

Disclosure



Arun Sanyal, VCU, VA USA

- Puneet Puri
- Faridoddin Mirshahi
- Kalyani Daita
- Amon
- Sophe
- Mulu

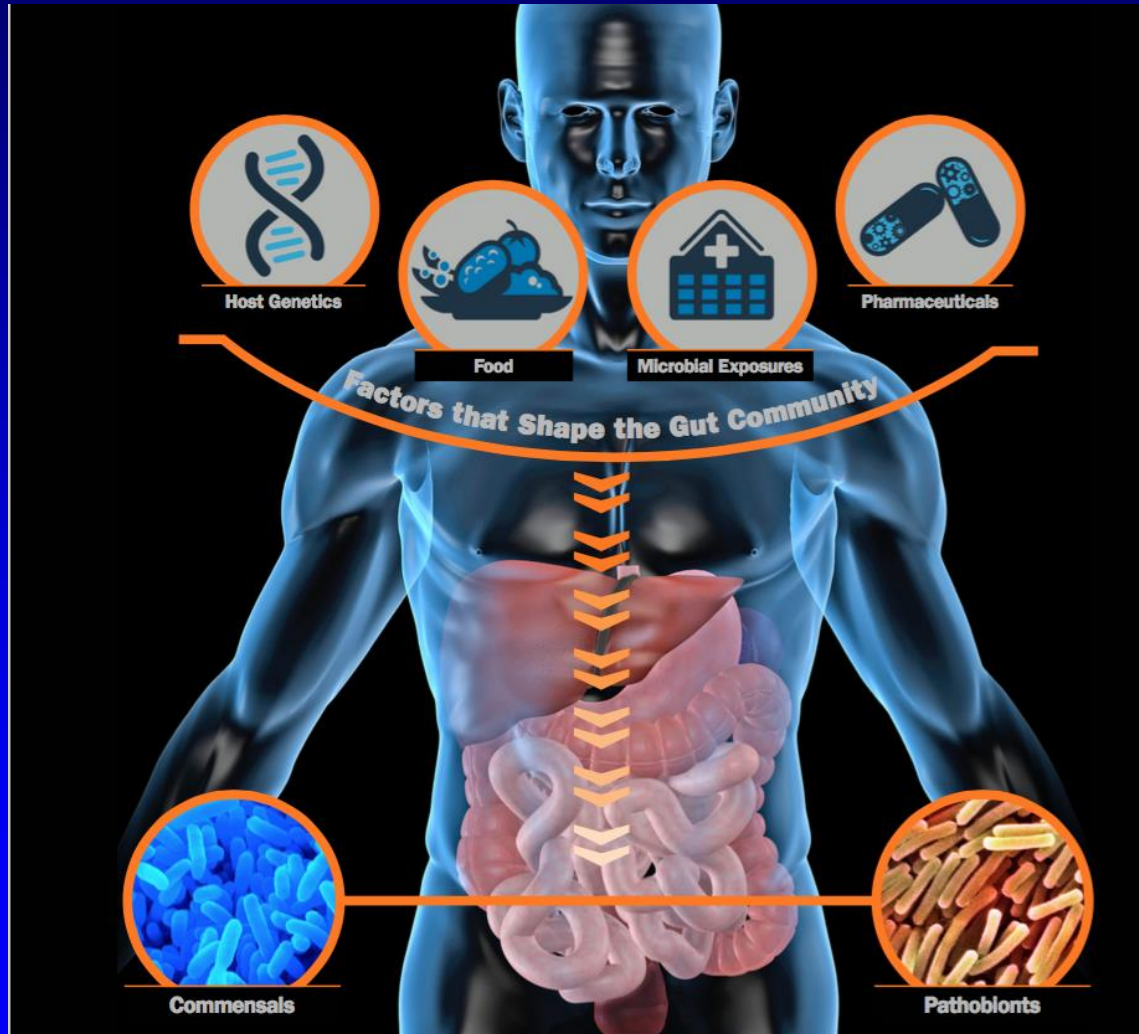


Patrick Gillevet, GMU, VA USA

- Masoumeh Sikaroodi
- Robert Brown
- Swati Dalmet
- Naga Betrapally
- Christine McGown

METABIOME

Gut-Brain-Liver-Immunome-Environment Axis

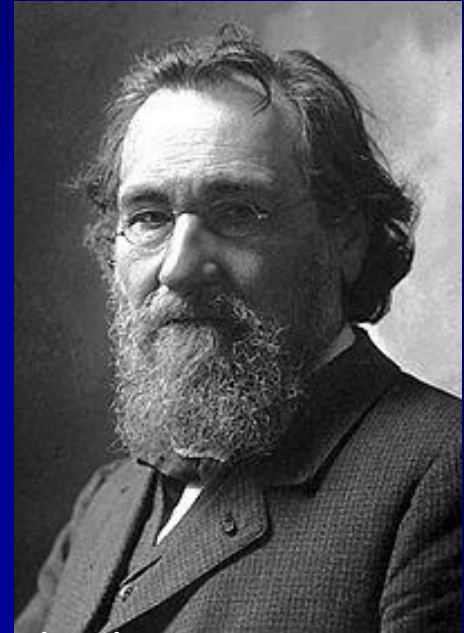


The Selfish Microbiome

Ilya Ilyich Mechnikov

1845-1916

(died when he was 71 years old)



- Microbiology and Immunology
- Noble Prize in 1908 – Phagocytosis
- Gerontology – toxic putrefying bacteria in gut
- Lactic acid bacteria – Probiotics
- Ate Kefir all his life

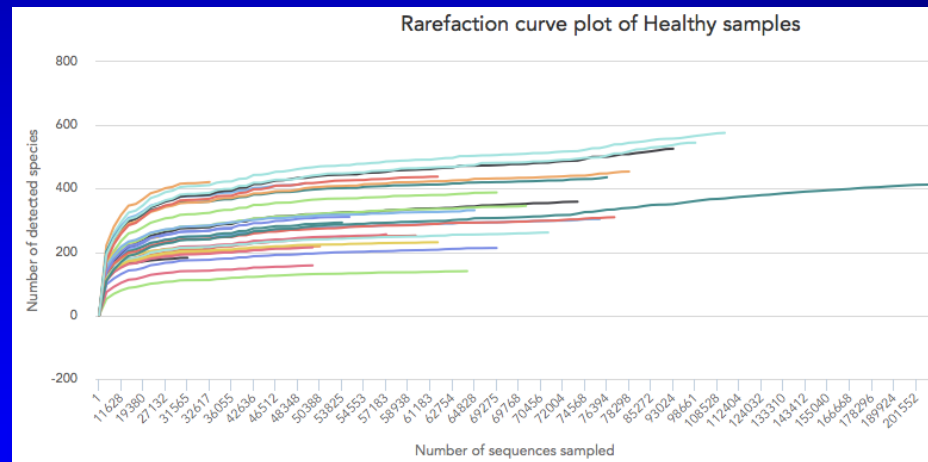
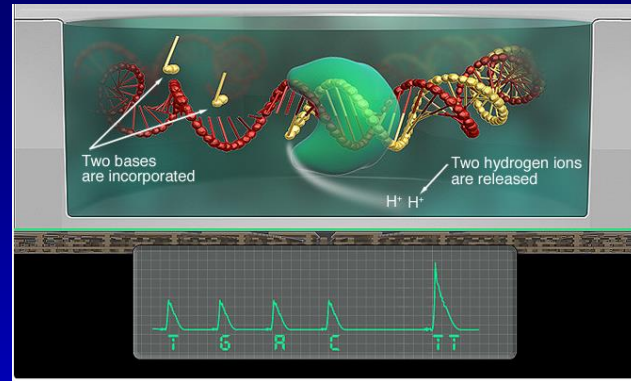
Human Microbiome Project is 100 years old

METABIOME

All interaction of host and microbes

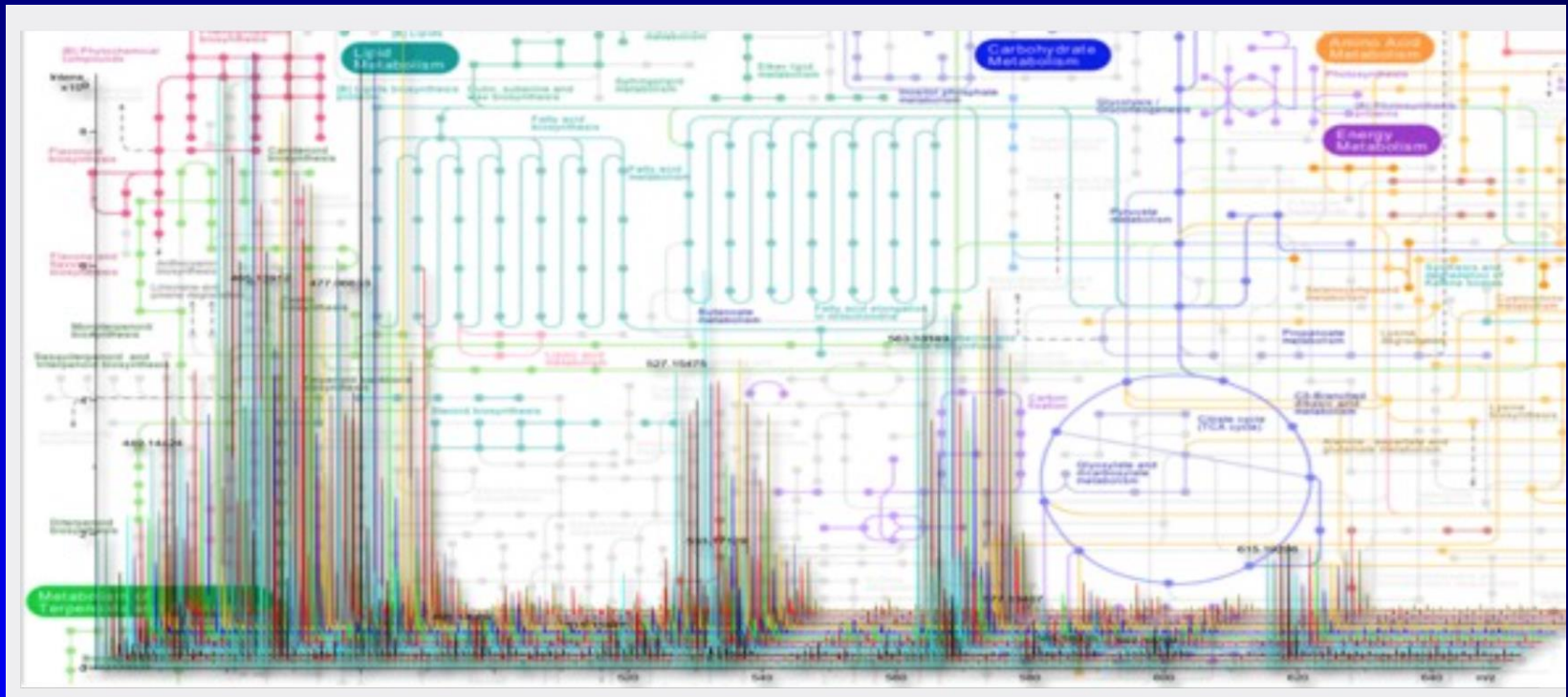
- **Analysis of Microbial Communities**
- **Ecological Modeling**
- **The Gut Liver Axis:**
 - **Bacteria**
 - **Drugs**
 - **Bile Acids**

Ion Torrent PGM (Thermo-Fisher)



4 million reads
10,000 reads / sample

Metabolome several thousand metabolites



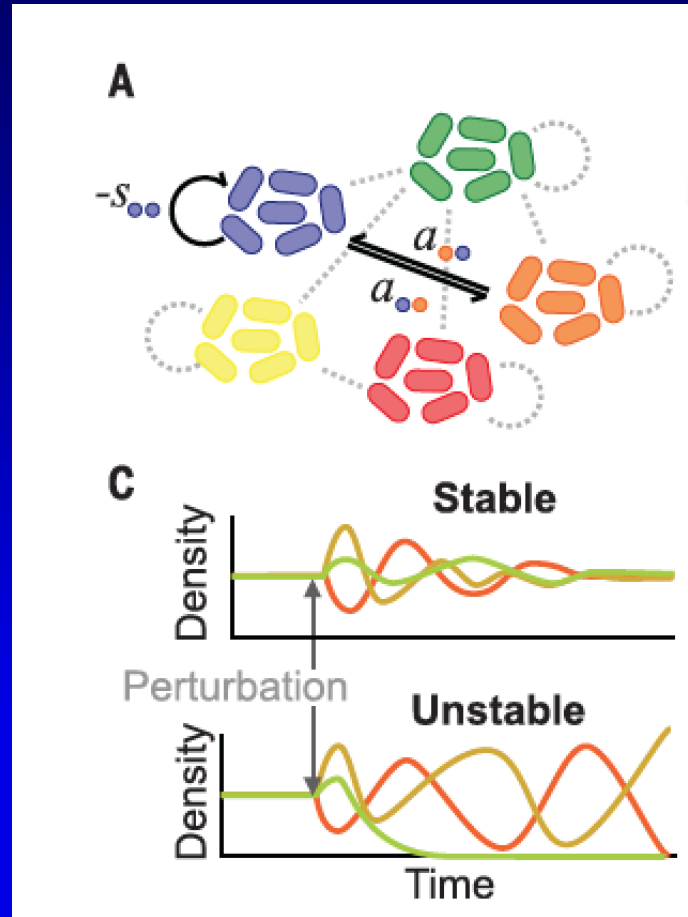
- GC-MS / LC-MS
- Data compatibility

METABIOME

All interaction of host and microbes

- Analysis of Microbial Communities
- **Ecological Modeling**
- The Gut Liver Axis:
 - Bacteria
 - Drugs
 - Bile Acids

Microbiome and Metabolome Oscillation

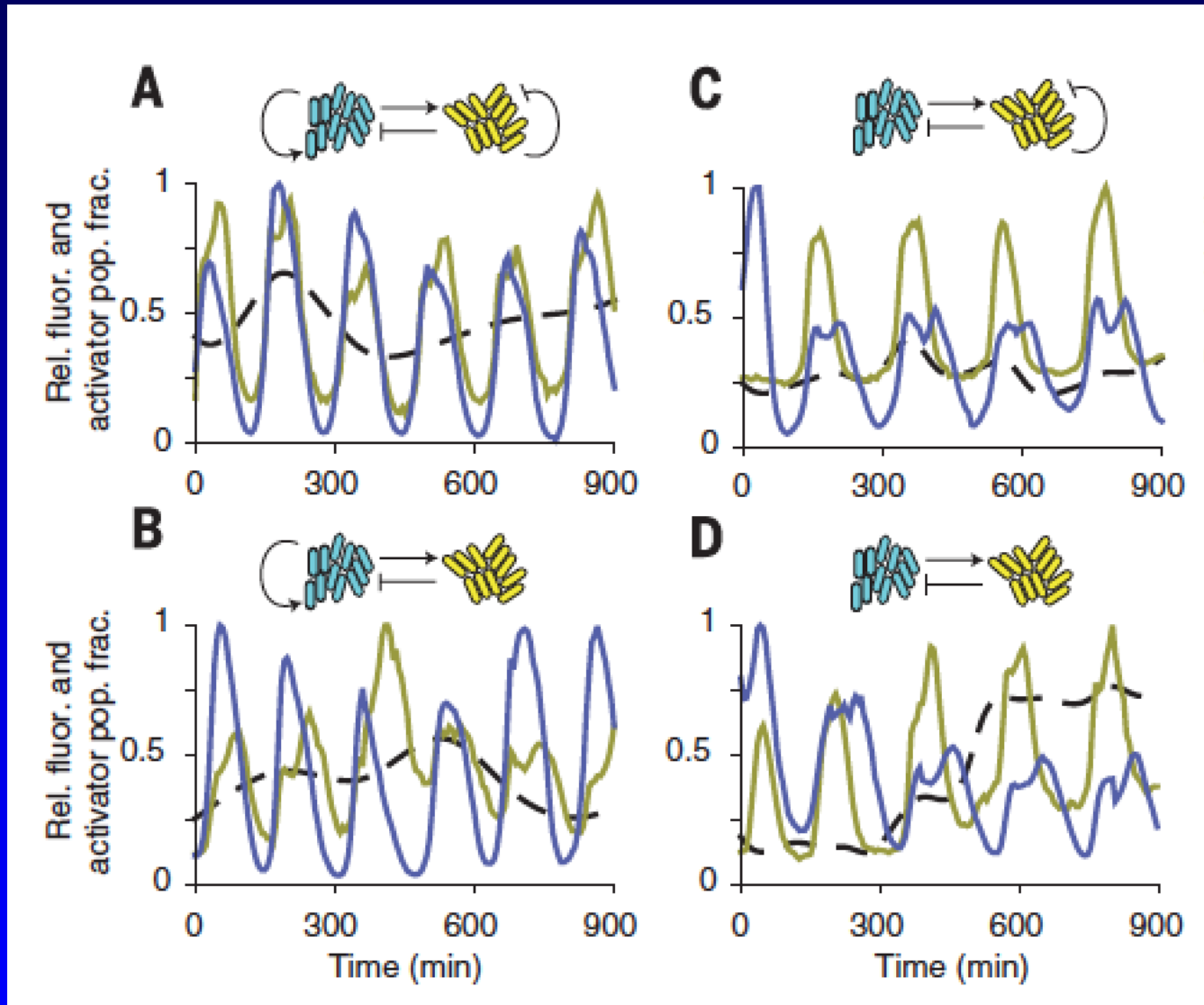


Healthy

Disease

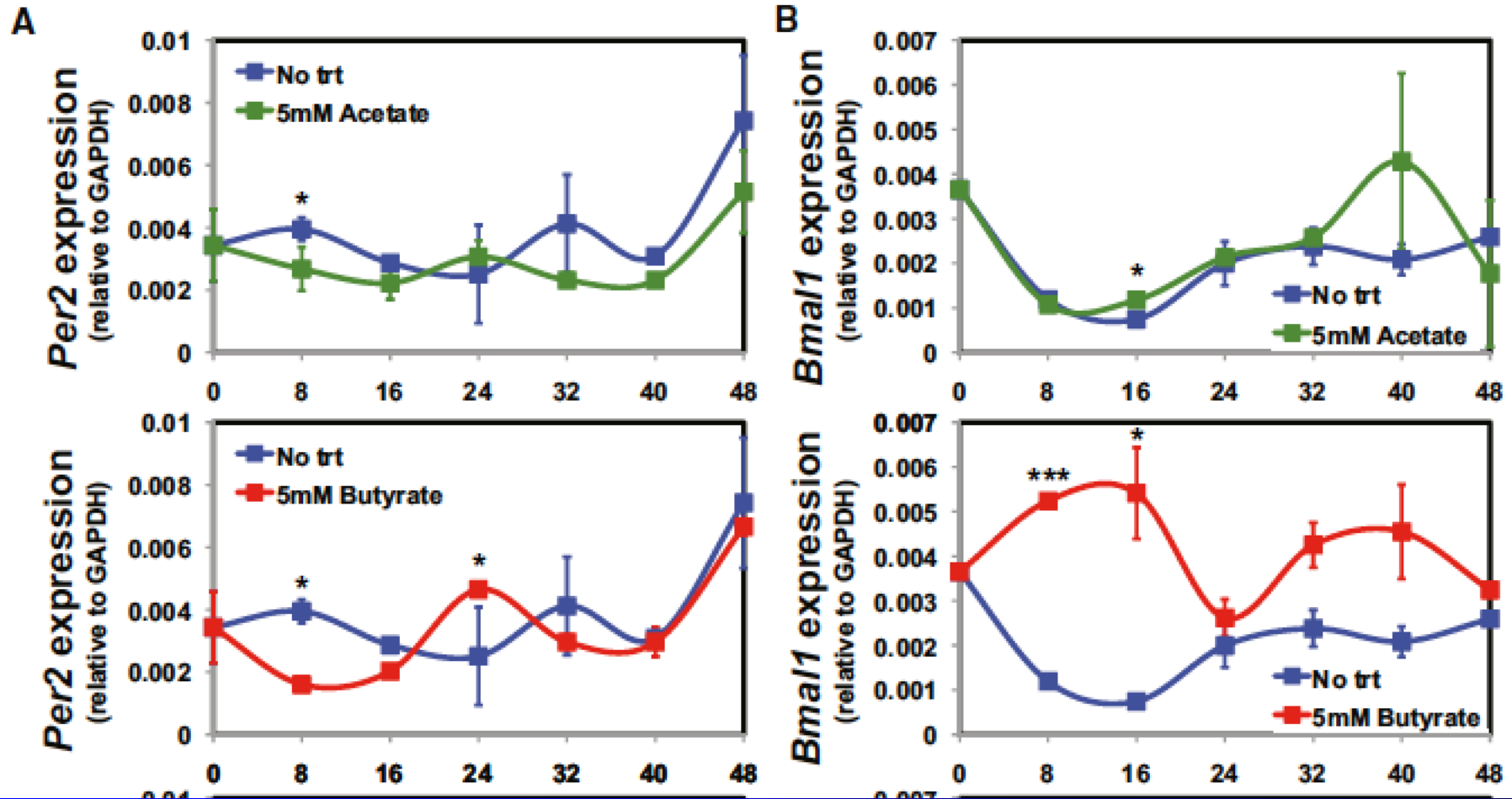
Coyte KZ, Schluter J, Foster KR (2015) The ecology of the microbiome: Networks, competition, and stability. *Science* 350(6261):663-6.

Model of Short Term Population Oscillations



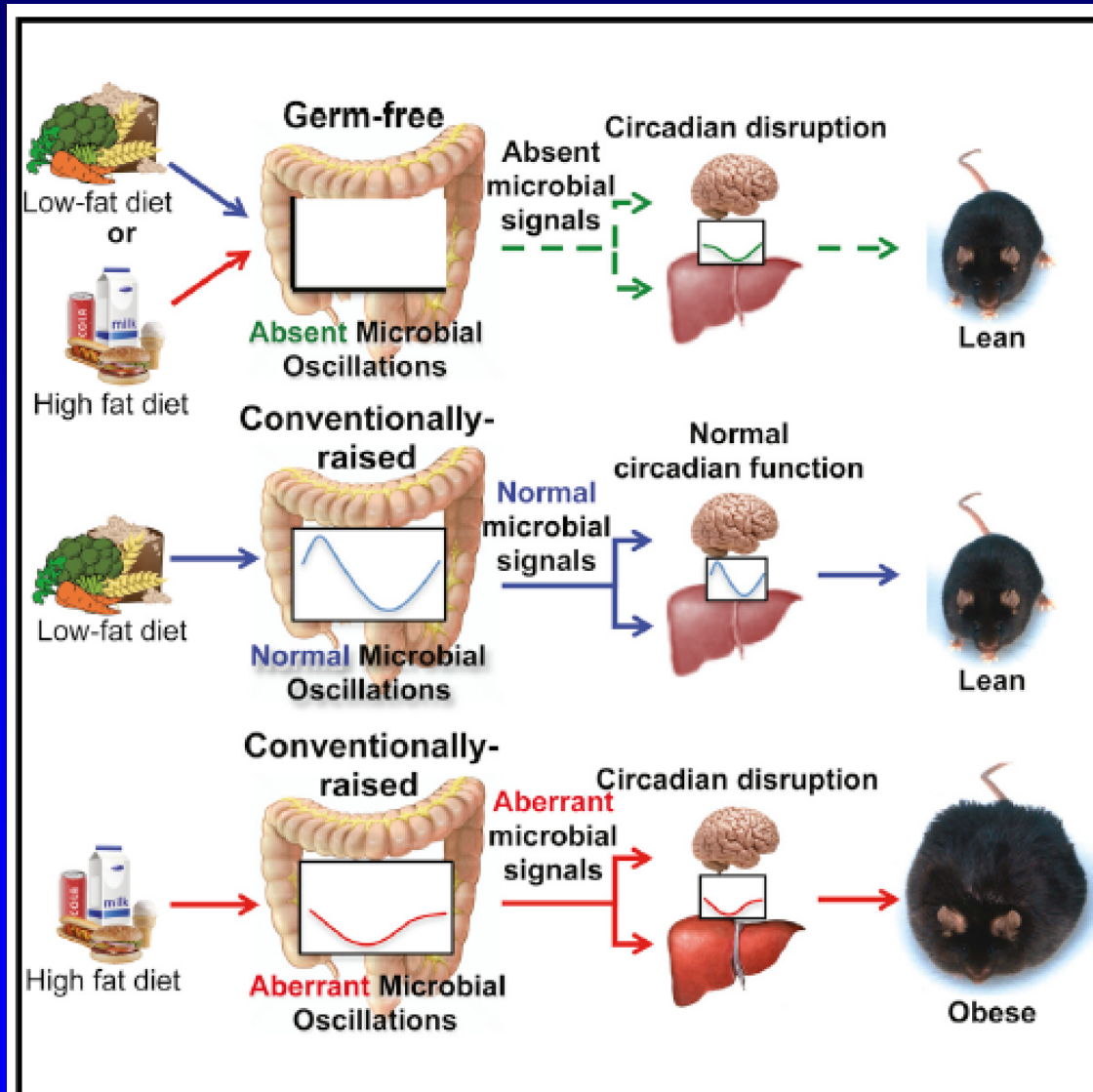
Chen Y, Kim JK, Hirning AJ, Josic K, Bennett MR (2015) SYNTHETIC BIOLOGY. Emergent genetic oscillations in a synthetic microbial consortium. *Science* 349(6251):986-9.

Diurnal Variation of Gut Microbes and High-Fat Feeding on Host Circadian Clock Function

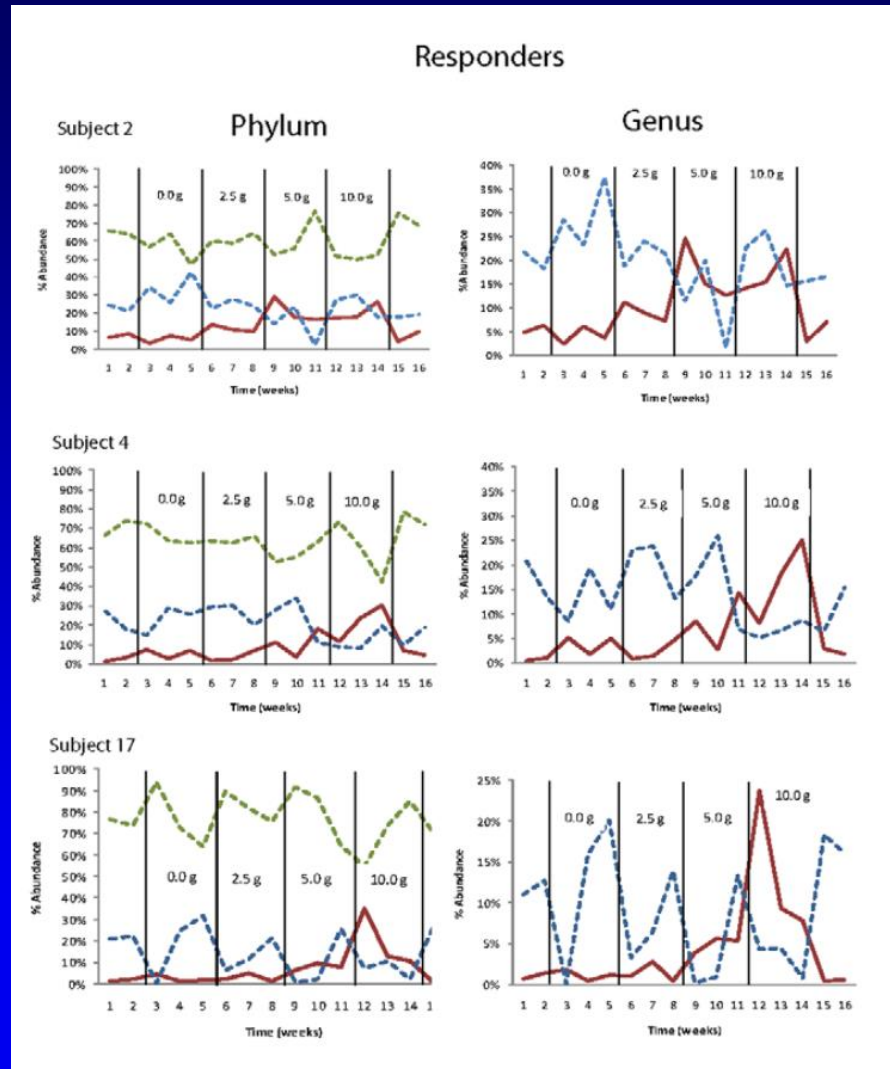


Leone et al (2015) Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host Microbe* 17(5):681-9.

Diurnal Variation of Gut Microbes and High-Fat Feeding on Host Circadian Clock Function



Observed Long Term Ecological Oscillations



Lauren M. G. Davis¹, Inés Martínez¹, Jens Walter¹, Caitlin Goin², Robert W. Hutkins¹ PLoS ONE
Volume 6 | Issue 9 | e25200 Barcoded Pyrosequencing Reveals That Consumption of
Galactooligosaccharides Results in a Highly Specific Bifidogenic Response in Humans

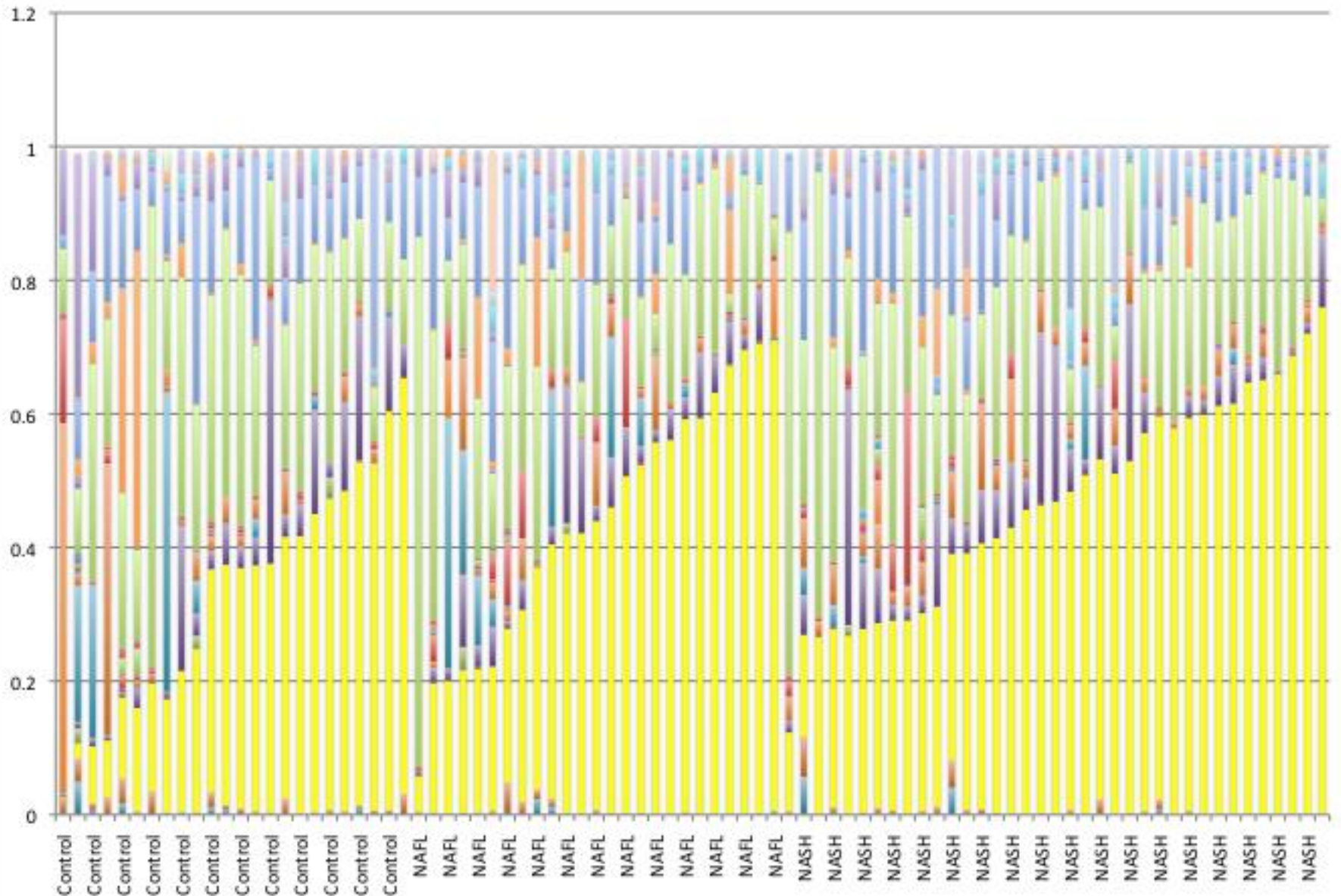
METABIOME

All interaction of host and microbes

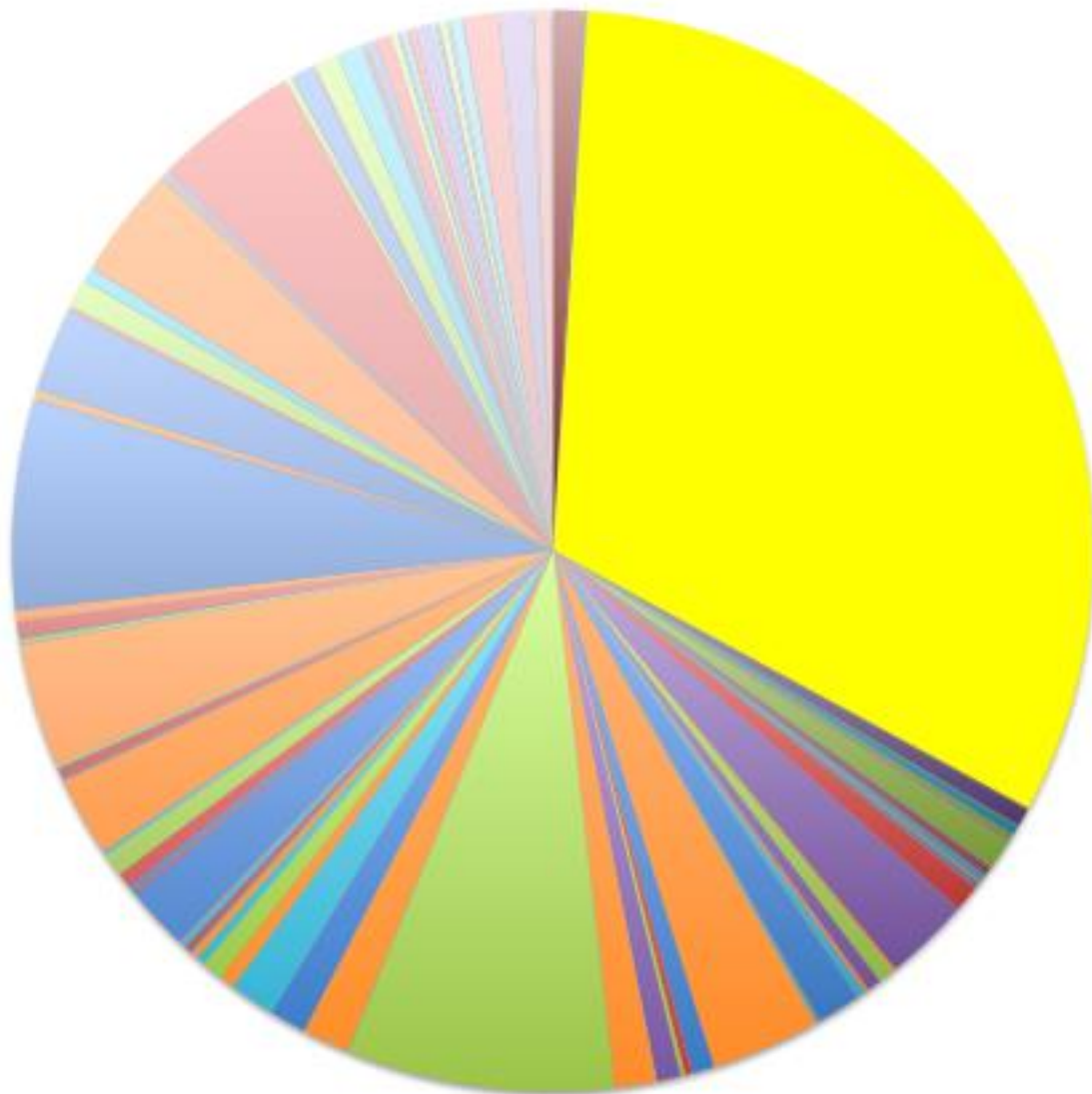
- **Analysis of Microbial Communities**
- **Ecological Modeling**
- **The Gut Liver Axis:**
 - **Bacteria**
 - **Drugs**
 - **Bile Acids**

NonLinear Dynamics: Bacteriodes Abundance

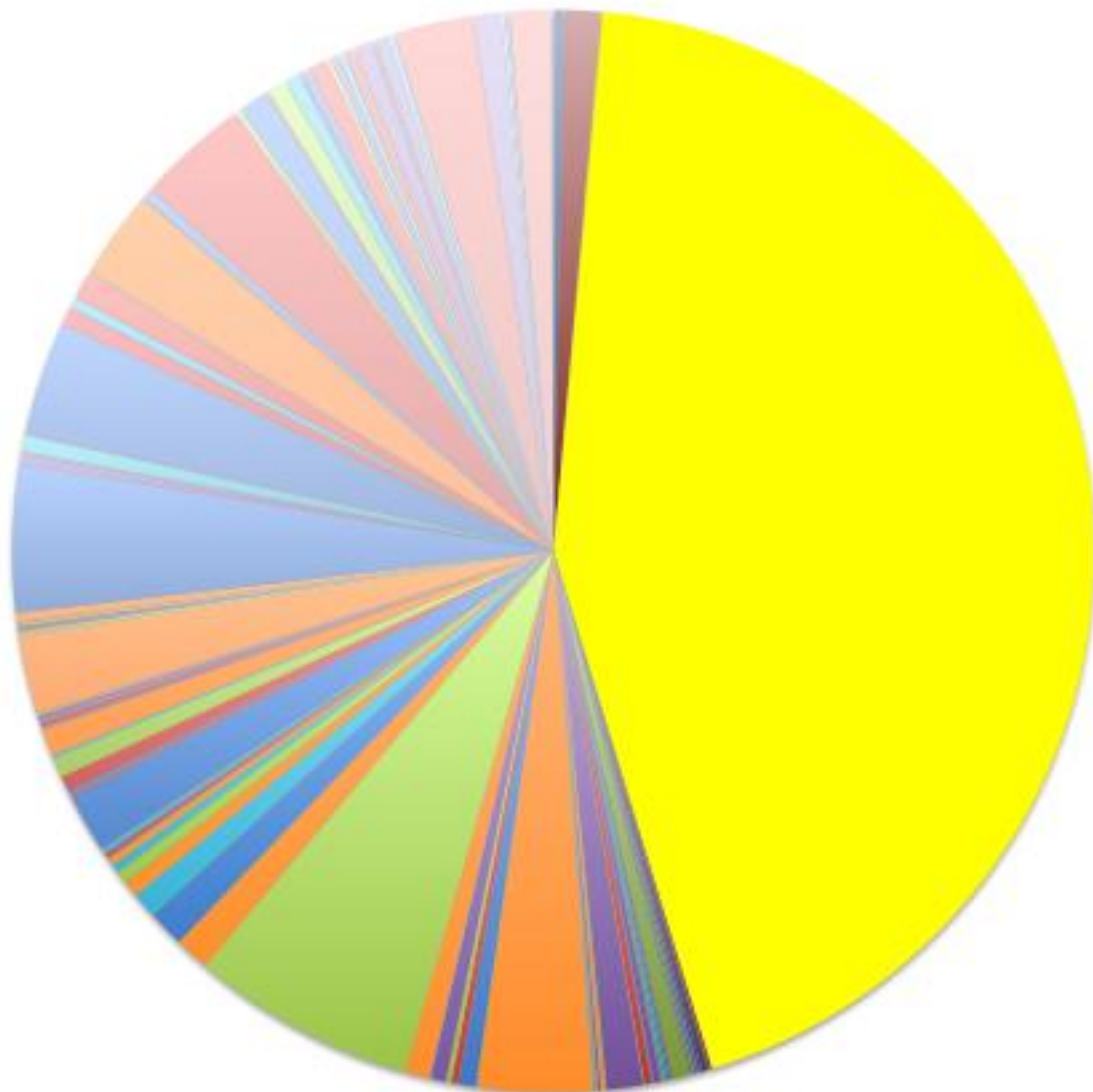
Sparse Nonparametric data



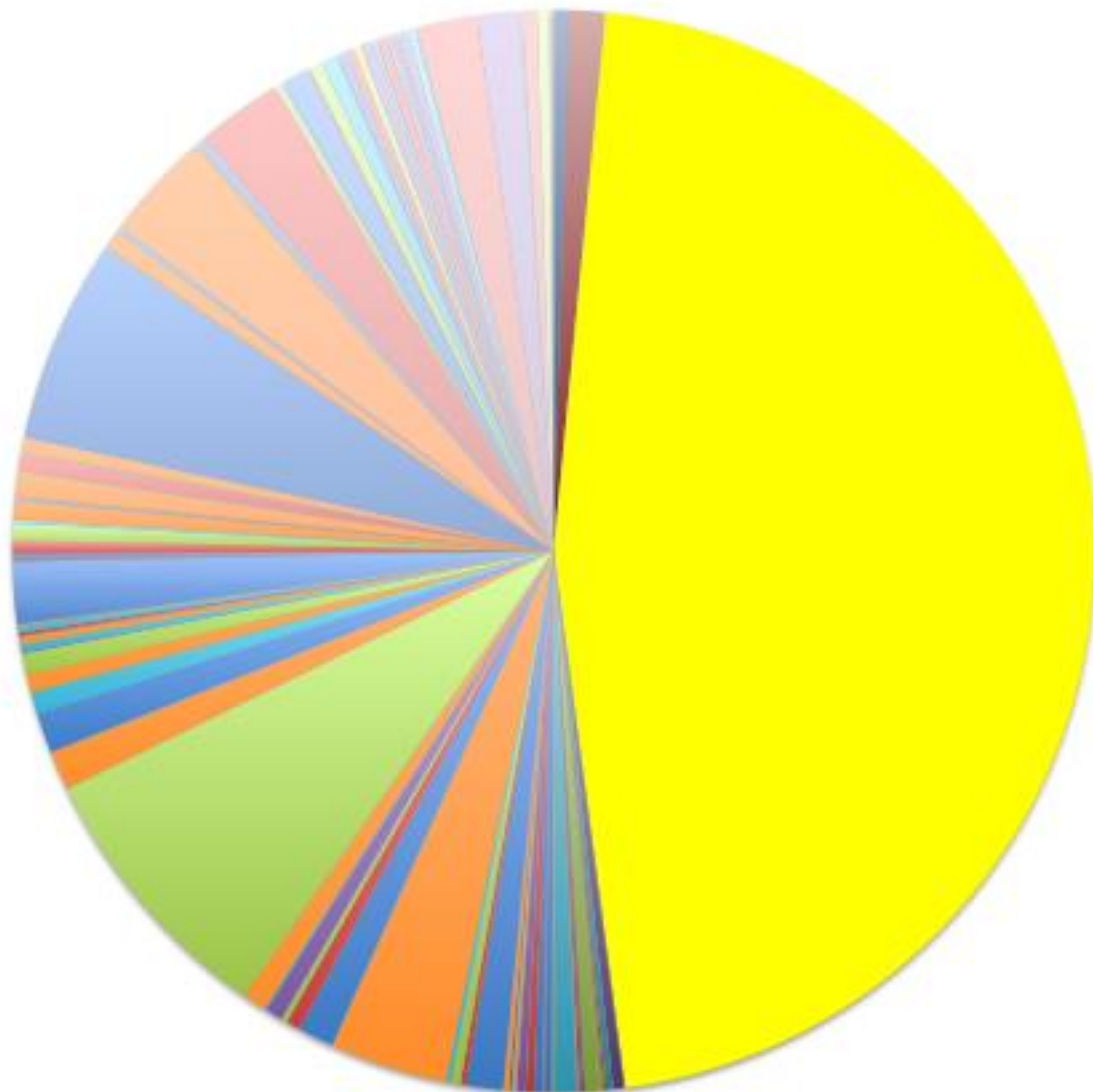
Control



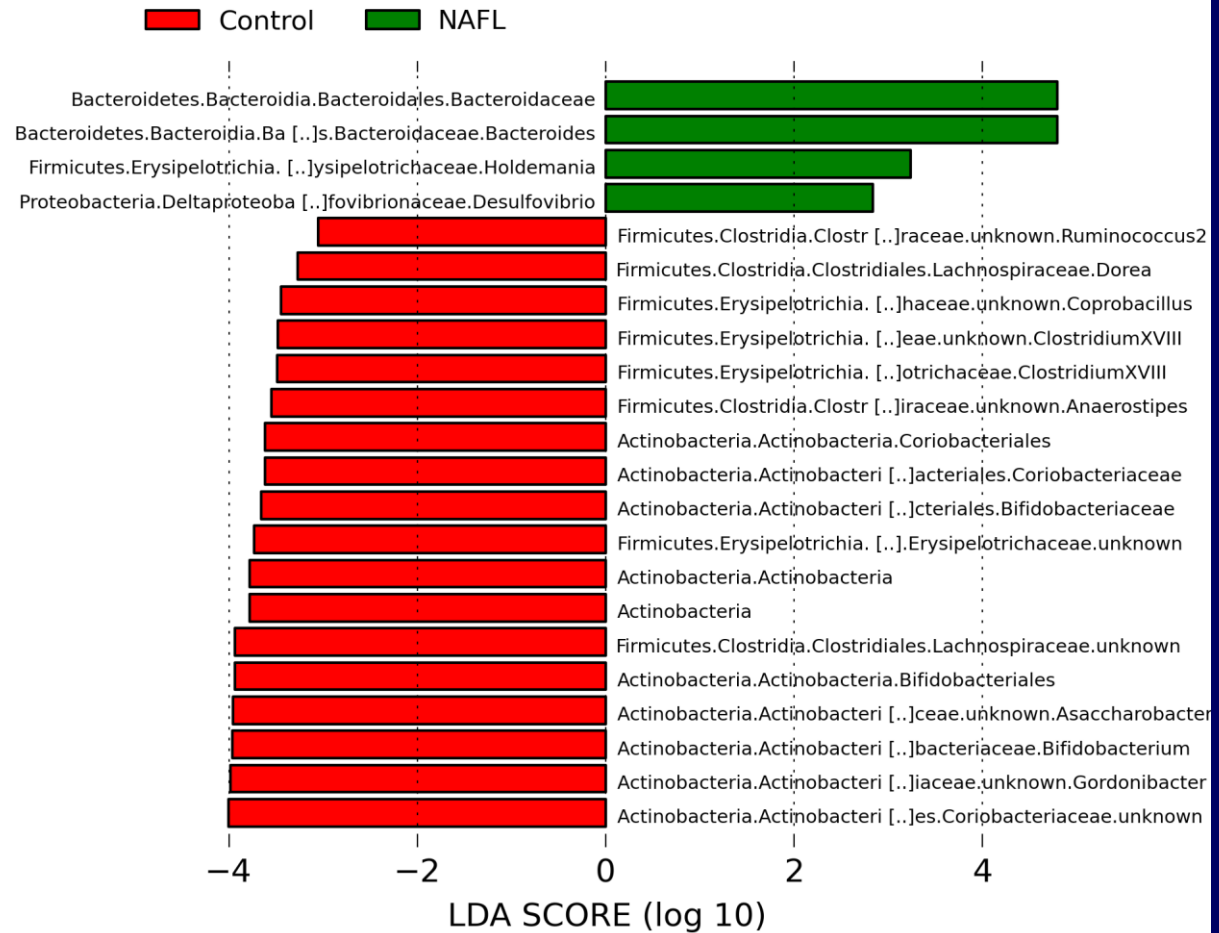
NAFL



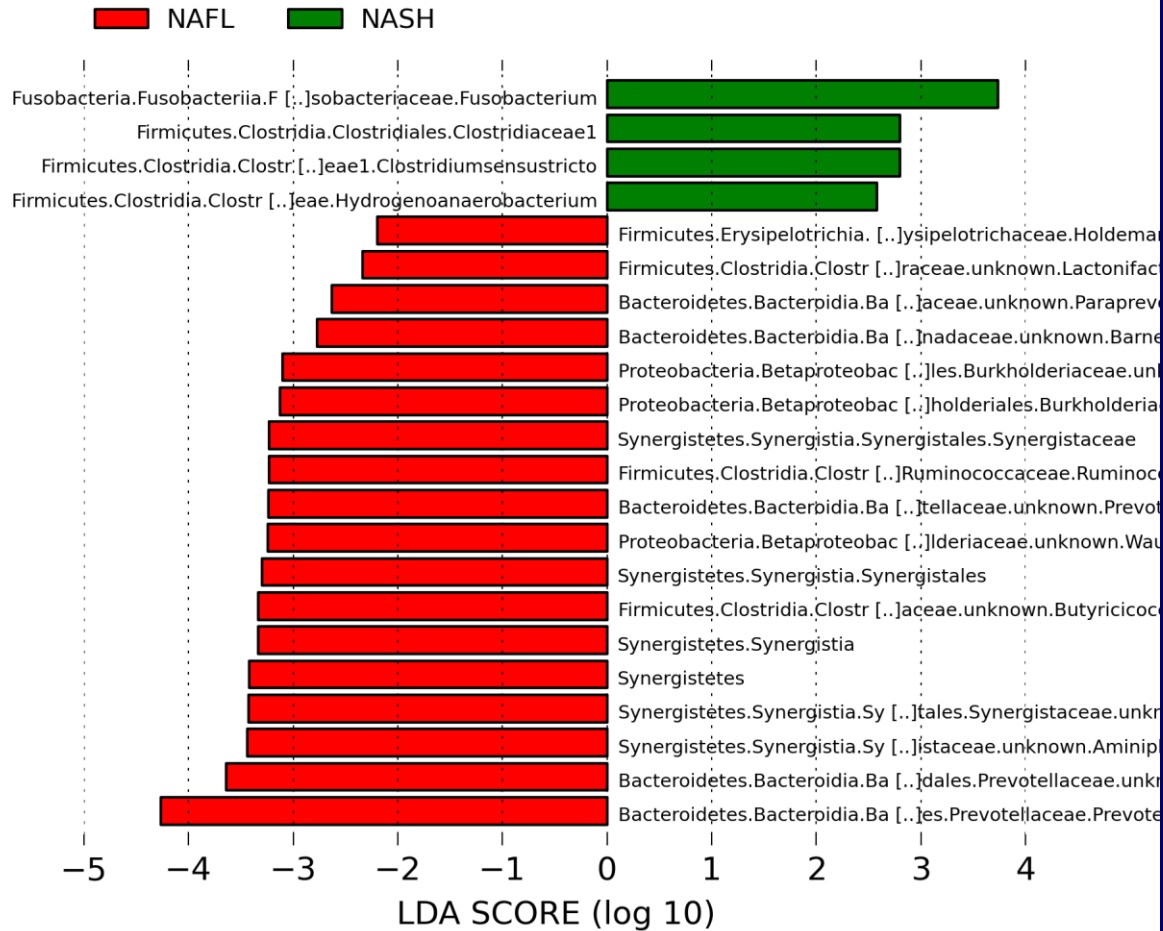
NASH



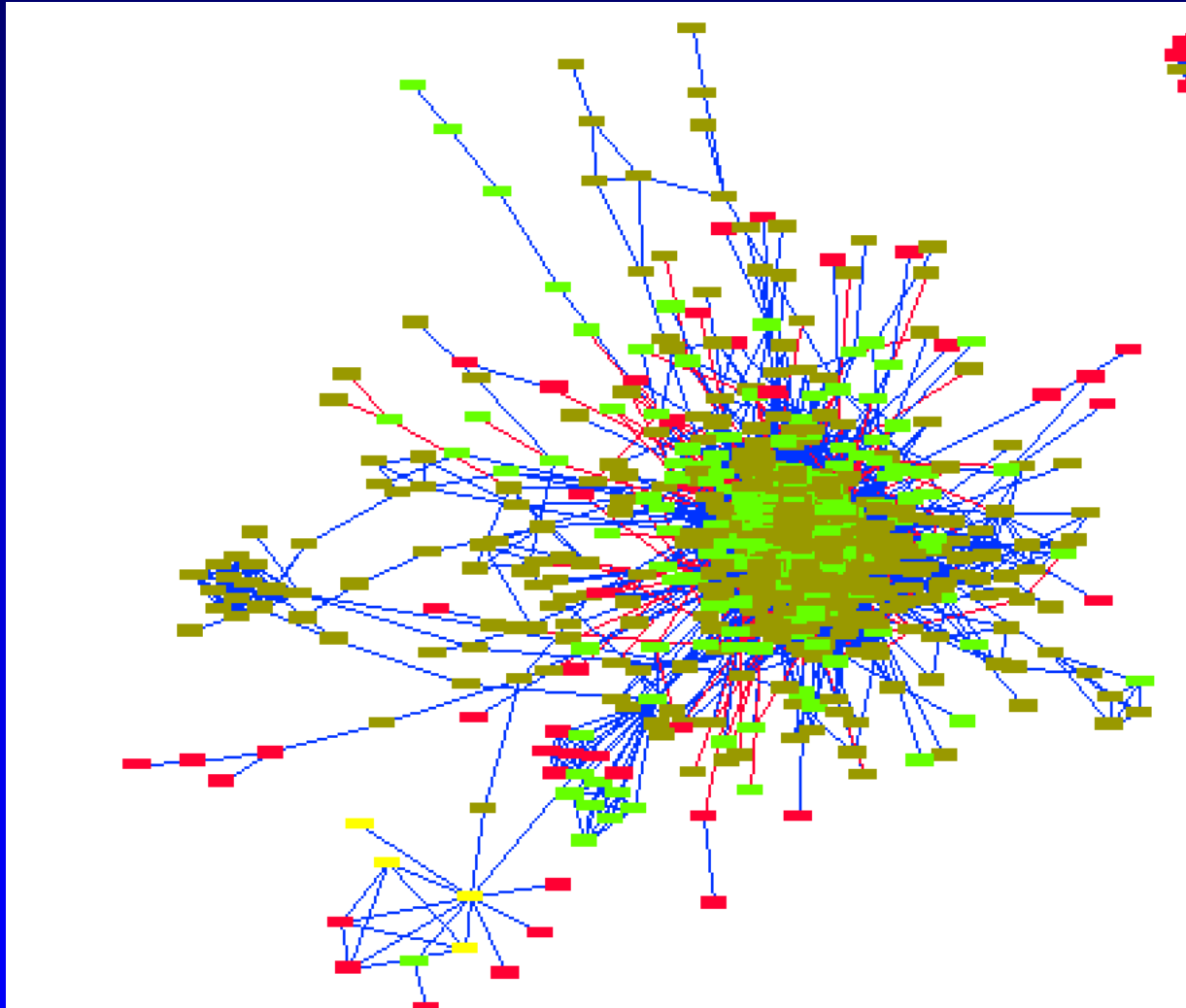
Control-NAFL LEFSE



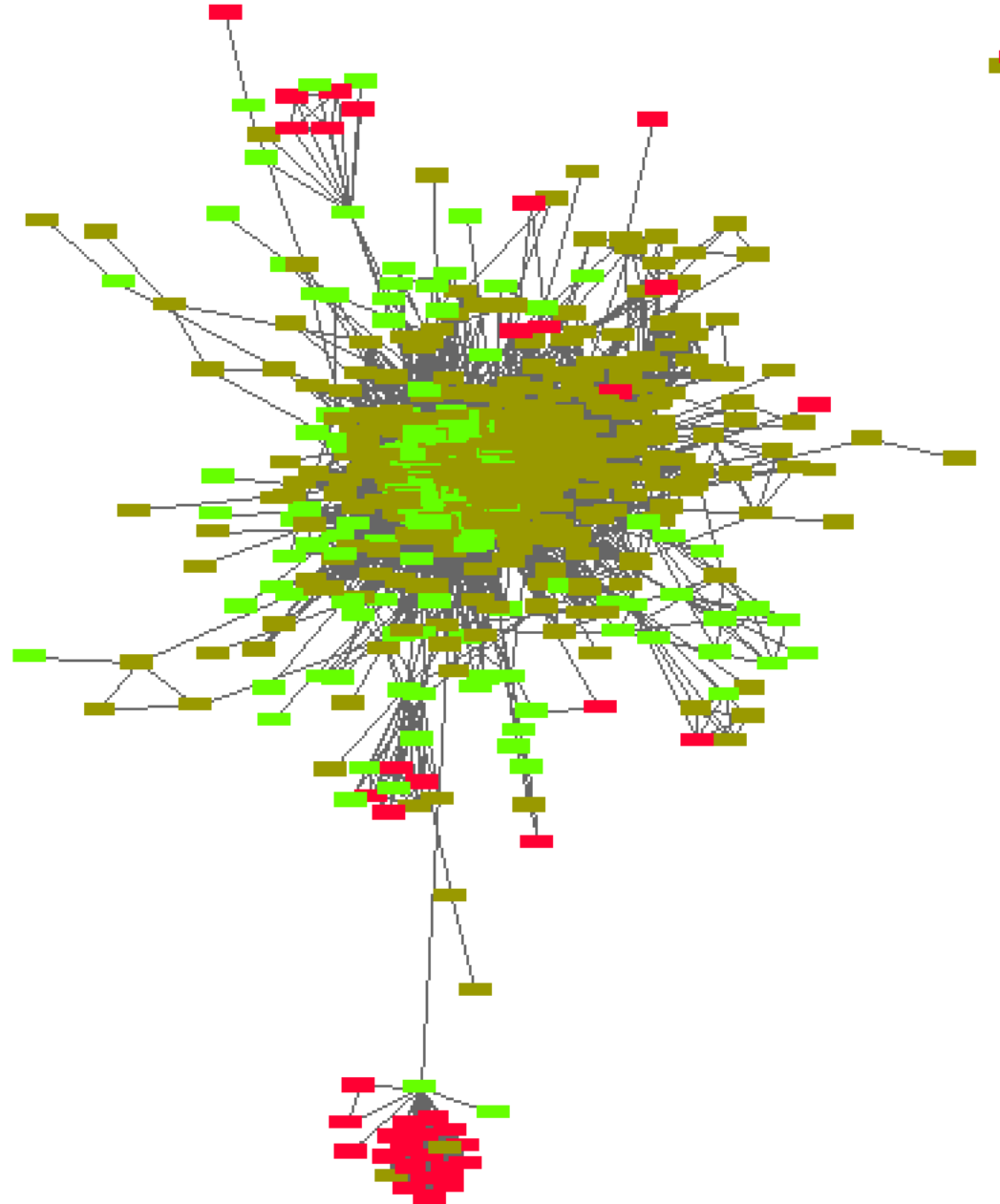
NAFL-NASH LEFSE



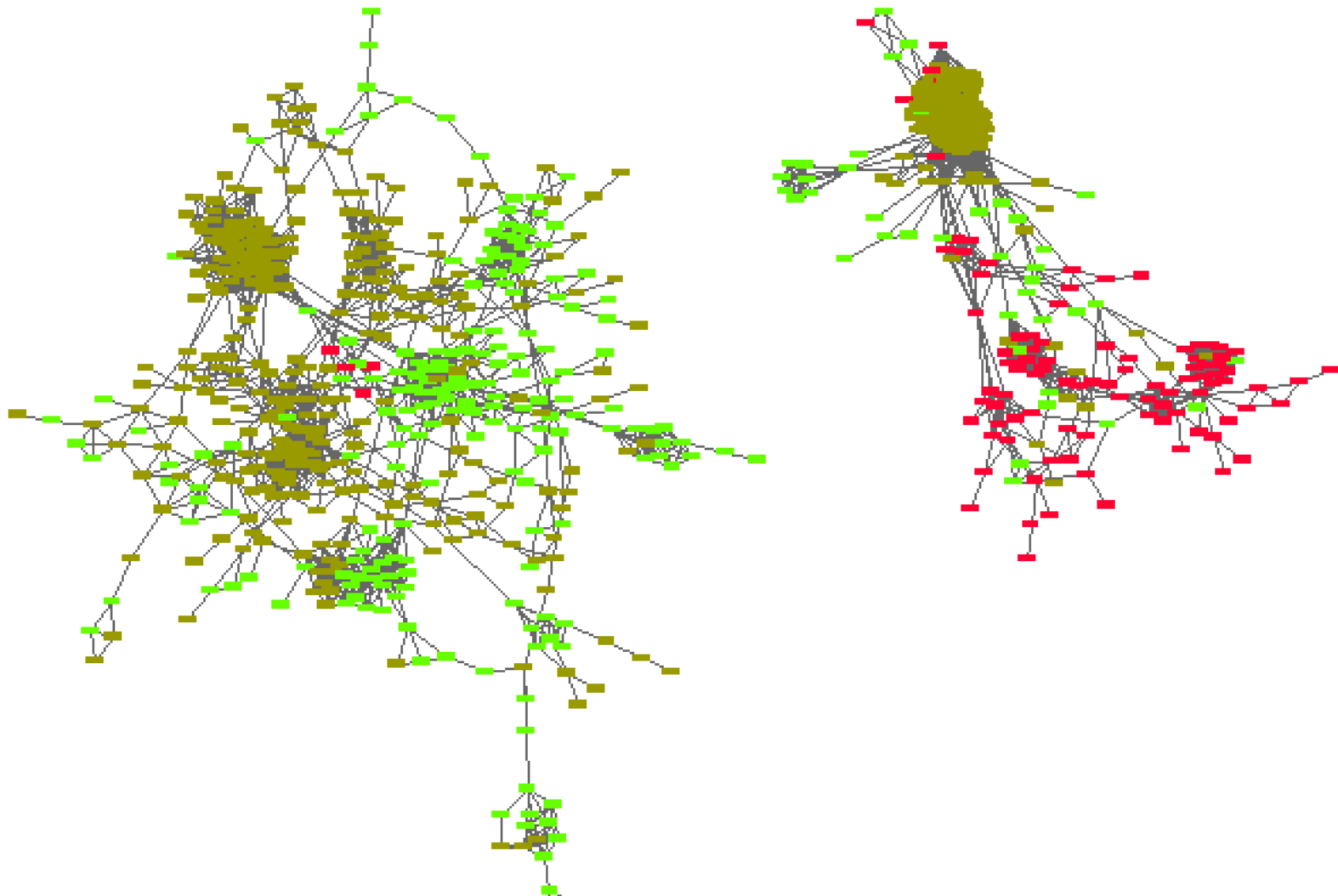
Control Correlation Network



NAFL Correlation Network



NASH Correlation Network



Machine Learning Bacteria + Metabolites

	CA	Sens	Spec	AUC	IS	F1	Prec	Recall	Brier	MCC
Naive Bayes	0.8286	0.8182	0.8462	0.9133	0.4559	0.8571	0.9000	0.8182	0.3478	0.6486
Random Forest	0.8571	0.9091	0.7692	0.9000	0.3243	0.8889	0.8696	0.9091	0.2958	0.6905
kNN	0.7429	0.7727	0.6923	0.7383	0.3951	0.7907	0.8095	0.7727	0.3861	0.4587
Classification Tree	0.8000	0.8636	0.6923	0.7733	0.4040	0.8444	0.8261	0.8636	0.3447	0.5659
Logistic regression	0.8000	0.9091	0.6154	0.8833	0.3675	0.8511	0.8000	0.9091	0.2971	0.5610
CN2 rules	0.7714	0.8636	0.6154	0.7483	0.3781	0.8261	0.7917	0.8636	0.4346	0.4986
Neural Network	0.8000	0.9091	0.6154	0.8833	0.2939	0.8511	0.8000	0.9091	0.3092	0.5610
SVM	0.7429	0.9091	0.4615	0.8133	0.2071	0.8163	0.7407	0.9091	0.3691	0.4265

Predictions

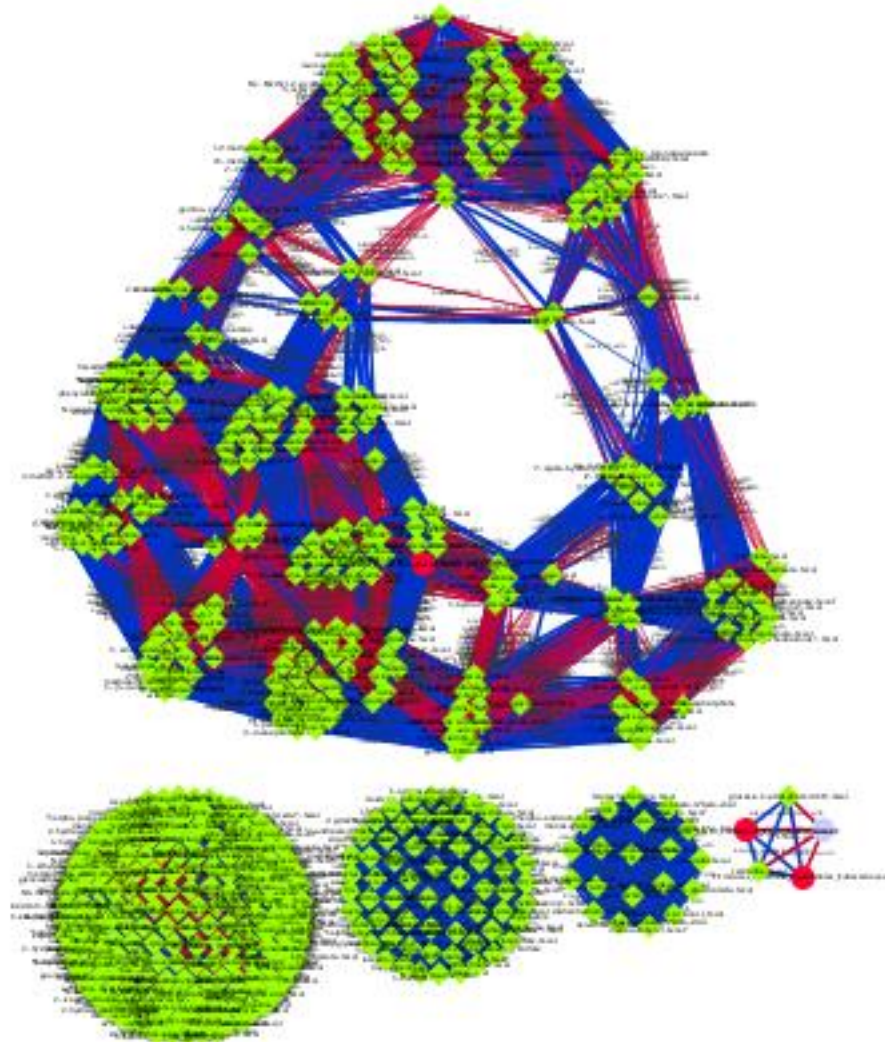
Truth

	Control	NASH	
Control	11	2	13
NASH	4	18	22
	15	20	35

Naive Bayes

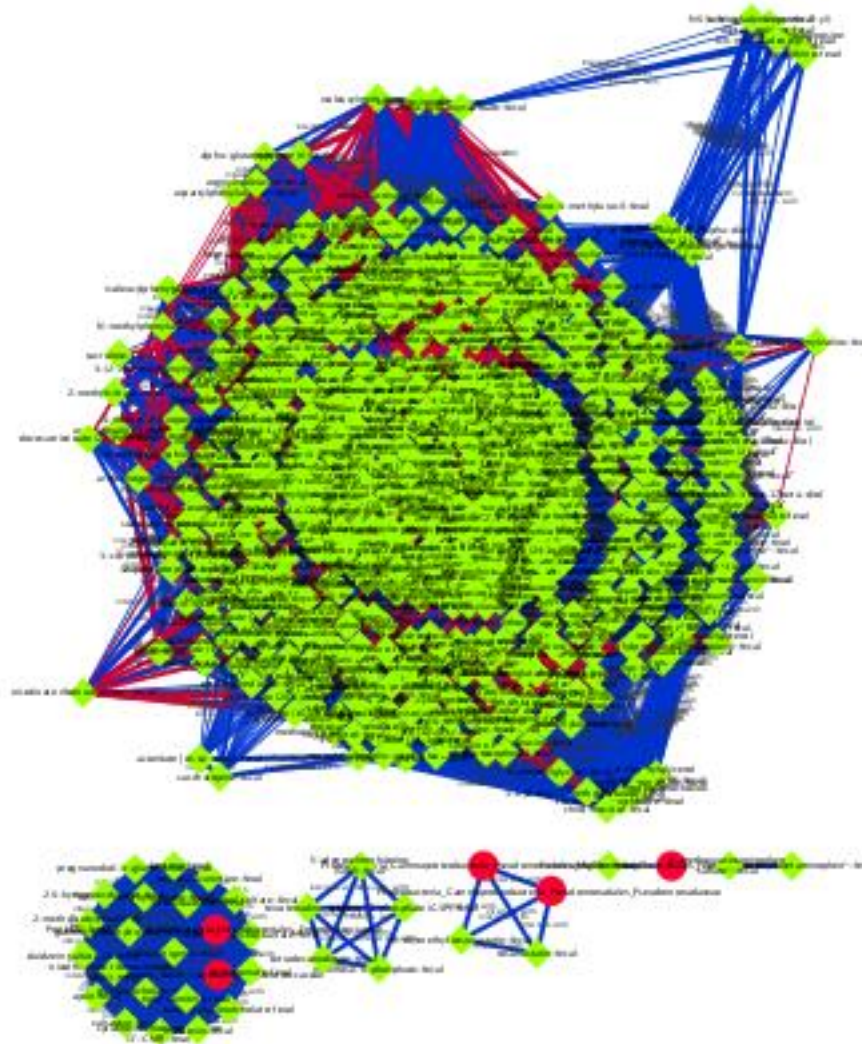
Drug Correlations – Controls

Confounders or Diagnostics?



Drug Correlations – NAFL

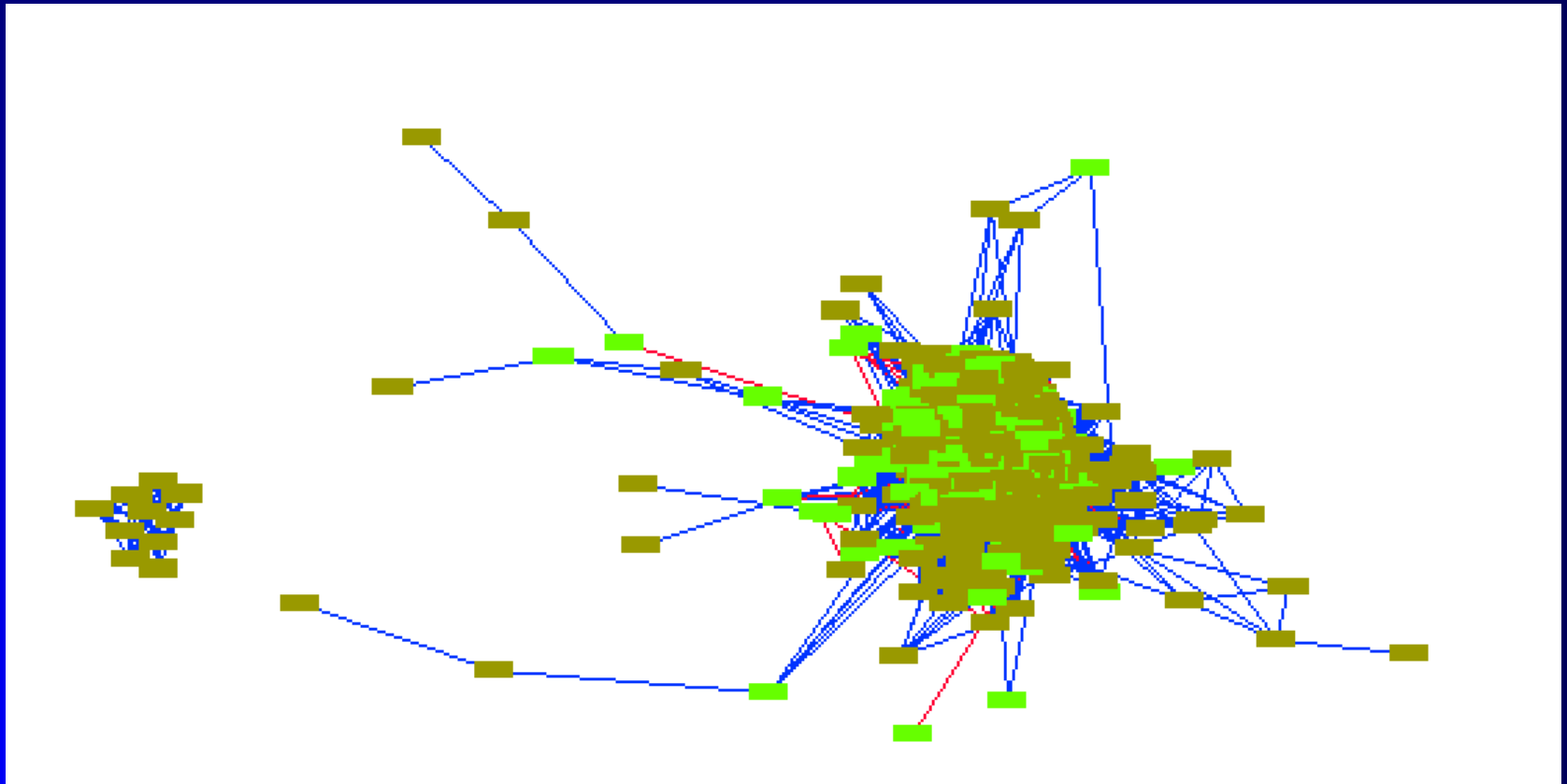
Confounders or Diagnostics?



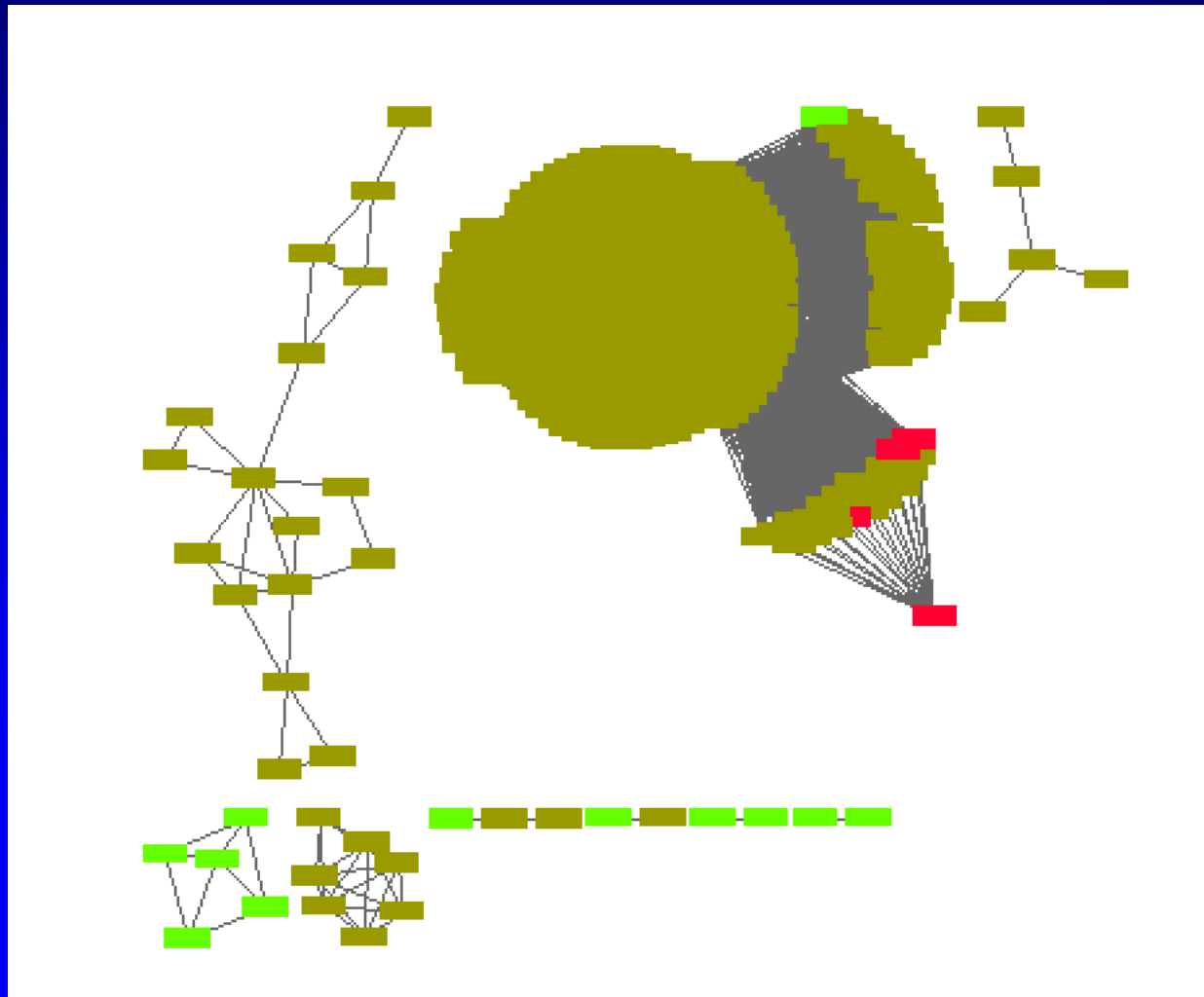
Sample of drugs

Control	celecoxib-fecal	NSAID
NASH	celecoxib-fecal	NSAID
NAFL	desmethylnaproxen sulfate*-fecal	metabolism of Naproxen- NSAID
Control	desmethylnaproxen sulfate*-fecal	metabolism of Naproxen- NSAID
NAFL	desvenlafaxine-fecal	Antidepressant (SNRI)
Control	desvenlafaxine-fecal	Antidepressant (SNRI)
NAFL	diltiazem-fecal	Calcium Channel Blocker- Hypertension
Control	diltiazem-fecal	Calcium Channel Blocker- Hypertension
Control	diphenhydramine-fecal	Antihistamine
NAFL	doxylamine-fecal	Antihistamine
Control	doxylamine-fecal	Antihistamine
NAFL	EDTA-fecal	??????????
NAFL	escitalopram-fecal	Antidepressant (SSRI)
Control	escitalopram-fecal	Antidepressant (SSRI)
NASH	escitalopram-fecal	Antidepressant (SSRI)
NASH	fenofibrate-fecal	Reduce Cholesterol
NAFL	fexofenadine-fecal	Reduce Cholesterol
NASH	fexofenadine-fecal	Reduce Cholesterol
NASH	fluoxetine-fecal	Antidepressant (SSRI)
NAFL	furosemide-fecal	Antidepressant (SSRI) - Prozac
Control	furosemide-fecal	Hypertension (Lasik)
NASH	furosemide-fecal	Hypertension (Lasik)
NAFL	gabapentin-fecal	Diabetic neuropathy
Control	gabapentin-fecal	Diabetic neuropathy
NASH	gabapentin-fecal	Diabetic neuropathy
NAFL	hydrochlorothiazide-fecal	Diuretic
Control	hydrochlorothiazide-fecal	Diuretic
NASH	hydrochlorothiazide-fecal	Diuretic
NAFL	hydroxypropylglucosamine (M-IV)-fecal	metabolite of pioglitazone- hypoglycemic
Control	hydroxypropylglucosamine (M-IV)-fecal	metabolite of pioglitazone- hypoglycemic
NAFL	ibuprofen-fecal	NSAID
Control	ibuprofen-fecal	NSAID
NASH	ibuprofen-fecal	NSAID
NAFL	ketopioglitazone-fecal	metabolite of pioglitazone- hypoglycemic
Control	ketopioglitazone-fecal	metabolite of pioglitazone- hypoglycemic
NAFL	lansoprazole-fecal	Proton Pump Inhibitor
Control	lansoprazole-fecal	Proton Pump Inhibitor

Control Bile Acids



NASH Bile Acids

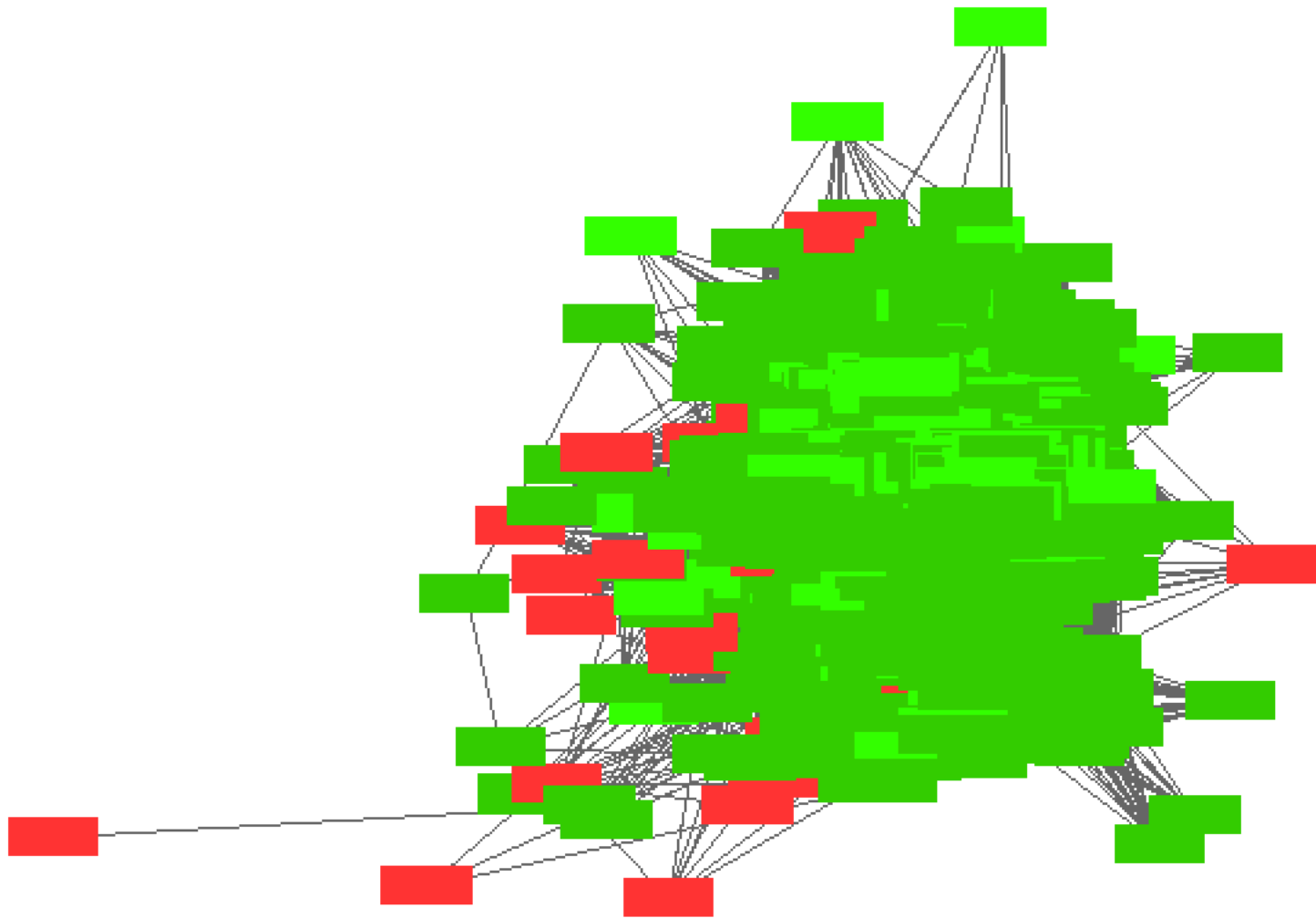


Bile Acid in Correlations

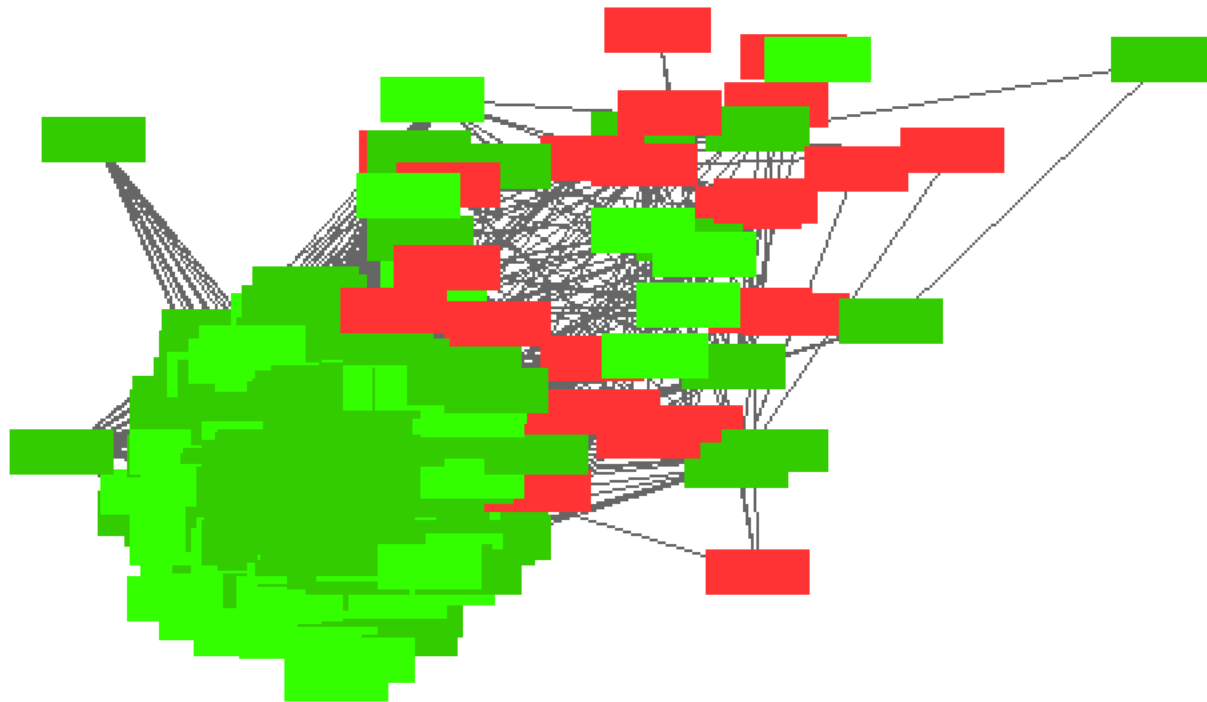
Class	Source	Metabolite	Sub-Pathway	Super_Pathway
Control	Fecal	taurocholate sulfate*-fecal	Bile acid metabolism	Lipid
Control	Fecal	alpha-muricholate-fecal	Bile acid metabolism	Lipid
Control	Fecal	lithocholate [6-oxo or 7-keto]-fecal	Bile acid metabolism	Lipid
Control	Fecal	dehydrocholic acid-fecal	Bile acid metabolism	Lipid
Control	Fecal	beta-muricholate-fecal	Bile acid metabolism	Lipid
Control	Plasma	taurocholate sulfate*-plasma	Bile acid metabolism	Lipid
NAFL	Fecal	lithocholate [6-oxo or 7-keto]-fecal	Bile acid metabolism	Lipid
NAFL	Fecal	beta-muricholate-fecal	Bile acid metabolism	Lipid
NAFL	Plasma	taurocholate sulfate*-plasma	Bile acid metabolism	Lipid
NASH	Fecal	beta-muricholate-fecal	Bile acid metabolism	Lipid
NASH	Fecal	alpha-muricholate-fecal	Bile acid metabolism	Lipid
NASH	Fecal	lithocholate [6-oxo or 7-keto]-fecal	Bile acid metabolism	Lipid

Need to look at overall bile acids and correlation with bacteria

Control-NAFL Correlation Differences

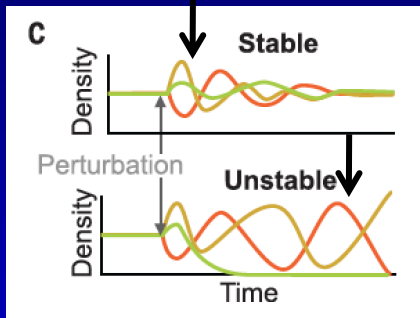


NAFL-NASH Correlation Differences

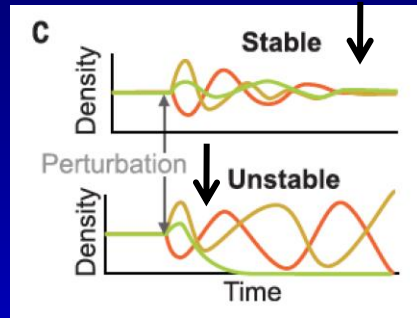


Can Cross Sectional Studies Recapitulate Longitudinal Studies???

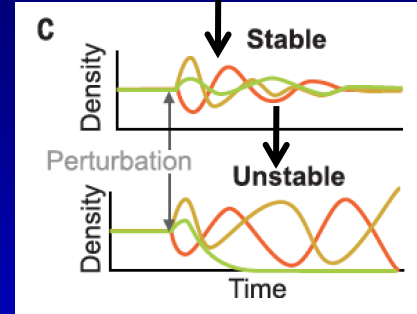
Patient1



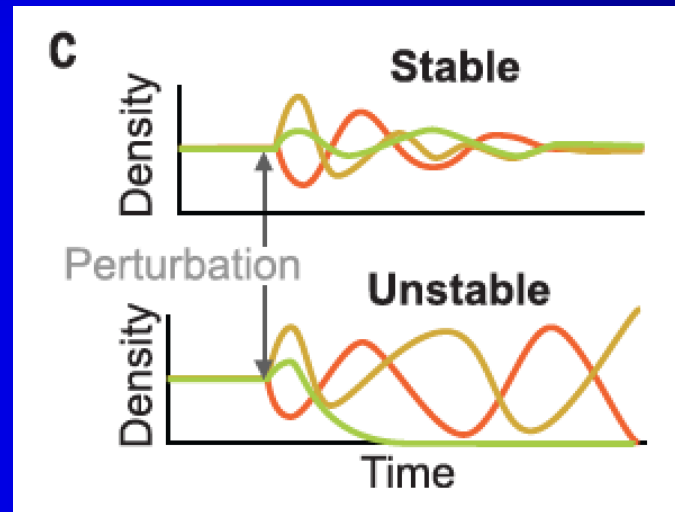
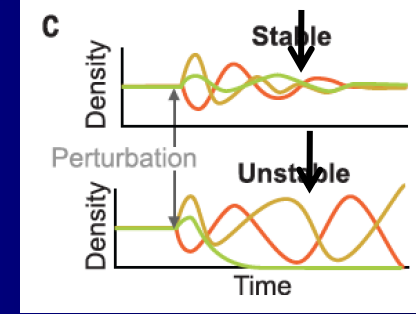
Patient2



Patient3

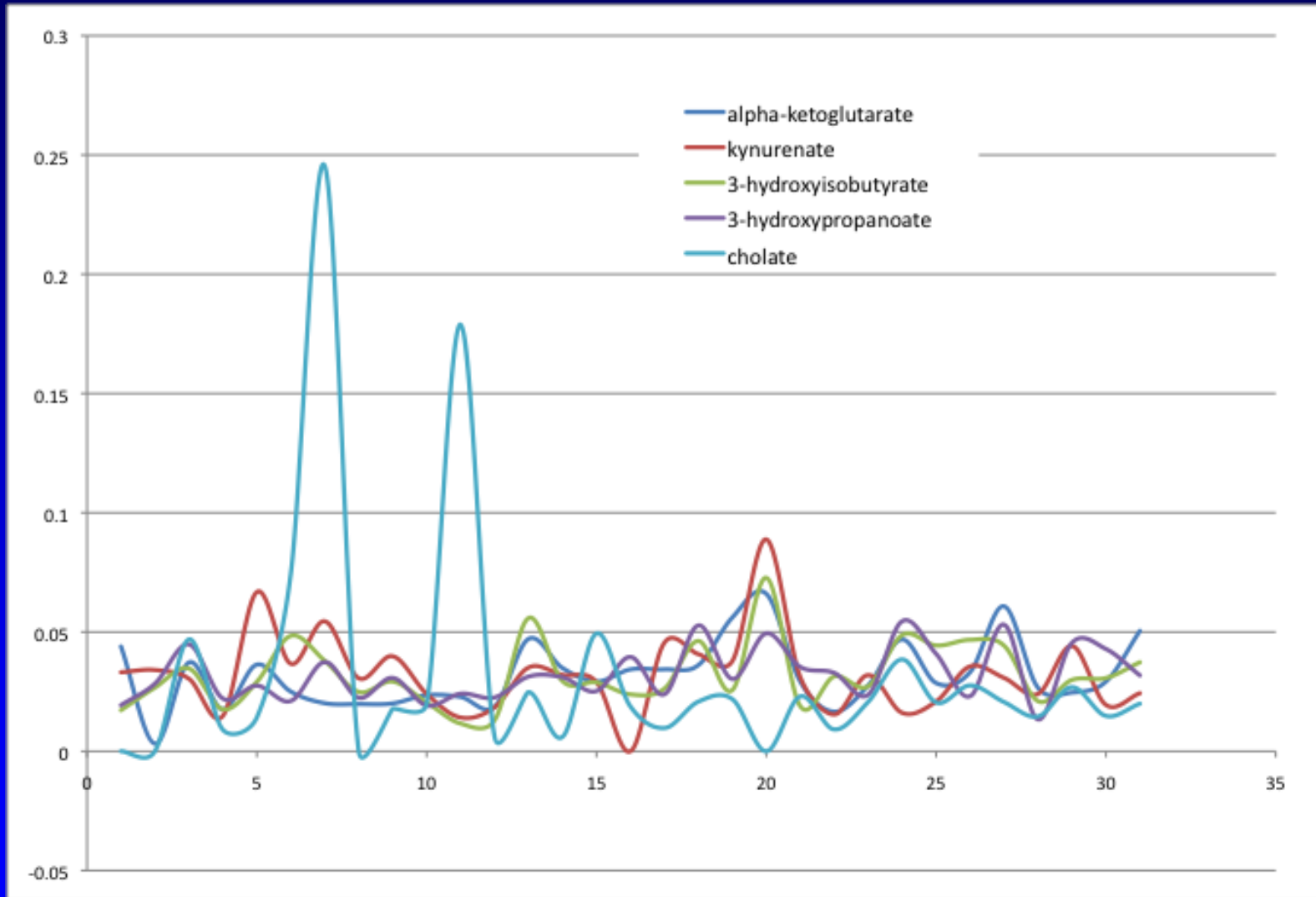


Patient4



Reconstructed Oscillations?

This is Why Spearman Correlations Work



Now Modeling Phase Shifts

Summary

- **Dynamic Ecosystem**
- **Interplay between host and microbiome**
- **Ecological modeling of system**
- **Drugs as Confounders (Diagnostics??)**
- **Focus on Bile Acid Metabiome**
- **Microbiome / Metabolome Non-Invasive**
 - primary screening ?

Caveate

CRC / Adenoma also shifts microbiome