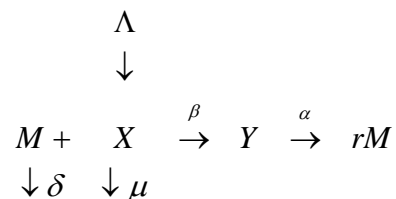


In-host infection dynamics

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Many micro-parasites (HIV, blood stage malaria, et al) invade special populations of host-cells (e.g. HIV - immune CD4+ cells, malaria - red-blood cells), replicate and release new copies to continue the process. In some cases each release of new parasites destroys infected cells (malaria), in other cases (HIV) infected cells can work continuously like “parasite factories”, but lose their protective (immune) function.

We call X, Y - uninvaded, invaded cell populations (measured as densities/ml of blood), and M - free parasite stage (per/ml), and think of invasion/destruction processes as 2nd and 1st order chemical kinetics:



Parameters: β - 2nd order reaction rate (invasion); 1st order rates: μ - natural cell mortality, δ - free stage mortality, α - bursting/death of infected cells ; Λ - source of cell production.

The models below are adopted from references [1-2].

In-host HIV model

HIV virus invades immune CD4+ cells replicates inside those, then newly produced viral particles (virions) are released in the blood to invade new CD4+. That same CD4+ are responsible for “recognizing” viral infections and “reporting” them to other immune cells for clearing. CD4+ are produced at some rate in the thymus, and released into plasma. But when stimulated by a pathogen they are stimulated to replicate and produce more copies.

The following dynamical model attempts to account for these processes.

Variables: X - CD4+ population, Y - iCD4+ (infected ones), V – free virions

$$\begin{aligned}
\dot{X} &= \underbrace{(\Lambda - \mu X)}_{\text{normal production/death}} + \underbrace{aVX}_{\text{CD4-proliferation}} - \underbrace{\beta XV}_{\text{invasion}} \\
\dot{Y} &= \beta XV - \alpha Y - \underbrace{\omega XY}_{\text{immune clearing}} \\
\dot{V} &= \underbrace{r\alpha Y}_{\text{replication}} - \delta V - \beta XV
\end{aligned} \tag{1}$$

Parameters:

r	-virion production/over cell life-span
β	-contact-invasion rate (by HIV)
$a < \beta$	-proliferation rate of CD4-population X, stimulated in proportion to V
ωXY	-“collision type” immune clearing (of infected CD4 by healthy CD4)
$\alpha > \mu$	-enhanced death rate in iCD4+ (they don't proliferate)

System (1) has BRN $R_0 = \frac{X_0 \beta (r-1)}{\delta}$, $X_0 = \Lambda / \mu$ - normal CD4 level; and equilibria:

$(X_0, 0, 0)$ - normal (w/o infection), and (X^*, Y^*, V^*)

$$\frac{X^*}{X_0} = \frac{1}{R_0}; \frac{Y^*}{X_0} = \frac{\mu(1-1/R_0)}{\alpha(1-a/\beta)}; V^* = \frac{\mu(R_0-1)}{\beta-a}$$

In reality, HIV does not equilibrate, but slowly decreases number of viable CD4+, and below the threshold level (25% of normal) any opportunistic infection can kill such host (Reference [3]).

In-host blood stage malaria model

No immune response

We first develop model w/o immune response, then discuss how immunity can affect it.

As above variables X, Y, M designate uninfected/infected (RBC, iRBC) and free merozoites, that obey

$$\left\{ \begin{aligned}
\dot{X} &= \underbrace{\Lambda}_{\text{RBC production}} - \underbrace{\mu X}_{\text{death}} - \underbrace{\beta XM}_{\text{Invasion}} \\
\dot{Y} &= \beta XM - \underbrace{\alpha Y}_{\text{bursting}}; \\
\dot{M} &= \underbrace{r\alpha Y}_{\text{merozoite release}} - (\delta + \beta X)M;
\end{aligned} \right. \tag{2}$$

Parameters: $\alpha = .5/\text{day}$ - bursting rate of infected RBC, $r = 8 - 12$ - replication number (merozoite release/per iRBC), δ - free merozoite death rate (1/few minutes); βXM - 2nd order chemical reaction rate.

A possible modification of the invasion term is $\beta(X)M$, with density dependent invasion rate/ per merozoite, instead of simple linear ('collision type') βX .

As free merozoites die rapidly (large mortality δ) we can reduce 3D system (2) by replacing the dynamic M-equation with quasi-equilibrated

$$M^* = \frac{r\alpha Y}{\delta + \beta(X)}; \lambda = \frac{r\alpha\beta(X)}{\delta + \beta(X)} - \text{per RBC force of invasion} \quad (3)$$

The reduced 2D system

$$\begin{aligned} \dot{X} &= \Lambda - \mu X - \lambda Y \\ \dot{Y} &= (\lambda - \alpha)Y \end{aligned} \quad (4)$$

Is a modified Volterra-Lotka with "satiated" predation λ .

System (4) has equilibrium

$$X^* = \begin{cases} \frac{\delta}{(r-1)\beta_0}; \text{ linear } \beta(X) = \beta_0 X \\ \frac{\delta X_c}{(r-1)\beta_0 - \delta}; \text{ saturation } \beta(X) = \frac{\beta_0 X}{X + X_c} \end{cases}; \quad (5)$$

$$Y^* = (\Lambda - \mu X^*) / \alpha;$$

and the corresponding BRN

$$R_0 = \frac{\Lambda}{\mu X^*} = \begin{cases} \frac{\Lambda\beta_0(r-1)}{\mu\delta} \\ \frac{\Lambda[\beta_0(r-1) - \delta]}{\mu\delta X_c} \end{cases} \quad (6)$$

System (4) can be rescaled relative to normal RBC level $X_0 = \Lambda / \mu = 5 \times 10^6 / \text{ml}$, $\mu = .01/\text{day}$.

The dimensionless form for variables $x = X / X_0; y = Y / X_0; t = \mu t$, gives

$$\begin{aligned}\dot{x} &= 1 - x - a \frac{x}{x_0 + x} y \\ \dot{y} &= \left(a \frac{x}{x_0 + x} - b \right) y\end{aligned}\tag{7}$$

with parameters $a = \frac{r\alpha}{\mu}$; $b = \frac{\alpha}{\mu} < a$; $x_0 = \frac{\delta}{\beta X_0}$.

Problem: Study equilibria, stability, bifurcations of system (7). Show that in all cases equilibria are either sinks or spiral sinks. Plot typical dynamic patterns (phase-plane and time series).

Immune regulation

The effect of immunity (T-cell population T) is given by a 4D system:

$$\begin{aligned}\dot{X} &= \underbrace{\Lambda}_{\text{production}} - \underbrace{\mu X}_{\text{death}} - \underbrace{\beta(X)M}_{\text{Invasion}}; \\ \dot{Y} &= \beta(X)M - \underbrace{(\alpha + \omega T)Y}_{\text{bursting+T-cell clear}}; \\ \dot{M} &= r\alpha Y - [\delta + \beta(X) + \omega T]M; \\ \dot{T} &= \underbrace{\gamma Y}_{\text{stimulation}} + \underbrace{T(\phi - bT)}_{\text{constrained logistic}};\end{aligned}\tag{8}$$

Merozoite reduction: $M \approx \frac{r\alpha Y}{\delta + \omega T + \beta(X)}$; $\lambda = \frac{r\alpha\beta(X)}{\delta + \omega T + \beta(X)}$, yields 3D

$$\begin{aligned}\dot{X} &= \Lambda - \mu X - \lambda Y \\ \dot{Y} &= (\lambda - \alpha - \omega T)Y \\ \dot{T} &= \gamma Y + T(\phi - bT)\end{aligned}\tag{9}$$

System (9) has 3 equilibria:

$I = (X_0, 0, 0)$ - normal non-immune;

$II = (X_0, 0, T_c)$ - normal immune ($X_0 = \Lambda / \mu$ - normal RBC-level, $T_c = \phi / b$ - carrying capacity for immune T-cells);

$III = (X^*, Y^*, T^*)$

$$X^* = \frac{\delta + \omega T^*}{\left[r \left(\frac{\alpha}{\alpha + \omega T^*} \right) - 1 \right] \beta_0};$$

$$Y^* = \frac{\Lambda - \mu X^*}{\alpha + \omega T^*} > 0;$$

$$T^* = \dots < T_c$$

The 'immune reduced' BRN is given by

$$R_0 = \frac{\Lambda}{\mu X^*} = \frac{\Lambda \beta \left[r \left(\frac{\alpha}{\alpha + \omega T^*} - 1 \right) \right]}{\mu (\delta + \omega T^*)}$$

Logistic-type T-cell dynamics (8)-(9) proposed in [1-2], indeed the whole idea on 'endemic equilibrium state' is not appropriate for malaria.

References

1. Austin DJ, White NJ, Anderson RM. The dynamics of drug action on the within-host population growth of infectious agents: melding pharmacokinetics with pathogen population dynamics. *J Theor Biol* 1998, 194: 313-339
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3. M. Novak and R. May, "Viral dynamics: the mathematical foundations of virology and immunology", by, Oxford UP, 2000