

Package ‘KWELA’

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Type Package

Title Hierarchical Adaptive 'RT-QuIC' Classification for Complex Matrices

Version 1.0.0

Description Extends 'RT-QuIC' (Real-Time Quaking-Induced Conversion) statistical analysis to complex environmental matrices through hierarchical adaptive classification. 'KWELA' is named after a deity of the Fore people of Papua New Guinea, among whom Kuru, a notable human prion disease, was identified. Implements a 6-layer architecture: hard gate biological constraints, per-well adaptive scoring, separation-aware combination, Youden-optimized cutoffs, replicate consensus, and matrix instability detection. Features dual-mode operation (diagnostic/research), auto-profile selection (Standard/Sensitive/Matrix-Robust), RAF integration for artifact detection, matrix-aware baseline correction, and multiple consensus rules. Methods include energy distance (Szekely and Rizzo (2013) <doi:10.1016/j.jspi.2013.03.018>), CRPS (Gneiting and Raftery (2007) <doi:10.1198/016214506000001437>), SSMD (Zhang (2007) <doi:10.1016/j.ygeno.2007.01.005>), and Jensen-Shannon divergence (Lin (1991) <doi:10.1109/18.61115>). This package implements methodology currently under peer review; please contact the author before publication using this approach. Development followed an iterative human-machine collaboration where all algorithmic design, statistical methodologies, and biological validation logic were conceptualized, tested, and iteratively refined by Richard A. Feiss through repeated cycles of running experimental data, evaluating analytical outputs, and selecting among candidate algorithms and approaches. AI systems ('Anthropic Claude' and 'OpenAI GPT') served as coding assistants and analytical sounding boards under continuous human direction. The selection of statistical methods, evaluation of biological plausibility, and all final methodology decisions were made by the human author. AI systems did not independently originate algorithms, statistical approaches, or scientific methodologies.

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KWELA-package

KWELA: Hierarchical Adaptive 'RT-QuIC' Classification

Description

Extends 'RT-QuIC' (Real-Time Quaking-Induced Conversion) statistical analysis to complex environmental matrices through hierarchical adaptive classification. 'KWELA' is named after a deity of the Fore people of Papua New Guinea, among whom Kuru, a notable human prion disease, was identified.

Value

No return value. This is a package documentation page.

6-Layer Architecture

- Layer 1: Hard Gate** Biological constraint filter
- Layer 2: Per-Well Scoring** Profile-dependent adaptive transforms
- Layer 3: Adaptive Combination** Separation-aware score combiner
- Layer 4: Adaptive Cutoff** Youden-optimized threshold
- Layer 5: Replicate Consensus** Treatment-level classification
- Layer 6: Instability Detection** Matrix interference override

Dual-Mode Operation

diagnostic Default mode. Deterministic classification from TTT/MP/RAF evidence only. No stochastic rescue or score blending.

research Full adaptive architecture with stochastic rescue and distributional scoring.

Main Functions

- `kwela_analyze` Main analysis function
- `kwela_summarize` Treatment-level summary
- `kwela_diagnostics` Diagnostic information
- `compute_instability_flags` Matrix instability detection

Plate/Batch Functions

- `kwela_plate_normalize` Multi-plate normalization
- `kwela_bootstrap_summary` Bootstrap confidence intervals

cohens_d

Separation Quality Assessment

Description

`cohens_d` computes Cohen's d effect size between two distributions.

`assess_separation` evaluates PC/NC separation quality and recommends a classification profile. Cohen's d thresholds are heuristic, calibrated against three RT-QuIC datasets.

Usage

```
cohens_d(x, y)
```

```
assess_separation(pc_mp, nc_mp, pc_ttt, nc_ttt)
```

Arguments

| | |
|--------|--------------------------------------|
| x | First distribution (numeric vector) |
| y | Second distribution (numeric vector) |
| pc_mp | Positive control MP values |
| nc_mp | Negative control MP values |
| pc_ttt | Positive control TTT values |
| nc_ttt | Negative control TTT values |

Value

cohens_d returns a single numeric value (positive = $x > y$), or NA_real_ if insufficient data.

assess_separation returns a list with:

d_mp Cohen's d for MP

d_ttt Cohen's d for TTT

d_combined Median of absolute d values

regime Separation regime: "poor_separation", "moderate_separation", or "strong_separation"

recommended_profile Recommended profile: "matrix_robust", "sensitive", or "standard"

Examples

```
set.seed(42)
pc_mp <- rnorm(8, 100, 10)
nc_mp <- rnorm(8, 20, 5)
pc_ttt <- rnorm(8, 8, 1)
nc_ttt <- rnorm(8, 72, 5)

cohens_d(pc_mp, nc_mp)
assess_separation(pc_mp, nc_mp, pc_ttt, nc_ttt)
```

compute_instability_flags

Compute Instability Flags for a Treatment

Description

Evaluates 6 deterministic metrics to detect matrix interference that compromises classification reliability. A treatment is flagged as unstable when it behaves unlike both positive and negative controls.

Usage

```
compute_instability_flags(
  trt_mp,
  trt_ttt,
  pc_mp,
  nc_mp,
  pc_ttt,
  nc_ttt,
  trt_raf = NULL,
  trt_mp_raf = NULL,
  pc_raf_mp_ratios = NULL,
  crossing_threshold = NA_real_,
  strictness = "moderate",
  has_raf = FALSE
)
```

Arguments

| | |
|--------------------|--|
| trt_mp | Finite MP values for treatment wells |
| trt_ttt | TTT values for treatment wells (may contain NA/Inf) |
| pc_mp, nc_mp | Positive/negative control MP values (finite) |
| pc_ttt, nc_ttt | Positive/negative control TTT values |
| trt_raf | RAF values for treatment wells (NULL if unavailable) |
| trt_mp_raf | MP values corresponding to RAF wells (NULL if unavailable) |
| pc_raf_mp_ratios | RAF/MP ratios from positive controls (NULL if unavailable) |
| crossing_threshold | TTT crossing threshold for this treatment's group |
| strictness | "moderate" (2+ flags), "strict" (1+), or "lenient" (3+) |
| has_raf | Whether RAF data is available |

Details

The six metrics evaluated are:

1. Fano factor deviation from positive controls
2. Crossing variability (ambiguous threshold crossing rate)
3. Wasserstein distance from BOTH controls (normalized by NC spread)
4. Energy distance from BOTH controls (normalized by NC spread)
5. TTT dispersion ratio vs positive controls
6. RAF-MP ratio inconsistency vs positive controls

All metrics are deterministic (no random number generation).

Value

List with components: `unstable` (logical), `reasons` (character vector), `n_flags` (integer), `min_flags_required` (integer), `metrics` (named list).

Examples

```
set.seed(42)
flags <- compute_instability_flags(
  trt_mp = rnorm(8, 50, 20),
  trt_ttt = rnorm(8, 40, 15),
  pc_mp = rnorm(8, 100, 10),
  nc_mp = rnorm(8, 20, 5),
  pc_ttt = rnorm(8, 8, 1),
  nc_ttt = rnorm(8, 72, 5),
  crossing_threshold = 40,
  strictness = "moderate"
)
```

compute_stochastic_profile

Compute Stochastic Profile

Description

Computes comprehensive stochastic metrics for a sample compared to controls.

Usage

```
compute_stochastic_profile(sample_values, pc_values, nc_values)
```

Arguments

| | |
|----------------------------|---|
| <code>sample_values</code> | Numeric vector of sample measurements |
| <code>pc_values</code> | Numeric vector of positive control measurements |
| <code>nc_values</code> | Numeric vector of negative control measurements |

Value

List containing comprehensive stochastic metrics:

mean, var, cv, fano Basic sample statistics

cv_ratio_pc, cv_ratio_nc CV ratios vs controls

fano_ratio_pc Fano factor ratio vs PC

stochastic_index Normalized position between NC and PC variance

ssmd_vs_nc, ssmd_vs_pc SSMD vs controls

snr Signal-to-noise ratio vs NC

js_vs_pc, js_vs_nc, js_ratio Jensen-Shannon metrics
energy_vs_pc, energy_vs_nc, energy_ratio Energy distance metrics
wasserstein_vs_pc, wasserstein_vs_nc, wasserstein_ratio Wasserstein metrics
log_dist_pc, log_dist_nc Log-space Euclidean distances

Examples

```
set.seed(42)
pc <- rnorm(20, 100, 10)
nc <- rnorm(20, 20, 5)
sample <- rnorm(20, 80, 15)
profile <- compute_stochastic_profile(sample, pc, nc)
```

crps_empirical *Proper Scoring Rules*

Description

Proper scoring rules for evaluating probabilistic forecasts.

Usage

```
crps_empirical(forecast_samples, observation)

dawid_sebastiani(observation, predicted_mean, predicted_var)

log_predictive_score(observation, predicted_mean, predicted_sd)

interval_score(observation, lower, upper, alpha = 0.1)
```

Arguments

| | |
|------------------|---|
| forecast_samples | Numeric vector of samples from forecast distribution |
| observation | Single observed value |
| predicted_mean | Predicted mean |
| predicted_var | Predicted variance |
| predicted_sd | Predicted standard deviation |
| lower | Lower bound of prediction interval |
| upper | Upper bound of prediction interval |
| alpha | Nominal miscoverage rate (default 0.1 for 90% interval) |

Value

All functions return a single numeric value or `NA_real_` if inputs are invalid.

`crps_empirical` returns a non-negative score (lower is better).

`dawid_sebastiani` returns the DS score (calibration metric).

`log_predictive_score` returns negative log density.

`interval_score` returns width plus penalties for miscoverage.

References

Gneiting T, Raftery AE (2007). Strictly proper scoring rules, prediction, and estimation. *Journal of the American Statistical Association* 102(477):359-378.

Examples

```
set.seed(42)
forecast <- rnorm(50, 5, 1)

crps_empirical(forecast, 5.5)
dawid_sebastiani(5.5, 5, 1)
log_predictive_score(5.5, 5, 1)
interval_score(5.5, 3, 7, alpha = 0.1)
```

cv

Stochasticity Metrics

Description

Functions for quantifying stochastic variability in RT-QuIC data.

Usage

```
cv(x)

fano_factor(x)

ssmd(treatment, control)

normalized_stochastic_index(treatment_var, pc_var, nc_var)

snr_vs_control(treatment, control)
```

Arguments

| | |
|---------------|------------------------------------|
| x | Numeric vector |
| treatment | Numeric vector of treatment values |
| control | Numeric vector of control values |
| treatment_var | Treatment variance |
| pc_var | Positive control variance |
| nc_var | Negative control variance |

Value

All functions return a single numeric value or NA_real_ if insufficient data.

cv returns the coefficient of variation (MAD-based).

fano_factor returns the variance-to-mean ratio.

ssmd returns the strictly standardized mean difference.

normalized_stochastic_index returns a value in [0, 1].

snr_vs_control returns the signal-to-noise ratio.

References

Zhang XHD (2007). A pair of new statistical parameters for quality control in RNA interference high-throughput screening assays. *Genomics* 89(4):552-61.

Examples

```
set.seed(42)
x <- rnorm(30, 10, 2)
y <- rnorm(30, 5, 2)

cv(x)
fano_factor(x + 10)
ssmd(x, y)
snr_vs_control(x, y)
normalized_stochastic_index(var(x), 4, 1)
```

energy_distance *Distance Metrics*

Description

Geometric distance metrics for comparing distributions.

energy_distance uses deterministic quantile subsampling for large datasets (no RNG dependency).

Usage

```
energy_distance(x, y, max_n = NULL)

wasserstein_1d(x, y)

log_euclidean_distance(x, y)

mahalanobis_distance(sample_params, reference_mean, reference_cov)
```

Arguments

| | |
|----------------|--|
| x | First distribution (numeric vector) |
| y | Second distribution (numeric vector) |
| max_n | Maximum sample size before subsampling (NULL = no limit) |
| sample_params | Named numeric vector of sample parameters |
| reference_mean | Named numeric vector of reference means |
| reference_cov | Covariance matrix of reference distribution |

Value

All functions return a single non-negative numeric value or `NA_real_` if insufficient data or computation fails.

References

Szekely GJ, Rizzo ML (2013). Energy statistics: A class of statistics based on distances. *Journal of Statistical Planning and Inference* 143(8):1249-72.

Examples

```
set.seed(42)
x <- rnorm(30, 0, 1)
y <- rnorm(30, 2, 1)

energy_distance(x, y)
wasserstein_1d(x, y)
log_euclidean_distance(exp(x), exp(y))
mahalanobis_distance(c(1, 2), c(0, 0), diag(2))
```

entropy

Information-Theoretic Metrics

Description

entropy computes Shannon entropy from discretized distribution.

jensen_shannon computes symmetric Jensen-Shannon divergence with Laplace smoothing.

Usage

```
entropy(x, n_bins = 10)

jensen_shannon(p, q, n_bins = 15)
```

Arguments

| | |
|--------|--------------------------------------|
| x | Numeric vector |
| n_bins | Number of histogram bins |
| p | First distribution (numeric vector) |
| q | Second distribution (numeric vector) |

Value

entropy returns entropy in nats, or NA_real_ if fewer than 3 values.

jensen_shannon returns JSD bounded in $[0, \ln(2)]$, or NA_real_ if either distribution has fewer than 5 values.

References

Lin J (1991). Divergence measures based on the Shannon entropy. *IEEE Transactions on Information Theory* 37(1):145-151.

Examples

```
entropy(rnorm(100))

set.seed(42)
p <- rnorm(50, 0, 1)
q <- rnorm(50, 2, 1)
jensen_shannon(p, q)
```

kwela_analyze

KWELA Main Analysis Function

Description

Implements hierarchical adaptive classification for 'RT-QuIC' data:

- Layer 1: Hard Gate** Biological constraint filter
- Layer 2: Per-Well Scoring** Profile-dependent transforms
- Layer 3: Adaptive Combination** Separation-aware combiner
- Layer 4: Adaptive Cutoff** Youden-optimized threshold
- Layer 5: Replicate Consensus** Treatment-level classification
- Layer 6: Instability Detection** Matrix interference override

Usage

```
kwela_analyze(
  data,
  pc_pattern = "\\bPositive\\s*Control\\b|^POS\\b|\\bPC\\b",
  nc_pattern = "\\bNegative\\s*Control\\b|^NEG\\b|\\bNC\\b|\\bTDB\\b|\\bBlank\\b",
  spiked_pattern = "\\+\\s*Pos|Pos\\s*\\d*%|spiked|\\+\\s*CWD",
  profile = c("auto", "standard", "sensitive", "matrix_robust"),
  consensus = c("majority", "strict", "flexible", "threshold"),
  consensus_threshold = 0.5,
  matrix_groups = NULL,
  use_raf = TRUE,
  mode = c("diagnostic", "research"),
  instability_check = TRUE,
  instability_strictness = c("moderate", "strict", "lenient"),
  verbose = TRUE
)
```

Arguments

| | |
|------------------------|--|
| data | Data frame with Treatment, TTT, MP columns (RAF optional) |
| pc_pattern | Regex for positive controls |
| nc_pattern | Regex for negative controls |
| spiked_pattern | Regex for spiked samples |
| profile | Classification profile: "auto", "standard", "sensitive", or "matrix_robust". "auto" selects based on separation quality. |
| consensus | Replicate consensus rule: "majority", "strict", "flexible", or "threshold" |
| consensus_threshold | For "threshold" consensus: minimum mean well score to classify treatment as positive (default 0.5) |
| matrix_groups | Optional: column name for matrix grouping (enables per-group baseline correction). NULL = global baselines. |
| use_raf | Logical: include RAF in scoring (default TRUE if present) |
| mode | "diagnostic" (deterministic, no stochastic rescue) or "research" (full adaptive architecture). Default: "diagnostic". |
| instability_check | Logical: run instability detection (default TRUE) |
| instability_strictness | "moderate" (2+ flags), "strict" (1+), or "lenient" (3+). Controls override sensitivity. |
| verbose | Print progress |

Value

Data frame with per-well results including:

Type Well type: "PC", "NC", or "Sample"

is_spiked Logical indicating if sample is spiked
crossed_threshold Logical for TTT threshold crossing
has_signal Logical for signal above NC threshold
hard_gate_pass Logical for Layer 1 gate passage
artifact_flag Logical for suspected artifacts
stoch_rescue Logical for stochastic rescue (research mode only)
ttt_score TTT component score (0-1)
signal_score Signal component score (0-1)
raf_score RAF component score (0-1, if available)
stoch_score Stochastic component score (0-1)
well_score Combined well score (0-1)
well_positive Logical for well-level positive classification
seed_score Alias for well_score
classification Well classification: "POSITIVE", "NEGATIVE", "INCONCLUSIVE", "ARTIFACT_SUSPECT", or "INVALID"
confidence Confidence level: "VERY_HIGH", "HIGH", "MODERATE", "LOW", or "CONTROL"
trt_classification Treatment-level consensus classification (may be "INCONCLUSIVE_MATRIX_EFFECT" if instability detected)
trt_confidence Treatment-level confidence
trt_positive_rate Fraction of positive wells in treatment
trt_mean_score Mean well score for treatment
matrix_instability Logical for Layer 6 instability override

Plus attributes: pc_stats, nc_stats, separation, profile, consensus, optimal_cutoff, youden_j, thresholds, trt_summary, control_check, score_semantics, version, mode, instability_check, instability_strictness, instability_summary, group_controls, group_profiles, group_separation.

Examples

```

set.seed(42)
df <- data.frame(
  Treatment = c(rep("Positive Control", 8), rep("Negative Control", 8),
               rep("Sample_A", 8)),
  TTT = c(rnorm(8, 8, 1), rnorm(8, 72, 5), rnorm(8, 12, 3)),
  MP = c(rnorm(8, 100, 10), rnorm(8, 20, 5), rnorm(8, 85, 15))
)
result <- kwela_analyze(df)
summary <- kwela_summarize(result)

```

kwela_plate_normalize *Plate Normalization and Bootstrap*

Description

kwela_plate_normalize normalizes TTT and MP values within each plate using negative control baselines.

kwela_bootstrap_summary computes bootstrap confidence intervals for treatment scores. Set seed externally for reproducibility.

Usage

```
kwela_plate_normalize(
  data,
  plate_col = "Plate",
  pc_pattern = "\\bPositive\\s*Control\\b|^POS\\b|\\bPC\\b",
  nc_pattern = "\\bNegative\\s*Control\\b|^NEG\\b|\\bNC\\b|\\bTDB\\b|\\bBlank\\b",
  method = c("zscore", "median_ratio")
)

kwela_bootstrap_summary(result, B = 1000, conf = 0.95)
```

Arguments

| | |
|------------|--|
| data | Data frame with Treatment, TTT, MP columns |
| plate_col | Name of plate identifier column |
| pc_pattern | Regex for positive controls |
| nc_pattern | Regex for negative controls |
| method | Normalization method: "zscore" or "median_ratio" |
| result | Output from kwela_analyze |
| B | Number of bootstrap replicates (default 1000) |
| conf | Confidence level (default 0.95) |

Value

kwela_plate_normalize returns a data frame with added columns:

plate_id Plate identifier
TTT_norm Normalized TTT values
MP_norm Normalized MP values

kwela_bootstrap_summary returns a data frame with:

Treatment Treatment name
n_wells Number of wells

mean_score Mean well score
score_lo Lower CI bound for mean score
score_hi Upper CI bound for mean score
positive_rate Observed positive rate
pr_lo Lower CI bound for positive rate
pr_hi Upper CI bound for positive rate

Examples

```
set.seed(42)
df <- data.frame(
  Treatment = c(rep("Positive Control", 4), rep("Negative Control", 4),
                rep("Sample_A", 4)),
  TTT = c(rnorm(4, 8, 1), rnorm(4, 72, 5), rnorm(4, 12, 3)),
  MP = c(rnorm(4, 100, 10), rnorm(4, 20, 5), rnorm(4, 85, 15)),
  Plate = rep("Plate1", 12)
)
normalized <- kwela_plate_normalize(df)

# Bootstrap example
result <- kwela_analyze(df, verbose = FALSE)
set.seed(123)
boot <- kwela_bootstrap_summary(result, B = 500)
```

| | |
|-----------------|--------------------------------------|
| kwela_summarize | <i>KWELA Summary and Diagnostics</i> |
|-----------------|--------------------------------------|

Description

kwela_summarize extracts treatment-level consensus results.

kwela_diagnostics returns detailed diagnostic information.

Usage

```
kwela_summarize(result)
```

```
kwela_diagnostics(result)
```

Arguments

result Output from kwela_analyze

Value

kwela_summarize returns a data frame with treatment-level results:

Treatment Treatment name
n_wells Number of wells
n_positive Number of positive wells
positive_rate Fraction positive
mean_score Mean well score
classification Treatment classification
confidence Confidence level
consensus_rule Consensus rule used
is_spiked Whether treatment is spiked

kwela_diagnostics returns a list with:

version KWELA version string
mode Analysis mode ("diagnostic" or "research")
profile Profile used
consensus Consensus rule used
optimal_cutoff Youden-optimized cutoff
youden_j Youden J statistic
separation Separation quality metrics
well_level Well-level statistics
treatment_level Treatment-level statistics
instability Instability detection results: check_enabled, strictness, n_inconclusive_matrix, treatments_flagged
n_samples Number of sample wells
n_spiked Number of spiked wells
n_unspiked Number of unspiked wells

Examples

```
set.seed(42)
df <- data.frame(
  Treatment = c(rep("Positive Control", 8), rep("Negative Control", 8),
               rep("Sample_A", 8)),
  TTT = c(rnorm(8, 8, 1), rnorm(8, 72, 5), rnorm(8, 12, 3)),
  MP = c(rnorm(8, 100, 10), rnorm(8, 20, 5), rnorm(8, 85, 15))
)
result <- kwela_analyze(df, verbose = FALSE)
summary <- kwela_summarize(result)
diag <- kwela_diagnostics(result)
```

| | |
|--------------|--------------------------|
| robust_scale | <i>Utility Functions</i> |
|--------------|--------------------------|

Description

robust_scale provides MAD-based scale estimation.
safe_sd provides a guaranteed-positive standard deviation.

Usage

```
robust_scale(x)  
  
safe_sd(x, na.rm = TRUE)
```

Arguments

| | |
|-------|---------------------------------------|
| x | Numeric vector |
| na.rm | Logical; should NA values be removed? |

Value

robust_scale returns a robust scale estimate using MAD with fallback to IQR/1.349 and SD. Returns NA_real_ if fewer than 2 values.

safe_sd returns standard deviation, guaranteed to be positive (returns machine epsilon if zero or NA).

Examples

```
robust_scale(rnorm(50))  
robust_scale(c(1, 2, 3, 100))  
  
safe_sd(c(5, 5, 5))
```

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