Optical Sensing Components for Nanodevices

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<u>Eight Steps to Creating a Functional Material</u>

STEP 1. CHOOSE AN IMPORTANT PROBLEM TO SOLVE

DIABETES MANAGEMENT: NON-INVASIVE AND MINIMALLY-INVASIVE METHODS FOR GLUCOSE MONITORING (AND/OR INSULIN DELIVERY!)

Methods for frequent and accurate blood glucose monitoring are needed.

1. Current meters are accurate to only 15 %.
2. Most require blood fingerstick.
3. Must be carried by patient.

Minimally- and non-invasive methods are highly desirable

See: (a) Alexeev, V. L. et. al. *Clin. Chem*. **2004**, *50*, 2353., (b) Klonov, D. *Diabetes Care* **1997**, *20*, 433, (c) Khalil, O. S. *Clin. Chem*. **1999**, *45*, 165.

Improvements in minimally- and non-invasive monitoring are needed

Recent review: Arnold, M. A.; Small, G. W. *Anal. Chem.* **2005**, 77, 5429.

To the best of our knowledge, no completely synthetic material has been demonstrated to work in a complex bodily fluid such as human blood plasma for the detection of glucose via a macroscopic size change, potentially affording the delivery of insulin in response to glucose concentration.

STEP 2. CHOOSE A SIMPLE AND PRACTICAL FORM OF SELECTIVE VISUAL SIGNAL TRANSDUCTION

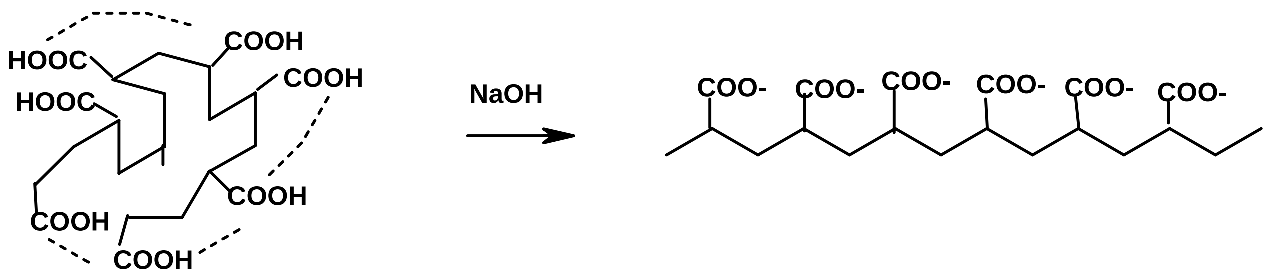
- COLOR CHANGE?
- SIZE CHANGE?

  can also serve as a molecular machine or nanovalve

Artificial muscles, actuators, "machines"

See e.g.:***Polymers, Sensors, Actuators*** (Y. Osada, D.E . De Rossi, Eds.,2000).

Viscosity change of polyanion solution by pH :



W. Kuhn, B. Hargitay, A. Katchalsky, H. Eisenberg, H., *Nature* **1950,** *165*, 514

Gel volume phase transitions T. Tanaka**,** *Phys. Rev. Lett.* **1978,** 820-3

Temperature effects: Wang, C.; Stewart, R.J.; Kopecek, J., *Nature*, **1999**, *397*, 417

pH and temperature effects : Chen, G.; Hoffman, A.S., *Nature*, **1995**, *373*, 49

EAP's : Electrically activated polymers Y. Osada, H. Okuzaki, H. Hori, *Nature* **1992,** *355*, 242

M. Shahinpoor et al *Smart Mater. Struct.* **2001,,** 819-33

Induction by light : Suzuki, A.; Tanaka, T., *Nature*, **1990**, *346*, 345

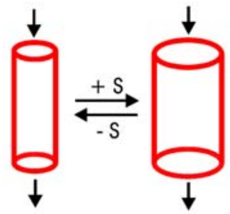
"Machines" based on natural fibers: M. V. Sussman, A. Katchalsky, *Science* **1970,** *167*, 45.

"Molecular machines" – but without macroscopic action :

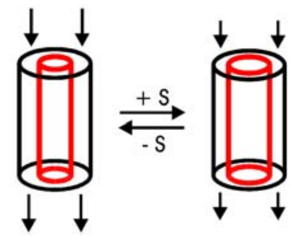
Stoddart et al *Acc. Chem. Res.* **2001**, *34*, 410; Sauvage et al *ibid.* **2001**, *34*, 477 Balzani et. al. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 814. Polymer with natural concanavalin (lectin) expands with carbohydrate : Chen, G. H.; Hoffman, A. S. *Nature*, **1995**, *373*, 49.

POSSIBLE APPLICATIONS

Flow control – also in Microfluidic systems ?



1



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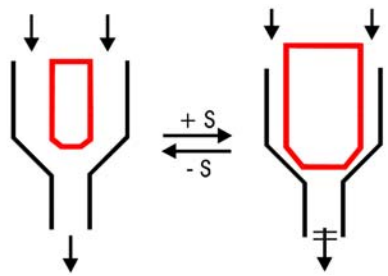

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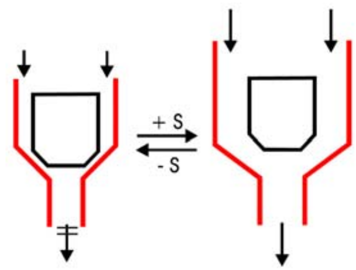

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STEP 3. CHECK THE LITERATURE

RELATED METHODS

- **First proposed synthetic hydrogels for glucose detection/insulin delivery:**

  Kataoka et. al. *J. Am. Chem. Soc*. **1998**, *120*, 12694, B*iomacromolecules* **2003,** *4,* 1410.

  Biomacromolecules **2004,** *5,* 1038.

- Amino and amide-functionalized phenylboronic acids develop charge upon glucose binding, increasing the polarity and water solubility of the polymer, resulting in expansion.
- Conditions: neutral buffer, elevated temp. No natural media studies reported.

SELECTED OTHER RELATED METHODS

Holographic gel from vinyl aminophenylboronic acid that expands in cell culture media:

- Lowe et al. *Anal. Chem.* **2004** *76*, 5748.

Colloidal photonic crystalline array arylboronic acid sensor responding to glucose in tear fluid:

- Alexeev, et al. *Clin. Chem.* **2004,** *50*, 2353**.**

Magnetoelastic sensor with pH-sensitive polymer (PEGD, AA, isooctyl acrylate) immobilized with glucose oxidase enzyme (GOx)

- Cai Q., et al. *Anal. Chem,* **2004,** *76*, 4038.

No examples of fully synthetic, volume change-driven hydrogels that function in complex biological media have been reported.

STEP 4. SET GOALS THAT EMBODY A CLEAR ADVANCE

- CRITERIA:

  1. simpler synthesis / “tunability”

  2. simple, reliable, reversible and selective mechanism of binding and shape change

  3. biocompatible and functional under physiological conditions in a difficult matrix

  4. material should benefit from miniaturization and

  5. be well-suited for nanofabrication techniques

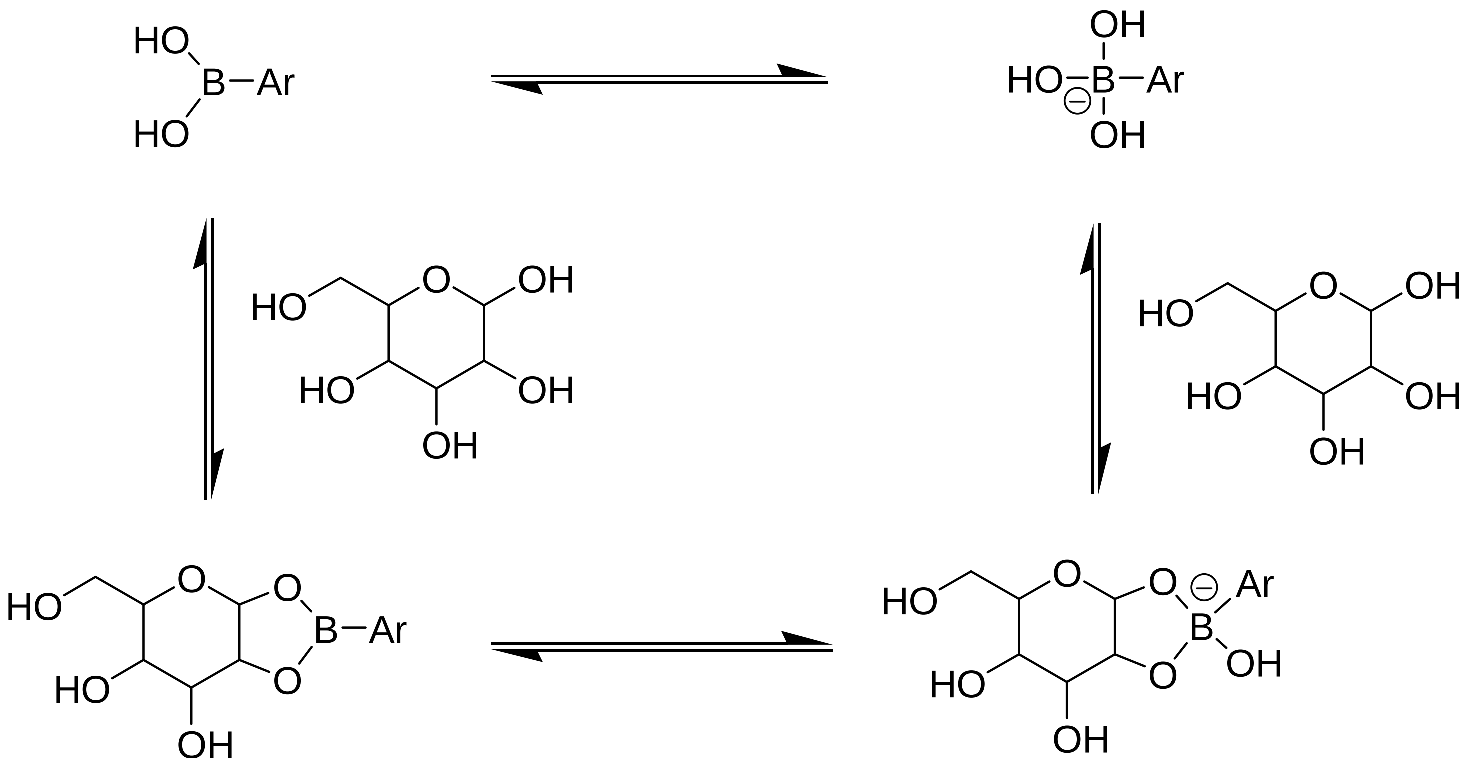
STEP 5. CHOOSE A MATERIAL

- PMMA is an invaluable tool in nanotechnology.
- Can be readily modified
- Relatively biocompatible
- Forms hydrogels which can shrink/expand
- Chemomechanical hydrogels are known to exhibit optimized responses upon miniaturization

STEP 6. SPECIFIC DESIGN APPROACHES FOR THE APPLICATION

- We must determine what clearly distinguishes the chemistry of glucose from other sugars and biomolecules and use this property to design and optimize the proposed material.

SACCHARIDE-INDUCED HYBRIDIZATION CHANGE: REMEMBER HOW ELECTROSTATIC REPULSION LED TO POLYMER EXPANSION IN EARLIEST CASES

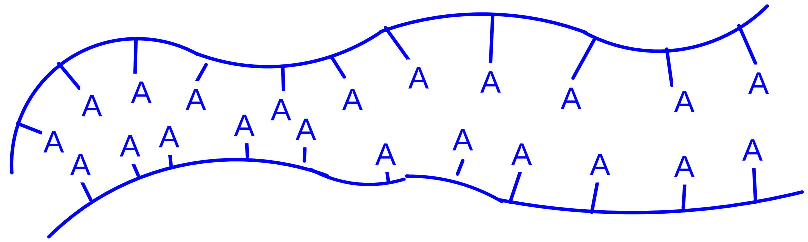


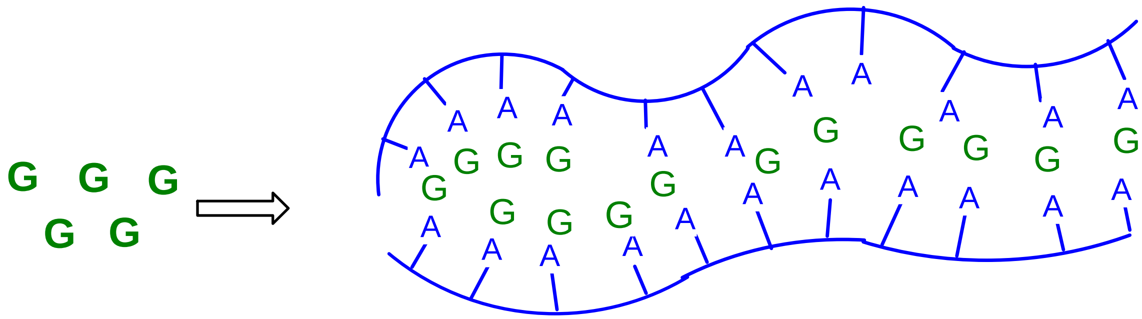
Lorand, J. P.; Edwards, J. D. *J. Org. Chem*. **1959**, *24*, 769.

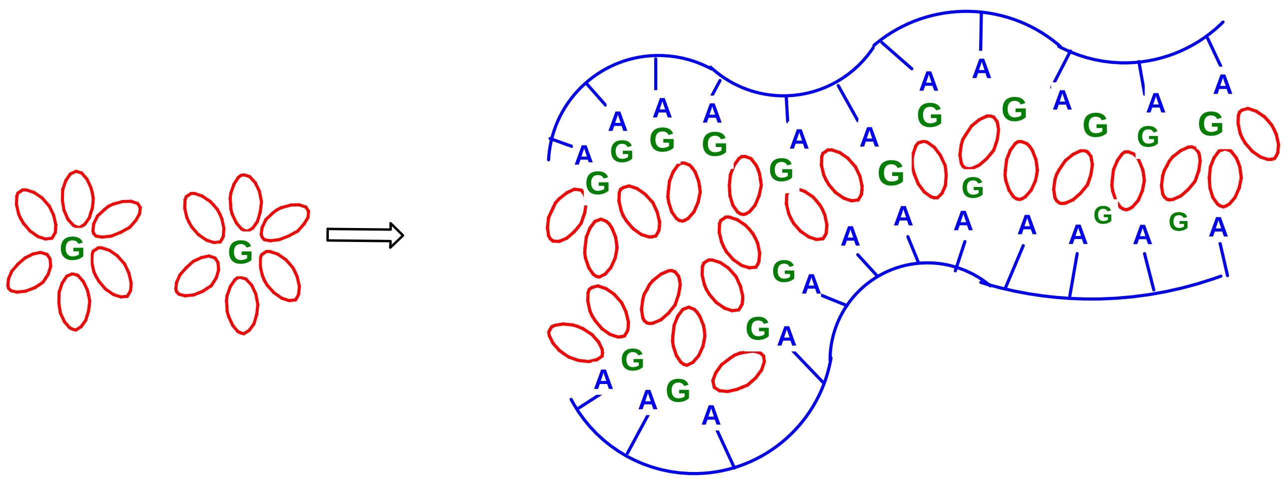
Recent Reviews:

James, T. D.; Shinkai, S. *Top. Curr. Chem*. **2002**, *218*, 159
Wang, W.; Gao, X.; Wang, B. *Curr. Org. Chem*. **2002**, *6*, 1285.

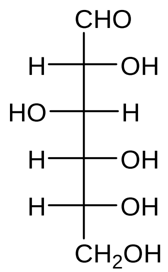
Hydrogel with binding sites A:



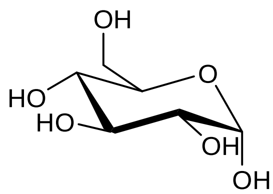




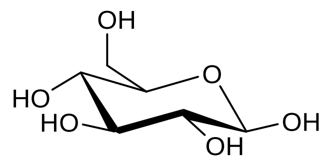
solvation: guest absorption is accompanied by uptake of more water



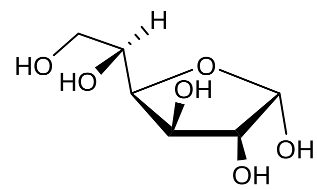
D-glucoaldose



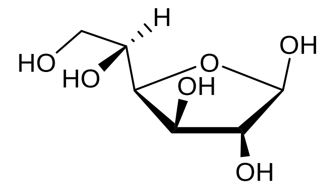
α -D-glucopyranose



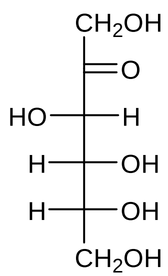
β -D-glucopyranose



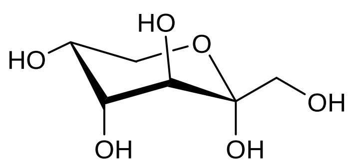
α -D-glucofuranose



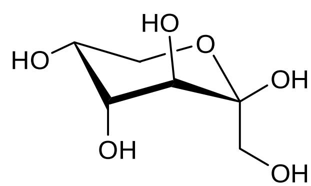
β -D-glucofuranose



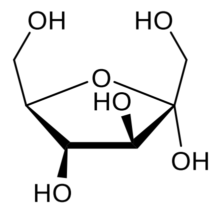
D-fructoketose



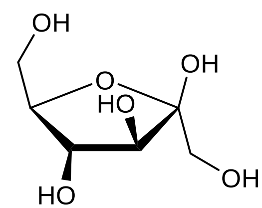
α -D-fructopyranose



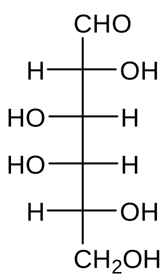
β -D-fructopyranose



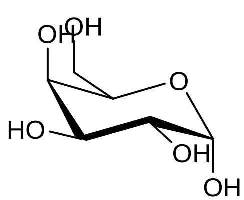
α -D-fructofuranose



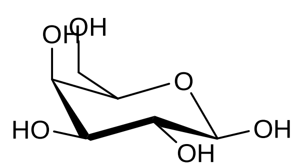
β -D-fructofuranose



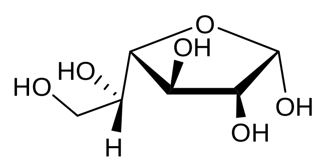
D-galactoaldose



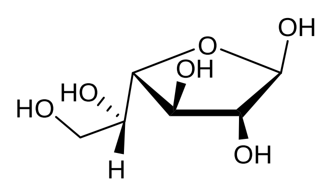
α -D-galactopyranose



β -D-galactopyranose

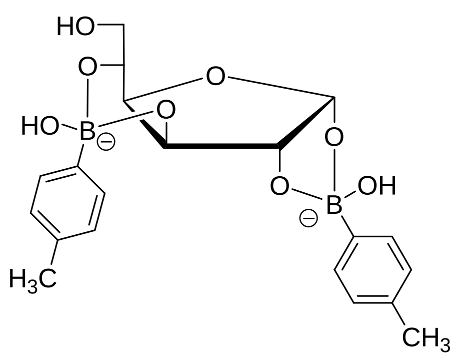


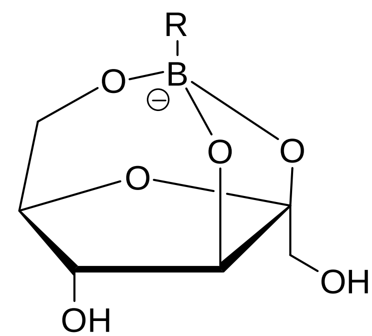
α -D-galactofuranose



β -D-galactofuranose

BORONIC ACID BINDING TO GLUCOSE/FRUCTOSE: SELECTIVITY CAN BE ACHIEVED VIA CHELATION



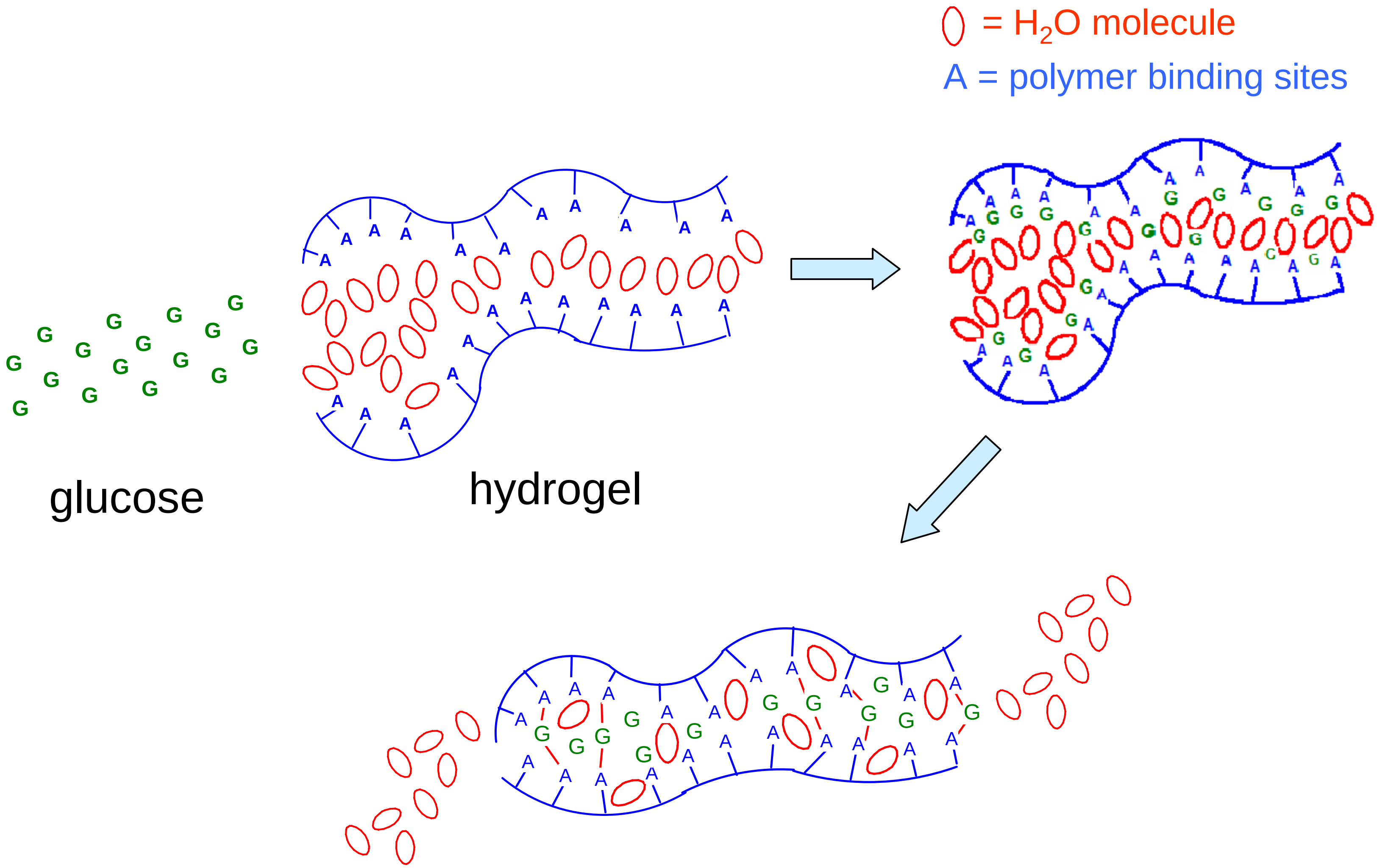


Structure proof; Norrild, J. C.; Eggert, H. *J. Am. Chem. Soc.* **1995**, *117*, 1479

It is well-known that glucose can be chelated by *bis*-boronic acids more readily than fructose and galactose, the other common blood sugars. For the initial evidence see:

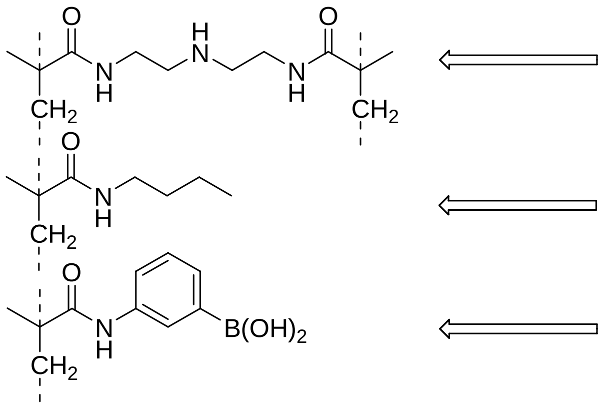
(a) M. Takeuchi, S. Yoda, T. Imada and S. Shinkai. Chiral sugar recognition by a diboronic-acid-appended binaphtyl derivative through rigidification effect *Tetrahedron* **1997**, *53*(25), 8335-8348.

(b) M. Takeuchi, T. Mizuno, H. Shinmori, M. Nakashima and S. Shinkai. Fluorescence and CD spectroscopic sugar sensing by a cyanine-appended diboronic acid probe *Tetrahedron* **1996,** *52*(4), 1195-1204.



Water is evacuated due to polymer cross-linking with glucose resulting in contraction

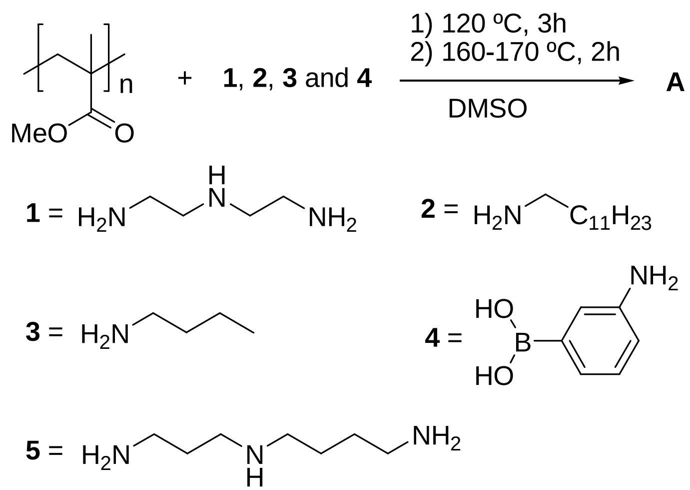
STEP 7. SYNTHESIS VIA BINDING SITE INCORPORATION
IN A PMMA SUBSTRATE



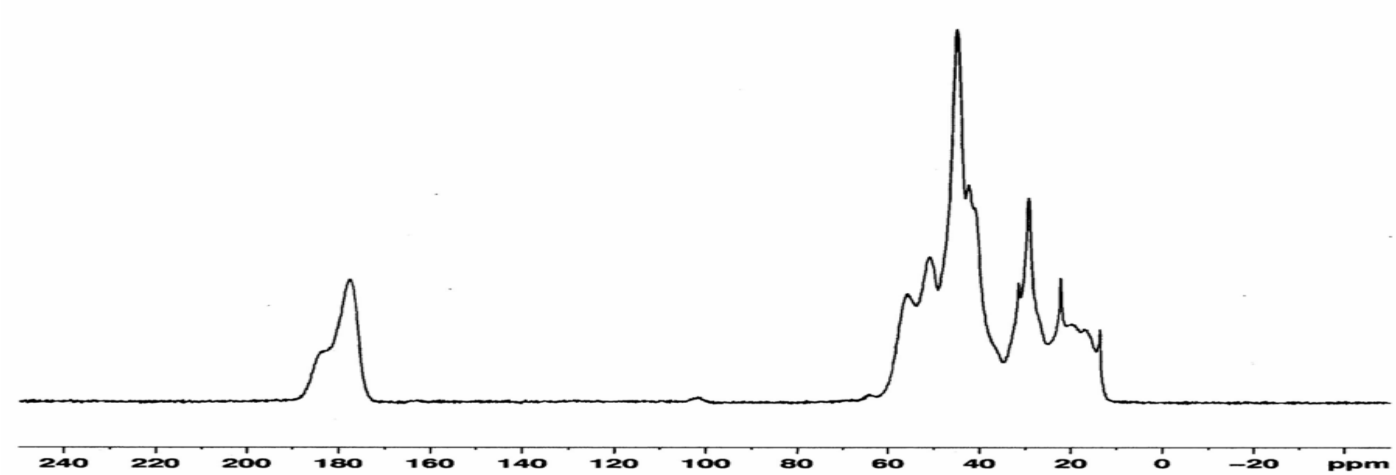
cross-linking, metal chelation
hydrogen bonding sites

CH-π, van der Waals
(increase hydrophobicity)

Reverse covalent binding
sites for glucose



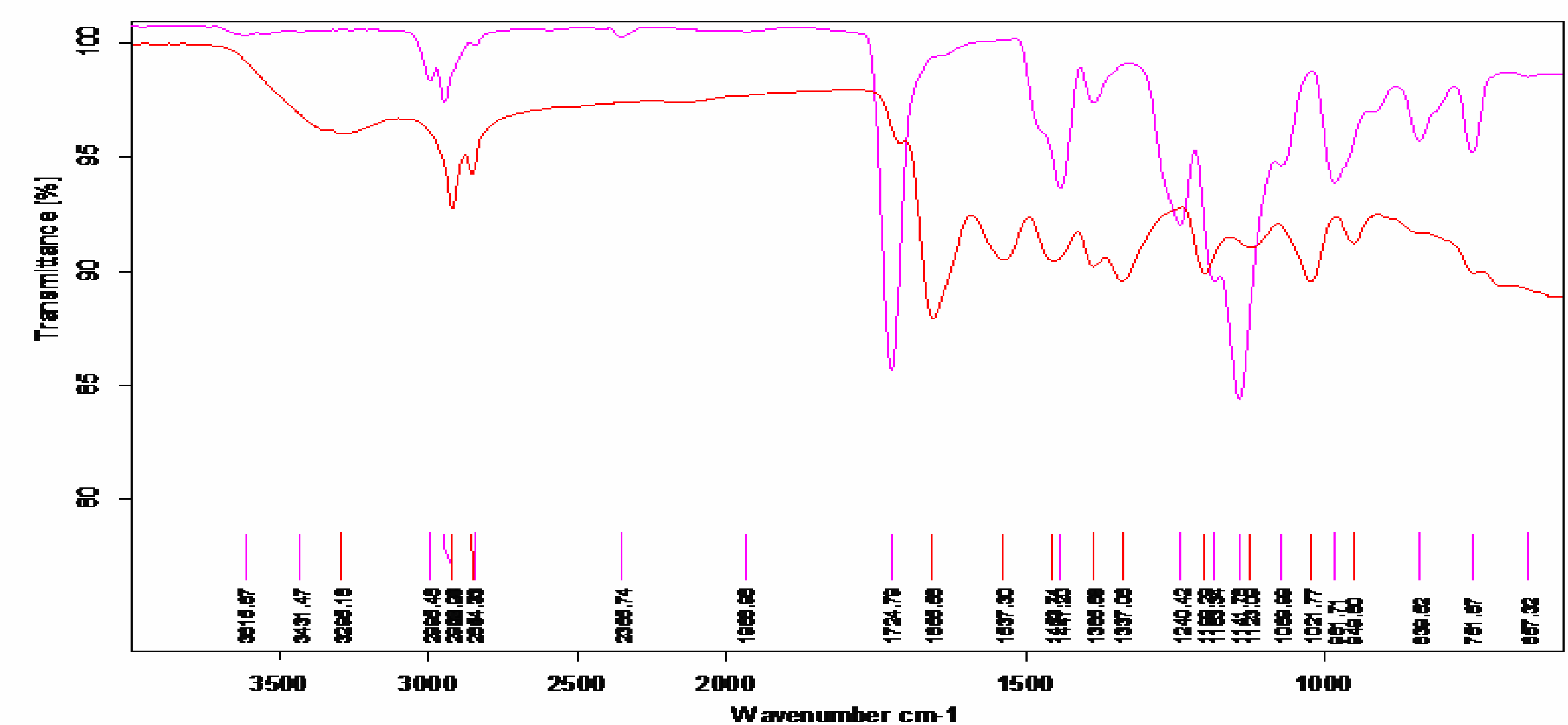
^{13}C NMR



Elemental Analysis

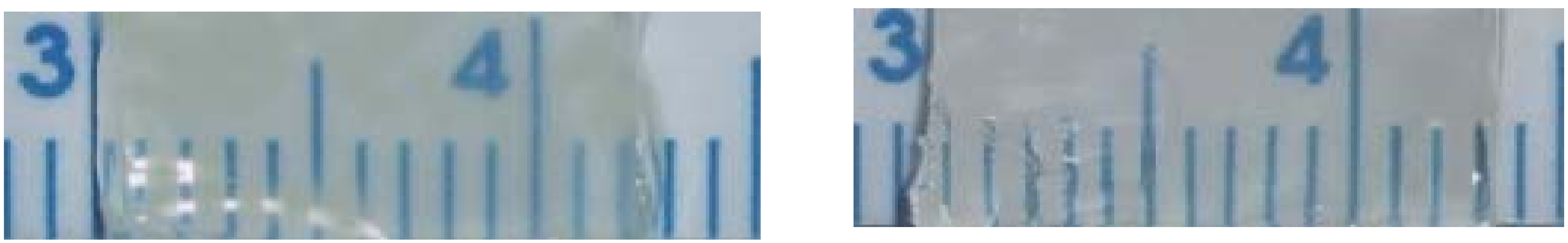
Elements	C	H	N	B
%	52.23	8.13	9.19	0.2

FT-IR OF PMMA AND POLYMER



SWOLLEN POLYMER IN GLUCOSE

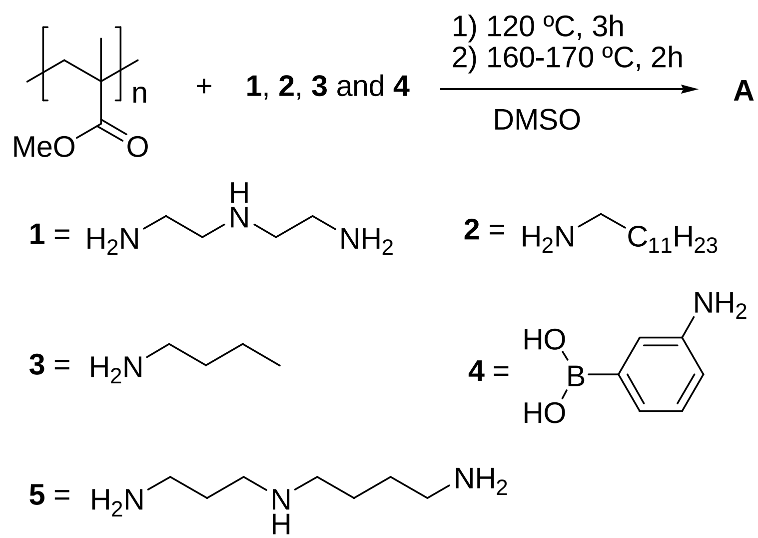
Behavior of polymer (with boronic acid) in response to 0.005 M Glucose.
Left: Original Swollen sample; Right: After 50 min in 0.005 M glucose



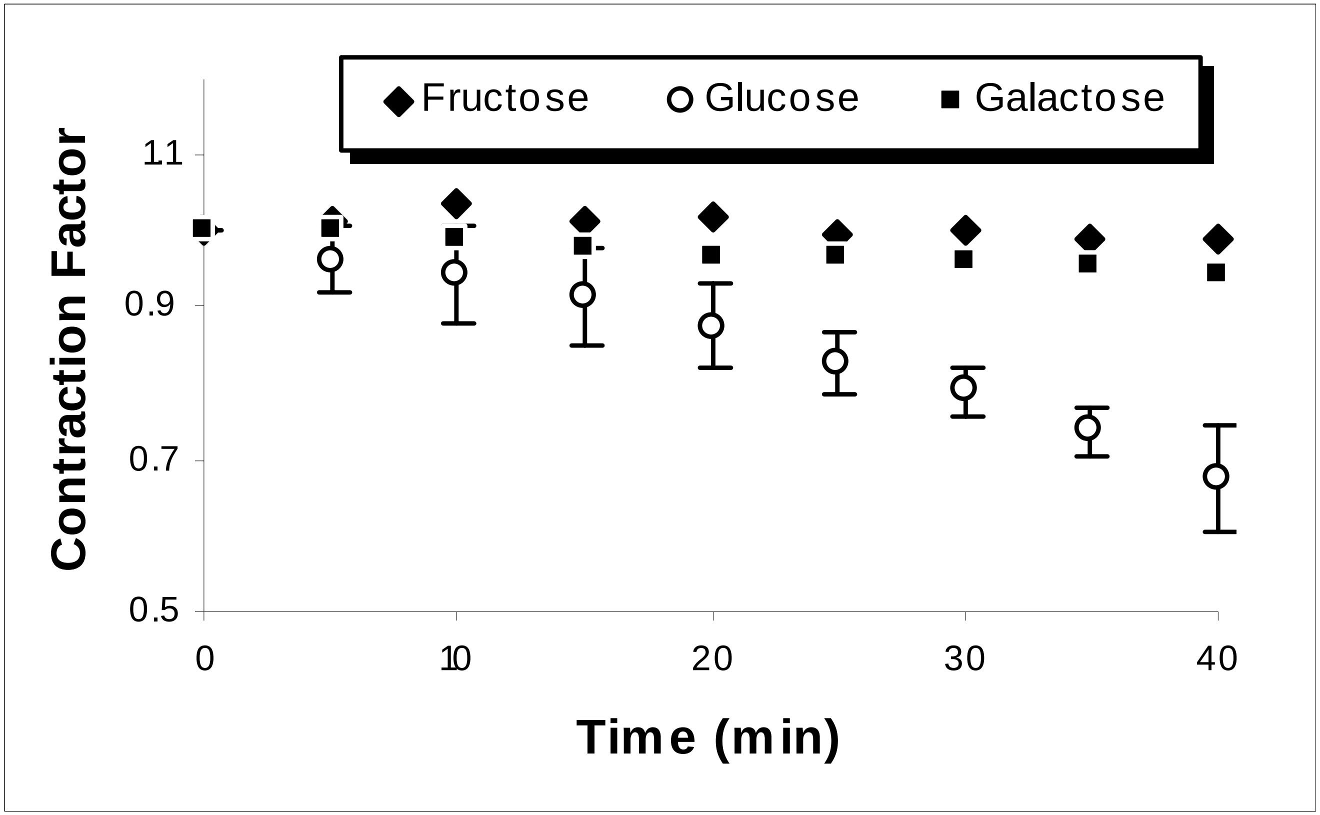
Similar polymer without boronic acid in response to 0.005 M Glucose.
Left: Original Swollen sample; Right: After 50 min in 0.005 M glucose

STEP 8. PROOF OF DESIGN HYPOTHESIS, OPTIMIZATION AND TESTING; CONTROL OVER SELECTIVITY AND CHEMOMECHANICAL RESPONSE

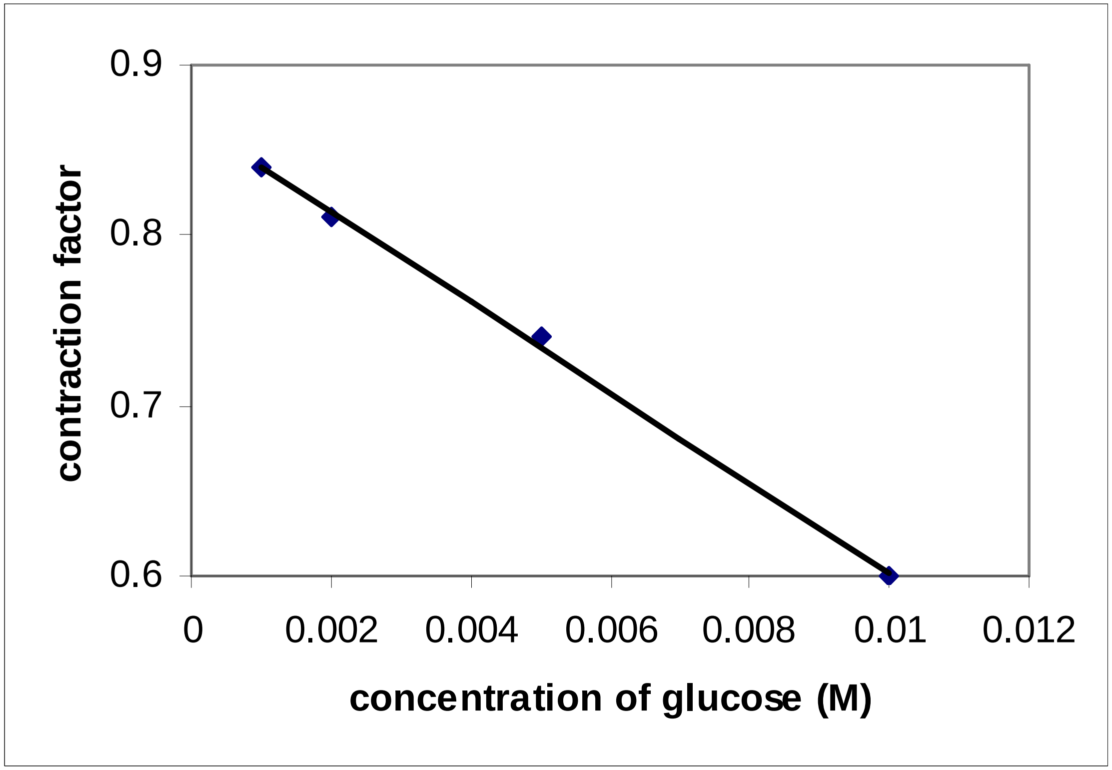
Entry	Polymer Modifiers	Contraction Factor		
		0.005M Glucose	0.005M Galactose	0.005M Fructose
1	**5** + **2** + **4**	1.70	1.61	1.50
2	**1** + **2** + **4**	1.22	1.25	1.31
3	**1 + 3 + 4**	0.63	0.96	0.93
4	**1** + **2** + **3** + **4**	0.83	0.99	0.97



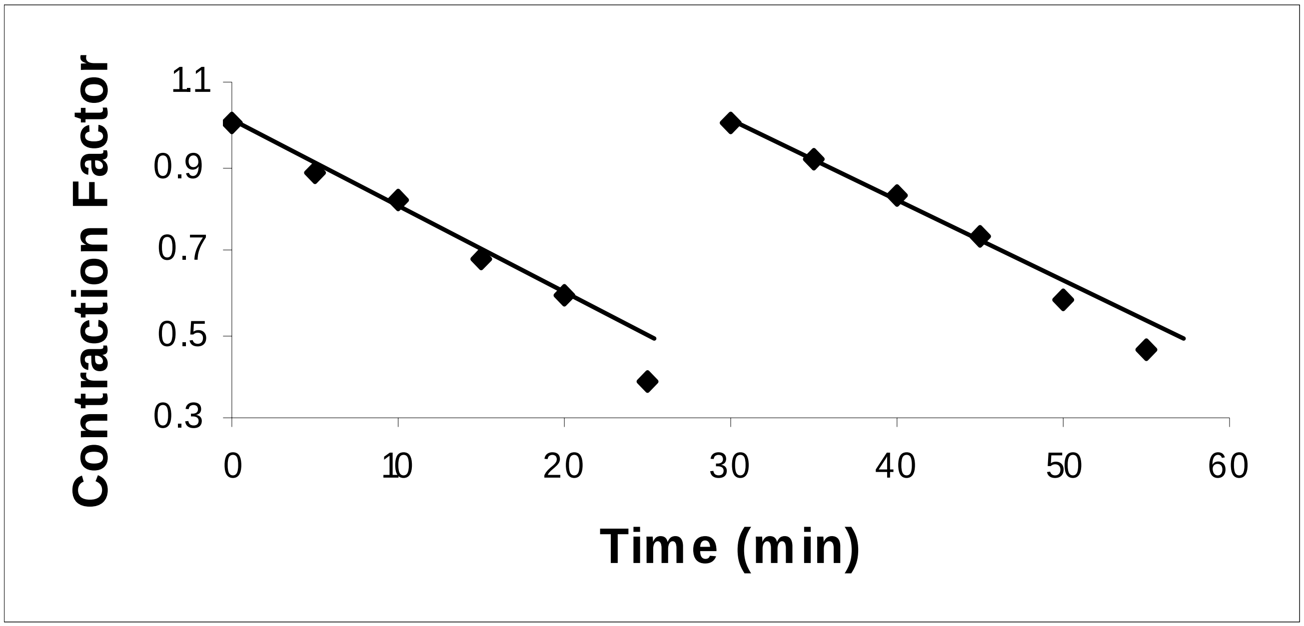
SELECTIVITY



CONTRACTION OF POLYMER VS. CONCENTRATION OF GLUCOSE IN WATER

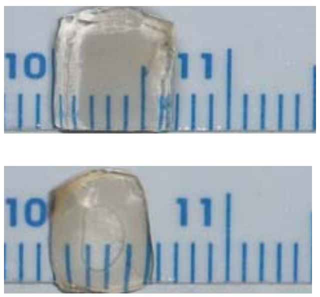


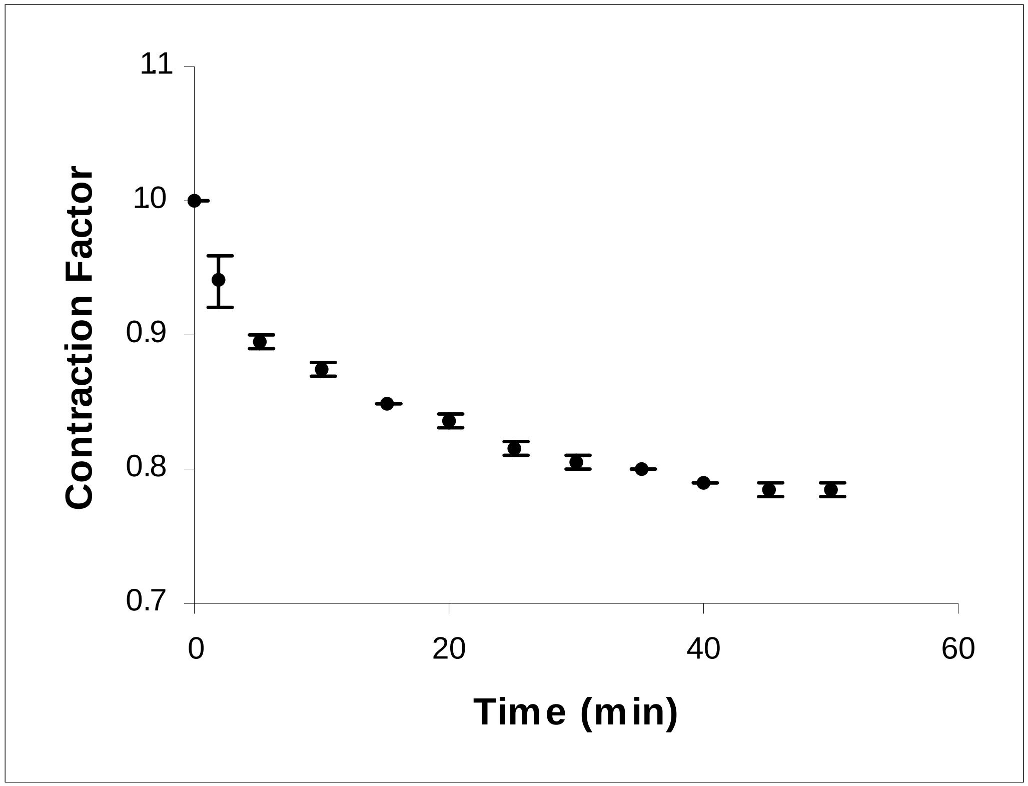
REVERSIBILITY



Contraction-expansion behavior of polymer in response to 0.005M Glucose. The polymer was expanded to its initial size between runs by rinsing with 0.05 M NaOH.

CONTRACTION OF POLYMER IN RECONSTITUTED HUMAN PLASMA





SOME SELECTED RECENT REVIEW ARTICLES FOR FURTHER READING. THIS IS FOR STARTERS—THERE IS MUCH MORE

Nanovalves:

Saha S, Leung KCF, Nguyen TD, Stoddart JF, Zink JI ADVANCED FUNCTIONAL MATERIALS 17 (5): 685-693, 2007

Molecular machines:

Willner I, Basnar B, Willner B ADVANCED FUNCTIONAL MATERIALS 17 (5): 702-717, 2007

Balzani V, Credi A, Venturi M NANO TODAY 2 (2): 18-25, 2007

Functional hydrogels for biomedicine:

Peppas NA, Hilt JZ, Khademhosseini A, Langer R ADVANCED MATERIALS 18 (11): 1345-1360, 2006

Nanofabricated drug delivery devices:

Hilt JZ, Peppas NA INTERNATIONAL JOURNAL OF PHARMACEUTICS 306 (1-2): 15-23, 2005

Hydrogels for glucose-triggered automated insulin delivery:

Peppas NA JOURNAL OF DRUG DELIVERY SCIENCE AND TECHNOLOGY 14 (4): 247-256, 2004