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PhD THESIS SUMMARY

Control Delay Differential Equations with Applications in Engineering and Medicine

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Delay Differential Equations (DDEs) are an important part of mathematical modeling and an accurate way to explain natural processes. DDEs are commonly used in various disciplines, such as medicine, finance, statistics, chemistry or engineering.

This type of differential equations can be applied in modeling a vehicle's flight, where the delay can be represented as the period elapsed from the moment the order was sent, to when it occurred, or in medicine, where DDEs can model, e.g. the reaction to treatment in a hematological disorder.

This thesis focuses on the analysis of some mathematical models described by delay differential systems from different fields. The first two are from aviation engineering and consist in modeling the *longitudinal flight of two unmanned aerial vehicles*, and the last two examples come from medicine and describe the *cellular evolution in Chronic Myeloid Leukemia* (CML).

The present work is composed of three chapters. The first chapter presents the mathematical framework; the next chapter presents the aviation framework and stability analysis of two UAV models, and the final chapter gives some biological aspects and the stability study of equilibria in two CML models.

In **Chapter 1**, we provide a brief presentation of DDEs theory. For the stability study of DDEs using the characteristic equation, we evoke some important theorems and the method of Lyapunov-Krasovskii functionals. We recall the theorem used for the existence of Hopf bifurcations and the theorem for stability by the first approximation.

In the first part of the **Chapter 2**, **Flight models**, we present the general information about the unmanned aerial vehicles (UAVs) and the general mathematical flight model for UAVs.

In the second part, we introduce two original mathematical models that describe the longitudinal flight of the UAVs. Three delay differential equations represent each mathematical model of the two UAVs that describe the evolution of the longitudinal flight at a specific moment when the automatic flight control system (AFCS) is decoupled and a feedback control is introduced.

The system of delay differential equations describing the longitudinal flight of ALFLEX

model with feedback control delay is represented by the next equations:

$$\begin{aligned}\dot{\alpha} =& a_{11}(\alpha - \alpha_0) + q + \varepsilon(\cos\theta - \cos\theta_0) + b_1 k_1[\cos\theta(t-\tau) - \cos\theta_0] \\ \dot{q} =& a_{21}(\alpha - \alpha_0) + a_{22} q + b_2 k_1[\cos\theta(t-\tau) - \cos\theta_0] \\ \dot{\theta} =& q\end{aligned} \tag{2.4}$$

Sufficient parameter conditions for the *stability* of equilibria arise from the study of the characteristic equation corresponding to the model.

For the same model was demonstrated the *stability of the limit cycle* by computing the first Lyapunov coefficient. The numerical simulations presented for this model validate the results.

Theorem 2.1. *[49] If the Lyapunov coefficient $l_1(0)$ is negative, periodic solutions (limit cycles) exist, for equations (2.4), if $\tau > \tau^*$, τ close to τ^*, and are orbitally stabe. They exist for $\tau < \tau_c$ and are unstable if $l_1(0) > 0$. Their period increases if $T_2 > 0$ and decreases for $T_2 < 0$.*

Proposition 2.4. *In the configuration of parameters given in Appendix A, the limit cycle that arises at $\tau > \tau^*$, τ close to τ^* is orbitally stable.*

For the second model, we give *sufficient parameter conditions* for stability using a Lyapunov-Krasovskii functional, as an analytic study of the characteristic equation is not possible. The result is described in Proposition 2.5

The longitudinal flight of ADMIRE can be described by a system of DDEs with a feedback control delay:

$$\begin{aligned}\dot{\alpha} &= m_{11}\alpha + m_{12} q + c\cos\theta + b_1 k_1 \alpha(t-\tau_1) + b_1 k_2 q(t-\tau_2) + b_1 k_3 \theta(t-\tau_2) \\ \dot{q} &= m_{21}\alpha + m_{22} q + c m_0 \cos\theta - c c_1 \sin\theta + b_2 k_1 \alpha(t-\tau_1) \\ &\quad + b_2 k_2 q(t-\tau_2) + b_2 k_3 \theta(t-\tau_2) \\ \dot{\theta} &= q.\end{aligned}$$

Proposition 2.5. *Assume the following conditions hold:*

$$\tilde{A}_1 = \beta_1 + \alpha_1(2m_{11} - b_1k_3 + 2m_{12} + 2m_{21} + b_1k_1) < 0$$

$$\tilde{A}_2 = \alpha_2(2m_{22} - a_{23} - b_2k_1 - b_2k_2 - b_2k_3 + 2m_{21} - 1) + 2\alpha_3 + \gamma_2 < 0$$

$$\tilde{A}_3 = -\alpha_2 a_{23} - \alpha_2 b_2 k_3 + \gamma_3 > 0$$

$$B_1 = -\alpha_1 b_1 k_1 - \beta_1 < 0$$

$$B_2 = -\alpha_1 b_1 k_2 - \alpha_2 b_2 k_2 - \gamma_2 < 0$$

$$B_3 = -\alpha_1 b_1 k_3 - \alpha_2 b_2 k_3 - \gamma_3 < 0$$

Then the equilibrium point is stable, independent of delays.

In **Chapter 3**, entitled **CML models**, first, we present the biological aspects and the notations that will be used in illustrating the models. Second, we present two mathematical models that describe the response to CML in two different situations.

The first model consists of 9 DDEs with 9 delays, which explains the immune system reaction to CML, taking into account the competition between leukemia and healthy cells.

The original results for this model, are the alternative we found, the rank-one perturbations, to handle the characteristic equation corresponding to $E_3$and E_4, and the *sufficient parameter conditions* for *stability* of the equilibrium point E_3. Numerical simulations showed that in a low number of healthy cells, the state of the patient may worsen or the patient may recover based primarily on the number of leukemic cells.

The second model includes 5 DDEs with 5 delays, which takes into account immune response and treatment resistance in the dynamic response of healthy and leukemic populations exposed to treatment.

The first four equations descriebe the time-evolution of healthy and CML cell populations and the last equation represnts the evolution of the immune cell population.

The state variables of the model are the healthy and leukemic cell populations with self-renewal ability (x_1 and x_3) called stem-like cells, mature healthy and leukemia leukocytes (x_2 and x_4) which lost their self-renewal ability and the immune system represented by the population of anti-leukemia cells CD8+ cytotoxic T-cells (x_5).

The system that models CML under Imatinib treatment is:

$$\begin{aligned}
\dot{x}_1 = \; & -\gamma_{1h}x_1 - (\eta_{1h}+\eta_{2h})k_h(x_2+x_4)x_1 - (1-\eta_{1h}-\eta_{2h})\beta_h(x_1+x_3)x_1 + \\
& +2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_h(x_{1\tau_1}+x_{3\tau_1})x_{1\tau_1} + \eta_{1h}e^{-\gamma_{1h}\tau_1}k_h(x_{2\tau_1}+x_{4\tau_1})x_{1\tau_1} \\
\dot{x}_2 = \; & -\gamma_{2h}x_2 + A_h(2\eta_{2h}+\eta_{1h})k_h(x_{2\tau_2}+x_{4\tau_2})x_{1\tau_2} \\
\dot{x}_3 = \; & -(\gamma_{1l}+k_1)x_3 - (\eta_{1l}+\eta_{2l})u_1k_l(x_2+x_4)x_3 - (1-\eta_{1l}-\eta_{2l})u_1\beta_l(x_1+x_3)x_3 + \\
& +2e^{-\tilde{\gamma_{1l}}\tau_3}(1-\eta_{1l}-\eta_{2l})u_1\beta_l(x_{1\tau_3}+x_{3\tau_3})x_{3\tau_3} + \eta_{1l}e^{-\tilde{\gamma_{1l}}\tau_3}u_1k_l(x_{2\tau_3}+x_{4\tau_3})x_{3\tau_3} - \\
& -b_1x_3x_5l_1(x_3+x_4) \\
\dot{x}_4 = \; & -\gamma_{2l}x_4 + A_l(2\eta_{2l}+\eta_{1l})u_1k_l(x_{2\tau_4}+x_{4\tau_4})x_{3\tau_4} - b_2x_4x_5l_1(x_3+x_4). \\
\dot{x}_5 = \; & -a_2x_5 - a_3u_2x_5l_2(x_4) + 2^{n_1}a_3e^{-a_2\tau_T}u_2x_{5\tau_5}l_2(x_{4\tau_5})
\end{aligned}$$

Where the controls k_1, u_1 and u_2 depend also on the solutions P of the following system, describing the pharmakodynamics.

$$\begin{aligned}
\dot{D} &= -\lambda_0 D + K \\
\dot{P} &= -\nu P + \lambda D
\end{aligned}$$

D is the concentration of Imatinib in the absorbtion compartment and P is the concentration of the active substance in the plasmatic compartment.

The model has four possible types of equilibrium points. The first two equilibrium points represent the death of the patient, (0,0,0,0,0), and a healthy state, $(x_1^*, x_2^*, 0, 0, 0)$. The stability of these points cannot be studied by linear approximation since, in the presence of resistence, the derivative with respect to x_3 in zero becomes infinite.

A Lyapunov-Krasovskii functional was used to provide *sufficient parameter conditions* for stability for the last two equilibrium points that represents an acute state $(0, 0, x_3^*, x_4^*, x_5^*)$ and a chronic state $(\hat{x_1}, \hat{x_2}, \hat{x_3}, \hat{x_4}, \hat{x_5})$. The numerical simulations performed for this model illustrate the effect of drug resistance cells on the evolution of the patient and the existence of periodic behaviour.

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