Controlled Drug Delivery

Spatial and temporal control over drug concentration
Usual Gold Standard in Controlled Release

- Zero Order Release

![Graph showing drug concentration in plasma over time with toxic and minimum effective concentration levels.](attachment:graph.png)
Zero order delivery ineffective when...

Minimum effective concentration changes with time

- Insulin (required level depends on glycemia)
- Addictive drugs, e.g. heroin, cocaine, etc.
- Down regulation of hormone receptors
- Other drugs (e.g. nitroglycerin)
“NONTRADITIONAL” DRUG DELIVERY

RESPONSIVE SYSTEMS (e.g. Glucose/Insulin)

AUTONOMOUS SYSTEMS (Ultradian Hormones)
Gonadotropin Hormone Releasing Hormone (GnRH)

• Hypogonadotrophic Hypogonadism
  – Failure of episodic GnRH secretion
    • Males: Failure to reach puberty
    • Females: Failure to sustain reproductive cycle

Treatment: Rhythmic, pulsatile delivery of GnRH
VALUE OF RHYTHMIC DELIVERY

PULSED vs CONTINUOUS GnRH in AMENORRHEA

Fig. 1. LH (determined by RIA) measured every 20 min for 6 h in patient 5 during the pretreatment period and during the continuous and pulsatile GnRH regimens.


Fig. 2. Hormone data obtained every 1–3 days throughout the continuous and pulsatile infusions of GnRH in patient 5. GnRH dosages are indicated in the cross-hatched areas. Menses occurred on day 68 of the pulsatile regimen and never during the continuous regimen.
OTHER HORMONES

**PULSED vs CONTINUOUS INSULIN**


**PULSED vs CONTINUOUS PLATELET DERIVED GROWTH FACTOR (PDGF) in LENS DEVELOPMENT**

<table>
<thead>
<tr>
<th>n</th>
<th>Growth condition</th>
<th>Appearance at 60 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>In vivo</td>
<td>Transparent</td>
</tr>
<tr>
<td>7</td>
<td>Pulsed without PDGF</td>
<td>Opaque</td>
</tr>
<tr>
<td>7</td>
<td>Pulsed PDGF</td>
<td>Transparent</td>
</tr>
<tr>
<td>5</td>
<td>Continuous PDGF</td>
<td>Opaque</td>
</tr>
</tbody>
</table>

**SIMPLE(ST) TOY MODEL**

**ASSUMPTIONS**
- Instantaneous conversion of glucose to $H^+$
- Instantaneous phase transition of membrane
- Constant permability to $H^+$

\[
\frac{dh}{dt} = \frac{A}{V} (P_{gH} G - P_h h) \quad \text{until} \quad h \uparrow h_{HL}
\]

\[
\frac{dh}{dt} = \frac{A}{V} (P_{gL} G - P_h h) \quad \text{until} \quad h \downarrow h_{ LH}
\]
TOY MODEL BEHAVIOR

CONDITION FOR OSCILLATION:

\[ \frac{P_h}{P_{gH}} h_{HL} < G < \frac{P_h}{P_{gL}} h_{LH} \]

Pulse Width:

\[ T_H = \frac{V}{A_P} \ln \frac{P_{gH} G - h_{HL} P_h}{P_{gL} G - h_{HL} P_h} = \frac{V}{A_P} \ln \frac{h_{SS,L} r h_{LH}}{h_{SS,L} r h_{HL}} \]

Interpulse Interval:

\[ T_L = \frac{V}{A_P} \ln \frac{P_{gL} G - h_{HL} P_h}{P_{gL} G - h_{HL} P_h} = \frac{V}{A_P} \ln \frac{h_{HL} - h_{SS,L}}{h_{HL} - h_{SS,L}} \]
Hydrogel materials

\[-(\text{CH}_2-\text{CH})_x\quad \text{CH}_3\]
\[\text{C} = \text{O}\]
\[\text{NH}\]
\[\text{CH}_2-\text{CH}-\text{CH}_2\]

\[-(\text{CH}_2-\text{C})_y\quad \text{C} = \text{O}\]
\[\text{OH}\]

NIPA (N-isopropylacrylamide)  MAA (methacrylic acid)

High pH: gel ionized and hydrophilic (swollen)
Low pH: gel unionized and hydrophobic (collapsed)
pH Oscillations with Corresponding r-GnRH Flux into Donor Cell
DELIVERY RATE
OBTAINED BY DECONVOLUTION

- Graph showing the rate of delivery over time in hours and minutes.
- The x-axis represents time in hours, ranging from 0 to 168 hours.
- The y-axis represents the rate of delivery in nmol/min, ranging from -1 to 8 nmol/min.
- The graph displays periodic fluctuations in delivery rate.
Effect of Changing MAA Doping

- 2% MAA, 15mM Glucose
- 5% MAA, 30mM Glucose
- 10% MAA, 50mM Glucose

pH vs. Time (hours)
What is a hydrogel?

Hydrogels are 3-D crosslinked hydrophilic polymer networks.
Discrete Hydrogel Volume Phase Transition (DVPT)

- Discrete
  - First-order phase transition
- Volume
  - Swells or collapses
- Polyelectrolytes
  - Ionizable groups
- Induced by changes in temperature, pH, organic solvents, light, and salt
Hydrogel Volume Phase Transition

\[ \text{pH} = 5.5 \ (> \text{pKa of MAA}) \]
Swelling Forces
Elasticity of Matrix

• Entropic
  – unperturbed state is most likely

• Modulus
  – due to cross-link density

\[ \pi_{el} = -\frac{RTv_e}{V_o} \left( \alpha - \frac{1}{2\alpha} \right) \]

Swelling Forces
Polymer-solvent Mixing

- Polymer-solvent mixing entropy
  - mixed state more probable
- Polymer-solvent interaction
  - Polymer prefers polymer
  - Solvent prefers solvent
  - Chi parameter quantifies preferences

\[
\pi_{\text{Mix}} = -\frac{RT}{V_s} \left( \ln \left( 1 - \frac{\phi_o}{\alpha} \right) + \frac{\phi_o}{\alpha} + \chi \left( \frac{\phi_o}{\alpha} \right)^2 \right)
\]
Swelling Forces--Ionic

- **Ion-solvent mixing**
  - Mixed state more probable
  - Ideal, dilute solution

- **Donnan Partitioning**
  - Negative charge on membrane
  - Positive ions drawn in to neutralize membrane

\[
\pi_{\text{Ion}} = RT\left( C_{\text{Na}} + C_{\text{Cl}} - 2C'_{\text{NaCl}} \right)
\]

\[
C_{\text{Na}} = \lambda C'_{\text{NaCl}}
\]
Hydrogen Ion Dissociation, Charge Density on Hydrogel

\[ K_a = \frac{[C_{\text{COO}^-}][C_H]}{[C_{\text{COOH}}]} \]

\[ \frac{C_{\text{COOo}}}{\alpha} = C_{\text{COOH}} + C_{\text{COO}^-} \]
Matrix Stress vs. Swelling Ratio

- Ionization $\rightarrow$ environmental sensitivity
- Bistability

Curve shifts with pH

![Graph showing stress on polymer matrix vs. swelling ratio with different concentrations of I (0.18 M, 0.24 M, 0.27 M). The graph indicates collapsed and swollen equilibrium with Swelling Ratio on the x-axis and Stress on Polymer Matrix on the y-axis.](image-url)
More Advanced Toy Model

Swelling of Hydrogel
\[
\frac{dL}{dt} = k_w (1 - \phi)[\ln(1 - \phi) + \phi + (\chi_1 + \chi_2 \phi)\phi^2 + \nu_w \rho_o \left(\frac{\phi_o}{\phi} - \frac{\phi}{2\phi_o}\right) - \nu_w C_s \left(\lambda + \frac{1}{\lambda} - 2\right)]
\]

H⁺ Concentration in Hydrogel
\[
\frac{d}{dt}\left[L(C^M_{\text{cooh}} + C^M_H)\right] = k_H (1 - \phi)\left[\lambda (C^I_H + C^{II}_H) / 2 - C^M_H\right]
\]

Glucose Transport/H⁺ Production
\[
\frac{d}{dt} C^{II}_H = \frac{A k^0_G}{V} e^{-\beta\phi} C_G - \frac{A k_H}{V} (1 - \phi)(\lambda C^{II}_H - C^M_H) - k_{\text{marble}} C^H_H
\]

Dissociation
\[
C^M_{\text{cooh}} = \frac{\phi}{\phi_0} \left(\frac{\sigma_0 C^M_H}{K_a + C^M_H}\right)
\]

Electroneutrality
\[
(1 - \phi)(\lambda - 1 / \lambda) C_s - (\phi / \phi_0)(1 + C^M_H / K_a)^{-1} \sigma_0 = 0
\]
SWELLING HYSTERESIS

- Swelling Ratio $L/L_0$ vs. $f_{\sigma_0}$ (M)
- Swelling Ratio $L/L_0$ vs. $pH_{II}$

- $\sigma_0 = 0.38M$
- $\sigma_0 = 0.28M$
- $\sigma_0 = 0.20M$
- $\sigma_0 = 0.15M$
HOPF BIFURCATIONS
PREDICTED OSCILLATIONS

\[ \sigma_0 = 0.20 \text{ M, } C_G = 10\text{ mM} \]
\[ \sigma_0 = 0.26 \text{ M, } C_G = 22\text{ mM} \]
\[ \sigma_0 = 0.38 \text{ M, } C_G = 50\text{ mM} \]
Acknowledgments

- John P. Baker
- Jean-Christophe Leroux
- Gauri Misra
- Anish Dhanarajan
- Jon Urban
- Yuandong Gu

- NSF, NIH