

# Human intestinal microbiota dynamics and stability in large population cohorts

Leo Lahti (1,2), Anne Salonen (3), Jarkko Salojärvi (1), Marten Scheffer (4), Willem M de Vos (1,2,3)

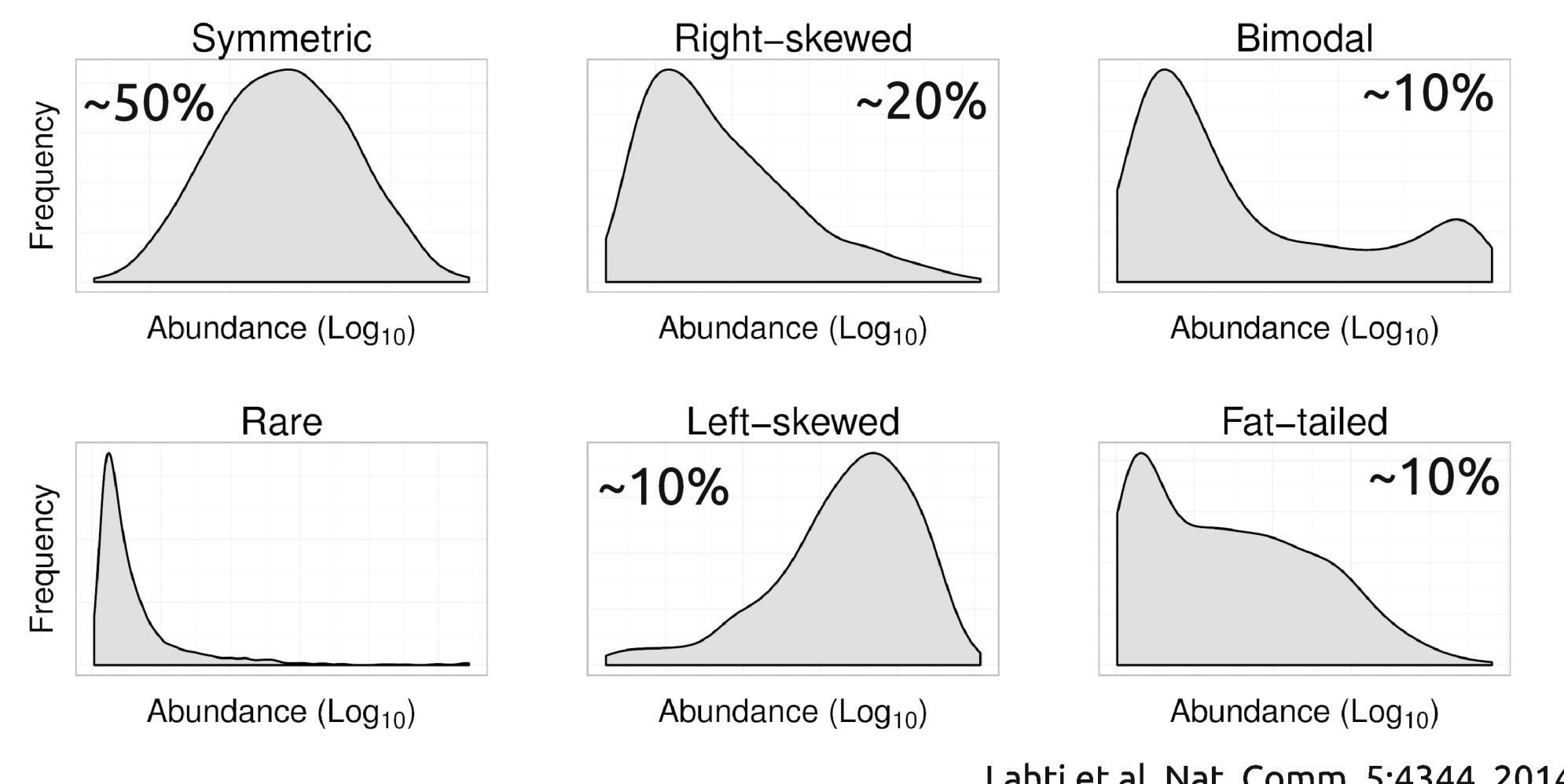
1. Department of Veterinary Biosciences, University of Helsinki, Finland. 2. Laboratory of Microbiology, Wageningen University, The Netherlands. 3. Department of Bacteriology and Immunology, Immunobiology Research Program, Haartman Institute, University of Helsinki, Finland. 4. Department of Aquatic Ecology, Wageningen University, The Netherlands.

Contact: <http://www.iki.fi/Leo.Lahti> - leo.lahti@iki.fi

Microbial communities of the human gut have a profound impact on our physiology and health. Although the composition and function of the intestinal microbiota has been studied extensively, we have only a limited understanding of the temporal dynamics governing this complex ecosystem. The limited availability of time series and remarkable individual variation in microbiota composition and dynamics sets challenges for analyses. We demonstrate that targeting specific subpopulations can provide tools to simplify the characterization and possible manipulation of the intestinal microbiota.

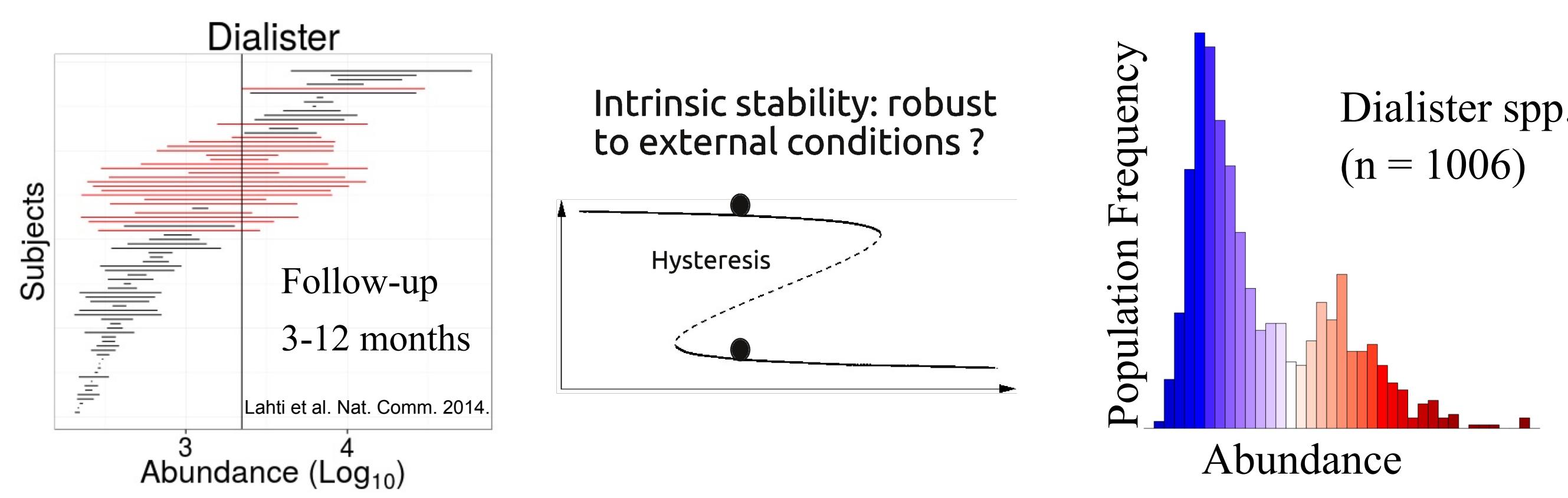
## Bacterial abundance types

Analysis of microbiota composition of fecal samples from a 1,000 healthy western adults indicates specific abundance types in intestinal microbes, including rare, symmetric, skewed and bimodal types (Lahti et al. 2014).

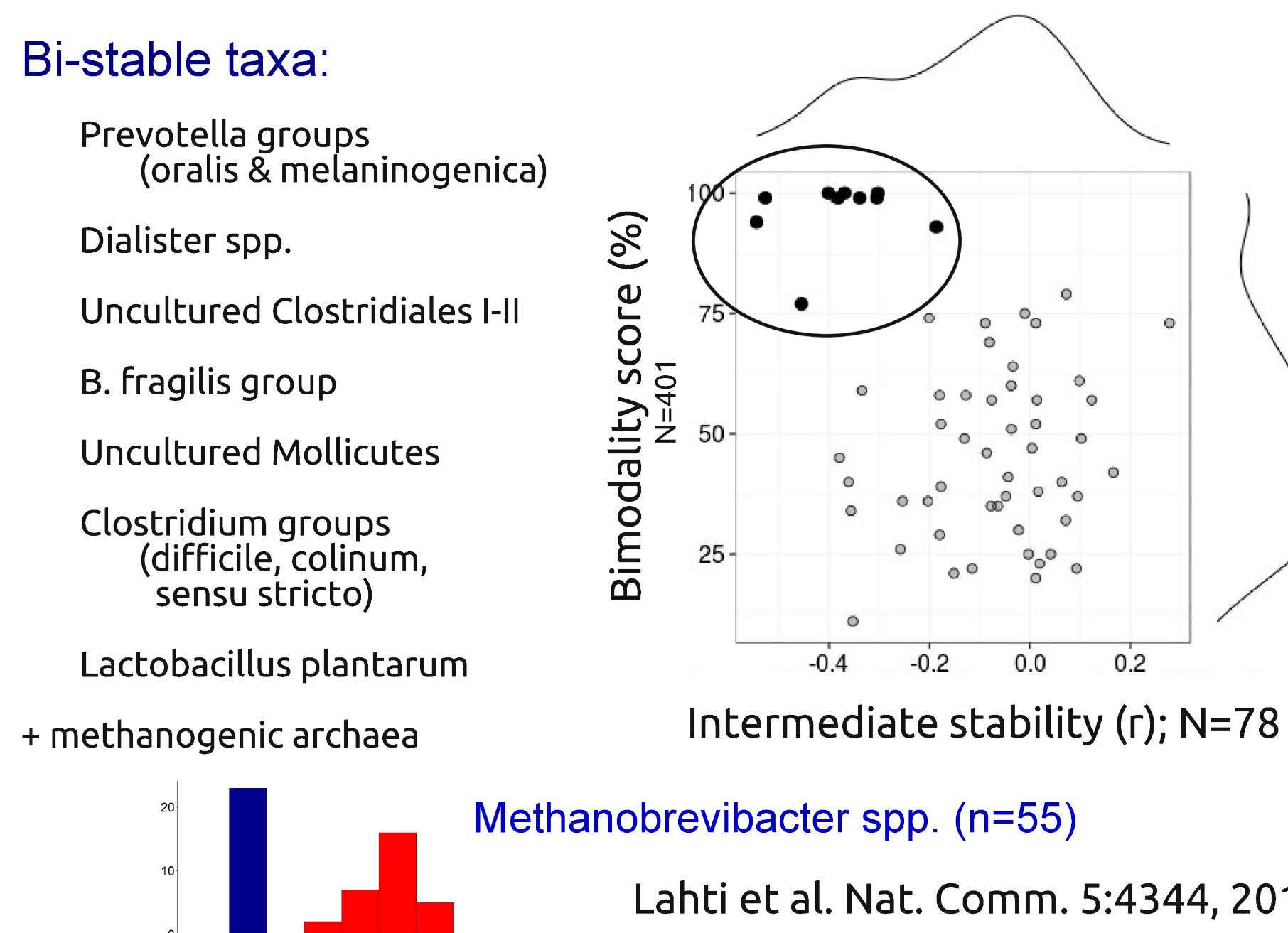


## Analysis of bi-stability

We combined information across multiple short time series from 78 individuals over 3-12 months helps to assess the stability in individual taxa. The analysis shows that in parallel to the dominating continuous, gradual variation in bacterial abundances, specific subpopulations within the intestinal microbiota exhibit contrasting, stable configurations of low and high abundance that are associated to host physiology and health. These include drivers of the previously reported enterotypes (Prevotella and Bacteroides; Arumugam et al. 2011) but also many less abundant bi-stable taxa that have been overlooked in ecosystem-level analyses.



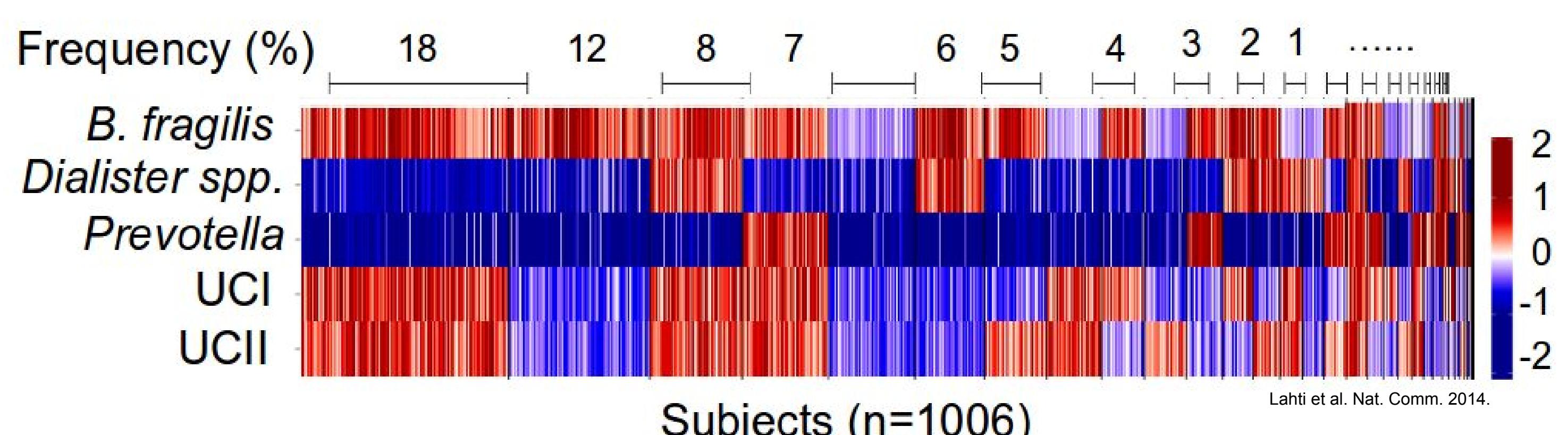
Analysis across a thousand healthy western individuals confirms that the bi-stable taxa are also associated with bimodal abundance distributions at the population level. Importantly, the bimodal taxa exhibit reduced temporal stability at the intermediate abundance range. This observation is central for establishing bi-stability.



## Data

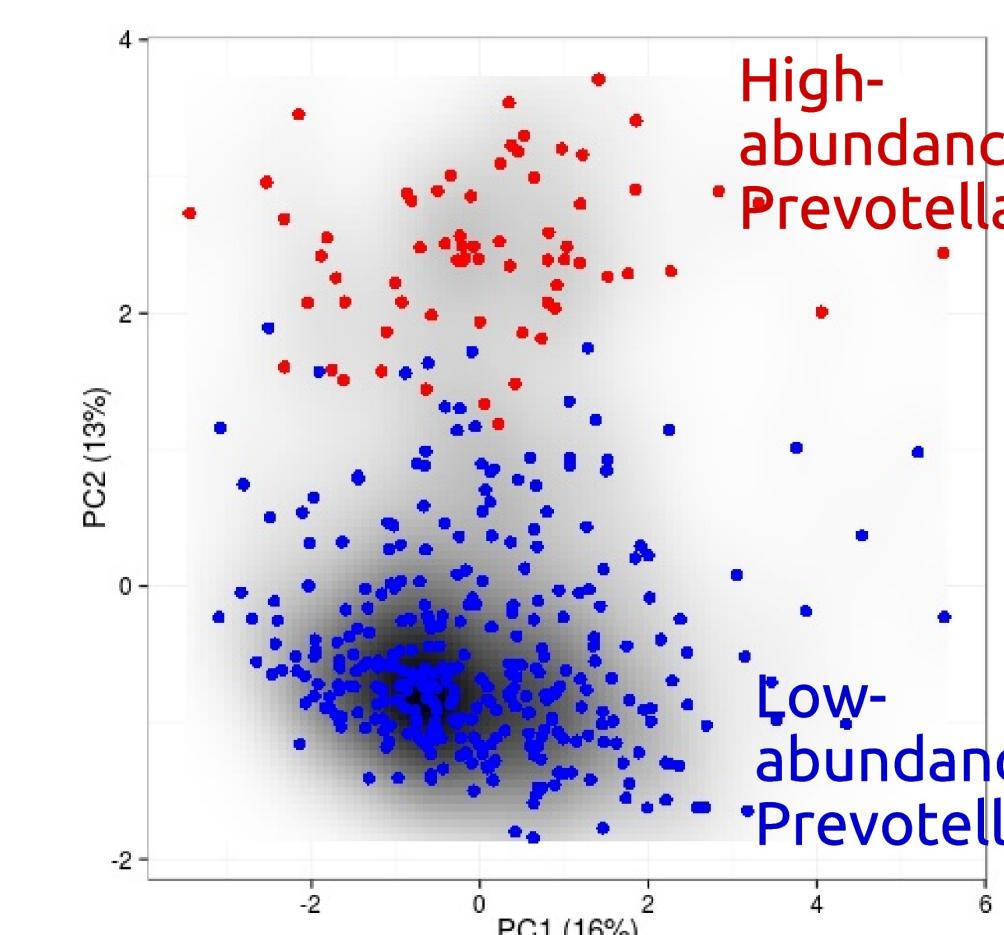
Phylogenetic Human Intestinal Tract Chip (HITChip; RajlicStojanovic et al. 2009) provides a sensitive, systematic, and highly reproducible analysis platform to assess relative phylotype abundance based on the 16S rRNA regions of >1000 specieslike phylotypes of the human gut. This provides comprehensive and deep analysis of the human microbiota, comparable to 200,000 NGS runs per sample (Claesson et al. 2009) and allows standardized collection of commensurable high throughput data sets suited for largescale meta-analysis. The data set used in this study is available via Data Dryad (<http://datadryad.org/handle/10255/dryad.64664>) and provides abundance (phylogenetic microarray signal) for 130 genus-like groups across 1006 western adults, together with subject metadata on age, body-mass index, nationality, time point, and other variables.

## Tipping elements of the intestinal microbiota

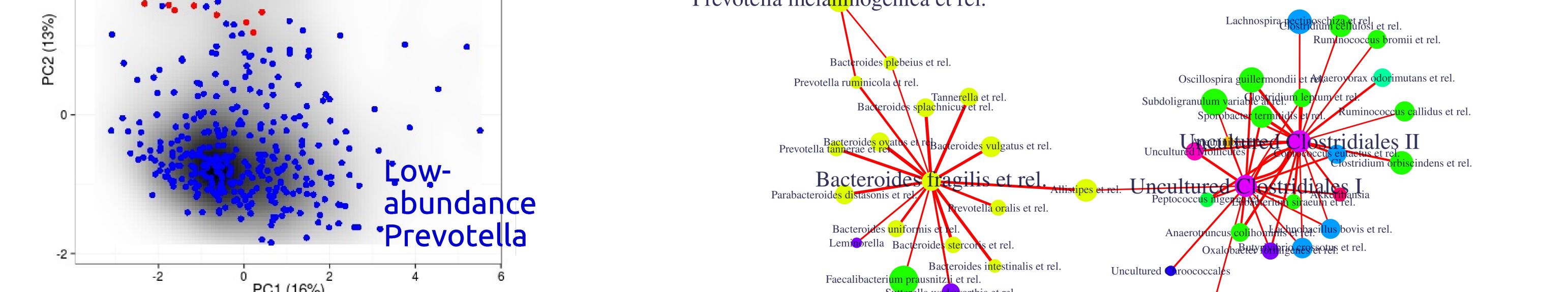


The bi-stable tipping elements vary quite independently and are frequently observed in various combinations. The bi-stable taxa exhibit largely distinct correlation networks with the other taxa. They appear robust to dietary interventions and exhibit notable differences in temporal stability and contributions to the overall community composition. This provides well-defined targets for potential therapeutic manipulation of the gut microbiota. Another key advantage is that the bi-stability in individual taxa can be detected more reliably than bi-stability at the ecosystem level. We characterize such individual bi-stable groups as "tipping elements" of the intestinal microbiota.

PCA (n = 401 healthy western adults)

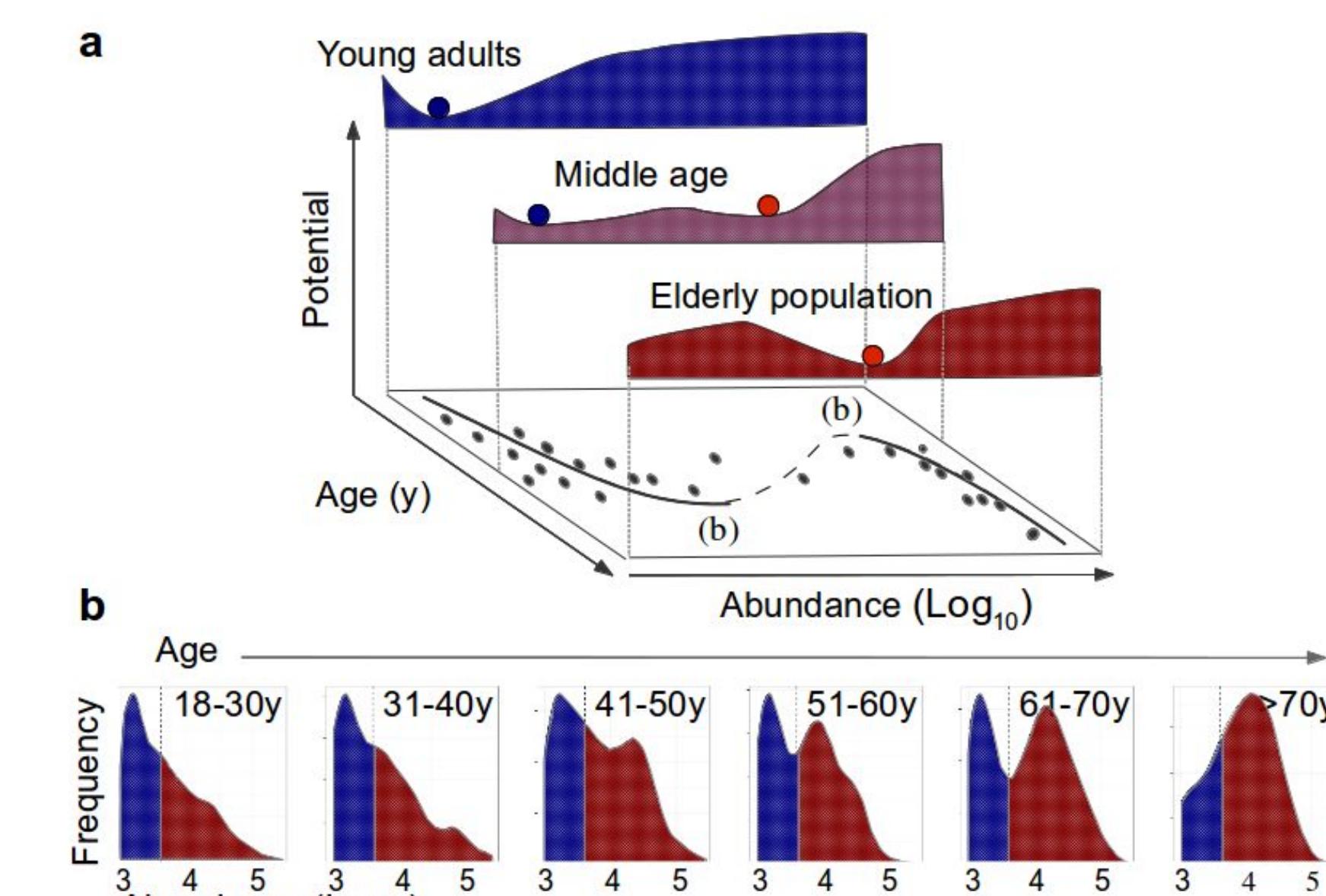


Correlation networks of the bi-stable tipping elements



The bi-stable variation in these sub-communities is often masked by continuous variation in more abundant taxa and hence easily overlooked in ecosystem-level multivariate analyses. Distinct subject clusters at the ecosystem level in the PCA visualization are driven by the low and high abundance of the Prevotella genus, which has also been reported as one of the enterotype drivers (Arumugam et al. 2010). However, whereas the Prevotella relative abundance in the high-abundance state is ~10%, the other bi-stable tipping elements have relative abundances of 1-2% and are hence masked by more dominating gradual variation by other taxa.

## Bi-stable taxa and host health



Host factors such as age can affect the resilience of the alternative states and move the system towards a tipping point of an abrupt switch between the contrasting states. Analysis of additional samples from compromised individuals suggests enrichment of specific bi-stable tipping elements in certain diseases.

Health status	Bimodal group	Enriched state	Compromised (%)	Controls (%)	FDR (%)
Severe obesity (n=136)	UCI	Low abundance	29	55	<0.1
Severe obesity	UCII	Low abundance	38	61	<0.1
IBS (n=106)	UCII	Low abundance	50	61	1
MetS (n=66)	B. fragilis group	High abundance	89	78	<0.1
MetS	Prevotella group	Low abundance	11	22	11
MetS	Dialister	High abundance	36	28	13

Lahti et al. Nat. Comm. 2014.

## References

Lahti L. et al. (2014). Tipping Elements of the Human Intestinal Ecosystem. *Nature Communications* 5:4344.

Claesson M. et al. (2009). Comparative Analysis of Pyrosequencing and a Phylogenetic Microarray for Exploring Microbial Community Structures in the Human Distal Intestine. *PLoS One* 4(8): e6669.

Rajilić-Stojanović M. et al (2009). Development and application of the human intestinal tract chip, a phylogenetic microarray: analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. *Environ Microbiol* 11: 1736-51.

Arumugam M. et al. (2011). Enterotypes of the human gut microbiome. *Nature* 473, 174–180.

Acknowledgements: LL has received research funding from the Academy of Finland (grant 256950).

This work is licensed under a Creative Commons Attribution 4.0 International License.

