Supplementary File: A survey of mathematical modeling of hormonal contraception and the menstrual cycle

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A Issues with units from dimensional analysis

We summarized the initial condition and parameter value along with units for five models (Harris Clark model, Margolskee model, Pasteur model, Wright model, and Gavina model) into a spreadsheet which is available on our public GitHub repository (https://github.com/rubyshkim/WiMBCode/blob/main/SupplementalMaterials/SupplementalTable.xlsx). Here we provide a few examples on discrepancy of units within each model that we identified with detailed dimensional analysis.

A.1 Gavina et al. model [2]

They provided the units for all the variables and parameters except p_0, but for some parameters we obtain different units by performing dimensional analysis on different model equations. For example, in their Table I, the unit of $Lut_4(t)$ is ng. If we try to identify the unit of $Lut_4(t)$ from their auxiliary equation

$$P_4(t) = p_0 + p_1 Lut_3(t) + p_2 Lut_4(t) + P_4^{\text{exo}}(t),$$

given that the unit of P_4 is ng/mL [2, Fig. 2] and the unit of p_2 is kL^{-1} [2, Table V], we obtain the unit of $Lut_4(t)$ to be

$$\frac{ng/mL}{kL^{-1}} = ng\frac{kL}{mL} = ng \times 10^6,$$

which does not match the unit they listed in their Table I. But if we try to identify the unit of $Lut_4(t)$ from their auxiliary equation

$$E_2(t) = e_0 + e_1 GrF(t) + e_2 DomF(t) + e_3 Lut_4(t) + E_2^{\text{exo}}(t),$$

given that the unit of E_2 is pg/mL [2, Fig. 2] and the unit of e_3 is L^{-1} [2, Table V], we obtain the unit of $Lut_4(t)$ to be

$$\frac{pg/mL}{L^{-1}} = pg\frac{L}{mL} = pg \times 10^3 = ng.$$

Similar issue is observed with the unit of $Lut_3(t)$, in their Table I, the unit of $Lut_3(t)$ is ng. From their auxiliary equation for E_2 given that the unit of p_1 is kL^{-1} [2, Table V], we obtain the unit of $Lut_3(t)$ to be

$$\frac{ng/mL}{kL^{-1}} = ng\frac{kL}{mL} = ng \times 10^6,$$

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which does not match the unit they listed in their Table I. But if we try to identify the unit of $Lut_4(t)$ from their auxiliary equation for

$$Inh(t) = h_0 + h_1 DomF(t) + h_2 Lut_2(t) + h_3 Lut_3(t),$$

given that the unit of Inh is IU/mL [2, Fig. 2] and the unit of h_3 is $IUmL^{-1}\mu g^{-1}$, we obtain the unit of $Lut_3(t)$ to be

$$\frac{IU/mL}{IUmL^{-1}\mu g^{-1}} = \mu g = ng \times 10^3,$$

which does not match the unit they listed in their Table I, ng.

A.2 Wright et al. model [7]

They did not provide the initial conditions used in their simulation. Additionally, they only provided the units for 5 out of 17 state variables: LH, FSH, E_2, P_4, and Inh. When we tried to determine the units for the rest of the state variables, we noticed similar issues as in Appendix A.1. For example, if we try to identify the unit of $Lut_4(t)$ from their auxiliary equation

$$P_4(t) = p_0 + p_1 Lut_3(t) + p_2 Lut_4(t) + p_{\text{dose}},$$

given that the unit of P_4 is ng/mL [7, Fig. 3] and the unit of p_2 is kL^{-1} [7, Table 1], we obtain the unit of $Lut_4(t)$ to be

$$\frac{ng/mL}{kL^{-1}} = ng\frac{kL}{mL} = ng \times 10^6 = mg;$$

but if we try to identify the unit of $Lut_4(t)$ from their auxiliary equation

$$E_2(t) = e_0 + e_1 GrF(t) + e_2 DomF(t) + e_3 Lut_4(t) + e_{\text{dose}},$$

given that the unit of E_2 is pg/mL [7, Fig. 3] and the unit of e_3 is L^{-1} [7, Table 1], we obtain the unit of $Lut_4(t)$ to be

$$\frac{pg/mL}{L^{-1}} = pg\frac{L}{mL} = pg \times 10^3 = ng,$$

which is different from the unit we obtained using dimensional analysis on the auxiliary equation for E_2 (mg). Another example is the unit of GrF, using the auxiliary equation for E_2 given that the unit of E_2 is pg/mL [7, Fig. 3] and the unit of e_1 is L^{-1} [7, Table 1], we obtain the unit of GrF to be

$$\frac{pg/mL}{L^{-1}} = pg\frac{L}{mL} = pg \times 10^3 = ng.$$

On the other hand, we first conclude that the unit of P_{app} should be the same as P_4 based on the auxiliary equation

$$P_{app} = \frac{P_4}{2}\left(1 + \frac{E_2^{\mu}}{Km_{P_{app}}^{\mu} + E_2^{\mu}}\right);$$

then using the ODE

$$\frac{d}{dt}RcF = (b + c_1 RcF)\frac{FSH}{(1 + P_{app}/Ki_{RcF,P})^{\xi}} - c_2 LH^{\alpha} RcF$$

with that the unit of b is $\frac{L}{IU}\frac{\mu g}{\text{day}}$ [7, Table 1], the unit of FSH is IU/L [7, Fig. 3], and P_{app} and $Ki_{RcF,P}$ have the same unit, we obtain the unit of RcF to be

$$\frac{L}{IU}\frac{\mu g}{\text{day}} \times \frac{IU}{L} \times \text{day} = \mu g;$$

and finally, using the ODE

$$\frac{d}{dt}GrF = c_2 LH^{\alpha} RcF - c_3 LH\ GrF$$

given that the unit of LH is IU/L [7, Fig. 3] and the unit of c_2 is $\frac{L}{IU}\frac{\mu g}{\text{day}}$ [7, Table 1], we obtain the unit of GrF to be

$$\frac{L}{IU}\frac{\mu g}{\text{day}} \times \left(\frac{IU}{L}\right)^{\alpha} \times \text{day} = \mu g,$$

which is different from the unit we obtain using the auxiliary equation for E_2 (ng).

A.3 Pasteur model [5, 6]

They did not provide the initial conditions or parameter values in the book chapter [5]. We were able to find the values and units for the parameters in the six-hormone model (the model presented in [5]) by piecing together the information they provided in the dissertation [6] for the five-hormone model and six-hormone model, we were able to locate the initial condition values they used in their simulation in the Appendix in the dissertation [6], but they only provided the units for 6 out of 20 state variables: LH, FSH, E_2, P_4, IhA, and IhB. Again, we noticed the discrepancy in units when we tried to derive the units of the rest of the state variables. Similar to the calculations showed in Appendices A.1 and A.2, we obtained different units for Lut_3 and Lut_4 when we perform the dimensional analysis on different equations of the model. Here we will demonstrate the discrepancy on the unit of PrF. From the auxiliary equation

$$IhA = h_0 + h_1 \cdot PrF + h_2 \cdot Lut_2 + h_3 \cdot Lut_3 + h_4 \cdot Lut_4$$

and that the unit of IhA is IU/mL [6, Table A.3] and the unit of h_1 is $IU/(\mu g \cdot mL)$ [6, Table 5.4], we can calculate the unit of PrF

$$\frac{IU/mL}{IU/(\mu g \cdot mL)} = \mu g;$$

if we use the auxiliary equation

$$IhB = j_0 + j_1 \cdot PrA2 + j_2 \cdot PrF + j_3 \cdot OvF$$

and that the unit of IhB is pg/mL [6, Table A.3] and the unit of j_2 is L^{-1} [6, Table 5.4], we can calculate the unit of PrF

$$\frac{pg/mL}{L^{-1}} = pg \times 10^3 = ng,$$

which is different from the unit we obtained, μg, using the auxiliary equation for InA; similary, if we use the auxiliary equation

$$E_2(t) = e_0 + e_1 \cdot SeF2 + e_2 \cdot PrF + e_3 \cdot Lut_4(t),$$

and that the unit of E_2 is pg/mL [6, Table A.3] and the unit of e_2 is L^{-1} [6, Table 5.4], we would get the unit of PrF to be ng.

A.4 Margolskee model [4]

Table 1 in [4] summarized the parameter values along with units they used in their simulation. Initial conditions (rounded to two decimal places) for all the 13 state variables were provided in their paper (bottom right on page 98). However, they did not provide the units for their state variables, not even in their figures. We were able to obtain the unit of P_4 to be ng/mL (same as the unit of p_0) and the unit of Inh to be IU/mL (same as the unit of h_0). Then from the auxiliary equation

$$P_4 = p_0 + p_1 Lut_3(t) + p_2 Lut_4$$

given that the unit of p_1 is kL^{-1} [4, Table 1], we obtain the unit of Lut_3 to be

$$\frac{ng/mL}{kL^{-1}} = ng \times 10^6 = mg;$$

but from the auxiliary equation

$$Inh = h_0 + h_1 PrF + h_2 Lut_2 + h_3 Lut_3$$

given that the unit of h_3 is $IU/(\mu g\ mL)$ [4, Table 1], we obtain the unit of Lut_3 to be

$$\frac{IU/mL}{IU/(\mu g\ mL)} = \mu g,$$

which does not agree with the unit we obtained using the auxiliary equation for P_4.

A.5 Harris Clark model [1, 3]

They did not provide the units for state variables RcF, SeF, PrF, Sc1, Sc2, Lut1, Lut2, Lut3, and Lut4. The only discrepancy we noticed in this paper is that the unit of LH is $\mu g/L$ in their Figs. 3 and 4 but mg/L in their Fig. 7. Note that Harris Clark recorded the dimensional analysis and the nondimensioanlization procedure they performed in their dissertation [3].

References

[1] L. H. Clark, P. M. Schlosser, and J. F. Selgrade. "Multiple stable periodic solutions in a model for hormonal control of the menstrual cycle." In: *Bulletin of Mathematical Biology* 65.1 (2003), pp. 157–173.

[2] B. L. A. Gavina, A. Aurelio, M. S. Olufsen, S. Lenhart, and J. T. Ottesen. "Toward an optimal contraception dosing strategy." In: *bioRxiv* (2022), pp. 2022–04.

[3] L. A. Harris. "Differential equation models for the hormonal regulation of the menstrual cycle." PhD thesis. North Carolina State University, 2002.

[4] A. Margolskee and J. F. Selgrade. "Dynamics and bifurcation of a model for hormonal control of the menstrual cycle with inhibin delay." In: *Mathematical Biosciences* 234.2 (2011), pp. 95–107.

[5] R. D. Pasteur and J. F. Selgrade. "A deterministic, mathematical model for hormonal control of the menstrual cycle." In: *Understanding the dynamics of biological systems*. Springer, 2011, pp. 39–58.

[6] R. D. Pasteur II. "A multiple-inhibin model of the human menstrual cycle." PhD thesis. North Carolina State University, 2008.

[7] A. A. Wright, G. N. Fayad, J. F. Selgrade, and M. S. Olufsen. “Mechanistic model of hormonal contraception.” In: *PLoS Computational Biology* 16.6 (2020), e1007848.