Solitary solutions to an androgen-deprivation prostate cancer treatment model

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A model of androgen deprivation treatment for prostate cancer is considered in this paper. Bright/dark solitary solutions to the model are constructed using inverse balancing and generalized differential operator techniques. It is shown that solitary solutions correspond to biomedically relevant sets of model parameters. Dynamical properties of solitary solutions are analyzed in the phase plane. It is demonstrated that such solutions closely reflect the real-world phenomena observed during androgen deprivation treatment. Computational experiments are used to illustrate these effects.

KEYWORDS

androgen deprivation therapy, prostate cancer model, solitary solution

1 | INTRODUCTION

Mathematical modeling of biomedical processes has come to the forefront of research in recent years. A plethora of models in a variety of biomedical fields has recently been modeled using differential equations, including research of viral infections,[1,2] treatment planning,[3] population dynamics,[4] and development of new treatment techniques.[5] However, one of the most active avenues of mathematical modeling in biomedicine remains as cancer research, as the field is particularly suited to such quantitative approaches.[6]

Prostate cancer (PCa), an enigmatic enough disease, is characterized to have different courses and is influenced by androgens. Localized PCa is treated radically (surgically or by radiotherapy). When PCa relapses, usually it is treated by androgen deprivation therapy—hormonal treatment (HT). During HT, the course of the disease is controlled with prostate-specific antigen (PSA) level. After initiation of HT, testosterone level in blood serum and PSA level decreases and usually for a long period. Depending on the malignancy of the disease, Gleason score, the time of PCa recurrence is different.[7] It also depends on the ratio of androgen-dependent and androgen-independent PCa cells.[8]

As Pca is the second most widespread type of cancer,[9] a great amount of attention has been devoted to modeling its evolution. A differential equation model is fit to observe sample in order to perform longitudinal analysis of prostate cancer tumor marker kinetics in de Charry et al.[10] An approach combining mathematical modeling and numerical simulation is used to develop a predictive computational model for the analysis of prostate cancer in Farhat et al.[11] A model that describes the interaction between the tumor environment, the PSA produced by hormone-dependent and hormone-independent tumor cells, and the level of androgens is developed in Draghi et al's study.[12] A model for the predictive simulation prostate of Pca is developed in Spyropoulos et al.[13] A comparison between several models of intermittent androgen suppression treatment for prostate cancer is given in Hatano et al.[14]

Solitary solutions (or solitons) are waves that maintain their shape as they move at a constant velocity. They possess many other properties, and the construction of such solutions to differential equations is a very active field of research.[15] More recently, solitary solutions have been found to be significant in biomedical research. A cold laser therapy method based on soliton tweezers is developed in Alavi et al.[16] Models demonstrating that angiogenesis is driven by and can be controlled using solitons are considered in Bonilla et al.[17] Applications of solitary solutions in multiphoton microscropy are discussed in Wang et al.[18] A multiple scale soliton perturbation analysis of DNA systems with inhomogeneity effects is performed in Okaly et al.[19] The role of solitary solutions in intracellular signaling is considered in Barvitenko et al.[20] Soliton-like traveling wave solutions to a model describing the growth of a solid tumor in the presence of an immune system response are constructed in Buzea et al.[21]

Algorithms for the construction of traveling-wave (soliton-like) solutions have been extensively discussed in literature. Techniques for constructing traveling-wave solutions to various partial differential equations (PDEs) used to model heat transfer are developed in Gao et al.[22] Traveling wave solutions falling within the scope of local fractional derivative formulation for the Korteweg-de-Vries equation and the class of two-dimensional Burgers-type equations are considered in Yang and Machado et al[23] and Yang and Gao et al[24] respectively. A method involving fractal special functions is used to efficiently find traveling-wave solutions to local fractional Boussinesq equation in fractal domain in Yang and Machado et al.[25] A new technique for constructing traveling-wave solutions based on factorization is proposed in Yang, Gao, and Srivastava.[26] Non-differentiable traveling-wave solutions to the modified Korteweg-de-Vries equation defined on a Cantor set are obtained via the fractal traveling-wave transformation in Gao, Yang, and Ju.[27] Traveling-wave solutions to a new type of nonlinear Burgers' equation are constructed in Yang and Machado.[28] All algebraic traveling-wave solutions to the Kadomtsev-Petviashvili equations, used to model shallow water waves, are obtained via planar dynamical systems and invariant algebraic curve in Liu et al.[29]

In this paper, the following model for the androgen deprivation therapy of prostate cancer analyzed in Zazoua and Wang[30] is considered:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \left(r_1 A_0 (1-u)\left(1 - \frac{x+\alpha y}{K}\right) - (d_1 + m_1)\, u\right) x; \tag{1}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = r_2 \left(1 - \frac{\beta x + y}{K}\right) y + m_1 u x. \tag{2}$$

Functions $x(t)$ and $y(t)$ represent the concentration of the androgen-dependent (AD) and androgen-independent (AI) cells respectively. All parameters of the system (Equations 1 and 2) are positive; A_0 is the normal androgen concentration; γ is the androgen clearance and production rate; $0 < u < 1$ represents the efficacy of applied continuous androgen suppression (CAS) therapy. Parameters r_1 and d_1 represent the growth and death rate of androgen-dependent cells, and r_2 represents the net growth rate of androgen-independent cells; α and β are positive competition coefficients the two types of cells; K is the carrying capacity of these cells; and m_1 denotes the irreversible mutation rate from androgen-dependent to androgen-independent cells.

By renaming its parameters, the system (Equations 1 and 2) can be restated in the following more general form:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = a_1 x + a_2 x^2 + a_3 x y; \tag{3}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = b_1 y + b_2 y^2 + b_3 x y + b_4 x, \tag{4}$$

where $a_1, \dots, a_3, b_1, \dots, b_4 \in \mathbb{R}$.

The main objective of this paper is to construct solitary solutions to Equations (1) and (2), compute the values of system parameters for which such solutions exist, and investigate the dynamics of solitary solutions. Since such solutions are known to have complex transient dynamics, they provide valuable insight into the androgen-deprivation treatment of prostate cancer that is modeled by the system (Equations 1 and 2).

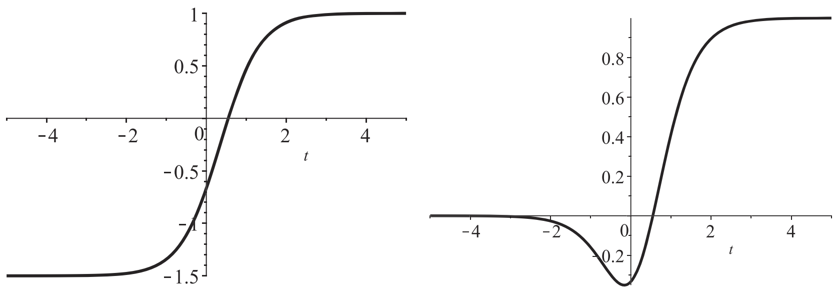

FIGURE 1 Kink solitary solution (part a) and bright/dark solitary solution (part b). Note that kink solutions can only describe the evolution of the system in a monotonous manner, which is not true for bright/dark solitary solutions. Parameters of Equation (5) are the following: $\sigma = 1, x_1 = 3, \tau_1^{(x)} = -2$ (part a), and additionally $x_2 = 0, \tau_2^{(x)} = -1$ (part b)

2 | PRELIMINARIES

2.1 | Solitary solutions

Soliton solutions to the system (Equations 1 and 2) are considered in the following form:

$$x(\tau) = \sigma \frac{\prod_{j=1}^{n} \left(\exp(\eta(\tau - c)) - x_j\right)}{\prod_{j=1}^{n} \left(\exp(\eta(\tau - c)) - \tau_j^{(x)}\right)}; \tag{5}$$

$$y(\tau) = \gamma \frac{\prod_{j=1}^{n} \left(\exp(\eta(\tau - c)) - y_j\right)}{\prod_{j=1}^{n} \left(\exp(\eta(\tau - c)) - \tau_j^{(y)}\right)}, \tag{6}$$

where η and c are real constants and $x_j, y_j, \tau_j^{(x)}, \tau_j^{(y)}, j = 1, \ldots, n$ are complex parameters that depend only on the initial conditions of the system of differential equations.

Note that choosing solitary solution order $n = 1$ leads to kink solitary solutions that can only describe monotonous transition from one concentration of AD (AI) cells to another (see Figure 1A). However, taking $n = 2$ results in more complex bright/dark solitary solutions that possess local minima or maxima (see Figure 1B). Important biomedical insights may be gleaned from the non-monotonous transient processes, for example, the minima in Figure 1B may represent a decrease in one cell population shortly after treatment is applied; however, further evolution of the system demonstrates the transition of the cell population to a higher level than treatment. Thus, in this paper, only solutions with order $n \geq 2$ are considered.

For algebraic computations, it is more convenient to restate Equations (5) and (6) in a different form by applying the following substitution:

$$t = \exp(\eta\tau); \quad \hat{c} = \exp(\eta c); \tag{7}$$

which transforms Equations (5) and (6) into

$$\hat{x}(t) = x\left(\frac{1}{\eta}\ln\tau\right) = \sigma \frac{\prod_{j=1}^{n} \left(t - \hat{x}_j\right)}{\prod_{j=1}^{n} \left(t - t_j^{(x)}\right)}; \tag{8}$$

$$\hat{y}(t) = y\left(\frac{1}{\eta}\ln\tau\right) = \gamma \frac{\prod_{j=1}^{n} \left(t - \hat{y}_j\right)}{\prod_{j=1}^{n} \left(t - t_j^{(y)}\right)}, \tag{9}$$

where $\hat{x}_j = \hat{c}x_j$; $\hat{y}_j = \hat{c}y_j$; $t_j^{(x)} = \hat{c}\tau_j^{(x)}$; $t_j^{(y)} = \hat{c}\tau_j^{(y)}$. The solitary solutions can be further rearranged as follows:

$$\hat{x}(t) = \sigma + \sum_{j=1}^{n} \frac{\lambda_j}{1-\rho_j\,(t-\hat{c})}; \tag{10}$$

$$\hat{y}(t) = \gamma + \sum_{j=1}^{n} \frac{\mu_j}{1-\nu_j\,(t-\hat{c})}, \tag{11}$$

where parameters λ_j, μ_j, ρ_j, and ν_j depend only on the initial conditions of the system of differential equations.

2.2 | Construction of solitary solutions

The generalized differential operator technique is used to construct solitary solutions of the Equations (5) and (6) to the considered model. A short description of this method is provided in this section.

2.2.1 | Generalized differential operator technique

Consider the following system of ordinary differential equations:

$$\frac{\mathrm{d}\hat{x}}{\mathrm{d}t} = P\,(t,\hat{x},\hat{y})\,; \quad \hat{x}\,(\hat{c}) = u; \tag{12}$$

$$\frac{\mathrm{d}\hat{y}}{\mathrm{d}t} = Q\,(t,\hat{x},\hat{y})\,; \quad \hat{y}\,(\hat{c}) = v, \tag{13}$$

where P and Q are analytic functions and $\hat{c}$, u, and v represent the initial conditions. The generalized differential operator that corresponds to the system (Equations 12 and 13) has the following form[31]:

$$\mathbf{D}_{\hat{c}uv} = \mathbf{D}_{\hat{c}} + P\,(\hat{c},u,v)\,\mathbf{D}_u + Q\,(\hat{c},u,v)\,\mathbf{D}_v. \tag{14}$$

By introducing the notations

$$p_j = \mathbf{D}_{\hat{c}uv}^{j} u; \quad q_j = \mathbf{D}_{\hat{c}uv}^{j} v; \quad j = 0,1,\,\dots\,, \tag{15}$$

the solution to Equations (12) and (13) can be expressed in the following power series form[31]:

$$\hat{x}(t) = \sum_{j=0}^{+\infty} \frac{(t-\hat{c})^j}{j!} p_j; \quad \hat{y}(t) = \sum_{j=0}^{+\infty} \frac{(t-\hat{c})^j}{j!} q_j. \tag{16}$$

2.2.2 | Construction of closed form solutions

Consider the sequences $(\hat{p}_0, \hat{p}_1, \dots)$ and $(\hat{q}_0, \hat{q}_1, \dots)$, where

$$\hat{p}_j = \frac{p_j}{j!}; \quad \hat{q}_j = \frac{q_j}{j!}; \quad j = 0,1,\,\dots\,. \tag{17}$$

The sequence $\left(\hat{p}_j; j = 0,1,\,\dots\right)$ is called a linear recurring sequence of order m if there exists such $m \in \mathbb{N}$ that satisfies the following condition[32]:

$$H_p^{(m)} \neq 0; \quad H_p^{(m+k)} = 0, \quad k = 1,2,\,\dots\,, \tag{18}$$

where $H_p^{(m)}$ is the mth order Hankel determinant constructed from the sequence $\left(\hat{p}_j; j = 0,1,\,\dots\right)$:

$$H_p^{(m)} = \det\left[\hat{p}_{j+k-2}\right]_{1\le j,k\le m+1}. \tag{19}$$

If Equation (19) holds true, the sequence can be expressed as

$$\hat{p}_j = \sum_{k=1}^{m} \lambda_k \rho_k^j; \quad j = 0,1,\,\dots\,, \tag{20}$$

where $\lambda_1, \dots, \lambda_m$ are constant coefficients and $\rho_1, \dots, \rho_m$ are roots of the characteristic polynomial

$$\begin{vmatrix} \hat{p}_0 & \hat{p}_1 & \cdots & \hat{p}_m \\ \hat{p}_1 & \hat{p}_2 & \cdots & \hat{p}_{m+1} \\ \vdots & \vdots & \ddots & \vdots \\ \hat{p}_{m-1} & \hat{p}_m & \cdots & \hat{p}_{2m-1} \\ 1 & \rho & \cdots & \rho^m \end{vmatrix} = 0. \tag{21}$$

Note that Equation (20) only holds when the roots of Equation (21) are distinct. The case of repeated roots is out of scope of this paper. If there is a zero root, we use the convention $0^0 = 1$.

Suppose that both $(\hat{p}_j; j = 0, 1, \dots)$ and $(\hat{q}_j; j = 0, 1, \dots)$ are the mth order linear recurring sequences. Then Equation (16) can be used to express $\hat{x}(t)$ in the closed form

$$\begin{aligned} \hat{x}(t) &= \sum_{j=0}^{+\infty} \frac{(t-\hat{c})^j}{j!} p_j = \sum_{j=0}^{+\infty} (t-\hat{c})^j \sum_{k=1}^{m} \lambda_k \rho_k^j \\ &= \sum_{k=1}^{m} \lambda_k \sum_{j=0}^{+\infty} (\rho_k (t-\hat{c}))^j = \sum_{k=1}^{m} \frac{\lambda_k}{1-\rho_k (t-\hat{c})}. \end{aligned} \tag{22}$$

It can be observed that Equation (22) corresponds to the form of solitary solution (Equation 10) where at least one characteristic root $\rho_s, s \in 1, \dots, m$ is zero.

Analogously, if

$$H_q^{(m)} \neq 0; \quad H_q^{(m+k)} = 0, \quad k = 1, 2, \dots, \tag{23}$$

then

$$\hat{q}_j = \sum_{k=1}^{m} \mu_k \nu_k^j; \quad j = 0, 1, \dots, \tag{24}$$

where $\mu_1, \dots, \mu_m$ are constants and $\nu_1, \dots, \nu_m$ are characteristic roots from a polynomial that is analogous to Equation (21). Such computations lead to

$$\hat{y}(t) = \sum_{k=1}^{m} \frac{\mu_k}{1-\nu_k (t-\hat{c})}. \tag{25}$$

The following theorem connects the results of this and Section 2.2.1.

Theorem 2.1. *Equations (12) and (13) admits the solutions Equations (22) and (25) if and only if the following conditions hold true for all $\hat{c}, u, v$:*

$$\mathbf{D}_{\hat{c}uv} \lambda_k = \lambda_k \rho_k; \quad \mathbf{D}_{\hat{c}uv} \mu_k = \mu_k \nu_k; \tag{26}$$

$$\mathbf{D}_{\hat{c}uv} \rho_k = \rho_k^2; \quad \mathbf{D}_{\hat{c}uv} \nu_k = \nu_k^2. \tag{27}$$

The proof of this theorem can be found in Navickas et al.[33]

2.3 | Inverse balancing method

Before applying the generalized operator method, the inverse balancing can be applied to the considered system of differential equations to determine the necessary conditions for the existence of solitary solutions. The main idea of the method is to insert a solution ansatz into the system and solve the resulting equations (which are linear in the case of Equations (3) and (4) as shown below) with respect to the system parameters. Note that this procedure does not provide any insight into the construction of the solution itself; however, if the system cannot admit solitary solutions, the resulting system of equations is degenerate. If there is a fewer number of system parameters $a_1, \dots, a_3, b_1, \dots, b_4$ than the number of resulting linear equations, necessary existence conditions of solitary solutions can be obtained via this procedure.

3 | DETERMINATION OF NECESSARY SOLITARY SOLUTION EXISTENCE CONDITIONS IN EQUATIONS (3) AND (4)

By the results provided in Telksnys et al,[34] the only case in which the number of balancing equations does not heavily outnumber the number of system parameters is solitary solutions of order $n = 2$.

3.1 | Transformation of the system (Equations 3 and 4)

The application of substitution (Equation 7) for the model (Equations 3 and 4) yields the following system of ordinary differential equations (ODEs):

$$\eta t\hat{x}_t = a_1\hat{x} + a_2\hat{x}^2 + a_3\hat{x}\hat{y};$$
$$\eta t\hat{y}_t = b_1\hat{y} + b_2\hat{y}^2 + b_3\hat{x}\hat{y} + b_4\hat{x}, \tag{28}$$

with initial conditions

$$\hat{x}\Big|_{t=\hat{c}} = u; \quad \hat{y}\Big|_{t=\hat{c}} = v. \tag{29}$$

Let $X(t), Y(t), T_x(t), T_y(t)$ be denoted as follows:

$$X(t) := (t-\hat{x}_1)(t-\hat{x}_2); \quad Y(t) := (t-\hat{y}_1)(t-\hat{y}_2); \tag{30}$$

$$T_x(t) := \left(t-t_1^{(x)}\right)\left(t-t_2^{(x)}\right); \quad T_y(t) := \left(t-t_1^{(y)}\right)\left(t-t_2^{(y)}\right). \tag{31}$$

Then solutions (Equations 5 and 6) are transformed to

$$\hat{x} = \sigma\frac{X(t)}{T_x(t)}; \quad \hat{y} = \gamma\frac{Y(t)}{T_y(t)}. \tag{32}$$

3.2 | Necessary soliton solution (Equation 32) existence conditions in (Equation 28)

Solitary solution ansatz (Equation 32) is inserted into the system (Equation 28) as the first step of inverse balancing technique. Therefore, the simplification of Equation (28) yields

$$\eta t\sigma T_y\left(X_tT_x - X(T_x)_t\right) = a_1\sigma T_xT_yX + a_2\sigma^2X^2T_y + a_3\sigma\gamma XYT_x; \tag{33}$$

$$\eta t\gamma T_x\left(Y_tT_y - Y\left(T_y\right)_t\right) = b_1\gamma T_yT_xY + b_2\gamma^2Y^2T_x + b_3\sigma\gamma YXT_y + b_4\gamma XT_y^2. \tag{34}$$

Equation (31) reads

$$T_x\left(t_1^{(x)}\right) = T_x\left(t_2^{(x)}\right) = T_y\left(t_1^{(y)}\right) = T_y\left(t_2^{(y)}\right) = 0; \tag{35}$$

$$(T_x)_t\Big|_{t=t_1^{(x)}} = t_1^{(x)} - t_2^{(x)}; \quad (T_x)_t\Big|_{t=t_2^{(x)}} = t_2^{(x)} - t_1^{(x)}; \tag{36}$$

$$\left(T_y\right)_t\Big|_{t=t_1^{(y)}} = t_1^{(y)} - t_2^{(y)}; \quad \left(T_y\right)_t\Big|_{t=t_2^{(y)}} = t_2^{(y)} - t_1^{(y)}. \tag{37}$$

Denote $t = t_1^{(x)}, t_2^{(x)}$ in Equation (33) and $t = t_1^{(y)}, t_2^{(y)}$ in Equation (34). Then the application of Equations (35) to (37) results in the following equations:

$$T_y\left(t_1^{(x)}\right)\left(a_2\sigma^2X^2\left(t_1^{(x)}\right) + \eta\sigma t_1^{(x)}\left(t_1^{(x)} - t_2^{(x)}\right)X\left(t_1^{(x)}\right)\right) = 0; \tag{38}$$

$$T_y\left(t_2^{(x)}\right)\left(a_2\sigma^2X^2\left(t_2^{(x)}\right) + \eta\sigma t_2^{(x)}\left(t_2^{(x)} - t_1^{(x)}\right)X\left(t_2^{(x)}\right)\right) = 0; \tag{39}$$

$$T_x\left(t_1^{(y)}\right)\left(b_2\gamma^2Y^2\left(t_1^{(y)}\right) + \eta\gamma t_1^{(y)}\left(t_1^{(y)} - t_2^{(y)}\right)Y\left(t_1^{(y)}\right)\right) = 0; \tag{40}$$

$$T_x\left(t_2^{(y)}\right)\left(b_2\gamma^2Y^2\left(t_2^{(y)}\right) + \eta\gamma t_2^{(y)}\left(t_2^{(y)} - t_1^{(y)}\right)Y\left(t_2^{(y)}\right)\right) = 0. \tag{41}$$

Solution for Equations (38) to (41) are nontrivial only if

$$t_1^{(x)} = t_1^{(y)}; \quad t_2^{(x)} = t_2^{(y)}, \tag{42}$$

thus, only solitary solutions with equal denominators are admitted by Equation (28) (and, consequently, Equations 3 and 4). Denoting $t_1 := t_1^{(x)} = t_1^{(y)}$ and $t_2 := t_2^{(x)} = t_2^{(y)}$ and using Equation (42) transforms Equation (32) into

$$\hat{x} = \sigma \frac{X(t)}{T(t)}; \quad \hat{y} = \gamma \frac{Y(t)}{T(t)}, \tag{43}$$

where $T(t) := (t - t_1)(t - t_2)$. Also, note that $\rho_k = \nu_k;\ k = 1, 2$ in Equations (10) and (11) when Equation (42) holds true.

3.3 | Necessary soliton solution (Equation 43) existence conditions in (Equation 28)

Let the conditions (Equation 42) hold true. Then Equations (33) and (34) read

$$\eta t \sigma \left(X_t T - X T_t \right) = a_1 \sigma X T + a_2 \sigma^2 X^2 + a_3 \sigma \gamma X Y; \tag{44}$$

$$\eta t \gamma \left(Y_t T - Y T_t \right) = b_1 \gamma Y T + b_2 \gamma^2 Y^2 + b_3 \sigma \gamma X Y + b_4 \sigma X T, \tag{45}$$

where

$$T(t_1) = T(t_2) = X(\hat{x}_1) = X(\hat{x}_2) = Y(\hat{y}_1) = Y(\hat{y}_2) = 0, \tag{46}$$

and

$$T_t = 2t - t_1 - t_2; \quad X_t = 2t - \hat{x}_1 - \hat{x}_2; \quad Y_t = 2t - \hat{y}_1 - \hat{y}_2. \tag{47}$$

Evaluating Equations (44) and (45) at $t = t_1, t_2$ and using Equations (46) and (47) yields

$$\eta t_1 (t_2 - t_1) = \sigma X(t_1) a_2 + \gamma Y(t_1) a_3; \tag{48}$$

$$\eta t_2 (t_1 - t_2) = \sigma X(t_2) a_2 + \gamma Y(t_2) a_3. \tag{49}$$

$$\eta t_1 (t_2 - t_1) = \gamma Y(t_1) b_2 + \sigma X(t_1) b_3; \tag{50}$$

$$\eta t_2 (t_1 - t_2) = \gamma Y(t_2) b_2 + \sigma X(t_2) b_3. \tag{51}$$

Solving Equations (48) to (51) with respect to parameters a_2, a_3, b_2, and b_3 results in

$$a_2 = b_3 = \frac{\eta}{\sigma} \frac{(t_2 - t_1)(t_1 Y(t_2) + t_2 Y(t_1))}{(X(t_1) Y(t_2) - X(t_2) Y(t_1))}; \tag{52}$$

$$b_2 = a_3 = \frac{\eta}{\gamma} \frac{(t_1 - t_2)(t_2 X(t_1) + t_1 X(t_2))}{(X(t_1) Y(t_2) - X(t_2) Y(t_1))}. \tag{53}$$

Analogously, evaluating Equation (44) at $t = \hat{x}_1, \hat{x}_2$ and Equation (45) at $t = \hat{y}_1, \hat{y}_2$ and solving obtained system for b_4 yields

$$b_4 = \frac{\eta \gamma (\hat{y}_2 - \hat{y}_1)(\hat{y}_1 T(\hat{y}_2) + \hat{y}_2 T(\hat{y}_1))}{\sigma (T(\hat{y}_1) X(\hat{y}_2) - T(\hat{y}_2) X(\hat{y}_1))}. \tag{54}$$

The remaining linear equations result in the following constraints on the solitary solution parameters:

$$\hat{x}_1 = \hat{x}_2; \tag{55}$$

$$\frac{X(\hat{y}_1)}{X(\hat{y}_2)} = -\frac{\hat{y}_1}{\hat{y}_2}. \tag{56}$$

Finally, evaluating Equations (44) and (45) at $t = 0$ results in a_1 and b_1:

$$a_1 = -\frac{1}{\sigma} \left(\sigma^2 a_2 + \sigma \gamma a_3 \right); \tag{57}$$

$$b_1 = -\frac{1}{\gamma} \left(\gamma^2 b_2 + \sigma \gamma b_3 + \sigma b_4 \right). \tag{58}$$

It can be observed that Equation (28) has seven parameters; thus, the linear balancing system consisting of 10 equations generated by Equations (44) and (45) is degenerate. Therefore, constraints (Equations 55 and 56) must be imposed on the parameters of the solution (Equation 43). Moreover, in order to admit solitary solution (Equation 43), the system (Equation 28) must satisfy the following conditions:

$$a_3 = b_2; \quad b_3 = a_2, \tag{59}$$

as shown in Equations (52) and (53).

4 | CONSTRUCTION OF EXPLICIT EXPRESSIONS OF SOLITARY SOLUTIONS TO EQUATIONS (3) AND (4)

4.1 | Determination of the parameter η of solitary solutions

Let the necessary existence conditions of Equations (42) and (59) hold true.

In Section 4.1, parameter η of solitary solutions (Equations 5 and 6) is determined as follows from Section 2.2.2 parameter η must satisfy the conditions below:

$$H_p^{(3)} = 0; \quad H_q^{(3)} = 0, \tag{60}$$

where $H_p^{(3)}$ and $H_q^{(3)}$ are Hankel determinants of the following form

$$H_p^{(3)} = \begin{vmatrix} \frac{p_1}{1!} & \frac{p_2}{2!} & \frac{p_3}{3!} \\ \frac{p_2}{2!} & \frac{p_3}{3!} & \frac{p_4}{4!} \\ \frac{p_3}{3!} & \frac{p_4}{4!} & \frac{p_5}{5!} \end{vmatrix}; \quad H_q^{(3)} = \begin{vmatrix} \frac{q_1}{1!} & \frac{q_2}{2!} & \frac{q_3}{3!} \\ \frac{q_2}{2!} & \frac{q_3}{3!} & \frac{q_4}{4!} \\ \frac{q_3}{3!} & \frac{q_4}{4!} & \frac{q_5}{5!} \end{vmatrix}. \tag{61}$$

Hankel determinants $H_p^{(3)}$ and $H_q^{(3)}$ can be rewritten as follows:

$$H_p^{(3)} = \frac{1}{\eta^9 \hat{c}^9} \left(A_6(u,v)\eta^6 + A_4(u,v)\eta^4 + A_2(u,v)\eta^2 + A_0(u,v) \right); \tag{62}$$

$$H_q^{(3)} = \frac{1}{\eta^9 \hat{c}^9} \left(B_6(u,v)\eta^6 + B_4(u,v)\eta^4 + B_2(u,v)\eta^2 + B_0(u,v) \right), \tag{63}$$

where

$$A_6 = \left(\frac{1}{2160} \right)^{1/3} K^3, \quad K := \left(u^2 a_2 + (a_3 v + a_1) u \right); \tag{64}$$

$$A_4 = F(u,v)K, \tag{65}$$

and F is a polynomial with respect to u and v. In order for the solitary solutions (Equations 5 and 6) to admit all initial conditions, parameter η must be a constant with respect to t, $\hat{c}$, u, and v. Thus, arbitrary values of u and v can be inserted into Equation (62). Denoting

$$v = f(u) = -\frac{a_2 u + a_1}{b_2}, \tag{66}$$

results in $A_6 = A_4 = 0$. Therefore, η^2 can be expressed from Equation (62) as

$$\eta^2 = -\frac{A_0(u, f(u))}{A_2(u, f(u))} = \frac{\alpha_1 u + \alpha_0}{\beta_1 u + \beta_0}, \tag{67}$$

where α_k and β_k depend on parameters $a_2, a_3; b_1, \dots, b_4$. Analogously, denoting

$$u = g(v) = -\frac{b_2 v^2 + b_1 v}{a_2 v + b_4}; \tag{68}$$

and using Equation (62) results in

$$\eta^2 = -\frac{B_0(g(v), v)}{B_2(g(v), v)} = \frac{\hat{\alpha}_1 v + \hat{\alpha}_0}{\hat{\beta}_1 v + \hat{\beta}_0}. \tag{69}$$

Note that parameter η is constant and does not depend on u and v only if

$$\alpha_1 \beta_0 - \alpha_0 \beta_1 = 0; \tag{70}$$

$$\hat{\alpha}_1 \hat{\beta}_0 - \hat{\alpha}_0 \hat{\beta}_1 = 0. \tag{71}$$

Thus, sufficient existence condition for solitary solutions to Equations (3) and (4) reads

$$3a_1 b_1^2 + 3b_1 a_1^2 - 2a_1^3 - 2b_1^3 = 0. \tag{72}$$

Parameter η can be obtained from Equation (67) or Equation (69) if Equation (72) holds true.

4.2 | Parameters of solitary solutions

The results of the generalized differential operator method together with the algorithm for determining η result in explicit expressions for the parameters of solitary solutions that are given below.

It can be observed that

$$\rho_k = \frac{\rho_k^*}{\hat{c}}; \quad k = 1, 2, \tag{73}$$

where $\rho_k^* = \rho_k^*(u, v)$.

The parameters of the solitary solutions (Equations 5 and 6) read

$$\tau_k = 1 + \frac{1}{\rho_k^*}; \quad k = 1, 2; \tag{74}$$

$$x_{1,2} = \frac{1}{2}\left(A_x \pm \sqrt{A_x^2 - 4B_x}\right); \tag{75}$$

$$y_{1,2} = \frac{1}{2}\left(A_y \pm \sqrt{A_y^2 - 4B_y}\right); \tag{76}$$

$$\sigma = u - \lambda_1 - \lambda_2; \quad \gamma = v - \mu_1 - \mu_2, \tag{77}$$

where

$$A_x := \frac{\lambda_1}{\sigma \rho_1^*} + \frac{\lambda_2}{\sigma \rho_2^*} + \tau_1 + \tau_2; \tag{78}$$

$$B_x := \tau_1 \tau_2 + \frac{\lambda_1 \tau_2}{\sigma \rho_1^*} + \frac{\lambda_2 \tau_1}{\sigma \rho_2^*}; \tag{79}$$

$$A_y := \frac{\mu_1}{\gamma \rho_1^*} + \frac{\mu_2}{\gamma \rho_2^*} + \tau_1 + \tau_2; \tag{80}$$

$$B_y := \tau_1 \tau_2 + \frac{\mu_1 \tau_2}{\gamma \rho_1^*} + \frac{\mu_2 \tau_1}{\gamma \rho_2^*}. \tag{81}$$

5 | ANALYSIS OF SOLITARY SOLUTIONS TO ANDROGEN DEPRIVATION PROSTATE CANCER TREATMENT MODEL

5.1 | Conditions of existence for bright/dark solitary solutions

As shown previously, conditions (Equations 59 and 72) must hold true to ensure the existence of bright/dark solitary solutions to Equations (3) and (4). These conditions can be restated with respect to the parameters of the original androgen deprivation prostate cancer treatment model as follows:

$$\alpha = \frac{1}{\beta} = \frac{r_2}{r_1 A_0 (1 - u)}; \tag{82}$$

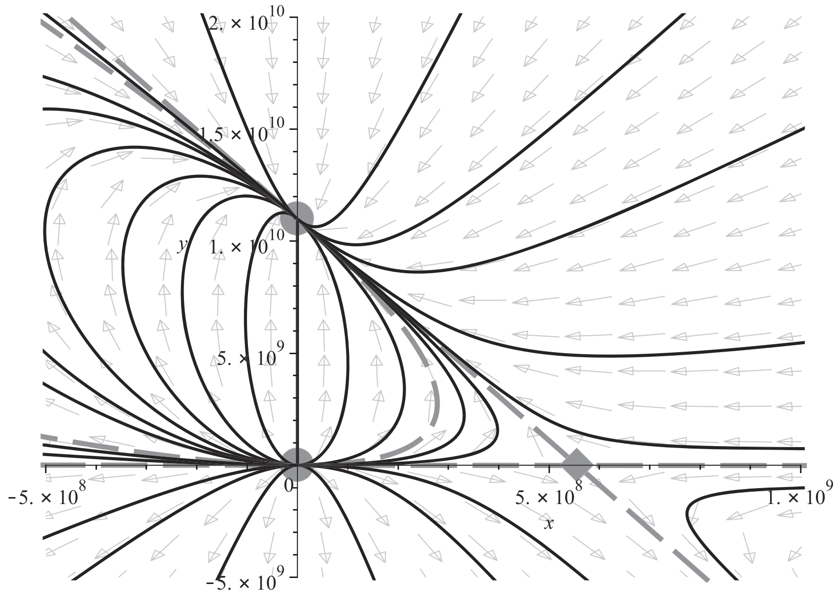

FIGURE 2 The phase portrait of the system (Equations 1 and 2) with parameter values (Equation 84). The gray circles denote stable and unstable nodes; the gray diamond denotes the saddle point. Dashed straight lines correspond to the stable and unstable manifolds of the saddle point; dashed parabola corresponds to the separatrix between solutions with and without singularities. Thin black lines denote solution trajectories

$$(\Theta - r_2)\left(\Theta + \frac{r_2}{2}\right)(\Theta + 2r_2) = 0, \tag{83}$$

where $\Theta = (A_0 r_1 + d_1 + m_1)\,u - A_0 r_1$.

Standard parameter values for studying the effect of androgen deprivation treatment are given in Zazoua and Wang[30]: $r_1 = 0.025$/day, $r_2 = 0.006$/day, $d_1 = 0.064$/day, $K = 1.1 \times 10^9$/day, $m_1 = 5 \times 10^{-5}$/day, $A_0 = 20$ng/mL, $\alpha, \beta > 0$, and $0 < u < 1$. Inserting these parameter values into Equations (82) and (83) yields three triples (α, β, and u) that correspond to cases in which the model admits solitary solutions:

$$\alpha = \frac{11281}{111750}; \quad \beta = \frac{111750}{11281}; \quad u = \frac{9940}{11281}, \tag{84}$$

$$\alpha = \frac{11281}{126750}; \quad \beta = \frac{126750}{11281}; \quad u = \frac{9760}{11281}, \tag{85}$$

$$\alpha = \frac{11281}{96750}; \quad \beta = \frac{96750}{11281}; \quad u = \frac{10120}{11281}. \tag{86}$$

The phase portrait of the system (Equations 1 and 2) with parameter values (Equation 84) is depicted in Figure 2. Note that there are three equilibria: the point $(0, 0)$ is an unstable node; the point $\left(\frac{186136500000000}{334753}, -\frac{2733500000000}{334753}\right)$ is a saddle point; and the point $\left(0, 1.1 \cdot 10^{10}\right)$ is a stable node. As can be seen from Figure 2, the well-known effect of androgen deprivation therapy is present in the model: The system eventually converges to the stable node, which has only androgen-independent cells. However, depending on how close the initial point is to the saddle point, this convergence may be non-monotonous (ie, the number of androgen dependent cells rises at some point during the treatment and drops in the late stages) or monotonous (the androgen-dependent cell population steadily declines). Such phenomena serve to illustrate that the model closely resembles real-world observations on prostate cancer treatment. Furthermore, if the initial point can be controlled via an external procedure, the amount of time it takes for the model to converge into the completely androgen-independent state can be lengthened or reduced.

6 | CONCLUSIONS

Solitary solutions to a model of androgen deprivation treatment of prostate cancer are constructed in this paper. The necessary and sufficient conditions for the existence of such solutions are derived in terms of the model parameters using the inverse balancing and generalized differential operator techniques. It is demonstrated that solitary solutions correspond to sets of biomedically relevant model parameters and tend to appear when androgen-deprivation treatment control parameter u is high.

Dynamical properties of solitary solutions to the considered models are discussed. It is shown that the solitary solutions describe medical processes that are well known in androgen deprivation therapy—the model eventually converges to a state where only androgen independent cells remain, but the speed and trajectory of this convergence may be controlled by moving the solution trajectory closer to the saddle point in the phase plane. These results provide a deeper insight into the phenomena governed by the treatment model.

CONFLICT OF INTEREST

This work does not have any conflicts of interest.

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