README

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| **Scripts used to generate results** | |
| main\_script.m | Script used to specify different simulation conditions and obtain output data |
| NOC\_nlme\_harm\_terms.m | Function that utilizes a nonlinear mixed effects model (NLME) to fit input female subject hormone data collected during their menstrual cycle.4 |
| NLME\_hormone\_profile\_breakdown.m | Function to generate descriptive values for NLME output of female hormone data. |
| ode\_ftn.m | Function that solves the differential equations |
| ode\_ftn\_Sobol.m | Function that solves the differential equations for Sobol analysis |
| cytokine\_hist.m | Function that sets the initial conditions for the differential equations and specifies the trigger of the inflammatory process |
| cytokine\_hist\_zero.m | Function called prior to cytokine\_hist that sets the initial conditions at 0 for the calculation of the initial conditions for the specified injury time (during the menstrual cycle). |
| all\_feedback\_ftns.m | Function to calculate the values of all the feedback functions during every step of the ODE solver code |
| all\_feedback\_functions\_Sobol.m | Function to calculate the values of all the feedback functions during every step of the Sobol ODE solver code. |
| rate\_coeffs.m | Contains rate coefficients for the differential equations |
| all\_parameter\_fits.m | Contains the estimates for all fitted parameters. Also includes the raw data extracted from the literature that was used to fit each parameter (citations are noted in the comments) |
| lhs\_script\_general.m | Function used to vary the simulation parameters with Latin Hypercube Sampling (LHS) and obtain median and IQR of all the different outputs. |
| lhs\_script\_ks\_and\_et.m | Function to simultaneously vary the concentrations of sex hormones and the simulation parameters LHS and obtain median and IQR of all the different outputs. |
| lhs\_script\_sobol.m | Function to simultaneously vary the simulation parameters in the absence of hormones with LHS and calculate the first order and total order Sobol sensitivity values for the input parameters with respect to the model outputs. |
| Sobol\_Analysis.m | Function that facilitates the calculation of Sobol sensitivities for the model inputs by the SAFE VBSA toolbox.3 |
| Vbsa\_indicies.m | SAFE VBSA function that calculates first and total order Sobol indices. |
| Vbsa\_resampling.m | SAFE VBSA function that resamples the parameter sampling matrix to calculate Sobol indices. |
| Ks\_mod.m | Function used to generate perturbed rate parameters during Latin Hypercube Sampling |
| abcs\_mod.m | Function used to generate perturbed feedback parameters during Latin Hypercube Sampling |
| E2\_mod.m | Function used to generate perturbed estrogen concentrations during Latin Hypercube Sampling |
| Pr\_mod.m | Function used to generate perturbed progesterone concentrations during Latin Hypercube Sampling |
| T\_mod.m | Function used to generate perturbed testosterone concentrations during Latin Hypercube Sampling |
| **Scripts used to generate plots** | |
| ciplot\_mod.m | Function modified from a freely available code by Raymond Reynolds that plots figures with confidence bands |
| plot\_concentrations.m | Function used to generate figures without concentration bands |
| plot\_concentration\_bands.m | Function used to generate figures with concentration bands |
| plot\_concentrations\_sweep.m | Function used to generate figures of model outputs with respect to sweeping female hormone concentrations during menstrual cycle. (injury simulation starts on cycle days 1-30) |
| steady\_hormone\_ept\_plots.m | Script used to generate plots for nominal model outputs that incorporate sex hormones. |
| male\_fem\_vary\_plots.m | Script is used to generate plots for LHS model outputs that incorporate sex hormones. |
| steady\_hormones\_female\_sweep\_plots.m | Script used to plot model outputs during the female menstrual cycle. |
| **Other files** |  |
| statistical\_comparisons\_hormones.m | Script used to perform Kruskal-Wallis and Mann-Whitney U tests between groups at different time points in the analysis of combined estrogen and testosterone |
| change\_injury\_timing.m | Function used to rearrange menstrual cycle hormone profiles with respect to user input of model injury start (Day 1-30) |
| Hormone\_profile\_NOC\_v2.csv | Female subject hormone data file used to evenly space time increments for NLME fitting. |
| Sobol\_Rank.m | Function used to rank the top 5 sensitivity indices at each simulated time point for each modeled substance. |
| RBC\_statistical\_comparisons\_female\_sweep.m | Function used to conduct Rank Based Covariate (RBC) analysis on model results from female cycle simulations. Day 0, Day 7, Day 15, Day 18, and Day 26 |
| RBC\_statistical\_comparisons\_male\_female.m | Function used to conduct Rank Based Covariate (RBC) analysis on model results from "Female Peak E," "Female Low E," and "Male" differ. |
| Parameter\_names.txt | Text file with all 49 rate parameter titles |
| Substance\_names.txt | Text file with the names of the 13 modeled substances |
| Dunn2.m | Dunn procedure for multiple non parametric comparisons. |
| tiedrankmin.m | This function returns the sample ranks of the values in a vector. Tied values will be replaced by their minimum |
| Wanova.m | Perform a Welch's alternative to one-way analysis of variance (ANOVA). |

**Instructions for generating plots found in the paper**

Figure 1: (this is a diagram created in Biorender, so it cannot be generated with the code)

Figure 2: (this is a diagram created in Biorender, so it cannot be generated with the code)

Figure 4, 5 and Supplemental Figure 1:

* Clear the workspace (type “clear all” in the command window)
* Set the variable lhs\_ks = 1 (line 71 in main\_script.m)
* Set lhs\_sobol\_female = 0; lhs\_sobol\_male = 0; nominal = 0; female\_cycle = 0, male = 0, female\_cycle\_sweep = 0, vary \_female = 0, vary \_male = 0; (lines 74, 77, 83, 88, 89, 90, 97, and 98 respectively, in main\_script.m)
* Run main\_script.m
  + This may take several days (~3days)
  + This will automatically generate the plots in Figure 4, 5 and Supplemental Figure 1
  + Figures in paper were generated using Graphpad Prism 10.0.1 with data outputs: Sii,STii,median\_sol,low\_sol,high\_sol
  + Data from Irie et al. 20032 and Haller et al. 20151 overlaid on model results

Figure 6 and statistical analysis:

* Clear the workspace (type “clear all” in the command window)
* Set the variable female\_cycle\_sweep = 1 (line 90 in main\_script.m)
* Set lhs\_ks = 0, lhs\_sobol\_female = 0; lhs\_sobol\_male = 0; nominal = 0; female\_cycle = 0, male = 0, vary \_female = 0, vary \_male = 0; (lines 71, 74, 77, 83, 88, 89, 97, and 98 respectively, in main\_script.m)
* Run main\_script.m
  + This may take several hours
* Without clearing the variables, run steady\_hormones\_female\_sweep\_plots.m
* Paper figures and statistical analysis generated using Graphpad Prism 10.0.1 with data output: sol\_female\_sweep\_cell

Figure 7 and statistical analysis:

* Clear the workspace (type “clear all” in the command window)
* Set the variable lhs\_sobol\_female = 1 (line 74 in main\_script.m)
* Set lhs\_ks = 0; lhs\_sobol\_male = 0; nominal = 0; female\_cycle = 0, male = 0, female\_cycle\_sweep = 0 vary \_female = 0, vary \_male = 0; (lines 71, 77, 83, 88, 89, 90, 97, and 98 respectively, in main\_script.m)
* Run main\_script.m
  + When prompted input day 0 (menses)
  + This simulation may take several days (~6days)
  + Save results as female\_sobol\_(day0)
* Clear the workspace (type “clear all” in the command window)
* Set the variable lhs\_sobol\_female = 1 (line 74 in main\_script.m)
* Set lhs\_ks = 0; lhs\_sobol\_male = 0; nominal = 0; female\_cycle = 0, male = 0, female\_cycle\_sweep = 0 vary \_female = 0, vary \_male = 0; (lines 71, 77, 83, 88, 89, 90, 97, and 98 respectively, in main\_script.m)
* Run main\_script.m
  + When prompted input day 15 (peri-ovulation)
  + This simulation may take several days (~6days)
  + Save results as female\_sobol\_(day15)
* Clear the workspace (type “clear all” in the command window)
* Set the variable lhs\_sobol\_male = 1 (line 77 in main\_script.m)
* Set lhs\_ks = 0; lhs\_sobol\_female = 0; nominal = 0; female\_cycle = 0, male = 0, female\_cycle\_sweep = 0 vary \_female = 0, vary \_male = 0; (lines 71, 74, 83, 88, 89, 90, 97, and 98 respectively, in main\_script.m)
* Run main\_script.m
  + This simulation may take several days (~3days)
* Paper figures and statistical analysis generated using Graphpad Prism 10.0.1 with data outputs for each simulation: median\_sol,high\_sol,low\_sol
* Plots will be automatically generated for each simulation

Supplemental Figure 2

* Clear the workspace (type “clear all” in the command window)
* Set the variable nominal = 1 (line 83 in main\_script.m)
* Set lhs\_ks = 0; lhs\_sobol\_female = 0; lhs\_sobol\_male = 0; female\_cycle = 0, male = 0, female\_cycle\_sweep = 0, vary \_female = 0, vary \_male = 0; (lines 71, 74, 77, 88, 89, 90, 97, and 98 respectively, in main\_script.m)
* Run main\_script.m
  + Save data as nominal.m
* Clear the workspace (type “clear all” in the command window)
* Set the variable nominal = 1 (line 83 in main\_script.m)
* Set lhs\_ks = 0; lhs\_sobol\_female = 0; lhs\_sobol\_male = 0; female\_cycle = 0, male = 0, female\_cycle\_sweep = 0, vary \_female = 0, vary \_male = 0; (lines 71, 74, 77, 88, 89, 90, 97, and 98 respectively, in main\_script.m)
* In script ode\_ftn set M1 and M2 to 0 (lines 18 and 19 respectively)
* Run main\_script.m
  + Save data as nominal\_no\_Macrophage.m
* Paper figures using Graphpad Prism 10.0.1 with data outputs for each simulation: sol\_nominal

References

1. Haller JM, Swearingen CA, Partridge D, McFadden M, Thirunavukkarasu K, Higgins TF. Intraarticular Matrix Metalloproteinases and Aggrecan Degradation Are Elevated After Articular Fracture. *Clin Orthop Relat Res*. 2015;473(10):3280-3288. doi:10.1007/s11999-015-4441-4

2. Irie K, Uchiyama E, Iwaso H. Intraarticular inflammatory cytokines in acute anterior cruciate ligament injured knee. *Knee*. 2003;10(1):93-96. doi:10.1016/S0968-0160(02)00083-2

3. Pianosi F, Sarrazin F, Wagener T. A Matlab toolbox for Global Sensitivity Analysis. *Environ Model Softw*. 2015;70:80-85. doi:10.1016/j.envsoft.2015.04.009

4. Soedirdjo SDH, Rodriguez LA, Chung YC, Casey E, Dhaher YY. Sex hormone-mediated change on muscle activation deactivation dynamics in young eumenorrheic women. *Front Physiol*. 2023;14(March):1-10. doi:10.3389/fphys.2023.1104578