NOTICE

These are the tests to check the influence of Hallmarks variables on probabilities.

In this way it does not matter that happens with the clones and how the clones depend on probabilities.

ONLY one process we want to check – how the probabilities depend on Hallmarks variables.

What is why we changed the code **TO STOP processes of division and death of cells/clones**.

Please, check the **FIRST and SECOND** steps, because the invasion/metastasis transformation occurs only after trial !!!!!

The results of tests in the ***RESULTS.docx***, which has information about the initial genes, clones, notes for each Hallmarks with the ***short*** results of simulations.

The example of simulation in the ***example.xlsx*** with the all results.

I) Hallmark Ha:

$$a^{'} = a - H_a = \frac{1}{1 + e^{-s_0(x-0.5)}} - H_a$$

where s_0 is constant, x - mutation density, H_a - Hallmarks of apoptosis.

In the cloneinit file we have several clones with a destroyed genes: clone number 1-9 with a same mutation density x= 12/20 = 0.6. With s_0 = 10 we have that a = 0.731058578630005.
For clones 2-4 we have changed some genes, keeping the number of destroyed genes, but we changed the value of H_a, adding the GA genes (GA1,GA2,GA3,GA4).
For clones 5-9 situation is same, but for metastasis clones, because we added the GIM gene.
The metastasis clones could be checked on second time step.

II) Hallmark Hb:

<u>For normal clones:</u>

$$d^{'} = d - E^{'}N = d - \frac{N}{N_{max}}$$

$$N_{max} = \frac{1 + F_0 \cdot H_b}{E_0}$$

$$E' = \frac{E_0}{1 + F_0 \cdot H_b}$$

where the F_0 and E_0 are constants of friction process for normal cells, H_b is friction Hallmark and

$$d = H_d$$

where H_d is division Hallmark.

What is why we have H_d=1 with 4 genes (GD1-GD4) in order to have d = 1.
We chose the F_0=2, E_0=0.05 in order to have N_{max} in the range 20–60 and to check the formula. Number of normal cells is **N=22**.

<u>For invasion/metastasis cells:</u>

$$d = H_d$$

d = 1 for all cases.

III) Hallmark Him:

This is a invasion/metastasis transformation, the probability

im` = Him *before* transformation and
im` = 1 *after* transformation.

IV) Hallmark Hi:

The probability $i` = 1 - H_{im}$, so the test is very simple - just to check that $i` = 1 - H_{im}$ for several values of H_{im}.

V) Hallmark Hd:

<u>For normal clones (same with Hb):</u>

$$d^{'} = d - E^{'}N = d - \frac{N}{N_{max}}$$

$$N_{max} = \frac{1 + F_0 \cdot H_b}{E_0}$$

where the F_0 and E_0 are constants of friction process for normal cells, H_b is friction Hallmark and

$$d = H_d$$

What is why for N=22 and N_{Max} = 20 d = 0.
For metastasis clones:

$$d = H_d$$

This is easy to check.