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Implementation of PK-PD Models for viral kinetics in patients with HCV

PK-PD models are used to describe the mechanisms of antiviral activity of drugs and combinations of drugs in patients with chronic viral diseases like HCV. They play an important role in drug development and optimizing antiviral therapy. In order to describe the viral kinetics we implemented a full PK-PD model using the ordinary differential equation system shown bellow. Target cells, T, are infected by HCV, V, with rate β. Infected cells are lost at rate δ per cell and free virions are cleared at rate c. Further details are given by the model equations basing on the general PK-PD model for Hepatitis C viral kinetics as proposed in Shudo et al.[1]

$\dot{V_I}(t) = (1-\varepsilon)(1-\varrho)pI(t) - cV(t)$
$\dot{V_N}(t) = (1-\varepsilon)\varrho pI(t) - cV_n(t)$
$\dot{I}(t) = \beta T(t)V(t) + p_I I(t)(1 - \frac{T(t)+I(t)}{T(0)+I(0)}) - \delta I(t)$
$\dot{T}(t) = \gamma(1 - \frac{T(t)+I(t)}{T(0)+I(0)})$

- T and I are the numbers of target cells and infected cells, resp.
- V represents infectious virons
- V_N represents non infectious virons
- $V = V_I + V_N$ is the viral load
- p is describing the viral production rate in the untreated chronic patient
- p_I is the proliferation rate, as in Dahari et al.[2]
- γ is the regeneration rate as in Herrmann et al.[3]
- $\varepsilon(t)$ is the effectiveness of IFN
- ϱ is describing the antiviral effect of Ribavirin to split the newly produced virus in infectable virus (V_I and V_N resp.) as in Dixit et al.[4]

For the PD model, we set $\varepsilon(t)$ to $\varepsilon(t) = \frac{C(t)^h}{IC_{50}^h + C(t)^h}$, where $C(t)$ is the drug concentration in serum, IC_{50} is the drug level which blocks the viral production by 50% and the parameter h is the Hill coefficient ($h \geq 1$). The drug effectiveness, $\varepsilon(t)$ gradually increases and then decreases during the first week of therapy, as $C(t)$ does the same for each patient. For fitting the equation of $C(t)$ to each patient's PK data, we estimate all the parameters of the equation. Afterwards PK parameters are used to fit individual patient's Log HCV RNA kinetic data by maximum likelihood in order to estimate c, δ, V_0, IC_{50} and h. We used an optimization algorithm basing on the Nelder and Mead method and an ODE solver for stiff equations. We also present an example of such an implementation in MatLab as well as with R to fit viral kinetic and pharmacokinetic data with the described full PK-PD model.

References

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