Analyzing Parameter Sensitivity in a Mathematical Model of the Ovulatory Cycle

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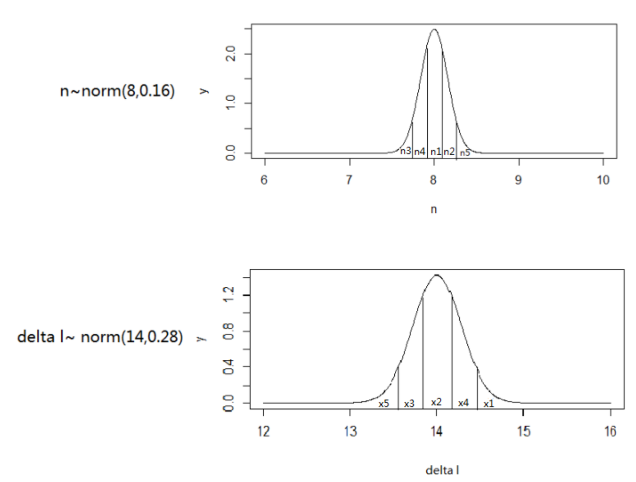
Abstract

Infertility in women is commonly caused by polycystic ovary syndrome (PCOS), which is characterized by some combination of elevated androgen levels, ovulatory dysfunction and a polycystic ovary morphology. Thus studying the factors causing PCOS would be helpful to solving the infertility problem. Although the mysteries behind PCOS are still completely unsolved, with the help of mathematical modeling, we can reduce the problem into smaller pieces and generate helpful information. Given an existing mathematical model of pituitary regulation and follicle dynamics within the ovulatory cycle, we examine further the accuracy and utility of the model through its associated variables and parameters. With more than 40 parameters, most of which are unknown, there is significant uncertainty in estimating model parameters to fit published data. Furthermore, a small deviation in one parameter may cause large difference in the final result. We seek to determine the sensitivity of the model to the unknown parameters using global sensitivity analysis. A combination of the Latin hypercube sampling (LHS) scheme and partial rank correlation coefficient (PRCC) analysis is applied to accomplish this. Results from this analysis can then be used to identify the biological implications of sensitive parameters and further refine the model.

Methods: LHS and PRCC

- Assign probability function to each parameter. In this project we use normal distribution, and the standard deviation of each parameter is 0.2 times its mean value.
- The actual item size used in the project is equal 100. But here for easier presentation, we assume item size is 5.Thus divide each interval into 5 subintervals. Using the example of δ_l and n.



- Calculate the Y values by each group of X values. Assume in this case $y_5 < y_3 < y_1 < y_4 < y_2$. Then rank the values from small to large.

B

LHS MATRIX → OUTPUT MATRIX

$$X = \begin{bmatrix} a_1 & b_1 & c_1 \\ a_2 & b_2 & c_2 \\ a_3 & b_3 & c_3 \\ a_4 & b_4 & c_4 \\ a_5 & b_5 & c_5 \end{bmatrix} \longrightarrow Y = \begin{bmatrix} y_1 = f(a_1, b_1, c_1) = 5.2 \\ y_2 = f(a_2, b_2, c_2) = 7.9 \\ y_3 = f(a_3, b_3, c_3) = 3.1 \\ y_4 = f(a_4, b_4, c_4) = 6.4 \\ y_5 = f(a_5, b_5, c_5) = 0.8 \end{bmatrix}$$

Ranking ↓ Ranking ↓

$$X_R = \begin{bmatrix} 2 & 3 & 4 \\ 5 & 1 & 3 \\ 4 & 5 & 2 \\ 1 & 2 & 5 \\ 3 & 4 & 1 \end{bmatrix} \qquad Y_R = \begin{bmatrix} 3 \\ 5 \\ 2 \\ 4 \\ 1 \end{bmatrix}$$

- Calculate PRCC using X_r and Y_r:

$$r_{x_j,y} = \frac{Cov(x_j, y)}{\sqrt{Var(x_j)Var(y)}} = \frac{\sum_{i=1}^{N}(x_{ij} - \hat{x})(y_i - \hat{y})}{\sqrt{\sum_{i=1}^{N}(x_{ij} - \hat{x})^2 \sum_{i=1}^{N}(x_i - \hat{y})^2}}$$
$$j = 1, 2, \dots, K$$

- Bootstrap simulations to gather significant number of PRCC values. Test for significance test using a t test. Compare the PRCC for each parameter with that of dummy variable in 99 percent confidence level. Dummy variable, introduced by Marino et al. (2008), eliminates the effect of natural variance in the model.

Acknowledgements

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Mathematical Model of the Ovulatory Cycle

Releasable FSH: $$FSH'_\rho(t) = \frac{v_F}{1 + c_{F,J}\frac{S\lambda}{K_{F,I}+S\lambda}} - k_F \frac{1 + c_{F,P}P_4}{1 + C_{F,E}{E_2}^2} FSH_\rho$$

Serum FSH: $$FSH'(t) = \frac{1}{v} \cdot K_F \frac{1 + c_{F,P}P4}{1 + C_{F,E}E2^2} FSH_\rho - \delta_F FSH$$

Releasable LH: $$LH'_\rho(t) = \left[v_{0L} \cdot \frac{T}{K_{L,T} + T} + v_{1L} \cdot \frac{{E_2}^n}{{K_{mL}}^n + E_2^n} \right] \cdot \frac{1}{1 + P_4/[K_{iL,P}(1 + c_{L,T}T)]} - k_L \frac{1 + c_{L,P}P_4}{1 + c_{L,E}E_2} LH_\rho$$

Serum LH: $$LH'(t) = \frac{1}{V} \cdot k_L \frac{1 + c_{L,P}P_4}{1 + c_{L,E}E_2} LH_\rho - \delta_L LH$$

Follicular Stage: $$\Phi'(t) = f_0 \cdot \frac{T}{T_0} + [\frac{f_1 FSH^2}{\left(\frac{h_1}{1+T/T_0}\right)^2 + FSH^2} - \frac{f_2 LH^2}{\left(\frac{h_2}{1+c_{\Phi,F}FSH}\right)^2 + LH^2}] \cdot \Phi$$

Ovulatory Stage: $$\Omega'(t) = \frac{f_2 LH^2}{\left(\frac{h_2}{1+c_{\Phi,F}FSH}\right)^2 + LH^2} \cdot \Phi - wS\Omega$$

Luteal Stage: $$\Lambda'(t) = wS\Omega - l(1 - S)\Lambda$$

LH Support: $$S'(t) = \frac{\hat{s}LH^m}{h_s^m + LH^m} \cdot (1 - S) - \delta_s S$$

Testosterone: $$T'(t) = t_0 - \delta_T T + [t_1 G_1(F_1 + c_{T,F_2}F_2) + t_2 G_1 G_2 F_1] \cdot \left[\Phi + \tau_1\Omega + \tau_2 S\Lambda + \tau_3 \left(1 - \frac{\Phi + \Omega + \Lambda}{\Psi}\right)\right]$$

Intermediate T: $$T'_y(t) = t_{g1} G_1 G_2 F_1 - \frac{t_{g2} FSH}{h_3 + FSH} T_y$$

Estradiol: $$E'_2(t) = e_0 - \delta_E E_2 + \frac{t_{g2} FSH}{h_3 + FSH} T_y \cdot [\Phi + \eta\Lambda S]$$

Progesterone: $$P'_4(t) = -\delta_P P_4 + \frac{pLH}{LH + h_p} \cdot \Lambda S$$

Parameters

	Parameter	Units	Mean	Standard Deviation
Fitted Parameters	$C_{F,E}$	$(ng/L)^{-2}$	2.273×10^{-3}	4.546×10^{-5}
	$C_{F,I}$	—	1.9488	3.898×10^{-2}
	$C_{F,P}$	$(\mu g/L)^{-1}$	60.428	1.209
	$C_{L,E}$	$(ng/L)^{-1}$	1.0404×10^{-3}	2.0808×10^{-5}
	$C_{L,P}$	$(\mu g/L)^{-1}$	9.9415×10^{-3}	1.9883×10^{-4}
	$C_{L,T}$	$(ng/L)^{-1}$	9.5942×10^{-3}	1.9188×10^{-4}
	δ_F	$1/d$	8.21	0.1642
	δ_L	$1/d$	14	0.28
	K_F	$1/d$	2.5412	5.0824×10^{-2}
	$K_{F,I}$	μg	107.01	2.1402
	$K_{iL,P}$	$\mu g/L$	0.3495	46.9904×10^{-3}
	$K_{L,T}$	ng/L	420	8.4
	K_{mL}	$\mu g/L$	183.56	3.6712
	K_L	$\mu g/L$	0.3495	1.4913×10^{-2}
	n	—	8	0.16
	V	1	2.5	0.05
	v_{0L}	$\mu g/d$	1051.7	21.034
	v_{1L}	$\mu g/d$	34838	696.76
	v_F	$\mu g/d$	3236.6	64.732
	$c_{/Phi,F}$	$(\mu g/L)^{-1}$	1.127×10^{-2}	2.254×10^{-4}
	δ_s	$1/d$	0.74702	1.494×10^{-2}
	f_0	$(\mu g/d)^{-1}$	2.5112×10^{-3}	5.0224×10^{-5}
	f_1	$1/d$	4.3764	8.7528×10^{-2}
	f_2	$1/d$	27.812	0.5562
	h_1	$(\mu g/L)^{-1}$	590.32	11.8064
	h_2	$(\mu g/L)^{-1}$	1815.3	36.306
	h_P	$(\mu g/L)^{-1}$	20.764	0.4153
	h_s	$(\mu g/L)^{-1}$	12.329	0.2466
	l	$1/d$	0.4902	9.8034×10^{-3}
	m	—	4	0.08
	$\hat{s}$	$1/d$	2.378	4.756×10^{-2}
	w	$1/d$	0.2317	4.6346×10^{-3}

	Parameter	Units	Mean	Standard Deviation
Fitted Parameters	c_{T,F_2}	$\mu g/L$	123.8136	2.4763
	δ_E	$1/d$	1.1	0.022
	δ_P	$1/d$	0.5	0.01
	δ_T	$1/d$	5.5	0.11
	e_0	$ng/L \cdot d$	44.512	0.8902
	η	—	1.1087	2.2174×10^{-2}
	h_3	$\mu g/L$	17.796	0.3559
	K_1	—	1.09	2.18×10^{-2}
	K_2	$\mu g/L$	22.2865	0.4457
	K_3	$(\mu g/L)^2$	113.9188	0.3559
	p	$1/L \cdot d$	0.3734	7.468×10^{-3}
	t_0	ng/L	741.68	14.8336
	t_1	$ng/L\mu gd$	0.5709	1.1418×10^{-2}
	t_2	$ng/L\mu gd$	1.3481	2.6962×10^{-2}
	τ_1	—	5.3989	0.1080
	τ_2	—	0	—
	τ_3	μg	430.91	8.6182
	t_{g1}	$ng/L\mu gd$	6.6548	0.1331
	t_{g2}	$1/d$	186.27	3.7125
	Ψ	μg	2004.3	20.086
	FSH	$\mu g/L$	142.5	—
	LH	$\mu g/L$	25.34	—
	FSH_ρ	μg	116.82	—
	LH_ρ	μg	250.35	—
	Φ	μg	0.5019	—
	Ω	μg	9.7509	—
	Λ	μg	4.102	—
	S	—	0.050498	—
	T_y	$ng/L\mu g$	0.003999	—
	T	ng/L	273.67	—
	E_2	ng/L	56.387	—
	P_4	ng/mL	0.468	—

*Standard deviation value is calculated by 0.02 times mean value. Last twelve rows are initial conditions of variable used in the model, thus no standard deviation needed.

Results: Sensitivity Analysis

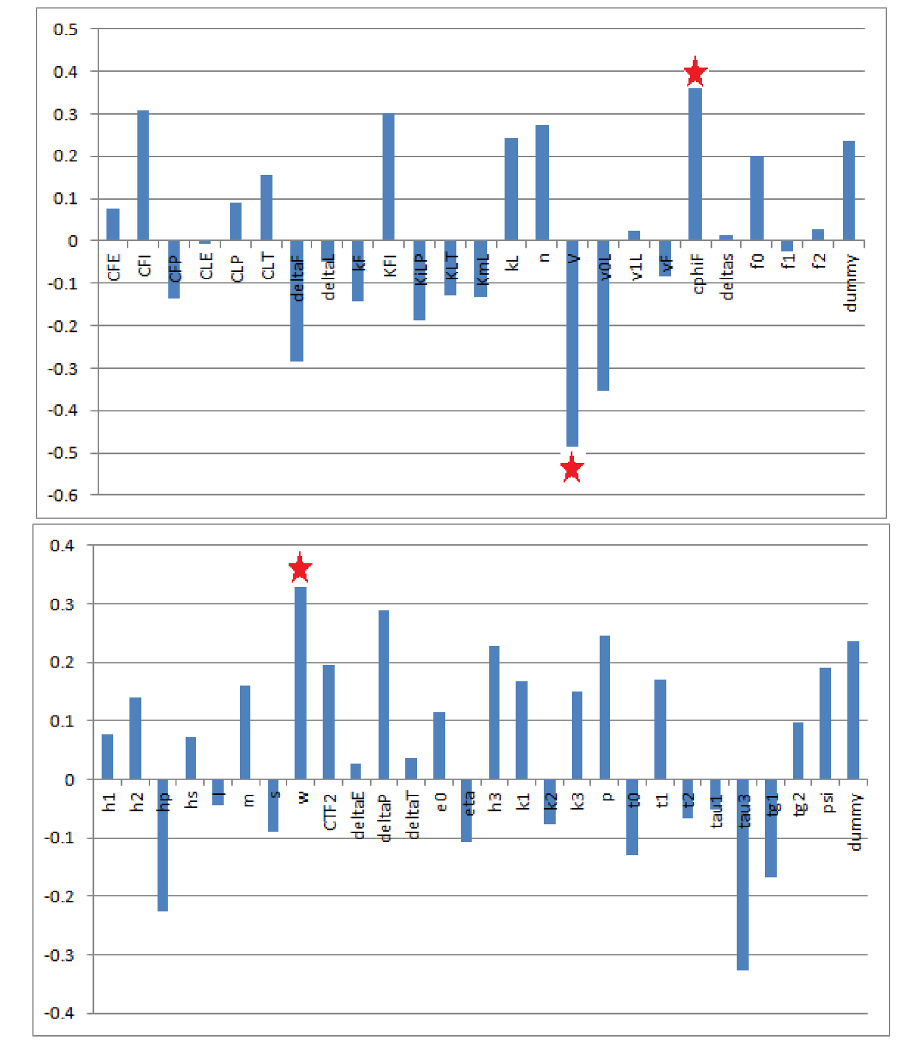
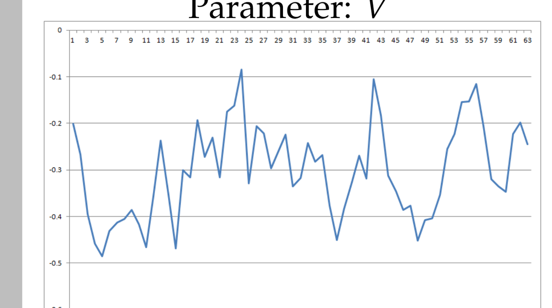


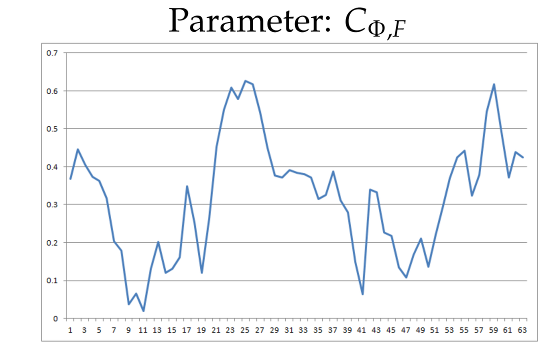
Figure: PRCC values of each parameter at $t = 5$. $\tau_2 = 0$ always and is omitted. PRCCs significantly different than those of dummy variable are indicated with a star.

Results: Time-dependent PRCC

Parameter: V



Parameter: $C_{\Phi,F}$



Parameter: w

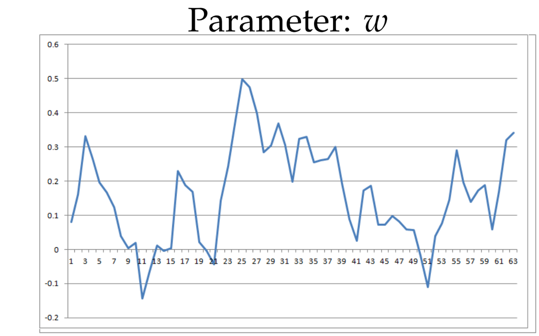


Figure: Change in PRCC as a function of time for the three most sensitive parameters, V, $C_{\Phi,F}$, and w.

Summary

- Through global sensitivity analysis and t tests, we found three very sensitive parameters, which will largely influence model results when changed.
- The PRCC is time-sensitive, possibly altering the conclusions of the global sensitivity analysis.
- Further work will determine how time-sensitivity influences parameter sensitivity and identify whether a single time point exists that characterizes global sensitivity.

Bibliography

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