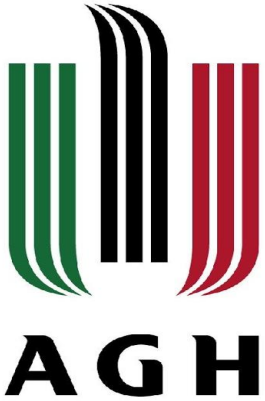


Particle automata model of heterogeneous melanoma progression

Marta Panuszewska

Aim of research

- create heterogeneous melanoma simulation based on Particle Automata model [1]
- create realistic model of skin tissue with complex vascular structure
- examine tumor's behavior in varying environment setups

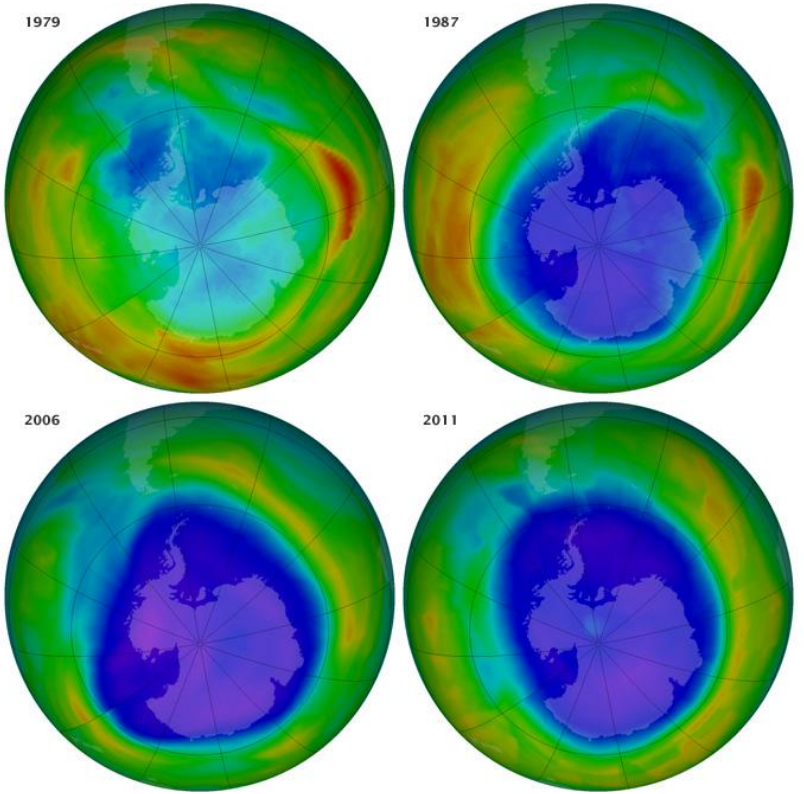
Challenges

- tumor and surrounding skin is a complex, multiscale system
- it is impossible to fully simulate and control melanoma growth scenario
- increasing number of model parameters results in its overfitting what decreases or completely disables its predictive power

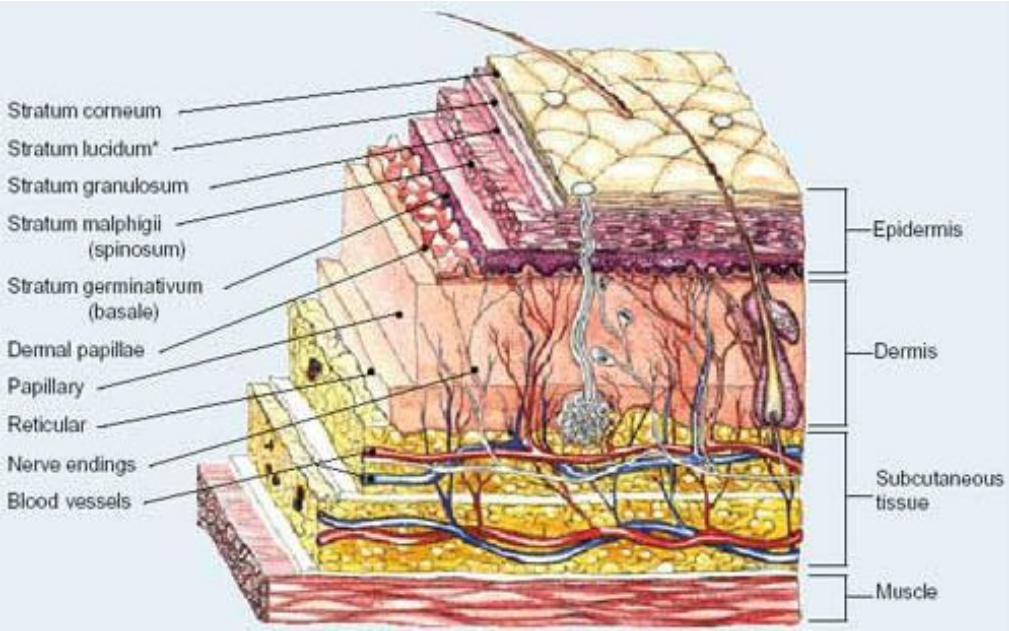
[1] Witold Dzwinel, Rafal Wcisło, David A Yuen, and Shea Miller. Pam: Particle automata in modeling of multiscale biological systems. *ACM Transactions on Modeling and Computer Simulation (TOMACS)*, 26(3):20, 2016.

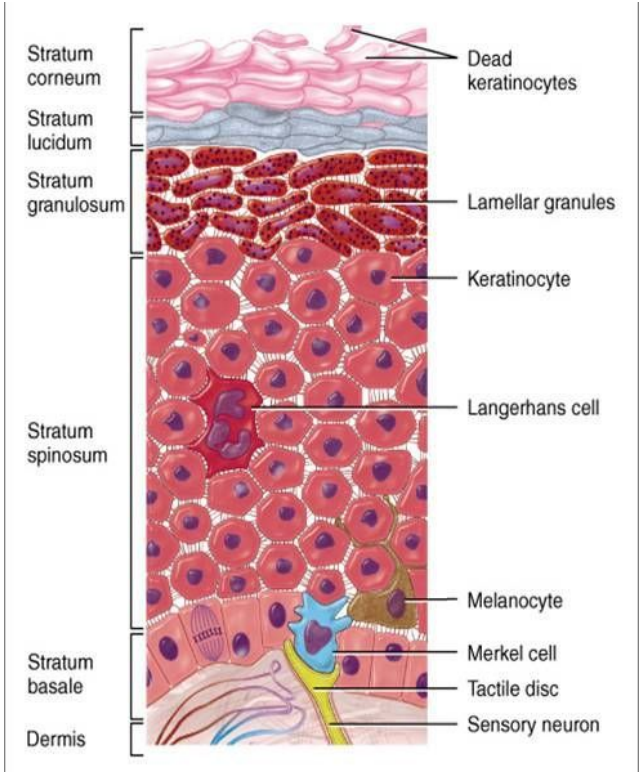
Motivation

- incidence and mortality rate is rapidly rising since at least 1975
- constant rise in number of patients due to depleting ozone levels
- 1 in 54 - lifetime risk to develop melanoma
- estimated 87,110 new cases and 9,730 deaths in 2017 in USA
- numerical cancer model allows for investigating and identification of the most crucial tumor growth factors and possible scenarios of its proliferation



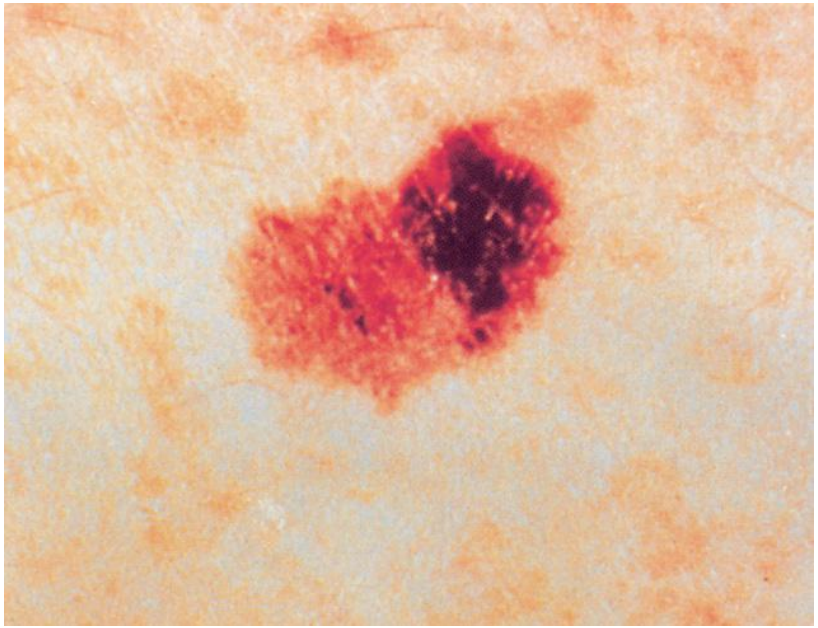
Human skin


Stratum corneum
Stratum lucidum*
Stratum granulosum
Stratum malphigii (spinosum)
Stratum germinativum (basale)
Dermal papillae
Papillary
Reticular
Nerve endings
Blood vessels
Epidermis
Dermis
Subcutaneous tissue
Muscle


Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Dermis
Dead keratinocytes
Lamellar granules
Keratinocyte
Langerhans cell
Melanocyte
Merkel cell
Tactile disc
Sensory neuron

Heterogeneous melanoma

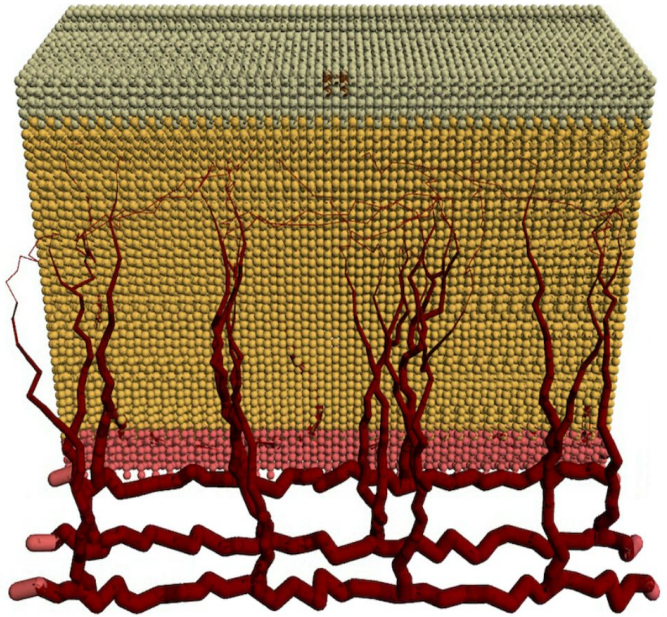
- many diseases with many identities
- may display diverse phenotypes
- key component in cancer progression and drug resistance
- provides population diversity and tumor robustness [2]



[2] Henry HQ Heng, Steven W Bremer, Joshua B Stevens, Karen J Ye, Guo Liu, and Christine J Ye. Genetic and epigenetic heterogeneity in cancer: A genome-centric perspective. *Journal of cellular physiology*, 220(3):538–547, 2009.

Skin model

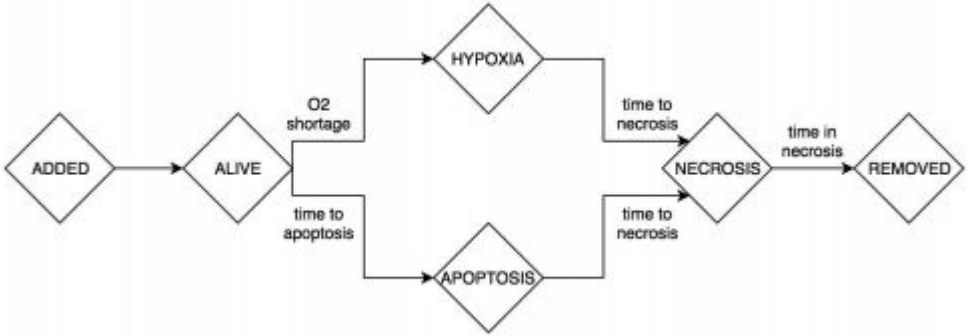
- three layers of the skin
- ~200 000 healthy cells
- 20 melanoma cells
- complex vascular structure [3]

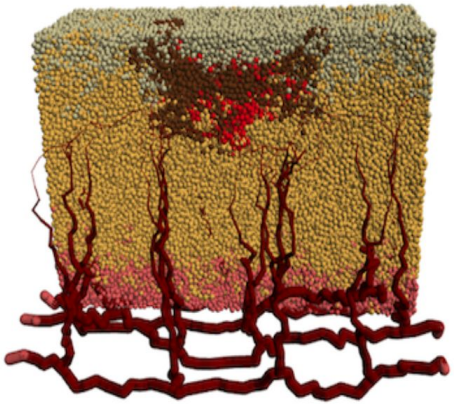


[3] Witold Dzwinel, Adrian Kłusek, Rafał Wcisło, Marta Panuszewska, and Paweł Topa. Continuous and discrete models of melanoma progression simulated in multi-gpu environment. In PPAM 2017: *Proceedings of International Conference on Parallel Processing and Applied Mathematics*, Lublin, 10-14 September 2017.

Simulation

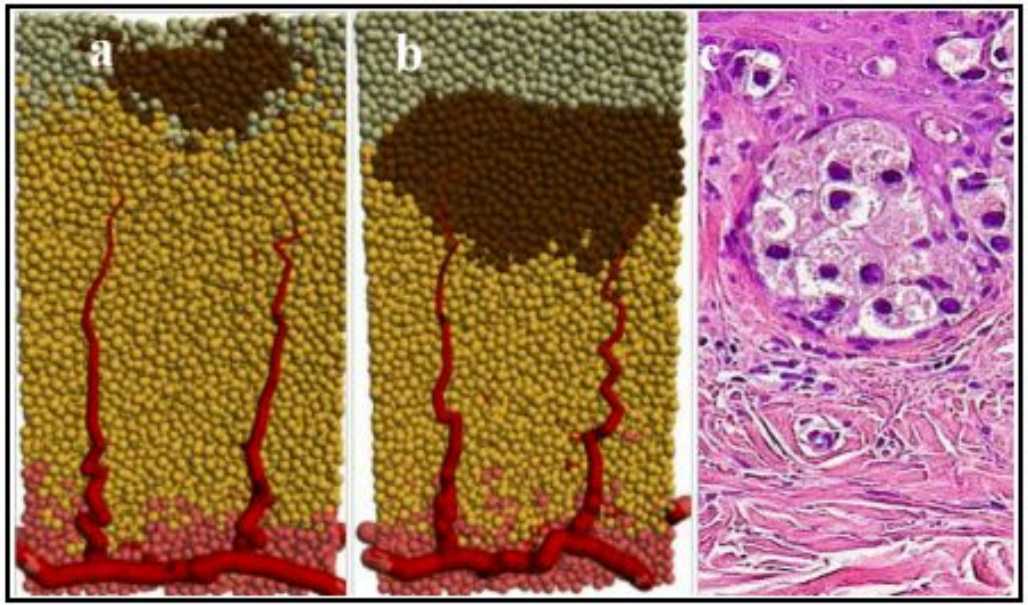
- behavior of the full network of objects determined by every object
- object behaves like a finite-state automation
- proceeds in discrete time steps:
  - blood flow
  - oxygen diffusion
  - forces between objects (attraction and repulsion)
  - new object position and state
  - chance of mutation

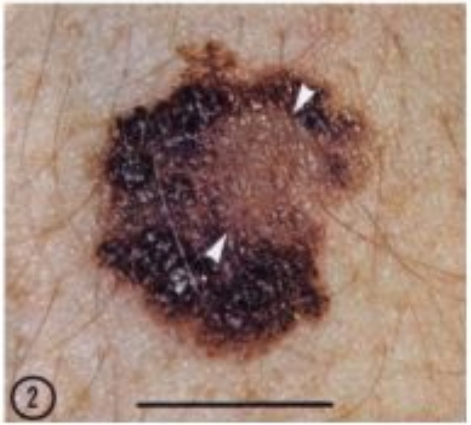


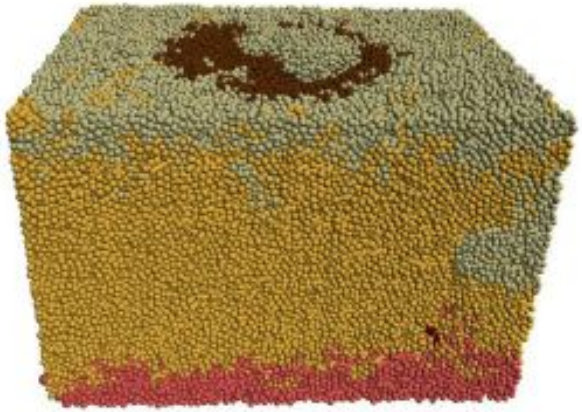


Results

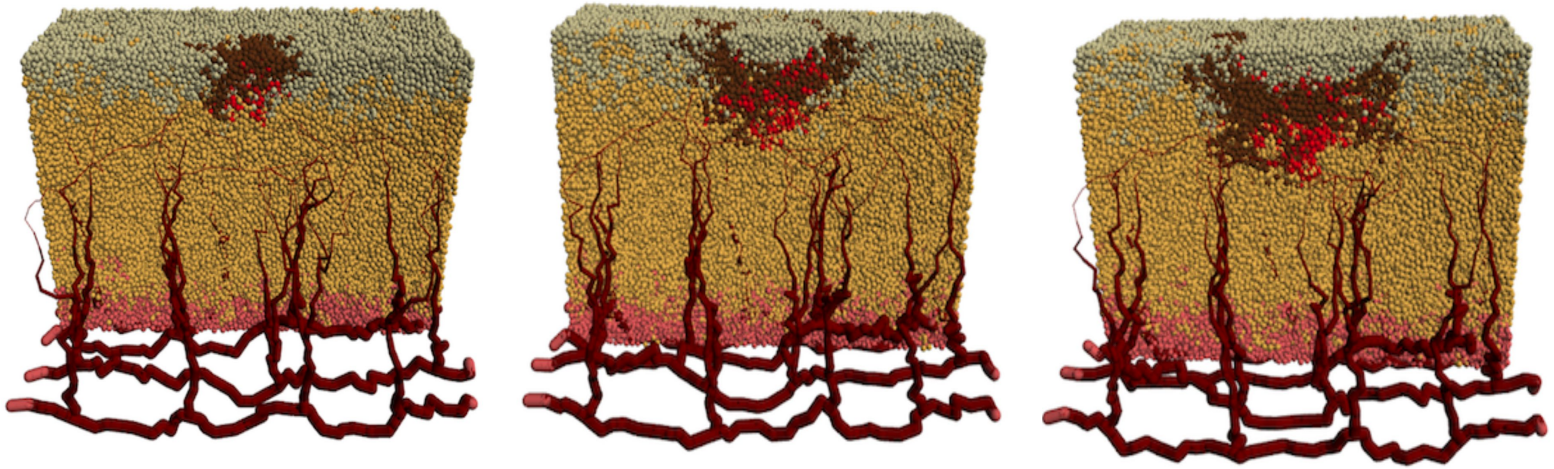
Reproduction of some biological mechanisms was possible.





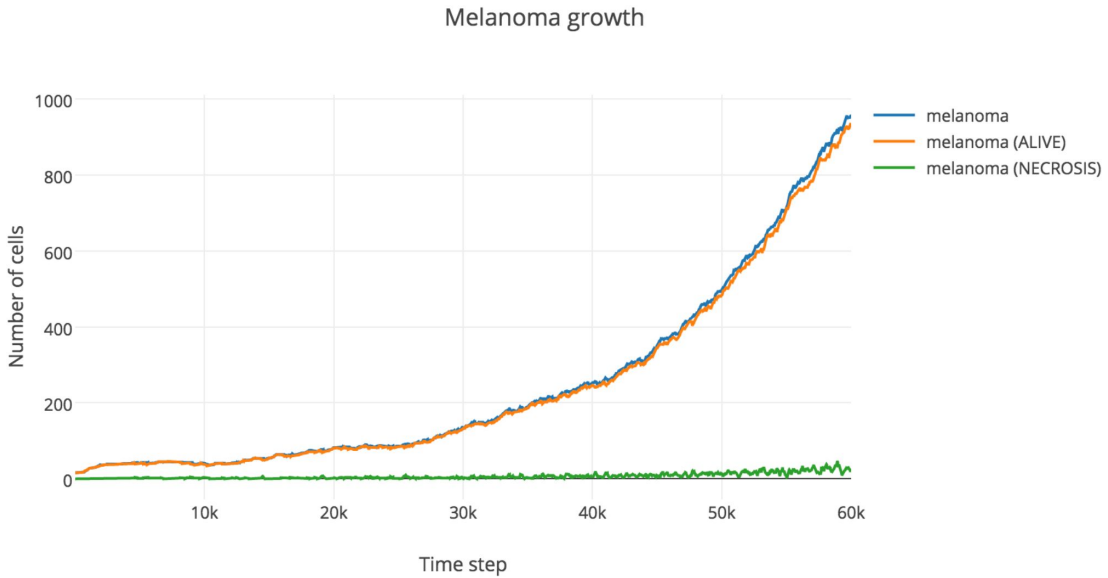


Results



Heterogeneous tumor growth, both types alive
and coexisting.
Day 104, 174 and 208.

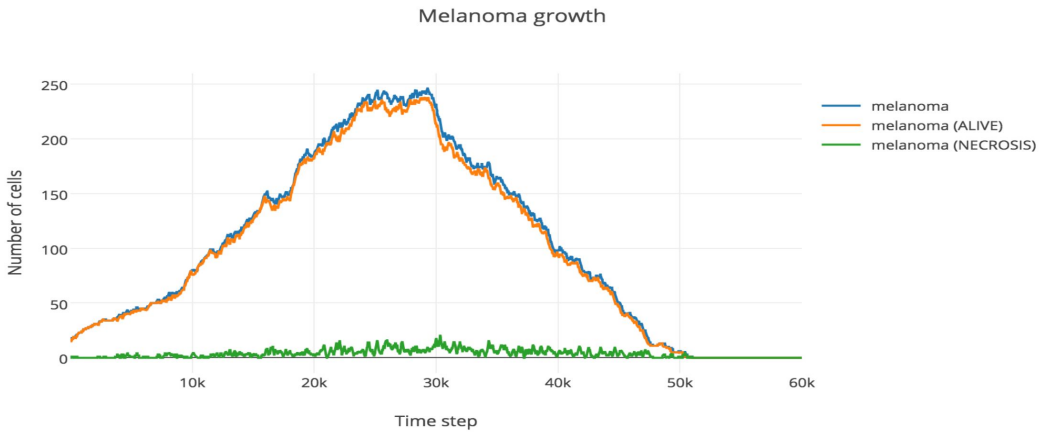
Results

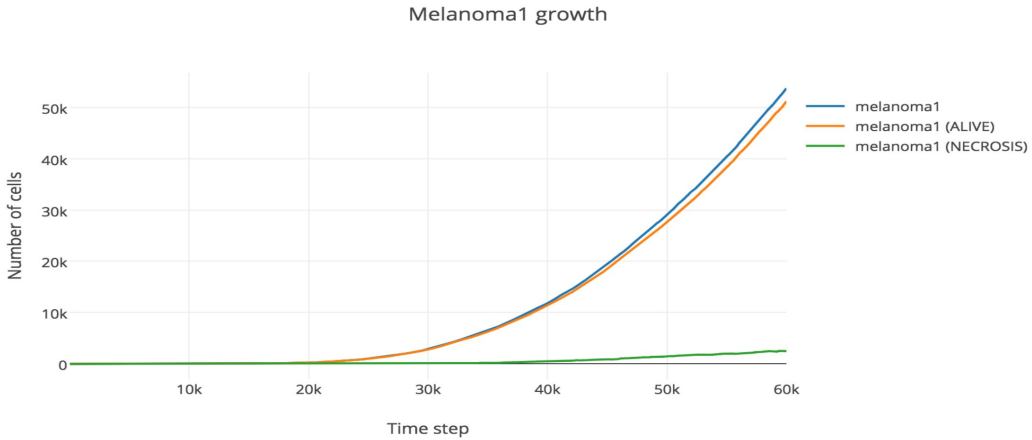


Rate of growth of homogeneous melanoma up to 104 days.

Results

Rate of growth of two types of heterogeneous melanoma – original (right) and mutated (bottom).





Mutated cells were more adjusted to the environment and caused original cells to die.

Conclusions and future work

- it is possible to simulate heterogeneous melanoma in the described environment
- it is possible to obtain a stable tissue with heterogeneous melanoma growing in time
- future work may include:
  - introducing various models of heterogeneity
  - testing various drug therapy scenarios for selected drug resistance mechanisms

Acknowledgements: The work has been supported by the Polish National Science Center (NCN) project 2013/10/M/ST6/00531 entitled: Multi-scale model of tumor dynamics as a key component of the system for optimal anti-cancer therapy.