Package: OncoSimulR (via r-universe)

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Type Package

Title Forward Genetic Simulation of Cancer Progression with Epistasis

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Description Functions for forward population genetic simulation in asexual populations, with special focus on cancer progression. Fitness can be an arbitrary function of genetic interactions between multiple genes or modules of genes, including epistasis, order restrictions in mutation accumulation, and order effects. Fitness (including just birth, just death, or both birth and death) can also be a function of the relative and absolute frequencies of other genotypes (i.e., frequency-dependent fitness). Mutation rates can differ between genes, and we can include mutator/antimutator genes (to model mutator phenotypes). Simulating multi-species scenarios and therapeutic interventions, including adaptive therapy, is also possible. Simulations use continuous-time models and can include driver and passenger genes and modules. Also included are functions for: simulating random DAGs of the type found in Oncogenetic Trees, Conjunctive Bayesian Networks, and other cancer progression models; plotting and sampling from single or multiple realizations of the simulations, including single-cell sampling; plotting the parent-child relationships of the clones; generating random fitness landscapes (Rough Mount Fuji, House of Cards, additive, NK, Ising, and Eggbox models) and plotting them.

biocViews BiologicalQuestion, SomaticMutation

License GPL (>= 3)

URL https://github.com/rdiaz02/OncoSimul, https://popmodels.cancercontrol.cancer.gov/gsr/packages/oncosimulr/

BugReports https://github.com/rdiaz02/OncoSimul/issues

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`allFitnessEffects` *Create fitness and mutation effects specification from restrictions, epistasis, and order effects.*

Description

Given one or more of a set of poset restrictions, epistatic interactions, order effects, and genes without interactions, as well as, optionally, a mapping of genes to modules, return the complete fitness specification.

For mutator effects, given one or more of a set of epistatic interactions and genes without interactions, as well as, optionally, a mapping of genes to modules, return the complete specification of how mutations affect the mutation rate.

This function can be used also to produce the fitness specification needed to run simulations in a frequency dependent fitness way. In that situation we presume that the effects must be considered as fitness effects and never as mutator effects (see `details` for more info).

The output of these functions is not intended for user consumption, but as a way of preparing data to be sent to the C++ code.

Usage

```
allFitnessEffects(rT = NULL, epistasis = NULL, orderEffects = NULL,
  noIntGenes = NULL, geneToModule = NULL, drvNames = NULL,
  genotFitness = NULL,  keepInput = TRUE, frequencyDependentBirth =
  FALSE, frequencyDependentDeath = FALSE, frequencyDependentFitness,
  frequencyType = NA, deathSpec = FALSE)

allMutatorEffects(epistasis = NULL, noIntGenes = NULL,
                  geneToModule = NULL,
                 keepInput =  TRUE)
```

Arguments

`rT` A restriction table that is an extended version of a poset (see `poset`). A restriction table is a data frame where each row shows one edge between a parent and a child. A restriction table contains exactly these columns, in this order:

parent The identifiers of the parent nodes, in a parent-child relationship. There must be at least on entry with the name "Root".

child The identifiers of the child nodes.

s A numeric vector with the fitness effect that applies if the relationship is satisfied.

sh A numeric vector with the fitness effect that applies if the relationship is not satisfied. This provides a way of explicitly modeling deviatons from the restrictions in the graph, and is discussed in Diaz-Uriarte, 2015.

typeDep The type of dependency. Three possible types of relationship exist:

AND, monotonic, or CMPN Like in the CBN model, all parent nodes must be present for a relationship to be satisfied. Specify it as "AND" or "MN" or "monotone".

OR, semimonotonic, or DMPN A single parent node is enough for a relationship to be satisfied. Specify it as "OR" or "SM" or "semimonotone".

XOR or XMPN Exactly one parent node must be mutated for a relationship to be satisfied. Specify it as "XOR" or "xmpn" or "XMPN".

In addition, for the nodes that depend only on the root node, you can use "–" or "-" if you want (though using any of the other three would have the same effects if a node that connects to root only connects to root).

This paramenter is not used if `frequencyDependentBirth` is TRUE.

`epistasis` A named numeric vector. The names identify the relationship, and the numeric value is the fitness (or mutator) effect. For the names, each of the genes or modules involved is separated by a ":". A negative sign denotes the absence of that term.

This paramenter is not used if `frequencyDependentBirth` is TRUE.

`orderEffects` A named numeric vector, as for `epistasis`. A ">" separates the names of the genes of modules of a relationship, so that "U > Z" means that the relationship is satisfied when mutation U has happened before mutation Z.

This paramenter is not used if `frequencyDependentBirth` is TRUE.

`noIntGenes` A numeric vector (optionally named) with the fitness coefficients (or mutator multiplier factor) of genes (only genes, not modules) that show no interactions. These genes cannot be part of modules. But you can specify modules that have no epistatic interactions. See examples and vignette.

Of course, avoid using potentially confusing characters in the names. In particular, "," and ">" are not allowed as gene names.

This paramenter is not used if `frequencyDependentBirth` is TRUE.

`geneToModule` A named character vector that allows to match genes and modules. The names are the modules, and each of the values is a character vector with the gene names, separated by a comma, that correspond to a module. Note that modules cannot share genes. There is no need for modules to contain more than one gene. If you specify a geneToModule argument, and you used a restriction table, the `geneToModule` must necessarily contain, in the first position, "Root" (since the restriction table contains a node named "Root"). See examples below.

This paramenter is not used if `frequencyDependentBirth` is TRUE.

`drvNames` The names of genes that are considered drivers. This is only used for: a) deciding when to stop the simulations, in case you use number of drivers as a simulation stopping criterion (see `oncoSimulIndiv`); b) for summarization purposes (e.g., how many drivers are mutated); c) in figures. But you need not specifiy anything if you do not want to, and you can pass an empty vector (as `character(0)`). The default has changed with respect to v.2.1.3 and previous: it used to be to assume that all genes that were not in the `noIntGenes` were drivers. The default now is to assume nothing: if you want `drvNames` you have to specify them.

genotFitness A matrix or data frame that contains explicitly the mapping of genotypes to birth and optionally death. For now, we only allow epistasis-like relations between genes (so you cannot code order effects this way).

Genotypes can be specified in two ways:

- As a matrix (or data frame) with g + 1 columns or g + 2 columns, depending if death is specified or not(where g > 1). Each of the first g columns contains a 1 or a 0 indicating that the gene of that column is mutated or not. Column g+ 1 contains the birth values. This is, for instance, the output you will get from `rfitness`. If the matrix has all columns named, those will be used for the names of the genes. Of course, except for column or row names, all entries in this matrix or data frame must be numeric, except when `frequencyDependentBirth` is TRUE. In this case, last column must be character and contains birth equations.
- As a two column data frame. The second column is birth, and the first column are genotypes, given as a character vector. For instance, a row "A, B" would mean the genotype with both A and B mutated. If `frequencyDependentBirth` is TRUE both columns must be character vectors.

When `frequencyDependentBirth = FALSE`, fitness must be `>= 0`. If any possible genotype is missing, its fitness is assumed to be 0, except for WT (if WT is missing, its fitness is assumed to be 1 —see examples); this also applies to frequency-dependent fitness.

In contrast, if `frequencyDependentBirth = TRUE`, the Fitness column must contain the fitness specification equations, like characters, using as variables the frequencies (absolute or relative) of the all possible genotypes. We use "f" to denote relative frecuencies and "n" for absolute. Letter "N" (UPPER CASE) is reserved to denote total population size, thus f=n/N for each possible genotype. Relative frequency variables must be f_ for wild type, f_1 or f_A if first gene is mutated, f_2 or f_B if is the case for the second one, f_1_2 or f_A_B, if both the first and second genes are mutated, and so on. For anything beyond the trivially simple, using letters (not numbers) is strongly recommended. Note also that you need not specify the fitness of every genotype (those missing are assumed to have a fitness of 0), nor do you need to pass the WT genotype. See the vignette for many examples.

If we want to use absolute numbers (absolute frequencies), just subtitute "f" for "n". The choice between relative or absolute frequencies may be specified also in `frequencyType` or, if using the default (auto) it can be automatically inferred.

Mathematical operations and symbols allowed are described in the documentation of C++'s library ExprTk that is used to parse and evaluate the fitness equations (see references for more information).

keepInput If TRUE, whether to keep the original input. This is only useful for human consumption of the output. It is useful because it is easier to decode, say, the restriction table from the data frame than from the internal representation. But if you want, you can set it to FALSE and the object will be a little bit smaller.

frequencyDependentBirth

If FALSE, the default value, all downstream work will be realised in a way not related to frequency depedent fitness situations. That implies that fitness specifications are fixed, except death rate in case of McFarland model (see

oncoSimulIndiv for more details). If TRUE, you are in a frequency dependent fitness situation, where fitness specification ecuations must be passed as characters at genotFitness.

frequencyDependentDeath
: If FALSE, the default value, all downstream work will be realised in a way not related to frequency depedent fitness situations. That implies that fitness specifications are fixed, except death rate in case of McFarland model (see oncoSimulIndiv for more details). If TRUE, you are in a frequency dependent fitness situation, where fitness specification ecuations must be passed as characters at genotFitness.

frequencyDependentFitness
: NA.

frequencyType
: frequencyType is a character that specify whether we are using absolute or relatives frequecies and can take tree values depending on frequencyDependentFitness. Use "abs", for absolute frequencies, or "rel", for relative ones. Remember that you must to use "f" for relative frequency and "n" for absolute in genoFitness. Set to NA for non-frequency-dependent fitness.

deathSpec
: If FALSE, the default value, all downstream work will be realised in a way in which we assume that death is not specified by the user in genotFitness. If TRUE, that means that death was specified by the user.

Details

allFitnessEffects is used for extremely flexible specification of fitness and mutator effects, including posets, XOR relationships, synthetic mortality and synthetic viability, arbitrary forms of epistatis, arbitrary forms of order effects, etc. allFitnessEffects produce the output necessary to pass to the C++ code the fitness/mutator specifications to run simulations. Please, see the vignette for detailed and commented examples.

allMutatorEffects provide the same flexibility, but without order and posets (this might be included in the future, but I have seen no empirical or theoretical argument for their existence or relevance as of now, so I do not add them to minimize unneeded complexity).

If you use both for simulations in the same call to, say, oncoSimulIndiv, all the genes specified in allMutatorEffects MUST be included in the allFitnessEffects object. If you want to have genes that have no direct effect on fitness, but that affect mutation rate, you MUST specify them in the call to allFitnessEffects, for instance as noIntGenes with an effect of 0. When you run the simulations in frequencyDependentBirth = TRUE or frequencyDependentDeath = TRUE only fitness effects are allowed, and must be codified in genotFitness.

If you use genotFitness then you cannot pass modules, noIntgenes, epistasis, or rT. This makes sense, because using genotFitness is saying "this is the mapping of genotypes to birth and maybe death. Period", so we should not allow further modifications from other terms. This is always the case when frequencyDependentBirth = TRUE or frequencyDependentDeath = TRUE.

If you use genotFitness you need to be careful when you use Bozic's model (as you get a death rate of 0).

If you use genotFitness note that we force the WT (wildtype) to always be 1 so birth rates (death rates) are rescaled in case of frequencyDependentBirth = FALSE (frequencyDependentDeath = FALSE). In contrast, when frequencyDependentBirth = TRUE (frequencyDependentDeath =

TRUE) you are free to determine the birth rate (death rate) as a function of the frequencies of the genotypes (see genotFitness and the vignette).

When using genotFitness, any genotype with a fitness <= 1e-9 is removed from the table of genotypes, thus making it a non-viable genotype during simulations.

Value

An object of class "fitnessEffects" or "mutatorEffects". This is just a list, but it is not intended for human consumption. The components are:

long.rt — The restriction table in "long format", so as to be easy to parse by the C++ code.

long.epistasis — Ditto, but for the epistasis specification.

long.orderEffects — Ditto for the order effects.

long.geneNoInt — Ditto for the non-interaction genes.

geneModule — Similar, for the gene-module correspondence.

graph — An igraph object that shows the restrictions, epistasis and order effects, and is useful for plotting.

drv — The numeric identifiers of the drivers. The numbers correspond to the internal numeric coding of the genes.

rT — If keepInput is TRUE, the original restriction table.

epistasis — If keepInput is TRUE, the original epistasis vector.

orderEffects — If keepInput is TRUE, the original order effects vector.

noIntGenes — If keepInput is TRUE, the original noIntGenes.

fitnessLandscape — A data.frame that contains number of genes + 1 columns, where the first columns are the genes (1 if mutated and 0 if not) and the last one contains the fitnesses.

fitnessLandscape_df — A data.frame with the same information of fitnessLandscape, but in this case ther are only two columns: Genotype, that has genotypes as vectors codified as characters, and Fitness.

fitnessLandscape_gene_id — A data.frame with two columns (Gene and GeneNumID), that map by rows genes as letters (Gene) with genes as numbers (GeneNumID).

fitnessLandscapeVariables — A character vector that contains the frequency variables necessary for the C++ code. The "fvars".

frequencyDependentBirth — TRUE or FALSE as we have explained before.

frequencyDependentDeath — TRUE or FALSE as we have explained before.

frequencyDependentFitness — DEPRECATED. Use instead of frequencyDependentFitness for old nomenclature.

`frequencyType` A character string "abs" or "rel" (or NULL).

`deathSpec` TRUE or FALSE as we have explained before.

`full_FDF_spec` For frequency-dependent birth (death), a complete data frame showing the genotypes (as matrix, letters, and "fvars") and the birth (death) specification, in terms of the original specification (Birth_as_letters (Death_as_letters) and with genotypes mapped to numbers according to the "fvars" (Birth_as_fvars (Death_as_fvars)). If birth (death) was originally specified in terms of numbers, these two columns will be identical. All the information in this data frame is implicitly above, but this simplifies checking that you are doing what you think you are doing.

Note

Please, note that the meaning of the fitness effects in the McFarland model is not the same as in the original paper; the fitness coefficients are transformed to allow for a simpler fitness function as a product of terms. This differs with respect to v.1. See the vignette for details.

The names of the genes and modules can be fairly arbitrary. But if you try hard you can confuse the parser. For instance, using gene or module names that contain "," or ":", or ">" is likely to get you into trouble. Of course, you know you should not try to use those characters because you know those characters have special meanings to separate names or indicate epistasis or order relationships. Right now, using those characters as names is caught (and result in stopping) if passed as names for noIntGenes.

At the moment, the variables you need to specify in the fitness equations when you are in a frequency dependent fitness situation are fixed as we have explained in `genotFitness`. Perhaps using different and strange combinations of "f_" or "n_" followed by letters and numbers you could confuse the R parser, but never the C++ one. For a correct performance please be aware of this.

Author(s)

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References

Diaz-Uriarte, R. (2015). Identifying restrictions in the order of accumulation of mutations during tumor progression: effects of passengers, evolutionary models, and sampling doi:10.1186/s12859-01504667.

McFarland, C.~D. et al. (2013). Impact of deleterious passenger mutations on cancer progression. *Proceedings of the National Academy of Sciences of the United States of America\/*, **110**(8), 2910–5.

Partow, A. ExprTk: C++ Mathematical Expression Library (MIT Open Souce License). `http://www.partow.net/programming/exprtk/`.

See Also

`evalGenotype`, `evalAllGenotypes`, `oncoSimulIndiv`, `plot.fitnessEffects`, `evalGenotypeFitAndMut`, `rfitness`, `plotFitnessLandscape`

Examples

```
## A simple poset or CBN-like example

cs <-  data.frame(parent = c(rep("Root", 4), "a", "b", "d", "e", "c"),
                  child = c("a", "b", "d", "e", "c", "c", rep("g", 3)),
                  s = 0.1,
                  sh = -0.9,
                  typeDep = "MN")

cbn1 <- allFitnessEffects(cs)

plot(cbn1)


## A more complex example, that includes a restriction table
## order effects, epistasis, genes without interactions, and moduels
p4 <- data.frame(parent = c(rep("Root", 4), "A", "B", "D", "E", "C", "F"),
                  child = c("A", "B", "D", "E", "C", "C", "F", "F", "G", "G"),
                  s = c(0.01, 0.02, 0.03, 0.04, 0.1, 0.1, 0.2, 0.2, 0.3, 0.3),
                  sh = c(rep(0, 4), c(-.9, -.9), c(-.95, -.95), c(-.99, -.99)),
                  typeDep = c(rep("--", 4),
                      "XMPN", "XMPN", "MN", "MN", "SM", "SM"))

oe <- c("C > F" = -0.1, "H > I" = 0.12)
sm <- c("I:J"  = -1)
sv <- c("-K:M" = -.5, "K:-M" = -.5)
epist <- c(sm, sv)

modules <- c("Root" = "Root", "A" = "a1",
             "B" = "b1, b2", "C" = "c1",
             "D" = "d1, d2", "E" = "e1",
             "F" = "f1, f2", "G" = "g1",
             "H" = "h1, h2", "I" = "i1",
             "J" = "j1, j2", "K" = "k1, k2", "M" = "m1")

set.seed(1) ## for repeatability
noint <- rexp(5, 10)
names(noint) <- paste0("n", 1:5)

fea <- allFitnessEffects(rT = p4, epistasis = epist, orderEffects = oe,
                         noIntGenes = noint, geneToModule = modules)

plot(fea)


## Modules that show, between them,
## no epistasis (so multiplicative effects).
## We specify the individual terms, but no value for the ":".

fnme <- allFitnessEffects(epistasis = c("A" = 0.1,
                                        "B" = 0.2),
                          geneToModule = c("A" = "a1, a2",
```

```
                                          "B" = "b1"))

evalAllGenotypes(fnme, order = FALSE, addwt = TRUE)


## Epistasis for fitness and simple mutator effects

fe <- allFitnessEffects(epistasis = c("a : b" = 0.3,
                                      "b : c" = 0.5),
                        noIntGenes = c("e" = 0.1))

fm <- allMutatorEffects(noIntGenes = c("a" = 10,
                                       "c" = 5))

evalAllGenotypesFitAndMut(fe, fm, order = FALSE)


## Simple fitness effects (noIntGenes) and modules
## for mutators

fe2 <- allFitnessEffects(noIntGenes =
                         c(a1 = 0.1, a2 = 0.2,
                           b1 = 0.01, b2 = 0.3, b3 = 0.2,
                           c1 = 0.3, c2 = -0.2))

fm2 <- allMutatorEffects(epistasis = c("A" = 5,
                                       "B" = 10,
                                       "C" = 3),
                         geneToModule = c("A" = "a1, a2",
                                          "B" = "b1, b2, b3",
                                          "C" = "c1, c2"))

evalAllGenotypesFitAndMut(fe2, fm2, order = FALSE)



## Passing fitness directly, a complete fitness specification
## with a two column data frame with genotypes as character vectors

(m4 <- data.frame(G = c("A, B", "A", "WT", "B"), F = c(3, 2, 1, 4)))
fem4 <- allFitnessEffects(genotFitness = m4)

## Verify it interprets what it should: m4 is the same as the evaluation
## of the fitness effects (note row reordering)
evalAllGenotypes(fem4, addwt = TRUE, order = FALSE)


## Passing fitness directly, a complete fitness specification
## that uses a three column matrix

m5 <- cbind(c(0, 1, 0, 1), c(0, 0, 1, 1), c(1, 2, 3, 5.5))
fem5 <- allFitnessEffects(genotFitness = m5)
```

```
## Verify it interprets what it should: m5 is the same as the evaluation
## of the fitness effects
evalAllGenotypes(fem5, addwt = TRUE, order = FALSE)


## Passing fitness directly, an incomplete fitness specification
## that uses a three column matrix

m6 <- cbind(c(1, 1), c(1, 0), c(2, 3))
fem6 <- allFitnessEffects(genotFitness = m6)
evalAllGenotypes(fem6, addwt = TRUE, order = FALSE)



## Plotting a fitness landscape

fe2 <- allFitnessEffects(noIntGenes =
                         c(a1 = 0.1,
                           b1 = 0.01,
                           c1 = 0.3))

plot(evalAllGenotypes(fe2, order = FALSE))

## same as
plotFitnessLandscape(evalAllGenotypes(fe2, order = FALSE))

## same as
plotFitnessLandscape(fe2)



###### Defaults for missing genotypes
## As a two-column data frame
(m8 <- data.frame(G = c("A, B, C", "B"), F = c(3, 2)))
evalAllGenotypes(allFitnessEffects(genotFitness = m8),
                 addwt = TRUE)

## As a matrix
(m9 <- rbind(c(0, 1, 0, 1, 4), c(1, 0, 1, 0, 1.5)))
evalAllGenotypes(allFitnessEffects(genotFitness = m9),
                 addwt = TRUE)


#########  Frequency Dependent Birth
genofit <- data.frame(A = c(0, 1, 0, 1),
                      B = c(0, 0, 1, 1),
                      Birth = c("max(3, 2*f_)",
                                "max(1.5, 3*(f_ + f_1))",
                                "max(2, 3*(f_ + f_2))",
                                "max(2, 5*f_ - 0.5*( f_1 + f_2) + 15*f_1_2)"),
                      stringsAsFactors = FALSE)

afe <- allFitnessEffects(genotFitness = genofit,
```

```
                        frequencyDependentBirth = TRUE,
                        frequencyType = "rel")

##Ploting fitness landscape in case of spPopSizes = c(5000, 2500, 3000, 7500)
plotFitnessLandscape(evalAllGenotypes(afe, spPopSizes = c(5000, 2500, 3000, 7500)))

## Reinitialize the seed
set.seed(NULL)
```

---

benchmarks *Summary results from some benchmarks reported in the vignette.*

Description

Summary results from some benchmarks reported in the vignette. Included are timings, sizes of return objects and key oputput from each simulation.

They are here mainly to facilitate creation of table from the vignette itself. The scripts are available under "inst/miscell".

Usage

```
data(benchmark_1)
data(benchmark_1_0.05)
data(benchmark_2)
data(benchmark_3)
```

Format

Data frames.

Examples

```
data(benchmark_1)
benchmark_1
```

---

createInterventions *Function that checks and creates an specification for interventions.*

Description

This functions checks that the user has specified correctly the interventions and also makes some modifications in the specification, so the "core" of the code that runs the simulation can "understand" them and execute them.

Usage

```
createInterventions(interventions, genotFitness, frequencyType = "auto")
```

Arguments

interventions	Interventions must be a list of lists, where each "sub-list" must have the following fields: * ID: The identifier of the intervention, must be unique. * Trigger: The situation in the simulation that triggers/activates the intervention. * What Happens: "What happens" in the simulation. Basically, once the trigger is satisfied, this defines how the population is affected by the intervention. * Periodicity: Defines the periodicity of the intervention. * Repetitions: Defines the maximum repetitions of each intervention in the simulation.
genotFitness	Object that `allFitnessEffects` returns, it is necessary to call that function before creating interventions. Also, when calling `allFitnessEffects` frequencyDependentFitness must be TRUE.
frequencyType	If you want to specify the frequency type of the simulation, by default is set to "auto"

Details

See the vignette for details about differences between intervening on the total population or over specific genotypes and when do each occur.

Value

Returns the same list of list that the user specifies, but with the following changes:

First, it transforms the arguments that refer to the genotipes, for example: n_A is the actual population of A in the simulation for a T given. But in the C++ part, "A" receives a Genotype ID, in this case 1, so n_A in the simulation is n_1. (For more info run `allFitnessEffects` with parameter `frequencyDependentFitness = TRUE`, then, check the data that returns, specificly, the field `$full_FDF_spec`. There you have more info about those transformations).

Then, it checks that all fields of the sub-lists are correctly specified.

Finally, it returns the list of interventions with the modifications needed for the code to interpret it correctly.

Examples

```
#first we create and the populations to simulate.
fa1 <- data.frame(Genotype = c("A", "B"),
                  Fitness = c("1.001 + (0*n_A)",
                              "1.002"))

afd3 <- allFitnessEffects(genotFitness = fa1,
                          frequencyDependentFitness = TRUE,
                          frequencyType = "abs")

# now we especify intervention to drastically reduce A population
```

```
 # depending on the T of the simulation
 list_of_interventions <- list(
     list(ID           = "intOverA",
         Trigger       = "(T >= 5)",
         WhatHappens   = "n_A = n_A * 0.1",
         Repetitions   = 0,
         Periodicity   = Inf
     )
 )

 # we transform the intervention to somthing the simulation can process
final_interventions <- createInterventions(interventions = list_of_interventions, afd3)

 # we run the simulations passing the interventions as an argument
 ep2 <- oncoSimulIndiv(
                 afd3,
                 model = "McFL",
                 mu = 1e-4,
                 initSize = c(20000, 20000),
                 initMutant = c("A", "B"),
                 sampleEvery = 0.01,
                 finalTime = 5.2,
                 onlyCancer = FALSE,
           interventions = final_interventions
                 )

 # you can also make the intervention depend on the total population
 list_of_interventions1 <- list(
     list(ID           = "intOverTotPop",
         Trigger       = "(N >= 5000)",
         WhatHappens   = "N = N * 0.1",
         Repetitions   = 0,
         Periodicity   = Inf
     )
 )

 # or depend over the population of a genotype
 list_of_interventions2 <- list(
     list(ID           = "intOverTotPop",
         Trigger       = "(n_A >= 5000)",
         WhatHappens   = "n_ = n_B * 0.1",
         Repetitions   = 0,
         Periodicity   = Inf
     )
 )

 # or mix it all together using logic conectors
 list_of_interventions2 <- list(
     list(ID           = "intOverTotPop",
         Trigger       = "((n_A >= 200) and (N >= 2000)) or (T > 20)",
         WhatHappens   = "n_ = n_B * 0.1",
         Repetitions   = 0,
         Periodicity   = Inf
```

```
    )
)
```

`createUserVars` *Functions that check and create specifications for user variables and rules.*

Description

This functions check that the user has specified correctly the user variables and rules and also makes some modifications in the specification, so the "core" of the code that runs the simulation can "understand" them and execute them.

Usage

```
createUserVars(userVars)

createRules(rules, genotFitness, frequencyType = "auto")
```

Arguments

`userVars`	userVars must be a list of lists, where each "sub-list" must have the following fields: * name: The name of the variable, must be unique. * Value: initial numeric value of the variable.
`rules`	rules must be a list of lists, where each "sub-list" must have the following fields: * ID: The identifier of the rule, must be unique. * Condition: boolean expression that, if true, determines the execution of the rule. * Condition: expression thatdetermines the variables that will be modified when the condition is true, it can be arbitrarily complex using other simulation parameters such as N, T and genotype populations and rates.
`genotFitness`	Object that `allFitnessEffects` returns, it is necessary to call that function before creating interventions. Also, when calling `allFitnessEffects` frequencyDependentFitness must be TRUE.
`frequencyType`	If you want to specify the frequency type of the simulation, by default is set to "auto"

Details

N/A

Value

For `createUserVars`, the same list that the user specifies, after checking that all the parameters are correctly specified. For `createRules` the same list of list that the user specifies, but with the following changes:

First, it transforms the arguments that refer to the genotipes, for example: n_A is the actual population of A in the simulation for a T given. But in the C++ part, "A" receives a Genotype ID, in this case 1, so n_A in the simulation is n_1. (For more info run `allFitnessEffects` with parameter `frequencyDependentFitness = TRUE`, then, check the data that returns, specificly, the field `$full_FDF_spec`. There you have more info about those transformations).

Then, it checks that all fields of the sub-lists are correctly specified.

Finally, it returns the list of rules with the modifications needed for the code to interpret it correctly.

Examples

```
#first we create and the populations to simulate.
fa1 <- data.frame(Genotype = c("A", "B"),
                Fitness = c("1.001 + (0*n_A)",
                            "1.002"))

afd3 <- allFitnessEffects(genotFitness = fa1,
                      frequencyDependentFitness = TRUE,
                      frequencyType = "abs")

# now we specify some user variables
userVars <- list(
    list(Name           = "user_var1",
        Value       = 0
    ),
    list(Name           = "user_var2",
        Value       = 3
    ),
    list(Name           = "user_var3",
        Value       = 2.5
    )
)

# we call the function to check the specification of the variables
userVars <- createUserVars(userVars = userVars)

# we determine the rules that modify the variables
rules <- list(
    list(ID = "rule_1",
        Condition = "T > 20",
        Action = "user_var_1 = 1"
    ),list(ID = "rule_2",
        Condition = "T > 30",
        Action = "user_var_2 = 2; user_var3 = 2*N"
    ),list(ID = "rule_3",
        Condition = "T > 40",
        Action = "user_var_3 = 3;user_var_2 = n_A*n_B"
```

```
    )
)

# we call the function to check the specification of the rules
rules <- createRules(rules = rules, afd3)

# we run the simulations passing theese lists as arguments
ep3 <- oncoSimulIndiv(
               afd3,
               model = "McFL",
               mu = 1e-4,
               initSize = c(20000, 20000),
               initMutant = c("A", "B"),
               sampleEvery = 0.01,
               finalTime = 5.2,
               onlyCancer = FALSE,
         userVars = userVars,
               rules = rules
               )

# you can also make the rules depend on the total population
 rules <- list(
        list(ID = "rule_1",
            Condition = "N > 5000",
            Action = "user_var_1 = 1"
        ),list(ID = "rule_2",
            Condition = "N <= 5000",
            Action = "user_var_1 = 2"
        ),list(ID = "rule_3",
            Condition = "N > 4000",
            Action = "user_var_2 = 1;user_var_3 = 1"
        ),list(ID = "rule_4",
            Condition = "N <= 4000",
            Action = "user_var_2 = 2;user_var_3 = 3"
        )
    )


# or depend on the population of each genotype
rules <- list(
        list(ID = "rule_1",
            Condition = "n_B > 300",
            Action = "user_var_1 = 1"
        ),list(ID = "rule_2",
            Condition = "n_B > 400",
            Action = "user_var_1 = 2"
        ),list(ID = "rule_3",
            Condition = "n_B <= 300",
            Action = "user_var_1 = 3"
        ),list(ID = "rule_4",
            Condition = "n_B <= 200",
            Action = "user_var_1 = 4"
        )
```

```
    )

# or depend on other previously defined user vars
rules <- list(
    list(ID = "rule_3",
        Condition = "T > 10",
        Action = "user_var_1 = 1"
    ),list(ID = "rule_1",
        Condition = "user_var_1 = 0",
        Action = "user_var_2 = 1"
    ),list(ID = "rule_2",
        Condition = "user_var_1 = 1",
        Action = "user_var_2 = 2"
    )
)


# or mix it all together using logic conectors
rules <- list(
    list(ID = "rule_3",
        Condition = "T > 10 and N < 5000",
        Action = "user_var_1 = 1"
    ),list(ID = "rule_1",
        Condition = "user_var_1 = 0 and n_B > 1000",
        Action = "user_var_2 = 1"
    )
)
```

`evalAllGenotypes` *Evaluate fitness/mutator effects of one or all possible genotypes.*

Description

Given a fitnessEffects/mutatorEffects description, obtain the fitness/mutator effects of a single or all genotypes.

Usage

```
evalGenotype(genotype, fitnessEffects, spPopSizes = NULL,
             verbose = FALSE, echo = FALSE, model = "",
             currentTime = 0)

evalGenotypeMut(genotype, mutatorEffects, spPopSizes = NULL,
                verbose = FALSE, echo = FALSE, currentTime = 0)

evalAllGenotypes(fitnessEffects, order = FALSE, max = 256, addwt = FALSE,
                 model = "", spPopSizes = NULL, currentTime = 0)

evalAllGenotypesMut(mutatorEffects, max = 256, addwt = FALSE,
```

```
                    spPopSizes = NULL, currentTime = 0)

evalGenotypeFitAndMut(genotype, fitnessEffects,
                      mutatorEffects, spPopSizes = NULL,
                      verbose = FALSE, echo = FALSE,
                      model = "", currentTime = 0)

evalAllGenotypesFitAndMut(fitnessEffects, mutatorEffects,
                          order = FALSE, max = 256, addwt = FALSE,
                          model = "", spPopSizes = NULL, currentTime = 0)
```

Arguments

genotype	(For evalGenotype). A genotype, as a character vector, with genes separated by "," or ">", or as a numeric vector. Use the same integers or characters used in the fitnessEffects object. This is a genotype in terms of genes, not modules. Using "," or ">" makes no difference: the sequence is always taken as the order in which mutations occurred. Whether order matters or not is encoded in the fitnessEffects object.
fitnessEffects	A fitnessEffects object, as produced by allFitnessEffects.
mutatorEffects	A mutatorEffects object, as produced by allMutatorEffects.
order	(For evalAllGenotypes). If TRUE, then order matters. If order matters, then generate not only all possible combinations of the genes, but all possible permutations for each combination.
max	(For evalAllGenotypes). By default, no output is shown if the number of possible genotypes exceeds the max. Increase as needed.
addwt	(For evalAllGenotypes). Add the wildtype (no mutations) explicitly? In case of frequencyDependentFitness = TRUE the fitness of WT is always shown.
model	Either nothing (the default) or "Bozic". If "Bozic" then the fitness effects contribute to decreasing the Death rate. Otherwise Birth rate is shown (and labeled as Fitness).
verbose	(For evalGenotype). If set to TRUE, print out the individual terms that are added to 1 (or subtracted from 1, if model is "Bozic").
echo	(For evalGenotype). If set to TRUE, show the input genotype and print out a message with the death rate or fitness value. Useful for some examples, as shown in the vignette.
spPopSizes	spPopSizes is only needed when frequencyDependentFitness = TRUE and you want to evaluate fitness with evalGenotype or evalAllGenotypes (see these functions for more info). spPopSizes is a numeric vector that contains the population sizes of the clones, in the same order of genotypes appear in the Genotype column of genotFitness. In your_object$full_FDF_spec you can see the genotypes (and the order) for which you need to pass the values (recall genotypes not specified explicitly are given a value of 0 and do not show up in this table). It is strongly recommended that spPopSizes be a named vector to allow for checks and matches to the actual genotypes.

`currentTime` The time of the simulation. It is possible to access to the current time and run interventions for example using the frequency-dependent-fitness functionality or modifying the mutation rate through oncoSimul functions such as oncoSimulIndiv. With evalAllGenotypes we can check if the fitness has changed before or after a specific timepoint.

Value

For `evalGenotype` either the value of fitness or (if `verbose = TRUE`) the value of fitness and its individual components.

For `evalAllGenotypes` a data frame with two columns, the Genotype ,the Birth Rate (or Death Rate, if Bozic) and the Death Rate (if `deathSpec = TRUE` in `fitnessEffects`. The notation for the Genotype column is a follows: when order does not matter, a comma "," separates the identifiers of mutated genes. When order matters, a genotype shown as "x > y _ z" means that a mutation in "x" happened before a mutation in "y"; there is also a mutation in "z" (which could have happened before or after either of "x" or "y"), but "z" is a gene for which order does not matter. In all cases, a "WT" denotes the wild-type (or, actually, the genotype without any mutations).

If you use both `fitnessEffects` and `mutatorEffects` in a call, all the genes specified in `mutatorEffects` MUST be included in the `fitnessEffects` object. If you want to have genes that have no direct effect on fitness, but that affect mutation rate, you MUST specify them in the call to `fitnessEffects`, for instance as `noIntGenes` with an effect of 0.

When you are in a frequency dependent fitness situation you must set `frequencydependentBirth = TRUE` and/or `frequencydependentDeath = TRUE` and `spPopSizes` must not be NULL and its length must be equal to the number of possible genotypes. Here only `evalGenotype` and `evalAllGenotypes` make sense.

Note

Modules are, of course, taken into account if present (i.e., fitness is specified in terms of modules, but the genotype is specified in terms of genes).

About the naming. This is the convention used: "All" means we will go over all possible genotypes. A function that ends as "Genotypes" returns only fitness effects (for backwards compatibility and because mutator effects are not always used). A function that ends as "Genotype(s)Mut" returns only the mutator effects. A function that ends as "FitAndMut" will return both fitness and mutator effects.

Functions that return ONLY fitness or ONLY mutator effects are kept as separate functions because they free you from specifyin mutator/fitness effects if you only want to play with one of them.

Author(s)

Ramon Diaz-Uriarte, Sergio Sanchez Carrillo, Juan Antonio Miguel Gonzalez

See Also

`allFitnessEffects`.

Examples

```
# A three-gene epistasis example
sa <- 0.1
sb <- 0.15
sc <- 0.2
sab <- 0.3
sbc <- -0.25
sabc <- 0.4

sac <- (1 + sa) * (1 + sc) - 1

E3A <- allFitnessEffects(epistasis =
                           c("A:-B:-C" = sa,
                             "-A:B:-C" = sb,
                             "-A:-B:C" = sc,
                             "A:B:-C" = sab,
                             "-A:B:C" = sbc,
                             "A:-B:C" = sac,
                             "A : B : C" = sabc)
                                          )

evalAllGenotypes(E3A, order = FALSE, addwt = FALSE)
evalAllGenotypes(E3A, order = FALSE, addwt = TRUE,  model = "Bozic")

evalGenotype("B, C", E3A, verbose = TRUE)

## Order effects and modules
ofe2 <- allFitnessEffects(orderEffects = c("F > D" = -0.3, "D > F" = 0.4),
                          geneToModule =
                              c("Root" = "Root",
                                "F" = "f1, f2, f3",
                                "D" = "d1, d2") )

evalAllGenotypes(ofe2, order = TRUE, max = 325)[1:15, ]

## Next two are identical
evalGenotype("d1 > d2 > f3", ofe2, verbose = TRUE)
evalGenotype("d1 , d2 , f3", ofe2, verbose = TRUE)

## This is different
evalGenotype("f3 , d1 , d2", ofe2, verbose = TRUE)
## but identical to this one
evalGenotype("f3 > d1 > d2", ofe2, verbose = TRUE)


## Restrictions in mutations as a graph. Modules present.

p4 <- data.frame(parent = c(rep("Root", 4), "A", "B", "D", "E", "C", "F"),
                 child = c("A", "B", "D", "E", "C", "C", "F", "F", "G", "G"),
                 s = c(0.01, 0.02, 0.03, 0.04, 0.1, 0.1, 0.2, 0.2, 0.3, 0.3),
                 sh = c(rep(0, 4), c(-.9, -.9), c(-.95, -.95), c(-.99, -.99)),
                 typeDep = c(rep("--", 4),
```

```
                       "XMPN", "XMPN", "MN", "MN", "SM", "SM"))
fp4m <- allFitnessEffects(p4,
                          geneToModule = c("Root" = "Root", "A" = "a1",
                              "B" = "b1, b2", "C" = "c1",
                              "D" = "d1, d2", "E" = "e1",
                              "F" = "f1, f2", "G" = "g1"))

evalAllGenotypes(fp4m, order = FALSE, max = 1024, addwt = TRUE)[1:15, ]

evalGenotype("b1, b2, e1, f2, a1", fp4m, verbose = TRUE)

## Of course, this is identical; b1 and b2 are same module
## and order is not present here

evalGenotype("a1, b2, e1, f2", fp4m, verbose = TRUE)

evalGenotype("a1 > b2 > e1 > f2", fp4m, verbose = TRUE)

## We can use the exact same integer numeric id codes as in the
##   fitnessEffects geneModule component:

evalGenotype(c(1L, 3L, 7L, 9L), fp4m, verbose = TRUE)



## Epistasis for fitness and simple mutator effects

fe <- allFitnessEffects(epistasis = c("a : b" = 0.3,
                                      "b : c" = 0.5),
                           noIntGenes = c("e" = 0.1))

fm <- allMutatorEffects(noIntGenes = c("a" = 10,
                                       "c" = 5))

evalAllGenotypesFitAndMut(fe, fm, order = "FALSE")


## Simple fitness effects (noIntGenes) and modules
## for mutators

fe2 <- allFitnessEffects(noIntGenes =
                         c(a1 = 0.1, a2 = 0.2,
                           b1 = 0.01, b2 = 0.3, b3 = 0.2,
                           c1 = 0.3, c2 = -0.2))

fm2 <- allMutatorEffects(epistasis = c("A" = 5,
                                       "B" = 10,
                                       "C" = 3),
                         geneToModule = c("A" = "a1, a2",
                                          "B" = "b1, b2, b3",
                                          "C" = "c1, c2"))

## Show only all the fitness effects
```

```
evalAllGenotypes(fe2, order = FALSE)

## Show only all mutator effects
evalAllGenotypesMut(fm2)

## Show all fitness and mutator
evalAllGenotypesFitAndMut(fe2, fm2, order = FALSE)

## This is probably not what you want
try(evalAllGenotypesMut(fe2))
## ... nor this
try(evalAllGenotypes(fm2))

## Show the fitness effect of a specific genotype
evalGenotype("a1, c2", fe2, verbose = TRUE)

## Show the mutator effect of a specific genotype
evalGenotypeMut("a1, c2", fm2, verbose = TRUE)

## Fitness and mutator of a specific genotype
evalGenotypeFitAndMut("a1, c2", fe2, fm2, verbose = TRUE)

## This is probably not what you want
try(evalGenotype("a1, c2", fm2, verbose = TRUE))

## Not what you want either
try(evalGenotypeMut("a1, c2", fe2, verbose = TRUE))

## Frequency dependent birth example
r <- data.frame(Genotype = c("WT", "A", "B", "A, B"),
                Birth = c("1 + 1.5*f_",
                            "5 + 3*(f_A + f_B + f_A_B)",
                            "5 + 3*(f_A + f_B + f_A_B)",
                            "7 + 5*(f_A + f_B + f_A_B)"),
                stringsAsFactors = FALSE)

afe <- allFitnessEffects(genotFitness = r,
                         frequencyDependentBirth = TRUE,
                         frequencyType = "rel")


evalAllGenotypes(afe, spPopSizes = c(5000, 2500, 2500, 500))
```

---

example-missing-drivers

An example where there are intermediate missing drivers.

Description

An example where there are intermediate missing drivers. This is fictitious and I've never seen it. But it is here to check plots work even if there are no cases of some intermediate value of drivers (2 in this case). b11 contains the full, original data, whereas b12 contains the same data where there are no cases with exactly 2 drivers.

Usage

```
data("ex_missing_drivers_b11"); data("ex_missing_drivers_b12")
```

Format

Two objects of class "oncosimul".

See Also

plot.oncosimul

Examples

```
data(ex_missing_drivers_b11)
plot(ex_missing_drivers_b11, type = "line")
dev.new()
data(ex_missing_drivers_b12)
plot(ex_missing_drivers_b12, type = "line")
```

---

examplePosets *Example posets*

Description

Some example posets. For simplicity, all the posets are in a single list. You can access each poset by accessing each element of the list. The first digit or pair of digits denotes the number of nodes.

Poset 1101 is the same as the one in Gerstung et al., 2009 (figure 2A, poset 2). Poset 701 is the same as the one in Gerstung et al., 2011 (figure 2B, left, the pancreatic cancer poset). Those posets were entered manually at the command line: see poset.

Usage

```
data("examplePosets")
```

Format

The format is: List of 13 $ p1101: num [1:10, 1:2] 1 1 3 3 3 7 7 8 9 10 ... $ p1102: num [1:9, 1:2] 1 1 3 3 3 7 7 9 10 2 ... $ p1103: num [1:9, 1:2] 1 1 3 3 3 7 7 8 10 2 ... $ p1104: num [1:9, 1:2] 1 1 3 3 7 7 9 2 10 2 ... $ p901 : num [1:8, 1:2] 1 2 4 5 7 8 5 1 2 3 ... $ p902 : num [1:6, 1:2] 1 2 4 5 7 5 2 3 5 6 ... $ p903 : num [1:6, 1:2] 1 2 5 7 8 1 2 3 6 8 ... $ p904 : num [1:6, 1:2] 1 4 5 5 1 7 2 5 8 6 ... $ p701 : num [1:9, 1:2] 1 1 1 1 2 3 4 4 5 2 ... $ p702 : num [1:6, 1:2] 1 1 1 1 2 4 2 3 4 5 ... $ p703 : num [1:6, 1:2] 1 1 1 1 3 5 2 3 4 5 ... $ p704 : num [1:6, 1:2] 1 1 1 1 4 5 2 3 4 5 ... $ p705 : num [1:6, 1:2] 1 2 1 1 1 2 2 5 4 6 ...

Source

Gerstung et al., 2009. Quantifying cancer progression with conjunctive Bayesian networks. *Bioinformatics*, 21: 2809–2815.

Gerstung et al., 2011. The Temporal Order of Genetic and Pathway Alterations in Tumorigenesis. *PLoS ONE*, 6.

See Also

poset

Examples

```
data(examplePosets)

## Plot all of them
par(mfrow = c(3, 5))

invisible(sapply(names(examplePosets),
                 function(x) {plotPoset(examplePosets[[x]],
                     main = x,
                     box = TRUE)}))
```

---

examplesFitnessEffects

Examples of fitness effects

Description

Some examples of fitnessEffects objects. This is a collection, in a list, of most of the fitnessEffects created (using allFitnessEffects) for the vignette. See the vignette for descriptions and references.

Usage

```
data("examplesFitnessEffects")
```

Format

The format is a list of fitnessEffects objects.

See Also

allFitnessEffects

Examples

```
data(examplesFitnessEffects)

plot(examplesFitnessEffects[["fea"]])

evalAllGenotypes(examplesFitnessEffects[["cbn1"]], order = FALSE)
```

---

freq-dep-simul-examples

Runs from simulations of frequency-dependent examples shown in the vignette.

Description

Simulations shown in the vignette. Since running them can take a few seconds, we have pre-run them, and stored the results.

Usage

```
data(woAntibS)
```

Format

For output from runs of oncoSimulIndiv a list of classes oncosimul and oncosimul2.

See Also

oncoSimulIndiv

Examples

```
data(woAntibS)
plot(woAntibS, show = "genotypes", type = "line",
     col = c("black", "green", "red"))
```

mcfLs *mcfLs simulation from the vignette*

Description

Trimmed output from the simulation mcfLs in the vignette. This is a somewhat long run, and we have stored here the object (after trimming the Genotype matrix) to allow for plotting it.

Usage

```
data("mcfLs")
```

Format

An object of class "oncosimul2". A list.

See Also

plot.oncosimul

Examples

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

plot(mcfLs, addtot = TRUE, lwdClone = 0.9, log = "")
summary(mcfLs)

## End(Not run)
```

oncoSimulIndiv *Simulate tumor progression for one or more individuals, optionally returning just a sample in time.*

Description

Simulate tumor progression including possible restrictions in the order of driver mutations. Optionally add passenger mutations. When used in frequency dependent fitness situation, only fitness effects are allowed. Simulation is done using the BNB algorithm of Mather et al., 2012.

Usage

```
oncoSimulIndiv(fp, model = "Exp",
               numPassengers = 0, mu = 1e-6, muEF = NULL,
               detectionSize = 1e8, detectionDrivers = 4,
               detectionProb = NA,
               sampleEvery = ifelse(model %in% c("Bozic", "Exp"), 1,
                            0.025),
               initSize = 500, s = 0.1, sh = -1,
               K = sum(initSize)/(exp(1) - 1), keepEvery = sampleEvery,
               minDetectDrvCloneSz = "auto",
               extraTime = 0,
               finalTime = 0.25 * 25 * 365, onlyCancer = FALSE,
               keepPhylog = FALSE,
               mutationPropGrowth = ifelse(model == "Bozic",
                                           FALSE, TRUE),
               max.memory = 2000, max.wall.time = 200,
               max.num.tries = 500,
               errorHitWallTime = TRUE,
               errorHitMaxTries = TRUE,
               verbosity = 0,
               initMutant = NULL,
               AND_DrvProbExit = FALSE,
               fixation = NULL,
               seed = NULL,
               interventions = NULL,
               userVars = NULL,
               rules = NULL)


oncoSimulPop(Nindiv, fp, model = "Exp", numPassengers = 0, mu = 1e-6,
               muEF = NULL,
               detectionSize = 1e8, detectionDrivers = 4,
               detectionProb = NA,
               sampleEvery = ifelse(model %in% c("Bozic", "Exp"), 1,
                            0.025),
               initSize = 500, s = 0.1, sh = -1,
               K = sum(initSize)/(exp(1) - 1), keepEvery = sampleEvery,
               minDetectDrvCloneSz = "auto",
               extraTime = 0,
               finalTime = 0.25 * 25 * 365, onlyCancer = FALSE,
               keepPhylog = FALSE,
               mutationPropGrowth = ifelse(model == "Bozic",
                                           FALSE, TRUE),
               max.memory = 2000, max.wall.time = 200,
               max.num.tries = 500,
               errorHitWallTime = TRUE,
               errorHitMaxTries = TRUE,
               initMutant = NULL,
```

```
                  AND_DrvProbExit = FALSE,
                  fixation = NULL,
                  verbosity = 0,
                  mc.cores = detectCores(),
                  seed = "auto",
                  interventions = NULL,
                  userVars = NULL,
                  rules = NULL)


oncoSimulSample(Nindiv,
                  fp,
                  model = "Exp",
                  numPassengers = 0,
                  mu = 1e-6,
                  muEF = NULL,
                  detectionSize = round(runif(Nindiv, 1e5, 1e8)),

                  detectionDrivers = {
                                  if(inherits(fp, "fitnessEffects")) {
                                      if(length(fp$drv)) {
                                          nd <- (2: round(0.75 * length(fp$drv)))
                                      } else {
                                          nd <- 9e6
                                      }
                                  } else {
                                      nd <- (2 : round(0.75 * max(fp)))
                                  }
                                  if (length(nd) == 1)
                                      nd <- c(nd, nd)
                                  sample(nd, Nindiv,
                                         replace = TRUE)
                              },
                  detectionProb = NA,
                  sampleEvery = ifelse(model %in% c("Bozic", "Exp"), 1,
                      0.025),
                  initSize = 500,
                  s = 0.1,
                  sh = -1,
                  K = sum(initSize)/(exp(1) - 1),
                  minDetectDrvCloneSz = "auto",
                  extraTime = 0,
                  finalTime = 0.25 * 25 * 365,
                  onlyCancer = FALSE, keepPhylog = FALSE,
                  mutationPropGrowth = ifelse(model == "Bozic",
                                                  FALSE, TRUE),
                  max.memory = 2000,
                  max.wall.time.total = 600,
```

```
max.num.tries.total = 500 * Nindiv,
typeSample = "whole",
thresholdWhole = 0.5,
initMutant = NULL,
AND_DrvProbExit = FALSE,
fixation = NULL,
verbosity  = 1,
showProgress = FALSE,
seed = "auto",
interventions = NULL,
userVars = NULL,
rules = NULL)
```

Arguments

`Nindiv`	Number of individuals or number of different trajectories to simulate.
`fp`	Either a poset that specifies the order restrictions (see `poset` if you want to use the specification as in v.1. Otherwise, a fitnessEffects object (see `allFitnessEffects`). You must always use a fitnessEffects object when you are in a frequency dependent fitness simulation; of course in this case fp$frequencyDependentFitness must be TRUE. Other arguments below (s, sh, numPassengers) make sense only if you use a poset, as they are included in the fitnessEffects object.
`model`	One of "Bozic", "Exp", "Arb", "McFarlandLog", "McFarlandLogD" (the last two can be abbreviated to "McFL" and "McFLD", respectively). The default is "Exp". (See vignette for the difference between "McFL" and "McFLD": in the former, death rate = $\log(1+N/K)$ where K is the initial equilibrium population size; when using "McFLD", death rate = $\max(1, \log(1 + N/K))$, so that death rate never goes below 1.). If "Arb" (arbitrary) model is specified, death must be present in `allFitnessEffects`, and vice versa.
`numPassengers`	This has no effect if you use the `allFitnessEffects` specification. This happens always when you are in a simulation that use frequency dependent fitness. If you use the specification of v.1., the number of passenger genes. Note that using v.1 the total number of genes (drivers plus passengers) must be smaller than 64. All driver genes should be included in the poset (even if they depend on no one and no one depends on them), and will be numbered from 1 to the total number of driver genes. Thus, passenger genes will be numbered from (number of driver genes + 1):(number of drivers + number of passengers).
`mu`	Mutation rate. Can be a single value or a named vector. If a single value, all genes will have the same mutation rate. If a named vector, the entries in the vector specify the gene-specific mutation rate. If you pass a vector, it must be named, and it must have entries for all the genes in the fitness specification. Passing a vector is only available when using fitnessEffects objects for fitness specification. Mutation rates `<10^-20` are not accepted. See also `mutationPropGrowth`.

muEF
: Mutator effects. A mutatorEffects object as obtained from allMutatorEffects. This specifies how mutations in certain genes change the mutation rate over all the genome. Therefore, this allows you to specify mutator phenotypes: models where mutation of one (or more) gene(s) leads to an increase in the mutation rate. This is only available for version 2 (and above) specifications.

  All the genes specified in muEF MUST be included in fp. If you want to have genes that have no direct effect on fitness, but that affect mutation rate, you MUST specify them in fp, for instance as noIntGenes with an effect of 0.

  If you use mutator effects you must also use fitnessEffects in fp.

detectionSize
: What is the minimal number of cells for cancer to be detected. For oncoSimulSample this can be a vector.

  If set to NA, detectionSize plays no role in stopping the simulations.

detectionDrivers
: The minimal number of drivers (not modules, drivers, whether or not they are from the same module) present in any clone for cancer to be detected. For oncoSimulSample this can be a vector.

  For oncoSimulSample, if there are drivers (either because you are using a v.1 object or because you are using a fitnessEffects object with a drvNames component —see allFitnessEffects—) the default is a vector of drivers from a uniform between 2 and 0.75 the total number of drivers. If there are no drivers (because you are using a fitnessEffects object without a drvNames, either because you specified it explicitly or because all of the genes are in the noIntGenes component) the simulations should not stop based on the number of drivers (and, thus, the default is set to 9e6). This is the case when you run the simulation with frequency dependent fitness.

  If set to NA, detectionDrivers plays no role in stopping the simulations.

detectionProb
: Vector of arguments for the mechanism where probability of detection depends on size. If NA, this mechanism is not used. If 'default', the vector will be populated with default values. Otherwise, a named vector with some of the following named elements (see 'Details'):

  - PDBaseline: Baseline size subtracted to total population size to compute the probability of detection. If not given explicitly, the default is 1.2 * initSize (or 1.2 * sum(initSize) when multiple initMutants).
  - p2: The probability of detection at population size n2. If you specificy p2 you must also specify n2 and you must not specify cPDetect. The fault is 0.1.
  - n2: The population size at which probability of detection is p2. The default is 2 * initSize.
  - cPDetect: The change in probability of detection with size. If you specify it, you should not specify either of p2 or n2. See 'Details'.
  - checkSizePEvery: Time between successive checks for the probability of exiting as a function of population size. If not given explicitly, the default is 20. See 'Details'.

  If you only provide some of the elements (except for the pair p2, n2, where you must provide both if you provide any), the rest will be filled with default values.

  This option can not be used with v.1 objects.

`sampleEvery` How often the whole population is sampled. This is not the same as the interval between successive samples that are kept or stored (for that, see `keepEvery`).

For very fast growing clones, you might need to have a small value here to minimize possible numerical problems (such as huge increase in population size between two successive samples that can then lead to problems for random number generators). Likewise, for models with density dependence (such as McF) this value should be very small.

`initSize` Initial population size. If you are passing more than one `initMutant`, the initial population sizes of each clone/species/genotype, given in the same order as in the `initMutant` vector. `initMutant` thus allows to start the simulation from arbitrary population compositions. Combined with `mu` it allows for multispecies simulations (see the vignette for examples).

`K` Initial population equilibrium size in the McFarland models.

`keepEvery` Time interval between successive whole population samples that are actually stored. This must be larger or equal to `sampleEvery`. If keepEvery is not a multiple integer of sampleEvery, the interval between successive samples that are stored will be the smallest multiple integer of `sampleEvery` that is larger than or equal to `keepEvery`.

If you want nice plots, set `sampleEvery` and `keepEvery` to small values (say, 5 or 2). Otherwise, you can use a `sampleEvery` of 1 but a `keepEvery` of 15, so that the return objects are not huge and the code runs a lot faster.

Setting `keepEvery = NA` means we only keep the very last sample. This is useful if you only care about the final state of the simulation, not its complete history.

`minDetectDrvCloneSz`

A value of 0 or larger than 0 (by default equal to `initSize` in the McFarland model). If larger than 0, when checking if we are done with a simulation, we verify that the sum of the population sizes of all clones that have a number of mutated drivers larger or equal to `detectionDrivers` is larger or equal to this `minDetectDrvCloneSz`.

The reason for this parameter is to ensure that, say, a clone with a certain number of drivers that would cause the simulation to end has not just appeared and is present in only one individual that might then immediately go extinct. This can be relevant in secenarios such as the McFarland model.

If `initSize` is larger than 1 (you are passing multiple initMutants), the sum is used.

See also `extraTime`.

`extraTime` A value larger than zero waits those many additional time periods before exiting after having reached the exit condition (population size, number of drivers).

The reason for this setting is to prevent the McFL models from always exiting at a time when one clone is increasing its size quickly (see `minDetectDrvCloneSz`). By setting an `extraTime` larger than 0, we can sample at points when we are at the plateau.

`finalTime` What is the maximum number of time units that the simulation can run. Set to NA to disable this limit.

`onlyCancer` Return only simulations that reach cancer?

If set to TRUE, only simulations that satisfy the `detectionDrivers` or the `detectionSize` requirements or that are "detected" because of the `detectionProb` mechanism will be returned: the simulation will be repeated, within the limits set by `max.num.tries` and `max.wall.time` (and, for `oncoSimulSample` also `max.num.tries.total` and `max.wall.time.total`), until one which meets the `detectionDrivers` or `detectionSize` or one which is detected stochastically under `detectionProb` is obtained.

If `onlyCancer = FALSE` the simulation is returned regardless of final population size or number of drivers in any clone and this includes simulations where the population goes extinct.

The default used to be `onlyCancer = TRUE`; on version 3.99.10 it was changed to `onlyCancer = FALSE` as this is the natural setting for simulating general scenarios. `onlyCancer = TRUE`, by design, leads to selection bias in the simulations returned: we only see those that "reach cancer".

`keepPhylog` If TRUE, keep track of when and from which clone each clone is created. See also `plotClonePhylog`.

`mutationPropGrowth`

If TRUE, make mutation rate proportional to growth rate, so clones that grow faster also mutate faster (laso have a larger mutation rate): $mutation_rate = mu * birth_rate$. With BNB mutation is actually "mutate after division": p.\ 1232 of Mather et al., 2012 explains: "(...) mutation is simply defined as the creation and subsequent departure of a single individual from the class". Thus, if we want to have individuals of clones/genotypes/populations that divide faster to also produce more mutants per unit time (per individual) we have to set `mutationPropGrowth = TRUE`. Of course, this only makes sense in models where birth rate changes.

`initMutant` For v.2: a string with the mutations of the initial mutant, if any. This is the same format as for `evalGenotype`. The default (if you pass nothing) is to start the simulation from the wildtype genotype with nothing mutated. For v.1 we no longer accept initMutant: it will be ignored.

(`evalGenotype` also accepts the genotype as a numeric vector; `initMutant` must be a character string.)

`max.num.tries` Only applies when `onlyCancer = TRUE`. What is the maximum number of times, for an individual simulation, we can repeat the simulation for it to reach cancer? There are certain parameter settings where reaching cancer is extremely unlikely and you might not want to run forever in those cases.

`max.num.tries.total`

Only applies when `onlyCancer = TRUE` and for `oncoSimulSample`. What is the maximum number of times, over all simulations for all individuals in a population sample, that we can repeat the simulations so that cancer is reached for all individuals? The idea is to set a limit on the average minimal probability of reaching cancer for a set of simulations to be accepted.

`max.wall.time` Maximum wall time for the simulation of one individual (over all `max.num.tries`). If the simulation is not done in this time, it is aborted.

`max.wall.time.total`

Maximum wall time for all the simulations (when using `oncoSimulSample`), in seconds. If the simulation is not completed in this time, it is aborted. To

prevent problems from a single individual simulation going wild, this limit is also enforced per simulation (so the run can be aborted directly from C++).

`errorHitMaxTries`
: If TRUE (the default) a simulation that reaches the maximum number of repetitions allowed is considered not to have succesfully finished and, thus, an error, and no output from it will be reported. This is often what you want. See `Details`.

`errorHitWallTime`
: If TRUE (the default) a simulation that reaches the maximum wall time is considered not to have succesfully finished and, thus, an error, and no output from it will be reported. This is often what you want. See `Details`.

`max.memory`
: The largest size (in MB) of the matrix of Populations by Time. If it creating it would use more than this amount of memory, it is not created. This prevents you from accidentally passing parameters that will return an enormous object.

`verbosity`
: If 0, run silently. Iincreasing values of verbosity provide progressively more information about intermediate steps, possible numerical notes/warnings from the C++ code, etc. Values less than 0 supress some default notes: use with care.

`typeSample`
: "singleCell" (or "single") for single cell sampling, where the probability of sampling a cell (a clone) is directly proportional to its population size. "wholeTumor" (or "whole") for whole tumor sampling (i.e., this is similar to a biopsy being the entire tumor). See `samplePop`.

`thresholdWhole`
: In whole tumor sampling, whether a gene is detected as mutated depends on thresholdWhole: a gene is considered mutated if it is altered in at least thresholdWhole proportion of the cells in that individual. See `samplePop`.

`mc.cores`
: Number of cores to use when simulating more than one individual (i.e., when calling oncoSimulPop).

`showProgress`
: If TRUE, provide information, during exection, of the individual done, and the number of attempts and time used.

`AND_DrvProbExit`
: If TRUE, cancer will be considered to be reached if both the `detectionProb` mechanism and `detectionDrivers` are satisfied. This is and AND, not an OR condition. Using this option with `fixation` is not allowed (as it does not make much sense).

`fixation`
: If non-NULL, a list or a vector, where each element of is a string with a gene or a gene combination or a genotype (see below). Simulations will stop as soon as any of the genes or gene combinations or genotypes are fixed (i.e., reach a minimal frequency). If you pass gene combinations or genotypes, separate genes with commas (not '>'); this means order is not (yet?) supported. This way of specifying gene combinations is the same as the one used for `initMutant` and `evalGenotype`.

  To differentiate between gene combinations and specific genotypes, genotypes are specified by prepending them with a "_,". For instance, `fixation = c("A", "B, C")` specifies stopping on any genotypes with those gene combinations. In contrast, `fixation = c("_,A", "_,B, C" )` specifies stopping only on genotypes "A" or "B, C". See the vignette for further examples.

In addition to the gene combinations or genotypes themeselves, you can add to the list or vector the named elements `fixation_tolerance`, `min_successive_fixation` and `fixation_min_size`. `fixation_tolerance`: fixation is considered to have happened if the genotype/gene combinations specified as genotypes/gene combinations for fixation have reached a frequency `> 1 - fixation_tolerance`. (The default is 0, so we ask for genotypes/gene combinations with a frequency of 1, which might not be what you want with large mutation rates and complex fitness landscape with genotypes of similar fitness.). `min_successive_fixation`: during how many successive sampling periods the conditions of fixation need to be fulfilled before declaring fixation. These must be successive sampling periods without interruptions (i.e., a single period when the condition is not fulfilled will set the counter to 0). This can help to exclude short, transitional, local maxima that are quickly replaced by other genotypes. (The default is 50, but this is probably too small for "real life" usage). `fixation_min_size`: you might only want to consider fixation to have happened if a minimal size has been reached (this can help weed out local maxima that have fitness that is barely above that of the wild-type genotype). (The default is 0).

Using this option with `AND_DrvProbExit` is not allowed (as it does not make much sense). This option is not allowed either with the old v.1 specification.

`s` Selection coefficient for drivers. Only relevant if using a poset as this is included in the fitnessEffects object. This will eventually be deprecated.

`sh` Selection coefficient for drivers with restrictions not satisfied. A value of 0 means there are no penalties for a driver appearing in a clone when its restrictions are not satisfied.

To specify "sh=Inf" (in Diaz-Uriarte, 2015) use sh = -1.

Only relevant if using a poset as this is included in the fitnessEffects object. This will eventually be deprecated.

`seed` The seed for the C++ PRNG. You can pass a value. If you set it to NULL, then a seed will be generated in R and passed to C++. If you set it to "auto", then if you are using v.1, the behavior is the same as if you set it to NULL (a seed will be generated in R and passed to C++) but if you are using v.2, a random seed will be produced in C++. If you need reproducibility, either pass a value or set it to NULL (setting it to NULL will make the C++ seed reproducible if you use the same seed in R via `set.seed`). However, even using the same value of `seed` is unlikely to give the exact same results between platforms and compilers. Moreover, note that the defaults for `seed` are not the same in `oncoSimulIndiv`, `oncoSimulPop` and `oncoSimulSample`.

When using oncoSimulPop, if you want reproducibility, you might want to, in addition to setting `seed = NULL`, also do `RNGkind("L'Ecuyer-CMRG")` as we use `mclapply`; look at the vignette of **parallel**.

`interventions` This has no effect if you do not specify `frequencyDependentFitness = TRUE` in `allFitnessEffects` function. Also, you must use `createInterventions` function to create the correct type of parameter for the function `oncoSimulPop` , `oncoSimulIndiv` , `oncoSimulSample` to process it correctly.

Use this argument in case you want to intervene in the simulation. With interventions, you can affect the total population size, or just some genotype-specific

population. You can complicate it as much as you want, or keep it simple, it is really up to you.

Formally, interventions must be a list of lists, where each "sub-list" must have the following fields:

* ID: The identifier of the intervention, must be unique. * Trigger: The situation in the simulation that triggers/activates the intervention.

* What Happens: "What happens" in the simulation. Basically, once the trigger is satisfied, this defines how the population is affected by the intervention. Please see the vignette for details about the differences between when interventions that affect a single genotype and those that affect the complete population occur.

* Periodicity: Defines the periodicity of the intervention. * Repetitions: Defines the maximum repetitions of each intervention in the simulation.

`userVars` This has no effect if you do not specify `frequencyDependentFitness = TRUE` in `allFitnessEffects` function. Also, you must use `createuserVars` function to create the correct type of parameter for the function `oncoSimulPop` , `oncoSimulIndiv` , `oncoSimulSample` to process it correctly.

Use this argument in case you want to define arbitrary variables that depend on other simulation values. With the yser Variables you can simulate Adaptive therapy by using this defined variables in the intervention's whatHappens definition, or simply get more detailed insight by defining some interesting values you desire as an output.

Formally, userVars must be a list of lists, where each "sub-list" must have the following fields:

* Name: The name that identifies the new variable, must be unique. * Value: The initial numeric value of the variable.

You must define the `rules` in order to determine how this variables will be modified.

`rules` This has no effect if you do not specify `frequencyDependentFitness = TRUE` in `allFitnessEffects` function. Also, you must use `createRules` function to create the correct type of parameter for the function `oncoSimulPop` , `oncoSimulIndiv` , `oncoSimulSample` to process it correctly. This also requires you to use `userVars` as these rules operate on them and will not have any effect if thses do not exist.

Use this argument in order to determine how the defined user variebles will be modified during the simulation. You can use any arbitrarily complex expression depending on other simulation parameters such as T, N, Genotype populations or genotype rates.

Formally, rules must be a list of lists, where each "sub-list" must have the following fields:

* ID: The identifier of the rule, must be unique. * Condition: The situation in the simulation that triggers/activates the user variable modification. * Action: The action that will take place once the condition is true. This defines wich user variables will be modified and the expression that defines the new values for them.

Details

The basic simulation algorithm implemented is the BNB one of Mather et al., 2012, where I have added modifications to fitness based on the restrictions in the order of mutations.

Full details about the algorithm are provided in Mather et al., 2012. The evolutionary models, including references, and the rest of the parameters are explained in Diaz-Uriarte, 2014, especially in the Supplementary Material. The model called "Bozic" is based on Bozic et al., 2010, and the model called "McFarland" in McFarland et al., 2013.

oncoSimulPop simply calls oncoSimulIndiv multiple times. When run on POSIX systems, it can use multiple cores (via mclapply).

The `summary` methods for these classes return some of the return values (see next) as a one-row (for class oncosimul) or multiple row (for class oncosimulpop) data frame. The `print` methods for these classes simply print the summary.

Changing options `errorHitMaxTries` and `errorHitWallTime` can be useful when conducting many simulations, as in the call to `oncoSimulPop`: setting them to TRUE means nothing is recorded for those simulations where ending conditions are not reached but setting them to FALSE would allow you to record the output; this would potentially result in a mixture where some simulations would not have reached the ending condition, but this might sometimes be what you want. Note, however, that `oncoSimulSample` always has both them to TRUE, as it could not be otherwise.

`GenotypesWDistinctOrderEff` provides the information about order effects that is missing from `Genotypes`. When there are order effects, the `Genotypes` matrix can contain genotypes that are not distinguishable. Suppose there are two genes, the first and the second. In the `Genotype` output you can get two columns where there is a 1 in both genes: those two columns correspond to the two possible orders (first gene mutated first, or first gene mutated after the second). `GenotypesWDistinctOrderEff` disambiguates this. The same is done by `GenotypesLabels`; this is easier to decode for a human (a string of gene labels) but a little bit harder to parse automatically. Note that when you use the default print method for this object, you get, among others, a two-column display with the `GenotypeLabels` information. When order matters, a genotype shown as "x > y _ z" means that a mutation in "x" happened before a mutation in "y"; there is also a mutation in "z" (which could have happened before or after either of "x" or "y"), but "z" is a gene for which order does not matter. When order does not matter, a comma "," separates the identifiers of mutated genes.

Detection of cancer can be a deterministic process, where cancer is always detected (and, thus, simulation ended) when certain conditions are met (`detectionSize`, `detectionDrivers`, `fixation`). Alternatively, it can be stochastic process where probability of detection depends on size. Every so often (see below) we assess population size, and detect cancer or not probabilistically (comparing the probability of detection for that size with a random uniform number). Probability of detection changes with population size according to the function

$$1 - e^{-cPDetect((populationsize - PDBaseline)/PDBaseline)}$$

.

You can pass `cPDetect` manually (you will need to set `n2` and `p2` to NA). However, it might be more intuitive to specify the pair `n2`, `p2`, such that the probability of detection is $p2$ for population size $n2$ (and from that pair we solve for the value of `cPDetect`). How often do we check? That is controlled by `checkSizePEvery`, the (minimal) time between successive checks (from among the sampling times given by `sampleEvery`: the interval between successive assessments will be the smallest

multiple integer of sampleEvery that is larger than checkSizePEvery —see vignette for details). checkSizePEvery has, by default, a different (and much larger) value than sampleEvery both to allow to examine the effects of sampling, and to avoid many costly random number generations.

Please note that detectionProb is NOT available with version 1 objects.

Value

For oncoSimulIndiv a list, of class "oncosimul", with the following components:

pops.by.time — A matrix of the population sizes of the clones, with clones in columns and time in row. Not all clones are shown here, only those that were present in at least on of the keepEvery samples.

NumClones — Total number of clones in the above matrix. This is not the total number of distinct clones that have appeared over all simulations (which is likely to be larger or much larger).

TotalPopSize — Total population size at the end.

Genotypes — A matrix of genotypes. For each of the clones in the pops.by.time matrix, its genotype, with a 0 if the gene is not mutated and a 1 if it is mutated.

MaxNumDrivers — The largest number of mutated driver genes ever seen in the simulation in any clone.

MaxDriversLast — The largest number of mutated drivers in any clone at the end of the simulation.

NumDriversLargestPop — The number of mutated driver genes in the clone with largest population size.

LargestClone — Population size of the clone with largest number of population size.

PropLargestPopLast — Ratio of LargestClone/TotalPopSize

FinalTime — The time (in time units) at the end of the simulation.

NumIter — The number of iterations of the BNB algorithm.

HittedWallTime — TRUE if we reached the limit of max.wall.time. FALSE otherwise.

TotalPresentDrivers — The total number of mutated driver genes, whether or not in the same clone. The number of elements in OccurringDrivers, below.

CountByDriver — A vector of length number of drivers, with the count of the number of clones that have that driver mutated.

OccurringDrivers — The actual number of drivers mutated.

PerSampleStats — A 5 column matrix with a row for each sampling period. The columns are: total population size, population size of the largest clone, the ratio of the two, the largest number of drivers in any clone, and the number of drivers in the clone with the largest population size.

other — A list that contains statistics for an estimate of the simulation error when using the McFarland model as well as other statistics. For the McFarland model, the relevant value is errorMF, which is -99 unless in the McFarland model. For the McFarland model it is the largest difference of successive death rates. The

entries named minDMratio and minBMratio are the smallest ratio, over all simulations, of death rate to mutation rate and birth rate to mutation rate, respectively. The BNB algorithm thrives when those are large.

For `oncoSimulPop` a list of length `Nindiv`, and of class `"oncosimulpop"`, where each element of the list is itself a list, of class `oncosimul`, with components as described above.

In v.2, the output is of both class "oncosimul" and "oncosimul2". The oncoSimulIndiv return object differs in

`GenotypesWDistinctOrderEff`
: A list of vectors, where each vector corresponds to a genotype in the `Genotypes`, showing (where it matters) the order of mutations. Each vector shows the genotypes, with the numeric codes, showing explicitly the order when it matters. So if you have genes 1, 2, 7 for which order relationships are given, and genes 3, 4, 5, 6 for which other interactions exist, any mutations in 1, 2, 7 are shown first, and in the order they occurred, before showing the rest of the mutations. See details.

`GenotypesLabels`
: The genotypes, as character vectors with the original labels provided (i.e., not the integer codes). As before, mutated genes, for those where order matters, come first, and are separated by the rest by a "_". See details.

`OccurringDrivers`
: This is the same as in v.1, but we use the labels, not the numeric id codes. Of course, if you entered integers as labels for the genes, you will see numbers (however, as a character string).

Note

Please, note that the meaning of the fitness effects in the McFarland model is not the same as in the original paper; the fitness coefficients are transformed to allow for a simpler fitness function as a product of terms. This differs with respect to v.1. See the vignette for details.

Author(s)

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References

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See Also

plot.oncosimul, samplePop, allFitnessEffects

Examples

```
#### A model similar to the one in McFarland. We use 270 genes.

set.seed(456)
nd <- 70
np <- 200
s <- 0.1
sp <- 1e-3
spp <- -sp/(1 + sp)
mcf1 <- allFitnessEffects(noIntGenes = c(rep(s, nd), rep(spp, np)),
                          drv = seq.int(nd))
mcf1s <-  oncoSimulIndiv(mcf1,
                         model = "McFL",
                         mu = 1e-7,
                         detectionSize = 1e8,
                         detectionDrivers = 100,
                         sampleEvery = 0.02,
                         keepEvery = 2,
                         initSize = 2000,
                         finalTime = 1000,
                         onlyCancer = FALSE)
plot(mcf1s, addtot = TRUE, lwdClone = 0.6, log = "")
summary(mcf1s)
plot(mcf1s)


#### Order effects with modules, and 5 genes without interactions
#### with fitness effects from an exponential distribution

oi <- allFitnessEffects(orderEffects =
               c("F > D" = -0.3, "D > F" = 0.4),
               noIntGenes = rexp(5, 10),
                          geneToModule =
                              c("Root" = "Root",
                                "F" = "f1, f2, f3",
                                "D" = "d1, d2") )
oiI1 <- oncoSimulIndiv(oi, model = "Exp")
oiI1$GenotypesLabels
oiI1   ## note the order and separation by "_"


oiP1 <- oncoSimulPop(2, oi,
                     keepEvery = 10,
```

```
                      mc.cores = 2)
summary(oiP1)


## Even if order exists, this cannot reflect it;
## G1 to G10 are d1, d2, f1..,f3, and the 5 genes without
## interaction
samplePop(oiP1)


oiS1 <- oncoSimulSample(2, oi)

## The output contains only the summary of the runs AND
## the sample:
oiS1

## And their sizes do differ
object.size(oiS1)
object.size(oiP1)



######## Using an extended poset for pancreatic cancer from Gerstung et al.
###      (s and sh are made up for the example; only the structure
###       and names come from Gerstung et al.)


pancr <- allFitnessEffects(data.frame(parent = c("Root", rep("KRAS", 4), "SMAD4", "CDNK2A",
                                          "TP53", "TP53", "MLL3"),
                                      child = c("KRAS","SMAD4", "CDNK2A",
                                          "TP53", "MLL3",
                                          rep("PXDN", 3), rep("TGFBR2", 2)),
                                      s = 0.05,
                                      sh = -0.3,
                                      typeDep = "MN"))
plot(pancr)

### Use an exponential growth model
(pancr1 <- oncoSimulIndiv(pancr, model = "Exp"))

summary(pancr1)
plot(pancr1)

## Pop and Sample
pancrPop <- oncoSimulPop(2,
                         pancr,
                         keepEvery = 10,
                         mc.cores = 2)
summary(pancrPop)
(pancrSPop <- samplePop(pancrPop))


(pancrSamp <- oncoSimulSample(2, pancr))
```

```
## Not run:
## Using gene-specific mutation rates
muv <- c("U" = 1e-3, "z" = 1e-7, "e" = 1e-6, "m" = 1e-5, "D" = 1e-4)
ni <- rep(0.01, 5)
names(ni) <- names(muv)
femuv <- allFitnessEffects(noIntGenes = ni)
oncoSimulIndiv(femuv, mu = muv)

## End(Not run)

######### Frequency dependent birth examples

## An example with cooperation. Presence of WT favours all clones
## and all clones have a positive effect on themselves
genofit <- data.frame(A = c(0, 1, 0, 1),
                      B = c(0, 0, 1, 1),
                      Birth = c("3 + 5*f_",
                                "3 + 5*(f_ + f_A)",
                                "3 + 5*(f_ + f_B)",
                                "5 + 6*(f_ + f_A_B)"))

afe <- allFitnessEffects(genotFitness = genofit,
                         frequencyDependentBirth = TRUE)

## Use gene-specific mutation rates and start the simulation from
## 5000 WT and 1000 A mutants.
osi <- oncoSimulIndiv(afe,
                      model = "McFL",
                      onlyCancer = FALSE,
                      finalTime = 50,
                      mu = c("A" = 1e-6, B = 1e-8),
                      initMutant = c("WT", "A"),
                      initSize = c(5000, 1000),
                      keepPhylog = FALSE,
                      seed = NULL,
                      errorHitMaxTries = FALSE,
                      errorHitWallTime = FALSE)
osi

plot(osi, show = "genotypes", type = "line")




## Not run:
## This can be slow
osp <- oncoSimulPop(5,
                    afe,
                    model = "McFL",
                    initSize = 5000,
                    mu = 1e-6,
                    keepEvery = 5,
```

```
                    mc.cores = 2,
                    finalTime = 5000)

sp <- samplePop(osp)

sp

## End(Not run)

## A little bit more complex example situation. WT favours clones A and B. A and
## B compete with each other. Presence of A and B favours clone A, B.
## Not run:
## This can be slow

genofit <- data.frame(A = c(0, 1, 0, 1),
                      B = c(0, 0, 1, 1),
                      Birth = c("3 + 5*f_",
                                "3 + 5*(f_ + f_1 - f_2)",
                                "3 + 5*(f_ + f_2 - f_1)",
                                "5 + 6*(f_1 + f_2 + f_1_2)"))

afe <- allFitnessEffects(genotFitness = genofit,
                         frequencyDependentBirth = TRUE,
                         frequencyType = "rel")

osi <- oncoSimulIndiv(afe,
                      model = "McFL",
                      onlyCancer = FALSE,
                      finalTime = 200,
                      mu = 1e-6,
                      initSize = 5000,
                      keepPhylog = FALSE,
                      seed = NULL,
                      errorHitMaxTries = FALSE,
                      errorHitWallTime = FALSE)
osi

plot(osi, show = "genotypes", type = "line")

## End(Not run)
## Not run:
## This can be slow
osp <- oncoSimulPop(5,
                    afe,
                    model = "McFL",
                    initSize = 5000,
                    onlyCancer = FALSE,
                    mu = 1e-6,
                    keepEvery = 5,
                    mc.cores = 2)

summary(osp)
```

```
sp <- samplePop(osp)

sp


oss <- oncoSimulSample(5,
                       afe,
                       model = "McFL",
                       initSize = 5000,
                       mu = 1e-6,
                       finalTime = 5000,
                       verbosity = 0)

oss

## End(Not run)


## Reinitialize the RNG
set.seed(NULL)
```

`OncoSimulWide2Long` *Convert the* `pops.by.time` *component of an* `oncosimul` *object into "long" format.*

Description

Convert the `pops.by.time` component from its "wide" format (with one column for time, and as many columns as clones/genotypes) into "long" format, so that it can be used with other functions, for instance for plots.

Usage

```
OncoSimulWide2Long(x)
```

Arguments

`x`	An object of class `oncosimul` or `oncosimul2`.

Value

A data frame with four columns: Time; Y, the number of cells (the population size); Drivers, a factor with the number of drivers of the given genotype; Genotype, the genotyp.

Author(s)

Ramon Diaz-Uriarte

See Also

oncoSimulIndiv

Examples

```
data(examplesFitnessEffects)

sm <-  oncoSimulIndiv(examplesFitnessEffects$cbn1,
                      model = "McFL",
                      mu = 5e-7,
                      detectionSize = 1e8,
                      detectionDrivers = 2,
                      sampleEvery = 0.025,
                      keepEvery = 5,
                      initSize = 2000,
                      onlyCancer = FALSE)
class(sm)
lsm <- OncoSimulWide2Long(sm)
head(lsm)
summary(lsm)
```

---

plot.fitnessEffects *Plot fitnessEffects objects.*

Description

Plot the restriction table/graph of restrictions, the epistasis, and the order effects in a fitnessEffects object. This is not a plot of the fitness landscape; for that, see plotFitnessLandscape.

Usage

```
## S3 method for class 'fitnessEffects'
plot(x, type = "graphNEL", layout = NULL,
expandModules = FALSE, autofit = FALSE,
scale_char = ifelse(type == "graphNEL", 1/10, 5),
return_g = FALSE, lwdf = 1, ...)
```

Arguments

x	A fitnessEffects object, as produced by allFitnessEffects.
type	Whether you want a "graphNEL" or an "igraph" graph.
layout	For "igraph", the layout. For example, if you know you really have only a tree you might want to use layout.reingold.tilford. Note that there is very limited support for passing options, etc. In most cases, it is either the default or the layout.reingold.tilford.

expandModules	If there are modules with multiple genes, if you set this to TRUE modules will be replaced by their genes.
autofit	If TRUE, we try to fit the edges to the labels. This is a very experimental feature, likely to be not very robust.
scale_char	If using autofit = TRUE, the scaling factor for the size of the rectangles as a function of the number of characters. You have to play with this because the best value can depend on a number of things.
return_g	It TRUE, the graph object (graphNEL or igrap) is returned.
lwdf	The multiplier factor for lwd when using "graphNEL".
...	Other arguments passed to plot. Not used for now.

Value

A plot.

Order and epistatic relationships have orange edges. OR (semimonotone) relationships blue, and XOR red. All others have black edges (so AND and unique edges from root). Epistatic relationships, being symmetrical, have no arrows between nodes and have a dotted line type. Order relationships have an arrow from the earlier to the later event and have a different dotted line (lty 3).

If return_g is TRUE, you are returned also the graph object (igraph or graphNEL) so that you can manipulate it further.

Note

The purpose of the plot is to get a quick idea of the relationships. Note that three-way (or higher order) epistatic relationships cannot be shown as such (we would show all possible pairs, but that is not quite the same thing). Likewise, there is no reasonable way to convey the pressence of a "-" in the epistatic relationship.

Genes without interactions are not shown.

Author(s)

Ramon Diaz-Uriarte

See Also

allFitnessEffects, plotFitnessLandscape

Examples

```
cs <-  data.frame(parent = c(rep("Root", 4), "a", "b", "d", "e", "c"),
                  child = c("a", "b", "d", "e", "c", "c", rep("g", 3)),
                  s = 0.1,
                  sh = -0.9,
                  typeDep = "MN")

cbn1 <- allFitnessEffects(cs)
plot(cbn1, "igraph")
```

```
library(igraph) ## to make layouts available
plot(cbn1, "igraph", layout = layout.reingold.tilford)


### A DAG with the three types of relationships
p3 <- data.frame(parent = c(rep("Root", 4), "a", "b", "d", "e", "c", "f"),
                 child = c("a", "b", "d", "e", "c", "c", "f", "f", "g", "g"),
                 s = c(0.01, 0.02, 0.03, 0.04, 0.1, 0.1, 0.2, 0.2, 0.3, 0.3),
                 sh = c(rep(0, 4), c(-.9, -.9), c(-.95, -.95), c(-.99, -.99)),
                 typeDep = c(rep("--", 4),
                     "XMPN", "XMPN", "MN", "MN", "SM", "SM"))
fp3 <- allFitnessEffects(p3)

plot(fp3)

plot(fp3, "igraph", layout = layout.reingold.tilford)


## A more complex example, that includes a restriction table
## order effects, epistasis, genes without interactions, and moduels
p4 <- data.frame(parent = c(rep("Root", 4), "A", "B", "D", "E", "C", "F"),
                 child = c("A", "B", "D", "E", "C", "C", "F", "F", "G", "G"),
                 s = c(0.01, 0.02, 0.03, 0.04, 0.1, 0.1, 0.2, 0.2, 0.3, 0.3),
                 sh = c(rep(0, 4), c(-.9, -.9), c(-.95, -.95), c(-.99, -.99)),
                 typeDep = c(rep("--", 4),
                     "XMPN", "XMPN", "MN", "MN", "SM", "SM"))

oe <- c("C > F" = -0.1, "H > I" = 0.12)
sm <- c("I:J"  = -1)
sv <- c("-K:M" = -.5, "K:-M" = -.5)
epist <- c(sm, sv)

modules <- c("Root" = "Root", "A" = "a1",
             "B" = "b1, b2", "C" = "c1",
             "D" = "d1, d2", "E" = "e1",
             "F" = "f1, f2", "G" = "g1",
             "H" = "h1, h2", "I" = "i1",
             "J" = "j1, j2", "K" = "k1, k2", "M" = "m1")

noint <- rexp(5, 10)
names(noint) <- paste0("n", 1:5)

fea <- allFitnessEffects(rT = p4, epistasis = epist, orderEffects = oe,
                         noIntGenes = noint, geneToModule = modules)


plot(fea)
plot(fea, expandModules = TRUE)
plot(fea, type = "igraph")
```

`plot.oncosimul` *Plot simulated tumor progression data.*

Description

Plots data generated from the simulations, either for a single individual or for a population of individuals, with time units in the x axis and nubmer of cells in the y axis.

In "drivers" plots, by default, all clones with the same number of drivers are plotted using the same colour (but different line types), and clones with different number of drivers are plotted in different colours. Plots can alternatively display genotypes instead of drivers.

Plots available are line plots, stacked area, and stream plots.

Usage

```
## S3 method for class 'oncosimul'
plot(x,
                            show = "drivers",
                            type = ifelse(show == "genotypes",
                                          "stacked", "line"),
                            col = "auto",
                            log = ifelse(type == "line", "y", ""),
                            ltyClone = 2:6,
                            lwdClone = 0.9,
                            ltyDrivers = 1,
                            lwdDrivers = 3,
                            xlab = "Time units",
                            ylab = "Number of cells",
                            plotClones = TRUE,
                            plotDrivers = TRUE,
                            addtot = FALSE,
                            addtotlwd = 0.5,
                            ylim = NULL,
                            xlim = NULL,
                            thinData = FALSE,
                            thinData.keep = 0.1,
                            thinData.min = 2,
                            plotDiversity = FALSE,
                            order.method = "as.is",
                            stream.center = TRUE,
                            stream.frac.rand = 0.01,
                            stream.spar = 0.2,
                            border = NULL,
                            lwdStackedStream = 1,
                            srange = c(0.4, 1),
                            vrange = c(0.8, 1),
                            breakSortColors = "oe",
```

```
                              legend.ncols = "auto", ...)

## S3 method for class 'oncosimulpop'
plot(x,
                                ask = TRUE,
                                show = "drivers",
                                type = ifelse(show == "genotypes",
                                              "stacked", "line"),
                                col = "auto",
                                log = ifelse(type == "line", "y", ""),
                                ltyClone = 2:6,
                                lwdClone = 0.9,
                                ltyDrivers = 1,
                                lwdDrivers = 3,
                                xlab = "Time units",
                                ylab = "Number of cells",
                                plotClones = TRUE,
                                plotDrivers = TRUE,
                                addtot = FALSE,
                                addtotlwd = 0.5,
                                ylim = NULL,
                                xlim = NULL,
                                thinData = FALSE,
                                thinData.keep = 0.1,
                                thinData.min = 2,
                                plotDiversity = FALSE,
                                order.method = "as.is",
                                stream.center = TRUE,
                                stream.frac.rand = 0.01,
                                stream.spar = 0.2,
                                border = NULL,
                                lwdStackedStream = 1,
                                srange = c(0.4, 1),
                                vrange = c(0.8, 1),
                                breakSortColors = "oe",
                                legend.ncols = "auto",
                                ...)
```

Arguments

x	An object of class oncosimul (for plot.oncosimul) or oncosimulpop (for plot.oncosimulpop).
ask	Same meaning as in par.
show	One of "drivers" or "genotypes". If "drivers" the legend will reflect the number of drivers. If "genotypes" you will be shown genotypes. You probably want to limit "genotypes" to those cases where only a relatively small number of genotypes exist (or the plot will be an unmanageable mess). The default is

"drivers".

`type` One of "line", "stacked", "stream".

If "line", you are shown lines for each genotype or clone. This means that to get an idea of the total population size you need to use `plotDrivers = TRUE` with `addtot = TRUE`, or do the visual calculation in your head.

If "stacked" a stacked area plot. If "stream" a stream plot. Since these stack areas, you immediately get the total population. But that also means you cannot use `log`.

The default is to use "line" for `show = "drivers"` and "stacked" for `show = "genotypes"`.

`col` Colour of the lines/areas. For `show = "drivers"` each type of clone (where type is defined by number of drivers) has a different color. For `show = "genotypes"` color refers to genotypes. The vector is recycled as needed.

The default is "auto". If you have `show == "genotypes"` we start from the "Dark2" palette from `brewer.pal` in the `RColorBrewer` package and extend the palette via `colorRampPalette`. For `show == "drivers"` and `type == "line"` we use a vector of eight colors (that are, then recycled as needed). If you use "stacked" or "stream", however, instead of "line", then we generate colors via a HSV specification that tries to: a) make it easy to differentiate between different drivers (by not having like colors for adjacent numbers of drivers); b) make it easy to have a "representative" driver color while using sligtly different colors for different clones of a driver. See the code by doing `OncoSimulR:::myhsvcols`.

You can specify your own vector of colors, but it will be ignored with `show == "drivers"`.

`log` See

`log` in `plot.default`. The default is to have "y" for `type == "line"`, and that will make the y axis logarithmic. Stacked and stream area plots do not allow for logarithmic y axis (since those depend on the additivity of areas but `log(a + b) != log(a) + log(b)`).

`ltyClone` Line type for each clone. Recycled as needed. You probably do not want to use lty=1 for any clone, to differentiate from the clone type, unless you change the setting for `ltyDrivers`.

`lwdClone` Line width for clones.

`ltyDrivers` Line type for the driver type.

`lwdDrivers` Line width for the driver type.

`xlab` Same as `xlab` in `plot.default`.

`ylab` Same as `ylab` in `plot.default`.

`plotClones` Should clones be plotted?

`plotDrivers` Should clone types (which are defined by number of drivers), be plotted? (Only applies when using `show = "drivers"`).

`addtot` If TRUE, add a line with the total populatino size.

`addtotlwd` Line width for total population size.

`ylim` If non NULL, limits of the y axis. Same as in `plot.default`. If NULL, the limits are calculated automatically.

`xlim` If non NULL, limits of the x axis. Same as in `plot.default`. If NULL, the limits are calculated automatically. Using a non-NULL range smaller than the range of observed values of time can also lead to speed ups of large figures (since we trim the data).

`thinData` If TRUE, the data plotted is a subset of the original data. The original data are "thinned" in such a way that the origin of each clone is not among the non-shown data (i.e., so that we can see when each clone/driver originates).

Thinning is done to reduce the plot size and to speed up plotting.

Note that thinning is carried out before dealing with the plot axis, so the actual number of points to be plotted could be a lot less (if you reduce the x-axis considerably) than those returned from the thinning. (In extreme cases this could lead to crashes when trying to use stream plots if, say, you end up plotting only three values).

`thinData.keep` The fraction of the data to keep (actually, a lower bound on the fraction of data to keep).

`thinData.min` Any time point for which a clone has a population size > thinData.min will be kept (i.e., will not be removed from) in the data.

`plotDiversity` If TRUE, we also show, on top of the main figure, Shannon's diversity index (and we consider as distinct those genotypes with different order of mutations when order matters).

If you set this to true, using `par(mfrow = c(2, 2))` and similar will not work (since we use `par(fig = )`) to display the diversity as the top plot).

`order.method` For stacked and stream plots. `c("as.is", "max", "first")`. `"as.is"`: plot in order of y column; `"max"`: plot in order of when each y series reaches maximum value. `"first"`: plot in order of when each y series first value > 0.

`stream.center` For stream plots. If TRUE, the stacked polygons will be centered so that the middle, i.e. baseline ("g0"), of the stream is approximately equal to zero. Centering is done before the addition of random wiggle to the baseline.

`stream.frac.rand`
For stream plots. Fraction of the overall data "stream" range used to define the range of random wiggle (uniform distribution) to be added to the baseline 'g0'.

`stream.spar` Setting for smooth.spline function to make a smoothed version of baseline "g0".

`border` For stacked and stream plots. Border colors for polygons corresponding to y columns (will recycle) (see `polygon` for details).

`lwdStackedStream`
border line width for polygons corresponding to y columns (will recycle).

`srange` Range of values of s in the HSV specification of colors (see `col` for details. Only applies when using "stacked" or "stream" plots and `col == "auto"`.)

`vrange` Range of values of v in the HSV specification of colors (see `col` for details.Only applies when using "stacked" or "stream" plots and `col == "auto"`.)

`breakSortColors`
How to try to minimize that similar colors be used for contiguous or nearby driver categories. The default is "oe" which resorts them in alternating way. The other two options are "distave", where we alternate after folding from the mean and "random" where the colors are randomly sorted. Only applies when using "stacked" or "stream" plots and `col == "auto"`.

legend.ncols	The number of columns of the legend. If "auto" (the default), will have one column for six or less entries, and two for more than six.
...	Other arguments passed to plots. For instance, main.

Value

Called for its side effects (plotting). Returns NULL invisibly.

Author(s)

Ramon Diaz-Uriarte. Marc Taylor for stacked and stream plots.

See Also

oncoSimulIndiv

Examples

```
## Show individual genotypes and drivers for an
## epistasis case with at most eight genotypes
set.seed(1)

sa <- 0.1
sb <- -0.2
sab <- 0.25
sac <- -0.1
sbc <- 0.25
sv2 <- allFitnessEffects(epistasis = c("-A : B" = sb,
                                       "A : -B" = sa,
                                       "A : C" = sac,
                                       "A:B" = sab,
                                       "-A:B:C" = sbc),
                         geneToModule = c(
                             "Root" = "Root",
                             "A" = "a1, a2",
                             "B" = "b",
                             "C" = "c"))
evalAllGenotypes(sv2, order = FALSE, addwt = TRUE)
e1 <- oncoSimulIndiv(sv2, model = "McFL",
                     mu = 5e-6,
                     sampleEvery = 0.02,
                     keepEvery = 1,
                     initSize = 2000,
                     finalTime = 2000,
                     seed = NULL,
                     onlyCancer = FALSE)


## Drivers and clones
plot(e1, show = "drivers")

## Stack
```

```
plot(e1, type = "stacked")

## Make genotypes explicit
plot(e1, show = "genotypes")

## Oh, but I want other colors
plot(e1, show = "genotypes", col = rainbow(8))

## and actually I want a line plot
plot(e1, show = "genotypes", type = "line")
```

---

plotClonePhylog *Plot a parent-child relationship of the clones.*

Description

Plot a parent-child relationship of the clones, controlling which clones are displayed, and whether to shown number of times of appearance, and time of first appearance of a clone.

Usage

```
plotClonePhylog(x, N = 1, t ="last", timeEvents = FALSE,
                keepEvents = FALSE, fixOverlap = TRUE,
                returnGraph = FALSE, ...)
```

Arguments

x	The output from a simulation, as obtained from oncoSimulIndiv, oncoSimulPop, or oncoSimulSample (see oncoSimulIndiv). This must be from v.2 and forward (no phylogenetic information is stored for earlier objects).
N	Show in the plot all clones that have a population size of at least N at time time and the parents of those clones (parents are shown regardless of population size —i.e., you can see extinct parents). If you want to show everything that ever appeared, set N = 0.
t	The time at which N should be satisfied. This can either be the string "last", meaning the last time of the simulation, or a range of two values. In the second case, all clones with population size of at least N in at least one time point between time[1] and time[2] will be shown (togheter with their parents).
timeEvents	If TRUE, the vertical position of the nodes in the plot will be proportional to their time of first appearance.
keepEvents	If TRUE, the graph will show all the birth events. Thus, the number of arrows shows the number of times a clone give rise to another. For large graphs with many events, this slows the graph considerably.

`fixOverlap`	When using `timeEvents = TRUE` nodes can overlap (as we modify their vertical location after igraph has done the initial layout). This attempts to fix that problem by randomly relocating, along the X axis, the nodes that have the same X value.
`returnGraph`	If TRUE, the igraph object is returned. You can use this to plot the object however you want or obtain the adjacency matrix.
`...`	Additional arguments. Currently not used.

.

Value

A plot is produced. If `returnGraph` the igraph object is returned.

Note

These are not, technically, proper phylogenetic trees and we use "phylogeny" here in an abuse of terminology. The plots we use, where we show parent child relationships are arguably more helpful in this context. But you could draw proper phylogenies with the information provided.

If you want to obtain the adjacency matrix, this is trivial: just set `returnGraph = TRUE` and use `as_adjacency_matrix` (formerly `get.adjacency`). See an example below.

Author(s)

Ramon Diaz-Uriarte

See Also

`oncoSimulIndiv`

Examples

```
data(examplesFitnessEffects)
tmp <-  oncoSimulIndiv(examplesFitnessEffects[["o3"]],
                       model = "McFL",
                       mu = 5e-5,
                       detectionSize = 1e8,
                       detectionDrivers = 3,
                       sampleEvery = 0.025,
                       max.num.tries = 10,
                       keepEvery = 5,
                       initSize = 2000,
                       finalTime = 3000,
                       onlyCancer = FALSE,
                       keepPhylog = TRUE)

## Show only those with N > 10 at end
plotClonePhylog(tmp, N = 10)

## Show only those with N > 1 between times 5 and 1000
plotClonePhylog(tmp, N = 1, t = c(5, 1000))
```

```
## Show everything, even if teminal nodes are extinct
plotClonePhylog(tmp, N = 0)


## Show time when first appeared
plotClonePhylog(tmp, N = 10, timeEvents = TRUE)

## Not run:
## Show each event
## This can take a few seconds
plotClonePhylog(tmp, N = 10, keepEvents = TRUE)

## End(Not run)

## Adjacency matrix
require(igraph)
as_adjacency_matrix(plotClonePhylog(tmp, N = 10, returnGraph = TRUE))
```

`plotFitnessLandscape` *Plot a fitness landscape.*

Description

Show a plot of a fitness landscape. The plot is modeled after (actually, mostly a blatant copy of) that of MAGELLAN.

Note: this is not a plot of the fitnessEffects object; for that, see `plot.fitnessEffects`.

Usage

```
plotFitnessLandscape(x, show_labels = TRUE,
                     col = c("green4", "red", "yellow"),
                     lty = c(1, 2, 3),
                     use_ggrepel = FALSE,
                     log = FALSE, max_num_genotypes = 2000,
                     only_accessible = FALSE,
                     accessible_th = 0,
                     ...)

## S3 method for class 'genotype_fitness_matrix'
plot(x, show_labels = TRUE,
                                  col = c("green4", "red", "yellow"),
                                  lty = c(1, 2, 3),
                                  use_ggrepel = FALSE,
                                  log = FALSE, max_num_genotypes = 2000,
                                  only_accessible = FALSE,
                                  accessible_th = 0,
```

```
                                    ...)

## S3 method for class 'evalAllGenotypes'
plot(x, show_labels = TRUE,
                                    col = c("green4", "red", "yellow"),
                                    lty = c(1, 2, 3),
                                    use_ggrepel = FALSE,
                                    log = FALSE, max_num_genotypes = 2000,
                                    only_accessible = FALSE,
                                    accessible_th = 0,
                                    ...)

## S3 method for class 'evalAllGenotypesMut'
plot(x, show_labels = TRUE,
                                    col = c("green4", "red", "yellow"),
                                    lty = c(1, 2, 3),
                                    use_ggrepel = FALSE,
                                    log = FALSE, max_num_genotypes = 2000,
                                    only_accessible = FALSE,
                                    accessible_th = 0,
                                    ...)
```

Arguments

x	One of the following: • A matrix (or data frame) with g + 1 columns. Each of the first g columns contains a 1 or a 0 indicating that the gene of that column is mutated or not. Column g+ 1 contains the fitness values. This is, for instance, the output you will get from rfitness. • A two column data frame. The second column is fitness, and the first column are genotypes, given as a character vector. For instance, a row "A, B" would mean the genotype with both A and B mutated. • The output from a call to evalAllGenotypes. Make sure you use order = FALSE in that call. • The output from a call to evalAllGenotypesMut. Make sure you use order = FALSE. • The output from a call to allFitnessEffects. The first two are the same as the format for the genotFitness component in allFitnessEffects.
show_labels	If TRUE, show the genotype labels.
col	A three-element vector that gives the colors to use for increase, decreases and no changes in fitness, respectively. The first two colours are also used for peaks and sinks.
lty	A three-element vector that gives the line types to use for increase, decreases and no changes in fitness, respectively.
use_ggrepel	If TRUE, use geom_label_repel in the ggrepel package to avoid overlap of labels.

`log` Log-scale the y axis.

`max_num_genotypes`
Maximum allowed number of genotypes. For some types of input, we make a call to `evalAllGenotypes`, and use this as the maximum.

`only_accessible`
If TRUE, show only accessible paths. A path is considered accesible if, at each mutational step (i.e., with the addition of each mutation) fitness increases by at least `accessible_th`. If you set `only_accessible = TRUE`, the number of genotypes displayed can be much smaller than the number of existing genotypes if many of those genotypes are not accessible via any path.

`accessible_th` The threshold for the minimal change in fitness at each mutation step (i.e., between successive genotypes) to be used if `only_accessible = TRUE`.

`...` Other arguments passed to `plot`. Not used for now.

Value

A fitness landscape plot: a plot showing paths between genotypes and peaks and sinks (local maxima and minima).

Note

I have copied most of the ideas (and colors, and labels) of this plot from MAGELLAN but MAGELLAN has other functionality that is not provided here such as epistasis stats for the landscape, and several visual manipulation options.

One feature of this function that is not available in MAGELLAN is showing genotype labels (i.e., annotated by gene names), which can be helpful if the different genotypes mean something to you.

In addition to the above differences, another difference between this plot and those of MAGELLAN is **how sinks/peaks of more than one genotype are dealt with**. This plot will show as sinks or peaks sets of one or more genotypes that are of identical fitness (and separated by a Haming distance of one). So a sink or a peak might actually be made of more than one genotype. In MAGELLAN, as far as I can tell, peaks and sinks are always made of a single isolated genotype.

Does this matter? In most realistic cases where not two genotypes can have exactly the same fittnes it does not. In some cases, though, it might matter. Are multi-genotype sinks/peaks really sinks/peaks? Arguably yes: suppose genotypes "AB" and "ABC" both have fitness 0, which is minimal among the fitness in the set of genotypes, and genotypes "A" and "ABCD" have fitness 0.1. To go from "A" to "ABCD", if you want to travel through "AB", you have to go through the valley of "AB" and "ABC"; once in "ABC" you can climb up to "ABCD"; and once in "AB" you can move to "ABC" since it has identical fitness to "AB". Mutatis mutandis for multi-genotype peaks. Ignoring the possibility of peaks/sinks made of more than one genotype actually makes code much simpler.

Sometimes not showing the any links that involve a decrease in fitness can help see non-accessible pathways (in strong selection, no multiple mutations, etc); do this by passing, for instance, an NA for the second element of `col`.

Finally, use common sense: for instance, if you pass a `allFitnessEffects` that specifies for, say, the fitness of a total of 5000 genotypes you'll have to wait a while for the plot to finish.

Author(s)

Ramon Diaz-Uriarte

References

MAGELLAN web site: (it seems this site is no longer available)

Brouillet, S. et al. (2015). MAGELLAN: a tool to explore small fitness landscapes. *bioRxiv*, **31583**. doi:10.1101/031583

See Also

`allFitnessEffects`, `evalAllGenotypes`, `allFitnessEffects`, `rfitness`, `plot.fitnessEffects`

Examples

```
## Generate random fitness for four genes-genotypes
## and plot landscape.

r1 <- rfitness(4)
plot(r1)


## Specify fitness in a matrix, and plot it

m5 <- cbind(A = c(0, 1, 0, 1), B = c(0, 0, 1, 1), F = c(1, 2, 3, 5.5))
plotFitnessLandscape(m5)


## Specify fitness with allFitnessEffects, and plot it

fe <- allFitnessEffects(epistasis = c("a : b" = 0.3,
                                      "b : c" = 0.5),
                        noIntGenes = c("e" = 0.1))

plot(evalAllGenotypes(fe, order = FALSE))

## same as
plotFitnessLandscape(evalAllGenotypes(fe, order = FALSE))
```

`plotPoset` *Plot a poset.*

Description

Plot a poset. Optionally add a root and change names of nodes.

Usage

```
plotPoset(x, names = NULL, addroot = FALSE, box = FALSE, ...)
```

Arguments

x	A poset. A matrix with two columns where, in each row, the first column is the ancestor and the second the descendant. Note that there might be multiple rows with the same ancestor, and multiple rows with the same descendant. See poset.
names	If not NULL, a vector of names for the nodes, with the same length as the total number of nodes in a poset (which need not be the same as the number of rows; see poset). If addroot = TRUE, then 1 + the number of nodes in the poset.
addroot	Add a "Root" node to the graph?
box	Should the graph be placed inside a box?
...	Additional arguments to plot (actually, plot.graphNEL in the Rgraphviz package

).

Details

The poset is converted to a graphNEL object.

Value

A plot is produced.

Author(s)

Ramon Diaz-Uriarte

See Also

examplePosets, poset

Examples

```
data(examplePosets)
plotPoset(examplePosets[["p1101"]])

## If you will be using that poset a lot, maybe simpler if

poset701 <- examplePosets[["p701"]]
plotPoset(poset701, addroot = TRUE)

## Compare to Pancreatic cancer figure in Gerstung et al., 2011

plotPoset(poset701,
          names = c("KRAS", "SMAD4", "CDNK2A", "TP53",
                    "MLL3","PXDN", "TGFBR2"))
```

```
## If you want to show Root explicitly do

plotPoset(poset701, addroot = TRUE,
          names = c("Root", "KRAS", "SMAD4", "CDNK2A", "TP53",
                     "MLL3","PXDN", "TGFBR2"))


## Of course, names are in the order of nodes, so KRAS is for node 1,
##   etc, but the order of entries in the poset does not matter:

poset701b <- poset701[nrow(poset701):1, ]

plotPoset(poset701b,
          names = c("KRAS", "SMAD4", "CDNK2A", "TP53",
                     "MLL3","PXDN", "TGFBR2"))
```

POM *Obtain Lines of Descent and Paths of the Maximum and their diversity from simulations.*

Description

Compute Lines of Descent (LOD) and Path of the Maximum (POM) for a single simulation or a set of simulations (from oncoSimulPop).

diversityPOM and diversityLOD return the Shannon's diversity (entropy) of the POM and LOD, respectively, of a set of simulations (it makes no sense to compute those from a single simulation).

Usage

```
POM(x)
LOD(x)
diversityPOM(lpom)
diversityLOD(llod)
```

Arguments

x	An object of class oncosimulpop (version >= 2, so simulations with the old poset specification will not work) or class oncosimul2 (a single simulation).
lpom	A list of POMs, as returned from POM on an object of class oncosimulpop.
llod	A list of LODs, as returned from LOD on an object of class oncosimulpop.

Details

Lines of Descent (LOD) and Path of the Maximum (POM) were defined in Szendro et al. (2013) and I follow those definitions here, as applied to a process in continuous time with sampling at user-specified periods.

For POM, the results can depend strongly on how often we sample (i.e., the `sampleEvery` argument to `oncoSimulIndiv` and `oncoSimulPop`), since the POM is computed by finding the clone with largest population size whenever we sample. This also explains why it is generally meaningless to use POM on `oncoSimulSample` runs: these only keep the very last sample.

For LOD, a single LOD per simulation is returned, with the same meaning as that in p. 572 of Szendro et al. (2013). "A given genotype may undergo several episodes of colonization and extinction that are stored by the algorithm, and the last episode before the colonization of the final state is used to construct the step.", and I check that this genotype (which is the one that will become the most populated at final time) does not become extinct before the final colonization.

Note *breaking changes*: for LOD we used to return all lines of descent in a given simulation. In v. 2.9.1 we also returned the LOD as explained above. Now we only return the LOD as defined above.

Beware, however, that if you use multiple initial mutants the LOD function will probably not do what you want. It is not even clear that the LOD is well defined in this case. We are working on this.

Value

For `POM` either a character vector (if `x` is a single simulation) or a list of character vectors. Each character vector is the ordered set of genotypes that contain the largest subpopulation at the times of sampling.

For `LOD`, if `x` is a single simulation, the line of descent as defined above (either an object of class "igraph.vs" (an igraph vertex sequence: see `vertex_attr`) or a character vector if there were no descendants). If `x` is a list (population) of simulations, then a list where each element is a list as just explained.

For `diversityLOD` and `diversityPOM` a single element vector with the Shannon's diversity (entropy) of the LODs (for `diversityLOD`) or of the POMs (for `diversityPOM`).

Author(s)

Ramon Diaz-Uriarte

References

Szendro, I. G., Franke, J., Visser, J. A. G. M. de, & Krug, J. (2013). Predictability of evolution depends nonmonotonically on population size. *Proceedings of the National Academy of Sciences*, 110(2), 571-576. doi:10.1073/pnas.1213613110

See Also

`oncoSimulPop`, `oncoSimulIndiv`

Examples

```
######## Using a poset for pancreatic cancer from Gerstung et al.
###      (s and sh are made up for the example; only the structure
###       and names come from Gerstung et al.)

pancr <- allFitnessEffects(data.frame(parent = c("Root", rep("KRAS", 4), "SMAD4", "CDNK2A",
```

```
                                        "TP53", "TP53", "MLL3"),
                                    child = c("KRAS","SMAD4", "CDNK2A",
                                        "TP53", "MLL3",
                                        rep("PXDN", 3), rep("TGFBR2", 2)),
                                    s = 0.05,
                                    sh = -0.3,
                                    typeDep = "MN"))

pancr1 <- oncoSimulIndiv(pancr, model = "Exp")

RNGkind("L'Ecuyer-CMRG")
set.seed(3)
pancr8 <- oncoSimulPop(3, pancr, model = "Exp",
                       finalTime = 600,
                       onlyCancer = TRUE,
                       seed = NULL,
                       mc.cores = 2)

POM(pancr1)
LOD(pancr1)

POM(pancr8)
LOD(pancr8)

diversityPOM(POM(pancr8))
diversityLOD(LOD(pancr8))
```

`poset` *Poset*

Description

Poset: explanation.

Arguments

x	The poset. See details.

Details

A poset is a two column matrix. In each row, the first column is the ancestor (or the restriction) and the second column the descendant (or the node that depends on the restriction). Each node is identified by a positive integer. The graph includes all nodes with integers between 1 and the largest integer in the poset.

Each node can be necessary for several nodes: in this case, the same node would appear in the first column in several rows.

A node can depend on two or more nodes (conjunctions): in this case, the same node would appear in the second column in several rows.

There can be nodes that do not depend on anything (except the Root node) and on which no other nodes depend. The simplest and safest way to deal with all possible cases, including these cases, is to have all nodes with at least one entry in the poset, and nodes that depend on no one, and on which no one depends should be placed on the second column (with a 0 on the first column).

Alternatively, any node not named explicitly in the poset, but with a number smaller than the largest number in the poset, is taken to be a node that depends on no one and on which no one depends. See examples below.

This specification of restrictions is for version 1. See `allFitnessEffects` for a much more flexible one for version 2. Both can be used with `oncoSimulIndiv`.

Note that simulating using posets directly is no longer supported. This function is left here only for historical purposes.

Value

A two-column integer matrix where each row specifies an ancestor-descendant relationship (see Details).

Author(s)

Ramon Diaz-Uriarte

References

Posets and similar structures appear in several places. The following two papers use them extensively.

Gerstung et al., 2009. Quantifying cancer progression with conjunctive Bayesian networks. *Bioinformatics*, 21: 2809–2815.

Gerstung et al., 2011. The Temporal Order of Genetic and Pathway Alterations in Tumorigenesis. *PLoS ONE*, 6.

See Also

`examplePosets`, `plotPoset`, `oncoSimulIndiv`

Examples

```
## Node 2 and 3 depend on 1, and 4 depends on no one
p1 <- cbind(c(1L, 1L, 0L), c(2L, 3L, 4L))
plotPoset(p1, addroot = TRUE)

## Node 2 and 3 depend on 1, and 4 to 7 depend on no one.
## We do not have nodes 4 to 6 explicitly in the poset.
p2 <- cbind(c(1L, 1L, 0L), c(2L, 3L, 7L))
plotPoset(p2, addroot = TRUE)

## But this is arguably cleaner
p3 <- cbind(c(1L, 1L, rep(0L, 4)), c(2L, 3L, 4:7 ))
```

```
plotPoset(p3, addroot = TRUE)

## A simple way to create a poset where no gene (in a set of 15) depends
## on any other.

p4 <- cbind(0L, 15L)
plotPoset(p4, addroot = TRUE)


## Specifying the pancreatic cancer poset in Gerstung et al., 2011
##   (their figure 2B, left). We use numbers, but for nicer plotting we
##   will use names: KRAS is 1, SMAD4 is 2, etc.

pancreaticCancerPoset <- cbind(c(1, 1, 1, 1, 2, 3, 4, 4, 5),
                               c(2, 3, 4, 5, 6, 6, 6, 7, 7))
storage.mode(pancreaticCancerPoset) <- "integer"

plotPoset(pancreaticCancerPoset,
          names = c("KRAS", "SMAD4", "CDNK2A", "TP53",
                    "MLL3","PXDN", "TGFBR2"))


## Specifying poset 2 in Figure 2A of Gerstung et al., 2009:

poset2 <- cbind(c(1, 1, 3, 3, 3, 7, 7, 8, 9, 10),
                c(2, 3, 4, 5, 6, 8, 9, 10, 10, 11))

storage.mode(poset2) <- "integer"
plotPoset(poset2)
```

`rfitness` *Generate random fitness.*

Description

Generate random fitness landscapes under a House of Cards, Rough Mount Fuji (RMF), additive (multiplicative) model, Kauffman's NK model, Ising model, Eggbox model and Full model

Usage

```
rfitness(g, c = 0.5, sd = 1, mu = 1, reference = "random", scale = NULL,
         wt_is_1 = c("subtract", "divide", "force", "no"),
         log = FALSE, min_accessible_genotypes = NULL,
         accessible_th = 0, truncate_at_0 = TRUE,
         K = 1, r = TRUE, i = 0, I = -1, circular = FALSE, e = 0, E = -1,
         H = -1, s = 0.1, S = -1, d = 0, o = 0, O = -1, p = 0, P = -1,
         model = c("RMF", "Additive", "NK", "Ising", "Eggbox", "Full"),
         seed_magellan = -1)
```

Arguments

g	Number of genes.
c	The decrease in fitness of a genotype per each unit increase in Hamming distance from the reference genotype for the RMF model (see reference).
sd	The standard deviation of the random component (a normal distribution of mean mu and standard deviation sd) for the RMF and additive models .
mu	The mean of the random component (a normal distribution of mean mu and standard deviation sd) for the RMF and additive models.
reference	The reference genotype: in the RMF model, for the deterministic, additive part, this is the genotype with maximal fitness, and all other genotypes decrease their fitness by c for every unit of Hamming distance from this reference. If "random" a genotype will be randomly chosen as the reference. If "max" the genotype with all positions mutated will be chosen as the reference. If you pass a vector (e.g., reference = c(1, 0, 1, 0)) that will be the reference genotype. If "random2" a genotype will be randomly chosen as the reference. In contrast to "random", however, not all genotypes have the same probability of being chosen; here, what is equal is the probability that the reference genotype has 1, 2, ..., g, mutations (and, once a number mutations is chosen, all genotypes with that number of mutations have equal probability of being the reference).
scale	Either NULL (nothing is done) or a two- or three-element vector. If a two-element vector, fitness is re-scaled between scale[1] (the minimum) and scale[2] (the maximum) and, later, if you have selected it, wt_is_1 will be enforced. If you pass a three element vector, fitness is re-scaled so that the new maximum fitness is scale[1], the new minimum is scale[2] and the new wildtype is scale[3]. If you pass a three element vector, none of the wt_is_1 options apply in this case, to ensure you obtain the range you want. If you want the wildtype to be one, pass it as the third element of the vector. As a consequence of using a three element vector, the amount of stretching/compressing (i.e., scaling) of fitness values larger than that of the wildtype will likely be different from the scaling of fitness values smaller than that of the wildtype. In other words, this argument allows you to change the spread of the positive and negative fitness values (and you can make this difference extreme and make most fitness values less than wildtype be 0 by using a huge negative number –huge in absolute value– for scale[2] if you then truncate at 0 –see truncate_at_9). Using a three element vector is probably the most natural way of changing the scale and range of fitness. See also log if you want the log-transformed values to respect the scale.
wt_is_1	If "divide" the fitness of all genotypes is divided by the fitness of the wildtype (after possibly adding a value to ensure no negative fitness) so that the wildtype (the genotype with no mutations) has fitness 1. This is a case of scaling, and it is applied after scale, so if you specify both "wt_is_1 = 'divide'" and use an argument for scale it is most likely that the final fitness will not respect the limits in scale. If "subtract" (the default) we shift all the fitness values (subtracting fitness of the wildtype and adding 1) so that the wildtype ends up with a fitness of 1. This is

also applied after scale, so if you specify both "wt_is_1 = 'subtract'" and use an argument for scale it is most likely that the final fitness will not respect the limits in scale (though the distorsion might be simpler to see as just a shift up or down).

If "force" we simply set the fitness of the wildtype to 1, without any divisions. This means that the scale argument would work (but it is up to you to make sure that the range of the scale argument includes 1 or you might not get what you want). Note that using this option can easily lead to landscapes with no accessible genotypes (even if you also use scale).

If "no", the fitness of the wildtype is not modified.

This option has no effect if you pass a three-element vector for scale. Using a three-element vector for scale is probably the most natural way of changing the scale and range of fitness while setting the wildtype to a value of your choice.

log — If TRUE, log-transform fitness. Actually, there are two cases: if wt_is_1 = "no" we simply log the fitness values; otherwise, we log the fitness values and add a 1, thus shifting all fitness values, because by decree the fitness (birth rate) of the wildtype must be 1.

If you pass a three-element vector for scale, you will want to pass exp(desired_max), exp(desired_min), and exp(desired_wildtype) to the scale argument. (We first scale values in the original scale and then log them). In this case, we ignore whatever you passed as wt_is_1, setting wt_is_1 = "no" to avoid modifying your requested value for the wildtype.

min_accessible_genotypes — If not NULL, the minimum number of accessible genotypes in the fitness landscape. A genotype is considered accessible if you can reach if from the wildtype by going through at least one path where all changes in fitness are larger or equal to accessible_th. The changes in fitness are considered at each mutational step, i.e., at each addition of one mutation we compute the difference between the genotype with k + 1 mutations minus the ancestor genotype with k mutations. Thus, a genotype is considered accessible if there is at least one path where fitness increases at each mutational step by at least accessible_th.

If the condition is not satisfied, we continue generating random fitness landscapes with the specified parameters until the condition is satisfied.

(Why check against NULL and not against zero? Because this allows you to count accessible genotypes even if you do not want to ensure a minimum number of accessible genotypes.)

accessible_th — The threshold for the minimal change in fitness at each mutation step (i.e., between successive genotypes) that allows a genotype to be regarded as accessible. This only applies if min_accessible_genotypes is larger than 0. So if you want to allow small decreases in fitness in successive steps, use a small negative value for accessible_th.

truncate_at_0 — If TRUE (the default) any fitness <= 0 is substituted by a small positive constant (a random uniform number between 1e-10 and 1e-9). Why? Because MAGELLAN and some plotting routines can have trouble (specially if you log) with values <=0. Or we might have trouble if we want to log the fitness. This is done after possibly taking logs. Noise is added to prevent creating several identical minimal fitness values. Note that allFitnessEffects will remove from

	the table of genotypes any genotype with a fitness <= 1e-9, thus making it a non-viable genotype during simulations.
K	K for NK model; K is the number of loci with which each locus interacts, and the larger the K the larger the ruggedness of the landscape.
r	For the NK model, whether interacting loci are chosen at random (r = TRUE) or are neighbors (r = FALSE).
i	For de Ising model, i is the mean cost for incompatibility with which the genotype's fitness is penalized when in two adjacent genes, only one of them is mutated.
I	For the Ising model, I is the standard deviation for the cost incompatibility (i).
circular	For the Ising model, whether there is a circular arrangement, where the last and the first genes are adjacent to each other.
e	For the Eggbox model, mean effect in fitness for the neighbor locus +/- e.
E	For the Eggbox model, noise added to the mean effect in fitness (e).
H	For Full models, standard deviation for the House of Cards model.
s	For Full models, mean of the fitness for the Multiplicative model.
S	For Full models, standard deviation for the Multiplicative model.
d	For Full models, a disminishing (negative) or increasing (positive) return as the peak is approached for multiplicative model.
o	For Full models, mean value for the optimum model.
O	For Full models, standard deviation for the optimum model.
p	For Full models, the mean production value for each non 0 allele in the Optimum model component.
P	For Full models, the associated stdev (of non 0 alleles) in the Optimum model component.
model	One of "RMF" (default) for Rough Mount Fuji, "Additive" for Additive model, "NK", for Kauffman's NK model, "Ising" for Ising model, "Eggbox" for Eggbox model or "Full" for Full models.
seed_magellan	The seed for the random number generator in models generated from MAGELLAN. If -1, the clock is used by MAGELLAN to generate a seed, but you probably want to pass a seed: see Details.

Details

When using model = "RMF", the model used here follows the Rough Mount Fuji model in Szendro et al., 2013 or Franke et al., 2011. Fitness is given as

$$f(i) = -cd(i, reference) + x_i$$

where $d(i, j)$ is the Hamming distance between genotypes i and j (the number of positions that differ) and x_i is a random variable (in this case, a normal deviate of mean mu and standard deviation sd).

When using `model = "RMF"`, setting $c = 0$ we obtain a House of Cards model. Setting $sd = 0$ fitness is given by the distance from the reference and if the reference is the genotype with all positions mutated, then we have a fully additive model (fitness increases linearly with the number of positions mutated), where all mutations have the same effect.

More flexible additive models can be used using `model = "Additive"`. This model is like the Rough Mount Fuji model in Szendro et al., 2013 or Franke et al., 2011, but in this case, each locus can have different contributions to the fitness evaluation. This model is also referred to as the "multiplicative" model in the literature as it is additive in the log-scale (e.g., see Brouillet et al., 2015 or Ferretti et al., 2016). The contribution of each mutated allele to the log-fitness is a random deviate from a Normal distribution with specified mean `mu` and standard deviation `sd`, and the log-fitness of a genotype is the sum of the contributions of each mutated allele. There is no "reference" genotype in the Additive model. There is no epistasis in the additve model because the effect of a mutation in a locus does not depend on the genetic background, or whether the rest of the loci are mutated or not.

When using `model = "NK"` fitness is drawn from a uniform (0, 1) distribution.

When using `model = "Ising"` for each pair of interacting loci, there is an associated cost if both alleles are not identical (and therefore 'compatible').

When using `model = "Eggbox"` each locus is either high or low fitness, with a systematic change between each neighbor.

When using `model = "Full"`, the fitness is computed with different parts of the previous models depending on the choosen parameters described above.

For `model = "NK" | "Ising" | "Eggbox" | "Full"` the fitness landscape is generated by directly calling the `fl_generate` function of MAGELLAN . See details in Ferretti et al. 2016, or Brouillet et al., 2015.

For OncoSimulR, we often want the wildtype to have a mean of 1. Reasonable settings when using RMF are `mu = 1` and `wt_is_1 = 'subtract'` so that we simulate from a distribution centered in 1, and we make sure afterwards (via a simple shift) that the wildtype is actuall 1. The `sd` controls the standard deviation, with the usual working and meaning as in a normal distribution, unless `c` is different from zero. In this case, with `c` large, the range of the data can be large, specially if `g` (the number of genes) is large.

Note that `allFitnessEffects` will remove from the table of genotypes any genotype with a fitness <= 1e-9, thus making it a non-viable genotype during simulations.

`seed_magellan`: if you run code in parallel or you use sequential code where you generate random fitness landscapes generated by MAGELLAN (`model = "NK" | "Ising" | "Eggbox" | "Full"`) in a short time, MAGELLAN would likely end up using the same seed as the different calls would be done within the same time (within second resolution). Thus, especially if you are generating the same kind of fitness landscape, you probably want to pass different seeds. The seed is read as a C long, so you should be able to use integers going from at least -2,147,483,647 to +2,147,483,647, in 32-bits, but probably a much larger range (-9,223,372,036,854,775,808 to 9,223,372,036,854,775,807) in 64-bits. Note, though, that some values can crash MAGELLAN (for example -9223372036854775806 or -2147483647). You do not want to pass numbers in scientific notation; for example, you could instead do `seed_magellan = format(2^40, scientific = FALSE)`.

Value

An matrix with g + 1 columns. Each column corresponds to a gene, except the last one that corresponds to fitness. 1/0 in a gene column denotes gene mutated/not-mutated. (For ease of use in other functions, this matrix has class "genotype_fitness_matrix".)

If you have specified `min_accessible_genotypes > 0`, the return object has added attributes `accessible_genotypes` and `accessible_th` that show the number of accessible genotypes under the specified threshold.

Note

MAGELLAN uses its own random number generating functions; using `set.seed` does not allow to obtain the same fitness landscape repeatedly.

Author(s)

Ramon Diaz-Uriarte for the RMF and general wrapping code. S. Brouillet, G. Achaz, S. Matuszewski, H. Annoni, and L. Ferreti for the MAGELLAN code. Further contributions to the additive model and to wrapping MAGELLAN code and documentation from Guillermo Gorines Cordero, Ivan Lorca Alonso, Francisco Muñoz Lopez, David Roncero Moroño, Alvaro Quevedo, Pablo Perez, Cristina Devesa, Alejandro Herrador.

References

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Franke, J. et al. (2011). Evolutionary accessibility of mutational pathways. *PLoS Computational Biology\/*, **7**(8), 1–9.

Brouillet, S. et al. (2015). MAGELLAN: a tool to explore small fitness landscapes. *bioRxiv*, **31583**. doi:10.1101/031583

Ferretti, L., Schmiegelt, B., Weinreich, D., Yamauchi, A., Kobayashi, Y., Tajima, F., & Achaz, G. (2016). Measuring epistasis in fitness landscapes: The correlation of fitness effects of mutations. *Journal of Theoretical Biology\/*, **396**, 132–143. doi:10.1016/j.jtbi.2016.01.037

MAGELLAN web site: (it seems this site is no longer available)

See Also

`oncoSimulIndiv`, `plot.genotype_fitness_matrix`, `evalAllGenotypes` `allFitnessEffects` `plotFitnessLandscape` `Magellan_stats`

Examples

```
## Random fitness for four genes-genotypes,
## plotting and simulating an oncogenetic trajectory


## NK model
rnk <- rfitness(5, K = 3, model = "NK")
plot(rnk)
oncoSimulIndiv(allFitnessEffects(genotFitness = rnk))
```

```
## Additive model
radd <- rfitness(4, model = "Additive", mu = 0.2, sd = 0.5)
plot(radd)


## Not run:
## Eggbox model
regg = rfitness(g=4,model="Eggbox", e = 2, E=2.4)
plot(regg)


## Ising model
ris = rfitness(g=4,model="Ising", i = 0.002, I=2)
plot(ris)


## Full model
rfull = rfitness(g=4, model="Full", i = 0.002, I=2,
                 K = 2, r = TRUE,
                 p = 0.2, P = 0.3, o = 0.3, O = 1)
    plot(rfull)

## End(Not run)
```

---

samplePop *Obtain a sample from a population of simulations.*

Description

Obtain a sample (a matrix of individuals/samples by genes or, equivalently, a vector of "genotypes") from an oncosimulpop object (i.e., a simulation of multiple individuals) or a single oncosimul object. Sampling schemes include whole tumor and single cell sampling, and sampling at the end of the tumor progression or during the progression of the disease.

sampledGenotypes shows the genotype frequencies from that sample; Shannon's diversity — entropy— of the genotypes is also returned. Order effects are ignored.

Usage

```
samplePop(x, timeSample = "last", typeSample = "whole",
          thresholdWhole = 0.5, geneNames = NULL, popSizeSample = NULL,
          propError = 0)

sampledGenotypes(y, genes = NULL)
```

Arguments

x	An object of class oncosimulpop or class oncosimul2 (a single simulation).
y	The output from a call to samplePop.
timeSample	"last" means to sample each individual in the very last time period of the simulation. "unif" (or "uniform") means sampling each individual at a time choosen uniformly from all the times recorded in the simulation with at least one driver between the time when the first driver appeared and the final time period. "unif" means that it is almost sure that different individuals will be sampled at different times. "last" does not guarantee that different individuals will be sampled at the same time unit, only that all will be sampled in the last time unit of their simulation. You can, alternatively, specify the population size at which you want the sample to be taken. See argument popSizeSample. Further clarification about "unif": suppose in a given simulation we have recorded times 1, 2, 3, 4, 5. And at times 2, 4, 5, there were clones with at least a mutant but at time 3 there were none (maybe they went extinct); the set of times to consider for sampling are 2, 4, 5, and time 3 is not considered. This might not always be what you want.
typeSample	"singleCell" (or "single") for single cell sampling, where the probability of sampling a cell (a clone) is directly proportional to its population size. "wholeTumor" (or "whole") for whole tumor sampling (i.e., this is similar to a biopsy being the entire tumor). "singleCell-noWT" or "single-nowt" is single cell sampling, but excluding the wild type.
thresholdWhole	In whole tumor sampling, whether a gene is detected as mutated depends on thresholdWhole: a gene is considered mutated if it is altered in at least thresholdWhole proportion of the cells in that individual.
geneNames	An optional vector of gene names so as to label the column names of the output.
popSizeSample	An optional vector of total population sizes at which you want the samples to be taken. If you pass this vector, timeSample has no effect. The samples will be taken at the first time at which the population size gets as large as (or larger than) the size specified in popSizeSample. This allows you to specify arbitrary sampling schemes with respect to total population size.
propError	The proportion of observations with error (for instance, genotyping error). If larger than 0, this proportion of entries in the sampled matrix will be flipped (i.e., 0s turned to 1s and 1s turned to 0s).
genes	If non-NULL, use only the genes in genes to create the table of genotypes. This can be useful if you only care about the genotypes with respect to a subset of genes (say, X), and want to collapse with respect to another subset of genes (say, Y), for instance if Y is a large set of passenger genes. For example, suppose the complete set of genes is 'a', 'b', 'c', 'd', and you specify genes = c('a', 'b'); then, genotypes 'a, b, c' and genotypes 'a, b, d' will not be shown as different rows in the table of frequencies. Likewise, genotypes 'a, c' and genotypes 'a, d' will not be shown as different rows. Of course, if what are actually different genotypes are not regarded as different, this will affect the calculation of the diversity.

Details

samplePop simply repeats the sampling process in each individual of the oncosimulpop object.

Please see oncoSimulSample for a much more efficient way of sampling when you are sure what you want to sample.

Note that if you have set onlyCancer = FALSE in the call to oncoSimulSample, you can end up trying to sample from simulations where the population size is 0. In this case, you will get a vector/matrix of NAs and a warning.

Similarly, when using timeSample = "last" you might end up with a vector of 0 (not NAs) because you are sampling from a population that contains no clones with mutated genes. This event (sampling from a population that contains no clones with mutated genes), by construction, cannot happen when timeSample = "unif" as "uniform" sampling is taken here to mean sampling at a time choosen uniformly from all the times recorded in the simulation between the time when the first driver appeared and the final time period. However, you might still get a vector of 0, with uniform sampling, if you sample from a population that contains only a few cells with any mutated genes, and most cells with no mutated genes.

Value

A matrix. Each row is a "sample genotype", where 0 denotes no alteration and 1 alteration. When using v.2, columns are named with the gene names.

We quote "sample genotype" because when not using single cell, a row (a sample genotype) need not be, of course, any really existing genotype in a population as we are genotyping a whole tumor. Suppose there are really two genotypes present in the population, genotype A, which has gene A mutated and genotype B, which has gene B mutated. Genotype A has a frequency of 60% (so B's frequency is 40%). If you use whole tumor sampling with thresholdWhole = 0.4 you will obtain a genotype with A and B mutated.

For sampledGenotypes a data frame with two columns: genotypes and frequencies. This data frame has an additional attribute, "ShannonI", where Shannon's index of diversity (entropy) is stored. This is an object of class "sampledGenotypes" with an S3 print method.

Author(s)

Ramon Diaz-Uriarte

References

Diaz-Uriarte, R. (2015). Identifying restrictions in the order of accumulation of mutations during tumor progression: effects of passengers, evolutionary models, and sampling doi:10.1186/s12859-01504667

See Also

oncoSimulPop, oncoSimulSample

Examples

```
######## Using an extended poset for pancreatic cancer from Gerstung et al.
###      (s and sh are made up for the example; only the structure
###       and names come from Gerstung et al.)


pancr <- allFitnessEffects(data.frame(parent = c("Root", rep("KRAS", 4), "SMAD4", "CDNK2A",
                                                 "TP53", "TP53", "MLL3"),
                                      child = c("KRAS","SMAD4", "CDNK2A",
                                                "TP53", "MLL3",
                                                rep("PXDN", 3), rep("TGFBR2", 2)),
                                      s = 0.15,
                                      sh = -0.3,
                                      typeDep = "MN"))


## (I set mc.cores = 2 to comply with --as-cran checks, but you
##  should either use a reasonable number for your hardware or
##  leave it at its default value).

p1 <- oncoSimulPop(4, pancr, mc.cores = 2)
(sp1 <- samplePop(p1))
sampledGenotypes(sp1)


## Sample at fixed sizes. Notice the requested size
## for the last population is larger than the any population size
## so we get NAs

(sp2 <- samplePop(p1, popSizeSample = c(1e7, 1e6, 4e5, 1e13)))
sampledGenotypes(sp2)


## Now single cell sampling

r1 <- oncoSimulIndiv(pancr)
samplePop(r1, typeSample = "single")

sampledGenotypes(samplePop(r1, typeSample = "single"))
```

---

simOGraph *Simulate oncogenetic/CBN/XMPN DAGs.*

Description

Simulate DAGs that represent restrictions in the accumulation of mutations.

Usage

```
simOGraph(n, h = ifelse(n >= 4, 4, n), conjunction = TRUE, nparents = 3,
multilevelParent = TRUE, removeDirectIndirect = TRUE, rootName = "Root",
geneNames = seq.int(n), out = c("adjmat", "rT"),
s = 0.1, sh = -0.1, typeDep = "AND")
```

Arguments

n	Number of nodes, or edges, in the graph. Like the number of genes.
h	Approximate height of the graph. See details.
conjunction	If TRUE, conjunctions (i.e., multiple parents for a node) are allowed.
nparents	Maximum number of parents of a node, when conjunction is TRUE.
multilevelParent	Can a node have parents at different heights (i.e., parents that are at different distance from the root node)?
removeDirectIndirect	Ensure that no two nodes are connected both directly (i.e., with an edge between them) and indirectly, through intermediate nodes. If TRUE, we return the transitive reduction of the DAG.
rootName	The name you want to give the "Root" node.
geneNames	The names you want to give the the non-root nodes.
out	Whether the ouptut should be an adjacency matrix or a "restriction table", as used in allFitnessEffects.
s	If using as output a restriction, the default value for s. See allFitnessEffects.
sh	If using as output a restriction, the default value for sh. See allFitnessEffects
typeDep	If using as output a restriction, the default value for "typeDep". See allFitnessEffects

Details

This is a simple, heuristic procedure for generating graphs of restrictions that seem compatible with published trees in the oncogenetic literature.

The basic procedure is as follows: nodes (argument n) are split into approximately equally sized h groups, and then each node from a level is connected to nodes chosen randomly from nodes of the remaing superior (i.e., closer to the Root) levels. The number of edges comes from a uniform distribution between 1 and nparents.

The actual depth of the graph can be smaller than h because nodes from a level might be connected to superior levels skipping intermediate ones.

See the vignette for further discussion about arguments.

Value

An adjacency matrix for a directed graph or a data frame to be used as input, as "restriction table" in allFitnessEffects.

Author(s)

Ramon Diaz-Uriarte. Code for transitive closure taken from the nem package, whose authors are Holger Froehlich, Florian Markowetz, Achim Tresch, Theresa Niederberger, Christian Bender, Matthias Maneck, Claudio Lottaz, Tim Beissbarth

Examples

```
(a1 <- simOGraph(10))
library(graph) ## for simple plotting
plot(as(a1, "graphNEL"))

simOGraph(3, geneNames = LETTERS[1:3])
```

---

to_Magellan *Create output for MAGELLAN and obtain MAGELLAN statistics.*

Description

Export a fitness landscape in a format that is understood by MAGELLAN and obtain fitness landscape statistics from MAGELLAN.

Usage

```
to_Magellan(x, file,
            max_num_genotypes = 2000)

Magellan_stats(x, max_num_genotypes = 2000,
               verbose = FALSE,
               use_log = FALSE,
               short = TRUE,
               replace_missing = FALSE)
```

Arguments

x	One of the following: • A matrix (or data frame) with g + 1 columns. Each of the first g columns contains a 1 or a 0 indicating that the gene of that column is mutated or not. Column g+ 1 contains the fitness values. This is, for instance, the output you will get from `rfitness`. • A two column data frame. The second column is fitness, and the first column are genotypes, given as a character vector. For instance, a row "A, B" would mean the genotype with both A and B mutated. • The output from a call to `evalAllGenotypes`. Make sure you use `order = FALSE` in that call. • The output from a call to `evalAllGenotypesMut`. Make sure you use `order = FALSE`.

- The output from a call to allFitnessEffects (with no order effects in the specification).

The first two are the same as the format for the genotFitness component in allFitnessEffects.

file The name of the output file. If NULL, a name will be created using tempfile.

max_num_genotypes
Maximum allowed number of genotypes. For some types of input, we make a call to evalAllGenotypes, and use this as the maximum.

verbose If TRUE provide additional information about names of intermediate files.

use_log Use log fitness when computing statistics. Note that the rfitness function outputs what should be interpreted as log-fitness values, and thus we set this option by default to FALSE.

short Give short output when computing statistics.

replace_missing
From MAGELLAN's fl_statistics: replace missing fitness values with 0 (otherwise check that all values are specified).

Value

to_Magellan: A file is written to disk. You can then plot and/or show summary statistics using MAGELLAN.

Magellan_stats: MAGELLAN's statistics for fitness landscapes. If you use short = TRUE a vector of statistics is returned. If short = FALSE, MAGELLAN returns a file with detailed statistics that cannot be turned into a simple vector of statistics. The returned object uses readLines and, as a message, you are also shown the path of the file, in case you want to process it yourself.

Note

If you try to pass a fitness specification with order effects you will receive an error, since that cannot be plotted with MAGELLAN.

Author(s)

Ramon Diaz-Uriarte

References

MAGELLAN web site: (it seems no longer available)

Brouillet, S. et al. (2015). MAGELLAN: a tool to explore small fitness landscapes. *bioRxiv*, **31583**. doi:10.1101/031583

See Also

allFitnessEffects, evalAllGenotypes, allFitnessEffects, rfitness

Examples

```
## Generate random fitness for four-genes genotype
## and export landscape.

r1 <- rfitness(4)
to_Magellan(r1, NULL)

## Specify fitness using a DAG and export it
cs <-  data.frame(parent = c(rep("Root", 3), "a", "d", "c"),
                      child = c("a", "b", "d", "e", "c", "f"),
                      s = 0.1,
                      sh = -0.9,
                      typeDep = "MN")

to_Magellan(allFitnessEffects(cs), NULL)

## Default, short output
Magellan_stats(allFitnessEffects(cs))

## Long output; since it is a > 200 lines file,
## place in an object. Name of output file is given as message
statslong <- Magellan_stats(allFitnessEffects(cs), short = FALSE)


## Default, short output of two NK fitness landscapes
rnk1 <- rfitness(6, K = 1, model = "NK")
Magellan_stats(rnk1)

rnk2 <- rfitness(6, K = 4, model = "NK")
Magellan_stats(rnk2)
```

---

vignette_pre_computed *Runs from simulations of interventions examples shown in the vignette. Most, but not all, are from intervention examples.*

Description

Simulations shown in the vignette. Since running them can take a few seconds, we have pre-run them, and stored the results.

They are here mainly to facilitate creation of table from the vignette itself. The script is available under "inst/miscell".

Usage

```
data(osi)
data(osi_with_ints)
data(atex4)
data(atex5)
```

```
data(atex2b)
data(uvex3)
data(smyelo3v57)
data(s_3_b)
data(uvex2)
data(simT2)
data(simul_period_1)
data(simT3)
data(s_3_a)
```

Format

Output from runs of oncoSimulIndiv, with some components removed to minimize size.

Examples

```
data(atex2b)
plot(atex2b)
```

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