Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Dec, 2015

February 10, 2016

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Meeting

- Review TADA (Transmission And De novo Association) model.
- Test the likelihood values of TADA on grids of parameters on **D0**.
- Estimate parameters using box-constrained optimization and MCMC on **D1** and **D2**:

D0. De Rubeis, Silvia, et al. "Synaptic, transcriptional and chromatin genes disrupted in autism." Nature 515.7526 (2014): 209-215.
D1. He, Xin, et al. "Integrated model of de novo and inherited genetic variants yields greater power to identify risk genes." PLoS Genet 9.8 (2013): e1003671.
D2. Only the FMRP gene set from the data set D0.
From Darnell: 842 genes.

TADA

Let π be the fraction of risk genes in all genes.

Main parameters		Variants (LoF and mis3)
$\begin{cases} \textit{Mutation rate} & (\mu) \\ \textit{Relative risk} & (\gamma) \\ \textit{Population frequency} & (q) \end{cases}$	$\Rightarrow$	$\begin{cases} \text{De novo mutation} \\ \text{Transmitted variations} \\ \text{Variants in case-control studies} \end{cases}$

For each i^{th} gene, TADA uses a Bayesian approach to test the hypothesis
$H_0 : \gamma_i = 1$ against the alternative $H_1 : \gamma_i \neq 1$
$\Rightarrow$ A fraction π of risk genes (per total genes) follows the H_1 model.

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

The model incorporates information across genes, assumming that:

- Relative risk γ:
  $\gamma \sim Gamma(\bar{\gamma} * \beta, \beta)$.
- Population frequency of variants q:
  - Risk genes: $q_1 \sim Gamma(\rho_1, \nu_1)$
  - Normal genes: $q_0 \sim Gamma(\rho_0, \nu_0)$

$=>$ Need to estimate $\boxed{\bar{\gamma}, \beta, \rho_1, \nu_1, \rho_0, \nu_0, \pi}$.

With each type of data/variants (x), at each gene:

$$P(x|paramterers) = \pi P(x|H_1) + (1 - \pi)P(x|H_0)$$

Two types of mutations are tested: Loss-of-function (LoF) and probably damaging (Mis3).

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Test two models:

External product

$$P(x|paramterers) = \prod_{i=1}^{m} \left[\pi P(x_{i_{LoF}}|H_1) + (1-\pi)P(x_{i_{LoF}}|H_0)\right] \left[\pi P(x_{i_{mis3}}|H_1) + (1-\pi)P(x_{i_{mis3}}|H_0)\right]$$

Internal product

$$P(x|paramterers) = \prod_{i=1}^{m} \left[\pi P(x_{i_{LoF}}|H_1)P(x_{i_{mis3}}|H_1) + (1-\pi)P(x_{i_{LoF}}|H_0)P(x_{i_{mis3}}|H_0)\right]$$

Bayes factor

$$BF = \frac{P(x|H_1)}{P(x|H_0)} = \frac{P(x_{LoF}|H_1)P(x_{mis3}|H_1)}{P(x_{LoF}|H_0)P(x_{mis3}|H_0)}$$

$$p_{dn} = 2 * \mu\gamma$$
$$p_{control} = q$$
$$p_{case} = q\gamma$$

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Model for case-control data

Relative riks:
$\gamma|H_1 \sim Gamma(\bar{\gamma} * \beta, \beta)$
Frequency of variants:
$q|H_1 \sim Gamma(\rho, \nu)$
$q|H_0 \sim Gamma(\rho_0, \nu_0)$
The model:
$P(x|H_0) = \int p(x|q, \gamma = 1)p(q|H_0)dq$
$P(x|H_1) = \int p(x|q, \gamma)p(q|H_1)p(\gamma|H_1)dqd\gamma$

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Model for case-control data (cont)

For simplicity, let $\boxed{q|H_1 = q|H_0 = q \sim Gamma(\rho, \nu)}$,
we will calculate the conditional distribution of variants in cases on total variants of cases and controls.
X_{case} $Pois(\lambda_1)$; $X_{control}$ $Pois(\lambda_0)$
With $\lambda_1 = N_{case} * q * \gamma$; $\lambda_0 = N_{control} * q$
$X = X_{case} + X_{control}$
$X \sim Pois(\lambda_1 + \lambda_0)$
Question:
1) should let $\boxed{q = \epsilon * q_0}$.
2) Relationship between q and μ.

Model for case-control data (cont2)

At the i^{th} gene,

$$P(X_{case} = k|X = n) = \frac{P(X_{case}=k, X=n)}{P(X=n)} = \frac{P(X_{case}=k, X_{contro}=n-k)}{P(X=n)}$$

$$= \frac{\frac{e^{-\lambda_1}\lambda_1^k}{k!}\frac{e^{-\lambda_0}\lambda_0^{n-k}}{(n-k)!}}{\frac{e^{-(\lambda_1+\lambda_0)}(\lambda_1+\lambda_0)^n}{n!}}$$

$$= \frac{n!}{(n-k)!k!}\frac{\lambda_1^k\lambda_0^{n-k}}{(\lambda_1+\lambda_0)^n} = C_n^k p^k (1-p)^{n-k}$$

With

$$\boxed{p = \frac{\lambda_1}{\lambda_1+\lambda_0} = \frac{N_{case}q\gamma}{N_{case}q\gamma+N_{control}q} = \frac{N_{case}\gamma}{N_{case}\gamma+N_{control}}}$$

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

- First way (**Poisson distribution)**
  $X_{dn}|H_1 \sim Pois(2N_{dn}\mu\gamma)$
  $X_{dn}|H_0 \sim Pois(2N_{dn}\mu)$
- **Second way (Binomial distribution)**
  $X_{dn}|H_1 \sim Binomial(N_{dn}, 2 * \mu\gamma)$
  $X_{dn}|H_0 \sim Binomial(N_{dn}, 2 * \mu)$

With
Relative risk:
$\gamma \sim Gamma(\bar{\gamma} * \beta_{dn}, \beta_{dn})$

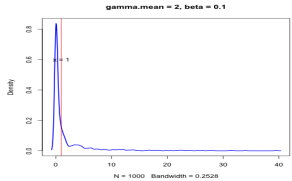
Can we simultaneously estimate all parameters based data + prior information from publications? => it will be easier to incorporate other information.
Some simple steps last month:

- => Re-write likelihood functions with two types of model.
- => Check there are overlapping intervals π between different variants.
- => Test whether we can constrain parameterers to estimate simultaneously.

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Some issues we have had:

- Internal OR external models.
- Constrain relative risks (γ).
  - Some relative risk parameters imply substantial proportions of protective genes.



- Improve the calculation of mutation rates for each genes/annotations.
- Use adjusted counts as data.
- Improve algorithm (eliminate numerical integration).

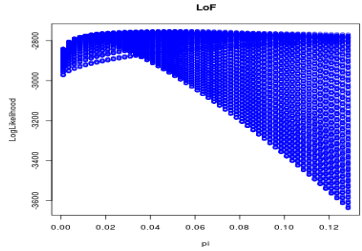
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

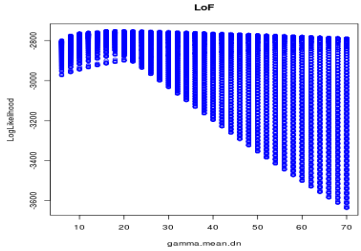
Grid on each data type

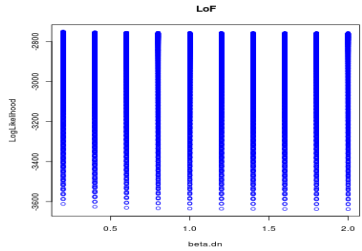
- Denovo LoF.
- Denovo Mis3.
- Case-control LoF.

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

LoF de novo

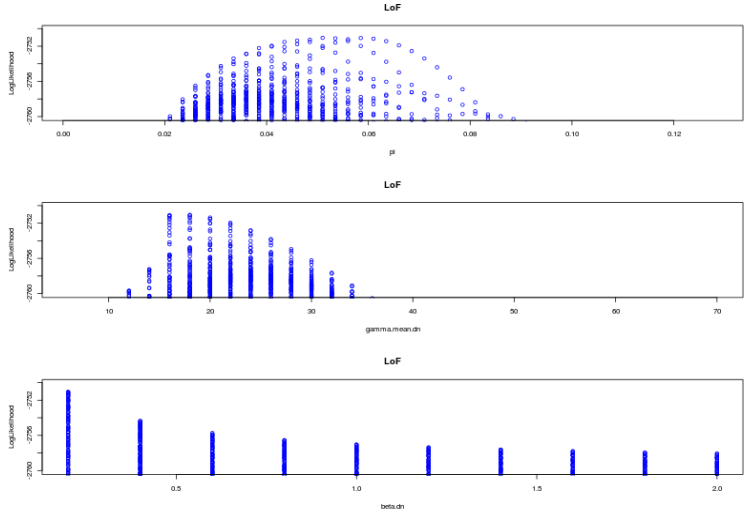






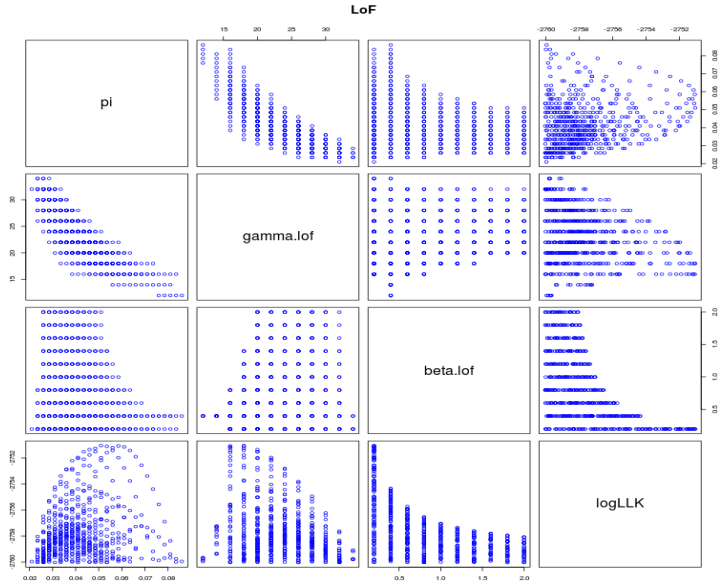
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

LoF de novo: top log LLK



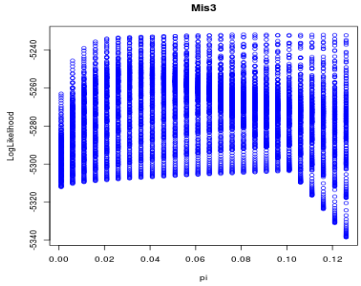
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

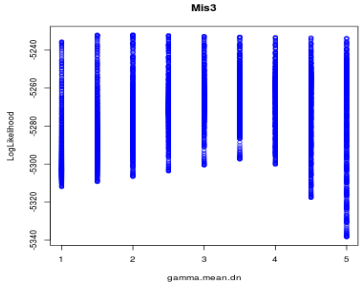
LoF de novo: check correlations between hyperparameters

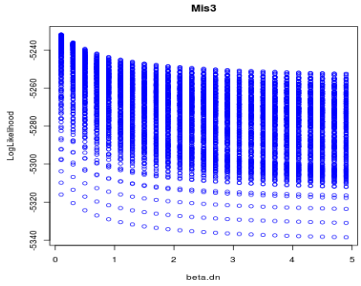


Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Mis3 de novo



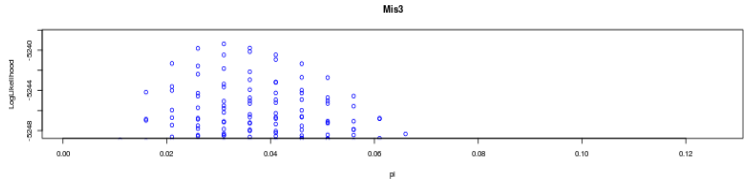


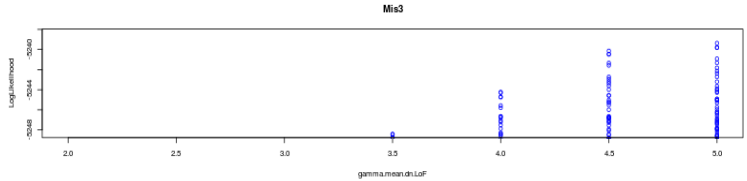


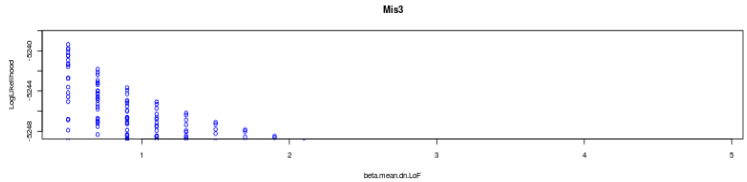
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Mis3 de novo: top LLK

less than 0.6% protective variants.

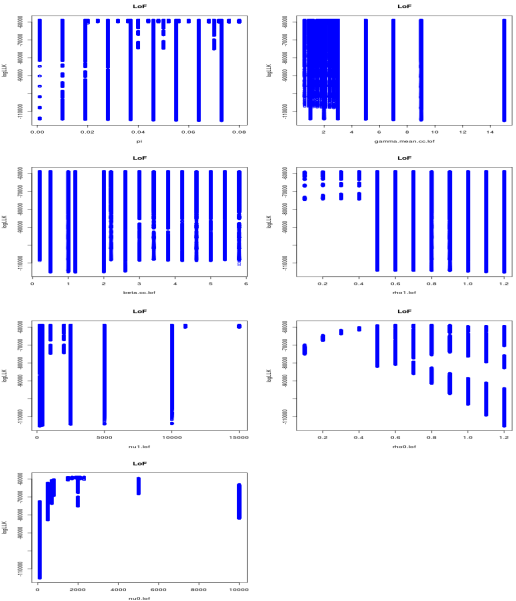






Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

LoF case-control



Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Estimate parameters

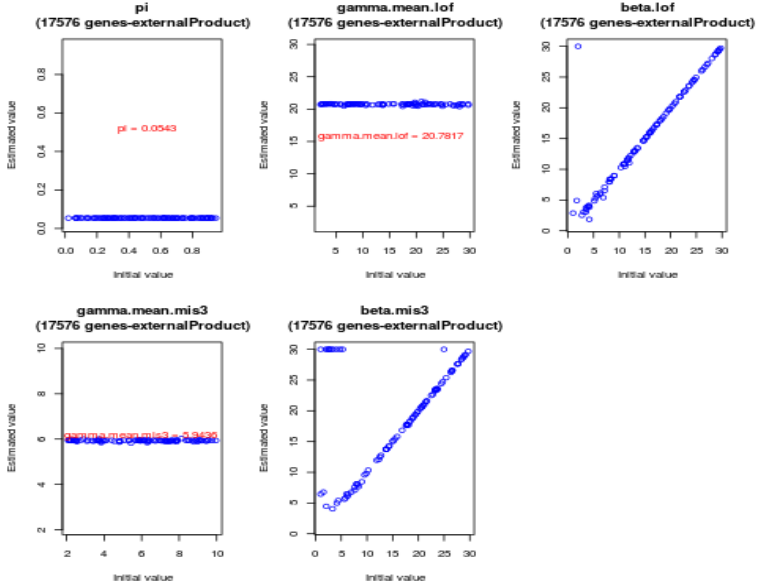
Use intervals of hyperparameters to set uniform priors for hyperparameters.

Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Constrained optimization

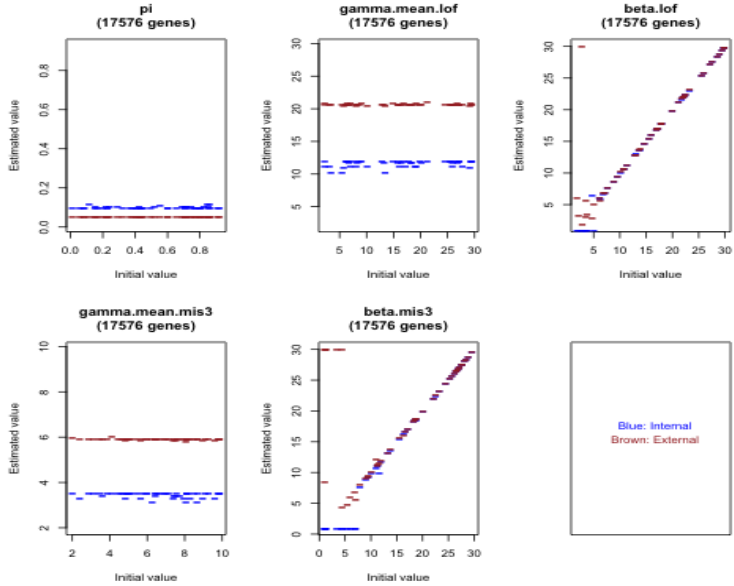
1. A set of random initial values was used => they can converge to approximately optimal values.
2. Some different algorithms (built in R) are used.

Test (external) for de novo data: LoF + mis3 for D1!



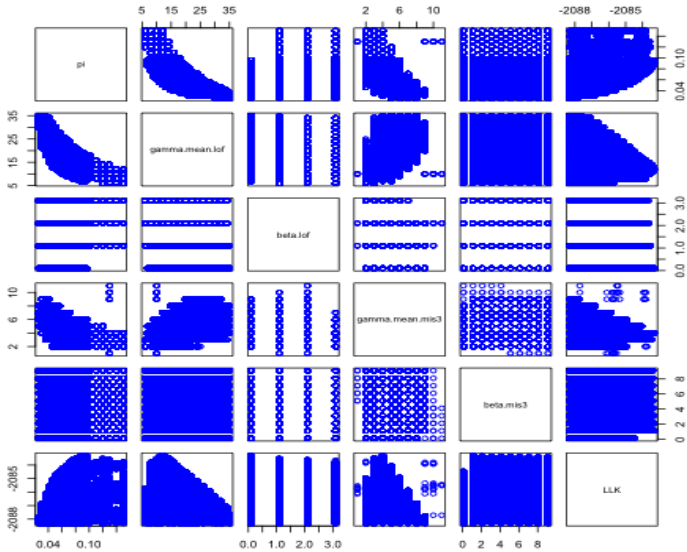
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Test (internal/external) for de novo data: LoF + mis3 for D1!



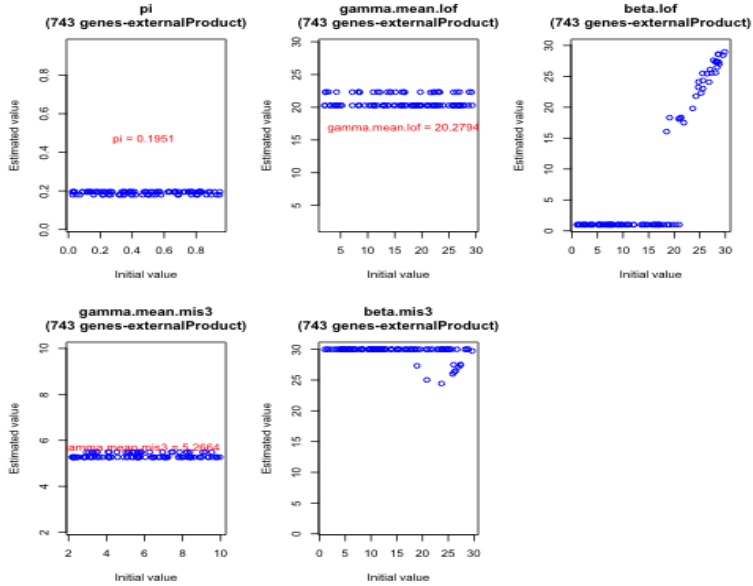
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Grid top LLK (internal) for de novo data: LoF + mis3 for D1!



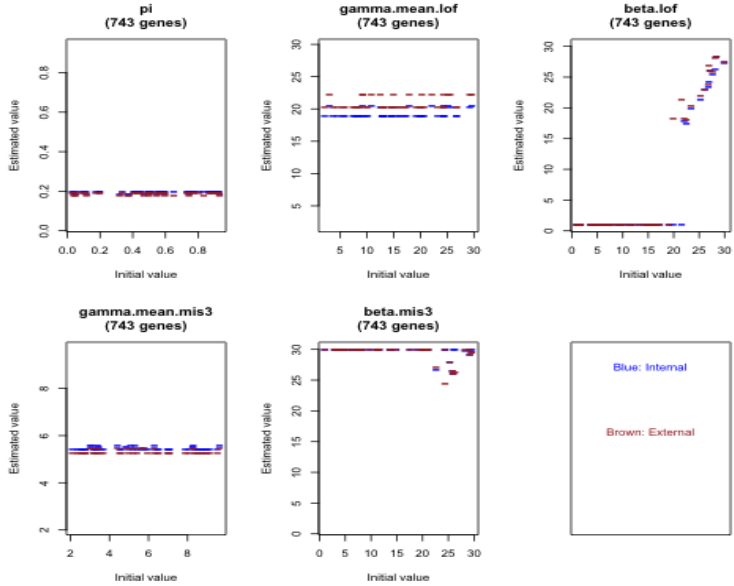
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

Test (external) for de novo data: LoF + mis3 for D2 (the FMRP gene set)!



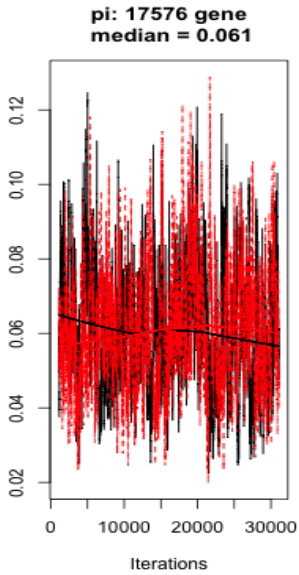
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

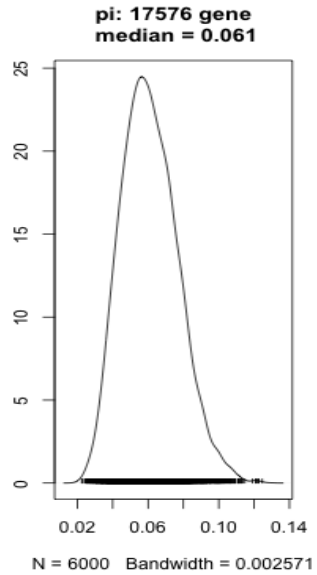
Test (internal/external) for de novo data: LoF + mis3 for D2 (the FMRP gene set)!



Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

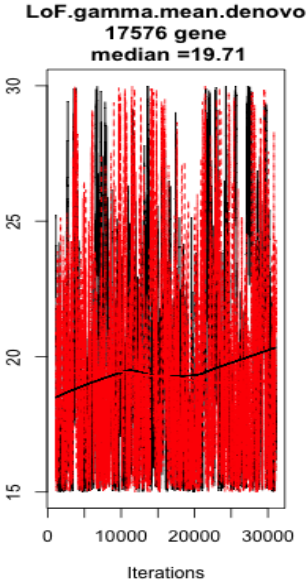
MCMC for D1: external product.

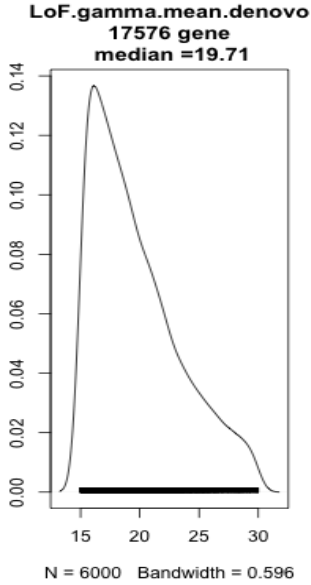




Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

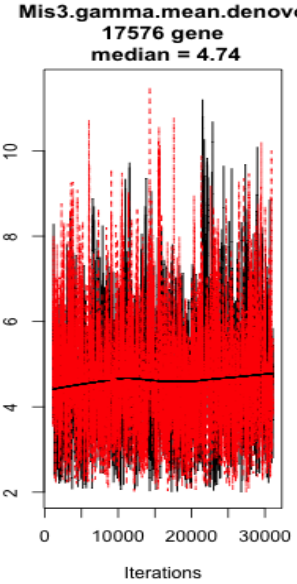
MCMC for D1: external product.

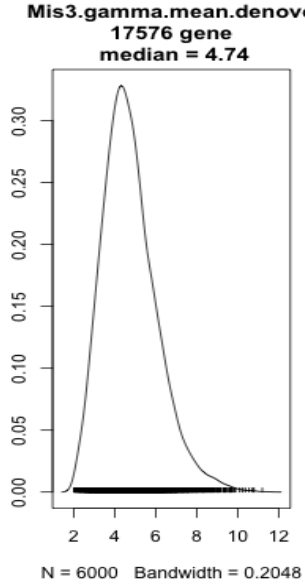




Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

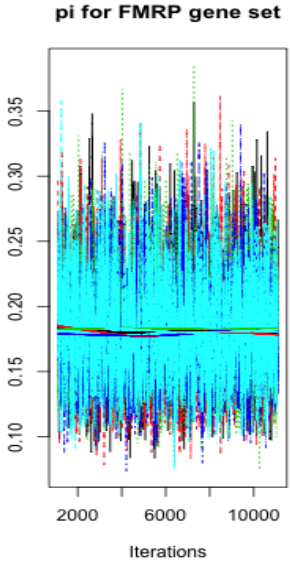
MCMC for D1: external product.





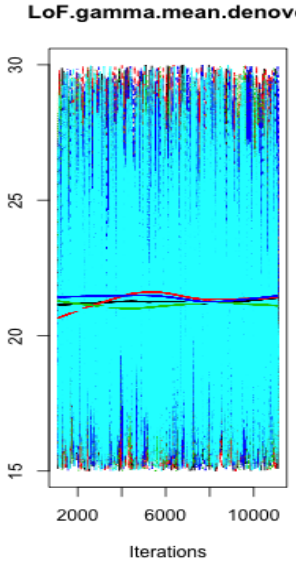
Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

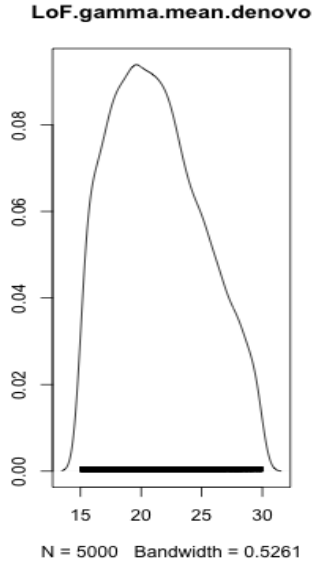
MCMC for **D2** **(the FMRP gene set,)**

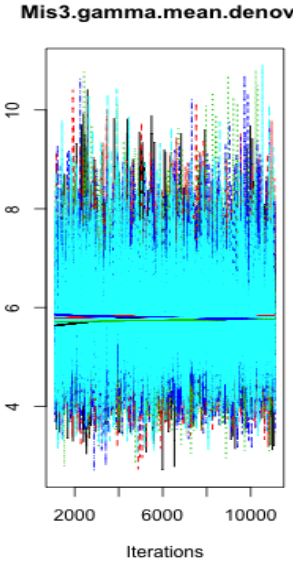
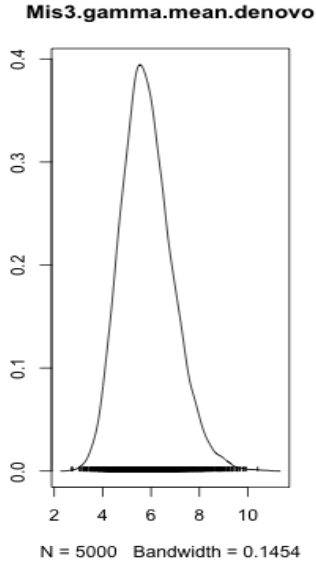


Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

MCMC for **D2** **(the FMRP gene set,)**





Review TADA
CC model
De novo model
Grids of parameters
De novo
Case-control
Estimate parameters
Constrained optimization
MCMC

MCMC for **D2** **(the FMRP gene set,)**