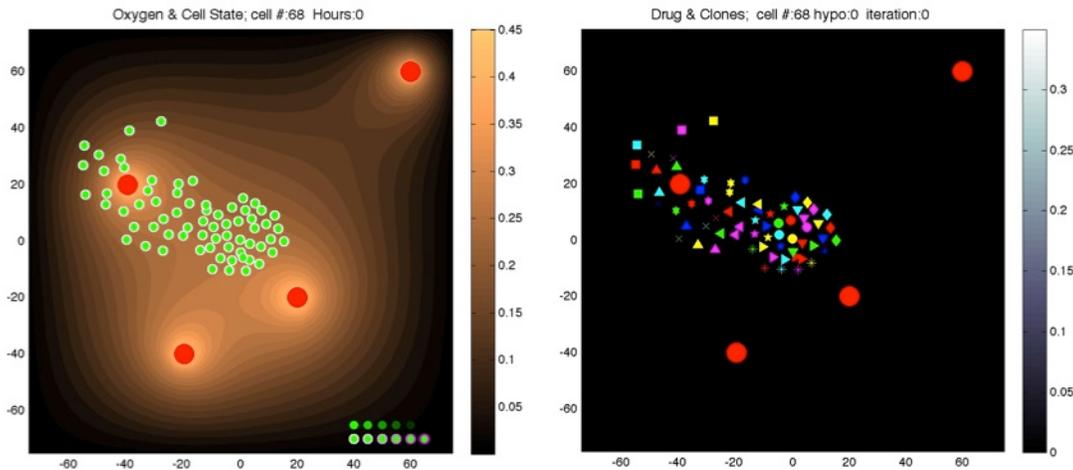Matlab routine *modelWhAM* will read file *oxyinit10.txt* with the initial data and you will see the following 2-panel screen:

The four red circles represent four vessels. Initially, there are 65 individual cells that will give rise to different cellular clones. The left panel shows the oxygen gradient (shades of brown) and the state of each cell, where cell edge represents the amount of drug absorbed by the host cell (light to dark pink), and cell interior shows cell viability—that is, whether the accumulated cell damage is close to cell death threshold (light to dark green). The right panel shows the drug gradient (shades of grey) and tumor clonal diversity—each of the 65 clones is represented by a unique combination of a symbol and a color.

Description of the problem:
1. given is the tissue architecture with four vessels that are the source of both oxygen and drug; initially there is no drug in the tissue, and the oxygen gradient is semi-stable; 65 individual tumor cells form a small cluster inside the tissue;
2. drug is continuously supplied from each vessels and moves through the tissue by diffusion;
3. cells absorbs the drug which upon accumulation increases DNA damage; each cell has prescribed tolerance to DNA damage, which we call the death threshold; if the damage exceeds the cell death threshold, this cell dies; however cell DNA is constantly being repaired, which can prolonged cell life; moreover, in the case of acquired resistance, cell damage tolerance can increase, if the cell is exposed to low drug concentrations for a prolonged time;

Goal:
Investigate differences in tumor evolution in cases of pre-existing and acquired drug resistance when the one of two cellular properties are varied, either the rate in cell death threshold (delta_death_rate) that determines cell tolerance to the drug in the case of acquired resistance; or, in the case of pre-existing resistance, the rate of cell DNA damage repair (p_dna_repair_rate).

Note:
All simulations described below have been tested using the 2011 Matlab software.

Exercises described below allow to reproduce time course images collected in Figure 1 of our manuscript. The *modelWhAM* Matlab routine requires the following parameters:

```
modelWhAM(IsResistance,KindOfResistance,PreExist_Location,
          delta_death_rate, p_dna_repair_rate)
```

where:

|			
IsResistance	:	0=no resistance,	1=resistance to drug level,
KindOfResistance	:	0=acquired resistance;	1=pre-existing resistance,
PreExist_Location	:	1=two cells closest to vessel are resistant,	
		2=two cells at intermediate distance are resistant,	
		3=two cells furthest from vessel are resistant,	
delta_death_rate	:	rate of increase of death threshold,	
p_dna_repair_rate	:	DNA repair rate,	

Note, that three last parameters are context-dependent,, and their mening is described in details below.

Exercise 1

Figure 1c shows evolution of a tumor cell cluster and its clonal composition in the case of no resistance. This result can be reproduced by running code with the following parameters:

```
modelWhAM(0,0,0,0,0.00015)
```

All three resistance parameters are set to 0, there is no change in the death threshold, since there is no resistance, the DNA damage repair parameter is set to 0.00015 which is a default value. The following sequence from Figure 1c should be reproduced.

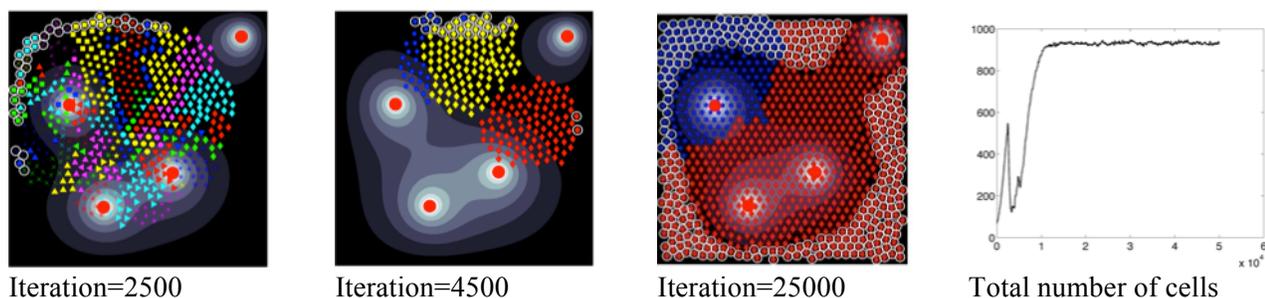| Iteration=0 | Iteration=2000 | Iteration=4000 | Iteration=5000 | Total number of cells |
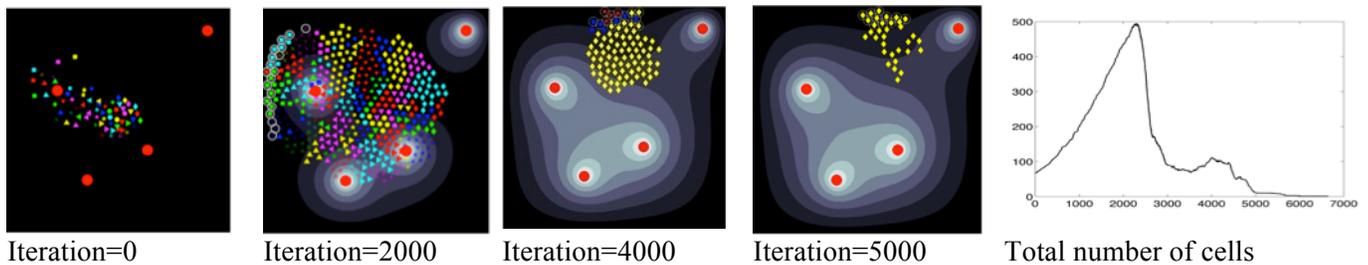
Exercise 2

Figure 1e shows evolution of a tumor cell cluster and its clonal composition in the case of pre-existing resistance. This result can be reproduced by running code with the following parameters:

```
modelWhAM(1,1,2,0,0.00015)
```

Two first resistance parameters are set to 1, the third parameter is set to 2 (two cells with higher level of tolerance to the drug are located at the intermediate distance from the vessel). There is no change in the death threshold, since resistance is pre-existing, the DNA repair parameter is set to a value of 0.00015. The following sequence from Figure 1e should be reproduced.

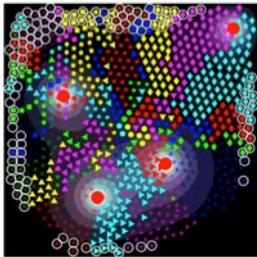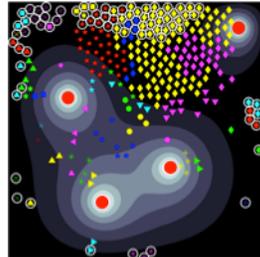| Iteration=2500 | Iteration=4500 | Iteration=25000 | Total number of cells |

Exercise 3

Figure 1f shows evolution of a tumor cell cluster and its clonal composition in the case of acquired resistance. This result can be reproduced by running code with the following parameters:

```
modelWhAM(1,0,0,0.000059,0.00015)
```
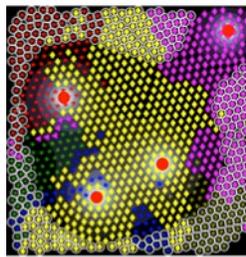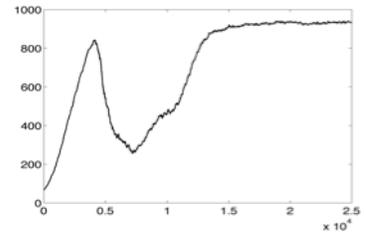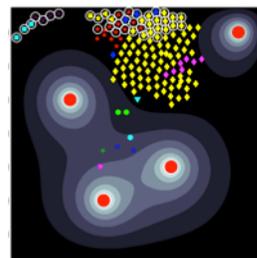
The first resistance parameter is set to 1, the second and third are 0. The rate of change in the death threshold is set up to 0.000059, the DNA repair parameter is set to 0.00015, the default value. The following sequence from Figure 1f should be reproduced.

| Iteration=4000 | Iteration=7500 | Iteration=25000 | Total number of cells |

Exercise 4

Figure 1g shows evolution of a tumor cell cluster and its clonal composition in the case of acquired resistance. This result can be reproduced by running code with the following parameters:

```
modelWhAM(1,0,0,0.000045,0.00015)
```

The first resistance parameter is set to 1, the second and third are 0. The rate of change in the death threshold is set up to 0.000045, the DNA repair parameter is set to 0.00015, the default value. The following sequence from Figure 1g should be reproduced.
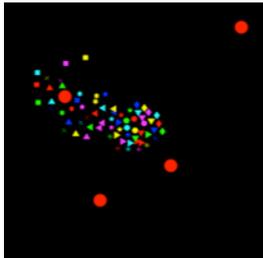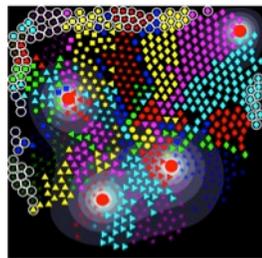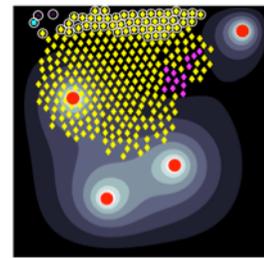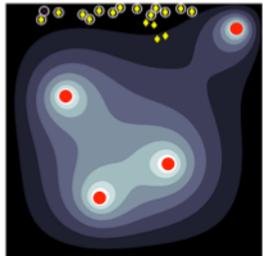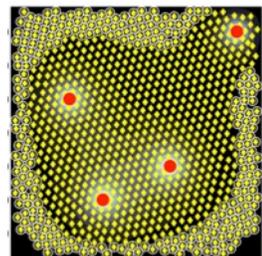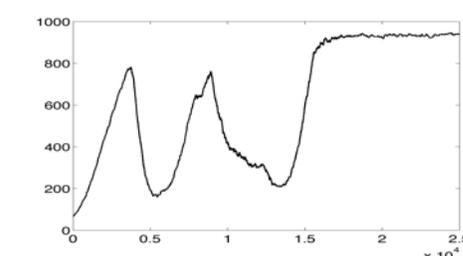

Iteration=0   Iteration=3700   Iteration=5000   Iteration=7000

Iteration=15000   Iteration=25000   Total number od cells over time

Have fun!