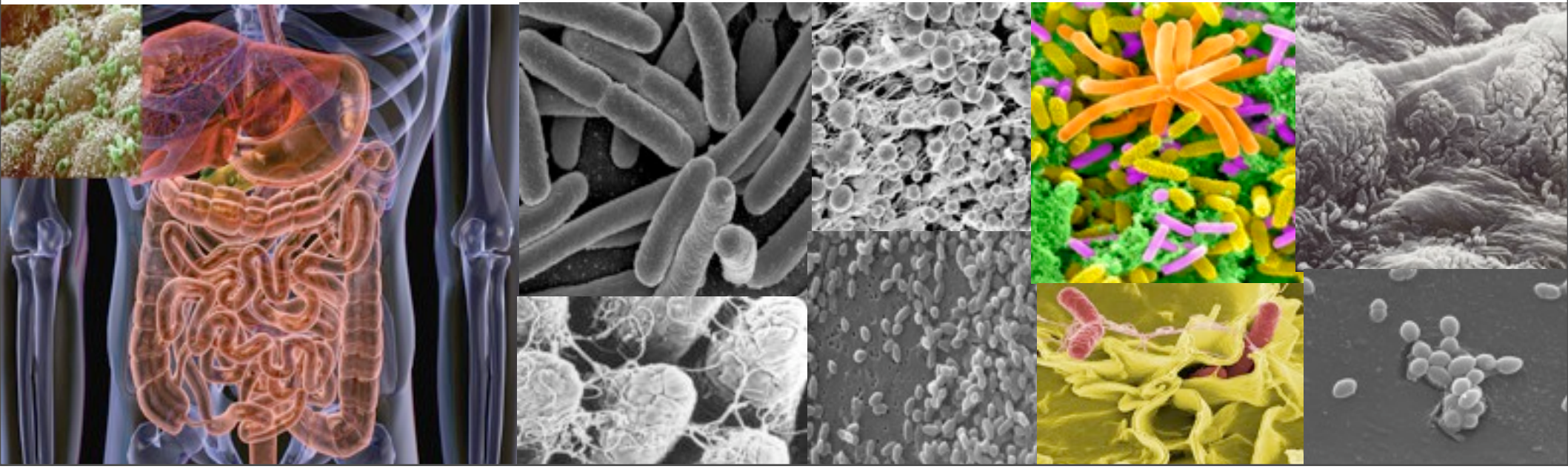
Human health and our other genome - Metagenomics of the human gut

H. Bjørn Nielsen
Center for Biological Sequence Analysis
Technical University of Denmark



Metaomics

Metagenomics ←
Metatranscriptomics ←
Metaproteomics ←
Metainteractomics ←
Metasecretome
Metametabolomics
Metafluxomics
Metaphenomics
….
(Metainformatics)

What is Metagenomics?

Metagenomics (Environmental Genomics, Ecogenomics or Community Genomics) is the study of genetic material recovered directly from environmental samples.

The New Science of Metagenomics

Metagenomics is both a set of *research techniques*, comprising many related approaches and methods, and a *research field*.

Metagenomics

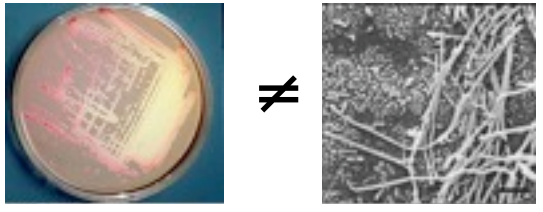
Is the study of the DNA from all genomes in an environment

CENTERFO
RBIOLOGI
CALSEQU
ENCEANA
LYSIS CBS

Why Metagenomics?

A) Most microbial activities are carried out by complex communities of microorganisms ...

B) 99% of microbial species cannot currently be cultivated



A hand full of soil ...

- Culturing: a few hundreds species per gram
- 16S sequencing: few thousands per gram
- DNA re-association: a few millions per gram

CENTERFOR BIOLOGICAL SEQUENCE ANALYSIS CBS

Who

is in there?

Interplay

How

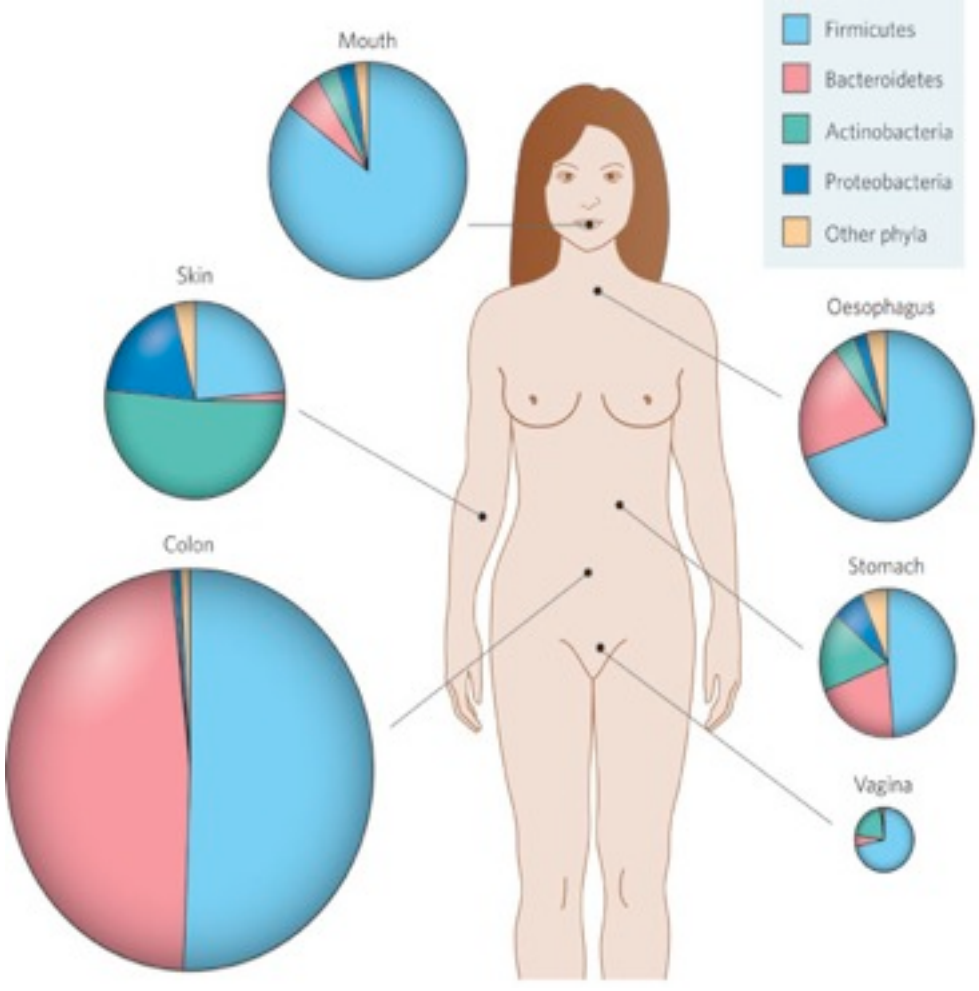
are they doing it?

What

are they doing?

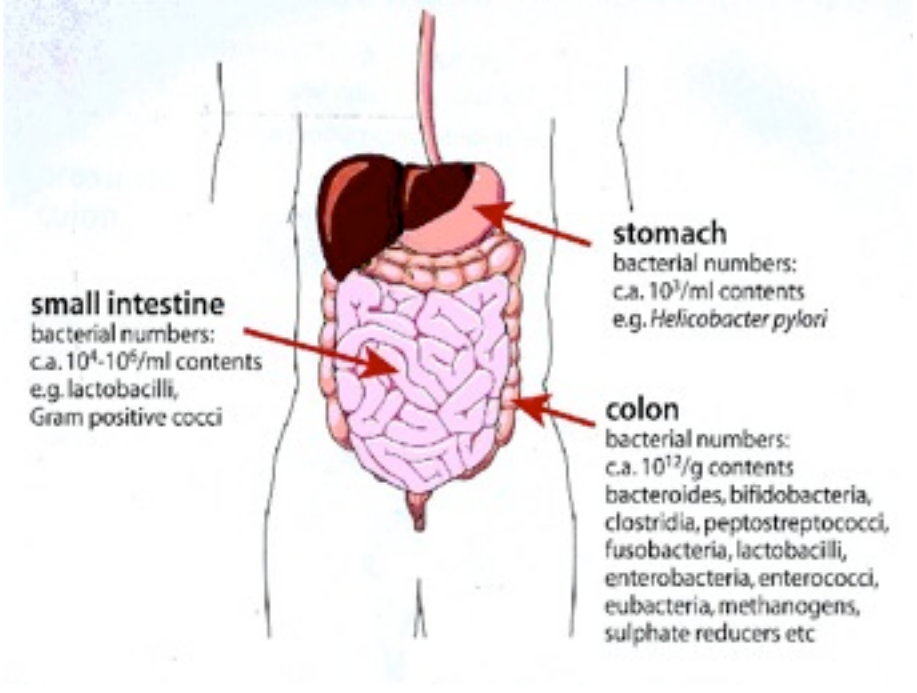
Human Microbiota

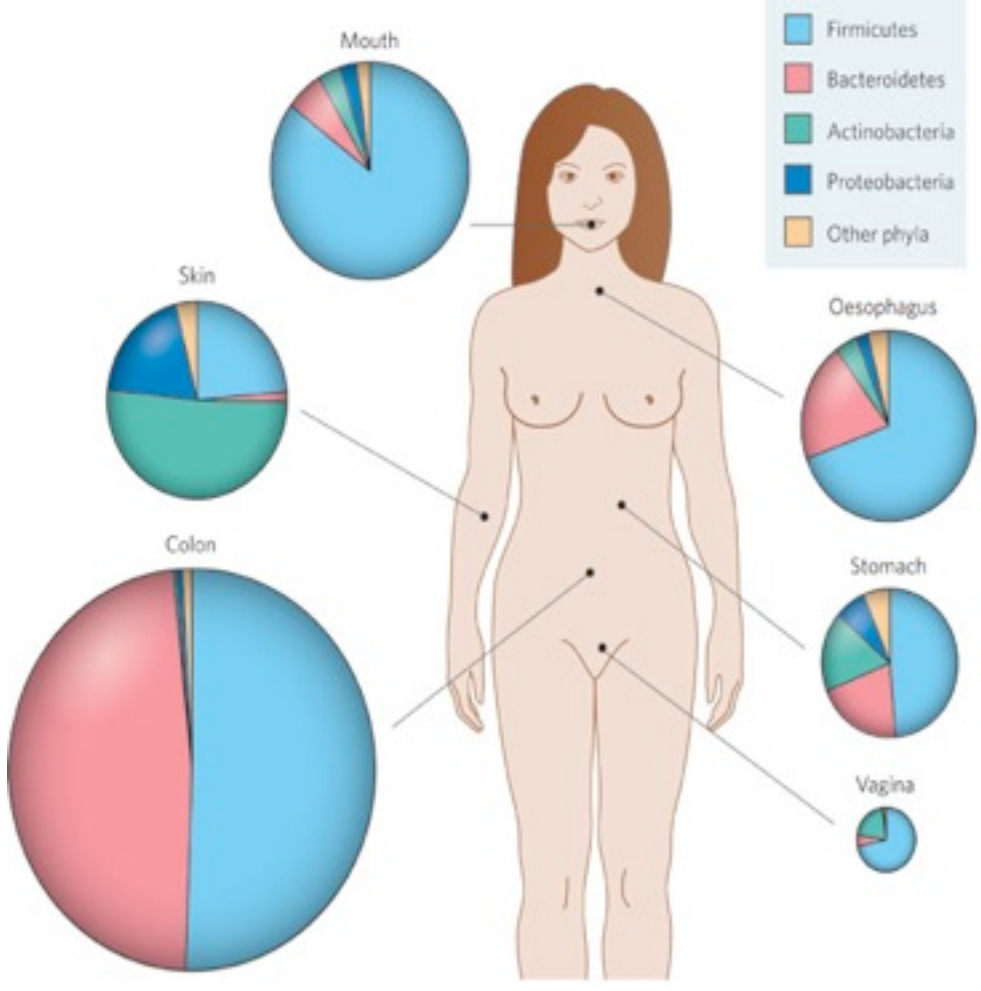
	Human cells	*Human Microbiota*
cells	10^{12}	10^{13}-10^{14}
genes	~30.000	>3.000.000
species	1	1,000 - 100,000



Human Microbiota

	Human cells	*Human Microbiota*
cells	10^{12}	10^{13}-10^{14}
genes	~30.000	>3.000.000
species	1	1,000 - 100,000

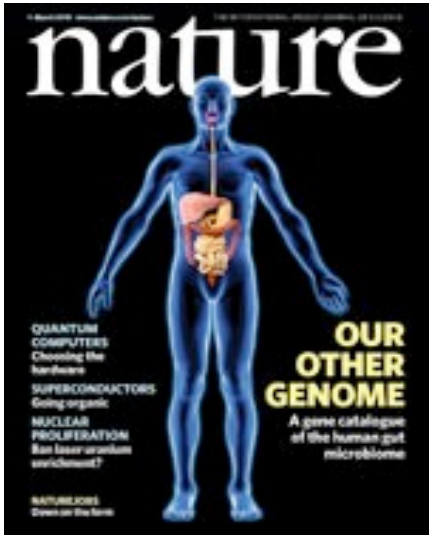




The International MetaHIT

(Metagenomics of the Human Intestinal Tract)

Step 1:
Gene catalogue of the human gut microbiome (3.2 million genes).



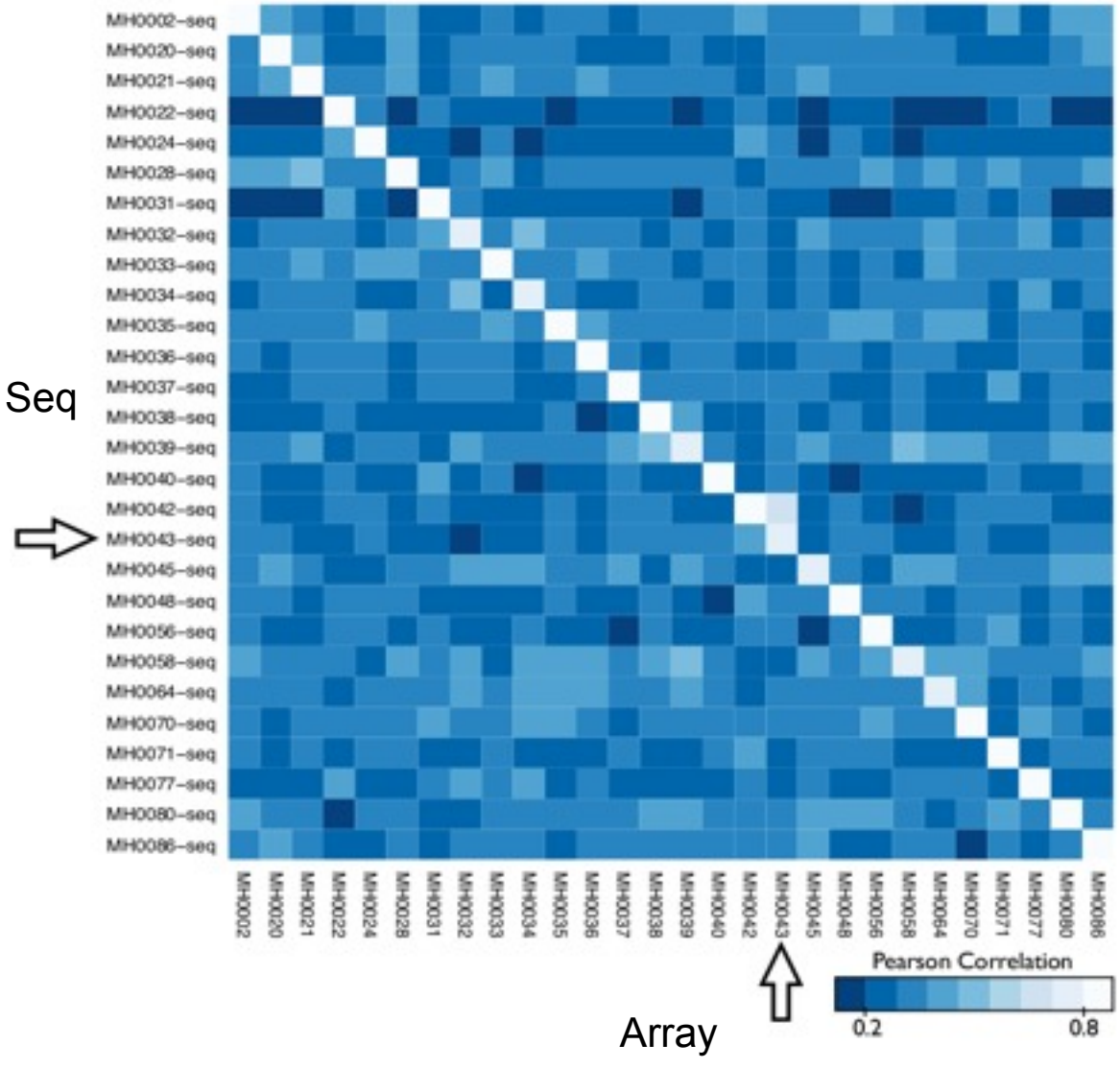
4 March 2010

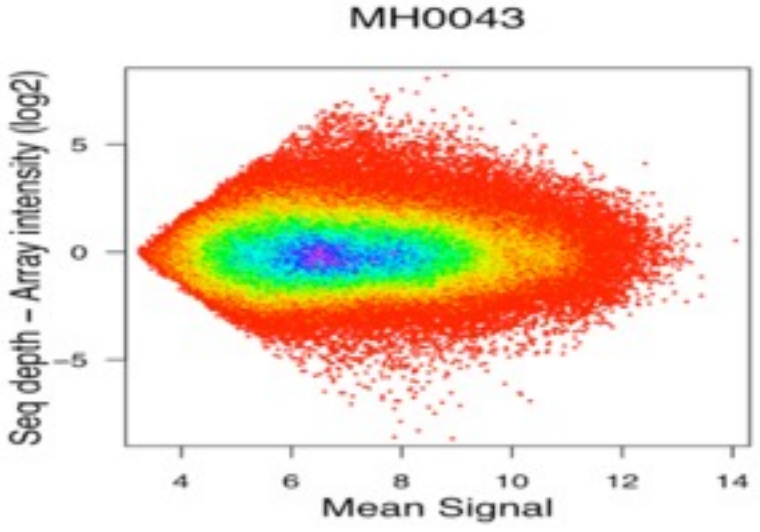
Step 2:
Profile obesity.

Step 3:
Profile inflammatory bowel disease (IBD).
Two types of IBD:
Crohn's disease and ulcerative colitis.

DNA microarray versus DNA sequencing

Highly consistent signal across technologies





Human gut profile

Phyla abundance in DNA samples

Division of labor

nature Vol 467|2 September 2010|doi:10.1038/nature09354

LETTERS

Bacterial charity work leads to population-wide resistance

Henry H. Lee[1,2], Michael N. Molla[1,2], Charles R. Cantor[2] & James J. Collins[1,2,3]

Bacteria show remarkable adaptability in the face of antibiotic therapeutics. Resistance alleles in drug target-specific sites and general stress responses have been identified in individual end-point isolates[1–7]. Less is known, however, about the population dynamics during the development of antibiotic-resistant strains. Here we follow a continuous culture of *Escherichia coli* facing increasing levels of antibiotic and show that the vast majority of isolates are less resistant than the population as a whole. We find that the few highly resistant mutants improve the survival of the population's less resistant constituents, in part by producing indole, a signalling molecule generated by actively growing, unstressed cells[8]. We show, through transcriptional profiling, that indole serves to turn on drug efflux pumps and oxidative-stress protective mechanisms. The indole production comes at a fitness cost to the highly resistant isolates, and whole-genome sequencing reveals that this bacterial altruism is made possible by drug-resistance mutations unrelated to indole production. This work establishes a population-based resistance mechanism constituting a form of kin selection[9] whereby a small number of resistant mutants can, at some cost to themselves, provide protection to other, more vulnerable, cells, enhancing the survival capacity of the overall population in stressful environments.

Antibiotic-resistant bacterial strains continually arise and their increasing prevalence poses significant clinical and societal challenges[7,10]. Functional analyses of resistant mutants and the study of the endogenous processes responsible for resistance by mutation have yielded valuable insights[1–7,11,12]. However, population dynamics and communal interactions that underlie the development of resistance through mutations are often overlooked. To study these neglected aspects, we tracked a bacterial population as it developed antibiotic resistance in a bioreactor. rare detection of HRIs was due to their low abundance in the population throughout most of the experiment. Indeed, when we plated daily populations under norfloxacin selection, we frequently detected low-abundance HRIs that emerged before increases in the group MIC (Fig. 1b). We were, however, surprised by the large number of

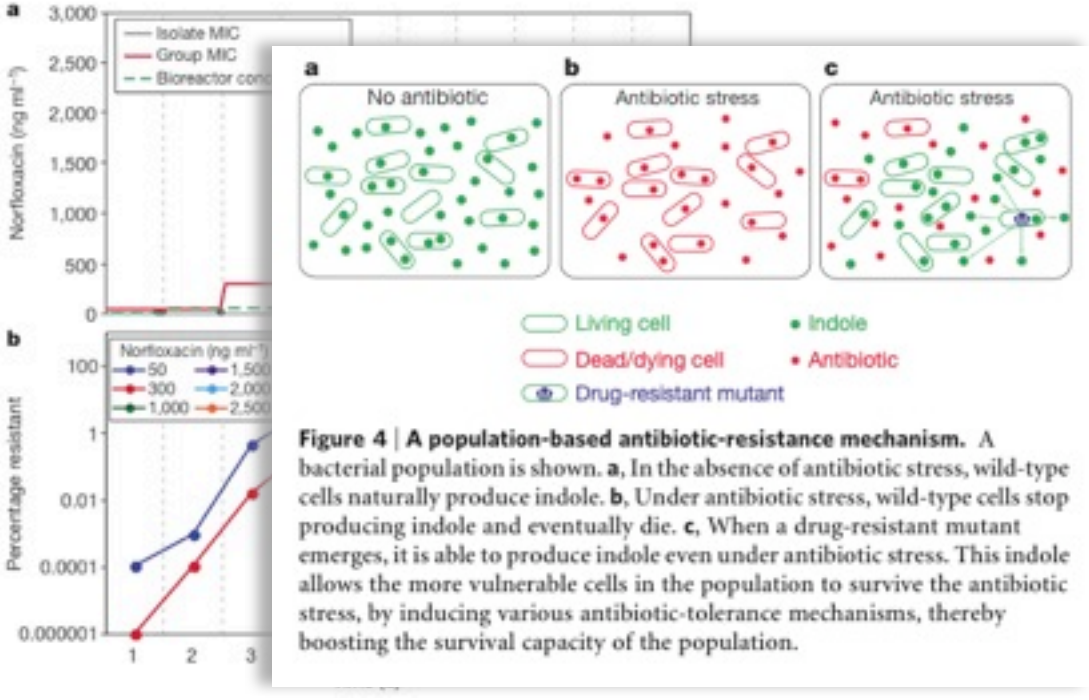
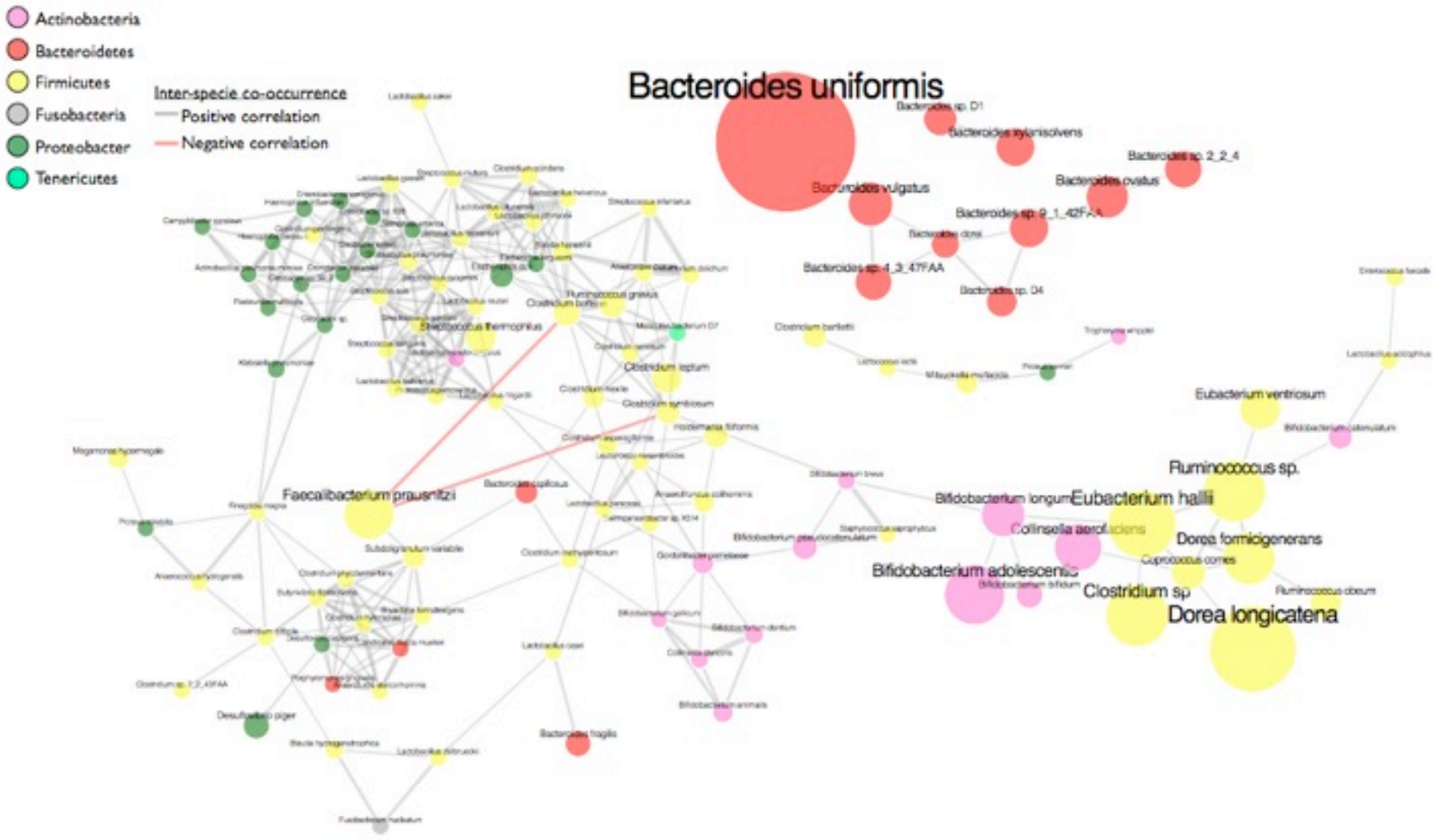


Figure 4 | A population-based antibiotic-resistance mechanism. A bacterial population is shown. **a**, In the absence of antibiotic stress, wild-type cells naturally produce indole. **b**, Under antibiotic stress, wild-type cells stop producing indole and eventually die. **c**, When a drug-resistant mutant emerges, it is able to produce indole even under antibiotic stress. This indole allows the more vulnerable cells in the population to survive the antibiotic stress, by inducing various antibiotic-tolerance mechanisms, thereby boosting the survival capacity of the population.

Species co-abundance network (DNA)



Qin et al., Nature, 2010

The CBS team

Marcelo Bertalan

Laurent Gautier

Pia Friis

Thomas Sicheritz Pontén

Søren Brunak

Lene Christiansen