5 Two-photon polymerization of inorganic-organic polymers for biomedical and microoptical applications

Abstract: Two-photon polymerization (2PP) is an attractive technique for the fabrication of arbitrary three-dimensional structures with feature sizes down to 100 nm. In this chapter, the potential of subwavelength structures for biomedical and microoptical applications is studied. We optimized the focusing of ultrashort laser pulses and developed new materials. Specially adapted refractive-diffractive hybrid optics were designed and constructed to maintain the sub-micrometer resolution of the fabrication process for the complete height of large-scale structures. New inorganic-organic polymers were synthesized and characterized with respect to their biocompatibility and biodegradability. Additionally, molecular modeling of inorganic-organic polymers was carried out to understand the structure and dynamics of monomers and polymerization products on a molecular level. 2PP-fabricated structures for the controlled growth of human endothelia in 2D and 3D cells are presented. Finally, microlenses, diffractive optical elements, and a diaphragm array for multi-aperture camera modules were fabricated and characterized with respect to their optical performance.

5.1 Introduction

Two-photon polymerization is a lithography technology capable of producing arbitrary three-dimensional structures with feature sizes as small as 100 nm [1, 2]. This is achieved by focusing ultrashort laser pulses into a UV-light curable resin, which is transparent for the applied laser wavelength. A polymerization reaction is initiated by two-photon absorption exclusively within the focal region, where the intensities are sufficiently high. By scanning the focus through the resin, arbitrary geometries can be fabricated with a resolution exceeding the diffraction limit of the applied wavelength. This unique property facilitates a wide range of applications such as photonic crystals [3–5], microoptical elements [6–8] and also biomedical devices, i.e. scaffolds for three-dimensional cell growth [9–11].

Modern applications impose challenging requirements on geometries and material properties of the structures fabricated. The desired structures should not only have sub-micrometer feature sizes but also large overall sizes. The materials should...
additionally be biocompatible and biodegradable for biomedical applications. Therefore, investigating illumination and applied materials is crucial for the fabrication of functionalized structures for biomedical and microoptical applications of 2PP.

In present state-of-the-art setups, the laser pulses are focused with oil immersion microscope objectives into the polymer. These objectives suffer from structuring-depth-dependent aberrations, due to the refractive index mismatch of polymer, immersion oil, and coverslip. As a consequence correction of these aberrations is required to maintain the intensity distribution (and consequently the resulting structure sizes) for different structuring depths. Inorganic-organic hybrid polymers such as ORMOCER®s\(^1\) have proven to be suitable materials for 2PP. However, on a molecular level the structure and polymerization reactions of these materials are not yet understood. Improved knowledge might enable synthesis of novel materials with smaller structure sizes.

In Section 5.2 the influence of aberrations on focal intensity distribution is investigated and a specially designed hybrid objective is introduced. Synthesis and properties of the applied inorganic-organic polymers, including the modeling of their molecular structures are discussed in Section 5.3. Finally, biomedical and microoptical applications are described in Section 5.4.

### 5.2 Hybrid optics

In the structuring process of 2PP, the polymerization reaction is triggered by the interaction of the polymer with the ultrashort laser pulses inside the focal volume of the optics. Thus, feature size and stability of the resulting structure is defined by the focal intensity distribution of the focusing optics employed. Since severe problems arise from the use of conventional microscope objectives, specially adapted focusing optics were constructed which might offer a solution to these problems.

#### 5.2.1 Conventional focusing with microscope objectives

In typical setups for 2PP, the laser pulses are focused by an oil immersion microscope objective with a numerical aperture (NA) of around 1.4 to achieve a minimized focal spot inside the polymer. These objectives are designed for a fixed setup determined by (1) the refractive index of the immersion oil \(n_d = 1.527\) and (2) the thickness \(d = 170\,\mu\text{m}\) and refractive index of the coverslip. Due to the large angles appearing in the beam path, even small deviations from these design conditions will result in

\(^1\) ORMOCER®: registered by the Fraunhofer-Gesellschaft zur Förderung der Angewandten Forschung in Deutschland e. V.
additional aberrations thus significantly increasing the focal spot size. In the case of 2PP, the most critical factor concerning aberrations is the refractive index mismatch between the polymer and the immersion oil. Additionally, standard microscope objectives are designed to focus on the back of the coverslip. If the focus is moved deeper into the volume of the polymer strong spherical aberrations will occur depending on the refractive index mismatch and focusing depth. These aberrations lead to decreased intensity with increasing structuring depth, changing the resulting structure sizes.

Several strategies have been proposed to compensate index-mismatch-induced aberrations in recent years. One method is to increase the applied laser power according to the focusing depth in order to compensate for the drop of peak intensity caused by the aberrations [12]. However, this method does not prevent focal spot enlargement and is cumbersome to implement experimentally. A more sophisticated technique uses a combination of a spatial light modulator (SLM) and an adaptive mirror [13]. This combination allows for the compensation of a large amount of aberrations, but requires the integration of additional devices into the setup. Another approach is to remove immersion oil and coverslip, and to dip the objective directly into the liquid polymer [14, 15]. In this configuration, the optical path will not change when the focus is scanned through the polymer and consequently the focal intensity distribution remains constant. However, it is challenging to achieve a diffraction limited focal spot, since the design conditions of the objective are not met. This can be achieved by using objectives with an integrated correction ring for spherical aberrations and the choice of a polymer with an appropriate refractive index.

Another major drawback of conventional microscope objectives is their limited working distance which is usually around 100μm and sets a fixed limit on the maximum structure height realizable. To overcome these drawbacks, specially adapted optics for focusing ultrashort laser pulses into a polymer were designed and assembled. These are corrected for refractive index mismatched induced aberrations and are not limited in the achievable structure height by the working distance.

### 5.2.2 Optical design

The layout of the optical design of the hybrid optics is shown in Fig. 5.1 (a) [16, 17]. The optics are optimized to focus 300 fs pulses with a central wavelength $\lambda = 515$ nm into the ORMOCER® OC-I. The centerpiece is an aspheric lens with NA = 0.66 (Edmund Optics, Stock No. #49-097). A half-ball lens is added as a solid immersion lens (ASIL) to further increase the NA without generating additional aberrations [18, 19]. An ASIL increases the NA of a lens by a factor of $n^2$, with $n$ being the refractive index of the ASIL [20]. The upper limit for the total NA is given by $n$. When looking at the optical layout (Fig. 5.1 (a)), the ASIL not only consists of the half-ball lens alone, but also the immersion liquid and the coverslip. The polymer without photoinitiator is used as the
immersion liquid. When the focus is moved deeper into the polymer, the thickness of the immersion oil is reduced by exactly the same distance. Consequently, the total thickness of the ASIL and the optical path remain constant. The final NA of asphere and ASIL is 1.30.

So far however, the optical design has only been discussed regarding monochromatic light without considering chromatic aberration. The optics work well at the central wavelength of the laser pulses ($\lambda = 515 \text{ nm}$) but show strong chromatic aberration for wavelengths at the edge of the spectrum. An approach to correct chromatic aberrations with as few optical elements as possible relies on the concept of refractive-diffractive hybrid optics. The basic idea is to exploit the reciprocal dependency on the wavelength to correct the chromatic aberration of a refractive lens with the diffractive power of a diffractive optical element (DOE) [21]. The phase function of the DOE was optimized using the commercial optical design software OpticStudio [22]. The resulting phase profile quantized by $2\pi$ was manufactured by means of laser lithography onto a 1.1 mm thick glass substrate (Borofloat, Schott). Figure 5.1 (b) shows the optical path difference for the hybrid optics including the DOE. The final optics have a diffraction-limited performance for the complete spectrum of laser pulses.

![Fig. 5.1](image)

**Fig. 5.1:** (a) Layout of the optical design of the hybrid optics. The DOE (diffractive optical element), asphere and half-ball lens are mounted as a fixed unit. The optics focuses on the back of the coverslip, where the polymer is drop casted. From [17]. (b) Optical path difference for the focusing optics. The DOE corrects the chromatic aberration for the complete spectrum of the laser pulses.

This first prototype was still limited by its working distance of 630 $\mu$m in achievable structure heights. To eliminate this restriction, a second design was realized where the coverslip was removed, as suggested by Bückmann et al. [14]. The hybrid optics are dipped directly into the polymer which can now be drop casted onto an arbitrary substrate.

Due to the aberration correction the hybrid objective enables structuring of sub-micron feature sizes with constant process parameters over the entire working distance range.
5.2.3 Experimental results

Prism-shaped structures with different heights were fabricated to demonstrate the improvements of the hybrid optics for three-dimensional structuring, using hybrid optics and an oil immersion microscope objective (Plan-Apochromat NA = 1.4, Zeiss MicroImaging GmbH, Germany) for focusing. The process parameters (average power, writing speed) were kept constant for all prisms. Scanning electron microscopy (SEM) pictures of the resulting structures are shown in Fig. 5.2. When focusing with the microscope objective, the prisms become more and more unstable with increasing heights, due to the writing-depth-dependent aberration. When hybrid optics are used for focusing, all prisms are stable and show sharp edges independent of their height. However, to verify diffraction-limited focusing of the hybrid optics direct measurement of either the point spread function or the wavefront of the optics is required, which is currently experimentally implemented.

![Fig. 5.2: Prism-shaped structures of different heights, fabricated with constant process parameters, for focusing with (a)–(c) microscope objective and (d)–(f) hybrid optics. The heights are (from left to right) 20 μm, 40 μm, and 60 μm, respectively. The surface qualities of the prism structures could be improved by applying adapted process parameters, e.g. smaller hatch distances.](image)

5.3 Inorganic-organic polymers

Inorganic-organic hybrid polymers such as ORMOCER®s are particularly suited for photonic and biomedical applications [23]. Their chemical and physical properties can be widely tailored to the specific application by the use of special alkoxy silane precursors and by control of the synthesis conditions [24]. The materials synergistically combine material properties of inorganic materials such as glass with those of polymer materials, typically resulting in thermally and chemically very stable materials which can be processed like classical photoresists via lithography methods in 2D and 3D.
Additionally, specific material compositions allow the control of the materials’ mechanical properties and surface functionalities which make them particularly suitable for cell growth investigations [25]. A completely new material feature makes it possible to physiologically degrade the materials [26] which can be processed analog to the classical ORMOCER® materials via one- or two-photon processes.

### 5.3.1 Synthesis and properties

A variety of ORMOCER®-materials were synthesized and specially adapted to the 2PP process in order to broaden the processing window for individual material formulations. The materials were chosen for optical and/or biomedical applications, and allow the generation of structures from sub100 nm [17] up to mm dimensions [23] which is a prerequisite for certain optical and biomedical applications. The synthesized ORMOCER®'s differ strongly in their chemical composition, their reaction kinetics, and their potential level of crosslinking behavior.

Table 5.1 summarizes some properties of the ORMOCER®'s used for 3D 2PP lithography.

<table>
<thead>
<tr>
<th>Material</th>
<th>–[SiO]_n (%)</th>
<th>Crosslinkable group</th>
<th>Degradable</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OPT</td>
</tr>
<tr>
<td>OC-I</td>
<td>25.5</td>
<td>methacrylate</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>OC-27sc</td>
<td>27.2</td>
<td>styryl</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>OC-DIM01</td>
<td>21.8</td>
<td>methacrylate</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>OC-IV</td>
<td>8.9</td>
<td>acrylate</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>OC-V</td>
<td>13.9</td>
<td>acrylate</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>OC-GM</td>
<td>8.8</td>
<td>methacrylate</td>
<td>✓</td>
<td>n. a.</td>
</tr>
<tr>
<td>OC-SVI</td>
<td>6.5</td>
<td>methacrylate</td>
<td>✓</td>
<td>n. a.</td>
</tr>
<tr>
<td>OC-SVII</td>
<td>7.5</td>
<td>methacrylate</td>
<td>✓</td>
<td>n. a.</td>
</tr>
<tr>
<td>OC-SVIII</td>
<td>14.7</td>
<td>methacrylate</td>
<td>✓</td>
<td>n. a.</td>
</tr>
</tbody>
</table>

Synthesis follows a general scheme of hydrolysis and polycondensation reactions, often referred to as a sol-gel reaction [24]. However, for the present material synthesis, gelation is often prevented by controlling the polycondensation reactions, thus providing materials which can be used analog to conventional negative tone resist materials [27, 28] with shelf lives of up to several years, depending on the material modification. Optical properties can be widely varied, yielding inorganic-organic hybrid polymer materials with low or high refractive indexes [29, 30], or low absorption losses at data and telecom wavelengths [27, 31]. In addition other material properties such as mechanical and thermal properties and surface functionalization can be
modified [24, 32]. Particularly with respect to applications in biomedicine, controlled variation of the mechanical properties (see Tab. 5.2) or the materials’ surface functionalization is a prerequisite for cell adhesion.

As shown in Tab. 5.1, most of the materials are suitable for photonic and/or biomedical applications. These materials are nonbiodegradable and extremely stable regarding their thermal, chemical, or mechanical properties. The materials’ inorganic content strongly varies, and is highest for the materials OC-I, OC-27sc, and OC-DIM01. OC-I and OC-27sc were also chosen for molecular modeling [33] (see Section 5.3.2) due to the fact that their still complicated chemical structure is the simplest of the synthesized material formulations and that their properties were thoroughly characterized. In addition, OC-I and OC-27sc are synthesized using identical synthesis conditions except for the exchange of the alkoxy silane precursor 3-methacryloxypropyltrimethoxysilane for p-styryl trimethoxysilane, thus changing the organic functional group for crosslinking.

OC-27sc in particular has yielded the smallest structure sizes via TPA patterning [17], making it an ideal candidate for molecular modeling. This is probably due to the styryl group which reacts slower than the methacrylate group in OC-I preventing a strong spatial propagation of the polymerization reaction. Figure 5.3 depicts fabrication results of a voxel size study (a) and photonic crystal structure (b) in OC-27sc revealing feature sizes of approx. 100 nm. Using μ-Raman spectroscopy, it was demonstrated that organic crosslinking in 2PP-fabricated structures can be as high as in UV-exposed layers (depending on the particular 2PP parameters). A C=C bond conversion of up to 75% was found for OC-I [17].

In the past, some ORMOCER®s have been reported to be biocompatible despite being typically nondegradable [23, 25, 34]. Since the latter feature is essential for certain tissue engineering and long-term biomedical applications, a new class of 2PP convenient ORMOCER®s was developed which contains biodegradable parts (see Tab. 5.1). Starting from a base material (OC-GM), the amount of organically crosslinkable groups, the spacer length connecting the inorganic and organic parts, the inorganic content, and the degree of polycondensation were modified in order to control the materials’ mechanical properties. In Tab. 5.2, the tensile strengths and Young’s moduli of the biodegradable hybrid polymer materials, henceforth referred to as RENACER®, are compared to those of natural tissue. The data clearly show that RENACER®s’ mechanical properties can be adjusted via their chemical composition and structure to meet those of natural tissue.

In order to investigate the degradation rate, a procedure was established to determine the mass loss of test samples prepared from the RENACER® modifications OC-GM, OC-SVI and OC-SVIII. The mass loss was determined using disks of about 200 mg which where incubated in different aqueous media at 37 °C. The medium was
Tab. 5.2: Mechanical data of RENACER® materials compared to natural tissue.

<table>
<thead>
<tr>
<th>Synthesized materials</th>
<th>Tensile strength (MPa)</th>
<th>Young’s modulus (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC-GM</td>
<td>4.3 ± 0.2</td>
<td>43.5 ± 2.6</td>
</tr>
<tr>
<td>OC-SVI</td>
<td>1.8 ± 0.2</td>
<td>18.9 ± 1.1</td>
</tr>
<tr>
<td>OC-SVII</td>
<td>30.3 ± 3.1</td>
<td>615 ± 116</td>
</tr>
<tr>
<td>OC-SVIII</td>
<td>12.5 ± 0.6</td>
<td>109 ± 11.1</td>
</tr>
</tbody>
</table>

Natural tissue

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tensile strength (MPa)</th>
<th>Young’s modulus (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>0.27 ± 0.14</td>
<td>n. a.</td>
</tr>
<tr>
<td>Vessel</td>
<td>1.4 to 11.1</td>
<td>n. a.</td>
</tr>
<tr>
<td>Aorta</td>
<td>1.72 ± 0.89</td>
<td>n. a.</td>
</tr>
<tr>
<td>Cartilage</td>
<td>≈ 5</td>
<td>n. a.</td>
</tr>
<tr>
<td>Hard tissue</td>
<td>n. a.</td>
<td>10 to 1500</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>n. a.</td>
<td>0.4 to 350</td>
</tr>
</tbody>
</table>

changed every week, and three disks were removed after one week, four weeks and four months, respectively. The disks were dried to constant weight using silica gel, and their mass loss was determined. Figure 5.3 (c) shows the mass loss of the base material in various buffer solutions. As the hydrolytic cleavage of most degradable groups is known to be pH-dependent [41, 42], buffers were chosen whose pH values differed significantly ranging from pH 4.5 (acetate buffer) to 9.5 (carbonate buffer). According to the literature physiological pH values also vary in a similar range, depending on specific body regions [43]. Thus, the influence of catalytically active ions like H3O+ or OH− on the mass loss was investigated.

As demonstrated in Fig. 5.3 (c) the samples show a pH-dependent mass loss with a maximum of 40% being observed for samples incubated in carbonate buffer (pH 9.5). This high mass loss is attributed to the presence of hydroxide ions in the setup.

In order to investigate the crosslinking behavior which is a prerequisite for further patterning by 2PP lithography, samples of the base material OC-GM formulated with a suitable photoinitiator were prepared between two cover slips separated by a 100μm thick spacer to ensure a preferably similar film thickness. Samples were light-irradiated in the range 380–520 nm, and subsequently analyzed by μ-Raman spectroscopy (WITEC Alpha 300). Since γ irradiation was used to sterilize these samples, spectra were taken from samples which had been irradiated, and also samples which hadn’t. The results are displayed in Fig. 5.3(d), where a close-up of the μ-Raman spectra is shown displaying just the stretching vibrations from the C=C bond at 1640 cm−1, and from the C=O bond at 1740 cm−1. Peak structure and shift of the C=O peak is a byproduct of the C=C conversion due to a lack of conjugation in the hybrid polymer compared to the former resin. These data indicate that the material is highly crosslinked. The material has a low residual monomer content which is required to achieve a high degree of biocompatibility. In addition, γ irradiation does not significantly impact the material’s structure, thus allowing the sterilization of the
samples prior to cell culture applications, for example which is a superior feature compared to the behavior of conventional ORMOCER®s which can only be sterilized in ethanol (cf. Section 5.4.1).

### 5.3.2 Molecular modeling

Considering structure sizes below 100 nm one of the most promising ORMOCER® materials is OC-27sc (see Tab. 5.1). Due to the large size of the molecules used in the polymerization reaction, the high molar masses, and the amorphous nature, the possibilities for experimental gathering of structural information are highly limited. However, an enhanced understanding of the underlying molecular structures is essential for a further reduction of possible structure sizes. Therefore, a modeling approach was applied, as described below.

Atomistic modeling of ORMOCER® materials is only feasible with force field methods for two main reasons: firstly, the resin consists of very large molecules; secondly, a proper description of the amorphous structure of the material itself demands large simulation cells containing more than one molecule. This results in simulation cells
with up to a few thousand atoms, which can only be described with force field methods employing acceptable CPU time.

In force fields, molecules are built up by hard spheres connected by springs, corresponding chemically to atoms and bonds between them. Typically, changes in bond lengths and bonding angles can be treated with harmonic potentials or with a combination of quadratic, cubic and quartic terms for increased accuracy. Other multi-body terms like torsions can be handled with different cosine-type functions. Cross-terms are added for a better description of vibrational modes. These allow for interactions between changes in bond lengths, bond angles and torsions. Intermolecular interactions are incorporated in terms of van der Waals and Coulomb forces. Any further influence of the electrons or the electronic structure is neglected. For this reason, only the different stages of a material during its synthesis can be modeled, excluding the reactions from one stage to another.

**Experimental procedure**

The chosen force field is crucial for the simulation, especially when complex systems like ORMOCER<sup>®</sup> materials are considered. The applicability of the COMPASS force field employed (Accelrys, BioVia) [44, 45] has already been proven in previous studies [33]. However, further validation procedures may be necessary if the system differs strongly from those previously treated (see below).

In contrast to [33], the models of the fluid phases and the resin were constructed using the “Amorphous Cell” module within Materials Studio, which uses a Monte Carlo search for the position of individual, in vacuo energy minimized molecules in the simulation cell under periodic boundary conditions (PBCs). For every model, 100 structures were generated and their energy was minimized. The structure with the lowest potential energy was chosen for the molecular dynamics simulations.

Molecular dynamics simulations for density calculation were performed under ambient conditions for 1 ns, the second half of the trajectory was used for analysis. All parameters used in the modeling can be found in the supplementary material (Section 5.6).

The synthesis of ORMOCER<sup>®</sup> materials is – as mentioned above – usually a two-step procedure: First, precursor molecules undergo condensation reactions between silanol groups forming siloxane bonds; the resulting product is called a resin, the resulting siloxane oligomers are designated as monomers for the following polymerization reaction. In the second step, the resin is polymerized via irradiation to the final material, the polymer. Molecular modeling methods may give valuable insight into the process at an atomistic level at each stage.
Results: precursors
At first, the precursors were modeled as pure condensed phases, either as crystals (diphenylsilanediol, DPD) or as liquids (p-styryltrimethoxysilane, pSTMS; see Fig. 5.4). The density is expected to be overestimated at small cell sizes, since in small cells only a few different orientations may be considered, leading to remaining ordered arrangements in the model. On the other hand, models comprising large cell sizes are computationally expensive. Therefore, it is necessary to find a suitable cell size which allows to use the density as a benchmark parameter for all models. In addition, these models may show the general suitability of the employed force field for density prediction and the use of molecular dynamics techniques for the compounds of the material.

![Structures of the molecules modeled as pure phases; the precursors of the material OC-27sc are shown in the top row.](image)

For the precursors, models containing more than 1000 atoms lead to stable results for the density (Fig. 5.5(a)). While the experimental value can be verified for DPD, the density of pSTMS is overestimated by about 1–2%. It was assumed that this effect might be attributed to the functional groups of pSTMS. In order to clarify this assumption the densities of three organic substances; trimethyl orthobenzoate (TMOB), benzene and styrene, were calculated in the same way. TMOB, a molecule with a structure comparable to pSTMS (the silicon atom is replaced by a carbon atom and the styryl functionality is missing; Fig. 5.4) shows similar behavior. In contrast, the calculated densities for benzene and styrene match the experimental ones (Fig. 5.5). However, very large models are needed in the case of benzene. It can therefore be assumed that the methoxy groups of pSTMS and TMOB cause higher densities for fluids showing low viscosities.
Fig. 5.5: (a) Densities obtained from molecular dynamics simulations for the precursors DPD (filled diamonds) and pSTMS (filled hexagons) versus the number of atoms in the simulation cell. Experimental values are shown as lines. For DPD, the experimental value is reached for cell sizes larger than 1000 atoms; for pSTMS, the predicted densities are overestimated by 1–2 % even for very large simulation cells. Results for the test substance trimethyl orthobenzoate (triangle, pointing down) obtained in a similar manner, show analog behavior to pSTMS, whereas for styrene (triangles, pointing up) and benzene (triangles, pointing left) the density calculations gave reasonable results.
(b) For resin models with the same composition (designated by one symbol each), large deviations of the calculated densities can be observed at small cell sizes. In most cases, enlargement of the cells by the construction of supercells of the starting structure led to a more precise prediction of the density (filled symbols).

Results: resins
A similar approach has already been published for another ORMOCER® system for the resin models [33]: forty resin cells were constructed from four different monomers, which were composed of four to fifteen precursor units each. Different types of monomers, containing rings, branched rings as well as linear and branched chains were considered. The deviations in density observed for the precursor models of pSTMS will influence the density calculations of the resin models as well. However, the effect is minimized since the number of methoxy groups is reduced in these mixed resins compared to the pure compound. The resin models typically contain only about 0.5–0.7 methoxy groups per silicon atom.

Differences in density between two different models with the same monomer composition can be observed for a few resin models (less than 10 %; Fig. 5.5 (b)). The precision of the density prediction can be increased by building supercells, i.e. increasing the cell size to a few thousand atoms to circumvent this effect. Nevertheless, these models are too large to gain results in reasonable CPU time if performed for all resin cells.

Most of the resin models resulted in densities which deviated from the experimental value by less than 3 %. There are no observable trends for special types of
monomers yielding better results. For example, models containing only linear chains exhibit similar deviations to models with branched chains or branched rings. This stands in contrast to the results of modeling of ORMOCER®-I, where the consideration of octaphenylcyclotetrasiloxane as a major condensation product led to a better description of the properties of the resin [33]. An analog behavior cannot be observed for OC-27sc, i.e. no preferred combination of the considered monomers was detected, each of the resin models led to reasonable results.

Results: polymers
The polymer models were obtained from all resin models by manually inserting bonds between two polymerizable groups and adding protons when needed until a conversion degree close to the experimental value of approximately 35–40% was reached. The deviation of the calculated densities from the experimental value is again mostly below 3% and even below 2% for 80% of the models. Typically, shrinkages of around 0.5–2.5% in volume can be observed (Fig. 5.6(a)).

Fig. 5.6: (a) Average densities from molecular dynamics calculations (0.5–1.0 ns) for polymerized models of OC-27sc versus equally computed densities of the corresponding resins. The styrene conversion was set near (triangles) or above (filled diamonds) the experimental value. The experimental densities are shown as grey bars, while the dark grey dotted lines illustrate the shrinkage during polymerization. Only two models with a high degree of conversion (i.e. the two diamonds in the upper left corner) of the resin and polymer models came close to the experimental density values. The estimated error for density prediction is calculated from the standard deviation and only plotted for one data point. (b) Shrinkage versus conversion degree for the models presented in (a). The experimental values are again shown as gray bars. The experimentally determined shrinkage can only be achieved at higher conversion degrees, while the shrinkage is underestimated at the expected conversion.
The shrinkage is underestimated in all models. Using higher conversion degrees than the experimentally determined ones can increase observed shrinkage (i.e. increase the polymer density; Fig. 5.6 (b)). However, with regard to the standard deviation calculated for density prediction, the results lead to a valuable conclusion: the models which are close to the experimental polymer density and exhibit good representation of behavior during polymerization are composed of monomers with less than ten precursor units and usually contain at least two branched monomers and rings. Therefore, it can be expected that such combinations of monomers lead to a good representation of the material OC-27sc.

A general drawback of the polymer model employed is the resulting polymer structure, which is only built up by very small units. This can result in an underestimation of polymer density and observed shrinkage. With more CPU time becoming available, the resin models may be enlarged and a more suitable polymer model with longer hydrocarbon backbones could be developed. On the other hand, the fact that a reasonable description of the polymer structure (as judged by the generally fair to good agreement of predicted experimental densities) is possible with small polymer building units suggests that the size of these units (mainly below 2 nm) will not influence the photochemical structuring process.

The studies published in [33] and in this section are the first serious approaches to the computational treatment of such complicated materials as ORMOCER®s. The complications arise from the generally amorphous state of the materials (as in all polymers), from their two step generation (different to many polymers), and especially from their organic-inorganic nature. Future work will concentrate on other ORMOCER® systems and will try to predict additional properties such as the Young’s modulus.

5.4 Applications

5.4.1 Biomedicine

Restoration of diseased or damaged tissue remains one of the great challenges in regenerative medicine. The growth of cells on 3D porous scaffolds for tissue engineering (TE) is a promising approach for the generation of autologous tissue.

In addition, to understand the interactions between cells and their microenvironment, new tools have to be created by combining surface chemistry, material sciences and microfabrication techniques. Since many cellular responses are the result of intracellular signaling events being triggered by the interaction of cell surface receptors with particular components of their environment [46] diverse aspects of cellular processes, such as proliferation, migration, differentiation or apoptosis cannot be analyzed correctly using standard cell-based assays. An interaction with appropriate surfaces is a general prerequisite for the survival of adherent cells in that it allows
the formation of adhesive forces required for subsequent cell spreading. Aside from the plain surface chemistry characterized by the types of interacting partners (like extracellular matrix (ECM) proteins) their density, spatial distribution and conformation have also been reported to be important surface features [46–50]. Thus, it could already be demonstrated that certain cellular responses depend on the mechanical compliance of cell-adhering substrates as well as on their local distributions [51, 52]. The ability to control the spatial chemistry, geometrical patterning and stiffness of the desired substrate might therefore provide important insights into the fundamental aspects of cell-scaffold interactions [53, 54]. This might be translated into tissue engineering approaches focusing on a precise control of cell adhesion, spreading, growth, and differentiation provided by chemically and spatially designed surfaces created by 2PP lithography. In particular, sub-micron feature sizes at the surface of 3D scaffolds are assumed to promote cell adhesion and growth.

The preparation of biological samples follows different routines, depending on which type of cells will be seeded onto the structures. The cells used for these investigations were primary endothelial cells, i.e. human microvascular endothelial cells (mvECs). These cells first have to be isolated from tissue samples as previously described [55].

Cells were cultured at 37 °C, 5% CO₂, and 95% relative humidity in standard cell culture incubators. Cells were propagated up to a maximum of 4 passages or unless they were transferred onto ORMOCER® structures. In order to evaluate the cell cultivation on 2PP patterned samples, different geometries (circular structures, crossed lines, parallel lines, etc.; see Fig. 5.7) with varying lattice sizes were fabricated in OC-I.

Cell viability was analyzed using the WST-1 (water soluble tetrazolium-1) reagent (Roche Diagnostics, Mannheim, Germany) according to the supplier’s instructions. Due to metabolic activities, WST-1 is reduced by cellular hydrogenases forming a formazan which can be photometrically analyzed at 450 nm. To visualize the cells in microscopy, HE (Hematoxilin/Eosin) stainings were performed according to standard protocols. The samples were mounted with DAPI-Fluoromount-G® in order to stain their nuclei (SouthernBiotech, Birmingham, AL, USA).

To initially determine whether residual compounds derived from ORMOCER® production processes might be cytotoxic, glass slides were covered with OC-I without having been structured by 2PP. After incubation, a development step was carried out analog to the development after 2PP patterning. As control samples, untreated glass slides were used. The glass slides were transferred into 6-well-plates and incubated with VascuLife® ECGMmv medium for 24 h at 37 °C, 5% CO₂ in a water-saturated atmosphere in a CO₂ incubator. After incubation, the medium was removed and hmvECs were seeded at a density of 2 x 10⁵ cells per well. After the cells were grown to confluence, the slides were removed from the 6-well plates, gently washed with PBS, fixed using a 4% para-formaldehyde solution, and afterwards stained with hematoxylin and eosin (HE).
Fig. 5.7: SEM images of structures on glass substrates fabricated for biomedical applications. (a)–(c) Test patterns for cell cultivation experiments fabricated from OC-I. (d)–(e) Tubular structures for cell cultivation with anchor points for promotion of cell adhesion (OC-V). (f) Test pattern to demonstrate applicability of OC-SVII for 2PP patterning.

The cells grew as a monolayer to confluence on both surfaces, indicating that the substrates used are not cytotoxic. However, cells detached partially from the untreated glass slides during the fixation process, which was not observed in case of the OC-I treated surfaces. Additionally, the cells grown on OC-I treated glass slides reveal slight differences in their overall morphology in that they appear more spread compared to those grown on the untreated controls (data not shown). This might indicate that more and/or stronger adhesion contacts were formed between the hmvECs and OC-I coated substrates, for example.

However, in cell biology interactions between adherent cells and their non-cellular environment (e.g. the extracellular matrix) are typically facilitated by the formation of so-called focal adhesions (FAs) which represent specific types of large macromolecular assemblies through which both, mechanical force and regulatory signals are transmitted to the cellular interior [56]. FAs resemble dynamic protein complexes which are in a state of constant flux in that they continuously associate and dissociate from the substrate. These interactions are limited to a clearly defined distance of 15 nm between the plasma membrane and the particular substrates, however [57]. The first experiments shown earlier did not answer the question of whether the observed adhesion is solely dependent on altered surface chemistry, a spatial topological distribution of the substrate, or on both parameters.

In order to test topological effects on cell adhesion or cell morphology, a variety of structures (linear, circular, or quadratic structures) fabricated by 2PP of OC-I on glass slides (Fig. 5.8 (a)–(d)) were used as substrates for hmvECs. The structures were fabri-
Fig. 5.8: Cultivation of hmvECs on 2PP patterned OC-I. (a)–(d) HE-stained cells grown on glass slides decorated with different OC-I structures. (e) Microvascular endothelial cell (Upcyte® HDMECs, Medicyte GmbH, Heidelberg) grown on OC-GM structures. Nuclei appear blue due to DAPI staining. Immunohistological staining of β-tubulin (filaments) appears green.

In order to visualize the overall morphology of the endothelial cells used, the samples were fixed and stained with HE. In general, cells grown on linear patterns show a more spindle-shaped morphology (see Fig. 5.8 (a) and (b)) compared to those grown on circular (Fig. 5.8 (c)) or quadratic patterns (Fig. 5.8 (d)). Also, the distance between 2PP-written ORMOCER® structures significantly influences cell growth and morphology. In the case of linear structures, the majority of cells grew within the structures if those were separated by 15 μm. Increasing the distances to 25 μm clearly resulted in altered cell growth and cell morphology. Using these distances, the cells seemed to grow – at least partially – on top of the structures. These phenotypological differences were further analyzed by immunohistological stainings of actin filaments, which are essential components of the cytoskeleton. These stainings clearly revealed that the actin filaments were oriented parallel to the linear OC-I structures only if those were separated by 15 μm. In all other cases, the actin filaments were found to be in a random orientation (data not shown). Astonishingly, using quadratic or circular struc-
tures the cells grew within the structures if separated by 25 μm, whereas they grew on top of structures with 15 μm distances, the opposite behavior to linear structures.

Alongside biocompatibility, scaffolds used for TE approaches should also be biodegradable. First 2PP patternings were therefore carried out using a RENACER® as biodegradable material. 2PP-written cubes were created in SV-II, and the first results are shown in Fig. 5.7 (f). The programmed cube dimensions are $10 \times 10 \times 7.5 \, \mu m^3$ fabricated with a variation in process parameters such as the average laser power (decreasing from top to bottom) and hatching distance (decreasing from left to right). It can be seen that only a certain set of laser power and hatching distance yielded well-shaped cubes. It turned out that a hatching distance of $\Delta x = 0.1 \, \mu m$ and laser power of $P = 1800 \, \mu W$ are suitable for structuring SV-II material. As for any other hybrid material synthesized so far (see Tab. 5.1), this material modification also shows promising patterning results for further scaffold fabrication to be used for cell growth. Primary endothelial cells (Upcyte®, Medicyte GmbH, Heidelberg, Germany) were grown on these as described above (see Fig. 5.8 (e)). The cells adhere well to the substrate, and show a typical cellular morphology. Cell division can be observed by immunostaining using DAPI and anti-Tubulin β antibodies.

In summary, the ORMOCER® structures obtained by 2PP fulfill all criteria of substrates which can be used in standard 2D cell culture systems as well as in innovative 3D tissue engineering approaches. First results, depicted in Fig. 5.7 (d) and (e), using conventional microscope objectives demonstrate the general feasibility of small tubular structures with varying diameters, randomly distributed pores, and tiny ($\approx 100 \, nm$) anchor points, which might promote cell adhesion (the results of these experiments will be published elsewhere). Current work focuses on the application of the hybrid objective (see Section 5.2) in order to produce large ($> 1 \, cm$ in length and $> 500 \, \mu m$ in diameter) artificial vessels possessing sub-micrometer anchor points which can subsequently be used as scaffolds for vascularization.

5.4.2 Microoptics

Microoptical applications can benefit from 2PP fabrication in multiple ways. Due to the intrinsic ability to fabricate arbitrarily shaped surfaces, new designs with complex topologies for microoptical structures can be implemented. Furthermore, 2PP can trigger refractive index modifications which enable the fabrication of three-dimensional waveguides [58]. In order to obtain microoptical elements with good optical performance, the roughness and waviness of the surfaces must be smaller than 100 nm.

2PP fabrication of diffractive optical elements

The fabrication of diffractive optical elements (DOEs) for laser beam manipulation is typically carried out using state-of-the-art lithography techniques such as electron
beam lithography [59, 60]. As these methods are two-dimensional processes, the DOE topographies realized are binary which affects the achievable diffraction efficiency. The conventional 2D processes must be repeated several times in order to fabricate multilevel DOEs, which significantly increases the price of fabrication and decreases the yield [61]. Jia et al. proposed 2PP for DOE fabrication in 2007 [62]. However, their strategy of fabrication is limited in throughput. Also the shape of the pixels, which make up the entire DOE, is aberrant.

In this study a new strategy for DOE fabrication was developed: instead of scanning the laser focus in 3D pixel by pixel, the entire DOE area is scanned with high velocity scan stages. The “position synchronized output” (PSO) feature of the positioning system controller is used to trigger the laser rapidly and accurately whenever the scanning path intersects with a DOE pixel. Thus, the feed rate can be increased to around 10 mm/s in contrast to commonly used techniques [7, 62]. The procedure is repeated for each of the desired DOE height levels – typically 16. Figure 5.9 (a) depicts a $640 \times 640 \mu m^2$ DOE fabricated from OC-V with very accurate reproduction of lateral pixel geometries. Here, a total interval between the lowest and highest pixels of 1.29 $\mu$m, corresponding to a $2\pi$ phase shift at the design wavelength $\lambda = 632.8$ nm was used. Topography characterization was carried out using laser scanning microscopy (LSM). The results shown in the inset of Fig. 5.9 (a) reveal good agreement between DOE design and the fabricated structure. As the entire height of the DOE is of the order of a micron, it is obvious that sub 100 nm height control is mandatory for the fabrication of functional DOEs. This could be accomplished by the choice of illumination and hatching strategy as well as by an appropriate choice of laser parameters and optical material. Despite the well-defined topography, the optical performance still has to be optimized. When observing the resulting diffraction image on a screen (Fig. 5.9 (b)), the Statue of Liberty can be identified as calculated by the design. However, the zero$^{\text{th}}$ order is still dominant and pronounced speckles occur over the entire image. For this reason, the influence of the structuring parameters on the resulting pixel heights is to be investigated in more detail in the future. Furthermore, the effect of the pixels’ edges on the diffracted intensity distribution will be taken into account.

**Microlenses**

The fabrication of microscopic beam steering or focusing elements applying 2PP is well-known in the literature [7]. Applications as collimators on fiber tips and as micro-Fresnel lenses have been demonstrated [59, 63]. Despite the impressive proof-of-principle in these papers, it is important to increase the throughput and to validate the performance of 2PP-fabricated microoptical components for real-life applications.

In the following section, 2PP-fabricated microlenses which were created with a new hatching strategy are demonstrated. In contrast to conventional 3D scanning of the entire lens volume, only the shells of the microlenses are polymerized by 2PP and the liquid core is solidified after the development process using conventional UV
illumination. In addition, the shell of the surface of the lens was hatched using an annular scanning strategy. This allowed for the fabrication of very smooth surfaces with low surface roughness. In order to achieve this goal, the beginning and end of each hatching circle was distributed randomly on the lens surface. Tangential lines for acceleration and deceleration were introduced to compensate for the mass inertia of the positioning system. Figure 5.9 (c) depicts an SEM image of lenses fabricated from OC-V using this strategy. Without additional measures, our fabrication strategy reduces the duration for the fabrication of a single lens to between one and two minutes (depending on the lens radius). This is still subject to further improvements as the axis feed rate was only set to 500 μm/s. As a result of this increase in throughput, microlens arrays can be rapidly fabricated with high surface finishes.

The characterization of lens topography was carried out using atomic force microscopy (AFM) and LSM, and both methods deliver consistent results. A typical surface scan is depicted in the inset of Fig. 5.9 (c). Both AFM and LSM topography characterization reveal negligible deviations from the design geometry and very low surface roughness.
As in 2PP the photon dose (feed rate and pulse energy) determines the resulting voxel size and as a result voxel size combined with hatching distance during structure formation impact surface topography. It is important to understand the impact of these parameters on the surface roughness. It was possible to show for example, that by using 1 mW of average power, a hatching distance of 0.4 μm at a feed rate of 500 μm/s resulted in an rms-roughness of 29 nm on planar surfaces. In comparison, the roughness resulting from 4 mW, 0.1 μm at the same feed rate is below 4 nm. However, the rms-roughness of the microlenses fabricated applying these parameters was considerably higher with 67 nm. In addition to the roughness investigation, AFM/LSM measurements also revealed that shrinkage after UV light polymerization is negligibly small.

The focusing behavior of the fabricated microlenses was investigated using a modified confocal microscope. The lens is illuminated by a collimated and spatially homogeneous laser intensity distribution and the focused intensity is then probed in 3D by a high-NA microscope objective. Figure 5.9 (d) illustrates the characterization by means of several slices of the focal intensity distribution and a fit through the lateral intensity in the focal plane \((z = 0)\). It could be demonstrated that focal distance, beam waist \((w_0 = 0.63 \, \text{μm})\), and the Rayleigh length corresponded well with theory.

Current work focuses on the implementation of custom-designed aspherical surfaces, particularly designed for aberration-free focusing. Moreover, the positioning system can provide feed rates higher than the 500 μm/s finally employed. Decreasing the fabrication time of a single microlens down to only some tens of seconds is conceivable in the future. This advance in process acceleration has to be accompanied by further material research as the ORMOCER®’s polymerization rate has to keep pace with increasing scanning speeds.

**Diaphragm array for multi-aperture cameras**

A multi-aperture approach relying on microlens arrays is a promising candidate to further miniaturize digital real-time vision systems [64–66]. In these multi-aperture camera modules, individual optical channels capture different portions of the overall field of view (FOV). A super resolution imaging approach in combination with the segmentation of the FOV allows for a reduction of the focal length of the microlenses and consequently leads to modules with shorter total track lengths. Furthermore, the fabrication is based on wafer-level process technology allowing the parallel and cost effective fabrication of several hundred modules at once.

Figure 5.10 (a) shows a schematic crosssection of the optical layout of a multi-aperture camera module. An important issue of these modules is optical cross talk, which appears when light is imaged from one microlens onto the sensor area of a neighboring channel and causes so called “ghost images”. To prevent this cross talk a special diaphragm array is necessary (Fig. 5.10 (a)). These diaphragm arrays consist of 600 μm high tubes with a tapered profile, a diameter of 38 μm at the top and
34 μm at the bottom (Fig. 5.10 (b)). Additionally, these tubes are undercut with angles up to 30 degrees depending on their position over the sensor. These challenging geometries are impossible to fabricate with conventional lithographic technologies. However, two-photon polymerization allows the direct structuring of these tilted tubes into the polymer. Because of the large height (600 μm) of these tubes, hybrid optics (see Section 5.2) are applied to focus the laser pulses during the structuring process. The feasible structure heights are not restricted by the working distance when using the hybrid optics which, furthermore, are corrected for structuring-depth-dependent aberrations. Figure 5.10 (c) shows a microscope image of the structured diaphragm array. It consists of 135 channels and its total size is 7 mm × 4 mm × 0.6 mm.

The intermediate spaces of the fabricated diaphragm array were subsequently filled with an epoxy resin, and then replicated into silicon. This silicon master structure was used as a mold to replicate the diaphragm arrays with a black epoxy resin as the final material. This process chain allows fast fabrication of the diaphragm arrays suitable for mass production, since only the master structure of the mold is fabricated using two-photon polymerization with its long writing times. Figure 5.10 (d) shows a replicated diaphragm array mounted on the imaging sensor. The segmented image of a test chart taken with the multi-aperture camera module without the diaphragm array is depicted in Fig. 5.10 (e). The central object reappears as ghost images in the outer channels. When the diaphragm array is integrated into the module, these ghost images are suppressed and the object only appears in the central channels (Fig. 5.10 (f)).
5.5 Conclusion

In order to utilize 2PP for applications in microoptics and biomedicine, illumination for the structuring process as well as the synthesis and properties of the applied materials were investigated. For the fabrication of structures combining smallest feature sizes with heights up to the mm range, a specially adapted refractive-diffractive hybrid objective was designed and assembled. This objective is corrected for structuring-depth-dependent aberrations and is not restricted by a working distance in achievable structure heights. Due to the aberration correction of the objective the sub-micrometer resolution of the structuring process can be maintained even for structures with heights in the mm range.

ORMOCER®s were investigated with respect to their mechanical and optical properties, their suitability for structuring with 2PP, and possible applications. With ORMOCER® OC-27sc, smallest structure sizes below 100 nm were obtained. In order to understand this complex material on a molecular level, molecular modeling simulations were carried out for its precursors, the resin, and the polymerization products. The results obtained are a first step towards prediction of material properties, thereby facilitating the synthesis of novel functionalized materials.

The novel biodegradable material class RENACER® was developed especially for biomedical applications. These polymers show good crosslinking behavior for patterning with 2PP and the mechanical properties of the solidified structures are similar to those of natural tissue, making them an excellent material choice for tissue engineering.

It was also shown for the first time that the ORMOCER® OC-I is biocompatible for the growth of primary human endothelial cells. These cells are crucial for the artificial creation of human blood vessels. A combination of suitable materials and 2PP structuring techniques might provide scaffolds e.g. for artificial vessels with all required pores and anchor points. Future work will focus on upscaling 3D structures towards the mm range and applying the newly synthesized RENACER® material.

Fabrication time and accuracy of microoptical elements fabricated with 2PP were improved with adapted structuring strategies demonstrated by a DOE with 16 levels and a writing speed of 10 mm/s. Microlenses with a surface roughness of 67 nm (RMS) were fabricated by applying an angular scanning method. Furthermore the focusing behavior of the microlenses was characterized. A large-area diaphragm array was fabricated to further improve the imaging quality of multi-aperture camera modules. The array consists of 135 diaphragms with heights of 600 μm and suppresses ghost images, which appear due to optical cross talk between neighboring channels.

In conclusion, combined with the use of existing and newly synthesized inorganic-organic polymers the novel focusing concept enabled the fabrication of structures featuring demanding geometries and adapted properties for biomedical and microoptical applications, using 2PP.
5.6 Supplementary material

Tab. 5.3: Molecular modeling – experimental parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>– Software</td>
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<tr>
<td>– Force field</td>
<td>COMPASS</td>
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<tr>
<td><strong>Energy summation:</strong></td>
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<td>– van der Waals interactions</td>
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<tr>
<td>– Coulomb interactions</td>
<td>Ewald summation, accuracy $10^{-5}$ kcal mol$^{-1}$</td>
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<tr>
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<tr>
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<tr>
<td><strong>Quenched dynamics:</strong></td>
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<td>NVT</td>
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<tr>
<td>– Temperature</td>
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<tr>
<td>– Time, time step</td>
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<tr>
<td>– minimized every</td>
<td>100 steps</td>
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<tr>
<td><strong>Molecular dynamics:</strong></td>
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<td>– Ensemble</td>
<td>NpT</td>
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<tr>
<td>– Integration scheme</td>
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<td>– Pressure</td>
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<td>– Output every</td>
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<td>– RAM</td>
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References


[41] Iordanskii AL, Rudakova TE, Zaikov GE. Interaction of polymers with bioactive and corrosive media. VSP Utrecht, The Netherlands; 994.


