Guidelines on combining genomic data across populations

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Interbull AM, Verona, June 1st, 2026

M3GE project

- **Goal**: Develop multi-breed multi-trait international genomic beef cattle evaluations
- Potential advantages:
  - Improve GEBVs accuracy by including data on (other) purebreed and crossbred
  - Leverage international collaboration for novel traits
  - Involve new (numerically-small and local) breeds (better usage of genetic resources, e.g., transboundary breeds)
  - Deliver GEBVs to breeders for traits not evaluated at national level

3 countries

7 national organizations

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Data collected

- Two trait groups:
  - FEED: Feed + indicator traits
  - LONG: Longevity + indicator traits
- Beef purebred, Crosses (Beef x Beef & Beef x Dairy), Dairy purebred (AI sel. candidates)
- Genotypes:
  - ~3.2M individual (imputed) genotypes
  - medium/high density (+30K SNPs)

Pedigree and (repeated) phenotypes

Genotypes

GENOEX
International Genotype Exchange Platform
International Genotype Exchange platform for Animal Breeding

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Chips available

- 11 chips in total (28k – 777k) from 2 assemblies (UMD 3.1, ARS1.2)
- Different chips for **different breeds**
- Different overlap between chips
- ~815k unique SNPs across all chips & ~160k unique SNPs across 2+ chips
- **~6.5k SNP in common** across all chips

	COU1_chip1*	COU1_chip2*	COU1_chip3	COU1_chip4	COU2_chip1	COU2_chip2	COU2_chip3	COU2_chip4	COU2_chip5	COU3_chip1	COU3_chip2
COU1_chip1*	132,665										
COU1_chip2*	26,952	28,289									
COU1_chip3	60,874	14,812	64,888								
COU1_chip4	37,420	9,582	37,555	42,172							
COU2_chip1	34,670	11,716	23,964	14,091	41,855						
COU2_chip2	37,863	10,491	38,040	37,685	14,745	44,460					
COU2_chip3	39,280	11,016	38,940	38,640	15,154	44,165	48,862				
COU2_chip4	39,280	11,016	38,940	38,640	15,154	44,165	48,862	48,862			
COU2_chip5	37,863	10,491	38,040	37,685	14,745	44,460	44,165	44,165	51,828		
COU3_chip1	37,796	10,511	37,990	37,564	14,689	44,210	43,922	43,922	50,390	50,493	
COU3_chip2	116,260	24,961	60,118	35,716	37,420	38,064	41,877	41,877	38,064	38,065	667,044
Unique SNPs	491	139	44	127	-	-	-	-	1,188	-	535,040

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*Same chip for ITA breeds, LIM&CHA

Genomic data harmonization

Information collected:

- Maps: `SNP name, chr, bp` (`rsID` if available)
- Genotypes: `0/1/2/5` following Illumina AB coding (GenoEX = `A` counts)

To combine genomic data across populations, ensure that:

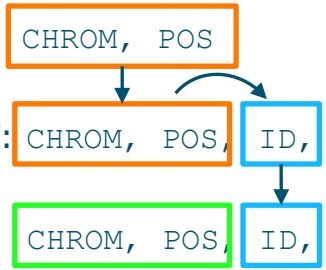
1. Maps are aligned across chips
2. Genotype information is aligned with corresponding map

1. Maps alignment

- Ensure genomic data is on same assembly version (UMD 3.1)
- Program to convert map information between assemblies
- "rs-ID bridging" approach:

	Chip1	Chip2
unmatched in source VCF	2%	8%
unmatched in target VCF	6%	6%
matched in both VCF	93%	86%

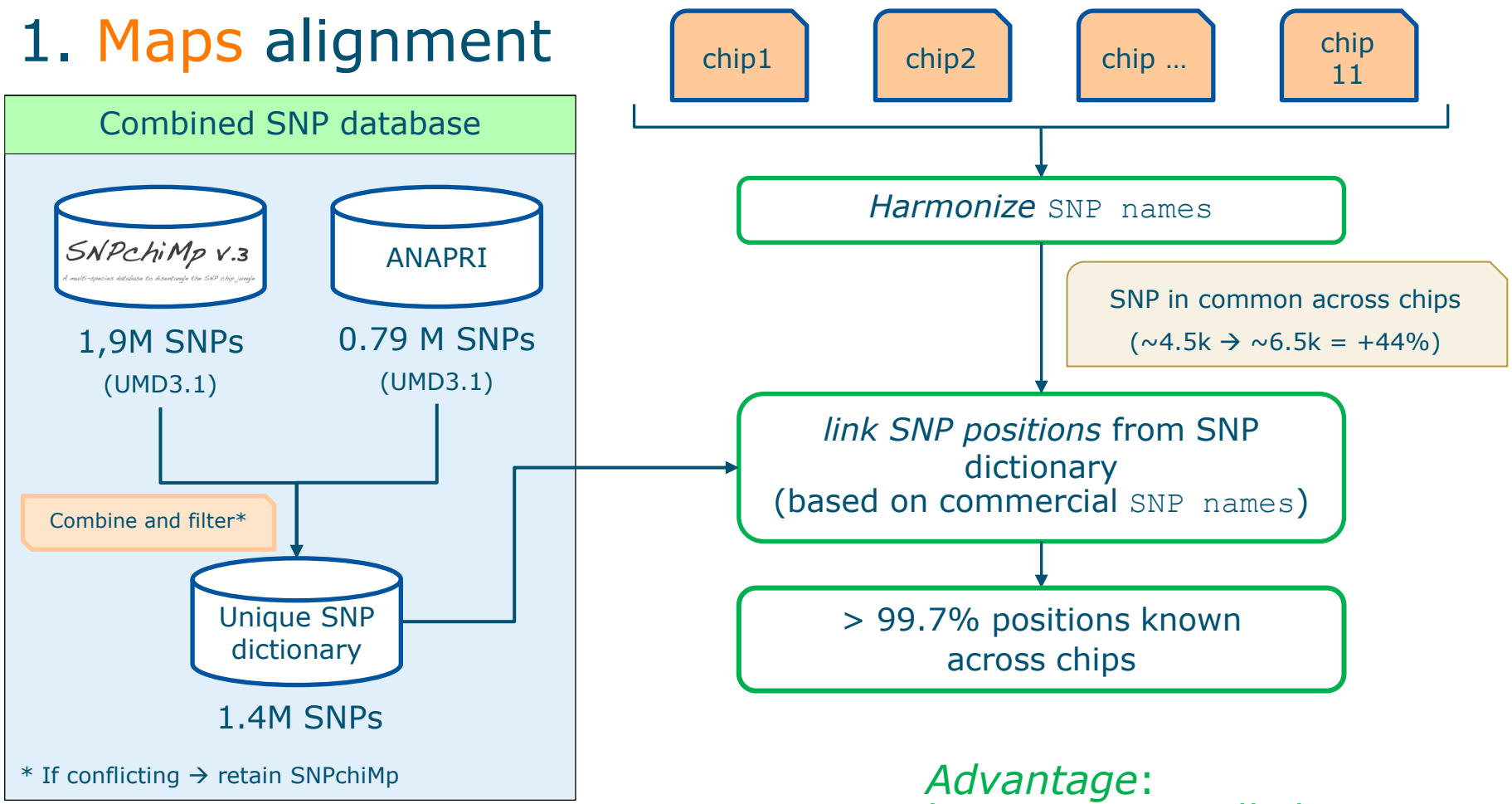
1. Map file: `SNP name, CHROM, POS`
2. Source assembly VCF: `CHROM, POS, ID, REF, ALT, QUAL, FILTER, INFO`
3. Target assembly VCF: `CHROM, POS, ID, REF, ALT, QUAL, FILTER, INFO`



\+ straightforward, fast, flexible, works well for arrays with dbSNP `IDs`

\- relies on `rsID` availability and consistency across assemblies, needs exact position matching (→ liftover approaches)

1. Maps alignment



Advantage:
same coordinates across all chips

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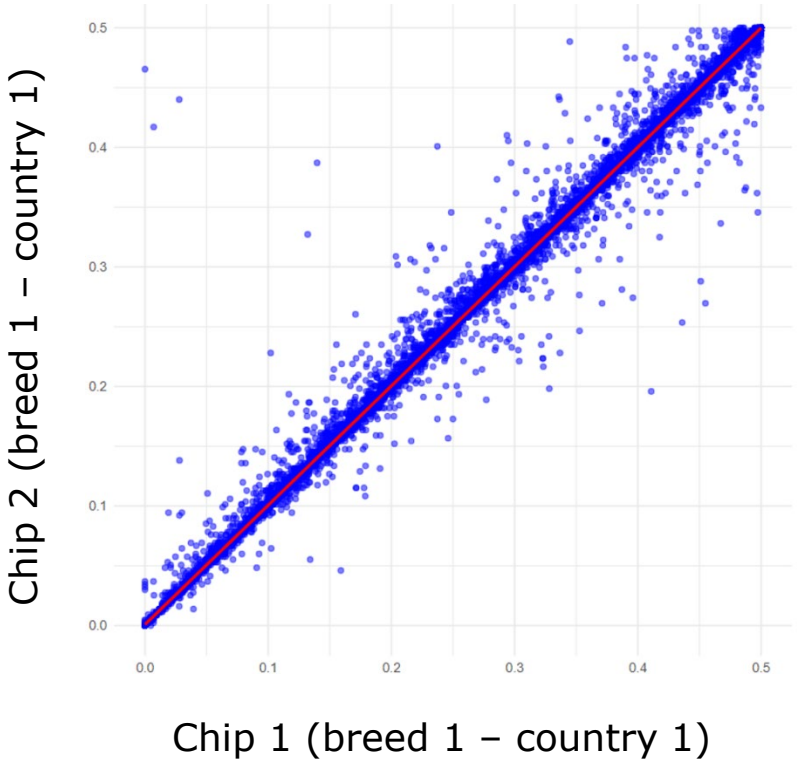
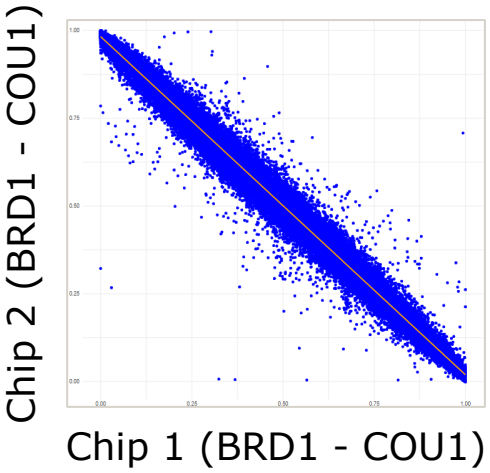
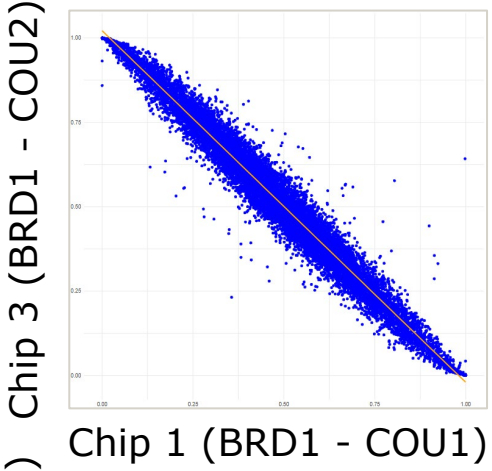
2. Genotype information alignment

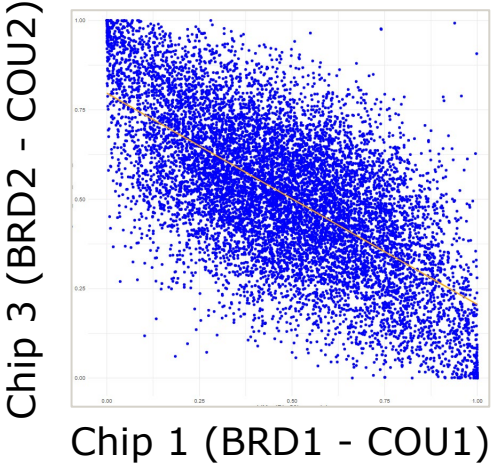
- Validate agreement:
  - between genotypes and corresponding map information
  - allele coding across chips
- Allele frequencies as a diagnostic tool
- Comparing chips (overlapping SNPs), two levels:
  - Within-breed within-country (possibly same animals), within-breed across-country
  - Across-breed across-country (more noisy but still useful)

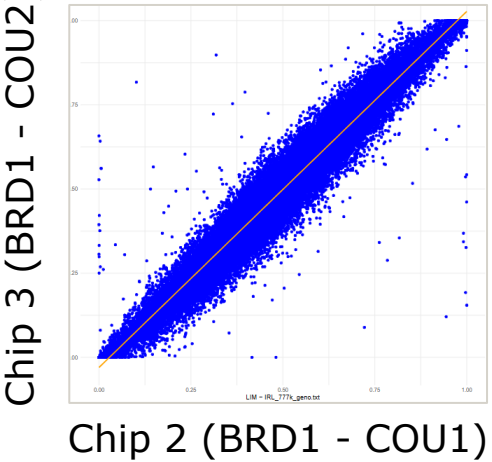


Examples of detected misalignments



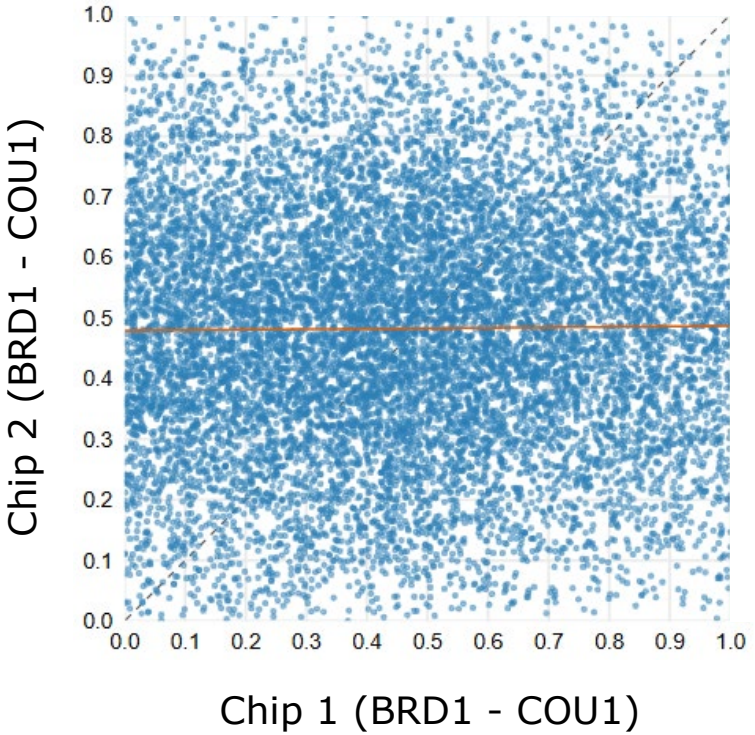






Allele coding switch in chip 1

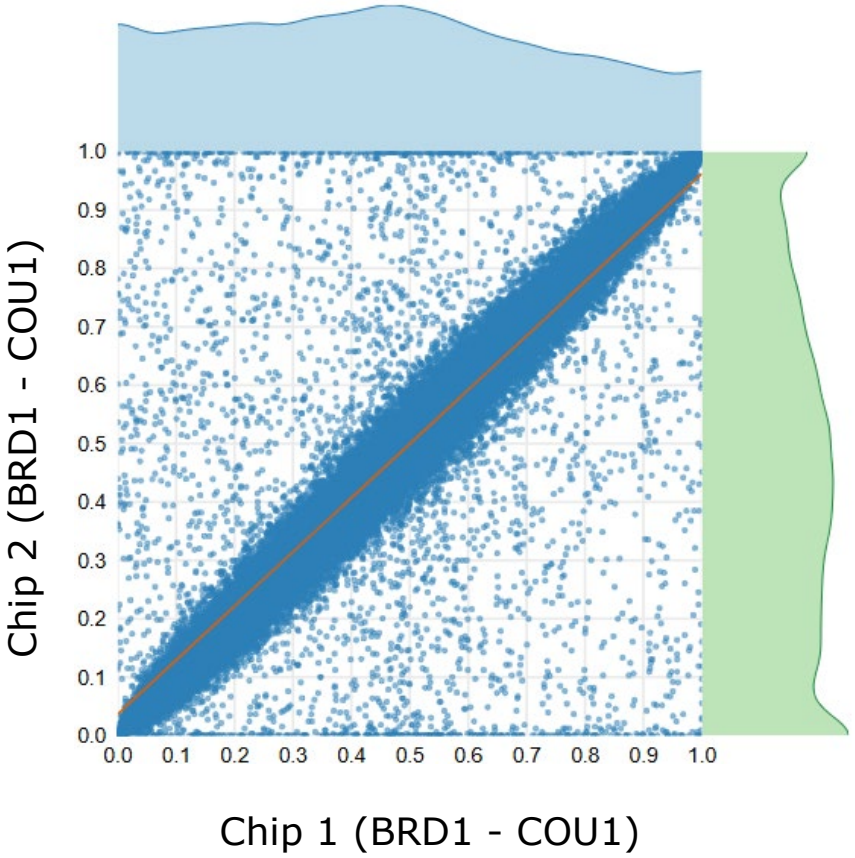
Examples of detected misalignments



Misaligned chip 2

ρ = 0.01
RMSE = 0.34

Examples of detected misalignments



Shift of +1 on SNP position

ρ = 0.90
RMSE = 0.12

Guidelines and recommendations

1. **Maps alignment**
   - Use public resources when possible (SNPchiMp)
   - Store `rsID` and assembly version
   - Keep complete manifest files (older chips not in public domain)
   - Add support for metadata to GenoEX (`rsID`, assembly version, manifest)

2. **Genotypes alignment**
   - Use consistent Illumina AB coding
   - Use AF checks as a diagnostic tool
   - Automated AF checks (ρ and RMSE) → detect issues on submission
   - "Already-approved" genotypes as reference

Implications

Unravelling the Genetic Structure of Local and Mainstream Red-Pied Cattle Breeds Using Genomics and Extended Pedigree Analysis

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- At international level
  - Projects needing collaboration (e.g., M3GE)
  - International evaluations (e.g., InterGenomics, SNP-MACE)
  - Studies across countries/organizations
  - Genotype exchange (e.g., GenoEX) for genomic evaluations or parentage analysis
- Public resources are of great help (SNPchiMp; Schnabel 2018) but are phasing out or incomplete
  - Need for new and updated tools → Let's talk!

Take-home messages

- Pooling and aligning genomic data can be challenging and prone to mistakes
- Guidelines and recommendations to avoid pitfalls
- AF diagnostic for quality control
- Public resources useful but phasing out

Thank you for your attention

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