Using evolutionary theory to predict microbes effect on host health

Camille Simonet

S18. Evolution of hosts and parasites with their microbiomes: a problem of unfaithful relationships

@CamilleASimonet

Compositional features

(Taxonomic composition)

Mechanistic features

(Metabolic pathways & Networks topology)

The microbiome in health and diseases

Compositional features

(Taxonomic composition)

Mechanistic features

(Metabolic pathways & Networks topology)

The microbiome in health and diseases

Evolutionary framework

A gut microbe's life

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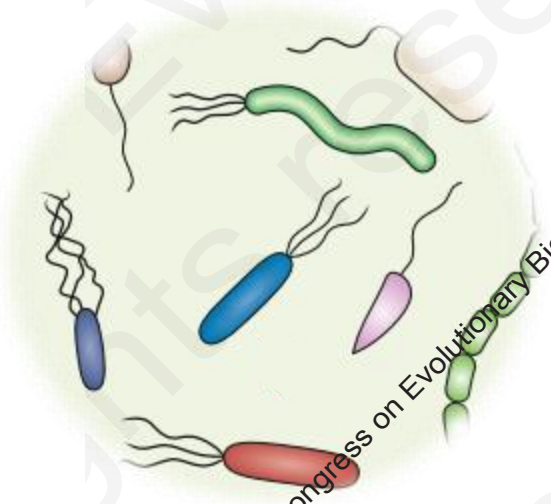
A gut microbe's life



Within-host competition

Transmission

A gut microbe's life

Within-host competition

Transmission

Fitness of an individual microbe

Focal individual's fitness =

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Fitness of an individual microbe

Within host competition and horizontal transmission

$$\text{Focal individual's fitness} = -c + b$$

Fitness of an individual microbe

Within host competition and horizontal transmission

$$\text{Focal individual's fitness} = -c\left(\text{focal individual's behaviour}\right) + b\left(\text{group average behaviour}\right)$$

Fitness of an individual microbe

Within host competition and horizontal transmission

$$\text{Focal individual's fitness} = -c\left(\text{focal individual's behaviour}\right) + b\left(\text{group average behaviour}\right)$$

effect on host health

< 0 : harm host

> 0 : help host

< 0 : benefit from harming host

> 0 : benefit from helping host

Fitness of an individual microbe

Within host competition and horizontal transmission | *Vertical transmission*

$$\text{Focal individual's fitness} = -c\left(\text{focal individual's behaviour}\right) + b\left(\text{group average behaviour}\right) + v\left(\text{group average behaviour}\right)$$

effect on host health

< 0 : harm host
> 0 : help host

< 0 : benefit from harming host
> 0 : benefit from helping host

> 0 : additional transmission

Fitness of an individual microbe

$$w = -c(x) + b(y) + v(y)$$

x^* **Predicted behaviour/effect on health**

Predicted microbe's effect on host health

Predicted effect on host health

< 0 : harm host

> 0 : help host

$$x^* = \frac{dy}{dx}\frac{b + v}{2c}$$

Predicted microbe's effect on host health

Predicted effect on host health

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$$x^* = \frac{dy}{dx}\frac{b + v}{2c}$$

Predicted microbe's effect on host health

Predicted effect on host health

< 0 : harm host

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$$x^* = R\frac{b+v}{2c}$$

Relatedness (Population genetic structure)

Predicted microbe's effect on host health

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Relatedness (Population genetic structure)

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Vertical transmission

Relatedness (Population genetic structure)

Predicted microbe's effect on host health

Predicted effect on host health

< 0 : harm host

> 0 : help host

$$x^* = R\frac{b + v}{2c}$$

Vertical transmission

SIGN → help/harm

Relatedness (Population genetic structure)

MULTIPLIER → effect size

Generating data under this hypothesis

Simulating data for 100 hypothetical species

$$Effect = R * \frac{b + v}{2c} + \varepsilon$$

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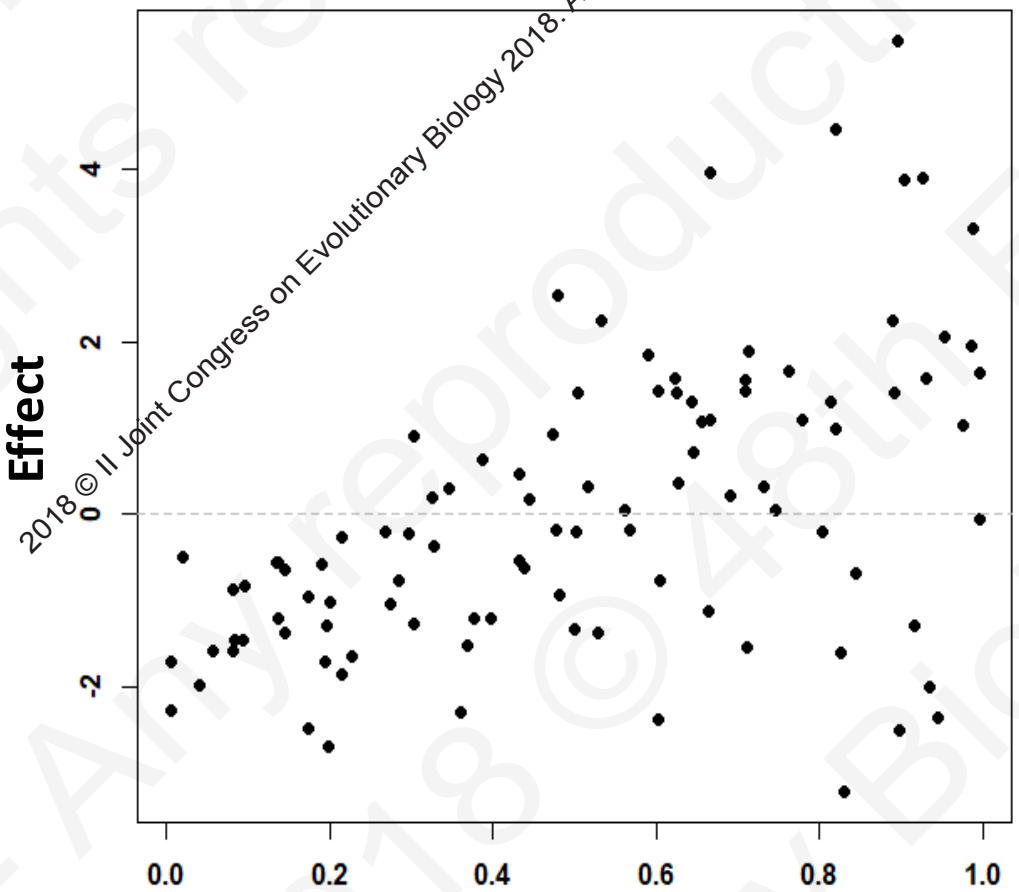
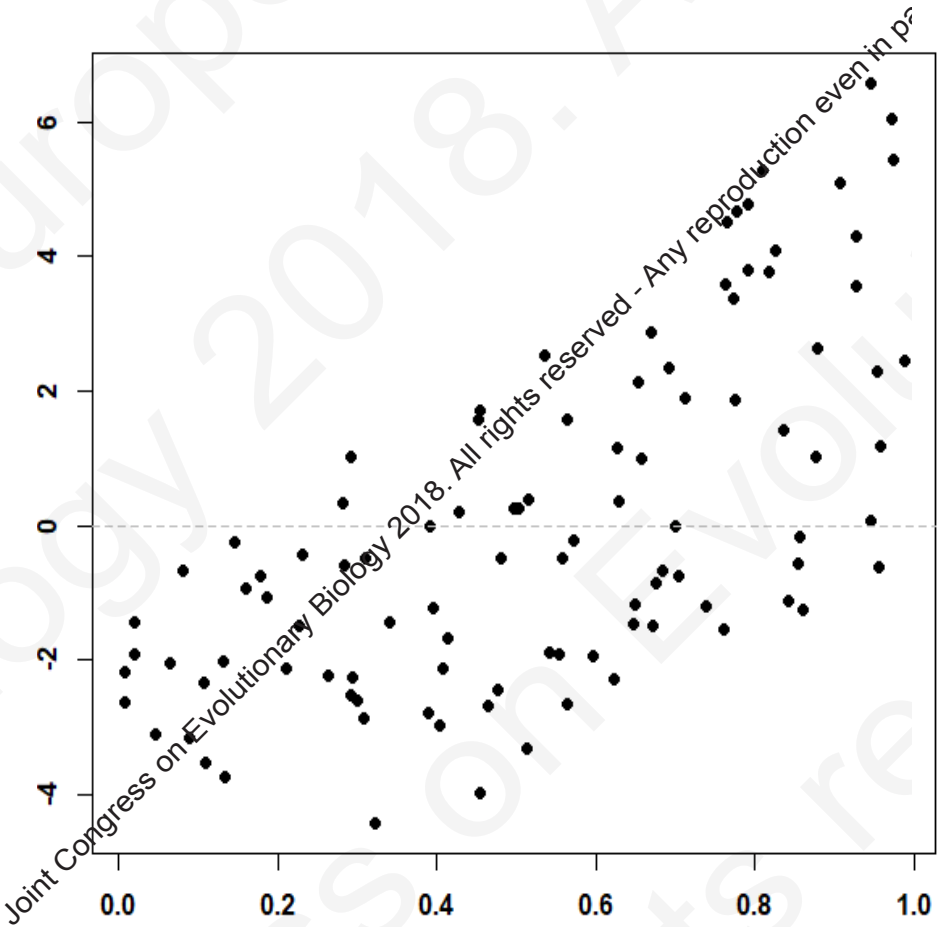
Simulating data for 100 hypothetical species

$$Effect = R * \frac{b + v}{2c} + \varepsilon$$



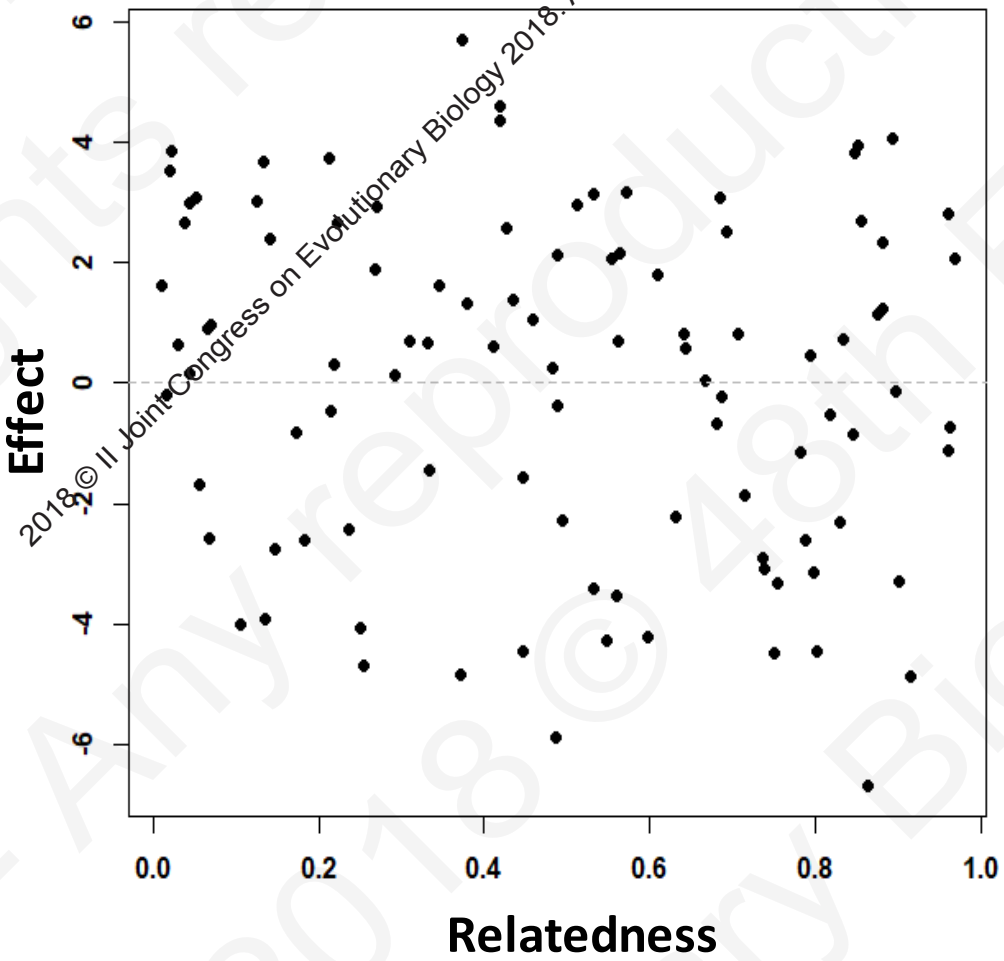


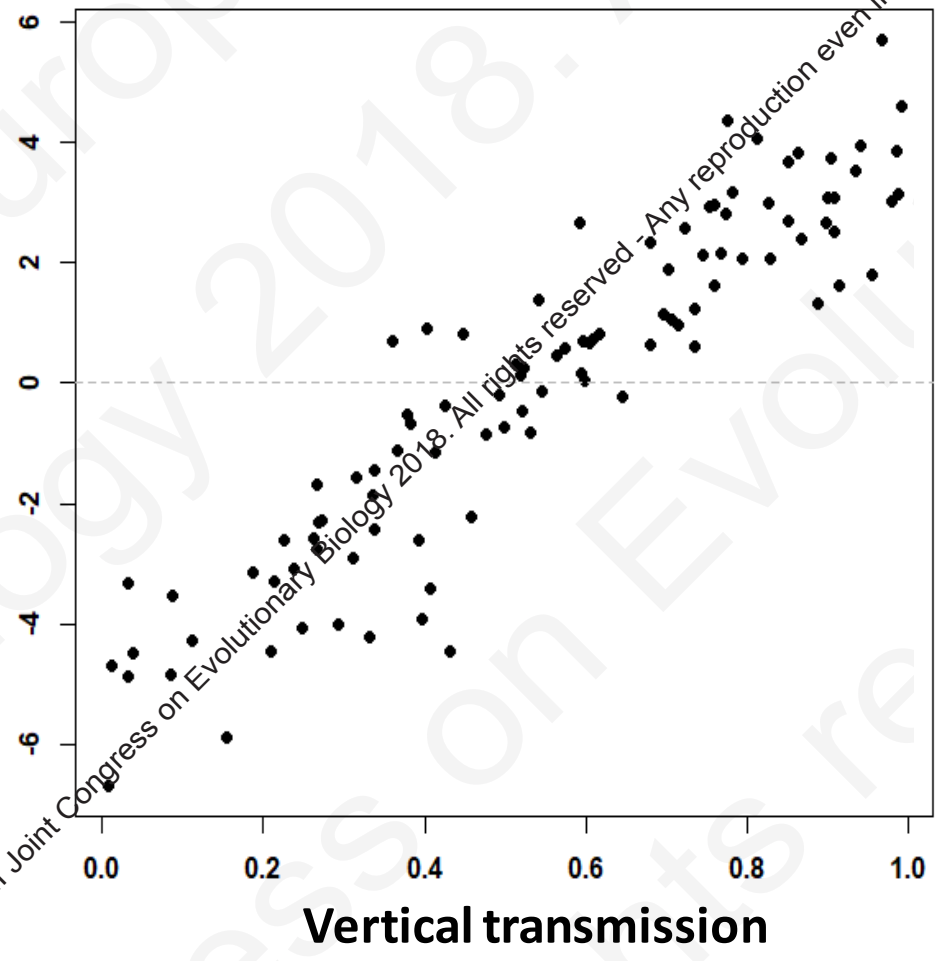
No effect of R

Generating data under this hypothesis

Simulating data for 100 hypothetical species

$$Effect = \frac{b + v}{2c} + \varepsilon$$



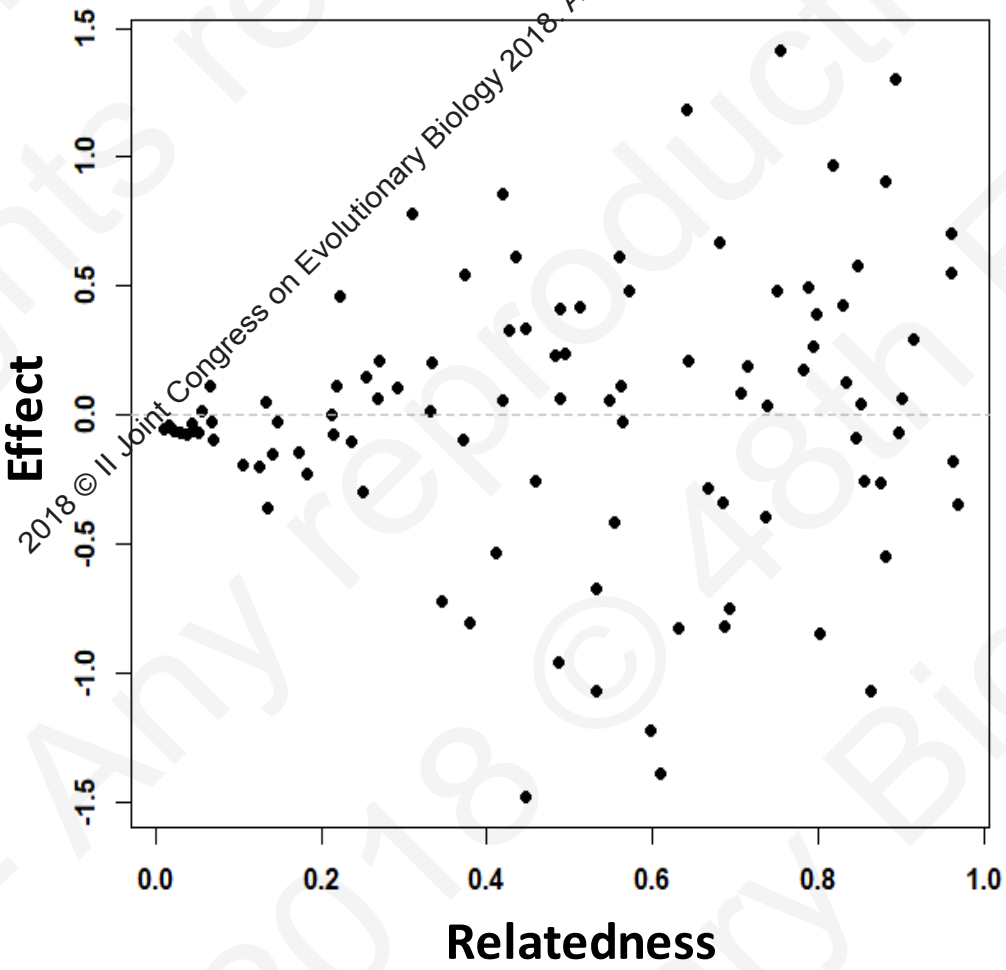


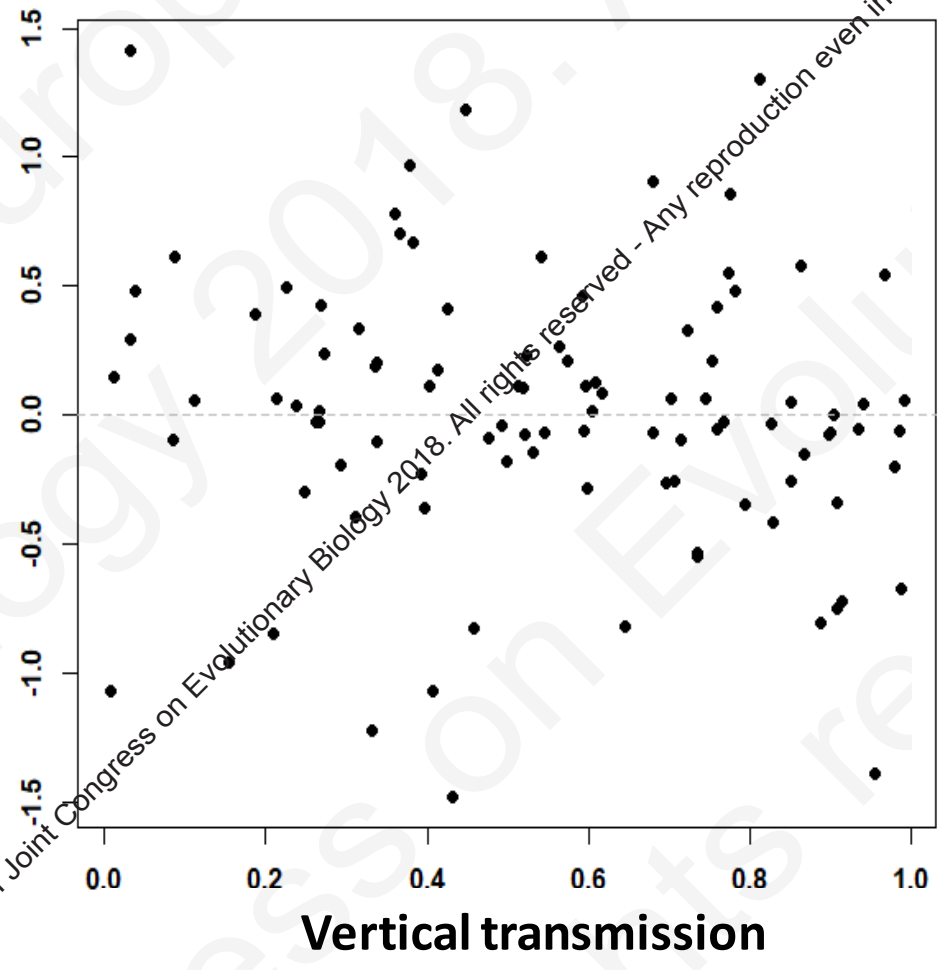
No effect of v

Generating data under this hypothesis

Simulating data for 100 hypothetical species

$$Effect = R * \frac{b}{2c} + \varepsilon$$





- R
- VT
- Effect

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- VT
- Effect

Getting real data: 1 - relatedness

Metagenomics ‘strains tracking’

MIDAS – Nayfach *et al.*, 2016

Resolve strain level composition of microbial population from metagenomics sequencing

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- R
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Resolve strain level composition of microbial population from metagenomics sequencing

Representative genome

↓

SNP calling

↓

Allele freq. at each loci

↓

Similarity

- R
- VT
- Effect

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↓

Similarity

MIDAS

↓

Within host similarity

$\overline{S}_w$

- R
- VT
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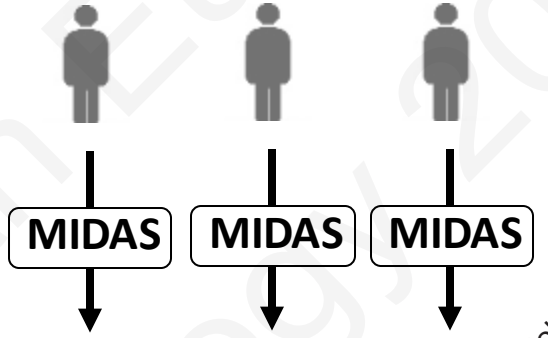
Similarity



Within host similarity

$\overline{S}_w$

Across hosts similarity

$\overline{S}_G$

- R
- VT
- Effect

Getting real data: 1 - relatedness

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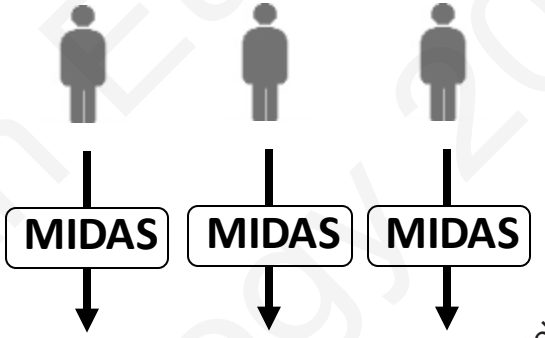
Similarity



Within host similarity $\overline{S}_w$

Across hosts similarity $\overline{S}_G$

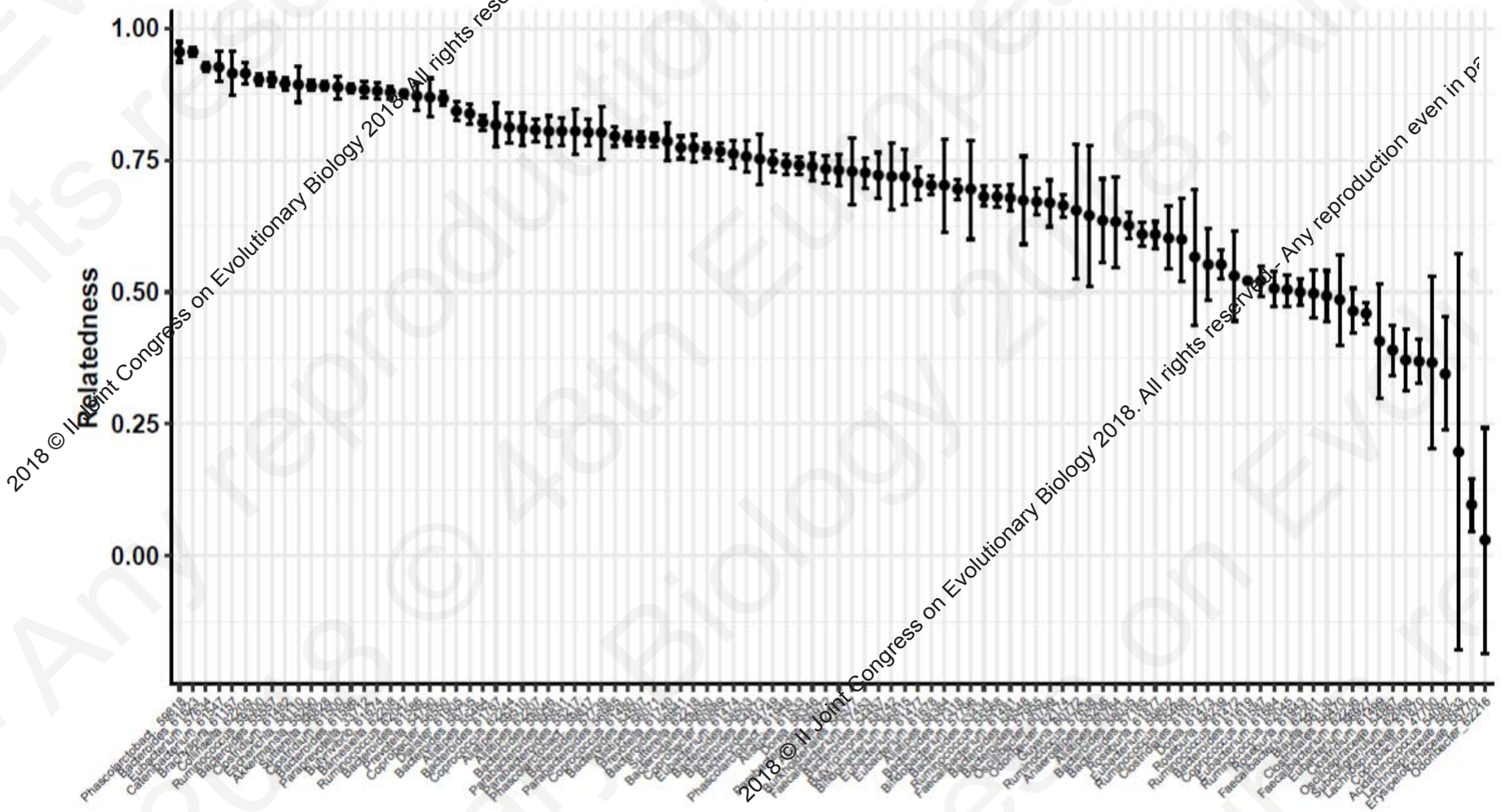
Average relatedness

$$\bar{r} = \frac{\overline{S}_w - \overline{S}_G}{1 - \overline{S}_G}$$

- R
- VT
- Effect

Getting real data: 1 - relatedness

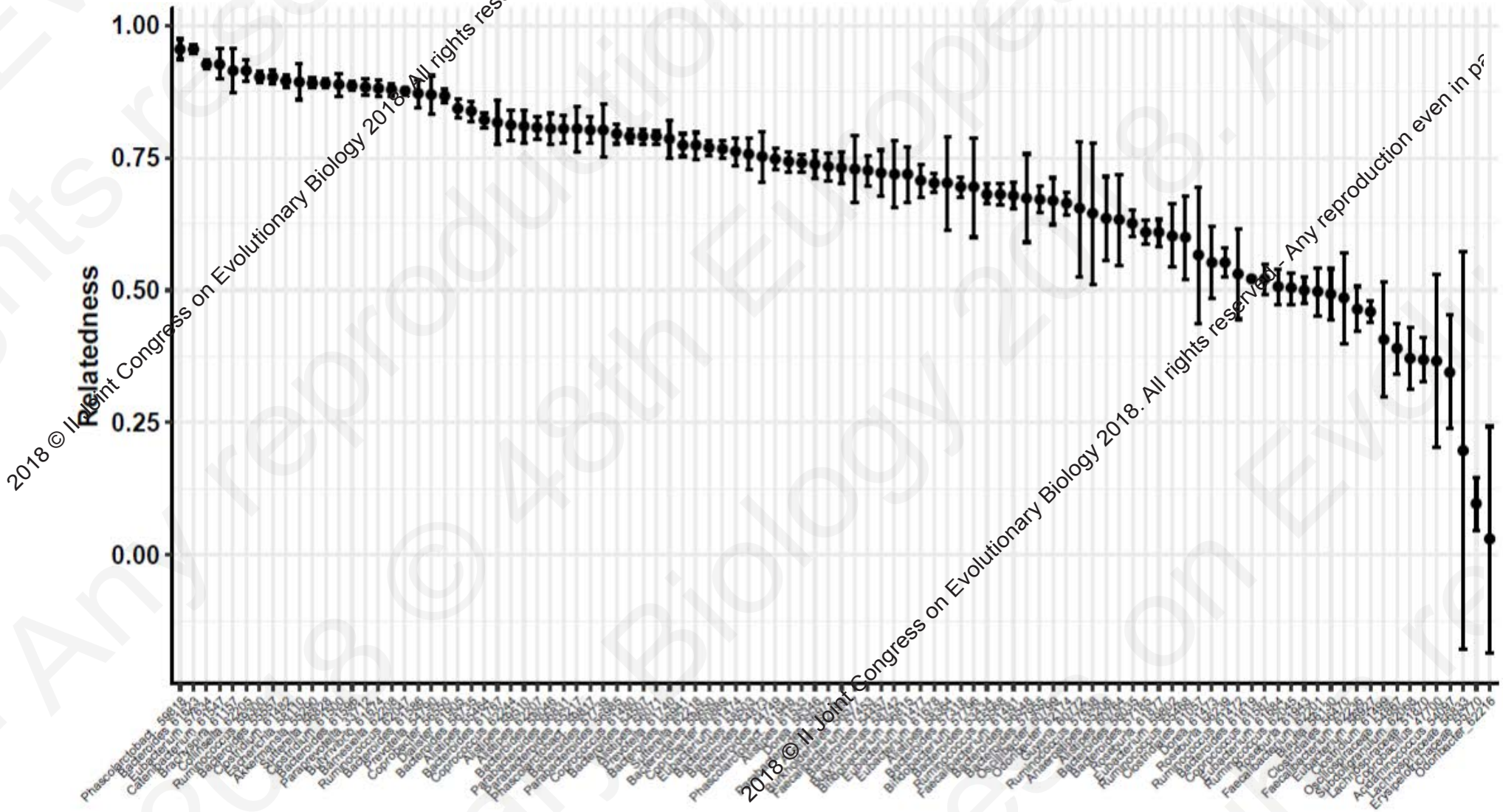
Relatedness measured for 100 gut microbes species



- [x] R
- [ ] VT
- [ ] Effect

Getting real data: 1 - relatedness

Relatedness measured for 100 gut microbes species

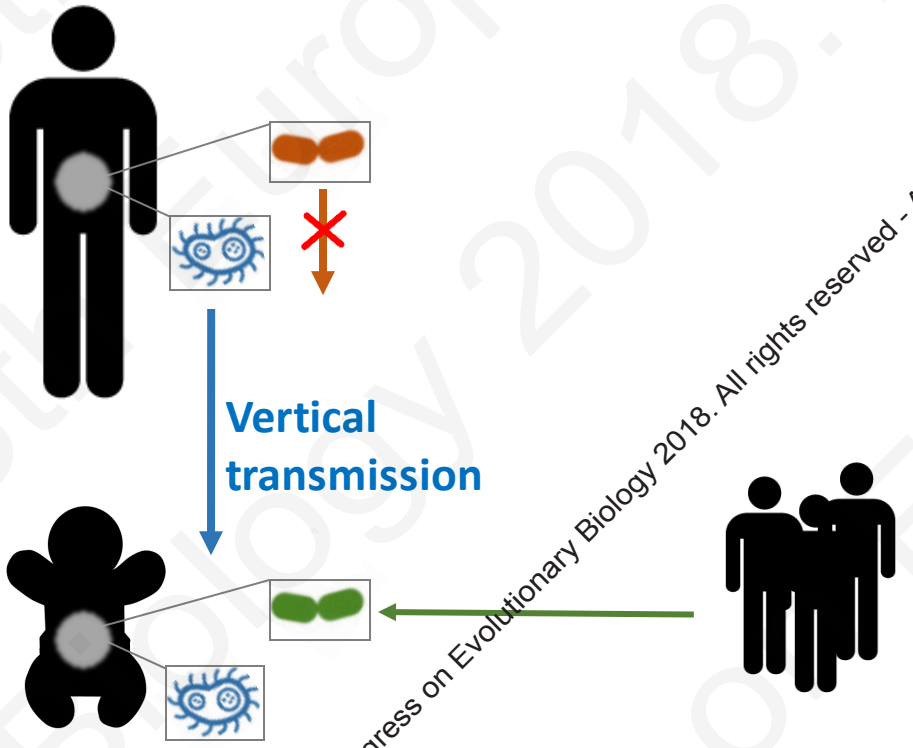


- [x] R
- [ ] VT
- [ ] Effect

Getting real data: 2 – vertical transmission

Metagenomics 'strains-tracking'

Track strain transmission between hosts using strain-specific SNPs



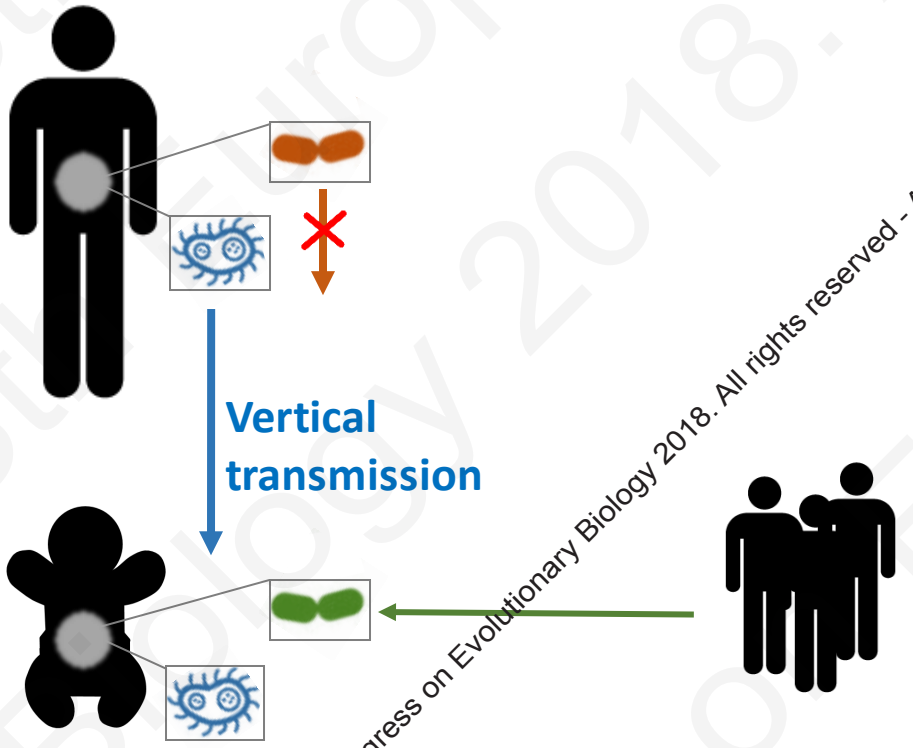
Data obtained from Nayfach *et al.*, 2016
(44 species)

- [x] R
- [x] VT
- [ ] Effect

Getting real data: 2 – vertical transmission

Metagenomics 'strains-tracking'

Track strain transmission between hosts using strain-specific SNPs

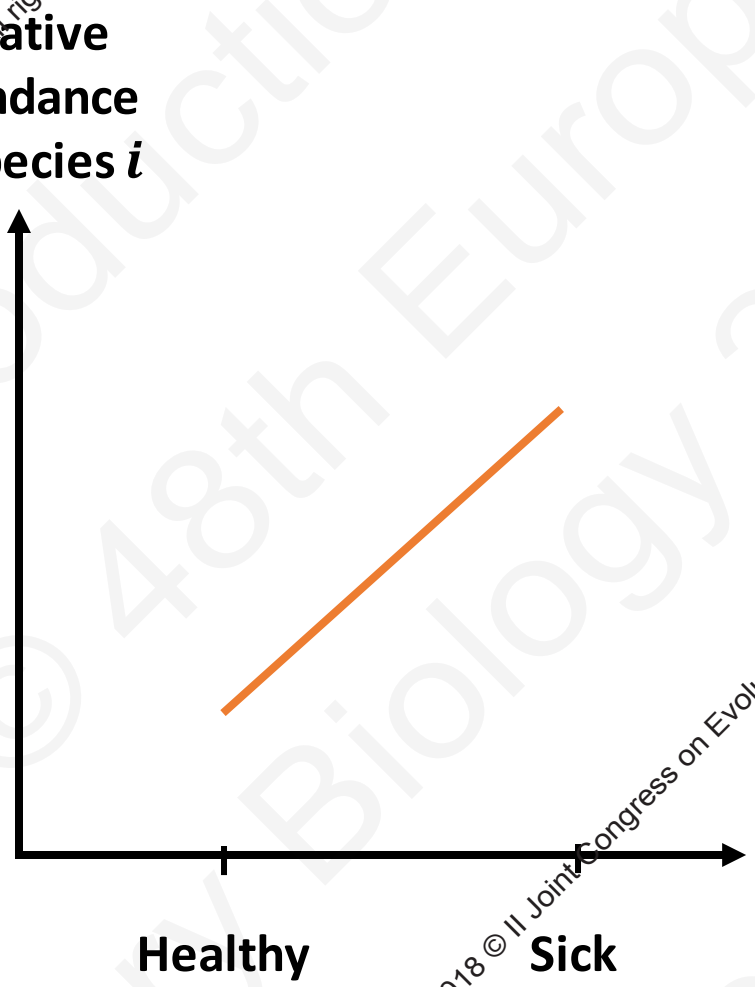


Data obtained from Nayfach *et al.*, 2016
(44 species)

- [x] R
- [x] VT
- [ ] Effect

Getting real data: 3 – effect on health

Metagenomic sequencing data → Quantify species relative abundances



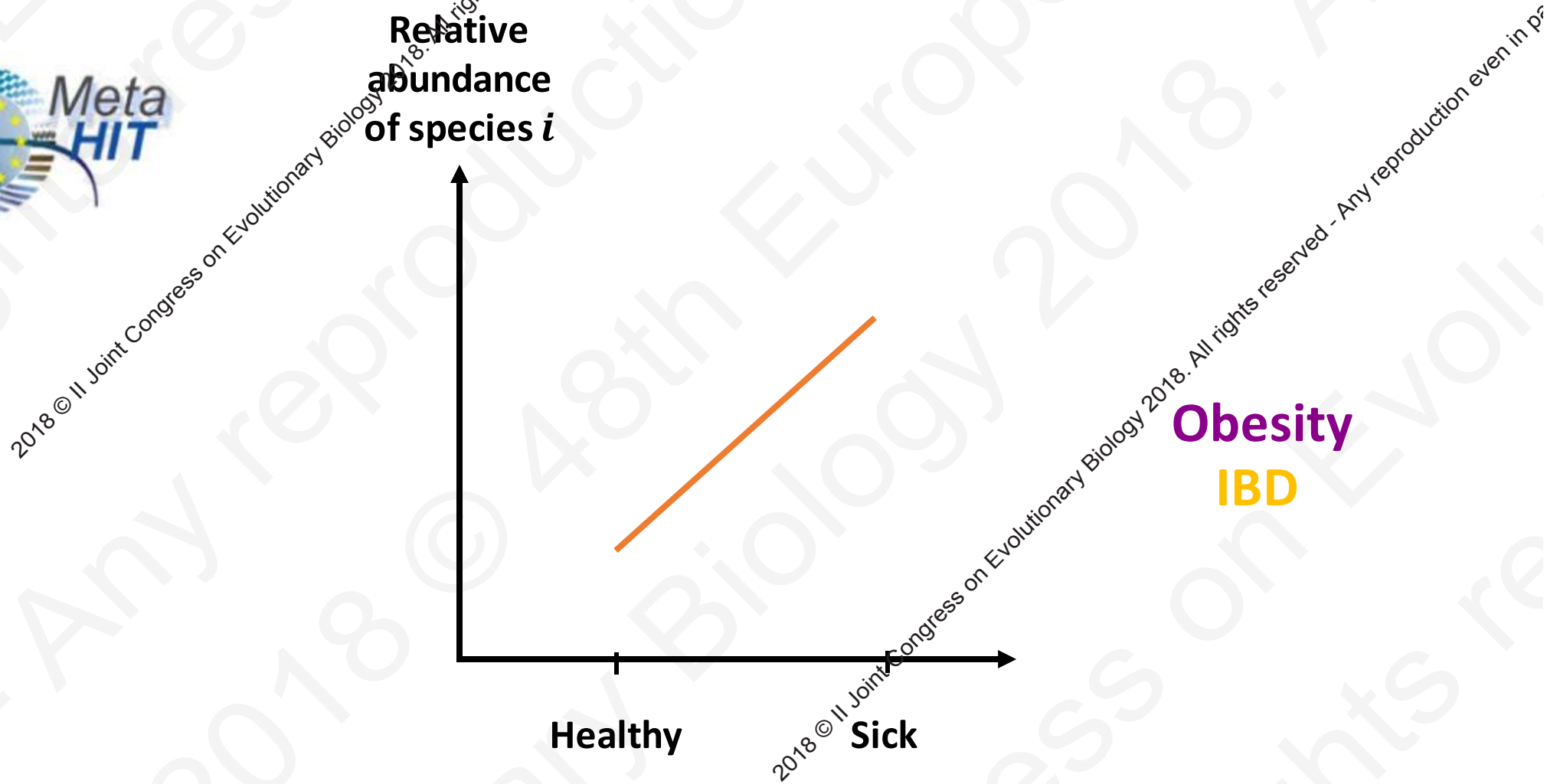
Obesity

IBD

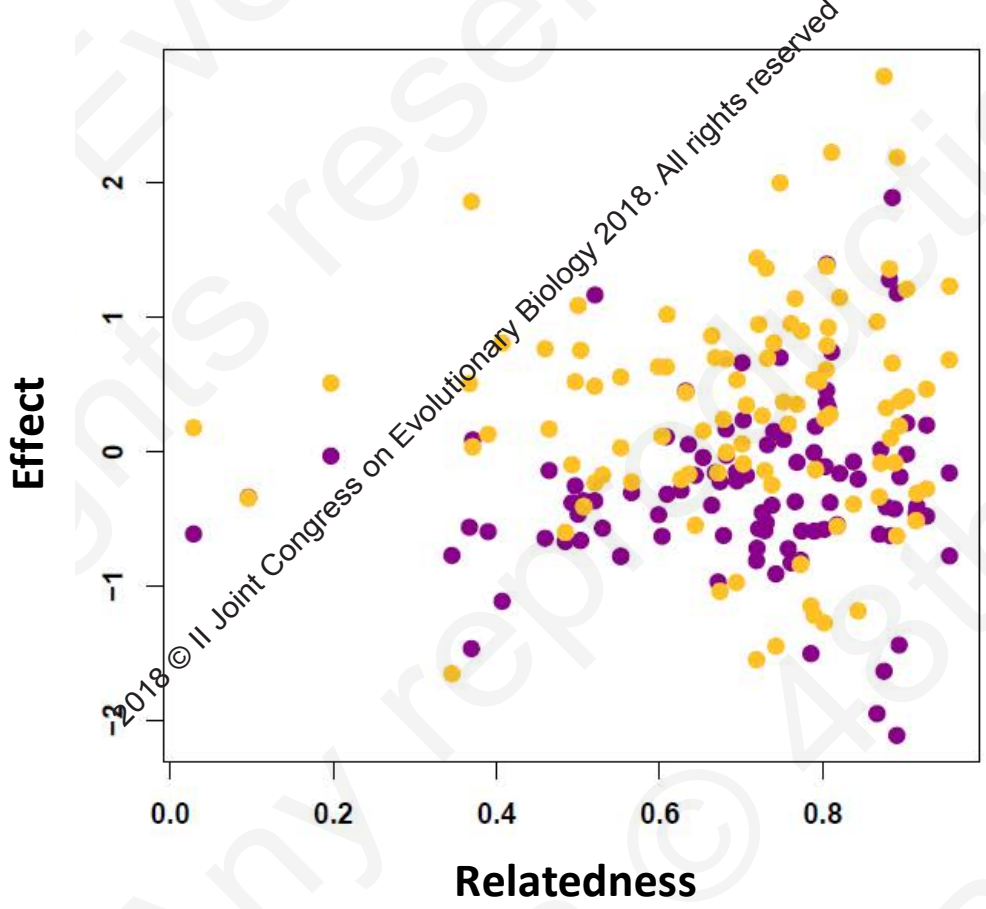
- [x] R
- [x] VT
- [x] Effect

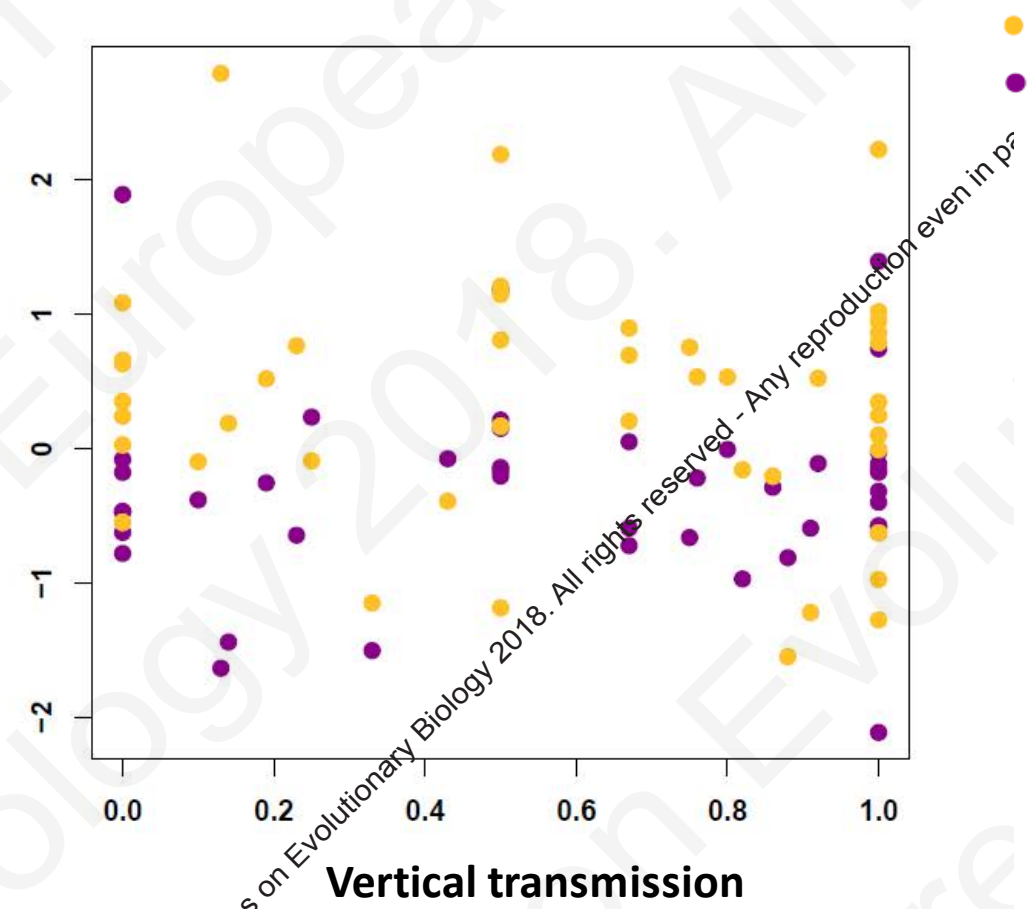
Getting real data: 3 – effect on health

Metagenomic sequencing data → Quantify species relative abundances



Testing the hypothesis with real data





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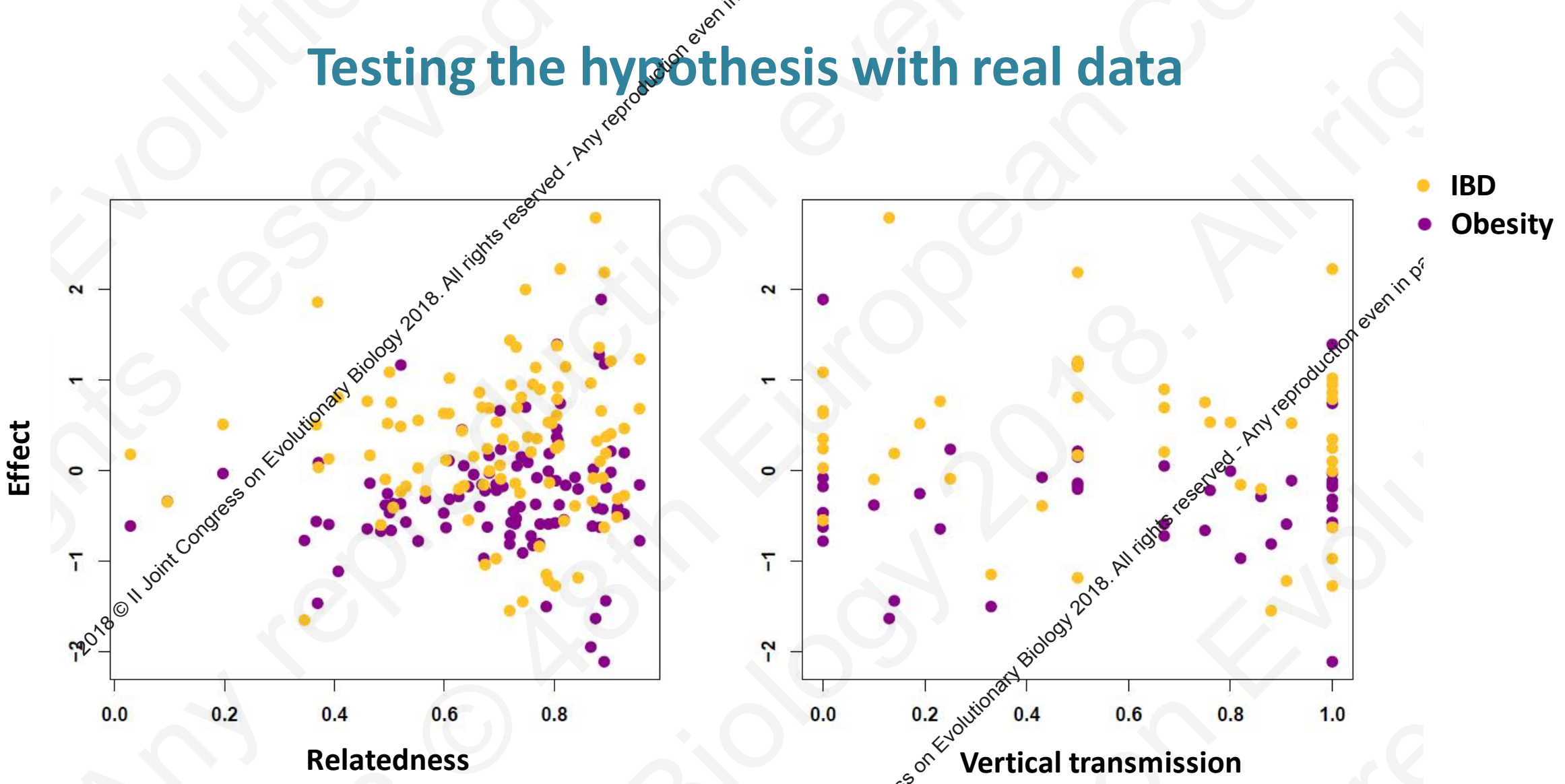
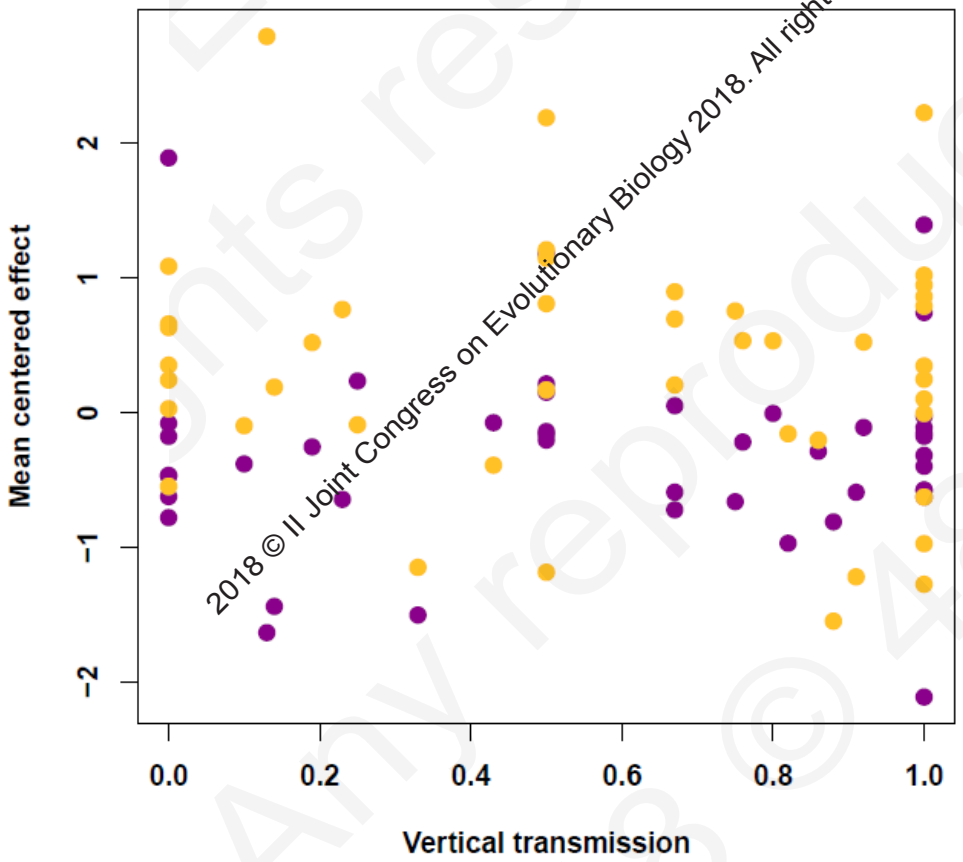
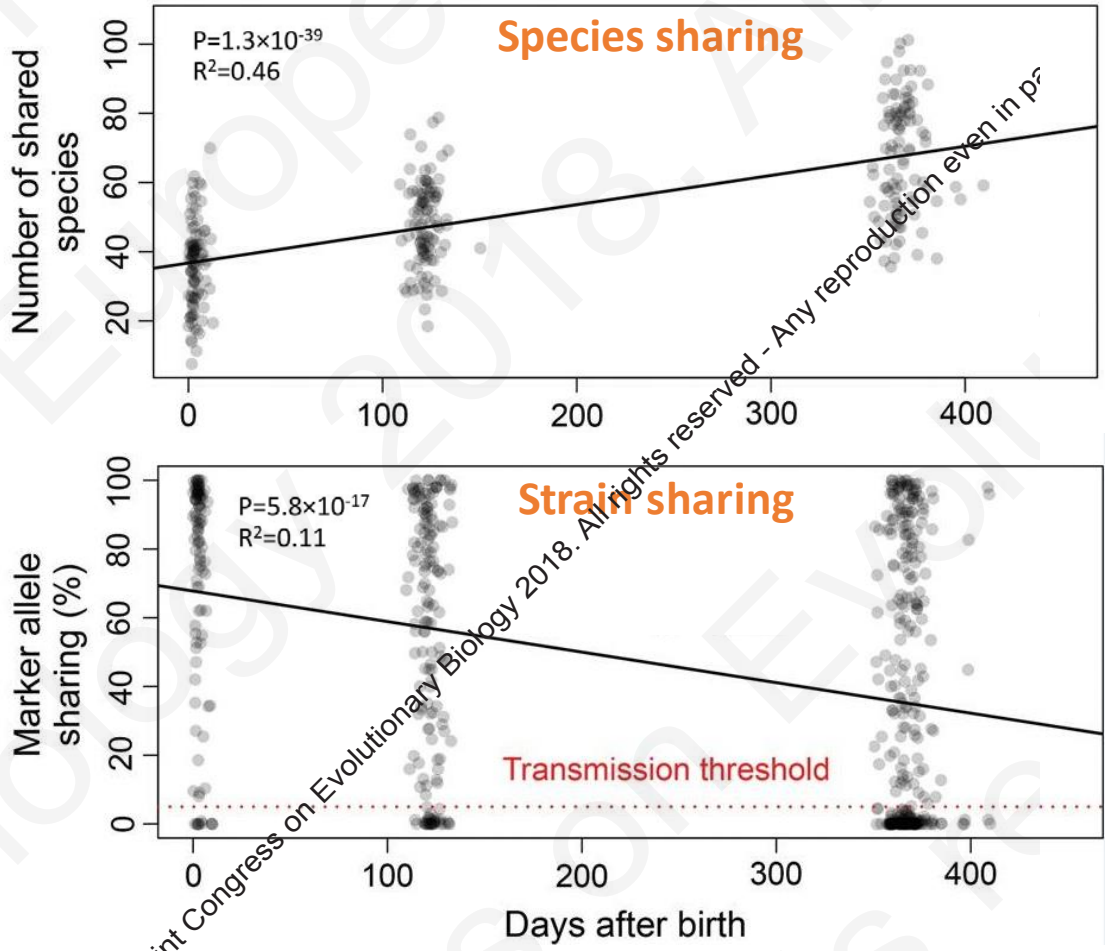


Variances increases significantly as relatedness increases (phylogenetic mixed model)

No effect detected for vertical transmission

No opportunity to gain fitness via vertical transmission?





Adapted from Nayfach *et al.*, 2016

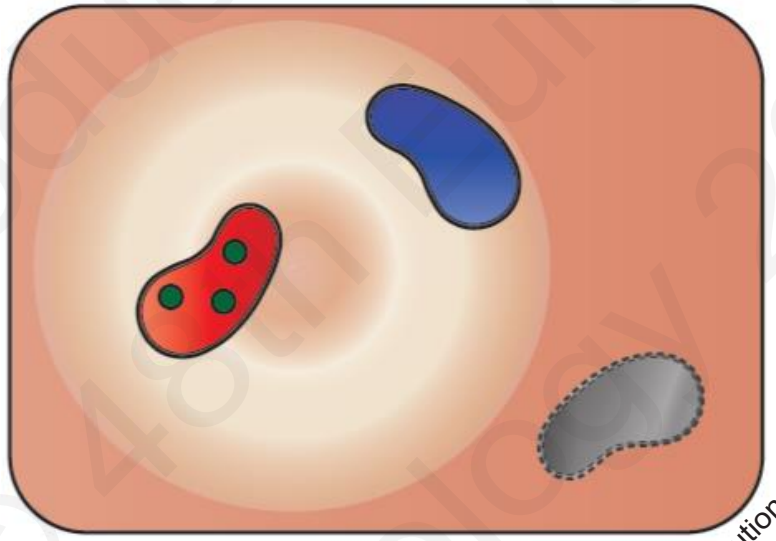
Importance of relatedness: because of collective behaviours

Modifying the environment
= large effect on host

Importance of relatedness: because of collective behaviours

Modifying the environment

= large effect on host

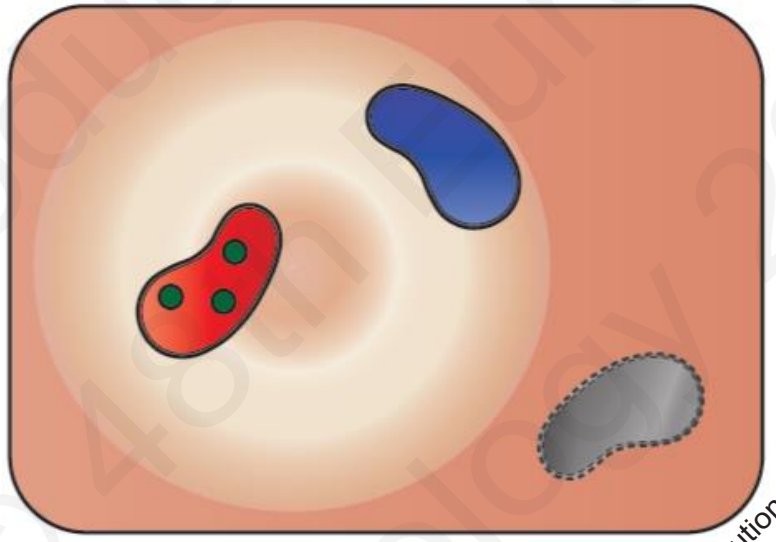


IS collective behaviour

Importance of relatedness: because of collective behaviours

Modifying the environment

= large effect on host



IS collective behaviour

↓

Favoured by high relatedness

Conclusion

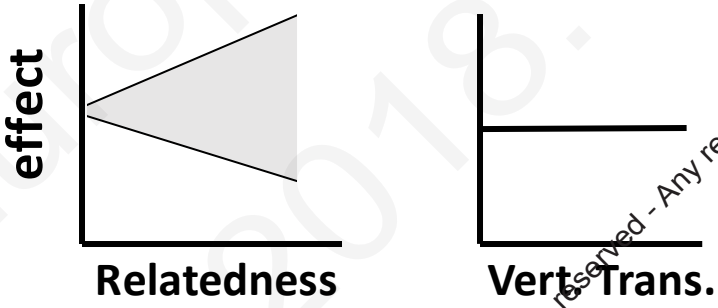
What does evolutionary theory tell us about the microbiome-health relationship?

Theory predicts

Relatedness → magnitude

Vertical transmission → direction

Data show

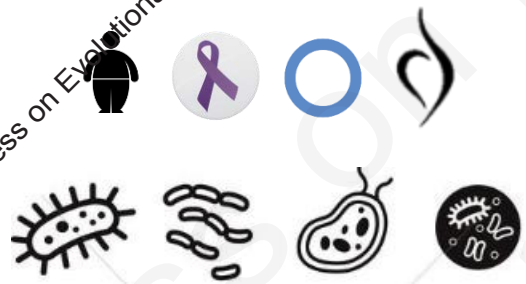


Candidate microbe approach

Microbes population genetics

Hamiltonian medicine

Generality



Acknowledgments

Luke McNally
Evolutionary microbiology

Rosalind Allen
Biological and soft condensed matter physics

THE UNIVERSITY of EDINBURGH

SynthSys
Centre for Synthetic and Systems Biology

Importance of relatedness: because of collective behaviours

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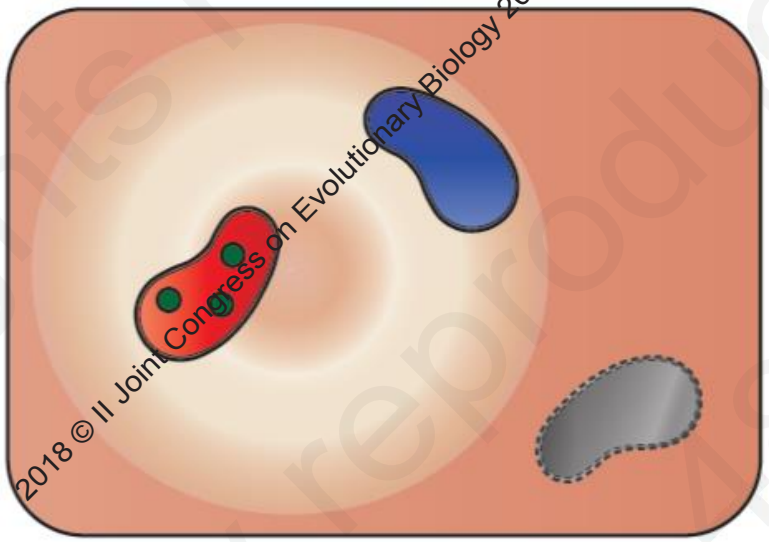

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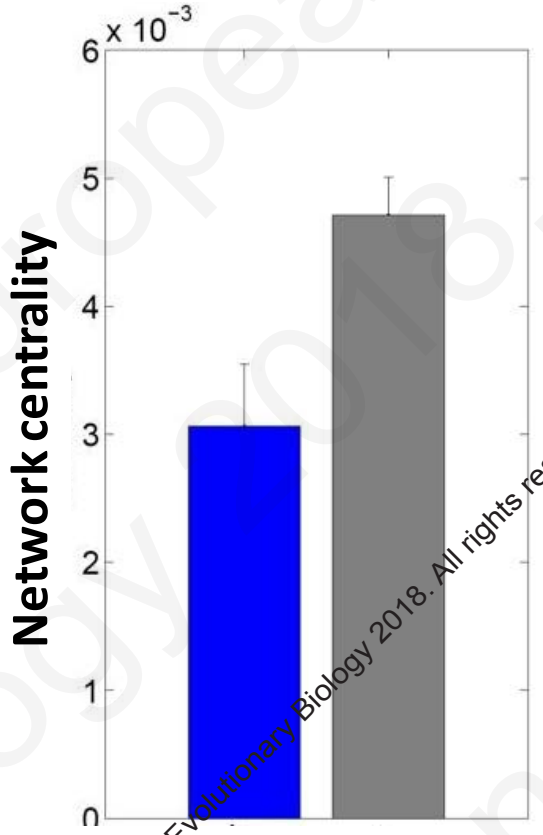

Obesity associated enzymes

Other enzymes

Adapted from Greenblum et al., 2012

Enzymes at periphery of metabolic network

= at the interface microbes – host environment