A Model for Dendritic Cell Vaccine with Intermittent Androgen Deprivation Therapy for Late-Stage Prostate Cancer

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Introduction and Biological Background

- Prostate requires androgen to function, so current treatment suppresses androgen, which is initially successful, but gives way to fatal castration-resistant prostate cancer (CRPC)
- Intermittent androgen suppression therapy (IAS) may increase both life and quality of life of patients instead of continual androgen suppression therapy (CAS)

- Dendritic cells (DCs) are antigen-presenting cells and target PAP from patient's own tumor
- Mature DC's present antigen material to naive and memory T-cells
- DCs secrete co-stimulatory signals that rally the immune system
- DC vaccines are created with patient-specific tumor (see figure on right)

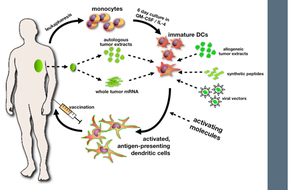

Figure : DC Vaccine

Motivating Questions

- Biological Questions
  - How does timing the DC vaccine dose influence time to CRPC?
  - Are DC vaccines effective in treating cancer which is not CRPC?
  - 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?

Mathematical Model

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

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

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

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

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

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

With growth and mutation functions:

- $r_1(A,X_1,X_2) = r_1 A\left(1-\frac{X_1+X_2}{K}\right) - d_1(a_0 - A)$
- $r_2(X_1,X_2) = r_2\left(1-\frac{X_1+X_2}{K}\right)$
- $m(A) = m_1(1-\frac{A}{a_0})$
- $m_2(A) = m_2(\frac{A}{A+k_4})$

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 $y(t) = c_1 X_1 + c_2 X_2$ represents serum PSA levels

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

- f_i are positive for positive values of X_1, X_2 and T.
- f_i are zero wen X_1, X_2 or T are zero.
- f_1, f_2 are decreasing in X_1, X_2 and increasing in T
- f_3 is increasing in X_1, X_2, and T.
- f_4 is increasing in X_1 and X_2

Vaccine Timing Sensitivity

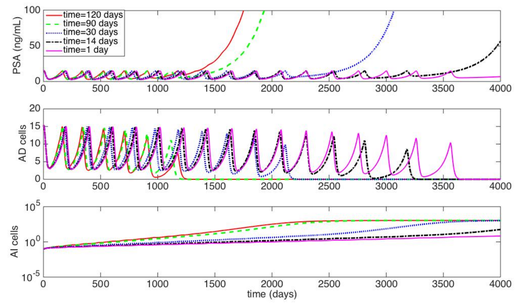

Figure : PSA, AI and AD levels varying frequency of injection. Higher frequency gives longer time to relapse

- f_i for all simulations will be:
  - $f_1(X_1,X_2,T) = \frac{e_1 T}{g_1+X_1+X_2}$
  - $f_2(X_1,X_2,T) = \frac{e_1 T}{g_1+X_1+X_2}$
  - $f_3(X_1,X_2,T) = \frac{e_3 T I_L}{g_3+I_L}$
- Hold total dosage constant but vary administration schedule from once every day to once every six months
- Increasing frequency of injection staves off CRPC, increasing survival time
- What if we could have a 'continual' injection?

Continual Injection Through IV

Assume DC vaccine continually administered, as if through an IV, then: $\frac{dD}{dt} = \underbrace{v}_{\text{injection}} - \underbrace{cD}_{\text{death}}$

- Determine behavior varying personalized parameter e_1, T-cell killing efficiency or cytotoxicity
- 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

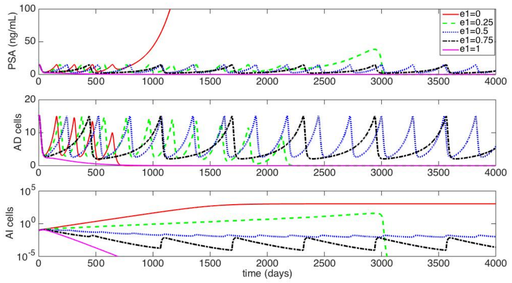

Figure : PSA, AI and AD levels for continual injection of DC, varying e_1, T-cell killing efficiency.

Analytical Results

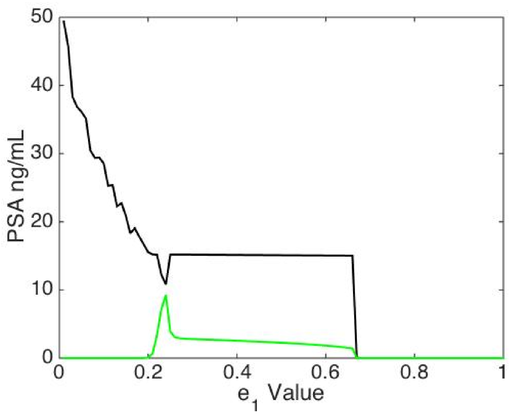

Figure : Bifurcation diagram for e_1, T-cell killing efficiency. For lowest levels of e_1, disease-free unstable. A Hopf bifurcation occurs for limit cyclical solutions, followed by stable disease-free equilibrium.

- Solutions that start positive remain positive
- The Disease-free equilibrium $E_0^* = (0,0,\frac{e_2 v(g_3+I_L^*)}{(cg_2+v)(\mu g_3+I_L^*(\mu-e_3))},0,0,\frac{v}{c})$, is locally asymptotically stable if $e_1 > \frac{g_1 r_2}{T^*}$, and unstable if $e_1 \le \frac{g_1 r_2}{T^*}$.
- $e_1 \le \frac{g_1 r_2}{T^*} \Leftrightarrow v > \frac{cg_2 g_1 r_2 \mu}{e_1 e_2 - g_1 r_2 \mu}$, so if we can measure other personalized parameters, can determine necessary dosage for locally stable cancer eradication
- $v_{\text{crit}} = \frac{cg_2 g_1 r_2 \mu}{e_1 e_2 - g_1 r_2 \mu}$
- Bifurcation diagram shows carrying capacity stalbe only for $e_1 = 0$, then a Hopf biufrcation, limi cycles until $e_1 \approx 0.66$ after which disease-free steady state is stable.
- No closed form expression for disease-state equilibrium E_1^*

Reduction of System

- Assume androgen deprivation therapy is constantly on
  - $\frac{dA}{dt} = \gamma(a_0 - A) - \gamma a_0 u(t) \to \frac{dA}{dt} = -\gamma A$
- Note cytokines (I_L), androgen (A), dendritic cells (D) operate on faster time scale than tumor cell growth and T cells, so let the fast-scale variables go to quasi-steady state:
  - $I_L = \frac{e_4 T(X_1+X_2)}{\omega(g_4+X_1+X_2)}$
  - $A = 0$
  - $D = \frac{v}{c}$

System reduces to:

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

System can be further reduced since it is apparent that $\lim_{t\to\infty} X_1(t) = 0$. Reduced system has similar dynamics to full system.

Analysis of Reduced System

Theorem

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

1. $\mu > f_3(I_L,T)$
2. $\frac{\partial}{\partial X_2} f_2(X_2,T) \ge -\frac{r}{K}$
3. $r_2 < f_2(0,T)$
4. $\frac{\mu^2(g_2+D)}{e_2 D} > \frac{\partial}{\partial T} f_3(0,T^*)$

The proof is based as follows:

- Proof of positivity and boundedness (condition 1)
- Proof of local asymptotic stability (conditions 2 and 3)
- Since only boundary equilibrium there are no limit cycles, so by Poincare-Bendixson, we have global stability

Biological meaning of stability conditions:

1. $\mu > f_3(I_L,T)$: the death rate of T cells is greater than the activation rate of T cells by the cytokines
2. $\frac{\partial}{\partial X_2} f_2(X_2,T) \ge -\frac{r}{K}$: killing function more responsive than growth function
3. $r_2 < f_2(0,T)$: the growth rate of the AI cancer cells is smaller than the death rate due to T cells

An analogous theorem is available for stability of the endemic equilibirum

Conclusions and Further Directions

Conclusions

- Keeping total dosages the same, more frequent injections are conducive to managing prostate cancer longer
- Determined critical dosage based on personalized parameters
- Analyzed local stability of full system and global stability conditions for reduced quasi-steady state system

Further Directions

- Would like to loosen strict biological conditions on global stability of disease-free steady state
- Find functions and conditions that generate limit cycle behavior

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