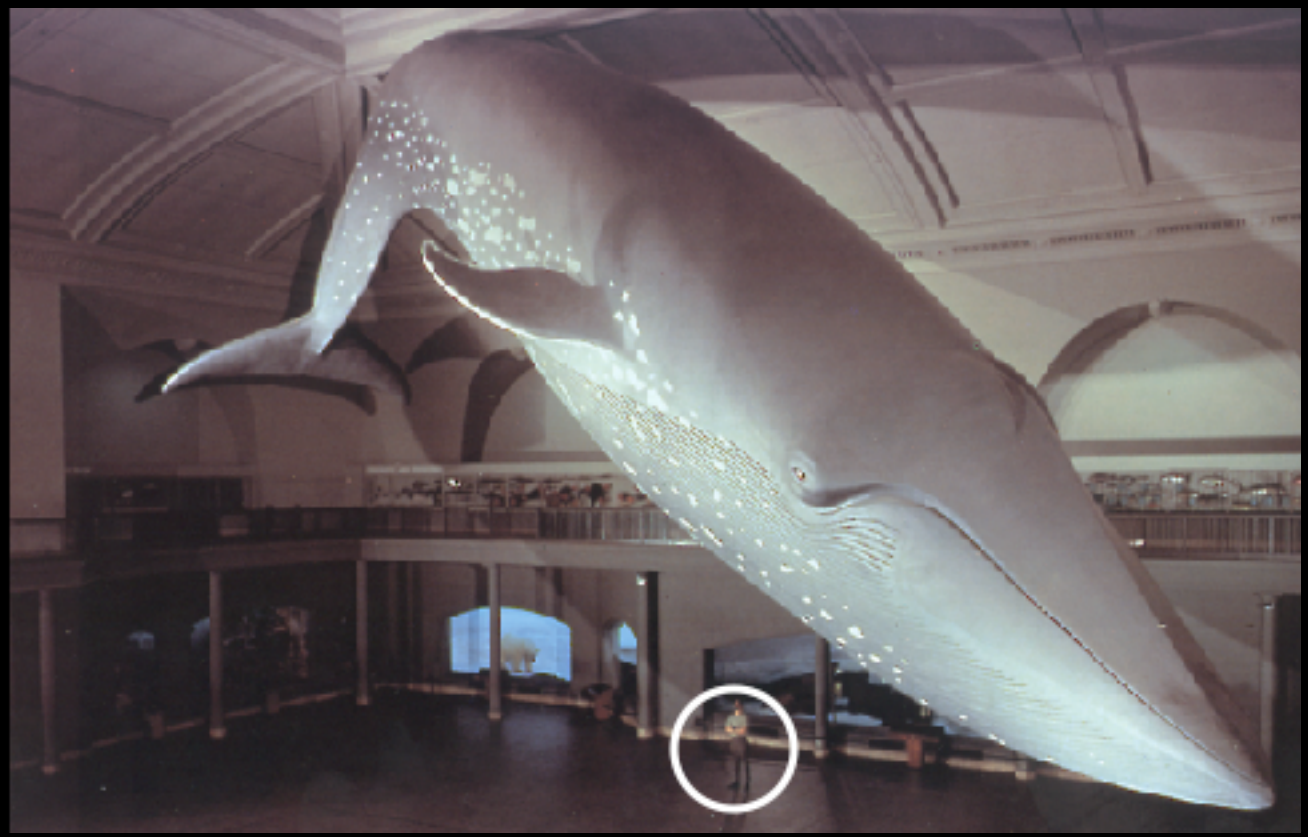
A Biologist's Perspective On Interesting Problems Requiring Statistical Applications

- **The Geneticist's Perspective**
- **The Purebred Dog Approach**
- **Biostatistics at the Interface**

Nature is a study of contrasts

Genetics: Differences in phenotype stem from causal differences in genotype



Making Sense of Natural Variation

- **Darwin = inter-specific diversity (1859)**
- **Mendel = intra-specific diversity (1865)**
- **The Principles => Tools & Perspectives**
- **Three general classes**
  - ‘Beanbag’ Genetics
    - Describing alleles in populations
  - Plant & Animal Science
    - Good x Good crosses = Improve specific traits
  - Classical Genetics
    - Good X Bad crosses = Understand gene differences

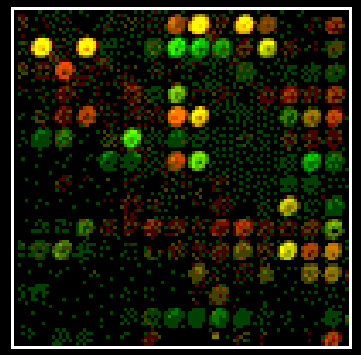
Classical Genetics

- **Identify all components of a biological process**
- **Assign function to each component**
- **Establish heirarchy of components**
- **Elucidate a pathway**
  - Systematic and comprehensive
  - Restricted to model organisms
  - Relies on induced variation (typically loss-of-function)

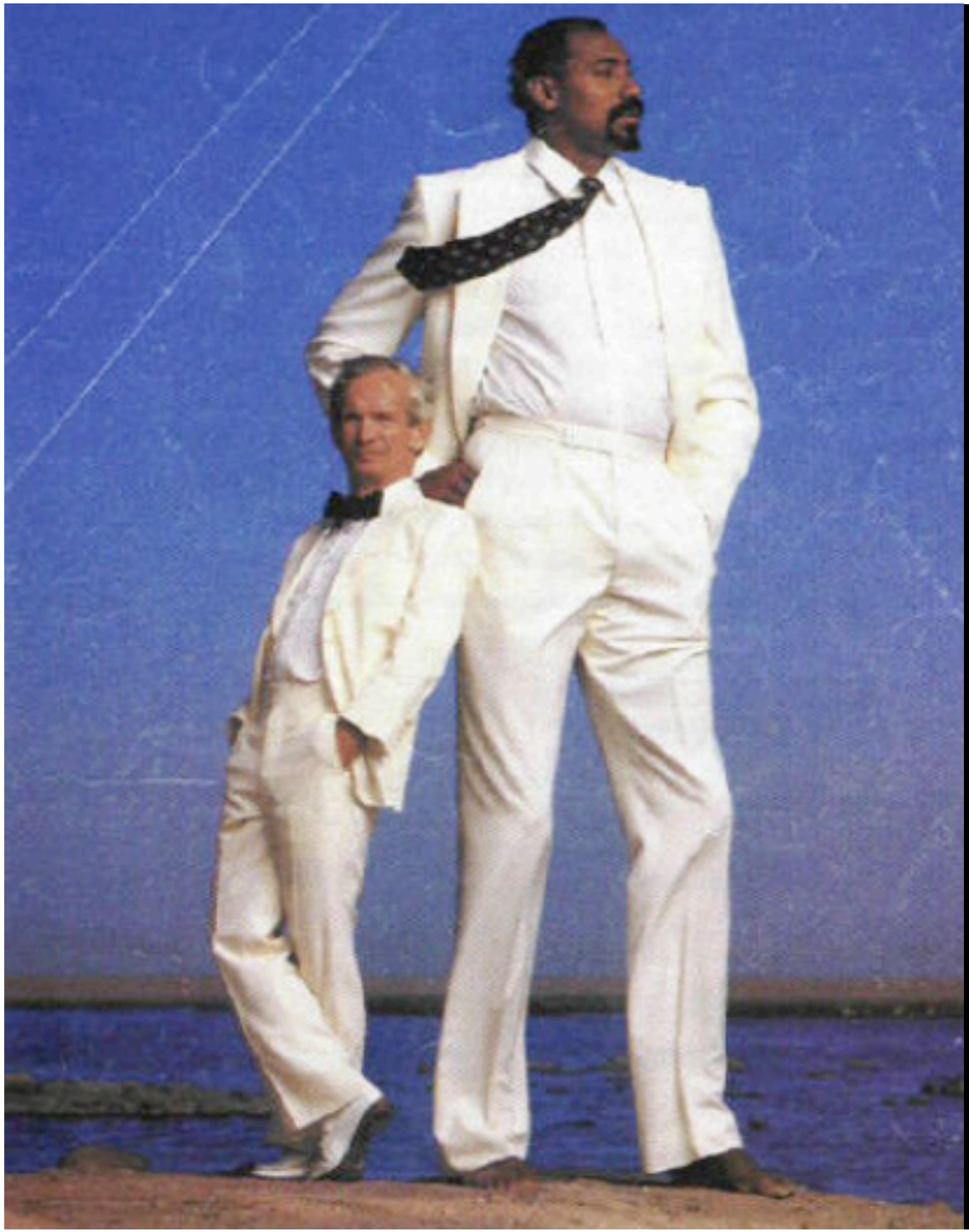
What about natural variation?

Genomics

- **With scale comes a new scope**
- **Extends genetics to every corner of biology**
- **The costs:**
  - De-emphasizes hypothesis-driven approach
  - Quantity over quality & style over substance?
- **The future?**



Signals a return to studying natural variation



Human

- Interesting; diverse
- Difficult; heterogeneous

Mouse

- Suitable for engineering
- Lacking in diversity

Pronounced phenotypic diversity….


… That breeds true.

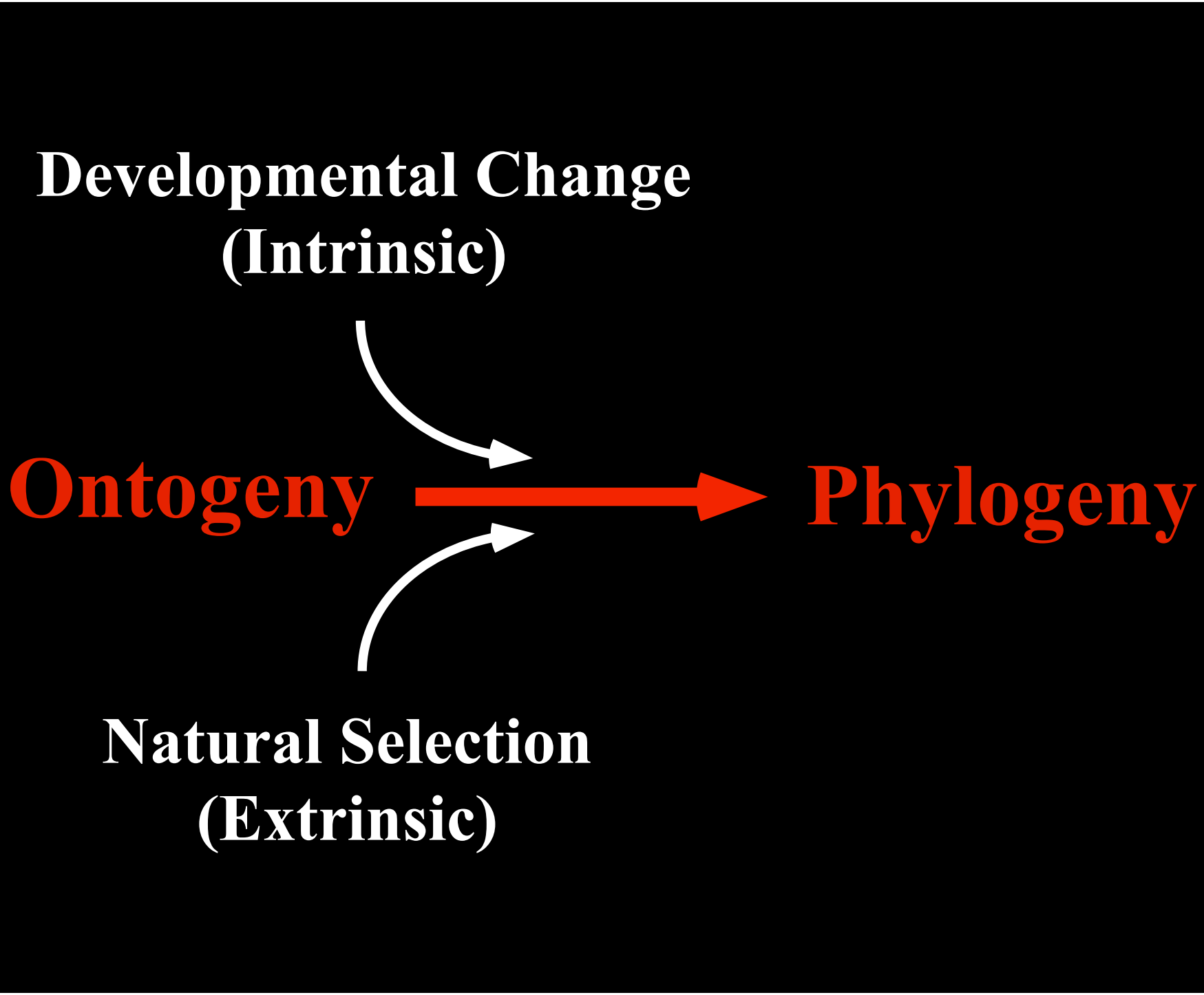
All dogs are descended solely from the wolf
=> artificial selection

- **Progenitor still exists**

=> Traits will have simple genetic architectures

“Nothing in biology makes sense except in light of evolution”

-- Theodosious Dobzhansky


Developmental Change
(Intrinsic)
Ontogeny
Phylogeny
Natural Selection
(Extrinsic)

Canine Genetics

4 Areas of Study

- Population Genetics
- Molecular Variation
- Breed Phylogeny
- Gene Mapping

Population Genetics

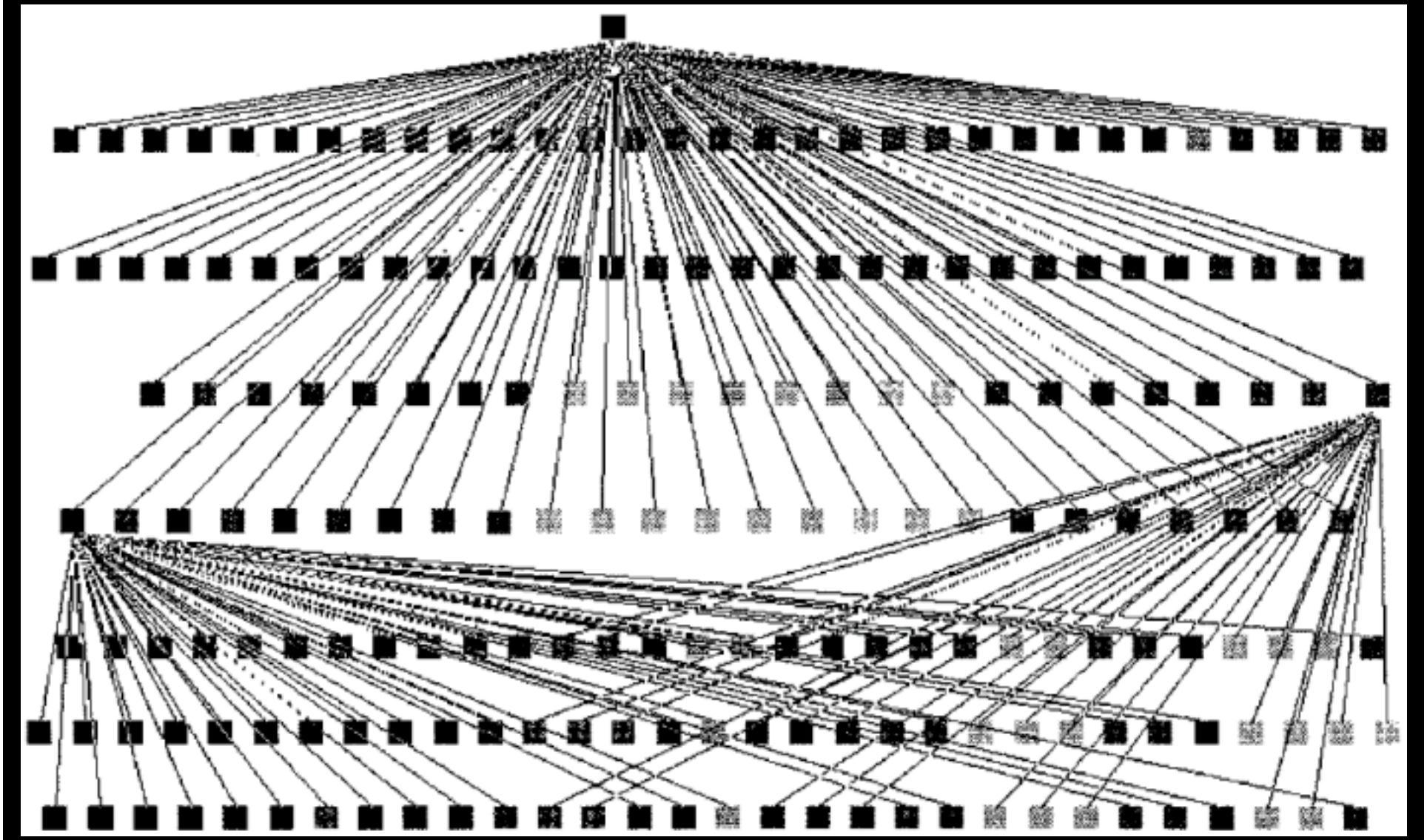
- Hardy-Weinberg
  - Mutation
  - Migration
  - Selection
  - Non-Random Mating

Genetic Isolates

- Founder Effects
- Historical Bottlenecks
- Favorite Sire Effects

=> Increased homozygosity

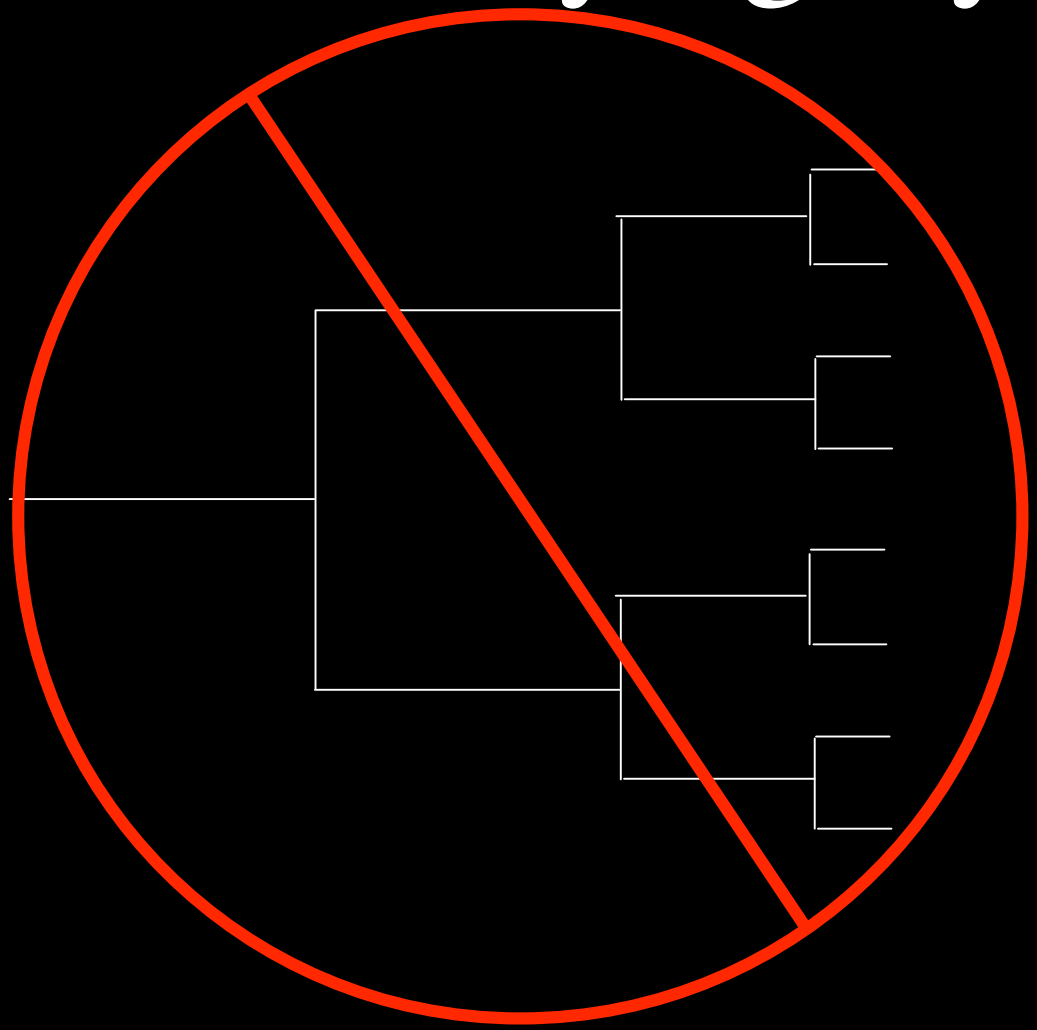
“Favorite Sires”



Assaying Molecular Variation

- Microsatellites
  - Ascertainment Bias
- SNPs
  - Standard Measure
- Jackpot Mutation Events
  - Tied to Population Dynamics

Breed Phylogeny



Breeds are aggregates of traits;
each trait will have a distinct phylogeny

Gene Mapping

3 Broad Opportunities

1) Simple Mendelian Traits

- ***Family-based***

2) Complex Intrabreed Variation

- ***Population-based***

3) Complex Interbreed Diversity

- *In Silico Mapping?*

Genetic basis for systems of skeletal quantitative traits: Principal component analysis of the canid skeleton

Kevin Chase*, David R. Carrier*, Frederick R. Adler*, Tyler Jarvik*, Elaine A. Ostrander†, Travis D. Lorentzen†, and Karl G. Lark*‡

*University of Utah, Department of Biology, 257 South 1400 East, Room 201, Salt Lake City, UT 84112-0840; and †Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D4-100, Seattle, WA 98109-1024

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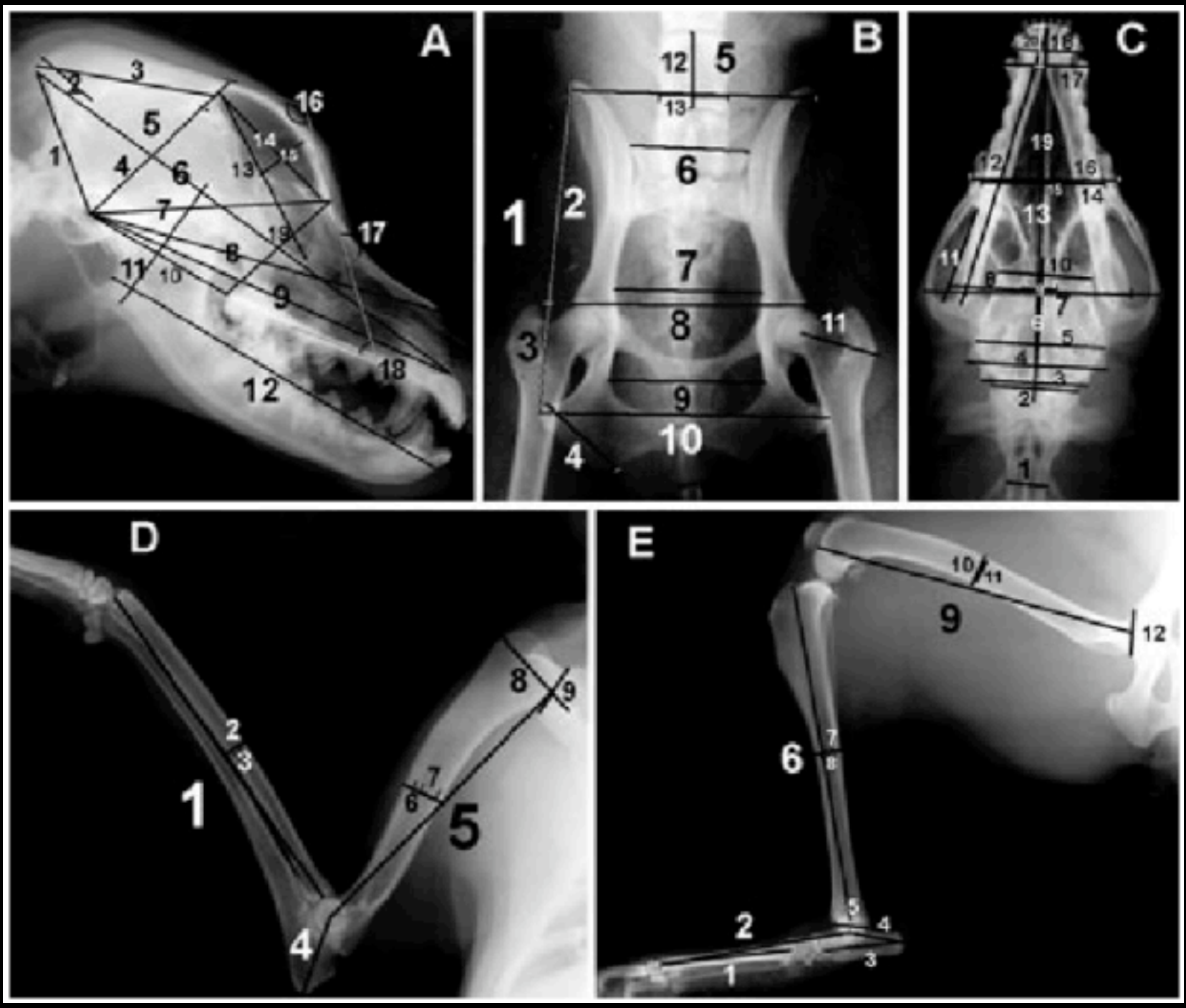
Genetics is limited by "phenotyping"


A
B
C
D
E

Principal Component Analysis

- Reduce complexity of datasets
  - Simplification comes at a cost
- Remove redundancy of multiple metrics
  - But exploit the descriptive value (& increased accuracy) of multiple measures
- Explore phenotype interactions
  - Addressing pleiotropy, etc
- Describe organizing principles
  - Puts forth testable hypotheses

Measuring Behavior

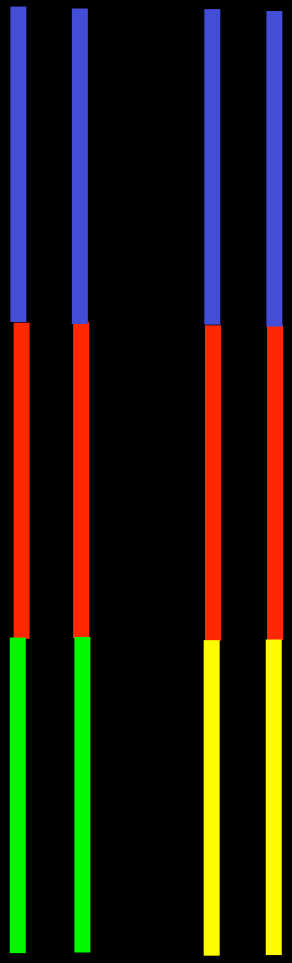
4 Quantifiable Components

- Latency
- Duration
- Frequency
- Intensity

In Silico Mapping

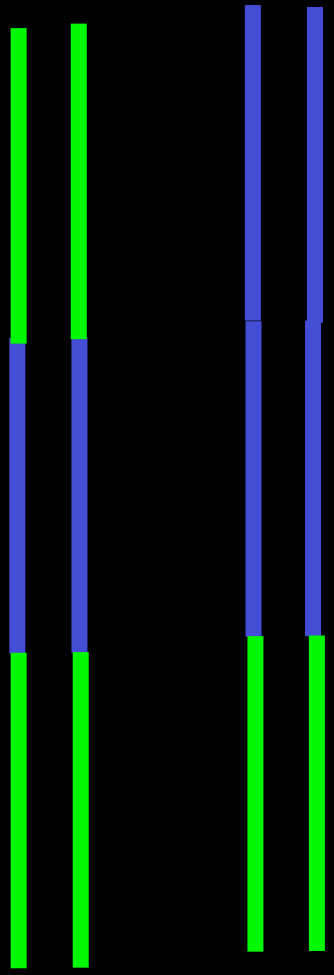
‘low’

‘high’



1. What’s common within each group

2. What’s different between the groups



In Silico Mapping

- Breed Genotype Profiles
  - Focus on IBD loci
  - Exclude variable loci
- Breed Phenomics
  - Quantitative
  - Penetrant
- Power of 400 breed comparisons

Good things happen at the Interface

Genomics: A convergence of genetics, molecular biology, statistics, and computer science

The Origins of Molecular Biology

‘What is Life?’

‘A Physicist’s view of biology’

These essays transformed biology

BioStatistics

- NASA versus Vegas
  - What's good enough?
- Education vs Production
  - Balancing "learning" & "doing"

Helping the biologist identify and optimize the next experiment