Introduction to Hail

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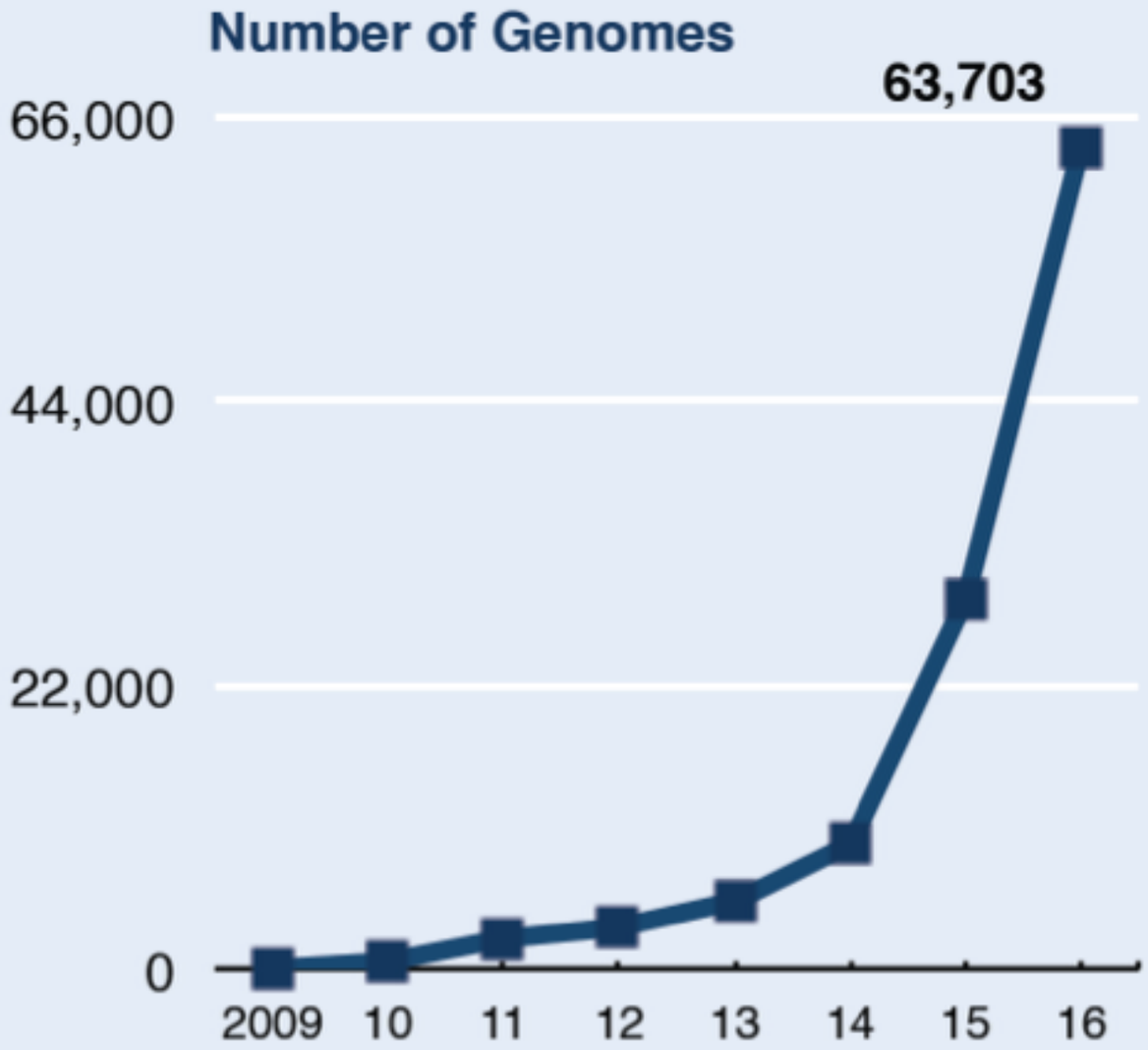
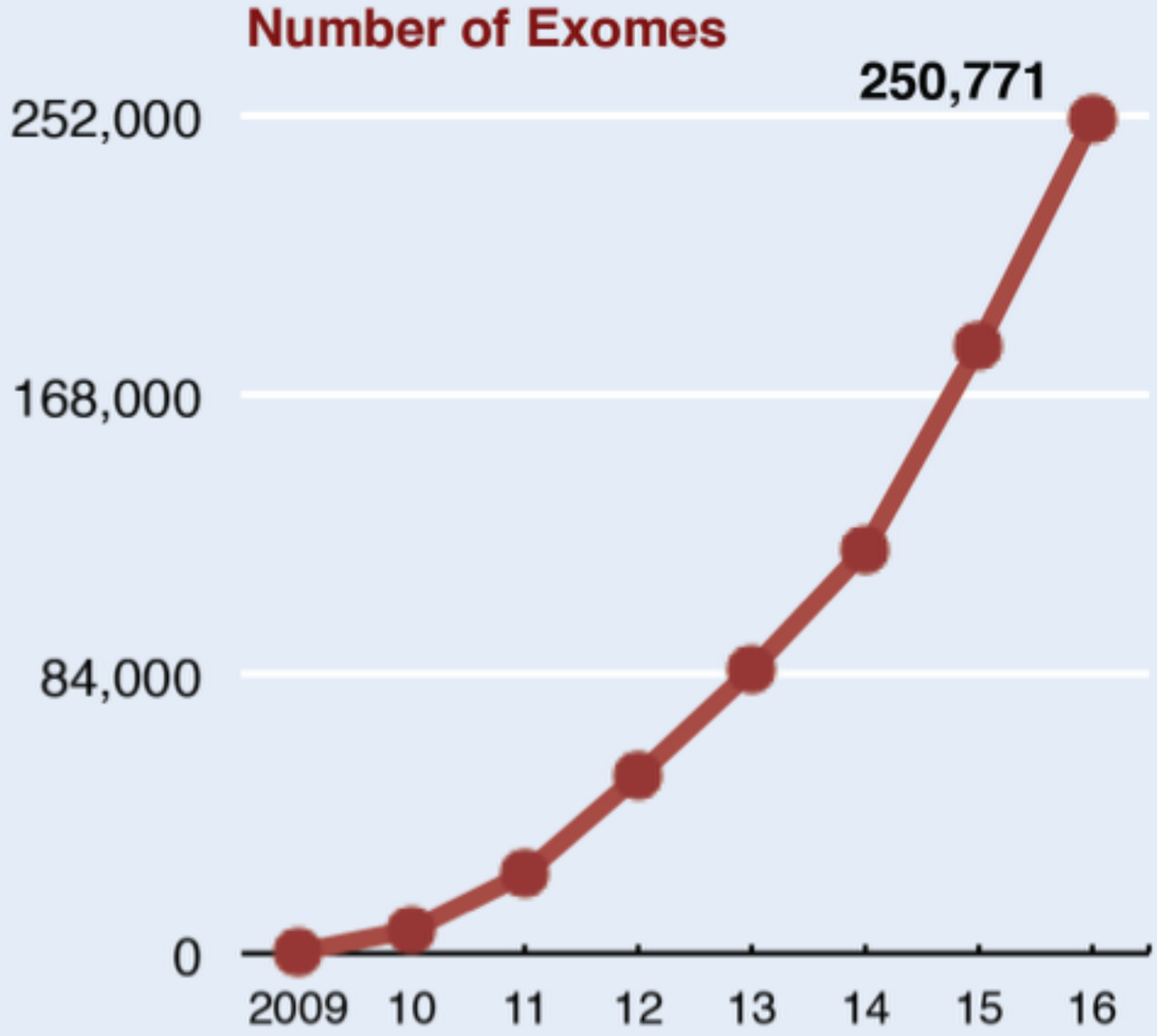
Broad Institute and MGH

Why Hail?

- Genetic data is becoming absolutely massive

Broad Genomics, by the numbers





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- Genetic data is becoming absolutely massive
    - gnomAD: 123K exomes, 15K WGS, 40TB compressed VCF
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- Power is proportional to Np(1 - p)
  - Need massive data, knowledge about the genome, functional annotation, reference datasets, burden methods, etc. to detect association

What is Hail?

Hail is a **scalable** tool for

for doing **data science**

on **genetic data**.

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- **Scalable**:
  - Add more CPUs, get your answer faster.
  - Add more resources, compute on bigger data.

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Hail is a **scalable** tool for

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- **Scalable**:
  - From 1 core (laptop) to 10,000 core clusters
  - Use for QC, analysis of gnomAD (20K WGS, 200K exomes), 40TB compressed VCF

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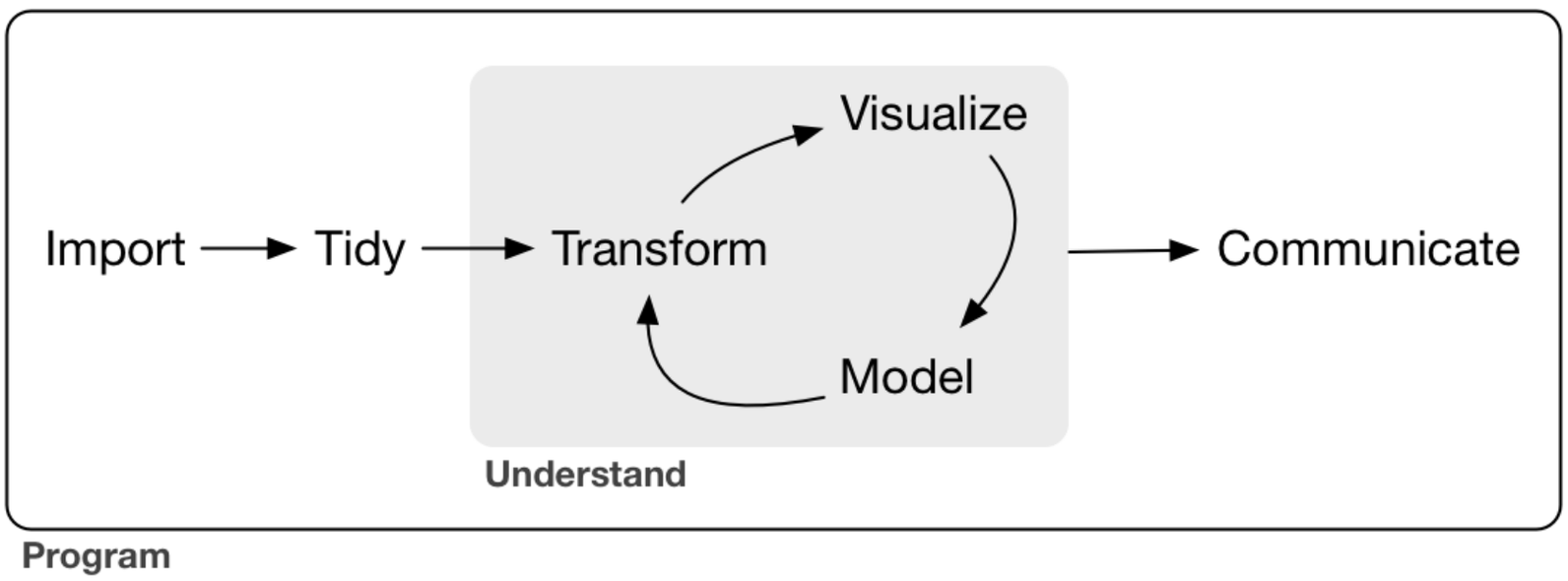

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Hail is a **scalable** tool for

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on **genetic data**.

No reads.

hail Functionality

Import/Export

VDS
VCF
GEN
BGEN
PLINK
TSV
UCSC BED
Interval List
FAM
synthetic
JSON
Python

Transform

Query
Filter
Aggregate
Join/Annotate

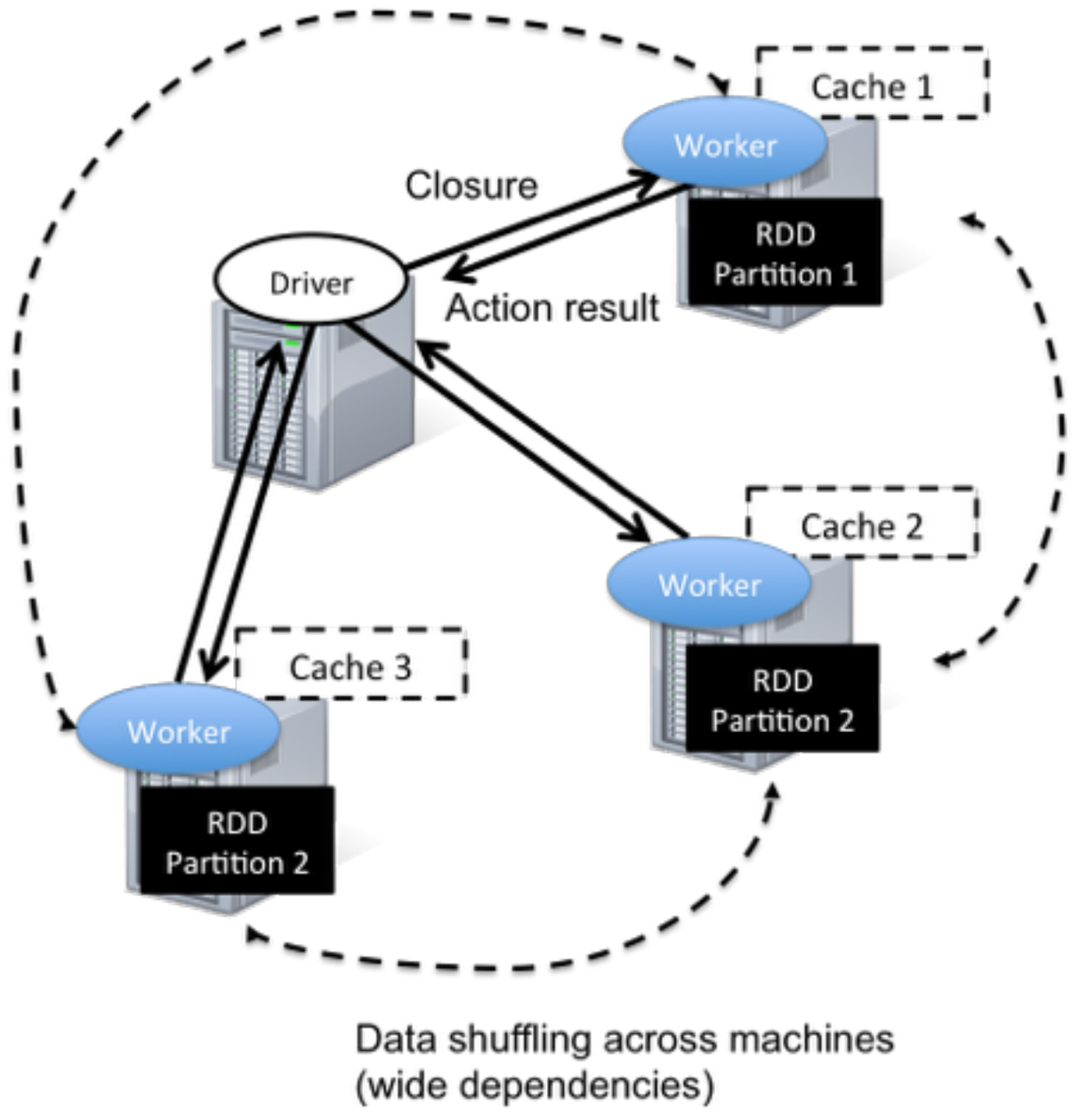
Analyze

Concordance
Fisher Exact Test
GRM
IBD
Impute sex
Mendel errors
PCA
Regressions:
  linear
  logistic
  linear-mixed
TDT
QC stats

hail Architecture

- Interface is Python
  - Python functions in turn use Hail expression language
    - Two languages! This is the most confusing part.
- Built on Spark, distributed computing framework
  - Hail users don't need to know Spark (but it can be useful…)

hail Architecture



Where can you run Hail?

- Single computer: laptop to big server
- On the cloud: Google and Amazon clouds both have products that can run Hail
- To use multiple machines in HPC cluster you probably need help from your local sysadmin.

Help!

- Extensive documentation: https://hail.is
- Another tutorial! https://hail.is/hail/tutorial.html
- Live chat: https://gitter.im/hail-is/hail
- Discussion forum: http://discuss.hail.is/
  - Updates: http://discuss.hail.is/c/updates

Read the docs!

- We've worked hard to make them not suck.

- Liberal links in the practicals to the documentation. Explore!

hail Caveats

- Hail is powerful but complicated.

hail Caveats

- Interface is beta
  - Interface changing (improving!) often
  - Moving towards versioned release next few months
- Does not support all VCF features
  - Fixed genotype schema GT:AD:DP:GQ:PL/GP, diploid genotypes only (but support for sex chromosomes), no phasing, no symbolic alleles, no CNVs, no gVCF support.
- GRCh37 hardcoded.

Main Python objects

- **`HailContext`**: main entry point for Hail functionality

- **`VariantDataset`**: Hail's representation of a dataset

- **`KeyTable`**: Table-like structure (think data frame)

HailContext

- Main entry point for Hail functionality
- Created once at the beginning of a Hail session or script:

```
import hail
hc = hail.HailContext()
```

- Calling functions on hc is you how access Hail functionality

Example

```
In [1]: import hail

In [2]: hc = hail.HailContext()
```

```
In [3]: (hc.import_vcf('hail-practical/sample.vcf')
   ...:  .count(genotypes=True))
Out[3]:
{u'callRate': 97.45664739884393,
 u'nCalled': 33720L,
 u'nGenotypes': 34600L,
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Example 2

```
In [4]: (hc.import_vcf('hail-practical/sample.vcf')
   ...:  .filter_genotypes('g.gq > 20')
   ...:  .count(genotypes=True))
Out[4]:
{u'callRate': 89.09537572254335,
 u'nCalled': 30827L,
 u'nGenotypes': 34600L,
 u'nSamples': 100,
 u'nVariants': 346L}
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- What is the type of `3.14`? **`Double`**
- What is the type of **`“Hello, world!”`**?

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- What is the type of `3`? `Int`
- What is the type of `3.14`? `Double`
- What is the type of `"Hello, world!"`? `String`
- We write `3: Int` to indicate that `3` has type `Int`. Similarly for `3.14: Double` and `"Hello, world!": String`.

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- The Hail expression language is **typed**.
- What is the type of `3`? `Int`
- What is the type of `3.14`? `Double`
- What is the type of `"Hello, world!"`? `String`
- `5` and `"5"` and `5.0` all have different types!

Types

- `Int`, `Double` and `String` are **primitive** types.

- What is the type of `[1, 2, 3]`?

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- What is the type of `[1, 3.14, “foo”]`?

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- `Int`, `Double` and `String` are **primitive** types.
- What is the type of `[1, 2, 3]`? `Array[Int]`
- What is the type of `[1, 3.14, "foo"]`? **No**.
- You can also have `Array[Double]`, `Array[Array[Double]]`, … `Array[T]`

Types

- `Int`, `Double` and `String` are **primitive** types.
- `Array[T]` is a **compound** type, since it contains types. We will learn about more compound types later.

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- Hail also has (primitive) types for genetic concepts like **`Variant`**, **`Genotype`**, **`Interval`**, etc. A genotype is printed like this:

```
Genotype(GT=0, AD=[21, 0], DP=21,
         GQ=60, PL=[0, 60, 759])
```

Main Python objects

- **`HailContext`**: main entry point for Hail functionality

- **`VariantDataset`**: Hail's representation of a dataset

- **`KeyTable`**: Table-like structure (think data frame)

From VCF …

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20      10026357        T       C       AF=0.23 0/0:23,0:23:60:0,60,900 0/0:22,0:22:60:0,60,900 0/0:26,0:
20      10030188        T       A       AF=0.219        0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10030452        G       A       AF=0.216        0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10030508        T       C       AF=0.002874     0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
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20      10256252        G       T       AF=0.118        0/1:2,5:7:60:166,0,60   0/0:6,0:6:15:0,15,219   0
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20      10389422        T       C       AF=0.001724     0/0:27,0:27:72:0,72,1080        0/0:32,0:32:87:0,
20      10389480        T       A       AF=0.244        0/1:10,17:27:99:550,0,285       0/1:19,17:36:99:4
20      10393145        C       G       AF=0.285        0/0:86,0:86:99:0,120,1800       0/0:89,0:89:99:0,
20      10393162        A       C       AF=0.189        0/1:87,71:158:99:2011,0,2500    0/1:72,56:128:99:
20      10393439        C       A       AF=0.001149     0/0:56,0:56:99:0,120,1800       0/0:62,0:62:99:0,
20      10393629        G       A       AF=0.187        0/1:52,63:115:99:1758,0,1651    0/1:50,60:110:99:
```

From VCF …

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20      10393629        G       A       AF=0.187        0/1:52,63:115:99:1758,0,1651    0/1:50,60:110:99:
```

From VCF …

```
##...
#CHROM  POS     REF     ALT             INFO    C1046::HG02024  C1046::HG02025  C1046::HG02026
20      10019093        A       G       AF=0.582        0/0:30,0:30:72:0,72,1080        0/1:49,45:94:99:1
20      10026348        A       G       AF=0.005172     0/0:23,0:23:60:0,60,900 0/0:22,0:22:60:0,60,900 0
20      10026357        T       C       AF=0.23 0/0:23,0:23:60:0,60,900 0/0:22,0:22:60:0,60,900 0/0:26,0:
20      10030188        T       A       AF=0.219        0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10030452        G       A       AF=0.216        0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10030508        T       C       AF=0.002874     0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10030573        G       A       AF=0.002874     0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10032413        T       G       AF=0.221        0/0:21,0:21:60:0,60,849 0/0:23,0:23:60:0,60,821 0
20      10036107        T       G       AF=0.032        0/0:26,0:26:66:0,66,990 0/0:16,0:16:39:0,39,585 0
20      10036141        C       T       AF=0.024        0/0:29,0:29:81:0,81,1215        0/0:16,0:16:39:0,
20      10036202        G       A       AF=0.047        0/0:29,0:29:81:0,81,1215        0/0:22,0:22:63:0,
20      10256252        G       T       AF=0.118        0/1:2,5:7:60:166,0,60   0/0:6,0:6:15:0,15,219   0
20      10273694        C       CT      AF=0.097        0/0:33,4:41:32:0,32,830 0/0:63,0:63:0:0,0,1271  0
20      10273694        CT      C       AF=0.187        0/0:33,4:41:43:0,43,947 0/0:63,0:63:0:0,0,1271  0
20      10277621        C       T       AF=0.132        0/1:35,34:69:99:1040,0,994      0/0:31,0:31:60:0,
20      10280082        A       G       AF=5.747E-4     0/0:28,0:28:69:0,69,1035        0/0:15,0:15:39:0,
20      10280083        G       A       AF=0.136        0/0:28,0:28:45:0,45,931 0/0:15,0:15:39:0,39,527 0
20      10286773        C       T       AF=0.027        0/0:26,0:26:75:0,75,1052        0/0:24,0:24:60:0,
20      10385849        C       A       AF=0.021        0/0:7,0:7:21:0,21,257   0/0:8,0:8:21:0,21,315   0
20      10385857        T       C       AF=0.021        0/0:7,0:7:15:0,15,225   0/0:8,0:8:21:0,21,315   0
20      10386013        C       A       AF=0.189        0/1:37,38:75:99:1036,0,1133     0/1:45,35:80:99:1
20      10386059        G       A       AF=0.19 0/1:48,38:86:99:1079,0,1318     0/1:52,33:85:99:949,0,149
20      10389422        T       C       AF=0.001724     0/0:27,0:27:72:0,72,1080        0/0:32,0:32:87:0,
20      10389480        T       A       AF=0.244        0/1:10,17:27:99:550,0,285       0/1:19,17:36:99:4
20      10393145        C       G       AF=0.285        0/0:86,0:86:99:0,120,1800       0/0:89,0:89:99:0,
20      10393162        A       C       AF=0.189        0/1:87,71:158:99:2011,0,2500    0/1:72,56:128:99:
20      10393439        C       A       AF=0.001149     0/0:56,0:56:99:0,120,1800       0/0:62,0:62:99:0,
20      10393629        G       A       AF=0.187        0/1:52,63:115:99:1758,0,1651    0/1:50,60:110:99:
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From VCF …

```
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20      10030188        T       A       AF=0.219        0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10030452        G       A       AF=0.216        0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
20      10030508        T       C       AF=0.002874     0/0:35,0:35:60:0,60,900 0/0:26,0:26:63:0,63,945 0
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20      10032413        T       G       AF=0.221        0/0:21,0:21:60:0,60,849 0/0:23,0:23:60:0,60,821 0
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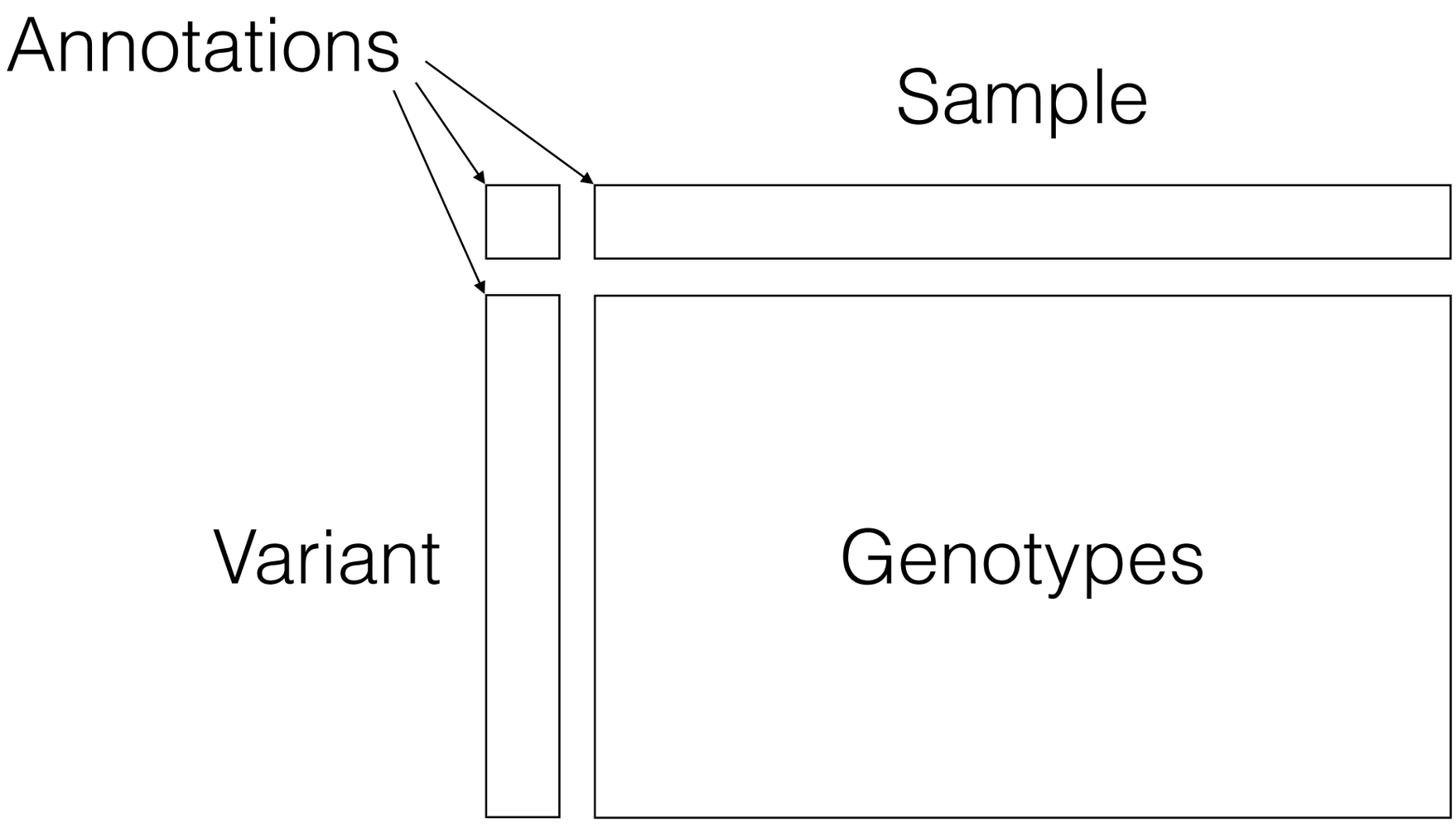
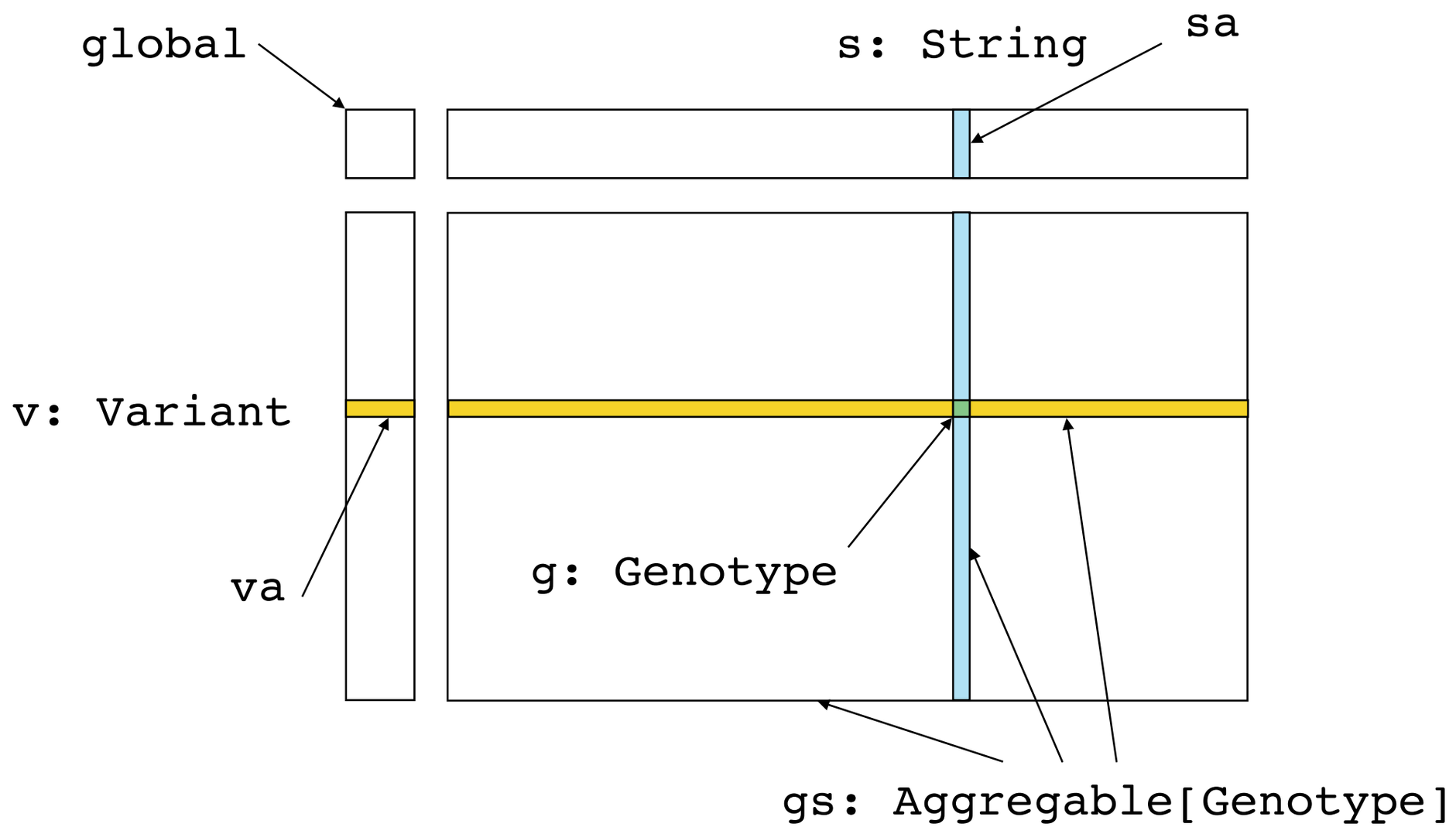
20      10036141        C       T       AF=0.024        0/0:29,0:29:81:0,81,1215        0/0:16,0:16:39:0,
20      10036202        G       A       AF=0.047        0/0:29,0:29:81:0,81,1215        0/0:22,0:22:63:0,
20      10256252        G       T       AF=0.118        0/1:2,5:7:60:166,0,60   0/0:6,0:6:15:0,15,219   0
20      10273694        C       CT      AF=0.097        0/0:33,4:41:32:0,32,830 0/0:63,0:63:0:0,0,1271  0
20      10273694        CT      C       AF=0.187        0/0:33,4:41:43:0,43,947 0/0:63,0:63:0:0,0,1271  0
20      10277621        C       T       AF=0.132        0/1:35,34:69:99:1040,0,994      0/0:31,0:31:60:0,
20      10280082        A       G       AF=5.747E-4     0/0:28,0:28:69:0,69,1035        0/0:15,0:15:39:0,
20      10280083        G       A       AF=0.136        0/0:28,0:28:45:0,45,931 0/0:15,0:15:39:0,39,527 0
20      10286773        C       T       AF=0.027        0/0:26,0:26:75:0,75,1052        0/0:24,0:24:60:0,
20      10385849        C       A       AF=0.021        0/0:7,0:7:21:0,21,257   0/0:8,0:8:21:0,21,315   0
20      10385857        T       C       AF=0.021        0/0:7,0:7:15:0,15,225   0/0:8,0:8:21:0,21,315   0
20      10386013        C       A       AF=0.189        0/1:37,38:75:99:1036,0,1133     0/1:45,35:80:99:1
20      10386059        G       A       AF=0.19 0/1:48,38:86:99:1079,0,1318     0/1:52,33:85:99:949,0,149
20      10389422        T       C       AF=0.001724     0/0:27,0:27:72:0,72,1080        0/0:32,0:32:87:0,
20      10389480        T       A       AF=0.244        0/1:10,17:27:99:550,0,285       0/1:19,17:36:99:4
20      10393145        C       G       AF=0.285        0/0:86,0:86:99:0,120,1800       0/0:89,0:89:99:0,
20      10393162        A       C       AF=0.189        0/1:87,71:158:99:2011,0,2500    0/1:72,56:128:99:
20      10393439        C       A       AF=0.001149     0/0:56,0:56:99:0,120,1800       0/0:62,0:62:99:0,
20      10393629        G       A       AF=0.187        0/1:52,63:115:99:1758,0,1651    0/1:50,60:110:99:
```

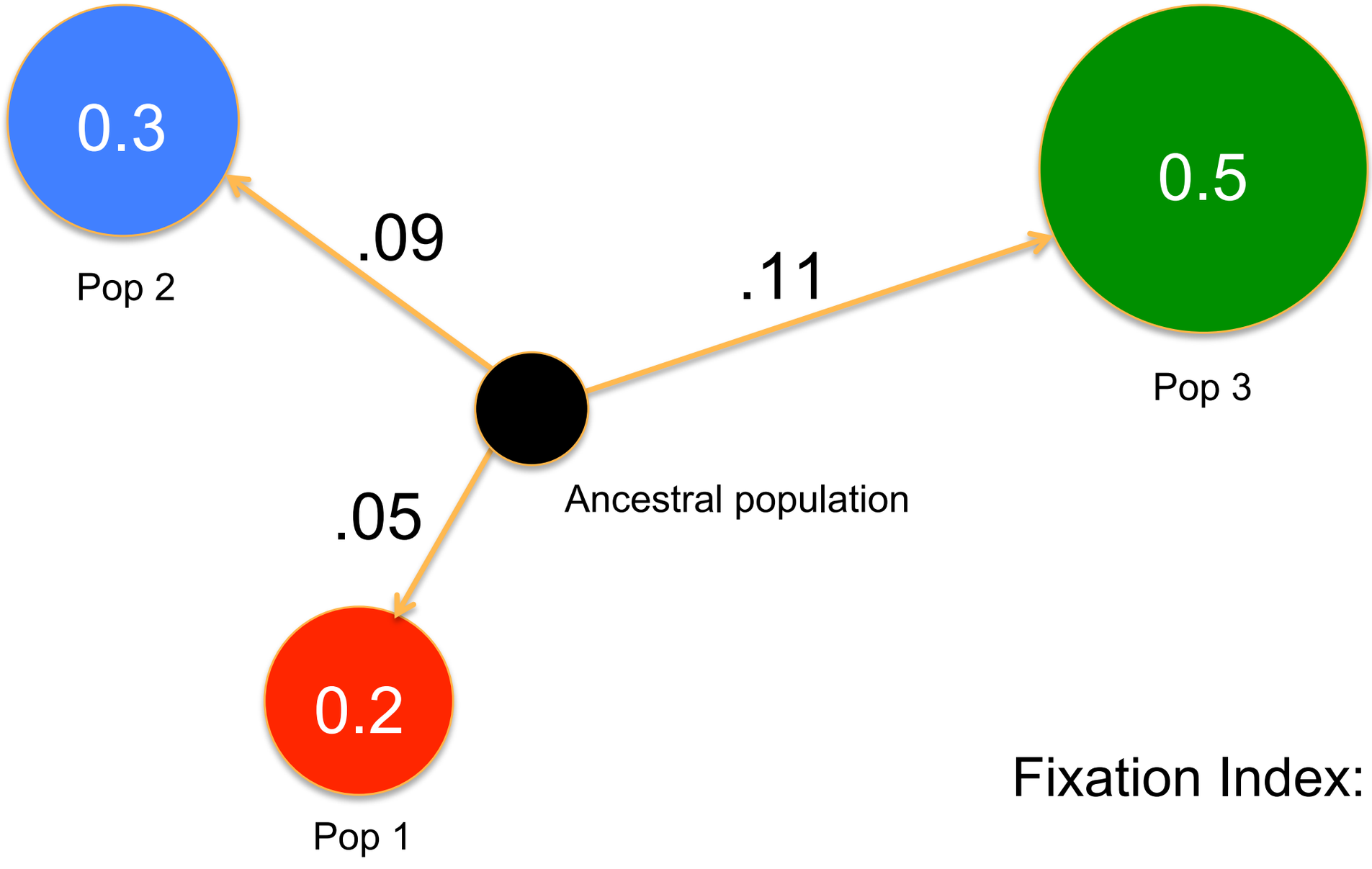
… To Variant Dataset



. . . To Variant Dataset



Balding-Nichols model



Fixation Index: F_{ST}

- K populations, N samples, M variants.
- π is the population distribution of samples
- P_0 is ancestral frequency spectrum (uniform distribution from 0.1 to 0.9)

$$
\begin{aligned}
k_n &\sim \pi \\
p_{0,m} &\sim P_0 \\
p_{k,m} \mid p_{0,m} &\sim \text{Beta}\big(\mu = p_{0,m},\, \sigma^2 = F_k p_{0,m}(1 - p_{0,m})\big) \\
g_{n,m} \mid k_n, p_{k,m} &\sim \text{Binomial}(2, p_{k_n,m}).
\end{aligned}
$$

Outline of Hail Practicals

1. **Importing, schemas, simulated data**
2. The Hail expression language
3. Annotation, query and plotting
4. Aggregables: working with massive data
5. Understanding GQ and DP in sequence data
6. Unmasking ancestry
7. Basic association analysis

Practical 1: What did we learn?

- Hail has its own file format, VDS. Why?
- `VariantDataset`s have three schemas. What are they?
- You can simulate genotypes and phenotypes in Hail.

Simulating data

In [22]:
```
(hc.balding_nichols_model(3, 2000, 2000,
                          pop_dist = [0.2, 0.3, 0.5],
                          fst = [.07, .11, .13])
 .annotate_samples_expr(['sa.cov1 = rnorm(0, 1)',
                         'sa.cov2 = rnorm(0, 1)'])
 .annotate_samples_expr(
        'sa.pheno = rnorm(1, 1) + 2 * sa.cov1 - sa.cov2 + .1 * sa.pop')
 .write('synth.vds', overwrite=True))

synth_vds = hc.read('synth.vds')
```

Hail Expression Language

- Used all over! filtering, export, annotating, calculating, covariates, …
- Syntax a mishmash styles. We apologize in advance.
- Built-in support for missing values: `NA`.
- Expression language. No user-defined functions, no loops.
- Typed language. All **expressions** are statically typed.
- Functional. Modifying makes a copy.

Hail Types

Primitive	**Compound**	**Genetic**
Boolean	Array[T]	Locus
Int	Set[T]	AltAllele
Long	Dict[K, V]	Variant
Float	Struct {	Interval
Double	f1: T1,	IntervalList
String	f2: T2, … }	Genotype
	Aggregable[T]*	

*This is the other most confusing part.

Hail Expression Language

- Don’t confuse the Hail expression language with Python!

- Hail expressions are written as **strings** in Python and passed to Hail python functions.

Hail Expression Language

- To evaluate a Python expression, you enter it in the Python interpreter:

```
In [5]: 1 + 1
Out[5]: 2
```

- To evaluate a Hail expression, you pass it as a string in Python to **`hc.eval_expr_typed`**:

```
In [6]: hc.eval_expr_typed('1 + 1')
Out[6]: (2, Int)
```

Hail Expression Language

- To evaluate a Hail expression, you pass it as a string in Python to `hc.eval_expr_typed`:

```
In [6]: hc.eval_expr_typed('1 + 1')
Out[6]: (2, Int)
```

- What is the return value?

Hail Expression Language

- `[1, 5, 10].filter(x => x < 10)`

- The => syntax describes a unnamed function. **`x`** refers to the elements of the array.

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Practical 2: What did we learn?

- Hail expression syntax is weird an annoying.
- Hail naturally handles missing values like R.
- You can transform **`Array`**s with functional operators map, filter
- You can reduce **`Array`**s with operators like **`max`** and **`mean`**.
- Hail supports **`Struct`**s. You had already seen this before. Where?

Aggregables

- Is that even a word?
- This is the hardest part of Hail. Once you get this, you're golden.
- How do you manipulate datasets that are bigger than one computer?
- How do you understand, say, the distribution of DP in a dataset with 100T genotypes?

Aggregables

- **`Aggregable[T]`** is an unordered, distributed collection of **`T`**.

- **`Aggregable[Int]`** is an distributed collection of **`Int`**s.

- The interface for **`Aggregable`** is modeled **`Array`**

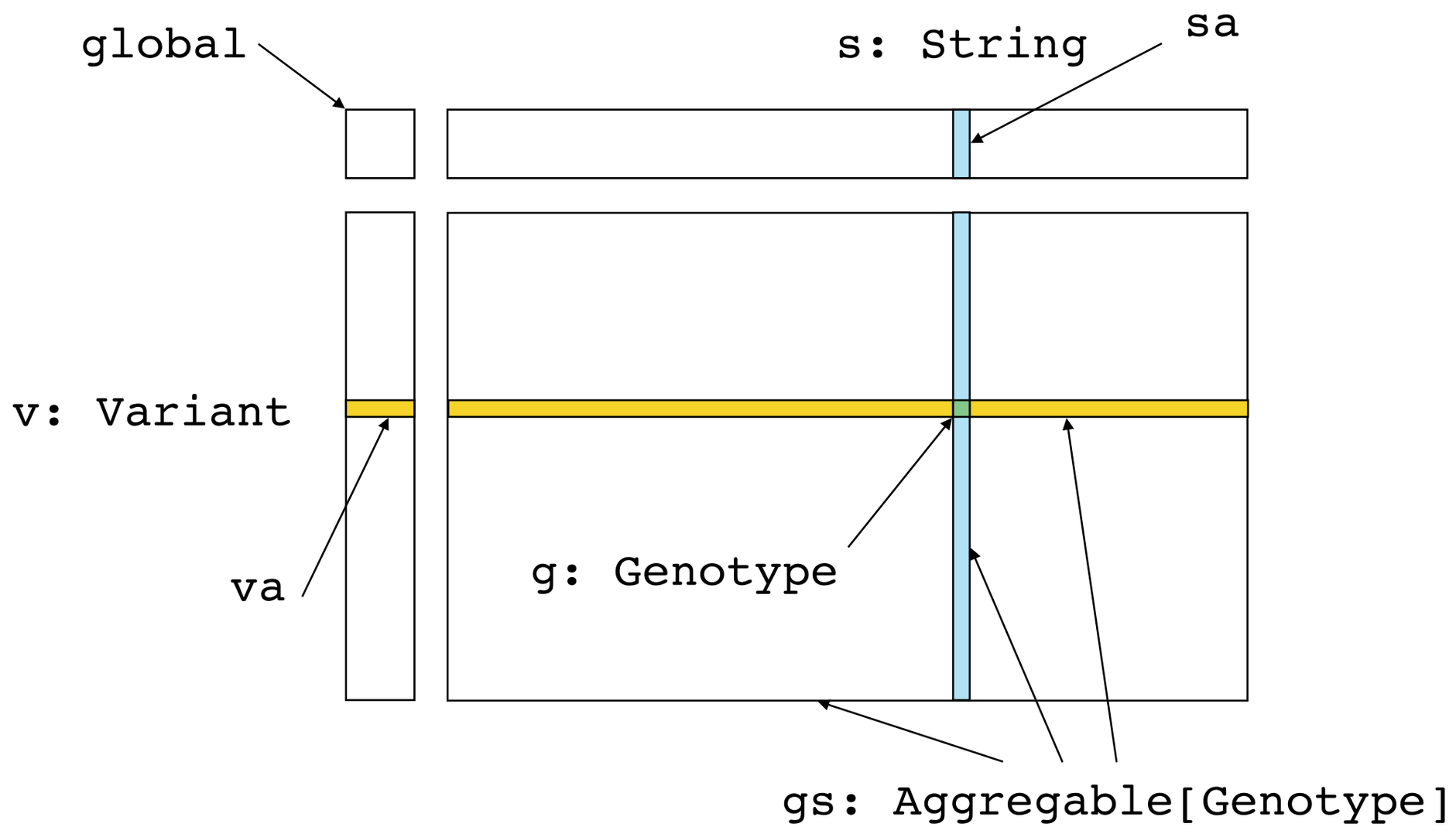
Aggregables

- `gs: Aggregable[Genotype]`
- `gs.map(g => g.dp)` is an `Aggregable[Int]`
- `gs.filter(g => g.gq > 20)` is a (smaller) `Aggregable[Genotype]`
- `gs.map(g => g.dp).max()` is an `Int`
- Reduction perations like **`max`** are called **aggregators**. **`Array`**s and **`Aggregable`**s support a slightly different set of reduction operators.

Aggregable Context

- `Aggregable`s have **contexts**. This is the second way the differ from `Array`s.

VariantDataset



Aggregable Context

- `Aggregable`s have **contexts**. This is the second way the differ from `Array`s.

- `map`, `filter` manipulate aggregable elements, **not** context.

- Examples:

```
gs.map(g => va.callRate)…
(gs.map(g => g.dp)
   .filter(dp => g.gq > 20)…)
```

- Aggregable context documented with the aggregagable. They can all be figured out from the previous diagram.

Genotype Context

- `global`
- `g: Genotype`
- `v: Variant`
- `s: Sample`
- `va`
- `sa`

Variant Context

- `global`
- `v: Variant`
- `va`
- `gs: Aggregable[Genotype]`

Outline of Hail Practicals

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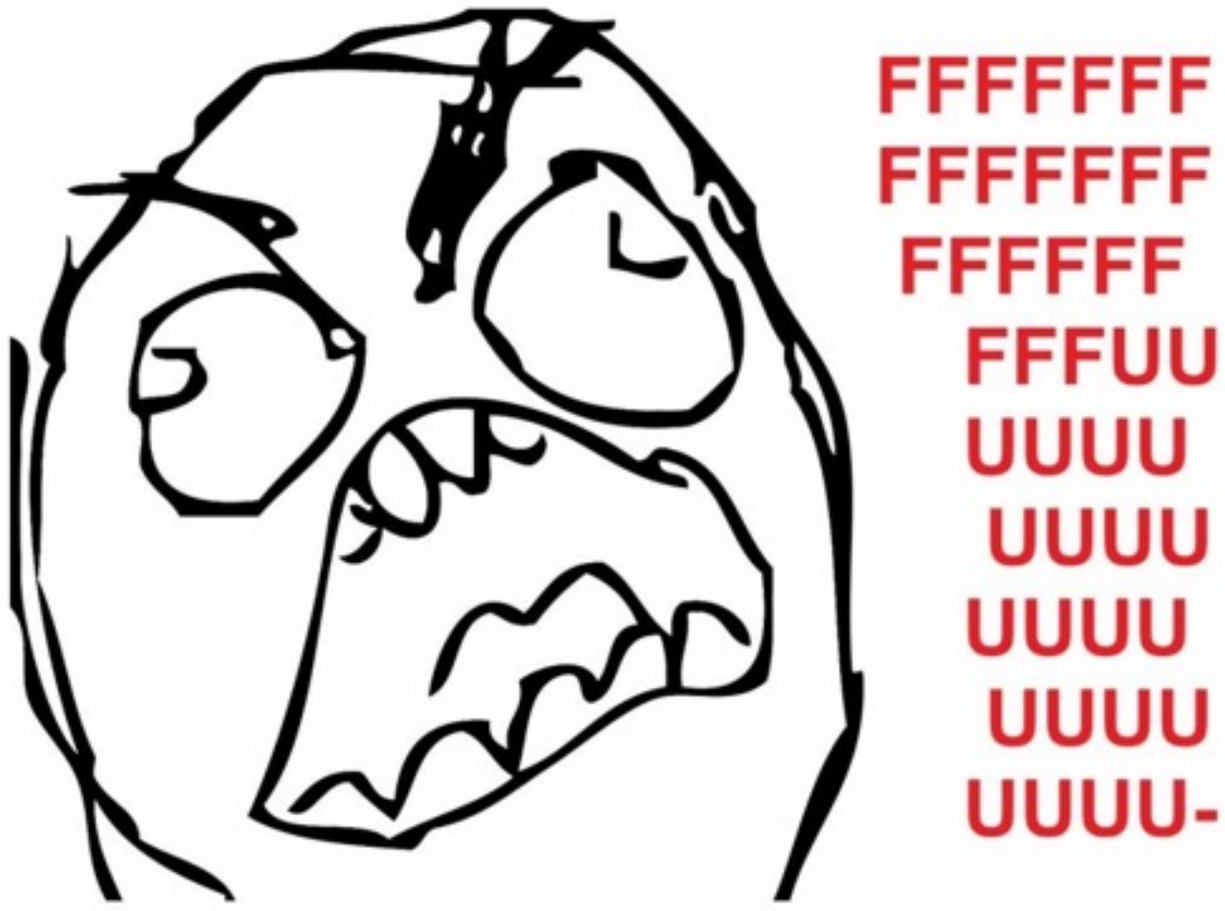
Practical 4: What did we learn?



Practical 4: What did we learn?

- Aggregables are a convenient and elegant way to manipulate large, distributed data objects.

- Aggregables can be manipulated similarly to arrays.

- Aggregables carry a natural context that is not changed by **`map`** and **`filter`**.

filter

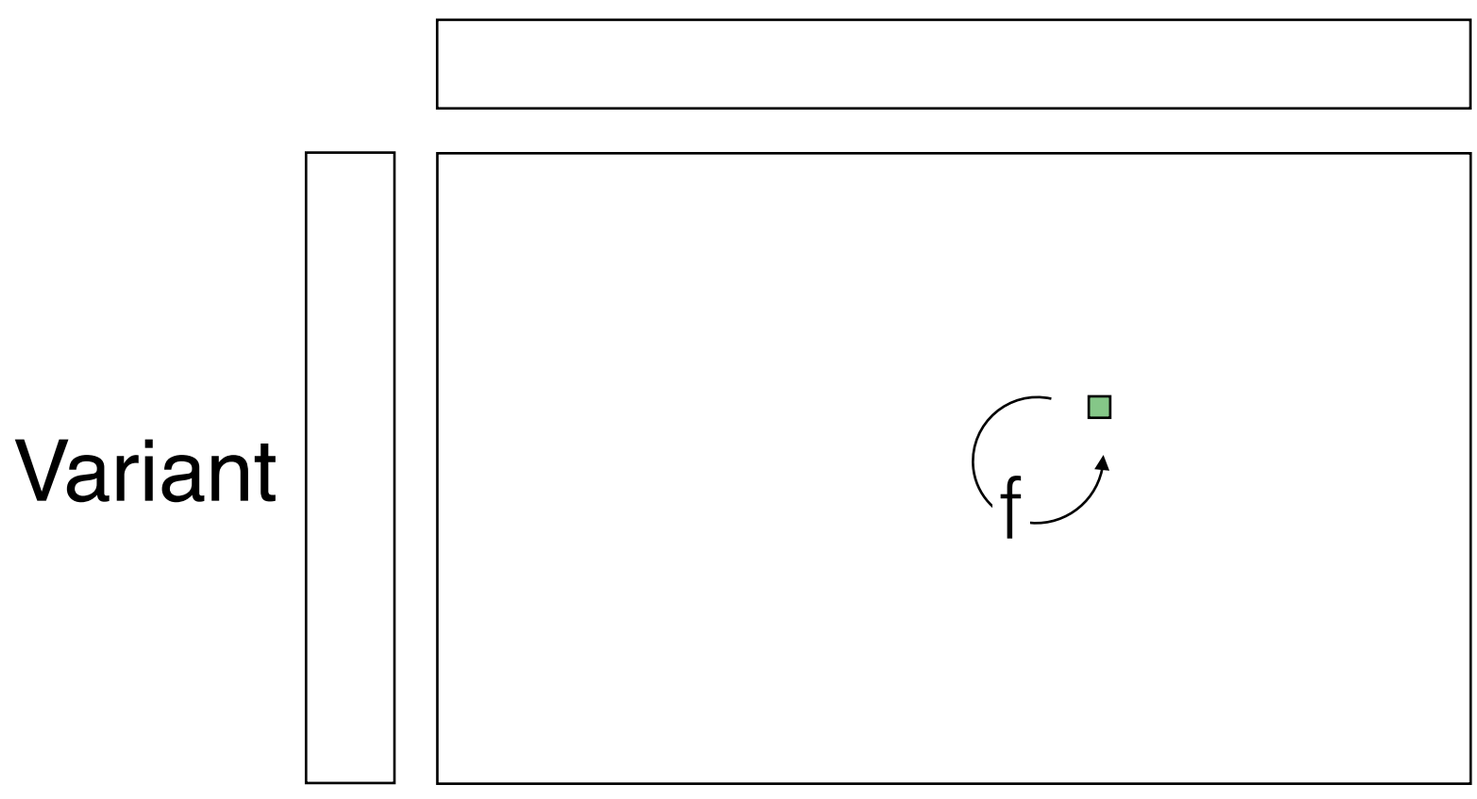
Sample

Variant

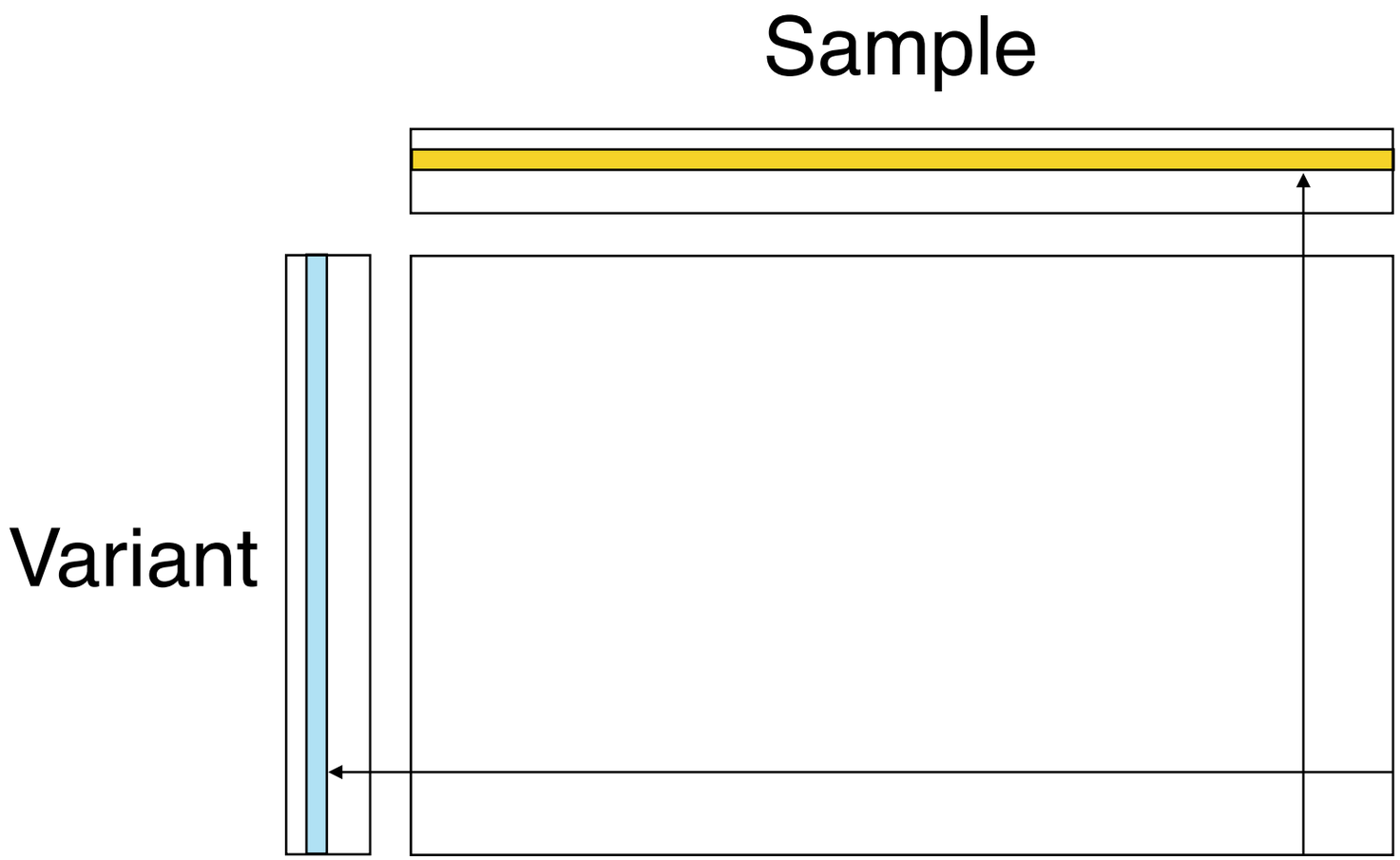
map

Sample

Variant



reduce



join