Mathematical Modeling of the Effects of Mutation on the Immune System

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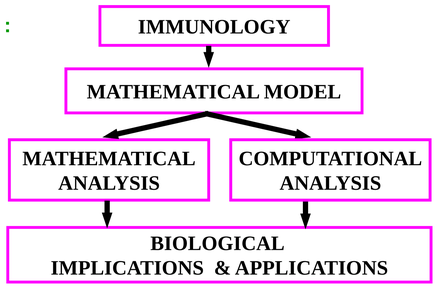
1. Introduction

Goal : develop a mathematical model to study the interactions b/w immune system, a target population (cancer cells or virus infection) & a mutative target

Process :



2. Immune System Model Hypotheses

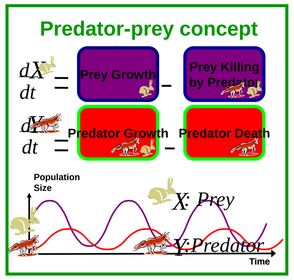
Populations:

- **Target cells (T):** infected (or tumor) cells surrounded by antigens
- **Effector cells (E):** immune system generates cells for fighting cells with specific antigen.
- **Mutant cells (M)** : infected cells that have undergone genetic changes (mutations)

Assumptions:

- cell population modeling
- E cells - saturated growth, T & M cells -exponential growth
- non specific response of immune system
- different antigenity for target & mutant
  - different stimulation of immune system by target & mutant
  - different immune response on target & mutant
- predator-prey type interactions b/w target-mutant & immune system

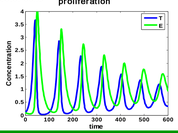
Predator-prey concept



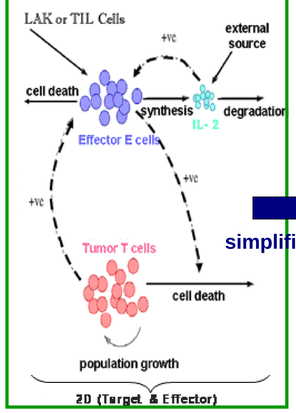
Target-effector cell interaction

$$\frac{dT}{dt} = \underbrace{r_T T}_{\text{proliferation}} - \underbrace{k_T ET}_{\text{immune killing}} \quad (\text{target cells})$$

$$\frac{dE}{dt} = \underbrace{\frac{\beta E}{\sigma_E + E}}_{\text{proliferation}} - \underbrace{dE}_{\text{death}} + \underbrace{\alpha TE}_{\text{stimulation by target T}} \quad (\text{effector cells})$$

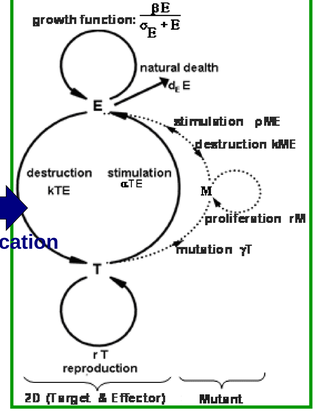


Biological Phenomena



simplification

Modeling Hypotheses



3. Mathematical Model

3D ODE Model for target-effector-mutant interactions

$$\frac{dT}{dt} = \underbrace{r_T T}_{\text{proliferation}} - \underbrace{k_T ET}_{\text{immune killing}} \quad (\text{target cells})$$

$$\frac{dM}{dt} = \underbrace{r_M M}_{\text{proliferation}} + \underbrace{\gamma T}_{\text{mutation}} - \underbrace{k_M EM}_{\text{immune killing}} \quad (\text{mutant cells})$$

$$\frac{dE}{dt} = \underbrace{\frac{\beta E}{\sigma_E + E}}_{\text{proliferation}} - \underbrace{dE}_{\text{death}} + \underbrace{\rho ME}_{\text{stimulation by mutant M}} + \underbrace{\alpha TE}_{\text{stimulation by target T}} \quad (\text{effector cells})$$

r_T ,r_M = reproduction rate for target T & mutant M respectively
k_T = contact rate between target T & effector E
k_M = contact rate between mutant M & effector E
γ = mutation rate
β, d = self generation & death rate of effector E respectively
α = stimulation of effector E by target / tumor T
ρ = stimulation of effector E by mutant M
σ = critical threshold for cooperative & autocatalytic process

4. Mathematical Analysis

(I) Equilibria

(i) $(T_1,M_1,E_1) = (\mathbf{0, 0, 0})$;

(ii) $(T_2,M_2,E_2) = \left(0, 0, \frac{\beta - d\sigma_E}{d}\right)$ (target- & mutant-free equilibrium)

(iii) $(T_3,M_3,E_3) = \left(0, \frac{(d\sigma_E - \beta)k_M + dr_M}{\rho(\sigma_E k_M + r_M)}, \frac{r_M}{k_M}\right)$ (target-free, mutant endemic)

(iv) $(T_4,M_4,E_4) = \left(\frac{(k_M E - r_M)M}{\gamma}, \frac{d - \frac{\beta}{\sigma_E + E}}{\rho + \frac{\alpha}{\gamma}\left(k_M \frac{r_T}{k_T} - r_M\right)}, \frac{r_T}{k_T}\right)$ (target & mutant endemic)

(II) Local Stability Analysis of Equilibria

Method:

- linearization of system (Jacobian Matrix)
- study of eigenvalues λ of the Jacobian J (e.g Routh Hurwitz Criteria)

Criteria for Locally Asymptotically Stability:

- If Re(λ) < 0; equilibrium is LAS
- If Re(λ) > 0; equilibrium is unstable

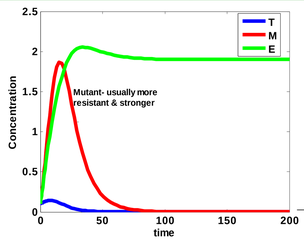
$$J = \begin{bmatrix} r_T - k_T E & 0 & -k_T T \\ \gamma & r_M - k_T E & -k_M M \\ \alpha E & \rho E & \frac{\beta}{\sigma_E + E} - \frac{\beta E}{(\sigma_E + E)^2} - d + \rho M + \alpha T \end{bmatrix}$$

(III) Condition of Existence & Stability of Equilibria

Equilibrium	Condition of Existence	Condition of Stability
(T_1,M_1,E_1)	N.A.	Unstable
(T_2,M_2,E_2)	$\frac{\beta - d\sigma_E}{d} > 0$	$\frac{\beta - d\sigma_E}{d} > \max\left(\frac{r_T}{K_T}, \frac{r_M}{K_M}\right)$
(T_3,M_3,E_3)	$\frac{\beta - d\sigma_E}{d} < \frac{r_M}{k_M}$	$\frac{r_M}{k_M} > \frac{r_T}{k_T}$
(T_4,M_4,E_4)	$\frac{r_T}{k_T} > \max\left(\frac{r_M}{k_M}, \frac{\beta - d\sigma_E}{d}\right)$	$k_M\sigma_E + r_M \geq k_T\sigma_E + r_T$

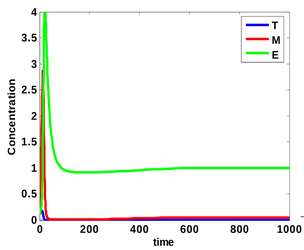
5. Computational Analysis

(I) Verification of Equilibrium Stability Conditions



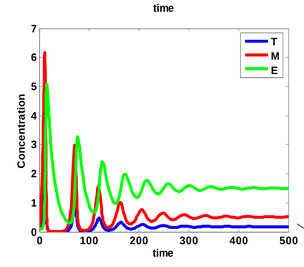
Parameter	Value
$\frac{\beta}{d} - \sigma_E$	1.9 (>0)
r_T	0.1
k_T	0.1
r_M	0.1
k_M	0.1
$\frac{\beta - d\sigma_E}{d} - \max\left(\frac{r_T}{k_T}, \frac{r_M}{k_M}\right)$	0.9 (> 0)

Target-free (T = 0)
Mutant-free (M = 0)



Parameters	Value
$\frac{\beta}{d} - \sigma_E$	0.9
r_T	0.1
k_T	0.2
r_M	0.1
k_M	0.1
$\frac{\beta - d\sigma_E}{d} - \frac{r_M}{k_M}$	-0.1 (<0)
$\frac{r_M}{k_M} - \frac{r_T}{K_T}$	0.5 (>0)

Target-free (T = 0)
Mutant-endemic (M ≠ 0)



Parameters	Value
$\frac{\beta}{d} - \sigma_E$	-0.1
r_T	0.3
k_T	0.2
r_M	0.1
k_M	0.3
$\left(\frac{\beta}{d} - \sigma_E\right) - \frac{r_T}{k_T}$	-1.6 (<0)
$\frac{r_M}{k_M} - \frac{r_T}{k_T}$	-1.167 (<0)
$(k_M\sigma_E + r_M) - (k_T\sigma_E + r_T)$	0.01 (>0)

Target-endemic (T ≠ 0)
Mutant-endemic (M ≠ 0)

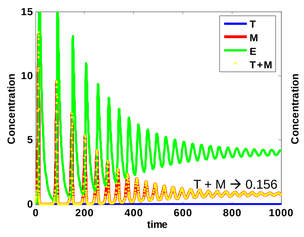
(II) Effect of Difference b/w Target & Mutant Fitnesses

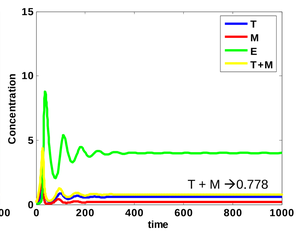
Fitness factor of immune E cells : $\frac{\beta - d\sigma_E}{d}$

Fitness factor of target T cells : $\frac{r_T}{k_T}$

Fitness factor of mutant M cells: $\frac{r_M}{k_M}$

	$\frac{r_T}{k_T}$	$\frac{r_M}{k_M}$	$\frac{\beta}{d} - \sigma_E$	$\frac{\beta - d\sigma_E}{d} - \frac{r_M}{k_M}$	$\frac{r_M}{k_M} - \frac{r_T}{K_T}$	$(k_M\sigma_E + r_M) - (k_T\sigma_E + r_T)$
$\frac{r_M}{k_M} > \frac{r_T}{k_T}$	1	4	-3	-7 (< 0) (met existence cond. of (T_3,M_3,E_3))	3 (> 0) (met stability cond. of (T_3,M_3,E_3))	0.3
$\frac{r_M}{k_M} < \frac{r_T}{k_T}$	4	1	-3	-4 (< 0) (met existence cond. of (T_4,M_4,E_4))	-3 (< 0) (met stability cond. of (T_4,M_4,E_4))	0.375 (met stability cond. of (T_4,M_4,E_4))





Case1: mutant 'fitter' than target
- mutant pop. higher than target
- target pop. → zero eventually (i.e. target-free eventually)

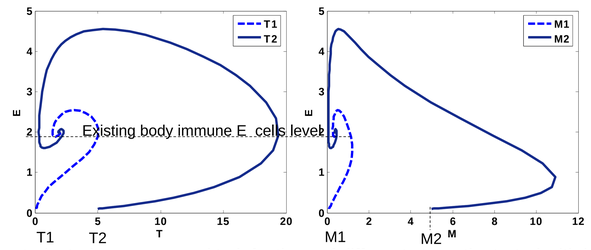
Case2: target 'fitter' than mutant
- target pop. higher than mutant
- approaches equilibrium 4 (i.e. target & mutant both exist)

6. Applications & Biological Implications

(I) Treatment and Strength of Infection

To study the effect of treatment and/or different strengths of infection

- Treatment yields a set of parameter values for T, M & E populations
  ➔Model can be used to predict the response of the populations to the treatment
- Different strength/stages of infection yields different initial conditions for T & M
  ➔Model can be used to predict the response of the populations

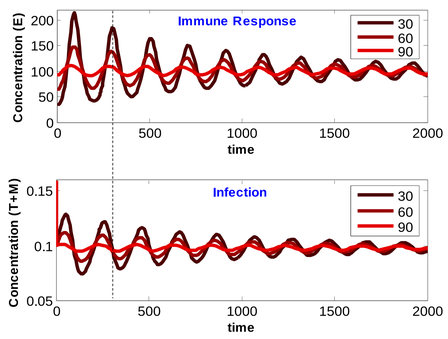


- Two trajectories correspond to infections of different strength started with initial conditions (T,E)= (T1, 0.1) and (T2,0.1) . Strength of T2 >T1.
- As T increases, E increases correspondingly to combat infection.
- Complete extermination of T & M is impossible. Targets, mutants & effector cells coexist.

Example of diseases with mutation: HIV

(II) Immune Memory of Effector Cell

To study the effect of immunological memory (acquired immune or vaccination)

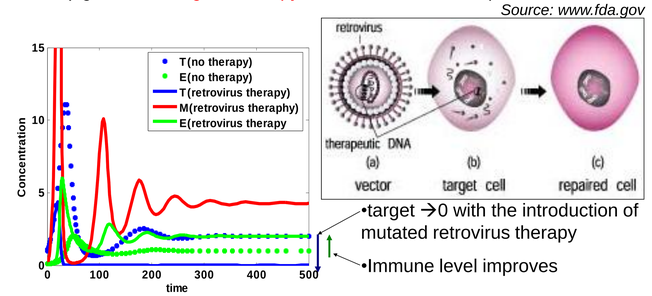


- Vaccination induces a higher initial immune response
- Immune response has less variations when fighting infection
- Correspondingly, fluctuation of infection is better controlled.

(III) Mutative retrovirus therapy for cancer treatment

To study the effect of introducing an engineered mutant cell (retrovirus) for treatment (eg. Retrovirus gene therapy to combat cancer cells)

Source: www.fda.gov



- target →0 with the introduction of mutated retrovirus therapy
- Immune level improves

Future Work

- Validation of model with clinical data