Package 'CNORfeeder'

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Type Package

Title Integration of CellNOptR to add missing links

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Description This package integrates literature-constrained and data-driven methods to infer signalling networks from perturbation experiments. It permits to extends a given network with links derived from the data via various inference methods and uses information on physical interactions of proteins to guide and validate the integration of links.

License GPL-3

LazyLoad yes

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R topics documented:

CNORfeeder-package *R package to integrate literature-constrained and data-driven methods to infer signalling networks from perturbation experiments*

Description

CNORfeeder permits to extend a network derived from literature with links derived strictly from the data via various inference methods using information on physical interactions of proteins to guide and validate the integration of links. The package is designed to be integrated with CellNOptR.

Details

Package:	CNORfeeder
Type:	Package
Version:	1.0.0.
Date:	2012-11-22
License:	GPLv2
LazyLoad:	yes

Author(s)

F. Eduati Maintainer: F. Eduati <eduati@ebi.ac.uk>

References

F. Eduati, J. De Las Rivas, B. Di Camillo, G. Toffolo, J. Saez-Rodriguez. Integrating literature-constrained and data-driven inference of signalling networks. Bioinformatics, 28(18):2311-2317, 2012.

Examples

```
library(CNORfeeder)

# this is an example of the main steps of the integrated CellNOptR - CNORfeeder pipeline

# load the data already formatted as CNOlist
data(CNOlistDREAM,package="CellNOptR")
# load the model (PKN) already in the CNO format
data(DreamModel,package="CellNOptR")
# see CellNOptR documentation to import other data/PKNs)

# A. INFERENCE - CNORfeeder
# FEED inference: codified in Boolean Tables
BTable <- makeBTables(CNOlist=CNOlistDREAM, k=2, measErr=c(0.1, 0))

# B. COMPRESSION - CellNOptR
# preprocessing step
model<-preprocessing(data=CNOlistDREAM, model=DreamModel)
```

```
# C. INTEGRATION - CNORfeeder
# integration with the compressed model
modelIntegr <- mapBTables2model(BTable=BTable,model=model,allInter=TRUE)
# see example in ?MapDDN2Model to use other reverse-engineering methods

# D. WEGHTING - CNORfeeder
# integrated links are weighted more according to the integratin factor integrFac
modelIntegrWeight <- weighting(modelIntegr=modelIntegr, PKNmodel=DreamModel,
                               CNOlist=CNOlistDREAM, integrFac=10)

# E. TRAINING - CellNOptR
initBstring<-rep(1,length(modelIntegr$reacID))
# training to data using genetic algorithm (run longer to obtain better results)
DreamT1opt<-gaBinaryT1W(
CNOlist=CNOlistDREAM,
model=modelIntegrWeight,
initBstring=initBstring,
maxGens=2,
popSize=5,
verbose=FALSE)
```

`Binference` *Bayesian network inference*

Description

This function uses data (CNOlist) to infer a Bayesian network using the catnet package.

Usage

```
Binference(CNOlist, mode="AIC", tempCheckOrders=10,
            maxIter=100, filename="BAYESIAN")
```

Arguments

`CNOlist`	a CNOlist structure, as produced by makeCNOlist
`mode`	a character, optimization network selection criterion such as "AIC" and "BIC", to be used in cnSearchSA
`tempCheckOrders`	an integer, the number of iteration, orders to be searched, with constant temperature, to be used in cnSearchSA
`maxIter`	an integer, the total number of iterations, thus orders, to be processed, to be used in cnSearchSA
`filename`	name of the sif file saved, default BAYESIAN

Details

This function transforms the data in a format compatible with catnet package, infers the network using the Stochastic Network Search as implemented in catnet (see cnSearchSA), computes the consensus model of the models returned by cnSearchSA considering only links that have a frequency of appearence greater than 0.1 and returns the model in the sif format.

Value

sif	the inferred data-driven network in sif format

Author(s)

F.Eduati

See Also

mapDDN2model

Examples

```
data(CNOlistDREAM,package="CellNOptR")
DDN<-Binference(CNOlistDREAM, tempCheckOrders=10, maxIter=100,
                filename="BAYESIAN")
```

---

gaBinaryT1W *Genetic algorithm used to optimise a model differently weighting links*

Description

This function is the genetic algorithm to be used to optimise a model by fitting to data containing one time point. It is the function gaBinaryT1 of CellNOptR modified in orter to differently weights for the integrated links

Usage

```
gaBinaryT1W(CNOlist, model, initBstring=NULL, sizeFac = 1e-04,
    NAFac = 1, popSize = 50, pMutation = 0.5, maxTime = 60, maxGens = 500,
    stallGenMax = 100, selPress = 1.2, elitism = 5, relTol = 0.1, verbose=TRUE,
    priorBitString=NULL, maxSizeHashTable=5000)
```

Arguments

CNOlist	a CNOlist on which the score is based (based on valueSignals[[2]], i.e. data at time 1)
model	a model structure, as created by readSIF, normally pre-processed but that is not a requirement of this function. If the linksWeight field is provided in model structure, all links are weighted according to that.
initBstring	an initial bitstring to be tested, should be of the same size as the number of reactions in the model above (model$reacID). Default is all ones.
sizeFac	the scaling factor for the size term in the objective function, default to 0.0001
NAFac	the scaling factor for the NA term in the objective function, default to 1
popSize	the population size for the genetic algorithm, default set to 50
pMutation	the mutation probability for the genetic algorithm, default set to 0.5
maxTime	the maximum optimisation time in seconds, default set to 60

maxGens	the maximum number of generations in the genetic algorithm, default set to 500
stallGenMax	the maximum number of stall generations in the genetic algorithm, default to 100
selPress	the selective pressure in the genetic algorithm, default set to 1.2
elitism	the number of best individuals that are propagated to the next generation in the genetic algorithm, default set to 5
relTol	the relative tolerance for the best bitstring reported by the genetic algorithm, i.e., how different from the best solution, default set to 0.1
verbose	logical (default to TRUE) do you want the statistics of each generation to be printed on the screen?
priorBitString	At each generation, the GA algorithm creates a population of bitstrings that will be used to perform the optimisation. If the user knows the values of some bits, they can be used to overwrite bit values proposed by the GA algorithm. If provided, the priorBitString must have the same length as the initial bitstring and be made of 0, 1 or NA (by default, this bitstring is set to NULL, which is equivalent to setting all bits to NA). Bits that are set to 0 or 1 are used to replace the bits created by the GA itself (see example).
maxSizeHashTable	a hash table is use to store bitstring and related score. This allows the GA to be very efficient is the case of small models. The size of the hash table is 5000 by default, which may be too large for large models.

Details

The whole procedure is described in details in Saez-Rodriguez et al. (2009). The basic principle is that at each generation, the algorithm evaluates a population of models based on excluding or including some gates in the initial pre-processed model (this is encoded in a bitstring with contains 0/1 entries for each gate). The population is then evolved based on the results of the evaluation of these networks, where the evaluation is obtained by simulating the model (to steady state) under the various conditions present in the data, and then computing the squared deviation from the data, to which a penalty is added for size of the model and for species in the model that do not reach steady state.

Value

This function returns a list with elements:

bString	the best bitstring
results	a matrix with columns "Generation", "Best_score", "Best_bitString", "Stall_Generation", "Avg_Score_Gen", "Best_score_Gen", "Best_bit_Gen", "Iter_time"
stringsTol	the bitstrings whose scores are within the tolerance
stringsTolScores	the scores of the above-mentioned strings

Author(s)

C. Terfve, T. Cokelaer, F.Eduati

References

J. Saez-Rodriguez, L. G. Alexopoulos, J. Epperlein, R. Samaga, D. A. Lauffenburger, S. Klamt and P. K. Sorger. Discrete logic modeling as a means to link protein signaling networks with functional analysis of mammalian signal transduction, Molecular Systems Biology, 5:331, 2009.

See Also

gaBinaryT1

Examples

```
data(CNOlistDREAM,package="CellNOptR")
data(DreamModel,package="CellNOptR")
model<-preprocessing(data=CNOlistDREAM, model=DreamModel)

BTable <- makeBTables(CNOlist=CNOlistDREAM, k=2, measErr=c(0.1, 0))
modelIntegr <- mapBTables2model(BTable=BTable,model=model,allInter=TRUE)

modelIntegrWeight <- weighting(modelIntegr=modelIntegr, PKNmodel=DreamModel,
                        CNOlist=CNOlistDREAM, integrFac=10)

initBstring<-rep(1,length(modelIntegr$reacID))
# training to data using genetic algorithm (run longer to obtain better results)
DreamT1opt<-gaBinaryT1W(
CNOlist=CNOlistDREAM,
model=modelIntegrWeight,
initBstring=initBstring,
maxGens=2,
popSize=5,
verbose=FALSE)
```

---

linksRanking *Ranking of links inferred from data*

Description

This function uses data (CNOlist) to rank links based on measurement error model as used by FEED method to reverse-engineer the network.

Usage

```
linksRanking(CNOlist, measErr=c(0.1, 0), savefile=FALSE)
```

Arguments

CNOlist	a CNOlist structure, as produced by makeCNOlist
measErr	a 2 value vector (err1, err2) defining the error model of the data as sd^2 = err1^2 + (err2*data)^2, default to c(0.1, 0)
savefile	TRUE to save the file in txt format, FALSE not. Default is FALSE.

Details

This function is similar to the fist step of FEED to reverse engineer the network strictly from data, i.e. the inference of Boolean tables, as described in (Eduati et al., PLoS ONE, 2010) and implemented in makeBTables. Links are ranked according to the upper limit value of parameterk allowing the presence of the link, where k is the parameter which is multiplied by the measurement error in order to assess the relevance of a link. The function returs link in decreasing order of importance and associate to each link a value (maximum value of k allowing the presence of the link) quantifying its relevance.

Value

this function returns a list with fields:

`Lrank`	a matrix in which each link is associated with a numerical value, links are ordered in decreasing order of reliability)

Author(s)

F.Eduati

References

F. Eduati, A. Corradin, B. Di Camillo, G. Toffolo. A Boolean approach to linear prediction for signaling network modeling. PLoS ONE; 5(9): e12789.

See Also

makeCNOlist, makeBTables

Examples

```
data(CNOlistDREAM,package="CellNOptR")
Lrank <- linksRanking(CNOlist=CNOlistDREAM, measErr=c(0.1, 0))
```

`makeBTables` *Make Boolean tables*

Description

This function uses data (CNOlist) to infer a Boolean table for each measured protein, codifying if a particular stimulus inhibitor combination affects the protein. A stimulus or an inhibitor significantly affects an output protein if it is able to modify its activity level of a quantity that exceeds the uncertainty associated with its measurement.

Usage

```
makeBTables(CNOlist, k=2, measErr=c(0.1, 0), timePoint=NA)
```

Arguments

CNOlist	a CNOlist structure, as produced by makeCNOlist
k	a parameter that determine the threshold of significancy of the effect of stimuli and inhibitors, default to 2
measErr	a 2 value vector (err1, err2) defining the error model of the data as sd^2 = err1^2 + (err2*data)^2, default to c(0.1, 0)
timePoint	the time point to be considered for the inference of the Boolean tables (i.e. "t1" or "t2"), if not specified all time points are consideres

Details

This function computes the fist step of FEED to reverse engineer the network strictly from data, i.e. the inference of Boolean tables, as described in (Eduati et al., PLoS ONE, 2010). For each protein, a Boolean table is inferred having one columns for each stimulus and one row for each inhibitor. If a stimulus produces a significant effect on the activity level of the protein this is codified with a 1 in the corresponding column, if also the inhibitor affects the protein there is a 2 in the corresponding cell. The sign of the regulation is coded in separate tables.

Value

this function returns a list with fields:

namesSignals	a vector of names of signals
tables	a list with one Boolean table for each protein codifying the effect of stimuli (columns) and inhibitors (rows), 1 if the stimulus affect the protein, 2 if also the inhibior does
NotMatStim	has the same format as tables but just contains a 1 if the regulation has a negative effect, and 0 otherwise
NotMatInhib	has the same format as tables but just contains a 1 if the regulation has a negative effect, and 0 otherwise

Author(s)

F.Eduati

References

F. Eduati, A. Corradin, B. Di Camillo, G. Toffolo. A Boolean approach to linear prediction for signaling network modeling. PLoS ONE; 5(9): e12789.

See Also

makeCNOlist, mapBTables2model

Examples

```
data(CNOlistDREAM,package="CellNOptR")
BTable <- makeBTables(CNOlist=CNOlistDREAM, k=2, measErr=c(0.1, 0))
```

`mapBTables2model` *Integrate Boolean tables with the model*

Description

This function infers the network from the Boolean tables and integrates it with the network encoded in the model (generally derived from prior knowledge), adding links that are missing.

Usage

```
mapBTables2model(BTable,model,optimRes=NA,allInter=TRUE,compressed=TRUE)
```

Arguments

`BTable`	a BTable list, as created by makeBTables
`model`	a model list, as created by readSif
`optimRes`	a bit string with the reaction of the model to be considered, default considers all reactions
`allInter`	one new link in the network can correspond to more links in the model, set it to TRUE if you want to add all possible links, FALSE to add only one link, default is TRUE
`compressed`	this argument is used to decede how to deal with unmeasured and unperturbed nodes (white nodes). As general guideline, it should be set to TRUE if the PKN has been compressed in the preprocessing step, FALSE otherwise. Default is TRUE.

Details

The function receive as input the Boolean Tables, infers the data-driven network form them (as descibed in (Eduati et al., PLoS ONE, 2010)) and integrates it with the model, returning a new model with the integrated links. If the Model is not given as input (Model=NULL), the data-driven network is returned as model.

Value

a new model with the integrated links and an additional field:

`indexIntegr`	a vector with the indexes of the integrated links

Author(s)

F.Eduati

References

F. Eduati, A. Corradin, B. Di Camillo, G. Toffolo. A Boolean approach to linear prediction for signaling network modeling. PLoS ONE; 5(9): e12789.

See Also

readSif, readMIDAS, makeBTables

Examples

```
data(CNOlistDREAM,package="CellNOptR")
data(DreamModel,package="CellNOptR")
model<-preprocessing(data=CNOlistDREAM, model=DreamModel)
BTable <- makeBTables(CNOlist=CNOlistDREAM, k=2, measErr=c(0.1, 0))
modelIntegr <- mapBTables2model(BTable=BTable,model=model,allInter=TRUE)
# modelIntegr$reacID[modelIntegr$indexIntegr] to see the integrated links
```

`mapDDN2model` *Integrate data-drive network with the model*

Description

This function integrates the data-driven network (in sif format) with the network encoded in the model (generally derived from prior knowledge), adding links that are missing.

Usage

```
mapDDN2model(DDN,model,CNOlist,allInter=TRUE)
```

Arguments

`DDN`	a sif file encoding a data-driven network, as created by Binference or MInference
`model`	a model list, as created by readSif
`CNOlist`	a CNOlist, as created by makeCNOlist
`allInter`	one new link in the network can correspond to more links in the model, set it to TRUE if you want to add all possible links, FALSE to add only one link, default is TRUE

Details

The function receives as input a sif file with the data-driven network, as created by Binference or MInference, and integrates it with the model, returning a new model with the integrated links.

Value

a new Model with the integrated links and an additional field:

`indexIntegr`	a vector with the indexes of the integrated links

Author(s)

F.Eduati

See Also

readSif, readMIDAS, Binference, MInference

Examples

```
data(CNOlistDREAM,package="CellNOptR")
data(DreamModel,package="CellNOptR")
model<-preprocessing(data=CNOlistDREAM, model=DreamModel)

## Not run:
DDN<-Binference(CNOlistDREAM, tempCheckOrders=10, maxIter=100,
                filename="BAYESIAN")

modelIntegr<-mapDDN2model(DDN=DDN,model=model,CNOlist=CNOlistDREAM)


## End(Not run)
```

`MIinference` *Mutual information based network inference*

Description

This function uses data (CNOlist) to infer a data-driven network using the mutual information based appoaches ARACNe and CLR as implemented in the minet package.

Usage

```
MIinference(CNOlist, method="ARACNE", PKNgraph=NULL,
            filename="ARACNE")
```

Arguments

`CNOlist`	a CNOlist structure, as produced by makeCNOlist
`method`	a character, the name of the method to be used: ARACNE or CLR. Default, ARACNE
`PKNgraph`	a network to be used for comparison to assess the directionality of some links. Default is NULL.
`filename`	name of the sif file saved, default ARACNE

Details

This function transforms the data in a format compatible with minet package, infers the network using aracne or clr as implemented in the minet package and returns the network in the sif format. It is important to notice that mutual information approaches do not allow for determining the directionality of the links thus both directions are considered. The function allows to give as input a network in graph format (graph package, see sif2graph to convert from sif to graph format) to be used as comparison to assess the directionality of some links, e.g. PKN.

Value

`sif`	the inferred data-driven network in sif format

Author(s)

F.Eduati

References

P. E. Meyer, F. Lafitte and G. Bontempi (2008). MINET: An open source R/Bioconductor Package for Mutual Information based Network Inference. BMC Bioinformatics, 9(1), 2008

See Also

mapDDN2model, sif2graph, model2sif

Examples

```
data(CNOlistDREAM,package="CellNOptR")
data(DreamModel,package="CellNOptR")
PKNgraph<-sif2graph(model2sif(DreamModel))

method="ARACNE"
#method="CLR"
DDN<-MIinference(CNOlist=CNOlistDREAM, method=method,
                 PKNgraph=PKNgraph, filename=method)
```

PPINigraph *Protein-protein interaction netwrok*

Description

The human protein-protein interaction network was built using a unified PPI dataset obtained as APID (Prieto,C. and De Las Rivas,J. 2006), by the combination of interactions coming from six source databases. The starting whole dataset was composed by 68488 human physical protein-protein interactions validated at least by one experimental method and reported in one article published in PubMed. From this dataset we obtained two PPI subsets with increasing confidence: a set of 28971 interactions validated by at least one binary experimental method (binary as defined in (De Las Rivas,J. and Fontanillo,C. 2010)); a set 6033 interactions validated by at least two experimental methods, one of them binary.

Usage

```
PPINigraph
```

Format

PPINigraph is an igraph with proteins as nodes and undirected links as physical protein interactions.

Source

This network was bult for the analysis performed in (Eduati,F. et al. 2012)

References

1. F. Eduati, J. De Las Rivas, B. Di Camillo, G. Toffolo, J. Saez-Rodriguez. Integrating literature-constrained and data-driven inference of signalling networks. Bioinformatics, 28(18):2311-2317, 2012.
2. C. Prieto, J. De Las Rivas. APID: Agile Protein Interaction DataAnalyzer. Nucleic Acids Res., 34, W298-302, 2006.
3. J. De Las Rivas, C. Fontanillo. Protein-protein interactions essentials: key concepts to building and analyzing interactome networks. PLoS Comput.Biol., 6, e1000807, 2010.

`UniprotIDdream` *Uniprot identifiers for proteins in DreamModel*

Description

This data object contains the Uniprot identifiers corresponding to DreamModel of CellNOptR package, in order to associat them with the corresponding nodes in the protein-protein interaction network (PPINigraph).

Usage

```
UniprotIDdream
```

Format

UniprotIDdream is a list where each element is a protien of the DreamModel and is associated with the respective Uniprot identifiers.

Source

This data object is manually derived from the Uniprot database.

References

1. F. Eduati, J. De Las Rivas, B. Di Camillo, G. Toffolo, J. Saez-Rodriguez. Integrating literature-constrained and data-driven inference of signalling networks. Bioinformatics, 28(18):2311-2317, 2012.
2. J. Saez-Rodriguez, L. G. Alexopoulos, J. Epperlein, R. Samaga, D. A. Lauffenburger, S. Klamt and P. K. Sorger. Discrete logic modeling as a means to link protein signaling networks with functional analysis of mammalian signal transduction, Molecular Systems Biology, 5:331, 2009.

`weighting` *Weight integrated links.*

Description

This function weights links integrated in the model using additional penalty and/or information from protien-protein interactions networks (PINs).

Usage

```
weighting(modelIntegr,PKNmodel,CNOlist,integrFac,UniprotID,PPI)
```

Arguments

`modelIntegr`	the integrated model as created by mapDDN2model or mapBTables2model
`PKNmodel`	the model of the original prior-knowledge network
`CNOlist`	a CNOlisi, as created by makeCNOlist
`integrFac`	a number indicating the penalty for integrated links
`UniprotID`	a list with the Uniprot identifiers of proteins in the PKN
`PPI`	an igraph of the PIN to be used, if no network is provided (=NULL) this information is not used. Default is NULL.

Details

Integrated links are less reliable than links from the PKN, thus should be penalized in the optimization process. This function allows to include a panalty for integrated links (integrFact). Furthermore links can be differently prioritized based on information derived from pritein interaction networks (PIN): the basic idea is that if, for a directed link A -> B integrated in the PKN, there is a corresponding path in the PIN, it is more plausible that there is a molecular pathway A -> B. Because shorter paths are more feasible, as a first approximation the shortest path length between A and B in the PIN can be used as a reliability score for the integrated link. Since the optimization is performed on a compressed version of the PKN, one link integrated in the compressed network generally corresponds to multiple possible links integrated in the PKN and the shortes path of all. The weight for each integrated link in the compressed network is thus computed as (1 + the inverse of the sum of the inverse of the corresponding PKN of the shortest paths in the PIN). A high quality network of known human physical protein-protein interaction assembled from multiple databases is provided with the package: interactions were included only if validated by at least one binary experimental method in a published paper and the number of experimental evidences was reported for each interaction.

Value

`modelIntegr`	the input modelIntegr with an additional field: a vector with the weights of the integrated links

Author(s)

F.Eduati

See Also

mapDDN2model, mapBTables2model, gaBinaryT1W

Examples

```
data(CNOlistDREAM,package="CellNOptR")
data(DreamModel,package="CellNOptR")
data(UniprotIDdream,package="CNORfeeder")

model<-preprocessing(data=CNOlistDREAM, model=DreamModel)

BTable <- makeBTables(CNOlist=CNOlistDREAM, k=2, measErr=c(0.1, 0))
modelIntegr <- mapBTables2model(BTable=BTable,model=model,allInter=TRUE)

modelIntegrWeight <- weighting(modelIntegr=modelIntegr, PKNmodel=DreamModel,
 CNOlist=CNOlistDREAM, integrFac=10)

# weighting using PPI might take some minutes
## Not run:
data(UniprotIDdream,package="CNORfeeder")
data(PPINigraph,package="CNORfeeder")
modelIntegrWeight2 <- weighting(modelIntegr=modelIntegr, PKNmodel=DreamModel,
  CNOlist=CNOlistDREAM, integrFac=10, UniprotID=UniprotIDdream,
  PPI=PPINigraph)

## End(Not run)
```

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