Assessing practical identifiability in hepatitis C viral kinetic modeling

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Mathematical models for hepatitis C viral kinetics have become an important tool to assess early virologic treatment response. Model calibration can be done in the framework of non-linear parametric regression analysis where the regression function is derived from a specific ordinary differential equation system. Most recently models including proliferation of infected and uninfected cells have been proposed [1]:

$$\begin{aligned}
\frac{dT(t)}{dt} &= s + r_T T(t)\left(1-\left(T(t)+I(t)\right)/T_{\max}\right) - d_T T(t) - \beta V_I(t) T(t) \\
\frac{dI(t)}{dt} &= \beta V_I(t) T(t) + r_I I(t)\left(1-\left(T(t)+I(t)\right)/T_{\max}\right) - d_I I(t) \\
\frac{dV_i(t)}{dt} &= \left(1-\rho(t)\right)(1-\varepsilon)\, p\, I(t) - c V_i(t) \\
\frac{dV_{ni}(t)}{dt} &= \rho(t)(1-\varepsilon)\, p\, I(t) - c V_{ni}(t)
\end{aligned}$$

where T and I are compartments of uninfected and infected target cells, V_i and V_{ni} are compartments of infectious and non-infectious virus, ε and ρ are treatment efficiency factors on viral production or viral infectivity, s is a general production rate of uninfected target cells, r_T and r_I are proliferation rates of uninfected and infected cells and d_T and d_I are degradation rates of uninfected and infected cells, respectively, β is the infection rate and c is the viral clearance rate. It can be assumed that the system is in steady state during untreated chronic infection (treatment efficiency factors ε and ρ equals zero) whereas this steady state is disturbed and virus decreases during antiviral treatment with nonzero treatment efficiency factors ε and/or ρ. Nevertheless, identifiability, especially practically identifiability of such models is difficult to assess.

Here we compare the above model and a simplified one which can both explain a triphasic viral decay pattern during the initial phase of antiviral treatment in patients with chronic hepatitis C infection. The parameter sets for the identifiability analysis are derived by random sampling from previously published values which are in part results of model calibration from patient data and in part biologically plausible values. We discuss results on practical identifiability based on two different approaches: (1) estimation of the Fisher Information Matrix and (2) analysis of potential functional relations between parameters with the alternating conditional expectation algorithm. Both approaches have been proposed recently in the context of non-linear dynamic models [2,3] and complement each other.

For the discussed viral kinetic models, these approaches highlight the specific requirements on design and a priori parameter choice which have to be handled when estimating viral kinetic parameters as treatment efficiency from limited data resources.

References.

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