11. Conclusions and outlook

This chapter is intended to give a concluding overview of the achievements of the present thesis. The contributions of this work to the scientific community and the physical results for the red blood cell simulations are reviewed in section 11.1. Open questions and suggestions for future research—both related to the physics and the code development—are pointed out in section 11.2.

11.1. Summary of own contributions and conclusions

During the course of preparing and writing this thesis, a series of new contributions to the skills of the research group in particular and to the knowledge of the community in general has been provided.

Own contributions

A computational model, based on the lattice Boltzmann method and the immersed boundary method, for the simulation of dense suspensions of deformable particles has been implemented and thoroughly analyzed (chapters 5, 6, 7, and 8). The algorithm is efficient in the sense that dense suspensions (65% volume fraction) with $\mathcal{O}(1000)$ particles can be simulated in a reasonable time (about 5 days for 10^5 time steps) on a modern single CPU with 3 GHz. The fluid viscosity, the applied shear rate or shear stress (see below), and the elastic particle properties can be directly controlled by the user. The numerical tool is not restricted to the simulation of red blood cells. Rather, a wide class of membrane-like particles for which the elastic constitutive law is provided can be simulated. It is hoped that the simulation tool will be further used in the future in order to study the rheology of dense suspensions of deformable particles (e.g., polydisperse capsules) or to investigate biomechanical processes relevant for medical research (such as platelet margination, cf. section 11.2).

In this context, some results regarding the numerical model (section 8.4) have already been published (Krüger et al. [187]). In this article, a single spherical, elastic capsule in simple shear has been simulated. The motivation for this investigation was to understand the reliability of the numerical method in the case of intermediate resolutions (particle radius about $8\Delta x$, Δx being the lattice constant). Higher resolutions are too expensive for the study of suspensions, and smaller resolutions do not permit high volume fractions. One of the major findings is that the hydrodynamic radius of the particles is slightly larger than the input radius ($r^* \approx r + 0.4\Delta x$, depending on the resolution and the interpolation stencil for the immersed boundary method). It is believed that the necessary interpolations between the Eulerian and the Lagrangian coordinate systems lead to the increase of apparent particle size. This has to be considered when results are compared with experiments or other simulations.

A shear stress boundary condition for the lattice Boltzmann method has been developed (section 5.4.2) and successfully tested (section 9.5). The primary importance of this boundary condition is that a shear flow can now be controlled by an applied shear *stress* rather than a shear *rate*. This is particularly important when the apparent viscosity of the fluid is not known as it is usually the case for complex fluids. Especially for future investigations of the yield stress in such systems, a shear stress boundary condition provides an interesting opportunity. As briefly

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described in section 2.3, one has to distinguish between the dynamic and the static yield stress of a system. The former is the shear stress which is found in the limit of vanishing but still *finite* shear rates. The latter is the stress below which the system deforms elastically and above which plastic deformations set in. The static is usually larger than the dynamic yield stress. It is now possible—within the lattice Boltzmann method—to identify both values independently. On the one hand, a fluid can be sheared with a small shear rate via standard velocity boundary conditions. This provides information about the dynamic yield stress. The new shear stress boundary condition, on the other hand, allows to access the static yield stress by increasing the load until the systems starts to deform plastically.

It is argued in appx. B.1.3 and shown via simulations in appx. B.1.4 that the deviatoric stress tensor in the lattice Boltzmann method is of second-order accuracy. These results have already been published (Krüger et al. [165, 258]). It is commonly claimed that boundary conditions for the lattice Boltzmann method should be designed in such a way that they maintain the second-order accuracy of the velocity field. The role of the stress tensor is usually neglected along the way, and its accuracy is affected. Therefore, it is hoped that those contributions help to improve the boundary conditions in such a way that they also retain the second-order convergence of the stress tensor.

Chap. 9 provides a coherent picture how stresses in the immersed boundary lattice Boltzmann method can be computed and evaluated. Especially the modified method of planes (section 9.4) turns out to be a useful tool for suspension rheology since it allows to compute the instantaneous and local[1] particle stress independently of the fluid stress (Krüger et al. [233]). Up to now, most researchers obtain the time-averaged particle stress from the total stress (which is known from macroscopic considerations for simple flow configurations, such as Poiseuille or simple shear flow) and the fluid stress computed within the lattice Boltzmann method. This approach, however, does not permit to access the spatio-temporal particle stress fluctuations.

The most important physical results and conclusions regarding the simulations of the red blood cell suspensions are collected in the following.

Conclusions from the simulations of the red blood cell suspensions

A major contribution to the understanding of the physical properties of red blood cell suspensions is provided in chap. 10 of the present work. For the first time, a systematic simulation study of the rheology of blood at intermediate shear rates is performed ($\dot{\gamma} \in [1, 100]\,\mathrm{s}^{-1}$ in physical units). The influence of the three major control parameters, the volume fraction Ht, the external shear rate $\dot{\gamma}$, and the particle rigidity κ_S, has been investigated.

It turns out that the three *input* control parameters (Ht, $\dot{\gamma}$, κ_S) are not best suitable for the description of the *outcome* of the simulations. Rather, the shear rate and the particle rigidity can be combined to a single parameter, the capillary number $\mathrm{Ca} := \eta_0 \dot{\gamma} r / \kappa_\mathrm{S}$. Here, η_0 is the viscosity of the suspending fluid, and r is the large red blood cell radius. Data points for the viscosity and particle properties (such as deformation, rotation, alignment, and shear-induced diffusivity, see below) with the same values for Ht and Ca collapse, irrespective of the values for $\dot{\gamma}$ and κ_S. Thus, only two, rather than three parameters are required to characterize the simulation data. This behavior was to be expected from dimensional considerations.

Shear thinning behavior was observed for all combinations of control parameters (fig. 10.7). As expected, denser suspensions are more viscous, and the flow curves can be described by Ht and Ca alone. The flow curve for the suspension with 35% volume fraction was found to match experimental results at 45% [54] over two orders of magnitude in the shear rate (fig. 10.9). The reason for the apparent mismatch of the volume fractions is the effective hydrodynamic radius

[1] averaged over planes parallel to the walls

of the red blood cells as mentioned above. Taking the hydrodynamic radius into account, the results agree well.

In the case of dense suspensions, the 'corrected' capillary number $\mathrm{Ca}^* := \eta\dot{\gamma}r/\kappa_\mathrm{S}$ turns out to be more useful than Ca. It contains the total suspension stress $\eta\dot{\gamma}$, rather than the fluid stress $\eta_0\dot{\gamma}$. It is shown in chap. 10 that—under certain conditions—some of the data sets (red blood cell rotation, deformation, and alignment) can be described by Ca^* alone: Instead of the three input parameters (Ht, $\dot{\gamma}$, κ_S), Ca^* is sufficient to describe the observations! The reason for this astonishing behavior is the so-called 'tank-treading' of red blood cells. Thorough investigations revealed that tank-treading sets in at $\mathrm{Ca}^*_\mathrm{cr} \approx 0.2$ (fig. 10.10 and fig. 10.11). This is the case when the suspension shear stress becomes so large that the elastic stress of the membrane cannot maintain its characteristic biconcave shape, and the particle starts to rotate about its perimeter (like the track of a tank). When red blood cells are tank-treading, they behave nearly like isolated particles which are aware of the presence of their neighbors only via the suspension stress $\eta\dot{\gamma}$. This explains why even curves for different volume fractions collapse to a master curve for $\mathrm{Ca}^* \geq \mathrm{Ca}^*_\mathrm{cr}$ when plotted as function of Ca^*.

This data collapse is especially important for four observables: the tumbling velocity (fig. 10.10), the deformation state (fig. 10.14), the inclination angle, and the orientational ordering (both in fig. 10.15) of the red blood cells. When the cells are tank-treading, their mutual interaction is reduced, and particle collisions become less important. There are several independent observations supporting this idea: (i) The average inclination angle of the red blood cells becomes a function of Ca^* alone and, on top, cannot be distinguished from that of an isolated cell under the same rheological conditions (fig. 10.15). (ii) The nematic order parameter dramatically increases at $\mathrm{Ca}^*_\mathrm{cr}$ and reaches a plateau with the value ≈ 0.9. This indicates that the cells are strongly aligned (fig. 10.15). (iii) The average tumbling frequencies of the red blood cells decrease by more than one order of magnitude when the capillary number crosses the critical value 0.2. The interpretation is that the cells are in a nearly perfect tank-treading state without the need to tumble additionally. (iv) The average deformation state of the particles is a function of Ca^*, independent of the volume fraction. This is a hint that the suspension stress is the only relevant deformation mechanism for the red blood cells.

The reasons for shear thinning of blood commonly reported in the literature are the deformation (elongation), the tank-treading rotation, and the alignment of red blood cells [46]. In fact, the present simulations reveal that these three effects are tightly connected and not just independent mechanisms. The particle deformability eventually permits tank-treading when $\mathrm{Ca}^* \geq \mathrm{Ca}^*_\mathrm{cr} \approx 0.2$, irrespective of volume fraction, shear rate, or particle rigidity. Due to tank-treading, the particles do not have to tumble any more and have the ability to align with their neighbors, increasing the orientational order. This way, layers of particles can slide over each other more easily. These combined effects lead to a significant reduction of the suspension viscosity in the region $\mathrm{Ca}^* \in [0.1, 0.3]$ (fig. 10.12). However, also below the tank-treading regime, $\mathrm{Ca}^* < \mathrm{Ca}^*_\mathrm{cr}$, the deformability leads to shear thinning behavior because particles can slightly give way and free themselves more efficiently when they are locked. The microscopic particle behavior (rotation and orientational alignment) differs strongly from that observed for a system of rigid ellipsoids [248]. This is a clear argument for the need of resolved *and* deformable red blood cells when hemorheology is studied via a bottom-up approach.

The present work shows, for the first time, a thorough investigation of red blood cell displacements for varying volume fraction, shear rate, and deformability in simple shear flow. MacMeccan [194] reported that the diffusive behavior was not obvious in his simulations, not even after 30 inverse shear rates. However, only 200 red blood cells have been used, and no additional independent runs have been performed. In contrast to this, it was possible, within the present simulations, to compute the shear-induced diffusivities of red blood cells along the vorticity and the velocity gradient directions (fig. 10.18). In dimensionless units, the diffusivities were found to be about one order of magnitude smaller as compared to sheared, non-Brownian hard sphere systems with comparable volume fractions [94]. The simulations reveal that the diffusion coefficients decrease with increasing Ca^*, especially in the regime where tank-treading sets in. This is additional evidence for the idea that tank-treading allows the particles to decouple their motion from their neighborhood to some extend. Collisions become less frequent, the particle motions are less distorted, and the diffusivity decreases. Still, the diffusivities increase with the volume fraction, supporting the expectation that a denser system leads to a larger number of particle collisions.

No clear sign of a yield stress could be found. The observations indicate that, in the present parameter space, even for volume fractions of 65%, glassy rheology plays no role. No plateau in the mean square displacements has been seen (fig. 10.17), the non-Gaussianity of the particle displacements does not significantly deviate from zero (fig. 10.22 and fig. 10.23), and the shear-induced diffusivity still seems to grow with the volume fraction (fig. 10.18). The flow curves (fig. 10.7) may lead to the assumption that a yield stress could be found for volume fractions larger than 45%. However, it is not clear how the viscosity behaves for $\dot{\gamma} \to 0$. Simulations with smaller shear rates are required.

It has also been found that the local shear rate and particle shear stress are correlated. The Pearson product-moment correlation coefficient is always negative with values between -0.1 and -0.8, depending on Ht and Ca^* (fig. 10.30). This means that a local increase of the shear rate leads to a local decrease of the stress. This may be interpreted in the following way: When red blood cells are locked during their rotation, they decelerate the ambient flow, and the shear rate decreases. At the same time, the stress builds up because the particle cannot move. After some time, the stress is large enough to push the particle out of its unfortunate situation. It rotates again, the shear rate increases, and the stress relaxes.

11.2. Outlook and suggestions for future research

In this section, the most relevant open questions arising from the present work are pointed out, and suggestions for future research are given. The list is divided into two parts: aspects of physical nature and issues related to possible extensions and improvements of the numerical model.

Physical aspects

The suspension behavior at small shear rates should be studied in more detail. It has been discussed in sections 10.3 and 11.1 that the present rheology data cannot provide clear evidence for the existence of a yield stress. Although the viscosity for volume fractions above 45% increases strongly when the shear rate is decreased, its fate in the limit of small shear rates is unclear. Additional simulations are required to distinguish between one of three possibilities: (i) existence of a Newtonian plateau, (ii) existence of a finite yield stress, (iii) continuing non-Newtonian properties in the absence of a yield stress. The second step would be the identification and understanding of the circumstances (e.g., volume fraction, particle shape, and deformability) under which each of these three possible behaviors can be found. Based on those insights, it may be possible to establish a proper rescaling for collapsing the flow curves. It can be inferred from fig. 10.7 that this rescaling must at least contain the volume fraction and the capillary number because the viscosity ratios depend on the capillary number. Later on, the similarities and differences to hard sphere suspensions may be worked out systematically. It has to be noted that simulations at small shear rates are expensive, which sets a lower bound to the accessible shear rates.

The suspension behavior in the large shear rate limit may be further investigated. In particular, it could be worked out for which capillary numbers a Newtonian plateau is fully developed and how its value depends on the microscopic details and the volume fraction. It is expected that higher spatial resolutions are required because the particle deformation becomes severe and large membrane curvatures are common. If the resolution is not sufficient, the simulations tend to become unstable.

Finite size effects cannot be completely ruled out in the present work. In principle, it should be tested which minimum system size (both along the directions with periodic boundary conditions and along the gradient direction between the walls) is required to obtain invariant statistical properties. Along this route, it would be important to check for the presence of a correlation length between, for example, the dynamics of particles and to test how this length depends on the shear rate and volume fraction. If this length becomes comparable to the size of the simulation box, the system size should be increased. It is expected that this type of correlation length, if ever, becomes important at high volume fractions only. Another source of finite size effects are hydrodynamic interactions which are well-known to be of long range. This type of finite size effect is, however, negligible at high volume fractions but should be considered when studying intermediate to low volume fractions. In all these cases, a careful study of system size-dependence is compulsory.

Another important question is how individual particle dynamics (e.g., instantaneous rotation, deformation, or non-affine motion) correlate with stress relaxation events in the suspension. One possible mechanism for stress relaxation may be the rotation of two particles about each other after they have been locked. This should be visible as an anti-correlation of the fluctuation of the angular velocity of the particles and the time derivative of their stress: Whenever particle rotations are hindered, the stress may increase. When particles can rotate again after being locked, the stress may relax. It is reasonable to assume that the deformation state of the particles also changes during these events. To this end, a more detailed description of the particle deformation may be required. The approach based on the inertia tensor (section 10.2) seems to be too simplistic for this purpose. Including the individual energy contributions (strain and bending) stored in the membrane deformation may also provide additional information. A robust and unique definition of the instantaneous rotation velocity of the particles (both for tumbling and tank-treading) would be of advantage. This way, not only an average, but also rotation velocity distributions could be reported. Yet, as discussed in sections 10.1 and 10.4, it is not clear if a unique rotation velocity can be defined for a strongly deformable object at all. A point not addressed in this work is the spatial distribution of the particles and their displacements: Can, at least for a finite time interval, layers or shear bands be identified? Can the concept of radial distribution functions be extended to non-spherical and deformable particles, and does it carry relevant information? Is it possible to assess non-affine displacements of the particles which may be another mechanism for stress relaxation? Such an analysis is aggravated by the deformability of the particles: A collision of two particles may not be directly visible when only their centers are tracked.

It may also be rewarding to study the local energy dissipation and the bidirectional transfer from fluid kinetic to membrane elastic energy. It is not clear which significance the fluctuations of the elastic energy stored in the membranes has and how it is related to particle diffusion and stress relaxation.

The developed code can and should be used to simulate biological systems, such as flows with resolved red blood cells and platelets and their hydrodynamic interactions. The code has already been extended for the inclusion of multiple kinds of particles with different properties (e.g., shape, size, and elastic moduli), including platelets and polydisperse suspensions. Albeit of its critical importance for the human body, platelet margination[2] in the circulatory system is still not understood [52, 259, 260].

[2] Margination is the tendency of the platelets to move towards the blood vessel walls where they can seal tissue ruptures.

Technical aspects

Each of the simulations performed in chap. 10 required between one day and three weeks computing time, depending on the shear rate and the volume fraction of the particles. The total CPU time for all simulations was about 2500 days, i.e., seven years. It is unlikely to significantly increase the single machine efficiency in the future. Instead, in order to simulate larger systems for a longer number of time steps, parallel simulations are eventually required. The implementation of a parallel version of the simulation code is well advanced [261] and should be ready for use within a few months after the completion of this thesis.

Wall effects can be avoided completely by the use of Lees-Edwards boundary conditions [144, 145]. This would circumvent the problems related to the definition of a bulk region. The major drawback, however, is that these boundary conditions and the method of planes (section 9.4) are not compatible. Within the Lees-Edwards approach, there seems to be no direct local access to particle stress fluctuations. It may still be worth to study additional possibilities for stress evaluation in Lees-Edwards simulations because their advantages over wall-driven simulations are considerable.

Viscosity ratios other than unity and viscoelastic membrane properties may be implemented in the code as well (e.g., [43, 93, 203] and [88, 89, 183], respectively). These features could be used to model specific biophysical or industrial suspensions. With some additional effort, the membrane code could also be extended in such a way that mesh reconfigurations are possible (e.g., [83, 183]). This way, vesicles and even droplets could be simulated with the immersed boundary method. However, it has to be noted that for fundamental questions, such as the possible existence of a yield stress in dense systems of deformable particles, the simulation parameter space should initially be kept as small as possible to allow simpler interpretations of the observations.