Breakout Session 4: Track A

IGVF Cloud Computing

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IGVF Cloud Computing

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FAIR Principles

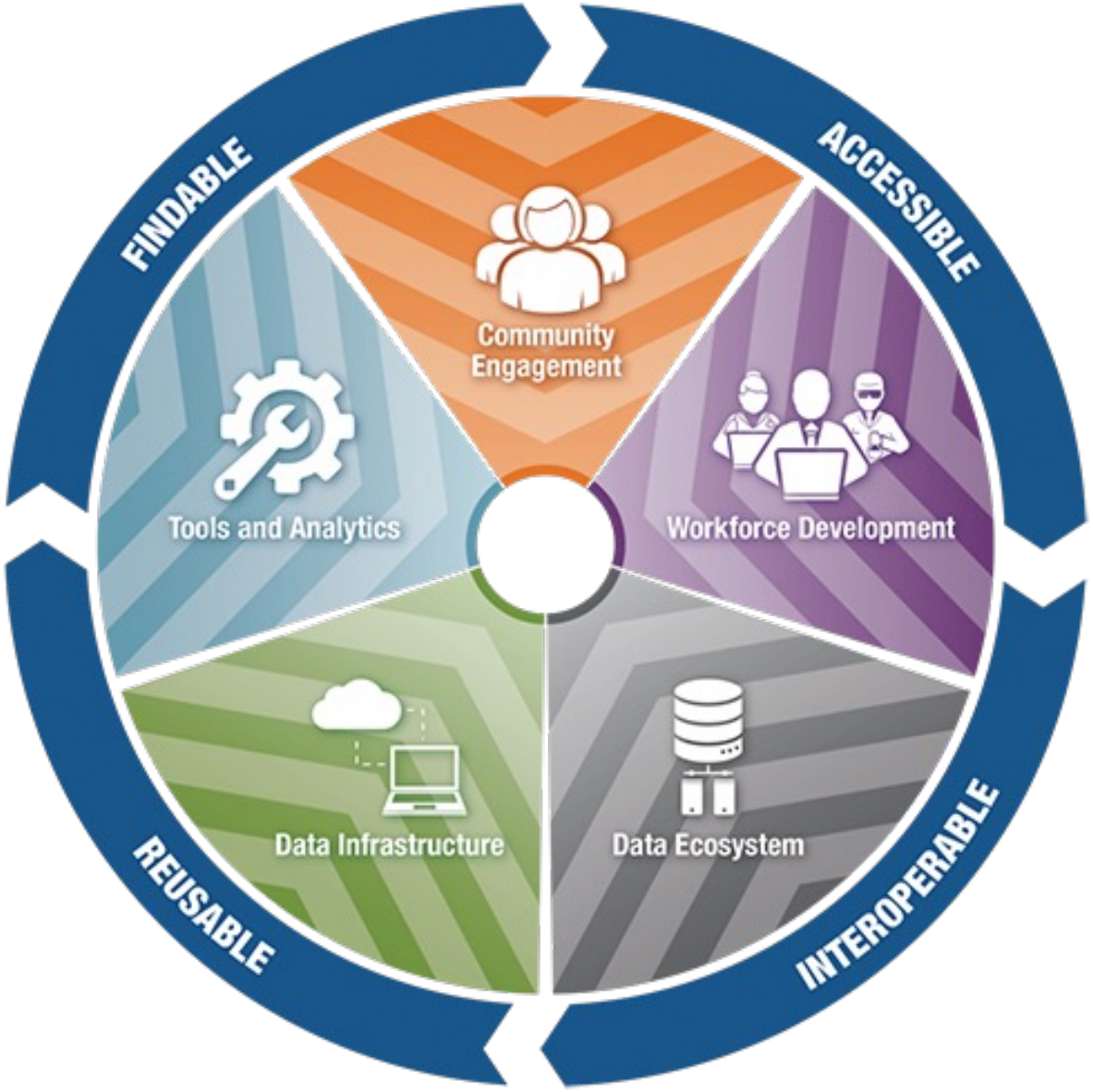


Image from ODSS site

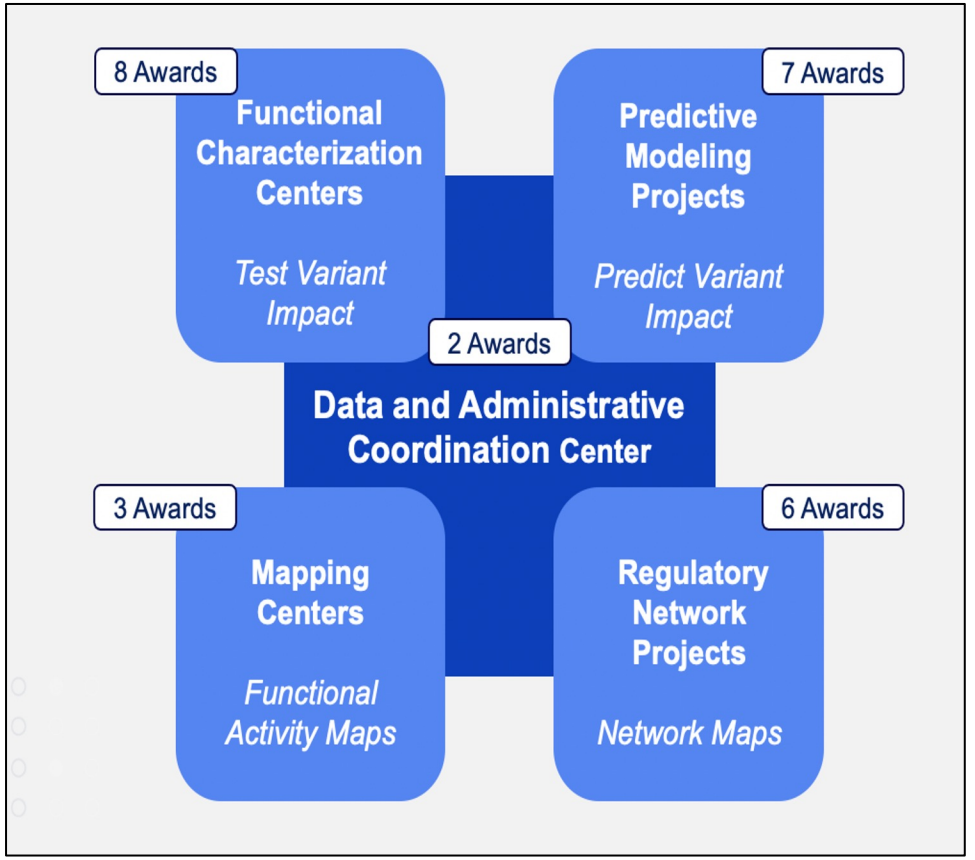
Impact of Genomic Variation on Function

Transforming our understanding of how variation impacts function and leads to phenotypes in health and disease by:

- Using systematic perturbation to assess genome function
- Identification of where and when genes and regulatory elements function at high-resolution
- Network-understanding of genome function
- Development of predictive models of genome function
- Generation of a catalog of elements, variants and phenotypes; share data, tools, and models
- Enabling others to apply these approaches

Organization of the Consortium

- What is the IGVF?
  - 24 grants 75 PIs in 4 areas
  - 7 working groups 18 focus groups
  - 40-something assays coding, noncoding, MPRAs, CRISPR screens
  - Emphasis on functional characterization and perturbation and single-cell (nuclei)

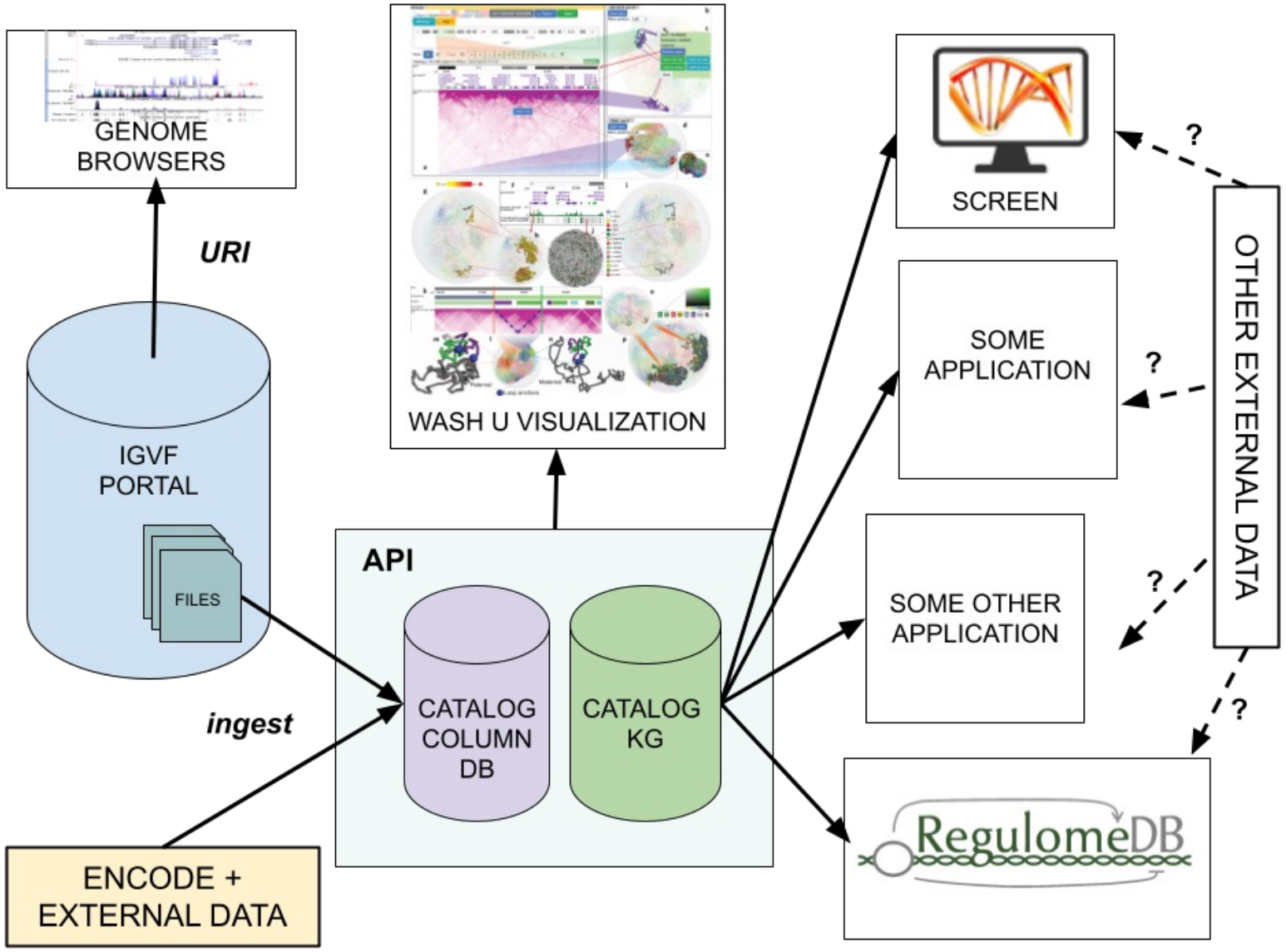


Cherry Lab Data Coordination Centers

- 12+ years of supporting the ENCODE Project and IGVF
- All computing done in the cloud since 2014
  - Web development environments in AWS
  - Over 1.2PB of storage in AWS S3, mirrored in Azure
  - Long term solutions can be hardware independent
  - Computation has essentially unlimited bursting capacity

- Development of Uniform Processing Pipelines for ENCODE
  - Developed hardened pipelines for 7 assays: ChIP-seq, RNA-seq (long and short reads), ATAC-seq, DNase-seq, HiC, WGBS over 8 years
  - Almost 15,000 experiments analyzed, several Terabases of sequence run in the cloud (ca. 5,000,000 CPU*GB Hours)
  - Quality Control metrics and file provenance available on the Portal
  - Reproducible, platform independent, supported pipeline code available in Github and Docker (WDL/Cromwell)

IGVF Data Ecosystem



Value of uniform pipelines for genomics

- Output of genomics pipelines are sensitive to:
  - Choice of genome, transcriptome reference
  - Choice of software, algorithms
- Uniform processing removes this technical variation that can confound results
- Uniform processing allows uniform quality metrics to be calculated
- Genomics is hard enough as it is

Goals of our proposal

- Primary Method: The “Jamboree”
  - A Jamboree is like a Hackathon but for data analysis
  - A way of doing collaborative development in a short time frame using a cloud compute platform like Terra
- Developing uniform pipelines for single-cell multi-omics and functional characterization
  - Test core pipline
  - Test and evaluate workflow engines and cloud platforms
  - Develop semi-automated interactive cell annoation
- Developing methods to benchmark models of enhancer-gene regulatory interactions
  - Collect, analyze, curate and harmonize genetic perturbations
  - Develop standards for formats and evaluation of models

Expanding our CRISPR benchmarking dataset

Fulco *et al.* 2019
Nasser *et al.* 2021

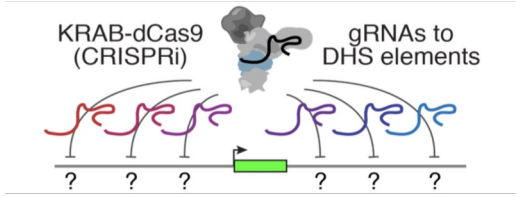
CRISPRi-FlowFISH at all peaks around 30 genes

Gasperini *et al.* 2019

CRISPRi-Perturb-seq at 5,000 predicted enhancers

Schraivogel *et al.* 2020

CRISPRi-TAP-seq at ~50 genes



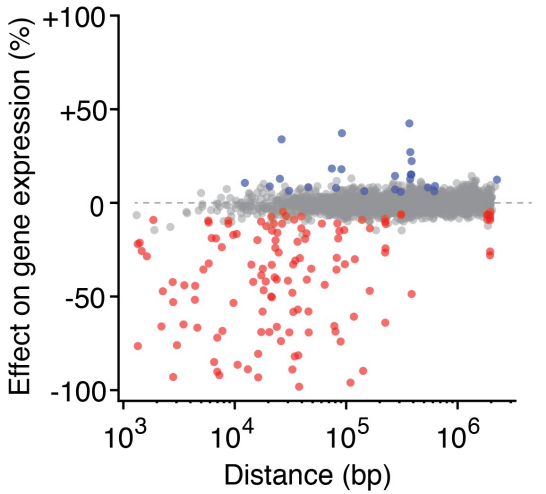
Reprocessing to harmonize:

Guide-peak assignment

Significance calling

Power calculations

Combined CRISPR dataset:



10,350 tested E-G pairs

472 positive pairs

Use benchmarking to improve E2G classifier

ENCODE-rE2G: A supervised classifier to predict E-G regulatory interactions

Idea: Could we extend ABC to include other possible molecular mechanisms?

ENCODE-rE2G modeling framework

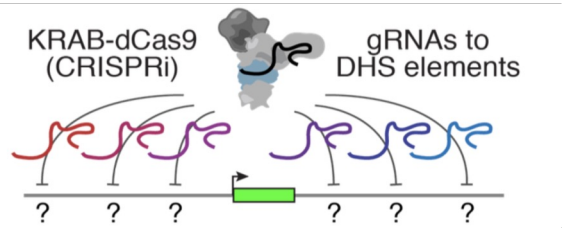
Input features:

Enhancer activity
3D contact
ABC score
Distance
...

Logistic regression

Hold out 1 chromosome cross-validation

Predict CRISPR data:



Features not included in ABC:

- Enhancer-promoter compatibility?
- Enhancer-enhancer synergy?
- Non-linear functions of A and C?
- …

Compare ENCODE and IGVF assays:

- DNase-seq
- H3K27ac and other ChIP-seq
- Hi-C, ChIA-PET
- …

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IGFV Single Cell, MPRA, and CRISPR Focus Groups

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