University of Twente
The Netherlands

Dr. Sascha Hilgenfeldt

Department of Applied Physics and
Institute for Biomedical Technology
University of Twente
P.O. Box 217
7500 AE Enschede
The Netherlands

Phone: +31-53-489-2568
Fax: +31-53-489-8068
e-mail: sascha@tn.utwente.nl

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Professor Rob de Ruyter van Steveninck
Biocomplexity Institute
Indiana University
Swain Hall West 117
Bloomington, IN 47405-7105
USA

Dear Professor de Ruyter,

I am writing to express my interest in a faculty position in Biocomplexity at Indiana University Bloomington. An advertisement was kindly forwarded to me by Professor James Glazier, who encouraged me to apply.

I hold an "universitair docent" position at University of Twente (Netherlands) – like an assistant professorship, but with tenure (as I am sure you know). I am considering both tenure and tenure-track positions as my wife lives and works in the US. Over the past three years, I have gathered experience supervising students and teaching physics and engineering courses on the graduate and undergraduate levels. Using funding I raised independently from government sources and research foundations, I have pursued novel research projects investigating the interfacial structure of soft matter, in particular the response of cells and vesicles to fluid-dynamical forces in bioengineering and microfluidic applications. I strongly believe that this work can contribute significantly to research on biocomplexity on the cellular and membrane levels.

A theorist by training, I have also developed a successful line of experimental research after my appointment at University of Twente. I currently study the interaction of bubbles with biomaterials (lipid vesicles and cells) in micromechanical and bioMEMS applications, including directed drug delivery and gene transfection. The structure, rheology, and aging of cellular matter is another of my interests. I use foam as a model system to investigate the relation between interfacial geometry and material properties.

Having collaborated with academic and industrial researchers from engineering, physics, applied mathematics, medicine, computer science, and chemistry, I would love to explore interactions with colleagues beyond the departmental borders. The US university system is familiar to me through my postdoctoral stay at Harvard University in the group of Howard Stone, who I continue to collaborate with, and also through my current visiting scholar appointment at the University of Chicago.

Please find enclosed with this letter of application my curriculum vitae, a list of publications and selected talks, and an outline of research interests, including visions for the future. I also add four recent representative reprints. I have asked Professors Howard Stone (Harvard), Tom Witten (Chicago), Leo Kadanoff(Chicago), and Detlef Lohse (Twente) to send letters of recommendation on my behalf. An expanded list of references is attached below.

I am looking forward to your reply. If you need additional information, please do not hesitate to contact me.

Yours sincerely,

S. Hilgenfeldt

Sascha Hilgenfeldt

The following colleagues are willing to send a letter of reference on my behalf:

- Professor Howard A. Stone
  Division of Engineering and Applied Sciences
  Harvard University
  29 Oxford St
  Cambridge, MA 02138
  e-mail: has@deas.harvard.edu
  Phone: (617) 495-3599
  Fax: (617) 495-9837

- Professor Thomas A. Witten
  James Franck Institute
  The University of Chicago
  5640 S Ellis Ave
  Chicago, IL 60637
  e-mail: t-witten@uchicago.edu
  Phone: (773) 702 0947
  Fax: (773) 702 2172

- Professor Leo P. Kadanoff
  James Franck Institute
  The University of Chicago
  5640 S Ellis Ave
  Chicago, IL 60637
  e-mail: leop@uchicago.edu
  Phone: (773) 702 7189
  Fax: (773) 702 2172

- Professor Detlef Lohse
  Department of Applied Physics and J. M. Burgers Centre
  for Fluid Dynamics, University of Twente
  P.O. Box 217
  7500 AE Enschede, The Netherlands
  e-mail: lohse@tn.utwente.nl
  Phone: +31-53-489-8076
  Fax: +31-53-489-8068

- Professor Michael P. Brenner
  Division of Engineering and Applied Sciences
  Harvard University
  29 Oxford St
  Cambridge, MA 02138
  e-mail: brenner@deas.harvard.edu
  Phone: (617) 495-3336
  Fax: (617) 496-0601

- Professor Andrea Prosperetti
  Department of Mechanical Engineering
  The Johns Hopkins University
  3400 N Charles St
  Baltimore, MD 21218
  e-mail: prosperetti@jhu.edu
  Phone: (410) 516-8534
  Fax: (410) 516-7254

- Professor Andrew J. Szeri
  Department of Mechanical Engineering
  6119 Etcheverry Hall
  University of California
  Berkeley, CA 94720-1740
  e-mail: aszeri@me.berkeley.edu
  Phone: (510) 643-0298
  Fax: (510) 642-6163

- Professor Thomas R. Powers
  Division of Engineering
  Brown University, Box D
  Providence, RI 02912-9104
  e-mail: Thomas_Powers@brown.edu
  Phone: (401) 863-2868
  Fax: (401) 863-9009

- Professor Siegfried Grossmann
  FB Physik
  University of Marburg
  Renthof 6
  D-35032 Marburg, Germany
  e-mail: grossmann_s@stat.physik.uni-marburg.de
  Phone: +49-6421-28-22049
  Fax: +49-6421-28-24110

SASCHA HILGENFELDT: RESEARCH STATEMENT

The scientific study of interfaces has become increasingly important in many different contexts. In micro- and nanotechnology, for instance, increasingly smaller scales are studied, stressing the importance of surface phenomena. In particular, interfaces of *soft matter* on these scales have significance in biomedicine and biomechanics. My research is focused on elucidating the shape, spatial organization, and dynamical properties of soft interfaces. I study these systems both theoretically and experimentally, working with accessible, well-controlled systems that allow for a quantitative comparison of the theoretical and experimental results.

I. Bubbles for Biotechnology

A single oscillating bubble driven by pressure variations or ultrasound is a particularly well-defined soft interface. My research concentrates on the bubble's intriguing ability to focus energy, forces, and stresses originally present at a large scale (say, an ultrasonic wavelength of several mm or cm) down to the scale of the bubble size (often just a few μm). Strongly collapsing (cavitating) bubbles give rise to many spectacular phenomena, from sonoluminescence [1] to sonochemistry [2] or xylem cavitation in plants [3]. But the focusing to micrometer scales works just as well with weakly driven bubbles, where we can exert much better control over the magnitude of energy and force densities. Bubbles are therefore a unique tool for probing the properties of *other* soft interfaces on micro- and nanoscales, such as the walls of living cells and lipid vesicles in the context of biomedical applications.

FIG. 1. (a) A fluorescence-marked vesicle of $\approx 40\mu m$ radius is trapped close to a microbubble (circle) and develops a conical tip; (b) Upon increasing the ultrasonic driving, the vesicle ruptures; (c) Violent rupture and ejection of vesicle material (arrows) is observed in the streaming flow generated by a larger bubble (left) and a solid particle (bright object between arrows).

My research on bubble – soft matter interaction on the microscale is motivated by experiments in biomedicine demonstrating that the presence of ultrasound-driven microbubbles greatly facilitates drug delivery and DNA transfection through the cell membrane [4]. Several mechanisms linked to the bubble energy focusing could effect the cell wall permeation (*sonoporation*). Recently, we quantified one of these mechanisms in experiment: in our set-up, cells and lipid vesicles are subjected to

controlled shear stress generated by oscillating bubbles on a substrate [5]. Depending on the driving parameters, the vesicles are transported in the flow, aggregated, or kept in place. A quantitative theoretical understanding of these processes is obtained using the theory of acoustic streaming and Stokes flow singularities [6]. Microscopy also reveals a variety of vesicle shape deformations in the flow, leading to oblate and prolate shapes, conical tips (Fig. 1), or lipid tethers [7] drawn out of the membrane. Even for weak driving, the forces generated are sufficient to open transient holes in the cell membrane (cf. [8]) and even rupture vesicles and cells [5] (Fig. 1).
The quantitative control over the lipid membrane stresses in our set-up makes it ideal for applications such as cell homogenization (gentle rupture of cell membranes), localized drug delivery, or gene transfection. I have been collaborating with pharmaceutical companies [9] interested in such uses of microbubbles.
Vision for future work: Develop and understand well-controlled, quantitative tools for transfecting cells with drugs and DNA, based on bubble streaming flow.

II. Bubble-powered Microfluidics

The abovementioned transfection and rupture experiments utilized a localized streaming flow around single bubbles. Figure 1c shows a different situation: the lipid debris is transported away from the bubble because a *solid particle* is present, acting as a passive flow element around which streaming is induced by the bubble. The sum of the streaming flows around the bubble and particle pair (which we call a *doublet*) is *directional* and allows for controlled *transport* of vesicles and cells along the substrate surface. The transport is fast and efficient because of the strong energy focusing of the microbubbles. We are developing hydrophobic substrates micro-patterned with pits (where bubbles attach) and bumps (playing the role of the particles). Figure 2a shows a single doublet, while 2b illustrates how a doublet transports fluorescent beads.

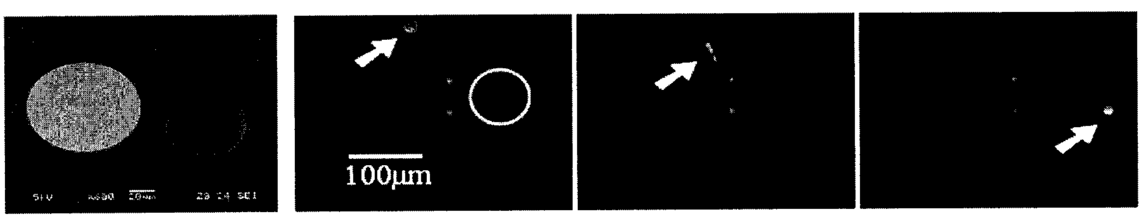

FIG. 2. (a) Electron micrograph of a (negative) pit/bump doublet structure etched in silicon. This structure is reproduced as a positive in PDMS, resulting in a pit on the left and a bump on the right. (b) A doublet in PDMS with a bubble (center), located in a pit, and a bump (indicated by a circle in frame 1). A fluorescent bead (arrows) is transported over the substrate. Interframe distance is ≈ 0.2s; note the motion blurring in frame 2.

Together with Albert van den Berg (University of Twente), I am optimizing these bubble-powered microfluidic transport devices for cell sorting, cytometry, or other lab-on-a-chip applications [10]. Such bubble MEMS do not need microchannels to achieve directed transport. As shear forces are always present (see I.), simultaneous transport and transfection is feasible.

Vision for future work: Develop new concepts and devices for lab-on-a-chip MEMS using bubble-powered microfluidics.

III. Foam Rheology: Fingers or Cracks?

The shape and dynamics of gas/liquid interfaces is important not only for single bubbles; it becomes more intricate where bubbles fill space. Foam [11] is a prototypical example for a whole class of space-filling, cellular structures including polycrystalline metals [12] (where the grain size distribution determines material properties), superconducting or ferromagnetic domains [13], or cells in biological tissues [14]. All these structures are governed by minimization of the total interfacial area, which is reflected in the *geometry* (shape) of the bubbles. I recently showed [15] that the geometry of a bubble in a 3-D foam determines the long-time evolution of its volume (coarsening), generalizing von Neumann's [16] 2-D coarsening law. This encouraged me to use information about interfacial geometry for *foam rheology* as well, setting up a *fingering experiment* for foams.

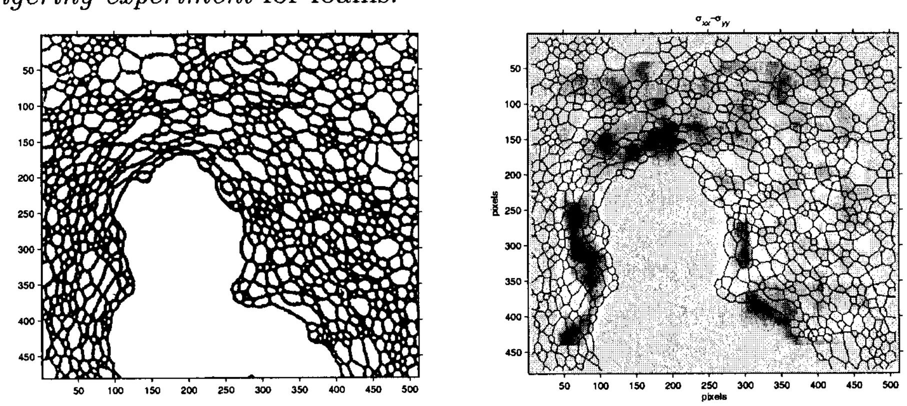

FIG. 3. (a) Experimental image of a propagating finger in a rectangular foam cell. (b) Contour map of deviatoric stress ($\sigma_{xx} - \sigma_{yy}$) extracted from the bubble shapes in (a).

Fingering of a viscous liquid between parallel plates (Hele-Shaw setup) has given rise to a vast literature since the work of Saffman and Taylor [17]. In an ideally elastic medium, fingering should be replaced by the formation of cracks [18], though few attempts have been made to describe intermediate stages that should exist in viscoelastic materials such as foams. In my experiment, dry foam is invaded by air at a controlled flow rate. Unlike in other materials, the stress tensor in a foam can be extracted directly from the geometry of the bubbles [19], which we record with high-speed photography. The results are compared with the predictions of continuum crack theory, as well as to a generalization of a recent fingering theory from diffusion-limited aggregation studies [20].

Vision for future work: Foams allow for direct extraction of stress and strain data from geometry. The results will link three very important areas of active research: viscous fingering, crack propagation, and diffusion-limited aggregation studies.

[1] S. Hilgenfeldt, S. Grossmann, and D. Lohse, Nature **398**, 402 (1999); R. Toegel, S. Hilgenfeldt, and D. Lohse, Phys. Rev. Lett. **88**, 034301 (2002); M. P. Brenner, S. Hilgenfeldt, and D. Lohse, Rev. Mod. Phys. **74**, 425 (2002).

[2] K. S. Suslick, Science **247**, 1439 (1990); R. Toegel, S. Hilgenfeldt, and D. Lohse, Phys. Rev. Lett. **84**, 2509 (2000).

[3] N. M. Holbrook, M. J. Burns, and C. B. Field, Science **270**, 1193 (1995).

[4] K. Tachibana et al., The Lancet **353**, 1409 (1999); D. L. Miller and J. Quddus, Ultrasound Med. Biol. **26**, 661 (2000).

[5] P. Marmottant and S. Hilgenfeldt, Nature **423**, 153 (2003).

[6] J. Lighthill, J. Sound Vib. **61**, 391 (1978); N. Amin and N. Riley, J. Fluid Mech. **210**, 459 (1990).

[7] T. R. Powers, G. Huber, and R. E. Goldstein, Phys. Rev. E **65**, 041901 (2002).

[8] O. Sandre, L. Moreaux, and F. Brochard-Wyart, Proc. Natl. Acad. Sci. USA **96**, 10591 (1999).

[9] S. Hilgenfeldt, D. Lohse, and M. Zomack, Eur. Phys. J. B **4**, 247 (1998); J. Acoust. Soc. Am. **107**, 3530 (2000).

[10] P. Marmottant and S. Hilgenfeldt, *A bubble-driven microfluidic transport element for bioengineering*, submitted to Proc. Natl. Acad. Science (2003).

[11] D. Weaire and S. Hutzler, *The Physics of Foams* (Oxford University Press, Oxford, 2000).

[12] C. S. Smith, in *Metal Interfaces*, ed. by C. Herring (Am. Soc. for Metals, Cleveland, OH, 1952), p. 65; A. E. Lobkovsky and J. A. Warren, Phys. Rev. E **63**, 051605 (2001).

[13] J. R. Iglesias, S. Goncalves, O. A. Nagel, and M. Kiwi, Phys. Rev. B **65**, 064447 (2002).

[14] E. Matzke, Am. J. Bot. **33**, 58 (1946); S. L. Ustin, S. Jacquemoud, and Y. Govaerts, Plant Cell Environment **24**, 1095 (2001).

[15] S. Hilgenfeldt, A. Kraynik, S. A. Koehler, and H. A. Stone, Phys. Rev. Lett. **86**, 2685 (2001).

[16] J. von Neumann, in *Metal Interfaces* (American Society for Metals, Cleveland, 1952), p. 108.

[17] P. G. Saffman and G. I. Taylor, Proc. R. Soc. Lond. A **245**, 312 (1958).

[18] M. Marder and J. Fineberg, Phys. Today **49**, 24 (1996); K. B. Bromberg, *Cracks and Fracture*, Academic Press (1999).

[19] R. C. Ball and R. Blumenfeld, Phys. Rev. Lett. **88**, 115505 (2002); M. Aubouy et al., Granular Matter **5**, 67 (2003).

[20] A. Levermann and I. Procaccia, Phys. Rev. Lett. **89**, 234501 (2002); L. P. Kadanoff, Nature **421**, 124 (2003).