

Mathematical modeling of cancer immunotherapy: the anti-tumor effect of immune cells versus the anti-tumor effect of oncolytic viruses

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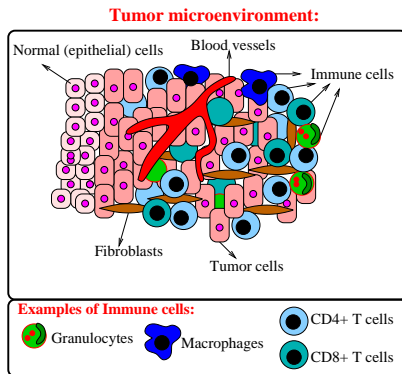
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Solid tumors

Solid tumors are formed not only of **tumor cells**, but also of **other cells which support their growth**

- various immune cells are recruited to the tumor site
- the anti-tumor effect of these cells is downregulated, mainly in response to tumor-derived signals

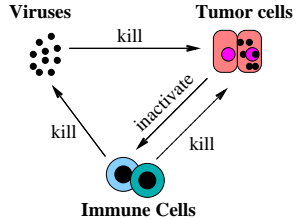


Solid tumors

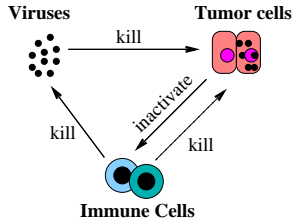
To stimulate the immune cells to attack the tumor: **cancer immunotherapies**

- **injection of cytokines** (e.g., IL-2, IFN- α ; frequently used to treat melanoma, kidney cancer , etc)
- **injection of monoclonal antibodies** (artificial antibodies against a particular cancer antigen); e.g. Herceptin->breast cancers
- **adoptive transfer of immune cells**
- **cancer vaccines** (immunize patients against cancer proteins, and thus trigger an immune reaction that could kill the cancer cells)
- **oncolytic viruses** (viruses that selectively infect and replicate inside cancer cells)

Cancer immunotherapy using oncolytic viruses

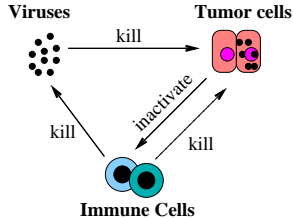


Cancer immunotherapy using oncolytic viruses



- **Virocentric** point of view: direct tumor cell lysis by the virus is the most important parameter
- **Immunocentric** point of view: lysis of cancer cells is important as long as it activates an immune response against cancer

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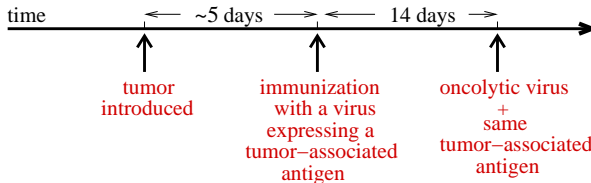


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Which one is more important for the elimination of tumor cells?

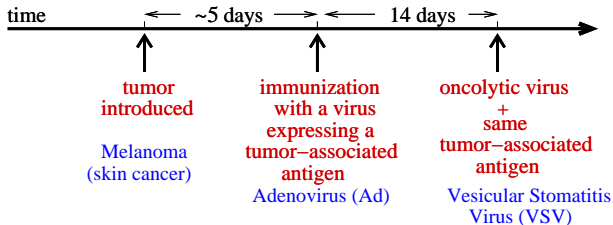
Cancer immunotherapy using vaccines & oncolytic viruses

- Researchers at McMaster University: **dual-immunization** protocol against tumor cells:



Cancer immunotherapy using vaccines & oncolytic viruses

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- ◆ Measure the immune response: **effector and memory** CD8⁺T cells

Cancer immunotherapy using vaccines & oncolytic viruses

Outcome:

- Increased mice survival: from averages of 15 days (VSV alone) or 28 days (Ad alone), to an average of 54 days (Ad+VSV)
- However, the tumor is not permanently eliminated

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- **However, the tumor is not permanently eliminated**

Goal:

- **Propose new mechanisms that could improve the treatment**
 - extend survival
 - even lead to permanent tumor elimination

Outline

- 1 Model description
- 2 Model validation
 - Tumor, virus and immune data
- 3 Ways to improve the oncolytic treatment

The model

E (Em) =effector (effector–memory) cells (kill tumor) Cm =central memory cells (proliferate)

Lymphoid Tissue (where cells get activated)

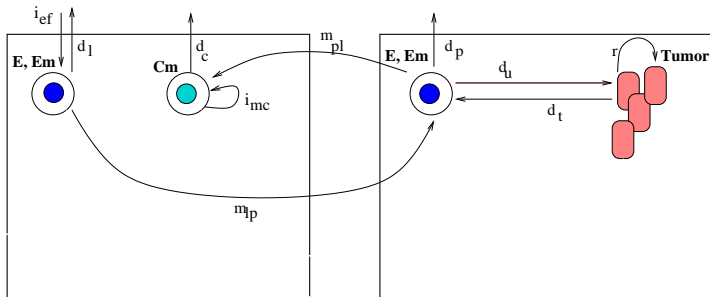
Peripheral Tissue (where tumor is)

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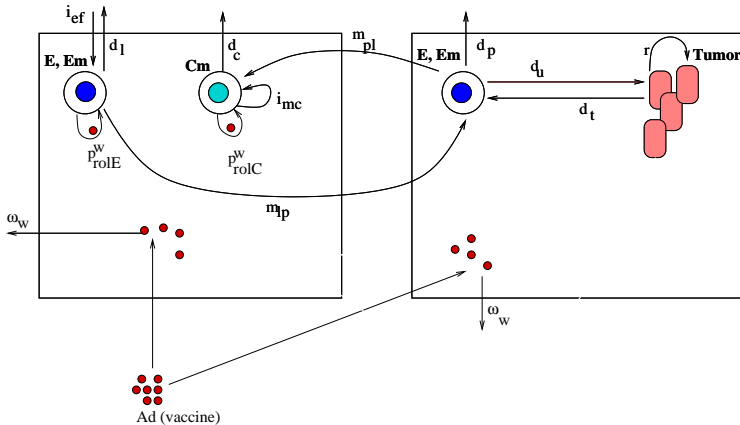


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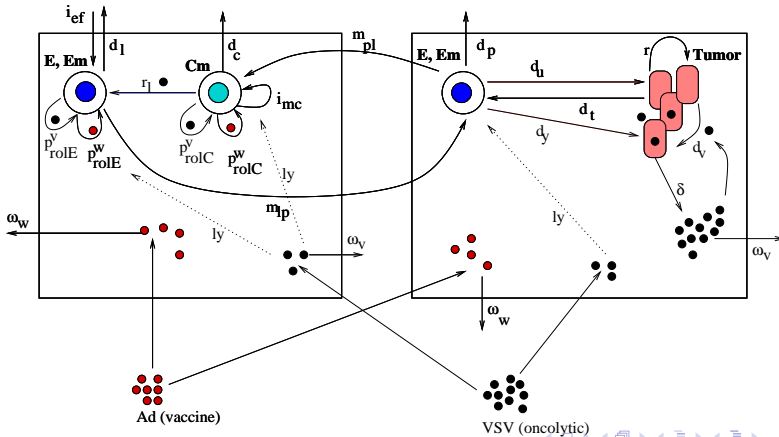


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Lymphoid Tissue (where cells get activated)

Peripheral Tissue (where tumor is)



The model

$$\text{Uninfected tumor: } x' = rx(1 - k(x + y)) - d_v \frac{x}{\eta + x} v - d_u x \frac{z_p}{\eta_0 + z_p}$$

$$\text{Infected tumor: } y' = d_v \frac{x}{\eta + x} v - \delta y - d_y y z_p$$

$$\text{VSV: } v' = c_v(t) + \delta B y - \omega_v v$$

$$\text{Ad: } w' = -\omega_w w$$

$$\text{Memory: } z'_c = i_{mc} z_c + p_C^w(w) + p_C^v(v) + m_{pl}(t) z_p - r_l(v) z_c - d_c z_c - l_y(t)$$

$$\text{Effector Lymph. } z'_l = i_l + p_E^w(w) z_l + p_E^v(v) z_l + r_l(v) z_c - d_l z_l - m_{lp} z_l - l_y(t)$$

$$\text{Effector Periph. } z'_p = m_{lp} z_l - d_p z_p - d_t x z_p - m_{pl}(t) z_p - l_y(t).$$

● Initial Conditions (day 0=day when Ad injected):

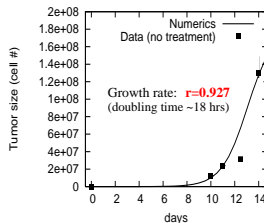
- Uninfected tumor: $x(0) = 9 \times 10^5$
- No infected tumor: $y(0) = 0$
- Ad just injected: $w(0) = 10^8$
- No VSV: $v(0) = 0$
- low immune response: $z_c(0) = 1, z_l(0) = 1.5, z_p(0) = 1.5$

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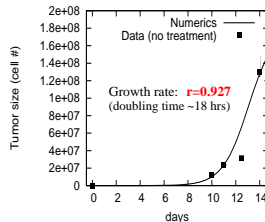
To validate the model: multiple data sets

**Tumor growth in the
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treatment**

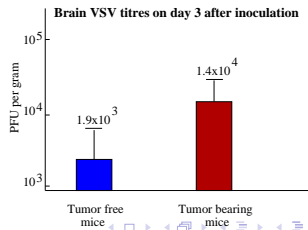


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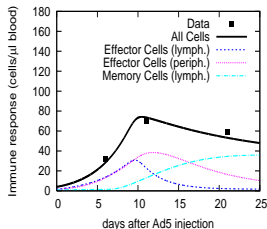


Viral load (VSV)

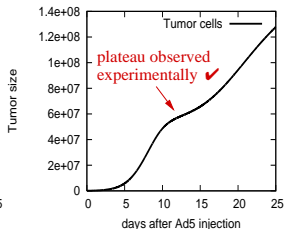


Model validation: immune response following Ad

● Immune response and tumor growth following Ad



- ◆ parameters governing immune cell proliferation & death

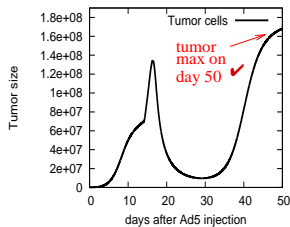
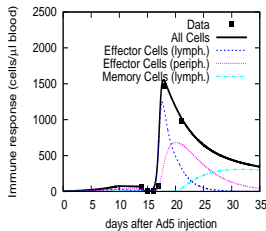


- ◆ parameters describing the killing of tumor cells by the immune cells (d_u)

Max reached 30 days after tumor injection ✓
(25 days after Ad)

Model validation: immune response following Ad+VSV

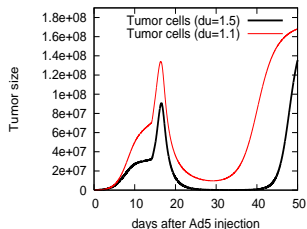
● Immune response and tumor growth following Ad+VSV



◆ Tumor reduced after Ad+VSV ✓

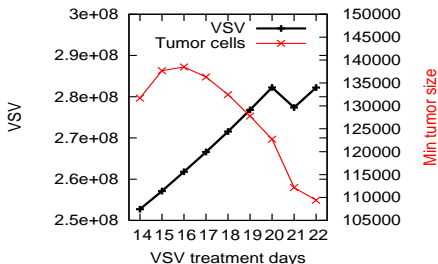
Improving the treatment: tumor lysis rate

- Investigate the role of d_u (=max. rate at which the immune cells lyse the tumor)
 - increasing d_u means increasing the functionality of immune cells



Improving the treatment: Delay the VSV

- Fix the parameters already identified and delay the administration of VSV

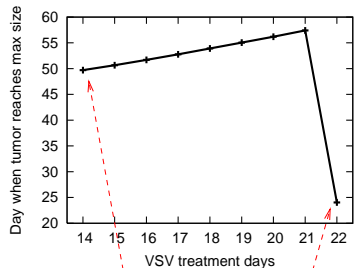
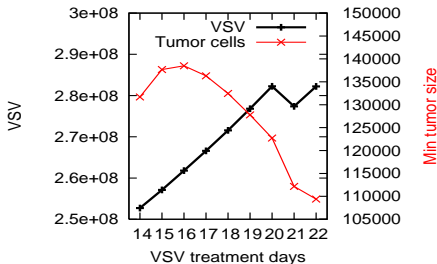


Delaying the VSV treatment:

- ◆ increases virus load ✓
- ◆ leads to better tumor killing ✓

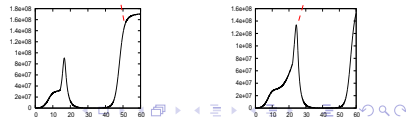
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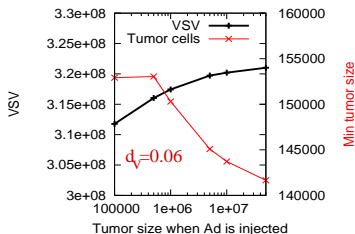
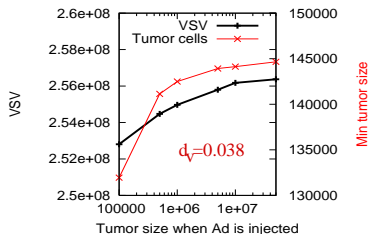
Improving the treatment: Role of tumor size

Since larger tumors => better VSV replication: increase tumor size

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Since larger tumors => better VSV replication: **increase tumor size**

- Change the **initial condition for the tumor** (i.e., tumor size 5 days after it was introduced)



- Increasing tumor size could lead to better reduction in tumor size following VSV
- The results **do depend** on the rate (d_v) at which the VSV infects the tumor cells

Summary

- The treatment could be improved by
 - increasing d_u (rate of tumor lysis by the immune cells)
 - delaying the VSV administration
 - slightly increasing the VSV load (not shown)
- However, **tumor grows back eventually**

Summary

Can we propose hypotheses regarding the conditions that could lead to **permanent elimination** of tumor cells?

When can the tumor be eliminated completely?

The full system (Ad+VSV) can evolve towards 3 steady states:

- **Tumor-free steady state:**

- **stable** when: $r < d_u \frac{z_p^*}{\eta + z_p^*}$, r =tumor growth rate z_p^* =immune effector cells
- **unstable** when: $r > d_u \frac{z_p^*}{\eta + z_p^*}$

- **Tumor-persistent steady state (without VSV)**

- exists only if $r > d_u \frac{z_p^*}{\eta + z_p^*}$

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- **Tumor-persistent steady state (without VSV)**

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- **Tumor-persistent steady state (with VSV)**

- exists only if $z_p^* = \frac{B\delta d_v \frac{x^*}{\eta_0 + x^*}}{d_v \omega_v}$ x^* =uninfected tumor, z_p^* =immune effector cells

- not very realistic state → **ignore it**

When can the tumor be eliminated completely?

- Hence **bi-stability** (between tumor-free and tumor-persistent s.s.) is **not possible given the model assumptions: immune cells can infiltrate the entire tumor** and destroy it:

$$d_u x^* \frac{z_p^*}{\eta + z_p^*}, \quad x^* = \text{uninfected tumor}, \quad z_p^* = \text{immune cells}$$

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- However, **bi-stability is possible** if one assumes that the **immune cells can infiltrate only a part of the tumor**:

$$d_u \frac{x^*}{\eta_0 + x^*} \frac{z_p^*}{\eta + z_p^*}, \quad x^* = \text{uninfected tumor}, \quad z_p^* = \text{immune cells}$$

When can the tumor be eliminated completely?

- **Stability of tumor-persistent steady state (without VSV)**

- Define the **Basic Reproductive Ratio** (for the VSV infection)

$$R_0 = \frac{d_v \delta B \frac{x^*}{\eta_0 + x^*}}{\omega_v (\delta + d_y z_p^*)}$$

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- **Bi-instability** is possible
 - For $R_0 > 1$: both tumor-free and tumor-persistent equilibria are **saddle points** → possible heteroclinic connection

Summing-up

- A mathematical model that can **fit multiple data sets**
- The **anti-tumor effect of immune cells** seems to be **more important** than the **anti-tumor effect of oncolytic viruses**
 - when the rate of tumor killing by the immune cells (d_u) is large -> **tumor eliminated permanently**
 - when VSV persists for a longer time (or higher initial load) -> system driven into a bi-instability regime with unknown consequences
- **Best to focus on methods to improve the lysis of tumor cells (d_u)**

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