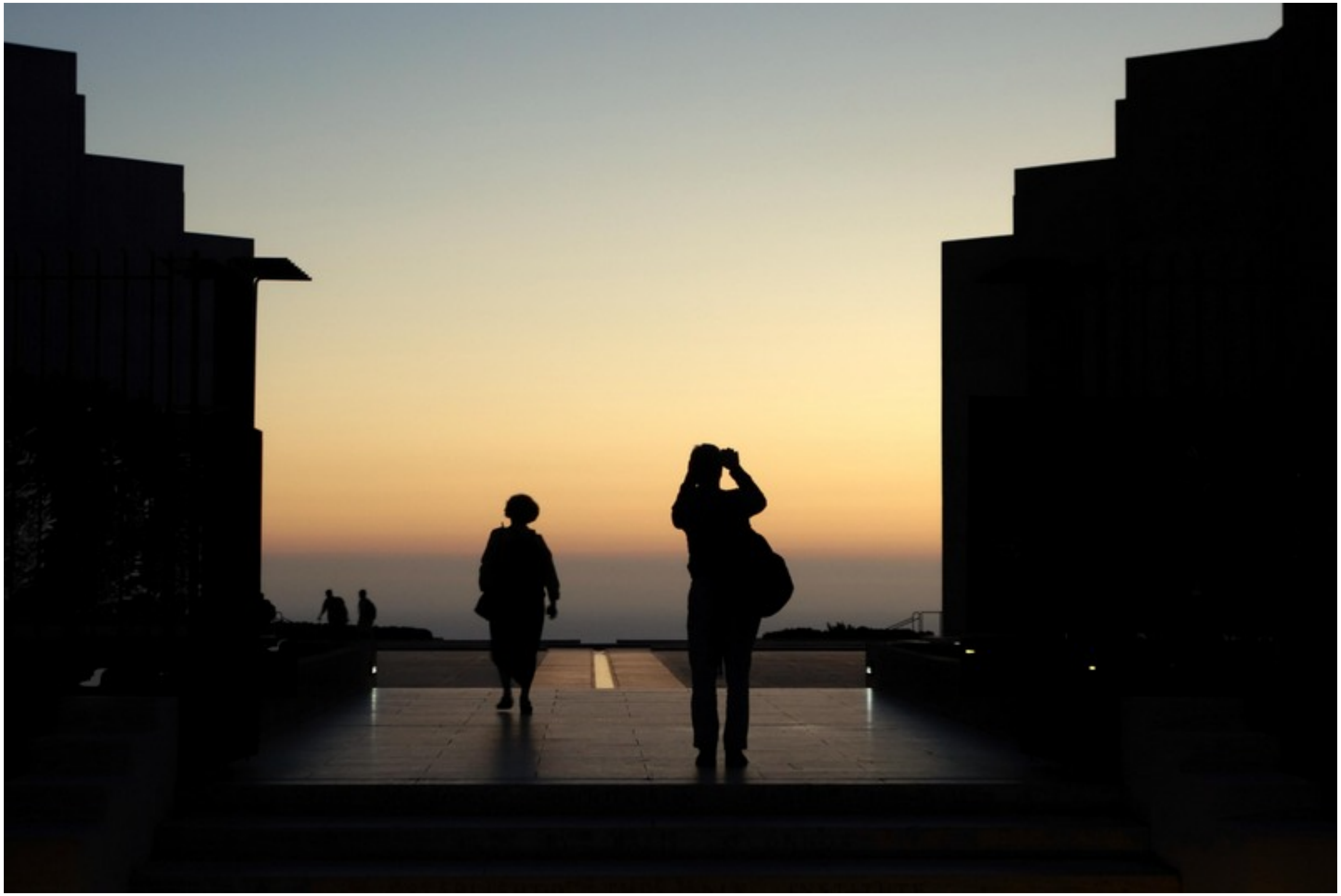
Brain Genomics:

Finding drug targets for neuropsychiatric disorders via deep-learning & Designing a predictor for the sensitivity of drugs to human population variation

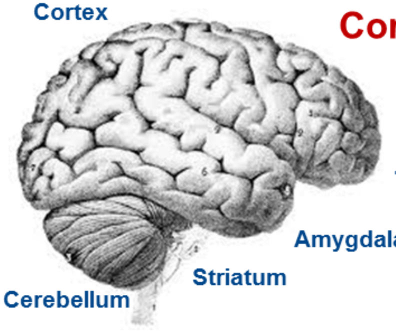


M Gerstein
Yale
(See last slide for more info.)

Slides freely downloadable
from **Lectures.GersteinLab.org**
& “tweetable” (via **@MarkGerstein**)

Sample Sources: >2,500 brains

Cross-disorder: ASD, SCZ, BP, Neurodevelopmental, Neurotypical



Anterior Cingulate Cortex

Dorsolateral Prefrontal Cortex

Orbitofrontal Cortex

Temporal Cortex

Subgenual Anterior Cingulate Cortex

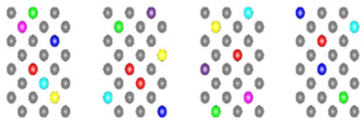
Amygdala

Striatum

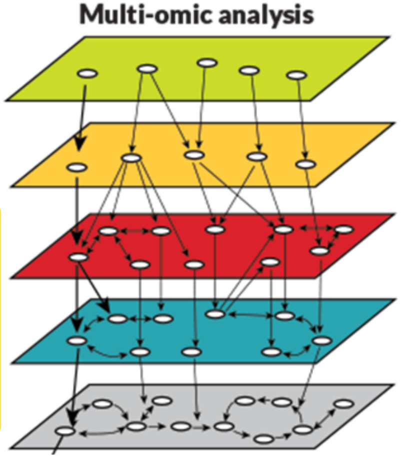
Cerebellum

Bulk Tissue

Neu –/Neu+ Sorted Cells



Single Cell

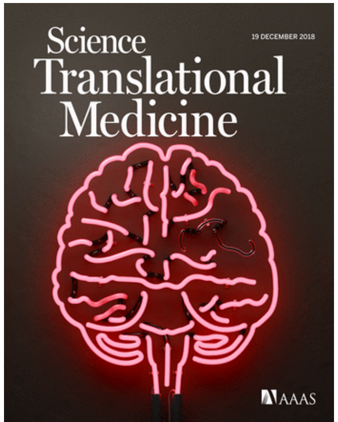


Genome:
WGS, genotype

Epigenome:
ChIP-seq, ATAC-seq, HiC, ERRBS, Array Methylation, NOMeSeq

Transcriptome:
RNA-seq, lncRNAseq,

Proteome:
MWP, LC-MS/MS



PsychENCODE

’18 rollout in Science

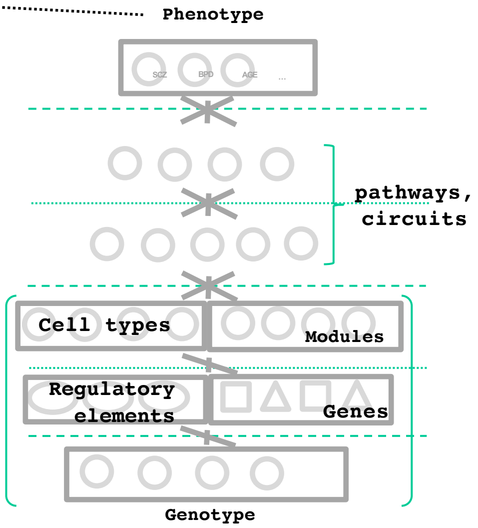
11 papers in total.
Major material in the 3 capstones:

Wang et al. (‘18), Li et al. (‘18), Gandal et al. ('18)

A core issue addressed by PsychENCODE: Using functional genomics to reveal molecular mechanisms between genotype and phenotype in brain disorders

Disease	Heritability*	Molecular **Mechanisms**
Schizophrenia	**81%**	**(C4A)**
Bipolar disorder	70%	-
Alzheimer's disease	58 - 79%	Apolipoprotein E (APOE), Tau
Hypertension	30%	Renin–angiotensin–aldosterone
Heart disease	34-53%	Atherosclerosis, VCAM-1
Stroke	32%	Reactive oxygen species (ROS), Ischemia
Type-2 diabetes	26%	Insulin resistance
Breast Cancer	25-56%	BRCA, PTEN

*https://www.snpedia.com/index.php/Heritability



Many psychiatric conditions are highly heritable

Schizophrenia: up to 80%

But we don’t understand basic molecular mechanisms underpinning this association

(in contrast to many other diseases such as cancer & heart disease)

Thus, interested in developing predictive models of psychiatric traits which:

Use observations at intermediate (molecular levels) levels to inform latent structure

Use the predictive features of these “molecular endo phenotypes” to begin to suggest actors involved in mechanism

Finding drug targets for neuropsychiatric disorders via deep-learning & Designing a predictor for the sensitivity of drugs to human population variation

- **PsychENCODE:** Population-level analysis of functional genomics data related to neuropsychiatric disease
  - Construction of an adult brain resource with 1866 individuals
  - Large-scale processing **creates a comprehensive QTL** resource (~2.5M eQTLs).
  - Connecting QTLs, enhancer activity relationships & Hi-C contacts into a **brain regulatory network**
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- **GenoDock:** Building a predictor for the sensitivity of drug binding to personal SNVs
  - Hybrid classifier connecting **physical modelling with statistical learning**
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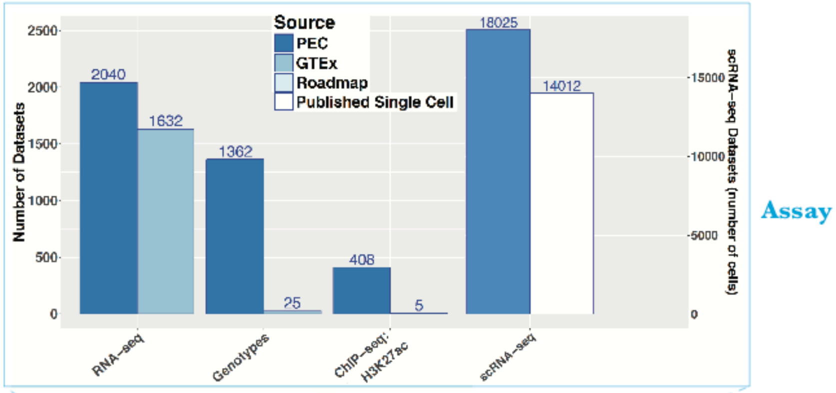
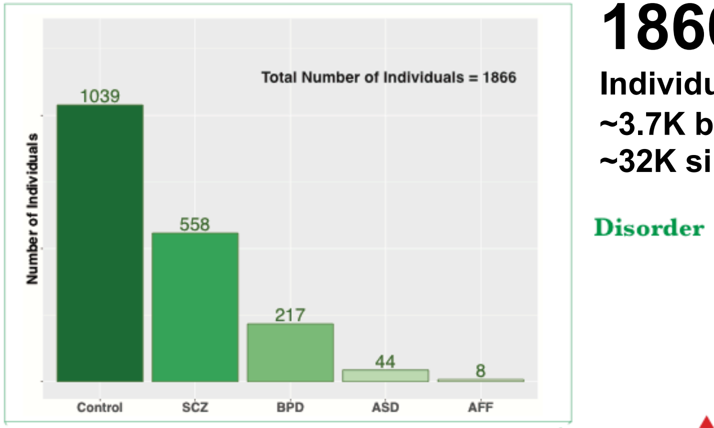
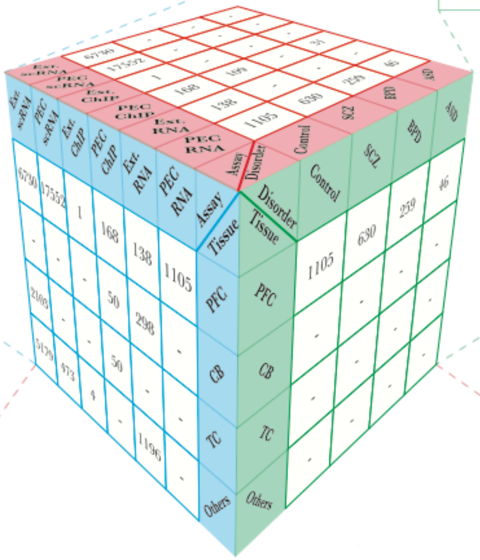
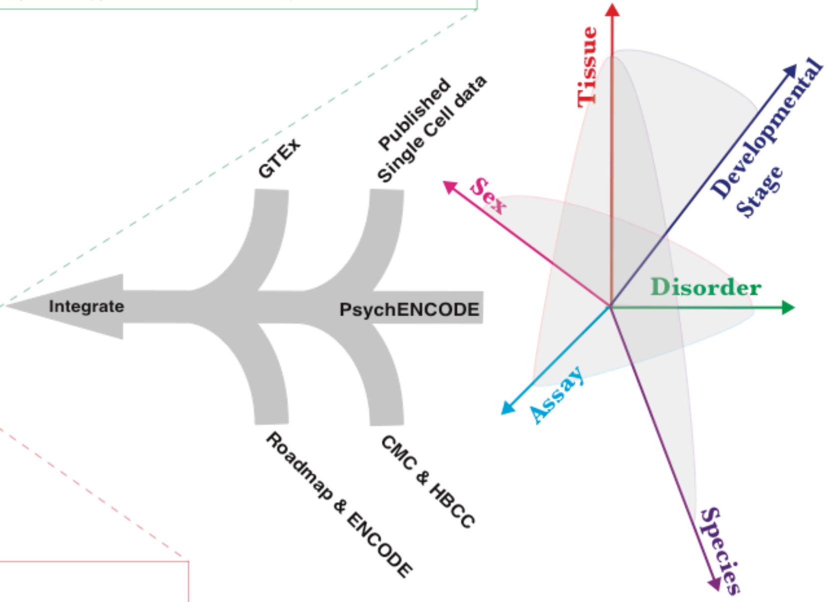




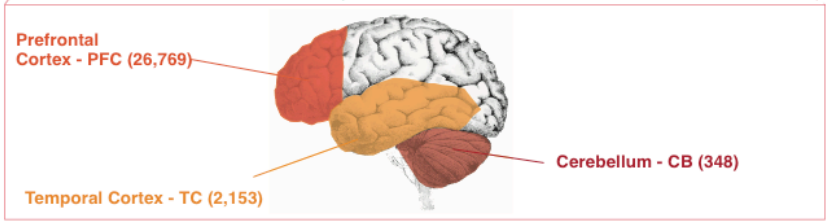
1866
Individuals
~3.7K bulk RNA-seq
~32K single-cells





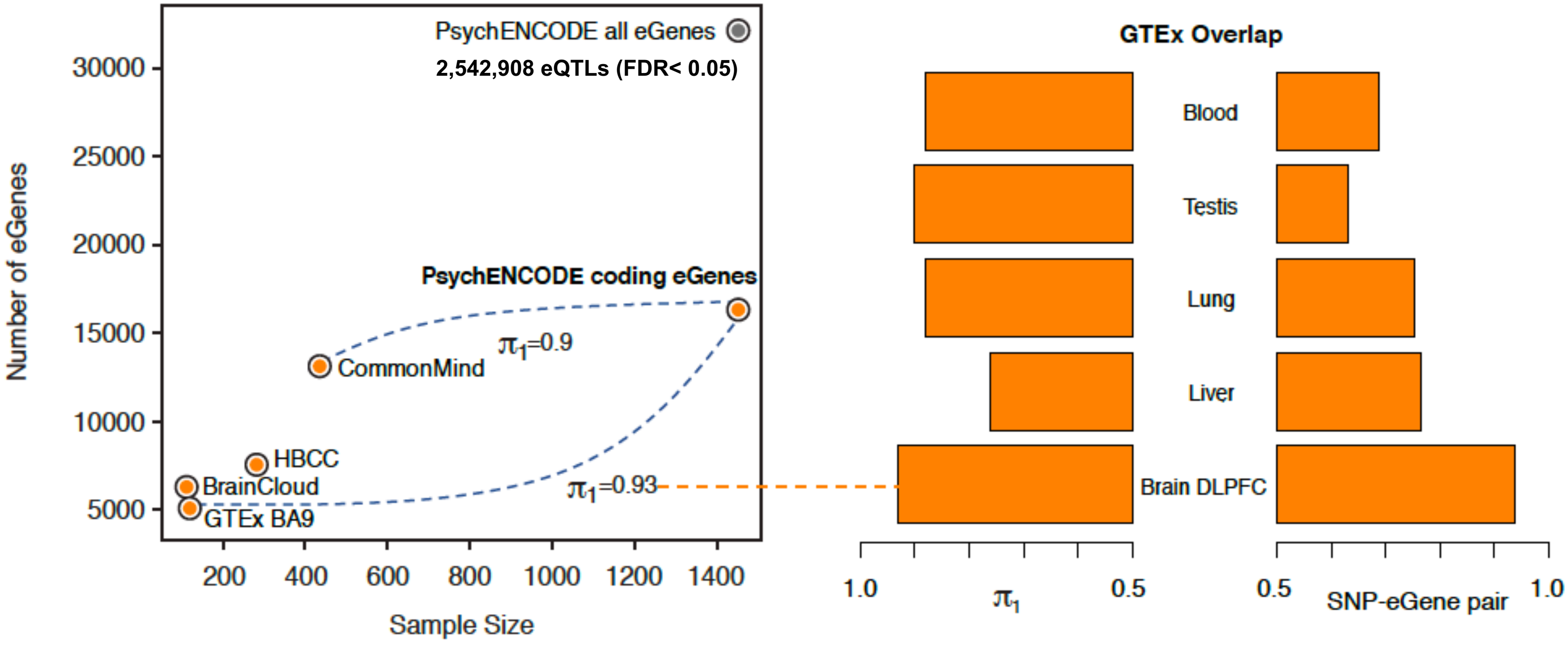
Collecting functional genomic datasets for the adult brain

from PsychENCODE, other large consortia & single cell studies



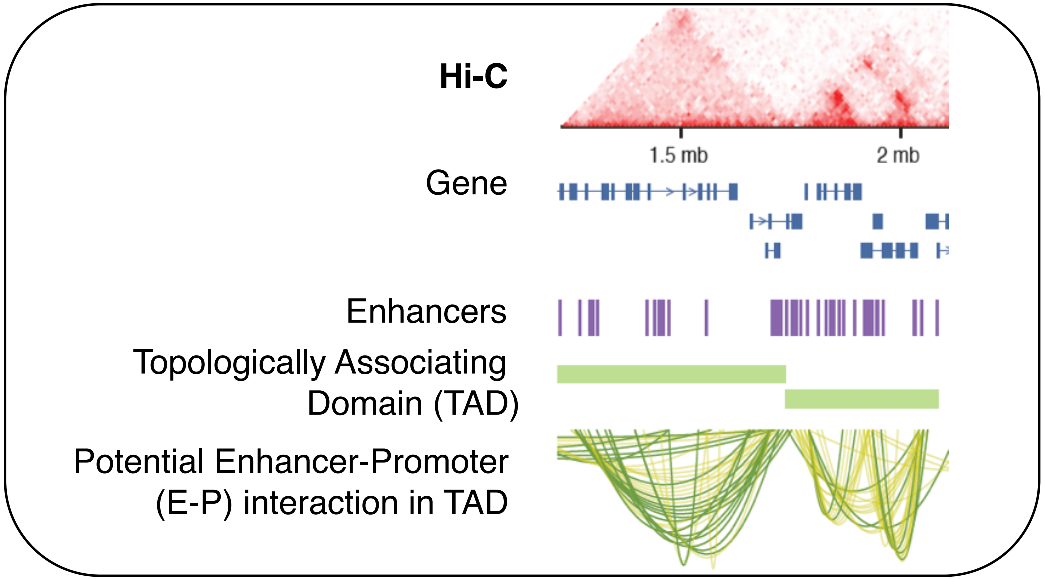
[Wang et al. ('18) Science]

Larger brain eQTL sets than previous studies, but strong overlap with them



[Wang et al. ('18) Science]

Gene regulatory network inference from Hi-C, QTLs & Activity Correlations



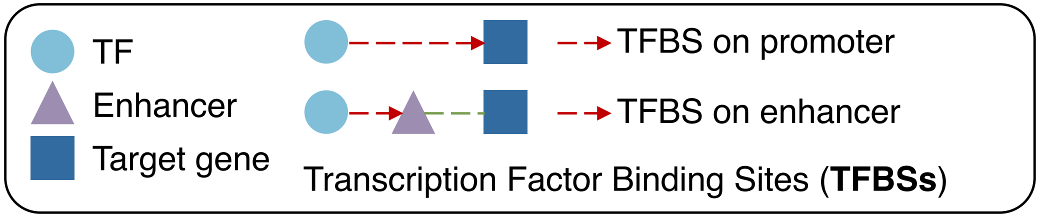
Hi-C

Gene

Enhancers

Topologically Associating Domain (TAD)

Potential Enhancer-Promoter (E-P) interaction in TAD



● TF

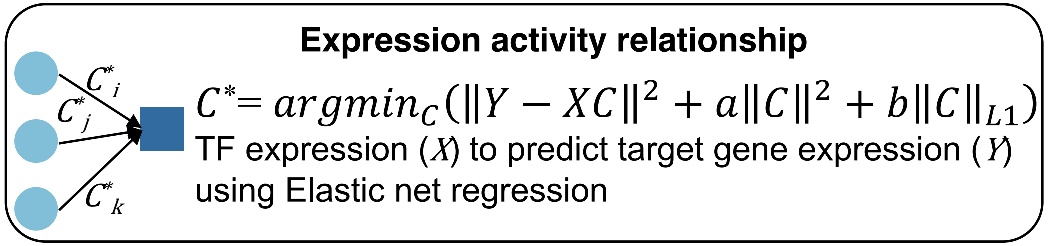
▲ Enhancer

■ Target gene

TFBS on promoter

TFBS on enhancer

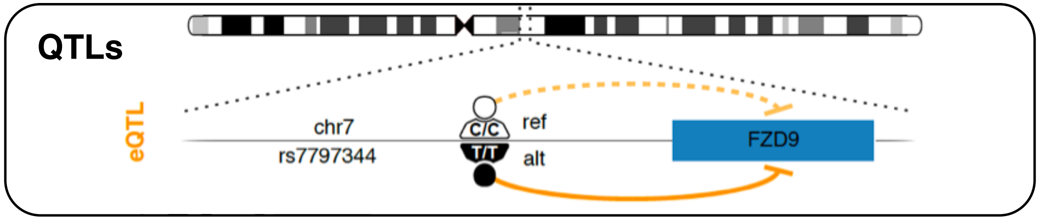
Transcription Factor Binding Sites (**TFBSs**)



Expression activity relationship

$$C^* = argmin_C(\|Y - XC\|^2 + a\|C\|^2 + b\|C\|_{L1})$$

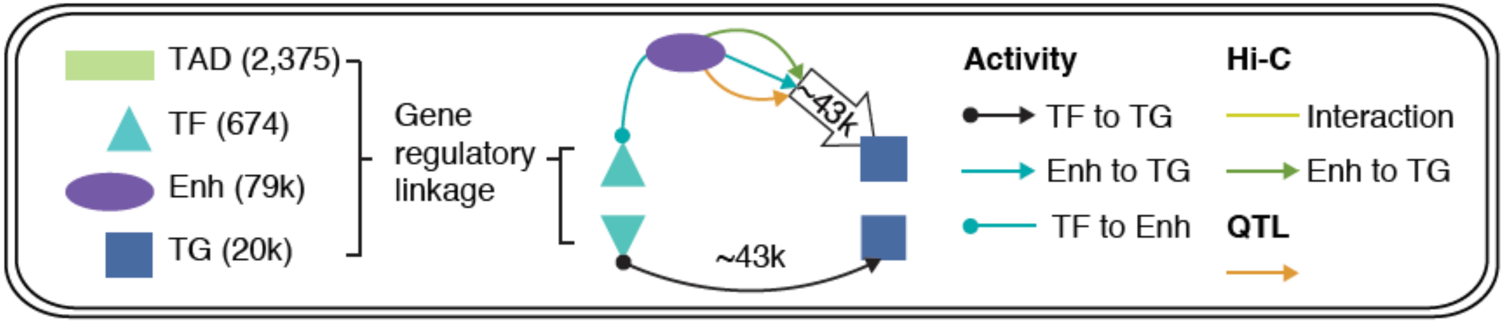
TF expression (X) to predict target gene expression (Y) using Elastic net regression

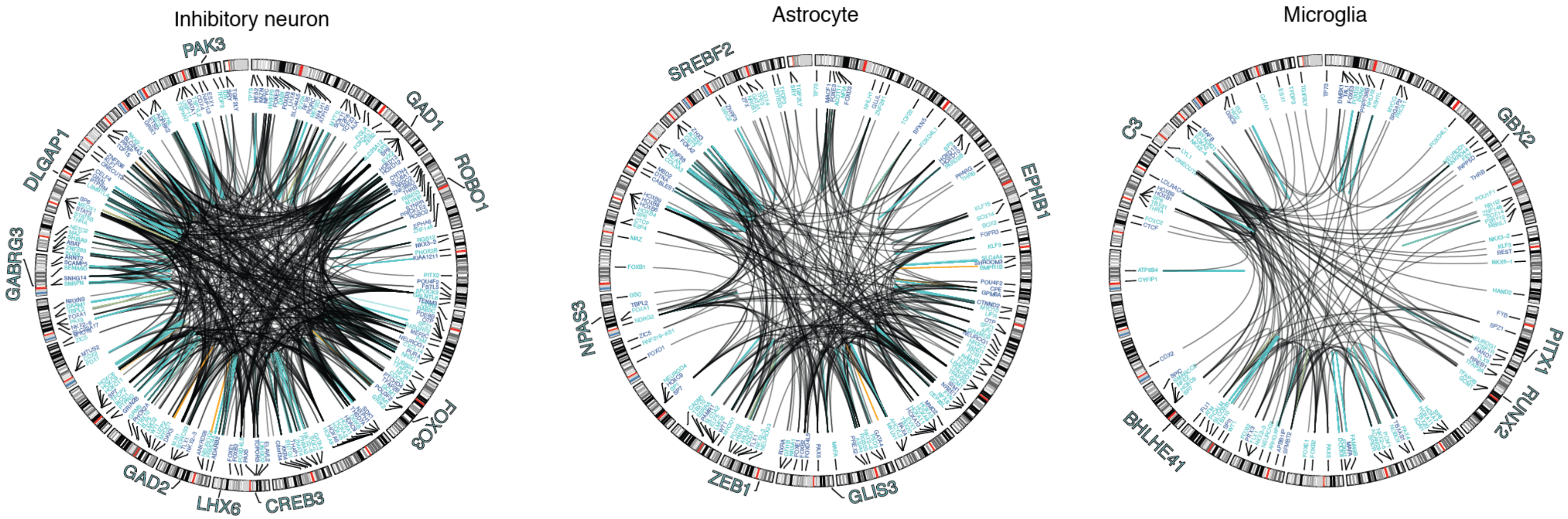


QTLs

[Wang et al. ('18) Science]

Imputed gene regulatory network for the human brain





subnetworks targeting single cell marker genes

[Wang et al. ('18) Science]

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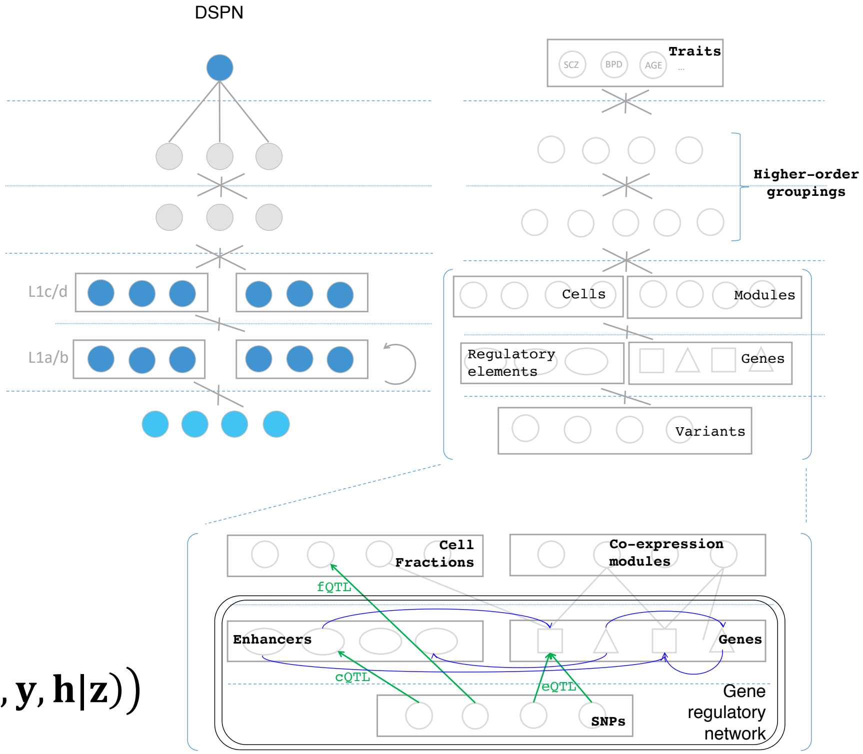
Deep Structured Phenotype Network (DSPN)

Gene regulatory network builds skeleton



Boltzmann machine

$\mathbf{y}$: phenotypes

$\mathbf{h}$: hidden units (e.g., circuits)

$\mathbf{x}$: intermediate phenotypes (e.g., genes, enhancers)

$\mathbf{z}$: genotypes (e.g., SNPs)

W: weights (e.g., regulatory network)

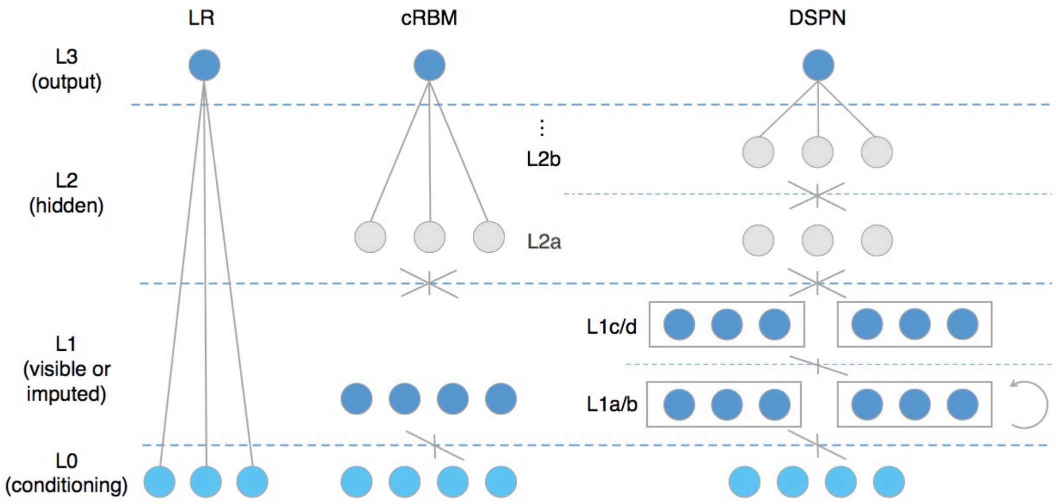
Energy model:

$$p(\mathbf{x},\mathbf{y},\mathbf{h}|\mathbf{z}) \propto \exp\big(-E(\mathbf{x},\mathbf{y},\mathbf{h}|\mathbf{z})\big)$$

$$E(\mathbf{x},\mathbf{y},\mathbf{h}|\mathbf{z}) = -\mathbf{z}^{\mathrm{T}}\mathbf{W}_1\mathbf{x} - \mathbf{x}^{\mathrm{T}}\,\mathbf{W}_2\mathbf{x} - \mathbf{x}^{\mathrm{T}}\mathbf{W}_3\mathbf{h} - \mathbf{h}^{\mathrm{T}}\mathbf{W}_4\mathbf{h} - \mathbf{h}^{\mathrm{T}}\mathbf{W}_5\mathbf{y} - \boldsymbol{Bias}$$

[Wang et al. ('18) Science]

DSPN improves brain disease prediction by adding deep layers



Method	LR-genotype	LR-transcriptome	cRBM	DSPN-imputation	DSPN-full
Schizophrenia	**54.6%**	63.0%	70.0%	59.0%	**73.6%**
Bipolar Disorder	**56.7%**	63.3%	71.1%	67.2%	**76.7%**
Autism Spectrum Disorder	**50.0%**	51.7%	67.2%	62.5%	**68.3%**

X 6.0

Accuracy = chance to correctly predict disease/health

[Wang et al. ('18) Science]

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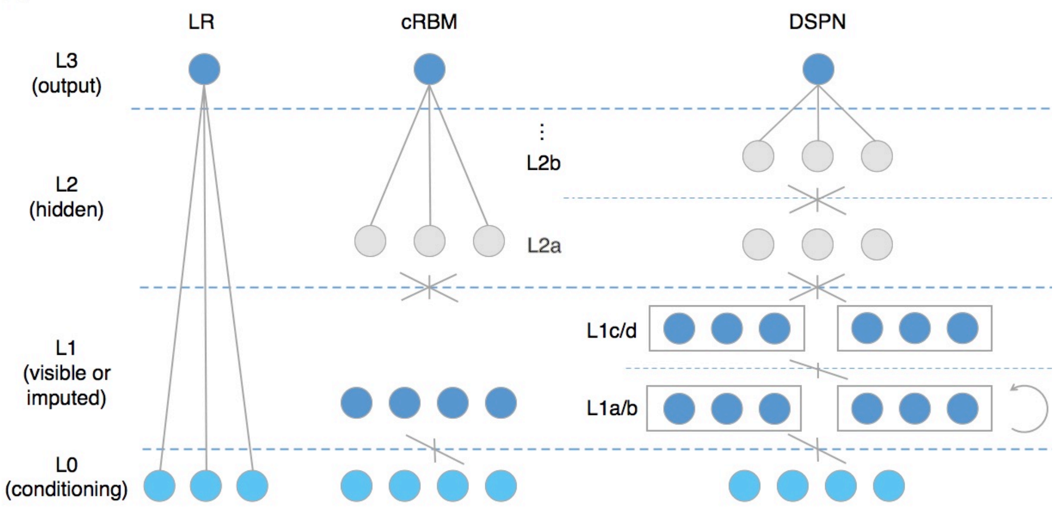

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X 2.5

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[Wang et al. ('18) Science]

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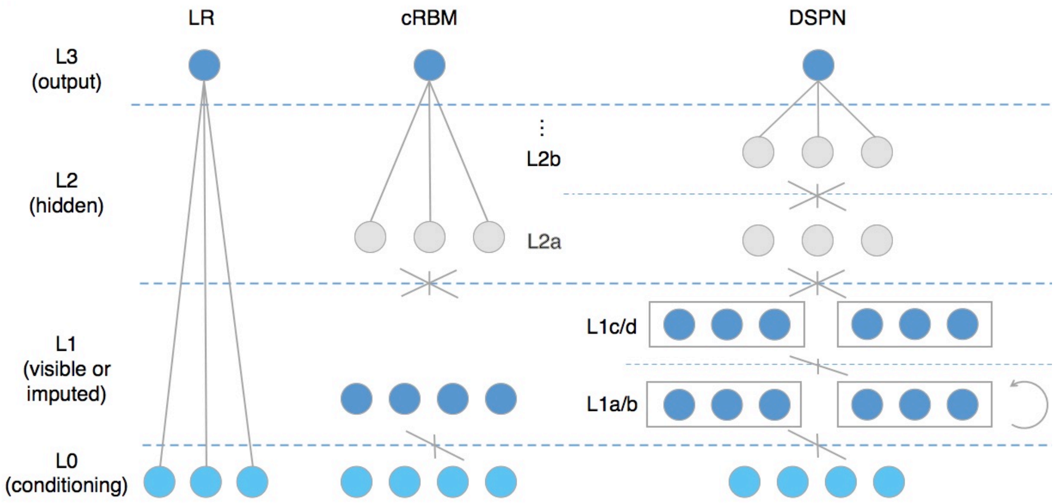

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X 3.1

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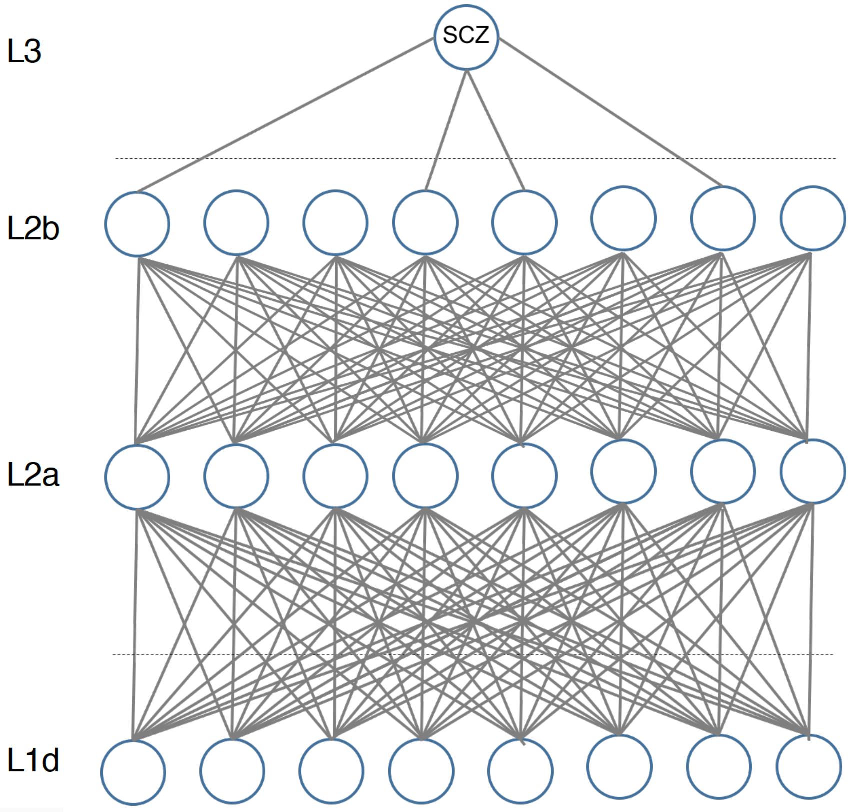
[Wang et al. ('18) Science]

Multilevel Network Interpretation

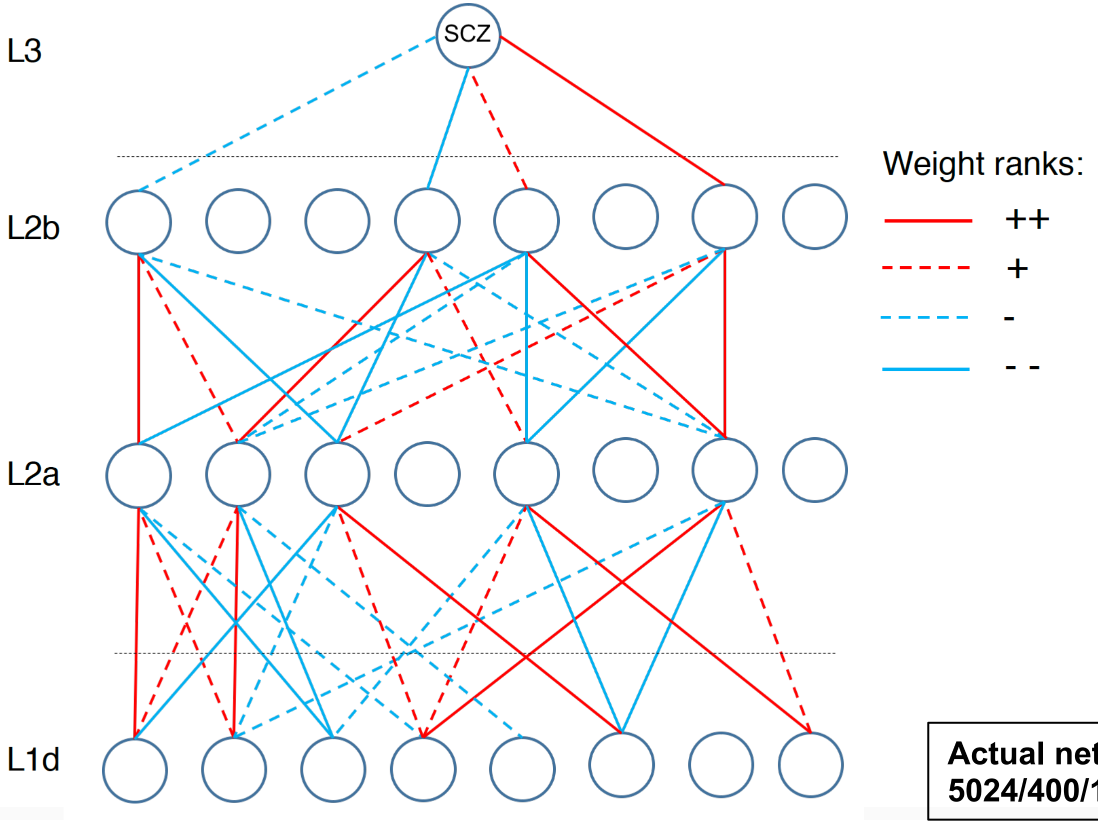


Actual network size:
5024/400/100/1 nodes

- Start with a fully connected trained network

[Wang et al. ('18) Science]

Multilevel Network Interpretation



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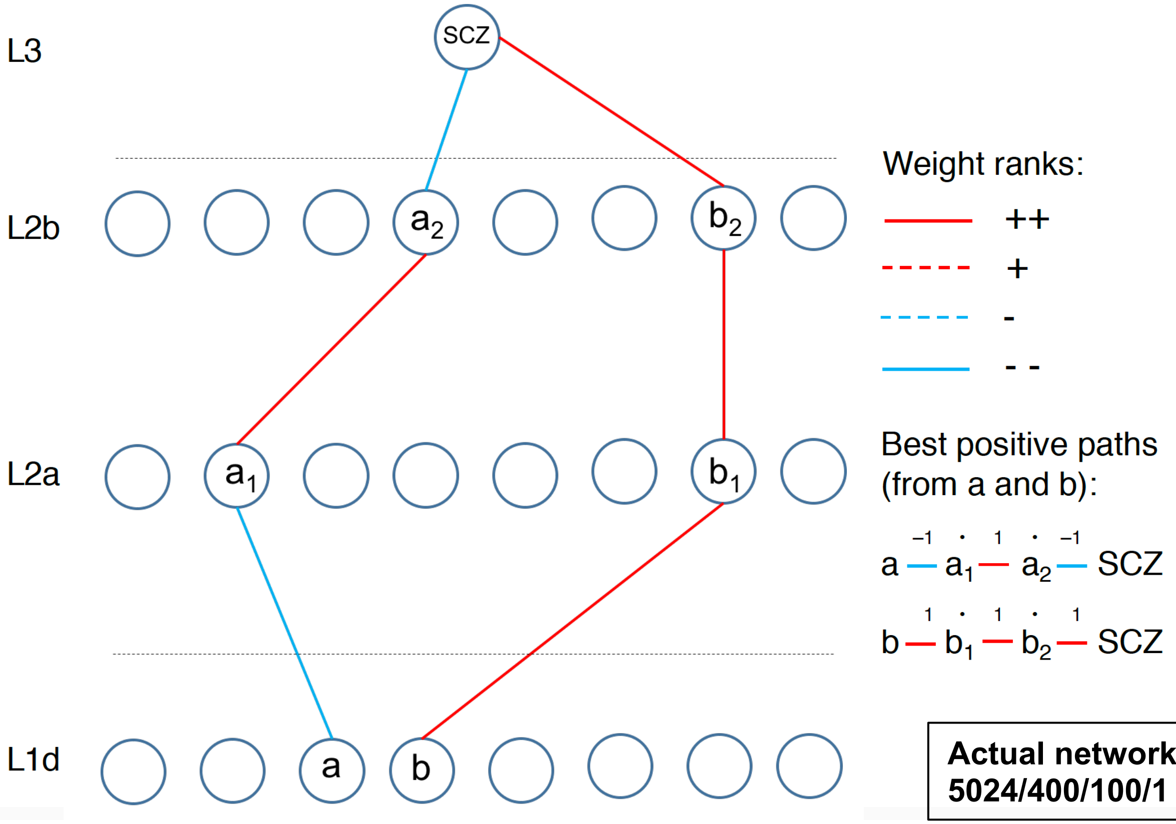


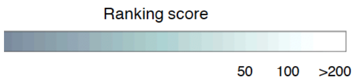
Actual network size:
5024/400/100/1 nodes

- Start with a fully connected trained network
- Sparsify network using edges with largest absolute weights (+/-)
- Extract 'best positive paths' to each prioritized module
  (e.g. a-a_1-a_2-SCZ) by summing weights and multiplying signs

[Wang et al. ('18) Science]

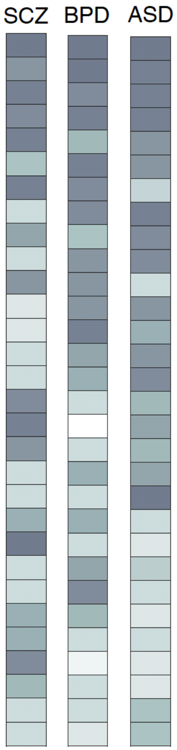
DSPN discovers enriched pathways and linkages to genetic variation

Cross-disorder MOD/HOG enrichment ranking

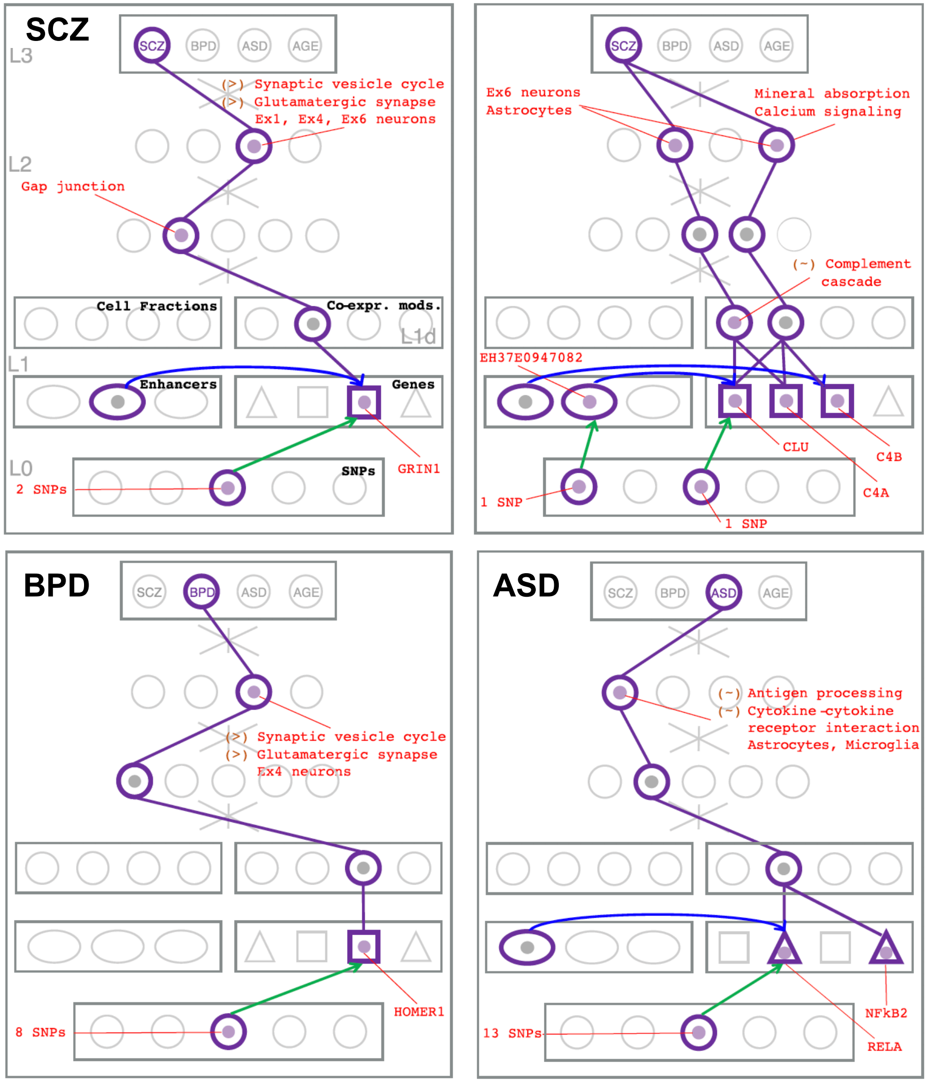


Functional categories

(*)	RNA proc.	(~)	Immune
(>)	Synaptic	(#)	Metabolic



- (*) Spliceosome / RNA splicing
- (>) Synaptic vesicle cycle
- (~) Antigen proc. and presentation
- Vesicle localization
- Proteasome
- (*) mRNA processing
- Chromatin modification
- (#) Oxidative phosphorylation
- Retrograde endocannabinoid sig.
- (>) Chemical synaptic transmission
- Peptidyl-lysine modification
- Endocytosis
- Ubiquitin mediated proteolysis
- (>) Anterograde trans-synaptic sig.
- (*) mRNA transport
- Phosphatidylinositol signaling
- Hippo signaling pathway
- (~) Staph./ Epstein-Barr virus inf.
- (>) Synaptic signaling
- Autophagy
- (>) Dop./GABA/Glutamatergic synapse
- (>) Calcium signaling
- (>) Endocrine calcium reabsorption
- (*) RNA degradation / transport
- (#) Ribosome
- Neuron projection morphogenesis
- (~) Fc receptor signaling pathway
- cGMP-PKG signaling pathway
- (~) mTOR signaling pathway
- (~) Cytokine-cytokine receptor int.



[Wang et al. ('18) Science]

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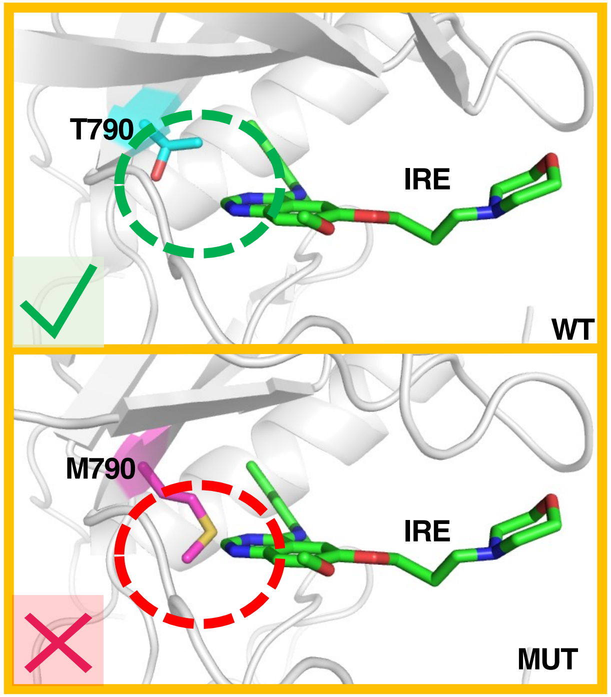
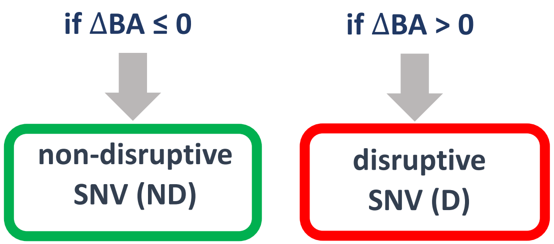
An Example of Binding Affinity Change between Protein & Drug Ligand under the Impact of Single Nucleotide Variants (SNV)



human EGFR & gefitinib (IRE)
PDB: 2ity, Chain A, amino acid 790
Modeling and Visualization: Modeller & PyMol

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) are used in the treatments of non-small cell lung cancer (NSCLC)



For protein-drug binding upon point mutation,

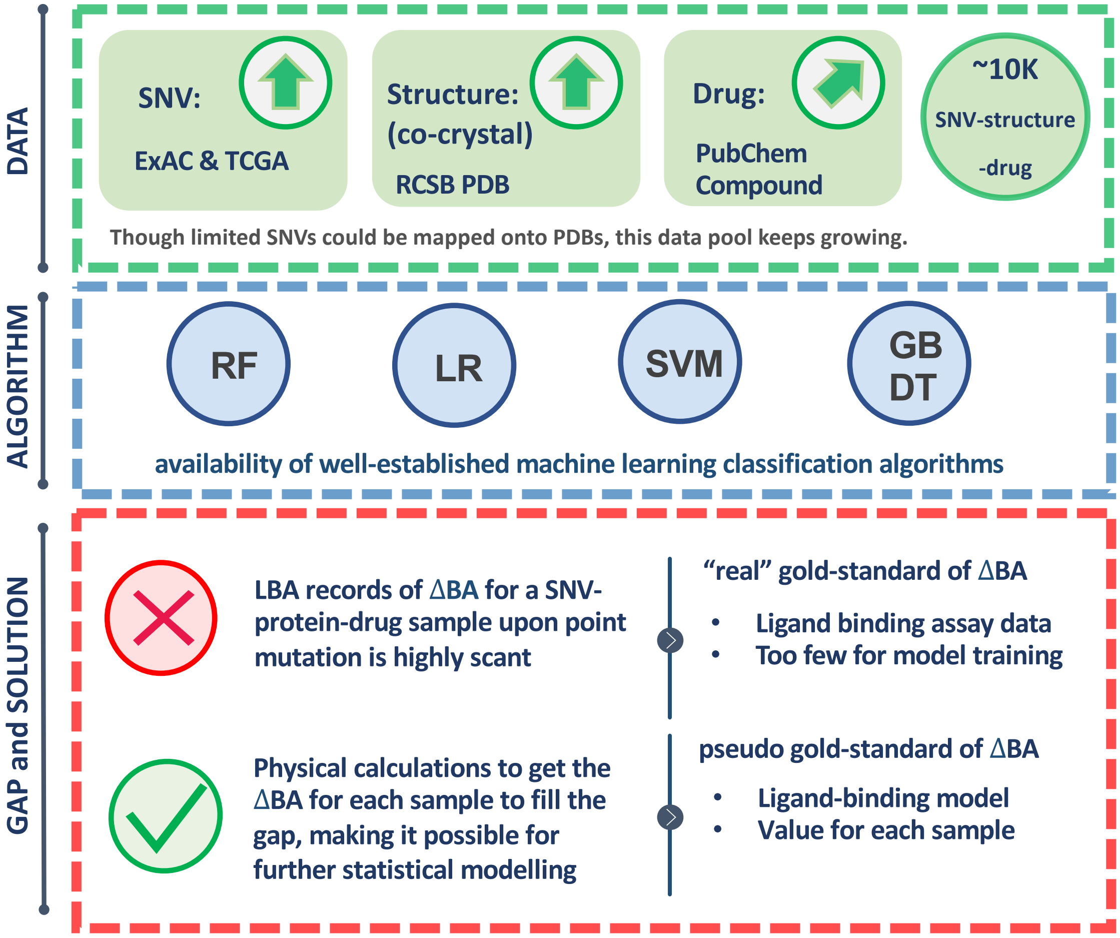
if $\Delta BA \leq 0$ → **non-disruptive SNV (ND)**

if $\Delta BA > 0$ → **disruptive SNV (D)**

Is there any method that could predict the effects of SNVs to drug binding (D or ND)?

Wang et al. Structure, 2019

Assessment of feasibility to build a supervised-learning classifier for binding-disruptive SNVs



SNV: ⬆

ExAC & TCGA

Structure: (co-crystal) ⬆

RCSB PDB

Drug: ↗

PubChem Compound

~10K SNV-structure -drug

Though limited SNVs could be mapped onto PDBs, this data pool keeps growing.

availability of well-established machine learning classification algorithms

✗ LBA records of ΔBA for a SNV-protein-drug sample upon point mutation is highly scant

“real” gold-standard of ΔBA

- Ligand binding assay data
- Too few for model training

✓ Physical calculations to get the ΔBA for each sample to fill the gap, making it possible for further statistical modelling

pseudo gold-standard of ΔBA

- Ligand-binding model
- Value for each sample

Wang et al. Structure, 2019

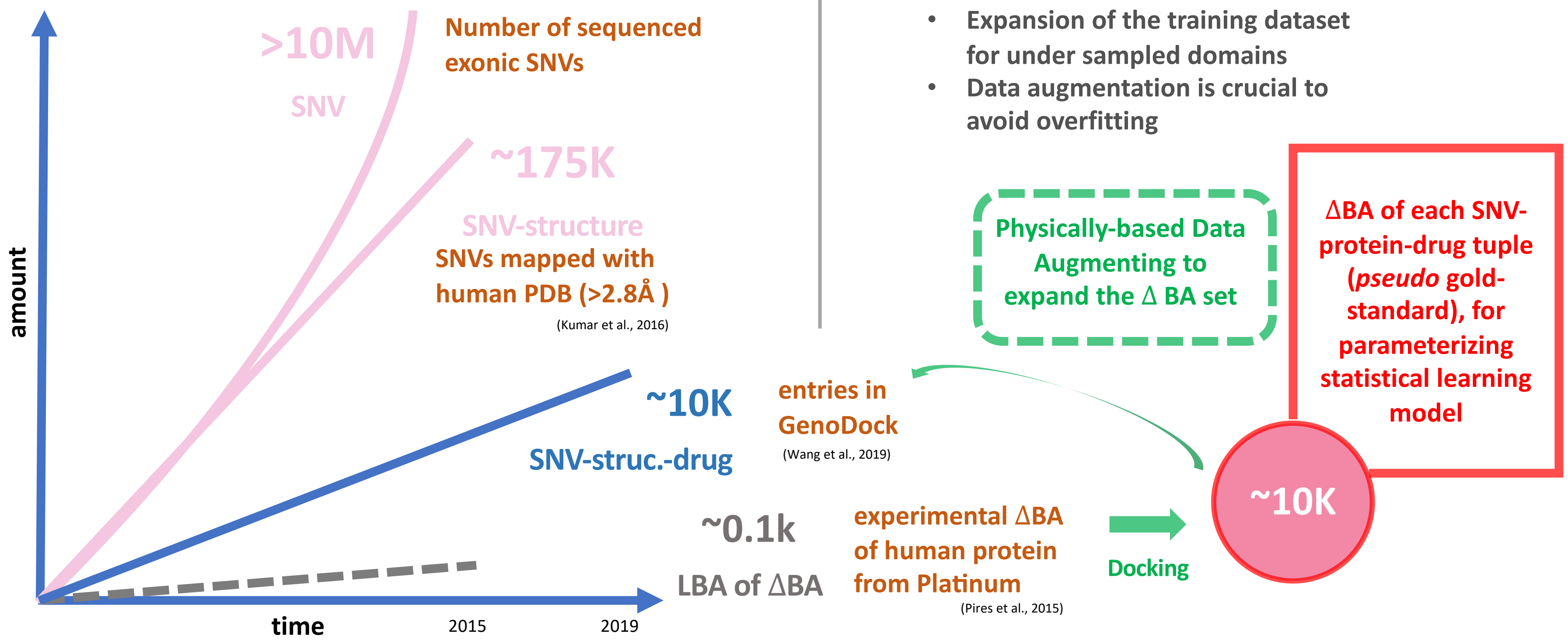
A Hot Topic in Machine Learning is "Hybrid" Model Integrating Physical & Statistical Calculations

The Major Hurdle:
Highly Scant Ligand Binding Assay Data for ΔBA

The Physically-based Data Augmentation Approach:
Leveraging Physical Calculations of ΔBA to Fill the Gap

(Reichstein *et al.*, **Nature**, 2019 & Xie et al., preprint, 2018)

- Expansion of the training dataset for under sampled domains
- Data augmentation is crucial to avoid overfitting



Number of sequenced exonic SNVs

SNVs mapped with human PDB (>2.8Å)

(Kumar et al., 2016)

entries in GenoDock

(Wang et al., 2019)

experimental ΔBA of human protein from Platinum

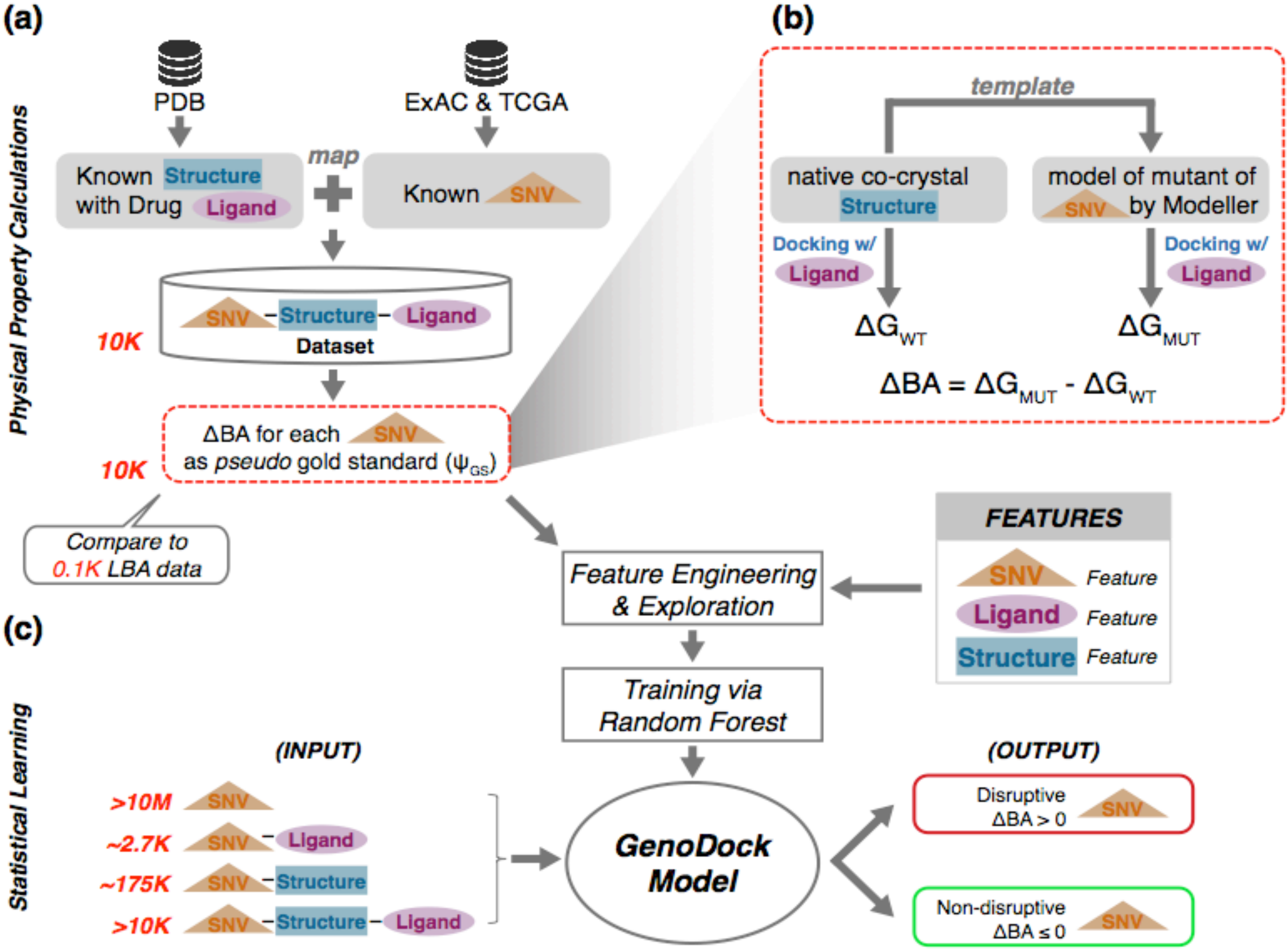
(Pires et al., 2015)

Physically-based Data Augmenting to expand the Δ BA set

ΔBA of each SNV-protein-drug tuple (*pseudo* gold-standard), for parameterizing statistical learning model

Wang et al. Structure, 2019

Framework for GenoDock: from Dataset Preparation to Model Construction



Wang et al. Structure, 2019

3 Feature Groups as Predictor, with 4 Application Cases Based on Info Availability

What are features are effective for prioritization of disruptive SNVs?

③ groups of features as predictors

SNV Feature

- Allele Frequency
- SIFT
- PolyPhen-2
- GERP
- Germline/Somatic

Ligand Feature

- Molecular Weight
- H-bond donor
- H-bond acceptor
- Rotatable Bond #
- Polar Surface Area

Structure Feature

- Distance
- Binding Site
- Polarity Change
- Volume Change

Will SNV of interest disrupt protein-ligand binding

④ random forest model trained based on information available

- SNV + Structure + Ligand
- SNV + Structure
- SNV + Ligand
- SNV only

validate the "full feature" case

then, expand the model to 3 more "feature poor" cases

Wang et al. Structure, 2019

List of Models & Datasets in the Study

Model 1: statistical model (GenoDock)
Model 2: ligand binding model (to calculate ΔBA)

Model	Role	Parameterization	Validation	Description
1	Core Model	Statistical model from Ψ_{GS}	Platinum	Supervised learning model using the pseudo gold-standard set as target feature. The direct validation of this model is to apply the model to an independent, experiment-based validation dataset.
2	Auxillery Model	Physically based	-	A physical-based, previously published computational ligand-docking model to calculate binding affinity change for the pseudo gold standard set.

Dataset	Role	Size	Source	Description
Ψ_{GS}	Trains 1	~10k	Built from 2	Core dataset constructed for training the statistical model. Contains pseudo gold standard set as the target feature.
Platinum	Validates 1	86	Experiment	The human protein subset from Platinum. used as direct validation dataset of our statistical method.

KEY TAKE-AWAY

- **The statistical model and ligand binding model are the two models for this study;**
- **The validation of the statistical model and the assessment of rigor of the ligand binding model are two independent process.**

Wang et al. Structure, 2019

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The *pseudo* Gold-Standard as Self-Constructed Prediction Target: Physical Calculations for Binding Affinity Score Change (ΔBA)

Dataset

ExAC: 8565 SNV-PDB native-mutant pairs
TCGA: 1718 SNV-PDB native-mutant pairs

Equation

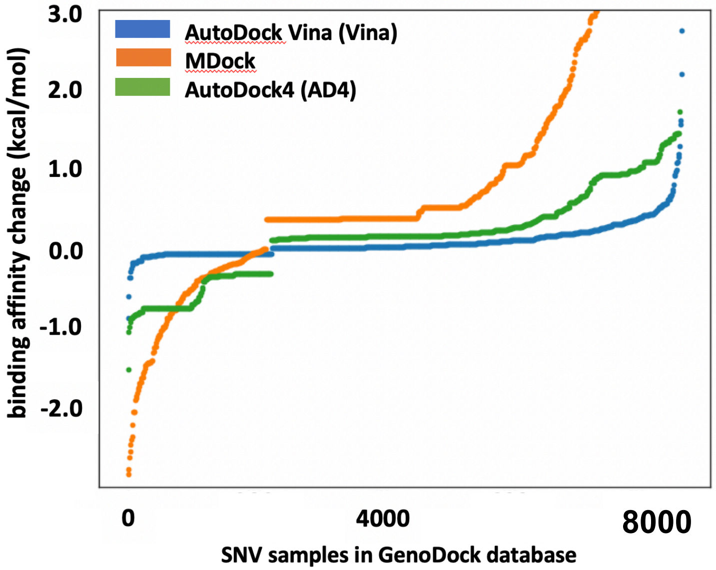
$$\Delta\Delta G(SNV) = \Delta G(SNV)\text{-}\Delta G(WT)$$

$\Delta G(WT)$: BA of WT protein-drug complex
$\Delta G(SNV)$: BA of point mutated protein-drug complex
$\Delta\Delta G(SNP)$: BA change

Approach

- MDock
- AutoDock Vina
- AutoDock 4

- Pearson Product-Moment Correlation (PMCC) reveals good consistency of different docking calculations
- PMCC (Vina & AD4) = 0.89
- PMCC (Vina & MDock) = 0.94



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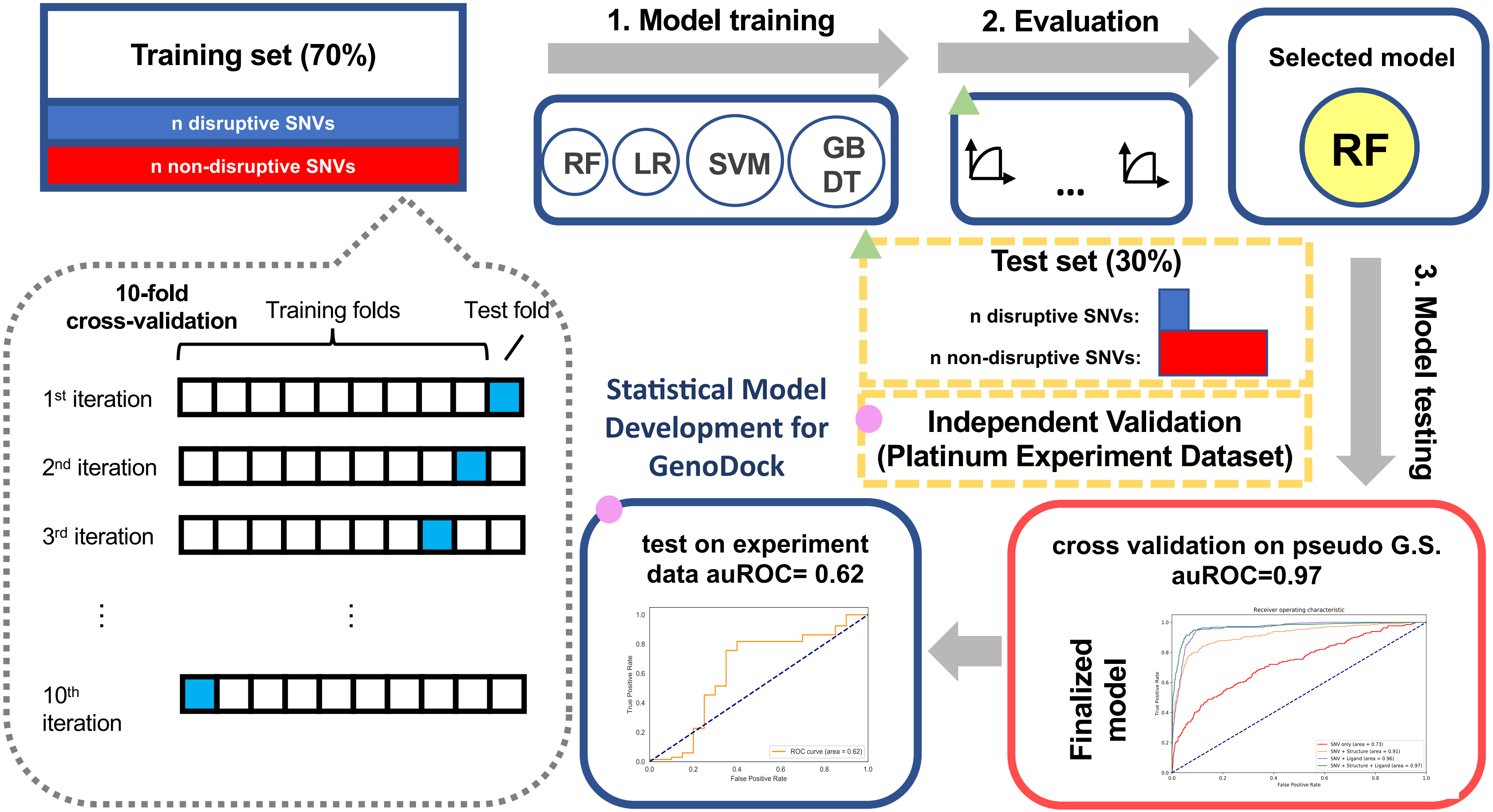
Given the pseudo Gold-Standard, the Workflow for Building the Statistical Model & its Performance in Cross-validation & Independent Testing



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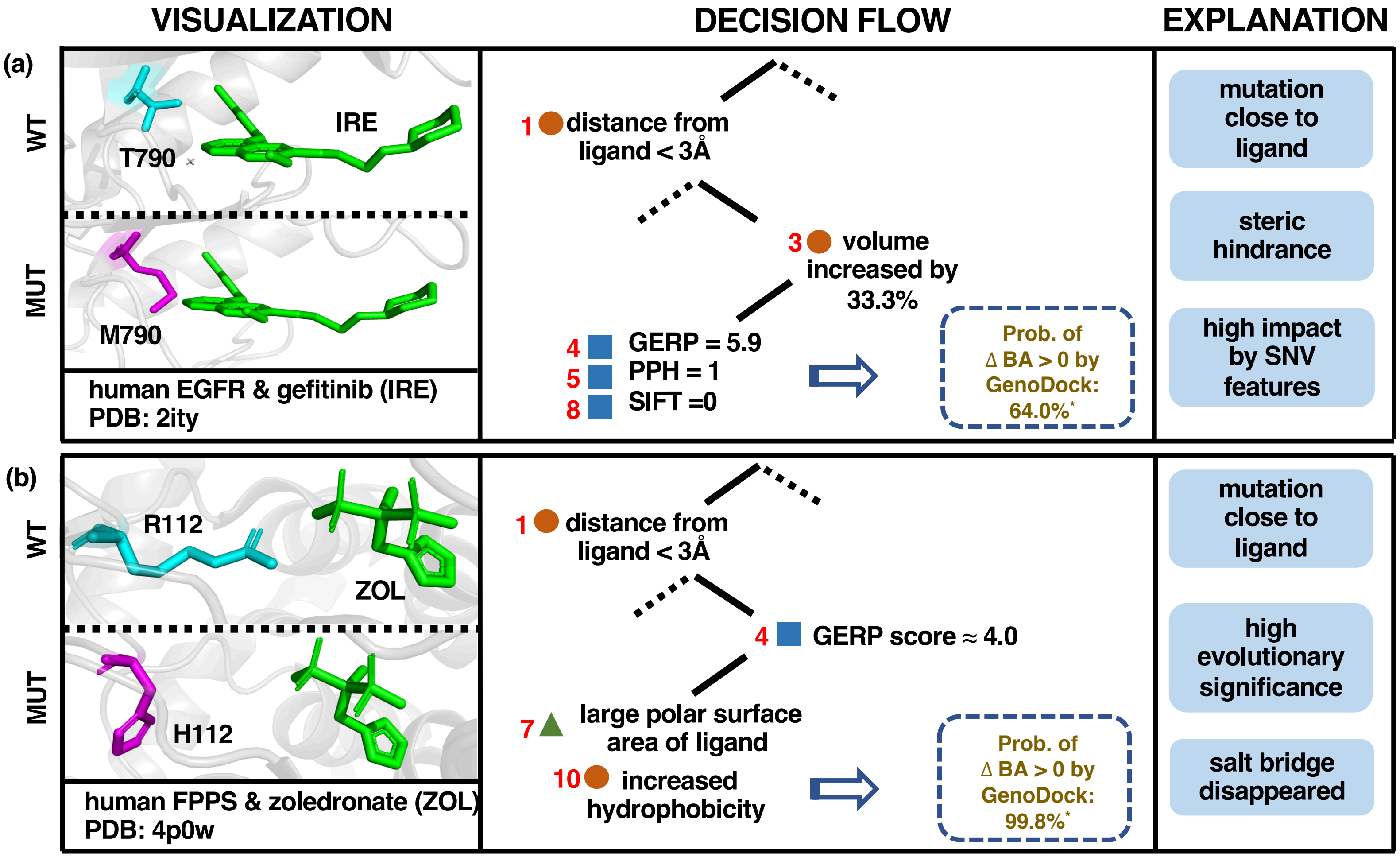
Example of the Output of the Classifier: GenoDock Helps Characterize Known & Unknown SNVs that Disrupt Protein-Ligand Binding



(a)

human EGFR & gefitinib (IRE)
PDB: 2ity

1 ● distance from ligand < 3Å

3 ● volume increased by 33.3%

4 🟦 GERP = 5.9
5 🟦 PPH = 1
8 🟦 SIFT =0

⇨ Prob. of Δ BA > 0 by GenoDock: 64.0%*

- mutation close to ligand
- steric hindrance
- high impact by SNV features

(b)

human FPPS & zoledronate (ZOL)
PDB: 4p0w

1 ● distance from ligand < 3Å

4 🟦 GERP score ≈ 4.0

7 ▲ large polar surface area of ligand
10 ● increased hydrophobicity

⇨ Prob. of Δ BA > 0 by GenoDock: 99.8%*

- mutation close to ligand
- high evolutionary significance
- salt bridge disappeared

● Structure Feature 🟦 SNV Feature ▲ Ligand Feature 1-10: Feature significance rank by Gini Distance for selected features

* Δ BA > 0 validated by docking calculations

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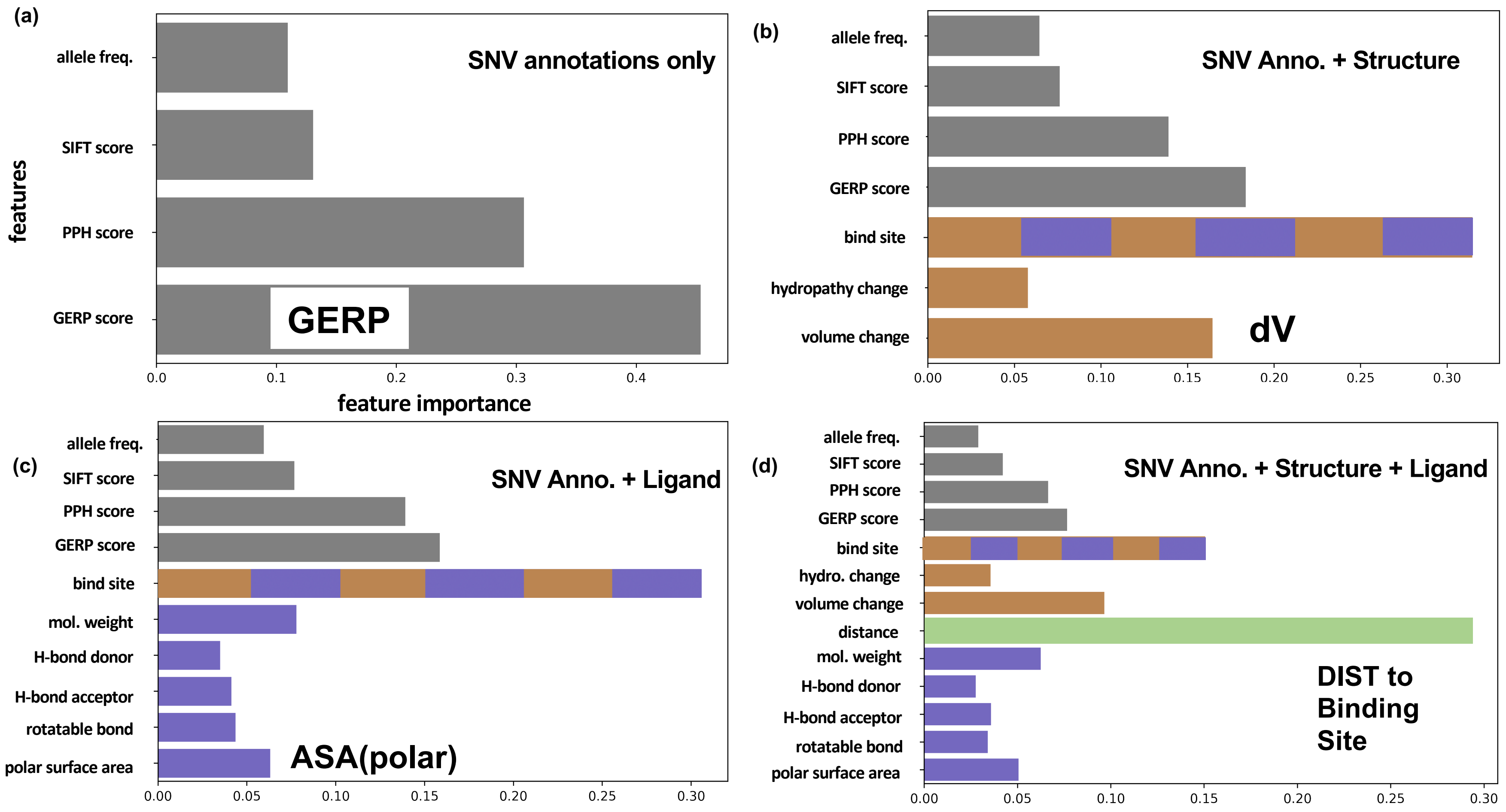
Gini Distance for Relative Feature Importance in 4 Models



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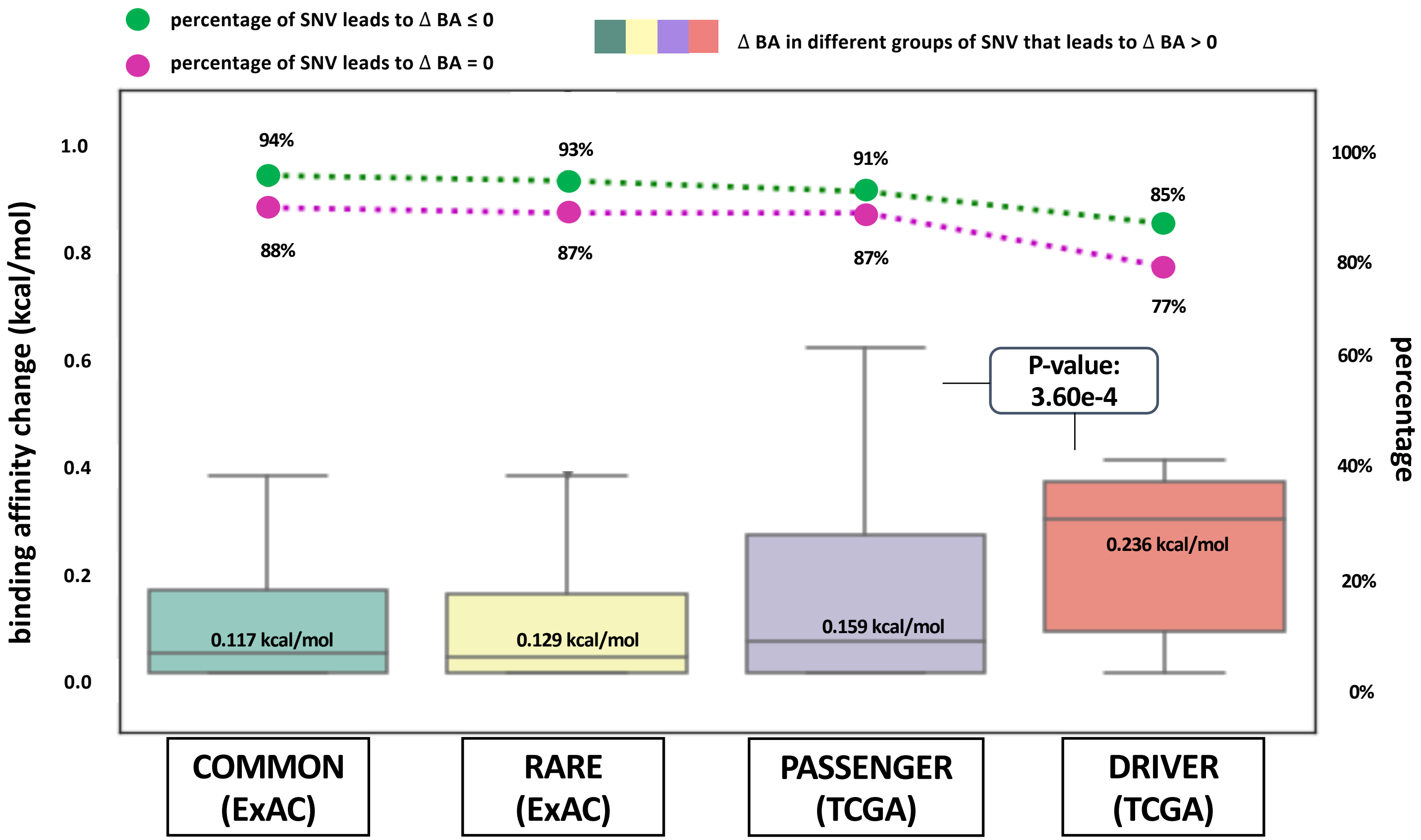
Boxplot of Overall Ligand Binding Affinity Changes for Different Types of SNVs in GenoDock



The more an SNV is considered disease-associated, the greater chance that this SNV would destabilize binding affinity of the protein and drug ligand.

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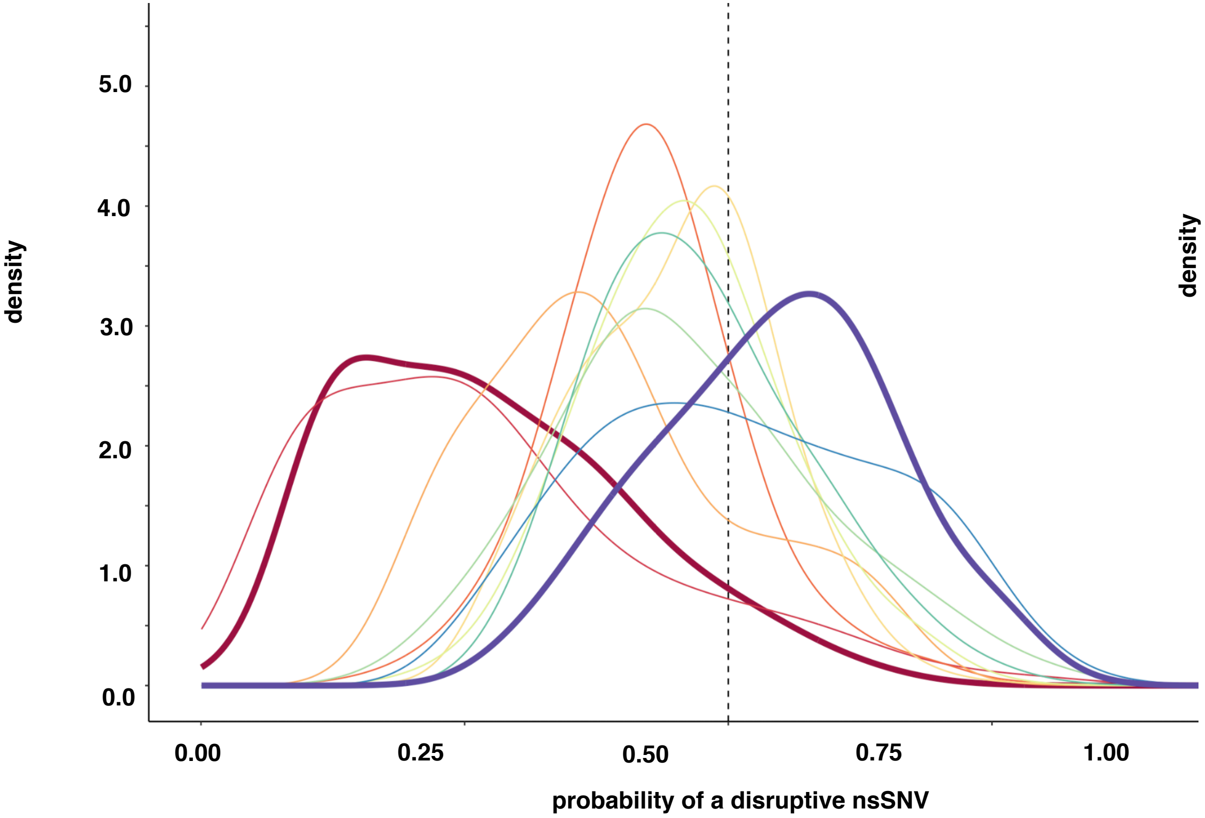
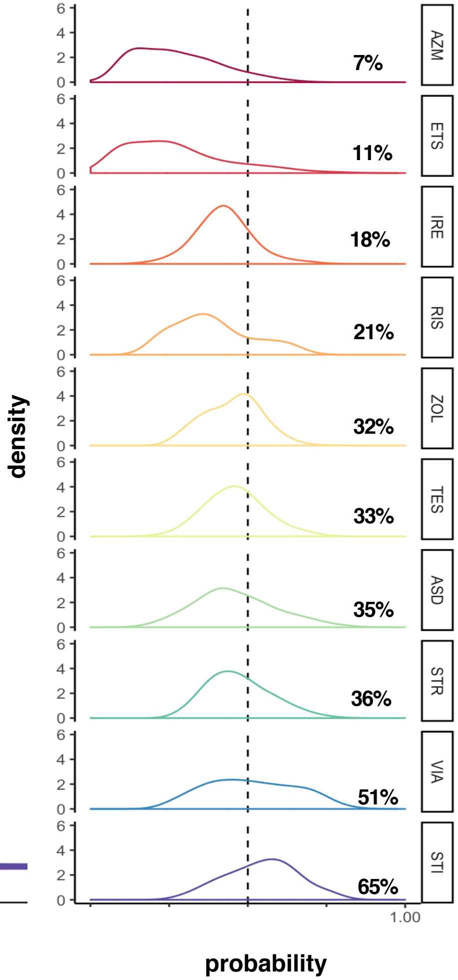
Application of GenoDock to large-scale screening of disruptive SNVs for Drug Ligand interactions





Aceta-zolamide (glaucoma)

Imatinib (cancer)

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Finding drug targets for neuropsychiatric disorders via deep-learning & Designing a predictor for the sensitivity of drugs to human population variation

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Dedicated to **Pamela Sklar**

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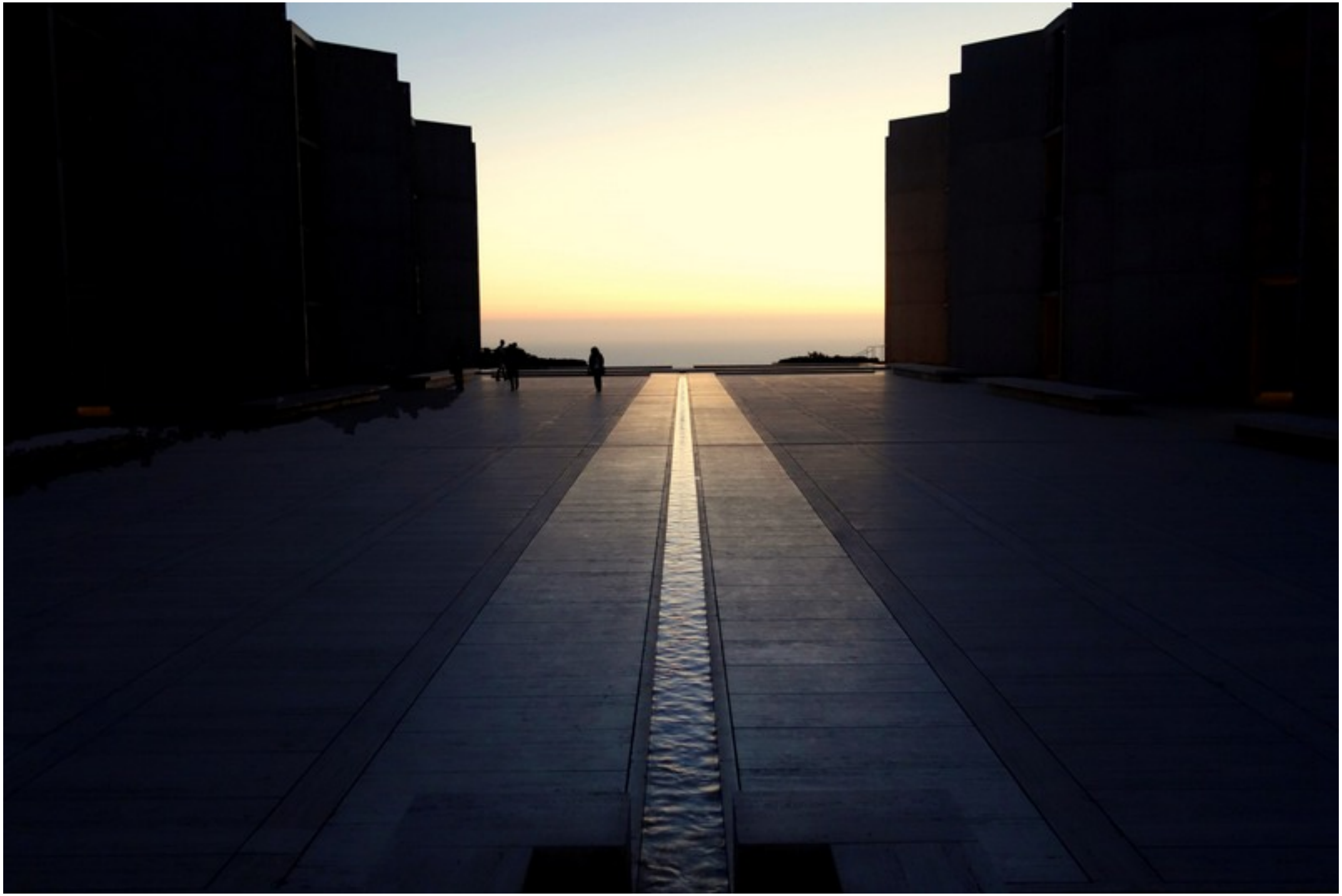

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