Eco-evolutionary theory of gut microbiome dysbiosis

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All macro-organisms populating our planet exist as holobionts

Holobionts are defined as animals or plants together with associated microorganisms living on them

HOLOBIONTS EXIST WITHIN A RANGE OF SYMBIOSIS

OBLIGATORY SYMBIOSIS

e.g. herbivores, termites, corals, sponges, legumes …

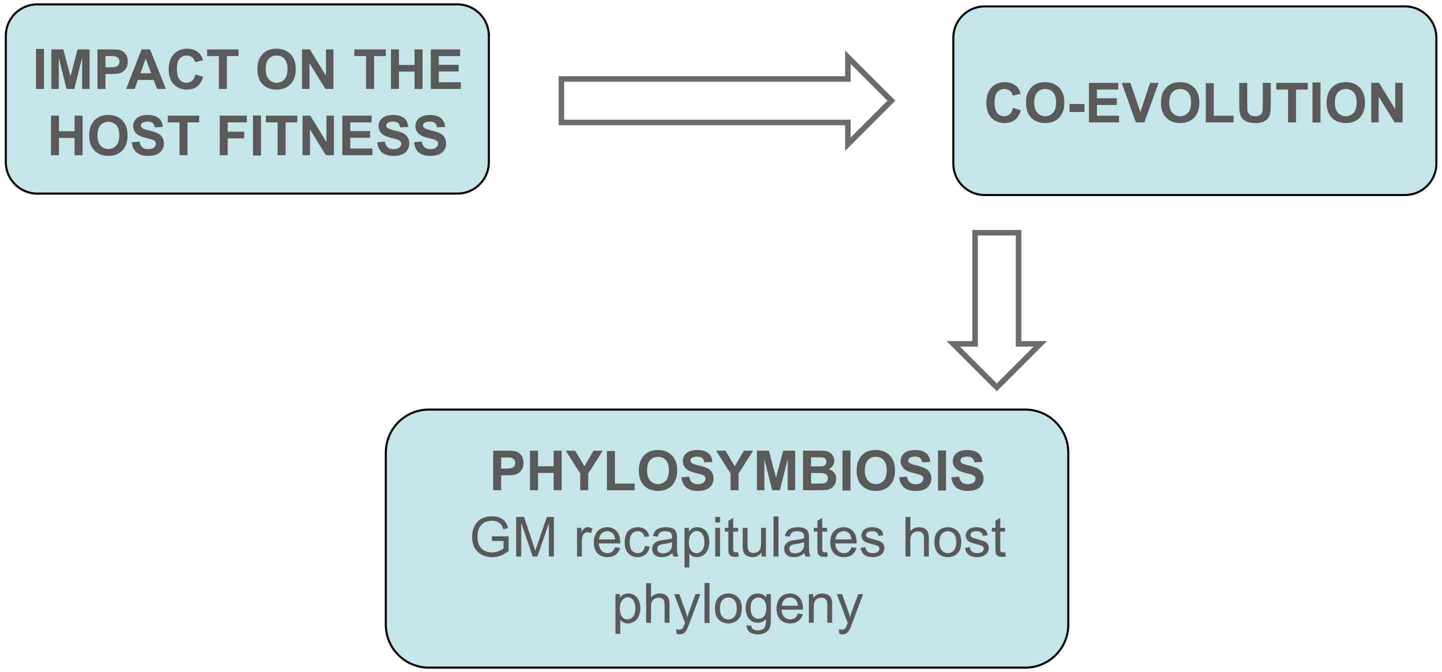
WEAK SYMBIOSIS

e.g. carnivores, omnivores, non-human primates and **human beings** …

The gut microbiome, phenotypic plasticity and co-evolution

Even under weak symbiosis the holobiont gut microbiome (GM) provides **functional traits integral to the host physiology**

(e.g. nutrition, protection and immune regulation for the human GM)



IMPACT ON THE HOST FITNESS

CO-EVOLUTION

PHYLOSYMBIOSIS
GM recapitulates host phylogeny

GM-host co-evolution needs selection and transmission

ECOLOGICAL PROCESSES INVOLVED

the selection process

HABITAT FILTERING

- type of digestive tract
- immune system
- host-derived molecules
- pH
- O_2 concentration
- dietary niche (herbivores, carnivores and omnivores)
- microbe-microbe interaction

→ Species-specific host selection forces driving to a **species-specific microbiome configuration**

microbes transmission

VERTICAL TRANSMISSION

- coprophagy
- birth
- breastfeeding
- nursing
- seeds

→ **restricted transmission** of bacterial lineages within host lineage

HORIZONTAL TRANSMISSION

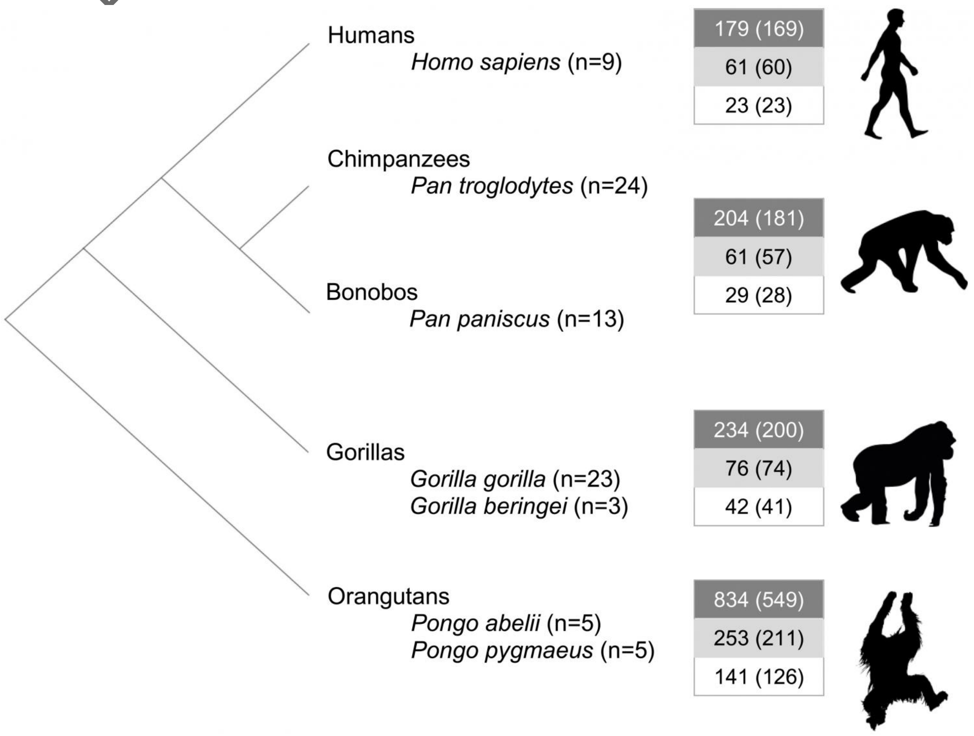
- acquisition of bacterial lineages from the environment (e.g. by eating foods and coprophagy)

→ **acquisition** of new bacterial lineages

What makes the human GM “human”?

The biology of an individual species cannot be understood in isolation!

… to understand the biology of our GM we **must look at our closest ancestors**, the non-human primates: gorillas, bonobos and chimpanzees



Humans
Homo sapiens (n=9)
179 (169)
61 (60)
23 (23)

Chimpanzees
Pan troglodytes (n=24)

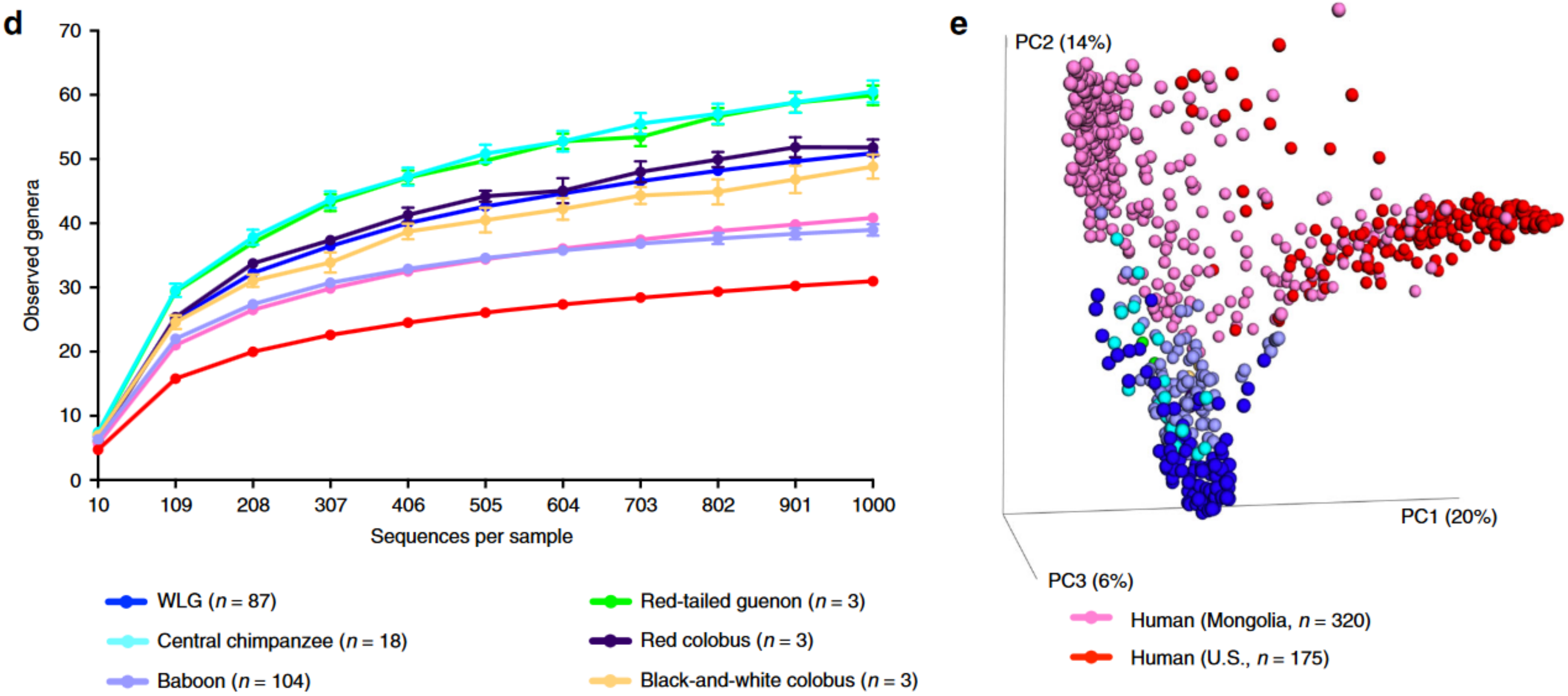
Bonobos
Pan paniscus (n=13)
204 (181)
61 (57)
29 (28)

Gorillas
Gorilla gorilla (n=23)
Gorilla beringei (n=3)
234 (200)
76 (74)
42 (41)

Orangutans
Pongo abelii (n=5)
Pongo pygmaeus (n=5)
834 (549)
253 (211)
141 (126)

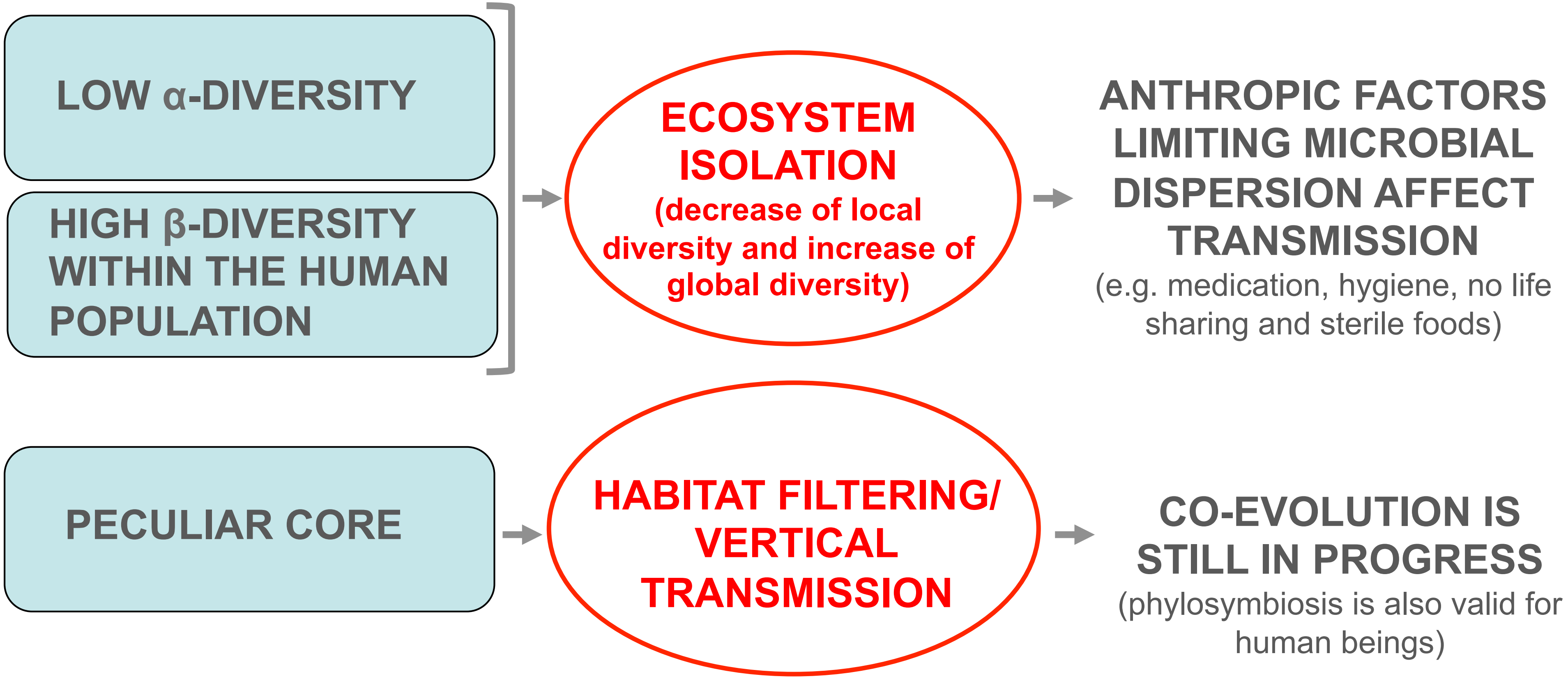
Comparative meta-analysis of the GM of human and non-human primates

(Hicks et al., Nat Commun 2018)



Distinctive features, ecological processes and driving forces shaping the human GM

Distinctive features | *Ecological processes* | *Driving forces*



LOW α-DIVERSITY

HIGH β-DIVERSITY WITHIN THE HUMAN POPULATION

→ **ECOSYSTEM ISOLATION** (decrease of local diversity and increase of global diversity) → **ANTHROPIC FACTORS LIMITING MICROBIAL DISPERSION AFFECT TRANSMISSION** (e.g. medication, hygiene, no life sharing and sterile foods)

PECULIAR CORE → **HABITAT FILTERING/ VERTICAL TRANSMISSION** → **CO-EVOLUTION IS STILL IN PROGRESS** (phylosymbiosis is also valid for human beings)

Peculiarities of the human core GM

(Moeller at al., PNAS 2014; Moeller et al., Science 2016; Groussin et al., Nat Commun 2017)

The global human core GM includes microorganisms present in at least 95% of the subjects and has been extracted from a dataset including ~ 4,000 subjects of different geographical origin and lifestyle

(Falony *et al.*, Science 2016)

14 dominant core GM components, including:

- *Roseburia*
- *Faecalibacterium*
- *Dorea*
- *Coprococcus*
- *Clostridium XIVa*
- *Blautia*
- *Bacteroides*
- *Bifidobacterium*

human peculiarities include co-speciating microorganisms linked with **host immune functions**

shared features involve cosmopolitan microorganisms showing **diet-related functions**

So, what makes the human GM “human”?

- THE SHRINKAGE OF THE INDIVIDUAL GM DIVERSITY
- THE HIGH DEGREE OF SPECIFICITY OF THE PERSONAL GM LAYOUT
- A POSITIVE SELECTION TOWARDS IMMUNOMODULATING GM COMPONENTS
- IT IS SHAPED BY ANTHROPIC FACTORS

Is the human microbiome evolving as a personal adjuvant of our immune function?

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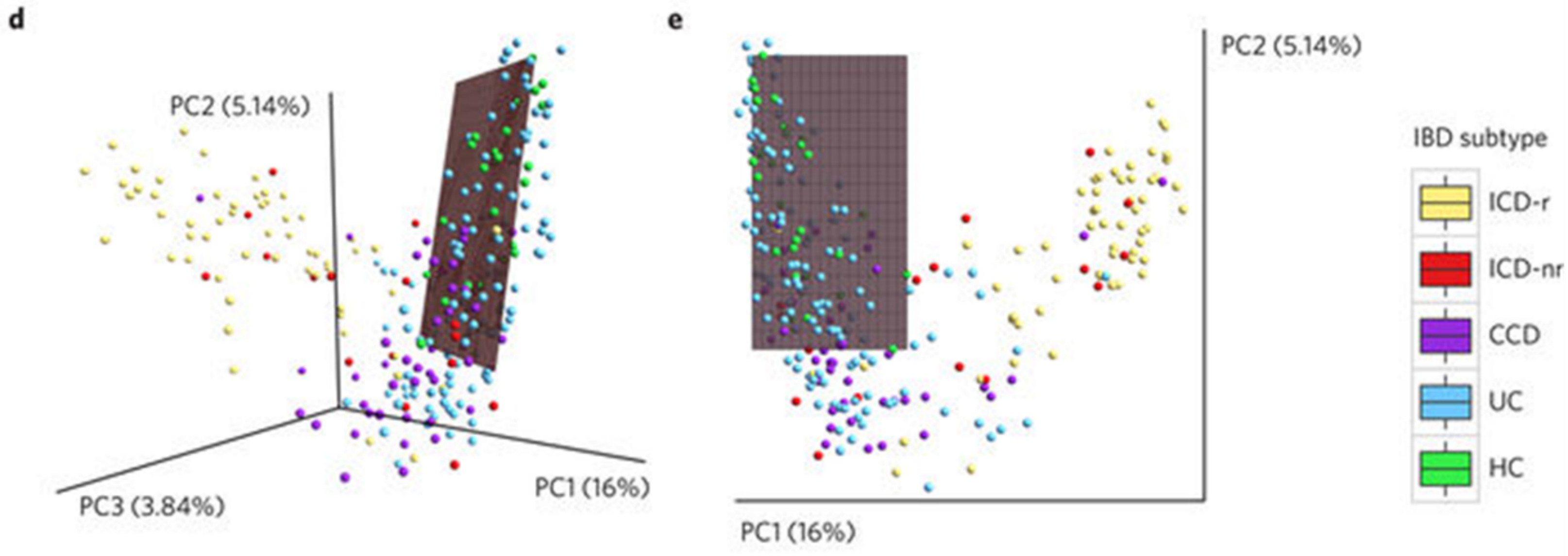
GM DYSBIOSES ARE PRINCIPALLY ASSOCIATED WITH INFLAMMATORY DISEASES!

The healthy plane of variation

(Halfvarson et al., Nat Microbiol 2017)

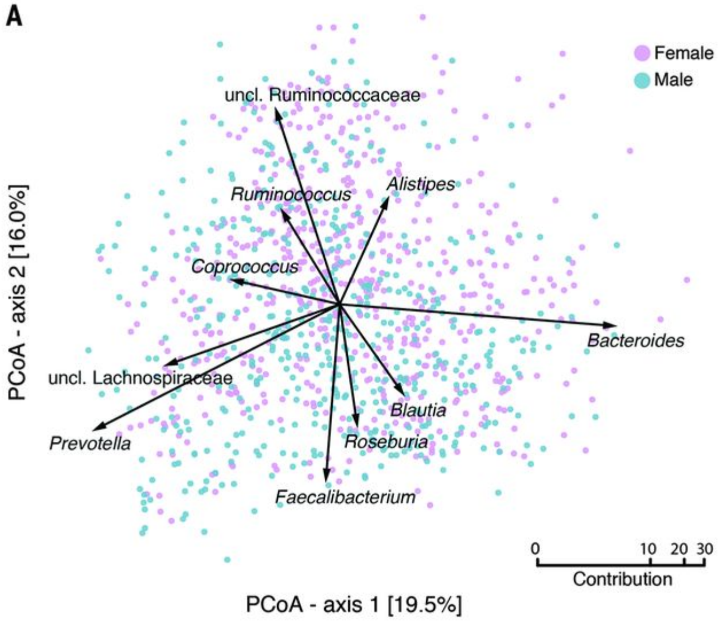
The human GM exists in a range of eubiotic configurations, which together define the **healthy plane of variation**

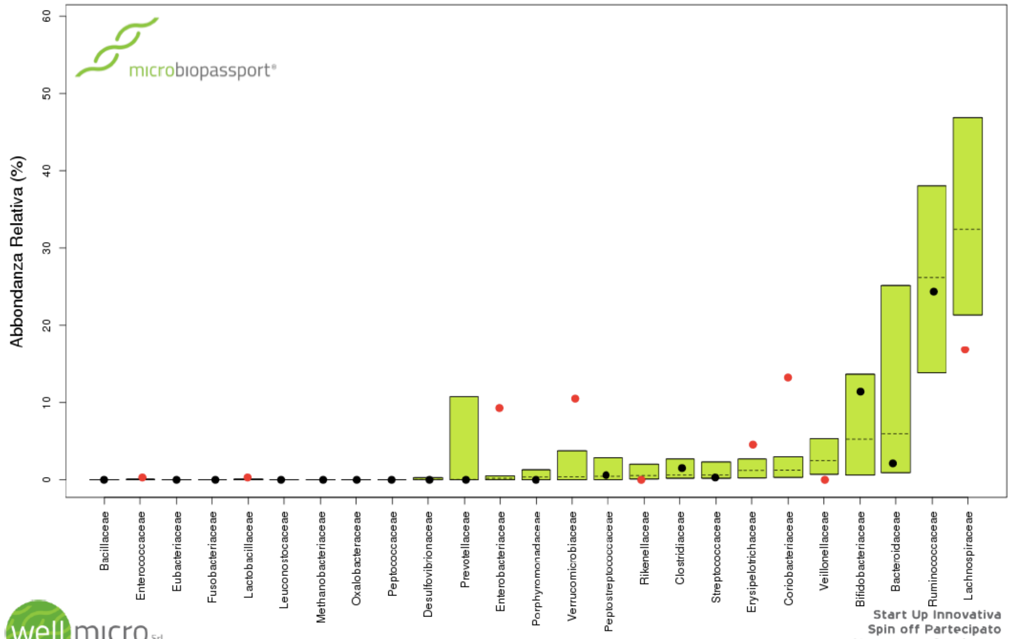


Ecological structure of the healthy plane

Inter-individual variation in GM composition within the healthy plane mainly results from **changes in the abundance of core taxa,** which are allowed to vary in specific and defined ranges of abundance

(Falony et al., Science 2016)





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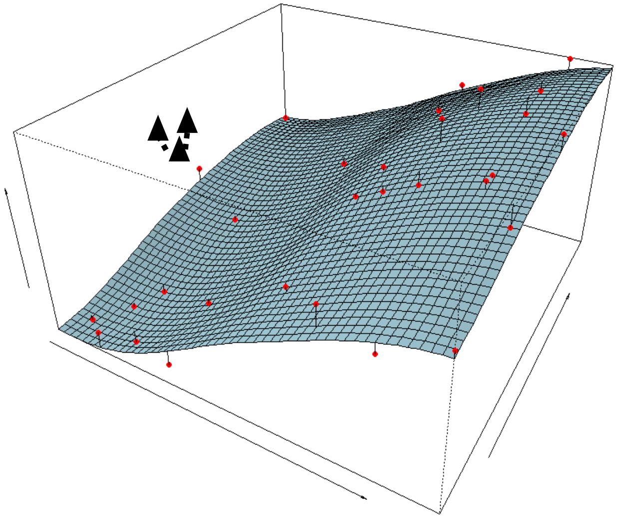
Eco-evolutionary view of human microbiome dysbioses

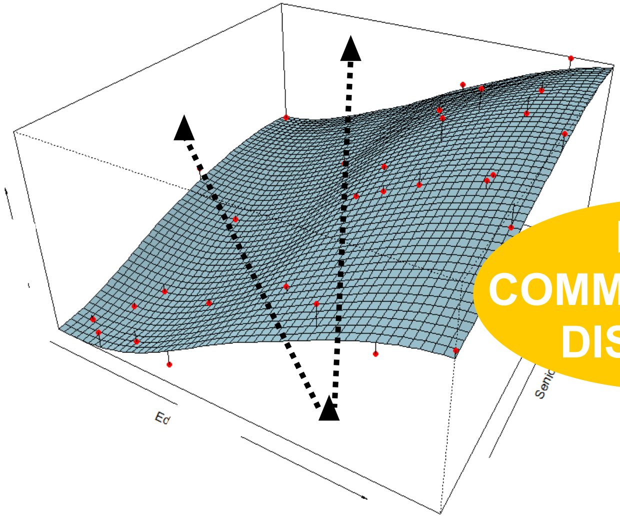
(Duvallet et al., Nat Commun 2017; Zaneveld et al., Nat Microbiol 2017)

Shift away from the healthy microbiome

LOCATION EFFECT
enrichment of disease-associated bacteria
(CRC, infection)

DISPERSION EFFECT
depletion of health-associated bacteria
(impaired immune function, IBD,
metabolic syndrome, obesity, T2D)





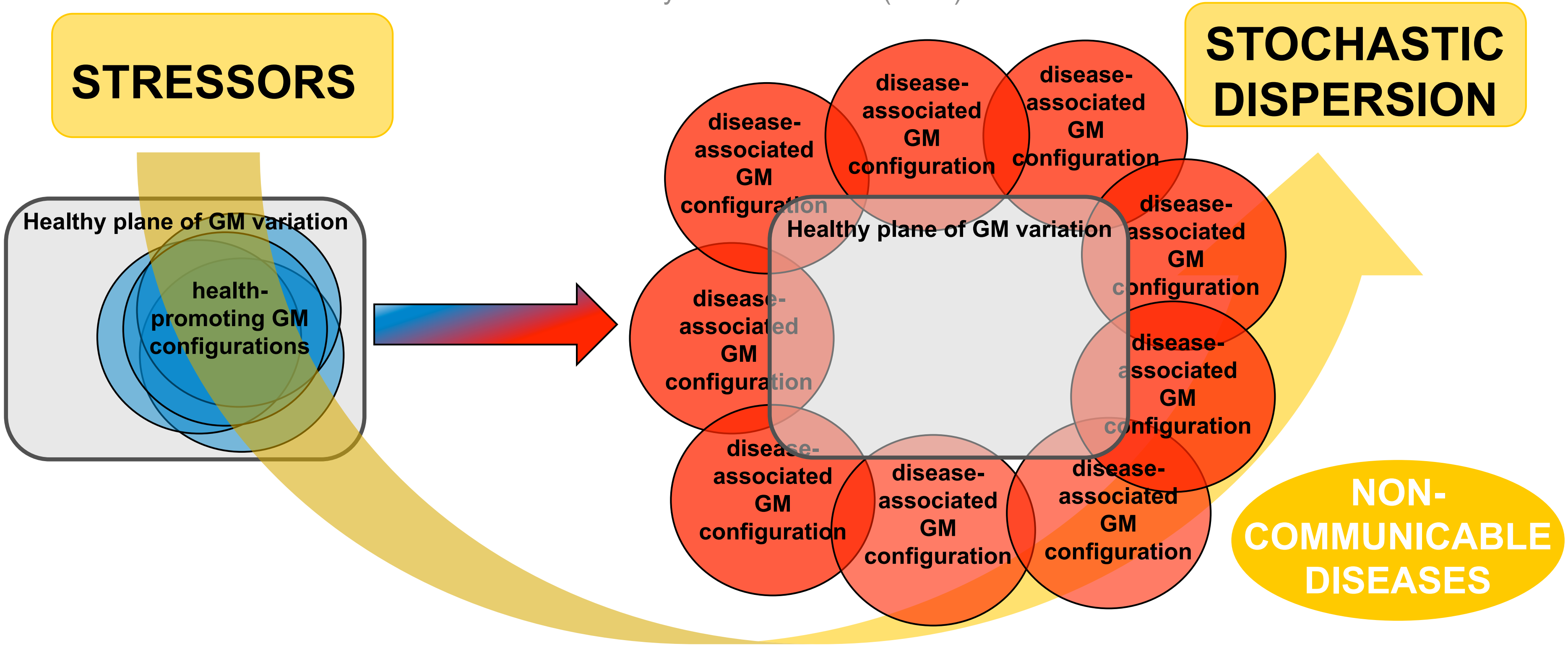
NON-COMMUNICABLE DISEASES

The microbial ecology of dysbiotic dispersions, the Anna Karenina principle

Zaneveld et al., Nat Microbiol 2017

"All happy families are alike; each unhappy family is unhappy in its own way"

Leo Tolstoy: Anna Karenina (1878)



STRESSORS

Healthy plane of GM variation

health-promoting GM configurations

disease-associated GM configuration

disease-associated GM configuration

disease-associated GM configuration

disease-associated GM configuration

Healthy plane of GM variation

disease-associated GM configuration

disease-associated GM configuration

disease-associated GM configuration

disease-associated GM configuration

disease-associated GM configuration

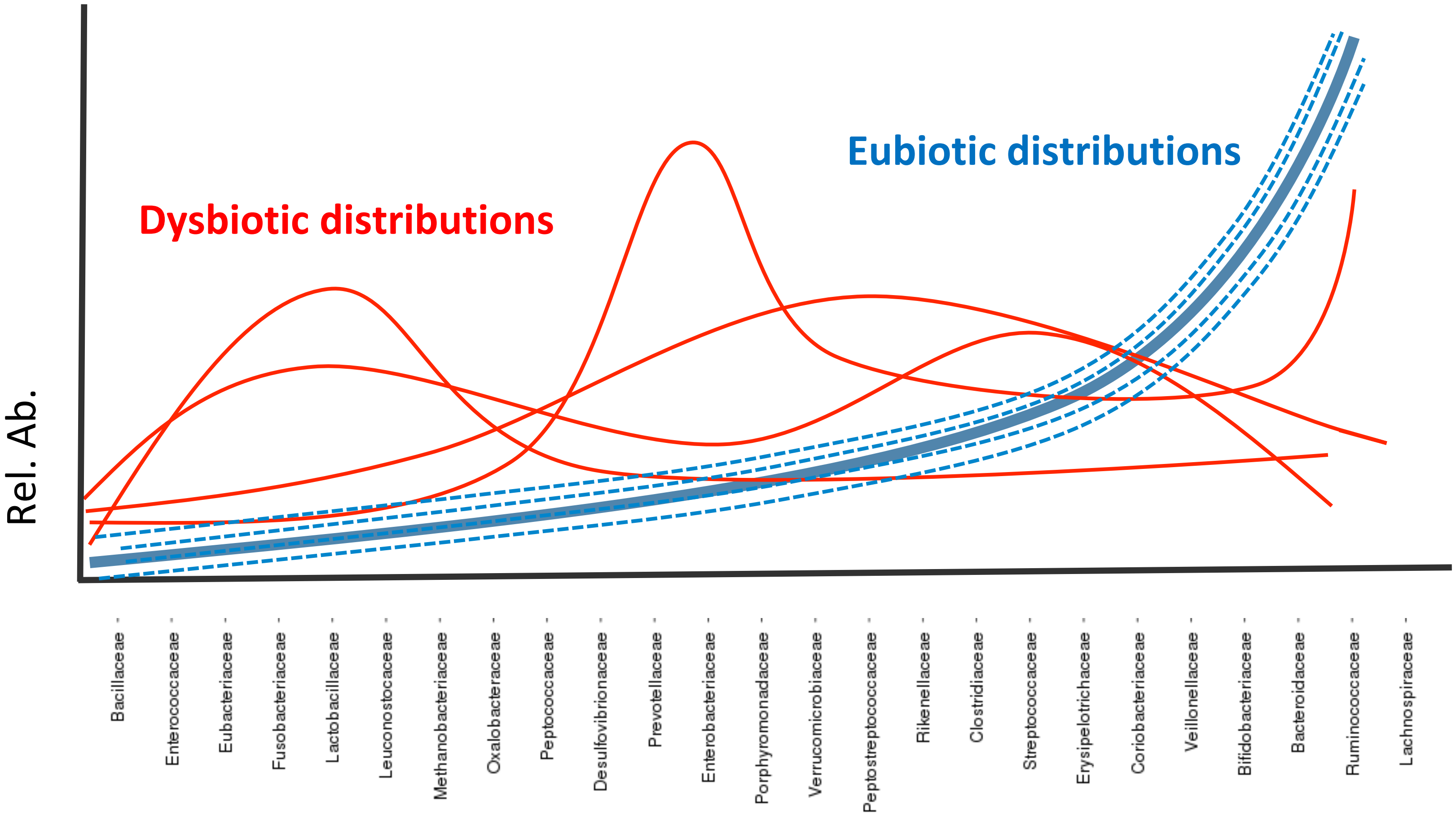
STOCHASTIC DISPERSION

NON-COMMUNICABLE DISEASES

All microbiomes are similar; each dysbiotic microbiome is dysbiotic in its own way

Eubiotic and dysbiotic distributions of the major GM families

there are **no disease-specific associations** … but all dysbiotic microbiomes share the reduction of the dominant eubiotic groups *Ruminococcaceae and Lachnospiraceae*



But … what are the main drivers of dysbioses?

(Falony et al., Science 2016; Zhernakova et al., Science 2016; Wang et al., Nat Genet 2016; Schmidt et al., Cell 2018)

A massive (muscular) effort to dissect determinants of GM variation has been recently performed, with an empiric **but not eco-evolutionary vision …**

(Falony et al., Science 2016; Zhernakova et al., Science 2016; Wang et al., Nat Genet 2016; Schmidt et al., Cell 2018)

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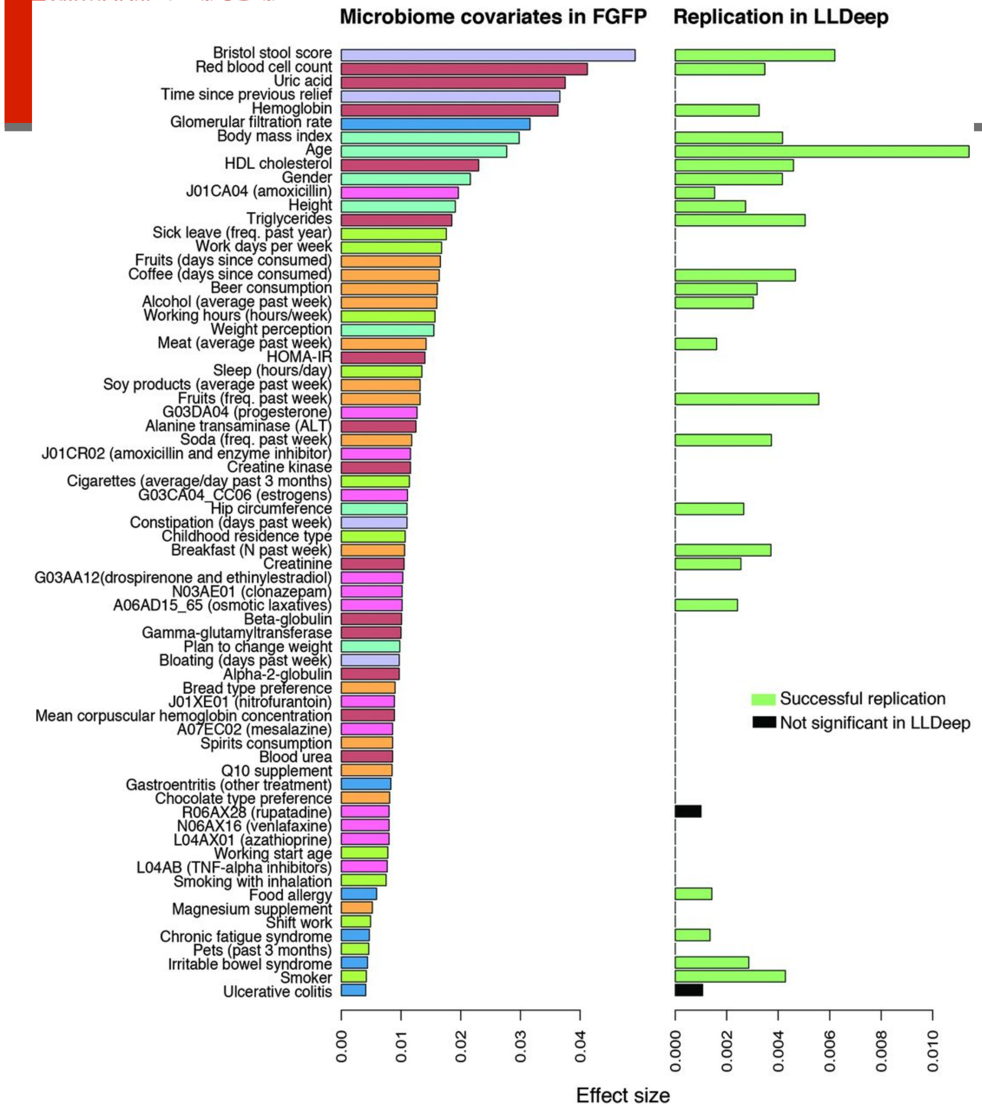
POPULATION-LEVEL ANALYSIS OF THE **GM VARIATION AND 503 METADATA IN ~ 4,000 SUBJECTS ACROSS THE GLOBE**, WITH DIFFERENT DIET AND LIFESTYLE

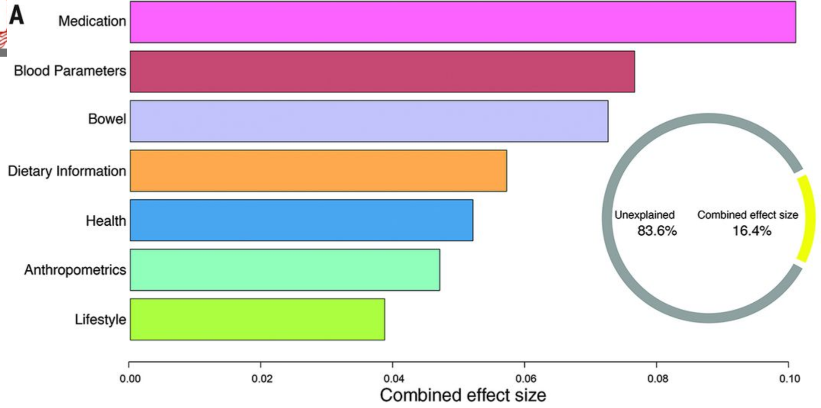
GUT MICROBIOME COVARIATES

(503 factors describing: physiology/pathology, anthropometric, lifestyle)

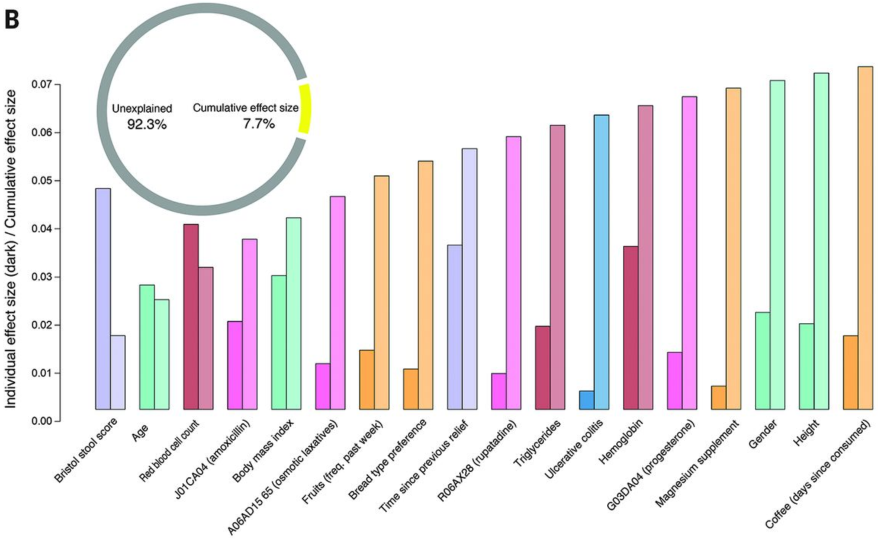


69 factors were shown to correlate with the overall gut community variation, each explaining between 1.50 and 14.74% of the genus abundance variation

COVARIATE COMBINED EFFECT SIZE PER PHENOTYPICAL CATEGORY



THE TOTAL ADDITIVE EFFECT SIZE OF ALL CATEGORIES IS 16.43% OF THE GENUS-LEVEL GM VARIATION

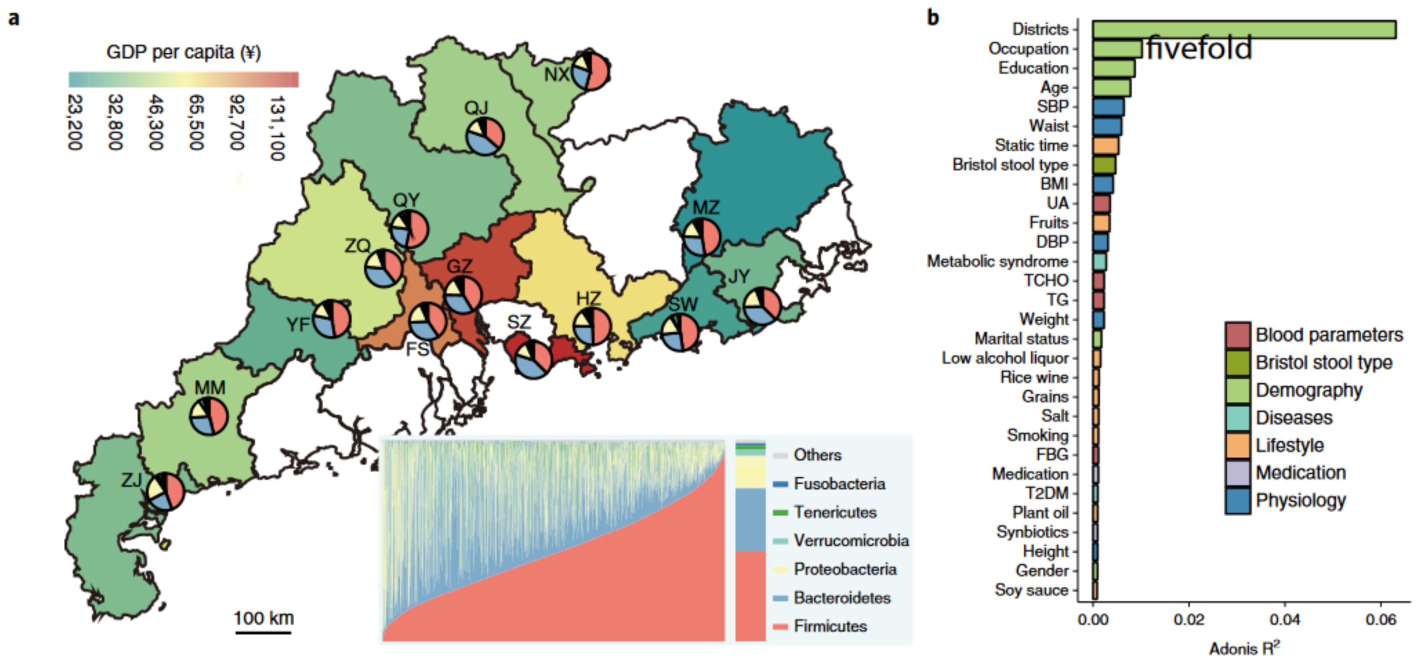


CUMULATIVE NON-REDUNDANT EFFECT SIZE IS 7.63% OF THE GENUS-LEVEL VARIATION

Sept 2018, the largest human microbiome survey

(He et al., Nat Med 2018)

GM and 72 covariates (e.g. dietary habits, age, health, lifestyle) in >7,000 persons, same ethnic group, 14 districts across 1 province in China



fivefold

LOCATION EXERTED THE STRONGEST EFFECT, FAR EXCEEDING THE EFFECT OF THE OTHER COVARIATES

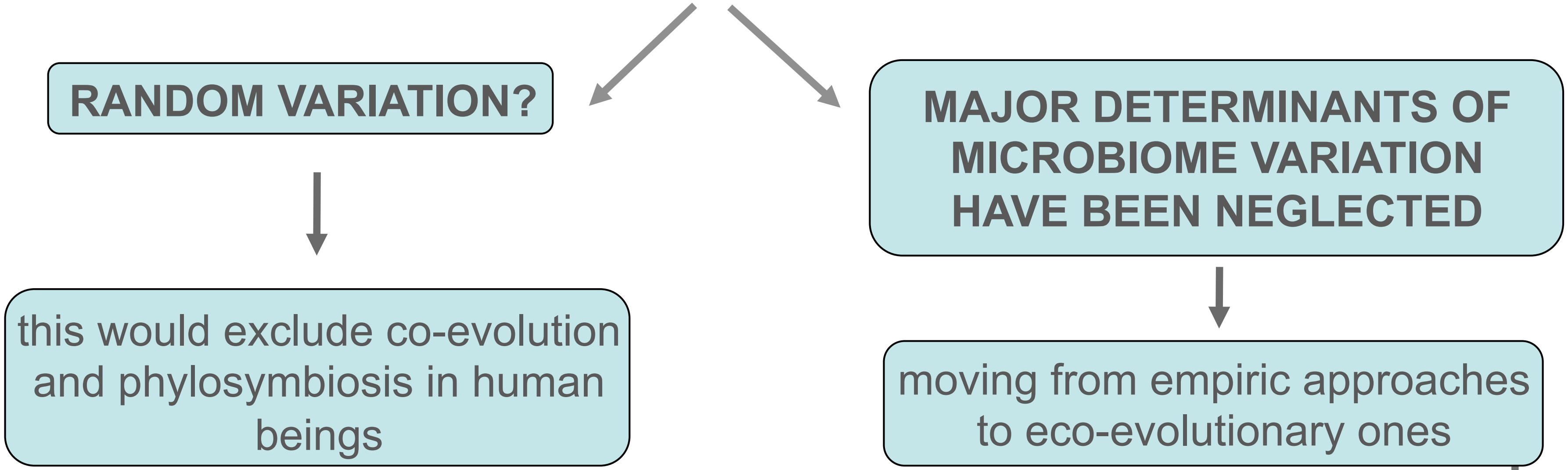
… ecological processes, such as dispersal, drift, local diversification, host interaction with environmental microbiota and xenobiotic exposure can be involved in the observed location-dependent effect…

Traditional covariates explain only a small fraction of microbiome variation

- **medication** is emerging as the major explanatory covariate, followed by age (not aging), drugs, gender and dietary information

- **dietary information explains only** 5.79% of microbiome variation

EVEN THE STRONGEST CO-VARYING FACTOR EXPLAINS ONLY A SURPRISINGLY SMALL FRACTION **(<10%)** OF THE HUMAN GM INTER-INDIVIDUAL VARIATION



RANDOM VARIATION?

this would exclude co-evolution and phylosymbiosis in human beings

MAJOR DETERMINANTS OF MICROBIOME VARIATION HAVE BEEN NEGLECTED

moving from empiric approaches to eco-evolutionary ones

The diet habits-microbiome paradigm

The most cited papers about human GM modulation by means of changing diet

Wu et al., Science 2011_2824 cit.
98 subjects

David et al., Nature 2014_2615 cit.
10 subjects

Le Chatelier et al., Nature 2013_1494 cit.
292 subjects of whom 169 obese

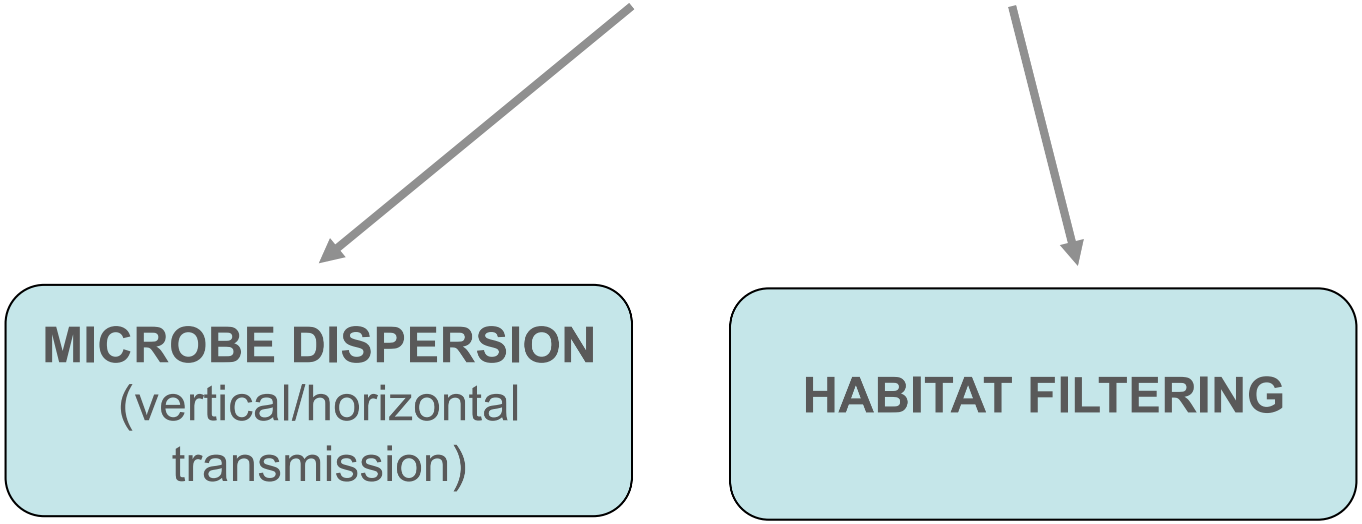
Walker et al., ISME J 2011_877 cit.
14 subjects, all obese

According to *Falony et al.*, Science 2016 - GM meta-analysis of 4,000 subjects - in microbiome studies the power of 80% is reached with 500 subjects

Do we need to change the paradigm?

The eco-evolutionary approach

The drivers of human GM variation need to be searched among the forces with the potential to impact the ecological processes driving microbiome **transmission and selection**



MICROBE DISPERSION
(vertical/horizontal transmission)

HABITAT FILTERING

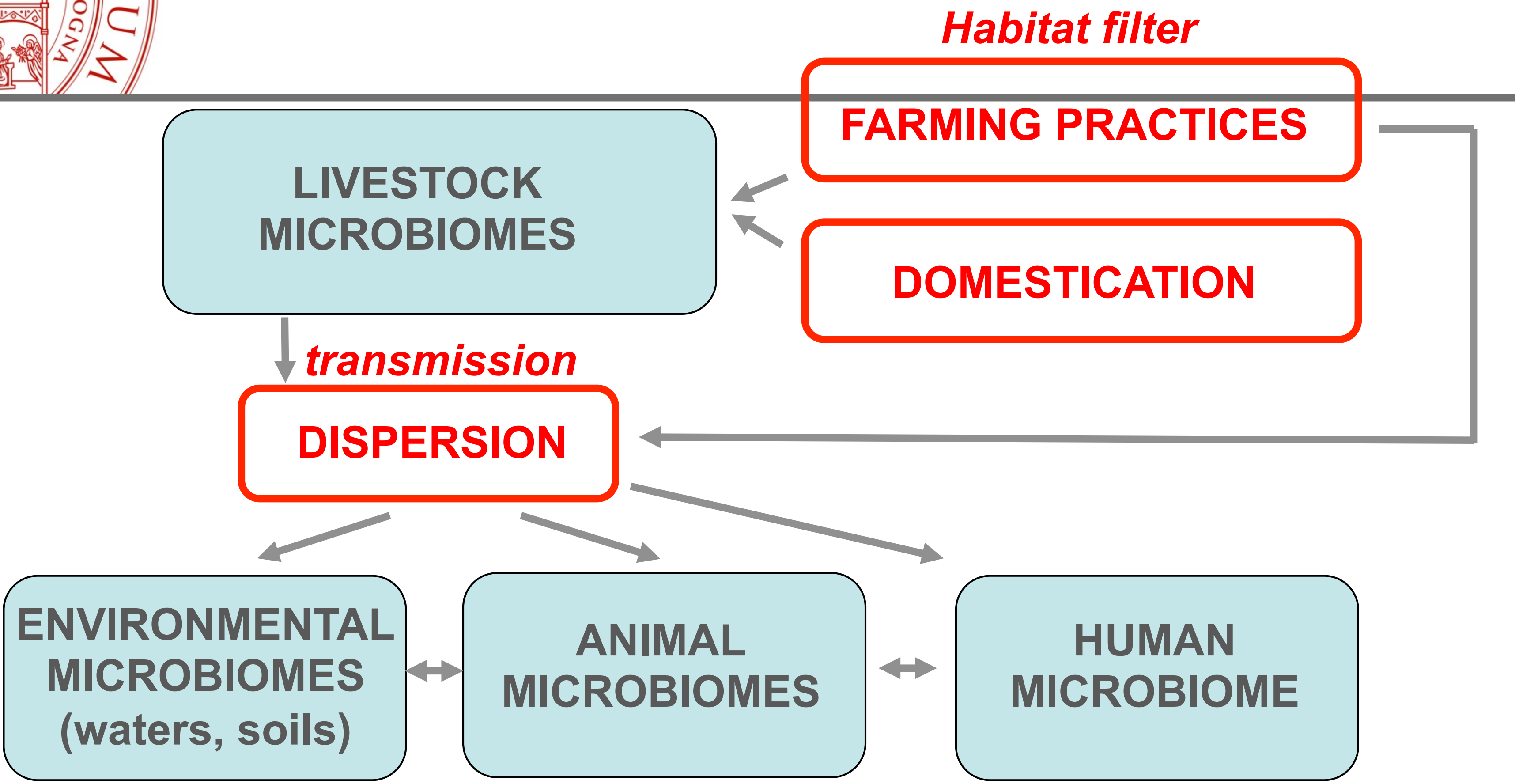
The One-Health Eco-health perspective of human GM variation

(Flaudry et al., Sci Total Environ 2018)

Human microbiome variation needs to be viewed **in the frame of the One Health Theory**, determinants of variation need to be searched in the **total environment**

Human microbiome reviewed at the connection between animals, plants, soil and oceans microbiomes, which are all challenged by anthropic factors

Anthropic factors impact “connection chains” linking the world microbiomes



Habitat filter

FARMING PRACTICES

DOMESTICATION

LIVESTOCK MICROBIOMES

transmission

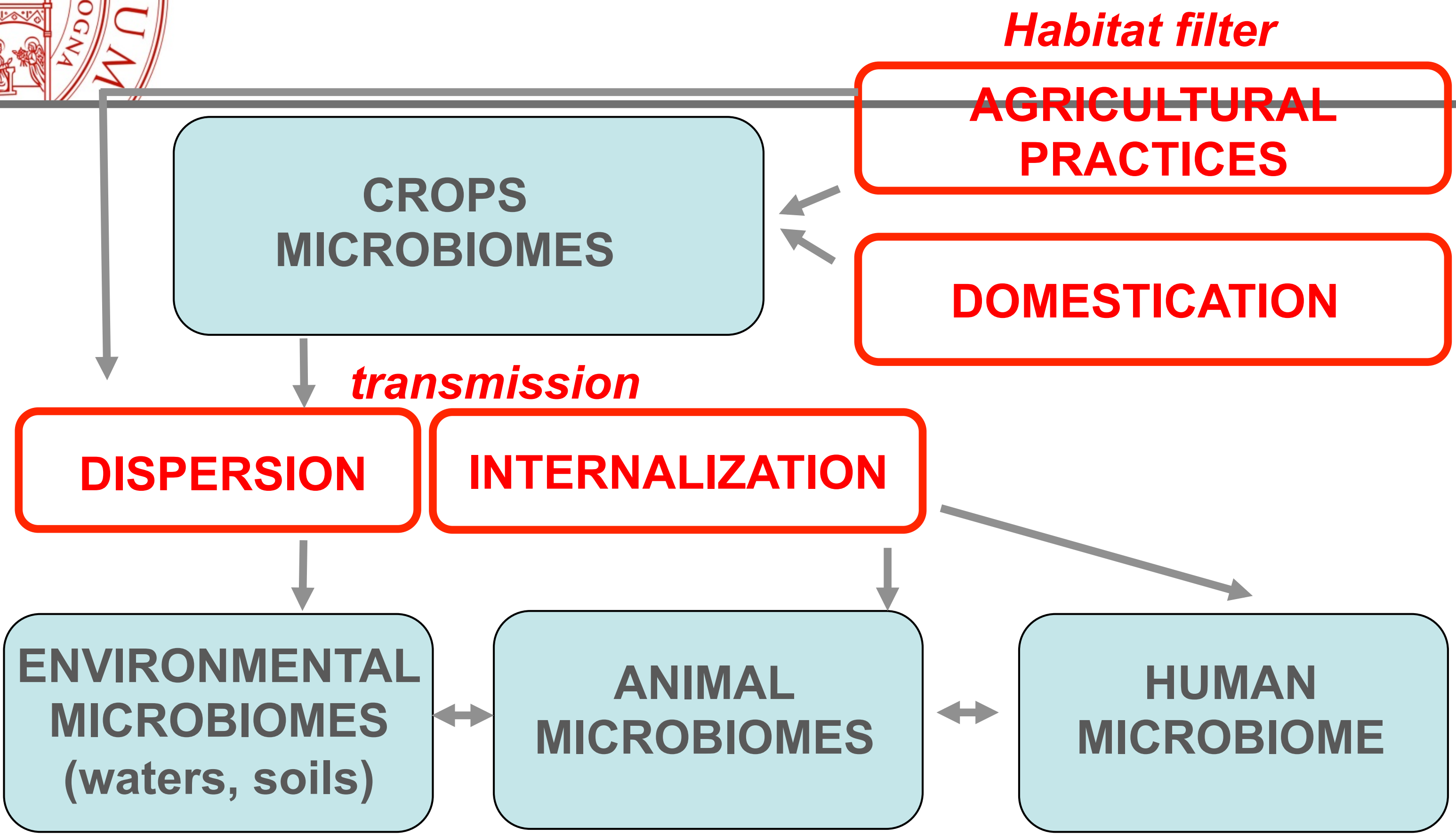
DISPERSION

ENVIRONMENTAL MICROBIOMES (waters, soils)

ANIMAL MICROBIOMES

HUMAN MICROBIOME

Crops, a critical factor regulating bacterial dispersion



Habitat filter

AGRICULTURAL PRACTICES

DOMESTICATION

CROPS MICROBIOMES

transmission

DISPERSION

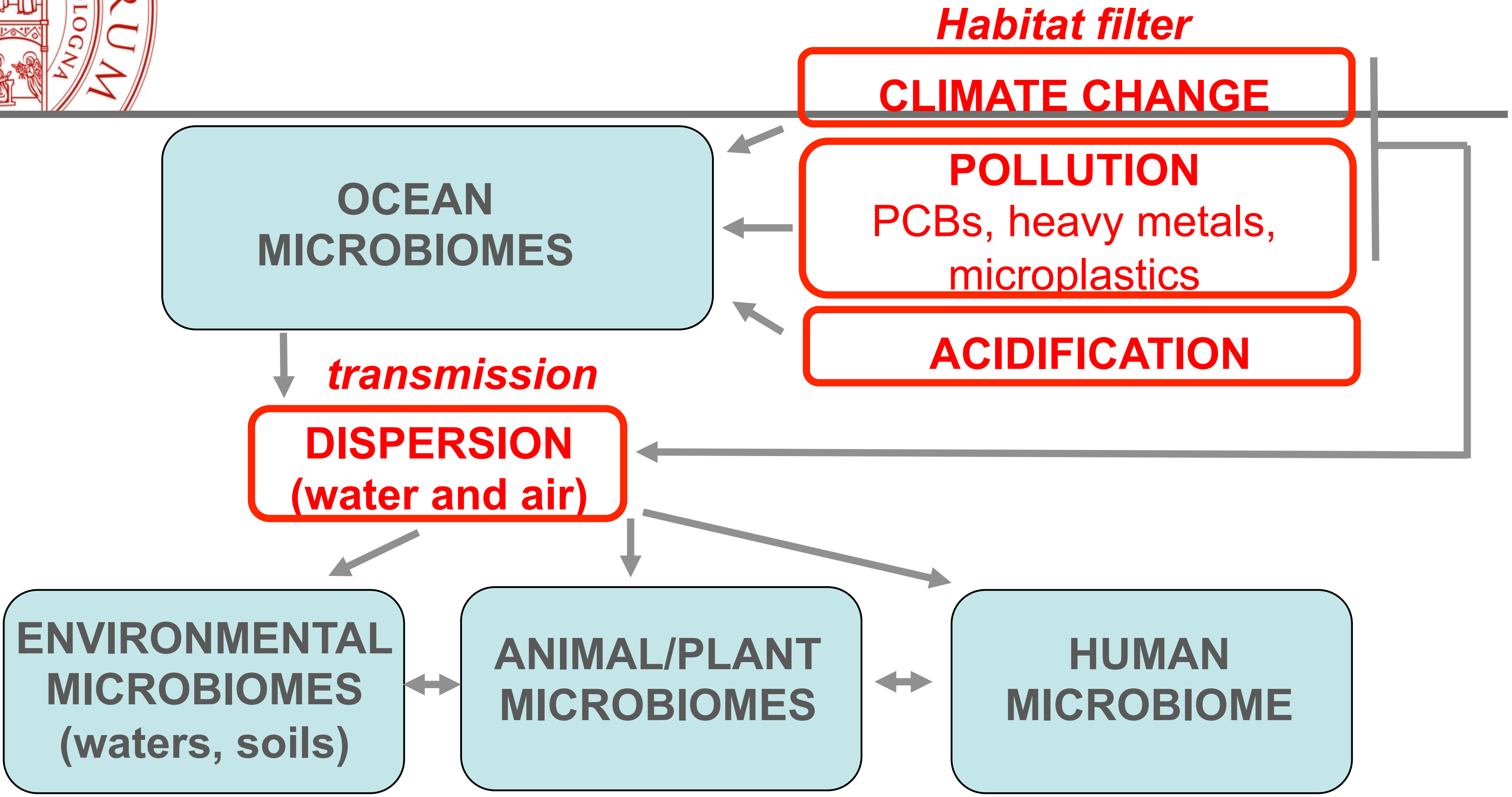
INTERNALIZATION

ENVIRONMENTAL MICROBIOMES (waters, soils)

ANIMAL MICROBIOMES

HUMAN MICROBIOME

Oceans, the largest reserve of world microorganisms



Habitat filter

CLIMATE CHANGE

POLLUTION
PCBs, heavy metals, microplastics

ACIDIFICATION

OCEAN MICROBIOMES

transmission

DISPERSION (water and air)

ENVIRONMENTAL MICROBIOMES (waters, soils)

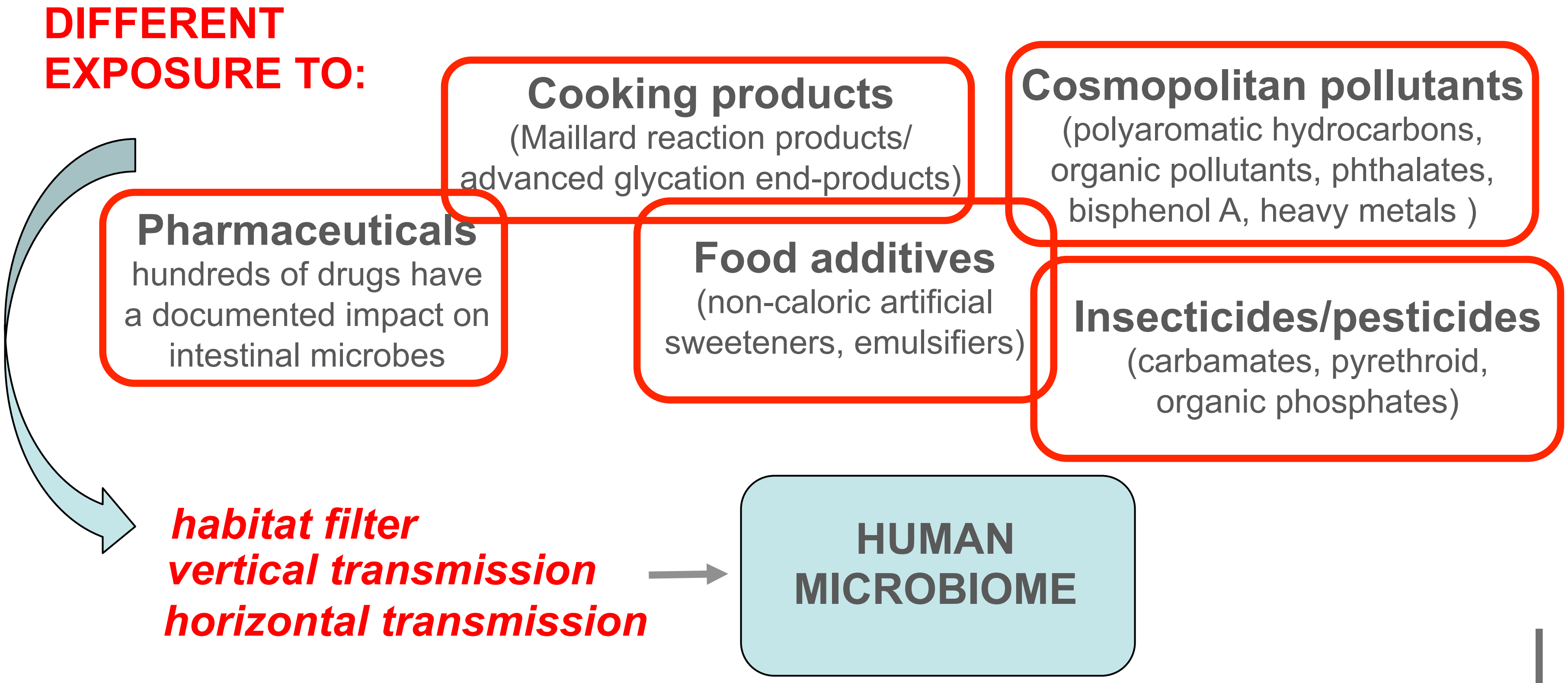
ANIMAL/PLANT MICROBIOMES

HUMAN MICROBIOME

Xenobiotics as major drivers of microbiome variation

With a strong impact on both dispersion and habitat filtering processes, xenobiotics of anthropic origin represent a major and direct driver of human GM variation

(Ferriero et al., Cell 2018; Maier et al., Nature 2018; Jackson et al., Nat Commun 2018; Zierer et al., Nat Genet 2018; Danchin et al., Env Microbiol 2018)



DIFFERENT EXPOSURE TO:

Cooking products
(Maillard reaction products/ advanced glycation end-products)

Cosmopolitan pollutants
(polyaromatic hydrocarbons, organic pollutants, phthalates, bisphenol A, heavy metals)

Pharmaceuticals
hundreds of drugs have a documented impact on intestinal microbes

Food additives
(non-caloric artificial sweeteners, emulsifiers)

Insecticides/pesticides
(carbamates, pyrethroid, organic phosphates)

habitat filter
vertical transmission
horizontal transmission

HUMAN MICROBIOME

Traditional drivers of human microbiome changes have been revealing weak

What has been generally considered as a main driver of human microbiome variation (e.g. dietary habits, physical activity, aging and lifestyle) showed a limited power to explain the observed human microbiome diversity

- Are these really major drivers of microbiome variation?
- Can these weak drivers really force the shift away from the healthy plane?

New determinants of dysbiosis come from the Eco-evolutionary perspective

A new eco-evolutionary vision is emerging, where determinants of microbiome variation are searched within **anthropic factors**, which can impact the human GM directly, or through the “connection chains” that connect the planet microbiomes, but always acting on the major ecological processes shaping the microbiomes (transmission and habitat filtering)

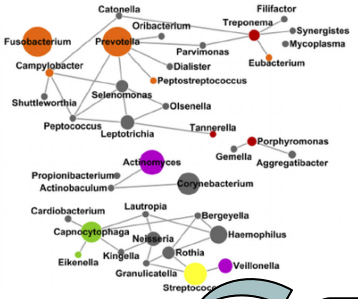
Research is urgently needed to explore whether the personal exposure to anthropic factors is responsible for the shift away from the healthy plane of the personal microbiome

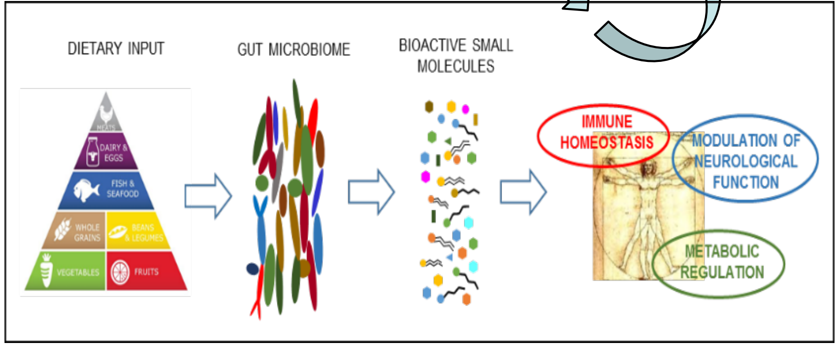
Scale down of Eco-Evo to the clinical practice

TREATMENT → **GM DYSBIOSIS** → **SIDE EFFECTS** / **RESPONSE**

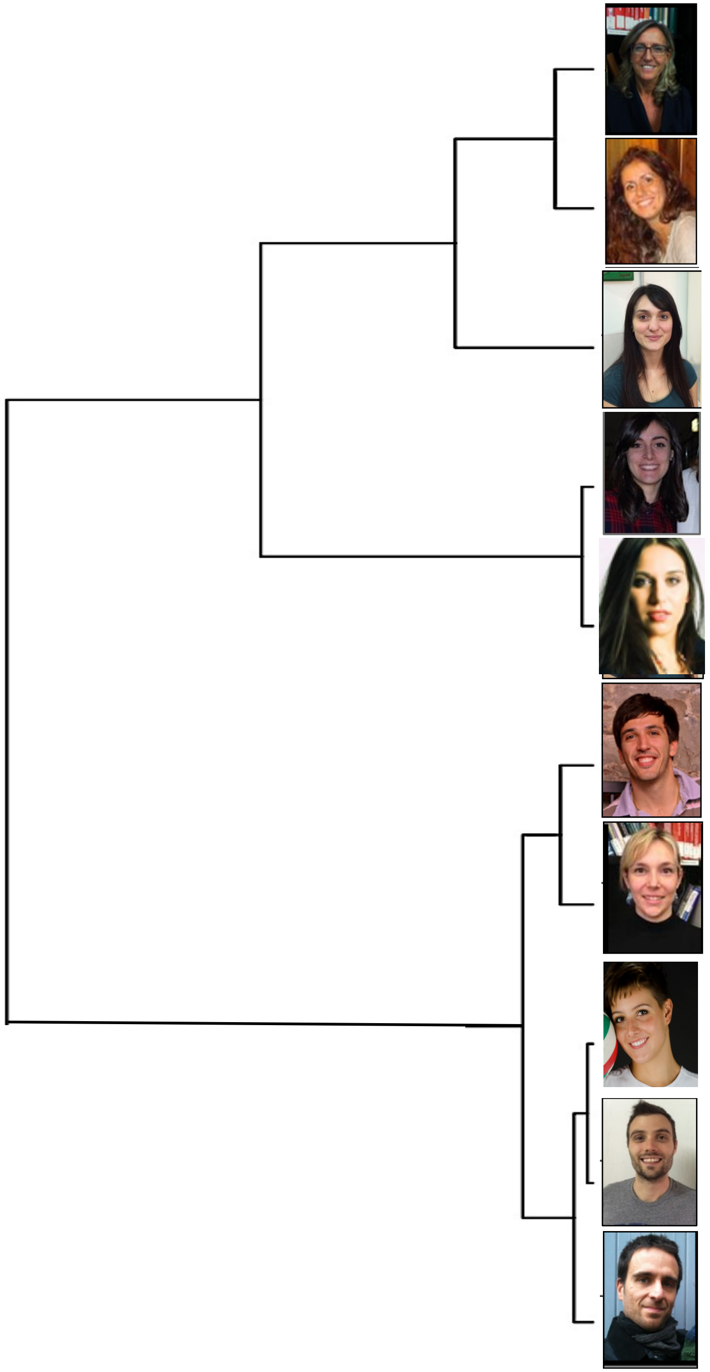
GM DYSBIOSIS → **DYSBIOSIS CHARACTERIZATION** → **UNDERSTANDING OF ECOLOGICAL PROCESSES** → **MITIGATION** / **DYSBIOSIS CORRECTION**

microbial hubs to guide microbe-microbe interaction network





diet-microbiome metabolites-host



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Circles

Controlling Microbiomes Circulations for Better Food Systems
H2020-SFS-2018-2020

My New GUT

Factors influencing the human gut microbiome and its effect on the development of diet-related diseases and brain development
KBBE.2013.2.2-02