Luteinizing Hormone Dynamics in Menstruation

Irene Lee, Swathi Prabhu, Meenakshi Singhal, Alice Tor
TABLE OF CONTENTS

01 INTRODUCTION
larger control system of menstruation, subsection of LH

02 DERIVATIONS
kinetic eqns; ODEs; inputting parameters to derive transfer fn

03 MODEL ANALYSIS
block diagram; output responses; bode plot; stability; applications
01 INTRODUCTION
control system of menstruation, subsection of LH
Background

Figure 1: demonstrates the complexity of hormone control during different stages (Draper et al.)

System: Menstruation

cyclic shedding of uterine layer
- multiple stages
- feedback dictated by hormones
  - stage latency
  - intensity

Modeling: Luteinizing Hormone (LH)

glycoprotein hormone
- stimulates:
  - ovulation: release of egg from follicle
  - corpus luteum: production of progesterone to sustain pregnancy
  - estradiol production
- model can identify:
  - downstream effects
  - therapeutic targets
DERIVATION
kinetic equations; ODEs; transfer function

\[ F(s) = \int_0^\infty e^{-st} f(t) \, dt. \]
Kinetic Equations and ODEs

- **hormone-receptor complex**
  - LH
- LH desensitization

- binding of LH to receptors
- formation of free LH receptors

- hormone-receptor complex dynamics
- desensitized complex dynamics

\[ \frac{d}{dt} R_{LH}(t) = k_{recy}^{LH} \cdot R_{LH,des}(t) - k_{on}^{LH} \cdot L_{blood}(t) \cdot R_{LH}(t) \]
\[ \frac{d}{dt} L_{H-R}(t) = k_{on}^{LH} \cdot L_{blood}(t) \cdot R_{LH}(t) - k_{des}^{LH} \cdot L_{H-R}(t) \]
\[ \frac{d}{dt} R_{LH,des}(t) = k_{des}^{LH} \cdot L_{H-R}(t) - k_{recy}^{LH} \cdot R_{LH,des}(t) \]

*eqn of interest: binding necessary for signal transduction and downstream processes

(↑ binding = ↑ physiological effects)
Redefining Parameters

hormone-receptor complex LH desensitization

desensitized complex dynamics

rate constants

\[ x = k^{LH}_{recy} \text{ free LH}_{\text{receptor}} \text{ formation rate} \]
\[ y = k^{LH}_{on} \text{ hormone to receptor binding rate} \]
\[ z = k^{LH}_{des} \text{ LH}_{\text{receptor}} \text{ desensitization rate} \]

terms

\[ a(t) = R_{LH} = [LH_{\text{receptor}}] \]
\[ b(t) = R_{LH, des} = \text{desensitized complex} \]
\[ c(t) = [LH_{\text{blood}}] \]
\[ d(t) = LH-R = [LH_{\text{hormone-receptor complex}}] \]

*eqn of interest: binding necessary for signal transduction and downstream processes

(↑ binding = ↑ physiological effects)
Transfer Function

input

\[ c(t) = L_{\text{blood}}(t) \]

equations

\[
\begin{align*}
    sA(s) - a_0 &= xB(s) - y_0 A(s) \\
    sD(s) - d_0 &= y_0 C(s) + y_0 A(s) - zD(s) \\
    sB(s) - b_0 &= zD(s) - xB(s)
\end{align*}
\]

output

\[ d(t) = L_{\text{blood}} - R(t) \]

transfer relationship:

\[
(s + z - \frac{yc_0xz}{(s+yc_0)(s+x)})D(s) - (d_0 + \frac{yc_0xb_0}{(s+yc_0)(s+x)} - \frac{yc_0a_0}{s+yc_0}) = (ya_0 + \frac{yc^2a_0}{(s+yc_0)})C(s)
\]
Transfer Function

assumptions

- **linearization**: assume that \(a(t)\), the concentration of free LH receptors, and \(d(t)\), the concentration of LH-receptor complex, are linear for small signals around the steady-state operating point
- **initial conditions**: assume that initial conditions for \(a(t)\), \(b(t)\), and \(d(t)\) are negligible

transfer function \(D(s)/C(s)\):

\[
(s + z - \frac{yc_0xz}{s+yc_0(s+x)})D(s) = (ya_0 + \frac{y^2c_0a_0}{s+yc_0})C(s)
\]

transfer function \(tf\):

\[
tf = \frac{(ya_0 (s + yc_0) - y^2a_0c_0) (s + x)}{(s+2)(s+x)(s+yc_0) - yc_0xz}
\]
MODEL ANALYSIS

block diagram; output response; bode plot; stability; applications
Transfer Function Response

- observe: given assumptions, $d(t)$ decreases over time
input: \( c(t) = \text{LH}_{\text{blood}} \)

output: \( d(t) = \text{LH-R} \)
output response

constants

\( LH_{\text{free receptors}} \) formation rate: \( X = K_{LH\text{recy}}^{LH} = 68.9491/\text{day} \)
\( LH_{\text{receptor binding rate}}: \ Y = K_{LH\text{on}}^{LH} = 2.143 \ \text{L/day\cdot IU} \)
\( LH_{\text{receptor complex desensitization rate}}: \ Z = K_{LH\text{des}}^{LH} = 183.36/\text{day} \)
\( LH-R(t) \) initial value: \( A_0 = 7.304 \ \text{nmol/L} \)
\( R_{LH,\text{des}} \) initial value: \( B_0 = 1.5032 \ \text{nmol/L} \)
\( LH_{\text{blood}}(t) \) initial value: \( C_0 = 6.619 \ \text{IU/L} \)

observe: \( d(t) = [LH_{\text{hormone-receptor complex}}] \) saturates quickly
Output response \( d(t) \) with parameter perturbation

- \( a(t) = 2 \text{ nmol/L} \)
- \( a(t) = 20 \text{ nmol/L} \)
- \( c(t) = 3 \text{ IU/L} \)
- \( c(t) = 30 \text{ IU/L} \)

\( a(t) = [\text{LH}_{\text{receptor}}] \)

\( c(t) = [\text{LH}_{\text{blood}}] \)
Output response $d(t)$ with parameter perturbation

- $k_{LH_{on}} = 1 \text{ L/(day·IU)}$
- $k_{LH_{recy}} = 30/\text{day}$
- $k_{LH_{on}} = 10 \text{ L/(day·IU)}$
- $k_{LH_{recy}} = 100/\text{day}$

$k_{LH_{on}}$ = LH to receptor binding rate

$k_{LH_{recy}}$ = free LH receptor formation rate
observe: $d(t)$ ($[\text{LH hormone-receptor complex}]$) saturates to a certain point then oscillates due to the parameter values

- Demonstrating underdamping
- One full day
**BODE PLOT**

**constants**

LH$_{\text{free receptors}}$ formation rate: \( X = K_{\text{LH recy}}^{\text{LH}} = 68.9491/\text{day} \)

LH$_{\text{receptor binding rate}}$: \( Y = K_{\text{LH on}}^{\text{LH}} = 2.143 \text{ L/day·IU} \)

LH$_{\text{receptor complex desensitization rate}}$: \( Z = K_{\text{LH des}}^{\text{LH}} = 183.36/\text{day} \)

LH-R(t) initial value: \( A_0 = 7.304 \text{ nmol/L} \)

R$_{\text{LH,des}}$ initial value: \( B_0 = 1.5032 \text{ nmol/L} \)

LH$_{\text{blood(t)}}$ initial value: \( C_0 = 6.619 \text{ IU/L} \)

**transfer function:**

\[
H = \frac{-206.4 s - 15086}{s^3 + 266.5 s^2 + 1.622e04 s - 2.6}
\]

Continuous-time transfer function.
System Stability

Under current assumptions:

- Negative Phase Margin → system will be less stable when the loop is closed
- No positive real pole components → system is stable
- Complex factors → system is underdamped

simplified transfer fxn:

\[ H_2 = \frac{-206.4 \ s - 15086}{s^3 + 226.5 \ s^2 + 1.622e04 \ s} \]

factored: = \( s \) (\( s + 113.3 + 58.3j \)) (\( s + 113.3 - 58.3j \))

simplified bode plot
MODEL APPLICATIONS

therapeutics
- Acquiring data on cycle latency for menstrual disorders

diagnosis
- Diagnosing pituitary disorder, anorexia, malnutrition

pregnancy
- Determining pregnancy based on LH peak latency

menopause
- Tracking onset of menopause

fertility
- Monitoring cyclic ovulation for family planning

future research
- Contributing to underserved body of knowledge on women’s health
THANK YOU!

Thanks to Professor Cauwenberghs and the TAs for your support this quarter!
References


