Simulating interventions and adaptive therapy in OncoSimulR

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Programming and Statistics in R
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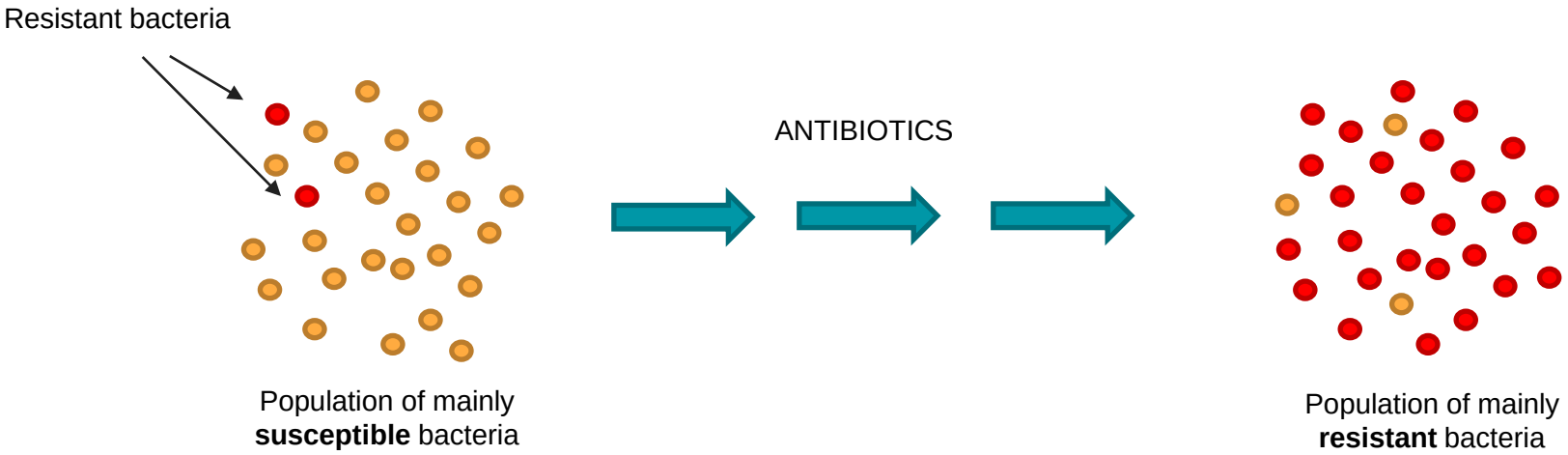
Introduction

Cancer evolves resistance to chemotherapy:

- Chemotherapy selects for the **rapid evolution of resistant clones**.
- Strong selection produces a rapid resistance response → same principle as in the evolution of antibiotic resistance in bacteria.



Introduction

1. Late-stage cancer patient → metastasized.
2. Surgery is ineffective, so they use **chemotherapy treatment**: kill the maximum number of cancer cells via the long-term administration of a drug at the MTD.
3. Tumour shrinks or disappears, but there could be cancer cells left.
4. A few months later, tumour reappears. Application of the same drug has no effect, so doctors try a different drug → **selection** of resistant cells.

The standard way of using chemotherapy is the most effective way to rapidly select resistance

Introduction

MTD therapy promotes growth of resistant cell population

- selects for adapted phenotypes
- eliminates all potentially competing populations

→ **rapid proliferation of resistant phenotypes**

Problem of traditional therapy: it ignores the underlying evolutionary dynamics of cancer

!

Adaptive therapy: evolutionary approach that aims to manage the disease without necessarily eradicating it

Evolutionary approach: adaptive therapy

Tumour is composed by two competing cancer cell types:

- **Therapy sensitive (S)**: fitter than resistant ones in the absence of treatment because of cost of resistance.
- **Therapy resistant (R)**: fitter than sensitive ones in the presence of treatment → dominance in tumors during prolonged therapy.

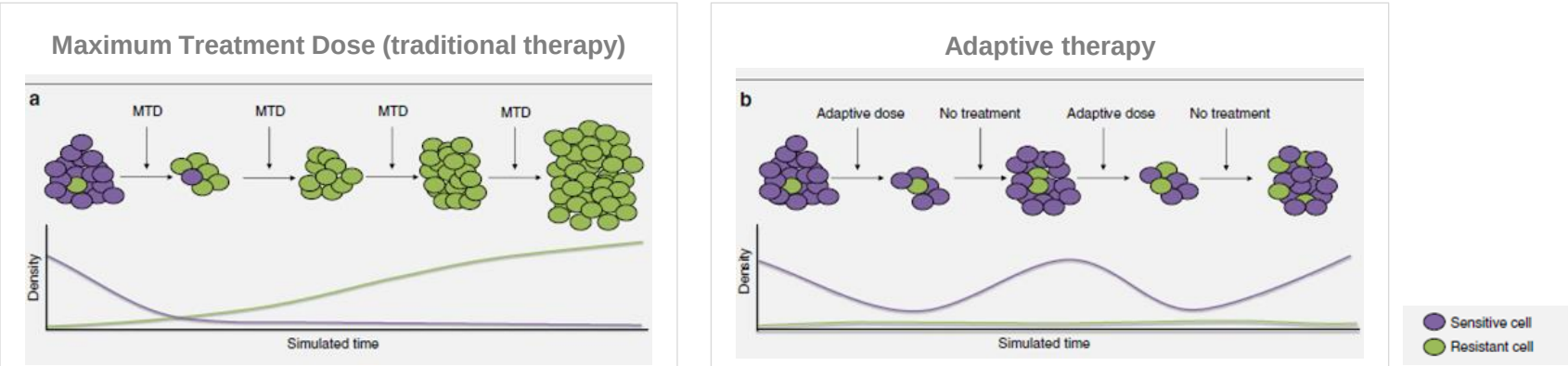
Adaptive therapy:

- Therapy is applied in small doses just to sufficiently reduce the tumour population to improve symptoms: **minimum necessary dose**.
- Treatment is then withdrawn. In the absence of chemotherapy, the sensitive cells will proliferate at the expense of resistant ones → **cost of resistance**.

Evolutionary approach: adaptive therapy

Adaptive therapy:

- No aggressive treatment.
- Abandons traditional goal of treating with the intent of obtaining the maximum regression of tumor volume.
- Its goal is to maximize the time of tumour control by using the tumour cells that are sensitive to treatment as cells that can suppress the proliferation of the resistant cells.



Zhang *et al*. (***Nature Communications***, 2017). Evolutionary dynamics in adaptive therapy in prostate cancer.

OncoSimulR

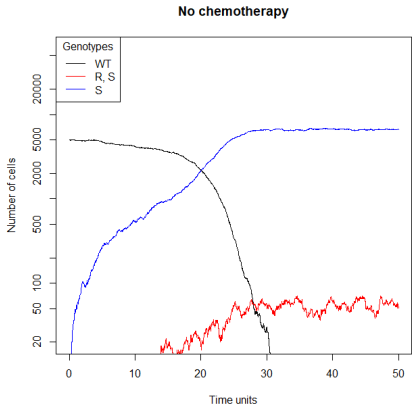
```
if (!require("BiocManager"))
       install.packages("BiocManager")

# BiocManager::install("OncoSimulR", version = "3.11")

if (!require("devtools"))
       install.packages("devtools")

# library(devtools)

# install_github("rdiaz02/OncoSimul/OncoSimulR", ref = "freq-dep-fitness")

library(OncoSimulR)

##  Fitness values for healthy (H) cells, and chemoresistant (R) or chemosensitive (S) cancer cells.
##  Healthy   Sensitive   Resistant
a <- 1;       b <- 0.5;   c <- 0.5    # Healthy
d <- 1;       e <- 1.2;   f <- 0.7    # Sensitive
g <- 0.9;     h <- -0.5;  i <- 0.8    # Resistant

wt_fitness   <- paste0(a,"*f_+", b,"*f_S+", c,"*f_S_R")
sens_fitness <- paste0(d,"*f_+", e,"*f_S+", f,"*f_S_R")
res_fitness  <- paste0(g,"*f_+", h,"*f_S+", i,"*f_S_R")
```

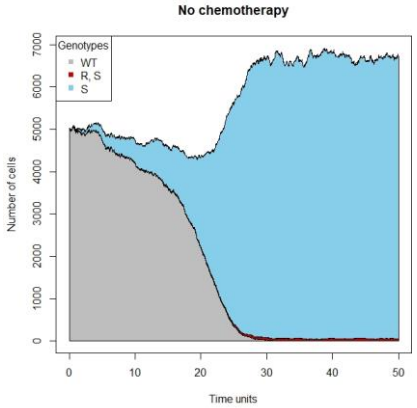
Tested scenarios:

1. **No treatment**
2. **Maximum Tolerated Dose (MTD) treatment**
3. **Adaptive therapy**

Scenario 1. No treatment

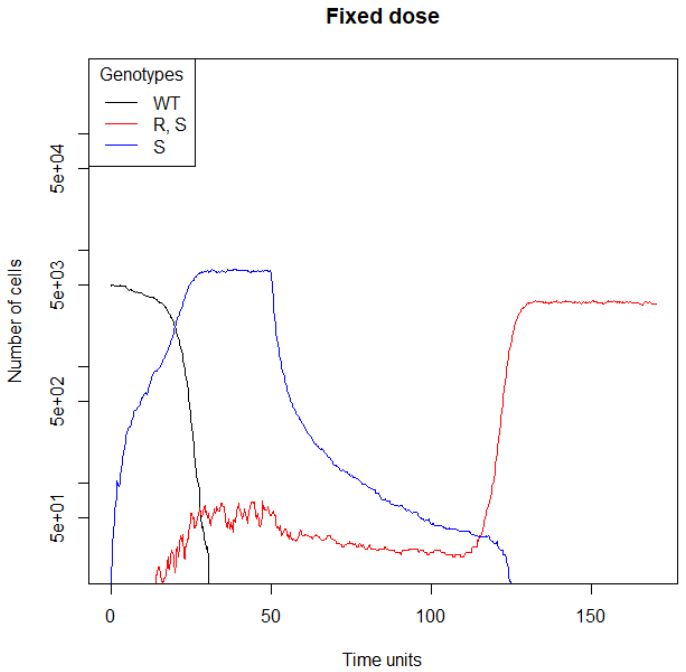
```
## Fitness definition

fit_cells <- data.frame(Genotype = c("WT","S","R","S,R"),
                        Fitness = c(wt_fitness,       #WT
                                    sens_fitness,     #S
                                    "0",              #R
                                    res_fitness),     #S,R
                        stringsAsFactors = FALSE)

all_fe <- allFitnessEffects(genotFitness = fit_cells,
                            frequencyDependentFitness = TRUE,
                            frequencyType = "rel")


## Simulation

set.seed(2)
simul <- oncoSimulIndiv(all_fe,
                            model = "McFL", onlyCancer = FALSE,
                            finalTime = 50, mu = 0.01,
                            initSize = 5000, keepPhylog = FALSE,
                            seed = NULL)


## Plots: number of cells vs time

plot(simul, show = "genotypes", type = "line",
     col = c("black", "red", "blue"), ylim = c(20, 50000),
     main = "No chemotherapy")

plot(simul, show = "genotypes", col = c("grey", "Red3", "Sky blue"),
     main = "No chemotherapy")
```





Scenario 2. Maximum Tolerated Dose (MTD) treatment

```
## Fitness definition

drug_eff <- 0.01  # effect of drug on fitness sensible tumor cells

fit_cells2 <- data.frame(Genotype = c("WT", "S", "R", "S, R"),
                         Fitness = c(wt_fitness,                          #WT
                                     paste0("if (T>50) ", drug_eff,
                                     "*(",sens_fitness, ")","     ;
                                     else ", sens_fitness, ";")   ,       #S
                                     "0",                                 #R
                                     res_fitness),                        #S,R
                        stringsAsFactors = FALSE)
```

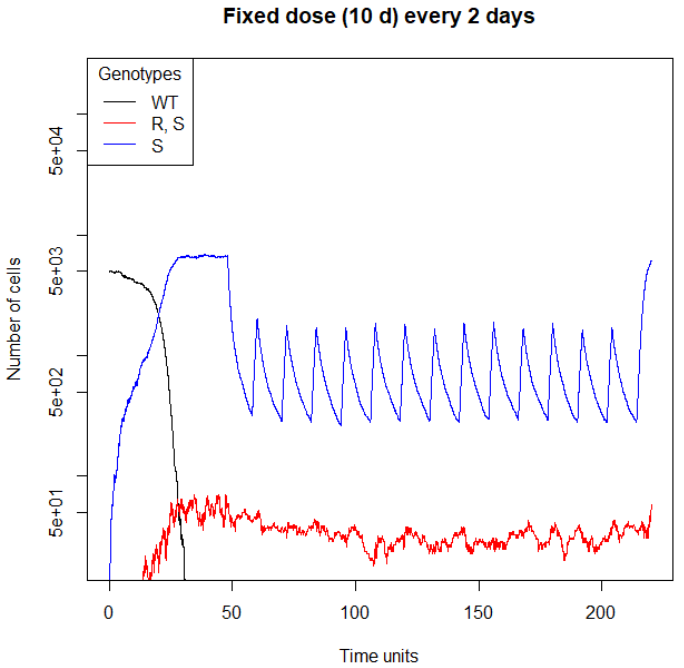


T ≤ 50 → no treatment

T > 50 → fixed dose treatment (MTD)

Scenario 3.1. Adaptive therapy: fixed doses ten days every two days

```
## Fitness definition

drug_eff2 <- 0.015

fit_cells3 <-data.frame(
              Genotype = c("WT", "S", "R", "S, R"),
              Fitness =
                 c(wt_fitness,                          #WT
                   paste0("if (T>48 & T<58)   ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>60 & T<70)    ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>72 & T<82)    ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>84 & T<94)    ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>96 & T<106)   ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>108 & T<118)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>120 & T<130)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>132 & T<142)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>144 & T<154)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>156 & T<166)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>168 & T<178)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>180 & T<190)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>192 & T<202)  ", drug_eff2,"*(",sens_fitness,")",
                   ";else if (T>204 & T<214)  ", drug_eff2,"*(",sens_fitness,")",
                   ;else", sens_fitness, ";"),          #S
                   "0",                                 #R
                   res_fitness),                        #S,R
              stringsAsFactors = FALSE)
```



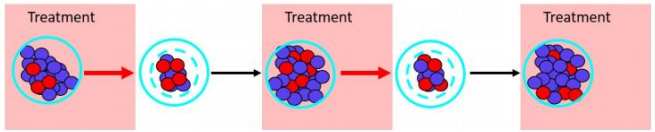
When **T > 50** start a cycle:

- Apply fixed dose for 10 days
- No treatment for 2 days

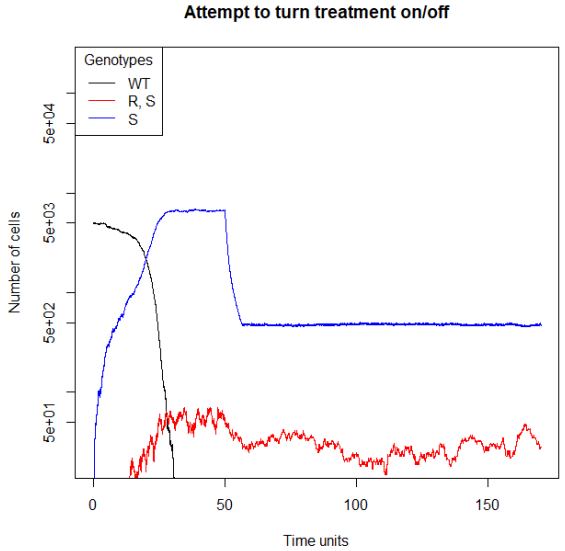
Zhang *et al*. (***Nature***, 2017). Metronomic therapy in prostate cancer

Scenario 3.2. Adaptive therapy: on/off treatment depending on the number of cells

```
## Fitness definition

drug_eff2 <- 0.015

fit_cells4 <-data.frame(
              Genotype = c("WT", "S", "R", "S, R"),
              Fitness = c(
                wt_fitness,                                          #WT
                paste0("var drug := true            ;
                if (T>50 & N>500 & drug = true)", drug_eff2, "*(",sens_fitness,");
                else if (T>50 & N=500) {drug := false; sens_fitness;}
                else if (T>50 & N=2500) {drug := true; drug_eff2, "*(",sens_fitness,");}
                else ", sens_fitness, ";"),                          #S
                          "0",                                       #R
                          res_fitness),                              #S,R
               stringsAsFactors = FALSE)
```



Hansen and Read (***Cancers***, 2020).
Treatment based on tumour size.

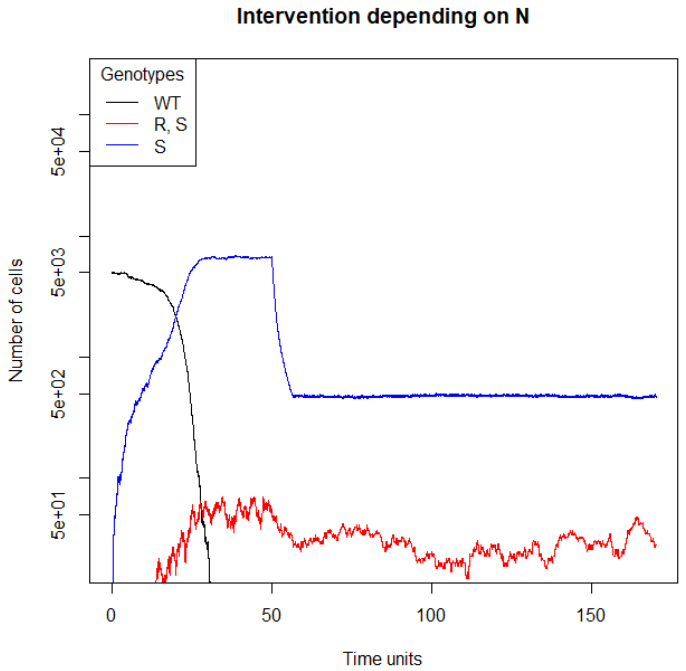


- When **T > 50** and **N > 500** → application of drug
- Once **N = 500** → 'turn' the treatment OFF → the tumor will increase in size
- Once **N = 2500** → 'turn' the treatment ON → the tumor will decrease in size

OncoSimulR **limitation**: variables are not saved after each iteration

Scenario 3.3. Adaptive therapy: cell number-depending intervention

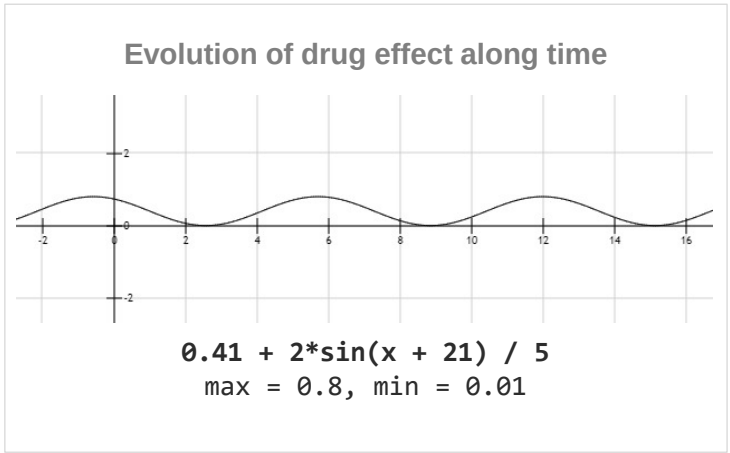
```
## Fitness definition

drug_eff <- 0.015

fit_cells5 <-data.frame(
              Genotype = c("WT", "S", "R", "S, R"),
              Fitness = c(wt_fitness,                                  #WT
                          paste0("if(T>50 & N>500)",drug_eff,
                          "*(",sens_fitness,")","          ;
                          else",sens_fitness,";")          ,           #S
                          "0",                                         #R
                          res_fitness),                                #S,R
              stringsAsFactors = FALSE)
```

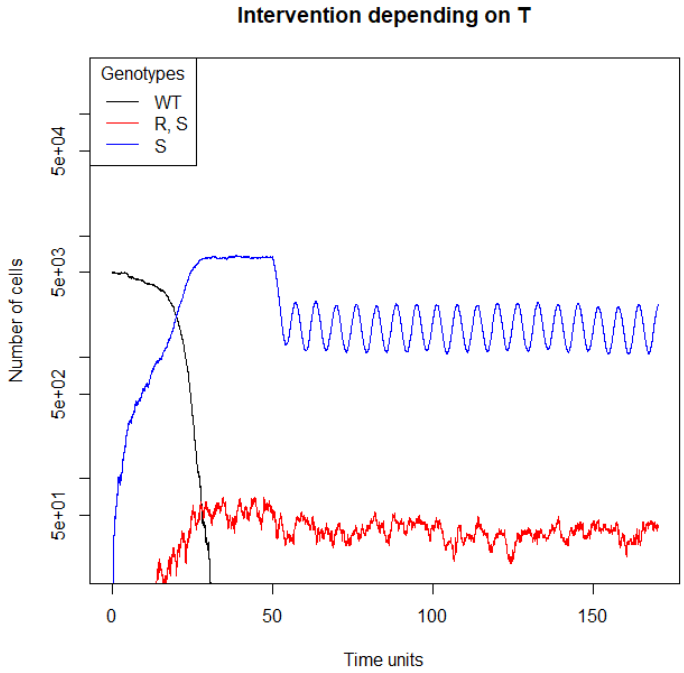


When **T > 50** and **N > 500**: apply fixed dose treatment

Scenario 3.4. Adaptive therapy: changing drug effect as a function of time

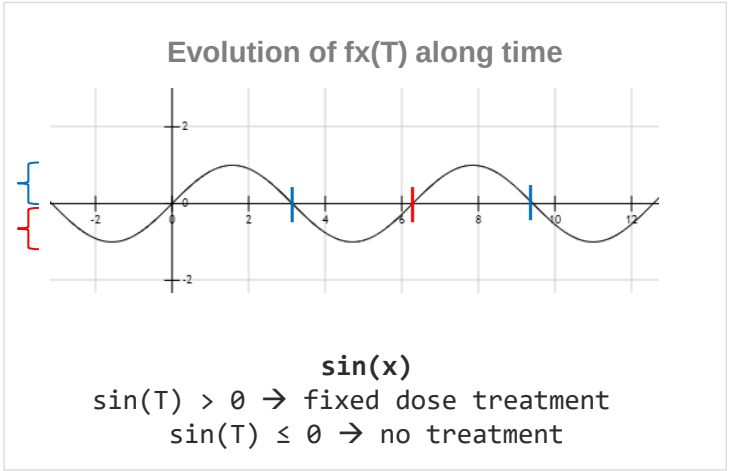
```
## Fitness definition

fit_cells6 <-data.frame(
              Genotype = c("WT", "S", "R", "S, R"),
              Fitness = c(wt_fitness,                                  #WT
                          paste0("if(T>50) (0.41+2*sin(T+21)/5)
                          *(",sens_fitness,");
                          else",sens_fitness,";"),                     #S
                          "0",                                         #R
                          res_fitness),                                #S,R
              stringsAsFactors = FALSE)
```

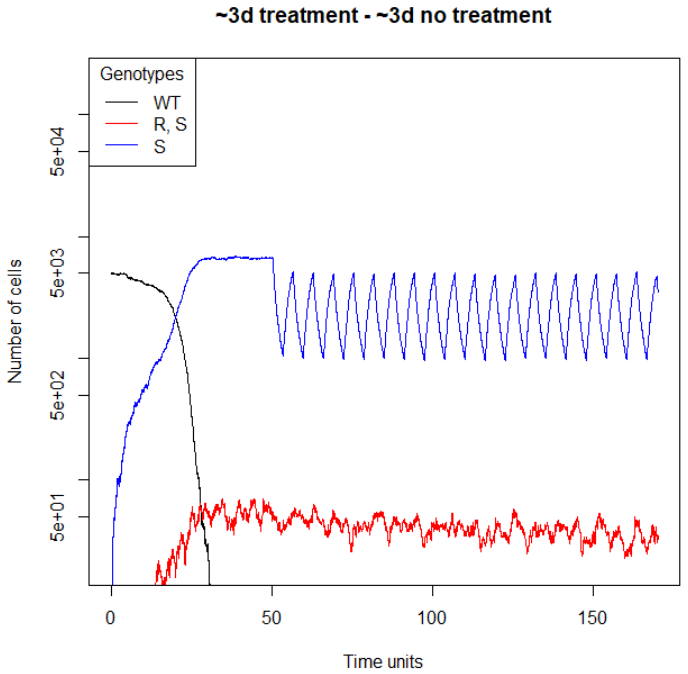




Scenario 3.5. Adaptive therapy: fixed dose application as a function of time

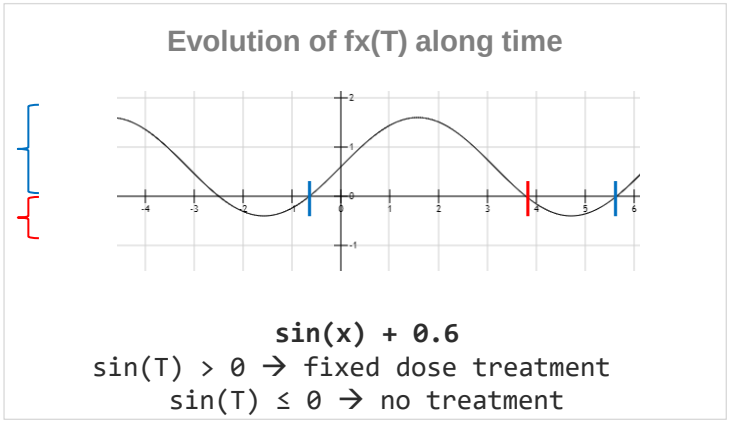
```
## Fitness definition

drug_eff <- 0.015

fit_cells7 <-data.frame(
             Genotype = c("WT", "S", "R", "S, R"),
             Fitness = c(wt_fitness,                                  #WT
                         paste0("if(T>50 & sin(T)>0)
                         drug_eff2, "*(", sens_fitness,");
                         else",sens_fitness,";"),                     #S
                         "0",                                         #R
                         res_fitness),                                #S,R
             stringsAsFactors = FALSE)
```

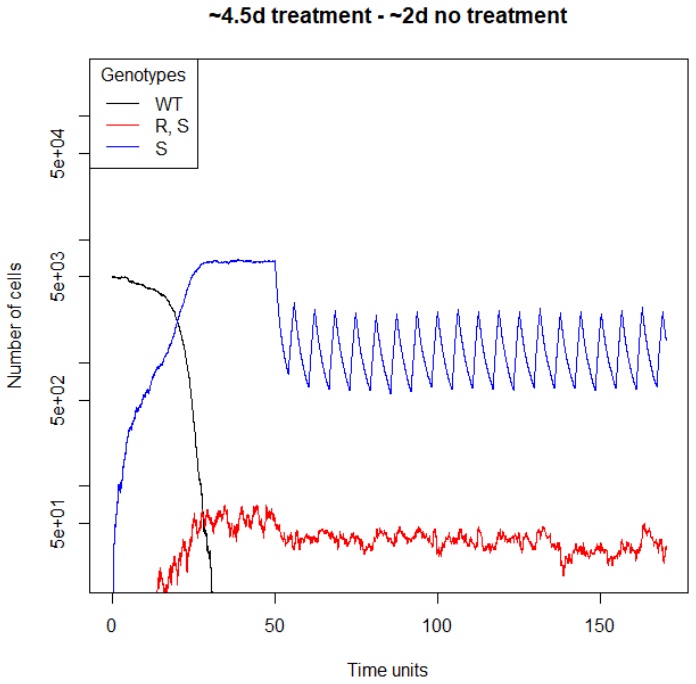




Scenario 3.6. Adaptive therapy: fixed dose application as a function of time

```
## Fitness definition

drug_eff <- 0.015

fit_cells7 <-data.frame(
             Genotype = c("WT", "S", "R", "S, R"),
             Fitness = c(wt_fitness,                                  #WT
                         paste0("if (T>50 & (sin(T) + 0.6)>0)",
                         drug_eff2, "*(", sens_fitness,");
                         else",sens_fitness,";"),                     #S
                         "0",                                         #R
                         res_fitness),                                #S,R
             stringsAsFactors = FALSE)
```





Conclusions

Regarding the simulations of an adaptive therapy in OncoSimulR:

- We were not able to introduce a **turn on/off mechanism** for drug administration (depending on N) in the OncoSimulR code in order to simulate the effects of a drug periodically applied.

- Simulation based on drug dose applied when a certain **number of cells** was exceeded showed that the treatment kept the number of cells constant, which does not happen in real-life scenarios.

- **Missing functionality:** cannot use an assignment to control the tumor size within a range of N.

- Simulation based on drug dose that change **along time** as a **sin(T)** function were the best approximations we found **so far**.

References

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Zhang, J., Cunningham, J. J., Brown, J. S. & Gatenby, R. A. (2017). Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Nature Communications, 8:1816.

```
> cat (“Thank you\n”)
> Thank you
>
```