TATA CONSULTANCY SERVICES
Experience certainty.

COMSOL CONFERENCE
BANGALORE2013

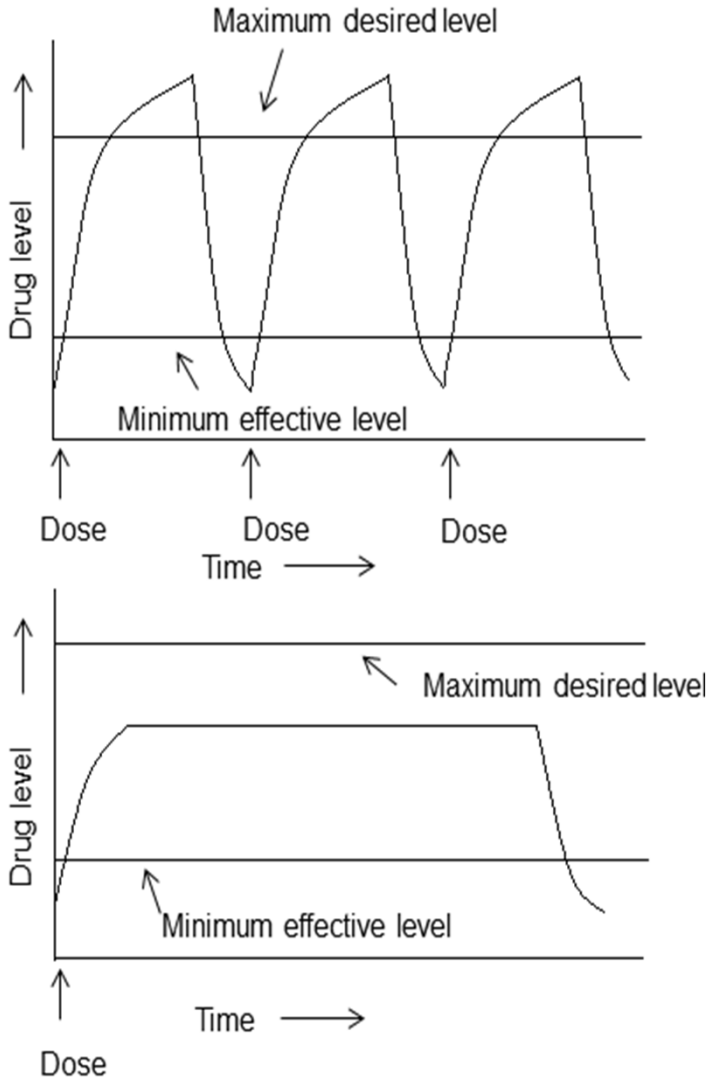
TATA

Modeling and simulation of drug release through polymer hydrogels

Shantanu Maheshwari, Sivakumar Cherlo, Rama Subba Thavva and Venkataramana Runkana

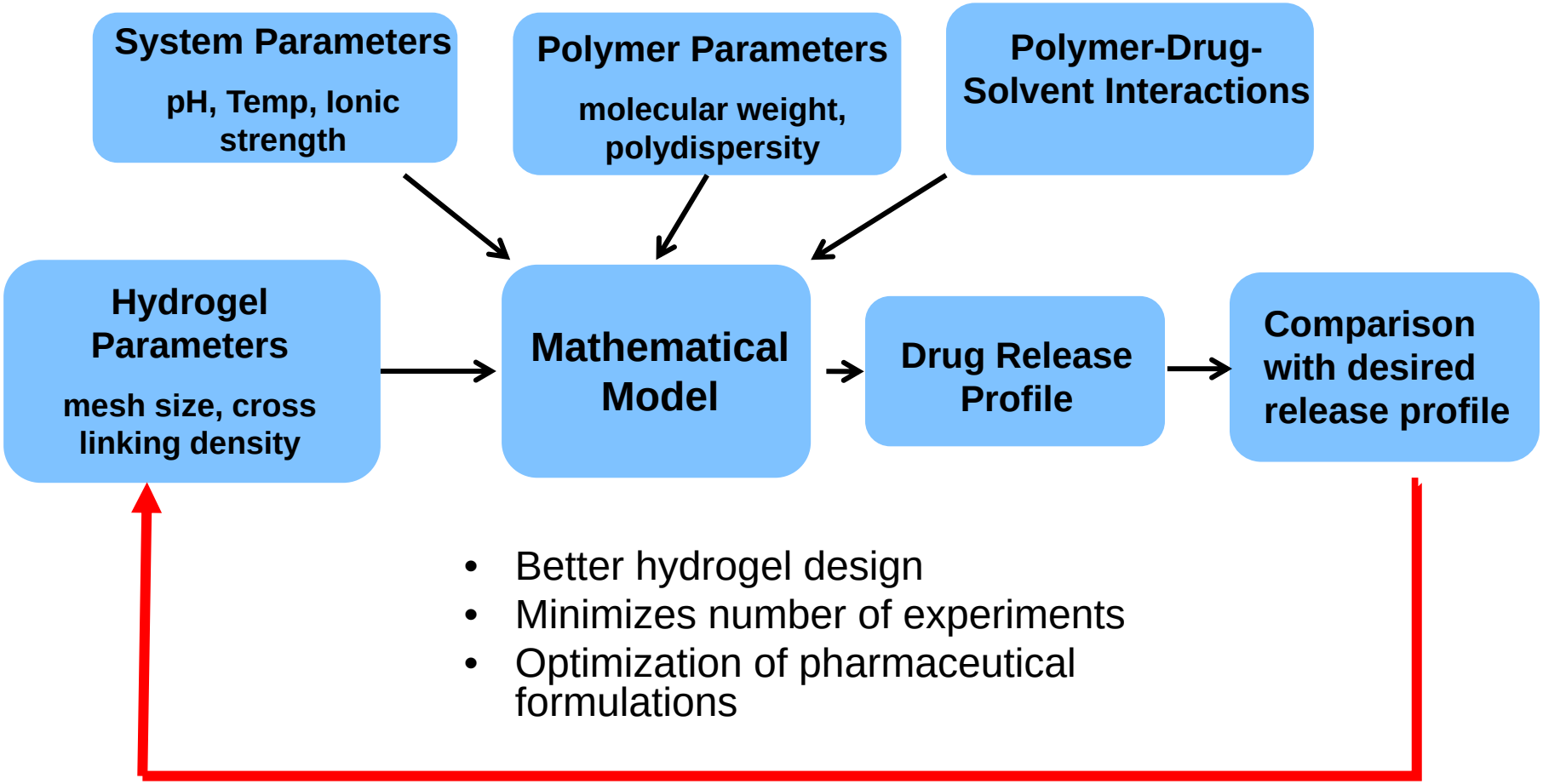
Drug delivery: Key challenges

- Oral delivery
  - Currently, 324 biotechnology drugs for 150 diseases are in preclinical stage (Proteins are most common)
  - Low *"bioavailability"* is a serious drawback
- Controlled and targeted release
  - Reducing side effects is a key objective
  - Eg. Diabetes, Cancer
    - In case of diabetes tight monitoring of blood glucose is required
    - Currently, chemotherapy is employed for cancer - Limited selectivity, toxic to both cancer and normal cells



Aim of this work

- Develop a generic mathematical model for controlled delivery of drugs with polymer hydrogels as carrier



Polymer hydrogels

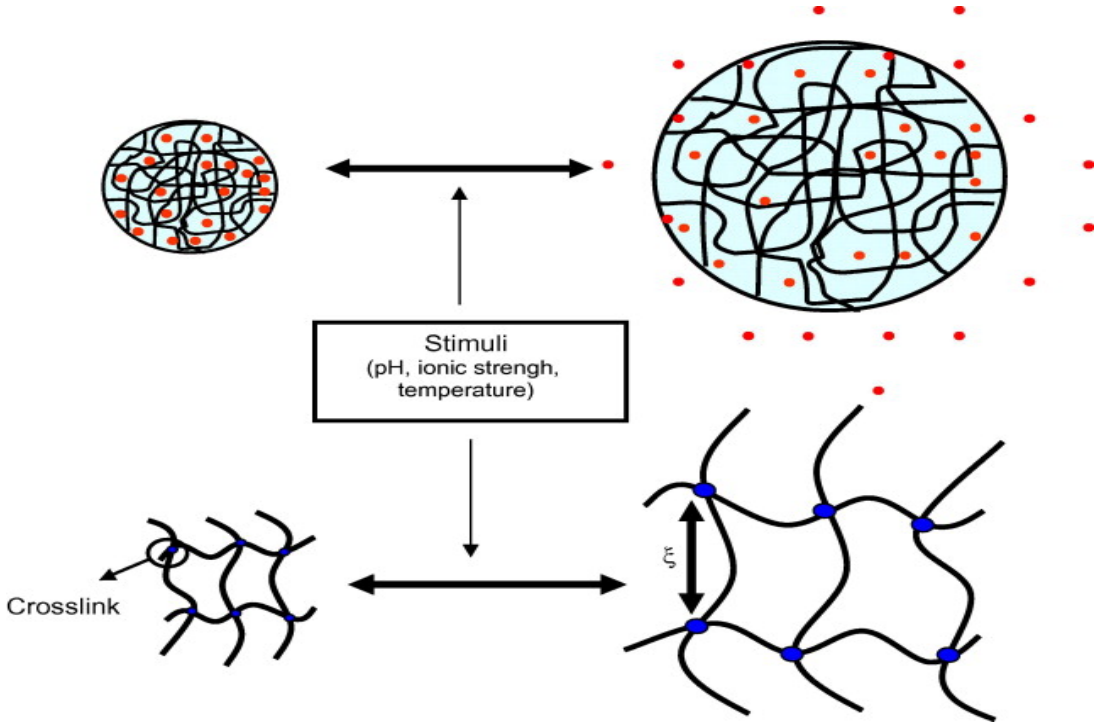
- Cross-linked polymer particles
- Densely cross-linked micro/nano domains embedded in a less cross-linked polymer matrix

- Why polymer hydrogels
  - Bio-compatibility
  - Drug release can be controlled by manipulating polymer properties like molecular weight, cross linking ratio etc.

- Challenge: Linking physico-chemical parameters to the drug release kinetics

Pharmacokinetic Model

- Diffusion of water and ions into the hydrogel – lead to swelling
  - Dependent on many external parameters like temperature, pH, ionic strength
- Diffusion of drug from hydrogel to external environment
  - Solubility of drug in solvent



Serra, L., Doménech, J., & Peppas, N. A. (2009). Engineering design and molecular dynamics of mucoadhesive drug delivery systems as targeting agents. *European journal of pharmaceutics and biopharmaceutics*, *71*(3), 519-528.

Swelling and drug release kinetics of hydrogels

- Modeling strategy
  - Solid mechanics, moving mesh (ALE) and diffusivity equation for water and drug is solved simultaneously in COMSOL
  - Transport of diluted species

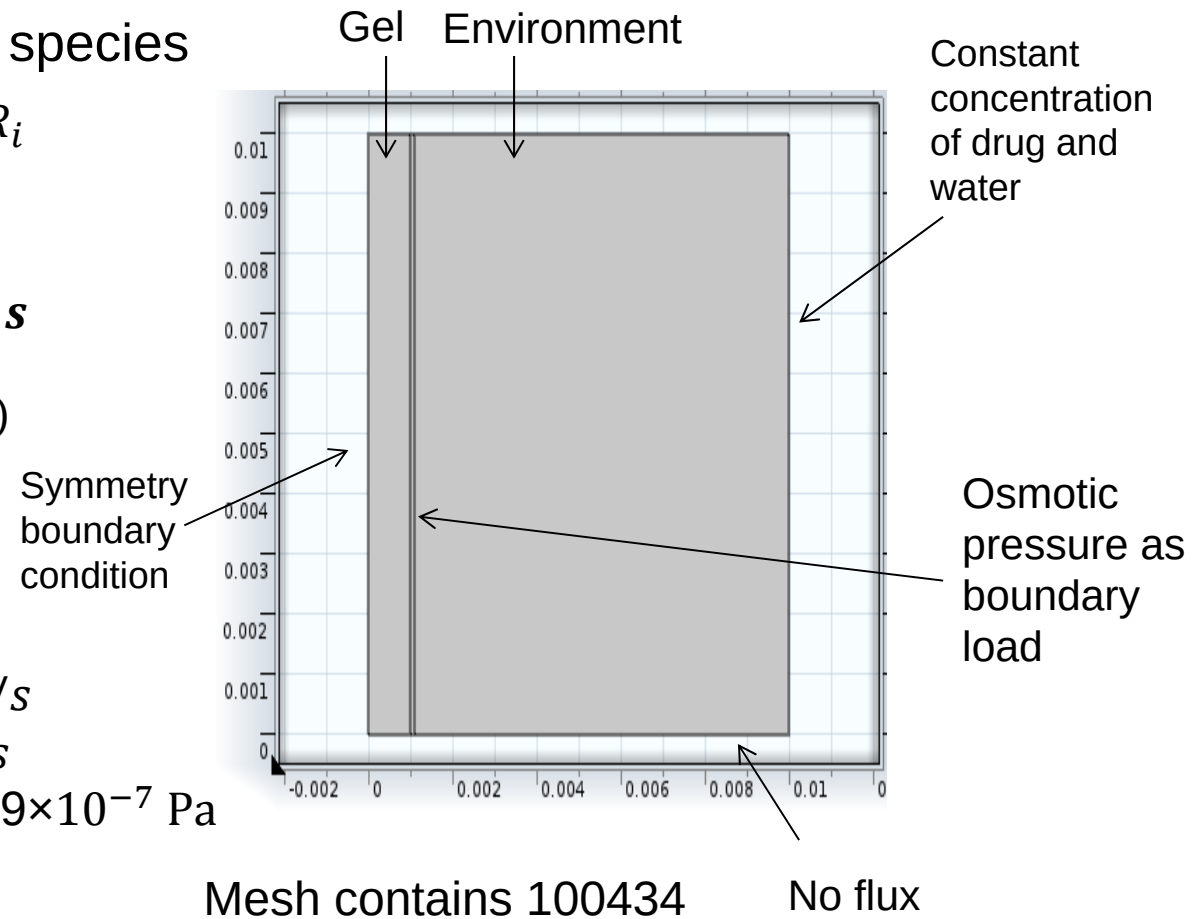
$$\nabla.(-D_i\nabla c_i) + \boldsymbol{u}.\nabla \boldsymbol{c_i} = R_i$$

  - Solid mechanics

$$\rho\frac{\partial^2 \boldsymbol{u}}{\partial t^2} - \nabla.\sigma = \boldsymbol{F}v, \qquad \sigma = \boldsymbol{s}$$

$$\boldsymbol{s} - \boldsymbol{S_0} = \boldsymbol{C}:(\varepsilon - \varepsilon_{\boldsymbol{0}} - \varepsilon_{\boldsymbol{inel}})$$

$$\varepsilon = \frac{1}{2}[(\nabla \boldsymbol{u})^T + \nabla \boldsymbol{u}]$$

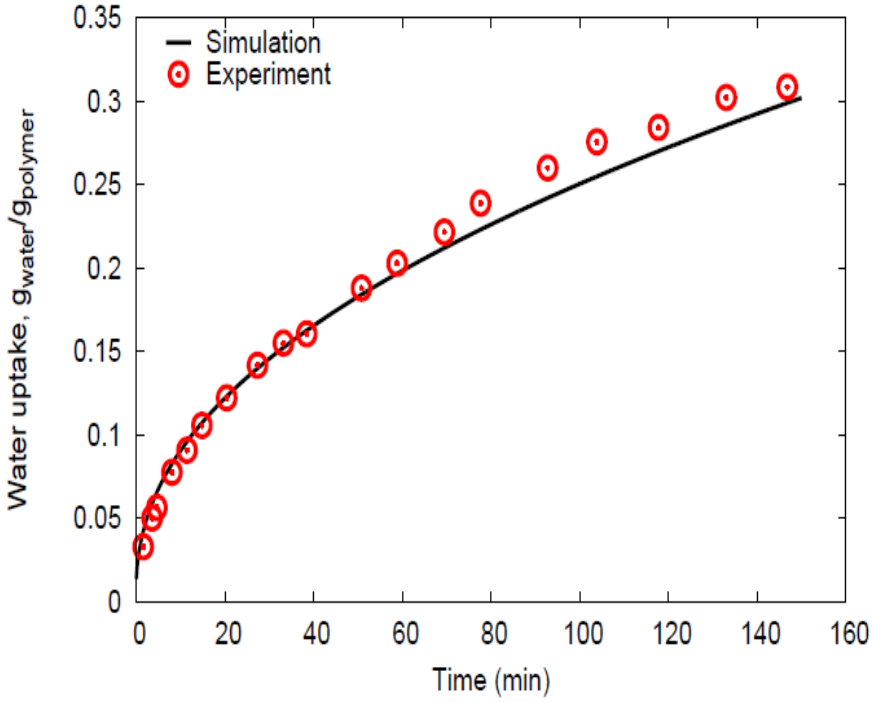


Diffusivity of water = $2\times10^{-11}\ m^2/s$
Diffusivity of drug = $5\times10^{-13}\ m^2/s$
Young's modulus of hydrogel = 2.9×10^{-7} Pa
Poisson's ratio of hydrogel = 0.3

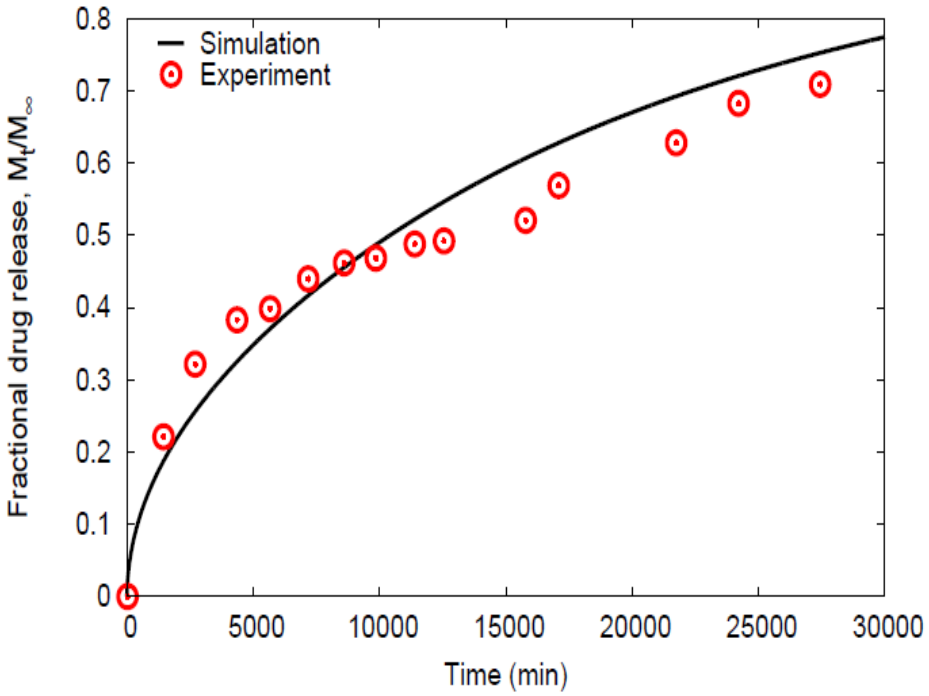
Mesh contains 100434 triangular elements

Comparison with experimental data

Water uptake kinetics



Drug release kinetics



Polymer used: HEMA-co-MMA (Hydroxyethyl methacrylate-co-Methay methaacrylate)
75 mol% HEMA formed by thermal initiation with a normal cross linking ratio of 0.01
Drug used : Vitamin B_{12}

Brazel, C. S., & Peppas, N. A. (2000). Modeling of drug release from Swellable polymers. *European journal of pharmaceutics and biopharmaceutics*, *49*(1), 47-58.

Ion transport modeling

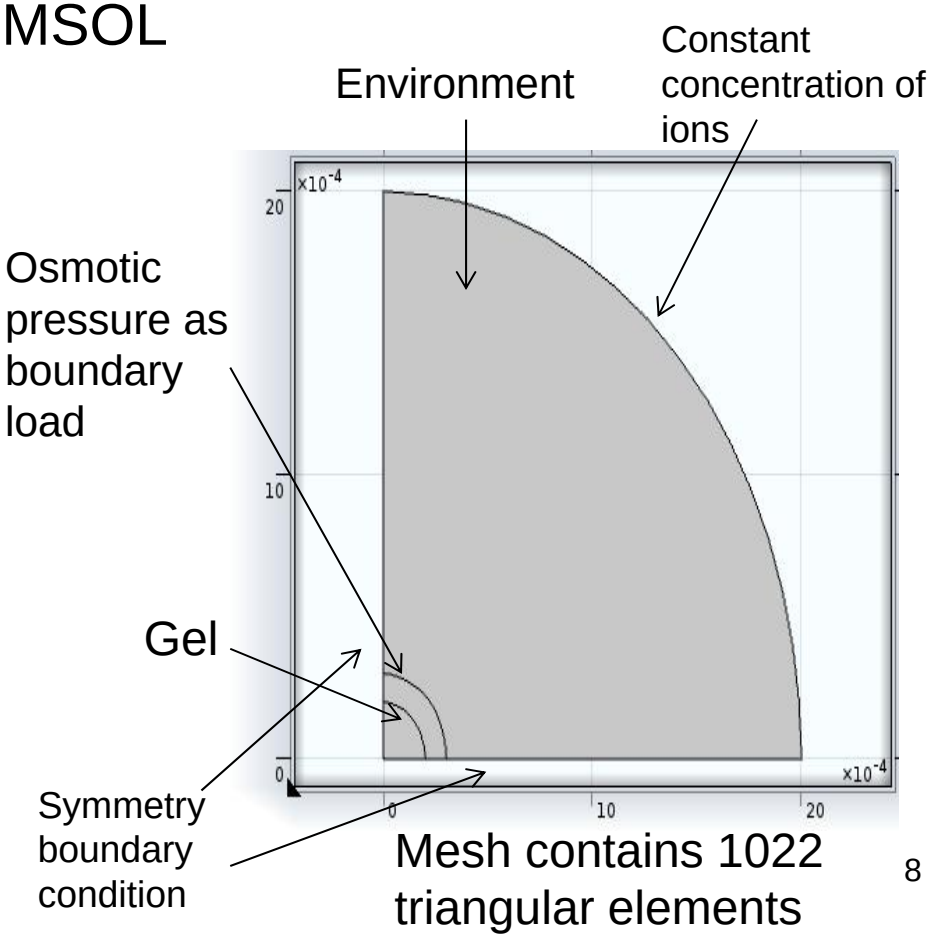
- Swelling due to transportation of ions and to evaluate the effect of pH and ionic strength on swelling and drug release
- Solid mechanics, moving mesh (ALE), diffusivity equation for different ionic species and Poisson equation for electrostatics is solved simultaneously in COMSOL
  - Transport of diluted species

    $\nabla.\left(-D_i\nabla c_i - z_i u_{m,i} F c_i \nabla V\right) = R_i$
  - Electrostatics

    $\nabla.(\varepsilon_0 \varepsilon_r \boldsymbol{E}) = \rho_v$
  - Solid mechanics

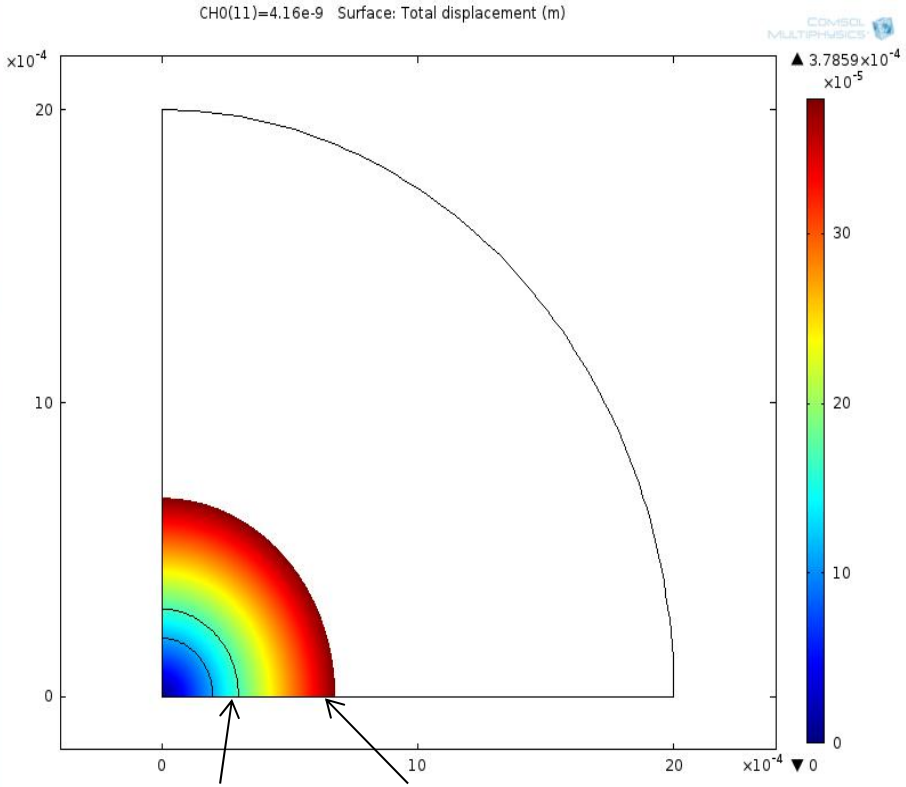
    pH dependent Young's modulus is used

Diffusivity of $\boldsymbol{Na^+}$ = $1.3\times10^{-11}\ m^2/s$
Diffusivity of $\boldsymbol{Cl^-}$ = $2.3\times10^{-11}\ m^2/s$
Poisson's ratio of hydrogel = 0.4



Comparison with experimental data

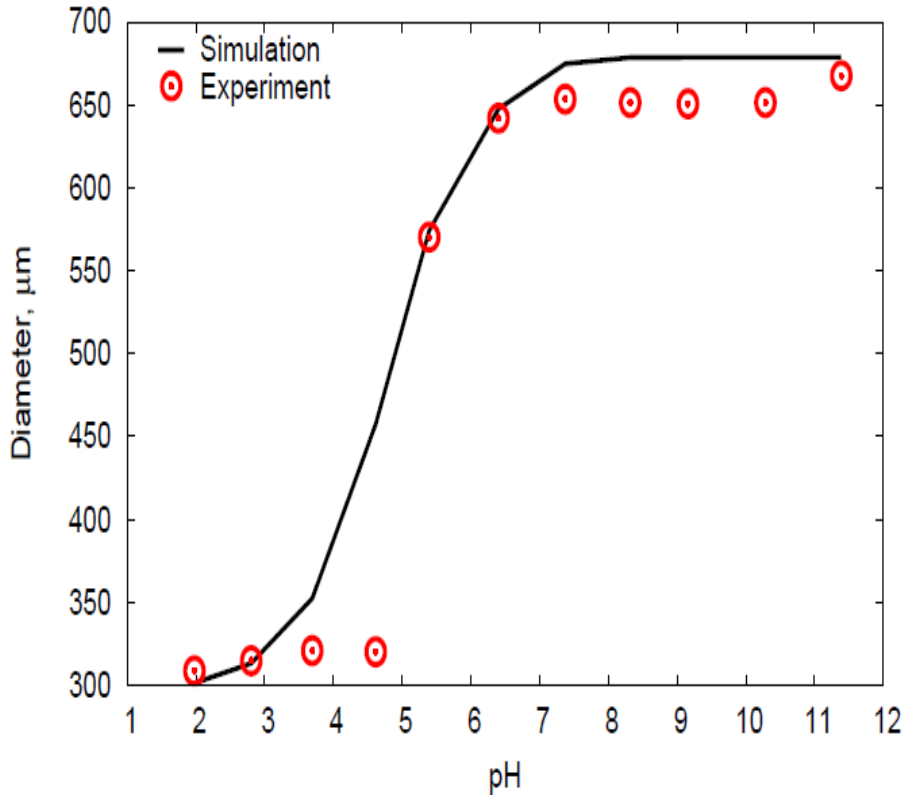
Swelling at pH = 12



Initial size of hydrogel

Size of hydrogel at equilibrium

Equilibrium swelling of hydrogel at different pH



Ionic strength = 0.3 M

Initial gel size = 300 µm

Equilibrium Hydration = 395.15% (Experiment)

= 411.64% (Simulation)

TATA CONSULTANCY SERVICES

Experience certainty.

De, S. K., Aluru, N. R., Johnson, B., Crone, W. C., Beebe, D. J., & Moore, J. (2002). Equilibrium swelling and kinetics of pH-responsive hydrogels: Models, experiments, and simulations. *Microelectromechanical Systems, Journal of*, *11*(5), 544-555.

Summary

- Modeling strategy for drug release from hydrogels has been developed
- Simulation results have been validated with experimental data available in literature
- This study can be extended to various polymer-drug combinations
- Various hydrogels parameters can be altered to get desired drug release profile

TATA CONSULTANCY SERVICES

Experience certainty.

Thank you