

Genomic relatedness strengthens genetic connectedness across management units

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Introduction

"Genetic Connectedness"

- In animal breeding, it refers to a measure of genetic relatedness across management units (e.g., herds and flocks).
- Best linear unbiased prediction (BLUP): genetic links or relatedness

Objective:

- Assess measures of genetic connectedness across management units with use of genomic information.

Prediction Error Variance (PEV)

Inverse of MME coefficient matrix:

$$\begin{aligned}\mathbf{C}^{-1} &= \begin{bmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}'\mathbf{Z} \\ \mathbf{Z}'\mathbf{X} & \mathbf{Z}'\mathbf{Z} + \mathbf{K}^{-1}\lambda \end{bmatrix}^{-1} \\ &= \begin{bmatrix} \mathbf{C}^{11} & \mathbf{C}^{12} \\ \mathbf{C}^{21} & \mathbf{C}^{22} \end{bmatrix}\end{aligned}$$

$$\begin{aligned}\text{PEV}(\hat{u}) &= (\mathbf{Z}'\mathbf{M}\mathbf{Z} + \mathbf{K}^{-1}\lambda)^{-1}\sigma_e^2 \\ &= \mathbf{C}^{22}\sigma_e^2\end{aligned}$$

where \mathbf{M} is the absorption matrix given by

$$\mathbf{M} = \mathbf{I} - \mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'$$

Statistics of Pairwise Genetic Connectedness

Prediction error variance of the difference (**PEVD_{ij}**)

$$\begin{aligned}\text{PEVD}(\hat{u}_i - \hat{u}_j) &= [\text{PEV}(\hat{u}_i) + \text{PEV}(\hat{u}_j) - 2\text{PEC}(\hat{u}_i, \hat{u}_j)] \\ &= (\mathbf{C}_{ii}^{22} - \mathbf{C}_{ji}^{22} - \mathbf{C}_{ij}^{22} + \mathbf{C}_{jj}^{22})\sigma_\epsilon^2 \\ &= (\mathbf{C}_{ii}^{22} + \mathbf{C}_{jj}^{22} - 2\mathbf{C}_{ij}^{22})\sigma_\epsilon^2,\end{aligned}$$

Coefficient of determination (**CD_{ij}**)

$$\text{CD}_{ij} = 1 - \lambda \frac{\mathbf{C}_{ii}^{22} + \mathbf{C}_{jj}^{22} - 2\mathbf{C}_{ij}^{22}}{\mathbf{K}_{ii} + \mathbf{K}_{jj} - 2\mathbf{K}_{ij}}.$$

Prediction error correlation (**r_{ij}**)

$$r_{ij} = \frac{\text{PEC}(\hat{u}_i, \hat{u}_j)}{\sqrt{\text{PEV}(\hat{u}_i)\text{PEV}(\hat{u}_j)}}.$$

Choice of K

- **Numerator Relationship Matrix (A)** : $a_{ij} = 1 + F_i$; a_{ij} is equal to twice the kinship coefficient between animal i and j
- **Genomic Relationship Matrix (G)** : $\mathbf{G} = \frac{\mathbf{Z}\mathbf{Z}'}{m}$, where
$$\mathbf{Z}_{\cdot j} = \frac{z_{\cdot j} - 2p_j}{\sqrt{2p_j(1-p_j)}}$$
- $\mathbf{G}_{0.5}$: MAF(p_j) in based generation is treated as 0.5
- **Scaled G matrix (Gs)** : $\mathbf{G}_{sij} = \frac{(\mathbf{G}_{smax} - \mathbf{G}_{smin})(\mathbf{G}_{ij} - \mathbf{G}_{min})}{\mathbf{G}_{max} - \mathbf{G}_{min}}$
- **H matrix:**

$$\begin{bmatrix} \mathbf{A}_{11} + \mathbf{A}_{12}\mathbf{G}\mathbf{A}_{22}^{-1}(\mathbf{G} - \mathbf{A}_{22})\mathbf{A}_{22}^{-1}\mathbf{A}_{21} & \mathbf{A}_{12}\mathbf{A}_{22}^{-1}\mathbf{G} \\ \mathbf{G}\mathbf{A}_{22}^{-1}\mathbf{A}_{21} & \mathbf{G} \end{bmatrix}$$

Materials

Mice Data:

- public real data from Wellcome Trust Centre for Human Genetics
- **1,814** individuals, **10,346** markers and **523** cages

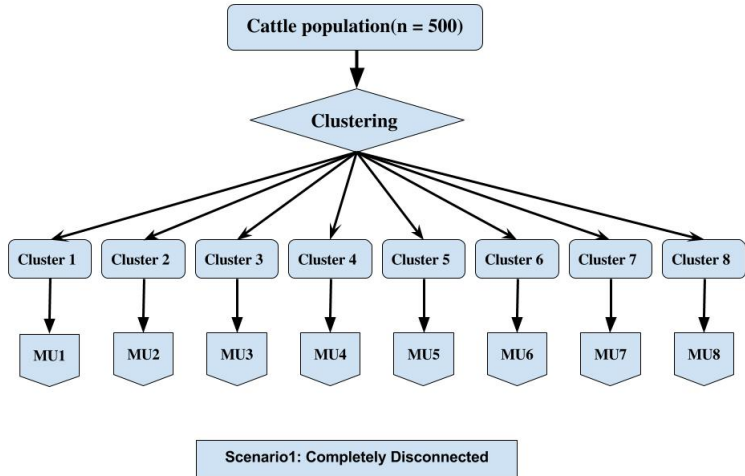
Cattle Data:

- real data coupled with simulated management units , publicly available in the synbreed R package
- **500** individuals and **7,250** markers
- simulated management units from **8** clusters (K-medoid and average silhouette width algorithm)

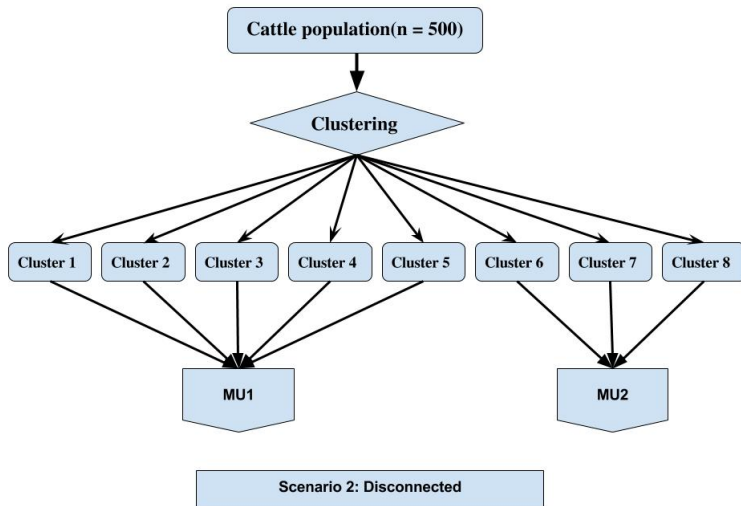
Average genetic connectedness measures across management units in the mice data

Methods	Kernels	Heritability (h^2)	
		0.8	0.2
PEVD	A	1.299	1.331
	G	0.456	1.037
	G_{0.5}	0.374	0.824
	G_s	0.532	1.254
CD	A	0.034	0.009
	G	0.662	0.234
	G_{0.5}	0.640	0.207
	G_s	0.690	0.270
r_{ij}	A	0.004	0.003
	G	-0.001	-0.001
	G_{0.5}	0.559	0.433
	G_s	0.496	0.270

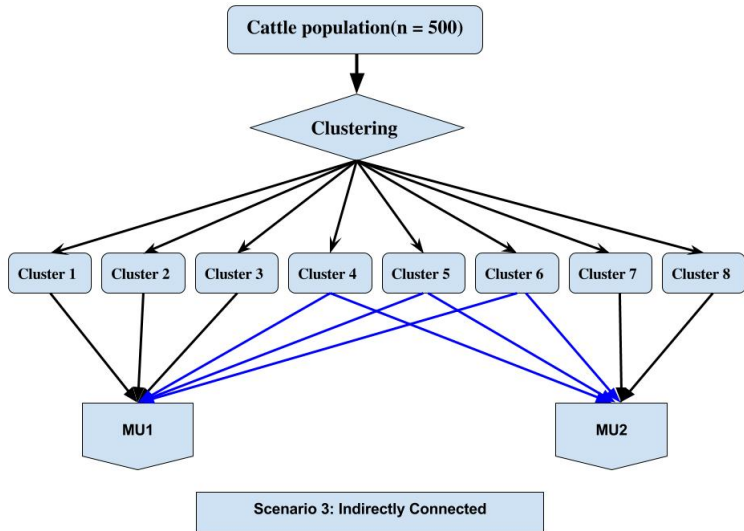
Cattle Management Units Simulation -Scenario 1



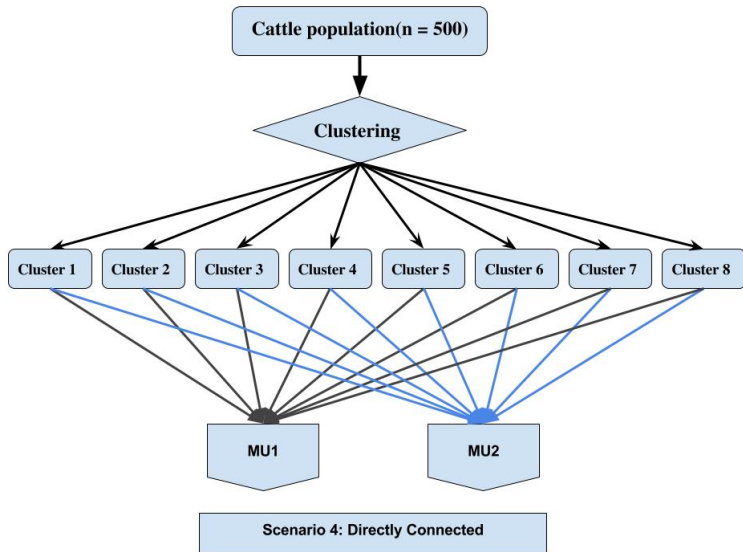
Cattle Management Units Simulation -Scenario 2



Cattle Management Units Simulation -Scenario 3



Cattle Management Units Simulation -Scenario 4

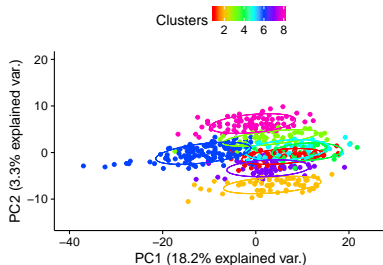
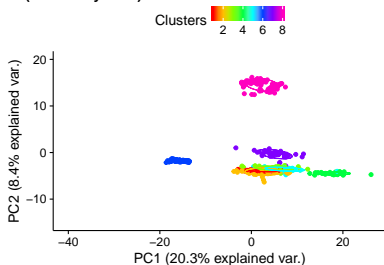


Average genetic connectedness across management units for cattle data

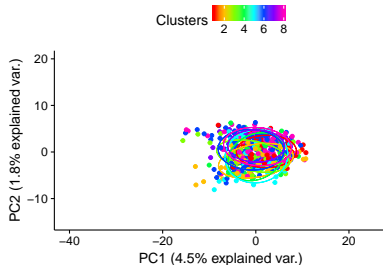
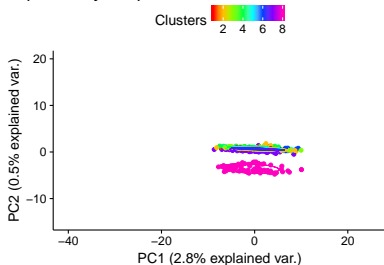
Scenarios	Methods	Kernels	Heritability (h^2)	
			0.8	0.2
S1	PEVD	A	0.077	0.102
		G	0.051	0.085
		G_{0.5} (G_s)	0.039 (0.066)	0.066 (0.110)
	CD	A	0.324	0.112
		G	0.539	0.224
		G_{0.5} (G_s)	0.528 (0.558)	0.195 (0.265)
	r_{ij}	A	0.017	0.005
		G	-0.014	-0.007
		G_{0.5} (G_s)	0.725 (0.468)	0.465 (0.174)
S4	PEVD	A	0.007	0.007
		G	0.005	0.007
		G_{0.5} (G_s)	0.004 (0.007)	0.005 (0.009)
	CD	A	0.125	0.048
		G	0.367	0.132
		G_{0.5} (G_s)	0.362 (0.384)	0.114 (0.158)
	r_{ij}	A	0.024	0.008
		G	-0.007	-0.002
		G_{0.5} (G_s)	0.741 (0.502)	0.470 (0.181)

Principle Component Analysis for CD

SC1 (heritability = 0.8)

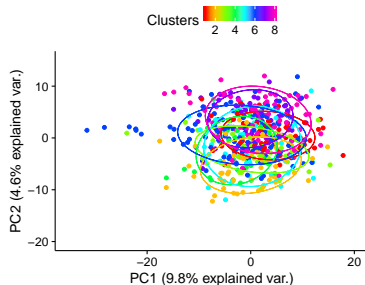
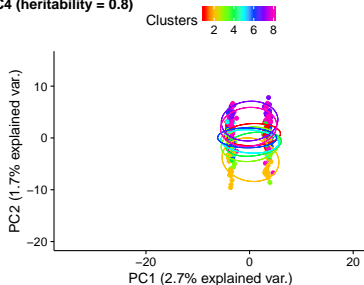


SC1 (heritability = 0.2)

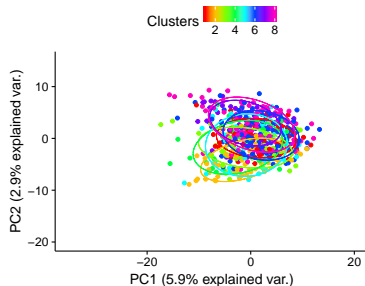
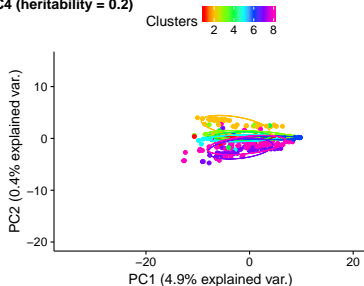


Principle Component Analysis for CD

SC4 (heritability = 0.8)



SC4 (heritability = 0.2)



Conclusion

- Genomic relatedness strengthens measures of genetic connectedness across management units compared to use of pedigree information.
- Coefficient of determination (R^2) yields consistent measures of connectedness.
- Genomics provides relationships between units that appear disconnected according to the pedigree (independence assumption at baseline population)

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