CSci 8980: Advanced Topics in Graphical Models

Analysis of Genetic Variation

Instructor: Arindam Banerjee

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- Repeated recombinations between ancestral haplotypes

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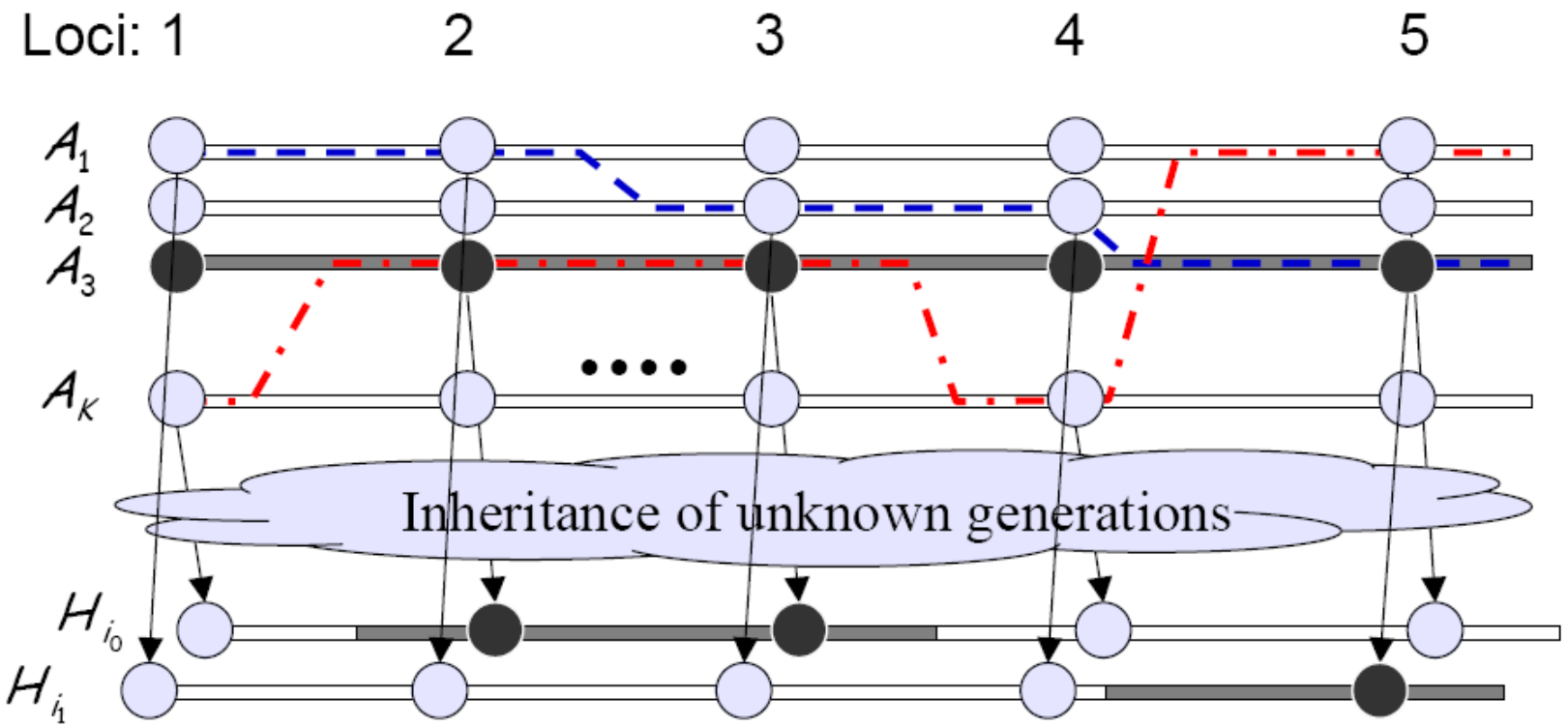
- Infer chromosomal recombination hotspots
  - Help understand origin and characteristics of genetic variation
- Analyze genetic variation to reconstruct evolutionary history

Haplotype Recombination and Inheritance



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- Implemented using a Hidden Markov Dirichlet Process (HMDP)

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  - For subsequent haplotypes

$$c_i | DP(\tau, Q_0) \sim \begin{cases} p(c_i = c_j \text{for some } j < i | c_1, \ldots, c_{i-1}) = \frac{n_{c_j}}{i-1+\alpha_0} \\ p(c_i \neq c_j \text{for all } j < i | c_1, \ldots, c_{i-1}) = \frac{\alpha_0}{i-1+\alpha_0} \end{cases}$$

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$$\begin{aligned} Q_0|\alpha, F &\sim DP(\alpha, F) \\ Q_j|\tau, Q_0 &\sim DP(\tau, Q_0) \end{aligned}$$

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- The transition probability to state k' is

$$P(C_{i,t} = k, C_{i,t+1} = k') = (1 - \exp(dr))\pi_{kk'}$$

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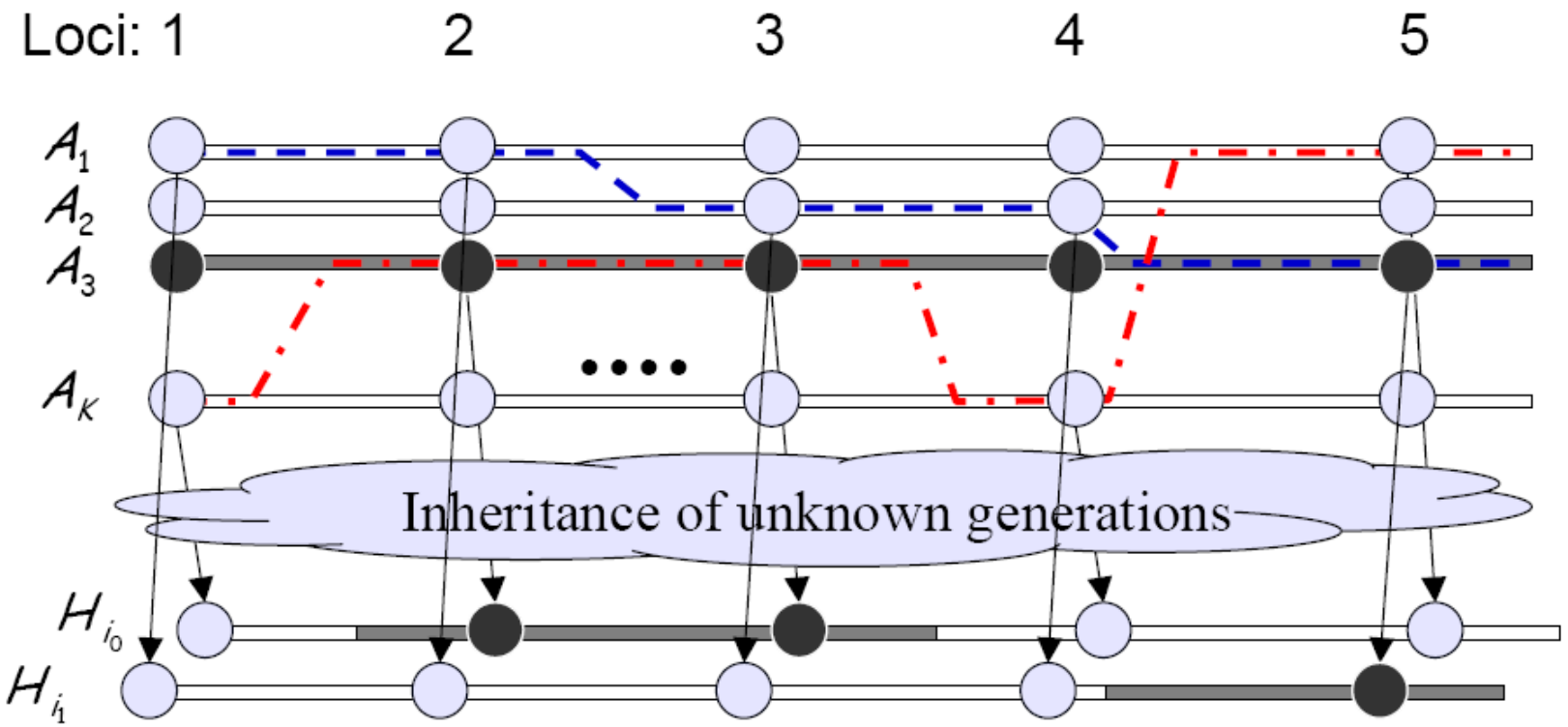
- Single locus mutation model for emission

$$p(h_t|a_t, \theta) = \theta^{\mathbb{I}(h_t=a_t)} \left(\frac{1-\theta}{|B|-1}\right)^{\mathbb{I}(h_t \neq a_t)}$$

Haplotype Recombination and Inheritance



HMDP for Recombination and Inheritance (Contd.)

Conditional probability of haplotype list h

$$
\begin{aligned}
p(h|c,a) &= \prod_k \int_{\theta_k} \prod_{i,t|c_{i,t}=k} p(h_{i,t}|a_{k,t},\theta_k) Beta(\theta_k|\alpha_h,\beta_h) d\theta_k \\
&= \prod_k \frac{\Gamma(\alpha_h+\beta_h)}{\Gamma(\alpha_h)\Gamma(\beta_h)} \frac{\Gamma(\alpha_h+\ell_k)\Gamma(\beta_h+\ell'_k)}{\Gamma(\alpha_h+\beta_h+\ell_k+\ell'_k)} \left(\frac{1}{|B|-1}\right)^{\ell'_k}
\end{aligned}
$$

where

$$
\ell_k = \sum_{i,t} \mathbb{I}(h_{i,t}=a_{k,t})\mathbb{I}(c_{i,t}=k) \quad \ell'_k = \sum_{i,t} \mathbb{I}(h_{i,t}\neq a_{k,t})\mathbb{I}(c_{i,t}=k)
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$$p(c_{t+1} : t+\delta | c_-, h, a) \propto \prod_{j=t}^{t+\delta} p(c_{j+1} | c_j, m, n) \prod_{j=t+1}^{t+\delta} p(h_j | a_{c_j,j}, \ell_{c_j})$$

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  - Assume probability of having two recombinations is small

$$p(c_{t+1} : t+\delta | c_-, h, a) \propto p(c_{t'} | c_{t'-1}, m, n) p(c_{t+\delta+1} | c_{t+\delta} = c_{t'}, m, n)$$

Inference (Contd.)

- Assuming d, r to be small, $\lambda = 1 - \exp(-dr) \approx dr$

$$p(c_{t'} = k | c_{t'-1} = k, m, n, r, d) = \begin{cases} \lambda\pi_{k,k'} + (1-\lambda)\delta(k,k') \text{for} k' \in \{1 \\ \lambda\pi_{k,K+1} \quad \text{for} k' = K+1 \end{cases}$$

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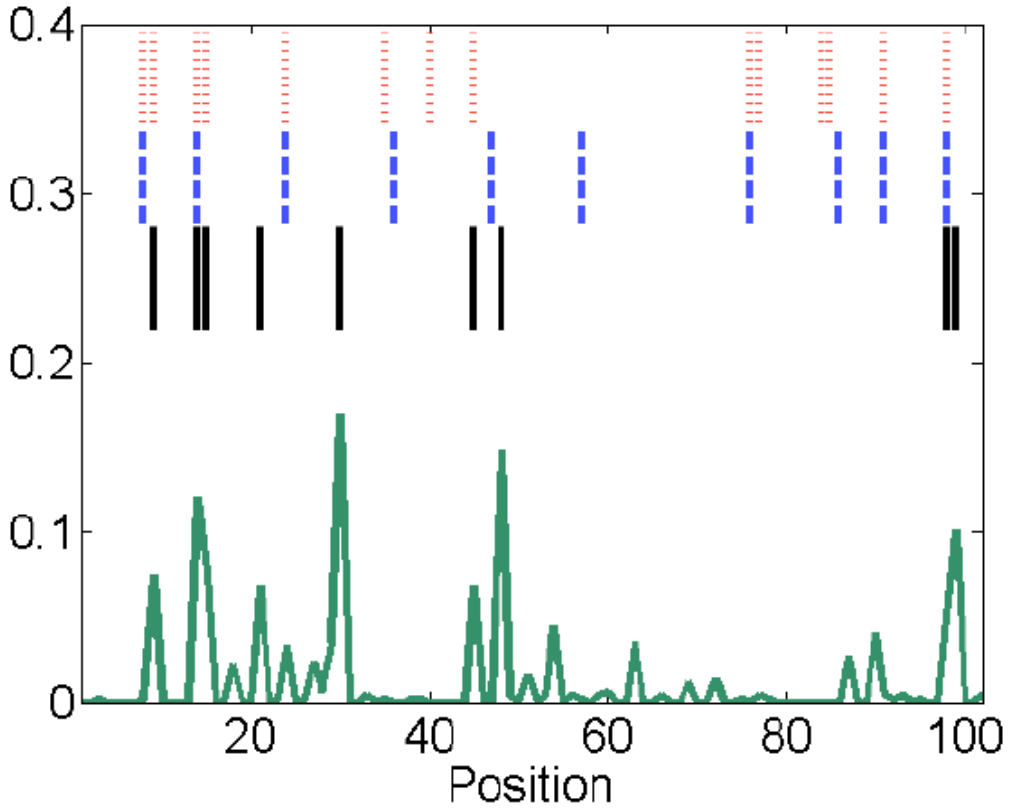
- Posterior distribution for ancestors

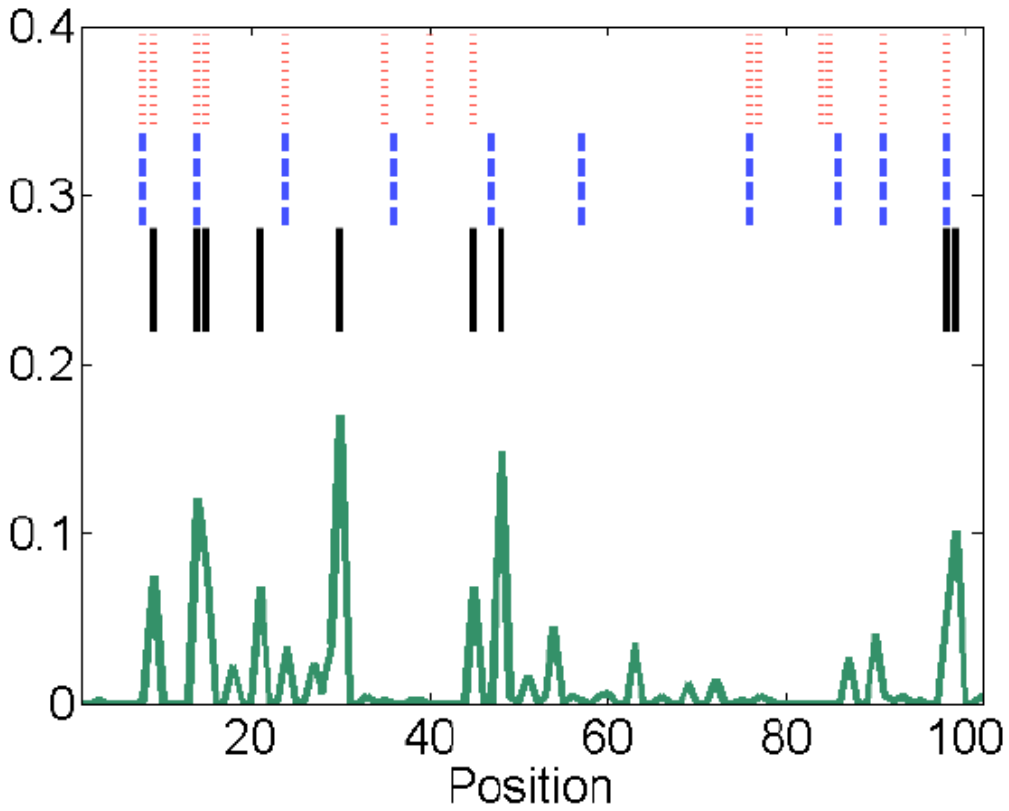
$$p(a_{k,t} | c, h) \propto \frac{\Gamma(\alpha_h + \beta_h)}{\Gamma(\alpha_h)\Gamma(\beta_h)} \frac{\Gamma(\alpha_h + \ell_{k,t})\Gamma(\beta_h + \ell'_{k,t})}{\Gamma(\alpha_h + \beta_h + \ell_{k,t} + \ell'_{k,t})} \left(\frac{1}{|B| - 1}\right)^{\ell'_{k,t}}$$

Single Population Data

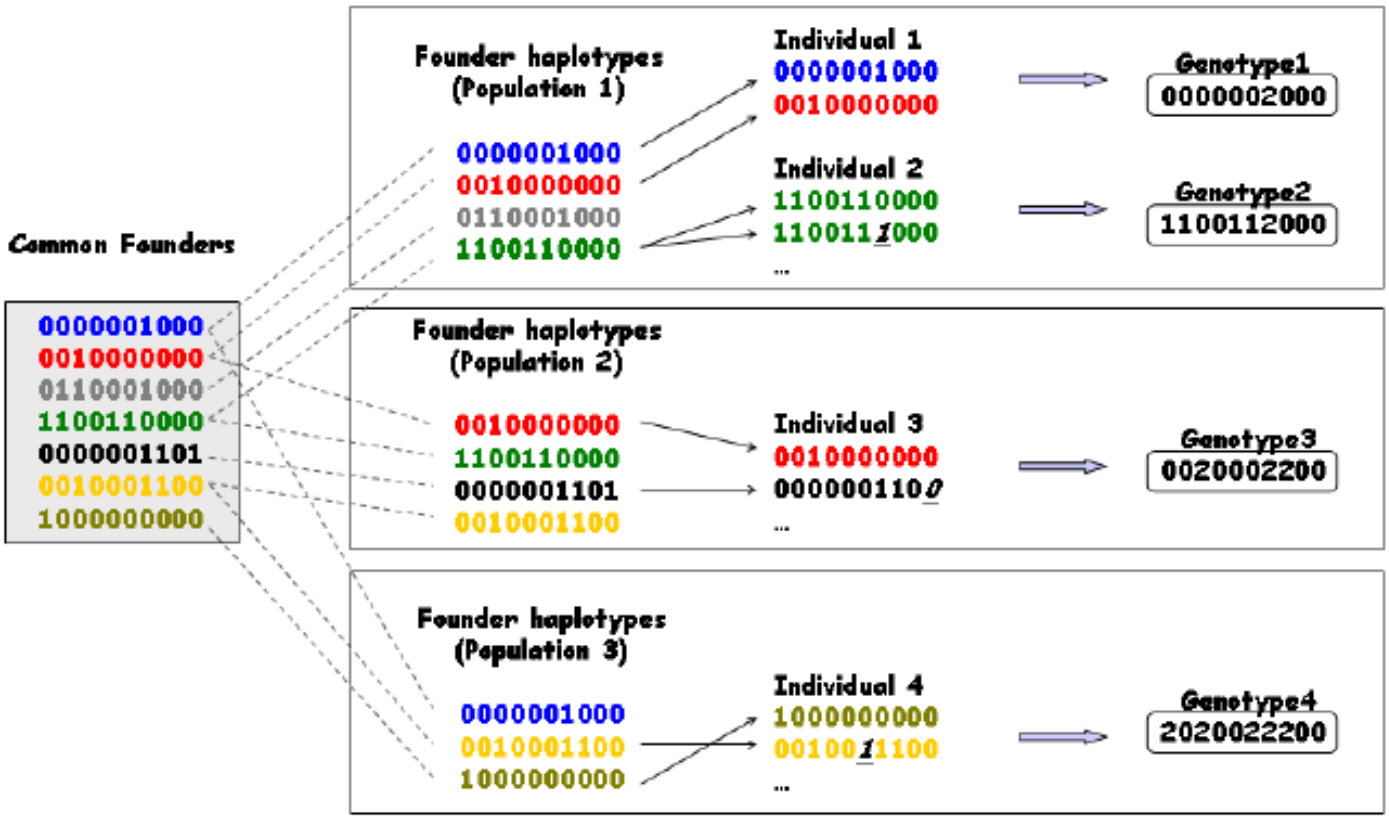


Haplotype block boundaries
HMDP (black solid), HMM (red dotted), MDL (blue dashed)

Two Population Data



Hierarchical DPM for Haplotype Inference



Hierarchical DPM for Haplotype Inference (Contd.)

$Q_0(\phi_1, \phi_2, \ldots)\|\gamma, F \sim \mathrm{DP}(\gamma, F)$,	sample a DP of founders for all populations;
$Q_j(\phi_1^{(j)}, \phi_2^{(j)}, \ldots)\|\tau, Q_0 \sim \mathrm{DP}(\tau, Q_0)$,	sample the DP of founders for each population;
$\phi_{i_e}^{(j)}\|Q_j \sim Q_j$,	sample the founder of haplotype i_e in population j;
$h_{i_e}^{(j)}\|\phi_{i_e}^{(j)} \sim P_h(\cdot\|\phi_{i_e}^{(j)})$,	sample haplotype i_e in population j;
$g_i^{(j)}\|h_{i_0}^{(j)}, h_{i_1}^{(j)} \sim P_g(\cdot\|h_{i_0}^{(j)}, h_{i_1}^{(j)})$,	sample genotype i in population j,

Experiments: Hapmap Data

- SNP genotypes from four populations

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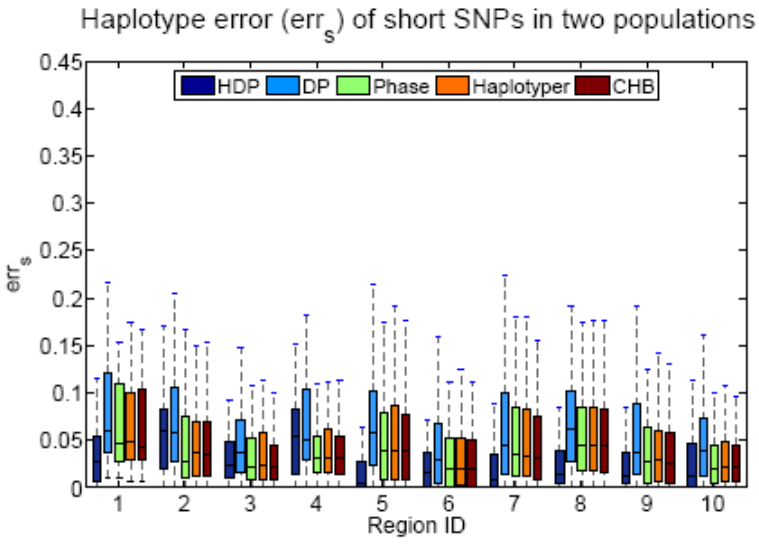
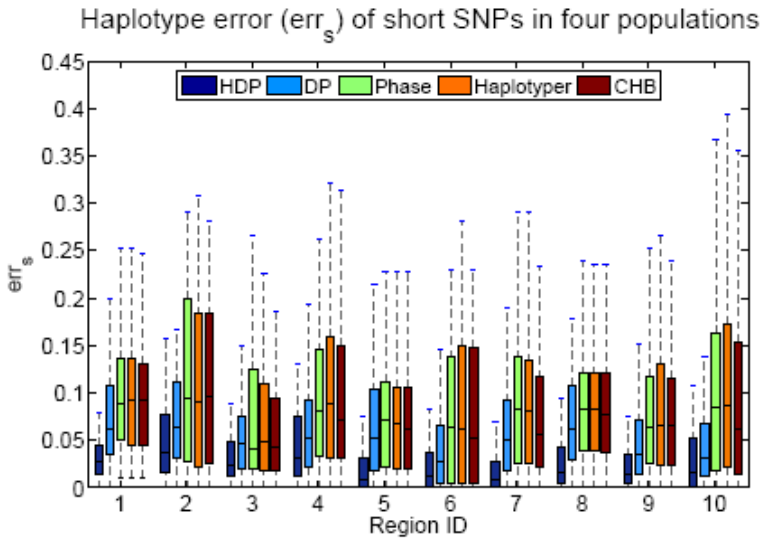
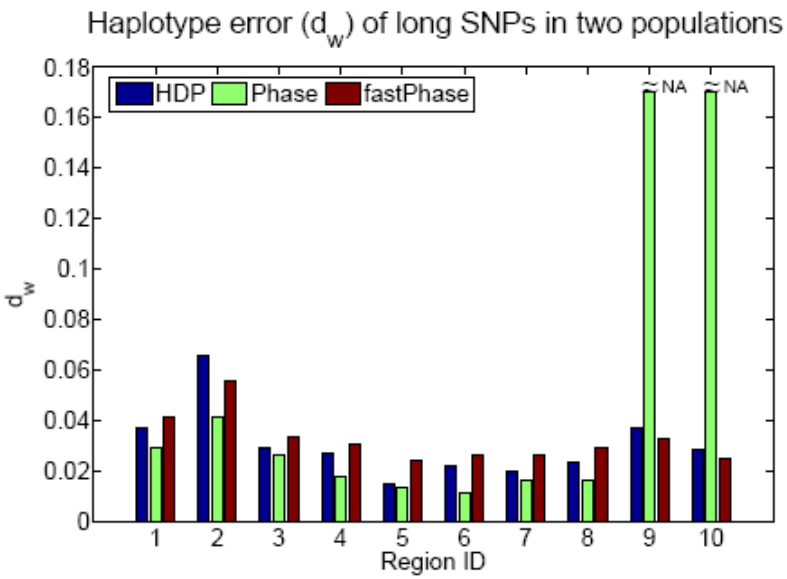
- Experiments on short (~ 10) and long ($\sim 10^2 - 10^3$) SNPs

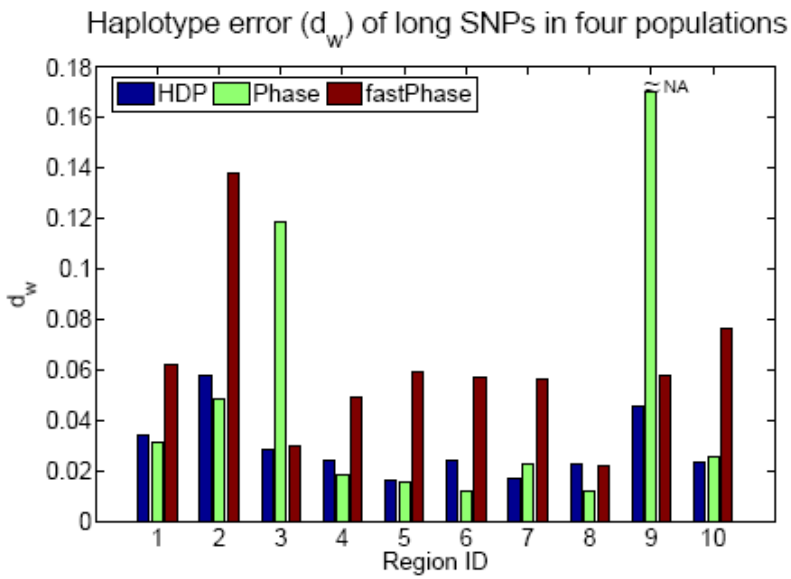
Short SNP Sequences



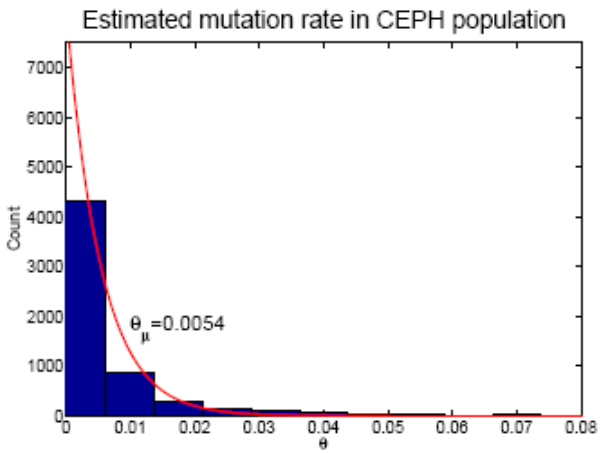


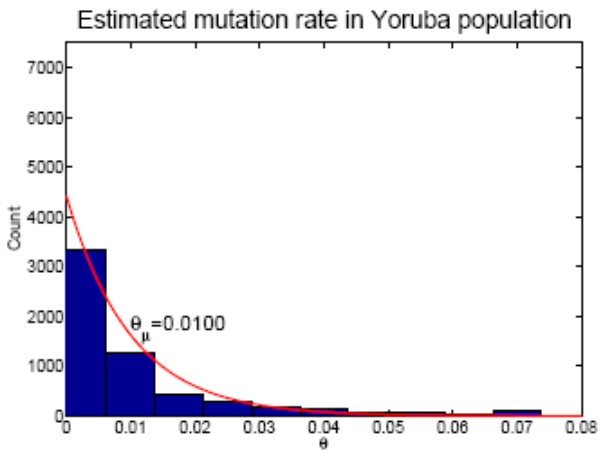
Long SNP Sequences



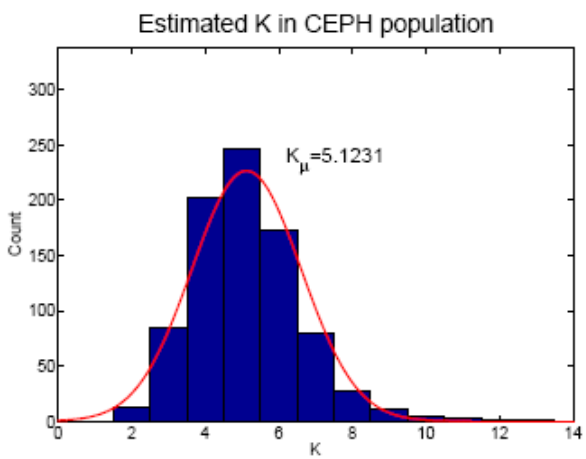


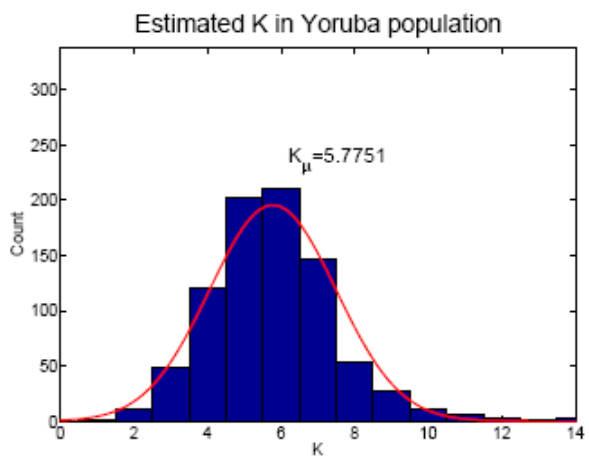
Mutation Rates and Diversity



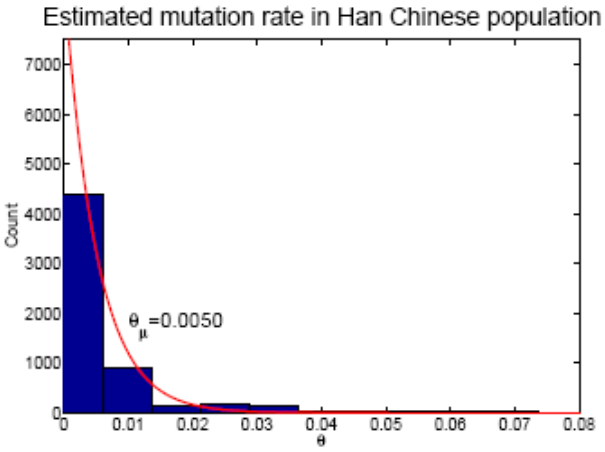


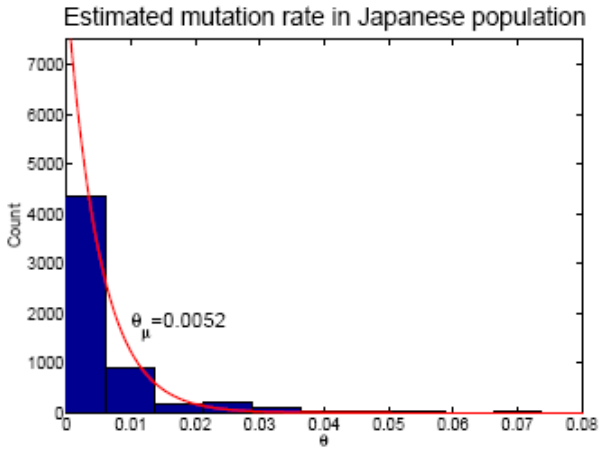
(a) CEPH (b) Yoruba





Mutation Rates and Diversity (Contd.)





(c) Han Chinese

(d) Japanese