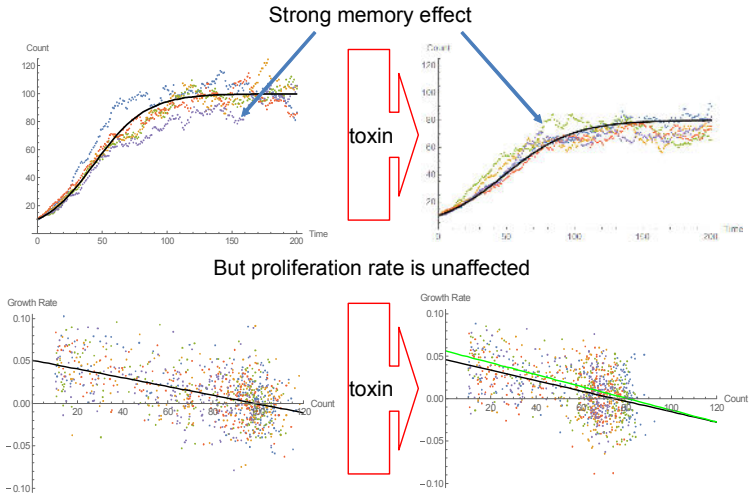
PROGRAM STATISTICS

It uses the model of cell proliferation of Hill type, well established in the literature. The proliferation rate is then dn/dt = n*r*(1-n/k), there n is the cell density, r is a base proliferation rate, and k is a limiting cell density. The influence of the toxic substance can lower the base proliferation rate r and/or limiting cell density k.

Proliferation process is essentially stochastic and as was shown by experiments of our collaborators, measurements of the cell density are quite noisy, so the method cannot rely on the fitting of experimental data to a solution of the differential equation by itself—due to the memory of the process starting from a small stochastic deviation experimental curve will deviate more and more from the computed one with the course of time. Instead, the relative proliferation rate, however noisy, does not have the memory effect and can be used to discriminate toxic substances from control.

Statistical analysis of cell proliferation under influence of biomaterial with low toxicity level



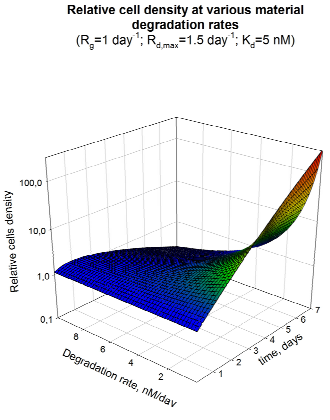
To detect the toxic effect we use least squares method applied to the relative proliferation rate (dn/dt)/n as a function of the cell density n, that should be represented by a straight line in the proliferation model adopted. From the parameters of the line the base proliferation rate and the limiting cell density are derived along with their uncertainties, and then they are compared between experiment and control to check whether any of them for the substance under the test is substantially lower than control.

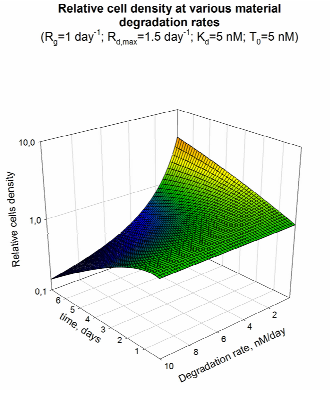
PROGRAM KINETIC PROLIFERATION

Biodegradation rate of the toxic material is the property of utmost importance for the cell proliferation. If the rate is small enough and toxin is not present in the system at the initial moment, the toxic effect will be masked at the beginning, and can be recovered from long-run observation only. You can see it on the left graph – for the toxicity parameters chosen cell density starts to grow similarly for any degradation rate, and start to deviate only at late times. This effect can be partially alleviated by the initial presence of toxin in the system, as you can see on the right graph.

When the toxin is continuously released from the biomaterial at a constant rate k [nM / day] and acting on the cells causes their proliferation or death. The concentration of toxin is not constant:, and the cell proliferation kinetics is described by the equation:

$$\ln\frac{\rho}{\rho_0} = R_g\left[\left(1-\frac{R_{d,m}}{R_g}\right)t + \frac{R_{d,m}}{R_g}\frac{K_d}{k}\ln\left(1+\frac{kt}{K_d+T_0}\right)\right]$$



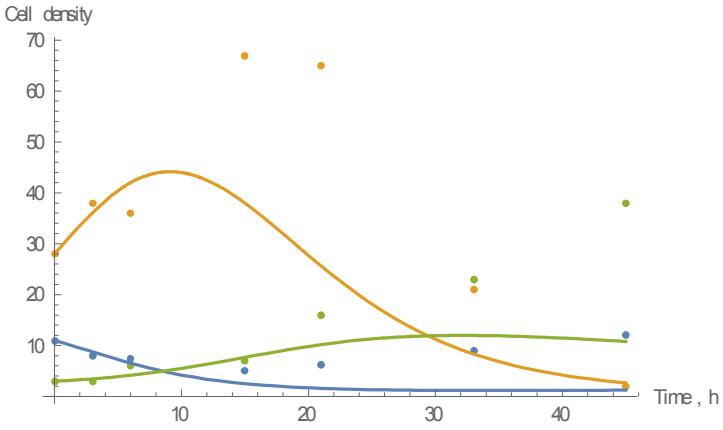


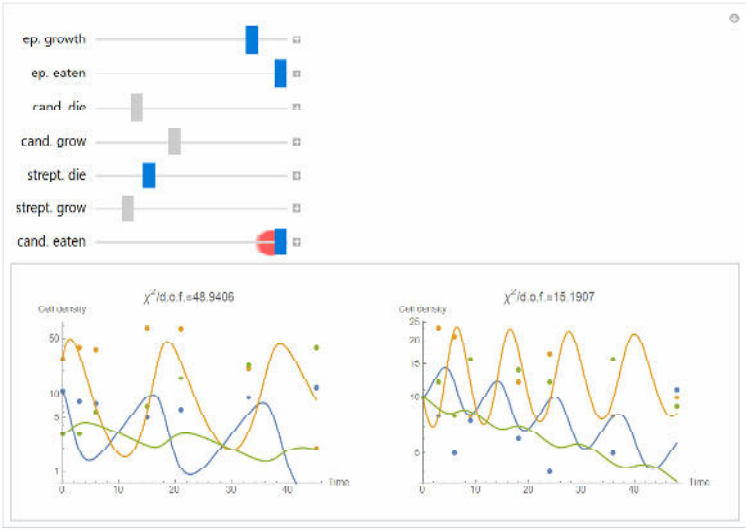
PROGRAM MICROBIOTA

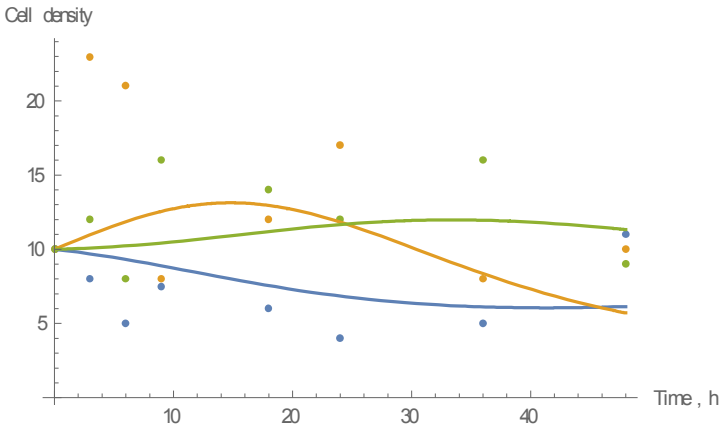
Lotka-Voltera model has been used to characterize the microbial population dynamics resulting from competitive and mutualistic interactions. The generalized LV (gLV) equations are able to describe various possible relationships between arbitrary numbers of species. The gLV model represents the population growth dynamics of species.
We take a model with epithelial cells x growing in the system with candida y that depress epithelium growth, and candida growth is in turn suppressed by streptococci bacterium z. The system of differential equations then is

$dx/dt=x(\alpha-\beta\, y)$
$dy/dt=y(-\gamma+\delta\, x-\epsilon\, z)$
$dz/dt=z(-\phi+\eta\, y)$

On the graphs presented epithelial cells are denoted by blue curve, candida by brown curve, streptococci as green curve. First plot represents the situation when streptococci had been suppressed by antibiotics so that candida start to grow and suppress epithelium substantially. Second plot show more or less equilibrium dynamics of all three cell types.







We constructed real-time system for dynamic evaluation and estimation of the model parameters on the base of Del 11 system. Parameters of the model can be changed by sliders and dynamic check of differences between theoretical curves and experimental dots is realized (assuming error of measurements of 20 %).