

The Swelling Responsiveness of pH-Sensitive Hydrogels in 3D Arbitrary Shaped Geometry

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Abstract: The pH-sensitive hydrogels are physically responsive to a change in the pH of surrounding solution, which often resemble to biomaterials. These hydrogels can expand up to 4 times to its original dimensions under certain pH of surrounding buffer. We present the simulation of swelling characteristic of 3D-arbitrary-geometry, pH-sensitive hydrogel in steady state conditions. Three nonlinear partial-differential equations that are representing responsible physical phenomena namely-chemical, electrical, and mechanical can describe the swelling responses to a chemical change in surrounding solution. Finite element analysis used for present study was carried out by full coupling of above three partial-differential equations with variable material properties in COMSOL Multiphysics®. Employing a moving mesh method for 3D geometry, the FEM simulation was performed to account for large-swelling of the pH-sensitive hydrogel.

Keywords: pH-sensitive hydrogel, FEM simulation of polyelectrolyte gel, hydrogel, Nernst-Planck equation, and Poisson's equation.

1. Introduction

Hydrogels are stimuli responsive materials. They have been widely used in various applications as sensing media. Polyelectrolyte hydrogels in particular, have proven to be an extremely useful material for sensing applications. In case of lab-on-chip devices, biofunctionalization of the hydrogel via lithographically patterning with various biomolecules can be built that can provide indicator matrix for the subjective protein adsorption and cell adhesion [1]. Several biocompatible polymers are already FDA approved for a variety of applications. These polyelectrolyte hydrogels are often environmental pH-sensitive materials. A

common method to produce such devices or matrix with biofunctionality is using optical lithography [2]. In addition, these hydrogels can be patterned with tunable physical and structural, and chemical properties. Their structural properties can be tuned by simply changing cross-linking via extent of polymerization by irradiation or by changing chemical composition of the base constituents. For predictable operation of devices, it is important to quantify the hydrogel responsiveness to a measurable environment stimulus. This quantifying measurement is usually amount of swelling of the patterned materials. Therefore, it is important to understand the spatial and temporal responses of the chemical versus mechanical signals in patterned hydrogel. To evaluate such swelling behavior in lieu of environmental change required extensive experimentation. Therefore, it is important to employ theoretical estimation of amount of swelling with change in chemical signal to save time and resources. In such cases, finite element analysis can become very useful because of its ability to simulate a given geometrical complexity. There are numerous research efforts that describe the simulation of the pH-sensitive hydrogel [3-7] however according to the knowledge of the authors, this is the first time a fully coupled successful FEM formulation of 3-dimensional arbitrary geometry is presented. Moreover, an arbitrary geometry can impose extra complexity in calculation. We present finite element simulation results of the pH-sensitive, 3-dimensional hydrogel patterns.

2. FEM Formulation

The swelling in a pH-sensitive hydrogel occur at a pH value equivalent to the pKa of the functional group on the polymer network. At a pH equal or higher value of pKa, the diffusion of mobile ions starts due to reactivity of the functional group, chemical potential, and

electrical potential difference between hydrogel and surrounding solution. These physical phenomena of diffusion can be described by the Nernst Planck (NP) equation via ionic transport due to mobile and fixed charged species; and Poisson's equation describes the equilibrium of electric potential of the charged species via equilibrium. The change in pH leads to change in osmotic pressure within the hydrogel. The swelling occurs due to a restoration force generated by the elasticity of the hydrogel. Thus, the expansion can be explained by mechanical deformation equation. Therefore, coupled formulation among these equations is necessary the swelling. This is so-called chemo-electro-mechanical behavior.

Here, the Nernst-Planck, Poisson's, and mechanical field equations are used to create chemo-electro-mechanical coupling that is described in detail in literature [3-8]. The fully coupled problem is solved based on a steady state model under equilibrium conditions. The details of present simulation are discussed in our previously published literature and finite element analysis of 2D hydrogel was validated against experimental data [6-8].

2.1 Steady State Form of Nernst-Planck (NP) Equation

$$D_i \frac{\partial^2 c_i}{\partial x^2} + \mu_i z_i \frac{\partial c_i}{\partial x} \frac{\partial \psi}{\partial x} + \mu_i z_i c_i \frac{\partial^2 \psi}{\partial x^2} = 0 \quad (1)$$

Where $\mu_i = D_i / RT$ is ionic mobility

2.2 Poisson's Equation

The electrical charge balance can be satisfied by Poisson's equation, which can be written as:

$$\nabla^2 \psi + \frac{\rho}{\epsilon_0 \epsilon} = 0 \quad (2)$$

where ρ is charge density in hydrogel

$$\rho = F \cdot \left(\sum_{i=1}^n z_i c_i + z_f c_f \right)$$

In the simulation of swelling response of the hydrogels to variation of the pH, the dependent variable, concentration inside the hydrogel is

obtained by coupling NP and Poisson's equations.

Fixed charge density can be given by equation:

$$c_f = \frac{c_{mo}^s(K)}{H(K + c_H)}$$

In fully coupled system of equations c_f is continuously updated at each converged step. The diffused ions generate osmotic pressure within the hydrogel. The osmotic pressure is given by:

$$P_{Osmotic} = RT \left(\sum_{i=1}^n (c_i - c_i^o) \right)$$

where n is number of ions, c_i is the concentration of ith ion in the hydrogel, and c_i^o is at the ith

2.4 Mechanical Field Equation

This internal pressure is restored by the elastic energy exerted by the polymer network, which is can be estimated by equation:

$$\nabla \sigma = \nabla ([C] E - P_{Osmotic} I) = 0 \quad (3)$$

In this paper, we have simulated lithographically patterned, two different structures of a pH-sensitive hydrogels in 3-dimensions. The schematic diagrams of top-view of two different cross-sections of freestanding structures are shown in following fig. 1. The FEM model for 2D was validated and results were discussed in previous publications [6-8].

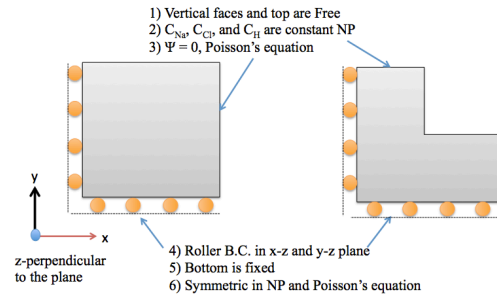


Figure 1: Schematic of top view of cross section of the hydrogel standing structure on a substrate (a) square pillar (thickness: 100 μm, side: 100 μm, height: 1mm), (b) Cross pillar (thickness: 50 μm, side: 100 μm)

μm, height: 1mm) in each case, the highlighted axisymmetric area is modeled.

Figure 1 also show schematic of boundary conditions for all three equations. Mechanical rollers are shown at the symmetric boundaries. The change in pH was applied to outer most boundaries by changing concentrations of the hydrogen ions while buffer ionic strength kept constant via constant concentration value for mobile ions. The electric potential was assumed zero at the interface. Outer boundary of the hydrogel was kept free while bottom was fixed. The hydrogel was free to roll in x-z and y-z plane.

3. Implementation in COMSOL Multiphysics

Simulation of hydrogel deformation was carried out using COMSOL (Version-4.3b) finite element software with following multiphysics modules:

1. Chemical Species Transport Module for Nernst-Planck equation without electroneutrality
2. Conductive Media DC from the AC/DC Module for Poisson's Equation
3. Plane Strain from the Structural Mechanics Module for Mechanical Field Equation

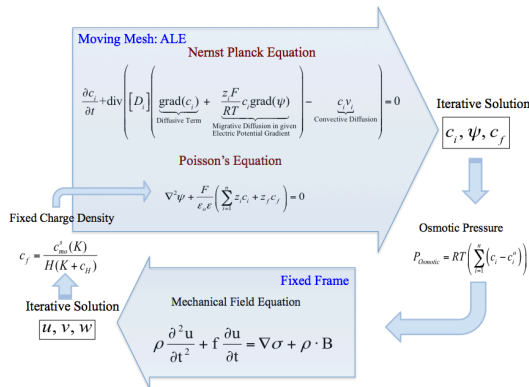


Figure 2: Coupling between different modules within COMSOL in moving mesh and fixed frames

Within COMSOL, the three different modules were fully coupled to each other in the two reference frames. The Chemical Species Transport Module and the AC/DC Module along with displaced mesh were evaluated in the moving mesh frame while Structural Mechanics

Module was evaluated in the fixed mesh frame with large deformation condition. For every simulation parameter all concentration terms and electrical potentials were re-profiled for the NP and Poisson's equations in a moving frame, while the deformation was calculated using the updated coordinates with the mechanical field equation in a fixed frame.

The Nernst-Planck and Poisson's equations were coupled with each other via Poisson's equation dependent variable (Ψ), c_i and (c_f) fixed charge density. The equation of fixed charge density has two parameters, hydration (H) and hydrogen ion concentration (c_H). The hydration of the hydrogel was defined as the change in volume ratio and it was used in the coupling the mechanical equilibrium equation. The hydration term is the Jacobean of the Cauchy-Greens' Tensor. Depending on the expansion and via c_f all concentrations were updated at every iteration. The resulting solutions of NP and Poisson's equations were concentrations and electric potentials. The osmotic pressure was used in the mechanical field equation to find the displacement. These displacements become the coupling parameter in the moving mesh module and the mesh moves in the x, y, and z directions. A new hydration was again calculated within the fixed mesh frame at each iteration. Thus, all three equations are fully coupled and solved for each increment in pH.

Three different mobile ions (Na^+ , Cl^- , and H^+) were considered in the simulation, resulting in a total of 10 dependent variables. There were 3 dependent variables (C_{Na} , C_{Cl} , and C_H) from the NP equation, the electric potential (ψ) from Poisson's equation, the displacements (u, v, w) from mechanical field equation, and the x, y and z coordinates (X, Y, Z) and three weak constraint variables from the moving mesh module.

Simulation was performed for the surrounding pH range 2-11. The converged solution was achieved for each step of pH value.

4. Results and Discussion

When the negatively charged (carboxylic acid group $\text{PKa} \sim 4.5$) hydrogel in dried condition is placed in a buffer solution, it absorbs the solvent and expands. Figure 3 shows the simulation profile for the maximum displacement of '+' cross-sectioned hydrogel

from pH 2-11. It can be seen from the graph that expansion starts nearly pH = 4 which is the pKa of the fixed charge on the hydrogel. As the solvent pH increases the maximum displacement increases which is indicating the expansion of the hydrogel. This absorption of the mobile ions in the hydrogel and expansion of the hydrogel are mainly depending on two processes: diffusion due to the concentration gradient and diffusion due to bound charges within the hydrogel. Upon a small increment in the surrounding pH, the mobile ions diffuse in the hydrogel and bind to the fixed charges on the network, generating the osmotic pressure difference between the hydrogel and the solution due to the mobile ion concentration gradient.

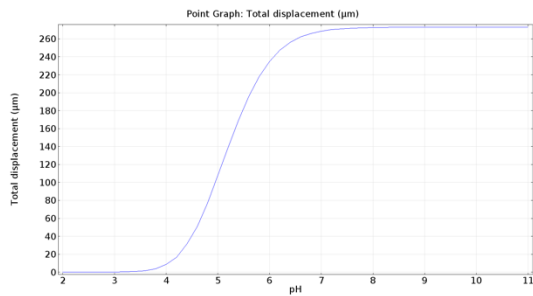


Figure 3: Maximum displacement of '+' cross-sectioned hydrogel with respect to a change in pH of the surrounding solution.

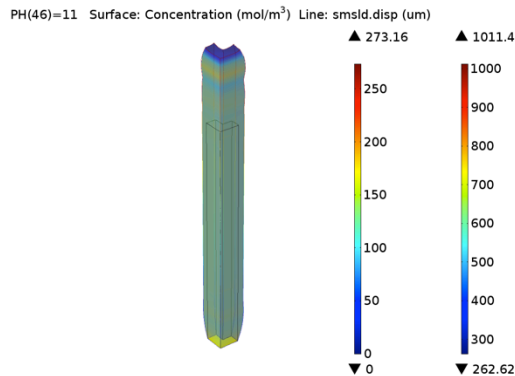


Figure 4: Simulation result of cross pattern cross-sectioned hydrogel. The rainbow color scale represent pH, which is corresponds to surface of the domain while thermal scale bar represent swelling in µm for line boundary of the domain.

In response to this internal osmotic pressure, the sponge-like structure of hydrogel counter balance with an elastic restoring force and tries to equilibrate by changing the volume. These

changes lead to a newly expanded region and the fixed charges within the hydrogel redistribute themselves. As a result, the polymer network opens up new fixed charge sites and promotes the diffusion of new mobile ions inside the gel until an equilibrium state is achieved.

Figure 4 and 5 show simulation results at surrounding pH 11 for '+' cross-sectioned hydrogel pillar. Figure 4 shows expansion on edge boundaries while Na⁺ ions concentration is shown on face boundaries. Figure 5 show distribution of electric potential due to fixed and mobile group charges at pH 11.

Figure 6 shows simulation results at surrounding pH 11 for square cross-sectioned hydrogel pillar.

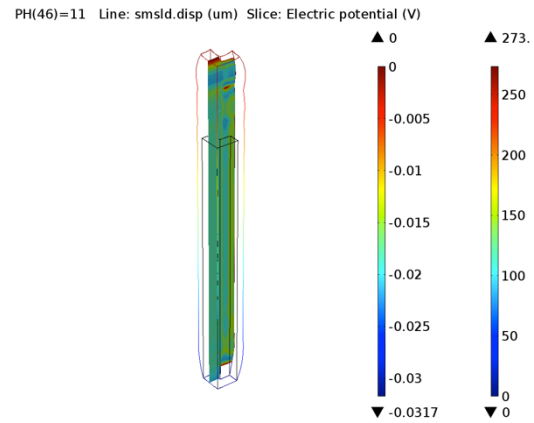


Figure 5: Electric potential within expanded hydrogel. Left hand side color bar represents electric potential and right hand side represent displacement.

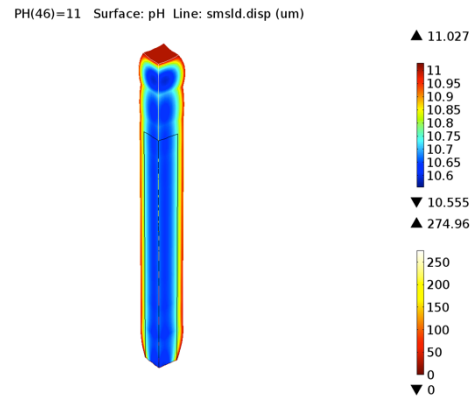


Figure 6: Simulation result of square pattern cross-sectioned hydrogel. The rainbow color scale represent pH, which is corresponds to surface of the domain

while thermal scale bar represent swelling in μm for line boundary of the domain.

Using present model, one can predict the swelling behavior by simply changing mechanical properties of the modeled hydrogel. The desired swelling can be achieved by tuning mechanical properties and fixed charge density of the hydrogel. The estimation of tuning parameters can be back calculated from above simulation method.

5. Conclusions

The swelling behavior of the negatively charged pH-sensitive hydrogel in 3-dimension with arbitrary shaped was successfully achieved using FEM. This problem of swelling is highly nonlinear even in the steady-state condition due to nonlinear equations, nonlinear properties, large deformation, and complex shape. All equations were fully coupled and converged solution was achieved for the surrounding change in pH from 2 to 11. Employing a moving mesh method for 3D geometry, the FEM simulation was performed to account for a large-deformation. Since, the pKa value of the carboxyl group is 4.5, a nonlinear swelling behavior of the hydrogel was found between pH 3.5 to 7. There was no significant swelling beyond pH 7.0. The simulation strategy can be employ to determine the hydrogel response to the change in different parametric conditions such as cross-linking density, fixed charge density, and ionic strength of the surrounding solution.

6. References

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10. Appendix

Table 1: Nomenclature and corresponding values used in present study

$D_h = 9.31 \times 10^{-9}$	Hydrogen ion Diffusion coefficient (m^2/s)
$D_{Na} = D_{Cl} = 9.31 \times 10^{-9}$	Sodium and Chlorine ions Diffusion coefficient (m^2/s)
$[C]$	Elasticity matrix

I	Identity matrix
$C_{mo}^s = 1800 \text{ mM}$	Fixed charge density
$Z_f = -1$	Valence number of fixed charge
c_i	Concentration of i^{th} ion
$c_{Na} = \text{Sodium ion concentration}$	300mM at initial condition
$c_{Cl} = \text{chlorine ion concentration}$	300mM at initial condition
$\psi = 0$	Electric potential
$pKa = 4.5 \text{ mM}$	Carboxylic acid group
$E = 0.21 \text{ (pH>4.5)} - 0.26 \text{ (pH<4.5) MPa}$	Modulus of elasticity
$F = 9.6485 \times 10^4 \text{ (C/mol)}$	Faraday's constant
$R = 8.314 \text{ (J/mol/K)}$	Universal gas constant
$T = 300 \text{ (K)}$	Temperature
$\epsilon_0 = 8.854 \times 10^{-12} \text{ (C}^2/\text{Nm}^2)$	Dielectric constant
$\epsilon = 80$	Relative dielectric constant of hydrogel
H	Hydration
Suffix	
Na	Sodium ion
Cl	Chlorine ion
H	Hydrogen ion
i	i^{th} ion
x	Independent variable can be x, y, z axis