

Optimisation with the SEIRD model

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```
library(comomodels)
library(ggplot2)
library(gridExtra)
library(glue)
library(dplyr)
library(tidyr)
```

Choose between plotting cached data or run optimisation

```
# TRUE to plot saved data, FALSE to run optimisation
cached_bool <- TRUE
set.seed(0)
```

Introduction

This document shows an application of the SEIRD model class within the `como-models` package to the COVID-19 data. By fitting the SEIRD model to the COVID-19 data, we can use the model to learn (such as) the transmission rate and the death rate of the epidemic. We can also make predictions of the pandemic using the fitted model. However, due to limited information and presence of uncertainty, the data may not be able to confine or identify a single set of model parameters for the data; that is, multiple sets of parameters can fit the model to the data whilst giving same objective value (in our example, it is the log-likelihood value). This is known as an issue of identifiability in the model parameters.

In this vignette, we show how optimisation can be done with the `como-models` package, and how the identifiability of parameters in the SEIRD model can be assessed. We also demonstrate that one has to be cautious when interpreting optimisation results.

Optimisation on real London COVID-19 data

First, we will try to optimise the model by fitting to the London COVID-19 data. The time period of data we used is set to be the period before any interventions was implemented, lockdown in this case. Each intervention can be thought as a change of the SEIRD model parameters. Since we are fitting only one set of parameters, constant throughout the whole period, we use the London COVID-19 data only up to the implementation of lockdown. The population size for London is assumed to be 9×10^6 ; it is the estimated population of London in 2020 extracted from Ref. [london_data].

```

# Load London COVID-19 data
df_london = read.csv('data/London_data.csv', header = TRUE)

# Extracting cases and deaths and renaming columns
cases_deaths_name_london = c('newCasesBySpecimenDate', 'newDailyNsoDeathsByDeathDate')
df_london = df_london[cases_deaths_name_london]
names(df_london)[names(df_london) == "newCasesBySpecimenDate"] <- "DailyCases"
names(df_london)[names(df_london) == "newDailyNsoDeathsByDeathDate"] <- "DailyDeaths"

population_size <- 9e6

```

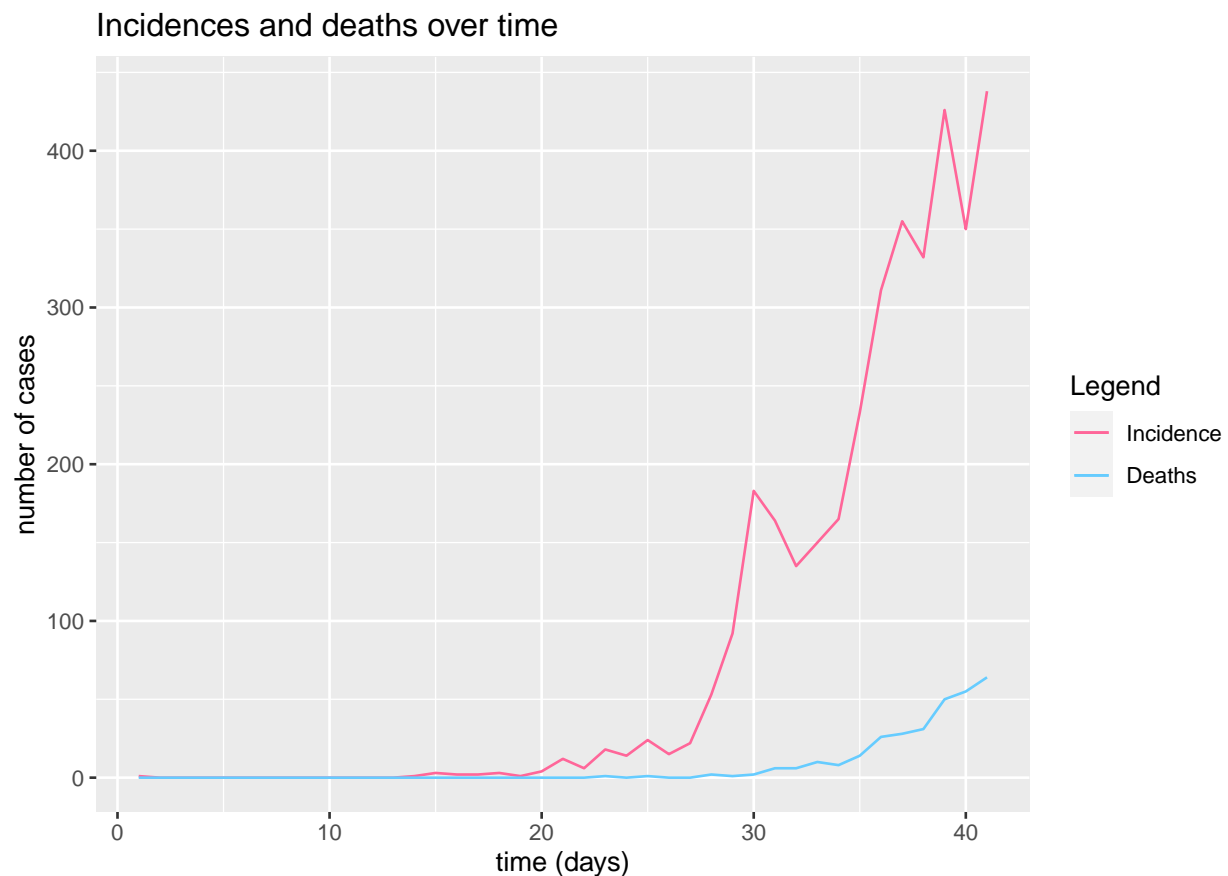
We first inspect the daily incidences and deaths in London, over the period of 1st January 2020 to 22 March 2020, where 23 March 2020 is the start of the lockdown.

```

London = df_london[42:82, 1:2] # Start of lockdown (23/03/2020) is 83rd day
rownames(London) = seq(length=nrow(London))
London$time <- seq(length=nrow(London))

ggplot() +
  geom_line(data=London, aes(x = time, y = DailyCases, color="Incidence")) +
  geom_line(data=London, aes(x = time, y = DailyDeaths, color="Deaths")) +
  scale_color_manual(name = "Legend",
    values = c("Incidence" = "#FF6699", "Deaths" = "#66CCFF")) +
  labs(x = "time (days)", y = "number of cases",
    title = glue("Incidences and deaths over time"))

```



The figure above shows the incidences and deaths in London, starting from 1st January 2020 to 22 March 2020.

In this example, we will perform maximum likelihood estimation; we first define a (log-)likelihood function to be maximised. We will use a Poisson likelihood to model (the noise of) the data. Note that it takes the average of the log-likelihood values of incidences and deaths. With L as the likelihood function, N as the size of the data, k as the actual data and λ as estimator of the SEIRD model, the log-likelihood function is

$$\log L = \sum_{i=1}^N (k_i \log \lambda_i - \lambda_i)$$

```
RealData_LogLikelihoodFn <- function(parameters, model=SEIRD(),
                                     inc_numbers=0, death_numbers=0) {

  # Set up parameters
  transmission_para <- list(beta=parameters[1],
                           kappa=parameters[2],
                           gamma=parameters[3],
                           mu=parameters[4])
  init_cond <- list(S0=parameters[5],
                   E0=parameters[6],
                   I0=parameters[7],
                   R0=parameters[8])

  transmission_parameters(model) <- transmission_para
  initial_conditions(model) <- init_cond

  # Simulate model
  times <- seq(0, length(inc_numbers), by = 1)
  out_df <- run(model, times)

  data_wide <- spread(out_df$changes, compartment, value)
  data_wide$Incidence <- abs(data_wide$Incidence) * population_size
  data_wide$Deaths <- abs(data_wide$Deaths) * population_size

  # Computation of log-likelihood function
  logIncidence <- log(data_wide$Incidence[-1])
  incidence_likelihood <- sum(inc_numbers * logIncidence - data_wide$Incidence[-1])
  logDeaths <- log(data_wide$Deaths[-1])
  death_likelihood <- sum(death_numbers * logDeaths - data_wide$Deaths[-1])

  (incidence_likelihood + death_likelihood)/2
}
```

Optimisation

The optimisation of the SEIRD model is repeated 100 times, with different initial values for all transmission parameters. Due to the heuristic approach of Nelder-Mead method, each run of optimisation will return different sets of optimised parameters.

```
repeat_num <- 5
for (repeats in 1:repeat_num){
  trans_params_guess <- runif(4, min = 0, max = 1)
```

```

init_conds_guess<- c(1-3e-7, 1e-7, 1e-7, 1e-7)
constraint_ui <- rbind(diag(8), -diag(8)[5:8,],
                      c(rep(0, 4), rep(1,4)),
                      c(rep(0, 4), rep(-1,4)))
constraint_ci <- c(rep(0, 8), rep(-1, 4), 0.99, -1.01)

result <- constrOptim(c(trans_params_guess, init_conds_guess), RealData_LogLikelihoodFn,
                     'NULL', constraint_ui, constraint_ci,
                     method = "Nelder-Mead", control=list(fnscale=-1, reltol=1e-6),
                     inc_numbers = London$DailyCases,
                     death_numbers = London$DailyDeaths)
if (repeats == 1){
  optimised_para <- data.frame("beta_opt" = result$par[1], "kappa_opt" = result$par[2],
                              "gamma_opt" = result$par[3], "mu_opt" = result$par[4],
                              "S0_opt" = result$par[5], "E0_opt" = result$par[6],
                              "I0_opt" = result$par[7], "R0_opt" = result$par[8],
                              "obj_fn" = result$value)
  initial_guesses <- data.frame("beta_init" = trans_params_guess[1],
                                "kappa_init" = trans_params_guess[2],
                                "gamma_init" = trans_params_guess[3],
                                "mu_init" = trans_params_guess[4])
} else {
  optimised_para[nrow(optimised_para) + 1,] <- c(result$par, result$value)
  initial_guesses[nrow(initial_guesses) + 1,] <- c(trans_params_guess)
}
}

opt_init_df <- merge(optimised_para, initial_guesses, by = 0)

# save optimised parameters
write.csv(opt_init_df, "data/London_parameters_100_optimisations.csv", row.names = FALSE)

# load saved results
opt_init_df <- read.csv("data/London_parameters_100_optimisations.csv")
repeat_num <- nrow(opt_init_df)

```

Visualising optimised result

```

optimised_para <- subset(opt_init_df, select=c(beta_opt, kappa_opt, gamma_opt, mu_opt,
                                              S0_opt, E0_opt, I0_opt, R0_opt))
colnames(optimised_para) <- c("beta", "kappa", "gamma", "mu", "S0", "E0", "I0", "R0")
for (repeats in 1:repeat_num){

  my_model <- SEIRD()

  transmission_parameters(my_model) <- optimised_para[repeats, 1:4]
  initial_conditions(my_model) <- optimised_para[repeats, 5:8]

  times <- seq(0, length(London$DailyCases), by = 1)
  out_df <- run(my_model, times)
}

```

```

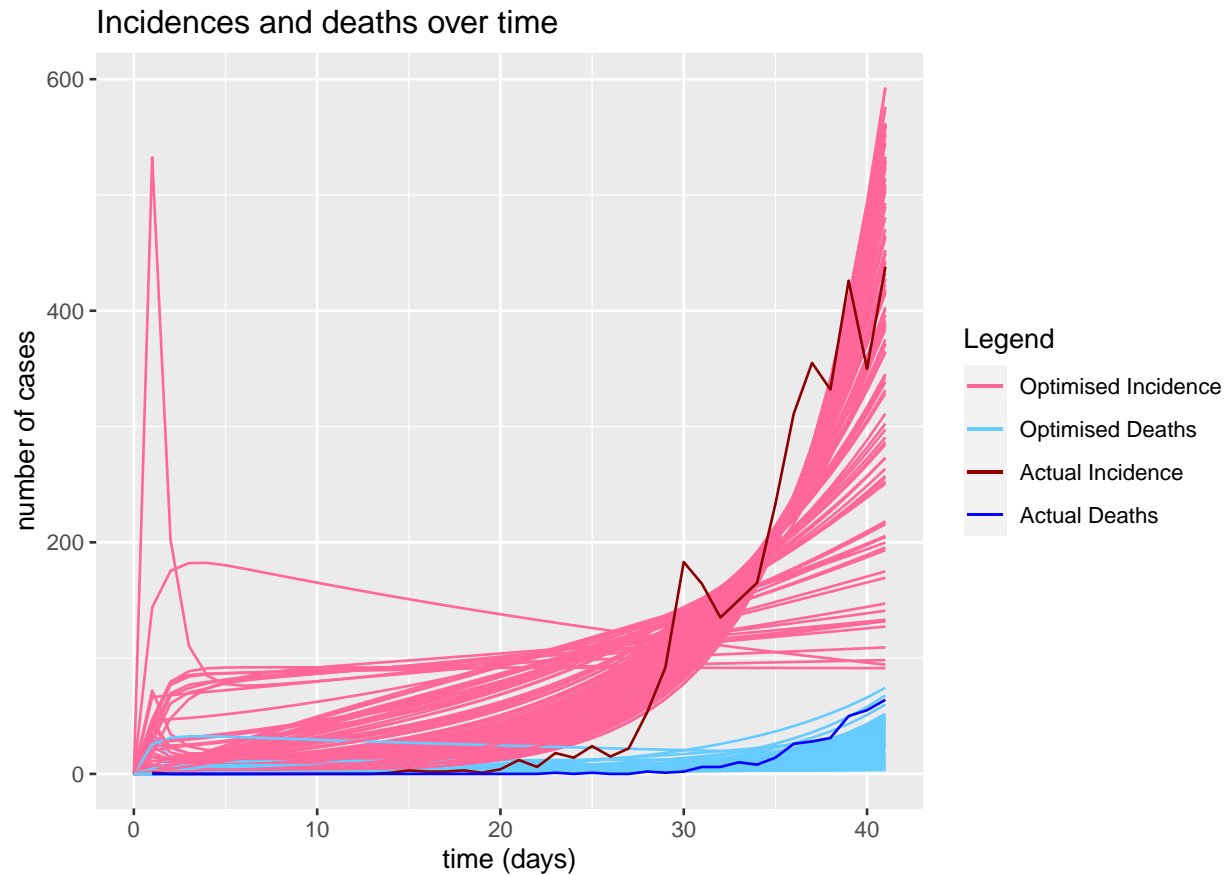
cases <- out_df$changes
cases$value <- cases$value * population_size
cases$repeat_id <- rep(repeats, length(cases$time))

if (repeats == 1){
  cases_repeats <- cases
} else{
  cases_repeats <- rbind(cases_repeats, cases)
}
}

cases_repeats <- spread(cases_repeats, compartment, value)
b <- ggplot()
for (i in 1:repeat_num){
  data_set <- cases_repeats[cases_repeats$repeat_id == i,]
  b <- b + geom_line(data=data_set, aes(x = time, y = Incidence,
                                         color="Optimised Incidence")) +
  geom_line(data=data_set, aes(x = time, y = Deaths, color="Optimised Deaths"))
}
b <- b + geom_line(data=London, aes(x = time, y = DailyCases, color="Actual Incidence")) +
  geom_line(data=London, aes(x = time, y = DailyDeaths, color="Actual Deaths")) +
  scale_color_manual(name = "Legend", values = c("Optimised Incidence" = "#FF6699",
                                                "Optimised Deaths" = "#66CCFF",
                                                "Actual Incidence" = "darkred",
                                                "Actual Deaths" = "blue")) +

  labs(x = "time (days)", y = "number of cases",
        title = glue("Incidences and deaths over time"))
print(b)

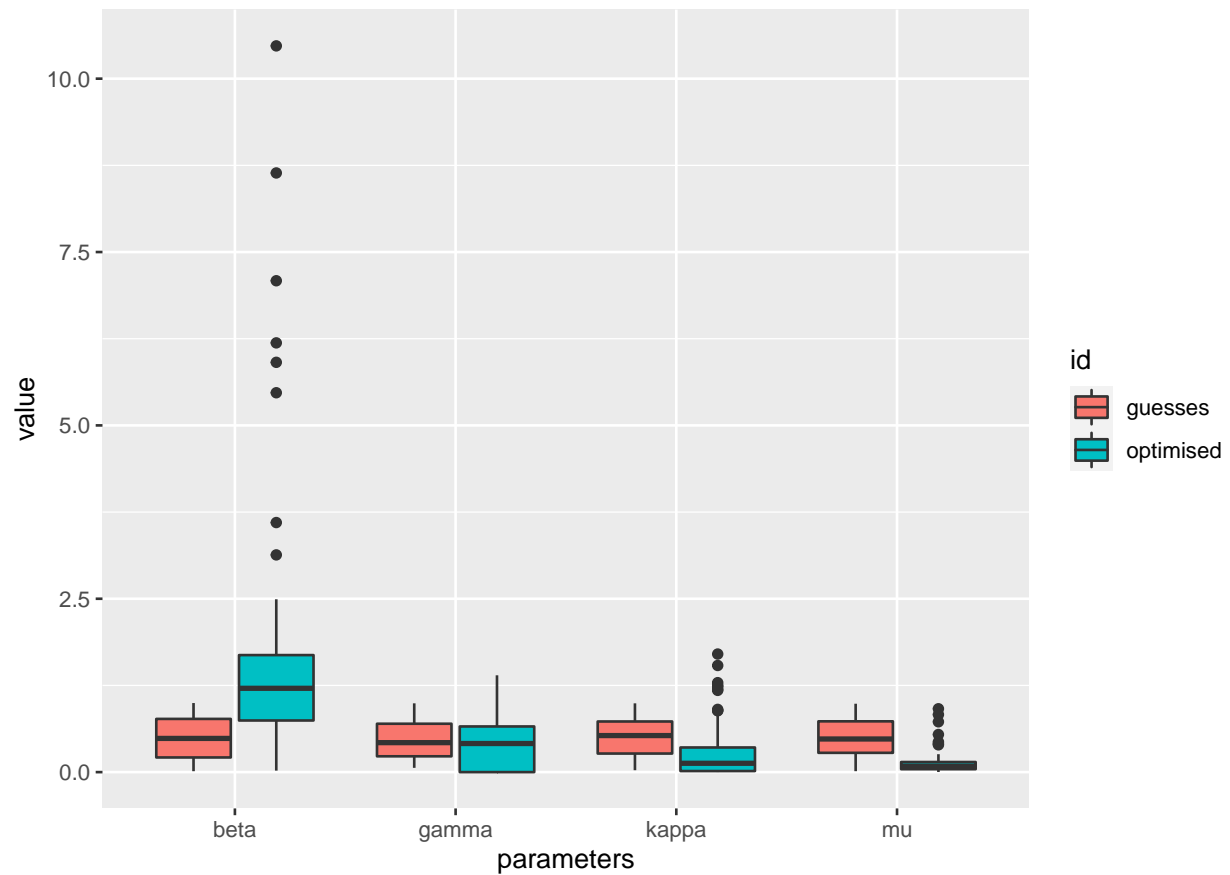
```



The figure above shows the 100 fitted models on the actual incidences and deaths. It can be observed from the figure that different runs of optimisation returns different results. Some of the fits even have their peaks in the first 10 days of the pandemic.

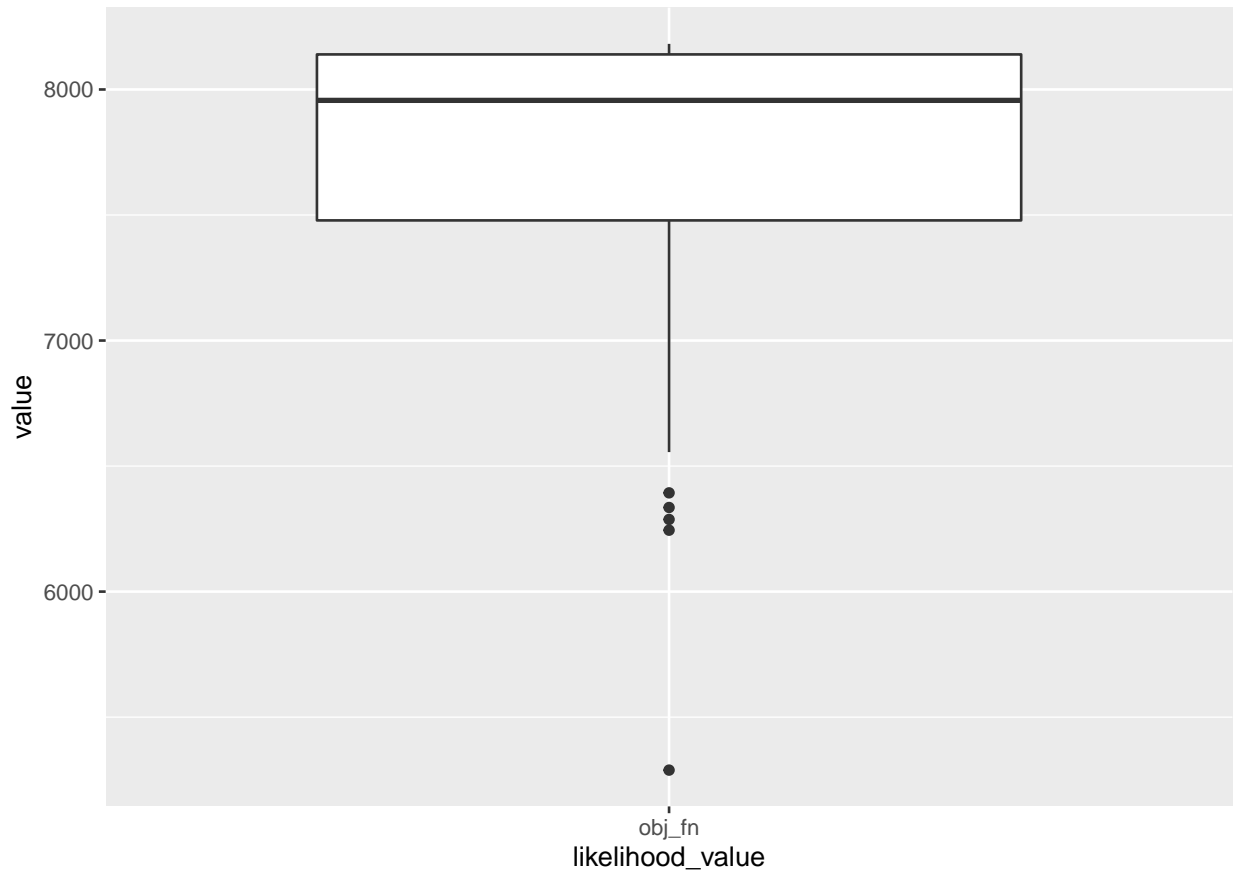
Box plot of estimated variables

```
plotting_data <- subset(opt_init_df, select=c(beta_opt, kappa_opt, gamma_opt, mu_opt))
colnames(plotting_data) <- c("beta", "kappa", "gamma", "mu")
plotting_data$index <- seq(1, repeat_num)
plotting_data$id <- rep("optimised", repeat_num)
initial_guesses <- subset(opt_init_df,
                          select=c(beta_init, kappa_init, gamma_init, mu_init))
colnames(initial_guesses) <- c("beta", "kappa", "gamma", "mu")
initial_guesses$index <- seq(1, repeat_num)
initial_guesses$id <- rep("guesses", repeat_num)
data <- rbind(plotting_data, initial_guesses)
data <- gather(data, key="parameters", value="value", -c(index, id))
ggplot(data, aes(x=parameters, y=value, fill=id)) +
  geom_boxplot()
```



The box plot compares the summary statistics of prior and posterior of transmission parameters, which are β , κ , γ and μ .

```
plotting_data <- subset(opt_init_df, select=c(obj_fn))
plotting_data$index <- seq(1, repeat_num)
data <- gather(plotting_data, key="likelihood_value", value="value", -c(index))
ggplot(data, aes(x=likelihood_value, y=value)) +
  geom_boxplot()
```



The box plot shows a range of log-likelihood values achieved from different runs of optimisation. Note that the Nelder-Mead algorithm used here is a local optimisation algorithm, which does not guarantee a convergence to the global optimum. The result confirms that some runs of optimisation perform better than others, which can happen when the optimising algorithm reaches a local optimum.

After sorting the obtained parameters according to the error value, we choose the top 20 optimisation with highest log-likelihood values as our final maximum-likelihood estimates.

```
chosen_repeats <- 2
opt_init_df <- opt_init_df[order(-opt_init_df$obj_fn),]
top_opt_init_df <- opt_init_df[1:chosen_repeats,]
top_optimised_para <- subset(top_opt_init_df, select=c(beta_init, kappa_init,
                                                    gamma_init, mu_init,
                                                    Row.names))

colnames(top_optimised_para) <- c("beta", "kappa", "gamma", "mu", "S0", "EO", "IO", "R0")
# top_initial_guesses <- subset(top_opt_init_df, select=c(beta_init, kappa_init,
#                                                    gamma_init, mu_init))

for (repeats in 1:chosen_repeats){

  my_model <- SEIRD()

  transmission_parameters(my_model) <- top_optimised_para[repeats, 1:4]
  initial_conditions(my_model) <- top_optimised_para[repeats, 5:8]}
```



```

times <- seq(0, length(London$DailyCases), by = 1)
out_df <- run(my_model, times)

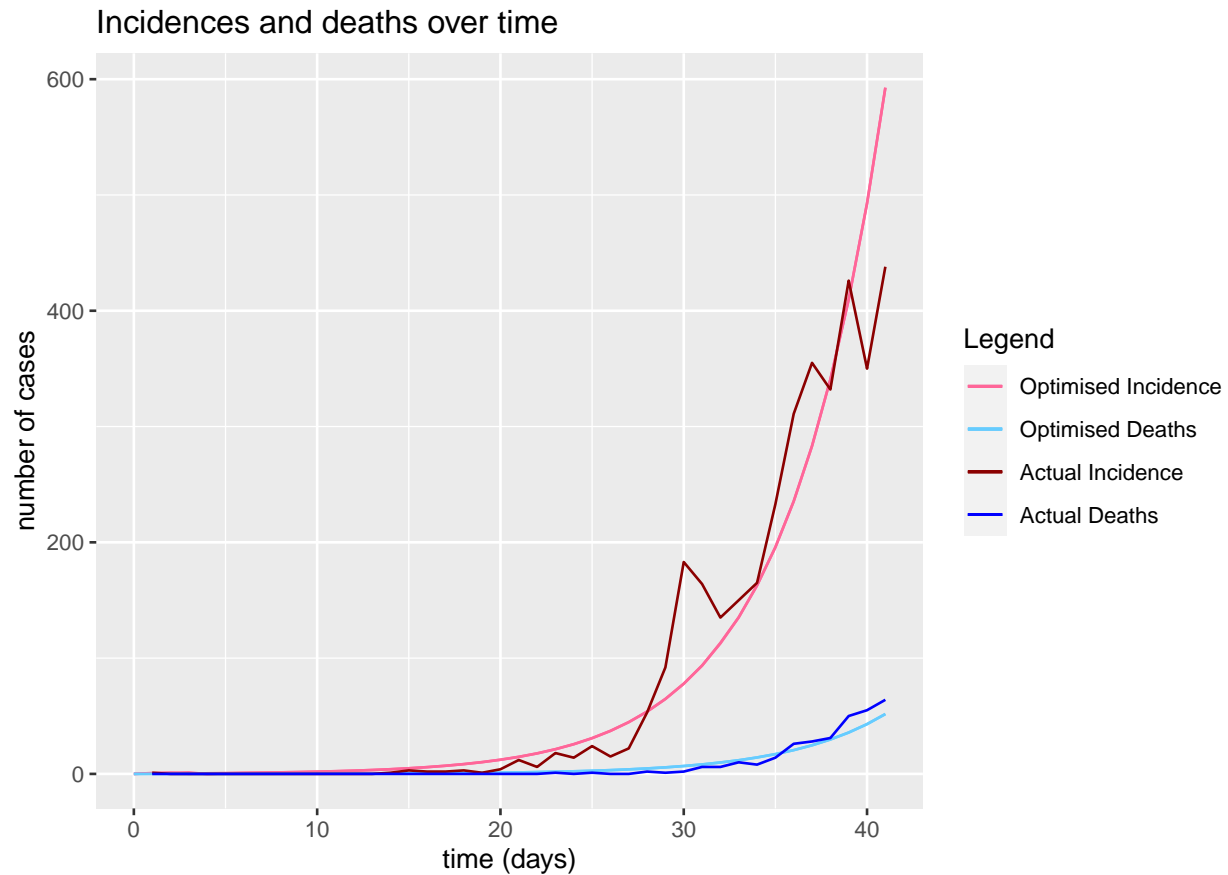
cases <- out_df$changes
cases$value <- cases$value * population_size
cases$repeat_id <- rep(repeats, length(cases$time))

if (repeats == 1){
  cases_repeats <- cases
} else{
  cases_repeats <- rbind(cases_repeats, cases)
}
}

cases_repeats <- spread(cases_repeats, compartment, value)
b <- ggplot()
for (i in 1:chosen_repeats){
  data_set <- cases_repeats[cases_repeats$repeat_id == i,]
  b <- b + geom_line(data=data_set, aes(x = time, y = Incidence,
                                         color="Optimised Incidence")) +
  geom_line(data=data_set, aes(x = time, y = Deaths, color="Optimised Deaths"))
}
b <- b + geom_line(data=London, aes(x = time, y = DailyCases, color="Actual Incidence")) +
  geom_line(data=London, aes(x = time, y = DailyDeaths, color="Actual Deaths")) +
  scale_color_manual(name = "Legend", values = c("Optimised Incidence" = "#FF6699",
                                                "Optimised Deaths" = "#66CCFF",
                                                "Actual Incidence" = "darkred",
                                                "Actual Deaths" = "blue")) +

  labs(x = "time (days)", y = "number of cases",
       title = glue("Incidences and deaths over time"))
print(b)

```



The figure above shows the 20 optimisations that achieve highest log-likelihood value.

Projection of the epidemic using the fitted SEIRD model

```
for (repeats in 1:chosen_repeats){

  my_model <- SEIRD()

  transmission_parameters(my_model) <- top_optimised_para[repeats, 1:4]
  initial_conditions(my_model) <- top_optimised_para[repeats, 5:8]

  times <- seq(0, length(London$DailyCases) * 5, by = 1)
  out_df <- run(my_model, times)

  cases <- out_df$changes
  cases$value <- cases$value * population_size
  cases$repeat_id <- rep(repeats, length(cases$time))

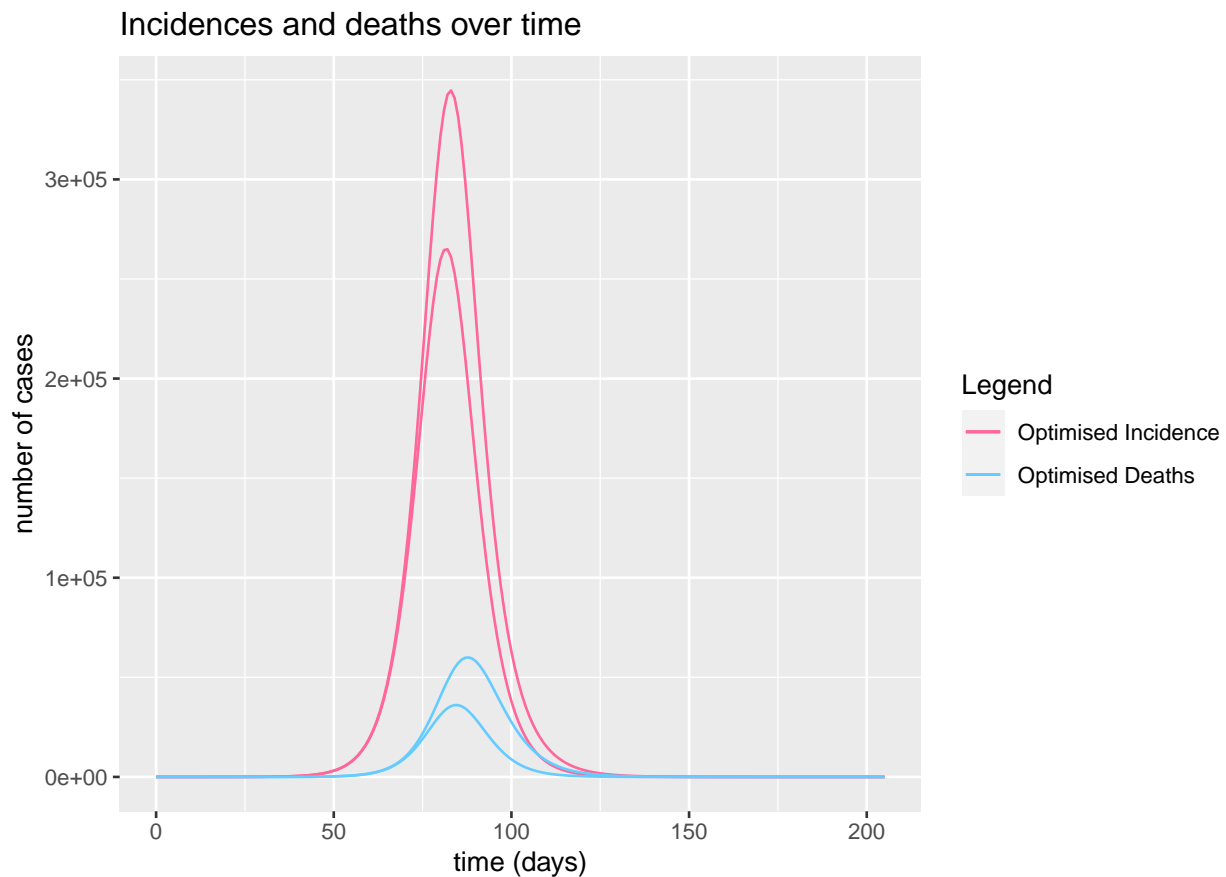
  if (repeats == 1){
    cases_repeats <- cases
  } else{
    cases_repeats <- rbind(cases_repeats, cases)
  }
}
```

```

}

cases_repeats <- spread(cases_repeats, compartment, value)
b <- ggplot()
for (i in 1:chosen_repeats){
  data_set <- cases_repeats[cases_repeats$repeat_id == i,]
  b <- b + geom_line(data=data_set, aes(x = time, y = Incidence,
                                         color="Optimised Incidence")) +
  geom_line(data=data_set, aes(x = time, y = Deaths, color="Optimised Deaths"))
}
b <- b + scale_color_manual(name = "Legend",
                           values = c("Optimised Incidence" = "#FF6699",
                                       "Optimised Deaths" = "#66CCFF")) +
  labs(x = "time (days)", y = "number of cases",
       title = glue("Incidences and deaths over time"))
print(b)

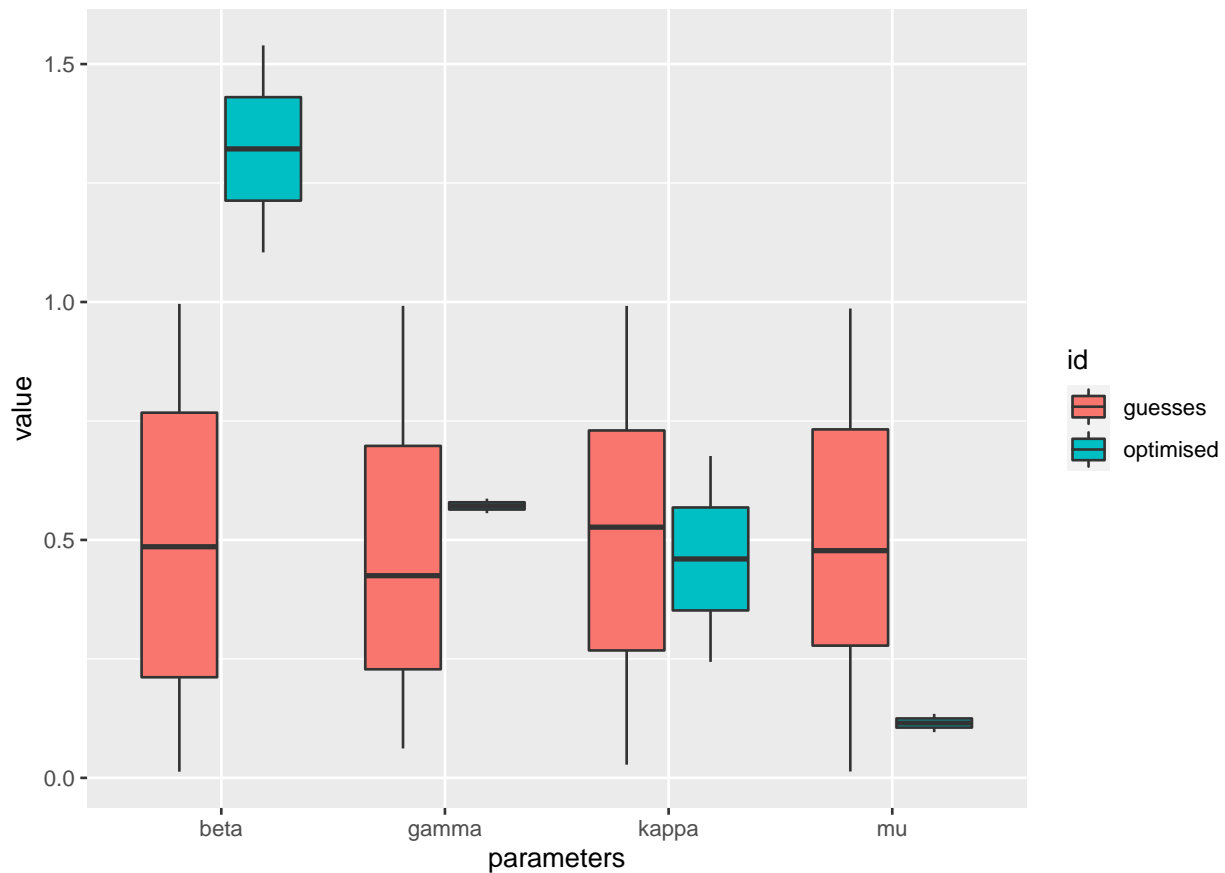
```



The figure above shows that even when the optimisation fits the real data well during early stages of the pandemic, (very) different outcomes are predicted. Given the estimated London population, the maximum difference in peak values of all projections is more than 2×10^5 for incidences and almost 1×10^5 for deaths.

Box plot of the estimated variables and log-likelihood value

```
plotting_data <- subset(top_optimised_para, select=c(beta, kappa, gamma, mu))
plotting_data$index <- seq(1, chosen_repeats)
plotting_data$id <- rep("optimised", chosen_repeats)
initial_guesses <- subset(opt_init_df, select=c(beta_init, kappa_init,
                                              gamma_init, mu_init))
colnames(initial_guesses) <- c("beta", "kappa", "gamma", "mu")
initial_guesses$index <- seq(1, chosen_repeats)
initial_guesses$id <- rep("guesses", chosen_repeats)
data <- rbind(plotting_data, initial_guesses)
data <- gather(data, key="parameters", value="value", -c(index, id))
ggplot(data, aes(x=parameters, y=value, fill=id)) +
  geom_boxplot()
```



The box plot shows the range of optimised parameters of optimisations with top 20 highest log-likelihood values. Despite achieving the largest objective value, the transmission parameters, except μ , display a distribution of optimised values, with large standard deviation. This shows that different sets of transmission parameters can achieve similar log-likelihood values. With the London COVID-19 data, the SEIRD model cannot identify the parameters uniquely.

Synthetic data studies and profile likelihood

To assess the identifiability issue observed in optimisations of the real data, we perform a profile likelihood analysis over some *synthetic data*. The profile likelihood is a series of maximum likelihood value obtained by fixing a parameter of interest to a range of values and optimising the remaining parameters.

Generating synthetic data

The mean value of the synthetic data is simulated with values that provide sufficient time points before the peak of the pandemic, which qualitatively replicates the London COVID-19 data shown above.

```
model <- SEIRD()
simulating_para <- list(beta=9.1e-1, kappa=8.7e-1, gamma=5.3e-1, mu=9.7e-2,
                        S0=9.999e-1, E0=1e-7, I0=1e-7, R0=1e-6)
transmission_para_name <- c("beta", "kappa", "gamma", "mu")
initial_conditions_name <- c("S0", "E0", "I0", "R0")
transmission_parameters(model) <- simulating_para[transmission_para_name]
initial_conditions(model) <- simulating_para[initial_conditions_name]

times <- seq(0, 150, by = 1)
out_df <- run(model, times)
```

```
model <- SEIRD()
simulating_para <- list(beta=9.1e-1, kappa=8.7e-1, gamma=5.3e-1, mu=9.7e-2,
                        S0=9.999e-1, E0=1e-7, I0=1e-7, R0=1e-6)
```

Adding noise to the synthetic data

The synthetic data is then generated by drawing samples from a Poisson distribution with λ as the incidences and deaths of model simulated value, as shown in the equations below. $C(t)$ and $D(t)$ are the number of incidences and deaths at time t respectively; $C^*(t)$ and $D^*(t)$ are the number of incidences and deaths with Poisson noise.

$$C^*(t) \sim \text{Pois}(C(t))$$

$$D^*(t) \sim \text{Pois}(D(t))$$

```
population_size <- 1e4

# generate synthetic data with Poisson noise
testing_data <- spread(out_df$changes, compartment, value)
testing_data$Incidence <- testing_data$Incidence * population_size
testing_data$Deaths <- testing_data$Deaths * population_size
inc_noise <- rpois(1, testing_data$Incidence[1])
death_noise <- rpois(1, testing_data$Deaths[1])
for (i in 2:length(testing_data$Incidence)){
  inc_rand <- rpois(1, testing_data$Incidence[i])
  inc_noise <- c(inc_noise, inc_rand)

  death_rand <- rpois(1, testing_data$Deaths[i])
  death_noise <- c(death_noise, death_rand)
}
```

```

testing_data$IncNoise <- inc_noise
testing_data$DeathNoise <- death_noise
testing_data <- testing_data[-1,]

# save results
write.csv(testing_data, "data/synthetic_data.csv", row.names = FALSE)

# load saved data
population_size <- 1e4
testing_data <- read.csv("data/synthetic_data.csv")

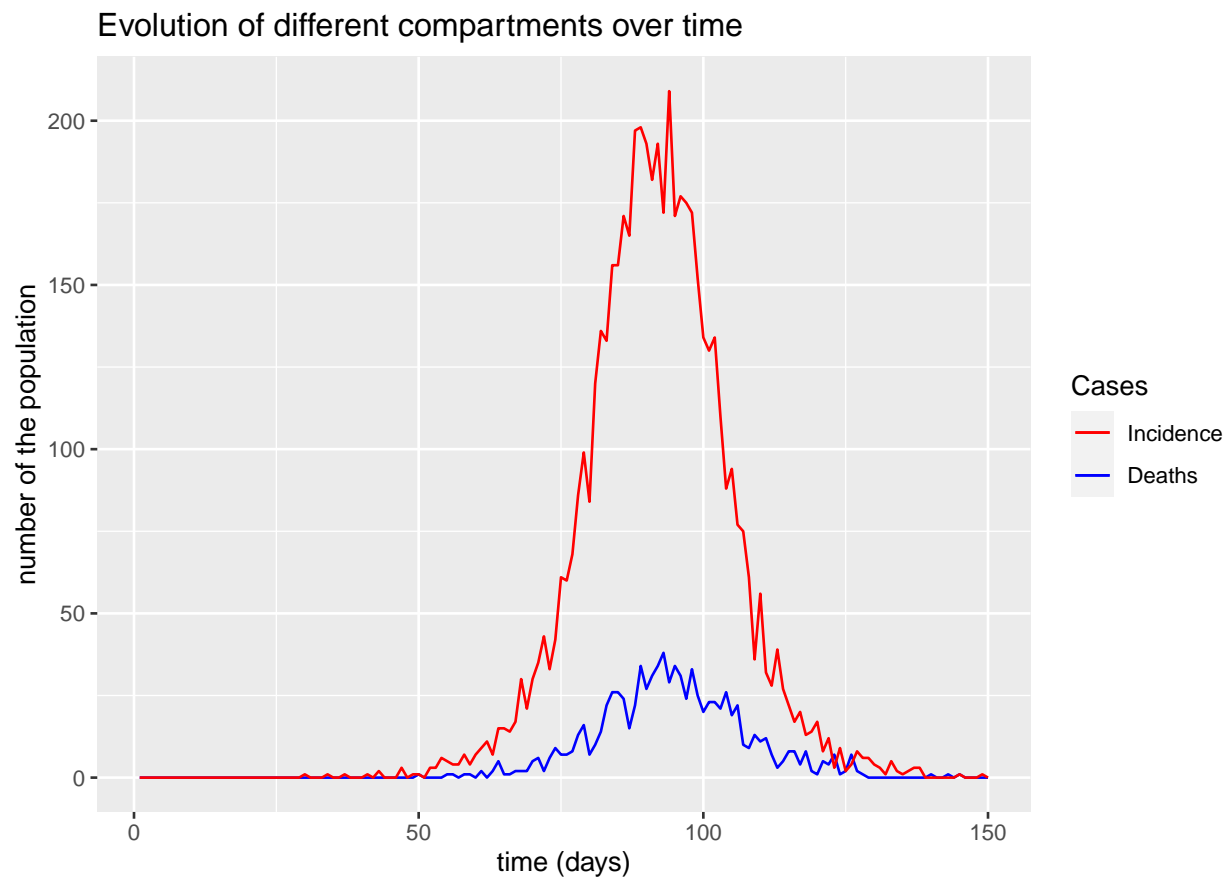
```

Visualising the synthetic data

```

ggplot() +
  geom_line(data=testing_data, aes(x = time, y = DeathNoise, color = "Deaths")) +
  geom_line(data=testing_data, aes(x = time, y = IncNoise, color = "Incidence")) +
  scale_color_manual(name = "Cases", values = c("Incidence" = "red", "Deaths" = "blue")) +
  labs(x = "time (days)", y = "number of the population",
       title = glue("Evolution of different compartments over time"))

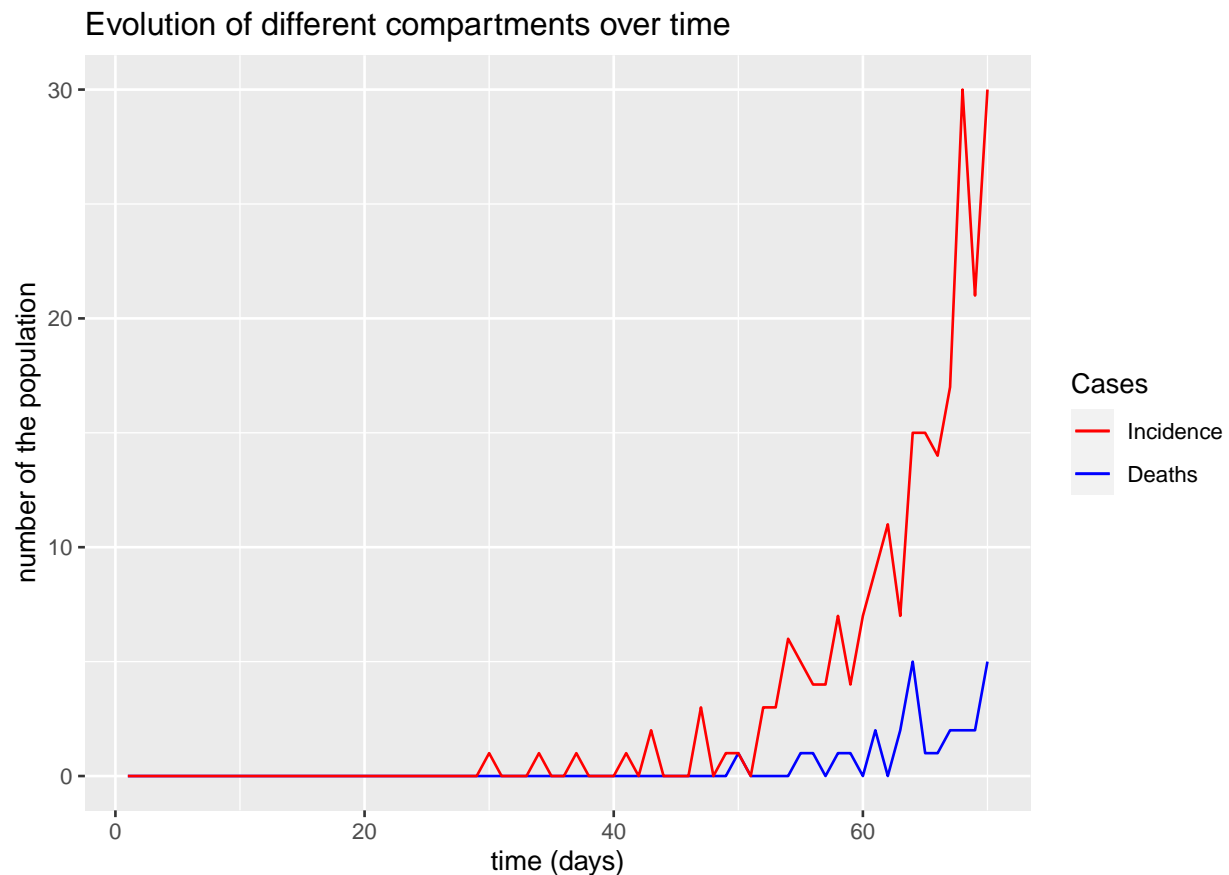
```



The figure above shows the synthetic data simulated for the full pandemic.

```
testing_data_short <- testing_data[1:70,]

ggplot() +
  geom_line(data=testing_data_short, aes(x = time, y = DeathNoise, color = "Deaths")) +
  geom_line(data=testing_data_short, aes(x = time, y = IncNoise, color = "Incidence")) +
  scale_color_manual(name = "Cases", values = c("Incidence" = "red", "Deaths" = "blue")) +
  labs(x = "time (days)", y = "number of the population",
       title = glue("Evolution of different compartments over time"))
```



The first 70 times points (days) of the simulated data is used, giving roughly 40 times points since the first case, which is similar to the London COVID-19 data.

Again, a Poisson log-likelihood function is used to fit the SEIRD model to the simulated data. The profile likelihood is then constructed for the transmission parameters, while the initial conditions are fixed at values used to generate the simulated data.

```
# Log-likelihood function when optimising all transmission parameters
LogLikelihoodFn4 <- function(parameters, model=SEIRD(), inc_numbers=0, death_numbers=0,
                              fixed_parameter=FALSE, fixed_parameter_value=0) {

  transmission_para <- list(beta=parameters[1],
                            kappa=parameters[2],
                            gamma=parameters[3],
                            mu=parameters[4])
```

```

# fixing parameter of interest
if (fixed_parameter != FALSE){
  transmission_para[names(transmission_para) == fixed_parameter] <-
    fixed_parameter_value}

init_cond <- list(S0=simulating_para[5],
                 E0=simulating_para[6],
                 I0=simulating_para[7],
                 R0=simulating_para[8])
transmission_parameters(model) <- transmission_para
initial_conditions(model) <- init_cond

# simulate model
times <- seq(0, length(inc_numbers), by = 1)
out_df <- run(model, times)

data_wide <- spread(out_df$changes, compartment, value)
data_wide$Incidence <- abs(data_wide$Incidence) * population_size
data_wide$Deaths <- abs(data_wide$Deaths) * population_size

# calculate log-likelihood value
logIncidence <- log(data_wide$Incidence[-1])
incidence_likelihood <- sum(inc_numbers * logIncidence - data_wide$Incidence[-1])
logDeaths <- log(data_wide$Deaths[-1])
death_likelihood <- sum(death_numbers * logDeaths - data_wide$Deaths[-1])

(incidence_likelihood + death_likelihood)/2
}

```

```

# Log-likelihood function when optimising beta and gamma
LogLikelihoodFn2 <- function(parameters, model=SEIRD(), inc_numbers=0, death_numbers=0,
                             fixed_parameter=FALSE, fixed_parameter_value=0) {

  transmission_para <- list(beta=parameters[1],
                           kappa=simulating_para[2],
                           gamma=parameters[2],
                           mu=simulating_para[4])

  # fixing parameter of interest
  if (fixed_parameter != FALSE){
    transmission_para[names(transmission_para) == fixed_parameter] <-
      fixed_parameter_value}

  init_cond <- list(S0=simulating_para[5],
                   E0=simulating_para[6],
                   I0=simulating_para[7],
                   R0=simulating_para[8])
  transmission_parameters(model) <- transmission_para
  initial_conditions(model) <- init_cond

  # simulate model
  times <- seq(0, length(inc_numbers), by = 1)
  out_df <- run(model, times)

```



```

data_wide <- spread(out_df$changes, compartment, value)
data_wide$Incidence <- abs(data_wide$Incidence) * population_size
data_wide$Deaths <- abs(data_wide$Deaths) * population_size

# calculate log-likelihood value
logIncidence <- log(data_wide$Incidence[-1])
incidence_likelihood <- sum(inc_numbers * logIncidence - data_wide$Incidence[-1])
logDeaths <- log(data_wide$Deaths[-1])
death_likelihood <- sum(death_numbers * logDeaths - data_wide$Deaths[-1])

(incidence_likelihood + death_likelihood)/2
}

```

Profile likelihood of β and γ

In some cases, identifiability issues arise when there are more parameters describing the model than the information can infer. In other words, parameters cannot be uniquely identified with limited data. When the number of parameters increases, the parameters might become unidentifiable. Here, we first create a profile likelihood for only two of the four transmission parameters in the SEIRD model.

Setting ranges for profile likelihood

```

constraint_ui <- rbind(diag(2))
constraint_ci <- c(rep(0,2))

profile_parameters <- c('beta', 'gamma')

# beta_range <- c(seq(simulating_para[1], 0.4, by = -0.02),
#                 seq(simulating_para[1], 1.5, by = 0.02))
# gamma_range <- c(seq(simulating_para[3], 0.1, by = -0.02),
#                 seq(simulating_para[3], 1.1, by = 0.02))

beta_range <- seq(simulating_para$beta, 0.4, by = -0.1)
gamma_range <- seq(simulating_para$gamma, 0.1, by = -0.1)

range_transmission <- data.frame(parameter=rep('beta', length(beta_range)),
                                fixed_value=beta_range)
range_transmission <- rbind(range_transmission, data.frame(
  parameter=rep('gamma', length(gamma_range)), fixed_value=gamma_range))

```

Optimisation

```

previous_param <- rep(0, 2)
profile_likelihood <- data.frame(parameter=character(), fixed_value=double(),
                                likelihood_value=double(), optim_beta=double(),
                                optim_gamma=double())
profile_likelihood$parameter <- as.character(profile_likelihood$parameter)

set.seed(0)

```

```

for (param_name in profile_parameters){
  err_value <- 0
  fixed_values <- range_transmission %>% filter(parameter == param_name)
  fixed_values <- fixed_values$fixed_value
  for (i in 1:length(fixed_values)){
    if (param_name == 'beta' & fixed_values[i] == simulating_para[1]){
      init_guess <- c(simulating_para[1], simulating_para[3])
    } else if (param_name == 'gamma' & fixed_values[i] == simulating_para[3]){
      init_guess <- c(simulating_para[1], simulating_para[3])
    } else {
      init_guess <- previous_param}

    result <- constrOptim(init_guess, LogLikelihoodFn2,
                        'NULL', constraint_ui, constraint_ci,
                        method = "Nelder-Mead",
                        control=list(fnscale=-1, reltol=1e-6),
                        model=model,
                        inc_numbers = testing_data_short$IncNoise,
                        death_numbers = testing_data_short$DeathNoise,
                        fixed_parameter = param_name,
                        fixed_parameter_value = fixed_values[i])
    err_value <- append(err_value, result$value)
    previous_param <- result$par
    profile_likelihood[
      nrow(profile_likelihood) + 1,] <- c(
        param_name, fixed_values[i],
        result$value, result$par)
  }
}

```

While working through the optimisations for different fixed values of parameter of interest, the previously optimised parameters were used as the initial guesses for the next round of optimisation. To ease the optimisation challenges for the profile likelihood, the parameters for the profile likelihood were swepted from the actual parameter value to the minimum, then from the actual parameter value to the maximum.

```

profile_likelihood <- transform(profile_likelihood, fixed_value=as.numeric(fixed_value))
profile_likelihood <- transform(profile_likelihood,
                                likelihood_value=as.numeric(likelihood_value))
profile_likelihood <- transform(profile_likelihood, optim_beta=as.numeric(optim_beta))
profile_likelihood <- transform(profile_likelihood, optim_gamma=as.numeric(optim_gamma))

# save results
write.csv(profile_likelihood, "data/synthetic_halftrend_2param_profilelikelihood.csv",
          row.names = FALSE)

```

```

profile_likelihood <- read.csv("data/synthetic_halftrend_2param_profilelikelihood.csv")

```

Profile likelihood

```

ymin <- floor(min(profile_likelihood$likelihood_value))
ymax <- ceiling(max(profile_likelihood$likelihood_value))
profile_beta <- ggplot(profile_likelihood %>% filter(parameter == 'beta'),

```

```

      aes(x = fixed_value, y = likelihood_value)) +
    geom_vline(xintercept = simulating_para[1]) + geom_point() +
    ylim(ymin, ymax) + ggtitle("beta")
profile_gamma <- ggplot(profile_likelihood %>% filter(parameter == 'gamma'),
      aes(x = fixed_value, y = likelihood_value)) +
    geom_vline(xintercept = simulating_para[3]) + geom_point() +
    ylim(ymin, ymax) + ggtitle("gamma")
grid.arrange(profile_beta, profile_gamma, nrow = 1, ncol = 2)
#> Error in is.finite(x): default method not implemented for type 'list'

```

The figure above shows the log-likelihood value obtained by fixing the parameter of interest and optimising the remaining transmission parameters. The actual parameter value is indicated by the vertical line. The profile likelihood shows a single peak for both β and γ , which implies that the parameters are identifiable when the SEIRD model has only two transmission parameters. However, there is a bias when using the maximum likelihood estimate (i.e. the parameter value with the maximum log-likelihood is not the same as the actual parameter value used to simulate the data). The bias is due to the Poisson noise added to the simulated data.

```

init_cond <- list(S0=9.999e-1,
  EO=1e-7,
  IO=1e-7,
  RO=1e-6)
times <- seq(0, length(testing_data_short$Incidence), by = 1)

profilelikelihood_fit <- function(profile_likelihood, profile_parameters, synthetic_data){

  count <- 0
  trans_param <- list(beta=simulating_para$beta, kappa=simulating_para$kappa,
    gamma=simulating_para$gamma, mu=simulating_para$mu)

  for (param_name in profile_parameters){
    temp <- profile_likelihood %>% filter(parameter == param_name)
    for (i in 1:nrow(temp)){
      model <- SEIRD()
      for (param_interest in profile_parameters){
        trans_param[names(trans_param) == param_interest] <-
          temp[i, paste('optim_', param_interest, sep = "")]
      }
      trans_param[names(trans_param) == param_name] <- temp[i,2]
      transmission_parameters(model) <- trans_param
      initial_conditions(model) <- init_cond

      out_df <- run(model, times)

      # plot simulated data
      fitted_cases <- out_df$changes
      fitted_cases <- spread(fitted_cases, compartment, value)
      fitted_cases$Incidence <- fitted_cases$Incidence * population_size
      fitted_cases$Deaths <- fitted_cases$Deaths * population_size
      fitted_cases <- fitted_cases[-1,]
      fitted_cases$parameter <- rep(param_name, length(fitted_cases$Incidence))
      fitted_cases$fixed_value <- rep(temp$fixed_value[i], length(fitted_cases$Incidence))
    }
  }
}

```

```

    if (count == 0){
      total_cases <- fitted_cases
    } else{
      total_cases <- rbind(total_cases, fitted_cases)
    }
    count <- count + 1
  }
}
total_cases <- transform(total_cases, fixed_value=as.numeric(fixed_value))
optimised_cases <- vector('list', length(profile_parameters))
for (i in 0:length(profile_parameters)){
  optimised_cases[[i]] <- ggplot(total_cases %>% filter(parameter == profile_parameters[i]),
    aes(x = time, y = Incidence, color=fixed_value)) +
    geom_line() +
    scale_color_gradient(low = "grey70", high = "grey40") +
    guides(colour = guide_colorbar(reverse=TRUE)) +
    geom_line(data=synthetic_data, aes(x = time, y = IncNoise), color='red') +
    geom_line(data=synthetic_data, aes(x = time, y = DeathNoise), color='blue') +
    ggtitle(profile_parameters[i])
  grid.arrange(optimised_cases, nrow = length(profile_parameters)%/%2, ncol = 2)
}
}

profilelikelihood_fit(profile_likelihood, profile_parameters, testing_data_short)
#> Error: Problem with 'filter()' input '...1'.
#> i Input '...1' is 'parameter == profile_parameters[i]'.
#> x Input '...1' must be of size 7490 or 1, not size 0.

```

The figure above shows the model simulations using the parameters identified in the profile likelihood.

Profile likelihood of all transmission parameters

The same procedure is repeated with all the transmission parameters (instead of two out of the four): β , κ , γ and μ .

Setting ranges for profile likelihood

```
{r profile-range2} # constraint_ui <- rbind(diag(4)) # constraint_ci
<- c(rep(0,4)) # # profile_parameters <- c('beta', 'kappa',
'gamma', 'mu') # # beta_range <- c(seq(simulating_para[1],
0.4, by = -0.02), # seq(simulating_para[1], 1.5,
by = 0.02)) # kappa_range <- c(seq(simulating_para[2], 0.6,
by = -0.02), # seq(simulating_para[2], 1.2,
by = 0.02)) # gamma_range <- c(seq(simulating_para[3], 0.2,
by = -0.02), # seq(simulating_para[3], 0.8,
by = 0.02)) # mu_range <- c(seq(simulating_para[4], 0.02, by
= -0.005), # seq(simulating_para[4], 0.2, by =
0.005)) # # range_transmission <- data.frame(parameter=rep('beta',
length(beta_range)), # fixed_value=beta_r
# range_transmission <- rbind(range_transmission, data.frame(
# parameter=rep('kappa', length(kappa_range)), fixed_value=kappa_range
# range_transmission <- rbind(range_transmission, data.frame(
# parameter=rep('gamma', length(gamma_range)), fixed_value=gamma_range
# range_transmission <- rbind(range_transmission, data.frame(
# parameter=rep('mu', length(mu_range)), fixed_value=mu_range))
#
```