Package ‘OncoSimulR’

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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. Mutation rates can differ between genes, and we can include mutator/antimutator genes (to model mutator phenotypes). 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 Tress, Conjunctive Bayesian Networks, and other tumor 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, and additive 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

Depends R (>= 3.3.0)

Imports Rcpp (>= 0.12.4), parallel, data.table, graph, Rgraphviz, gtools, igraph, methods, RColorBrewer, grDevices, car, dplyr, smatr, ggplot2, ggrepel

Suggests BiocStyle, knitr, Oncotree, testthat (>= 1.0.0), rmarkdown, bookdown

LinkingTo Rcpp

VignetteBuilder knitr

NeedsCompilation yes
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.

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

```r
allFitnessEffects(rT = NULL, epistasis = NULL, orderEffects = NULL, noIntGenes = NULL, geneToModule = NULL, drvNames = NULL, genotFitness = NULL, keepInput = TRUE)

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 one 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 deviations 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).

- `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.

- `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.

- `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.

- `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.

- `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 specify 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 fault 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
fitness. 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. 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. If the matrix has all columns named, those
  will be used for the names of the genes.

- As 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.

In all cases, fitness must be \( \geq 0 \). If any possible genotype is missing, its fitness
is assumed to be 1.

**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.

**Details**

**allFitnessEffects** is used for extremely flexible specification of fitness and mutator effects, in-
cluding posets, XOR relationships, synthetic mortality and synthetic viability, arbitrary forms of
epistasis, arbitrary forms of order effects, etc. Please, see the vignette for detailed and commented
examples.

**allMutatorEffects** provide the same flexibility, but without order and posets (this might be in-
cluded 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.

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 fitness. Period",
so we should not allow further modifications from other terms.

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 fitnesses are
rescaled.

**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.

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.

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 http://www.biomedcentral.com/1471-2105/16/41/abstract


See Also
evalGenotype, 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 modules
s = c(0.01, 0.02, 0.03, 0.04, 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"))

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))
allFitnessEffects

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 =
evalAllGenotypes

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)

## Reinitialize the seed
set.seed(NULL)

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, verbose = FALSE, echo = FALSE, model ="")
evalGenotypeMut(genotype, mutatorEffects, verbose = FALSE, echo = FALSE)
evalAllGenotypes(fitnessEffects, order = FALSE, max = 256, addwt = FALSE, model ="")
evalAllGenotypesMut(mutatorEffects, max = 256, addwt = FALSE)
evalGenotypeFitAndMut(genotype, fitnessEffects, mutatorEffects, verbose = FALSE, echo = FALSE, model ="")
evalAllGenotypesFitAndMut(fitnessEffects, mutatorEffects, order = FALSE, max = 256, addwt = FALSE, model ="")

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.
evalAllGenotypes

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?

**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.

**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 and the Fitness (or Death Rate, if Bozic). The notation for the Genotype column is as 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.

**Note**

Fitness is used in a slight abuse of the language. Right now, mutations contribute to the birth rate for all models except Bozic, where they modify the death rate. The general expression for fitness is the usual multiplicative one of \( \prod (1 + s_i) \), where each \( s_i \) refers to the fitness effect of the given gene. When dealing with death rates, we use \( \prod (1 - s_i) \).

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 specifying mutator/fitness effects if you only want to play with one of them.

Author(s)
Ramon Diaz-Uriarte

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.

```r
t## Restrictions in mutations as a graph. Modules present.
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", "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"))
```

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

## Epistasis for fitness and simple mutator effects
```r
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
```r
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, c3"))
```
## 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))
```

---

### 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). \texttt{b11} contains the full, original data, whereas \texttt{b12} contains the same data where there are no cases with exactly 2 drivers.

**Usage**

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

**Format**

Two objects of class "oncosimul".

**See Also**

\texttt{plot.oncosimul}
### Examples

```r
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")
```

### 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

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

### Format

The format is: List of 13

- `p1101`: num [1:10, 1:2] 1 1 3 3 7 7 8 9 10 ...
- `p1102`: num [1:9, 1:2] 1 1 3 3 7 7 8 10 ...
- `p1103`: num [1:9, 1:2] 1 1 3 3 7 7 8 10 2 ...
- `p1104`: num [1:9, 1:2] 1 1 3 3 7 7 2 10 2 ...
- `p901`: num [1:8, 1:2] 1 1 3 3 7 7 12 3 ...
- `p902`: num [1:6, 1:2] 1 1 3 3 7 7 9 2 10 2 ...
- `p903`: num [1:6, 1:2] 1 1 3 3 7 7 8 1 2 3 6 8 ...
- `p904`: num [1:6, 1:2] 1 1 3 3 7 7 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 1 1 1 2 2 5 4 6 ...

### Source


### See Also

- `poset`

### Examples

```r
data(examplePosets)

## Plot all of them

par(mfrow = c(3, 5))
invisible(sapply(names(examplePosets),

  function(x) {plotPoset(examplePosets[[x]],

```
mcfLs

```
main = x,
box = TRUE))
```

---

text

**Examples of fitness effects**

**Description**

Some examples 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**

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

**Format**

The format is a list of fitnessEffects objects.

**See Also**

`allFitnessEffects`

**Examples**

```r
data(examplesFitnessEffects)
plot(examplesFitnessEffects[["fea"]])
evalAllGenotypes(examplesFitnessEffects[["cbn1"]], order = FALSE)
```

---

text

**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**

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

**Format**

An object of class "oncosimul2". A list.
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. Simulation is done using the BNB algorithm of Mather et al., 2012.

Usage

```r
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 = initSize/(exp(1) - 1), keepEvery = sampleEvery, minDetectDrvCloneSz = "auto", extraTime = 0, finalTime = 0.25 * 25 * 365, onlyCancer = TRUE, 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, seed = NULL)
```

```r
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),
```

See Also

`plot.oncosimul`

Examples

```r
data(mcfLs)
plot(mcfLs, addtot = TRUE, lwdClone = 0.9, log = "")
summary(mcfLs)
```
oncoSimulIndiv

initSize = 500, s = 0.1, sh = -1,
K = initSize/(exp(1) - 1), keepEvery = sampleEvery,
extraTime = 0,
finalTime = 0.25 * 25 * 365, onlyCancer = TRUE,
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,
verbosity = 0,
mc.cores = detectCores(),
seed = "auto")

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 = initSize/(exp(1) - 1),
minDetectDrvCloneSz = "auto",
extraTime = 0,
finalTime = 0.25 * 25 * 365,
onlyCancer = TRUE, keepPhylog = FALSE,
oncoSimulIndiv

```r
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,
verbosity = 1,
showProgress = FALSE,
seed = "auto"
```

**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](#)). 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", "McFarlandLog" (the last one can be abbreviated to "McFL"). The default is "Exp".
- **numPassengers**: This has no effect if you use the [allFitnessEffects](#) specification. 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 \((\text{number of driver genes} + 1):(\text{number of drivers} + \text{number of passengers})\).

- **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.

  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.
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).

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 $1.2 \times initSize$.
- p2: The probability of detection at population size $n2$. If you specify 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 $2 \times initSize$.
- 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.

detectionDrivers
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.

s Selection coefficient for drivers. Only relevant if using a poset as this is included in the fitnessEffects object.

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.

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 scenarios such as the McFarland model.

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.

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. Thus, $\text{mutation rate} = \mu * \text{birth rate}$. This is a simple way of approximating that mutation happens at cell division (it is not strictly making mutation happen at cell division, since mutation is not strictly coupled with division). 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.

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 each individual simulation run. 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 successfully 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 successfully 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. Increasing 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 execution, of the individual done, and the number of attempts and time used.
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("LC颀uer-CMRG") as we use mclapply; look at the vignette of parallel.

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). 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

\[ 1 - e^{-cPDetect(populationsize - PDBaseline)} \]

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 one 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.
oncoSimulIndiv

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 names minDMratio and minBMratio are the smallest ratio, over all simulations, of death rate to mutation rate or birth rate to mutation rate. 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 ".

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)
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 http://www.biomedcentral.com/1471-2105/16/41/abstract


See Also

`plot.oncosimul, examplePosets, samplePop, allFitnessEffects`

Examples

```
#################################
##### Examples using v.1
#####
#################################

## use poset p701
data(examplePosets)
p701 <- examplePosets["p701"]

## Exp Model
b1 <- oncoSimulIndiv(p701)
summary(b1)
plot(b1, addtot = TRUE)

## McFarland; use a small sampleEvery, but also a reasonable keepEvery.
## We also modify mutation rate to values similar to those in the original paper.
## Note that detectionSize will play no role
## finalTime is large, since this is a slower process
## initSize is set to 4000 so the default K is larger and we are likely to reach cancer. Alternatively, set K = 2000.

m1 <- oncoSimulIndiv(p701,
                    model = "McFL",
                    mu = 5e-7,
                    initSize = 4000,
                    sampleEvery = 0.025,
                    finalTime = 15000,
                    keepEvery = 10,
                    onlyCancer = FALSE)
plot(m1, addtot = TRUE, log = "")
```

## Simulating 4 individual trajectories
## (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, p701,
  keepEvery = 10,
  mc.cores = 2)

summary(p1)
samplePop(p1)

p2 <- oncoSimulSample(4, p701)

#########################################
###### Examples using v.2:              
#########################################

#### A model similar to the one in McFarland. We use 2070 genes.

set.seed(456)
nd <- 70
np <- 2000
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")
oncoSimulIndiv

```r
oiI1$GenotypesLabels

## 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 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")

plot(pancr)

### Use an exponential growth model

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

pancr1

summary(pancr1)

plot(pancr1)

pancr1$GenotypesLabels

## Pop and Sample

pancrPop <- oncoSimulPop(4, pancr,
                         keepEvery = 10,
                         mc.cores = 2)

summary(pancrPop)
```
OncoSimulWide2Long

```r
pancrSPop <- samplePop(pancrPop)
pancrSPop

pancrSamp <- oncoSimulSample(2, pancr)
pancrSamp

## 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)

## 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**

```r
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

```r
data(examplePosets)
## An object of class oncosimul
p705 <- examplePosets["p705"]
p1 <- oncoSimulIndiv(p705)
class(p1)
lp1 <- OncoSimulWide2Long(p1)
head(lp1)
summary(lp1)
```

```r
## An object of class oncosimul2
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**

```r
## 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`.

---
plot.fitnessEffects  

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 If TRUE, the graph object (igraph 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 presence 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

```r
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"))
```

```r
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 module

```r
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"))
```

```r
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)
```

```r
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)
```

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

```r
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 number 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

```r
## 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,
     ...)
```
plot.oncosimul

1tyDrivers = 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
\[\log(a + b) \neq \log(a) + \log(b)\]).

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 con-
siderably) 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`.

**Author(s)**

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

**See Also**

`oncoSimulIndiv`

**Examples**

```r
data(examplePosets)
p701 <- examplePosets[["p701"]]

## Simulate and plot a single individual, including showing
## Shannon's diversity index
b1 <- oncoSimulIndiv(p701)
plot(b1, addtot = TRUE, plotDiversity = TRUE)

## A stacked area plot
plot(b1, type = "stacked", plotDiversity = TRUE)
```
## And what if I show a stream plot?

```r
plot(b1, type = "stream", plotDiversity = TRUE)
```

### Simulate and plot 2 individuals

(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).

```r
p1 <- oncoSimulPop(2, p701, mc.cores = 2)
```

![plot](image)

```
par(mfrow = c(1, 2))
plot(p1, ask = FALSE)
```

Stacked; we cannot log here, and harder to see patterns

```r
plot(p1, ask = FALSE, type = "stacked")
```

### Show individual genotypes and drivers for an epistasis case with at most eight genotypes

```r
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"))
```

```r
evalAllGenotypes(sv2, order = FALSE, addwt = TRUE)
e1 <- oncoSimulIndiv(sv2, model = "McFL",
                     mu = 5e-6,
                     sampleEvery = 0.02,
                     keepEvery = 1,
                     initSize = 2000,
                     finalTime = 3000,
                     onlyCancer = FALSE)
```

### Drivers and clones

```r
plot(e1, show = "drivers")
```

### Make genotypes explicit

```r
plot(e1, show = "genotypes")
```

### Oh, but I want other colors

```r
plot(e1, show = "genotypes", col = rainbow(8))
```

### and actually I want a line plot

```r
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**

```r
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 `t` 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 (together 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 `get.adjacency`. See an example below.
plotFitnessLandscape

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 terminal 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)
get.adjacency(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, [http://wwwabi.snv.jussieu.fr/public/Magellan/](http://wwwabi.snv.jussieu.fr/public/Magellan/).

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

Usage

```r
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,
...)
```

```r
## 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,
...)
```

```r
## 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,
...)
```

```r
## 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 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 accessible 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 (http://wwwabi.snv.jussieu.fr/public/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
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 fitness 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: http://wwwabi.snv.jussieu.fr/public/Magellan/


See Also

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

Examples

```r
## 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)
pplotPoset(examplePosets["p1101"])

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

poset701 <- examplePosets["p701"]
pplotPoset(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, ]
pplotPoset(poset701b,
          names = c("KRAS", "SMAD4", "CDNK2A", "TP53",
                    "MLL3", "PXDN", "TGFBR2"))

### 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`.

### Author(s)
Ramon Diaz-Uriarte

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


### See Also
`examplePosets`, `plotPoset`, `oncoSimulIndiv`

### Examples
```r
## 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, or additive model.

Usage

rfitness(g, c = 0.5, sd = 1, reference = "random", scale = NULL,
  wt_is_1 = TRUE, log = FALSE, min_accessible_genotypes = 0,
  accessible_th = 0)

Arguments

g  Number of genes.

c  The decrease in fitness of a genotype per each unit increase in Hamming distance from the reference genotype (see reference).

sd  The standard deviation of the random component (a normal distribution of mean 0 and standard deviation sd).

reference  The reference genotype: 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-element vector. If a two-element vector, fitness is re-scaled between \( \text{scale}[1] \) (the minimum) and \( \text{scale}[2] \) (the maximum).

wt_is_1
If TRUE, fitness will be scaled so that the wildtype (the genotype with no mutations) has fitness of 1. This is applied after \( \text{scale} \), so if you specify both it is most likely that the final fitness will not respect the limits in \( \text{scale} \).

log
If TRUE, log-transform fitness.

min_accessible_genotypes
If larger than 0, the minimum number of accessible genotypes in the fitness landscape. A genotype is considered accessible if you can reach it from the wildtype by going through at least one path where all changes in fitness are larger or equal to \( \text{accessible}_\text{th} \). 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 \( \text{accessible}_\text{th} \).

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

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 \( \text{min_accessible_genotypes} \) is larger than 0. So if you want to allow small decreases in fitness in successive steps, use a small negative value for \( \text{accessible}_\text{th} \).

Details
The model used here follows the Rough Mount Fuji model in Szendro et al., 2013 or Franke et al., 2011. Fitness is given as

\[
 f(i) = -cd(i, \text{reference}) + x_i
\]

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 0 and standard deviation \( sd \)).

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).

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 \( \text{min_accessible_genotypes} > 0 \), the return object has added attributes \( \text{accessible_genotypes} \) and \( \text{accessible_th} \) that show the number of accessible genotypes under the specified threshold.

Author(s)
Ramon Diaz-Uriarte
References


See Also

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

Examples

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

r1 <- rfitness(4)
plot(r1)
oncoSimulIndiv(allFitnessEffects(genotFitness = r1))
```

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.

Usage

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

Arguments

- `x` An object of class oncosimulpop.
- `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 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.
- `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).
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.

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 chosen 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.

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 http://www.biomedcentral.com/1471-2105/16/41/abstract

See Also

oncoSimulPop, oncoSimulSample
Examples

```r
data(examplePosets)
p705 <- examplePosets[["p705"]]

## (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, p705, mc.cores = 2)
samplePop(p1)

## Sample at fixed sizes. Notice the requested size
## for the last population is larger than the any population size
## so we get NAs
samplePop(p1, popSizeSample = c(1e7, 1e6, 4e5, 1e13))

## Now single cell sampling
r1 <- oncoSimulIndiv(p705)
samplePop(r1, typeSample = "single")
```

---

**simOGraph**

*Simulate oncogenetic/CBN/XMPN DAGs.*

**Description**

Simulate DAGs that represent restrictions in the accumulation of mutations.

**Usage**

```r
simOGraph(n, h = 4, conjunction = TRUE, nparents = 3,
multilevelParent = TRUE, removeDirectIndirect = TRUE, rootName = "Root")
```

**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, the direct connections are removed from the graph starting from the bottom.
- `rootName` The name you want to give the "Root" node.
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 remaining 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.

Author(s)

Ramon Diaz-Uriarte

Examples

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

Description

Create a fitness landscape in a format that is understood by MAGELLAN http://wwwabi.snv.jussieu.fr/public/Magellan/.

Usage

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

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.

Value

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

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


See Also

`allFitnessEffects, evalAllGenotypes, allFitnessEffects, rfitness`

Examples

```r
## 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)
```
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