SHADE Workflow Demo with Simulated Spatial Data

Overview

This demo illustrates the SHADE model described in the paper "SHADE: A Multilevel Bayesian Framework for Modeling Directional Spatial Interactions in Tissue Microenvironments". SHADE is a Bayesian hierarchical model designed to estimate asymmetric spatial associations between cell types across spatial scales and biological levels (image, patient, cohort).

We will:

- Simulate spatial point patterns with biologically plausible asymmetry
- Construct interaction features using radial basis functions
- Prepare data for Bayesian inference using logistic approximation
- Fit the SHADE model
- Summarize and compare posterior results to ground truth

1. Load Packages

We start by loading all necessary libraries, including your SHADE package and its dependencies.

```
knitr::opts_chunk$set(echo = TRUE, message = FALSE, warning = FALSE)
library(SHADE)
library(dplyr)
library(tidyr)
library(stringr)
library(ggplot2)
library(tibble)
library(Matrix)
library(spatstat.geom)
```

```r
library(spatstat.random)
library(posterior)
```

2. Set Simulation Parameters

We simulate a small dataset of tissue images with three cell types. One of these is treated as the "target" cell type whose spatial intensity is influenced by the presence of others.

```r
num_pts_per_group <- 10
images_per_pt     <- 2
num_pt_groups <- 2
num_pts <- num_pts_per_group * num_pt_groups

num_types <- 3
np <- 150 # number of cells per type
ratio <- 2 # ratio of dummy points (for logistic approximation) to real points
n_dummy <- floor(np * ratio)
num_basis <- 3 # number of basis functions
basis <- make_rbfs(n_basis_functions = num_basis,
                        max_dist = 75, basis_function_sigma = 15)
mean_alpha <- log(np / (1500^2)) # mean baseline intensity for each cell type

params <- make_simulation_parameters(
  mean_alpha = mean_alpha,
  sigma_beta_global = 0.5,
  sigma_beta_indiv  = 0.1,
  sigma_beta_local  = 0.1,
  scale_sigmas = 5,
  num_pt_groups = num_pt_groups,
  num_types = num_types,
  num_combos = num_types - 1,
  num_pot = num_basis,
  indiv_to_group = rep(1:num_pt_groups, each=num_pts_per_group),
  num_pts = num_pts,
  num_images = num_pts * images_per_pt,
  sample_to_indiv = rep(1:num_pts, each = images_per_pt),
  seed = 2025
)
betas_local <- params$betas_local[-1, ]
```

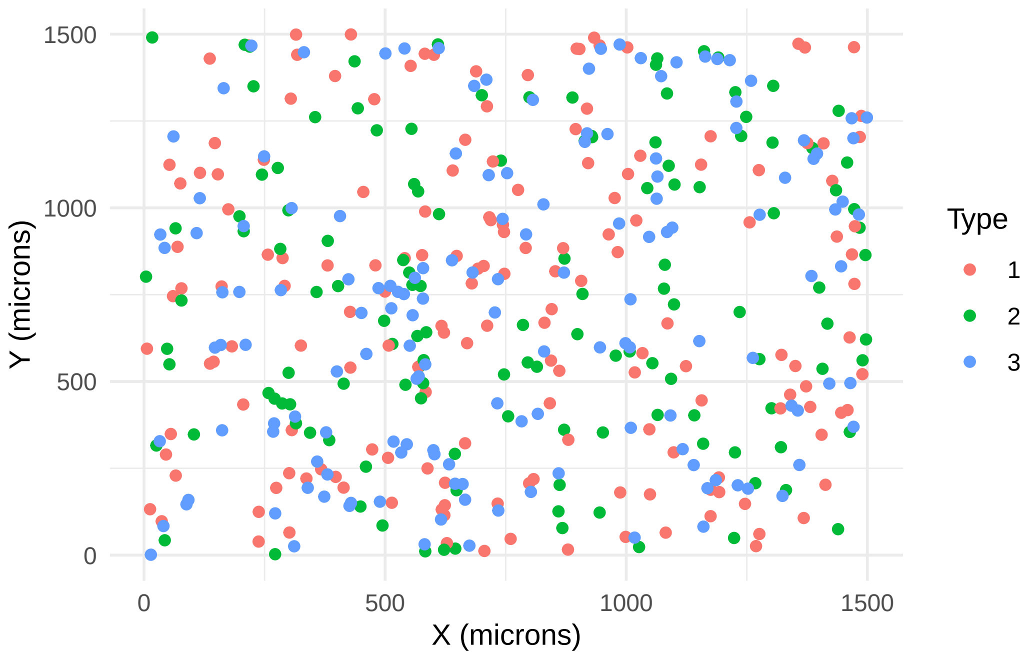
3. Simulate Spatial Point Patterns

We simulate images where target cell placement depends on background cell types. Conditional intensities are generated using spatial interaction fields, which are sums of RBFs weighted by coefficients.

```r
W <- owin(c(0, 1500), c(0, 1500))
area <- 1500^2
num_images <- num_pts * images_per_pt

sim_data <- lapply(1:num_images, function(i) {
  # cat(paste0(i,"/",num_images,"\n"))
  if (num_types == 2) {
    pat <- rpoispp(lambda = np / area, win = W)
    marks(pat) <- factor("t1")
  } else {
    pat <- rmpoispp(lambda = rep(np / area, num_types - 1), win = W)
  }

  dens_list <- lapply(1:(num_types - 1), function(j) {
    coeffs <- betas_local[((j - 1) * num_basis + 1):(j * num_basis), i]
    custom_kernel <- Vectorize(function(x, y) {
      d <- sqrt(x^2 + y^2)
      sum(sapply(seq_along(coeffs),
                 function(k) coeffs[k] * basis[[k]](d)))
    })
    subs <- unmark(subset(pat, marks == j))
    smooth_density_fft(subs, custom_kernel, resolution = 128)
  })

  int_dens <- Reduce("+", dens_list)
  lambda_integral <- sum(
    exp(int_dens$v)) * (int_dens$xstep * int_dens$ystep)
  beta0 <- log(np / lambda_integral)
  target_pat <- rpoispp(lambda = exp(int_dens + beta0))
  marks(target_pat) <- factor(num_types)

  final_pat <- superimpose(pat, target_pat)
  list(pat = final_pat, beta0 = beta0)
})
```

Here is what an example point pattern from this simulated dataset would look like:

```r
sim_data[[1]]$pat %>%
  as.data.frame() %>%
  ggplot(aes(x,y,color=marks)) +
  geom_point() +
  theme_minimal() +
  labs(x="X (microns)",y="Y (microns)",color="Type")
```



4. Prepare the Data for SHADE

We extract spatial coordinates and cell type labels, and format metadata for hierarchical modeling. SHADE models variation across images, patients, and groups.

```r
coords <- do.call(rbind, lapply(seq_along(sim_data), function(i) {
  pat <- sim_data[[i]]$pat
  raw_marks <- as.character(pat$marks)
  relabeled_marks <- paste0("t", raw_marks)

  tibble(
    x = pat$x,
    y = pat$y,
    type = factor(relabeled_marks, levels = paste0("t", 1:num_types)),
    image_id = factor(paste0("img_", i))
  )
}))

image_ids <- levels(coords$image_id)
patient_ids <- rep(paste0("pt_", 1:num_pts), each = images_per_pt)
patient_metadata <- tibble(
  Spot = image_ids,
  Patient = patient_ids,
  Group = rep(paste0("group_",1:num_pt_groups),
              each=num_pts_per_group * images_per_pt)
)

prep <- prepare_spatial_model_data(
  x = coords$x,
  y = coords$y,
  cell_type = coords$type,
  image_id = coords$image_id,
  patient_metadata = patient_metadata,
  type_idx = num_types,
  n_dummy = n_dummy,
  n_basis_functions = num_basis
)
```

5. Fit the SHADE Model

We use a logistic regression approximation to fit the conditional intensity function. Inference is performed via HMC using `cmdstanr`.

```r
set.seed(2025)
fit <- run_SHADE_model(
  prep$stan_data,
  chains = 1,
  iter_warmup = 300,
  iter_sampling = 100,
  refresh = 0,
  output_dir = "Introduction_cache/"
)
```

```
Running MCMC with 1 chain...
```

```
Chain 1 finished in 52.7 seconds.
```

6. Summarize Posterior Estimates

We summarize the posterior draws for global-level coefficients using an `rvar` object. Posterior draws capture uncertainty in spatial association curves (SICs).

```
rvars <- posterior::as_draws_rvars(fit$draws())
beta_global_rvar <- rvars$beta_global[-1, ]

posterior_global_tbl <- posterior::summarise_draws(
  beta_global_rvar,
  mean, median, sd, mad,
  `5%` = ~quantile(.x, 0.05),
  `95%` = ~quantile(.x, 0.95),
  rhat, ess_bulk
) %>%
  filter(str_detect(variable, "\\[")) %>%
  separate(variable, into = c("param", "row", "col"),
           sep = "\\[|,|\\]", convert = TRUE) %>%
  mutate(term = paste0(" _global[", row, "] (Group ", col, ")"))

posterior_global_tbl %>%
  select(term, mean, sd, `5%`, `95%`, rhat, ess_bulk) %>%
  arrange(term)
```

```
# A tibble: 12 x 7
   term                         mean     sd    `5%`    `95%`  rhat ess_bulk
   <chr>                       <dbl>  <dbl>   <dbl>    <dbl> <dbl>    <dbl>
 1 _global[1] (Group 1)  0.616  0.0799  0.482   0.740    1.01      23.3
 2 _global[1] (Group 2)  0.303  0.0984  0.111   0.450    1.16       5.41
 3 _global[2] (Group 1)  0.351  0.0334  0.302   0.408    1.00      21.9
 4 _global[2] (Group 2) -0.175  0.0427 -0.241  -0.113    1.26       3.66
 5 _global[3] (Group 1) -0.0388 0.0222 -0.0762 -0.00638 0.999     26.6
 6 _global[3] (Group 2) -0.187  0.0347 -0.248  -0.133    1.04      24.4
 7 _global[4] (Group 1)  0.273  0.103   0.102   0.403    1.28      10.1
 8 _global[4] (Group 2) -0.587  0.125  -0.788  -0.358    1.06      20.4
 9 _global[5] (Group 1)  0.233  0.0352  0.177   0.292    1.05      38.2
10 _global[5] (Group 2)  0.265  0.0344  0.213   0.328    1.00      38.4
11 _global[6] (Group 1) -0.0373 0.0237 -0.0769 -0.00170 1.18       5.40
12 _global[6] (Group 2) -0.194  0.0282 -0.240  -0.153    1.00      21.6
```

7. Compare to Ground Truth Coefficients

We validate inference by comparing posterior estimates to the known coefficients used to generate the spatial interaction curves.

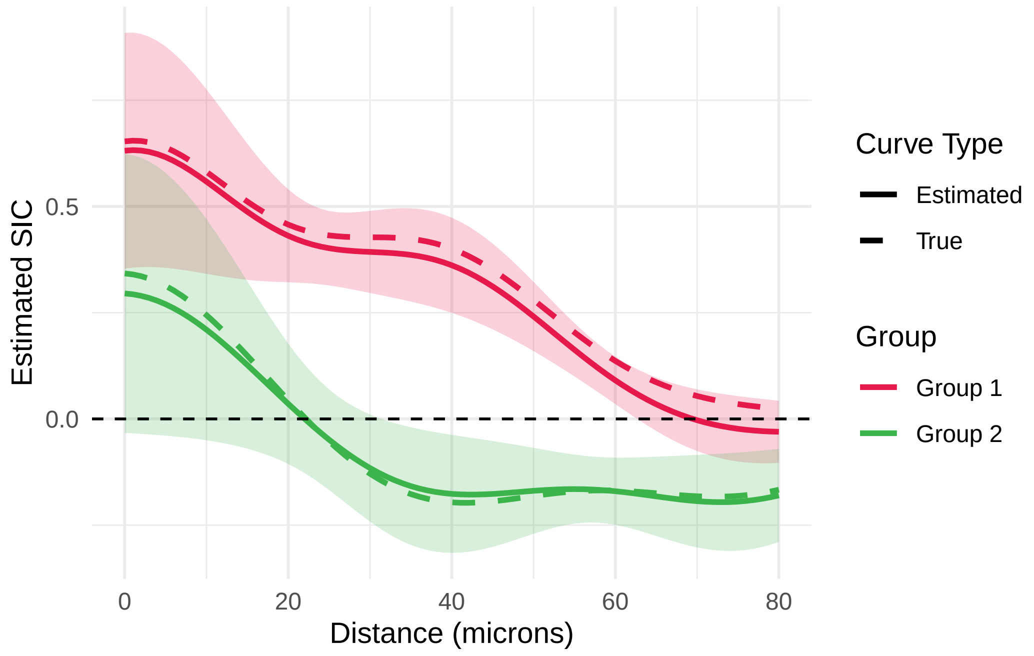
```
c(t(params$betas_global[-1, ]))
```

```
 [1]  0.63624454  0.35107568  0.38657724 -0.19784820  0.01782070 -0.17248259
 [7]  0.19855594 -0.87752702  0.18548772  0.38245481 -0.08142717 -0.21048188
```

8. Visualize SICs across groups

Lastly, we construct the estimated SICs for both groups and compare them with the true SICs, along with 95% simultaneous credible intervals for the estimated SICs.

```
alpha <- 0.05  # for 95% simultaneous bands
x_seq <- seq(0, 80, 1)
x_des <- lapply(basis, \(pot) pot(x_seq)) %>% do.call(cbind, .)

# Loop over both groups
plot_data <- lapply(1:2, function(i) {
  # Linear predictor samples
  lp <- x_des %*% rvars$beta_global[2:4, i]
  beta_true <- params$betas_global[2:4, i]
  lp_true <- as.vector(x_des %*% beta_true)

  # Step 1: Extract mean and SD per x
  df_summary <- lp %>%
    as.matrix() %>%
    as.data.frame() %>%
    mutate(x = x_seq) %>%
    mutate(
      mn = as.vector(E(V1)),
      sd = as.vector(sd(V1))
    )

  # Step 2: Standardize residuals across samples
  lp_std <- lp %>%
    as.matrix() %>%
    as.data.frame() %>%
    mutate(across(
      everything(),
      ~ (. - mean(.)) / sd(.)
    ))

  # Step 3: Max absolute deviation across x per sample
  max_dev <- lp_std %>%
    summarise(across(everything(), ~ max(abs(.)))) %>%
    pivot_longer(everything(),
                 names_to = "sample", values_to = "max_dev") %>%
    pull(max_dev)

  # Step 4: Critical value for simultaneous coverage
  z_score_band <- quantile(max_dev, probs = 1 - alpha)

  # Step 5: Simultaneous bands
  df_summ <- df_summary %>%
    mutate(
      lo_simul = mn - z_score_band * sd,
      hi_simul = mn + z_score_band * sd,
      lp_true = lp_true,
      group = paste0("Group ", i)
    )

  return(df_summ)
}) %>% bind_rows()

# Long-format for plotting
df_lines <- plot_data %>%
  select(x, group, mn, lp_true) %>%
  pivot_longer(cols = c(mn, lp_true),
               names_to = "type", values_to = "value") %>%
  mutate(type = ifelse(type == "mn", "Estimated", "True"))

df_ribbons <- plot_data %>%
  mutate(type = "Estimated") %>%
  select(x, group, type, ymin = lo_simul, ymax = hi_simul)

# Final plot
p_final <- ggplot() +
  geom_ribbon(data = df_ribbons,
              aes(x = x, ymin = ymin, ymax = ymax, fill = group),
              alpha = 0.2) +
  geom_line(data = df_lines,
            aes(x = x, y = value, color = group, linetype = type),
            size = 1) +
  geom_hline(yintercept = 0, color = "black", linetype = "dashed") +
  scale_color_manual(
    values = c("Group 1" = "#e6194b", "Group 2" = "#3cb44b")) +
  scale_fill_manual(
    values = c("Group 1" = "#e6194b", "Group 2" = "#3cb44b")) +
  scale_linetype_manual(
    values = c("Estimated" = "solid", "True" = "dashed")) +
  labs(
    x = "Distance (microns)",
    y = "Estimated SIC",
    color = "Group",
    linetype = "Curve Type"
  ) +
  guides(fill = "none") +
  theme_minimal()

p_final
```



Next Steps

- Perform posterior predictive checks
- Apply SHADE to real multiplexed imaging data