Physiologically Structured Population Model of Intracellular Hepatitis C Virus Dynamics

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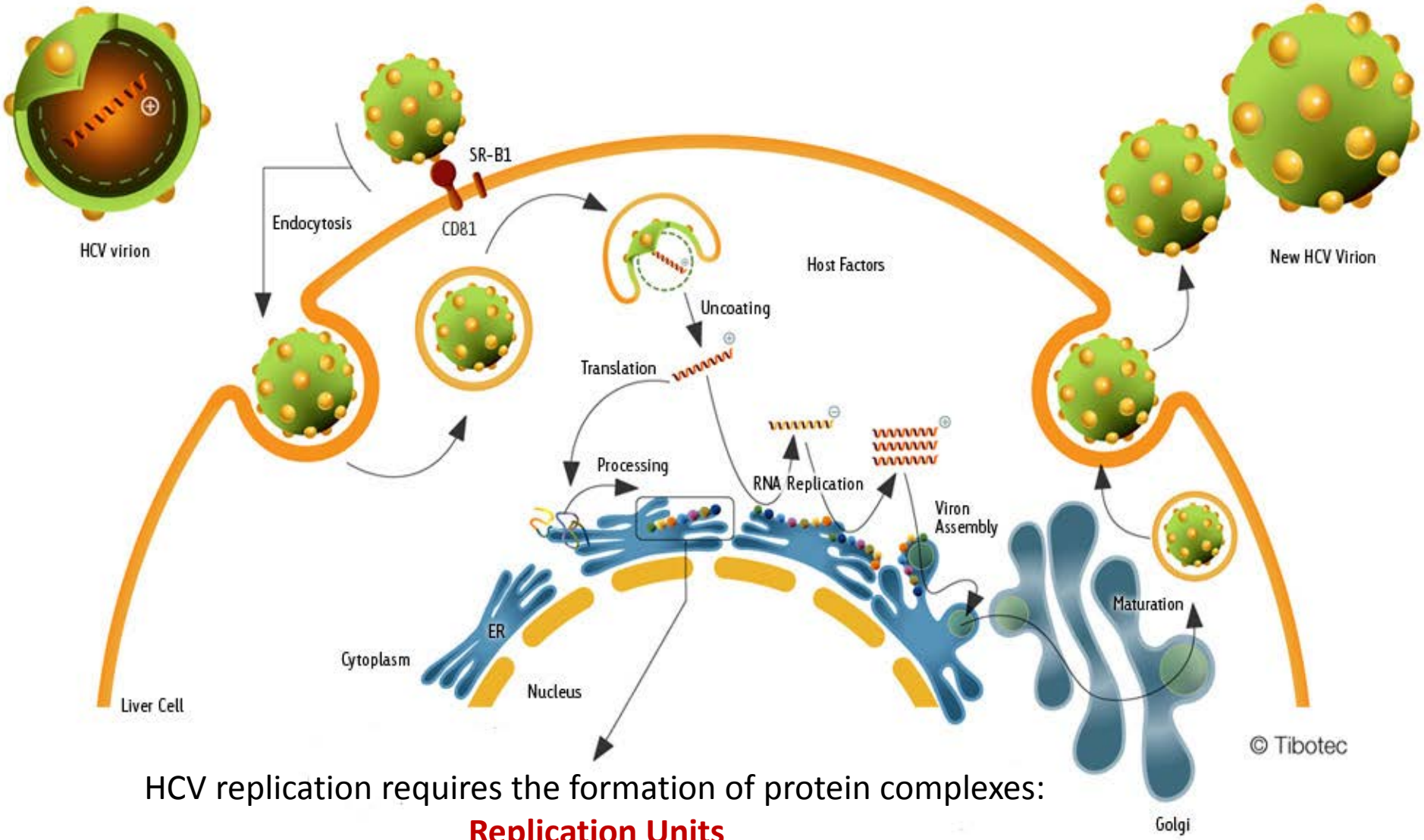
Outline

- Overview of current models of HCV infection aiming at describing drug effects on intracellular viral replication.
- Basics of physiologically structured population models.
- Introduction of PSP model of HCV dynamics.
- Comparison between PSP model and current models.

Overview

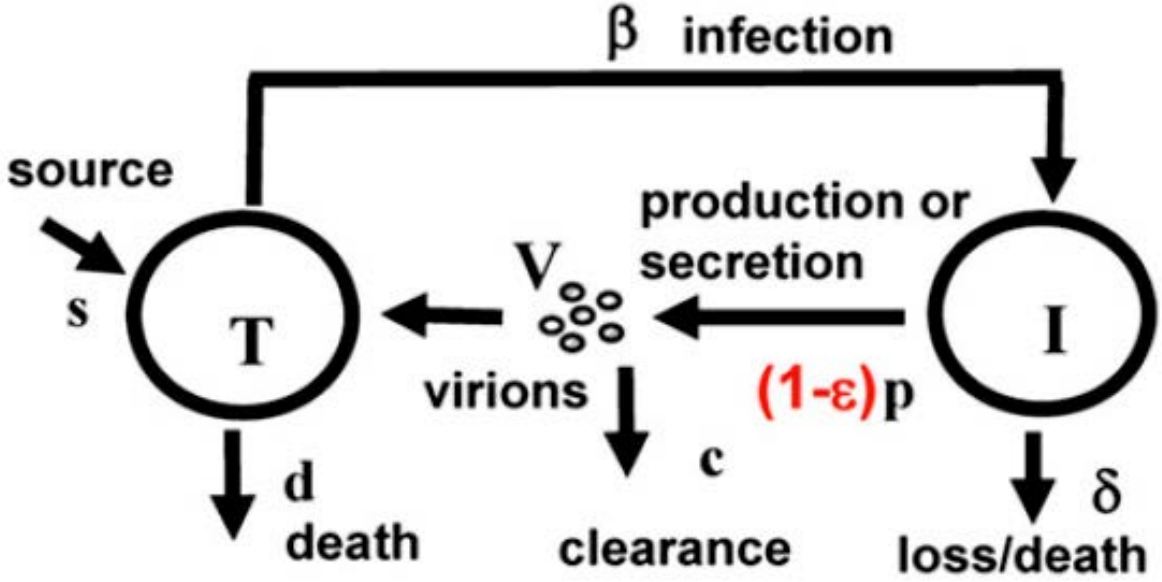
Life Cycle of Hepatitis C Virus



HCV replication requires the formation of protein complexes:

Replication Units

Standard Viral Kinetics Model:



$$\frac{dT}{dt} = s - dT - \beta VT$$

$$\frac{dI}{dt} = \beta VT - \delta I$$

$$\frac{dV}{dt} = (1-\varepsilon)pI - cV$$

$$T(0) = T_{ss} \quad I(0) = I_{ss} \quad V(0) = V_{ss}$$

I- infected cells, T- target cells, V – circulating HCV.

The virion production rate: pI

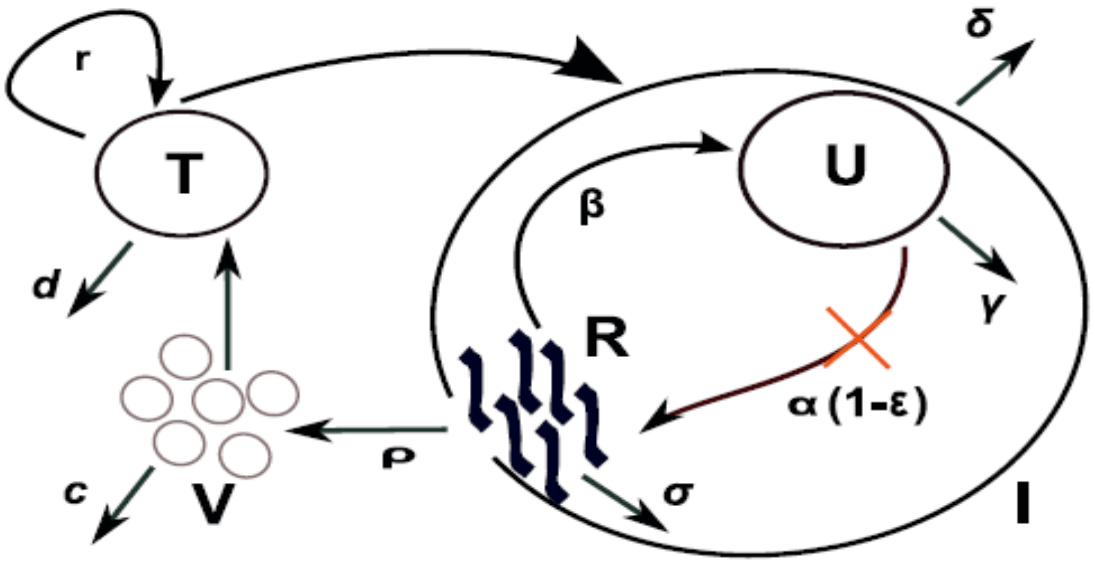
⇨ Drug inhibits the production of virions

Guedj et al. Proc Natl Acad Sci U S A. 110:3991-6 (2013).

Standard Model Assumptions:

- Discrete transition from uninfected to infected states.
- Total vRNA production is proportional to I.
- Drugs do NOT affect intracellular viral replication.

Intracellular Cell Infection (ICCI) Model:



$$\frac{dT}{dt} = r\left(1 - \frac{T+I}{T_{max}}\right)T - bVT - dT$$

$$\frac{dI}{dt} = bVT - \delta I$$

$$\frac{dV}{dt} = \rho RI - cV$$

$$\frac{dU}{dt} = \beta R\left(1 - \frac{U}{U_{max}}\right) - \gamma U$$

$$\frac{dR}{dt} = \alpha(1-\varepsilon)U - (\rho + \mu)R$$

$$T(0) = T_{ss} \quad I(0) = I_{ss} \quad V(0) = V_{ss}$$

$$U(0) = U_{ss} \quad R(0) = R_{ss}$$

U - Replication unit in a single infected cell synthesizing viral RNA R.

The virion production rate: ρRI

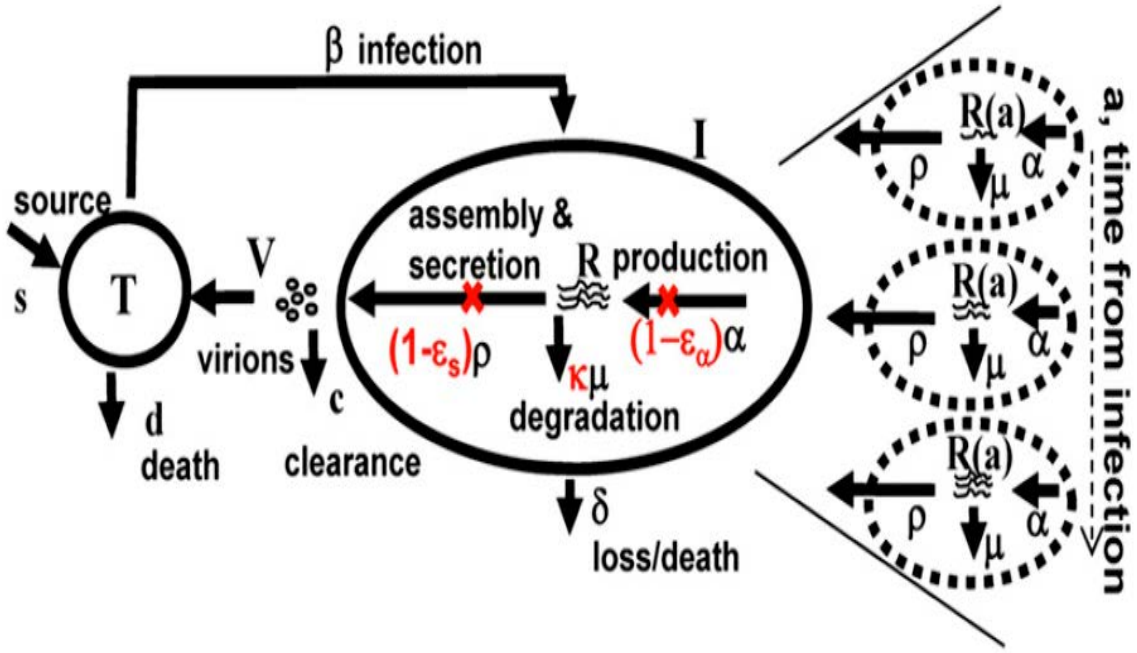
⇨ Drug blocks RNA production.

Guedj and Neumann, J. Theor. Biol. 267:330-340 (2010).

ICCI Model Assumptions

- Mean-field assumption: R(t) is same for all cells.
- No distinction between new and ‘mature’ infected cell

Multiscale Model:



$$\frac{dT}{dt} = s - dT - \beta VT$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = -\delta I$$

$$I(0,t) = \beta VT \qquad I(a,0) = I_{ss}(a)$$

$$\frac{\partial R}{\partial t} + \frac{\partial R}{\partial a} = (1-\varepsilon_\alpha)\alpha - \kappa\mu R - (1-\varepsilon_s)\rho R$$

$$R(a,0) = R_{ss}(a) \qquad R(0,t) = 1$$

$$\frac{dV}{dt} = (1-\varepsilon_s)\rho\int_0^\infty R(a,t)I(a,t)da - cV$$

$$T(0) = T_{ss} \qquad V(0) = V_{ss}$$

a – is age of infected hepatocytes. R(*a*) is the vRNA in a hepatocyte of age *a*.

The virion production rate: $\rho\int_0^\infty R(a,t)I(a,t)da$

⇨ Drug affects synthesis of R and the assembly and secretion of virons.

Simplifying Assumptions

- Short term kinetics:
  - Target cells are constant throughout the study

$$T(t) \equiv T_{ss}$$

- Effective treatment:
  - Production of new infected cells is negligible

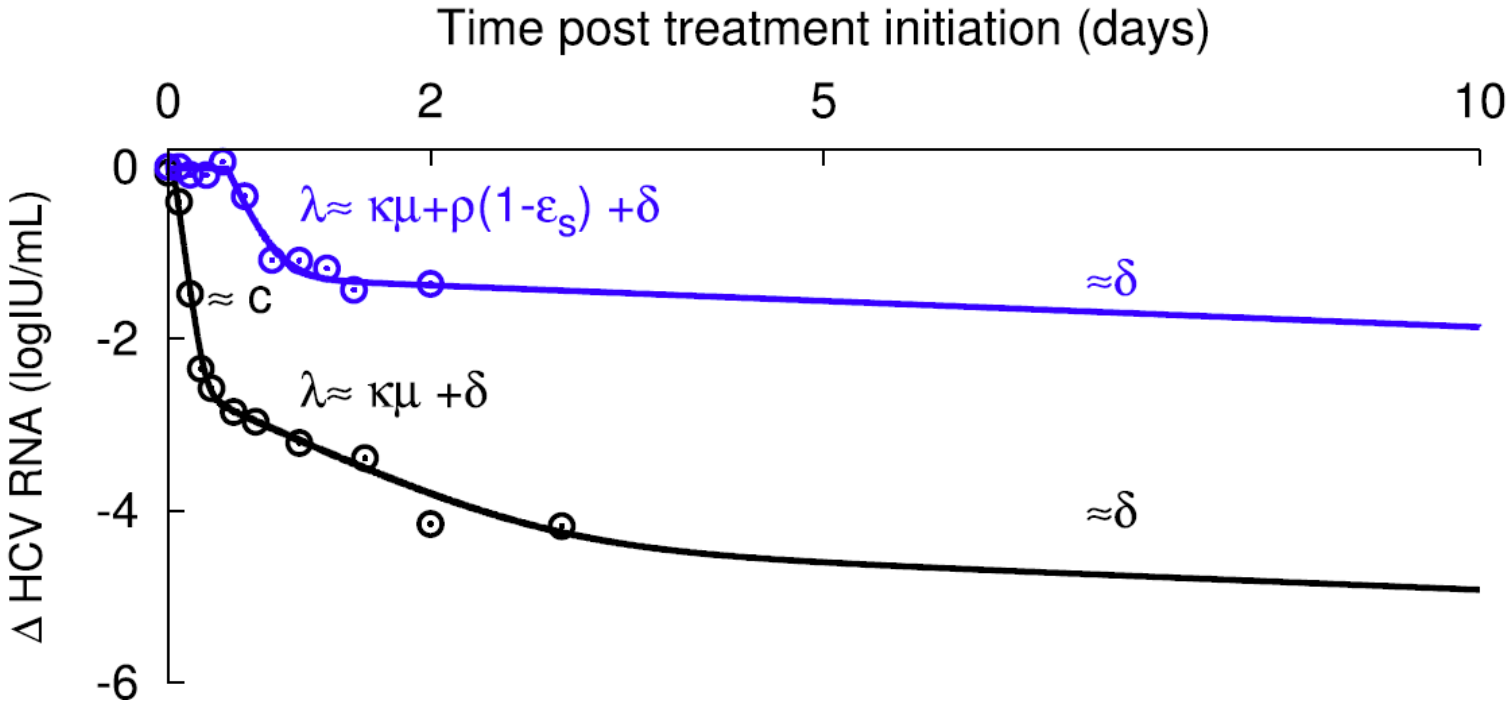
$$\beta T_{ss} V << \delta I$$

- Solution:

$$V(t) = V_0 \exp(-c(t-t_0)) + B(\exp(-c(t-t_0)) - \exp(-\delta(t-t_0)))$$
$$+ C(\exp(-c(t-t_0)) - \exp(-(\delta + (1-\varepsilon_s)\rho + \mu\kappa)(t-t_0)))$$

$$B = V_0 \frac{\alpha c(1-\varepsilon_s)(1-\varepsilon_\alpha)(\mu+\rho+\delta)}{(\alpha+\delta)(\delta-c)((1-\varepsilon_s)\rho+\mu\kappa)} \qquad C = V_0 \frac{c(1-\varepsilon_s)}{\delta-c+(1-\varepsilon_s)\rho+\mu\kappa} - \frac{\alpha c(1-\varepsilon_s)(1-\varepsilon_\alpha)(\mu+\rho+\delta)}{(\alpha+\delta)((1-\varepsilon_s)\rho+\mu\kappa)(\delta-c+(1-\varepsilon_s)\rho+\mu\kappa)}$$

Multiscale Model: Patterns of Viral Response.



Viral load decline from baseline in a patient treated with daclatasvir (black ○) compared with the decline seen in a patient treated with 10 MIU IFN (blue ○) , and the corresponding best-fit model prediction (solid lines) using the multiscale model.

Guedj et al. Proc Natl Acad Sci U S A. 110:3991-6 (2013).

Physiologically structured population (PSP) models

Structure

- Individual characteristic that can vary between the subjects.

- Distinguishes individuals according to certain physiological traits.

- Examples of physiological structures:
  - Age
  - Size (length, body weight)

Density

- Let ***s*** be a structure.

  ⇨ The density of s in the population at time t is define as:

$$n(t,\mathrm{s})\Delta s = \#\text{subjects of structure between s and } (\mathrm{s}+\Delta\mathrm{s}) \text{ at time t}$$

  ⇨ Number of subjects in population at time t:

$$N(t) = \int_0^\infty n(t,s)ds$$

  ⇨If ***s*** is amount of substance in a subject (e.g. mass of a marker in a subject) then the total amount of s in the population is

$$s_{tot}(t) = \int_0^\infty s \cdot n(t,s)\, ds$$

‘Individual’ i-state

- i-state is a vector of structures $x = (x_1, \ldots, x_m)$ such that:
  - It fully determines the population dynamical properties of a subject.
  - The future of the subject is fully determined by its i-state and the environmental history.

- The time evolution of i-state is described by a system of ODEs

$$\frac{dx}{dt} = g(t, x)$$

‘Population’ p-state

- The p-state is a distribution or density function n(t,x) such that:
  - The size and composition of the structured population is uniquely determined.

- Evolution of p-state:

$$\frac{\partial n(t,x)}{\partial t} + \underbrace{div(gn)(t,x)}_{\text{Divergence of i-state}} = \underbrace{b(t,x)}_{\text{Influx rate}} - \underbrace{\lambda(t,x)n(t,x)}_{\text{Per capita mortality rate (hazard function)}}$$

$$div(gn) = \sum_{i=1}^{m} \frac{\partial(g_i n)}{\partial x_i}$$

Impact of i-state progression on the p-state distribution

Physiologically Structured Population Model

- A PSP model describes dynamics of a population in terms of the behavior of its constituent individuals. It consists of:
  - i-state equations

$$\frac{dx}{dt} = g(t,x) \qquad t > 0, x \in \Omega$$

  - p-state equations

$$\frac{\partial n(t,x)}{\partial t} + div(gn)(t,x) = b(t,x) - \lambda(t,x)n(t,x) \qquad t > 0, x \in \Omega$$

  - Boundary conditions

$$\nu(x) \cdot g(t,x)n(t,x) = \alpha(t,x) \qquad t > 0, x \in \partial\Omega$$

  - Initial conditions

$$n(0,x) = n_0(x) \qquad x \in \Omega$$

R-Structured HCV Model

- Each infected hepatocyte contains a certain amount of vRNA which makes the R(t) a physiological structure.
  - **i-state:**

$$\frac{dR}{dt} = (1-\varepsilon_\alpha)\alpha - \kappa\mu R - (1-\varepsilon_s)\rho R = g(R)$$

  - **p-state:** density of vRNA in infected hepatocytes *i(t,R)*

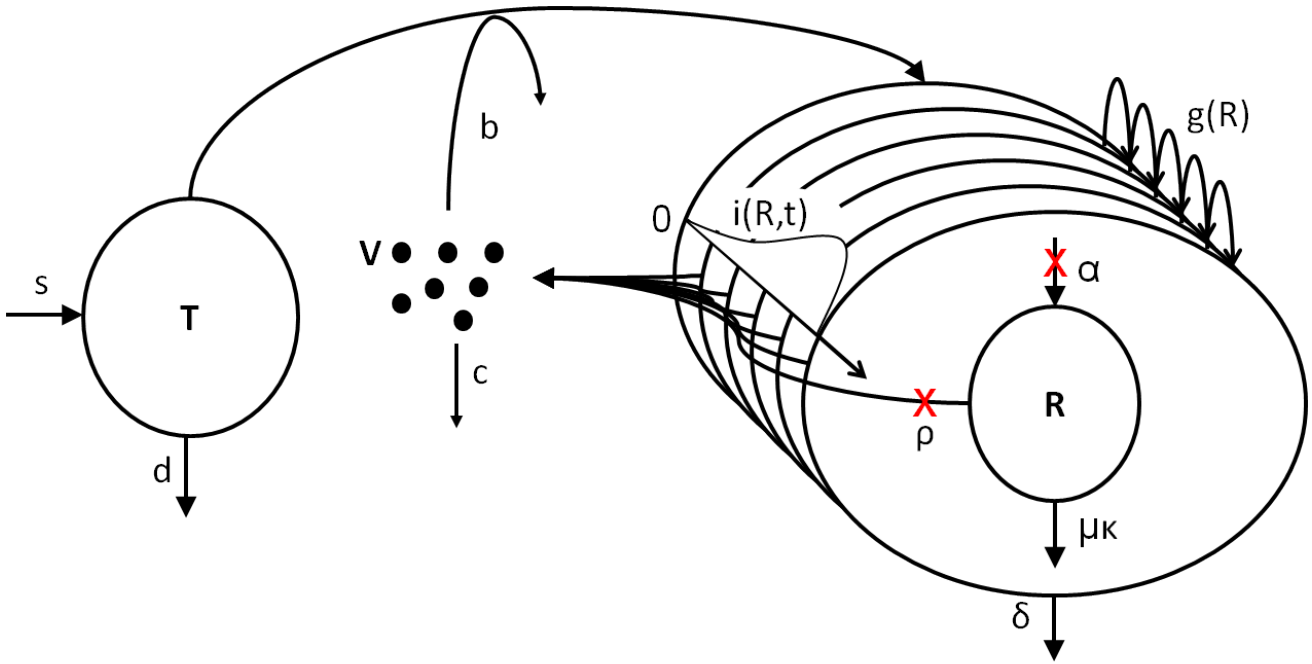
$$\frac{\partial i}{\partial t} + \frac{\partial\left(g(R)i\right)}{\partial R} = -\delta i \qquad \frac{dV}{dt} = (1-\varepsilon_s)\rho R_{tot} - cV$$

$$R_{tot}(t) = \int_0^\infty Ri(t,R)dR \qquad \frac{dT}{dt} = s - dT - \beta VT$$

  - **Conditions:**

$$i(0,t) = \beta V(t)T(t) \qquad i(R,0) = i_{ss}(R) \qquad V(0) = V_{ss} \qquad T(0) = T_{ss}$$

R-Structured HCV Model



R - intra-cellular vRNA. i(R,t) - distribution of vRNA over infected hepatocytes *(time=t)*

The virion production rate: ρR_{tot}

⇨ Drug affects synthesis of R and the production of virons.

ODE Model of HCV Dynamics

The p-state can be integrated over R resulting in a simplified ODE model:

$$\frac{dT}{dt} = s - dT - \beta VT$$

$$\frac{dI}{dt} = \beta VT - \delta I$$

$$\frac{dV}{dt} = (1-\varepsilon_s)\rho R_{tot} - cV$$

$$\frac{dR_{tot}}{dt} = (1-\varepsilon_\alpha)\alpha I - (\kappa\mu + (1-\varepsilon_s)\rho + \delta)R_{tot}$$

$$T(0) = T_{ss} \quad I(0) = I_{ss} \quad V(0) = V_{ss} \quad R_{tot}(0) = R_{totss}$$

The new model differs from the standard model by presence of $R_{tot}(t)$ that determines the viron production rate:

$(1-\varepsilon)pI$ **standard** vs. $(1-\varepsilon_s)\rho R_{tot}$ **new**

Solutions under Simplifying Conditions

$$V(t) = V_0 \exp(-ct) + B(\exp(-ct) - \exp(-\delta t)) + C(\exp(-ct) - \exp(-(\delta + (1-\varepsilon_s)\rho + \mu\kappa)t))$$

- Triple exponential: exp(-ct); exp(-δt); exp(-...t)

$$B = V_0 \frac{c(1-\varepsilon_s)(1-\varepsilon_\alpha)(\mu+\rho+\delta)}{(\delta-c)((1-\varepsilon_s)\rho+\mu\kappa)}$$

$$C = V_0 \frac{c(1-\varepsilon_s)}{\delta - c + (1-\varepsilon_s)\rho + \mu\kappa} \frac{c(1-\varepsilon_s)(1-\varepsilon_\alpha)(\mu+\rho+\delta)}{((1-\varepsilon_s)\rho+\mu\kappa)(\delta - c + (1-\varepsilon_s)\rho + \mu\kappa)}$$

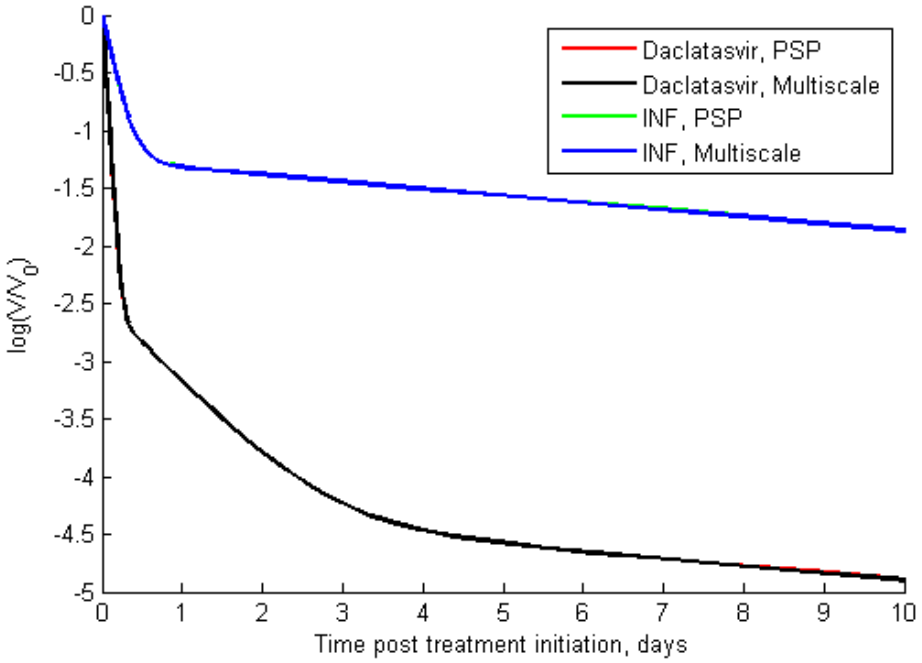
$$\frac{\alpha}{\alpha+\delta}$$

missing compared to the multiscale model solution

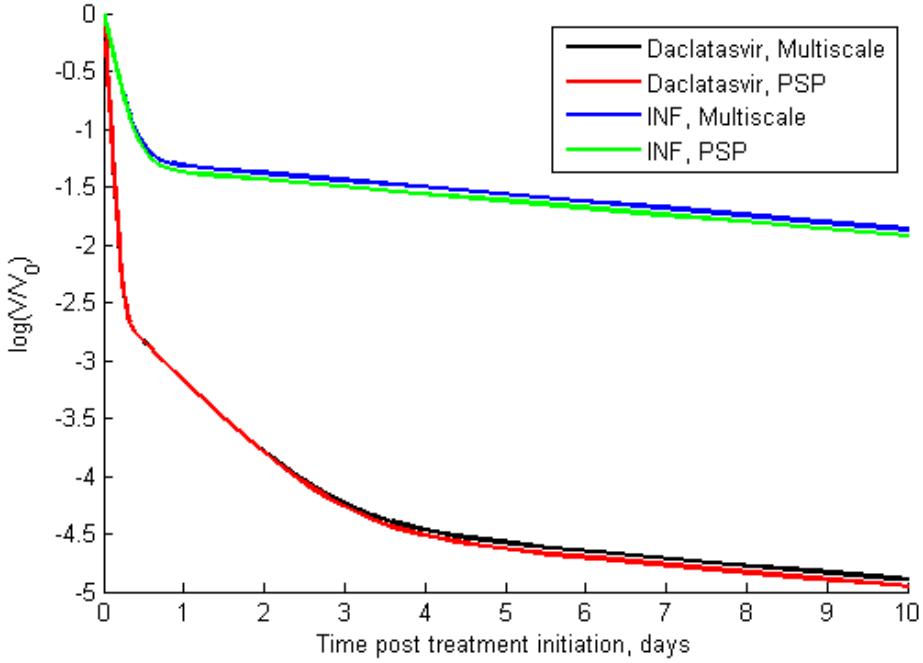
Comparison with current models

Viral Load Time Course: Multiscale vs. PSP Model

$\alpha = 40, t_0 = 0$

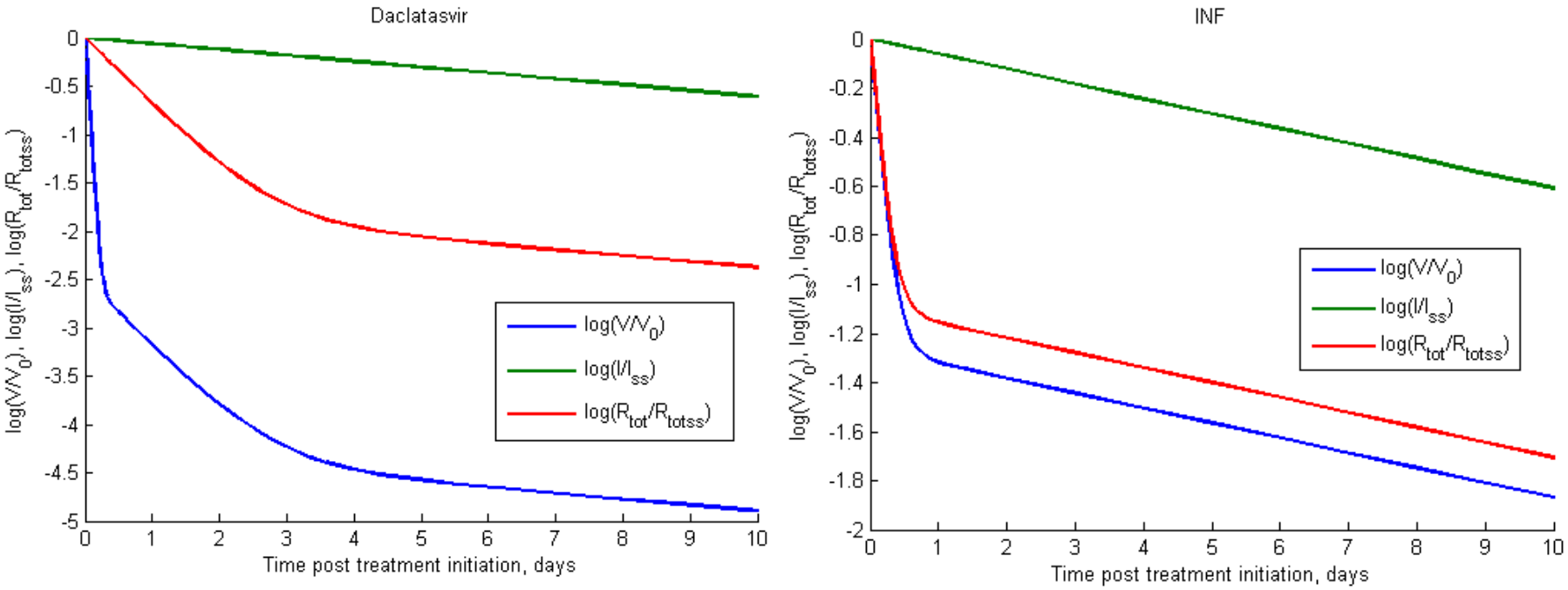


$\alpha = 1, t_0 = 0$



Simulated time courses of viral loads in two patients treated with daclatasvir and INF using multiscale and PSP models. For the original parameters the time courses overlap. They slightly differ if α =1.0.

Time Courses of V, I, and R_{tot}



Simulated time courses of V, I, and R_{tot} in two patients receiving treatment with daclatasvir (left) and INF (right).

Conclusions

- Inclusion intracellular vRNA dynamics in models of HCV infection permits more adequate quantification of drug effects for direct-acting antiviral agents.

- Structure population models integrate in a natural way a single cell model with the total amount of vRNA in infected cells.

- R-structured population model provides almost identical description of the viral load dynamics as the multiscale model.

- PSP model is simpler and more mechanistic than the multiscale model.

Acknowledgments

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