Horizontal gene transfer in brolier's gut

The idea is mainly motivated by the existing studies in the literature, with the aim to model the transfer of the predominant ESBL gene bla_CTX-M-1 located on lncl1 plasmids.

Résumé of existing studies:

Study 1:

Fischer et al. [2014] did a *in vitro* study to determine the fitness cost of the plasmid for the bacterium. They estimated the intrinsic growth rate ψ, maximum density K, lag phase λ and conjugation coefficient γ considering three different types of populations, namely donor (D), recipent (R) and transconjugants (T).

The conjugation coefficient γ is defined as the number of conjugation events per bacteria per hour. γ_D and γ_T respectively denote the conjugation coefficients (per bacteria per hour) for donor-recipient and recipient-transconjugant.

Results:

- Plasmid carriage did not impose a demonstrable fitness cost on its bacterial host in vitro.
- No differences in growth parameters observed between D, T and R.
- No plasmid loss was observed.
- Estimated: $\gamma_T = 4.4e{-}10$ and $\gamma_D = 2.4e{-}14$ (repression-depression system).

Study 2:

Fischer et al. [2019] did a *in vivo* study with broiler chickens to examine whether plasmid carriage would increase by conjugation or whether plasmid-carrying *E. coli* variants would be outcompeted by plasmid-free *E. coli* variants, i.e., representing competitive exclusion.

Results:

- Competitive exclusion of plasmid-carrying variants was counteracted by conjugation.
- HGT is relevant in broliers' gut and needs to be implemented.

Incorporation in farm module:

To incorporate the HGT among different population classes, I propose using the following plasmid-dynamics model based on ODEs as used by Fischer et al. [2014] but modified according to our model assumptions.

$$\frac{dD}{dt} = \psi D \left(1 - \frac{D}{K}\right)$$

$$\frac{dR}{dt} = \psi R \left(1 - \frac{R}{K}\right) - \gamma_D DR - \gamma_T TR$$

$$\frac{dT}{dt} = \psi T \left(1 - \frac{T}{K}\right) + \gamma_D DR + \gamma_T TR$$

with initial population sizes D_0, R_0 and T_0.

Assumptions:

- A bacteria cell remains a donor even after donating a plasmid (Fischer et al. [2014]).
- There is no plasmid loss observed (Fischer et al. [2014]).
- Same growth parameters ψ and K are considered for three subpopulations (Fischer et al. [2014]).
- No lag phase λ is considered in our model. The intuition of using the lag phase, as explained by Baranyi [1995] is to model the early growth inhibition which occurs when the bacteria are transferred in a new environment (inoculated for e.g.). For for us there is no inoculation hence no change of environment.
- Two different conjugation coefficients are used: γ_D for D-R and γ_T for T-R.
- This formulation assumes conjugation coefficients are jointly proportional to the densities of donor and recipient cells. That is why they are multiplied by the to the total number of bacteria pairs possible for conjugation. Similar formulations of dynamics model are available in the literature (see, e.g. Volkova et al. [2013])

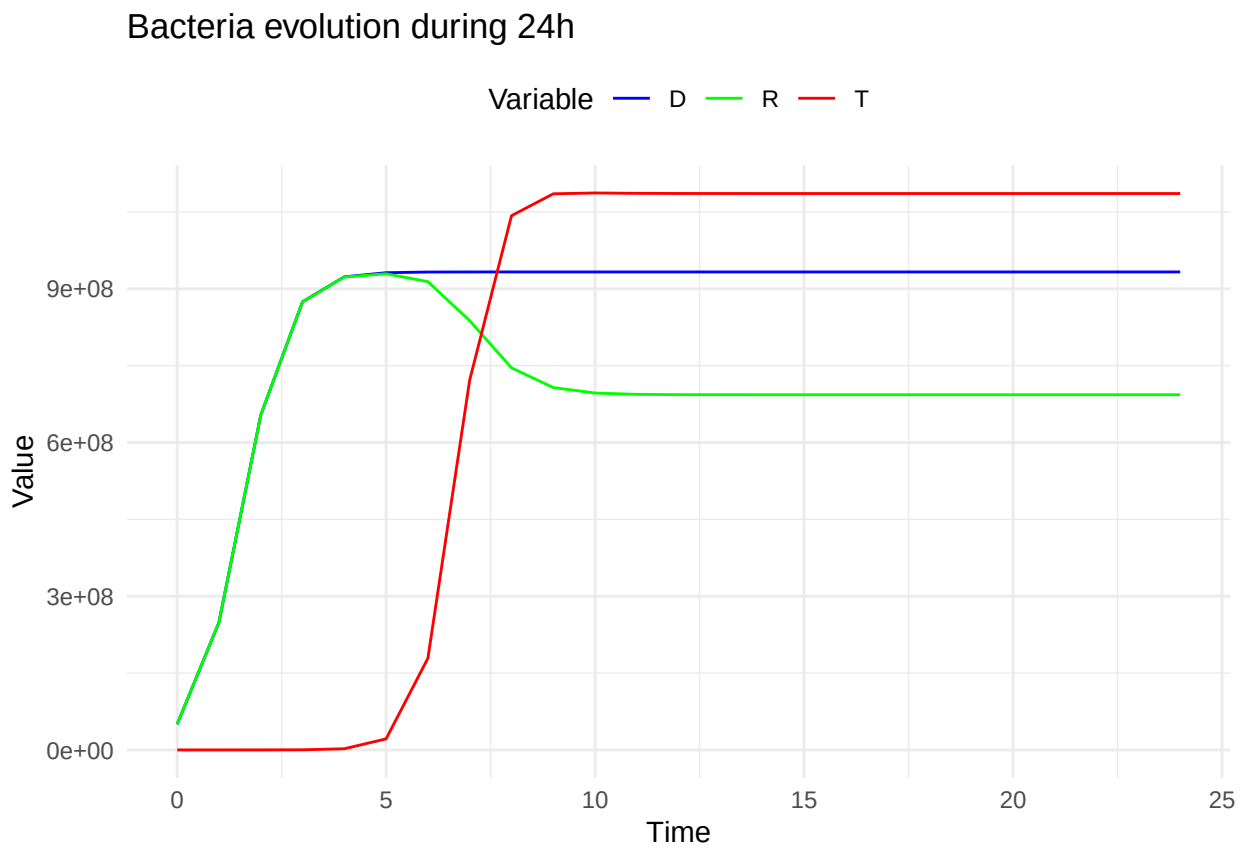
MWE:

```
# Import necessary libraries
library(deSolve)
```

```
## Warning: le package 'deSolve' a été compilé avec la version R 4.1.3
```

```
library(ggplot2)

# Define the ODE system
ode_system <- function(time, state, parameters) {
  with(as.list(c(state, parameters)), {
    dD <- psi * D * (1 - D/K)
    dR <- psi * R * (1 - R/K) - gamma_T * R * T - gamma_D * D * R
    dT <- psi * T * (1 - T/K) + gamma_T * R * T + gamma_D * D * R
    return(list(c(dD, dR, dT)))
  })
}

# Initial conditions
initial_state <- c(D = 0.5e8, R = 0.5e8, T = 0)

# Parameters
parameters <- c(gamma_T = 4.4e-10, gamma_D = 2.4e-14, psi = 1.86, K = 9.33e8)
parameters_0 <- c(gamma_T = 4.4e-10, gamma_D = 2.4e-14, psi = 0, K = 9.33e8)

# Time vector
times <- seq(0, 24, by = 1)

# Solve the ODE system
solution <- ode(y = initial_state, times = times, func = ode_system, parms = parameters)
```

```r
# Plot the results
df <- as.data.frame(solution)
df$time <- as.numeric(df$time)

# Reshape the dataframe from wide to long format
df_long <- reshape2::melt(df, id.vars = "time")

# Plot dynamics
ggplot(df_long, aes(x = time, y = value, color = variable)) +
  geom_line() +
  labs(x = "Time", y = "Value", title = "Bacteria evolution during 24h") +
  scale_color_manual(values = c("D" = "blue", "T" = "red", "R" = "green")) +
  theme_minimal() +
  theme(legend.position = "top") +
  labs(color = "Variable")
```



The Blue line shows the evolution of the D class which is equivalent to the ESBL *E. coli* population in our model (without HGT). In presence of HGT we will have an additional population of ESBL *E. coli* corresponding the T class as denoted by the Red line.

Parameter selection:

- The parameters in the MWE are taken from the *in vitro* study by Fischer et al. [2014].
- The conjugation coefficients depend on the initial inoculation/concentration as shown in the *in vivo* experiments by Fischer et al. [2019] (Table 3). Any idea about what should we use?

References

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