MATHEMATICAL MODELING OF GLUCOSE RESPONSIVE HYDROGELS

Tanmay Mathur\(^1\)*, Aditya Pareek\(^2\), Venkataramana Runkana\(^2\)

\(^1\)Dept. of Chemical Engineering, IIT Delhi
\(^2\)Tata Research Development and Design Centre, Pune
INTRODUCTION

• For any diabetic patient, Insulin can be injected inside the body using two prominent methods: *Injections & Insulin Pumps*

• Glucose levels need to be closely monitored either using a glucose meter or a CGM sensor to decide the amount of insulin to be delivered

• A Doctor needs to closely monitor the patient conditions to avoid hyperglycemia and hypoglycemic events

• A novel delivery system is required that can *sense* and *deliver* insulin
INTRODUCTION

Insulin dosages are of two types: Basal and Bolus

- Type 1 diabetes patients require 3-4 injections/day
- Thus, there is a need to provide this automatic and customized dosing

A general guideline required for insulin infusion is:
- 0.2 IU/Kg/day of basal insulin
- 0.05-0.1 IU/Kg of insulin before consuming meal

Insulin release in response to resulting high blood glucose level (meal intake) may help in reducing the number of injections required
**WHY HYDROGELS?**

A hydrogel is a network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure.

Example: Poly Acrylic Acid (PAA), Polyacrylamide (PAM) etc.

[Diagram of hydrogel with various applications such as transdermal drug delivery, wound dressing, tissue engineering, drug delivery system, contact lens, and stimuli responsive hydrogel.


**Figure**: Schematic representation of a glucose-responsive glucose-oxidase-loaded membrane (Priya Bawa et al; Biomed. Mater. 4 (2009))
PHENOMENA INVOLVED

• Hydrogel is loaded with Glucose oxidase & Catalase that helps the conversion of Glucose to Gluconic acid and decomposes H₂O₂ respectively:

\[ \text{Glucose} + \frac{1}{2} O_2 \xrightarrow{\text{GOX}} \text{Gluconic Acid} + H_2O_2 \]

\[ H_2O_2 \xrightarrow{\text{Catalase}} \frac{1}{2} O_2 + H_2O \]

which follow the following reaction order:

\[ R = \frac{V_{\text{max}} C_{\text{Ox}} C_{\text{Glu}}}{C_{\text{ox}} (K_{\text{Glu}} + C_{\text{Glu}}) + K_{\text{ox}} C_{\text{Glu}}} \]

\[ R = \frac{V_{\text{max}} C_{H_2O_2}}{K_{H_2O_2} + C_{H_2O_2}} \]

• In the presence of Glucose, the reaction proceeds to form Gluconic Acid which lowers the pH of the solution inside the HG

• This causes a change of osmotic Pressure inside the HG making it change shape and release Insulin
MECHANISM OF HYDROGEL SWELLING

**ANIONIC**

Example: Carboxylic, Sulphonic acid based Hydrogels

- Glucose diffuses inside
- Protonation of the groups
- Net reduction of negative charges
- De-swelling of HG

Reaction:
- In the presence of GOX
- pH decreases
- H⁺ increases

Gluconic Acid formation

**CATIONIC**

Example: Ammonium based Hydrogels

- Protonation of the groups
- Net production of positive charges
- Swelling of HG

Reaction:
- pH decreases
- H⁺ increases
- (Due to reduction in electrostatic repulsion)
- (Due to increase in electrostatic repulsion)

\[
\begin{align*}
  A^- + H^+ &\rightarrow AH \\
  B + H^+ &\rightarrow BH^+ 
\end{align*}
\]
MATHEMATICAL MODEL

NERNST-PLANCK EQUATION:

\[ \frac{\partial c_k}{\partial t} = \nabla \cdot (D_k \nabla c_k) + \nabla \cdot (F \ c_k \nabla \psi) + R \]

(k=1,2,...,N_{ion})

POISSON EQUATION:

\[ \nabla^2 \psi = \frac{F}{Q} \left( \sum_k z_k c_k + z_f c_f \right) \]

FIXED CHARGE EQUATION:

\[ C_f = \frac{C_{m0} s}{Q} \frac{K_a}{K_a + C_{H^+}} \]

MECHANICAL EQUILIBRIUM EQUATION:

\[ \frac{\partial^2 u}{\partial t^2} \nabla \cdot \sigma = \nabla P_{\text{osmotic}} \]


Where, \( c_k \): Species concentration;
\( D_k \): Species Diffusion Coefficient;
\( z_k \): charge on mobile specie;
\( \psi \): Electric Potential;
\( \mu_k \): Ionic mobility of specie;
\( z_f \): charge on fixed specie;
\( c_f \): Fixed charge concentration;
\( K_a \): Dissociation constant of the gel;
\( C_{m0} \): Total pendant group concentration;
\( C_{H^+} \): Total proton concentration;
\( H \): Swelling Ratio;
\( \sigma \): Cauchy stress tensor

SCALING LAW:

\[ \frac{D_{i,\text{eff}}}{D_i} = (1 - i) \cdot \exp \left( \frac{1}{Q} \right) \]

\[ = Q^{1/3} N^{1/2} l_c \]

\( n_k \): Stoichiometric Coefficient
\( R \): rate of Reaction;
\( P_{\text{osmotic}} \): Osmotic Pressure at interface
MATHEMATICAL MODEL

NERNST-PLANCK EQUATION:

\[
\frac{\partial c_k}{\partial t} = \nabla \cdot (D_k \nabla c_k) + \nabla \cdot (F_k c_k \nabla y) + R_k
\]

POISSON EQUATION:

\[
\nabla^2 = \frac{F}{0} \left( \sum_k z_k c_k + z_f c_f \right)
\]

MATHEMATICAL MODEL

**FIXED CHARGE EQUATION:**

Anionic:

\[ C_f = \frac{C_{m0}^s K_a}{Q (K_a + C_{H^+})} \]

Cationic:

\[ C_f = \frac{C_{m0}^s C_{H^+}}{Q (K_a + C_{H^+})} \]

**MECHANICAL EQUILIBRIUM EQUATION:**

\[ \frac{\partial^2 u}{\partial t^2} - \nabla \cdot \nabla P_{osmotic} = 0 \]

\[ P_{osmotic} = RT \sum_{i=1}^{N} (C_{i,in} - C_{i,out}) \]

**INITIAL & BOUNDARY CONDITIONS**

\[ \psi = 0 \]
\[ C_i = 0 (i = \text{Glu, Ox, Buffer, GA, } H_2O_2) \]
\[ C_{\text{insulin}} = C_{\text{insulin}} \]

\[ C_i = C_i^0 (i = \text{Glu, Ox, Buffer, GA, } H_2O_2) \]
\[ C_{\text{insulin}} = 0 \]

\[ \frac{\partial \psi}{\partial x} = 0, \frac{\partial C_i}{\partial x} = 0, u = 0, v = 0 \]
\[ \psi = 0, C_i = C_i^0 \]

- Radial geometry
- Neumann BC: \( r=0 \)
- Dirichlet BC: \( L_{\text{bulk}} \)
EXPERIMENTAL STUDY

- A sulfonamide (Sulphadimethoxine, SDM) based glucose-sensitive hydrogel, bonded with an acrylamide monomer was synthesized.
- Glucose oxidase and catalase enzymes were immobilized on the hydrogel.
- Reversible swelling from 12 to 8 on a glucose concentration change in the range 0-16.5 mol/m³ at a pH of 7.4 was observed.
- Swelling ratio calculated as:

$$\frac{\text{Weight}_{\text{final}}}{\text{Weight}_{\text{initial}}} = \frac{\text{Weight}_{\text{initial}}}{\text{Weight}_{\text{initial}}}$$

(Kang et al, Journal of Controlled Release (2003))
The anionic hydrogel swells as the pH of bathing solution is increased.
MODEL VALIDATION (CONTINUED)

Swelling Ratio VS Glucose Concentration

Hydrogel shrinks with increase in glucose concentration
Glucose is changed as step inputs (as done in experiments)

Reversible swelling of the hydrogel is obtained which is similar to experimental data
EXPERIMENTAL STUDY (Cationic Hydrogel)

- This data has been taken from Peppas et al
- They have done experiments using a *poly(diethylaminoethyl methacrylate)* hydrogel (cationic)

**Swelling Ratio VS pH**

<table>
<thead>
<tr>
<th>pH</th>
<th>Swelling Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

**EXPERIMENTAL OBSERVATIONS**

1. Swelling ratio around 2 at high pH and 11 at low pH
2. Mesh size of HG is 10Å at high pH and 68Å at low pH
3. Sharp change in swelling at pH=7.4

(Peppas et al, AIChE (2013))

Hydrogel (cationic) shrinks with increasing pH
INSULIN RELEASE IN RESPONSE TO MEAL INTAKE

Two peaks in glucose profile corresponds with two different sized meals
Insulin is released at glucose concentrations greater than 7 mmol/L.
CONCLUSIONS

• We modeled the swelling behavior of glucose sensitive hydrogels using a multi-effect of model

• The model was validated with relevant experimental data

• We explored the use of cationic hydrogels for bolus Insulin delivery

• Hydrogels are capable of achieving reversible swelling/shrinking by changing the process conditions
THANK YOU!
References


3. A chemo-electro-mechanical model for simulation of responsive deformation of glucose-sensitive hydrogels with the effect of enzyme catalysis; Hua Li, Rongmo Luo, Erik Birgersson, Khin Yong Lam; Journal of the Mechanics and Physics of Solids 57, 2009 (369–382)

4. Smart Hydrogel Modeling; Hua Li; Springer (2009)


6. A sulfonamide based glucose-responsive hydrogel with covalently immobilized glucose oxidase and catalase; Seong Il Kang, You Han Bae; Journal of Controlled release 86, 2003 (115–121)


8. Characterization of glucose-sensitive insulin release systems in simulated in vivo conditions; Tamar Traitel, Yachin Cohen, Joseph Kost; Biomaterials 21, 2000 (1679-1687)
# Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{gel}$</td>
<td>600 µ</td>
</tr>
<tr>
<td>$R_{bulk}$</td>
<td>4000 µ</td>
</tr>
<tr>
<td>$C_{M0}$</td>
<td>1900 mol/m³</td>
</tr>
<tr>
<td>$C_0$</td>
<td>138 mol/m³</td>
</tr>
<tr>
<td>$C^H_0$</td>
<td>1 mol/m³</td>
</tr>
<tr>
<td>$C^o_x_0$</td>
<td>0.274 mol/m³</td>
</tr>
<tr>
<td>$C^glu_0$</td>
<td>0-16.5 mol/m³</td>
</tr>
<tr>
<td>$C_{GOX}$</td>
<td>0.15625 mol/m³</td>
</tr>
<tr>
<td>$C_{Catalase}$</td>
<td>0.048 mol/m³</td>
</tr>
</tbody>
</table>

- $V_{GOX} = 860(1/s) \times C_{GOX}$
- $V_{Catalase} = 860(1/s) \times C_{Catalase}$
- $K_{glu} = 69.92$ mol/m³
- $K_{oxygen} = 0.6178$ mol/m³
- $D_{Na} = 1.3 \times 10^{-9}$ m²/s
- $D_{Cl} = 2.3 \times 10^{-9}$ m²/s
- $D_{H} = 9.3 \times 10^{-9}$ m²/s
- $D_{glu} = 6.75 \times 10^{-10}$ m²/s
- $D_{ox} = 2.29 \times 10^{-9}$ m²/s

(Kang et al, Journal of Controlled Release (2003))