# Mathematical Modeling of Circannual Prolactin Cycles

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# Introduction to Biological Rhythms

Biological rhythms are an organism's way of keeping track of time. During the course of a day, month, season, or year their bodies will undergo changes in energy level, alertness, reproductive behavior, and hormone levels. These changes follow a rhythmic pattern in accordance with environmental cues called entrainment stimuli. Without these cues, their bodies still follow the same rhythmic pattern but will a slightly different period and amplitude until altered by an entrainment stimuli (same or different as before). One such example is the sleep-wake cycle caused by circadian rhythms.

## Circadian Rhythms

These are endogenous 24-hour rhythms that control sleep-wake cycle, alertness, pituitary gland functions and hormones.

- They are significantly affected by light. The time period of light availability is called photoperiod.
- During the summer, days are long and so is the photoperiod. During winter, days are short and so is the photoperiod.
- When light is available, the pineal gland cannot produce melatonin (hormone produced at night that causes sleepiness).

## Marking Photoperiod with per and cry genes

Sheeps' brains have a way of marking the length of photoperiod. (Lincoln, 2003)

- Per and Cry are two clock genes in the pituitary gland.
- The gene expression of *per* takes place in early day when melatonin production stops. The expression of *cry* takes place when melatonin production begins at night.
- During LP the time interval between *per* and *cry* expression is longer. This daily measurement of time causes a rhythmic cycle of prolactin production during the summer.

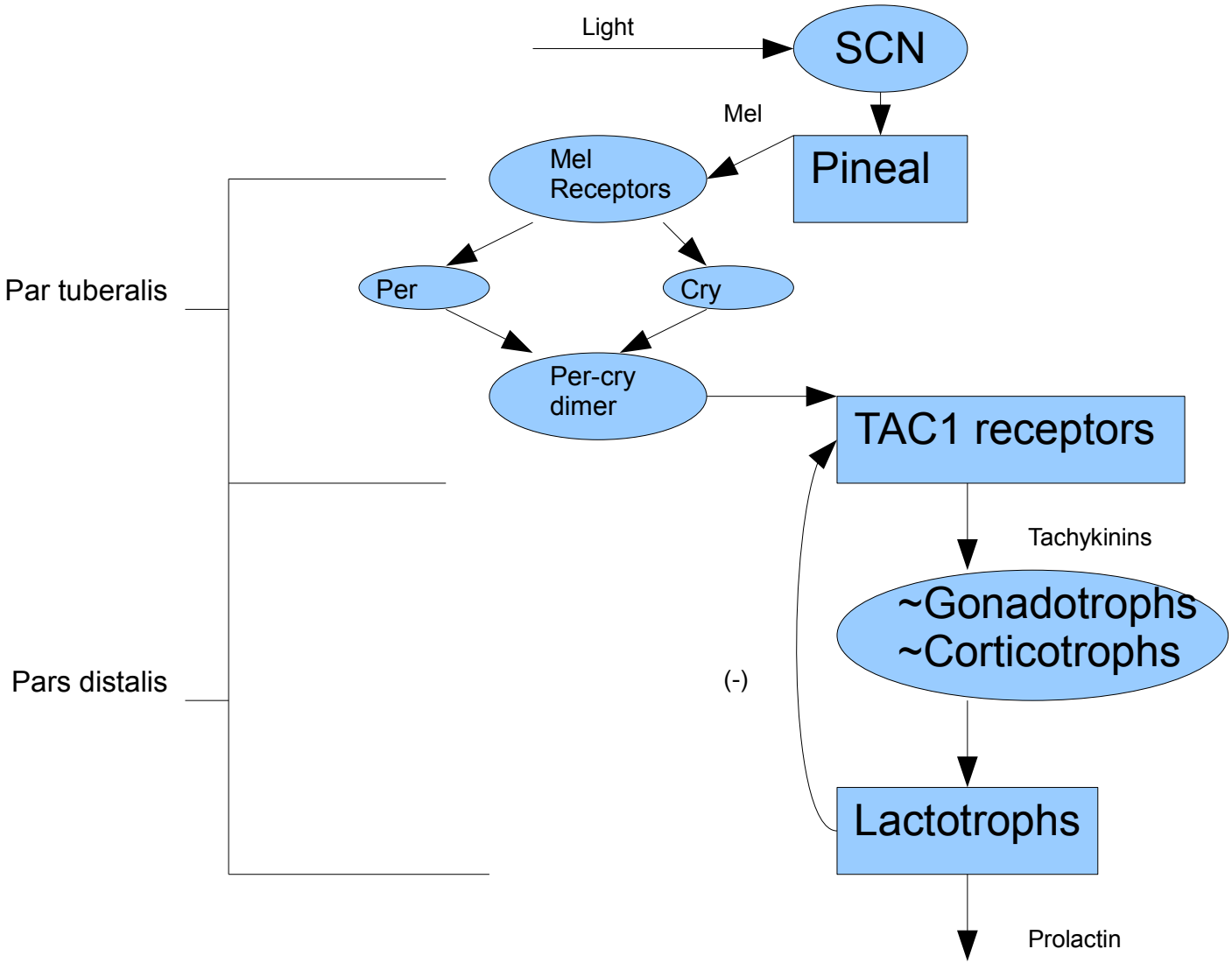
## Experiment on Sheep

Experiment using HPD Soay rams( Lincoln et all, 2006).

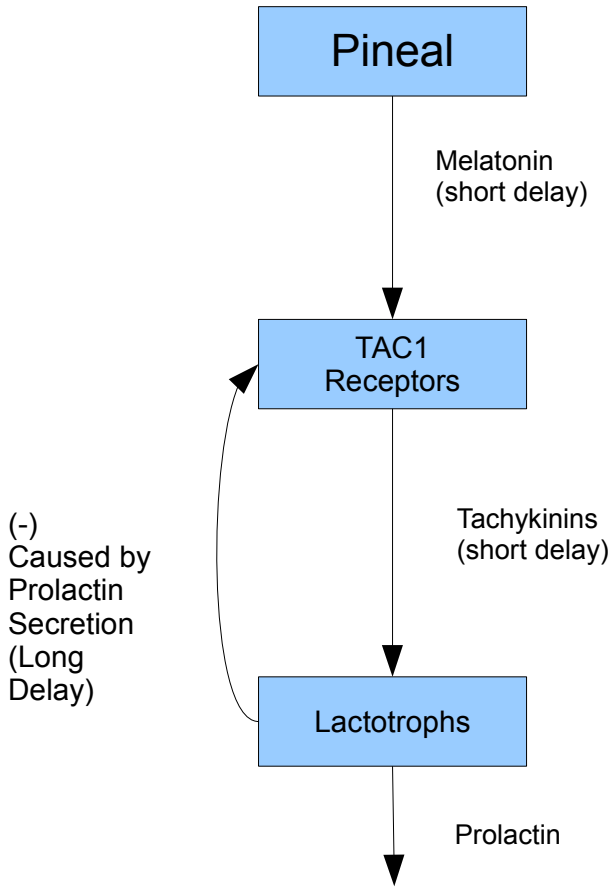
- Purpose was to study the regulation of the circannual cycle of prolactin production over 144 weeks of constant LP.
- They were then put in constant SP for 48 weeks
- Their blood was taken at specific times to find out melatonin and prolactin concentration levels.
- The hypothalamus regulates how much prolactin is produced (or inhibited). Even when disconnected, prolactin was still secreted in a rhythmic pattern.
- Pituitary gland controls prolactin secretion via melatonin signals. The most prolactin was produced during LP. The least, during SP.

# Sheep Pituitary Gland

(Dupre, 2010; MacGregor, 2008)

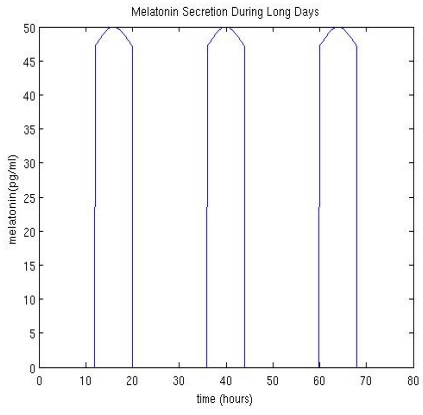


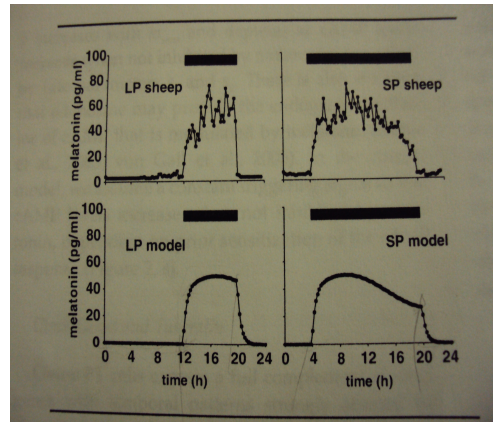
# Simplified Model

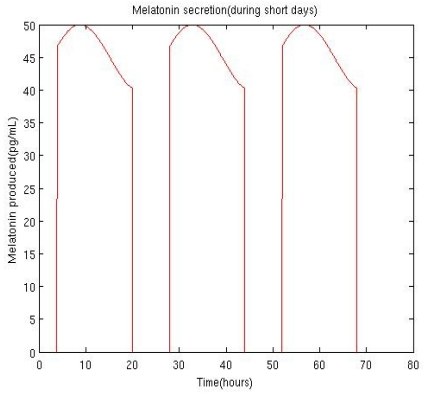


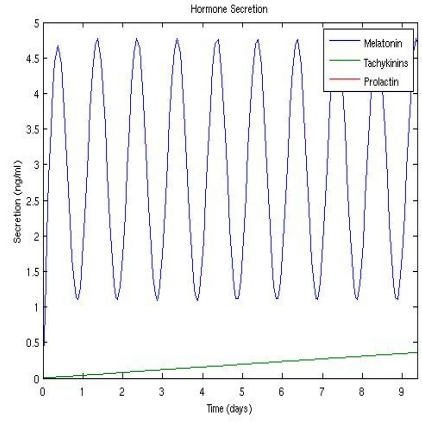
# Daily Melatonin Signals

(MacGregor. 2008: Hazlerigg. 2004)



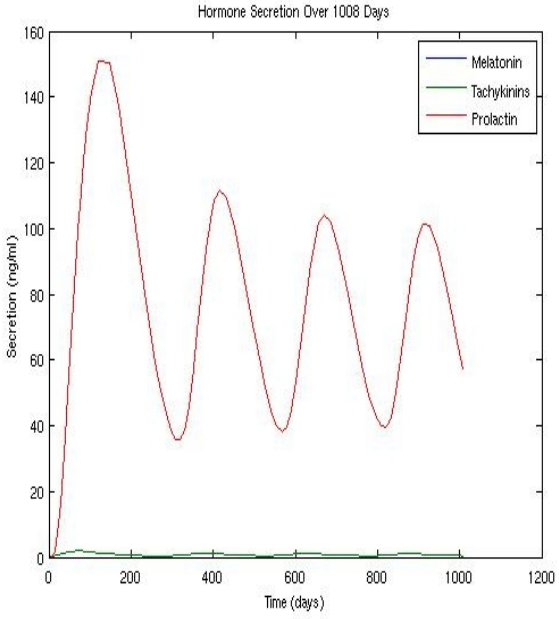



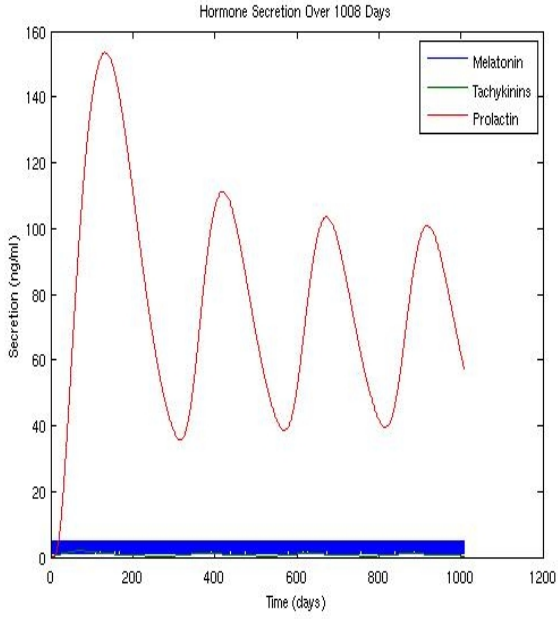



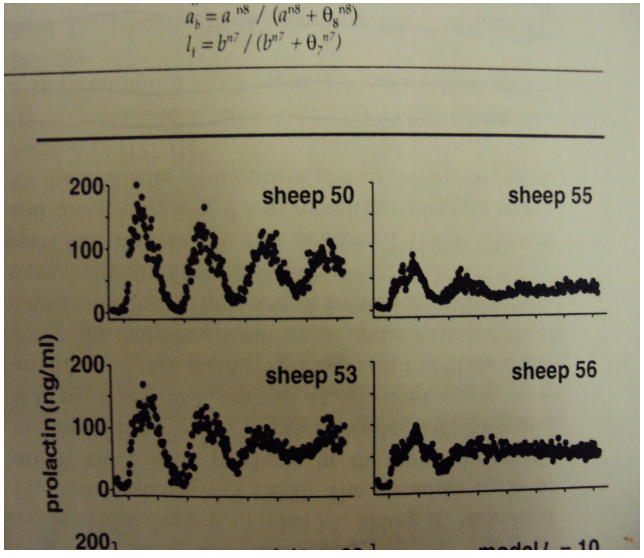



# Tachykinin and Prolactin Production

(MacGregor, 2008; Lincoln, 2006)



# Mathematical Model

$$\frac{d\widetilde{M}}{dt} = a_1 I - a_2 \widetilde{M} \quad (1)$$

$$\frac{d\widetilde{T}}{dt} = \frac{b_1}{1 + (P(t-\tau_3)/K_1)^n} + \frac{b_3(\widetilde{M}(t-\tau_1)/K_2)^m}{1 + (\widetilde{M}(t-\tau_1)/K_2)^m} - b_2 \widetilde{T} \quad (2)$$

$$\frac{dP}{dt} = \frac{c_1(\widetilde{T}(t-\tau_2)/K_3)^l}{1 + (\widetilde{T}(t-\tau_2)/K_3)^l} - c_2 P \quad (3)$$

where $I = 22 + 18 * sin(2\pi t)$ and $\widetilde{M}$=100$M$ and $\widetilde{T}$=100$T$

# Parameters of Mathematical Model

| Parameters | Description | Value |
|---|---|---|
| $a_1$ | Production rate constant | 1 |
| $a_2$ | Degradation rate constant | 7.5 |
| $b_1$ | Production rate constant | 0.04 |
| $b_2$ | Degradation rate constant | 0.01 |
| $b_3$ | Production rate constant | 1 |
| $c_1$ | Production rate constant | 3.7 |
| $c_2$ | Degradation rate constant | 0.015 |
| $K_1$ | Threshold of prolactin | 40 |
| $K_2$ | Threshold of melatonin | 40 |
| $K_3$ | Threshold of tachykinin | 1 |
| $n, m$ | Hill coefficients affecting sensitivity | 4 |
| $l$ | Hill coefficient affecting sensitivity | 3 |
| $\tau_1$ | Time delay of melatonin(days) | 0.1 |
| $\tau_2$ | Time delay of tachykinin(days) | 0.1 |
| $\tau_3$ | Time delay of prolactin(days) | 31 |

# Parameter Analysis of Time Delays

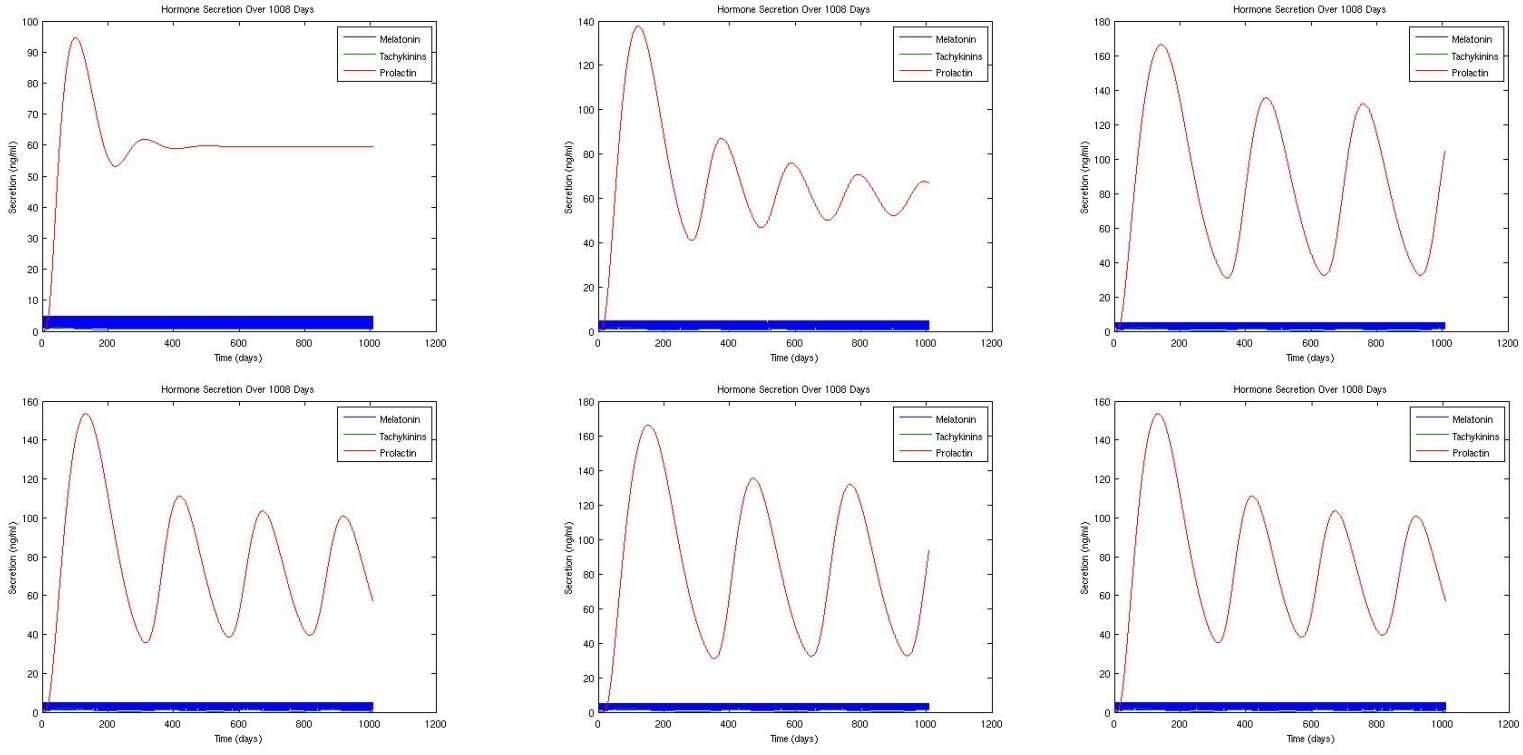



Figure: Clockwise from top left: No delays,
$\tau_3 = 21, \tau_3 = 41, \tau_1 = 10, \tau_2 = 10, \mathit{normal}(0.1, 0.1, 31)$

# Parameter Analysis of Prolactin Production and Degradation Parameters

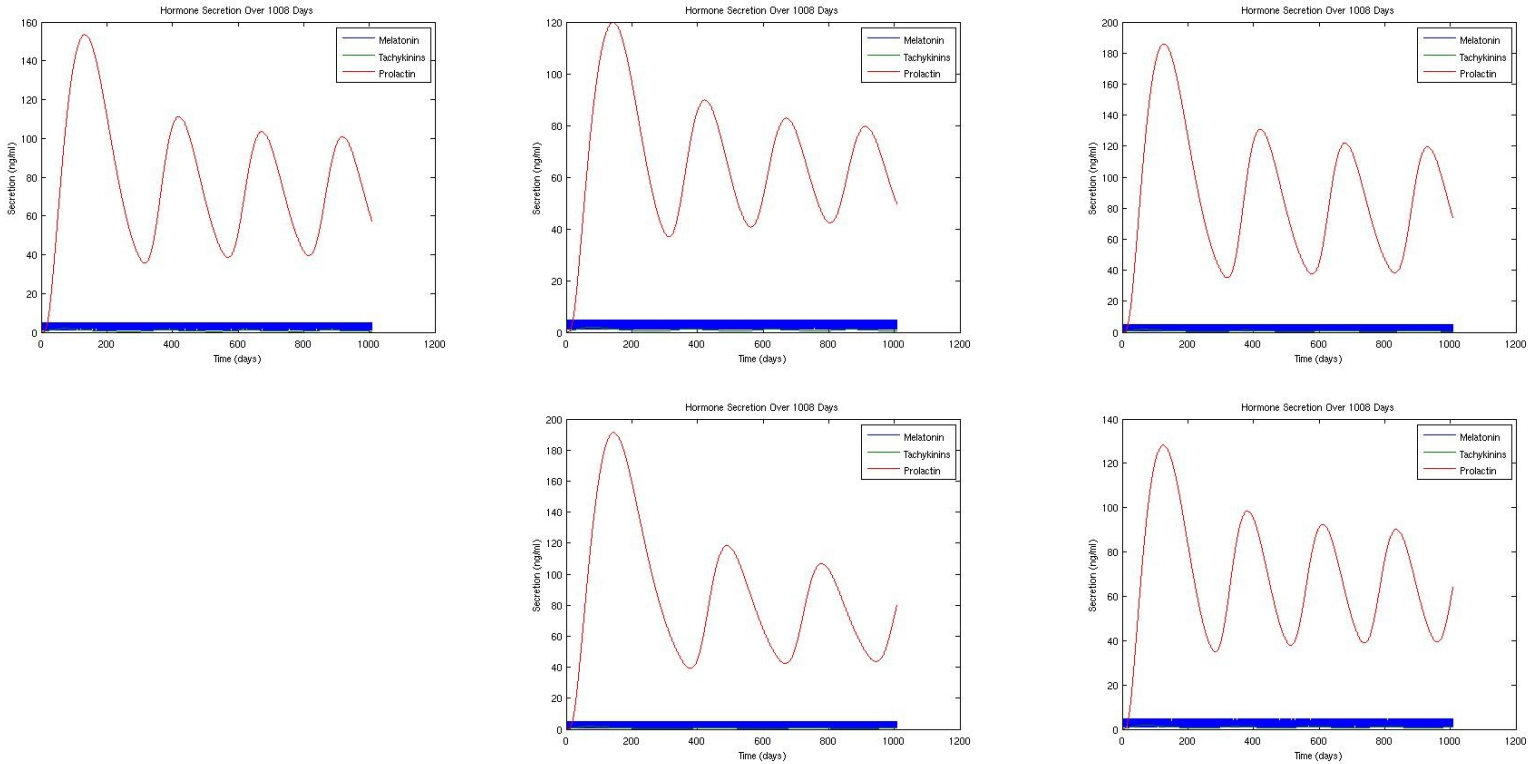



Figure: Clockwise from top left: Normal ($c_1 = 3.7$,$c_2 = 0.015$), $c_1 = 2.7$, $c_1 = 4.7$, $c_2 = 0.02$,$c_2 = 0.01$

# Parameter Analysis of Tachykinin Production and Degradation Parameters

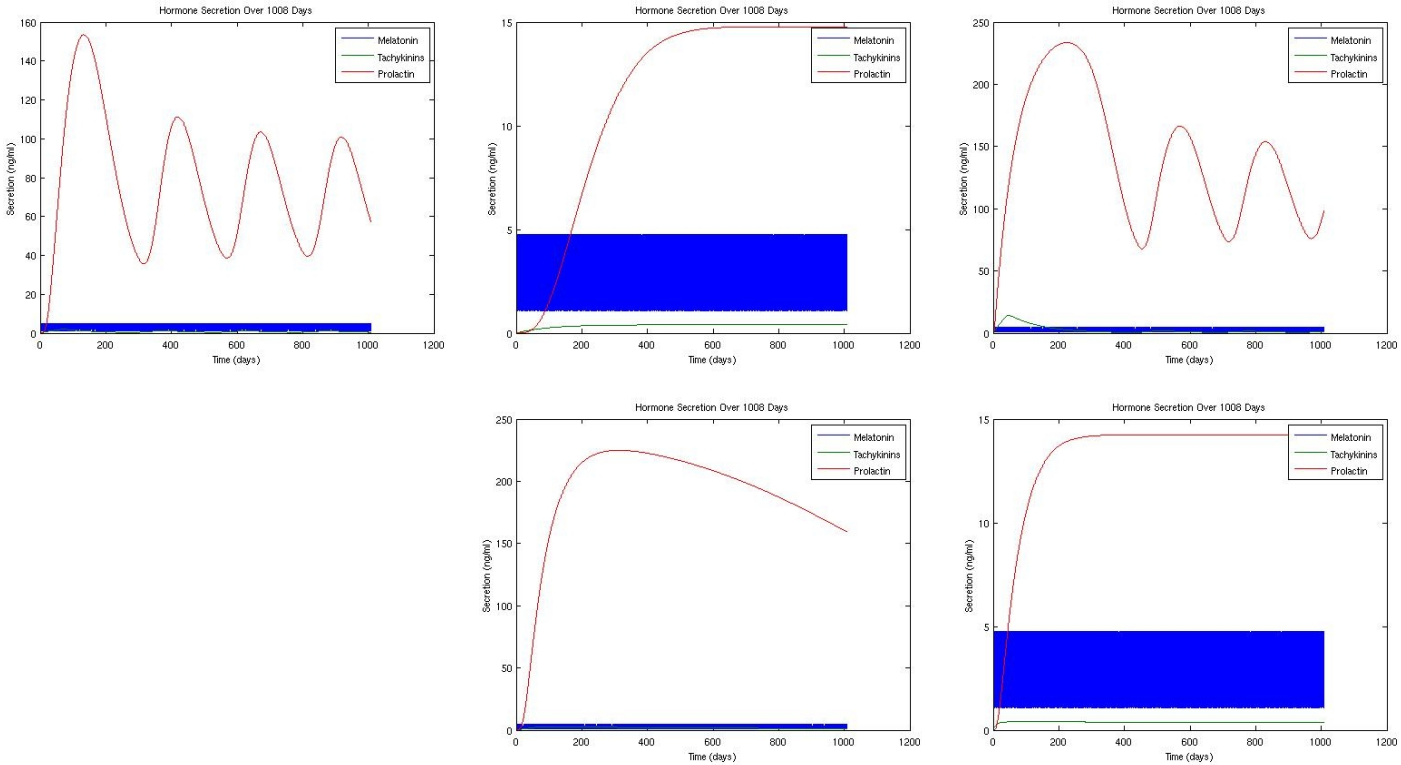



Figure: Clockwise from top left: Normal
$(b_1 = 0.04, b_2 = 0.01), b_1 = 0.004, b_1 = 0.4,\ b_2 = 0.1, b_2 = 0.001$

# Parameter Analysis of Hill Coefficients

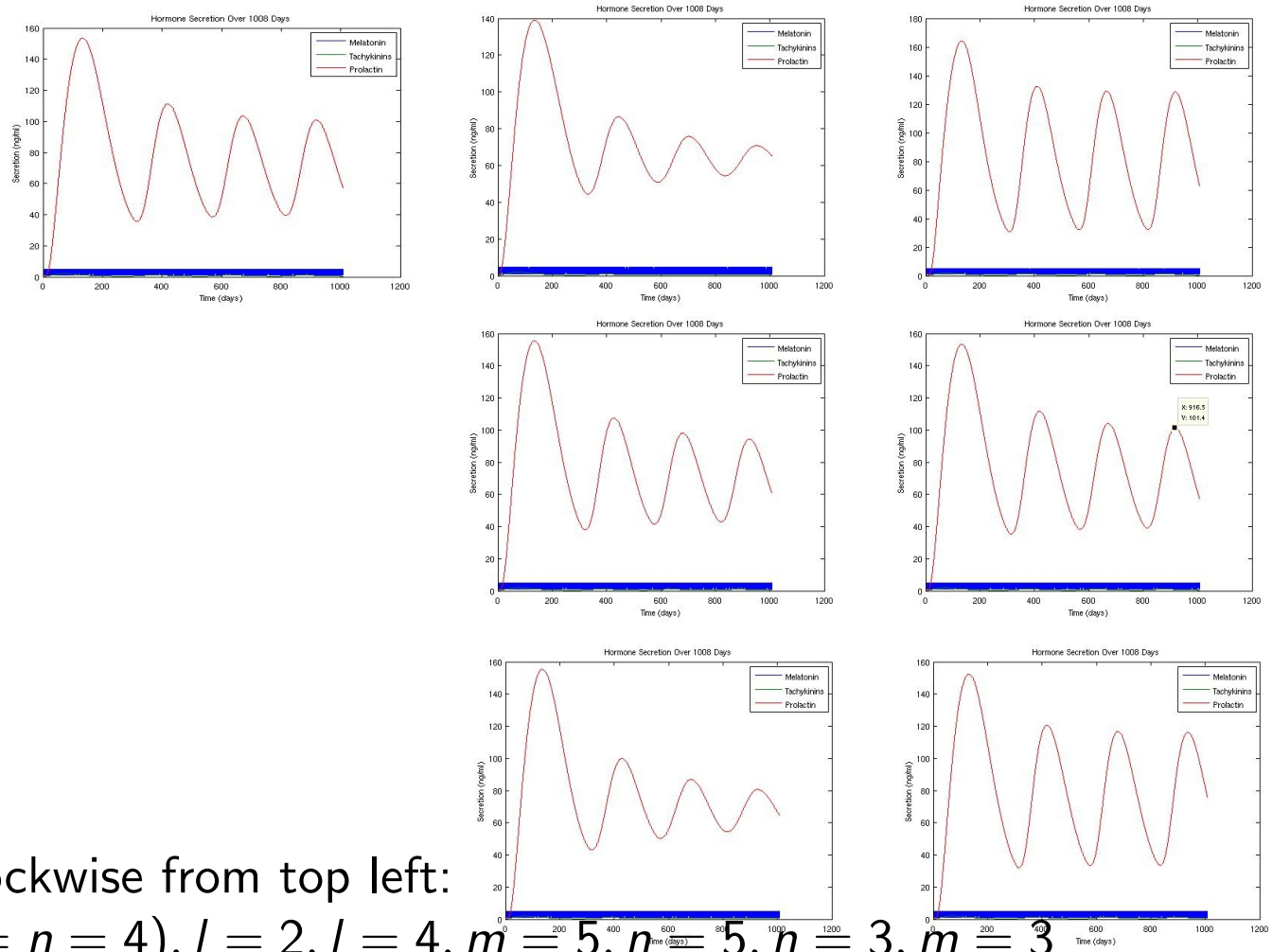



Figure: Clockwise from top left:
$(l = 3, m = n = 4), l = 2, l = 4, m = 5, n = 5, n = 3, m = 3$

# Parameter Analysis of Threshold Parameters

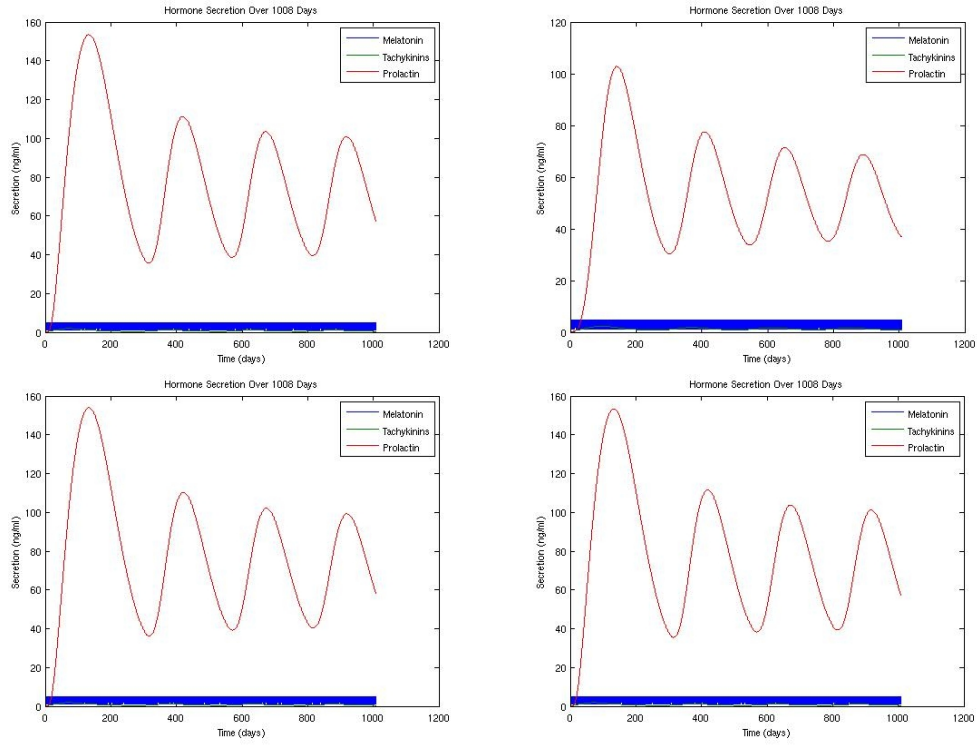



Figure: Clockwise from top left: $K_3 = 1, K_1 = K_2 = 40$; $K_3 = 2$; $K_1 = K_2 = 50$; $K_1 = K_2 = 30$

# Steady State Equilibrium

When melatonin production stops, eq. 1 becomes $0 = \frac{d\widetilde{M}}{dt} = 0 - 0$. This gives us

$$\frac{b_1}{1 + (P*/K_1)^n} - b_2 \widetilde{T}* = \frac{d\widetilde{T}}{dt} = 0 \tag{1}$$

$$\frac{c_1(\widetilde{T}*/K_3)^l}{1 + (\widetilde{T}*/K_3)^l} - c_2 P* = \frac{dP}{dt} = 0 \tag{2}$$

In both equations, we solve for $\widetilde{T}$ as a function of P. After substituting the parameters we graph the two equations to find the steady state equilibrium $(P*, \widetilde{T}*)$

# Steady State Equilibrium cont'd

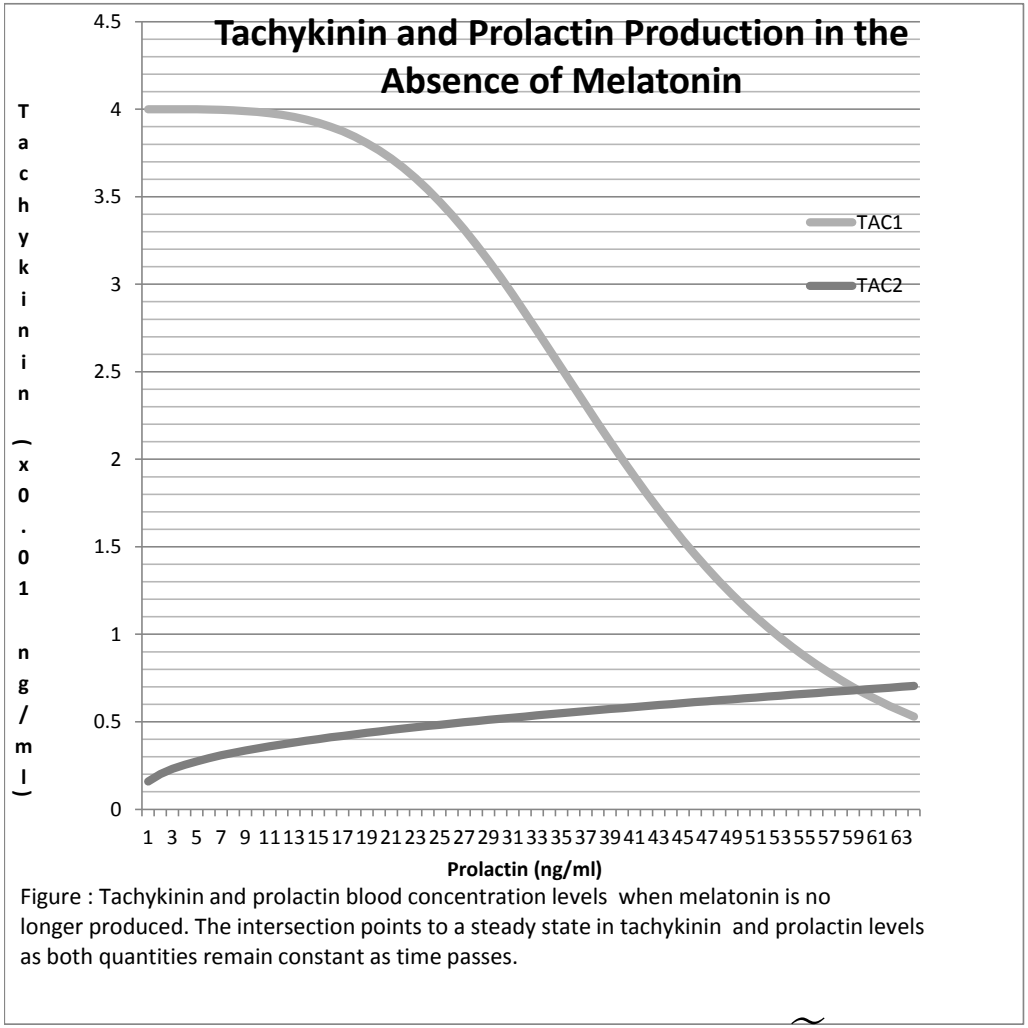



Figure : Tachykinin and prolactin blood concentration levels when melatonin is no longer produced. The intersection points to a steady state in tachykinin and prolactin levels as both quantities remain constant as time passes.

The steady state is $P*=59.4$ and $\widetilde{T}*=0.682$ . This is needed to do linear stability analysis.

# Linear Stability Analysis 1

Consider $\begin{bmatrix} \dot{M} \\ \dot{T} \\ \dot{P} \end{bmatrix} = \begin{bmatrix} F(M,T,P,M_\tau,T_\tau,P_\tau) \\ G(M,T,P,M_\tau,T_\tau,P_\tau) \\ H(M,T,P,M_\tau,T_\tau,P_\tau) \end{bmatrix} =$

$$\begin{bmatrix} a_1 I - a_2 M \\ \frac{b_1}{1+(P(t-\tau_3)/K_1)^n} + \frac{b_3(M(t-\tau_1)/K_2)^m}{1+(M(t-\tau_1)/K_2)^m} - b_2 T \\ \frac{c_1(T(t-\tau_2)/K_3)^l}{1+(T(t-\tau_2)/K_3)^l} - c_2 P \end{bmatrix}$$ with $(M^*, T^*, P^*)$ as the equilibrium point. We then consider solutions close to it in the form $\begin{bmatrix} M \\ T \\ P \end{bmatrix} = \begin{bmatrix} M^* \\ T^* \\ P^* \end{bmatrix} + \begin{bmatrix} \xi_1(t) \\ \xi_2(t) \\ \xi_3(t) \end{bmatrix}$. Because of time delay, we split $\xi$ into two components. Thus $\begin{bmatrix} \xi_1(t) \\ \xi_2(t) \\ \xi_3(t) \end{bmatrix} = \begin{bmatrix} \varepsilon_1(t) \\ \varepsilon_2(t) \\ \varepsilon_3(t) \end{bmatrix} +$

$$\begin{bmatrix} \varepsilon_1(t-\tau_1) \\ \varepsilon_2(t-\tau_2) \\ \varepsilon_3(t-\tau_3) \end{bmatrix}.$$

# Linear Stability Analysis 2

Taking the derivative we get $\begin{bmatrix} \dot{\xi}_1(t) \\ \dot{\xi}_2(t) \\ \dot{\xi}_3(t) \end{bmatrix} = \begin{bmatrix} \dot{\varepsilon}_1(t) \\ \dot{\varepsilon}_2(t) \\ \dot{\varepsilon}_3(t) \end{bmatrix} +$

$$\begin{bmatrix} \dot{\varepsilon}_1(t-\tau_1) \\ \dot{\varepsilon}_2(t-\tau_2) \\ \dot{\varepsilon}_3(t-\tau_3) \end{bmatrix} = \begin{bmatrix} F_{\varepsilon,1} & F_{\varepsilon,2} & F_{\varepsilon,3} \\ G_{\varepsilon,1} & G_{\varepsilon,2} & G_{\varepsilon,3} \\ H_{\varepsilon,1} & H_{\varepsilon,2} & H_{\varepsilon,3} \end{bmatrix} \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{bmatrix} +$$

$$\begin{bmatrix} F_{\tau,\varepsilon_1} & F_{\tau,\varepsilon_2} & F_{\tau,\varepsilon_3} \\ G_{\tau,\varepsilon_1} & G_{\tau,\varepsilon_2} & G_{\tau,\varepsilon_3} \\ H_{\tau,\varepsilon_1} & H_{\tau,\varepsilon_2} & H_{\tau,\varepsilon_3} \end{bmatrix} \begin{bmatrix} \varepsilon_1(t-\tau_1) \\ \varepsilon_2(t-\tau_2) \\ \varepsilon_3(t-\tau_3) \end{bmatrix}$$

# Linear Stability Analysis 3

Note that $\frac{\partial F}{\partial \varepsilon_n} = \frac{\partial F}{\partial M}\frac{\partial M}{\partial \varepsilon_n} = \frac{\partial F}{\partial M}\frac{d(M^*+\varepsilon_n)}{d\varepsilon_n} = \frac{\partial F}{\partial M}$ ... giving us

$$\begin{bmatrix} \dot{\xi}_1 \\ \dot{\xi}_2 \\ \dot{\xi}_3 \end{bmatrix} = \begin{bmatrix} F_M & F_T & F_P \\ G_M & G_T & G_P \\ H_M & H_T & H_P \end{bmatrix} \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{bmatrix} +$$

$$\begin{bmatrix} F_{M,\tau_1} & F_{T,\tau_2} & F_{P,\tau_3} \\ G_{M,\tau_1} & G_{T,\tau_2} & G_{P,\tau_3} \\ H_{M,\tau_1} & H_{T,\tau_2} & H_{P,\tau_3} \end{bmatrix} \begin{bmatrix} \varepsilon_1(t-\tau_1) \\ \varepsilon_2(t-\tau_2) \\ \varepsilon_3(t-\tau_3) \end{bmatrix}$$

# Linear Stability Analysis 4

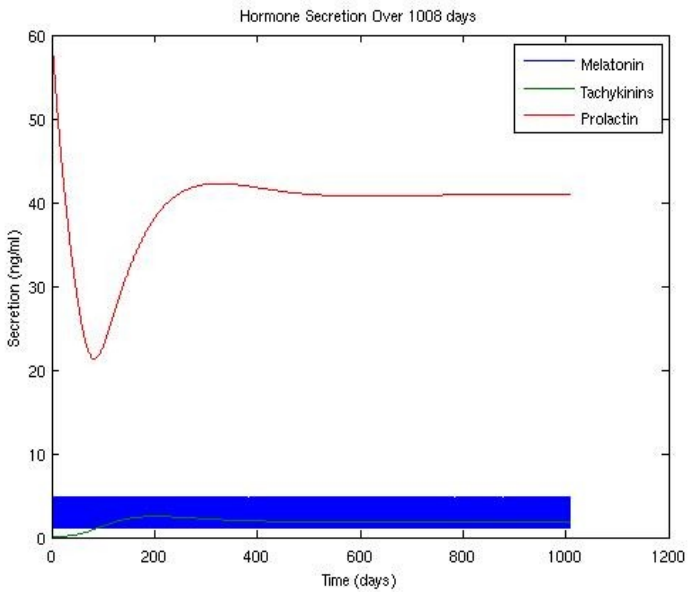
Because $M$ and $\dot{M}$ are both zero during the steady state, $T(t)$ and $P(t)$ will both have a constant quantity which means there are no time delays to consider. This in turn results in $\begin{bmatrix} \dot{\xi}_2 \\ \dot{\xi}_3 \end{bmatrix} =$

$$\begin{bmatrix} -b_2 & \frac{-b_1 n(P*/K_1)^n}{P*(1+(P*/K_1)^n)^2} \\ \frac{1}{(1+T*^l)^2} & -c_2 \end{bmatrix} \begin{bmatrix} \varepsilon_2 \\ \varepsilon_3 \end{bmatrix} = \begin{bmatrix} -0.01 & -0.0003811 \\ 0.5764 & -0.015 \end{bmatrix} \begin{bmatrix} \varepsilon_2 \\ \varepsilon_3 \end{bmatrix}$$

From the trace $T$=−0.025 and determinant $D$=0.00037 of this Jacobian, the eigenvalues are complex numbers whose real component is less than zero. We can conclude that the equilibrium point is a stable spiral.

# What about the Prolactin Cycle for SP?

(MacGregor, 2008; Lincoln et all, 2000)



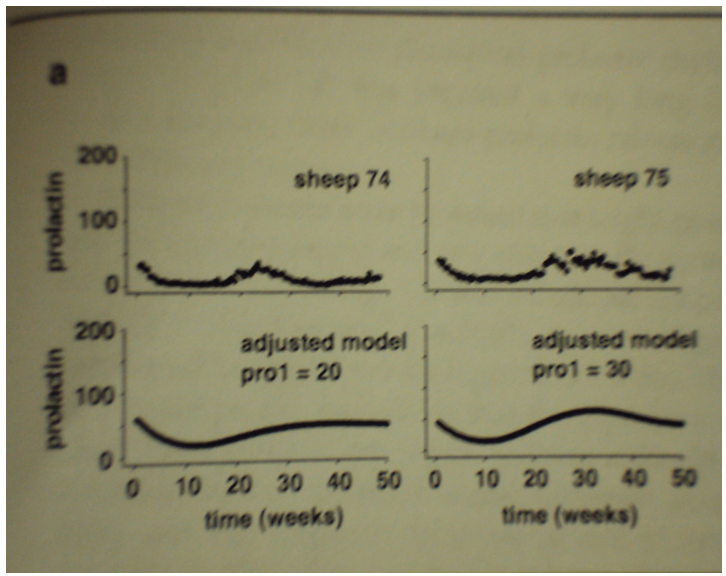




Figure: From left: Math model for SP($c_1 = 0.7$), actual data (Lincoln, 2000

What happened?

# Loss of Prolactin Cyclicity in SP

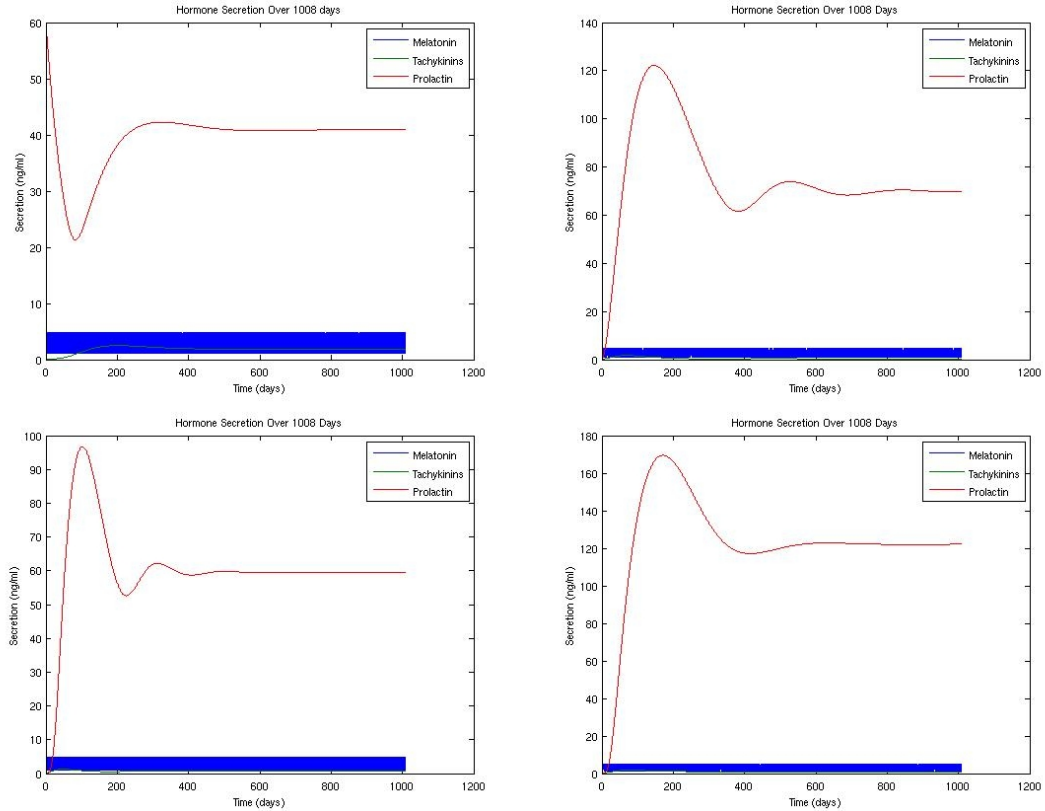



Figure: Clockwise from top left: $c_1 = 0.7$, $l = 1$, $n = 1$, $\tau_3 = 1$

What does this mean?

## Possible Causes

Decline in cyclicity may be caused by...

- cells undergoing changes in their capability to produce prolactin.
- biological changes in cells affecting the sensitivity of their receptors.
- biological changes resulting in decreasing time delay of negative feedback.
- other factors responsible that are still unknown.
- any two or more of the above factors working together.

Conclusion: *per* and *cry* may determine response to photoperiod, but it's not the only cause. Something else in the pituitary gland (perhaps in the pars distalis) is also responsible. This is also verified by experimental data (Dupre, 2007).

# Why Study This?

- It describes how mammalian neuroendocrine systems work.
- It gives us insight on how to correct neuroendocrine system disorders.
- It's more ethical to test on sheep than it is on people.

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