Frequency dependent fitness

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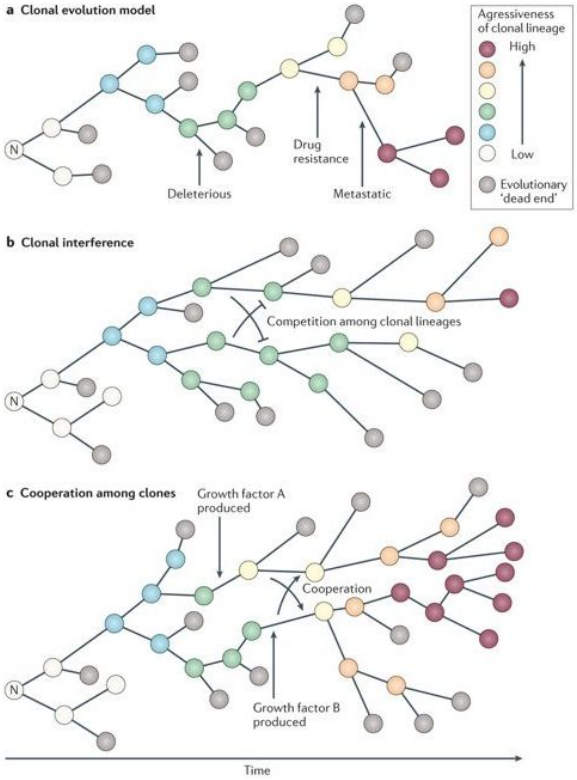
Introduction

By using game theory, we will see how the interaction between different genotypes with different capabilities or strategies can produce different evolutionary paths, some of them leading to tumor spread while others not.

We will use the package OncoSimulR to model the dynamics of an heterogeneous tumor population depending on the frequencies of each mutant.

We make the following assumptions:

- Different tumor genotypes (strategies) evolve from WT cells, being its initial count 0.
- Genotypes are distributed homogeneously in the tumour and probability of cell interaction depends only on genotype frequency, not in its spatial arrangement.



Source: Korolev, Xavier, Gore. "*Turning ecology and evolution against cancer*" https://doi.org/10.1038/nrc3712

Models

Hallmarks of cancer

- Evasion of apoptosis
- Angiogenesis
- Motility
- Cytotoxic interactions between tumor cells

Tumor-Stroma Interactions in Multiple Myeloma

Affine functions

Stochastic tunneling

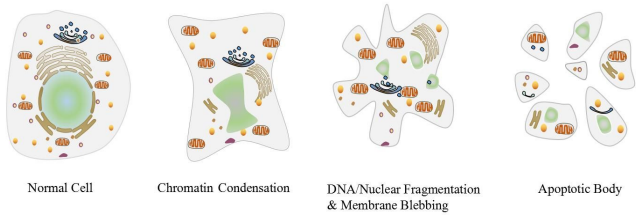
Evasion of Apoptosis

Three strategies:

A. Cells produce a growth factor to prevent apoptosis of neighboring cells. This factor has not effect on the cells producing it (paracrine). The cost of producing it is a.
B. Cells produce a growth factor to prevent apoptosis of themselves (autocrine) with no cost and benefit c
C. Cells don't produce any growth factor but get advantage from the factor produced by cells of type A with a benefit b

	A	**B**	**C**
A	1-a+b	1+b+c	1+b
B	1 − a	1 + c	1
C	1 − a	1 + c	1

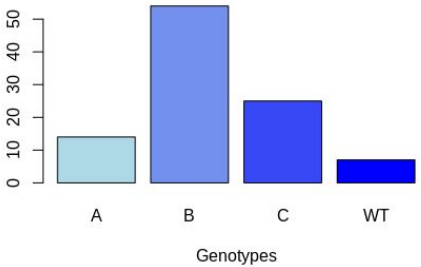
$F_{WT}=1$
$F_A = 1 + f\_A*(1 - a + b) + f\_B*(1 - a) + f\_C*(1 - a)$
$F_B = 1 + f\_A*(1 + b + c) + f\_B*(1 + c) + f\_C*(1 + c)$
$F_C = 1 + f\_A*(1 + b) + f\_B + f\_C$



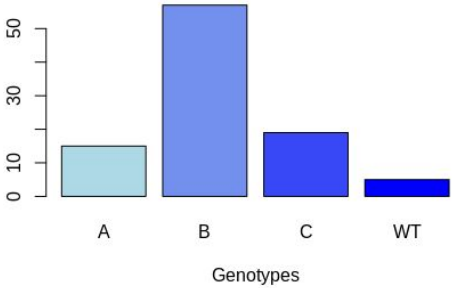
Tomlinson, Bodmer. Modelling the consequences of interactions between tumour cells. Brit. J. Cancer, 75(2):157–60, 1997

Evasion of Apoptosis

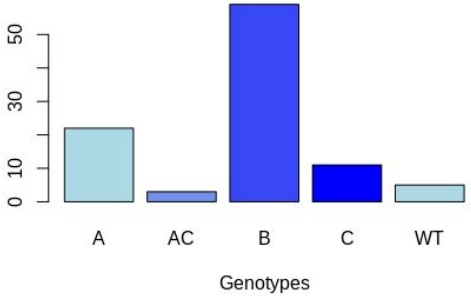
Strong selection for strategy B (producer of autocrine growth factor) as long as autocrine benefit c>0



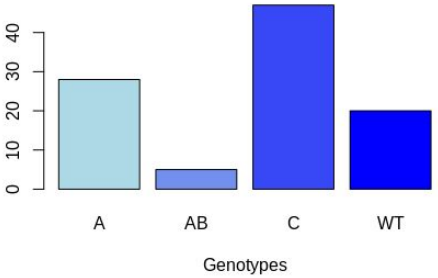

```
a <- 1
b <- 3
c <- 2
isize <- 5000
mutrate <- 1e-5
fintime <- 1000
iter <- 100
```




```
a <- 1
b <- 8
c <- 2
isize <- 5000
mutrate <- 1e-5
fintime <- 1000
iter <- 100
```




```
a <- 0
b <- 3
c <- 2
isize <- 5000
mutrate <- 1e-5
fintime <- 1000
iter <- 100
```

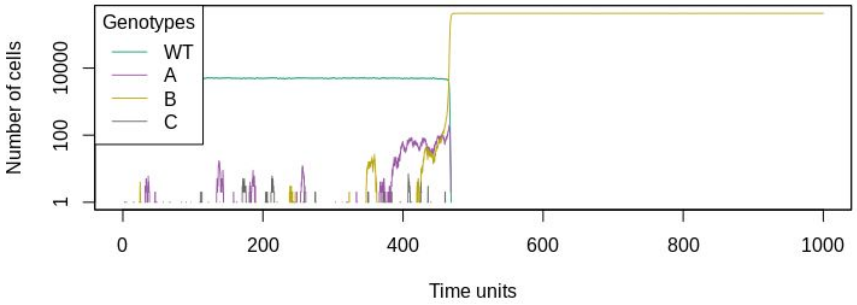



```
a <- 1
b <- 3
c <- -1
isize <- 5000
mutrate <- 1e-5
fintime <- 1000
iter <- 100
```

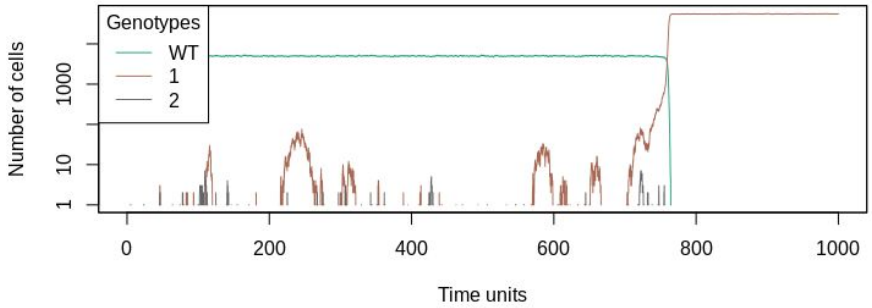
Evasion of Apoptosis

When considering only strategies B and C alone, B also wins but it takes more time to outgrow WT cells.
This indicates, even though strategy A is always the loser if a>0, its presence can lead to faster tumor growth.

a = 0, b = 2, c = 3



c=3



Angiogenesis

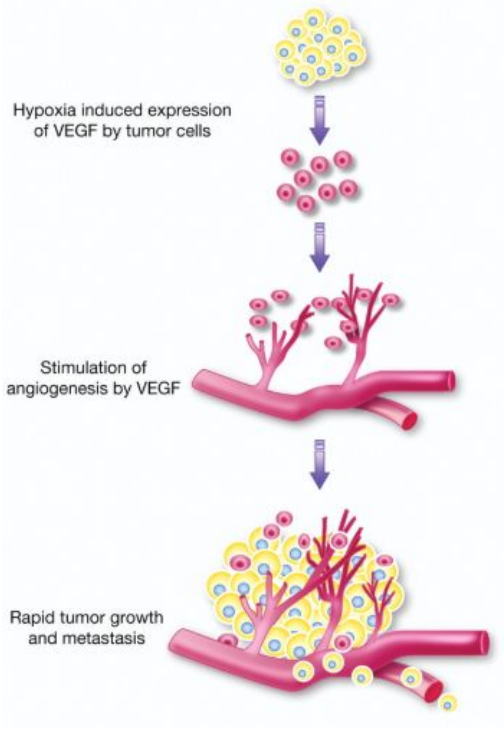
Two strategies:

1. Cells can produce angiogenic factors at a fitness cost i
2. Cells produce no angiogenic factors.

In any case cells will get a benefit j when there is an interaction involving an angiogenic factor producing cell.

	1	**2**
1	1-i+j	1+j
2	1-i+j	1

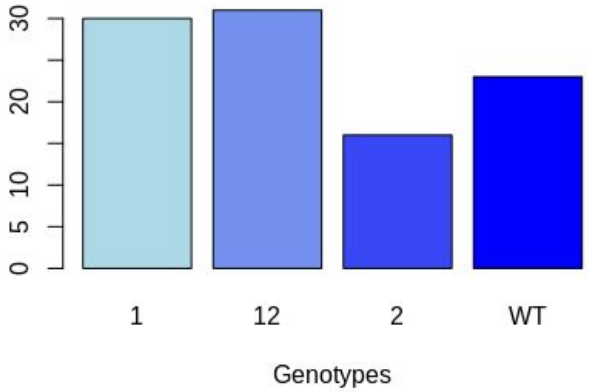
$F_{WT} = 1$
$F_1 = 1 + f\_1(1-i+j) + f\_2(1-i+j)$
$F_2 = 1 + f\_1(1+j) + f\_2$



Tomlinson, Bodmer. Modelling the consequences of interactions between tumour cells. Brit. J. Cancer, 75(2):157–60, 1997

Angiogenesis

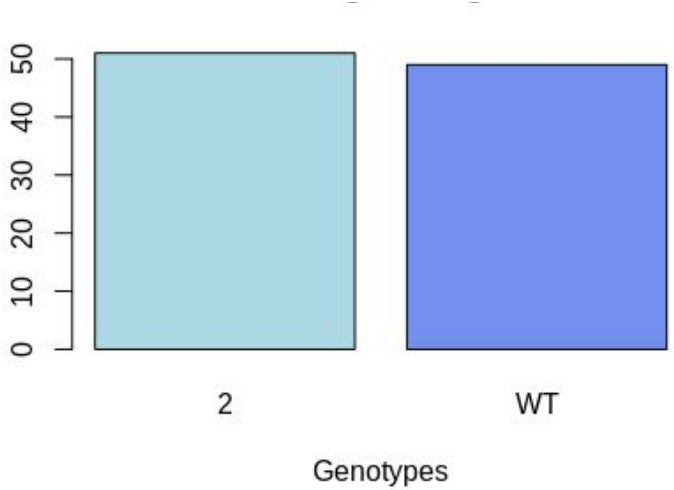
- Results from the simulations don’t quite match the main theoretical insight extracted from Tomlinson and Bodmer.
- For them, as long as the benefit j of angiogenesis is greater than the cost i of producing angiogenic factors then both types of strategies will be present in a tumour in a polymorphic equilibrium.




```
j <- 2
i <- 1
isize <- 5000
mutrate <- 1e-5
fintime <- 1000
iter <- 100
```

Angiogenesis

In the case in which the cost is bigger than the benefit the result is the advantage of strategy 2 as stated in the paper, although there is an important fraction of the simulations in which mutants don’t get to outgrow WT cells:




```
j <- 1
i <- 2
isize <- 5000
mutrate <- 1e-5
fintime <- 1000
iter <- 100
```

Motility - The theory

Fitness change table

	AG	INV	GLY
AG	0.5	1-c	0.5+n-k
INV	1	1-c/2	1-k
GLY	0.5 - n	1-c	0.5-k

3 Cell types

1. Increased replicative potential (AG)
2. Glycolytic cells (GLY)
3. Invasive (INV)

c = cost of movement, k = fitness cost of less efficient glycolysis, n = Fitness cost of acidity

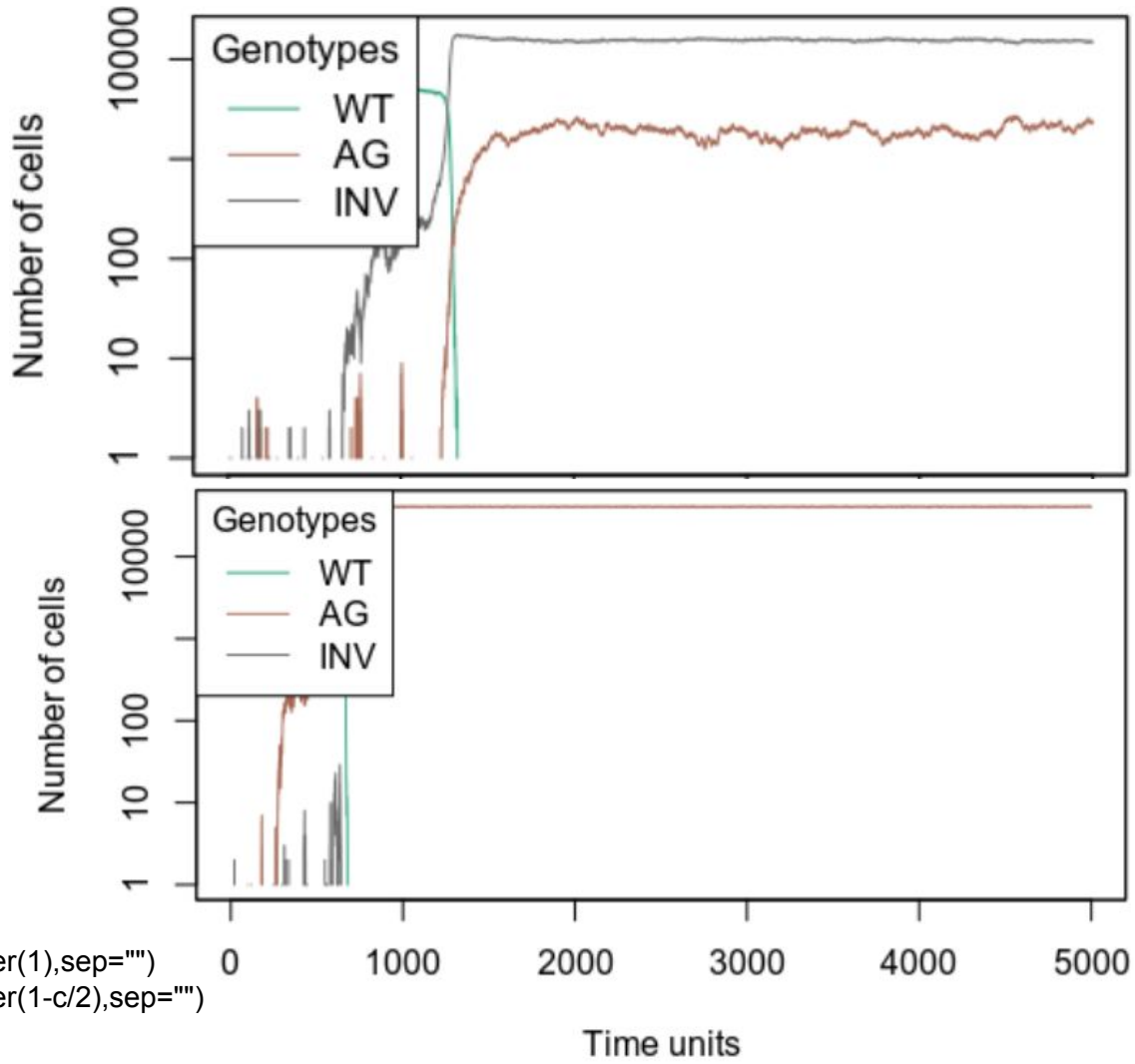
What do we expect to happen when cells interact with each other?

AG:INV	Can coexist provided (c) is not too high
AG:GLY	Cannot coexist. High (n) will result in GLY dominating, high (k) will result in AG dominating
AG:INV:GLY	INV will be more prevalent provided (c) isn't too high

Motility - The Results

AG:INV

- The two cells can coexist together
- INV in a larger proportion as it will move to a new location rather than share resources. (C <- 0.1, mutrate = 1e-5)
- Increasing the cost of moving will allow AG to dominate (C <- 0.7, mutrate = 1e-5)



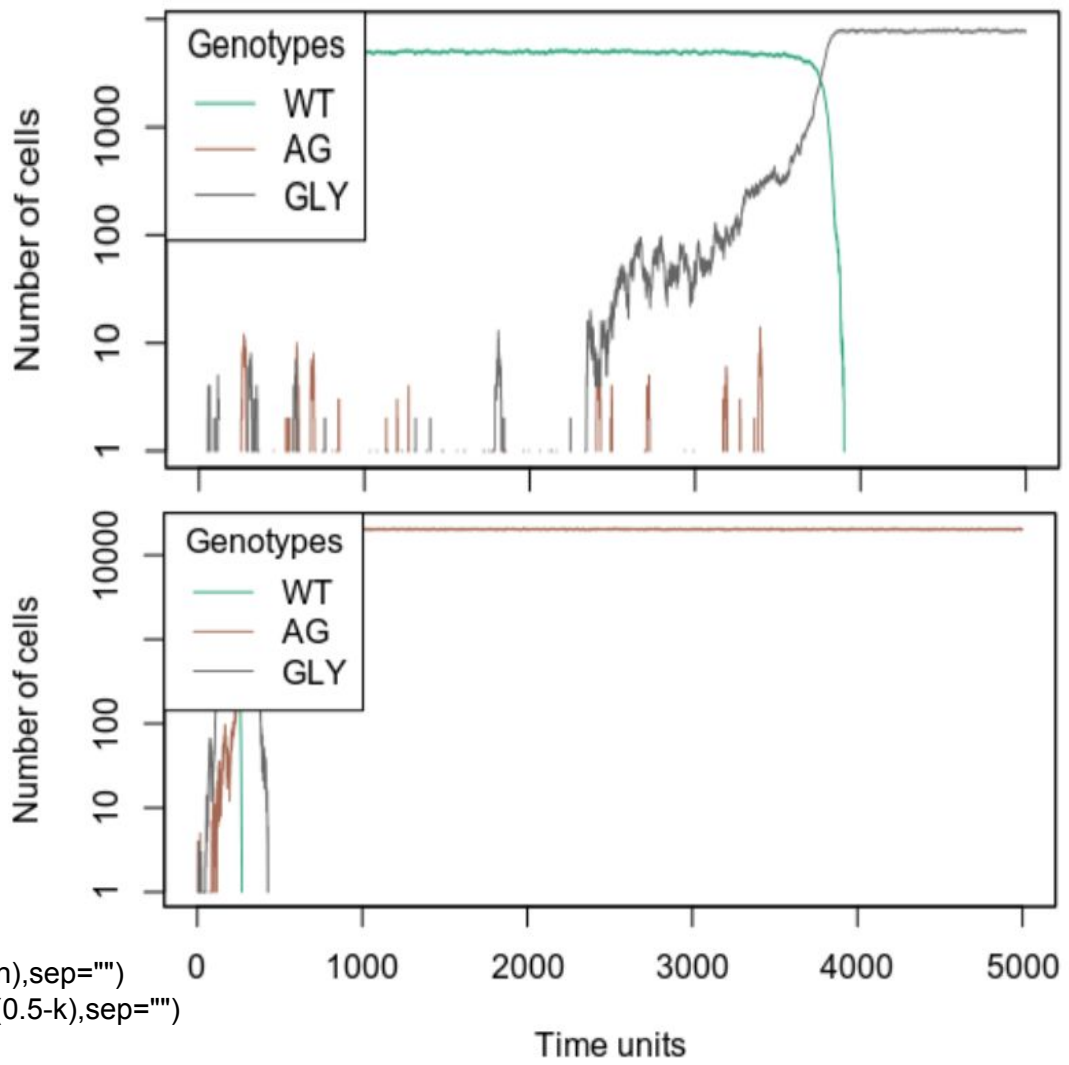
Fitness functions:

```
f1 <- paste("1+f_1*",as.character(0.5),"+f_2*",as.character(1),sep="")
f2 <- paste("1+f_1*",as.character(1-c),"+f_2*",as.character(1-c/2),sep="")
```

Motility - The Results

AG:GLY

- The two cells don't coexist together
- By having higher effects of acidity, GLY will dominate (k <- 0.1, n <- 0.3)
- By having higher effects of glycolysis, AG will dominate (k <- 0.3, n <- 0.1)



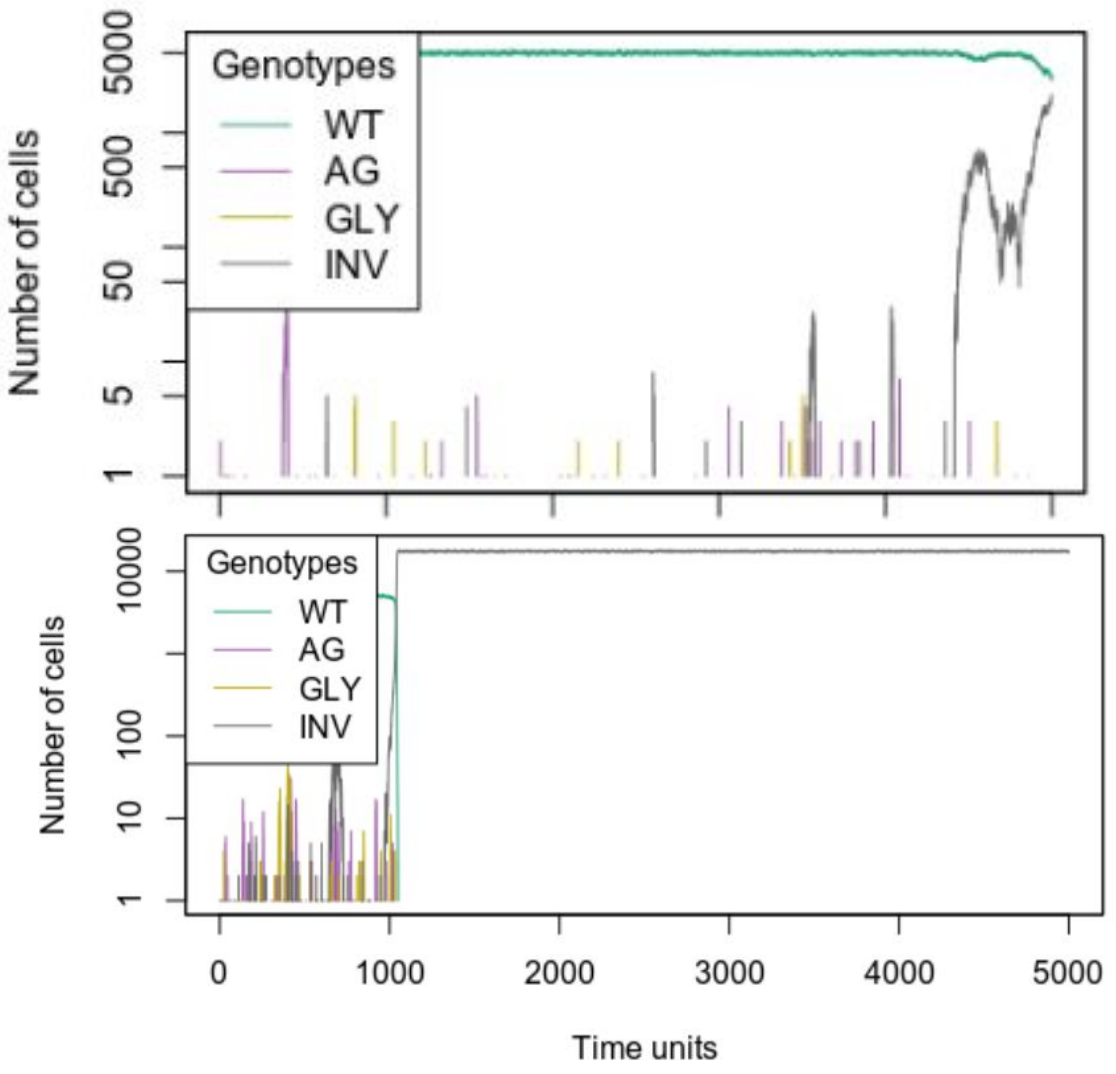
Fitness functions:

```
f1 <- paste("1+f_1*",as.character(0.5),"+f_2*",as.character(0.5-n),sep="")
f2 <- paste("1+f_1*",as.character(0.5+n-k),"+f_2*",as.character(0.5-k),sep="")
```

Motility - The Results

AG:INV:GLY

- When the cost of glycolytic fitness is high (c=0.1, k=0.7, n=0.15), INV cells will struggle to dominate.
- When the glycolytic cost is reduced (c=0.1, k=0.2, n=0.15), INV cells will dominate faster.



Fitness functions:

```
f1 <- paste("1+f_1*",as.character(0.5),"+f_2*",
        "+f_3*",as.character(0.5-n),sep="")
f2 <- paste("1+f_1*",as.character(1-c),"+f_2*",
        as.character(1-c/2),"+f_3*",as.character(1-c),sep="")
f3 <- paste("1+f_1*",as.character(0.5+n-k),"+f_2*",
        as.character(1-k),"+f_3*",as.character(0.5-k),sep="")
```

Motility - Conclusion

For the invasive phenotype to dominate in a tumor environment, it will depend on the same factors that determine the fate of the glycolytic phenotype.

The study suggests that if you want to reduce the probability of the emergence of the invasive phenotype cells (INV), you should select

1. Therapies that increase the fitness cost of glycolysis (k)
2. Therapies that reduce the effects of the acidic environment (n) on healthy cells

Cytotoxic interactions between tumor cells

Tumour cells might boost their own replicative potential at the expense of other tumour cells by evolving the capability of producing cytotoxic substances

Three cell types:

WT: cells producing neither cytotoxins nor resistance
A: Cells producing cytotoxic substances against other cells
B: cells producing resistance to external cytotoxic substances

Results:
Two-strategy polymorphisms between A and WT and between A and B may occur. A, B or WT may also become fixed in the population:

1. WT is favoured by small f
2. A is favoured by small e, large g, small f and large g
3. B is favoured by small h

Fitness functions:

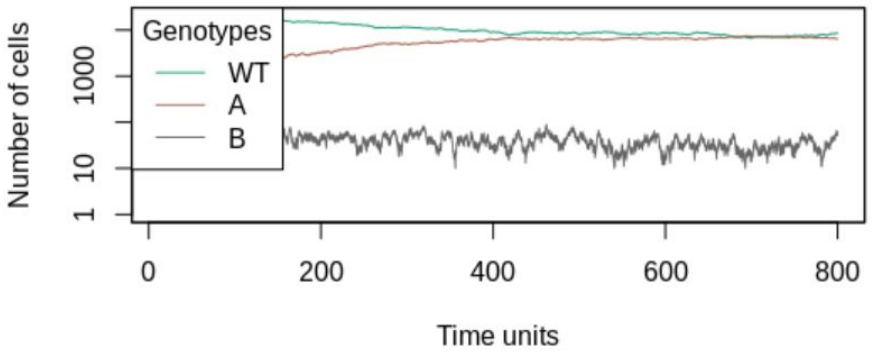
F_{WT} = (z-f)*f_A + z*f_B + z*f_
F_{A} = (z-e-f+g)*f_A + (z-e)*f_B + (z-e+g)*f_
F_{B} = (z-h)*f_A + (z-h)*f_B + (z-h)*f_

Where:
z= Baseline fitness
e= Cost of producing cytotoxin
f= Disadvantage of being affected by cytotoxin
g= Advantage conferred after having subjected another cell to the cytotoxin
h= Cost of resistance to cytotoxin

Cytotoxic interactions between tumor cells

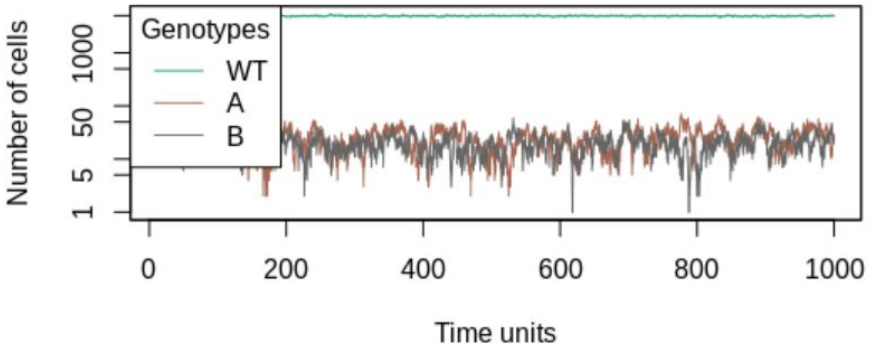
Scenario 1:
Expected frequencies: WT= 0.542, A=0.458, B=0

z= 1
e= 0.1
f= 0.4
g= 0.1
h= 0.4



Scenario 2:
Expected frequencies: WT= 1, A=0, B=0

z= 1
e= 0.3
f= 0.4
g= 0.1
h= 0.25



Tumor-Stroma Interactions in Multiple Myeloma

In multiple myeloma, cancer cells and stromal cells cooperate by exchanging diffusible factors that sustain tumor growth

Three cell types:

Osteoclasts (OC)
Osteoblast (OB)
Malignant plasma cells (MM)

Fitness functions:

$F_{OC} = 1 + bz*f\_C + ay*f\_B$
$F_{OB} = 1 + ax*f\_A - dz*f\_C$
$F_{MM} = 1 + bx*f\_A$

Where:
x = Contribution of OC
y = Contribution of OB
z = Contribution of MM

Absent genotypes:

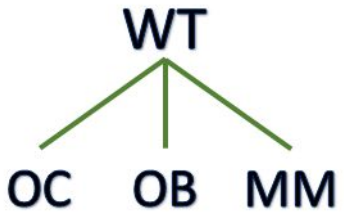
$F_{WT} = 0.5$
$F_{AB} = 0$

Summary of effects of diffusible factors:

	GOC	GOB	GMM
OC	Neutral	Equilibrium	Stimulation
OB	Equilibrium	Neutral	Inhibition
MM	Stimulation	Neutral	Neutral

Multiplication factors:

	GOC	GOB	GMM
OC	0	a	b
OB	a	0	-d
MM	b	0	0

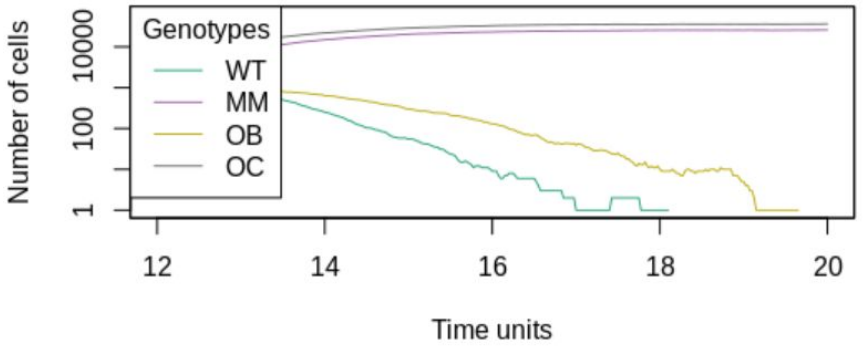


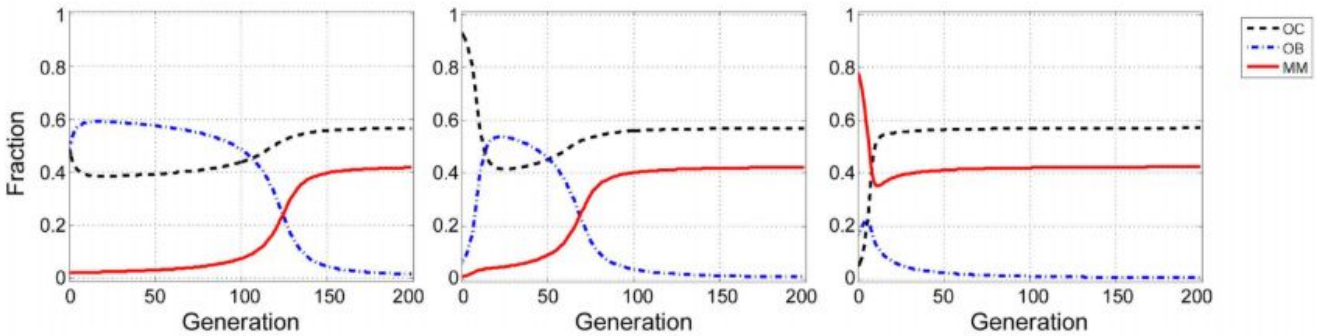
Tumor-Stroma Interactions in Multiple Myeloma

Scenario 1: OB contribution < OC < MM contribution

The benefit of diffusible factors that are secreted by MM cells is greater than the benefit that OC cells can obtain through the diffusible factors produced by OB.

Result: There exists a polymorphic stable point between MM and OC





Sourse: Sartakhti (2016)

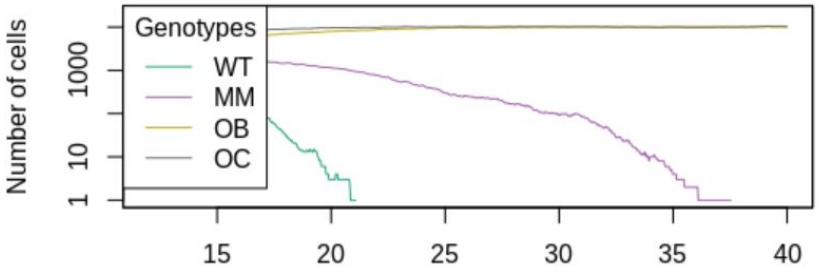
Multiplication factors:
a = 1
b = 2.5
d = 0.3

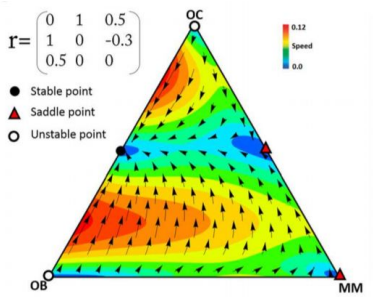
Contributions:
Contribution of OC = 1
Contribution of OB = 1.2
Contribution of MM = 1.4

Tumor-Stroma Interactions in Multiple Myeloma

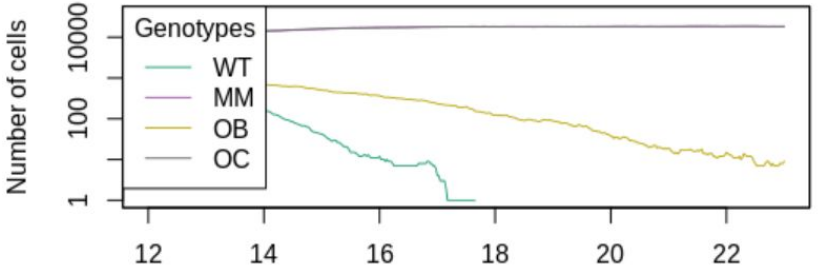
Scenario 2: Costs for OC, OB and MM are equal

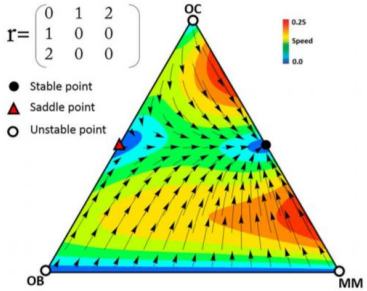
As the difference between b and d increases, the stable equilibrium moves from the healthy OB-OC polymorphism to the MM-OC polymorphism typical of multiple myeloma





Multiplication factors:
a = 1
b = 0.5
d = 0.3





Multiplication factors:
a = 1
b = 2
d = 0

Sourse: Sartakhti (2016)

Affine fitness functions

- Fitness is defined as an affine function of the expected payoff and a constant contribution.

$$f(\mathbf{x}) = \boldsymbol{M}\mathbf{x} + \mathbf{r}$$

- **The goal**: apply the affine fitness function in a model for tumor–normal cell interactions to determine which are the most successful tumor strategies.

The case of two-players:

- Strategies *A* and *B*
- They found that the two-player dynamics only depends on the difference between *α*, *β* and *σ*, where

  α = a - c, *β = b - d* and *σ = t - s*

$$\boldsymbol{M} = \begin{matrix} \\ A \\ B \end{matrix} \begin{matrix} \begin{matrix} A & B \end{matrix} \\ \begin{pmatrix} a & b \\ c & d \end{pmatrix} \end{matrix} \quad \text{and} \quad \mathbf{r} = \begin{pmatrix} s \\ t \end{pmatrix}$$

Behavior	Schematic	Parameter range
Stable internal equilibrium	$A \rightarrow x^* \leftarrow B$	$\alpha < \sigma < \beta$
Unstable internal equilibrium	$A \leftarrow x^* \rightarrow B$	$\alpha > \sigma > \beta$
A dominates B	$A \longleftarrow B$	$\sigma < \alpha, \beta$
B dominates A	$A \longrightarrow B$	$\sigma > \alpha, \beta$

Gerstung M, Nakhoul H, Beerenwinkel N. **Evolutionary games with affine fitness functions: applications to cancer.** Dynam Games Appl. 2011

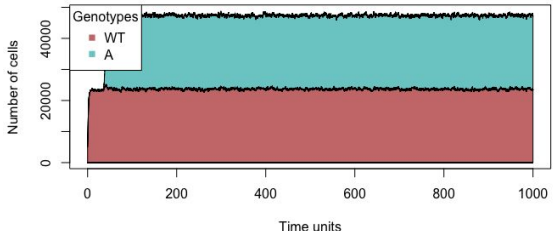
Affine fitness functions

The case of two players:

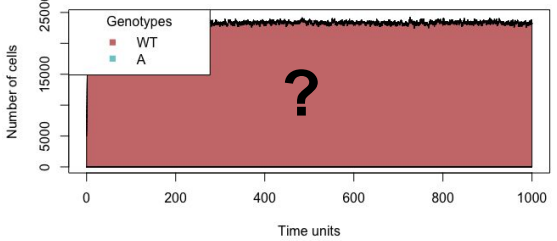
- In the following scenarios, the proportion of cells is set to 0.5/0.5, which is close to the experimentally observed ratio of 49% tumor cells (in tumor tissue)

WT — normal cells
A — tumor cells

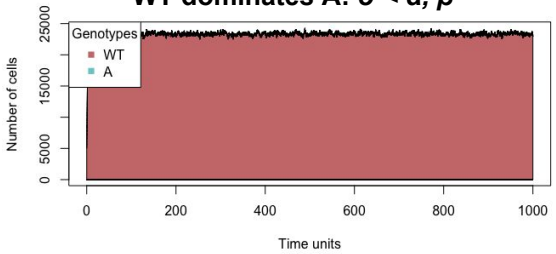
Stable internal equilibrium: $\alpha < \sigma < \beta$



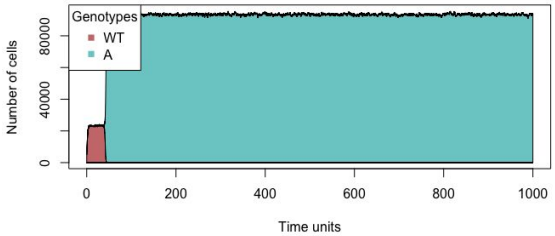
Unstable internal equilibrium: $\alpha > \sigma > \beta$



WT dominates A: $\sigma < \alpha, \beta$



A dominates WT: $\sigma > \alpha, \beta$



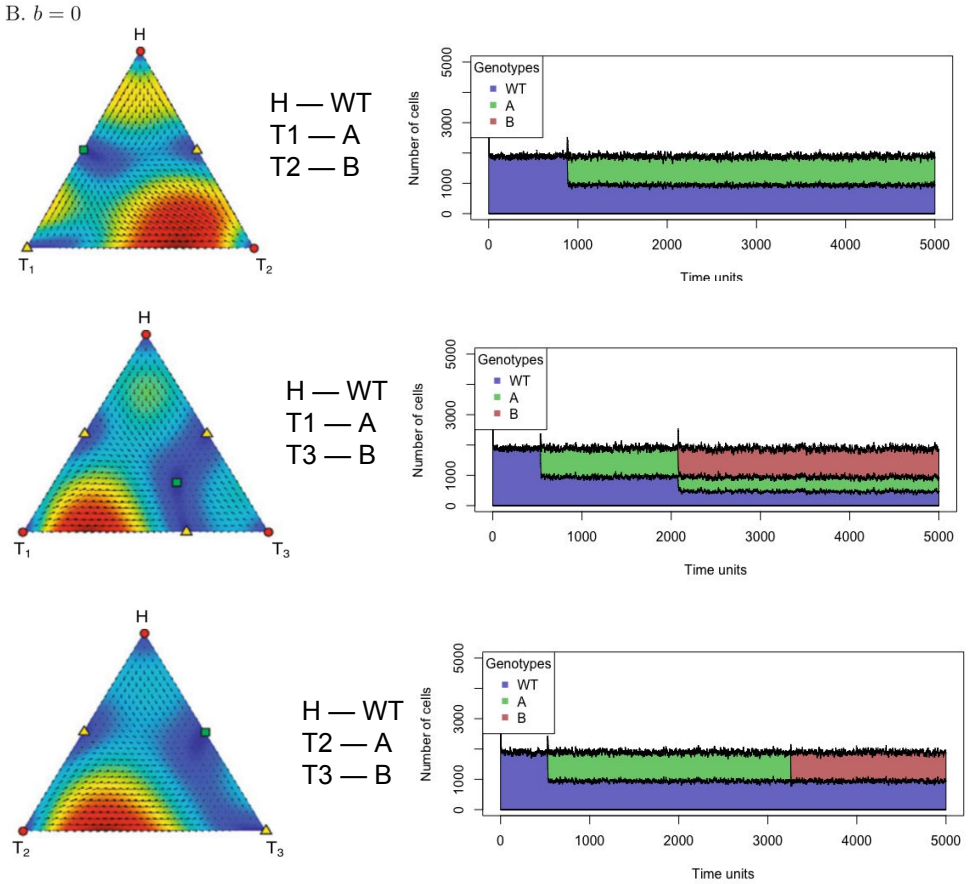
Gerstung M, Nakhoul H, Beerenwinkel N. **Evolutionary games with affine fitness functions: applications to cancer.** Dynam Games Appl. 2011

Affine fitness functions

The case of three players:

- T1 : exploitation and attraction of normal cells without additional advantage
  $\alpha = -1 \quad \beta = 1 \quad \sigma = 0$
- T2 : strong exploitation at the cost of a disadvantage
  $\alpha = -2 \quad \beta = 0 \quad \sigma = -1$
- T3 : strong attraction of normal cells with constant fitness advantage
  $\alpha = 0 \quad \beta = 2 \quad \sigma = 1$

Observing fixed stable points



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Affine fitness functions

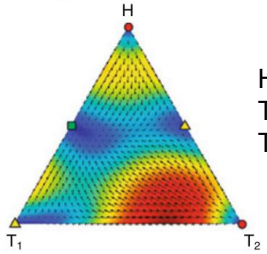
The case of three players:

- T1 : exploitation and attraction of normal cells without additional advantage
- T2 : strong exploitation at the cost of a disadvantage
- T3 : strong attraction of normal cells with constant fitness advantage

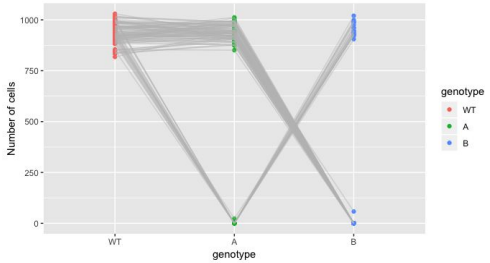
They concluded that T3 is the most successful strategy. And we also can see, that T3 wins T1 and T2 in our scenarios.

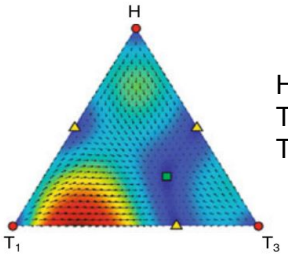
Observing possible scenarios (100 simulations)

B. $b = 0$

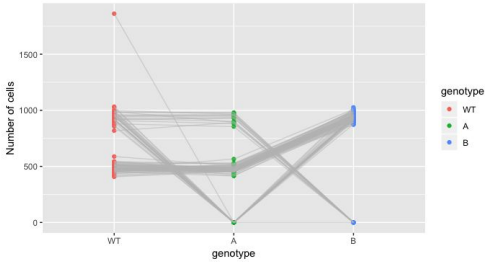


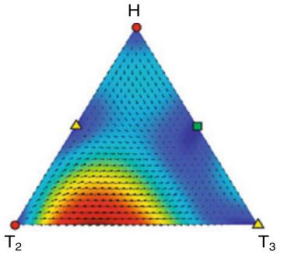
H — WT
T1 — A
T2 — B



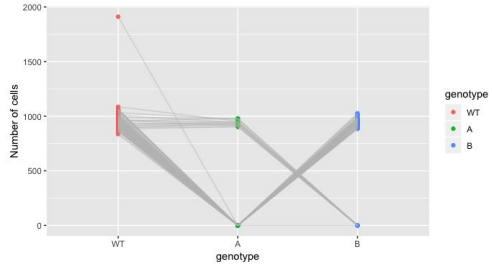


H — WT
T1 — A
T3 — B





H — WT
T2 — A
T3 — B



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Stochastic tunnelling

We have three types of cells:

WT — have 2 intact copies of the gene
A — have 1 intact copy
AB — have both copies inactivated

WT mutate into **A** with rate *μ1*
A mutate into **AB** with rate *μ2*

r — "reproductive rate" or relative probability to be chosen for reproduction (which is different for each type of cells)

N — a population size

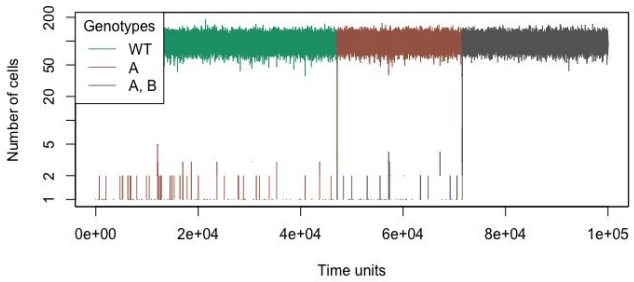
The probability that a cell of type **WT** reproduces is proportional to its frequency and the reproductive rate:

$$r_{WT}f_{WT} / (r_{WT}f_{WT} + r_Af_A + r_{AB}f_{AB})$$

Genuine two-step process

all **WT**(r_1) → all **A**(r_2) → all **AB**(r_3)

$\mu 2 \approx 1/N$

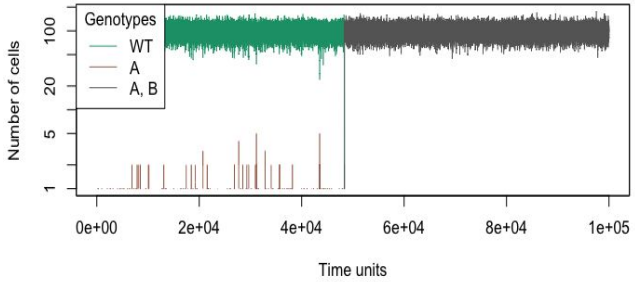


Tunnelling

all **WT**(r_1) → all **A**(r_2) → all **AB**(r_3)

tunnel

$\mu 2 \gg 1/N$



Komarova N, Sengupta A, Nowak M. **Mutation–selection networks of cancer initiation: tumor suppressor genes and chromosomal instability.** Journal of Theoretical Biology. 2003

Discussion

All our code for simulations and vignettes is available from the repository:
https://github.com/liubovch/exam_OncoSimulR

“Mathematicians think differently, but this may not necessarily be a bad thing.”

Komarova N. **Mathematical modeling of tumorigenesis: mission possible.** Curr Opin Oncol. 2005