Package: fracprolif (via r-universe)

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Type Package

Title Fraction Proliferation via a Quiescent Growth Model

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Author Shawn Garbett, Darren Tyson

Maintainer Shawn Garbett <Shawn@Garbett.org>

Description Functions for fitting data to a quiescent growth model,
i.e. a growth process that involves members of the population
who stop dividing or propagating.

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LazyLoad yes

Depends emg (>= 1.0.5), numDeriv, methods, stats4

NeedsCompilation no

Repository https://spgarbet.r-universe.dev

RemoteUrl https://github.com/spgarbet/fracprolif

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Contents

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fracprolif-package   *Fractional Proliferation.*

Description

This package contains all the functions necessary for analyzing population size based on the behavior of individual members within the population using a methodology termed Fractional Proliferation. The methodology was specifically designed to analyze the behavior of a population of cultured cells and requires fitting data to a newly developed model of proliferation, the Quiescence-Growth Model (see below). This package contains functions to determine rates of division (d) quiescence (q) and apoptosis (a) as well as predict the change in the fraction of cells within the dividing and nondividing compartments over time.

Quiescence-Growth Model

The Quiescence-Growth Model is based on an exponentially dividing population that transition into a nondividing population at a specified rate. This model is different from Gompertz and logisitic models of proliferation that assume a limiting resource or factor that prevents proliferation above a fixed amount, the carrying capacity. In contrast, the Quiescence-Growth Model assumes that members of the population may stop dividing, e.g. in response to perturbations. The resulting proliferation curves from these models may appear very similar, but the underlying assumptions are different.

The Quiescence-Growth Model assumes that there are two populations, a proliferating population (x) and a non-proliferating population (y). The proliferating population has a rate of division (d), analogous to the exponential growth rate of a population. There is also a rate of quiescence (q), the rate at which members of the dividing population become non-dividing. Each subpopulation can have a different death rate (a_d and a_q). Such a model is formulated as follows using coupled ordinary differential equations:

$$x' = (d - q - a_d)x$$

$$y' = qx - a_q y$$

Where d is the division rate, q is the quiescence rate and a_d and a_q are the respective death rates. This admits the following solution,

$$x = x_0 e^{(d-q-a_d)t}$$

$$y = \frac{1}{d - q + a_q - a_d} e^{-a_q t} \left(q(x_0(e^{(d-q+a_q-a_d)t} - 1) - y_0) + (d + a_q - a_d)y_0 \right)$$

Fitting such a model with solid statistics depends greatly upon how the data are measured. Differing rates of death and quiescence can create similar curvatures in the resulting population model on shorter time scales. Because of this, accurate estimation of the rates requires more than a curve fit to the population counts using `nls`. Direct measurement of individual behavior within the population provides the necessary information to accurately quantify these rates and predict the change in the size of each compartment (x and y) over time. The Fractional Proliferation method utilizes obtainable information at the individual and population levels to make these predictions. We include two example data sets to illustrate the approach: `ca1d.erlotinib` and `ca1d.erlotinib.totals`. These data sets were obtained by automated microscopy of a cancer cell line (CA1d) in the presence of a targeted therapeutic drug (erlotinib). Normally these cells exhibit minimal entry into quiescence, but in the presence of erlotinib the population of quiescent cells increases substantially.

Example - Single-Cell Data

To begin with an example, load the observed single-cell data by copying and pasting the following code into the R console:

```
data(ca1d.erlotinib)
```

To view the scatterplot of birthtime versus lifespan of the cell behaviors in 16microM erlotinib, copy and paste the example code below into the R console. (Note: All later examples are executable in the same manner.)

```
d <- subset(ca1d.erlotinib, !Death & !is.na(Lifespan))
plot(d$Birthtime,
     d$Lifespan,
     main="CA1d 16micromolar erlotinib",
     xlab="Birth time (h)",
     ylab="Lifespan (h)",
     ylim=c(5,90), xlim=c(0,25))
n <- length(d$Lifespan)
text(20,80,substitute("n" == n,list(n=n)))
p <- 100*length(subset(d, End.of.Expt)$Lifespan) / n
text(15,85,substitute(p * "% EoE", list(p=round(p))))
```

This plot shows the raw data with the birth time of a cell in the experiment plotted along the x-axis and the lifespan plotted along the y-axis. Note that the data include cells that die during the experiment because they also have an observed lifespan, as well as cells that are observed until the end of the experiment without having divided, which are seen along the downward sloped line at the top of the plot. The end of the experiment creates a censoring effect on the data in this regard, and we do not know if these cells eventually divide or not.

Example - Intermitotic Time Distribution

To view the intermitotic time distribution (i.e. the distribution of cell cycle times) the data `ca1d.erlotinib` must first be split into `mitotic.lifespans`, which include cells that divide before the end of the experiment, and `censored.lifespans` that reach the end of the experiment without division, excluding death events.

```
mitotic.lifespans <- subset(ca1d.erlotinib,  !End.of.Expt &
                                             !Death       &
                                             !is.na(Lifespan))$Lifespan

censored.lifespans <- subset(ca1d.erlotinib, End.of.Expt  &
                                             !Death       &
                                             !is.na(Lifespan))$Lifespan
```

An exponentially growing population of CA1d cells have intermitotic times that can be described by an Exponentially Modified Gaussian (EMG) distribution (Nature Methods submitted and reference therein), a Gaussian with an exponential right tail. This can be seen in the following plot:

```
hist(mitotic.lifespans,
     main='CA1d 16micromolar erlotinib',
     sub="Observed Intermitotic Times (h)",
     breaks=20)
```

Example - Quiescence Likelihood

A survival model with knowledge of the distribution, can estimate the distribution parameters and quiescent percentage. This uses the negative log likelihood of a survival model. This package provides a function, qsurvival.nllik, that will work with most of the core distributions provided by R. The following call demonstrates estimation with the sample data. The survival model assumes that the censored observations may or may not divide based on the observed divisions.

```
est <- q.mle.emg.estimate(mitotic.lifespans, censored.lifespans)

summary(est)
```

Using this estimate we can visualize the fit with the following:

```
hist(mitotic.lifespans,
     main='CA1d 16micromolar erlotinib',
     xlab="Observed Intermitotic Times (h)",
     breaks=20,
     freq=FALSE)
curve(demg(x, coef(est)['mu'], coef(est)['sigma'], coef(est)['lambda']), add=TRUE, col='red', lwd=2)
text(40, 0.07, pos=4, labels=substitute("n"==n, list(n=length(mitotic.lifespans))))
text(40, 0.065, pos=4, labels=substitute(mu==m, list(m=round(coef(est)['mu'],2))))
text(40, 0.06, pos=4, labels=substitute(sigma==s, list(s=round(coef(est)['sigma'],2))))
text(40, 0.055, pos=4, labels=substitute(kappa==l, list(l=round(1/coef(est)['lambda'],2))))
```

To test for lack of fit of the data to an EMG distribution, the following snippet performs the Kolmogorov-Smirnov test and adds the results to the previous plot:

```
ks <- ks.test(mitotic.lifespans, "pemg",
              mu=coef(est)['mu'],
```

```
            sigma=coef(est)['sigma'],
            lambda=coef(est)['lambda'])

text(40, 0.05, pos=4, labels=substitute("ks p-value"==p, list(p=round(ks$p.value,2))))
```

The `q.mle.emg.estimate` function call assumes an EMG distribution, but a normal function `q.mle.norm.estimate` is also provided, and the following snippet shows the internals of this function, which can be changed to accommodate any distribution dependence since the inner function `qsurvival.nllik` makes no assumptions about distribution.

```
mle(function(mean, sd, Q){
    qsurvival.nllik("norm", mitotic.lifespans, censored.lifespans, Q, mean, sd)},
    method='L-BFGS-B',
    lower=list(mean=8,  sd=0.1, Q=0.01),
    upper=list(mean=30, sd=20,  Q=0.9),
    start=list(mean=mean(mitotic.lifespans),
               sd=sd(mitotic.lifespans),
               Q = 0.5))
```

Example - Division and Quiescence Rate Estimation

To estimate the rates of division (d) and quiescence (q), the distribution of the divided cell population is used, and, in this example, we will continue with the emg fit since the distribution's parameters have been estimated (see above). To transform the emg fit into a rate of division, we use the method of Powell (1956) and then subsequently derive the quiescence rate. Note this function is independent of the distribution used but must match the one used in the `mle` call (see above).

```
r <- q.rates("emg", est)
r
```

Example - Death Rate Estimation

Now we calculate the death rates from the compartments. In our example we first allow this parameter to float to optimally fit the model to the population counts using the previous estimates of division rate and quiescence rate. First, we load a set of population counts (in a log base 2 scale over time) of ca1d cells in the presence of various concentrations of erlotinib.

```
data(ca1d.erlotinib.totals)
```

The single-cell data used to plot the intermitotic time distribution and calculate the rates of division and quiescence were obtained in the presence of 16microM erlotinib and the goal is to determine how well the estimates of the rates obtained from the single-cell data predict the population-level cell counts over time. However, the drug is known to affect cells within a particular phase of the cell cycle and does not immediately effect all cells in a population. Thus, population-level behavior switches from the rates of untreated cells to the treated cells after a delay of approximately half of the average cell cycle time. To estimate the rate of division of the untreated cells we assume that all cells are dividing and the rate of growth of the population is equal to the division rate.

```
m <- lm(DMSO ~ Time_h, ca1d.erlotinib.totals)
untreated.division.rate <- coef(m)['Time_h']*log(2)
```

The estimated time before the drug takes effect is approximately half of the average intermitotic time (cell lifespan).

```
half.imt <- log(2)/untreated.division.rate/2
```

The death rate is initially fit using the Quiescence-Growth Model. When fitting the model, we do not know which compartment the cells die from, so we assign each compartment the same variable. Also the initial rates are those from the control population, i.e. zero for the quiescence and death rates.

```
# y is in terms of doublings, i.e. base log(2)
y <- ca1d.erlotinib.totals$e_16000 - ca1d.erlotinib.totals$e_16000[1]
t <- ca1d.erlotinib.totals$Time_h

# Let the Death rates float
fit <- nls(y ~ log(split_tot(t, 1, 0,
                             untreated.division.rate, r['d'],
                             0.0, r['q'],
                             0.0, 0.0, a, a,
                             half.imt), 2),
          start=list(a=0.003),
          lower=list(a=0),
          algorithm="port")
a <- coef(fit)
summary(fit)
```

Example - Final Fractional Proliferation Graph

Now with the death rate parameters estimated, we can plot the resulting model as follows:

```
plot (t, y,
      main="CA1d 16micromolar erlotinib",
      xlab="Time (h)",
      ylab="Population Doublings",
      ylim=c(0,1.5))

model.total <- log(split_tot(t, 1, 0, untreated.division.rate, r['d'], 0.0, r['q'], 0, 0, a['a'], a['a'
lines(t,model.total,col="green")

lines(t,model.total*split_fq(t, 1, 0, untreated.division.rate, r['d'], 0.0, r['q'], 0, 0, a['a'], a['a'
lines(t,model.total*split_fd(t, 1, 0, untreated.division.rate, r['d'], 0.0, r['q'], 0, 0, a['a'], a['a'

text(2, 1.1, pos=4, substitute("d" == d, list(d=round(r['d'], 4))))
text(2, 1.0, pos=4, substitute("q" == q, list(q=round(r['q'], 4))))
text(2, 0.9, pos=4, substitute("a" == a, list(a=round(a['a'], 4))))
```

Plotted on a log(2) scale, which shows doublings, the circles are the experimental data. The lines are the time-dependent estimates of total size of the population (green line) and the dividing (blue line) and quiescent (red line) fractions of this population based on the Quiescence-Growth Model. Drug is introduced at time 0, and we assume that the population initially has no quiescence.

Author(s)

Darren Tyson, Shawn Garbett Vanderbilt University

Maintainer: Shawn Garbett <Shawn@Garbett.org>

References

Darren R. Tyson, Shawn P. Garbett, Peter L. Frick and Vito Quaranta (2012) Fractional Proliferation: A method to deconvolve cell population dynamics from single-cell data. Nature Methods (In Press)

The method of determining growth rate is taken from *Powell E.0. (1956). Growth Rate and Generation Time of Bacteria, with Special Reference to Continuous Culture. J.Gen.Microbial V15,492-511.* This makes a robust estimator in the presence of skewed distributions.

Ulm (1990). Simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am. J. Epidemiol. V131 (2): 373-375.

See Also

emg nls

---

ca1d.erlotinib	*CA1d cells in 16 micromolar erlotinib*

Description

CA1d cells were plated on a 96-well plate and imaged on a BD Pathway 855 every 10 minutes for 92 hours on 11/22/2010. The image stack was analyzed manually and observed cell lifespans were recorded. Each cell lifespan is defined by a start event (mitosis) and an end event (mitosis, death or end of experiment). Start events are shared among siblings (sister cells) and assigned an identifier comprised of the frame number and a letter. End events are assigned an identifier of frame number and a letter if mitotic. In some cases a mitotic end event identifier corresponds to another start event identifier (i.e. cell progeny). Events are converted to time units based on the frame acquisition rates (sampling interval); cell birth time and lifespan are expressed in hours.

1. When a mitotic event occurs, the daughter cells are each assigned the next rows available in a data.frame.

2. The frame number of the event is recorded in the Birth.frame column of the rows assigned in (1).

3. The event from (1) is given an alphabetic identifier not previously used within the same Birth.frame.

4. The last frame a cell is observed in is recorded in the End.frame.

5. If the last frame is a mitotic event, assign letter as (3) in `End.ID`.

6. If the cell is present in the last frame of the image stack, the column `End.of.Expt` is marked `TRUE`, otherwise it is marked `FALSE`.

7. If a cell is observed to die, this is recorded in the column `Death` as a `TRUE`, otherwise as `FALSE`.

8. Create `Birthtime` column in hours by multiplying `Birth.frame` by 1/5.

9. Create `Lifespan` column in hours by multiplying (`End.frame` – `Birth.frame`) by 1/5.

Information about the cell line used (CA1d) can be found in the following reference: *Fred R. Miller, Herbert D. Soule, Larty Tait, Robert J. Pauley, Sandra R. Wolman, Peter J. Dawson, and Gloria H. Heppner. Xenograft Model of Progressive Human Proliferative Breast Disease. JNCI J Natl Cancer Inst (1993) 85(21): 1725-1732 doi:10.1093/jnci/85.21.1725*

Usage

```
data(ca1d.erlotinib)
```

Value

A data frame of lifespan CA1d observations in the presence of 16 micromolar erlotinib.

Author(s)

Darren Tyson, Shawn Garbett

Examples

```
data(ca1d.erlotinib)
```

---

ca1d.erlotinib.totals   *CA1d cell counts in various concentrations erlotinib*

Description

CA1d cells expressing a fluorescent nuclear tag (histone H2B-RFP) were plated on a 96-well plate and imaged on a BD Pathway 855 every hour for 72 hours on 11/22/2010. Each column contains the number of cells (expressed in log 2) at each unit of time in the presence of various concentrations of erlotinib.

Information on the CA1d cells is in the following reference: *Fred R. Miller, Herbert D. Soule, Larty Tait, Robert J. Pauley, Sandra R. Wolman, Peter J. Dawson, and Gloria H. Heppner. Xenograft Model of Progressive Human Proliferative Breast Disease. JNCI J Natl Cancer Inst (1993) 85(21): 1725-1732 doi:10.1093/jnci/85.21.1725*

Usage

```
data(ca1d.erlotinib.totals)
```

Value

A data frame of CA1d cells counts (in log 2 scale) in the presence of various concentrations of erlotinib.

Author(s)

Darren Tyson, Shawn Garbett

Examples

```
data(ca1d.erlotinib.totals)
```

---

prolif_d	*Expected Propagating Subpopulation*

Description

Computes the expected count of a subpopulation that is propagating inside population undergoing quiescent growth.

Usage

```
prolif_d(t, x0, q0=0, d, q, ad, aq, tol=1e-6)
```

Arguments

t	A vector time points to return expected population size.
x0	The size of the initial propagating (or dividing) population at t=0.
q0	The size of the quiescent or non-propagating population at t=0.
d	The rate of growth of the propagating population.
q	The rate at which propagating population members join the quiescent population.
ad	The rate of death from the dividing or propagating population.
aq	The rate of death from the quiescent population.
tol	The tolerance between parameters before switching to limit models. The solution to the quiescent growth model has some boundary cases that would result in a division by zero. These happen when the rate of growth (d) is equal to rate of quiescence (q). When the absolute difference between these parameters is less than the tolerance, the model switches to the limit cases. The default value is good for most common cases. Preferably a very small number, that must be greater than zero.

Value

A numerical vector of expected dividing subpopulation totals.

Author(s)

Shawn Garbett

See Also

prolif_q prolif_tot prolif_fq prolif_fd q.rates

Examples

```
prolif_d(1:100, 0.5, 0.5, 0.04, 0.03, 0.001, 0.001)
```

---

prolif_fd   *Fraction of Population Propagating*

Description

Compute the fraction of population that is propagating or dividing when undergoing quiescent growth.

Usage

```
prolif_fd(t, x0, q0=0, d, q, ad, aq, tol=1e-6)
```

Arguments

t	A vector time points to return expected population size.
x0	The size of the initial propagating (or dividing) population at t=0.
q0	The size of the quiescent or non-propagating population at t=0.
d	The rate of growth of the propagating population.
q	The rate at which propagating population members join the quiescent population.
ad	The rate of death from the dividing or propagating population.
aq	The rate of death from the quiescent population.
tol	The tolerance between parameters before switching to limit models. The solution to the quiescent growth model has some boundary cases that would result in a division by zero. These happen when the rate of growth (d) is equal to rate of quiescence (q). When the absolute difference between these parameters is less than the tolerance, the model switches to the limit cases. The default value is good for most common cases. Preferably a very small number, that must be greater than zero.

Value

A numerical vector of the fraction of total population that is propagating.

Author(s)

Darren Tyson, Shawn Garbett

See Also

prolif_q prolif_d prolif_fq prolif_tot q.rates

Examples

```
prolif_fd(1:100, 0.5, 0.5, 0.04, 0.03, 0.001, 0.001)
```

---

prolif_fq	*Fraction of Population Quiescent*

Description

Compute the fraction of population that is quiescent when undergoing quiescent growth.

Usage

```
prolif_fq(t, x0, q0=0, d, q, ad, aq, tol=1e-6)
```

Arguments

t	A vector time points to return expected population size.
x0	The size of the initial propagating (or dividing) population at t=0.
q0	The size of the quiescent or non-propagating population at t=0.
d	The rate of growth of the propagating population.
q	The rate at which propagating population members join the quiescent population.
ad	The rate of death from the dividing or propagating population.
aq	The rate of death from the quiescent population.
tol	The tolerance between parameters before switching to limit models. The solution to the quiescent growth model has some boundary cases that would result in a division by zero. These happen when the rate of growth (d) is equal to rate of quiescence (q). When the absolute difference between these parameters is less than the tolerance, the model switches to the limit cases. The default value is good for most common cases. Preferably a very small number, that must be greater than zero.

Value

A numerical vector of the fraction of total population that is quiescent.

Author(s)

Darren Tyson, Shawn Garbett

See Also

[prolif_q](#) [prolif_d](#) [prolif_tot](#) [prolif_fd](#) [q.rates](#)

Examples

```
prolif_fq(1:100, 0.5, 0.5, 0.04, 0.03, 0.001, 0.001)
```

---

prolif_q	*Expected Quiescent Subpopulation*

Description

Computes the expected count of a subpopulation that is not-propagating, or quiescent inside a population undergoing quiescent growth.

Usage

```
prolif_q(t, x0, q0=0, d, q, ad, aq, tol=1e-6)
```

Arguments

t	A vector time points to return expected population size.
x0	The size of the initial propagating (or dividing) population at t=0.
q0	The size of the quiescent or non-propagating population at t=0.
d	The rate of growth of the propagating population.
q	The rate at which propagating population members join the quiescent population.
ad	The rate of death from the dividing or propagating population.
aq	The rate of death from the quiescent population.
tol	The tolerance between parameters before switching to limit models. The solution to the quiescent growth model has some boundary cases that would result in a division by zero. These happen when the rate of growth (d) is equal to rate of quiescence (q). When the absolute difference between these parameters is less than the tolerance, the model switches to the limit cases. The default value is good for most common cases. Preferably a very small number, that must be greater than zero.

Value

A numerical vector of expected quiescent subpopulation totals.

Author(s)

Shawn Garbett

See Also

[prolif_q](#) [prolif_tot](#) [prolif_fq](#) [prolif_fd](#) [q.rates](#)

Examples

```
prolif_q(1:100, 0.5, 0.5, 0.04, 0.03, 0.001, 0.001)
```

---

prolif_tot	*Expected Proliferation Total*

Description

Returns the expected population size over time given quiescent growth model parameters.

Usage

```
prolif_tot(t, x0, q0=0, d, q, ad, aq, tol=1e-6)
```

Arguments

t	A vector time points to return expected population size.
x0	The size of the initial propagating (or dividing) population at t=0.
q0	The size of the quiescent or non-propagating population at t=0.
d	The rate of growth of the propagating population.
q	The rate at which propagating population members join the quiescent population.
ad	The rate of death from the dividing or propagating population.
aq	The rate of death from the quiescent population.
tol	The tolerance between parameters before switching to limit models. The solution to the quiescent growth model has some boundary cases that would result in a division by zero. These happen when the rate of growth (d) is equal to rate of quiescence (q). When the absolute difference between these parameters is less than the tolerance, the model switches to the limit cases. The default value is good for most common cases. Preferably a very small number, that must be greater than zero.

Value

A numerical vector of expected population totals.

Author(s)

Shawn Garbett

See Also

prolif_q prolif_d prolif_fq prolif_fd q.rates

Examples

```
prolif_tot(1:100, 0.5, 0.5, 0.04, 0.03, 0.001, 0.001)
```

---

q.mle.emg.estimate   *Estimate Distribution Parameters based on EMG survival*

Description

Estimation of the emg distribution parameters from data using a survival function and maximum likelihood.

Usage

```
q.mle.emg.estimate(complete.lifespans, censored.lifespans)
```

Arguments

complete.lifespans

Vector of time observations of complete lifespans that span the entire life of an entity.

censored.lifespans

Vector of time observations that are incomplete about the life of an entity.

Value

An object of mle-class containing the parameter estimates.

Author(s)

Shawn Garbett

See Also

mle-class q.mle.norm.estimate q.rates qsurvival.nllik [emg](emg)

Examples

```
data(ca1d.erlotinib)
mitotic.lifespans <-
  subset(ca1d.erlotinib, !End.of.Expt &
                         !Death        &
                         !is.na(Lifespan))$Lifespan
censored.lifespans <-
  subset(ca1d.erlotinib, End.of.Expt  &
                         !Death        &
                         !is.na(Lifespan))$Lifespan
q.mle.emg.estimate(mitotic.lifespans, censored.lifespans)
```

---

q.mle.norm.estimate	*Estimate Distribution Parameters based on EMG survival*

Description

Estimation of the norm distribution parameters from data using a survival function and maximum likelihood.

Usage

```
q.mle.norm.estimate(complete.lifespans, censored.lifespans)
```

Arguments

complete.lifespans

  Vector of time observations of complete lifespans that span the entire life of an entity.

censored.lifespans

  Vector of time observations that are incomplete about the life of an entity.

Value

An object of mle-class.

Author(s)

Shawn Garbett

See Also

mle-class q.mle.emg.estimate q.rates qsurvival.nllik

Examples

```
data(ca1d.erlotinib)
mitotic.lifespans <-
  subset(ca1d.erlotinib, !End.of.Expt &
                         !Death        &
                         !is.na(Lifespan))$Lifespan
censored.lifespans <-
  subset(ca1d.erlotinib, End.of.Expt  &
                         !Death        &
                         !is.na(Lifespan))$Lifespan
q.mle.norm.estimate(mitotic.lifespans, censored.lifespans)
```

---

q.rates   *Estimate Quiescence-Growth Model Rates*

Description

Given an mle estimate of the distribution parameters transform into rates of growth and quiescence.
The transformation into a growth rate is the exact method of Powell. The quiescence rate uses
Poisson estimation. Standard errors are computed using the numerical delta method.

Usage

```
q.rates(dist, est)
```

Arguments

dist	This distribution to use for estimation, e.g. "emg" or "norm"
est	An object of class [mle-class](#) containing distribution estimates.

Value

An object of [class](#) q_rate containing (d) the growth rate and (q) the quiescence rate as a numeric
vector, as well as additional attributes of stderr, n and df used.

Author(s)

Darren Tyson, Shawn Garbett

References

The method of determining growth rate is taken from *POWELL E.0. (1956). Growth Rate and Generation Time of Bacteria, with Special Reference to Continuous Culture. J.Gen.Microbial V15,492-511.* This makes a robust estimator in the presence of skewed distributions.

See Also

[mle-class](#) [q.mle.norm.estimate](#) [q.mle.emg.estimate](#) [qsurvival.nllik](#)

Examples

```
data(ca1d.erlotinib)
mitotic.lifespans <-
  subset(ca1d.erlotinib, !End.of.Expt &
                         !Death       &
                         !is.na(Lifespan))$Lifespan
censored.lifespans <-
  subset(ca1d.erlotinib, End.of.Expt  &
                         !Death       &
                         !is.na(Lifespan))$Lifespan
r <- q.rates("emg", q.mle.emg.estimate(mitotic.lifespans, censored.lifespans))

summary(r)

r['d'] # Rate of division
r['q'] # Rate of quiescense
```

---

qrate-class   *Class* "qrate"

Description

A class to return from rate estimation.

Objects from the Class

Objects can be created by calls of the form new("qrate", ...).

Slots

.Data: This contains two entries, the division rate and the quiescence rate.

stderr: Standard error of the rate estimates

n: Number of data points used in estimate

df: degrees of freedom left in estimate

Extends

Class *"numeric"*, from data part. Class *"vector"*, by class "numeric", distance 2.

Methods

show signature(object = "qrate"): ...

Author(s)

Shawn Garbett

References

Standard errors are derived by the delta method. See: Casella, G. and Berger, R. L. (2002), Statistical Inference, 2nd ed.

See Also

q.rates

---

qsurvival.nllik	*Negative Log-Likelihood of a Survival Function*

Description

Using a survival function on a specified distribution with a given set of parameters, computes the negative log-likelihood

Usage

```
qsurvival.nllik(dist, complete.lifespans, censored.lifespans, Q, ...)
```

Arguments

dist	A text description of the distribution to use, e.g. emg or norm
complete.lifespans	
	A vector of observations of complete lifespans
censored.lifespans	
	A vector of incomplete observations of lifespans
Q	The percent of population in quiescence or non-dividing
...	Specific parameters to the dist specified

Value

A numeric value of the negative log-likelihood for the given parameters.

Author(s)

Darren Tyson, Shawn Garbett

See Also

mle-class q.mle.norm.estimate q.mle.emg.estimate q.rates

Examples

```
data(ca1d.erlotinib)
mitotic.lifespans <-
  subset(ca1d.erlotinib, !End.of.Expt &
                         !Death        &
                         !is.na(Lifespan))$Lifespan
censored.lifespans <-
  subset(ca1d.erlotinib, End.of.Expt  &
                         !Death        &
                         !is.na(Lifespan))$Lifespan

mle(function(mean, sd, Q){
    qsurvival.nllik("norm", mitotic.lifespans, censored.lifespans, Q, mean, sd)
  },
  method='L-BFGS-B',
  lower=list(mean=8,  sd=0.1, Q=0.01),
  upper=list(mean=30, sd=20,  Q=0.9),
  start=list(mean=mean(mitotic.lifespans),
             sd=sd(mitotic.lifespans),
             Q = 0.5))
```

---

split	*Piecewise curves for rates which change in the middle of an experiment*

Description

This helper functions provide the same functionality as the prolif_tot set of functions, but with the additional assumption that rates change at some breakpoint during the dataset.

Usage

```
split_tot(t, x0, q0, d1, d2, q1, q2, ad1, aq1, ad2, aq2, br=20)
split_d( t, x0, q0, d1, d2, q1, q2, ad1, aq1, ad2, aq2, br=20)
split_q( t, x0, q0, d1, d2, q1, q2, ad1, aq1, ad2, aq2, br=20)
split_fd( t, x0, q0, d1, d2, q1, q2, ad1, aq1, ad2, aq2, br=20)
split_fq( t, x0, q0, d1, d2, q1, q2, ad1, aq1, ad2, aq2, br=20)
```

Arguments

t	A vector time points to return expected population size.
x0	The size of the initial propagating (or dividing) population at t=0.
q0	The size of the quiescent or non-propagating population at t=0.
d1	The rate of growth of the propagating population in the first section.
d2	The rate of growth of the propagating population in the second section.
q1	The rate at which propagating population members join the quiescent population in the first section.

q2	The rate at which propagating population members join the quiescent population in the second section.
ad1	The rate of death from the dividing or propagating population in the first section.
aq1	The rate of death from the quiescent population in the first section.
ad2	The rate of death from the dividing or propagating population in the second section.
aq2	The rate of death from the quiescent population in the second section.
br	The time breakpoint for the change in rate

Value

A numerical vector of expected (sub)population totals (or fraction)

Author(s)

Darren Tyson, Shawn Garbett

References

The method of determining growth rate is taken from *Powell E.0. (1956). Growth Rate and Generation Time of Bacteria, with Special Reference to Continuous Culture. J.Gen.Microbial V15,492-511.* This makes a robust estimator in the presence of skewed distributions.

See Also

prolif_tot prolif_d prolif_q prolif_fd prolif_fq

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