

Equation Development of Tumor-Immune ODE System *

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TUMOR-IMMUNE EQUATION DEVELOPMENT

Overview

1. Choosing the Cell Populations to Model
2. Types of Models
3. Choosing a Model Type
4. Cell Growth Laws
5. Modeling Tumor-Immune Interactions
6. Initial System of ODEs
7. Simplifying Assumptions

Tumor-Immune Equation Development

Cell Populations

Our initial model will take the form of a **population model**, in which we describe the number of each type of cell in the system. Of the many cell types involved, we will consider only two types of cells.

Question: Which cell populations should we look at?

Answer: **IMMUNE/KILLER** cells and **TUMOR** cells influence the visible progress of the cancer more than other cells, so we'll begin our model by looking at those cell populations.

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Tumor-Immune Equation Development

Notes for Cell Populations slide:

Answers:

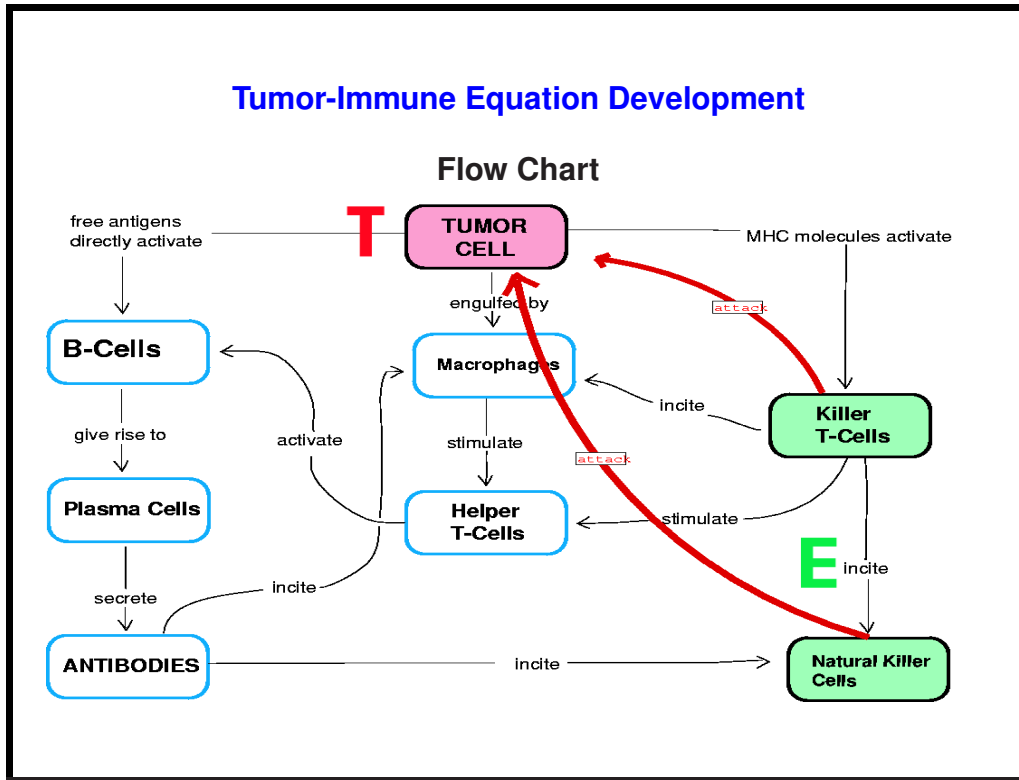
(1) Killer (Immune)

(2) tumor

Note: We bear in mind, however, that interactions between these two cell types are mediated and influenced by many other cell types.

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Tumor-Immune Equation Development



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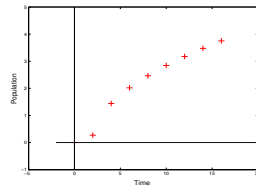
Tumor-Immune Equation Development

Notes for Flowchart Graphic:

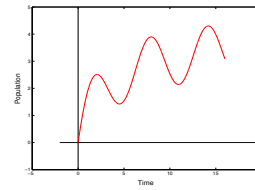
In this model we will just consider natural killer cells and cytotoxic T-cells as one population ("effector cells" E), and tumor cells (T).

Tumor-Immune Equation Development

Types of Models



(a) Discrete Time



(b) Continuous Time

- **Discrete Time** – Populations change at points in time (Figure (a))
- **Continuous Time** – Populations change continuously over time (Figure (b))
- **Deterministic** – Populations change according to a fixed law, e.g.

$$P(t_{i+1}) = F(P(t_i)) \text{ (discrete) or } \frac{dP}{dt} = F(P) \text{ (continuous)}$$

- **Stochastic** – Population changes are random events described by a probability distribution

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Tumor-Immune Equation Development

Choosing a Model Type

We start with a continuous-time deterministic system (*i.e.*, a system of differential equations).

Why?

- Physiological processes evolve continuously, relative to our perceptual resolution \Rightarrow **CONTINUOUS**.
- Inter-cellular reactions are described by (empirically determined) rates \Rightarrow **DETERMINISTIC**.

This gives

$$\begin{aligned} \frac{dE}{dt} &= F_1(E, T) \\ \frac{dT}{dt} &= F_2(E, T) \end{aligned}$$

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Tumor-Immune Equation Development

Notes for Choosing a Model Type slide:

Answers:

- (1) Continuous
- (2) Deterministic

After this slide and before the next slides:

- Suggest reading the first 2 sections of Kuznetzov.
- Have the students suggest what graphs of $\frac{dT}{dt}$ as a function of T or E look like, then $\frac{dE}{dt}$ as a function of T or E look like.

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Tumor-Immune Equation Development

Interactions and Growth Laws

Next step: Determining F_1 and F_2

The growth of each cell population can be divided into two components:

- Population growth **in isolation**.
- **Competitive interactions** between populations.

Questions to ask:

- How do each of the cell populations grow? For example, do the tumor cells divide at a constant rate? This would imply **EXPONENTIAL** growth, described by the differential equation:

$$\frac{dT}{dt} = kT, k > 0$$

- How do the cell populations affect each other?

Tumor-Immune Equation Development

Notes for Interactions and Growth Laws slide:

Answers:

(1) exponential growth

(2) kT , $k > 0$

Notes: The implication of exponential growth is that a tumor large enough to be detected clinically is approximately *one cubic centimeter in volume*. This corresponds to a population of 10^8 cells. With a doubling rate of 2 days, the tumor population would grow to 10^{11} cells and *weigh one kilogram, in only 20 days!* The students generally come up with self-limiting growth fairly quickly. Someone should sketch a graph of an imaginary growth curve: tumor population over time.

Possible point of confusion: The slope of the growth curve doesn't necessarily give the differential equation which *models* the growth. For example, in the case of the tumor-cell population, we are interested in describing how the rate of growth depends on the population itself, *i.e.* we want dT/dt as a function of T . In a calculus class, students are used to thinking of the slope of graphs as functions of the independent variable, in this case t . So a student may suggest creating an equation that looks like $dT/dt = f(t)$, whereas we really need to develop an equation that looks like $dT/dt = f(T)$.

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This involves thinking about the actual *mechanisms* that control growth, and cannot necessarily be directly inferred from looking at the growth curve $T(t)$.

Assuming the students have done the background reading (see *A Brief Background of the Immune System*), the source of immune cells should be discussed. The emphasis in this model is on immune cells which actually kill the tumor cells: hence, primarily *Natural Killer (NK) cells, and Cytotoxic T-cells*. The natural killer cells are always present in the system, while the production of tumor-specific T-cells is induced by the presence of the tumor itself.

Suggested in class exercise: Ask the class to come up with a system of two differential equations before proceeding to the next slides. They might start by drawing possible graphs of the following:

- dT/dt as a function of T
- dT/dt as a function of E
- dE/dt as a function of E
- dE/dt as a function of T

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Slides 7 through 11 carry out this process, resulting in the system studied in [KMTP94]. If there are differences in the equations presented, discuss how these differences might be resolved through experimentation.

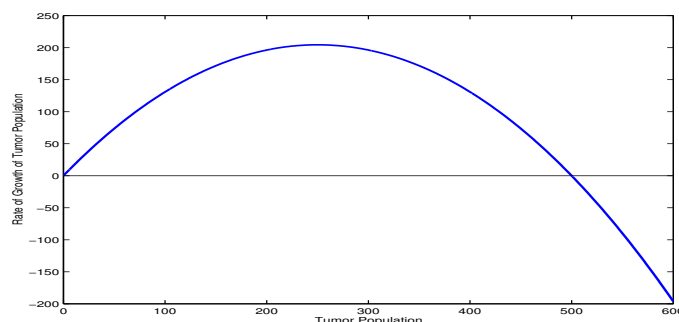
Suggested reading assignment: Read and discuss the first two sections of the Kuznetsov paper [KMTP94].

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Tumor-Immune Equation Development

Tumor Growth Law

Experiments show that tumor cells grow exponentially when the population is small, but growth slows down when the population is large. A graph that reflects this growth pattern might look like:



This curve could be described by the quadratic equation: $\frac{dT}{dt} = aT(1 - bT)$ or $\frac{dT}{dt} = aT(k - T)$ if $k = \frac{1}{b}$, the 'carrying capacity'. Equilibria occur at 0 and 500 (Note: $k = 500$).

Tumor-Immune Equation Development

Notes for Tumor Growth Law slide:

Answer:

(1) $\frac{dT}{dt} = aT(1 - bT)$, $a, b > 0$; or perhaps $\frac{dT}{dt} = aT(k - T)$.

Notes: It should be clear that one root of the quadratic is zero. It might be evident to some students that $k = 1/b = 500$. This number is called the “carrying capacity”, since it represents the largest equilibrium of the system, (in fact, the only non-zero equilibrium).

This slide may be extraneous if they have come up with a self-limiting growth model already. If not the graph can serve as a reminder of the interpretation of a differential equation. The class could be asked to:

- interpret the meaning of the portion of the growth curve which lies below the horizontal axis;
- identify any equilibria;
- come up with some other possible forms for the equation, other than a quadratic.

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Suggested reading assignment: Find several research articles on mathematical models of tumor growth. According to the authors, what equation best describes tumor growth, and why?

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Tumor-Immune Equation Development

Production of Immune Cells

- Cytotoxic effector cells, i.e. those immune cells which are capable of killing tumor cells can be either **NK** cells or **KILLER T CELLS**.
- If we assume that there is a constant source of effector cells, in particular the NK cells, and that a constant fraction of these cells die off, we get the differential equation:

$$\frac{dE}{dt} = s - \delta E, \delta > 0$$

- What function might represent how the production of *tumor-specific* effector cells respond to the presence of the tumor? This function must incorporate the recognition of antigen by the immune system. This could take different forms, we'll get there in a few slides.

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Tumor-Immune Equation Development

Notes for Production of Immune Cells slide:

Answers:

- (1) Natural Killer
- (2) Cytotoxic T-cells, or Killer T-cells.
- (3) $\frac{dE}{dt} = s - dE$, where $s, d > 0$.

Notes: Other immune cells may also be able to lyse tumor cells. The features of these two cell types which are important in this model are that some effector cells are always present, while the presence of the tumor stimulates the production of other effector cells.

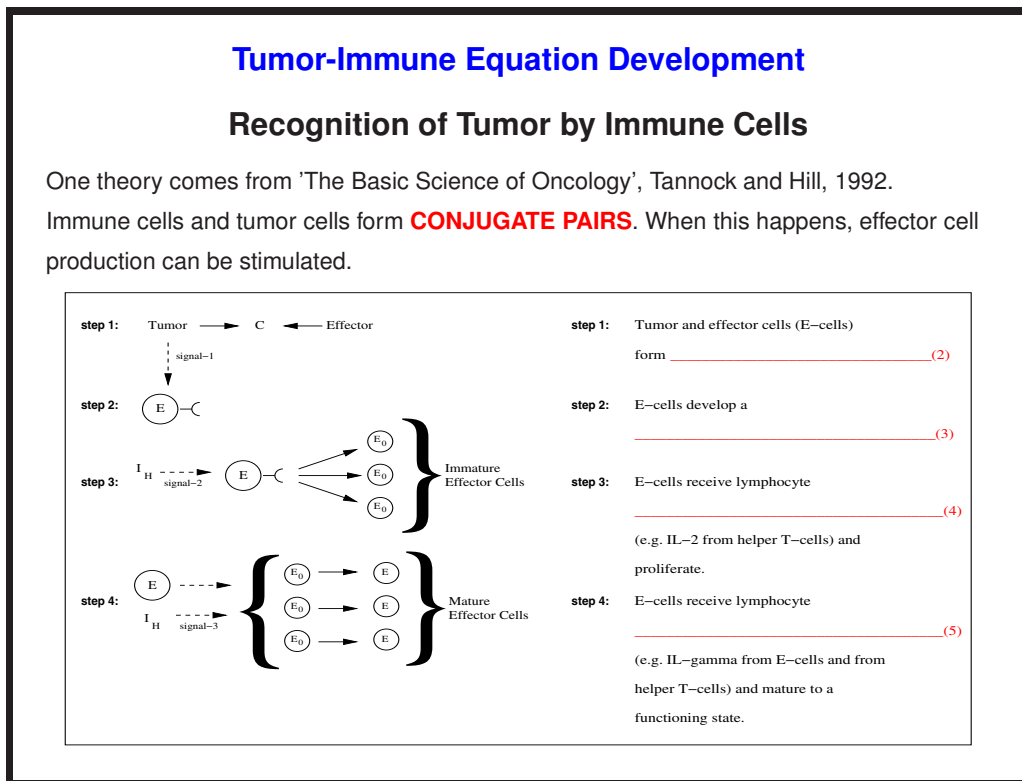
It has been argued that the presence of immune cells might actually stimulate the growth of tumor cells as well, but this possibility is neglected in this model.

The rate of production of tumor-specific effector cells is difficult to measure experimentally. It seems logical, however, that it should be an increasing function of the number of tumor cells, but that it should be bounded above by some constant. Experiments with mice indicate that stimulation of the production of antigen-specific immune cells is mediated by chemicals released when immune cells and antigen bind together

8-1

to form *conjugates*, denoted in later slides by *C*.

8-2



Tumor-Immune Equation Development

Notes for Recognition of Tumor by Immune Cells slide:

Answers:

- (1) conjugate pairs
- (2) conjugate pairs
- (3) growth factor receptor
- (4) growth factor
- (5) differentiation factor

This description can be found in [TH92]. This detailed description of the formation of conjugate pairs is not going to be included in the final model. However, it gives justification for the development of the equations in Kuznetsov's model [KMTP94].

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Tumor-Immune Equation Development

Tumor-Immune Interaction Schematic

The Formation of Effector-Tumor Conjugates

$$E + T \xrightleftharpoons[k_{-1}]{k_1} C \begin{cases} \xrightarrow{k_2} E + T^* \\ \searrow_{k_3} E^* + T \end{cases}$$

$E + T^*$: programmed tumor cell lysis; $E^* + T$: effector inactivated
 E, E^* active, inactive **EFFECTOR** cells
 T, T^* active, lethally hit **TUMOR** cells
 C tumor-effector cell **CONJUGATE**

The parameters k_1, k_{-1}, k_2, k_3 are non-negative constants:

k_1 rate of **BINDING** of E to T
 k_{-1} rate of **DETACHMENT** of E from T without damaging cells
 k_2 rate at which E-T interactions program T-cells for lysis
 k_3 rate at which E-T interactions **INACTIVATE** E-cells

Tumor-Immune Equation Development

Notes for Tumor-Immune Interaction Schematic slide:

Answers:

- (1) effector
- (2) tumor
- (3) conjugates
- (4) binding
- (5) detachment
- (6) inactivate

The schematic shows that effector and tumor cells bind together, resulting in one of three outcomes:

1. The interaction leaves both effector cells and tumor cells undamaged.
2. The interaction leaves the effector cell undamaged, but the tumor cell dies shortly after detachment (this is what is known as "*programmed lysis*" of the tumor cell).
3. The interaction leaves the tumor cell undamaged, but the effector cell is no longer able to function (it becomes "*inactivated*"), and dies shortly after detachment.

10-1

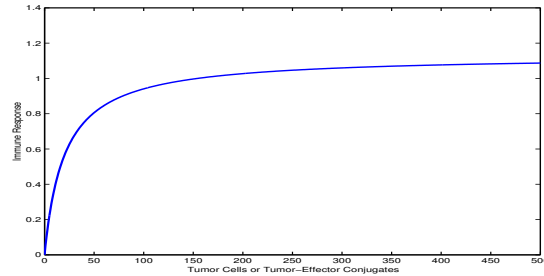
In following the model development of Kuznetsov, we do not consider an outcome in which the effector cell and the tumor cell kill each other simultaneously. Additionally, we have not seen this outcome addressed in the literature.

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Tumor-Immune Equation Development

Immune Response Curve

So the Response Function $F(C, T)$ is a function of the number of **CONJUGATE PAIRS and TUMOR CELLS**.



The production of tumor-specific cytotoxic T-cells is stimulated by the amount of tumor present, both alone and in conjugates:

$$F(C, T) = \frac{fC}{g + T}$$

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Tumor-Immune Equation Development

Notes for Immune Response Curve slide:

Answers:

(1) conjugate pairs.

Kuznetsov justifies the derivation of the form of this response function by referring to some of his earlier papers. These references can be found in [KMTP94]. We note, however, that the response function used here is generally accepted as a reasonable description of the stimulation of the cytotoxic immune response.

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Tumor-Immune Equation Development

A Quasi-Steady-State Approximation

Tumor-effector conjugates form and break apart at a rate which is much **FASTER** than the rate at which cells are produced or die.

On the time-scale of cell growth, then, we assume that the process of binding and disassociation is at an equilibrium, so that the rate of change of the conjugate pairs is **ZERO**.

In terms of the kinetic rate constants:

$$\frac{dC}{dt} = k_1 ET - (k_{-1} + k_2 + k_3)C$$

so that at equilibrium $C = kET$ where $k = \frac{k_1}{k_{-1} + k_2 + k_3}$.

We call this a *quasi*-steady state, because the other cell populations, E and T , are **not** assumed to be at equilibrium.

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Tumor-Immune Equation Development

Notes for Quasi-Steady State Approximation slide:

Answers:

(1) faster

(2) zero

(3) $C = \frac{k_1}{(k_{-1} + k_2 + k_3)} ET = kET$

Notes: This last equation could be interpreted as “the number of conjugates is a fixed fraction of the number of possible effector-tumor pairs”. Later we will assume that this fraction is negligible.

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Tumor-Immune Equation Development

Initial System of ODEs

Putting it all together: (letting $C = kET$)

$$\begin{aligned}dE/dt &= s + \frac{fkET}{g+T} - dE + (k(k_{-1} + k_2) - k_1)ET \\dT/dt &= aT(1 - bT_{\text{Tot}}) + (k(k_{-1} + k_3) - k_1)ET \\dE^*/dt &= kk_3ET - d_{E^*}E^* \\dT^*/dt &= kk_2ET - d_{T^*}T^*\end{aligned}$$

where T_{Tot} is the total number of *living* tumor cells, i.e. $T_{\text{Tot}} = T + C$.

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Tumor-Immune Equation Development

Notes for Initial System of ODEs slide

Answers:

(1) $T_{\text{Tot}} = T + C$.

Notes: In the development of the model, we argued that in the absence of an immune response $dT/dt = aT(1 - bT)$ since:

1. At small tumor populations growth is exponential
2. As the population increases, the growth rate decreases, and the population cannot grow beyond the carrying capacity, $1/b$.

The equation for dT/dt on this slide suggests that *only unbound tumor cells proliferate*. However, tumor cells in conjugate pairs, although not proliferating, still contribute to the crowding effect.

Tumor-Immune Equation Development

Simplifying Assumptions

Some further simplifying assumptions and remarks:

- The number of conjugate pairs is a *tiny* fraction of the total number of effector-tumor pairs.
(The parameter k is very small).
- Therefore, $T_{\text{Tot}} \approx \mathbf{T}$
- The equations for E^* and T^* do not affect the equations for E and T , i.e. the system is **UNCOUPLED**. If we know $E(t)$ and $T(t)$ we can readily solve for $E^*(t)$ and $T^*(t)$.

Thus, the system reduces to **2** differential equations with **8** parameters given by $s, d, a, b, g, p = fk, m = k(k_{-1} + k_2) - k_1, n = k(k_{-1} + k_3) - k_1$.

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Tumor-Immune Equation Development

Notes for Simplifying Assumptions slide:

Answers:

- (1) k
- (2) T
- (3) uncoupled. **Note:** Check that the students can “readily solve” these DEs. See details below.
- (4) two
- (5) eight (6): The eight parameters are s, d, a, b, g and the new parameters $p = fk, m = k(k_{-1} + k_2) - k_1, n = k(k_{-1} + k_3) - k_1$. These new parameters are also defined on slide entitled “Reduction to two ODEs” in the Qualitative Analysis module.

Details: We need to solve

$$dE^*/dt = kk_3E(t)T(t) - d_{E^*}E^* \quad (1)$$

where $E(t)$ and $T(t)$ are known functions. For simplicity, let $h(t) = kk_3E(t)T(t)$.

We can use an integrating factor to solve

$$\begin{aligned}dE^*/dt + d_{E^*}E^* &= h(t) \\ \Rightarrow E^*(t)e^{d_{E^*}t} - E^*(0) &= \int_0^t e^{d_{E^*}s}h(s)ds \\ \Rightarrow E^*(t) &= E^*(0)e^{-d_{E^*}t} + e^{-d_{E^*}t} \int_0^t e^{d_{E^*}s}h(s)ds\end{aligned}$$

The equation for T^* can be solved in the same way.

References

- [KMTP94] Vladimir A. Kuznetsov, Iliya A. Makalkin, Mark A. Taylor, and Alan S. Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2), 1994.
- [TH92] Ian F. Tannock and Richard P. Hill. *The Basic Science of Oncology*, chapter 14. McGraw-Hill, 1992.