Nonparametric Clustering with Variational Inference for Tumor Heterogeneity

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Reader: Prof Erik Sudderth

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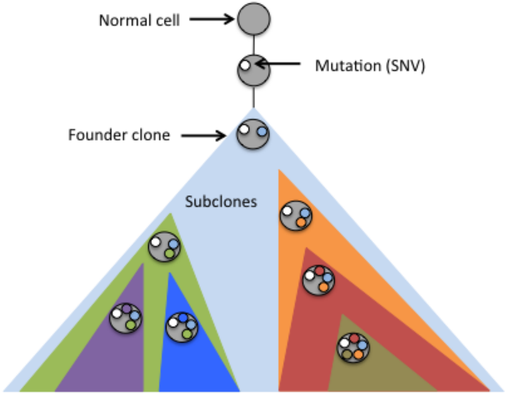
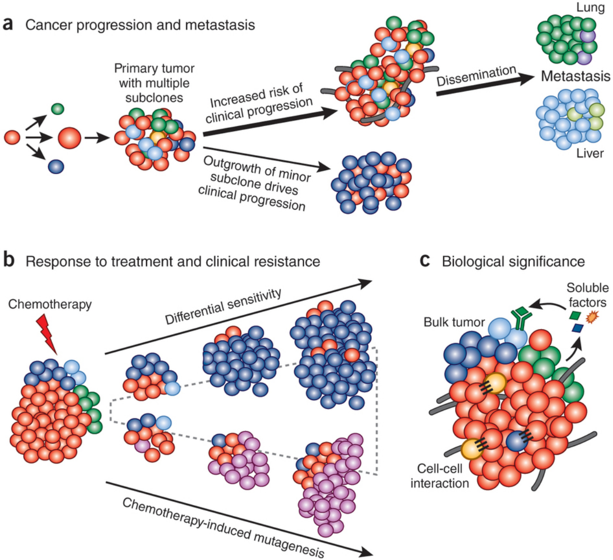
Cancer is an evolutionary disease.



[1] El-Kebir 2015

Clinical significance.


a Cancer progression and metastasis
Primary tumor with multiple subclones
Increased risk of clinical progression
Outgrowth of minor subclone drives clinical progression
Dissemination
Lung
Metastasis
Liver
b Response to treatment and clinical resistance
Chemotherapy
Differential sensitivity
Chemotherapy-induced mutagenesis
c Biological significance
Soluble factors
Bulk tumor
Cell-cell interaction

[1] Kleppe 2014

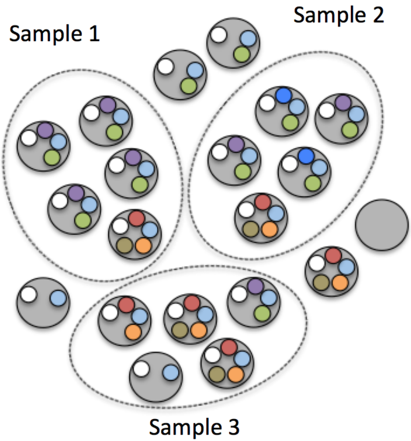
Clonal mixture from bulk-sequencing data.

- We observe DNA bulk-sequencing data.
    - Reference and variant reads.

Clonal mixture from bulk-sequencing data.

- We observe DNA bulk-sequencing data.
    - Reference and variant reads.
- Cluster mutations that occur with similar frequency.
    - Mutations from the same cluster should occur with the same frequency.

Multiple samples increase resolution.



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$$\mathbf{d_n} \triangleq \begin{bmatrix} d_{1n} \\ d_{2n} \\ \vdots \\ d_{Mn} \end{bmatrix}, \quad \mathbf{v_n} \triangleq \begin{bmatrix} v_{1n} \\ v_{2n} \\ \vdots \\ v_{Mn} \end{bmatrix}.$$

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Let $\mathbf{x}_n$ be general notation for $\{\mathbf{d}_n, \mathbf{v}_n\}$, where the use of the total or variant reads will be clear from context.

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- Latent variables $\mathbf{z}_n$, a 1-of-K indicator vector that denotes the cluster assignment of SNV n to cluster k.
- We don't know the number of clusters in advance.

Problem statement

SNV clustering problem

Suppose that for SNVs $n \in \{1, ..., N\}$ in samples $m \in \{1, \ldots M\}$. Further suppose that there exists clones (clusters) $k \in \{1, \ldots, K\}$ and a true clustering $\mathbf{z}$. Given total reads $\mathbf{d}_1, \ldots, \mathbf{d}_n$ and variant reads $\mathbf{v}_1, \ldots, \mathbf{v}_n$, we seek to infer $\mathbf{z}$.

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- Then

$$\mathbf{v_n} \sim \begin{bmatrix} \mathrm{Bin}(v_{1n}; d_{1n}, \phi_{1k}) \\ \mathrm{Bin}(v_{2n}; d_{2n}, \phi_{2k}) \\ \vdots \\ \mathrm{Bin}(v_{Mn}; d_{Mn}, \phi_{Mk}) \end{bmatrix} \triangleq \mathbf{Bin}(\boldsymbol{\phi_k})$$

Dirichlet Process

Definition (Dirichlet Process)

For any measurable finite partition $\{B_i\}_{i=1}^n$ of a measurable set S ,

$$\text{if } X \sim \mathrm{DP}\left(H, \alpha\right)$$
$$\text{then } \left(X\left(B_1\right), \ldots, X\left(B_n\right)\right) \sim \mathrm{Dir}\left(\alpha H\left(B_1\right), \ldots, \alpha H\left(B_n\right)\right)$$

where Dir denotes the Dirichlet distribution.

- A non-parametric prior on the number of clusters.

Dirichlet Process

It is convenient to represent the Dirichlet Process in terms of its stick-breaking representation:

$$\pi_i(\mathbf{v}) = v_i \prod_{j=1}^{i-1} (1 - v_j)$$

$$DP = \sum_{i=1}^{\infty} \pi_i(\mathbf{v}) \delta_{\phi_i}$$

where ϕ_i are the parameters for the realized distribution, and v_i are iid $\mathrm{Beta}(1, \alpha)$.

We will use the stick breaking representation here.

Binomial Mixture Model with DP prior

Likelihood of data given its cluster membership:

$$\Pr(\mathbf{x_n}|\phi_k) = \prod_{m=1}^{M} \mathrm{Bin}(v_{mn}; d_{mn}, \phi_k)$$

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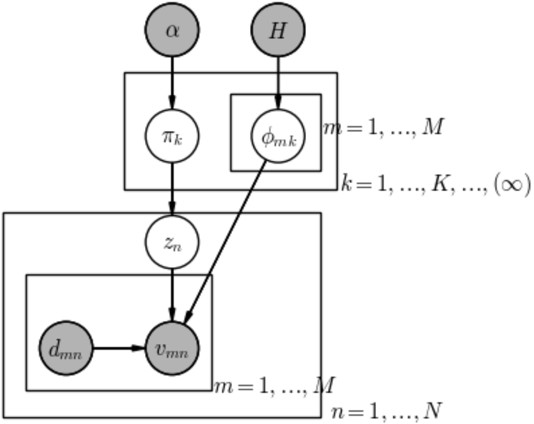
Joint likelihood of observed data and cluster memberships:

$$\Pr(\mathbf{x_n}, \mathbf{z}|\boldsymbol{\pi}, \phi) = \prod_{k=1}^{K} \prod_{m=1}^{M} (\pi_k \mathrm{Bin}(v_{mn}; d_{mn}, \phi_{mk}))^{\mathbf{z}_{nk}}$$

Binomial Mixture Model with DP prior



Binomial Mixture Model with DP prior

The full cluster assignment posterior

$$p(\mathbf{z}|\mathbf{x}, \alpha, H) = \int p(\mathbf{x}|\phi)p(\phi|\mathbf{x}, \alpha, H)\, d\phi$$

involves a Dirichlet Process and is thus analytically intractable. We must use some sort of computational technique, such as variational inference, to perform inference on this posterior.

Variational Inference

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- Generalized version of EM; deterministic given an initialization.
- Faster than MCMC.
- Scales well on large datasets.

Overview of Variational Inference: I

Let $\mathbf{z}$ denote the latent variables, and $\mathbf{x}$ denote the data. We seek to approximate the posterior $p(\mathbf{z}|\mathbf{x})$ from a family of distributions $\mathcal{D}$ by solving the following optimization problem:

$$q^*(z) = \arg\min_{q(\mathbf{z})\in\mathcal{D}} \mathrm{KL}\left((q(\mathbf{z})||p(\mathbf{z}|\mathbf{x}))\right).$$

where KL is the KL-divergence, which measures the "distance" between two distributions.

[1] Blei 2006

Overview of Variational Inference: II

However, the KL-divergence requires us to compute the log evidence (which is intractable over the space of all $\mathbf{z}$), since

$$\mathrm{KL}\left(q(\mathbf{z}) \| p(\mathbf{z} \mid \mathbf{x})\right) = \mathrm{E}\left[\log q(\mathbf{z})\right] - \mathrm{E}\left[\log p(\mathbf{z}, \mathbf{x})\right] + \log p(\mathbf{x}).$$

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Instead, we optimize the an objective function which is not dependent on $\log p(\mathbf{x})$, called the evidence lower bound (ELBO):

$$\mathrm{ELBO}(q) = \mathrm{E}[\log p(\mathbf{z}, \mathbf{x})] - \mathrm{E}[\log q(\mathbf{z})].$$

The ELBO is a lower bound for the log evidence.

Overview of Variational Inference: III

The standard technique is to select a simple family of distributions for $\mathcal{D}$, the mean-field variational family. In this family, the latent variables $\mathbf{z}$ are mutually independent so that the joint distribution factorizes:

$$q(\mathbf{z}) = \prod_{j=1}^{m} q_j(z_j).$$

where q_j is a bounded variation dependent only on z_j. The structure of the model will dictate the optimal form of q_j.

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Let $\mathbf{z}_{-j}$ denote the set of latent variables $\mathbf{z}_l$ such that $l \neq j$. Then we can show that

$$\begin{aligned} \mathrm{ELBO}(q) &= \int \prod q_i(\mathbf{z}_i) \left(\log p(\mathbf{z}, \mathbf{x}) - \sum_i \log q_i(\mathbf{z}_i) \right) \, d\mathbf{z} \\ &\propto \int q_j(z_j) \mathrm{E}_{-j} \left[\log p(\mathbf{x}, \mathbf{z}) \right] \, d\mathbf{z}_j - \int q_j(z_j) \log q_j(\mathbf{z}_j) \, d\mathbf{z}_j \end{aligned}$$

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Now suppose that we fix z_{-j} and maximize the ELBO. It can be shown that

$$q_j^*(\mathbf{z}_j) \propto \exp\left(\mathrm{E}_{-j}\left[\log p(\mathbf{x}, \mathbf{z})\right]\right)$$

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By iterating through these coordinate updates, we reach a local optimum of the ELBO.

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Recall that a distribution is in exponential form if it can parameterized by

$$f_X(x \mid \theta) = h(x) \exp\left(\theta^T \cdot T(x) - A(\theta)\right)$$

where $T(x)$ are the sufficient statistics, θ are the natural parameters,$A(\theta)$ is the cumulant, and $h(x)$ is the base measure.

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The intuition is that because $q^* \propto \exp(\mathrm{E}[\log(.)])$, then writing the distribution in exponential form reveals dependencies that hold for all exponential family members.

[1] Hughes 2015

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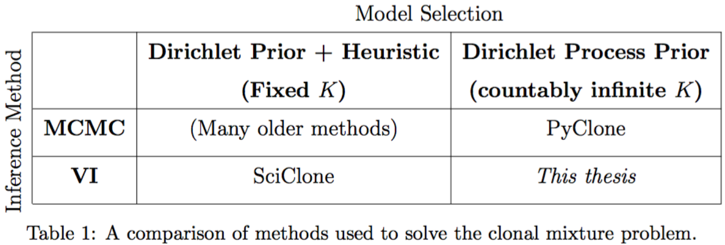
- MCMC, like Gibbs sampling, is typically easier to implement.
    - No need for painful derivations.

Existing methods



Model Selection

Inference Method		**Dirichlet Prior + Heuristic (Fixed K)**	**Dirichlet Process Prior (countably infinite K)**
	MCMC	(Many older methods)	PyClone
	VI	SciClone	*This thesis*

Table 1: A comparison of methods used to solve the clonal mixture problem.

VI for the DP/Binomial mixture model

By beta-binomial conjugacy,

$$\begin{aligned} q(\phi_k) &= \prod_{m=1}^{M} q(\phi_{mk}) \\ &= \prod_{m=1}^{M} \mathrm{Beta}(\phi_k | \alpha_{mk}, \beta_{mk}) \end{aligned}$$

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Thus, combined with the DP variational parameters,

$$q(\mathbf{z}, \mathbf{v}, \phi) = \underbrace{\prod_{k=1}^{K} q(\phi_k)}_{\substack{\text{Observation: likelihoods} \\ \text{Product of betas} \\ 2MK \text{ variational parameters} \\ \{\alpha_{mk},\beta_{mk}\}_{m=1,k=1}^{M,K}}} \times \underbrace{\prod_{k=1}^{K} q(\mathbf{v}_k)}_{\substack{\text{Allocation: cluster proportions} \\ \text{Product of betas} \\ 2K \text{ variational parameters} \\ \{\eta_{k0},\eta_{k1}\}_{k=1}^{K}}} \times \underbrace{\prod_{n=1}^{N} q(z_n)}_{\substack{\text{Allocation: cluster responsibilities} \\ \text{Product of categoricals} \\ 2NK \text{ variational parameters} \\ \{\hat{r}_{nk}\}_{n=1,k=1}^{N,K}}}$$

Most of the details are in the thesis appendices.

MAP estimates

For each cluster we pool reads by cluster membership:

$$v_{mk}^{\text{pooled}} = \sum_n (v_{mn})^{\mathbf{z}_n}$$

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and we can make MAP estimates by converting from the variational parameters back to the original parameters of the posterior:

$$\mathbf{z}_n^{\text{MAP}} = \arg\max_k \hat{r}_{nk}$$

$$\phi_{mk}^{\text{MAP}} = \frac{v_{mk}^{\text{pooled}} + \alpha_{mk} - 1}{d_{mk}^{\text{pooled}} + \alpha_{mk} + \beta_{mk} - 2}.$$

Implementation

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Everything was implemented in Python.

Coordinate ascent algorithm

```
Algorithm 1: CAVI FOR THE DP BINOMIAL MIXTURE MODEL
Input: Data $\mathbf{x}_n$, where each $x_i$ is an integer vector with $M$ entries.
       $\gamma_0, \gamma_1, \alpha_0, \beta_0$, hyperparameters
Output: Converged variational parameters
       $\{\alpha_{mk}, \beta_{mk}\}_{m=1,k=1}^{M,K}, \{\eta_{k0}, \eta_{k1}\}_{k=1}^{K}, \{\hat{r}_{nk}\}_{n=1,k=1}^{N,K}$
Initialize: $\alpha_0 = \beta_0 = \alpha_{mk} = \beta_{mk} = 1, \forall m, k$
       $\gamma_1 = \eta_1 = 1.0, \gamma_0 = \eta_0 = 1.5$
       $\hat{r}_{nk} \leftarrow \texttt{kmeans++}(\mathbf{x})$
while the ELBO has not converged do
    ▷ Compute data-specific (local) parameters
        $\mathrm{E}_q[\log p(x_n|\alpha_{mk}, \beta_{mk})] \leftarrow \mathrm{E}_q[\log \left( \binom{d_{mn}+v_{mn}}{v_{mn}} (\phi_k)^{v_{mn}} (1-\phi_k)^{d_{mn}} \right)]$
        $\hat{r}_{nk} \leftarrow \exp(S_k)$
    ▷ Compute sufficient statistics
        $S_k = \sum_{n=1}^{N} \hat{r}_{nk} s(x_n) = \sum_{n=1}^{N} \hat{r}_{nk} \left[ \begin{bmatrix} v_{1n} & d_{1n} \end{bmatrix} \quad \cdots \quad \begin{bmatrix} v_{Mn} & d_{Mn} \end{bmatrix} \right]$
        $N_k = \sum_{n=1}^{N} \hat{r}_{nk}$
        $N_k^{>} = \sum_{k+1}^{K} N_k$
    ▷ Compute cluster-specific (global) parameters
        $\eta_{k1} \leftarrow 1 + \sum_n \hat{r}_{nk} = 1 + N_k$
        $\eta_{k0} \leftarrow \gamma + \sum_n \sum_{j=k+1}^{K} \hat{r}_{nj} = N_k^{>}$
        $\alpha_{mk} \leftarrow (\alpha_0 - 1) + S_{km}$
        $\beta_{mk} \leftarrow (\beta_0 - 1) + S_{km}$
    Compute $\mathrm{ELBO}(q) = \mathbb{E}[\log p(\mathbf{z}, \mathbf{x})] - \mathbb{E}[\log q(\mathbf{z})]$
end
return Converged variational parameters
```

Simulated Data

Number of clusters (K)	10
Number of SNVs (N)	100
Number of samples (M)	4, 5, 6
Coverage	50, 100, 1000

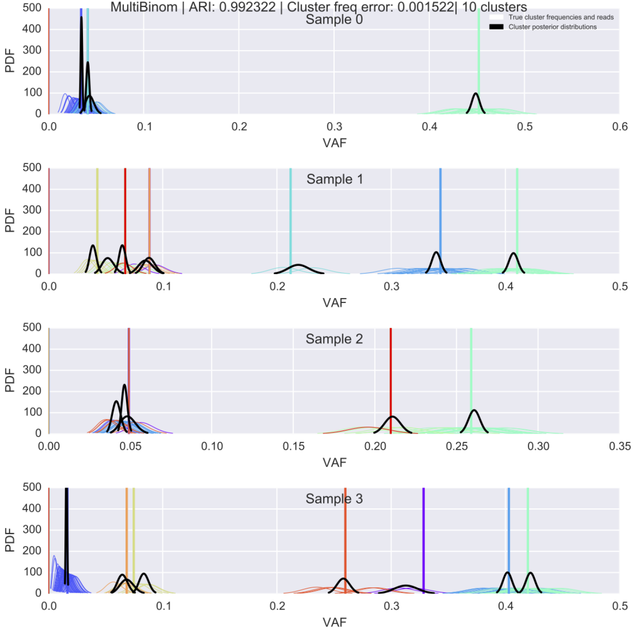
Parameters for the simulated datasets.

Evaluating results

The DP/VI coordinate ascent algorithm was benchmarked against SciClone (VI) and PyClone (DP/MCMC).

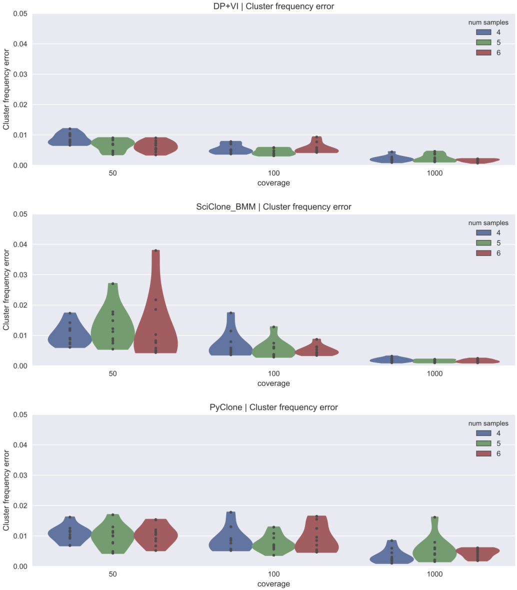
- Evaluate clustering: Adjusted Rand Index (ARI)
- Evaluate parameters: Cluster frequency error (CFE)

$$\mathrm{CFE}(\phi^{\mathrm{MAP}}) \triangleq \frac{1}{C} \sum_{c=1}^{C} \min_{k \in \{1,\dots,K\}} \left\| \phi_c^{\mathrm{MAP}} - \phi_k \right\|$$

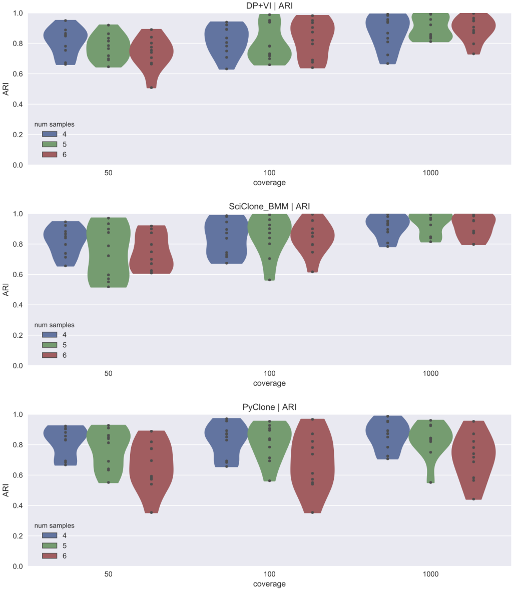


Cluster posteriors (black) and true clusters (colored, vertical lines) with $\mathbf{x}_n$ *(colored beta curves).*

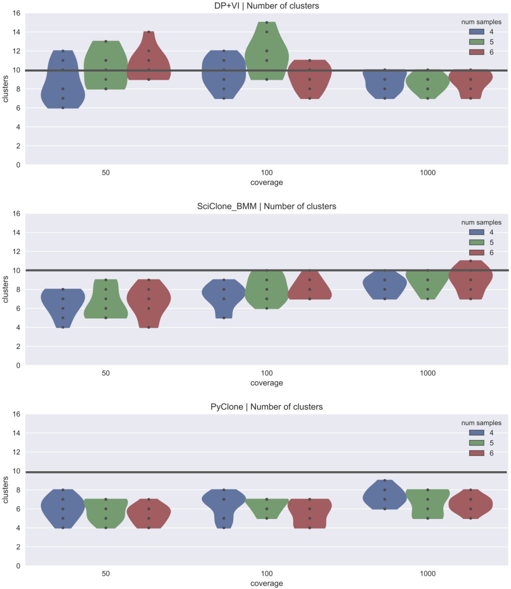
Cluster Frequency Error



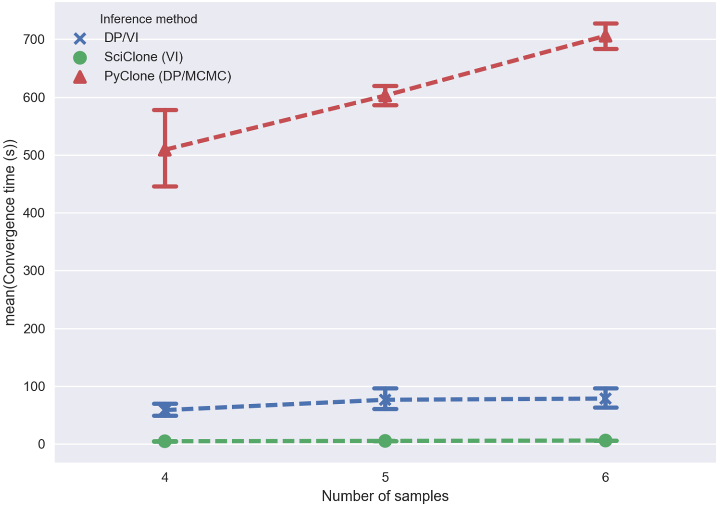
Adjusted Rand Index



Number of clusters



Runtime


Inference method
DP/VI
SciClone (VI)
PyClone (DP/MCMC)
mean(Convergence time (s))
0
100
200
300
400
500
600
700
4
5
6
Number of samples

Discussion

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- Comparable to SciClone (other variational method)
    - Better at lower coverages.
    - Added benefit: nonparametric prior.

Future Work

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- Try on real data

Acknowledgments

Thanks to:

- Prof Ben Raphael
- Mohammed El-Kebir, Gryte Satas, and the rest of the Raphael Lab
- Prof Erik Sudderth and Mike Hughes
- My friends and family
  - Especially the support of the others doing theses:
    Uthsav Chitra, Vaki Nikitopoulos, Matt Chin, and Keshav Vemuri