Luteinizing Hormone Dynamics in Menstruation

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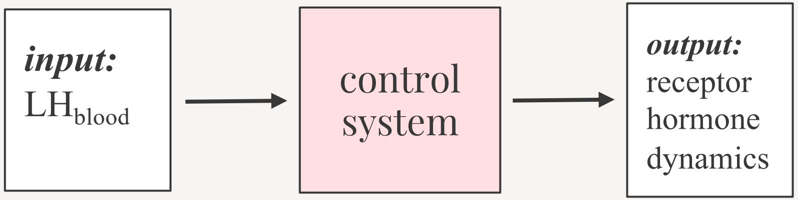
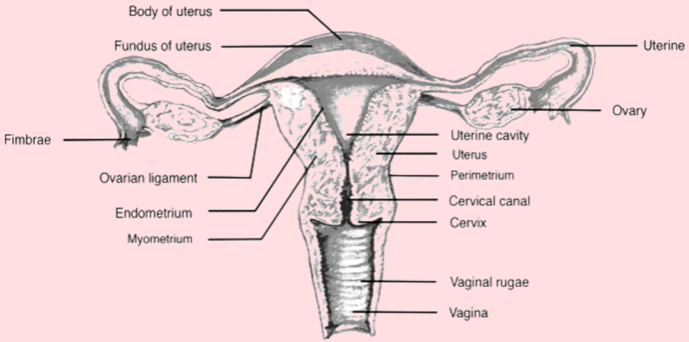


01

INTRODUCTION

control system of menstruation, subsection of LH



Background

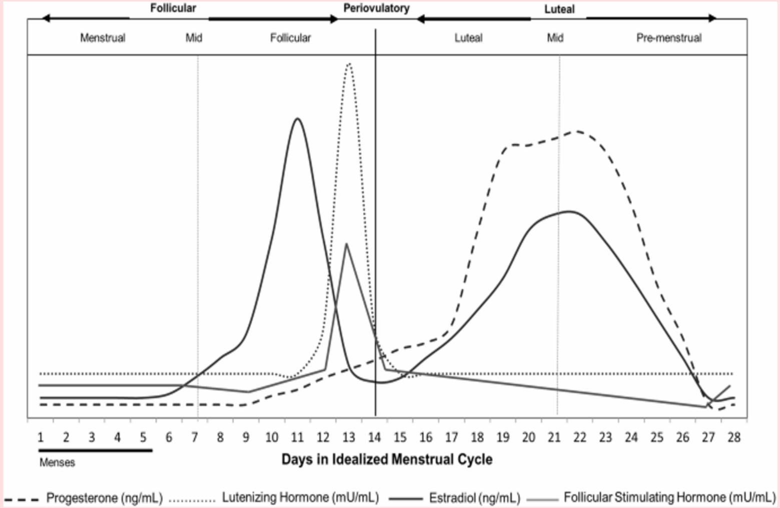


Figure 1: demonstrates the complexity of hormone control during different stages [(Draper et al.)]

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

02

DERIVATION

kinetic equations; ODEs; transfer function

$$F(s) = \int_0^\infty e^{-st} f(t) \mathrm{d}t.$$

Kinetic Equations and ODEs

hormone-receptor complex LH desensitization

$$\mathrm{LH}_{blood} + \mathrm{R}_{\mathrm{LH}} \xrightarrow{k_{on}^{\mathrm{LH}}} \mathrm{LH\text{-}R}$$

$$\mathrm{LH\text{-}R} \xrightarrow{k_{des}^{\mathrm{LH}}} \mathrm{R}_{\mathrm{LH},des}$$

$$\mathrm{R}_{\mathrm{LH},des} \xrightarrow{k_{recy}^{\mathrm{LH}}} \mathrm{R}_{\mathrm{LH}}$$

binding of LH to receptors

formation of free LH receptors

hormone-receptor complex LH desensitization

desensitized complex dynamics

$$\frac{d}{dt}\mathrm{R}_{\mathrm{LH}}(t) = k_{recy}^{\mathrm{LH}} \cdot \mathrm{R}_{\mathrm{LH},des}(t) - k_{on}^{\mathrm{LH}} \cdot \mathrm{LH}_{blood}(t) \cdot \mathrm{R}_{\mathrm{LH}}(t)$$

$$\frac{d}{dt}\mathrm{LH\text{-}R}(t) = k_{on}^{\mathrm{LH}} \cdot \mathrm{LH}_{blood}(t) \cdot \mathrm{R}_{\mathrm{LH}}(t) - k_{des}^{\mathrm{LH}} \cdot \mathrm{LH\text{-}R}(t)$$

$$\frac{d}{dt}\mathrm{R}_{\mathrm{LH},des}(t) = k_{des}^{\mathrm{LH}} \cdot \mathrm{LH\text{-}R}(t) - k_{recy}^{\mathrm{LH}} \cdot \mathrm{R}_{\mathrm{LH},des}(t)$$

receptor-hormone complex dynamics

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

(↑ binding = ↑ physiological effects)

Redefining Parameters

hormone-receptor complex LH desensitization

desensitized complex dynamics

$$\frac{d}{dt}\mathrm{R}_{\mathrm{LH}}(t) = k^{\mathrm{LH}}_{recy} \cdot \mathrm{R}_{\mathrm{LH},des}(t) - k^{\mathrm{LH}}_{on} \cdot \mathrm{LH}_{blood}(t) \cdot \mathrm{R}_{\mathrm{LH}}(t)$$

$$\frac{d}{dt}\text{LH-R}(t) = k^{\mathrm{LH}}_{on} \cdot \mathrm{LH}_{blood}(t) \cdot \mathrm{R}_{\mathrm{LH}}(t) - k^{\mathrm{LH}}_{des} \cdot \text{LH-R}(t)$$

$$\frac{d}{dt}\mathrm{R}_{\mathrm{LH},des}(t) = k^{\mathrm{LH}}_{des} \cdot \text{LH-R}(t) - k^{\mathrm{LH}}_{recy}(t) \cdot \mathrm{R}_{\mathrm{LH},des}(t)$$

receptor hormone dynamics

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

(↑ binding = ↑ physiological effects)

terms

$a(t) = R_{\mathrm{LH}} = [\mathrm{LH}_{\mathrm{receptor}}]$

$b(t) = R_{\mathrm{LH},\,des}$ = desensitized complex

$c(t) = [\mathrm{LH}_{\mathrm{blood}}]$

$d(t) = \text{LH-R} = [\mathrm{LH}_{\text{hormone-receptor complex}}]$

rate constants

$x = k^{\mathrm{LH}}{}_{recy}$ = free $\mathrm{LH}_{\mathrm{receptor}}$ formation rate

$y = k^{\mathrm{LH}}{}_{on}$ = hormone to receptor binding rate

$z = k^{\mathrm{LH}}{}_{des}$ = $\mathrm{LH}_{\mathrm{receptor}}$ desensitization rate

Transfer Function

input

$c(t)$ = $LH_{blood}(t)$

equations

$sA(s) - a_0 = xB(s) - ya_0C(s) - yc_0A(s)$
$sD(s) - d_0 = ya_0C(s) + yc_0A(s) - zD(s)$
$sB(s) - b_0 = zD(s) - xB(s)$

output

$d(t)$ = LH-R(t)

transfer relationship:

$$\left(s + z - \frac{(yc_0xz)}{(s+yc_0)(s+x)}\right)D(s) - \left(d_0 + \frac{yc_0xb_0}{(s+yc_0)(s+x)} - \frac{yc_0a_0}{s+yc_0}\right) = \left(ya_0 + \frac{y^2c_0a_0}{(s+yc_0)}\right)C(s)$$

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 relationship with assumptions:

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

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

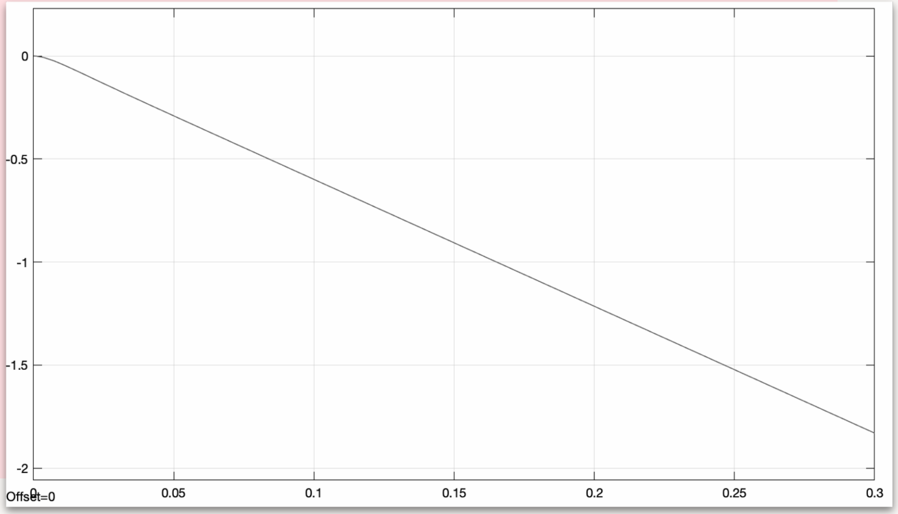
$$tf = \frac{(ya_0(s+yc_0) - y^2a_0c_0)(s+x)}{(s+2)(s+x)(s+yc_0) - yc_0xz}$$

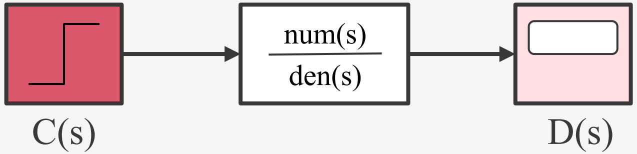
03

MODEL ANALYSIS

block diagram; output response; bode plot; stability; applications

Transfer Function Response



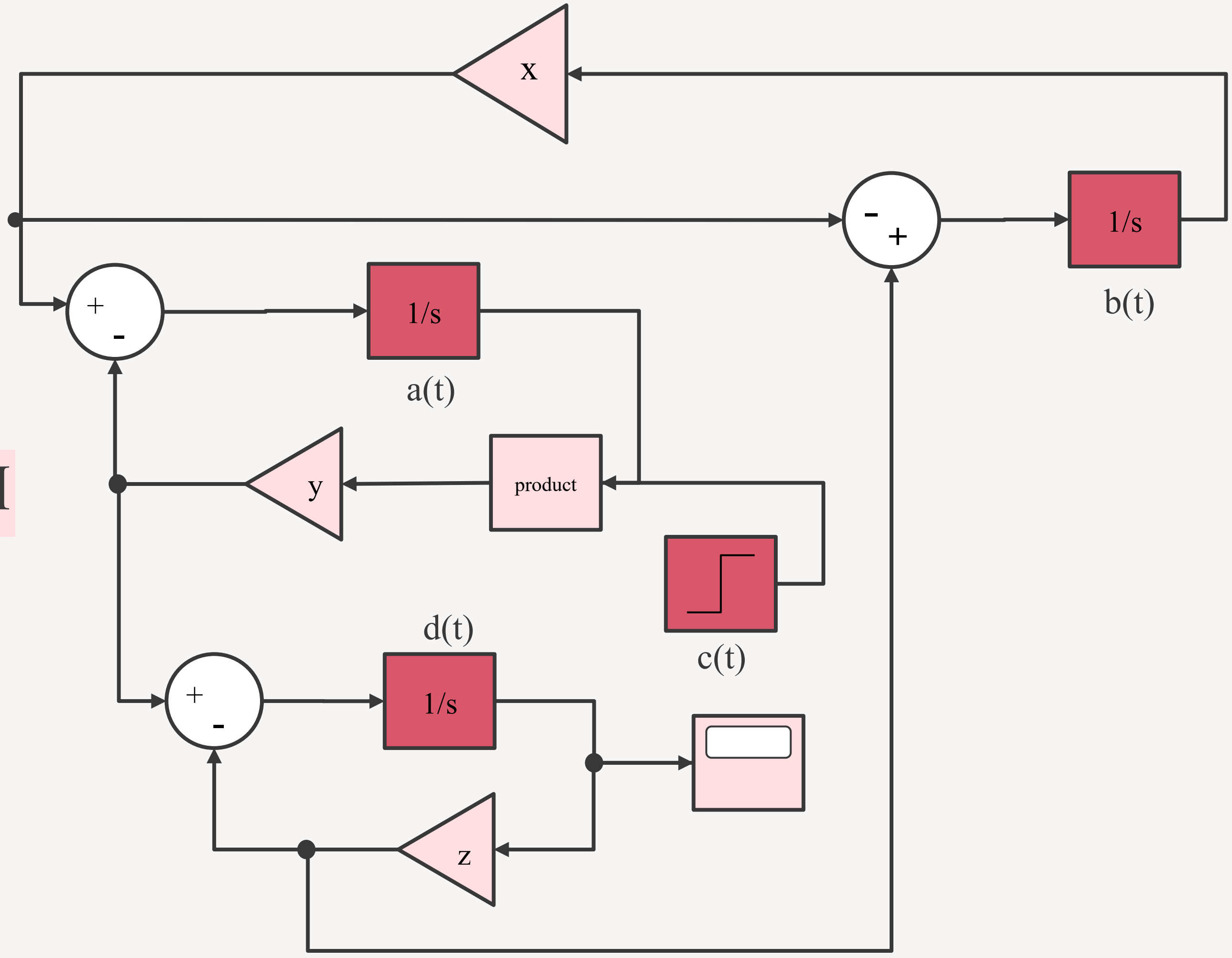


- observe: *given assumptions*, *d(t) decreases over time*

BLOCK DIAGRAM

input: ***c(t)*** = LH_{blood}

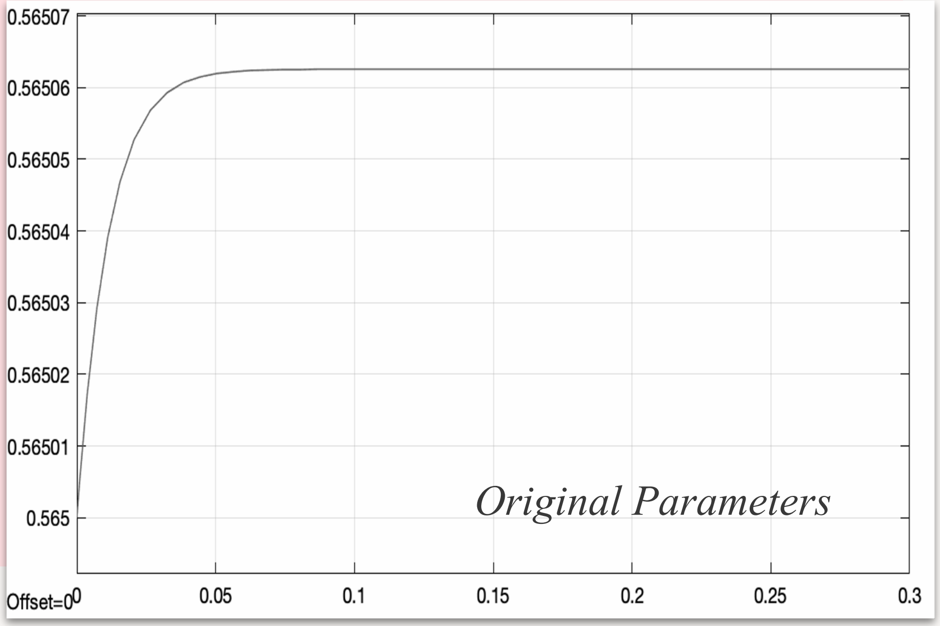
output: ***d(t)*** = LH-R



OUTPUT RESPONSE

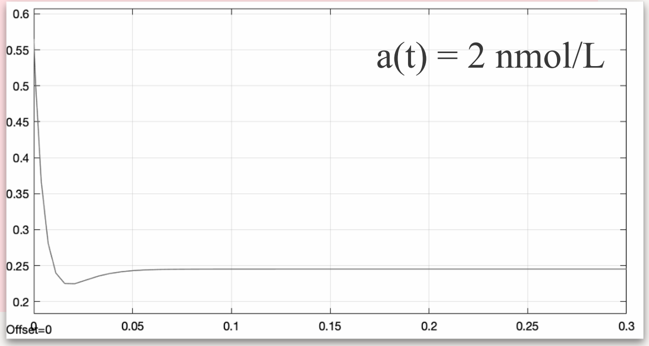
constants

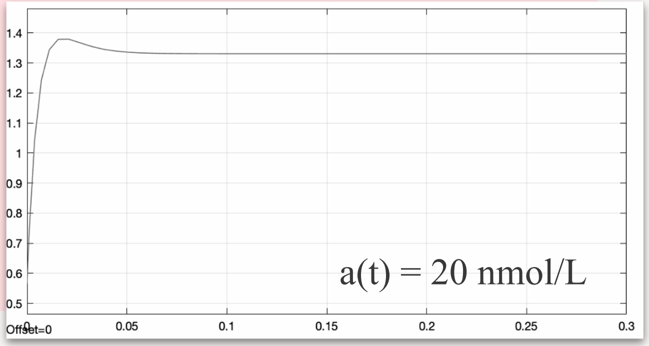
$LH_{\text{free receptors}}$ formation rate : $X = K^{LH}_{recy} = 68.9491/\text{day}$
LH_{receptor} binding rate: $Y = K^{LH}_{on} = 2.143$ L/day·IU
$LH_{\text{receptor complex}}$ desensitization rate: $Z = K^{LH}_{des} = 183.36/\text{day}$
LH-R(t) initial value: $A_0 = 7.304$ nmol/L
$R_{LH,des}$ initial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



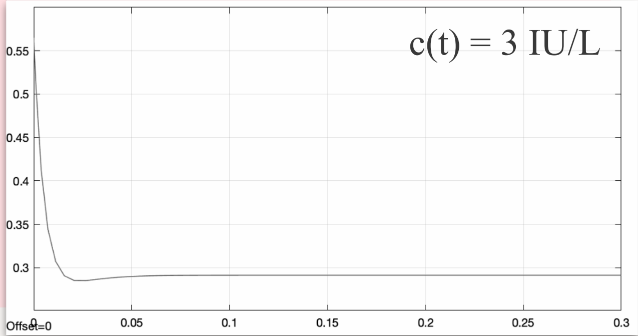
- observe: $d(t)$ = [LH $_{\text{hormone-receptor complex}}$] saturates quickly

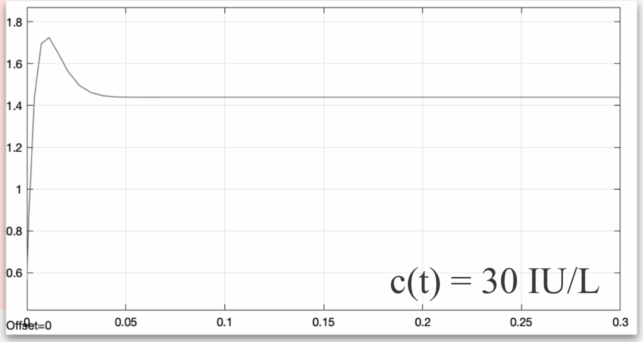
Output response d(t) with parameter perturbation





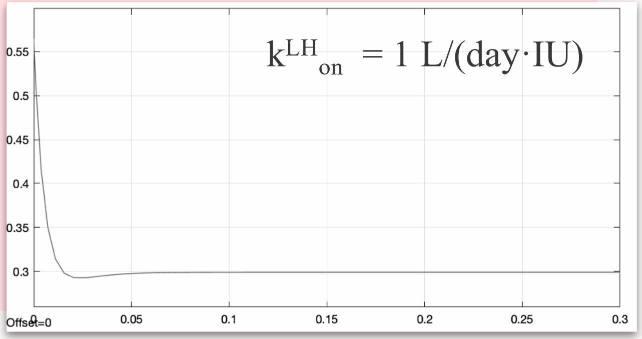
$a(t) = [\ LH_{receptor}\ ]$

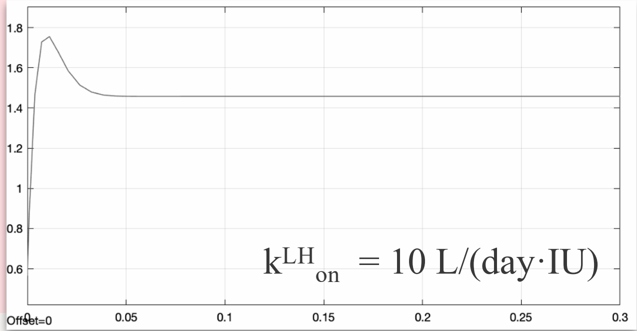




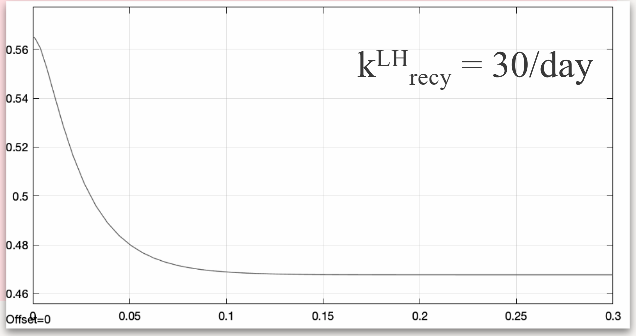
$c(t) = [LH_{blood}]$

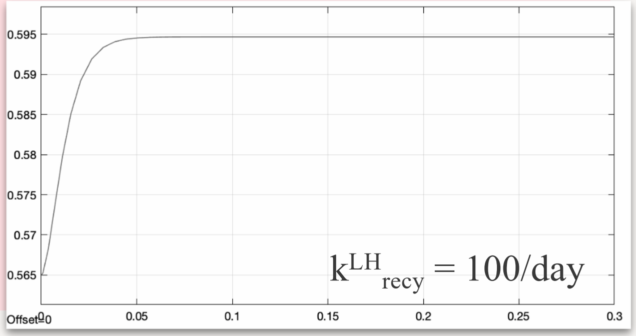
Output response d(t) with parameter perturbation





k^{LH}_{on} = LH to receptor binding rate





k^{LH}_{recy} = free LH receptor formation rate

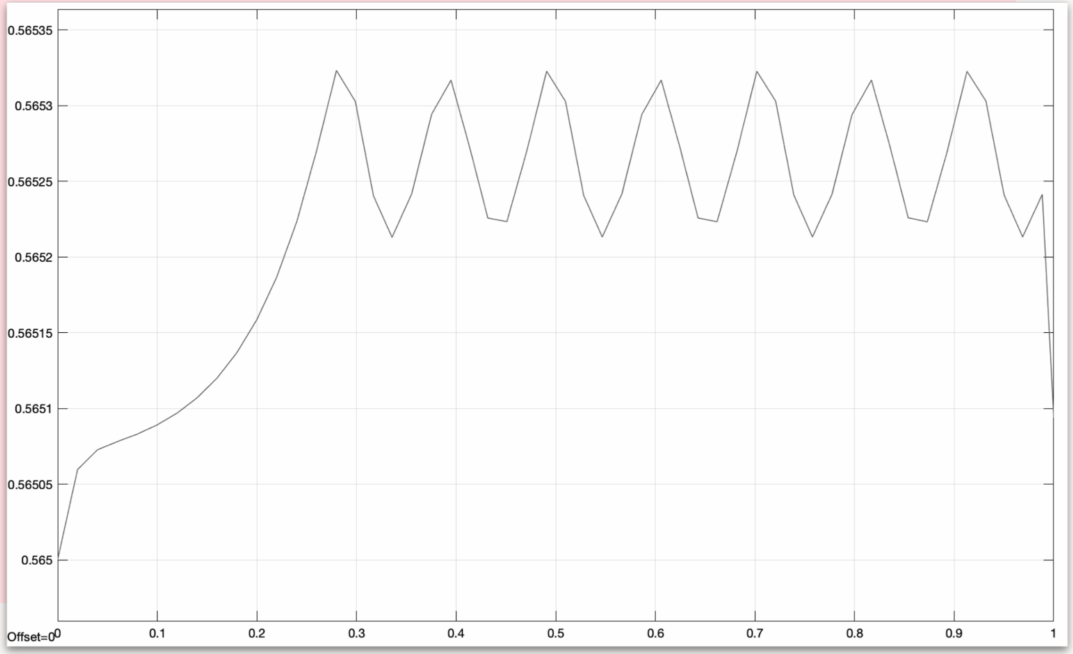
OUTPUT RESPONSE

$$\frac{d}{dt}\mathrm{R}_{\mathrm{LH}}(t) = k_{recy}^{\mathrm{LH}} \cdot \mathrm{R}_{\mathrm{LH},des}(t) - k_{on}^{\mathrm{LH}} \cdot \mathrm{LH}_{blood}(t) \cdot \mathrm{R}_{\mathrm{LH}}(t)$$

$$\frac{d}{dt}\mathrm{LH\text{-}R}(t) = k_{on}^{\mathrm{LH}} \cdot \mathrm{LH}_{blood}(t) \cdot \mathrm{R}_{\mathrm{LH}}(t) - k_{des}^{\mathrm{LH}} \cdot \mathrm{LH\text{-}R}(t)$$

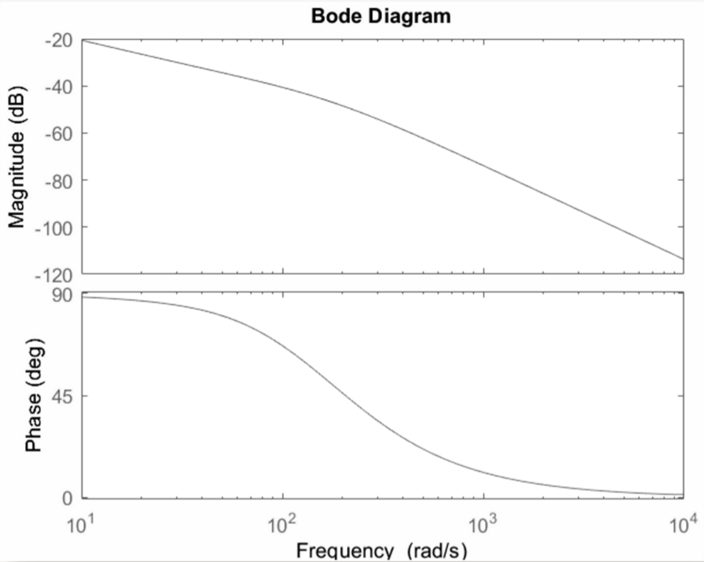
$$\frac{d}{dt}\mathrm{R}_{\mathrm{LH},des}(t) = k_{des}^{\mathrm{LH}} \cdot \mathrm{LH\text{-}R}(t) - k_{recy}^{\mathrm{LH}} \cdot \mathrm{R}_{\mathrm{LH},des}(t)$$

Original ODEs



- observe: *d(t)* ([LH $_{\text{hormone-receptor complex}}$]) saturates to a certain point then oscillates due to the parameter values
- Demonstrating underdamping
- One full day

BODE PLOT



constants

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LH-R(t) initial value: $A_0 = 7.304$ nmol/L

$R_{LH,des}$ initial value: $B_0 = 1.5032$nmol/L

LH_{blood}(t) initial value: $C_0 = 6.619$ IU/L

plug into tf:

transfer function:

```
H =

          -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***

To simplify, assume that constant term in the denominator of the original equation is negligible because it is 2 orders of magnitude smaller than other terms

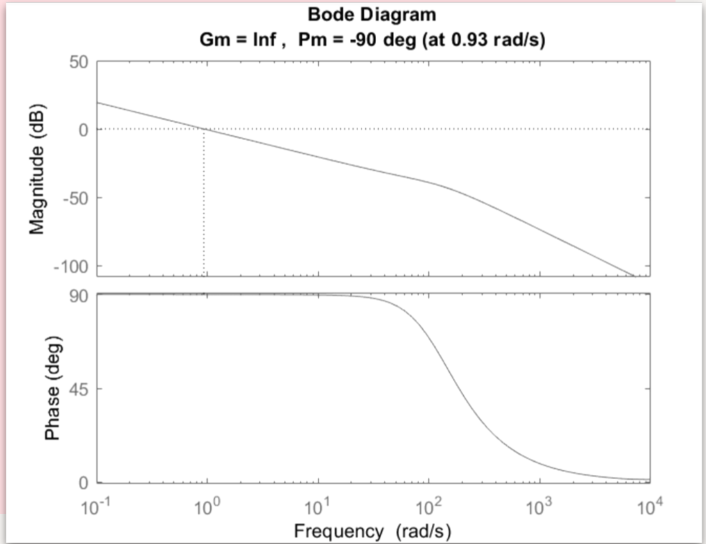
simplified transfer fxn:

```
H2 =

      -206.4 s - 15086
  ----------------------------
  s^3 + 226.5 s^2 + 1.622e04 s
```

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

simplified bode plot



MODEL APPLICATIONS

pregnancy

Determining pregnancy based on LH peak latency

fertility

Monitoring cyclic ovulation for family planning

therapeutics

Acquiring data on cycle latency for menstrual disorders

diagnosis

Diagnosing pituitary disorder, anorexia, malnutrition

menopause

Tracking onset of menopause

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!

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