Package ‘CNORfuzzy’

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Description This package is an extension to CellNOptR. It contains additional functionality needed to simulate and train a prior knowledge network to experimental data using constrained fuzzy logic (cFL, rather than Boolean logic as is the case in CellNOptR). Additionally, this package will contain functions to use for the compilation of multiple optimization results (either Boolean or cFL).
License GPL-2
Depends R (>= 2.15.0), CellNOptR (>= 1.4.0), nloptr (>= 0.8.5)
Suggests xtable, Rgraphviz, RUnit, BiocGenerics
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R topics documented:

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CNORfuzzy-package

R version of CNOFuzzy, a Constrained Fuzzy Logic Network Optimisation

Description
This package does optimisation of constrained Fuzzy logic networks of signalling pathways based on a previous knowledge network and a set of data collected upon perturbation of some of the nodes in the network.

Details
- **Package:** CNOR
- **Type:** Package
- **Version:** 1.4.0
- **Date:** 2013-08-28
- **License:** GPL-2
- **LazyLoad:** yes
- **Depends:** R (>= 2.15.0), CellNOptR (>= 1.3.29), nloptr (>= 0.8.5)

Author(s)
M.K. Morris
Maintainer: T. Cokelaer <cokelaer@ebi.ac.uk>

References

See Also
CellNOptR package.

Examples
```r
# Get data from CellNOptR package
data(CNOlistToy,package="CellNOptR")
data(ToyModel,package="CellNOptR")

# Use the default parameters and set Data and Model
```
CNORwrapFuzzy

paramsList=defaultParametersFuzzy()
paramsList$data=CNOlistToy
paramsList$model=ToyModel

## Not run:
# Run the simulator
Res = CNORwrapFuzzy(data=CNOlistToy, model=ToyModel, paramsList=paramsList)

## End(Not run)

CNORwrapFuzzy

CNORfuzzy analysis wrapper

Description

This function is a wrapper around the whole CNOR Fuzzy analysis. It performs the following steps:

1. Plot the CNOlist
2. Checks data to model compatibility
3. Pre-processing steps
4. Prepare for simulation (see prep4simFuzzy)
5. Optimisation using Fuzzy transfer function (see gaDiscreteT1)
6. Refinement and reduction steps (see getRefinedModel and reduceFuzzy).

Usage

CNORwrapFuzzy(data, model, paramsList=NULL, verbose=TRUE)

Arguments

data a CNOlist structure (as created by makeCNOlist) that contains the data that you will use (see readMIDAS and readSIF from CellNOptR).

model the model that you want to optimise

paramsList Use defaultParametersFuzzy function to create a template. Entries are 3-types: (i) GA algorithm parameters for the optimisation, (ii) Fuzzy parameters for the transfer functions and (iii) internal optimisation parameters within the refinement step.

See defaultParametersFuzzy function for details on the parameters.

verbose

Details

If you do not provide a parameter list argument, defaultParametersFuzzy is called internally to populate the paramsList argument.

Value

This function returns an object containing the results that can be used by other functions such as compileRes.
Author(s)
M.K. Morris

References
CNORWrap function from CellNOptR package

See Also
defaultParametersFuzzy, compileMultiRes

Examples

# Load some data
data(CNOlistToy, package="CellNOptR")
data(ToyModel, package="CellNOptR")
# Get some default parameters to play with, limiting the duration of the GA
# algorithm and optimisation step
paramsList = defaultParametersFuzzy()
paramsList$maxTime = 20
paramsList$optimisation$maxtime = 10
results = CNORwrapFuzzy(CNOlistToy, ToyModel, paramsList)

compileMultiRes
Compiles results from multiple runs and produces graph for choosing Post Refinement Threshold

Description
This function takes a list of objects returned by CNORwrapfuzzy (run using identical parameters, models, and data) and packages them together so they can be compared with plotMeanFuzzyFit and writeFuzzyNetwork. Because almost all training of cFL models are underdetermined problems, analyzing multiple runs together is essential.

Usage

compileMultiRes(allRes, tag=NULL, show=TRUE)

Arguments

allRes list of objects returned by the CNORwrapFuzzy function.
tag If provided, save the results in 3 files. Each file starts with the string "filename" that is provided. (<tag>_allRes.RData, <tag>_allFinalMSEs.RData and <tag>_allFinalNumParams.RData)
show plot the MSE and mean number of parameters versus threshold. Can be switch off if show=FALSE

Author(s)
M.K. Morris, T. Cokelaer
**Examples**

```r
data(ToyModel, package="CellNOptR")
data(CNOlistToy, package="CellNOptR")
paramsList = defaultParametersFuzzy(CNOlistToy, ToyModel)
N = 10
allRes = list()
## Not run:
  for (i in 1:N){
    Res = CNORwrapFuzzy(CNOlistToy, ToyModel, paramsList)
    allRes[[i]] = Res
  }

summary = compileMultiRes(allRes)
summary$allFinalMSEs
summary$allFinalNumParams

# You can save the results in files using the tag argument
compileMultiRes(allRes, "output")
## End(Not run)
```

**computeScoreFuzzy**: Compute Score of a model compared to the data for a given intString.

**Description**

compute and return score of a model (cut using a bitstring).

**Usage**

```r
computeScoreFuzzy(CNOlist, model, simList=NULL, indexList=NULL, paramsList, intString=NULL, sizeFac=0.0001, NAFac=1)
```

**Arguments**

- `CNOlist`: a CNOlist on which the score is based (based on valueSignals[[2]], i.e. data at t1)
- `model`: a model list
- `simList`: a list that contains additional fields for the simulator, as created by prep4sim applied to the model above
- `indexList`: a list of indexes of species stimulated/inhibited/signals, as produced by indexfinder applied on the model and CNOlist above
- `paramsList`: list of parameters. See `defaultParametersFuzzy`
- `intString`: a bitstring of the same size as the number of reactions in the model above
- `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
defaultParametersFuzzy

Create a list of default parameters

Description
Parameters are required at different levels in the Fuzzy optimisation. This function provides a list with all parameters that are necessary.

Usage
defaultParametersFuzzy(data=NA, model=NA, nTF=7)

Arguments
- **data**: the CNOlist that contains the data that you will use
- **model**: the model that you want to optimise
- **nTF**: number of discrete values to be used for each transfer function parameter.

Details
The list contains 3 types of parameters:

- Fuzzy parameters (e.g, Type1Funs, Type2Funs, RedThresh, DoRefinement)
- GA parameters similar to those used in CellNOptR package (see `gaDiscreteT1` or `defaultParametersFuzzy`
- optimisation parameters related to the refinement step.
  1. algorithm='NLOPT_LN_SBPLX'
  2. xtol_abs=0.001
  3. maxEval=1000
  4. maxTime=5*60
- In addition, you can set Model and Data (CNOlist).

Value
- **params**: a list of default parameters.

Author(s)
T. Cokelaer
Examples

```r
data(ToyModel, package="CellNOptR")
data(CNOlistToy, package="CellNOptR")
params = defaultParametersFuzzy(CNOlistToy, ToyModel)
```

\[ \text{gaDiscreteT1} \]

**Genetic algorithm used to optimise a cFL model**

Description

This function is the genetic algorithm to be used to optimise a cFL model by fitting to data containing one time point.

Usage

```r
gaDiscreteT1(CNOlist, model, paramsList, initBstring=NULL, sizeFac=0.0001,
NAFac=1, popSize=50, pMutation=0.5, maxTime=60, maxGens=500,
stallGenMax=100, selPress=1.2, elitism=5, relTol=0.1,
verbose=TRUE, maxSizeHashTable = 1000)
```

Arguments

- **CNOlist**: a CNOlist on which the score is based (based on valueSignals[2], i.e. data at t1)
- **model**: a Model list
- **paramsList**: CellNOptR software parameters (this function uses transfer functions to choose from)
- **initBstring**: an initial bitstring to be tested, should be of the same size as the number of reactions in the model above.
- **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 set 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 can solutions be to be reported as well, default set to 0.1.
- **verbose**: logical (default to TRUE) do you want the statistics of each generation to be printed on the screen?
- **maxSizeHashTable**: a hash table is used 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.
The GA procedure is implemented based on the gaBinaryT1 in CellNOptR (see those man pages for a basic description). Necessary extensions to optimize a string of numbers rather than zero and one have been made. Additionally, since the scoring function is defined inside the function, it has also been altered for this function.

The parameters are similar to those used in CellNOptR and the returned list contains similar results as well.

This function returns a list with elements:

- **bString**: The best bitstring
- **stringsTol**: The bitstrings whose scores are within the tolerance
- **stringsTolScores**: The scores of the above-mentioned strings

M. Morris based on gaBinaryT1 function by C. Terfve (CellNOptR package)

See Also

prep4simFuzzy, simFuzzyT1

Examples

data(CNOlistToy, package="CellNOptR")
data(ToyModel, package="CellNOptR")

# pre-process model
model <- preprocessing(CNOlistToy, ToyModel, verbose=FALSE)

# set parameters
paramsList <- defaultParametersFuzzy(CNOlistToy, ToyModel)

# the GA algorithm
ToyT1opt<-gaDiscreteT1(
    CNOlist=CNOlistToy,
    model=model,
    paramsList=paramsList,
    maxTime=3,
    verbose=FALSE)
getRefinedModel

Refinement of Parameters of cFL model

Description

Performs refinement of cFL model parameters

Usage

getRefinedModel(res, CNOlist, cutModel, cutSimList, refParams)

Arguments

- **res**: Optimum returned by `gaDiscreteT1`
- **CNOlist**: a CNOlist on which the score is based (based on `valueSignals[[2]]`, i.e. data at T1)
- **cutModel**: Model (with unnecessary edges cut in `reduceFuzzy` or `interpretDiscreteGA`)
- **cutSimList**: Fields for simulation based on `cutModel` (again, cut with `reduceFuzzy` or `interpretDiscreteGA`)
- **refParams**: parameter list object as returned by `defaultParametersFuzzy`.

Details

After the discreteGA chooses transfer functions from a discrete set of transfer functions and removing interactions inconsistent with the data, this function ‘refines’ the parameters by using optim to go to the local minimum of error to data

Value

- **refModel**: A refined model
- **finalSet**: Set of final fuzzy parameter
- **MSE**: The MSE value

Author(s)

M.K. Morris

See Also

`gaDiscreteT1`, `reduceFuzzy`, `interpretDiscreteGA`
interpretDiscreteGA  
**Interpreter of output of discrete genetic algorithm**

Description

This function takes the integer string output by the discrete genetic algorithm for training a cFL model and generates the corresponding model based on the Fuzzy parameters.

Usage

```
interpretDiscreteGA(model, paramsList, intString, bitString=NULL)
```

Arguments

- **model**: PKN trained (same model input as to gaDiscrete).
- **paramsList**: List containing parameters (see defaultParametersFuzzy). Only the fuzzy parameters are used.
- **intString**: Integer string resulting from gaDiscrete (in bString field of gaDiscreteT1 output).
- **bitString** (optional) if you want to cut additional interactions from the model. Used in reduceFuzzy function.

Details

After the discreteGA chooses transfer functions from a discrete set of transfer functions and removing interactions inconsistent with the data, this function interprets the output and returns an actual model using these transfer functions as well as a model from which logical redundancy was cut.

Value

- **model**: The selected initial model based on the provided bitstring.
- **simList**: The corresponding data related to Model field
- **bitString**: The bitstring corresponding to the Model field
- **cutModel**: Same as Model but redundant reactions are also removed.
- **cutSimList**: The corresponding data related to cutModel field
- **cutBitString**: The corresponding bitstring related to cutModel field.

Author(s)

M.K. Morris

See Also

- gaDiscreteT1
Examples

```r
data(ToyModel, package="CellNOptR")
data(CNOlistToy, package="CellNOptR")
paramsList = defaultParametersFuzzy()
## Not run:
# preprocessing (see CNORwrapFuzzy or gaDiscreteT1)
T1opt = gaDiscreteT1(...) # see CNORwrapFuzzy or gaDiscreteT1 for details
interpretDiscreteGA(ToyModel, paramsList, T1opt$bString)
## End(Not run)
```

---

**plotMeanFuzzyFit**  
Simulates models returned from multiple cFL runs and plots mean fit to data

---

Description

Uses post refinement threshold (selection threshold) to choose reduced refined model resulting from each run. Simulates model and plots result and fit to data

Usage

```r
plotMeanFuzzyFit(postRefThresh, allFinalMSEs, allRes, plotPDF=FALSE, tag=NULL, show=TRUE, plotParams=list(cex=0.8, cmap_scale=1))
```

Arguments

- **postRefThresh**: Post refinement threshold (selection threshold) chosen from plot produced by `compileMultiRes`.
- **allFinalMSEs**: matrix containing MSEs produced by `compileMultiRes`
- **allRes**: list containing results of several `CNORwrapFuzzy` runs
- **plotPDF**: TRUE or FALSE depending on if a PDF file should be saved
- **tag**: String to include in filename of PDF plot
- **show**: If the plot should be displayed
- **plotParams**: a list of option related to the PDF and plotting outputs. (1) cex is the font size of the header. (2) cmap_scale below 1 allows to put more emphasizes on low errors (default 1 means all colors have the same weight). See `plotOptimResultsPan` from `CellNOptR` for other fields.

Value

This function does not have any output, it just plots and saves results if applicable.

Author(s)

M.K. Morris
Examples

```r
# Load data
data(ToyModel, package="CellNOptR")
data(CNOlistToy, package="CellNOptR")
paramsList = defaultParametersFuzzy(CNOlistToy, ToyModel)
N = 10
allRes = list()

## Not run:
for (i in 1:N){
  Res = CNORwrapFuzzy(CNOlistToy, ToyModel, paramsList)
  allRes[[i]] = Res
}

summary = compileMultiRes(allRes)
plotMeanFuzzyFit(0.1, summary$allFinalMSEs, allRes)

## End(Not run)
```

---

**prep4simFuzzy**

Prepare a model for simulation

**Description**

Adds to the model some fields that are used by the simulation engine and calls prep4sim function from CellNOptR package

**Usage**

```
prep4simFuzzy(model, paramsList, verbose=TRUE)
```

**Arguments**

- `model` A model, as output by readSIF, normally pre-processed but that is not a requirement of this function.
- `paramsList` A parameters list that must contain at least the CNOlist parameter in the Data field (param = list(data=cnolist)) and possibly optional arguments related to the fuzzy logic (see `defaultParametersFuzzy`)
- `verbose` a verbose option set to TRUE by default.

**Details**

This adds fields that are necessary for the simulation engine for both Boolean and constrained Fuzzy logic simulation.

**Value**

In addition to the fields returned by the prep4sim function of CellNOptR, this function appends the following fields:

- `finalCube` stores, for each reac(row) the location of its inputs (col)
**reduceFuzzy**

stores, for each reac(row) and each input (col) whether it is a negative input

logical matrix of the same size as the 2 above, that tells whether the particular cell is filled or not

row vector that stores, for each reac, the location of its output

stores the name of the model from which these fields were derived

**Author(s)**

C. Terfve, modified by M.K. Morris and T. Cokelaer

**See Also**

simFuzzyT1

**Examples**

```r
data(ToyModel, package="CellNOptR")
data(CNOlistToy, package="CellNOptR")
params <- defaultParametersFuzzy()
params$data = CNOlistToy
fields4sim <- prep4simFuzzy(ToyModel, params)

reduceFuzzy
```

---

**Description**

Determine if interactions in cFL model are necessary to fit the data

**Usage**

```
reduceFuzzy(firstCutOff, CNOlist, model, res, params)
```

**Arguments**

- `firstCutOff`: Threshold for removing or replacing and edge. If the score doesn’t get any worse than this, its removed or replaced
- `CNOlist`: a CNOlist on which the score is based (based on valueSignals[[2]], i.e. data at t1)
- `model`: Model input into gaDiscreteT1 (uncut)
- `res`: Optimum returned by gaDiscrete
- `params`: parameters (as generated from defaultParametersFuzzy (only Fuzzy parameters required)

**Details**

After gaDiscrete removes interactions that are inconsistent with the data, this function asks if they are necessary to fit the data. For all interactions, it asks if they can be removed without making the score worse by a value of the firstCutOff. For AND interactions, it asks if they can be replaced with an OR gate.
**Value**

redModel
redSimList
bitString
intString
MSE

**Author(s)**

M.K. Morris

**See Also**

gaDiscreteT1

---

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<th>Simulation of a cFL model</th>
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**Description**

This is the simulator, inspired from CNOfuzzySimEngv23 in the Matlab CellNOpt, to be used on one time point simulations

**Usage**

`simFuzzyT1(CNOlist, model, simList)`

**Arguments**

- **CNOlist**: a CNOlist
- **model**: a Model that only contains the reactions to be evaluated
- **simList**: a SimList as created by prep4simFuzzy, that has also already been cut to contain only the reactions to be evaluated

**Details**

I’m not sure if this applies to the one I wrote, which was based on I think an older version by Camille maybe? Differences from the BoolSimEngMKM simulator include: the valueInhibitors has not been previously flipped; the function outputs the values across all conditions for all species in the model, instead of only for the signal species. This is because then the output of this function can be used as initial values for the version of the simulator that works on time point 2 (not implemented in this version).

If you would like to compute the output of a model that contains some of the gates in the model but not all, we suggest that you use the function SimulateT1 and specify in the bStringT1 argument which gates you want to be included. Indeed, SimulateT1 is a wrapper around simulatorT1 that takes care of cutting the model for you before simulating it.
writeFuzzyNetwork

Value

This function outputs a single matrix of format similar to valueSignals in the CNOlist but that contains an output for each species in the model. This matrix is the simulated equivalent of valueSignals at time 1, if you consider only the columns given by indexSignals.

Author(s)

M.K. Morris based on function by C. Terfve from CellNOptR package.

See Also

SimulateT1 from CellNOptR

Examples

# This computes the output of the full model, which is normally not done on a stand alone basis, but if you have
data(CNOlistToy, package="CellNOptR")
data(ToyModel, package="CellNOptR")
paramsList <- defaultParametersFuzzy(data=CNOlistToy, model=ToyModel)
indicesToy<-indexFinder(CNOlistToy, ToyModel, verbose=TRUE)
ToyFields4Sim<-prep4simFuzzy(ToyModel, paramsList)
Sim<-simFuzzyT1(
  CNOlist=CNOlistToy,
  model=ToyModel,
  simList=ToyFields4Sim)

writeFuzzyNetwork

Despict the network results of training a cFL model to data in multiple runs.

Description

Fuzzy network results output.

Usage

writeFuzzyNetwork(postRefThresh, allFinalMSEs, allRes, tag=NULL, verbose=FALSE)

Arguments

postRefThresh  Post refinement threshold (selection threshold) chosen from plot produced by compileMultiRes
allFinalMSEs   matrix containing MSEs produced by compileMultiRes
allRes        list containing all results produced by compileMultiRes
tag           String to include in filename of pdf plot
verbose       If extra warnings should be displayed
writeFuzzyNetwork

Details

The weights of the edges are computed as the mean across models using post refinement threshold (selection threshold) to choose reduced refined model resulting from each run. As with writeNetwork, this function maps back the edges weights from the optimised (expanded and compressed) model to the original model. The mapping back only works if the path has length 2 at most (i.e. you have node1-comp1-comp2-node2, where comp refer to nodes that have been compressed).

Value

This function does not have any output, it just writes a SIF file, an edge attribute file, and a node attribute file

Note

The mapback of this function is still an open question, even in the Matlab version. Future developments will include more robust versions of the mapping back algorithm, probably as a separate mapback function.

Author(s)

M.K. Morris based on code by C. Terfve

See Also

writeNetwork

Examples

data(ToyModel, package="CellNOptR")
data(CNOlistToy,package="CellNOptR")
paramsList = defaultParametersFuzzy(CNOlistToy, ToyModel)
N = 10
allRes = list()
## Not run:
for (i in 1:N){
  Res = CNORwrapFuzzy(CNOlistToy, ToyModel, paramsList)
  allRes[[i]] = Res
}

summary = compileMultiRes(allRes)
summary$allFinalMSEs
summary$allFinalNumParams

writeFuzzyNetwork(postRefThresh, summary$allFinalMSEs, allRes)

## End(Not run)
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