Characterization of spheroid growth based on a new dynamical model.

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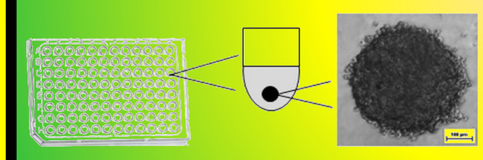
Abstract

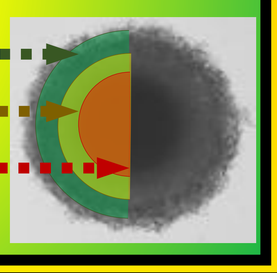
Cell cultures are a recognized model that helps understand interaction of cells with certain external factors, such as radiation or drugs [1,2]. 3D cultures are characterized by greater similarities to tumours in the conditions occurring in the body. A new, dynamic model of spheroid growth will be presented, allowing to characterize the above-mentioned parameters and additionally better reflecting the spheroid growth curve. Additionally, the simulations performed using dedicated software allowed for a detailed characterization of the WM266-4 skin cancer cell line, as well as for the theoretical visualization of the distribution of various zones inside the spheroid at different growth times.

Spheroids

- 3D cell culture model
- Similiar to the solid tumours (structure, microenvironment, cell signaling)
- Three zones are distinguished in spheroids

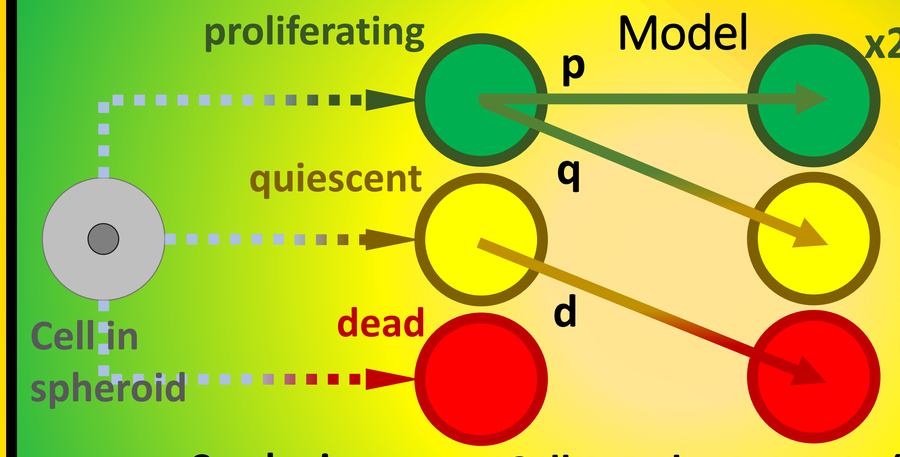


Spheroids formed into 96-well, low adhesive plate



Model

$0 \leq p,q,d \leq 1$



Number of proliferating cells P in time

$$\frac{dP}{dt} = (p - pq - q)P$$

Size of spheroid ~ Total number of cells

Similar: $\frac{dQ}{dt} = qP$

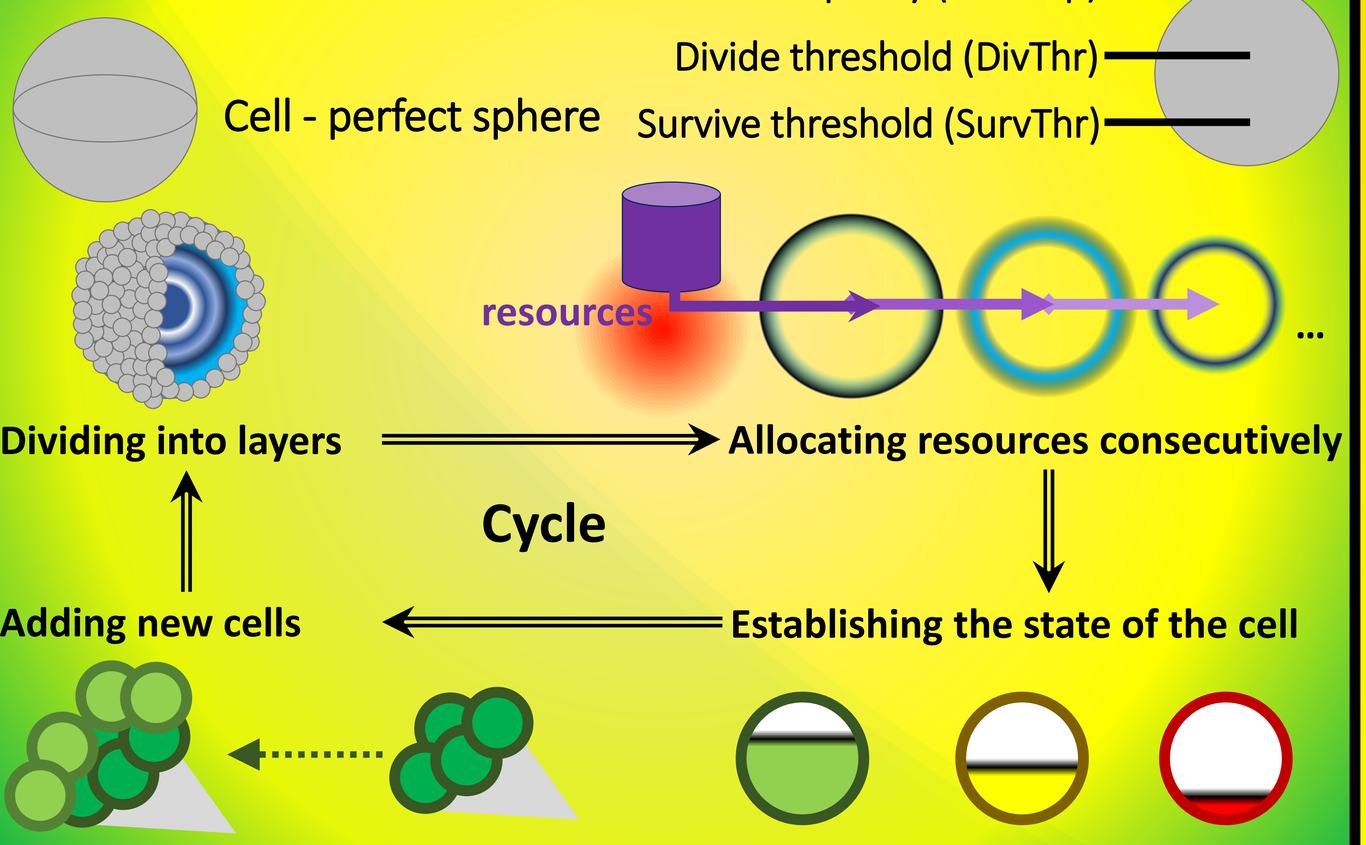
$\frac{dD}{dt} = dQ$

Can be in one of three states

Cell can change state (divide) with probabilites q,d (p)

Simulations

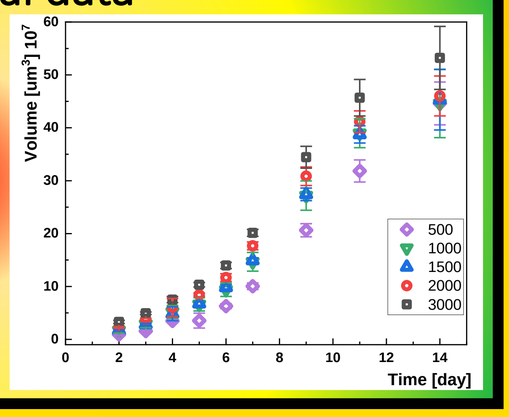
Dedicated software written in C++ which simulates growth of the spheroid between the cell cycles.



Experimental data

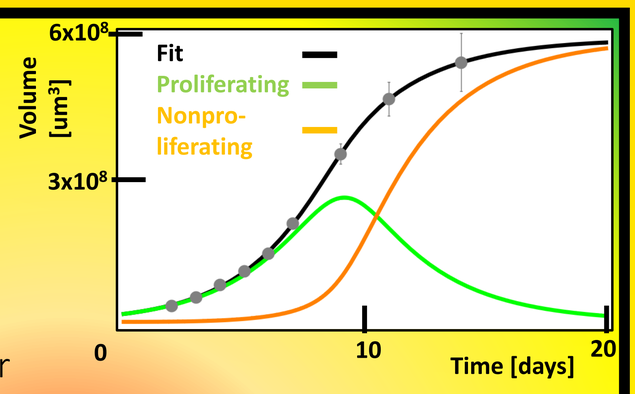
Microscopic images of spheroids taken in different days of culture

For each image Feret diameter was estimated. Volume was calculated as a volume of a sphere with estimated Feret diameter



Results

Experimental distribution was fitted with the new dynamic model, based on the determination of the (p-pq-q)

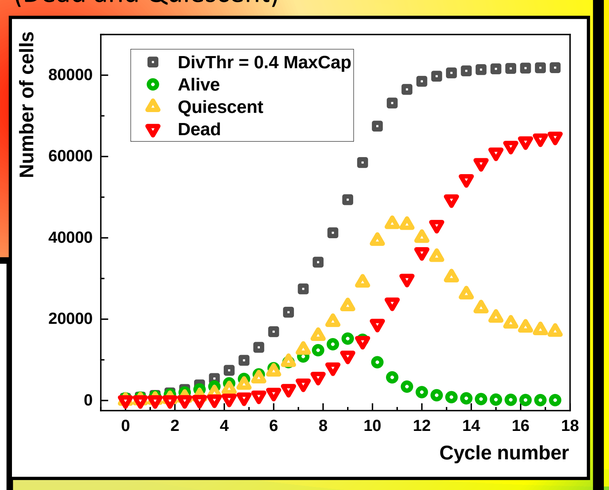


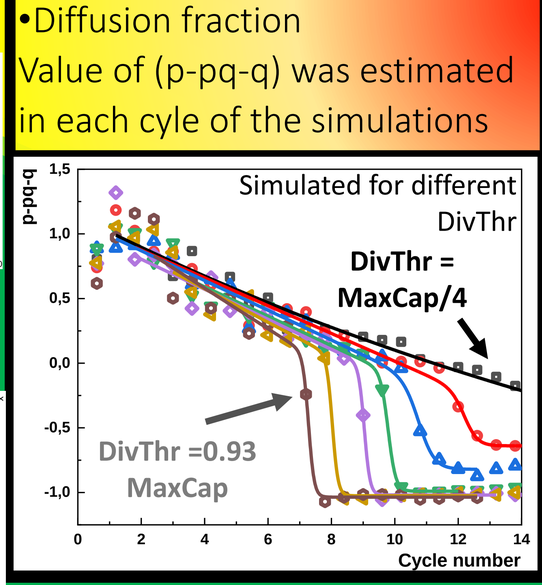
Fitted model: Volume = V_0 (P(t) + QD(t))
QD(t) total numer of non-proliferating cells (Dead and Quiescent)

Simulations were performed for different parameters of the simulations:

- Initial amount of resources
- Division of the resources level
- Diffusion fraction

Value of (p-pq-q) was estimated in each cyle of the simulations





Fitted with glued function: linear + Fermi

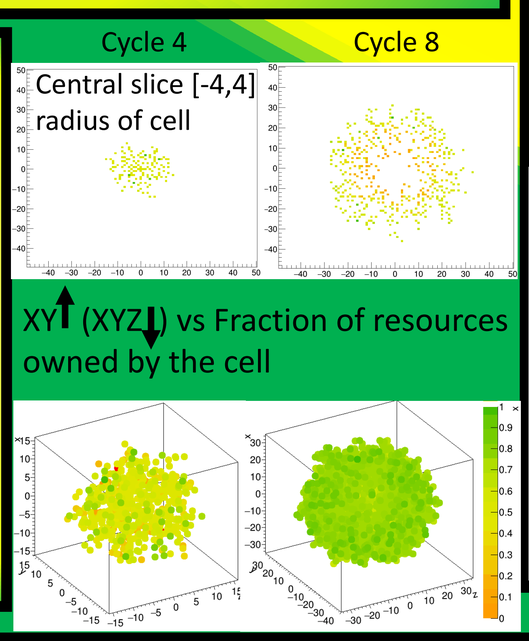
$$(p - pq - q)(t) = p - (p+1)\left(\frac{v_1 t - v_k}{1 + \exp((t-\alpha)/\beta)} + v_k\right)$$

Conclusions

New model of the spheroid growth is proposed based on the determination of the growth parameter (p-pq-q) as a function of time.

Proposed model was fitted to the experimental data, with the extraction of the growth parameter.

Experimental growth was compared with the simulated curves and to estimate simulations parameters that will reflect the experimental conditions



Acknowledgment

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