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MATHEMATICAL MODELING OF GLUCOSE RESPONSIVE HYDROGELS

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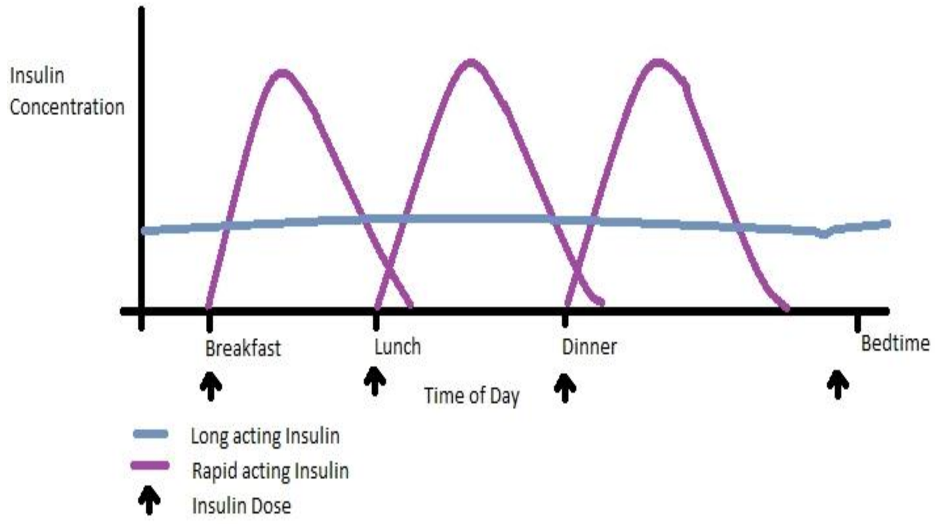
INTRODUCTION

- 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**



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

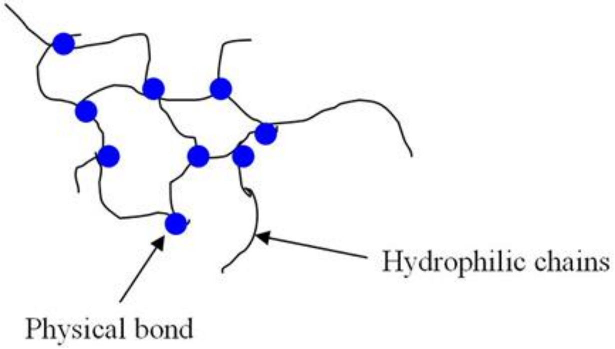
- Type 1 diabetes patients require 3-4 injections/ day
- Thus, there is a need to provide this automatic and customized dosing

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.



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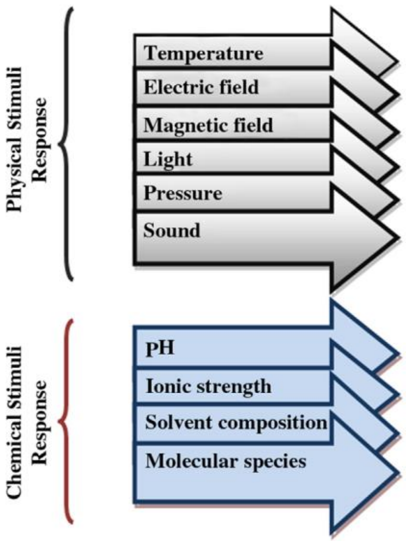
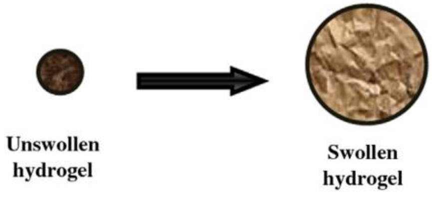


Stimuli responsive hydrogel



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GLUCOSE SENSITIVE HYDROGELS

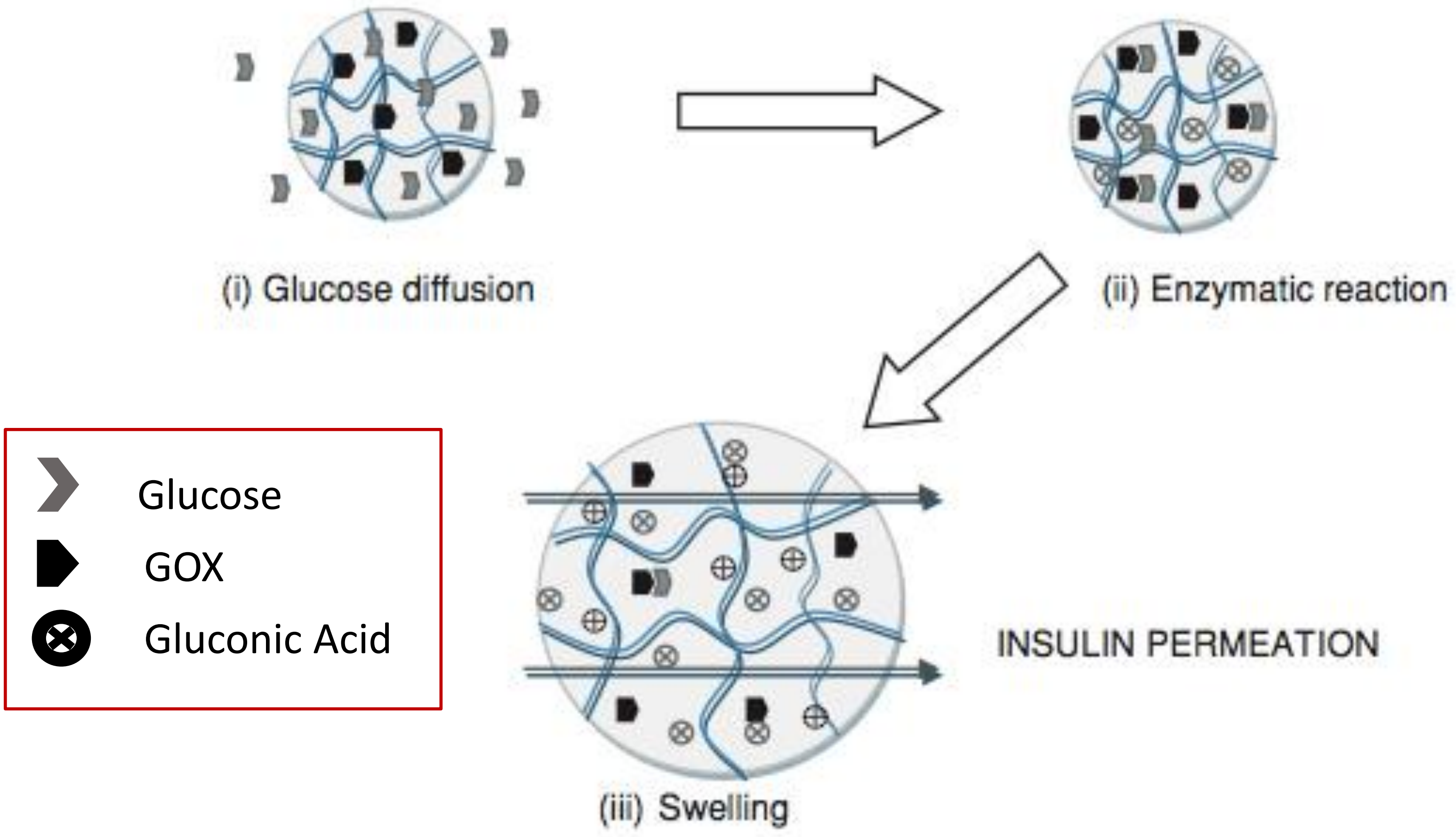


Figure: Schematic representation of a glucose-responsive glucose-oxidase-loaded membrane (Priya Bawa et al; Biomed. Mater. 4 (2009))

PHENOMENA INVOLVED

- Hydrogel is loaded with Glucose oxidase & Catalase that helps the conversion of Glucose to Gluconic acid and decomposes H_2O_2 respectively:

$$Glucose + \frac{1}{2}O_2 \xrightarrow{GOX} GluconicAcid + H_2O_2$$

$$H_2O_2 \xrightarrow{Catalase} \frac{1}{2}O_2 + H_2O$$

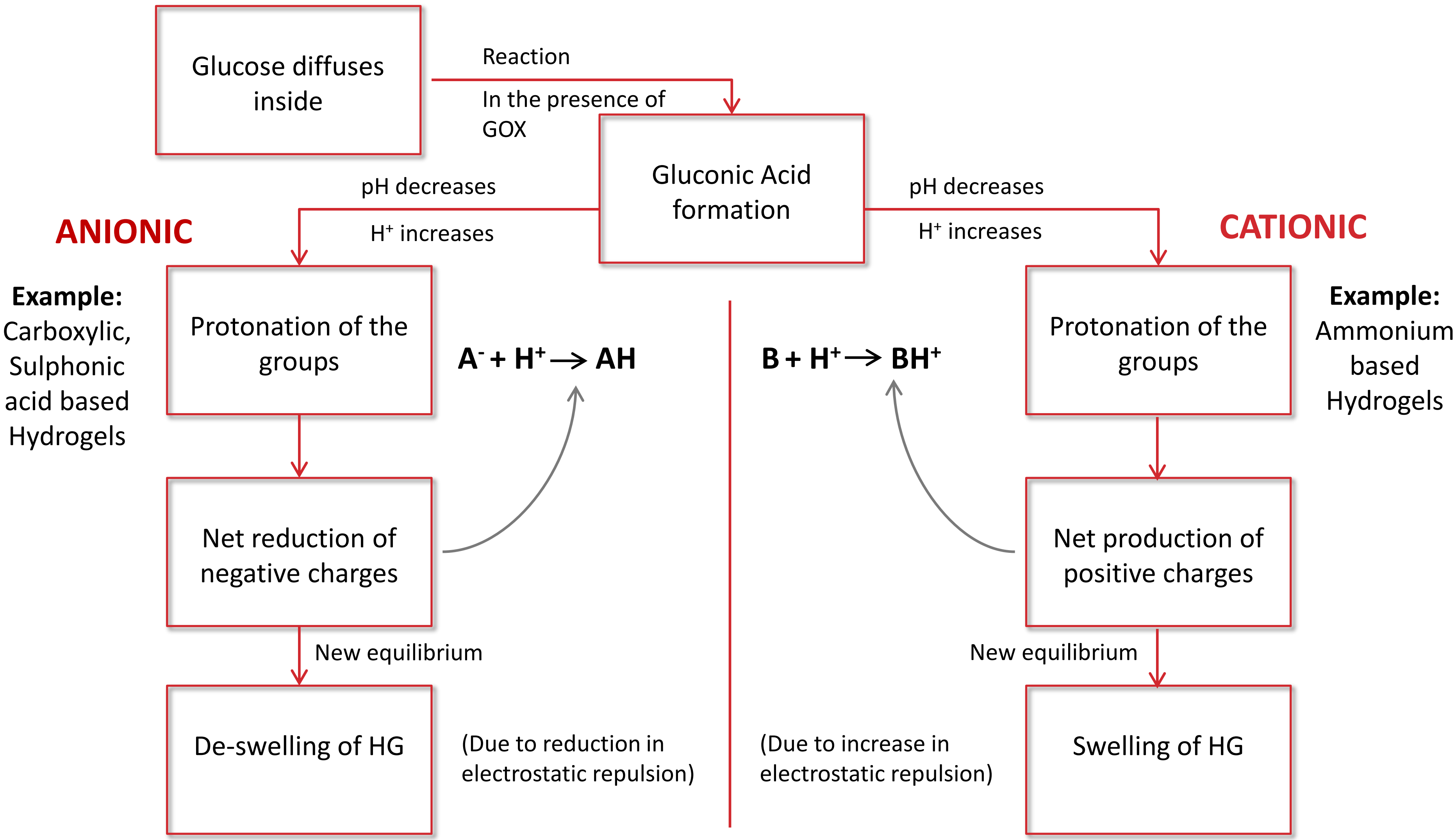
which follow the following reaction order:

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

$$R = \frac{V_{\max} C_{H_2O_2}}{K_{H_2O_2} + C_{H_2O_2}}$$

- 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



MATHEMATICAL MODEL

NERNST-PLANCK EQUATION:

$$\frac{\partial c_k}{\partial t} = \nabla.(D_k \nabla c_k) + \nabla.(F m_k c_k \nabla y) + n_k R$$

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

POISSON EQUATION:

$$\nabla^2 y = -\frac{F}{ee_0}\left(\sum_k z_k c_k + z_f c_f\right)$$

FIXED CHARGE EQUATION:

$$C_f = \frac{C^s_{m0}}{Q}\frac{K_a}{K_a + C_{H^+}}$$

SCALING LAW:

$$\frac{D_{i,eff}}{D_i} = \left(1 - \frac{d_i}{x}\right).\exp\left(\frac{-1}{Q-1}\right)$$

$$x = Q^{1/3} N^{1/2} l_c$$

MECHANICAL EQUILIBRIUM EQUATION:

$$r\frac{\partial^2 u}{\partial t^2} - \nabla.s = \nabla P_{osmotic}$$

(H. Li et al; Journal of the Mechanics and Physics of Solids (2008))

Where, c_k : Species concentration;
D_k: Species Diffusion Coefficient;
z_k: charge on mobile specie;
ψ: Electric Potential;
μ_k: Ionic mobility o specie;
z_f: charge on fixed specie;
c_f: Fixed charge concentration;
K_a: Dissociation constant of the gel;
C_{mo}: Total pendant group concentration;
H: Swelling Ratio;
σ: Cauchy stress tensor
ν_κ: Stoichiometric Coefficient
R: rate of Reaction;
$P_{osmotic}$: Osmotic Pressure at interface

MATHEMATICAL MODEL

NERNST-PLANCK EQUATION: $\frac{\partial c_k}{\partial t} = \nabla.(D_k \nabla c_k) + \nabla.(F m_k c_k \nabla y) + n_k R$

Unsteady Transport

Diffusion due to Concentration Gradient

Diffusion due to Potential Gradient

Production/ Consumption due to Reaction

POISSON EQUATION: $\nabla^2 y = -\frac{F}{e e_0}\left(\sum_k z_k c_k + z_f c_f\right)$

Total Charges Balance (Charge Density, ρ)

Spatial Distribution of Potential

Total Mobile Charges

Fixed Charges

(H. Li et al; Journal of the Mechanics and Physics of Solids (2008))

MATHEMATICAL MODEL

FIXED CHARGE EQUATION:

Anionic:

$$C_f = \frac{C^s_{m0}}{Q}\frac{K_a}{K_a + C_{H^+}}$$

Cationic:

$$C_f = \frac{C^s_{m0}}{Q}\frac{C_{H^+}}{K_a + C_{H^+}}$$

Hydrogen ion Concentration

Net Pendant Group Concentration

MECHANICAL EQUILIBRIUM EQUATION:

$$\rho \frac{\partial^2 u}{\partial t^2} - \nabla . \sigma = \nabla P_{osmotic}$$

Net force per unit volume on the gel

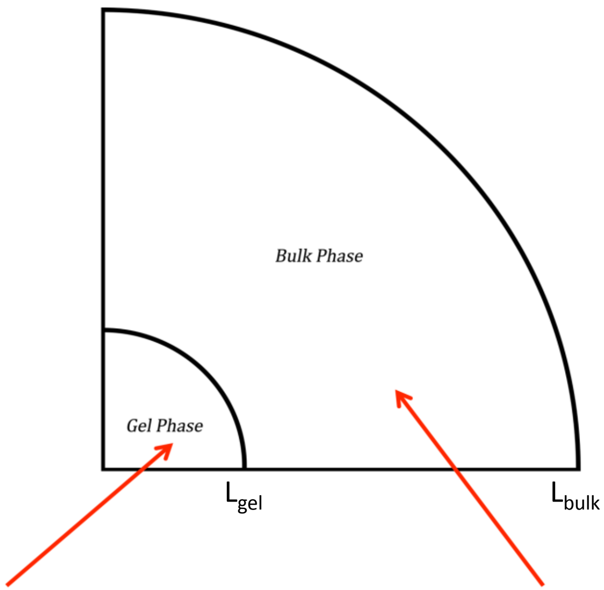
Force due to stress

Force due Osmotic Pressure

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

(H. Li et al; Journal of the Mechanics and Physics of Solids (2008))

INITIAL & BOUNDARY CONDITIONS



$\psi = 0$

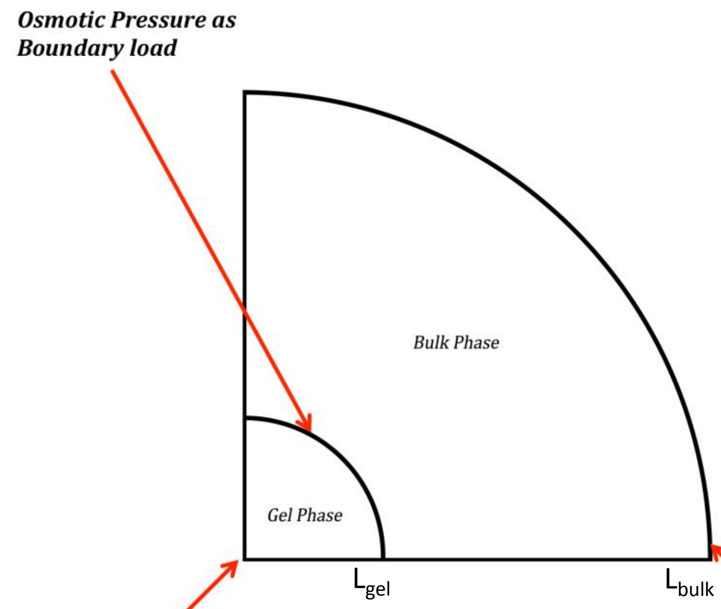
$C_i = 0 (i = Glu, Ox, Buffer, GA, H_2O_2)$

$C_{insulin} = C_{insulin}$

$y = 0$

$C_i = C_i^0 (i = Glu, Ox, Buffer, GA, H_2O_2)$

$C_{insulin} = 0$



$$\frac{\partial \psi}{\partial x} = 0, \frac{\partial C_i}{\partial x} = 0, u = 0, v = 0$$

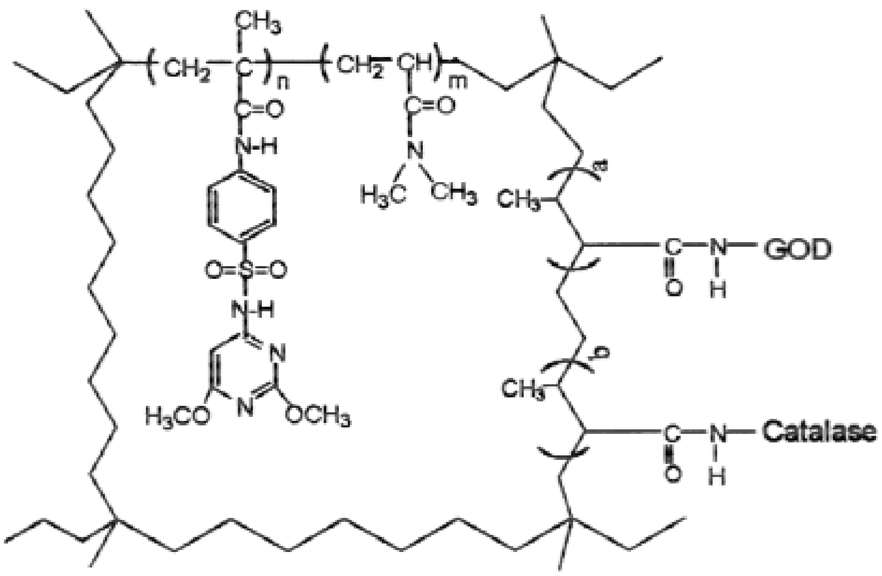
$$\psi = 0, C_i = C_i^o$$

- Radial geometry
- Neumann BC: r=0
- Dirichlet BC: L_{bulk}

EXPERIMENTAL STUDY

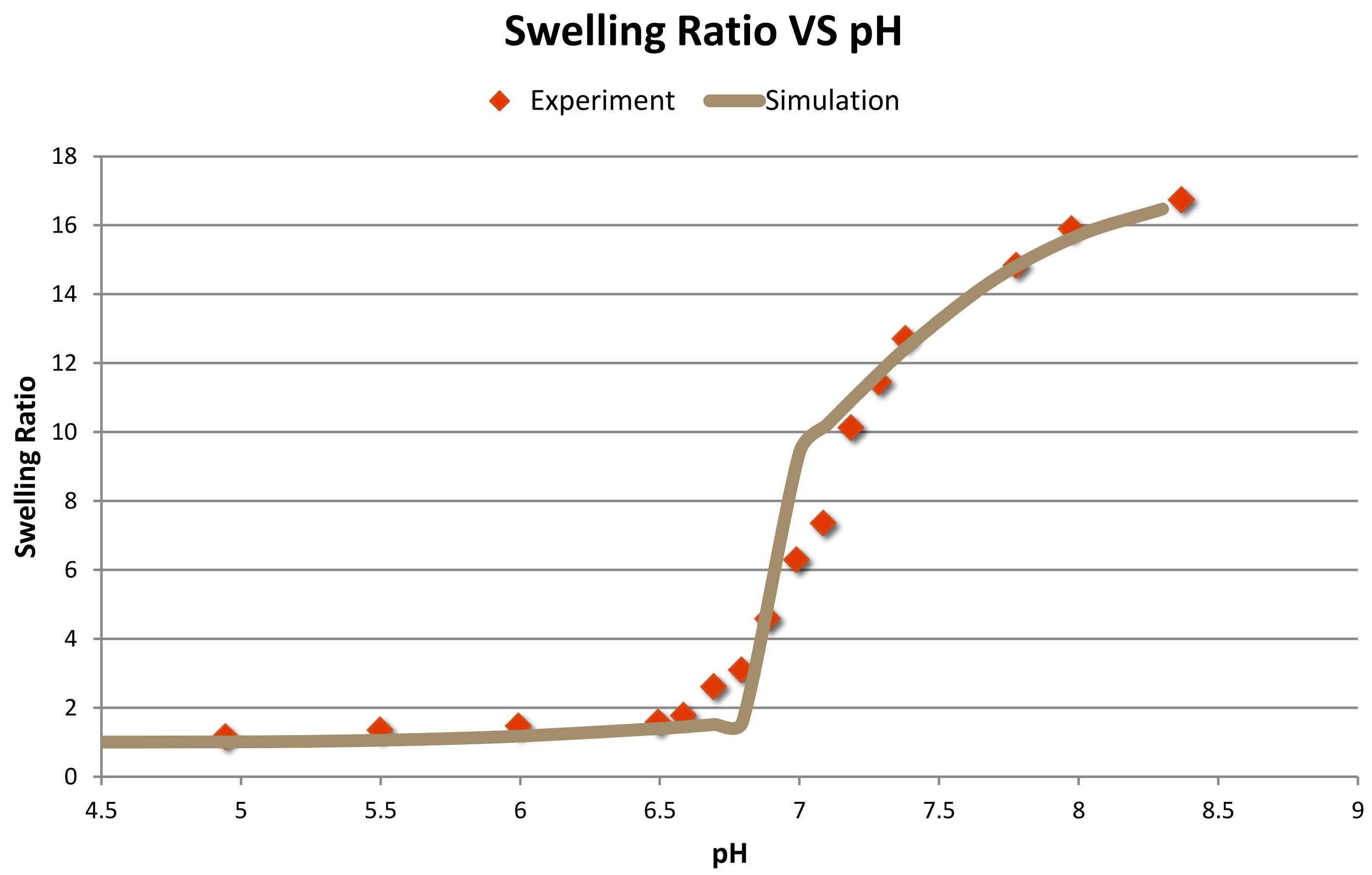
- A sulfonamide (Sulphadimethoxine, SDM) based glucose-sensitive hydrogel, bonded with an acrylamide monomer was synthesized
- Glucose oxidase and catalase enzymes were immobilized on the hydrogel
- Reversible swelling from 12 to 8 on a glucose concentration change in the range 0-16.5 mol/m^3 at a pH of 7.4 was observed
- Swelling ratio calculated as:

$$\frac{Weight_{final} - Weight_{initial}}{Weight_{initial}}$$



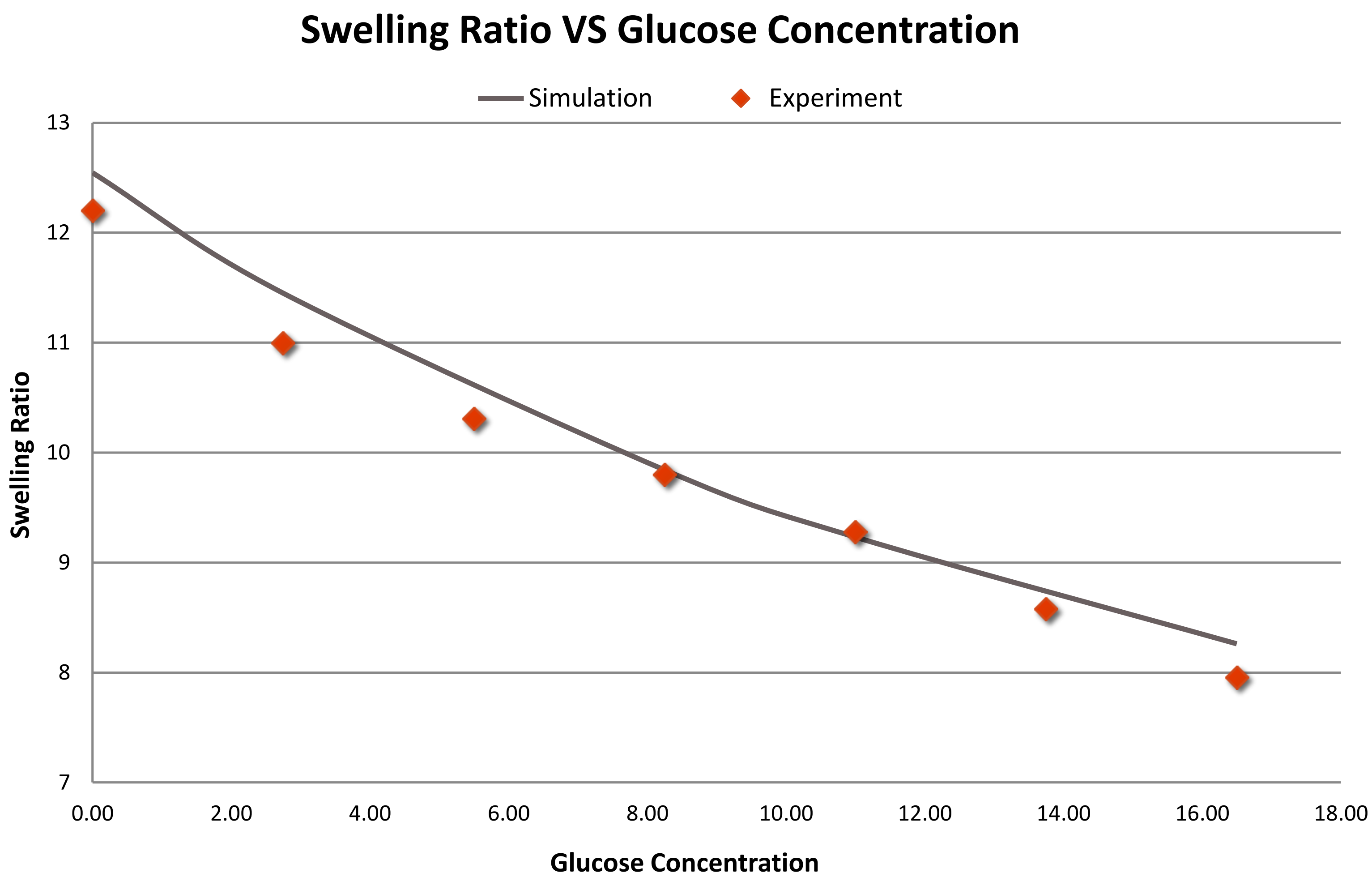
(Kang et al, Journal of Controlled Release (2003))

MODEL VALIDATION



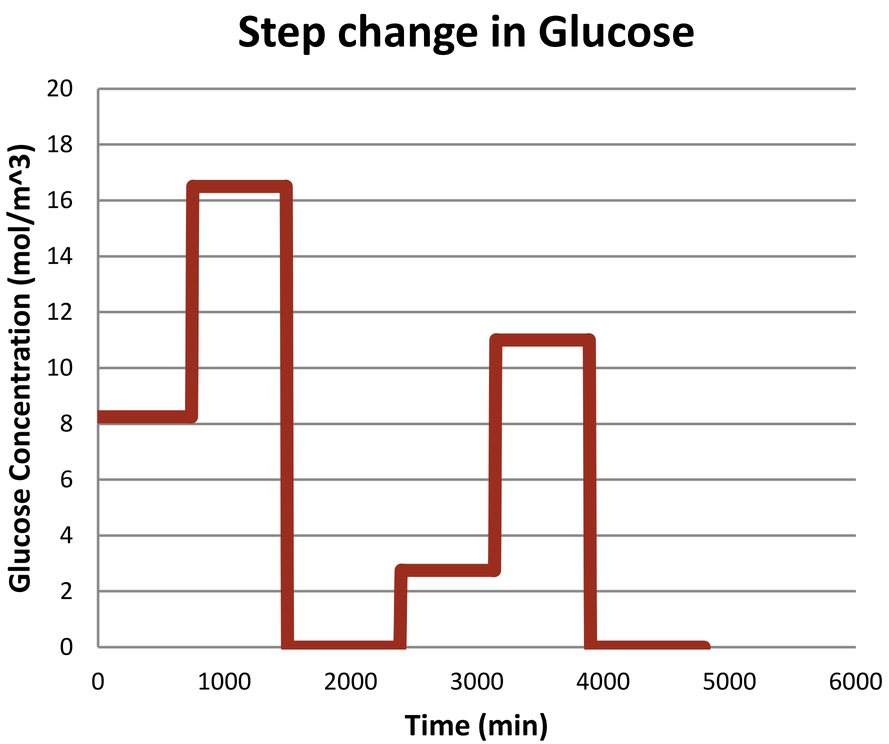
The anionic hydrogel swells as the pH of bathing solution is increased

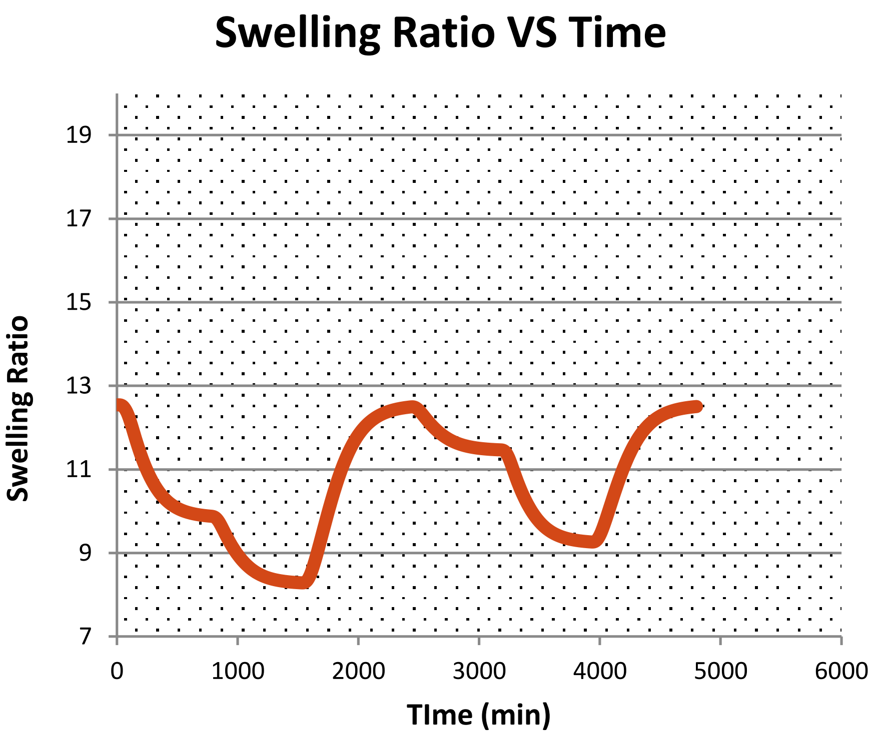
MODEL VALIDATION (CONTINUED)



Hydrogel shrinks with increase in glucose concentration

MODEL RESULTS (Transient Simulation)



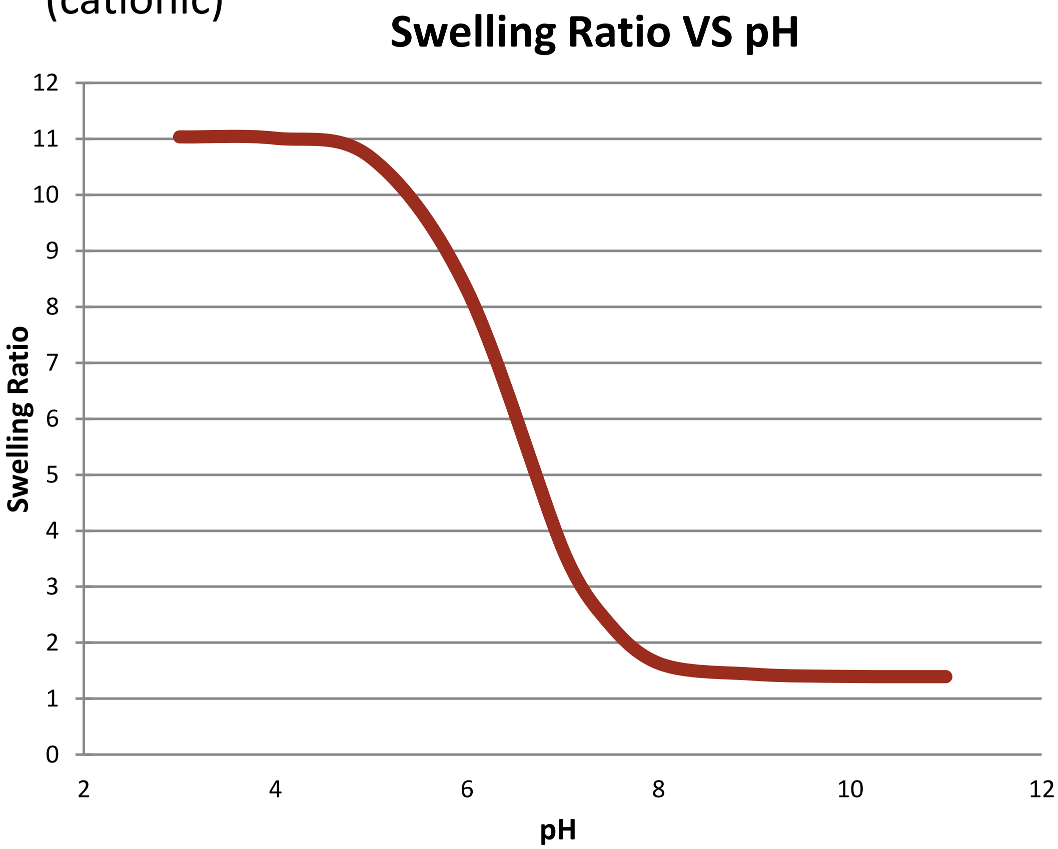


Glucose is changed as step inputs (as done in experiments)

Reversible swelling of the hydrogel is obtained which is similar to experimental data

EXPERIMENTL STUDY (Cationic Hydrogel)

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



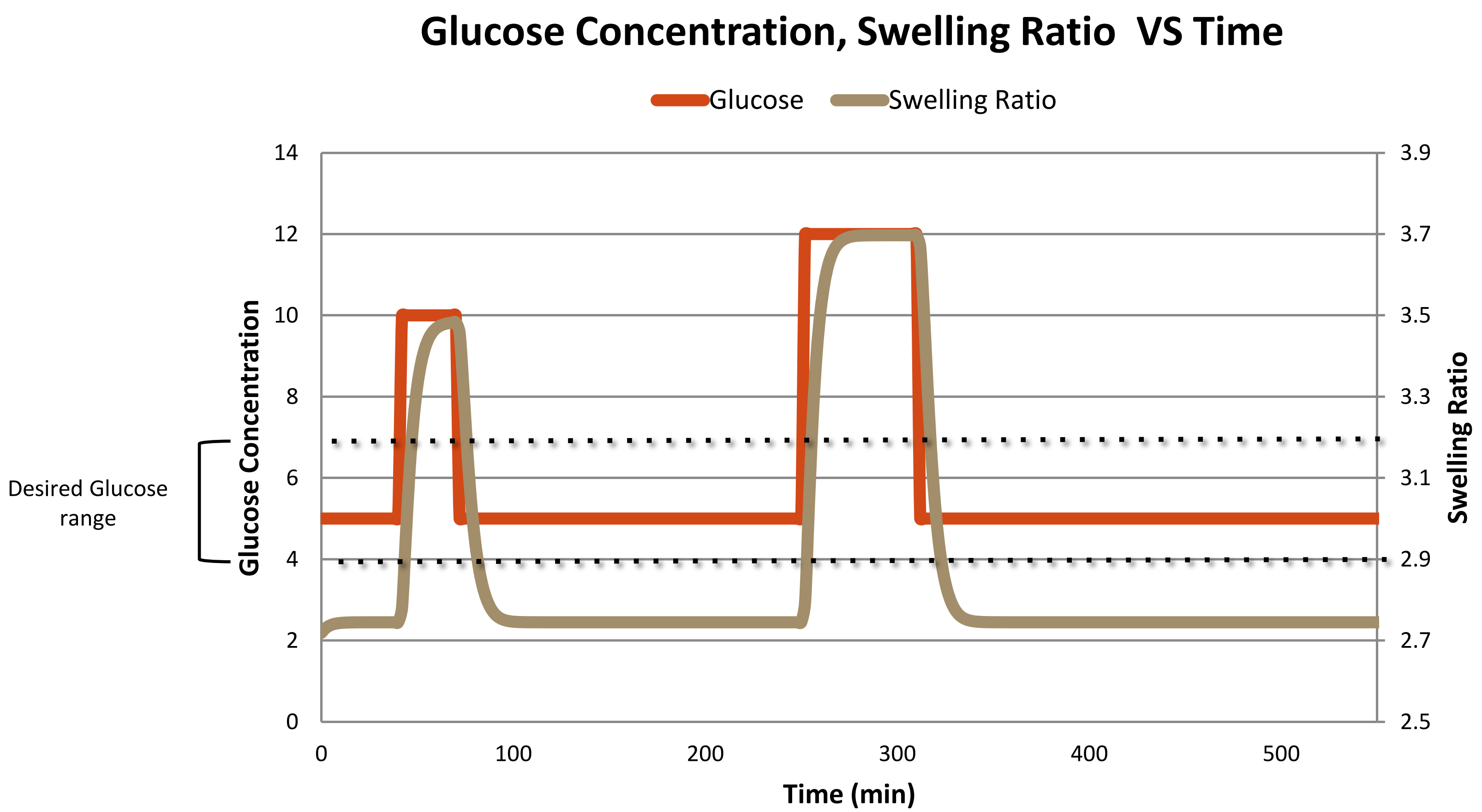
EXPERIMENTAL OBSERVATIONS

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))

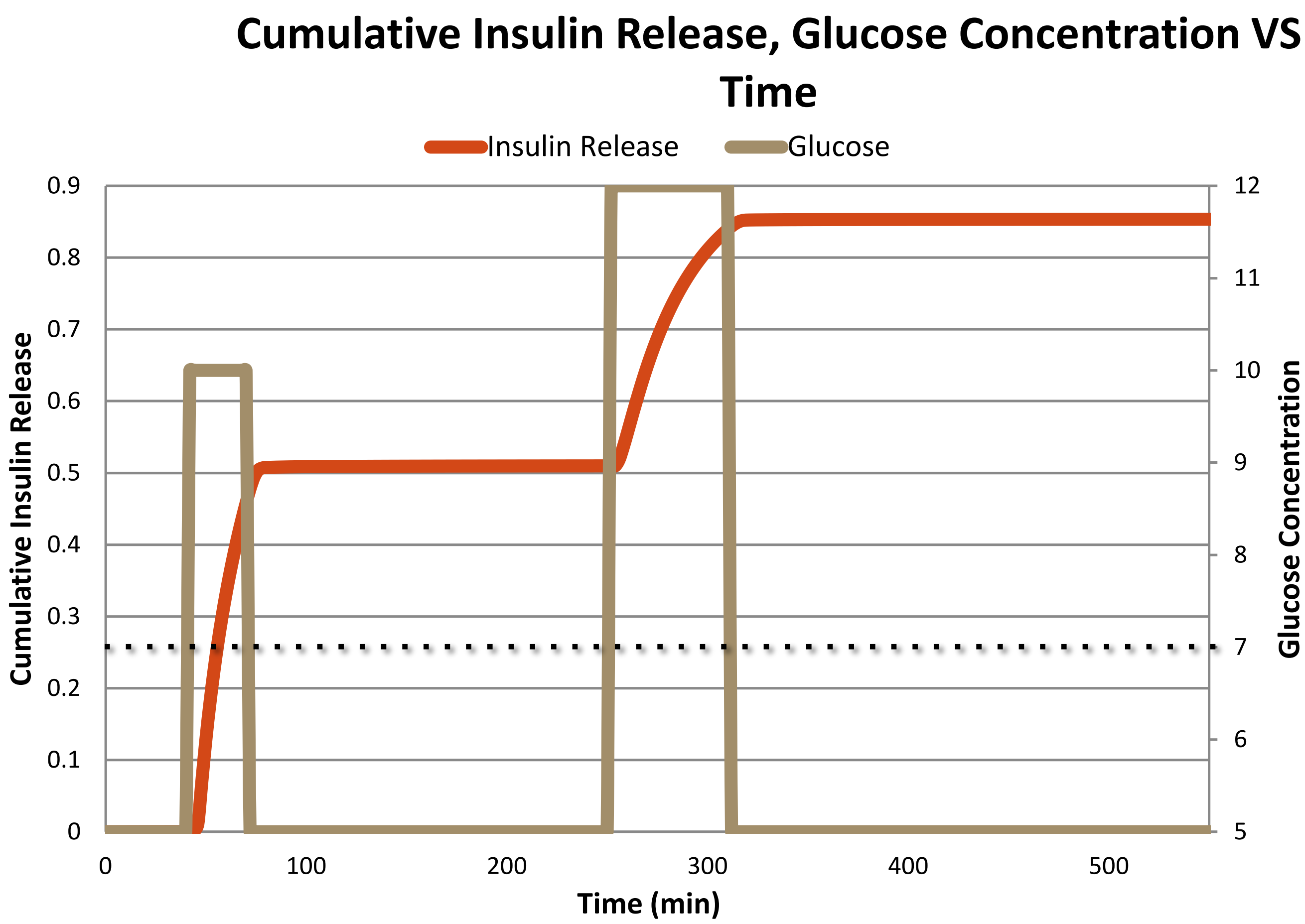
Hydrogel (cationic) shrinks with increasing pH

INSULIN RELEASE IN RESPONSE TO MEAL INTAKE



Two peaks in glucose profile corresponds with two different sized meals

INSULIN RELEASE IN RESPONSE TO MEAL INTAKE



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

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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

Parameter	Value
R_{gel}	600µ
R_{bulk}	4000µ
C_{M0}	1900 mol/m^3
C_0	138 mol/m^3
$C^H{}_0$	1 mol/m^3
$C^{ox}{}_0$	0.274 mol/m^3
$C^{glu}{}_0$	0-16.5 mol/m^3
C_{GOX}	0.15625 mol/m^3
$C_{Catalase}$	0.048 mol/m^3

Parameter	Value
V_{GOX}	860(1/s)*C_{GOX}
$V_{Catalase}$	860(1/s)*$C_{Catalase}$
K_{glu}	69.92 mol/m^3
K_{oxygen}	0.6178 mol/m^3
D_{Na}	1.3x10^{-9} m^2/s
D_{Cl}	2.3x10^{-9} m^2/s
D_H	9.3x10^{-9} m^2/s
D_{glu}	6.75x10^{-10} m^2/s
D_{ox}	2.29x10^{-9} m^2/s

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