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Modelling cell-population growth of in-vitro monolayers

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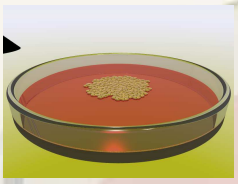
Introduction

Simulation of cell-populations



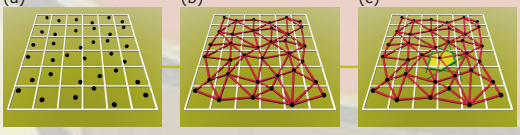
- Detailed understanding of the basic mechanisms that determine cell population growth is an active field of research; Particularly in-vitro experiments constitute an important and successful investigation tool, since the growth conditions can be varied in a wide range
- By definition of models one can study specific mechanisms neglecting unknown influences in experiments
- Detailed off-lattice models and lattice models exist [1,2] however lattice models are more promising to reduce the computational demand but might generate lattice artefacts.
- Single-cell-based models allow for the consideration of cellular heterogeneity, spatio-temporal fluctuations of the interface between cell population and growth medium and intracellular regulation mechanisms.

→ Necessity of: Fast Simulation tool combining advantages of off-lattice models (no lattice symmetry) with computing speed of lattice models.

Model

Concept of unstructured lattice

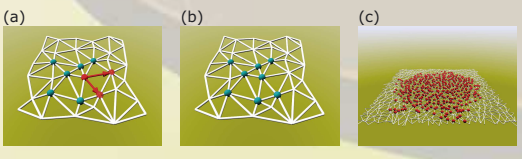
(a) (b) (c)



- Random distribution of Voronoi Points on a square lattice by setting exactly one point to each square (a)
- Define neighbors by a ***Delauney Triangulation*** (b)
- Corresponding cells are accessible by the dual graph of Delauney diagram, the ***Voronoi diagram*** (c)

Kinetic Monte Carlo Simulation

(a) (b) (c)



(1) time increment

$$\Delta t = -\frac{\ln(1-\xi)}{\sum_i p_{i\to i'}}$$

(2) Gyration radius

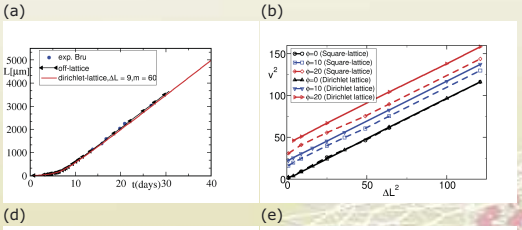
$$R_{gyr} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(r_i - R_{cm})^2}$$

- Definition of probabilities for basic processes by average rates of migration ϕ and cellular division $\lambda = 1/\tau$ with cell-cycle times τ, every single state is defined by all possible changes in configurational space
- ***Stepwise random selection*** of possible changes (a), (b) generates the dynamics of cell population development with an increasing time Δt (1), resulting in a simulated population (c)
- Growth conditions now can be investigated by change of the initial parameters ϕ, λ, k and m where k = ΔR - 1 is the proliferating rim at the border of the population and m is the control strength of the dispersion of cell-cycle distribution (m=1 is Poissonian)
- Additional parameters define the possibility for cell-cycle mutation, transmitted from the mothercell and apoptosis as a third basic process

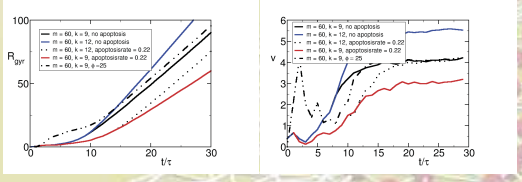
Results

Dynamics and Morphology

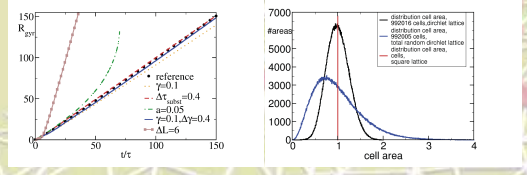
(a) (b)



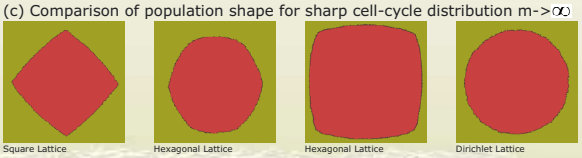
(d) (e)



(f) (g)



(c) Comparison of population shape for sharp cell-cycle distribution m->∞



- ***Biological interpretation:*** Biomechanical form of contact inhibition determines qualitative growth regimes.
- Growth simulations with free diffusion satisfy the kinetic properties with a linear phase after an initial phase of exponential growth and agree with experiments (a)
- Expansion velocity increases with cell migration activity ϕ (a), threshold for contact inhibition (via k), and width of cycle time distribution (decreasing m)
- an underlaying structure of standard lattices shows strong lattice effects, where the Voronoi-structure shows ***no lattice artefacts*** (b),(c).
- Apoptosis change the dynamics of the cell-population growth where different parameters of apoptosis, migration and proliferating rim can lead to the same expansion velocity with different initial phases (d),(e)
- Mutations affect expansion kinetics and shape of cell populations, apoptosis lead to a delay of this effect, but deactivate it (f).
- Cell area distribution is a realistic in contrast to structured lattice appoaches or total random distributions (g)

Conclusion

Summary

The presented Voronoi-lattice model can reproduce the dynamics of tumor cell population growth observed in experiments [4] and simulated [2,3] by means of a Kinetic Monte Carlo method.
We are able to identify the different basic mechanisms that change the specific morphologies and dynamics in experiments.
Hence a detailed understanding of cell population growth mechanisms is achieved.

References

[1] M. Block, D. Drasdo and E. Schöll, in preparation, 2006.
[2] D. Drasdo, Adv. Compl. Syst. 2 & 3, 285-318, 2005.
[3] D. Drasdo, S. Höhme and M. Block, submitted, 2006.
[4] Bru et al, Biophys. J. 85, 2948-2961, 2003.