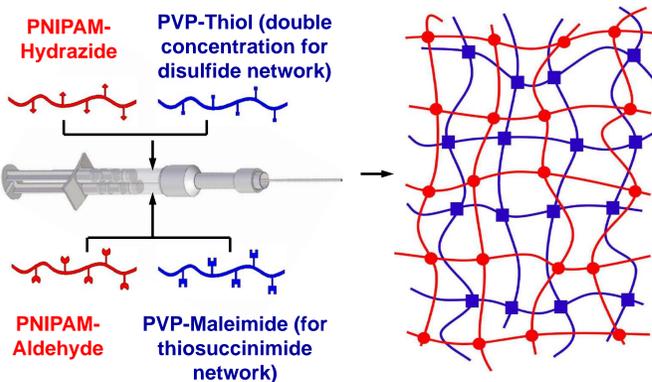




## Introduction

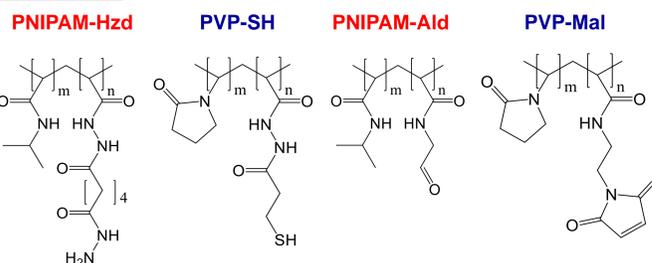
Interpenetrating polymer networks (IPNs) are cross-linked polymeric materials consisting of two distinct networks overlapping in the same bulk volume without chemical connection. Physical entanglement between networks reinforces mechanical properties, and macroscopic miscibility can be enhanced.

Reported IPN hydrogels in the literature are either not injectable or require *in situ* polymerization (1), which can be problematic for *in vivo* applications due to reaction toxicity, heating, and/or UV exposure (2). Alternatively, hydrogels can be produced by reactive mixing of functionalized prepolymers. Using two orthogonal covalent cross-linking schemes, such as the hydrazone and thiosuccinimide reactions (3), an injectable IPN hydrogel can be produced (4).



## Experimental

Hydrogel	Barrel 1	Barrel 2
<b>Composition</b>	<b>Nucleophiles</b>	<b>Electrophiles</b>
<b>PNIPAM</b>	6 wt% PNIPAM-Hzd	6 wt% PNIPAM-Ald
<b>PVP</b>	9 wt% PVP-SH	9 wt% PVP-Mal
<b>Semi-IPN</b>	6 wt% PNIPAM-Hzd 9 wt% unfunctionalized PVP	6 wt% PNIPAM-Ald 9 wt% unfunctionalized PVP
<b>Inverse</b>	6 wt% unfunctionalized	6 wt% unfunctionalized
<b>Semi-IPN</b>	PNIPAM 9 wt% PVP-SH	PNIPAM 9 wt% PVP-Mal
<b>IPN</b>	6 wt% PNIPAM-Hzd 9 wt% PVP-SH	6 wt% PNIPAM-Ald 9 wt% PVP-Mal
<b>Disulfide IPN</b>	6 wt% PNIPAM-Hzd 13 wt% PVP-SH	6 wt% PNIPAM-Ald



**PNIPAM-Hydrazide (Hzd):** carbodiimide-mediated conjugation of excess adipic dihydrazide to PNIPAM-co-acrylic acid

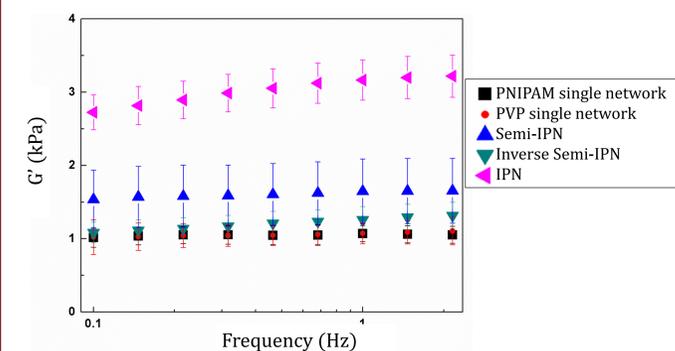
**PNIPAM-Aldehyde (Ald):** copolymerize NIPAM with acetal-protected comonomer; acidic hydrolysis to aldehyde

**PVP-Thiol (SH):** conjugate dithiobis(propanoic dihydrazide) to PVP-co-acrylic acid; reduce central disulfide with dithiothreitol

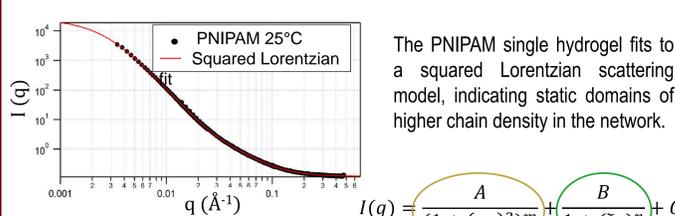
**PVP-Maleimide (Mal):** carbodiimide-mediated conjugation of aminoethyl maleimide to PVP-co-acrylic acid

## Rheology – Thiosuccinimide IPN

Shear storage moduli ( $G'$ ) for the IPN's significantly exceeded both the single-network and semi-IPN controls, clearly showing synergistic reinforcement beyond that attributable to the increased mass fraction of polymer in the composite.

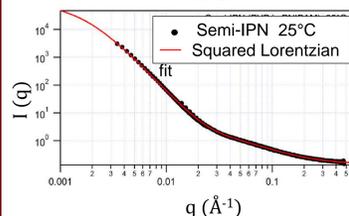


## Small-Angle Neutron Scattering

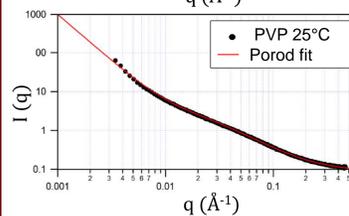


The PNIPAM single hydrogel fits to a squared Lorentzian scattering model, indicating static domains of higher chain density in the network.

$$I(q) = \frac{A}{(1 + (\gamma q)^2)^m} + \frac{B}{1 + (\xi q)^n} + C$$

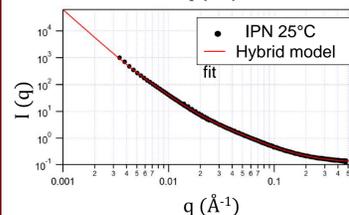


The semi-IPN of free PVP in a PNIPAM network fits to the same model, showing the entrapped PVP does not suppress PNIPAM domain formation



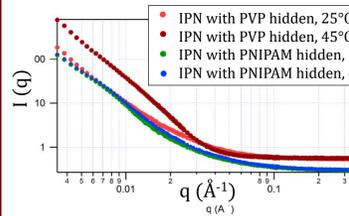
The PVP single network fits to a Porod model, indicating non-static mass clusters.

$$I(q) = \frac{A}{q^m} + \frac{B}{1 + (\xi q)^n} + C$$



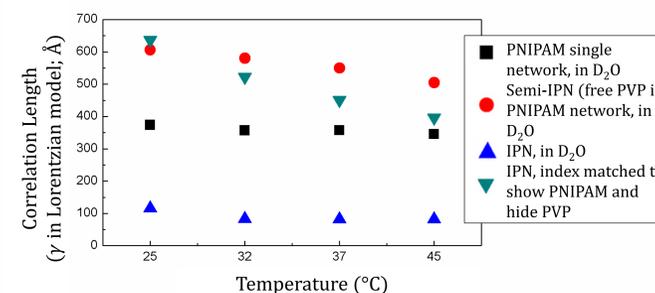
The thiosuccinimide IPN does not fit well to either model, instead requiring a hybrid model summing the network terms from each with a common term for average chain solvation, suggesting both static domains and transient clusters are present.

$$I(q) = \frac{A}{q^l} + \frac{B}{(1 + (\gamma q)^2)^m} + \frac{C}{1 + (\xi q)^n} + D$$



Contrast matching can be used to selectively examine the scattering contributions from PVP and deuterated PNIPAM in IPN's. Each fits according to the model expected of the corresponding single network.

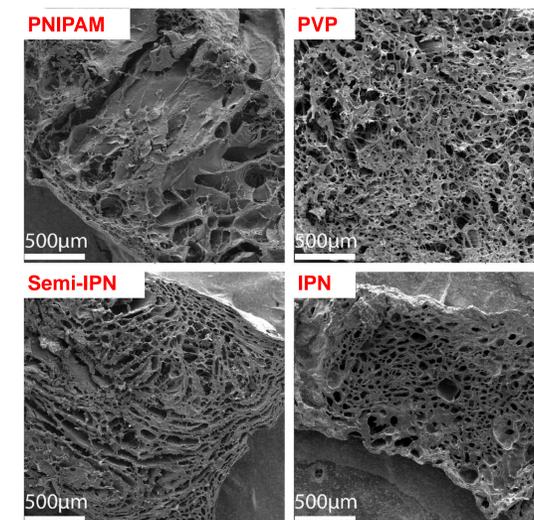
## SANS Continued



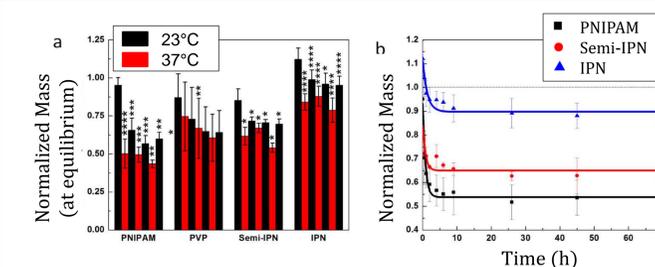
Correlation lengths from the Lorentzian fits / Lorentzian component of the hybrid model indicate distance between domains. The significantly lower result in the IPN in  $\text{D}_2\text{O}$  is attributed to correlations between PNIPAM-rich domains and surrounding transient clusters in the PVP-rich matrix.

## Freeze-Fracture SEM

Hydrogel discs were flash-frozen in liquid nitrogen, cut, lyophilized, and gold-sputtered for SEM imaging. Pore sizes in the semi-IPN and IPN are intermediate between the large pores of PNIPAM and smaller pores of PVP. Additionally, the IPN pores tend to be more rounded than those of the semi-IPN's, which are more flattened. The samples' distinctive responses to freeze-drying indirectly indicate the existence of structural differences between networks in the hydrated state.



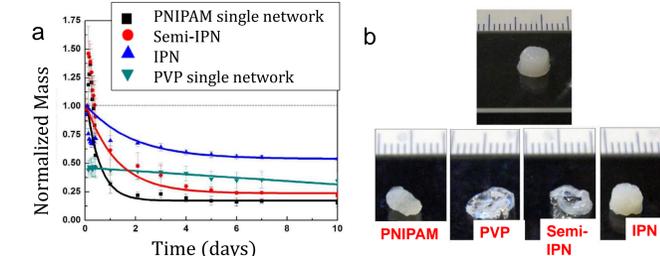
## Thermosensitive Swelling Cycles



a) Equilibrium hydrogel masses over temperature cycling, showing markedly reduced hysteresis in IPN's (re-swelling after first PNIPAM collapse cycle)

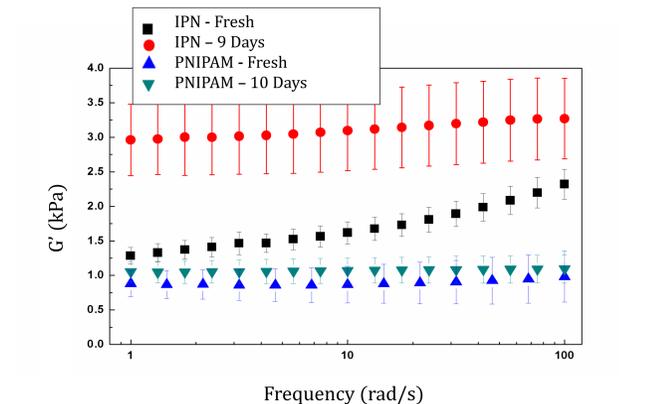
b) Kinetics and exponential fits of first de-swelling transition, showing hydrophilic PVP Network slows PNIPAM collapse (implications for burst release)

## Hydrolytic Degradation



a) Degradation kinetics in accelerated model conditions (0.1M HCl)  
b) Top: representative freshly molded hydrogel. Bottom: PVP, PNIPAM, and semi-IPN largely degraded after 10 days incubation in acid, whereas IPN retains its shape after 40 days

## Disulfide IPN Rheology



IPN's based on disulfide cross-linking of the PVP network develop mechanical reinforcement slowly, compared to single network PNIPAM control which rapidly reaches its equilibrium strength. PVP single network was below the linear viscoelastic measurement range.

## Conclusions

- Demonstrated ability to make IPN hydrogels by kinetically orthogonal reactive mixing
- Resulting hydrogels have distinctive micro- and nano-scale structures, significant mechanical reinforcement, and modulated swelling and degradation behaviour

## References & Acknowledgements

1. Zhao J, Zhao X, Guo BL, Ma PX. Multifunctional Interpenetrating Polymer Network Hydrogels Based on Methacrylated Alginate for the Delivery of Small Molecule Drugs and Sustained Release of Protein. *Biomacromolecules*. 2014;15(9):3246-52.
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