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Swiss Confederation

Federal Department of Economic Affairs FDEA
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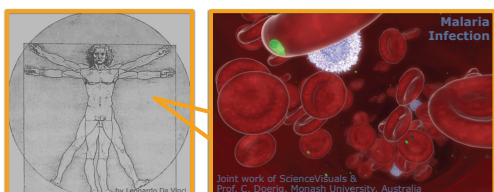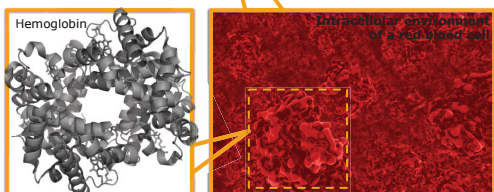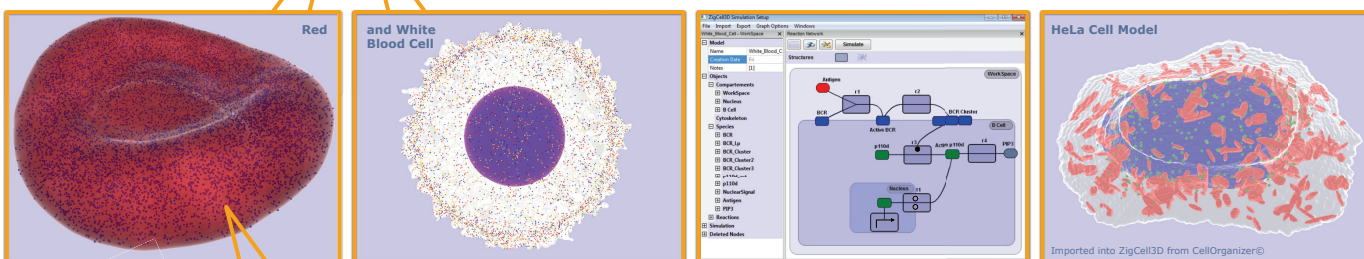
CTI Medtech Event 2012

ZigCell3D

An Interactive Simulation and Visualization Tool for Intracellular Signaling Dynamics

Project number 12532.1
Starting date: 01. November 2011, duration 24 months

Main applicant	ETH Zürich Prof. Heinz Koeppl
Main industrial partner	ScienceVisuals Sarl, Lausanne Pablo de Heras Ciechomski, PhD

by Leonardo Da Vinci

Malaria Infection
Joint work of ScienceVisuals & Prof. C. Doerig, Monash University, Australia

Red

and White Blood Cell

Hemoglobin

Intracellular environment of a red blood cell

HeLa Cell Model
Imported into ZigCell3D from CellOrganizer©

Motivation and Implementation

- The 3D cellular shape and the organization of molecules in space can have a significant impact on cellular signaling.
- Events on the molecular level occur stochastically and can lead to a broad cell to cell variation, therefore every molecule has to be tracked.
- The combined modeling, simulation and visualization tool helps biologists understand complex diseases, which is a basis for new drugs.

Visualization - Based on the ScienceVisuals BioInspire Engine

- The realtime 3D raytracing platform for navigating, exploring and analyzing massive data environments allows visual inspection of highly populated simulations.
- Precise modeling up to the atomic level of proteins.
- State-of-the-art algorithms to render dense scenes with a specialization on biological structures such as cells and signaling molecules.

Simulation – Based on Algorithm by M.Klann, ETH Zurich

- M. Klann developed a powerful lattice free simulator to investigate signaling on the molecular level – in 3D, with all stochastic effects, and compatible with the reaction diffusion master equation.
- The advanced simulator includes several cell geometries and can take into account molecular crowding to model physiological conditions.
- Parallelization and multi-scale modeling increase the performance.

Graphical User Interface – Main Developer: R.Mange, ETH Zurich

- The intuitive GUI enables easy setup and analysis of signaling models.
- The structured interaction graph in the GUI highlights interactions and dependencies in the system.
- Interactive control on the simulation, such that parameters can be changed or reactions such as inhibitions by drug candidates can be added and investigated during the simulation.

Example: White Blood Cell Signaling

B Cell Receptors activate PI3K isoforms. The activation is much stronger if the B Cell Receptors are clustered [1]. This effect can be easily simulated in **ZigCell3D**:

B-Cell with Receptor Clusters

Clusterd vs. Nonclustered Simulation Results

PI3Kinase (p110delta) Activation
Clustered
Uniformly distributed receptor

- Receptors are placed on the plasma membrane either in clusters with given sizes or uniformly distributed.
- The PI3K has to be activated in 2 steps sequentially, where the intermediary state is very unstable.
- Thus high receptor densities in clusters have a higher chance to fully activate PI3K if diffusion of PI3K is relatively fast (cf. [2]).

References:
[1] J.J. Limon and D.A. Fruman. B Cell Receptor Signaling: Picky About PI3Ks. Science Signaling 2012, 3 (134), pe25.
[2] A. Mugler et al. Membrane clustering and the role of rebinding in biochemical signaling. Biophys. J. 2012, vol. 102, 1069-1078.

From Microscope Images to Volumes

Source TEM Image

Computer Generated 3D Shapes

Image Statistics

Pr(b | w,w,w)
Pr(b | w,w,b)
Pr(b | w,b,w)
Pr(b | w,b,b)
Pr(b | b,w,w)
Pr(b | b,w,b)
Pr(b | b,b,w)
Pr(b | b,b,b)
TEM images
xyz of volume
0.0 0.2 0.4 0.6 0.8

… based on statistics learned from TEM images and used for diffusion simulation, rendered in BioInspire.
→ N. Hiroi, M. Klann, K. Iba, P. Ciechomski, … R. Mange, M. Unger, A. Funahashi, H. Koeppl. From Microscopy Data to *in silico* Environments for *in vivo* Oriented Simulations, EURASIP Journal on Bioinformatics and Systems Biology 2012, 2012:7

Conclusion

- **ZigCell3D** is an innovative simulation tool with a wide set of possible applications in biology and pharmacology.
- The virtual **ZigCell3D** environment streamlines the research process from candidate models to final results in one tool, including high quality graphical representations.

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