Description

Options for fitting the hidden Markov model.

Objects from the Class

Objects can be created by calls of the form `new("HmmOptions", snpset, states, copyNumber.location, copyNumber.scale, copyNumber.ICE, calls.ICE, probHomCall, term5).

Slots

- **states**: Object of class "character". Hidden states of the HMM.
- **snpset**: "SnpLevelSet" instance.
- **copyNumber.location**: Object of class "numeric". Ignored when snpset is an instance of SnpCallSet. See `copyNumber.location`.
- **copyNumber.scale**: Object of class "NULLOrNumeric". This slot is not currently used. If one has standard errors for the copy number estimates, the inverse of the standard errors should be stored in the `cnConfidence assayData` element of the snpset object.
- **copyNumber.ICE**: Object of class "logical". See `copyNumber.ICE`.
- **calls.ICE**: Object of class "logical". See `calls.ICE`.
- **probHomCall**: Object of class "numeric". The probability of a homozygous genotype call corresponding to each of the states. When `calls.ICE` is TRUE, only the first two elements will be used.
- **term5**: Object of class "NULLOrNumeric". User-specified probabilities of f(HOM | genotype call, state). Ignored when `calls.ICE` is FALSE. For more details, see Equation 2.7 in the manuscript that this package references.
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Methods
HmmParameter-class

Arguments

object HmmOptions instance
value see the signature of the corresponding methods

Value

copyNumber.location, probHomCall and term5 each return numeric vectors.
snpset returns an instance of SnpLevelSet

See Also

HmmOptions-class

HmmParameter-class Class "HmmParameter"

Description

Parameters needed for the Viterbi algorithm, including emission probabilities, the genomic distance, and the initial state probabilities

Objects from the Class

Objects can be created by calls of the form new("HmmParameter", states, initialStateProbability, emission, genomicDistance, transitionScale).

Slots

states: Object of class "character"
initialStateProbability: Object of class "numeric"
emission: Object of class "array"
genomicDistance: Object of class "numeric"
transitionScale: Object of class "matrix"

Methods

[ signature(x = "HmmParameter"):
emission signature(object = "HmmParameter"):
emission<- signature(object = "HmmParameter", value = "array"):
genomicDistance signature(object = "HmmParameter"):
genomicDistance<- signature(object = "HmmParameter", value = "numeric"):
hmm signature(object = "HmmOptions", params = "HmmParameter"):
initialize signature(.Object = "HmmParameter"):
pi signature(object = "HmmParameter"):
show signature(object = "HmmParameter"):
states signature(object = "HmmParameter"):
states<- signature(object = "HmmParameter", value = "character"):
tau signature(object = "HmmParameter"):
transitionScale signature(object = "HmmParameter"):
transitionScale<- signature(object = "HmmParameter", value = "matrix"):
HmmPredict-class

Class for the hidden Markov model results

Description

Contains the predictions for the hidden states and a list of breakpoint matrices. Each element in the list corresponds to the breakpoints identified in one sample.

Objects from the Class

Objects can be created by calls of the form `new("HmmPredict", states, predictions, breakpoints, SnpClass)`.

Slots

- `states`: Object of class `character`. Character string of the hidden states.
- `predictions`: Object of class `matrix`. Matrix of predictions.
- `breakpoints`: Object of class `list`. List of matrices. Each element is the matrix of breakpoints for one sample.
- `SnpClass`: Object of class `character`. The class of SNP data (e.g., `oligoSnpSet`)
- `featureData`: Object of class `AnnotatedDataFrame`

Methods

- `SnpClass signature(object = "HmmPredict")`: Accessor for class of SNP data
- `[ signature(x = "HmmPredict")`: Subsetting the predictions
- `breakpoints signature(object = "HmmPredict")`: Accessor for the list of breakpoints
- `breakpoints<- signature(object = "HmmPredict", value = "data.frame")`: Replacement method for breakpoints
- `fData signature(object="HmmPredict")`: Accessor for the data frame of all feature-level (SNP-level) annotation (e.g., physical position)
- `featureData signature(object = "HmmPredict")`: Accessor for the featureData
- `featureNames signature(object = "HmmPredict")`: Character string of SNP identifiers

Note

See HmmParameter vignette

Author(s)

RS

See Also

HmmOptions-class

Examples

```r
showClass("HmmParameter")
```
**addFeatureData**

`getPar` signature(object = "HmmPredict"): Graphical parameters.

`initialize` signature(.Object = "HmmPredict")

`position` signature(object = "HmmPredict"): Accessor for the physical position of SNPs in the object HmmPredict

`predictions` signature(object = "HmmPredict"): Accessor for the predictions

`predictions<-` signature(object = "HmmPredict", value="matrix"): Replacement method for predictions

`sampleNames` signature(object = "HmmPredict"): Sample names

`show` signature(object = "HmmPredict")

`states` signature(object = "HmmPredict"): Accessor for hidden states

Author(s)

R. Scharpf

See Also

`hmm`

Examples

```
showClass("HmmPredict")
```

---

**addFeatureData**  
*Adds chromosomal arm annotation to the featureData*

Description

Adds chromosomal arm annotation to the featureData

Usage

`addFeatureData(snpset)`

Arguments

snpset  
An object inherited from class SnpLevelSet

Value

An AnnotatedDataFrame

Author(s)

R. Scharpf

See Also

`class.AnnotatedDataFrame`
calculateBreakpoints

Calculate breakpoints for altered states from the prediction matrix

Description

Wrapper for findBreaks

Usage

calculateBreakpoints(object, ...)

Arguments

object Object of class HmmPredict
... Not implemented

Details

Returns a matrix with information on size of region (Mb), predicted state, number of SNPs in region, chromosome number, and position.

Value

A matrix

Author(s)

R. Scharpf

See Also

findBreaks

calculateCnSE

Calculates copy number standard errors

Description

Calculates SNP-specific standard errors for copy number using a reference set.

Usage

calculateCnSE(object, referenceSet, epsilon = 0.1)
**calculateDistance**

### Arguments

- **object**: An object of class `SnpCopyNumberSet` or `oligoSnpSet`.
- **referenceSet**: An object of class `SnpCopyNumberSet` or `oligoSnpSet`. If missing, this function uses the samples in the `object` to estimate across sample standard deviations.
- **epsilon**: minimum standard error

### Details

Calculates SNP-specific standard errors from a reference distribution as the product of the within copy number standard deviation of the sample (test set) and the across samples standard deviation from a reference set. The across samples standard deviation is scaled by the median (e.g., across sample sd = across sample sd / median(across sample sd)).

### Value

A matrix of standard errors

### Author(s)

R. Scharpf

---

**calculateDistance**  
*Calculates the physical distance between adjacent SNPs*

### Description

Calculates the distance between adjacent SNPs.

### Usage

```
calculateDistance(object)
physicalDistance(object)
```

### Arguments

- **object**: Object inheriting from `SnpLevelSet`

### Details

Calculates the physical distance between adjacent SNPs along a chromosome.

### Value

A vector of integers

### Note

The transition probabilities in the Viterbi algorithm are calculated as a function of the physical distance (d) between adjacent SNPs.

\[
\text{probability of staying in state } S = \exp(-2 \times d/100*1e6)
\]
calls.ICE

Indicates whether to use confidence scores of the observed copy number estimates in the HMM

Description

In the current framework, the confidence scores are assumed to be the inverse of the standard error

Usage

calls.ICE(object)
calls.ICE(object) <- value

Arguments

object An object of class HmmOptions
value Logical. If TRUE, confidence scores of the genotype calls are used to calculate emission probabilities

Value

Logical

Author(s)

R. Scharpf

See Also

See the VanillaICE vignette


**calls.emission**  
*Calculates emission probabilities for the genotype calls*

**Description**  
Emission probabilities for the genotype calls

**Usage**  
calls.emission(object)

**Arguments**  
object Object inheriting from class HmmOptions

**Details**  
If calls.ICE = TRUE in the HmmOptions object, then the emission probabilities for the genotype calls take into account the confidence scores for the called genotypes.

**Value**  
Array of emission probabilities for the genotype calls (on the log scale)

**Author(s)**  
R. Scharpf

**See Also**  
calls.ICE

---

**chromosomel**  
*Simulated chromosome 1*

**Description**  
Simulated genotype calls and copy number estimates for chromosome 1 (Affymetrix 100k platform).

**Usage**  
data(chromosomel)
Details

The simulation comprises one subject’s genotype, copy number, and confidences scores for 9165 SNPs on chromosome 1. A description of the 5 features simulated in chromosome 1, referred to by regions A-E, and the underlying hidden states in these regions follows.

Genotype calls: With the exception of three regions in this chromosome, we simulated 9165 genotypes (the approximate number of SNPs in the two 50k SNP chips) from a Bernoulli distribution with probability 0.7 of a homozygous genotype. Confidence scores for genotype estimates were obtained by random draws of confidence scores in the Hapmap data when the CRLMM genotype calls agreed with the gold-standard as defined by consensus of the HapMap genotyping centers.

Copy number: The Affymetrix CNAT tool (version 3.0) was used to obtain copy number estimates for the 9165 SNPs from a presumably normal individual in the HapMap dataset (sample identifier NA06993). Deletions and amplifications were simulated from Gaussian distributions with location parameters log2(1) and log2(3), respectively. For the scale parameter, we used a robust estimate of the log2 transformed copy number standard deviation. To illustrate how a confidence score such as a standard error of the copy number estimate could be useful, we simulated standard errors from a shifted Gamma: Gamma(1, 2) + 0.3, where 1 is the shape parameter and 2 is the rate parameter. To ascertain the effect of qualitatively high confidence scores on the ICE HMM, we scaled the robust standard deviation estimate by 1/2. Similarly, to simulate less precise copy number estimates, we multiplied the robust standard deviation estimate by a factor of 2.

For additional information on the five abnormalities simulated in this chromosome, see the manuscript referenced below.

References


Examples

data(chromosome1)
chromosome1

---

```markdown
**copyNumber.ICE**

*Indicates whether to use confidence scores of the observed copy number estimates in the HMM*
```

Description

In the current framework, the confidence scores are assumed to be the inverse of the standard error

Usage

```r
copyNumber.ICE(object)
copyNumber.ICE(object) <- value
```

Arguments

- `object` An object of class `HmmOptions`
- `value` Logical. If TRUE, confidence scores of the copy number estimates are used to calculate emission probabilities.
Details
If TRUE, the confidence scores (assumed to be inverse standard errors) are used by the hidden Markov model. This has the desirable consequence of providing more local smoothing for precise estimates of copy number and more global smoothing for copy number estimates with higher standard errors. When FALSE, a robust estimate of the chip variability is calculated across all of the autosomes.

Value
Logical

Author(s)
R. Scharpf

See Also
See the VanillaICE vignette

---

**copyNumber.emission**

*Calculate emission probabilities for copy number*

Description
Calculate emission probabilities for the copy number

Usage
copyNumber.emission(object)

Arguments
- **object**: Instance of class HmmOptions

Details
If *copyNumber.ICE* = TRUE in the HmmOptions object, then the emission probabilities for the copy number estimates take into account the confidence scores stored in the cnConfidence slot of the object inheriting from class SnpLevelSet. The confidence scores are assumed to be inverse standard errors.

Value
Array of emission probabilities for the copy number estimates (on the log scale)

Author(s)
R. Scharpf

See Also
copyNumber.ICE
copynumberEmission  *Emission probabilities for copy number*

**Description**

Emission probabilities for copy number

**Usage**

```r
copynumberEmission(copynumber, states, mu, uncertainty, takeLog, verbose = TRUE)
```

**Arguments**

- `copynumber`: class matrix
- `states`: class character
- `mu`: class numeric: mean of hidden states for Gaussian
- `uncertainty`: uncertainty of copy number estimates
- `takeLog`: whether to take the log of the copy number AND the mu argument
- `verbose`: logical

**Value**

`array`  
Array of emission probabilities. Dimension 1: SNPs, Dimension 2: samples, Dimension 3: states

---

**emission**  *
* *Accessor for emission probabilities*

**Description**

Accessor for emission probabilities for the hidden Markov model

**Usage**

```r
emission(object)
emission(object) <- value
```

**Arguments**

- `object`: An object of class `HmmParameter`
- `value`: An array of emission probabilities (log scale)

**Value**

An array.

**Author(s)**

R. Scharpf
findBreaks

See Also
HmmParameter-class, HmmOptions-class

findBreaks  Identify breakpoints from the hidden Markov model predictions

Description
Identify breakpoints: physical position of breaks, number of SNPs in region, and the called hidden state.

Usage
findBreaks(x, states, position, chromosome, sample, lik1, lik2)

Arguments
- x: matrix of predicted hidden states (integer)
- states: character string giving the hidden states
- position: physical position of the SNPs
- chromosome: chromosome number
- sample: sample name
- lik1: likelihood under alternative model
- lik2: likelihood under NULL model

Value
data.frame: data.frame describing regions of normal and altered states

fit
Object of class HmmPredict

Description
Object of class HmmPredict

Usage
data(fit)

Details
This object was created from the chromosome1 as described in the VanillaICE vignette.

See Also
chromosome1

Examples
data(fit)
genomicDistance  

*Description*

A rough estimate of the genomic distance between SNPs.

*Usage*

```r
genomicDistance(object)
tau(object)
genomicDistance(object) <- value
```

*Arguments*

- `object`: An object inheriting from `HmmOptions`.
- `value`: A vector of length T - 1, where T is the number of SNPs.

*Details*

The genomic distance is calculated as $\exp(-2 \times d)$, where $d$ is the physical distance in 100MB units.
In the Viterbi algorithm, the probability of remaining in state S at SNP t+1 is the genomic distance.
The probability of transitioning to one of the alternative states is 1 - the genomic distance. The `transitionScale` function can be used to give more weight to transitioning back to the baseline (‘normal’) state.

*Value*

A numeric vector with length T-1.

*Author(s)*

R. Scharpf

*See Also*

`transitionScale`

---

genotypeEmission  

*Description*

Emission probabilities for di-allelic genotype calls.

*Usage*

```r
genotypeEmission(genotypes, states, probHomCall, probMissing, verbose=TRUE)
```
getChromosomeArm

Arguments

- **genotypes**: matrix of integers (1=AA, 2=AB, 3=BB, 4=other)
- **states**: character string of hidden states
- **probHomCall**: numeric; probability of a homozygous genotype call specified in the same order as the hidden states
- **probMissing**: numeric; probability of a missing genotype call specified in the same order as the hidden states
- **verbose**: logical

Details

By default, missing genotype calls will be assumed to be independent of the hidden state. This is not always appropriate, but is easiest to implement in terms of a default.

Value

- **array**: Array of emission probabilities. Dimension 1: SNPs, Dimension 2: samples, Dimension 3: states

getChromosomeArm  Get the chromosome arm

Description

Retrieves the chromosome arm (p or q) for each SNP.

Usage

getChromosomeArm(snpset)

Arguments

- **snpset**: An object inheriting from class SnpLevelSet

Value

A vector of class ’character’.

Note

This function uses data(chromosomeAnnotation) in the SNPchip package to retrieve this information.

Author(s)

RS

See Also

chromosomeAnnotation
**hmm**  
*Fits the hidden Markov model*

**Description**
Fits the hidden Markov model

**Usage**
```
  hmm(object, params)
```

**Arguments**
- `object`: An object of class `HmmOptions`
- `params`: An object of class `HmmParameter`

**Details**
None yet.

**Value**
An object of class `HmmPredict`

**Author(s)**
R. Scharpf

**References**

**See Also**
`HmmParameter-class` `HmmPredict-class` `SnpLevelSet-class`

**Examples**
```
data(chromosome1)
chromosome1 <- chromosome1[1:500, ]
options <- new("HmmOptions",
    states=c("D", "N", "L", "A"),
    snpset=chromosome1,
    copyNumber.location=c(1, 2, 2, 3),
    probHomCall=c(0.99, 0.7, 0.99, 0.7))
validObject(options)
params <- new("HmmParameter",
    states=states(options),
    initialStateProbability=0.99)
cn.emission <- copyNumber.emission(options)
gt.emission <- calls.emission(options)
emission(params) <- cn.emission + gt.emission ##log scale
```
### genomicDistance

```r
# no scaling
genomicDistance(params) <- exp(-2 * calculateDistance(options)/(100*1e6))
```

```r
transitionScale(params) <- matrix(1, length(states(options)), length(states(options)))
if(validObject(params)) fit <- hmm(options, params)
```

---

**Pi**

*Accessor for the initial state probabilities of the hidden Markov model*

**Description**

Accessor for the initial state probabilities of the hidden Markov model

**Usage**

```r
Pi(object)
```

**Arguments**

- `object`: object of class `HmmParameter`

**Value**

Numeric vector with length equal to the number of hidden states

**Author(s)**

RS

**See Also**

`HmmParameter-class`

---

**scaleTransitionProbability**

*Scales the probability of transitioning between two states in the Viterbi algorithm*

**Description**

Function only returns a matrix of 1’s (by default, no scaling of the transition probabilities). This may be changed in future releases.

**Usage**

```r
scaleTransitionProbability(states, SCALE = 2, normalLabel = "N")
```

**Arguments**

- `states`: character string of hidden states
- `SCALE`: Numeric. See details.
- `normalLabel`: Character: label used for the baseline state.
Value

A matrix of dimension S x S, where S is the number of states. The diagonal should always be 1 (we do not scale the probability of remaining in the same state). A slot for storing this matrix is provided in the `HmmParameter` class.

Author(s)

RS

See Also

genomicDistance, transitionScale, HmmParameter-class

---

```r
states(object)
states(object) <- value
```

Arguments

- `object` An object of class `HmmOptions` or `HmmParameter`
- `value` Vector of class `character`

Value

Character string of hidden states

Author(s)

RS
transitionScale

Scales the transition probabilities of the hidden Markov model

Description
Accessor and replacement methods for scaling the transition probabilities

Usage
transitionScale(object)
transitionScale(object) <- value

Arguments
object An object of class HmmParameter
value A matrix of dimension STATES x STATES, where STATES is the number of hidden states.

Details
The probability of remaining in the same state, \( P(S_t = S_{t+1}) \) (the diagonal of the transition probability matrix) is a function of the distance between SNPs. The probability of transitioning to some other state is epsilon, where epsilon = 1 - \( P(S_t = S_{t+1}) \). The epsilon is split among STATES-1 states. By default, the probability of transitioning from an altered state back to the normal state is twice as likely as the probability of transitioning between two altered states. The weights for epsilon are provided in the transitionScale matrix in objects of class HmmParameter.

Value
A matrix

Author(s)
R. Scharpf

See Also
scaleTransitionProbability

viterbi

viterbi algorithm

Description
The Viterbi algorithm for computing the most likely state sequence given a model

Usage
viterbi(initialStateProbs, emission, tau, arm, tau.scale, verbose = TRUE, return
Arguments

initialStateProbs
initial state probabilities (log scale)

emission
matrix of log emission probabilities (one sample is a matrix)

tau
transition probabilities (original scale)

arm
numeric or character string indicating chromosomal arm

tau.scale
matrix to scale the probability of transitioning between states.

verbose
Logical

returnLikelihood
whether to return the 'loglikelihood'

Details

The Viterbi algorithm is fit independently to each chromosomal arm if arm is specified. Argument tau.scale is a matrix that scales the probability of transitioning from an altered state to a normal state to the probability of transitioning between two altered states. If missing, tau.scale is 1 (no scaling)

returnLikelihood is experimental

Value

matrix predicted states

Author(s)

R. Scharpf
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