“Exploring Our Inner Universe Using Supercomputers and Gene Sequencers”

Physics Department Colloquium

UC San Diego

October 24, 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

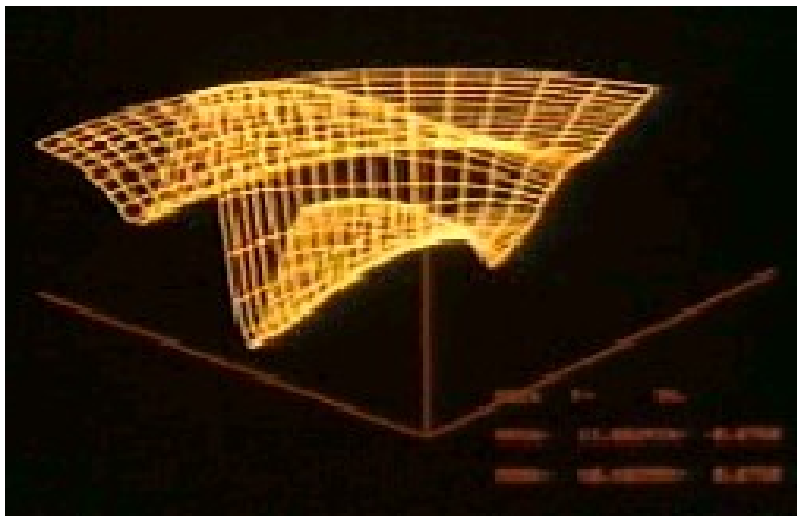
http://lsmarr.calit2.net

Abstract

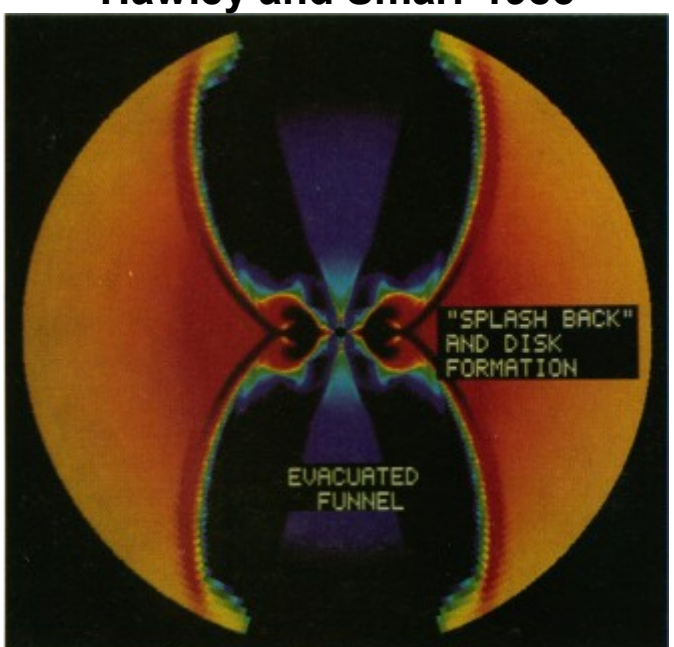
Having spent 25 years exploring computational and observational astrophysics, I have recently started using this physics perspective to explore our inner universe. Note that while our Milky Way galaxy contains 100 billion stars, each of our human bodies contains 1000 times as many microbes. Until recently, we knew more about our galaxy's stellar distribution than we did about the ecological distribution of our human microbiome. However, that is rapidly changing because of the million-fold reduction in cost of genome sequencing over the last 15 years. I will give an overview of the vast diversity of this microbial universe and then show how our research team has used deep genome sequencing, combined with large amounts of SDSC supercomputer time, to map out the time changing landscape of my own gut microbiome. In a healthy state, the microbiome is in homeostasis with the body's immune system, but as I will demonstrate, people with certain human genetic pre-dispositions can develop autoimmune diseases, in which components of the immune system and the distribution of microbial species undergo wild oscillations. This new found ability to "read out" the state of our superorganism body and its time rate of change is leading to an integrated system biology, detailed computational models, and hopefully new classes of therapies.

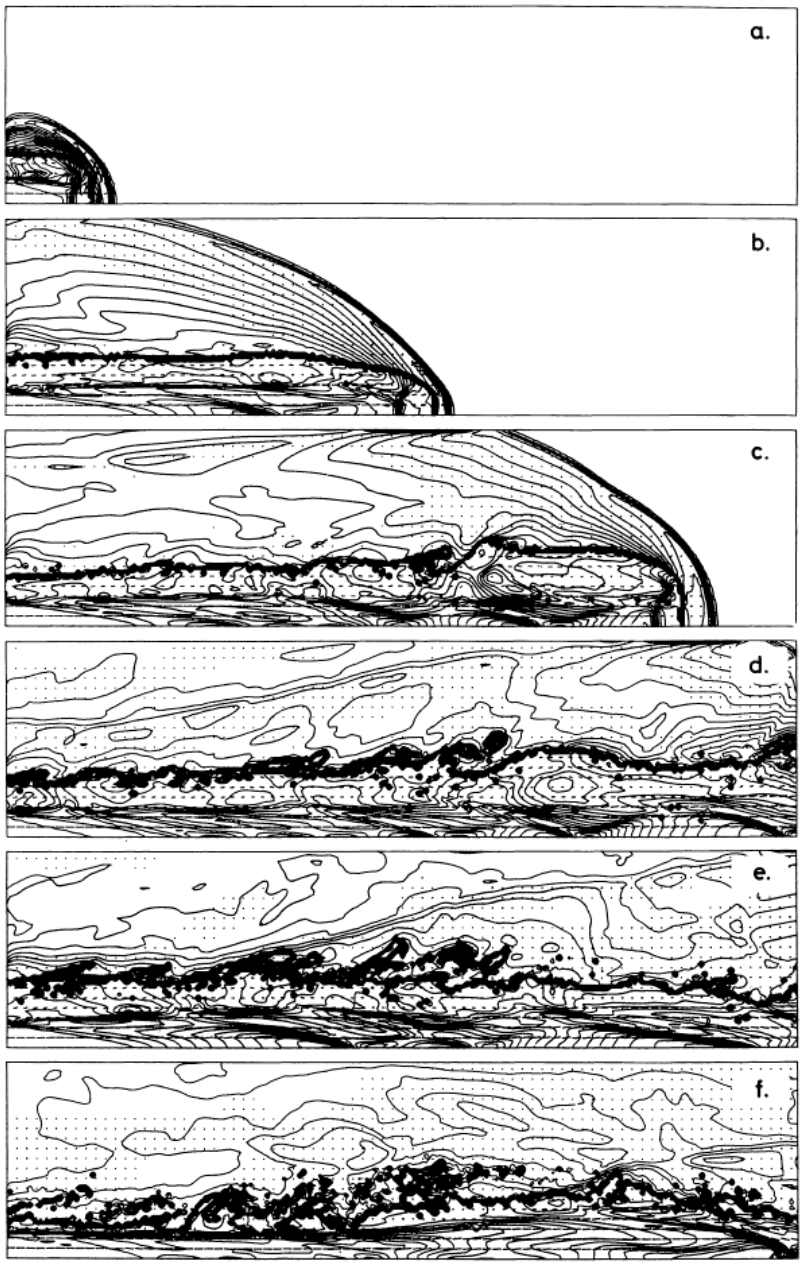
My Early Research was on Computational Astrophysics – I Learned To Think About Nonlinear Dynamic Systems

Eppley and Smarr 1977



Hawley and Smarr 1985





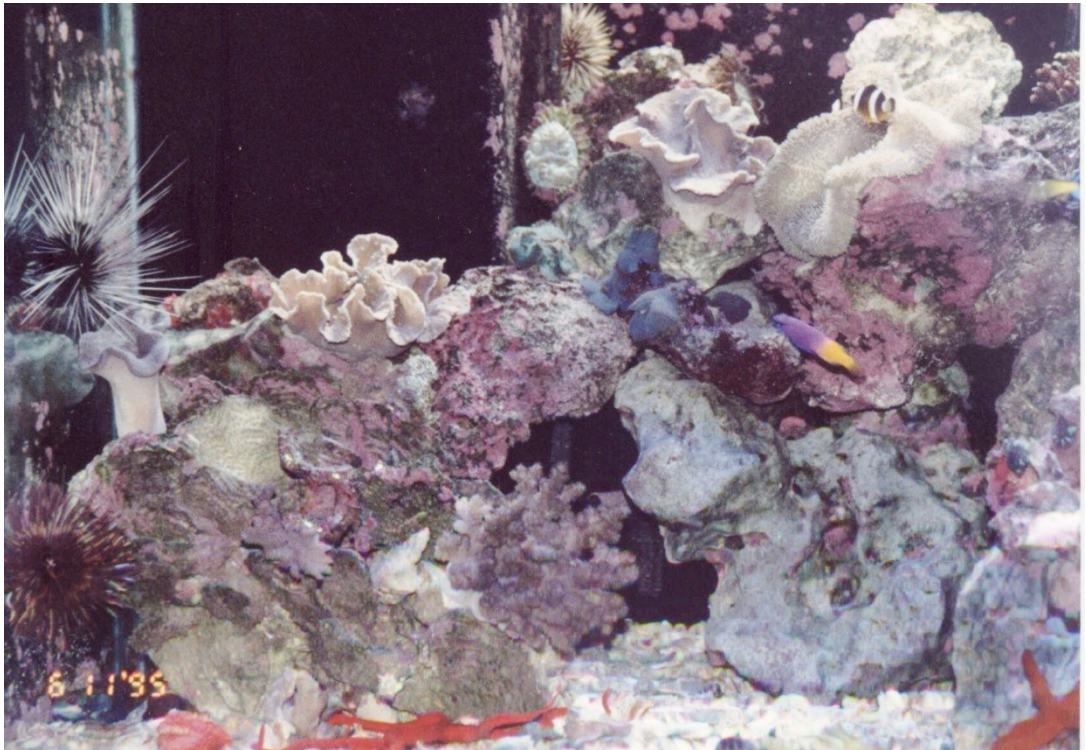
Norman, Winkler, Smarr, Smith 1982

I Spent Years in Illinois Experimentally Studying the Stability and Instabilities of Multi-Phyla Ecosystems





120 Gallon Home Salt Water Coral Reef Aquarium



I Arrived in La Jolla in 2000 After 20 Years in the Midwest and Decided to Move Against the Obesity Trend

Age 41



Age 51



Age 61



I Reversed My Body's Decline By Quantifying and Altering Nutrition and Exercise

http://lsmarr.calit2.net/repository/LS_reading_recommendations_FiRe_2011.pdf

From Measuring Macro-Variables to Measuring Your Internal Variables

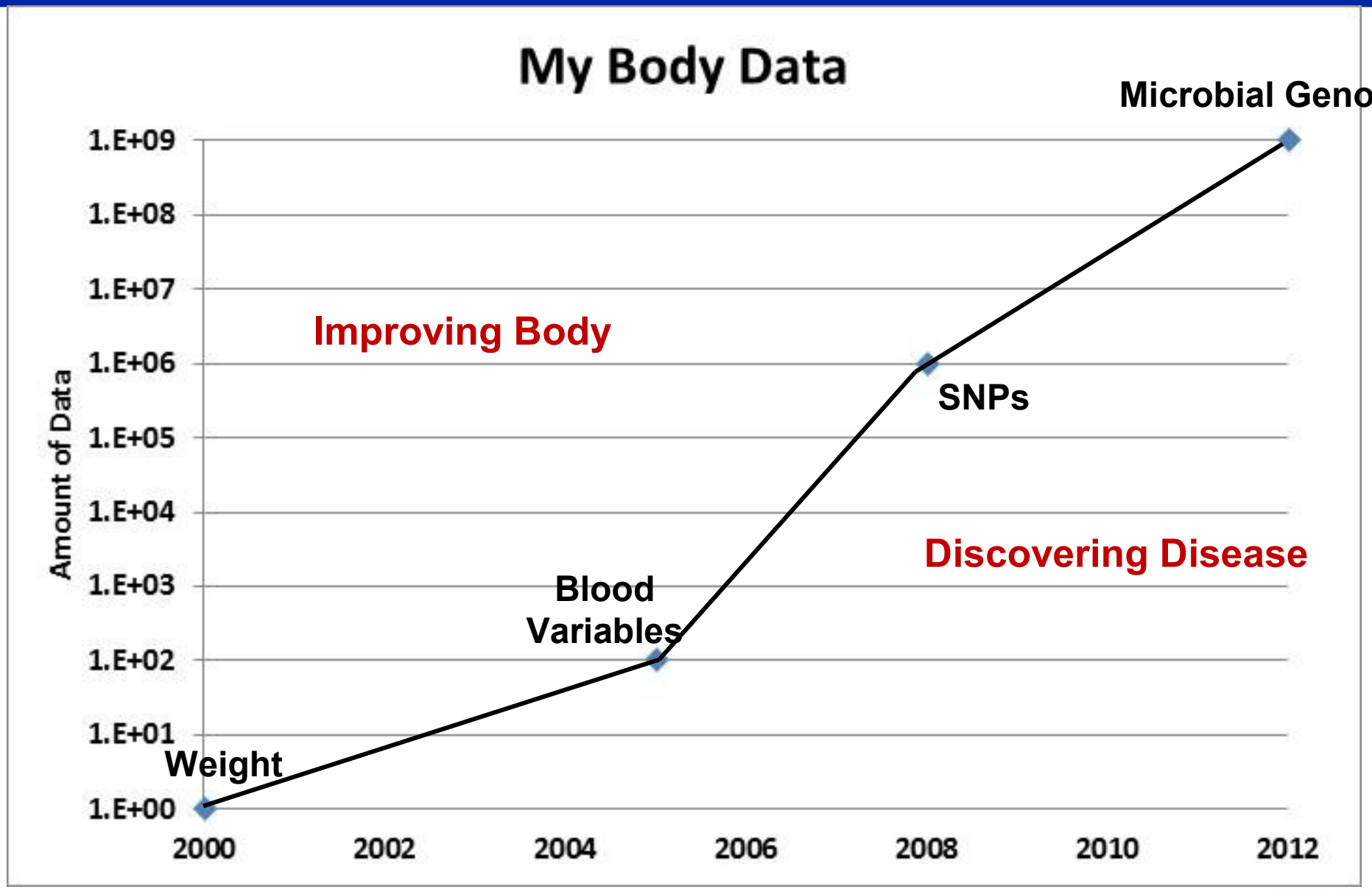


The Patient of the Future

Internet pioneer Larry Smarr's quest to quantify everything about his health led him to a startling discovery, an unusual partnership with his doctor, and more control over his life.

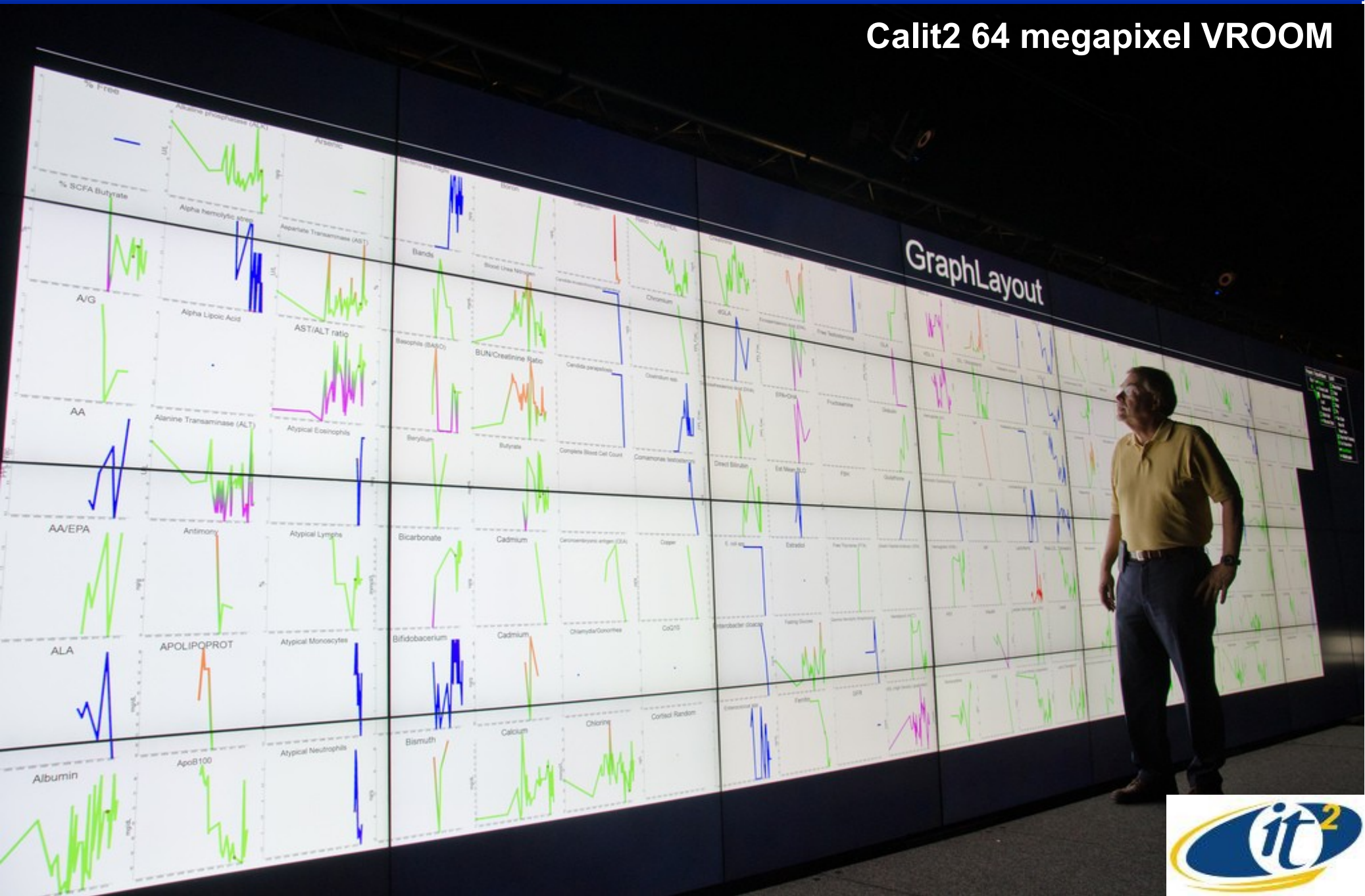
www.technologyreview.com/biomedicine/39636

From One to a Billion Data Points Defining Me: The Exponential Rise in Body Data in Just One Decade!

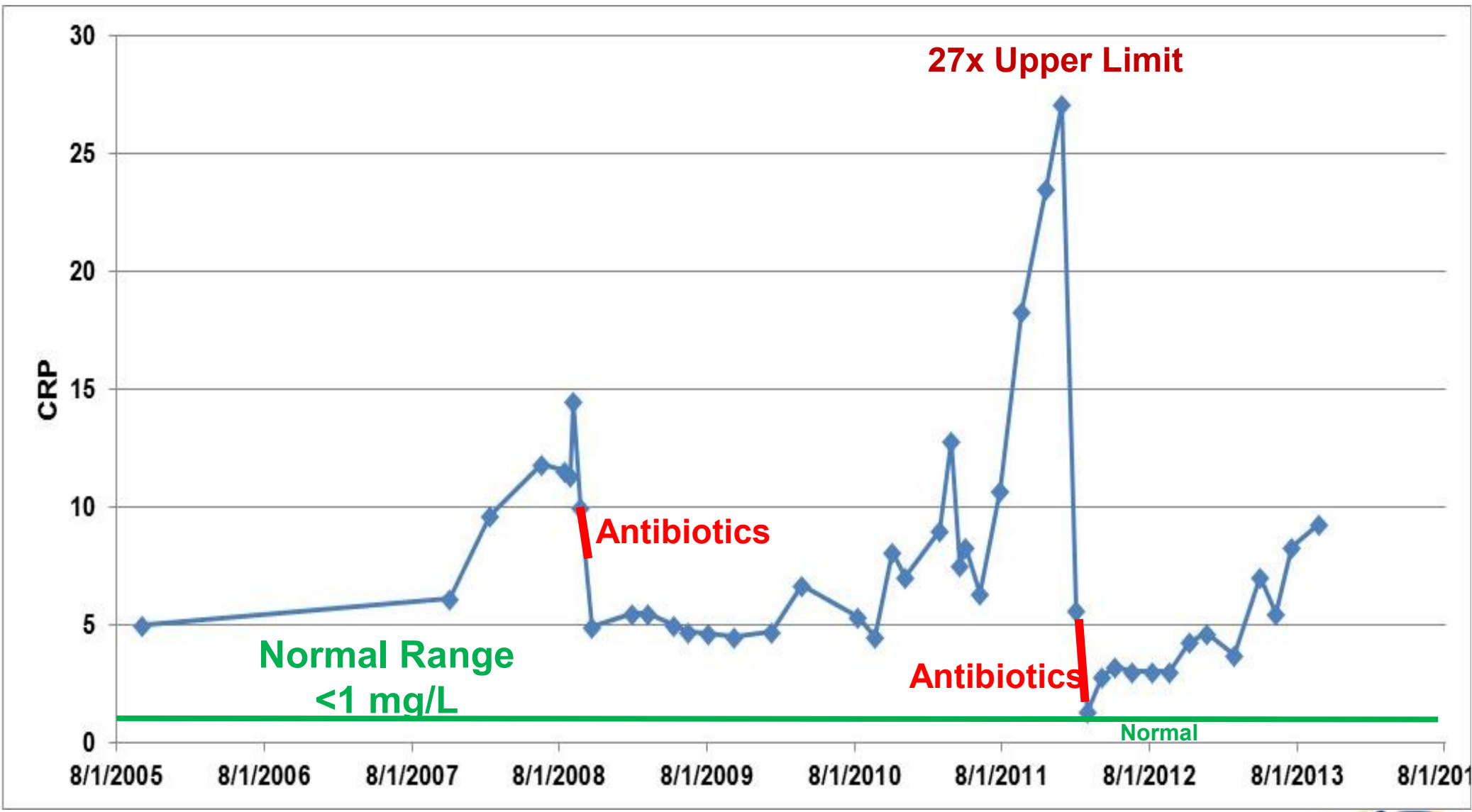


Each is a Personal Time Series
And Compared Across Population

Visualizing Time Series of 150 LS Blood and Stool Variables, Each Over 5-10 Years

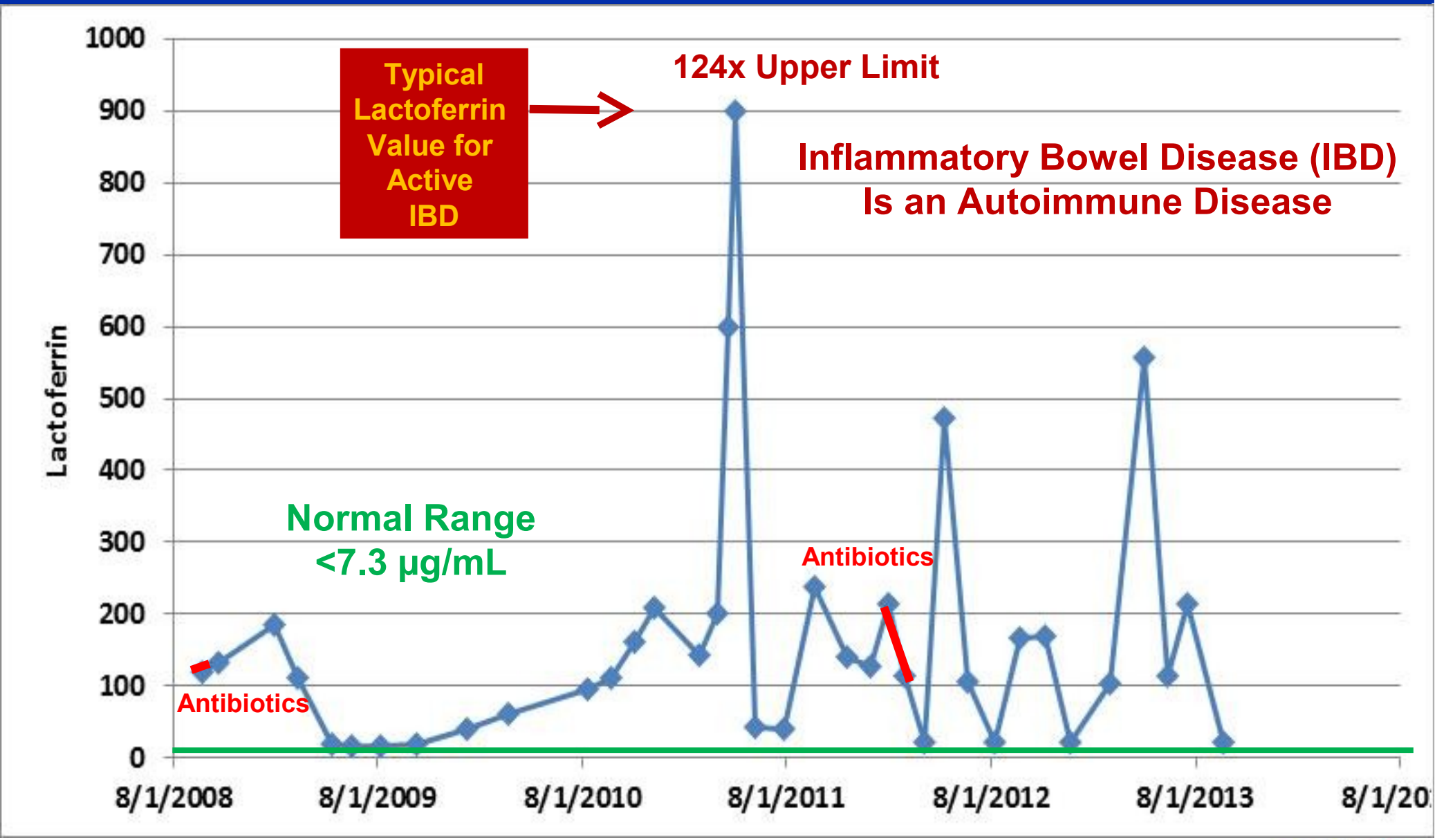


I Discovered I Had Episodic Chronic Inflammation by Tracking Complex Reactive Protein In My Blood Samples



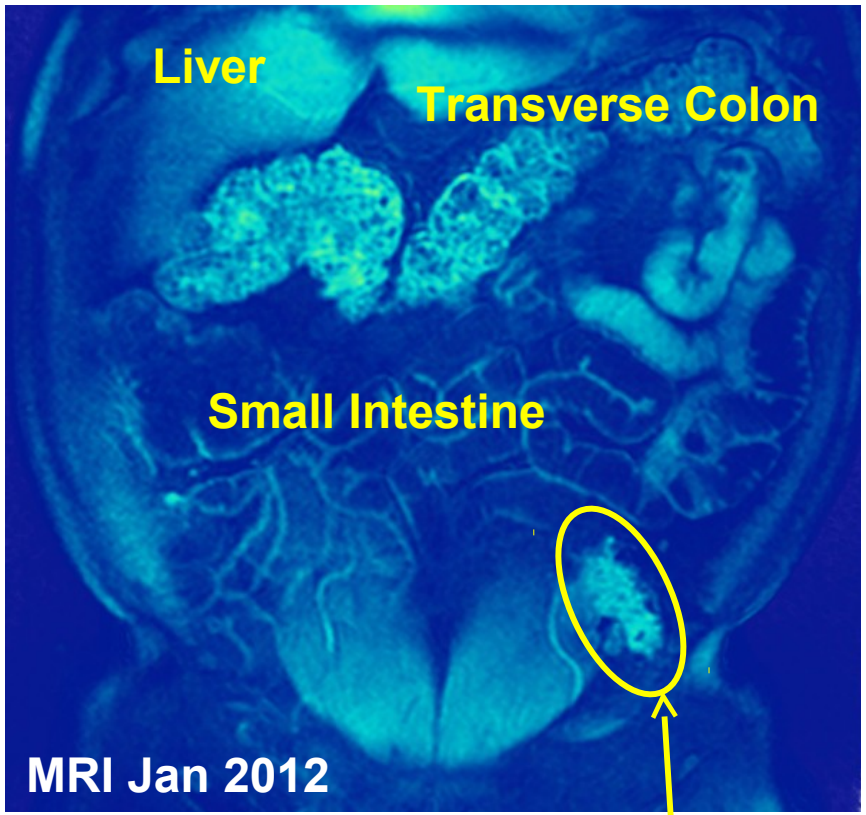
CRP is a Generic Measure of Inflammation in the Blood

By Adding Stool Samples, I Discovered I Had High Levels of the Protein Lactoferrin



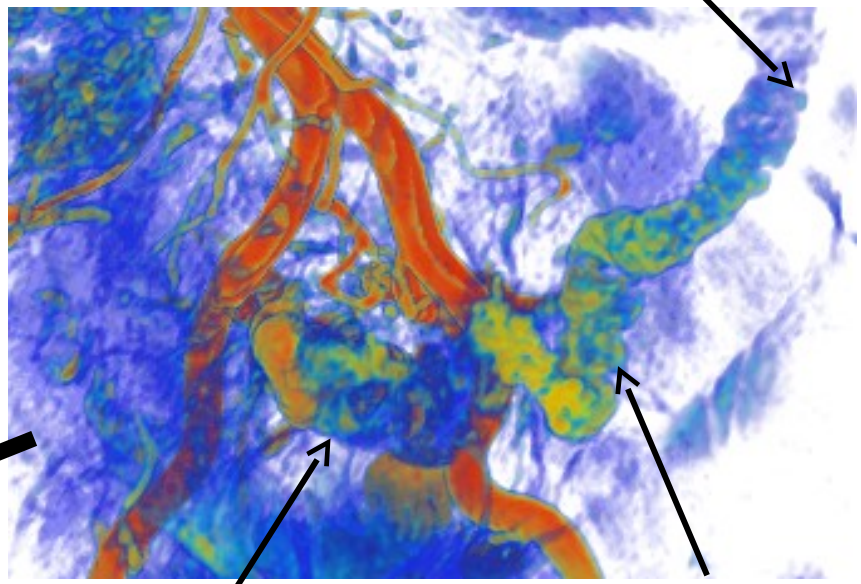
Lactoferrin is a Protein Shed from Neutrophils - An Antibacterial that Sequesters Iron

Confirming the IBD Hypothesis: Finding the "Smoking Gun" with MRI Imaging



I Obtained the MRI Slices From UCSD Medical Services and Converted to Interactive 3D Working With Calit2 Staff & DeskVOX Software

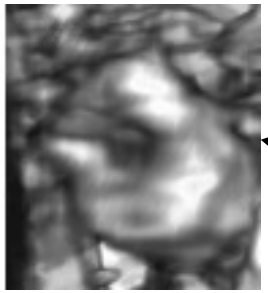
Descending Colon



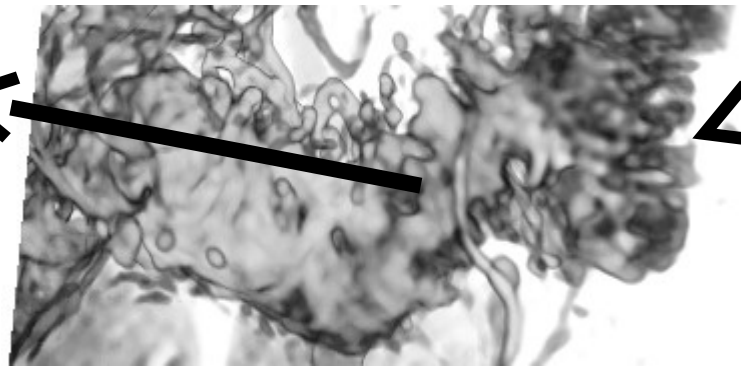
Major Kink

Sigmoid Colon Threading Iliac Arteries

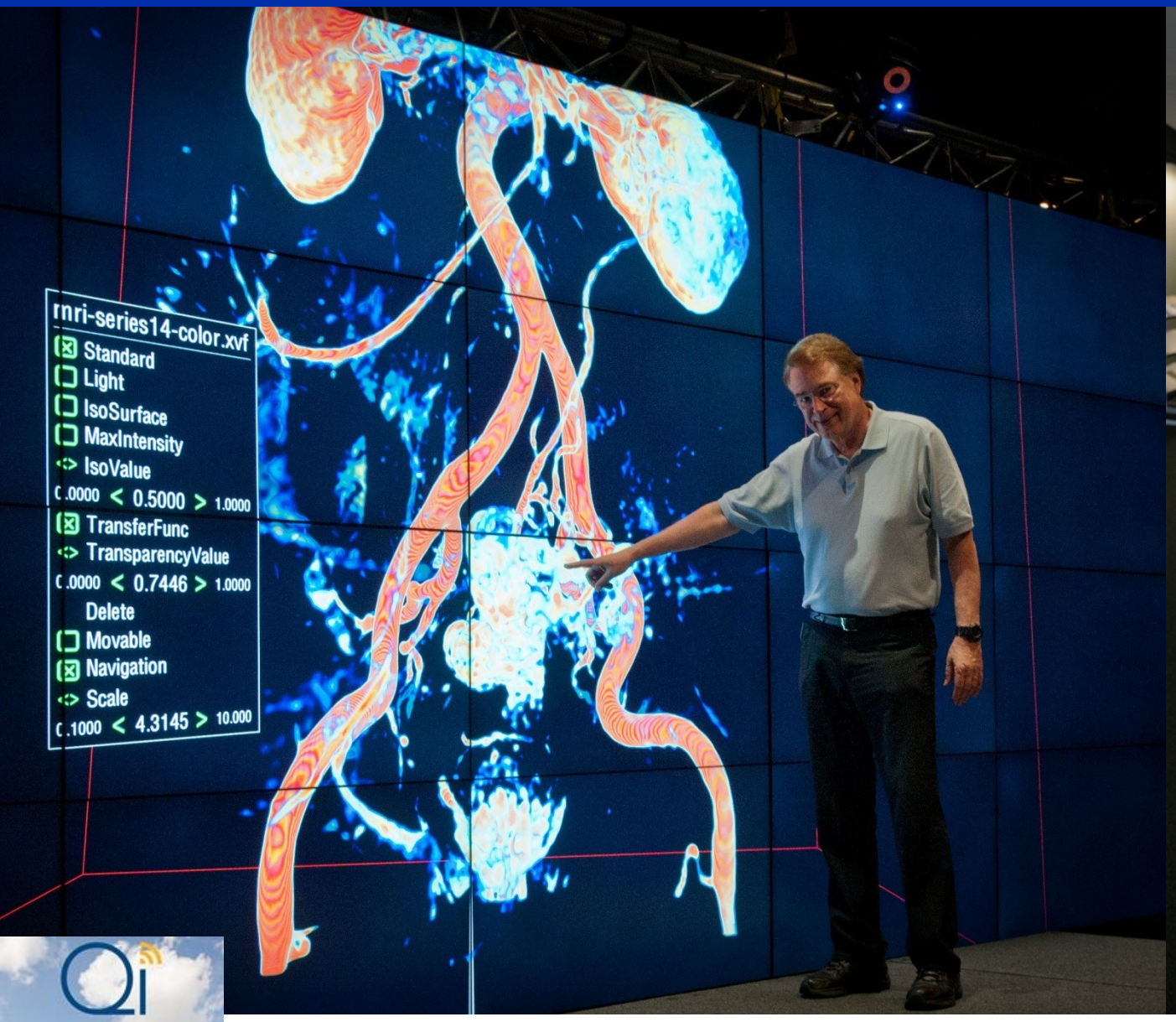
Cross Section



Diseased Sigmoid Colon



Converting MRI Slices Into 3D Interactive Virtual Reality AND 3-D Printing







Research: Calit2 FutureHealth Team

Why Did I Have an Autoimmune Disease like IBD?

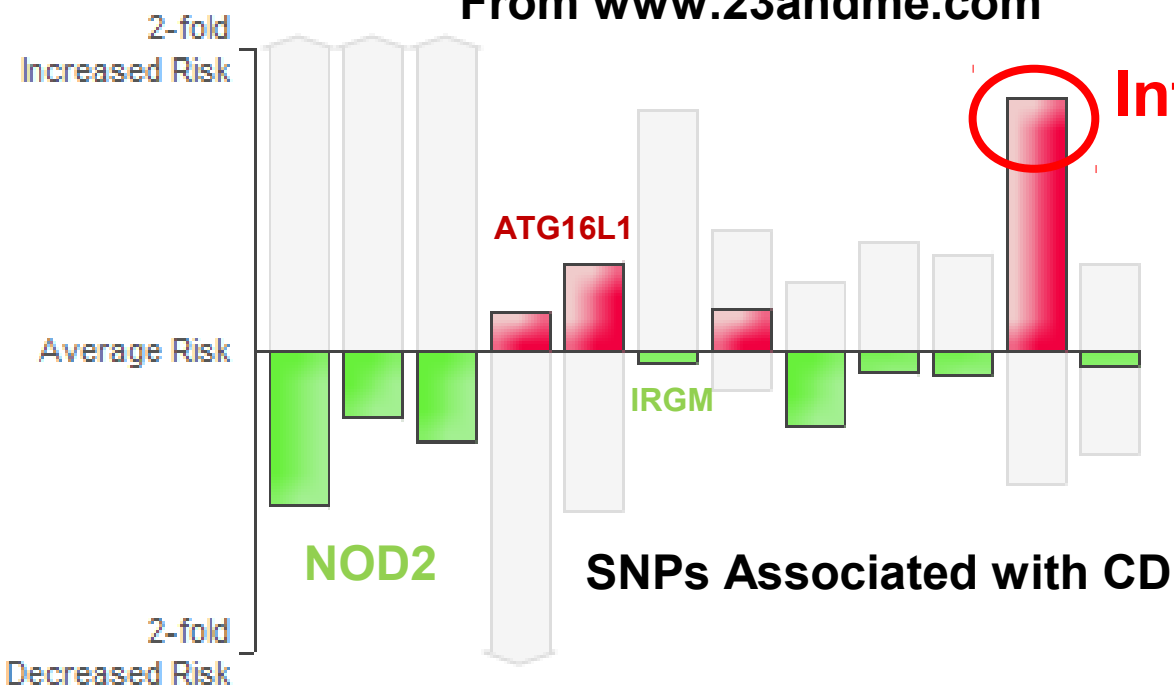
Despite decades of research,
the etiology of Crohn's disease
remains unknown.
Its pathogenesis may involve
a complex interplay between
host genetics,
immune dysfunction,
and microbial or environmental factors.
--*The Role of Microbes in Crohn's Disease*

So I Set Out to Quantify All Three!

Paul B. Eckburg & David A. Relman
Clin Infect Dis. 44:256-262 (2007)

I Wondered if Crohn's is an Autoimmune Disease, Did I Have a Personal Genomic Polymorphism?

From www.23andme.com



Polymorphism in Interleukin-23 Receptor Gene — 80% Higher Risk of Pro-inflammatory Immune Response

Now Comparing 163 Known IBD SNPs with 23andme SNP Chip

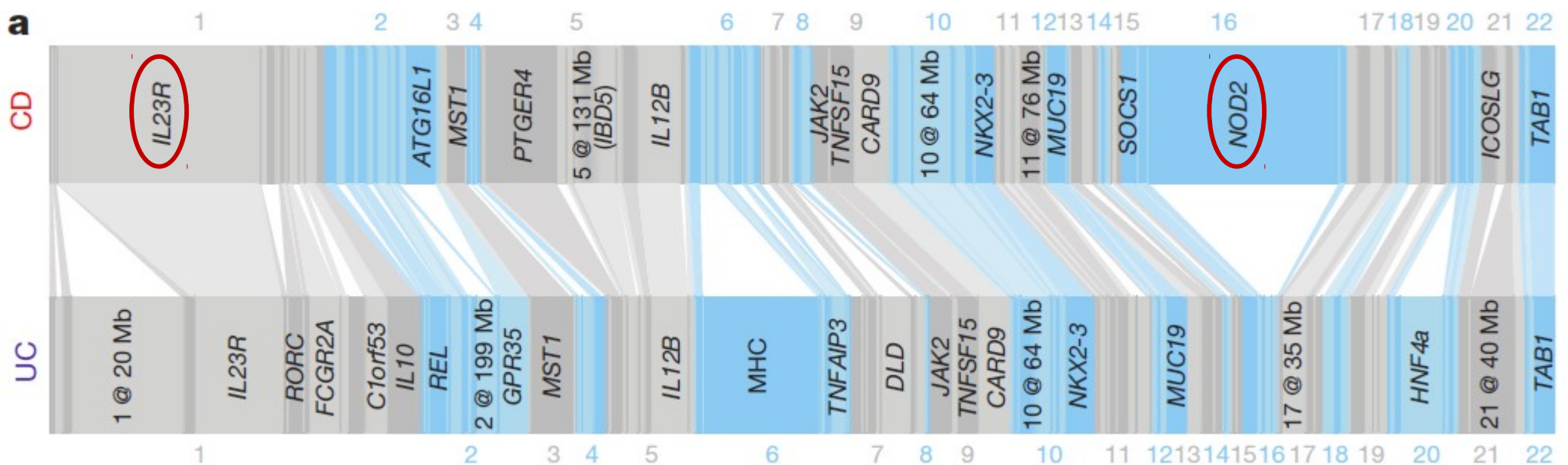
News and Views

Nature Medicine **13**, 26 - 28 (2007)
doi:10.1038/nm0107-26

IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

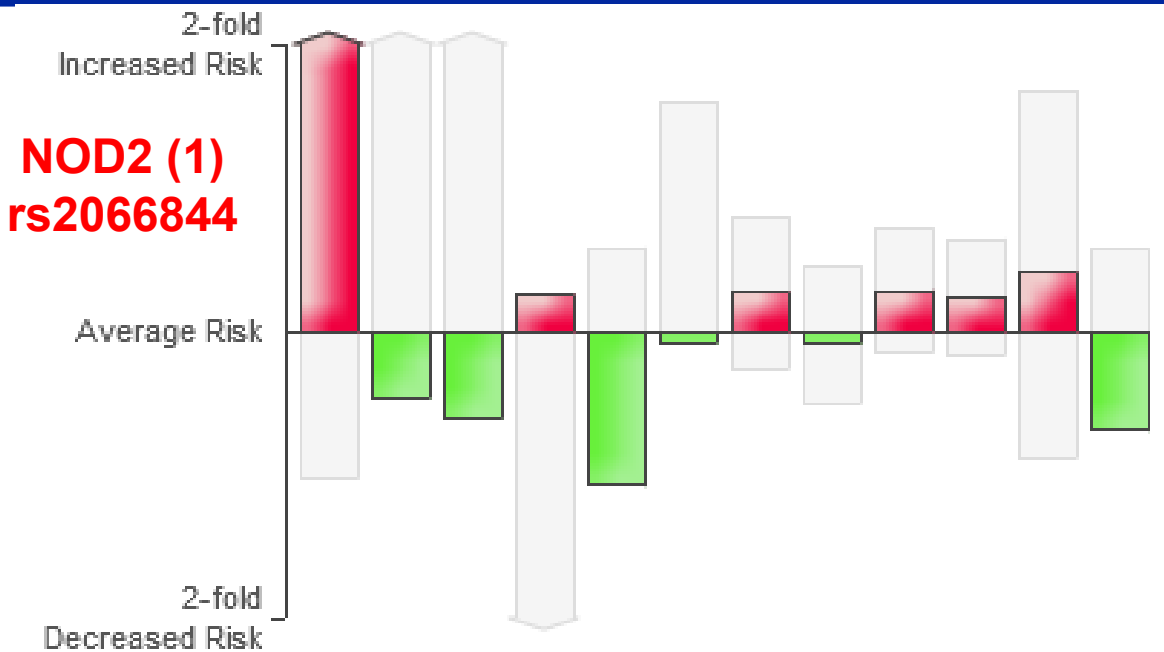
Variance Explained by Each of the 163 SNPs Associated with IBD



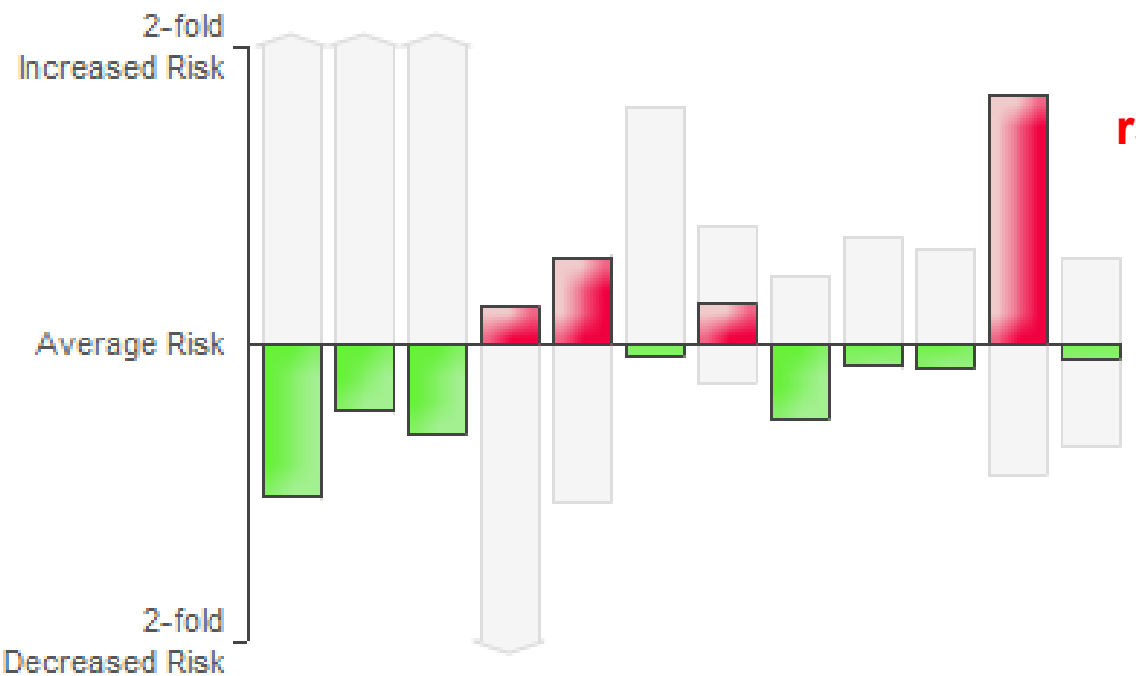
- The width of the bar is proportional to the variance explained by that locus
- Bars are connected together if they are identified as being associated with both phenotypes
- Loci are labelled if they explain more than 1% of the total variance explained by all loci

"Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease," Jostins, et al. Nature 491, 119-124 (2012)

Crohn's May be a Related Set of Diseases Driven by Different SNPs



Female
CD Onset
At 20-Years Old



Il-23R
rs1004819

Me-Male
CD Onset
At 60-Years Old

I Had My Full Human Genome Sequenced in 2012 - 1 Million/Year by 2015

Next Step: Compare Full Genome With IBD SNPs



PGP Used Complete Genomics, Inc. to Sequence my Human DNA

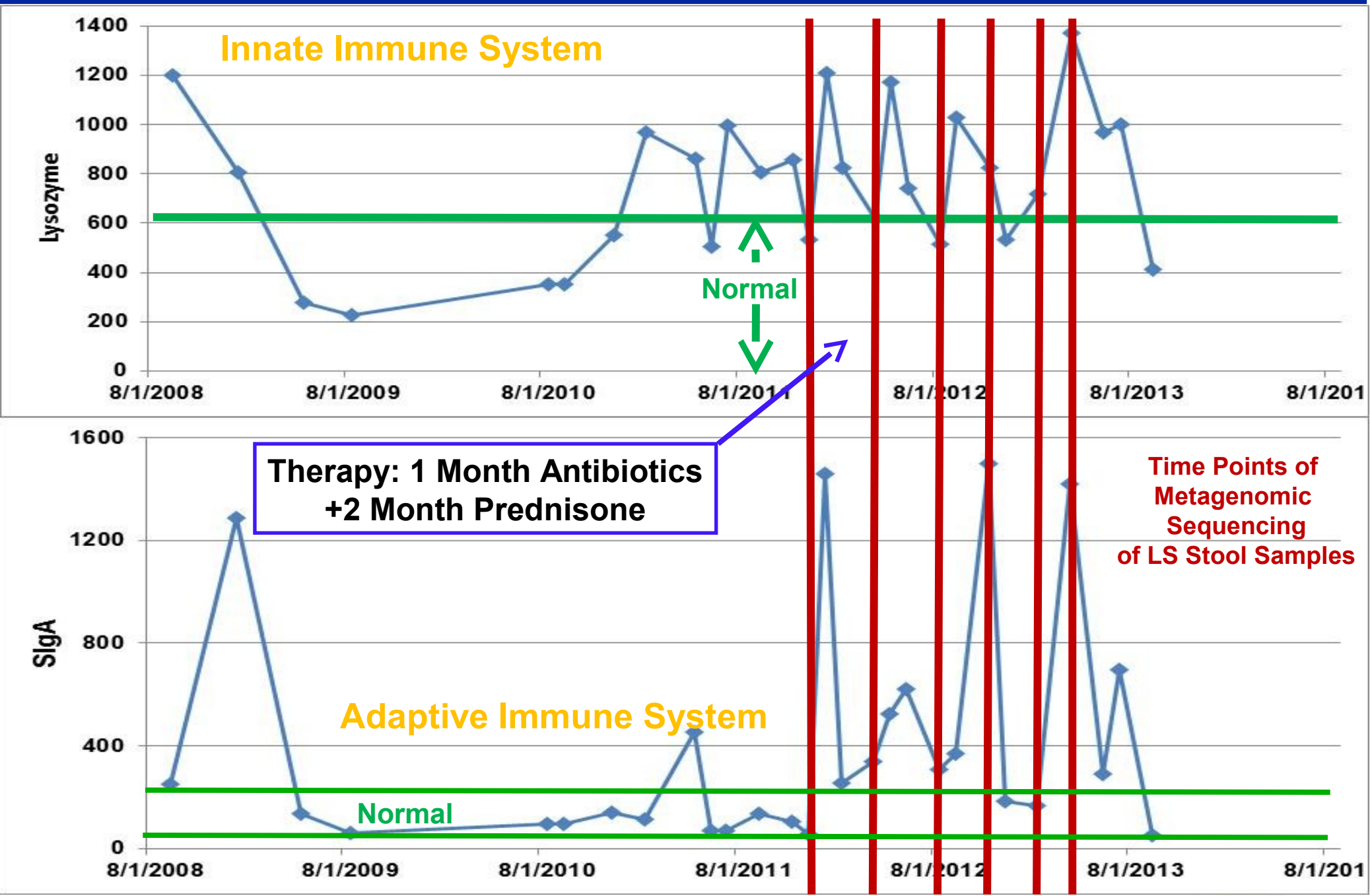
My Anonymized Human Genome is Available for Download

Personal Genome Project



www.personalgenomes.org

Fine Time Resolution Sampling Reveals Unexpected Oscillations of Innate and Adaptive Immune System

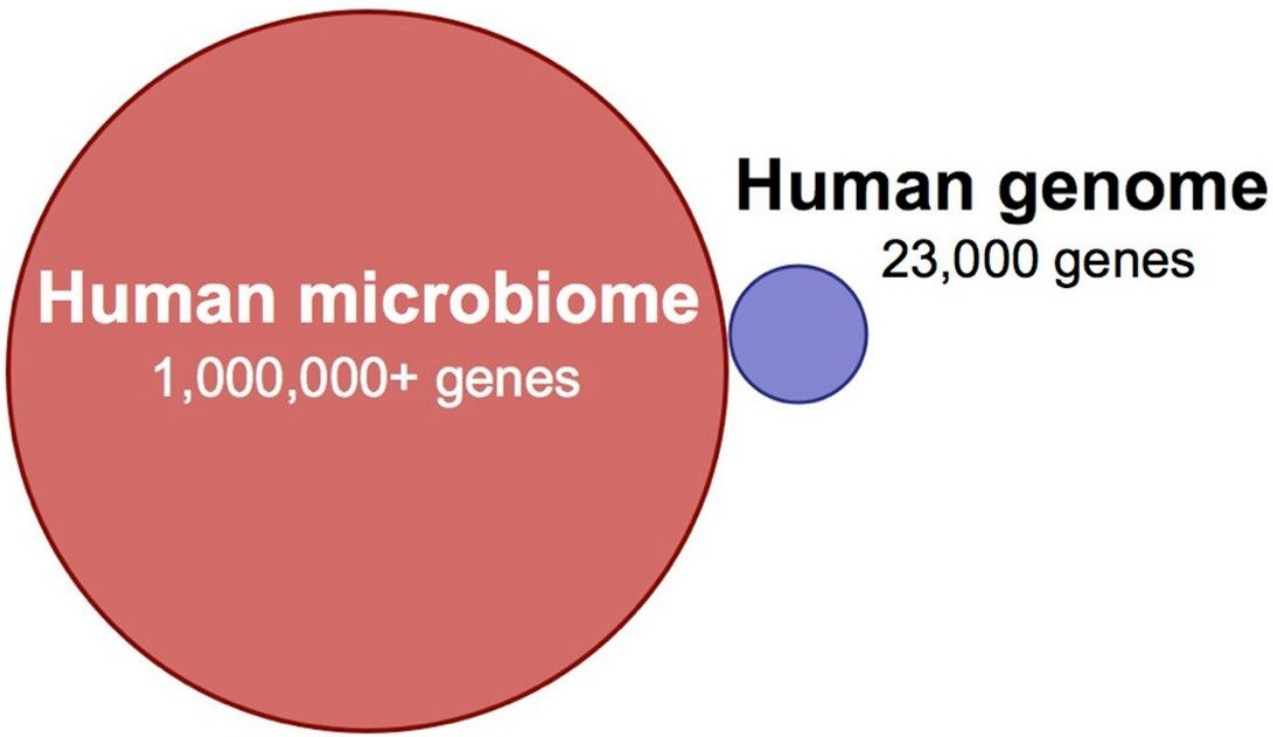


I Carried Out Observations in Optical, Radio, and X-Ray on the Andromeda Galaxy in the 1980s



Now I am Observing the 100 Trillion Non-Human Cells in My Body

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

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it²

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

All images from Wikimedia Commons.
Photos are public domain or by Trisha Shears & Richard Bartz

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



Phylum Chordata



Phylum Cnidaria



Phylum Echinodermata



Phylum Annelida



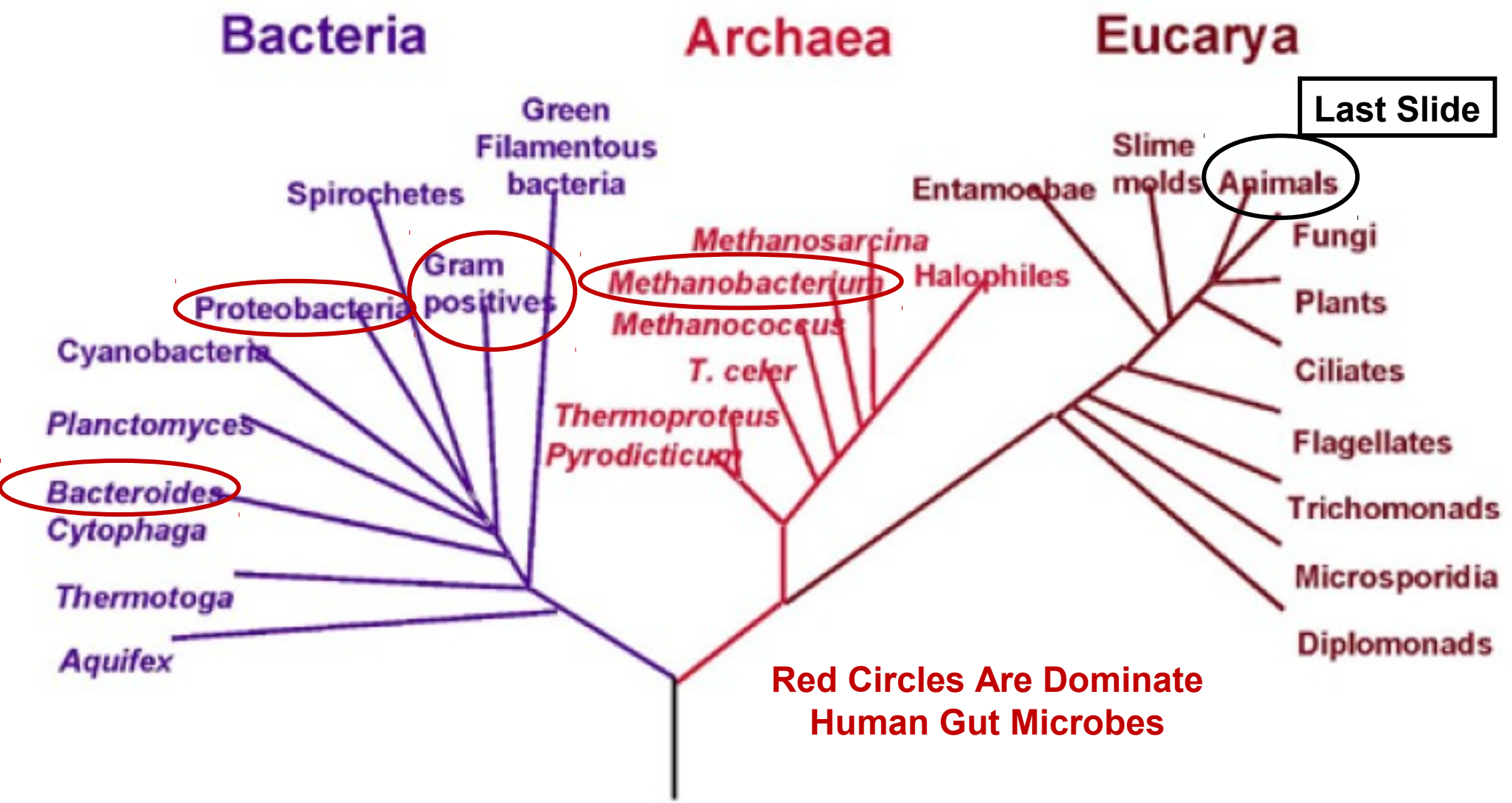
Phylum Mollusca



Phylum Arthropoda

All images from WikiMedia Commons.
Photos are public domain or by Dan Hershman, Michael Linnenbach, Manuae, B_cool

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



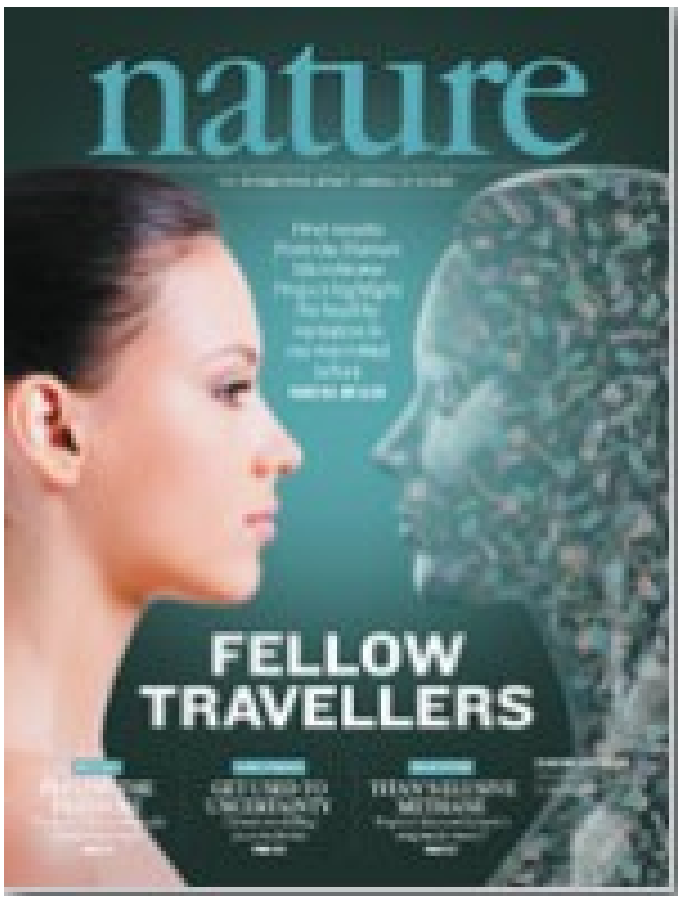
Evolutionary Distance Derived from Comparative Sequencing of 16S or 18S Ribosomal RNA

Source: Carl Woese, et al

Intense Scientific Research is Underway on Understanding the Human Microbiome



June 8, 2012



June 14, 2012

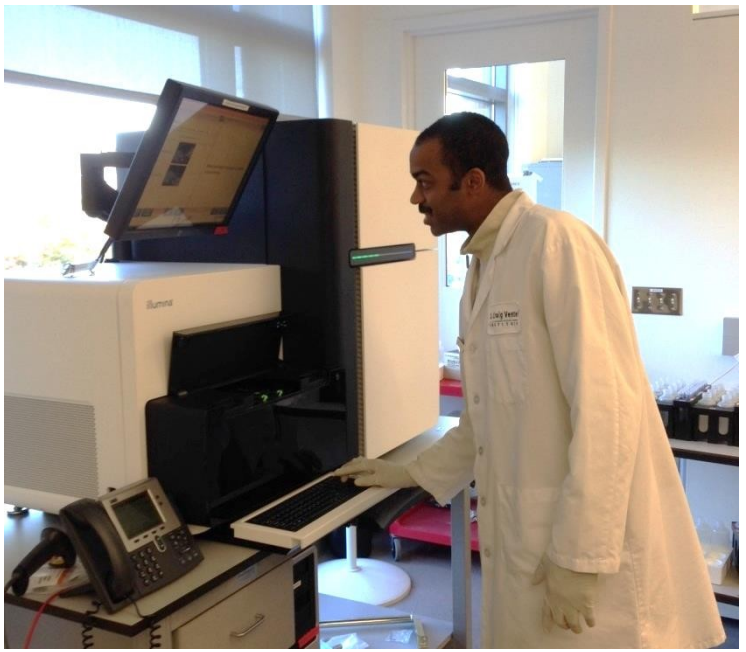
From Culturing Bacteria to Sequencing Them

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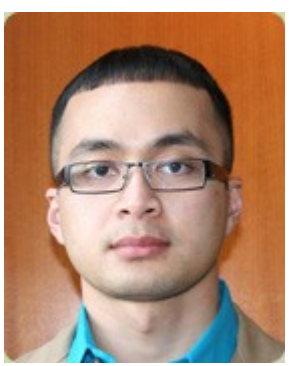
it²

J. Craig Venter Institute Performed Metagenomic Sequencing on Seven of My Stool Samples

- Sequencing on Illumina HiSeq 2000 at JCVI
  - Generates 100bp Reads
  - Run Takes ~14 Days
- My 7 Samples Produced
  - 190.2 Gbp of Data
- DNA Extraction Uses
  - Standard MOBio Powersoil DNA Extraction
- JCVI Lab Manager, Genomic Medicine
  - Manolito Torralba
- IRB PI Karen Nelson
  - President JCVI
- Funded by
  - UCSD Health Sciences & Harry E. Gruber Chair



Illumina HiSeq 2000 at JCVI



Manolito Torralba, JCVI



Karen Nelson, JCVI

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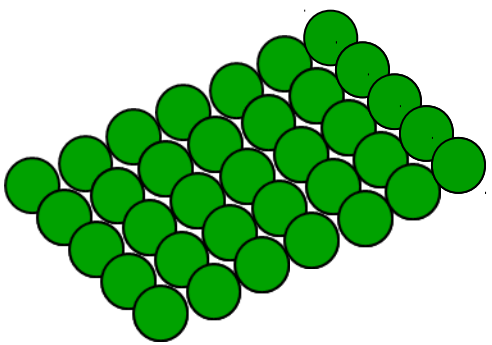
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Additional Phenotypes Added from NIH HMP For Comparative Analysis

Download Raw Reads
~100M Per Person

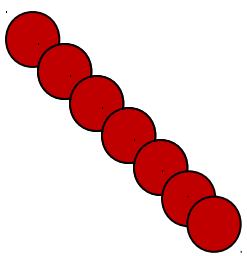
"Healthy" Individuals

35 Subjects
1 Point in Time



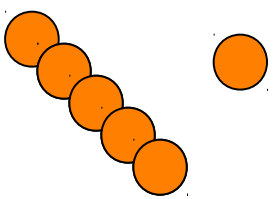
Larry Smarr

7 Points in Time

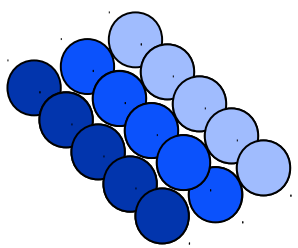


IBD Patients

2 Ulcerative Colitis Patients,
6 Points in Time



5 Ileal Crohn's Patients,
3 Points in Time



Total of 5 Billion Reads

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

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

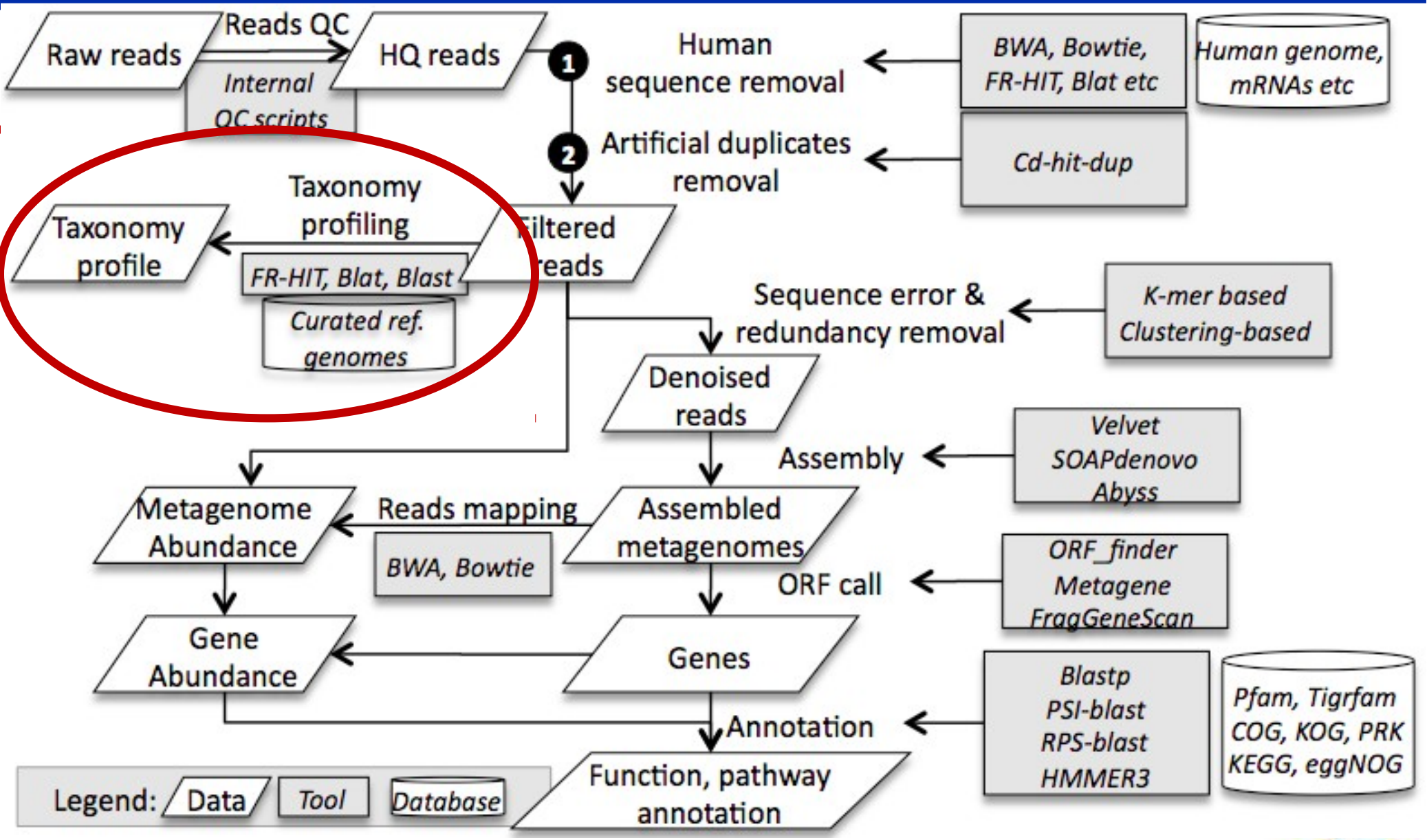
NIH

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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

- ~180,000 Core-Hrs on Gordon
  - KEGG function annotation: 90,000 hrs
  - Mapping: 36,000 hrs
    - Used 16 Cores/Node and up to 50 nodes
  - Duplicates removal: 18,000 hrs
  - Assembly: 18,000 hrs
  - Other: 18,000 hrs
- Gordon RAM Required
  - 64GB RAM for Reference DB
  - 192GB RAM for Assembly
- Gordon Disk Required
  - Ultra-Fast Disk Holds Ref DB for All Nodes
  - 8TB for All Subjects



SDSC

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

NSF NIH HMP

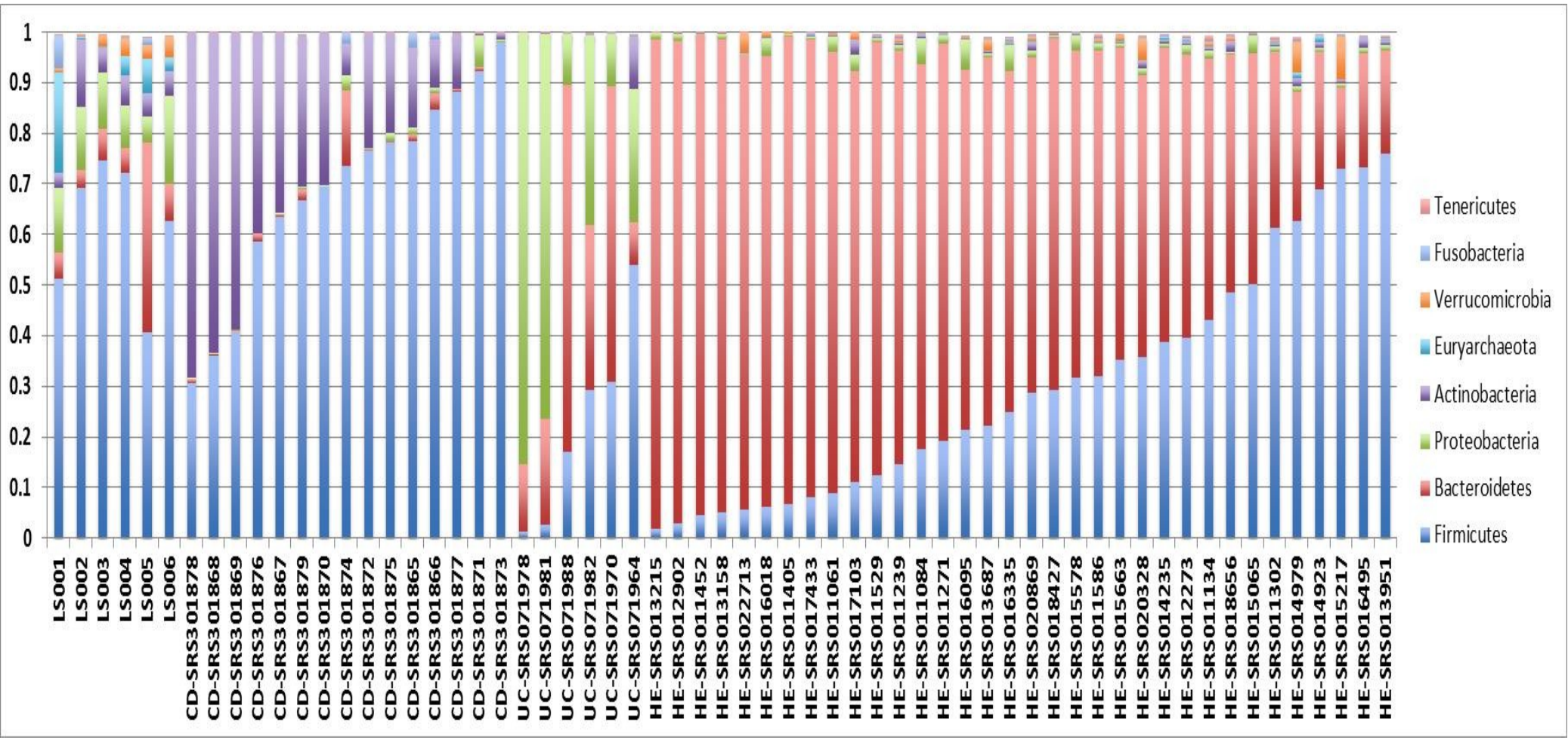
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CRBS it²

Weizhong Li, CRBS, UCSD

Phyla Gut Microbial Abundance Without Viruses: LS, Crohn's, UC, and Healthy Subjects

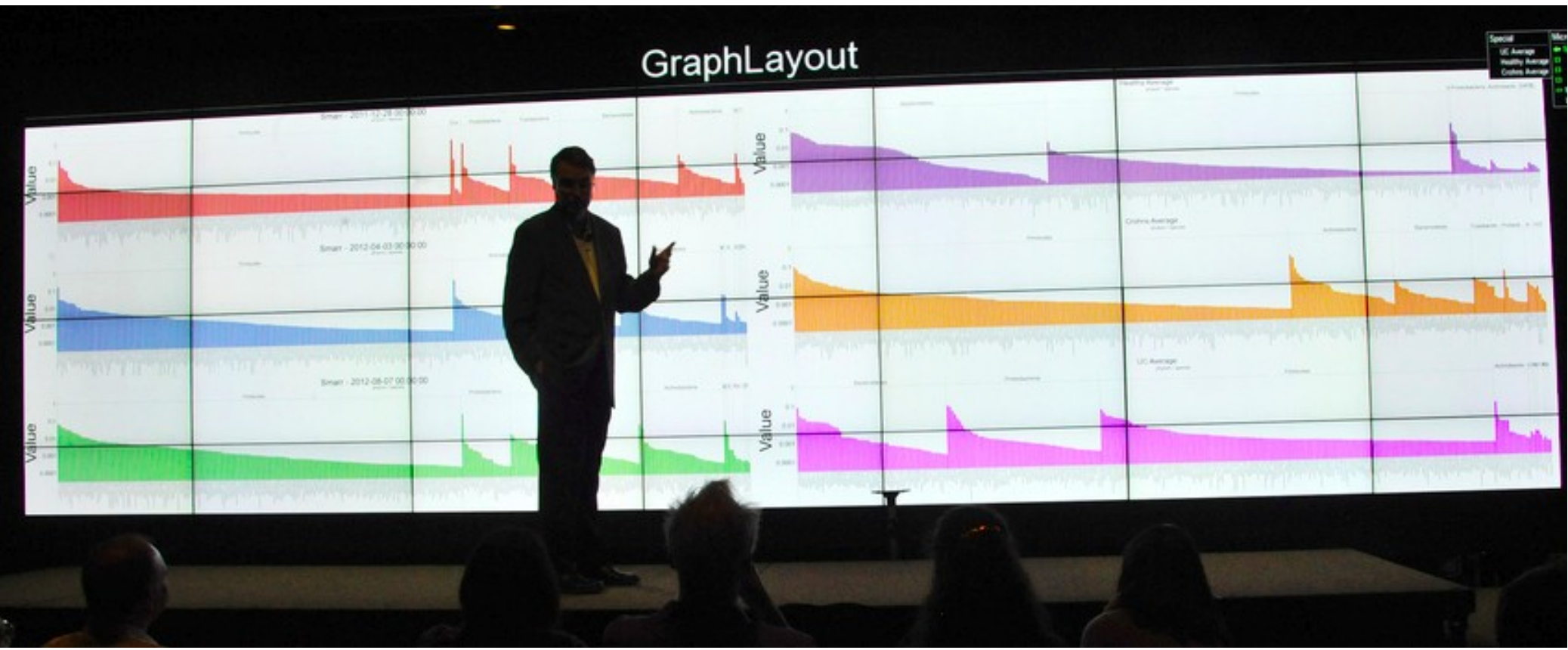
Source: Weizhong Li, Sitao Wu, CRBS, UCSD



LS **Crohn's** **Ulcerative Colitis** **Healthy**

Toward Noninvasive Microbial Ecology Diagnostics

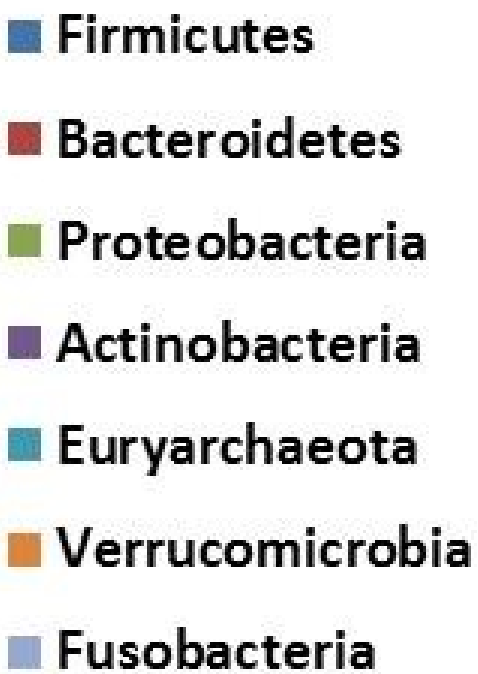
Using Scalable Visualization Allows Comparison of the Relative Abundance of 200 Microbe Species

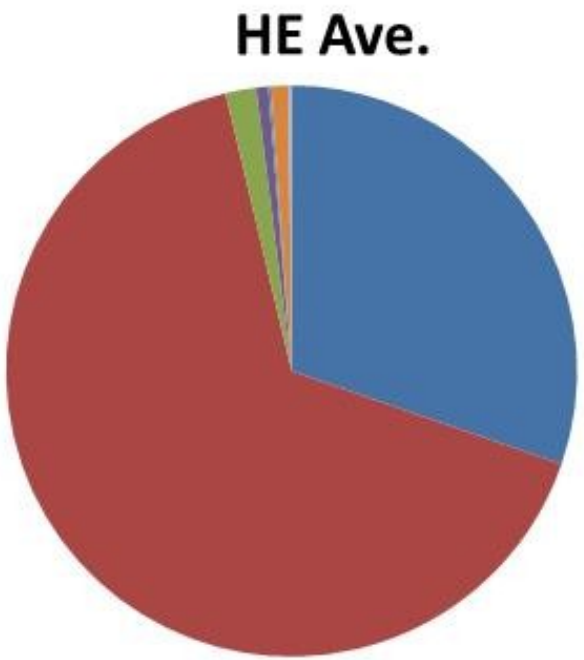


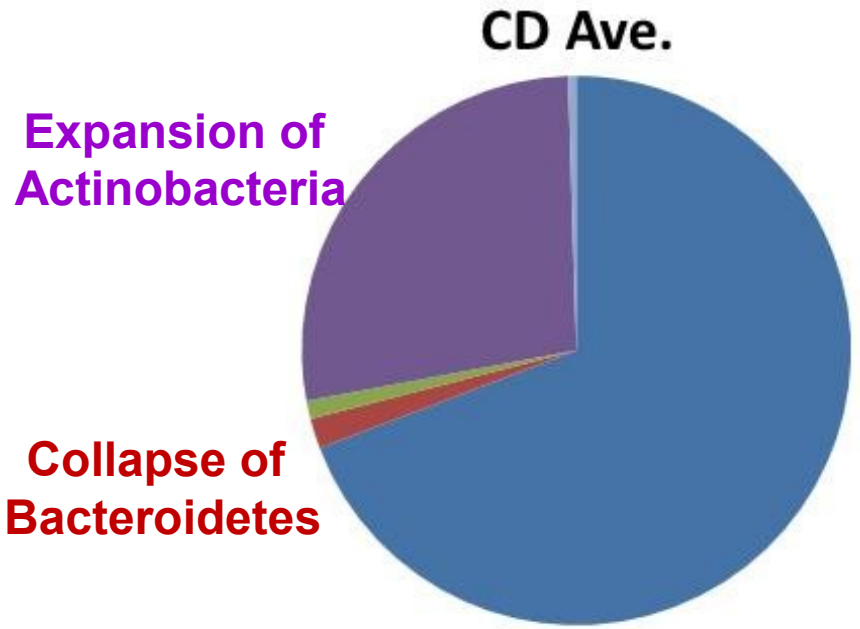
Comparing 3 LS Time Snapshots (Left)
with Healthy, Crohn's, UC (Right Top to Bottom)

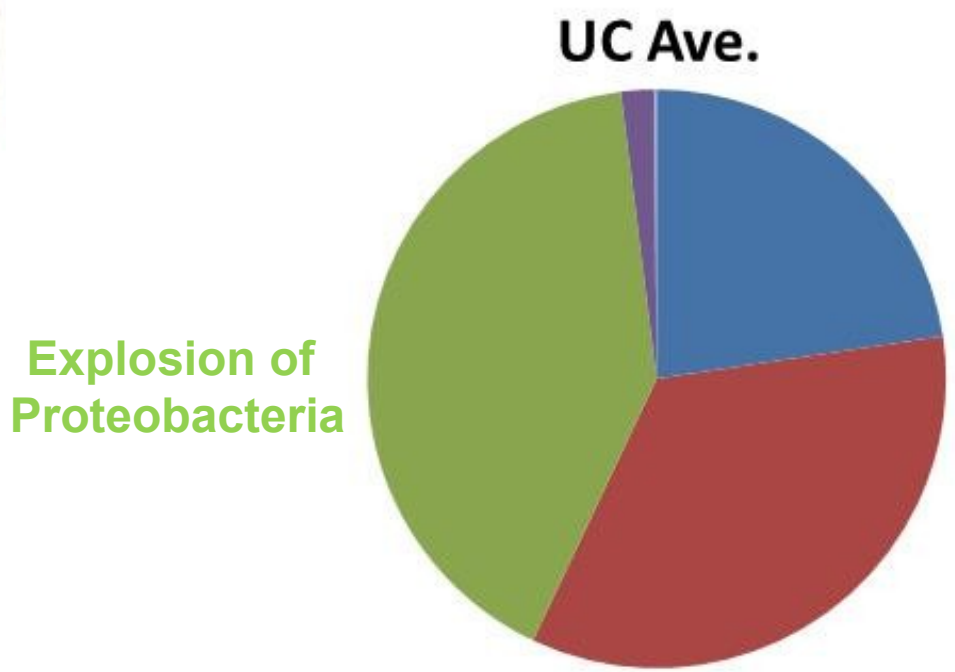
Calit2 VROOM-FuturePatient Expedition

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

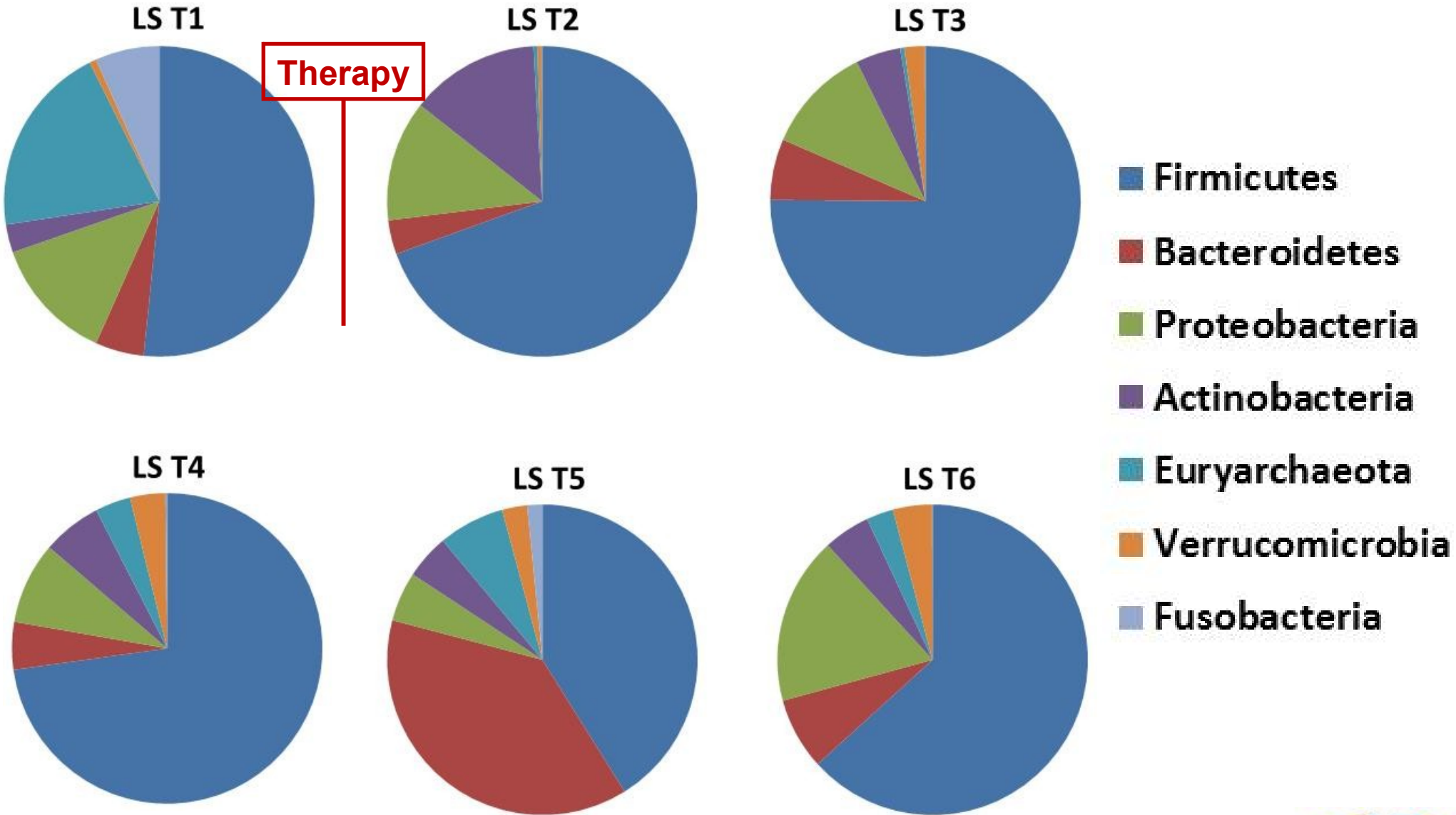








Time Series Reveals Autoimmune Dynamics of Gut Microbiome by Phyla

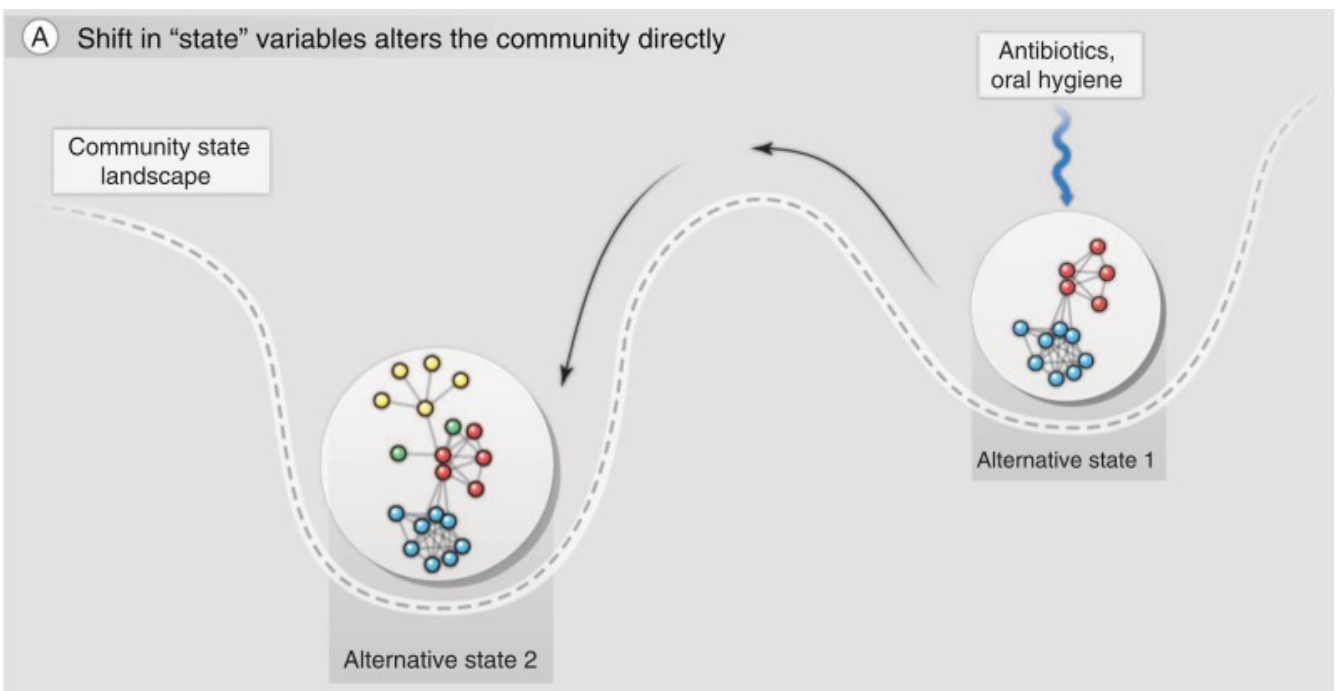


Six Metagenomic Time Samples Over 16 Months

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

"One important property to emerge from theoretical studies of ecosystems as dynamical systems is the potential for multi-stability, [which] has long been recognized as a key concept for understanding behaviors of ecological communities, including bacterial communities."

From The emerging medical ecology of the human gut microbiome, John Pepper & Simon Rosenfeld, NCI *Trends in Ecology and Evolution (2012)*



"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)

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.”

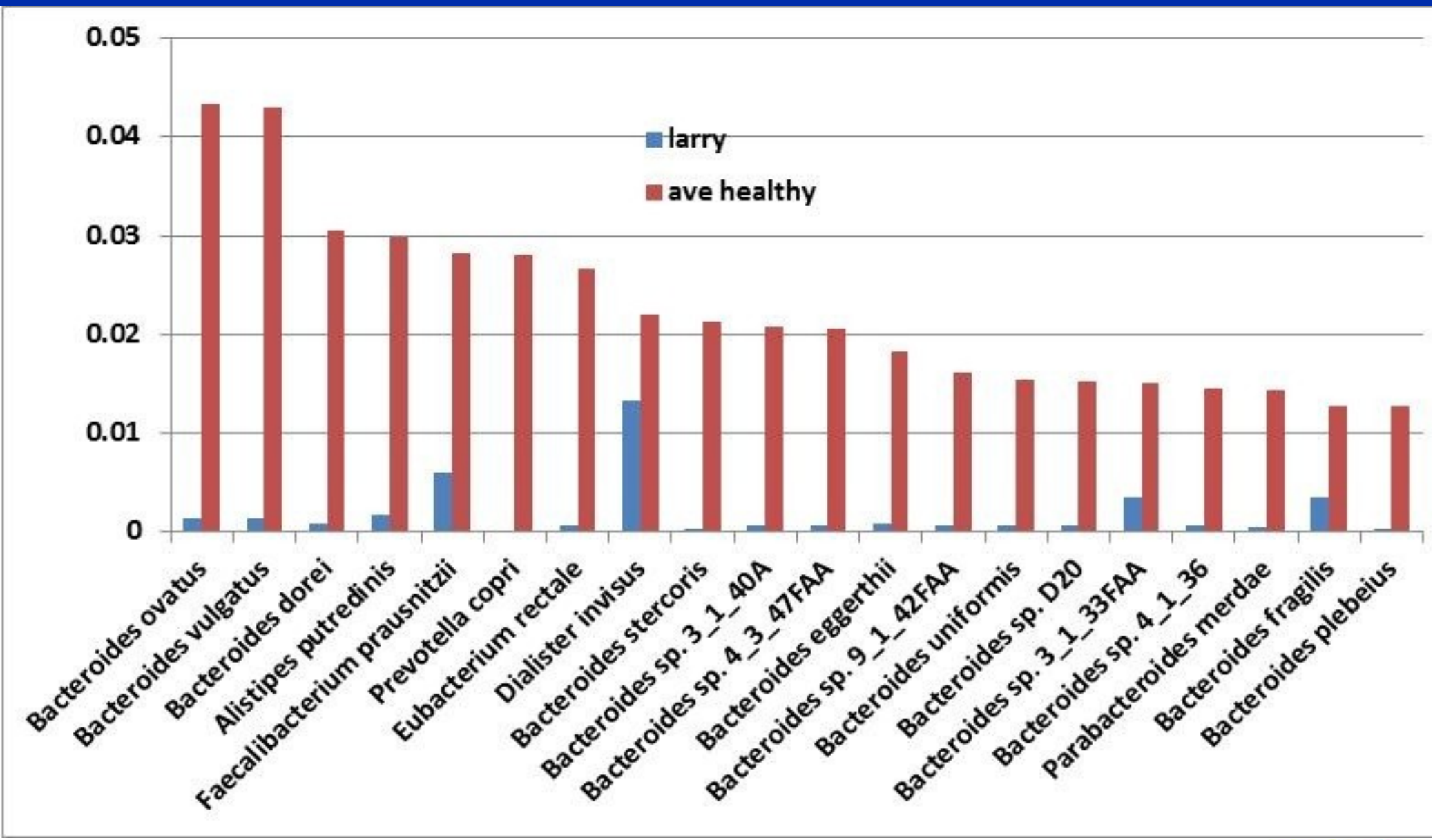
Source: Ponderosa Pine Fire Ecology
http://cpluhna.nau.edu/Biota/ponderosafire.htm

Lessons From Ecological Dynamics III: From Equilibrium to Chaos

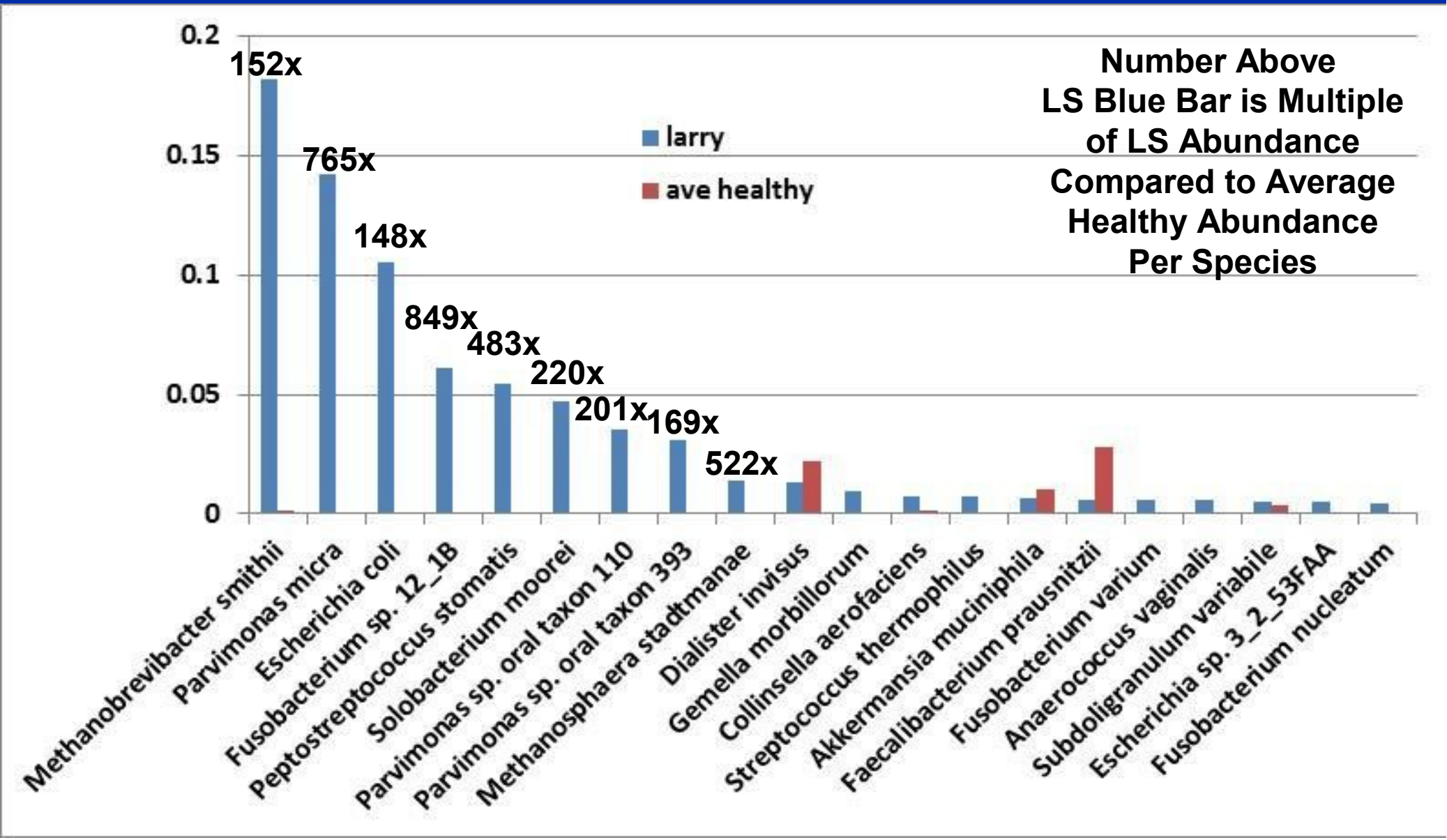
In addition to chaos,
other forms of complex dynamics,
such as regular oscillations & quasiperiodic oscillations,
are preeminent features of many biological systems.

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

Almost All Abundant Species (≥1%) in Healthy Subjects Are *Severely Depleted* in LS Gut Microbiome

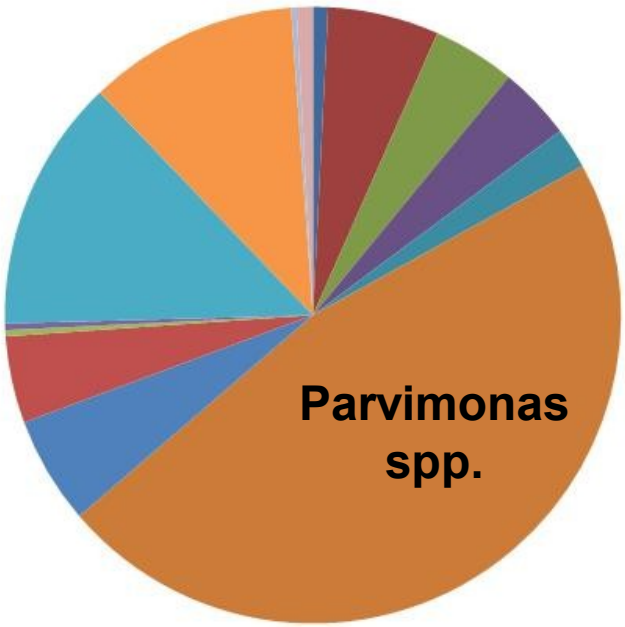


Top 20 Most Abundant Microbial Species In LS vs. Average Healthy Subject

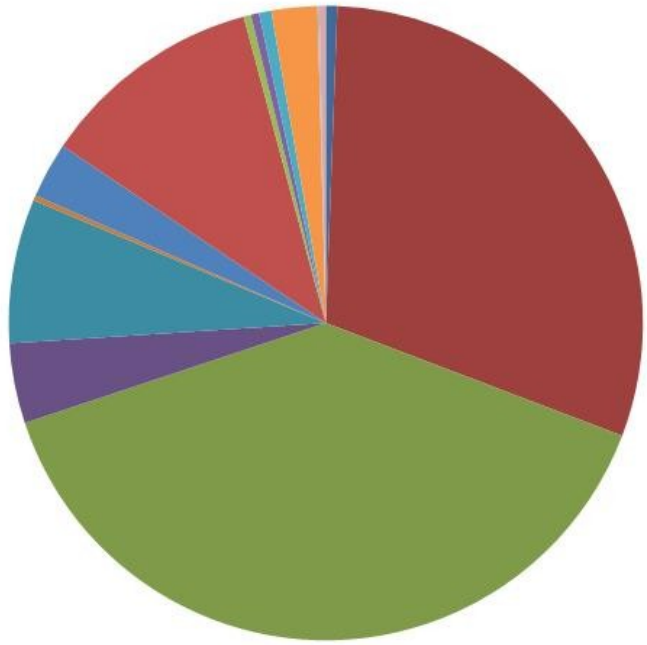


Source: Sequencing JCVI; Analysis Weizhong Li, UCSD
LS December 28, 2011 Stool Sample

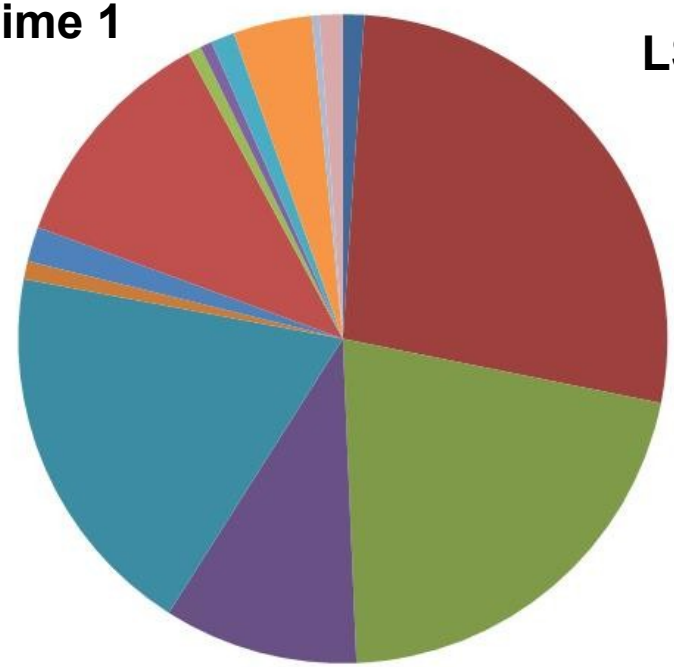
Rare Firmicutes Bloom in Colon Disappearing After Antibiotic/Immunosuppressant Therapy



LS Time 1



LS Time 2

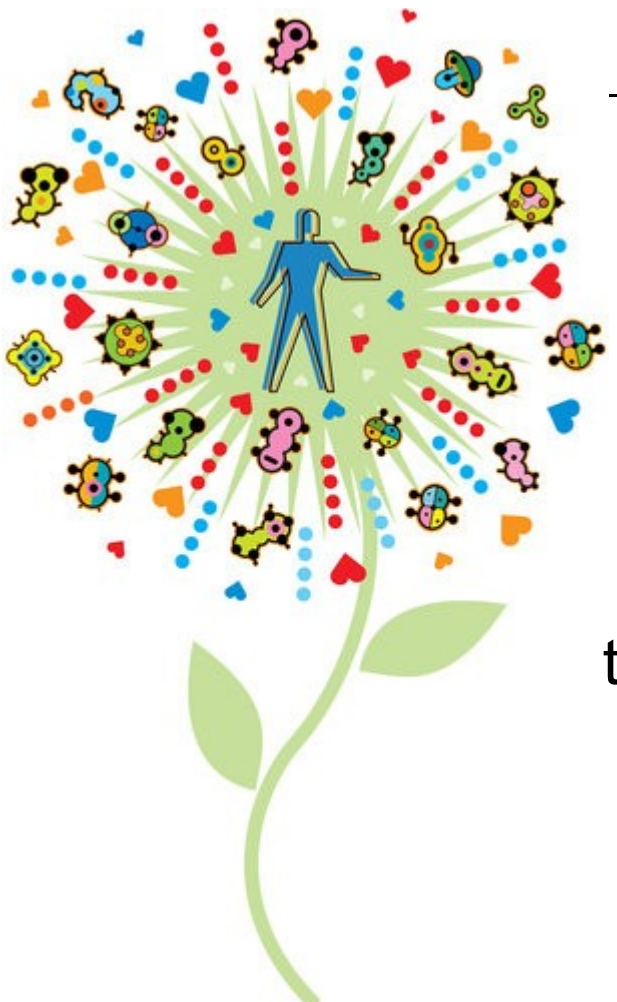


Healthy Average

Firmicutes Families

- Lactobacillaceae
- Lachnospiraceae
- Ruminococcaceae
- Veillonellaceae
- Eubacteriaceae
- Clostridiales Family XI. Incertae Sedis
- Streptococcaceae
- Clostridiaceae
- Enterococcaceae
- Bacillaceae
- Peptostreptococcaceae
- Erysipelotrichaceae
- Staphylococcaceae
- Acidaminococcaceae

From War to Gardening: New Therapeutical Tools for Managing the Microbiome



The New York Times

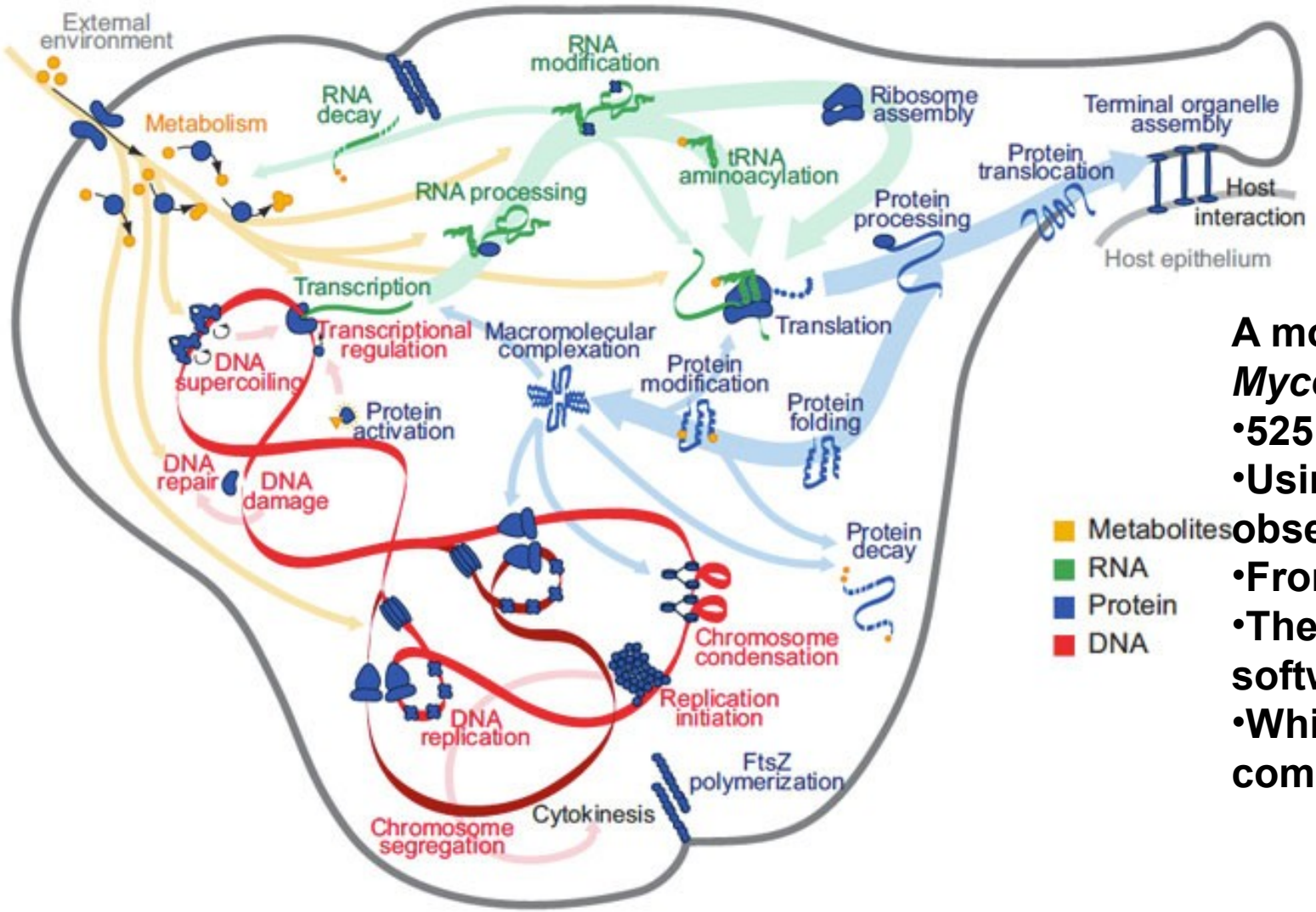
Science

Tending the Body's Microbial Garden

By CARL ZIMMER
Published: June 18, 2012

"I would like to lose the language of warfare," said Julie Segre, a senior investigator at the National Human Genome Research Institute. "It does a disservice to all the bacteria that have co-evolved with us and are maintaining the health of our bodies."

"A Whole-Cell Computational Model Predicts Phenotype from Genotype"



Cell

Cell *150*, 389–401, July 20, 2012

A model of *Mycoplasma genitalium,*
- **525 genes**
- **Using 1,900 experimental observations**
- **From 900 studies,**
- **They created the software model,**
- **Which requires 128 computers to run**

Jonathan R. Karr,[1,4] Jayodita C. Sanghvi,[2,4] Derek N. Macklin,[2] Miriam V. Gutschow,[2] Jared M. Jacobs,[2] Benjamin Bolival, Jr.,[2] Nacyra Assad-Garcia,[3] John I. Glass,[3] and Markus W. Covert[2,*]

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The Dawn of Virtual Cell Biology

Systems Biology Immunology Modeling: An Emerging Discipline

Systems immunology: a survey of modeling formalisms, applications and simulation tools

Vipin Narang · James Decraene · Shek-Yoon Wong · Bindu S. Aiswarya · Andrew R. Wasem · Shiang Rong Leong · Alexandre Gouaillard

Immunol Res 53:251–265 (2012)

Systems Biology in Immunology – A Computational Modeling Perspective

Ronald N. Germain*, **Martin Meier-Schellersheim**, **Aleksandra Nita-Lazar**, and **Iain D. C. Fraser**
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Annu Rev Immunol. 29: 527–585 (2011)

Early Attempts at Modeling the Systems Biology of the Gut Microbiome and the Human Immune System

Trends in Biotechnology June 2011, Vol. 29, No. 6

Prospects for systems biology and modeling of the gut microbiome

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2012 IEEE 26th International Parallel and Distributed Processing Symposium

High-Performance Interaction-Based Simulation of Gut Immunopathologies with ENteric Immunity SImulator (ENISI)

Keith Bisset*, Md. Maksudul Alam*, Josep Bassaganya-Riera*, Adria Carbo*, Stephen Eubank*, Raquel Hontecillas*, Stefan Hoops*, Yongguo Mei*, Katherine Wendelsdorf*, Dawen Xie*, Jae-Seung Yeom*†, and Madhav Marathe*†

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

Goal: Understand
The Coupled Human Immune-Microbiome Dynamics
In the Presence of Human Genetic Predispositions

Thanks to Our Great Team!

UCSD Metagenomics Team

Weizhong Li
Sitao Wu

JCVI Team

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Shibu Yooseph
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