


Research Article

Analysis and Control of the Bacterial Meningitis Disease Model

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Received: 13 October, 2025

Accepted: 21 October, 2025

Published: 22 October, 2025

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Keywords: Bifurcation; Optimization; Control; Meningitis; Multiobjective; Limit cycle; Therapy; Diagnosis

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Abstract

In this study, bifurcation analysis and multiobjective nonlinear model predictive control is performed on a bacterial meningitis disease model. Bifurcation analysis is a powerful mathematical tool used to deal with the nonlinear dynamics of any process. Several factors must be considered, and multiple objectives must be met simultaneously. The MATLAB program MATCONT was used to perform the bifurcation analysis. The MNLMPC calculations were performed using the optimization language PYOMO in conjunction with the state-of-the-art global optimization solvers IPOPT and BARON. The bifurcation analysis revealed the existence of Hopf bifurcation point, limit and branchpoint. The MNLMC converged to the utopia solution. The Hopf bifurcation point, which causes an unwanted limit cycle, is eliminated using an activation factor involving the tanh function. The limit and branch points (which cause multiple steady-state solutions from a singular point) are very beneficial because they enable the Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the model.

Background

Bacterial meningitis is one of the most serious infectious diseases known to affect humans, characterized by inflammation of the protective membranes surrounding the brain and spinal cord, known as the meninges. This condition is primarily caused by bacteria invading the Cerebrospinal Fluid (CSF), triggering a severe immune response that can lead to rapid deterioration of neurological function. Despite advances in medicine and the availability of effective antibiotics, bacterial meningitis remains a global health concern due to its potential for high morbidity and mortality, especially when diagnosis and treatment are delayed. Understanding the causes, mechanisms, symptoms, and prevention strategies is vital in reducing the burden of this life-threatening disease.

The onset of bacterial meningitis typically begins when pathogenic bacteria breach the body's natural defense mechanisms. Common causative agents include *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae*

(pneumococcus), and *Haemophilus influenzae* type b (Hib). However, other bacteria such as *Listeria monocytogenes* or *Group B Streptococcus* may also be responsible, particularly in specific populations such as newborns, elderly individuals, and immunocompromised patients. These bacteria are often transmitted through respiratory droplets or close contact with an infected person. Once they colonize the nasopharynx, they can enter the bloodstream and cross the blood-brain barrier, allowing them to infect the meninges. The body's immune response to this invasion results in inflammation, increased permeability of the blood-brain barrier, and accumulation of inflammatory cells and cytokines within the CSF, all of which contribute to the hallmark symptoms of the disease.

The pathophysiology of bacterial meningitis involves a complex interplay between bacterial virulence factors and the host immune system. When bacteria reach the subarachnoid space, they multiply rapidly because the CSF provides a nutrient-rich environment with limited immune surveillance. The immune system responds with an influx of white blood

cells, particularly neutrophils, which release enzymes and reactive oxygen species to combat the infection. However, these defensive mechanisms inadvertently damage brain tissue and lead to cerebral edema, elevated intracranial pressure, and reduced cerebral perfusion. These processes can cause irreversible neurological damage if not promptly controlled. In severe cases, disseminated infection can occur, leading to sepsis, septic shock, and multiorgan failure. The disease progresses quickly, which is why early detection and intervention are essential for survival.

Clinically, bacterial meningitis presents with a combination of symptoms that vary depending on the age and immune status of the patient. The classic triad of meningitis includes fever, neck stiffness, and altered mental status, though not all patients exhibit all three. Other common symptoms include severe headache, photophobia, nausea, vomiting, and sensitivity to bright light or loud sounds. In infants and young children, symptoms may be nonspecific, such as irritability, poor feeding, or a bulging fontanelle, making diagnosis more challenging. In adults, additional signs such as confusion, lethargy, and seizures can occur. Meningococcal meningitis may also be accompanied by a characteristic petechial or purpuric rash, indicating bloodstream infection. Without rapid treatment, the disease can lead to complications such as hearing loss, cognitive impairment, hydrocephalus, or even death within hours or days of onset.

Diagnosis of bacterial meningitis requires immediate medical evaluation and laboratory confirmation. The cornerstone of diagnosis is lumbar puncture, through which cerebrospinal fluid is collected and analyzed. The CSF in bacterial meningitis typically shows elevated white blood cell count, predominantly neutrophils, increased protein concentration, and decreased glucose levels compared to serum. Gram staining and bacterial culture of the CSF remain the gold standard for identifying the causative organism, although these tests can take time. In urgent situations, polymerase chain reaction (PCR) and antigen detection tests provide faster results and help guide appropriate antibiotic therapy. Additional diagnostic tools such as blood cultures, neuroimaging (CT or MRI), and serological tests may be employed to assess the extent of infection and rule out other causes of neurological symptoms.

Treatment of bacterial meningitis must begin as soon as the disease is suspected, often even before confirmatory tests are completed. Empirical antibiotic therapy is initiated immediately, typically with broad-spectrum antibiotics that cover the most likely pathogens, such as a combination of a third-generation cephalosporin (like ceftriaxone or cefotaxime) and vancomycin. Once the causative organism is identified and its antibiotic sensitivity is known, therapy is adjusted accordingly. For certain bacteria like *Listeria monocytogenes*, ampicillin is added to the regimen. In addition to antibiotics, corticosteroids such as dexamethasone are sometimes administered to reduce inflammation and prevent neurological complications, particularly in cases of pneumococcal meningitis. Supportive treatments, including fluids, oxygen,

and anticonvulsants, are used as needed to stabilize the patient and manage complications.

Despite effective treatment, bacterial meningitis can leave survivors with long-term disabilities. Hearing loss is one of the most common sequelae, often resulting from damage to the cochlea or auditory nerve. Other neurological complications include learning disabilities, motor deficits, seizures, and behavioral problems. The severity of outcomes is influenced by factors such as the speed of diagnosis, age of the patient, immune status, and the specific causative agent. Infants and elderly patients are particularly vulnerable to poor outcomes, underscoring the importance of early detection and preventive measures. Rehabilitation and long-term follow-up are often necessary to address residual disabilities and improve quality of life.

Prevention plays a critical role in reducing the global burden of bacterial meningitis. Vaccination has proven to be the most effective preventive strategy. The widespread use of conjugate vaccines against *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae* has dramatically reduced the incidence of meningitis caused by these pathogens, especially in developed countries. Routine immunization programs for infants and adolescents have been highly successful, and travel-related vaccination is recommended for individuals visiting areas with high meningococcal disease prevalence. In addition to vaccination, prophylactic antibiotics may be given to close contacts of infected individuals to prevent secondary cases. Public health measures such as maintaining good hygiene, reducing overcrowding, and prompt reporting of suspected cases are also crucial to controlling outbreaks.

Globally, the epidemiology of bacterial meningitis varies by region, age group, and vaccination coverage. In sub-Saharan Africa, particularly in the so-called "meningitis belt," recurrent epidemics of meningococcal meningitis have historically caused widespread illness and death. Mass vaccination campaigns in recent years have significantly reduced these outbreaks, yet challenges remain in resource-limited areas where access to vaccines and healthcare facilities is still restricted. In high-income countries, the disease is now relatively rare, but sporadic cases continue to occur, emphasizing the need for continued vigilance and research into emerging bacterial strains and antibiotic resistance.

Bacterial meningitis is a medical emergency that demands immediate recognition and treatment to prevent devastating consequences. It is caused by the invasion of bacteria into the meninges, leading to inflammation, brain damage, and potentially death if untreated. Advances in microbiology, vaccination, and antimicrobial therapy have transformed the prognosis of this disease, yet it continues to pose significant challenges in many parts of the world. Preventive vaccination, early diagnosis, and prompt initiation of appropriate therapy remain the cornerstones of effective management. As global health efforts continue to improve access to vaccines and medical care, the vision of eliminating bacterial meningitis as a public health threat becomes increasingly achievable,

offering hope that fewer lives will be lost to this preventable and treatable disease.

Martcheva, et al. [1] discussed the transmission of meningococcal infection using a mathematical model. Irving, et al. [2] modeled meningococcal meningitis in the African meningitis belt. Bloch, et al. [3] discussed the molecular approaches to the diagnosis of meningitis and encephalitis. Blyuss [4] mathematically modelled the dynamics of meningococcal meningitis in Africa. Elmojtaba, et al. [5] developed a mathematical model for meningitis disease. Oordt-Speets, et al. [6] investigated the global etiology of bacterial meningitis. Asamoah, et al. [7] modelled the bacterial meningitis transmission dynamics with control measures. Yusuf [8] modeled and simulated the meningitis transmission dynamics. Agusto, et al. [9] performed optimal control studies and cost-effective analysis of the 2017 meningitis outbreak in Nigeria. Koutangni [10] developed compartmental models for seasonal hyperendemic bacterial meningitis in the African meningitis belt.

Asamoah, et al. [11] performed backward bifurcation and sensitivity analysis for bacterial meningitis transmission dynamics with a nonlinear recovery rate. Musa, et al. [12] modelled and analyzed meningitis transmission dynamics. Baba, et al. [13] performed a theoretical analysis of a meningitis model. Ali, et al. [14] demonstrated an antimicrobial resistance pattern of bacterial meningitis among patients in Pakistan. Mazamay, et al. [15] performed an overview of bacterial meningitis epidemics in Africa from 1928 to 2018 with a focus on epidemics “outside-the-belt”. Workineh, et al. [16] performed optimal control of the spread of meningitis in the presence of societal behavior change and information-dependent vaccination. Veronica, et al. [17] performed mathematical modeling and stability analyses on the transmission dynamics of bacterial meningitis. AfolabiM, et al. [18] developed a mathematical model on transmission dynamics of meningococcal meningitis. Crankson [19] modeled and performed optimal control studies of the Transmission Dynamics of Bacterial Meningitis Population in Ghana. Yano, et al. [20] performed an optimal control analysis of meningococcal meningitis disease with varying population sizes. Belay, et al. [21,22] developed and analyzed a mathematical model for the transmission dynamics of the bacterial meningitis disease.

In this work, bifurcation analysis and multiobjective nonlinear model predictive control is performed on the bacterial meningitis disease model described in Belay, et al. [21,22]. The paper is organized as follows. First, the model equations are presented, followed by a discussion of the numerical techniques involving bifurcation analysis and multiobjective nonlinear model predictive control (MNLMPC). The results and discussion are then presented, followed by the conclusions.

Model equations [21,22]

The variables (sv, cv, iv, vv, dv, rv) represent the individuals susceptible to bacteria, meningitis carrier individuals, infected individuals, vaccinated individuals, individuals who are drug-resistant, and recovered individuals. The control variables u_1 ,

u_2 , and u_3 stand for appropriate personal preventive measures, treatment to infected individuals to reduce their number, and screening applied to carrier individuals to detect bacterial meningitis disease in populations who do not have symptoms of the disease.

The model equations are

$$\begin{aligned}
 qv &= \beta(1-u_1)((q1cv)+(q2iv)+(q3dv)); \\
 \frac{d(sv)}{dt} &= \pi(1-k)+v(rv)+\gamma_1(vv)-qv(sv)-(\mu+\gamma_2)sv \\
 \frac{d(vv)}{dt} &= \pi k+\gamma_2(sv)-\varepsilon(qv)vv-(\mu+\gamma_1)vv \\
 \frac{d(cv)}{dt} &= qv(sv)+\varepsilon(qv)vv-(u_3+\delta+\omega+\mu)cv \\
 \frac{d(iv)}{dt} &= (\delta+u_3)cv-(\eta+u_2+\sigma+\mu)iv \\
 \frac{d(dv)}{dt} &= (1-\alpha)(1-u_2)\eta(iv)-(\theta+\mu)dv \\
 \frac{d(rv)}{dt} &= \omega cv+(u_2+\alpha\theta)iv+\theta dv-(v+\mu)rv
 \end{aligned} \tag{1}$$

The base parameter values are

$$\begin{aligned}
 \pi &= 111; \beta = 0.343; \eta = 0.56; \delta = 0.31; \text{gamal} = 0.32; \text{gama2} = 0.92; \\
 \mu &= 0.02; k = 0.21; \omega = 0.1118; \sigma = 0.27; q1 = 0.0016; q2 = 0.08; \\
 q3 &= 0.02; \alpha = 0.125; \varepsilon = 0.0845; \theta = 0.82; v = 0.0839; u1 = 0; u2 = 0; u3 = 0
 \end{aligned}$$

Bifurcation analysis

The MATLAB software MATCONT is used to perform the bifurcation calculations. Bifurcation analysis deals with multiple steady-states and limit cycles. Multiple steady states occur because of the existence of branch and limit points. Hopf bifurcation points cause limit cycles. A commonly used MATLAB program that locates limit points, branch points, and Hopf bifurcation points is MATCONT [23,24]. This program detects Limit points (LP), branch points (BP), and Hopf bifurcation points (H) for an ODE system.

$$\frac{dx}{dt} = f(x, \alpha) \tag{2}$$

$x \in R^n$ Let the bifurcation parameter be. Since the gradient is orthogonal to the tangent vector,

The tangent plane at any point $w = [w_1, w_2, w_3, w_4, \dots, w_{n+1}]$ must satisfy.

$$Aw = 0$$

Where A is

$$A = [\partial f / \partial x \quad | \quad \partial f / \partial \alpha] \tag{4}$$

Where $\partial f / \partial x$ is the Jacobian matrix. For both limit and branch points, the Jacobian matrix $J = [\partial f / \partial x]$ must be singular.

For a limit point, there is only one tangent at the point of singularity. At this singular point, there is a single non-zero vector, y, where $Jy=0$. This vector is of dimension n. Since there

is only one tangent the the vector

$y = (y_1, y_2, y_3, y_4, \dots, y_n)$ must align with $\hat{w} = (w_1, w_2, w_3, w_4, \dots, w_n)$. Since

$$J\hat{w} = Aw = 0 \quad (5)$$

The $n+1^{\text{th}}$ component of the tangent vector $w_{n+1} = 0$ at a limit point (LP).

For a branch point, there must exist two tangents at the singularity. Let the two tangents be z and w. This implies that

$$\begin{aligned} Az &= 0 \\ Aw &= 0 \end{aligned} \quad (6)$$

Consider a vector v that is orthogonal to one of the tangents (say w). v can be expressed as a linear combination of z and w ($v = \alpha z + \beta w$). Since $Az = Aw = 0$; $Av = 0$ and since w and v are orthogonal,

$w^T v = 0$. Hence $Bv = \begin{bmatrix} A \\ w^T \end{bmatrix} v = 0$ which implies that B is singular.

Hence, for a branch point (BP) the matrix $B = \begin{bmatrix} A \\ w^T \end{bmatrix}$ must be singular. At a Hopf bifurcation point,

$$\det(2f_x(x, \alpha) @ I_n) = 0 \quad (7)$$

@ indicates the bialternate product while I_n is the n-square identity matrix. Hopf bifurcations cause limit cycles and should be eliminated because limit cycles make optimization and control tasks very difficult. More details can be found in Kuznetsov [25,26] and Govaerts [27].

Hopf bifurcations cause limit cycles. The tanh activation function (where a control value u is replaced by) $(u \tanh u / \varepsilon)$ is used to eliminate spikes in the optimal control profiles [28–31]. Sridhar [32] explained with several examples how the activation factor involving the tanh function also eliminates the Hopf bifurcation points. This was because the tanh function increases the oscillation time period in the limit cycle.

Multiobjective Nonlinear Model Predictive Control(MNL MPC)

The rigorous multiobjective nonlinear model predictive control (MNL MPC) method developed by Flores Tlacuahuaz, et al. [33] was used.

Consider a problem where the variables. $\sum_{t_i=0}^{t_f} q_j(t_i)$ ($j = 1, 2, \dots, n$) have to be optimized simultaneously for a dynamic problem

$$\frac{dx}{dt} = F(x, u) \quad (8)$$

t_f Being the final time value, and n the total number of objective variables ad the control parameter. The single objective optimal control problem is solved individually optimizing each

of the variables. $\sum_{t_i=0}^{t_f} q_j(t_i)$ The optimization of $\sum_{t_i=0}^{t_f} q_j(t_i)$ will lead to the values q_j^* . Then, the multiobjective optimal control (MOOC) problem that will be solved is

$$\begin{aligned} \min & \left(\sum_{j=1}^n \left(\sum_{t_i=0}^{t_f} q_j(t_i) - q_j^* \right)^2 \right) \\ \text{subject to} & \frac{dx}{dt} = F(x, u); \end{aligned} \quad (9)$$

This will provide the values of u atvarious times. The first obtained control value of u is implemented and the rest arediscarded. This procedure is repeated until the implemented and the first obtained control values are the same or if the

Utopia point where $\left(\sum_{t_i=0}^{t_f} q_j(t_i) = q_j^* \text{ For all } j \right)$ is obtained.

Pyomo [34] is used for these calculations. Here, the differential equations areconverted to a Nonlinear Program (NLP) using the orthogonal collocation method The NLP is solved using IPOPT [35]and confirmed as a global solution with BARON [36].

The steps of the algorithm are as follows

1. Optimize and obtain q_j^* .
2. Minimize $\left(\sum_{j=1}^n \left(\sum_{t_i=0}^{t_f} q_j(t_i) - q_j^* \right)^2 \right)$ and getthe control values at various times.
3. Implement the first obtained control values.
4. Repeat steps 1 to 3 until there is an insignificant difference between the implemented and the first obtained value of the control variables or if the Utopia point is achieved.

The Utopia point is when $\sum_{t_i=0}^{t_f} q_j(t_i) = q_j^* \text{ For all } j$.

Sridhar [37] demonstrated that when the bifurcation analysis revealed the presence of limit and branch points the MNL MPC calculations to converge to the Utopia solution. For this, the singularity condition, caused by the presence of the limit or branch points was imposed on the co-state equation [38]. If the minimization of q_1 lead to the value q_1^* and the minimization of q_2 lead to the value q_2^* The MNL MPC calculations will minimize the function. $(q_1 - q_1^*)^2 + (q_2 - q_2^*)^2$. The multiobjective optimal control problem is

$$\min (q_1 - q_1^*)^2 + (q_2 - q_2^*)^2 \text{ subject to } \frac{dx}{dt} = F(x, u) \quad (10)$$

Differentiating the objective function results in

$$\frac{d}{dx_i}((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2) = 2(q_1 - q_1^*)\frac{d}{dx_i}(q_1 - q_1^*) + 2(q_2 - q_2^*)\frac{d}{dx_i}(q_2 - q_2^*) \quad (11)$$

The Utopia point requires that both. $(q_1 - q_1^*)$ And $(q_2 - q_2^*)$ Are zero. Hence

$$\frac{d}{dx_i}((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2) = 0 \quad (12)$$

The optimal control co-state equation [43] is

$$\frac{d}{dt}(\lambda_i) = -\frac{d}{dx_i}((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2) - f_x \lambda_i; \quad \lambda_i(t_f) = 0 \quad (13)$$

λ_i Is the Lagrangian multiplier. t_f Is the final time. The first term in this equation is 0 and hence.

$$\frac{d}{dt}(\lambda_i) = -f_x \lambda_i; \quad \lambda_i(t_f) = 0 \quad (14)$$

At a limit or a branch point, for the set of ODE $\frac{dx}{dt} = f(x, u)$

f_x Is singular. Hence there are two different vectors-values for $[\gamma_i]$ where $\frac{d}{dt}(\lambda_i) > 0$ and $\frac{d}{dt}(\lambda_i) < 0$. In between there is a

vector $[\gamma_i]$ where $\frac{d}{dt}(\lambda_i) = 0$. This coupled with the boundary

condition. $\lambda_i(t_f) = 0$ Will lead to $[\gamma_i] = 0$ This makes the problem an unconstrained optimization problem, and the optimal solution is the Utopia solution.

Results and discussion

With u_1 as the bifurcation parameter, one branch point and a limit point were found at

(sv vv cv iv dv rv u1) values of (1479.119048, 4070.880952, 0, 0, 0, 0, 0.979832), and

(1479.122086, 4070.889488, -0.001283 -0.000468, -0.000273, -0.003996, 0.979832) (Figure 1a).

With u_2 as the bifurcation parameter, one branch point and a Hopf bifurcation point were found at

(sv vv cv iv dv rv u2) values of (1479.119048, 4070.880952, 0, 0, 0, 0, 8.331833)

and (1479.119048, 4070.880952, 0, 0, 0, 0, 9.228870) (Figure 1b). The limit-cycle produced by this Hopf bifurcation is seen in Figure 1c.

When u_2 is modified to $u_2 = u_2(\tanh(u_2))/0.01$ a branch point occurs at

(1479.119048, 4070.880952, 0, 0, 0, 0, 0.292719),

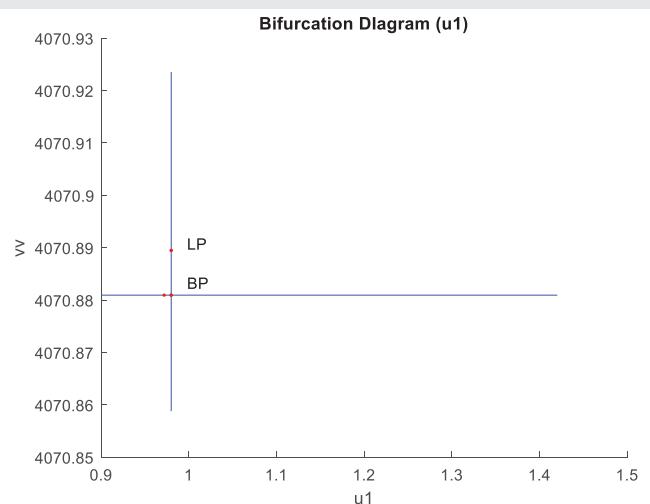


Figure 1a: Bifurcation diagram with u_1 as bifurcation parameter.

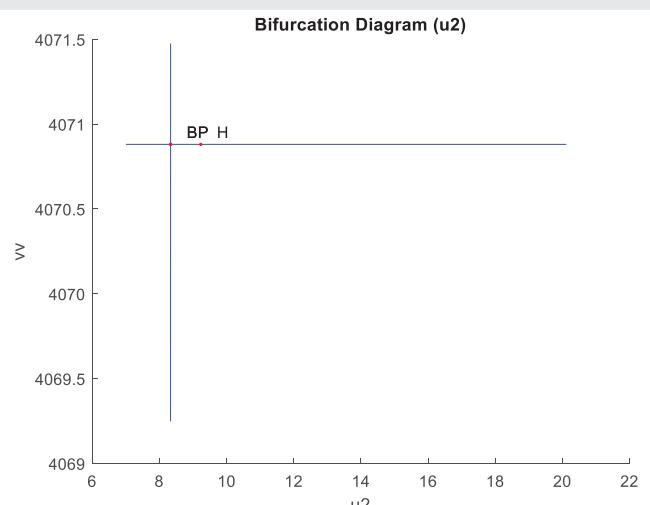


Figure 1b: Bifurcation Diagram (u_2 is the bifurcation parameter).

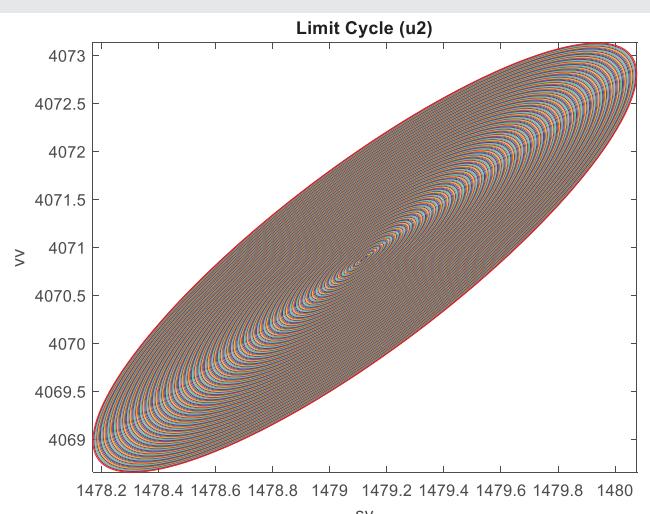


Figure 1c: Limit cycle(u_2 is bifurcation parameter).

and the Hopf bifurcation point disappears (Figure 1d), thereby validating the hypothesis presented in Sridhar [32].

For the MNLMPC calculations u_1 , u_2 , and u_3 are the control

parameters, and were minimized individually, and each minimization led to a value of 0. The overall optimal control problem will involve the minimization of u_1 was minimized subject to the equations governing the model. This led to a value of zero (the Utopia point). The MNLMPC values of the control variables, u_1 , u_2 , and u_3 , were 0.2264, 0.23, and 0.8293, respectively. The MNLMPC profiles are shown in Figures 2a-2d. The control profiles of u_1 , u_2 , and u_3 exhibited noise, and

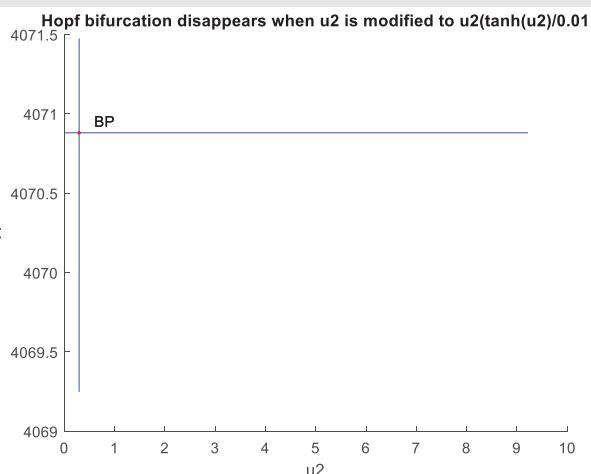


Figure 1d: Hopf bifurcation disappears when u_2 is modified to $u_2(\tanh(u_2))/0.01$.

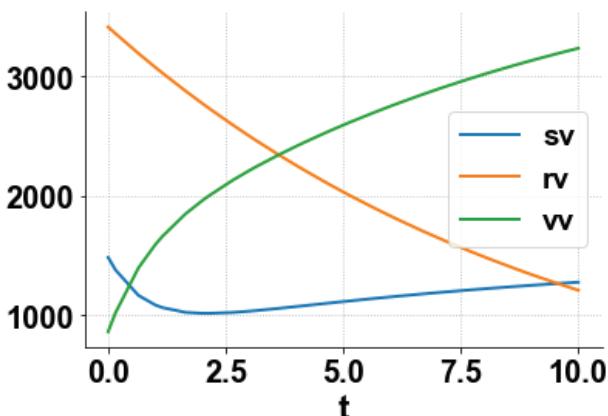


Figure 2a: MNLMPC (sv, rv, vv).

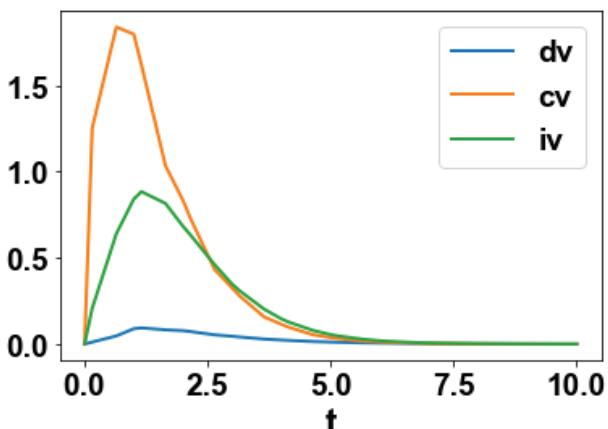


Figure 2b: MNLMPC (dv, cv, iv).

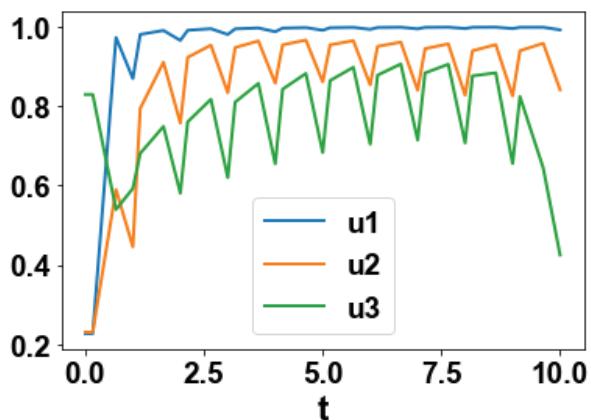


Figure 2c: MNLMPC (u_1 , u_2 , u_3).

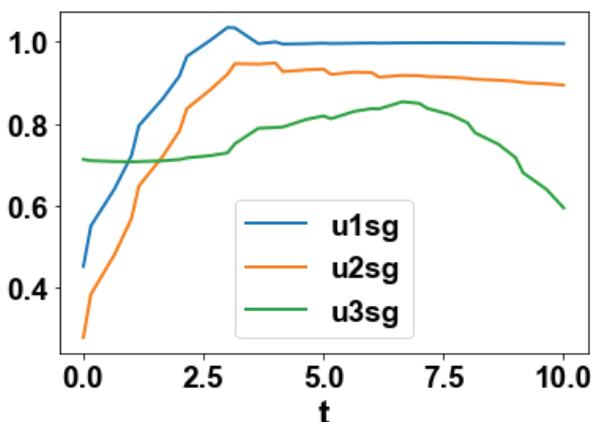


Figure 2d: MNLMPC (u_{1sg} , u_{2sg} , u_{3sg}).

this was remedied using the Savitzky-Golay filter to produce the smooth profiles u_{1sg} , u_{2sg} , and u_{3sg} . The presence of the limit and branch points is beneficial because it allows the MNLMPC calculations to attain the Utopia solution, validating the analysis of Sridhar [37].

Conclusion

Bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies on a bacterial meningitis disease model. The bifurcation analysis revealed the existence of Hopf bifurcation points, limit points, and branch points. The Hopf bifurcation point, which causes an unwanted limit cycle, is eliminated using an activation factor involving the tanh function. The limit and branch points (which cause multiple steady-state solutions from a singular point) are very beneficial because they enable the Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the models. A combination of bifurcation analysis and Multiobjective Nonlinear Model Predictive Control (MNLMPC) for a bacterial meningitis disease model is the main contribution of this paper.

Data availability statement

All data used is presented in the paper.



Acknowledgement

Dr. Sridhar thanks Dr. Carlos Ramirez and Dr. Suleiman for encouraging him to write single-author papers.

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