Stability of Non-autonomous Co-infection Models

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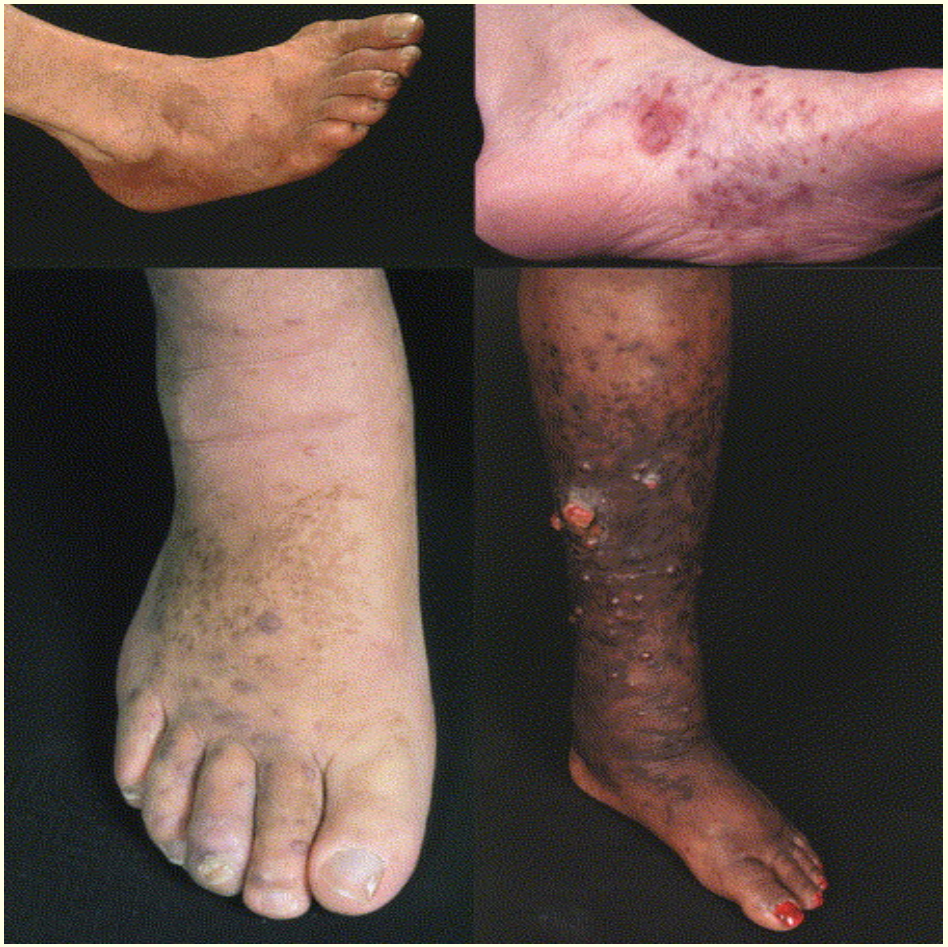
Main HIV Co-infections

1. Main HIV co-infections are ranked as follows:
   (a). HIV/TB
   (b). HIV/Malaria
   (c). HIV/Pneumonia
   (d). HIV/KS
2. Even though up to 20% of the individuals co-infected with HIV die of Kaposi's sarcoma, the HIV/KS has received little attention.
3. In sub-Sahara Africa, the number of deaths due to HIV/KS is on the increase.

Types of Kaposi's Sarcoma

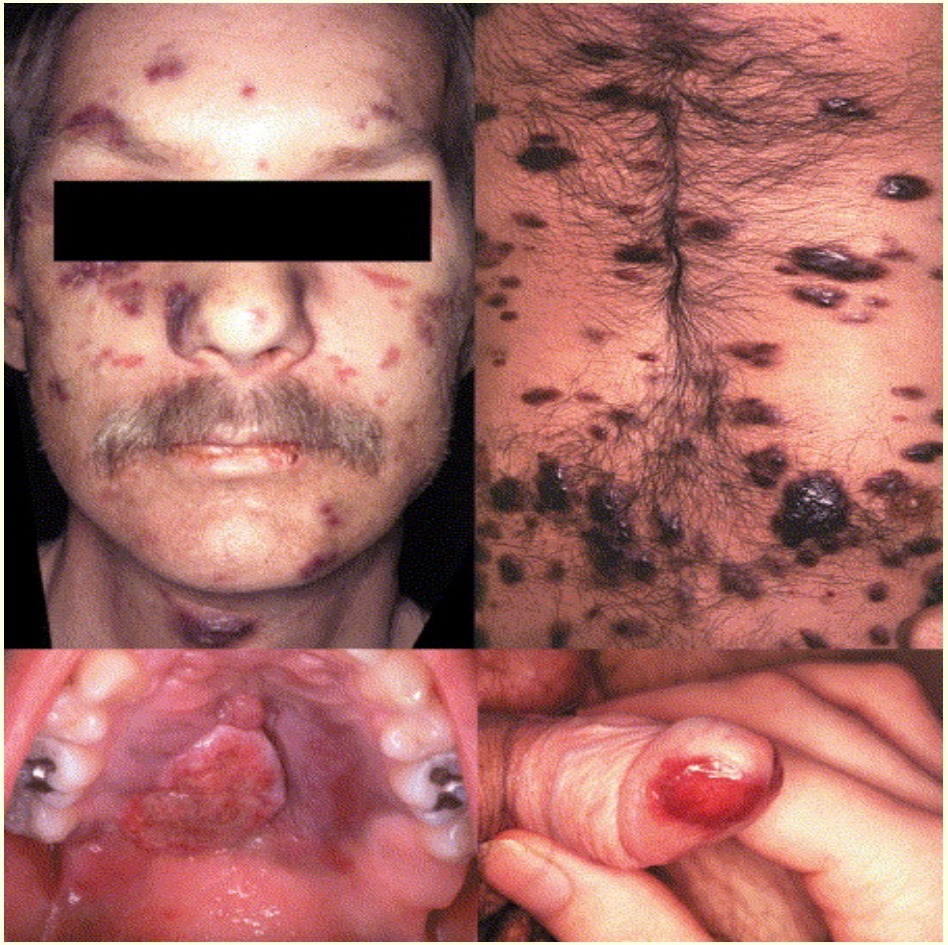
1. Endemic African KS
2. Classical Kaposi's sarcoma
   - It's primarily a skin disease affecting elderly people of Mediterranean, East European, or Jewish heritage.
3. Immunosuppressive KS
   - Most frequently found in organ-transplant recipients.
   - It accounts for about 1.0% of all cancers in the world.
4. Epidemic or AIDS-associated KS
   - Most common AIDS-related malignancy.

Clinical Illustrations of Kaposi's Sarcoma



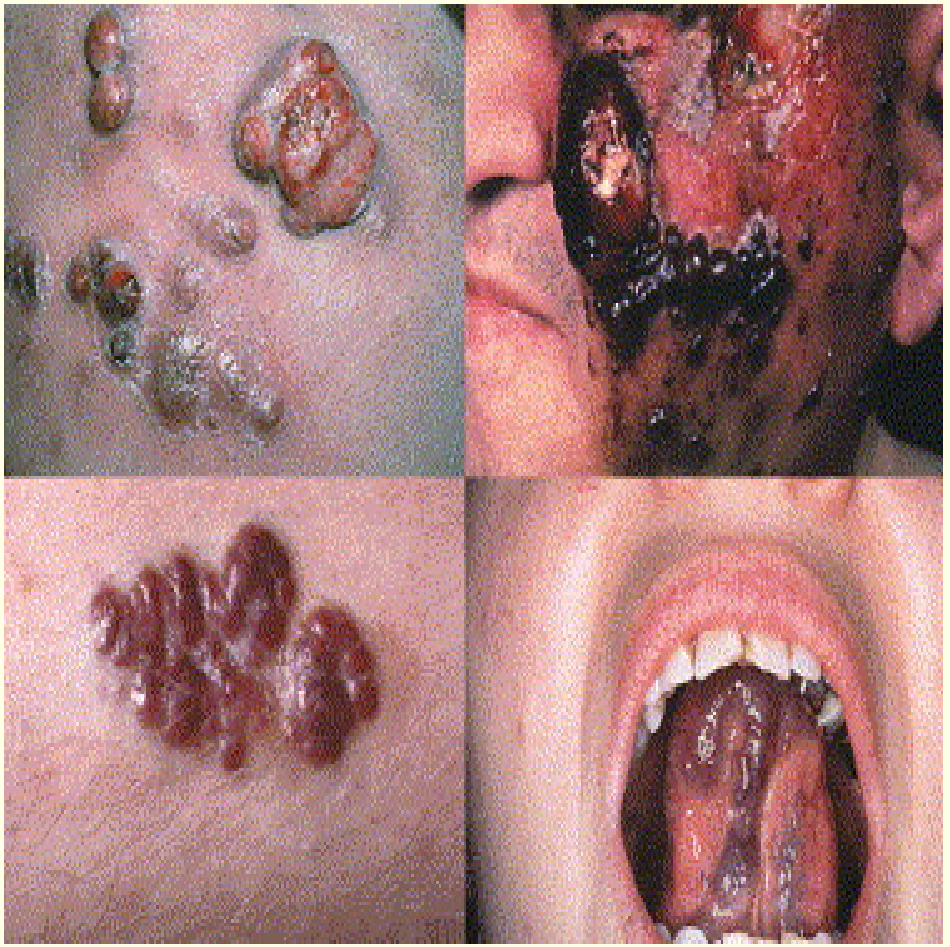
- Upper left: classical KS
- Lower left: immunosuppression KS
- Upper right: AIDS-KS
- Lower right: endemic African AIDS-KS

KS can attack other parts of the body



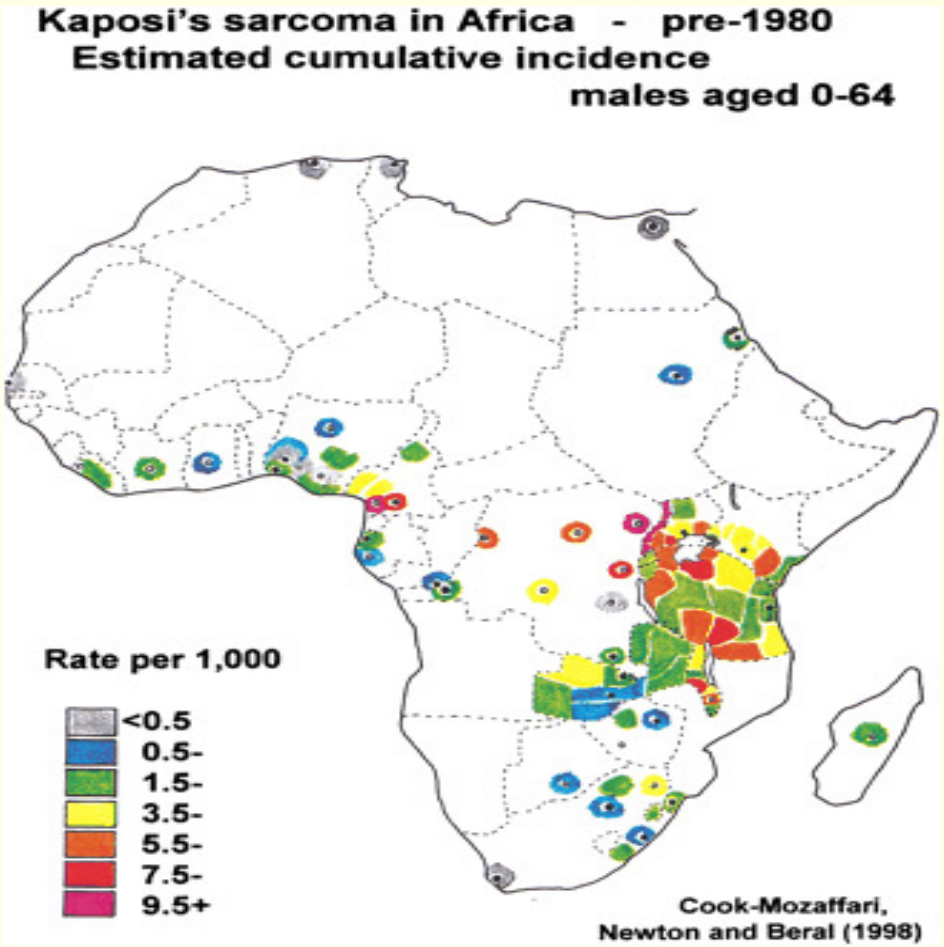
- Upper left: disfigures face
- Lower left: upper gum
- Upper right: chest/abdomen
- Lower right: genitals

KS can attack other parts of the body



- Upper left: back
- Lower left: abdomen
- Upper right: face
- Lower right: tongue

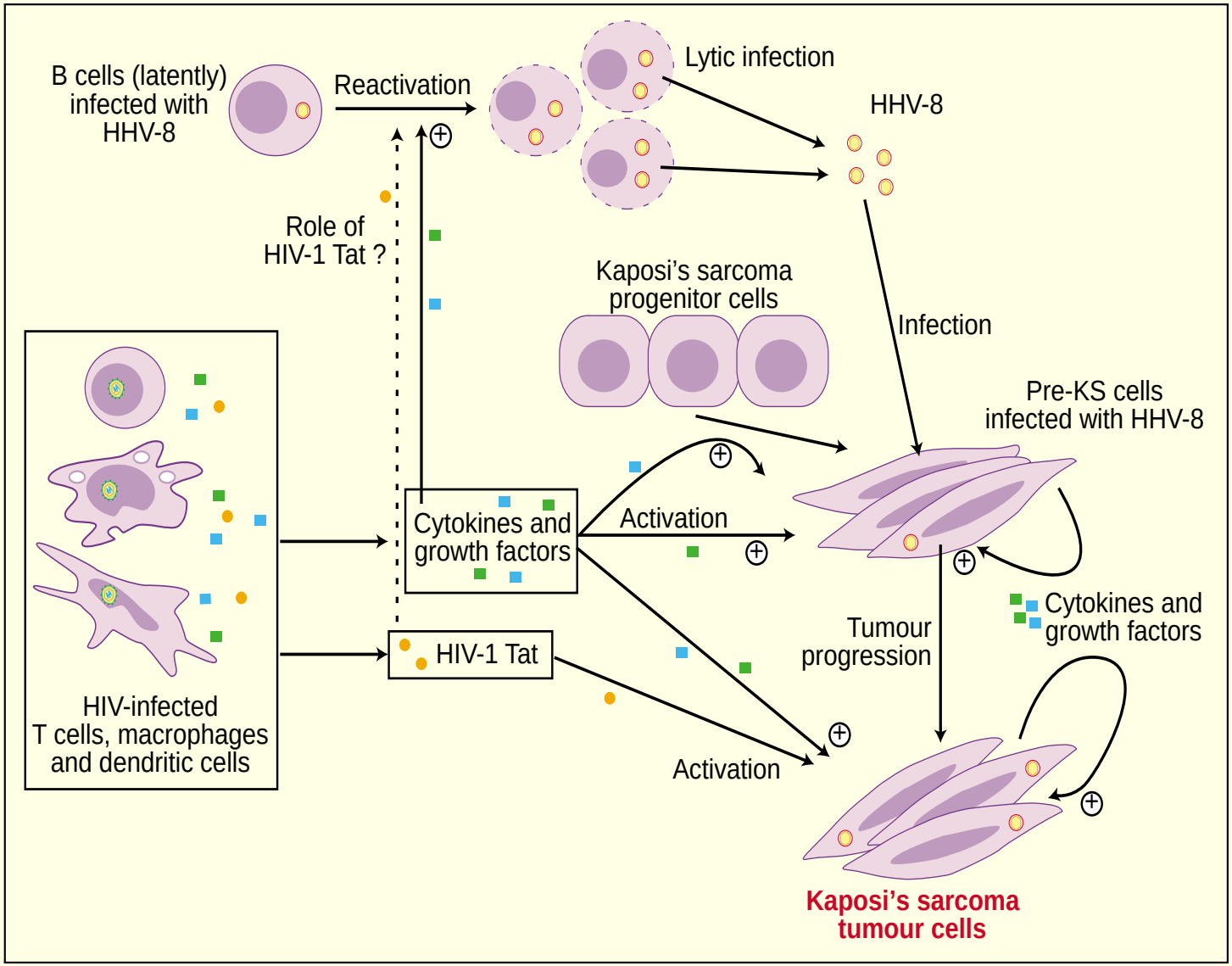
KS before the outbreak of HIV/AIDS



- The distribution of KS is concentrated in sub-Sahara Africa
- The heaviest burden of HIV-AIDS is also concentrated in the same region
- It's no surprise that co-infection of HIV/KS is concentrated in Southern and East Africa.

Interraction between HIV-1 and HHV-8

The interraction between the two viruses is explained by the diagram below:



Interraction between HIV-1 and HHV-8

The figure represents two scenarios of Kaposi's Sarcoma:

(I). In the abscence of HIV-1, the infection of B-cells could remain in latency or could develop into Classical KS.

(II). Most of the individuals could carry the disease in its latency form and never develop clinical conditions of the disease.

(III). In the presence of HIV-1, the latently infected B-cells are activated and this accelerates the production of HHV-8.

(IV). The HHV-8 could in turn infect the progenitor cells, a situation that could lead to the growth of KS.

Classical KS model formulation

We introduce the following variables:

T	$=$	Density of immune effector cells	$cell/ml$
B	$=$	Density of B cells	$cell/ml$
B_a	$=$	Density of infected B cells	$cell/ml$
V	$=$	Density of free virus	$virions/ml$
P	$=$	Density of Health Progenitor cells	$cell/ml$
P_i	$=$	Density of infected Progenitor cells	$cell/ml$
K	$=$	Density of Kaposi's Sarcoma cells	$cell/ml$

Classical KS model equations

$$\dot{T} = \omega_T \left(1 - \frac{T}{r_T}\right) T, \tag{1}$$

$$\dot{B} = \omega_B \left(1 - \frac{B}{r_B}\right) B - \beta_1 BV, \tag{2}$$

$$\dot{B_a} = \beta_1 BV - \delta B_a - k_1 B_a T, \tag{3}$$

$$\dot{V} = n\delta B_a - \mu_v V, \tag{4}$$

$$\dot{P} = \omega_P \left(1 - \frac{P}{r_P}\right) P - \beta_2 PV, \tag{5}$$

$$\dot{P_i} = \beta_2 PV - \alpha P_i - k_2 P_i T, \tag{6}$$

$$\dot{K} = \alpha P_i - \gamma KT. \tag{7}$$

Equilibrium points

The system has two equilibrium points:

1. $E_0 = (r_T,\ r_B,\ 0,\ 0,\ r_P,\ 0,\ 0)$,
2. $E_1 = (r_T,\ B^*,\ B_a^*,\ V^*,\ P^*,\ P_i^*,\ K^*)$, where;

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$$
\begin{aligned}
B^* &= \frac{\mu_V\left(\delta + k_1 T_{max}\right)}{n\delta\beta_1} \\
B_a^* &= \frac{\mu_V \omega_B}{n^2\delta\beta_1}\left(n - n_{crit}\right) \\
V^* &= \frac{\omega_B}{n\beta_1}\left(n - n_{crit}\right)
\end{aligned}
$$

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V^* &= \frac{\omega_B}{n\beta_1}\left(n - n_{crit}\right) \\
P^* &= r_P\left(1 - \frac{\beta_2\omega_B}{n\beta_1\omega_P}\left(n - n_{crit}\right)\right) \\
P_i^* &= \frac{r_P\beta_2\omega_B}{n\beta_1\left(\alpha + k_2 r_T\right)}\left(1 - \frac{\beta_2\omega_B}{n\beta_1\omega_P}\left(n - n_{crit}\right)\right)\left(n - n_{crit}\right) \\
K^* &= \frac{\alpha r_P\beta_2\omega_B}{n\gamma\beta_1 r_T\left(\alpha + k_2 r_T\right)}\left(1 - \frac{\beta_2\omega_B}{n\beta_1\omega_P}\left(n - n_{crit}\right)\right)\left(n - n_{crit}\right)
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K^* &= \frac{\alpha r_P\beta_2\omega_B}{n\gamma\beta_1 r_T\left(\alpha + k_2 r_T\right)}\left(1 - \frac{\beta_2\omega_B}{n\beta_1\omega_P}\left(n - n_{crit}\right)\right)\left(n - n_{crit}\right) \\
n_{crit} &= \frac{\mu_v\left(\delta + k_1 r_T\right)}{r_B\delta\beta_1}, \\
R_0 &= \frac{r_B\delta\beta_1 n}{\mu_v(\delta + k_1 r_T)},
\end{aligned}
$$

Existence of the EEP

Theorem

The endemic equilibrium point, E_1, exists if $n > n_{crit}$ and $R_P < R_B$, where $R_P = \beta_2/\omega_P$ is the average reproduction number measuring the infection of progenitor cells and $R_B = \beta_1/\omega_B$ is the average reproduction number measuring the infection of B cells.

Remark

(i). The condition $n > n_{crit}$ ensures the existence of the virus population.

(ii). The condition $R_P < R_B$ ensures that the B cell population is not depleted.

(iii). The condition $n > n_{crit}$ ensures continuation of primary infection of B-cells by HHV-8.

Global stability of the DFE

Theorem

The disease free equilibrium point is globally stable for $n < n_{crit}$, $\frac{\mu_V}{r_B\beta_1} < 1$, *and* $\left(\frac{\mu_V}{r_B\beta_1}\right)\left(\frac{\mu_V}{r_P\beta_2}\right) > 1$.

Proof.

Let us consider a Lyapunov function of the form:

$$
\begin{aligned}
L &= T - r_T - r_T \ln\left(\frac{T}{r_T}\right) + B - r_B - r_B \ln\left(\frac{B}{r_B}\right) + P - r_P - r_P \ln\left(\frac{P}{r_P}\right) \\
&+ B_a + P_I + V + K \\
\dot{L} &= \left(\frac{T - r_T}{T}\right)\dot{T} + \left(\frac{B - r_B}{B}\right)\dot{B} + \left(\frac{P - r_P}{P}\right)\dot{P} + \dot{B}_a + \dot{P}_I + \dot{V} + \dot{K} \\
&= -\frac{(r_T - T)^2\,\omega_T}{r_T} - \frac{(r_B - B)^2\,\omega_B}{r_B} - \frac{(r_P - P)^2\,\omega_P}{r_P} \\
&+ \beta_1 r_B V + \beta_2 r_P V - \mu_V V - k_2 P_I T - \alpha K T \\
&+ \delta\,(n - n_{crit}) + \frac{\delta\,(\mu_V - r_B\beta_1) + k_1\,(\mu_V r_T - r_B\beta_1 T)}{r_B\delta\beta_1} \\
&\leq 0 \qquad \text{if} \quad n < n_{crit}, \quad \frac{\mu_V}{r_B\beta_1} < 1, \quad \left(\frac{\mu_V}{r_B\beta_1}\right)\left(\frac{\mu_V}{r_P\beta_2}\right) > 1.
\end{aligned}
$$

□

Implication of this result

1. Stability of the DFE is independent of the initial data.

2. This is clinicllly meaningless if the individual has no immunity against the disease

Co-infection of HIV-1 and HHV-8

$$
\begin{aligned}
\frac{dT(t)}{dt} &= s_T - \mu_T T + f_1(V_1, T) + f_2(V_8, T) - \beta_1 T V_1, \\
\frac{dI(t)}{dt} &= \beta_1 T V_1 - \mu_I I, \\
\frac{dV_1(t)}{dt} &= N_1 \mu_I I - \mu_{V_1} V_1, \\
\frac{dB(t)}{dt} &= s_B - \mu_B B + f_3(V_1, B) + f_4(V_8, B) - \beta_2 B V_8, \\
\frac{dB_L(t)}{dt} &= \psi_1 \beta_2 B V_8 - f_5(V_1, B_L) - \mu_{B_L} B_L, \\
\frac{dB_A(t)}{dt} &= \psi_2 \beta_2 B V_8 + f_5(V_1, B_L) - \mu_{B_A} B_A, \\
\frac{dV_8(t)}{dt} &= N_8 \mu_{B_A} B_A - \mu_{V_8} V_8, \\
\frac{dP(t)}{dt} &= f_6(V_8) - \mu_P P - \beta_3 P V_8, \\
\frac{dP_I(t)}{dt} &= \beta_3 P V_8 - f_7(V_1, P_I) - \mu_{P_I} P_I, \\
\frac{dK(t)}{dt} &= f_7(V_1, P_I) - \mu_K K.
\end{aligned}
$$

Stability of the DFE

Theorem

If the DFE is disturbed by a small amount $\varepsilon(t)$, the disturbance decays provided: $n < n_{crit}$, $\frac{\mu_V}{r_B\beta_1} < 1$, and $\left(\frac{\mu_V}{r_B\beta_1}\right)\left(\frac{\mu_V}{r_P\beta_2}\right) > 1.$

Remark

- These conditions agree with the global stability conditions for the model with constant parameters.

Theorem

If the DFE is disturbed by a larger amount $\frac{1}{\varepsilon(t)}$, the disturbance decays provided: $n > n_{crit}$, $\frac{\mu_V}{r_B\beta_1} > 1$, and $\left(\frac{\mu_V}{r_B\beta_1}\right)\left(\frac{\mu_V}{r_P\beta_2}\right) < 1.$

Remark

- These conditions do not agree with the global stability conditions for the model with constant parameters.
- The results of these two theorems show that the DFE can not be globally stable, even though in both cases the eigen values are all negative.