OncoSimulR:
simulating interventions and adaptive therapy

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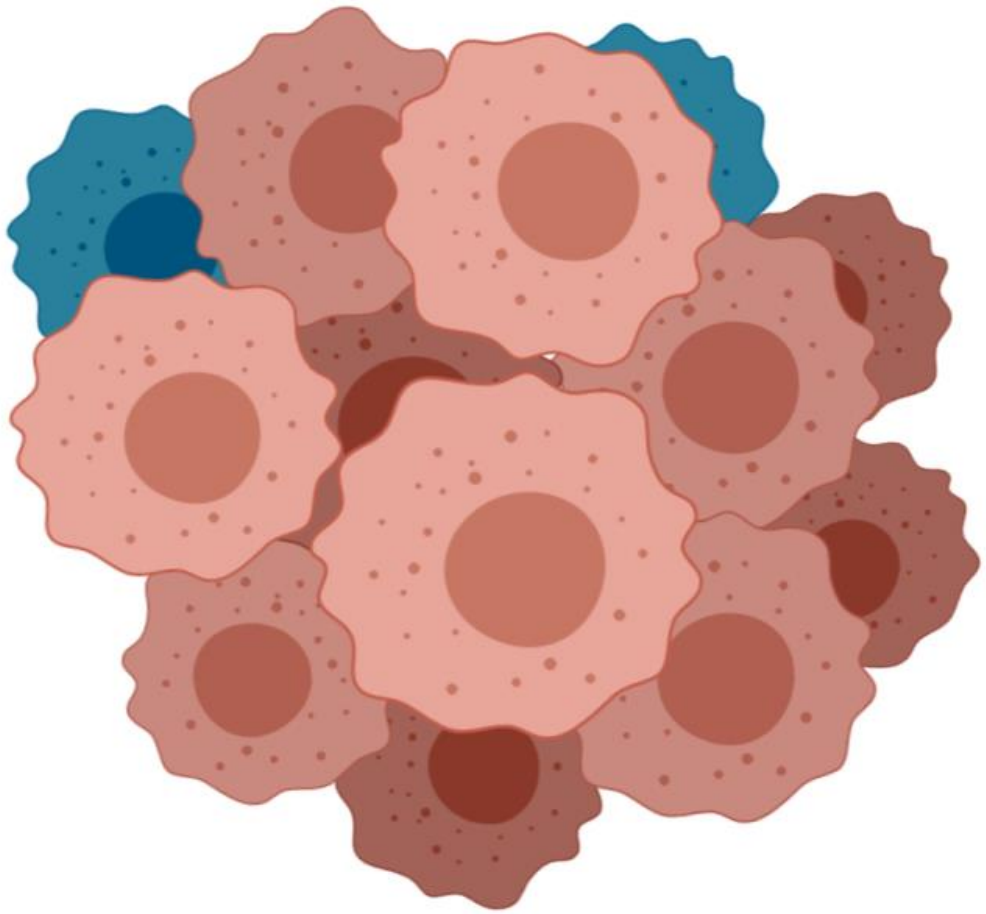
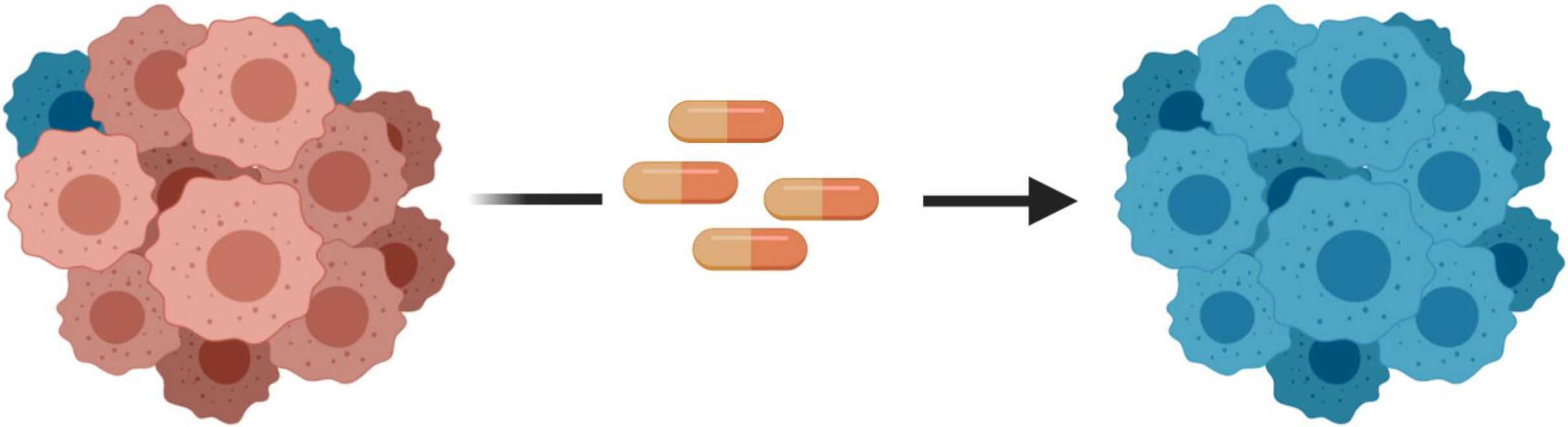
Introduction

- Fitness
- Frequency-dependent fitness
- Evolutionary game theory
- Therapy

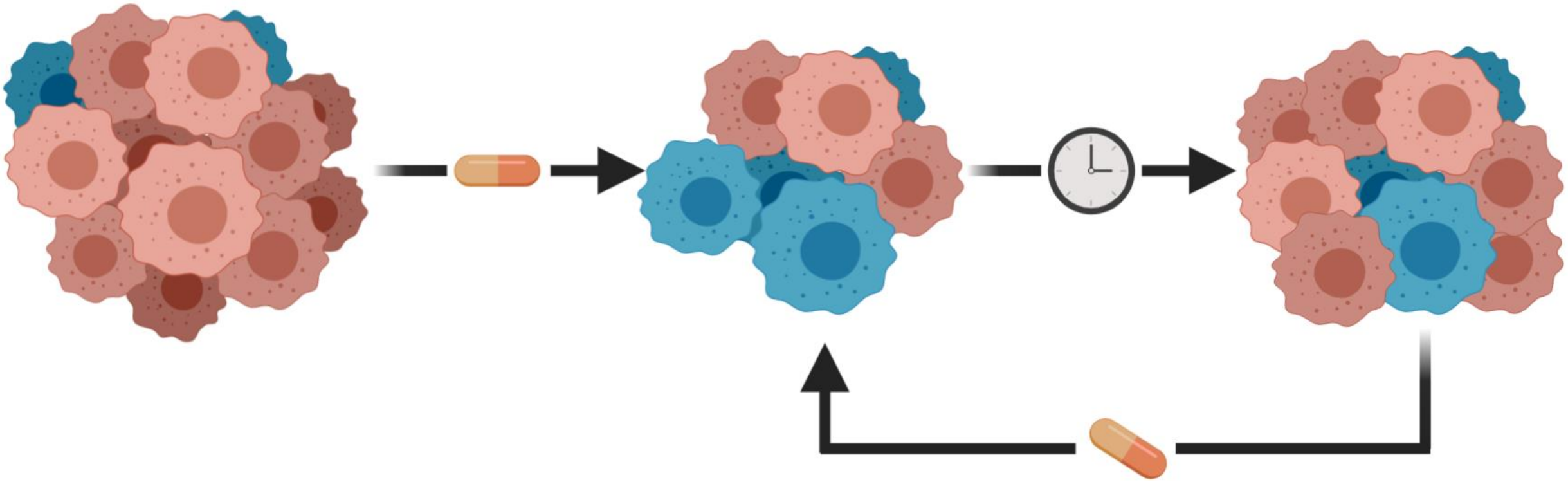
Classical vs adaptive therapy



Classical therapy



Adaptive therapy



Adaptive therapy simulations

1. General, theoretical case
2. Bacterial population
3. Resistant prostate cancer

RESEARCH ARTICLE

Exploiting evolutionary trade-offs for posttreatment management of drug-resistant populations

Sergey V. Melnikov, David L. Stevens, Xian Fu, Hui Si Kwok, Jin-Tao Zhang, Yue Shen, Jeffery Sabina, Kevin Lee, Harry Lee, and Dieter Söll

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Contributed by Dieter Söll, June 2, 2020 (sent for review February 24, 2020; reviewed by Michael Ibba and Babak Javid)

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Convergence and Technologies

Towards Multidrug Adaptive Therapy

Jeffrey West, Li You, Jingsong Zhang, Robert A. Gatenby, Joel S. Brown, Paul K. Newton, and Alexander R.A. Anderson

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1. Fitness equations

cS = 0.2 → cohabit cost

cR = 0.1 → resistance cost

S_fitness = 1 - cS * (f_SM + f_RM)

R_fitness = 1 - cS * (f_SM + f_RM) - cR

2. Dataframe of the genotypes

```
# Define fitness of the genotypes
std_df <- function(cS, cR, gt = c("WT", "S", "R")) {
  data.frame(Genotype = gt,
             Fitness = c("1",
                         paste0("if (T > 20) ", drug, "*(", S_fitness, ")",";
                                else ", S_fitness, ";"),
                         R_fitness),
             stringsAsFactors = FALSE)
}
```

3. allFitnessEffects function

```
# Fitness effects specification
std_eff <- allFitnessEffects(genotFitness = std_df(cS, cR),
                             frequencyDependentFitness = TRUE,
                             frequencyType = "rel")
```

4. oncoSimulIndiv

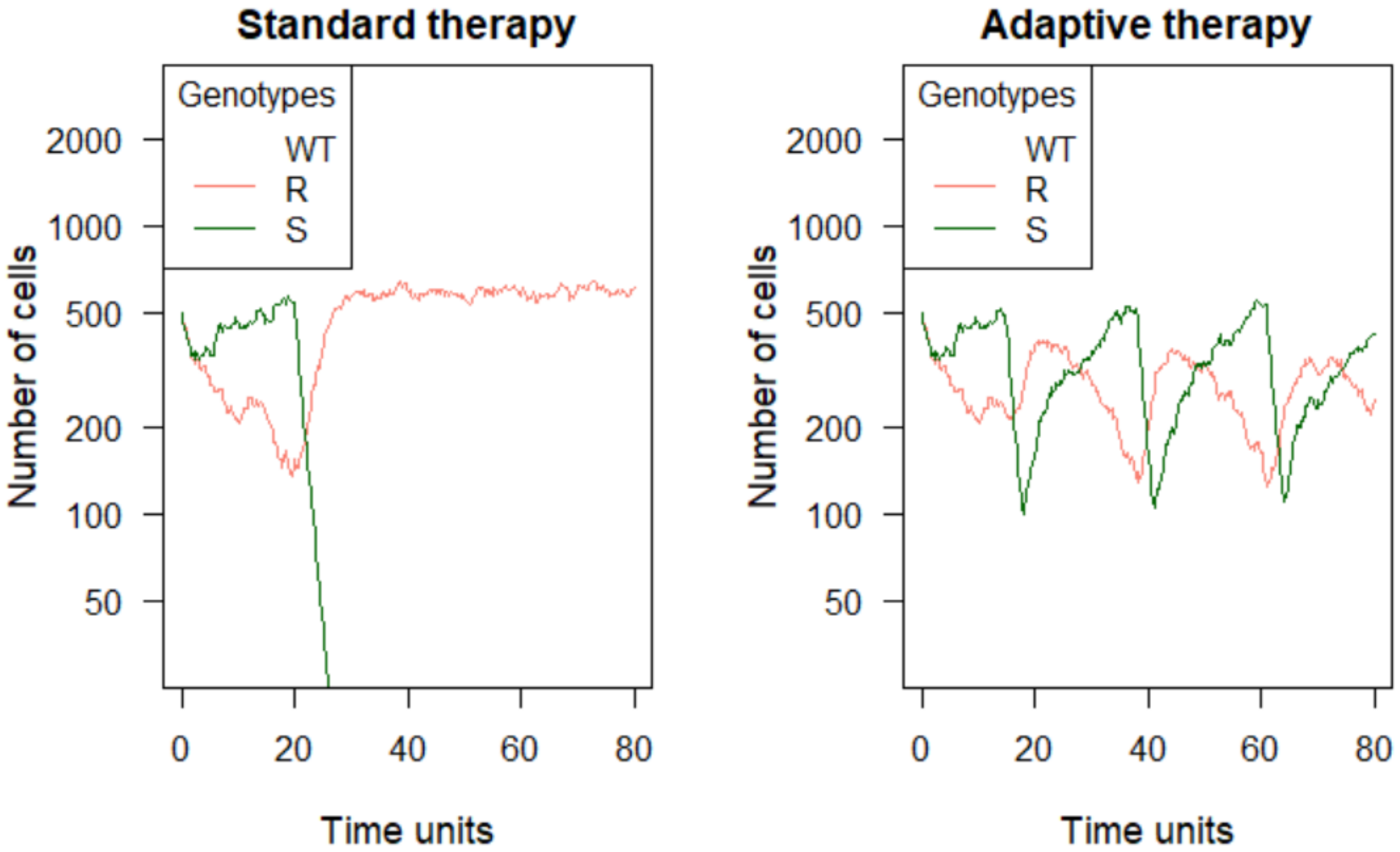
```
set.seed(1) # for reproducibility
std_simul <- oncoSimulIndiv(std_eff,
                            model = "McFL",
                            onlyCancer = FALSE,
                            mu = 0.01,
                            finalTime = 80,
                            initSize = c(WT=1,S=500, R=500),
                            seed = NULL,
                            initMutant = c("WT", "S", "R"))
```

5. Graphics

```r
# Plot representation
plot(std_simul, show = "genotypes", type = "line",
     thinData = TRUE, col = c("white", "salmon", "darkgreen"),
     ylim = c(30, 3000), las = 1,
     cex.lab=1.1, main = "Standard therapy")
```

```r
plot(adapt_simul, show = "genotypes", type = "line",
     thinData = TRUE, col = c("white", "salmon", "darkgreen"),
     ylim = c(30, 3000), las = 1,
     cex.lab=1.1, main = "Adaptive therapy")
```

5. Graphics


Standard therapy
Genotypes
WT
R
S
Number of cells
2000
1000
500
200
100
50
0
20
40
60
80
Time units
Adaptive therapy
Genotypes
WT
R
S
Number of cells
2000
1000
500
200
100
50
0
20
40
60
80
Time units

Resistant bacterial subpopulations

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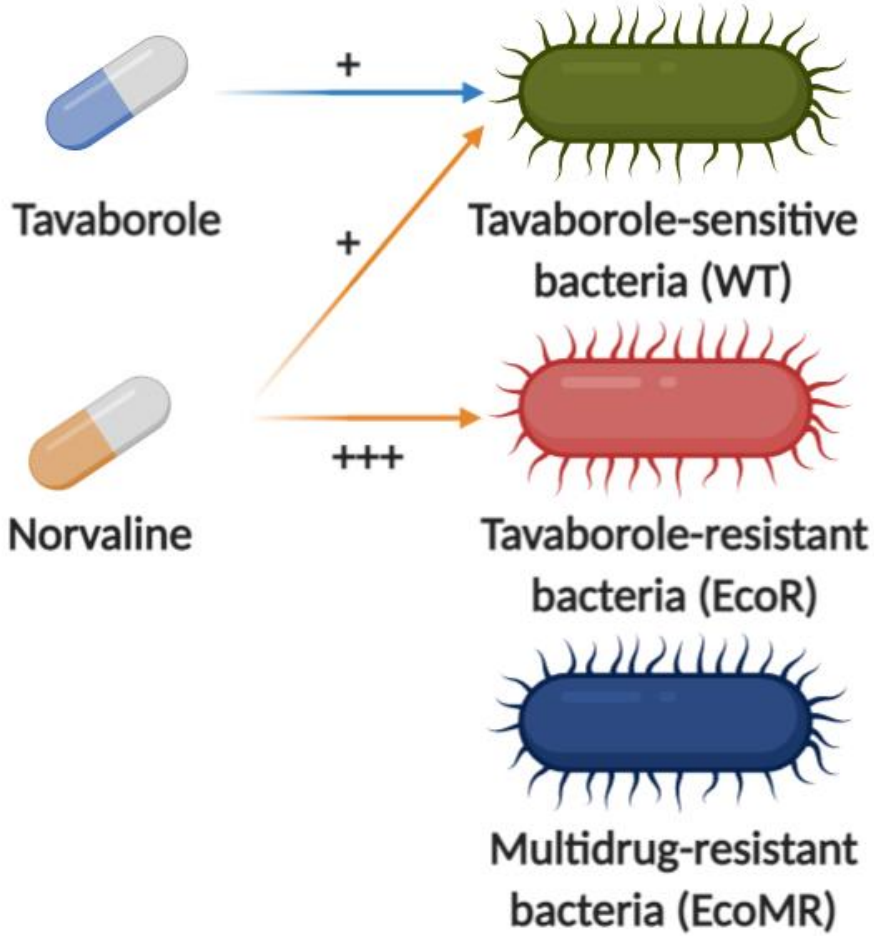

Resistant bacterial subpopulations

cS = 0.2 → cohabit cost

cR = 0.1 → resistance cost of EcoR

cMR = 0.4 → resistance cost of EcoMR

WT_fitness = 1 - cS * (f_ + f_EcoR + f_EcoMR)

EcoR_fitness = 1 - cS * (f_ + f_EcoR + f_EcoMR) - cR

EcoMR_fitness = 1 - cS * (f_ + f_EcoR + f_EcoMR) - cRM

Resistant bacterial subpopulations

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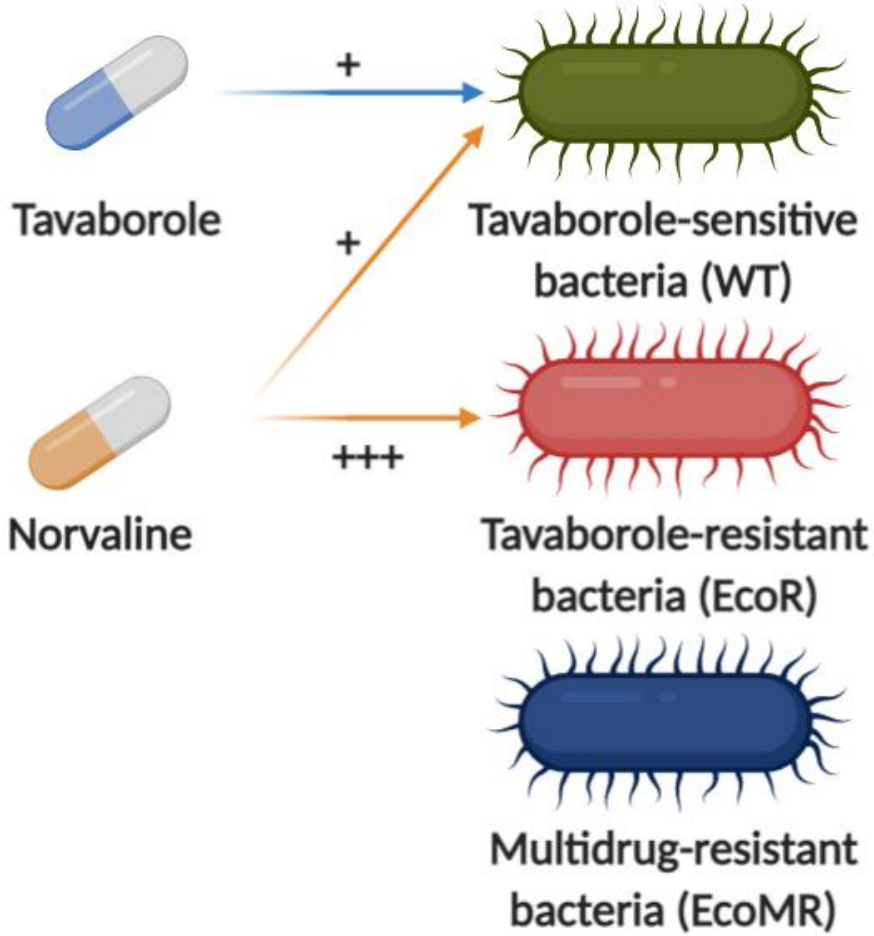
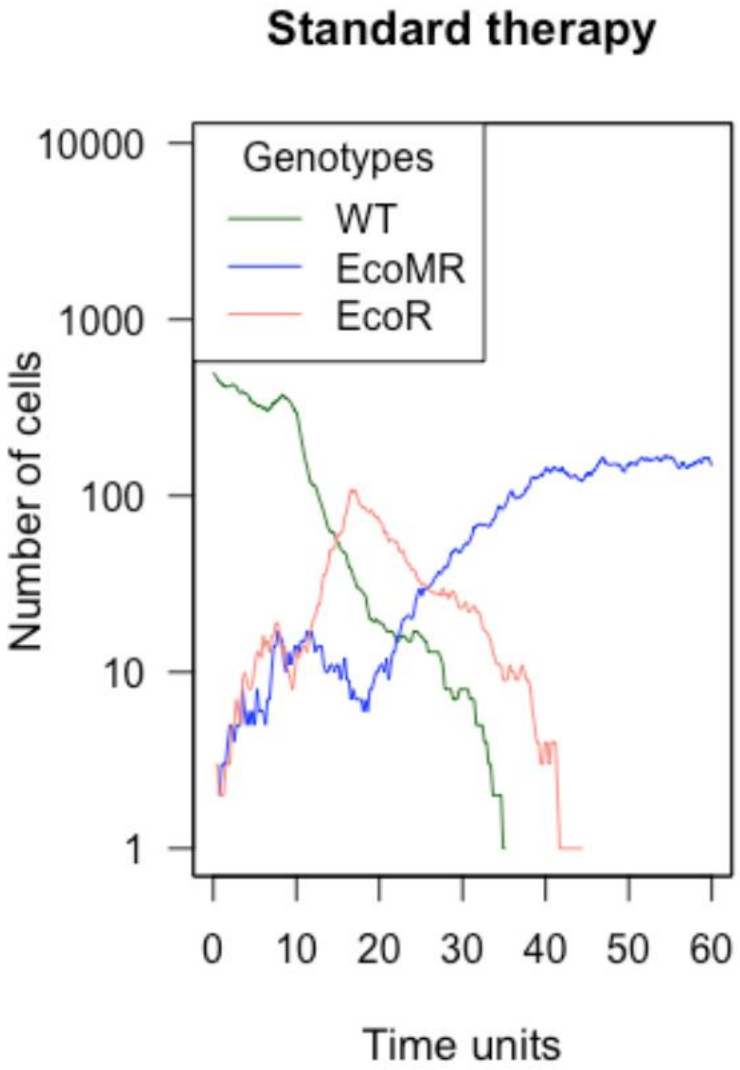
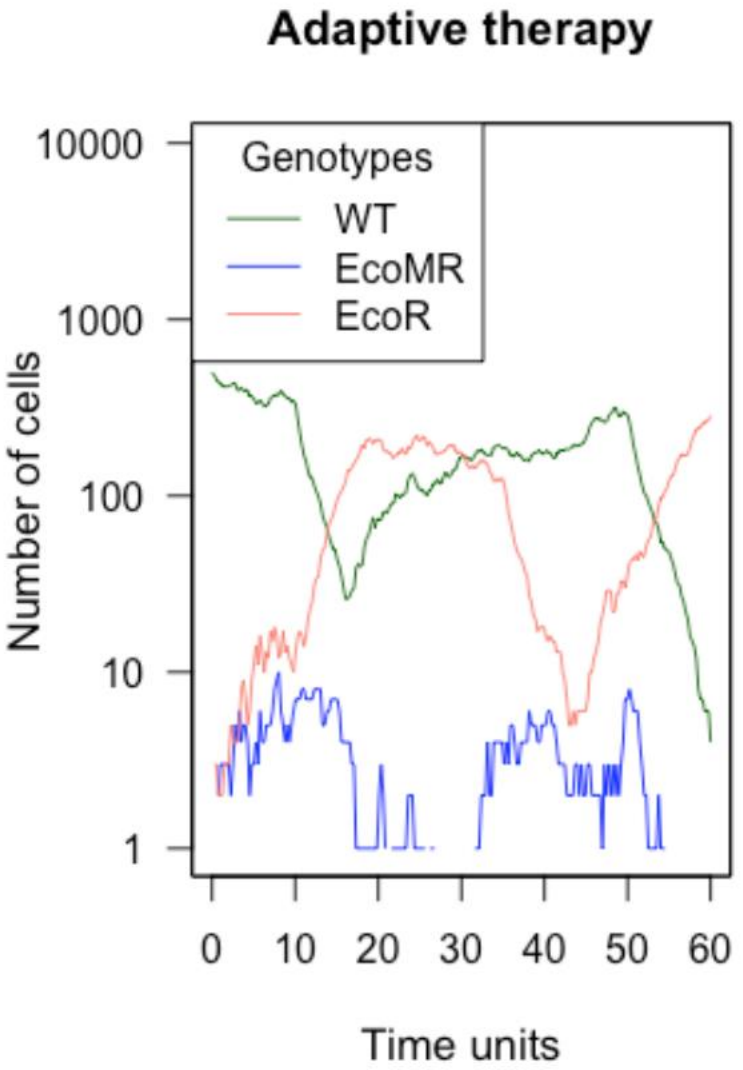
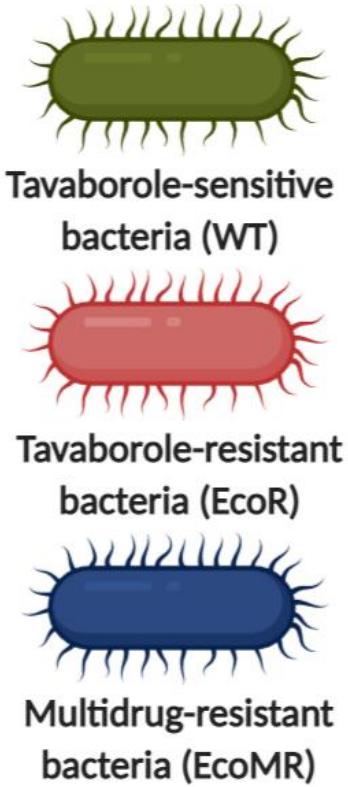


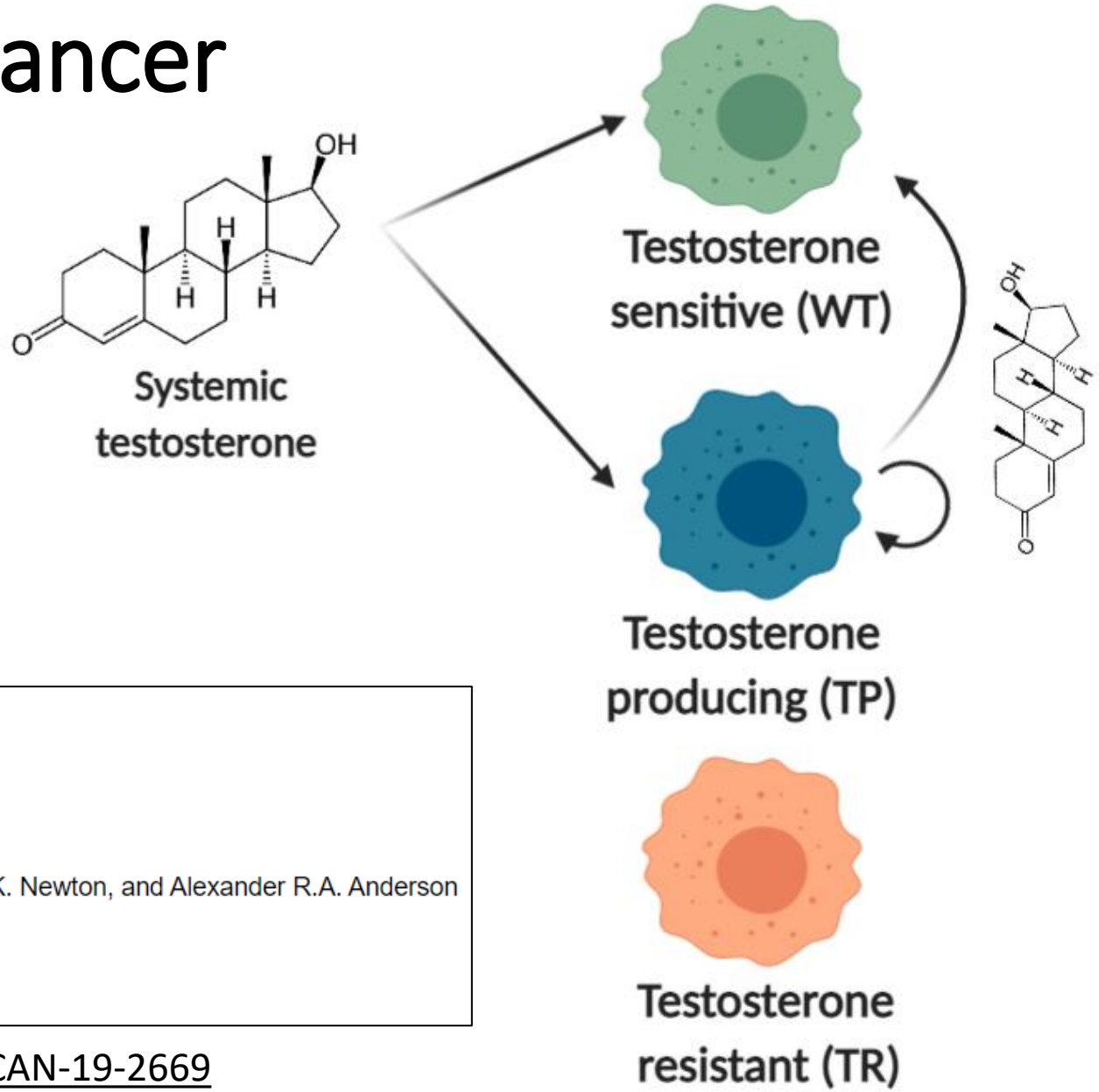
Bacterial subpopulations: adaptive therapy







Resistant prostate cancer



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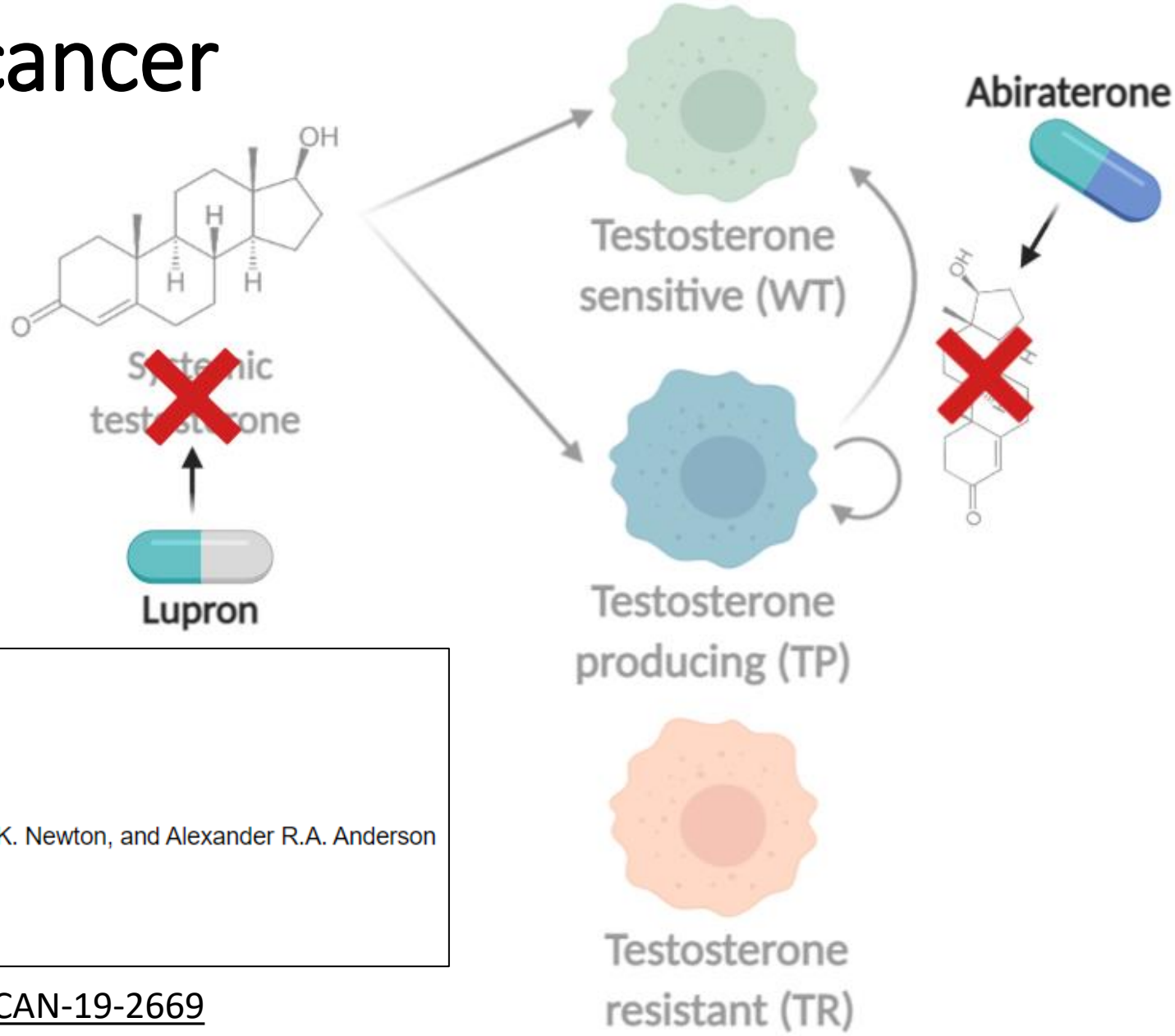

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Resistant prostate cancer

bT = 0.7 → Benefit of TP producing testosterone

cS = 0.2 → Cohabit cost

cT = 0.3 → Cost of producing testosterone

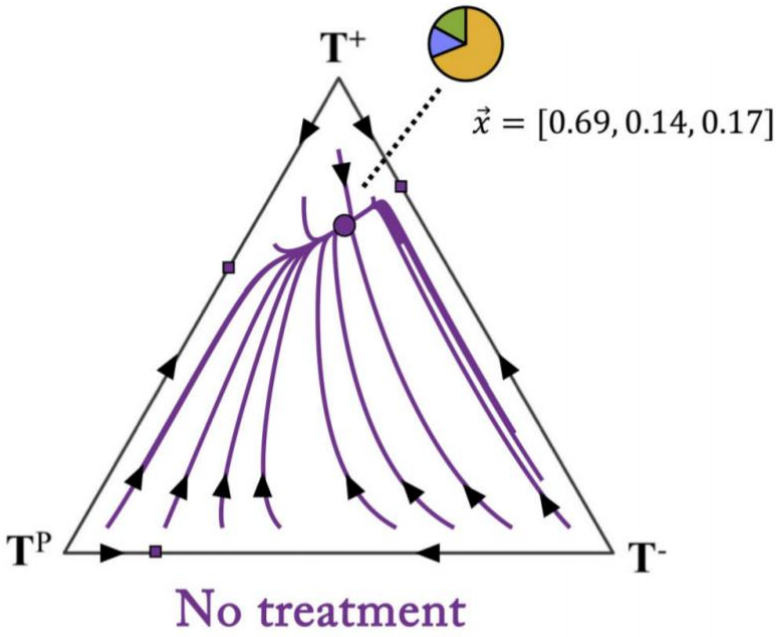
cR = 0.3 → Cost of resistance

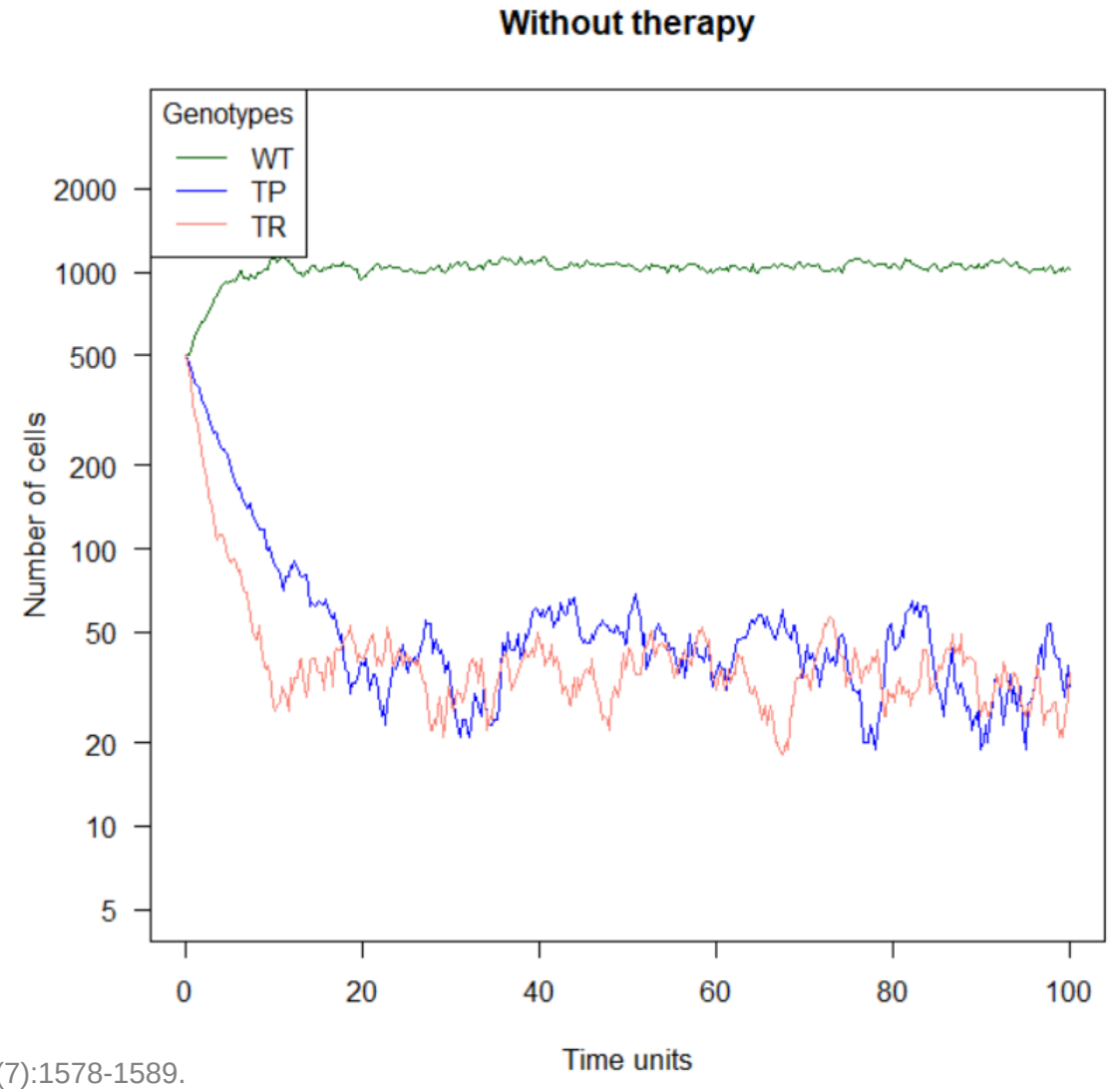
WT_fitness = 1 + bT * (f_TP) - cS * (f_ + f_TP + f_TR)

TP_fitness = 1 + bT * (f_TP) - cS * (f_ + f_TP + f_TR) - cT

TR_fitness = 1 - cS * (f_ + f_TP + f_TR) – cR

Resistant prostate cancer: no treatment





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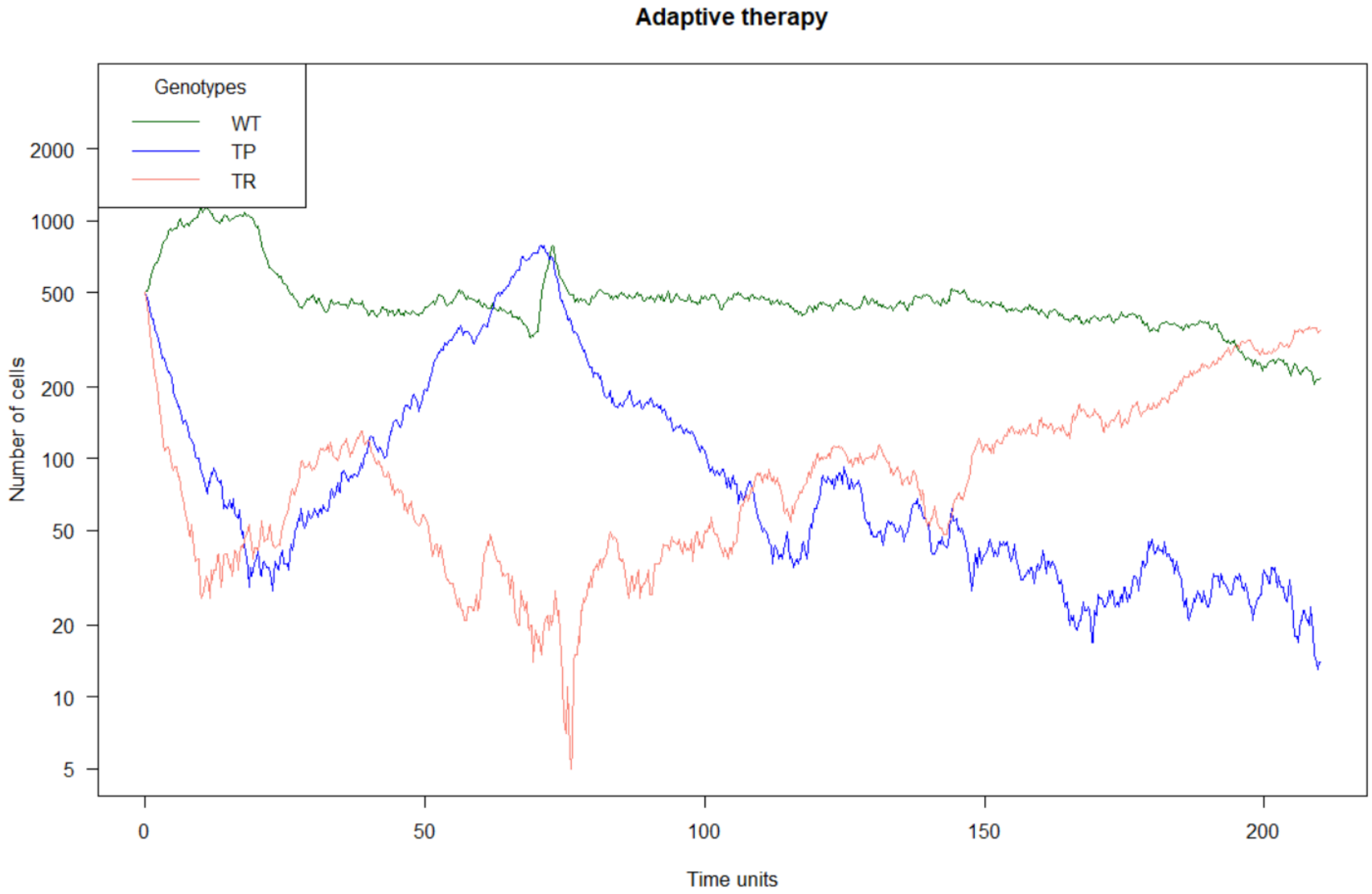
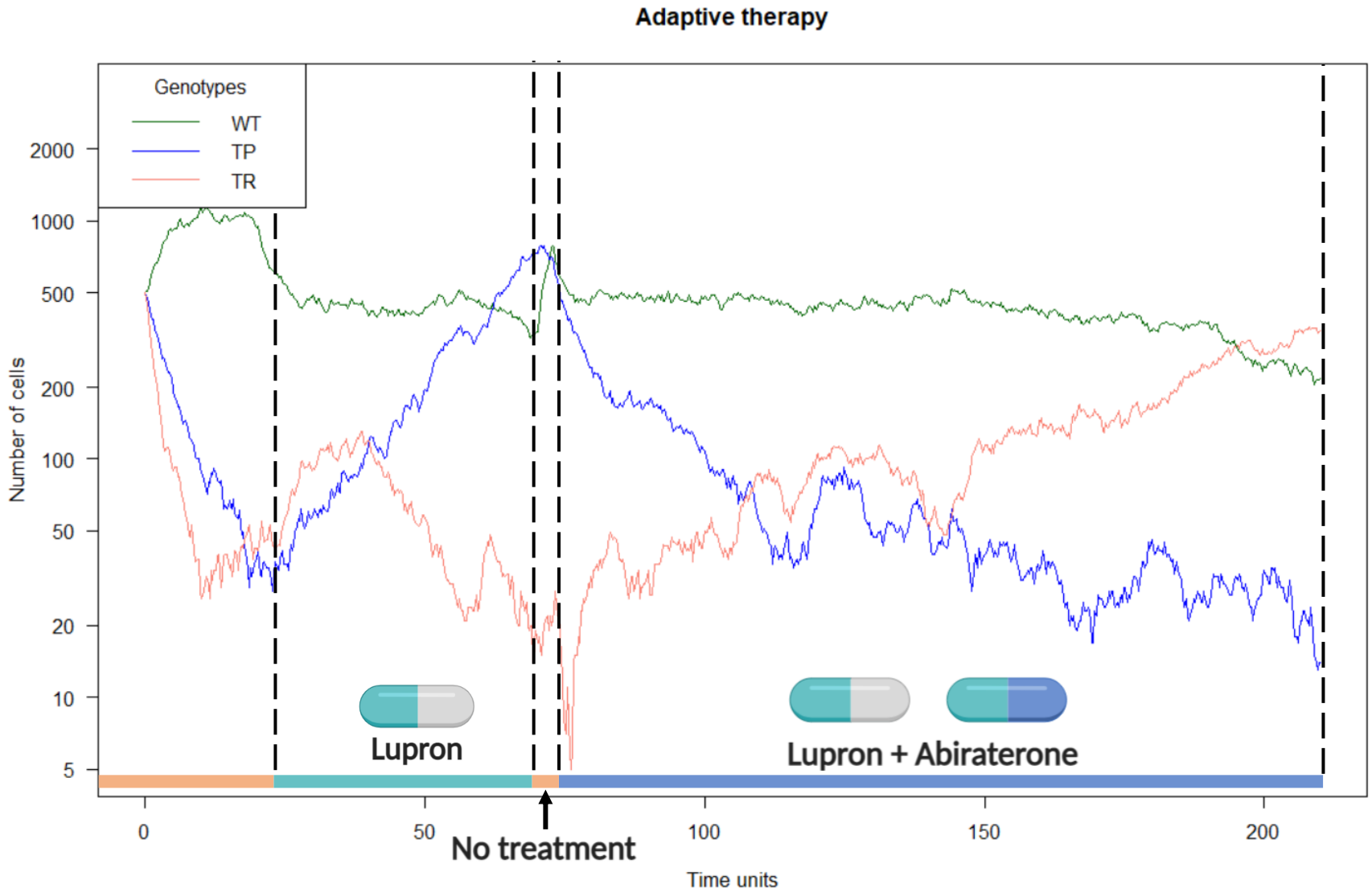
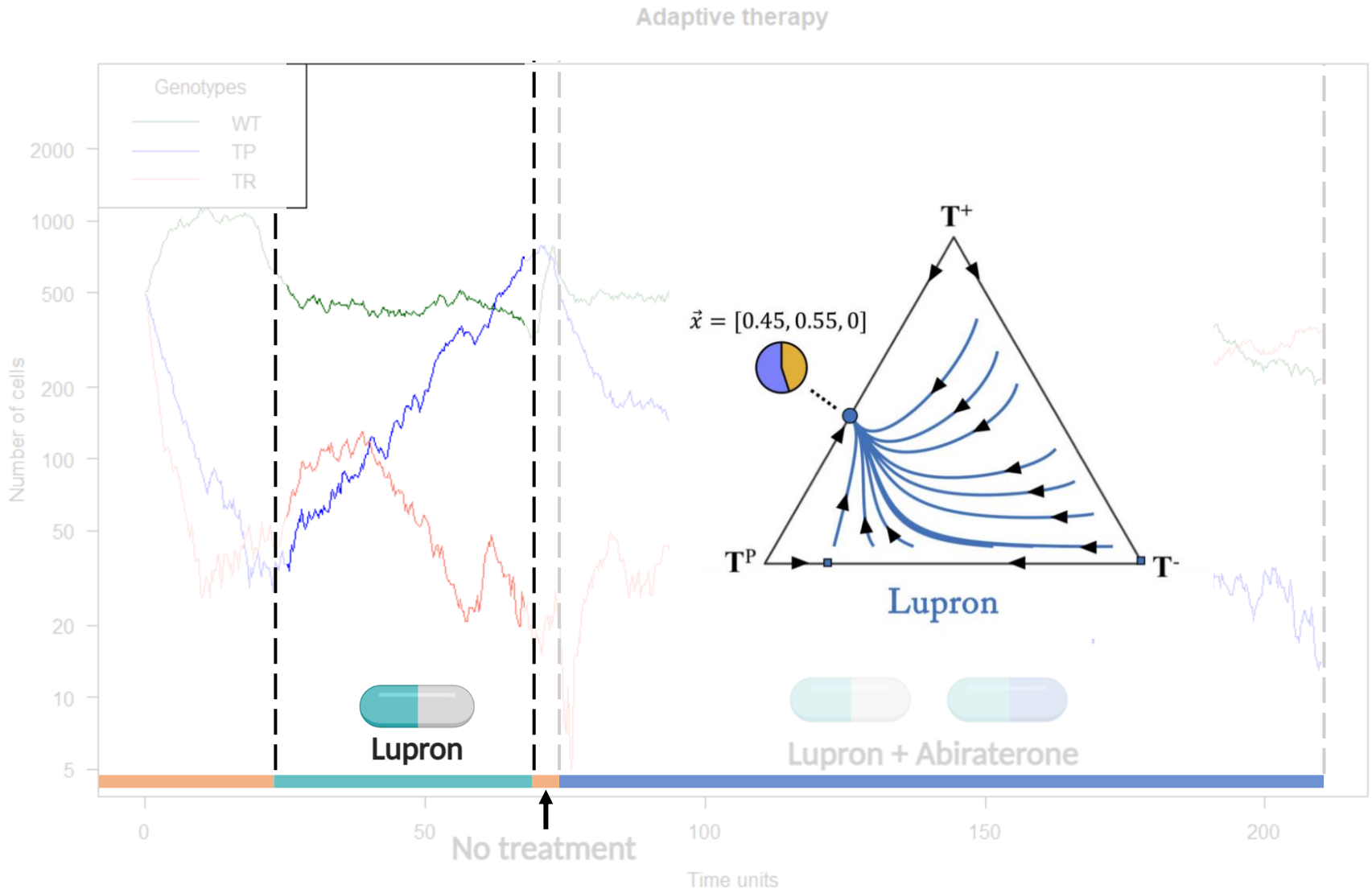
Prostate cancer: adaptive therapy cycle



Resistant prostate cancer: adaptive therapy



Resistant prostate cancer: adaptive therapy



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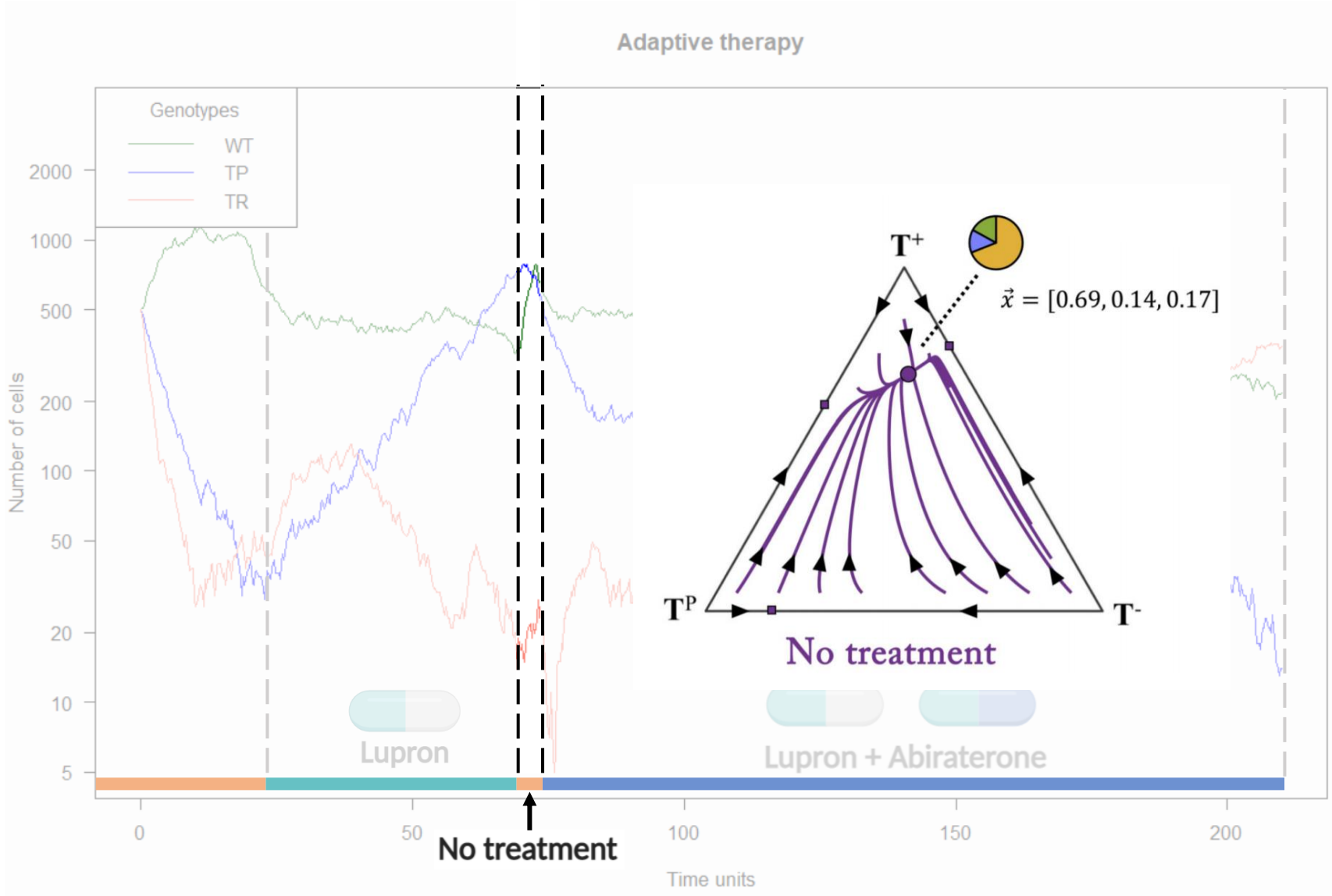
Resistant prostate cancer: adaptive therapy



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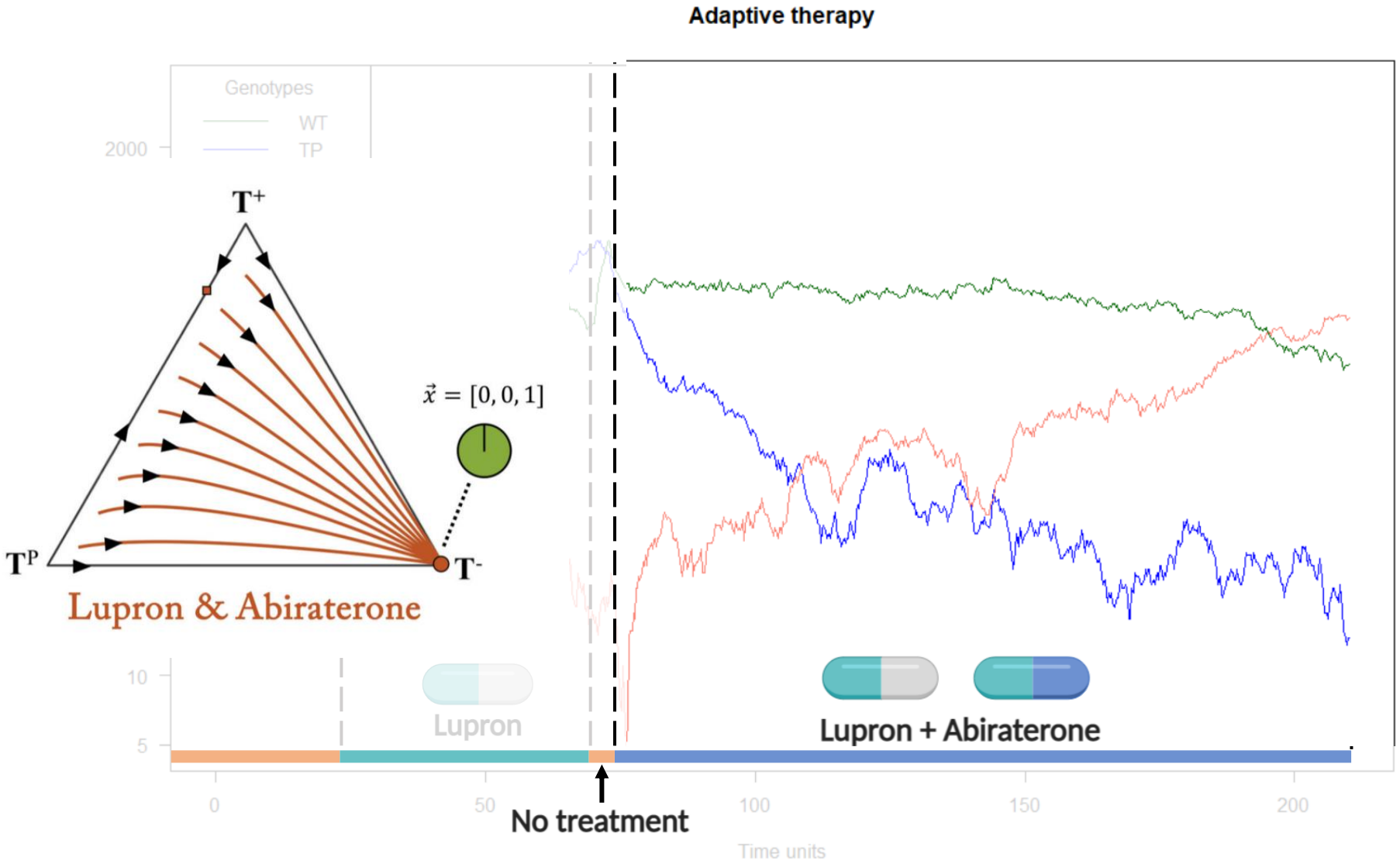

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Resistant prostate cancer: adaptive therapy