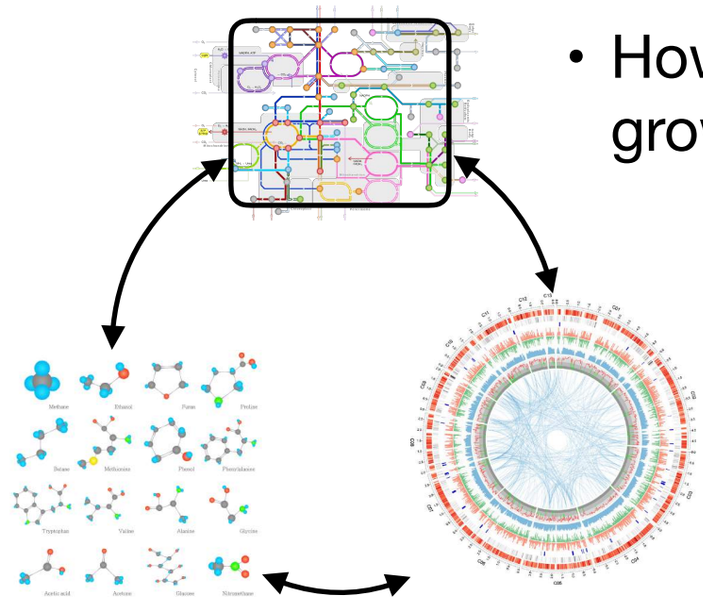
- How fast are they growing?





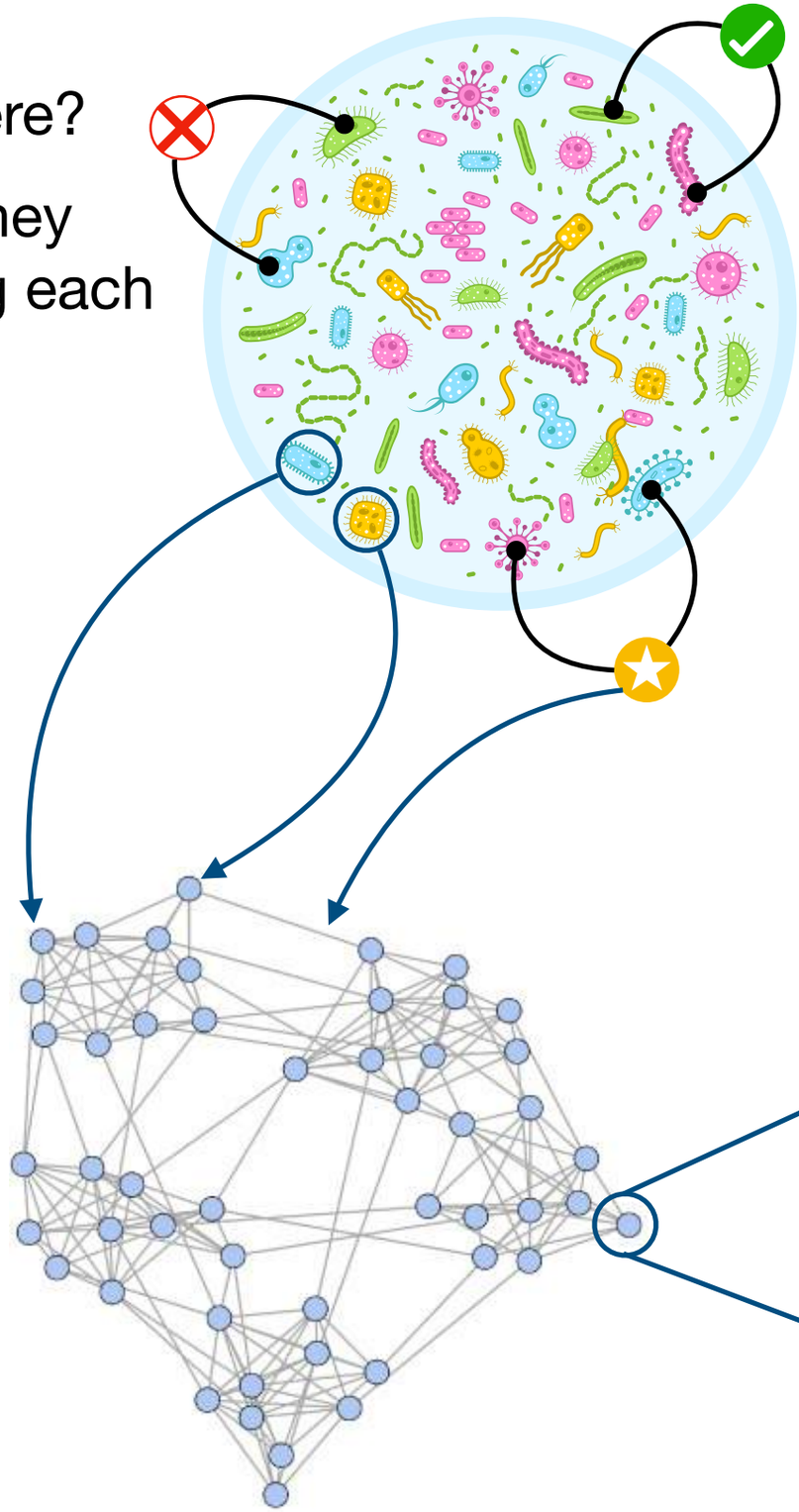
- Who is there?
- How are they influencing each other?





- What are they doing?
- How fast are they growing?

- Who is there?
- How are they influencing each other?



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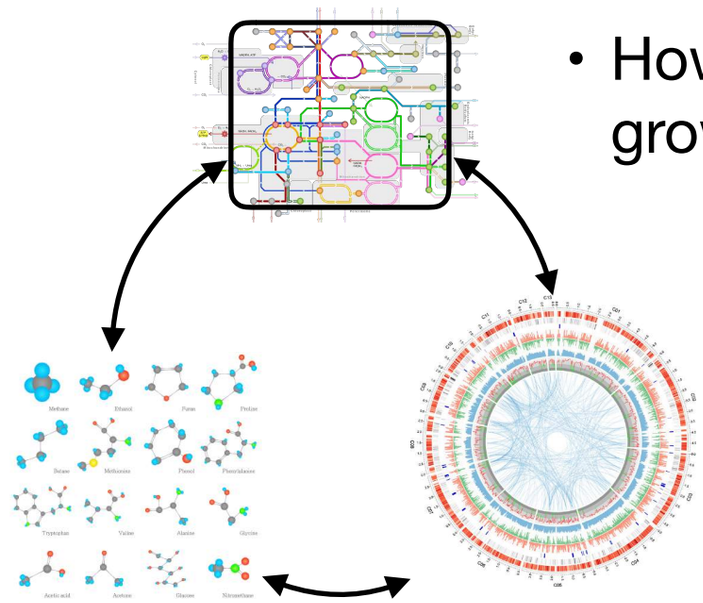
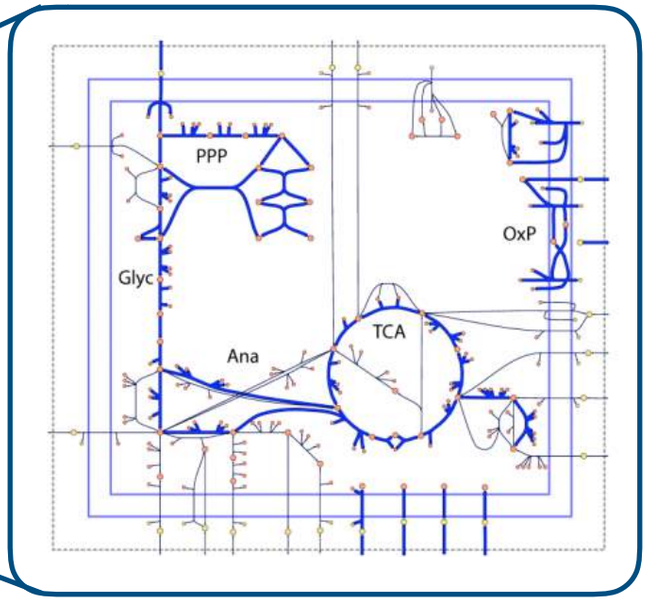
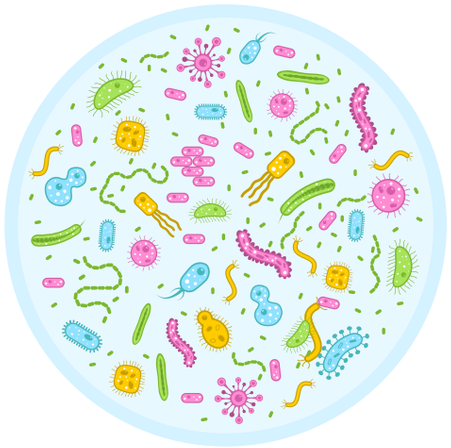




How can we model such complex interactions?

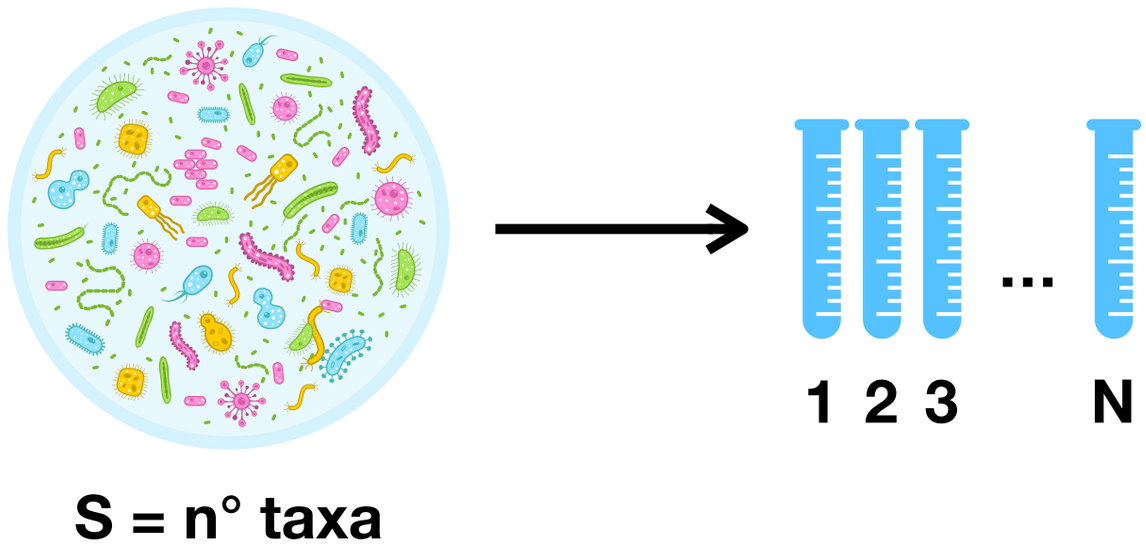
Community profiling



S = n° taxa

Community profiling

Community sampling



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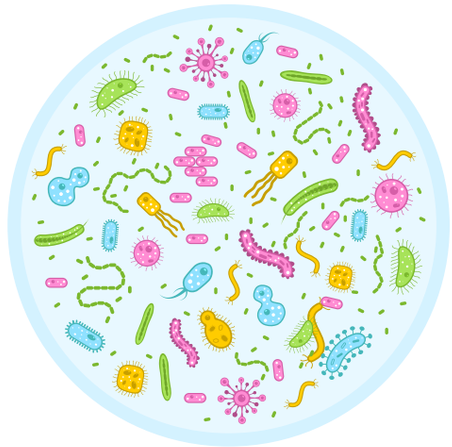

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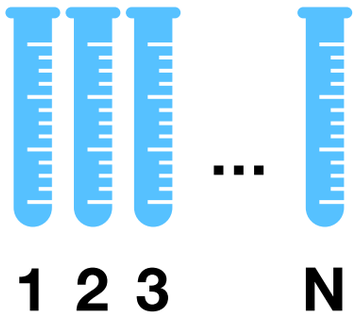


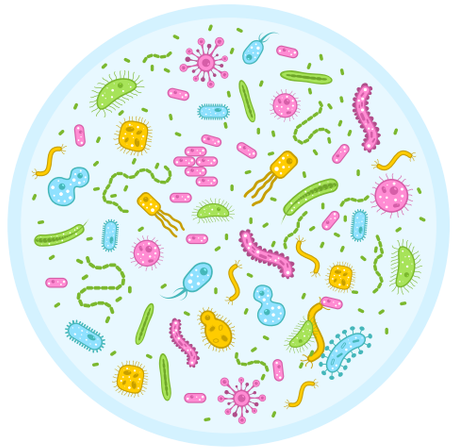
N x S matrix

$$\begin{pmatrix} X_{1,1} & X_{1,2} & \cdots & X_{1,S} \\ X_{2,1} & X_{2,2} & \cdots & X_{2,S} \\ X_{3,1} & X_{3,2} & \cdots & X_{3,S} \\ \vdots & \vdots & \ddots & \vdots \\ X_{N,1} & X_{N,2} & \cdots & X_{N,S} \end{pmatrix}$$

Taxonomic profiling

Community profiling

Community sampling



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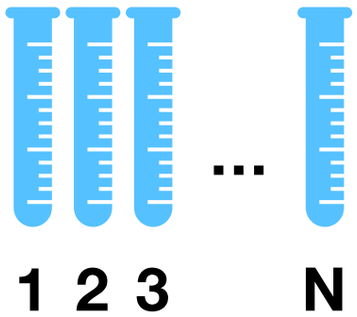

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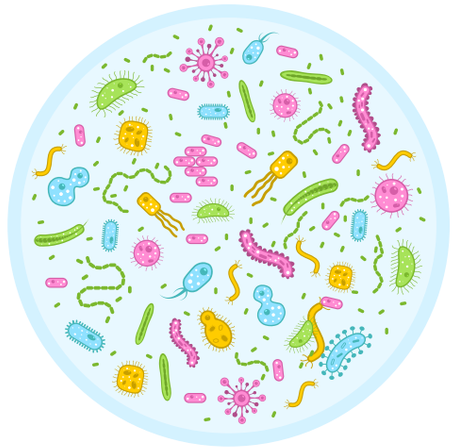
Taxonomic profiling

target gene (taxonomic marker)
shotgun metagenomics
T-RFLP
DGGE
...

Community profiling

Community sampling



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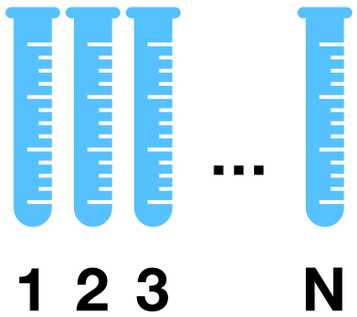

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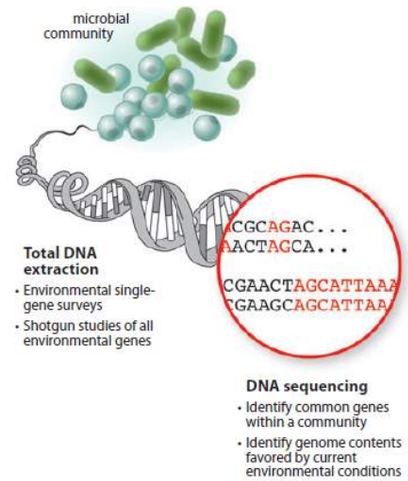
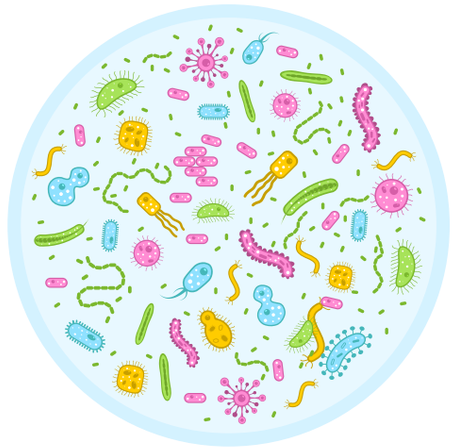


Community profiling

Community sampling



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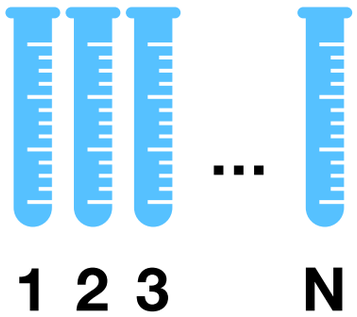

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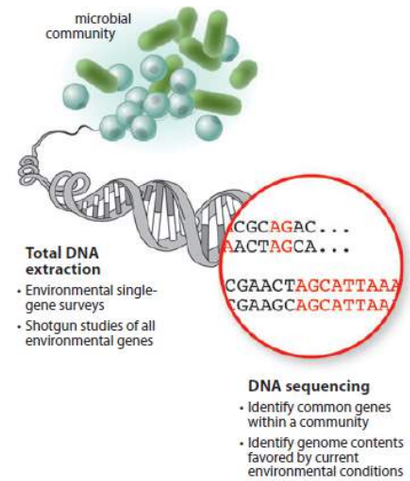
How can we use quantitative information to infer community structure?

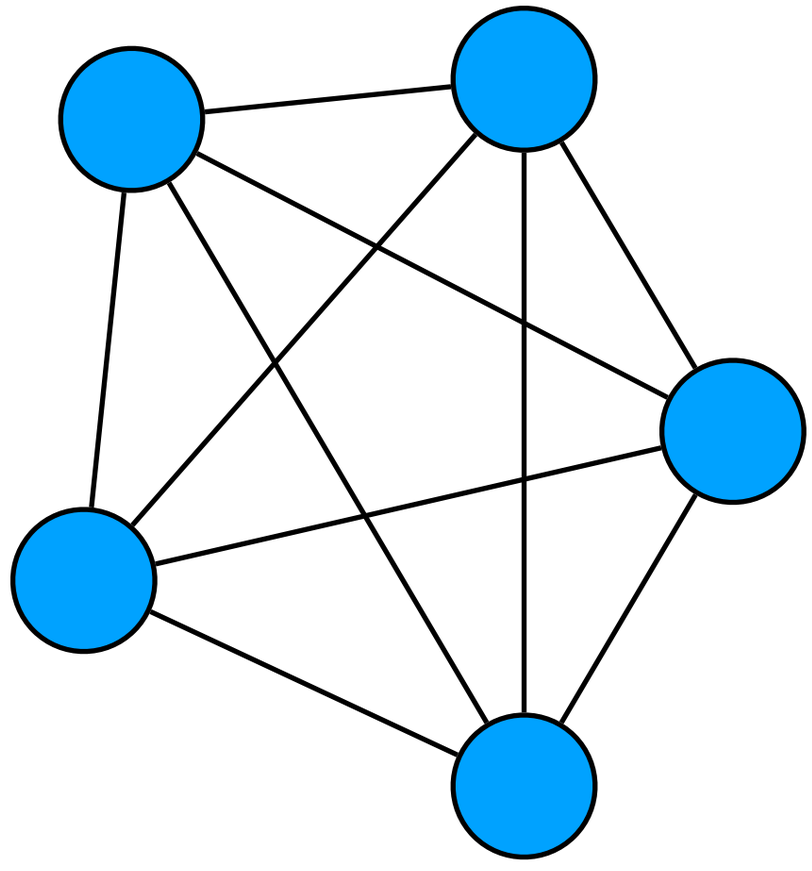
Taxonomic profiling

target gene (taxonomic marker)
shotgun metagenomics
T-RFLP
DGGE
…



Machine Learning

- All nodes (taxa) are predicted using all other nodes in the network



Machine Learning

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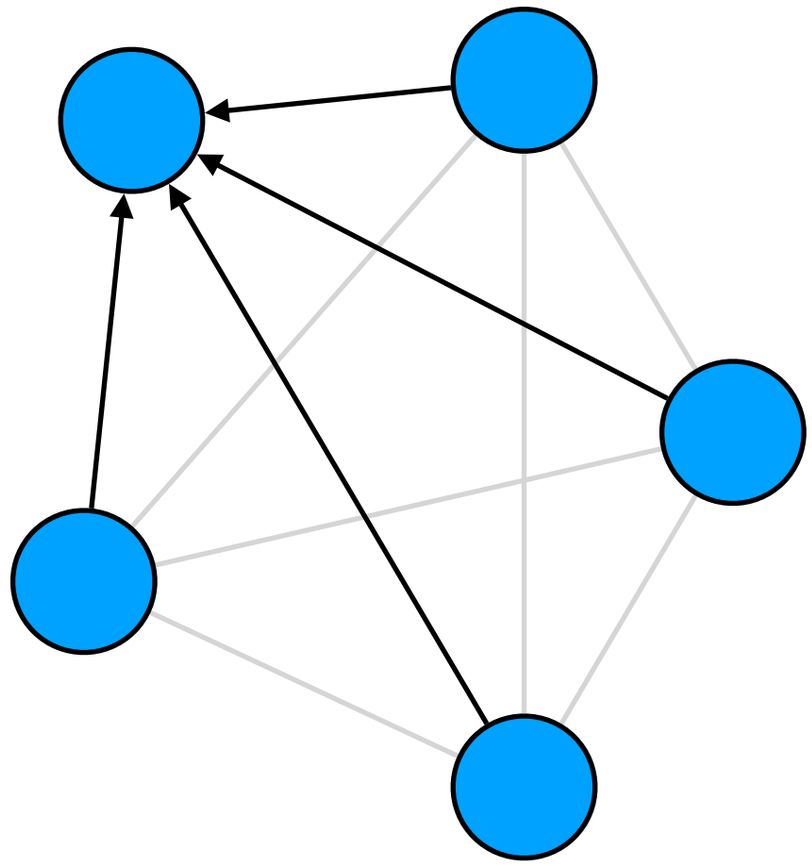

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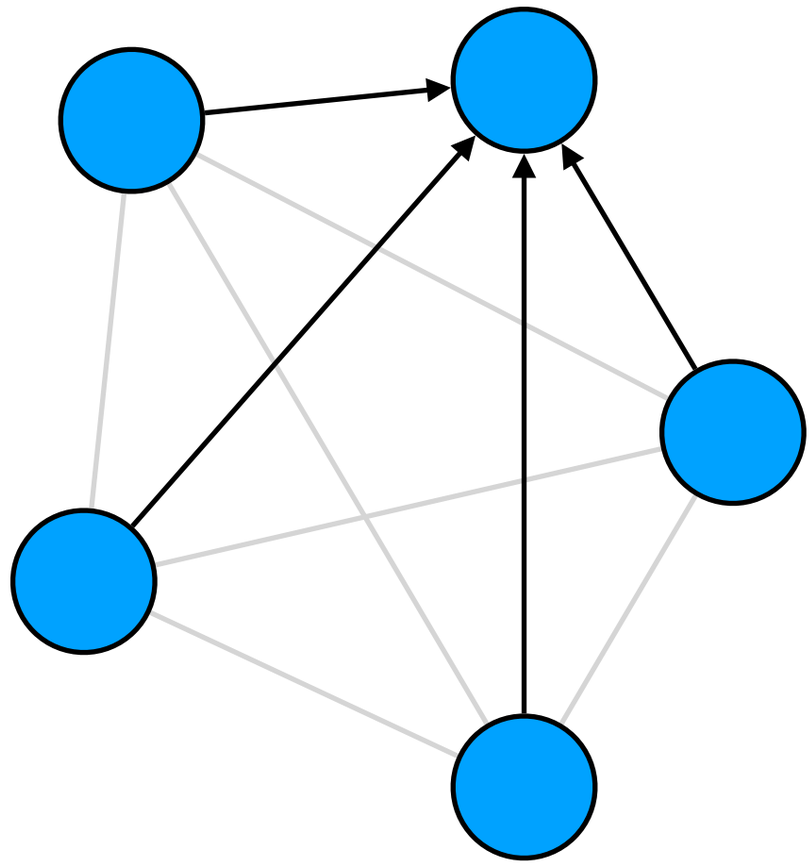

Machine Learning

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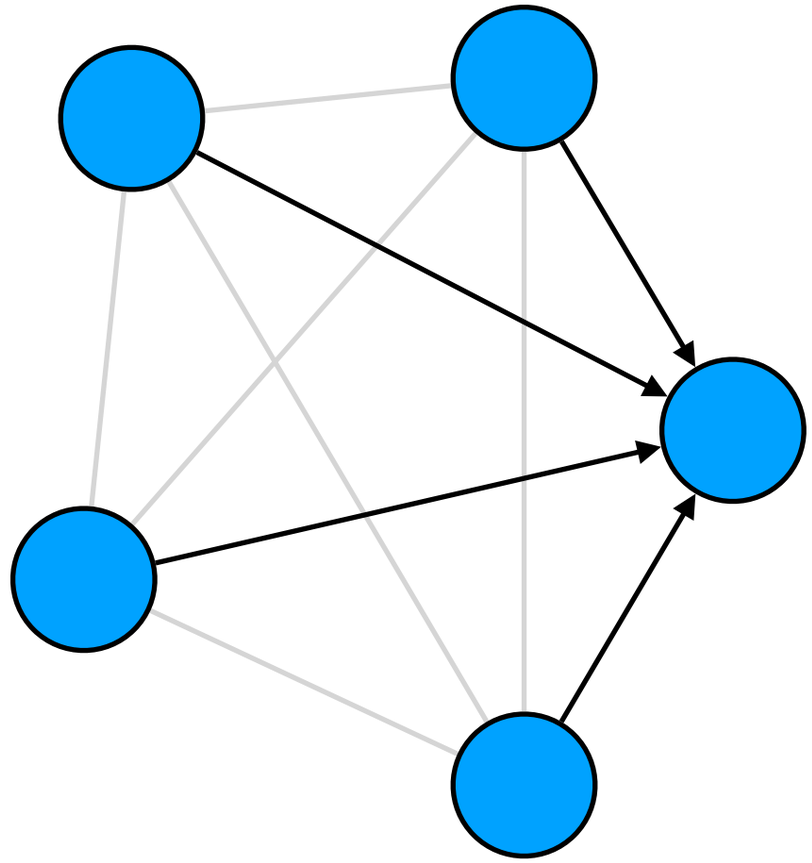
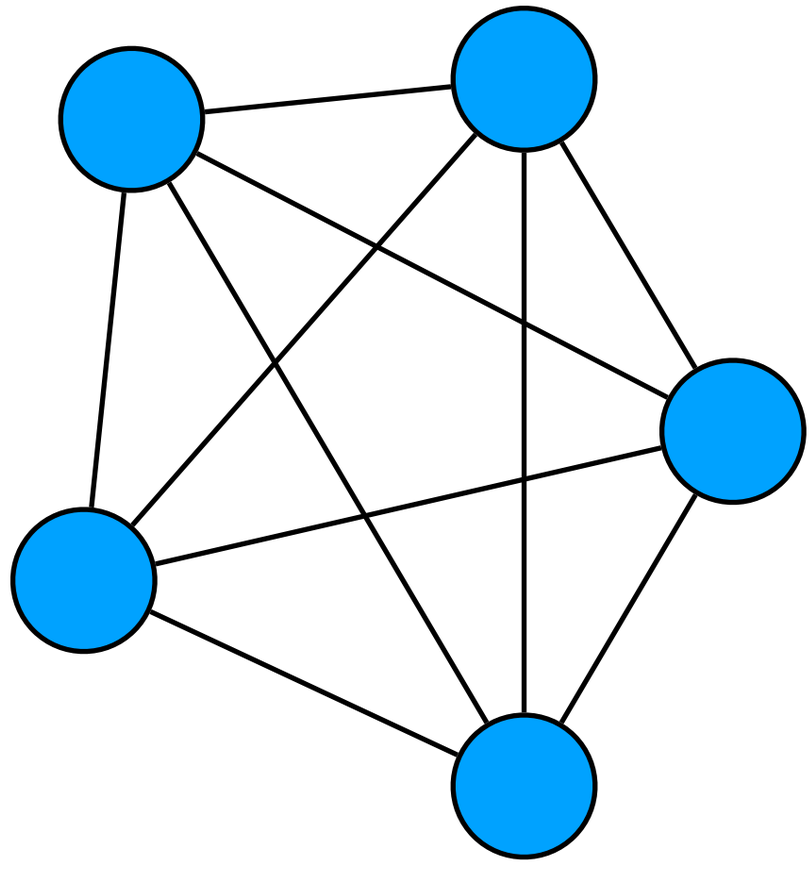


Machine Learning

- All nodes (taxa) are predicted using all other nodes in the network
- The effect of each predictor is estimated using root mean squared error



$$\mathbb{R}^{NxN} = \begin{pmatrix} - & d_{1,2} & \cdots & d_{1,N} \\ d_{2,1} & - & \cdots & d_{2,N} \\ \vdots & \vdots & \ddots & \vdots \\ d_{N,1} & d_{N,2} & \cdots & - \end{pmatrix}$$

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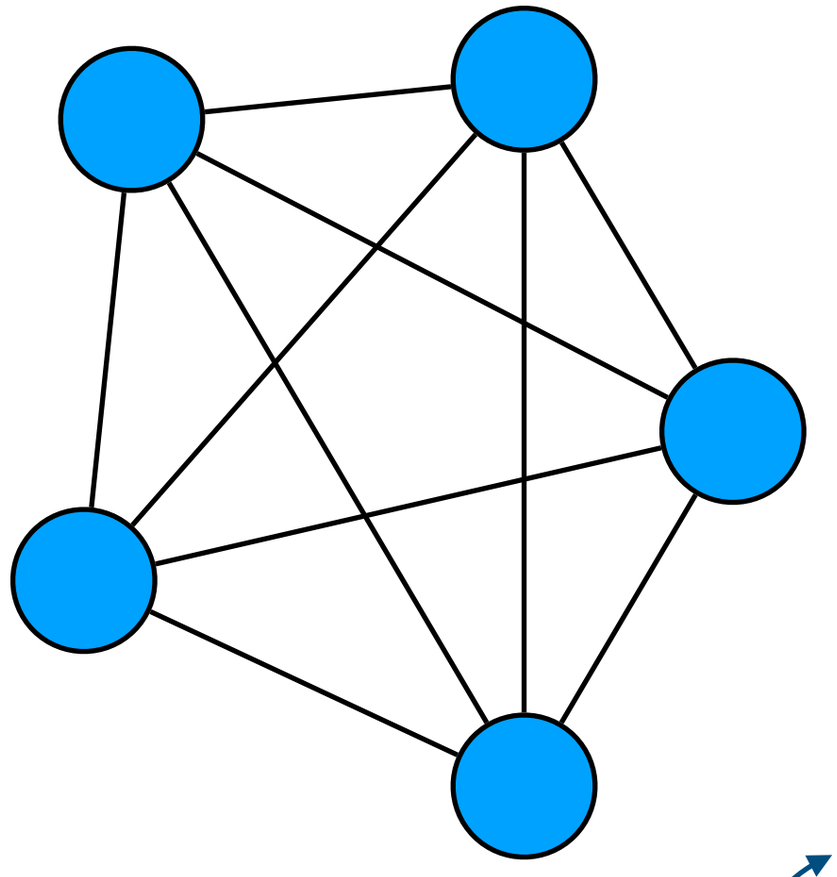

#nodes

$$\mathbb{R}^{NxN} = \begin{pmatrix} - & d_{1,2} & \cdots & d_{1,N} \\ d_{2,1} & - & \cdots & d_{2,N} \\ \vdots & \vdots & \ddots & \vdots \\ d_{N,1} & d_{N,2} & \cdots & - \end{pmatrix}$$

Machine Learning

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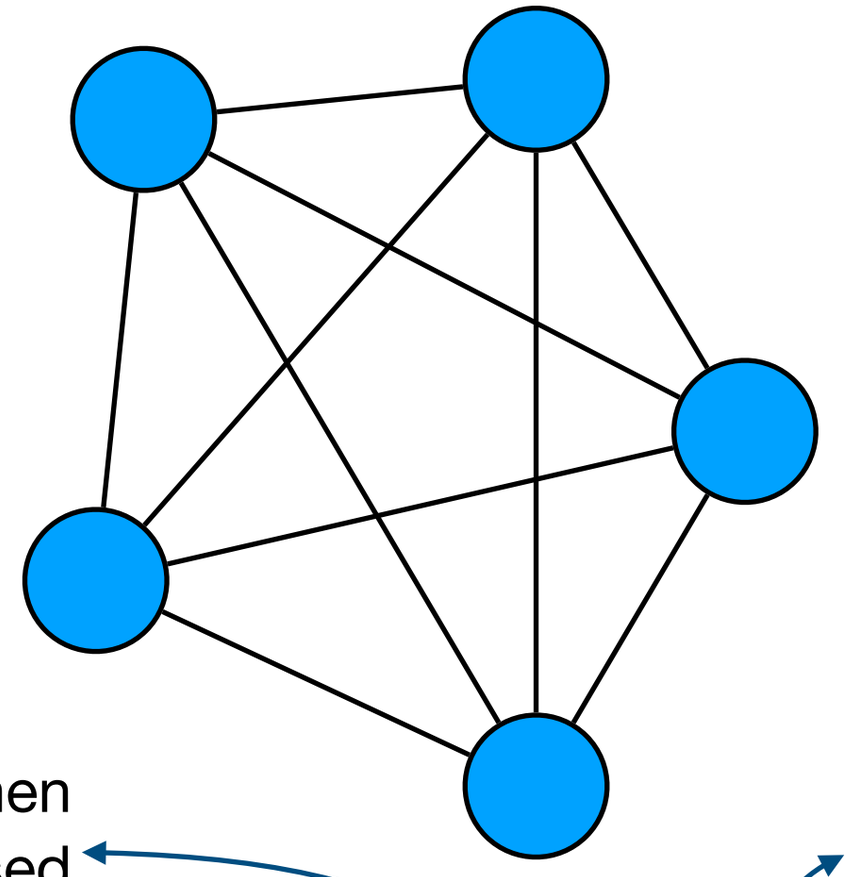


Δ(RMSE) when node 2 is not used in predicting node 1

#nodes

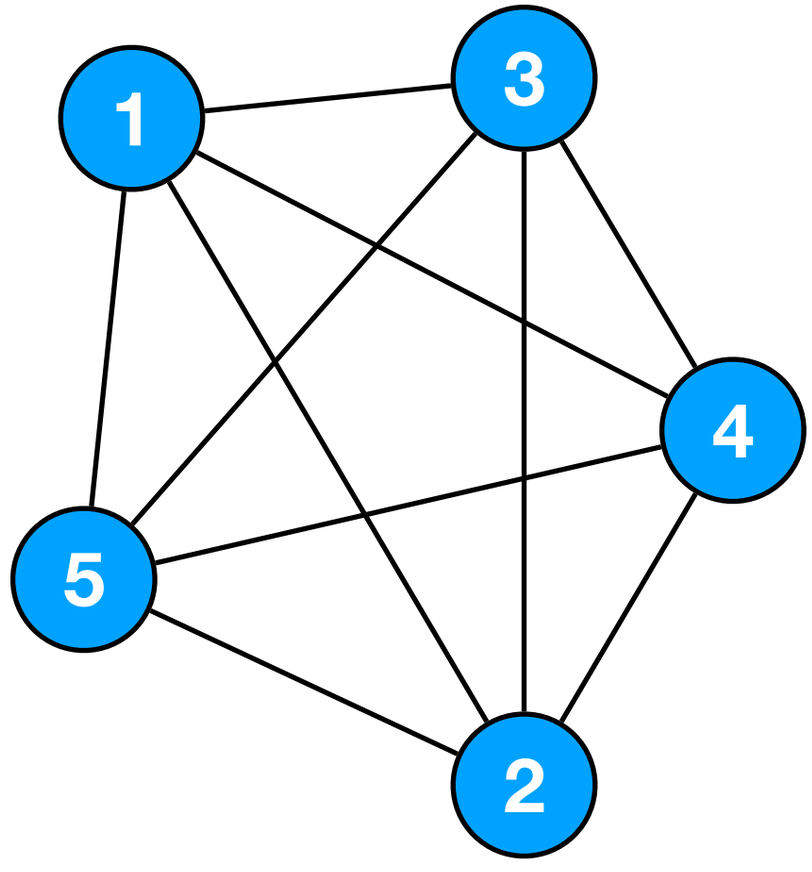
$$\mathbb{R}^{NxN} = \begin{pmatrix} - & d_{1,2} & \cdots & d_{1,N} \\ d_{2,1} & - & \cdots & d_{2,N} \\ \vdots & \vdots & \ddots & \vdots \\ d_{N,1} & d_{N,2} & \cdots & - \end{pmatrix}$$

Machine Learning

- All nodes (taxa) are predicted using all other nodes in the network

- The effect of each predictor is estimated using root mean squared error

- Nodes are ranked according to their prediction power



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Machine Learning

- All nodes (taxa) are predicted using all other nodes in the network
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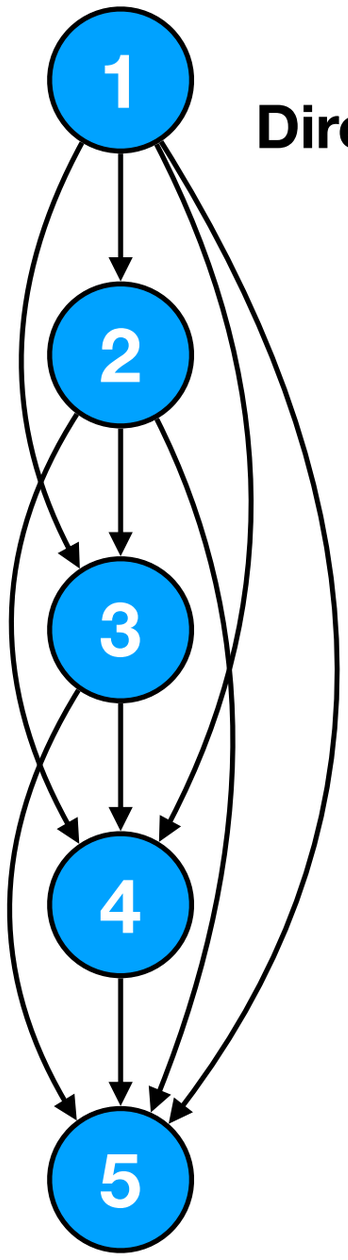
- The system is optimised using genetic algorithm



Directed Acyclic Graph
DAG

Machine Learning

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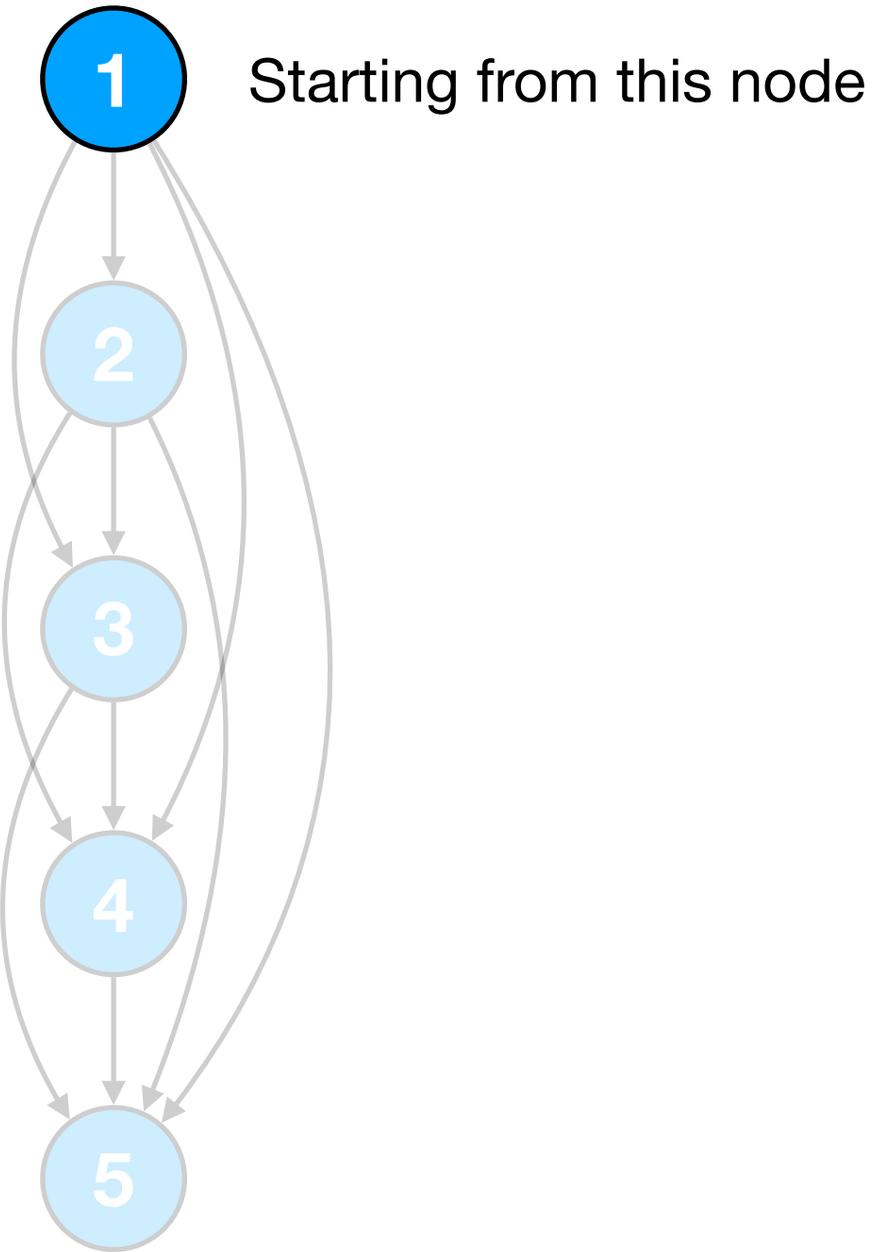

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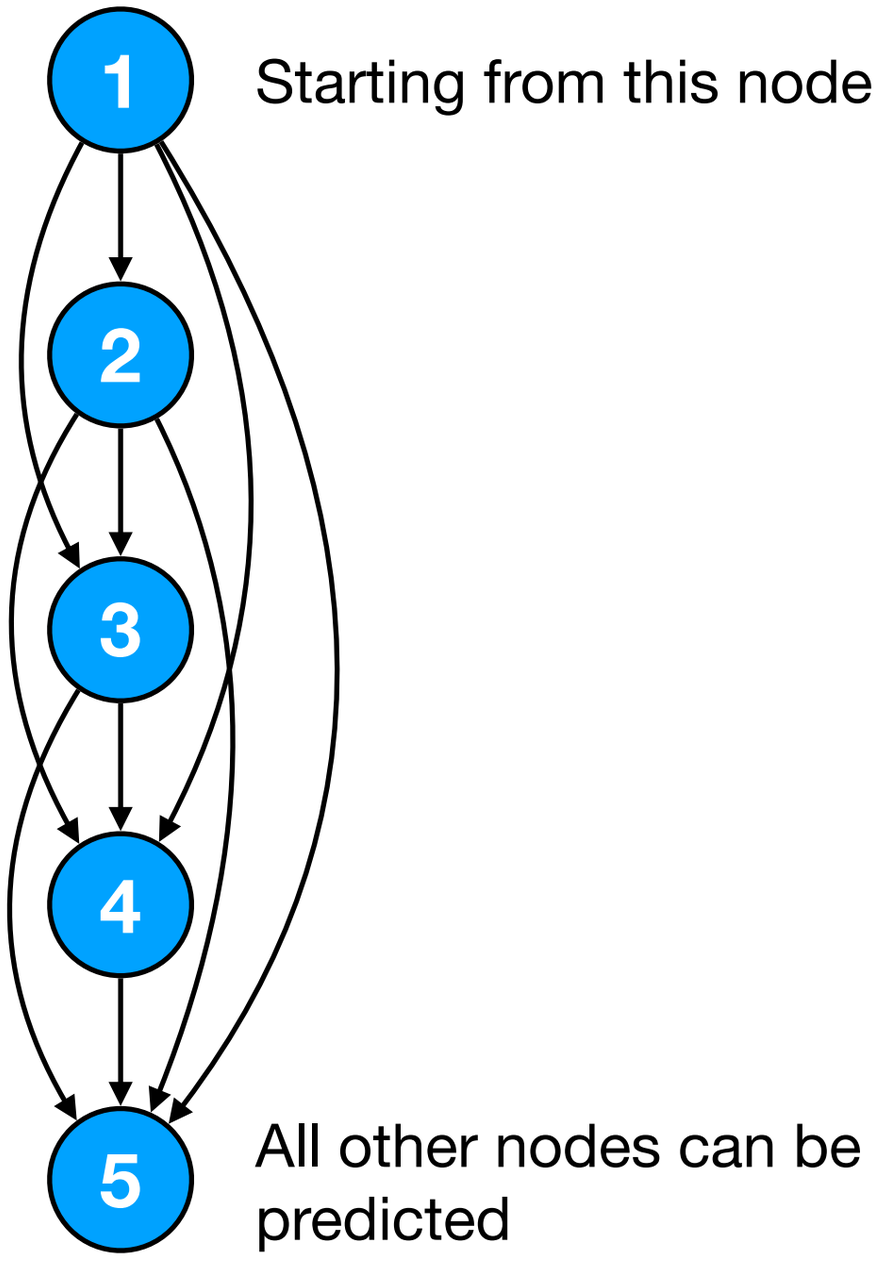
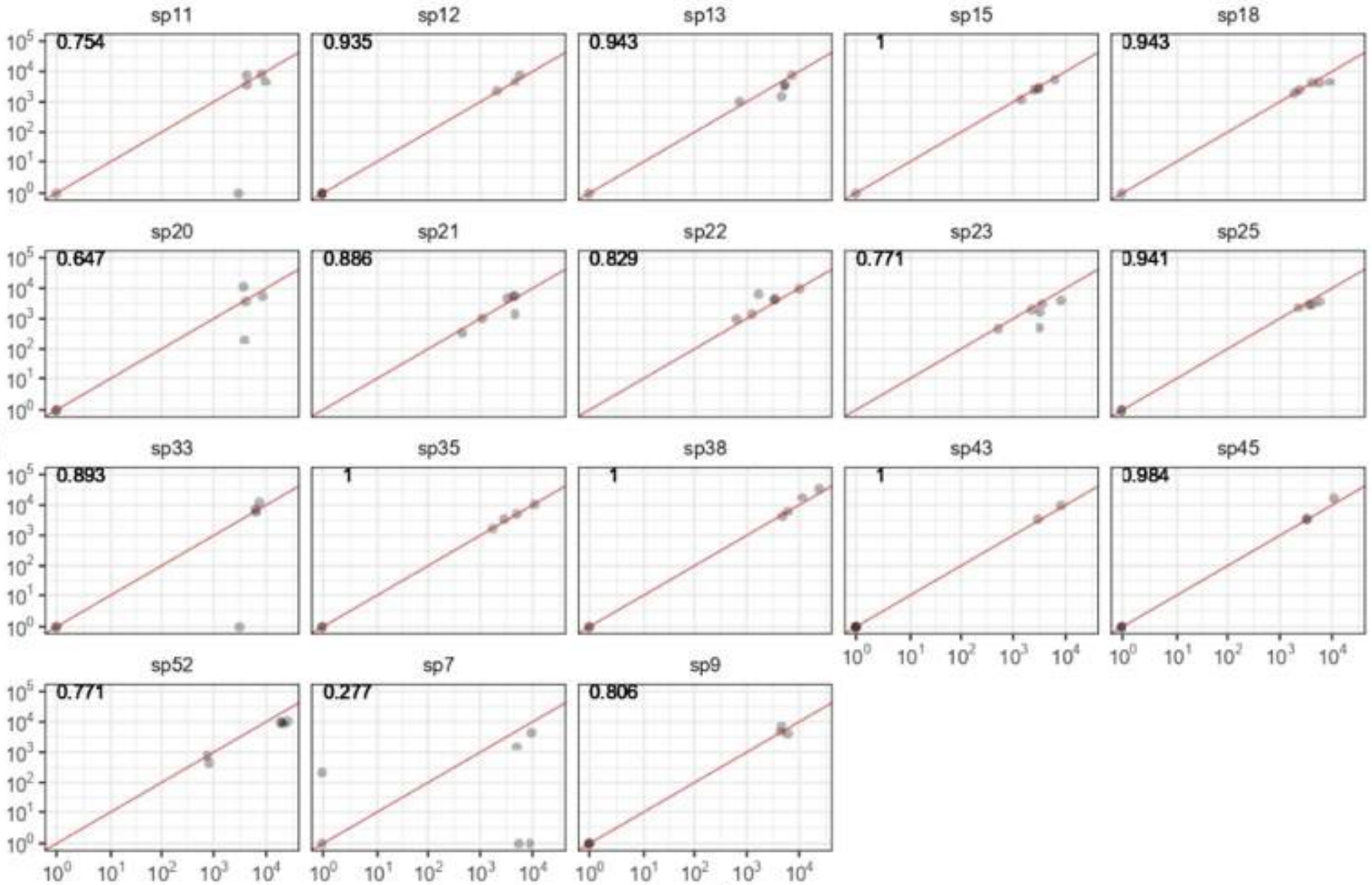




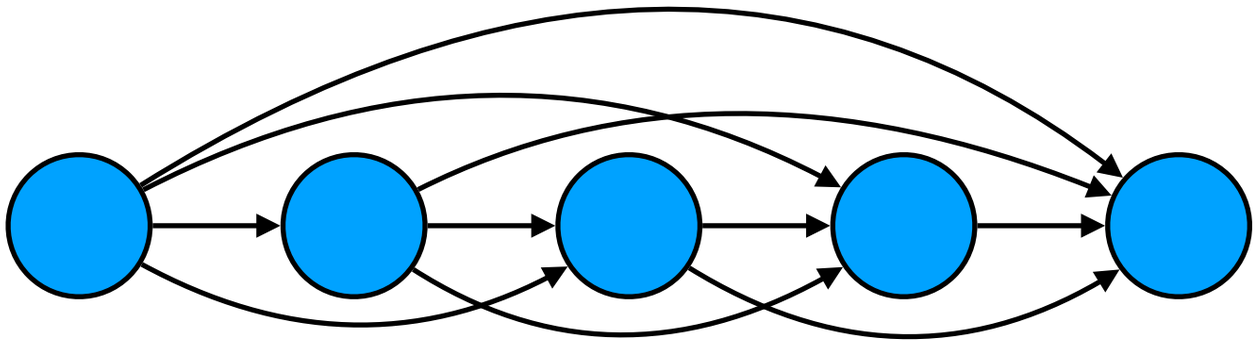
Preliminary results

R^2 value ranging from 0.65 to 1 (except for sp7)

Thaiss et al 2016 - Persistent microbiome alterations modulate the rate of post-dieting weight regain

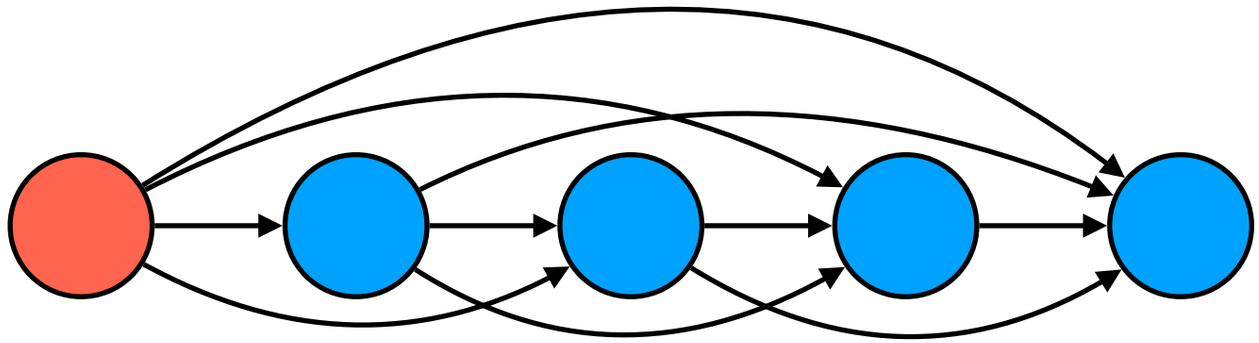
What about metabolism?

Community modulation



Community modulation

Not predicted by the model



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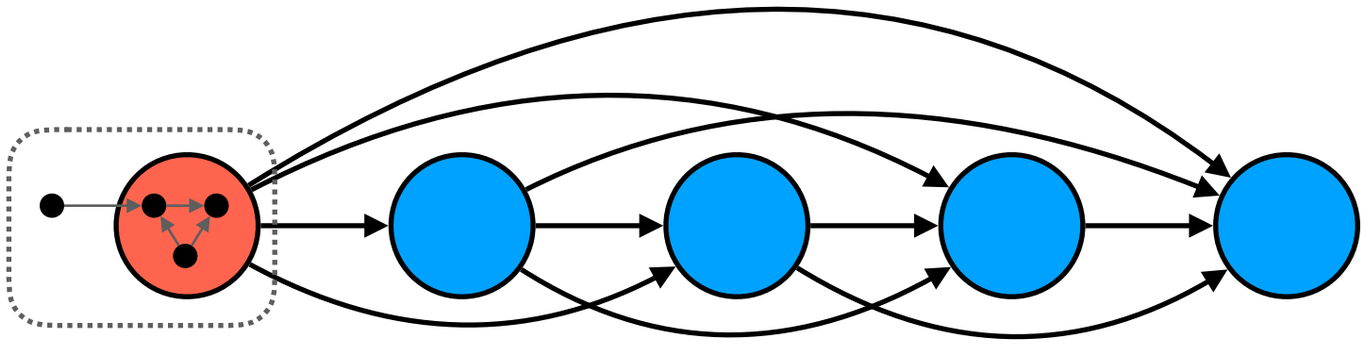
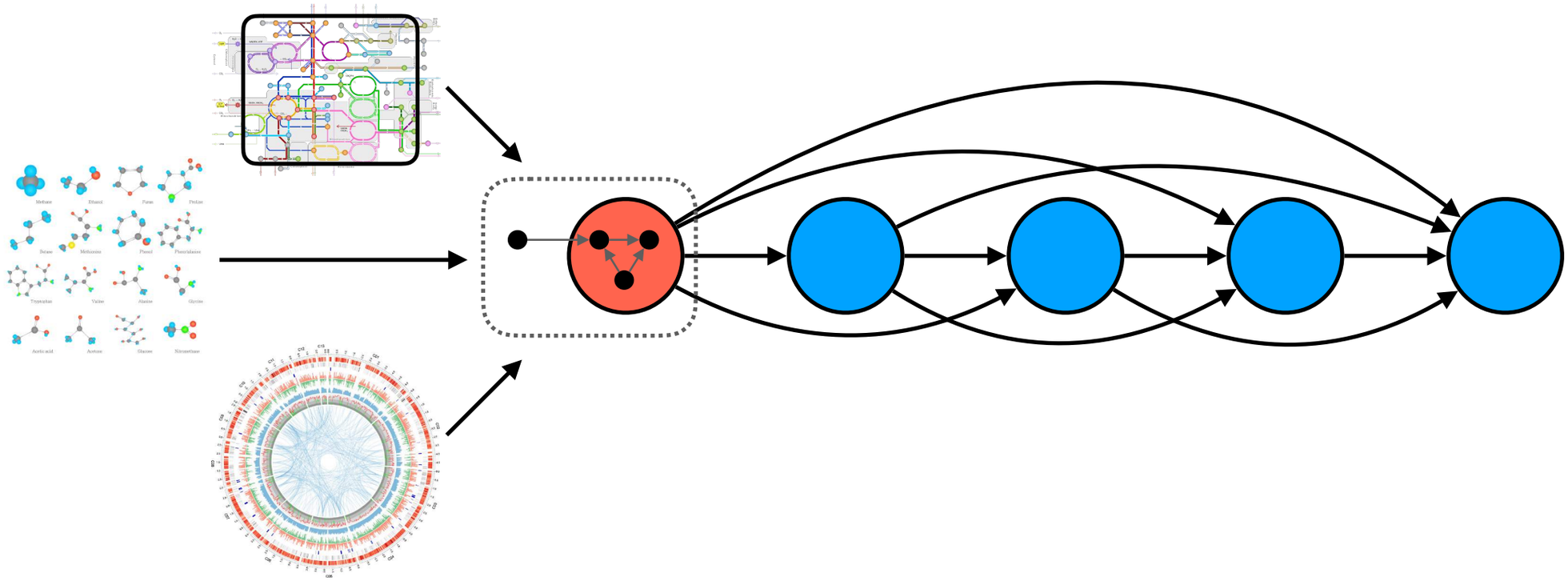


Community modulation



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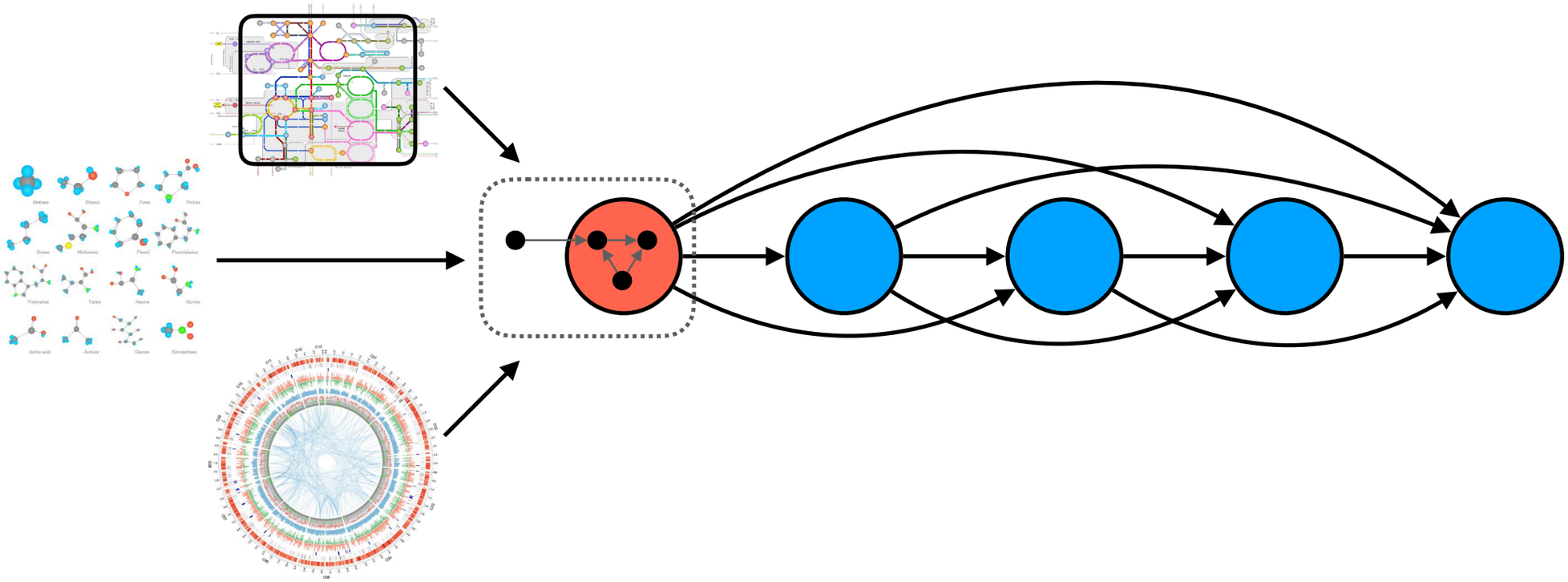
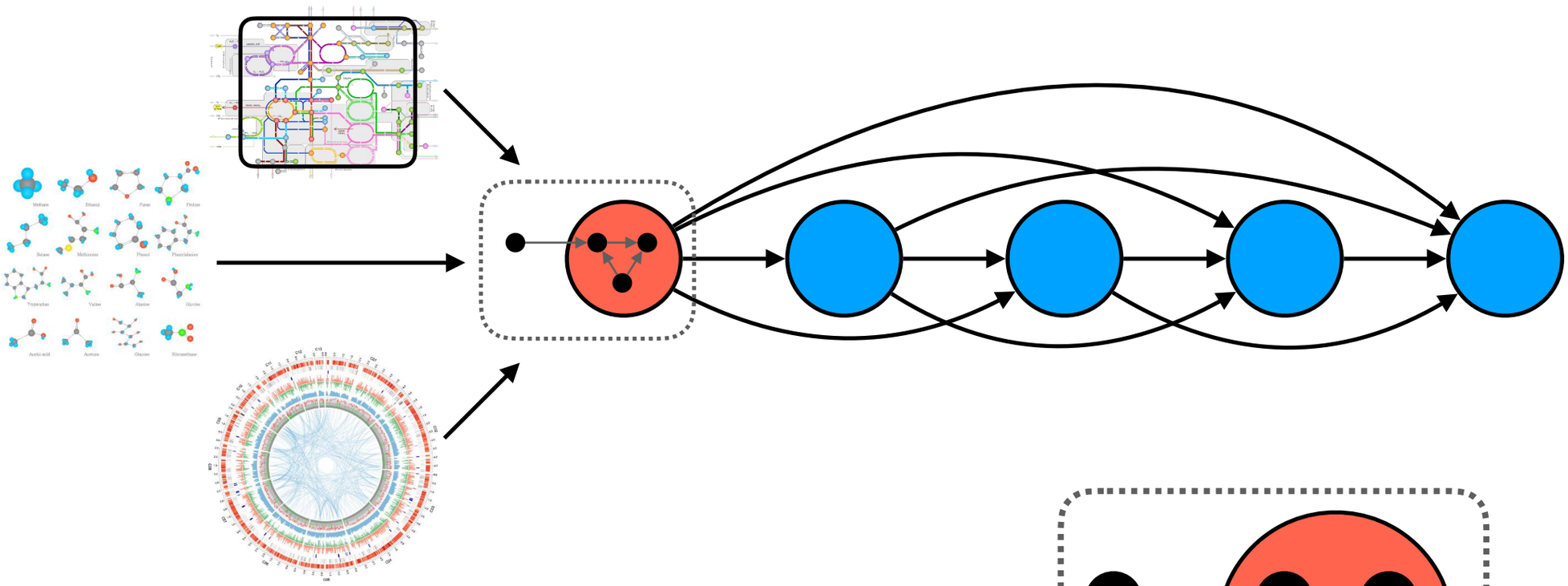
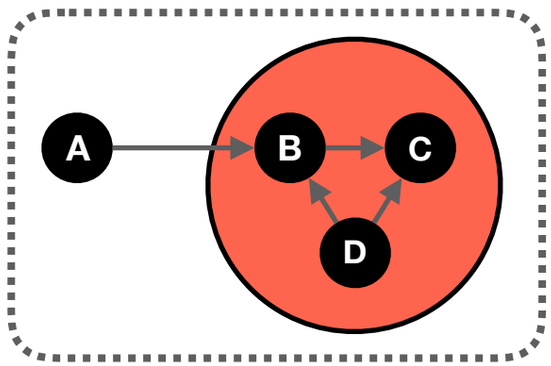


- Nutrient effect simulation
- Effect of antibiotic molecules
- Changes in metabolic assets

Community modulation





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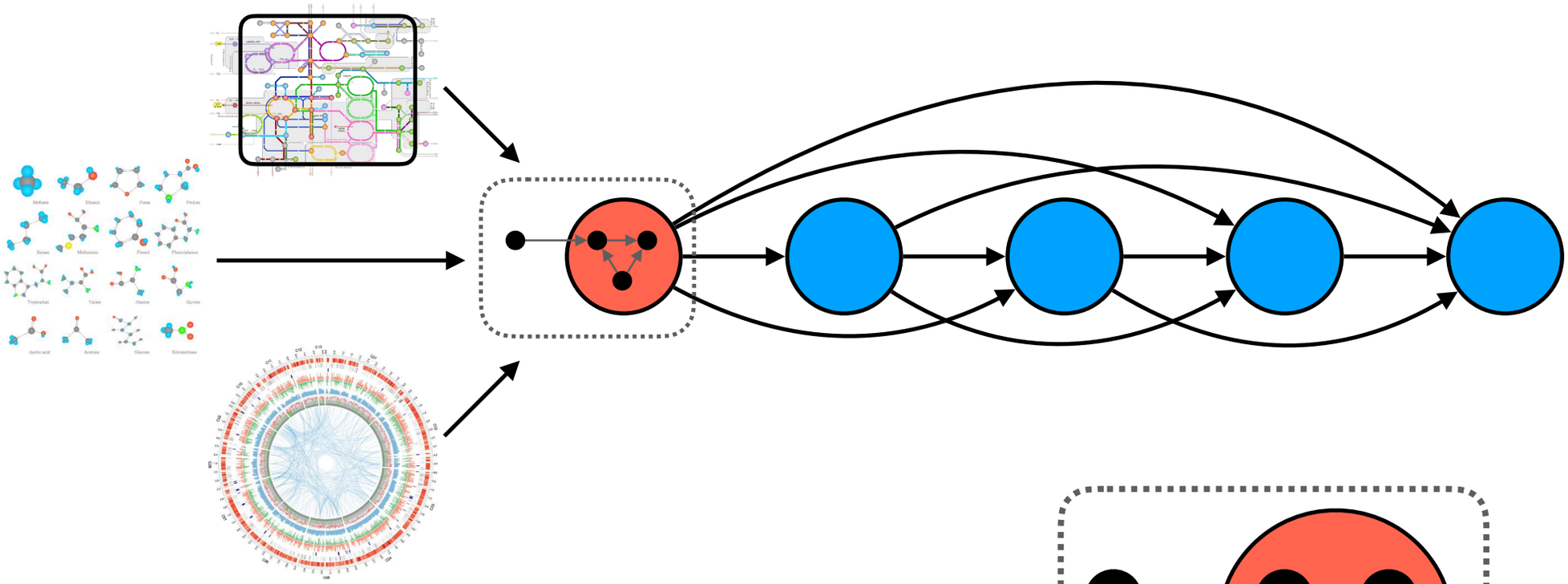
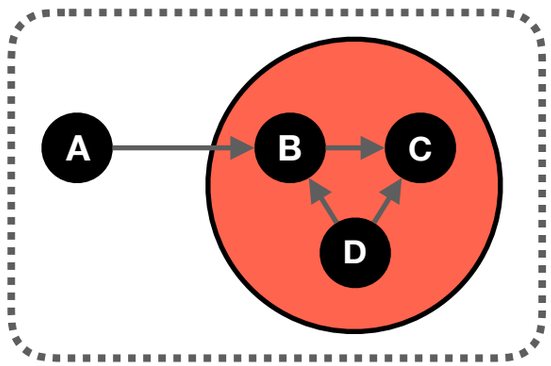
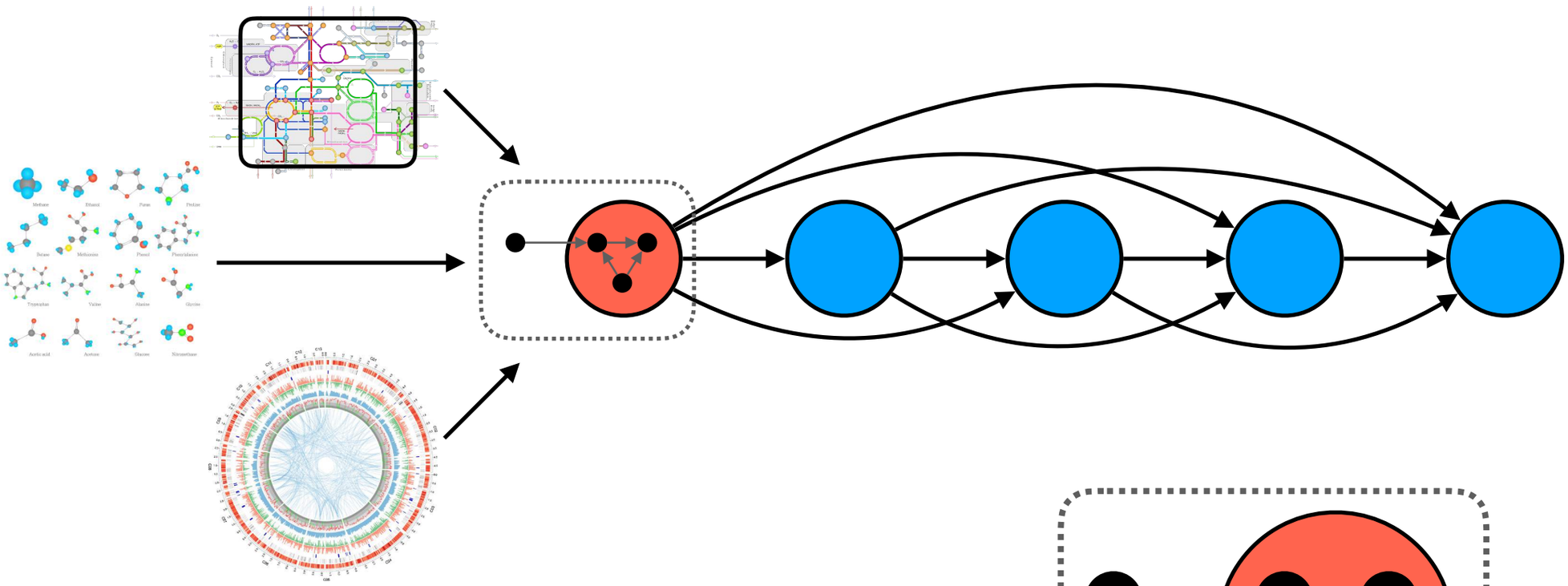




$$Biomass = f(A) = \mu(h^{-1})$$

- Nutrient effect simulation
- Effect of antibiotic molecules
- Changes in metabolic assets

Community modulation



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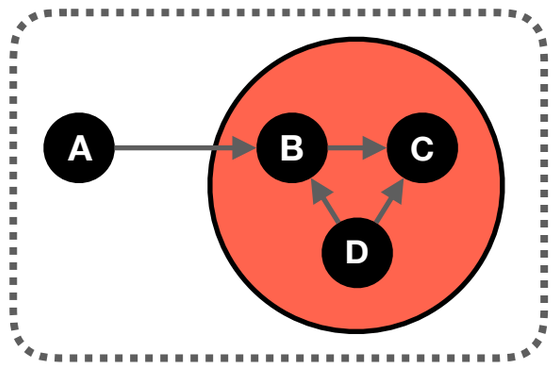
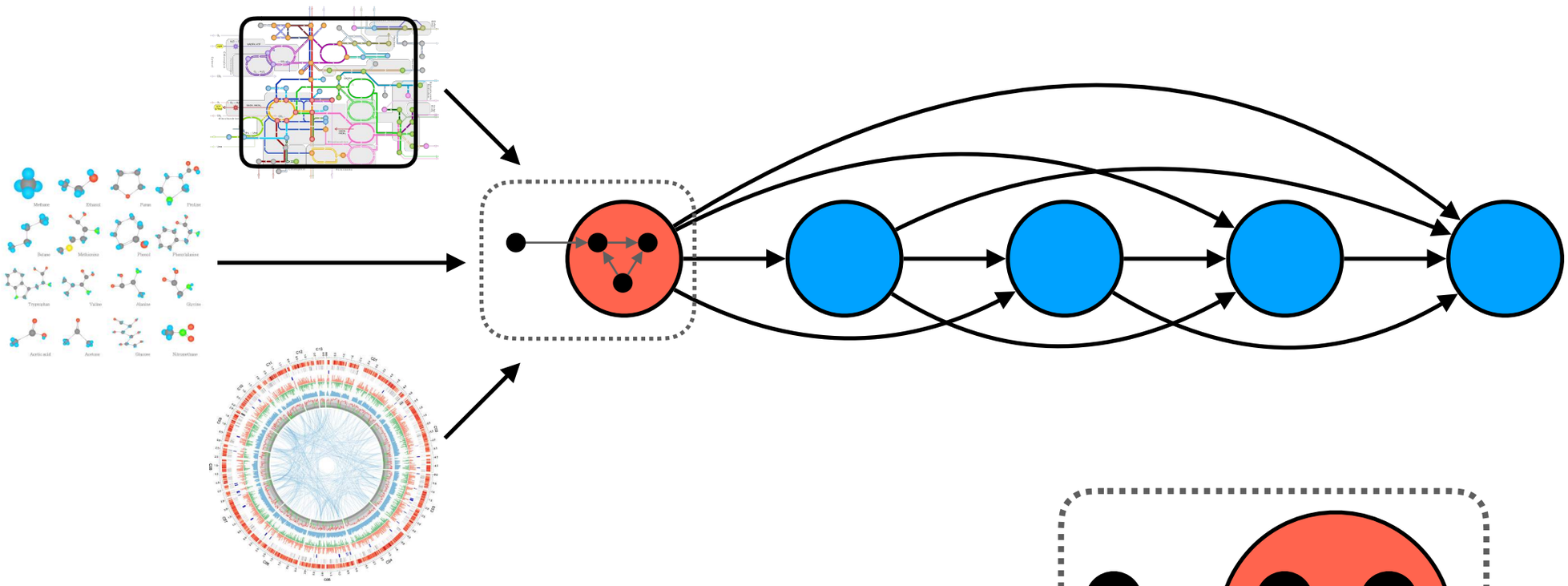
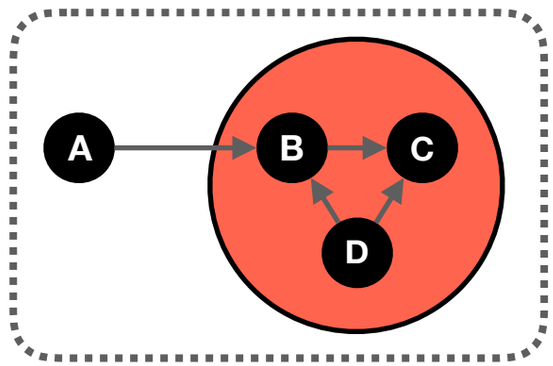


$$Biomass = f(A) = \mu(h^{-1})$$

$$Coverage = n_{reads}$$

Community modulation





- Nutrient effect simulation
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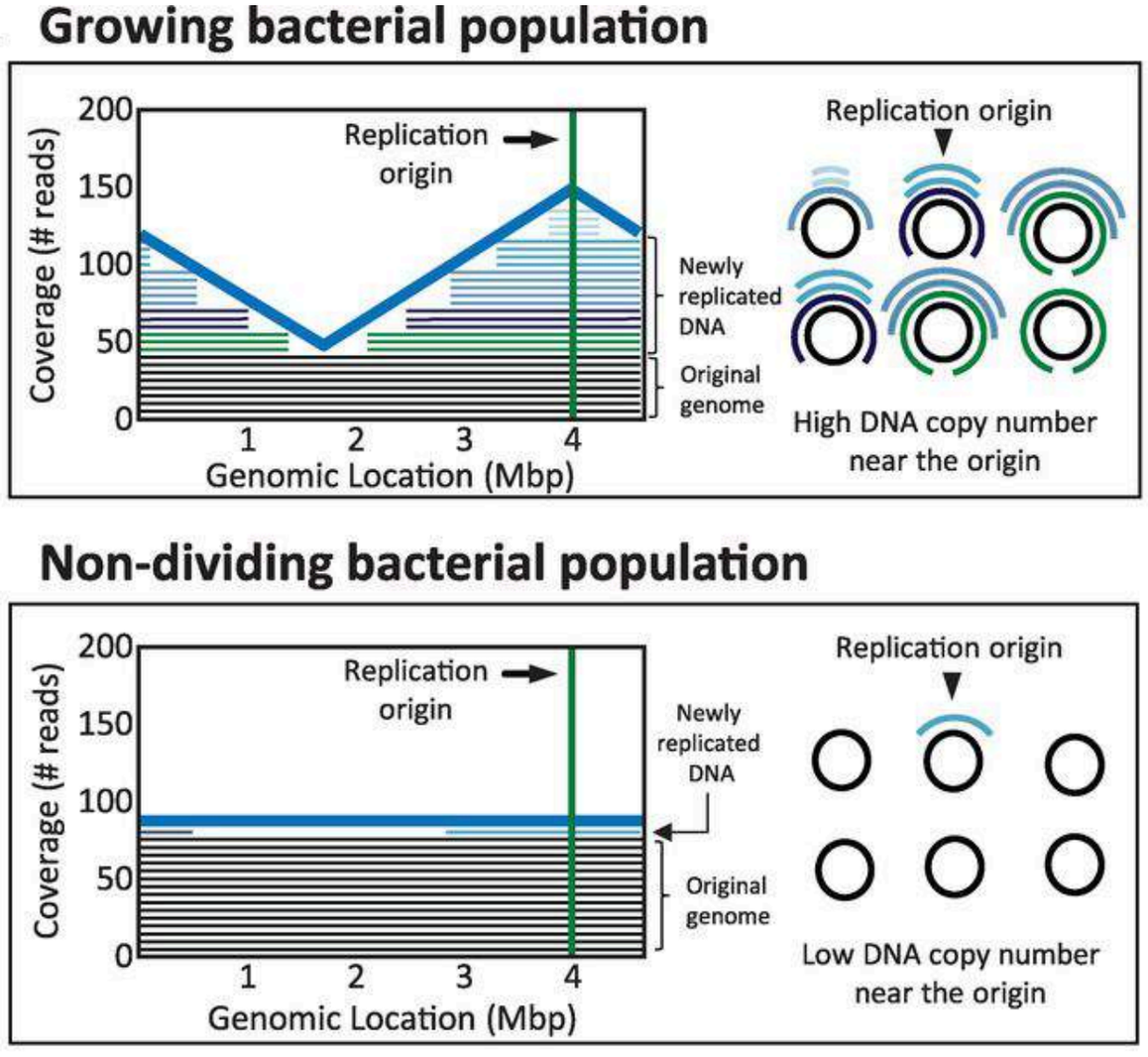
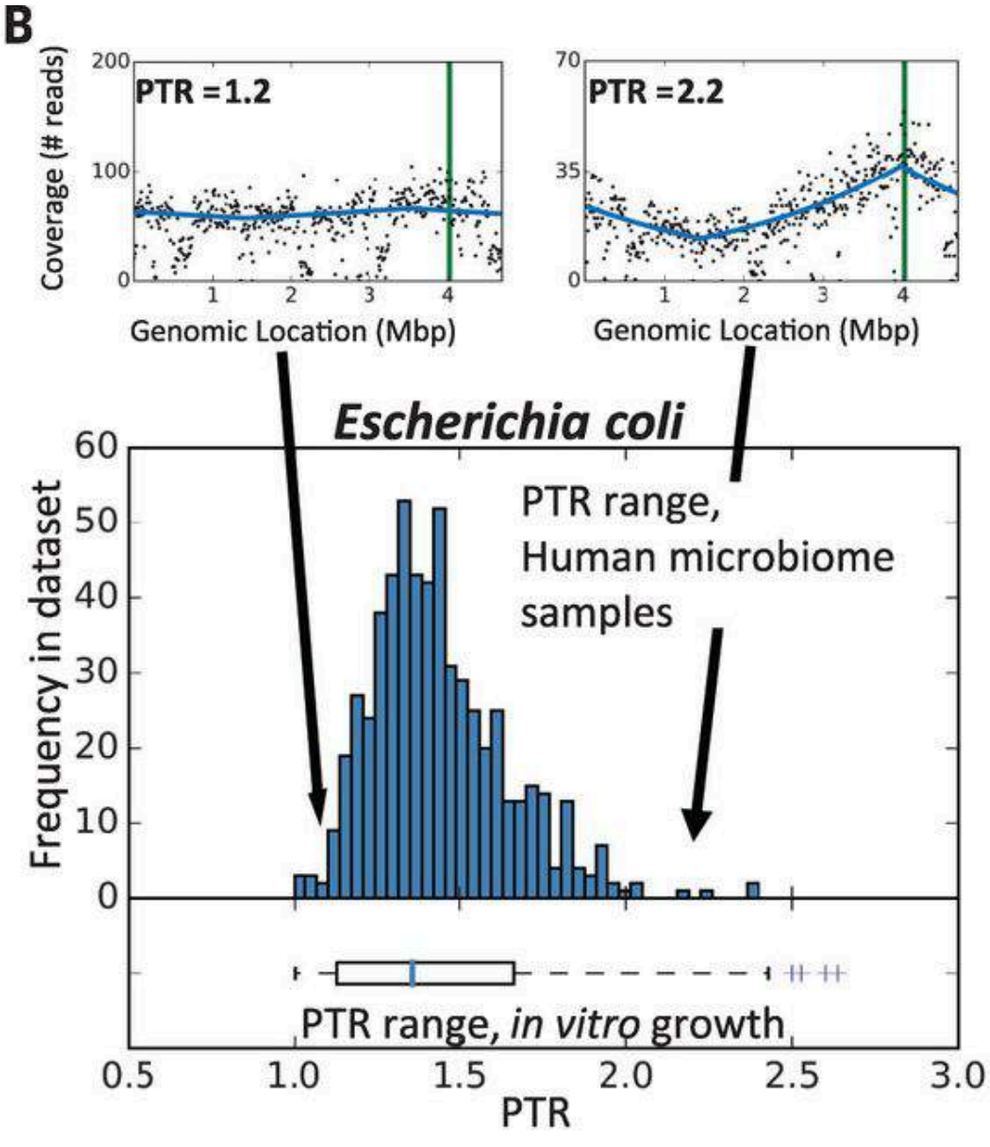
$$Biomass = f(A) = \mu(h^{-1})$$

$$Coverage = n_{reads}$$

$$Coverage = f(Biomass)$$

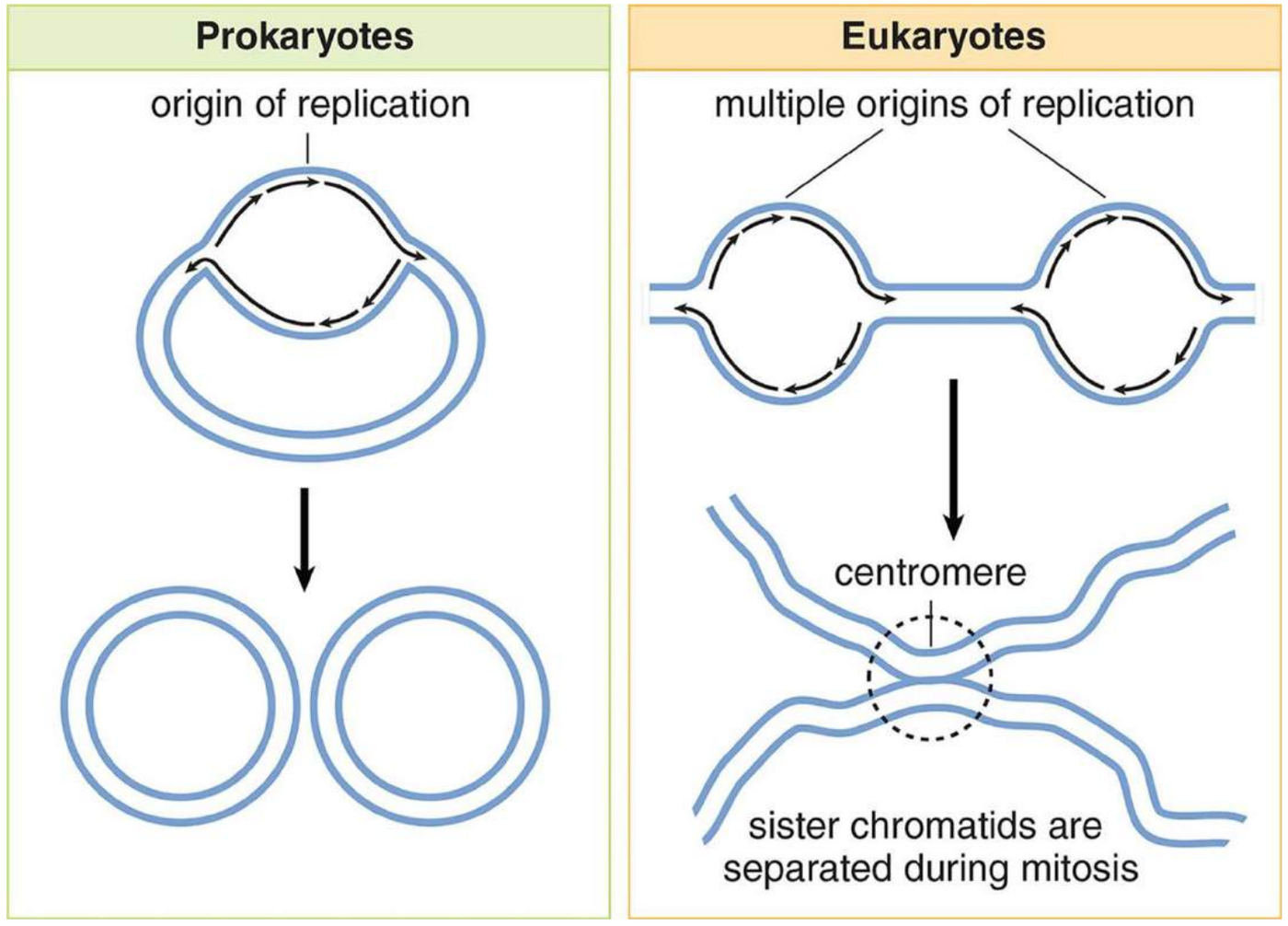




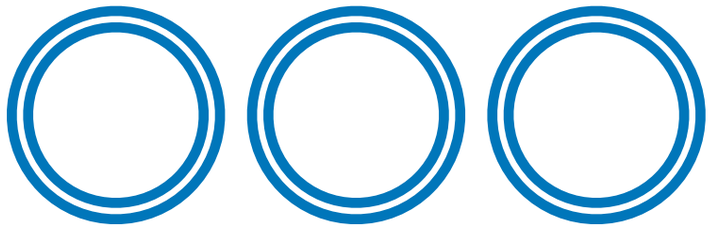
Growth rates estimation from metagenomes

Korem et al 2015 - Growth dynamics of gut microbiota in health and disease inferred from single metagenomic samples

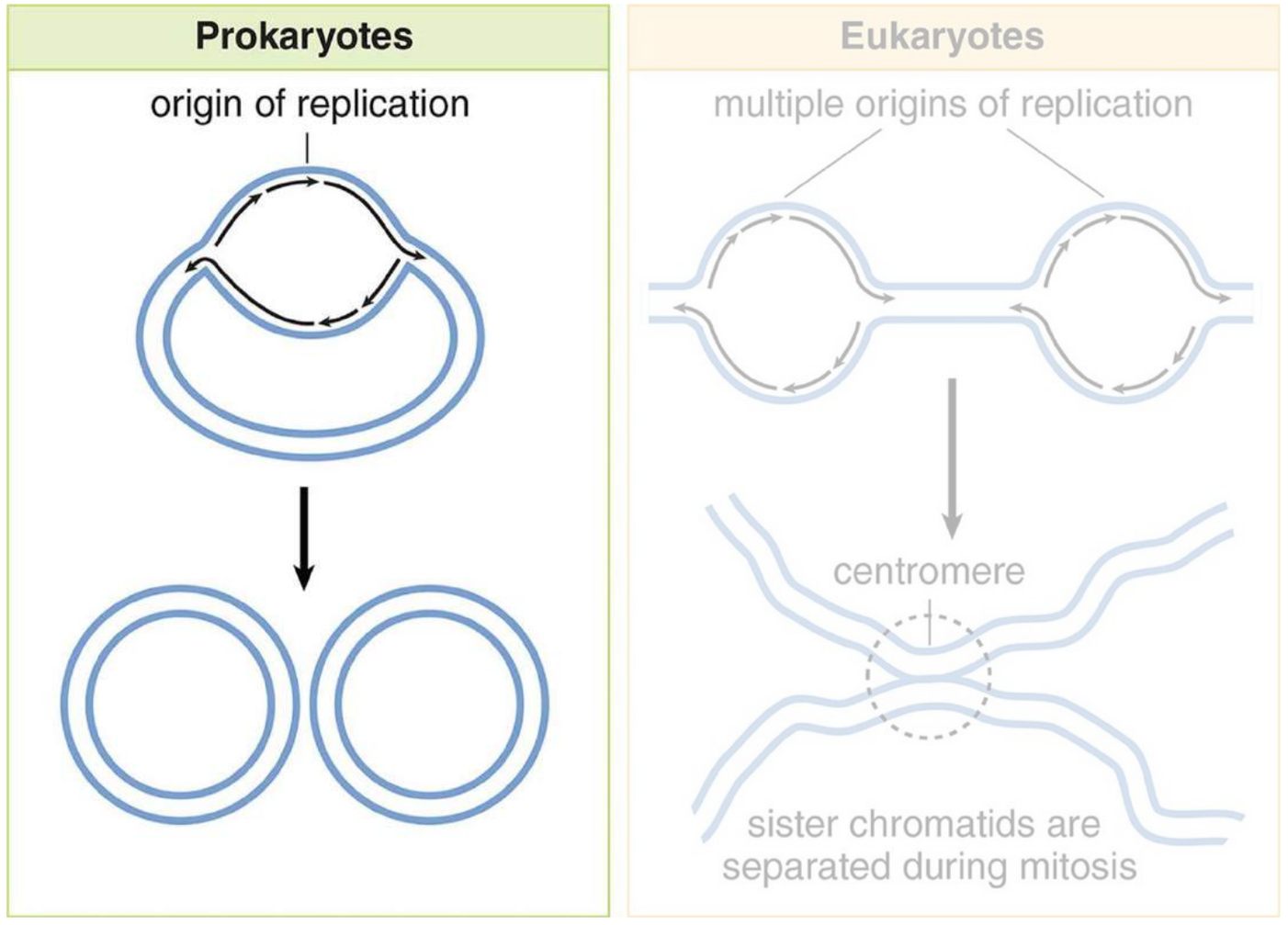
Prokaryotic DNA replication



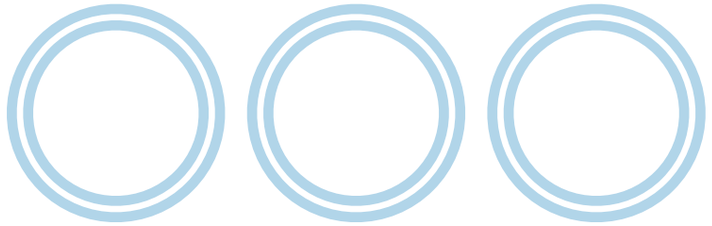
Prokaryotic DNA replication



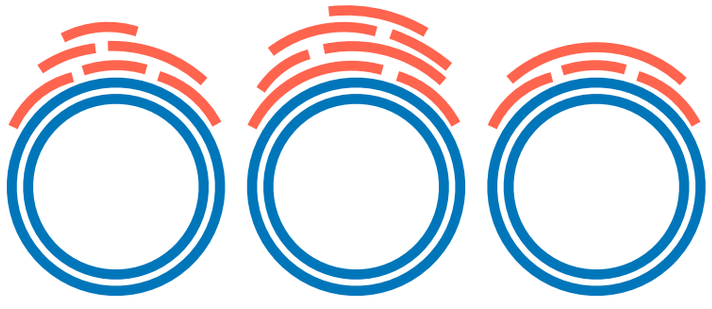
During stationary phase coverage is evenly distributed along the entire genome

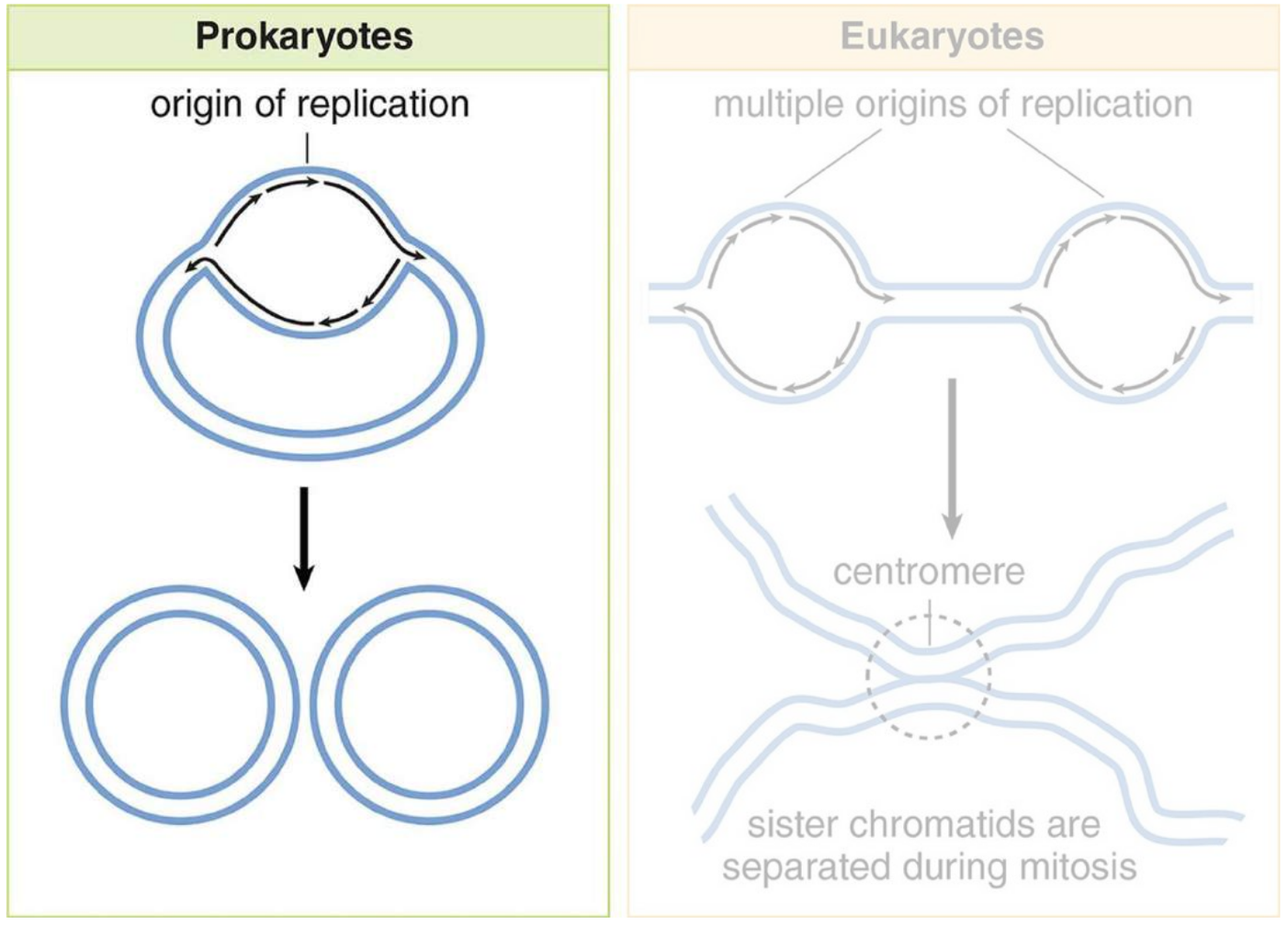


Prokaryotic DNA replication

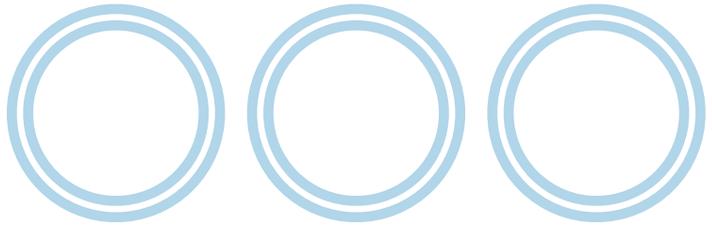


During exponential phase coverage increases near the origin of replication





Prokaryotic DNA replication



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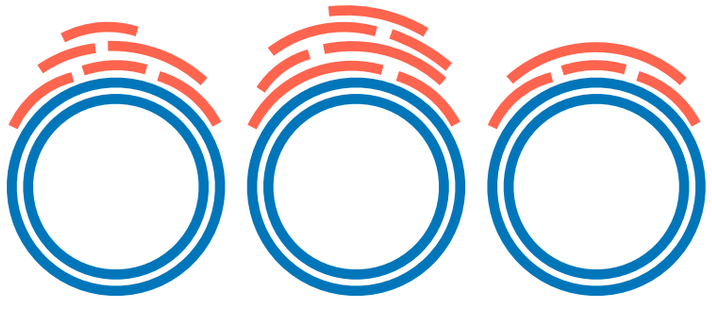
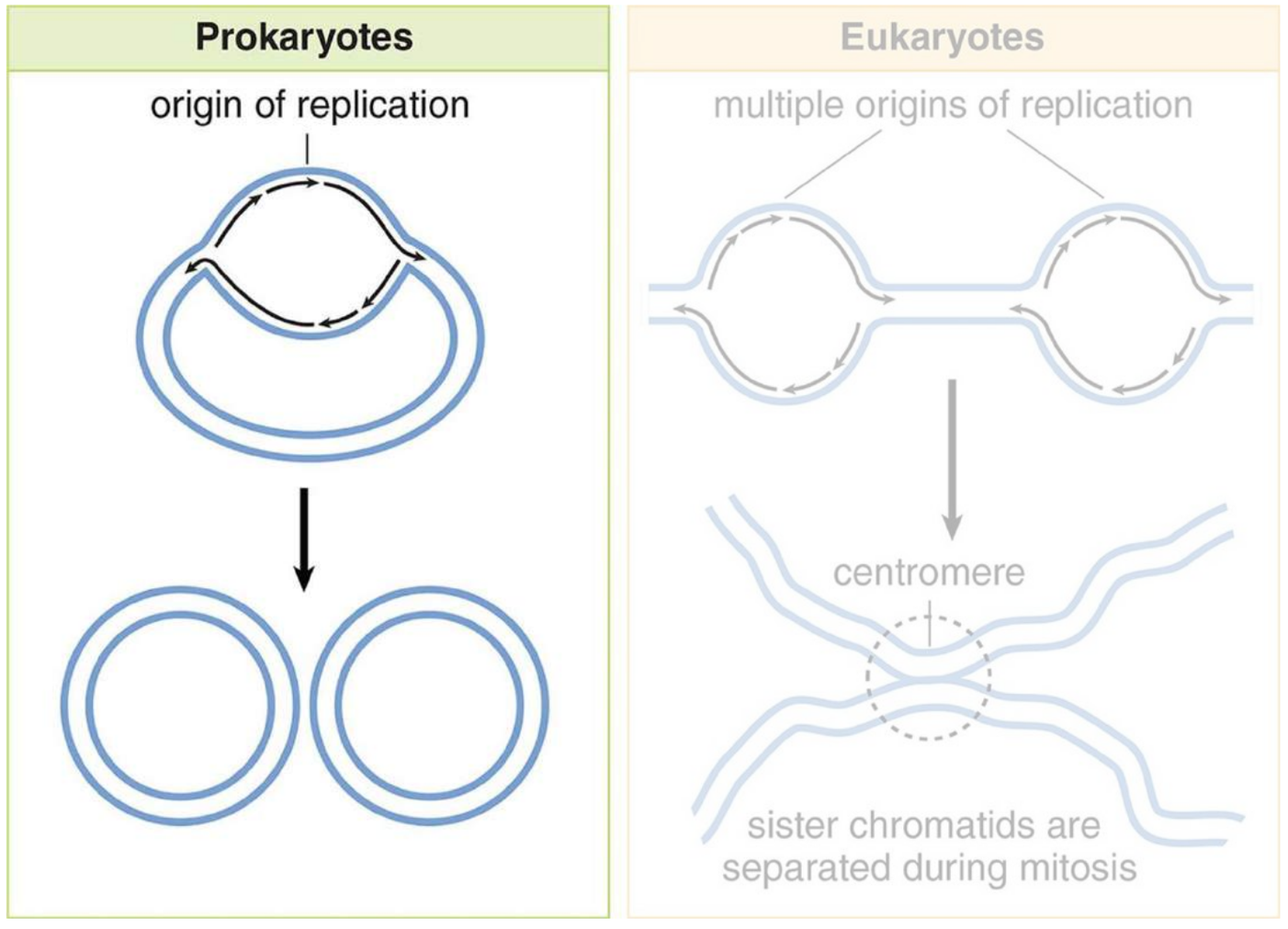
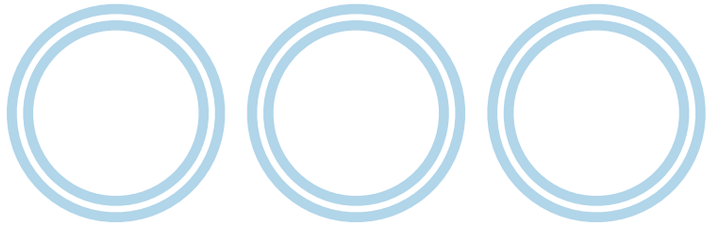


$$PTR = \frac{2^{ori}}{2^{ter}}$$



Prokaryotic DNA replication



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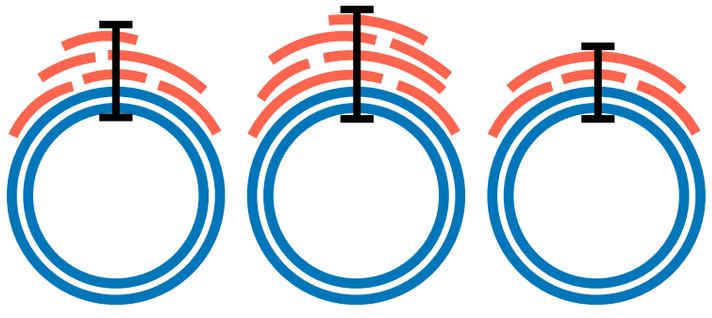
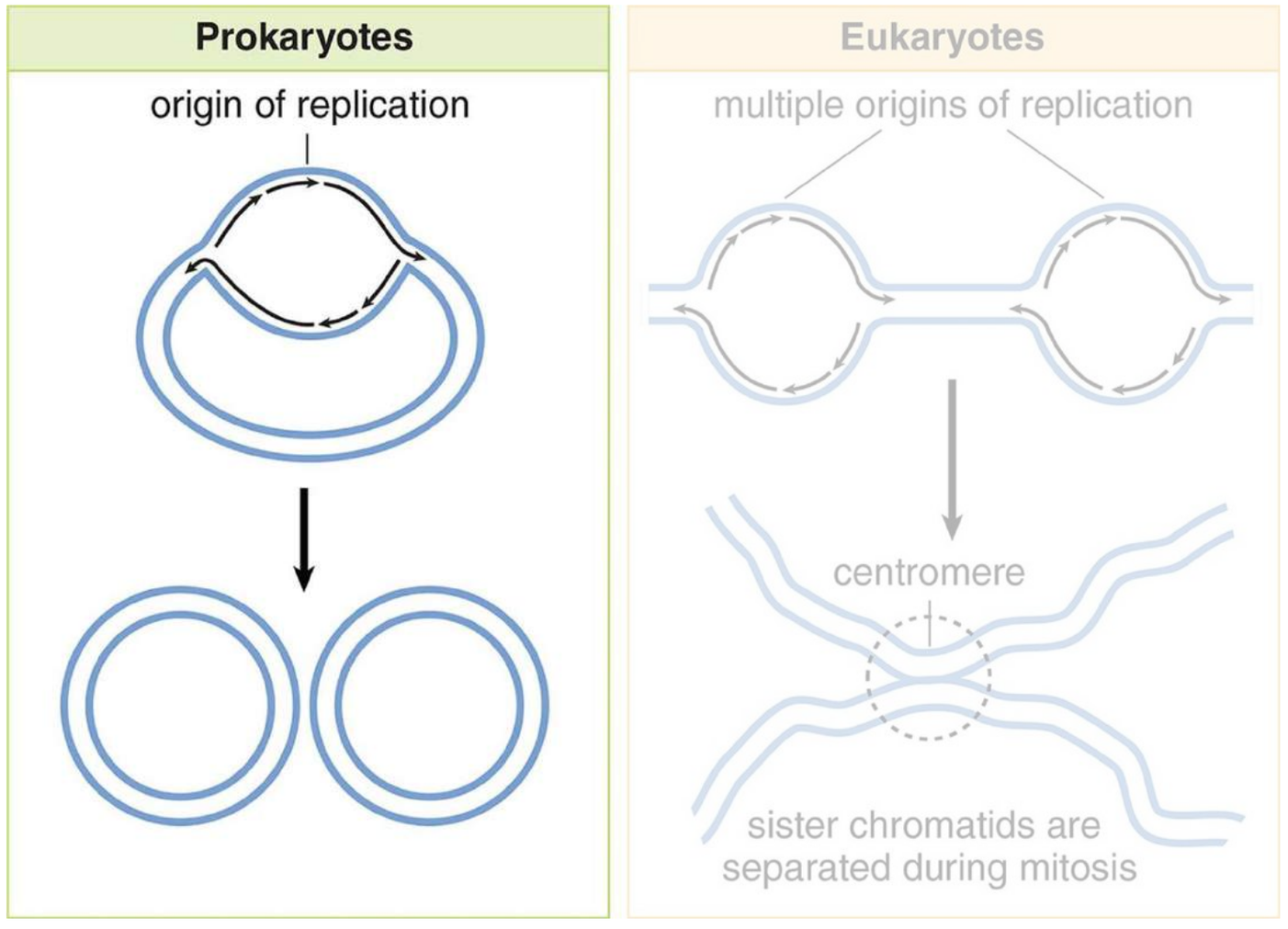
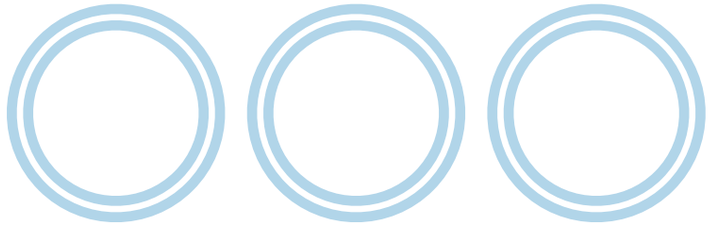


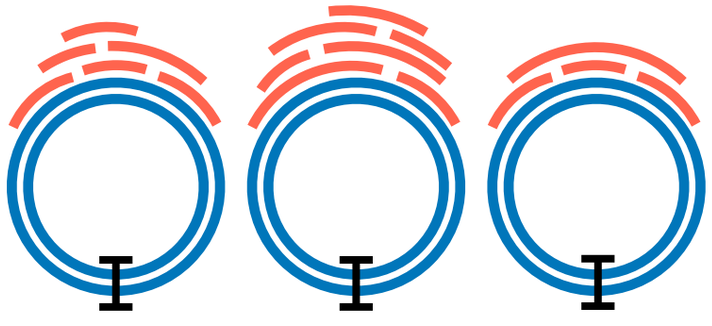


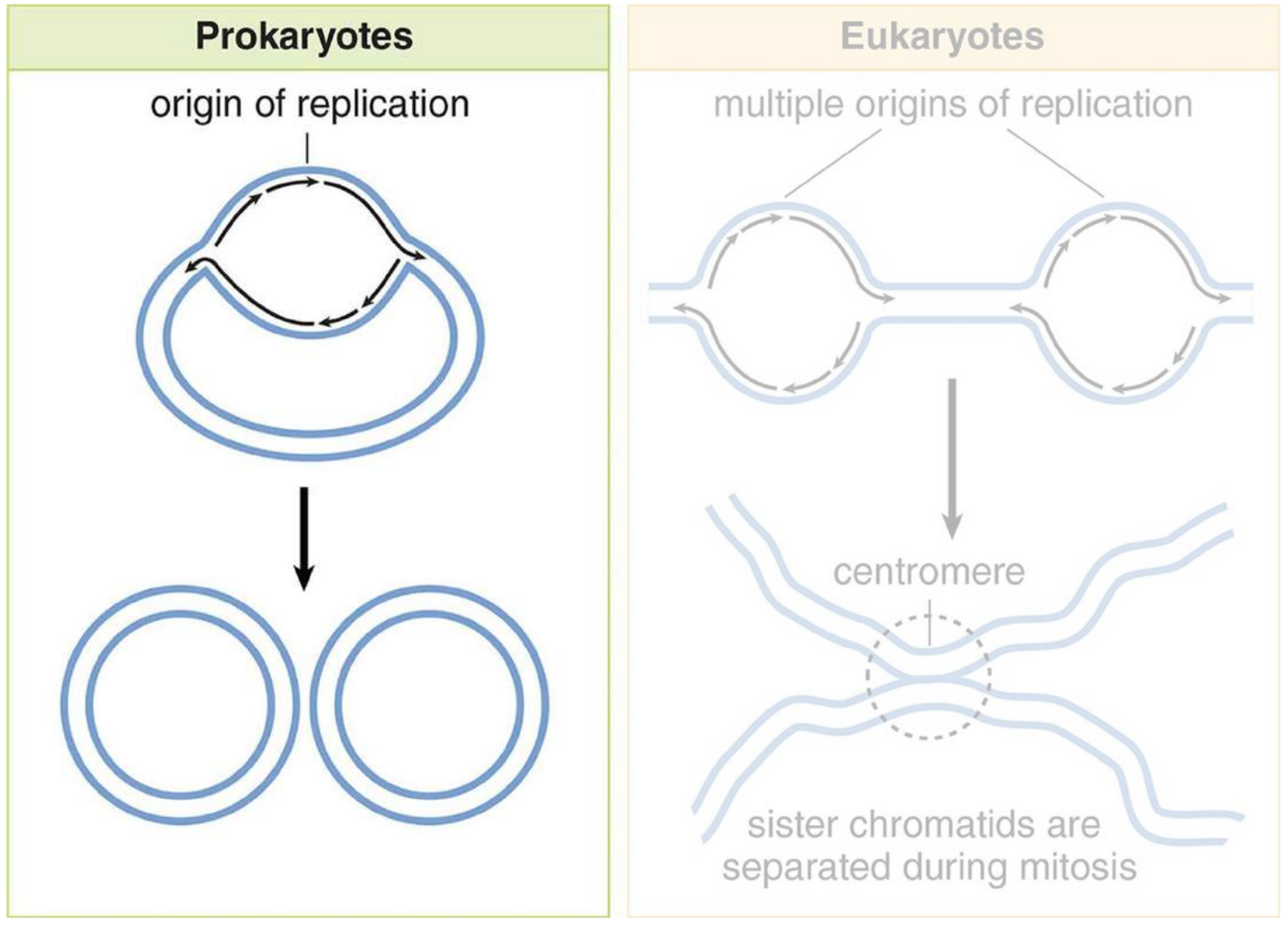
$$PTR = \frac{2^{ori}}{2^{ter}}$$ = coverage close to the origin of replication

Prokaryotic DNA replication



During exponential phase coverage increases near the origin of replication



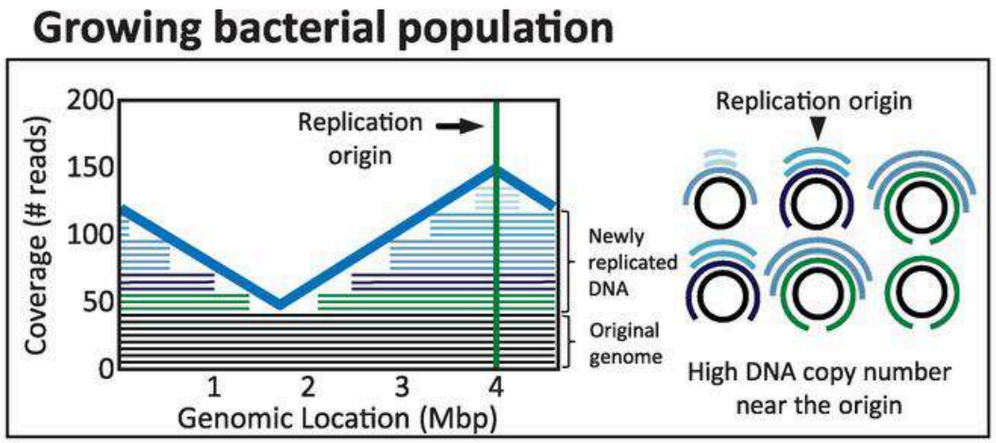


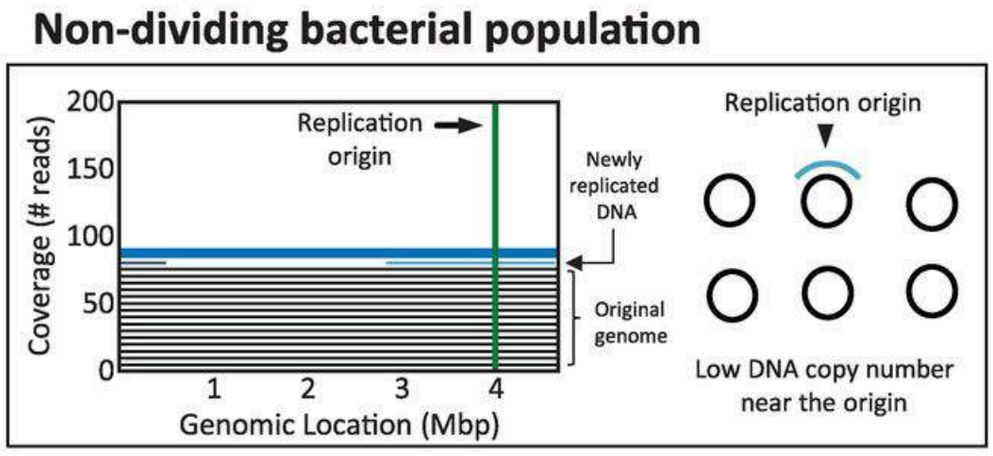
$$PTR = \frac{2^{ori}}{2^{ter}}$$

= coverage close to the origin of replication

= coverage close to the termination

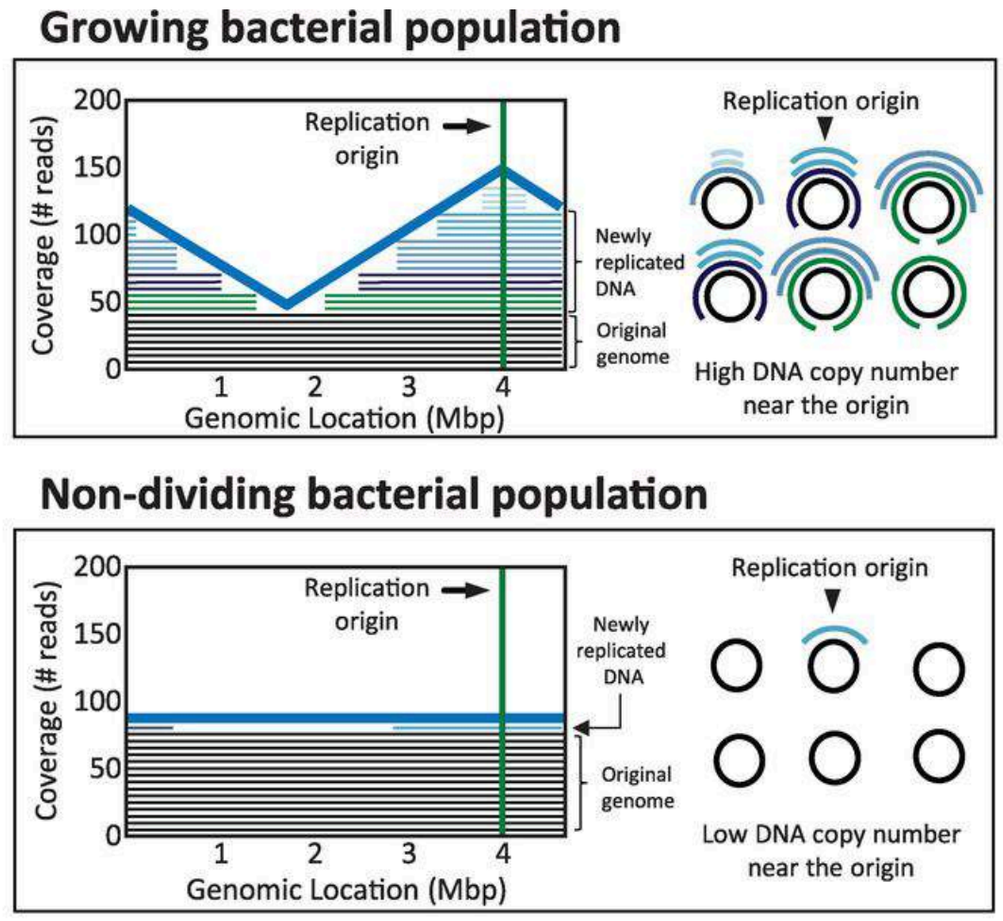
PTR and Growth rate





PTR and Growth rate

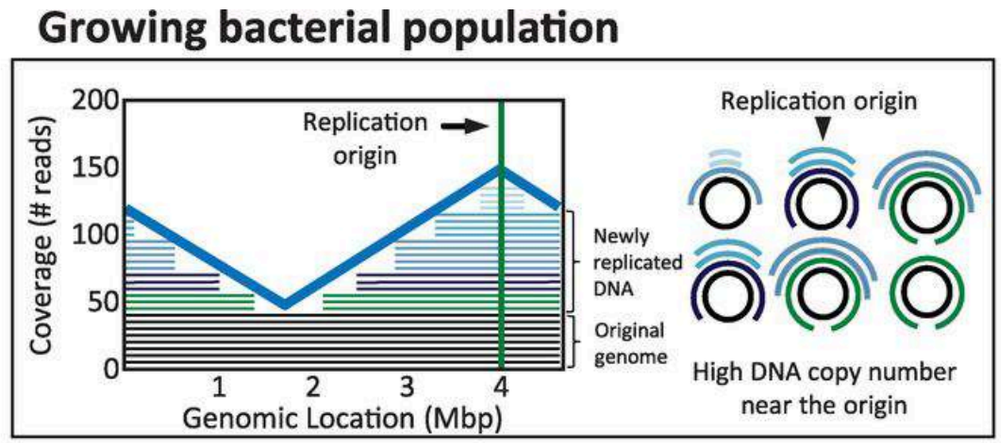
- PTR can be inferred from the same data used for community profiling



PTR and Growth rate

- PTR can be inferred from the same data used for community profiling

- Reference complete genome must be available



PTR and Growth rate

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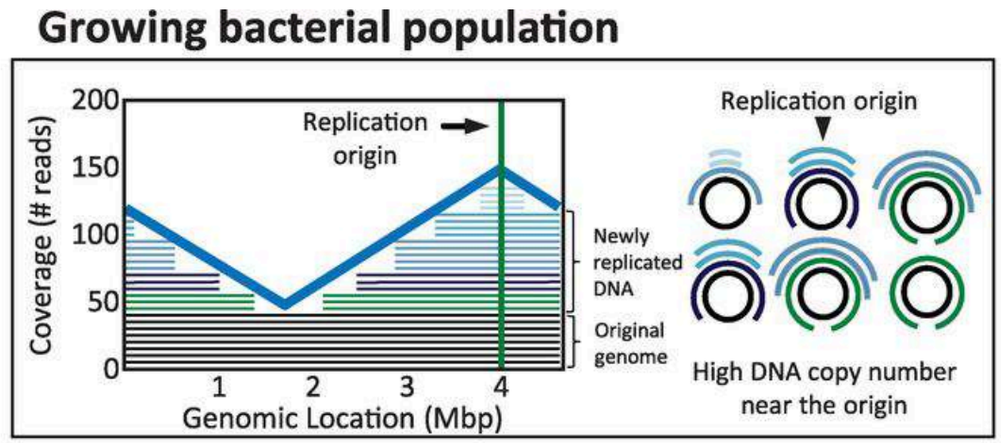
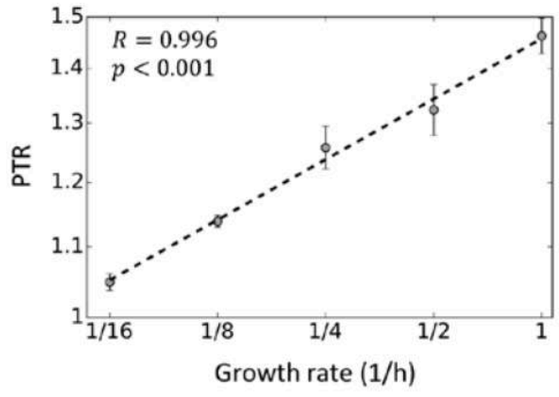
- PTR and Growth rate are highly correlated





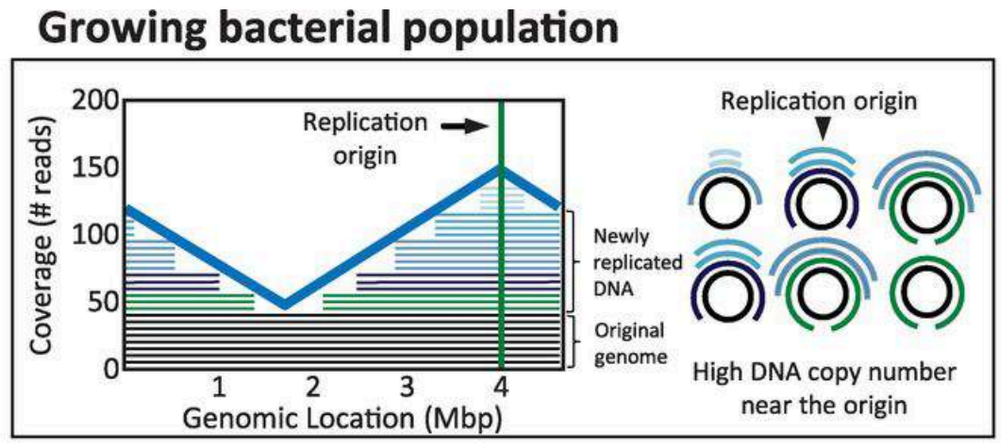
PTR and Growth rate

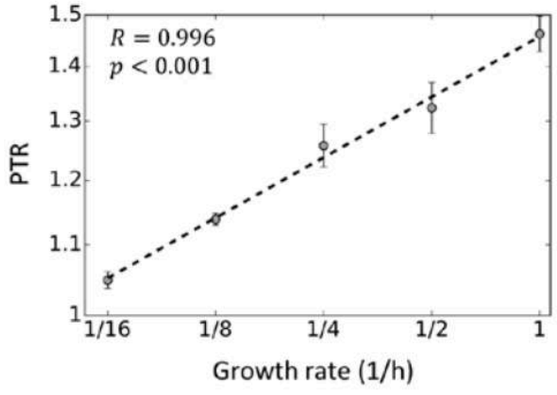
- PTR can be inferred from the same data used for community profiling

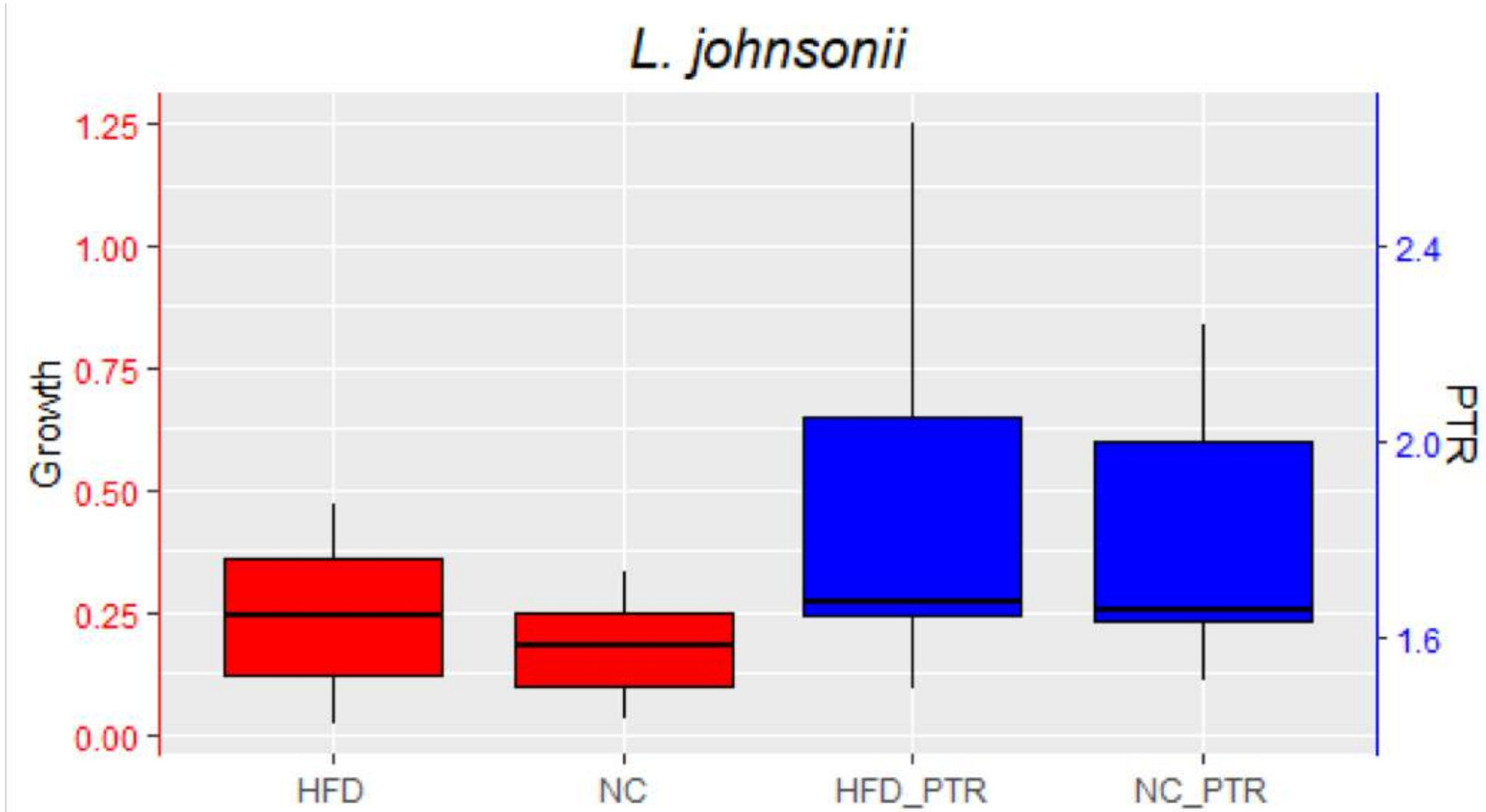
- Reference complete genome must be available

- PTR and Growth rate are highly correlated

- We need to find a relation between different growth rate indexes, PTR and coverage

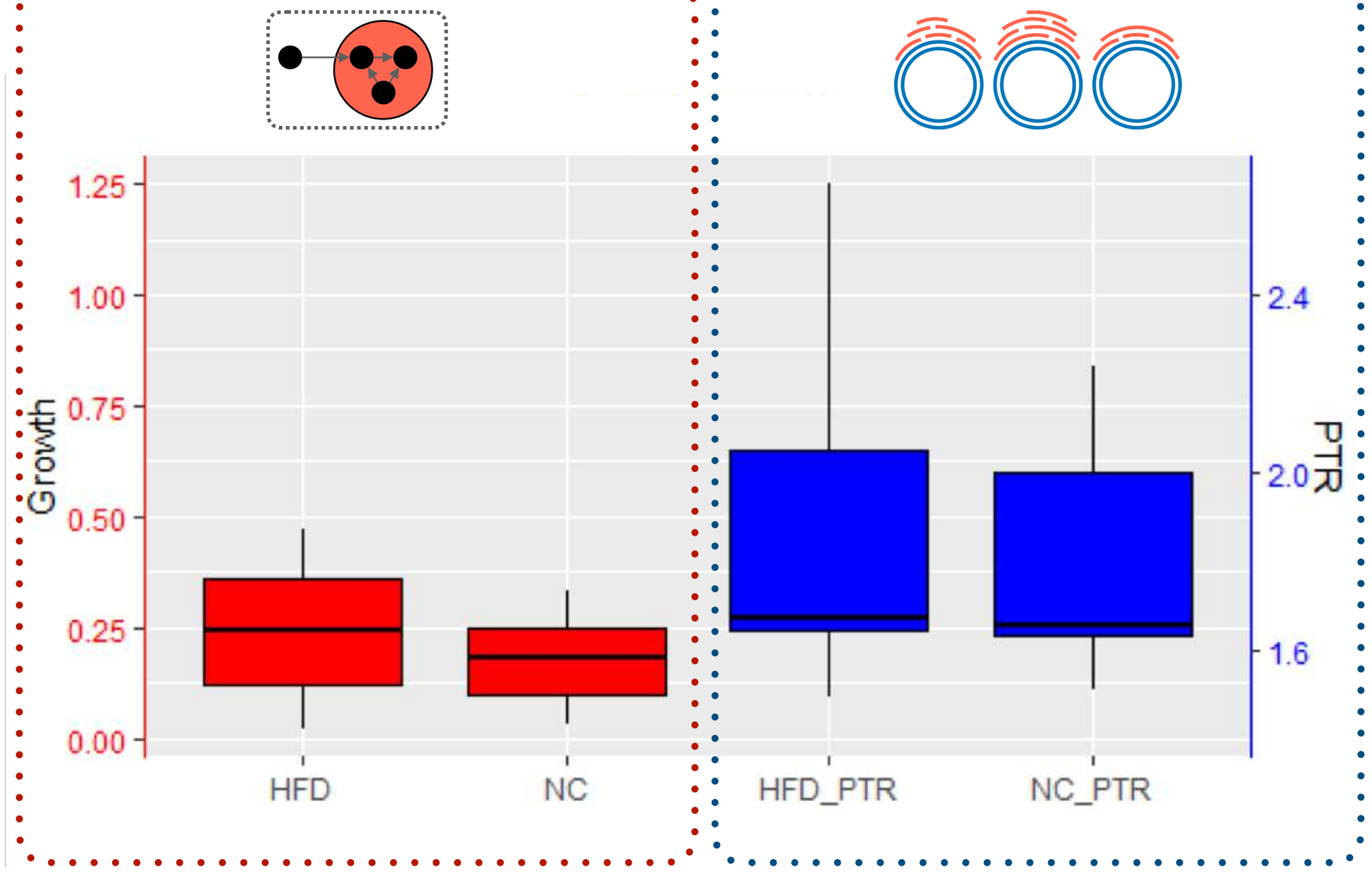






Other preliminary results

In two different conditions (NC and HFD) PTR and growth rate seem to be correlated



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THANKS FOR THE ATTENTION!

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Questions, suggestions, and collaborations are welcome