CHMM: an R package for coupled Hidden Markov Models

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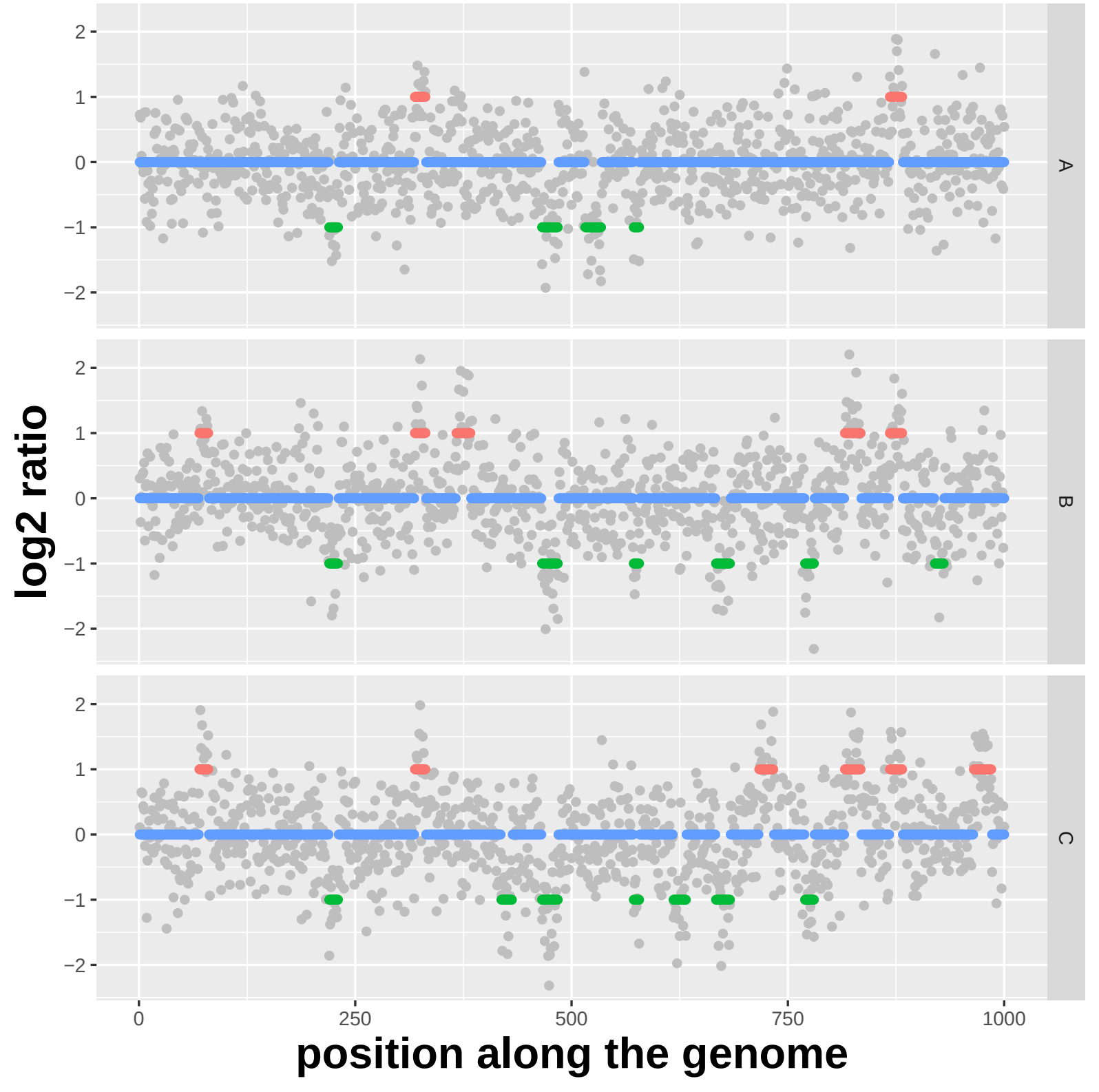
Detection of CNV taking into account dependency between individuals

Copy number variations (CNVs) are genomic alterations that result in an abnormal number of copies of one or more genes: duplication (green), normal (blue), deletion (red).



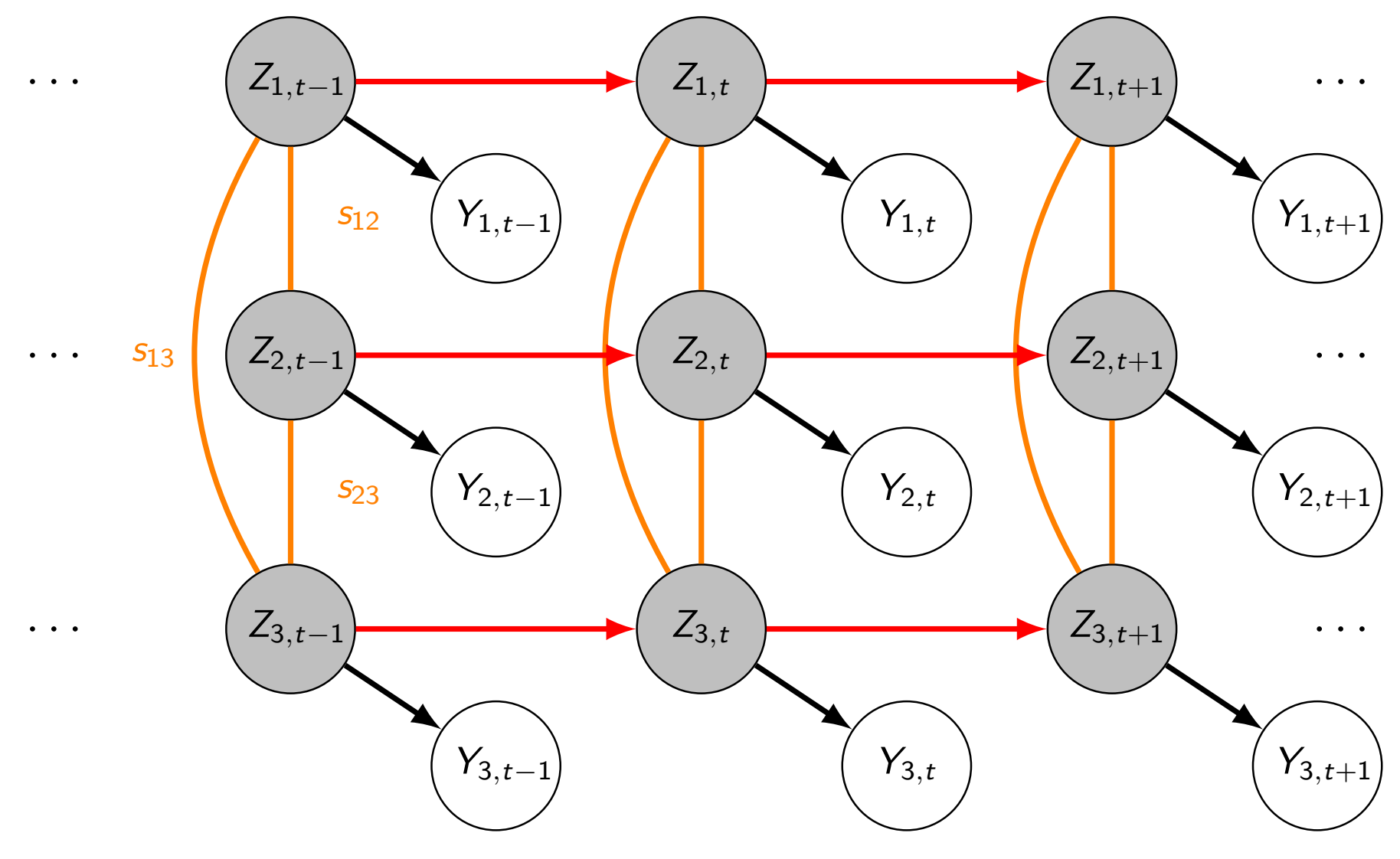
CNV detection of a simulated sample.

	A	B	C
A	1	0.61	0.56
B	0.61	1	0.75
C	0.56	0.75	1

Kinship data

Kinship measures pairwise genetic relatedness between individuals.

Coupled Hidden Markov Models: graphical representation [2]



Notations

- $Y_{i,t}$: observation
- $Z_{i,t}$: hidden status
- s_{ij}: similarity between i and j

within series dependence:
$(Z_{i,t-1}, Z_{i,t})$ are Markov-dependent

between series dependence:
$\forall (i \neq j), (Z_{i,t}, Z_{j,t})$ are not independent

Coupled Hidden Markov Models (CHMM): model

- **Observed** process:

$$(Y_{i,t}|Z_{i,t} = q) \sim \mathcal{N}(\mu_q, \sigma^2)$$

  where μ_q is the mean value in the state q ($q = 1, \cdots, Q$).
- Joint **hidden** process: $(\mathbf{Z}_t)_t$, with $\mathbf{Z}_t = (Z_{1,t}, \cdots, Z_{I,t})$: Q^I states.

$$P(\mathbf{Z}_t = \ell | \mathbf{Z}_{t-1} = k) \propto W_\ell \prod_i \pi_{k_i,\ell_i}$$

  where
  - π is a $Q \times Q$ transition matrix
  - dependency relationships among individuals is encoded in $W_\ell = \prod_{i,j\neq i} \omega^{s_{ij}\mathbb{1}_{\{q_j^\ell \neq q_i^\ell\}}}$ with $\omega < 1$.
  - $\omega = 1$: independent case. Equivalent to independent HMM (*iHMM*).

Variational inference [1,2]

When I (the number of individuals) is large, $P(\mathbf{Z}|\mathbf{Y})$ is not computable.
Mean-field approximation

$$\tilde{P}(Z) = \arg\min_{\tilde{P}\in\mathcal{P}} \mathcal{KL}\left[\tilde{P}(Z); P(Z|Y)\right]$$

where $\mathcal{P} = \left\{\tilde{P}(Z) \,|\, \tilde{P}(Z) \propto \prod_i \prod_t \tilde{P}(Z_{i,t}|Z_{i,t-1})\right\}$ (independent Markov chains)

Forward part of the VE-step

Let denote $p_{itqr} = \tilde{P}(Z_{i,t} = r | Z_{i,t-1} = q)$, then we obtain a set of fixed point equations for p_{itqr}:

$$p_{itqr} \propto \pi_{qr}\ f(Y_{i,t}, \mu_r, \sigma^2) \ \times \omega^{\sum_{j\neq i} s_{ij}\left(1-\mathbb{E}_{\tilde{P}} Z_{j,t}^r\right)}$$

References and acknowledgements

[1] Ghahramani, Z. and Jordan, M. (1997). Machine learning, 29(2-3):245-273.
[2] Wang, X. et al. (2017). *Submitted.*
[3] Daudin, J.-J., Picard, F. and Robin, S. (2008). Stat. Comput. 18, 173-83.

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Selection criterion [2,3]

$$\widehat{Q} = \arg\max_Q \mathcal{J}_Q(Y, \widehat{\theta}, \tilde{P}) - [1 + Q(Q-1)]\log(IT)/2,$$

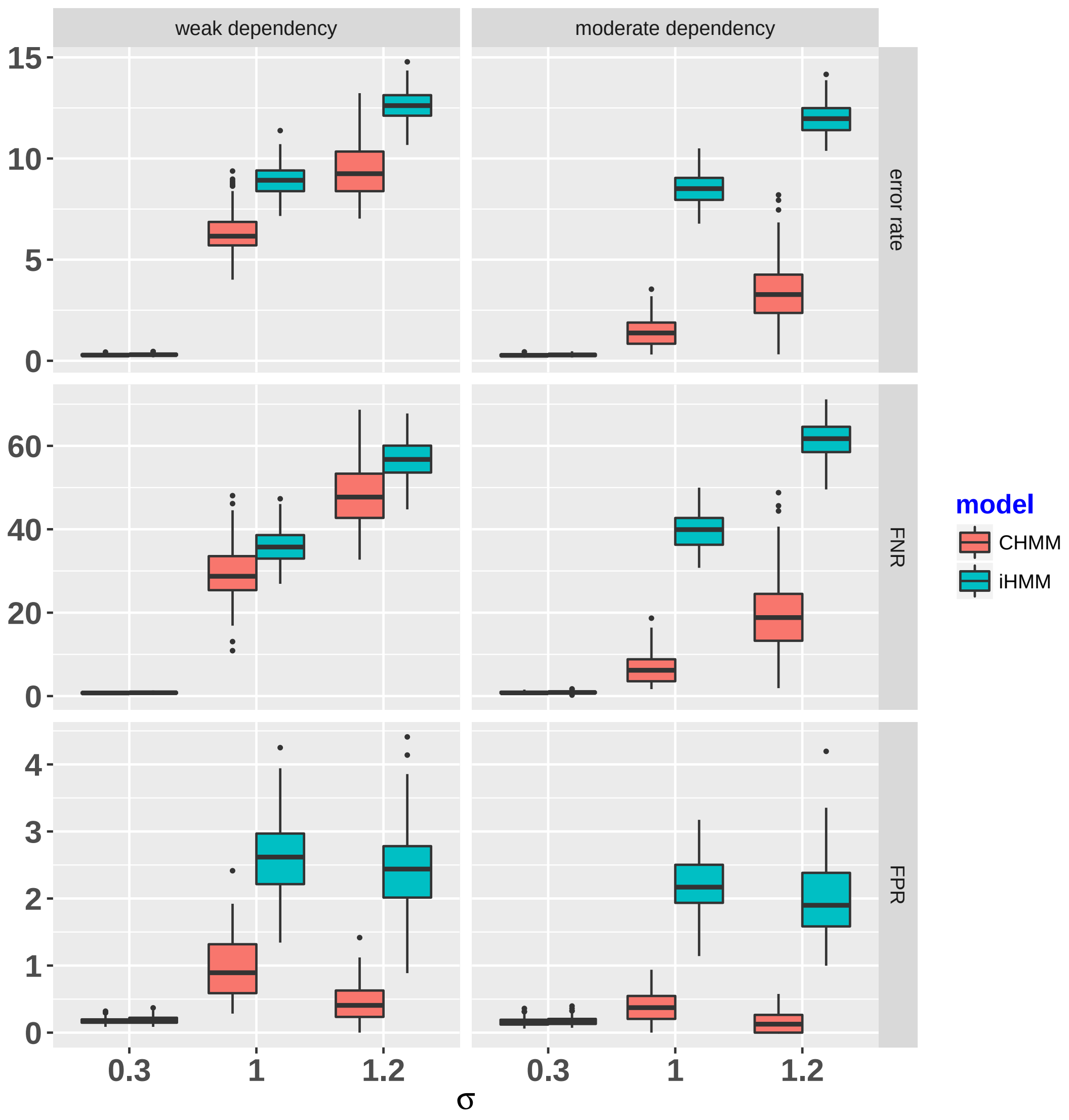
where $\mathcal{J}_Q(Y, \widehat{\theta}, \tilde{P})$ is the maximized lower bound of the Q-state model.

Simulation study

Runtime (in second), Weak dependency, $\sigma = 1$, I: number of lines

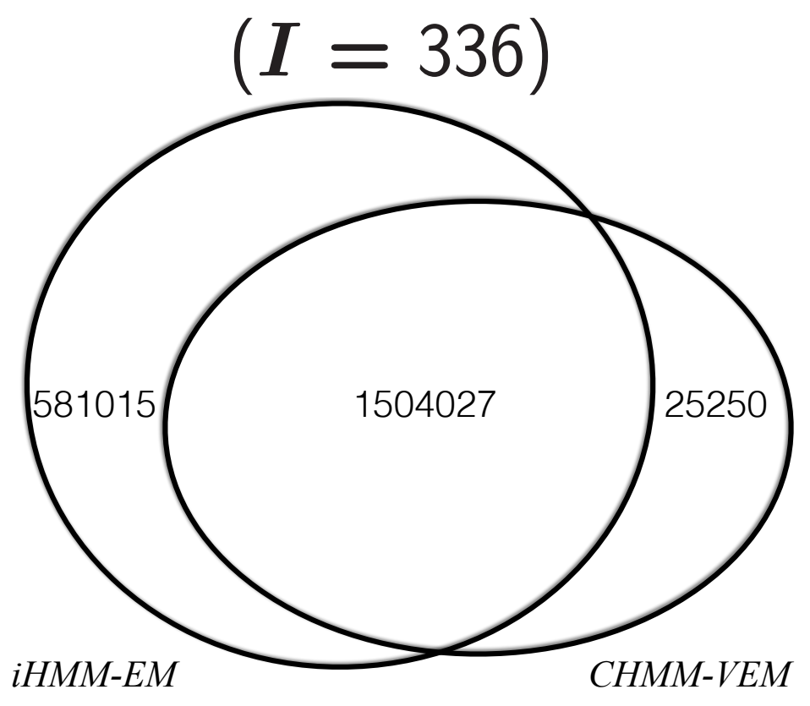
I	*iHMM-EM*	*CHMM-VEM*	*CHMM-EM*
2	0.8	0.4	2.0
3	1.1	0.5	11.2
4	1.2	0.6	79.4
5	1.6	0.8	920.2

Classification accuracy (%) for $I = 3$



Coupled HMM applied to the detection of CNV in the maize

Loci detected as deleted ($I = 336$)



Classification accuracy
(validated 58 Fv2 alterations)

I	1	6	49	80	153	336
$\bar{s}_I$	1.0	0.7	0.7	0.7	0.6	0.6
FPR(%)	12.6	10.4	10.0	9.3	8.9	8.9
FNR(%)	24.1	24.1	24.1	25.9	25.9	25.9

$\bar{s}_I$: mean kinship within the panel.

The joint analysis with correlated lines reduces the proportion of falsely detected alterations.

CHMM package

```
library(CHMM)
data(toyexample)
# Variational inference of a coupled hidden Markov Chains
resCHMM <- coupledHMM(X = toydata, nb.states = 3, S =
    cor(toystatus), omega.list = c(0.3, 0.5, 0.7, 0.9))
# Breakpoints positions and status of segments
info <- clusterseg(resCHMM$status)
```

```
    sample    posbegin posend status
1 Sample_5           1     17      2
2 Sample_5          18     30      1
3 Sample_5          31     66      2
```

Conclusions

A model and associated inference for the detection of CNV taken into account dependency.

- Selection criterion
- Heuristic for choosing the value of the parameter ω.
- CHMM R package available from the CRAN.