Clustering Algorithms

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ELIXIR-IIB – Population Genomics: background and tools
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Introduction

- this lecture/practical will cover *clustering algorithms*
- these classify individuals based on genetic similarity, so that interesting patterns emerge
- we will use SNP data, though some programs (e.g. *STRUCTURE*) should cope with microsatellites

Outline

STRUCTURE/ADMIXTURE/FRAPPE

CHROMOPAINTER/fineSTRUCTURE

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CHROMOPAINTER/fineSTRUCTURE

STRUCTURE (Pritchard et al 2000, *Genetics* **155**:945)

- **Aim:** classify individuals into K clusters based on genetic similarity
- let $\{S_{i1}, ..., S_{iL}\}$ be genetic data at locus l (L total loci) for ind i (note: $\times 2$ for diploids)
- assume individual i is assigned to cluster k
- then $\Pr(S_{il} = j) = p_{kjl}$, where p_{kjl} is frequency of allele j at locus l in cluster k

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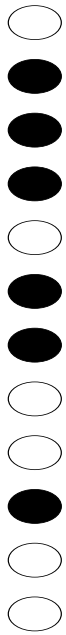
- then $\Pr(S_{il} = j) = p_{kjl}$, where p_{kjl} is frequency of allele j at locus l in cluster k
- can infer p_{kjl}'s and cluster assignments of each ind by:
  A. start with random assignment of inds to clusters 1,...,K
  B. infer each p_{kjl} by using freq(j) at locus l among inds currently assigned to cluster k
  C. test how well (probability) each ind in k fits the inferred p_{kjl} from (B); if bad fit $\rightarrow$ move ind to different cluster
  D. repeat (B)-(C) using Markov-Chain-Monte-Carlo (MCMC)

STRUCTURE (Pritchard et al 2000, *Genetics* **155**:945)

1-SNP Example: classify 12 (haploid) individuals into $K = 2$ clusters:



A. start with random assignment of inds to clusters 1 and 2
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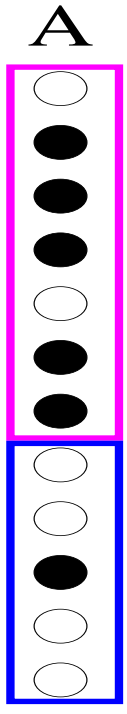

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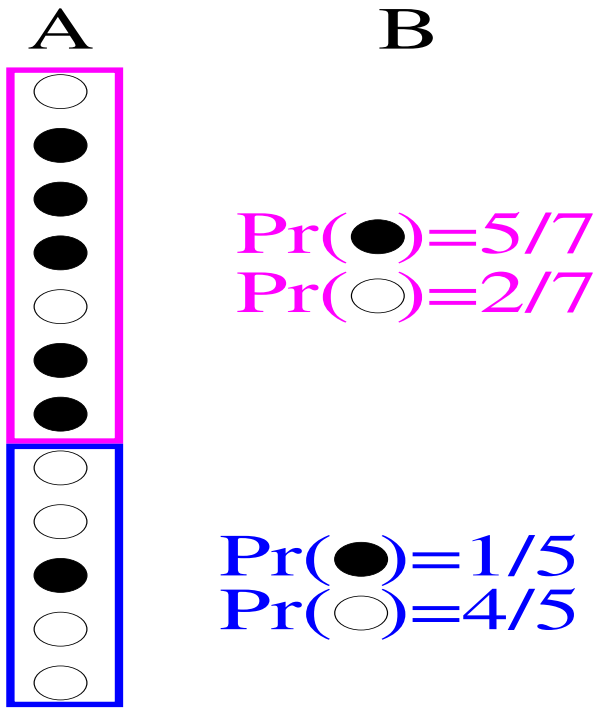

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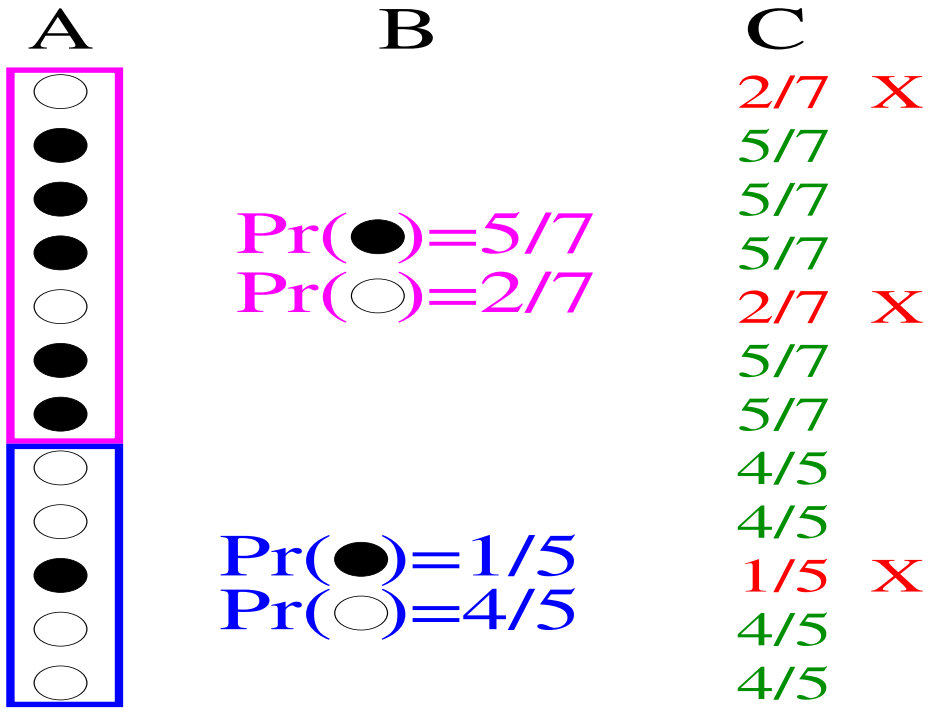

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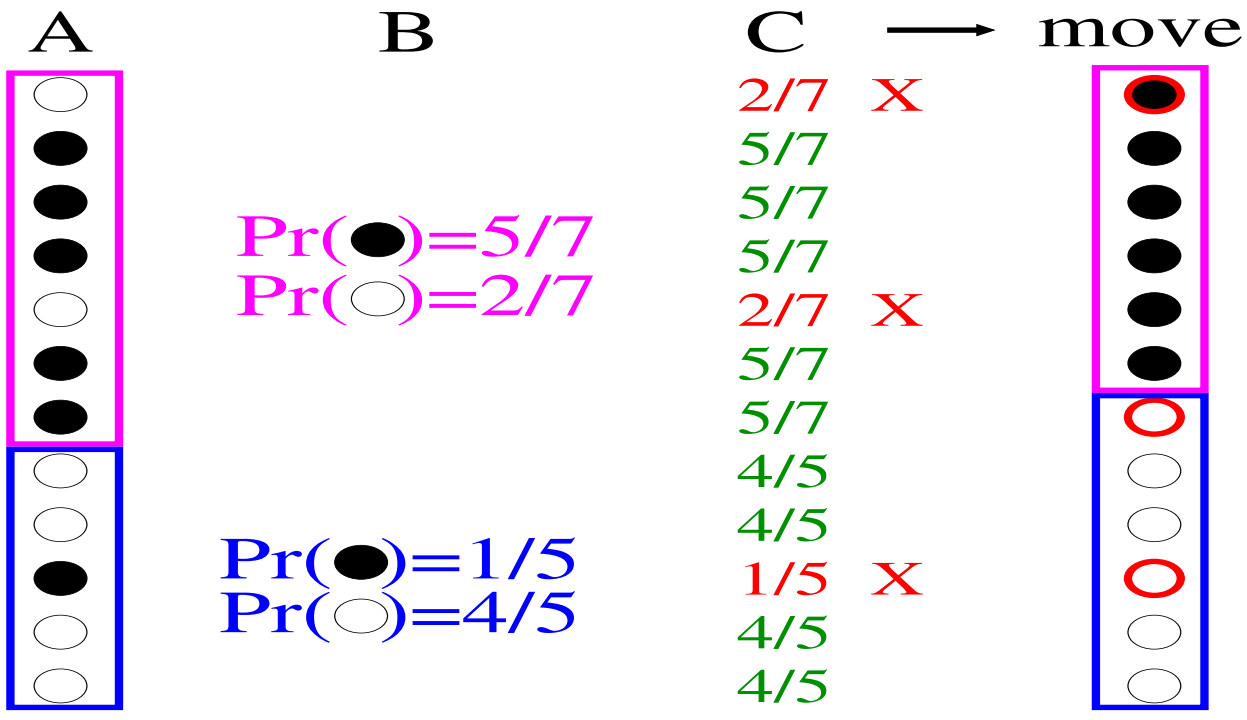

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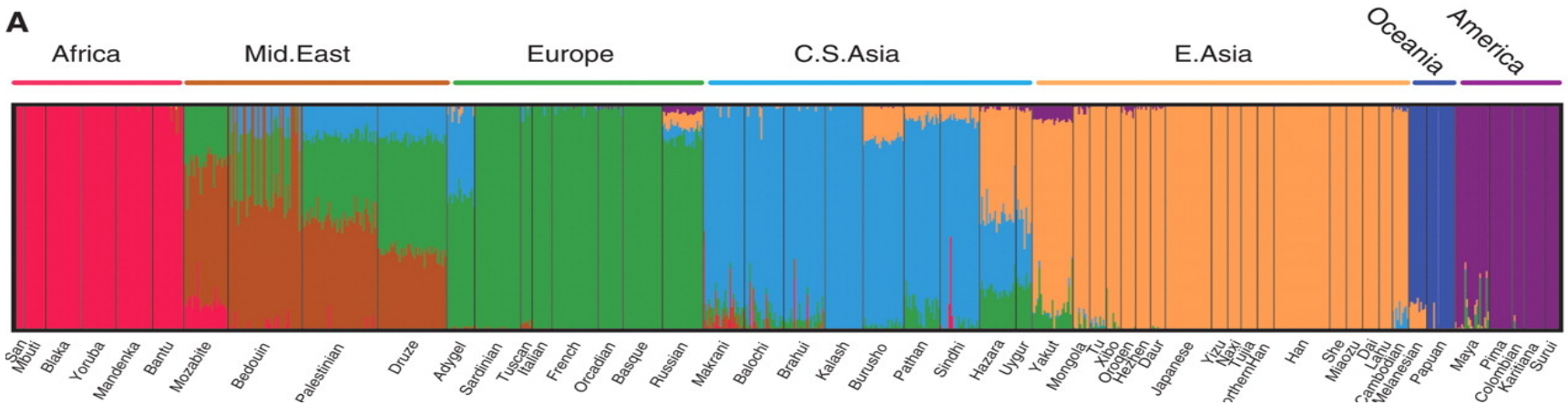
STRUCTURE (Pritchard et al 2000, *Genetics* **155**:945)

- There are different, much faster variants of *STRUCTURE*, which maximize the likelihood rather than sampling via MCMC:
  1. *FRAPPE* (Tang et al 2005, *Am J Hum Genet* **79**:1) – maximize likelihood using Expectation-Maximization (E-M)
  2. *ADMIXTURE* (Alexander et al 2009, *Genome Research* **19**:1655) – maximize likelihood using high-dimensional optimisation



example of *FRAPPE* on HGDP (Li et al 2008, *Science* **319**:1100)

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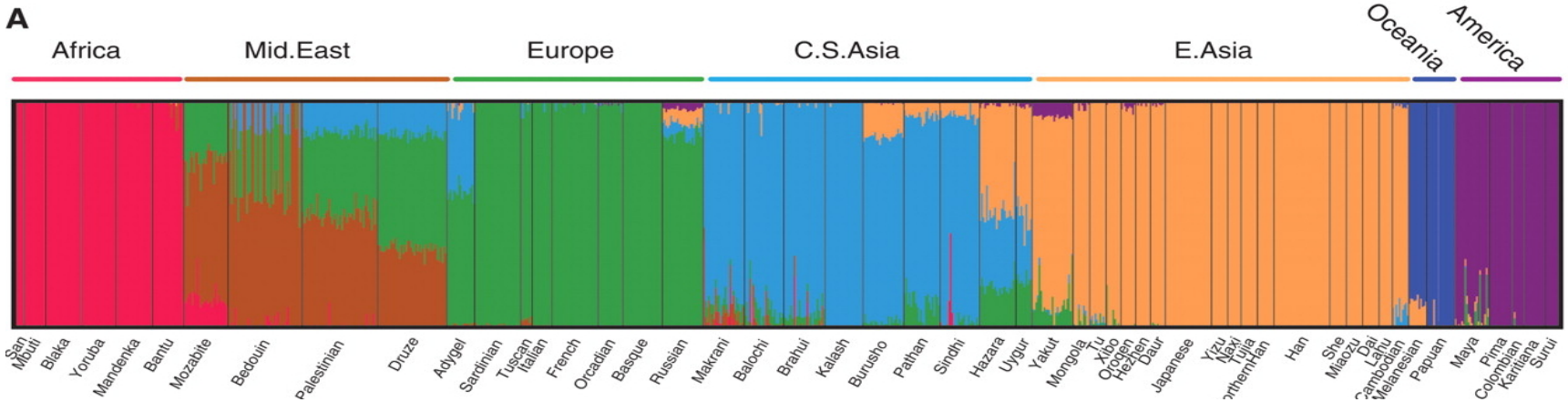
- There are different flavors of *STRUCTURE*:
  - *"no admixure model"* – assign each ind *i* to single cluster *k*
  - *"admixure model"* – assign each ind to multiple clusters (i.e. infer % of ind *i*'s genome assigned to clusters 1, ..., *K*)
  - *"linkage model"* – can identify regions of ind *i* assigned to each cluster (Falush et al 2003, *Genetics* **164**:1567)



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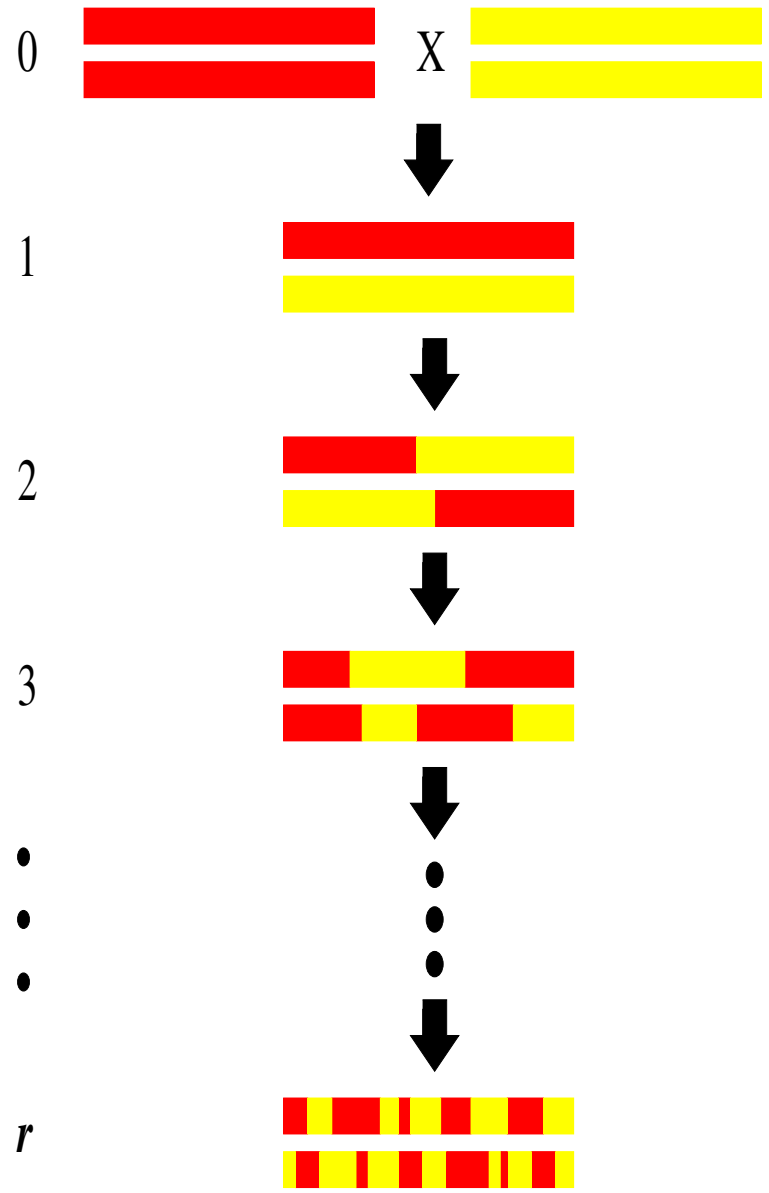
“linkage model” STRUCTURE – motivation

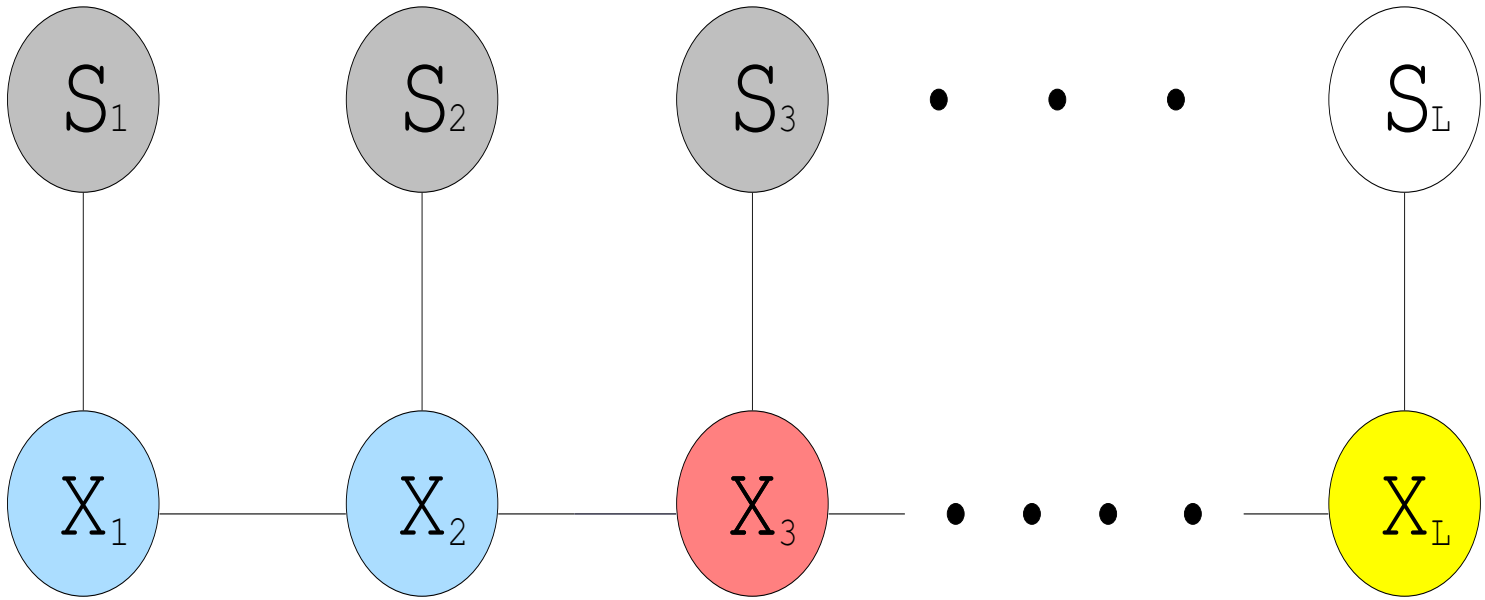
- two populations (**red**,**yellow**) admix *r* generations ago, followed by random mating
- genetic pieces from each population get smaller each subsequent generation due to recombination
- assuming no crossover interference, boundaries between contiguous **red** and **yellow** segments (from ancestor at time of admixture) in present-day DNA form a Poisson process with rate *r* per Morgan

(Falush et al 2003, *Genetics* **164**:1567)



“linkage model” STRUCTURE – Hidden Markov Model (HMM)

- S_l = (observed state) SNP data at locus l of haploid i
- X_l = (hidden state) cluster 1,...,k assignment at SNP l



- each cluster is depicted with a unique color here
- assume “switches” in cluster assignment occur as a Poisson process of rate $\propto r$, the “time since admixture”
- “switches” also depend on genetic distance (cM) between SNPs

"linkage model" STRUCTURE (Falush et al 2003, *Genetics* **164**:1567)

Some mathematical details of "linkage model" STRUCTURE:

- models $\Pr(x_{l+1}^{(i)})$, the probability that haploid i is assigned to cluster k at SNPs$(l+1)$, as:

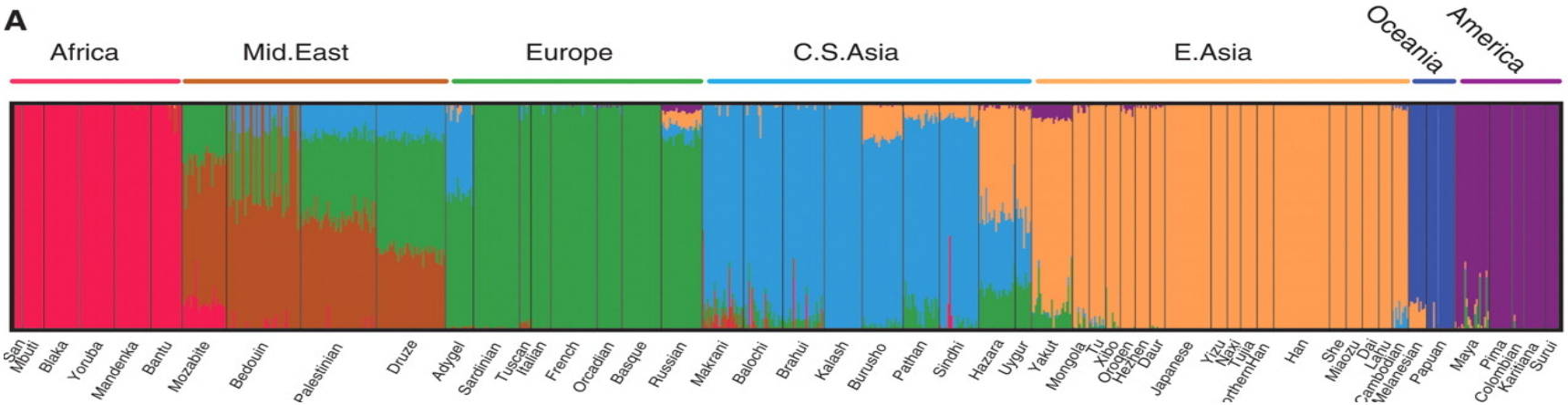
$$\Pr(x_{l+1}^{(i)} = k \mid x_l^{(i)} = k') = \begin{cases} \exp(-d_l r) + \Big(1 - \exp(-d_l r)\Big) q_k^{(i)} & \text{if } k = k' \\ \Big(1 - \exp(-d_l r)\Big) q_k^{(i)} & \text{otherwise} \end{cases}$$

$$\Pr(s_{l+1}^{(i)} = a \mid x_{l+1}^{(i)} = k) = \Pr(\text{cluster } k \text{ carries allele } a \text{ at site } l+1) \equiv P_{(l+1)a}^{(k)}$$

- where $s^{(i)}$ = data, d_l = genetic distance btwn l and $l+1$, r = "time since admixture"
- estimate $\Pr(x_l^{(i)})$ and $q_k^{(i)}$, for fixed number of clusters K using MCMC

STRUCTURE (Pritchard et al 2000, *Genetics* **155**:945), etc

- **Advantages:**
  - *ADMIXTURE, FRAPPE* are computationally fast
  - find clear structure in data (e.g. separate continents)
  - can detect admixture (e.g. **Europe** in **Maya** from Mexico)



example of *FRAPPE* on HGDP (Li et al 2008, *Science* **319**:1100)

- **Disadvantages:**
  - how to interpret results? Drift/admixture/other can result in similar signals
  - genetic loci (e.g. SNPs) assumed independent
  - *K* is fixed (though see *STRUCTURAMA* – (Huelsenbeck & Andolfatto 2007, *Genetics* **175**:1787))

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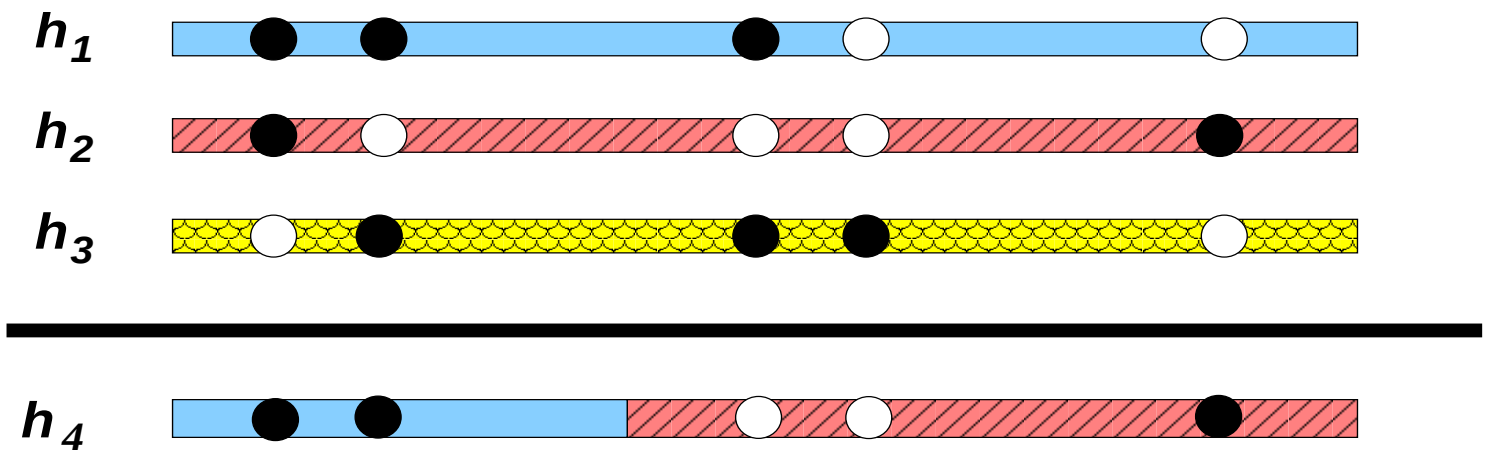
CHROMOPAINTER/fineSTRUCTURE

Incorporating haplotype information: chromosome painting (Lawson et al 2012, *PLoS Genet* **8**:e1002453)



- use some sampled chromosomes (e.g. h_1, h_2, h_3) as "donors"
- match (or "paint") other chromosomes (e.g. h_4) to donors' DNA
- $\longrightarrow$ cluster based on who shares many **blocks of SNPs** rather than who shares similar **SNP frequencies**

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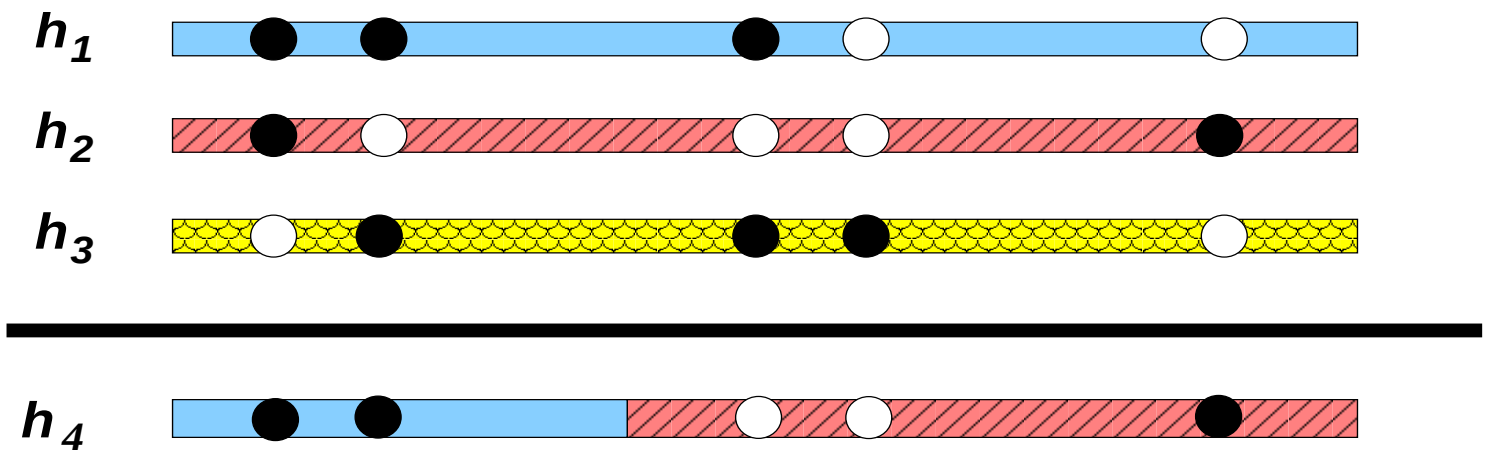

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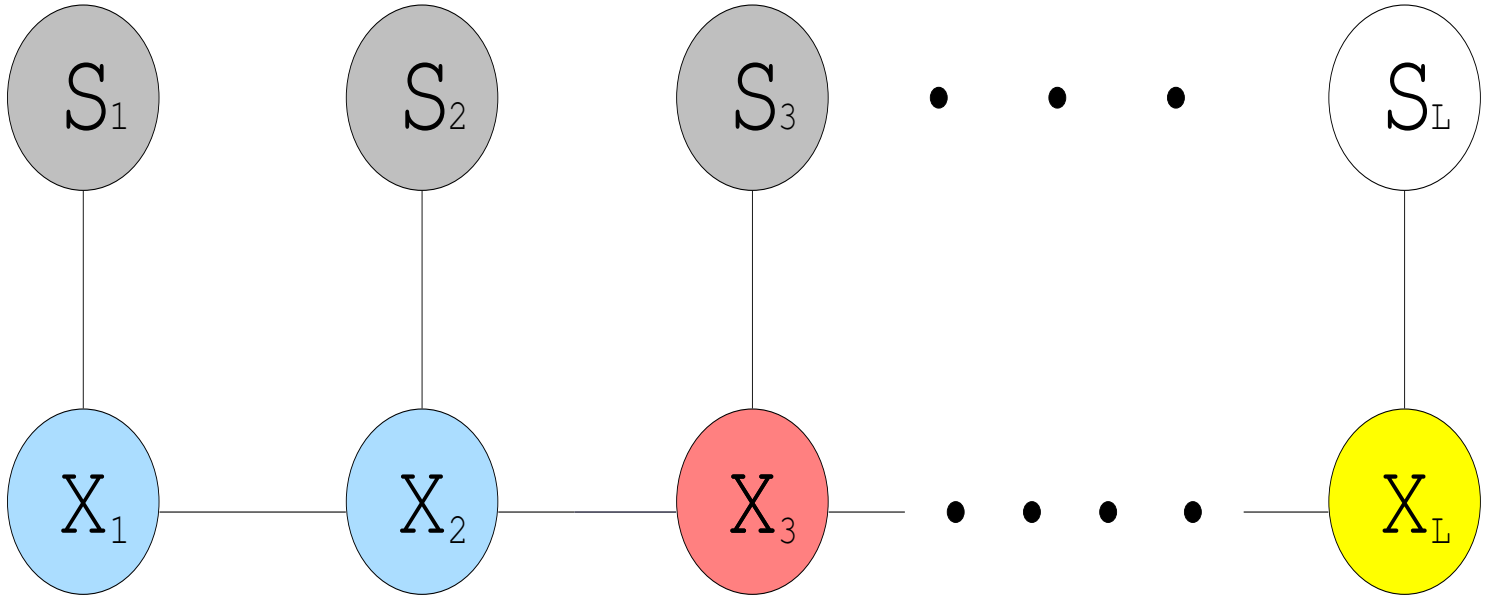
- match (or "paint") other chromosomes (e.g. h_4) to donors' DNA
- $\longrightarrow$ cluster based on who shares many **blocks of SNPs** rather than who shares similar **SNP frequencies**
- can do "painting" using many approaches, e.g:
  1. *CHROMOPAINTER* (Lawson et al 2012, *PLoS Genet* **8**:e1002453)
  2. *HAPMIX* (Price et al 2009, *PLoS Genet* **5**:e1000519)
  3. *RFMIX* (Maples et al 2013, *AJHG* **93**:278)
  4. *MULTIMIX* (Churchhouse & Marchini 2013, *Genet Epidemiol* **37**:1)

CHROMOPAINTER – Hidden Markov Model (HMM)

- S_l = (observed state) SNP data at locus l of haploid i
- X_l = (hidden state) donor haploid 1,...,d copied at SNP l



- each donor haploid is depicted with a unique color here
- assume “switches” in donor copied occur as a Poisson process of rate $\propto g_l$, the cM distance between SNPs l and $l+1$

Copying Model (HMM) (Lawson et al 2012, *PLoS Genet* **8**:e1002453)

(based on Li & Stephens 2003, *Genetics***165**:2213)

$X_l =$ (unknown) "donor" haplotype copied at SNP l

$S_l =$ observed data at SNP l

$$\Pr(X_{l+1} = d \mid X_l = d') = \begin{cases} \exp(-g_l N_e) + \Big(1 - \exp(-g_l N_e)\Big) q_d & \text{if } d = d' \\ \Big(1 - \exp(-g_l N_e)\Big) q_d & \text{otherwise} \end{cases}$$

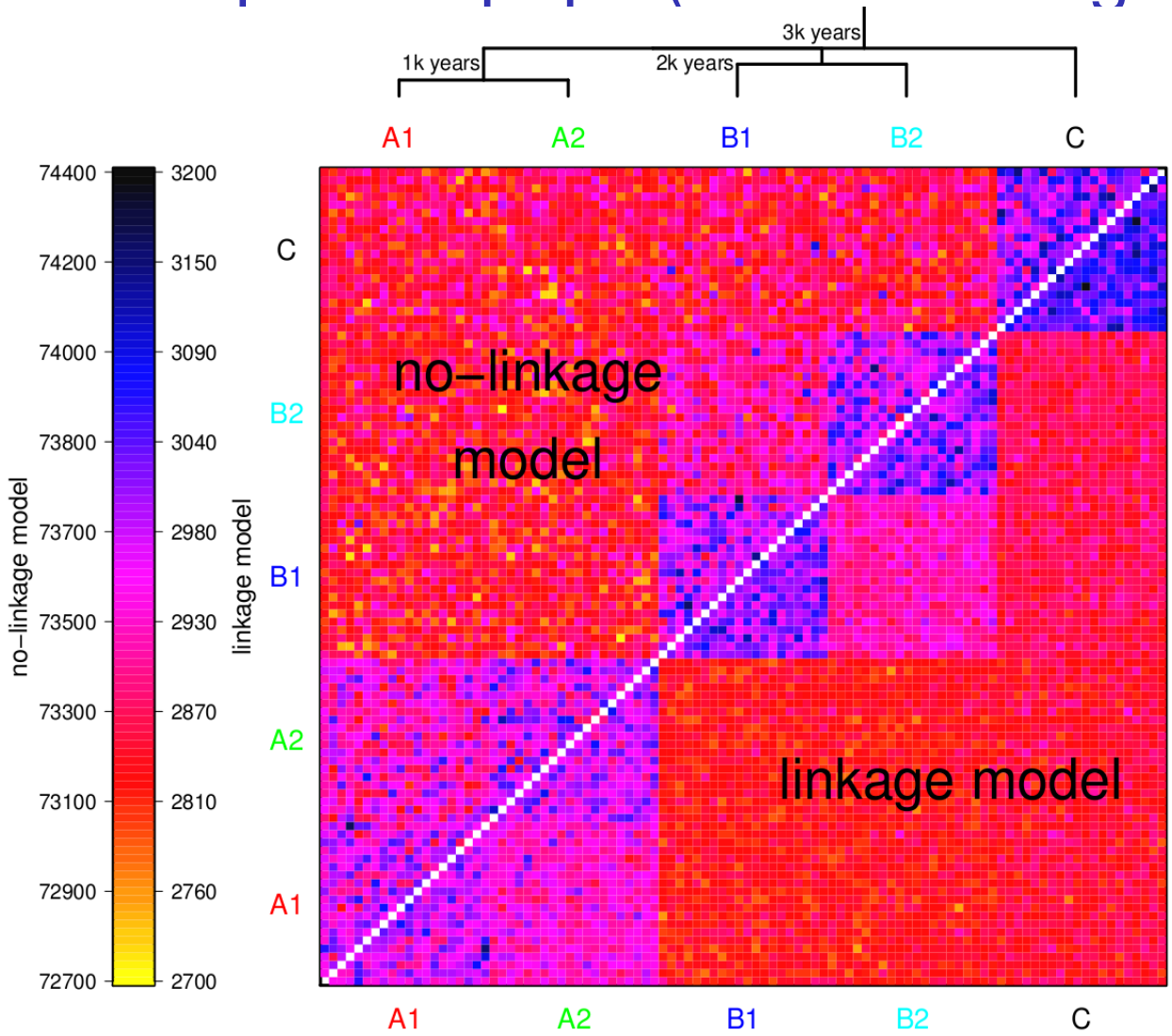
$$\Pr(S_{l+1} = s \mid S_{X_{l+1}} = s_X) = \begin{cases} 1 - \theta & s = s_X \\ \theta & s \neq s_X \end{cases}$$

- where g_l = genet distance btwn SNPs l and $l + 1$, N_e = "scaling term", θ = mutation (emission) rate, $q_d = \Pr(\text{copy } d)$
- estimates proportion copied from donor d conditional on data
- can sample X_l along genome

Summarizing *CHROMOPAINTER* painting: Heatmaps

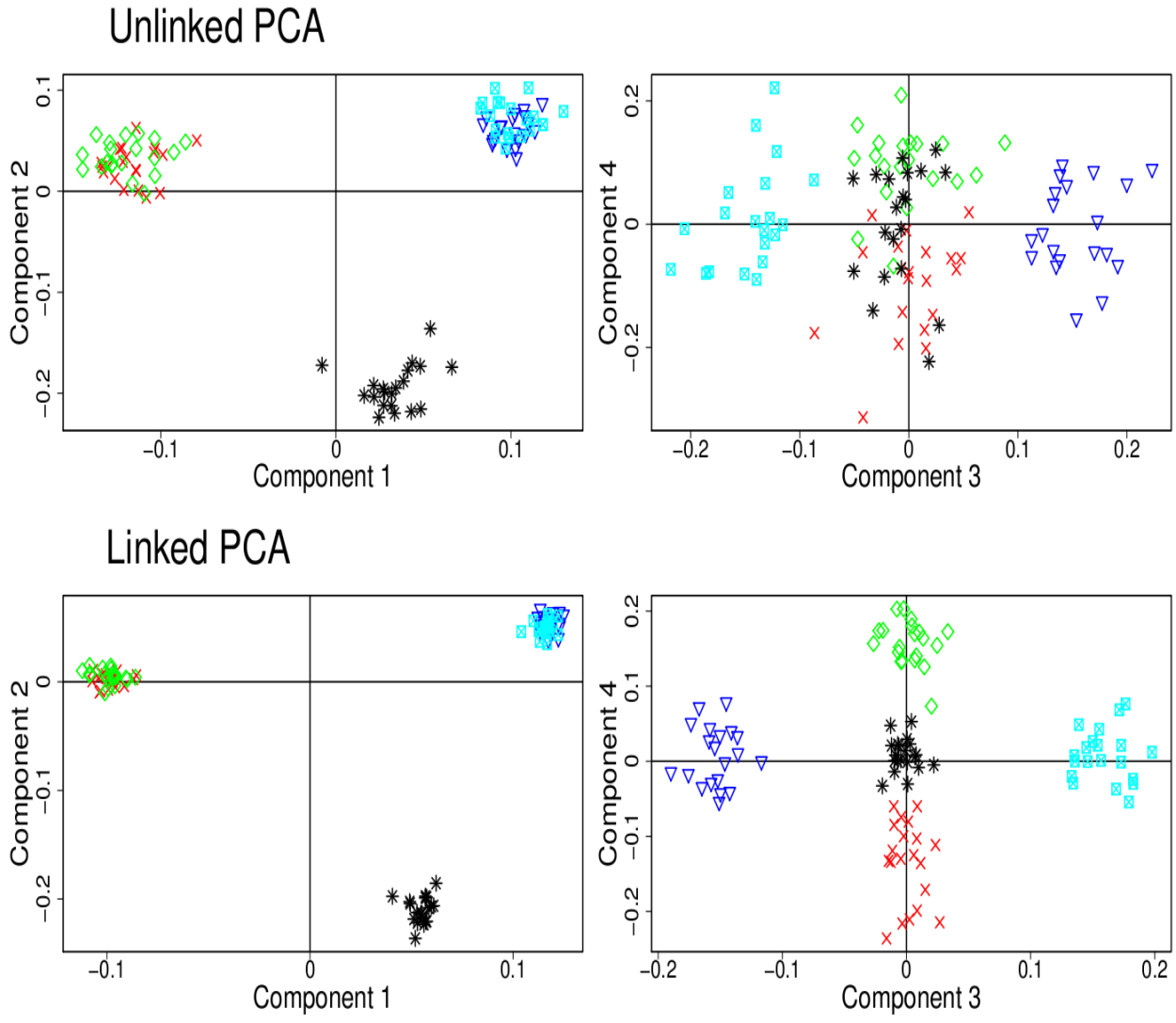
- allow each individual i to copy from every other individual $j \neq i$ using the copying model
- calculate y_{ij} – expected number of "chunks" ind i copies from ind j
  - if you assume each SNP is a "chunk" (i.e. "no-linkage" model) you capture information equivalent to PCA of genetic data
  - considerably more power if you use haplotype-based model

Simulated Example – 5 pops (150 5-Mb regions)



- Heatmap: each square is the number of DNA segments that each row (recipient) copies from each column (donor)
- upper left triangle: ignoring haplotypes
  lower right triangle: using haplotypes

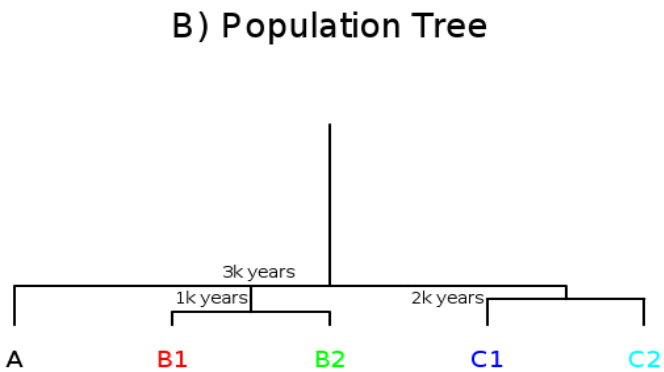
Simulated Example – 5 pops (PCA of heatmap)



top row: ignoring haplotypes (equivalent to regular PCA)

bottom row: using haplotypes

fineSTRUCTURE: cluster using *CHROMOPAINTER* paintings



(Lawson et al 2012, *PLoS Genet* **8**:e1002453)

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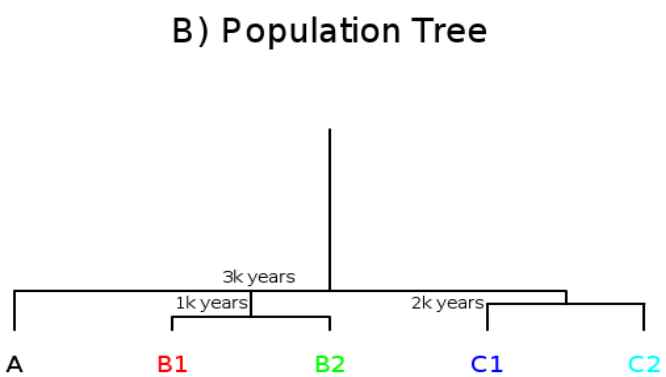

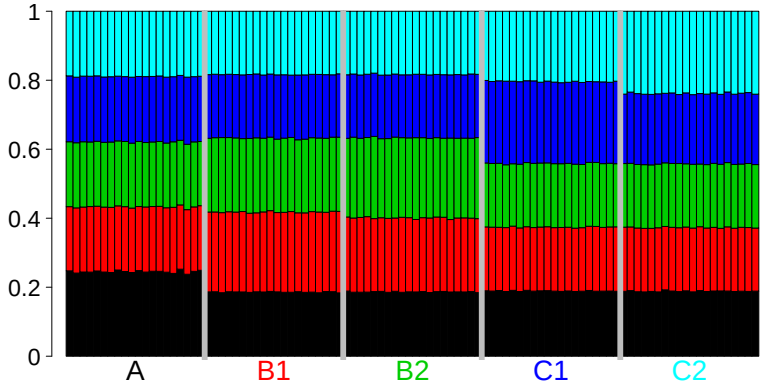

- paint each individual *i* using all other inds as “donors”
- calculate y_{ij} – number of DNA segments of ind *i* painted by ind *j*

(Lawson et al 2012, *PLoS Genet* **8**:e1002453)

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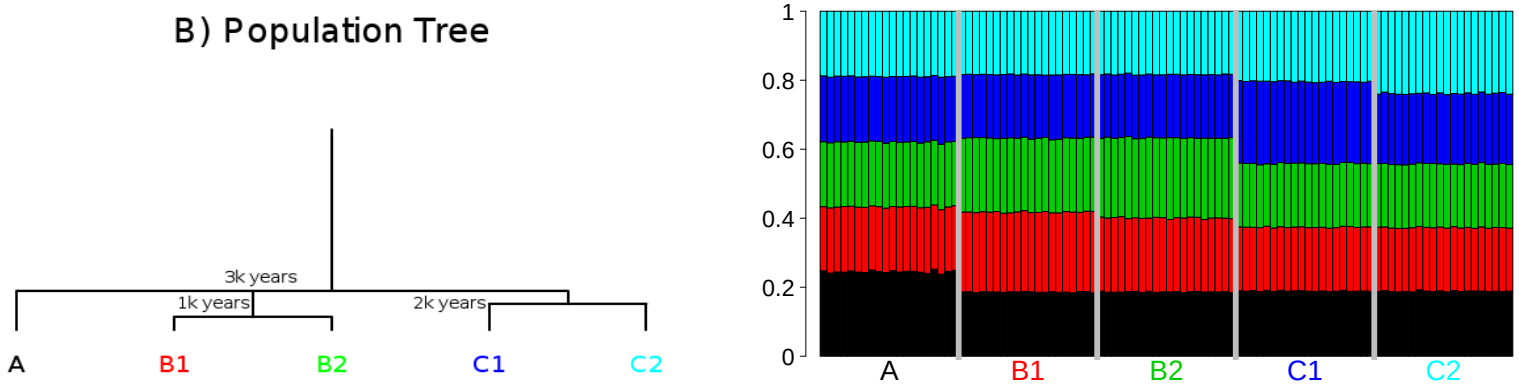
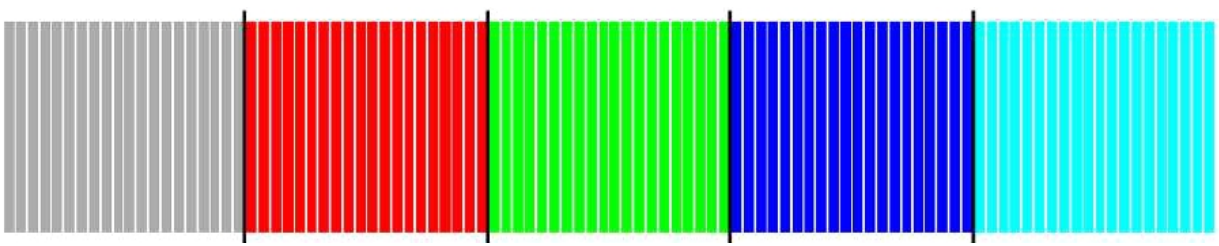
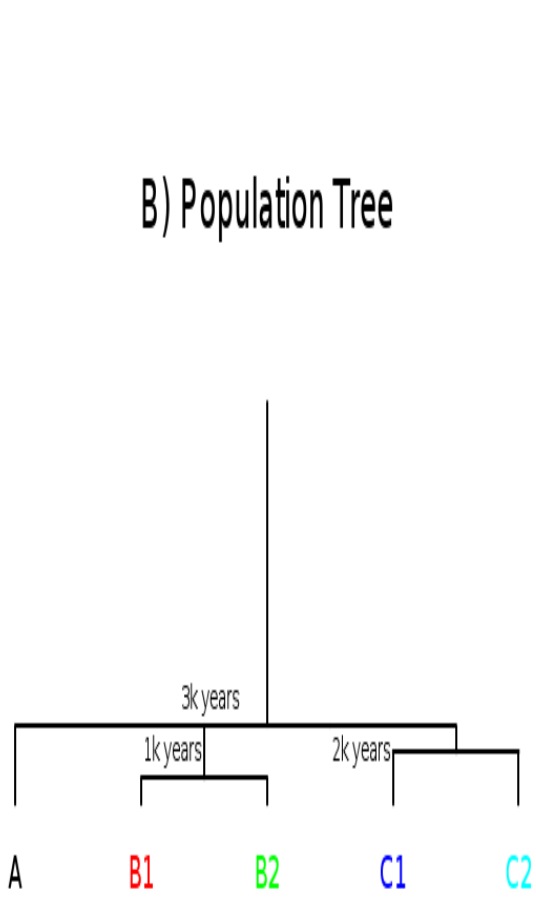


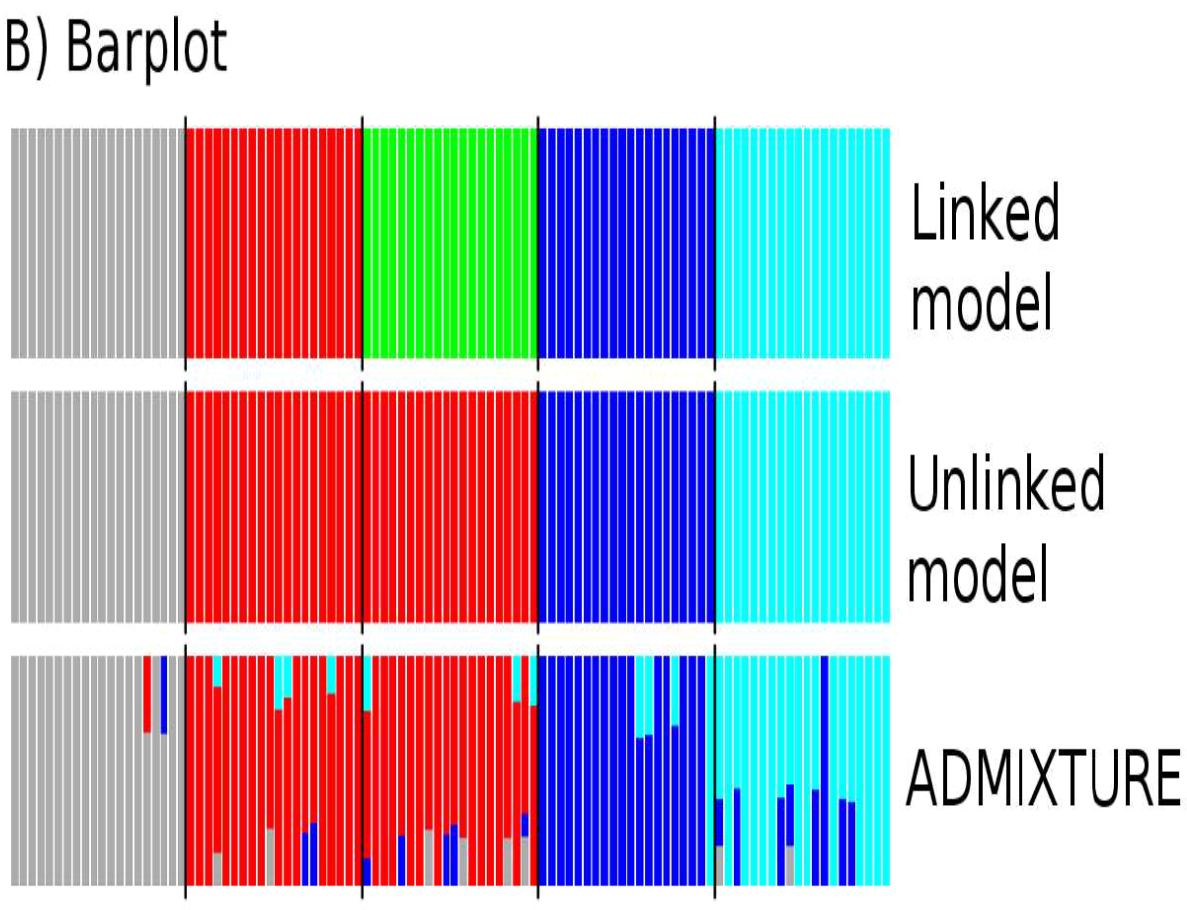
- paint each individual i using all other inds as "donors"
- calculate y_{ij} – number of DNA segments of ind i painted by ind j
- cluster individuals who have similar painting patterns (MCMC):
  1. start with random assignment of inds to clusters 1,...,K
  2. $(y_{i1}, ..., y_{iK}) \sim \text{Mult}(P_{A1}, ..., P_{AK})$ for ind i assigned to cluster A
  3. infer P_{Ak} by using number of segments inds in cluster A are painted with inds in cluster k
  4. if $\Pr(y_{i1}, ..., y_{iK})$ low $\longrightarrow$ move ind i to different cluster



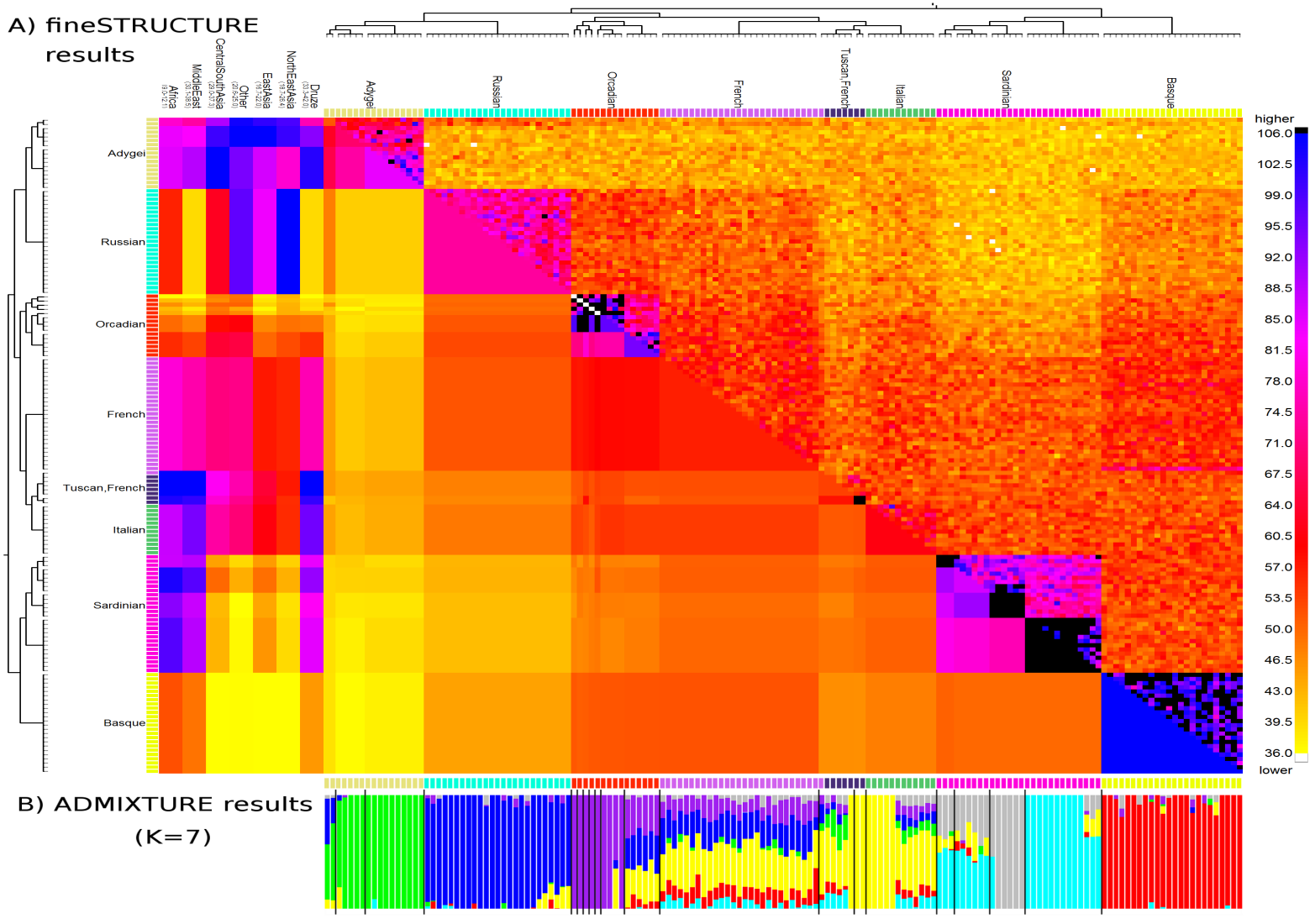
(Lawson et al 2012, *PLoS Genet* **8**:e1002453)

Simulated Example – 5 pops (classification)



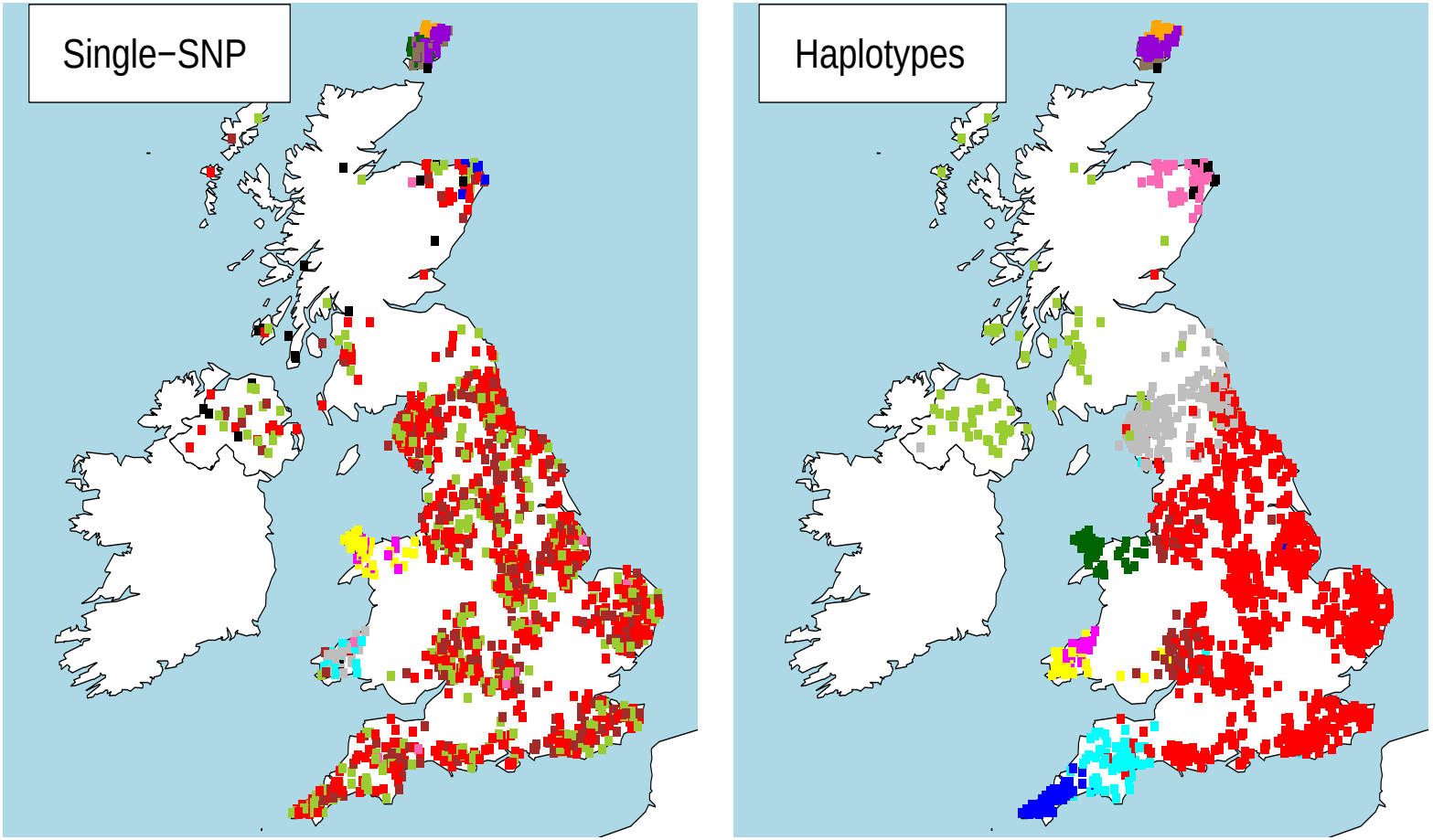


European populations (Lawson et al 2012, *PLoS Genet* **8**:e1002453)



(rows = recipients / columns = donors)

United Kingdom – clustering using haplotype info



(Leslie et al 2015, *Nature* **519**:309)

- dots = individuals / colors = clusters
- **left:** ignore haplotypes (as in PCA, STRUCTURE/ADMIXTURE)
- **right:** using haplotypes shows more localised (though subtle!) correspondence of genetics and geography

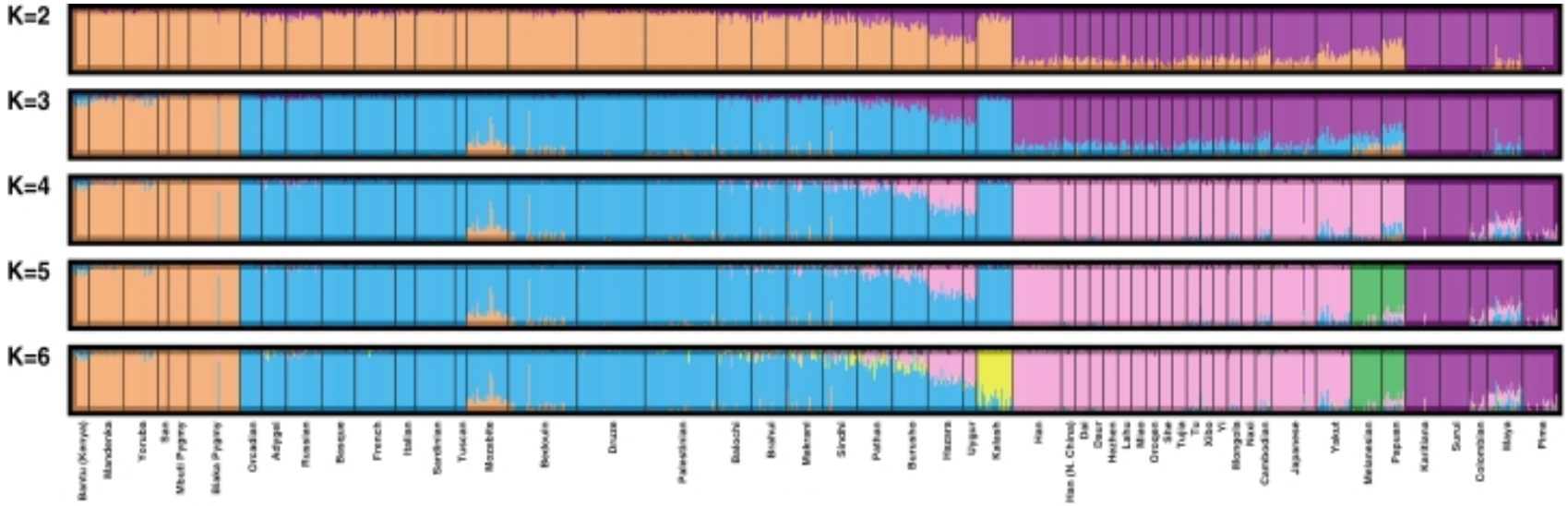
fineSTRUCTURE (Lawson et al 2012, *PLoS Genet* **8**:e1002453)

- **Advantages:**
  - increased power – finds more subtle structure in data missed by *ADMIXTURE* (e.g. Europe, United Kingdom)
  - heatmaps can show clear structure/admixture
  - current implementation infers number of clusters *K* automatically, and builds "tree" relating these clusters

- **Disadvantages:**
  - how to interpret results? Drift/admixture/other can result in similar signals
  - requires phased data (e.g. using *SHAPEIT*)
  - currently only has "no admixture" model only
  - computationally slow (relative to *ADMIXTURE*), more complicated to use

Caution: Clustering individuals

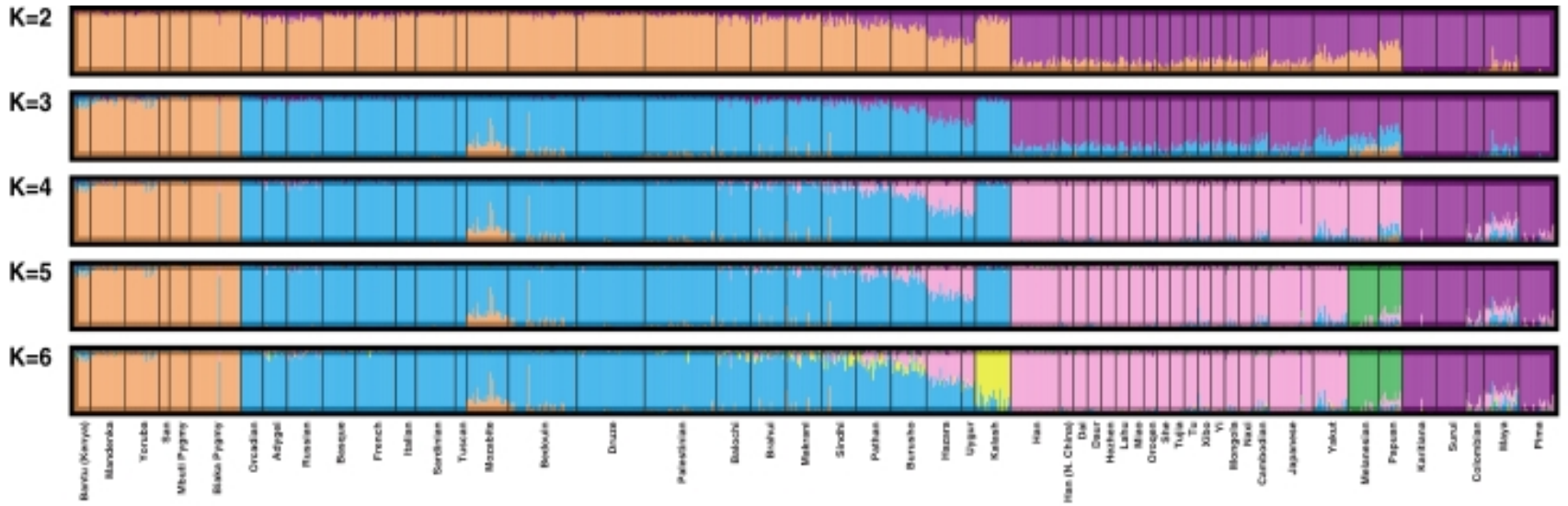
- can be difficult to interpret → drift, admixture, ancient relatedness can give similar signals



example of *STRUCTURE* (Rosenberg et al 2002, *Science* **298**:2381)

Caution: Clustering individuals

- can be difficult to interpret → drift, admixture, ancient relatedness can give similar signals



example of *STRUCTURE* (Rosenberg et al 2002, *Science* **298**:2381)

- with $K = 6$ clusters, the *Kalash* of Pakistan assigned to own **yellow** cluster because they are relatively drifted (live within mountainous region → genetically isolated)
- has been interpreted as the Kalash being an ancient genetic isolate (Ayub et al 2015, *AJHG* **96**:775)
- but recent work has shown ancestors of Kalash have recently intermixed with outside groups within last ≈3k years (Hellenthal et al 2014 *Science* **343**:747; Loh et al 2013 *Genetics* **193**:1233)

Summary

- clustering algorithms highlight genetic differences/similarities among groups (e.g. correlations between genetics and geography)
- more challenging to get at factors driving genetic differences
- *STRUCTURE/ADMIXTURE/FRAPPE* – assumes SNPs are independent, computationally quick (the latter two methods)
- *CHROMOPAINTER* + *fineSTRUCTURE* – uses correlations among SNPs (haplotype information) to increase power, computationally slower, individuals cannot be mixtures of multiple clusters