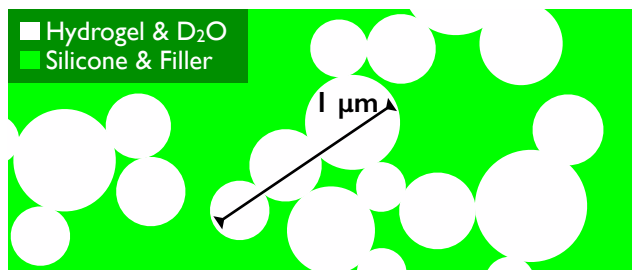


Graphical Abstract

The microscopic distribution of hydrophilic polymers in interpenetrating polymer networks (IPNs) of medical grade silicone

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Highlights

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- Swelling IPNs with D₂O introduces contrast for neutron scattering experiments
- Spin-echo small-angle neutron scattering (SESANS) can resolve IPN structure
- The different regions in IPNs are several hundred nm in diameter

The microscopic distribution of hydrophilic polymers in interpenetrating polymer networks (IPNs) of medical grade silicone

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ABSTRACT

By introducing hydrophilic polymers into silicone medical devices, highly beneficial biomedical properties can be realized. An established solution to introduce hydrophilic polymers is to form an interpenetrating polymer network (IPN) hyperforming the hydrogel synthesis in the presence of silicone swollen in supercritical carbon dioxide. The precise distribution of the two polymers was unknown, and determining this is the goal of this study. Neutron scattering and microscopy were used to determine the distribution of the hydrophilic guest polymer. Atomic force microscopy revealed that the important length scale on the surface of these materials is 10–100 nm, and spin-echo small-angle neutron scattering (SESANS) on IPNs submerged in D₂O revealed structures of the same scale within the interior and enabled quantification of their size. SESANS with hydration by D₂O proved to be the only scattering technique that could determine the structure of the bulk of these types of materials, and it should be used an important tool for characterizing polymer medical devices.

1. Introduction

Many medical devices are made of silicone elastomers due to their advantageous properties, soft and flexible, yet tough and robust, highly chemically resistant, and with good biocompatibility. The hydrophobic surface of silicones makes them prone to bacterial attachment, which can lead to biofilm formation and hospital acquired infections [1]. Due to the high surface tension of water [2], it is energetically favorable for cells to attach to surfaces rather than remain in the medium, and making the surface of medical devices more hydrophilic can alleviate this. Hydrophilic surfaces could be created in several ways. Biomaterials could be produced solely from hydrogels, but these have poor mechanical properties [3, 4]. Hydrophilic coatings could be applied, but they are difficult to maintain. Interpenetrating polymer networks (IPNs), networks of interlaced materials on a molecular scale that are not covalently bonded and cannot be separated unless chemical bonds are broken [5], are another way to increase the surface tension of medical devices [4]. These are the type of materials that will be studied here.

Two types of manufacturing techniques for producing IPN exist: the simultaneous method, where the two networks are synthesized simultaneously via orthogonal paths, and the sequential method, where one network is synthesized within

an already prepared one, [6]. We prepared IPNs using the sequential method from silicones and hydrogels where supercritical CO₂ was used to introduce the hydrophilic, hydrogel-forming monomers into the swollen silicone, as previously reported in the literature [7, 8, 9, 10, 11, 12]. Supercritical CO₂ ($T_c = 31.1$ °C, $P_c = 73.8$ bar) is an attractive synthesis medium, due to its gas-like diffusion and liquid-like density, which can be tuned easily by changes in pressure [13]. Polydimethylsiloxane (PDMS), an example silicone, is known to have, for a non-fluorinated polymer, an extremely high solubility in supercritical CO₂, which makes cross-linked silicones swellable in the solvent [14].

Despite this previous work, the precise distribution of the two polymers is not yet well-understood. Are the two networks fully intertwined? Do they phase separate into hydrophilic and hydrophobic domains? Significant previous research effort has shown that these IPNs are known to act as efficient drug delivery systems [7, 8, 9, 15, 16], to treat or inhibit infections associated with catheters [17, 18], and to release antibiotics and provide effective antimicrobial surfaces [7, 8, 11, 12]. The efficacy of these beneficial properties will be controlled by the distribution of the two polymers (hydrophilic hydrogel and silicone), but previous efforts using microscopy have not been able to reveal this [19, 7, 10]. Therefore, finding a way of characterizing the structure of these IPNs is important.

As imaging techniques have so far prevented direct determination of the distribution of the hydrogel network, scattering techniques were used as the primary tools. Although there are several reports on investigating the structure of IPNs by small-angle scattering (SAS) [20, 21, 22, 23, 24, 25, 26],

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Compound	ρ_m (g cm ⁻³)	ρ_X (10 ⁻⁶ Å ⁻²)	ρ_N (10 ⁻⁶ Å ⁻²)
PHEMA [28]	1.315	12.0	1.21
PDMS [29]	0.969	8.95	0.06
Silica (SiO ₂) [30]	2.305	19.8	3.64
H ₂ O [31]	0.998	9.45	-0.56
D ₂ O [32]	1.105	9.41	6.36

Table 1

Mass densities (ρ_m) and X-ray (at Cu K α) and neutron scattering length densities (ρ_X and ρ_N , respectively) of materials used. PHEMA and PDMS are used for the hydrogel and silicone components respectively. (Note that the SLDs for PHEMA and PDMS are shown, but the actual SLDs in this study may differ as the hydrogel is a copolymer of PHEMA and the silicone is crosslinked elastomer.)

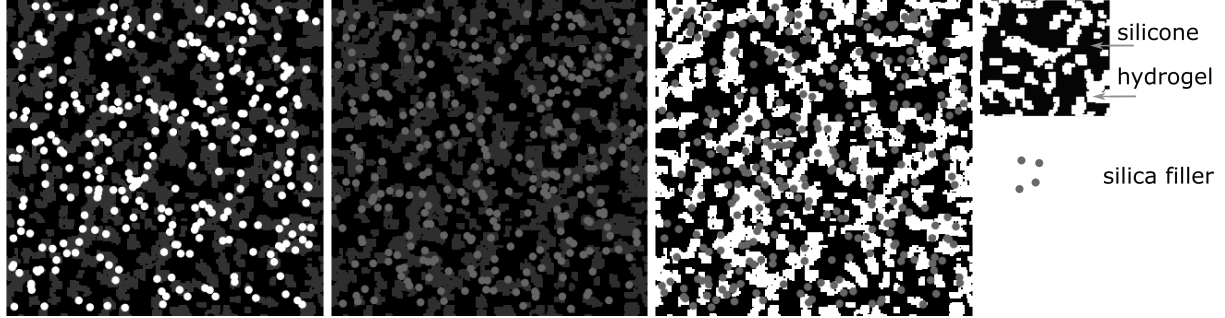


Figure 1: Schematic of the contrast for hydrated-hydrogel in silicone for different scattering measurement. (Left) In an X-ray scattering measurement, the hydrogel is effectively matched to the silicone and the structure of the silica filler is dominating. (Middle) For H₂O-hydrated hydrogel in a neutron scattering measurement, the hydrogel has a small contrast with the silicone but so does the silica filler. (Right) For D₂O-hydrated hydrogel in a neutron scattering measurement, the hydrogel has a very large contrast with the silicone and the hydrogel structure dominates the scattering.

the number of reports on the structure of silicone-hydrogel IPNs is limited [27, 25, 26, 21]. Data analysis on commercial silicones can be plagued by the presence of silica filler particles, which are introduced to improve the mechanical stability, but they can dominate the scattering. Despite the presence of fillers, devices made from medical grade silicones contain them, and to find methods that can study application-relevant systems requires accounting for their presence.

Neutron scattering, in particular, makes for an ideal method to study a material like this because it can highlight specific parts of the material, for example, by swelling the hydrogel with heavy water. The deuterium nuclei (²H or D) in heavy water (D₂O) interact differently with neutrons than protium nuclei (¹H). When contrast is obtained in this way, the scattering from deuterated material should dominate over the scattering from the filler particles, and thus enable investigation of the hydrogel structure. A further advantage is that D₂O will only enter surface connected hydrogel, and it is thus exactly the hydrogel volume responsible for transporting polar small molecules (water or drugs) that will be highlighted. The differences in scattering length density (SLD), characterizing the molecular ability to scatter either X-rays or neutrons, between all the species used in this study are shown in Table 1. In Figure 1, the contrasts for the different scattering techniques are shown schematically.

To achieve our goal of determining the distribution of the polymers in these IPNs, we use a combination of mi-

croscopy and scattering to study them. Atomic force microscopy (AFM) was used to image the surface of the IPNs. Neutron scattering (specifically the variant, spin-echo small-angle neutron scattering or SESANS) was used to study the morphology of the IPN. SESANS can access longer length scales (on order of 10 μ m) than accessible by conventional SANS and in real space. Together these techniques enable a structural characterization of these IPNs in more detail than has previously been possible. As the potential of using these IPNs as medical devices has already been demonstrated by various assays [8, 9, 10], the focus is to study the distribution of the two polymers in the IPNs, which AFM and SESANS have been used to determine for the first time.

2. Experimental

2.1. Materials

Square SR330MA/MB silicone is a medical grade material that was supplied by Shenzhen Square Silicone Materials Co., Ltd. (China). Sylgard 184 silicone was supplied by Dow Corning.

2-Hydroxyethyl methacrylate (HEMA, 97%) with 200 ppm monomethyl ether hydroquinone (MEHQ) as inhibitor, poly(ethylene glycol) methyl ether acrylate (PEGMEA, average $M_n = 480$ g mol⁻¹) with 100 ppm butylated hydroxytoluene (BHT) and 100 ppm MEHQ as inhibitor, and ethylene glycol dimethacrylate (EGDMA) cross-linker were used

as monomers for the hydrogel synthesis. An inhibitor remover column packed with quatamine divinylbenzene/styrene copolymer beads on Cl ion form (De-Hibit 200) supplied by Polysciences (USA) was used (following instructions given on the technical data sheet) to remove inhibitor before use. HEMA was further purified by distillation at reduced pressure, the fraction at 67 °C and 3.5 mbar was collected. Both monomers are stored at 5 °C.

The cosolvents ethanol (EtOH, 99.9%) and tetrahydrofuran (THF) were all used as received. Oxygen-free CO₂ 4.0 was supplied by Aga Denmark A/S (Denmark) and used as received.

All chemicals were supplied by Sigma–Aldrich (Germany), unless otherwise stated.

2.1.1. Host Polymer

Two types of commercial silicone elastomer are used for the IPNs. Square SR330MA/MB silicone was hot plate molded to hollow cylindrical specimens (length 4 cm, inner diameter 4.0 mm, wall thickness 0.5 mm). Sylgard 184 was mixed 20:1 then entrapped air was removed by applying a vacuum, the mixture was poured into Petri dish to make flat samples with a thickness of 2.0 mm. The silicone samples were then cured in an oven at 150 °C for 18 h. We know from previous experience that the Square silicone contains nanoparticulate silica particles as mechanical fillers. These particles dominate the scattering of X-rays, and for this reason the samples based on Sylgard 184 silicone, which do not show the same amount of scattering from filler material, were also studied.

2.1.2. Initiator synthesis

Diethyl peroxydicarbonate (DEPDC) was synthesized according to literature [33, 34] by reacting 12 ml ethyl chloroformate (122.5 mmol) with 6.64 ml 30% H₂O₂ (58.59 mmol) and 24 ml 5 M NaOH (120 mmol) in 100 ml pre-cooled demineralized water under stirring. The reactants were added drop-by-drop to ensure that the temperature never exceeded 10 °C. After gentle stirring for another 10 min, 50 ml of pre-cooled hexane was added, to extract DEPDC under increased stirring speed for 5 min. The mixture was transferred to a separation funnel and the organic phase was collected. The separation was repeated twice. The produced DEPDC was stored in hexane at −18 °C. The concentration of DEPDC in hexane was measured by titration with iodine to 0.2 M according to ASTM method E298-17a. The initiator mixture is regularly examined by semi-quantitative peroxide test stick Quantofix method supplied by Macherey–Nagel (Germany).

2.1.3. Fabrication of IPNs

In a typical experiment a 0.5–1.0 g silicone specimen was placed on a metal grid in a 16 ml stainless steel high-pressure reactor equipped with a magnet for stirring. 0.60–1.60 ml HEMA, 1.60 ml PEGMEA, 0.096 ml EGDMA, 0.80 ml 0.20 M DEPDC in hexane, 1.12 ml EtOH and 1.12 ml THF were added and the mixture was stirred while heating the reactor to 40 °C. Then CO₂ was added through a P-50 high pressure pump from Thar (USA) to ensure a pressure of 300 bar at 40 °C. After 19 hours the pressure was slowly

Hydrogel content f_{hydr} (%)	Water content $EW C$ (%)
20	23
26	25
34	33
42	40
51	43

Table 2

Equilibrium water content of silicone-hydrogel IPNs as function of hydrogel content.

released. The IPNs were then collected and washed gently in tap-water for removal of excess polymer. Excess monomer and non-cross-linked polymer was extracted by placing the IPN samples in 96 vol. % EtOH for one week. The hydrogel content of the IPNs were determined gravimetrically.

The procedure resulted in the following sample series. The parameter xx denote the wt. % of hydrogel.

- Samples based on Square silicone: Sqr- xx series, xx = 00, 20, 26, 34, 42, 51
- Samples based on Sylgard 184 silicone: Syl- xx series, xx = 00, 12, 22, 32

For the different experiments, samples that were dry, samples that were soaked in deionized H₂O (Milli-Q), and samples that were soaked in 99.9 atom % D D₂O (purchased from Cambridge Isotope Laboratories) were prepared.

2.2. Water content

The equilibrium water content ($EW C$) of the IPNs was measured by measuring the masses $m_{swelled}$ and m_{dry} of the samples before and after drying.

$$EW C = \frac{m_{swelled} - m_{dry}}{m_{swelled}} \quad (1)$$

Sqr-IPN samples were soaked in water for one week to ensure that the degree of swelling had reached equilibrium, by monitoring the sample mass. According to literature, 20 hr should be sufficient to reach $EW C$ of similar IPNs [7], but thickness and morphology affects the kinetics of water uptake.

The $EW C$ determined for IPNs containing between 20% and 51% hydrogel are shown in Table 2. A monotonic relationship is found between the amount of hydrogel and $EW C$, indicating that all hydrogel in the IPNs is surface-connected and that swelling is not restricted by the silicone host polymer.

2.3. Atomic Force Microscopy (AFM)

AFM measurements were performed using an Asylum Research MFP-3DAFM with software from AtomicforceDE to generate the AFM images and force maps. The tip was an Olympus AC240, with nominal spring constant of 2 N m^{−1} and a resonance frequency around 70 kHz. To generate the AFM images, an AC-mode with a scan rate of 1 Hz was used.

To generate force maps, the maximum adhesion during a 1 μm pull after indenting the tip with a 10 nN trigger force with a scan rate of 4 Hz and 50×50 data points over an $1 \times 1 \mu\text{m}^2$ area was recorded. The force map was done using the same instrument and tip, now in deionized ultrapure water.

2.4. Scattering

Small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS), and spin-echo small-angle neutron scattering (SESANS) measurements were all performed. SAXS and SANS measurements were not able to provide conclusive information, and full details of these are only provided in the Supporting Information.

2.4.1. Small-angle X-ray scattering (SAXS)

SAXS experiments were performed with a lab-based micro-focus SWAXS camera (Ganesh, Xenocs, Grenoble, France) at the Niels Bohr Institute (University of Copenhagen, Copenhagen, Denmark). Additional information is provided in the Supporting Information.

2.4.2. Small-angle neutron scattering (SANS)

SANS measurements were performed at the KWS-2 beamline [35] at Maier-Leibnitz Zentrum in Garching (Garching, Germany) on the Syl-IPN and Sqr-IPN series of samples. Samples were measured at four instrument configurations to cover a wide Q range. Q is defined as the magnitude of the momentum transfer (or scattering) vector (\vec{Q}) and is given in Equation 2, where λ is the wavelength of the radiation and θ is half the scattering angle [36].

$$Q = \frac{4\pi \sin \theta}{\lambda} \quad (2)$$

Three sample-detector distances (1.605 m, 7.605 m, and 19.505 m) and three neutron wavelengths (5.15 Å, 10.31 Å, and 19.60 Å). Either measurements at longer sample-detector distances or measurements with longer wavelengths make it possible to access smaller scattering angles, as can be seen in Equation 2. Additional information is provided in the Supporting Information.

2.4.3. Spin-echo SANS (SESANS)

SESANS measurements were performed on the SESANS instrument located at the Reactor Institute Delft, TU Delft (The Netherlands). As opposed to conventional small-angle scattering measurements, which measure scattering intensity as a function Q (Equation 2), SESANS measures the degree of depolarization as a function of the so-called the spin-echo length Z , essentially the length scale over which correlations in scattering length density are probed in the sample. Z is an instrumental quantity which is defined in Equation 3, where c is a constant ($4.6368 \times 10^{-14} \text{ T}^{-1} \text{ m}^{-2}$), λ is the wavelength of the neutron, L is the magnetic field length, B is the strength of the magnetic field and θ_0 is the angle of the magnetized foil flipper with respect to the neutron beam [37].

$$Z = \frac{c\lambda^2 L B \cot \theta_0}{\pi} \quad (3)$$

Sample	T	d (cm)
Syl-22	0.486	0.170
Sqr-20	0.648	0.103
Sqr-34	0.715	0.0766
Sqr-51	0.586	0.117

Table 3

Experimentally measured neutron transmissions (T) and calculated sample thicknesses (d)

The SESANS technique has been well described elsewhere [38, 37, 39]. In a SESANS measurement, the average polarization of a neutron beam that has passed through a sample is the quantity that is being measured. The polarization of this beam ($P(Z)$) has to be normalized by the original empty beam polarization ($P_0(Z)$). The degree of depolarization is given in Equation 4.

$$\frac{P(Z)}{P_0(Z)} = \exp \{ \Sigma_t [G(Z) - 1] \} \quad (4)$$

The total scattering (Σ_t) is the average number of scattering events for a neutron passing through a sample of thickness t , and $G(Z)$ is a correlation function that is related, via an Abel transform, to a Debye-type autocorrelation function $\gamma(r)$ [40, 39, 41, 42]. Σ_t is normalized by the square of the neutron wavelength (λ^2) and the sample thickness (t). Therefore, the following quantity has emerged as a useful y-axis for SESANS measurements [39, 42].

$$\frac{\Sigma_t}{\lambda^2 t} (G(Z) - 1) = \frac{1}{\lambda^2 t} \ln \left[\frac{P(Z)}{P_0(Z)} \right] \quad (5)$$

The effective thicknesses of the samples used for these measurements could not be well controlled, as flat samples for scattering measurements were cut from curved tubing. The thicknesses were, therefore, calculated from the experimentally measured neutron transmissions and the known absorbance and incoherent cross-sections of the nuclei in the material (including the polymers but excluding D_2O) [43, 44]. The scattering transmission (T) can be related to the scattering power (τ), which is in turn related to the sample thickness (d) and the scattering cross-section per sample volume (Σ), by the following relationship [45].

$$T = \exp(-\tau) \equiv \exp(-d \cdot \Sigma) \quad (6)$$

The thicknesses that are calculated in this way (Table 3) are reasonable for the anticipated thickness of the IPNs.

The SESANS measurements were performed using a monochromatic beam with a theoretical Z ranging from 5 nm to 20 μm [37]. To perform a scan of spin-echo length Z the magnetic field B is varied and different Z measured point-by-point. In the configuration used for these measurements, a range from about 28 nm to 16.3 μm was covered.

Three samples of Sqr-IPNs (Sqr-20, Sqr-36, and Sqr-51) and one sample of Syl-IPN (Syl-22) were studied. They were placed in a cuvette filled with D_2O prior to measurement and allowed to reach *EW C* before measurements.

$G(Z)$ can be related to the scattering cross section per unit volume $I(Q)$ encountered in a conventional SAS measurement, as shown in Equation 7. $J_0(x)$ is the zeroth order cylindrical Bessel function.

$$G(Z) = \frac{\lambda^2 t}{2\pi \Sigma_t} \int_0^\infty J_0(QZ) I(Q) Q dQ \quad (7)$$

The data for the primary objects were fit using a spherical form factor, which, in Q -space, is given by Equation 8, where R is the sphere radius [46]. This does not necessarily mean that the objects are discrete spheres, but rather that the overall structure can formally be represented well by spherical subunits.

$$I(Q, R) = \frac{4}{3} \pi R^3 \Delta \rho^2 \left[3 \frac{\sin(QR) - QR \cos(QR)}{(QR)^3} \right]^2 \quad (8)$$

The distribution in particle size was included by convoluting the form factor with a size distribution function, as given generally by Equation 9, where $f(R, R', \sigma)$ is the size distribution function [47].

$$I(Q) = \int_0^\infty f(R, R', \sigma) I(Q, R') dR' \quad (9)$$

For the data studied here, a Schulz distribution [48] with mean radius R and width of the size distribution σ was used, which has been shown to be appropriate for many colloidal systems [49]. It was necessary to include a structure factor to satisfactorily fit the data. As the spherical regions are not well-defined, an analytical solution to the structure factor is not suitable, and instead, the numerical method of Robertus *et al.* is used [50]. The data in this study can be well fit if “stickiness parameter” τ_{nm} is set equal to a large value (99), and in this instance, the interparticle interaction is solely as hard spheres. Samples with the lowest concentrations of hydrogel (Sqr-20, Syl-22) could be fit as dilute spheres without invoking a structure factor. However, to ensure consistency and satisfactory fits to the data, the volume fraction was set to a low value (0.01) and the data fit using this same model.

To account for correlations over even longer length scales, a further contribution to the SESANS signal was introduced for all samples, using the Debye–Anderson–Brumberger (DAB) model [51], also known as the Debye–Büchle model [52]. This represents very long-range scattering length density fluctuations in the materials. The DAB model describes a randomly distributed two-phase system and is given by Equation 10.

$$I(Q) = \text{scale} \cdot \frac{\xi^3}{(1 + (Q \cdot \xi)^2)^2} \quad (10)$$

The correlation length (ξ) is the only structural parameter in Equation 10.

The SASfit software package was used for fitting the SESANS data [53, 54, 42]. The appropriate transformation from Q -space to real-space is performed in the software and was integrated over a finite Q range, defined by the maximum Q of the detector of the instrument ($0 < Q < 0.052 \text{ \AA}^{-1}$).

3. Results

The IPNs studied here are composed of multiple components: the silicone elastomer, silica filler particles, hydrophilic hydrogel, and solvating water. This is already a complex system, but it is further complicated by the many variables that could impact the final structure, such as diffusion rates of monomers into the silicone during production, cross-linking density, silicone type (hardness and shape), and type of filler. This means that it is challenging to determine the overall structure from a single measurement alone. Multiple techniques, as well as multiple contrasts (different types of radiation or labeling) using a single technique, are necessary to improve the ability to highlight the different components. Our goal is to develop tools that can be used despite the material complexity to reveal the morphology of the IPNs.

3.1. Microscopy visualizes the hydrogel structure

Inspired by our previous attempts to determine the degree of homogeneity or heterogeneity of these IPNs, we used AFM to visualize the surface. Our AFM images show that there are structures that are greater than 10s of nm but smaller than a μm . We performed two types of measurements on the surface of a single IPN (Syl-22). We imaged the surface under dry condition using normal AFM, and we performed forcemapping in water to measure the surface forces and the hydrophobicity of the sample surface. Figure 2 shows a set of AFM images of the dry surface. Figure 2(A) shows the surface features and Figure 2(B) shows the phase image of the same area. Contrast in the phase image typically relates differences in energy dissipation in the AFM recording. Differences in energy dissipation are linked to different surface properties. This could be hardness, stickiness, or hydrophobicity.

The AFM image shows that there really are two distinct components on the surface of the IPN. One is smooth and gives rise to strong change in the phase image, and the other has features with a characteristic scale of $\sim 10 \text{ nm}$ size that does not affect the phase significantly.

This trend is mirrored in the forcemapping (Figure 3), which shows features that are consistent with the images that were recorded on the dry sample (Figure 2). There are low areas having high adhesion (Figure 3) compatible with strong phase shift (Figure 2) and vice versa for parts that protrude from the surface.

The result agrees with the low (pink) areas being more sticky and the protruding parts (blue) being less sticky. Our interpretation is that the low areas are more hydrophobic than the protruding areas.

These images clearly show that the structure of the IPNs is heterogenous on the nanometer to micrometer scale. However, as AFM is a surface technique, it is only sensitive to heterogeneities on the surface. The surface technique must be complemented by techniques that can probe the interior of materials to study the bulk structure. That the IPNs are known to phase separate from AFM suggests that this should be informative.

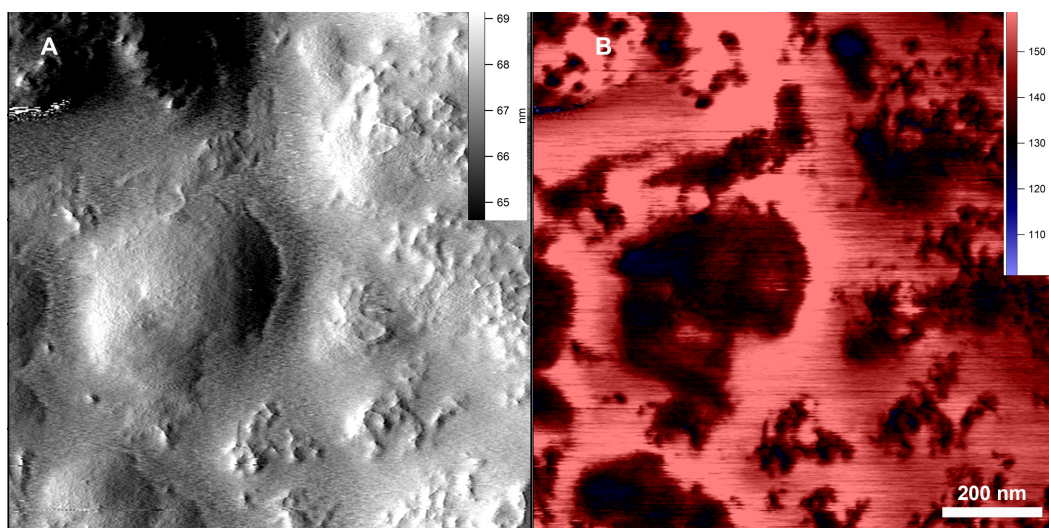


Figure 2: $1 \times 1 \mu\text{m}^2$ AFM tappingmode image of the surface of Syl-22. (A) amplitude. (B) Phase.

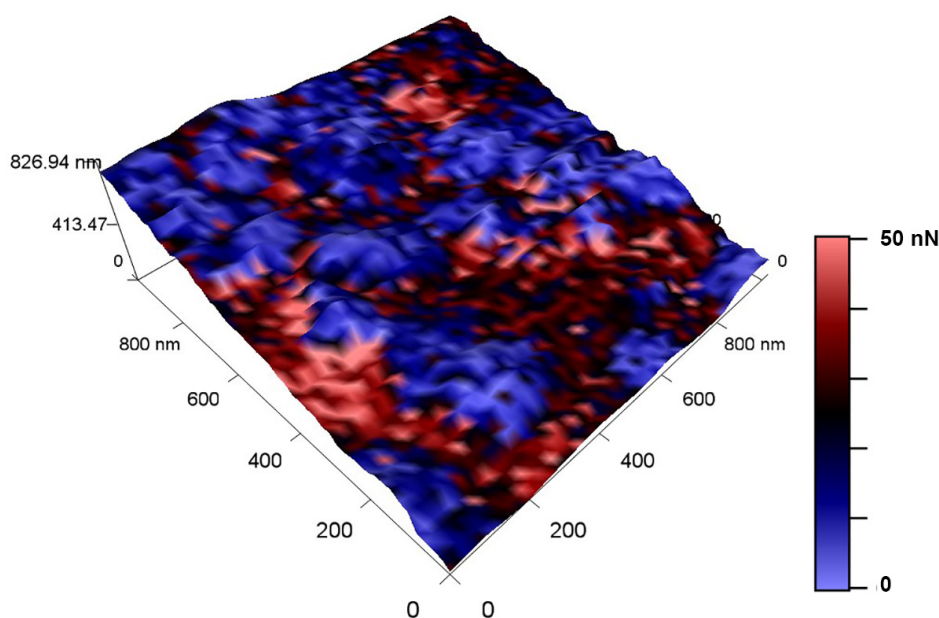


Figure 3: Forcemapping showing the 3D perspective of the topography with adhesion as the coloroverlay across a $1 \times 1 \mu\text{m}^2$ area of the surface of Syl-22. The color scale for the adhesion is going from light blue (low adhesion) to black (medium adhesion) to pink (strong adhesion).

3.2. Scattering quantifies the hydrogel structure

From the AFM micrographs (Figure 2), it is clear that there are inhomogeneities on the order of hundreds of nanometers in these materials, on the surface at least. To study features throughout the interior, several variants of X-ray and neutron scattering were used. Unfortunately, the more readily accessible and commonly used forms of scattering were unsuitable to studying these materials. The limitations of the

techniques will be discussed below.

3.2.1. Small-angle X-ray and neutron scattering measurements

Small-angle X-ray scattering (SAXS) measurements were performed on IPN samples in both their dry and wet states and for different hydrogel concentrations, but these were unable to provide useful information about the distribution of

hydrogel. The results from on wet and dry samples are broadly the same and the variation in hydrogel concentration also gives rise to only very small (but systematic) changes in the SAXS signal, and the SAXS data from a hydrogel-free sample (Sqr-00) are essentially the same as those containing hydrogel. This was due to silica filler particles that are known to be present in commercial silicones and dominate the scattering [55, 25], which can be explained by the much higher X-ray scattering length density of silica (Table 1). SAXS data obtained for Syl silicones, which do not contain mechanical silica filler, confirm this hypothesis. (Data are discussed in the Supporting Information.)

Small-angle neutron scattering (SANS) measurements were also performed on IPN sample. When H_2O is used to hydrate the hydrogel in the IPN, the SANS data are very similar to the SAXS data. The silica filler particles do scatter significantly over much of the Q range of the measurements, but no one component dominates overall. This makes disentangling the origin of the scattering challenging. The most dilute sample (Sqr-20 H_2O) can be modeled by considering two populations (compact hydrogel objects and silica filler) to be independent species, which because the hydrogel is “dilute” means that there is no structure factor peak as is the case for more concentrated samples (Supporting Information, Figure S6). Assuming that the scattering from the silica filler is significant at high Q and that the scattering from dilute hydrogel objects is significant at low Q , a reasonable fit to the data can be obtained (Supporting Information, Figure S7).

When D_2O is used to hydrate the hydrogel, however, there is significant scattering intensity with a single component dominating. The SANS data are shown in the Supporting Information (Figure S8), and the curves do not change significantly with hydrogel concentration. The large amount of scattering intensity, resulting from the large contrast between the D_2O swollen hydrophilic material and D_2O free hydrophobic material as well as the thickness of the samples means that there is the possibility of multiple scattering. This was confirmed by modeling the scattering from the most dilute sample (Sqr-20) as a dispersion of spheres that scatter multiply. The multiple scattering calculations were performed in accordance with the literature and as implemented in SASfit [56, 45, 57]. By accounting for multiple scattering, the SANS data could thus be modeled successfully, with hydrogel that is phase separated on a length scale of 10s to 100s of nanometers with a wide size distribution. These length scales are on the high limit of what can be studied with SANS, which further limits the ability to quantify them. While multiple scattering is a problem for SANS, it is not a problem for SESANS [58]. This makes the SESANS technique well-suited to studying these materials.

The data from these SANS measurements are different than previous SANS measurements on hydrophilic polymer and silicone IPNs, which found that data could be modeled with correlation length on the order of 10 nm [20, 21, 22]. Possible multiple scattering is not discussed in these references. The difference in the interpretation of the SANS data

between these previous studies and ours could be down to different syntheses, the existence of multiple scattering, or different materials. Multiple scattering is, generally, considered to be insignificant for scattering from polymers [59], and the data that we present in this study, therefore, are an interesting example of a polymer system where multiple scattering cannot be discounted. This is because the IPNs that we report in this study, despite being made up of polymers and D_2O , consist of large regions that have a high scattering power, exactly the conditions that will result in a large degree of multiple scattering [45]. Multiple scattering impacts the low Q part of the SANS data (long length scales) whereas the high Q part is not impacted, and the SANS data shows that there are no significant structures on shorter length scales (from 1 to 20 nm).

3.2.2. Spin-echo small-angle neutron scattering measurements

The main interest is to study the structure of the hydrogel in the Sqr IPN, and as SAXS and SANS are unsuitable for this for the reasons discussed above, the SESANS technique was used. However, to determine if any of the observed structural features are related to the structure of the filler particles in the Sqr samples, the Syl-22 sample was also studied with SESANS. The data from Syl-22 and Sqr-20 are displayed in Figure 4. The left panel of the figure shows the SESANS signal up to spin-echo lengths of $2.7 \mu m$. Over this Z range, the SESANS signal is almost completely dominated by the compact hydrogel objects, as can be seen by the nearly complete overlap of the grey dashed line (compact objects) and black line (total). The curves for the two samples look qualitatively similar, with a rapid depolarization followed by a rather flat plateau for spin-echo lengths greater than around $0.5 \mu m$. However, the depolarization is more rapid for Syl-20 than Sqr-22 and plateaus at significantly shorter spin-echo lengths.

The SESANS signal varies when structures are present over that length scale, and it is constant when there are not. The rapid depolarization followed by a flattening thus suggests that there are only structures at length scales up to about $0.5 \mu m$ but nothing larger. However, on closer inspection, the curves are not actually a flat plateau. To study this in more detail, the samples were measured at spin-echo lengths up to $16.3 \mu m$ (Figure 4 right). Looking at the data measured to longer spin-echo lengths the curves are very similar for the two samples, and it is clear that the depolarization curve has not reached a plateau at $0.5 \mu m$. The depolarization continues slowly to longer spin-echo lengths, showing that inhomogeneities exist up to the maximum length scale accessible. The scattering from these, shown by the dotted lines in the right hand panel of Figure 5, is only significant at large Z .

The obtained SESANS data on three of the samples in the Sqr-series are shown in Figure 5. The left panel of the figure shows the SESANS signal up to spin-echo lengths of $2.7 \mu m$. The data for all samples follow the same overall trend with a rapid depolarization up to spin-echo lengths of

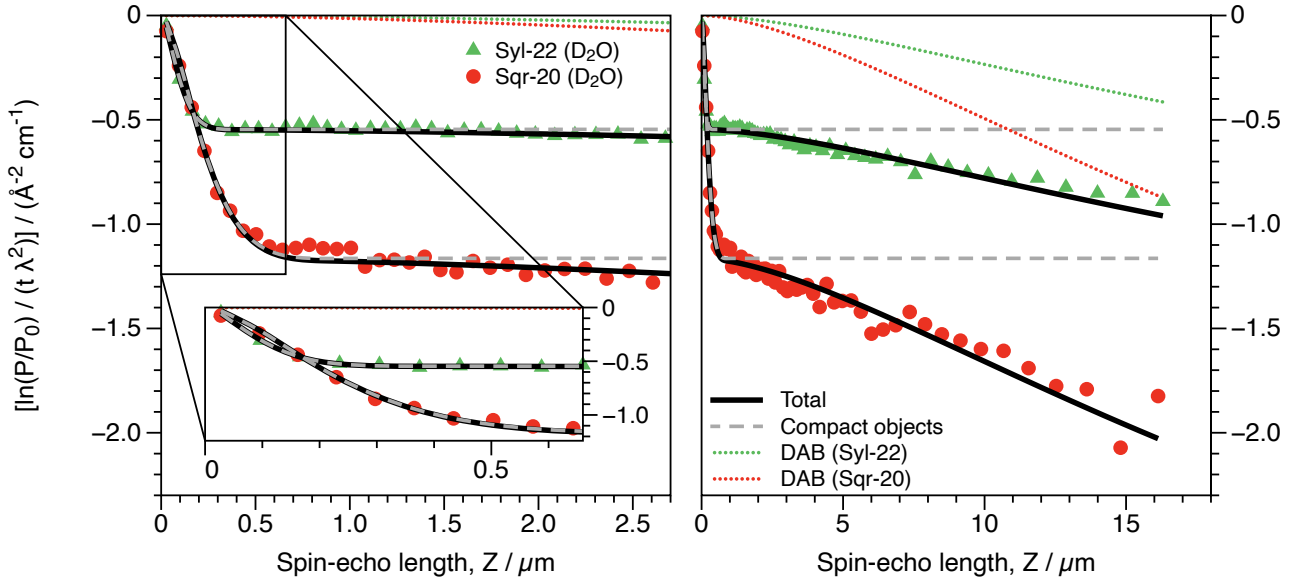


Figure 4: Comparison of SESANS data from D₂O-hydrated Sqr-20 and Syl-22 samples. The solid lines show fits to both components (compact hydrogel objects and long-range inhomogeneities) whereas the dashed lines show the contribution from the hydrogel objects only and the dotted lines show the contribution from the long-range inhomogeneities only. Left and right panels show data up to spin-echo lengths of 2.7 and 18 μm , respectively.

about 0.5 μm followed by a much slower depolarization in the entire probed range of spin-echo lengths. On closer inspection, the curves for the more concentrated samples, Sqr-36 and Sqr-51 have a local minimum in the data at $\sim 0.5 \mu\text{m}$. This can mathematically be accounted for as a structure factor, representing a non-random distribution of the scattering regions. Over this Z range, the scattering is nearly completely dominated by the hydrogel, as can be seen by the overlapping grey dashed lines (compact objects) and solid black line (total).

As described in the Experimental Section, the SESANS data from the compact hydrogel objects were modeled as spheres with a Schulz size distribution plus an additional (DAB) term to take correlations at longer length scales into account. A hard-sphere structure factor was included in the fit of the Sqr-36 and Sqr-51 data but was not necessary for the two low-concentration samples. This is probably not a reflection of different interactions in the samples but just a consequence of the relative low concentration in Sqr-20 and Syl-22. Although a model of discrete spheres are used to fit the data, this does not mean that the structures should be considered to be isolated spheres. Rather, the structure of the IPN at this length scale is a phase-separated, two-phase system that can be represented by spherical subunits, as described above.

The parameters from the fits of the SESANS data are displayed in Table 4. For the two low-concentration samples, the width of the size distribution is very large and uncertain, and this parameter in particular is poorly determined. This is because there is no clear structure factor peak in the data, and therefore, the best fit value is somewhat ambiguous. Fur-

Table 4

Best fit parameters for the compact hydrogel objects of the SESANS data for the D₂O-hydrated Sqr and Syl IPNs. R is mean value of the sphere radius, and σ is the width of the Schulz distribution. All samples were fit with a hard ($\tau = 99$ fixed) sphere structure factor according to the Robertus model, where ϕ denotes the volume fraction of the hydrogel objects.

Sample	R / nm	σ	ϕ
Syl-22	40	0.7	0.01*
Sqr-20	90	0.8	0.01*
Sqr-36	240	0.5	0.51
Sqr-51	370	0.4	0.63

* Fixed to this value as the spheres were too dilute to fit this parameter with precision.

thermore, to avoid undue computational complexity, there are a finite number of points in the Schulz size distribution used for these calculations, which may introduce uncertainty from bin selection. The fit results should thus not be taken as accurate measures of the sizes of the hydrogel domains, but rather an estimate. For both Sqr-20 and Syl-22 the modeling results in spheres with a radius on the order of 10s of nm and a very wide size distribution. For higher hydrogel concentrations the structure factor term helps to stabilize the modeling. The model results in sphere radii of a few hundred nm and a broad size distribution.

4. Discussion

The combination of an imaging technique (AFM) and a scattering technique (SESANS) has revealed the formation

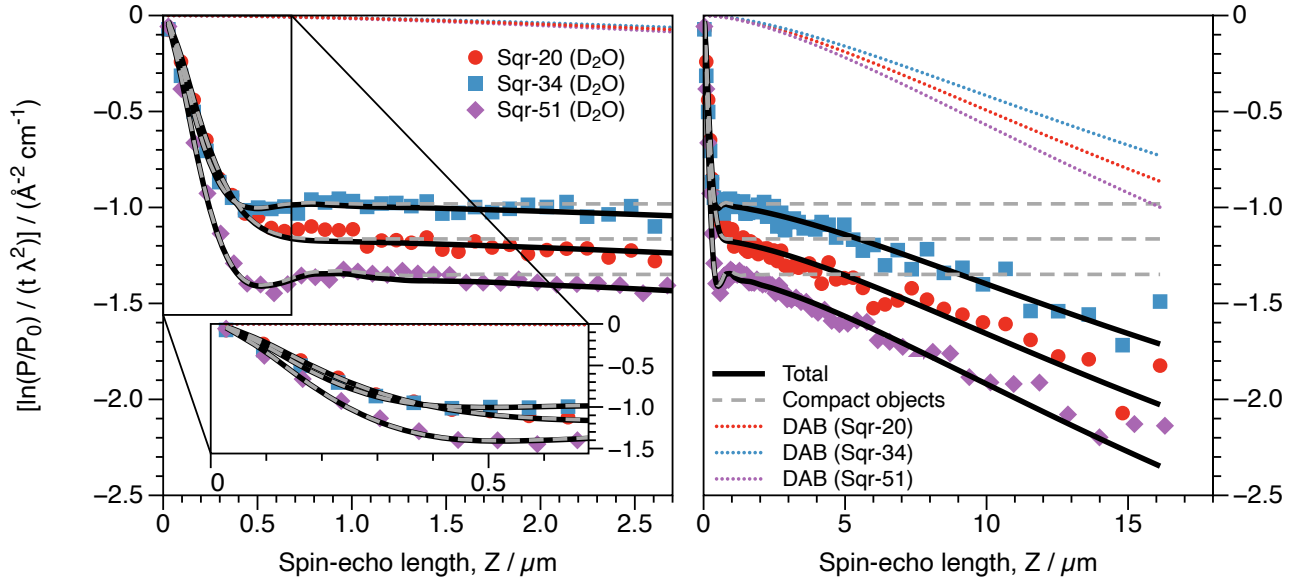


Figure 5: SESANS data of different D₂O-hydrated Sqr samples. The solid lines show fits to both components (compact hydrogel objects and long-range inhomogeneities), whereas the dashed lines show the contribution from the hydrogel objects only and the dashed dotted show the contribution from the long-range inhomogeneities only. Left and right panels show data up to spin-echo lengths of 2.7 and 18 μm , respectively.

of hierarchical hydrogel domains in these IPNs with length scales up to more than 100 nm. Using D₂O as a swelling and contrast agent for SESANS was essential to study the water-swollen structure of the IPN. The silicone in the Sqr series clearly contains filler particles, determined from X-ray scattering measurements, where filler dominates the scattering as it has been also observed elsewhere [55, 25]. This silicone is medical grade and is, therefore, highly relevant for application in medical devices.

From a consideration of the density fluctuations observed by SESANS and the inhomogeneities imaged by AFM, we can draw several conclusions about the structure of these hydrophilic-hydrophobic IPNs. There are regions of hydrophilic and hydrophobic polymer interpenetrating on a length scale on the order of 100s of nanometers. Therefore, the schematics of a two-phase system that were used to demonstrate the contrast in scattering experiments in Figure 1 are broadly correct. These, however, do not fill the material homogeneously, and on larger length scales (100s of nanometers to 10s of micrometers), there are density fluctuations with more hydrogel-rich and more hydrogel-poor regions. These may arise from the cross-linked nature of the silicone host polymer or may arise from the polymerization kinetics of the guest polymer. From these data, it is not possible to say. Despite these density fluctuations, the hydrogel does form a system spanning network, although this could not be proven from the scattering data alone. For example, McGarey *et al.* used the diffusion of KCl through their IPN membranes to prove this [60]. For the studied IPNs in this study, it has been already shown elsewhere through dye diffusion and drug release experiments that the hydrophilic do-

main is connected in bulk and with the surface [7, 8, 9].

All the neutron scattering contrasts and techniques give a consistent description of the structure of the IPN with the lowest concentration of hydrogel. We assume that the same would be true for higher concentrations, if data could all be fully analyzed. They consist of large (10s to 100s on nanometers) phase separated regions of hydrogel and silicone. The compact hydrogel objects can be modeled as spheres with a broad distribution, which are distributed as noninteracting hard spheres when sufficiently concentrated. The reciprocal space SANS measurements suffer from multiple scattering, and furthermore, the largest sizes in the structure are not accessible with conventional SANS. This makes determining the structure from SANS alone impossible. When H₂O is used to hydrate the hydrogel, the hydrophilic regions have insufficient contrast with the remaining material, and the scattering is too complicated to model. When D₂O is used to hydrate the hydrogel, the hydrophilic regions now have too high a scattering power, and the resulting multiple scattering means that analyzing the data unambiguously becomes problematic. Real space SESANS measurements, on the other hand, provide a way of quantitatively determining the structure of the materials. Data are obtained over a broad range of length scales (up to 18 μm), and the multiple scattering arising from the high scattering power is simply addressed in the data modeling.

Given the insight into these structures that have been obtained using techniques from neutron scattering, SESANS in particular, it is immediately clear that these IPNs in commercial Sqr and Syl silicones have a very hierarchical structure with potentially important structures at all these length

scales. The results from both Sqr and Syl IPNs show that, despite the length scales of these features being broadly similar, the precise size is dependent on the host silicone polymer. This seems to impact the feature size more than the concentration of guest hydrogel polymer, which, aside from impacting concentration dependent parameters (scale and structure factor), does not significantly impact the structures.

5. Conclusions

The structural complexity of these hydrophilic-hydrophobic IPNs demanded the use of many analytical techniques, with AFM and SESANS proving particularly informative. We find these IPN materials to consist of locally phase-separated and interpenetrating regions of hydrogel and silicone on the nanometer scale, which presumably provides a large amount of surface area between the hydrophilic and hydrophobic polymers. This way of modelling data differs from other neutron scattering data analyzed by others from similar IPNs, and it may be important for characterizing these specific IPNs for their desired application.

The domains of hydrogel are likely to be the origin of the biomedically advantageous properties of these IPNs. The patches of hydrogel identified at the interface make an unfavorable surface for bacterial adsorption, and the regions of hydrogel in the bulk provide a route for drug molecules to diffuse through. Interactions at the silicone-hydrogel interface within the material, in particular, will determine how different drugs, which differ in their degrees of hydrophobicity and hydrophilicity, diffuse through the IPNs. Determining the size and concentration of regions of hydrogel will improve the understanding of this process. IPNs synthesized in commercial, medical-grade silicones also contain fractal silica particles (as clearly observed by SAXS), which necessitated the use of D₂O hydration to study the hydrogel structure using SANS and SESANS. The fillers impact the macroscopic properties of the materials, but it is not clear whether or not these fillers impact the structure of the hydrogel or the diffusion of molecules, although it might be speculated that they do. These IPNs are clearly highly complex and structured.

The determination of the structure of materials is, of course, interesting, but it is finding what can be done with this information that will be crucial for the development of future medical devices. The identification of the important length scales and the important structures is a promising start. Future work should help reveal how the material properties relate to the structural parameters as well as what structures and what dimensions are the important ones for the properties of the materials and their clinical application. Overcoming the negative health outcomes arising from urinary tract infections by avoiding them through infection-resistant devices and treating them with targeted drug delivery justifies this effort. In tandem with advances in the use of these devices in the clinical setting, structural measurements will be highly valuable.

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Supporting Information

Additional information on scattering models used; SAXS data; SANS and SESANS data on H₂O-hydrated and D₂O-hydrated IPNs

CRediT authorship contribution statement

Gregory N. Smith: Formal analysis, Investigation, Writing - Original Draft. **Erik Brok:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing, Visualization. **Martin Schmiele:** Conceptualization, Methodology, Formal analysis, Writing - Review & Editing, Visualization. **Kell Mortensen:** Conceptualization, Formal analysis, Supervision, Writing - Review & Editing. **Wim G. Bouwman:** Methodology, Formal analysis, Investigation, Writing - Review & Editing. **Chris P. Duif:** Methodology, Investigation, Data Curation, Writing - Review & Editing. **Tue Hassenkam:** Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing - Review & Editing, Visualization. **Martin Alm:** Conceptualization, Resources, Writing - Original Draft. **Peter Thomsen:** Resources, Writing - Review & Editing, Funding acquisition. **Lise Arleth:** Conceptualization, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

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