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# Model Averaging in Viral Dynamic Models

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## 13 **Abstract**

14 The paucity of experimental data makes both inference and prediction particularly challenging  
15 in viral dynamic models. In presence of several candidate models, a common strategy is  
16 model selection (MS), in which models are fitted to the data but only results obtained with the  
17 “best model” are presented. However, this approach ignores model uncertainty, which may  
18 lead to inaccurate predictions. When several models provide a good fit to the data, another  
19 approach is model averaging (MA) that weights the predictions of each model according to its  
20 consistency to the data.

21 Here we evaluated by simulations in a nonlinear mixed-effect model framework the  
22 performances of MS and MA in two realistic cases of acute viral infection: i) inference in  
23 presence of poorly identifiable parameters, namely initial viral inoculum and eclipse phase  
24 duration ii) uncertainty on the mechanisms of action of the immune response.

25 MS was associated in some scenarios with a large rate of false selection. This led to a  
26 coverage rate lower than the nominal coverage rate of 0.95 in the majority of cases and below  
27 0.50 in some scenarios. In contrast, MA provided better estimation of parameter uncertainty,  
28 with coverage rates ranging from 0.72 to 0.98 and mostly comprised within the nominal  
29 coverage rate. Finally, MA provided similar predictions than those obtained with MS.

30 In conclusion, parameter estimates obtained with MS should be taken with caution, especially  
31 when several models well describe the data. In this situation, MA has better performances and  
32 could be performed to account for model uncertainty.

33

## 34 **Introduction**

35        Since 1995 and the two seminal papers providing an estimate of the half-life of HIV  
36 particles in blood (1,2), the use of viral dynamic models has considerably expanded.  
37 Applications have been summarized in a recent issue of Immunological Reviews (3), showing  
38 their relevance for understanding the host-pathogen interactions in both chronic and acute  
39 infections (4–6). In the last decade, parameter estimation of these models has increasingly  
40 relied on nonlinear mixed effect models (NLMEM), a statistical approach that improves both  
41 precision and accuracy of estimates by explicitly taking into account the between-subjects  
42 variability in the model (7,8). This is particularly true in the case of antiviral drug  
43 development where NLMEM have become central to support optimal treatment strategies in  
44 presence of a large variability in the response (9,10).

45 Although inference has been greatly facilitated by the use of NLMEM, viral dynamic models  
46 remain often characterized by a lack of theoretical or practical identifiability (7,8). In fact the  
47 availability of powerful algorithms for inference has mechanically led to the development of  
48 increasingly complex models, questioning the reliability of viral kinetic parameter estimates.  
49 In order to improve identifiability of these models, a commonly used strategy is to fix  
50 parameters to plausible values and then to check the impact of these choices by conducting  
51 sensitivity analyses. For instance in acute viral infection, one can fix the initial viral inoculum  
52 or the eclipse phase duration, two parameters that can hardly be estimated using only viral  
53 load data (11,12). Data fitting can also be used to evaluate the plausibility of different  
54 biological assumptions. In that case the usual approach is model selection (MS), where a  
55 predefined set of candidate models are fitted to the data and the model providing the best fit to  
56 the data (based on Akaike or Bayesian Information Criteria) is selected and carried forward in  
57 the analysis. In both contexts, these approaches, by focusing the predictions on a single

58 model, ignore the model uncertainty and may lead to wrong predictions (13) and potentially  
59 inaccurate biological conclusions (14–16).

60 In this paper, we propose to use model averaging (MA) as an alternative approach to MS in  
61 viral dynamics. MA is a conceptually simple approach, where the uncertainty related to each  
62 candidate model is taken into account and predictions associated to each model are weighted  
63 based on their consistency with the data (17,18). Through an extensive simulation study, we  
64 compare parameter estimates and predictive performances of model averaging versus model  
65 selection. We discuss the benefits and limits of model averaging compared to model selection.  
66 Simulations are inspired from recent works in Zika and Ebola virus dynamics (19,20)  
67 representing two typical settings encountered in viral dynamic modeling: i) a set of  
68 parameters are fixed to arbitrary values of a given biological model to ensure identifiability;  
69 ii) model selection relies on the comparison of fitting criterion of a set of pre-defined different  
70 biological models.

71

## 72 **Material and methods**

### 73 **Model selection and model averaging**

74 **Model for the observations.** Let  $Y_{ijm}$  denote the  $j^{\text{th}}$  log viral load measurement of subject  $i$  at  
75 time  $j$ , and suppose that  $m=1,\dots,M$  candidate models can be used to simulate the data. The  
76 model for the observations is defined as:

$$77 \quad Y_{ijm} = \log_{10}[V_m(t_j, \theta_{im})] + e_{ijm} \quad (1)$$

78 where  $V_m$  is the viral load prediction function given by model  $m$ ,  $\theta_{im}$  is the vector of  
79 individual parameters under model  $m$ ,  $t_j$  the time of viral load measurement, assumed to be  
80 similar for all patients and all models, and  $e_{ijm}$  the residual error. Individual parameters  $\theta_{im}$   
81 are log-normally distributed and depend on the vector of fixed effects  $\mu_m$  and the vector of  
82 random effects  $\eta_{im} \sim \mathcal{N}(0, \Omega_m)$  with  $\theta_{im} = \mu_m \times e^{\eta_{im}}$ . The variance-covariance matrix  $\Omega_m$  is  
83 assumed to be diagonal. Residuals errors are assumed to be independent and normally  
84 distributed  $e_{ijm} \sim \mathcal{N}(0, \sigma_m^2)$ . Each biological model  $m$  is therefore associated with a set of  
85 population parameters,  $\Psi_m$ , of dimension  $p_m = \dim(\mu_m, \Omega_m, \sigma_m)$ .

86 **Inference and model selection.** For each candidate model, one can estimate the parameters  
87 using maximum likelihood estimates, providing, for each model, an estimate of the population  
88 parameters, noted  $\hat{\Psi}_m$ . One can also provide the confidence intervals of the parameters of  
89 interest under each model. This can be done using the asymptotic approximation where the  
90 density function of the estimated parameter  $\hat{\Psi}_m$ ,  $p(\hat{\Psi}_m)$ , is assumed to be Gaussian with a  
91 variance-covariance matrix given by the inverse of the Fisher Information Matrix ( $\text{FIM}^{-1}$ ).

92 Then, the most common approach is to select the model that best describes the data. This can  
93 be done using various criteria that rely on penalizations of the log-likelihood (LogL), such as

94 the Akaike information criteria (AIC), the consistent Akaike (CAIC) or the Bayesian  
95 information criteria (BIC) (21–24). In line with previous analysis (25,26), we relied on AIC  
96 given by  $AIC_m = -2\text{LogL}(\hat{\Psi}_m) + 2p_m$ . The analysis then focuses on the results (i.e., parameter  
97 estimates, confidence intervals, and predictions) obtained with the “best” model, i.e., the  
98 model associated with the lowest AIC among the  $m$  candidate models, noted  $AIC_{\min}$ , with  
99 parameter estimates noted  $\hat{\Psi}_{MS}$ .

100 **Model averaging.** As explained above, MS is limited in the sense that it ignores the  
101 uncertainty associated with each model and only focuses on a post hoc selected model (14).

102 Alternatively, one can use model averaging (MA) to take into account the fact that several  
103 candidate models may provide a reasonable fit to the data . In this approach a weight is

104 attributed to each candidate model,  $w_m$ , proportional to AIC, such as  $w_m = \frac{e^{-\frac{\Delta AIC_m}{2}}}{\sum_{m=1}^M e^{-\frac{\Delta AIC_m}{2}}}$  where

105  $\Delta AIC_m = AIC_m - AIC_{\min}$  (14,17,18). In that case the MA estimator of  $\Psi_m$  is given by  $\hat{\Psi}_{MA}$ ,

106 with a density function given by  $p(\hat{\Psi}_{MA}) = \sum_{m=1}^M w_m p(\hat{\Psi}_m)$ . Another approach could be to

107 consider only the models that are responsible for the majority of the weight (0.9 or 0.8), and

108 equally average them (see Discussion section).

109

## 110 **Viral dynamic settings**

111 Our objective is to compare model selection and model averaging in two typical contexts of

112 viral dynamic models. In the first setting, we focus on the issue arising from using model

113 selection when some parameters of the model cannot be identified and are fixed to arbitrary

114 values. In the second setting, we focus on the issue arising from using model selection when

115 several different biological models can be proposed to fit the data.

116 **Setting I: viral dynamic models in presence of poorly identifiable parameters.** We here  
117 focus on the standard target cell limited (TCL) model given by:

$$\frac{dT}{dt} = -\beta TV \quad (2)$$

$$\frac{dI_1}{dt} = \beta TV - kI_1 \quad (3)$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2 \quad (4)$$

$$\frac{dV}{dt} = \pi I_2 - cV \quad (5)$$

$$T_{t=0} = T_0; I_{1,t=0} = 0; I_{2,t=0} = 0; V_{t=0} = V_0$$

118 where, T are the target cells,  $I_1$  the infected cells in eclipse phase,  $I_2$  the productive infected  
119 cells and V the viral load in plasma. The model depends on the following disease parameters:  
120  $\beta$  the infectivity rate constant,  $k$  the eclipse rate,  $\delta$  the infected cell elimination rate,  $\pi$  the viral  
121 production rate constant,  $c$  the clearance of free virus,  $T_0$  the initial number of target cells and  
122  $V_0$  the initial viral load. For the ease of interpretation and fitting, we reparametrized the model  
123 as  $R_0 = \frac{\beta\pi T_0}{c\delta}$ , the basic reproductive ratio, instead of  $\beta$ , where  $R_0$  represents the number of  
124 secondary infection caused by one infected cells when the target cells are abundant. For the  
125 sake of simplificty we focused here on a simple, exponentially distributed, duration for the  
126 eclipse phase, but more complex models can be considered (27).

127 Not all parameters of the TCL model can be uniquely identified when only the viral load data  
128 are available (28–30) and this issue is not circumvented when parameters are estimated using  
129 NLMEM. This can be shown by analyzing the expected standard errors obtained with the  
130 approximated Fisher Information Matrix (<http://www.pfim.biostat.fr/>; see more details in  
131 (30)). Table I provides the expected standard errors obtained with 30 individuals sampled 3  
132 days from day 3 up to day 18 post infection using typical parameter values close to those  
133 found during Zika infection in nonhuman primates (19). Although being theoretically  
134 identifiable, several parameters are associated with a very large expected standard error. This



135 can be corrected by fixing  $V_0$  and  $k$  to some arbitrary values, leading to expected relative  
136 standard errors lower than 30% for all parameter values. We here aim to evaluate the impact  
137 of the choice of  $k$  and  $V_0$  on parameter estimates.

138 We also conducted a sensitivity analysis on the parameters variability of setting I ( $k=4 \text{ d}^{-1}$  and  
139  $V_0=10^{-4} \text{ copies.mL}^{-1}$ ). We reported the influence of lower and higher variabilities ( $\omega=0.1$  and  
140  $\omega=1$ , respectively) on the performances of MS and MA.

141

142 **Setting II: viral dynamic models including the immune response.** In order to evaluate the  
143 impact of testing different biological assumptions in parameter estimates and predictions, we  
144 considered 4 additional models integrating the role of innate or adaptive immune response in  
145 the control of viral replication and inspired from the models used to describe Ebola infection  
146 in nonhuman primates (20). These models extend the TCL model with an additional  
147 compartment, noted F. This compartment is not observed and can therefore represent any  
148 biological entity involved in viral clearance, such as cytokine, macrophages, T-cell or  
149 antibodies (5,32,33). We assumed that F is produced at a rate  $q$  proportional to the number of  
150 productively infected cells,  $I_2$ , and is eliminated at a rate  $d_F$  (20). Thus F could either i)  
151 increase the number of refractory infected cells (refractory model, R), ii) decrease the viral  
152 production (production inhibition model, PI), iii) increase the clearance of productive infected  
153 cells (cytotoxic model, C) or iv) increase the clearance of the virus (virus-killing model, V).  
154 In all models, the effects of F followed an  $E_{\max}$  relationship with  $\phi$  the maximal effect of F  
155 and  $\theta$  the sensitivity parameter. Table II displays the four model equations.

156

## 157 **Simulations and parameter estimation**

158 For each setting, the simulation procedure and parameter estimation under both MS  
159 and MA are described below.

160 **Parameter values.** In the first setting, we aimed to evaluate the impact of fixing the two  
161 poorly identifiable parameters,  $k$  and  $V_0$ , in the target cell limited model. For that purpose we  
162 defined a set of  $M=9$  candidate models with values for  $V_0$  and  $k$  equal to  $V_0 = 10^{-5}; 10^{-4}$  or  $10^{-3}$   
163  $\text{copies.mL}^{-1}$  and  $k = 1; 4$  or  $20 \text{ d}^{-1}$ . The other parameter values are given in Table III. Figure  
164 1A shows that viral load is biphasic with a peak close to  $10 \log_{10} \text{copies.mL}^{-1}$  in all 9  
165 scenarios, but the time to peak depends on  $k$  and  $V_0$  to a lesser extent.

166 In the second setting  $V_0$  and  $k$  were fixed to  $10^{-4} \text{ copies mL}^{-1}$  and  $4 \text{ d}^{-1}$ , respectively. To  
167 ensure a fair comparison between the models, parameters were chosen to predict a similar  
168 contribution of the immune response to viral control, as measured by the area under the curve  
169 of the  $\log_{10}$  viremia from 0 to 20 days (AUC). Thus, in all four models, the parameter values  
170 were such that  $\text{AUC}=100 \log_{10} \text{copies.days.mL}^{-1}$  while assuming  $\phi^* = 0$  would lead to AUC  
171  $120 \log_{10} \text{copies.days.mL}^{-1}$  (i.e., the absence of an immune system would lead to a 20%  
172 increase in AUC) (Figure 1B). The values of the TCL model were chosen to lead to a similar  
173  $\text{AUC}=100 \log_{10} \text{copies.days.mL}^{-1}$ .

174 We assumed that  $R_0$ ,  $\delta$ ,  $\pi$ ,  $\theta$  and  $\phi$  were the estimated fixed effects. Those parameters,  
175 with the exception of  $\theta$ , were associated to an intermediate between-subject variability,  $\omega$ ,  
176 equal to 0.3. Other parameters were assumed to be known with values given in Table III.

177 **Data simulation.** For each model we simulated  $S=300$  datasets of  $N=30$  individuals using the  
178 same population parameter values,  $\Psi_m^*$ , given in Table III. Therefore  $S \times M = 2700$  datasets  
179 were simulated in the setting I, and 1500 datasets were simulated in the setting II. We  
180 assumed measurements were made at days 3, 6, 9, 12, 15 and 18, with a lower limit of

181 quantification (LLOQ) of  $1 \log_{10} \text{copies.mL}^{-1}$  (20), and a measurement error term,  $\sigma$ , equal to  
182  $0.7 \log_{10} \text{copies.mL}^{-1}$ .

183 **Parameter estimation.** Each of the  $s=1, \dots, S$  dataset, was fitted using the  $M$  candidate  
184 models of each setting. The set of parameter estimates obtained on the dataset  $s$  using the  
185 model  $m$ , namely  $R_0$ ,  $\delta$ ,  $\pi$ ,  $\theta$  and  $\phi$  and their corresponding between-subjects variabilities if  
186 specified, was noted without loss of generality  $\hat{\Psi}_m^s$ . Parameter estimates were obtained by  
187 maximization of the likelihood using the SAEM algorithm implemented in the MONOLIX  
188 software (version 2018, release 2). We used  $k_1=800$  and  $k_2=200$  iterations for the exploratory  
189 and smoothing phases, respectively. We used the asymptotic approximation to derive the  
190 probability density function of  $\hat{\Psi}_m^s$ , noted  $p(\hat{\Psi}_m^s)$ , assumed to be Gaussian with a variance-  
191 covariance matrix given by the inverse of the Fisher Information Matrix ( $\text{FIM}^{-1}$ ). The FIM  
192 was computed by stochastic approximation with at least 100 and up to 800 iterations. Of note,  
193 among the  $M$  models used to fit the data, only one is the true model (noted TM), i.e., the  
194 model used to generate the data, and we note  $\hat{\Psi}_{TM}^s$  the parameter estimates obtained by fitting  
195 the dataset  $s$  with TM.

196 For MA, 95% confidence intervals of  $\hat{\Psi}_{MA}^s$  was then calculated by sampling 10,000 values in  
197 the mixture distribution  $p(\hat{\Psi}_{MA}^s) = \sum_{m=1}^M w_m^s p(\hat{\Psi}_m^s)$  and computing the associated 2.5<sup>th</sup> and  
198 97.5<sup>th</sup> percentiles (14,18,34).

199

## 200 **Performances of model averaging and model selection for estimation**

201 **Model selection.** For each scenario, we reported the distribution weight of each candidate  
202 model as well as the proportion of simulations where each candidate model was selected  
203 (based on AIC, see above).

204 **Parameter estimates and comparison with true parameter value.** For each scenario, we  
205 reported the coverage rate obtained for each parameter with estimator based on MS, MA or  
206 TM, defined as the proportion of simulated datasets for which the true value of the parameter  
207 was contained in the 95% confidence interval of the estimated parameter. The coverage rates  
208 were compared with the prediction interval of a Binomial distribution with  $p=0.95$  and  $S=300$ ,  
209 i.e.,  $[0.923; 0.973]$  and were reported for parameters  $R_0$ ,  $\pi$  and  $\delta$  in setting I and  $R_0$  and  $\delta$  in  
210 setting II.

211

## 212 **Performances of model averaging and model selection for prediction**

213 Finally, we aimed to evaluate MA in the context of prediction, i.e., the capability to anticipate  
214 the effect of a change in the experimental setting. We focused on the prediction of the impact  
215 of an antiviral treatment limiting the viral production  $\pi$  with efficacy  $\varepsilon$  ( $0 < \varepsilon < 1$ ) on the  
216 predicted proportion of patients with undetectable viral load ( $10 \text{ copies mL}^{-1}$ ) at a given time  
217 point. We assumed that treatment was initiated at time  $t=6$  and lasted until  $t=20$  days, which  
218 coincides with the end of the follow-up. We considered 3 levels of efficacy on decreasing  
219 viral production with a factor  $1 - \varepsilon$ , namely  $\varepsilon = 0.90, 0.95$  and  $0.99$ , and we focused on the  
220 prediction at  $t=20$ . For each model and each value of  $\varepsilon$ , Monte-Carlo simulations were used to  
221 the expected proportion of patients below the limit of detection noted  $P_m^{*,\varepsilon}(\%) =$   
222  $P[V_m(t = 20, \Psi_m^*, \varepsilon) < 10]$ .

223 Following what has been done above, one can calculate, for each simulated dataset, the  
224 estimate that would be given by model selection, given by  $P_{MS}^{S,\varepsilon} = P[V_{MS}(t = 20, \hat{\Psi}_{MS}^S, \varepsilon) <$   
225  $10]$  or by model averaging  $P_{MA}^{S,\varepsilon} = \sum_{m=1}^M w_m^S P[V_m(t = 20, \hat{\Psi}_m^S, \varepsilon) < 10]$ . Likewise for the  
226 sake of comparison, one can also calculate the probability obtained by fitting the data under

227 the true model,  $P_{TM}^{s,\varepsilon} = P[V_m(t = 20, \hat{\Psi}_{TM}^s, \varepsilon) < 10]$ . These values were summarized by  
228 calculating the bias and root mean square error (RMSE), given by  $\frac{1}{S}\sum(P_{MA}^{s,\varepsilon} - P_m^{*,\varepsilon})$  and  
229  $\sqrt{\frac{1}{S}\sum(P_{MA}^{s,\varepsilon} - P_m^{*,\varepsilon})^2}$  in the case of MA (similar applies to calculate the bias and RMSE in the  
230 case of MS or TM). For the sake of graphical representation, proportions of patients below the  
231 limit of detection were presented as percentages and biases and RMSE were therefore  
232 expressed in percentages.

233

## 234 **Results**

### 235 **Setting I**

236 The first setting focused on the comparison between model averaging and model  
237 selection when parameters of the model (e.g., the eclipse phase,  $k$ , and the initial inoculum  $V_0$ )  
238 cannot be identified and are fixed to arbitrary values (see Table III).

239 Overall, the true set of parameter values was selected up to 62% of the simulations. The  
240 two parameters did not have the same rate of selection, with the correct values for  $k$  and  $V_0$   
241 being selected up to 71% and 96%, respectively (Figure 2A). Although the true model was not  
242 systematically associated with the lowest AIC, it was associated in all scenarios with the  
243 largest weight among the candidate models with a median value comprised between 0.32 and  
244 0.55 (Figure 2B). In all cases considered, at least two models had a weight greater than 0.20.

245 We next evaluated the impact of these results on parameter estimates and coverage rates.  
246 The estimation of  $R_0$  using model selection was associated with a poor coverage rate between  
247 0.46 and 0.63 (Figure 3). Results for the loss rate of infected cells,  $\delta$ , were better with a  
248 coverage rate ranging from 0.53 and 0.94, and was comprised in the nominal 0.95 coverage

249 rate in 3 out of 9 scenarios. For the viral production  $\pi$ , MS showed coverage rates ranging  
250 from 0.68 and 0.96, and was comprised in the nominal 0.95 coverage rate in 5 out of 9  
251 scenarios. Model averaging largely improved the coverage rates for all parameters and gave  
252 results close to those obtained with the true model. The coverage rates was between 0.91 and  
253 0.98 for  $R_0$ , between 0.72 and 0.95 for  $\delta$  and between 0.78 and 0.98 for  $\pi$ . Further the  
254 coverage rates were comprised in the nominal 0.95 coverage rate in 7 out 9 scenarios for  $R_0$   
255 and 5 out of 9 scenarios for  $\delta$  and  $\pi$ . All confidence intervals can be found in supplemental  
256 figures S1, S2 and S3.

257 Lastly we explored the effect of simulating with less ( $\omega=0.1$ ) or more ( $\omega=1$ ) inter-  
258 subjects variability. In both cases, MS provided subnominal coverage rates but MA corrected  
259 them (see Supplemental Figure S4). Eventually, we observed poorer coverage rates with  
260  $\omega=0.1$  and improved with  $\omega=1$  compared to  $\omega=0.3$ .

261

## 262 **Setting II**

263 In the second setting, we assessed the properties of parameter estimates when several  
264 biological models can be proposed. We focused on models characterizing the effect of the  
265 immune response, considering that the immune response compartment could alternatively  
266 make cells refractory to infection, limit the production of virus, increase the elimination of  
267 infected cells or increase the elimination of free virions (see Table III).

268 Unlike what was found in the previous setting, the chance of selecting the true model was  
269 largely dependent on the model considered. In fact these chances were equal to 97% for the  
270 refractory model but this percentage could decrease to 58% with the cytotoxic model (Figure  
271 4A). Conversely, the models were also associated with a large rate of false selection with rates

272 ranging from 3 to 10% for the refractory model, and up to 20% for the production inhibition  
273 model. In the case of the target cell limited model, the chances of correctly selecting it were  
274 equal to 88% and the rate of false selection were ranging from 1 to 19%. The median weight  
275 associated to the true model ranged from 0.43 to 0.99 (Figure 4B).

276

277 Accordingly, MS provided satisfactory coverage rates for target cell limited and  
278 refractory model (Figure 5); however it failed to achieve the nominal coverage rate in all other  
279 models, with values ranging from 0.62 to 0.91 for  $R_0$  and from 0.50 to 0.89 for  $\delta$ . This could  
280 be improved by taking into account model uncertainty and using model averaging. Indeed the  
281 coverage rates ranged from 0.86 to 0.99 for both parameters in all models considered. In fact,  
282 MA had even better performances than the true model in some cases, which achieved  
283 subnominal coverage rate in 3 of the 5 considered scenarios (Figure 5). All confidence  
284 intervals can be found in supplemental figures S5 and S6.

285

286 Finally, we compared the predictive performances of MS, MA and the true model. For  
287 that purpose, we predicted the effect of a putative antiviral treatment on the proportion of  
288 patients having undetectable viremia at end of follow up (day 20). Here as well the  
289 performances obtained using model selection and model averaging were compared. In all  
290 cases, the percentage of undetectable viral loads at end of treatment was accurately predicted  
291 for both MS and MA, with no more than 4% of bias in all cases considered (Figure 6). In term  
292 of precision of estimation, the results were also largely similar in most scenarios, with RMSE  
293 ranging from 0.4 to 30.5% in all cases. In one case, namely  $\varepsilon=0.95$ , we found that MA  
294 outperformed the results obtained by MS. Here as well, the results obtained by model  
295 averaging were largely comparable with those obtained with the true model.

## 296 **Discussion**

297 The objective of this study was to compare the estimation and the predictive  
298 performances of model selection and model averaging in the context of viral dynamic models.  
299 We explored two frequent issues encountered when developing viral dynamic models with  
300 uncertainty related either to (I) unidentifiable parameters or (II) the presence of several  
301 candidate biological models. In the two settings MS provided poor coverage rates of typical  
302 parameters. This stems from the fact that MS neglects model uncertainty and focuses on one  
303 single “best model”, leading to overconfidence in the parameter estimates. This can be  
304 corrected under certain conditions using MA, which provided better coverage rates and  
305 achieved the nominal coverage rate in most scenarios studied. MA can also be relevant to  
306 predict the effect of intervention, such as the percentage of patients that would achieve  
307 undetectable viral loads during treatment. Thus extending results found in other contexts, in  
308 particular dose finding studies (25,35).

309 By offering a simple framework to take into account model uncertainty, MA accounts for the  
310 fact that in many situations several biological models are plausible. Our study shows the  
311 limitations of reporting only the best model. For instance, in the case of the target cell limited  
312 model, we found that the chance to conclude wrongly to an immune response controlling the  
313 infection was equal to 11%. In the case of the refractory model, which has been proposed as a  
314 driving force in several acute infection (33,36), our results were more reassuring, with a rate  
315 of false rejection of only 3%. This risk was larger with other models integrating an immune  
316 response, with rates of false rejection greater than 60% in some cases. By weighing the  
317 predictions of alternative models, MA avoids the caveat of MS. As advocated in other  
318 contexts (37,38), MA can be used to more transparently discuss model uncertainty and to  
319 stimulate new data acquisition (13).



320           Although MA offers a simple alternative to MS, it also presents the defects of its  
321 virtue. As MA weighs the models according to their information criterion, using MA is  
322 relevant only if one model does not largely outperform the others. The weight value leading to  
323 “outperformance” is arbitrary, and depends also on the number of candidate models.  
324 Accordingly, one may question the need to use weights when making predictions. As  
325 suggested by a reviewer, we conducted a simulation where all models having a weight greater  
326 than a given threshold (0.1 or 0.2) were considered as equally likely in the prediction, and this  
327 approach provided results close to those obtained with MA (Supplemental Figure S7).  
328 MA still requires to make important assumptions that need to be kept in mind. First we used  
329 the asymptotic Gaussian approximations to calculate the standard errors. This assumption  
330 may not hold for all models, depending on their complexity and data paucity, as can be seen  
331 in some cases of Figures 3 & 5. Other approaches have been proposed in the context of  
332 NLMEM to calculate the standard error more precisely, such as bootstrapping (38), sampling  
333 importance resampling (39) or Hamiltonian Monte-Carlo methods (HMC) (40). Future work  
334 will be needed to evaluate in which contexts these methods, which are computationally  
335 demanding, are beneficial. Second in our simulations, we assumed that there was a true model  
336 and that it was part of the candidate models. Although there is no “true model” in real data,  
337 we made this hypothesis to stress that MA should be performed only with biologically  
338 relevant models. Likewise, MA should not be used to “blindly” average predictions of any  
339 models and modelers should, prior to the analysis, develop other models at hand and, if  
340 possible, discuss and perform new experiments to discriminate between them (13). In that  
341 perspective, using MA to calculate CI is meaningful only if parameter have the same  
342 interpretation across the candidate models. This is the case for half-life or viral production  
343 rates but is less evident for derived parameters such the basic reproductive number  $R_0$  (39,40).  
344 Finally, MA does not substitute to a proper analysis of parameter identifiability. In fact the

345 differences between MA and MS may simply reveal a poor practical identifiability, i.e., the  
346 fact that data available are not sufficient to precisely estimate parameters (8) and/or that the  
347 biological question is wrongly formulated (13). This is also what we observed here, with the  
348 wrong selection of models being in part due to the fact that the models had a poor practical  
349 identifiability, at least for some parameters. In order to be performant, MA requires that only  
350 a limited number of models are tested. It is only when a reasonable number of models remain  
351 that MA can be relevant, as an alternative to Bayesian approaches, that may be tedious in  
352 particular a non-linear mixed effect framework.

353

## 354 **Acknowledgments**

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358 Lionel de la Tribouille for the use of CATIBioMed calculus facility.

359

## 360 **Supplemental information**

361 A readily usable R code to compute weights and confidence intervals in MA is provided in  
362 supplementary material. The example is based on digitized Zika data of Best et al. *PNAS* 2017  
363 and illustrates model averaging in the context of poorly identifiable parameters (setting I).

364

365 **References**

- 366 1. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid  
367 turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*. 1995 Jan  
368 12;373(6510):123–6.
- 369 2. Wei X, Ghosh SK, Taylor ME, Johnson VA, Emini EA, Deutsch P, et al. Viral dynamics  
370 in human immunodeficiency virus type 1 infection. *Nature*. 1995 Jan 12;373(6510):117–  
371 22.
- 372 3. Perelson AS, Ribeiro RM. Introduction to modeling viral infections and immunity.  
373 *Immunological Reviews*. 2018;285(1):5–8.
- 374 4. Perelson AS. Modelling viral and immune system dynamics. *Nat Rev Immunol*. 2002  
375 Jan;2(1):28–36.
- 376 5. Best K, Perelson AS. Mathematical modeling of within-host Zika virus dynamics.  
377 *Immunological Reviews*. 2018;285(1):81–96.
- 378 6. Ciupe SM. Modeling the dynamics of hepatitis B infection, immunity, and drug therapy.  
379 *Immunological Reviews*. 2018;285(1):38–54.
- 380 7. Lavielle M, Mentré F. Estimation of population pharmacokinetic parameters of  
381 saquinavir in HIV patients with the MONOLIX software. *J Pharmacokinet  
382 Pharmacodyn*. 2007 Apr;34(2):229–49.
- 383 8. Guedj J, Thiébaud R, Commenges D. Practical identifiability of HIV dynamics models.  
384 *Bulletin of Mathematical Biology*. 2007 Oct 25;69(8):2493–513.
- 385 9. Snoeck E, Chanu P, Lavielle M, Jacqmin P, Jonsson EN, Jorga K, et al. A  
386 comprehensive Hepatitis C viral kinetic model explaining cure. *Clinical Pharmacology  
387 & Therapeutics*. 2010 Jun;87(6):706–13.
- 388 10. Nguyen T, Guedj J. HCV kinetic models and their implications in drug development:  
389 HCV kinetic models and their implications. *CPT: Pharmacometrics & Systems  
390 Pharmacology*. 2015 Apr;4(4):231–42.
- 391 11. Handel A, Longini IM, Antia R. Towards a quantitative understanding of the within-host  
392 dynamics of influenza A infections. *Journal of The Royal Society Interface*. 2010 Jan  
393 6;7(42):35–47.
- 394 12. Smith AM, Adler FR, Ribeiro RM, Gutenkunst RN, McAuley JL, McCullers JA, et al.  
395 Kinetics of coinfection with influenza A virus and streptococcus pneumoniae. Grenfell  
396 BT, editor. *PLoS Pathogens*. 2013 Mar 21;9(3):e1003238.
- 397 13. Ganusov VV. Strong inference in mathematical modeling: a method for robust science in  
398 the twenty-first century. *Frontiers in Microbiology* [Internet]. 2016 Jul 22 [cited 2019  
399 Apr 4];7. Available from:  
400 <http://journal.frontiersin.org/Article/10.3389/fmicb.2016.01131/abstract>

- 401 14. Buckland ST, Burnham KP, Augustin NH. Model selection: an integral part of inference.  
402 *Biometrics*. 1997 Jun;53(2):603.
- 403 15. Boulesteix A-L. Ten simple rules for reducing overoptimistic reporting in  
404 methodological computational research. Lewitter F, editor. *PLOS Computational*  
405 *Biology*. 2015 Apr 23;11(4):e1004191.
- 406 16. Kirk PDW, Babbie AC, Stumpf MPH. Systems biology (un)certainties. *Science*. 2015  
407 Oct 23;350(6259):386–8.
- 408 17. Burnham KP, Anderson DR. Model selection and multimodel inference: a practical  
409 information-theoretic approach. 2. ed., [4. printing]. New York, NY: Springer; 2010. 488  
410 p.
- 411 18. Claeskens G, Hjort NL. Model selection and model averaging [Internet]. Cambridge:  
412 Cambridge University Press; 2008 [cited 2019 Sep 30]. Available from:  
413 <http://ebooks.cambridge.org/ref/id/CBO9780511790485>
- 414 19. Best K, Guedj J, Madelain V, de Lamballerie X, Lim S-Y, Osuna CE, et al. Zika plasma  
415 viral dynamics in nonhuman primates provides insights into early infection and antiviral  
416 strategies. *Proceedings of the National Academy of Sciences*. 2017 Aug  
417 15;114(33):8847–52.
- 418 20. Madelain V, Baize S, Jacquot F, Reynard S, Fizet A, Barron S, et al. Ebola viral  
419 dynamics in nonhuman primates provides insights into virus immuno-pathogenesis and  
420 antiviral strategies. *Nature Communications*. 2018 Dec;9(1).
- 421 21. Bertrand J, Comets E, Mentré F. Comparison of model-based tests and selection  
422 strategies to detect genetic polymorphisms influencing pharmacokinetic parameters.  
423 *Journal of Biopharmaceutical Statistics*. 2008 Nov 7;18(6):1084–102.
- 424 22. Bozdogan H. Model selection and Akaike's Information Criterion (AIC): The general  
425 theory and its analytical extensions. *Psychometrika*. 1987 Sep;52(3):345–70.
- 426 23. Anderson DR, Burnham KP. Understanding information criteria for selection among  
427 capture-recapture or ring recovery models. *Bird Study*. 1999 Jan;46(sup1):S14–21.
- 428 24. Neath AA, Cavanaugh JE. The Bayesian information criterion: background, derivation,  
429 and applications: The Bayesian information criterion. *WIREs Comp Stat*. 2012  
430 Mar;4(2):199–203.
- 431 25. Buatois S, Ueckert S, Frey N, Retout S, Mentré F. Comparison of model averaging and  
432 model selection in dose finding trials analyzed by nonlinear mixed effect models. *AAPS*  
433 *J*. 2018 29;20(3):56.
- 434 26. Aoki Y, Röshammar D, Hamrén B, Hooker AC. Model selection and averaging of  
435 nonlinear mixed-effect models for robust phase III dose selection. *J Pharmacokinet*  
436 *Pharmacodyn*. 2017 Dec;44(6):581–97.
- 437 27. Kakizoe Y, Nakaoka S, Beauchemin CAA, Morita S, Mori H, Igarashi T, et al. A  
438 method to determine the duration of the eclipse phase for in vitro infection with a highly  
439 pathogenic SHIV strain. *Sci Rep*. 2015 Sep;5(1):10371.

- 440 28. Xia X, Moog CH. Identifiability of nonlinear systems with application to HIV/AIDS  
441 models. *IEEE Transactions on Automatic Control*. 2003 Feb;48(2):330–6.
- 442 29. Wu H, Zhu H, Miao H, Perelson AS. Parameter identifiability and estimation of  
443 HIV/AIDS dynamic models. *Bulletin of Mathematical Biology*. 2008 Apr;70(3):785–99.
- 444 30. Miao H, Dykes C, Demeter LM, Cavanaugh J, Park SY, Perelson AS, et al. Modeling  
445 and estimation of kinetic parameters and replicative fitness of HIV-1 from flow-  
446 cytometry-based growth competition experiments. *Bulletin of Mathematical Biology*.  
447 2008 Aug;70(6):1749–71.
- 448 31. Dumont C, Lestini G, Le Nagard H, Mentré F, Comets E, Nguyen TT, et al. PFIM 4.0,  
449 an extended R program for design evaluation and optimization in nonlinear mixed-effect  
450 models. *Computer Methods and Programs in Biomedicine*. 2018 Mar;156:217–29.
- 451 32. Baccam P, Beauchemin C, Macken CA, Hayden FG, Perelson AS. Kinetics of influenza  
452 A virus infection in humans. *J Virol*. 2006 Aug;80(15):7590–9.
- 453 33. Pawelek KA, Huynh GT, Quinlivan M, Cullinane A, Rong L, Perelson AS. Modeling  
454 within-host dynamics of influenza virus infection including immune responses. *PLoS*  
455 *Comput Biol* [Internet]. 2012 Jun 28 [cited 2019 Jun 26];8(6). Available from:  
456 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3386161/>
- 457 34. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model  
458 uncertainty using general parametric models. *Statist Med*. 2014 May 10;33(10):1646–61.
- 459 35. Schorning K, Bornkamp B, Bretz F, Dette H. Model selection versus model averaging in  
460 dose finding studies: K. SCHORNING *ET AL*. *Statistics in Medicine*. 2016 Sep  
461 30;35(22):4021–40.
- 462 36. Saenz RA, Quinlivan M, Elton D, MacRae S, Blunden AS, Mumford JA, et al.  
463 Dynamics of influenza virus infection and pathology. *J Virol*. 2010 Apr;84(8):3974–83.
- 464 37. Hoeting JA, Adrian E. Raftery, Madigan D. Bayesian model averaging: a tutorial. *Statist*  
465 *Sci*. 1999 Nov;14(4):382–417.
- 466 38. Burnham KP, Anderson DR. Model selection and multimodel inference: a practical  
467 information-theoretic approach. 2. ed., [4. printing]. New York, NY: Springer; 2010. 488  
468 p.
- 469 39. Lloyd AL. The dependence of viral parameter estimates on the assumed viral life cycle:  
470 limitations of studies of viral load data. *Proceedings: Biological Sciences*.  
471 2001;268(1469):847–54.
- 472 40. Ribeiro RM, Qin L, Chavez LL, Li D, Self SG, Perelson AS. Estimation of the initial  
473 viral growth rate and basic reproductive number during acute HIV-1 infection. *Journal of*  
474 *Virology*. 2010 Jun 15;84(12):6096–102.

475

476

477 **List of Tables**

478 **Table I: Expected standard error (SE) of the fixed effect parameters using a target cell**  
 479 **limited model when the estimated parameters include or do not include the initial**  
 480 **inoculum,  $V_0$ , and the eclipse rate,  $k$ .** Expected standard errors were calculated using PFIM  
 481 software and for a study design including 30 subjects sampled every 3 days from day 3 to day  
 482 18.

Parameter (units)	Estimation of $R_0$ , $\delta$ , $V_0$ , $k$ and $\pi$			Estimation restricted to $R_0$ , $\delta$ and $\pi$		
	Estimate	SE	Relative SE(%)	Estimate	SE	Relative SE(%)
$R_0$	12	62.0	516%	12	0.84	7.0%
$\delta$ ( $d^{-1}$ )	1	0.10	10%	1	0.063	6.3%
$\pi$ (copies.cell $^{-1}$ .d $^{-1}$ )	6000	3625	604%	6000	1446	24.1%
$V_0$ (copies.mL $^{-1}$ )	$10^{-4}$	29.7	743%	$10^{-4}$ (fixed)	-	-
$k$ ( $d^{-1}$ )	4	38.9	971%	4 (fixed)	-	-
$c$ ( $d^{-1}$ )	20 (fixed)	-	-	20 (fixed)	-	-
$T_0$ (cells.mL $^{-1}$ )	$10^8$ (fixed)	-	-	$10^8$ (fixed)	-	-

483

484

485 **Table II: Differential equations system of immune response models.** At  $t=0$  we have

486  $T_{t=0} = T_0; I_{1,t=0} = 0; I_{2,t=0} = 0$  and  $V_{t=0} = V_0$ .

487

	Target cell limited	Refractory	Production inhibition	Cytotoxic	Virus-killing
$\frac{dT}{dt} =$	$-\beta TV$	$-\beta TV - \frac{\phi TF}{F + \theta}$	$-\beta TV$	$-\beta TV$	$-\beta TV$
$\frac{dI_1}{dt} =$	$\beta TV - kI_1$	$\beta TV - kI_1$	$\beta TV - kI_1$	$\beta TV - kI_1$	$\beta TV - kI_1$
$\frac{dI_2}{dt} =$	$kI_1 - \delta I_2$	$kI_1 - \delta I_2$	$kI_1 - \delta I_2$	$kI_1 - \delta I_2 - \frac{\phi I_2 F}{F + \theta}$	$kI_1 - \delta I_2$
$\frac{dV}{dt} =$	$\pi I_2 - cV$	$\pi I_2 - cV$	$\pi \left(1 - \frac{\phi F}{F + \theta}\right) I_2 - cV$	$\pi I_2 - cV$	$\pi I_2 - cV - \frac{\phi F V}{F + \theta}$
$\frac{dF}{dt} =$	$qI_2 - d_F F$	$qI_2 - d_F F$	$qI_2 - d_F F$	$qI_2 - d_F F$	$qI_2 - d_F F$

488

489

490 **Table III: Parameter values used for simulations**

Parameter (units)	Setting I	Setting II				
	Target cell limited	Target cell limited	Refractory	Production Inhibition	Cytotoxic	Virus- killing
$R_0^a$	12	12				
$\delta^a$ ( $d^{-1}$ )	1	1				
$\pi^a$ (copie.cell $^{-1}$ .d $^{-1}$ )	6000	250	6000			
$\phi^a$	-	-	1	0.99	0.9	36.5
$\theta$	-	-	2200	325000	3	0.001
$V_0$ (copies.mL $^{-1}$ )	{ $10^{-5}$ ; $10^{-4}$ ; $10^{-3}$ }	$10^{-4}$				
$k$ ( $d^{-1}$ )	{1; 4; 20}	4				
$c$ ( $d^{-1}$ )	20	20				
$T_0$ (cells.mL $^{-1}$ )	$10^8$	$10^8$				
$q$ ( $d^{-1}$ )	1	1				
$d_F$ ( $d^{-1}$ )	0.4	0.4				
<b>SD of the additive error</b>	0.7	0.7				

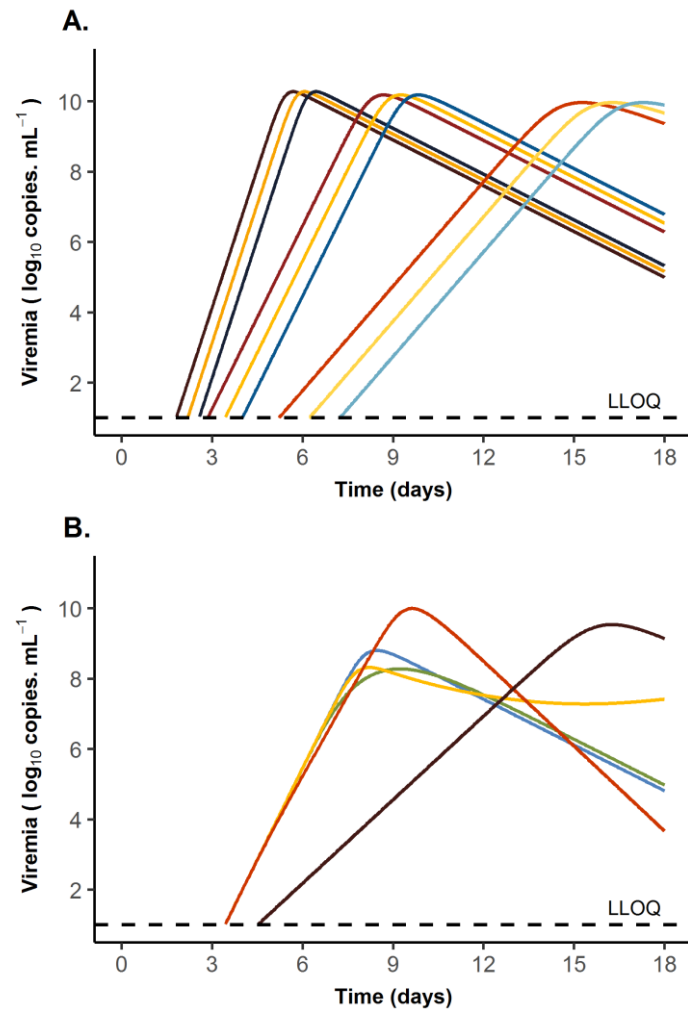
<sup>a</sup>: parameters for which inter-individual variability  $\omega=0.3$

491

492



493 **Legend to Figures**



494

495 **Figure 1.** Viral kinetics profiles obtained with the population parameters for each

496 candidate model. (A) and (B) correspond to the simulation settings I and II, respectively. In

497 Panel A, curves are regrouped by 3. At left, the first 3 curves correspond to models with  $k =$

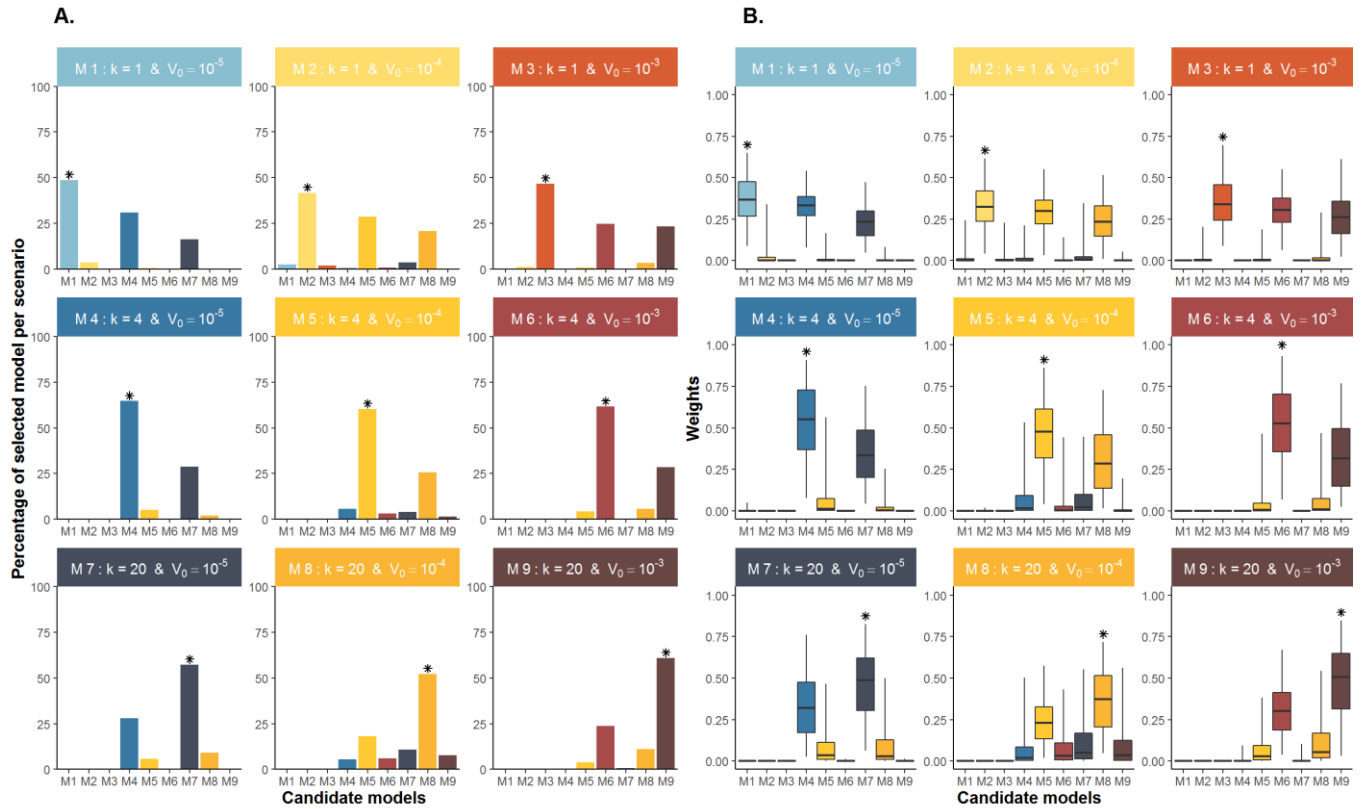
498  $20 \text{ d}^{-1}$ ; center, models with  $k = 4 \text{ d}^{-1}$  and right, models with  $k = 1 \text{ d}^{-1}$ . Within each group, red

499 curves correspond to models with  $V_0 = 10^{-5} \text{ copies.mL}^{-1}$ , yellow curves to models with  $V_0 =$

500  $10^{-5} \text{ copies.mL}^{-1}$  and blue curves to models with  $V_0 = 10^{-5} \text{ copies.mL}^{-1}$ .

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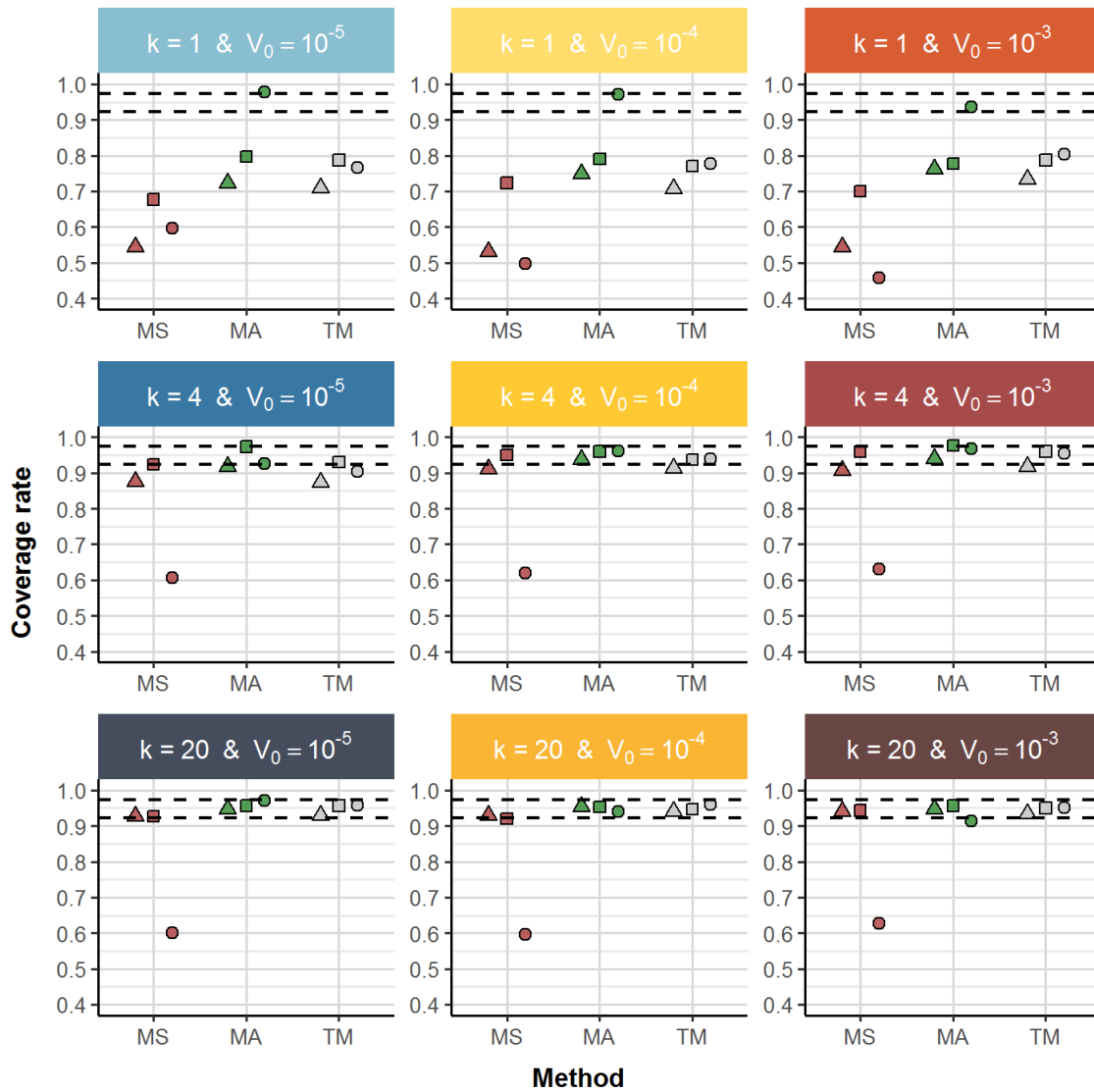
502



503

504 **Figure 2. Setting I.** (A) For each scenario, the percentage of simulations where each  
 505 candidate model was selected using AIC. Title of the facet indicates the true model. (B)  
 506 Boxplots of weights (whiskers from the 2.5<sup>th</sup> to the 97.5<sup>th</sup> percentile) associated with each  
 507 candidate model using AIC values. The asterisk denotes the true model in each scenario.

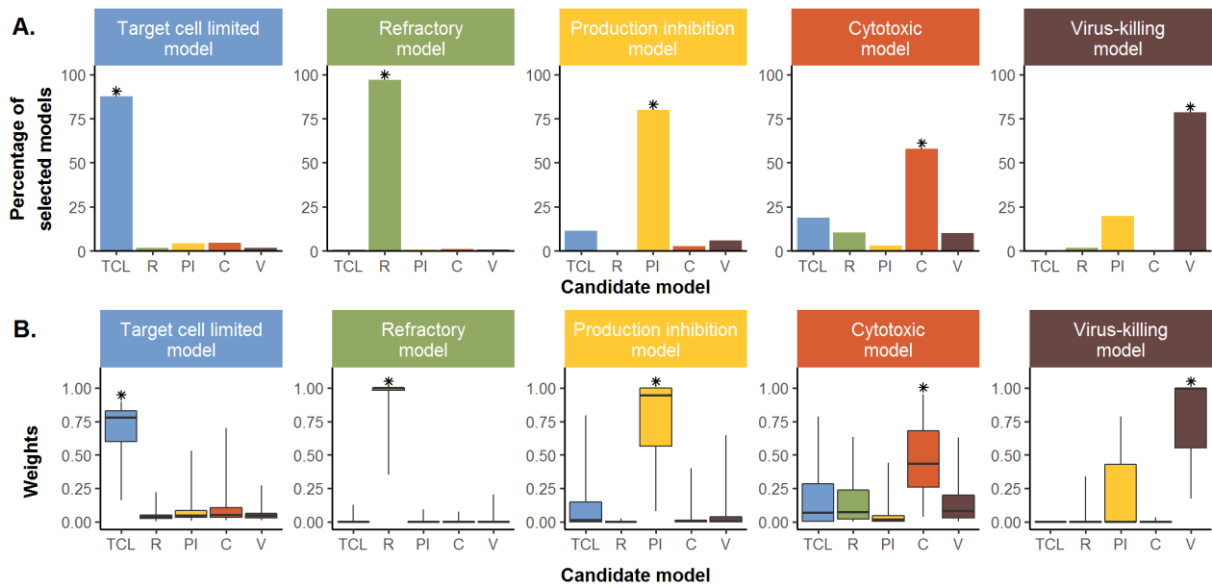
508



509

510 **Figure 3. Coverage rate of  $R_0$  and  $\delta$  in setting I.** Coverage rate of the parameters  $R_0$  (dots),  
 511  $\pi$  (squares) and  $\delta$  (triangles) for each scenario using model selection, model averaging or the  
 512 true model. Dashed lines represents the prediction interval around 0.95.

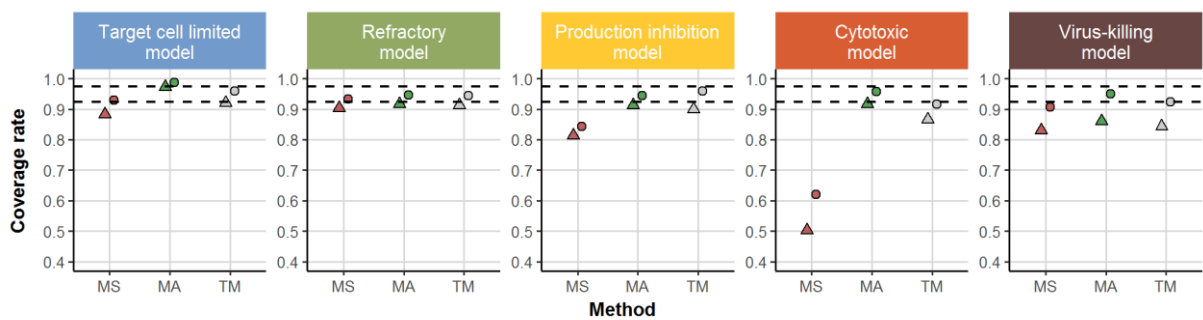
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514

515 **Figure 4. Setting II.** (A) For each scenario, the percentage of simulations where each  
 516 candidate model was selected using AIC. Title of the facet indicates the true model. (B)  
 517 Boxplots of weights (whiskers from the 2.5<sup>th</sup> to the 97.5<sup>th</sup> percentile) associated with each  
 518 candidate model using AIC values. The asterisk denotes the true model in each scenario.

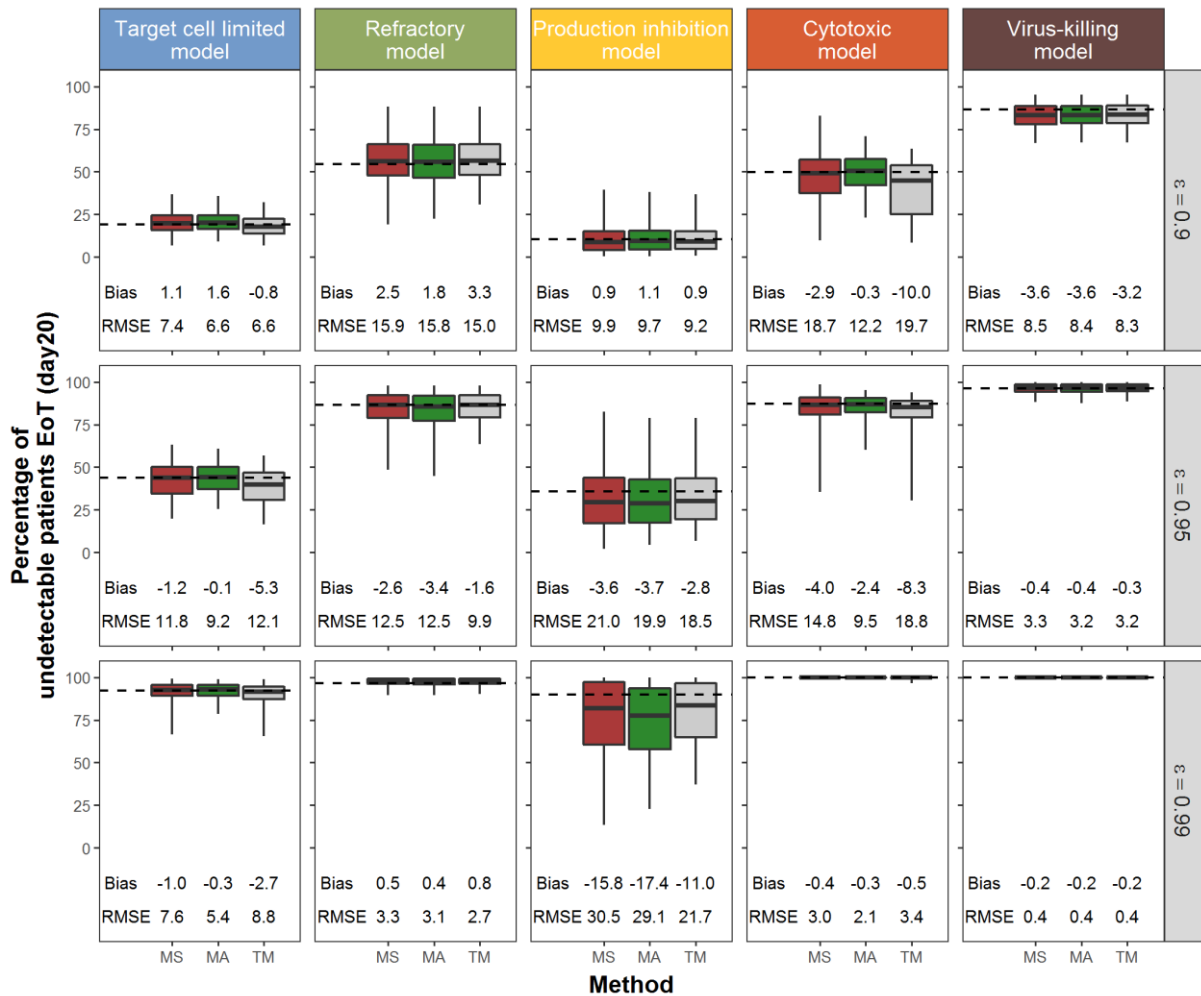
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520

521 **Figure 5. Coverage rate of  $R_0$  and  $\delta$  in setting II.** Coverage rate of the parameters  $R_0$  (dots)  
 522 and  $\delta$  (triangles) for each scenario using model selection, model averaging or the true model.  
 523 Dashed lines represents the prediction interval around 0.95.

524



525

526 **Figure 6. Distribution of the expected proportion of patients below the limit of detection**  
 527 **at day 20 using model selection (red), model averaging (green) or the true model (grey).**

528 For each scenario, whiskers represent the 2.5<sup>th</sup> to the 97.5<sup>th</sup> percentile and each row  
 529 corresponds to a different value of the treatment effect, noted  $\epsilon$ .

530

531