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

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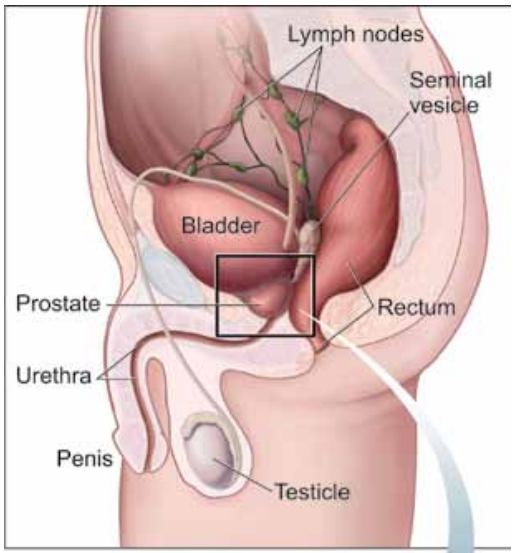
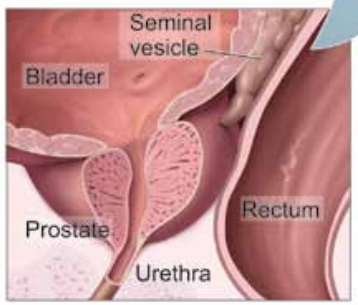
July 1, 2016

# Outline

# Introduction: Prostate Cancer Statistics

- 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




**Estimated New Cases**

| | Males | | | Females | |
|---|---|---|---|---|---|
| Prostate | 220,800 | 26% | | Breast | 231,840 | 29% |
| Lung & bronchus | 115,610 | 14% | | Lung & bronchus | 105,590 | 13% |
| Colon & rectum | 69,090 | 8% | | Colon & rectum | 63,610 | 8% |
| Urinary bladder | 56,320 | 7% | | Uterine corpus | 54,870 | 7% |
| Melanoma of the skin | 42,670 | 5% | | Thyroid | 47,230 | 6% |
| Non-Hodgkin lymphoma | 39,850 | 5% | | Non-Hodgkin lymphoma | 32,000 | 4% |
| Kidney & renal pelvis | 38,270 | 5% | | Melanoma of the skin | 31,200 | 4% |
| Oral cavity & pharynx | 32,670 | 4% | | Pancreas | 24,120 | 3% |
| Leukemia | 30,900 | 4% | | Leukemia | 23,370 | 3% |
| Liver & intrahepatic bile duct | 25,510 | 3% | | Kidney & renal pelvis | 23,290 | 3% |
| **All Sites** | **848,200** | **100%** | | **All Sites** | **810,170** | **100%** |

**Estimated Deaths**

| | Males | | | Females | |
|---|---|---|---|---|---|
| Lung & bronchus | 86,380 | 28% | | Lung & bronchus | 71,660 | 26% |
| Prostate | 27,540 | 9% | | Breast | 40,290 | 15% |
| Colon & rectum | 26,100 | 8% | | Colon & rectum | 23,600 | 9% |
| Pancreas | 20,710 | 7% | | Pancreas | 19,850 | 7% |
| Liver & intrahepatic bile duct | 17,030 | 5% | | Ovary | 14,180 | 5% |
| Leukemia | 14,210 | 5% | | Leukemia | 10,240 | 4% |
| Esophagus | 12,600 | 4% | | Uterine corpus | 10,170 | 4% |
| Urinary bladder | 11,510 | 4% | | Non-Hodgkin lymphoma | 8,310 | 3% |
| Non-Hodgkin lymphoma | 11,480 | 4% | | Liver & intrahepatic bile duct | 7,520 | 3% |
| Kidney & renal pelvis | 9,070 | 3% | | Brain & other nervous system | 6,380 | 2% |
| **All Sites** | **312,150** | **100%** | | **All Sites** | **277,280** | **100%** |

NCI www.cancer.gov

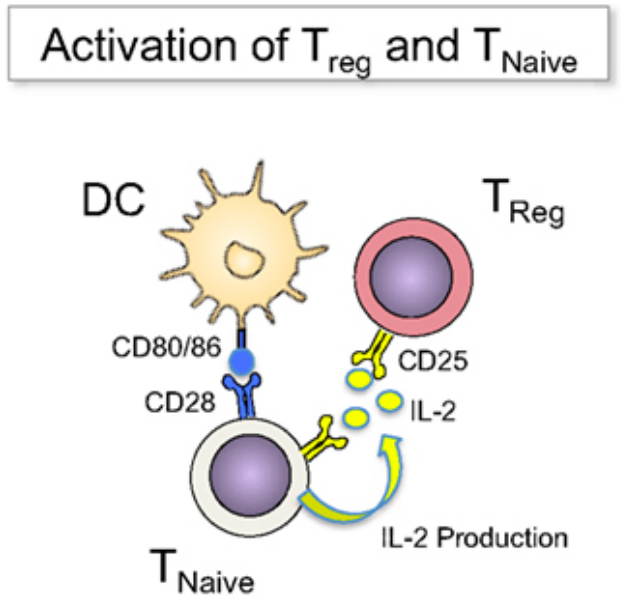
Cancer Statistics, 2015

# Androgen Suppression Therapy

- Androgens are male sex hormones
- Androgen suppression therapy decreases androgens, either by castration or the use of drugs
- Initial response great, advances to a castration-resistant prostate cancer (CRPC)
- Side effects unpleasant:
  - 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.

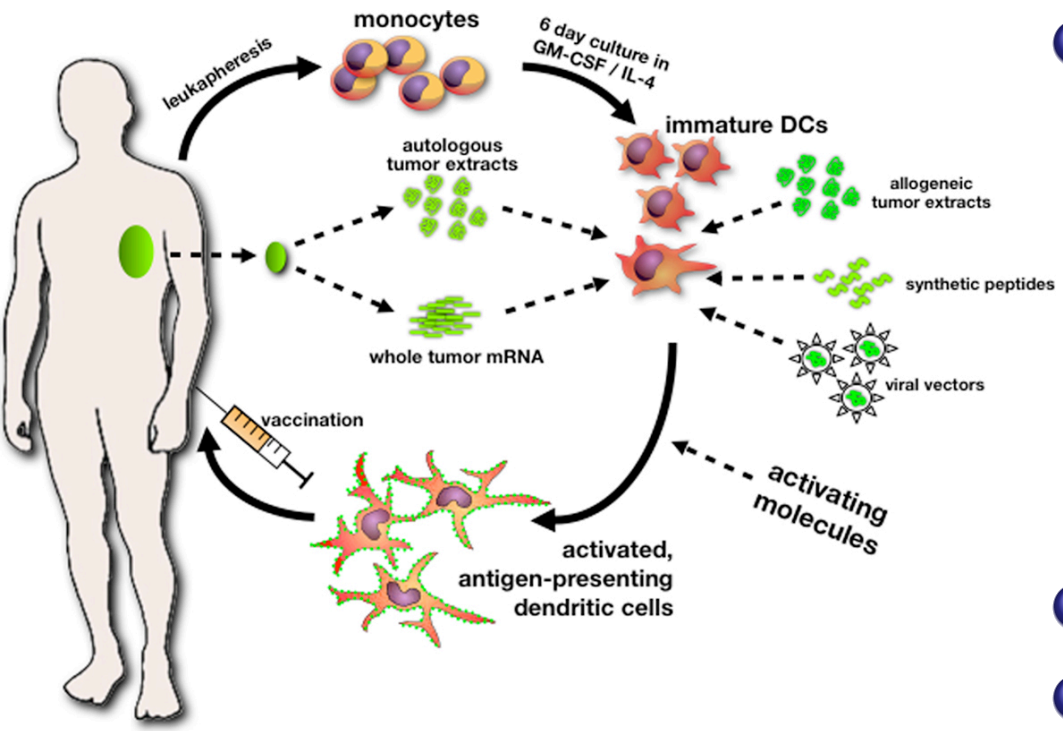
# Immune System Basics

- Dendritic Cells (DC's) present antigens on surface to (cytotoxic) T cells
- T-cells attack tumor cells with antigen on surface and produce IL-2
- IL-2 is a cytokine (interleukin), promoting differentiation of immature T cells




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 cell vaccines




Source: Surmont, Veerle F., et al. "Investigational approaches for mesothelioma." Frontiers in oncology 1 (2011). [10]

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)
- 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

# Our Model

AD cells:
$$\frac{dX_1}{dt} = \underbrace{r_1(A, X_1, X_2)X_1}_{\text{growth and death}} - \underbrace{m_1(A)X_1}_{\text{mutation to AI}} + \underbrace{m_2(A)X_2}_{\text{mutation from AI}} - X_1 \underbrace{f_1(X_1, X_2, T)}_{\text{death by T cell}}$$

AI cells:
$$\frac{dX_2}{dt} = \underbrace{r_2(X_1, X_2)}_{\text{growth and death}} + \underbrace{m_1(A)X_1}_{\text{mutation from AD}} - \underbrace{m_2(A)X_2}_{\text{mutation to AD}} - X_2 \underbrace{f_2(X_1, X_2, T)}_{\text{death by T cell}}$$

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

IL-2 conc:
$$\frac{dI_L}{dt} = \underbrace{Tf_4(X_1, X_2)}_{\text{secretion}} - \underbrace{\omega I_L}_{\text{degradation}}$$

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

# Our Model - Cont'd

With growth and mutation functions:

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

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

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

# Biological and Mathematical Questions

Major changes

- Consider allowing AI cells to mutate back into AD cells when in an androgen-rich environment
- Lack of androgen actively kills AD cells and prevents growth
- Little is known about immune system interactions, so use generalized functions

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?

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

# Our functions

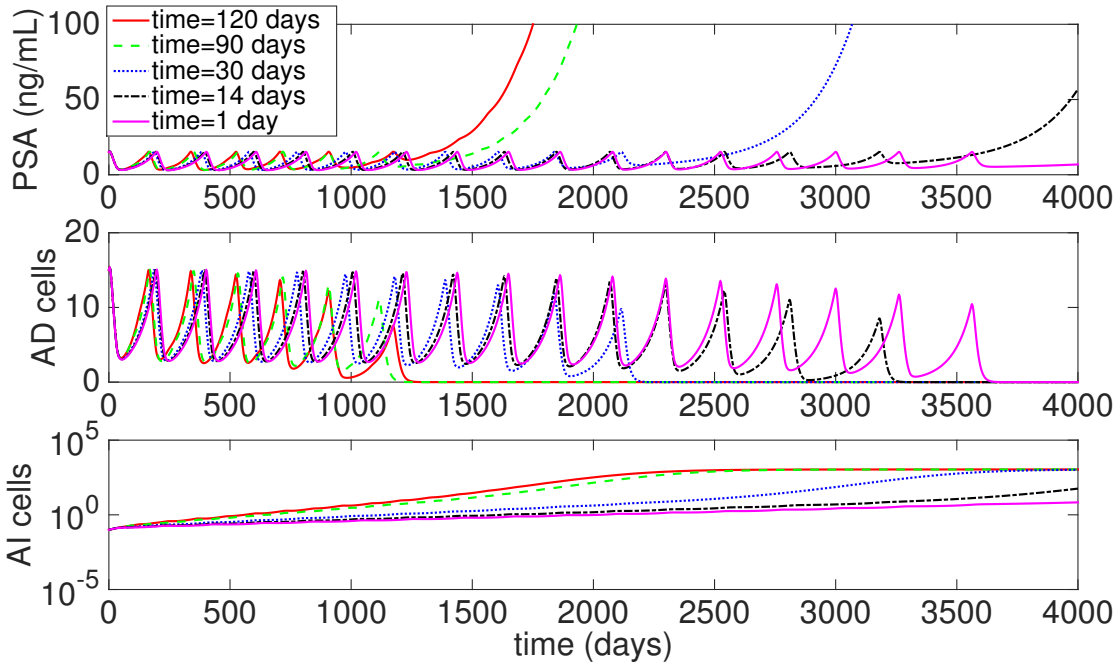
The functions we propose for simulation results are

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

and they satisfy the previous conditions.

# Vaccine Timing Results

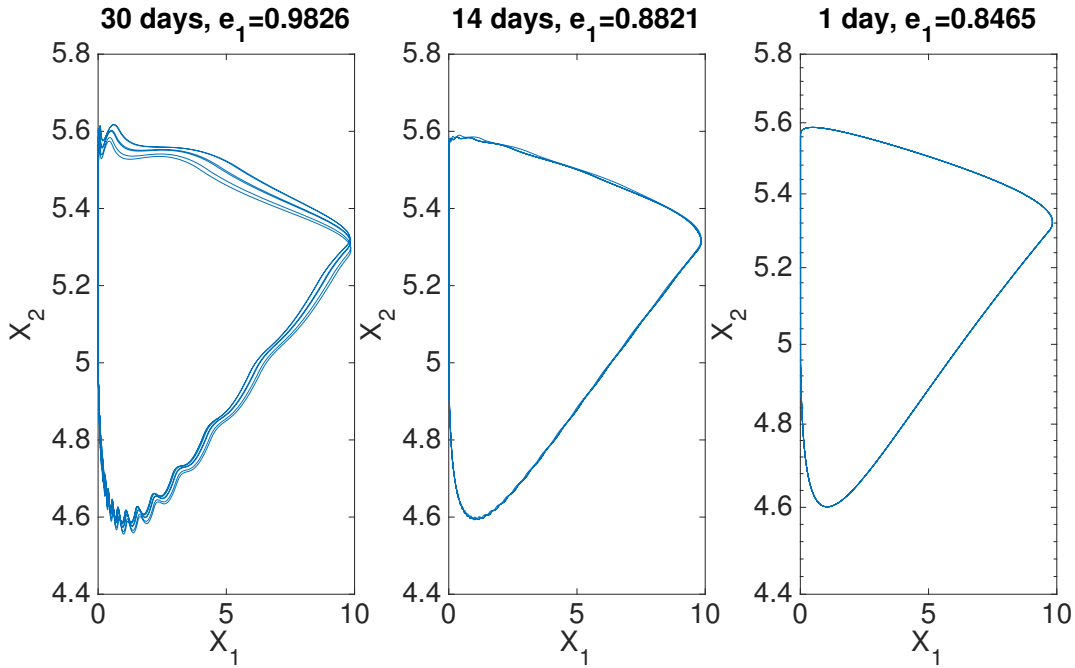
- Keep total dosage of vaccine constant
- Vary how often dendritic cell vaccine is administered




- More frequent injections delay androgen independent relapse

# Minimal $e_1$

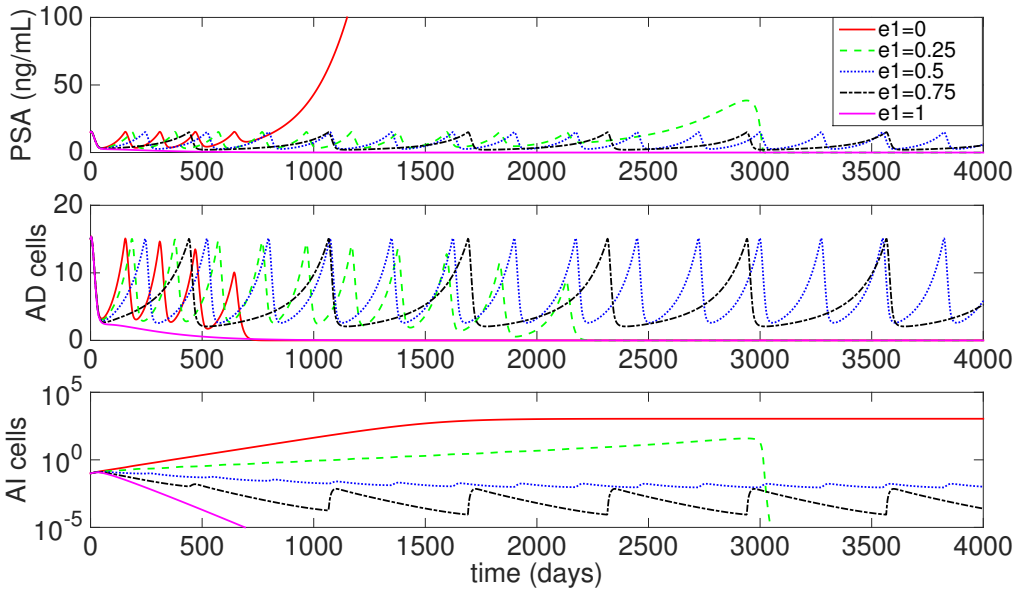
- $e_1$ represents maximum rate T cells kill cancer cells, may be personalized parameter
- numerically investigate minimal $e_1$ value to prevent relapse (stable cyclical disease).

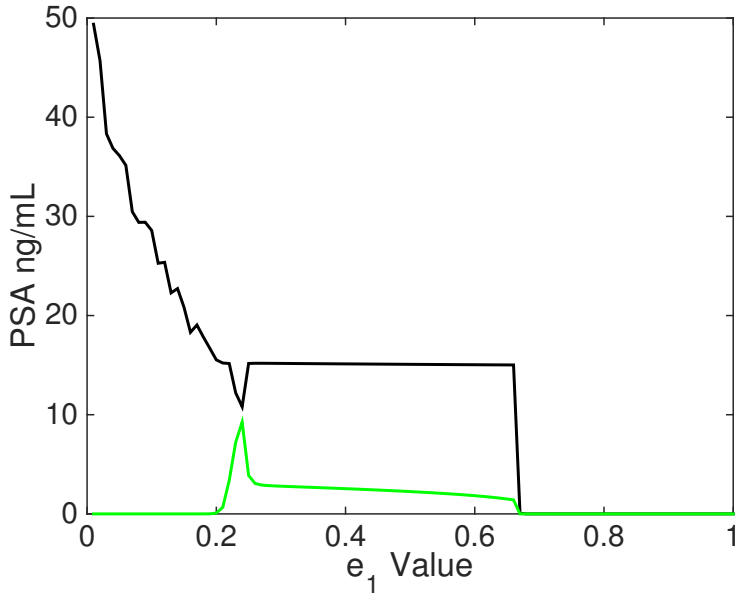



- More frequent injections can assist weaker immune systems

# Continuous Model

- Assume continual injection $v$ (as through an IV drip)
- $\frac{dD}{dt} = \underbrace{v}_{\text{injection}} - \underbrace{cD}_{\text{death}}$



# Analysis of Continuous Model

$$\frac{dX_1}{dt} = r_1(A, X_1, X_2)X_1 - m_1(A)X_1 + m_2(A)X_2 - X_1 f_1(X_1, X_2, T)$$
$$\frac{dX_2}{dt} = r_2(X_1, X_2)X_2 + m_1(A)X_1 - m_2(A)X_2 - X_2 f_2(X_1, X_2, T)$$
$$\frac{dT}{dt} = \frac{e_2 D}{g_2 + D} - \mu T + T f_3(I_L, T)$$
$$\frac{dI_L}{dt} = T f_4(X_1, X_2) - \omega I_L$$
$$\frac{dA}{dt} = -\gamma A$$
$$\frac{dD}{dt} = v - cD$$

**Theorem**

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

# Analysis Cont'd

**Theorem**

*The model system has a disease-free equilibrium* $E_0^* = (0, 0, \frac{ev}{\mu(cg+v)}, 0, 0, \frac{v}{c})$, *which is unstable if* $r_2 > f_2(0, 0, T_0^*)$, *where* $T_0^* = \frac{ev}{\mu(cg+v)}$, *and locally asymptotically stable if* $r_2 \leq f_2(0, 0, T_0^*)$. *When* $r_2 > f_2(0, 0, T_0^*)$, *a positive endemic equilibrium* $E^* = (X_1^*, X_2^*, T^*, I_L^*, A^*, D^*)$ *emerges, stability unknown.*

- All variables except $X_2$ are easily solvable and only have one steady state
- if $r_2 - f_2(0, 0, T_0^*) < 0$, there is no biologically relevant $X_2$ value ($X_2 < 0$).
- if $r_2 - f_2(0, 0, T_0^*) > 0$, there must be some $X_2^* \in (0, K)$ giving us an endemic equilibrium $E_1^* = (0, X_2^*, T_1^*, I_{L1}^*, 0, \frac{v}{c})$ (AI relapse)

Jacobian for $E_0^*$

$$\begin{pmatrix} -d_1 a_0 - m_1 - f_1(0,0,T^*) & 0 & 0 & 0 & 0 & 0 \\ m_1 & r_2 - f_2(0,0,T^*) & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu & T^* \frac{\partial}{\partial I_L} f_3(0,T^*) & 0 & \frac{ceg}{cg+v} \\ T^* \frac{\partial}{\partial X_1} f_4(0,0) & T^* \frac{\partial}{\partial X_2} f_4(0,0) & 0 & -\omega & 0 & 0 \\ 0 & 0 & 0 & 0 & -\gamma & 0 \\ 0 & 0 & 0 & 0 & 0 & -c \end{pmatrix}$$

$\lambda = (-d_1 a_0 - m_1 - f_1(0,0,T^*), r_2 - f_2(0,0,T^*), -\mu, -\omega, -\gamma, -c)$

$\lambda_2 = r_2 - f_2(0,0,T^*)$ determines stability

# Biological Implications

If we use our functions from the simulations,
$r_2 < f_2(0, 0, T^*) \Leftrightarrow e_1 \leq \frac{g_1 r_2}{T^*}$

- We cannot control parameters $e_1, e_2, g_1, c, \mu$, or $g_2$, some are personalized parameters
- We can control dosage, $v$
- $e_1 \leq \frac{g_1 r_2}{T^*} \Leftrightarrow v > \frac{c g_2 g_1 r_2 \mu}{e_1 e_2 - g_1 r_2 \mu}$,
- $v_{\text{crit}}$ 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
  - $I_L = \frac{Tf_4(X_, + X_2)}{\omega}$
  - $A = 0$
  - $D = \frac{v}{c}$

System reduces to:

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

# Further Reduction of System

$$\begin{aligned}\frac{dX_1}{dt} &= X_1\left[-d_1 a_0 - m_1 - f_1(X_1, X_2, T)\right] \\ &\leq X_1\left[-\beta_1 k_2 - m_1\right] \\ &\leq -aX_1\end{aligned}$$

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

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

The end behaviors of this system and the previous system are asymptotically equivalent [11]

**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) $r_2 < f_2(0, 0, T_0^*)$,

iii) $\frac{\mu^2(cg+v)}{ev} > \frac{\partial}{\partial T} f_3(0, T_0^*)$.

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

# 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 production of T cells due to the cytokine $IL_2$. This helps keep our T cells at a temperate value.

ii) $r_2 < f_2(0, T)$, : The intrinsic growth rate of AI cells needs to be smaller than the killing rate of AI cells by T cells. This was a condition also present in the full system and is biologically sensible.

iii) $\frac{\mu^2(g+D)}{eD} > \frac{\partial}{\partial T} f_3(0, T^*)$: Unsure how to interpret this condition in a biological manner.

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.

# 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) $r_2 > f_2(0, 0T_0^*)$,

iii) $\mu - f_3(I_L, T) > -X_2 \frac{\partial}{\partial X_2} f_2(X_1, X_2, T) + T \frac{\partial}{\partial T} f_3(I_L, T) - \frac{r_2 X_2}{K} \forall X_2, T \geq 0.$

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

1. Positivity and boundedness (condition i)
2. Local asymptotic stability (condition ii-iii)
3. Dulac Criteria (condition iii)
4. Global asymptotic stability

# Local Asymptotic Stability of $E_0^*$

**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)). The disease-free equilibrium is a saddle point (under conditions ii) and iii)).*

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

$$\begin{pmatrix} r_2 - f_2(0, T_0^*) & 0 \\ T_0^* \frac{\partial}{\partial X_2} f_3(0, T_0^*) & -\mu + T_0^* \frac{\partial}{\partial T} f_3(0, T_0^*) \end{pmatrix}$$

and the eigenvalues are given by:

- $\lambda_1 = r_2 - f_2(0, T_0^*) > 0$ by condition ii)
- $\lambda_2 = -\mu + T_0^* \frac{\partial}{\partial T} f_3(0, T_0^*) < 0$, by condition iii).

$E_0^*$ is a saddle point.

# Local Asymptotic Stability of $E_1^*$

The local stability of $E_1^*$ is exhibited in the Jacobian:

$$\begin{pmatrix} -\frac{r_2 X_2^*}{K} - X_2^* \frac{\partial}{\partial X_2} f_2(X_2^*, T_1^*) & -X_2^* \frac{\partial}{\partial T} f_2(X_2^*, T_1^*) \\ T_1^* \frac{\partial}{\partial X_2} f_3(I_L^*, T_1^*) & -\mu + T_1^* \frac{\partial}{\partial T} f_3(I_L^*, T_1^*) + f_3(I_L^*, T_1^*) \end{pmatrix}.$$

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

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

and the determinant is given by

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

In order for $E_1^*$ to be stable we require $\tau < 0, \Delta > 0$: $\tau < 0$ is given by assuming condition iii), and $\Delta$=?. Therefore, $E_1^*$ is either a stable node/spiral or a saddle point

# Elimination of Limit Cycles

**Proposition**

*The limiting system* (1) *has no limit cycles as long as condition iii) 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

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

# Dulac - cont'd

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

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

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

# Global Stability

By Poinecare-Bendixson, since solutions are positive, bounded and there are two fixed points, one of which is a saddle, solutions do one of three things:

- All solutions tend to a fixed point (global stability)
- All solutions tend to a periodic orbit (ruled out by Dulac Criterion)
- Heteroclinic or homoclinic orbits connect our two fixed points

We must show there are no heteroclinic or homoclinic orbits connecting our fixed points

# Heteroclinic orbits and homoclinic orbits

We examine the stable manifold of $E_0^*$

$$\begin{pmatrix} X_2 \\ T \end{pmatrix} = \begin{pmatrix} 0 \\ 1 \end{pmatrix}.$$

- By assumption ii), $dX_2(t)/dt > 0$ near $E_0^*$, so there cannot be a heteroclinic orbit connecting $E_0^*$ to $E_1^*$
- Assumption ii) also precludes a homoclinic orbit originating from $E_0^*$
- If $E_1^*$ is stable, there cannot be any homoclinic orbits originating from $E_1^*$
- If $E_1^*$ is a saddle, there is no homoclinic orbits (by Dulac)

By Poincare-Bendixson Theorem, the only option remaining is that all solutions of (1) converge to $E_1^*$. Thus, $E_1^*$ is globally asymptotically 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 production of T cells due to the cytokine $IL_2$. This helps keep our T cells at a temperate value. This showed up as a condition in Theorem 4.1 as well.

ii) $r_2 > f_2(0, 0, T_0^*)$, : The intrinsic growth rate of AI cells needs to be larger than the killing rate of AI cells by T cells. This is a logical assumption considering that we want stability of an equilibrium that has non-zero $X_2$ values.

iii) $\mu - f_3(I_L, T) > -X_2 \frac{\partial}{\partial X_2} f_2(X_1, X_2, T) + T \frac{\partial}{\partial T} f_3(I_L, T) - \frac{r_2 X_2}{K} \forall X_2, T \geq 0$.: Unsure how to interpret this condition in a biological manner.

# 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 $v_{\text{crit}}$ needed to eradicate prostate cancer
- Analyzed global dynamics for the reduced sysem, translated some of the conditions back into biological meaning

# Future Work & Acknowledgements

- Future work
  - Finish analysis for quasi-steady state system: are there limit cycles?
  - Analysis of reduced system under no androgen deprivation therapy
  - Compare to data
- Acknowledgements
  - Dr. Yang Kuang
  - Alex P. Farrell
  - Rebecca Everett

# Works Cited I


Richard R Berges, Jasminka Vukanovic, Jonathan I Epstein, Marne CarMichel, Lars Cisek, Douglas E Johnson, Robert W Veltri, Patrick C Walsh, and John T Isaacs.
Implication of cell kinetic changes during the progression of human prostatic cancer.
*Clinical Cancer Research*, 1(5):473–480, 1995.

Nicholas Bruchovsky, Laurence Klotz, Juanita Crook, and S Larry Goldenberg.
Locally advanced prostate cancerbiochemical results from a prospective phase ii study of intermittent androgen suppression for men with evidence of prostate-specific antigen recurrence after radiotherapy.
*Cancer*, 109(5):858–867, 2007.

Kirschner D. and Panetta J. C.
Modeling immunotherapy of the tumor-immune reaction.
*J Math Biol*, 1998.

Georg Gasteiger and Wolfgang Kastenmuller.
Foxp3+ regulatory t-cells and il-2: the moirai of t-cell fates?
*Frontiers in immunology*, 3, 2012.

Aiko Miyamura Ideta, Gouhei Tanaka, Takumi Takeuchi, and Kazuyuki Aihara.
A mathematical model of intermittent androgen suppression for prostate cancer.
*Journal of nonlinear science*, 18(6):593–614, 2008.

Michael T Lotze and Angus W Thomson.
*Dendritic cells: biology and clinical applications*.
Access Online via Elsevier, 2001.

Travis Portz, Yang Kuang, and John D Nagy.
A clinical data validated mathematical model of prostate cancer growth under intermittent androgen suppression therapy.
2012.

# Works Cited II


Steven A Rosenberg and Michael T Lotze.

Cancer immunotherapy using interleukin-2 and interleukin-2-activated lymphocytes.
*Annual review of immunology*, 4(1):681–709, 1986.

Eric J Small, Paige Fratesi, David M Reese, George Strang, Reiner Laus, Madhusudan V Peshwa, and Frank H Valone.

Immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells.
*Journal of Clinical Oncology*, 18(23):3894–3903, 2000.

Veerle F Surmont, Eric RE Van Thiel, Karim Vermaelen, and Jan P Van Meerbeeck.

Investigational approaches for mesothelioma.
*Frontiers in oncology*, 1, 2011.

Horst R Thieme.

Convergence results and a poincaré-bendixson trichotomy for asymptotically autonomous differential equations.
*Journal of mathematical biology*, 30(7):755–763, 1992.

# Parameters

| Parameter | Biological Meaning | Value | Source |
|---|---|---|---|
| $\alpha_1$ | AD cell proliferation rate | 0.025/day | [1] |
| $\beta_1$ | 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 | [7] |
| $a_0$ | base level androgen concentration | 30 ng/ml | [5] |
| $\gamma$ | androgen clearance and production rate | 0.08/day | [5] |
| $\omega$ | cytokine clearance rate | 10/day | [8] |
| $\mu$ | T cell death rate | 0.03//day | [3] |
| $c$ | dendritic cell death rate | 0.14/day | [6] |
| $e_1$ | maximum rate T cells kill cancer cells | 0-1/day | [3] |
| $g_1$ | cancer cell saturation level form T cell kill rate | $10 \times 10^9$ cells | [3] |
| $e_2$ | T cell maximum activation rate | $20 \times 10^6$ cells/day | [3] |
| $g_2$ | DC saturation level for T cell activation | $400 \times 10^6$ cells | [9] |
| $e_3$ | 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 | $5 \times 10^{-6}$ ng/ml/cell/day | [3] |
| $g_4$ | cancer cell saturation level for T cell stimulation | $10 \times 10^9$ cells | [3] |
| $D_1$ | DC vaccine dosage | $300 \times 10^6$ cells | [9] |
| $c_1$ | AD cell PSA level correlation | $1 \times 10^{-9}$ ng/ml/cell | [5] |
| $c_2$ | AI cell PSA level corelation | $1 \times 10^{-9}$ ng/ml/cell | [5] |