

BACKGROUND

Oncolytic viral therapy represents a promising class of immunotherapy which relies on the ability of the oncolytic virus to selectively replicate in cancer cells leading to direct and/or immune dependent tumor lysis [1].

Although intratumoral (i.t.) administration route is most frequently used, **intravenous (i.v.) administration could expand viral treatment** to less accessible tumors if sufficient viral exposure can be achieved.

The aim of this work was to **develop a mechanistic framework** to quantitatively understand **viral kinetics, dynamics, distribution to tumor lesions and tumor response** of a novel oncolytic virus V937 following i.t. and i.v. administration in human xenograft tumor models in immunodeficient mice.

METHODS

Experimental data

- ❖ **In vitro V937 replication data** (TCID₅₀/mL) in three different cell lines [2] to characterize viral dynamics.
- ❖ **Viral RNA measurements of V937 in serum** (TCID₅₀/mL or copies/mL) and **tumor** (copies/μg RNA) after i.v. administration of a single V937 dose to characterize viral kinetics and distribution to tumor.
- ❖ **Tumor size (mm³) data in control and V937-treated immunodeficient mice** bearing one or two tumor lesions after i.v. or i.t. single administration of V937 [2,3] to characterize drug effect.

Mechanistic-based modelling

- ❖ A **sequential approach** was followed integrating in vitro and in vivo data using NONMEM 7.4 and FOCEI algorithm.
- ❖ The final model (**Figure 1**) accounted for the following **biological processes**:
 - clearance of serum viral load (VL_S)
 - physiologically-based distribution to tumor vasculature
 - proliferation of uninfected tumor cells (uTC)
 - infection of uTC by the viral load present in tumor vasculature (VL_{VAS})
 - viral replication in infected tumor cells (iTC)
 - viral induced death of iTC
- ❖ Simulations and a global sensitivity analysis were performed.

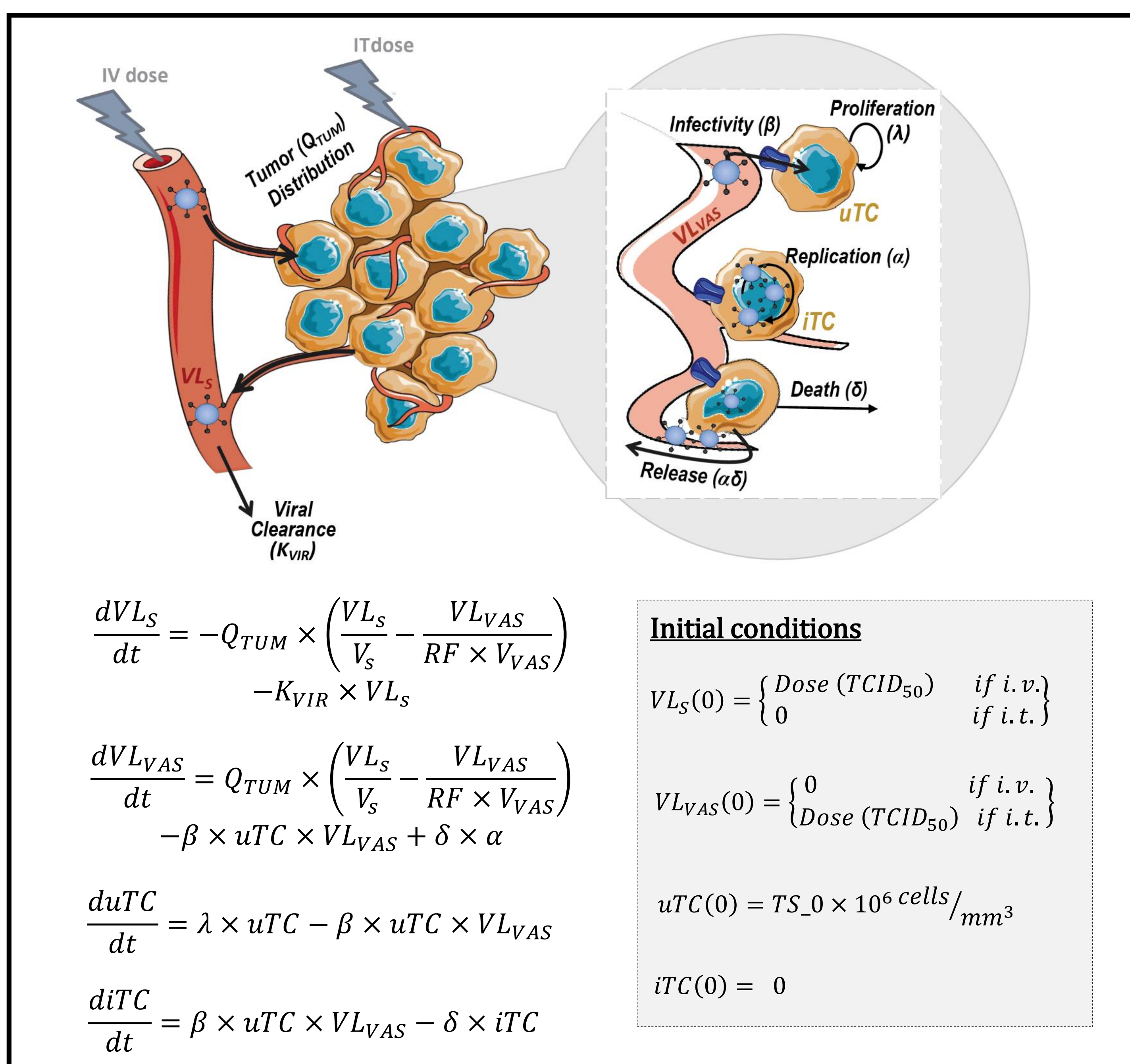


Figure 1. Mathematical and schematic representation of in vivo model. Model entities defined with text. α : Viral particles released per infected cell; β : infectivity rate; δ : Death rate of infected cells in vivo; λ : growth rate; K_{VIR} : viral degradation rate; Q_{TUM} : blood flow to tumor; RF : Retention factor reflecting V937 affinity for the tumor; $TCID_{50}$: half-maximal tissue culture infectious dose; TS_0 : baseline tumor size; V_S : serum volume; V_{VAS} : vasculature volume. Reproduced from Parra-Guillen et al [5]. See publication for in vitro model and parameter estimates.

RESULTS

- ❖ **In vitro estimates** of infection ($\beta=0.489 \times 10^{-8}$ 1/TCID₅₀/h) and replication ($\alpha=208$ copies/cell) **were successfully used** to describe all sources of **in vivo** data (**Figure 2**).
- ❖ Despite the predicted high viral clearance ($t_{1/2}=4.3$ min), **high viral replication was observed resulting in similar tumor shrinkage** with both routes of administration.
- ❖ **Only** increments in viral replication (α), viral infectivity (β) or tumor retention (RF) **were able to modify the course response** (i.e. from non-responders to responders).

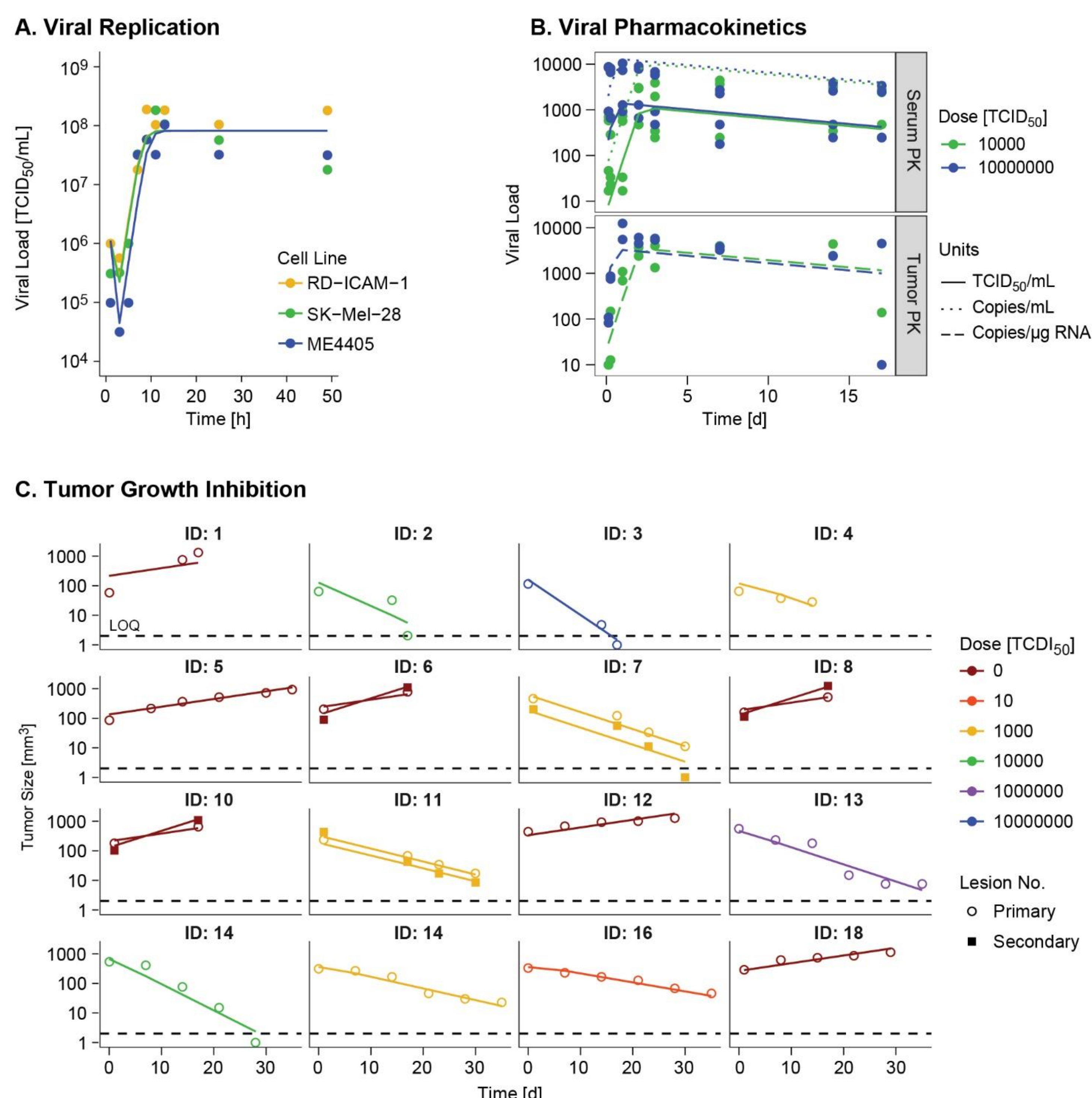
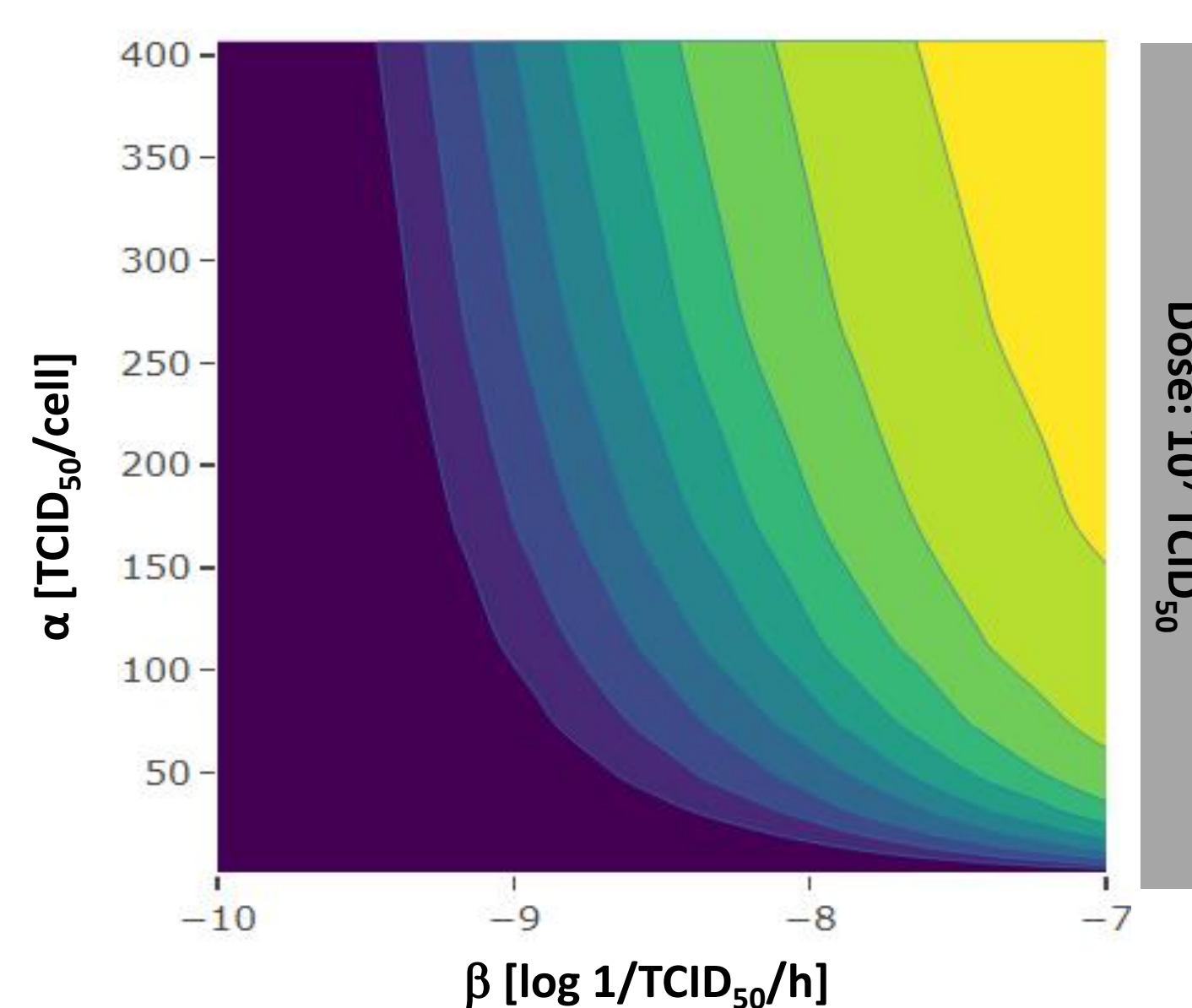


Figure 2. Model evaluation. Model predictions (lines) versus real observations (dots) for (A) in vitro viral replication model and (B) in vivo viral kinetic model at typical level, and (C) tumor growth inhibition model at individual (ID) level. Reproduced from Parra-Guillen et al [5]. See publication for additional information on derivation of predicted variables.



- ❖ Simulations allow us to identify the parameter space where probability of observing tumor response are higher (**Figure 3**).

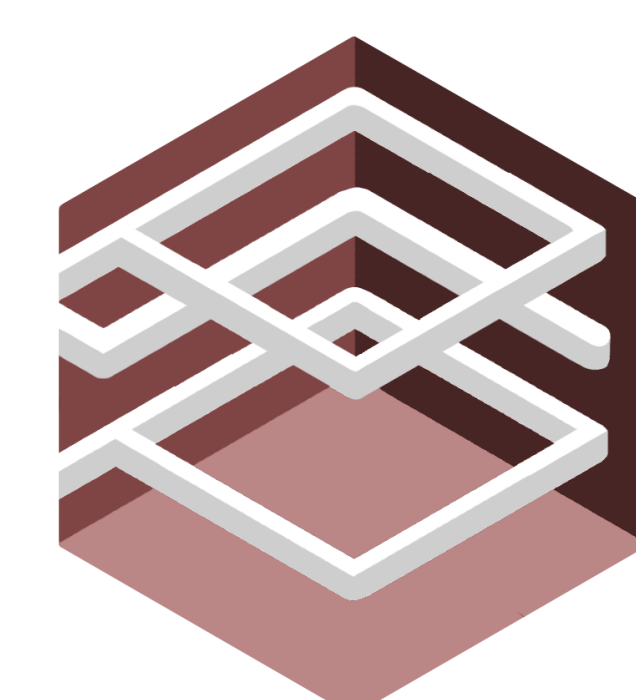
Figure 3. Model applicability. Probability of observing at least 20% of tumor shrinkage at day 14 obtained at different infectivity (β) and replication (α) parameter estimates in a simulated virtual population ($n=1000$) generating when varying all other parameters within a plausible parameter space. Reproduced from Parra-Guillen et al [5]. See publication for additional scenarios.

CONCLUSION

- ❖ First quantitative characterization of viral distribution, replication, and oncolytic effect of a novel oncolytic virus following i.t. and i.v. administrations in the absence of an immune response.
- ❖ This model allows for a better understanding of the role that the different processes play in the final outcome.
- ❖ The model may be expanded to integrate the role of the immune system to support the clinical development of oncolytic viruses.

REFERENCES

- [1] Kaufman et al. Nat Rev Drug Discov (2015)
- [2] Au et al. Int J Oncol (2005)
- [3] Shafren et al. Clin Cancer Res (2004)
- [4] Titze et al. Eur J Pharm Sci (2017)
- [5] Parra-Guillen et al. Front Pharmacol (2021)



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