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Introduction

- Proper understanding of viral dynamics is of key importance to optimizing antiviral therapies and virus-based therapies.
- Studies on phages [1, 2] showed evidence of heterogeneity among target cells that might greatly impact viral dynamics.
- However, target-cell heterogeneity is rarely accounted for in classical modeling approaches.

Aims

Using bacteriophage dynamics as a use-case, we aim to:

- Develop a multi-scale model bridging together single-cell and cell population dynamics.
- Investigate and quantify how single-cell variability impacts cell population dynamics.
- Compare different modeling approaches to help inform model selection in viral dynamics.

Methods

1. Capturing cell-level variability

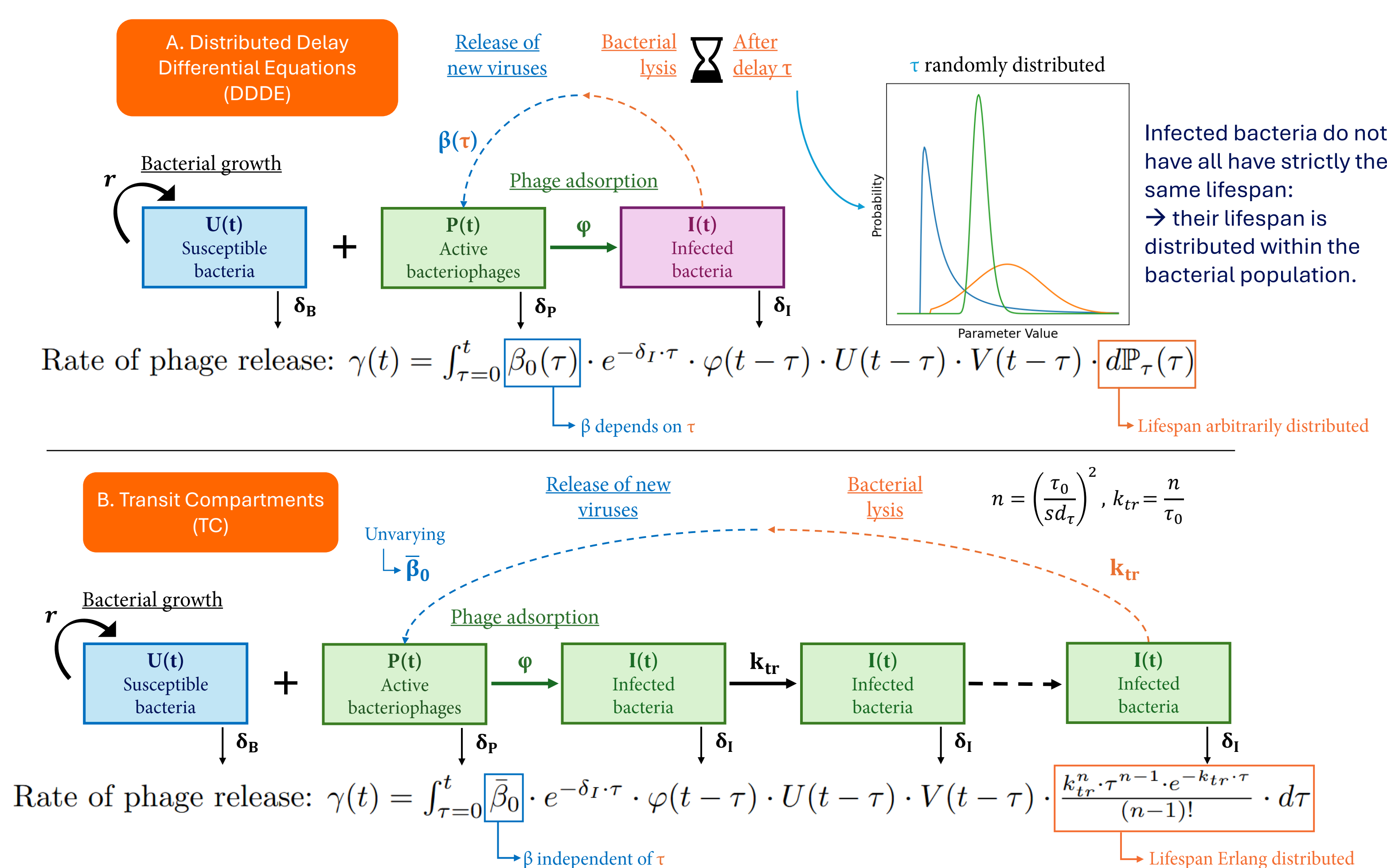


Figure 1. Distributed approaches of bacteriophage dynamics modeling [1, 2].

$$\frac{dU}{dt}(t) = r(t) \cdot U(t) - \varphi_0(t) \cdot U(t) \cdot P(t) - \delta_U \cdot U(t)$$

$$\frac{dI}{dt}(t) = \varphi_0(t) \cdot U(t) \cdot P(t) - \int_{\tau=0}^t e^{-\delta_I \tau} \cdot \varphi_0(t-\tau) \cdot U(t-\tau) \cdot P(t-\tau) \cdot f_{\tau}(\tau) d\tau - \delta_I \cdot I(t)$$

$$\frac{dP}{dt}(t) = \int_{\tau=0}^t \beta_0(\tau) \cdot \varphi_0(t-\tau) \cdot e^{-\delta_I \tau} \cdot U(t-\tau) \cdot P(t-\tau) \cdot f_{\tau}(\tau) d\tau - \varphi_0(t) \cdot [U(t) + I(t)] \cdot P(t) - \delta_P \cdot P(t)$$

2. Modeling the intracellular (IC) viral replication dynamics

- After entering a host bacteria, viruses actively replicate before inducing its lysis after a delay called latent period [3].

$$\beta_0(\tau) = \beta_{max} \frac{e^{r_{\beta}(\tau-D)} - 1}{e^{r_{\beta}(\beta\tau_{50}-D)} + e^{r_{\beta}(\tau-D)} - 2}$$

where $\beta_0(\tau)$ is the mean burst size for a latent period τ ,
 β_{max} : maximal burst size, r_{β} : intracellular replication rate,
 $\beta\tau_{50}$: τ to half β_{max} , D : minimal time to replication.

3. Quantify the impact on population dynamics

- Taking the full DDDE model as reference, we compared the performance of the simpler model structures (DDE / TC).

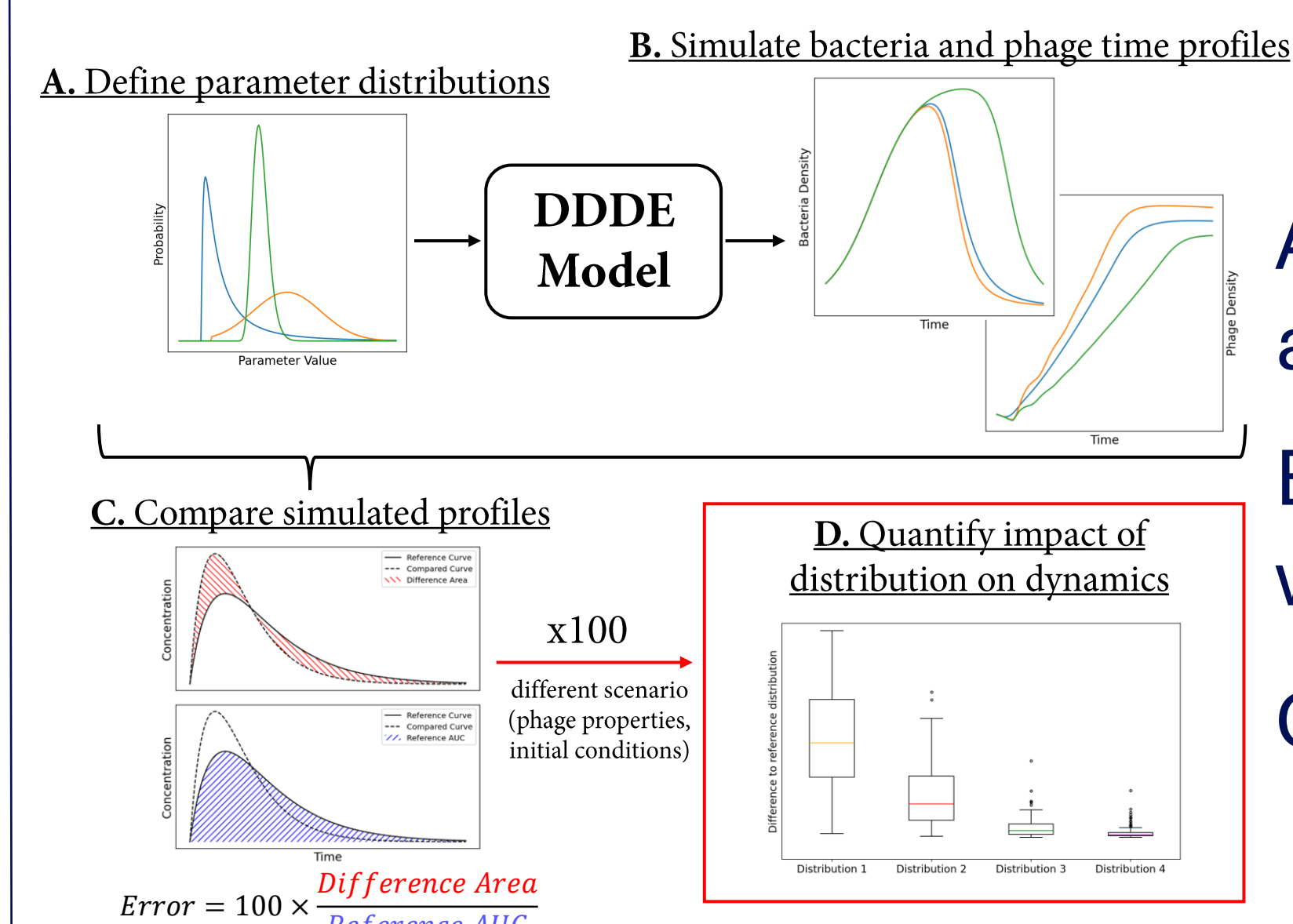


Figure 2. Workflow of the systematic quantification.

Results

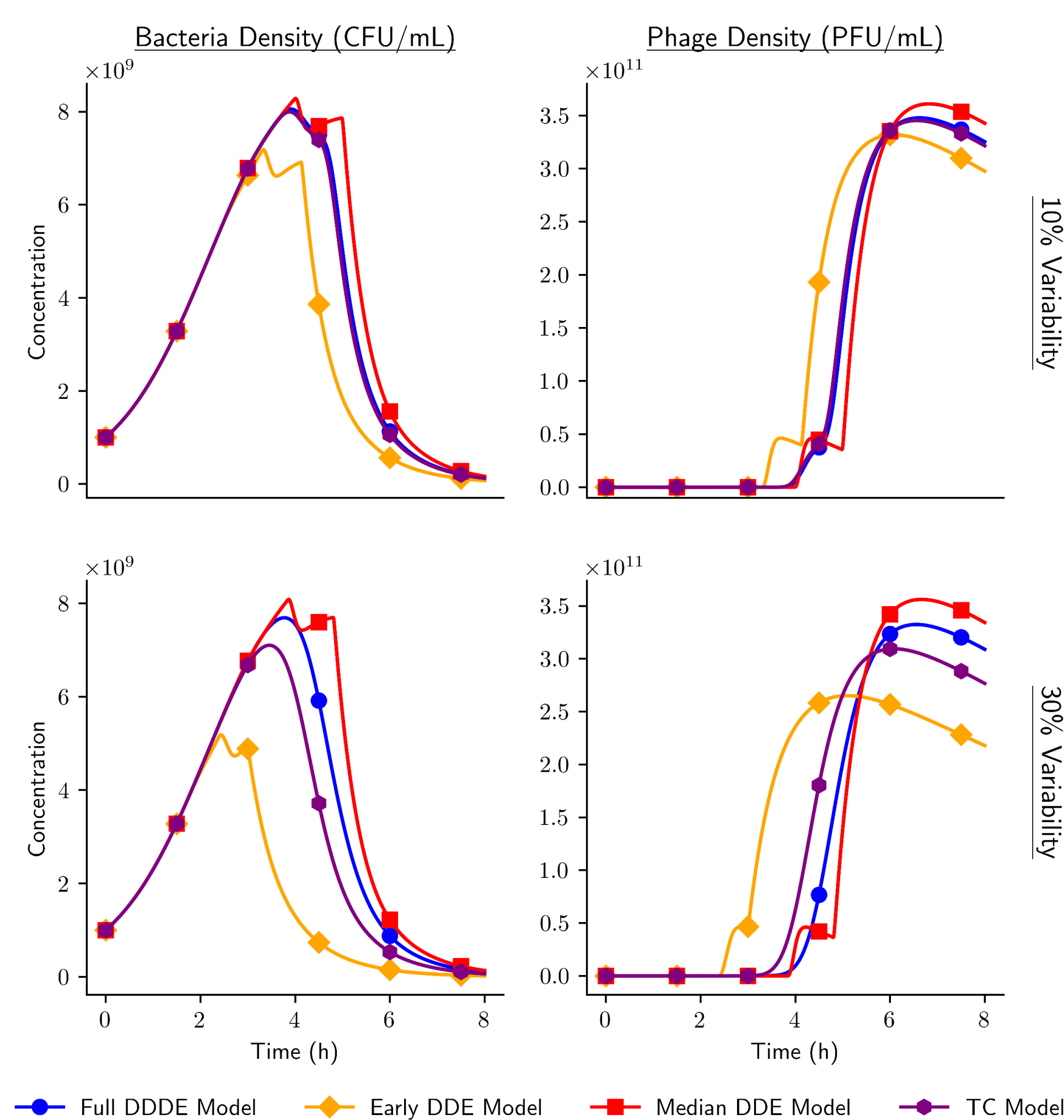


Figure 3. Example of simulated time profiles of bacterial load and phage load for the different model structures explored.

- The Early DDE Model introduces considerable bias ($\geq 20\%$) at all variability levels.
- The Median DDE and TC Models approximate well the full DDDE Model at low variability.
 $\rightarrow$ Error $\leq 10\%$ when $\Delta\tau \leq 20\%$.
- This approximation breaks at higher variability.
 $\rightarrow$ Error $\geq 25\%$ when $\Delta\tau = 50\%$.

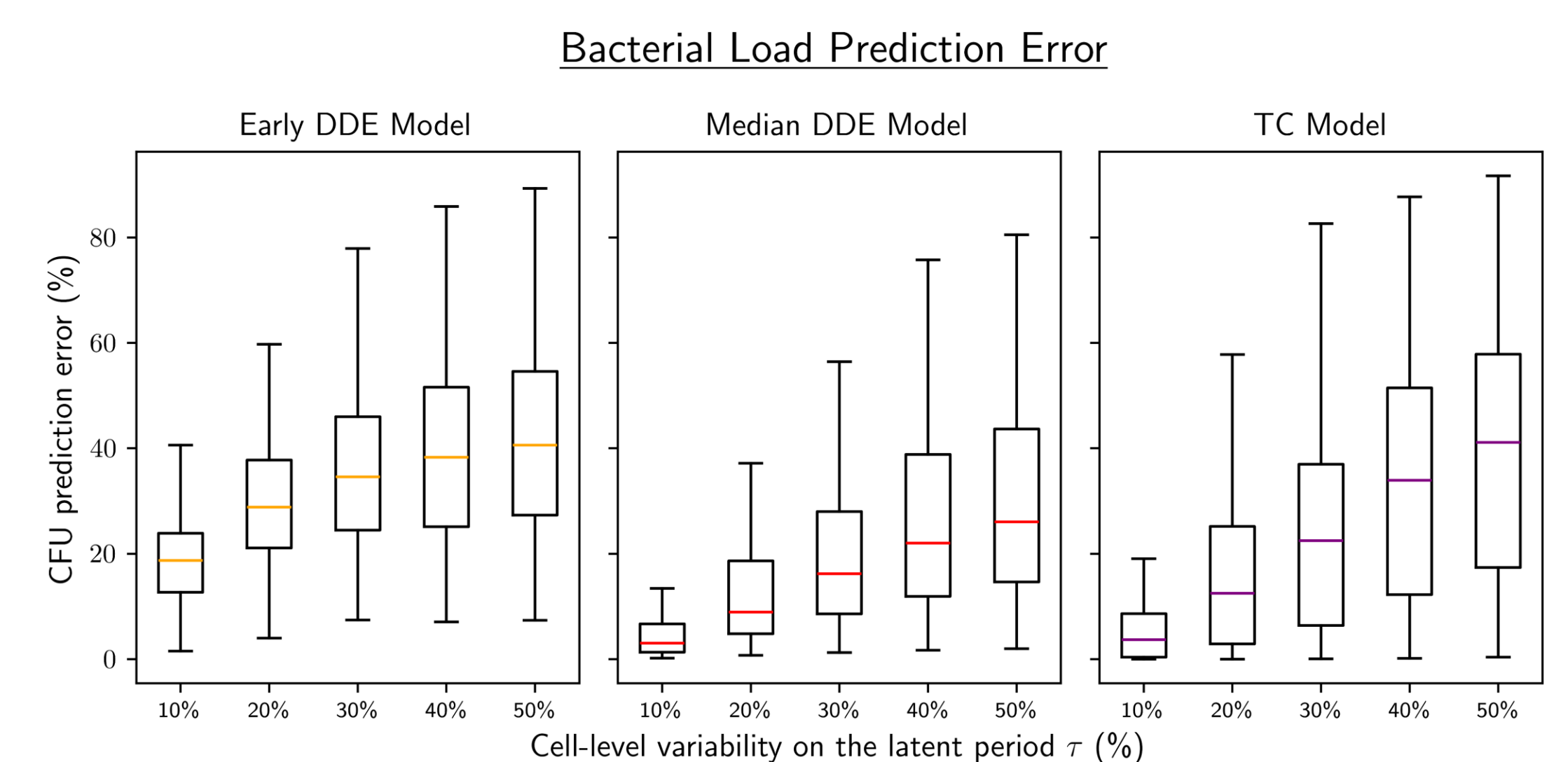


Figure 4. Comparison of bacterial load prediction from the different model structures compared to the full DDDE model with IC replication.

- Left: Early DDE with τ fixed at time of first observed lysis.
- Middle: Median DDE with τ fixed at median lysis time.
- Right: TC with τ Erlang-distributed but no IC dynamics.

Conclusions

- The model successfully described intracellular viral replication and cell-level variability in viral dynamics.
- When using the DDE model, the median (or mean) latent period should be used instead of the early lysis time.
- The DDE and TC models are good approximation at low latent period variability, but the full DDDE model remains warranted at higher variability.