Modeling Cyclophosphamide's Effect on Leukocytes

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Math Modeling in Biology 2014 Summer REU

July 23rd, 2014

Agenda

- Motivation For Project
- Background Biology and Chemistry
- Model Construction
- Differential Equations
- Results
- Further Study

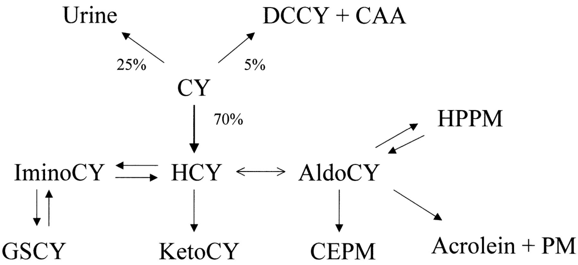
Background on Cyclophosphamide

- Pro-drug typically used in immune suppression and chemotherapy
- Can assist in oncolic virotherapy, the use of engineered viruses to combat cancerous cells
- Used to suppress the immune system enough so that the viruses can infect and kill the cancerous cells in the body
- Necessary to control the timing and amount of doses due to its toxicity

Pharmacodynamics of Cyclophosphamide (CY)

- Inactive until it reaches the liver and is metabolized to hydroxycyclophosphamide(HCY)
- About 70% of CY is metabolized to HCY, the rest is primarily excreted unchanged in urine
- HCY lives in equilibrium with its tautomer aldophosphamide(AP)
- AP is what kills cells at tissue level
- HCY is primarily eliminated through AP

Pharmacodynamics of Cyclophosphamide

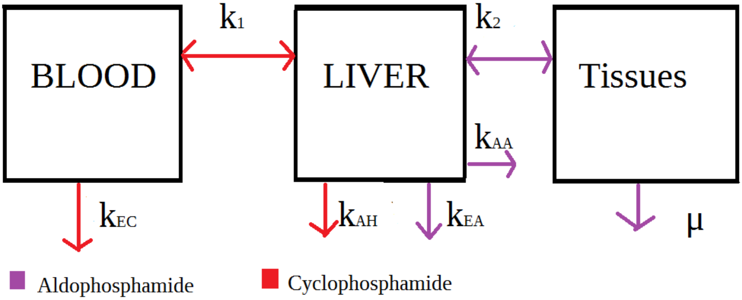


Credit: Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoieitic stem cell transplantation

Model Building for CY

- Focused on CY concentrations in the liver and blood and the AP concentration in the liver and tissue
- Didn't include HCY in the model, AP is what interacts chemically in tissues and degrades in the liver
- Assumed that a third of the amount of HCY being activated in the liver directly converted to AP
- Blood is simply a means of transport between the liver and tissues

Pharmacodynamics of Cyclophosphamide



Differential Equations For CY Pharmacodynamics

$$\frac{dC_B}{dt} = k_1(C_L - C_B) - C_B k_{EC} + D(t) \tag{1}$$

$$\frac{dC_L}{dt} = -k_1(C_L - C_B) - C_L k_{AH} \tag{2}$$

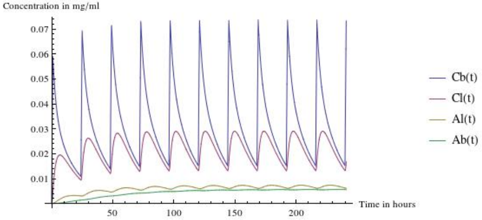
$$\frac{dA_L}{dt} = k_{AA}C_L - k_2(A_L - A_T) - k_{EA}A_L \tag{3}$$

$$\frac{dA_T}{dt} = -k_2(A_T - A_L) - \mu A_T \tag{4}$$

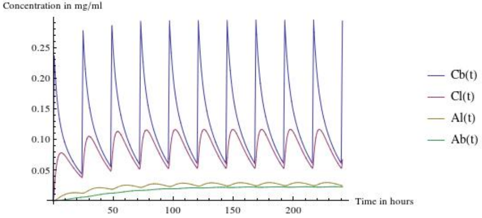
D(t) is the controlled dose given every 24 hours, denoted as a piecewise function

Some Results

Dose of 5 mg/kg



Dose of 20 mg/kg

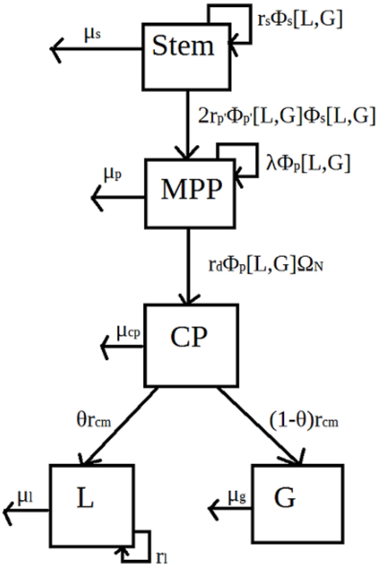


Population Dynamics of Leukocytes

- Stem cells (S), multipotent progenitor cells(MPP), common progenitor cells(CM), lymphocytes (L) and granulocytes(G)
- S $\rightarrow$ MPP $\rightarrow$ CM $\rightarrow$ L&G
- S and MPP also regenerate depending on L and G cell concentration
- Together L and G make up all the Leukocytes

Leukocyte Model

- ϕ -feedback functions (L and G)
- μ - death rates
- λ, r_d, $r_{p'}$, r_{cm} - rates
- θ - fixed proportion L is made from CM



Leukocyte Model Differential Equations

$$\frac{dS}{dt} = S\ln(\frac{K}{S})(r_s - r_{p'}\phi_{p'}[L,G])\phi_s[L,G] - \mu_s S \quad (5)$$

$$\frac{dMPP}{dt} = S\ln(\frac{K}{S})(r_s + 2r_{p'}\phi_{p'}[L,G])\phi_s[L,G] +$$

$$MPP((\lambda - r_d)\phi_p[L,G] - \mu_p - \alpha_1 A_t(t)) \quad (6)$$

$$\frac{dCM}{dt} = MPPr_d\phi_p[L,G]\Omega_N - CM(\mu_{cm} + r_{cm} + \alpha_2 A_t(t)) \quad (7)$$

$$\frac{dL}{dt} = CMr_{cm}\theta\frac{10}{3003} + L(r_l - \mu_l - \mu_{l*}I_{vt>vth} - \alpha_3 A_t(t)) \quad (8)$$

$$\frac{dG}{dt} = CMr_{cm}(1-\theta)\frac{10}{3003} + G\mu_g \quad (9)$$

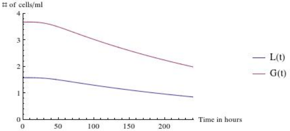
Some Issues With Interpreting this Model

- Could not find the α_3 value
- My model doesnt work with only α_2 & α_1
- Because of the feedback functions, effects of the doses are extremely complicated

10 days 5 mg/kg a day

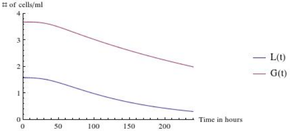
$\alpha = 0$

L and G decreases 46%



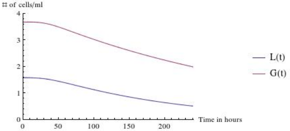
$\alpha = 1$

L decreases 81%



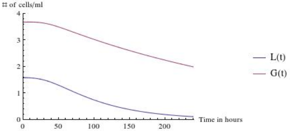
$\alpha = 0.5$

L decreases 68%



$\alpha = 2$

L decreases 93%



Finding Optimal Doses

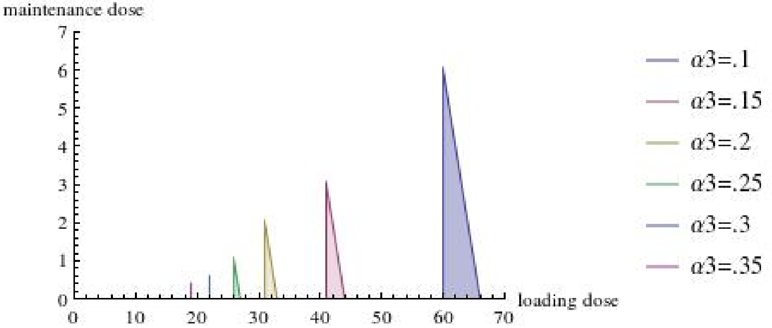
My solution of differential equations as a function of a loading dose, maintenance dose, and time in Mathematica

- A loading dose is a high dose given to achieve a drastic effect quickly
  - First three days
- A maintenance dose is a lower dose to maintain that effect
  - Following seven days

Examples of Optimal Loading and Maintenance Doses depending on α_3

α_3 value	LD	MD	ΔL 3 days	ΔL 10 days
0	200	10	17.3%	50.2%
.1	60	1	30.3%	73.6%
.2	30	1.5	29.6%	73.8%
.25	25	1.5	29.9%	74.6%
.3	22	0.5	30.4%	74.9%
.35	19	0	30.3%	74.5%

The end product



Future Work

- Taking the viral response into account
- Finding a more definitive α_3 parameter or maybe α_1 & α_2 are functions rather than rates
- Fit data to my model
- Using elements of Control theory to find optimal dosage

Thanks for listening!