Model averaging in viral dynamics

Antonio Gonçalves[1], France Mentré[1], Annabelle Lemenuel-Diot[2] & Jérémie Guedj[1]

[1]IAME, UMR 1137, INSERM, Paris Diderot University, Paris, France
[2]Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel

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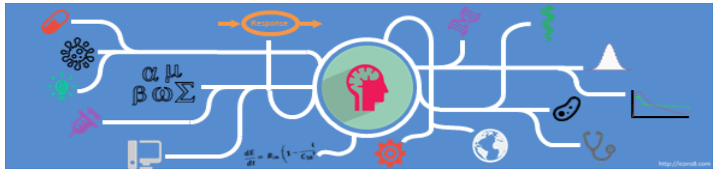

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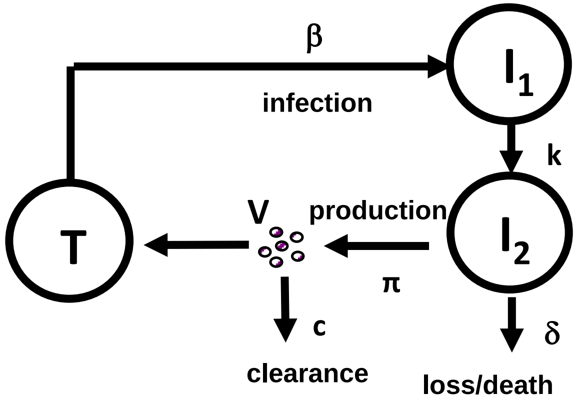

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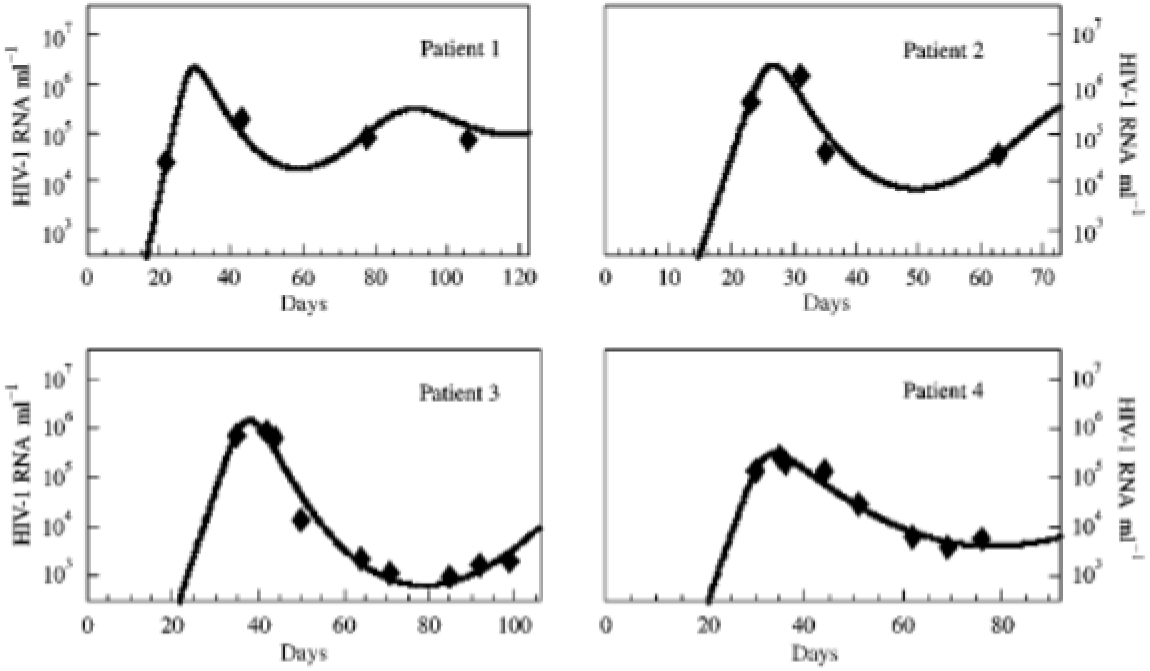

[1] Nowak et al. *Proc Natl Acad Sci* 1996
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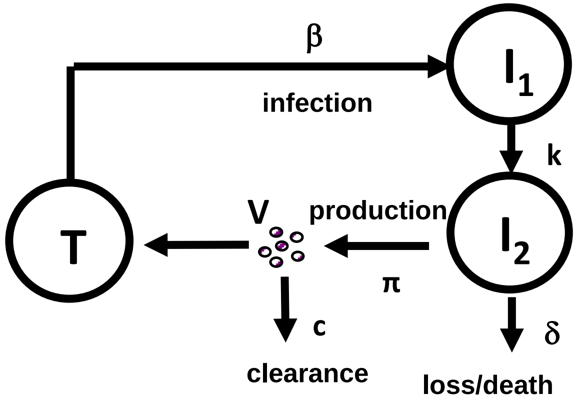

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Table 1. HBV versus HIV dynamics

	HBV [1]	HIV [2,3]
Plasma virus		
Half-life	24 hr	6 hr
Daily turn-over	50%	90%
Total production (periphery)	10^{11}	10^{9}
Load	2×10^{11}	10^{9}
Infected cell		
Half-life	10–100 days	2 days
Daily-turnover	1–7%	30%

[1] Nowak et al. *Proc Natl Acad Sci* 1996
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Challenges in viral dynamics

- Some parameters of complex viral dynamics models can hardly be estimated
  - Parameters related to unobserved compartments
  - Poorly identifiable parameters are often fixed to arbitrary values[1,2]
  - Sensitivity analyses are carried out[2,3]

[1] Guedj et al *Bull Math Biol* 2007
[2] Handel et al *J R Soc Interface* 2010
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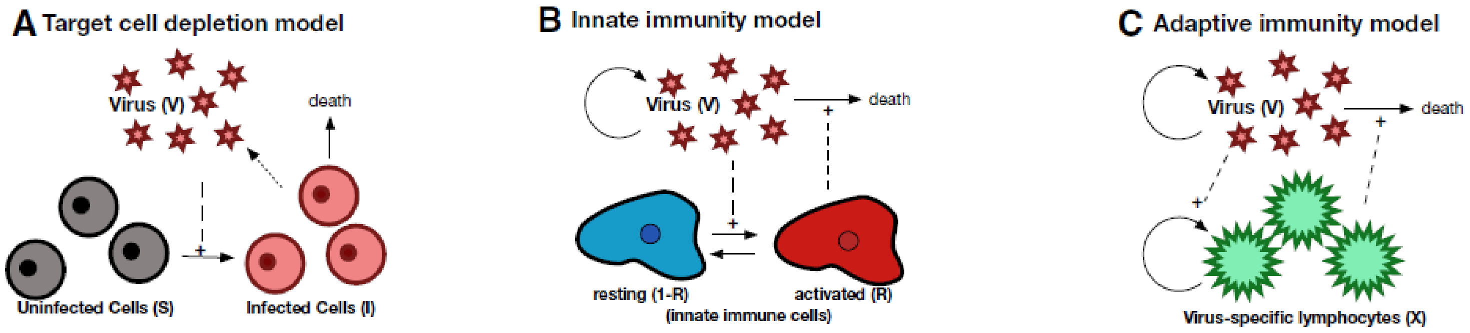
Challenges in viral dynamics

- Some parameters of complex viral dynamics models can hardly be estimated
  - Parameters related to unobserved compartments
  - Poorly identifiable parameters are often fixed to arbitrary values[1,2]
  - Sensitivity analyses are carried out[2,3]
- Various complex models can also be used to compare different biological assumptions[4,5,6]
  - Ex: Influenza A



[1] Guedj et al *Bull Math Biol* 2007
[2] Handel et al *J R Soc Interface* 2010
[3] Best et al *Proc Natl Acad Sci* 2017
[4] Moore et al *Bull Math Biol* 2018
[5] Li and Handel *J Theor Biol.* 2014
[6] Baccam et al *J Virol.* 2006

Model selection

- Model selection (MS):
  - Most commonly used approach
  - Model that « best » descibes the data, based on an information criteria (e.g. AIC)
  - Selected model is carried forward in prediction step
    - Ignores model uncertainty[1]
    - Impairs predictive performances[2,3]

[1] Buckland et al. *Biometrics* 1997
[2] Ganusov *Front Microbiol* 2016
[3] Evans et al. *Trends Ecol Evol* 2013

Model averaging

- Model averaging (MA):
  - Allows measuring model uncertainty by weighting a set of M candidate models in function of an information criteria[1] (e.g. AIC)

$$w_m = \frac{e^{\frac{-AIC_m}{2}}}{\sum_{m=1}^{M} e^{\frac{-AIC_m}{2}}}$$

  - Applications to NL[2,3] and NLME models[4,5,6]
    - Concentration-effect relationship
    - Dose finding studies

[1] Buckland et al. *Biometrics* 1997
[2] Ganusov *Front Microbiol* 2016
[3] Evans et al. *Trends Ecol Evol* 2013
[4] Dosne et al. *Stat Med* 2016
[5] Buatois et al. *AAPS* 2018
[6] Aoki et al. *JPKPD* 2017

Objectives

- To develop model averaging as an alternative to model selection in viral dynamic models

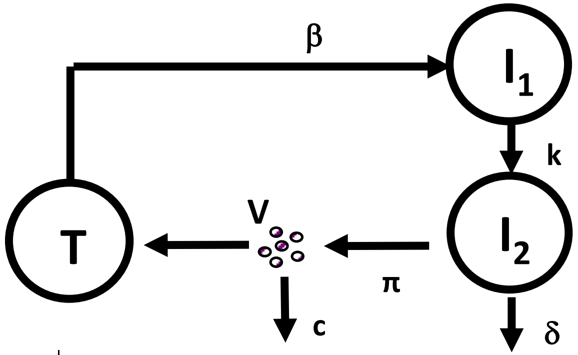
- To compare parameter estimates and predictive performances of model averaging and model selection in the context of:

  1) Poorly identifiable parameters

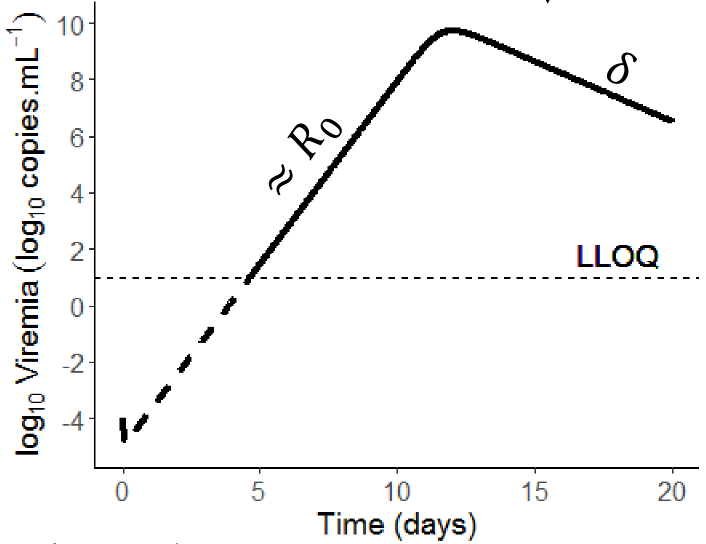
  2) Multiple biological models

Setting 1: viral dynamic models in presence of poorly identifiable parameters

- Target cell limited model[1,2,3]:



$$R_0 = \frac{\beta \pi T_0}{c\delta}$$



- Expected RSE% using PFIM[4]:
  - N = 30
  - Design = 3, 6, 9, 12, 15 and 18 days

	Estimation of R_0, δ, V_0, k and π	
Parameter (units)	Estimate	Expected RSE%
R_0	12	516%
δ (d^{-1})	1	10.8%
c (d^{-1})	20 (fixed)	-
T_0 ($cells.mL^{-1}$)	10^8 (fixed)	-
V_0 ($copies.mL^{-1}$)	10^{-4}	743%
k (d^{-1})	4	971%
π ($copie.cell^{-1}.d^{-1}$)	6000	604%
ω R_0	0.3	28.6%
ω δ	0.3	41%
ω π	0.3	460%
σ	0.7	7%

[1] Smith et al *PLoS Pathog* 2013
[2] Handel et al *J R Soc Interface* 2010
[3] Best et al *Proc Natl Acad Sci* 2017
[4] Dumont et al. *Comput Methods Programs Biomed* 2018

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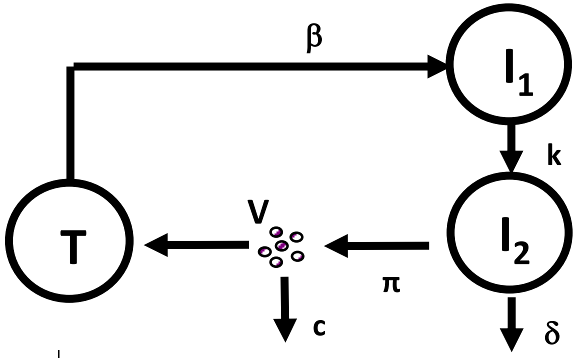

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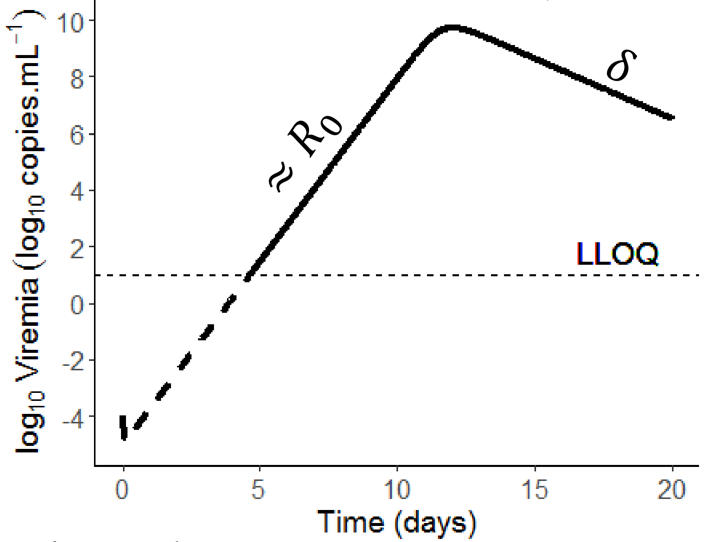

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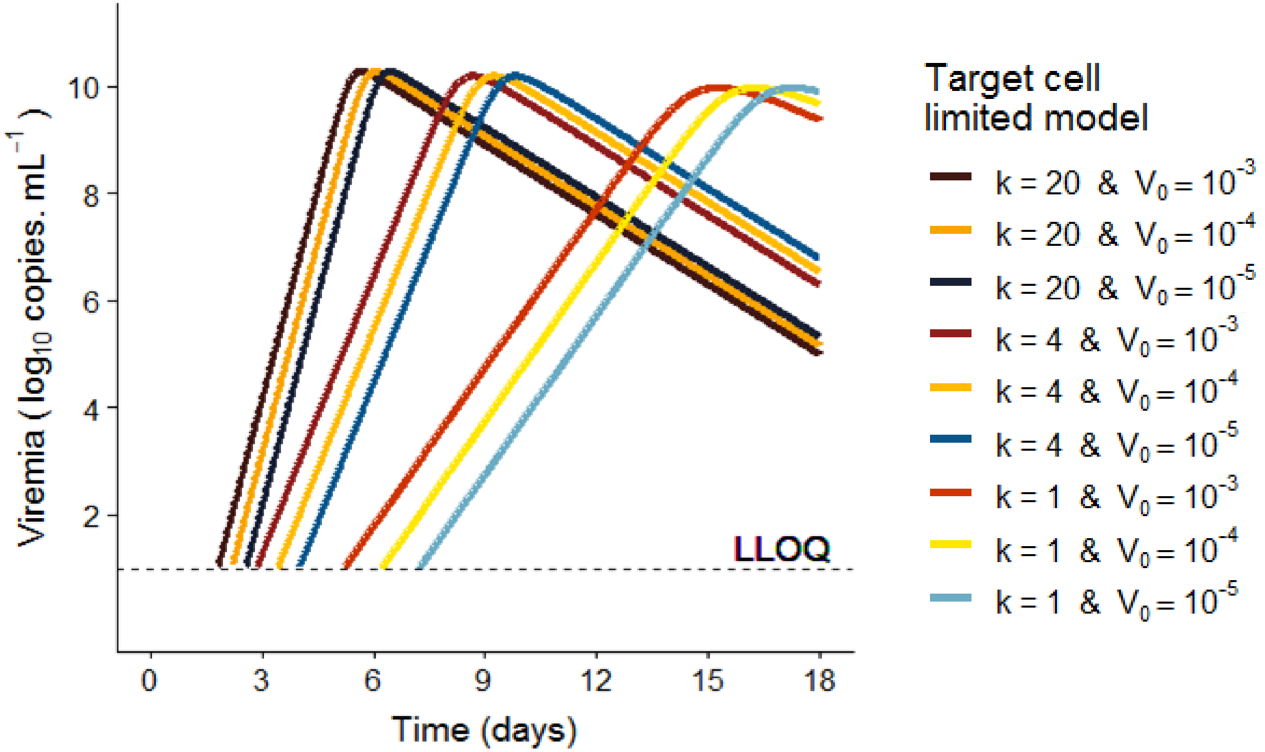
	Estimation of R_0, δ, V_0, k and π		Estimation restricted to R_0, δ and k	
Parameter (units)	Estimate	Expected RSE%	Estimate	Expected RSE%
R_0	12	516%	12	7.0%
δ (d^{-1})	1	10.8%	1	6.3%
c (d^{-1})	20 (fixed)	-	20 (fixed)	-
T_0 (cells.mL^{-1})	10^8 (fixed)	-	10^8 (fixed)	-
V_0 (copies.mL^{-1})	10^{-4}	743%	10^{-4} (fixed)	-
k (d^{-1})	4	971%	4 (fixed)	-
π (copie.$cell^{-1}$.d^{-1})	6000	604%	6000	24.1%
ω R_0	0.3	28.6%	0.3	28.6%
ω δ	0.3	41%	0.3	41%
ω π	0.3	460%	0.3	460%
σ	0.7	7%	0.7	7%

Setting 1: viral dynamic models in presence of poorly identifiable parameters

- We defined M=9 candidate models resulting from the combination of 3 values for V_0 and k[1]:
  - $V_0 = 10^{-5}$; 10^{-4} or 10^{-3} copies.mL^{-1}
  - k = 1; 4 or 20 d^{-1}



Parameters Ψ_m^*	μ	Ω
R_0	12	0.3
$\delta\ (d^{-1})$	1	0.3
$\pi\ (copies.cell^{-1}.mL^{-1})$	6000	0.3
$c\ (d^{-1})$ fixed	20	-
$V_0\ (copies.mL^{-1})$ fixed	10^{-5}; 10^{-4} or 10^{-3}	-
$k\ (d^{-1})$ fixed	1, 4 or 20	-
σ	0.7	

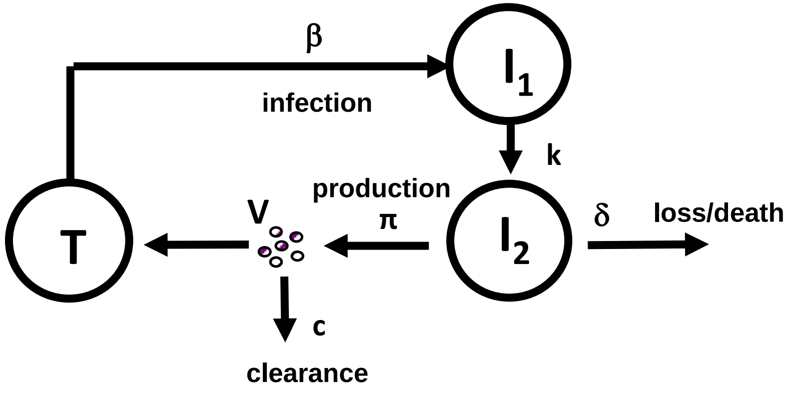
[1] Best et al *Proc Natl Acad Sci* 2017

Methods

Setting 2: viral dynamic models including the immune response

- 4 models additionnal models to account for immunity roles during infection can by derived from a target cell model[1,2,3,4]

Target cell limited model (TCL)



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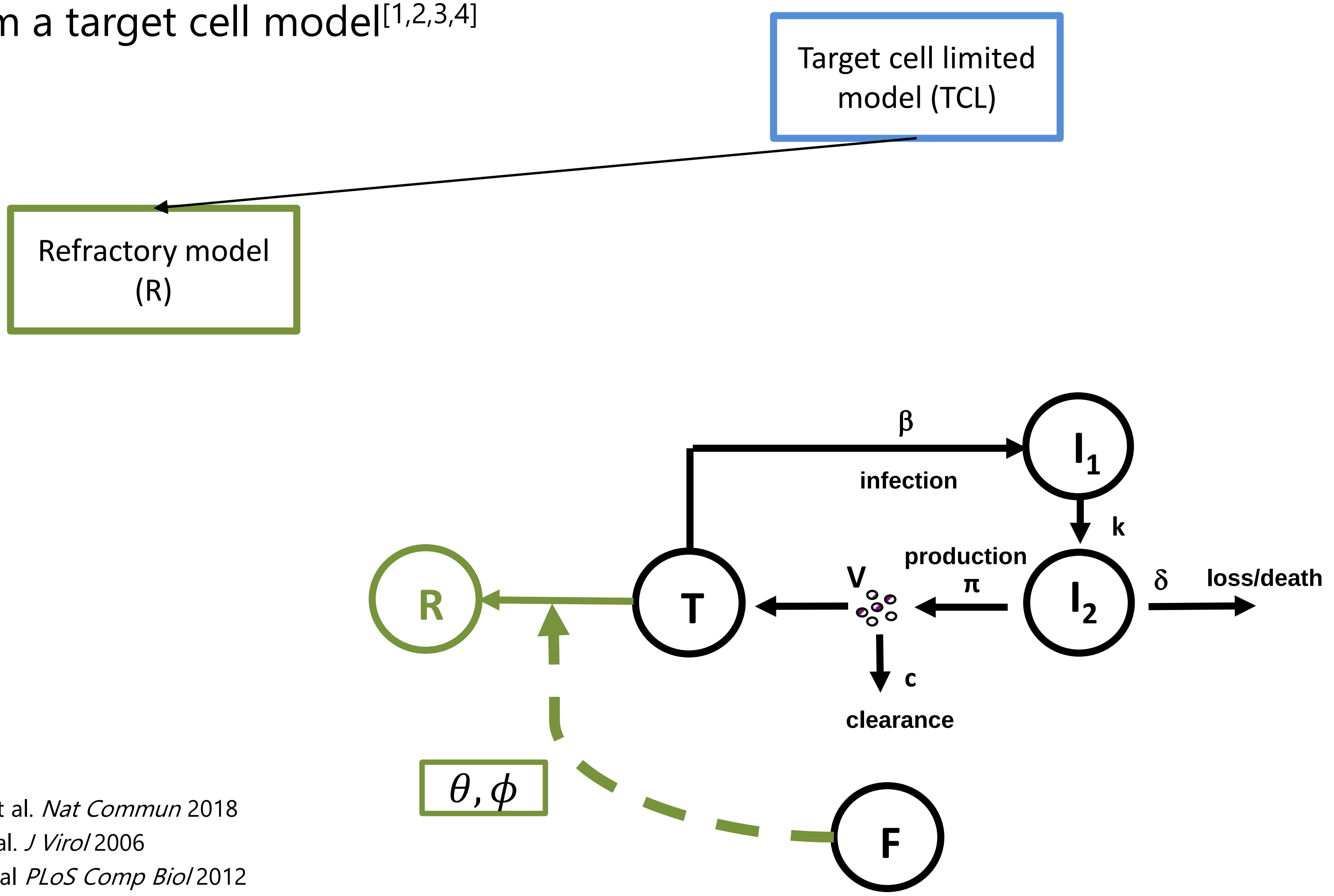

$$\frac{dT}{dt} = -\beta T V - \frac{\boldsymbol{\phi T F}}{\boldsymbol{F + \theta}}$$

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$$\frac{dV}{dt} = \pi I_2 - cV$$

$$\frac{dF}{dt} = q I_2 - d_F F$$

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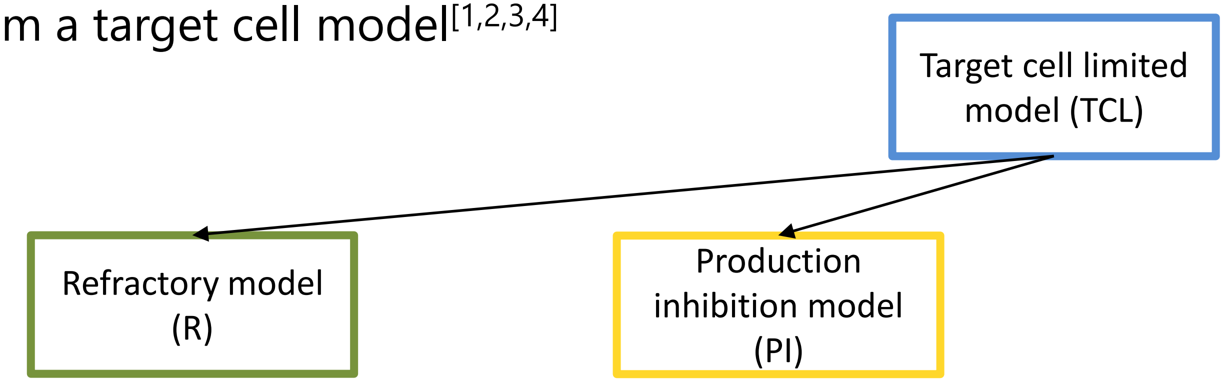

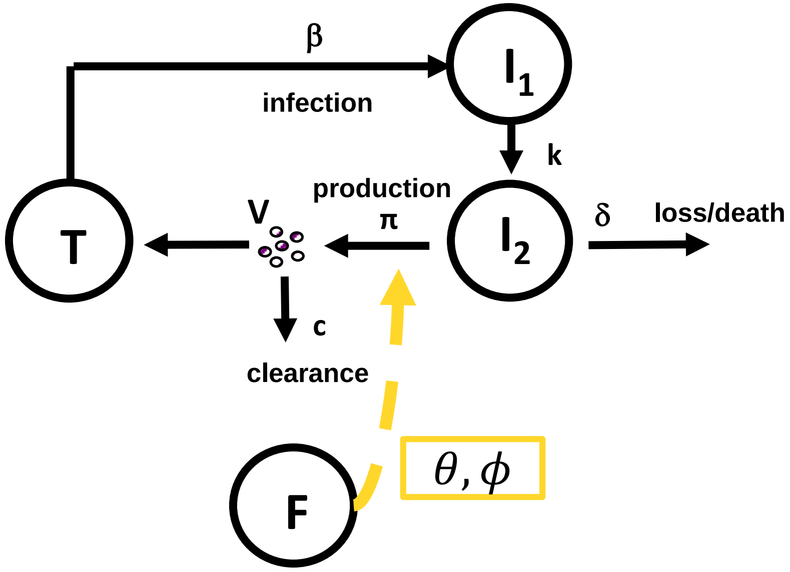

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$$\frac{dV}{dt} = \pi\left(1 - \frac{\boldsymbol{\phi F}}{\boldsymbol{F + \theta}}\right) I_2 - cV$$

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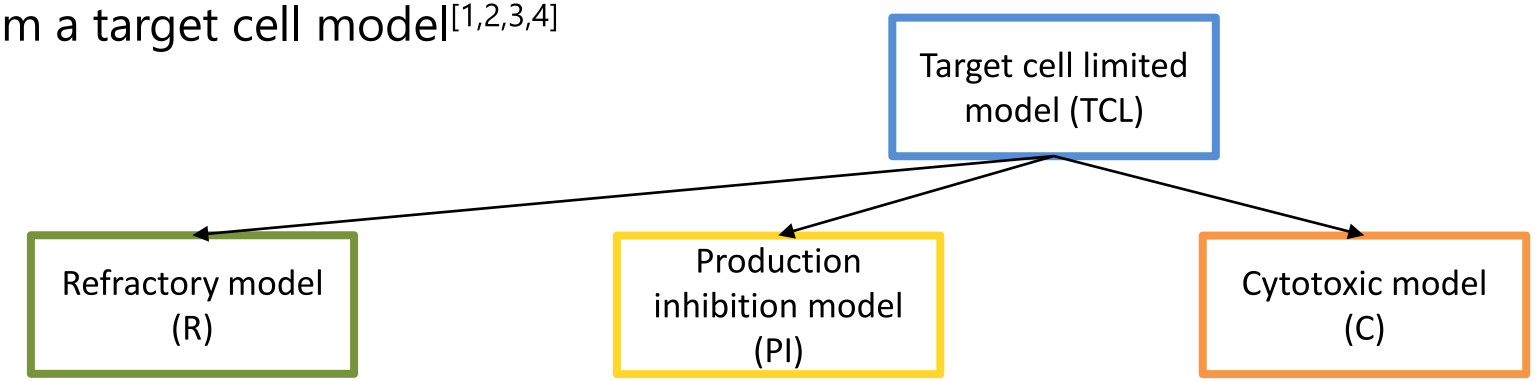

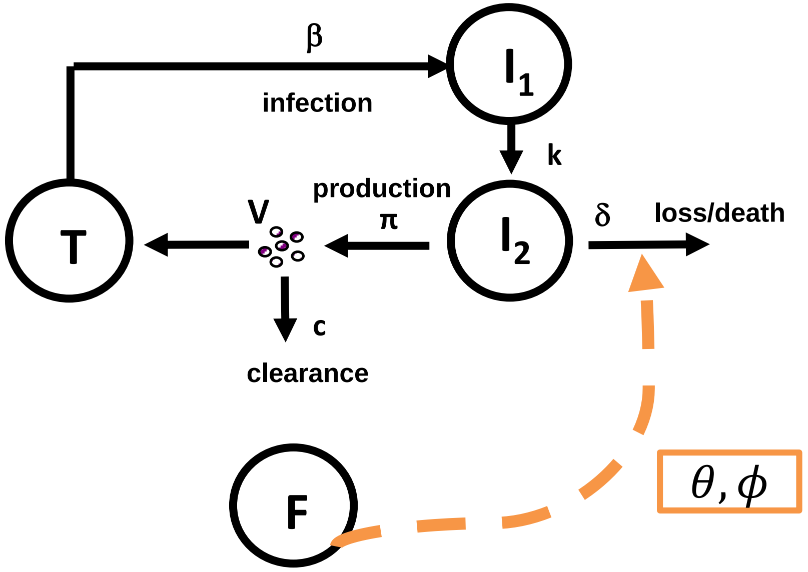

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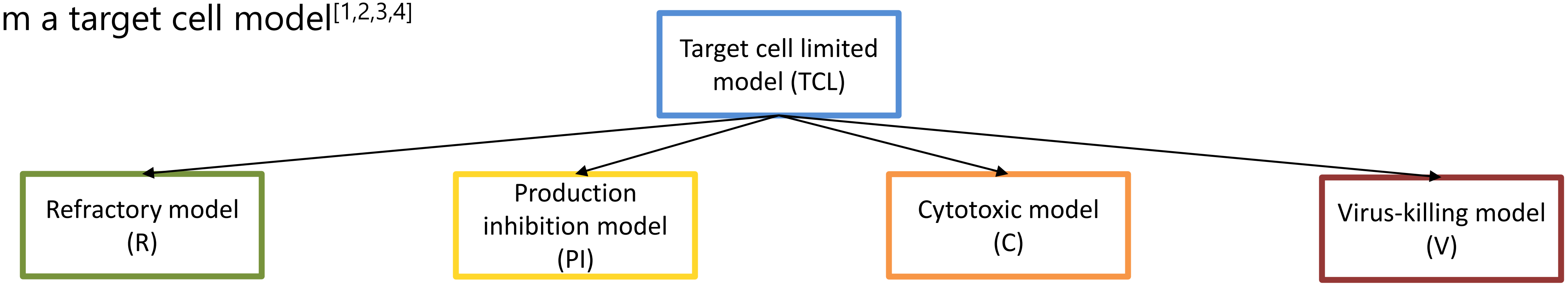

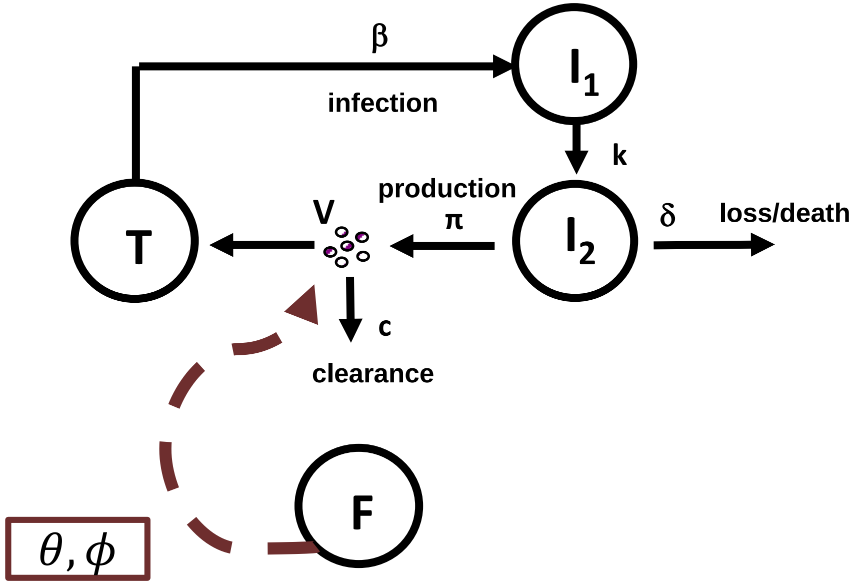

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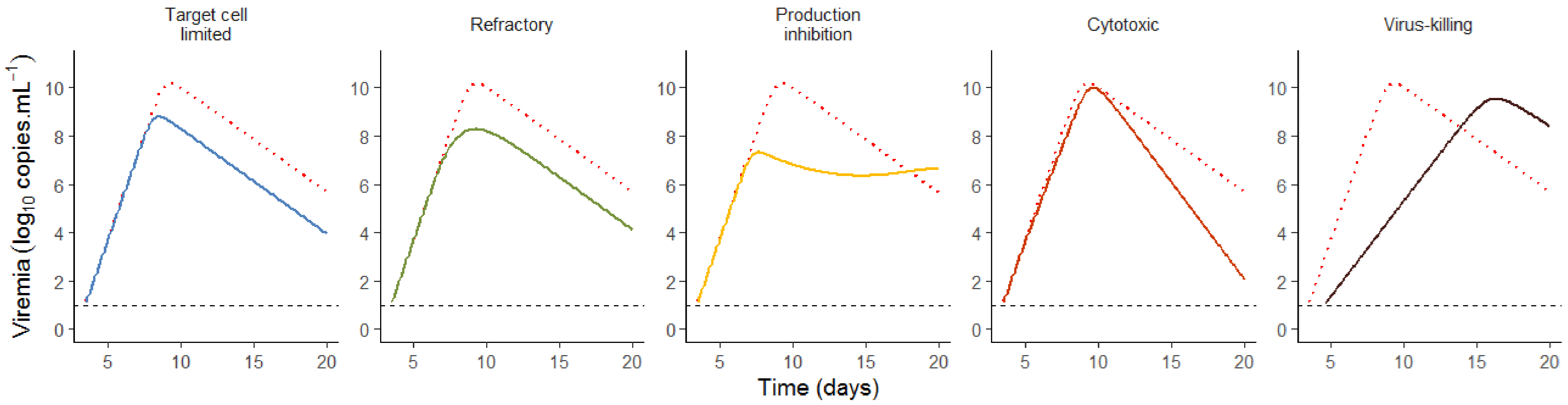
Setting 2: viral dynamic models including the immune response

- We defined M=5 candidate models[1,2,3,4]
  - Parameters chosen to provide a 20% reduction of the log $AUC_{0\rightarrow 20}$ in presence of immune response

Parameters Ψ_m^*	TCL	R	PI	C	V	ω
π (copies. $cell^{-1}$. mL^{-1})	250	6000	6000	6000	6000	0.3
θ	0	2200	$32.5.10^4$	3	0.001	-
ϕ	0	1	0.99	0.9	36.5	0.3
R_0	12					0.3
δ (d^{-1})	1					0.3
$c(d^{-1})$ fixed	20					-
$V_0(copies.mL^{-1})$ fixed	10^{-4}					-
$k(d^{-1})$ fixed	4					-



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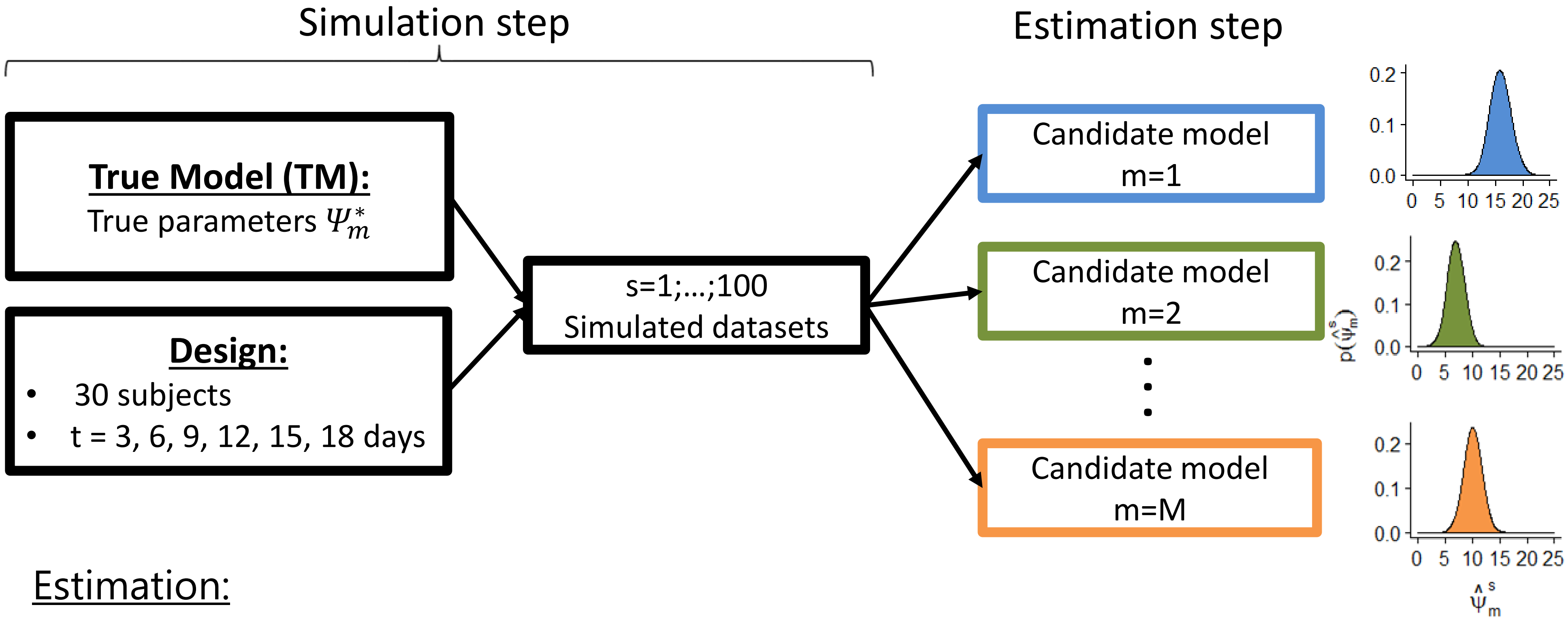
Simulations & estimation

Simulation scenario:



Estimation:

- Estimation of $\widehat{\Psi}_m^s$ by maximizing the likelihood function
  - SAEM algorithm using importance sampling
- Asymptotic approximation of$p(\widehat{\Psi}_m^s)$ supposed Gaussian with standard errors given by FIM^{-1}
- MONOLIX version 2018 release 2

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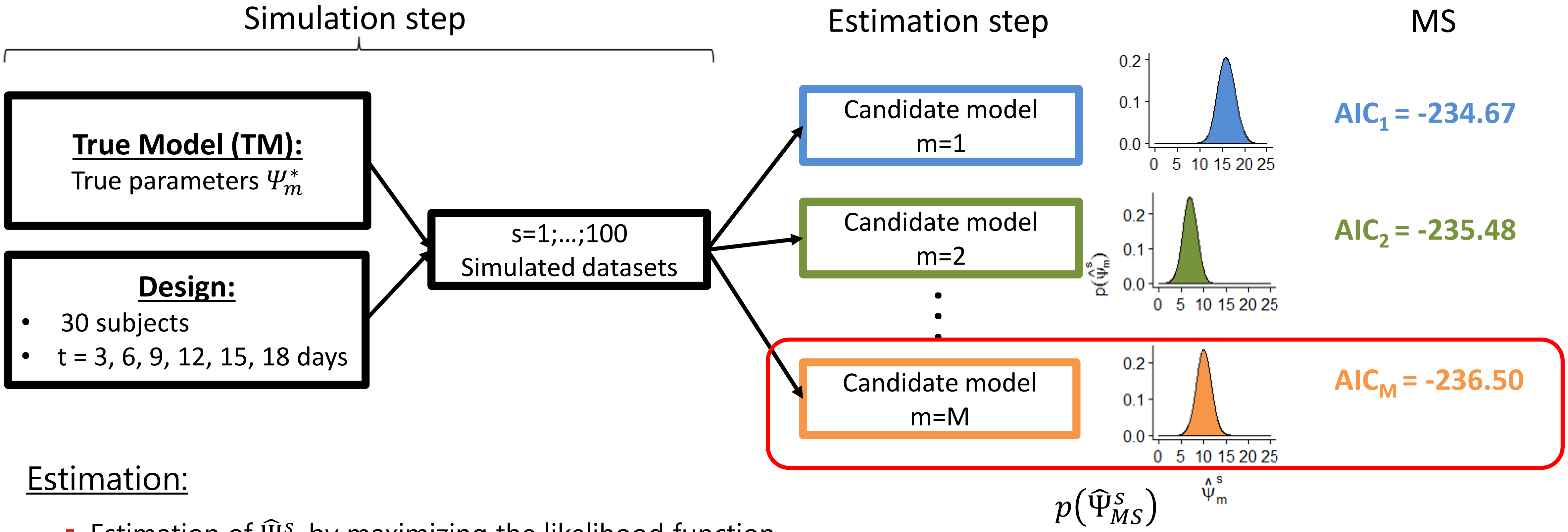

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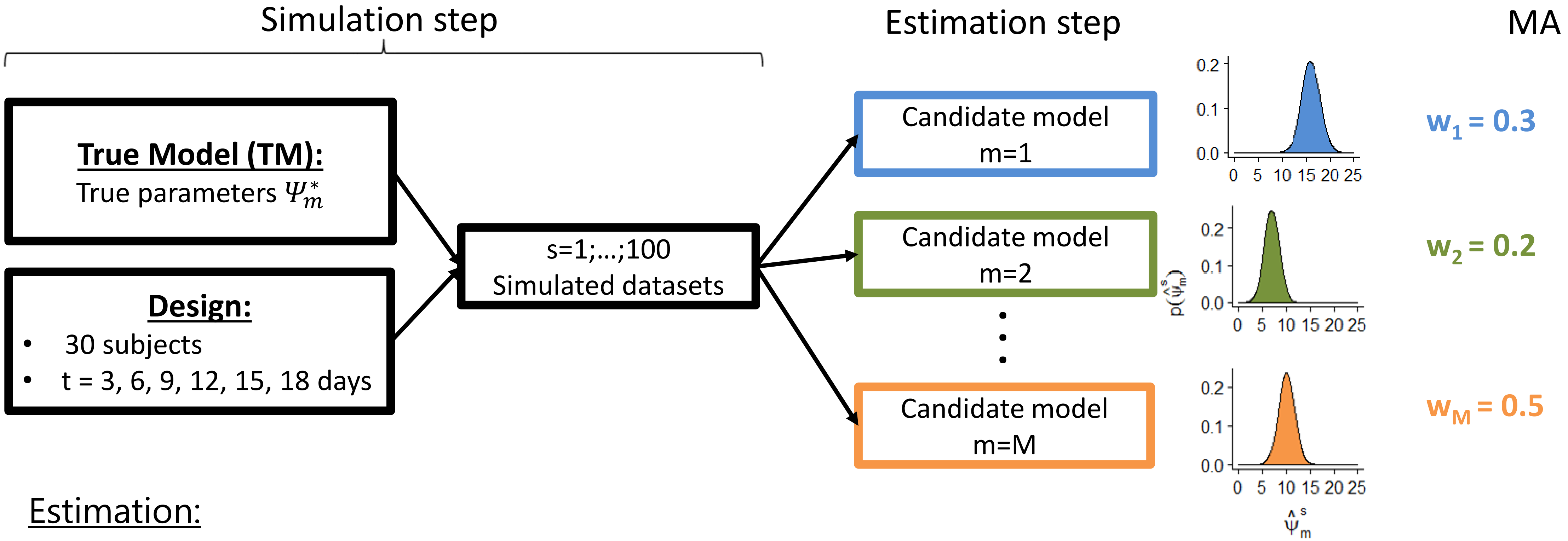

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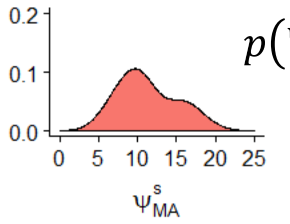
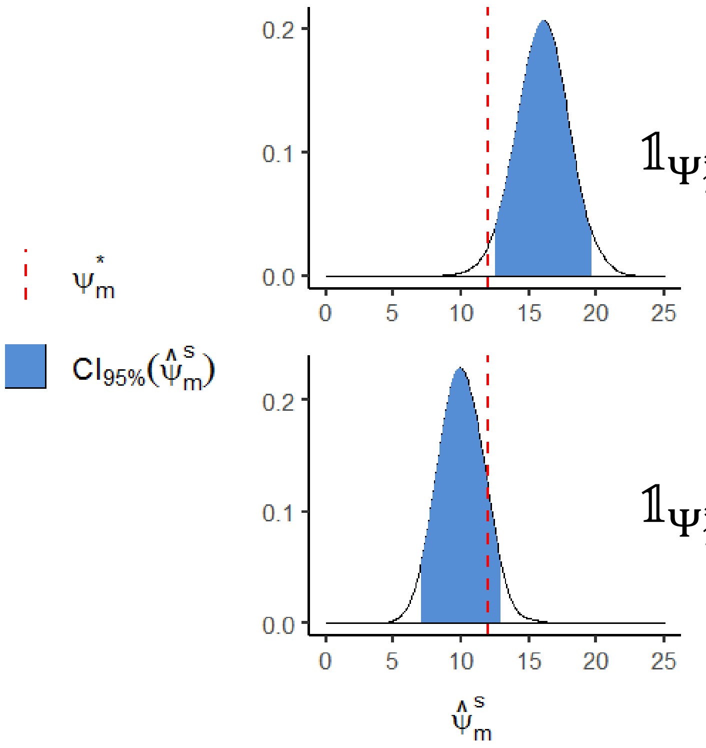


$$p(\hat{\Psi}_{MA}^s) = \sum_{m=1}^{M} w_m^s \, p(\hat{\Psi}_m^s)$$

Performances of MS and MA for parameter estimation

For each setting, scenario and approach:

- Percentage of selected models
- Distribution of weights
- Coverage rates (CR) of parameters R_0 and δ



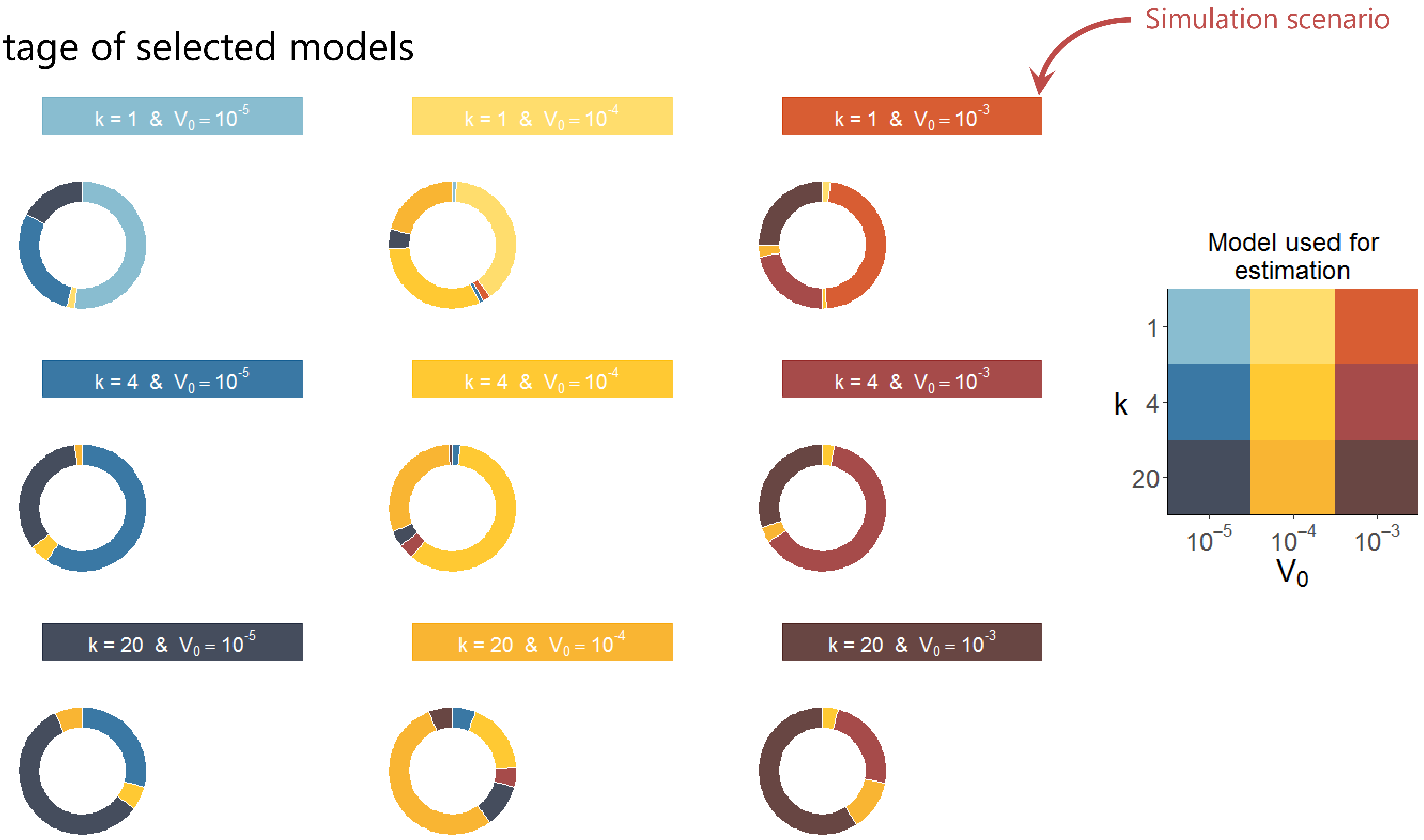
$$\mathbb{1}_{\Psi^*_m \in CI_{95\%}}(\hat{\Psi}^s_m) = 0$$

$$\mathbb{1}_{\Psi^*_m \in CI_{95\%}}(\hat{\Psi}^s_m) = 1$$

$$CR = \frac{1}{S} \sum_{s=1}^{S} \mathbb{1}_{\Psi^*_m \in CI_{95\%}}(\hat{\Psi}^s_m)$$

Setting 1: viral dynamic models in presence of poorly identifiable parameters

Percentage of selected models



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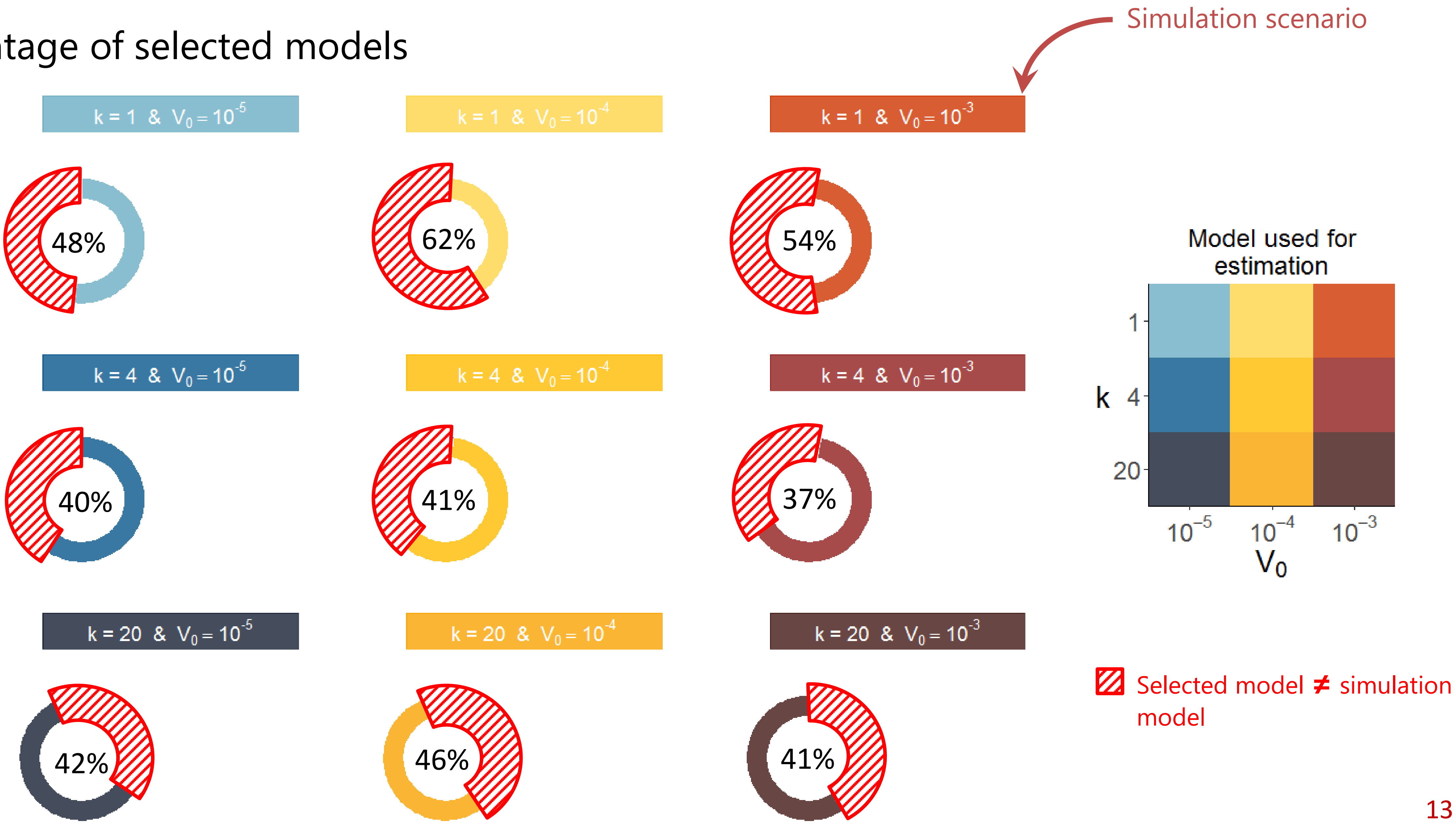
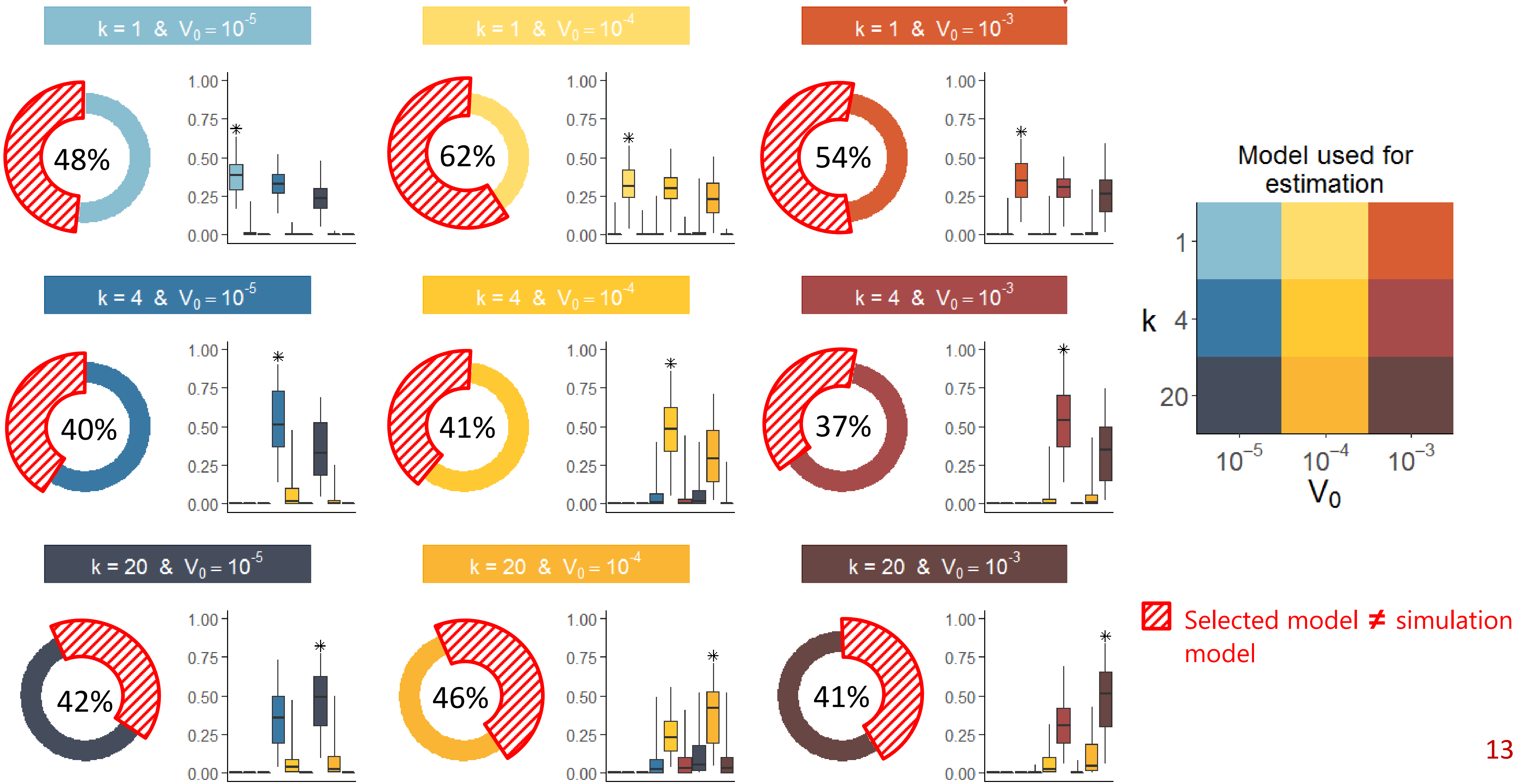


Setting 1: viral dynamic models in presence of poorly identifiable parameters

Percentage of selected models & distribution of weights

Simulation scenario



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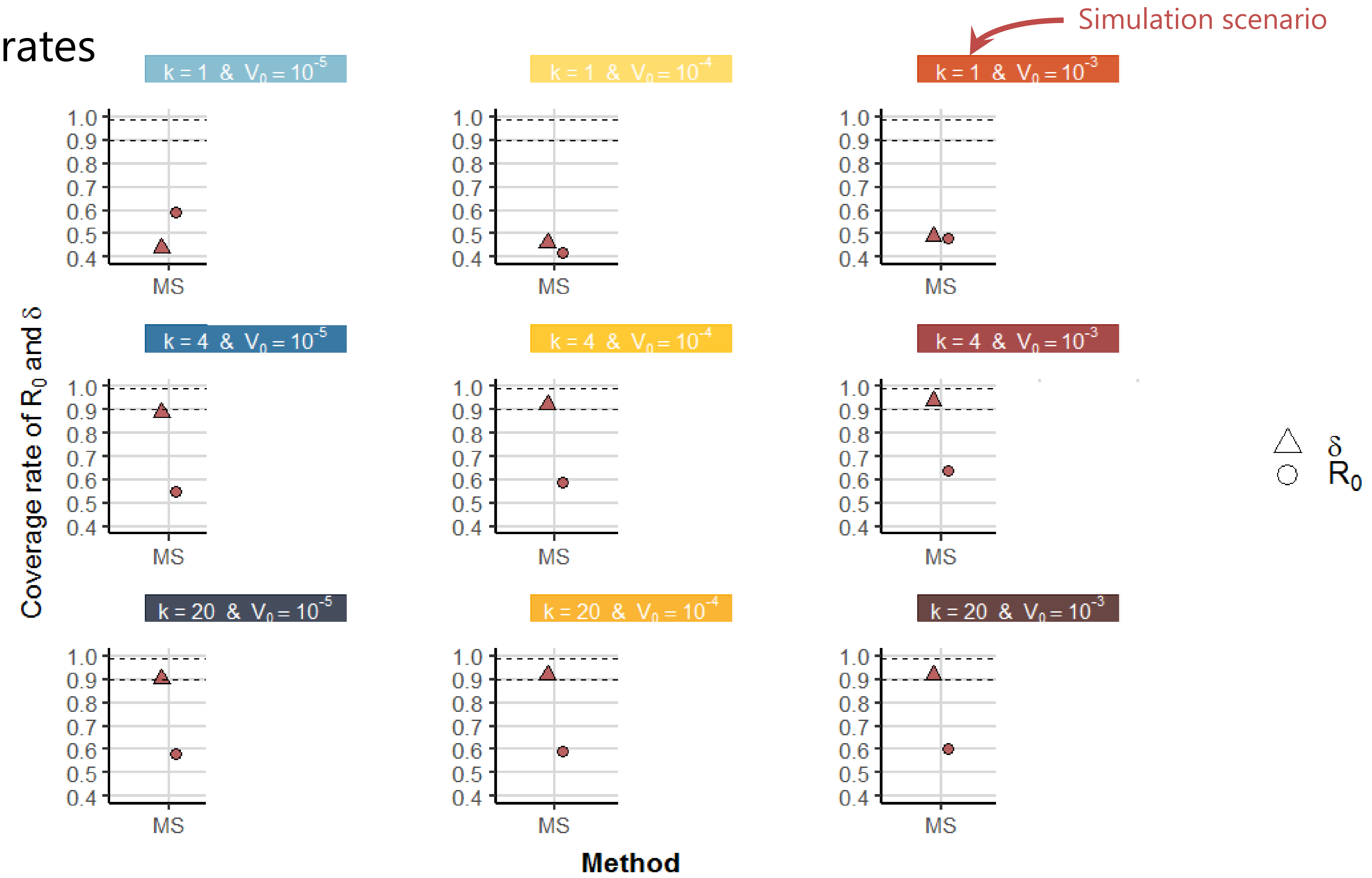
Coverage rates



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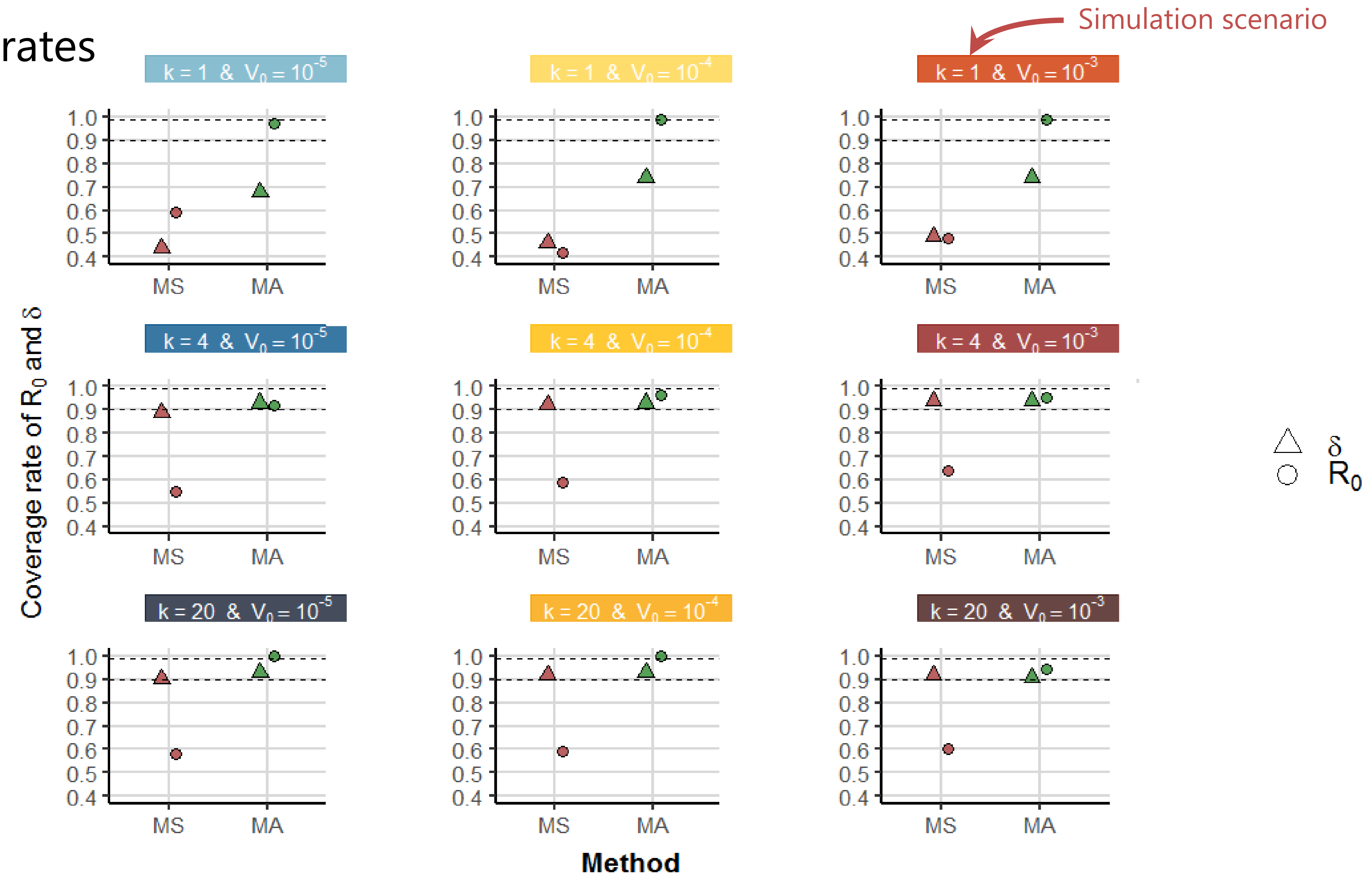

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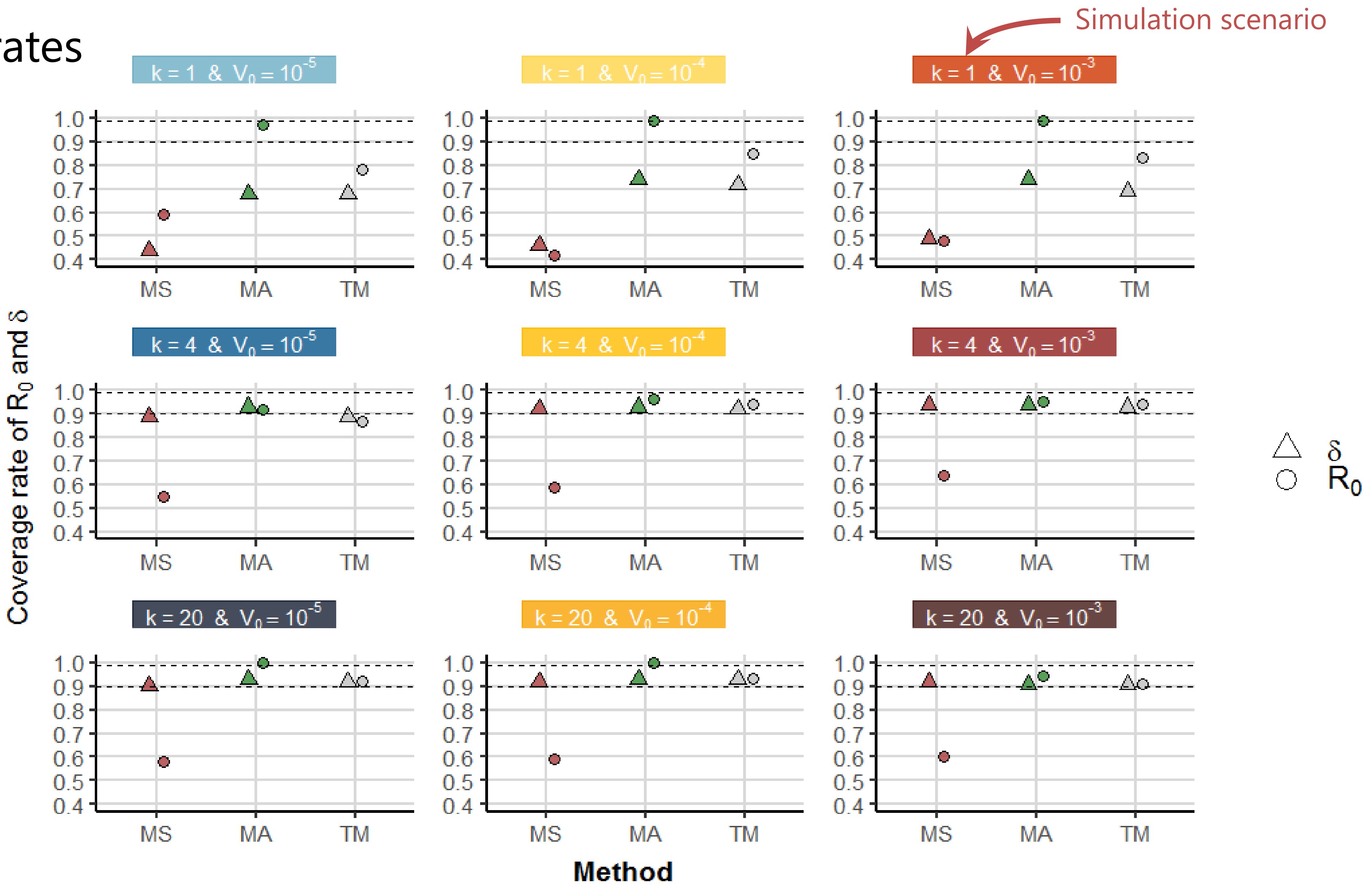
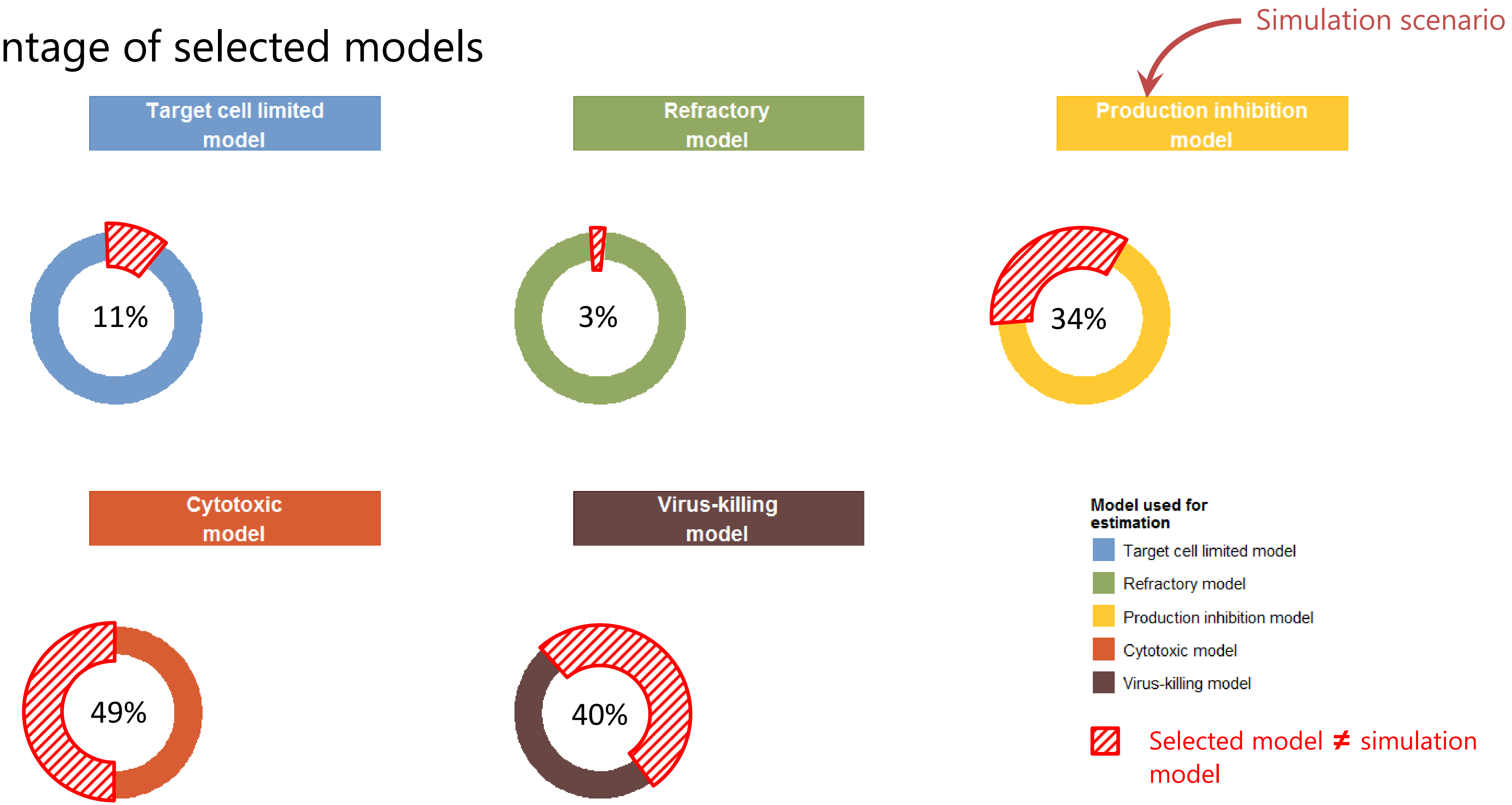


Setting 2: viral dynamic models including the immune response

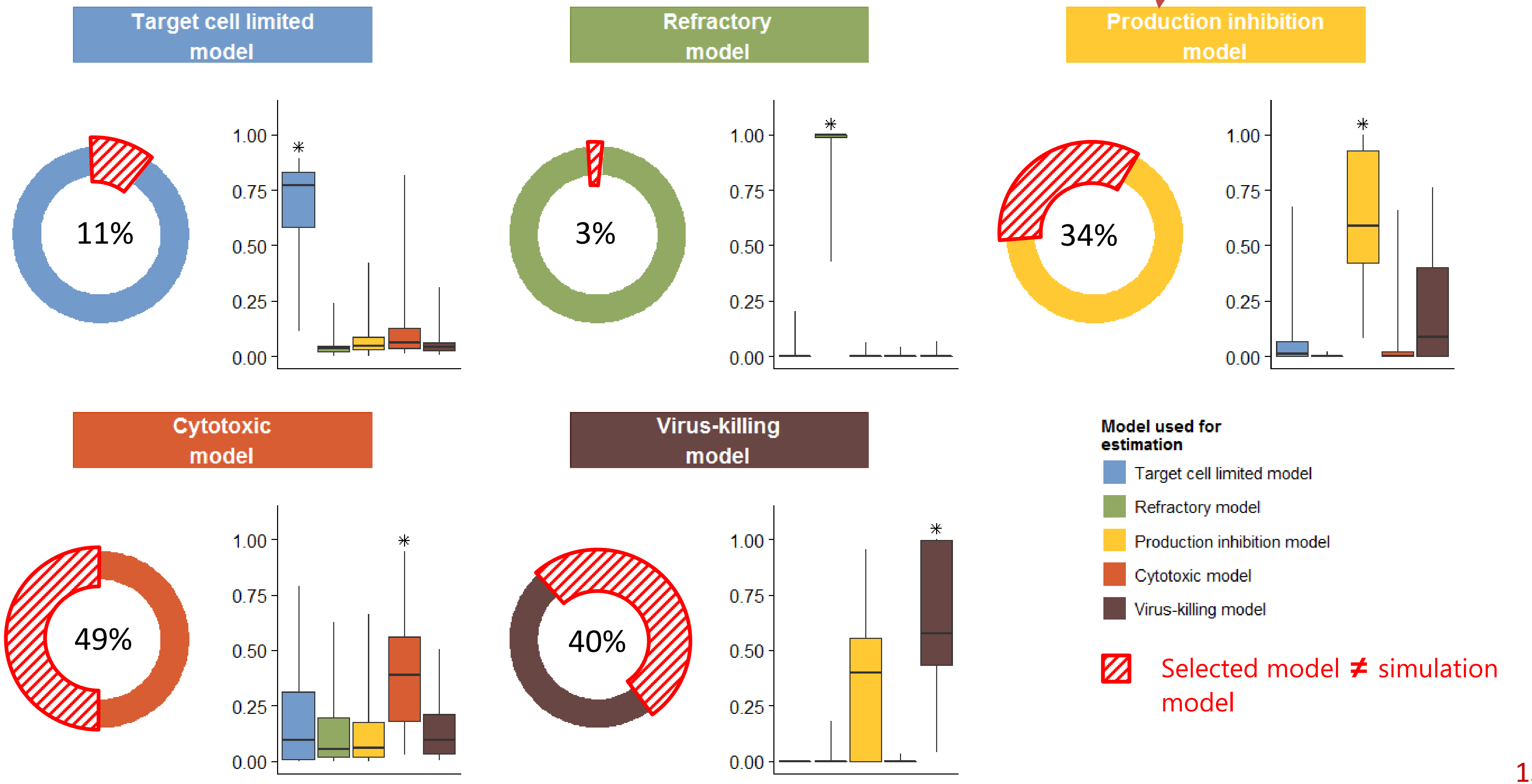
Percentage of selected models



Setting 2: viral dynamic models including the immune response

Percentage of selected models & distribution of weights

Simulation scenario



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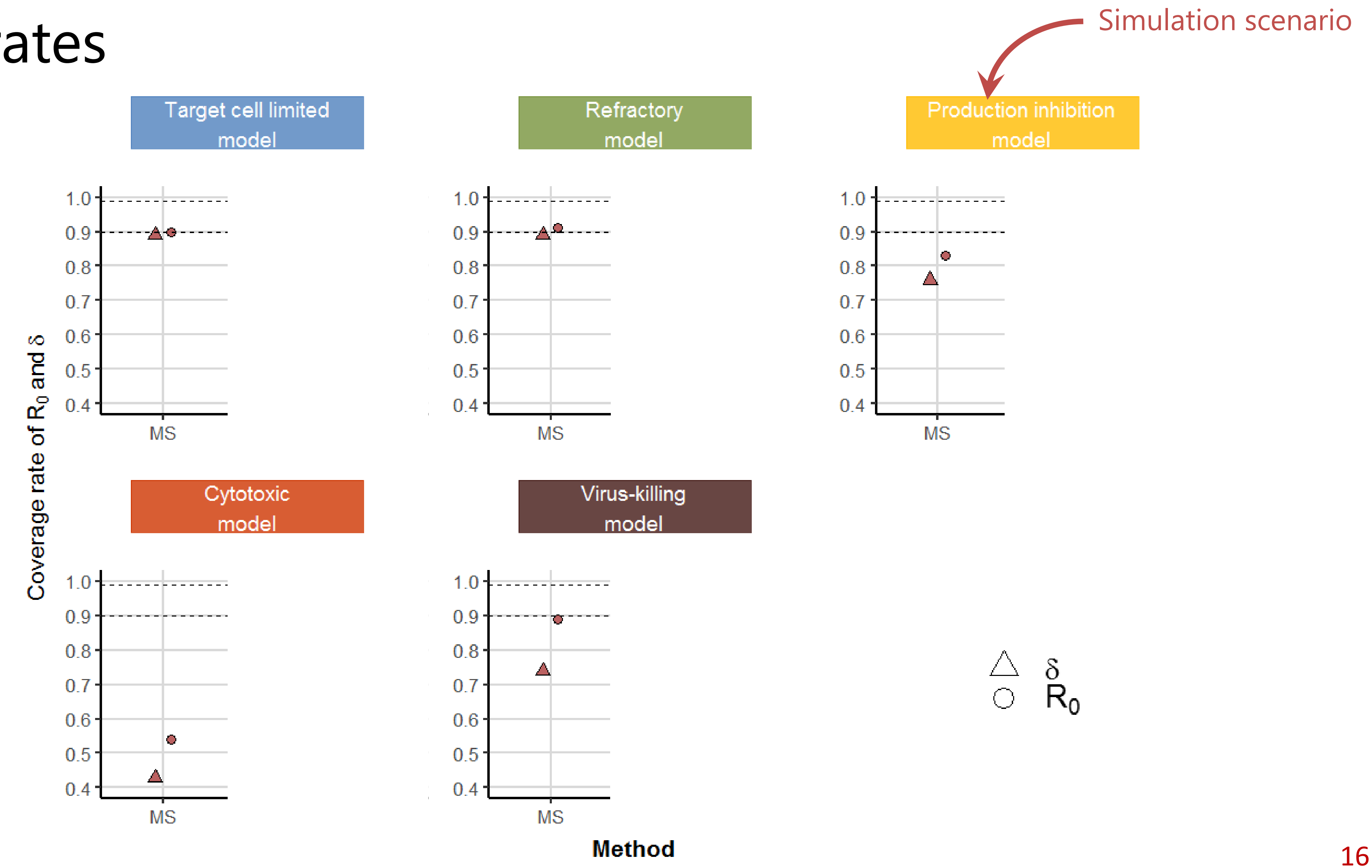

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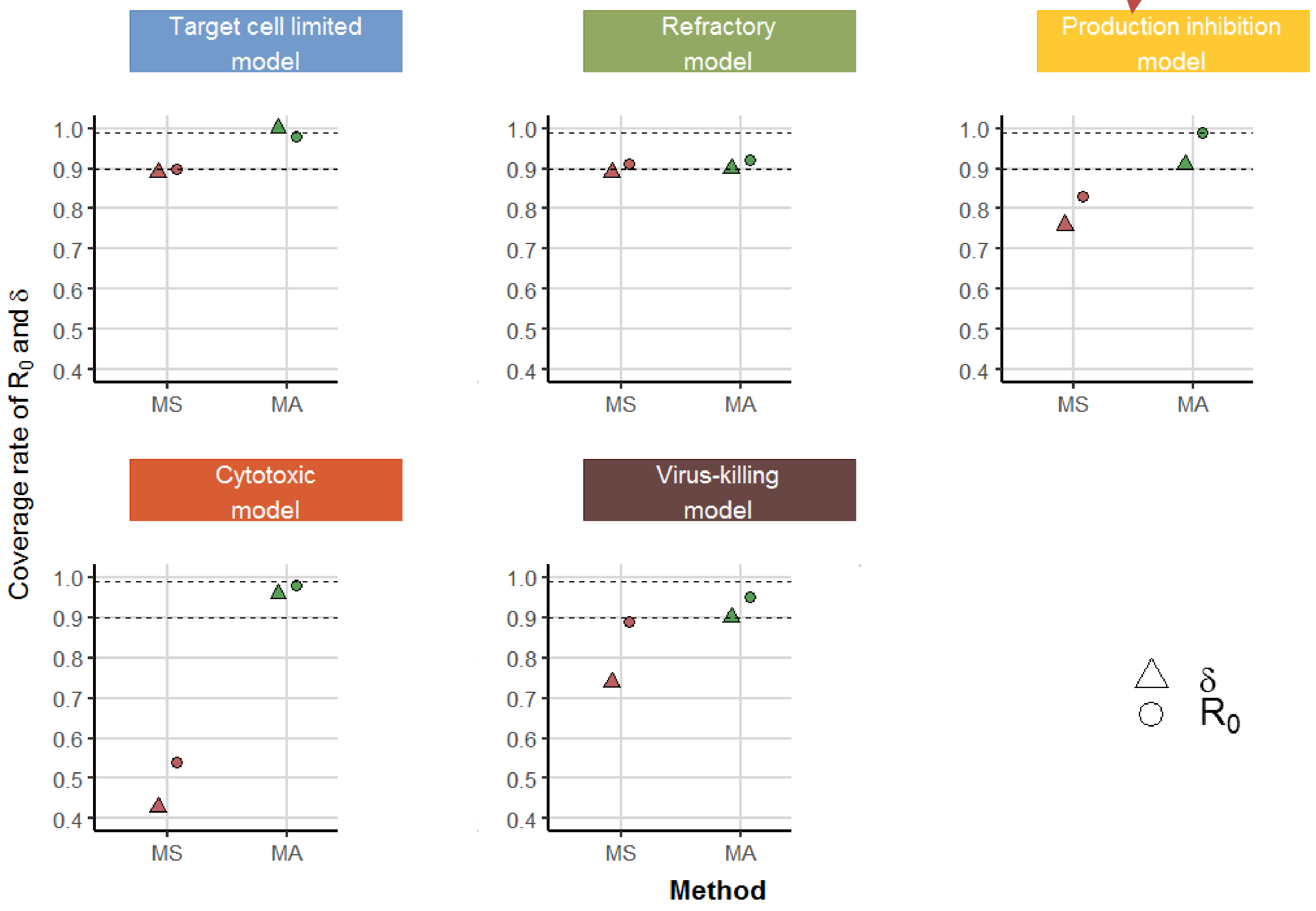
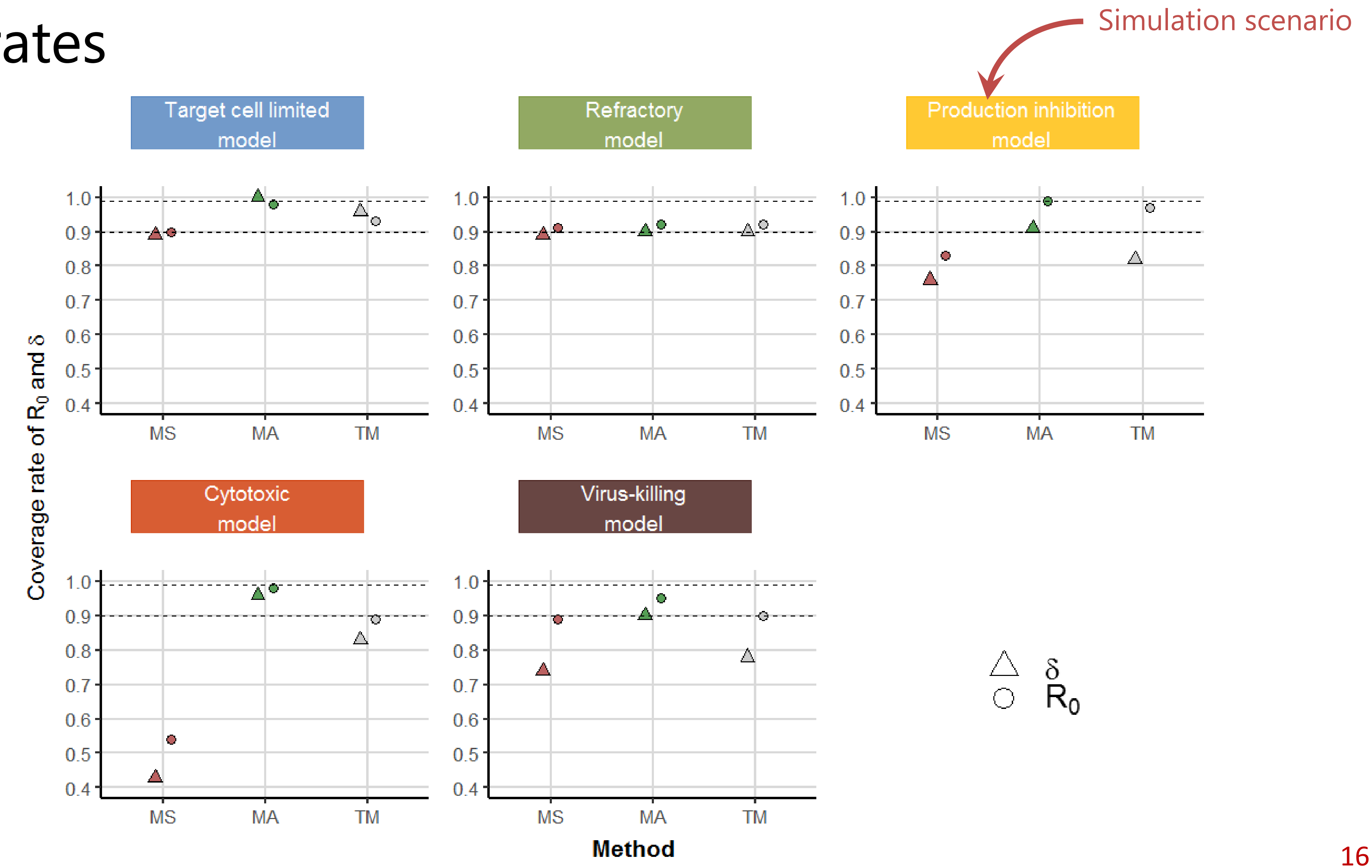
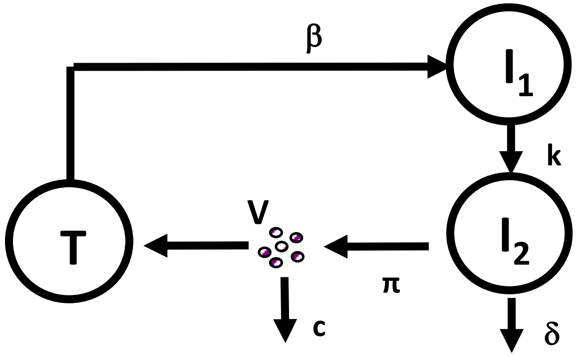


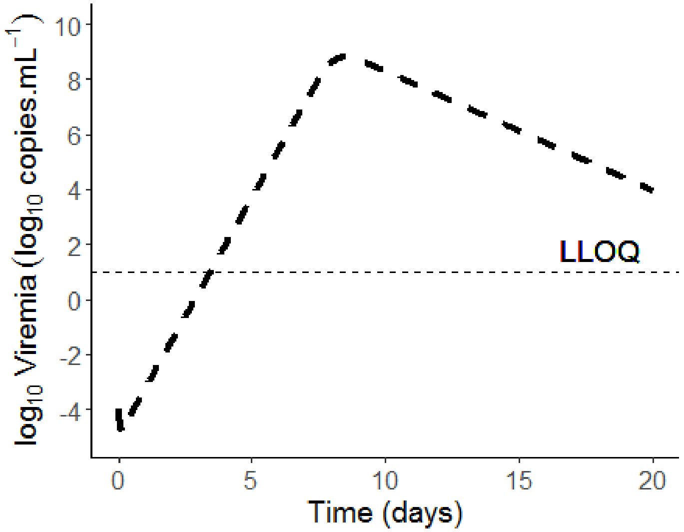
Setting 2: viral dynamic models including the immune response

Coverage rates



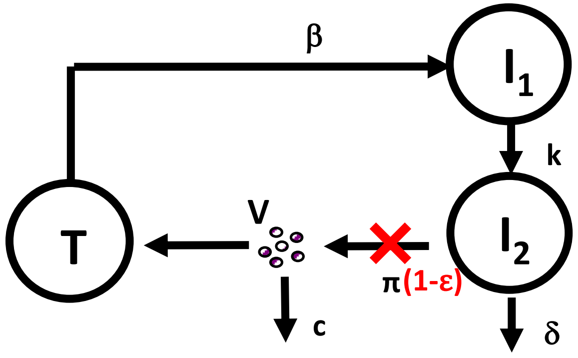
Predictive performances of MS and MA

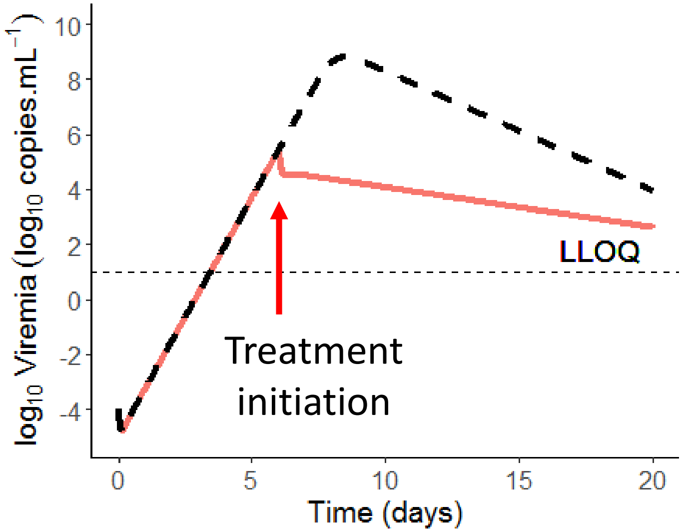




- Capability of MS and MA to anticipate the effect of a treatment

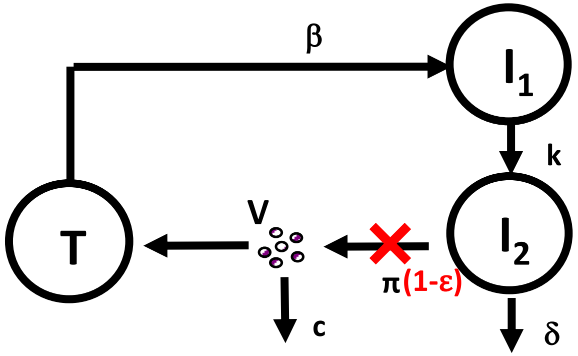
Predictive performances of MS and MA

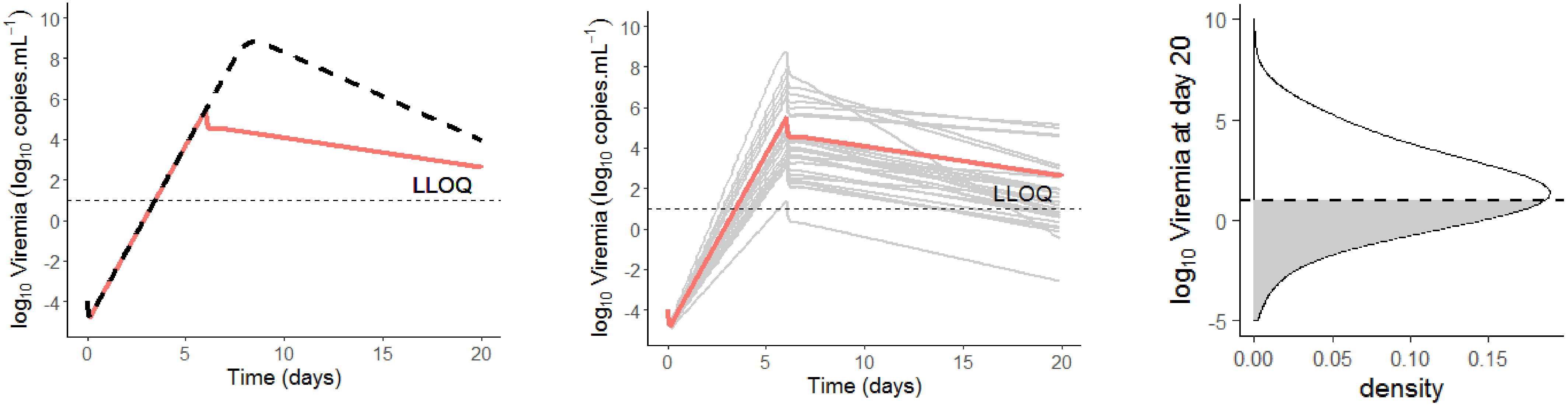




- Capability of MS and MA to anticipate the effect of a treatment
- Treatment initiated at day 6 and up to day 20

Predictive performances of MS and MA



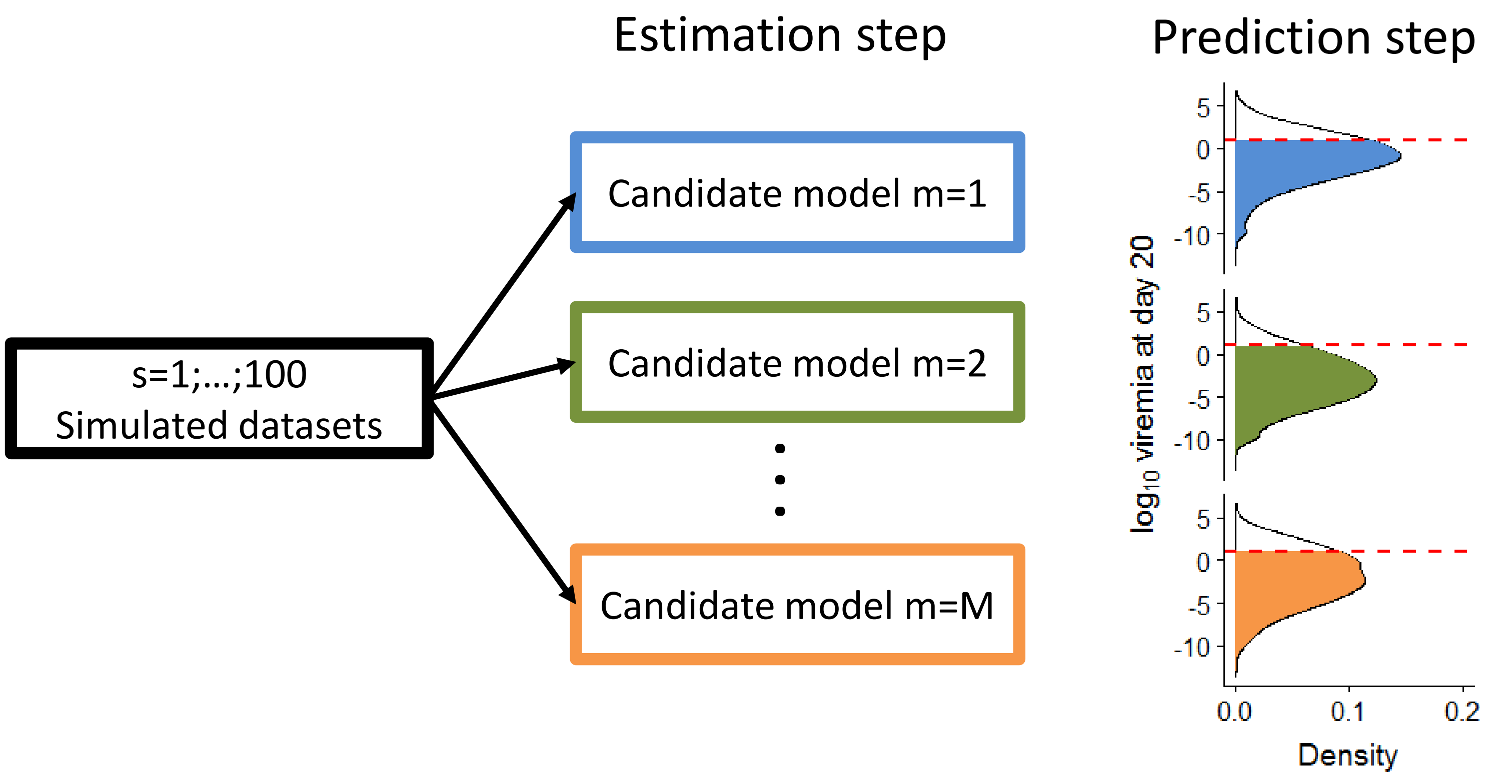


- Capability of MS and MA to anticipate the effect of a treatment
- Treatment initiated at day 6 and up to day 20

$$P_m^s = Pr(V_m^s(t = 20) < LLOQ)$$

Predictive performances of MS and MA

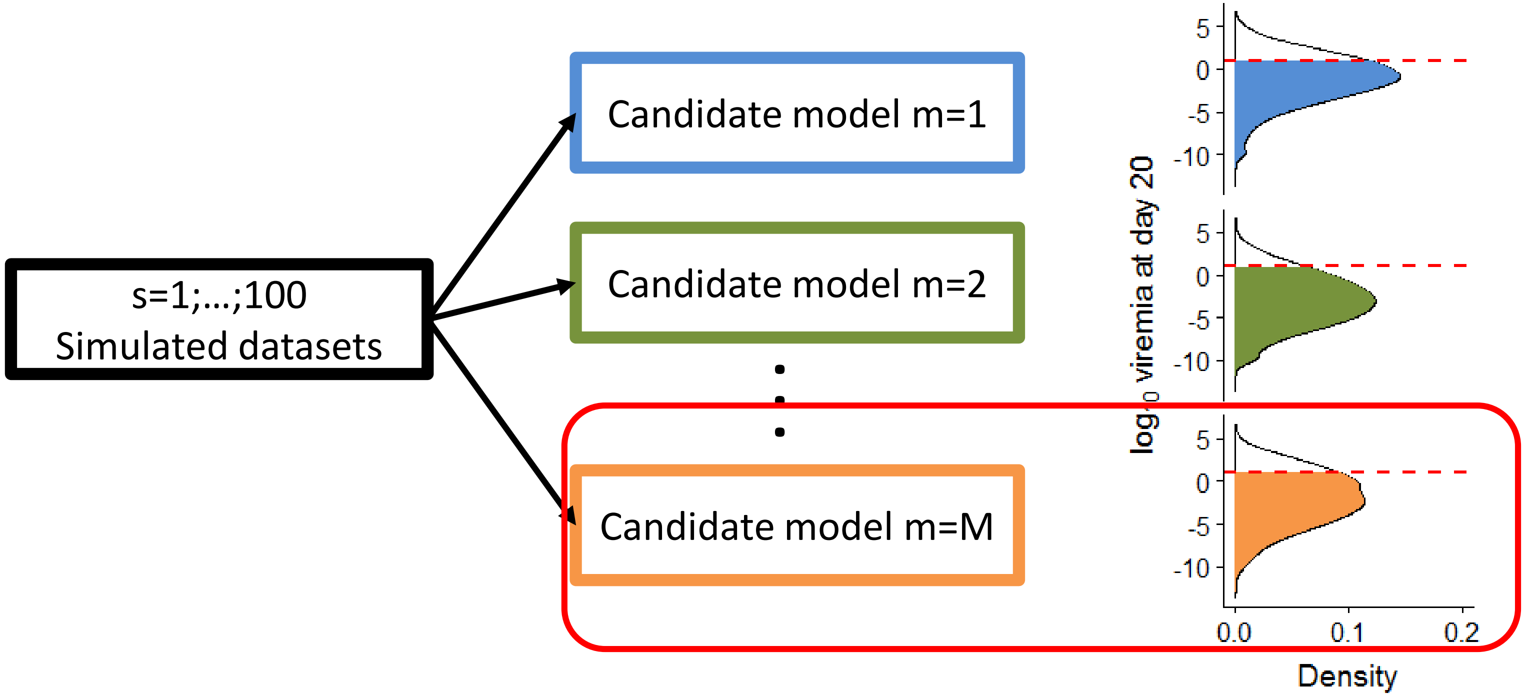
- Prediction of the percentage of patients with undetectable viral load (i.e. below 10 copies.mL^{-1}) at EoT
- 3 levels of efficacy: 90,95 or 99% initiated at day 6 and up to day 20



Predictive performances of MS and MA

- Prediction of the percentage of patients with undetectable viral load (i.e. below 10 copies.mL^{-1}) at EoT
- 3 levels of efficacy: 90,95 or 99% initiated at day 6 and up to day 20

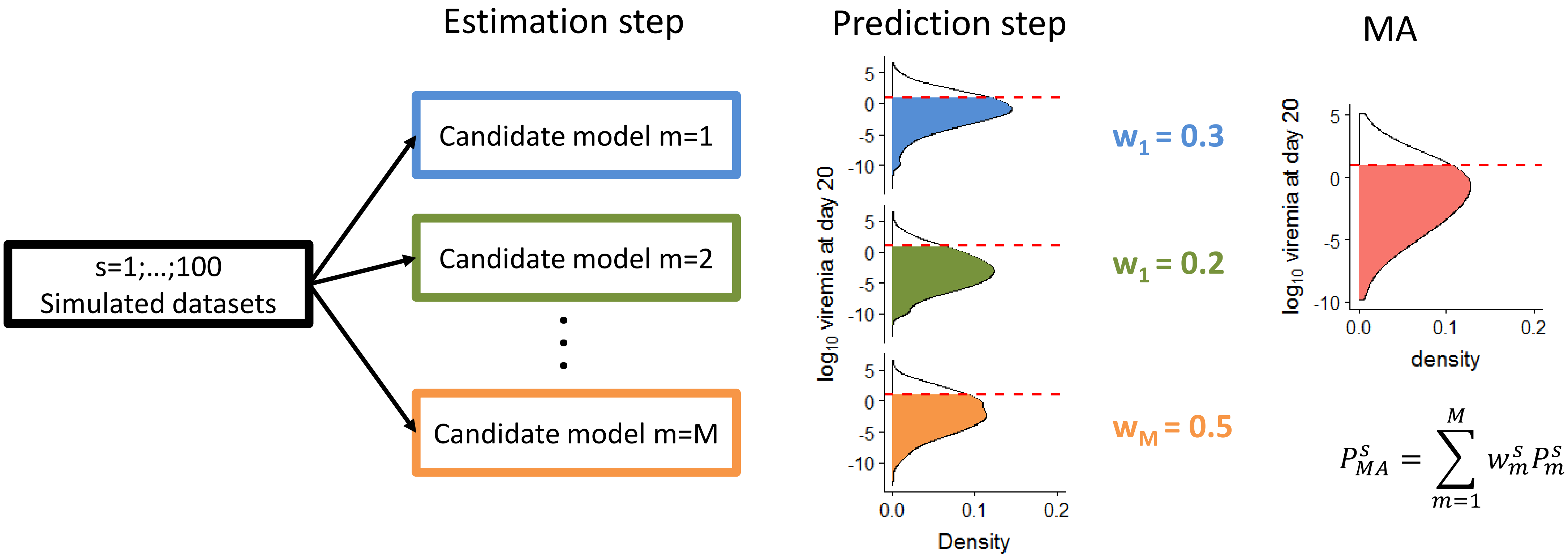
Estimation step   Prediction step   MS



$$P_{MS}^{s} = Pr(V_{MS}^{s}(t = 20) < LLOQ)$$

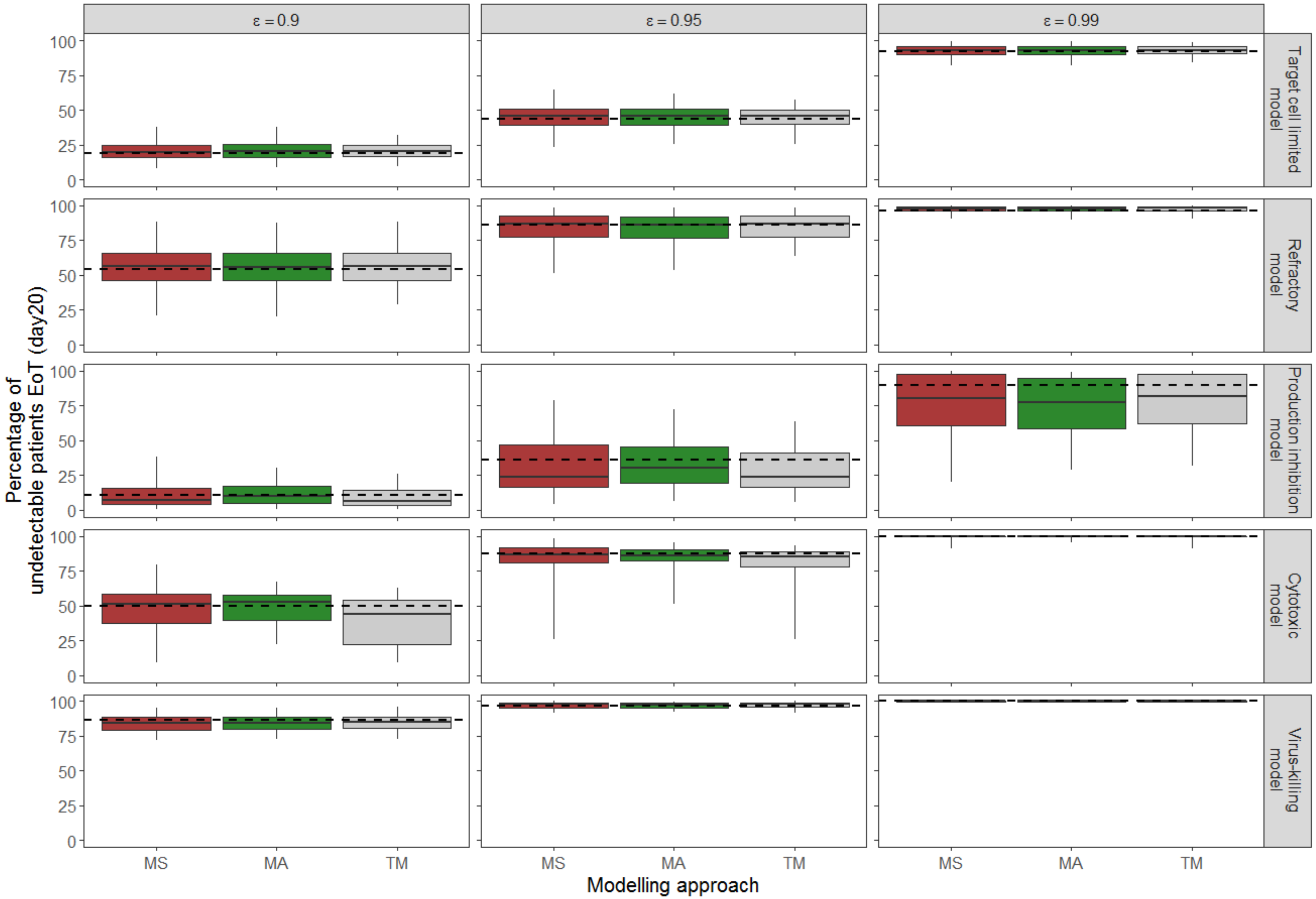
Predictive performances of MS and MA

- Prediction of the percentage of patients with undetectable viral load (i.e. below 10 copies.mL^{-1}) at EoT
- 3 levels of efficacy: 90,95 or 99% initiated at day 6 and up to day 20

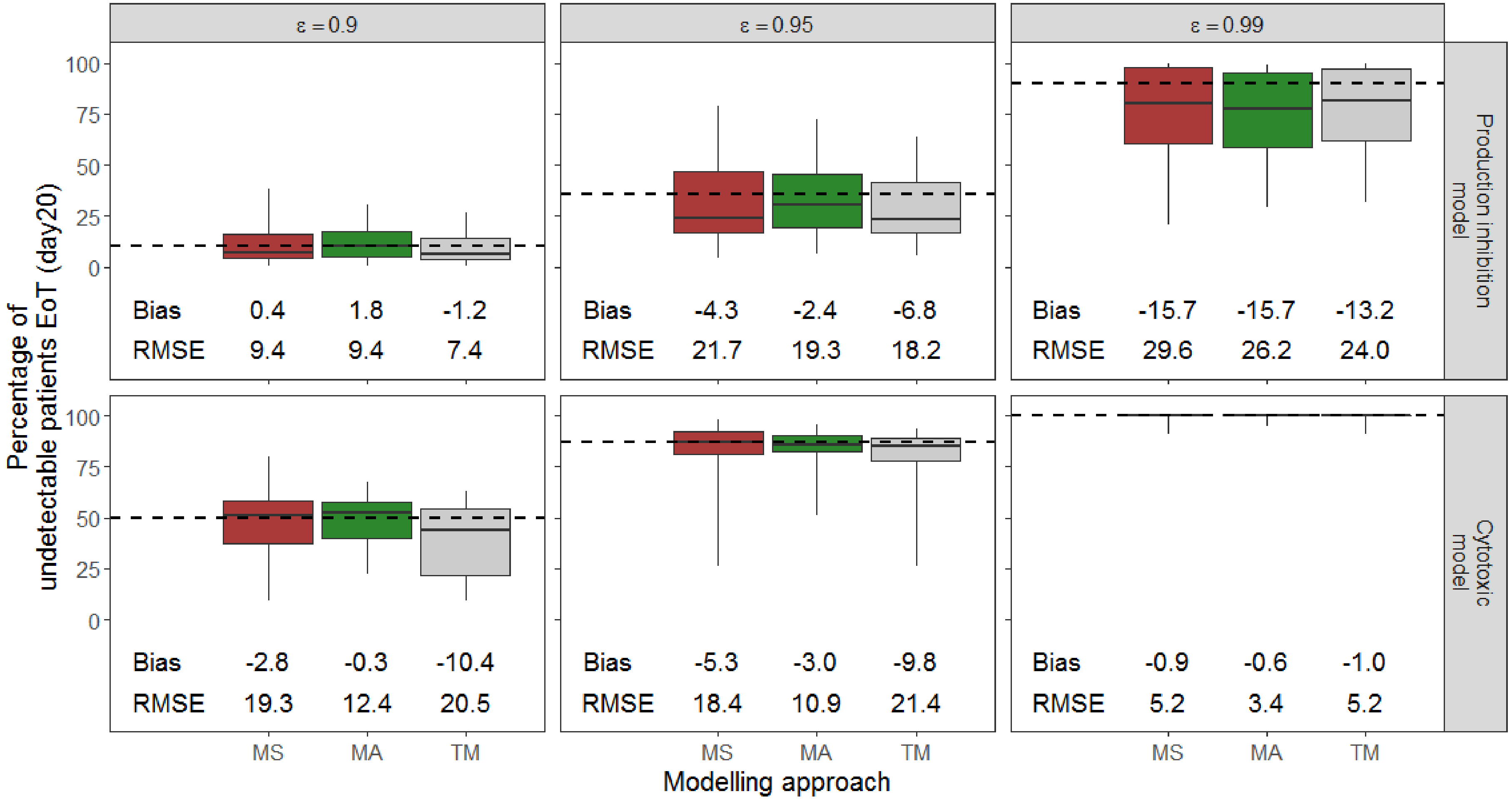


$$P_{MA}^{s} = \sum_{m=1}^{M} w_m^s P_m^s$$

Predicted percentage of undetectable viral loads



Predicted percentage of undetectable viral loads



Conclusion

- MS in viral dynamics can lead to poor coverage rates for parameter estimates
- MA can improve coverages by taking into account both parameter and model uncertainty
- MS has provided good predictions in our scenarios

➔ MA is easy to implement and should be used to refine parameter estimates and predictions

Perspectives

- Explore settings where the true model is not part of the candidate models
- Find an alternative to asymptotic approximation for parameter uncertainties
  - Implement other methods to compute the FIM such as HMC[1] or SIR[2]

[1] Ueckert et al. 2015
[2] Dosne et al. *J Pharmacokinet Pharmacodyn* 2016

Announcement

Organizers: - **Jérémie Guedj**, INSERM, jeremie.guedj@inserm.fr

- **Mélanie Prague**, INRIA Bordeaux, melanie.prague@inria.fr

See info: https://viraldynamics.sciencesconf.org/

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