

The Human Microbiome in Health and Disease



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The Forum for Medical Affairs
Annual Educational Program
November 9, 2014

Topics



- Perspectives on human-microbe relations: different "lens"
- Sources variation in patterns of diversity
- Stability, resilience and restoration
- Challenges in study of human microbiome

Microbes as threats




<http://www.artchive.com/artchive/b/bruegel/death.jpg>



<http://www.usatoday.com>



The New Yorker

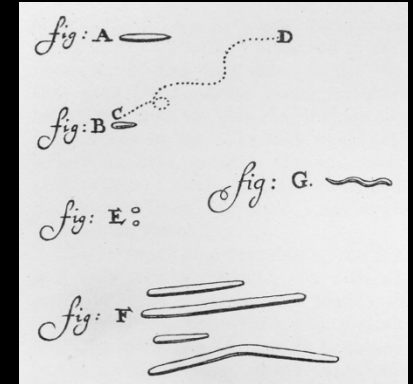


Microbes as beneficial symbionts: co-evolution, co-adaptation, co-dependency

<http://blog.lib.umn.edu/denis036/thisweekinevolution/TrefoilNodules2.jpg>

How we have looked at microbial world

- Antony van Leeuwenhoek, 1683 ('animalcules')

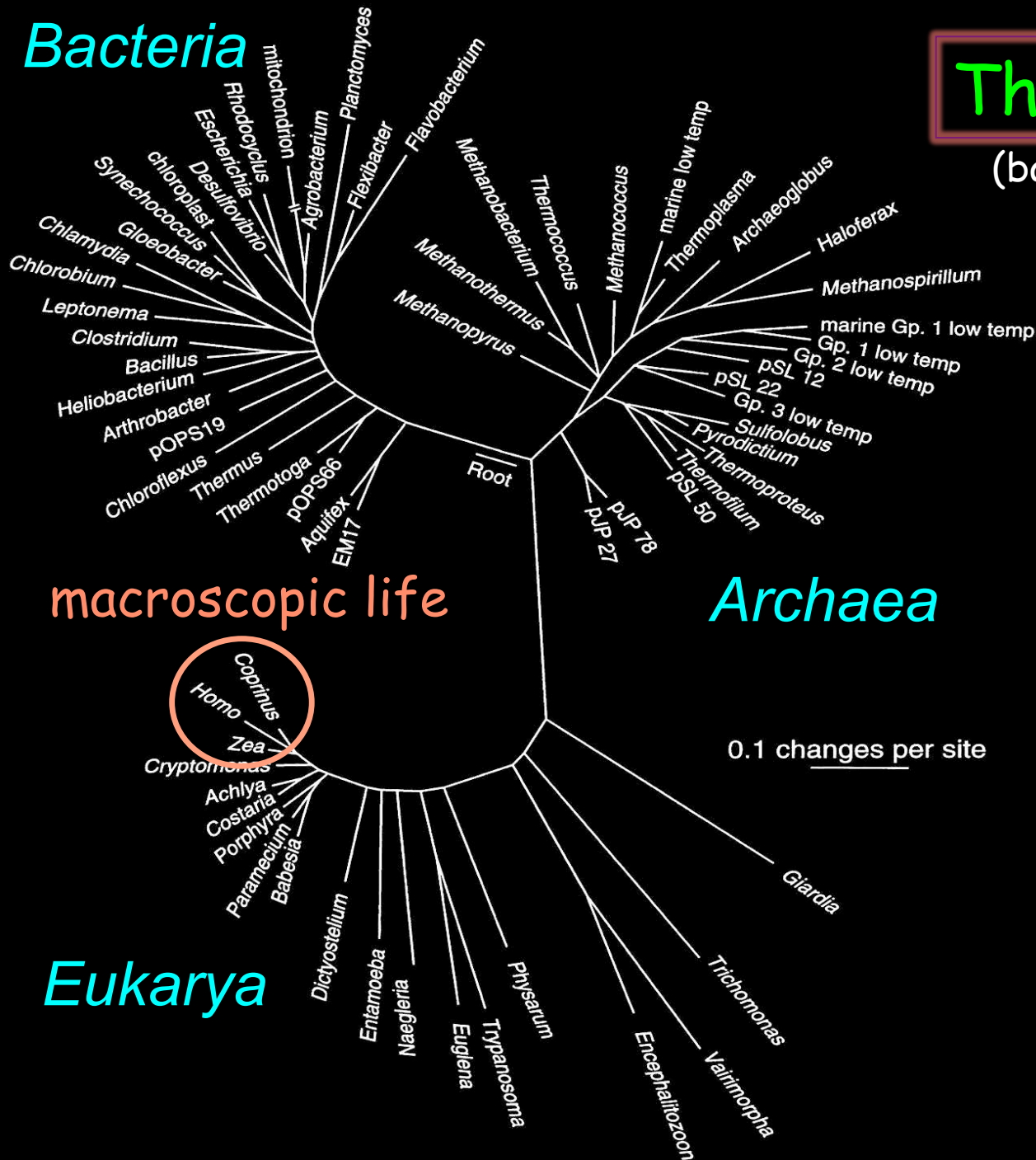


- Razumov AS, 1932 ('Great plate anomaly')
- Dubos R *et al.*, 1965 (co-evolution)
- Moore W, 1975, 76; Savage DC, 1977 (cell counts, ecology)



The Tree of Life

(based on rRNA sequences)



Carl Woese



Grand Prismatic Spring

An evolving view of our relationship with the microbial world



“We should think of each host and its parasites as a superorganism with the respective genomes yoked into a chimera of sorts.”

Science 288:287, 2000

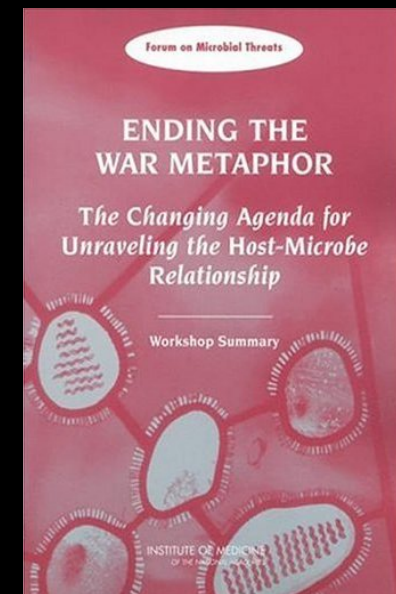
Opinion

TRENDS in Microbiology Vol.9 No.5 May 2001

“A second human genome project”

David A. Relman and Stanley Falkow

The characterization of life is immeasurably enhanced by determination of complete genome sequences. For organisms that engage in intimate interactions with others, the genome sequence from one participant, and associated tools, provide unique insight into its partner. We discuss how the human genome sequence will further our understanding of microbial pathogens and commensals, and vice versa. We also propose criteria for implicating a host gene in microbial pathogenesis, and urge consideration of a 'second human genome project'.



2006

Perspective

Human Microbiome: Communities of microbes (and viruses) that make human body their home



- Re-defining what it means to be "human"
- Humans...as "islands" or habitat patches, occupied by microbial communities

(Based on cell counts, we are 10 parts bacterial, 1 part human...and based on unique genes, we are 150 parts bacterial, 1 part human...)

- Long-term co-adaptation, cross-talk
- Humans as ecological system under selection to minimize conflict between individual members of microbiota and maximize host fitness...

Our 'extended self': human-microbe mutualism

Our benefits (incomplete list)

- Food digestion
- Nutrition (vitamins, energy)
- Xenobiotic processing
- Metabolic regulation, cometabolism
- Development: terminal differentiation of mucosa
- "Education", regulation of immune system
- Epithelial "homeostasis", barrier integrity
- Colonization resistance to pathogens

Our 'extended self': human-microbe mutualism

Their benefits (incomplete list)

- Nutrition
- Habitat
- Dispersal

Shouldn't we be focusing a bit more on their needs?

Perspective

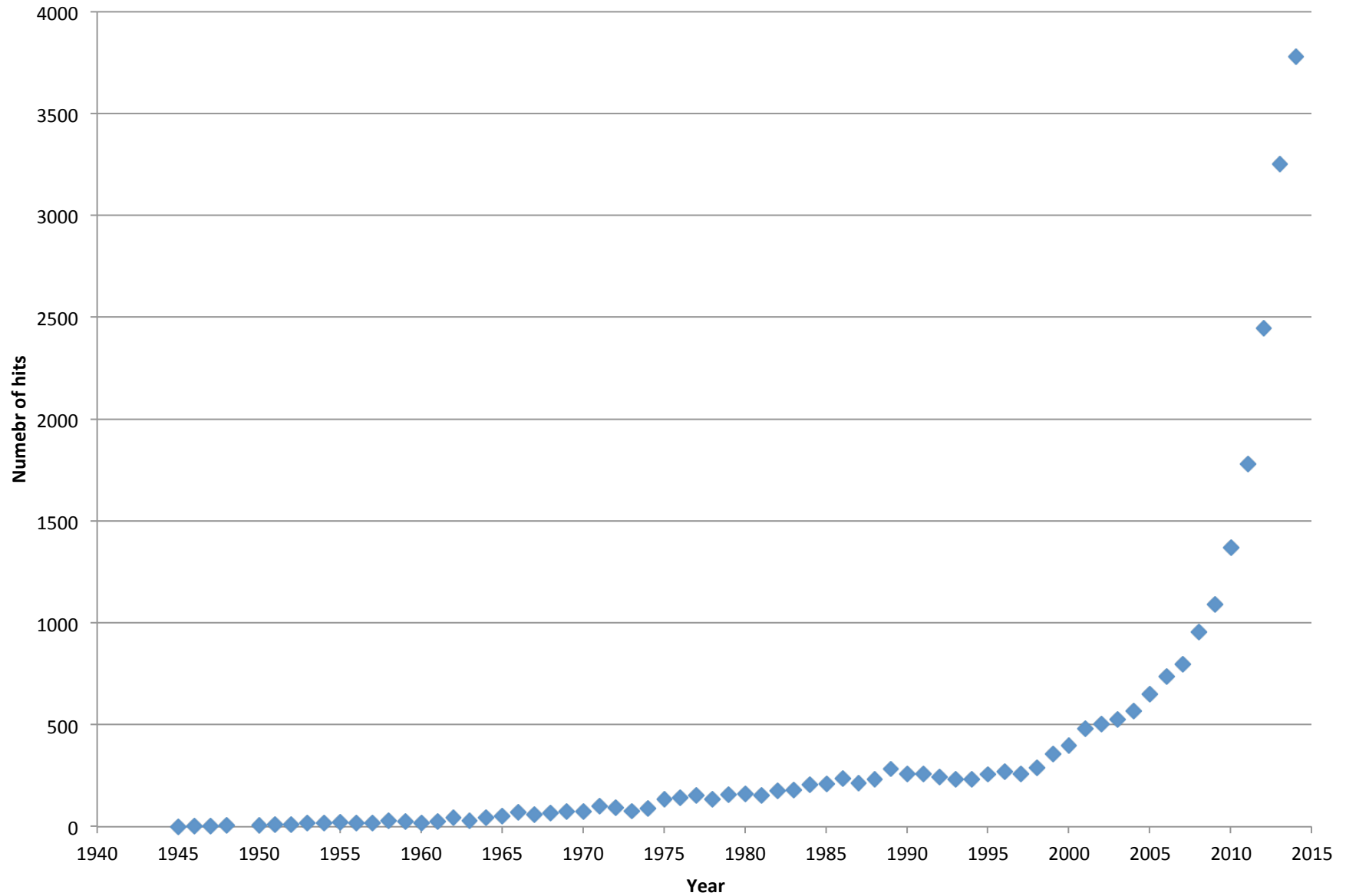
Human Microbiome: Communities of microbes (and viruses) that make human body their home



- Key ecosystem services (benefits)?
- Individuality?
- Stability, resilience?
- Clinical applications?: disease mechanism, risk assessment, new approaches for health maintenance, restoration

(Why now?...technology, convergence of disciplines)

Pubmed Hits for "Microbiome OR Microbiomes OR Microbiota OR Microflora"



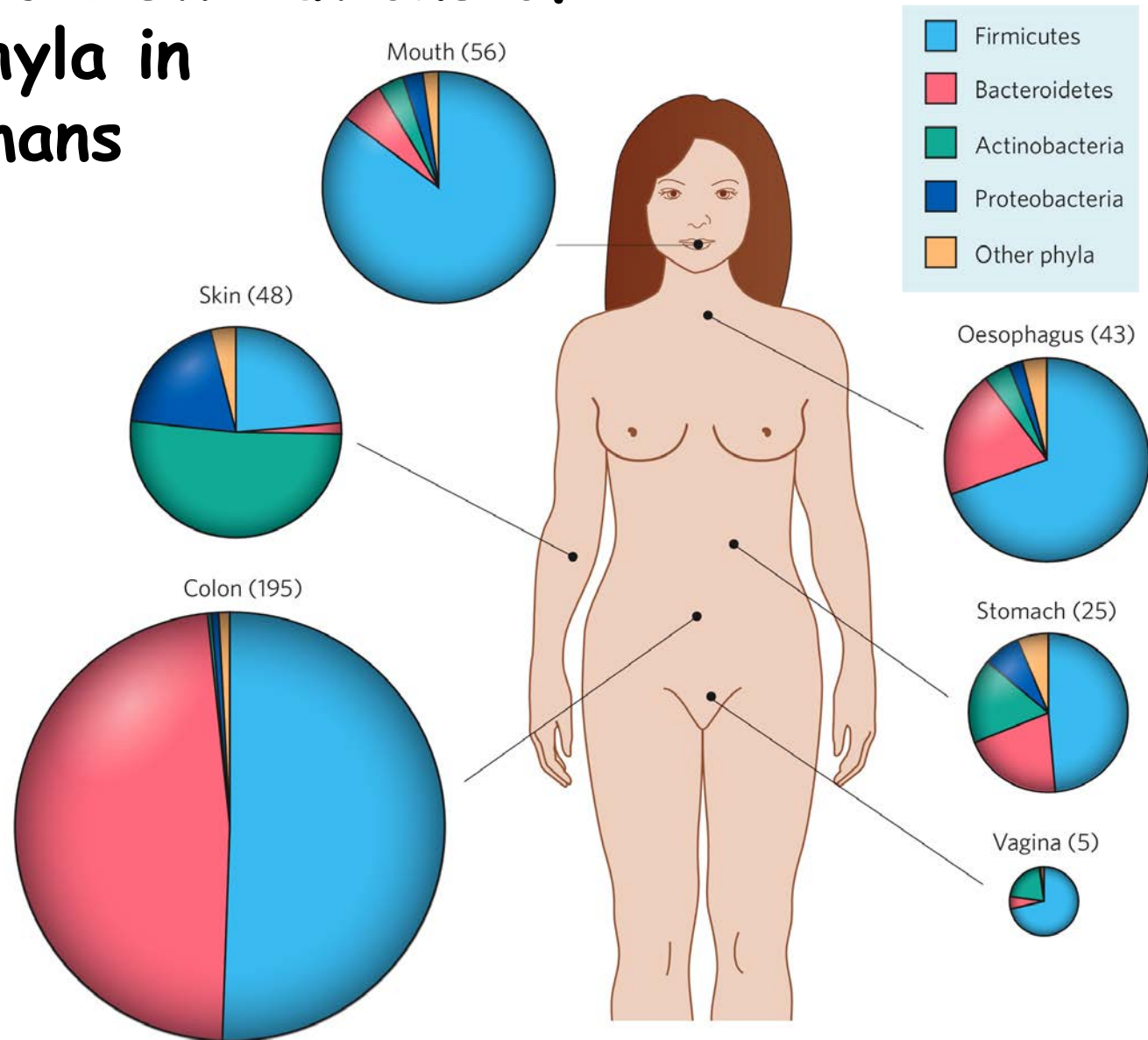
Humans and other animals are special places!



- Who's there?
- What are they doing?

Site-specific distributions of bacterial phyla in healthy humans

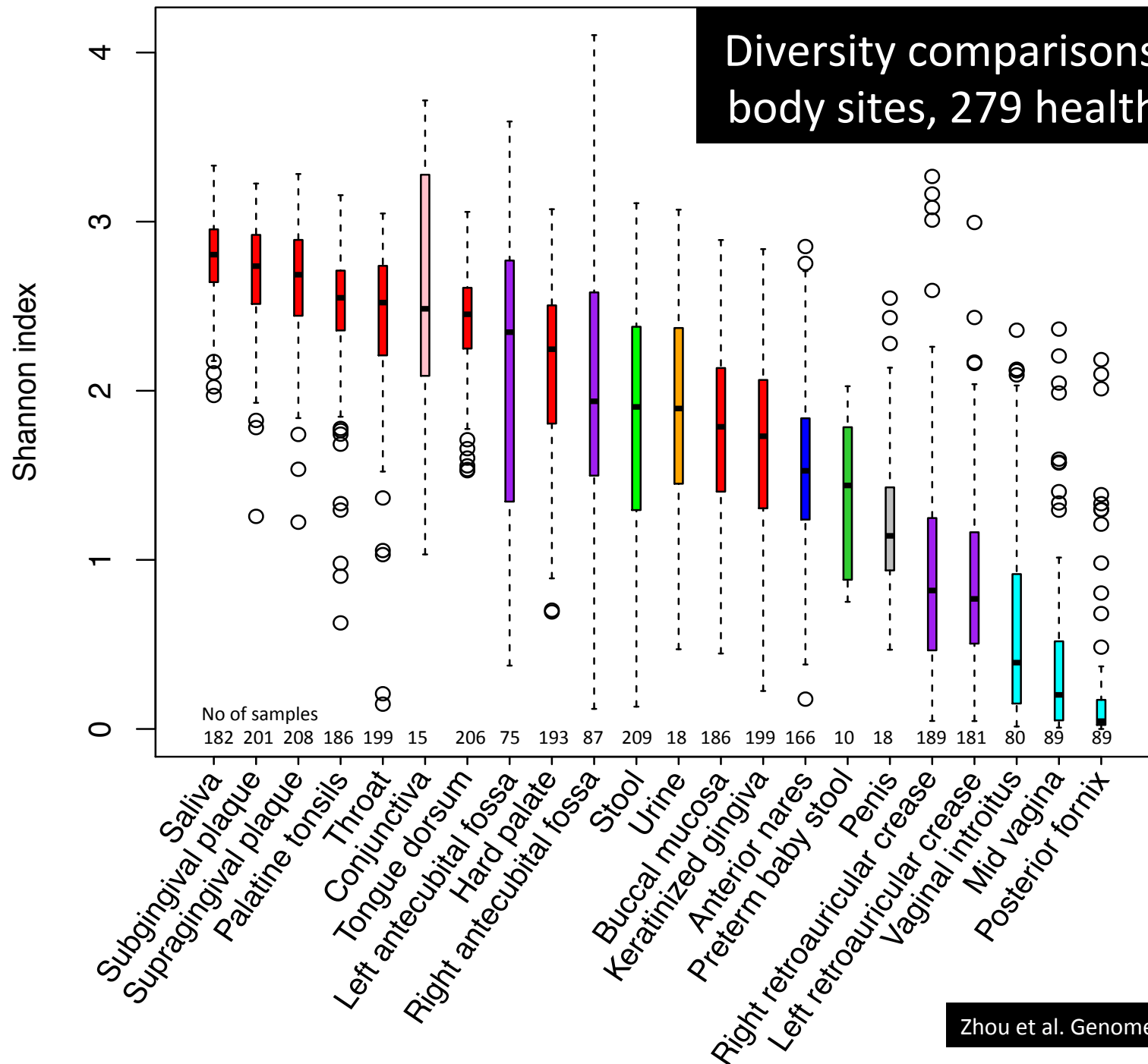
Size of circles is proportionate to average number of species-level phylotypes per individual (in parentheses)



Sources of variation in patterns of diversity

- Space (habitat, body site)
- Individual
- Health status
- Host genetics
- Environmental exposures
 - Diet
 - Chemical/drug/mechanical disturbance
 - Other aspects of lifestyle? (e.g. geography)
 - Other mammals/hosts
- Time (esp. early in life)

Diversity comparisons across 22 body sites, 279 healthy humans



Assessments of the microbiome

- Taxonomic composition (phylogenetically informative genes)
- Metagenomic (gene, genome) composition
- Community-wide transcript profiles
- Community-wide protein profiles
- Community-wide metabolite profiles

(Community-wide functions?)

- Host (clinical measurements, genetics, gene expression, chemical, etc)

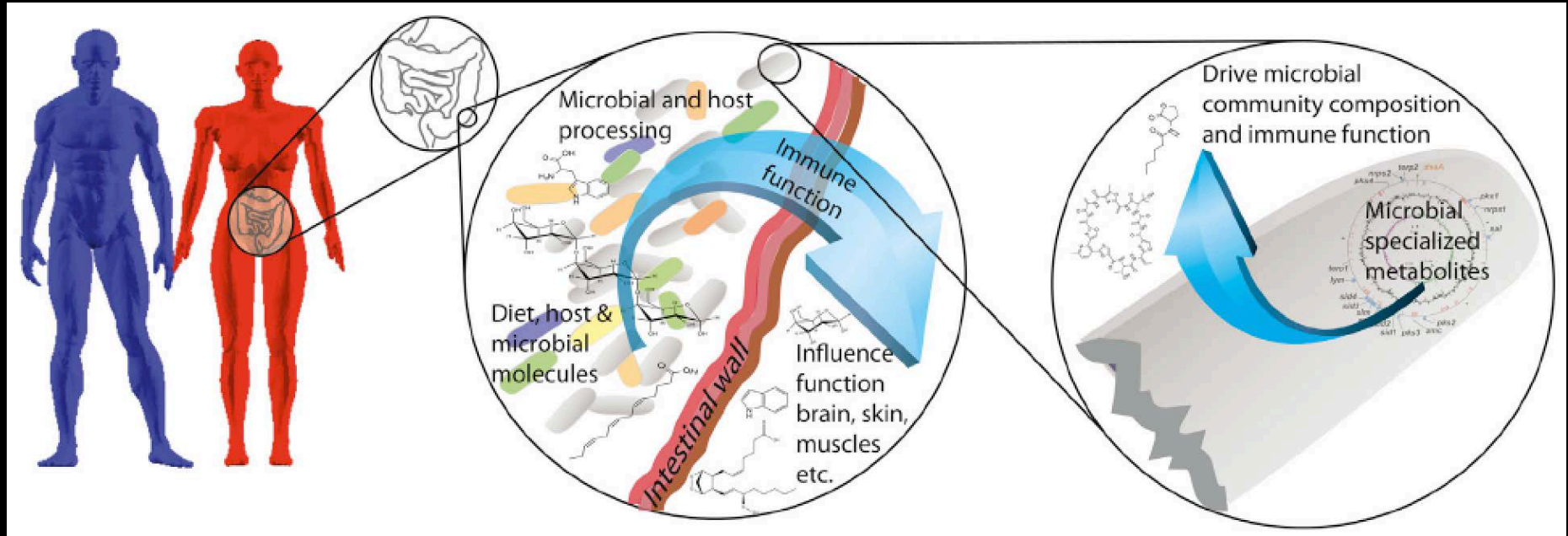
A human gut microbial gene catalogue established by metagenomic sequencing

Qin J *et al.* Nature 464:59-65, (4 March) 2010

- 576.7 Gb sequence, fecal samples, 124 individuals
- 3.3 million non-redundant genes; 536,000/person
- ~6300 functional groups in minimal gut metagenome
 - biodegradation of complex sugars and glycans (e.g., degradation and uptake pathways for pectin and sorbitol, sugars which are omnipresent in fruits and vegetables, but which are not or poorly absorbed by humans)
 - capacity to ferment (e.g., mannose, fructose, cellulose and sucrose)

Donia et al, *Cell* (2014), **158**, 1402

They are 'talking' to each other and with us



Community stability landscape

Shift in community state variables

Shift in environmental parameters

Costello EK *et al.*,
Science **336**, 1255 (2012)

(A) Shift in "state" variables alters community directly

The community state landscape



Alternative state 2

Antibiotics,
oral hygiene



Alternative state 1

(B)

Shift in environmental "parameters" alters the community indirectly

The community state landscape



Alternative state 2

Diet intervention,
immunosuppressive drug



Alternative state 1

Disturbance



- Disturbances remove or kill some fraction of the community, creating opportunities for remaining community members or new colonists...effects directed at community and/or host
- Increasingly prominent in "modern" societies?

(A) Shift in "state" variables alters community directly

The community state landscape



Antibiotics,
oral hygiene



depth \propto resilience

Resilience:
capacity of
ecosystem to
absorb
disturbance
and retain
same
function(s)...



C. S. "Buzz" Hollings
(1973)

<http://www.flickr.com/photos/sfupamr/5515528060/sizes/l/in/photostream/>

Costello EK *et al.*,
Science **336**, 1255 (2012)

Study design



- Healthy subjects ("D", "E", "F"), no abx x 1 yr
- Ciprofloxacin twice, 6 months apart (pulse perturbation)
- Stool samples over 10 months

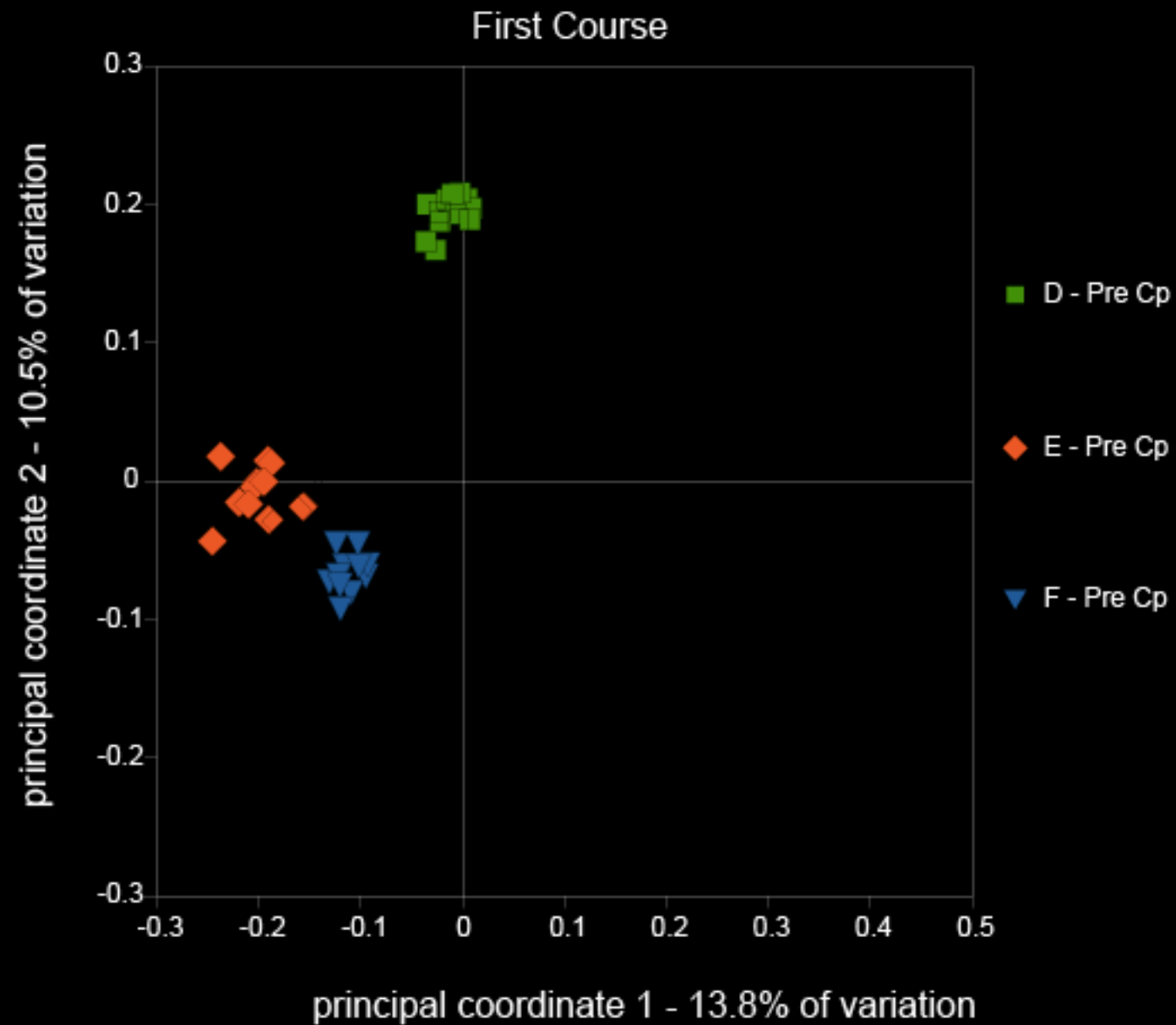
Dethlefsen et al. PLoS Biology 2008; 6:e280

Dethlefsen L, Relman DA. PNAS 2011; 108:4554-61

16S rDNA data

Unweighted Unifrac Analysis

PC2 vs PC1



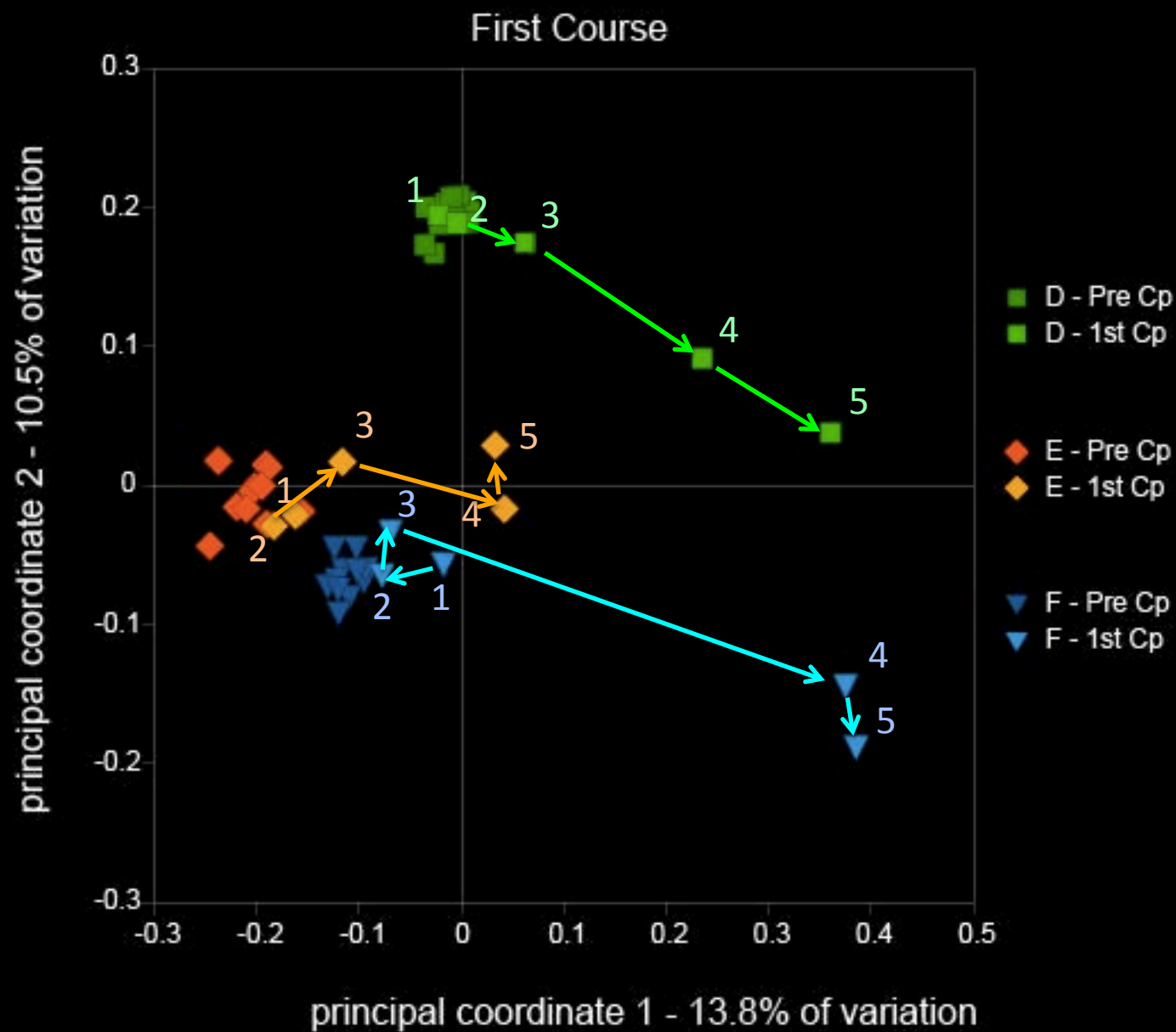
Individualized patterns of phylogenetic
compositional diversity

Relative stability over two months in
absence of gross disturbance

16S rDNA data

Unweighted Unifrac Analysis

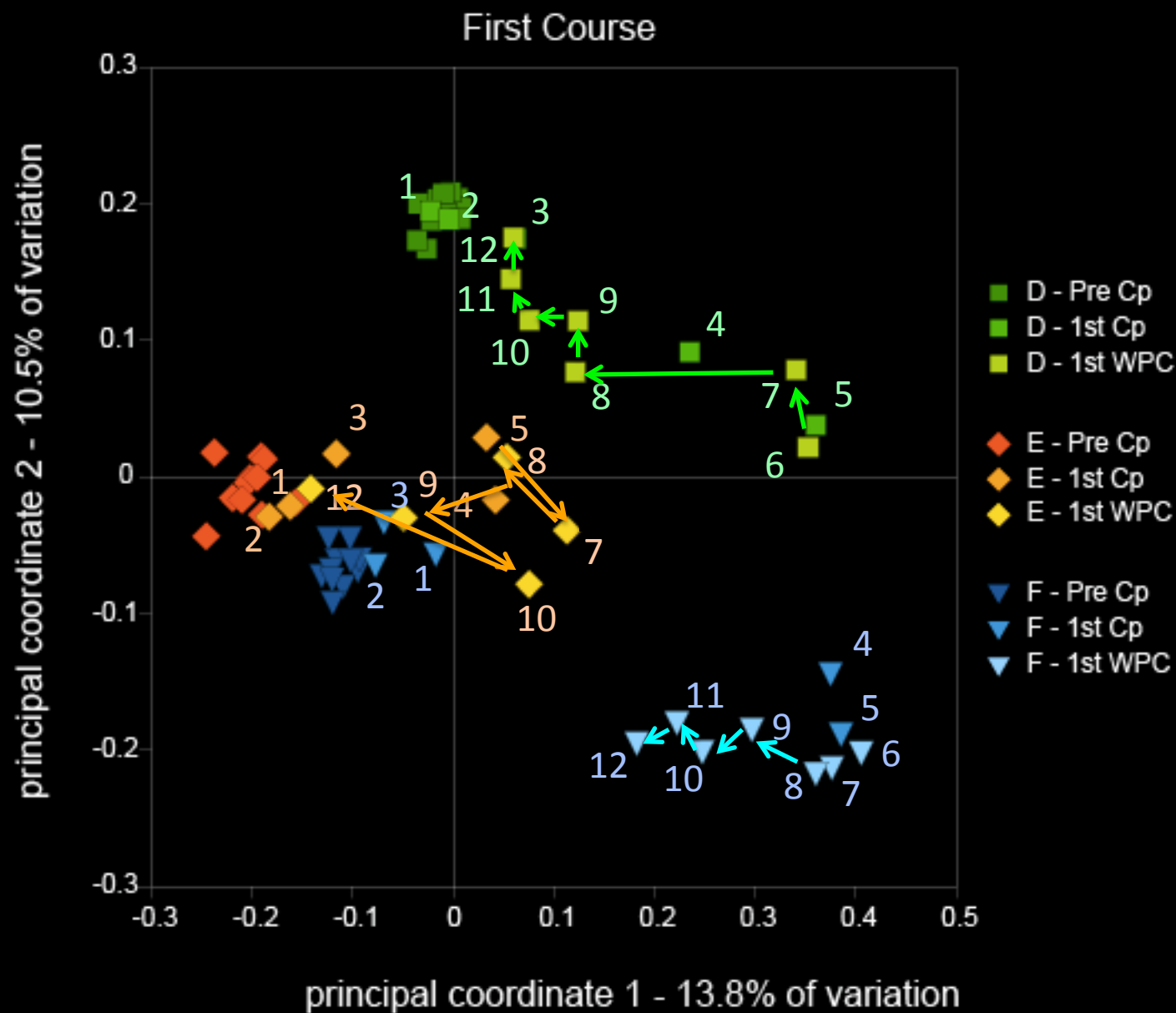
PC2 vs PC1



16S rDNA data

Unweighted Unifrac Analysis

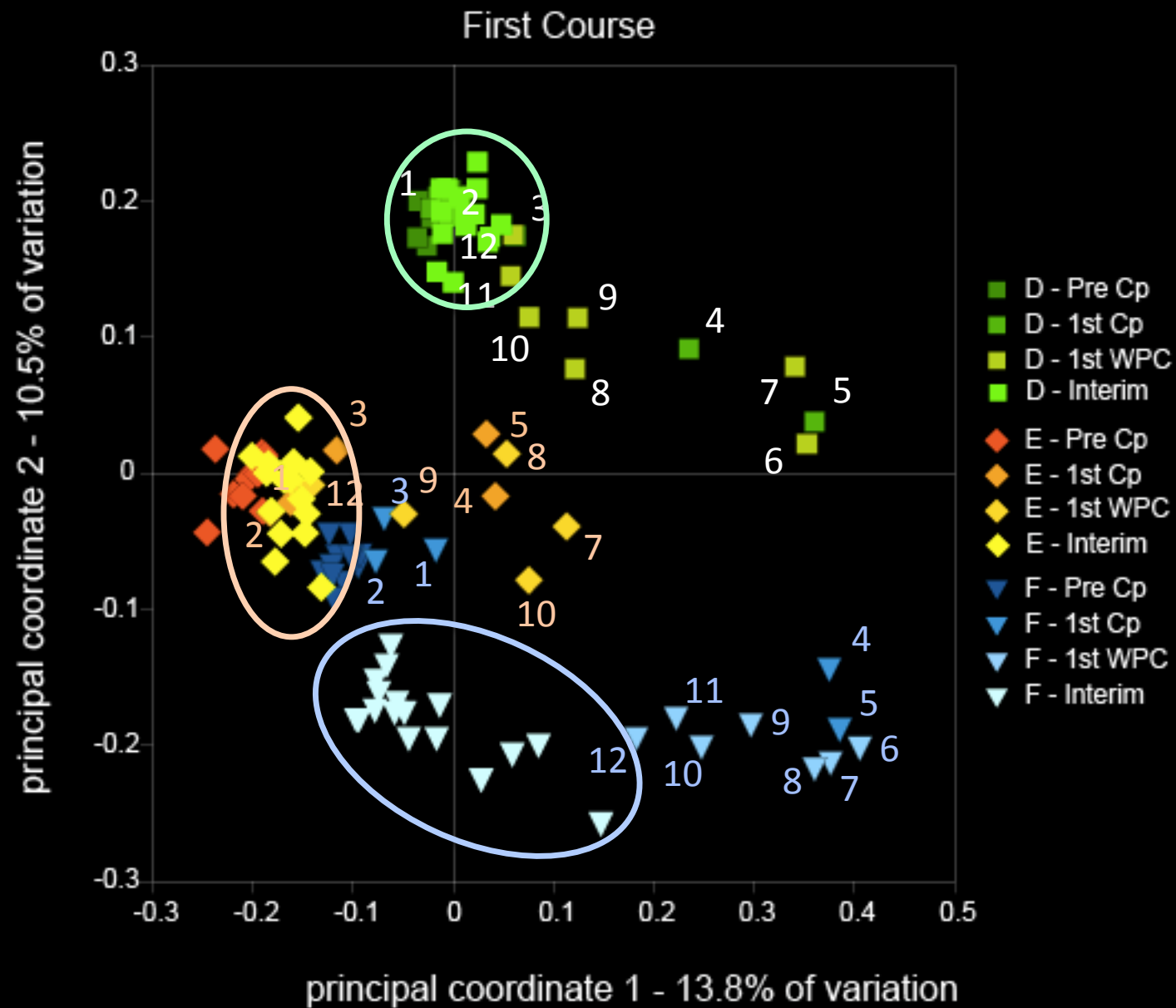
PC2 vs PC1



16S rDNA data

Unweighted Unifrac Analysis

PC2 vs PC1

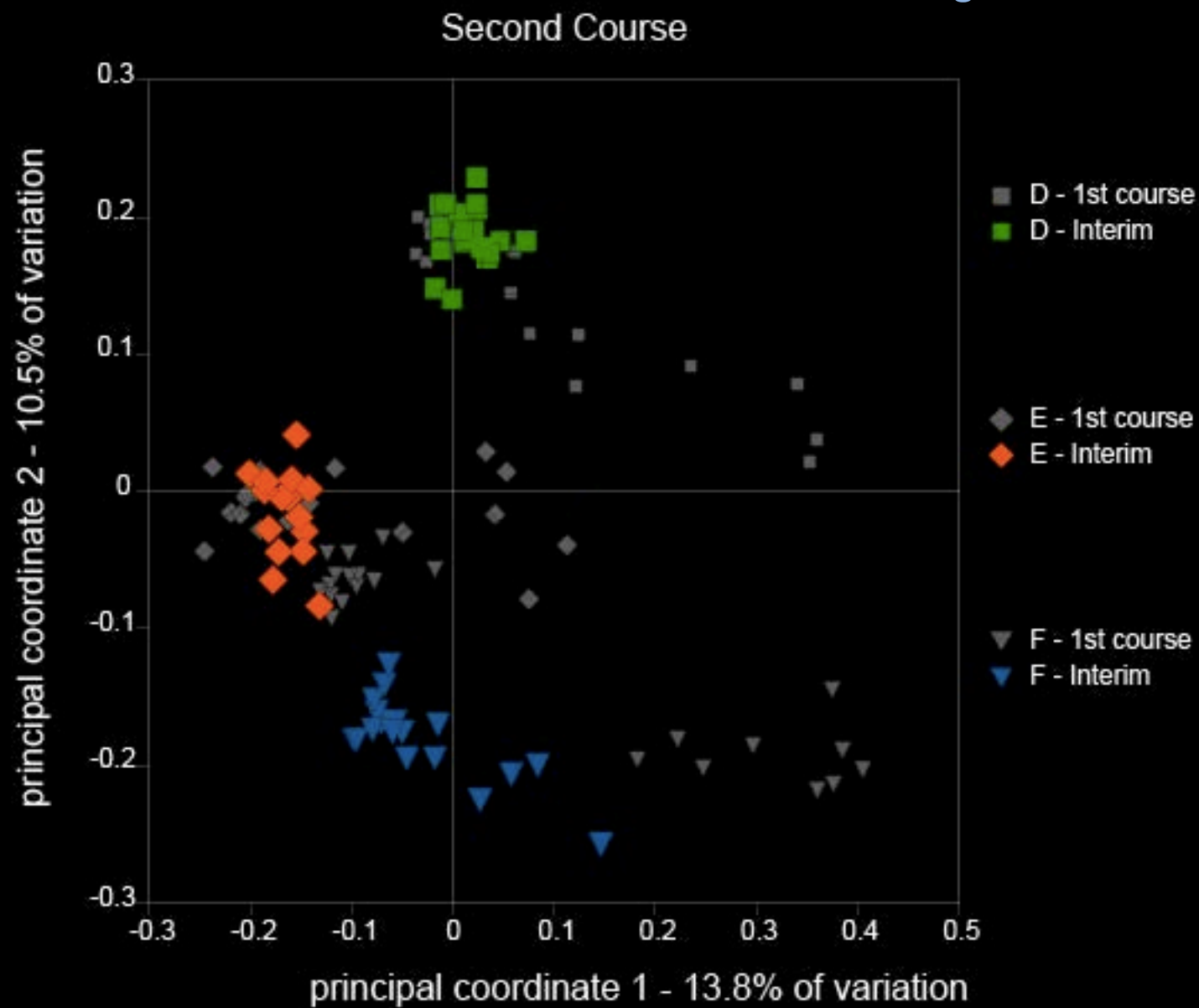


Shared, as well as
individualized responses
(complete vs. partial recovery)

16S rDNA data

Unweighted Unifrac Analysis

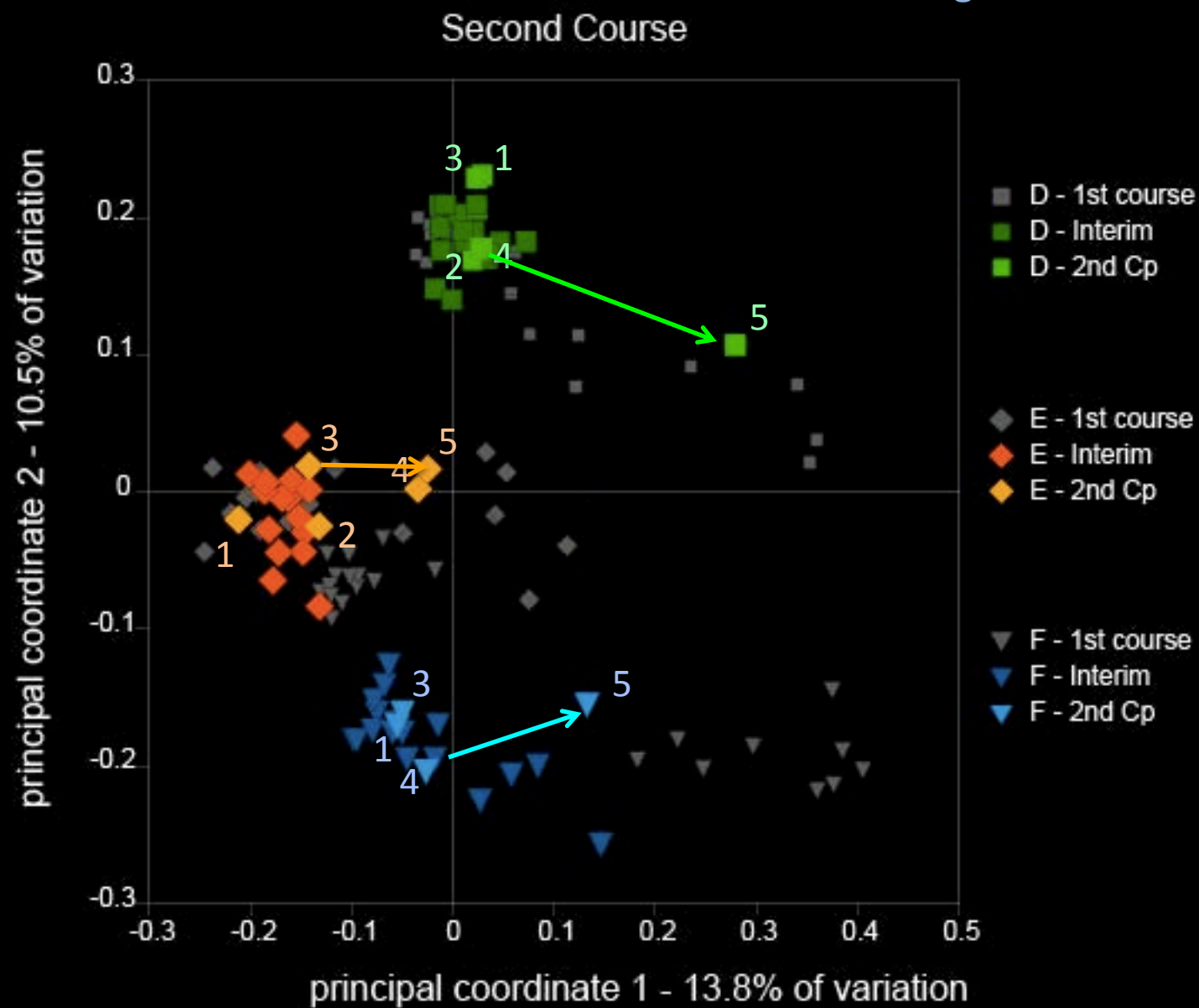
PC2 vs PC1



16S rDNA data

Unweighted Unifrac Analysis

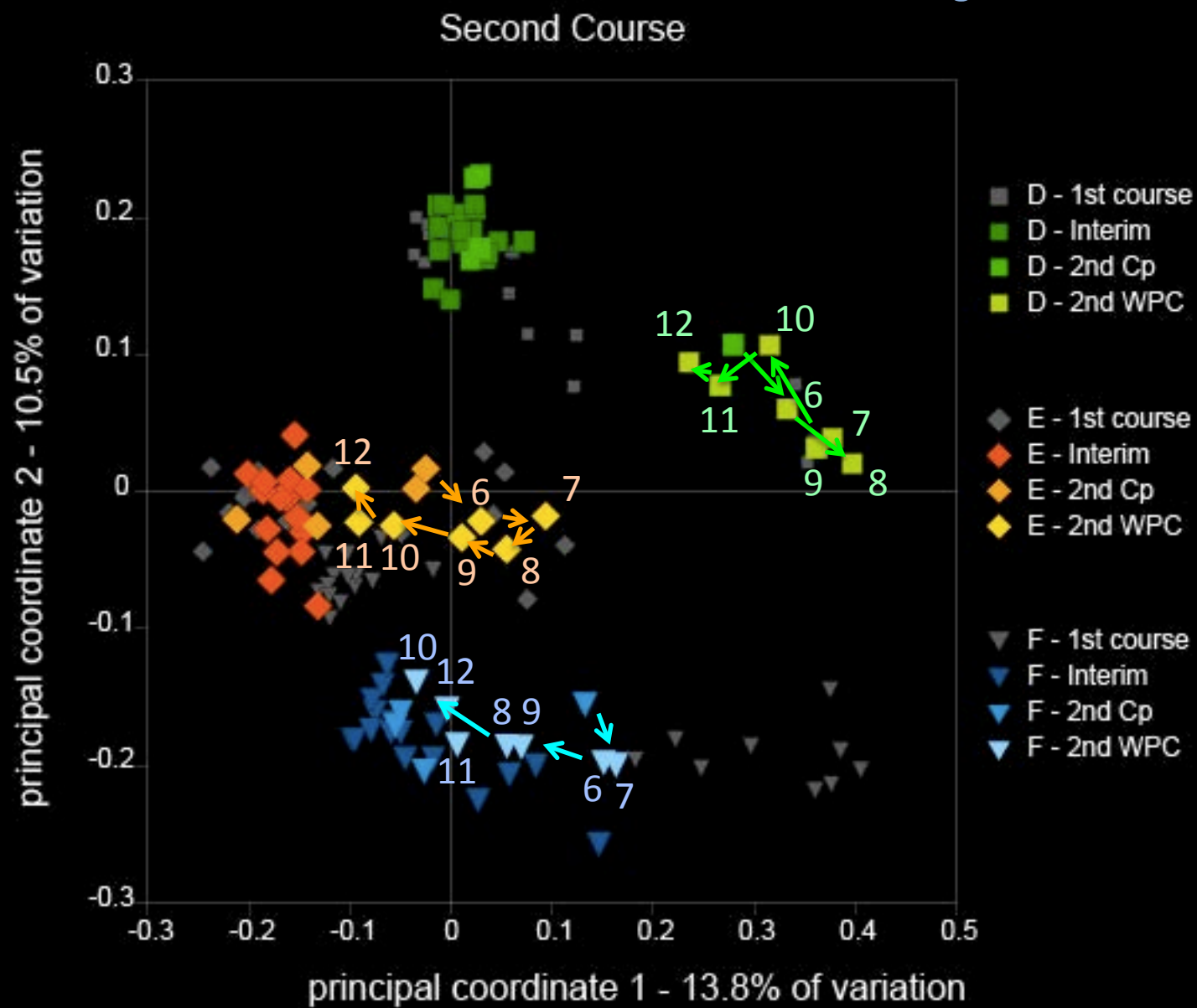
PC2 vs PC1



16S rDNA data

Unweighted Unifrac Analysis

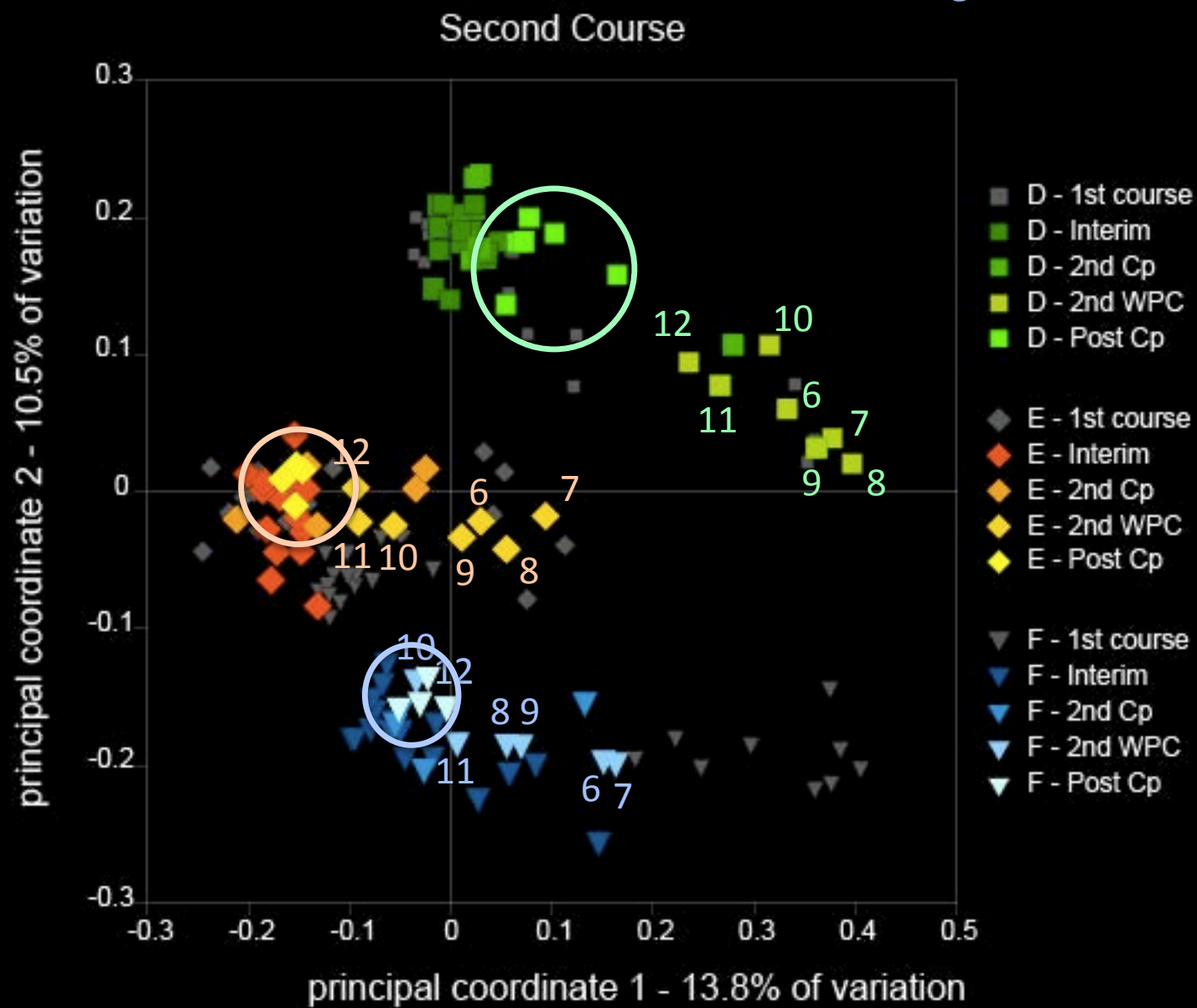
PC2 vs PC1



16S rDNA data

Unweighted Unifrac Analysis

PC2 vs PC1



Community 'memory' ?

Compounded perturbations: alteration
of fitness landscape?

Paine RT, Tegner MJ, Johnson EA. Compounded perturbations yield
ecological surprises. *Ecosystems* 1:535-545, 1998.

Compounded Perturbations Yield Ecological Surprises

Robert T. Paine,^{1*} Mia J. Tegner,² and Edward A. Johnson³

¹Department of Zoology, University of Washington, Seattle, Washington 98195, USA; ²Scripps Institution of Oceanography, University of California, San Diego, La Jolla, California 92093-0201, USA; and ³Department of Biological Sciences and Kananaskis Field Station, University of Calgary, Calgary, Alberta, Canada T2N 1N4.

Ecosystems (1998) 1: 535–545

ABSTRACT

All species have evolved in the presence of disturbance, and thus are in a sense matched to the recurrence pattern of the perturbations. Consequently, disturbances within the typical range, even at the extreme of that range as defined by large, infrequent disturbances (LIDs), usually result in little long-term change to the system's fundamental character. We argue that more serious ecological consequences result from compounded perturbations within the normative recovery time of the community in question. We consider both physically based disturbance (for example, storm, volcanic eruption, and forest fire) and biologically based disturbance of populations, such as overharvesting, invasion, and disease, and their interactions. Dispersal capability and measures of generation time or age to first reproduction of the species of interest seem to be the important metrics for scaling the size

and frequency of disturbances among different types of ecosystems. We develop six scenarios that describe communities that have been subjected to multiple perturbations, either simultaneously or at a rate faster than the rate of recovery, and appear to have entered new domains or "ecological surprises." In some cases, three or more disturbances seem to have been required to initiate the changed state. We argue that in a world of ever-more-pervasive anthropogenic impacts on natural communities coupled with the increasing certainty of global change, compounded perturbations and ecological surprises will become more common. Understanding these ecological synergisms will be basic to environmental management decisions of the 21st century.

Key words: altered community states; dispersal; multiple disturbances; recovery intervals; scaling disturbances.

ECOSYSTEMS

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Study of the human microbiome: Challenges



- Strain-level characterization
- Getting at function (new *ex vivo* assays)
- Understanding dynamics (time, space)
- Data integration
- Assessing possible causation

"Community as pathogen"

that is,

disease due to a
community disturbance

"pathogenic states"

Clinical problems associated with the indigenous microbiota

- Chronic periodontitis
- Crohn's disease & other IBD
- Irritable bowel syndrome
- Tropical sprue
- Antibiotic-associated diarrhea
- Obesity, undernutrition
- Bacterial vaginosis
- Premature labor and delivery

Clinical problems associated with the indigenous microbiota

- Chronic periodontitis

Cause or effect?
Initiating or propagating?
Mono- or polyfactorial?

- Bacterial vaginosis
- Premature labor and delivery

Clinical Relevance



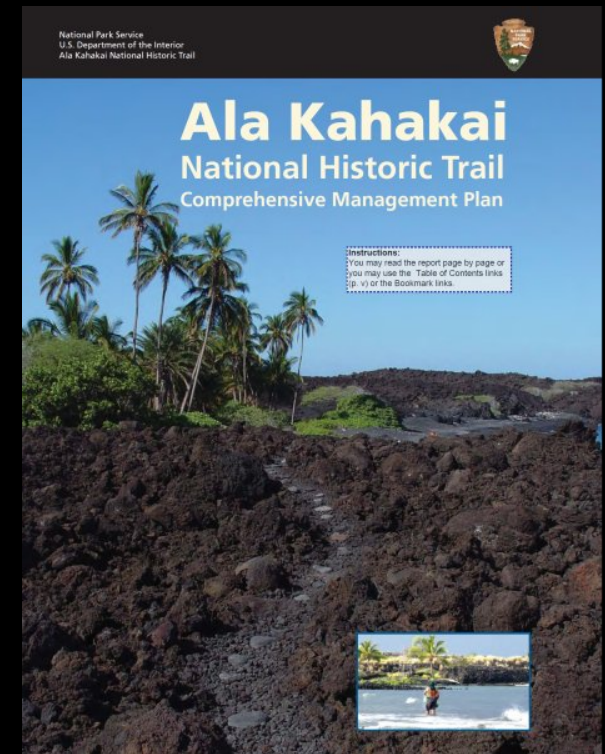
- Ecosystem resilience as critical feature of health; loss leads to increased invasibility (by exotics, e.g., *Salmonella*), blooms (by natives, e.g., *C. difficile*)
- Disturbance as a clinical tool: prognostics (pre-disturbance assessment of resilience), therapeutics (establishment of alternative stable state)
- Key ecosystem services?

Park Management Plan

(for human microbial ecosystem)



- Habitat restoration
- Promotion of native species
- Targeted removal of invasive species
- Ecosystem service providers?
Community and host context?
- Adaptive management: system
monitoring to inform decisions



Acknowledgements

Stanford University

Elies Bik
Liz Costello
Les Dethlefsen
Wei-Ting Liu
Katie Shelef
Dan DiGiulio
Diana Proctor
Sunje Pamp
Miling Yan

& rest of Relman Lab

Susan Holmes (Statistics)



U.C. San Francisco

Gary Armitage
Peter Loomer
Michael Fischbach

U. Colorado

Antonio Peña
Rob Knight

U.C. Berkeley

Jill Banfield

U.C. San Diego

Pieter Dorrestein

Funding: NIH (NIDCR/OD/NIAID/NIGMS/NIEHS),

US Navy, March of Dimes Foundation,

Keck Foundation, Helmsley Trust, Thomas & Joan Merigan Endowment