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**The simulation of tumor heterogeneity
and cancer-cell evolution using
hallmarks approach**

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*The model and the results of
the simulation for the colorectal cancer*

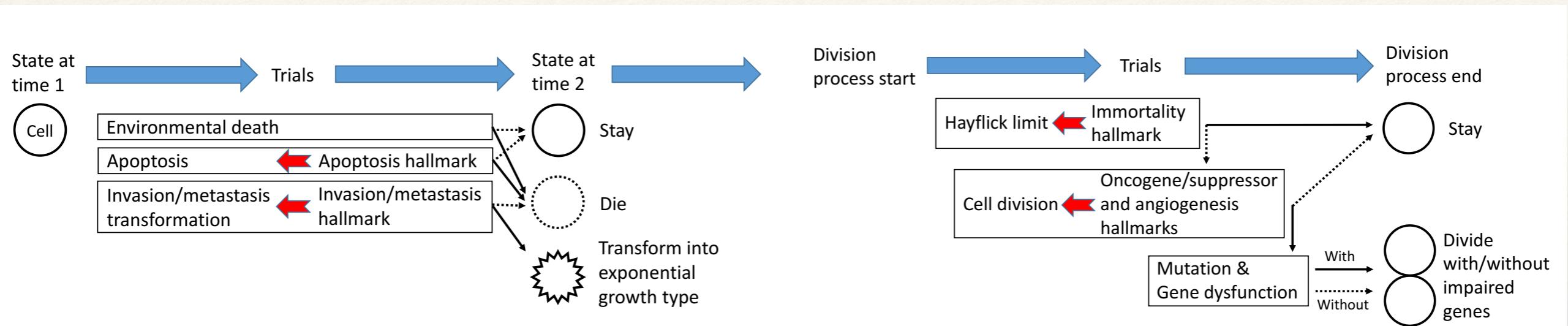
Department of Bioinformatics

Goal and tasks of simulation

- ❖ **Motivation:** to research and simulate Darwinian selection of the tumor cells and it's interrelation with DNA of survived cancer cells
- ❖ **GOAL:** *the program code and the calculation with a suggested model for colorectal cancer cells as an example*

Model for Cancer Cell Evolution

proposed by prof. Mamoru Kato



The oncogene/suppressor hallmark variable, H_d , for example:

$$H_d = w_1^d \cdot g_1^d + w_2^d \cdot g_2^d + w_3^d \cdot g_3^d + w_4^d \cdot g_4^d$$

$$\text{Let } (w_1^d, w_2^d, w_3^d, w_4^d) = (0.1, 0.2, 0.3, 0.4)$$

$$\text{When } (g_1^d, g_2^d, g_3^d, g_4^d) = (1, 1, 0, 0)$$

$$H_d = 0.1 \cdot 1 + 0.2 \cdot 1 + 0.3 \cdot 0 + 0.4 \cdot 0 = 0.3$$

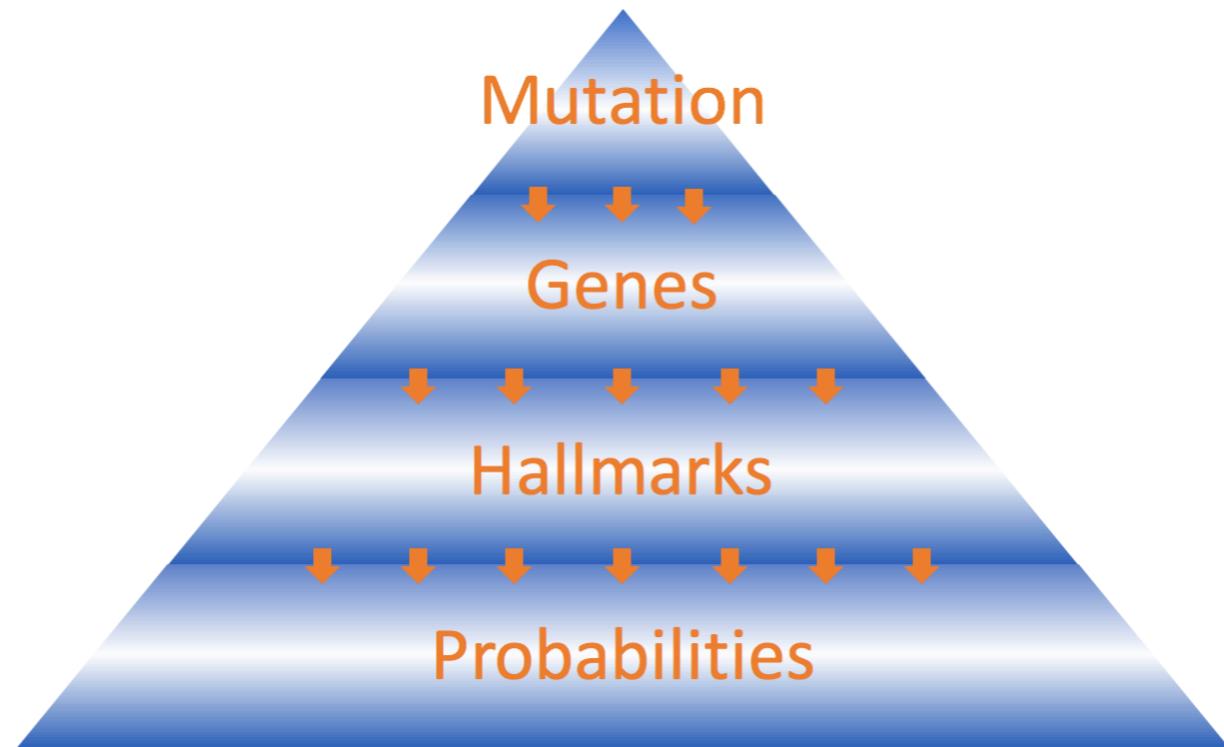
H_d interferes with a probability value of the cell division trial:

$$d' = d_0 + H_d = 0 + 0.3 = 0.3$$

The simplest model to examine the effects of hallmarks themselves

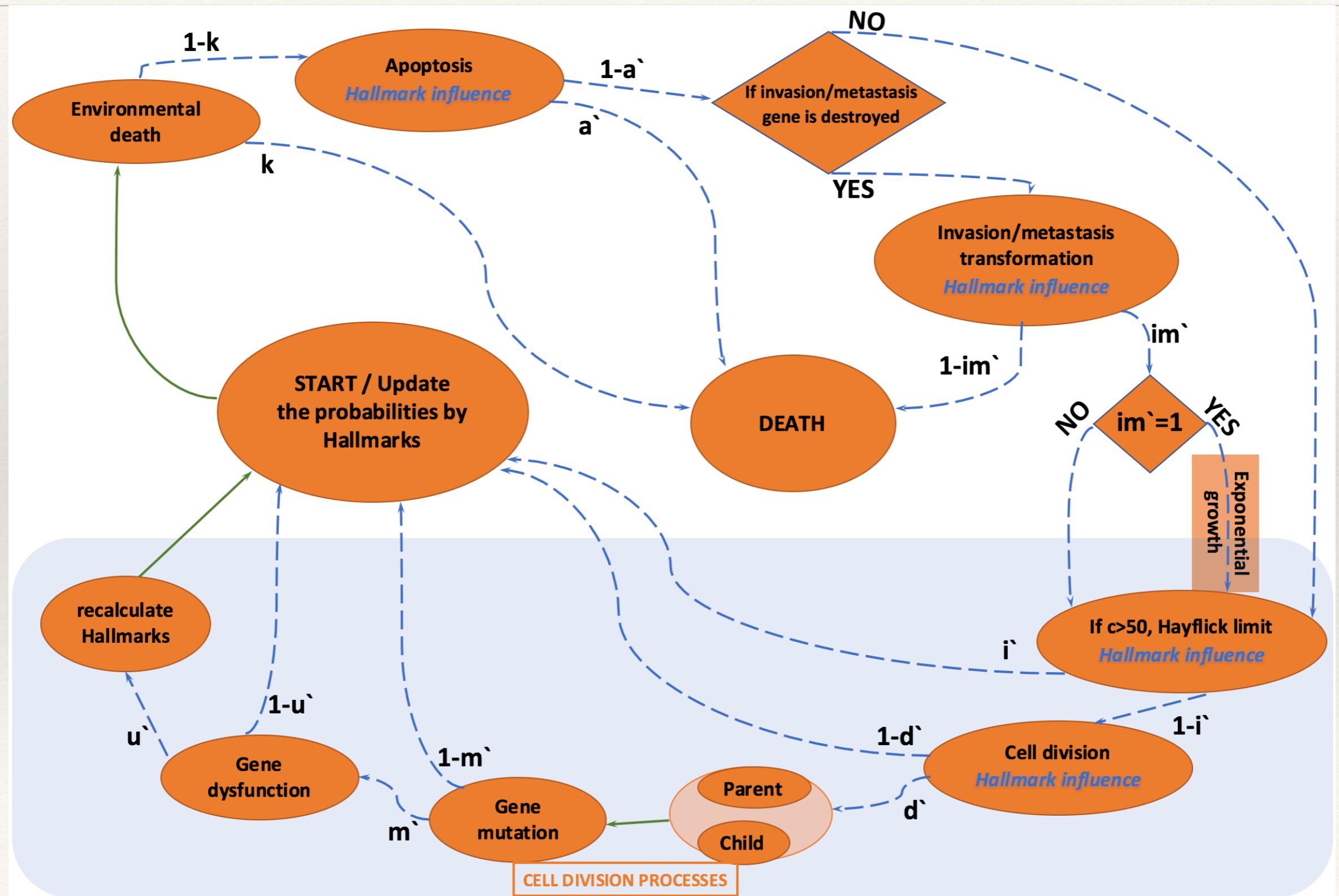
$$\begin{bmatrix} H_a \\ H_{im} \\ H_i \\ H_d \\ H_b \end{bmatrix} = \begin{bmatrix} w_1^a \cdot g_1^a \\ w_1^{im} \cdot g_1^{im} \\ w_1^i \cdot g_1^i \\ w_1^d \cdot g_1^d \\ w_1^b \cdot g_1^b \end{bmatrix} = \begin{bmatrix} 1 \cdot I_a \\ 1 \cdot I_{im} \\ 1 \cdot I_i \\ 1 \cdot I_d \\ 1 \cdot I_b \end{bmatrix}$$

“The four floors model”



MUTATION						
<i>Ga</i>	<i>Destroyed Genes / ALL Genes</i>	<i>Gi</i>	<i>Gim</i>	-	<i>Gd</i>	<i>Gb</i>
$H_a = \sum_k (G_a)_k$	x - mutation density	$H_i = \sum_k (G_i)_k$	$H_{im} = \sum_k (G_{im})_k$	-	$H_d = \sum_k (G_d)_k$	$H_b = \sum_k (G_b)_k$
Apoptosis $a' = a - H_a$ $a = \frac{1}{1 + e^{-s_0(x-0.5)}}$	Hayflick limit (immortalization) $i' = 1 - H_i$	Invasion/metastasis transformation $im' = H_{im}$	Environmental death k'	Division process $d' = \begin{cases} d - E' \cdot N & , \text{for normal cells} \\ d & , \text{for metastasis cells} \end{cases}$ $E' = \frac{E_0}{1 + F_0 \cdot H_b}$ $d = d_0 + H_d$ $N - \text{number of normal cells}$		

Scheme of simulation with processes and states



The simulation for the colorectal cancer

- ❖ The relations between genes and hallmarks variables

3. The case of colorectal cancer			
			List Hallmarks
APC		Ha Hb Hi Him Hd	Ha, Hi, Him, Hd
KRAS		Ha Hb Hi Him	Ha, Hb, Hi, Him, Hd
TP53		Ha Hb Hi	Ha, Hb, Him, Hd
PIK3CA		Him Hd	Him, Hd

Gene file and Hallmark's weights

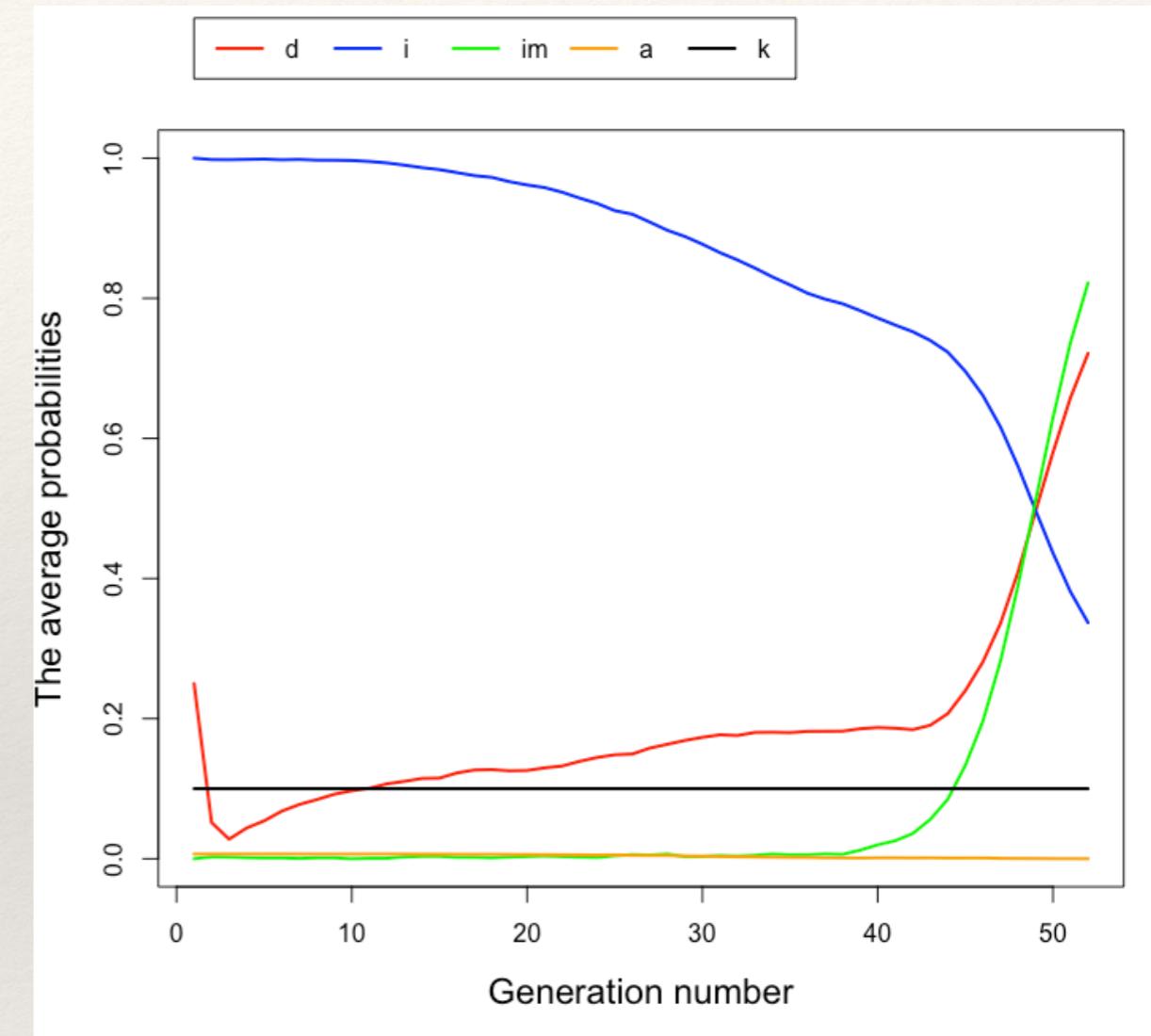
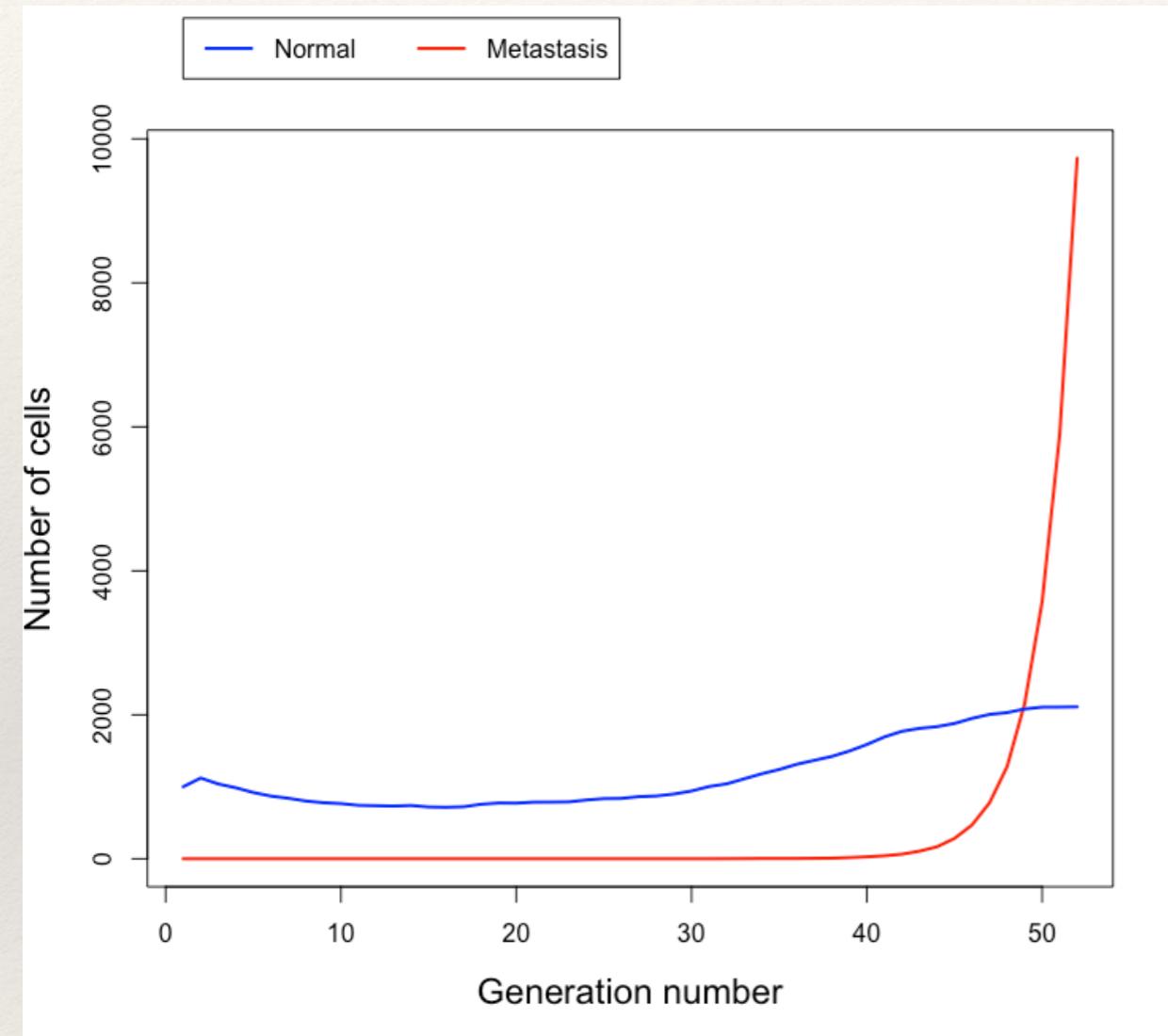
Gene file format

Column	Contents
1	Gene name
2	CDS length
3	Distinction of oncogene/suppressor o: oncogene s: suppressor ?: unknown (will be randomly assigned)
4	Hallmark name: apoptosis immortalization growth anti-growth angiogenesis invasion
5	Hallmark weights. * For convenience, hallmark weights are automatically generated in random (rbeta) when this column is blank.

Example of gene file with Hallmark's weights

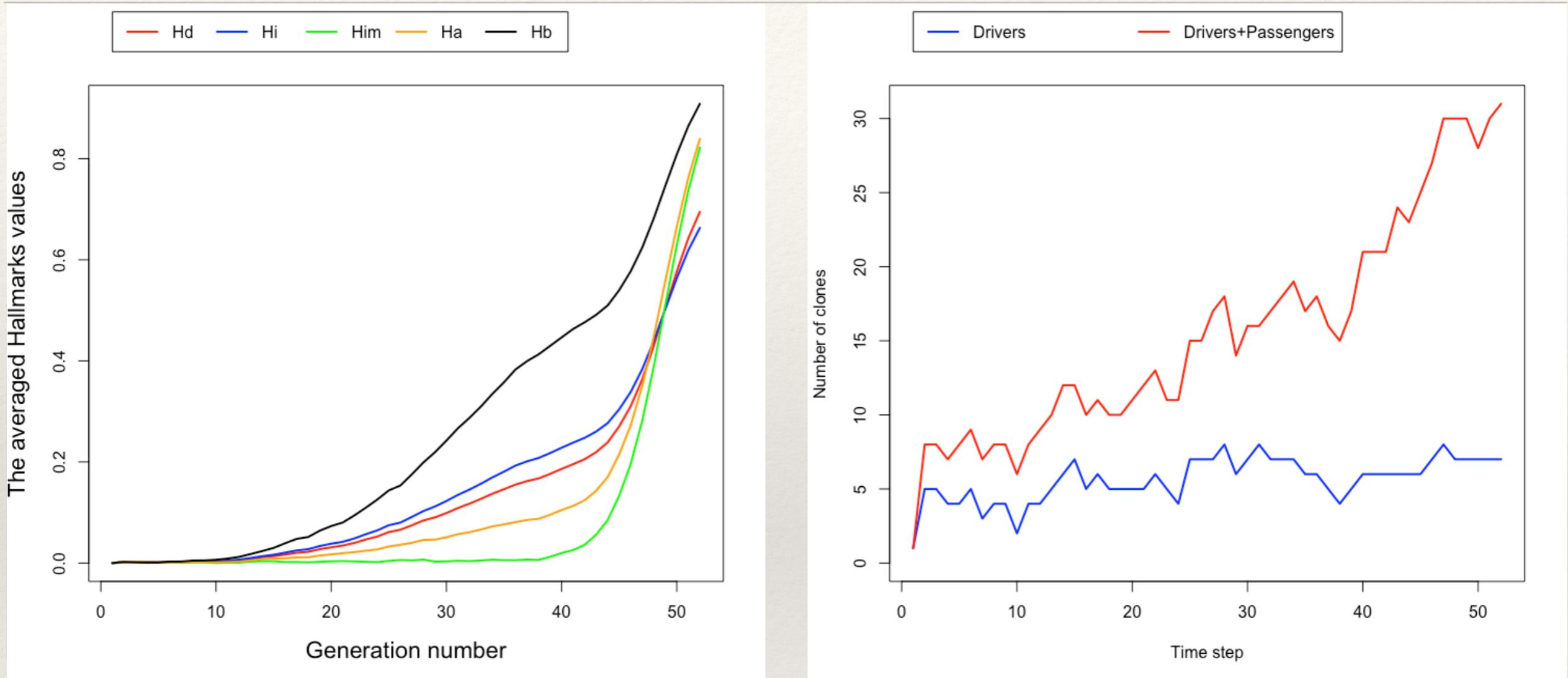
Gene name	Length CDS	Hallmark's name	onco/suppressor	weight
APC	10804	apoptosis	s	0.333
KRAS	5889	apoptosis	s	0.333
TP53	2724	apoptosis	s	0.333
APC	10804	growth	o	0.25
KRAS	5889	growth	o	0.25
TP53	2724	growth	o	0.25
PIK3CA	2344	growth	o	0.25
APC	10804	immortalization	o	0.25
KRAS	5889	immortalization	o	0.25
TP53	2724	immortalization	o	0.25
PIK3CA	2344	immortalization	o	0.25
TP53	2724	angiogenesis	o	0.5
KRAS	5889	angiogenesis	o	0.5
APC	10804	invasion	s	0.5
KRAS	5889	invasion	o	0.5

Number of cells and the average values of probabilities



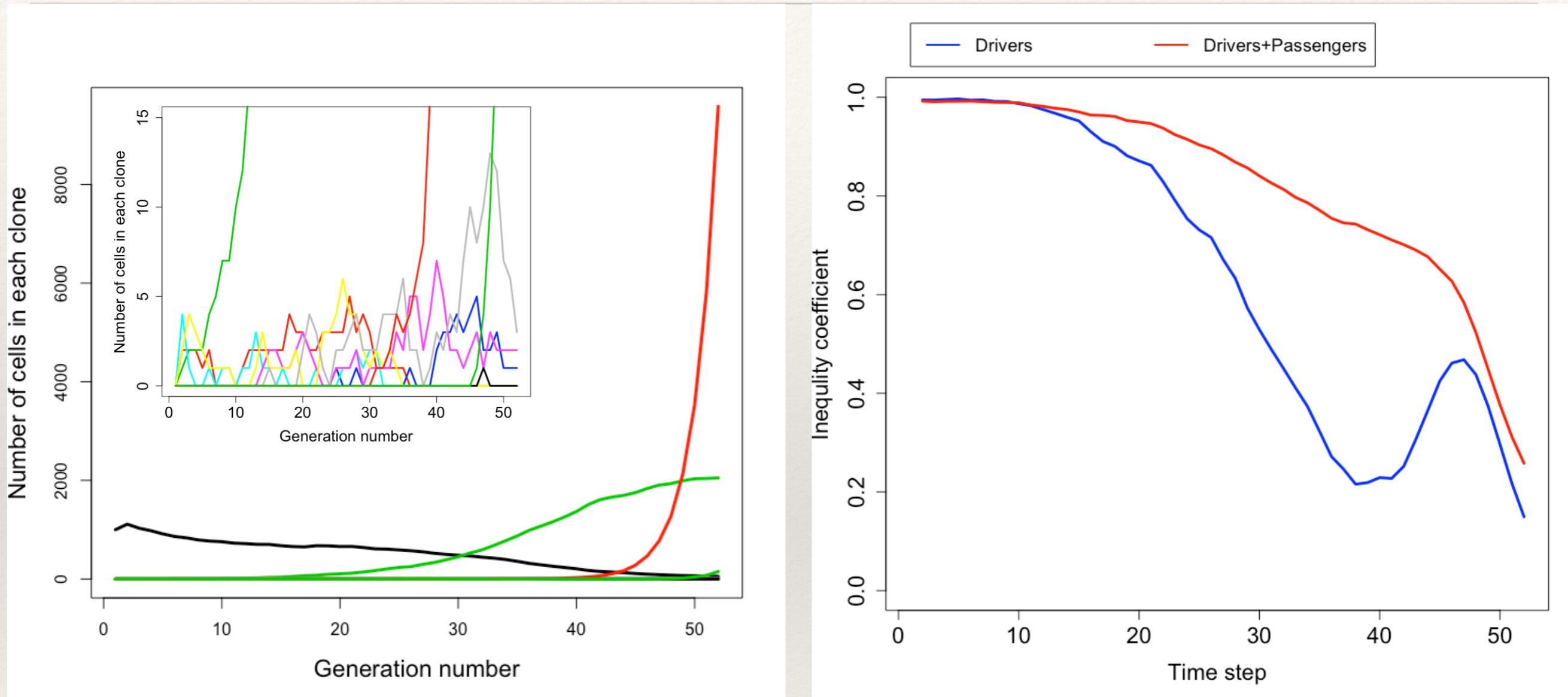
- ❖ The data for one simulation

Hallmarks values and number of clones



- ❖ The data for one simulation

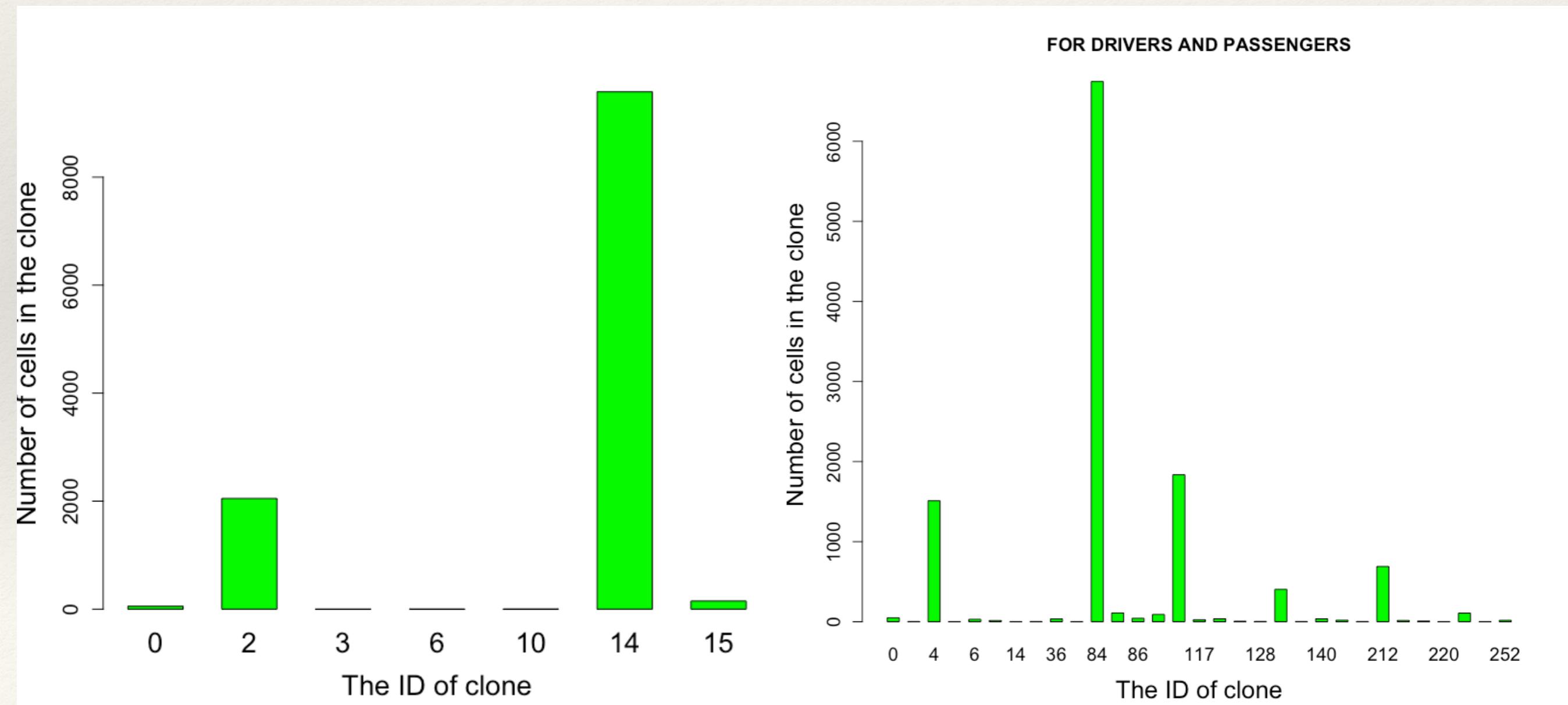
Clones and inequality coefficient



The data for one simulation

The number of cells in each clone

- ❖ The data for one simulation ! at the last step !



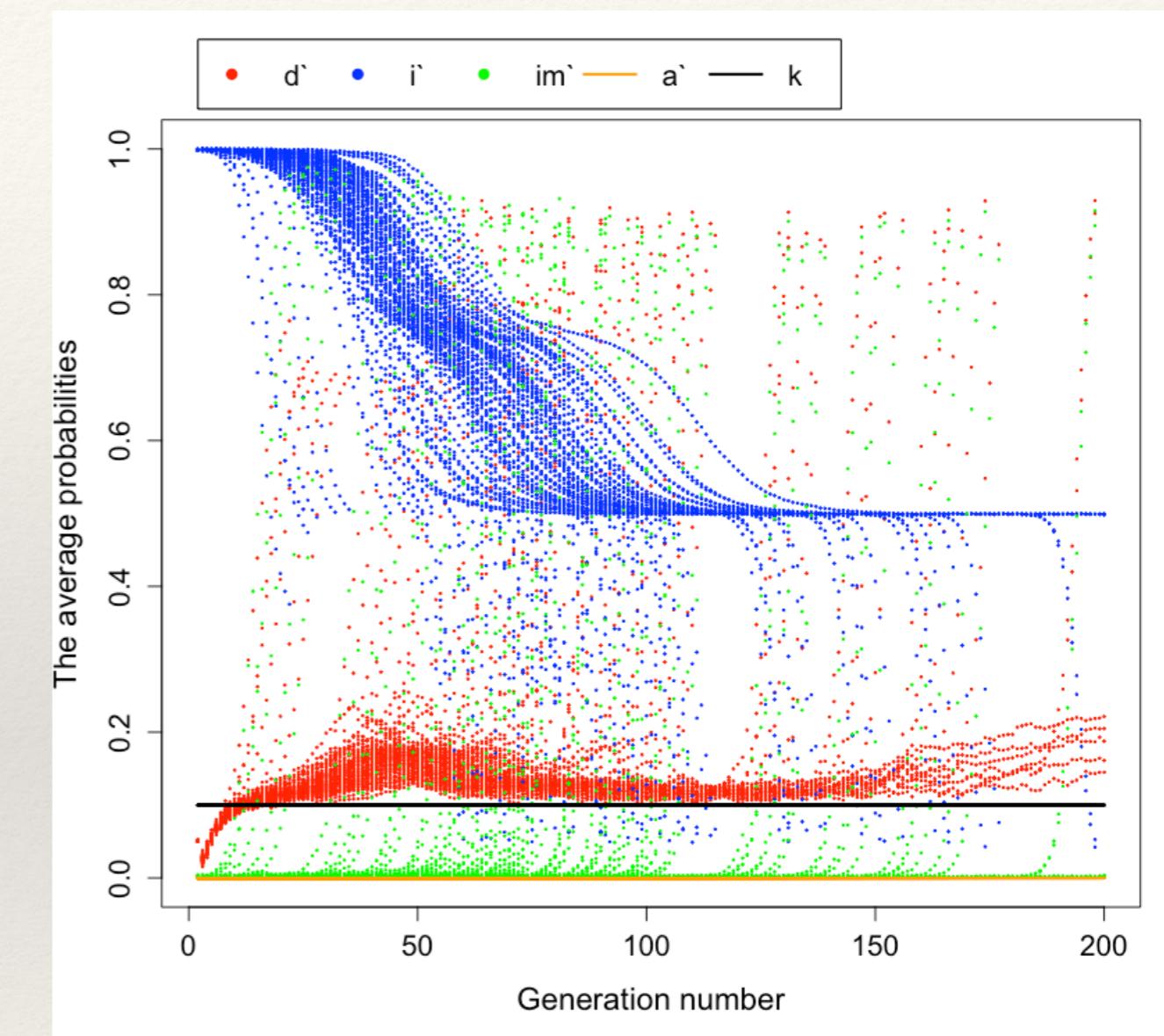
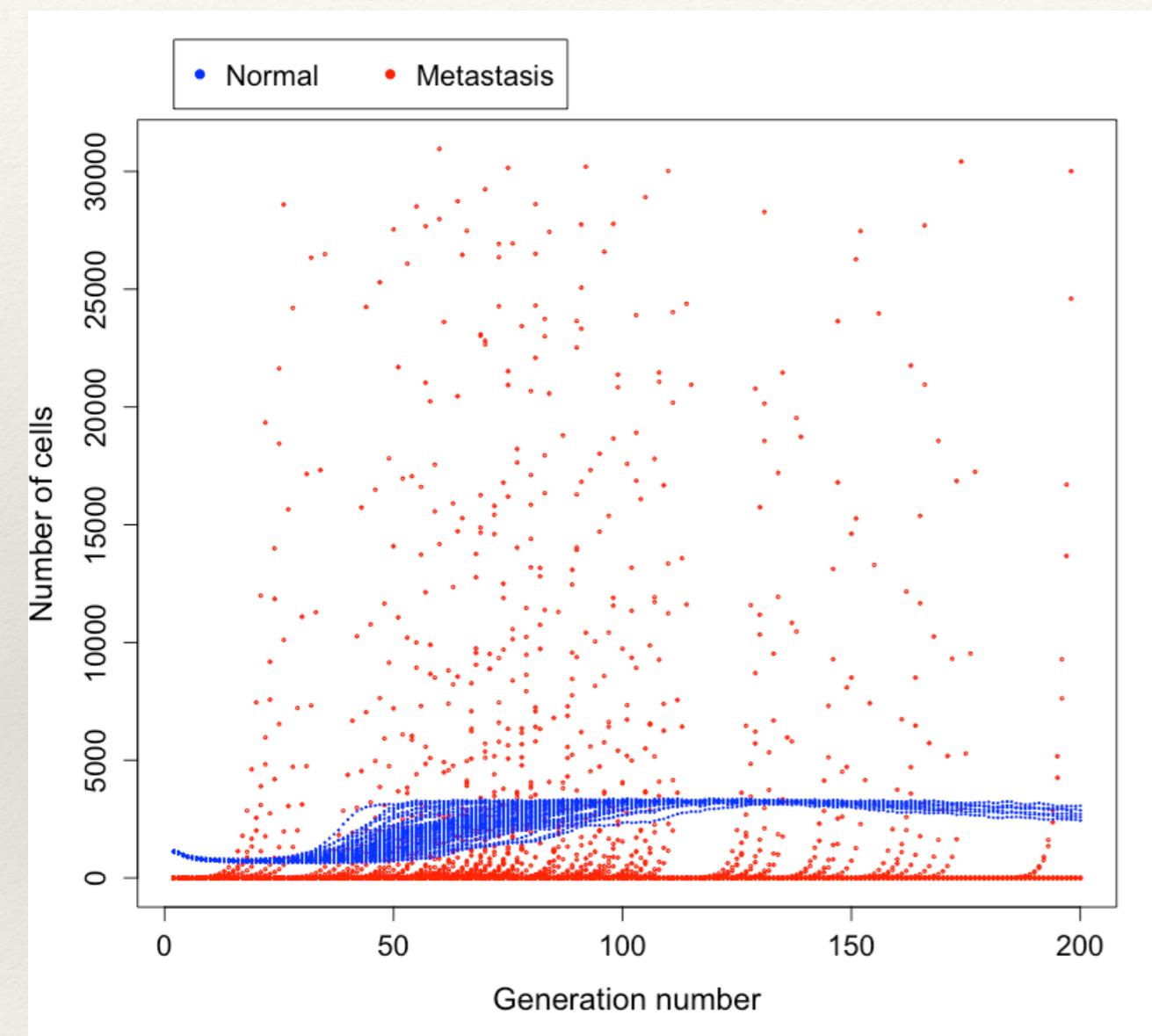
The order of genes dysfunction

Order of genes dysfunction	Number of cells
"TP53 APC KRAS"	9581
"TP53"	2050
"TP53 APC KRAS PIK3CA"	151
"Normal"	54
"TP53 APC"	3
"TP53 KRAS"	2
"TP53 PIK3CA"	1

- ❖ The data for one simulation

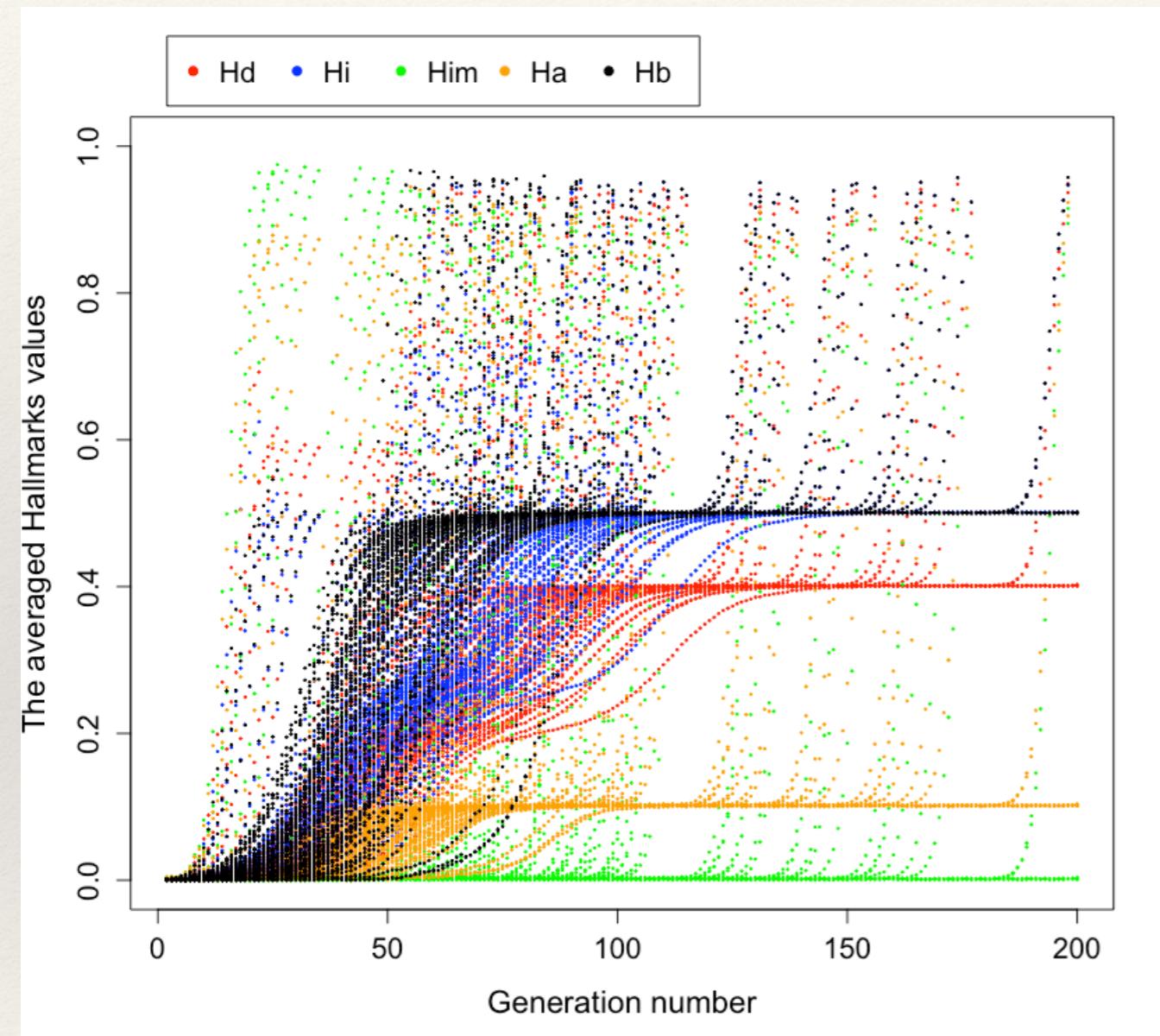
The 100 trials of the same simulation

Number of cells and probabilities



The data for one hundred simulations

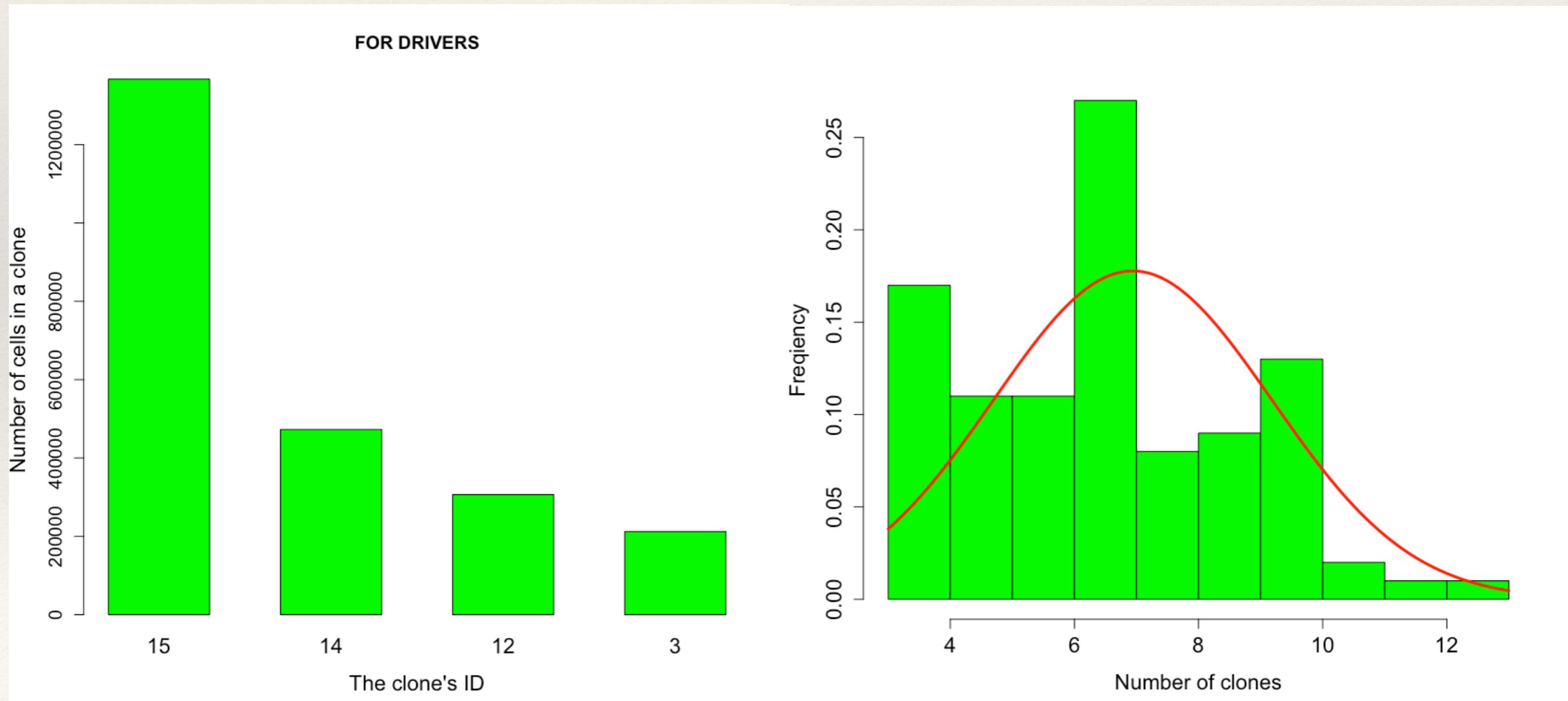
Hallmarks values and number of clones



The data for one hundred simulations

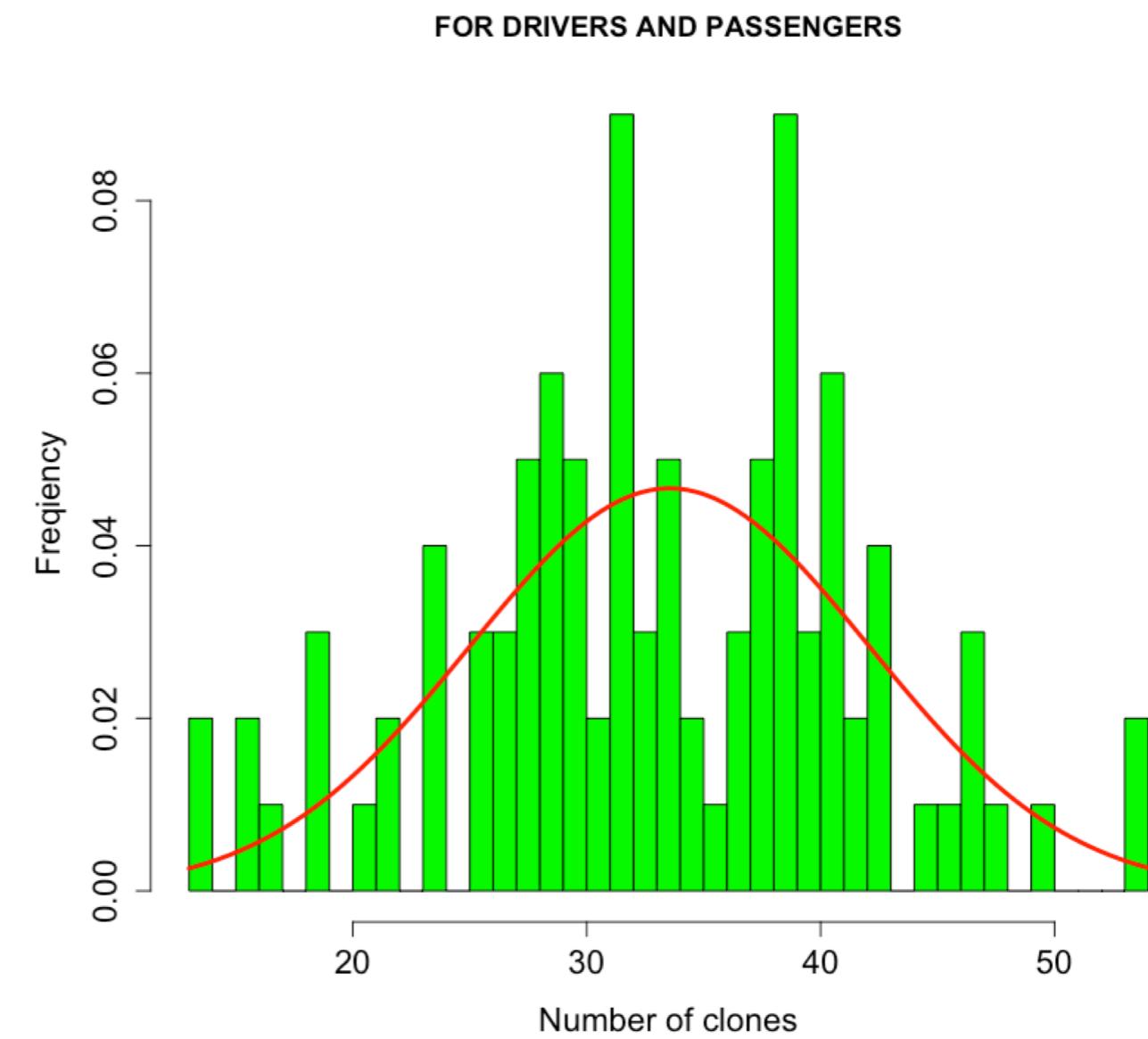
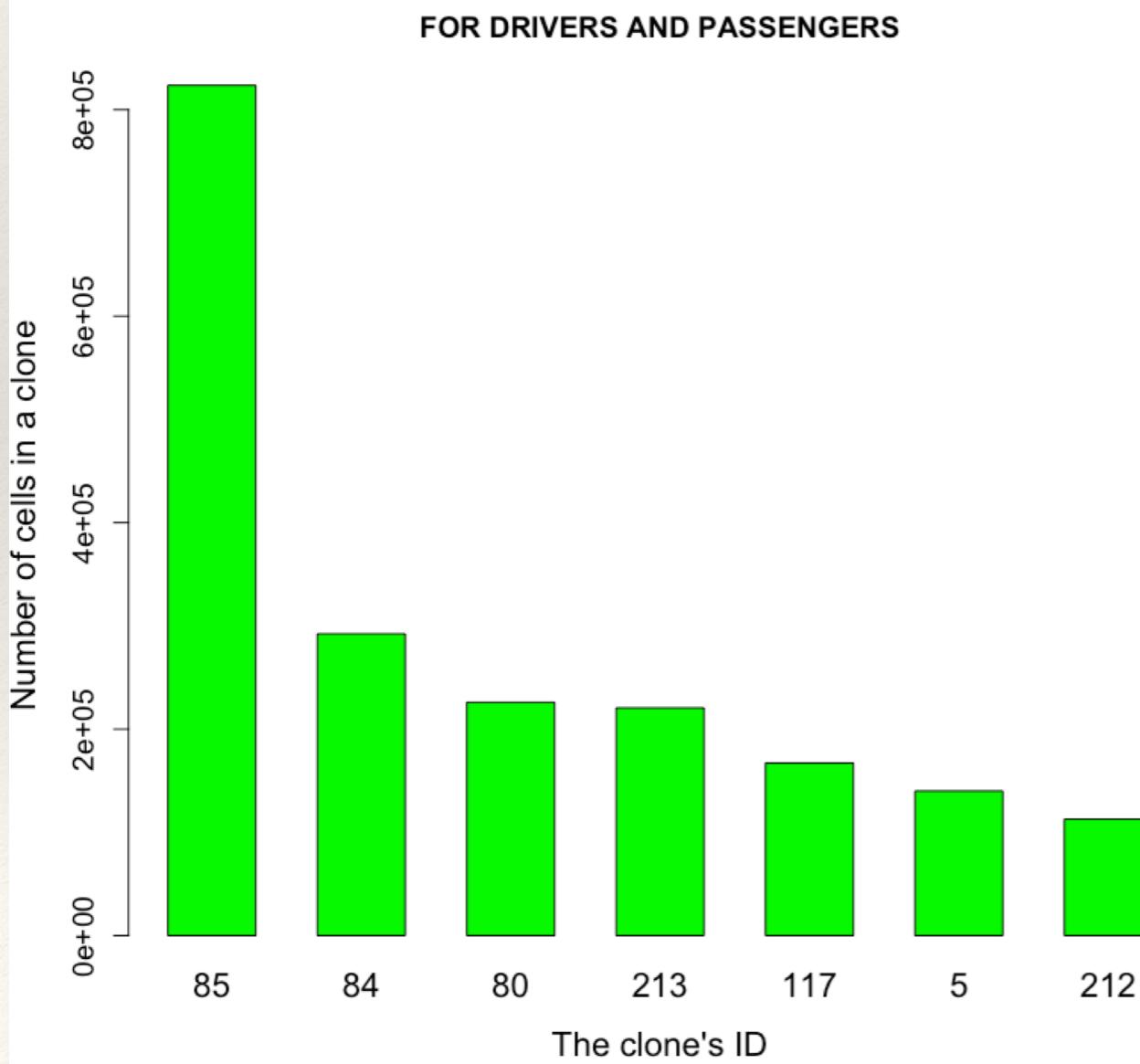
The number of clones and cells in each clone

The data for one hundred simulations

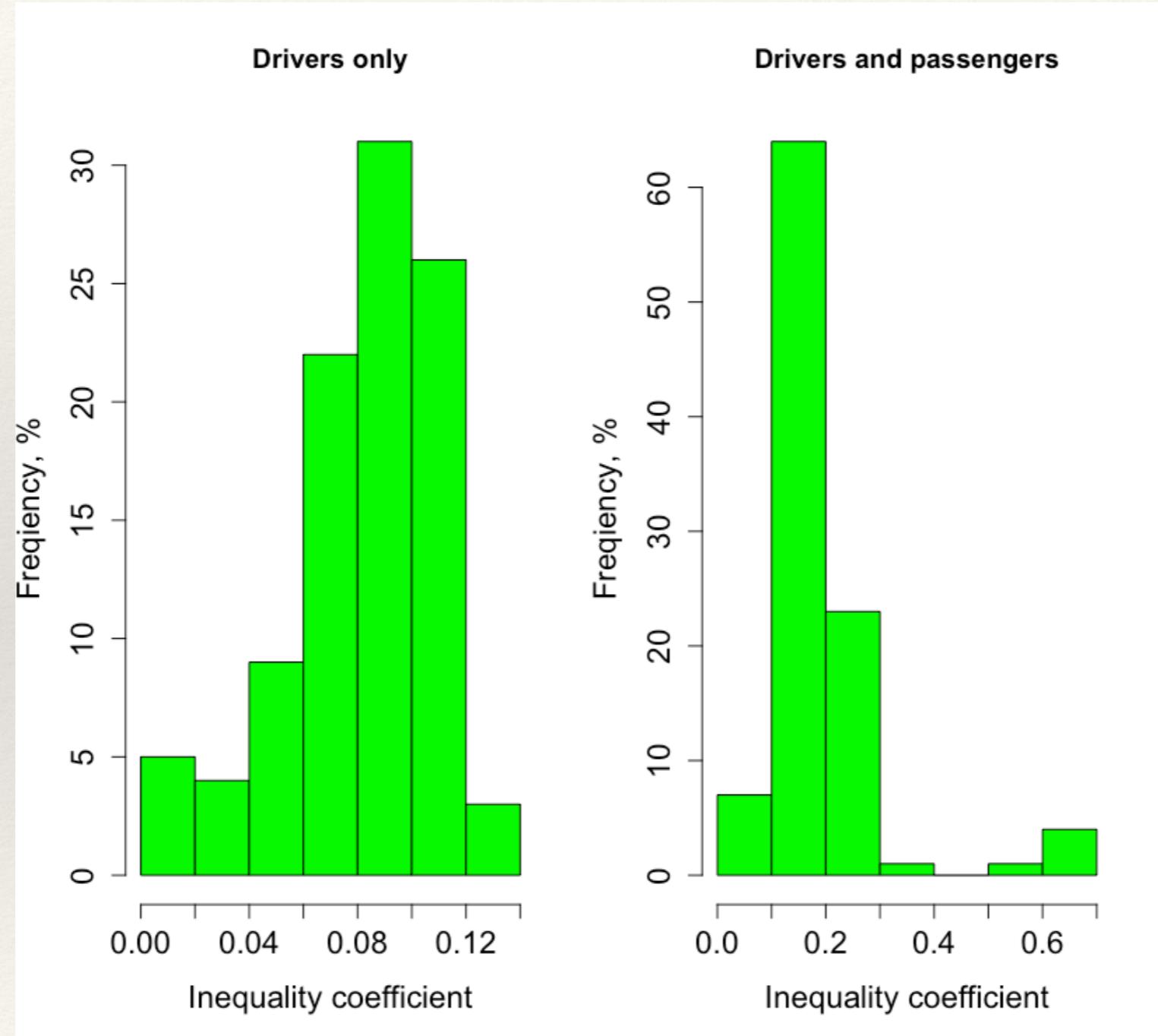


The number of clones and cells in each clone

The data for one hundred simulations



The inequality coefficient



The data for one hundred simulations

The fraction of the mutated genes

The data for one hundred simulations

! at the last step !

