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

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`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<-CellNOptR::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,
 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

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


## End(Not run)
```

`buildFeederObjectDynamic`

Building Feeder-Object for the integration to the PKN

Description

This function estimates the possible mechanisms of interactions to be added to the PKN from a database of interactions for improving the fitting cost.

Usage

```
buildFeederObjectDynamic(model = model, cnolist = cnolist, indices = indices, database = NULL, DDN = TRU
```

Arguments

`model`	a model as returned by readSIF. Alternatively, the filename can also be provided
`cnolist`	a cnolist structure, as produced by makeCNOlist
`indices`	a list of indices of poorly fitted measurements as returned from identifyMisfitIndices
`database`	a database of interactions which can be optionally provided as an interaction matrix with 3 or 4 colums (source of interaction, sign of interaction, target of interaction and optionally a weight value from 0 to 1 indicating the significance of that interaction in the database). Default: database=NULL
`DDN`	a parameter indicating whether integrating links inferred from the Data-Driven FEED approach. Default: DDN = TRUE
`pathLength`	a path length parameter for the maximal path length of additional interactions to search for in the database. Default: pathLength = 2
`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`	time-points to be considered. By default set to NA, which means that the function will search for poorly fitted measurements at each time-point.

Details

The function identifies and proposes the new links to integrate in the PKN either either by means of the data-driven method from the FEED algorithm or from the provided database of interactions or from both of them.

Value

this function returns a list with fields:

`Original PKN` the original PKN

`Feed mechanisms`
the list of proposed interactions to integrate to the PKN (if both the database and the data-driven method are considered by the user, the last mechanism corresponds to the data-driven approach)

Author(s)

E.Gjerga

Examples

```
data(ToyModel_Gene, package="CNORfeeder")
data(CNOlistToy_Gene, package="CNORfeeder")
data(simData_toy,package="CNORfeeder")

model <- CellNOptR::preprocessing(data=CNOlistToy_Gene, model=model)

indices = identifyMisfitIndices(cnolist = CNOlistToy_Gene, model = model,
                                simData = simData, mseThresh = 0.05)

feederObject = buildFeederObjectDynamic(model = model, cnolist = CNOlistToy_Gene,
                                        indices = indices, database = NULL,
                                        DDN = TRUE, pathLength = 2)
```

---

cnolist *CNOlist*

Description

CNOlist object containing the perturbation experimental data.

Usage

```
cnolist
```

Format

cnolist is the object which contains the data in the MIDAS file.

Source

This object is generated from the dynamic-feeder example

---

database *OmniPath PPI*

Description

Data-frame containing signed and directed interactions from Omnipath.

Usage

```
database
```

Format

database is the object which contains new interactions which can potentially be integrated.

Source

This object is generated from the dynamic-feeder example

---

feederObject *Feeder Object*

Description

Object list as obtained from the buildFeederObjectDynamic() function.

Usage

```
feederObject
```

Format

feederObject is a list containing interactions suggested to be added in the PKN.

Source

This object is generated from the dynamic-feeder example

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<-CellNOptR::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)
```

`identifyMisfitIndices` *Identifying indices of poorly fitted measurements*

Description

This function identifies poorly fitted measurements for specific experimental conditions. It returns a list of possible indices and mse's pointing to possible connections to be added during the feeding process.

Usage

```
identifyMisfitIndices(cnolist = cnolist, model = model, simData = NULL, mseThresh = 0)
```

Arguments

`cnolist`	a cnolist structure, as produced by makeCNOlist
`model`	a model as returned by readSIF. Alternatively, the filename can also be provided.
`simData`	a matrix of simulated data values for a specific model as returned by plotLBodeFitness (default set to NULL in which case users do not need to do an initial fit of the model and the FEED algorithm will search for new links indiscriminately)
`mseThresh`	thrreshold parameter for minimal misfit to be considered - if the initial fit (mse) for a node in a specific condition is larger/wrose than the threshold value, it will be considered as poorly fitted (mseThresh = 0 by default)

Details

This function computes the misfits (MSE values) between the actual measured data points and the data values for a specific set of inferred model parameters. Once the MSE values are calculated for each of the measurements over each experimental condition, the poorly fitted measurements are then identify. A measurement is considered as poorly fitted if the corresponding inferred MSE value is higher than the specified MSE threshold value (mseThresh).

Value

this function returns a list with fields:

`indices`	a list of indices pointing to the poorly fitted measurements and the corresponding ms value
`use`	a matrix of use values indicating the mismatch between model simulations and data for each measurement at each experimental condition

Author(s)

E.Gjerga

Examples

```
data(ToyModel_Gene, package="CNORfeeder")
data(CNOlistToy_Gene, package="CNORfeeder")
data(indices,package="CNORfeeder")
data(database, package="CNORfeeder")
data(simData_toy,package="CNORfeeder")


indices = identifyMisfitIndices(cnolist = CNOlistToy_Gene, model = model,
                                simData = simData, mseThresh = 0.05)
```

---

indices *Mis-fit indices*

Description

Simulation data as obtained from the identifyMisfitIndices() function.

Usage

```
indices
```

Format

indices is a list of poorly predicted measurements.

Source

This object is generated from the dynamic-feeder example

integratedModel *Integrated Model*

Description

PKNlist object as obtained from the integrateLinks() function.

Usage

```
integratedModel
```

Format

integratedModel is the model we obtain after the integration of the new links.

Source

This object is generated from the dynamic-feeder example

integrateLinks *Integrating the new links to the PKN*

Description

This function integrates the new links inferred via the FEED method or from the database to the original PKN.

Usage

```
integrateLinks(feederObject = feederObject, cnolist = cnolist, database = NULL)
```

Arguments

feederObject	a feederObject structure, as produced by buildFeederObjectDynamic
cnolist	a cnolist structure, as produced by makeCNOlist
database	a database of interactions which can be optionally provided as an interaction matrix with 3 or 4 colums (source of interaction, sign of interaction, target of interaction and optionally a weight value from 0 to 1 indicating the significance of that interaction in the database). Default: database=NULL

Details

This function integrates the new links inferred via the FEED method or from the database to the original PKN. Moreover it indicates which are the integrated links and if a weighted database has been used it also shows the weights assigned to each integrated link. Links that are present in the original PKN are assigned a database weight of 0, integrated links that have been inferred via the FEED method and are not present in the database are assigned a database penalty of Inf, while integrated links present in the database take values between 0 and 1.

Value

this function returns a list with fields:

`model`	the integrated model
`integLinksIdx`	indices pointing towards the newly integrated links of the model
`integSpeciesIdx`	indices pointing towards the newly integrated species of the model
`databaseWeight`	weights assigned based on the presence of links in the database

Author(s)

E.Gjerga

Examples

```
data(feederObject_toy,package="CNORfeeder")
data(CNOlistToy_Gene, package="CNORfeeder")
data(CNOlistToy_Gene, package="CNORfeeder")

integratedModel = integrateLinks(feederObject = feederObject, cnolist = CNOlistToy_Gene,
                                 database = NULL)
```

`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<-CellNOptR::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, MIinference

Examples

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

```
library(CellNOptR)
library(CNORfeeder)
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)
```

---

model *Prior Knowledge Network*

Description

Model object from the dynamic-feeder example.

Usage

```
model
```

Format

model is an PKNlist with proteins as nodes and undirected links as physical protein interactions.

Source

This object is generated from the dynamic-feeder example

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.

runDynamicFeeder *Modelling the integrated PKN with CNORode*

Description

This function evaluates the effects of possible feeder mechanisms which are added to the PKN.

Usage

```
runDynamicFeeder(cnolist = cnolist, integratedModel = integratedModel, ode_parameters = ode_parameters
```

Arguments

cnolist	a cnolist structure, as produced by makeCNOlist
integratedModel	the integrated model as returned from integrateLinks
ode_parameters	a list with the ODEs parameter information.
penFactor_k	a penalty factor for the new integrated links obtained from the FEED algorithm and which are not present in the database (if the database was given). Default: penFactor_k = 100
penFactor_tau	a penalty factor for all the new nodes integrated in the PKN. Default: penFactor_tau = 1
penFactorPIN_k	a penalty factor for the new integrated links and which are present in the database (for the cases when the database was given). Default: penFactorPIN_k = 10
paramsSSm	a list of SSm parameters. default is the list returned by defaultParametersSSm

Details

This function evaluates the effects of possible feeder mechanisms which are added to the PKN. The analysis performed is a simple CNORode analysis over the integrated network where the newly integrated links are supposed to be penalised more than the links present in the original PKN. If a database of interactions is also provided by the user, than normally the links inferred from the FEED mechanism and which re not present in the database should be more penalised than the ones that are. There is also the opportunity to weight database interactions based on their relevance (i.e. number of resources, etc.).

Value

this function returns a list with fields:

Parameters	the inferred optimal ODE parameters
Integrated-Model	the integrated model which was optimised
CNOlist	the CNOlist object containing the data

Author(s)

E.Gjerga

Examples

```
data(integratedModel_toy, package="CNORfeeder")
data(CNOlistToy_Gene, package="CNORfeeder")
data(simData_toy,package="CNORfeeder")


## To be run with the recent version of the CNORode package:
## https://github.com/saezlab/CNORode
#
# library(CNORode)
```

```
#
# paramsSSm=defaultParametersSSm()
#
# ode_parameters=createLBodeContPars(integratedModel$model, LB_n = 1, LB_k = 0,
#                                LB_tau = 0, UB_n = 3, UB_k = 1, UB_tau = 1, default_n = 3,
#                           default_k = 0.5, default_tau = 0.01, opt_n = FALSE, opt_k = TRUE,
#                                     opt_tau = TRUE, random = TRUE)
#
# result = runDynamicFeeder(cnolist = CNOlistToy_Gene, integratedModel = integratedModel,
#                             ode_parameters = ode_parameters, paramsSSm = paramsSSm,
#                             penFactor_k = 2, penFactorPIN_k = 0.1, penFactor_tau = 1)
#
```

`simData` *CNORode simuation data*

Description

Simulation data as obtained from the plotLBodeFitness() function.

Usage

```
simData
```

Format

simData is a list containing simulated values for a specific set of ode parameters.

Source

This object is generated from the dynamic-feeder example

`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.

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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<-CellNOptR::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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