

**COMPUTATIONAL MODELLING OF CANCER
STEM CELL WITH HYPOXIA AND THEIR
THERAPEUTIC RESPONSE**

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by

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Submitted

in fulfilment of the requirements of the degree of Doctor of Philosophy
to the



INDIAN INSTITUTE OF TECHNOLOGY DELHI

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CERTIFICATE

This is to certify that the thesis entitled “**Computational Modelling of Cancer Stem Cell with Hypoxia and their Therapeutic Response**” submitted by **Kumari Neelam Verma** to the Department of Mechanical Engineering, Indian Institute of Technology Delhi, India for an award of degree of **Doctor of Philosophy** is a record to bonafide research work carried out by her. Kumari Neelam Verma has worked under my supervision for the submission of this thesis, which to my knowledge has reached the requisite standard.

The thesis or any part of it has not been presented or submitted to any university or institute for any degree or diploma.

Place: New Delhi

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DECLARATION

I hereby declare that the project entitled “Computational Modelling of Cancer Stem Cell with Hypoxia and their Therapeutic Response” submitted to the Indian Institute of Technology Delhi in fulfillment of the requirements for the award of the degree of Doctor of Philosophy in Mechanical Engineering is a record of bonafide work carried out by myself independently under the guidance of Dr. Debabrata Dasgupta, Department of Mechanical Engineering, Indian Institute of Technology Delhi, India.

I further declare that the work reported in this project has not been submitted and will not be submitted, either in part or full, for the award of any other degree in this institution or any other institute or university.

Kumari Neelam Verma

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Kumari Neelam Verma

ABSTRACT

Cancer stem cells (CSCs), constituting a subset of tumor cells, play a pivotal role in tumor initiation, metastasis, and recurrence, their stemness as a hallmark of cancer. These cells exhibit characteristics such as self-renewal, enhanced proliferation, ability to instigate cancer relapse. During cancer progression, epithelial-mesenchymal transition (EMT) transforms epithelial cells into mesenchymal cells contributing to metastasis. The EMT process, intricately linked with cancer stem cell properties, facilitates differentiation and self-renewal. The orchestration of these functions relies on the microenvironment within tissues, specifically within the structure known as stem cell niche, formed through interaction between a stem cell, and exterior cell, i.e., the surrounding cell, and the extracellular matrix (ECM).

The ECM comprised of macromolecules and minerals like enzymes, collagen, and glycoproteins, modulates various signaling pathways by secreting the proteases, cytokines, chemokines, and vesicles. The urokinase-type plasminogen activator (uPA), a crucial component of the ECM, is part of a system including binding proteins, serpin inhibitors, active enzymes, and proenzymes. The uPA system's intricate molecular arrangement regulates the activation and inhibition of plasminogen and matrix-degrading protein plasmin, leading to extracellular matrix (ECM) degradation. Notably, overexpression of uPA/uPAR induces EMT in cancer cells, fostering invasiveness, metastasis, and chemoresistance upon interaction with CSC. Given its involvement in tumor progression, the uPA system contributes to poor prognoses and therapeutic resistance.

Understanding the interplay between EMT, plasminogen activation within microenvironment and CSCs provides a promising avenue for cancer strategies. Additionally, the rapid growth and metastatic potential of cancer cells are sustained by the availability of nutrients and oxygen, further emphasizing the importance of exploring these aspects of cancer therapeutics.

Insufficient oxygen in the tumor microenvironment gives rise to a localized oxygen-deprived region known as hypoxia, a crucial factor in preserving the stemness properties of CSCs and conferring resistance to chemotherapy and other tumor treatments. CSCs play a pivotal role in various aspects of tumorigenesis including invasion, proliferation, metastasis, drug resistance, and relapse. Hypoxia emerges as a significant contributor to the maintenance of stemness within the tumor microenvironment, facilitating the activation of

surrounding proteases that contribute to metastasis. These critical attributes contribute to unfavorable prognoses of tumors and the development of therapeutic resistance. Consequently, investigating the interplay between the hypoxic microenvironment and CSCs presents an avenue for devising effective treatment strategies.

Hypoxia influences the tumor microenvironment's stemness, with the activation of surrounding proteases playing a key role in promoting metastasis. These features collectively contribute to poor prognosis and therapeutic resistance. Central to the hypoxic pathway is Hypoxia-inducible factor-1 alpha ($\text{HIF-1}\alpha$) a transcription factor released by the tumor in response to decreased oxygen levels. This response extends to both the tumor and the immune system. Additionally, Cancer stem cells play a pivotal role in dedifferentiation, tumor cell recurrence, and resistance to treatment, coupled with augmented metabolic potential. Furthermore, the survival of tumor cells and suppression of immune response to cancer cells are influenced by the stimulation of transforming growth factor ($\text{TGF-}\beta$) in tumor microenvironment (TME).

Firstly, this study investigates the invasion dynamics of cancer cells and stem cells, considering chemotaxis and haptotaxis in both one-dimensional and two-dimensional scenarios. The study delves into the role of uPA in conjunction with the EMT process. Specifically, the focus is on understanding the dynamics of uPA and stem cells, their interplay with EMT, and the impact of these parameters on cancer progression and migration. A Mathematical model of tumor growth, is developed, employing Keller Segel taxis to describe the invasion in the reaction-diffusion equation of the system. The resulting nonlinear partial differential equation elucidates the tumor growth dynamics of stem cells and EMT in integration with the plasminogen activation microenvironment. The findings underscore the significant influence of the plasminogen activation system on cancer stem cells in the presence of EMT.

Secondly, this study examines the impact of hypoxic conditions on cancer stem cells in the context of EMT. A Mathematical model of tumor growth is developed for both one-dimensional and two-dimensional cases, capturing the nonlinear partial differential equation that characterizes stem cell tumor growth in a hypoxic microenvironment. The results highlight the substantial effect of oxygen on cancer stem cells when EMT is present.

Thirdly, the novelty of this work lies in the incorporation of $\text{TGF-}\beta$, cancer stem cells, and HIF in association with tumor cells and TME. The proposed mathematical model induces a system of differential equations to explore the interaction between cancer cells and the

immune system. Notably, natural killer (NK) cells, CD4+T cells, circulating lymphocytes, and CD8+T cells are considered to investigate their impact on tumor growth. The model is designed to elucidate the temporal dynamics of these interactions.

This proposed computational model stands as a robust method for studying tumor growth in the context of immune and chemo interaction, providing valuable insights for the investigation, planning, and implementation of host treatment.

Keywords: Cancer stem cell, HIF, Tumour growth, urokinase plasminogen activator, Mathematical model, EMT, Immunotherapy and Chemotherapy

सारांश

कैंसर स्टेम कोशिकाएँ (सीएससी), जो ट्यूमर कोशिकाओं का एक उपसमूह बनाती हैं, ट्यूमर की शुरुआत, मेटास्टेसिस और पुनरावृत्ति में महत्वपूर्ण भूमिका निभाती हैं, उनकी स्टेमनेस कैंसर की एक विशिष्ट विशेषता है। ये कोशिकाएँ आत्म-पुनर्निर्माण, उन्नत प्रसार और कैंसर पुनरावृत्ति को प्रेरित करने की क्षमता जैसे गुण प्रदर्शित करती हैं। कैंसर प्रगति के दौरान, एपिथेलियल-मेसेन्काइमल ट्रांजिशन, एपिथेलियल कोशिकाओं को मेसेन्काइमल कोशिकाओं में बदल देता है, जो मेटास्टेसिस में योगदान देती हैं। ईएमटी प्रक्रिया, जो कैंसर स्टेम कोशिकाओं के गुणों से जटिल रूप से जुड़ी होती है, विभेदन और आत्म-पुनर्निर्माण की सुविधा प्रदान करती है। इन कार्यों का संचालन ऊतकों के सूक्ष्म वातावरण पर निर्भर करता है, विशेष रूप से स्टेम सेल निश नामक संरचना पर, जो एक स्टेम सेल, बाहरी कोशिका और बाह्यकोशिकीय मैट्रिक्स (ईसीएम) के बीच परस्पर क्रिया के माध्यम से बनती है।

ईसीएम, एंजाइम, कोलेजन और ग्लाइकोप्रोटीन जैसे मैक्रोमोलेक्यूल और खनिजों से बना होता है, प्रोटीज, साइटोकिन्स, केमोकिन्स और वेसिकल्स को स्रावित करके विभिन्न सिग्नलिंग मार्गों को मॉड्यूलेट करता है। ईसीएम का एक महत्वपूर्ण घटक, यूरोकाइनेज-टाइप प्लास्मिनोजन एक्टिवेटर (यूपीए), बाइंडिंग प्रोटीन, सर्पिन इन्हिबिटर, सक्रिय एंजाइम और प्रोएंजाइम्स सहित एक प्रणाली का हिस्सा है। यूपीए प्रणाली की जटिल आणविक व्यवस्था प्लास्मिनोजन और मैट्रिक्स-क्षयकारी प्रोटीन प्लास्मिन के सक्रियण और निरोध को नियंत्रित करती है, जिससे ईसीएम का क्षय होता है। विशेष रूप से, यूपीए / यूपीएआर की अधिक अभिव्यक्ति कैंसर कोशिकाओं में ईएमटी को प्रेरित करती है, जिससे आक्रामकता, मेटास्टेसिस और सीएससी के साथ परस्पर क्रिया पर कीमोरेसिस्टेंस को बढ़ावा मिलता है। इसके ट्यूमर प्रगति में शामिल होने के कारण, यूपीए प्रणाली खराब प्रोग्नोसिस और चिकित्सीय प्रतिरोध में योगदान करती है।

ईएमटी, प्लास्मिनोजन सक्रियण और सीएससी के बीच परस्पर क्रिया को समझना कैंसर रणनीतियों के लिए एक संभावित मार्ग प्रदान करता है। इसके अलावा, पोषक तत्वों और ऑक्सीजन की उपलब्धता के द्वारा कैंसर कोशिकाओं की तेजी से वृद्धि और मेटास्टेटिक क्षमता बनी रहती है, जिससे कैंसर उपचार के इन पहलुओं का पता लगाने के महत्व को और अधिक उजागर किया जाता है। ट्यूमर सूक्ष्म पर्यावरण में अपर्याप्त ऑक्सीजन के कारण एक स्थानीयकृत ऑक्सीजन-हीन क्षेत्र, जिसे हाइपोक्सिया के रूप में जाना जाता है, उत्पन्न होता है, जो सीएससी की स्टेमनेस गुणों को संरक्षित

करने और कीमोथेरेपी और अन्य ट्यूमर उपचारों के प्रति प्रतिरोध प्रदान करने में महत्वपूर्ण कारक है।

सीएससी ट्यूमोरोजेनेसिस के विभिन्न पहलुओं में महत्वपूर्ण भूमिका निभाते हैं, जिनमें आक्रमण, प्रसार, मेटास्टेसिस, दवा प्रतिरोध और पुनरावृत्ति शामिल हैं। हाइपोक्सिया, ट्यूमर सूक्ष्म पर्यावरण में स्टेमनेस को बनाए रखने में महत्वपूर्ण योगदानकर्ता के रूप में उभरता है, जो मेटास्टेसिस में योगदान करने वाले आस-पास के प्रोटीज के सक्रियण की सुविधा प्रदान करता है। ये महत्वपूर्ण विशेषताएँ ट्यूमर के प्रतिकूल प्रोग्नोसिस और चिकित्सीय प्रतिरोध के विकास में योगदान करती हैं। परिणामस्वरूप, हाइपोक्सिक सूक्ष्म पर्यावरण और सीएससी के बीच परस्पर क्रिया की जांच प्रभावी उपचार रणनीतियों को तैयार करने के लिए एक संभावित मार्ग प्रस्तुत करती है।

हाइपोक्सिया ट्यूमर सूक्ष्म पर्यावरण की स्टेमनेस को प्रभावित करता है, जिसमें मेटास्टेसिस को बढ़ावा देने में आस-पास के प्रोटीज की सक्रियता प्रमुख भूमिका निभाती है। ये विशेषताएँ मिलकर खराब प्रोग्नोसिस और चिकित्सीय प्रतिरोध को बढ़ावा देती हैं। हाइपोक्सिक मार्ग के केंद्र में हाइपोक्सिया-इंड्यूसिबल फैक्टर-1 अल्फा (एचआईएफ -1 α) है, जो ट्यूमर द्वारा ऑक्सीजन के स्तर में कमी के जवाब में रिलीज होता है। यह प्रतिक्रिया ट्यूमर और प्रतिरक्षा प्रणाली दोनों तक फैली हुई है। इसके अलावा, सीएससी पुनः विभेदन, ट्यूमर कोशिका पुनरावृत्ति और उपचार के प्रति प्रतिरोध में महत्वपूर्ण भूमिका निभाते हैं, जिसके साथ चयापचय क्षमता बढ़ती है। इसके अलावा, ट्यूमर कोशिकाओं की उत्तरजीविता और ट्यूमर सूक्ष्म पर्यावरण (टीएमई) में ट्रांसफॉर्मिंग ग्रोथ फैक्टर (टीजीएफ - β) के उत्तेजना द्वारा प्रतिरक्षा प्रतिक्रिया का दमन प्रभावित होता है।

पहले, यह अध्ययन केमोटैक्सिस और हायोटैक्सिस को ध्यान में रखते हुए एक-आयामी और दो-आयामी परिदृश्यों में कैंसर कोशिकाओं और स्टेम कोशिकाओं के आक्रमण गतिशीलता की जांच करता है। यह अध्ययन यूपीए की भूमिका पर ईएमटी प्रक्रिया के संयोजन के साथ गहराई से अध्ययन करता है। विशेष रूप से, यूपीए और स्टेम कोशिकाओं की गतिशीलता को समझने, ईएमटी के साथ उनकी परस्पर क्रिया और कैंसर प्रगति और प्रवास पर इन मापदंडों के प्रभाव पर केंद्रित है। एक गणितीय मॉडल विकसित किया गया है, जिसमें प्रणाली की प्रतिक्रिया-प्रसार समीकरण में आक्रमण का वर्णन करने के लिए केलर सेगल टैक्सिस को नियोजित किया गया है। परिणामी गैर-रेखीय आंशिक अंतर समीकरण, प्लास्मिनोजन सक्रियण सूक्ष्म पर्यावरण के एकीकरण में स्टेम कोशिकाओं और ईएमटी की ट्यूमर वृद्धि की गतिशीलता को स्पष्ट करता है। निष्कर्ष में, ईएमटी की उपस्थिति में कैंसर स्टेम कोशिकाओं पर प्लास्मिनोजन सक्रियण प्रणाली के महत्वपूर्ण प्रभाव को उजागर करते हैं।

दूसरे, अध्ययन में ईएमटी के संदर्भ में हाइपोक्सिक स्थितियों में कैंसर स्टेम कोशिकाओं पर प्रभाव की जांच करता है। एक गणितीय मॉडल विकसित किया गया है जो एक-आयामी और दो-आयामी मामलों के लिए ट्यूमर वृद्धि को चित्रित करता है, जिसमें एक गैर-रेखीय आंशिक अंतर समीकरण कैप्चर किया गया है जो हाइपोक्सिक सूक्ष्म पर्यावरण में स्टेम कोशिका ट्यूमर वृद्धि को दर्शाता है। परिणामों से पता चलता है कि ईएमटी की उपस्थिति में ऑक्सीजन का कैंसर स्टेम कोशिकाओं पर पर्याप्त प्रभाव पड़ता है।

तीसरे, इस कार्य की नवीनता ट्यूमर कोशिकाओं और टीएमई के साथ एसोसिएशन में टीजीएफ- β , कैंसर स्टेम कोशिकाओं और एचआईएफ को शामिल करने में निहित है। प्रस्तावित गणितीय मॉडल प्रतिरक्षा प्रणाली और कैंसर कोशिकाओं के बीच परस्पर क्रिया का पता लगाने के लिए एक प्रणाली को प्रेरित करता है। विशेष रूप से, प्राकृतिक किलर (एनके) कोशिकाएँ, सीडी4+टी कोशिकाएँ, परिपत्र लिम्फोसाइट्स और सीडी8+टी कोशिकाएँ शामिल हैं, ताकि ट्यूमर वृद्धि पर उनके प्रभाव की जांच की जा सके। मॉडल को इन परस्पर क्रियाओं की अस्थायी गतिशीलता को स्पष्ट करने के लिए डिज़ाइन किया गया है।

प्रस्तावित कम्प्यूटेशनल मॉडल, प्रतिरक्षा और कीमो परस्पर क्रिया के संदर्भ में ट्यूमर वृद्धि का अध्ययन करने के लिए एक मजबूत विधि के रूप में खड़ा है, जो जांच, योजना और मेजबान उपचार के कार्यान्वयन के लिए मूल्यवान अंतर्दृष्टि प्रदान करता है।

कीवर्ड: कैंसर स्टेम सेल, एच आई एफ, ट्यूमर वृद्धि, यूरोकाइनेज प्लास्मिनोजन सक्रियक, गणितीय मॉडल, ईएमटी, इम्यूनोथेरेपी और कीमोथेरेपी

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LIST OF SYMBOLS AND ABBREVIATIONS

EMT			
λ^{DCC}	Average bound EGFR receptor per cell	k_D	EGF binding/unbinding
μ_0	EMT rate	Γ	Average of total EGF
$\mu_{1/2}$	Critical EGF concentration	λ^{CSC}	Average free EGFR receptor per cell
μ_{EMT}	EMT coefficient	S	oxygen concentration
\mathcal{E}	Characteristic deviation of oxygen to critical oxygen concentration	\tilde{g}_f	The free EGFR constant in a given space
Ω	computational domain		
CSC and uPA			
δ	Rate of ECM degradation by MDE	β_{41}	Decay rate of MDE
α_{41}	Production rate of MDE by DCC	d_{cd}	Diffusion coefficient of DCCs
α_{42}	Production rate of MDE by CSC	d_{cs}	Diffusion coefficient of CSC
α_{51}	Production rate of uPA by DCC	d_u	Diffusion of uPA
d_m	Diffusion of MDE	γ_{cs}	Haptotaxis coefficient of CSC
γ_u	Haptotaxis coefficient of uPA	β_{51}	The decay rate of uPA by DCC
ϕ_{23}	DCC surface receptors recycling rate	ϕ_{13}	CSC surface receptors recycling rate
μ_{23}	The proliferation rate constant of ECM	β_{52}	The decay rate of uPA by CSC
γ_p	Haptotaxis coefficient of CSC	ϕ_{32}	Neuralization of ECM through PAI-1 interaction
α_{61}	Production caused by MDE	ϕ_{51}	Reduction due to uPA and PAI-1
ϕ_{31}	Production through PAI-1 and uPA interaction	ϕ_{61}	Loss caused by ECM and PAI-1 interaction
ϕ_{41}	Production through PAI-1 and ECM interaction	ϕ_{62}	Loss due to uPA and PAI-1 interaction
D_p	Diffusion of PAI-1	ϕ_{42}	Degradation caused by PAI-1 and uPA interaction
α_{52}	Production rate of uPA by CSC	β_{52}	The decay rate of uPA by CSC
γ_{cd}	Haptotaxis coefficient of DCC	ζ_{cd}, ξ_{cd}	Chemotaxis coefficient of DCC

HYPOXIA

ρ	Decay of oxygen	β_1	Cancer cell division rate of CSCs
S_{crit}	Critical oxygen concentration	λ	Maximal death rate
μ	Oxygen consumption rate by DCCs	d_s	Diffusion coefficient of oxygen
μ_1	Oxygen consumption rate by CSCs	ε	Characteristic deviation of oxygen to critical oxygen concentration
β	Cancer cell division rate of DCCs	v	Production rate of oxygen
γ	Haptotaxis Parameter	k_1	Production of MDE by CSC
k	Production of MDE by DCC	σ	Decay of MDE
ϕ_{31}	Production through PAI-1 and uPA interaction	ϕ_{11}	Loss caused by PAI-1 and uPA interaction
D_u	Diffusion of uPA	ϕ_{32}	Production of concentration due to CSC and uPA
μ_{11}	Loss caused by uPA and DCC interaction	ϕ_{12}	Production through ECM and PAI-1 interaction
μ_{12}	Loss caused by uPA and CSC interaction	ϕ_{33}	Loss of concentration due to DCC and uPA
α_{32}	Production of concentration due to CSC	α_{31}	Production of concentration due to DCC
ϕ_{41}	Loss caused by PAI-1 and uPA interaction	ϕ_{52}	Production through PAI-1 and ECM interaction
ϕ_{21}	Growth of ECM through PAI-1 and uPA interaction	α_{41}	Production through MDE
ϕ_{22}	Neuralization of ECM through PAI-1 interaction	ϕ_{53}	Production of concentration through DCC and uPA
ϕ_{42}	Loss caused by ECM and PAI-1 interaction	D_p	Diffusion of PAI-1
ϕ_{51}	Reduction caused by uPA and PAI-1	ϕ_{54}	Production of concentration through CSC and uPA
c^s	Concentration of cancer stem (CSCs)	D_{cs}	Diffusion coefficient of CSC
c^d	Differentiated cancer cell concentration	D_{cd}	Diffusion coefficient of DCCs
$P(s)$	The rate of cell death	D_s	Diffusion coefficient of oxygen
s	Oxygen concentration	χ	Haptotaxis coefficient
m	MDE concentration	D_m	Diffusion of MDE
f	ECM concentration	p	PAI-1 concentration
χ_{cs}	Haptotaxis coefficient of CSC	u	uPA concentration

χ_{cd}	Haptotaxis coefficient of DCC	μ_2	The proliferation rate constant of DCC
CHEMOTHERAPY			
a	Tumour growth rate (day ⁻¹)	e	Fraction of circulating lymphocytes that become natural killer cells
a ₁	Half Saturation constant of the tumour-killing rate	f	Death rate of natural killer cells
b	1/b is the tumor-carrying capacity	g	Recruitment of maximum natural killer cell through ligand-transduced tumor cells
c	Fraction of tumor cell without ligand transduced killed by natural killer cells	g _i	Steepness of the recruitment curve for CD8+T cell influenced by cytokines
c ₁	Maximum tumour-killing rate by cytokine	h	Steepness coefficient of natural killer cell recruitment curve
d	The saturation point of fractional tumor cells is killed by CD8+T cells. The cells are primed with ligand-transduced cells and challenged with ligand transduced cells.	j	Maximum CD8+T cell recruitment rate. Primed with ligand-transduced cells, challenged with ligand-transduced cells
l	The exponent of fractional tumor cell killed by CD8+T cells. Primed with ligand-transduced cells, challenged with ligand-transduced cells	k	The steepness coefficient of the CD8+T cell recruitment curve
m	Death rate of CD8+T cells	K _T	Fractional tumor cell kills by chemotherapy
p	Natural killer cell inactivation rate by tumor cells	K _N	Fractional natural killer cells are killed by chemotherapy
p _i	Maximum CD8+T cell recruitment rate by cytokine.	K _L	Fractional CD8+T cells kill by chemotherapy
q	CD8+T cell inactivation rate by tumor cells	K _C	Fractional circulating lymphocyte cells are killed by chemotherapy
r ₁	The simulated production rate of CD8+T cells influences the killing of tumor cells by natural killer cells	δ_2	The loss rate of CD4+T cells due to interaction with tumor cells
r ₂	The rate at which CD8+T cells are stimulated to be produced; as a	a _B	Maximum rate of TGF- β production

	result, tumor cells interact with circulating lymphocytes		
s	The steepness coefficient of tumor - CD8+T cell lysis term D when primed with ligand-transduced cells and challenged with ligand-transduced cells	a_{S1}	Probability of symmetric division of a CSC
u	Regulatory function of CD8+T cells by natural killer cells	a_{S2}	Probability of asymmetric division of a CSC
α	A constant source of circulating lymphocytes	a_{S3}	Probability of symmetric differentiation of a CSC
α_1	Half saturation constant of the CD4+T cells production rate	α_{BY}	Activation of CD4+T cells by TGF- β
α_2	Half saturation constant of cytokine production rate	α_{YB}	Production of TGF- β by CD4+T
β	Spontaneous demise and differentiation of circulating lymphocytes	c_{B1}	TGF- β inhibitory parameter for induction of tumor death
β_1	Maximum CD4+T cell production rate	c_{B2}	Steepness coefficient of TGF- β production
β_2	Maximum production rate cytokine	c_{B3}	The magnitude of inhibition associated with tumor growth and TGF- β
γ	Rate of chemotherapy drug decay	δ_B	Natural death of TGF- β
μ_1	Spontaneous demise rate of CD4+T cells	δ_S	Natural death of CSCs
μ_i	Rate of cytokine decay	μ_{LT}	CD8+T induced tumor death/removal rate
δ_h	Concentration of chemo when production of HIF is half ((cell)	μ_{LS}	Interaction of CSCs and CD8+T leading to CSC death
b_h	HIF constant	a_h	Production of HIF