Towards Understanding Microgel Volume Phase Transitions

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Abstract

Microgels are polymer-based particles which are able to change size and shape during volume phase transition in response to external stimuli. We have investigated microgels which respond to changes in temperature for eventual use in drug-delivery systems on the nano to micro scale. Light scattering data on Hydroxypropylcellulose (HPC) microgels has been analyzed to determine microgel parameters such as radii, molecular weight, and polydispersity at various temperatures. The classic Flory-Huggins approach to mixing polymer-solvent solution is used to model a temperature-size dependence for the microgels. Existing theory on the microgel size dependence on the amount of crosslinker is examined. A new term is added to account for a minimum microgel size at large crosslink densities. We find that many microgels behave with the expected Lower Critical Solution Temperature (LCST) and are generally matched with FH theory despite not accounting for the crosslinker in the model. Several sample runs have exhibited other interesting temperature dependent functions which are likely due to non-homogeneous crosslinking occurring during synthesis. We discuss such inhomogeneities and the relevant models at length. New attempts at reconciling the Flory-Huggins theory with a crosslinker-dependent model as well as ways to model unusual swelling behaviors are being considered.

Temperature-Dependent Microgels

Microgels are polymer particles in which chains are interconnected by self-tangling and crosslinking. Due to the amphiphilic nature of the polymer used (HPC), a reversible volume phase transition is observed in aqueous solutions. The microgels are able to change their volume up to 10 times at their transition temperature (LCST, ~41C). HPC polymer chains on their own will exhibit a reversible phase transition between a good solvent at low temperatures due to their exposed hydrophilic groups (OH) and a poor solvent at high temperatures due to their hydrophobic groups (CH2, CH3: see below and right).

HPC Polymer Chains
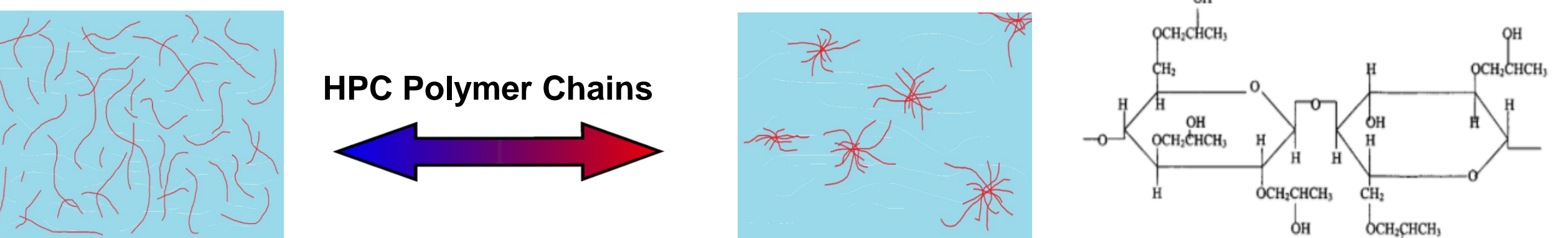
When a microgel is created from the polymer and crosslinking connections (purple), a similar phase transition occurs (see below). Note that the semi-spherical network structure that is formed has two distinct radii. An outer radius (hydrodynamic) includes dangling chains that can trap water as they diffuse in solution; and an inner radius (of gyration) which remains constant under rotation. These are often referred to as the core and shell, respectively. We are interested in controlling microgel size for various applications.

Crosslinked Microgel

Hydrodynamic / Gyration
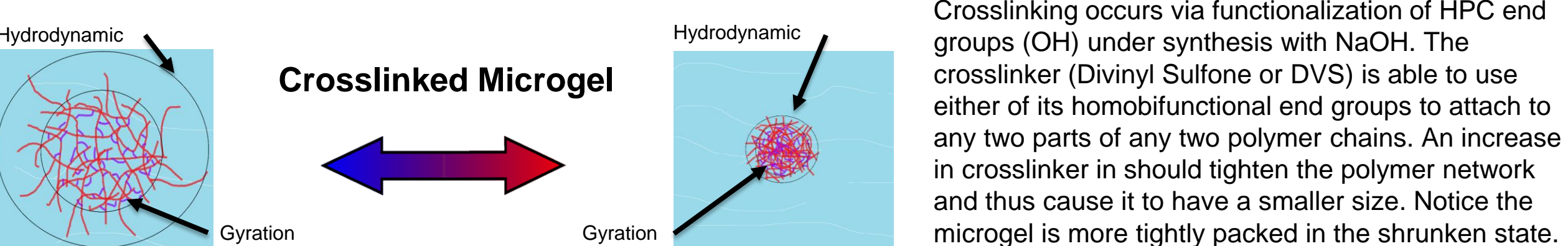
Crosslinking occurs via functionalization of HPC end groups (OH) under synthesis with NaOH. The crosslinker (Divinyl Sulfone or DVS) is able to use either of its homobifunctional end groups to attach to any two parts of any two polymer chains. An increase in crosslinker in should tighten the polymer network and thus cause it to have a smaller size. Notice the microgel is more tightly packed in the shrunken state.

Flory-Huggins Polymer-Solvent Theory

We consider the free energy in the polymer-solvent lattice structure for mixing as well as the free energy for elasticity of the crosslinked chains. Then, we convert to osmotic pressure via the thermodynamic relation shown. This allows for substitution into the equilibrium condition corresponding to stability of the microgel in an aqueous solution. Solving this for temperature provides a temperature-size dependence (after substitution of the Flory-chi parameter) which can be used to fit our data on microgel size at various temperatures.

$$\Delta G_{mix} = (1-\phi)\ln(1-\phi) + \chi\phi(1-\phi)$$

$$\Delta G_{elas} = \frac{-3kTv_e}{2}\left(\left(\frac{\phi}{\phi_0}\right)^{2/3} - 1 - \ln\left(\frac{\phi}{\phi_0}\right)\right)$$

$$\Pi = \frac{\phi^2}{a^3}\frac{\partial \Delta F/\phi}{\partial \phi}$$

$$\Pi_{mix} = -\frac{k_B T}{a^3}[\phi + \ln(1-\phi) + \chi\phi^2]$$

$$\Pi_{elas} = \frac{k_B T}{a^3}\frac{\phi_0}{N_x}\left[\frac{1}{2}\left(\frac{\phi}{\phi_0}\right) - \left(\frac{\phi}{\phi_0}\right)^{1/3}\right]$$

$$\Pi_{mix} + \Pi_{elas} = 0$$

$$T = \frac{\Delta H}{k_B\left(\frac{\phi_0}{N_x\phi^2}\left[\frac{1}{2}\left(\frac{\phi}{\phi_0}\right) - \left(\frac{\phi}{\phi_0}\right)^{1/3}\right] - \frac{1}{\phi} - \frac{\ln(1-\phi)}{\phi^2}\right) + \Delta S}$$

$$\frac{\phi}{\phi_0} = \frac{R_{min}}{R}$$

$$\chi = \frac{\Delta H - T\Delta S}{k_B T}$$

Crosslink Dependence on Size

Flory[1] has stated the total free energy (first line) as the sum of elastic and mixing contributions. K is used as a similar variable to the formerly defined Flory-chi parameter. Using the swollen approximation (volume fraction close to zero), the natural logarithm is expanded. An equilibrium condition is posed (assuming pure solvent) and molecular weight of the chain is solved for. Under Flory's statement, the molecular weight of a crosslinked polymer chain is inversely proportional to the amount of crosslinker per chain. Using this, and converting from volume fraction to radius, we solve for the relationship between size of (swollen) microgel and density of crosslinker.

$$\Delta F = RT\left[\frac{K\phi^2}{2} + \ln(1-\phi) + \phi + \frac{\rho V_1}{M_c}\phi^{1/3}\right]$$

$$K = 2BV_1/RT$$

$$\Delta F = RT\phi^2\left[\frac{K-1}{2} - \frac{\phi}{3} - \frac{\phi^2}{4} + \dots\right] + \frac{RT\rho V_1}{M_c}\phi^{1/3}$$

$$\Delta F = 0$$

$$M_c = -\rho V_1\phi^{1/3} / \left[\frac{K\phi^2}{2} + \ln(1-\phi) + \phi\right]$$

$$M_c = \frac{-2\rho V_1\phi^{1/3}}{(K-1)\phi^2}$$

$$M_c \propto n_c^{-1}$$

$$\phi = \left[\frac{2\rho V_1}{M_c(1-K)}\right]^{3/5}$$

$$R = An_c^{-1/5} \qquad R = An_c^{-1/5} + R_{min}$$

$$\frac{\phi}{\phi_0} = \frac{R_{min}}{R}$$

We have added a minimum radius asymptote here due to the non-physicality of the high crosslink limit.

Effect of Synthesis Temperature

In this set of data (provided by Dr. K. Freeman) we change the synthesis temperature T_{syn} of the microgels (in reference to transition temperature T_c, ~41C) to find its effect on the size and deswelling of the microgels. Here we plot radius of microgels at various temperatures for different $\Delta T = T_{syn} - T_c$.

Legend: 1.0C, 1.0C, 2.5C, 3.5C, 5.5C, 8.5C, 10C, 12C, 13C, 15C, 16C, 18.5C
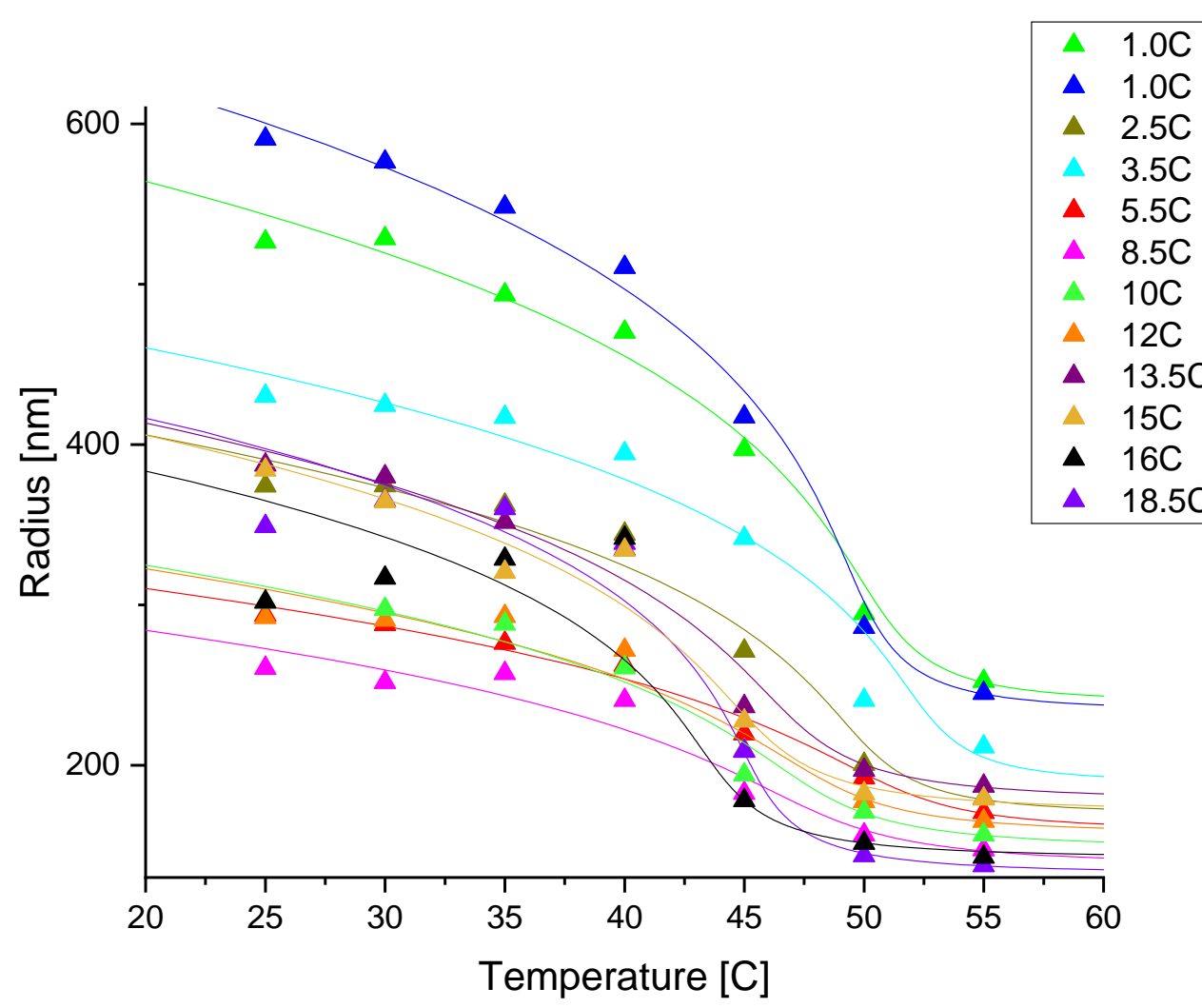
Python's scipy "curve_fit" function is used to fit these datasets with the temperature-size relationship shown in the Flory-Huggins section. Chains per volume, leftover entropy and enthalpy (ΔH and ΔS shown in fit function) are the output optimized fit parameters.
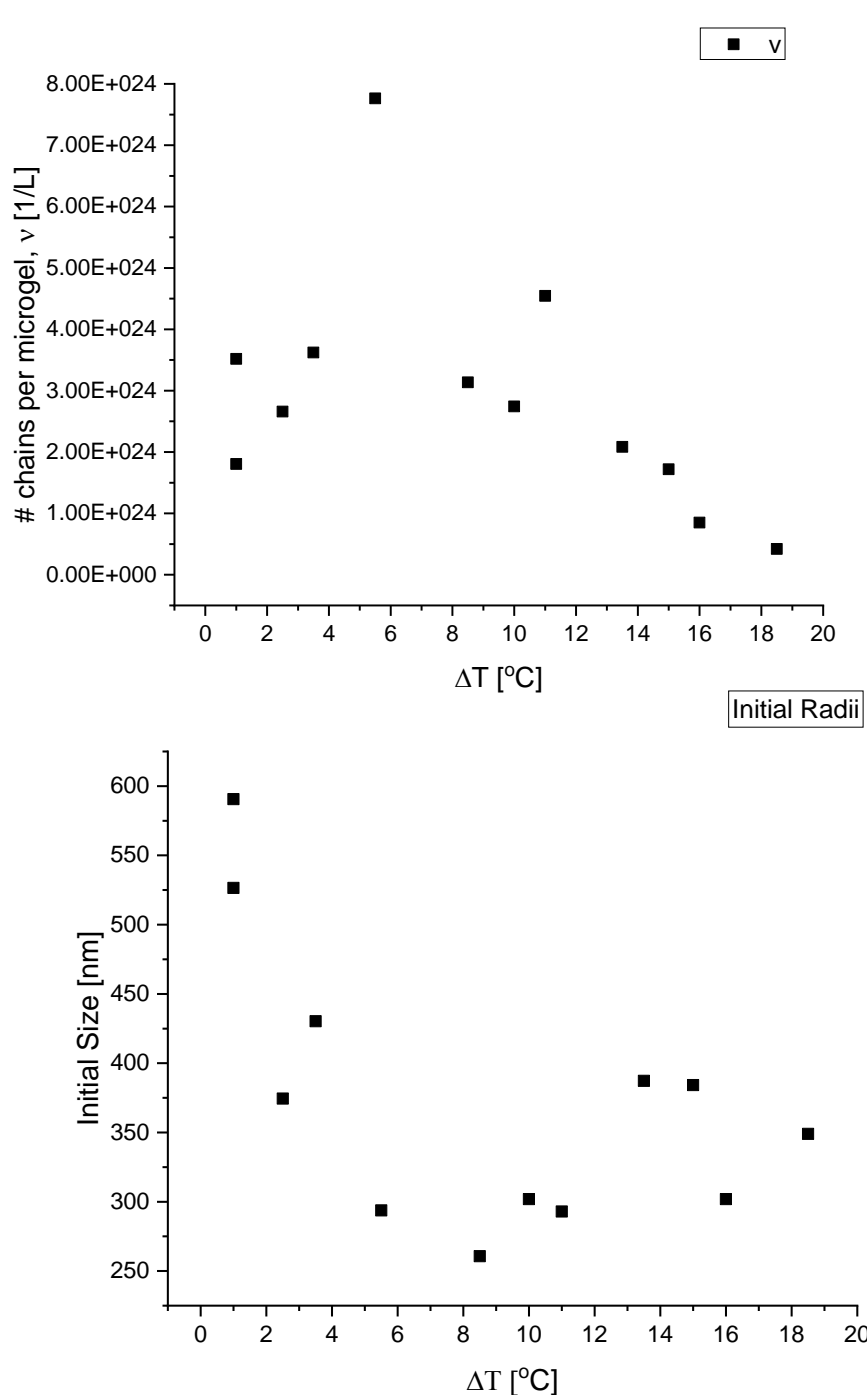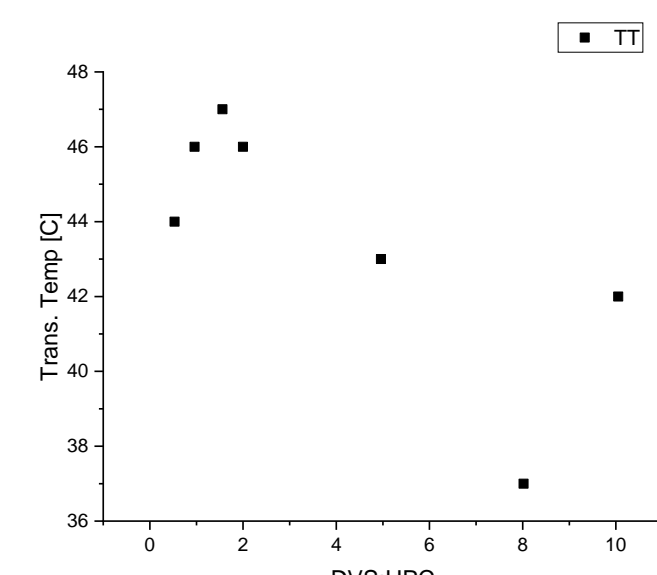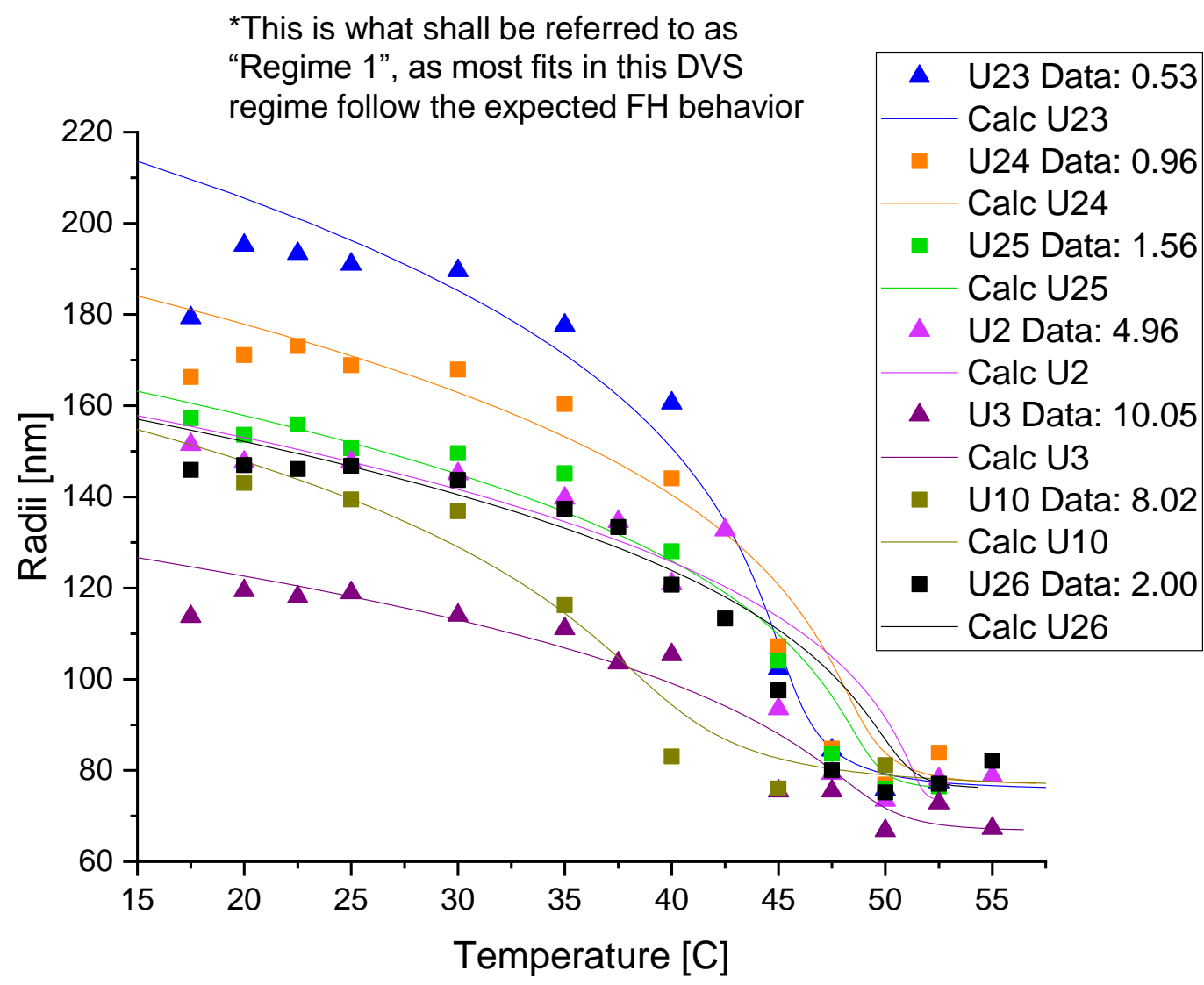
FH fits yield peculiar relationships between (apparent) number of chains per microgel and ΔT and the radius at 25C and ΔT. When the two plots of chains (coming from optimized fit parameters) and swollen size (taken as initial data point) are compared, we see an extremum in both data sets near 5-10 C. The minimum microgel size appears to align with the maximum of calculated chains per volume in the microgel. This suggests that there is a very dense packing of the microgel (at constant crosslink density) near a synthesis temperature of 46-51C.

Effect of Crosslinking Density

*This is what shall be referred to as "Regime 1", as most fits in this DVS regime follow the expected FH behavior

Legend: U23 Data: 0.53, Calc U23, U24 Data: 0.96, Calc U24, U25 Data: 1.56, Calc U25, U2 Data: 4.96, Calc U2, U3 Data: 10.05, Calc U3, U10 Data: 8.02, Calc U10, U26 Data: 2.00, Calc U26
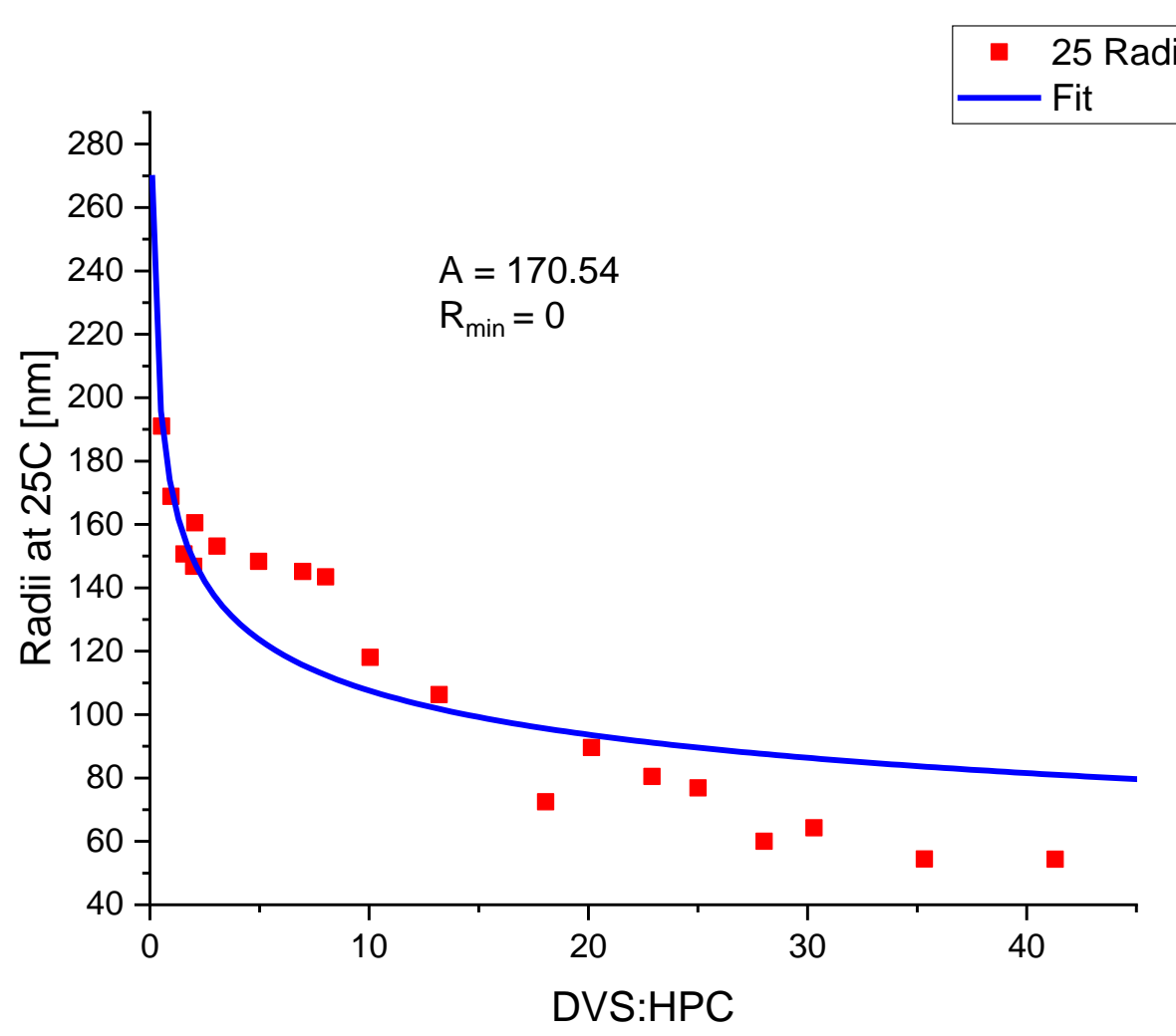
We have also studied how the amount crosslinker impacts the size distribution and temperature dependent behavior of microgels in depth. We denote the DVS:HPC as a unitless ratio from [g/L] used in synthesis. This is shown in the legend to the left.

We are interested to see if crosslinker affects the swollen microgel size in the way theory predicts (see "Crosslink Dependence on Size" and "Radial Dependence on Crosslink Density"). There seems to be a slight negative correlation between transition temperature and DVS crosslinker, however this is difficult to determine with much certainty (see plot in bottom right).

One should note that there seems to be an apparent increase in size at low temperature which is not predicted by theory. (Standard FH theory predicts a monotonically decreasing size as a function of temperature.) One should also see that there is a rather drastic difference between 0.53 DVS:HPC and 2.00 DVS:HPC in terms of their initial size and thus volume change. Nevertheless, this general trend is expected to occur since a more heavily crosslinked microgel should exhibit both of these properties.

Radial Dependence on Crosslink Density

A = 170.54
$R_{min} = 0$

$$R = An_c^{-1/5} + R_{min}$$

We allow A to be unitless in order to avoid any confusion arising in its value. It may simply be considered as a "volume parameter" for the particular polymer stock.
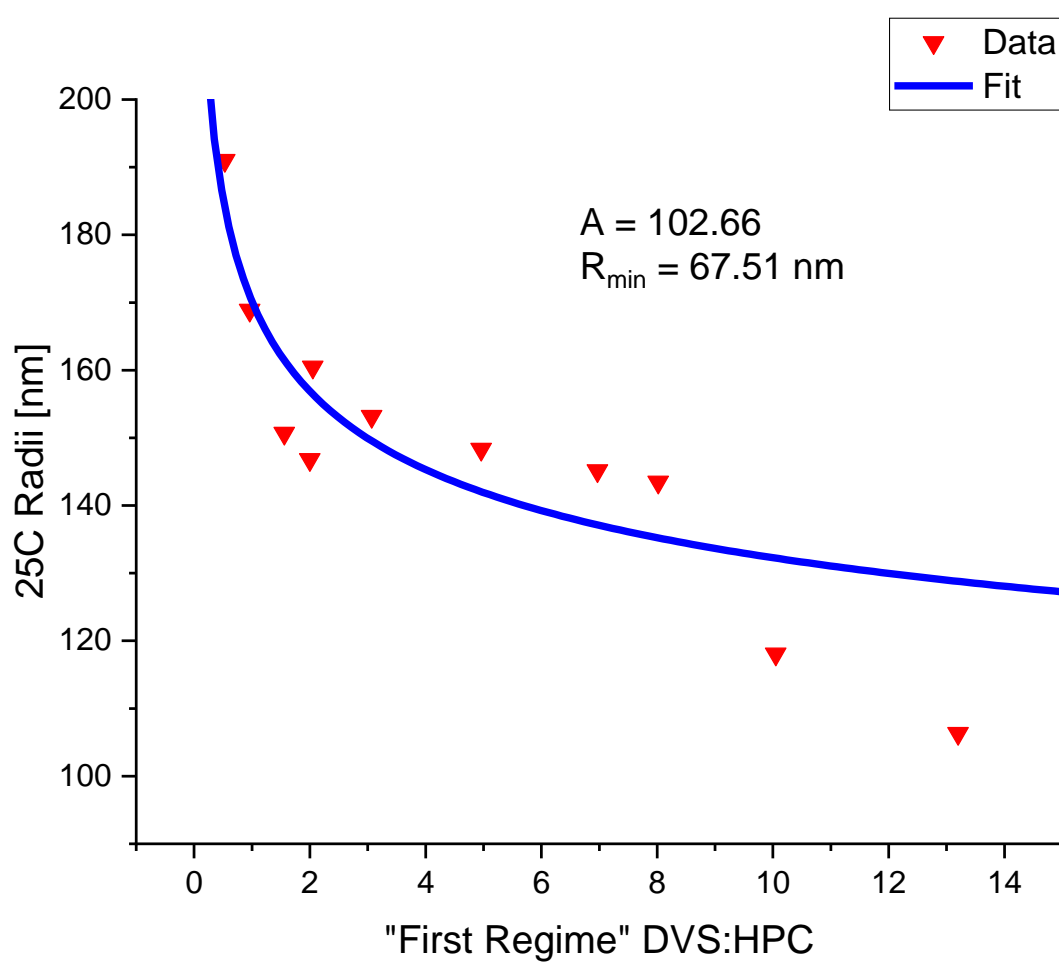
A = 102.66
$R_{min} = 67.51$ nm

Due to the possibility of non-homogeneous crosslinking (which is discussed in "Three Regimes"), we are negating the premises of the theory involved for fitting. The value of R_{min} has to be defaulted to zero in order for it to be nonnegative.

In the future, we hope to use the value of A to further characterize a particular (parent polymer of) microgel stock using the volume fraction equation set up in the corresponding theory section.
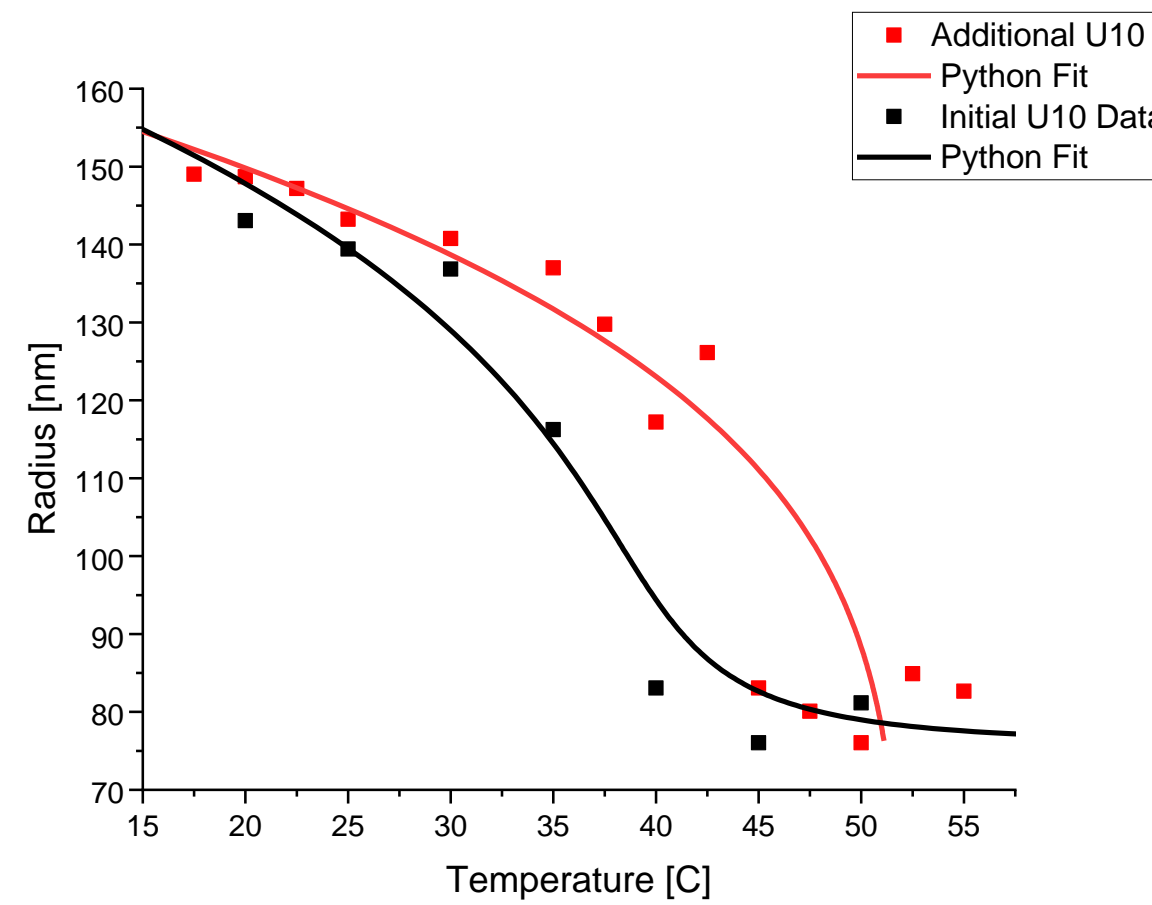
We split off only the first regime of data from the previous (left) full run. We see a general decrease in size with crosslink density and we are able to obtain a minimum size. This 68 nm corresponds quite well to the minimum size observed on the previous graph (left).

Failed Fits

Legend: Additional U10, Python Fit, Initial U10 Data, Python Fit

Python's scipy fitting tools were used to help automate the fitting procedure and to have more control over the parameters and viewing compared to Mathcad. While this was successful for the most part, there were some peculiar issues after adding more data to the current set. The example on the left depicts a fit working for a standard temperature step of 5C. After adding in intermediate points in half the step size, the fit fails unexpectedly and yields fit parameters that are off by several orders of magnitude from expected values.

We are currently looking into ways to "repair" these peculiarities. Origin 2018b has been used to attempt a fit (but provided a similarly poor "failure" in terms of provided parameters. Ideally, we will write our own script to optimize fit parameters by a regression of least squares.
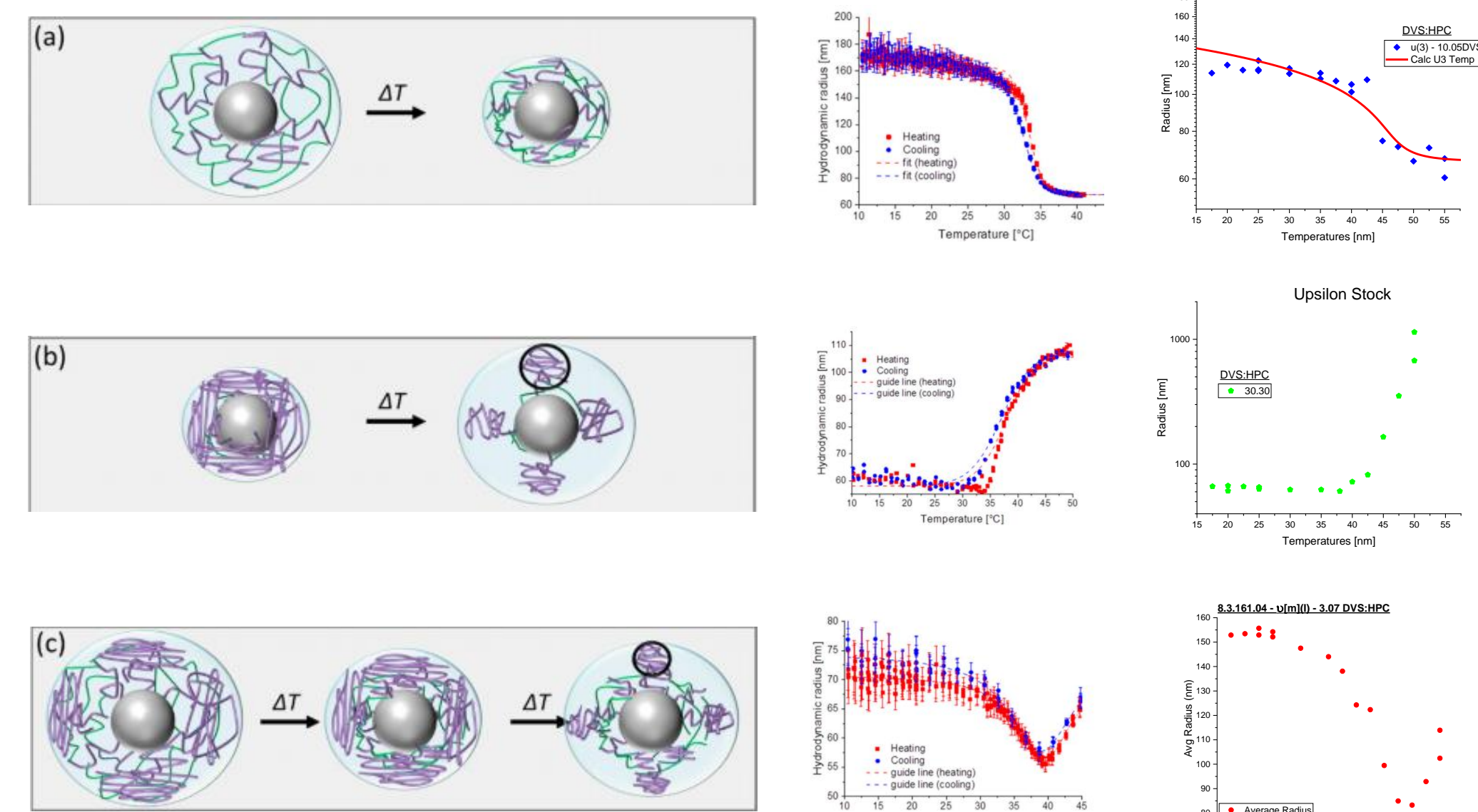
Three Regimes

We have observed three "regimes" corresponding to behaviors found in literature [2], in which a silica-gel based microgel is synthesized with differing crosslinker gradients. The first two columns (graphic, sample run) are taken from that literature by N. Nun et. al.

In the first regime, there is homogeneous (random, well distributed) crosslinking occurring throughout the microgel. This produces the expected temperature dependence (governed by FH). In the second regime, heavy crosslinking occurs near the surface of the microgel balls, and at the peripheral. Together, this forms smaller "microgel balls" which are interconnected by the internal crosslink connections. Similar behavior is observed in our system. In the third regime, there is a superposition between the first two regimes which results in the expected drop in size, then an increase at higher temperatures. We currently believe our system is somehow exhibiting similar internal compositions despite the lack of a silica-gel center.

Conclusions

- Flory-Rehner-Huggins (FH) solution theory and crosslink dependence on radius has been successfully applied to our microgels.
- We have found a reproducible FH temperature dependence on the size of microgels in our most recent stock (Upsilon)
- Software for fitting was updated to handle large sets of data and improve quick visualization
- A dependence between smallest size, largest amount of chains per microgel, and optimal synthesis temperature has been found
- We have observed and used literature to fit a crosslinker dependence on the swollen microgel size
- Three regimes have been observed which are very similar to those seen in literature

Future Work

Future work should be sure to involve:
- Determining the radius of gyration as a function of temperature in addition to hydrodynamic radius in order to learn more about the core-shell structure of our particles
- "Repair" Python's curve fitting program for our specific issue on hand
- Use the calculated volume parameters in order to compare theoretically predicted molecular weight, density, and volume with measurements
- **Make advances in the FH theory to account for non-homogeneous crosslinking**

References and Acknowledgements:
Ref[1]: Flory, P.J., Rehner, J.; J.Chem. Phys. **11**, 521 (1943)
Ref[2]: N. Nun et. al. Gels 2017, 3, 34