T-cell kinetics

We wish to deduce a half-life for the CTL population. This analysis is based on the assumption, discussed in the main body of the paper, that after the peak of infection the latently infected B cell population (mBLat) decays with a simple exponential half-life to become lytically infected B cells (BLyt) expressing IE proteins. These in turn stimulate a population of CTLs (CTLIE) that are directed against and kill the lytically infected cells. We further assume that at the time patients enter the clinic, the time from which data was collected, that the peak of infection and the immune response has already passed and the levels of infection and immune response have started to decay, but they have not yet reached a steady state. This assumption is substantiated by our observation that, by the time of the patients’ first clinical visit, the populations of mBLat and CTLIE are always observed to be declining. As we will see, under reasonable assumptions this can be modeled as:

\[
CTL_{IE}(t) = ae^{-\frac{\ln(2)}{H_T}t} + be^{-\frac{\ln(2)}{H_B}t}
\]

where \(H_T\) is an intrinsic half-life of the CTL population and \(H_B\) is the half-life of the B cell population.

The notion of an intrinsic T cell half life deserves some explanation. We are assuming that CTLs die at a rate proportional to their total population and that the number of CTLs undergoing cell division at any point is also proportional to this population. During the period in question, the death rate exceeds the birth rate, and their difference yields an intrinsic rate of decay. We are distinguishing the births due to proliferation of activated CTLs from the activation of new CTLs and excluding these latter from our notion of an intrinsic half-life.

During the phase in question, the number of mBLat being created is small compared to the decay of the mBLat population, and this latter is proportional to the mBLat population. We thus have

\[
\frac{d}{dt} B_{Lat}(t) \propto -B_{Lat}(t).
\]

Thus, the mBLat population exhibits exponential decay

\[
B_{Lat}(t) = b_0 e^{-\frac{\ln(2)}{H_B}t}.
\]

Here \(H_B\) is the half-life of the mBLat population. We observe values in the range of 2.4 – 15.2 (mean 7.3 + 5.7) days.

The rate of production of CTLIE is also proportional to the rate of decay of the mBLats. The size of the CTLIE population is governed by the percentage of mBLats turning into BLyts and the survival rate of these lytic BLyts once they are created. Thus the population of BLyts at time \(t\) is given by:
\[ B_{Ly}(t) = \int_{t-\delta}^{t} c_0 B_{Lat}(s) S_s(t-s) \, ds \]

where \( \delta \) is the maximum lifespan for a BLy, \( c_0 \) is a proportionality constant relating BLy production to mBLat population, and \( S_s(r) \) gives the fraction of BLys created at time \( s \) surviving for at least the length of time \( r \leq \delta \). The maximum lifespan \( \delta \) is short, on the order of hours, not days, so we may approximate mBLat(s) by mBLat(t) and replace \( S_s(t-s) \) by its average value \( S_t \) in the interval \( 0 \leq t-s \leq \delta \). If we approximate this average survival rate as being constant over this phase of the infection, we have:

\[ B_{Ly}(t) \propto \frac{d}{dt} B_{Lat}(t) \propto -B_{Lat}(t). \]

What should be the effect of this on the CTLIE population? Under these conditions, the CTLIE population should exhibit its own intrinsic half-life, which reflects the difference between decay and propagation. In addition, during infection, fresh CTLIEs will be recruited in response to the BLy population. The details of the kinetics of CTL recruitment are not known. We will approximate this process as being proportional to the BLy population. We then have:

\[ \frac{d}{dt} CTL_{IE}(t) = -c_1 CTL_{IE}(t) + c_2 B_{Lat}(t) \]

\[ = -c_1 CTL_{IE}(t) + c_3 e^{-\frac{ln(2)}{H_B} t}. \]

The general solution has the form:

\[ CTL_{IE}(t) = a e^{-\frac{ln(2)}{H_B} t} + b e^{-\frac{ln(2)}{H_T} t}. \]

As we will see, the half-life of the mBLats is much shorter than that of the CTLIEs, so the second component decays more quickly than the first. In particular, we can expect the mBLat half-life to dominate for a limited time after which the intrinsic CTLIE half-life dominates.

In Figures 1-6 we exhibit data from six patients. In each case, we have the mBLat half-life \( HB \) from independent measurement. We have taken \( a, b, \) and \( HT \) as free parameters and have used these to exhibit a best fit of \( \log(CTL_{IE}(t)) \) to the data points. We have excluded data points at day 360 for patients 1199 and 1203 since these lie in the persistent phase. Patients 1199, 1203, and 1256 demonstrate a visible transition from an \( HB \) regime to an \( HT \) regime, and their best fit curves yield values of \( HT \) of 89, 47, and 83 respectively. The remaining patients do not seem to have undergone this transition during the time period shown in their data. Consequently, the values of \( HT \) listed for them seem to be the result of over-fitting to the fluctuations.