

Morphology Trajectories

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Loading packages

```
library(tidyverse)
library(here)
library(ggtrastr)
library(cowplot)
library(princurve)
library(scico)
library(ggbridges)

umap_df <- read_rds(here::here(params$data))

umap_df_sample <- tibble(file = list.files(here::here(params$sample), full.names = TRUE)) %>% mutate(drug =
  mutate(data = purrr::map(file, ~ readRDS(.x))) %>%
  dplyr::select(data) %>%
  unnest(data)

umap_tidy <- rbind(umap_df, umap_df_sample) # for pseudotime fit

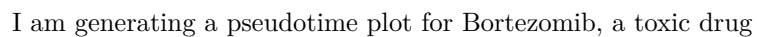
source(here("src/models/misc/pseudotime.R"))
```

Bortezomib Transition

```
set.seed(123)

gg_bortezomib <- umap_df %>%
  filter(partition %in% c(1,2)) %>%
  dplyr::select(-line, -concentration) %>%
  ggplot(aes(v1, v2)) +
  geom_point_rast(alpha = 1, size = 0.35, color = "#f1f1f1") +
  geom_point_rast(data = umap_df_sample %>%
    filter(grepl(drug, pattern = "Bortezomib")) %>%
    filter(line %in% c("D007T01", "D019T01", "D018T01")) %>%
    filter(concentration != "1.0") %>% # removing the maximum concentration as it is not adding fur
    group_by(concentration) %>%
    sample_n(10000, replace = TRUE),
  aes(color = line), alpha = 1, size = 0.35, shape=16) +
  scale_color_brewer(type = "qual", palette = "Set2") +
  facet_wrap(~ concentration, ncol = 2) +
  labs(x = "UMAP 1",
```

gg_bortezomib

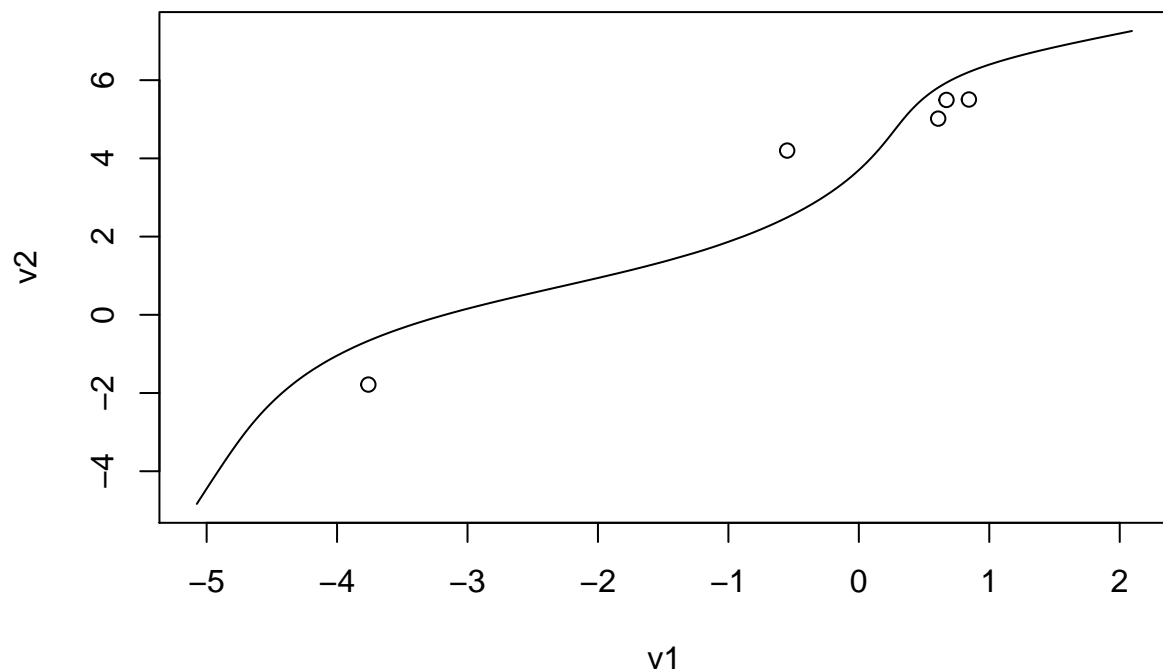
[illegible]

2

```

## Iteration 8---distance^2: 2591.754
## Iteration 9---distance^2: 2575.216
## Iteration 10---distance^2: 2561.11
## Iteration 11---distance^2: 2548.819
## Iteration 12---distance^2: 2538.777
## Iteration 13---distance^2: 2530.808
## Iteration 14---distance^2: 2524.718
## Iteration 15---distance^2: 2520.287
## Iteration 16---distance^2: 2517.269
## Iteration 17---distance^2: 2515.212

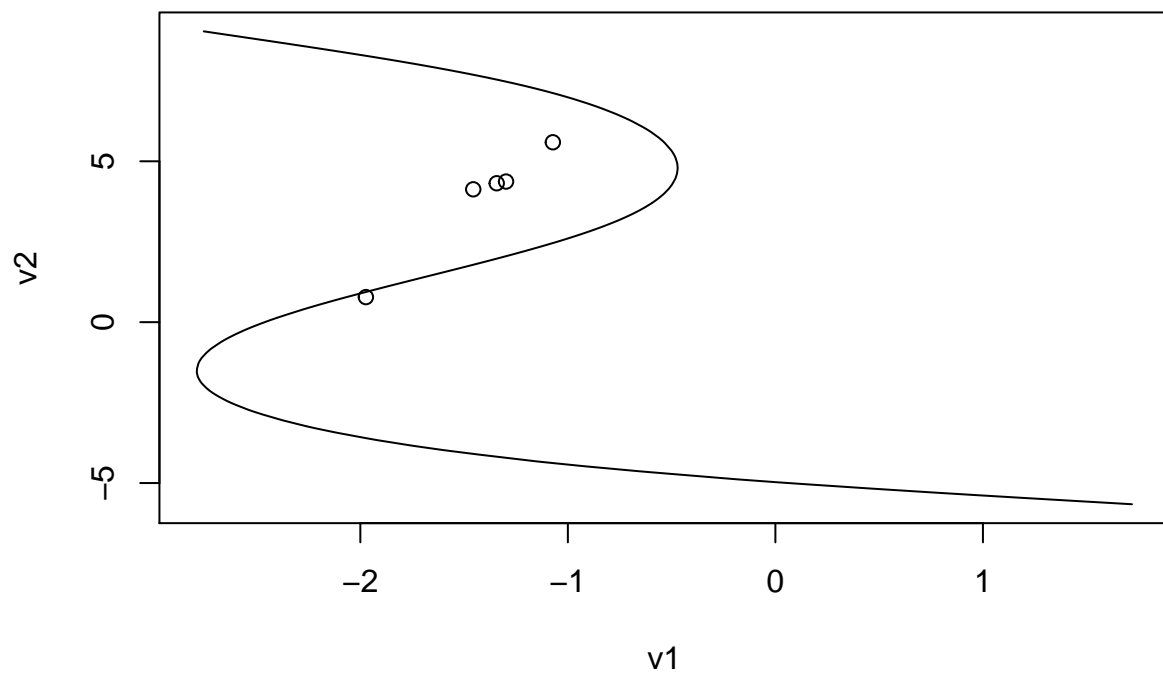
```



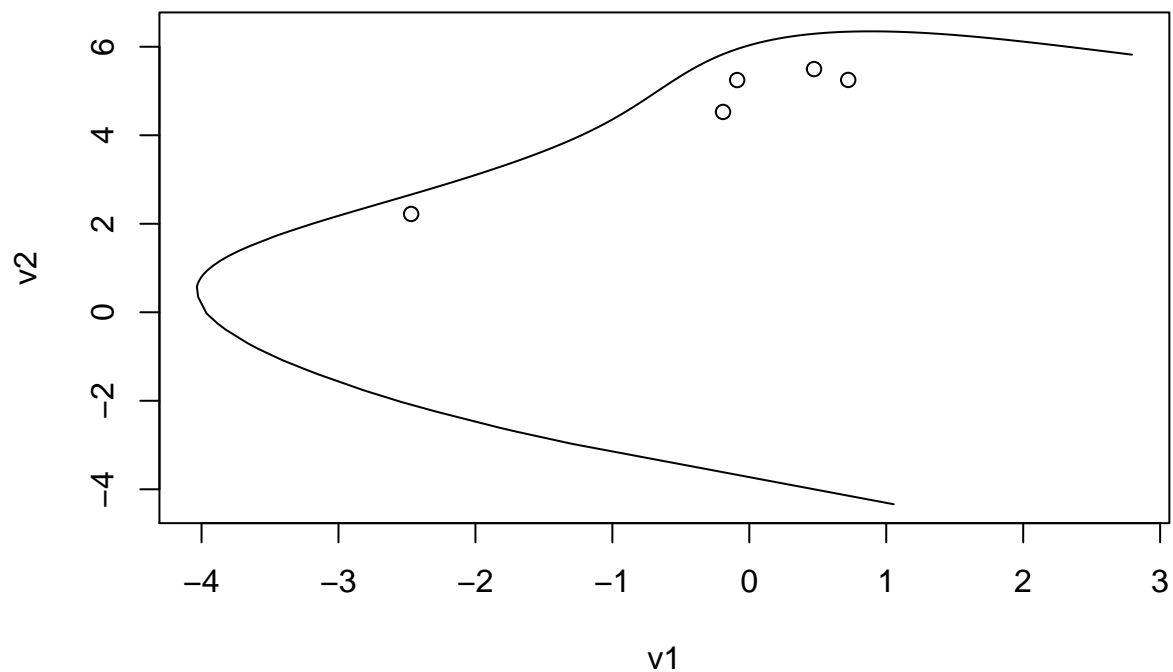
```

## Starting curve---distance^2: 22320.49
## Iteration 1---distance^2: 7311.392
## Iteration 2---distance^2: 4366.299
## Iteration 3---distance^2: 3281.056
## Iteration 4---distance^2: 3193.239
## Iteration 5---distance^2: 3042.677
## Iteration 6---distance^2: 2665.67
## Iteration 7---distance^2: 2560.964
## Iteration 8---distance^2: 2525.297
## Iteration 9---distance^2: 2509.164
## Iteration 10---distance^2: 2501.1
## Iteration 11---distance^2: 2497.064
## Iteration 12---distance^2: 2494.993

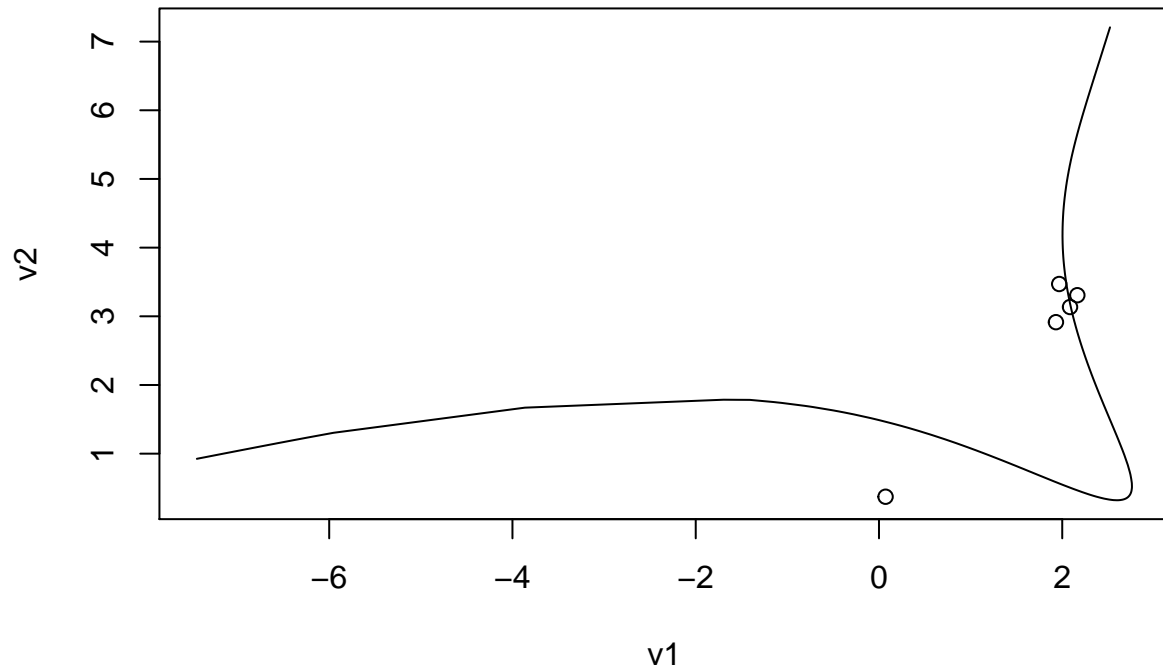
```



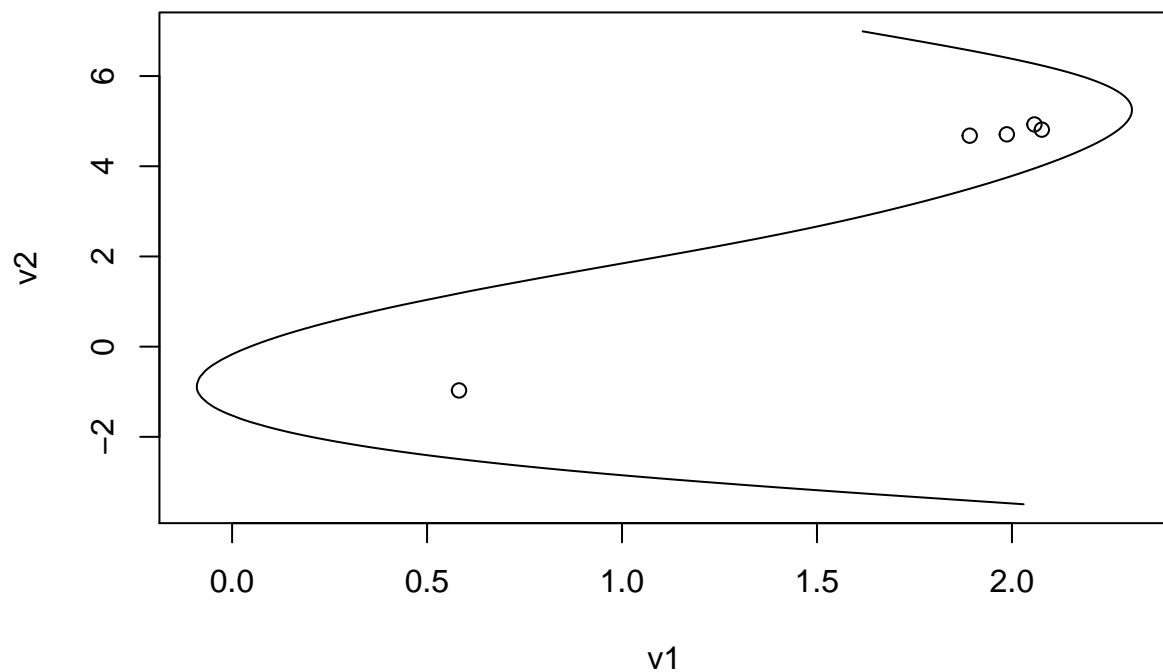
```
## Starting curve---distance^2: 9258.826
## Iteration 1---distance^2: 4286.348
## Iteration 2---distance^2: 3625.018
## Iteration 3---distance^2: 3287.906
## Iteration 4---distance^2: 2733.201
## Iteration 5---distance^2: 2486.007
## Iteration 6---distance^2: 2402.714
## Iteration 7---distance^2: 2350.676
## Iteration 8---distance^2: 2294.797
## Iteration 9---distance^2: 2250.427
## Iteration 10---distance^2: 2249.56
```



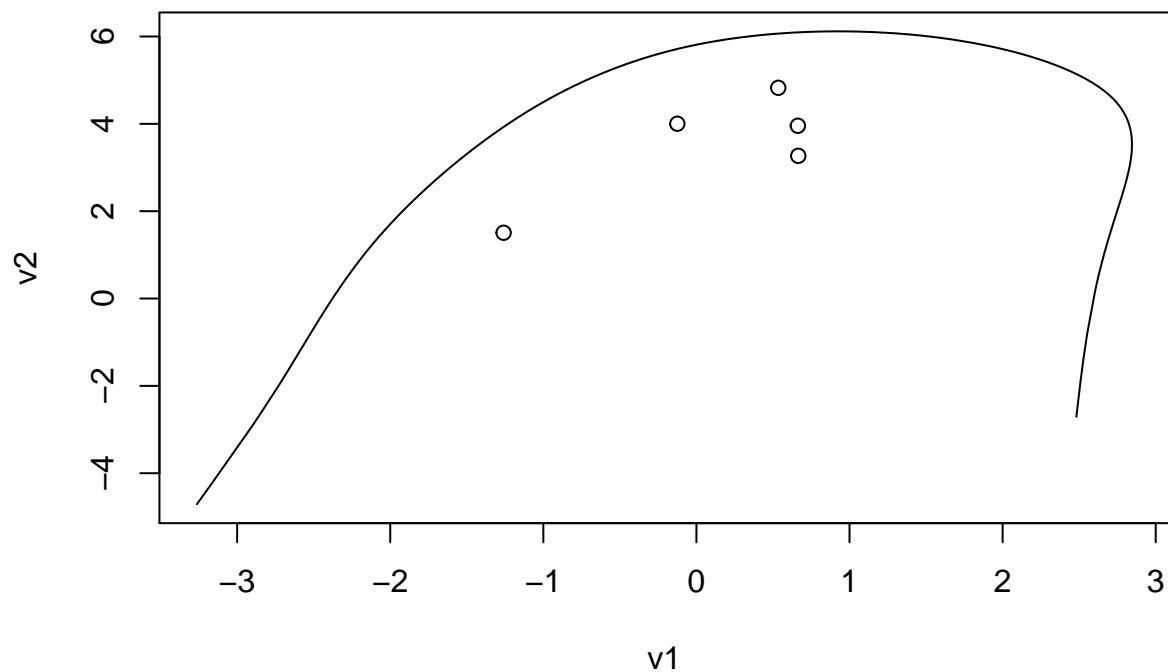
```
## Starting curve---distance^2: 17818.75
## Iteration 1---distance^2: 3879.162
## Iteration 2---distance^2: 1634.857
## Iteration 3---distance^2: 1587.207
## Iteration 4---distance^2: 1605.169
## Iteration 5---distance^2: 1633.437
## Iteration 6---distance^2: 1658.009
## Iteration 7---distance^2: 1677.896
## Iteration 8---distance^2: 1694.304
## Iteration 9---distance^2: 1710.728
## Iteration 10---distance^2: 1730.266
## Iteration 11---distance^2: 1745.779
## Iteration 12---distance^2: 1747.044
```



```
## Starting curve---distance^2: 4910.536
## Iteration 1---distance^2: 2387.613
## Iteration 2---distance^2: 2020.734
## Iteration 3---distance^2: 1914.154
## Iteration 4---distance^2: 1870.209
## Iteration 5---distance^2: 1842.44
## Iteration 6---distance^2: 1819.73
## Iteration 7---distance^2: 1800.767
## Iteration 8---distance^2: 1785.536
## Iteration 9---distance^2: 1773.615
## Iteration 10---distance^2: 1763.846
## Iteration 11---distance^2: 1755.139
## Iteration 12---distance^2: 1746.564
## Iteration 13---distance^2: 1737.674
## Iteration 14---distance^2: 1728.247
## Iteration 15---distance^2: 1718.655
## Iteration 16---distance^2: 1709.725
## Iteration 17---distance^2: 1703.35
## Iteration 18---distance^2: 1699.688
## Iteration 19---distance^2: 1697.722
## Iteration 20---distance^2: 1697.108
```



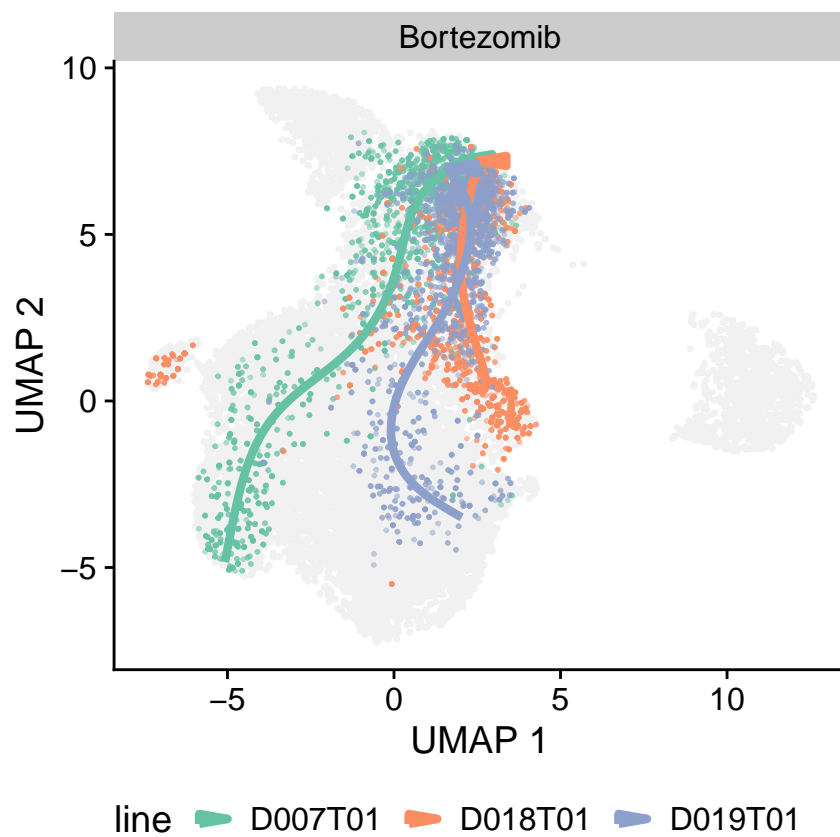
```
## Starting curve---distance^2: 12610.93
## Iteration 1---distance^2: 5254.146
## Iteration 2---distance^2: 3779.518
## Iteration 3---distance^2: 3471.257
## Iteration 4---distance^2: 3439.146
## Iteration 5---distance^2: 3566.97
## Iteration 6---distance^2: 3806.137
## Iteration 7---distance^2: 4077.759
## Iteration 8---distance^2: 4394.948
## Iteration 9---distance^2: 4777.317
## Iteration 10---distance^2: 5240.603
## Iteration 11---distance^2: 5210.229
## Iteration 12---distance^2: 3239.859
## Iteration 13---distance^2: 2959.096
## Iteration 14---distance^2: 2897.409
## Iteration 15---distance^2: 2882.383
## Iteration 16---distance^2: 2886.99
## Iteration 17---distance^2: 2889.456
```



```
plot_df <- plot_df_raw %>%
  filter(line %in% c("D007T01", "D019T01", "D018T01")) %>%
  mutate(plot_trace = case_when(line == "D018T01" ~ purrr::map(plot, ~ .x$fit %>% .[550:2500,]),
                                TRUE ~ purrr::map(plot, ~ .x$fit)))

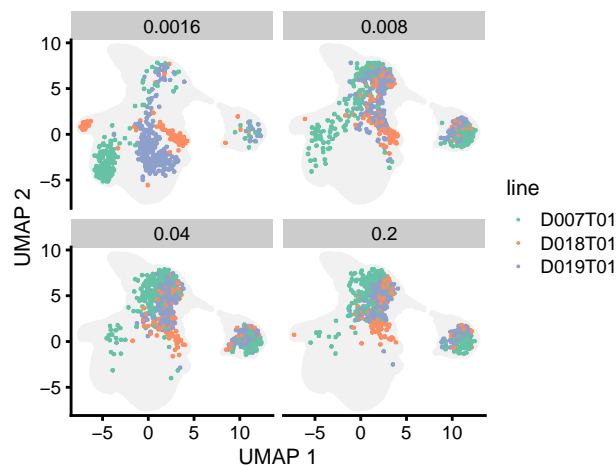
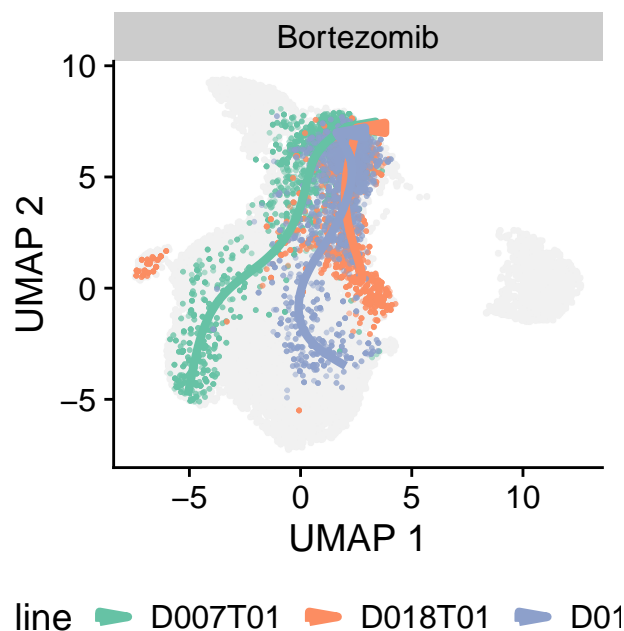
gg_bortezomib_traj <- draw_trajectory(plot_df)

gg_bortezomib_traj +
  coord_fixed()
```

e-7 good

```
plot_grid(gg_bortezomib + coord_fixed(), gg_bortezomib_traj + coord_fixed(),
  labels = c('A', 'B'), label_size = 12, ncol = 2) +
  ggsave(here::here("reports/panels/panel_bortezomib.pdf"), width = 8, height = 4)
```

A**B**

Irinotecan Transition

I am repeating a similar plot with SN-38, the active metabolite of Irinotecan.

```
set.seed(123)

gg_irinotecan <- umap_df %>%
  filter(partition %in% c(1,2)) %>%
  dplyr::select(-line, -concentration) %>%
  ggplot(aes(v1, v2)) +
  geom_point_rast(alpha = 1, size = 0.35, color = "#f1f1f1") +
  geom_point_rast(data = umap_tidy %>%
    filter(grepl(drug, pattern = "Irinotecan / SN-38")) %>%
    filter(line %in% c("D007T01", "D019T01", "D018T01")) %>%
    filter(concentration != "1.0") %>% # removing the maximum concentration as it is not adding fur
    group_by(concentration) %>%
    sample_n(1000, replace = TRUE),
    aes(color = line), alpha = 1, size = 0.35, shape=16) +
  scale_color_brewer(type = "qual", palette = "Set2") +
  facet_wrap(~ concentration, ncol = 2) +
  labs(x = "UMAP 1",
       y = "UMAP 2") +
  theme(legend.position = "none") +
  theme_cowplot(font_size = 8) +
```

```
coord_fixed()

gg_irinotecan
```

I am generating a pseudotime plot for Irinotecan, a toxic drug

```
set.seed(168763)

plot_df_raw <- create_plot_df(drug_order = c("Irinotecan / SN-38"),
                             loi = c("D007T01", "D010T01", "D013T01", "D018T01", "D019T01", "D027T01", "D030T01", "D033T01", "D036T01", "D039T01", "D042T01", "D045T01", "D048T01", "D051T01", "D054T01", "D057T01", "D060T01", "D063T01", "D066T01", "D069T01", "D072T01", "D075T01", "D078T01", "D081T01", "D084T01", "D087T01", "D090T01", "D093T01", "D096T01", "D099T01", "D102T01", "D105T01", "D108T01", "D111T01", "D114T01", "D117T01", "D120T01", "D123T01", "D126T01", "D129T01", "D132T01", "D135T01", "D138T01", "D141T01", "D144T01", "D147T01", "D150T01", "D153T01", "D156T01", "D159T01", "D162T01", "D165T01", "D168T01", "D171T01", "D174T01", "D177T01", "D180T01", "D183T01", "D186T01", "D189T01", "D192T01", "D195T01", "D198T01", "D201T01", "D204T01", "D207T01", "D210T01", "D213T01", "D216T01", "D219T01", "D222T01", "D225T01", "D228T01", "D231T01", "D234T01", "D237T01", "D240T01", "D243T01", "D246T01", "D249T01", "D252T01", "D255T01", "D258T01", "D261T01", "D264T01", "D267T01", "D270T01", "D273T01", "D276T01", "D279T01", "D282T01", "D285T01", "D288T01", "D291T01", "D294T01", "D297T01", "D300T01", "D303T01", "D306T01", "D309T01", "D312T01", "D315T01", "D318T01", "D321T01", "D324T01", "D327T01", "D330T01", "D333T01", "D336T01", "D339T01", "D342T01", "D345T01", "D348T01", "D351T01", "D354T01", "D357T01", "D360T01", "D363T01", "D366T01", "D369T01", "D372T01", "D375T01", "D378T01", "D381T01", "D384T01", "D387T01", "D390T01", "D393T01", "D396T01", "D399T01", "D402T01", "D405T01", "D408T01", "D411T01", "D414T01", "D417T01", "D420T01", "D423T01", "D426T01", "D429T01", "D432T01", "D435T01", "D438T01", "D441T01", "D444T01", "D447T01", "D450T01", "D453T01", "D456T01", "D459T01", "D462T01", "D465T01", "D468T01", "D471T01", "D474T01", "D477T01", "D480T01", "D483T01", "D486T01", "D489T01", "D492T01", "D495T01", "D498T01", "D501T01", "D504T01", "D507T01", "D510T01", "D513T01", "D516T01", "D519T01", "D522T01", "D525T01", "D528T01", "D531T01", "D534T01", "D537T01", "D540T01", "D543T01", "D546T01", "D549T01", "D552T01", "D555T01", "D558T01", "D561T01", "D564T01", "D567T01", "D570T01", "D573T01", "D576T01", "D579T01", "D582T01", "D585T01", "D588T01", "D591T01", "D594T01", "D597T01", "D600T01", "D603T01", "D606T01", "D609T01", "D612T01", "D615T01", "D618T01", "D621T01", "D624T01", "D627T01", "D630T01", "D633T01", "D636T01", "D639T01", "D642T01", "D645T01", "D648T01", "D651T01", "D654T01", "D657T01", "D660T01", "D663T01", "D666T01", "D669T01", "D672T01", "D675T01", "D678T01", "D681T01", "D684T01", "D687T01", "D690T01", "D693T01", "D696T01", "D699T01", "D702T01", "D705T01", "D708T01", "D711T01", "D714T01", "D717T01", "D720T01", "D723T01", "D726T01", "D729T01", "D732T01", "D735T01", "D738T01", "D741T01", "D744T01", "D747T01", "D750T01", "D753T01", "D756T01", "D759T01", "D762T01", "D765T01", "D768T01", "D771T01", "D774T01", "D777T01", "D780T01", "D783T01", "D786T01", "D789T01", "D792T01", "D795T01", "D798T01", "D801T01", "D804T01", "D807T01", "D810T01", "D813T01", "D816T01", "D819T01", "D822T01", "D825T01", "D828T01", "D831T01", "D834T01", "D837T01", "D840T01", "D843T01", "D846T01", "D849T01", "D852T01", "D855T01", "D858T01", "D861T01", "D864T01", "D867T01", "D870T01", "D873T01", "D876T01", "D879T01", "D882T01", "D885T01", "D888T01", "D891T01", "D894T01", "D897T01", "D900T01", "D903T01", "D906T01", "D909T01", "D912T01", "D915T01", "D918T01", "D921T01", "D924T01", "D927T01", "D930T01", "D933T01", "D936T01", "D939T01", "D942T01", "D945T01", "D948T01", "D951T01", "D954T01", "D957T01", "D960T01", "D963T01", "D966T01", "D969T01", "D972T01", "D975T01", "D978T01", "D981T01", "D984T01", "D987T01", "D990T01", "D993T01", "D996T01", "D999T01"),
                             n_sample = 500,
                             vl_cut = 5,
                             stretch = 0.001)

plot_df <- plot_df_raw %>%
  filter(line %in% c("D007T01", "D019T01", "D018T01")) %>%
  mutate(plot_trace = case_when(line == "D018T01" ~ purrr::map(plot, ~ .x$fit %>% .[1:2000,]),
                                line == "D007T01" ~ purrr::map(plot, ~ .x$fit %>% .[1:1500,]),
                                TRUE ~ purrr::map(plot, ~ .x$fit)))

gg_irinotecan_traj <- draw_trajectory(plot_df)

gg_irinotecan_traj

# e-7 good
```

5 major drug induced phenotypes

```
set.seed(123)
anno <- read_delim(here("references/layouts/Layouts.csv"), ";", escape_double = FALSE, trim_ws = TRUE) %>%
  dplyr::rename(drug = product_name) %>%
  filter(library_id != 1) %>%
  dplyr::select(drug, target, pathway) %>%
  distinct()

anno = anno %>% mutate(group = case_when(grepl(pattern = "CDK", x= target) ~ "CDK",
                                         grepl(pattern = "mTOR", x= target) ~ "mTOR",
                                         grepl(pattern = "MEK", x= target) ~ "MEK",
                                         grepl(pattern = "EGFR", x= target) ~ "EGFR",
                                         grepl(pattern = "GSK", x= target) ~ "GSK",
                                         drug == "DMSO" ~ "CTRL",
                                         TRUE ~ "other"
                                         ))

activity = umap_tidy %>% distinct(line, drug) %>%
  nest(-line) %>%
  mutate(activity = purrr::map(line, ~ read_csv(here::here("data/interim/FeatureAnalysis/drug_effects/1
                                                         janitor::clean_names() %>%
                                                         dplyr::rename(drug = x1)
                                                         )
  )
```

```

) %>%
dplyr::select(-data) %>%
unnest(activity)

gg_big5_density <- umap_df %>%

  filter(partition %in% c(1,2)) %>%
  dplyr::select(-line, -concentration) %>%
  ggplot(aes(v1, v2)) +
  geom_point_rast(alpha = 1, size = 0.35, color = "#f1f1f1") +
  stat_density_2d(geom = "polygon",
    data = umap_tidy %>%
      semi_join(anno %>% filter(group != "other")) %>%
      left_join(anno) %>%
      semi_join(activity %>% filter(auc_mean >= 0.85 | drug == "DMSO")) %>%
      filter(line %in% c("D004T01", "D030T01")) %>% # "D007T01", "D030T01", "D027T01", "D046T01" # 4
      filter(concentration == "nan") %>% # keeping single dose drugs
      filter(group %in% c("DMSO", "MEK", "mTOR", "CDK")) %>%
    group_by(drug, line) %>%
    sample_n(1000, replace = TRUE),

  aes(alpha = ..level.., fill = group)) +
  scale_fill_brewer(type = "qual", palette = "Set2") +
  facet_grid(line ~ group) + # ~ line
  labs(x = "UMAP 1",
    y = "UMAP 2")+
  theme(legend.position = "none") +
  theme_cowplot(font_size = 8) +
  coord_fixed()

gg_mekgsk_density <- umap_df %>%
  filter(partition %in% c(1,2)) %>%
  dplyr::select(-line, -concentration) %>%
  ggplot(aes(v1, v2)) +
  geom_point_rast(alpha = 1, size = 0.35, color = "#f1f1f1") +
  stat_density_2d(geom = "polygon",
    data = umap_tidy %>%
      semi_join(anno %>% filter(group != "other")) %>%
      left_join(anno) %>%
      semi_join(activity %>% filter(auc_mean >= 0.85 | drug == "DMSO")) %>%
      filter(line %in% c("D004T01", "D007T01", "D019T01")) %>% # "D007T01", "D030T01", "D027T01", "D0
      filter(concentration == "nan") %>% # keeping single dose drugs
      filter(group %in% c("DMSO", "MEK", "GSK")) %>%
    group_by(drug, line) %>%
    sample_n(1000, replace = TRUE),

  aes(alpha = ..level.., fill = group)) +
  scale_fill_brewer(type = "qual", palette = "Set2") +
  facet_grid(line ~ group) + # ~ line
  labs(x = "UMAP 1",
    y = "UMAP 2")+
  theme(legend.position = "none") +
  theme_cowplot(font_size = 8) +

```

```
coord_fixed()
```

Unlabeled

```
gg_mtor_all <- umap_df %>% rbind(umap_df_sample) %>%
  filter(partition %in% c(1,2)) %>%
  filter(drug == "DMSO" | grepl(drug, pattern = "WYE-132")) %>%
  #filter(line %in% c("D030T01", "D027T01", "D013T01")) %>%
  filter(line %in% c("D027T01")) %>%

  group_by(drug) %>%
  sample_n(700, replace = TRUE) %>%
  ggplot(aes(v1, v2)) +

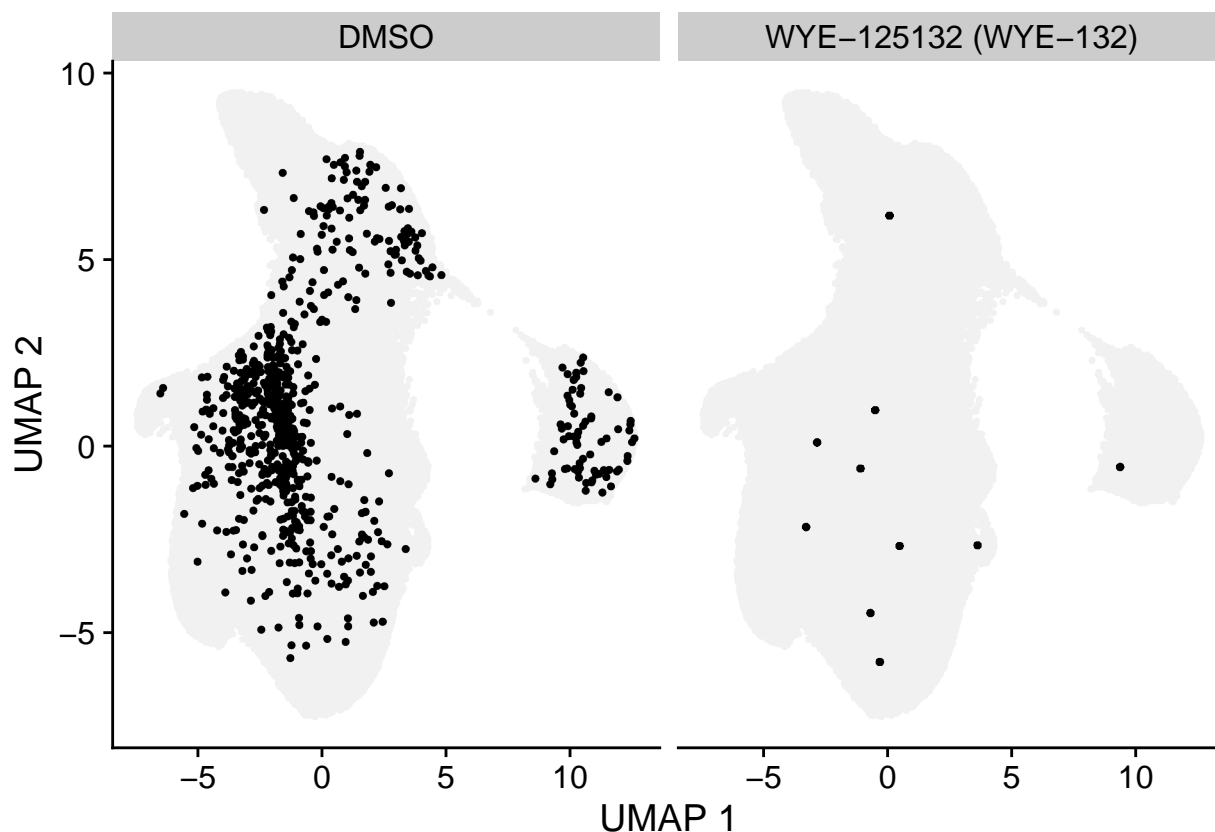
  geom_point_rast(data = umap_df %>% dplyr::select(-drug), alpha = 1, size = 0.35, color = "#f1f1f1") +

  geom_point_rast(aes(color = drug), alpha = 1, size = 1, shape=16, color = "black") +
  facet_wrap(~ drug) +

  theme_cowplot() +
  labs(x = "UMAP 1",
       y = "UMAP 2")+

  theme(legend.position = "nothing")

gg_mtor_all
```



```
set.seed(123)
drug_order <- c("CHIR-98014", "DMSO")

center_df <- umap_tidy %>%
  filter(drug %in% drug_order) %>%

  filter(partition %in% c(1,2)) %>%

  #filter(line %in% c("D030T01", "D027T01", "D013T01")) %>%
  group_by(drug, line, concentration) %>%
  sample_n(500, replace = TRUE) %>% ungroup()

gg_gsk_all <- umap_tidy %>%

  filter(partition %in% c(1,2)) %>%

  filter(drug == "DMSO" | grepl(drug, pattern = drug_order[1])) %>%
  #filter(line %in% c("D030T01", "D027T01", "D013T01")) %>%

  group_by(drug) %>%
  sample_n(500) %>%
  ggplot(aes(v1, v2)) +

  geom_point_rast(data = umap_df %>% dplyr::select(-drug), alpha = 1, size = 0.35, color = "#f1f1f1") +

  geom_point_rast(aes(color = drug), alpha = 1, size = 1, shape=16, color = "black") +
```

```

facet_wrap(~ drug) +

theme_cowplot() +
labs(x = "UMAP 1",
     y = "UMAP 2")+

theme(legend.position = "nothing")

set.seed(123)
drug_order <- c("Ulixertinib (BVD-523, VRT752271)",
               "TAK-733",
               "Trametinib (GSK1120212)",
               "Cobimetinib (GDC-0973, RG7420)",
               "MEK162 (ARRY-162, ARRY-438162)",
               "PDO325901",
               "Refametinib (RDEA119, Bay 86-9766)",
               "AZD8330",
               "Pimasertib (AS-703026)",
               "Selumetinib (AZD6244)",
               "PD318088",
               "VX-11e",
               "DMSO")

center_df <- umap_tidy %>% filter(concentration == "nan") %>%
  filter(drug %in% drug_order) %>%

  filter(partition %in% c(1,2)) %>%

  group_by(drug, line, concentration) %>%
  sample_n(500, replace = TRUE) %>%
  summarise(v1 = mean(v1),
            v2 = mean(v2)) %>%
  ungroup()

center_df %>%
  ggplot(aes(v1, v2)) +
  geom_point_rast(data = umap_df %>% dplyr::select(-drug, -line), alpha = 1, size = 0.35, color = "#f1f1f1") +
  geom_point_rast(aes(color = drug), alpha = 1, size = 1, shape=16) +
  facet_wrap(~ line) +
  theme_cowplot() +
  labs(x = "UMAP 1",
       y = "UMAP 2")+
  theme(legend.position = "nothing")

```

Differential drug activity

I am focusing on a set of two lines, D019T01 and D004T01

```

i_dist_in = 0.05
j_nn_in = 30
k_res_in = .1

```

```

loi = "D019T01"
obj <- readRDS(here::here(paste0("data/processed/PhenotypeSpectrum/drug_effects/lm_umap", loi, "_", i_d
umap_tidy_drug <- reducedDims(obj)$UMAP %>% cbind(colData(obj),
                                     cluster = clusters(obj),
                                     partition = partitions(obj)) %>% as_tibble() %>% janit
                                     mutate(line = loi)

loi = "D004T01"
obj <- readRDS(here::here(paste0("data/processed/PhenotypeSpectrum/drug_effects/lm_umap", loi, "_", i_d

umap_tidy_drug <- rbind(umap_tidy_drug, reducedDims(obj)$UMAP %>% cbind(colData(obj),
                                     cluster = clusters(obj),
                                     partition = partitions(obj)) %>% as_tibble() %>% janit

anno <- read_delim(here("references/layouts/Layouts.csv"), ";", escape_double = FALSE, trim_ws = TRUE) %
  dplyr::rename(drug = product_name) %>%
  filter(library_id != 1) %>%
  dplyr::select(drug, target, pathway) %>%
  distinct()

diff_drug <- umap_tidy_drug %>%
  left_join(anno) %>%
  drop_na() %>%
  mutate(target = case_when(grepl(pattern = "src", target, ignore.case = TRUE) == TRUE &
                             grepl(pattern = "Aurora", target, ignore.case = TRUE) == FALSE ~ "Src",
                             TRUE ~ target))

gg_target <- diff_drug %>%
  #filter(auc_mean > 0.85 | drug == "DMSO") %>%
  ggplot(aes(v1, v2, text = target)) +
  geom_point(color = "grey") +
  geom_point(data = df %>% filter(target %in% c("PLK", "mTOR", "Src")), aes(color = target), size = 2) +
  ggforce::geom_mark_ellipse(data = diff_drug %>% filter(target %in% c("mTOR", "PLK"), cluster %in% c(5
  ggforce::geom_mark_ellipse(data = diff_drug %>% filter(target %in% c("mTOR", "Src"), cluster %in% c(2
  scale_color_brewer(type = "qual", palette = "Set2") +
  theme_cowplot() +
  facet_wrap(~ line) +
  labs(x = "UMAP1",
       y = "UMAP2",
       caption = "active drugs plotted by separating plane, selected drugs are highlighted")

gg_target

gg_target_density <- umap_df %>%

  filter(partition %in% c(1,2)) %>%

  dplyr::select(-line, -concentration) %>%
  ggplot(aes(v1, v2)) +
  geom_point_rast(alpha = 1, size = 0.35, color = "#f1f1f1") +
  stat_density_2d(geom = "polygon",

                  data = umap_tidy %>%

```



```

left_join(diff_drug %>% dplyr::select(drug, target)) %>%
filter(line %in% c("D004T01", "D019T01")) %>%
filter(target %in% c("mTOR", "PLK", "Src") | drug == "DMSO") %>%
  # removing reference for clarity
  filter(target %in% c("mTOR", "PLK", "Src")) %>%
mutate(target = ifelse(drug == "DMSO", "CTRL", target)) %>%
  filter(concentration == "nan") %>% # keeping single dose drugs
group_by(drug) %>%
sample_n(500, replace = TRUE),

aes(alpha = ..level.., fill = target)) +
scale_fill_brewer(type = "qual", palette = "Set2") +
facet_wrap( ~ line, ncol = 2) +
labs(x = "UMAP 1",
      y = "UMAP 2")+
theme(legend.position = "none") +
theme_cowplot(font_size = 8) +
coord_fixed()

gg_target_density

plot_grid(gg_target, gg_target_density,
  labels = c('A', 'B'), label_size = 12, ncol = 1) +
ggsave(here::here("reports/enrichment_drugtarget.pdf"), width = 4, height = 4)

```

MEK inhibitor Pseudotimes

```

set.seed(1323)

plot_df_raw <- create_plot_df(drug_order = c("Binimetinib", "Trametinib"),
  loi = c("D027T01", "D019T01"),
  n_sample = 500,
  v1_cut = 5)

plot_df <- plot_df_raw %>%
  mutate(plot_trace = case_when(TRUE ~ purrr::map(plot, ~ .x$fit)))

gg_mek_traj_sel <- draw_trajectory_bulk(plot_df) + coord_fixed()

gg_mek_traj_sel

traj_df <- plot_df %>%
  mutate(proj = purrr::map2(data, plot_trace, ~ project_to_curve(.x %>% dplyr::select(v1, v2) %>% as.matrix(),
    .y %>% dplyr::select(v1, v2) %>% as.matrix(),
    threshold = purrr::map(proj, ~ median(.x$dist_ind) + 0*sd(.x$dist_ind)),
    df = purrr::map(proj, ~ cbind(dist = .x$dist_ind, ord = .x$ord, lambda = .x$lambda) %>% as_tibble())
  )

traj_df <- traj_df %>% dplyr::select(-plot, -plot_trace, -proj) %>% unnest(df, threshold, data)

```

```

traj_df %>%
  ggplot(aes(v1, v2, color = dist <= threshold)) +
  geom_point_rast() +
  scale_color_viridis_d() +
  theme_cowplot() +

  facet_grid(line ~ drug) +
  coord_fixed() +
  labs(x = "UMAP 1",
       y = "UMAP 2")

```

```

doi = "Trametinib"
loi = "D027T01"

```

```

gg_traj_incl <- traj_df %>%
  filter(drug == doi & line == loi) %>%
  #filter(lambda >= 5) %>% # hyperparameter tuned to avoid undershooting treatment effects
  filter(dist <= threshold) %>%
  ggplot(aes(v1, v2)) +
  geom_point_rast(data = umap_df %>% dplyr::select(-line, -concentration), alpha = 1, size = 0.35, color = lambda) +
  geom_point(aes(color = lambda)) +
  scale_color_viridis_c() +
  theme_cowplot() +
  facet_grid(~ line) +
  theme(legend.position = "bottom") +
  coord_fixed() +
  labs(x = "UMAP 1",
       y = "UMAP 2")

```

```

gg_size_pc <- traj_df %>%
  filter(drug == doi & line == loi) %>%
  #filter(lambda >= 5) %>% # hyperparameter tuned to avoid undershooting treatment effects
  ggplot(aes(lambda, size)) +
  #geom_point() +
  #scale_color_viridis_d() +
  theme_cowplot() +
  geom_smooth(color = "black") +
  geom_vline(xintercept = 8, linetype = "dashed") +
  geom_vline(xintercept = 9.5, linetype = "dashed") +
  labs(x = "lambda",
       y = "size [pixels]")

```

```

gg_conc_pc <- traj_df %>%
  filter(drug == doi & line == loi) %>%
  # filter(lambda >= 5) %>% # hyperparameter tuned to avoid undershooting treatment effects

  ggplot(aes(lambda, fill = concentration)) +
  geom_density(alpha = 0.2, position = "fill") +
  theme_cowplot() +
  scale_fill_viridis_d() +
  theme(legend.position = "bottom") +
  facet_grid(~ drug) +
  geom_vline(xintercept = 8, linetype = "dashed") +

```

```

    geom_vline(xintercept = 9.5, linetype= "dashed")

plot_grid(plot_grid(gg_traj_incl,gg_size_pc, labels = c('A', 'B'), label_size = 12, ncol = 2),
          gg_conc_pc,
          labels = c('', 'C'), label_size = 12, ncol = 1) +
  ggsave(here::here(paste0("reports/pseudotime_meki_", loi, "_", doi, ".pdf")), width = 8, height = 8)

tmp <- runif(100, -1, 1)
x <- cbind(tmp, tmp ^ 2) + rnorm(200, sd = 0.05)
s <- matrix(c(-1, 0, 1, 1, 0, 1), ncol = 2)

proj <- project_to_curve(x, s)

plot(x)
lines(s)
segments(x[, 1], x[, 2], proj$s[, 1], proj$s[, 2])

```

Plot Export

```

gg_bortezomib + ggsave(here::here("reports/figures/gg_bortezomib.pdf"), width = 2, height = 8)

gg_mtor_all + ggsave(here::here("reports/figures/gg_mtor.pdf"), width = 6, height = 3)
gg_mtor_all + ggsave(here::here("reports/figures/gg_gsk.pdf"), width = 6, height = 3)

gg_mek_traj_sel + ggsave(here::here("reports/figures/gg_mek_traj_sel.pdf"), width = 4, height = 4)
gg_bini_traj_sel + ggsave(here::here("reports/figures/gg_bini_traj_sel.pdf"), width = 4, height = 4)
gg_tram_traj + ggsave(here::here("reports/figures/gg_tram_traj.pdf"), width = 4, height = 4)

gg_big5_density + ggsave(here::here("reports/figures/gg_big5_density.pdf"), width = 16, height = 8)
gg_mekgsk_density + ggsave(here::here("reports/figures/gg_mekgsk_density.pdf"), width = 12, height = 12)

```

Supplement

Here I collect pieces of code that did not make it into the final analysis but can be run in theory. In order to access these peaces of code, you have to open the *.RMD* file.

```
knitr::knit_exit()
```