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

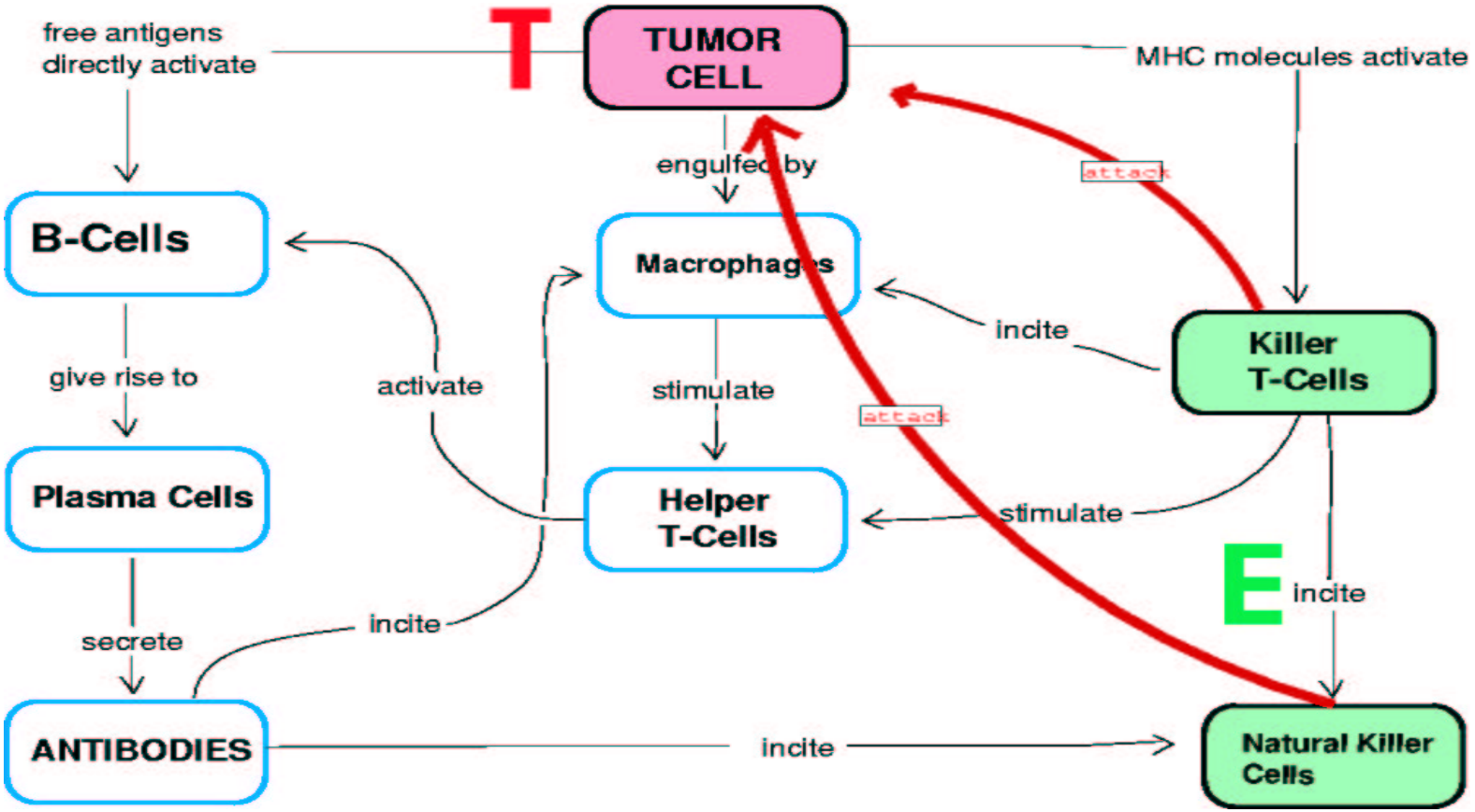
Our initial model will take the form of a **population model**, in which we describe the number of each type of cell in the system. Of the many cell types involved, we will consider only two types of cells.

Question: Which cell populations should we look at?

Answer: _____(1) cells and _____(2) cells influence the visible progress of the cancer more than other cells, so we'll begin our model by looking at those cell populations.

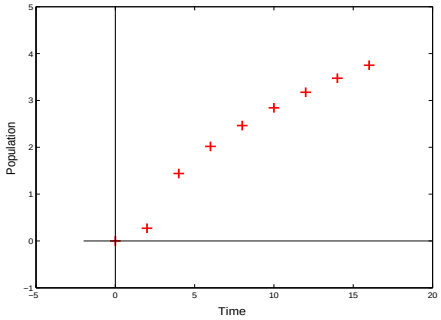
Tumor-Immune Equation Development

Flow Chart

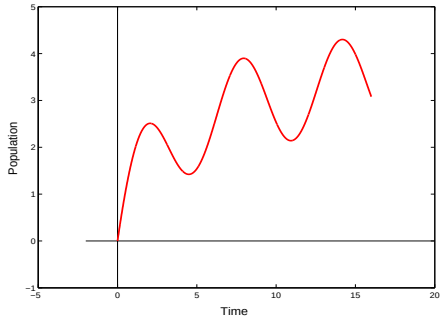


Tumor-Immune Equation Development

Types of Models



(a) Discrete Time



(b) Continuous Time

- Discrete Time – Populations change at equally spaced points in time (Figure (a))
- Continous Time – Populations change continously 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

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 $\Rightarrow$ _____(1).
- Inter-cellular reactions are described by (empirically determined) rates $\Rightarrow$ _____(2).

This gives

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

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.

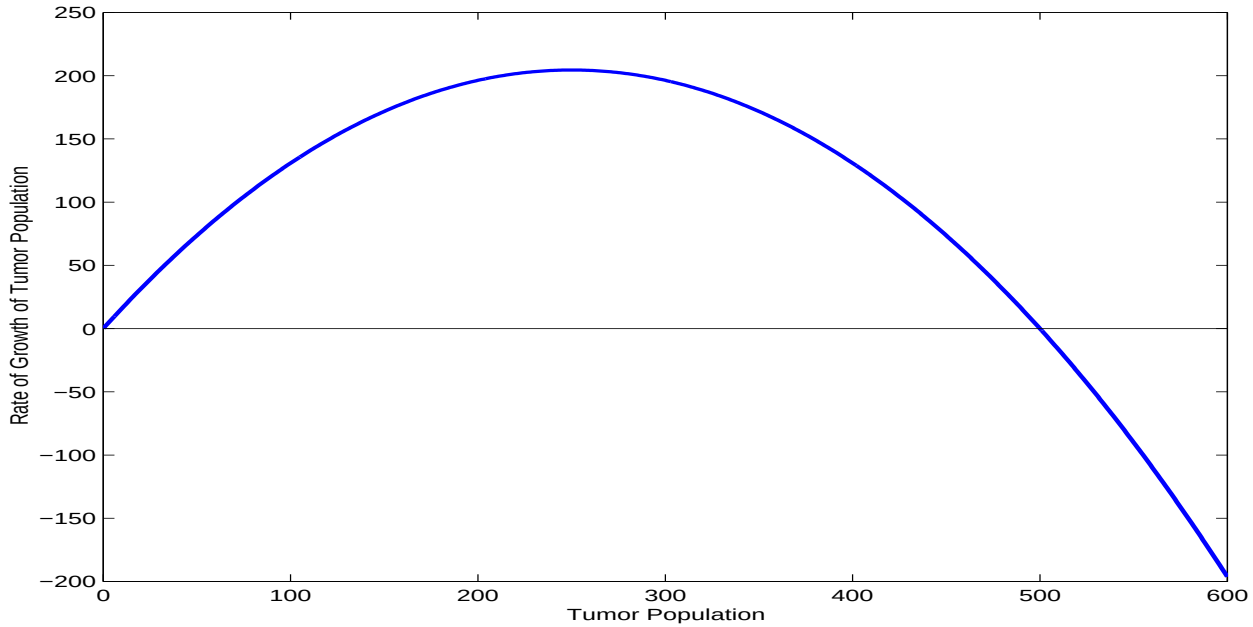
Questions to ask:

- How do each of the cell populations grow? For example, do the tumor cells divide at a constant rate? This would imply _____ (1) growth, described by the differential equation:
  $\frac{dT}{dt} =$ _____ (2)
- How do the cell populations affect each other?

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: $\frac{dT}{dt} =$ _____ (1)

Tumor-Immune Equation Development

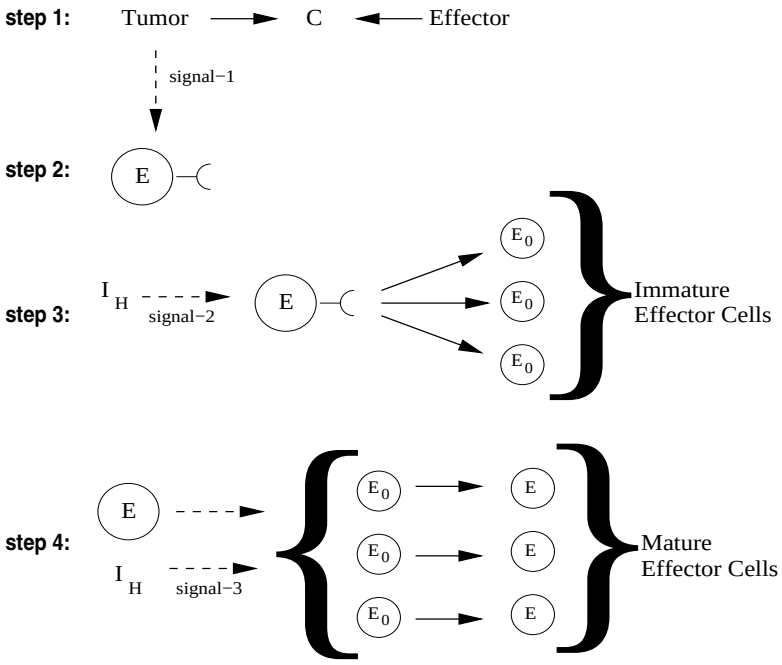
Production of Immune Cells

- Cytotoxic effector cells, i.e. those immune cells which are capable of killing tumor cells can be either _____ (1) cells or _____ (2)
- 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:
  $\frac{dE}{dt} =$ _____ (3)
- What function might represent how the production of *tumor-specific* effector cells responds to the presence of the tumor? This function must incorporate the recognition of antigen by the immune system.

Tumor-Immune Equation Development

Recognition of Tumor by Immune Cells

Immune cells and tumor cells form _____(1). When this happens, effector cell production can be stimulated.



step 1: Tumor and effector cells (E−cells) form _____(2)

step 2: E−cells develop a _____(3)

step 3: E−cells receive lymphocyte _____(4) (e.g. IL−2 from helper T−cells) and proliferate.

step 4: E−cells receive lymphocyte _____(5) (e.g. IL−gamma from E−cells and from helper T−cells) and mature to a functioning state.

Tumor-Immune Equation Development

Tumor-Immune Interaction Schematic

The Formation of Effector-Tumor Conjugates

$$E + T \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \begin{array}{l} \overset{k_2}{\nearrow} \; E + T^* \\ \underset{k_3}{\searrow} \; E^* + T \end{array}$$

E, E^* ..... active, inactive _____(1) cells

T, T^* ..... active, lethally hit _____(2) cells

C ..... tumor-effector cell _____(3)

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

k_1 ..... rate of _____(4) of E to T

k_{-1} ..... rate of _____(5) of E from T without damaging cells

k_2 ..... rate at which E-T interactions program T-cells for lysis

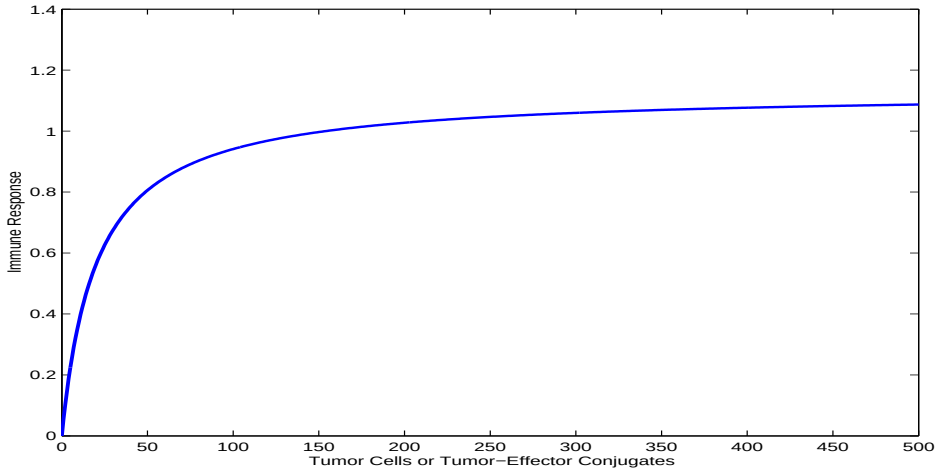
k_3 ..... rate at which E-T interactions _____(6) E-cells

Tumor-Immune Equation Development

Immune Response Curve

So the Response Function $F(C,T)$ is a function of the number of

$$\text{(1)}$$



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

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

Tumor-Immune Equation Development

A *Quasi-Steady-State* Approximation

Tumor-effector conjugates form and break apart at a rate which is much _____ (1) 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 _____ (2).

In terms of the kinetic rate constants:

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

so that at equilibrium $C =$ _____ (3)

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

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. $T_{\text{Tot}} =$ _____ (1)

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 _____ (1) is very small).

- Therefore, $T_{\text{Tot}} \approx$ _____ (2)

- The equations for E^* and T^* do not affect the equations for E and T, i.e. the system is _____ (3). If we know $E(t)$ and $T(t)$ we can readily solve for $E^*(t)$ and $T^*(t)$.

Thus, the system reduces to _____ (4) differential equations with _____ (5) parameters.