Variable selection in binomial regression with latent Gaussian field models for analysis of epigenetic data

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Overview

Introduction

- More precise estimation of the methylation status of locations
- Discovery of methylated and unmethylated regions and corresponding local and global structures:
  - Represented by nucleotides sequences patterns (CG-islands, CPG-islands)
  - Represented by such structures as genes on the whole, promoters, expressions and their sequences
- Finding covariates (location within the gene, underlying genetic structure, chromosome etc.) significantly influencing methylation patterns along the genome
- Linking genetic and epigenetic data to phenotypic responses (expressions of genes, presence of transposons, etc.) in a statistically significant way

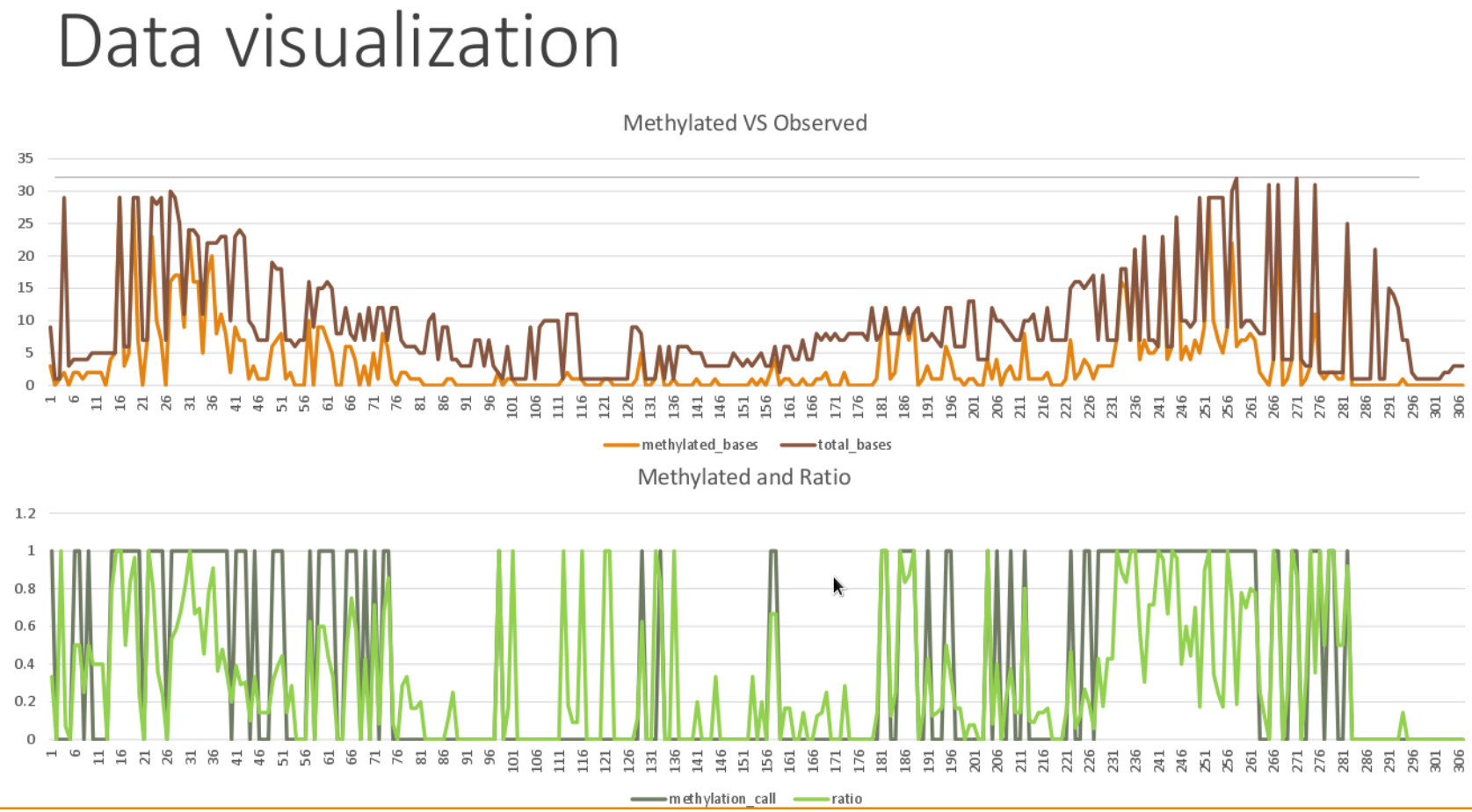


Figure: Total reads and methylated reads for some part of the genome

The model

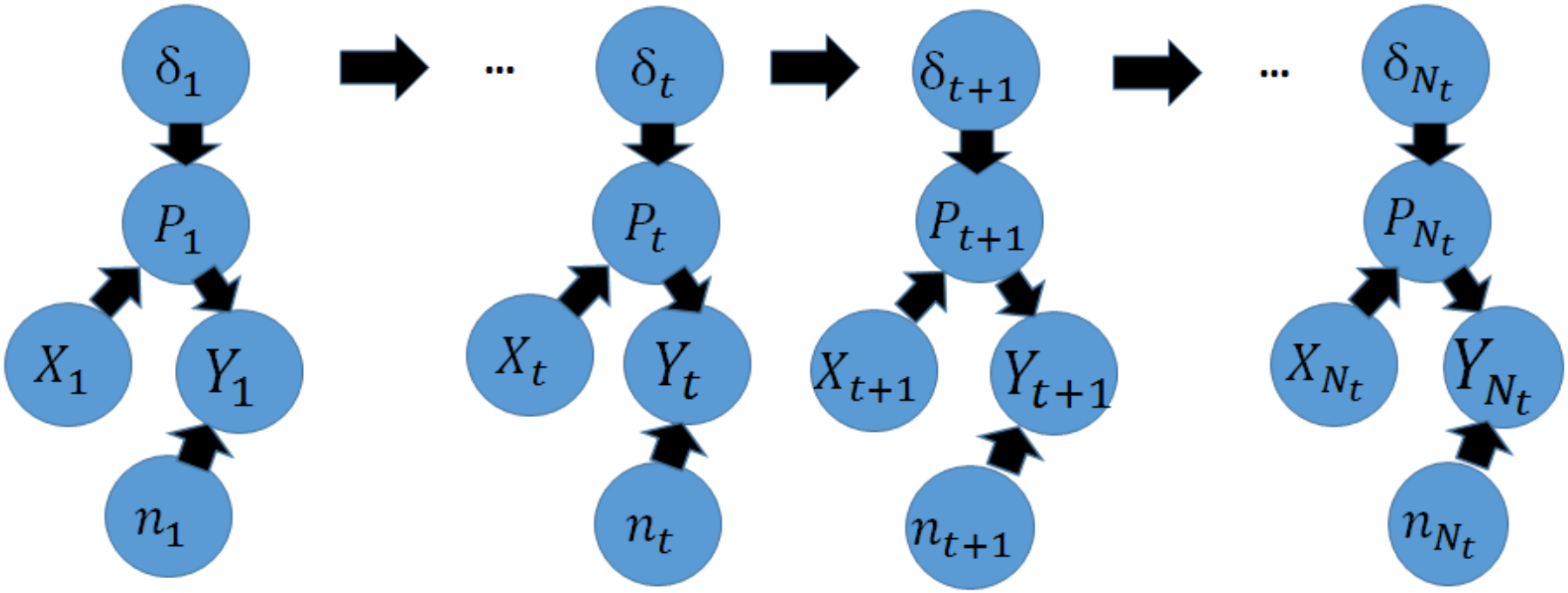


Figure: The model

The model

Generalized Binomial Regression With Gaussian Latent Field Model **(GBR-WGLF)**

$$\Pr(y_t = y | n_t = n, p_t) = \binom{n}{y} p_t^y (1 - p_t)^{n-y} \tag{1}$$

$$p_t = \frac{e^{\gamma_0 \beta_0 + \sum_{i=1}^{M} \gamma_i \beta_i X_{t,i} + \delta_t}}{1 + e^{\gamma_0 \beta_0 + \sum_{i=1}^{M} \gamma_i \beta_i X_{t,i} + \delta_t}} \tag{2}$$

$$\delta_t = \rho \delta_{t-1} + \epsilon_t \tag{3}$$

- $y_t \in \{1, ..., N_t\}$ is the number of methylated reads per loci t
- $n_t \in \mathbb{N}$ is the total number of reads per loci t
- $\beta_i \in \mathbb{R}, i \in \{0, ..., N_\gamma\}$ are regression coefficients of the covariates of the model
- $\gamma_i \in \{0, 1\}, i \in \{0, ..., N_\gamma\}$ are latent indicators, defining if covariate i is included into the model
- $\rho \in \mathbb{R}$ is the coefficient of latent $AR(1)$ process

Hyper-parameters of the model

$$\gamma_i \sim Binom(1, q) \tag{4}$$
$$q \sim Beta(\alpha_q, \beta_q) \tag{5}$$
$$\beta_i|\gamma_i \sim \mathbb{I}(\gamma_i = 1)N(\mu_\beta, \sigma^2_\beta) \tag{6}$$
$$\begin{pmatrix}\psi_1 \\ \psi_2\end{pmatrix} \sim N_2(\mu_{\rho,\epsilon}, \Sigma_{\rho,\epsilon}) \tag{7}$$
$$\epsilon_t \sim N(0, \sigma^2_\epsilon) \tag{8}$$

- $\psi_1 = \log \frac{1}{\sigma^2_{\epsilon,t}}(1-\rho^2)$ and $\psi_2 = \log \frac{1+\rho}{1-\rho}$ are scaled hyper-parameters of the latent model
- ϵ_t is the error term of $AR(1)$ model
- q is the prior probability of including any covariate into the model

Inference on the model

Let:

- $\mathbb{M} : \vec{\gamma}$ define a subset of parameters of GBRWGLF
- $\Theta = \{\vec{\beta}, \rho, \sigma_\epsilon^2\}$ define all other parameters of GBRWGLF
- $\Theta|\mathbb{M}$ define parameters of GBRWGLF model conditioned on fixed $\vec{\gamma}$, further addressed as a Binomial Regression With Gaussian Latent Field Model **(BRWGLF)** or simply a model
- $\exists L = 2^{N_\gamma+1}$ different BRWGLF models

Goals:

- $\Pr(\mathbb{M}, \Theta|\mathbb{D})$ posterior distribution of parameters of GBRWGLF
- $\Pr(\mathbb{M}|\mathbb{D})$ marginal posterior distribution of the models
- Set of estimated BRWGLF performing well in terms of some model selection criteria (MAP, WAIC, DIC, MLIK) to explain the phenomena optimally

Procedure

- Note that $\Pr(\mathbb{M}, \Theta|\mathbb{D}) = \Pr(\Theta|\mathbb{M}, \mathbb{D}) \Pr(\mathbb{M}|\mathbb{D})$
- $\Pr(\Theta|\mathbb{M}, \mathbb{D})$ and $\log \Pr(\mathbb{D}|\mathbb{M})$ can be efficiently obtained by INLA
- Note that $\Pr(\mathbb{M} = M|\mathbb{D}) = \frac{e^{\log \Pr(\mathbb{D}|\mathbb{M}=M)+\log \Pr(\mathbb{M}=M)}}{\sum_{M' \in \Omega_{\mathbb{M}}} e^{\log \Pr(\mathbb{D}|\mathbb{M}=M')+\log \Pr(\mathbb{M}=M')}}$
- $\widehat{\Pr}(\mathbb{M} = M|\mathbb{D}) = \frac{e^{\log \Pr(\mathbb{D}|\mathbb{M}=M)+\log \Pr(\mathbb{M}=M)}}{\sum_{M' \in \mathbb{V}} e^{\log \Pr(\mathbb{D}|\mathbb{M}=M')+\log \Pr(\mathbb{M}=M')}}$
- $\mathbb{V}$ is the subspace of $\Omega_{\mathbb{M}}$ to be efficiently explored
- Note that for $\Pr(\mathbb{M} = M) = \Pr(\mathbb{M} = M') \forall M, M' \in \Omega_{\mathbb{M}}$:
- $\Pr(\mathbb{M} = M|\mathbb{D}) \gg \Pr(\mathbb{M} = M'|\mathbb{D})$ if $\log \Pr(\mathbb{D}|\mathbb{M} = M) > \log \Pr(\mathbb{D}|\mathbb{M} = M')$ often $\Longrightarrow$
- Near modal values in terms of MLIK are particularly important for construction of reasonable $\mathbb{V} \subset \Omega_{\mathbb{M}}$, missing them can dramatically influence posterior in the original space $\Omega_{\mathbb{M}}$

INLA overview

Say we study some
Observation model: $\pi(y|\eta)$
Parameter model: $\pi(\eta|\upsilon) \sim N_u(\mu(\upsilon), Q(\upsilon))$
Hyperparameter: $\upsilon \sim f(\upsilon)$

The models are assumed to satisfy some properties:

- The parameter model is usually of large dimension, however it has numerous conditionally independent components, so its precision matrix $Q(\upsilon)$ is sparse
- The dimension of the hyperparameter vector υ is relatively small
- Laplace or Gaussian approximation method of integration of the posterior density can be used for the addressed model

INLA provides:

- The marginal posterior distribution of parameters which can be summarized by means, variances and quantiles
- Model selection criteria DIC, WAIC, MLIK (exactly $\log \Pr(\mathbb{D}|\mathbb{M} = M)$)
- Predictive measures (CPO, PIT)

INLA fundamentals

INLA approach approximates posterior marginals of hyperparameters

$$\tilde{\pi}(\upsilon_j|y) = \int_{\Omega_{\upsilon-j}} \tilde{\pi}(\upsilon|y)d\upsilon_{-j} \approx \sum_{k\in\mathbb{K}} \tilde{\pi}(\upsilon_j, \upsilon_{-j}^k|y) \triangle_k \tag{9}$$

and posterior marginals of parameters

$$\tilde{\pi}(\eta_i|y) = \int_{\Omega_\upsilon} \tilde{\pi}(\eta_i|\upsilon, y)\tilde{\pi}(\upsilon|y)d\upsilon \approx \sum_{k\in\mathbb{K}} \tilde{\pi}(\eta_i|\upsilon_k, y)\tilde{\pi}(\upsilon_k|y) \triangle_k \tag{10}$$

where $\tilde{\pi}(.|.)$ denotes an approximated conditional density of its arguments. Numerical integration over Ω_υ is possible since its dimension is small by assumptions.

Note that

Choice of knots υ_{-j}^k and υ_k and measures of the space $\triangle_k$ for numerical integration with efficient exploration of $\Omega_{\upsilon_{-j}}$ and Ω_υ correspondingly is vital.

INLA fundamentals

INLA approach is based on the following approximation of the marginal posterior of υ

$$\tilde{\pi}(\upsilon|y) \propto \left. \frac{\pi(\eta, \upsilon, y)}{\tilde{\pi}_G(\eta|\upsilon, y)} \right|_{\eta=\eta^*(\upsilon)} \tag{11}$$

where $\tilde{\pi}(\eta|\upsilon, y)$ is a Gaussian approximation to the full conditional of η and $\eta^*(\upsilon)$ is the posterior mode of this full conditional. and of the conditional marginal posterior of η_i

$$\tilde{\pi}_{LA}(\eta_i|\upsilon, y) \propto \left. \frac{\pi(\eta, \upsilon, y)}{\tilde{\pi}_{GG}(\eta_{-i}|\eta_i, \upsilon, y)} \right|_{\eta_i=\eta_i^*(\eta_i,\upsilon)} \tag{12}$$

where $\tilde{\pi}_{GG}(\eta_i|\eta_{-i}, \upsilon, y)$ is the Gaussian approximation for $\eta_i|\eta_{-i}, \upsilon, y$ given its mode $\eta_i^*(\eta_i, \upsilon)$

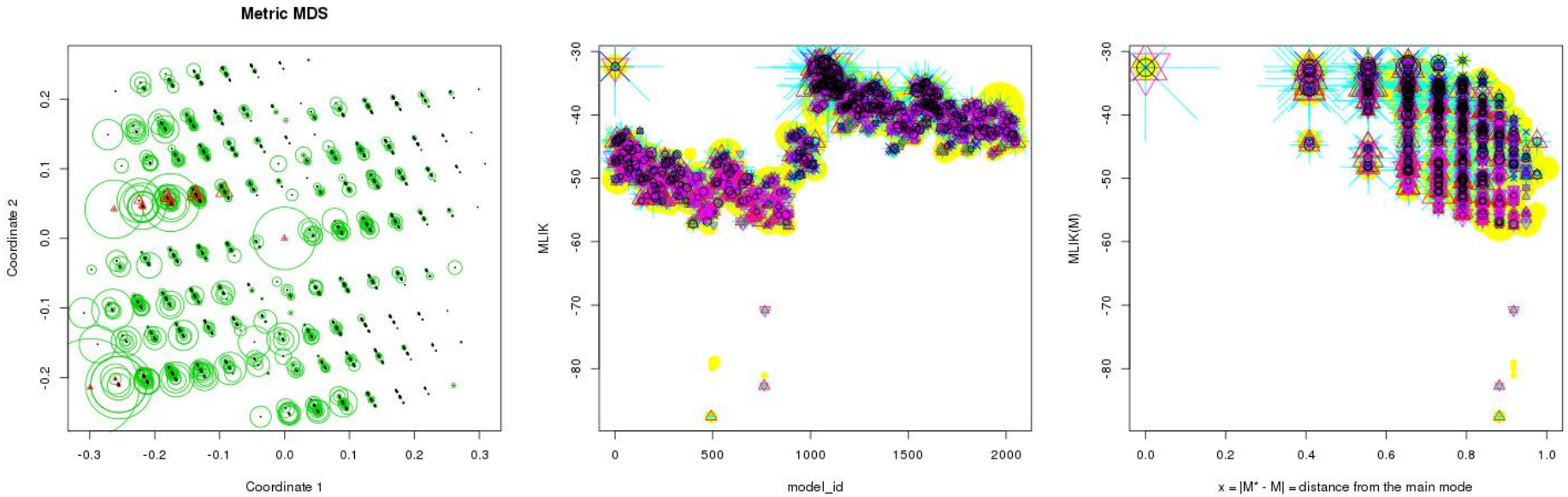
Some conclusions

We are now done with INLA. Address the rest:

- Note that $\Pr(\mathbb{M}, \Theta|\mathbb{D}) = \Pr(\Theta|\mathbb{M}, \mathbb{D}) \Pr(\mathbb{M}|\mathbb{D})$
- $\Pr(\Theta|\mathbb{M}, \mathbb{D})$ and $\log \Pr(\mathbb{D}|\mathbb{M} = M)$ are obtained by INLA

Proceed with efficient exploration of $\mathbb{V}$ in the subspace of $\Omega_{\mathbb{M}}$ to estimate $\Pr(\mathbb{M} = M|\mathbb{D})$, $\underset{M \in \Omega_{\mathbb{M}}}{\operatorname{argmax}} \Pr(\mathbb{M} = M|\mathbb{D})$, and $\underset{M \in \Omega_{\mathbb{M}}}{\operatorname{argmax}} \text{WAIC}(M)$

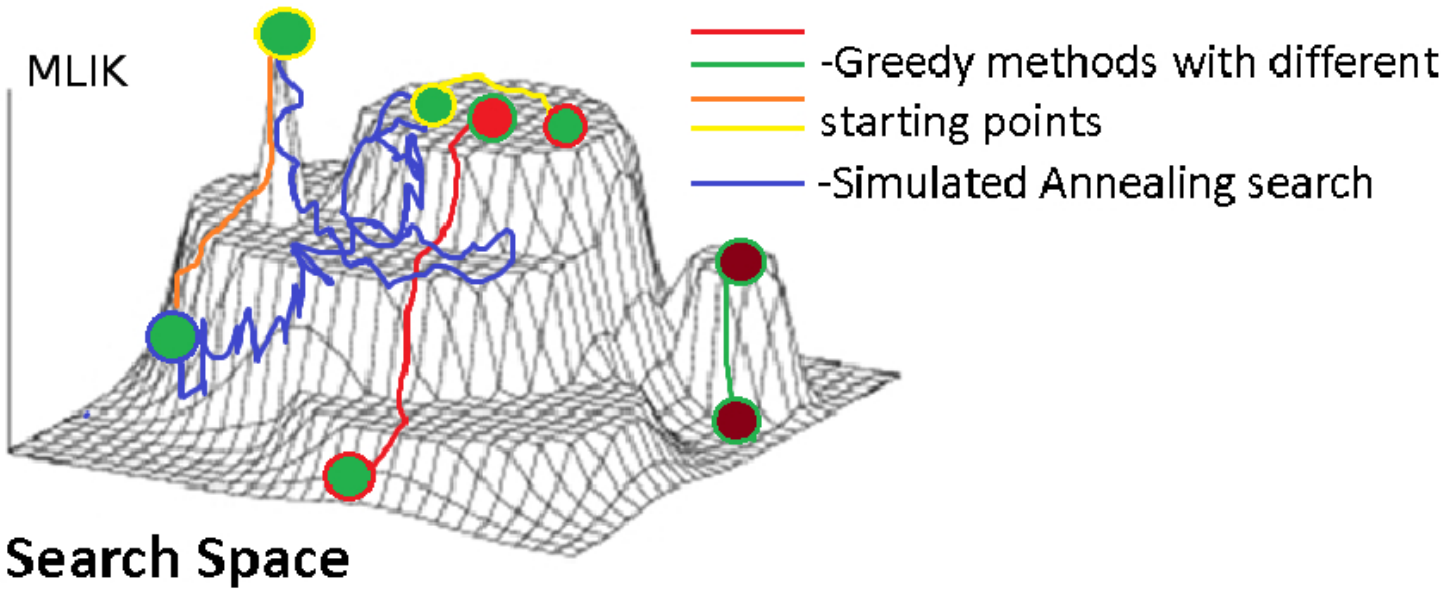
Main challenges are multimodality in $\Omega_{\mathbb{M}}$ and its size:



Possible ways to explore $\mathbb{V} \subset \Omega_{\mathbb{M}}$

Main challenges are multimodality in $\Omega_{\mathbb{M}}$ and its size.

- Full enumeration of $\Omega_{\mathbb{M}}$ - infeasible for large dimensions
- Random walk in $\Omega_{\mathbb{M}}$ including simple MCMC - does not take advantage of the structure of $\Omega_{\mathbb{M}} \Longrightarrow$ too slow
- Greedy optimization - end up in local optima
- SA - ends up with random descent with almost no chance to change the mode
- Random walk with mode jumping proposals seems to be a good idea



MCMC balance with no mode jumping proposals

Balance equation for MCMC with MH algorithm. Consider transitions from state x to y, then in a general MH setting we have

$$\blacktriangleright \pi(x)A(x,y) = \pi(x)Q(y|x)r_m(x,y) = \pi(x)Q(y|x)\min\left\{1, \frac{\pi(y)Q(x|y)}{\pi(x)Q(y|x)}\right\} =$$

$$= \min\left\{\pi(x)Q(y|x), \frac{\pi(y)Q(x|y)}{1}\right\} =$$

$$= \frac{\pi(y)Q(x|y)}{\pi(y)Q(x|y)}\min\left\{\pi(x)Q(y|x), \frac{\pi(y)Q(x|y)}{1}\right\} =$$

$$= \pi(y)Q(x|y)\min\left\{\frac{\pi(x)Q(y|x)}{\pi(y)Q(x|y)}, 1\right\} = \pi(y)A(y,x) \blacktriangleleft \quad (13)$$

MCMC balance with mode jumping proposals

Assume the current state to be $y \sim \pi(y)$. If we generate $(x^*, y^*) \sim q(x^*, y^*|y)$ and then $x|y, x^*, y^* \sim h(x|y, x^*, y^*)$ as some auxiliary variables for some arbitrary chosen h. Then in the extended space of both x and y we have the proof (14). Thus in (14) $\pi(y)$ is the target distribution in the original space.

$$\blacktriangleright \pi(y,x)A(y,x;y^*,x^*) = \pi(y)\mathrm{q}(y^*,x^*|y)h(x|y^*,x^*,y)r_m(y,x;y^*,x^*) =$$

$$= \pi(y)\mathrm{q}(y^*,x^*|y)\min\left\{1, \frac{\pi(y^*)\mathrm{q}(y,x|y^*)h(x^*|y,x,y^*)}{\pi(y)\mathrm{q}(y^*,x^*|y)h(x|y^*,x^*,y)}\right\} =$$

$$= \min\left\{\pi(y)\mathrm{q}(y^*,x^*|y,x)h(x|y^*,x^*,y), \frac{\pi(y^*)\mathrm{q}(y,x|y^*)h(x^*|y,x,y^*)}{1}\right\} =$$

$$= \pi(y^*)\mathrm{q}(y,x|y^*)h(x^*|y,x,y^*)\min\left\{\frac{\pi(y)\mathrm{q}(y^*,x^*|y,x)h(x|y^*,x^*,y)}{\pi(y^*)\mathrm{q}(y,x|y^*)h(x^*|y,x,y^*)}, 1\right\} =$$

$$= \pi(y^*,x^*)A(y^*,x^*;y,x) \blacktriangleleft \quad (14)$$

MCMC with mode jumping proposals

Notice that

Locally annealed, locally optimized, locally simulated and locally multiple try simulated proposals and their combination are all of this type of extension of the original space and therefore their detailed balanced equation is proved in (14), the same concerns multiply try proposals in local multiple try MCMC.

Also notice

Also note that within this setting of locally optimized MTMCMC we get an alternative MCMC based approximations for posterior probabilities of the models, namely $\tilde{\Pr}(\mathbb{M} = M|\mathbb{D}) = \frac{\sum_{i=1}^{W} \mathbb{I}(M_i = M)}{W} \xrightarrow[W\to\infty]{d} \Pr(\mathbb{M} = M|\mathbb{D})$ and $\underset{i\in 1,\ldots,W}{\operatorname{argmax}} \text{WAIC}(M_i) \xrightarrow[W\to\infty]{} \underset{M \in \Omega_{\mathbb{M}}}{\operatorname{argmax}} \text{WAIC}(\mathbb{M} = M)$. Whist $\mathbb{V} = \bigcup_{i=1}^{W} M_i \xrightarrow[W\to\infty]{} \Omega_{\mathbb{M}}$.This allows us to verify the results.

MTMCMC with SA proposals

Algorithm 1 Simulated annealing optimization

procedure ANNEAL($T_c, \Pr_a(.,.|.), f(.), x_0$) ▷ cooling schedule, acceptance probabilities, objective function and initial point
  $x \leftarrow x_0$
  $x_b \leftarrow x_0$
  for t in T_c **do** ▷ for all temperatures in the cooling schedule
    $x_c \leftarrow \mathbb{N}(x)$ ▷ pick a random neighbor of the current solution
    if $\mathsf{G}(x_c) > \mathsf{G}(x_b)$ **then**
      $x_b \leftarrow x_c$ ▷ update the best found solution
    end if
    if $\Pr_a(x, x_c|t) > u \sim Unif[0; 1]$ **then**
      $x \leftarrow x_c$ ▷ accept the move with some probability
    end if
  end for
  return x, x_b ▷ return the final solution
end procedure

MTMCMC with SA proposals

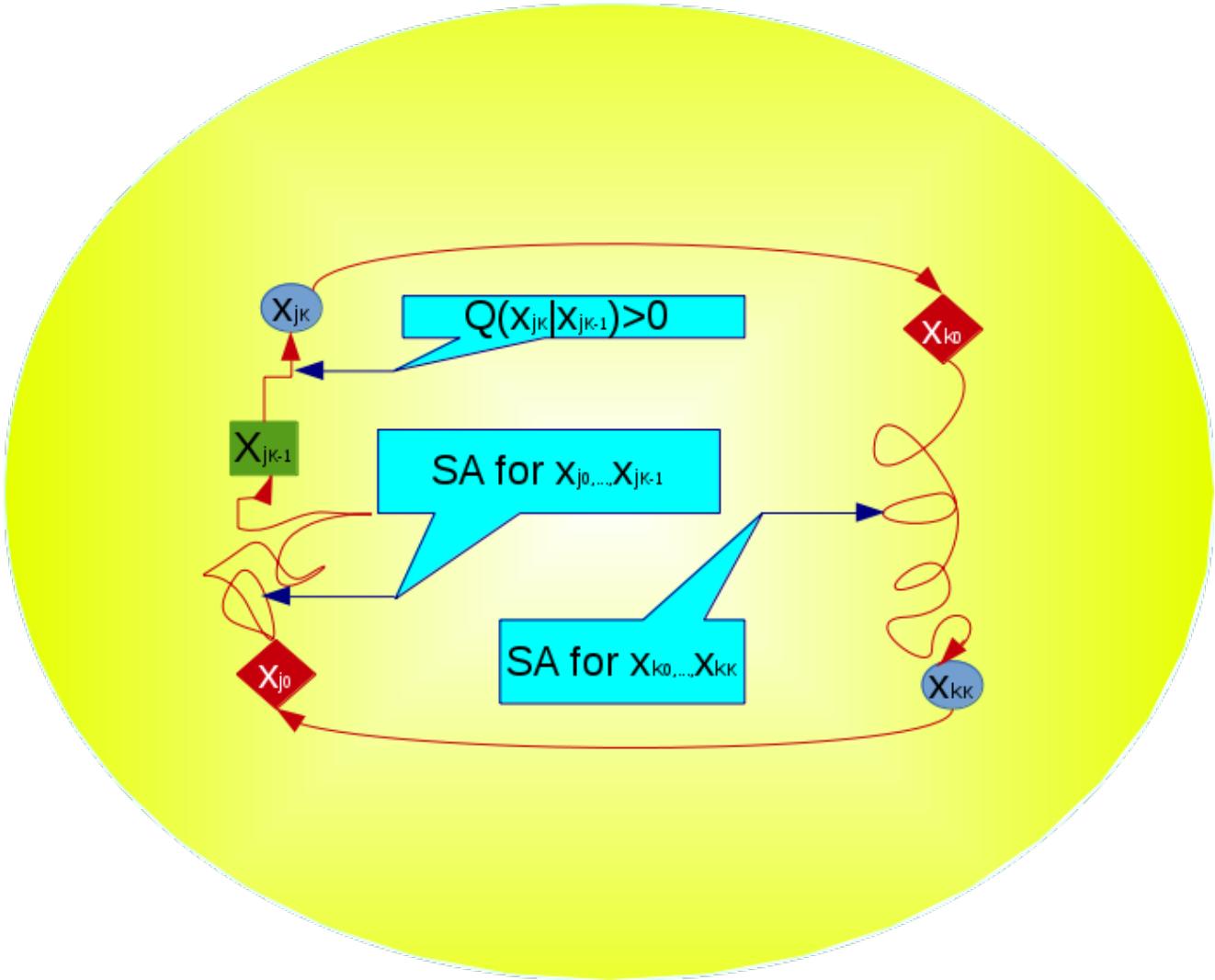


Figure: Simulated annealed symmetric proposals

MTMCMC with SA proposals

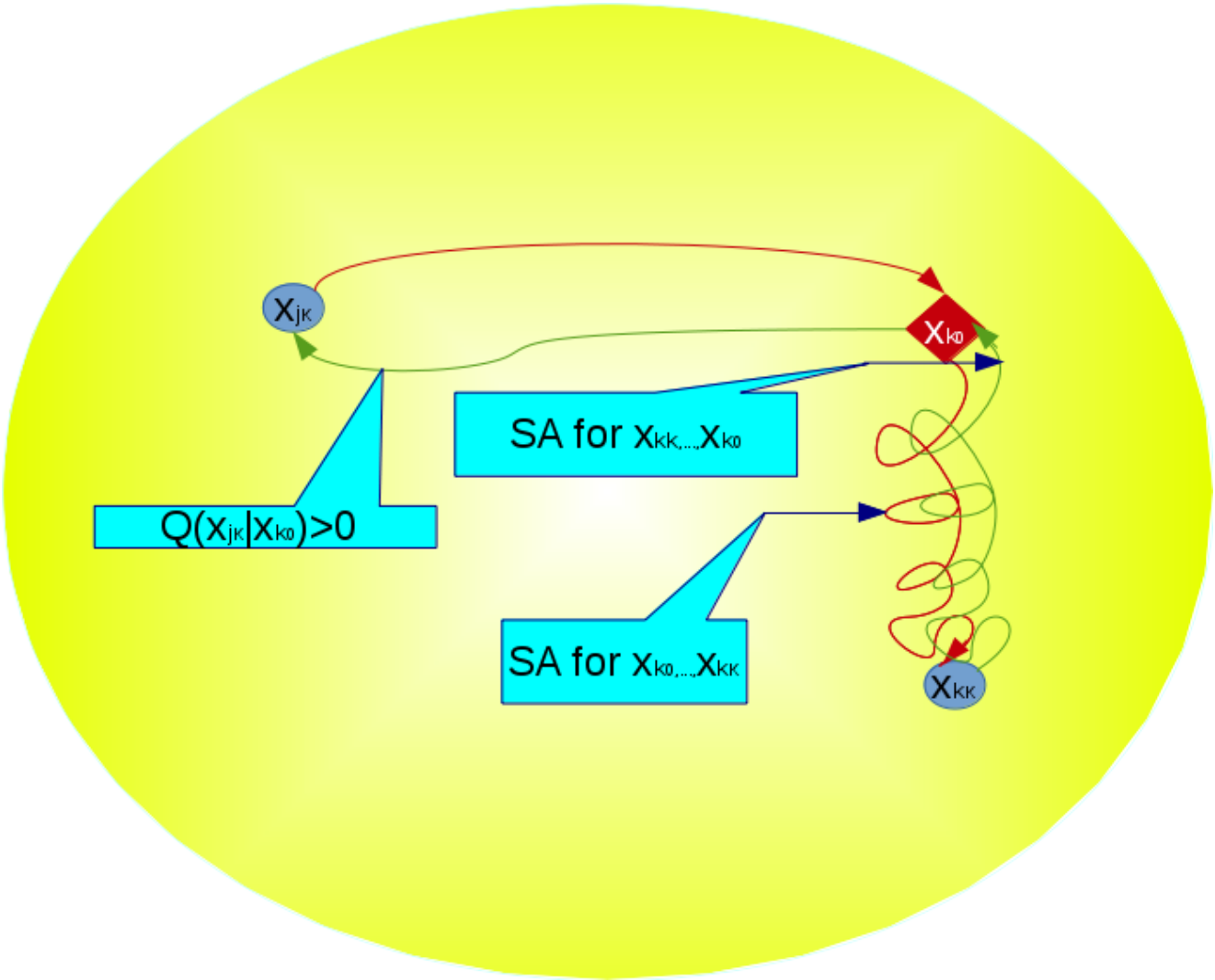


Figure: Simulated annealed forward-backward proposals

MTMCMC with LMTMCMC proposals

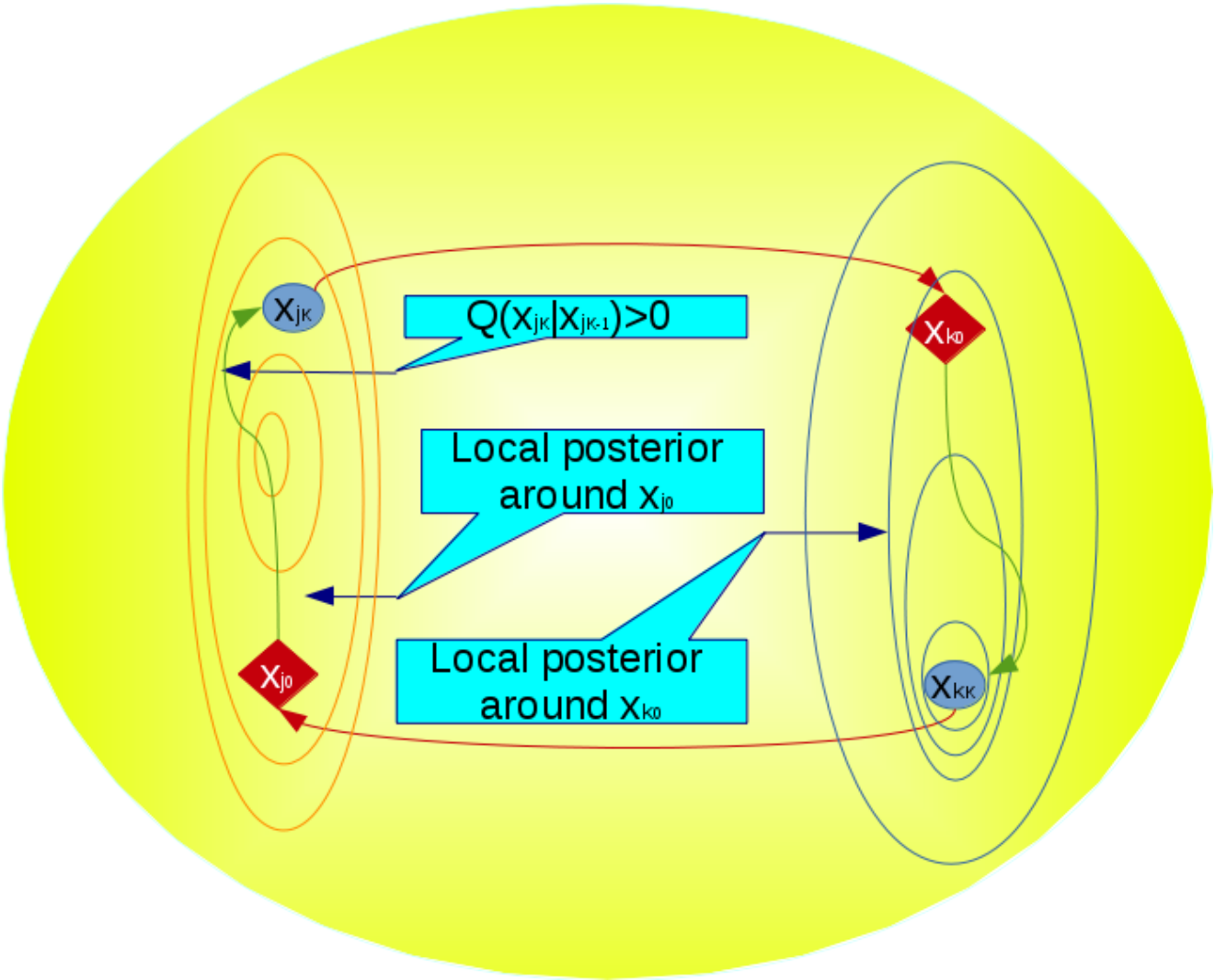


Figure: Locally simulated proposals

MTMCMC with greedily optimized proposals

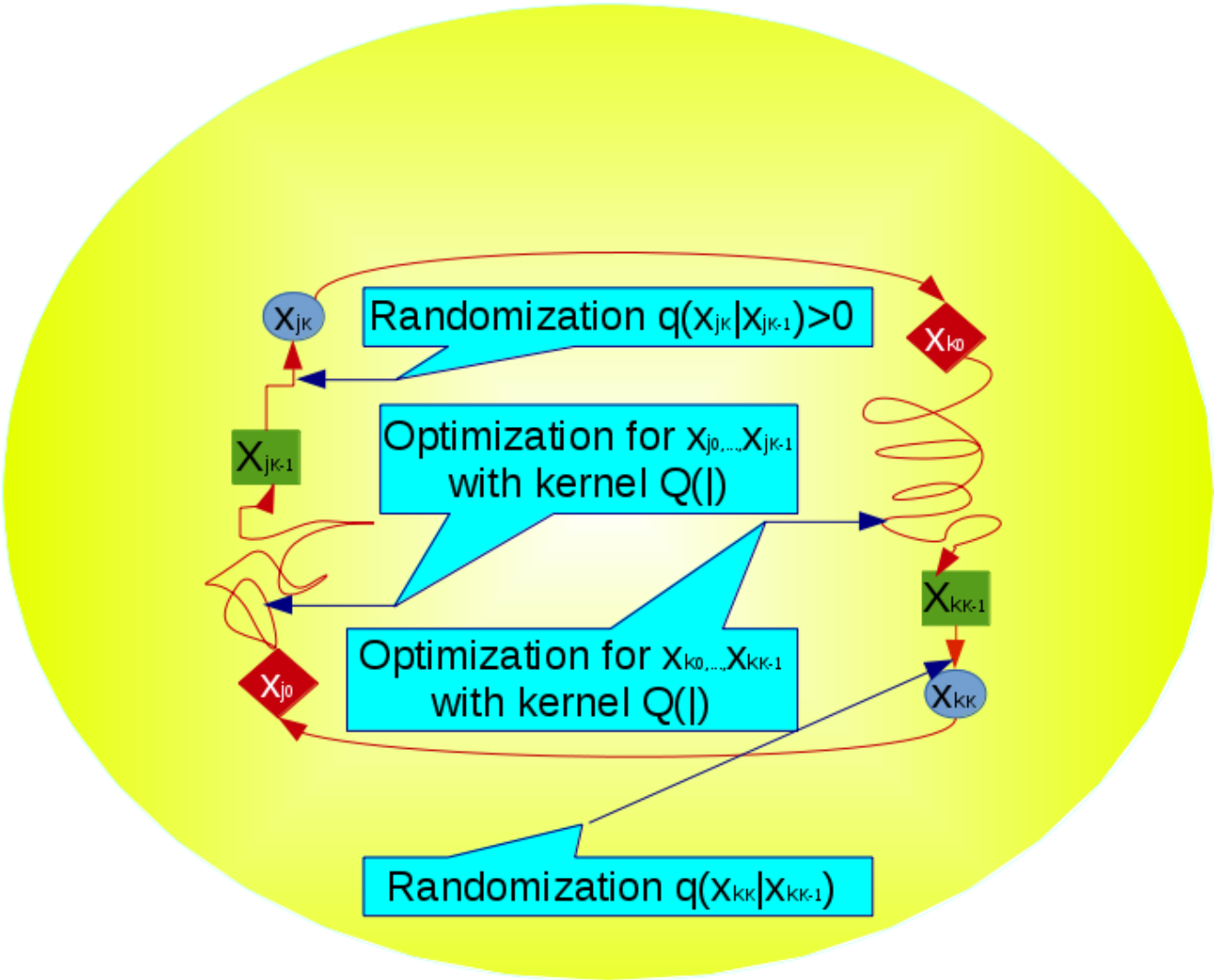


Figure: Locally optimized with randomization proposals

Multicore and shared memory issues

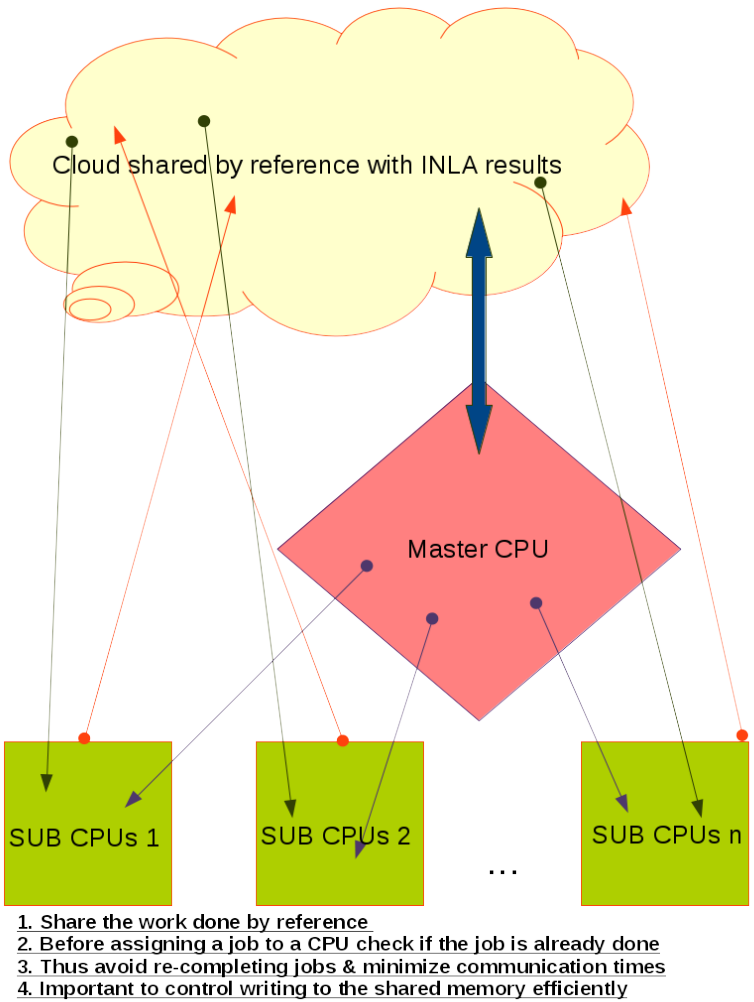


Figure: Multiprocessing architecture

Results

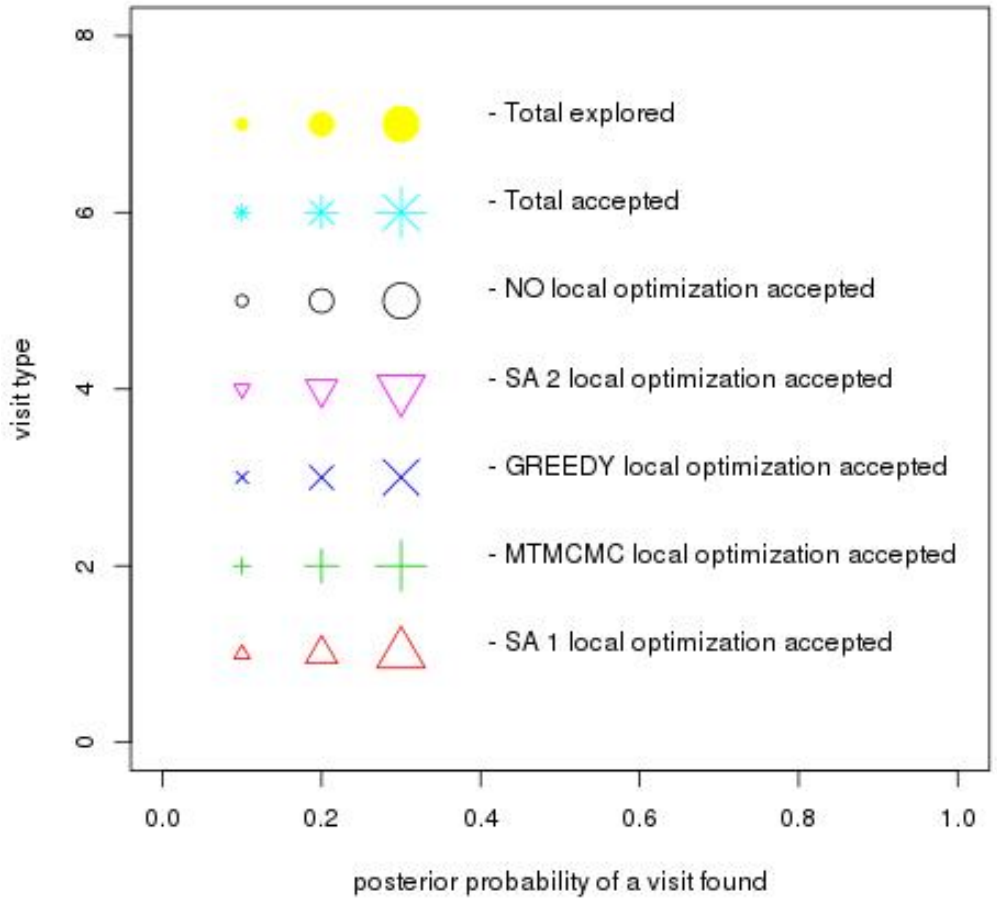
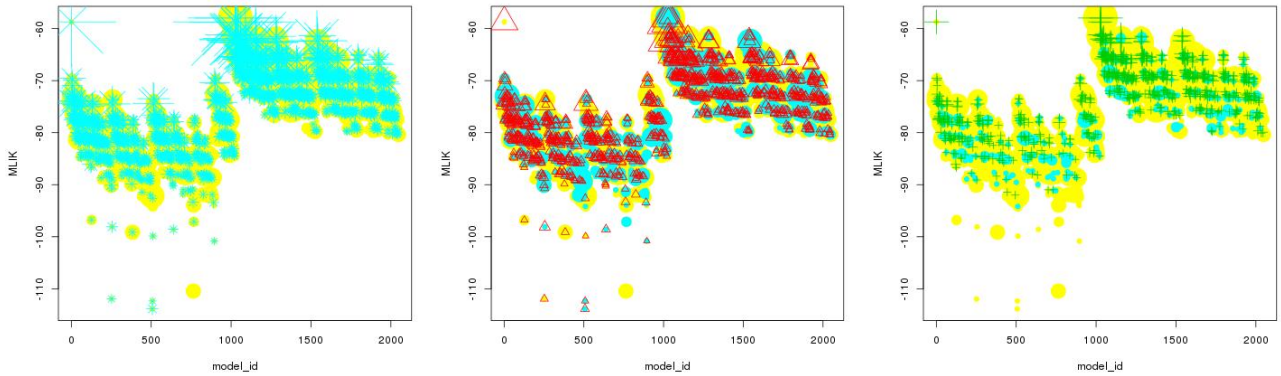
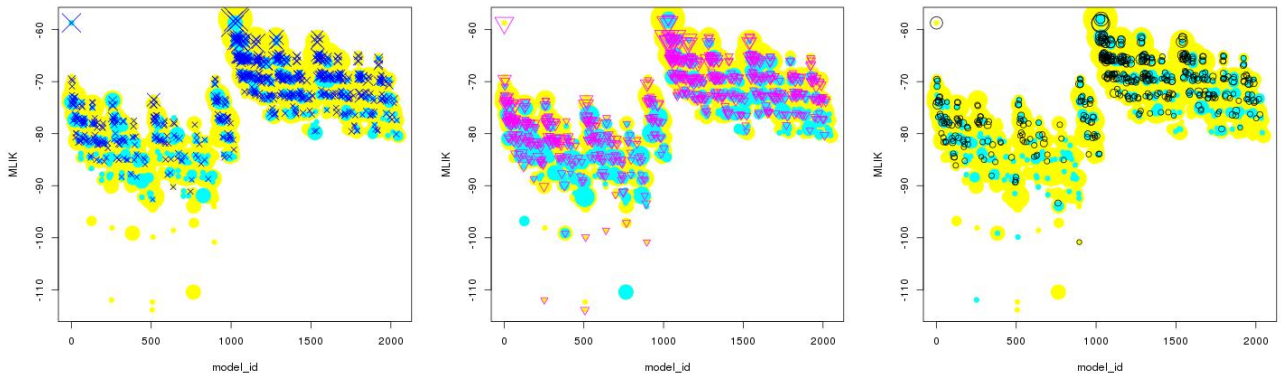


Figure: Notation

Results



(a) totally explored (b) plus SA 1 (c) plus locMCMC



(d) plus greedy (e) plus SA 2 (f) no local opt.

Figure: MLIK against model index different methods

Results

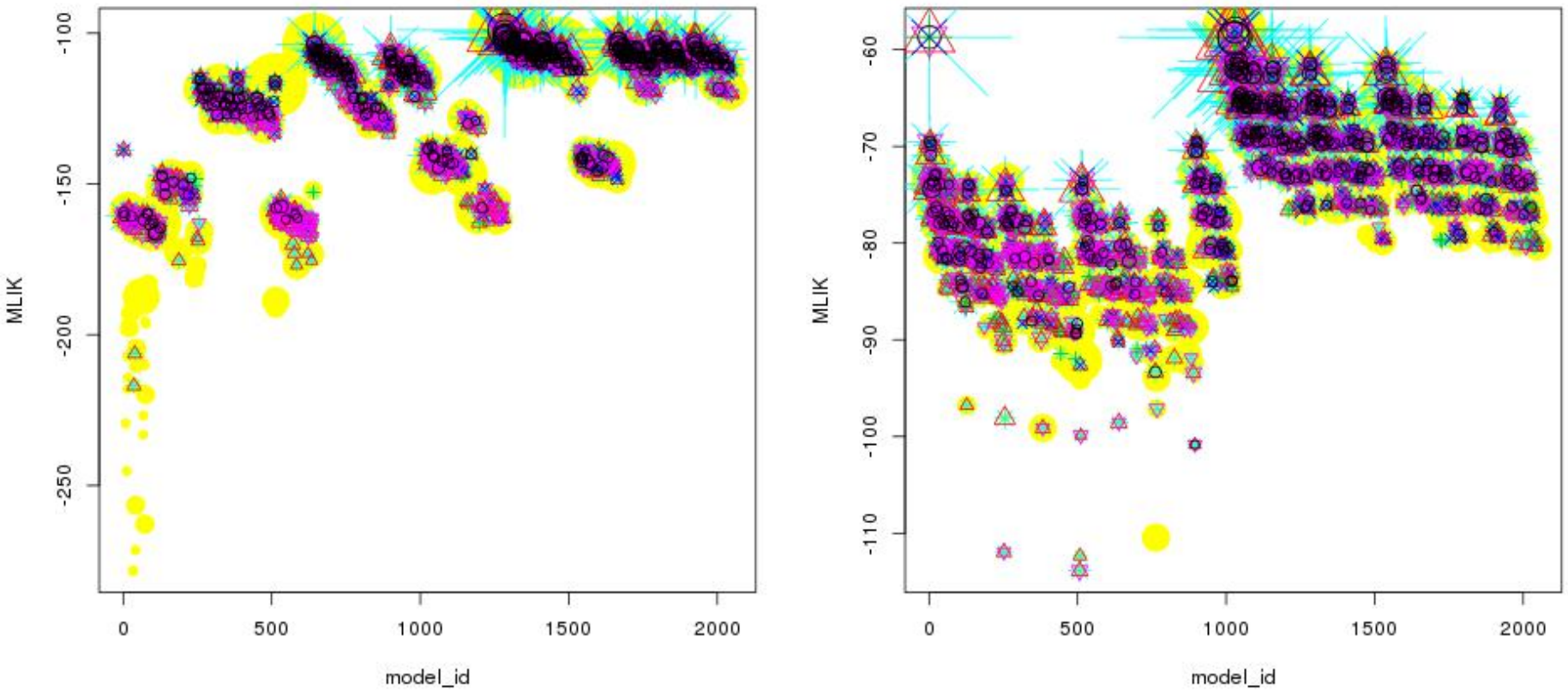


Figure: MLIK against model index

Results

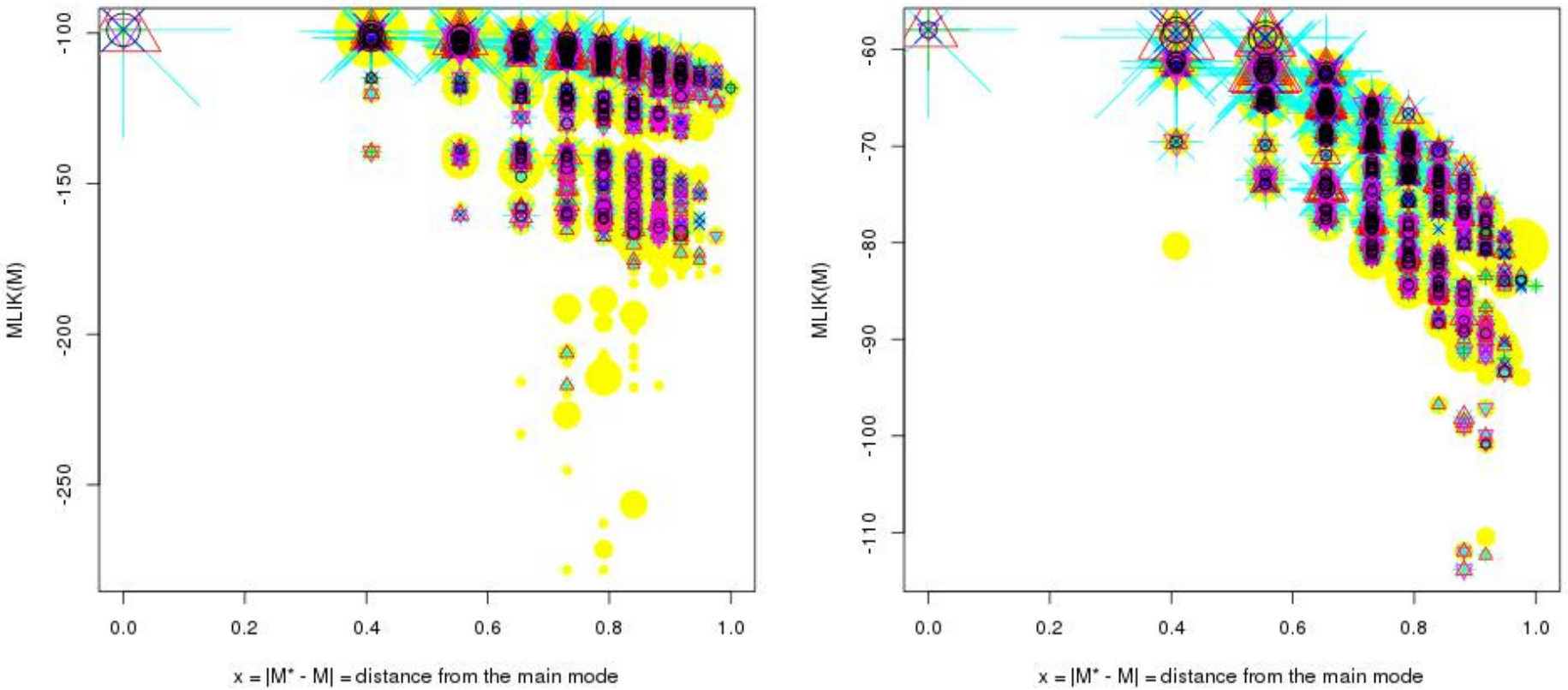


Figure: MLIK against distance from mcmc posterior mode

Results

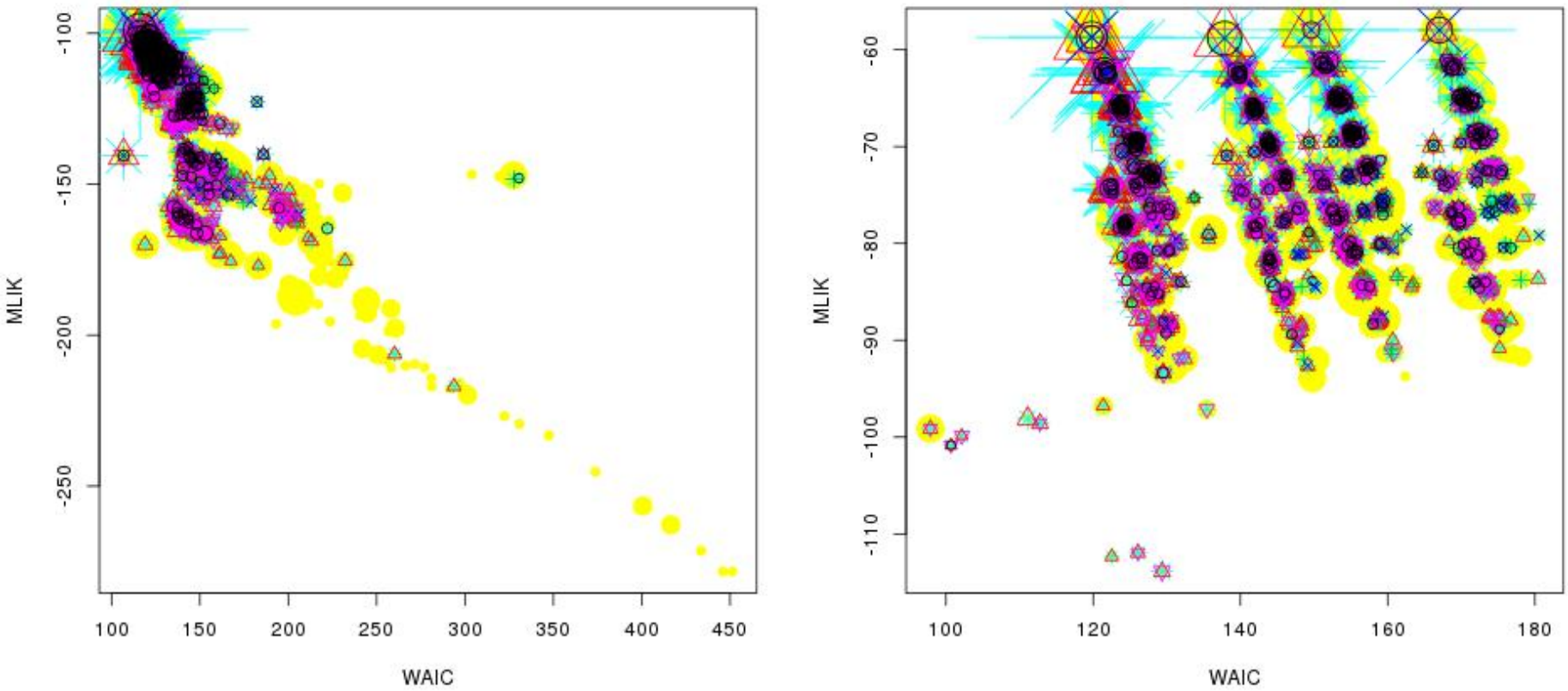


Figure: MLIK against WAIC

Results

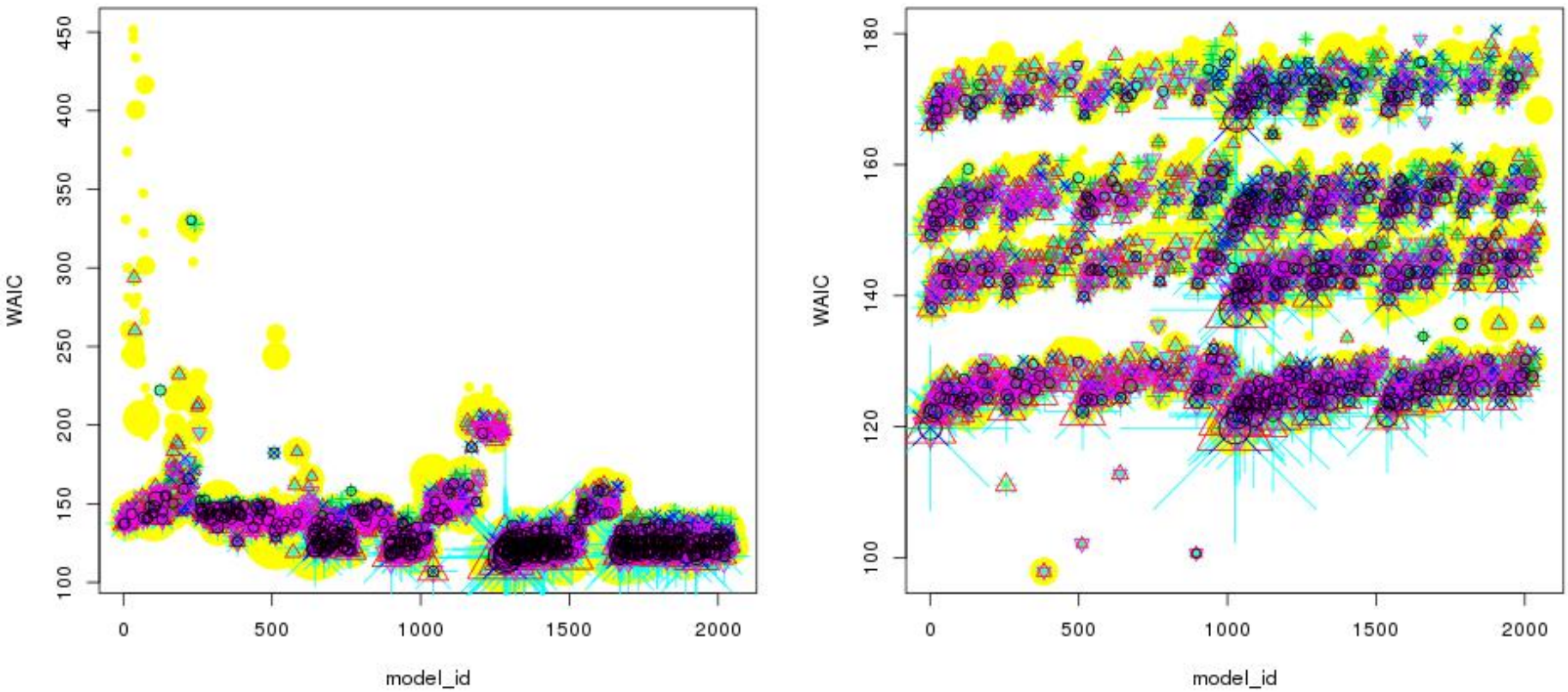


Figure: WAIC against model index

Results

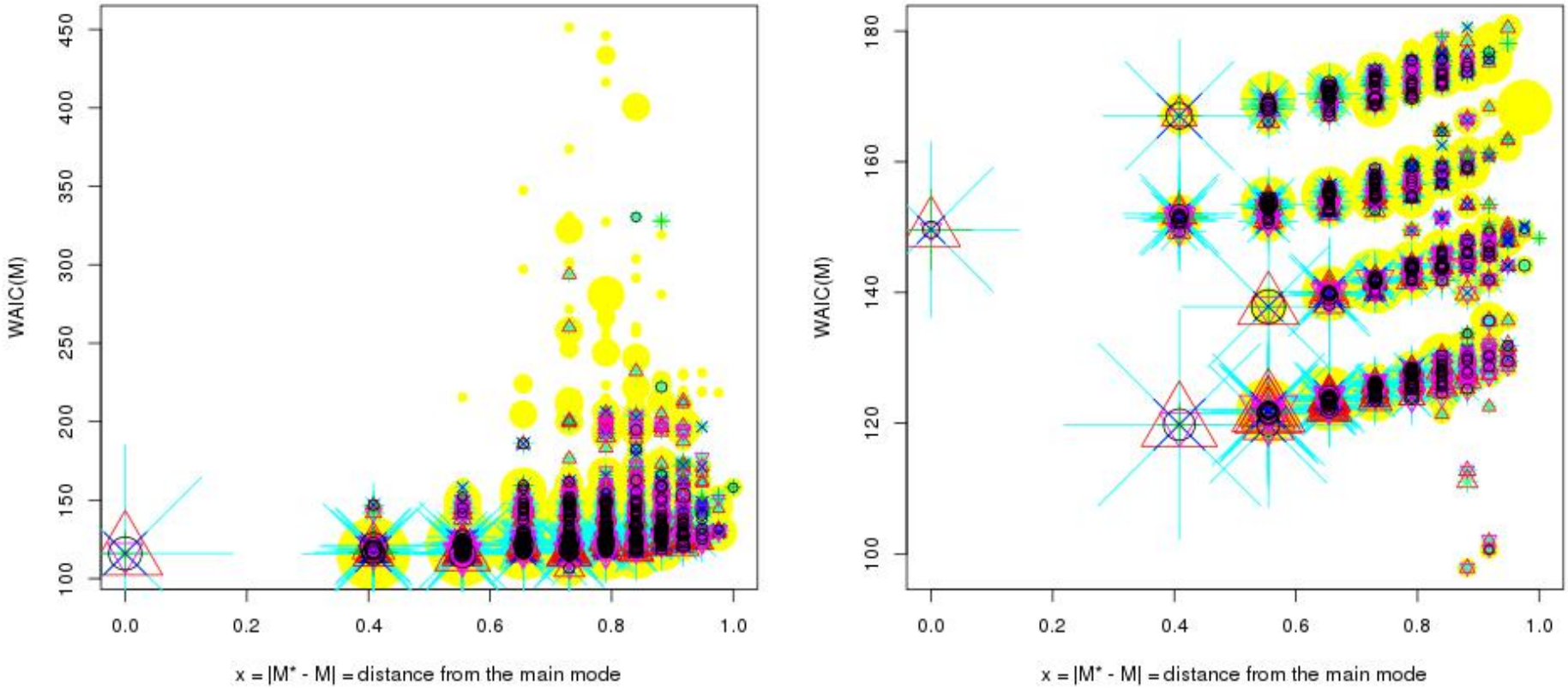


Figure: WAIC against distance from mcmc posterior mode

Results

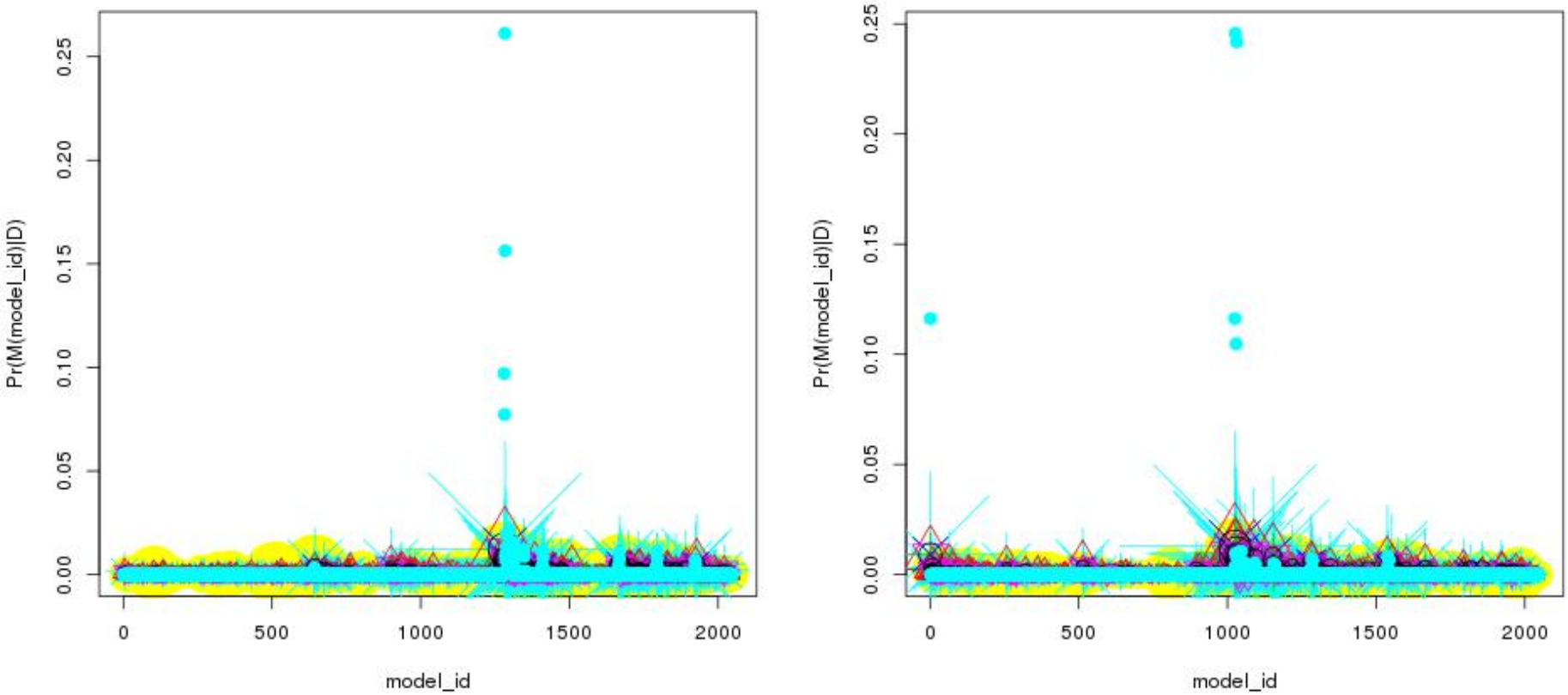


Figure: $\Pr(\mathbb{M}|\mathbb{D})$ against model index

Results

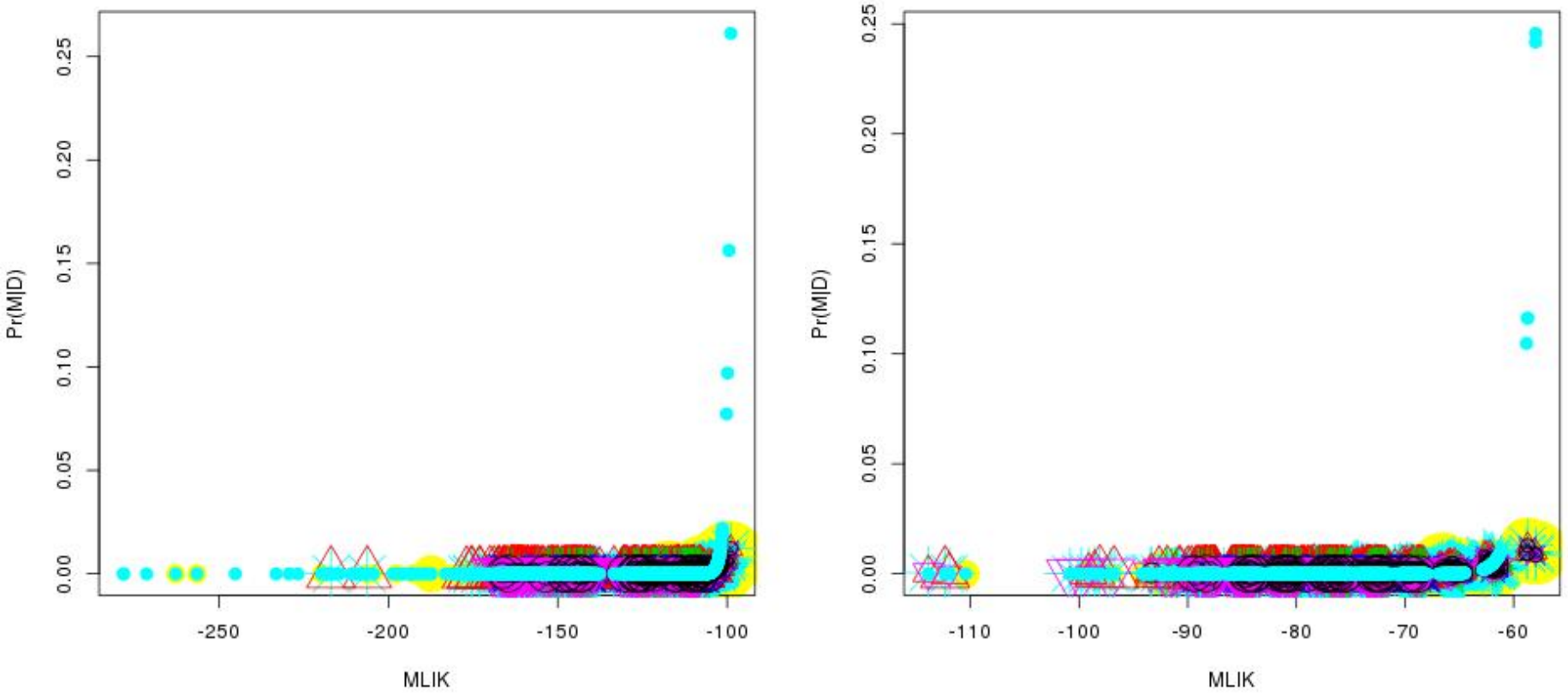
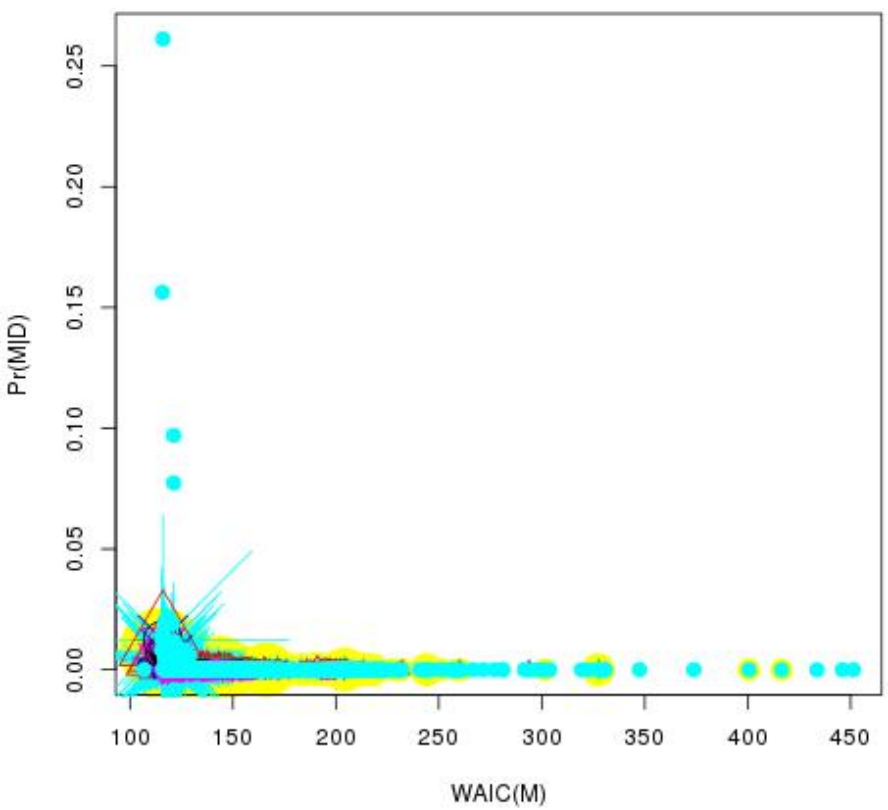


Figure: $\Pr(\mathbb{M}|\mathbb{D})$ against MLIK

Results



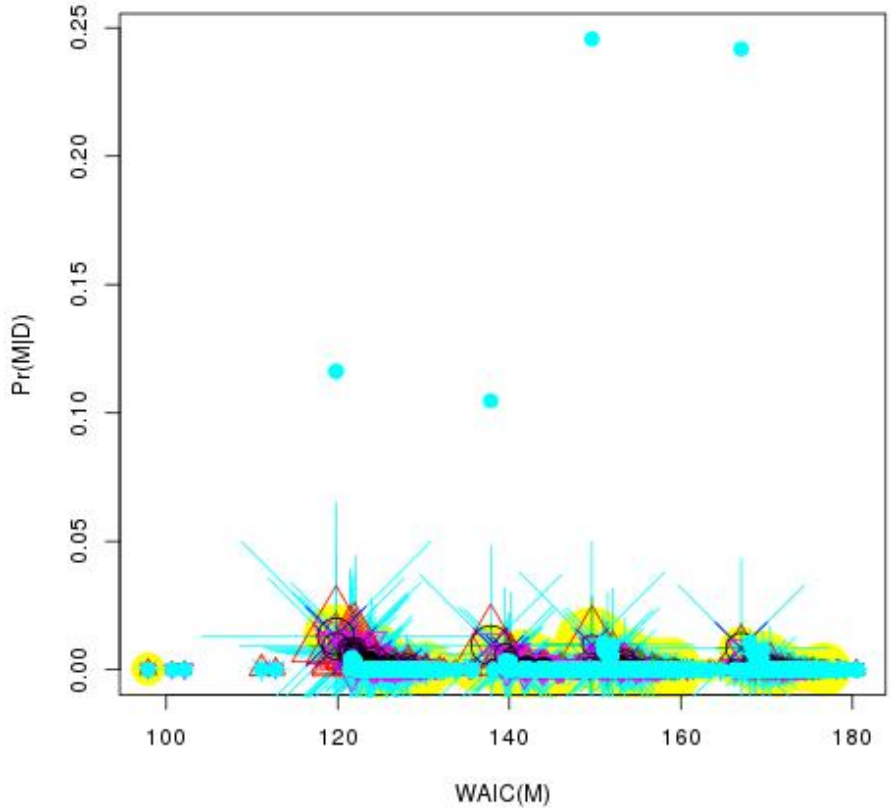


Figure: $\Pr(\mathbb{M}|\mathbb{D})$ against WAIC

Results

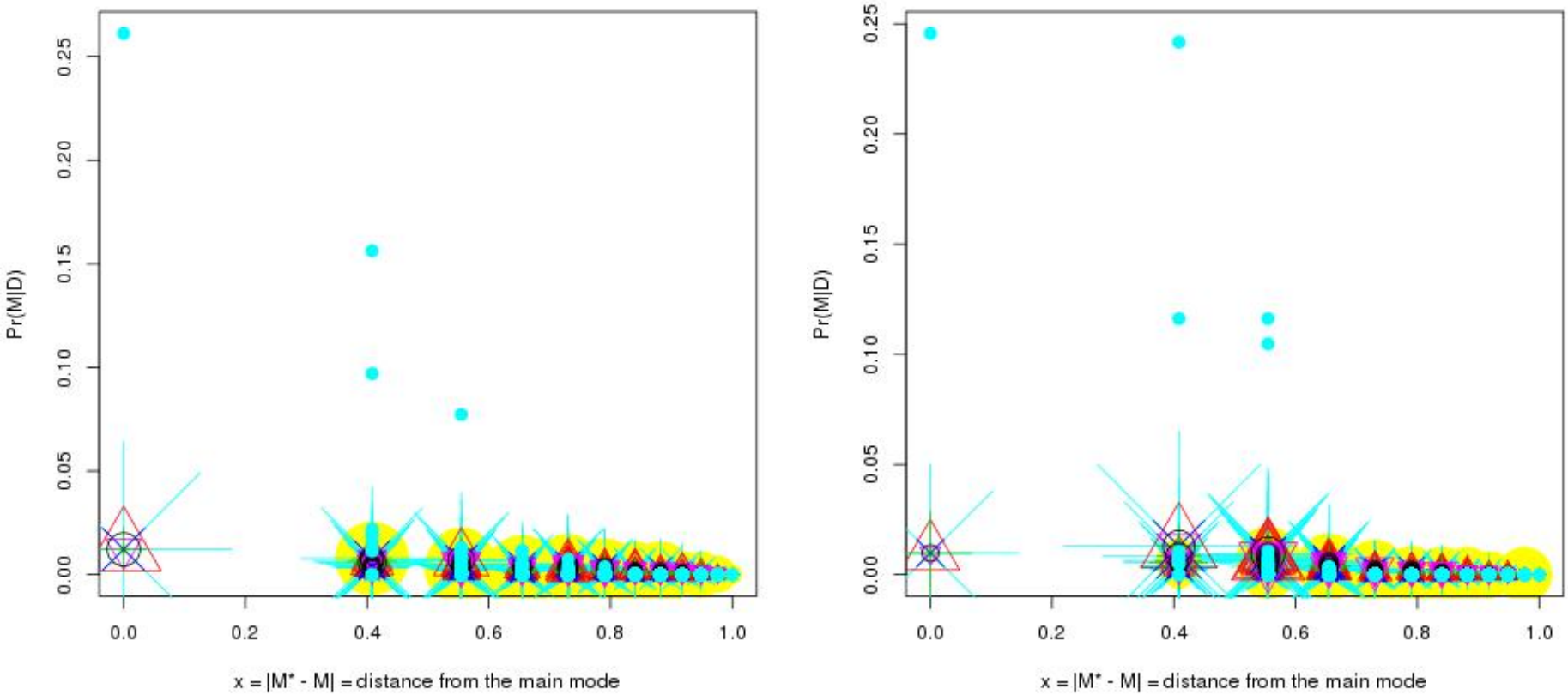


Figure: $\Pr(\mathbb{M}|\mathbb{D})$ against distance from MCMC posterior mode

Results

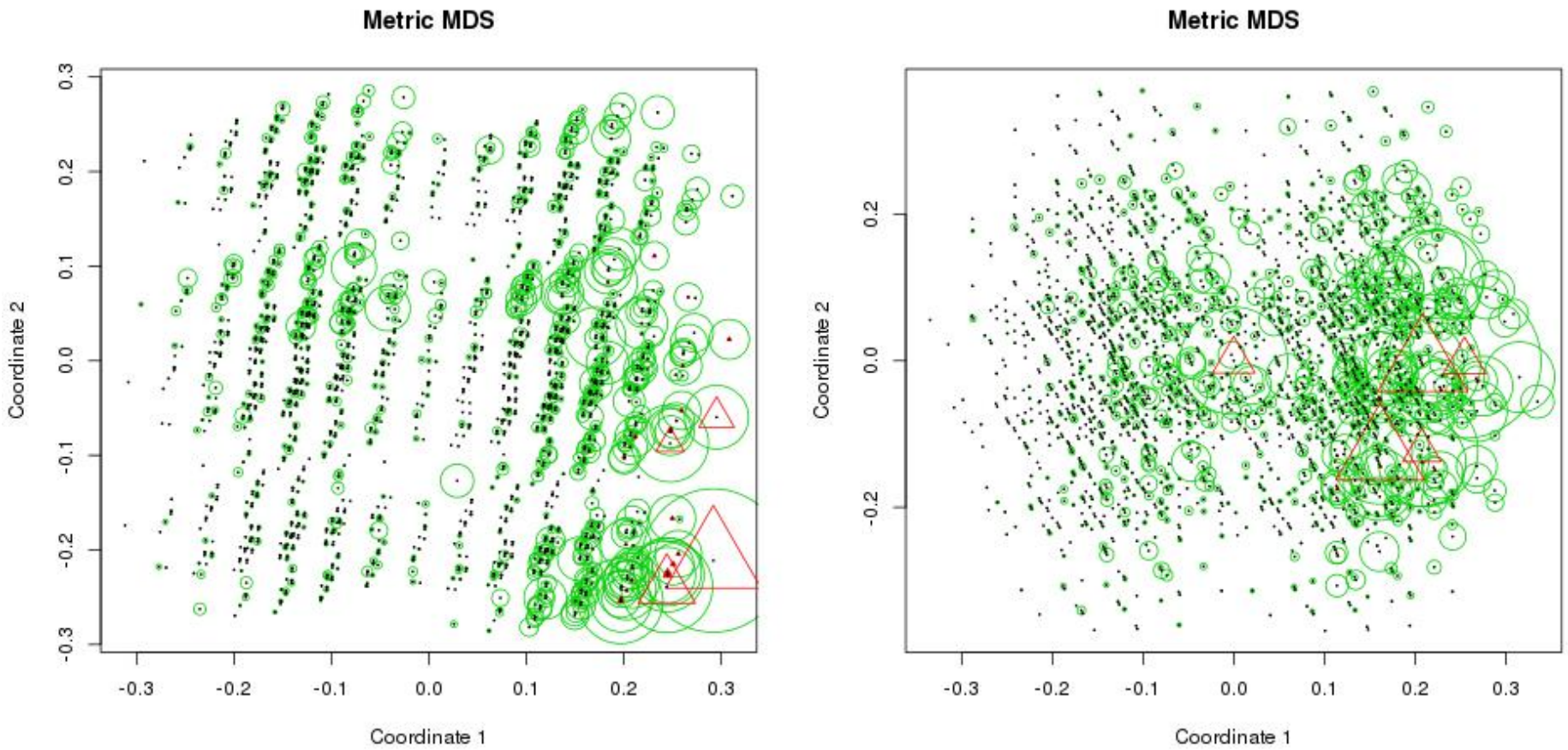


Figure: MDS plots with posterior modes

Some selected by WAIC models

Ch	LkB	UkB	Solution	WAIC	MLIK	kTIME
1	6485	6485	00101111110	97	-99	19266691
1	5906	5907	10001000001	60	-34	19049891
1	4851	4852	01001111110	78	-81	18950460
1	2572	2572	10100000000	203	-137	20660607
1	4395	4396	10000010001	106	-140	21329179

Table 1. Some results

Further discussion

- We see some heterogeneity of results, thus in order to achieve a stationary solution along the genome should we address one of the following:
  - Apply assessment of the subsets of the best solutions from different regions
  - Continue adding covariates which might be lacking
  - Somehow combine the strategies above
- The space of models $\Omega_{\mathbb{M}}$ can be extremely large for a large number of covariates to select, thus in order to achieve meaningful results should we
  - Carry out expert assessment of the found solutions in space $\Omega_{\mathbb{M}}$ a posteriori
  - Predefine biologically meaningful constraints $\mathbb{M} \in \Upsilon_{\mathbb{M}} \subset \Omega_{\mathbb{M}}$ before the search using standard mathematical modeling tools and thus limit down the search space
  - Combine the strategies above by both including constraints and carrying out a posteriori filtering of the results

Concluding remarks

- We suggest using a model based approach for inference on methylation pattern along the genome
- We benefit of capturing local spatial correlation
- We suggest using different covariates to improve precision of inference
- We choose the combination of covariates optimally in order to reduce the amount of false positive and false negative discoveries
- Approach might be computationally expensive, thus efficient numerical algorithms are applied and/or developed

References

REFERENCES

[1] C. Becker, J. Hagmann, J. Müller, D. Koenig, O. Stegle, K. Borgwardt, and D. Weigel. Spontaneous epigenetic variation in the arabidopsis thaliana methylome. *Nature*, 480 (7376):245–249, 2011.

[2] D. Denilson, B. Mallick, and A. Smith. Automatic bayesian curve fitting. *Journal of the Royal Statistical Sosciety*, 60(2):333–350, 1998.

[3] M. Denis and N. Molinary. Free knot splines with rjmcmc for logistic models and treshold selection. *JP Journal of Biostatistics*, 5(1):17–34, 2011.

[4] A. Gelman, J. Hwang, and A. Vehtari. Understanding predictive information criteria for bayesian models. *Statistics and Computing*, 24(6):997–1016, 2014. ISSN 0960-3174. . URL http://dx.doi.org/10.1007/s11222-013-9416-2.

[5] E. I. George and R. E. Mcculloch. Approaches for bayesian variable selection. *Statistica Sinica*, pages 339–374, 1997.

The End.

Thanks!