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Optimization of the force exerted by the synergistic treatment-immune response interaction

Optimización de la fuerza ejercida por la interacción sinérgica tratamiento-respuesta inmunitaria

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Keywords

Optimization, Dynamical systems, Antimicrobial resistance, Plasmids, Immune response, Synergy.

Abstract: In physics, synergy is an action that involves the coordination of two or more causes or parts, whose effects will be greater than the sum of the individual effects. Measuring the synergistic strength of the treatment and the immune response working together is of vital importance to control physicochemical parameters in bacterial infections. In this sense, in this article we focus on analyzing the impact of synergy through an optimal control problem. To formulate and solve the problem we use conservation laws that characterize the main properties of the physical phenomenon. Specifically, we use the Pontryagin Minimum Principle to minimize a performance functional that measures the strength of the synergy between treatment and immune response. The numerical results suggest that the forces synergies must be proportional to each other to control bacterial spread.

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Palabras clave

Optimización, Sistemas dinámicos, Resistencia antimicrobiana, Plásmidos, Respuesta inmune, Sinergia.

Resumen: En física, la sinergia es una acción que implica la coordinación de dos o más causas o partes, cuyos efectos serán mayores que la suma de los efectos individuales. Medir la fuerza sinérgica del tratamiento y la respuesta inmune trabajando conjuntamente es de vital importancia para controlar los parámetros fisicoquímicos en las infecciones bacterianas. En este sentido, en este artículo nos centramos en analizar el impacto de la sinergia a través de un problema de control óptimo. Para formular y resolver el problema utilizamos leyes de conservación que caracterizan las principales propiedades del fenómeno físico. En concreto, utilizamos el Principio Mínimo de Pontryagin para minimizar un funcional de rendimiento que mide la fuerza de la sinergia entre el tratamiento y la respuesta inmune. Los resultados numéricos sugieren que las sinergias de las fuerzas deben ser proporcionales entre sí para controlar la propagación bacteriana.

Introduction

Antimicrobial resistance (AMR) of microorganisms such as bacteria is among the latent threats to public health worldwide. Due to the fact that humanity had to focus its efforts on overcoming the Covid-19 pandemic, the surveillance of critical factors in public health, such as antimicrobial resistance, was neglected. Transmission of resistant bacteria to multiple antibiotics increased. Mainly, the acquisition of resistance due to the transfer of resistance genes carried by resistance plasmids is generating a global emergency (Ibargüen-Mondragón et al., 2022).

Through dynamical systems, different characteristics of AMR have been addressed. The approaches that assess the impact of these drugs (Udekwu & Weiss, 2018), or optimize their use (Lowden et al., 2014) (Massad et al., 2008), or those that focus on the importance of the immune response (Handel et al., 2009), or the fight of the immune system against antimicrobial resistance (Ibargüen-Mondragón & Esteva, 2013), or develop antimicrobial protocols (Udekwu & Weiss, 2018) (Leung (Joey) & Weitz, 2017).

The synergy between the immune system and drugs is a fundamental factor in controlling the spread of antimicrobial resistance within the host (Leung (Joey) & Weitz, 2017). Similarly to (Landersdorfer et al., 2013) (Ankomah & Levin, 2014), several synergistic properties and immune response were analized for combination of antibiotics.

Dynamics of bacterial competition within the host

The mathematical model that describe de competition dynamics of bacteria is giveng by:

$$\begin{aligned}\frac{dS}{dt} &= \beta_s S\left(1-\frac{S+R}{K}\right) - qS - \delta PS - \mu_s S\\ \frac{dR}{dt} &= \beta_r S\left(1-\frac{S+R}{K}\right) + qS + \delta PS - \mu_r R\\ \frac{dP}{dt} &= \sigma_p R - \mu_p P,\end{aligned} \tag{1}$$

where $S(t)$ and $R(t)$ are the number of drug-sensitive and pre-existing resistant bacteria in the host at time t, respectively and $P(t)$ is the number of plasmids in the host at time t. K is the carrying capacity. β_s and β_r are the reproduction rates of bacteria, sensitive and resistant, respectively, where q is the mutation rate of sensitive bacteria due to exposure to antibiotics, μ_s and μ_r are per capita natural death rates of bacteria, sensitive and resistant respectively, δ is the transfer rate of resistant plasmids among bacteria., σ_p is the plasmid replication rate, and they degrade at a constant rate μ_p.

The invariant set for the solutions of system (1) is

$$\Omega = \{(S,R;\ P) \in (\mathbb{R}^0_+)^3 : 0 \leq S + R \leq K, 0 \leq P \leq \sigma_p K/\mu_p\}. \quad (2)$$

In fact, we have the following result

Proposition 1. *The set Ω defined in Equation (2) is positively invariant for the solutions of Equation (1).*

For the proof of Proposition 1 see Lema 2.1 in (Ibargüen-Mondragón et al., 2019). The existence of equilibria is condensed in Proposition 2.

Proposition 2. *Let*

$$R_r = \frac{\beta_r}{\mu_r} \text{ and } R_s = \frac{\beta_s}{q + \mu_s}, \quad (3)$$

Equation (1) *always has a trivial point* E_0= (0,0,0). *If* $R_r > 1$, *there exists an endemic point* $E_1 = \left(0, \frac{(R_r-1)K}{R_r}, \frac{\sigma_p}{\mu_p}\frac{(R_r-1)K}{R_r}\right)$ *If* $R_s > 1$ *and* $R_r < R_r^*$, *there exists an endemic point* $E_2=(S_2,R_2,P_2)$ *where*

$$R_r^* = \frac{1 - \frac{1}{R_s}}{1 + \frac{\delta\sigma_p K}{\beta_s \mu_p}}.$$

For the proof of the Proposition 2 see Proposition 3.1 in (Ibargüen-Mondragón et al., 2021). The stability results of equilibrium solutions are condensed in Proposition 3.

Proposition 3. *If* $R_s \leq 1$ *and* $R_r \leq 1$ *then* E_0 *is globally asymptotically stable in the set Ω defined in Equation (2). If* $R_r > 1$ *and* $R_s \leq 1$, *then* E_1 *is globally asymptotically stable in Ω defined in Equation (2). If* σ_p δ *small enough, the equilibrium* E_2 *is locally asymptotically stable in Ω. In addition, when* E_2 *loses its stability, the existence of a hopf bifurcation is verified.*

Proof. The global stability of E_0 and E_1 are followed from the Liapunov's direct method using the functions $V = S/\beta_s + R/\beta_r$ and $V=S$, respectively. The Local stability of E_2 is followed from the The Routh-Hurwitz criterium (see (Ibargüen-Mondragón et al., 2019)) to the proof of the Hopf bifurcacion see (Ibargüen-Mondragón et al., 2021).

Qualitative analysis reveals the following scenarios can be deduced (Ortega Bejarano et al., 2018):

(i): An infection can always be cleared (the global stability of E_0 when $R_s \leq 1$ and $R_r \leq 1$).

(ii): An infection can progress only with resistant bacteria (the global stability of E_1 when $R_s \leq 1$ and $R_r \leq 1$).

(iii): An infection can progress with the coexistence of both types of bacteria (the local stability of E_2 when $\delta\sigma_p << 1$, $R_s > 1$ and $R_r \leq R_r^*$, or the appearance of limit cycles when E_2 loses its stability).

Optimal control problem

The mathematical modeling that we will carry out reduces the bacterial population in a fixed period. In this sense, the strategies to control bacterial progression are the immune response and antibiotic treatment. u_1 (t) and u_2 (t) are the elimination rate of sensitive bacteria due to action of antibiotic treatment and elimination rate of sensitive and resistant bacteria due to specific immune response, respectively. Equation (1) is rewritten as

$$\begin{aligned}
\frac{dS}{dt} &= \beta_s S\left(1 - \frac{S+R}{K}\right) - (q + u_1(t))S - \delta PS - u_2(t)S - \mu_s S \\
\frac{dR}{dt} &= \beta_r R\left(1 - \frac{S+R}{K}\right) + qS + \delta PS - u_2(t)R - \mu_r R \\
\frac{dP}{dt} &= \sigma_p R - \mu_p P
\end{aligned} \quad (4)$$

with $S(0) = S_0 \geq 0$, $R(0) = R_0 \geq 0$ and $P(0) = P_0 \geq 0$. The cost function is

$$I(x,u_1,u_2) = \frac{1}{2}\int_0^T [c_1(S^2+R^2) + c_2S^2 + c_3u_1^2 + c_4u_2^2]\,dt \quad (5)$$

where $x = (S,R,P)^T$, c_1, c_2, c_3 and c_4 are relative weights associated with the e ciency of the bacterial elimination by the immune system, effectiveness

of the elimination of sensitive bacteria by the treatment, u_1 and u_2, respectively. Functional I defined in Equation (5) measures the cost associated to antibiotic treatment and stimulation of the immune response. Minimization process of I is subjected to state Equation (4) and the boundary conditions

$$x(0) = x_e \ \ and \ x(T) = x_f, \qquad (6)$$

where the initial state x_e is an endemic equilibrium or a limit cycle of Equation (1) and the final state x_f is variable.

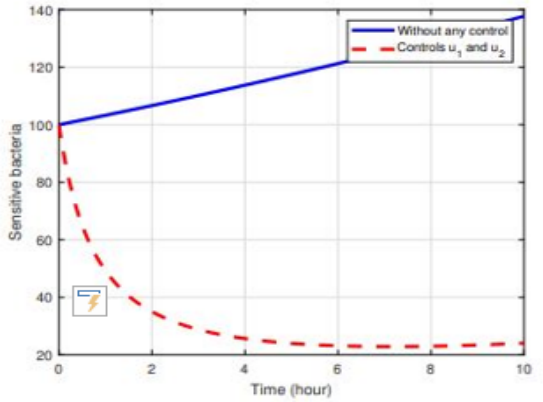
Deduction of an optimal solution

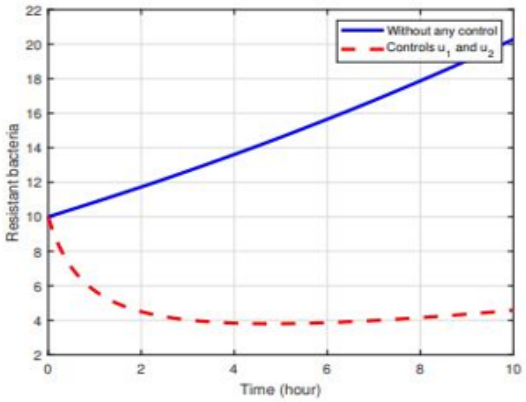
With the purpose of optimizing bacterial elimination rates, we consider the following Hamiltonian function

$$\begin{aligned} H(t,x,u,z) = {} & \frac{1}{2}[c_1(S^2+R^2) + c_2S^2 + c_3u_1^2 + c_4u_2^2] \\ & + z_1\left[\beta_s S\left(1-\frac{S+R}{K}\right) - (q+u_1)S - \delta PS - u_2S - \mu_s S\right] \\ & + z_2\left[\beta_r R\left(1-\frac{S+R}{K}\right) + qS + \delta PS - u_2R - \mu_r R\right] \\ & + z_3\left(\sigma_p R - \mu_p P\right), \end{aligned} \qquad (4)$$

where z_i for i =1,...,3 are the adjoint variables that determine the adjoint system. From Hamiltonian defined in Equation (8) we deduced the following adjoint system

$$\begin{aligned} \frac{dz_1}{dt} &= -(c_1+c_2)S + \left[-\beta_s\left(1-\frac{2S+R}{K}\right) + (q+u_1+\delta P+u_2+\mu s))\right]z_1 \\ &\quad + \left[\frac{\beta_r R}{K} - (q+\delta P)\right] z_2 \\ \frac{dz_2}{dt} &= -c_1R + \frac{\beta_s S}{K}z_1 - \sigma_p z_3 + \left[u_2+\mu_r - \beta_r\left(1-\frac{S+2R}{K}\right)\right]z_2 \\ \frac{dz_2}{dt} &= \delta S(z_1-z_2) + \mu_p z_3, \end{aligned} \qquad (8)$$





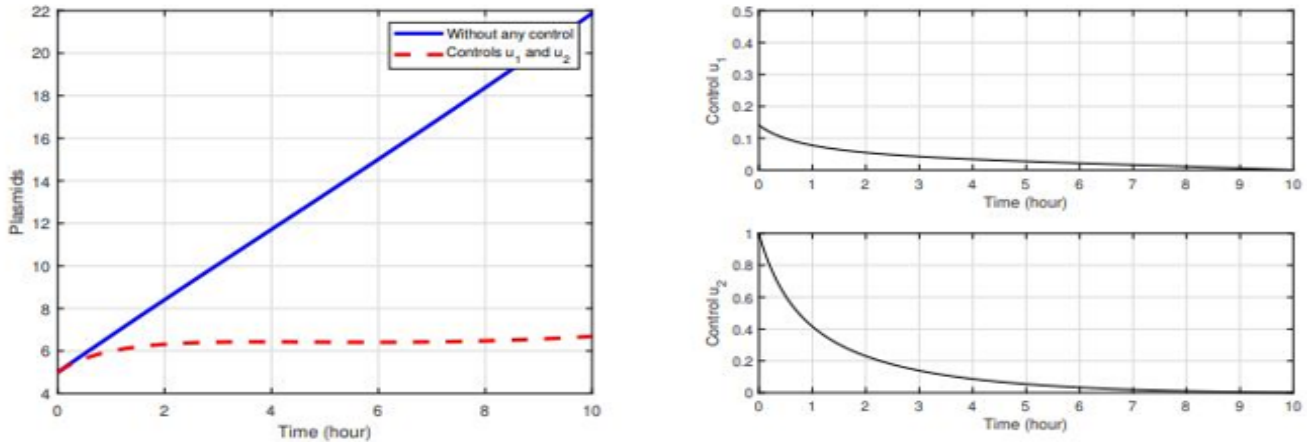


Figure 1. Numerical simulations of the control problem defined in Equations (4-6). The synergistic collaboration between the controls u_1 and u_2 allows the elimination of both bacterial populations (These simulations were carried out in MATLAB 2022B (Lic Universidad de Nariño)).

with transversality condition $z_i(t) = 0$ for $i = 1,...,3$. The optimal conditions for the Hamiltonian are given by $\partial H/\partial u_1^* = \partial H/\partial u_2^* = 0$, or equivalently

$$\frac{\partial H}{\partial u_1} = c_3 u_1 - z_1 S = 0$$

$$\frac{\partial H}{\partial u_2} = c_3 u_2 - z_1 S - z_2 R = 0.$$

From the above equations, we obtain

$$u_1 = \frac{z_1 S}{c_3}$$

$$u_2 = z_1 S + \frac{z_2 R}{c_4}$$

Numerical results

We use the *forward-backward sweep method* to perform numerical simulations of the optimal control problem defined in Equations (4-6), (Ankomah & Levin, 2014). To analyze the relation between the control variables u_1 and u_2 during the reduction of the bacterial population, we simultaneously activate both controls. The numerical simulations of the Figure 1 were performed with the following values β_s=2.4,β_r=0.2,q=0.0063785,μ_s=0.2,μ_r=0.18,σ_p=0.25 ,δ=10^{-6},μ_p=0.15 and K=20000. Figure 2 were made with the same values, except for δ=10^{-7} . The values of the relative weights used for the Figure u_1 are c_1=10^{-8},c_2=2*10^{-7},c_3=0.02 and c_4=0.01. For Figure u_2 the values of the relative weights were c_1=10^{-7},c_2=2*10^{-8},c_3=0.02 and c_4=1.1.

As we can see, in the Figure 1 the progression of both bacterial populations is controlled due to the synergistic collaboration of both controls. While in the Figure 2, the control u_2 is not activated, which prevents the control of the progression of resistant bacteria.

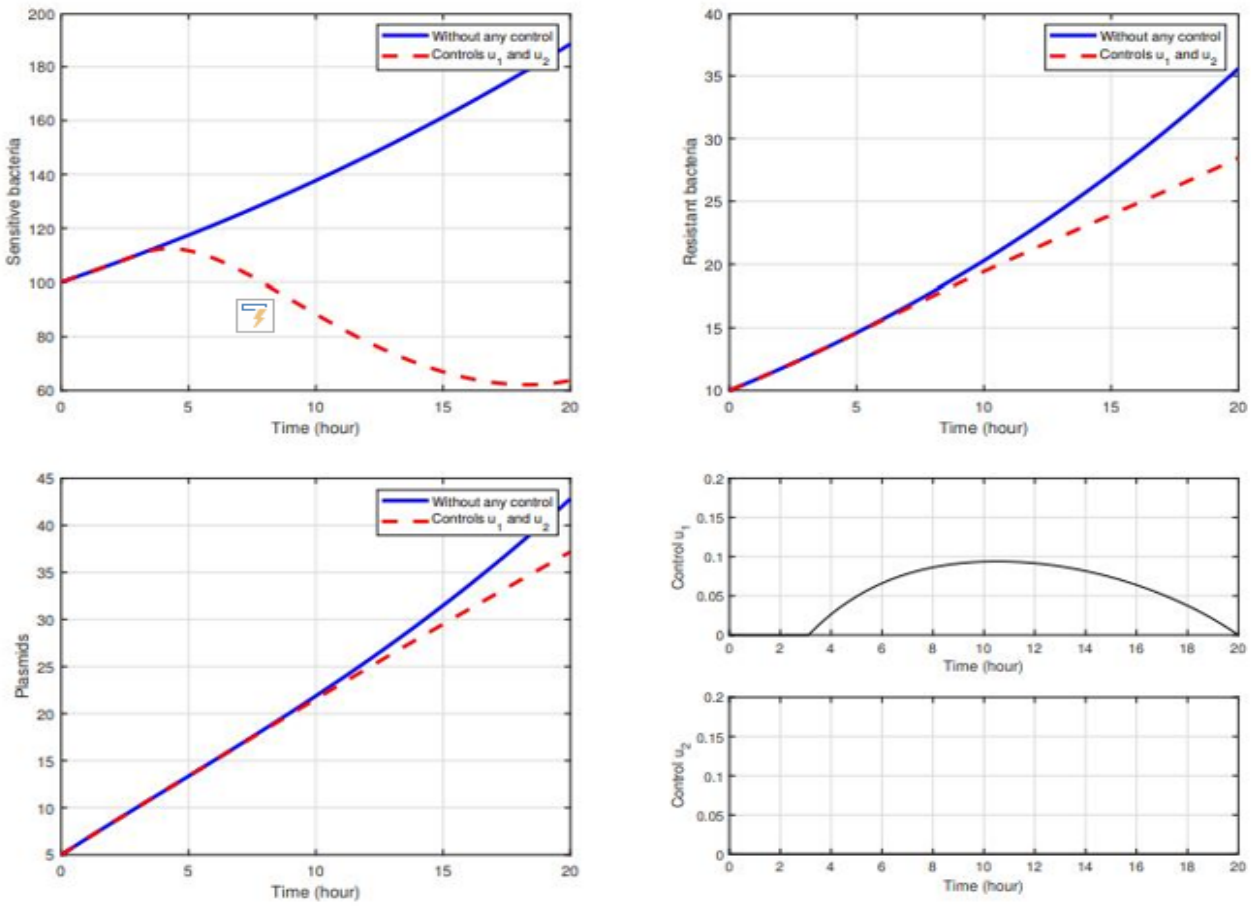


Figure 2. Numerical simulations of the control problem defined in Equations (4-6). In this case, there was no synergistic collaboration between the controls u_1 and u_2 due to u_2 was not activated. (These simulations were carried out in MATLAB 2022B (Lic Universidad de Nariño)).

Conclusion

It is a fact that the synergy between the immune system and the therapeutic action of drugs is of great relevance in the epidemiological surveillance of antimicrobial resistance. For this reason, both the models between and within the host are part of the necessary tools to face this challenge. In this work, we contribute with the analysis of an optimal control problem that arises from the model within the host. The results suggest that at this level, it is necessary to enhance the synergy of both factors in favor of the host.

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