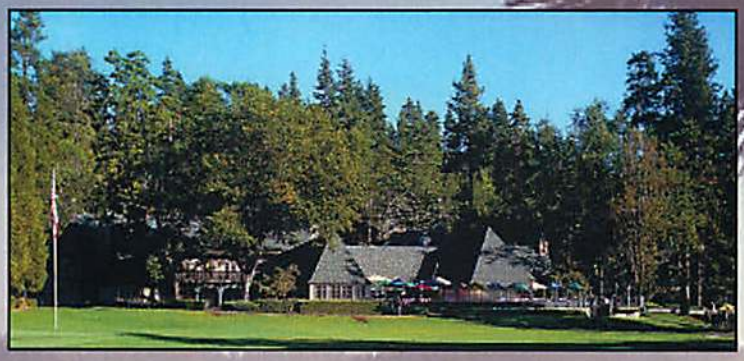
19th International Microbial Genomes Conference



September 16-20, 2012

UCLA Conference Center
Lake Arrowhead
California

ACKNOWLEDGEMENTS

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THE 19th INTERNATIONAL MICROBIAL GENOMES CONFERENCE

SEPTEMBER 16-20, 2012

UCLA CONFERENCE CENTER

LAKE ARROWHEAD

CALIFORNIA

SCIENTIFIC PROGRAM ORGANIZERS

Dr. Jeffrey H. Miller
University of California, Los Angeles, CA

Dr. Ashlee Earl
The Broad Institute of MIT and Harvard, Cambridge, MA

Dr. Jonathan Eisen
University of California, Davis, CA

Dr. Elisabeth Raleigh
New England Biolabs, Ipswich, MA

CONTACT NUMBER

The Arrowhead Conference Center phone number is (909) 337-2478

SCIENTIFIC PROGRAM

SUNDAY, SEPTEMBER 16

4:00-6:00 pm	Arrival and Check-in at Lake Arrowhead Conference Center
6:15-7:45 pm	Dinner (Dining Room)
Opening of Meeting	(Pineview Room)
7:45-8:05 pm	Jeffrey H. Miller University of California, Los Angeles **"Welcome"**
8:05-9:00 pm	**Keynote Address** Jonathan Eisen University of California, Davis,, CA **"Phylogeny-Driven Approaches to Genomics and Metagenomics"**
9:00 pm	Reception (Iris Room)

MONDAY, SEPTEMBER 17

7:45-8:30 AM	Breakfast (Dining Room)
Opening Session	**(Pineview Room)**
8:45-9:00 am	Introduction/Announcements
Session I	**Microbial Communities I: Microbiomes/Biodiversity**
Session Chair	Ashlee Earl, Broad Institute MIT and Harvard, Cambridge, MA
9:00-9:30 am	Nina R. Salama Fred Hutchinson Cancer Research Center, Seattle, WA **"*H. pylori* – Microbiome Interactions in the Esophagus and Stomach"**
9:30-10:00 am	Frederic Bushman University of Pennsylvania, Philadelphia, PA **"Host-Microbe Interactions in the Human Microbiome"**

10:00-10:30 am	Kristine Wylie Washington University, St. Louis, MO **"Novel Organisms and Viruses in the Human Microbiome"**
10:30-10:50 am	Break
10:50-11:20 am	Janet K. Jansson Lawrence Berkeley National Laboratory, Berkeley, CA **"Prairie Soil Metagenome"**
11:20-11:50 am	Forest Rohwer San Diego State University, San Diego, CA **"Metagenomics of the Global Virome"**
11:50-12:20 pm	Curtis Huttenhower Harvard School of Public Health, Boston, MA **"The Human Microbiome Project: A Systems Biology Approach"**
12:30 pm	Lunch (Dining Room)
4:00-6:00 pm	Poster Session (Lakeview Room) Social/Mixer (Lakeview Room)
6:15-7:45 pm	Dinner (Dining Room)
Session II	**Microbial Communities II: Metagenomics/Biodiversity/Pathogens**
7:45-8:15 pm	Tanja Woyke DOE Joint Genome Institute, Walnut Creek, CA **"Providing a Glimpse into the Coding Potential of Microbial Dark Matter"**
8:15-8:45 pm	Maomeng Tong David Geffen School of Medicine,University of California, Los Angeles, CA **"Redefining the Ecology of Intestinal Microflora through Mucosal Functional Neighborhoods"**
8:45-9:00 pm	Break
9:00-9:30 pm	Jeffery Cox University of California, San Francisco, CA **"Host-Pathogen Interactions Responsible for M. tuberculosis Virulence"**

9:30-10:00 pm	Susannah Tringe DOE Joint Genome Institute, Walnut Creek, CA **"Wetland Metagenomics"**

TUESDAY, SEPTEMBER 18

7:45-8:30 am	Breakfast (Dining Room)
Session III	**Pathogens/Antibiotics/Resistance**
9:00-9:30 am	Julian Parkhill Welcome Trust Sanger Insitute, Cambridge, UK **"Comparative Genomics of Pathogens"**
9:30-10:00 am	**Extremophiles/Evolution** Rustem F. Ismagilov California Institute of Technology, Pasadena, CA **"Complex Networks of Reactions, Cells and Organisms in Microbial Communities"**
10:00-10:30 am	Gautam Dantas Washington University School of Medicine, St. Louis, MO **"Disseminating Antibiotic Resistomes of Human and Environmental Microbiota"**
10:30-10:50 am	Break
10:50-11:20 am	Pamela Yeh Portland State University, Portland, OR **"Evolution of Bacteria in Multidrug Environments"**
11:20-11:50 am	Mike Gilmore Harvard Medical School, Boston MA **"Evolution of Enterococci and Staphylococci into Multidrug Resistant Hospital Pathogens"**
11:50-12:20 pm	Lance B. Price Translational Genomics Research Institute, Flagstaff, AZ **"Livestock-associated MRSA ST398: The Birth of a Superbug"**

12:30 pm	Lunch (Dining Room)
4:00-6:00 pm	Poster Session (Lakeview Room) Social/Mixer (Lakeview Room)
6:15-7:45 pm	Dinner (Dining Room)
Session IV	**Microbiology of the Built Environment**
Session Chair:	"Alfred P. Sloan Foundation Workshop" Jonathan Eisen, University of California, Davis
7:45-8:15 pm	James Meadow University of Oregon, Eugene, OR **"Microbial Ecology of the Built Environment"**
8:15-8:45 pm	Jason E. Stajich University of California, Riverside, CA **"Fungi in the Built Environment"**
8:45-9:15 pm	Laura Sauder University of Waterloo, Waterloo, Ontario **"Archaea in the Built Environment"**
9:15-9:25 pm	Break
9:25-9:55 pm	Scott Kelley San Diego State University, San Diego, CA **"The Indoor Microbiome: Bacterial and Metagenomic Approaches for Studying the Built environment"**
9:55-10:25 pm	Susanna Remold University of Louisville, Louisville, KY **"Pseudomonas as a Model for Studies of Microbes in the Home"**

WEDNESDAY, SEPTEMBER 19

7:45-8:30 am	Breakfast (Dining Room)
Session V	**Networks, Metabolomics, Synthetic Biology.**
9:00 - 9:30 am	Bernhard Palsson University of California, Sand Diego, CA **"iKnow *E. coli* and its GEMS: The New Generation of Genome-Scale Models"**
9:30-10:00 am	Anca Segall San Diego State University, San Diego, CA **"Artificial Neural Networks Trained to Detect Phage Structural Proteins"**
10:00-10:30 am	Trent Northern Lawrence Berkeley National Laboratory, Berkeley, CA **"Enigma Biotechnology: Systems Approaches to Studying Microbial Communities"**
10:30-10:50 am	Break
10:50-11:20 am	Rick Morgan New England Biolabs, Ipswich, MA **"The Complete Methylome of Six Bacterial Strains"**
11:20-11:50 am	Beth Shank Harvard Medical School, Boston, MA **"Microbial Interspecies Interactions"**
11:50-12:10 am	Morgan Langille Dalhousie University, Halifax, Nova Scotia, Canada **"Inferring Microbial Community Function from Taxonomic Composition"**
12:10-12:30	Anthony A. Fodor University of North Carolina at Charlotte, Charlotte, NC **"Illumina 16S Sequencing Reveals the Time Scale of Changes to the Gut Microbial Community due to Inflammation and Cage Effects in a Mouse Model of Inflammation"**
12:30 pm	Lunch (Dining Room)

Session VI A	**Strategies**
4:30-5:00 pm	Peter Karp SRI International, Menlo Park, CA **"Pathway Annotation in Microbial Genomics"**
5:00-5:30 pm	Tatiana Tatusova NIH/NLM/NCBI **"Paradigm Shift: From Reference Genome to Pan-Genome"**
5:30-6:00 pm	Timothy Harkins Life Technologies, Inc., Beverly, MA **"Microbial and Megagenomic Sequencing using Ion Torrent's PGM™ System"**
6:15-7:45 pm	Dinner (Dining Room)
Session VI B	**Poster Talks**
7:45-8:00 pm	**Nanopore Poster Awards Presentations**
8:00 -8:20 pm	Katrine Whiteson San Diego State University, San Diego, CA **"Breath Gasses as Biomarkers in Cystic Fibrosis"**
8:20-8:40 pm	Mallory Embree University of California San Diego, San Diego, CA **"Metabolic Interactions of an Alkane-oxidizing Methanogenic Consortium Revealed by Single Cell Sequencing and Metatranscriptomics"**
8:40-9:00 pm	Varum Mazumdar Boston University, Boston, MA **"The Metabolic Distance Sweet Spot in Microbial Succession"**
9:00 – 9:20	Abigail McGuire The Broad Institute of MIT and Harvard, Cambridge, MA **"Potential Role of Protein Domain and Bacteriophages in Evolution of Virulence in Fusobacterium"**
9:20 pm	Reception/Party (Iris Room)

THURSDAY, SEPTEMBER 20

7:30-8:45 am	Breakfast (Dining Room)
Session VII	**Bioenergetics/Regulatory and Metabolic Pathways/Modeling**
8:45-9:15 am	Ee-Been Goh Joint Energy Institute, Lawrence Berkeley National Laboratory, Berkeley, CA **"Engineering of Bacterial Methyl Ketones Synthesis for Biofuels"**
9:15-9:45 am	Shota Atsumi University of California, Davis, CA **"Alternative Biofuel Production in Non-Natural Hosts"**
9:45-10:15 am	Howard Xu California State University, Los Angeles, CA **"Antisense RNA Modulated Essential Gene Expression for Antibacterial Drug Discovery"**
10:15-10:20 am	Closing remarks
10:45 am	**Checkout**
11:00 am	**Departure of Bus for LAX**
12:00 noon	**Lunch**
1:00 pm	**Departure of Bus for LAX**

Examining key phenotypes for soil fitness in *Variovorax paradoxus* EPS using a Tn5 mutant library

Niki Arab, Jenny Stone, and Paul Orwin
Department of Biology, California State University, San Bernardino

Variovorax paradoxus is a gram negative bacterium that plays a number of roles in the environment, including biotransformations and plant growth promotion. We have shown that *V. paradoxus* EPS forms biofilms and swarms on agar plates, and promotes growth of *Helianthus annuus*. We utilized screening and enrichment approaches to identify genes that play a role in motility and solubilization of phosphate, two traits that we suspect play an important role in rhizosphere fitness. Most phosphorus in the soil exists in an insoluble form bound to calcium or iron that is inaccessible to plants. Solubilizing insoluble phosphate by secreting organic acids is an important trait in plant growth promoting rhizobacteria (PGPR). A clear halo was observed around *V. paradoxus* EPS on Pikovskaya (PVK) medium, indicating that it has this capacity *in vitro*. We screened a Tn5 mutant library for strains that failed to produce this halo, and identified two mutants with defects in this character. We determined the growth rate, pH, and phosphate solubilization.

Recently, the genome sequences of two strains of *Variovorax paradoxus*, S110 and EPS, were completed. Surprisingly, the sequence from strain EPS does not contain the clearly annotated flagellum operon that is in S110, although it is demonstrably motile. A putative Type III secretion locus was identified, and we expect these genes are in fact a component of the flagellar apparatus. We enriched for non-motile mutants from the Tn5 library by repeated selection from the center of a motility plate. The enriched population was then screened using swarming motility assays to identify mutants with potential defects in flagellar activity.

The mutants isolated in these experiments have been identified by rescue cloning, and will be assessed by complementation analysis in vitro and plant association experiments to determine what roles these genes play in the phenotypes of interest.

In silco identification of clade-specific canonical SNPs for the *Staphylococcus aureus* CC398

Maliha Aziz[1*], Cindy M. Liu[1], Marc Stegger[2], Tania Contente-Cuomo[1] and Katerina Soldanova[1], and Lance B Price[1]

[1]Translational Genomics Research Institute (TGen), Pathogen Genomics Division, Flagstaff, Arizona, USA; [2]Department of Microbiological Surveillance and Research, Statens Serum Institut, Copenhagen, Denmark

Since 2003, a newly recognized methicillin-resistant *S. aureus* (MRSA) lineage called CC398 has emerged in livestock and begun spreading to humans. Phylogenomic analyses indicate that the livestock-associated strain was derived from a more ancestral human-associated methicillin-susceptible (MSSA) sublineage. Differentiating these two sublineages is critical to understanding the epidemiology of CC398. In the current study, we sought to identify canonical SNPs (canSNPs) as targets for genotyping assays that could rapidly differentiate the major CC398 sublineages. Illumina WGS data sets were aligned against the chromosome of a published ST398 reference genome using the short-read alignment component of the Burrows-Wheeler Aligner. Each alignment was analyzed for SNPs using SolSNP. Phylogenetic trees were generated using the maximum-parsimony method in PAUP. Potential clade-specific canSNPs were identified using a custom Perl script. Flanking regions of approx. 500 bp for each of the selected canSNPs were extracted from the reference genome. The clade-specific canSNP sequences were blasted against the NCBI nt database to identify homology and to facilitate assay design. Finally PCR primers and probes were designed using these canSNP sequences. Through this process we identified 15 potential canSNPs with a high consistency index values for the clade of interest: clade IIa (dominated by livestock-associated strains). After detailed analysis, we developed real-time PCR assays for three canSNPs. A preliminary validation of the three assays conducted against our 88 reference isolates showed a 99.6% sensitivity and 100% sensitivity. We developed a framework that enabled us to leverage phylogenomics to identify canonical SNPs and finally design lineage-specific PCR assays. Using this framework, we successfully developed three robust real-time PCR assays to differentiate livestock-associated and human-associated CC398 strains. These assays are currently being used to better characterize the epidemiology of CC398 in the US and Europe.

Microdiversity revealed by single cell sequencing of uncultured oral bacteria.

Beall, Clifford J.[1]*, Campbell, James, H.[2], Campbell, Alisha G.[2,3], Dayeh, Danny[1], Podar, Mircea[2,3], Griffen, Ann L.[1], and Leys, Eugene J.[1] [1]The Ohio State University College of Dentistry, [2]Biosciences Division, Oak Ridge National Laboratories, and [3]Genome Science and Technology Program University of Tennessee, Knoxville.

The genus *Tannerella* comprises 3 species, two of which are currently uncultivated. Although the cultivated representative, *T. forsythia*, is strongly correlated with chronic periodontitis, the uncultivated species *Tannerella BU063* (aka Human Oral Taxon 286) despite its closeness phylogenetically has been shown to be health-associated. To gain insight into possible mechanisms of pathogenicity, we carried out whole genome amplification and sequencing of isolated *BU063* cells. Cells were randomly sorted from subgingival dental plaque and their genomes were amplified with Phi29 polymerase. Twelve *Tannerella BU063* genomes were identified by 16S rRNA gene analysis and sequenced in the Illumina HiSeq. Genome assemblies were carried out with velvet following digital normalization with khmer. Nucleotide comparisons with the usearch aligner revealed that the amplified genomes were incompletely and randomly represented, as is commonly found with whole genome amplification. The amount of overlap between cell isolates suggested that the genome is a similar size as *T. forsythia*, about 4Mb. It also suggested we were able to assemble about half the genome from each original cell. There appeared to be 8 strains present among the 12 isolates. One group of three and two groups of two had >99% average nucleotide identity, while all other pairs had 95-98%. The result suggests that multiple strains of even a relatively rare bacterium (less than 1% abundance in 16S surveys) are present in the human microbiome. We examined the literature on *T. forsythia* to identify possible virulence genes. Out of 8 loci that have been associated with virulence in *T. forsythia*, 5 appeared to be present in *BU063*.

The genome of *Varibaculum cambriense* reconstructed via community (meta)genomics of fecal samples from a premature infant

C.T. Brown*, I. Sharon, B.C. Thomas, M.J. Morowitz, & J.F. Banfield. University of California, Berkeley.

To study early colonization of the premature infant intestine, nine stool samples were taken during the third week of life of a premature male infant delivered via Caesarean section. 30 gigabases of Illumina community genomic data were collected and analyzed. Sequencing reads were assembled into scaffolds and binned, resulting in 12 near-complete and 7 partial genomes. On average, 11 of the near-complete genomes share 99% ortholog amino acid identity with their closest reference strains, validating the *de novo* genome reconstruction strategy. The notable exception was a genome of a species with only 86% ortholog amino acid identity with the draft genome of *Actinomyces viscoscus,* its closest genomically characterized relative. Manual assembly curation resulted in a genome with only three gaps, all associated with defined repeats. The 16S rRNA gene sequence shares 99% nucleotide identity with that of *Varibaculum cambriense.* Thus, this represents the first genome reported for the genus *Varibaculum. V. cambriense* is a pathogen with global distribution that has been characterized by isolates from human skin abscesses. However, due to its relatively low abundance in the human intestine, *V. cambriense* has never been cultured from this environment. *Varibaculum* have been previously observed through culture-independent studies of the vagina in adults and the intestine of premature and full-term infants. The genome was compared to 24 other publicly available genomes of the family Actinomycetaceae. Results define three clusters for Actinomycetaceae based on sequence similarity: two associated with sequenced *Actinomyces* and *Arcanobacterium* strains, and one with *Mobiluncus* strains. The *V. cambriense* strain shares many functional traits with members of the genus *Actinomyces,* despite being phylogenetically closer to *Mobiluncus. V. cambriense* is neither motile nor chemotactic, and lacks the capacity to synthesize antibiotics. These results indicate that community genomics can be used to better understand microbial colonization and reveal genome-level variations between previously uncharacterized microbial species.

Exploiting Single-Molecule, Real-Time DNA Sequencing for Improved Genome Assembly and Methylome Analysis

Tyson A. Clark, Khai Luong, Matthew Boitano, Stephen W. Turner, and Jonas Korlach

Pacific Biosciences, Menlo Park, CA 94025

Recent advances in our understanding of biological complexity have propelled the development of new tools. In the field of DNA sequencing, next-generation sequencers have dramatically increased throughput and provided novel insights into the structure and function of the genome. Despite these capabilities, researchers continue to face challenges in finishing genomes, characterizing variations, and understanding the function of key biological markers.

Pacific Biosciences' Single-Molecule, Real-Time (SMRT) DNA sequencing technology is capable of sequencing reads that are thousands of base pairs in length with very high consensus accuracy. These factors have played an important role in the use of SMRT sequencing in *de novo* genome assembly. In addition there has been an emergence of new bioinformatics approaches that harness the rich kinetic information that SMRT sequencing produces. The information about the rate of DNA base incorporation during sequencing allows for direct detection and identification of modified DNA bases. We demonstrate these capabilities using DNA from a previously unfinished bacterium; walking through the sample preparation, sequencing, and informatics steps required to both *de novo* assemble the genome and map its methylome to identify previously unknown methyltransferase specificities from the same data.

Developing Novel Technologies to Advance Single Cell Genomics: Inducing Artificial Polyploidy and Gel Microdroplets (GMD)

AEK Dichosa*, MS Fitzsimons, M Novotny, CC Lo, JL Yee-Greenbaum, LL Weston, LG Preteska, JP Snook, W Gu, KW Davenport, X Zhang, K McMurry, CD Gleasner, PL Wills, B Parsons-Quintana, LD Green, PS Chain, JC Detter, RS Lasken, and CS Han.
Bioscience Division: Los Alamos National Laboratory.

Single cell genomics (SCG) with fluorescence activated cell sorting (FACS) allows for the targeted isolation of a single cell for the rapid phylogenetic and, potentially, genomic identification of the isolate. SCG is often coupled with multiple displacement amplification (MDA) to achieve whole genome amplification, generating up to micrograms of genomic amplicons from a single genomic template. As vital as MDA is to SCG, however, there are known inherent drawbacks to MDA, which include amplification biases and chimeras found in the genome assemblies. At best, 50% of the genome is typically completed from a single cell template.

LANL Bioscience presents two novel technologies to simultaneously address the problems surrounding MDA, while improving genome recovery from a single cell.

Inducing Polyploidy: We inhibited the bacterial/archaeal cell division protein, FtsZ, in *B. subtilis* to prevent cytokinesis, while maintaining viability. The result was a larger-than-normal cell that contained, at least, two copies of its chromosome. Using FACS, we sorted these treated cells for MDA and subsequent genome assemblies. Compared to untreated controls, we increased genome recovery by 20% in the polyploid cells (assembled *de novo*) with a near four-fold reduction in amplification bias. **Gel Microdroplets**: We captured single cells inhabiting the human mouth and gut (fecal isolates) in agarose spheres called gel microdroplets (GMD). Captured cells proliferated into microcolonies, ultimately providing multiple copies of identical chromosomes. FACS-sorting these colonized GMD for MDA and genome sequencing, we generated near-complete genomes from single GMD isolates and found remarkable intragenomic variation within the same bacterial [oral] species. These methods holds promise to improve SCG, and LANL Bioscience continues to develop novel methods to advance this vital field.

Functional Characterization of a Novel Pneumococcal Restriction Modification System and its Putative Role in Strain Diversification

Rory A. Eutsey[1], Evan Powell[1], Azad Ahmed[1], Garth D. Ehrlich[1,2], N. Luisa Hiller*[1],

1. Center for Genomic Sciences, Pittsburgh, USA.
2. Drexel University College of Medicine, Pittsburgh, USA.

The bacterium *Streptococcus pneumoniae* is a major human pathogen. There is a high degree of genomic plasticity and extensive genomic variation among strains of this species. We are studying a restriction modification system unique to the PMEN1 lineage, a group of highly-related pandemic and multi-drug resistant strains. Our studies have relied on the comparison between a WT strain, and a deletion mutant of the RM system (RM-KO). Preliminary results suggest that this endonuclease recognizes the sequence "GATC", while the methylase modifies the cysteine within this sequence. We are examining how presence of this RM system affects the frequency of homologous recombination with DNA fragments that contain non-methylated instances of this cleavage site. When an erythromycin sensitive WT strain is transformed with genomic DNA from WT or RM-KO erythromycin resistant strain, the rate of transformation with the RM-KO is much lower than with the WT. This difference is not observed if the recipient strain is RM-KO. These observations suggest that the WT PMEN1 strain is less likely to incorporate non-methylated DNA, while a RM-KO strain is insensitive to the methylation state at this site. This cleavage site is abundant in most pneumococcal genomes (>3500 instances), thus we are currently investigating the hypothesis that this RM system effects genomic diversification of PMEN1 strains by decreasing the frequency of homologous recombination with DNA from other pneumococcal lineages.

Prediction of Wild-type Enzyme Thermostability

Henrik M. Geertz-Hansen[1,2,3]*, Thomas Nordahl Petersen[1,2], Nikolaj Blom[1,2] and Lars Kiemer[3], [1]NNF Center for Biosustainability, Technical University of Denmark (DTU), Denmark; [2]Center for Biological Sequence Analysis, DTU, Denmark; Novozymes A/S, Bagsværd, Denmark

This study aims at facilitating the prediction of enzyme thermostability from a data set of 650 biochemically characterized wild-type glycoside hydrolases. Next generation sequencing technologies have resulted in a rapid explosion in both total numbers and diversity of putative protein sequences derived from genomic, transcriptomic and metagenomic samples. In order to take advantage of the massive sequence influx for commercial and industrial applications it is highly desirable to enable rational gene selection as the costs associated with classical biochemical characterization renders an experimentally based screening of all candidates impossible.

Several sequence and structure-derived features have been proposed to contribute towards protein thermostability. Here, a set of such features has been selected by a statistical comparison of enzymes sharing the same fold and used for training of several artificial neural networks for prediction of the thermal transition midpoint (T_m) or classification of thermo- and mesostable enzymes.

The best performing artificial neural network for prediction of T_m for sequences of the $(a/b)_8$-fold has an average absolute prediction error of 8.0°C obtained using 5-fold cross-validation with external validation.

Gene Fragmentation as an Indicator of Orthopoxvirus Evolution

E.L. Hatcher*, R.C. Hendrickson, & E.J. Lefkowitz. University of Alabama at Birmingham.

Although the most pathogenic member of the virus family *Poxviridae*, variola virus, has been eradicated in nature, other closely related viruses may have the potential to develop more highly pathogenic phenotypes. In particular, the genus *Orthopoxvirus* contains several members that are capable of causing disease in humans as well as in agriculturally-important animals.

As poxviruses evolve, certain genes experience changes to, or loss of selection pressure to maintain function, as evidenced by accumulation of mutations. These mutations may be progressive, starting with the accumulation of SNPs, followed by gene truncation, gene fragmentation, and loss of promoter function, eventually leading to loss of expression (translational and subsequently transcriptional). Examination of these fragmentation patterns leading to gene loss inform us about the roles individual genes may play in virus biology, and how selection pressures impacting virus replication may affect gene and virus evolution. Our previous work has demonstrated that gene loss is one of the major observable effects of orthopoxvirus evolution. Investigating the fragmentation pattern of orthopoxvirus genes will allow us to reconstruct the evolutionary history of this *Poxviridae* genus in greater detail.

Using PGAS, a program that allows visualization, annotation, and curation of poxvirus genomes, we were able to identify and quantify the level of fragmentation of each gene in each orthologous orthopoxvirus gene family. Using 17 representative orthopoxvirus strains, we systematically predicted the complete functional gene set for each strain, as well as assessed the presence of gene fragmentation. Once identified, regions of fragmentation were examined in more detail to identify nucleotide-level fragmentation patterns. These patterns were then used to reconstruct the gene-level evolutionary history of the *Orthopoxvirus* genus. By clarifying the operative mechanisms and products of virus evolution, we will be better able to understand poxvirus biology, virus-host interactions, and the future evolutionary potential of these virus pathogens.

Simultaneous transcriptional profiling of bacteria and their host cells

Michael Humphrys & Garry S. A. Myers*. Institute for Genome Sciences, University of Maryland School of Medicine.

Bacterial pathogens subvert host cells by using their gene products to manipulate cellular pathways for survival and replication; in turn, host cells respond to invading pathogens through cascading changes in gene expression. Deciphering this complex temporal and spatial interplay is crucial for improved diagnostics and therapeutics. However, the technical limitations of existing methods of expression profiling, such as microarray analysis, significantly reduce their utility for obtaining both bacterial and host expression profiles from infected cells.

We developed heterogeneous RNA-Seq (hRNA-Seq) to simultaneously capture prokaryotic and eukaryotic expression profiles of bacteria-infected cells. hRNA-Seq employs affinity-based counter selection of both prokaryotic and eukaryotic rRNA to enrich mRNA from infected cells in one step. Enriched mRNA mixtures are then sequenced, with prokaryotic and eukaryotic sequence reads subsequently separated and analyzed by a custom bioinformatic pipeline.

As proof of principle, we applied hRNA-Seq to a time series of *Chlamydia*-infected cells. We readily distinguished chlamydial and host gene expression despite the low multiplicity of infection and overwhelming amounts of host rRNA. We found substantial temporal changes of both chlamydial and host cell gene expression, and identified novel host non-coding RNA expression in response to chlamydial infection.

The hRNA-Seq methodology allowed simultaneous transcriptional profiling of *Chlamydia*-infected cells, yielding novel insights into the biology of infected cells. hRNA-Seq is applicable to any bacteria/host cell combination, and can be used to decipher the complexity of host-bacteria interactions from *in vivo* infections.

One-step bacterial genome closure with single-molecule hybrid assembly

Sergey Koren, Gregory Harhay, Timothy Smith, Dayna Harhay, James Bono, Adam Phillippy*. National Biodefense Analysis and Countermeasures Center, Frederick Maryland.

Due to read error rates as high as 15%, current *de novo* assemblers are unable to effectively use the long-read sequencing data generated by emerging single-molecule sequencing technologies. To address this limitation, we have developed a correction algorithm and assembly strategy that utilizes short, high-accuracy sequences to correct the error in long, single-molecule sequences. We have recently demonstrated the benefit of this approach on viral, bacterial, and eukaryotic genomes and transcriptomes[†]. High-quality assemblies are critical for all aspects of genomics, especially genome annotation and comparative genomics, but producing finished sequence remains prohibitive, as the cost of finishing is proportional to the number of gaps in the original assembly.

We have applied our hybrid assembly approach to multiple bacterial genome projects and show that the combination of ~200x of PacBio long reads with 50x of short reads reliably closes the genomes of bacteria that lack large-scale repeats (e.g. >10 Kbp). This recipe has resulted in the successful closure of *Escherichia coli* K12, *Salmonella enterica* Newport, and *Bibersteinia trehalosi* 192 when using combinations of PacBio-Illumina, PacBio-454, and PacBio-CCS (PacBio Circular Consensus Sequencing). In all cases, the assembly software generated closed molecules without user intervention. In the cases of 454 and CCS, only unpaired libraries were required, and in the case of Illumina, only short, paired-end style libraries were required. Thus, this single-molecule hybrid approach presents an automated and cost effective alternative to the traditionally manual and expensive, process of genome finishing. In addition, our approach drastically improves the quality of complex genomes that remain outside the reach of automated closure.

[†] Hybrid error correction and *de novo* assembly of single-molecule sequencing reads. Koren S, Schatz MC, Walenz BP, Martin J, Howard JT, Ganapathy G, Wang Z, Rasko DA, McCombie WR, Jarvis ED, Phillippy AM. Nat Biotechnol. 2012 July 1.

Transcriptional regulation of a major virulence factor (vHiSLR) and an anaerobic respiration switch by Autoinducer-2 quorum sensing in the non-typeable *Haemophilus influenzae* (NTHi)

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The Lsr locus genes bind, import and process autoinducer-2 (AI-2), a quorum sensing molecule produced in many bacterial species. Lsr was not previously observed among the non-typeable *Haemophilus influenzae* (NTHi), but whole genome sequencing and genomic hybridizations revealed its' presence in 43/187 (23%) of strains. The CZ4126/02 (CZ) strain contains a complete Lsr region (nine genes in two operons) which we removed completely to generate a knockout strain (Lsr-KO). Using the *Vibrio harveyi* bioassay to measure the levels of AI-2, in defined media, we show that the CZ WT strain takes up AI-2 in early stationary phase while the Lsr-KO doesn't. The transcriptional effect of Lsr was established using a custom-designed NTHi Supragenome hybridization chip to compare RNA levels between the CZ WT and Lsr-KO strains, before and after early stationary phase. Two major virulence factors were found to be under the control of the Lsr locus: vHiSLR and Hgp (Hemoglobin-binding proteins). These genes were also differentially regulated between the CZ WT and Lsr-KO in 2D-DIGE proteome comparisons. Studies in strain PittII demonstrate that vHiSLRs are virulence determinants. Construction of a vHiSLR deletion mutant (SLR-KO) in PittII revealed that vHiSLR homologues are required for in vitro macrophage invasion and survival and also provide a major fitness advantage in the chinchilla otitis media model. Furthermore, the SLR-KO strain was unable to invade into the brain, whereas most of WT-infected animals developed meningitis. Additional genes differentially regulated between CZ WT and Lsr-KO strains showed strong overlap with the anaerobic NarPQ regulon. These same genes were also found in transcriptional comparisons between PittII WT:SLR-KO and CZ WT:SLR-KO. These results demonstrate that the Lsr operon is linked to major virulence factors (vHiSLR, Hgp) and that the vHiSLR acts as an intermediate switch to a large anaerobic regulon implicating this entire network in pathogenesis.

Evolutionary dynamics of *Chlamydophila psittaci*

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Chlamydophilaia psittaci is an obligate gram-negative intracellular bacterium of the order *Chlamydiaceae*. *C. psittaci* is known as a particularly virulent pathogen in feral birds and domesticated poultry, causing respiratory and intestinal diseases, and the agent of life-threatening pulmonary and systemic disease in humans. Humans are customarily thought of as a rare secondary host, although a recent study found widespread psittacosis among poultry farmers, suggesting a great underestimation of the extent of zoonoses. Because of its infectiousness as an aerosol agent, C. *psittaci* was developed as an offensive bioweapon in the last century. Although the *Chlamydiaceae* only replicate within eukaryotic hosts, one of the more remarkable recent results to emerge from comparative genomic studies is the finding of frequent homologous recombination across the genome of the sexually transmitted and trachoma pathogen *C. trachomatis*. In order to understand the evolutionary dynamics of this important pathogen, we sequenced 12 phylogenetically diverse strains from a range of infections in birds and mammals (including human) and added 8 genome sequences of other strains to our analysis. Genome sizes of the sequenced strains were about 1.1-1.2 Mbp and draft annotation revealed ~1,100 genes per genome with a core genome found in all 20 strains of 800 genes. Comparative genome analysis and reconstructions of history of the clades using the ClonalFrame program revealed a genome wide history of homologous recombination between clades in *C. psittaci*. We also determined the number of ancestral populations that would explain the current population structure in *C. psittaci*. This preliminary analysis revealed that *C. psittaci* strains have a history of frequently switching hosts and undergoing recombination. We also found that certain strains might be a part of a clonal epidemic expansion. Molecular clock analysis using BEAST and ClonalFrame estimated the tMRCA of this clonal expansion as early 1850's suggesting they probably arose from a single introduction into the US probably from Europe.

Metatranscriptomic study of the human skin microbiome associated with acne

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Acne is one of the most common skin diseases affecting 85% of the adolescents in the US. To investigate the role of the skin microbiota in acne pathogenesis, we used RNA-Seq to perform metatranscriptomic comparison of the microbiota in pilocebaceous units from acne patients and healthy subjects. *Propionibacterium acnes*, a dominant skin commensal, was found to be the most transcriptionally abundant bacterium. The gene expression profile of *P. acnes* separated acne patients from healthy subjects. In total, we identified 136 differentially expressed microbial genes between acne patients and healthy subjects. In acne patients, 109 genes were up-regulated and 27 genes were down-regulated. To our knowledge, this study is the first metatranscriptomic study on the human skin microbiome. The findings from the study will help us better understand how microbial activity contributes to human skin health and disease.

Inferring microbial community function from taxonomic composition

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It is often most efficient to characterize microbial communities using taxonomic markers such as the 16S ribosomal small subunit rRNA gene. The 16S gene is typically used to describe the organisms or taxonomic units present in a sample, but data from such markers do not inherently reveal the molecular functions or ecological roles of members of a microbial community. We have developed and validated a novel computational method that takes a set of observed taxonomic abundances and infers abundance profiles of enzymes and pathways from multiple functional classification schemes (KEGG, PFAM, COG, etc.). We use ancestral state reconstruction to determine approximate genomic content, taking into account 16S copy number and known functional abundance profiles from all currently available microbial genomes. We have evaluated the accuracy of this inference for different groups of taxa and for different areas of biological function. Our method, implemented as the PI-CRUST software (Phylogenetic Investigation of Communities by Reconstruction of Unobserved STates) (http://picrust.sourceforge.net), allows 16S metagenomic based studies to be extended to predict the functional abilities of microbiomes as well as to compare expected versus observed functions in shotgun based metagenomic experiments.

TGen Pyrosequencing Database: A web application for executing modular analysis pipelines.

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The emergence of next-generation sequencing (NGS) technologies has revolutionized our capacity to characterize microbial communities in a culture-independent manner. Typically, sequence analysis is performed using a variety of tools in conjunction with custom scripts. These scripts, however, are both system-specific and difficult to read and maintain. Often, there are no precise records of how an analysis was performed, or what versions of the tools were used for the analyses. Modifying scripts to include new tools or functionality after the fact can be cumbersome, even in cases where using the tool itself is straightforward. To address these challenges, the Pyrosequencing Database (PyroDB) was designed to provide an analysis framework providing accessibility, modularity and consistency. We developed this platform through combination of a PHP-based LAMP stack, Java RMI message passing, and Python wrappers. Through PyroDB, non-bioinformaticians can execute pipelines assembled from interchangeable analysis modules. A bioinformaticist can integrate new tools based on a consistent API. In addition, the system checks both its own modules and external tools for the correct version before use. This provides assurance that analysis is performed with consistent software versions and ensures the integrity of those tools using cryptographic hash functions. Through these techniques, PyroDB is a step in the process of bringing sequence analysis to the same standard of precision and accountability as the procedures used in the lab. While currently applied towards 16S rRNA classification, this platform is applicable to a wide array of NGS analyses. By allowing the biologists to initiate analysis on the data and providing access to a permanent record of how the final results were reached, research institutions can achieve a higher level of innovation and quality.

Genomic diversity of *Propionibacterium acnes* bacteriophages and bacterium-phage interactions in the human skin microbiome

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Bacteriophages are important components of microbial communities and play essential roles in regulating the community dynamics. *Propionibacterium acnes* is a major human skin commensal and has been linked to acne vulgaris, one of the most common skin diseases. *P. acnes* bacteriophages have been identified in the human skin microbiome, however, the understanding of the genetic diversity of *P. acnes* phages has been limited with only three available genome sequences. To determine the diversity and host range and specificity of *P. acnes* phages in the skin microbiome, we isolated 93 *P. acnes* phages from the skin of normal individuals and acne patients and sequenced 13 of them using 454 sequencing. The genomes of the 13 phages were fully assembled, completed and annotated. Our comparative genome analysis demonstrated that *P. acnes* phages are more genetically diverse than previously observed with distinct lineages of phage strains. In addition, we determined the interactions of these phages with different species of Propionibacteria and multiple strains of *P. acnes* found in the skin microbiota. The susceptibility/resistance of the bacterial strains to these phages correlated with the lineages of *P. acnes*. Our study suggests that diverse groups of *P. acnes* phages exist in the human skin microbiome and that bacteria-phage interactions may play a role in regulating the strain population of *P. acnes,* which has can affect in the dynamic skin microbiome in health and disease.

Sequence Non-Specific Adenine Methyltransferases: Do Phages Carry Prophylactics?

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Bacterial DNA methyltransferases often form one half of a Restriction-Modification (RM) system, which acts against invading foreign DNAs. Recently a family of broad-specificity N6-adenine (m6A) methyltransferases was identified from the observation that the methyltransferase gene directly replaced the DNA modifying mom gene in some Mu-like prophage elements. These methyltransferases were shown to modify a remarkably high percentage of adenine residues, from 29% to as much as 61% methylated. We have taken advantage of SMRT sequencing technology's revolutionary ability to directly read DNA methylation status to discover two additional families of sequence non-specific methyltransferases, demonstrating that broad-specificity m6A DNA methyltransferases have evolved to form at least 3 distinct protein families. We observe hundreds of putative homologs for each protein family in bacterial genome sequences: these often occur alongside putative prophage elements and are found most commonly, although not exclusively, in the enteric bacteria. We have expressed several enzymes of the beta-class methyltransferase family and find that these modify adenine bases in any sequence context, including poly-A tracts, producing 83% methylated adenine *in vivo*. The broad-specificity N6A methyltransferases appear to not be expressed in their bacterial host during normal culture since the host bacterial genomic DNA is not extensively m6A modified. These methyltransferases typically occur within prophages in the genome suggesting that they served a prophylactic function against host restriction enzymes during infection and prior to establishing lysogeny.

The metabolic distance sweet spot in microbial succession

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Bacteria and other micro-organisms are often organized in spatially and temporally structured ecosystems. Spatially organized communities (biofilms) can be resistant to anti-microbial agents, posing unresolved biomedical challenges. Structured communities are often the result of a well-defined microbial succession, which creates organization by an incremental and selective introduction of organisms to the pre-existing community. While the order of succession in communities such as the dental biofilm, and the gut microbiome is partially known, the factors driving succession remains largely uncharacterized. To address this question, we analyzed, from a metabolic perspective, the temporal succession of microbial genera in the gut, and the spatial organization in the dental biofilm. Enzyme and reaction data were extracted from the KEGG database and converted into enzyme profiles across relevant genera. We leveraged these profiles to create organism-to-organism metabolic distance matrices. Based on this information, and on literature-available data on the process of colonization, we evaluated the average pairwise metabolic distance between adjacent organisms in the succession. This average distance was then compared to a distribution of average metabolic distances between adjacent organisms for randomized orders of succession. We found that in both communities there is a tendency towards a minimal metabolic distance between temporally and spatially adjacent organisms. A paradox ensuing from this result is that, unless counter-balanced by an opposite trend, this tendency would lead to the collapse of the community into a competitive struggle between metabolically similar species. We hypothesize that a tendency towards maximal metabolic versatility could serve as the counter-acting force. In particular, using elementary flux modes, we demonstrate how a specific range of metabolic distances between two networks can synergistically give rise to a maximal number of joint metabolic functions. Such a range suggests the existence of a metabolic distance "sweet spot" of potential broader relevance.

**Illumina 16S sequencing reveals the time scale of changes to the gut microbial community due to
inflammation and cage effects in a mouse model of inflammation.**

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The state of the gut microbial community has in humans been associated with inflammation and progression to colorectal cancer. IL10 is an important anti-inflammatory cytokine and the IL10-/mouse model has long been used to study the consequences of inflammation. In this study, we report on changes that occur over time to the gut microbial community between wild-type and IL10-/-knockout mice. Using paired end Illumina sequencing of 16S V6 rRNA amplicons, we find pervasive cage effects established within the first 2 weeks of removal from gnobiotic conditions; in both WT and IL10-/mice, much of the first 5 principle components of microbial variation can be explained by the cage in which the animals were housed. Superimposed on this variation, however, are significant differences in the microbial community between WT and IL10-/-mice that become more pronounced over time. Changes associated with the IL10-/-phenotype include a drop in diversity and an expansion of Proteobacteria. We conclude that the IL10-/-genotype can take several months to fully influence the composition of the microbial community and that great care must be taken to separate cage artifacts associated with animal husbandry from true biological signals.

Potential role of novel protein domain and bacteriophages in evolution of virulence in Fusobacterium

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Elucidation of the mechanism of inhibition of antisense RNA in *Escherichia coli* using real time PCR

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There is a widely recognized unmet medical need to discover and develop novel antibiotics due to the emergence and spread of multidrug-resistant bacterial pathogens. Previously our laboratory constructed shot-gun *Escherichia coli* genomic libraries using a pair-termini expression vector (pHN678) and screened 250,000 individual library clones for inducible growth inhibition. Over 600 inducer sensitive clones were identified and sequenced. Among these clones, we identified 152 separate antisense (as) RNA constructs which could silence essential genes. These asRNA cell clones were further classified as highly, moderately or slightly sensitive to the inducer IPTG (isopropyl-beta-D-thiogalactopyranoside) based on a quantitative inducer sensitivity profiling (QISP) assay. To elucidate the mechanism of asRNA inhibition in *E. coli*, quantitative real time PCR assays were developed. In cell clone PT304, the asRNA directly targets the *rplL* gene of the *rplKAJL-rpoBC* operon. When PT304 was induced, there was a significant reduction in mRNA of *rplJ* gene, which is directly upstream of *rplL*, compared to non-induced conditions, while the transcripts of other genes within the same operon remain unchanged in the presence of IPTG. In another cell clone PT1580C, whose asRNA targets the *rplK* gene of the same operon, the transcript level corresponding to the *rplK* gene was significantly reduced in the presence of IPTG. Our preliminary results indicated that induction of asRNA molecules appear to result in instability of transcripts at or immediately upstream of the gene region targeted by the asRNA.

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Selective Capture: A Technology for Retrieving Specific DNA Sequences.

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Selective capture is a method for retrieving and concentrating specific DNA sequences from a complex mixture of genomic DNA. The method uses a biotinylated oligonucleotide that targets a sequence of interest removing that sequence and at least 5000 base pairs of adjacent DNA with high specificity. Biotinylated oligonucleotides from 18-200 bases performed equally well in the capture protocol. Positive results were obtained from samples containing as little as 70 femtograms of target DNA. A mock community consisting of genomic DNA from 21 bacteria with concentrations varying by as much as four orders of magnitude was used to evaluate the method for estimating metagenomic communities. We targeted the 16S rRNA gene of the species within the mixture using a universal primer (U1406R). The captured fragments were retrieved and made double-stranded using another universal primer (E8F). Capture material was sequenced using Illumina HiSeq 2000. Partial 16S rRNA gene sequences from all 21 organisms in the mock community were identified regardless of their concentrations. The relative distribution of species-specific rRNA genes detected approximates that of known concentrations found in the mock community. This protocol is a fast and effective method for retrieving specific sequences from mixtures of DNA. Our results suggest that this method could be helpful in metagenomic studies, providing a means of retrieving low abundances sequences from complex mixtures.

The Database of Mycoplasma Evolution: Connecting Genotype to Phenotype

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Mycoplasma are a genus of interest for studying reductive evolution. All Mycoplasma are saprophitic or parasitic, and the reductive evolution associated with host adaptation is of interest to researchers from fields as diverse as biomedicine, bioenergy and genome evolution. Here we present the Database of Mycoplasma Evolution (DOME), which will act as a prime resource fro comparative genomics study of Mycoplasma.. Using GMOD's GBrowse as a visualization tool, this database will store the genomic information of Mycoplasma in one place. The genomic information is associated with an image database, awhere connections can be made between genotypes and phenotypes. Using tags within images, we can specifically relate cellular components of Mycoplasma to their genes. Finally, DOME will provide a hub for communication between Mycoplasmologists and help the community of mycoplamsa researches in a rapid exchange of genomic and phenotypic information.

Primary immunodeficiencies alter the landscape of the human skin microbiome

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While recent work has explored how immune cells are activated and educated by microbiota, little is known of how the human immune system selects and regulates microbial diversity. Here, we describe the skin microbiome of three primary immunodefciency (PID) patient populations arising from monogenic mutations with subsequent loss of distinct lymphocytic populations. We surveyed the skin microbiomes of 41 patients with Hyper IgE, Wiskott-Aldrich, & Dedicator of Cytokinesis 8 syndromes. All three of these disorders share a common phenotype of skin atopic dermatitis (AD; eczema). Compared with both healthy controls and AD patients, we found that primary immunodeficiency increases the permissiveness of skin microbial colonization. We observed decreased site specificity and longitudinal stability in PID patients, as well as colonization by environmental microbiota not observed in healthy or AD controls. Distinct taxa such as *Staphylococcus epidermidids* and *Corynebacteria* are significantly correlated to key features of PID disease incidence and severity. These data provide the first illustration of how immune cells shape microbial prevalence, diversity, and dynamics in the context of skin disease, and lend insight into the complexity of host-microbiome-environment interactions.

Pathological changes in homeostatic microbiome of the human corneal epithelium.

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Infections of the ocular surface (OS), including microbial keratitis and conjunctivitis, are major causes of visual disability and blindness in the US and world-wide. Although the healthy cornea is considered free of microbiota through bactericidal action of tear film, the new experimental evidence indicates the presence of a resident microbiome. In this study cross-sectional study we analyzed diversity, relative abundance, individual and gender-related variations in bacterial composition of the corneal microbiome.

The healthy homeostatic bacterial community at the corneal epithelium is dominated by species of *Propionibacterium, Staphilococcus* and *Bradyrhizobium*, however, the composition is heavily influenced by gender and is significantly perturbed by ulcerating infectious keratitis. More than 90% of all reads were composed by five most prevalent genera in women and only 2 in men. About 25% of all reads that remained unclassified beyond Bacteria by RDP-II Classifier v.10 and were further analyzed against NCBI database using our new BlastN-based script. This approach allowed us to classify 27% of reads rejected by RDP-II down to the genus level and 1% down to the species level. Nearly all remaining sequences showed at least one holomology hit by BlastN.

The group composition of homeostatic bacterial communities indicated that they are influenced by gender. In addition to a healthy group of subjects, we analyzed an age-matched group of individuals with ulcerative bacterial keratitis. Between-group comparison has revealed the perturbation caused to it by bacterial infection in ulcerative keratitis. The community associated with the onset of keratitis was always dominated by *Pseudomonas* sp. and small cohort of typical satellites, indicating multibacterial mode of infection. Our results suggest that homeostatic corneal microbiome correlates with ocular surface health, while the onset of pathology severely disrupts this community.

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Transcriptome analysis of *Variovorax paradoxus* EPS biofilms suggests a role for small secreted DNA binding proteins in biofilm structure

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Variovorax paradoxus strain EPS is a widespread mucoid β-proteobacterium involved in many important environmental biotransformations. This species promotes plant growth, which we have demonstrated with our strain using *Helianthus annuus*. We have previously identified numerous genes involved in biofilm formation in *V. paradoxus*, and utilizing the recently finished genome sequence we have embarked on transcriptome analysis using RNA-seq to identify genes up and down-regulated during this mode of growth. Using triplicate biological samples from log phase growth and 48h static biofilm samples we examined paired-end Illumina sequencing results with 14-15 million reads per sample. We utilized the Galaxy framework (https://main.g2.bx.psu.edu) to map our data to the finished sequence followed by gene-level analysis of transcription using the IMG annotation of the genome. To determine FPKM levels we utilized Cufflinks, and we employed the DeSeq algorithm via the Rätch lab Galaxy mirror site (http://galaxy.fml.mpg.de) to test for significance. Based on this initial analysis we identified a total of 1639 genes as significantly altered in expression ($p<0.001$). Of those, 1398 genes that were altered >2 fold up or down from log phase, and 591 were altered >4-fold. The global expression data largely supported our previous mutagenesis and qPCR based analysis. We identified two genes with very large increases in biofilm expression, Varpa_0407 and Varpa_3832, that encode small, secreted proteins with homology to the Snf2 superfamily of DNA binding proteins. Our hypothesis going forward is that these proteins are involved in stabilizing the structure of the biofilm matrix, which includes extracellular DNA. If this is verified biochemically, it represents a discovery that would have been impossible without RNA-seq interrogation of the system.

The Rate of Operon evolution in Proteobacteria

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How operons evolve in an open question in genome evolution, and several models have been proposed to explain observed evolutionary patterns. However, there is no uniform method to describe operon evolution, which is necessary for a large-scale examination over many genomes and operons. Here we propose a computational method to classify operons by their evolutionary trajectory. This method will enable us to examine how operons evolve on a case-by-case basis, and classify them by their mode of evolution.

We propose that the construction and/or destruction of clusters of co-transcribed genes can be described as a sequential series of defined events. By examining these events we can employ statistical learning to classify evolutionary paths of operons, and connect these paths with biological function. At the most basic level, clusters of genes can undergo a few basic operations. Clusters can be broken into smaller groups, and constituent genes can be duplicated, deleted, rearranged, or fused.

Using a set of 36 proteobacteria species and 46 different experimentally verified *E. coli* operons, containing five genes or more, we have examined the frequency of events for the study of operon evolution. The events that we track correlate with evolutionary distance between individual taxa. Event tracking has allowed us to compare the relative rate of evolution against evolutionary time. Some operons appear to have consistently high or low frequency of events making them fast or slow evolving, respectively.. Slow evolvers comprise essential gene complexes, including core metabolic functions like H^+-ATPase, components of the transcriptome, and essential auxiliary functions such as CRISPER elements. Fast evolving operons tend to be non-essential or have variable functions, like the utilization of alternate metabolites such as glycolate, serine, or construction of the LPS, certain transporters and two-component systems

Targeted genome reconstruction strategy for endosymbionts in eukaryotic meta-genomes

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The availability of low-cost high-throughput next generation sequencing technologies presents an opportunity for *in-silico* discovery of endosymbionts. We describe a method for mining a whole genome shotgun metagenome from an insect vector of the disease, citrus greening, to identify members of the endosymbiont community followed by reconstruction and validation of a high-quality draft microbial genome.

The Asian citrus psyllid (D. citri Kuwayama or ACP) is host to 7+ bacterial endosymbionts and is the insect vector of Ca. liberibacter asiaticus, causal agent of citrus greening, a disease that has cost the Florida citrus industry $3.63 billion since 2006. Citrus greening is a complex patho-system which involves interactions between the psyllid vector, the citrus hosts, and Ca. liberibacter asiaticus. Within the psyllids are a living fauna of microbes whose identity and functions are unknown.

DNA from D. citri was sequenced to 108X coverage to produce paired-end and mate-pair Illumina read libraries. The sequences were mined for wolbachia (wACP) reads using 4 sequenced Wolbachia genomes as bait. Putative wACP reads were then assembled using Velvet and MIRA3 assemblers. The resulting wACP contigs were annotated using the RAST and compared to the closest sequenced wolbachia from an insect genome, Wolbachia endosymbiont of Culex quinquefasciatus (wPip). MIRA3 was able to reconstruct a majority of the wPip CDS regions and was therefore, selected for scaffolding using large insert mate-pair libraries. The wACP scaffolds were further improved using Abacas and Mauve contig mover with wPip as reference genome to orient and order the contigs.

In order to determine the presence of the core Wolbachia proteins in our wACP scaffold, we compared them to core Wolbachia proteins identified by OrthoMCL. 1164/1213 wACP proteins had matches of which 669 were to core proteins. This number compares favorably to the number of core proteins (670) found in sequenced Wolbachias.

Title: Discovering species-level co-variation and co-occurrence patterns in the human microbiome

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Background: Microbial ecology has long investigated the symbiotic relationships commonplace within microbial communities, but projects such as the Human Microbiome Project (HMP) and MetaHIT have only recently allowed their investigation within the human body. Methodological challenges arise in detecting statistically significant quantitative co-variation or qualitative co-occurrence among microbes . These have likewise been well-studied, but must be adapted to the high-dimensional measurements provided by modern sequencing. Such metagenomic sequencing can now provide species-level microbial measurements, to complement the genus-level measurements of 16S pyrosequencing.

Results: Here, we assessed 682 metagenomes from the HMP, describing six body site habitats profiled using MetaPhlAn, extending recent work on co-variation networks to species-level data in the human microbiome using two approaches. First, we applied the ReBoot procedure determine significant co-variation in relative abundances while avoiding spurious correlation from compositionality, resulting in a network of 4,464 within- and between-site associations among 501 site-specific clades. These recapitulated the basic characteristics of earlier 16S-based networks, including little (<15%) between-site interaction and few "hub" microbes (scale-freeness). A surprising degree of positive co-variation among species within genera was detected, suggesting a combination of species-specific niche specialization with general environmental favorability. Second, to differentiate co-variation from co-occurrence, we assessed patterns of microbial presence and absence, resulting in a smaller network of 96 associations among 87 clade/site combinations. These represented less prevalent microbes absent from a substantial portion of the population, such as the cross-site co-occurrence of rare species from *Porphyromonas*, *Prevotella*, and *Neisseria* in the oral cavity.

Conclusions: As some correlational measures such as Spearman do not adequately account for sparse data, we are extending the ReBoot procedure to utilize more robust measures. Together, these newly accessible methods and data will allow the detection of species and, eventually, sub-species level ecological interactions within the human microbiome and other microbial communities.

A Metagenomic Study of Diet-Dependent Interaction Between Gut Microflora and Host in Infants

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Gut flora species and functional composition strongly affect the health and well-being of the host. With the advent of genomic-based personalized medicine, it is important to develop a synthetic approach to study the host transcriptome and the microbiome simultaneously. Early microbial colonization in infants is critically important for directing neonatal intestinal and immune development, and is especially attractive for studying the development of human-commensal interactions. Here we report the results from a study of the gut microbiome and host epithelial transcriptome of three month old exclusively breast-fed and formula-fed infants. Both host mRNA expression and the microbiome phylogenetic and functional profiles provided strong feature sets that distinctly classified the formula-fed from the breast-fed infants. To determine the relationship between host epithelial cell gene expression and the bacterial metagenomic-based profiles, the host transcriptome and functionally profiled microbiome data were subjected to multivariate statistical analyses. Gut microbiota metagenome virulence characteristics strongly differed between the formula-fed and the breast-fed infants, while concurrently immunity/mucosal related gene expression in epithelial cells differed as well. Our data provide insight into the integrated responses of the host and microbiome to dietary substrates in the early neonatal period. We demonstrate that differences in diet can affect, through gut colonization, both infant gut development and the innate immune system. Furthermore, the methodology presented in this study can be adapted to assess other host-commensal and host-pathogen interactions using genomic and transcriptomic data, providing a synthetic genomics-based picture of host-commensal relationships.

Design and validation of a real-time PCR assay for the detection of extraintestinal pathogenic *E. coli*

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Escherichia coli can be classified into three major groups: commensal, diarrheagenic and extraintestinal pathogenic. In the developed world, extraintestinal pathogenic *E. coli* (ExPEC) contributes the greatest public health burden. Urinary tract infections (UTIs), sepsis, and meningitis are the most common ExPEC infections, resulting in US $1.6 to $2.5 billion in medical expenses. Rapid and reliable ExPEC identification is important, but current molecular techniques such as standard PCR are time-consuming and yield equivocal results. To address this, we designed and validated six real-time PCR assays to screen *E. coli* for the hallmark ExPEC virulence genes. DNA sequences for the hallmark ExPEC virulence genes—*papA, papC, kpsMII, afaC,* sfaE or *iutA*—were downloaded from public databases; sequences were aligned to define conserved regions; a set of target-specific primers and TaqMan® probes were designed for each gene. The six assays were combined into two triplexes and validated against a set of 167 poultry-associated *E. coli* isolates and 52 UTI isolates that were also whole-genome sequenced. The individual assays and the combined triplexes performed well in terms of sensitivity and specificity. Multiplexing saved time and reagent costs by reducing the number of reaction from six to two. The hallmark gene assays represent a valuable tool for public health since they are fast, easy to perform, and can be applied to clinical, environmental, and foodborne isolates to reliably differentiate ExPEC from other types of *E. coli.*

Characterization of Genomic Islands in Plant Pathogenic *Streptomyces* spp.

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Streptomyces species are typically saprophytes, but those rare members of the genus that are pathogenic, impact agricultural economies due their ability to cause important crop diseases such as potato scab. Plant-pathogenic *Streptomyces* species encode the pathway for the biosynthesis of a phytotoxin, thaxtomin, and a variable set of other virulence molecules. In *S. turgidiscabies* (St), pathogenesis-associated genes are clustered in a 600 Kb genomic island (PAIst). PAIst can be transferred to other streptomycetes, and integrates at an 8-bp palindromic sequence (*att*-PAI) within the 3' end of the recipient's bacitracin resistance gene (*bacA*). PAIst has two flanking and one internal *att*-PAI that divide the island into 100 Kb and 500 Kb modules; the smaller module contains pathogenesis-associated genes, and the larger encodes a thaxtomin biosynthesis cluster. Two types of circular intermediates have been detected in *S. turgidiscabies,* suggesting that the island is transferred in modules as an Integrative Mobilizable Element (IME). Smaller versions of PAIst exist in the pathogens *S. scabies* (Ss), *S. acidiscabies* (Sa). These two pathogens contain an identical copy of the 100 Kb module, however, the thaxtomin cluster is located in other regions of their chromosomes. Interestingly, there is no evidence for recombination at the *bacA* locus in another pathogen, *S. ipomoeae* (Si). The presence of the 100 Kb module in Ss, St, and Sa, but not in Si, suggests a model for evolution of these pathogens in which gene erosion fixed the island in Sa and Ss, and in which acquisition of virulence genes through site-specific recombination is occurring in other pathogenic *Streptomyces*.

MetAMOS: A modular and open source metagenomic assembly and analysis pipeline

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Metagenomics has opened the door to unprecedented comparative & ecological studies of microbial communities, ranging from the sea to soil (Terragenome), and even the human body (HMP, MetaHIT). While several tools have started to emerge to tackle specific tasks that often arise when analyzing metagenomic data, there is a current need for robust analysis pipelines which are able to combine existing tools and facilitate biologically relevant analyses. In an attempt to address this need, we have developed MetAMOS, a modular and customizable framework for metagenomic assembly and analysis. To researchers without bioinformatics expertise, MetAMOS provides a push-button solution for obtaining a first analysis of metagenomic datasets irrespective of the sequencing technology used. In addition to the actual assembly, MetAMOS outputs a taxonomic profile of the community, gene predictions, and potential genomic variants.

MetAMOS has three principal outputs: (1) subdirectories containing FASTA sequence of the contigs/scaffolds/variant motifs belonging to a pre-specified taxonomic level; (2) a collection of all unclassified/potentially novel contigs contained in the assembly; and (3) a HTML report with detailed assembly statistics and charts estimating abundance of a given taxonomy, also offering the capability of comparing related assemblies.

We have extensively compared MetAMOS to metagenomic assembly tools, Meta-IDBA and MetaVelvet, in addition to genome assemblers that have been used in published studies to assemble metagenomic data (SOAPdenovo, Velvet). In our experimental analysis we used both a mock/artificial dataset generated for the HMP project in addition to real metagenomic samples generated by the HMP and MetaHIT. On simulated and real datasets, MetAMOS produces more contiguous assemblies with fewer errors than existing tools, and offers several novel features such as: metagenomic repeat detection, assembly validation, biological variant identification, and propagation of annotations.

MetAMOS is open source and can be downloaded from: https://github.com/treangen/MetAMOS.

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Comparative Genomic Analysis of *Propionibacterium acnes* Bacteriophages

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Abstract:

Bacteriophages (phages) are the most ubiquitous biological entities in the biosphere, and those that have been characterized represent only a minute fraction of the entire phage population. Exploration of phage diversity as well as comparative analysis of phage genomes is significant because information is unveiled regarding phage function in the environment, their role in HGT among other ecological interactions with microbial communities, and the potential to be exploited as therapeutic agents against antibiotic resistant bacterial strains.

Acne vulgaris is a disease that affects 40-50 million individuals in the U.S. The disease occurs when conditions in microcomedones favor overproduction of *Propionibacterium acnes*, leading to inflammation and formation of lesions in the infected area. Currently, there is a lack of efficient and safe treatments for acne stemming from inadequate knowledge of the skin microbiome.

Undergraduates in a discovery-based research course at UCLA, many of whom have dealt with the manifestation of acne themselves, are tackling this problem by isolating novel *P. acnes* phages from bioré strips applied to their own noses. At present, only three *P. acnes* phage have annotated genomes available in GenBank. UCLA students have purified eight *P. acnes* phages with varying plaque morphologies representative of lytic and potentially pseudo-lysogenic life cycles. Electron microscopy has revealed they all share a *Siphoviridae* morphotype. 454 whole genome sequencing has been completed for four of these phages. The average size of published *P. acnes* phage genomes is between 29-30 kbp, with around 48-50 ORFs. Student annotation of new *P. acnes* phage genomes is consistent with published data. Their efforts also have evoked questions about integration potential and evolutionary history. A more extensive presentation of the curriculum as well as comparative analysis of the genomes will be presented here.

Revealing of the Human Gut Microbes Antibiotic Resistance from MetaHIT Data

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Abstract

Antibiotics resistance has become a serious issue because of the widespread use of antibiotics both inside and outside of medicine. Understanding the antibiotic resistance in the human intestine microbes have been initiated since last decade. However, the traditional screening methods are very labor intensive and only allow the study the bacteria which can be cultured on the media. The high-throughput metagenomic sequencing provides a great opportunity to study the human microbial antibiotic resistance through high-throughput method. Human intestine microbial project (MetaHIT) have been successfully finished through Illumina-based metagenomic sequencing, which assembled and characterized 3.3 million non-redundant microbial genes from faecal samples of 124 European individuals. The MetaHIT sequencing data provide some information for us understanding the prevalence of antibiotic resistance genes in the human intestine microbial community. The MetaHIT project sequencing data were downloaded from BGI website, and then were analyzed through a customized pipeline. A total of 868 antibiotic resistance genes were identified from 124 individual metagenomic sequencing data respectively. These antibiotic resistance genes contain most common antibiotic resistance genes, including penicillin, vancomycin, tetracyclin, chloramphenicol, macrolipid, aminoglycoside resistance genes, drug efflux pump, etc. The number of antibiotic resistance genes in each individual is ranging from 15 to 173, with an average number of 75 genes. The number of resistance genes identified in each individual may be related to two important factors, the metagenomic sequencing output and personal antibiotic usage history. Over 20 antibiotic resistance genes have been found within more than 75% surveying samples, which suggest these antibiotics resistance were high prevalence among these samples. Taken together, the high-throughput metagenomic sequencing along with bioinformatics approaches provide us a powerful approach to study the antibiotic resistance in the human intestine microbial community, and estimate the prevalence of antibiotic resistance.

Phenotypic and Molecular Characterization of Clinical Outbreak Isolates of *Acinetobacter baumannii* from Los Angeles County Hospitals.

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Multi-drug resistant strains of *Acinetobacter baumannii* have been responsible for an increasing number of nosocomial infections including bacteremia and ventilator assisted pneumonia. Recently, we analyzed 38 clinical isolates of *A. baumannii* obtained from hospital outbreaks in Los Angeles County. Antimicrobial susceptibility testing using 18 antibiotics indicated that all of these isolates were multidrug resistant. In particular, 29 (76 %) and 33 (87 %) of 38 isolates were found to be resistant to imipenem and meropenem, respectively. Additionally, all isolates were found to be resistant to ciprofloxacin, gatifloxacin (except one) and levofloxacin. Pulsed field gel electrophoresis showed that there were two main clonal types. Trilocus multiplex PCR confirmed the clonal types to be European Clone I and II. Multi locus sequence typing showed that representative isolates belong to sequence type 1 and 2. ISAba1 was detected immediately upstream of the bla_{OXA23} gene which is associated with carbapenem resistance. Sequence analysis of the *gyrA* and *parC* Quinolone Resistance Determinant Regions revealed mutations conferring simultaneous substitutions such that GyrA serine-83 was changed to leucine in all isolates and ParC serine-80 was changed to leucine in all except two. These results are consistent with the fluoroquinolone resistant phenotypes of the isolates. This study will enhance our understanding of the mechanisms of transmission, antimicrobial resistance, clonal dissemination, effective hospital infection control and improved clinical outcomes of *A. baumannii*.

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Breath gasses as biomarkers in Cystic Fibrosis

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Long-term microbial infections in the lungs of Cystic Fibrosis (CF) patients are complex, individual, and difficult to correlate with patient condition or response to treatment. Gasses found in the breath of CF patients may enable detection of the presence of specific microbial metabolism in a particular microbial community and disease state. Our goal is to find molecules in breath samples that are specific to microbial metabolism and unique to CF patients. Ultimately, we would like to unveil mechanisms that explain how bacteria persist in the CF lung. This information could be used to diagnose and treat infection specifically.

Using the Gas Chromotography and Mass Spectrometry methods established in the Rowland-Blake lab at UCI, we have analyzed seven triplicate breath samples at approximately monthly timepoints from a cystic fibrosis patient and three gender-matched controls along with a room sample to establish the background. We also took induced sputum samples from the same CF patient, at different timepoints, and sequenced the total viral DNA, microbial DNA and RNA.

We find elevated levels of 2,3-butanedione in the CF patient, which is not present in the three healthy controls. 2,3-butanedione is a fermentation product specific to a subset of bacteria including *Enterobacter* spp, *Streptococcus* spp and *Klebsiella* spp. In a bacterial fuel cell model recently published by the Angenent lab at Cornell University, 2,3-butanediol produced by *Enterobacter aerogenes* fueled increased growth rates in *Pseudomonas aeruginosa*. When *P. aeruginosa* had access to 2,3-butanediol as a carbon source, production of a particular phenazine, pyocyanin, greatly increased. Phenazines are redox active compounds that have been described as antibiotics, however they can also reduce Fe(III) to Fe(II), which *P. aeruginosa* is equipped to uptake with an Fe(II) specific transporter, FeoB. Phenazines can also act as electron acceptors, enabling anaerobic respiration in the low oxygen conditions of CF sputum. We find hits to genes involved in 2,3-butanedione metabolism and catabolism, along with phenazine production and Fe(II) transport in our CF microbial metagenomes.

The combination of 2,3-butanedione in the CF patient's breath with the presence of genes encoding enzymes required for butanedione and phenazine metabolism suggest that this CF patient's lung harbors the same productive bacterial interaction as the bacterial fuel cell model. Access to scarce iron resources and the ability to carry out anaerobic respiration could both give *P. aeruginosa* a survival advantage in the lungs of a CF patient. Synergism between bacteria which arises in the biogeochemical circumstances unique to an individual CF lung may be an important driver of microbial growth and provide explanations for difficult to diagnose exacerbations in CF patients.

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