Optimal Control–Based Dosing of Combined Oral Contraceptives via Pharmacokinetic Modeling

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Abstract— **The problem of contraception dosing, aiming also at reducing side effects, is analysed. The hormonal role, whose primary mechanism of action is the prevention of ovulation by inhibiting follicular development, is studied, to include also the effects of oral contraceptives; more precisely, the dynamics of the drug is introduced, thus coupling a pharmacokinetics (PK) model with a hormonal dynamics one. The optimal dosage scheduling is determined in the framework of the Pontryagin principle, comparing the results of three different existing contraceptive pills with each other on the basis of existing physiological criteria.**

I. INTRODUCTION

To date, several types of contraceptive methods exist, such as the Intrauterine Device (IUD) implant or the patch, to name a few, [1]; however, the most widely used method is the oral contraceptive pill (OCP), [2]. The primary characteristic of preventing pregnancy in the pill is progesterone, whose mechanism of action is the prevention of ovulation by inhibiting follicular development. Progesterone acts as a natural inhibitor for both the production of FSH and LH hormones, responsible for ovulation, acting as a negative feedback on the hypothalamus-pituitary-ovaries (HPO) axis.

As far as the oral contraceptive pill, several issues are associated with this type of therapy, as the concept of personalized medication is still not fully established. Indeed, many women experience adverse effects related to the intake of this type of medication because the prescribed dosage is often not tailored to individual needs. Some side effects are mild and, with continued use, generally disappear: breakthrough bleeding, nausea, headaches, abdominal cramping, breast tenderness. Also increased vaginal discharge or decreased libido are mentioned. Moreover, serious adverse effects are reported: an analysis of the literature indicates that the current use of current low-dose oral contraceptives (OCs) significantly increases the risk of both cardiac and arterial vascular events, including a notable risk of arterial vascular complications associated with third-generation OCs [3]. Nonetheless, higher dosages are linked to adverse outcomes such as an increased risk of thrombosis and myocardial infarction [4], [5]. This highlights the need for personalized therapeutic approaches.

Mathematical modeling has been showing its power in many fields, being able to provide simplified and effective description of the phenomenon under investigation. Modeling complex phenomenon, often involving many variables and parameters, allows understanding relations not easily recognizable among them and apply control strategies in a verified environment saving time and resources. This is mandatory when referring to specific applications on human beings, like epidemiology, pharmacodynamics and pharmacokinetics, [6], [7]. In particular, in [8], the problem of modeling hormonal dynamics has been faced. The authors modeled the menstrual cycle by focusing on ovarian steroid production as a function of stage-dependent follicle maturation. The model specifically incorporates the physiological impact of insulin on testosterone concentrations to highlight the direct link between elevated androgen production and the development of Polycystic Ovary Syndrome (PCOS). Then, in [9], which is the model we will refer to to solve our problem, the authors chose to reduce the model presented in [8] because they thought that it was more amenable the reductions in the parameter space while retaining normal ovulatory dynamics, in contrast to other related models that are based on delay differential equations [10], [11], [12].

The problem of contraception dosing strategy, aiming also at reducing negative side effects, has been faced in [13] determining the minimum total estrogen/progesterone dose, with the suitable timing of administration to induce anovulation; the model adopted was a modified version of the one proposed in [14] and the optimal strategy is obtained making the progesterone tracking a reference value by acting on exogenous estrogen/progesterone dose. It is interesting to take into account also the dynamics of the drug introducing a pharmacokinetics (PK) model coupled with an hormonal dynamics one, [15]; it involves studying how the drug is absorbed, metabolized and eliminated from the body, as opposed to pharmacodynamics in which attention is focused on the therapeutic and toxic effects that a certain dose of drug causes in the patient.

In this work, the optimal dosage of oral contraceptives is determined by coupling pharmacokinetics with a hormonal dynamics model, introducing a novel PKPD control framework as a solution method not yet explored in literature. Optimal contraceptive effects are achieved by minimizing FSH and LH hormones while keeping the drug dosage as low as possible.

The work is structured as follows: in Section II the new formulation with coupling of pharmacokinetics and hormonal dynamics models is introduced, along with the optimal control problem definition; next, in Section III, numerical results describe the dynamics of hormones with the application of optimal dosage. Finally a discussion of the present topic is outlined with possible future developments and advances in

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Section IV.

II. MATERIALS AND METHODS

This section is dedicated to presenting the model used for the optimal control problem resolution. The aim is to find an optimal dosage $u_D^*(t)$ and $u_{EE}^*(t)$ (exogenous synthetic progestins and estrogens, like drospirenone and ethynilestradiol, in mg and in µg respectively) so that the system enters an anovulatory cycle, that is a menstrual cycle in which ovulation and the luteal phase are absent. Its duration may also differ from that of a regular menstrual cycle: in fact, the normal menstrual pattern may be disrupted, with women experiencing anovulatory cycles typically having shorter cycles.

For the purposes of this work, the anovulatory cycle has a central significance, being the state that must be reached by a woman that would like to achieve contraception. Usually, patients manage to do so by using a cyclic combined estrogen-progesterone or progestin supplementation like the *pill*. This pill contains synthetic forms of the hormones estrogen (ethynilestradiol) and progesterone (drospirenone), which are similar to the hormones naturally produced by the ovaries. The main mechanism of action of combined oral contraceptives is the inhibition of ovulation through the suppression of the hypothalamic-pituitary-ovarian axis. This is achieved by providing exogenous hormones that maintain relatively constant levels in the bloodstream, preventing the natural hormonal fluctuations that trigger ovulation. In particular, progesterone acts decreasing the pulse frequency of the gonadotropin-releasing hormone, which helps the stimulation of the pituitary gland and consequently the production of *LH* and *FSH* hormones. This, in turn, will reduce follicle-stimulating hormone (*FSH*) secretion and decrease luteinizing hormone (*LH*). The progestogen-negative feedback and lack of estrogen-positive feedback on *LH* secretion stop the mid-cycle *LH* surge.

A. The Model

The model employed is derived from the coupling of a model describing the pill pharmacokinetics, Σ_{PK}, and a highly nonlinear model describing hormonal fluctuations, Σ_{HD}; the latter modified by the pill intake is indicated by $\tilde{\Sigma}_{HD}$. This coupling is achieved through a series interconnection. Since the objective is to determine the effective dosage in mg (or µg), the control input $u(t)$ represents the actual mass of the hormone administered.

1) Pharmacokinetics: Pharmacokinetic modeling provides a well-defined mathematical description of how the effective drug dosage is absorbed by body tissues. A primary approach to modeling these dynamics is the use of compartmental modeling techniques: tissues are divided into so-called *compartments* based on the rate at which they assimilate the drug, [15]. Specifically, the resulting compartments represent the time course of serum concentration within the tissues. Typically, these models range from one to three compartments; however, in our case, a one-compartment model is sufficient. Furthermore, increasing complexity risks compromising the structural identifiability of the overall system. Additionally, it is necessary to define *how* the drug is administered and absorbed. A natural choice for this application is first-order absorption, which is modeled using a first-order ordinary differential equation (ODE). Usually, it is possible to graphically represent the compartments of such models, and in our case, it would take the form shown in Fig. 1. The mathematical model is therefore described as follows:

$$\frac{dA_D}{dt} = -k_{a,D}A_D + u_D(t) \tag{1}$$

$$\frac{dA_E}{dt} = -k_{a,E}A_E + u_E(t) \tag{2}$$

$$\frac{dC_D}{dt} = \frac{k_{a,D}}{V_D}A_D - k_D C_D \tag{3}$$

$$\frac{dC_E}{dt} = \frac{k_{a,E}}{V_E}A_E - k_E C_E \tag{4}$$

where the state A_i identifies the dosing compartment and the state C_i identifies the serum concentration compartment of the pill. The subscript i stands for the synthetic hormone that is chosen to be described: the choice is the combination of drospirenone (D) and ethynilestradiol (E); the parameters of the model, along with the numerical values assumed, are represented in Tab. I.

TABLE I: Parameter values for the Drospirenone-EE type of pill PK model.

Parameter	Description	Value [Unit]
$k_{a,D}$	Absorption rate (Drospirenone)	32.4 $[day^{-1}]$
$k_{a,E}$	Absorption rate (Ethinyl estradiol)	26.4 $[day^{-1}]$
k_D	Elimination rate (Drospirenone)	0.521 $[day^{-1}]$
k_E	Elimination rate (Ethinyl estradiol)	0.693 $[day^{-1}]$
V_D	Volume of distribution (Drospirenone)	4 [L]
V_E	Volume of distribution (Ethinyl estradiol)	4.5 [L]

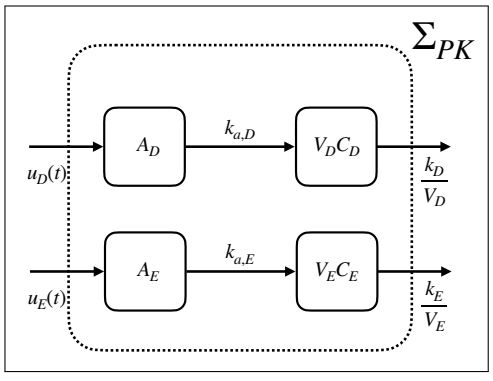


Fig. 1: Compartments graph: arrows entering a compartment indicate something that sums up to the state dynamics of that compartment; arrows going out indicate the rate at which the dynamics state is eliminated from that compartment. Since the compartments are four, the dimension of Σ_{PK} will be of $n = 4$.

2) Hormonal dynamics and coupling: Regarding hormonal dynamics, the selected model is the reduced Graham

model [9], derived from the validation and reduction of the model originally proposed in [8].

A key advantage of this model is that, unlike other models such as [16], it does not include time delays, significantly facilitating the simulation process. Furthermore, it exhibits superior parametric identifiability, as a reduction was performed during validation, resulting in a more streamlined representation. The original model dynamics Σ_{HD} is divided into three main subsystems, corresponding to three distinct dynamics: the *pituitary regulation* subsystem, the *follicle dynamics* subsystem and the *ovarian steroidogenesis* one. It is described as follows:

$$\frac{dFSH_\rho}{dt} = \frac{v_F}{1+c_{F,I}\frac{S\Lambda}{K_{i,F,I}+S\Lambda}} - k_F\frac{1+c_{F,P}P_4}{1+c_{F,E}E_2^2}FSH_\rho \tag{5}$$

$$\frac{dFSH}{dt} = \frac{1}{V}\cdot k_F\frac{1+c_{F,P}P_4}{1+c_{F,E}E_2^2}FSH_\rho - \delta_F FSH \tag{6}$$

$$\frac{dLH_\rho}{dt} = \left[\frac{v_{0L}+\frac{v_{1L}E_2^n}{K_{mL}^n+E_2^n}}{1+\frac{1}{P_4/K_{iL,P}}}\right] - k_L\frac{1+c_{L,P}P_4}{1+c_{L,E}E_2}LH_\rho \tag{7}$$

$$\frac{dLH}{dt} = \frac{1}{V}\cdot k_L\frac{1+c_{L,P}P_4}{1+c_{L,E}E_2}LH_\rho - \delta_L LH \tag{8}$$

$$\frac{d\Phi}{dt} = \left(\frac{f_1FSH^2}{h_1^2+FSH^2} - \frac{f_2LH^2}{h_2^2+LH^2}\right)\cdot\Phi \tag{9}$$

$$\frac{d\Omega}{dt} = \frac{f_2LH^2}{h_2^2+LH^2}\cdot\Phi - wS\Omega \tag{10}$$

$$\frac{d\Lambda}{dt} = wS\Omega - l(1-S)\Lambda \tag{11}$$

$$\frac{dS}{dt} = \frac{\hat{s}LH^4}{LH^4+h_s^4}(1-S) - \delta_S S \tag{12}$$

$$\frac{dE_2}{dt} = e_0 - \delta_E E_2 + t_{g1}\frac{LH}{LH+\kappa_2}\cdot(\Phi+\eta\Lambda S) \tag{13}$$

$$\frac{dP_4}{dt} = -\delta_P P_4 + p\Lambda S \tag{14}$$

where the states are: FSH_ρ, which is the releasable FSH; FSH which is the circulating follicle-stimulating-hormone; LH_ρ is the releasable LH; LH is the circulating luteinizing hormone; Φ represents the number of growing follicles during the follicular phase; Ω the number of follicles passing through the ovulation phase; Λ is the number of follicles in the luteal phase; S is the activation state; E_2 is the endogenous concentration of estrogen; finally P_4 is the endogenous concentration of progesterone. In the model, the *pituitary regulation* subsystem is composed by $FSH_\rho, FSH, LH_\rho, LH$; the *follicle dynamics* subsystem involves the states Φ, Ω, Λ, S, and the *ovarian steroidogenesis* subsystem regards the evolution of E_2 and P_4. The parameters of the model are in Tab. II. The influence of the drug on hormonal dynamics affects specific hormone production processes and follicular growth. This insight suggests a method for coupling the pharmacokinetic models with the hormonal model: the use of Hill functions is of fundamental importance here as well, given that biological reality does not exhibit instantaneous switching dynamics. Instead, it is characterized by continuous saturation over time, representing the activation or inhibition of specific processes. Based on the underlying physiology of these biological processes, it is known that the pill *inhibits* the endogenous production of E_2 and P_4, as well as the basal production of gonadotropins, specifically FSH_ρ and LH_ρ. Furthermore, it suppresses follicular growth; consequently, Φ is also affected, [17]. Specifically, the main processes that will be of our interest are the following:

- *Synthesis of the releasable pituitary hormones*: meaning that both

$$k_{FSH_\rho} = \frac{v_F}{1+c_{F,I}\frac{S\Lambda}{K_{i,F,I}+S\Lambda}},\ k_{LH_\rho} = \left[\frac{v_{0L}+\frac{v_{1L}E_2^n}{K_{mL}^n+E_2^n}}{1+\frac{1}{P_4/K_{iL,P}}}\right]$$

  will be affected by the drospirenone dynamics;
- *Follicular growth*: the function representing growth of follicles will be modified respectively:

$$k_{growth} = \frac{f_1FSH^2}{h_1^2+FSH^2}$$

- *Endogenous production of ovarian hormones*: the pill tricks the body in the production of endogenous hormones particularly the accumulation of both states E_2 and P_4 will be affected:

$$k_{basal,E} + k_{aromatization} = e_0 + t_{g1}\frac{LH}{LH+\kappa_2}\cdot(\Phi+\eta\Lambda S)$$
$$k_{secretion} = p\Lambda S$$

Then, the nonlinear modified model after taking the pill, $\tilde{\Sigma}_{HD}$, is given by:

$$\frac{dFSH_\rho}{dt} = \frac{v_F}{1+c_{F,I}\frac{S\Lambda}{K_{i,F,I}+S\Lambda}}(1-I_D) - k_F\frac{1+c_{F,P}P_4}{1+c_{F,E}E_2^2}FSH_\rho \tag{15}$$

$$\frac{dFSH}{dt} = \frac{1}{V}\cdot k_F\frac{1+c_{F,P}P_4}{1+c_{F,E}E_2^2}FSH_\rho - \delta_F FSH \tag{16}$$

$$\frac{dLH_\rho}{dt} = \left[\frac{v_{0L}+\frac{v_{1L}E_2^n}{K_{mL}^n+E_2^n}}{1+\frac{1}{P_4/K_{iL,P}}}\right](1-I_D) - k_L\frac{1+c_{L,P}P_4}{1+c_{L,E}E_2}LH_\rho \tag{17}$$

$$\frac{dLH}{dt} = \frac{1}{V}\cdot k_L\frac{1+c_{L,P}P_4}{1+c_{L,E}E_2}LH_\rho - \delta_L LH \tag{18}$$

$$\frac{d\Phi}{dt} = \left((1-I_E)(1-I_D)\frac{f_1FSH^2}{h_1^2+FSH^2} - \frac{f_2LH^2}{h_2^2+LH^2}\right)\cdot\Phi \tag{19}$$

$$\frac{d\Omega}{dt} = \frac{f_2LH^2}{h_2^2+LH^2}\cdot\Phi - wS\Omega \tag{20}$$

$$\frac{d\Lambda}{dt} = wS\Omega - l(1-S)\Lambda \tag{21}$$

$$\frac{dS}{dt} = \frac{\hat{s}LH^4}{LH^4+h_s^4}(1-S) - \delta_S S \tag{22}$$

$$\frac{dE_2}{dt} = (1-I_E)\left(e_0 + t_{g1}\frac{LH}{LH+\kappa_2}\cdot(\Phi+\eta\Lambda S)\right) - \delta_E E_2 \tag{23}$$

$$\frac{dP_4}{dt} = (1-I_D)p\Lambda S - \delta_P P_4 \tag{24}$$

where

$$I_i = \frac{C_i(t)^{n_{Hi}}}{EC_{50_i}^{n_{Hi}} + C_i(t)^{n_{Hi}}}, \quad i = D, E \tag{25}$$

and $C_i(t)$ represents the respective serum concentration. In the modified model, this mechanism is integrated by scaling the corresponding physiological processes by a factor of $(1 - I_i)$, depending on which active component of the pill governs the specific pathway. As detailed in Table III, both the half-maximal effective concentrations (EC_{50_i}) and the Hill coefficients (n_{Hi}) have been determined via calibration.

B. The Optimal control problem

The aim is to determine an optimal dose to ensure contraception. This involves suppressing surges in hormones such as LH and FSH, specifically those followed by an elevation P_4 that exceeds 5 ng/mL. The *optimal dosage* is obtained by minimizing the total mass $u(t)$ of synthetic hormone required to achieve contraception. From a mathematical point of view the problem can be defined as follows:

$$\text{minimize}_{x(t),u(t)} \int_{t_i}^{t_f} L(x(\tau),u(\tau))d\tau + G(x_f)$$

subject to:

$$\dot{x}(t) = f(x(t),u(t)), \quad x(t_i) = x_0 \tag{26}$$

$$u(t) \in U, \quad \forall t \in [t_i, t_f] \tag{27}$$

where $x(t)$ represents the state variables of the system (in this case, the hormone concentrations and other relevant physiological states); $u(t)$ represents the control variables (the doses of exogenous hormones); $f(x(t),u(t))$ represents the dynamics of the system, defined by the set of ordinary differential equations (ODEs) that govern the hormonal cycle; U is the set of admissible controls, which may include constraints on dosages (e.g., maximum allowable doses). Then, Pontryagin's Minimum Principle (PMP) provides necessary conditions for optimality in such problems.

Problem 1: Let (1)-(4) and (15)-(24) be the nonlinear dynamical system affine with respect to the control $u(t) = \begin{bmatrix} u_D(t) & u_E(t) \end{bmatrix}^\top$ with

$$y(t) = \begin{pmatrix} A_D & A_E & C_D & C_E \end{pmatrix}^\top,$$

$$z(t) = \begin{pmatrix} FSH_\rho & FSH & LH_\rho & LH & \Phi & \Omega & \Lambda & S & E_2 & P_4 \end{pmatrix}^\top$$

so that

$$x(t) = \begin{pmatrix} y(t) & z(t) \end{pmatrix}^\top \in \mathbb{R}_+^{14}$$

where $\mathbb{R}_+$ is the set of nonnegative real numbers. It is possible to rewrite the entire system in the following form:

$$\dot{x}(t) = f(x(t)) + Bu(t) \tag{28}$$

since the control enters linearly in the system, with

$$B = \begin{pmatrix} e_1 & e_2 \end{pmatrix} \in \mathbb{R}^{14\times 2} \tag{29}$$

where e_i is the canonical basis vector. Let $u(t) \in [0, u_{MAX}]$ and assume the following expression for the cost index:

$$J = \frac{1}{2}\int_0^T FSH^2(t) + LH^2(t) + u_D^2(t) + u_E^2(t)dt + \frac{x_f^\top x_f}{2} \tag{30}$$

The control must be assumed bounded to take into account limitations in dosage, $u^*(t) \in [0, u_{MAX}]$.

Theorem 1: The optimal control law that minimizes (30) and solves Problem 1 is:

$$u^*(t) = \frac{u_{MAX}}{2}\left[1 - sat\left(\frac{2B^\top \lambda(t)}{u_{MAX}} + 1\right)\right] \tag{31}$$

Proof: The Hamiltonian is given by the following form:

$$\begin{aligned} H(x,u,\lambda,t) &= FSH^2 + LH^2 + u_D^2 + u_E^2 + \lambda^\top(t)\big[f(x) + Bu(t)\big] \\ &= x^\top Qx + u^\top u + \lambda^\top(t)\big[f(x) + Bu(t)\big] \end{aligned}$$

Then, from the Pontryagin inequality:

$$H(x,\omega,\lambda,t) \geq H(x,u^*,\lambda,t), \quad \forall \omega \in U \tag{32}$$

one gets:

$$\omega^\top \omega + \lambda(t)^\top B\omega \geq u^{*\top}u^* + \lambda(t)^\top Bu^*, \quad \forall \omega \in U \tag{33}$$

by adding both sides $\frac{\lambda^\top BB^\top \lambda}{4}$ one obtains:

$$\begin{aligned} &\left(\omega + \frac{B^\top\lambda(t)}{2}\right)^\top \left(\omega + \frac{B^\top\lambda(t)}{2}\right) \geq \\ &\geq \left(u^* + \frac{B^\top\lambda(t)}{2}\right)^\top \left(u^* + \frac{B^\top\lambda(t)}{2}\right), \quad \forall \omega \in U \end{aligned}$$

From which the theorem is proved. ■

Remark 1: This optimal control problem does not present any singular solutions since the cost index is quadratic and the Lebisch conditions on the Hamiltonian are satisfied:

$$\nabla_u H = 0, \quad \nabla_u^2 H > 0$$

III. NUMERICAL RESULTS

In this section, it is shown how optimal control laws were derived through simulations; they were implemented in Python 3 using the CasADi software framework and its integrated IPOPT solver. Since the optimization problem is non-convex, multiple candidates for optimality (local optima) exist, presenting an additional challenge in determining the appropriate starting point for the algorithm. Consequently, within the CasADi environment [18], the model using the protocols of existing pills containing the same active ingredients (specifically, drospirenone and ethinylestradiol) were simulated over a three-month period: *Yasminelle*, *Yaz*, and *Yasmin*. The solution converged to three distinct optimal candidates, depicted in Fig. 2a, 3a and 4a, one for each corresponding initial guess (i.e., one for each simulated pill protocol). The pill protocol has been simulated by knowing that one period blister is always $T = 28$, in particular:

$$T = T_{con} + T_{sus}$$

where T_{sus} is the suspension period of the selected pill protocol. Therefore, the control law that describes the normal intake is the following:

$$u(t) = \begin{cases} \sum_{j=1}^m D_i \delta(t - t_j) & t_j \in \Omega_t \\ 0 & \text{otherwise} \end{cases} \tag{34}$$

where D_i is the quantitative dosage of the i-th hormone, $\delta(t - t_j)$ is the impulse at time $t = t_j$ and

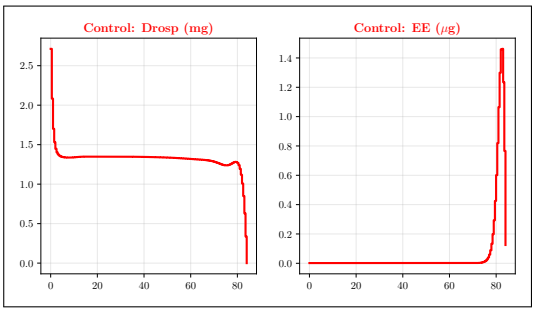
$$\Omega_t = \{t \in \mathbb{R} \colon k(T_{cont} + T_{sus}) \leq t \leq (k+1)T_{cont} + kT_{sus}, \forall k \in \mathbb{N}\}$$

Along with the optimal control solutions, the reference states obtained by applying the optimal control found, for identifying anovulatory cycles, are also depicted in Figs. 2 3 and 4: FSH and LH are monitored to check for the occurrence of so-called *surges* (spikes of hormonal concentrations in a brief time period like 2 days), potentially followed by high concentrations of E_2 and P_4. Ultimately, the levels of all hormones remain low throughout the simulation period, suggesting that the identified optimal therapy leads to anovulatory cycles and, consequently, contraception. About total dosage, the lowest intake of drospirenone among the three candidates is the one associated to the Yasmin initial guess with a total of 107.2 mg in 3 months, in Fig. 4a; while the lowest intake of ethinylestradiol is the optimal solution associated to the Yaz initial guess, with a total of 0.096 µg in 3 months, in Fig. 3a. In general, the total amount of drug intake in all the determined optimal candidates are lower than the total intake of the associated initial guess. Another challenge encountered during the simulations concerned solver stability: the discretization of the optimal control problem was addressed using a Direct Multiple Shooting approach. The time horizon was divided into control intervals of length $dt = 0.5$ days. However, employing a single 4th-order Runge-Kutta (RK4) integration step to span the entire interval dt proved insufficient due to the stiffness of the hormonal dynamics. To ensure the numerical stability of the explicit integrator and guarantee that the integration step size $h = dt/N_{sub}$ remained within the absolute stability region of the RK4 method, a substepping technique was implemented. Specifically, within each control interval, the system dynamics are integrated using 20 intermediate substeps ($N_{sub} = 20$).

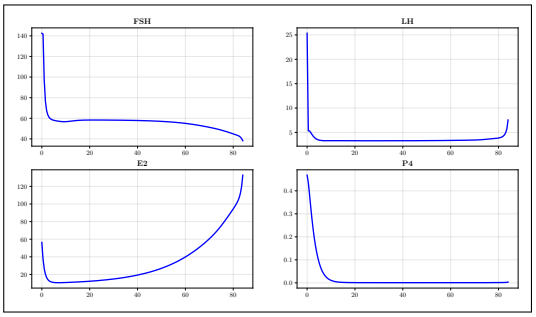
From the figures, it can be observed that the optimal control does not exhibit a purely *bang-bang* behavior. This suggests that the control signal remains within the bounds (i.e., it does not reach saturation).

IV. CONCLUSIONS

In this paper, an optimal control problem for therapy dosage is faced, yielding solutions significantly more realistic than the state of the art by coupling a pharmacokinetic (PK) model with a highly nonlinear hormonal one. The approach is tested on three existing pills with identical active ingredients, comparing hormone levels and total requested dosages while accounting for inter-patient variability to reflect physiological constraints. Ongoing data acquisition for model validation is proving highly complex due to the low number of patients willing to undergo invasive daily blood tests, thus demanding the search for improved, less invasive monitoring techniques.

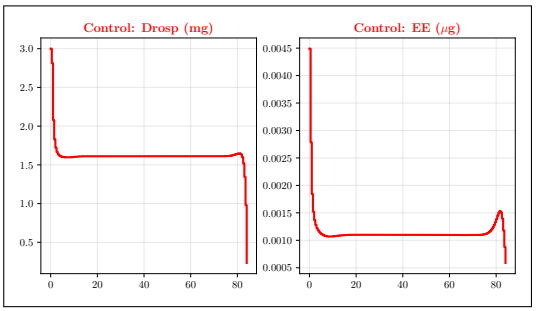


(a) Optimal control if the initial guess are the evolutions obtained with the Yasminelle intake.

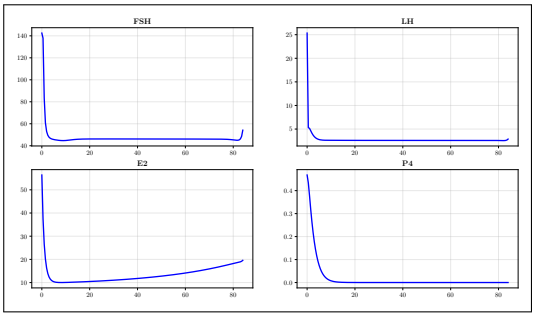


(b) Optimal trajectories of FSH, LH, E_2 and P_4 if the initial guess are the evolutions obtained with the Yasminelle intake.

Fig. 2: Optimization results considering Yasminelle intake as initial guess.

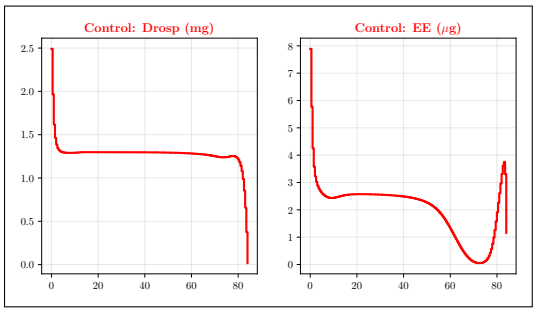


(a) Optimal control if the initial guess are the evolutions obtained with the Yaz intake.

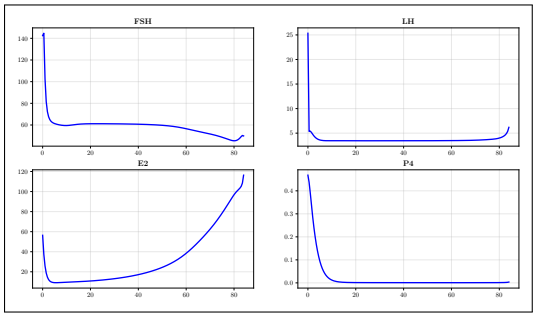


(b) Optimal trajectories of FSH, LH, E_2 and P_4 if the initial guess are the evolutions obtained with the Yaz intake.

Fig. 3: Optimization results considering Yaz intake as initial guess.



(a) Optimal control if the initial guess are the evolutions obtained with the Yasmin intake.



(b) Optimal trajectories of FSH, LH, E_2 and P_4 if the initial guess are the evolutions obtained with the Yasmin intake.

Fig. 4: Optimization results considering Yasmin intake as initial guess.

TABLE II: Parameter values used in Σ_{HD}.

Parameter	Unit	Value
$c_{F,E}$	$(\text{ng/L})^{-2}$	0.0024047
$c_{F,I}$	#	3.0188
$c_{F,P}$	$(\mu\text{g/L})^{-1}$	65.229
$c_{L,E}$	$(\text{ng/L})^{-1}$	0.00068867
$c_{L,P}$	$(\mu\text{g/L})^{-1}$	0.015844
δ_F	1/d	8.21
δ_L	1/d	14
k_F	1/d	3.0212
$K_{iF,I}$	μg	149.76
$K_{iL,P}$	μg/L	3.2279
K_{mL}	μg/L	226.37
k_L	1/d	0.67146
n	#	8
V	L	2.5
v_{0L}	μg/d	308.35
v_{1L}	μg/d	44700
v_F	μg/d	3219.9
δ_S	1/d	0.38256
f_1	1/d	1.0958
f_2	1/d	46.225
h_1	μg/L	146.31
h_2	μg/L	798.39
h_s	μg/L	11.691
l	1/d	0.64178
$\hat{s}$	1/d	2.6338
w	1/d	0.23497
δ_E	1/d	1.1
δ_P	1/d	0.5
e_0	ng/L·d	9.6377
η	#	0.81426
κ_2	μg/L	8.276
p	1/L·d	0.22851
t_{g1}	ng/L·μg·d	6.3594

TABLE III: New parameter values introduced with the Hill functions needed for the coupling.

Parameter	Description	Value [Unit]
EC_{50_D}	Half-maximal (Drospirenone)	2 [mg/L]
EC_{50_E}	Half-maximal (Ethinyl estradiol)	10 [μg/L]
n_{HD}	Hill constant (Drospirenone)	2 [#]
n_{HE}	Hill constant (Ethinyl estradiol)	2 [#]

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