

# Package ‘consensus’

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**Title** Cross-platform consensus analysis of genomic measurements via interlaboratory testing method

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**Description** An implementation of the American Society for Testing and Materials (ASTM) Standard E691 for interlaboratory testing procedures, designed for cross-platform genomic measurements. Given three (3) or more genomic platforms or laboratory protocols, this package provides interlaboratory testing procedures giving per-locus comparisons for sensitivity and precision between platforms.

**Depends** R (>= 3.5), RColorBrewer

**Imports** matrixStats, gplots, grDevices, methods, graphics, stats, utils

**biocViews** QualityControl, Regression, DataRepresentation, GeneExpression, Microarray, RNASeq

**Suggests** knitr, RUnit, rmarkdown, BiocGenerics

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### Description

An implementation of the American Society for Testing and Materials (ASTM) Standard E691 for interlaboratory testing procedures, designed for cross-platform genomic measurements. Given three (3) or more genomic platforms or laboratory protocols, this package provides interlaboratory testing procedures giving per-locus comparisons for sensitivity and precision between platforms.

### Author(s)

Tim J. Peters <t.peters@garvan.org.au>

### Examples

```
data("TCGA")
tcga_mm <- MultiMeasure(names=c("U133A", "Huex", "Agilent", "RNA-Seq"),
data=list(U133A, Huex, Agilent, RNASeq))
fit <- fitConsensus(tcga_mm)
```

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Agilent	<i>Agilent microarray gene expression data</i>
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---

### Description

Gene expression data from 27 Glioblastoma Multiforme (GBM) patients measured on a custom Agilent Gene Expression Microarray.

### Usage

```
data("TCGA")
```

**Format**

Numeric matrix.

**Source**

[https://tcga-data.nci.nih.gov/docs/publications/gbm\\_exp/UNC202.txt](https://tcga-data.nci.nih.gov/docs/publications/gbm_exp/UNC202.txt)

**References**

Verhaak, R. G. W., Hoadley, K. A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M. D., ..., Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*, 2010, 17(1), 98-110.

**Examples**

```
data("TCGA")
```

---

consensus-internal      *Internal consensus objects and functions*

---

**Description**

Internal consensus objects and functions

---

ConsensusFit-class      *Row-linear fit from multiple platforms/conditions - class*

---

**Description**

An S4 class that stores parameter value output from [fitConsensus](#).

**Slots**

This class has eight slots, each containing parameters from the row-linear fit:

**a\_i**: Platform-wise average (intercepts).

**b\_i**: Platform-wise sensitivity (slopes).

**d\_i**: Platform-wise precision (residual mean squares). Note that higher values correspond to lower precision.

**V\_a**: Variance of **a\_i**. High values indicate high discordance in dynamic range.

**V\_b**: Variance of **b\_i**. High values indicate high discordance in sensitivity.

**V\_d**: Averaged precision across platforms.

$z_0$ : Point of approximate concurrence for all regression lines. Only applicable when  $a_i$  and  $b_i$  are highly correlated. See Equations 13.16 and 13.39 of Mandel (2012).

$V_{\text{delta}}$ : Residual variance about the line when  $b_i$  is regressed against  $a_i$ . Lower values indicate a higher degree of concurrence, assuming that  $a_i$  and  $b_i$  are highly correlated. See Equation 13.36 of Mandel (2012).

## Methods

ConsensusFit objects have a show method that describes the dimensions of the data, in the form: "ConsensusFit object with  $i$  platforms/conditions and  $k$  measured loci".

## Author(s)

Tim Peters <t.peters@garvan.org.au>

## References

Mandel, J. (2012). The statistical analysis of experimental data. Courier Corporation. Chapter 13: *The Systematic Evaluation of Measuring Processes*.

## See Also

[fitConsensus](#): outputs ConsensusFit objects.

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fitConsensus	<i>Fit row-linear models to all loci</i>
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## Description

The main function of this package. Fits a number of row-linear models from a [MultiMeasure](#) object, one for each matching row of the data matrices contained within it. Outputs a ConsensusFit object containing per-platform, per locus consensus values for average, sensitivity and precision.

## Usage

```
fitConsensus(multimeas)
```

## Arguments

multimeas      An object of class [MultiMeasure](#).

## Details

For each locus, a row-linear model (Mandel 1994) is fit of the form

$$Z_{ij} = a_i + b_i(x_j - \bar{x}) + d_{ij}$$

where  $Z_{ij}$  is a matrix of measurements at the same genomic locus  $k$ , the row index  $i = 1, \dots, p$  labels the platform or condition (microarray, library prep method for sequencing assay etc.) used and the column index  $j = 1, \dots, n$  labels the biological samples that are interrogated at that locus on each of the  $p$  platforms. Hence  $a_i$  is the intercept (row averages of  $Z_{ij}$ ),  $b_i$  the slope of the regression line (sensitivity) and  $d_i = (n - 2)^{-1} \sum_j d_{ij}^2$  the residual mean square (precision) about the  $i$ th fitted line, noting that higher  $d_i$  corresponds to lower precision. Values of  $a_i$ ,  $b_i$  and  $d_i$  can be found in the slots of the ConsensusFit object.

For `MultiMeasure` objects with 10,000 loci or more, a progress message is printed for every 10,000 loci fitted.

## Value

A ConsensusFit object with slots containing various parameter values from the row-linear fits. More information can be found in the linked class description. Output from this function can then be passed to various plotting functions for data exploration.

## Author(s)

Tim Peters <t.peters@garvan.org.au>

## References

Mandel, J. (1994). Analyzing Interlaboratory Data According to ASTM Standard E691. In *Quality and Statistics: Total Quality Management* (pp. 59-59-12). 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959: ASTM International.

Mandel, J. (2012). The statistical analysis of experimental data. Courier Corporation. Chapter 13: "The Systematic Evaluation of Measuring Processes".

Ku, H.H. (1969). Precision Measurement and Calibration. Volume 1. Statistical Concepts and Procedures (No. NBS-SP-300-VOL-1). Issued February 1969. US Department of Commerce. Chapter 3.7: "The Interlaboratory Evaluation of Testing Methods". Mandel, J. and Lashof, T.W. p. 170.

## Examples

```
data("TCGA")
tcga_mm <- MultiMeasure(names=c("U133A", "Huex", "Agilent", "RNA-Seq"),
data=list(U133A, Huex, Agilent, RNASeq))
fit <- fitConsensus(tcga_mm)
```

Huex

*Affymetrix Huex gene expression data*

---

**Description**

Gene expression data from 27 Glioblastoma Multiforme (GBM) patients measured on the Affymetrix HuEx GeneChip.

**Usage**

```
data("TCGA")
```

**Format**

Numeric matrix.

**Source**

[https://tcga-data.nci.nih.gov/docs/publications/gbm\\_exp/LBL202.txt](https://tcga-data.nci.nih.gov/docs/publications/gbm_exp/LBL202.txt)

**References**

Verhaak, R. G. W., Hoadley, K. A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M. D., ..., Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*, 2010, 17(1), 98-110.

**Examples**

```
data("TCGA")
```

---

MultiMeasure

*MultiMeasure Constructor*

---

**Description**

Creates a MultiMeasure object from a set of 3 or more numeric matrices, in preparation to pass to fitConsensus.

**Usage**

```
MultiMeasure(names=NA_character_, data=list())
```

**Arguments**

names	character vector contains the names of each data type (e.g. RNA-Seq, Agilent etc.). Must be the same length as data.
data	list of numeric matrices of identical dim, rownames and colnames where each matrix contains the measurements from the platform/condition described in names. Rows of each matrix correspond to genomic features and columns to samples. Must be the same length as, and have order correspond to, names.

**Details**

A MultiMeasure contains a list of numeric matrices with identical dimensions and matching row names and column names, to which multiple row-linear models can be fit using `fitConsensus`. Users should pass a vector of names describing the platform/conditions the genomic measurements are made under, and a corresponding list of matrices to the data argument. A series of validity checks will be made on data correctness and a helpful error message will be returned if the structure does not conform to the above description.

**Value**

a `MultiMeasure` object

**Author(s)**

Tim Peters <t.peters@garvan.org.au>

**See Also**

`MultiMeasure-class`

**Examples**

```
data(TCGA)
tcga_mm <- MultiMeasure(names=c("U133A", "Huex", "Agilent", "RNA-Seq"),
data=list(U133A, Huex, Agilent, RNASeq))
```

---

`MultiMeasure-class`     *Multi-platform genomic measurements across the same samples - class*

---

**Description**

An S4 class that stores normalised matched genomic data from multiple platforms and/or laboratory conditions (e.g. from microarrays, RNA-Seq and other sequencing assays).

**List Components**

This class has two slots, names and data.

**names:** character vector contains the names of each data type (e.g. RNA-Seq, Agilent etc.). Must be the same length as data.

**data:** list of numeric matrices of identical dim, rownames and colnames where each matrix contains the measurements from the platform/condition described in names. Rows of each matrix correspond to genomic features and columns to samples. Must be the same length as names.

**Methods**

MultiMeasure objects have a show method that describes the dimensions of the data, in the form: MultiMeasure object with *i* platforms/conditions, *j* samples and *k* measured loci.

**Author(s)**

Tim Peters <t.peters@garvan.org.au>

**See Also**

[MultiMeasure](#) constructs MultiMeasure objects.

---

plotMarginals

*Density plots of per-platform marginal distributions*

---

**Description**

Plots a series of marginal densities for each platform for either (a) average, (b) sensitivity or (c) precision.

**Usage**

```
plotMarginals(consfit,
               param=c("average", "sensitivity", "precision"),
               pal=palette(), xlim=NULL, ...)
```

**Arguments**

consfit	An object of class ConsensusFit.
param	Whether average ( $a_i$ ), sensitivity ( $b_i$ ) or precision ( $d_i$ ) is plotted.
pal	Colour palette. Length must be at least the number of platforms/conditions.
xlim	Range of values to be plotted. If NULL then the entire density is plotted.
...	Extra arguments passed to legend().

**Details**

Precision is plotted on the log scale.

**Value**

A plot to the current device.

**Author(s)**

Tim Peters <t.peters@garvan.org.au>

**Examples**

```
data("TCGA")
tcga_mm <- MultiMeasure(names=c("U133A", "Huex", "Agilent", "RNASeq"),
  data=list(U133A, Huex, Agilent, RNASeq))
fit <- fitConsensus(tcga_mm)
plotMarginals(fit, "sensitivity", brewer.pal(n = 4, name = "Dark2"))
```

---

plotMostDiscordant      *Plot a heatmap showing a selection of loci*

---

**Description**

Plots a heatmap of a specified number of loci showing per-platform, values for either (a) average ( $a_i$ ), (b) sensitivity ( $b_i$ ) or (c) precision ( $d_i$ ) for the most discordant for each. Discordance is ranked by  $V(a_i)$ ,  $V(b_i)$  or  $\frac{\Sigma(d_i)}{p-1}$  where  $p$  = the number of platforms/conditions.

**Usage**

```
plotMostDiscordant(consfit, param=c("average", "sensitivity", "precision"),
  numloci=20, pal=colorRampPalette(brewer.pal(9, "RdYlGn")))
```

**Arguments**

consfit	An object of class ConsensusFit.
param	Whether average ( $a_i$ ), sensitivity ( $b_i$ ) or precision ( $d_i$ ) is plotted.
numloci	The number of loci to plot.
pal	Colour palette. Length must be at least the number of platforms/conditions.

**Value**

A plot to the current device.

**Author(s)**

Tim Peters <t.peters@garvan.org.au>

## Examples

```
data("TCGA")
tcga_mm <- MultiMeasure(names=c("U133A", "Huex", "Agilent", "RNASeq"),
data=list(U133A, Huex, Agilent, RNASeq))
fit <- fitConsensus(tcga_mm)
plotMostDiscordant(fit, "sensitivity", 25)
```

---

plotOneFit

*Plot a single row-linear fit from a genomic locus*

---

## Description

Plots a series of regressions of platform measurements against their consensus mean.

## Usage

```
plotOneFit(multimeas, idx, pal=palette(), ...)
```

## Arguments

multimeas	An object of class MultiMeasure.
idx	Row index of the set of matrices in multimeas.
pal	Color palette. Length must be at least the length of multimeas@data.
...	Extra arguments passed to legend().

## Details

Visualises a row-linear fit explicitly in the measurement space. Steeper (positive) slopes mean greater sensitivity, and greater scatter around the regression line indicates lower precision.

## Value

A plot to the current device.

## Author(s)

Tim Peters <t.peters@garvan.org.au>

## Examples

```
data("TCGA")
tcga_mm <- MultiMeasure(names=c("U133A", "Huex", "Agilent", "RNASeq"),
data=list(U133A, Huex, Agilent, RNASeq))
plotOneFit(tcga_mm, "TP53", brewer.pal(n = 4, name = "Dark2"))
```

---

RNASeq

*RNA-Seq gene expression data*

---

**Description**

Limma-voom normalised gene expression data from 27 Glioblastoma Multiforme (GBM) patients measured via RNA-Seq.

**Usage**

```
data("TCGA")
```

**Format**

Numeric matrix.

**Source**

<https://portal.gdc.cancer.gov/>

**References**

Verhaak, R. G. W., Hoadley, K. A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M. D., ..., Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*, 2010, 17(1), 98-110.

**Examples**

```
data("TCGA")
```

---

U133A

*Affymetrix U133A gene expression data*

---

**Description**

Log-transformed gene expression data from 27 Glioblastoma Multiforme (GBM) patients measured on the Affymetrix-HT-HG-U133A GeneChip.

**Usage**

```
data("TCGA")
```

**Format**

Numeric matrix.

**Source**

[https://tcga-data.nci.nih.gov/docs/publications/gbm\\_exp/Broad202.txt](https://tcga-data.nci.nih.gov/docs/publications/gbm_exp/Broad202.txt)

**References**

Verhaak, R. G. W., Hoadley, K. A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M. D., ..., Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*, 2010, 17(1), 98-110.

**Examples**

```
data("TCGA")
```

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