Chapter 4

STRUCTURE OF A SELF-ASSEMBLED SEMI-INTERPENETRATING HYDROGEL

4.1 Introduction.....IV-1
4.2 Experimental.....IV-3
4.3 Results.....IV-6
4.4 Discussion.....IV-9
4.5 Conclusion.....IV-12
4.6 Figures.....IV-14
4.7 References.....IV-23

4.1 Introduction

In some cases, multi-component hydrogels have been shown to have improved tribological characteristics compared to their single-component parent gels[1, 2]. Gong and Osada, in particular, looked at triple hydrogels formed from successive polymerizations of an anionic acrylamide (PAMPS), neutral acrylamide (PAm) and again PAMPS[2]. The first network is highly crosslinked, porous and rigid while the second network is only loosely crosslinked and flexible[3]. The third and final polymerization can either be performed with or without crossliking agent, since acrylamide gels crosslink by chain transfer during long polymerizations even in the absence of crosslinking agents. The friction is lowest when this third polymerization uses no crosslinking agent, leading Gong and Osada to speculate that the very low friction coefficient of this system is due to the presence of charged linear, dangling chains on the gel surface. The gel appears to have no free chains when the friction is tested due to a long (1 week) soaking to rid the gel of mobile components.

We here test a novel class of hydrogels, inspired by the work of Gong and Osada, but focusing on self-assembled rather than polymerized systems. Self-assembled hydrogels have many benefits over polymerized hydrogels: benign starting materials eliminate the need to purify away toxic monomers and initiators, ease of preparation, and potential to form coatings on substrates of any shape. Unfortunately, the properties of self-assembled hydrogels can not be tuned as easily as chemically prepared hydrogels can using such variables as crosslink density, monomer concentration, and comonomer addition. We choose agarose as our starting material since, as with the first network in the gels of Gong and Osada, agarose forms a very rigid, porous network. Rather than a second, interpenetrating network, we simply include a linear polymer as the second component. Unlike Gong and Osada, we chose this second polymer so that it has the mobility to move out of the hydrogel.

Agarose is a polysaccharide derived from red sea algae.[4] During the purification of agarose from sea weed, most of the negatively charged sulfate groups present in the raw agar are removed.[5] A small number of these sulfate groups remain and cause agarose to have a slight negative charge. Like gelatin, agarose exists as free polymer chains in water at high temperatures and a crosslinked network at low temperatures. Unlike gelatin, the network formed by agarose is highly inhomogeneous. Three steps occur during the gelation of agarose: spinodal decomposition, formation of double helixes, and bundling of these helixes. Even before double helices are formed, agarose chains are fairly rigid. As an agarose solution is cooled, these rigid chains phase separate by spinodal demixing into polymer rich and polymer poor regions.[6, 7] This partitioning of material is thought to be responsible for the porous structure of the final gel. As the agarose solution is further cooled, a transition from single chains to double helices occurs.[8] Imperfections in the disaccharide repeat unit of agarose cause breaks in helices, and these breaks result in portions of a single chain forming double helices with multiple other chains.[5] Upon further cooling, agarose double helices undergo aggregation into bundles.[8] The final network created by these three processes contains pores with a mean diameter in the hundreds of nanometers: the mean pore radius measured by AFM was 364 nm for a 2% agarose gel, and 289 nm for a 3% agarose gel[9].

The porous structure of agarose has been used to host linear polymers and form a semi-interpenetrating network.[10, 11] Geissler and coworkers found that only concentrations of dextran up to the overlap concentration could be incorporated into the agarose host network. Dynamic light scattering on these double networks showed that the agarose forms a rigid host network (the scattering from the agarose is invariant in time), while the dextran diffused within the pores.

Rather than using neutral dextran, we examine agarose self assembly in the presence of polyelectrolytes, specifically dextran sulfate (an anionic polymer) and DEAE dextran (a cationic polymer). We anticipate that the phase behavior of polyelectrolytes might differ from the phase behavior of neutral polymers in agarose due to both electrostatic interactions between the agarose and the charged dextran and due to conformation differences between charged and uncharged polymers. Our choice of polyelectrolytes—a polyanion and a polycation whose base polymer is itself water-soluble, precludes collapse at extreme pH or ion concentration into the "pearl necklace" structures seen in systems where the base polymer of the polyelectrolyte is hydrophobic.[12]

Our study of agarose gels doped with charged dextrans will begin with an examination of the phase behavior of both systems. We will then use rheology and light scattering to characterize the change in structure of the agarose when these polyelectrolytes are added to it. Rheology will be used to gain information about the crosslinking within the gel, and light scattering used to understand the development of the porous structure of the gel. Finally, the swelling and loss of materials from the gels will be examined in excess water, both for as-prepared hydrated gels as well as dehydrated gels.

4.2 Experimental

Materials. Dextran sulfate sodium salt, DEAE-dextran hydrochloride, and agarose were purchased from Sigma and used as received. Both dextran sulfate and DEAE-dextran

have a nominal molecular weight of 500k. Agarose type 1-B, low EEO was chosen for its high strength and low sulfate group content.

Sample Preparation. Stock solutions of dextrans were prepared in twice-distilled water with a polymer concentration of 20% by weight. Dextran stock solutions were mixed overnight before use. Dry agarose, dextran stock solution, and water were measured to give ten gram samples of the desired weight percent of polymer: 2% agarose and 0% to 3% dextran sulfate or DEAE-dextran. Samples were alternately stirred for five minute intervals in a heat bath maintained at 95º C and mixed on a vortex mixer. This was repeated three times for a total heating time of 15 minutes.

Rheology. A stress rheometer (model AR 1000, TA Instruments, New Castle, Delaware) was used for all measurements. Upper and lower 25 mm cleated plates were used for all rheological measurements, and published correction factors applied to all data.[13] Gels were formed *in situ* on the rheometer, eliminating variability associated with cutting and mounting of the gel. The hot polymer solution was pipetted onto the lower plate heated to 45º C. The upper plate was lowered to the desired gap, and the solution was cooled to 25º C. The gel was allowed to equilibrate for 15 minutes at 25º C. (Preliminary time sweeps indicate gelation occurs in approximately nine minutes.) Wet sponges were placed around the plates to minimize evaporation from the gel during equilibration and data collection. Frequency sweeps were performed from 0.1 rad/sec to 100 rad/sec with a torque of 1000 μN·m (shear stress = 17.68 Pa). Preliminary strain sweeps showed that this torque was within the linear response range of the gels.

Viscosity measurements of dextran sulfate solutions were performed on the same rheometer using a cone and plate geometry. A 60 mm, 1º cone was used for solutions with viscosity less than 0.5 Pa·s, and a 40 mm, 2º cone was used for solutions with viscosity greater than 0.5 Pa·s.

Small Angle Light Scattering (SALS). A green helium-neon laser (543 nm, 4 mW) was used for light scattering experiments. A CCD camera (Photometrics Sensys 4000 series)

was used for collecting scattering patters from a screen of onion paper; the sample was held 15.4 cm in front of this screen (Figure 4.1). Gels were prepared between two glass plates held 1.0 mm apart. Prior to scattering experiments, the glass plates were separated and the sheet of gel pushed so that it extended below the edge of the glass plate. The plates were then held together so that the scattering could be measured through the hydrogel, free of any cell (Figure 4.1). Observations are limited to short times since the gel surfaces quickly became contaminated with dust: within a couple minutes of exposing the gel to air, scattering pattern began to change due to contamination. The procedure for collecting the scattering patterns involved sliding the gel out from the glass plates, quickly securing it in the beam, darkening the room, and acquiring the image. Analysis of the scattering images was performed using Matlab. The intensity of all pixels the same distance from the center of the scattering pattern were averaged. Then all averaged data points within intervals of 0.1 degrees were binned together and averaged to smooth the data.

Swelling and Dextran Sulfate Release. 2% agarose or 2% agarose and 2% dextran sulfate solutions were prepared as detailed above and poured into Petri dishes, where they were allowed to cool overnight. From these hydrogel plates, cylinders 1.1 cm high and 1.5 cm in radius were cut using a leather punch. For swelling experiments, these hydrogel cylinders were placed in 20 ml of water. At specific intervals, the hydrogel cylinders were removed from the water, weighed and placed in 20 ml of water. The "used water" was saved and analyzed for the presence of carbohydrate. To analyze the presence of dextran sulfate, 1 ml of used water was added to 1 ml of phenol solution (5g phenol in 100 ml of water) and 5 ml concentrated sulfuric acid.[14] After mixing, the solution was allowed to sit for 20 minutes, and then the absorption was measured at 485 nm. A calibration curve was generated using known concentrations of dextran sulfate. The water in which agarose gels alone (no dextran sulfate present) were equilibrated gave no response to the carbohydrate assay, indicating minimal loss of materials from agarose gels. For dehydration, these cylinders were placed in a vacuum oven at room temperature until the mass stopped decreasing.

4.3 Results

To understand the phase behavior of agarose and polyelectrolyte semi-interpenetrating hydrogels, gels were prepared ranging from 1% agarose to 4% agarose. When DEAE-dextran was mixed with agarose, the agarose could easily be dissolved upon heating, regardless of the concentration of DEAE-dextran (concentrations up to 7% were examined). The gels formed when these solutions cooled scattered progressively less light as the mass of DEAE-dextran was increased. At the higher concentrations of DEAE-dextran examined, the gels were transparent rather than the translucence typical of agarose gels. Also, the mechanical integrity of the gels decreased with increasing concentration of DEAE-dextran. While no abrupt phase change occurred at increased DEAE-dextran concentrations, the gels became more and more liquid-like and less solid-like as the concentration of DEAE dextran was increased.

In contrast, mixtures of agarose and dextran sulfate behaved quite differently: high concentrations of dextran sulfate prevented agarose from dissolving. For a 1% agarose solution, 8% dextran sulfate prevented the agarose from dissolving; for a 4% agarose solution, 5% dextran sulfate was sufficient to prevent dissolution of the agarose. Even when the agarose did dissolve, at higher dextran sulfate concentrations a transparent, single phase solution was not formed. For 2% agarose, this multi-phase solution occurred at dextran sulfate concentrations greater than 4%. The gels formed when these cloudy solutions cooled had a “grainy” feel; therefore, they were not used for friction experiments.

Unlike the experiments of Geissler and coworkers using neutral dextran, the anionic and cationic derivatives of dextran could be incorporated into agarose hydrogels above the overlap concentration of the polymer. The overlap concentration of dextran sulfate measured from viscometery was 0.1 % (Figure 4.2). Such low overlap concentrations are typical of polyelectrolytes.[15] The entanglement concentration of dextran sulfate was not clearly evident in the specific viscosity versus concentration curve since no sharp transition occurred between the semi-dilute and entangled regimes. At 3%, the specific

viscosity started to deviate upward from the slope characteristic of the semi-dilute regime. The polymer dynamics at 3%, therefore, were still consistent with the semi-dilute, rather than the entangled regime.

Based on this phase behavior, the characterization of gels by rheology and light scattering was limited to gels with less than 4% dextran sulfate (1%, 2%, and 3%). The concentration of agarose was maintained at 2% since this concentration was optimal for tribology studies[16]. Hydrogels with DEAE-dextran concentrations of 1%, 2% and 3% were also characterized even though their delicate mechanical properties made them unsuitable for friction measurements. It was hoped that contrasting the gels formed with the cationic dextran with the gels formed with the anionic dextran would shed light on the anionic gels that were the main focus of this study.

The frequency sweeps of agarose hydrogels were typical of strongly physically crosslinked hydrogels: both *G'* and *G''* were weak functions of frequency, and no crossover occurred within the frequencies examined, 0.1 rad/sec to 100 rad/sec (Figure 4.3). At all frequencies probed, the storage modulus is greater than the loss modulus. A subtle change in tan(δ) occurred between 2% agarose hydrogels and 2% hydrogels doped with 2% dextran sulfate: a peak in tan(δ) at 3 rad/sec in 2% agarose switched to a frequency of 0.4 rad/sec when doped with 2% dextran sulfate.

The addition of dextran sulfate and DEAE-dextran changed the mechanical properties of agarose in different ways. The storage modulus of agarose remained unchanged when 1% or 2% dextran sulfate was added to the gel (Figure 4.4a). Only with the addition of 3% dextran sulfate did *G'* begin to decrease. The storage modulus of the gel doped with DEAE-dextran, however, decreased with increasing DEAE-dextran content. The loss modulus of agarose increased both with the addition of 1% of dextran sulfate and with the addition of 1% DEAE-dextran (Figure 4.4b). As more dextran sulfate was added to the gel, the loss modulus of the semi-interpenetrating hydrogel remained greater than the base, agarose hydrogel. With the addition of DEAE-dextran, however, at concentrations greater than 1%, the loss modulus fell to values lower than the loss modulus of agarose.

To understand how the addition of charged dextrans might change the pore structure of agarose, light scattering was collected at angles from 1.4º to 6.5º (Figure 4.5), corresponding to q values from 0.00028 nm^{-1} to 0.0013 nm^{-1} (length scales from 3.5 μm to 670 nm). The addition of dextran sulfate increased scattering of the gels above the level observed for agarose alone. The scattering increased as 1% and then 2% dextran sulfate were added to the gels, but then decreased slightly with the addition of 3% dextran sulfate. When 1% DEAE-dextran was added to the gels, the scattering at small angles was hardly changed from that of agarose alone. Subsequent addition of 2% and 3% DEAE-dextran caused the scattering to decrease to intensities below that of unmodified agarose.

Swelling of the gels was investigated for plain agarose and agarose doped with 2% dextran sulfate. When placed in excess water these gels hardly swelled: the measured mass increased less than 2% (Figure 4.6a) for the plain agarose gel and increased between 3.5% and 5% for the gels with 2% agarose with 2% dextran sulfate. Undoubtedly, some increase was due to experimental error: removing a hydrogel from excess water leaves the material coated with a layer of water, some of which remains even after gently blotting with a Kimwipe. Swelling on the gels containing dextran sulfate gradually decreased after the first hour (data was taken for 3.5 days). Even after the gels gradually deswelled, the final volume of the hydrogels with the dextran sulfate was greater than the unmodified agarose: on average, the gels were swollen 3.75%.

Most of the dextran sulfate diffused out of the gels during the 3.5 days of the experiment (Figure 4.6b). On average, 20% of the dextran sulfate remained when the last data point was measured. Most of this loss occurred during the first 500 minutes of the experiment.

Finally reswelling from the dry state was examined for 2% plain agarose and for 2% agarose doped with 2% dextran sulfate. Once dehydrated, agarose gels placed in water swelled painfully slowly. After 3.5 days, their mass was only 15% of the mass of the gel before dehydration (Figure 4.7a). In contrast, gels with 2% dextran sulfate regained their

original shape and mass. This dramatic reswelling was complete in 2 hours. After 3.5 days, between 50% and 80% of the dextran sulfate was lost from these gels (Figure 4.7b). Most of this loss occurred after the gels have returned to their original shape; at 2 hours, 90% of the dextran sulfate was still retained in the gel.

4.4 Discussion

Due to the nature of agarose hydrogels—the porous structure, crosslinks formed by double helix formation, and bundling of helices—it is impossible to map their microstructure onto an ideal network model. To a first approximation, the storage modulus of the material must reflect the number density of double helices. The near linear decline of the storage modulus with increasing addition of DEAE-dextran suggests that DEAE-dextran disrupts the formation of double helices. The observation that addition of up to 2% dextran sulfate shows no effect on the storage modulus suggests that dextran sulfate does not interfere with agarose double helix formation when the dextran sulfate is maintained at low (< 2%) concentration. Due to the residual sulfate groups on agarose, the difference in the ability of helices to form in the presence of these two dextran derivatives can be ascribed to electrostatic interactions. Attraction between the positively charged DEAE-dextran and anionic moieties on the agarose can hinder helix self-assembly. Dextran sulfate, on the other hand, may be repelled by the charges on agarose and, therefore, not hinder helix formation.

Besides changing the ability of agarose to form double helices, SALS shows that DEAE-dextran can also alter the pore structure of the gel. SALS patterns of gels doped with DEAE-dextran show a decrease in light scattering consistent with a destruction of the pore structure of the gel. These findings are consistent with the qualitative observation that, at high DEAE-dextran content, agarose gels become transparent rather than translucent. Attraction between the negatively charged agarose and the positively charged DEAE-dextran would discourage phase separation of agarose as the solution cools. Without strong phase separation, agarose is more homogenously distributed in solution

when helix formation occurs and the final gel is less spatially segregated than pure agarose. This more spatially segregated gel would give decreased scattering.

To better understand the increased scattering of agarose upon introduction of dextran sulfate, SALS data was evaluated using models of scattering from materials with phase-separated regions of differing scattering contrast. Perod's law, which assumes phase-separated regions have well-defined boundaries,[17] gave a poor fit to the data. The Ornstein-Zernicke formalism, however, assumes that phase-separated regions have diffuse boundaries (such as solvent-swollen polymers);[18, 19] this formalism might be useful in representing our data:

$$I(q) = \left(\frac{2}{\pi}\right)^{1/2} \frac{\xi^3 \langle n^2 \rangle}{1 + q^2 \xi^2}, \tag{4.1}$$

where ξ is the correlation length of the scattering entities and $\langle n^2 \rangle$ is the mean square fluctuations in index of refraction; q is defined as $q = (4\pi/\lambda)\sin(\theta/2)$, where λ is the wavelength of the laser and θ is the scattering angle. In this formalism, when $1/I(q)$ is plotted against q^2, the scattering data will give a line. Scattering from gels with 0% or 1% dextran sulfate show a region of near-linear behavior at small q ($q < 0.3$). Scattering from 2% agarose gels doped with 2% or 3% dextran sulfate show linear behavior over a wider range of q (nearly the whole q range investigated) with a smaller slope than the gels with ≤ 1% dextran sulfate. The slope in the Ornstein-Zernicke formalism is given by:

$$\text{slope} = \frac{1}{\xi \langle n^2 \rangle \sqrt{2/\pi}} \tag{4.2}$$

The decrease in slope with dextran sulfate concentrations ≥ 2% indicate either an increase in ξ, an increase in $\langle n^2 \rangle$, or an increase in both ξ and $\langle n^2 \rangle$. Unfortunately, the data does not fit the formalism well enough to give a positive intercept, prohibiting us from solving for ξ and $\langle n^2 \rangle$ independently.

We can hypothesize that the increase in ξ or $\langle n^2 \rangle$ might be caused by dextran sulfate raising the temperature at which spinodal decomposition of agarose occurs. If spinodal decomposition were to occur at higher temperatures, it may allow for more complete phase separation to occur before reaching the temperature at which helix formation locks in the structure.

Plausibility of this mechanism for dextran sulfate's ability to alter the pore structure of agarose is supported by the phase behavior of agarose and polyelectrolyte solutions at elevated (>90ºC) temperatures. Dextran sulfate prevented agarose from dissolving when the polyanion was present at sufficient concentrations. Even at elevated temperatures, the agarose and dextran sulfate were unable to form a single phase system.

The micro-phase separation occurring in agarose + dextran sulfate gels, identified by MALS and rheology, offers a possible explanation for the ability of dehydrated agarose gels with dextran sulfate to reswell. The most striking difference in swelling between dehydrated agarose and dehydrated agarose doped with 2% dextran sulfate is the ability of the gel with dextran sulfate to swell quickly to its original shape. When submerged in excess water for over three days hydrated agarose gels swell less than 1%, indicating that the gel is at equilibrium with the surrounding water. The fact that the dehydrated agarose does not return to this equilibrium state after three days in water indicates that either the kinetics of reswelling are too slow to allow the gel to reach its original mass during the duration of the experiment or that dehydration alters the structure of the polymer network in a manner that prohibits the gel from swelling back to its original dimensions. In the first case, the addition of dextran sulfate might increase the kinetics of swelling due to the great ability of polyelectrolytes to absorb water—similar, for example, to the ability of poly(acrylic acid) in baby diapers to absorb and retain water. In the second case, the inability of pure agarose to reswell might be tied to collapse of the pore structure occurring during dehydration. Attraction between helix bundles from opposite sides of a pore might be large enough when those bundles are brought together to effectively increase the crosslink density of the network and prevent swelling back to the original

dimensions. Dextran sulfate may help maintain the integrity of the network architecture during dehydration. The shape memory of the gels doped with dextran sulfate indicates retention of the connectivity of the agarose network during dehydration of these gels.

The results of this chapter establish an upper bound on the amount of dextran sulfate that can be incorporated into a gel containing 2% agarose: specifically, up to 2% dextran sulfate can be incorporated without reducing the elastic character of the unmodified agarose gels, whereas incorporation of 3% dextran sulfate causes G' to fall. It will be shown in Chapter 5 that a 2% doping of dextran sulfate also maximizes the lubricity of semi-interpenetrating hydrogels. In relation to the clinical motivation for coatings that are not slippery until they are wet (e.g. in contact with biological fluids or tissue), addition of dextran sulfate enables the gels to be completely dried and still recover their swollen and lubricious hydrogel state.

4.5 Conclusion

Semi-interpenetrating hydrogels have been formed from agarose and dextran derivatives, both anionic dextran sulfate and cationic DEAE-dextran. The attraction between DEAE-dextran and agarose hinders spinodal decomposition of the agarose, resulting in gels with a less porous structure. DEAE-dextran also interferes with double helix formation, meaning that the gels become more liquid-like as the amount of DEAE dextran is increased. In contrast, the repulsion between dextran sulfate and agarose keeps the dextran sulfate from interfering with the formation of agarose double helices, resulting in a hydrogel that maintains its mechanical strength. A doping of 2% dextran sulfate maximizes the loading of polyelectrolyte without altering the storage modulus. At this concentration, light scattering indicates that dextran sulfate also makes the pore structure of the agarose more monodisperse. Both the mechanism behind this more monodisperse distribution of scatterers and any implication this structure might have on the gel's tribology, however, remain unclear. The pore size of the agarose doped with 2% dextran sulfate is large enough to allow the dextran sulfate to diffuse away in excess water; in the next chapter the possibility that these hydrogels might be self-lubricating will be

examined. The gel's rapid swelling from a dehydrated state might be utilized to create a surface that can be stored in a dry, stable state a then swollen with water to become lubricious.

4.6 Figures

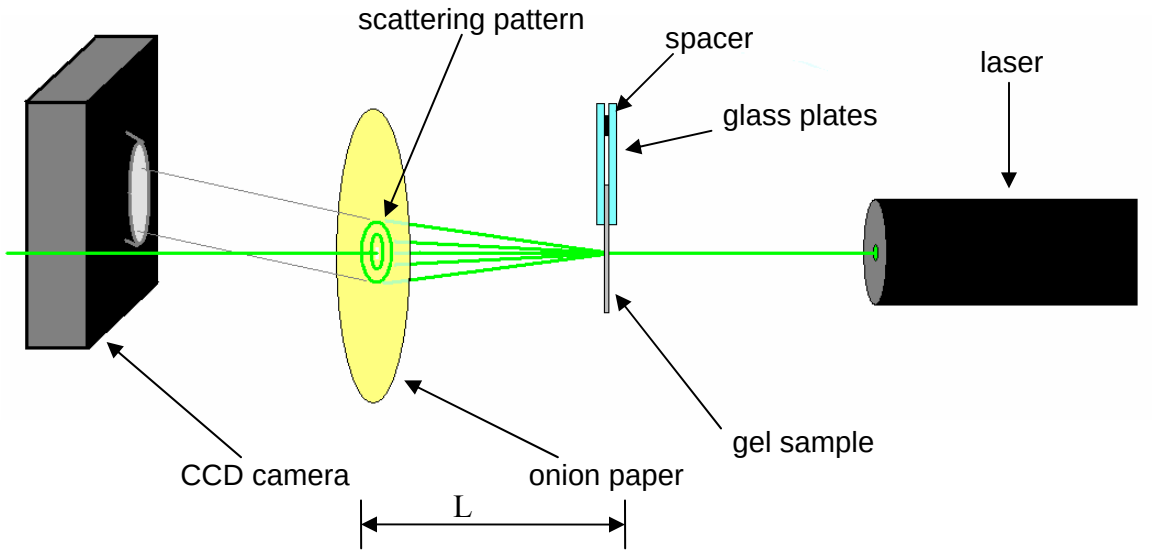

Figure 4.1 Schematic of apparatus used to collect small angle light scattering from hydrogel samples. The distance between the hydrogel and the screen (onion paper) used to image the scattering pattern was L = 15.4 cm. A small hole in the center of the screen was cut to the same size as the laser spot. The CCD camera was set slightly off center, out of the path of the incident beam. See text for description of gel mounting.

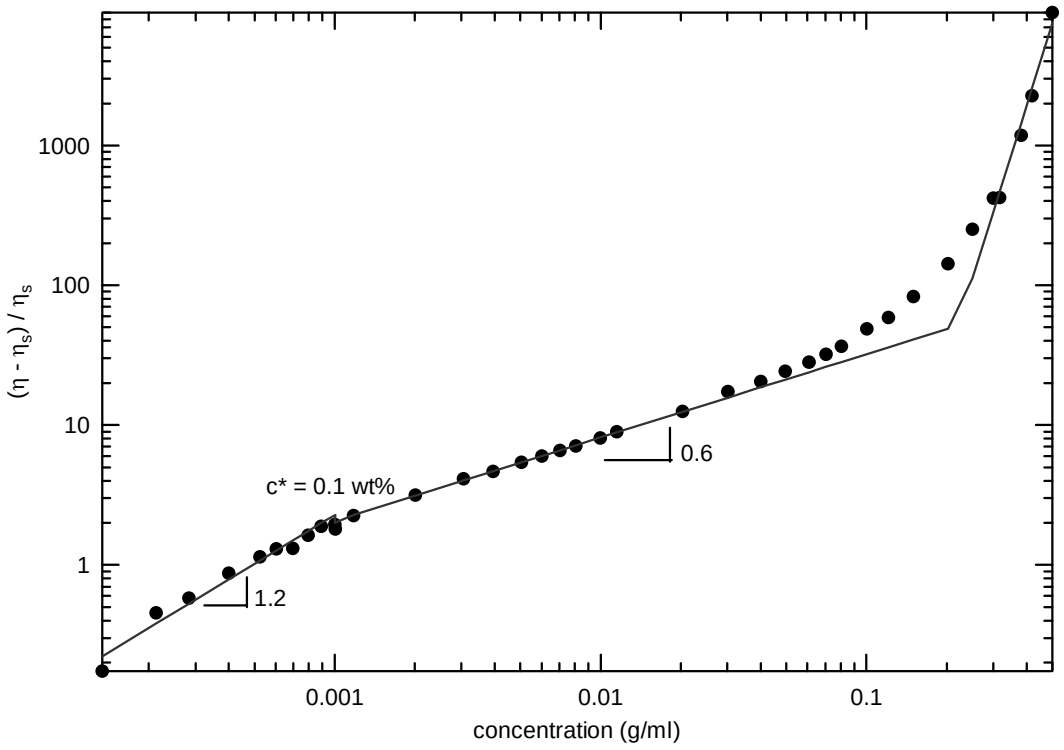

Figure 4.2 Viscosity of dextran sulfate solutions. Change in the slope of the specific viscosity versus concentration curve indicates an overlap concentration of 0.1%. The slope of the reduced viscosity versus concentration curve is 1.2 below in the dilute regime; in theory the slope should be 1. In the semi-dilute region, the slope of the curve is 0.6, close to the theoretical value of 0.5 for a polyelectrolyte.

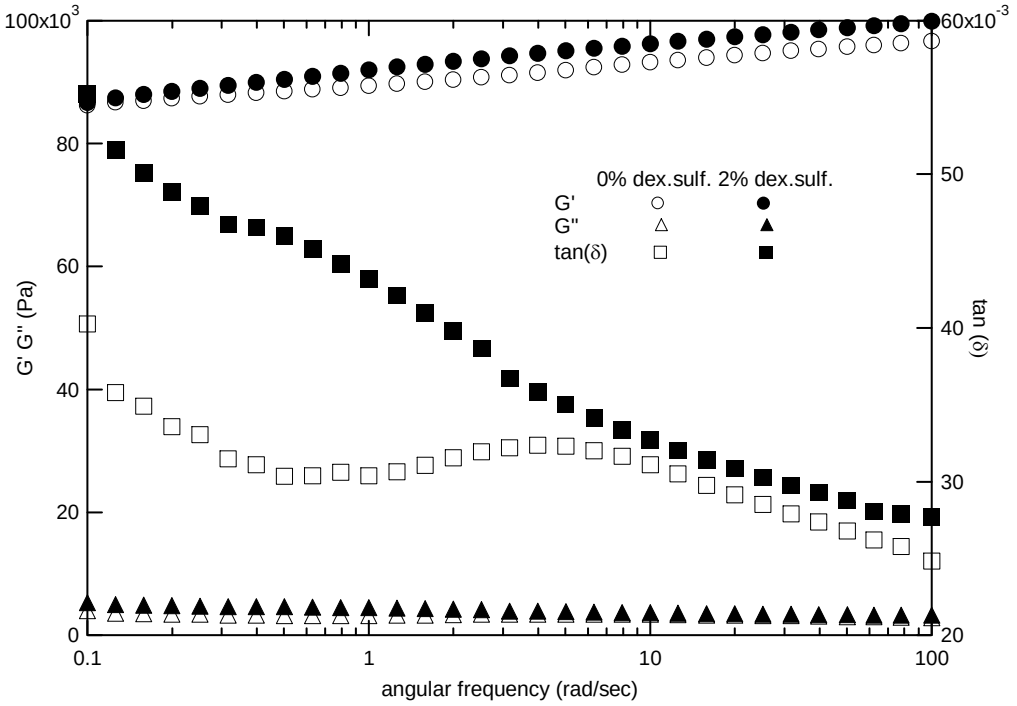

Figure 4.3 Typical frequency sweeps of 2% agarose and 2% agarose and 2% dextran sulfate hydrogels.

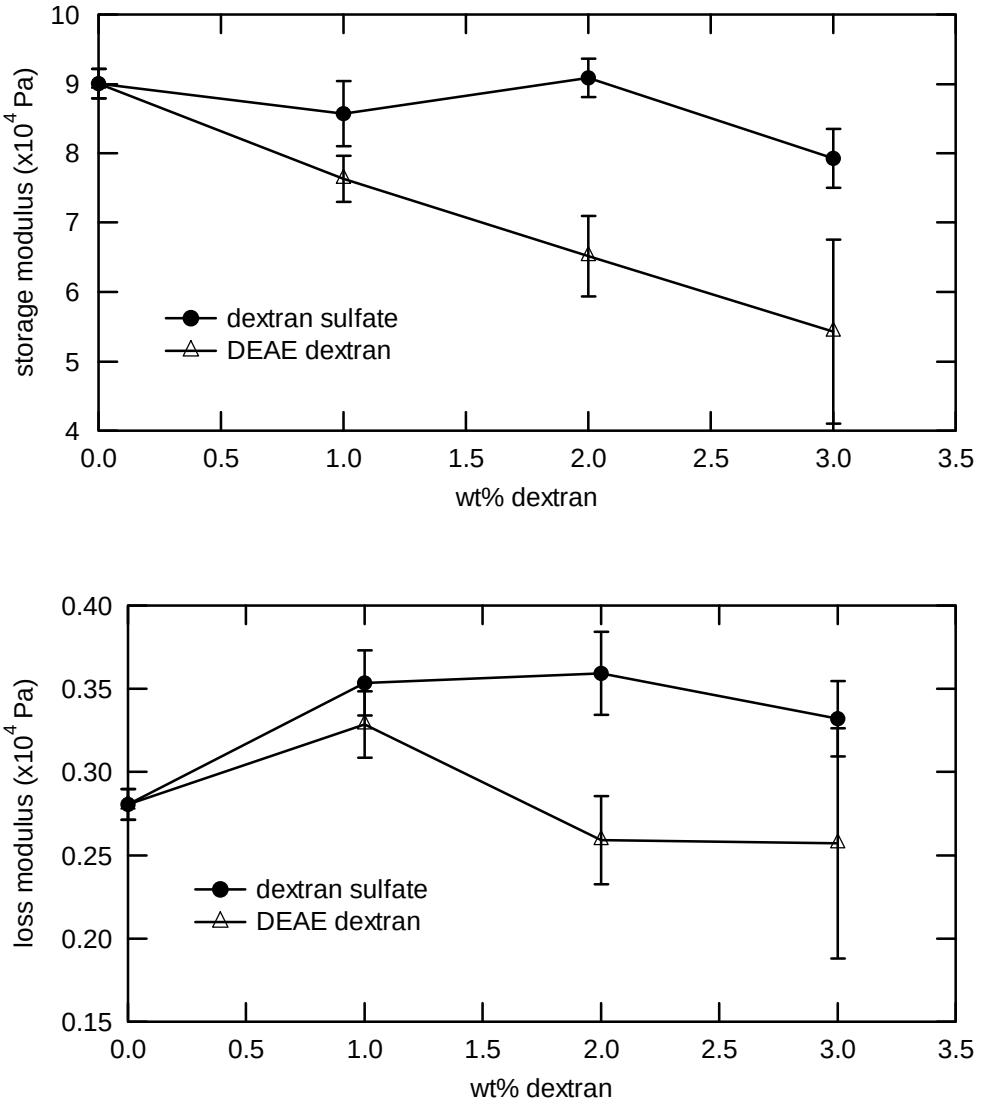

Figure 4.4 Change in rheology of agarose as fraction of added dextran sulfate or DEAE-dextran is increased. Data taken at 1 rad/sec and 1000 μN·m. Average of four independent measurements; error bars are one standard deviation.

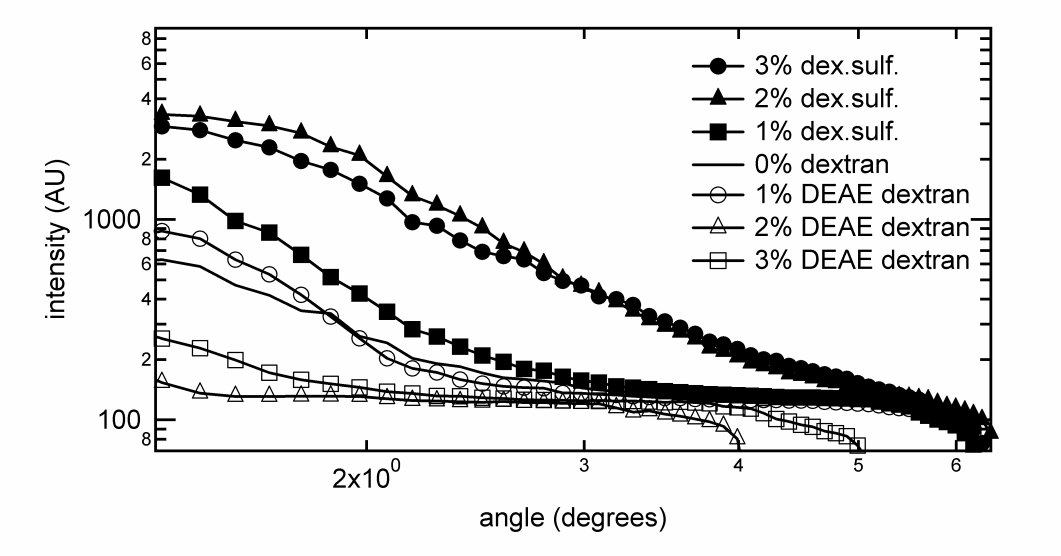

Figure 4.5 Small angle light scattering from semi-interpenetrating gels of agarose and charged dextrans. Agarose is 2% in all samples. Semi-interpenetrating gels formed with agarose and dextran sulfate show an increase in scattering over agarose alone. Semi-interpenetrating gels of agarose and DEAE dextran show a decrease in scattering compared to agarose alone when present in 2% or 3%.

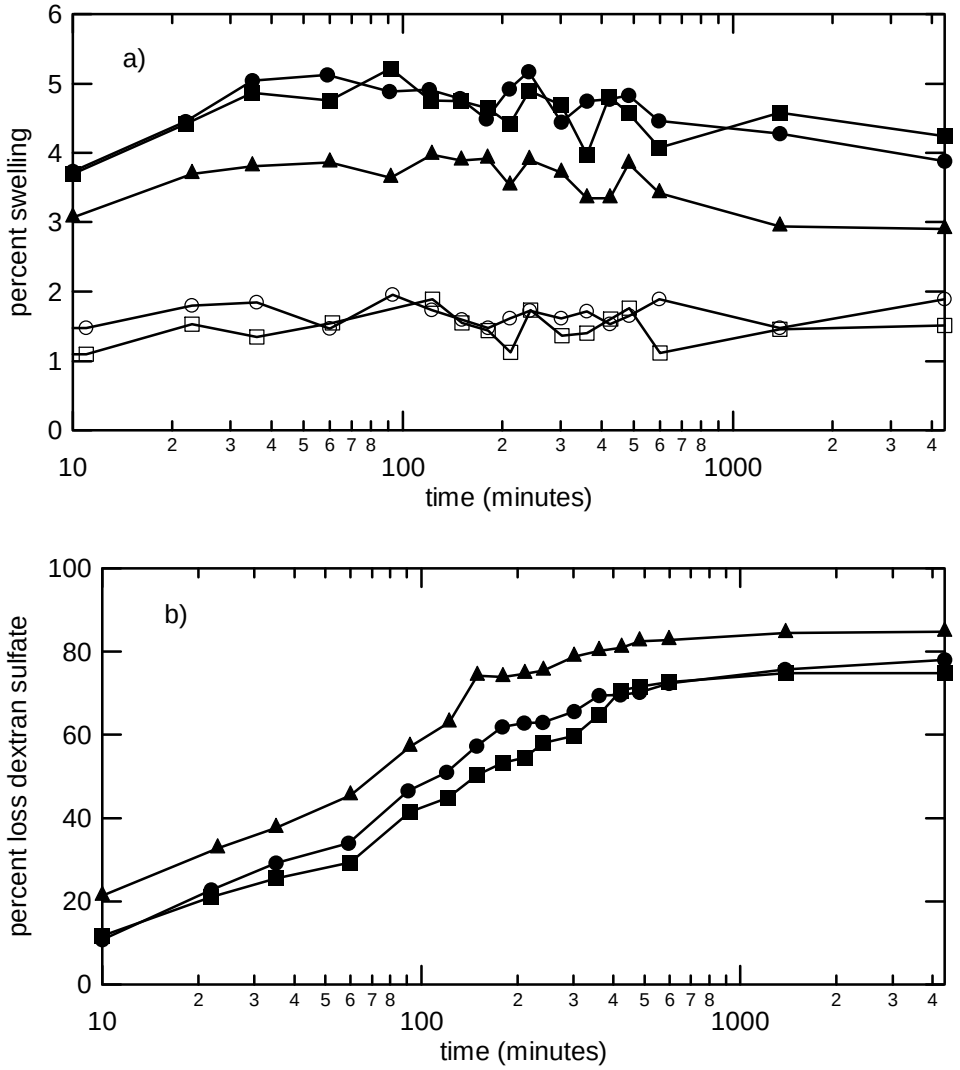

Figure 4.6 Swelling (a) and release of dextran sulfate (b) from 2% agarose (open symbols) and 2% agarose and 2% dextran sulfate (filled symbols). Gels were cut into cylinders 1.5 cm in diameter and 1.1 cm high. Percent swelling is defined as 100 times the difference between the mass of the gel at a given time and the mass of the sample at the initial time divided by the mass of the sample at the initial time:

$$percent\ swelling = \frac{mass - mass_0}{mass_0} \times 100.$$

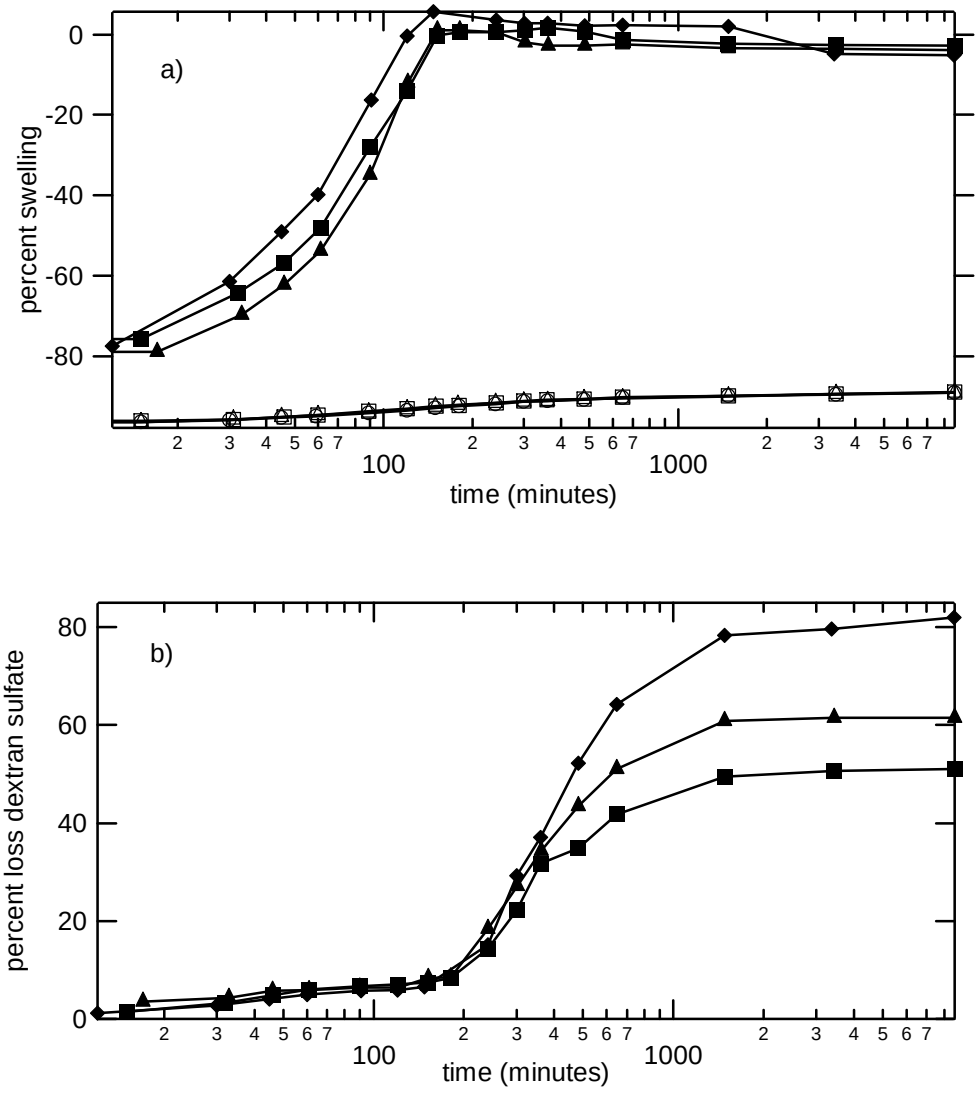

Figure 4.7 Swelling (a) and release of dextran sulfate (b) from hydrogels prepared at 2% agarose (open symbols) and semi-interpenetrating hydrogels prepared at 2% agarose and 2% dextran sulfate (filled symbols) and dehydrated. Hydrogels are cylinders 1.5 cm in diameter and 1.1 cm high. Percent swelling is defined as 100 times the difference between the mass of the gel at a given time and the mass of the sample before dehydration divided by the mass of the sample before dehydration:

$$percent\ swelling = \frac{mass - mass_0}{mass_0} \times 100.$$

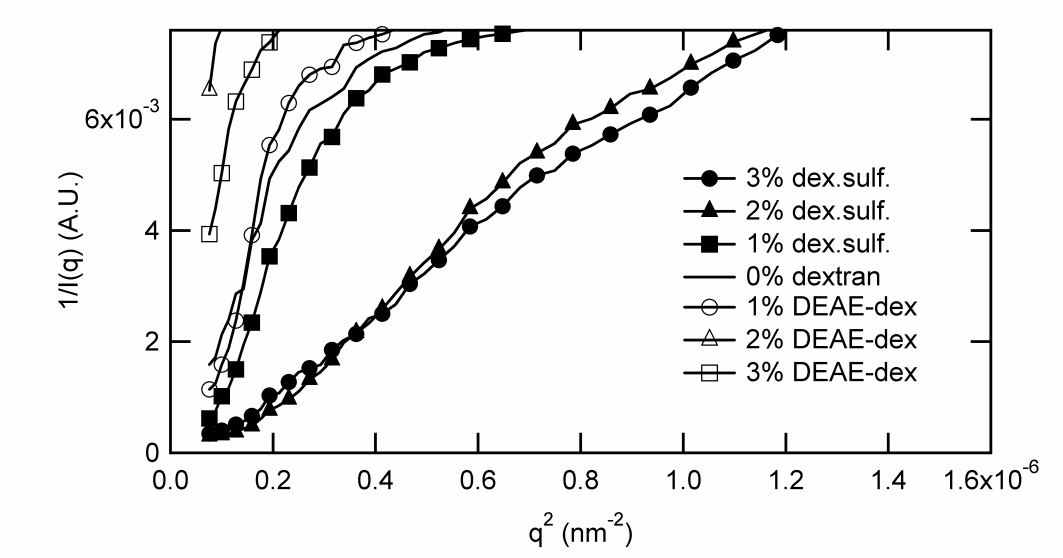

Figure 4.8 SALS of dextran-doped agarose hydrogels plotted using Ornsitein-Zernicke formalism.

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