Package 'iBATCGH'

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Title Integrative Bayesian Analysis of Transcriptomic and CGH Data

Author Alberto Cassese

Maintainer Alberto Cassese <`alberto.cassese@maastrichtuniversity.nl`>

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Description Bayesian integrative models of gene expression and comparative genomic hybridization data. The package provides inference on copy number variations and their association with gene expression.

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`iBATCGH-package` *Integrative Bayesian Analysis of Transcriptomic and CGH data*

Description

Bayesian integrative models of gene expression and comparative genomic hybridization data. The package provides inference on copy number variations and their association with gene expression

Details

Package:	iBATCGH
Type:	Package
Version:	1.3
Date:	2015-07-06
License:	GNU

The package takes as inputs gene expression, Comparative Genomic Hybridization (CGH) data, and the physical distance between CGH probes. It returns posterior probabilities of inclusion for each potential association gene expression - CGH, and inference on the CGH latent states. Two different models have been considered, see references for details. Available functions are classified in four classes: Preprocessing, Main, Postprocessing, Simulated Data.

Author(s)

Alberto Cassese, Marina Vannucci, Michele Guindani, Mahlet G. Tadesse.

Maintainer: Alberto Cassese <alberto.cassese@maastrichtuniversity.nl>

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.
Guha S, Li Y, Neuberg D. Bayesian hidden Markov modelling of array cgh data. JASA. 2008;103(482):485-497.

Examples

```
## Not run:
data(NCI_60)

Y <- NCI_60$Affy
X <- NCI_60$aCGH
distance <- NCI_60$distance
disfix <- 146274826
xi <- InitXi(X)
tran <- Tran(xi)
mu <- InitMu()
d=0.2587288

Y <- Center(Y)

res <- iBAT(Y=Y,X=X,distance=distance,disfix=disfix,xi=xi,tran=tran,mu=mu,d=d)

summRes <- Inference(res,G=dim(Y)[[2]],M=dim(X)[[2]],niter=niter,burnin=bi,threshold=0.5)

## End(Not run)
```

`Center` *Preprocessing - Center gene expression data*

Description

This function takes as argument a matrix of gene expression measurements Y, and returns the matrix obtained after centering each column with respect to its mean.

Usage

```
Center(Y)
```

Arguments

`Y`	The matrix of data to be centered.

Details

This function center each column of the gene expression matrix.

Value

The matrix of data obtained after centering each column with respect to its mean.

Author(s)

Alberto Cassese

Examples

```
data(NCI_60)
Y <- NCI_60$Affy
Y<-Center(Y)
```

`iBAT` *Main - Mixture selection prior*

Description

Perform MCMC iterations of the model, as described in the reference.

Usage

```
iBAT(Y, X, distance, disfix, intercept=1, xi,
R=-1, tran, mu, sigma=((rgamma(4,1,1))^(-0.5)),
cmu=1/1000000, c=10, delta=3, d, e=0.001, f=0.999,
alpha=20, deltak=c(-1,0,0.58,1), tauk=c(1,1,1,2),
upp_bounds=c(-0.1, 0.1, 0.73, Inf),
low_bounds=c(-Inf, -0.1, 0.1, 0.73),
alpha_IG=c(1,1,1,1), beta_IG=c(1,1,1,1),
low_IG=c(0.41,0.41,0.41,1), a=c(1,1,1,1),
niter=500000, burnin=200000, Cout=1000,
phi=0.5, pR=0.4, selectioncgh=-1, pXI=0.6, indep=0)
```

Arguments

`Y`	Matrix of gene expression data
`X`	Matrix of CGH data
`distance`	Vector of distance between CGH probes
`disfix`	Length of the chromosome under investigation
`intercept`	If set to one an intercept is included in the regression model
`xi`	Initialized matrix of latent states
`R`	Initialized association matrix in a vector form. Default set to -1, that automatically creates a vector with all the positions set to zero
`tran`	Initialized transition matrix
`mu`	Initialized state specific mean vector
`sigma`	Initialized state specific standard deviation vector
`cmu`	Parameter that controls the variance of the prior on the intercept
`c`	Parameter that determines the shrinkage in the model
`delta`	Parameter of the Inverse-Gamma prior on the error variance
`d`	Parameter of the Inverse-Gamma prior on the error variance
`e`	Parameter of the Beta prior on the inclusion probability

`f`	Parameter of the Beta prior on the inclusion probability
`alpha`	Parameter that regulates the strength of the independent part of the mixture
`deltak`	Vector of mean of the prior on the state specific mean
`tauk`	Vector of sd of the prior on the state specific mean
`upp_bounds`	Vector of upper bounds of the prior on the state specific mean
`low_bounds`	Vector of lower bounds of the prior on the state specific mean
`alpha_IG`	Vector of parameters of the prior on the state specific standard deviation
`beta_IG`	Vector of parameters of the prior on the state specific standard deviation
`low_IG`	Truncation of the prior on the state specific standard deviation
`a`	Vector of parameters of the prior on the transition matrix
`niter`	Number of Monte Carlo Markov Chain iterations
`burnin`	Burn-in
`Cout`	Print the number of iterations ran every Cout iterations
`phi`	Probability of an A/D step
`pR`	Parameter of the distribution used to select the rows to be updated at every MCMC iteration
`selectioncgh`	Number of samples not in neutral state in order to consider a CGH as a potential candidate for association with gene expression. Default set to -1 that automatically set it to 10% of the samples
`pXI`	Parameter of the distribution used to select the rows to be updated at every MCMC iteration
`indep`	If set to an integer different from zero, run the analysis with an independent prior, see reference.

Value

The output consists of an R list composed by 4*niter+3 elements objects, where niter is the number of MCMC iterations. The first niter objects of the list are vectors, each containing the positions of the association matrix set to one, at the corresponding MCMC iteration. Each of the following niter objects of the list are the transition matrices at the corresponding MCMC iteration, while the third and the fourth set of niter objects are the vectors of state specific mean and state specific variance, respectively. The last three objects of the list consist of three matrices counting the number of times the corresponding latent state has been set to 1,3 and 4, respectively.

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.

Examples

```
## Not run:
data(NCI_60)

Y <- NCI_60$Affy
X <- NCI_60$aCGH
distance <- NCI_60$distance
disfix <- 146274826
xi <- InitXi(X)
tran <- Tran(xi)
mu <- InitMu()
d=0.2587288

Y <- Center(Y)

res <- iBAT(Y=Y,X=X,distance=distance,disfix=disfix,xi=xi,tran=tran,mu=mu,d=d)

summRes <- Inference(res,G=dim(Y)[[2]],M=dim(X)[[2]],niter=niter,burnin=bi,threshold=0.5)

## End(Not run)
```

`iBATProbit` *Main - Probit selection prior*

Description

Perform MCMC iterations of the model described in the reference.

Usage

```
iBATProbit(Y, X, distance, disfix, intercept=1, xi,
R=-1, tran, mu, sigma=((rgamma(4,1,1))^(-0.5)),
cmu=1/1000000, c=10, delta=3, d, alpha0=2.32,
alpha1=1, deltak=c(-1,0,0.58,1), tauk=c(1,1,1,2),
upp_bounds=c(-0.1, 0.1, 0.73, Inf),
low_bounds=c(-Inf, -0.1, 0.1, 0.73),
alpha_IG=c(1,1,1,1), beta_IG=c(1,1,1,1),
low_IG=c(0.41,0.41,0.41,1), a=c(1,1,1,1),
niter=500000, burnin=200000, Cout=1000,
phi=0.5, pR=0.4, selectioncgh=-1, pXI=0.6)
```

Arguments

`Y`	Matrix of gene expression data
`X`	Matrix of CGH data
`distance`	Vector of distance between CGH probes
`disfix`	Length of the chromosome under investigation

`intercept`	If set to one an intercept is included in the regression model
`xi`	Initialized matrix of latent states
`R`	Initialized association matrix in a vector form. Default set to -1, that automatically creates a vector with all the positions set to zero
`tran`	Initialized transition matrix
`mu`	Initialized state specific mean vector
`sigma`	Initialized state specific standard deviation vector
`cmu`	Parameter that controls the variance of the prior on the intercept
`c`	Parameter that determines the shrinkage in the model
`delta`	Parameter of the Inverse-Gamma prior on the error variance
`d`	Parameter of the Inverse-Gamma prior on the error variance
`alpha0`	Baseline intercept of the selection prior
`alpha1`	Parameter that regulates the strength of the spatially informed dependence
`deltak`	Vector of mean of the prior on the state specific mean
`tauk`	Vector of sd of the prior on the state specific mean
`upp_bounds`	Vector of upper bounds of the prior on the state specific mean
`low_bounds`	Vector of lower bounds of the prior on the state specific mean
`alpha_IG`	Parameter of the prior on the state specific standard deviation
`beta_IG`	Parameter of the on the state specific standard deviation
`low_IG`	Truncation of the prior on the state specific standard deviation
`a`	Vector of parameters of the prior on the transition matrix
`niter`	Number of Monte Carlo Markov Chain iteration
`burnin`	Burn-in
`Cout`	Print the number of iterations ran every Cout iterations
`phi`	Probability of an A/D step
`pR`	Parameter of the distribution used to select the rows to be updated at every MCMC iteration
`selectioncgh`	Number of samples not in neutral state in order to consider a CGH as a potential candidate for association with gene expression. Default set to -1 that automatically set it to 10% of the samples
`pXI`	Parameter of the distribution used to select the rows to be updated at every MCMC iteration

Value

The output consists of an R list composed by 4*niter+3 objects, where niter is the number of MCMC iterations. The first niter objects of the list are vectors, each containing the positions of the association matrix set to one, at the corresponding MCMC iteration. Each of the following niter objects of the list are the transition matrices at the corresponding MCMC iteration, while the third and the fourth set of niter objects are the vectors of state specific mean and state specific variance, respectively. The last three objects of the list consist of three matrices counting the number of times the corresponding latent state has been set to 1,3 and 4, respectively.

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

Examples

```
## Not run:
data(TCGA_lung)

Y <- TCGA_lung$Affy
X <- TCGA_lung$aCGH
distance <- TCGA_lung$distance
disfix <- 199446827
xi <- InitXi(X)
tran <- Tran(xi)
mu <- InitMu()
d=0.2587288

Y <- Center(Y)

res <- iBATProbit(Y=Y,X=X,distance=distance,disfix=disfix,xi=xi,tran=tran,mu=mu,d=d)

summRes <- Inference(res,G=dim(Y)[[2]],M=dim(X)[[2]],niter=niter,burnin=bi,threshold=0.5)

## End(Not run)
```

`Inference` *Postprocessing - Posterior Inference*

Description

Performs posterior inference on the output of the main function

Usage

```
Inference(listComplete, G, M, niter, burnin, threshold = 0.5)
```

Arguments

`listComplete`	Output of the main function
`G`	Number of gene expression probes
`M`	Number of CGH probes
`niter`	Number of Monte Carlo Markov Chain iterations
`burnin`	Burn-in
`threshold`	Threshold on the posterior probabilities of inclusion of the association matrix

Details

Wrapper function which calls InferenceR, InferenceXi, InferenceA, InferenceMu, InferenceSd on the output of the main function.

Value

A list made by the following items

`R`	Binary matrix of estimated association
`Xi`	Matrix of estimated copy number states
`A`	Estimated transition matrix
`Mu`	Estimated vector of state specific means
`Sd`	Estimated vector of state specific standard deviations

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

See Also

See Also `InferenceR`,`InferenceXi`

Examples

```
## Not run:
data(NCI_60)

Y <- NCI_60$Affy
X <- NCI_60$aCGH
distance <- NCI_60$distance
disfix <- 146274826
xi <- InitXi(X)
tran <- Tran(xi)
mu <- InitMu()
d=0.2587288

Y <- Center(Y)

res <- iBAT(Y=Y,X=X,distance=distance,disfix=disfix,xi=xi,tran=tran,mu=mu,d=d)

summRes <- Inference(res,G=dim(Y)[[2]],M=dim(X)[[2]],niter=niter,burnin=bi,threshold=0.5)
```

```
## End(Not run)
```

`InferenceA` *Postprocessing - Inference on the transition matrix*

Description

This function returns a matrix obtained as the elementwise mean of the association matrices, output of the Monte Carlo Markov Chain iterations, after removing burn-in.

Usage

```
InferenceA(listA, niter, burnin)
```

Arguments

`listA`	Second niter objects of the output of the main function
`niter`	Number of Monte Carlo Markov Chain iterations
`burnin`	Burn-in

Value

Estimated transition matrix.

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

See Also

See Also as `Inference`

Examples

```
##See Inference
```

`InferenceMu` *Postprocessing - Inference on the vector of state specific mean*

Description

This function returns a vector obtained as the elementwise mean of the vectors of state specific mean, output of the Monte Carlo Markov Chain iterations, after removing burn-in.

Usage

```
InferenceMu(listMu, niter, burnin)
```

Arguments

`listMu`	Third niter objects of the output of the main function
`niter`	Number of Monte Carlo Markov Chain iteration
`burnin`	Burn-in

Value

Estimated vector of state specifc mean.

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

See Also

See Also as `Inference`

Examples

```
##See Inference
```

`InferenceR` *Postprocessing - Inference on the association matrix*

Description

This function performs posterior inference on the association matrix, returning the matrix of posterior probabilities of inclusion for each association gene expression - CGH. It also returns the binary matrix of significant links that exceed a threshold given as argument.

Usage

```
InferenceR(listR, G, M, niter, burnin, threshold = 0.5)
```

Arguments

`listR`	First niter objects of the output of the main function
`G`	Number of gene expression probes
`M`	Number of aCGH probes
`niter`	Number of Monte Carlo Markov Chains iterations
`burnin`	Burn-in
`threshold`	Threshold on the posterior probability of inclusion

Value

A list made of the following items

`FreqMat`	Matrix of posterior probabilities of inclusion
`final`	Binary association matrix

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

See Also

See Also as `Inference`

Examples

```
##See Inference
```

`InferenceSd` *Postprocessing - Inference on the vector of state specific sd*

Description

This function returns a vector obtained as the elementwise mean of the vectors of state specific standard deviation, output of the Monte Carlo Markov Chain iterations, after removing burn-in.

Usage

```
InferenceSd(listSd, niter, burnin)
```

Arguments

`listSd`	Fourth niter objects of the output of the main function
`niter`	Number of Monte Carlo Markov Chain iterations
`burnin`	Burn-in

Value

Estimated vector of state specific sd.

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

See Also

See Also as `Inference`

Examples

```
##See Inference
```

`InferenceXi` *Postprocessing - Inference on the latent states*

Description

This function returns the modal latent states.

Usage

```
InferenceXi(listXi, niter, burnin)
```

Arguments

`listXi`	Last three objects of the output of the main function
`niter`	Number of Monte Carlo Markov Chain iterations
`burnin`	Burn-in

Details

Must use the same burn-in as in the main function.

Value

Matrix of modal latent states, i.e. estimated Copy Number Variants. A four class classification is considered:

1. Loss
2. Neutral
3. Gain
4. Amplification

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

See Also

See Also as `Inference`

Examples

```
##See Inference
```

`InitMu` *Preprocessing - Initialize state specific mean vector*

Description

Initializes the state specific mean vector, by sampling each element independently from its prior, i.e. truncated normal distribution..

Usage

```
InitMu(deltak = c(-1, 0, 0.58, 1), tauk = c(1, 1, 1, 2),
low_bounds = c(-Inf, -0.1, 0.1, 0.73), upp_bounds = c(-0.1, 0.1, 0.73, Inf))
```

Arguments

`deltak`	Vector of means of the truncated Normal distributions
`tauk`	Vector of standard deviations of the truncated Normal distributions
`low_bounds`	Vector of lower bounds of the truncated Normal distributions
`upp_bounds`	Vector of upper bounds of the truncated Normal distributions

Value

A vector of state specific mean, that could be used as input of the main function.

Author(s)

Alberto Cassese

References

Guha S, Li Y, Neuberg D. Bayesian hidden Markov modelling of array cgh data. JASA. 2008;103(482):485-497.

Examples

```
mu <- InitMu()
```

`InitXi` *Preprocessing - Initialize matrix of latent states*

Description

This function takes a matrix of CGH data as the only argument and returns a crude estimate of the corresponding latent copy number states.

Usage

```
InitXi(X, bounds = c(-0.5, 0.29, 0.79))
```

Arguments

`X`	Matrix of aCGH data
`bounds`	Vector of threshold used to estimate the latent states

Details

Given as argument a vector of threshold bounds the function simply applies the thresholding to the data and groups them into four subsets. Each subset is associated to a specific latent state.

Value

Return a matrix of estimated latent states, that could be used as input of the main function.

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

See Also

See Also `Tran`

Examples

```
data(NCI_60)
X <- NCI_60$aCGH
xi <- InitXi(X)
```

`NCI_60` *NCI-60 cancer cell lines data*

Description

Processed and filtered NCI-60 cancer cell lines data, as described in the reference.

Usage

```
data(NCI_60)
```

Format

The format is a list of 3 objects
$ aCGH
$ Affy
$ distance

Source

Full matrix of data downloaded from `discover.nci.nih.gov/cellminer`.

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.

Examples

```
data <- data(NCI_60)
```

`RListToVector` *Internal function*

Description

Internal function

Usage

```
RListToVector(xList, G, T)
```

Arguments

`xList`	List of included associations (C format)
`G`	Number of gene expression probes
`T`	Number of CGH probes

Details

This is an internal function.

Value

Returns a vector whose elements are the number of times, across the MCMC iterations, the corresponding position of the transition matrix has been set to one.

Author(s)

Alberto Cassese

`Scenario1` *Simulated data - Scenario 1*

Description

Simulates the data as described in the reference provided below (Scenario 1).

Usage

```
Scenario1(sigmak = 0.1)
```

Arguments

`sigmak`	Standard deviation of the error term

Value

Return a list made of the following items

`Y`	Matrix of simulated gene expression
`X`	Matrix of simulated CGH
`Xi`	True matrix of hidden states
`A`	Empirical transition matrix
`mu`	True vector of state specific mean
`Sd`	True vector of state specific sd
`coeff`	True matrix of association coefficients between gene expression and CGH probes
`distance`	Vector of distance between CGH probes
`disfix`	Length of the chromosome

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

Examples

```
data <- Scenario1(sigmak = 0.1)
```

`Scenario2` *Simulated data - Scenario 2*

Description

Simulates the data as described in the reference provided below (Scenario 2).

Usage

```
Scenario2(sigmak = 0.1)
```

Arguments

`sigmak`	Standard deviation of the error term

Value

Return a list made of the following items

`Y`	Matrix of simulated gene expression
`X`	Matrix of simulated CGH
`Xi`	True matrix of hidden states
`A`	Empirical transition matrix
`mu`	True vector of state specific mean
`Sd`	True vector of state specific sd
`coeff`	True matrix of association coefficients between gene expression and CGH probes
`distance`	Vector of distance between CGH probes
`disfix`	Length of the chromosome

Author(s)

Alberto Cassese

References

Cassese A, Guindani M, Tadesse M, Falciani F, Vannucci M. A hierarchical Bayesian model for inference of copy number variants and their association to gene expression. Annals of Applied Statistics, 8(1), 148-175.
Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

Examples

```
data <- Scenario2(sigmak = 0.1)
```

`TCGA_lung` *TCGA lung squamous cell carcinoma data*

Description

Processed and filtered TCGA lung squamous cell carcinoma data, as described in the reference.

Usage

```
data(TCGA_lung)
```

Format

The format is a list of 3 objects
$ aCGH
$ Affy
$ distance

Source

Full matrix of data obtained from `https://tcga-data.nci.nih.gov/tcga/`.

References

Cassese A, Guindani M, Vannucci M. A Bayesian integrative model for genetical genomics with spatially informed variable selection. Cancer Informatics.

Examples

```
data <- data(TCGA_lung)
```

`Tran` *Preprocessing - Tran*

Description

This function computes the transition matrix corresponding to a specific matrix of latent states.

Usage

```
Tran(xi)
```

Arguments

`xi`	Matrix of estimated latent states

Details

The matrix of latent states must consider only 4 states:

1. Loss
2. Neutral
3. Gain
4. Amplification

Value

A 4 by 4 matrix with transition probabilities derived from the input matrix of latent states.

Author(s)

Alberto Cassese

References

Guha S, Li Y, Neuberg D. Bayesian hidden Markov modelling of array cgh data. JASA. 2008;103(482):485-497.

Examples

```
data(NCI_60)

X <- NCI_60$aCGH
xi <- InitXi(X)
tran <- Tran(xi)
```

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