PROCEEDINGS

55. IWK

Internationales Wissenschaftliches Kolloquium
International Scientific Colloquium

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Impressum
Published by

Publisher:	Rector of the Ilmenau University of Technology Univ.-Prof. Dr. rer. nat. habil. Dr. h. c. Prof. h. c. Peter Scharff
Editor:	Marketing Department (Phone: +49 3677 69-2520) Andrea Schneider (conferences@tu-ilmenau.de) Faculty of Computer Science and Automation (Phone: +49 3677 69-2860) Univ.-Prof. Dr.-Ing. habil. Jens Haueisen
Editorial Deadline:	20. August 2010
Implementation:	Ilmenau University of Technology Felix Böckelmann Philipp Schmidt

USB-Flash-Version.

Publishing House:	Verlag ISLE, Betriebsstätte des ISLE e.V. Werner-von-Siemens-Str. 16 98693 Ilmenau
Production:	CDA Datenträger Albrechts GmbH, 98529 Suhl/Albrechts
Order trough:	Marketing Department (+49 3677 69-2520) Andrea Schneider (conferences@tu-ilmenau.de)

ISBN: 978-3-938843-53-6 (USB-Flash Version)

Online-Version:

Publisher:	Universitätsbibliothek Ilmenau ilmedia Postfach 10 05 65 98684 Ilmenau

Home / Index:
http://www.db-thueringen.de/servlets/DocumentServlet?id=16739

MONTO CARLO SIMULATION OF NANOPARTICLE TRACKING UNDER CELL CULTURE CONDITIONS STUDIED BY IMAGE BASED ANALYSIS

Dominic Swarat [a], Martin Wiemann[b], Hans-Gerd Lipinski [a]

[a]Biomedical Imaging Group; University of Applied Sciences and Arts Dortmund, Emil-Figge-Str. 42, 44227 Dortmund, Germany

[b]Institute for Lung Health (IBE R&D gGmbH) Marl, Elbestr. 10, 45768 Marl, Germany

ABSTRACT

Based on time-lapse videos of nanoparticle motion captured with the Nano Sight™ device, we created a software to study the three dimensional Brownian motion projected to two spatial dimensions. We tested the influence of this dimensional reduction on the calculation of nanoparticel (NP) size by a Monte Carlo model which simulated the Brownian motions of NP in a virtual liquid. The 3D-Brownian motion was described by a random walk model, defined for equally-spaced time steps, such that all increments are isotropic, independent, and random. We found that the diffusion coefficients obtained from real experiments were equal to those gathered from the simulations.

Index Terms *Nanoparticles, diffusion, Monte Carlo simulation, visualisation toolkit VTK*

1. INTRODUCTION

Nanoparticles (NP) are increasingly important for both industrial and biomedical applications. However, some clinical findings suggest that air-born NP, which reaches the lung and other tissues of the body after inhalation, may provide a health hazard [1,2]. Up to now the health effects of NPs are not completely understood [3]. Cell culture experiments, however, can help to examine toxic effects of NPs and, moreover, may reduce the number of necessary animal experiments [4]. However, to compare results from in vivo and in vitro tests an equal cellular particle dose should be ascertained, which means that the uptake of particles by either cell type needs to be quantified.

To visualise NP within the culture media we used the NanoSight™ device which optically tracks the Brownian Motion of NP in liquid suspensions by a special configured laser beam. Motion of NP was captured as a sequence of images, from which NP light scattering intensity can be derived and particle size can be computed using the Stokes-Einstein relation.

Since the Nano-Sight™ method reduces the observed Brownian motion from three to two spatial dimensions, we studied the influence of this reduction on the calculation of NP size by a Monte Carlo model which simulated the Brownian motions of NP in a virtual liquid.

2. MEASUREMENT OF DIFFUSING NANOPARTICLES IN LIQUIDS

NP can be individually tracked in real-time by the NanoSight™ device which uses a solid-state single mode laser diode (638 nm). It is configured to launch a finely focused beam through a liquid bath of approximately 250 µl volume containing a dilute suspension of NPs. Diffusing NPs in the beam are visualised by a conventional optical microscope which collects light scattered from NPs in the field of view (cf. Fig.1) and registered as a video sequence of 20-60 s duration.

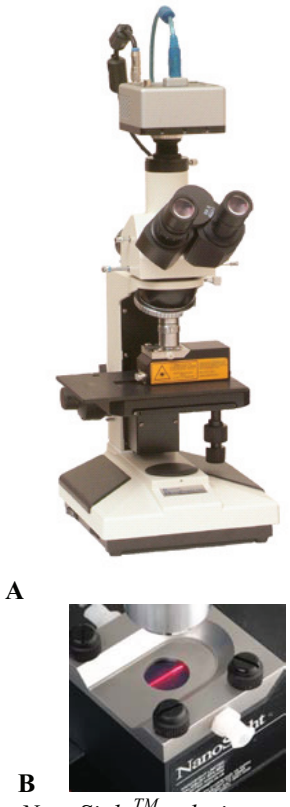

Fig. 1. The NanoSight™ device. A: microscopic arrangement; B: laser beam observed by microcope.

However, images obtained from the microscope are 2D projections of a 3D diffusion process. NPs which diffuse into the scattering volume are identified and their optical centres are tracked while they are present within the measured volume.
From the video sequence the track of each diffusing NP can be obtained and converted into its mean squared displacement. Using the well known Stokes-Einstein equation the diffusion coefficient could be calculated from these data.

3. THE MONTE CARLO MODEL OF NANOPARTICEL TRACKING IN VIRTUAL LIQUIDS

The movement of an individual NP in a liquid, identified as a 3D-Brownian motion, was described by a random walk model, defined for equally-spaced time steps, such that all increments are isotropic, independent, and random. Such models were efficiently used in diverse cases of NP diffusion [5,6,7]. We introduced a virtual clock which delivers a minimum time step δt. Since the NP moving velocity depends on its mass (small particles move faster then bigger ones), we simulate the individual time step as

$$\Delta t(k) = n \cdot \delta t \quad . \tag{1}$$

Δt(k) represents the time step of a NP of type k, which is n times the minimum time step. The parameter k reflexes the mass of the NP. The displacement of particle with mass k was calculated according to the following algorithm:

```
while time < time-out do
        if int(time/delta_t(k))-time/delta_t(k)=0 then
                j=int(random*3)
                NP(j)=NP(j)+displace
        end if
        time=time+1
end while
```

The random generator generates real random numbers equally distributed between 0 and <1. The parameter j describes the direction in which the NP is moved. Since the simulation was carried out in a three dimensional Cartesian coordinate system with coordinates x, y, and z, the NP was moved from the actual spatial position either in x-direction (if j=0), in y-direction (if j=1), or in z-direction (if j=2) by the shift value derived from the parameter "displace" (e.g. displace=1). From the 3D scene (x,y,z) a 2D scene (x,y) was also visualised where the z-value, at which the NanoSight scene took place, was selected according to the experimental conditions.

From experimental studies it derives that the illumination of a NP was not homogenous. At the centre of the NP the illumination was maximal with a non-linear decrease towards its border. We adapted the model NP illumination J_r by the following model:

$$J_r(x, y, z) = 255 \cdot \Psi(x, y) \cdot \Phi(z) \tag{2}$$

with

$$\Psi(x,y) = \begin{cases} 1 - \dfrac{(x-x_p)^2 + (y-y_p)^2}{R_p^2} & \text{if} \quad (x-x_p)^2 + (y-y_p)^2 \le R_p^2 \\ 0 & \text{else} \end{cases} \tag{3}$$

$$\Phi(z) = \begin{cases} 1 - p \cdot \left(\dfrac{z}{z_S} - 1 \right)^2 & \text{if} \quad p \cdot \left(\dfrac{z}{z_S} - 1 \right)^2 \le 1 \\ 0 & \text{else} \end{cases} \tag{4}$$

R_p is the radius of the illuminated NP, xp and yp are the centre coordinates of the illuminated particle, z_S is the selected depth which is given mainly by the aperture of the objective of the NanoSight device.
The program was developed by the Visualization Toolkit (VTK), which is a comprehensive accumulation of functions specially designed for the visualization and presentation of image data. The functions are arranged in libraries and are generated with c++. The VTK Framework is an open source project, so everybody can use, change and extend it [8].

4. RESULTS

Illumination, scattering, and particle motion of the virtual scene were adapted to real measurements. Image sequences derived from virtual scenes were analysed in three and two spatial dimensions according to the NanoSight™ method. We found that the 3D simulation model matched the experimental situation. Furthermore the created simulation could be used to generate results which were superior to those calculated from two dimensional projections: Using the simulation it was possible to locate each single particle and to identify any particle at any time, especially in cases of collision, agglomeration or

optical interference. Figure 2 shows a typical result of both, a NanoSight experiment and a Monte Carlo simulation.

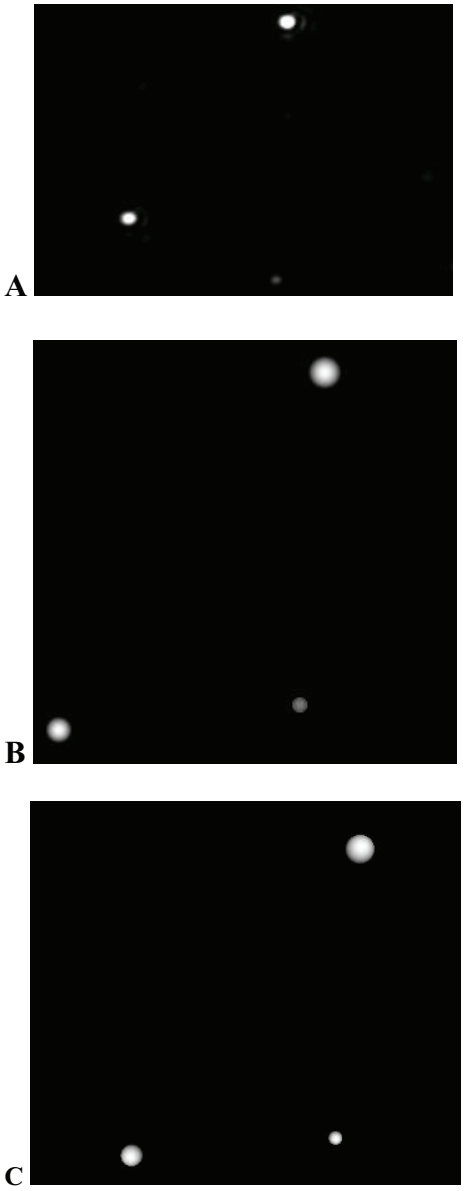

Fig. 2. Scenes of diffusing nanoparticles. A: real scene obtained from an experiment; B: corresponding 2D image of the Monte Carlo exper-imen.; C: 3D-scene derived from a Monte Carlo experiment.

To compare real experiments with Monte Carlo simulations, we arranged the starting conditions of selected particles according to the real experimental situation. Then simulation started for a 20 – 60 s sequence. Next the diffusion coefficients of the selected NPs were calculated from the simulation and compared to experimental data. We found that diffusion coefficients obtained from experiment and after simulation did not differ significantly.

Figure 3 shows a collision of two NP and there subsequent merging.

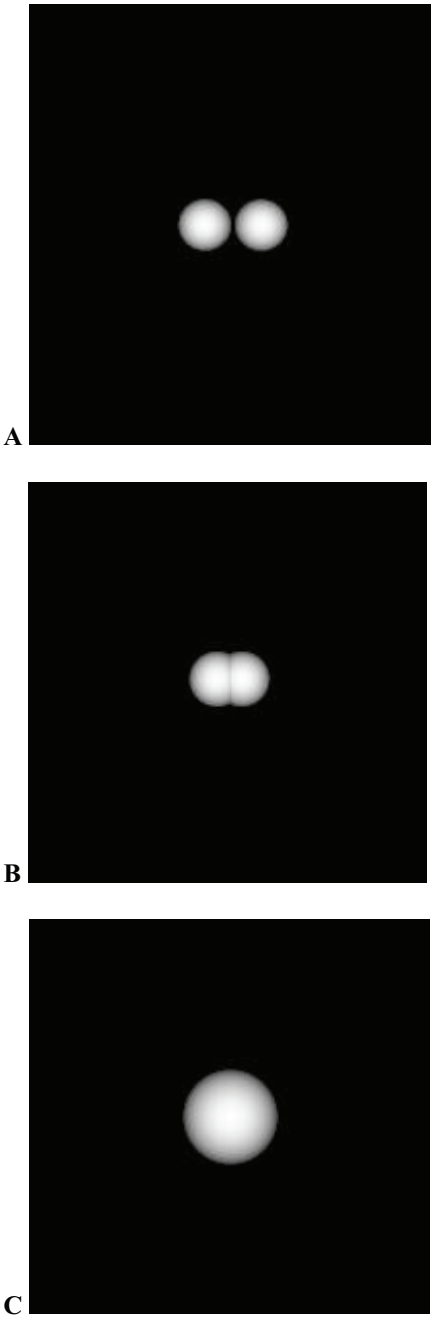

Fig. 3. 3D-Scenes of merging nanoparticles. A: 3D-scene of two nanoparticles; B: 3D-scene of merging nanoparticles; C:3D-scene of a new particle.

If two or more NP clash with each other, this might result in an agglomerated NP with larger surface and increased mass. The new particles will exhibit a slower diffusion compared to the original particles.

5. CONCLUSION

Our Monte Carlo simulation model allows us to compare the NP diffusion process taken from real experiments with simulations of Brownian motions in a discrete volume. Furthermore, on the basis of the 3D simulations corresponding 2D-scenes could be created related to compare simulation and experiment. The main finding was that the diffusion coefficients obtained from real experiments were equal to those of Monte Carlo simulations. Additionally, collisions of NPs leading to agglomerated NPs could be simulated and compared to those observed in real experiments.

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7. ACKNOWLEDGEMENT

This work was funded by the North-Rhine Westphalian Ministry of Innovation, Science, Research and Technology (NRW-Geräteprogramm 2009/Lipinski).