Harmonization Function and Parameter Errors

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Contents

Data loading

In this document we harmonize calibration curves between two matrices:

- **SU** (reference matrix)
- **POOL** (target matrix to be scaled and shifted)

We work with two analytes: *anisole* and *heptanone*.

```
## 'data.frame':    28 obs. of  2 variables:
##  $ concentration: num  10.326 30.326 0.326 20.326 5.326 ...
##  $ intensity    : num  1331.8 2088.8 44.6 1862 885.7 ...
```

```
## 'data.frame':    28 obs. of  2 variables:
##  $ concentration: num  10 30 0 20 5 10 30 0 20 5 ...
##  $ intensity    : num  1013 1593.2 21.9 1462.2 642.6 ...
```

Harmonization function

Methodology

The objective is to determine the **scale** and **shift** parameters that optimally transform the SU calibration curve so that it aligns with the POOL measurements.

The procedure is:

1. Fit a **third-degree polynomial model** to the SU calibration data (no intercept).
2. Evaluate this polynomial on a dense concentration grid to obtain a smooth SU curve.
3. For each candidate pair *(scale, shift)* in a predefined grid:
    - Transform the SU concentration axis using

$$C \mapsto \frac{C}{\text{scale}} - \text{shift}$$

* Interpolate the transformed SU curve onto the POOL concentration points. * Compute a loss value (with optional variance normalisation). 4. Select the *(scale, shift)* pair that **minimises the loss**. 5. Fit a **local quadratic surface (paraboloid)** to the loss landscape around the optimum to estimate parameter uncertainties.

Quadratic model (local paraboloid approximation)

Locally around the optimum (s_0, t_0), the normalised loss function is expanded up to second order:

$$L(s,t) \approx L_{\min} + a\,(s-s_0)^2 + b\,(t-t_0)^2 + c\,(s-s_0)(t-t_0).$$

Defining the displacement vector

$$\mathbf{x} = \begin{pmatrix} s - s_0 \\ t - t_0 \end{pmatrix},$$

the quadratic term can be written in matrix form:

$$L(s,t) - L_{\min} \;\approx\; \mathbf{x}^T M\,\mathbf{x},$$

where

$$M = \begin{pmatrix} a & c/2 \\ c/2 & b \end{pmatrix}.$$

The **Hessian** of the loss at the optimum is then:

$$H = 2M$$

Covariance of (s, t) from the Hessian

Because the loss is a normalised weighted least-squares function, the variance of the residuals is given by the minimal loss value:

$$\sigma^2 \approx L_{\min}.$$

Under the quadratic approximation, the covariance matrix of the parameters is:

$$\Sigma \;=\; \sigma^2 \, H^{-1} \;=\; L_{\min} \, H^{-1}.$$

Thus,

$$\Sigma = \begin{pmatrix} \Sigma_{ss} & \Sigma_{st} \\ \Sigma_{st} & \Sigma_{tt} \end{pmatrix}, \qquad \Delta s = \sqrt{\Sigma_{ss}}, \qquad \Delta t = \sqrt{\Sigma_{tt}}.$$

The quantities Δs and Δt represent the **standard uncertainties** (standard errors) of the estimated scale and shift parameters, respectively.

Interpretation

- The matrix H describes the **local curvature** of the loss surface.
- Its inverse H^{-1} quantifies how **flat** the minimum is along each direction.
- Multiplying by $L_{\min}$ rescales the curvature by the residual variance of the normalised problem.

Therefore, the uncertainties reported are:

$$s_0 \pm \Delta s, \qquad t_0 \pm \Delta t.$$

Function definition

Principal Function

```r
harmonize <- function(df_target, df_sub,
                      scale_range = c(0.2, 2),
                      shift_range = c(0, 5),
                      n_scale = 200,
                      n_shift = 200,
                      n_grid = 200,
                      min_fraction = 0.5,
                      optimize_shift = TRUE,
                      loss_factor = 2) {

  # 1. Validate & prepare input
  x <- check_and_prepare_input(df_target, df_sub)
  df_target <- x$df_target
  df_sub    <- x$df_sub

  # 2. Fit SU model
  model_su <- fit_su_model(df_sub)

  # 3. Grid SU
  su_grid <- make_su_grid(df_sub, n_grid, model_su)

  # 4. Variance normalisation
  vn <- compute_variance_normalisation(df_target)
  df_target <- vn$df_target

  # 5. Grid search
  scale_seq <- seq(scale_range[1], scale_range[2], length.out = n_scale)
  shift_seq <- if (optimize_shift) seq(shift_range[1], shift_range[2], length.out = n_shift) else 0

  loss_grid <- compute_loss_grid(df_target, su_grid, scale_seq, shift_seq, min_fraction)

  best <- find_best_parameters(loss_grid)

  best_pred <- predict_best_curve(su_grid, df_target, best$best_scale, best$best_shift)

  # 6. Local paraboloid with Hessiana
  parab <- fit_local_paraboloid(
    loss_grid,
    best_scale = best$best_scale,
    best_shift = best$best_shift,
    best_loss  = best$best_loss,
    loss_factor = loss_factor
  )

  # Output structure
  list(
    scale = best$best_scale,
    shift = best$best_shift,
    loss  = best$best_loss,

    scale_error = parab$scale_error,
    shift_error = parab$shift_error,
    loss_threshold = parab$loss_threshold,
    paraboloid = parab,

    fitted_points = df_target %>%
      dplyr::mutate(intensity_pred = best_pred),

    su_grid = su_grid,
    su_grid_trans = tibble::tibble(
      concentration = su_grid$concentration / best$best_scale - best$best_shift,
      intensity     = su_grid$intensity
    ),

    loss_grid = loss_grid,
    variance_norm = vn$use_var_norm,
    min_fraction = min_fraction,
    optimize_shift = optimize_shift
  )
}
```

Auxiliar Functions

```r
# AUXILIAR FUNCTIONS

# VALIDATE AND PREPARE INPUT
check_and_prepare_input <- function(df_target, df_sub) {

  if (!all(c("concentration", "intensity") %in% colnames(df_target)))
    stop("df_target must contain columns 'concentration' and 'intensity'.")

  if (!all(c("concentration", "intensity") %in% colnames(df_sub)))
    stop("df_sub must contain columns 'concentration' and 'intensity'.")

  df_target <- df_target %>%
    dplyr::mutate(
      concentration = as.numeric(concentration),
      intensity     = as.numeric(intensity)
    )

  df_sub <- df_sub %>%
    dplyr::mutate(
      concentration = as.numeric(concentration),
      intensity     = as.numeric(intensity)
    )

  list(df_target = df_target, df_sub = df_sub)
}

# FIT SU MODEL AND PREDICT

fit_su_model <- function(df_sub) {
  lm(intensity ~ poly(concentration, 3, raw = TRUE) - 1, data = df_sub)
}

predict_su <- function(model_su, C) {
  cf <- coef(model_su)
  cf[1] * C + cf[2] * C^2 + cf[3] * C^3
}

# MAKE SU GRID (sample the polynomial model)
make_su_grid <- function(df_sub, n_grid, model_su) {
  C_grid <- seq(0, max(df_sub$concentration, na.rm = TRUE), length.out = n_grid)
  I_grid <- predict_su(model_su, C_grid)
  tibble::tibble(concentration = C_grid, intensity = I_grid)
}

# CHOOSE IF VARIANCE NORMALIZATION IS APPLIED IN THE LOSS

compute_variance_normalisation <- function(df_target) {

  df_var <- df_target %>%
    dplyr::group_by(concentration) %>%
    dplyr::summarise(
      n              = dplyr::n(),
      var_intensity = if (n() > 1) var(intensity) else NA_real_,
      .groups       = "drop"
    )

  use_var_norm <- all(!is.na(df_var$var_intensity)) &&
                  all(df_var$var_intensity > 0) &&
                  all(df_var$n >= 2)

  df_target <- df_target %>%
    dplyr::left_join(df_var, by = "concentration") %>%
    dplyr::mutate(denom = ifelse(use_var_norm, var_intensity, 1))

  list(df_target = df_target, use_var_norm = use_var_norm)
}


# LOSS GRID COMPUTATION

compute_loss_grid <- function(df_target, su_grid, scale_seq, shift_seq, min_fraction) {

  C_t <- df_target$concentration
  I_t <- df_target$intensity
  D_t <- df_target$denom
  n_total <- length(C_t)

  C_grid <- su_grid$concentration
  I_grid <- su_grid$intensity

  loss_grid <- expand.grid(scale = scale_seq, shift = shift_seq)
  loss_grid$loss <- NA_real_

  for (i in seq_len(nrow(loss_grid))) {

    sc <- loss_grid$scale[i]
    sh <- loss_grid$shift[i]

    C_trans <- C_grid / sc - sh

    # Strict interpolation (no extrapolation)
    I_pred <- approx(x = C_trans, y = I_grid, xout = C_t, rule = 1)$y

    # Check the fraction of points within range
    valid <- !is.na(I_pred)

    # Not enough coverage → reject this (scale, shift)
    if (sum(valid) < min_fraction * n_total) {
      loss_grid$loss[i] <- Inf
      next
    }

    # Linear extrapolation only above the SU range
    above <- which(is.na(I_pred) & C_t > max(C_trans))
    if (length(above) > 0) {
      x1 <- C_trans[length(C_trans) - 1]
      x2 <- C_trans[length(C_trans)]
      y1 <- I_grid[length(I_grid) - 1]
      y2 <- I_grid[length(I_grid)]
      slope <- (y2 - y1) / (x2 - x1)
      I_pred[above] <- y2 + slope * (C_t[above] - x2)
    }

    # Compute loss using all points
    res_sq <- (I_t - I_pred)^2
    loss_grid$loss[i] <- mean(res_sq / D_t)
  }

  # Identify non-covered region and report approximate boundary line
  bad <- loss_grid[!is.finite(loss_grid$loss), , drop = FALSE]

  if (nrow(bad) > 2) {

    fit_line <- lm(shift ~ scale, data = bad)
    b0 <- coef(fit_line)[1]   # intercept
    b1 <- coef(fit_line)[2]   # slope

    # Linear boundary in:  a*shift + b*scale >= c
    a <- 1
    b <- -b1
    c <- b0


    cat(
      "Warning: insufficient SU coverage in part of the search grid.\n",
      "Approximate boundary of the uncovered region:\n",
      "   ", a, " * shift  +  ",
                b, " * scale  >=  ",
                c, "\n",
      "Points above this boundary typically fail the minimum coverage criterion.\n",
      "Consider avoiding this region or reducing the 'min_fraction' parameter."
    )
  }

  loss_grid
}


# OPTIMAL PARAMETERS SELECTION

find_best_parameters <- function(loss_grid) {

  finite <- which(is.finite(loss_grid$loss))

  if (length(finite) == 0) {
    return(list(
      best_scale = NA_real_,
      best_shift = NA_real_,
      best_loss  = Inf
    ))
  }

  idx <- finite[which.min(loss_grid$loss[finite])]

  list(
    best_scale = loss_grid$scale[idx],
    best_shift = loss_grid$shift[idx],
    best_loss  = loss_grid$loss[idx]
  )
}

# OPTIMAL CURVE PREDICTION

predict_best_curve <- function(su_grid, df_target, best_scale, best_shift) {

  C_grid <- su_grid$concentration
  I_grid <- su_grid$intensity
  C_t    <- df_target$concentration

  C_trans <- C_grid / best_scale - best_shift
  approx(x = C_trans, y = I_grid, xout = C_t, rule = 1)$y
}


# PARABOLOID AND HESSIAN MATRIX

fit_local_paraboloid <- function(loss_grid,
                                 best_scale,
                                 best_shift,
                                 best_loss,
                                 loss_factor = 2) {

  # ------------------------------------------------------------------
  # SELECT LOCAL REGION AROUND THE MINIMUM
  #
  # We take all points satisfying:
  #       L(scale, shift) <= loss_factor * L_min
  #
  # This defines a contour around the minimum consistent with
  # quadratic approximation theory. It replaces rectangular windows.
  # ------------------------------------------------------------------

  if (!is.finite(best_loss) || best_loss <= 0) {
    return(list(
      a = NA, b = NA, c = NA,
      M = matrix(NA, 2, 2),
      H = matrix(NA, 2, 2),
      H_inv = matrix(NA, 2, 2),
      cov = matrix(NA, 2, 2),
      scale_error = NA,
      shift_error = NA,
```

```r
    loss_threshold = NA
  ))
}

loss_threshold <- loss_factor * best_loss

local <- loss_grid %>%
  dplyr::filter(
    is.finite(loss),
    loss <= loss_threshold
  )

if (nrow(local) < 10) {
  return(list(
    a = NA, b = NA, c = NA,
    M = matrix(NA, 2, 2),
    H = matrix(NA, 2, 2),
    H_inv = matrix(NA, 2, 2),
    cov = matrix(NA, 2, 2),
    scale_error = NA,
    shift_error = NA,
    loss_threshold = loss_threshold
  ))
}

# ------------------------------------------------------------------
# FIT QUADRATIC SURFACE AROUND THE MINIMUM
# ------------------------------------------------------------------

x1 <- local$scale - best_scale
x2 <- local$shift - best_shift
y  <- local$loss - best_loss

model <- try(lm(y ~ I(x1^2) + I(x2^2) + I(x1 * x2) - 1), silent = TRUE)

if (inherits(model, "try-error")) {
  return(list(
    a = NA, b = NA, c = NA,
    M = matrix(NA, 2, 2),
    H = matrix(NA, 2, 2),
    H_inv = matrix(NA, 2, 2),
    cov = matrix(NA, 2, 2),
    scale_error = NA,
    shift_error = NA,
    loss_threshold = loss_threshold
  ))
}

cf <- coef(model)

a <- unname(cf["I(x1^2)"])
b <- unname(cf["I(x2^2)"])
c <- unname(cf["I(x1 * x2)"])
```

```r
  # Quadratic form matrix
  M <- matrix(c(a, c/2,
                c/2, b),
              nrow = 2, byrow = TRUE)

  # Hessian of the loss surface
  H <- 2 * M


  H_inv <- tryCatch(solve(H), error = function(e) NULL)

  if (is.null(H_inv)) {
    return(list(
      a = a, b = b, c = c,
      M = M,
      H = H,
      H_inv = matrix(NA, 2, 2),
      cov = matrix(NA, 2, 2),
      scale_error = NA,
      shift_error = NA,
      loss_threshold = loss_threshold
    ))
  }

  sigma2 <- best_loss  # justified mathematically
  cov_mat <- sigma2 * H_inv

  scale_error <- sqrt(max(cov_mat[1, 1], 0))
  shift_error <- sqrt(max(cov_mat[2, 2], 0))

  list(
    a = a, b = b, c = c,
    M = M,
    H = H,
    H_inv = H_inv,
    cov = cov_mat,
    scale_error = scale_error,
    shift_error = shift_error,
    loss_threshold = loss_threshold
  )
}
```

Visualization of harmonized curves

We now define a simple plotting function to compare:

- POOL original points
- SU original curve
- SU transformed curve (using the optimized scale and shift)

```r
plot_harmonization <- function(h, title = "Calibration Curve Harmonization") {

  # POOL original points
```

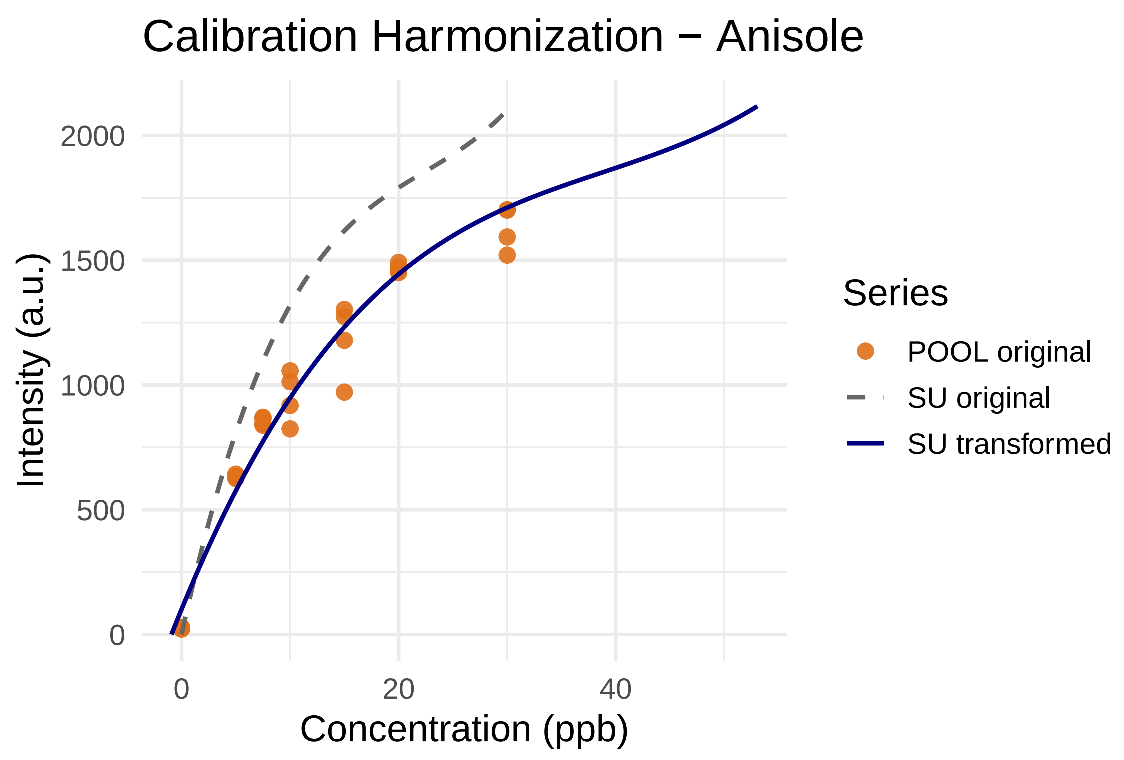
```r
pool_orig <- h$fitted_points %>%
  dplyr::transmute(
    concentration = concentration,
    intensity     = intensity,
    type          = "POOL original"
  )

# SU original curve
su_orig <- h$su_grid %>%
  dplyr::mutate(type = "SU original")

# SU transformed curve
su_trans <- h$su_grid_trans %>%
  dplyr::mutate(type = "SU transformed")

combined_df <- dplyr::bind_rows(
  pool_orig,
  su_orig,
  su_trans
)

ggplot(
  combined_df,
  aes(x = concentration, y = intensity, color = type, linetype = type)
) +
  # POOL points
  geom_point(
    data = dplyr::filter(combined_df, type == "POOL original"),
    size = 2.2,
    alpha = 0.9
  ) +
  # SU curves
  geom_line(
    data = dplyr::filter(combined_df, type != "POOL original"),
    linewidth = 0.8
  ) +
  scale_color_manual(values = c(
    "POOL original"  = "#E0711A",
    "SU transformed" = "navy",
    "SU original"    = "grey40"
  )) +
  scale_linetype_manual(values = c(
    "POOL original"  = "blank",
    "SU transformed" = "solid",
    "SU original"    = "dashed"
  )) +
  labs(
    title    = title,
    x        = "Concentration (ppb)",
    y        = "Intensity (a.u.)",
    color    = "Series",
    linetype = "Series"
  ) +
    theme_minimal(base_size = 14)
}
```

Anisole

```
res_anisole <- harmonize(pool_anisole, su_anisole)
```

Table 1: Harmonization parameters and uncertainty (Anisole)

Parameter	Value	Error	Units
Scale	0.562	±0.095	–
Shift	0.930	±1.619	ppb



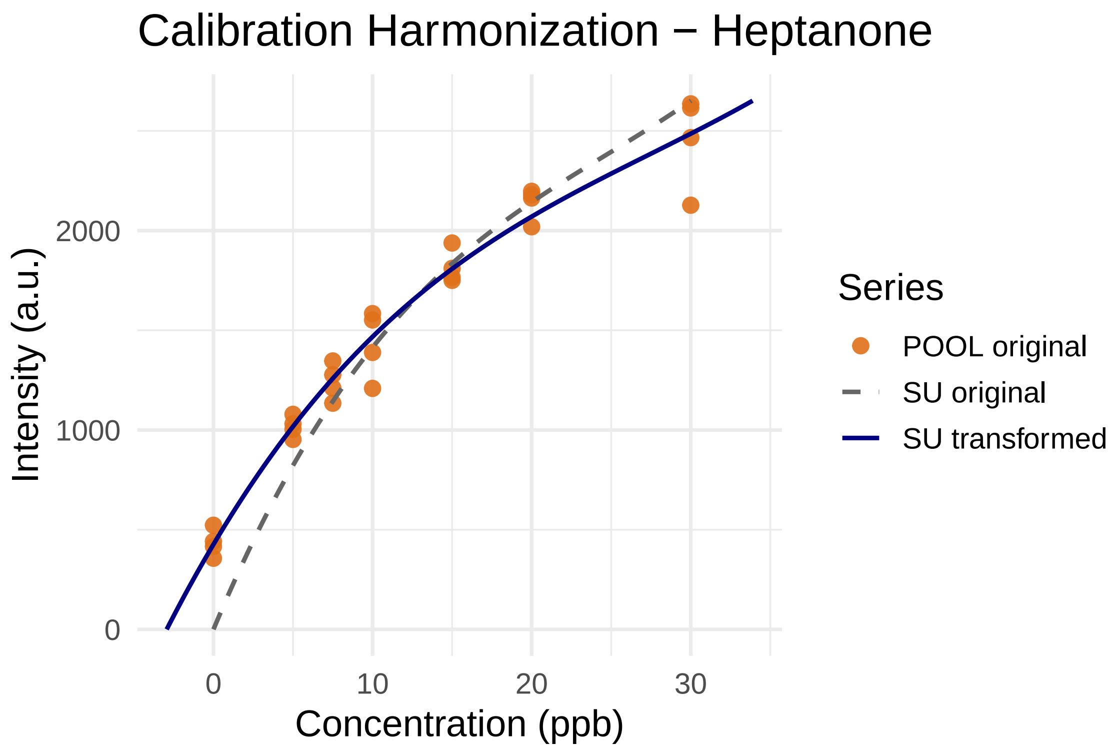
Heptanone

```
res_heptanone <- harmonize(pool_heptanone, su_heptanone)
```

Table 2: Harmonization parameters and uncertainty (Heptanone)

Parameter	Value	Error	Units
Scale	0.815	±0.11	–
Shift	2.940	±1.611	ppb

```r
plot_harmonization(res_heptanone, title = "Calibration Harmonization - Heptanone")
```



Loss landscape and paraboloid approximation

In this section we visualize the loss landscape and the paraboloid approximation.

- A **2D heatmap** of the loss over (scale, shift).
- A **2D heatmap** of the fitted paraboloid on the same grid.
- **1D profiles**:
  - Loss vs scale (shift fixed at its optimum).
  - Loss vs shift (scale fixed at its optimum).

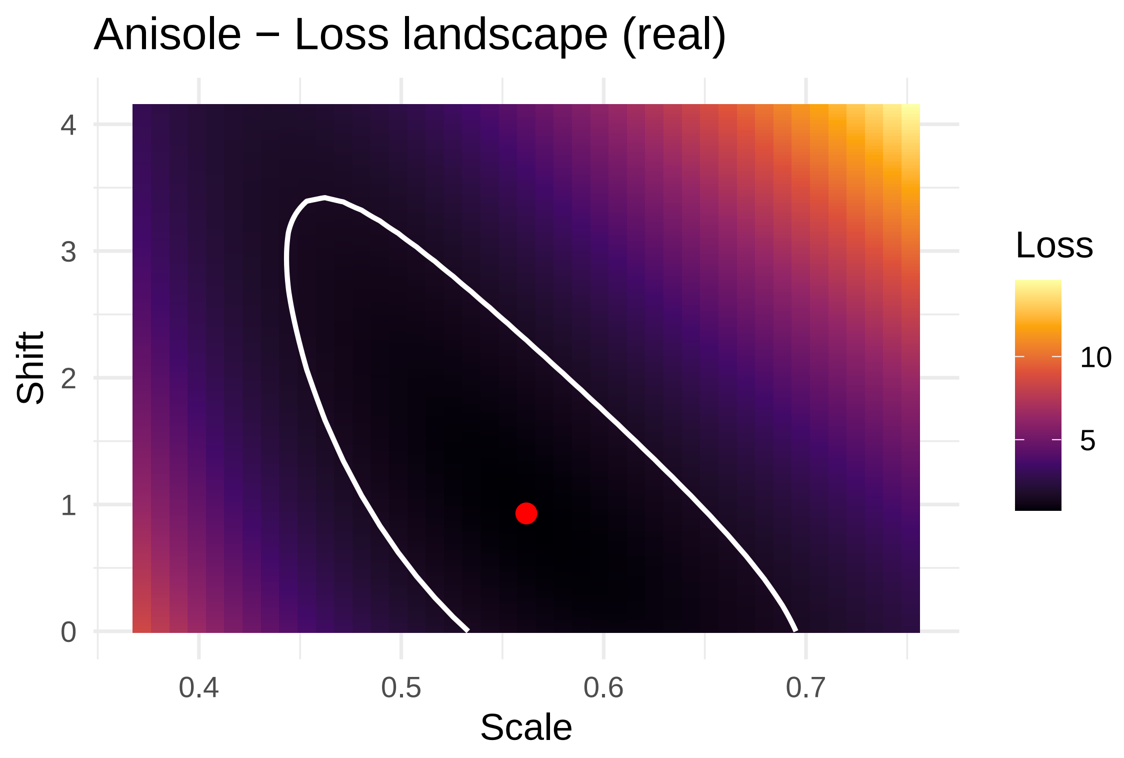
In the 1D plots:

- Real loss: **black**.
- Paraboloid: **navy** (dashed).
- Optimal point: **red** vertical line.

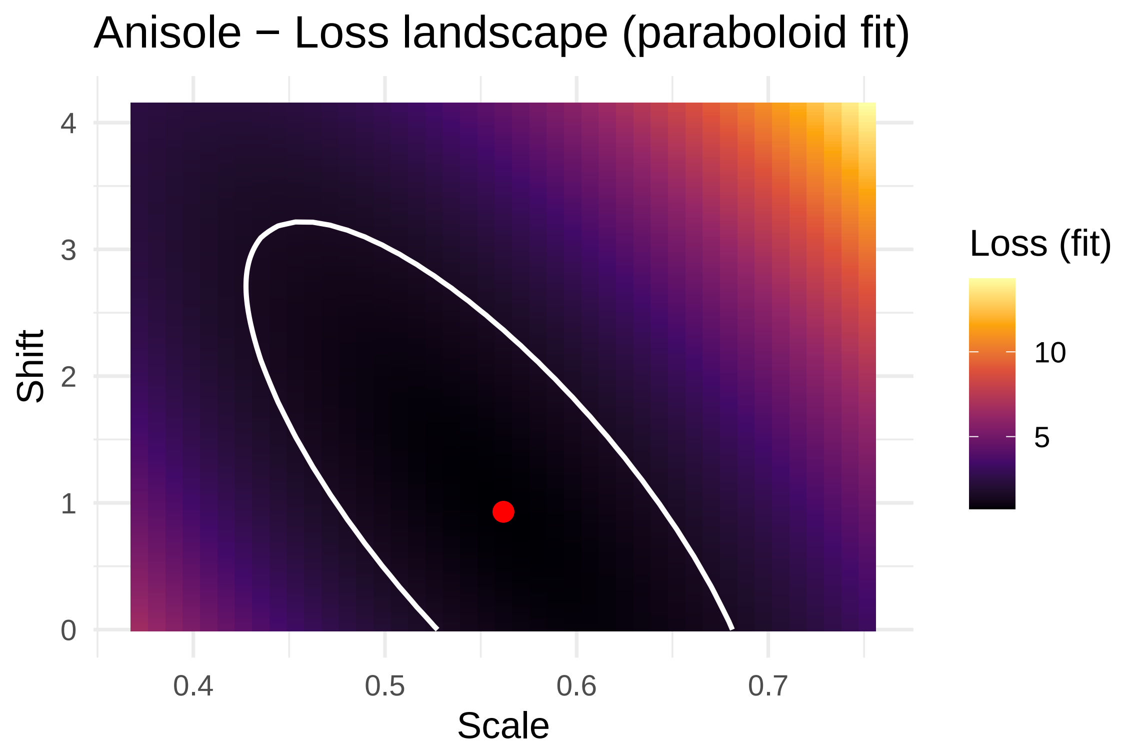
2D heatmaps: real loss vs paraboloid

Anisole

```r
hm_anisole <- plot_loss_heatmaps(res_anisole, title_prefix = "Anisole - ", )
hm_anisole$real
```

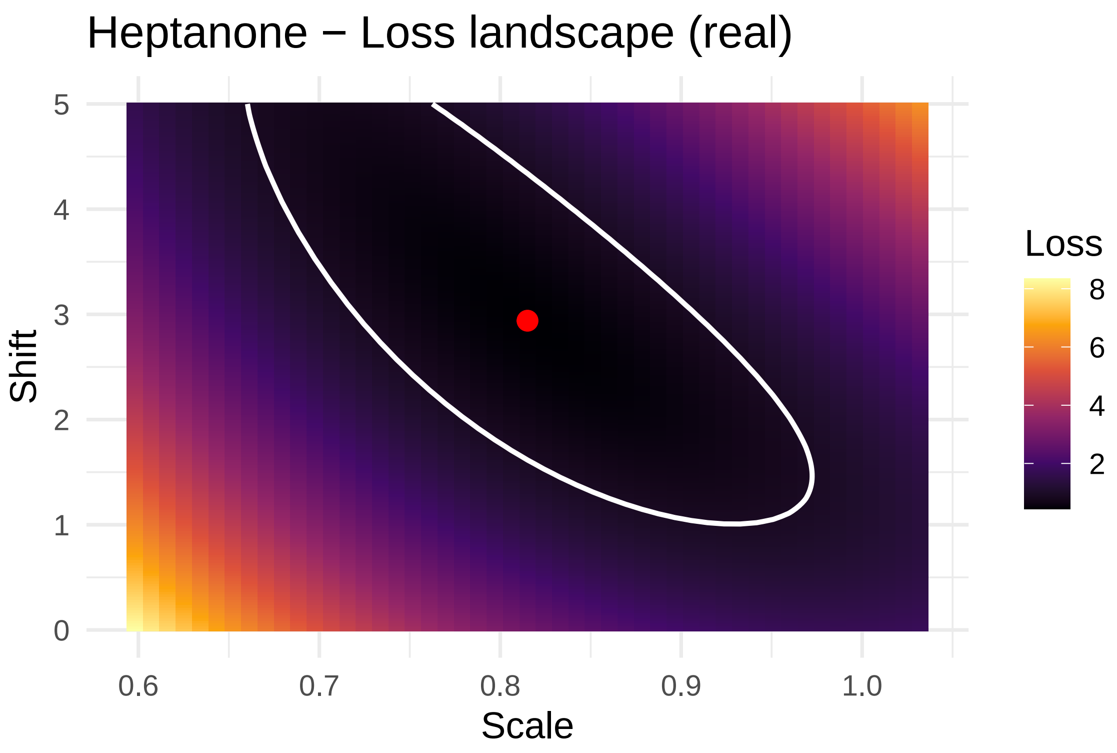


```
hm_anisole$paraboloid
```

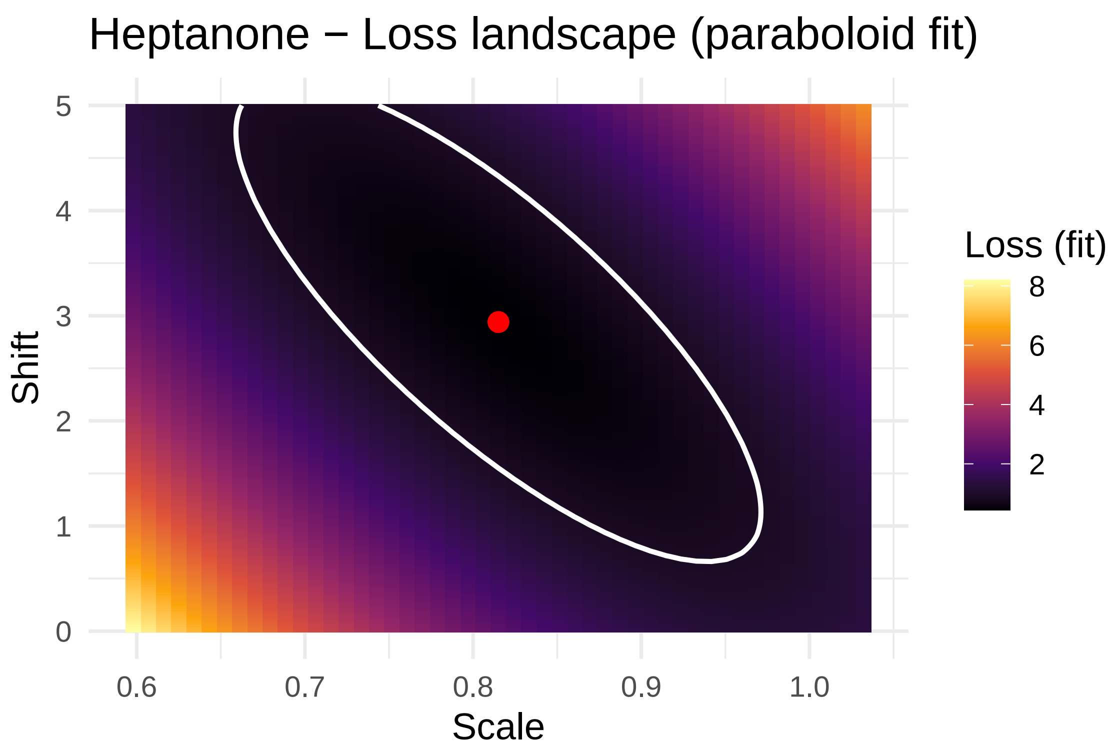


Heptanone

```
hm_heptanone <- plot_loss_heatmaps(res_heptanone, title_prefix = "Heptanone - ")
hm_heptanone$real
```



```
hm_heptanone$paraboloid
```



1D profiles: loss vs scale and shift

We now plot the loss as a function of a single parameter:

- **Loss vs scale**, with shift fixed at its optimal value.
- **Loss vs shift**, with scale fixed at its optimal value.

We overlay:

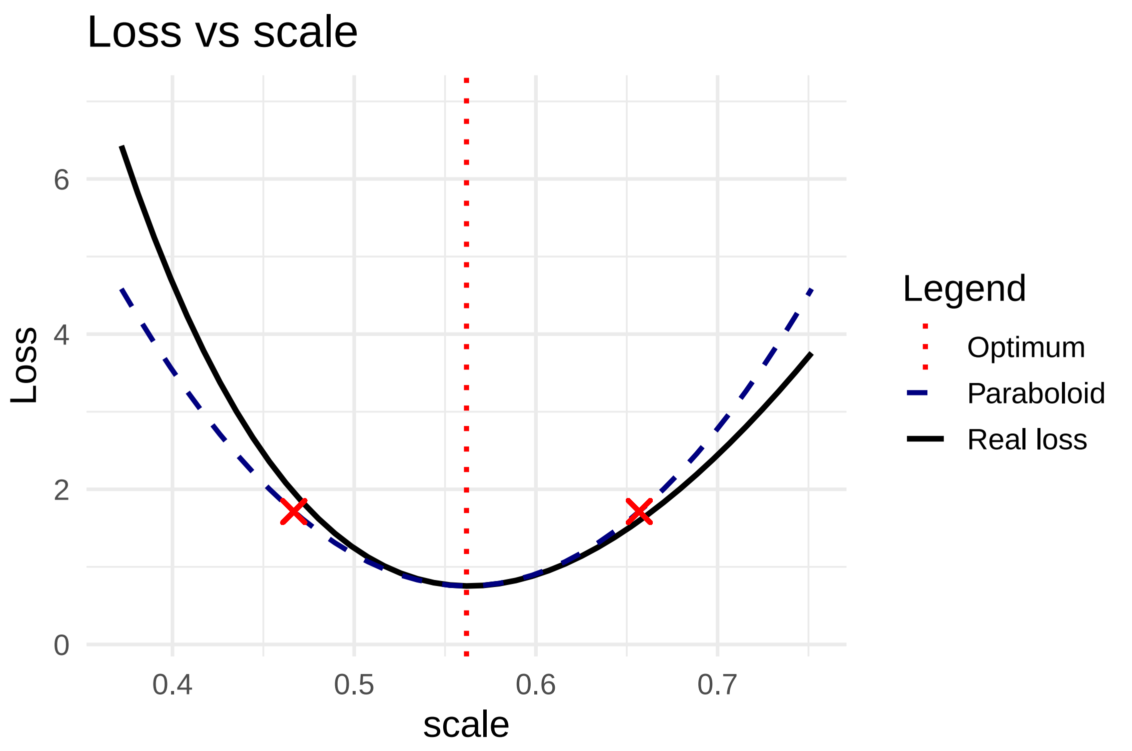
- Real loss (black).
- Paraboloid approximation (navy, dashed).
- Optimal point (red vertical line).

```
plot_loss_1d <- function(h,
                         param = c("scale", "shift"),
                         range_limit = NULL,
                         loss_limits = NULL,
                         tol = 1e-6,
                         title = NULL) {

  param <- match.arg(param)

  if (is.null(h$paraboloid))
    stop("No paraboloid fit available.")

  # Extract optimum and curvature
  if (param == "scale") {
    a <- h$paraboloid$a
    if (is.na(a)) stop("Paraboloid coefficient 'a' is NA.")

    x0  <- h$scale
```

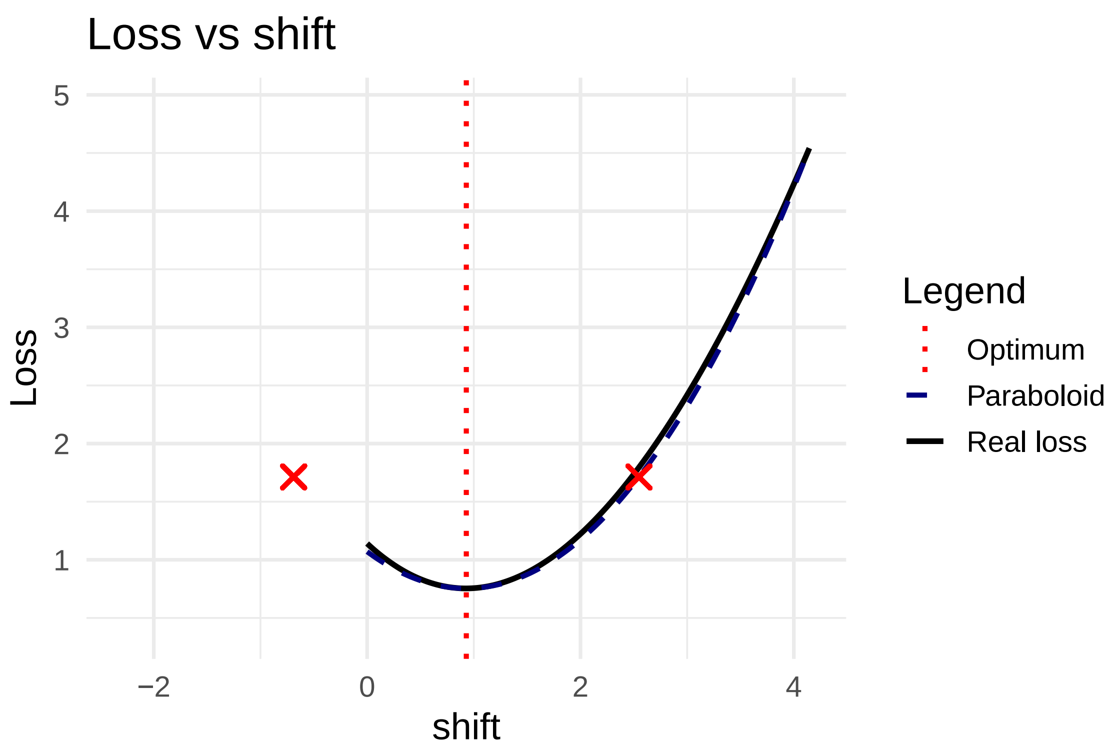
```r
    err <- h$scale_error

    lg <- h$loss_grid %>%
      dplyr::filter(
        is.finite(loss),
        abs(.data$shift - h$shift) < tol
      ) %>%
      dplyr::arrange(.data$scale) %>%
      dplyr::mutate(
        x = .data$scale,
        loss_parab = h$loss + a * (x - x0)^2
      )

  } else {  # param == "shift"

    b <- h$paraboloid$b
    if (is.na(b)) stop("Paraboloid coefficient 'b' is NA.")

    x0  <- h$shift
    err <- h$shift_error

    lg <- h$loss_grid %>%
      dplyr::filter(
        is.finite(loss),
        abs(.data$scale - h$scale) < tol
      ) %>%
      dplyr::arrange(.data$shift) %>%
      dplyr::mutate(
        x = .data$shift,
        loss_parab = h$loss + b * (x - x0)^2
      )
  }

  # Default X-limits = ±2×error
  if (is.null(range_limit)) {
    range_limit <- c(x0 - 2 * err, x0 + 2 * err)
  }

  # Subset
  lg_local <- lg %>% dplyr::filter(x >= range_limit[1], x <= range_limit[2])

  # Default Y-limits
  if (is.null(loss_limits)) {
    ymin <- min(lg_local$loss, lg_local$loss_parab, na.rm = TRUE)
    ymax <- max(lg_local$loss, lg_local$loss_parab, na.rm = TRUE)
    pad  <- 0.10 * (ymax - ymin)
    loss_limits <- c(ymin - pad, ymax + pad)
  }

  if (is.null(title)) {
    title <- paste0("Loss vs ", param)
  }
  # Error bounds
  x_lower <- x0 - err
  x_upper <- x0 + err

  # Corresponding Y-values on the fitted paraboloid
  if (param == "scale") {
    y_lower <- h$loss + a * (x_lower - x0)^2
    y_upper <- h$loss + a * (x_upper - x0)^2
  } else {
    y_lower <- h$loss + b * (x_lower - x0)^2
    y_upper <- h$loss + b * (x_upper - x0)^2
  }

  # Plot
  p <- ggplot(lg_local, aes(x = x)) +

    geom_line(aes(y = loss, linetype = "Real loss"),
              color = "black", linewidth = 1) +

    geom_line(aes(y = loss_parab, linetype = "Paraboloid"),
              color = "navy", linewidth = 0.9) +

    geom_vline(aes(xintercept = x0, linetype = "Optimum"),
               color = "red", linewidth = 0.9) +

    # The corrected uncertainty markers:
    geom_point(aes(x = x_lower, y = y_lower),
               color = "red", shape = 4, size = 3, stroke = 1.3) +
    geom_point(aes(x = x_upper, y = y_upper),
               color = "red", shape = 4, size = 3, stroke = 1.3) +

    scale_linetype_manual(values = c(
      "Real loss"  = "solid",
      "Paraboloid" = "dashed",
      "Optimum"    = "dotted"
    )) +

    labs(
      title = title,
      x = param,
      y = "Loss",
      linetype = "Legend"
    ) +

    theme_minimal(base_size = 14) +
    theme(legend.position = "right") +

    xlim(range_limit) +
    ylim(loss_limits)

  p
}
```

Anisole

```
plot_loss_1d(res_anisole, param = "scale")
```

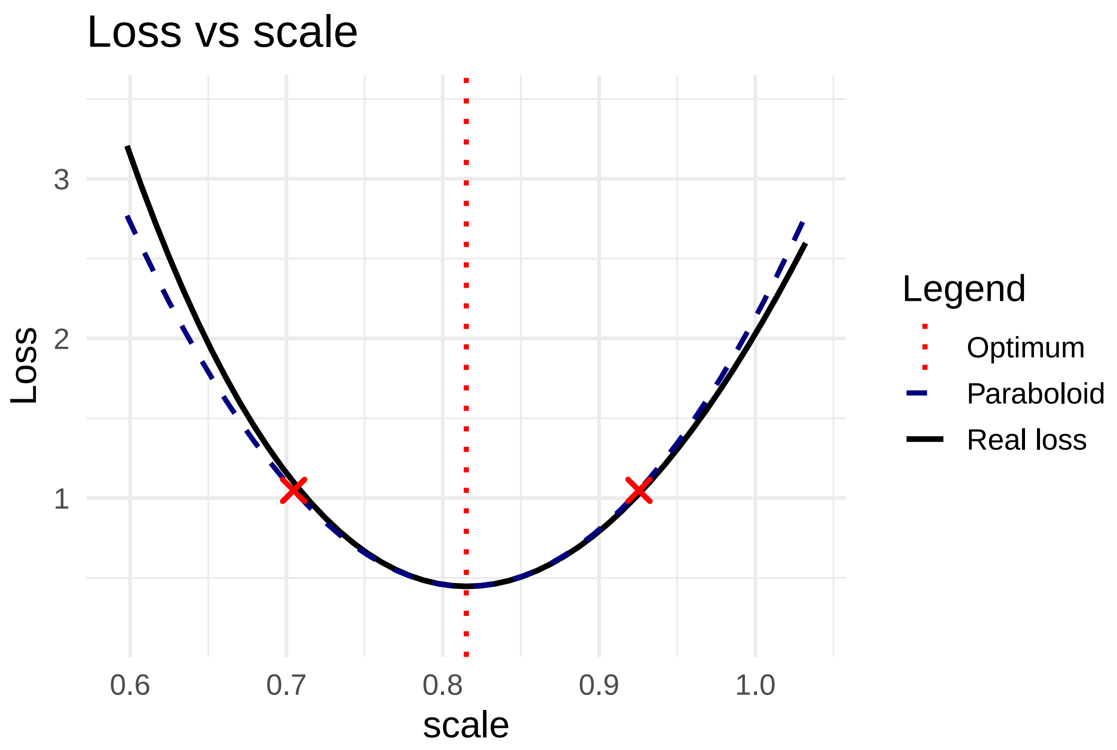


```
plot_loss_1d(res_anisole, param = "shift")
```

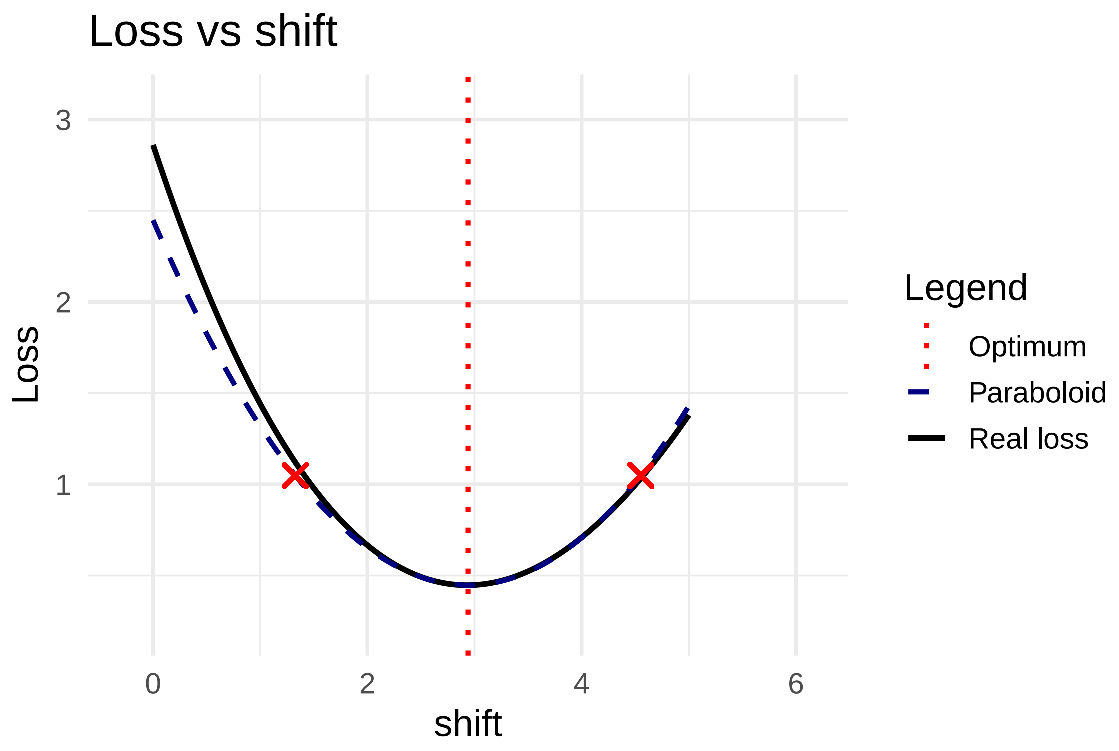


Heptanone

```
plot_loss_1d(res_heptanone, param = "scale")
```



```r
plot_loss_1d(res_heptanone, param = "shift")
```


Loss vs shift
Loss
shift
Legend
Optimum
Paraboloid
Real loss