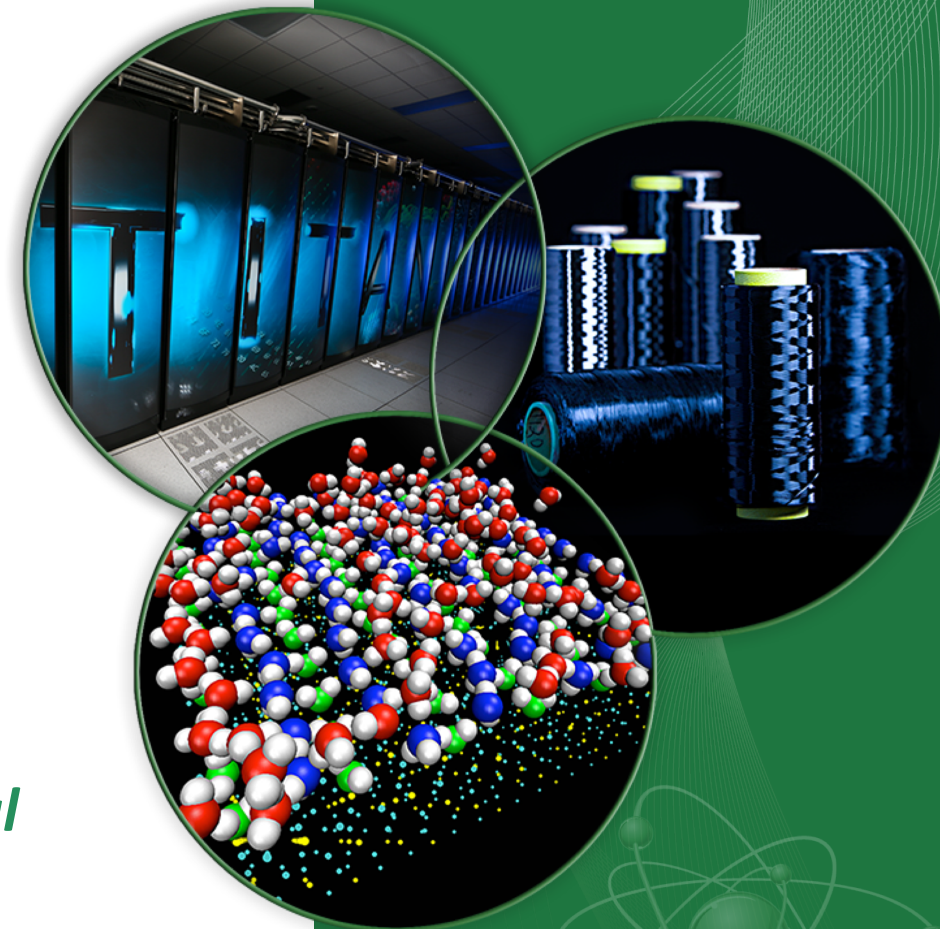
Computational Systems Biology: Approaches Ranging from Bioenergy to the Opioid Epidemic with Exascale Genomics

Data Analytics, Explainable-AI and Supercomputing as the New Microscope/Telescope for Complex Systems



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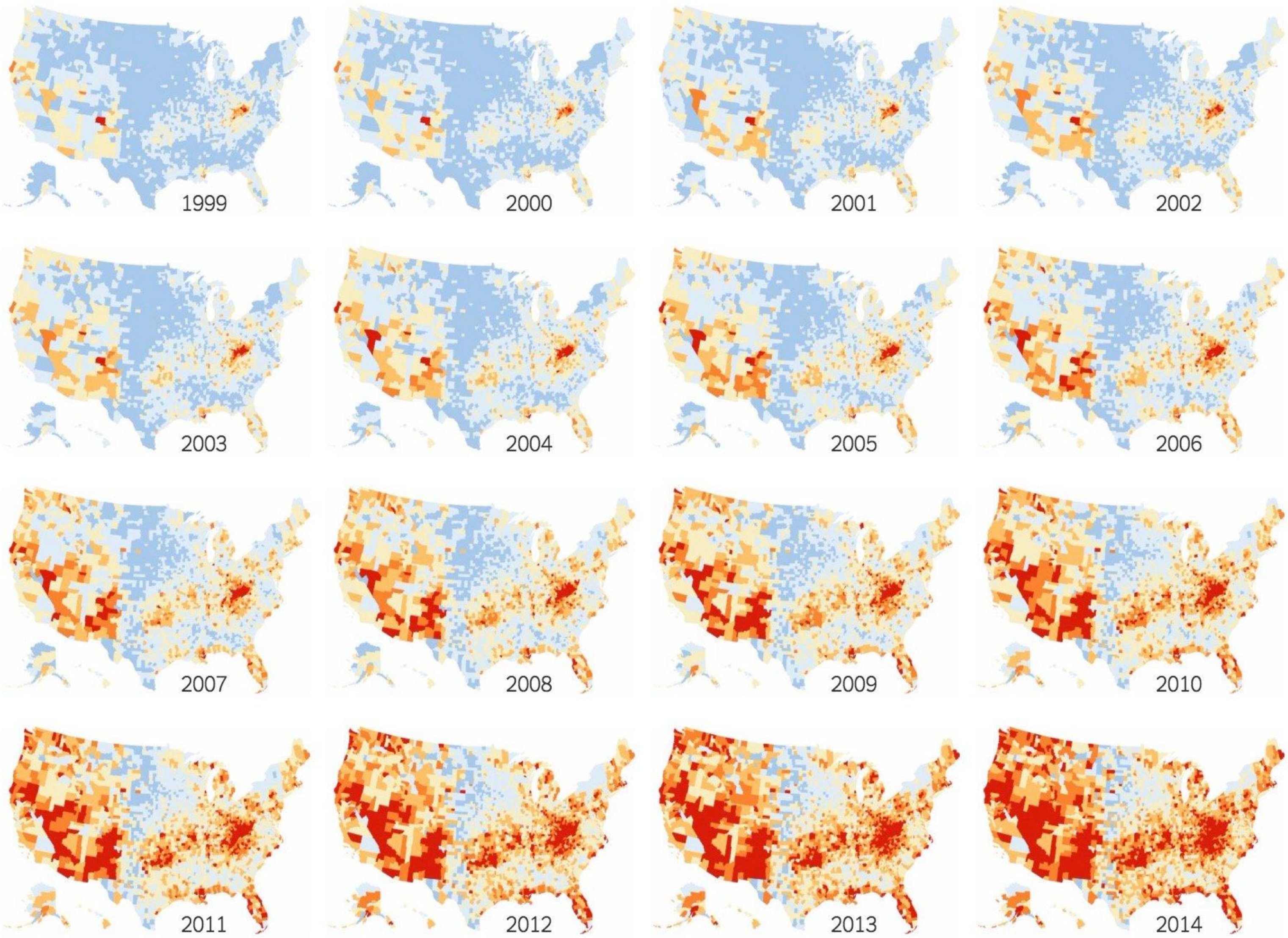
U.S. DEPARTMENT OF ENERGY

ORNL is managed by UT-Battelle
for the US Department of Energy

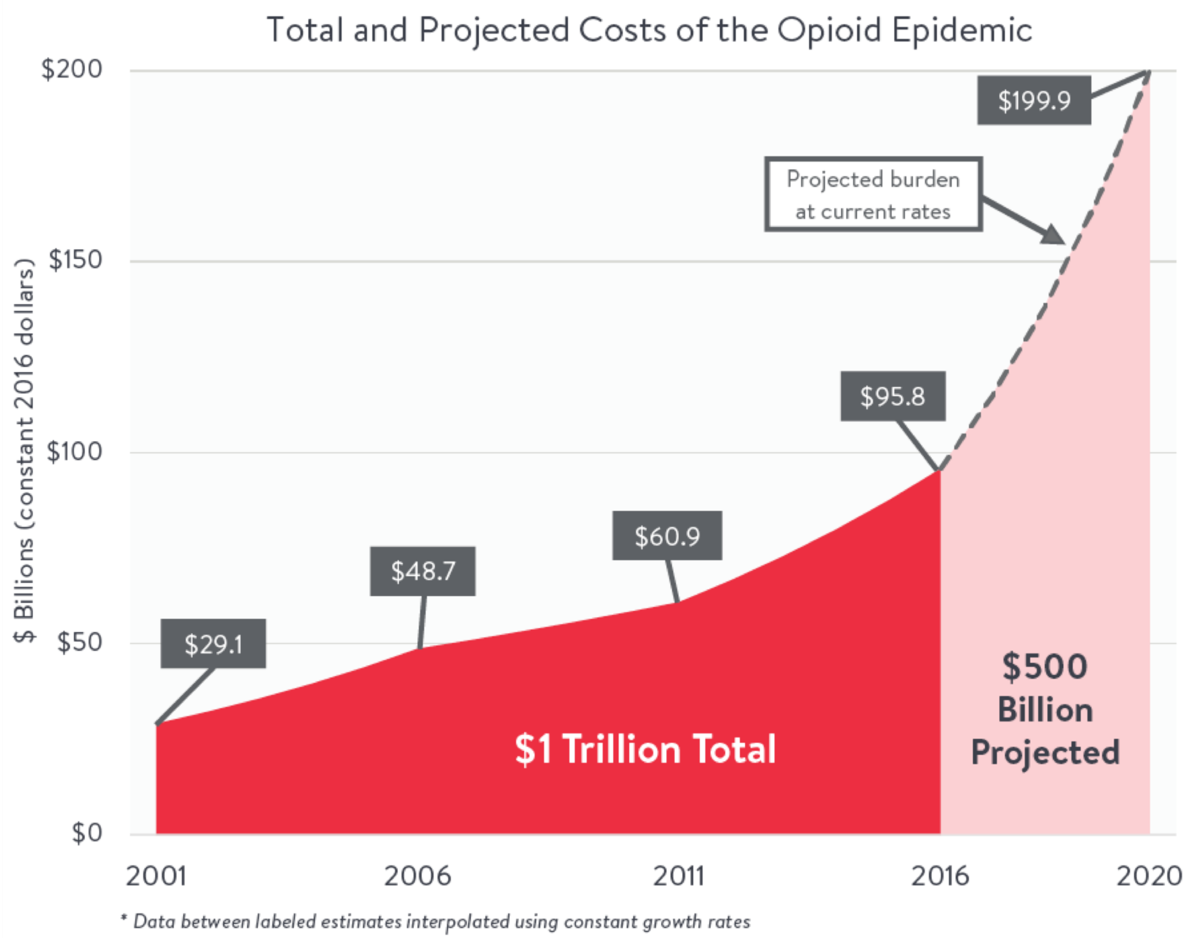
OAK RIDGE National Laboratory

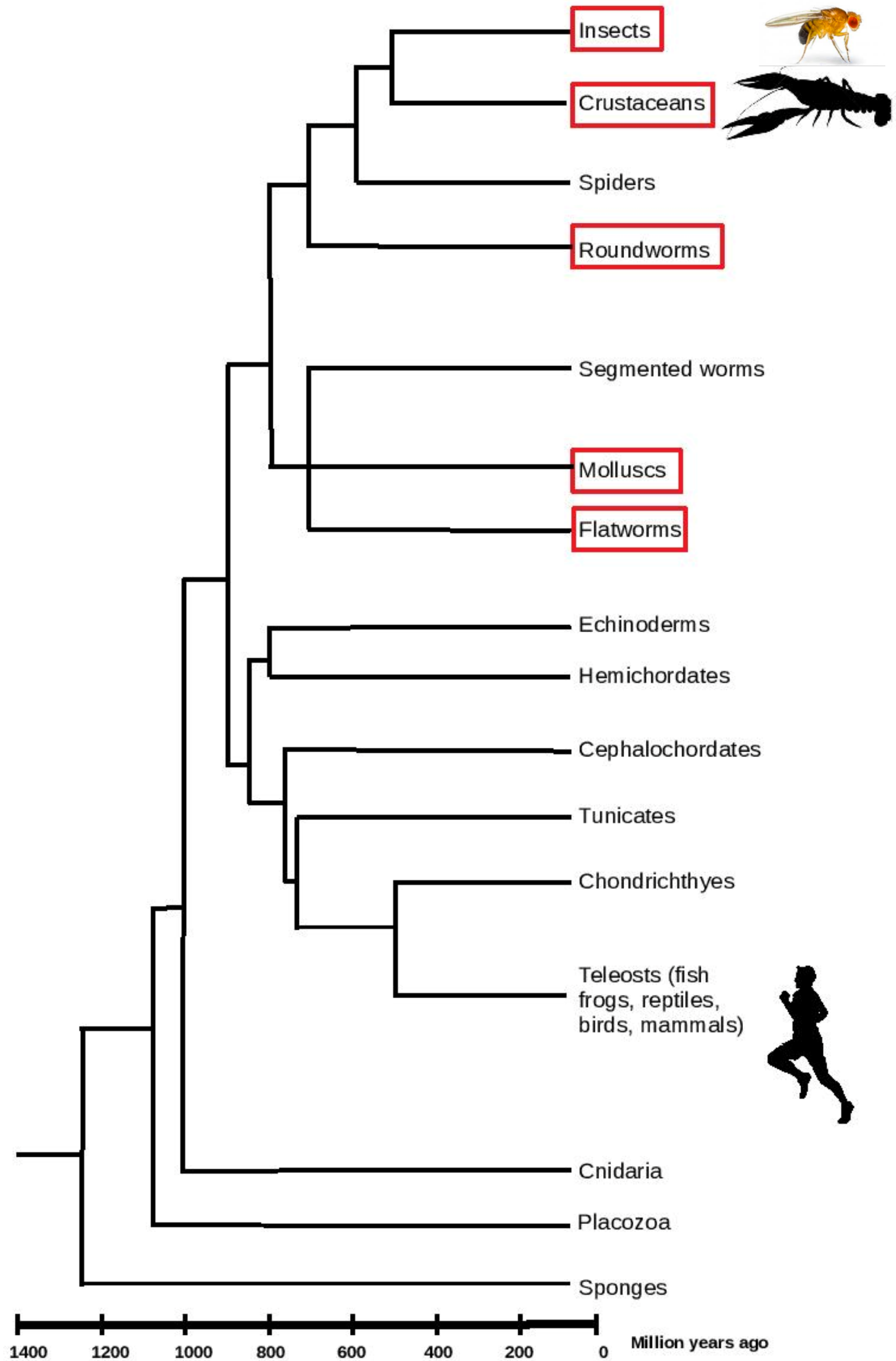
Opioids Epidemic



Opioids Crisis

- 30% of patients misuse opioids
- 10% developing an opioid use disorder.
- 30% increase in opioid overdoses from July 2016 through September 2017 in 52 areas in 45 states

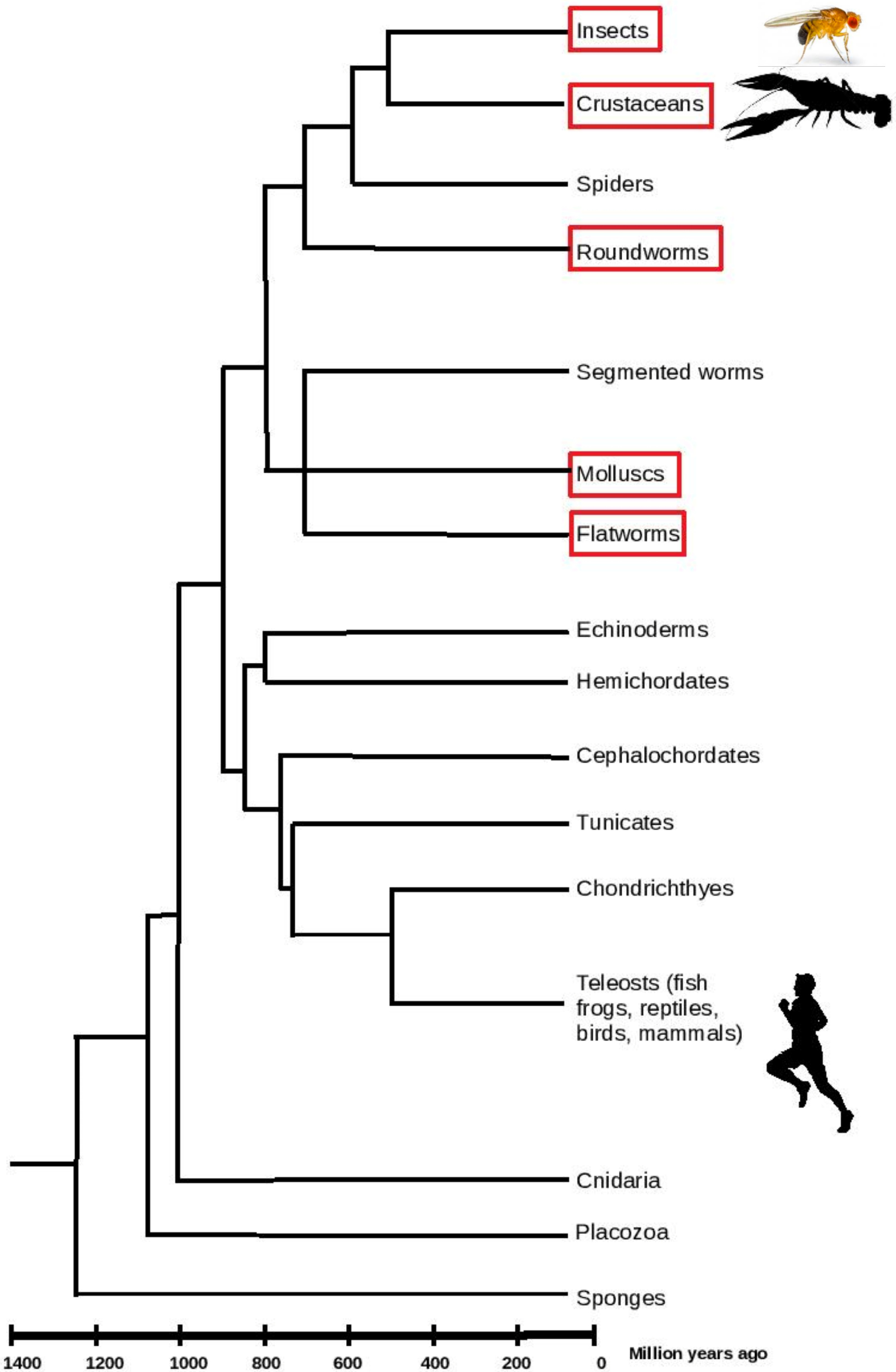




The Deep Evolutionary Roots of Addiction

- **Addictive plant alkaloids, as secondary metabolites, evolved primarily to counter insect herbivory.**
- **Addiction would seem to be an odd defense strategy**
  - ***Survival of an intoxicated herbivore is probably quite short. It will either fall off or will be an easy prey for the predators which are abundant in most ecosystems*.**

van Staaden MJ, Hall FS, Huber R. J Mental Health & Clin Psychology (2018) 2(3): 8-13



The Deep Evolutionary Roots of Addiction

- **Addictive plant alkaloids**
  - **Affect learning and motivation**
    - **Mechanisms which are shared by taxa since the early evolution of bilateral metazoans.**

- **Addiction is fundamentally an invertebrate phenomenon**
  - **Humans can be viewed as collateral damage in this coevolutionary arms race.**

van Staaden MJ, Hall FS, Huber R. J Mental Health & Clin Psychology (2018) 2(3): 8-13

Addiction is a complex, multigenic, epistatic trait

Environmental components/stress likely plays a role

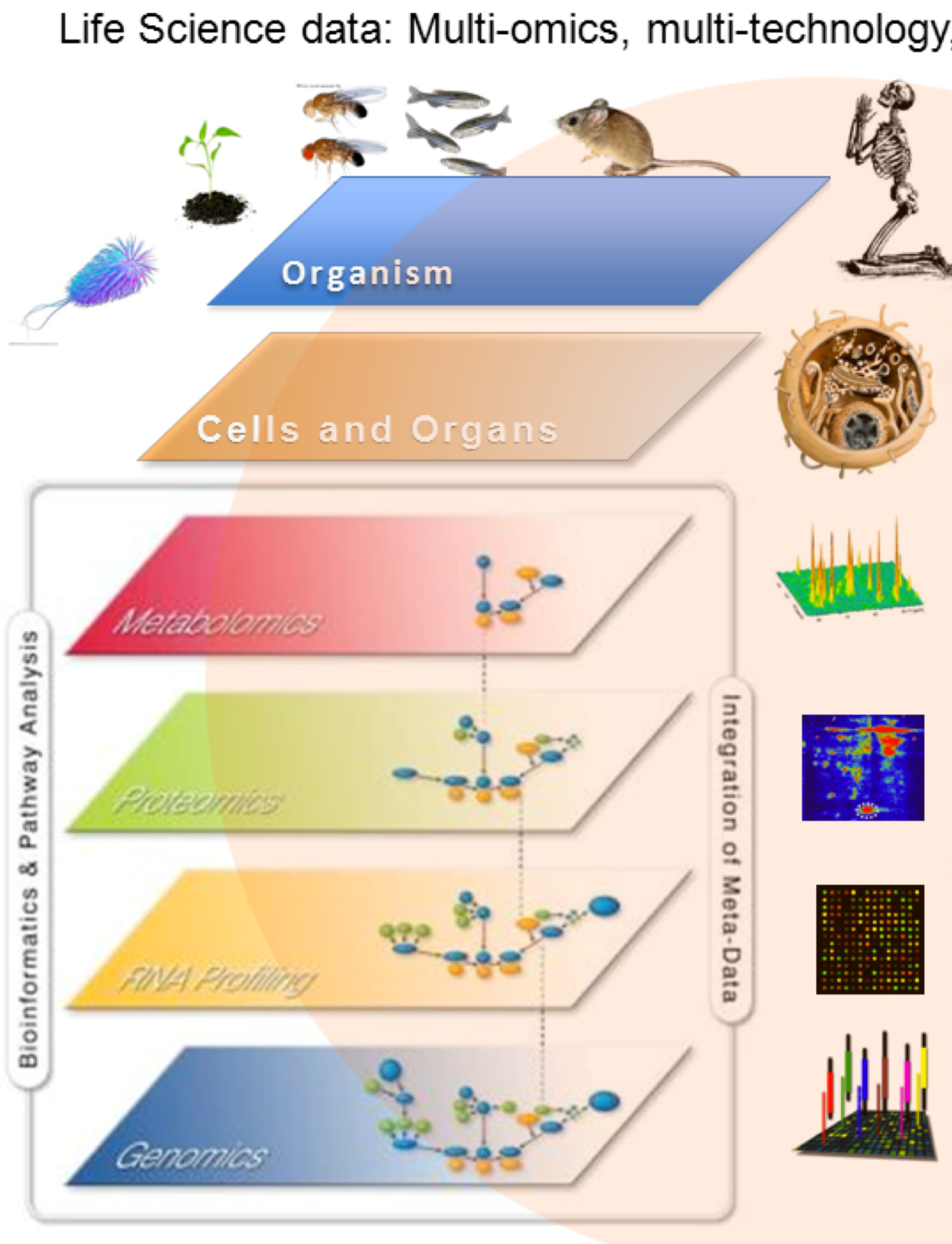
The combinatorial space that we need to search is huge….

Why do we think we can do this?

Because we are already doing it for Bioenergy

Bioenergy Experimental Data Types

- Natural Variation
  - Genome Wide Association Studies
  - 28 Million SNPs
  - ~160,000 Primary Phenotypes
    - Morphology/Phenology
    - Molecular
- Microbiomes & Metagenomes
- Omics & Meta-omics
  - Genomics, Transcriptomics, Proteomics, Metabolomics
- All publically available Genomes
- Differential/Time Series Expression Studies
- Systems Biology Approach
  - Combining datasets across omics layers, sample sets, and species

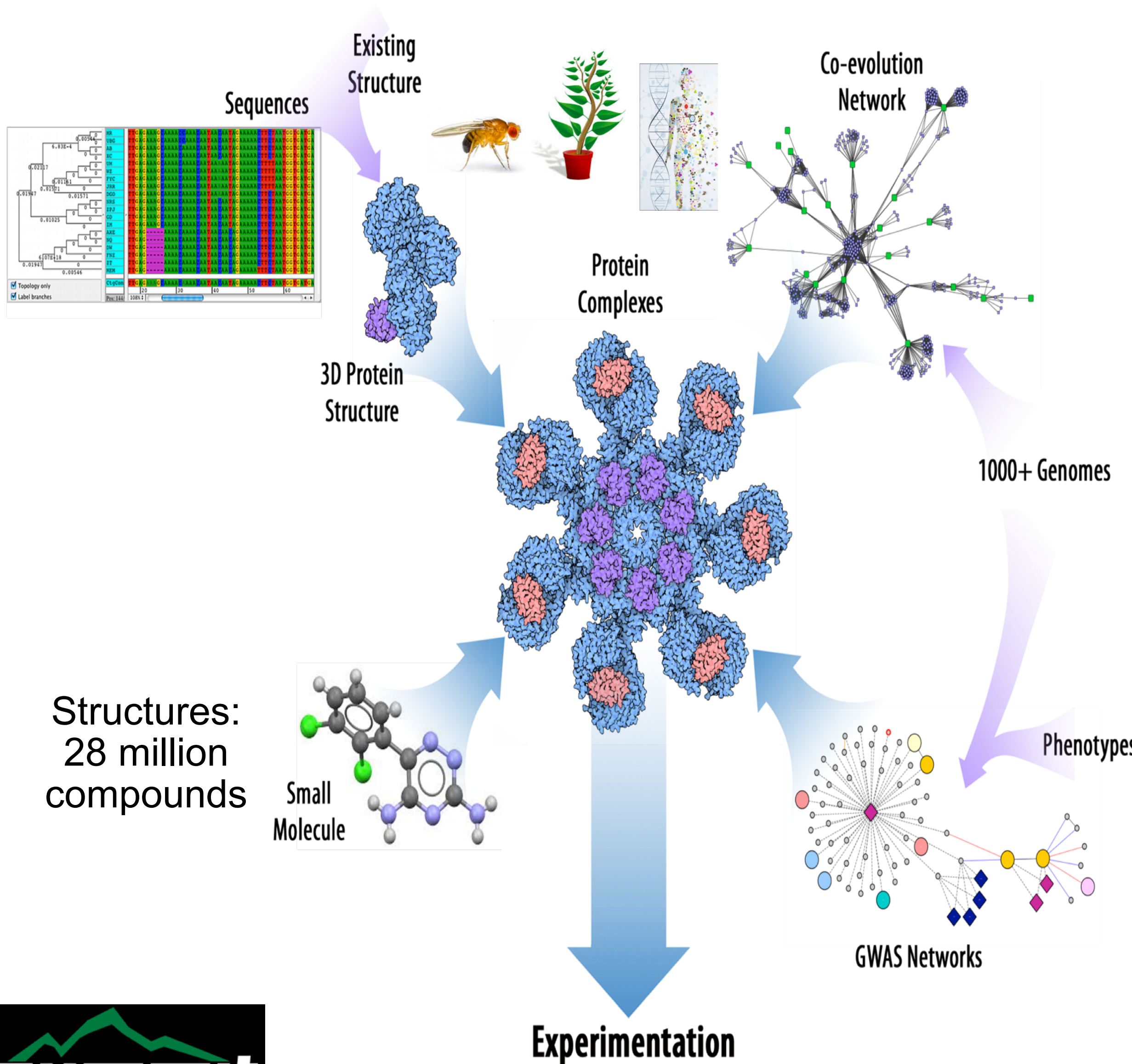


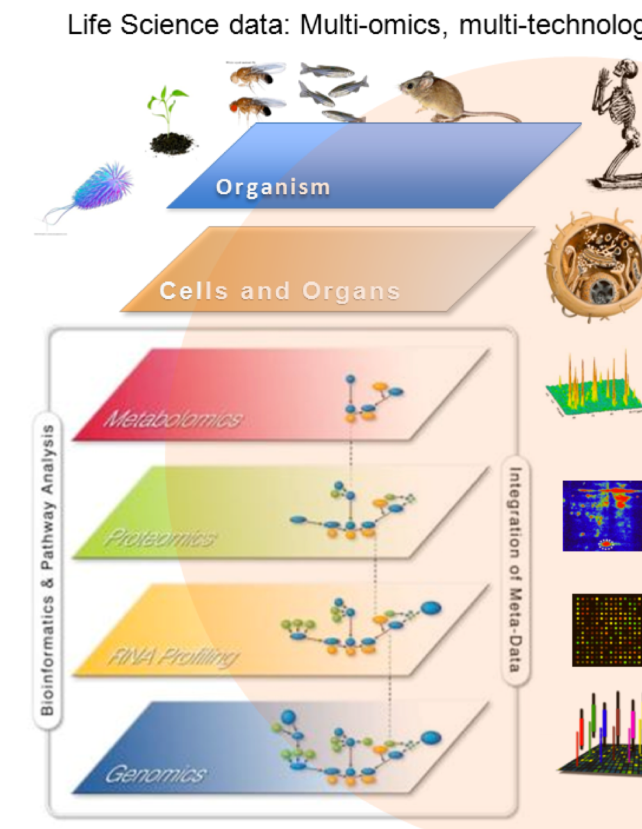
Traditional Results

Gene	baseMean	log2FoldChange	lfcSE	stat	pvalue	padj
Pavir.Aa00004	23.03260874	-0.772176419	0.235718754	-3.275837864	0.00105349	0.036650136
Pavir.Aa00067	3.617339133	-3.277187207	0.925328577	-3.541647029	0.000397637	0.016344905
Pavir.Aa00318	11.69495376	-1.375554763	0.421360908	-3.264552399	0.001096372	0.037862673
Pavir.Aa01140	432.2298561	-0.920355344	0.087912301	-10.46901667	1.20E-25	1.26E-22
Pavir.Aa01336	14.76644122	-7.964343955	1.643802037	-4.84507488	1.27E-06	0.000109099
Pavir.Aa01612	63.51089454	1.524126268	0.377624869	4.03608552	5.44E-05	0.002965915
Pavir.Aa01614	86.61299946	1.970704034	0.235133135	8.381226395	5.24E-17	2.16E-14
Pavir.Aa01686	45.57577197	-2.776318341	0.3350917	-8.285249514	1.18E-16	4.66E-14
Pavir.Aa01805	7.784684493	1.72469978	0.269249957	6.405571227	1.50E-10	2.64E-08
Pavir.Aa01856	15.77390176	-3.03656463	0.739522148	-4.106117228	4.02E-05	0.00228249
Pavir.Aa01950	246.4158349	0.749398201	0.130879565	5.725861023	1.03E-08	1.35E-06
Pavir.Aa02015	194.2868719	0.55688662	0.146656817	3.797209232	0.000146334	0.007032352
Pavir.Aa02104	71.8661413	-0.945676165	0.223959112	-4.222539364	2.42E-05	0.001454015
Pavir.Aa02130	45.08826603	-2.821545181	0.381707372	-7.391906442	1.45E-13	3.90E-11
Pavir.Aa02199	82.09354863	2.652283666	0.48092843	5.514923839	3.49E-08	4.08E-06
Pavir.Aa02377	48.01170214	1.765138681	0.318940668	5.534379463	3.12E-08	3.70E-06
Pavir.Aa02382	4.900020424	-6.641133503	1.55203963	-4.278971603	1.88E-05	0.001166295
Pavir.Aa02400	3.536707907	-2.288869563	0.396004267	-5.779911361	7.47E-09	1.01E-06
Pavir.Aa02455	100.2653536	0.851939179	0.154407276	5.517480799	3.44E-08	4.03E-06
Pavir.Aa02456	74.76890191	0.900755926	0.267107154	3.372264319	0.000745529	0.027702451
Pavir.Aa02462	129.7507991	1.878568856	0.195429139	9.612532015	7.08E-22	5.19E-19
Pavir.Aa02463	0.855875118	-3.952874961	1.177355482	-3.357418402	0.00078674	0.028956754
Pavir.Aa02517	239.8175815	3.424148863	0.634311687	5.398211843	6.73E-08	7.46E-06
Pavir.Aa02526	20.12897762	-1.829988585	0.513742501	-3.56207357	0.000367937	0.015318345
Pavir.Aa02574	1.957536218	-5.978272647	1.222823914	-4.888907208	1.01E-06	8.89E-05
Pavir.Aa02621	0.909365395	-6.53529993	1.672432432	-3.907661562	9.32E-05	0.004726253
Pavir.Aa02666	26.2769212	0.691682664	0.195671446	3.534918755	0.000407901	0.01668753
Pavir.Aa02688	20.64051337	1.419916888	0.311120505	4.563880767	5.02E-06	0.000367199
Pavir.Aa02777	32.70837314	0.824566433	0.256714392	3.211999243	0.001318147	0.044226251
Pavir.Aa02799	5.953157198	1.635139531	0.489562315	3.340002856	0.000837775	0.030512025
Pavir.Aa02841	4.061306867	-1.69398357	0.345840001	-4.898171305	9.67E-07	8.51E-05
Pavir.Aa03067	7.20334301	-6.09679446	1.535018046	-3.971806374	7.13E-05	0.003773958

Integrated Vision: From Human & Plant Systems Biology to 3D Structural Interactions – From Bioenergy to Opioids Addiction

Structures:
28 million compounds



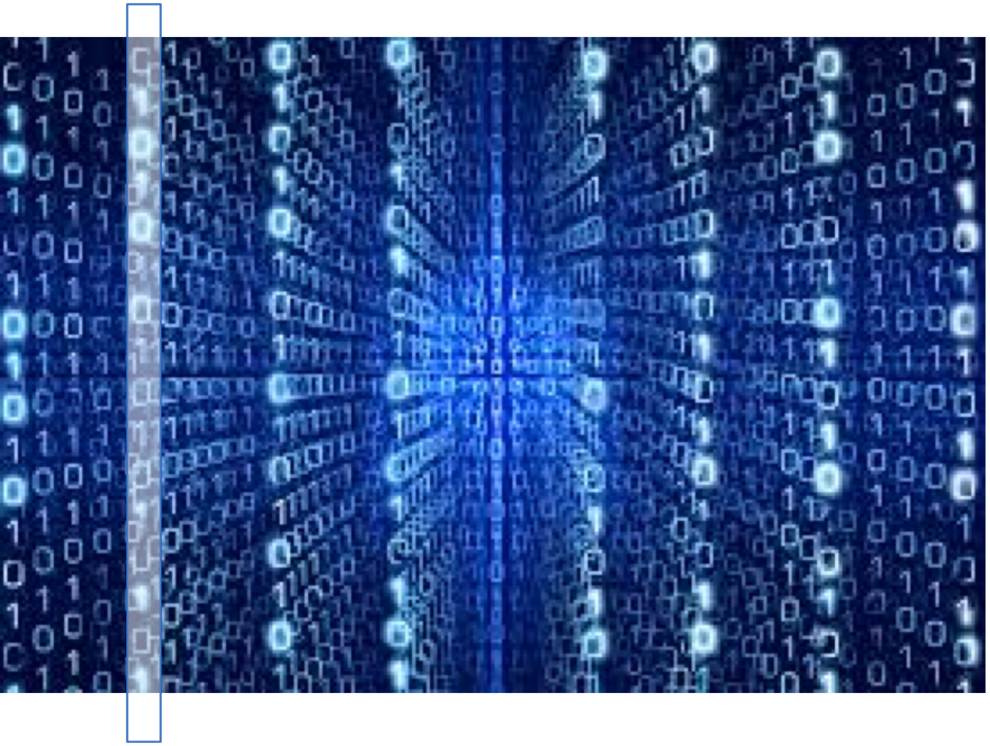


U.S. DEPARTMENT OF ENERGY INCITE LEADERSHIP COMPUTING

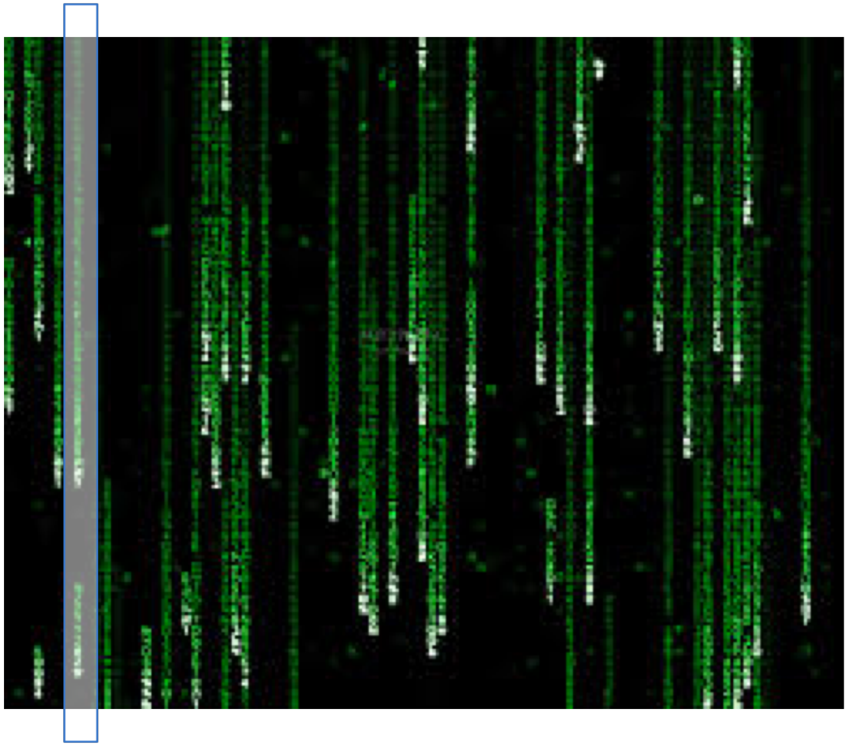
summit

Genome Wide Association Studies (GWAS)
&
Quantitative Trait Loci (QTL)

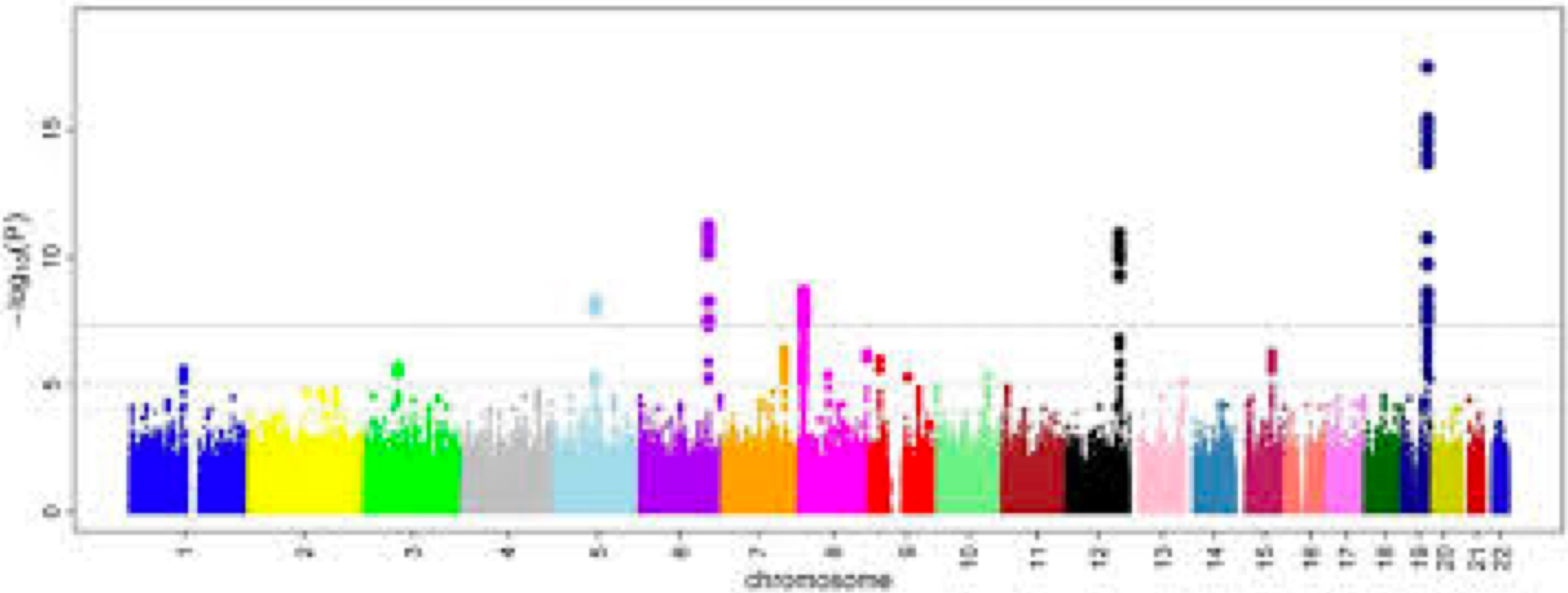
Single QTL mapping: 28 million tests per phenotype



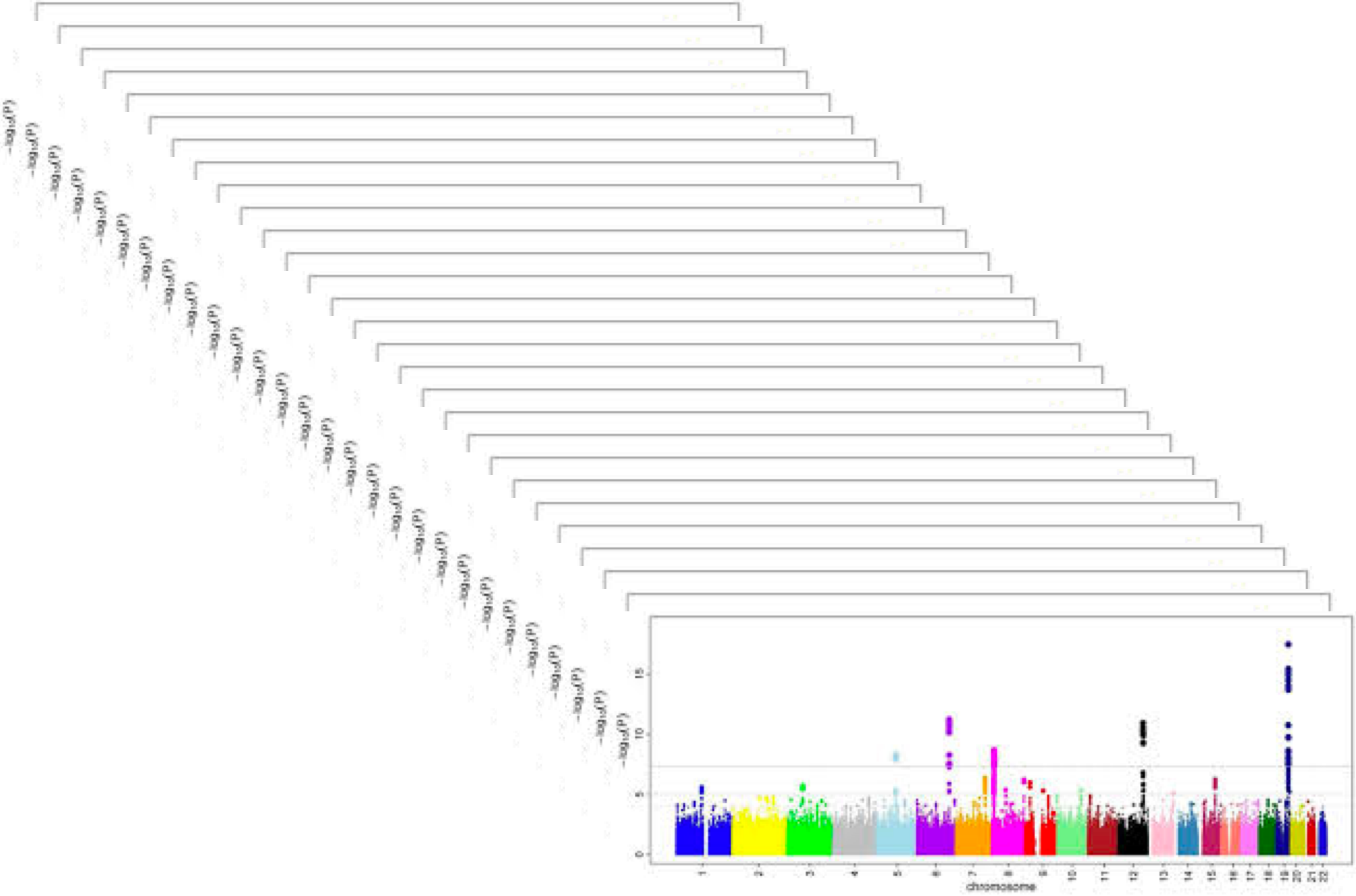
SNP Vectors



Phenotype Vectors

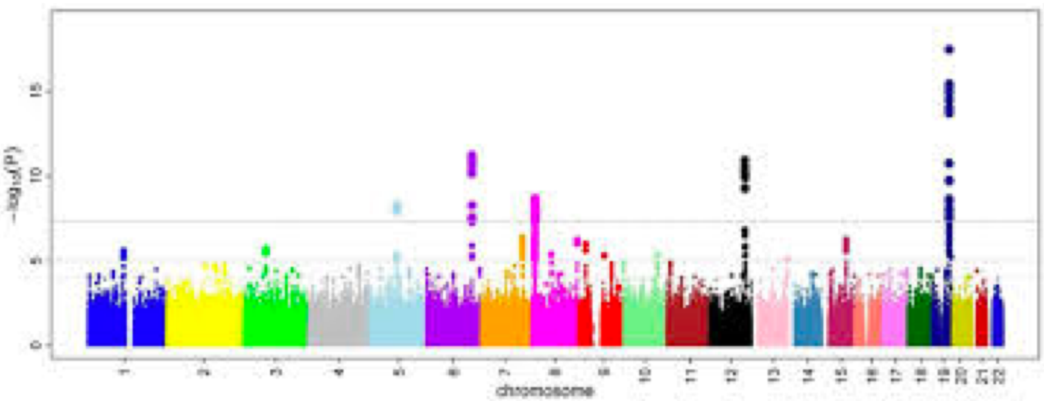


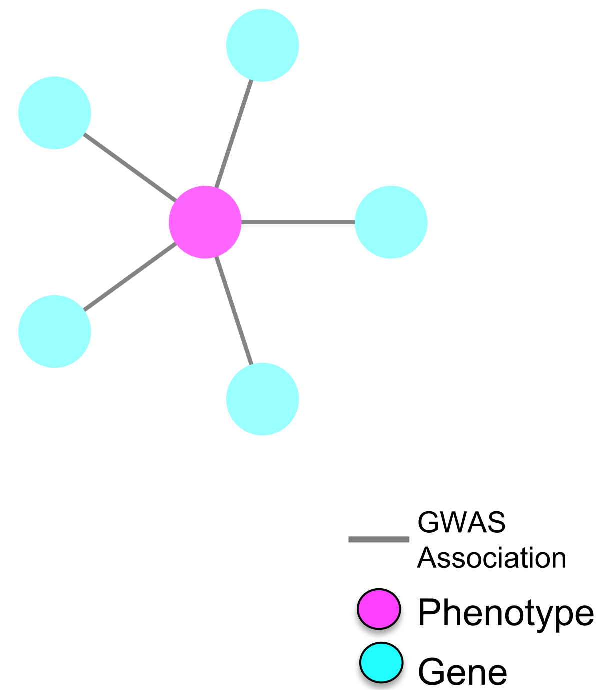
https://en.wikipedia.org/wiki/Manhattan_plot

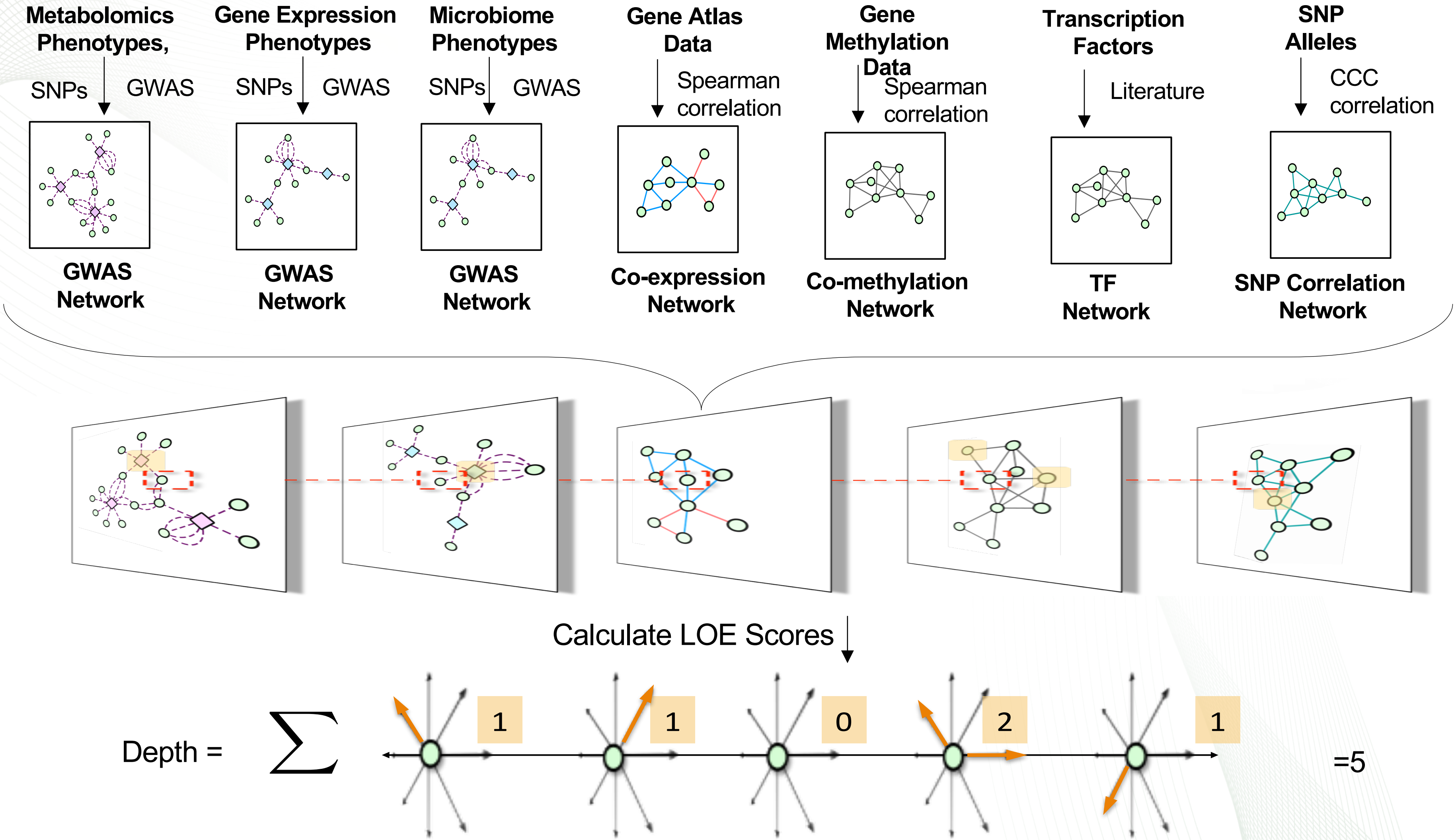


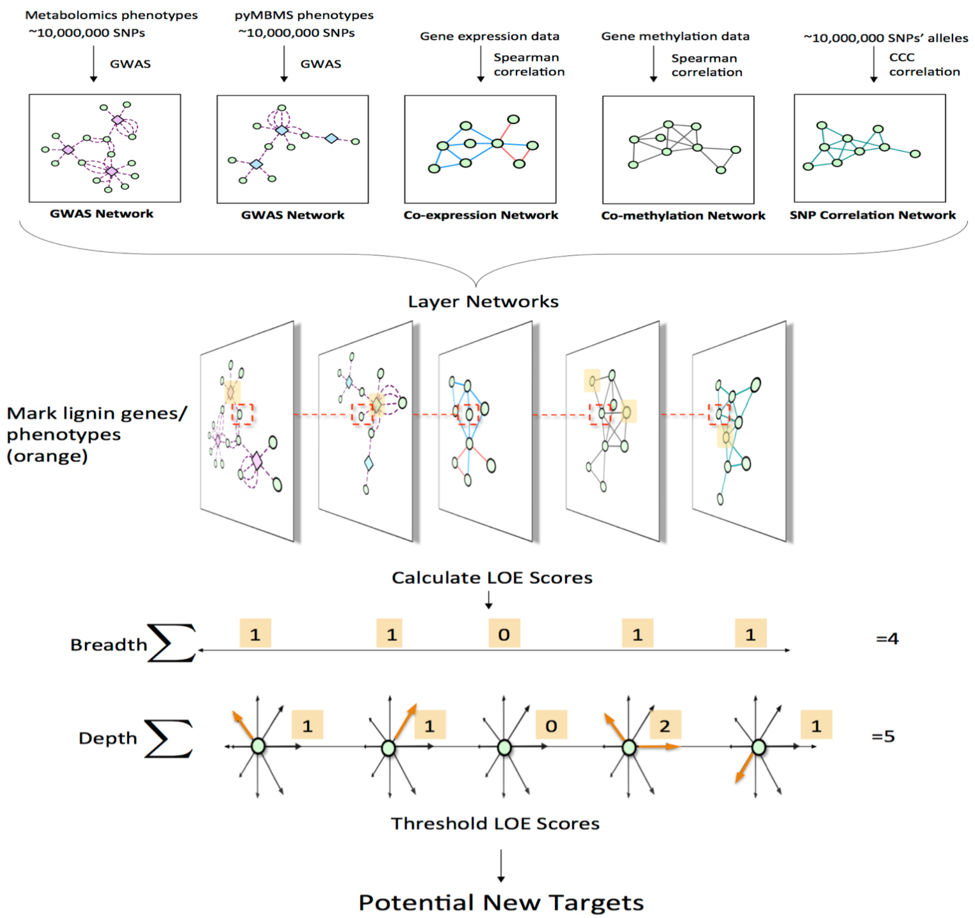
Hundreds of Thousands of Manhattan Plots???

Building GWAS Networks






Metabolomics Phenotypes,
SNPs
GWAS
GWAS Network
Gene Expression Phenotypes
SNPs
GWAS
GWAS Network
Microbiome Phenotypes
SNPs
GWAS
GWAS Network
Gene Atlas Data
Spearman correlation
Co-expression Network
Gene Methylation Data
Spearman correlation
Co-methylation Network
Transcription Factors
Literature
TF Network
SNP Alleles
CCC correlation
SNP Correlation Network
Calculate LOE Scores
Depth =
1
1
0
2
1
=5



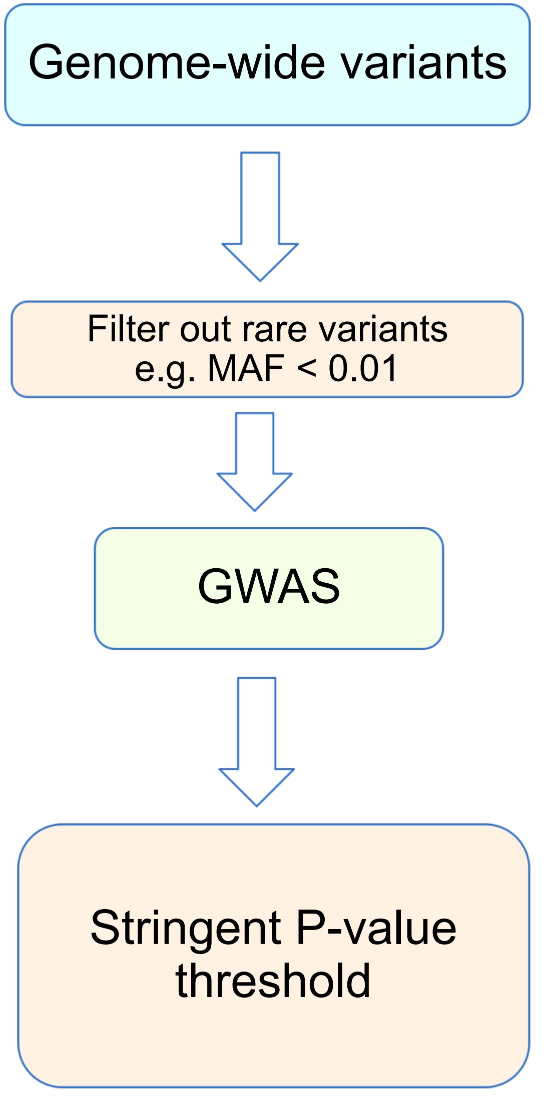
Pleiotropic and Epistatic Network-Based Discovery: Integrated Networks for Target Gene Discovery. Deborah Weighill , Piet Jones, Manesh Shah, Priya Ranjan, Wellington Muchero, Jeremy Schmutz, Avinash Sreedasyam, David Macaya Sanz, Robert Sykes, Nan Zhao, Madhavi Martin, Stephen DiFazio, TImothy Tschaplinski, Gerald Tuskan, **Daniel Jacobson.** *Front. Energy Res. - Bioenergy and Biofuels*, DOI: 10.3389/fenrg.2018.00030

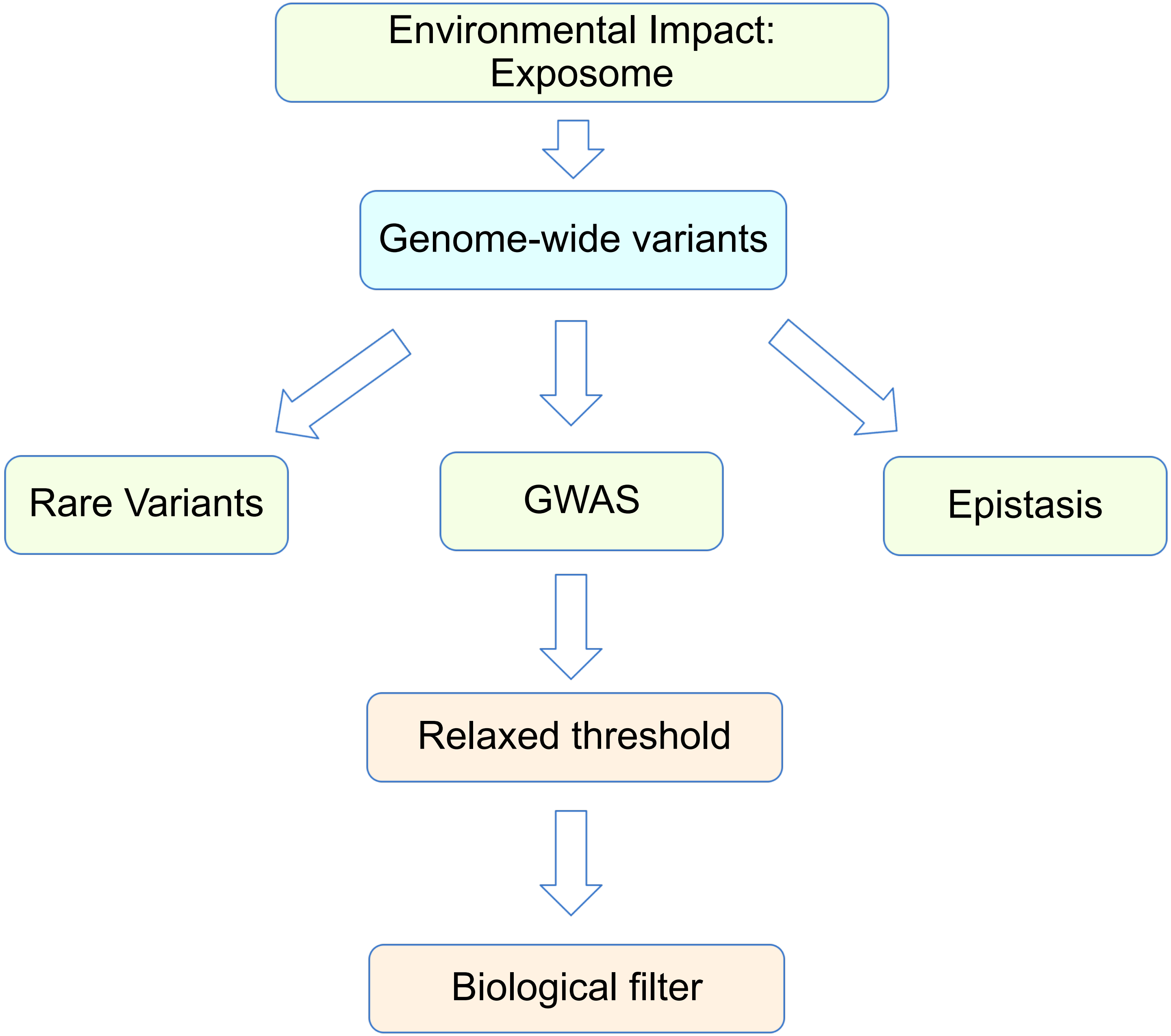
Deeper Discoveries in Systems Biology: The Balance Between False Positives and False Negatives (Type 1 vs Type 2 Error)

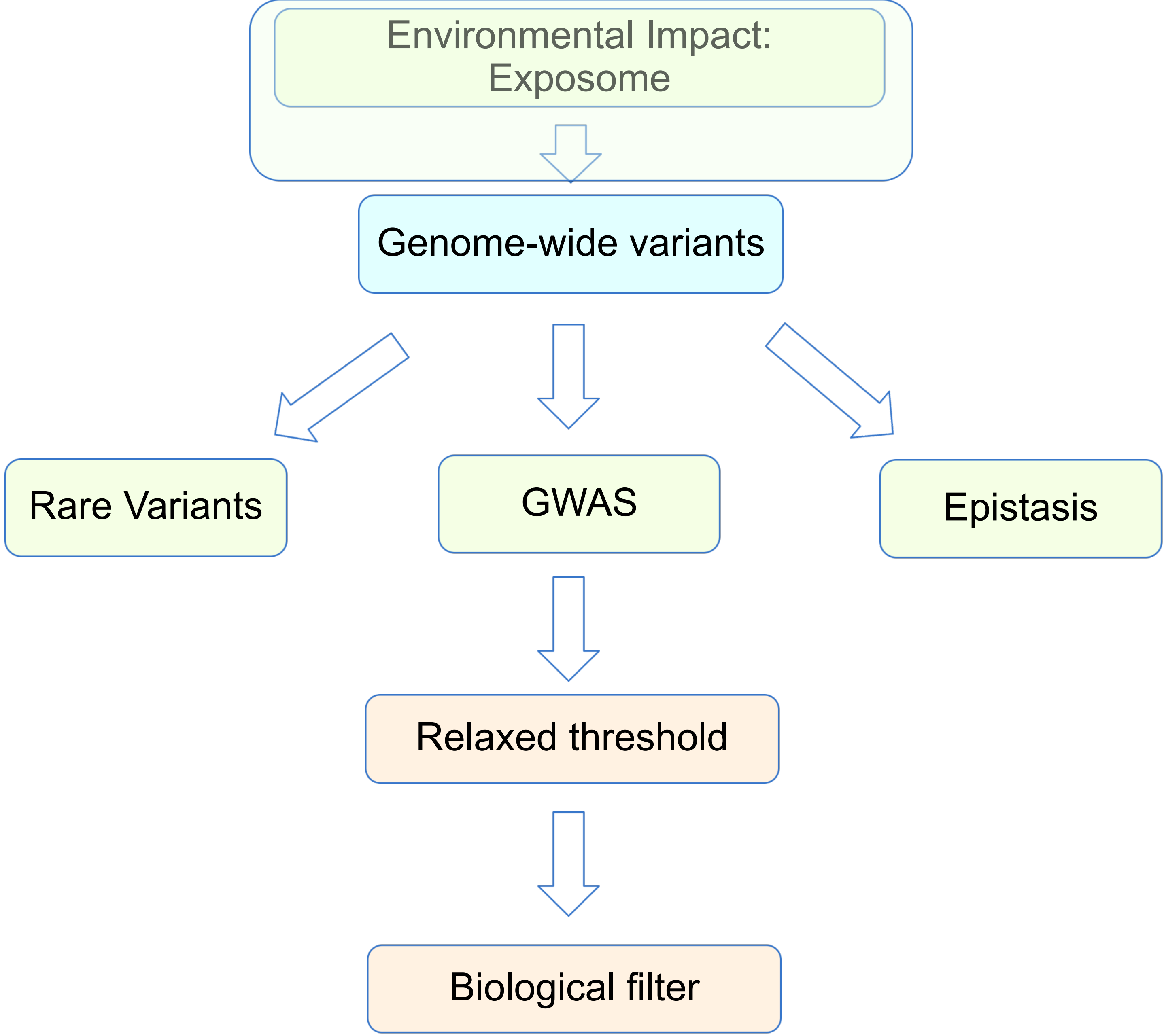
Our ability to reconstruct the entirety of a complex biological system improves as the number of population-scale endo-, meso- and exo-phenotypes are measured and combined with deep layers of experimental data collected on individual genotypes.

GWAS: Single QTL/SNP Mapping

- Very Powerful
- Misses a significant portion (often the majority) of the genetic signal
  - Rare Variants
    - MAF filters
  - Environmental impact
    - Exposome
  - Often does not find complete genetic architectures for complex phenotypes
    - Epistasis


Genome-wide variants
Filter out rare variants
e.g. MAF < 0.01
GWAS
Stringent P-value threshold


Environmental Impact: Exposome
Genome-wide variants
Rare Variants
GWAS
Epistasis
Relaxed threshold
Biological filter



Environmental Impact:
Exposome
Genome-wide variants
Rare Variants
GWAS
Epistasis
Relaxed threshold
Biological filter

Set-based Methods in Action:

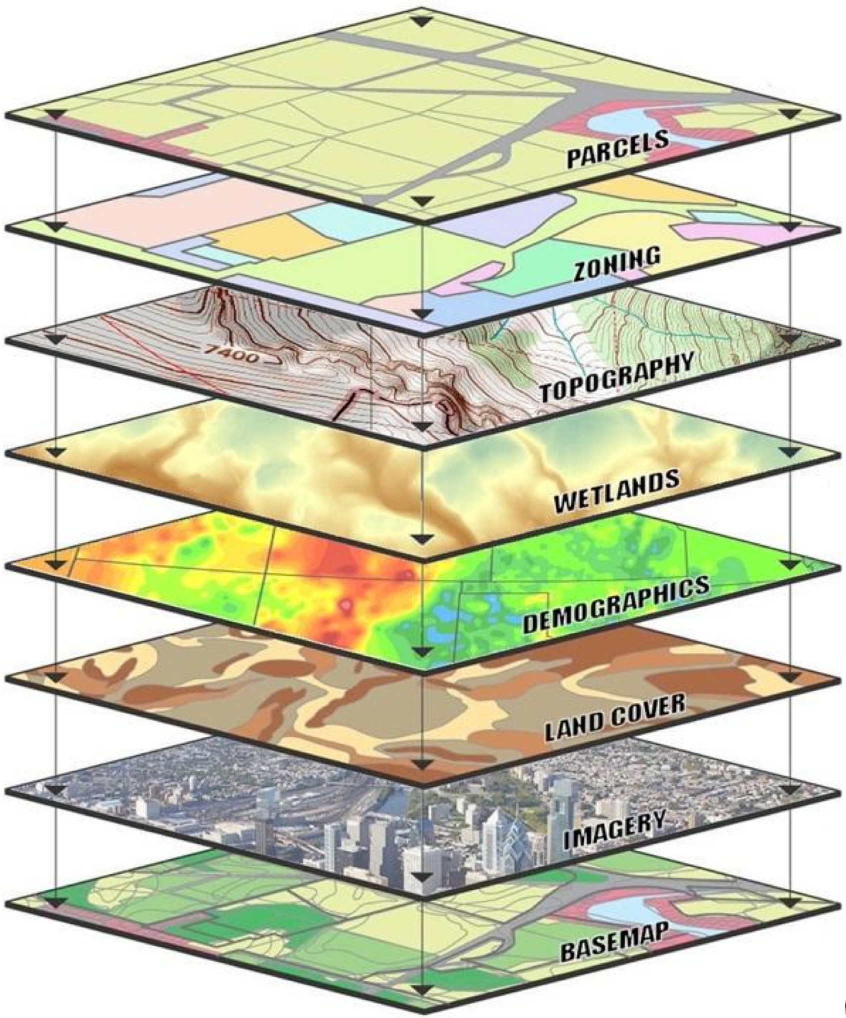
Finding genetic architectures responsible for climate adaptation

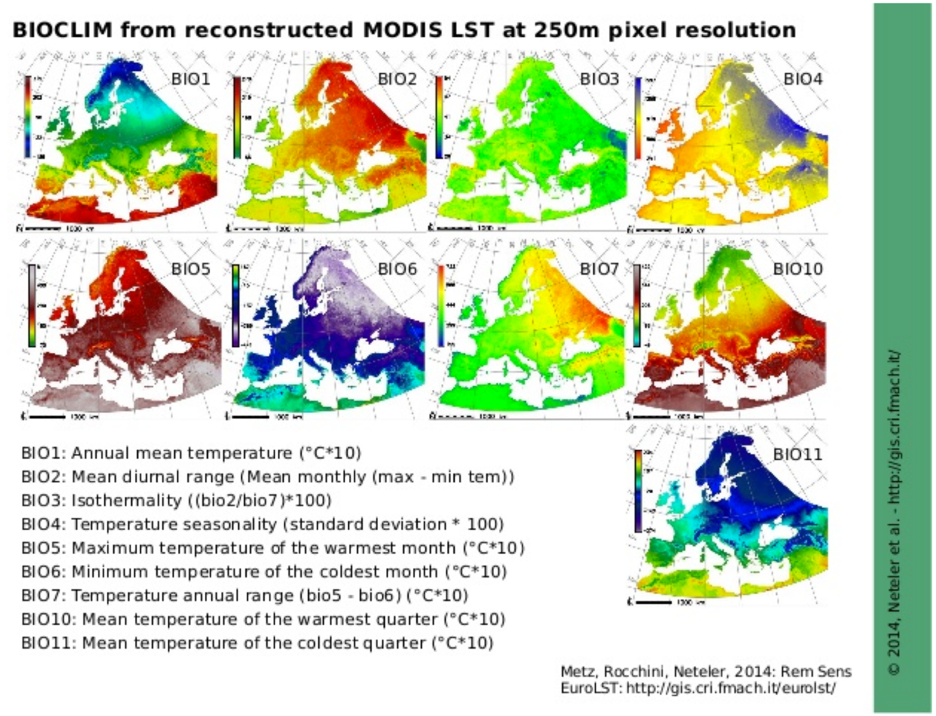
Genome Wide Association of Time Series (GWATS)

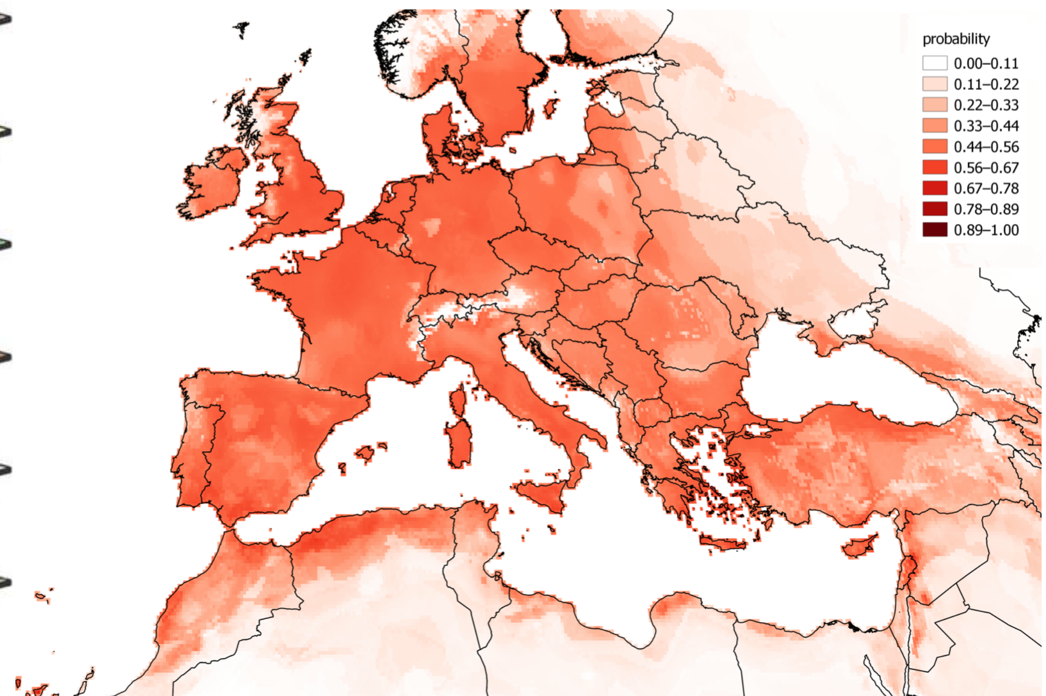
From nucleotides to Climate…


Canada
BRITISH COLUMBIA
ALBERTA
SASKATCHEWAN
MANITOBA
ONTARIO
QUEBEC
NEWFOUNDLAND AND LABRADOR
NB
PE
NOVA SCOTIA
WASHINGTON
OREGON
IDAHO
MONTANA
NORTH DAKOTA
SOUTH DAKOTA
MINNESOTA
WISCONSIN
MICHIGAN
WYOMING
Ottawa
Toronto
NEW YORK
MAINE
VT
NH
MA
CT
RI
PENN
NJ
MD
DE
Washington
Chicago
IOWA
ILLINOIS
INDIANA
OHIO
WEST VIRGINIA
NEBRASKA
NEVADA
San Francisco
UTAH
United States
COLORADO
KANSAS
MISSOURI
Oak Ridge National Laboratory Visitor Center
CALIFORNIA
Las Vegas
Los Angeles
San Diego
ARIZONA
NEW MEXICO
OKLAHOMA
ARKANSAS
TENNESSEE
SOUTH CAROLINA
MISSISSIPPI
ALABAMA
GEORGIA
Dallas
TEXAS
LOUISIANA
Houston
FLORIDA
Gulf of California
Gulf of Mexico
Mexico
Cuba
Dominican Republic

Raster Layers,
Geographic Information Systems (GIS),
And Environmental Data….

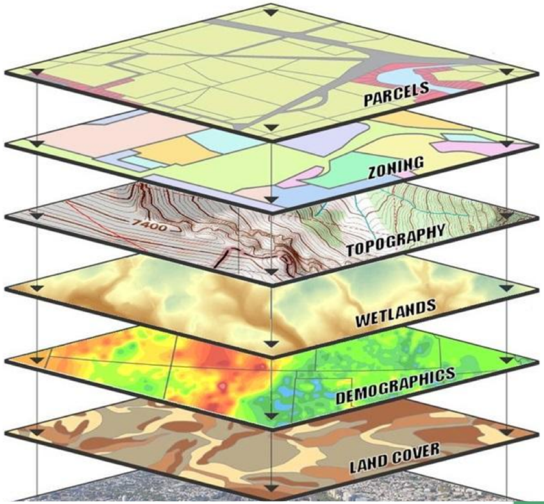




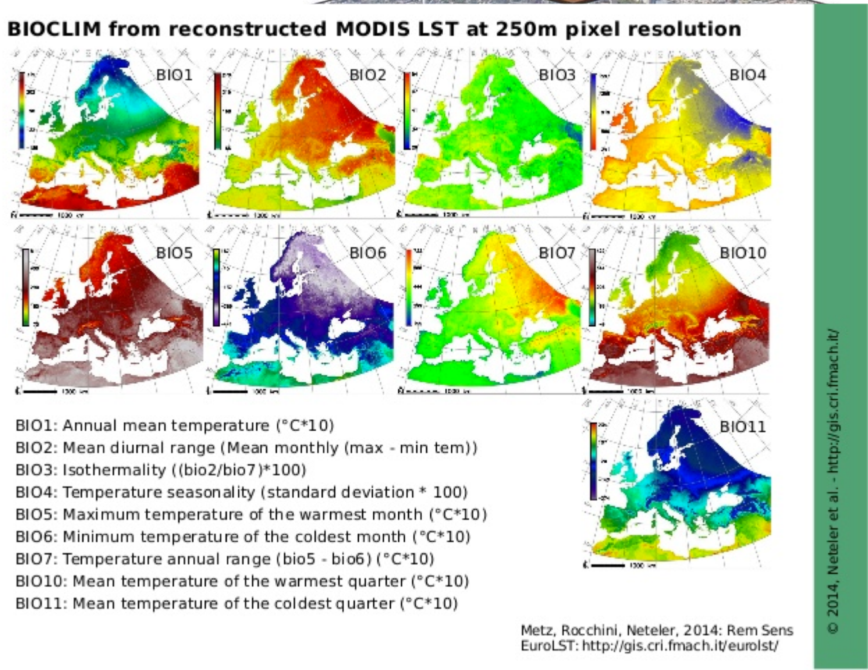


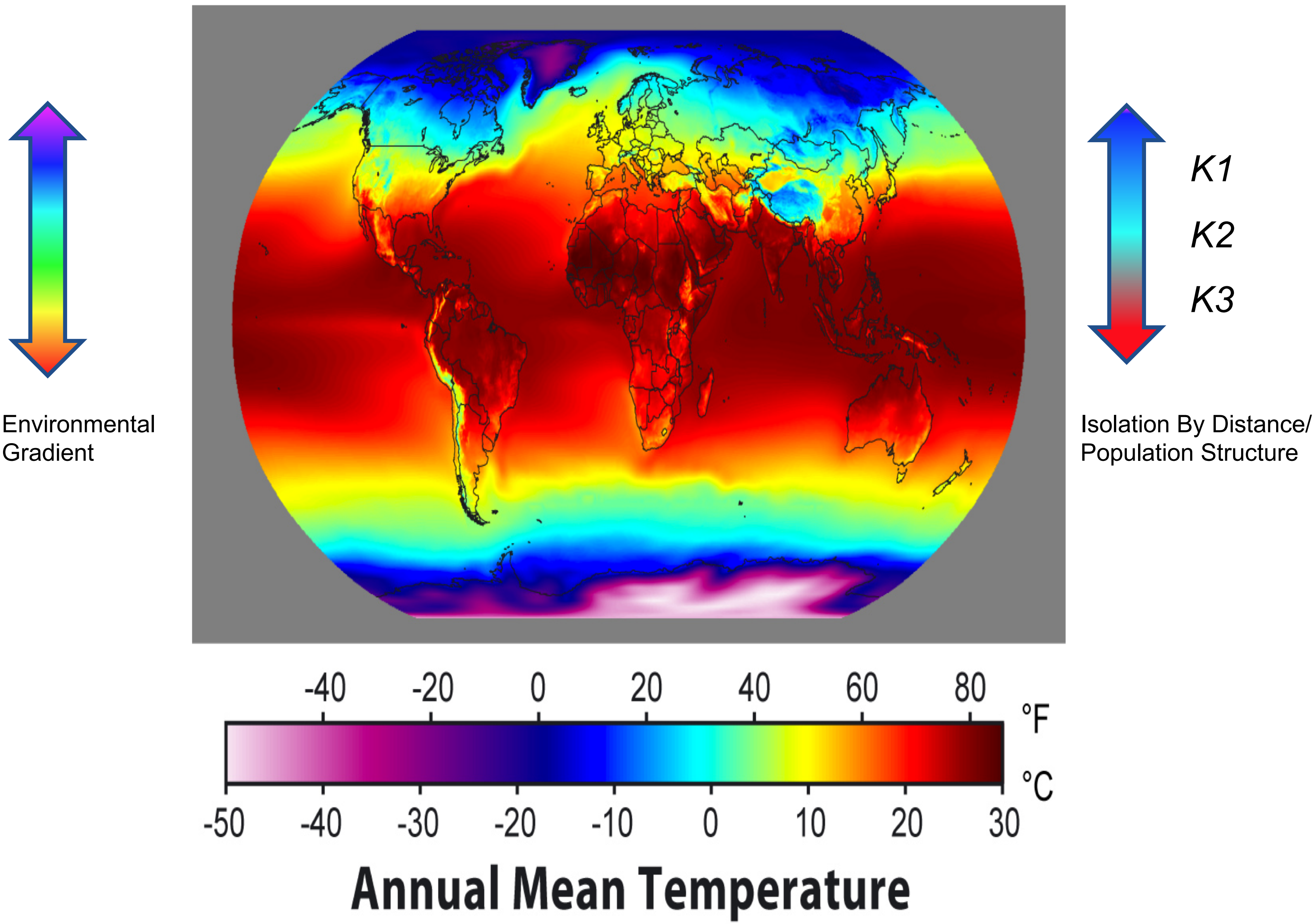
What does a plant think its season is?

Seasons start and end at different times at each geographic location
BioClim doesn't provide enough information

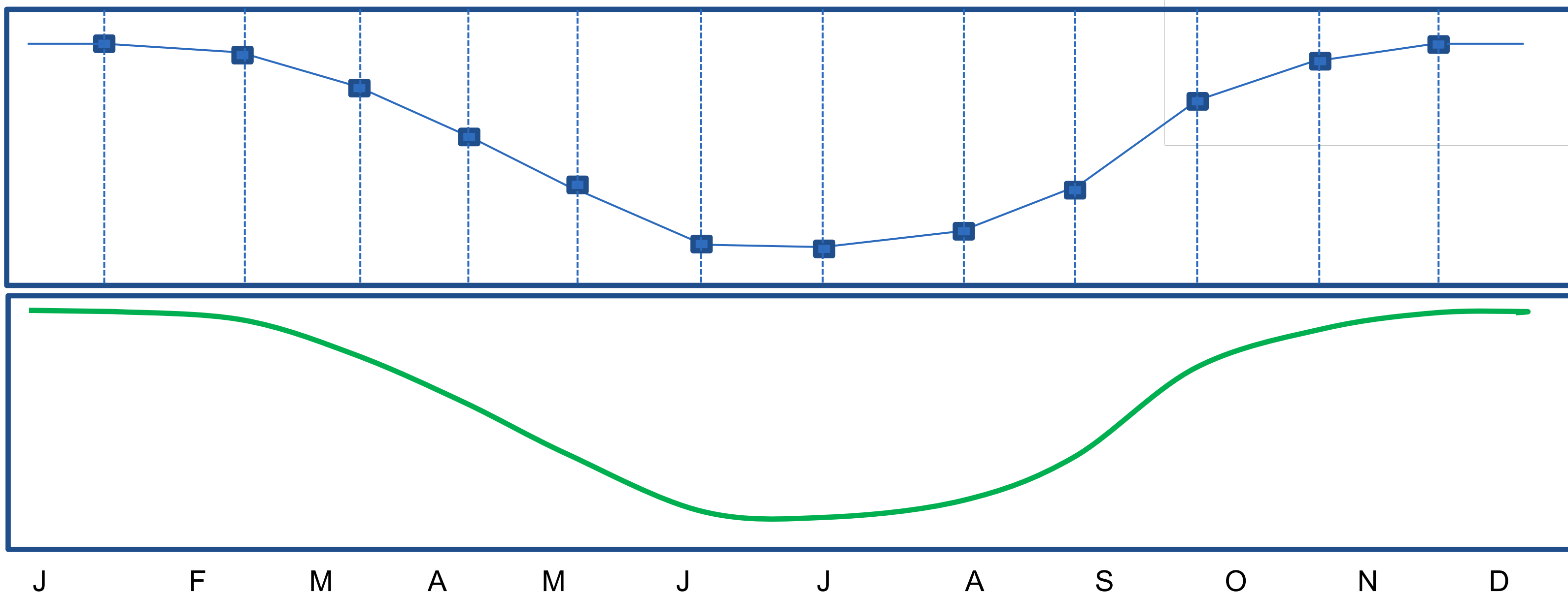


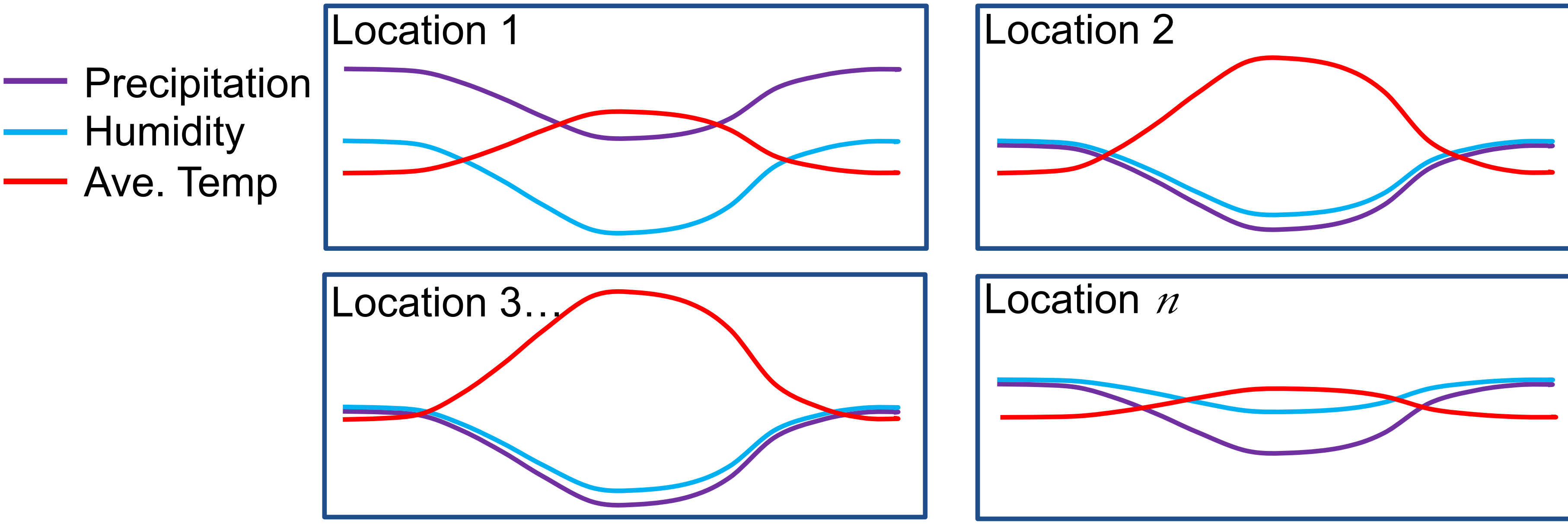
BIO1 = Annual Mean Temperature
BIO2 = Mean Diurnal Range (Mean of monthly (max temp - min temp
BIO3 = Isothermality (BIO2/BIO7) (* 100)
BIO4 = Temperature Seasonality (standard deviation *100)
BIO5 = Max Temperature of Warmest Month
BIO6 = Min Temperature of Coldest Month
BIO7 = Temperature Annual Range (BIO5-BIO6)
BIO8 = Mean Temperature of Wettest Quarter
BIO9 = Mean Temperature of Driest Quarter
BIO10 = Mean Temperature of Warmest Quarter
BIO11 = Mean Temperature of Coldest Quarter
BIO12 = Annual Precipitation
BIO13 = Precipitation of Wettest Month
BIO14 = Precipitation of Driest Month
BIO15 = Precipitation Seasonality (Coefficient of Vari
BIO16 = Precipitation of Wettest Quarter
BIO17 = Precipitation of Driest Quarter
BIO18 = Precipitation of Warmest Quarter
BIO19 = Precipitation of Coldest Quarter



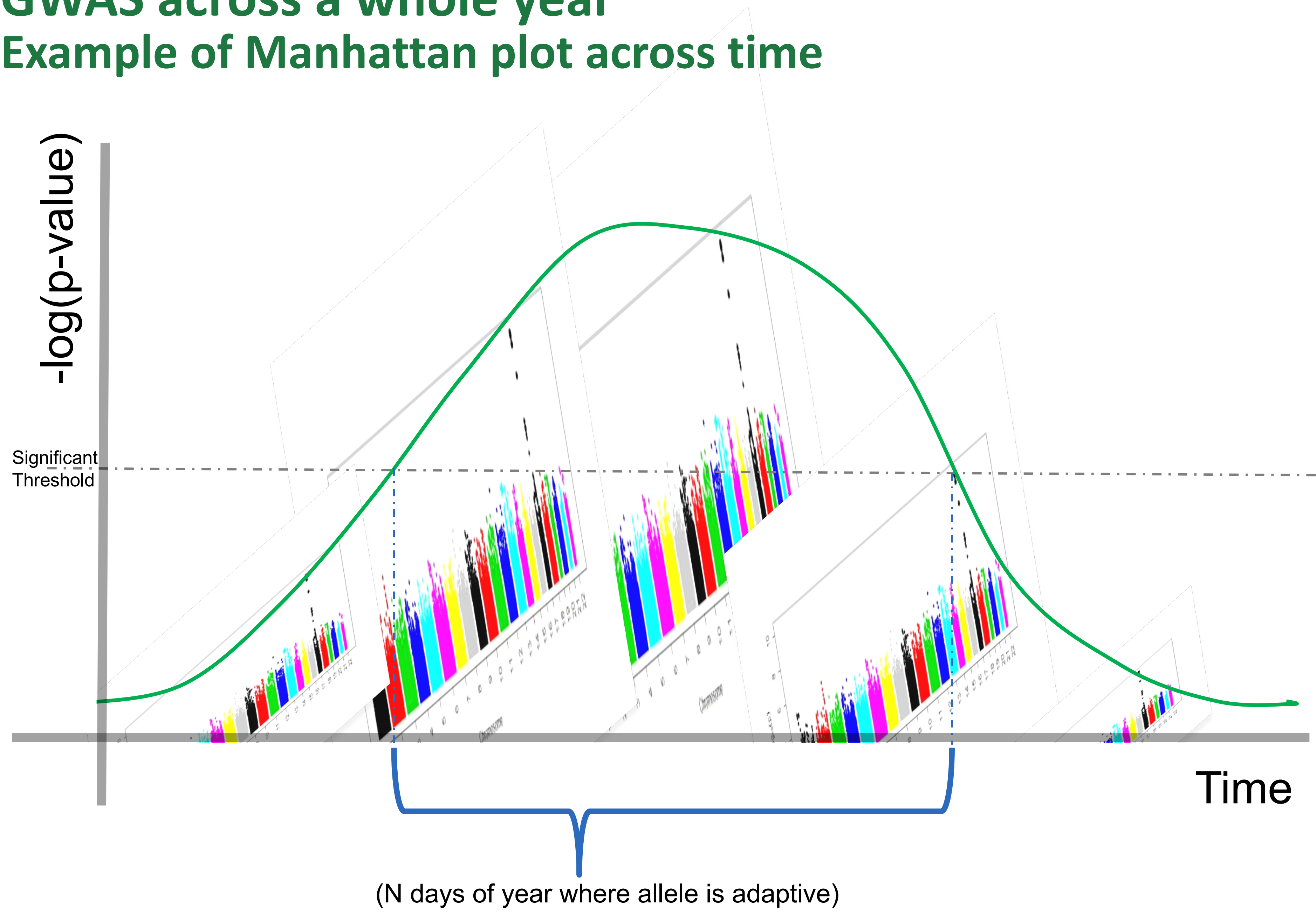

Environmental Gradient
K1
K2
K3
Isolation By Distance/ Population Structure
-40 -20 0 20 40 60 80
°F
°C
-50 -40 -30 -20 -10 0 10 20 30
Annual Mean Temperature

Interpolate Climate Data to a full year





GWAS across a whole year
Example of Manhattan plot across time



> 9500 Environmental Variables

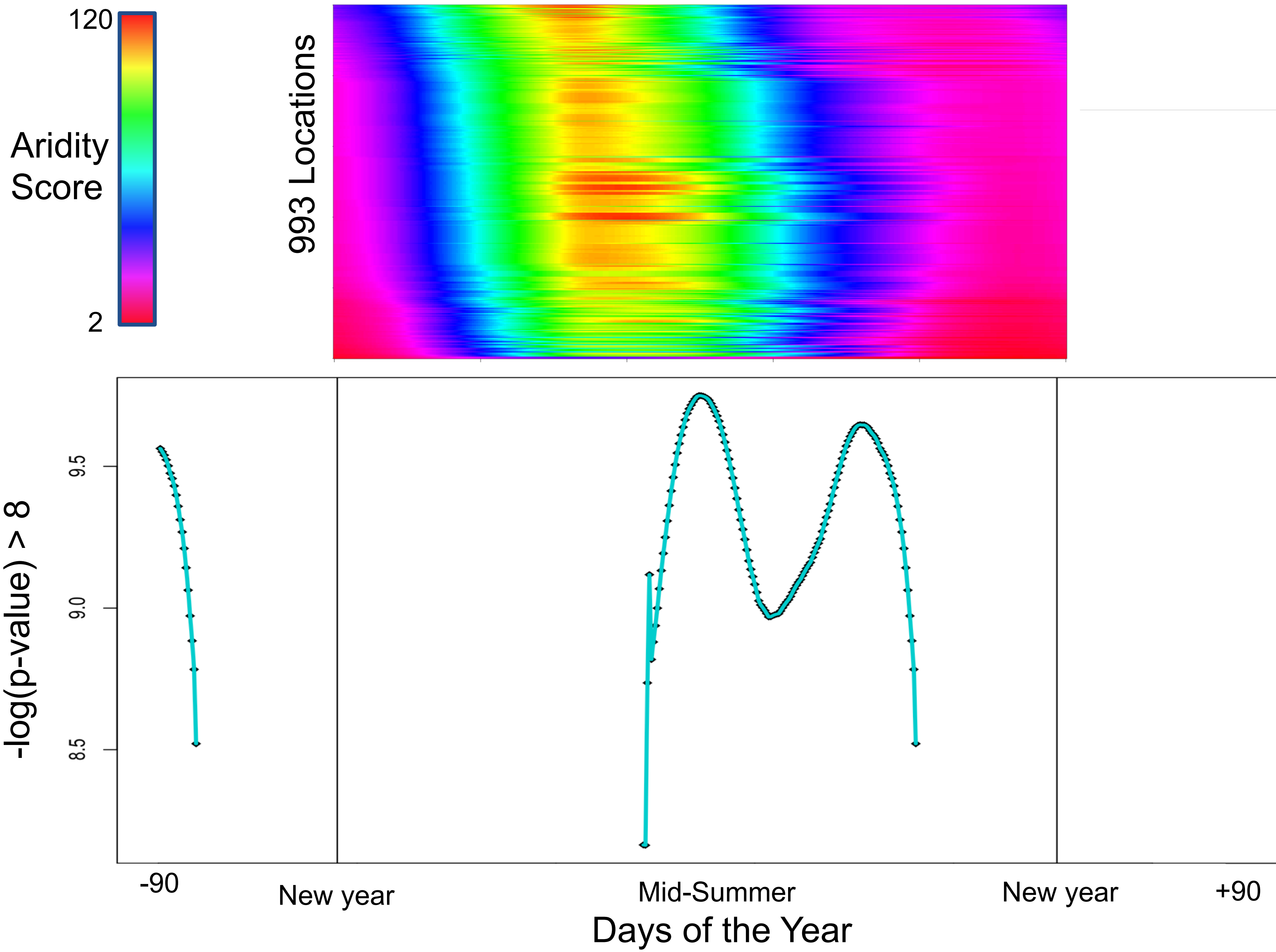
26 Time-Fluctuating Variables (365 days across year)

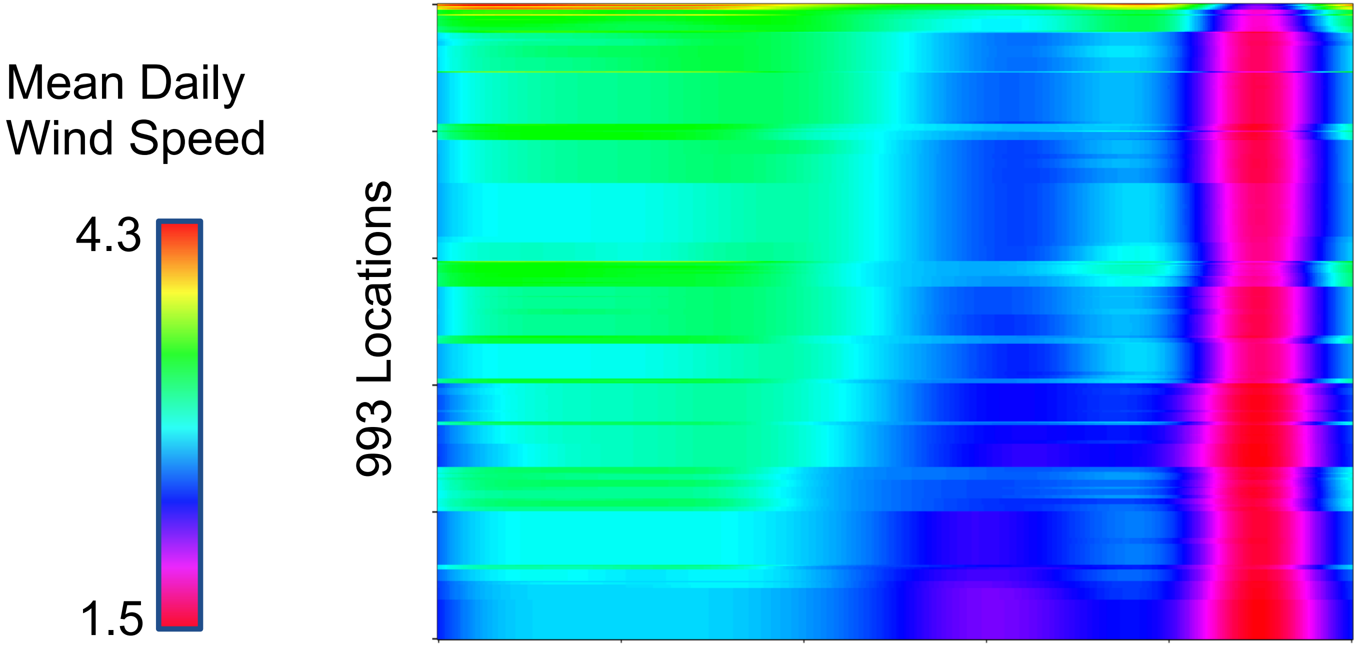
- Mean Temperature
- Temperature Range
- Min Temperature
- Max Temperature
- Mean Humidity
- Max Humidity
- Min Humidity
- Humidity Range
- Mean Aridity Index
- Vapor Pressure (kPa)
- Wind Speed (m/s)
- Solar Radiation (kJ/m^2)
- Mean Solar hours
- Precipitation Quantity
- Precipitation Chance
- Soil Water Capacity
- Light Hours (4 layers): UV, Red, Blue, Far-Red Light Hours
- Light Intensity (4 layers) UV, Red, Blue, Far-Red
- Cloudiness Chance
- Percent Cloud Cover

37 Non-time dependent Variables

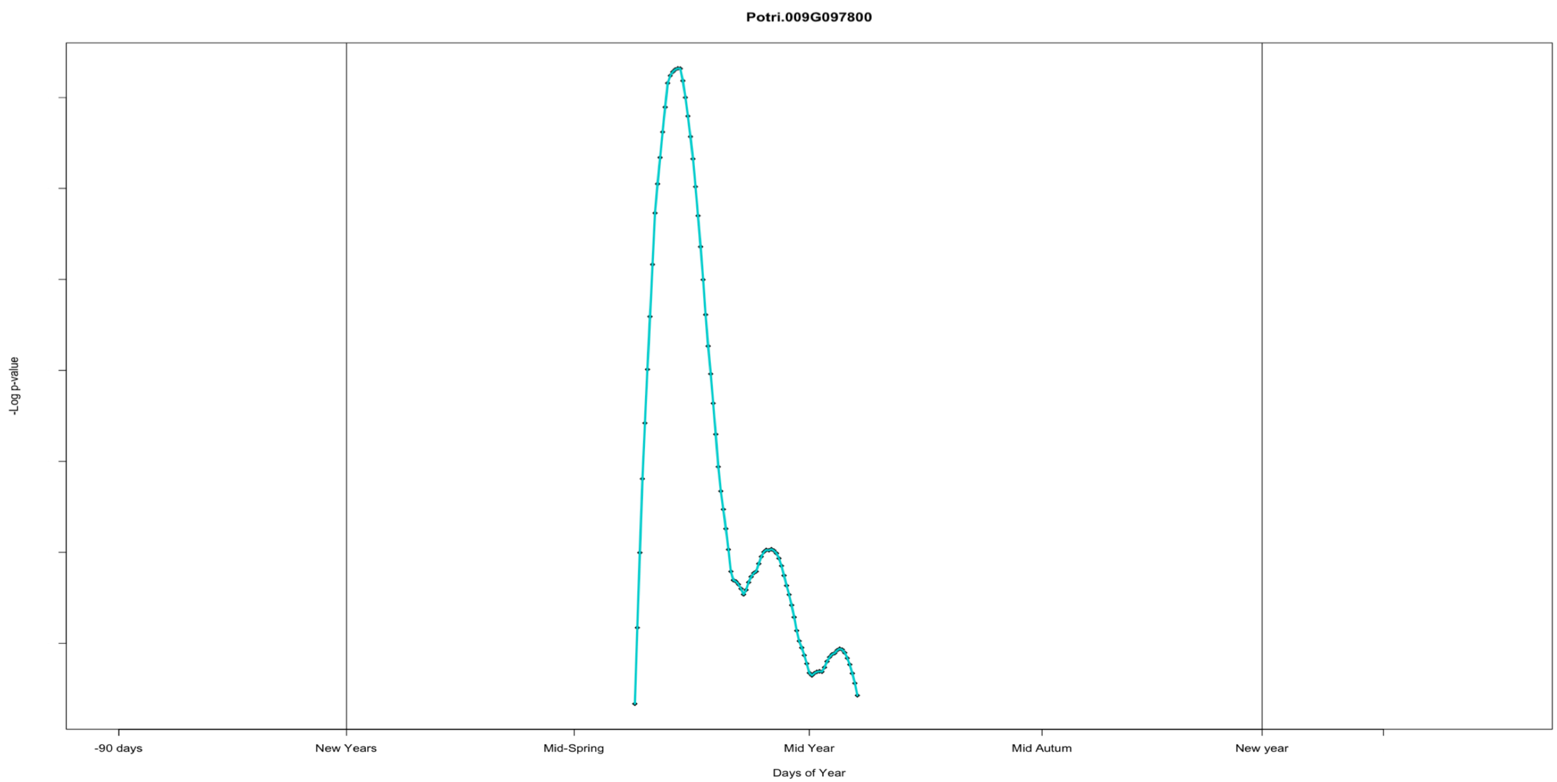
- Mean Annual Temperature (Bio1)
- Mean Diurnal Range (Bio2)
- Isothermality (mean monthly) * (annual range). (Bio3)
- Temperature Seasonality (standard deviation * 100). (Bio4)
- Max Temperature Warmest Month (Bio5)
- Min Temperature coldest month (Bio6)
- Temperature Annual Range (Bio7)
- Mean Temperature of Wettest Quarter (Bio8)
- Mean Temperature of Driest Quarter (Bio9)
- Mean Temperature Warmest Quarter (Bio10)
- Mean Temperature Coldest Quarter (Bio11)
- Annual Precipitation (Bio12)
- Precipitation of Wettest Month (Bio13)
- Precipitation of driest Month (Bio14)
- Precipitation Seasonality (Bio15)
- Precipitation of Wettest Quarter (Bio16)
- Precipitation of Driest Quarter (Bio17)
- Precipitation of Warmest Quarter (Bio18)
- Precipitation of Coldest Quarter (Bio19)
- Soil Water Retention (Mean)
- Soil Cultivation
- Soil Salinity
- Soil Nutrient Availability
- Nutrient Retention
- Oxygen Availability
- Excess Salts
- Rooting Conditions
- Workability (general particle size)
- % Grassland
- % Forest Land
- % Herbaceous Cover
- % Desert
- Elevation
- Aspect (4 layers)
- Slope (8 Layers)
- Proximity to water body (custom layer
- Snow Cover

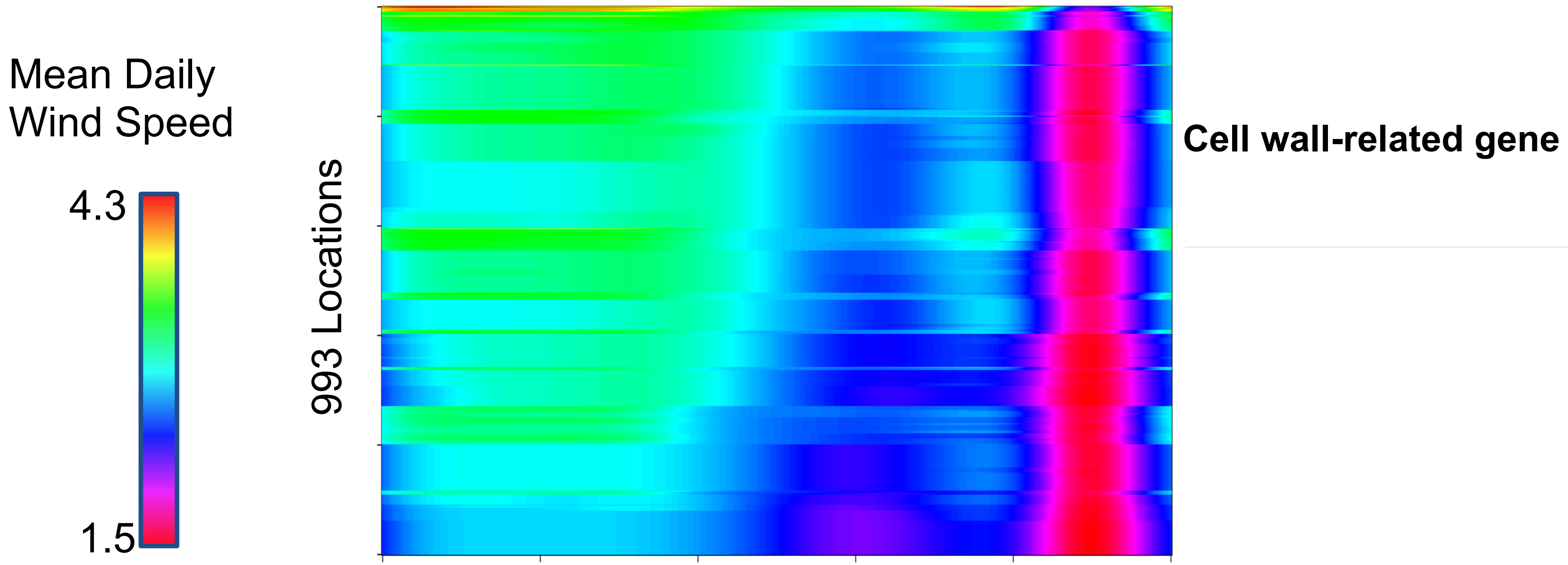
Wax-related Gene Across Season



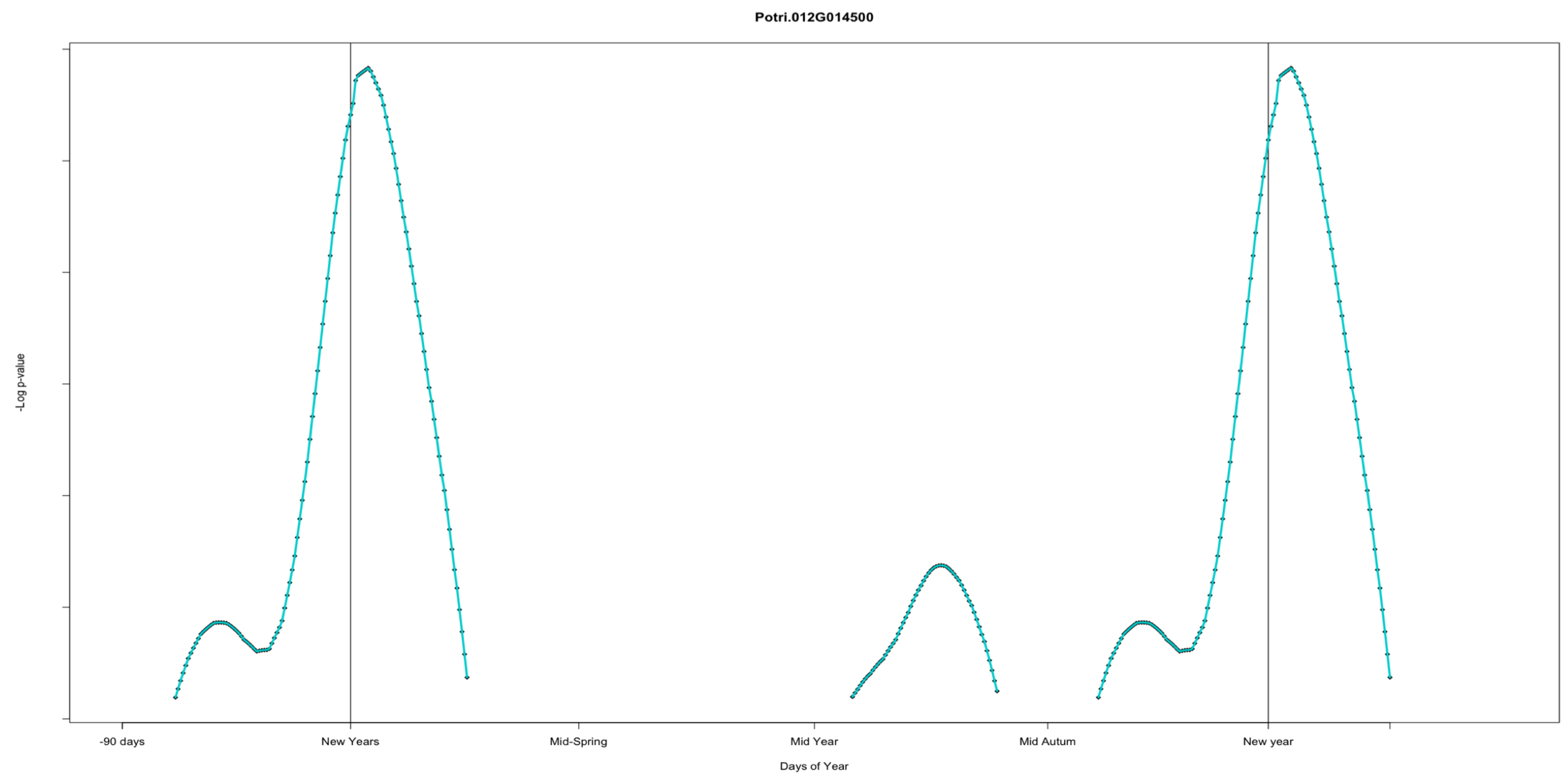


Gene involved in leaf development and senescence





Mean Daily Wind Speed
4.3
1.5
993 Locations
Cell wall-related gene



Potri.012G014500
-Log p-value
-90 days
New Years
Mid-Spring
Mid Year
Mid Autum
New year
Days of Year

Possibilities

- Time Accurate to One Day of the Year Variants are Potentially Important for Climate Stress
- Many Different Climate Variables can be used such as Aridity, Heat Stress, Drought Stress
- Variants that are Important for Specific Climates Can be used for Selective Breeding to improve Yield Traits per region

- Epistatic and Pleiotropic interactions will also be determined
- Exposome Networks become another layer of data for LOE
  - Better understanding

Addiction is a complex, multigenic, epistatic trait

The combinatorial space that we need to search is huge….

Why do we think we can do this?

We have learned a lot of lessons and developed methods to find increasingly complex patterns

We population-scale have observational datasets

We are developing population-scale experimental systems

Obervational Data: MVP CHAMPION: DOE-VA Collaboration

- Clinical records for 23 million patients, past 20 years at ORNL
- 600,000 genotypes --> 2 million genotypes
- Unprecedented clinical genomics resource
- Amy Justice: Expert co-PI in drug use and epidemiology in the VA population

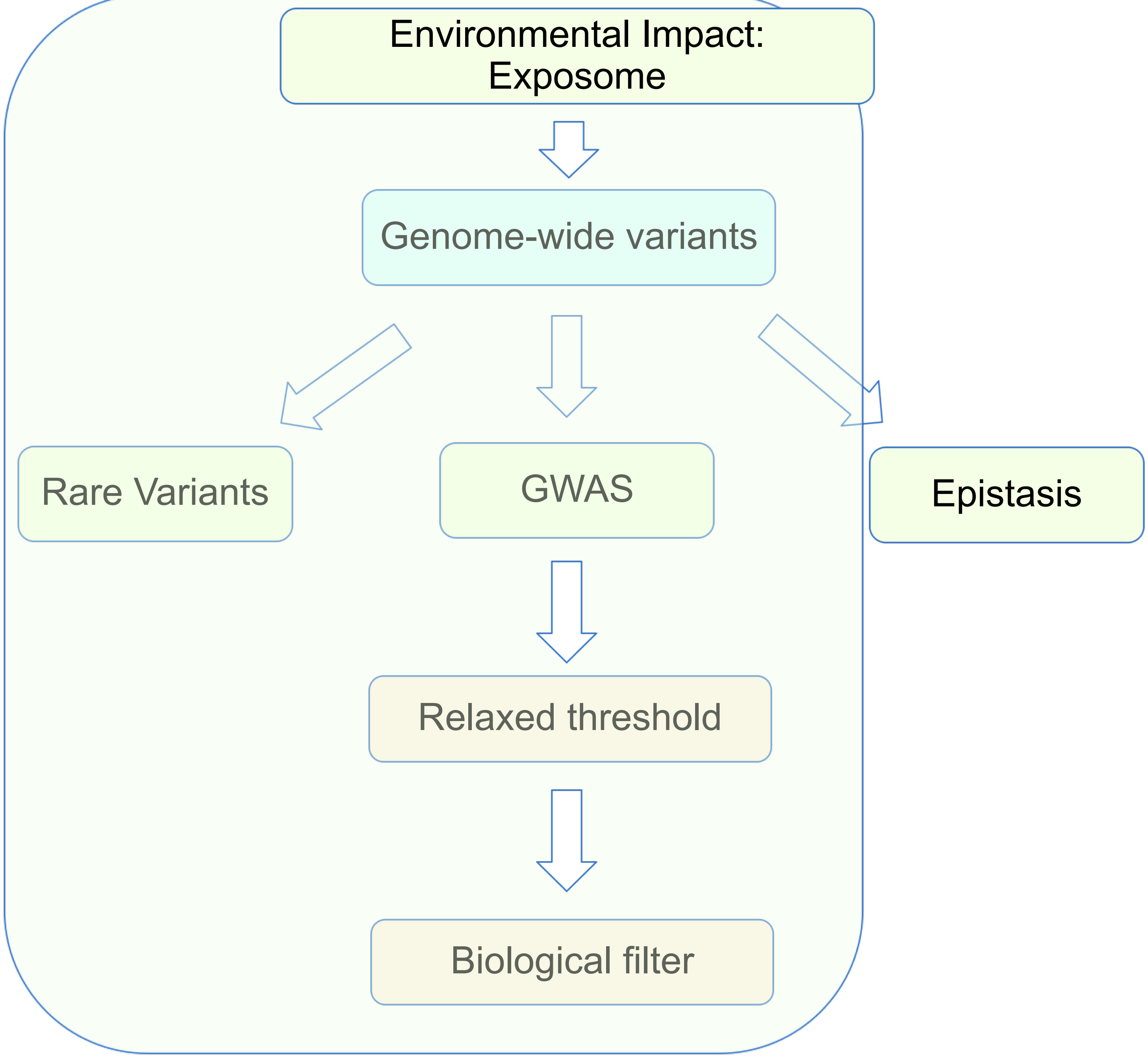
Experimental Data: Integrated, Scalable *Drosophila* Phenotyping

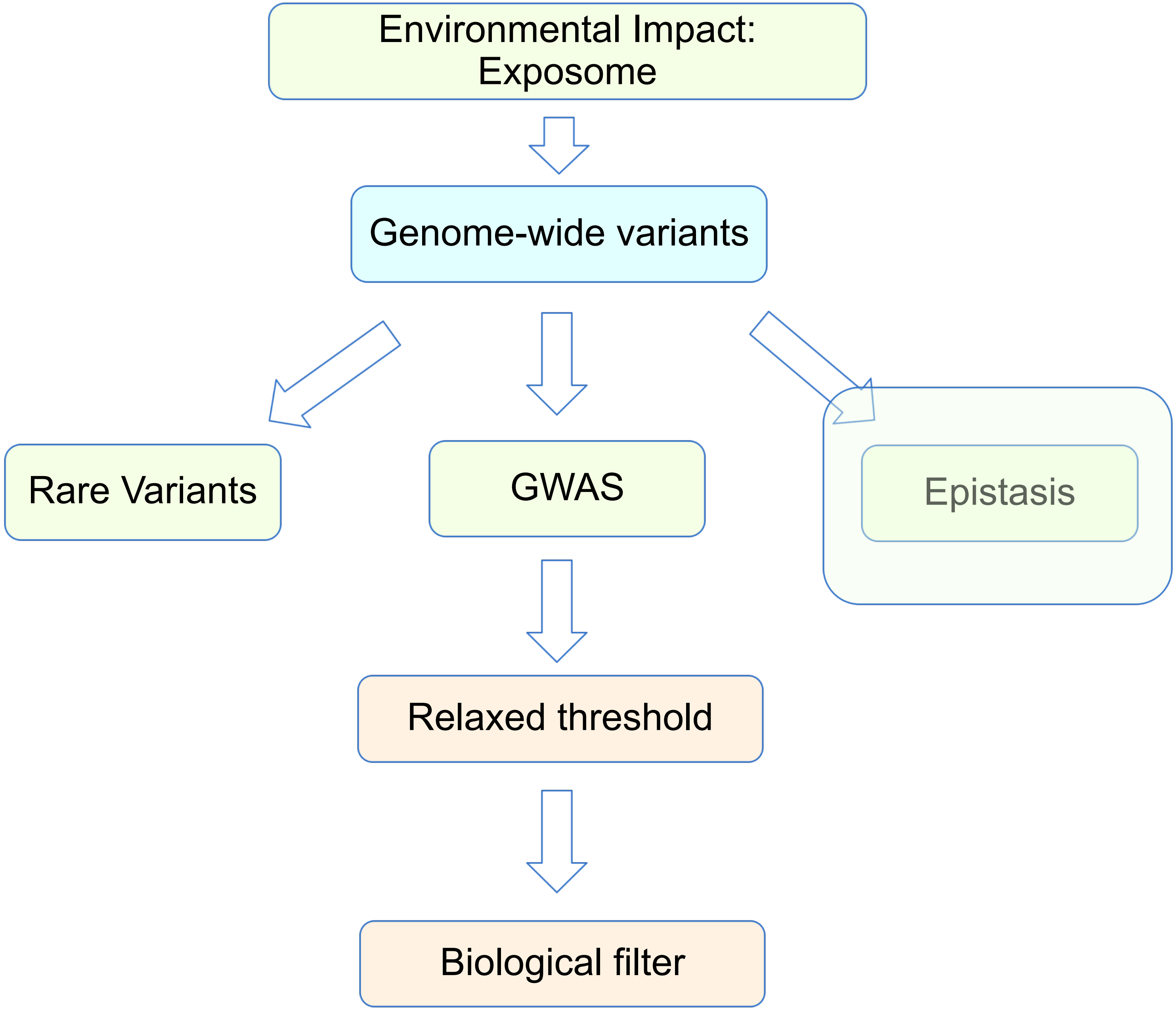
Intoxication:
- Impaired motor coordination (ARC)
- Reduced responsiveness to external stimuli (ARC, Activity)
- Coma/Sleep (ARC, Activity)

Opioid-sensitive changes in learning and memory:
- Conditioned place preference (Memory)
- Aversive cue learning and analgesic effects (Memory)
- Changes in motivation to seek out drug-paired cues (Treadmill)

Psychostimulation/depression:
- Changes in activity (ARC, Activity, Treadmill)
- Changes in space utilization (ARC, Activity)
- Disruption of circadian patterns (ARC, Activity)

Extinction, withdrawal, and reinstatement:
- Motor effects of drug cessation (ARC, Activity)
- Changes in conditioned place preference (Memory)
- Compulsive behaviors (ARC, Activity, Treadmill)


Environmental Impact:
Exposome
Genome-wide variants
Rare Variants
GWAS
Epistasis
Relaxed threshold
Biological filter


Environmental Impact:
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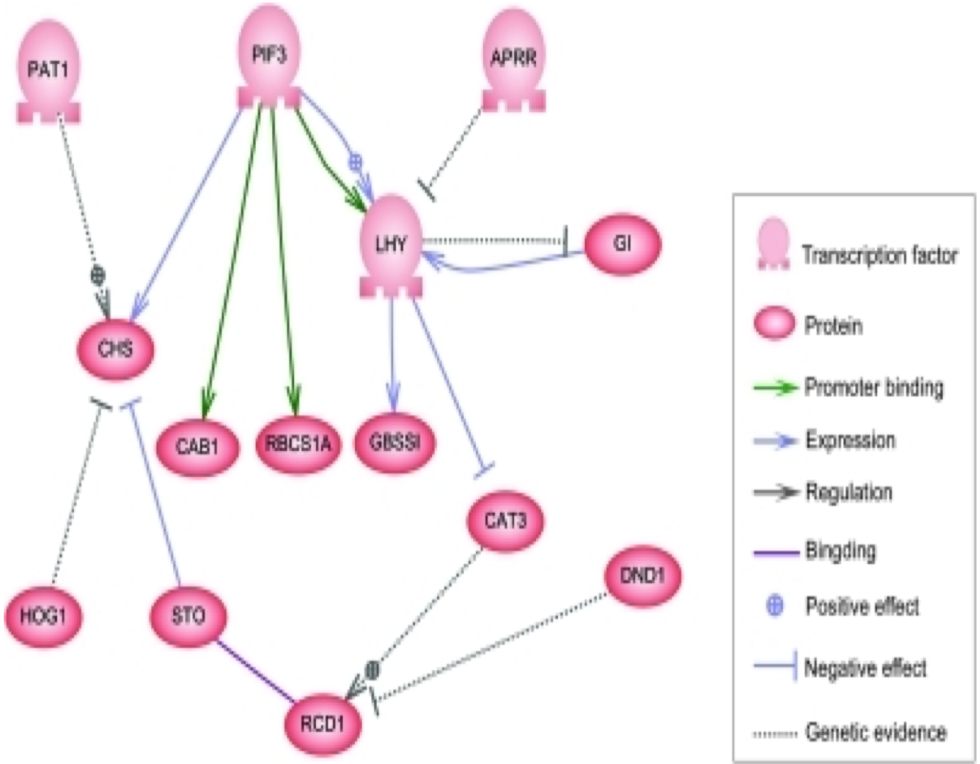
Epistatic Interactions

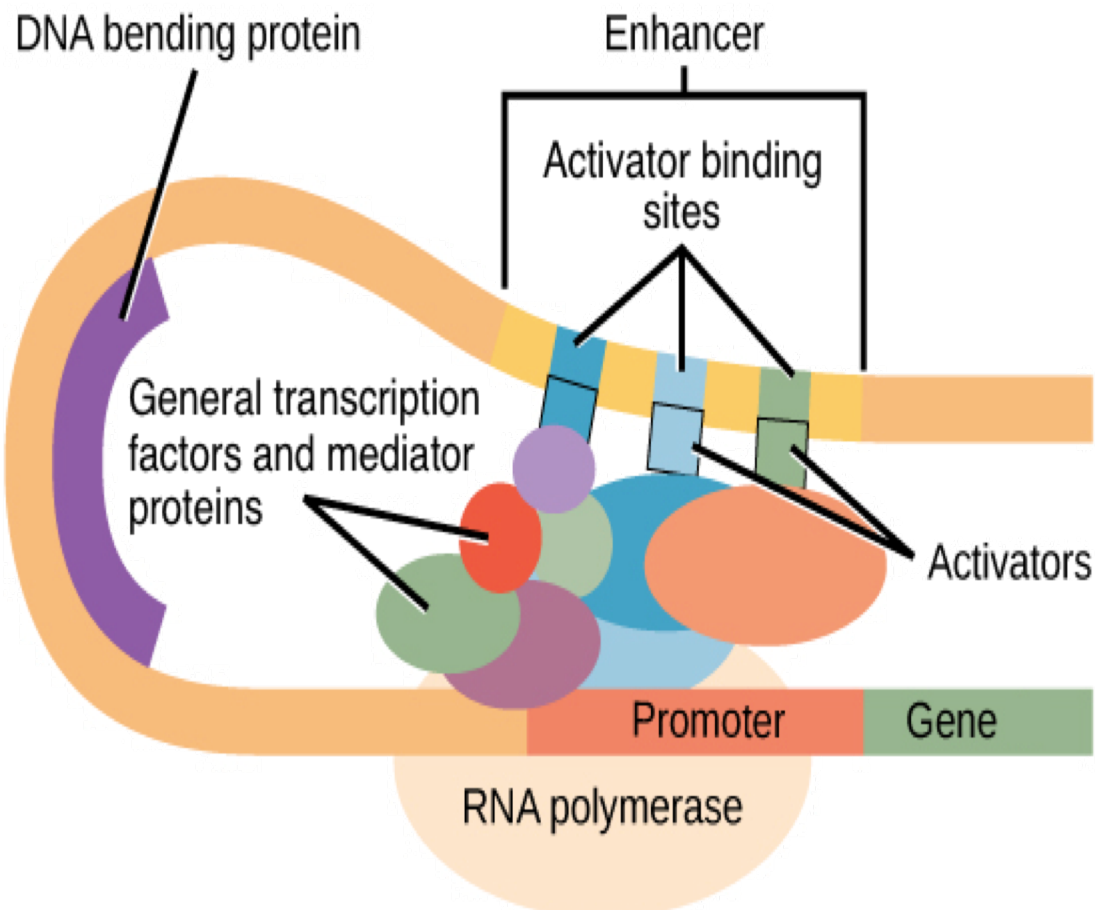


- Additive and epistatic contributions
- For phenotype y and QTL Q_m, where m represents a locus in the genome, we want to determine $\beta_m \, \forall m$.

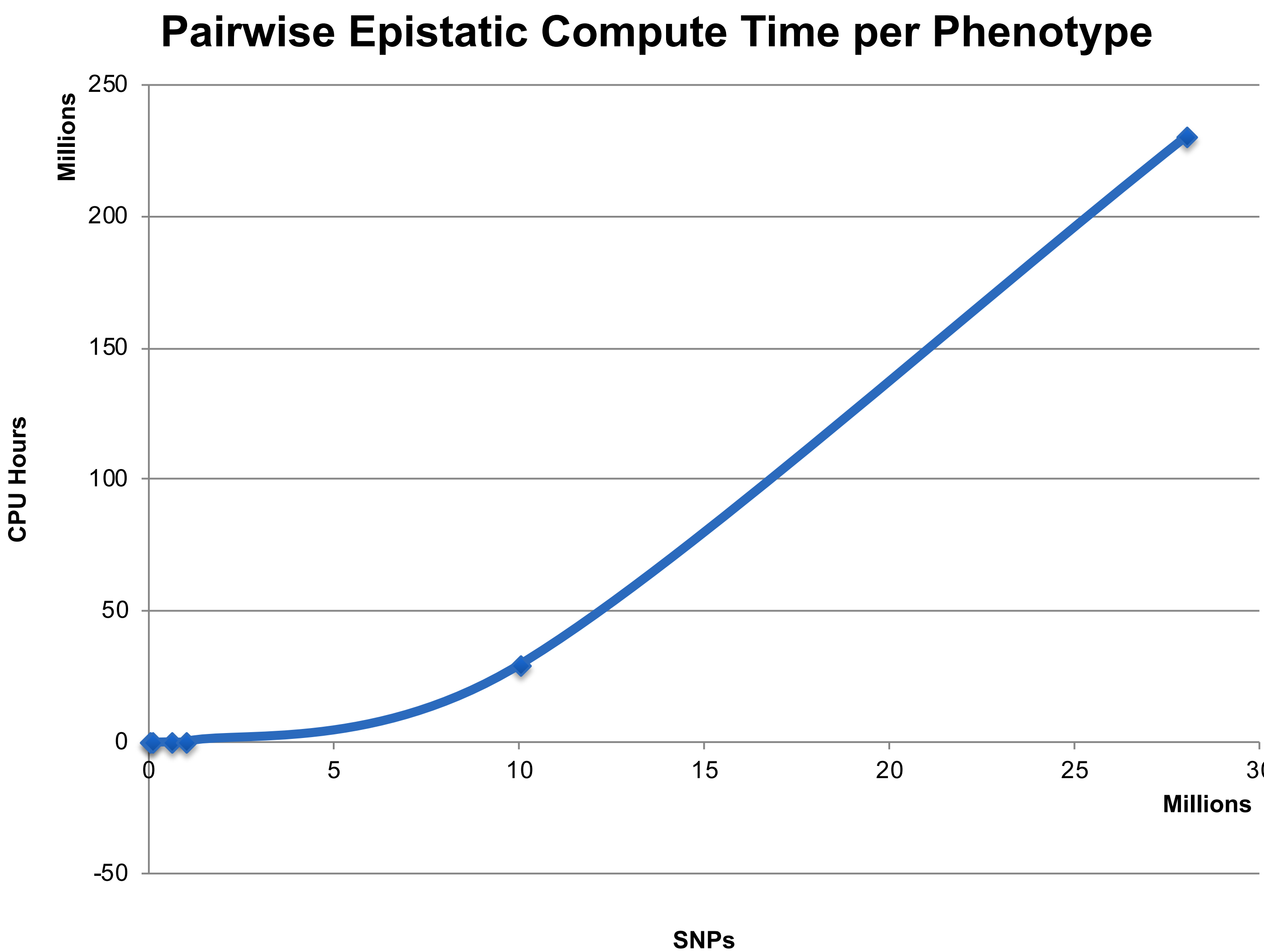
$$y = \sum_{i}^{m} \beta_i \boxed{Q_i} + \sum_{\substack{i,j \\ i \neq j}}^{m} \beta_{i,j} \boxed{Q_i} : \boxed{Q_j}$$

- **Epistasis may be important to consider in genomic association studies, as a gene with a weak main effect may be identified only through its interaction with another gene or other genes**
- **This requires a test to be done (with permutations) for all possible pairs of SNPs.**

Epistatic Example: Transcription Initiation Complex

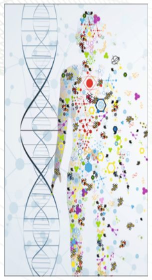


The Need for Speed



8-way combinations = 2.4 x 10^{60} CPU hours per phenotype

Breaking the curse of dimensionality



10M Genetic Variants in 20k - 40k genes

Genes do not work in isolation: 10^{170} potential interactions among variants

Linking genetic variants to phenotypes requires the exploration of an enormous space

To obtain accuracy and insight, we are developing procedures to detect interactions of any form or order at the same computational cost as main effects

Set-based thinking

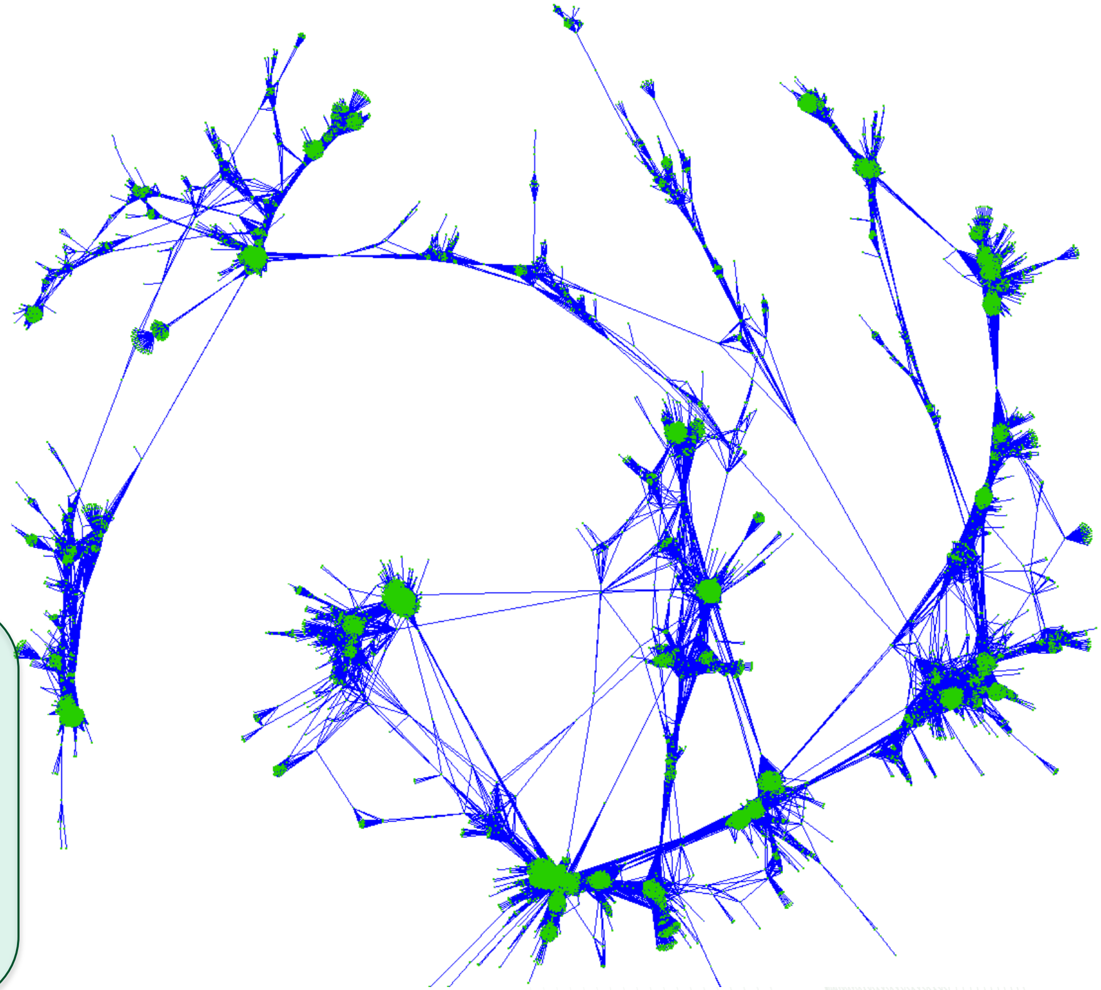
- ***SNP Correlation Networks***
- ***Explainable-AI***

Co-evolution Networks: SNP Correlations

- Identify SNPs which have become fixed relative to one another
  - Linkage Disequilibrium
  - Selective pressure
  - Potentially co-evolving

Co-evolution: Big data and high performance computing reveals the underlying biological signatures

- **85 million SNPs**
- **600,000 Genotypes**
- **3.6 x 10^{15}** allele-specific SNP correlations calculated
- Billions of significant correlations
- Results modeled as a co-evolution network
- **Network topology reflects the underlying biology**
  - **Genes under the same or similar selective pressures tend to co-evolve – which is reflected in SNP correlations and therefore, network topology**



One connected component of the SNP Correlation Network

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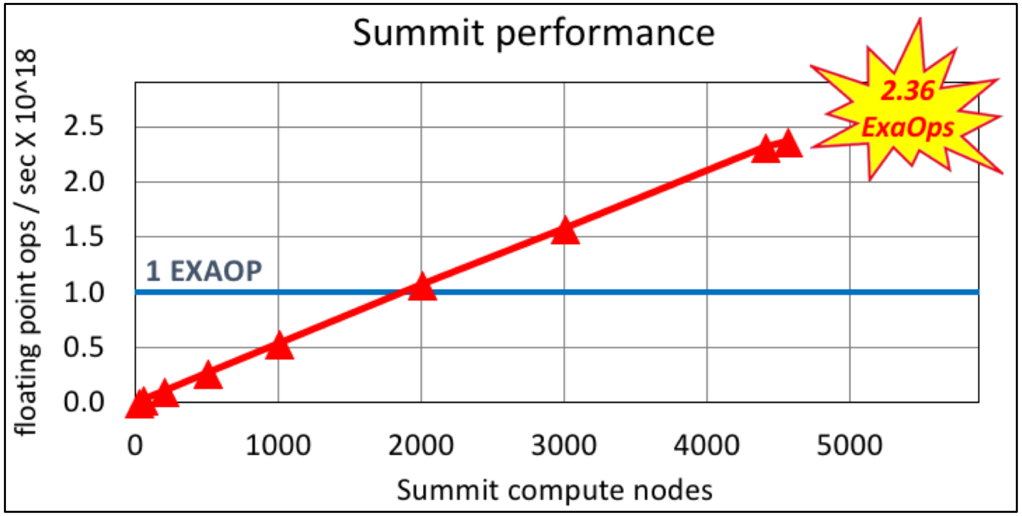
SNP Correlation/Co-evolution – Leading the Way to Exascale

- Thus far we have achieved **2.36 ExaOps** (mixed precision ExaFlops) at 4,560 nodes (99% of Summit) using the Tensor Cores
- Equivalent to **86.4 TF** per GPU for the whole computation (including communications and transfers) at 4,560 nodes
- Excellent scaling made possible by Summit fat tree network with adaptive routing
- **> 15,000X faster** than the closest competing code

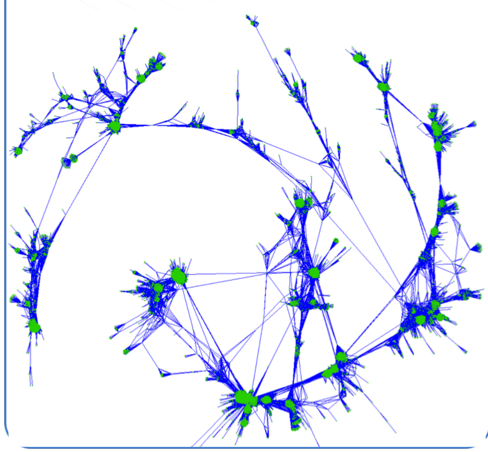


Gordon Bell Prize

First ever for Genomics or Systems Biology

inputs → define sets → association test → LOE Biological filter → High scoring Sets/genes

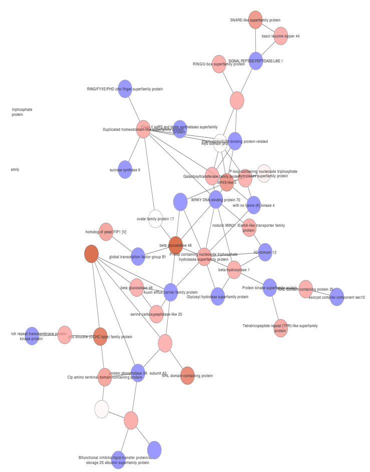
Genome-Wide SNPS



SNP Set 1 → P_1

SNP Set 2 → P_2

SNP Set N → P_N



G	8
G	6
G	5
G	5

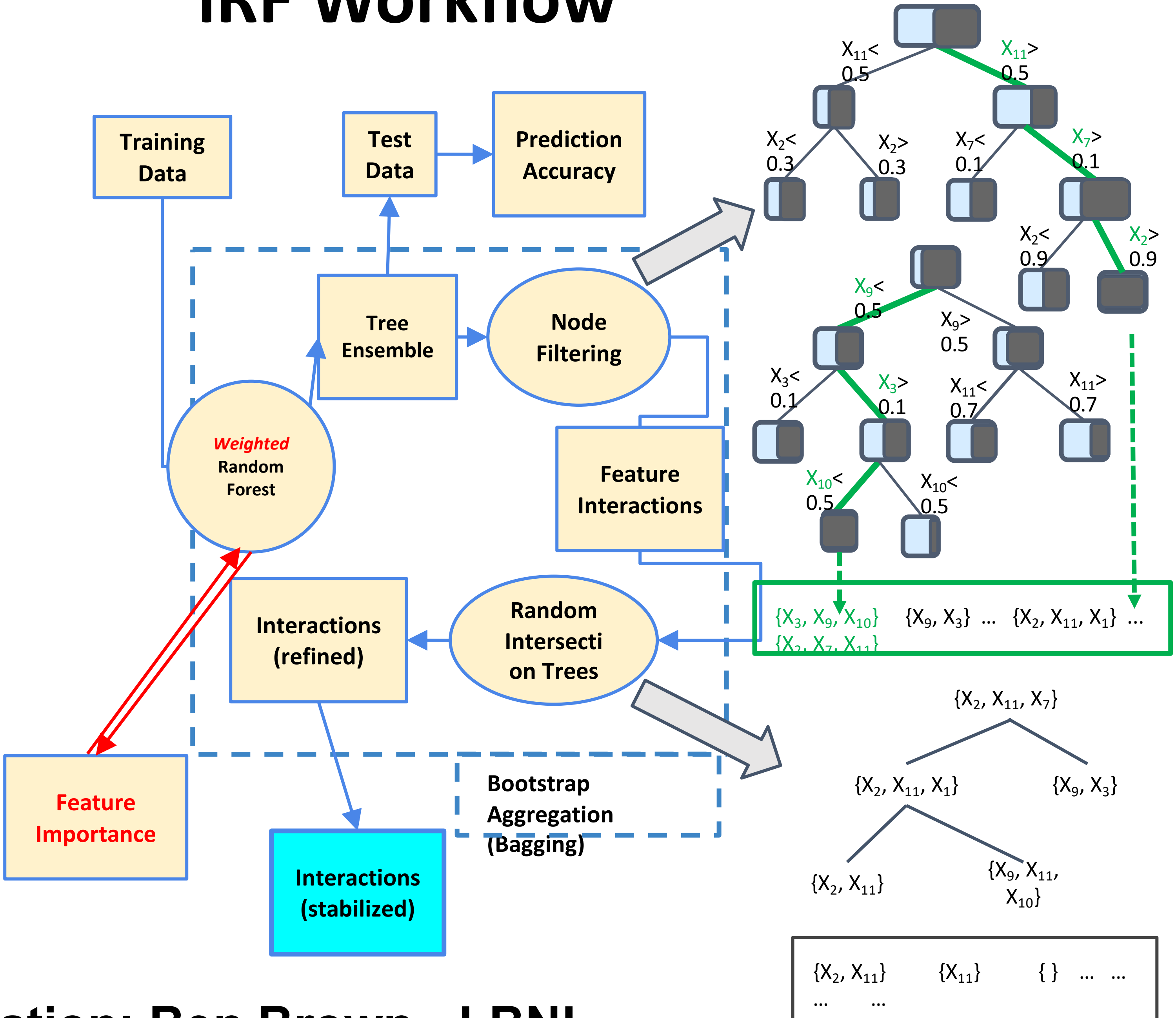
Other Approaches to Epistasis: Machine and Deep Learning Algorithms

- Great at classification
- Essentially black boxes
  - Don’t reveal the interactions between variables that lead to the classification
- Need Explainable AI

Finding Higher Order Combinatorial Interactions in Complex Systems

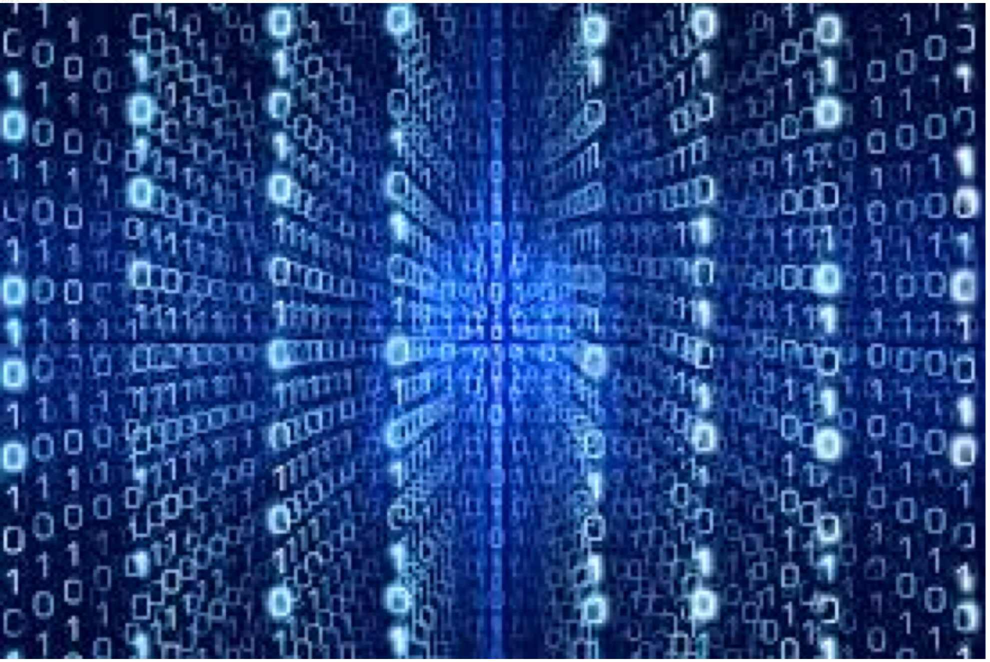
- X matrix and Y vector
- Iterative Random Forests

iRF Workflow



Collaboration: Ben Brown - LBNL

iRF – X Matrix and 1 Y Vector



SNP Vectors

Phenotype Vectors

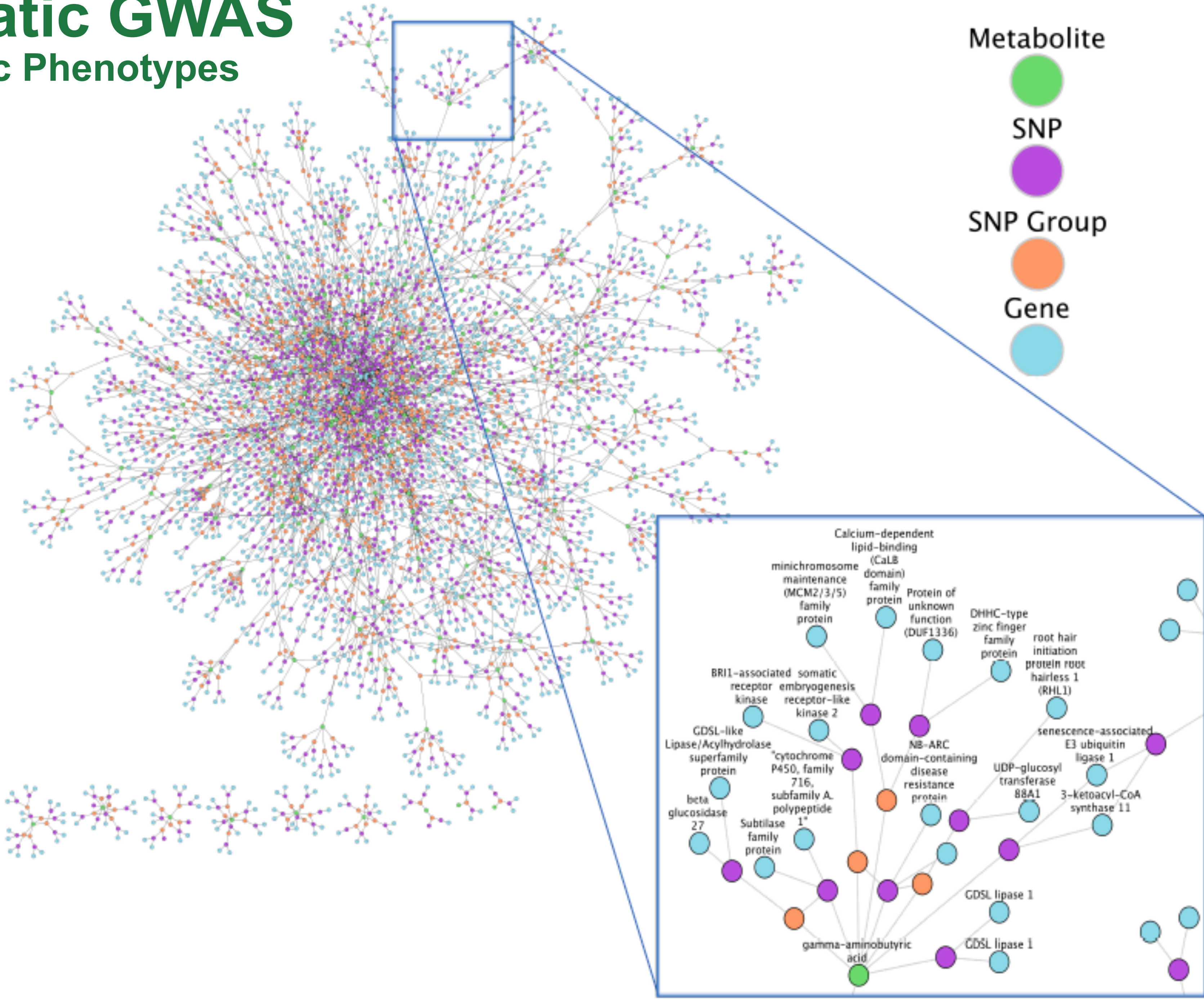
iRF – X Matrix and 1 Y Vector

SNP Vectors

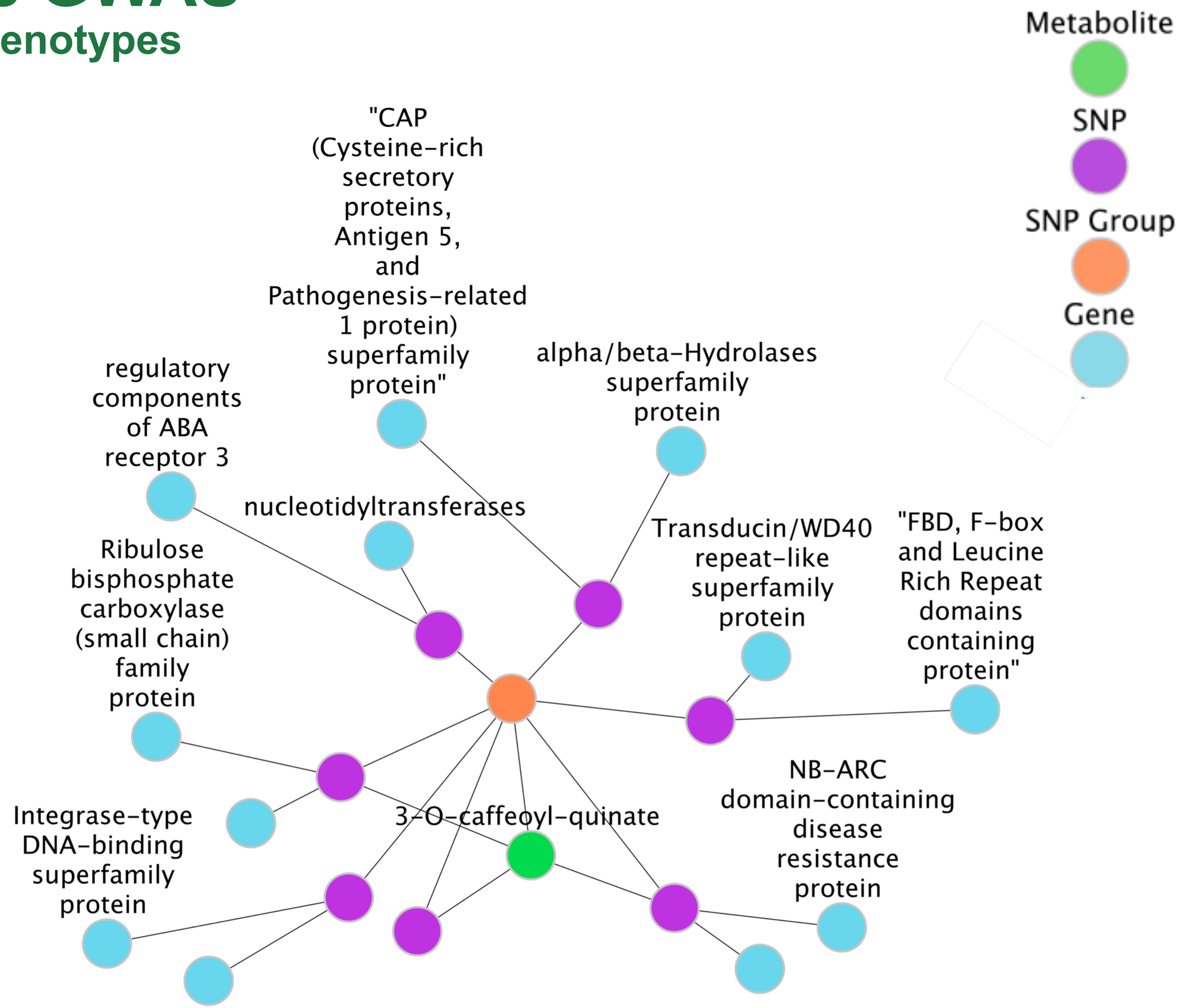
Phenotype Vectors

9-way combination = 1000 CPU hours per phenotype (160,000 phenotypes)

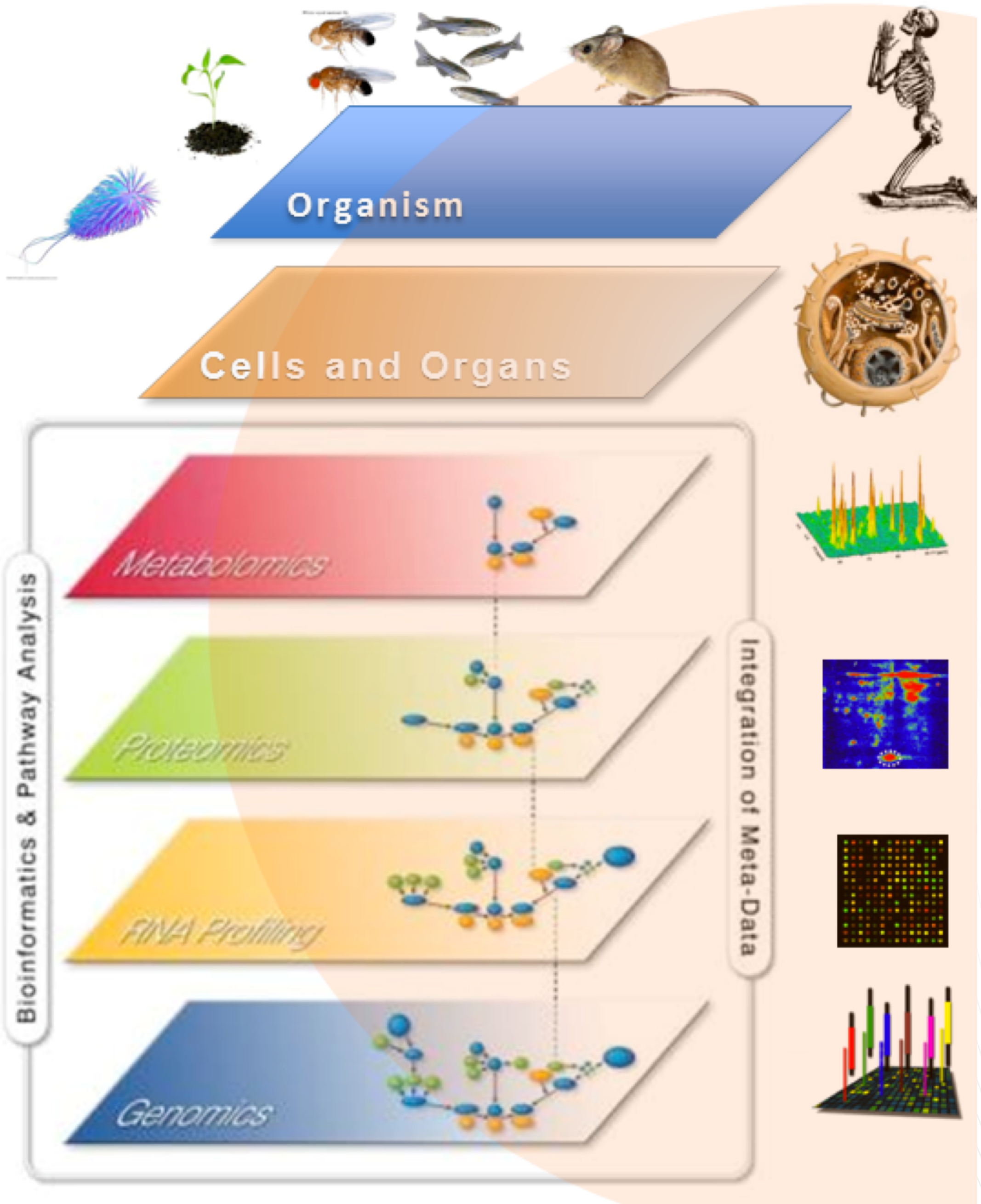
Epistatic GWAS
Metabolic Phenotypes



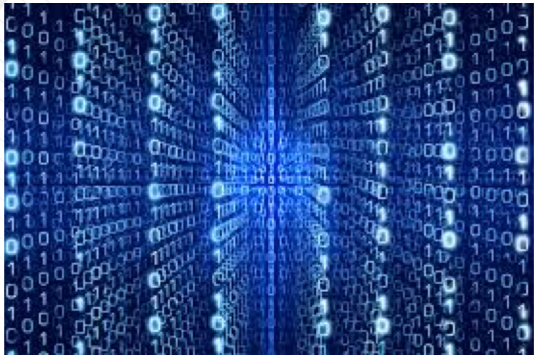
Epistatic GWAS
Metabolic Phenotypes

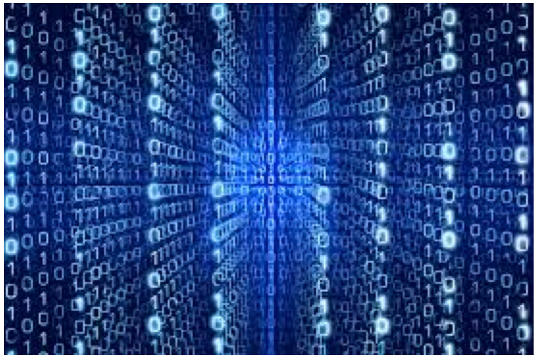


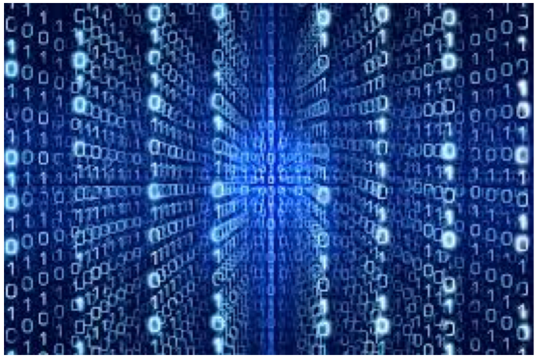
Life Science data: Multi-omics, multi-technology



TiRF – Any Set of Matrices or Tensor Dimensions *Simultaneously*

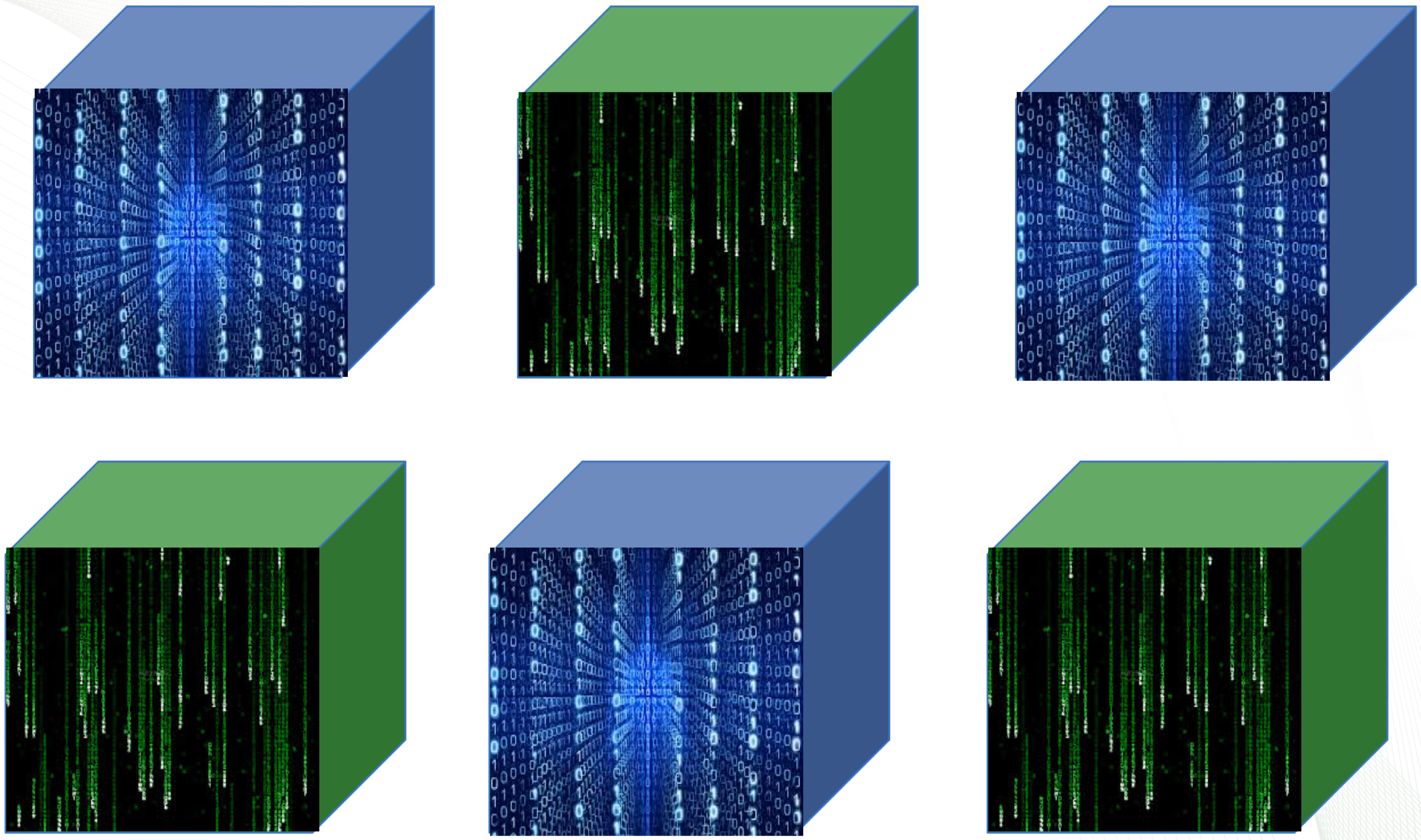




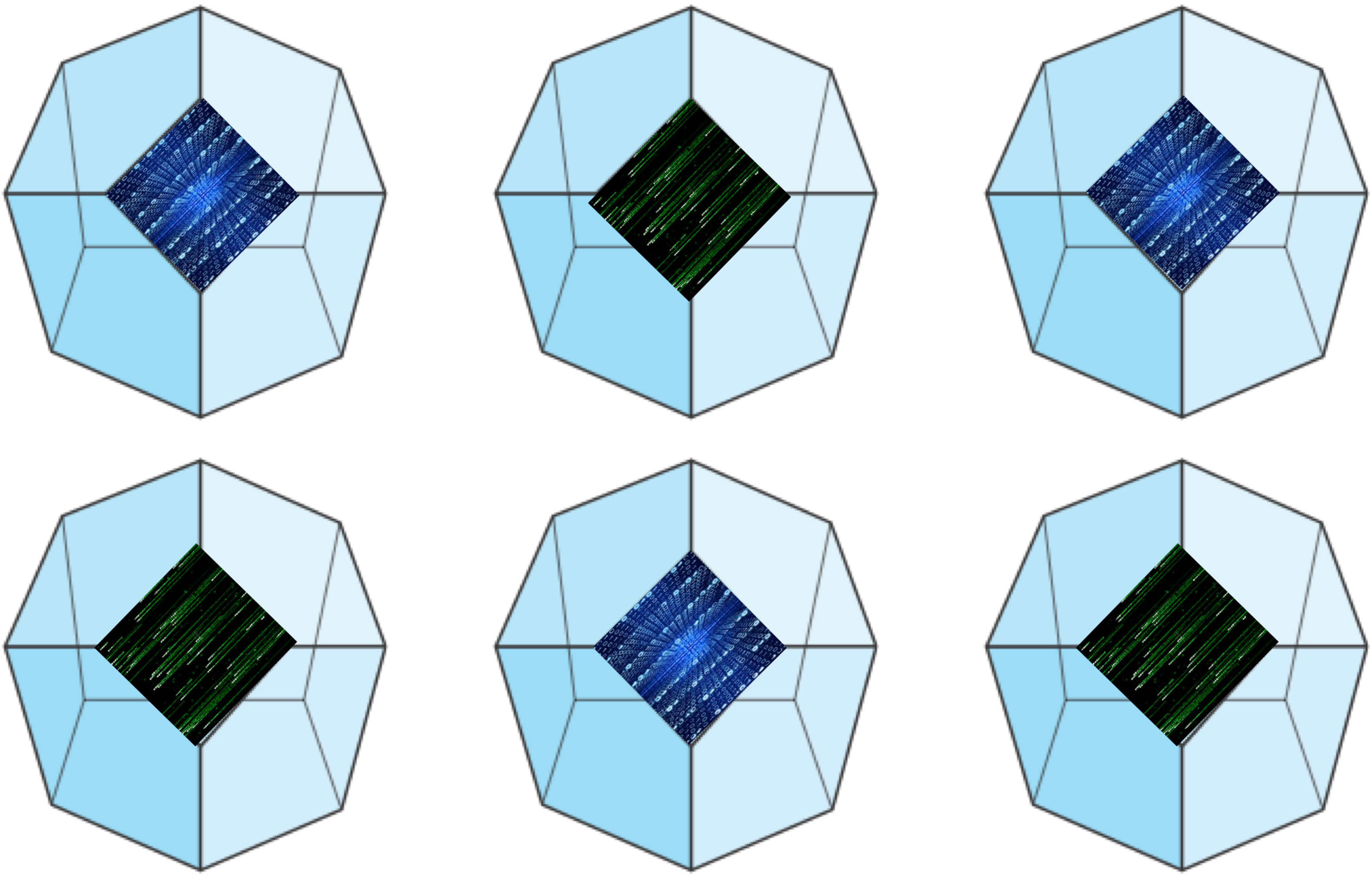


- Spatial and temporal/longitudinal information
- Different Omics layers (genome, transcriptome, proteome, metabolome, microbiome…)
- Quantum chemical tensors

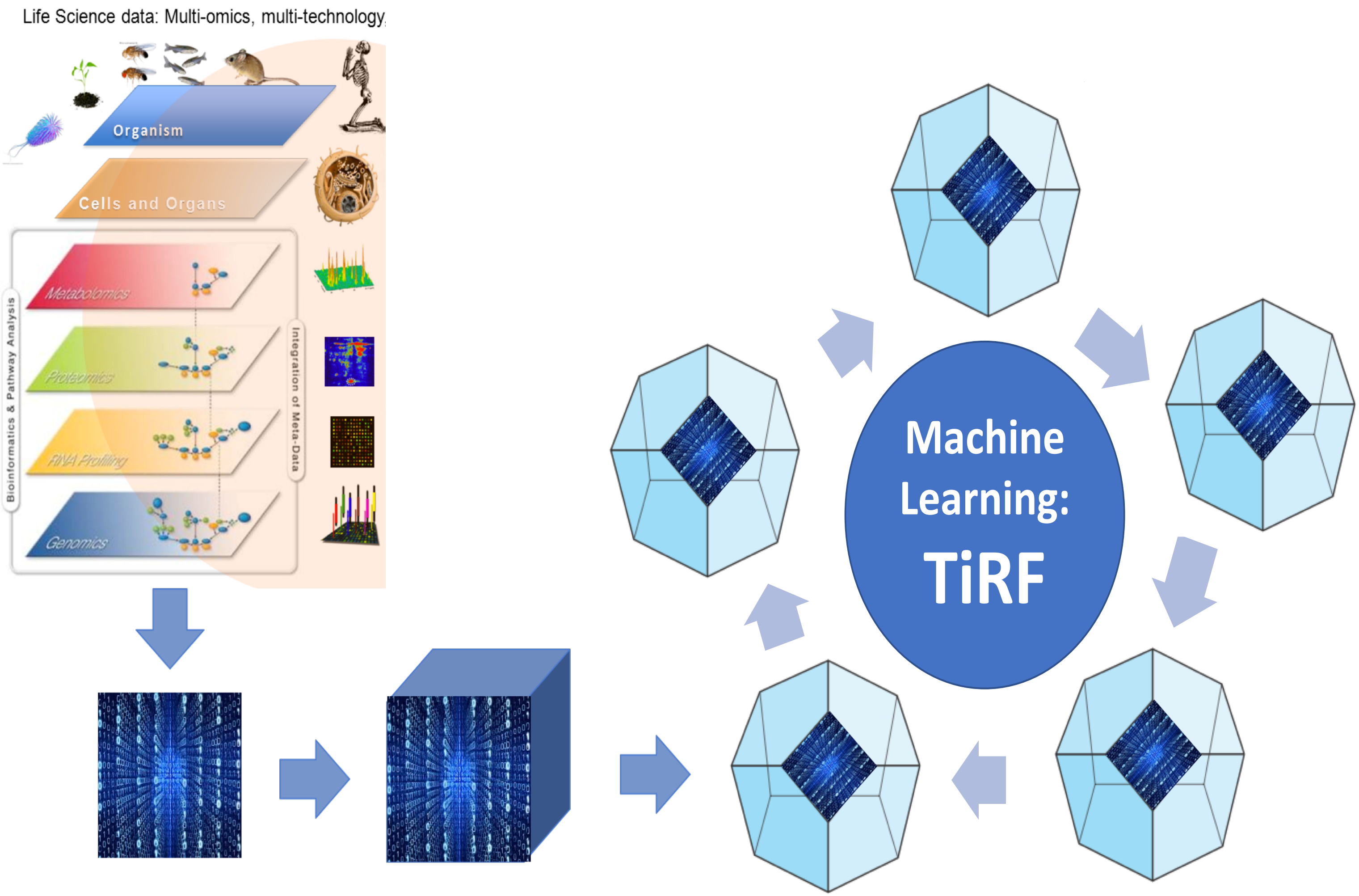
Tensors: Matrices ➡ Cubes



Tensors: Matrices ➡ Cubes ➡ Polytopes



From data matrix to cube to polytopes.



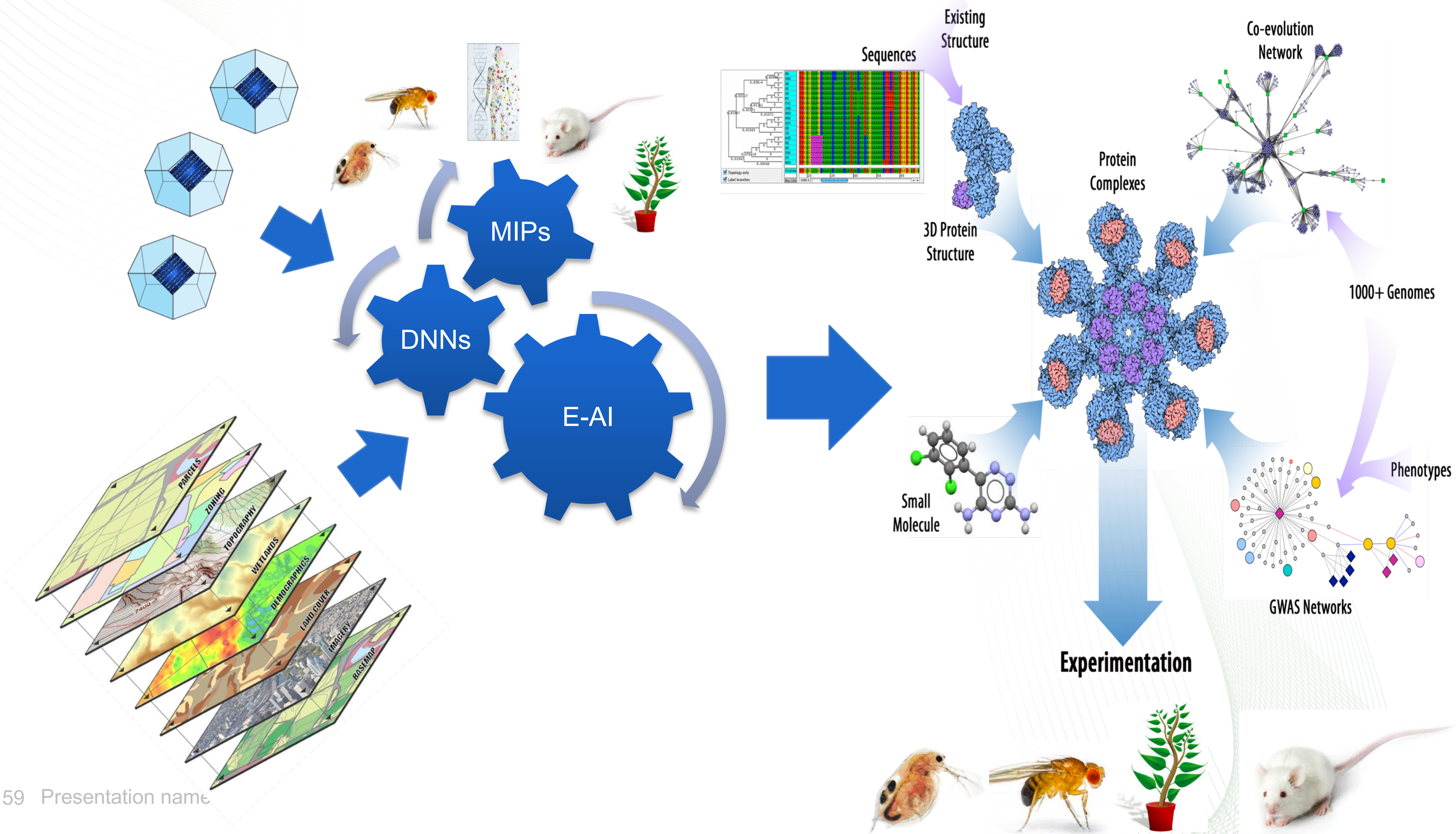
Tensor iterative Random Forests (TiRFs)

- Effectively build forests that can be mined for interactions within a multi-dimensional X, a multi-dimesional Y and interactions between multiple dimensions in X and Y, all at the same time.
- Applications in Systems Biology
  - Plants
  - Microbes
  - Humans
- Applications in Text Mining
  - Electronic Health Records
  - Scientific Literature
- Simulation Models
  - Combinatorial parameter sweeps (X) model output (Y)
- **Any domain with high a dimensional set of matrices**

Iterative Deep Neural Networks (iDNNs)

- Unpacking the black box
- Discovering the interactions encoded in DNNs

High Order Interactions:
Exposome
Explainable AI: Machine and Deep Learning Integration



Infrastructure

- This is being achieved as a collaboration between Biosciences, and the Oak Ridge Leadership Computing Facility (OLCF) and the Compute & Data Environment for Science (CADES)
  - Large clusters
    - ~200,000 CPU cores
    - 27,000 GPUs
  - Storage platform
    - 250 Petabytes of storage
  - Large Memory Platforms
    - SGI 24 Tbyte Memory
  - Map Reduce/Hadoop Systems
    - Cray Urika XA

Future Projects: Exploring Higher Order Combinatorial Complexity

~2 Billion (Titan) CPU hours

- **340,000 years on a single computer**
- **17 days**
  - **Summit**

Acknowledgements

- Funding/Allocations
  - Bioenergy Research Centers (BER)
    - BESC
    - CBI
  - Plant Microbe Interface SFA (BER)
  - LDRD (ORNL)
  - INCITE (ASCR)
  - Summit Early Science (OLCF/ASCR)

- ORNL
  - Oak Ridge Leadership Computing Facility (OLCF) at ORNL
  - Compute and Data Environment for Science (CADES) at ORNL
  - Plant Systems Biology Group at ORNL
  - Computational Systems Biology Team

- Joint Genome Institute (JGI)
- Veterans Administration (VA)
- The International Genome Sample Resource (ISGR)

- Bredesen Center for Interdisciplinary Research and Graduate Education, University of Tennessee, Knoxville

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  - Jesse Marks
  - Ian Hodge
  - Angie Walker
  - Elizabeth Koning

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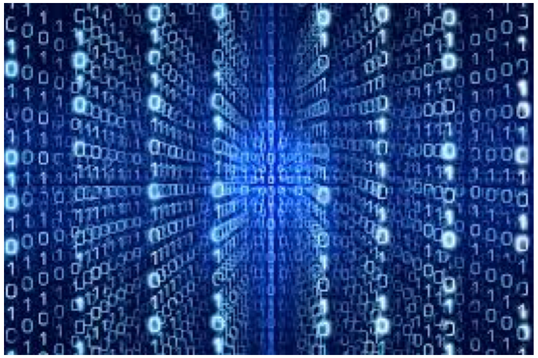
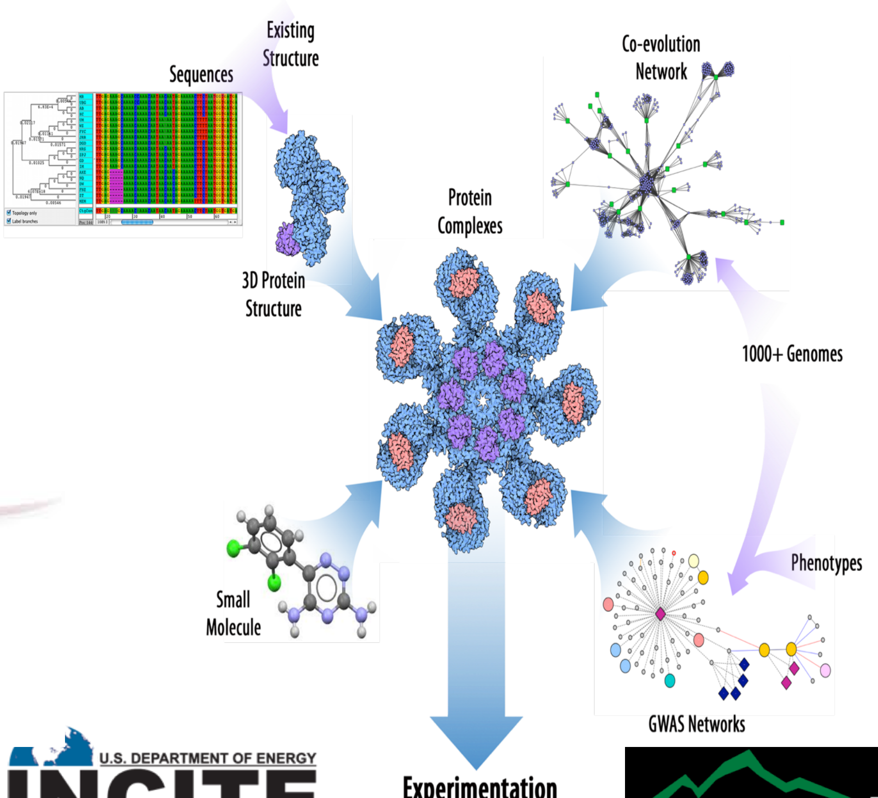
Collaborations anyone?

- Machine Learning
  - TiRFs
- Deep Learning
  - iDDNs
- GPU Implementations
- Applied Mathematics
- Systems Biology
- Bioenergy
- Microbiomics (Plants, Insects, Mice)
- Neuroscience
- Human Health
- Clinical Genomics
- Evolutionary Ecotoxicology

Questions?





U.S. DEPARTMENT OF ENERGY INCITE LEADERSHIP COMPUTING

summit