"How Studying Astrophysics and Coral Reefs Enabled Me to Become an Empowered, Engaged Patient"

Invited Talk

FutureMed at the Hotel Del

Coronado, CA

November 4, 2013



Dr. Larry Smarr

Director, California Institute for Telecommunications and Information Technology

Harry E. Gruber Professor,

Dept. of Computer Science and Engineering

Jacobs School of Engineering, UCSD

http://lsmarr.calit2.net

This FutureMed Talk Builds on My February 2013 FutureMed Presentation

Tweet Feb. 5, 2013



Daniel Kraft, MD @daniel_kraft

"With a 3D printed part of his Colon @lsmarr is an empowered patient #futuremed http://futuremed2020.com/live"



Download My Previous Presentation From:
http://lsmarr.calit2.net/presentations?slideshow=16384993

My View on My Own Body Was Shaped by My Lifetime of Scientific Experience

- **No Formal Training in Biology or Medicine**
- **Instead, Decades of:**
  - **Observational & Computational Astrophysics**
  - **Observing & Building Coral Reef Ecologies**

I Spent Decades Studying the Ecological Dynamics of Multi-Phyla Coral Reefs



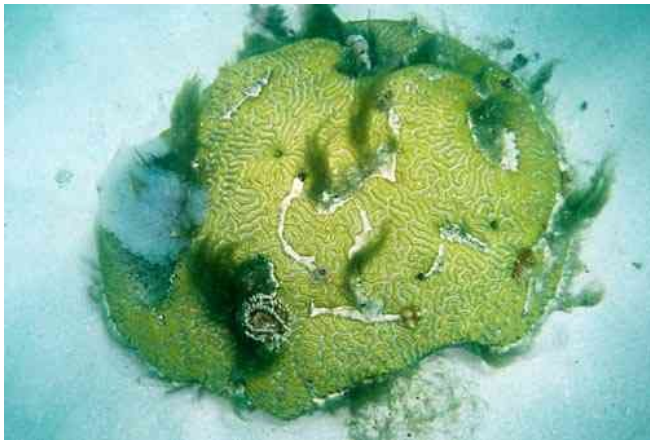


My 120 Gallon Home Salt Water Coral Reef Aquarium in Illinois



Pristine

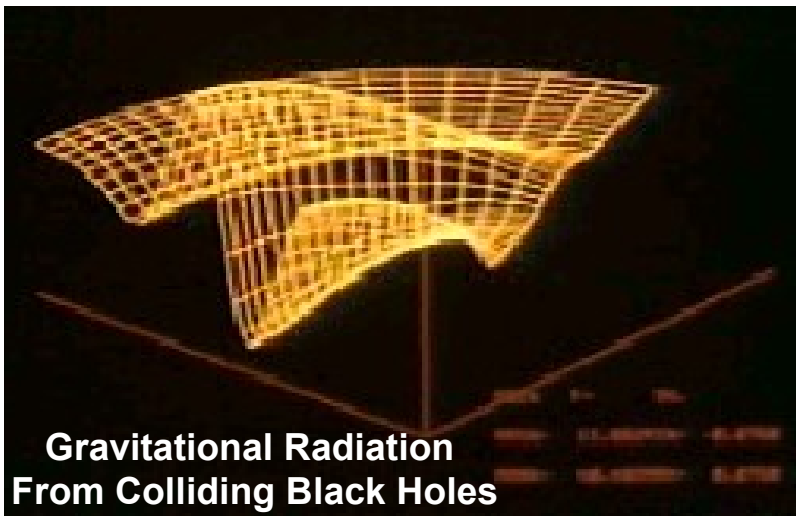
Degraded



My Snorkeling Photos From Coral Reefs

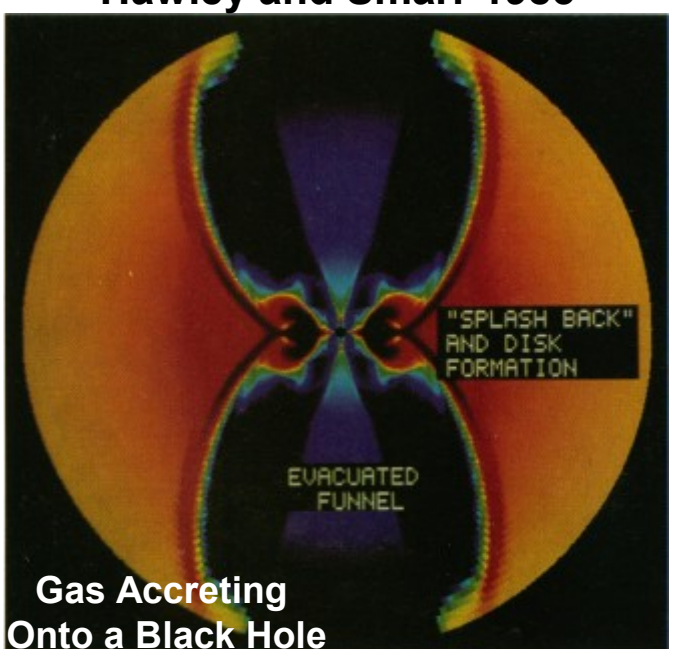
My Early Research was on Computational Astrophysics – I Learned To Think About Nonlinear Dynamic Systems

Eppley and Smarr 1977

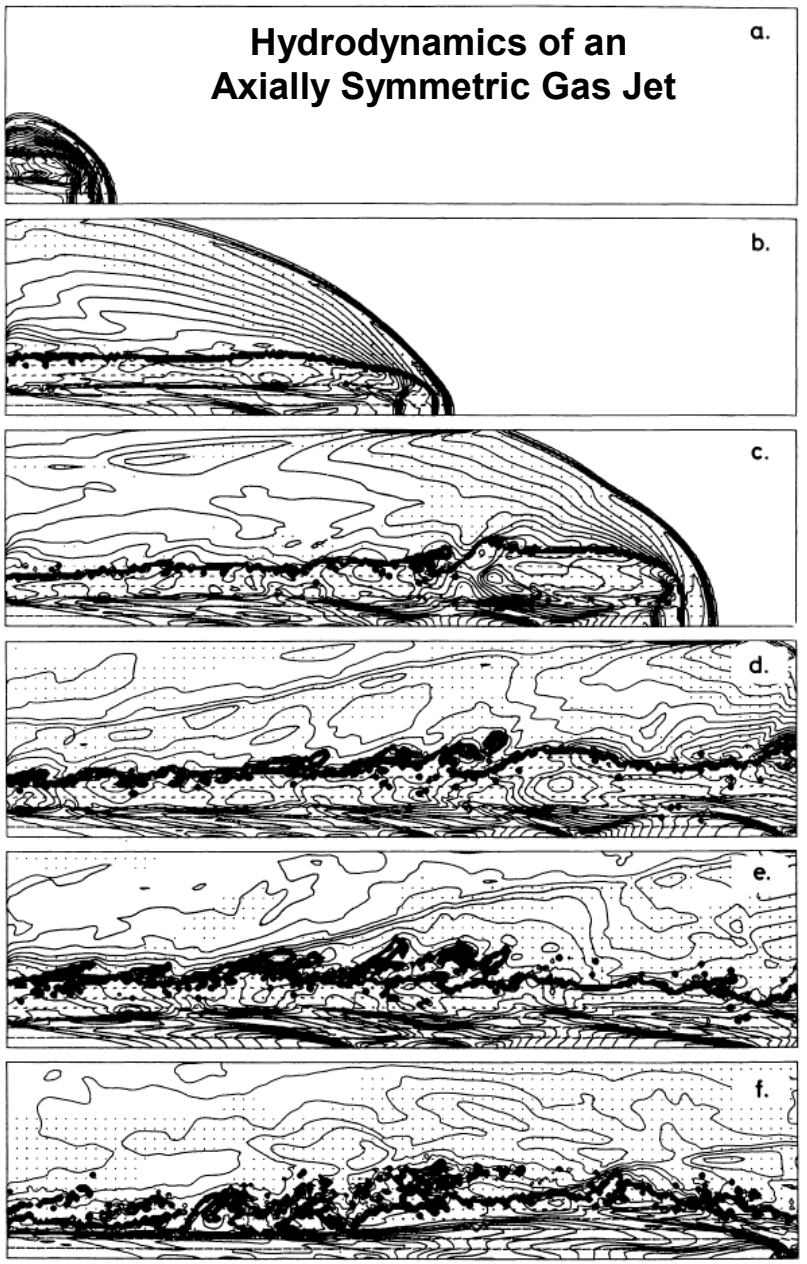


Gravitational Radiation
From Colliding Black Holes

Hawley and Smarr 1985

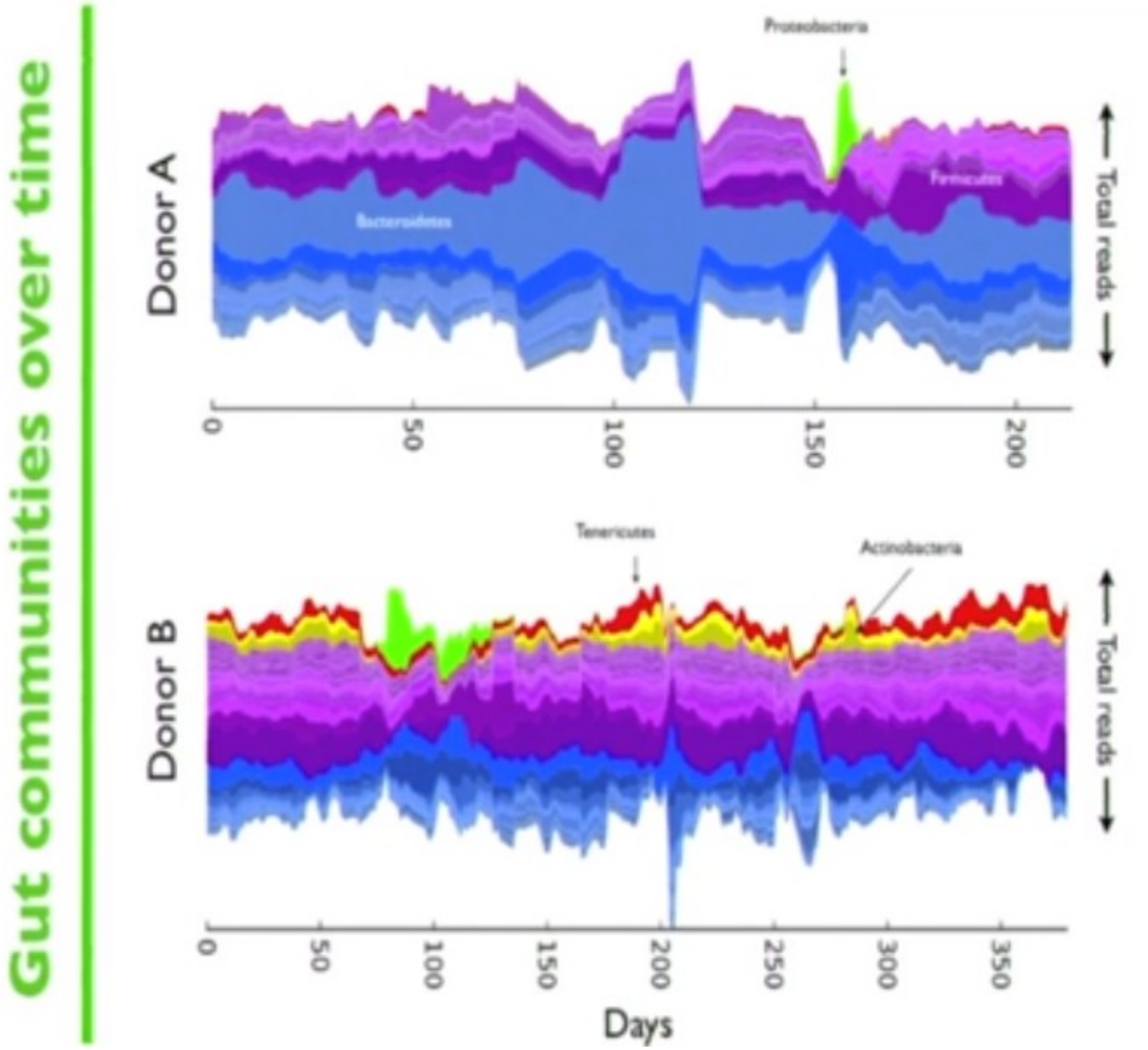


Gas Accreting
Onto a Black Hole



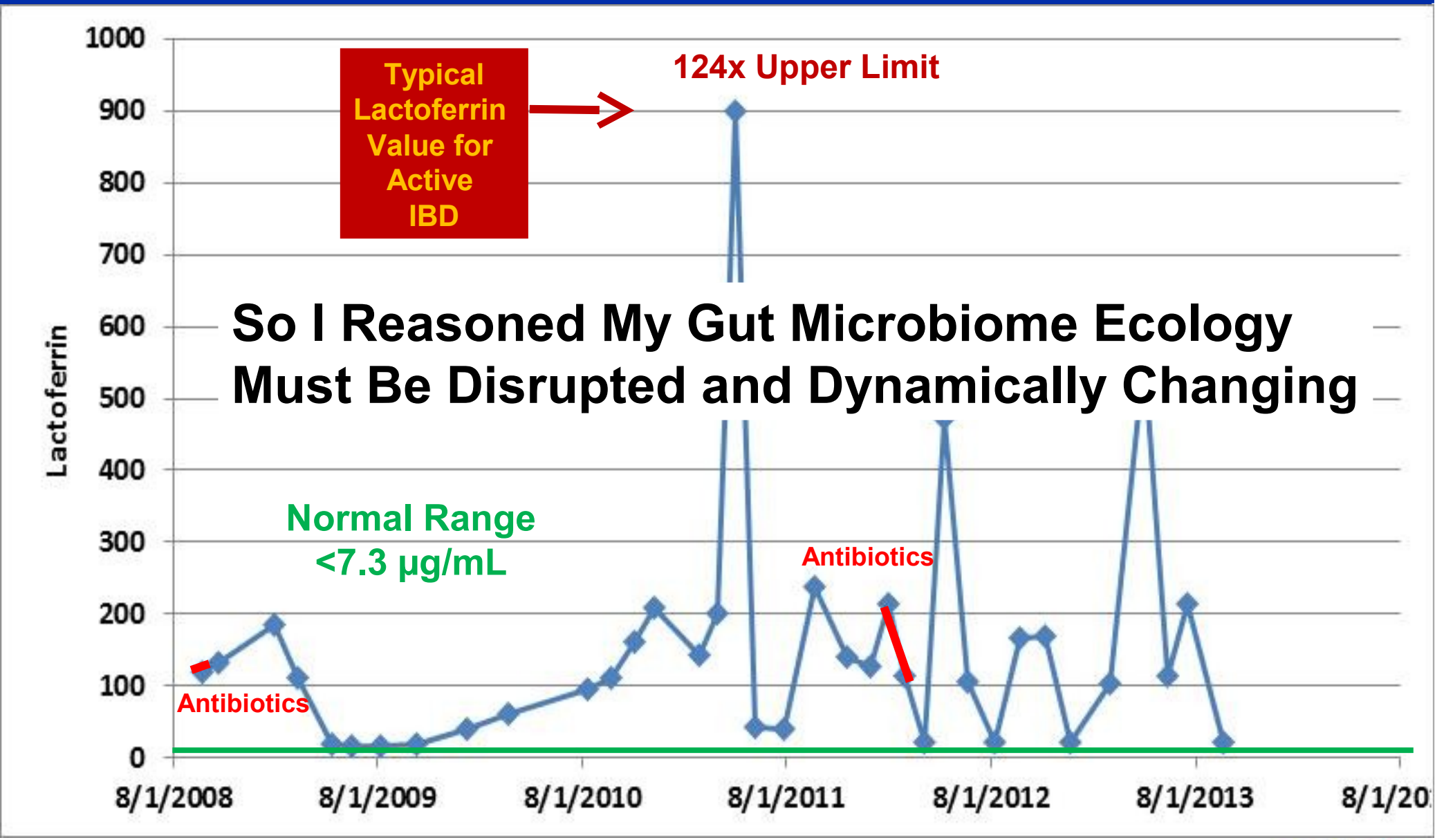
Norman, Winkler, Smarr, Smith 1982

The Immune System & the Gut Microbiome are a Coupled Dynamic Ecological System Normally in Homeostasis



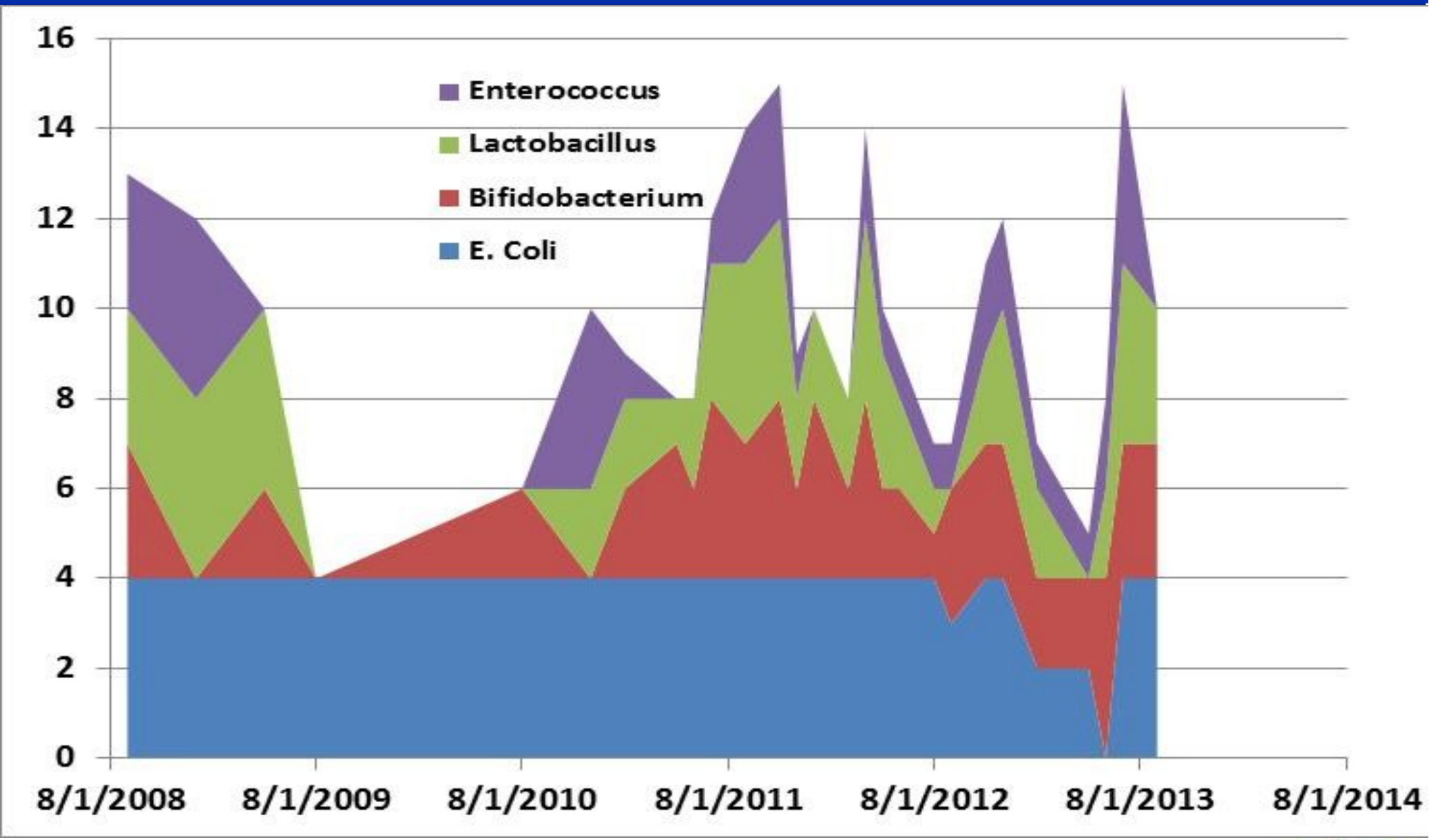
Source: Eric Alm, MIT

But by Using Stool Analysis Time Series, I Discovered I Had Episodically Excursions of My Immune System



Lactoferrin is a Protein Shed from Neutrophils -
An Immune System Antibacterial that Sequesters Iron

Indeed, My Cultured Gut Bacterial Abundance Time Series Revealed an Oscillatory Microbiome Ecology



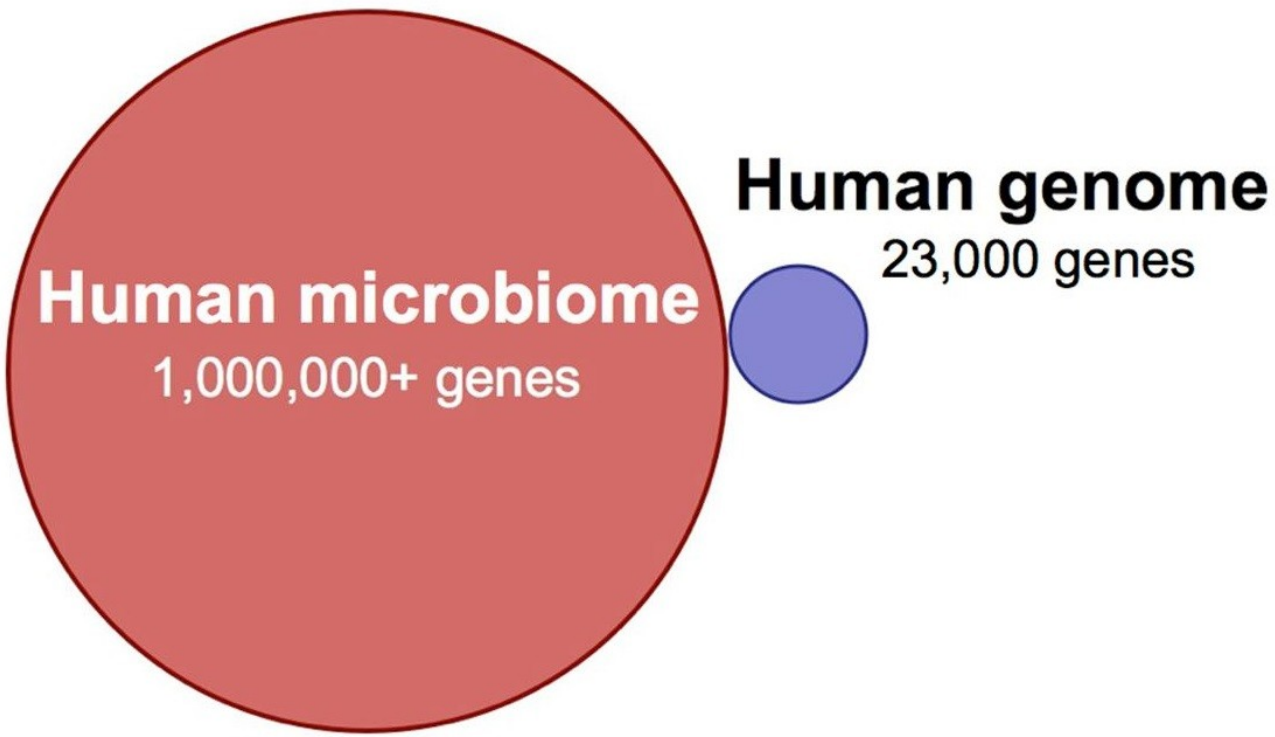
LS Data from Yourfuturehealth.com

I Had Carried Out Observations in Optical, Radio, and X-Ray on the Andromeda Galaxy in the 1980s



So I Set Out to Observe the 100 Trillion Non-Human Cells in My Gut

Your Body Has 10 Times As Many Microbe Cells As Human Cells



99% of Your DNA Genes Are in Microbe Cells Not Human Cells

Inclusion of the Microbiome Will Radically Change Medicine

J. Craig Venter™ INSTITUTE

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When We Think About Biological Diversity We Typically Think of the Wide Range of Animals






But All These Animals Are in One SubPhylum Vertebrata of the Chordata Phylum

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Think of These Phyla of Animals When You Consider the Biodiversity of Microbes Inside You



Phylum Chordata



Phylum Cnidaria



Phylum Echinodermata



Phylum Annelida



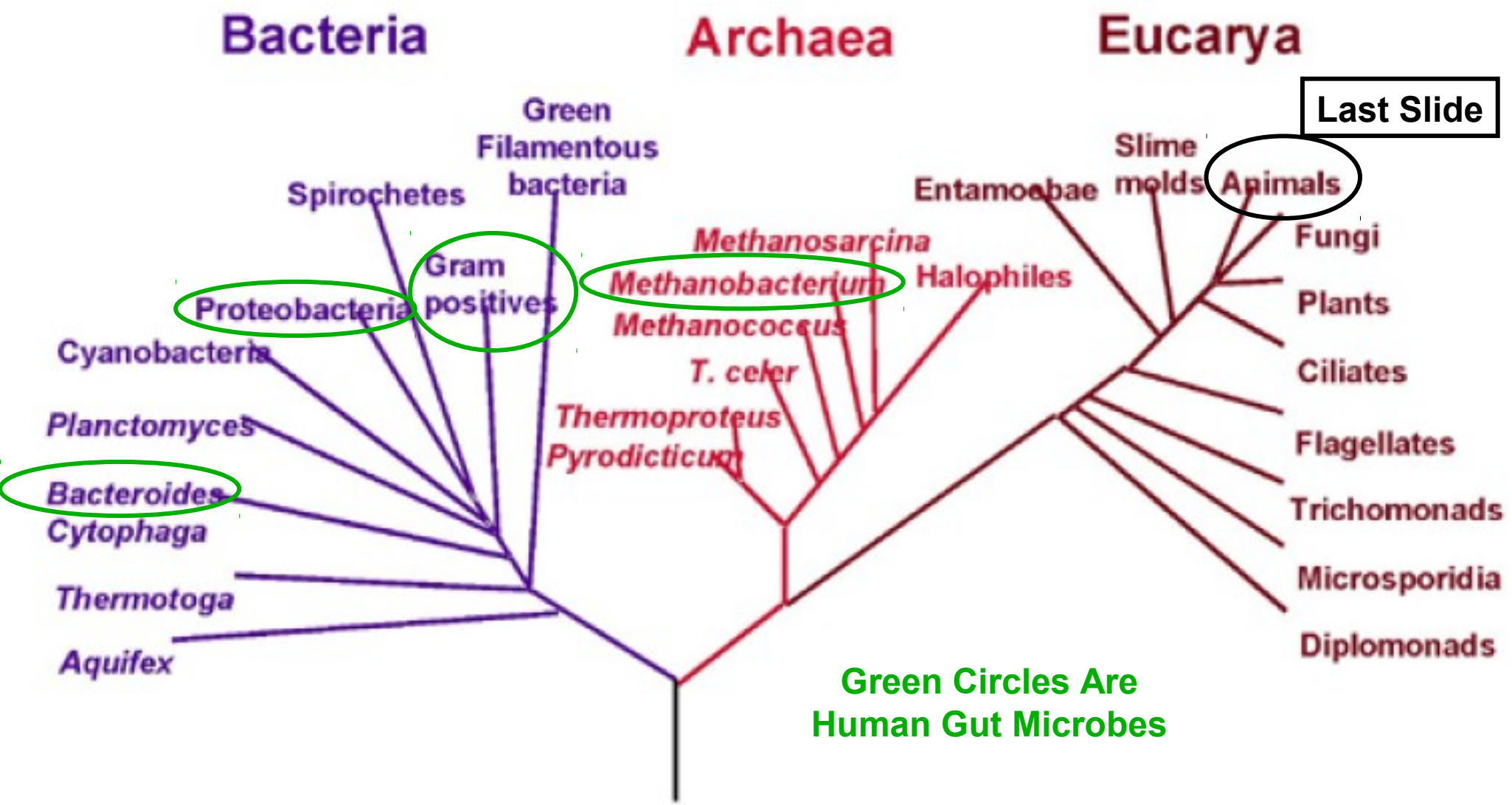
Phylum Mollusca



Phylum Arthropoda

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However, The Evolutionary Distance Between Your Gut Microbes Is Much Greater Than Between All Animals

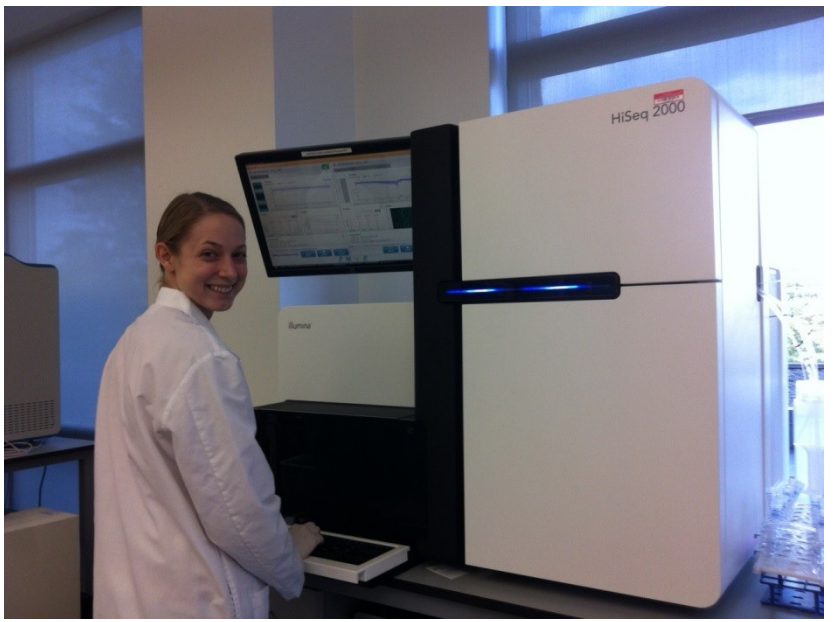


Evolutionary Distance Derived from Comparative Sequencing of 16S or 18S Ribosomal RNA

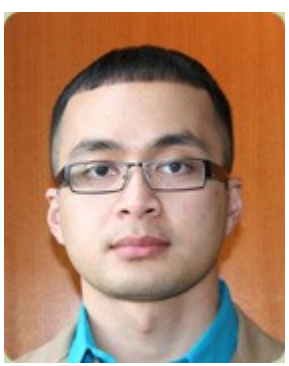
Source: Carl Woese, et al

To Map Out the Dynamics of My Microbiome Ecology I Partnered with the J. Craig Venter Institute

- JCVI Did Metagenomic Sequencing on Six of My Stool Samples Over 1.5 Years
- Sequencing on Illumina HiSeq 2000
  - Generates 100bp Reads
  - Run Takes ~14 Days
  - My 6 Samples Produced
    - 190.2 Gbp of Data
- JCVI Lab Manager, Genomic Medicine
  - Manolito Torralba
- IRB PI Karen Nelson
  - President JCVI



Illumina HiSeq 2000 at JCVI


Manolito Torralba, JCVI


Karen Nelson, JCVI

J. Craig Venter INSTITUTE

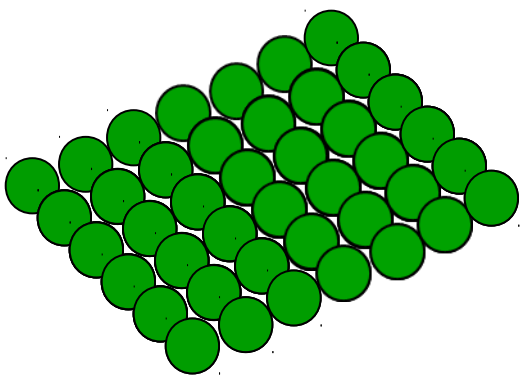
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We Downloaded Additional Phenotypes from NIH HMP For Comparative Analysis

Download Raw Reads
~100M Per Person

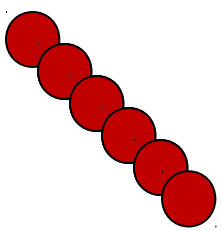
"Healthy" Individuals

35 Subjects
1 Point in Time



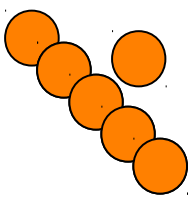
Larry Smarr

6 Points in Time

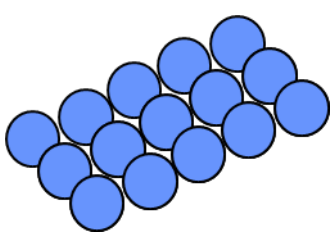


IBD Patients

2 Ulcerative Colitis Patients,
6 Points in Time



5 Ileal Crohn's Patients,
3 Points in Time



NIH

HMP

Total of 5 Billion Reads

Source: Jerry Sheehan, Calit2
Weizhong Li, Sitao Wu, CRBS, UCSD

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We Created a Reference Database Of Known Gut Genomes

- **NCBI April 2013**
  - **2471 Complete + 5543 Draft Bacteria & Archaea Genomes**
  - **2399 Complete Virus Genomes**
  - **26 Complete Fungi Genomes**
  - **309 HMP Eukaryote Reference Genomes**
- **Total 10,741 genomes, ~30 GB of sequences**

NCBI National Center for Biotechnology Information

HMP

Now to Align Our 5 Billion Reads Against the Reference Database

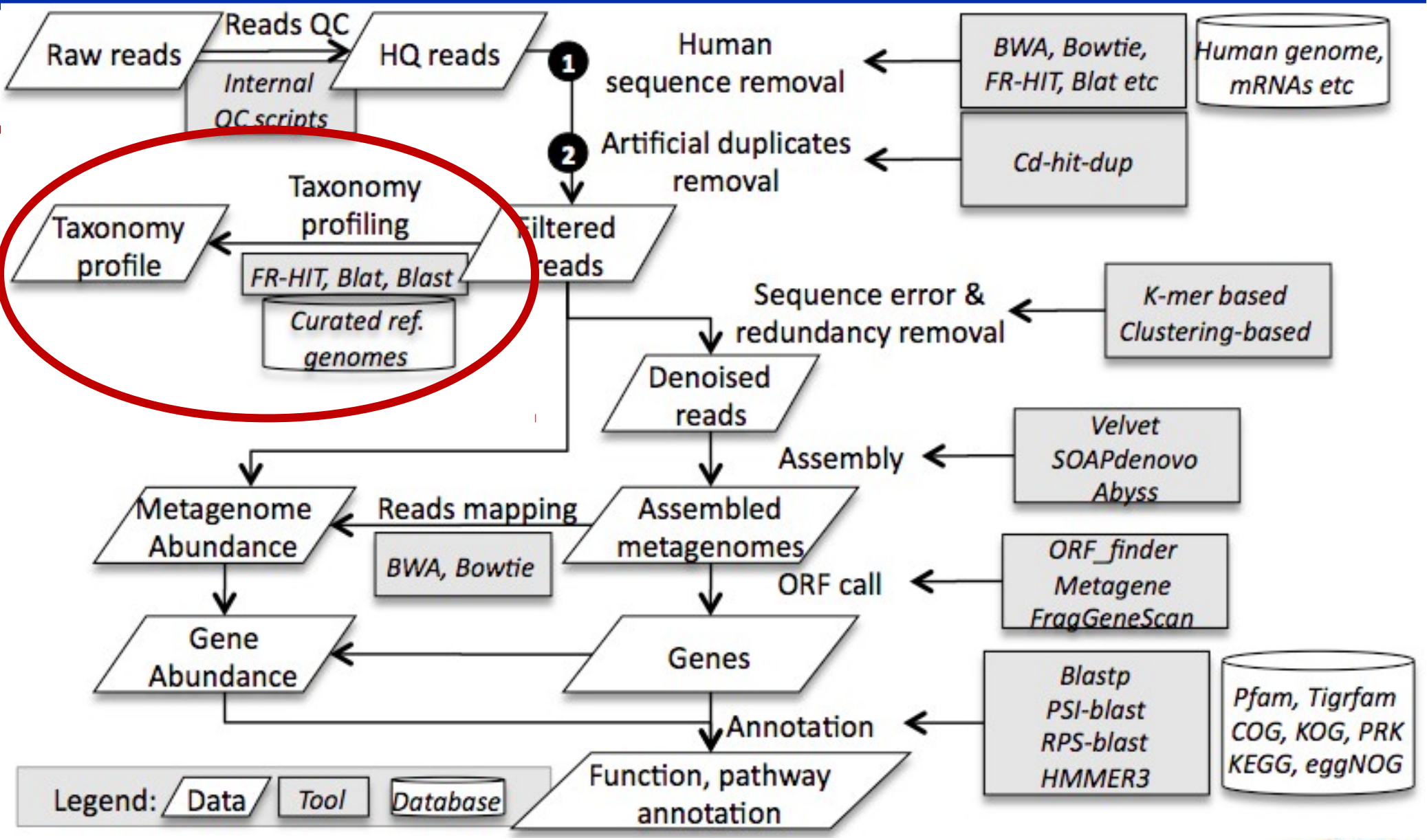
NIH

J. Craig Venter INSTITUTE

Source: Weizhong Li, Sitao Wu, CRBS, UCSD

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Computational NextGen Sequencing Pipeline: From "Big Equations" to "Big Data" Computing



National Human Genome Research Institute

HMP

PI: (Weizhong Li, CRBS, UCSD):
NIH R01HG005978 (2010-2013, $1.1M)

CRBS

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We Used SDSC's Gordon Data-Intensive Supercomputer to Analyze a Wide Range of Gut Microbiomes

Source: Weizhong Li, Sitao Wu, CRBS, UCSD



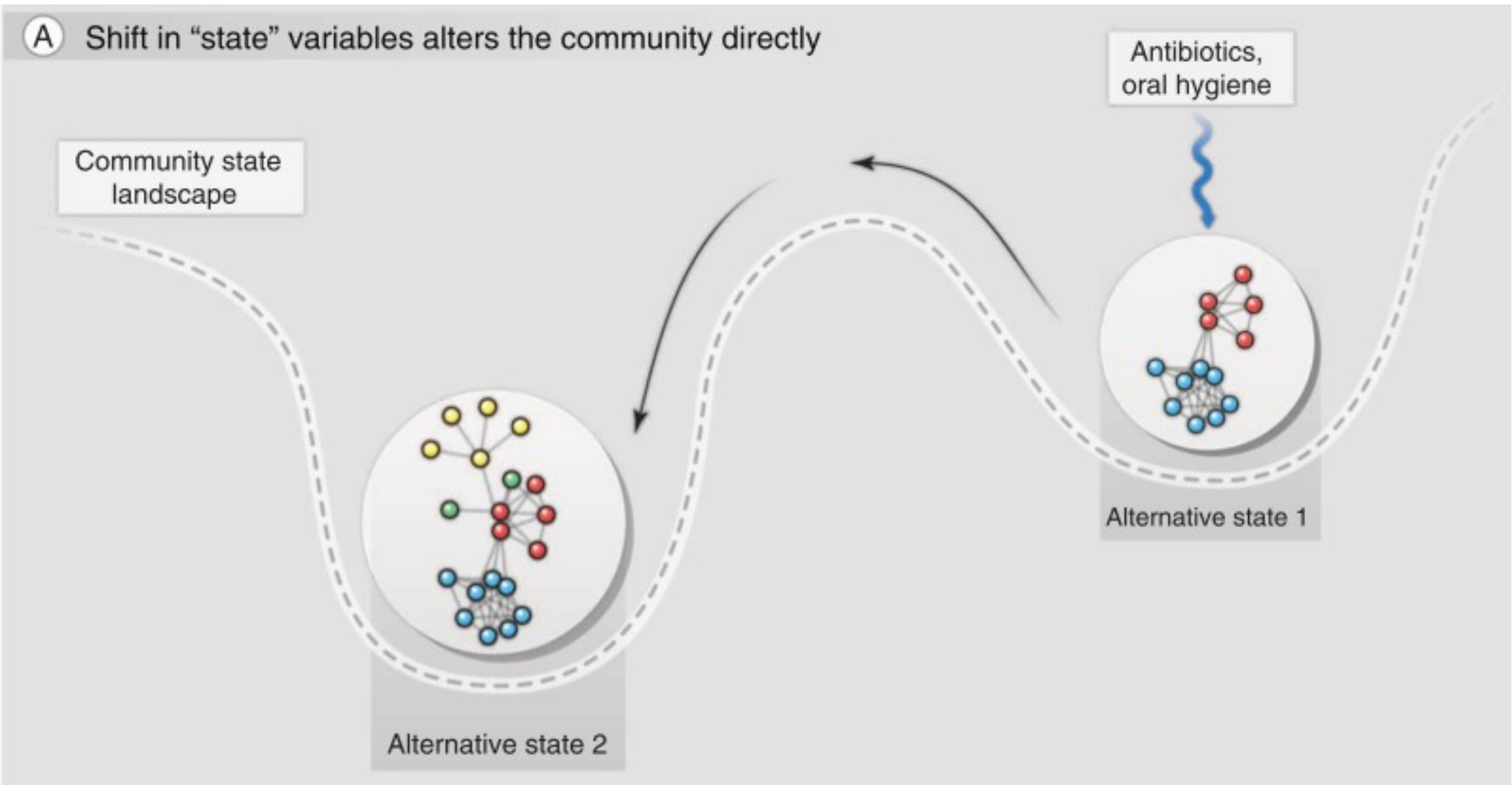
Our Team Used 25 CPU-Decades
To Compute
the Comparative Gut Microbiome
of My Time Samples
and Our Healthy and IBD Controls
Starting With
the 5 Billion Illumina Reads
Received from JCVI

Enabled by
a Grant of Time
on Gordon from SDSC
Director Mike Norman

NSF NIH HMP J. Craig Venter INSTITUTE CRBS SDSC it²

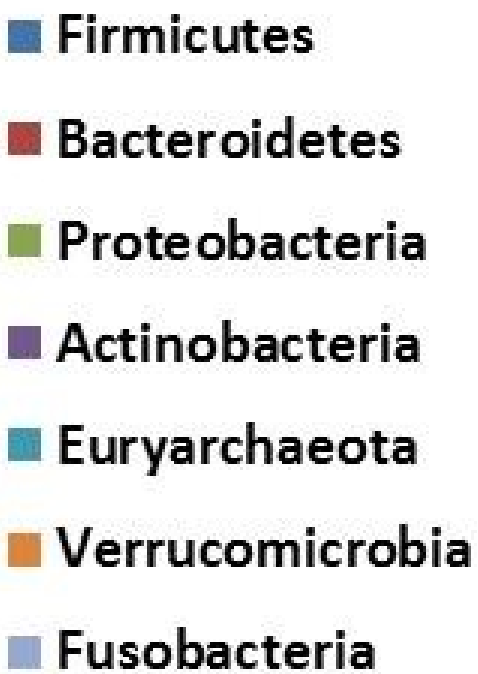
I Will Share a Few Preliminary Findings

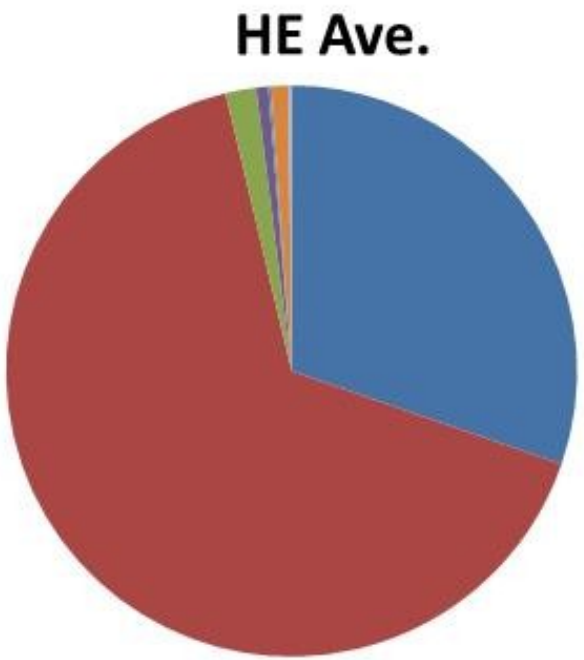
Lessons from Ecological Dynamics I: Gut Microbiome Has Multiple Relatively Stable Equilibria

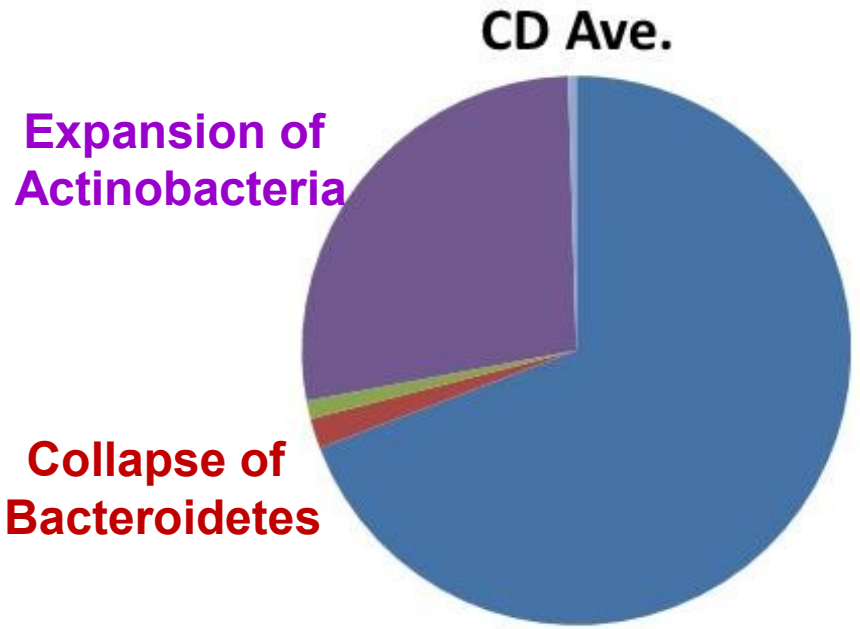


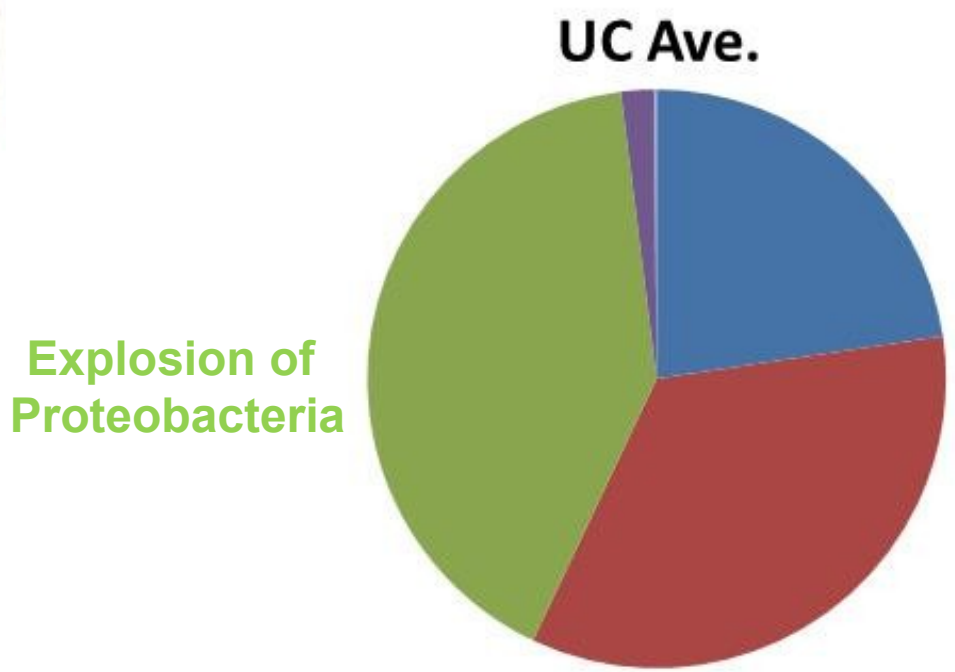
"The Application of Ecological Theory Toward an Understanding of the Human Microbiome,"
Elizabeth Costello, Keaton Stagaman, Les Dethlefsen, Brendan Bohannan, David Relman
Science 336, 1255-62 (2012)

Comparison of 35 Healthy to 15 CD and 6 UC Gut Microbiomes at the Phyla Level









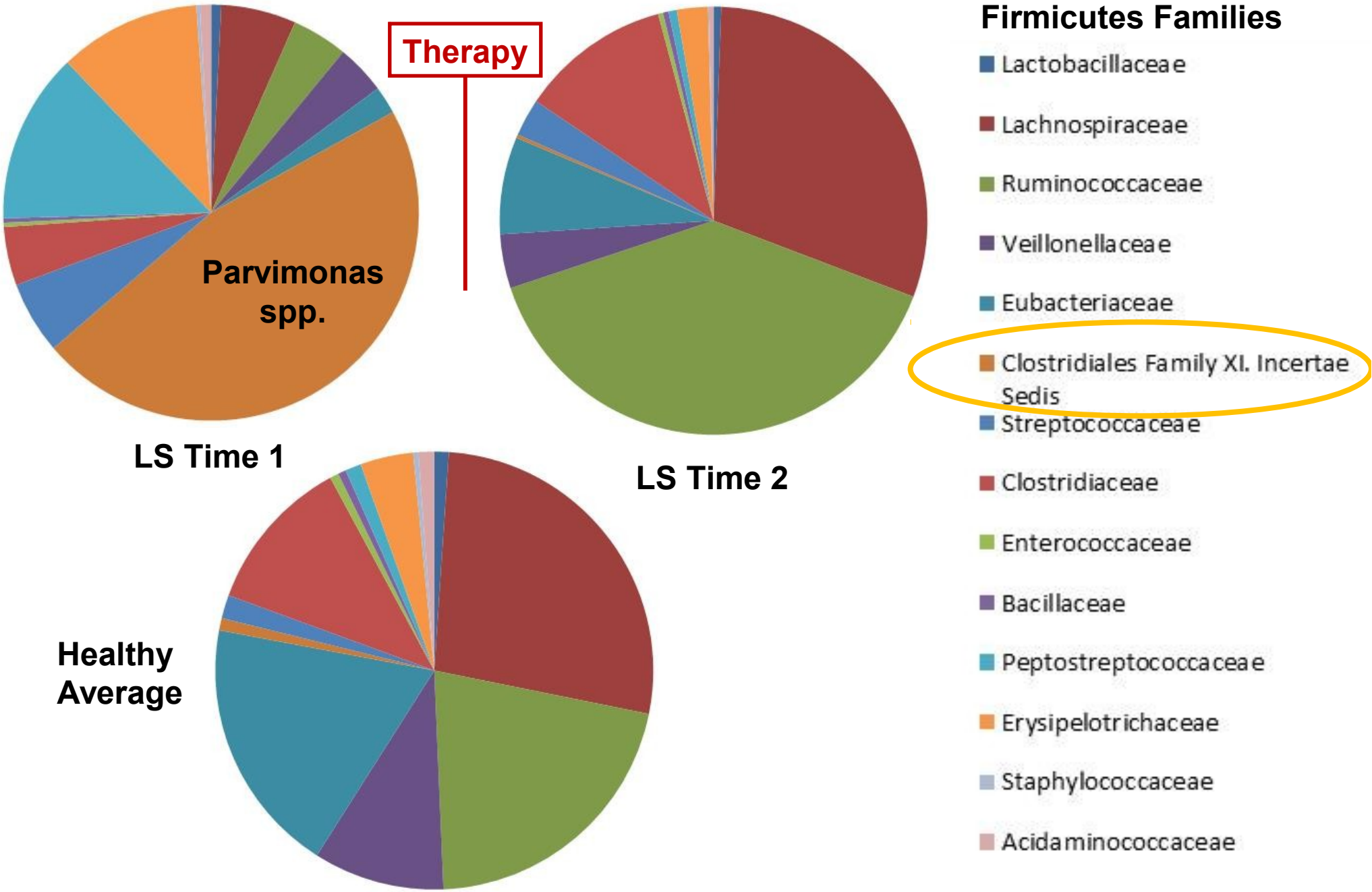
Lessons From Ecological Dynamics II:
Invasive Species Dominate After Major Species Destroyed



”In many areas following these burns invasive species are able to establish themselves, crowding out native species.”

Source: Ponderosa Pine Fire Ecology
http://cpluhna.nau.edu/Biota/ponderosafire.htm

Rare Firmicutes Bloom in Colon Disappearing After Antibiotic/Immunosuppressant Therapy



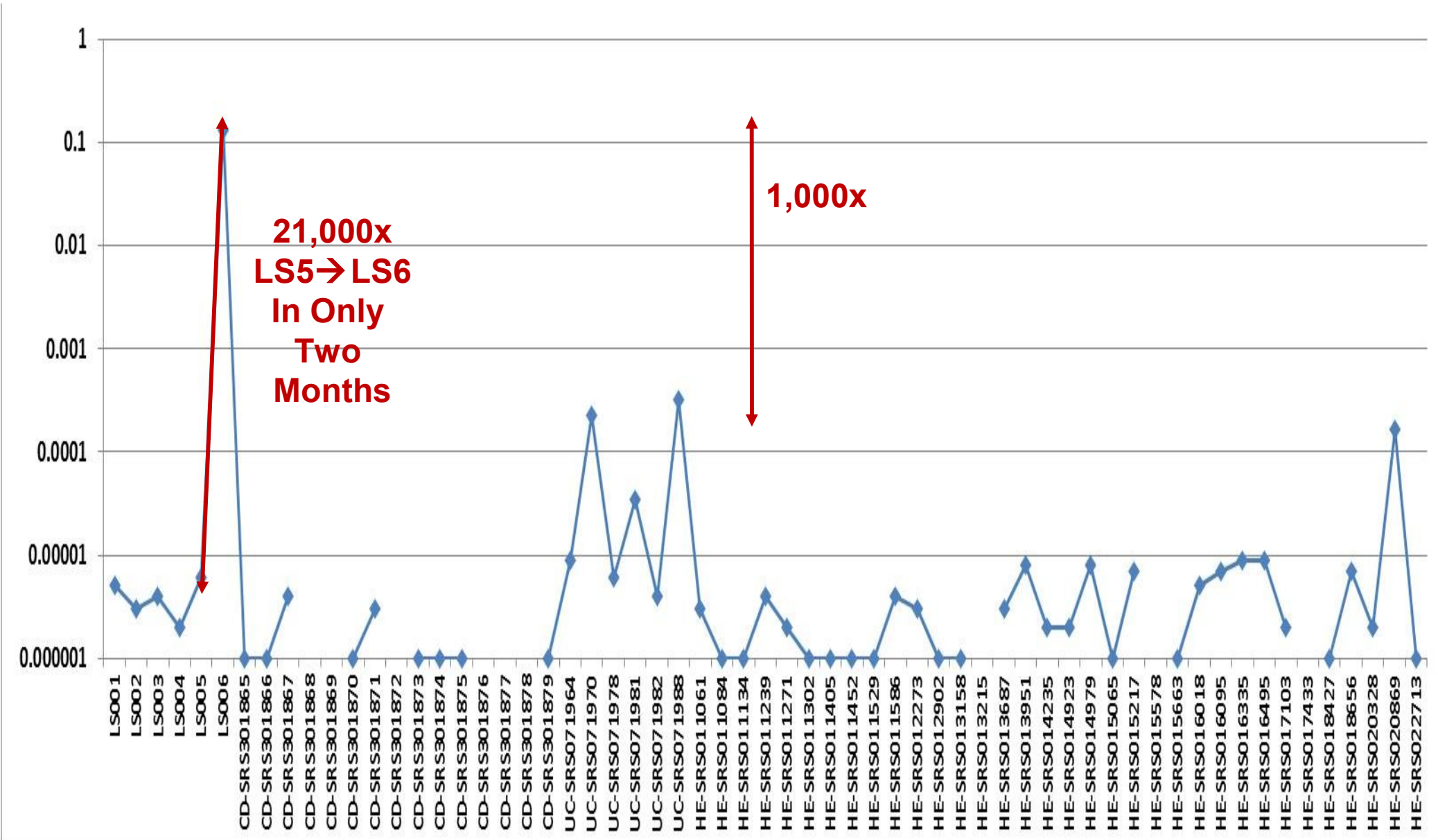
Lessons From Ecological Dynamics III: From Equilibrium to Chaos

In addition to chaos,
other forms of complex dynamics,
such as regular oscillations & quasiperiodic oscillations,
are preeminent features of many biological systems.

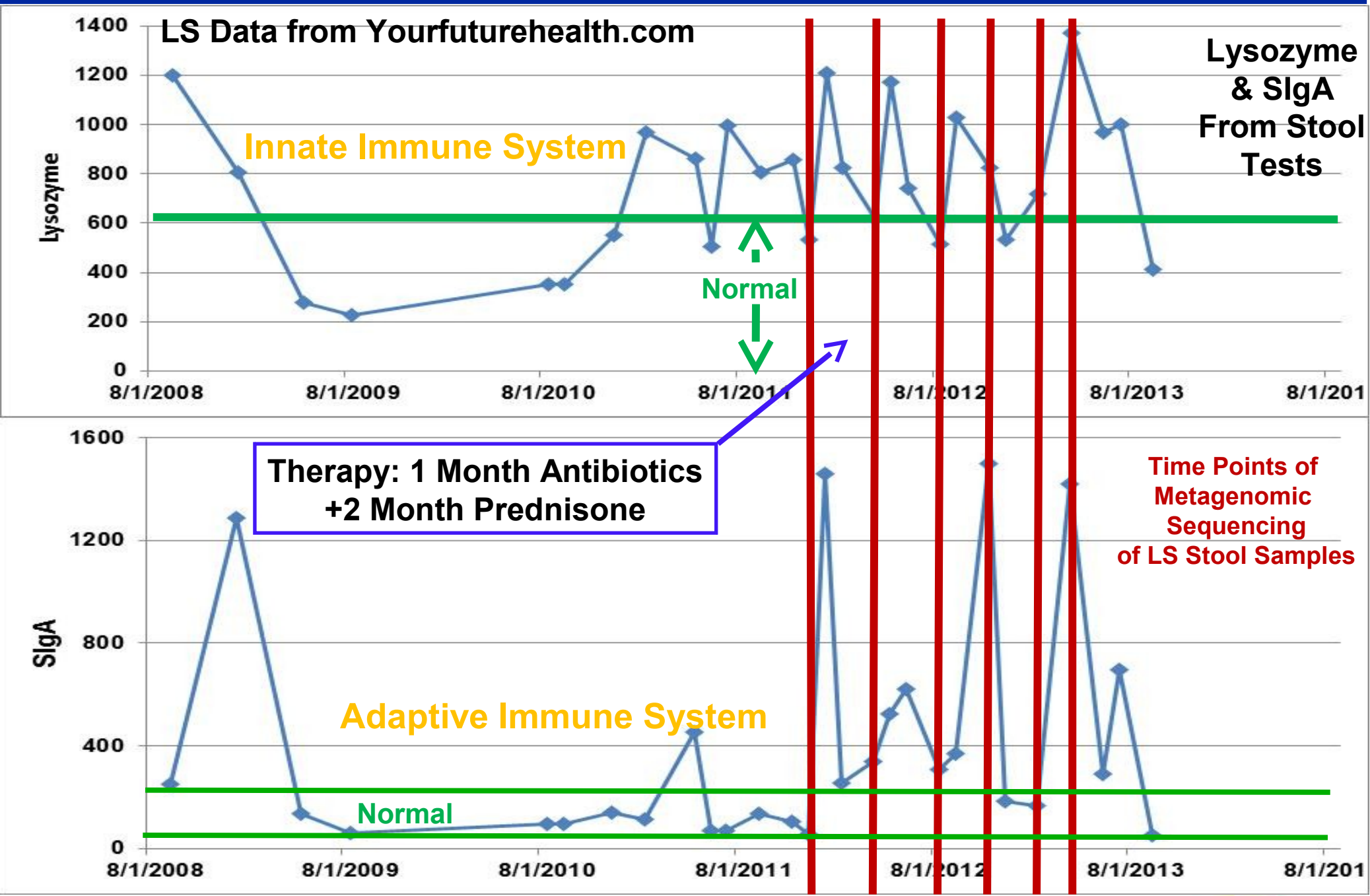
- From "Biological Chaos and Complex Dynamics"
David A. Vasseur
Oxford Bibliographies Online

Chaos: Large Fast Changes From Small Initial Conditions: Dramatic Bloom of Enterobacteriaceae bacterium 9_2_54FAA

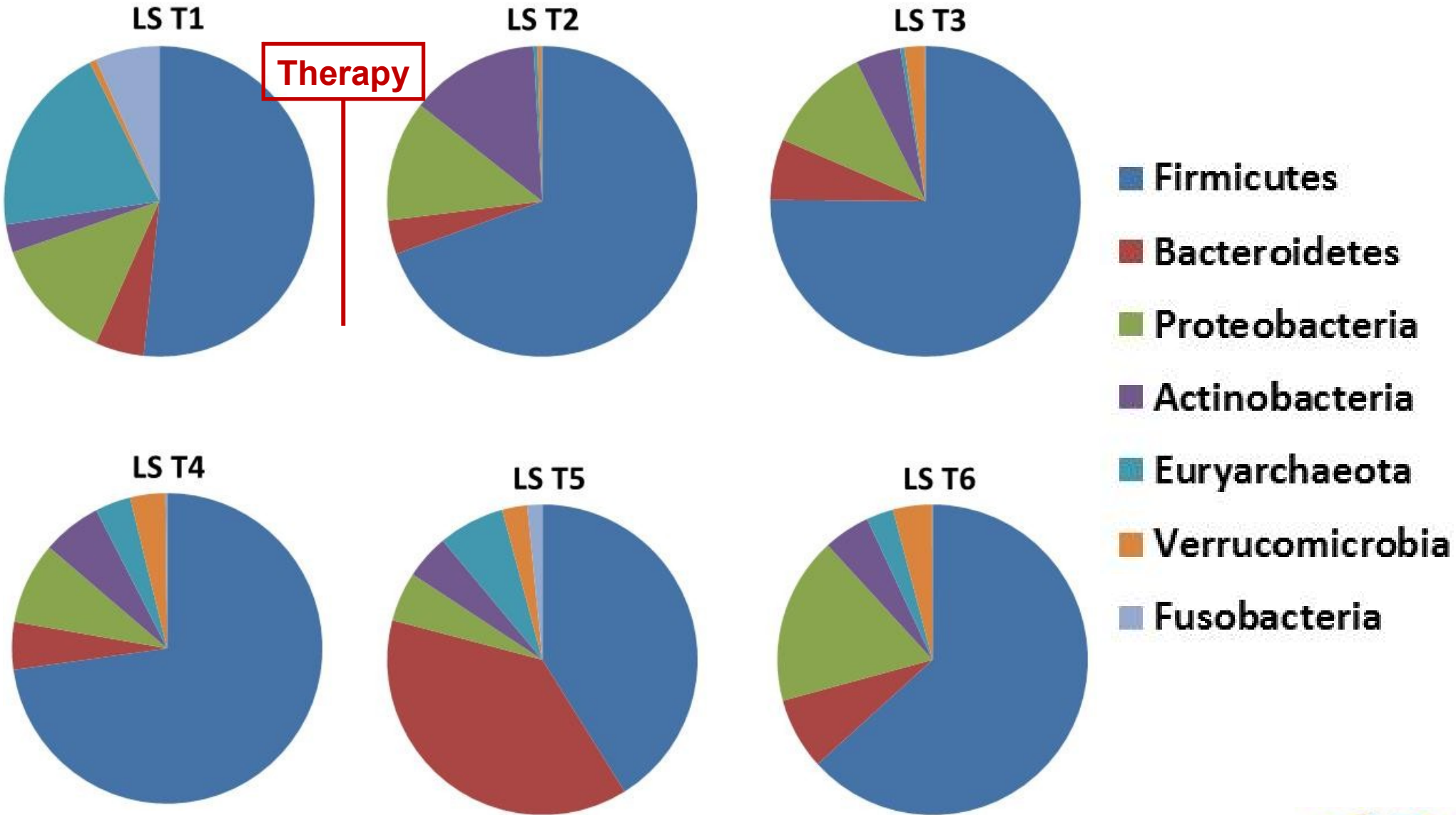
This Microbe is a Proteobacteria Targeted by the NIH HMP



Fine Time Resolution Sampling Revealed Regular Oscillations of the Innate and Adaptive Immune System



Time Series Reveals Autoimmune Dynamics of Gut Microbiome by Phyla



Six Metagenomic Time Samples Over 16 Months

Next Step: Time Series of Metagenomic Gut Microbiomes and Immune Variables in an N=100 Clinic Trial

Goal: Understand the Dynamics of
The Coupled Human Immune-Microbiome System

From Quantified Self to National-Scale Biomedical Research Projects

DELSA

DATA-ENABLED LIFE SCIENCES ALLIANCE

Accelerate the impact of

Data-Enabled Life Sciences Research

on the pressing needs of the global society.

The Quantified Human Initiative is an effort to combine our natural curiosity about self with new research paradigms. **Rich datasets of two individuals, Drs. Smarr and Snyder**, serve as 21st century personal data prototypes.

My Anonymized Human Genome is Available for Download

Personal Genome Project



www.delsaglobal.org

www.personalgenomes.org

it²

We Will See This Techniques Become Widespread Over the Next Ten Years

All of These Technologies Are Getting Exponentially Cheaper and Faster!

Thanks to Our Great Team!

UCSD Metagenomics Team

Weizhong Li
Sitao Wu

JCVI Team

Karen Nelson
Shibu Yooseph
Manolito Torralba

Calit2@UCSD Future Patient Team

Jerry Sheehan
Tom DeFanti
Kevin Patrick
Jurgen Schulze
Andrew Prudhomme
Philip Weber
Fred Raab
Joe Keefe
Ernesto Ramirez



SDSC Team

Michael Norman
Mahidhar Tatineni
Robert Sinkovits

UCSD Health Sciences Team

William J. Sandborn
Elisabeth Evans
David Brenner