Dynamics of the Kirschner-Panetta Model

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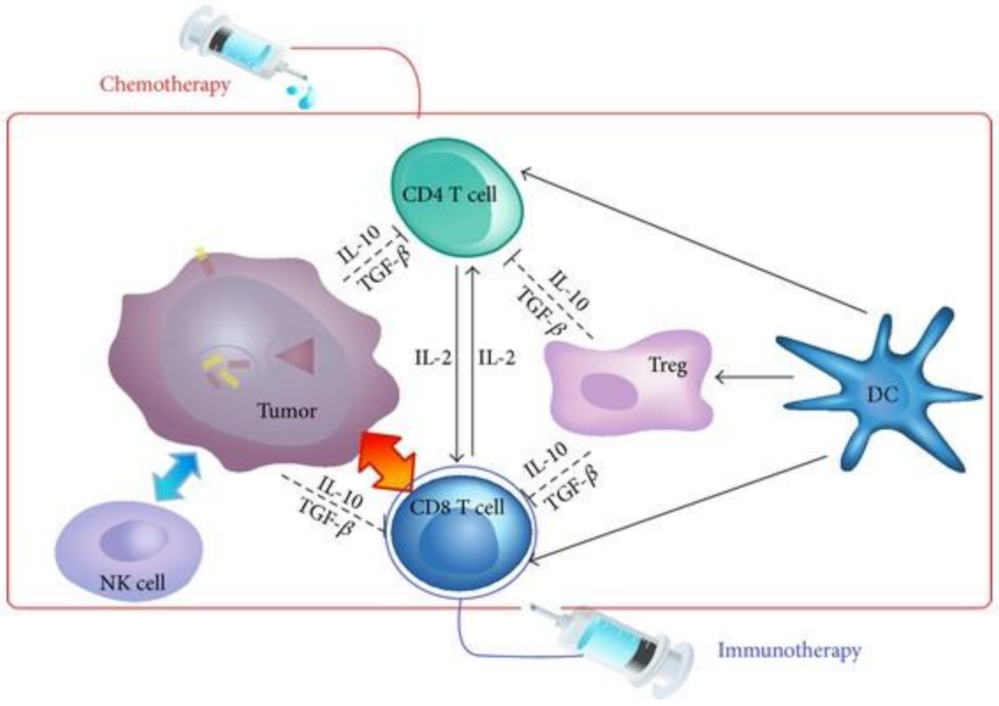
About the model

- Created by Denise Kirschner and John Carl Panetta.
- Published in Journal of Mathematical Biology (1998).
- Wanted a model for short and long-term tumor behavior.
- Rich dynamics for exploring tumor oscillation, relapse, and elimination.



Kim, Kwang Su, Cho, Giphil, Jung, Il Hyo, Optimal Treatment Strategy for a Tumor Model under Immune Suppression, *Computational and Mathematical Methods in Medicine*, 2014, 206287, 13 pages, 2014. https://doi.org/10.1155/2014/206287

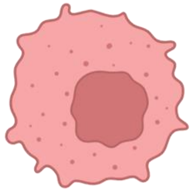
Defining the model

$$\frac{dT}{dt} = r_2(T)T - \frac{\alpha E T}{g_2 + T}$$

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 E I_{L2}}{g_1 + I_{L2}} + s_1$$

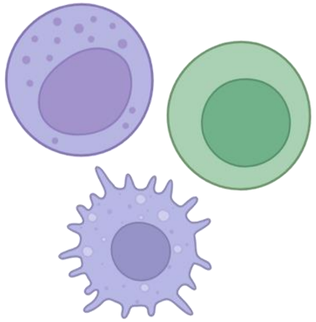
$$\frac{dI_{L2}}{dt} = \frac{p_2 E T}{g_3 + T} - \mu_3 I_{L2} + s_2$$

Tumor Cells

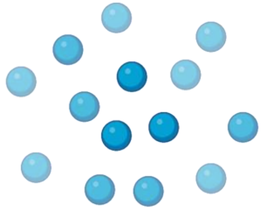


Effector Cells

NK Cells,
T Cells,
Macrophages



Interleukin-2
(IL-2)



Non-dimensionalization

- The model is non-dimensionalized for computation.
- This handles large changes more smoothly.

$$\frac{dy}{d\tau} = r_2(1 - by)y - \frac{\alpha xy}{g_2 + y}$$

$$\frac{dx}{d\tau} = cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1$$

$$\frac{dz}{d\tau} = \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2$$

Constants in the model

Parameter	Value	Unit	Description
c	$0 \leq c \leq 0.05$	day^{-1}	The antigenicity of tumour; larger values of *c* represent well recognized antigens
μ_2	3.00×10^{-2}	day^{-1}	Multiplicative inverse of the natural lifespan for effector cells
p_1	1.245×10^{-1}	day^{-1}	Proliferation rate of effector cells estimated by using experimental data (see Kuznetsov et al. 1994)
g_1	2.00×10^{7}	$\mathrm{IU.\,L}^{-1}$	Threshold for proliferation of effector cells stimulated by IL-2
s_1		$\mathrm{cell.\,day}^{-1}$	External source of effector cells
r_2	1.80×10^{-1}	day^{-1}	The logistic growth rate of tumour cells in the absence of an immune response
b	1.00×10^{-9}	cell^{-1}	Multiplicative inverse of the tumour's carrying capacity
a	1.00	day^{-1}	Immune system's strength to eliminate cancer cells
g_2	1.00×10^{5}	cell	Threshold for cancer removal
p_2	5.00	$\mathrm{IU.\,L}^{-1}.\,\mathrm{cell}^{-1}.\,\mathrm{day}^{-1}$	production rate of IL-2
g_3	1.00×10^{3}	cell	Threshold for production of IL-2 due to the interaction between cancer cells and effector cells
μ_3	1.00×10^{1}	day^{-1}	Multiplicative inverse of the lifespan for IL-2
s_2		$\mathrm{IU.\,L}^{-1}.\,\mathrm{day}^{-1}$	External source of IL-2

Hamiltonian of the model

Functional:

$$F(s_1, s_2) = \int_0^{t_f} Ax(t) - By(t) - C_1 s_1(t) - C_2 s_2(t) + Dx(t)z(t) - \gamma z(t)^2 dt$$

Lagrangian:

$$\mathcal{L} = -Ax(t) + By(t) + C_1 s_1(t) + C_2 s_2(t) - Dx(t)z(t) + \gamma z(t)^2$$

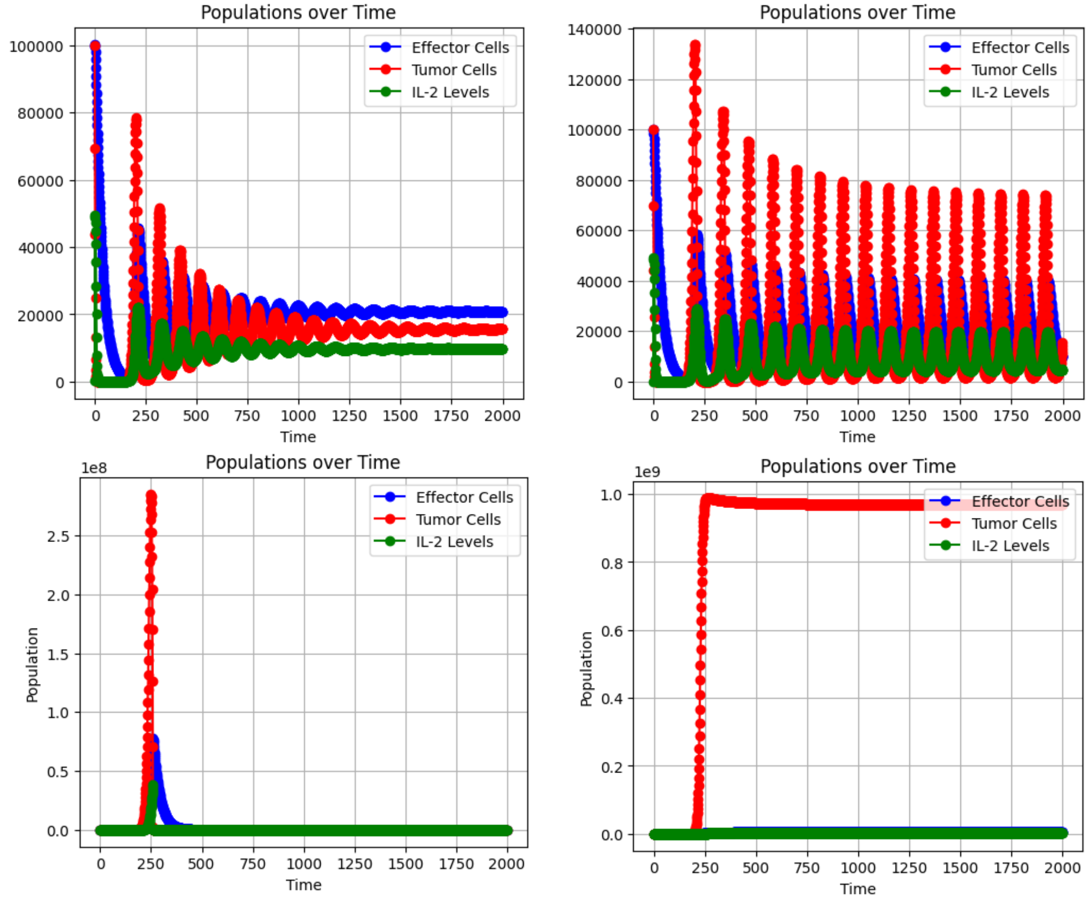
Hamiltonian:

$$\mathcal{H}(x, y, z, \lambda_1, \lambda_2, \lambda_3) = -\mathcal{L} + \lambda_1 \frac{dx}{dt} + \lambda_2 \frac{dy}{dt} + \lambda_3 \frac{dz}{dt}$$

Model behavior without treatment

- Effector cell dose, $s_1 = 0$
- IL-2 dose, $s_2 = 0$

- Changing antigenicity (c) can lead to oscillatory population dynamics.

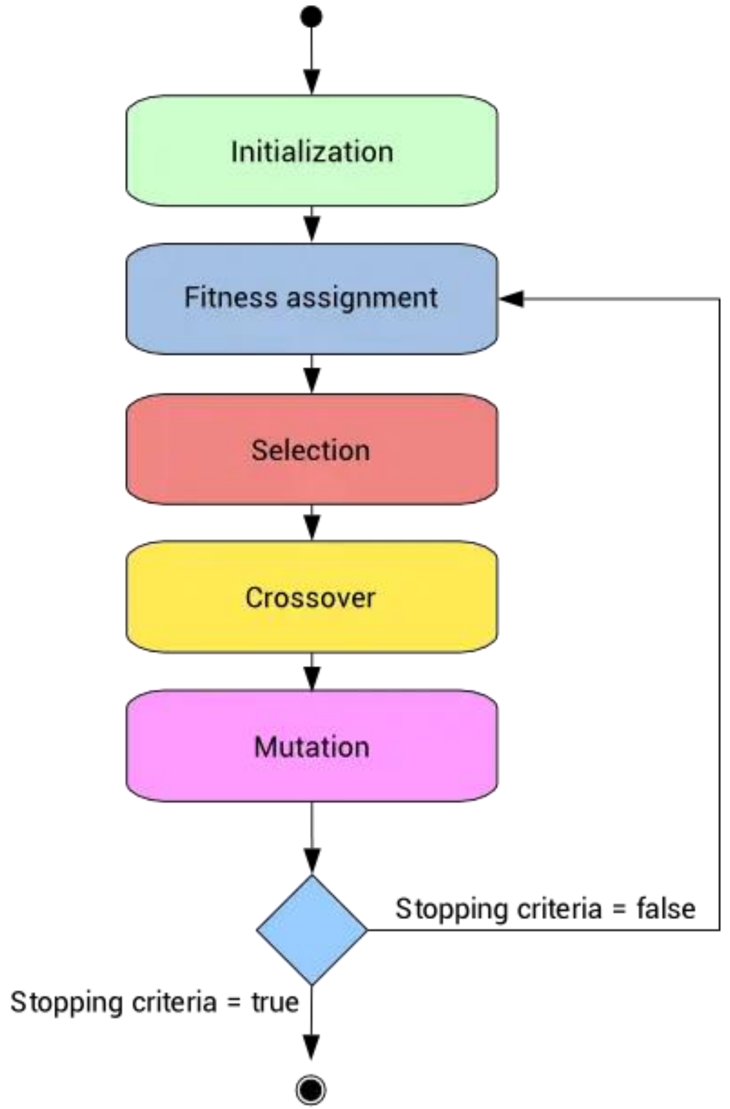


c = 0.04, 0.0297, 8e-3, 8e-5

Genetic Algorithm (GA)

- Shown to help control chaotic systems
- Fitness function defines how ‘good’ the GA’s solution is.

- GA defines s_1 and s_2 doses.



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GA: Fitness function

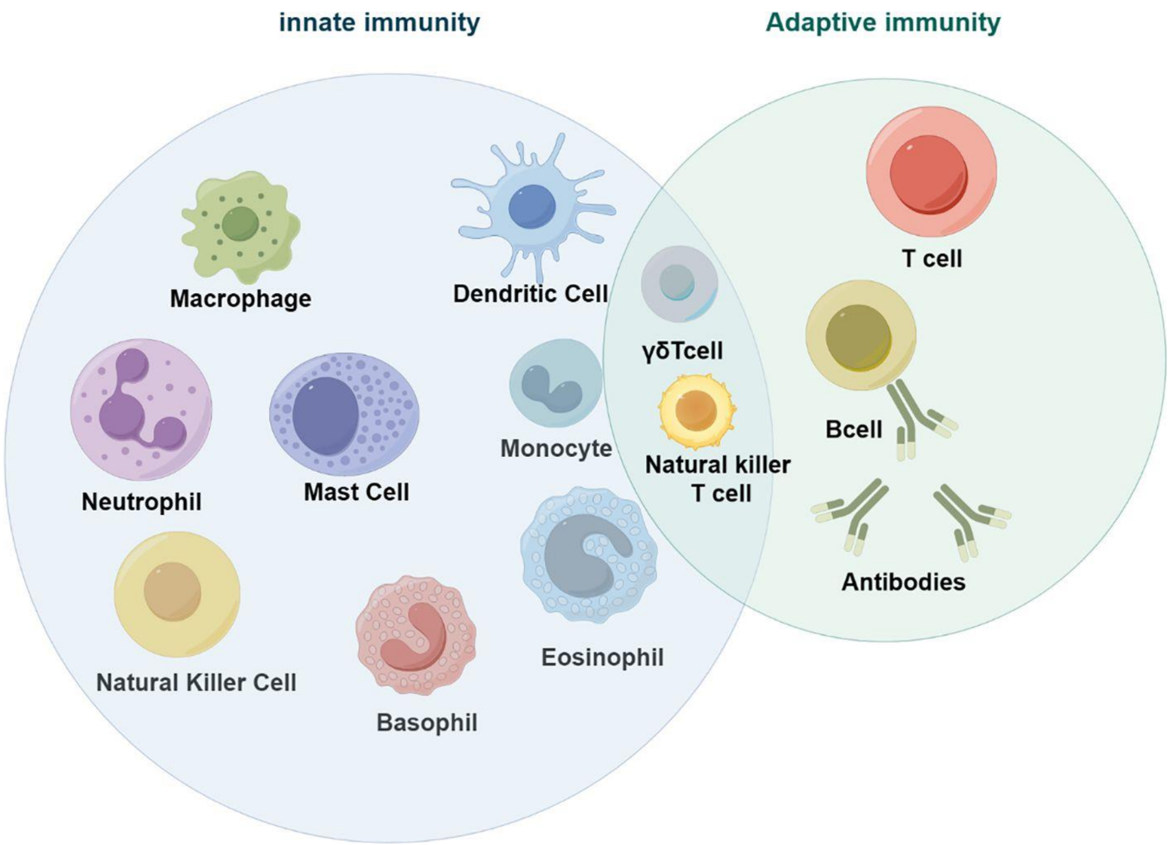
- Can tune for biological relevance.

- Similar but not the same as the integrand of the functional.

```python
def fitness_func(ga_instance, solution, solution_idx):
    """
    Fitness function maximizing E and minimizing T.
    """
    t = ga_instance.environment['t']
    x = ga_instance.environment['x']
    y = ga_instance.environment['y']
    z = ga_instance.environment['z']

    # Extract genes from solution
    genes1 = solution[0:4]
    genes2 = solution[4:8]

    # Calculate s_1 and s_2 based on genes and current state
    s_1 = genes1[0]*x + genes1[1]*y + genes1[2]*z + genes1[3]
    s_2 = genes2[0]*x + genes2[1]*y + genes2[2]*z + genes2[3]

    # Restrict negative input
    s_1 = max(0, s_1)
    s_2 = max(0, s_2)

    E_input = s_1  # Effector cell input from GA
    IL_input = s_2  # IL-2 input from GA

    t_step = 1  # time step for prediction

    # Calculate derivatives using non-dimensional KP model equations
    x_pred = x + dx_dt(t=t,x=x, y=y, z=z,
                        c=0.02, mu_2=0.03, p_1=0.1245, g_1=2e4, s_1=E_input) * t_step

    y_pred = y + dy_dt(t=t, y=y, x=x, z=z,
                       r_2=0.18, b=1e-5, alpha=0.002, g_2=1e5) * t_step

    z_pred = z + dz_dt(t=t, z=z, x=x, y=y,
                       p_2=5e-7, g_3=1e4, mu_3=10, s_2=IL_input) * t_step


    # Define fitness as maximizing dE_dt and minimizing dT_dt.
    # Penalize over dose of IL-2.

    a1, a2 = 0.1, 0.1 # weights for immunotherapy components
    b1, b2, b3, b4 = 0.1, 0.1, 0.1, 0.1  # weights for toxicity components

    immunotherapy = a1*(x_pred) - a2*(y_pred)  # Reward high effector cells and low tumor cells
    toxicity = b1*s_2 + b2*s_1 + b3*(x_pred*s_2) + b4*(z_pred)**2  # Penalty for IL-2 overdose

    c1, c2 = 1.0, 3.0

    fitness = c1*immunotherapy - c2*toxicity # final fitness
```

Immunology and cancer

- Immune cell exhaustion
- Autoimmune response
- Cytokine storm
- Mutational burden
- Immunotherapy



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