

# avocado: A Variant Caller, Distributed

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## Background

Three stages in modern DNA processing pipelines:

1. **Sequencing:** Generate 100-250 base pair reads
2. **Alignment:** Align these reads to the reference genome
3. **Variant Calling:** Determine gene variants & genotypes

Variant calling is an interesting area: “Accurate” algorithms are slow and don’t scale (60 hrs/genome), and are inaccurate for high complexity regions (error is  $> 75\%$ ).

### Goals:

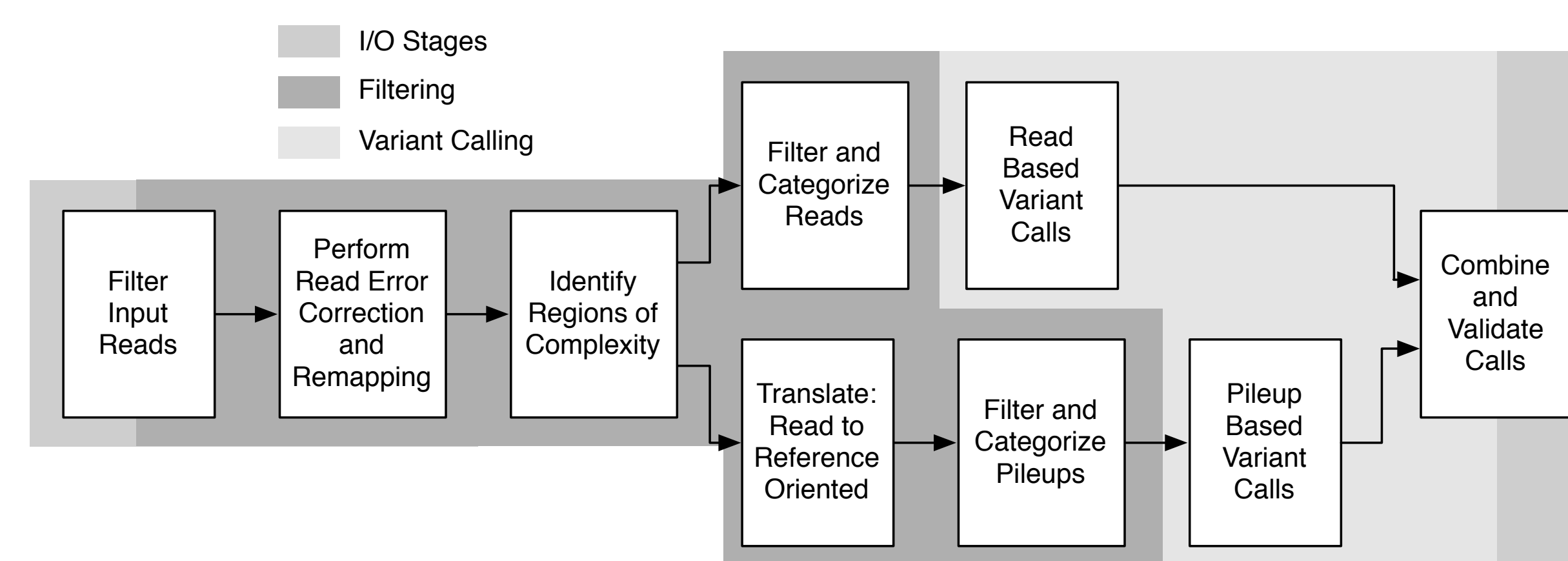
1. Build a variant caller designed for distributed computing
2. Develop an open-source alternative to the GATK

## Pipeline

### Tech Specs:

- Built in Scala on top of Parquet and BDAS Spark
- Leverages new ADAM read/pileup/variant call format
- Scalability well past 30+ nodes; other pipelines are limited to 26 (1/chromosome)

### Pipeline:



### Design Principles:

- Reuse read processing stages from ADAM
- Use mapping quality/coverage as filtering heuristic
- Design is modular: easy to add new calling algorithms

## Performance

## Local Assembly

## Base SNP Calling

For calling SNPs on a single sample, we look at genome loci that show evidence of a SNP (at least one non-reference base). Genotype likelihoods are calculated by:

$$\mathcal{L}(g) = \frac{1}{m^k} \prod_{j=1}^l (m - g)\epsilon + g(1 - \epsilon) \prod_{j=l+1}^k (m - g)(1 - \epsilon) + g\epsilon$$

$m$  = ploidy,  $g$  = genotype state,  $\epsilon$  = likelihood of error,  
 $l$  = bases matching reference,  $k$  = bases at locus

Genotyping is biased towards the reference. We compensate by the allele frequency and call a non-reference genotype if  $g \in (1, 2)$  has the highest probability.

## Sufficient Statistics/Joint Calling

For a few samples, one may look-up the MAF  $\phi$  in a reference and compensate the the single sample likelihood

$$\hat{g} = \arg \max_g \mathcal{L}(g) \mathbf{P}(g|\phi)$$

When many samples are collected it can be desirable to compute a population MAF while performing genotype calling. For each SNP  $a$ , this is done via EM:

$$\phi_{a,t+1} = \frac{1}{M} \sum_{i=1}^N \frac{\sum_{g_i} g_i \mathcal{L}(g_i) \mathbf{P}(g_i|\phi_{a,t})}{\sum_{g_i} \mathcal{L}(g_i) \mathbf{P}(g_i|\phi_{a,t})}$$

$M = \sum_i m_i$  = total number of chromosomes  $N$  = number of individuals