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Original article

Computational model to explore the endocrine response to trastuzumab action in HER-2/neu positive breast cancer

Fuzhang Wang [a,b,c,*], Qurat-Ul-Ain Azim [d], Ayesha Sohail [d], Alessandro Nutini [e], Robia Arif [d], João Manuel R.S. Tavares [f]

[a] School of Mathematical and Statistics, Xuzhou University of Technology, Xuzhou 221018, Jiangsu, China
[b] Nanchang Institute of Technology, Nanchang 330044, China
[c] College of Computer Science and Technology, Huaibei Normal University, 235000 Huaibei, China
[d] Department of Mathematics, Comsats University Islamabad, Lahore Campus 54000, Pakistan
[e] Centro Studi Attività Motore - Biology and Biomechanics Dept., Via di tiglio 94 Lucca, Italy
[f] Instituto de Ciência e Inovação em Engenharia Mecânica e Engenharia Industrial, Departamento de Engenharia Mecânica, Faculdade de Engenharia, Universidade do Porto, Porto, Portugal

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ABSTRACT

Breast cancer is a very frequent type of cancer and much attention is paid to therapy with considerable efforts both in the pharmacological and clinical fields.The present work aims to create a non-linear dynamic model of action of the drug Trastuzumab against HER-2 + breast cancer, mainly considering its action of ADCP (antibody-dependent phagocytosis) killing of cancer cells. The model, while also considering the other therapeutic effects induced by Trastuzumab, shows how the action of this monoclonal antibody in the induction of ADCP through the action of macrophages, is strictly connected to the formation of a multi-complex "Trastuzumab -HER-2 - macrophage" that shows a prolonged action over time, responsible for the increase in the Overall Survivor (OS) parameter reported in various. The model shows the correlation between the various therapeutic effects and the killing action of cancer cells through the variation of the dynamic fluctuation of the representative "c" parameter.

1. Introduction

In 1987, Slamon et al. (1987) reported the"HER-2/NEU gene" involvement and prognosis in breast cancer, with alteration and amplification of the gene in several types of breast cancers. HER (Human EGF Receptor) is a part of the family of epidermal growth factor receptors (EGFR - Epidermal Growth Factor Receptor) which has four members: HER-1 (erbB-1), HER-2/ neu (erbB-2), HER-3 (erbB-3), HER-4 (erbB-4).

HER-2 does not bind to known ligands, but is activated by hetero-dimerization with other members of the EGFR family.

The frequent amplification and over-expression of HER-2 in breast cancer is responsible for the cancer invasion, progression and death of the patient, if untreated.

Direct evidence of its oncogenic activity was reported via experiments on the transgenic mice, where an activated form of the "HER-2/ neu" oncogene is expressed in the mammary epithelium which lead to the development of breast cancer.

Four subtypes of the tumour are:

1. Luminal type (divided in turn into A and B),
2. HER-2 type positive/ estrogen receptor-negative,
3. "Normal" type,
4. Basal type.

The basal type shows an absence of the progesterone receptor and HER-2 but has a strong expression of EGFR. Clinical studies shows that HER-2 positive and basal type have worse prognosis than the luminal and "normal" types (Sørlie et al., 2001).

The difference between human HER-2 genes and murine neu is that, in the neu mouse, it requires tumor activation through mutagenesis, while HER-2 possesses an oncogenic capacity linked only to its overexpression.

The breast cancer also develops and progresses as a result of a dysfunction of the steroid hormones.

Lifetime exposure to estrogen can lead to an increased risk of breast cancer in the postmenopausal period. The importance of

* Corresponding author.
E-mail addresses: wangfuzhang1984@163.com (F. Wang), nutini@centrostudiattivitamotorie.it (A. Nutini).

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estrogen in this pathology is due to the fact that about 70% of these tumors express an estrogen receptor and proliferate in the presence of the latter and they are defined as HR + tumors. In fact, some studies have correlated the high and constant presence of estrogen in the blood with the risk of having this type of tumor (Melmed et al., 2015).

A high risk of breast cancer is also given by a high level of the presence of androstenedione and testosterone in the blood. Many breast tumors are positive for the presence of estrogen (ER) and/or progesterone (PR) receptors and their presence indicates a prognostic factor favorable to treatment.

1.1. HER-2 Signaling Mechanism

HER-2 is a part of the transmembrane type-I receptors and is responsible for the growth factors, linked to the extracellular signals. In mammals, the signaling system is complex since it resides on the interaction between twelve (up-to a maximum) ligands and four receptors.

Once HER-2 binds to the ligand, this protein undergoes dimerization and transphosphorylation of its cytoplasmic domains. These phosphorylated domains represent the anchor points of several intracellular molecules. They activate the signaling process through the recruitment of second messengers and molecular "cross-talk" activity with other transmembrane signaling systems (Oflazoglu et al., 2007).

The extracellular domain of HER-2 is configured as a closed-inhibited and an open-active conformation.

The binding with the ligand induces a conformation change that induces the open-active state in the extracellular portion of the receptor. It stimulates the dimerization and the consequent transphosphorylation (Yarden and Sliwkowski, 2001).

This dimerization process favors the heterodimeric composition, which has strong signaling capacity (Weiner and Adams, 2000).

Unlike the other members of its family, HER-2 does not oscillate between the inactive and active conformation. It is activated by the bond with the heterodimeric partner (Shi et al., 2015).

The family of HER receptors in mammals has evolved according to the functional needs and to the promotion of both, the independent and redundant functions and this is why both HER-2 and HER-3 are functionally incomplete receptors.

Although HER-2 and HER-3 are functionally inactive (functionally incomplete molecules), numerous studies indicate their dimeric complex (HER-2/ HER-3) as the most active of the entire family (Onda et al., 1996; Tzahar et al., 1996).

1.2. HER-2 and Tumor Genesis

The overexpression of HER-2 has been noted in about 30% of breast and ovarian cancers and is either due to the gene amplification or through deregulation of transcription factors (Slamon et al., 1987; Slamon et al., 1989); this event identifies a difficult prognosis.

Amplification of HER-2 identifies a type of breast cancer with molecular characteristics different from other types of cancer that are maintained both in the progression and in the process of metastasis (Morrison et al., 2006).

These characteristics involve sensitivity to certain chemotherapeutic agents and resistance to hormonal agents, including a certain ability to create brain metastases (Ross et al., 2003).

Overexpression of HER-2 has also been noted in endometrial and gastric cancer, although the definite role of its presence is not yet well understood (Morrison et al., 2006).

Some somatic mutations in the kinase domain of HER-2 increase its activity and increase the efficiency of the neoplastic transformation capacity, although direct evidence of this oncogenic function has not yet been clarified. The main point to consider, therefore, remains the overexpression of HER-2 or its gene amplification.

1.3. The Estrogen: Physiological Mechanisms

Estrogen is a sex steroid hormone that has a broad spectrum of physiological functions ranging from the regulation of the menstrual cycle to reproduction, the modulation of bone density as well as the brain functions.

Aromatase is the enzyme that functions as the main mediator of estrogen biosynthesis in postmenopausal conditions and is found in the ovaries, adipose tissue, bones, brain, and placenta (Mantas et al., 2016).

1.4. Trastuzumab and its Mechanism of Action

The strategy of making HER-2 a therapeutic target has proved very important for treating breast cancer.

One drug that has proven capable of achieving this goal is Trastuzumab, a humanized monoclonal antibody which, by binding to an extracellular portion of HER-2, inhibits neoplastic proliferation.

Trastuzumab is a bi-specific antibody that binds to an extracellular juxtamembrane domain of HER-2 and prevents the activation of its intracellular tyrosine kinase; in fact, this antibody is a humanized "IgG" with a preserved Fc moiety 1.

The possible mechanisms by which Trastuzumab exerts its action are different. After the binding of the monoclonal antibody to the target, there is an attenuation of the signal that induces the dimerization of the HER-2 receptor, an increase in the destruction of the receptor by endocytosis, a decrease in the presentation of the extracellular domains of HER-2 and immune activation 2. Some preclinical studies show that Trastuzumab recruits immune effector cells responsible for antibody-mediated toxicity and preoperative use of this antibody has reported increased infiltration of lymphoid cells into the tumor (Weiner and Adams, 2000).

This type of antibody can also be used to deliver certain conjugated toxins or radioisotopes to the target.

Furthermore, a study on animal models relating to breast cancer where HER-2 overexpression is detected, indicates that angiogenesis can be inhibited by Trastuzumab which can induce a normalization and regression of the tumor vascular system through modulation of the factors. proangiogenic and antiangiogenic.

Among the effects of Trastuzumab, there is, in addition to the inhibition of the signal by HER-2, also the facilitation of ADCC (Antibodies-dependent cell-mediated cytotoxicity) (Arnould et al., 2006), which occurs through the engagement of FcR receptors expressed by some immune cells that bind target cells opsonized by Trastuzumab itself. Natural Killer (NK) cells play an important role in this function, so much so that their increased

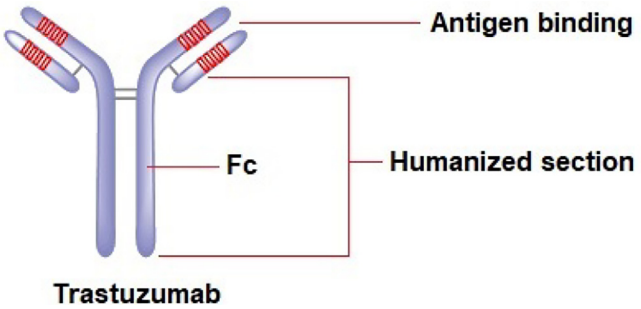

Fig. 1. Descriptive image of the Trastuzumab monoclonal antibody.

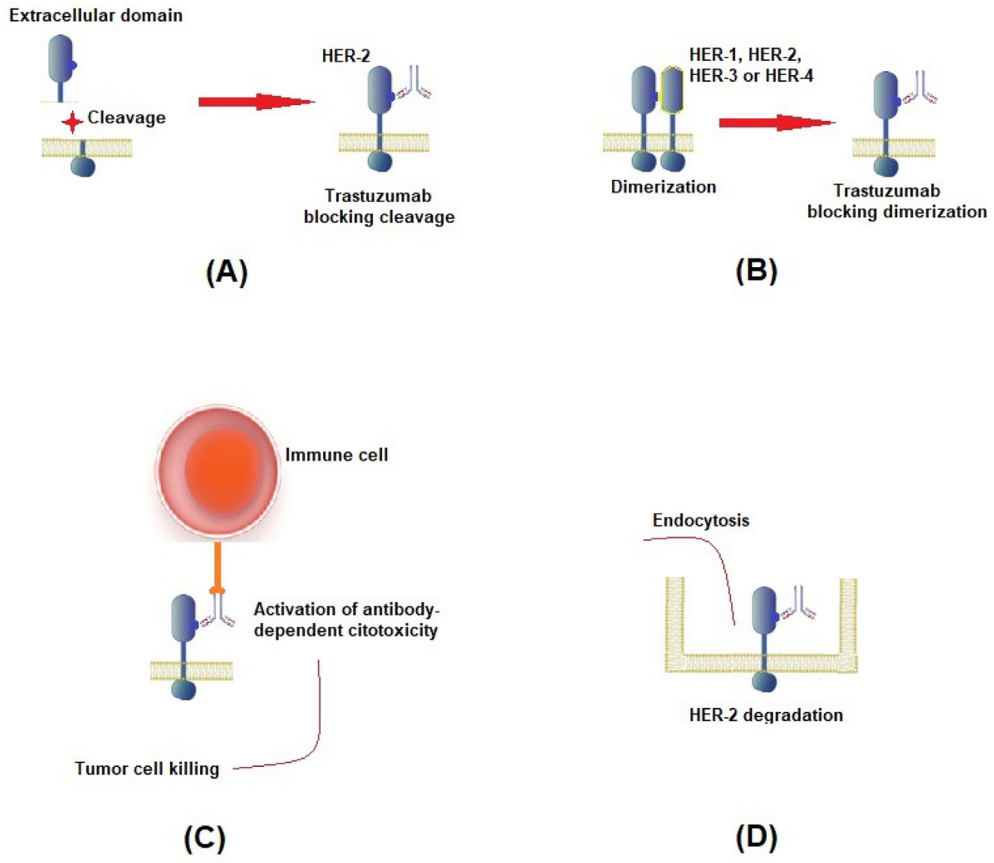

Fig. 2. Mechanisms of action of Trastuzumab. (A) Block of receptor cleavage; (B) Blockade of receptor dimerization; (C) Activation of cell-mediated antibody-dependent toxicity and (C) endocytosis and receptor degradation.

presence in the tumor infiltrate indicates a good efficacy of this monoclonal antibody.

In vitro experiments show that Trastuzumab can effectively mediate ADCP phagocytosis through the action of macrophages (Lazar et al., 2006) and even if in vivo this has not yet been sufficiently demonstrated, it is worth paying attention to this event.

A study by Shi et al. (2015) investigates this phenomenon both through in vitro cultures of macrophages and tumor cells, and in vivo through xenografts on mouse models and demonstrates that the FcR-IV receptor expressed on the surface of guinea pig macrophages interacts with the Fc part of Trastuzumab bound to the tumor cell, inducing ADCP phagocytosis and subsequent elimination of the tumor. This study, therefore, hypothesizes a further action of Trastuzumab and shows how activation of macrophages can improve the action of this monoclonal antibody.

Motivated from the treatment strategies available in the literature, in Fig. 3, we have provided a useful flowchart, that can help the readers to understand the selection criteria for the most accurate treatment strategy. Basically, different types of breast cancer treatments, depends on the patient's estrogen and progesterone levels and the positive or negative receptors reports respectively. In step 1, the breast cancer is removed or treated and is labelled as "Treatment", next, the tests are performed and for the positive Her-2 ("human epidermal growth factor receptor 2 protein", a protein that promotes the growth of the cancer cells) cases, the chemotherapy and/or hormonal therapy along with the drug Trastuzumab is suggested. The action of Trastuzumab can be better understood with the aid of schematic presented in Fig. 4.

This article aims to build a mathematical model that illustrates this additional mechanism of action of Trastuzumab against HER-2/ neu positive breast cancer, based on the assumption that there is the ability of macrophages to engage the Fc part of the monoclonal antibody and that ADCP phagocytosis occurs. This action is presented in Fig. 5.

2. Mathematical Model

In the field of computational biology, the chemical kinetics are translated to mathematical models with the aid of the kinetic modeling, the resulting mathematical models with drug therapy help to explore the dynamics in a cost effective manner (Yu et al., 2020; Yu et al., 2021). Breast cancer patients are now suggested the combined treatment strategies. Since the data for different treatment combinations is really rare, the mathematical modeling can help to explore the resulting dynamics and the likelihood of the success of such interventions. In this manuscript, we have modelled the action of drug, with the aid of system of nonlinear differential equations. The action of macrophages is enhanced by the drug "Trastuzumab" and help to kill the tumour cells (with her-2 receptors). This action is presented in the schematic 6. For the sake of clarity, the population of the cancer cells with HER-2 receptor and Trastuzumab-ligand is defined as x_1, the activated macrophages under the influence of x_1 are defined as x_2, the multi-complex of x_1 and x_2 is defined as x_3

$$\begin{aligned} \frac{dx_1}{dt} &= ax_1 - sx_1^2 - \beta_1 x_2 x_1, \\ \frac{dx_2}{dt} &= \beta_1 x_1(t-\tau)x_2(t-\tau) - bx_2 - \beta_2 x_3 x_2, \\ \frac{dx_3}{dt} &= \beta_2 x_2 x_3 - cx_3. \end{aligned} \tag{1}$$

With initial conditions

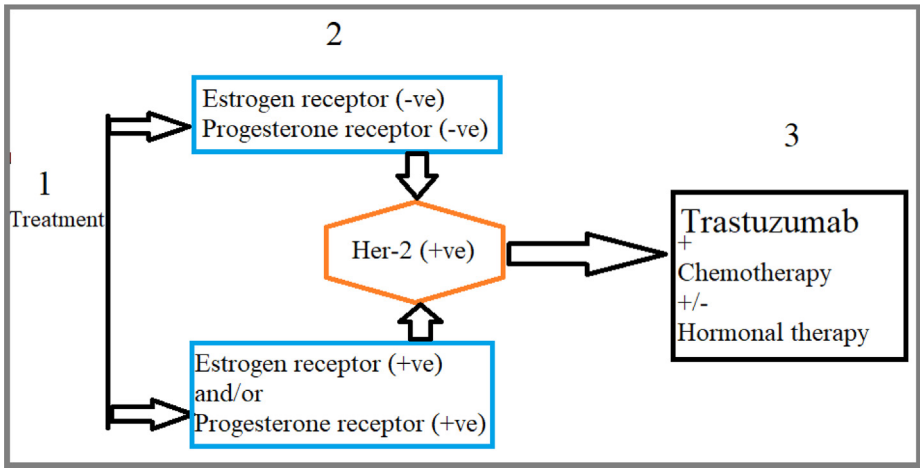

Fig. 3. Flow chart for the accurate treatment strategy of trastuzumab.

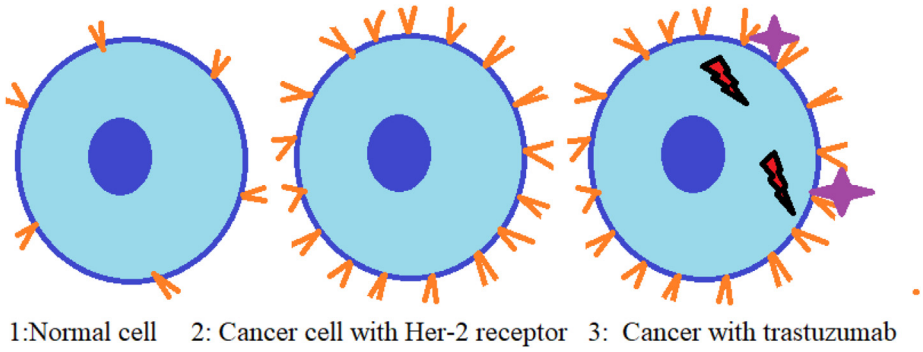

Fig. 4. 1: normal cell with moderate number of Her-2 receptors, 2: cancerous cell, with increased Her-2 receptors, 3: treated cell, via blocking Her-2 receptors through the drug trastuzumab.

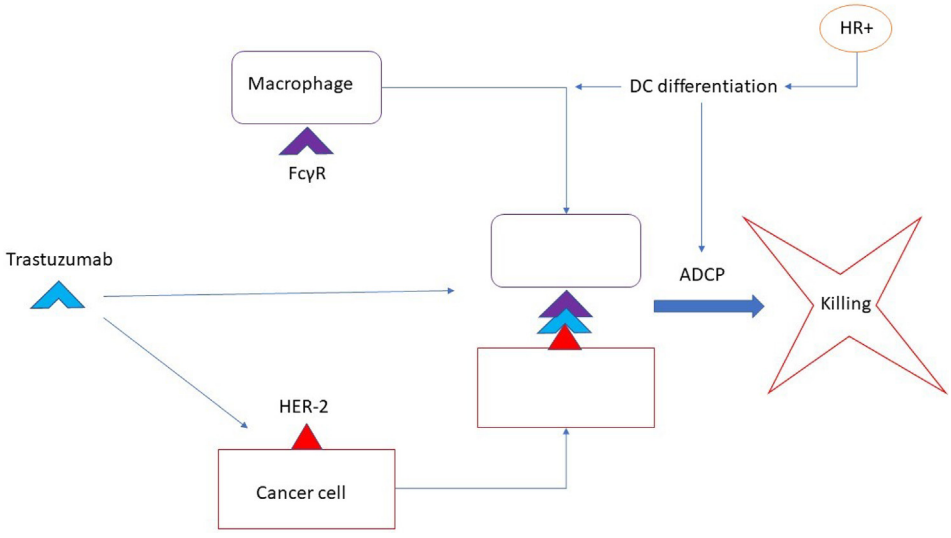

Fig. 5. Schematic of the additional mechanism of action of Trastuzumab.

$$\begin{aligned} x_1(\phi) &= \theta_1(\phi), \\ x_2(\phi) &= \theta_2(\phi) \end{aligned} \tag{2}$$

where $\theta_i(\phi) > 0$ as $i = 1:2$ and $\phi \in (-\tau, 0)$. The biological explanation of variables and parameters is given in Table (1) and (2).

2.1. Theoretical Approach

The stability analysis of a mathematical model helps to understand the dynamical analysis of a given system and to develop intervals, to satisfy the convergence criteria for simulations

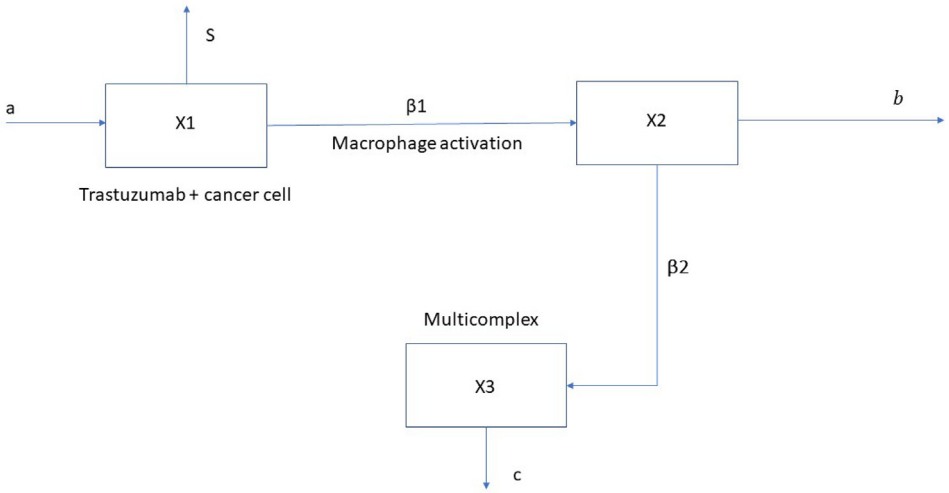

Fig. 6. Schematic of the action of Cancer cells with HER-2 receptor and Trastuzumab-ligand. Cancer-HER2 cells and drug complex is represented as x_1, the activated macrophages under the influence of x_1 are defined as x_2, the multi-complex of x_1 and x_2 is defined as x_3.

Table 1
Description of Compartments.

Symbols	Description
$x_1(t)$	Cancer cells and drug complex
$x_2(t)$	Macrophages activated by x_1
$x_3(t)$	Multi-complex

Table 2
Description of parameters.

Symbols	Biological Description
s	Auto-killing rate
β_1	Interaction rate between x_1 and x_2
β_2	Interaction rate between x_2 and x_3
b	Death rate of x_2
c	Death rate ofx_3

(Tunç, 2010; Yu et al., 2021; Omeike, 2014). In this section, we will work on the stability of the model.

Theorem 2.1. If initial history functions $x_1(0), x_2(0)$ and $x_3(0)$ are positive, then all the solutions of model (1) remains positive for all values of time $t \geqslant 0$.

Proof. Suppose that $x_i(0) \geqslant 0$ where $i = 1:3$. From first equation of model (1)

$$\frac{dx_1}{dt} = ax_1 - sx_1^2 - \beta_1 x_2 x_1$$

separating the variable $x_1(t)$ and integrating

$$x_1(t) = x_1(0)\exp\{(a - \beta_1 x_2 - sx_1)t\} \geqslant 0. \tag{3}$$

Which shows that $x_1(t)$ remain positive as long as $x_1(0)$ is positive. To prove positivity of second equation of model (1), suppose the interval $[0, \tau]$ where we use the positivity of $\theta_1(t)$ and $\theta_2(t)$

$$x_1(t-\tau)x_2(t-\tau) = \theta_1(\phi)\theta_2(\phi) \geqslant 0. \tag{4}$$

in interval $[0, \tau]$, the equation gives

$$\frac{dx_2}{dt} \geqslant -bx_2 - \beta_2 x_3 x_2 \tag{5}$$

by separating the variable $x_2(t)$ and integrating we have

$$x_2(t) \geqslant x_2(0)\exp\{-bt - \beta_2 x_3 t\}. \tag{6}$$

Similarly, in interval $[\tau, 2\tau]$ by using the positivity of $x_2(t)$ on the interval $[0, \tau]$ second equation of model (1) after integrating gives an inequality

$$x_2(t) \geqslant x_2(\tau)\exp\{-bt - \beta_2 x_3 t\}. \tag{7}$$

Continuing this we can find out any finite interval $[0, t]$. It concludes that $x_2(t)$ remains positive as $x_2(0)$ is positive for all values of $t \geqslant 0$.

From third equation of model (1) by integrating

$$x_3(t) = x_3(0)\exp\{\beta_2 x_2 t - ct\} \geqslant 0. \tag{8}$$

Since $x_3(t)$ depends on $x_3(0)$ which shows that $x_3(t)$ remains positive as $x_3(0)$ is positive.

Hence, all the solutions of model (1) positive invariant.

The equilibrium points of model (1) exists for all parametric values. The model (1) has following equilibrium points

$$E_0 = (0, 0, 0). \tag{9}$$

The equilibrium point E_0 is always saddle, where the population zero.

$$E_1 = (\frac{a}{s}, 0, 0). \tag{10}$$

The endemic equilibrium point is only exists if $\frac{\beta_1}{\beta_2} < \frac{a}{c}$,

$$E^* = (\frac{a\beta_2 - \beta_1 c}{\beta_2 s}, \frac{c}{\beta_2}, \frac{a\beta_2\beta_1 - b\beta_2 s + \beta_1^2(-c)}{\beta_2^2 s}). \tag{11}$$

2.1.1. Local stability Analysis

The local stability can be simply determined by a Jacobian matrix evaluated at equilibrium points. The Jacobian matrix at equilibrium point E_0 is

$$J_0 = \begin{pmatrix} a & 0 & 0 \\ 0 & -b & 0 \\ 0 & 0 & -c \end{pmatrix}. \tag{12}$$

Thus, the equilibrium point E_0 is stable manifold lying on yz plane which is non-negative.

Jacobian matrix at equilibrium point E_1 is as follows

$$J_1 = \begin{pmatrix} -a - \lambda & -\frac{a\beta_1}{s} & 0 \\ 0 & \frac{a\beta_1 e^{-\lambda\tau}}{s} - b - \lambda + \frac{a\beta_1}{s} & 0 \\ 0 & 0 & -c - \lambda \end{pmatrix}. \tag{13}$$

This Jacobian matrix has two negative eigenvalues -a and -c. Hence the stability is obtained if

$$\frac{a\beta_1 e^{-\lambda\tau}}{s}+\frac{a\beta_1}{s}-b-\lambda=0 \tag{14}$$

contain only negative roots. The theorem give sufficient condition for this equilibrium point to be locally stable.

Theorem 2.2. If $\frac{2a\beta_1}{s}>b$, the equilibrium point E_1 is always locally stable for all values of delay parameter (τ).

Proof. Suppose that the equilibrium point E_1 is stable at delay zero ($\tau=0$). In other words at zero delay the Eq. (14) gives negative real roots.

$$\lambda<\frac{2a\beta_1}{s}-b<0 \tag{15}$$

which proves that $\frac{2a\beta_1}{s}>b$.

Now suppose that delay parameter τ is continuously changed in positive direction such that there exist a $\tau\prime$ say $\lambda=i\delta$. Putting in Eq. (14)

$$\begin{aligned}\tfrac{a\beta_1}{s}\cos\tau\delta &= b-\tfrac{a\beta_1}{s},\\ \tfrac{a\beta_1}{s}\sin\tau\delta &= -\delta.\end{aligned} \tag{16}$$

By simplifying we have

$$\delta^2=\left(\frac{a\beta_1}{s}\right)^2-\left(\frac{a\beta_1}{s}-b\right)^2 \tag{17}$$

From the Eq. (17) $\delta^2<0$ always if $\frac{2a\beta_1}{s}>b$.

2.1.2. Basic Reproductive number with stability Criteria

The Basic reproduction number of model (1) is

$$R_0=\frac{a\beta_1}{bs}. \tag{18}$$

By this definition of the basic reproduction number, stability of the equilibrium point can be proved.

Theorem 2.3. The equilibrium point E_1 is locally stable for all the values of time delay parameter $\tau\geqslant 0$ if $R_0<1$ and the endemic equilibrium point exists if $R_0>1$.

Proof. By the definition of reproduction number and theorem (2.2) it is clear that if $R_0<1$, all the conditions of the theorem are valid and $R_0>1$ shows the existence of positive equilibrium.

2.1.3. Local Stability of endemic equilibrium

Here we determine conditions for the occurrence of Hopf bifurcation where time delay as bifurcation parameter. During this analysis we will suppose that the basic reproductive number $R_0>1$, that the endemic equilibrium exists. To analyze stability of endemic equilibrium, the Jacobian matrix at endemic equilibrium point E^* is

$$J^*=\begin{pmatrix} J_1-\lambda & J_2 & 0\\ J_3+J_3e^{-\lambda\tau} & J_4-J_2e^{-\lambda\tau}-\lambda & -c\\ 0 & J_5 & -\lambda\end{pmatrix} \tag{19}$$

where the coefficients are

$$\begin{aligned}J_1 &= \tfrac{2a(\beta_1 c-a\beta_2)}{\beta_2}-\tfrac{\beta_1 c}{\beta_2},\\ J_2 &= \tfrac{\beta_1(\beta_1 c-a\beta_2)}{\beta_2 s},\\ J_3 &= \tfrac{\beta_1 c}{\beta_2},\\ J_4 &= \tfrac{b\beta_2 s-a\beta_2\beta_1+\beta_1^2 c}{\beta_2 s}-\tfrac{\beta_1(\beta_1 c-a\beta_2)}{\beta_2 s}-b,\\ J_5 &= \tfrac{a\beta_2\beta_1-b\beta_2 s-\beta_1^2 c}{\beta_2 s}.\end{aligned} \tag{20}$$

The transcendental characteristic equation of above matrix

$$\lambda^3+\alpha_1\lambda^2+\alpha_2\lambda+\alpha_3+e^{-\lambda\tau}(\gamma_1\lambda^2+\gamma_2\lambda+\gamma_3)=0. \tag{21}$$

where the constants are

$$\begin{aligned}\alpha_1 &= -J_1-J_4,\\ \alpha_2 &= cJ_5-J_2J_3+J_1J_4,\\ \alpha_3 &= -cJ_1J_5,\\ \gamma_1 &= J_2,\\ \gamma_2 &= -J_1J_2-J_2J_3,\\ \gamma_3 &= 0.\end{aligned} \tag{22}$$

To initiate bifurcation analysis of model (1), first of all it is supposed that time delay is zero in Eq. (21), such that it gives negative real roots. Here, Routh-Hurwitz theorem can be used to get desired conditions for negative real roots of the Eq. (21), which proves the stability criteria. By applying Routh-Hurwitz theorem, we can get following conditions

$\alpha_1+\gamma_1>0, \alpha_3+\gamma_3>0$ and $(\alpha_1+\gamma_1)(\alpha_2+\gamma_2)>(\alpha_3+\gamma_3)$.

Since the time delay is increasing from from zero to onward, some negative real part of the roots in left half complex plane goes toward the right half complex plane. This will make endemic equilibrium point unstable. Condition for Hopf Bifurcation is that equation should give at least one positive root as the bifurcation parameters are continuously changed. This is conceivable if roots of equation also give root with zero parts by the Rouche's Theorem. We again suppose that $\lambda=i\eta$ in Eq. (21) we have equation of real and imaginary part

$$\begin{aligned}\alpha_2\eta-\eta^3 &= (\gamma_3-\gamma_1\eta^2)\sin\tau\eta-\gamma_2\eta\cos\tau\eta,\\ \alpha_3-\alpha_1\eta^2 &= (\gamma_1\eta^2-\gamma_3)\cos\tau\eta-\gamma_2\eta\sin\tau\eta.\end{aligned} \tag{23}$$

We eliminate the trigonometric function by squaring and adding then, we have

$$\eta^6+\eta^4(\alpha_1^2-2\alpha_2-\gamma_1^2)+\eta^2(\alpha_2^2-2\alpha_1\alpha_3-\gamma_2^2+2\gamma_1\gamma_3)+\alpha_3^2-\gamma_3^2=0. \tag{24}$$

To make it third order equation we suppose that $\eta^2=\rho$ then, the above equation will become

$$\rho^3+\rho^2 z_1+\rho z_2+z_3=0 \tag{25}$$

where:

$$\begin{aligned}z_1 &= \alpha_1^2-2\alpha_2-\gamma_1^2,\\ z_2 &= \alpha_2^2-2\alpha_1\alpha_3-\gamma_2^2+2\gamma_1\gamma_3,\\ z_3 &= \alpha_3^2-\gamma_3^2.\end{aligned} \tag{26}$$

The following theorems helps to conclude the condition that lead the stability of endemic equilibrium point.

Theorem 2.4. If $z_1\geqslant 0, z_3\geqslant 0$ and $z_2>0$ then, Eq. (25) has no positive roots.

Proof. Suppose that

$$h(\rho)=\rho^3+\rho z_2+\rho^2 z_1+z_3$$

Taking the derivative on both sides with respect to ρ we have

$$h\prime(\rho) = 3\rho^2 + 2\rho z_1 + z_2. \tag{27}$$

We can see that for $\rho \geqslant 0$ the $h\prime(\rho) > 0$. Hence the function is the increasing function for $\rho \geqslant 0$ and $h(0) = z_3$.It is prove that Eq. (25) has no positive real root.

By the rule of signs of Descartes Eq. (21) has at least on positive real root if $z_1 > 0, z_2 > 0$ and $\alpha_3^2 < \beta_3^2$ holds.

Now by eliminating $\sin\tau\eta$ at $\eta = \eta_0$ from Eq. (23) we can get τ value that is

$$\tau_j = \frac{1}{\eta_0}\arccos\left\{\frac{\beta_2\eta_0^2(\eta_0^2-\alpha_2)+\alpha_1\eta_0^2(\beta_3-\beta_1\eta_0^2)+\alpha_3(\beta_1\eta_0^2-\beta_3)}{\beta_1^2\eta_0^4+\beta_2^2\eta_0^2-2\beta_1\beta_3\eta_0^2+\beta_3^2}\right\}+\frac{2\pi j}{\eta_0} \tag{28}$$

where $j = 0, 1, 2, \ldots$.

The hopf bifurcation occurs if $\left(\frac{d\lambda}{d\tau}\right)^{-1} > 0$ for $\eta = \eta_0$. we can obtain $\left(\frac{d\lambda}{d\tau}\right)^{-1}$ by taking the derivative of Eq. (21) with respect to delay parameter τ that is

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{2\alpha_1\lambda+\alpha_2+3\lambda^2}{\lambda\left(\alpha_1\lambda^2+\alpha_2\lambda+\alpha_3+\lambda^3\right)} - \frac{2\beta_1\lambda+\beta_2}{\lambda\left(\beta_1\lambda^2+\beta_2\lambda+\beta_3\right)} - \frac{\tau}{\lambda}. \tag{29}$$

Thus,

$$Sign\left\{\frac{dR\lambda}{d\tau}\right\}_{\lambda=i\eta_0} = Sign\left\{\frac{\left(3\eta_0^2-\alpha_2\right)\left(-\alpha_1\eta_0-\alpha_2+\eta_0^2\right)-2\alpha_1\alpha_3}{\eta_0^2\left(\alpha_1\eta_0+\alpha_2-\eta_0^2\right)^2+\alpha_3^2} + \frac{2\beta_1^2\eta_0^3-2\beta_1\beta_3\eta_0+\beta_2^2}{\eta_0\left(\left(\beta_3-\beta_1\eta_0^2\right)^2+\beta_2^2\right)}\right\}. \tag{30}$$

3. Results

3.1. Theoretical summary

The above analysis is summarized theoretically as:

Theorem 3.1. Suppose that $R_0 > 1$, if either $z_3 < 0$ or $z_3 \geqslant 0$ and $z_2 < 0$ is satisfied there exist a positive parameter η_0 such that the endemic equilibrium point is asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$. Furthermore, the model will undergoes hopf bifurcation for $\tau = \tau_0$ where

$$\tau_0 = \frac{1}{\eta_0}\arccos\left\{\frac{\beta_2\eta_0^2(\eta_0^2-\alpha_2)+\alpha_1\eta_0^2(\beta_3-\beta_1\eta_0^2)+\alpha_3(\beta_1\eta_0^2-\beta_3)}{\beta_1^2\eta_0^4+\beta_2^2\eta_0^2-2\beta_1\beta_3\eta_0^2+\beta_3^2}\right\}. \tag{31}$$

By using the time delay τ as a bifurcation parameter, the above analysis indicates that the introduction of time delay model at a certain value τ_0 of time delay could exhibit Hopf bifurcation if parameters satisfy the conditions. It is concluded that introduction of the time delay in model can destabilize system.

4. Discussion

In this section, we will work on the numerical experiments. The graphs below are produced with the aid of the parametric values, which are arbitrarily chosen, by keeping in view the ideal percentages of the targeted cells. By this we mean to say that it is desired that maximum number of cancer cells with HER2 receptor, get killed by the macrophages. To achieve this goal, nondimensional formalism of the model was adopted in a manner similar to Destexhe et al. (1994). Secondly, different transition rates and interaction rates were simulated to achieve maximum cancer cell killing.

4.1. Variation in Delay

The action of drug on cancer cells with HER2 receptors is not straightforward. Furthermore, the activation of the macrophages in response to the drug binding to HER2 cells is a delayed process. For this reason, we have considered the delay τ in time. For different values of τ we obtained different results. In Fig. 7, we have compared the two cases, with higher and lower values of τ. The rest of the parameters were set to normal values as presented in Table 1. The value of s, which presents the autoaction of cancer cells ("Tricking a Cancer Cell into Committing Suicide or Apoptosis"), was kept higher than the initial value of $s = s_0$. We can see a twist in the phase space portraits and for lower value of τ, the multi-complex concentration approach zero with the passage of time, whereas for higher values of τ (right panel), there is a limit cycle and the fluctuation in the concentration continues with the passage of time, without approaching to zero. (see Fig. 8).

4.2. Variation in Interaction Rates β_1

For different values of β_1 different dynamics were observed. For lower values of β, we see higher concentration of the multi-complex whereas for higher values of β, we see lower concentration of multi-complex with a shift in phase (as shown in Fig. 7).

In Fig. 9, we have fixed all the other parametric values, including the delay (lower value) and β_1 = 1, and have given variation to

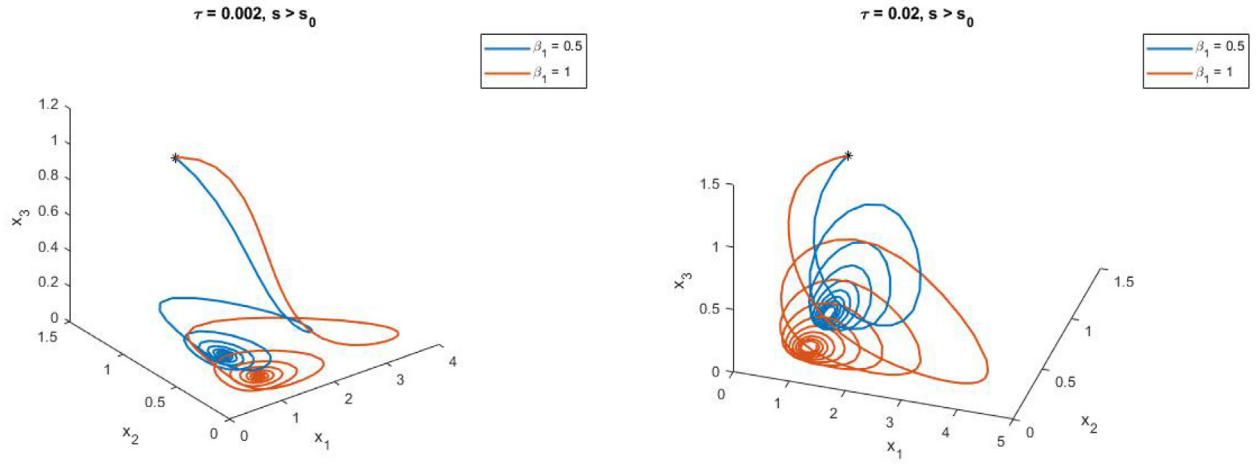

Fig. 7. Dynamics relative to the variation in time delay τ.

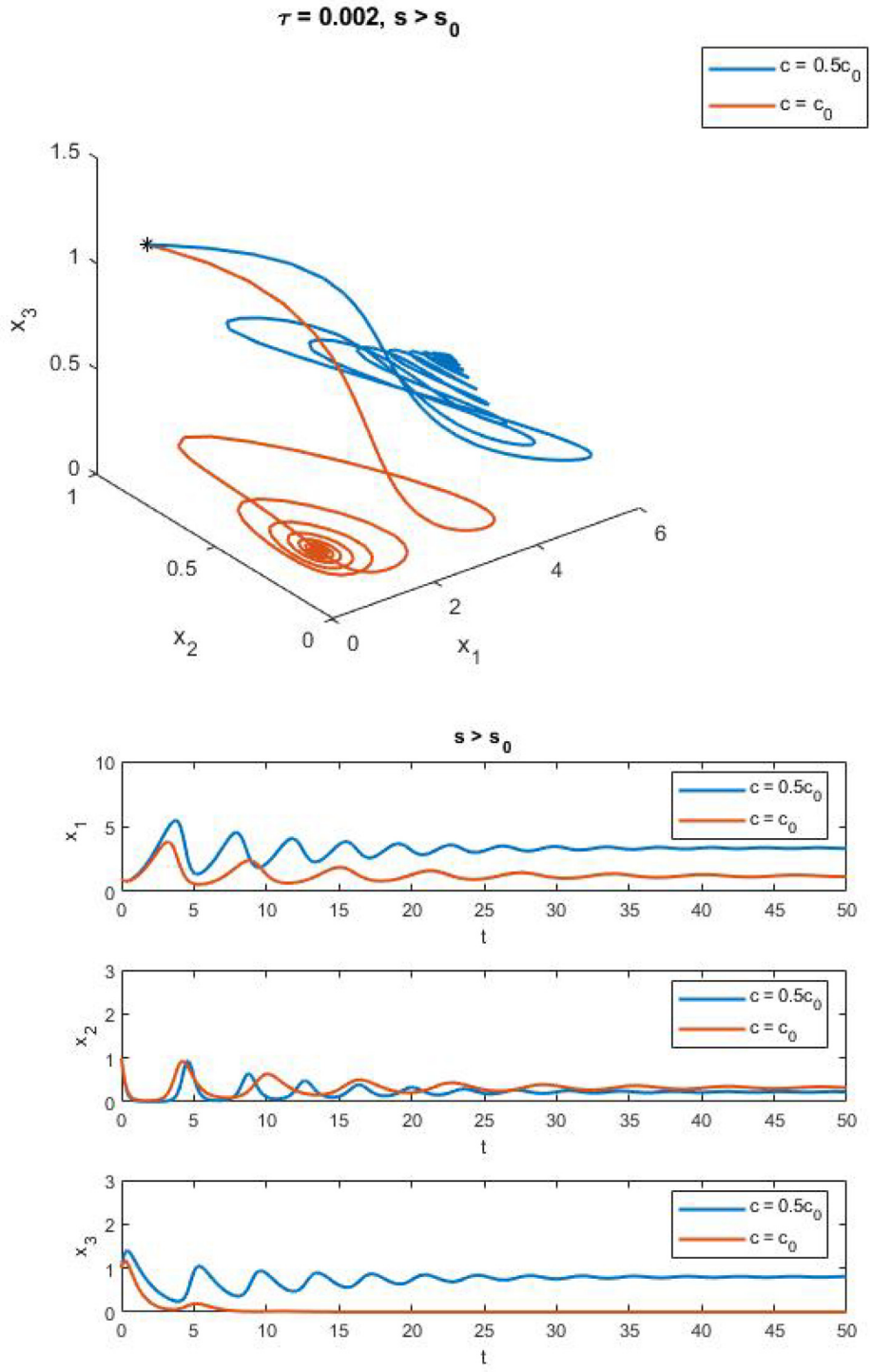

Fig. 8. Dynamics relative to the variation in *c*.

c. For higher values of *c*, i.e. for reduced concentration of the multi-complex, we have seen declination in the amplitude of the three variables. The proposed model selectively analyzes the killing action of cancer cells by antibody-dependent phagocytosis (ADCP), but indirect control of the further effects of the monoclonal antibody (inhibition of HER receptor dimerization, for example) are reflected in the model itself. considering the parameter "ax1" which is an index of formation of the x1 complex (Trastuzumab + can cer cells) which has a natural logical connection with the variation of the parameter "c" whose dynamic fluctuation is represented in Fig. 7. The model, therefore, while analyzing the efficiency of Trastuzumab in killing by ADCP, indirectly includes the control of the additional therapeutic effects that the monoclonal antibody itself exerts.

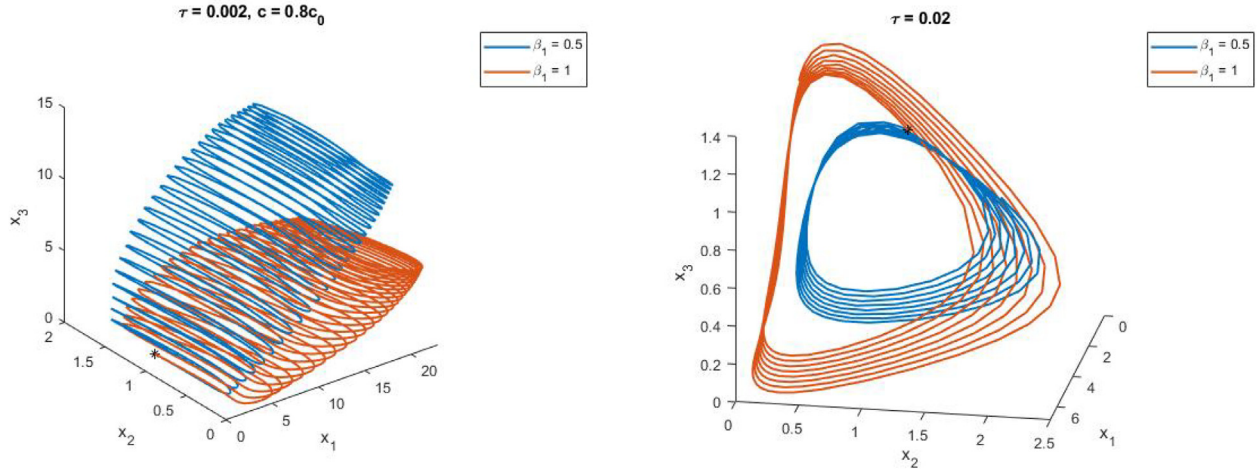

Fig. 9. Dynamics relative to the variation in time delay τ and for reduced values of decay rate of multi-complex c.

5. Conclusions

A mathematical model is developed to demonstrate the action of breast cancer treatment. The model predicts a delay in the action of macrophages about the binding of Trastuzumab to HER-2 + cancer cells. The model shows that the multi-complex (x_3) shows a therapeutic dynamic. The temporal fluctuation never decays to zero, but which persists, showing efficacy over time. This explains the positive follow up of the Overall Survivor (OS) parameter that several studies report regarding Trastuzumab therapy in HER-2 + breast cancer (Buzdar et al., 2019).

We, therefore, believe that this type of model can represent a logical basis to understand the therapeutic efficacy of Trastuzumab. It represents a dynamical system with "plasticity" that can be further extended for combined therapies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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