Global Dynamics of a Model of Joint Hormone Treatment with Dendritic Cell Vaccine for Prostate Cancer

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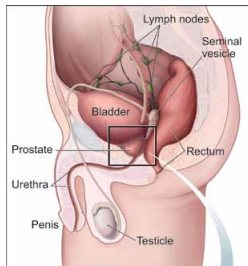
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Outline

- In the US, prostate cancer is the most common non-skin cancer in men and the second most fatal
- The estimated probability of developing prostate cancer for men in a lifetime is 1 in 6

NCI www.cancer.gov

Cancer Statistics, 2015

Treatment Options

- Screening/Diagnosis: prostate specific antigen (PSA) levels
- Local Treatment: active surveillance, surgery (radical prostatectomy), radiation therapy
- Advanced, Relapsed: hormone therapy/androgen suppression therapy
    - Orchiectomy (removal of the testes)
    - Luteinising hormone-releasing hormone (LHRH) agonists
    - Anti-androgens
    - Total androgen blockade
    - Intermittent Androgen Suppression Therapy (IAS)
- Castration Resistant: chemotherapy (Docetaxel, Capazitaxel), cancer vaccine (Sipuleucel-T), Denosumab (if spread to bone)

Androgens: the male sex hormones

- Androgens are produced in the testes and adrenal gland
- Testosterone circulates in the blood
- Free testosterone enters the prostate cells and 90% is converted to DHT by 5α reductase enzyme
- DHT binds to the androgen receptor (AR)
- Causes growth, survival, and production of prostate-specific antigen (PSA)
- PSA is a marker for prostate cancer
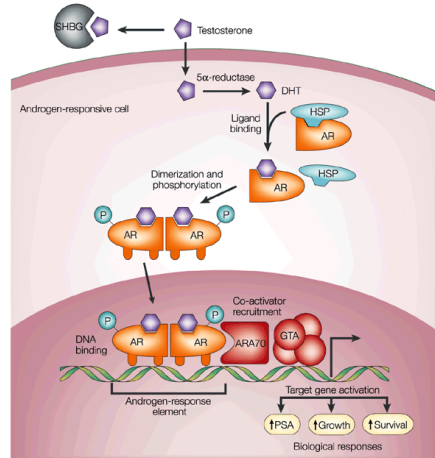
Feldman and Feldman 2001

Nature Reviews | Cancer

Androgen Suppression Therapy

- Both normal and cancerous prostate cells depend on androgens for growth and survival
- Androgen suppression therapy decreases these androgens, either by castration or the use of drugs
- Primary response rate of about 80%-90%
- Most advance to a castration-resistant prostate cancer (CRPC)
- Side effects include:

  - Loss of libido
  - Erectile dysfunction
  - Loss of testicular mass and penile length
  - Breast growth
  - Increased body fat
  - Loss of muscle mass

  - Osteoporosis
  - Anemia
  - Cognitive dysfunction
  - Depression
  - Fatigue
  - Hot flashes

- Intermittent androgen suppression therapy (IAS) improves quality of life, reduces side effects and therapy costs.

Immunotherapy

Immunotherapy uses the bodies own immune system to fight cancer

- Non-specific antibodies boost immune system response
  - Can be suppressive or boosting
  - Cytokines such as Interleukin-2 can be injected to help immune system cells grow and divide
  - Unpleasant flu-like side effects and possible fatal heart conditions
- Synthetic antibodies
  - Lab-designed antibodies specifically target antigens found on cancer cells
  - Which antigen to attack?
- Train system to attack specific cancer cells
  - Targeted therapies which use the patient's specific tumor to induce a response

T cells

- T cells drive cell-mediated immunity
- Many types of T cells:
  - Helper (matures B cells and activates cytotoxic T cells),
  - Cytotoxic (atttacks virus-infected cells and tumor cells and recognizes their target by binding to antigens on cell surfaces),
  - Memory (remain after infections have gone away in case they are needed again), etc
  - Regulatory (stop T-cell production as the disease ends, suppresses autoreactive T cells)

Cytokines

- Cytokines are small proteins that effect cell signaling
- Produced by immune cells such as macrophages, T cells, B cells and are released to influence other cells
- Can be chemokines (chemotaxis), interferon (viral replication, activate immune cells), interleukins (promote development and differentiation of T and B cells), and other types
- Regulate maturation, growth, death of cell populations
- Different types of cytokines interact with each other, keeping body in homeostasis
- Many have adverse side effects and can be fatal in large doses

IL-2

- IL-2 is a cytokine (interleukin)
- Directly promotes differentiation of immature T cells into regulatory T cells, preventing attack on healthy cells
- Promotes differentiation of T cells into effector T cells and memory T cells
- Dangerous side effects if dosage too high: seizure, heart complications, breathing problems

Activation of T_{reg} and T_{Naive}
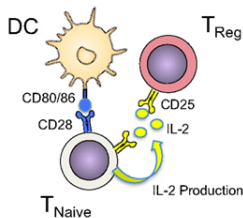
Source: Gasteiger, Georg, and Wolfgang Kastenmuller. "Foxp3+ regulatory T-cells and IL-2: the Moirai of T-cell fates?." Frontiers in immunology 3 (2012).[4]

Dendritic Cells

- Most potent of the antigen-presenting cells
- Ingest antigens while immature in blood
- Once activated, DC's migrate to lymph nodes to interact with T and B cells
- Present the antigen material on cell surface to naive and memory T-cells
- Secrete costimulatory signals
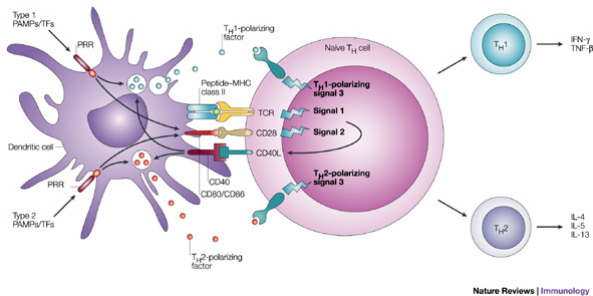
Source: Kapsenberg, Martien L. "Dendritic-cell control of pathogen-driven T-cell polarization." Nature Reviews

Dendritic cell vaccines

Source: Surmont, Veerle F., et al. "Investigational approaches for mesothelioma." Frontiers in oncology 1 (2011). [12]
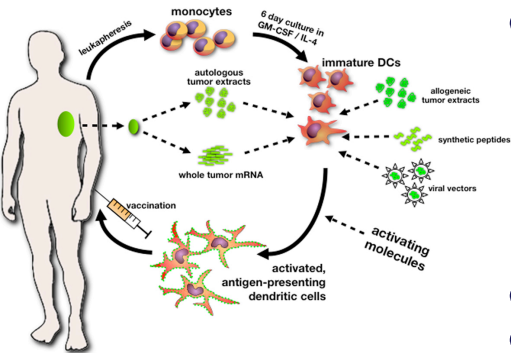
1. Blood is extracted from patient and monocytes are differentiated into DC
2. DCs loaded with tumor derived antigens
   - proteins from autologous tumor lysate
   - electroplated with tumor-derived mRNA
   - if autologous tumor unavailable, loaded
3. Activate DCs with cytokines
4. Tumor antigen-presenting DC is reinjected into patient

DC Vaccines

- For prostate cancer, target antigen is Prostatic acid phosphatase (PAP)
  - PAP is an enzyme produced by prostate and is elevated in prostate cancer patients (used to be biomarker of the disease)
  - Highest levels of PAP are found in patients for whom cancer has metastasized
- Sipuleucel-T (Provenge) currently only approved DC treatment for prostate cancer
- DC vaccines tend to be safe with mild limited side effects (flu-like symptoms)
- DC vaccine efficacy is mitigated by radiation and chemotherapy
- Used for advanced prostate cancer that is no longer helped by hormone therapy (AI)
- Current trials to examine DC vaccines for prostate cancer which is not yet castration resistant

Outline

- Presents a mathematical model to describe and compare prostate tumor growth under IAS and CAS therapy
- Consider AD (X_1) and AI (X_2) cell populations with androgen concentration (A) dependent proliferation and apoptotic rates

$$\frac{dX_1}{dt} = \underbrace{\alpha_1 p_1(A) X_1}_{\text{proliferation}} - \underbrace{m(A) X_1}_{\text{mutation to AI}} - \underbrace{\beta_1 q_1(A) X_1}_{\text{apoptosis}}$$

$$\frac{dX_2}{dt} = \underbrace{\alpha_2 p_2(A) X_2}_{\text{proliferation}} + \underbrace{m(A) X_1}_{\text{mutation from AD}} - \underbrace{\beta_2 q_2(A) X_2}_{\text{apoptosis}}$$

$$\frac{dA}{dt} = \underbrace{\gamma(a_0 - A)}_{\text{homeostasis of androgen}} - \underbrace{\gamma a_0 u(t)}_{\text{depletion of androgen if on therapy}}$$

- note that $u(t)$ is either 0 (if treatment off), or 1 (if treatment on)
- $p_1(A), q_1(A), p_2(A), q_2(A)$ are from Jackson paper

- Presents a mathematical model to describe tumor/immune interaction
- Considers tumor cells (X), activated immune cells, such as T cells (T), and cytokine IL-2 (I_L)

$$\frac{dX}{dt} = \underbrace{r_2(X)X}_{\text{growth and death}} - \underbrace{\frac{aTX}{g_2 + X}}_{\text{death by T cell}}$$

$$\frac{dT}{dt} = \underbrace{cX}_{\text{recruitment due to tumor}} - \underbrace{\mu T}_{\text{death}} + \underbrace{\frac{p_1 TI_L}{g_1 + I_L}}_{\text{activation by cytokines}} + \underbrace{s_1}_{\text{injected therapies}}$$

$$\frac{dI_L}{dt} = \underbrace{\frac{p_2 XT}{g_3 + X}}_{\text{secretion}} - \underbrace{\omega I_L}_{\text{degradation}} + \underbrace{s_2}_{\text{external injection}}$$

Marries Ideta et al. and Kirschner and Panetta models:

AD cells:
$$\frac{dX_1}{dt} = \underbrace{r_1(A)X_1}_{\text{growth and death}} - \underbrace{m(A)X_1}_{\text{mutation to AI}} - \underbrace{\frac{e_1 X_1 T}{g_1 + X_1}}_{\text{death by T cell}}$$

AI cells:
$$\frac{dX_2}{dt} = \underbrace{r_2 X_2}_{\text{growth and death}} + \underbrace{m(A)X_1}_{\text{mutation from AD}} - \underbrace{\frac{e_1 X_2 T}{g_1 + X_2}}_{\text{death by T cell}}$$

T cells:
$$\frac{dT}{dt} = \underbrace{\frac{e_2 D}{g_2 + D}}_{\text{activation of T cell by DC}} - \underbrace{\mu T}_{\text{death}} + \underbrace{\frac{e_3 T I_L}{g_3 + I_L}}_{\text{activation of T cell by cytokines}}$$

IL-2 conc:
$$\frac{dI_L}{dt} = \underbrace{\frac{e_4 T(X_1 + X_2)}{g_4 + X_1 + X_2}}_{\text{secretion}} - \underbrace{\omega I_L}_{\text{degradation}}$$

Androgen conc:
$$\frac{dA}{dt} = \underbrace{\gamma(a_0 - A)}_{\text{homeostasis of androgen}} - \underbrace{\gamma a_0 u(t)}_{\text{depletion of androgen if on therapy}}$$

DC cells:
$$\frac{dD}{dt} = - \underbrace{cD}_{\text{death}}$$

- What effect does timing and amount of dosage have on cancer dynamics?
- Why is it assumed that the mutation only goes from AD to AI?
- Do results hold with more realistic (and general) T-cell and tumor cell interactions?
- Can we mathematically analyze this system and find conditions for global stability?

Outline

Our Model

AD cells:
$$\frac{dX_1}{dt} = \underbrace{r_1(A, X_1, X_2)X_1}_{\text{growth and death}} - \underbrace{m(A)X_1}_{\text{mutation to AI}} + \underbrace{m_2(A)X_2}_{\text{mutation from AI}} - \underbrace{X_1 f_1(X_1, X_2, T)}_{\text{death by T cell}}$$

AI cells:
$$\frac{dX_2}{dt} = \underbrace{r_2(X_1, X_2)}_{\text{growth and death}} + \underbrace{m(A)X_1}_{\text{mutation from AD}} - \underbrace{m_2(A)X_2}_{\text{mutation to AD}} - \underbrace{X_2 f_2(X_1, X_2, T)}_{\text{death by T cell}}$$

T cells:
$$\frac{dT}{dt} = \underbrace{\frac{e_2 D}{g_2 + D}}_{\text{activation of T cell by DC}} - \underbrace{\mu T}_{\text{death}} + \underbrace{f_3(X_1, X_2, T)}_{\text{activation of T cell by cytokines}}$$

IL-2 conc:
$$\frac{dI_L}{dt} = \underbrace{T f_4(X_1, X_2)}_{\text{secretion}} - \underbrace{\omega I_L}_{\text{degradation}}$$

Androgen conc:
$$\frac{dA}{dt} = \underbrace{\gamma(a_0 - A)}_{\text{homeostasis of androgen}} - \underbrace{\gamma a_0 u(t)}_{\text{depletion of androgen if on therapy}}$$

DC cells:
$$\frac{dD}{dt} = - \underbrace{cD}_{\text{death}}$$

With growth and mutation functions:

- $r1(A, X_1, X_2) = r_1 A X_1 \left(1 - \frac{X_1 + X_2}{K}\right) - d_1(a_0 - A)$

- $r_2(X_1, X_2) = r_2 X_2 \left(1 - \frac{X_1 + X_2}{K}\right)$

- $m(A) = m_1(1 - \frac{A}{a_0})$

- $m_2(A) = m_2(\frac{A}{A + k_4})$

and on/off treatment switch as:

$u(t) = \begin{cases} 0 \to 1 & \text{if } y(t) > L_1 \text{ and } \frac{dy}{dt} > 0 \\ 1 \to 0 & \text{if } y(t) < L_0 \text{ and } \frac{dy}{dt} < 0 \end{cases}$

where y represents serum PSA levels:

$y(t) = c_1 X_1 + c_2 X_2$

Our Model - Cont'd

Imposed conditions on $f_i(X_1, X_2, T)$:

- $f_i(X_1, X_2, T) \geq 0 \quad \forall \quad X_1, X_2, T \geq 0$
- $f_1(X_1, X_2, 0) = f_2(X_1, X_2, 0) = 0 \quad \forall \quad X_1, X_2 \geq 0$
- $f_3(0, T) = 0 \quad \forall \quad T \geq 0$
- $f_4(0,0) = 0 \quad \forall \quad T \geq 0$
- $\frac{\partial f_1}{\partial X_1} \leq 0$
- $\frac{\partial f_2}{\partial X_2} \leq 0$
- $\frac{\partial f_1}{\partial T} \geq 0$
- $\frac{\partial f_2}{\partial T} \geq 0.$
- $\frac{\partial f_3}{\partial I_L} \geq 0$
- $\frac{\partial f_4}{\partial X_i} \geq 0$

Our Mathematical Model

- Based on the Portz et. al model, which marries the Ideta et. al model with the Kirschner and Panetta model
- AI is too strong – the cancer cells are not independent of androgen, but just less sensitive to lower levels of androgen
- Consider allowing AI cells to mutate back into AD cells when in an androgen-rich environment
- AI cells are able to survive in an androgen-depleted environment, but when there are 'normal' androgen levels, they use the androgen to grow
- We also consider death by T-cells on the entire cancer population, as opposed to each cancer independently

- Biological Questions
  - How does timing the DC vaccine dose effect time to AI cell growth?
  - Can DC vaccines be effective in treating cancers which are not AI?
  - Are DC vaccines more or less effective with CAS vs IAS?
- Mathematical Questions
  - Can we determine optimal dosing quantities to stabilize or eradicate the disease?
  - Can we determine mathematically the steady-state behavior and translate that back into biological meaning?

Outline

The functions we propose for simulation results are

- $f_1(X_1, X_2, T) = \frac{e_1 T}{g_1 + X_1 + X_2}$
- $f_2(X_1, X_2, T) = \frac{e_1 T}{g_1 + X_1 + X_2}$
- $f_3(X_1, X_2, T) = \frac{e_3 T I_L}{g_3 + I_L}$
- $f_4(X_1, X_2) = \frac{e_4(X_1 + X_2)}{g_4 + X_1 + X_2}$

and they satisfy the previous conditions.

Parameters

Parameter	Biological Meaning	Value	Source
α_1	AD cell proliferation rate	0.025/day	[1]
β_1	AD cell death rate	0.008/day	[1]
k_1	AD cell proliferation rate dependence on androgen	2ng/ml	[5]
k_2	low androgen level effect on AD cell death rate	8	[2]
k_3	AD cell death rate dependence on androgen	0.5ng/ml	[5]
k_4	AI to AD mutation half-saturation	1.7	
r_2	AI net cell growth rate	0.006/day	[1]
m_1	maximum mutation rate from AD to AI	0.00005/day	[5]
m_2	maximum mutation rate from AI to AD	0.00015/day	[9]
a_0	base level androgen concentration	30 ng/ml	[5]
γ	androgen clearance and production rate	0.08/day	[5]
ω	cytokine clearance rate	10/day	[10]
μ	T cell death rate	0.03//day	[3]
c	dendritic cell death rate	0.14/day	[7]
e_1	maximum rate T cells kill cancer cells	0-1/day	[3]
g_1	cancer cell saturation level form T cell kill rate	10×10^9 cells	[3]
e_2	T cell maximum activation rate	20×10^6 cells/day	[3]
g_2	DC saturation level for T cell activation	400×10^6 cells	[11]
e_3	maximum clonal expansion rate	0.1245/day	[3]
g_3	IL-2 saturation level for T cell clonal expansion	1000 ng/ml	[3]
e_4	maximum rate T cells produce IL-2	5×10^{-6} ng/ml/cell/day	[3]
g_4	cancer cell saturation level for T cell stimulation	10×10^9 cells	[3]
D_1	DC vaccine dosage	300×10^6 cells	[11]
c_1	AD cell PSA level correlation	1×10^{-9} ng/ml/cell	[5]
c_2	AI cell PSA level corelation	1×10^{-9} ng/ml/cell	[5]

Vaccine Timing Resuts

- Keep total dosage of vaccine constant
- Vary how often dendritic cell vaccine is administered
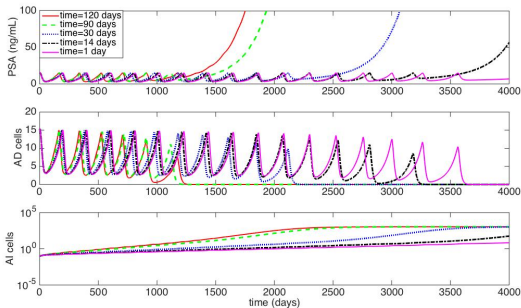
- More frequent injections delay androgen independent relapse

- e_1 represents maximum rate T cells kill cancer cells, may be personalized parameter
- numerically investigate minimal e_1 value to prevent relapse (stable cyclical disease).
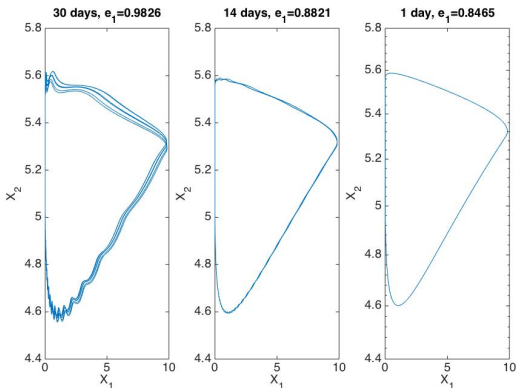
- More frequent injections can assist weaker immune systems

Continuous Model

- Increasing frequency of injection staves off relapse – take this idea to the limit
- Assume continual injection v (as through an IV drip)
- $\frac{dD}{dt} = \underbrace{v}_{\text{injection}} - \underbrace{cD}_{\text{death}}$

Varying e_1

- set injection rate $v = 0.04$ billion cells
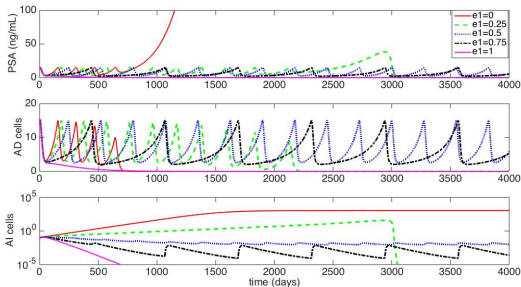
- varying e_1:
    - if $e_1 < 0.25$ androgen independent relapse
    - if $0.25 < e_1 < 0.75$ stable disease state (increasing e_1 elongates cycles)
    - If $e_1 > 0.75$ disease eradicated

Bifurcation of e_1

- For $e_1 = 0$, disease free equilibrium unstable
- For $e_1 \in (0.2, 0.65)$, stable limit cycles of disease
- For $e_1 > 0.65$ stability of disease free equilibirum
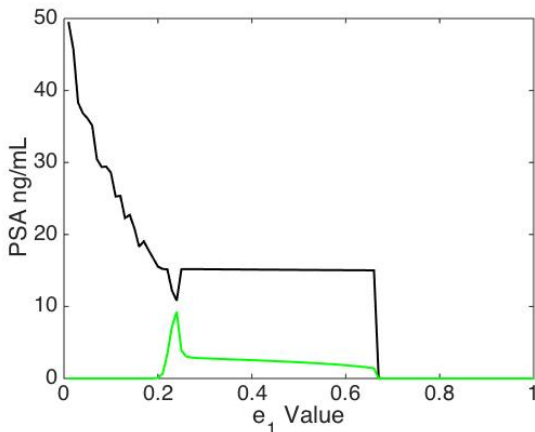
Analysis of Continuous Model

$$\frac{dX_1}{dt} = r_1(A, X_1, X_2)X_1 - m(A)X_1 + m_2(A)X_2 - X_1 f_1(X_1, X_2, T)$$

$$\frac{dX_2}{dt} = r_2(X_1, X_2)X_2 + m(A)X_1 - m_2(A)X_2 - X_2 f_2(X_1, X_2, T)$$

$$\frac{dT}{dt} = \frac{e_2 D}{g_2 + D} - \mu T + T f_3(I_L, T)$$

$$\frac{dI_L}{dt} = T f_4(X_1, X_2) - \omega I_L$$

$$\frac{dA}{dt} = -\gamma A$$

$$\frac{dD}{dt} = v - cD$$

Theorem

Solutions system above with positive initial conditions remain positive for all time

Theorem

The disease-free equilibrium $E_0^* = (0, 0, \frac{e_1 v}{\mu(cg_2 + v)}, 0, 0, \frac{v}{c})$ and is unstable if $e_1 \leq \frac{g_1 r_2}{T^*}$, and locally asymptotically stable if $e_1 > \frac{g_1 r_2}{T^*}$

- If $e_1 \leq \frac{g_1 r_2}{T^*}$, only $E_0^* = (0, 0, \frac{e_2 v}{\mu(cg_2 + v)}, 0, 0, \frac{v}{c})$ exists (disease eradication).
- $e_1 > \frac{g_1 r_2}{T^*}$ also have $E_1^* = (0, X_2^*, T^*, I_L^*, 0, \frac{v}{c})$ (AI relapse)

Analysis Cont'd

Jacobian for E_0^*

$$\begin{pmatrix} -d_1 a_0 - m_1 - \frac{e_1 e_2 v}{g_1 \mu (c g_2 + v)} & 0 & 0 & 0 & 0 & 0 \\ m_1 & r_2 - \frac{e_1 e_2 v}{g_1 \mu (c g_2 + v)} & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu & \frac{e_3 e_2 v}{g_3 \mu (c g_2 + v)} & 0 & \frac{e_2}{g_2} \\ \frac{e_4 e_2 v}{(g_4 \mu (c g_2 + v)} & \frac{e_4 e_2 v}{(g_4 \mu (c g_2 + v)} & 0 & -\omega & 0 & 0 \\ 0 & 0 & 0 & 0 & -\gamma & 0 \\ 0 & 0 & 0 & 0 & 0 & -c \end{pmatrix}$$

$\lambda = (-- d_1 a_0 - m_1 - \frac{e_1 e_2 v}{g_1 \mu (c g_2 + v)}, r_2 - \frac{e_1 e_2 v}{g_1 \mu (c g_2 + v)}, -\mu, -\omega, -\gamma, -c)$

$\lambda_2 = r_2 - \frac{e_1 e_2 v}{g_1 \mu (c g_2 + v)}$ determines stability

$r_2 - \frac{e_1 e_2 v}{g_1 \mu (c g_2 + v)} \leq 0 \Leftrightarrow e_1 \leq \frac{g_1 r_2}{T^*}$

Biological Implications

- We cannot control parameters e_1, e_2, g_1, c, μ, or g_2, some are personalized parameters
- We can control dosage, v
- $e_1 \leq \frac{g_1 r_2}{T^*} \Leftrightarrow v > \frac{c g_2 g_1 r_2 \mu}{e_1 e_2 - g_1 r_2 \mu}$,
- v_{crit} is minimal dosage to eradicate cancer
- If able to measure other parameters individually, can set proper dosage

Outline

Reduction of System

- Assume androgen deprivation therapy is constantly on
  - $u(t) = 1$
  - $\frac{dA}{dt} = \gamma(a_0 - A) - \gamma a_0 u(t) \rightarrow \frac{dA}{dt} = -\gamma A$
- Note cytokines (I_L), androgen (A), dendritic cells (D) operate on faster time scale
- Let these variables go to steady state
  - $I_L = \frac{T f_4 (X_1 + X_2)}{\omega}$
  - $A = 0$
  - $D = \frac{v}{c}$

System reduces to:
$$\frac{dX_1}{dt} = -d_1 a_0 X_1 - m_1 X_1 - X_1 f_1(X_1, X_2, T)$$
$$\frac{dX_2}{dt} = r_2 X_2 \left(1 - \frac{X_1 + X_2}{K}\right) + m_1 X_1 - X_2 f_2(X_1, X_2, T)$$
$$\frac{dT}{dt} = \frac{e_2 D}{g_2 + D} - \mu T + T f_3(I_L, T)$$

$$\frac{dX_1}{dt} = X_1 \left[-d_1 a_0 - m_1 - f_1(X_1, X_2, T) \right]$$
$$\leq X_1 \left[-\beta_1 k_2 - m_1 \right]$$
$$\leq -a X_1$$

It is apparent X_1 that $\lim_{t \to \infty} X_1(t) = 0$, so can further reduce system to:

$$\frac{dX_2}{dt} = r_2 X_2 \left(1 - \frac{X_2}{K} \right) - X_2 f_2(0, X_2, T)$$
$$\frac{dT}{dt} = \frac{e_2 D}{g_2 + D} - \mu T + T f_3(I_L, T) \tag{1}$$

The end behaviors of this system and the previous system are asymptotically equivalent [13]
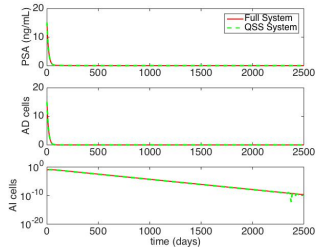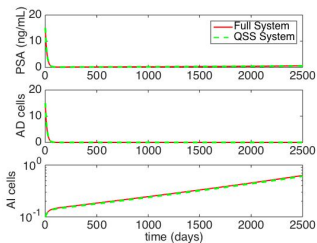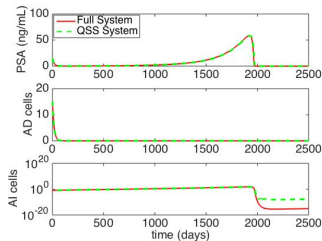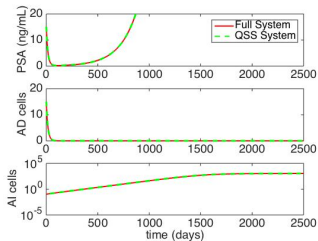
Representative diagrams for various values of e_1. We can see that disease dynamics are similar in the reduced case to the full case

Theorem

The disease-free steady state of the reduced system (1) is globally asymptotically stable under the following conditions:

i) $\mu > f_3(I_L, T)$

ii) $\frac{\partial}{\partial X_2} f_2(X_2, T) \geq -\frac{r}{K}$

iii) $r_2 < f_2(0, T)$

iii) $\frac{\mu^2(g_2 + D)}{e_2 D} > \frac{\partial}{\partial T} f_3(0, T^*)$

In order to prove this theorem with simplicity, we break the proof into several propositions:

1. Positivity and boundedness

2. Local asymptotic stability

3. Global asymptotic stability

Positivity and Boundedness

Proposition

If $\mu > f_3(I_L, T)$ (condition i) then solutions of the reduced system remain positive and bounded.

Positivity:

- T:
  In order for $T(t) < 0$ for some t, we would require that $\frac{dT}{dt} < 0$ when $T = 0$. However, $\frac{dT}{dt}|_{T=0} = \frac{e_2 D}{g_2 + D} > 0$

- X_2 (proof by contradiction):
  - there must exist some t_1 such that $X_2(t) > 0 \forall t \in [0, t_1)$ and $X_2(t_1) = 0$
  - $\frac{dX_2}{dt} \geq r_2 X_2 \forall t \in [0, t_1]$
  - $X_2 \geq X_2(0)e^{r_2 t}$, and as such $X_2(t_1) \geq X_2(0)e^{r_2 t_1} \geq 0$

Boundedness:

- T:

$$\frac{dT}{dt} = \frac{e_2 D}{g_2 + D} + T(f_3(I_L, T) - \mu)$$
$$\leq c - \bar{g}T$$

(2)

  where $\bar{g} = \min[\mu - f_3(I_L, T)] > 0$ by assumption.
- X_2: Bounded above by K

Local Asymptotic Stability

Proposition

Under the assumption ii, the limiting system contains two equilibria: the disease-free equilibrium and a negative equilibrium. The disease-free equilibrium is locally asymptotically stable under condition iii and condition iv .

Equilibria:

- $\frac{dX_2}{dt} = r_2 X_2 \left(1 - \frac{X_2}{K}\right) - X_2 f_2(X_2, T) = 0$:
    - $X_2^* = 0$
    - $f_2(X_2^*, T^*) = r_2 \left(1 - \frac{X_2^*}{K}\right)$
- $\frac{dT}{dt} = \frac{e_2 D}{g_2 + D} - \mu T + T f_3(0, X_2, T) = 0$:
    - $T^* = \frac{e_2 D}{(g_2 + D)(\mu - f_3(0, X_2, T))}$.

We get $E_0^* = (0, T^*)$ and $E_1^* = (X_2^*, T^*)$, which is not biologically relevant by our assumption

The local stability of the disease-free steady state E_0^* is exhibited in the Jacobian:

$$\begin{pmatrix} r_2 - f_2(0, T^*) & 0 \\ \\ T^* \frac{\partial}{\partial X_2} f_3(0, T^*) & -\mu + T^* \frac{\partial}{\partial T} f_3(0, T^*) \end{pmatrix}$$

and the eigenvalues are given by:

- $\lambda_1 = r_2 - f_2(0, T^*) < 0$ (condition iii)
- $\lambda_2 = -\mu + T^* \frac{\partial}{\partial T} f_3(0, T^*) < 0$, (condition iv)

so we have local asymptotic stability.

We are now ready to prove global asymptotic stability

- Solutions are positive and bounded
- No limit cycles since we have boundary equilibrium only

By Poincare-Bendixson, all solutions tend towards E_0^*, so the disease-free steady state is globally asymptotical stable.

Biological interpretation of results

What do these conditions mean biologically?

  i) $\mu > f_3(I_L, T)$: the death of T cells is greater than the activation of T by the cytokines

  ii) $\frac{\partial}{\partial X_2} f_2(X_2, T) \geq -\frac{r}{K}$:killing function more responsive than growth

  iii) $r_2 < f_2(0, T)$: the growth rate of the AI cancer cells is smaller than the death due to T cells

  iii) $\frac{\mu^2(g_2+D)}{e_2 D} > \frac{\partial}{\partial T} f_3(0, T^*)$: unsure

These biological conditions are very strong, and quite unlikely. The growth rate of cancer cells tends to be extremely large, so these assumptions may not be applicable in actual clinical setting.
What about stable disease steady state?

Stable Disease State

Theorem

The diseased steady state of (1) is globally asymptotically stable under the following conditions:

i) $\mu > f_3(I_L, T)$

ii) $\exists X_2^*, T^* \geq 0$ *such that* $f_2(X_2^*, T^*) = r_2 \left(1 - \frac{X_2^*}{K}\right)$

iii) $r_2 > f_2(0, T^*)$

iv) $\mu - f_3(I_L, T) >$
$-X_2 \frac{\partial}{\partial X_2} f_2(X, T) + T \frac{\partial}{\partial T} f_3(I_L, T) - \frac{r_2 X_2}{K} \forall X_2, T \geq 0$

v)
$\left(-\frac{r_2 X_2^*}{K} - X_2^* \frac{\partial}{\partial X_2} f_2(X_2^*, T^*)\right) \left(-\mu + f_3(I_L,^* T^*) + T^* \frac{\partial}{\partial T} f_3(I_L^*, T^*)\right) +$
$\left(X_2^* \frac{\partial}{\partial T} f_2(X_2^*, T^*) T^* \frac{\partial}{\partial X_2} f_3(I_L^*, T^*)\right) > 0$

Proof of Global Stability

In order to prove this theorem with simplicity, we break the proof into several propositions:

1. Positivity and boundedness (condition i) Proof similar to previous
2. Local asymptotic stability (condition ii-v)
3. Dulac Criteria
4. Global asymptotic stability

Proposition

The limiting system (1) contains two equilibria: the disease-free equilibrium, E_0^*, and a secondary equilibrium, E_1^*. The secondary equilibrium is positive (assuming condition ii)) and is locally asymptotically stable if conditions iii)-v) from the theorem are satisfied.

The local stability of the disease-free steady state E_0^* is exhibited in the Jacobian:

$$
\begin{pmatrix}
r_2 - f_2(0, T^*) & 0 \\[2ex]
T^* \frac{\partial}{\partial X_2} f_3(0, T^*) & -\mu + T^* \frac{\partial}{\partial T} f_3(0, T^*)
\end{pmatrix}
$$

and the eigenvalues are given by:

- $\lambda_1 = r_2 - f_2(0, T^*) > 0$ by condition iii)
- $\lambda_2 = -\mu + T^* \frac{\partial}{\partial T} f_3(0, T^*) < 0$, by condition iv).

Local Asymptotic Stability of E_1^*

The local stability of the diseased steady state E_1^* is exhibited in the Jacobian:

$$
\begin{pmatrix}
-\frac{r_2 X_2^*}{K} - X_2^* \frac{\partial}{\partial X_2} f_2(X_2^*, T^*) & -X_2^* \frac{\partial}{\partial T} f_2(X_2^*, T^*) \\
\\
T^* \frac{\partial}{\partial X_2} f_3(I_L^*, T^*) & -\mu + T^* \frac{\partial}{\partial T} f_3(I_L^*, T^*) + f_3(I_L^*, T^*)
\end{pmatrix}
$$

Thus, the trace is given by (and < 0 by condition iv)

$$
\tau = -\frac{r_2 X_2^*}{K} - X_2^* \frac{\partial}{\partial X_2} f_2(X_2^*, T^*) - \mu + T^* \frac{\partial}{\partial T} f_3(I_L^*, T^*) + f_3(I_L^*, T^*)
\tag{3}
$$

and the determinant is given by (and > 0 by condition v)

$$
\Delta = \left(-\frac{r_2 X_2^*}{K} - X_2^* \frac{\partial}{\partial X_2} f_2(X_2^*, T^*) \right) \left(-\mu + f_3(I_L,^* T^*) + T^* \frac{\partial}{\partial T} f_3(I_L^*, T^* \right.
$$

$$
+ \left(X_2^* \frac{\partial}{\partial T} f_2(X_2^*, T^*) T^* \frac{\partial}{\partial X_2} f_3(I_L^*, T^*) \right)
$$

Elimination of Limit Cycles

Proposition

The limiting system (1) has no limit cycles as long as condition iv) is satisfied.

We will be using the Dulac criterion to establish that there are no periodic orbits within. Using $h(X_2, T) = \frac{1}{X_2}$, we can see that

$$
\begin{aligned}
\Delta &= \frac{\partial}{\partial X_2} \left[\frac{1}{X_2} \left(r_2 X_2 \left(1 - \frac{X_2}{K} \right) - X_2 f_2(X_2, T) \right) \right] \\
&\quad + \frac{\partial}{\partial T} \left[\frac{1}{X_2} \left(\frac{e_2 D}{g_2 + D} - \mu T + T f_3(I_L, T) \right) \right] \\
&= \frac{\partial}{\partial X_2} \left[r_2 - \frac{r_2 X_2}{K} - f_2(X_2, T) \right] + \frac{\partial}{\partial T} \left[\frac{e_2 D}{X_2(g_2 + D)} - \frac{\mu T}{X_2} + \frac{T(f_3(I_L,}{X_2} \right. \\
&= -\frac{r_2}{K} - \frac{\partial}{\partial X_2} f_2(X_2, T) - \frac{\mu}{X_2} + \frac{f_3(I_L, T)}{X_2} + \frac{T}{X_2} \frac{\partial}{\partial T} f_3(I_L, T)
\end{aligned}
$$

To ensure that there are no periodic orbits, we must prove that this quantity Δ does not change sign. We re-write this condition:

$$\Delta = -\frac{r_2 X_2}{K} - X_2 \frac{\partial}{\partial X_2} f_2(0, X_2, T) - \mu + f_3(0, X_2, T) + T \frac{\partial}{\partial T} f_3(0, X_2, T)$$
(5)

We know that for $X_2, T \geq 0$, $\Delta < 0$ by condition iv). Thus, the Dulac criterion has ensured that we will have no periodic orbits in our domain.

- Solutions are positive and bounded
- One equilibrium is locally stable, the other is a saddle point
- No limit cycles via Dulac

By Poincare-Bendixson, all solutions tend towards E_1^*, so the disease-free steady state is globally asymptotical stable

What do these conditions mean biologically?

i) $\mu > f_3(I_L, T)$: the death of T cells is greater than the activation of T by the cytokines

ii) $\exists X_2^*, T^* \geq 0$ such that $f_2(X_2^*, T^*) = r_2 \left(1 - \frac{X_2^*}{K}\right)$

iii) $r_2 > f_2(0, T)$: the growth rate of the AI cancer cells is larger than the death due to T cells

iv) $\mu - f_3(I_L, T) > -X_2\frac{\partial}{\partial X_2}f_2(X, T) + T\frac{\partial}{\partial T}f_3(I_L, T) - \frac{r_2 X_2}{K} \forall X_2, T \geq 0$:unsure

v)
$\left(-\frac{r_2 X_2^*}{K} - X_2^*\frac{\partial}{\partial X_2}f_2(X_2^*, T^*)\right)\left(-\mu + f_3(I_L,^* T^*) + T^*\frac{\partial}{\partial T}f_3(I_L^*, T^*)\right) +$
$\left(X_2^*\frac{\partial}{\partial T}f_2(X_2^*, T^*)T^*\frac{\partial}{\partial X_2}f_3(I_L^*, T^*)\right) > 0$:unsure

Outline

Conclusions

- Keeping total dosages the same, more frequent injections are conducive to managing prostate cancer longer
- Considered the case where injections are continuous (as in an IV)
  - Increasing e_1, the T-cell killing efficiency, disease shifts from AI relapse to stable limit cycle behavior to eradication of disease
  - Determined personalized critical dosage value v_{crit} needed to eradicate prostate cancer
- Analyzed global dynamics for the reduced sysem, translated some of the conditions back into biological meaning

- Future work
  - Finish analysis for quasi-steady state system: are there limit cycles?
  - Analysis of reduced system under no medication
  - Comparison to data
  - Any way to loosen restrictions for global stability of either equilibrium
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Questions?

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