

Estimations of mechanistic models by sequential and variational approach. Application to SARS-CoV-2.

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Internship objectives

Objectives of this internship :

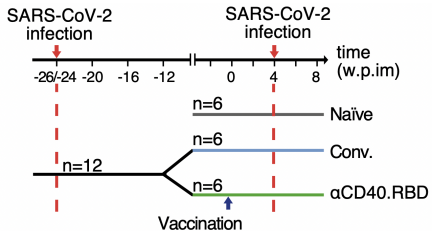
- Comparing sequential and variational approach
- Apply variational approach to a modelling problem for SARS-Cov-2

Table of contents

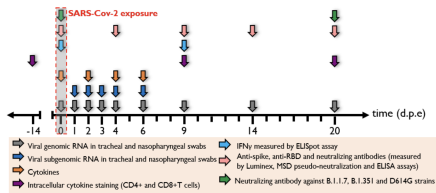
- 1 Thematic of study
 - About data
 - A mechanistic model
- 2 Sequential approach
 - A simplified model
 - Comparison of time-schemes
- 3 Variational approach
 - Simulation scheme
 - Application of simulation scheme
- 4 Modelization
 - Basic reproduction number
 - Mathematical models
 - Results

Thematic of study

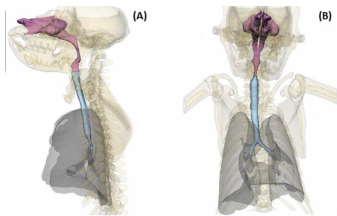
Case study



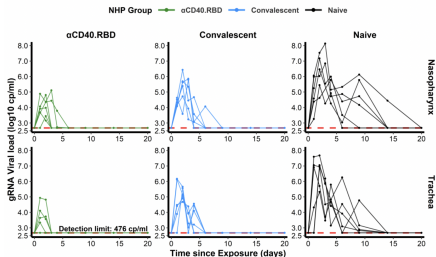
(a) Study design



(b) Prelevement design

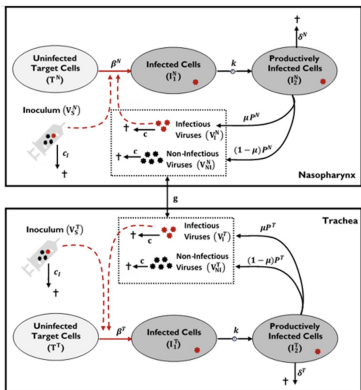


3D representation of the NHP respiratory system: (A) Sagittal view, (B) Coronal view: Lung (Grey), Trachea (Blue) and Nasal Region (Purple)



A mechanistic model

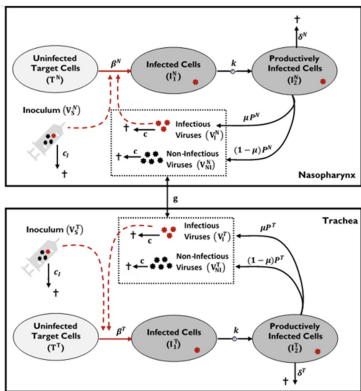
For $X \in \{N = \text{Nasopharynx} ; T = \text{Trachea}\}$, we define mathematical model ¹ by :



$$\left\{ \begin{array}{l} \dot{T}^X = -\beta T^X V_i^X - \mu\beta T^X V_S^X \\ \dot{I}_1^X = \beta T^X V_i^X + \mu\beta T^X V_S^X - kI_1^X \\ \dot{I}_2^X = kI_1^X - \delta I_2^X \\ \dot{V}_i^X = \mu P^X I_2^X - cV_i^X - \beta T^X V_i^X \\ \dot{V}_{ni}^X = (1-\mu)P^X I_2^X - cV_{ni}^X \\ \dot{V}_S^X = -\mu\beta T^X V_S^X - c_I V_S^X \end{array} \right.$$

¹Marie Alexandre et al. (2022). "Modelling the response to vaccine in non-human primates to define SARS-CoV-2 mechanistic correlates of protection". In: *eLife*.

A mechanistic model



The statistical model is defined by :

$$\begin{cases} \log_{10}(\beta_i) = \log_{10}(\beta_{pop}) + u_i^\beta \\ \log(\delta_i) = \log(\delta_{pop}) + u_i^\delta \end{cases}$$

where $u_i^\beta \sim \mathcal{N}(0, \omega_\beta^2)$ and $u_i^\delta \sim \mathcal{N}(0, \omega_\delta^2)$.

And, the observation model is defined by :

$$\begin{cases} gRNA_{ij}^X = \log_{10}(V_i^X + V_{ni}^X + V_S^X)(t_{ij}, \psi_i^X) + \epsilon_{ij,g}^X \\ sgRNA_{ij}^X = \alpha_{sgRNA} \log_{10}(I_1^X + I_2^X)(t_{ij}, \psi_i^X) + \epsilon_{ij,sg}^X \end{cases}$$

where $\epsilon_{ij,g}^X \sim \mathcal{N}(0, \sigma_{g,X}^2)$, $\epsilon_{ij,sg}^X \sim \mathcal{N}(0, \sigma_{sg,X}^2)$.

\Rightarrow These 3 models define our **non linear mixed effects model**.

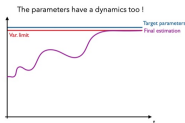
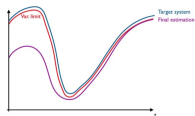
Two approaches to estimating parameters

Estimating parameters

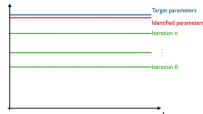
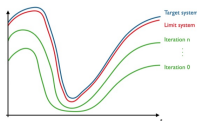
Sequential approach

Variational approach

by using Kalman Filter



by using MONOLIX software



Sequential approach

Simplified model

We only focus on nasopharynx compartment with the mathematical model :

$$\left\{ \begin{array}{l} \dot{T} = -\beta TV_i - \mu\beta TV_S \\ \dot{I}_1 = \beta TV_i + \mu\beta TV_S - kI_1 \\ \dot{I}_2 = kI_1 - \delta I_2 \\ \dot{V}_i = \mu PI_2 - cV_i - \beta TV_i \\ \dot{V}_{ni} = (1 - \mu)PI_2 - cV_{ni} \\ \dot{V}_S = -\mu\beta TV_S - cI V_S \end{array} \right. \quad (1)$$

and the observation model :

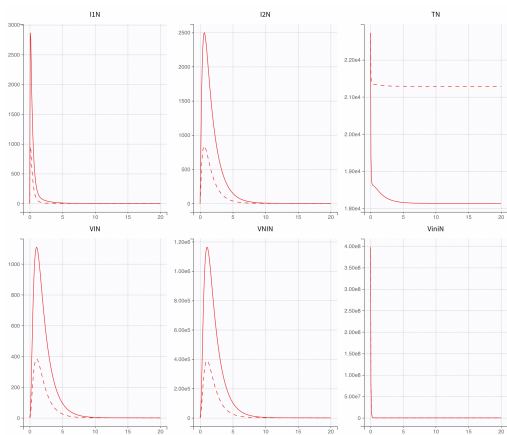
$$gRNA_{ij} = \log_{10}(V_i + V_{ni} + V_S)(t_{ij}, \psi_i) + \epsilon_{ij} \quad (2)$$

where $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$.

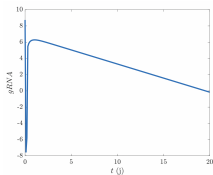
Stiffs equations

Figure: Simulation of the dynamics of the compartments of the previous model for different values of β and $\delta = 0.85$.

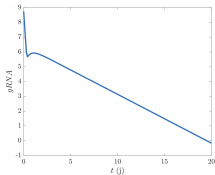
dashed line : $\beta = 10^{-5.5}$, continuous line : $\beta = 10^{-5}$.



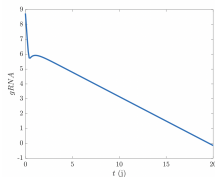
Comparison of explicit and implicit time-schemes



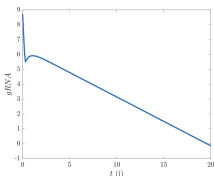
(a) Euler explicit
 $\beta = 10^{-5.44}$ et $\delta = 0.85$
 Time step 10^{-1}



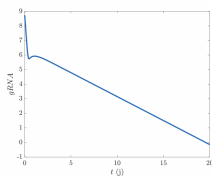
(b) Euler explicit
 $\beta = 10^{-5.44}$ et $\delta = 0.85$
 Time step 10^{-2}



(c) Euler explicit
 $\beta = 10^{-5.44}$ et $\delta = 0.85$
 Time step 10^{-3}



(d) Implicit RK 3
 $\beta = 10^{-5.44}$ et $\delta = 0.85$
 Time step 10^{-1}



(e) Implicit RK 3
 $\beta = 10^{-5.44}$ et $\delta = 0.85$
 Time step 10^{-2}

Working prospects

For the two next weeks, we have to :

- Solve issue about the numerical resolution method.
- Finish implementation of Kalman filter algorithm.
- Compare sequential approach with the variational approach.

Variational approach

Simulation scheme

$$\left\{ \begin{array}{l} \dot{T} = -\beta TV_i - \mu\beta TV_S \\ \dot{I}_1 = \beta TV_i + \mu\beta TV_S - kI_1 \\ \dot{I}_2 = kI_1 - \delta I_2 \\ \dot{V}_i = \mu PI_2 - cV_i - \beta TV_i \\ \dot{V}_{ni} = (1 - \mu)PI_2 - cV_{ni} \\ \dot{V}_S = -\mu\beta TV_S - cV_S \end{array} \right.$$

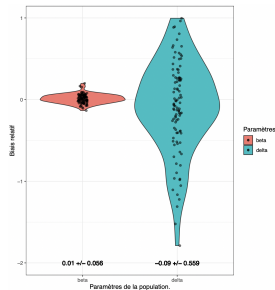
The observation model :

$$gRNA_{ij} = \log_{10}(V_i + V_{ni} + V_S)(t_{ij}, \psi_i) + \epsilon_{ij}$$

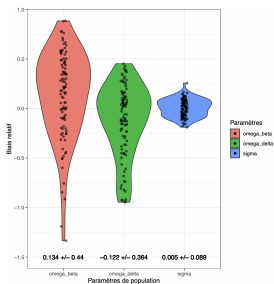
where $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$.

- Variability on β and δ + others parameters are fixed
- Simulation of 100 groups of 10 fictive monkeys on days 0, 1, 2, 3, 4, 6, 9, 14 and 20.
- Estimation of parameters with simulated data with MONOLIX software
- Comparison between estimated and real parameters

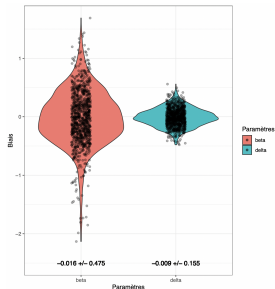
Application of simulation scheme



(a) Relative bias of parameters β_{pop} and δ_{pop} .



(b) Relative bias of parameters ω_β , ω_δ and σ



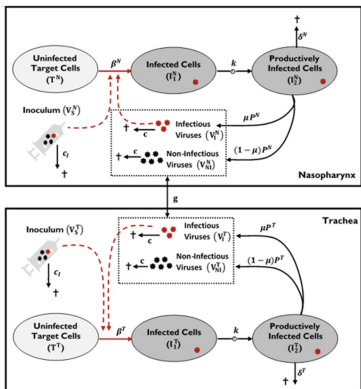
(c) Individual bias of parameters β and δ .

Application of simulation scheme

Approach	Parameters	Population		Individual	
		Relative bias	Coverage rate	Individual bias	Coverage rate
Variational	β	0.01 ± 0.056	0.95	-0.016 ± 0.475	0.92
	ω_β	0.134 ± 0.44	0.85	Undefined	
	δ	-0.09 ± 0.559	0.90	-0.009 ± 0.155	0.88
	ω_δ	-0.122 ± 0.364	0.92	Undefined	
	σ	0.005 ± 0.089	0.94	Undefined	
Sequential

Modelization

A new model



We modify the observation model :

$$\begin{cases} gRNA_{ij}^X &= \log_{10}(V_i^X + V_{ni}^X + V_S^X)(t_{ij}, \psi_i^X) + \epsilon_{ij,g}^X \\ sgRNA_{ij}^X &= \alpha_{sgRNA} \log_{10}(\boxed{I_1^X + I_2^X})(t_{ij}, \psi_i^X) + \epsilon_{ij,sg}^X \end{cases}$$

by :

$$\begin{cases} gRNA_{ij}^X &= \log_{10}(V_i^X + V_{ni}^X + V_S^X)(t_{ij}, \psi_i^X) + \epsilon_{ij,g}^X \\ sgRNA_{ij}^X &= \alpha_{sgRNA} \log_{10}(\boxed{I_2^X})(t_{ij}, \psi_i^X) + \epsilon_{ij,sg}^X \end{cases}$$

where $\epsilon_{ij,g}^X \sim \mathcal{N}(0, \sigma_{g,X}^2)$, $\epsilon_{ij,sg}^X \sim \mathcal{N}(0, \sigma_{sg,X}^2)$.

Basic reproduction number

$$F = \begin{pmatrix} 0 & 0 & \beta T^X(0) & \mu\beta T^X(0) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad \text{et} \quad V = \begin{pmatrix} k & 0 & 0 & 0 \\ -k & \delta & 0 & 0 \\ 0 & -\mu P^X & c + \beta T^X(0) & 0 \\ 0 & 0 & 0 & c_I + \mu\beta T^X(0) \end{pmatrix}$$

By taking the spectral radius of FV^{-1} , we get the basic reproduction number in $X \in \{N; T\}$ ² :

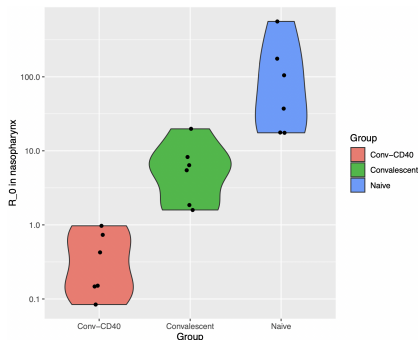
$$R_0^X = \frac{\beta T^X(0)\mu P^X}{\delta(c + \beta T^X(0))} \quad (3)$$

²Odo Diekmann, J.A.P. Heesterbeek, and Johan Metz (1990). "On the Definition and the Computation of the Basic Reproduction Ratio R_0 in Models For Infectious-Diseases in Heterogeneous Populations". In: *Journal of mathematical biology*; Odo Diekmann, J.A.P. Heesterbeek, and M.G. Roberts (2009). "The construction of next-generation matrices for compartmental epidemic models". In: *Journal of the Royal Society, Interface / the Royal Society*; Jane Heffernan, R.J. Smith, and L.M. Wahl (2005). "Perspectives on the Basic Reproductive Ratio". In: *Journal of the Royal Society, Interface / the Royal Society*

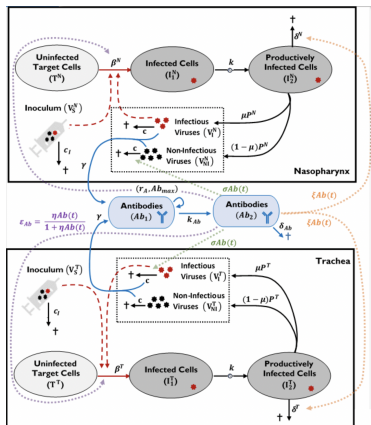
Distribution of R_0 by group

$$R_0^X = \frac{\beta T^X(0)\mu P^X}{\delta(c + \beta T^X(0))} \quad (4)$$

Figure: Distribution of basic reproduction number R_0 in nasopharynx by group



The starting mathematical model

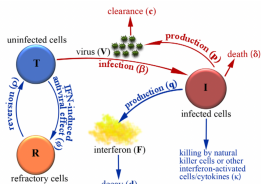


For $X \in \{N = \text{Nasopharynx} ; T = \text{Trachea}\}$, we define mathematical model by :

$$\left\{ \begin{array}{l} \dot{T}^X = -(1 - \epsilon_{Ab})\beta V_i^X T^X - \mu(1 - \epsilon_{Ab})\beta V_S^X T^X \\ \dot{I}_1^X = (1 - \epsilon_{Ab})\beta V_i^X T^X + \mu(1 - \epsilon_{Ab})\beta V_S^X T^X - k I_1^X \\ \dot{I}_2^X = k I_1^X - \delta I_2^X - \xi Ab_2 I_2^X \\ \dot{V}_i^X = P^X \mu I_2^X - c V_i^X - (1 - \epsilon_{Ab})\beta V_i^X T^X \\ \dot{V}_{ni}^X = P^X (1 - \mu) I_2^X - c V_{ni}^X \\ \dot{V}_S^X = -c_I V_S^X - \mu(1 - \epsilon_{Ab})\beta V_S^X T^X \\ \dot{Ab}_1 = \gamma V + r_A \left(1 - \frac{Ab_1}{Ab_{max}}\right) Ab_1 - k_{Ab} Ab_1 \\ \dot{Ab}_2 = k_{Ab} Ab_1 - \xi Ab_2 I_2 - \delta_{Ab} Ab_2 \end{array} \right.$$

Review of scientific literature

Figure: Models incorporating a refractory cell compartment.



$$\frac{dT}{dt} = -\beta VT - \phi FT + \rho R$$

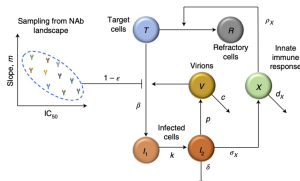
$$\frac{dI}{dt} = \beta VT - \delta I - \kappa IF$$

$$\frac{dR}{dt} = \phi FT - \rho R$$

$$\frac{dV}{dt} = pI - cV$$

$$\frac{dF}{dt} = qI - dF$$

(a) Voir Kasia A. PAWELEK and al. ³



$$\frac{dT}{dt} = -\beta(1 - \epsilon)VT - \rho_X XT$$

$$\frac{dR}{dt} = \rho_X XT$$

$$\frac{dI_1}{dt} = \beta(1 - \epsilon)VT - \kappa I_1$$

$$\frac{dI_2}{dt} = \kappa I_1 - \delta I_2$$

$$\frac{dV}{dt} = pI_2 - cV$$

$$\frac{dX}{dt} = \frac{\sigma_X I_2 (1 - X)}{\phi_X + I_2} - d_X X$$

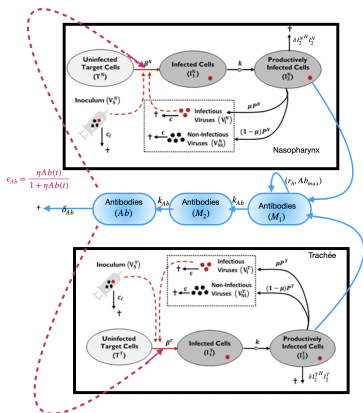
(b) See Pranesh PADMANABHAN and al. ⁴

³Kasia A. Pawelek et al. (2012). "Modeling Within-Host Dynamics of Influenza Virus Infection Including Immune Responses". In: *PLOS Computational Biology*

⁴Pranesh Padmanabhan, Rajat Desikan, and Narendra Dixit (2022). "Modeling how antibody responses may determine the efficacy of COVID-19 vaccines". In: *Nature Computational Science*

A new model

For $X \in \{N = \text{Nasopharynx} ; T = \text{Trachea}\}$, we define mathematical model⁵ by :



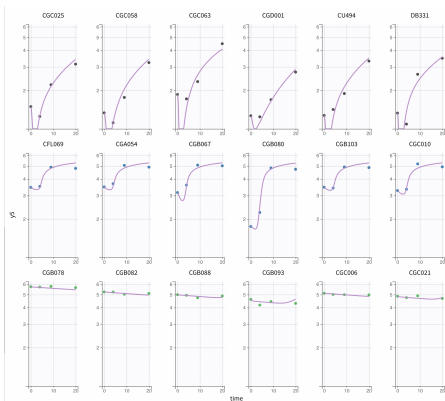
$$\left\{ \begin{array}{l} \dot{T}^X = -(1 - \varepsilon_{Ab})\beta V_i^X T^X - \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X \\ \dot{I}_1^X = (1 - \varepsilon_{Ab})\beta V_i^X T^X + \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X - kI_1^X \\ \dot{I}_2^X = kI_1^X - \delta(I_2^X)^{H_2} I_2^X \\ \dot{V}_i^X = P^X \mu I_2^X - cV_i^X - (1 - \varepsilon_{Ab})\beta V_i^X T^X \\ \dot{V}_{ni}^X = P^X (1 - \mu) I_2^X - cV_{ni}^X \\ \dot{V}_S^X = -c_I V_S^X - \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X \\ \dot{M}_1 = \gamma I_2 + r_A \left(1 - \frac{M_1}{Ab_{max}}\right) M_1 - k_{Ab} M_1 \\ \dot{M}_2 = k_{Ab} M_1 - k_{Ab} M_2 \\ \dot{Ab} = k_{Ab} M_2 - \delta_{Ab} Ab \end{array} \right.$$

⁵Ashish Goyal, E. Fabian Cardozo-Ojeda, and Joshua T. Schiffer (2020). "Potency and timing of antiviral therapy as determinants of duration of SARS-CoV-2 shedding and intensity of inflammatory response". In: *Science Advances*

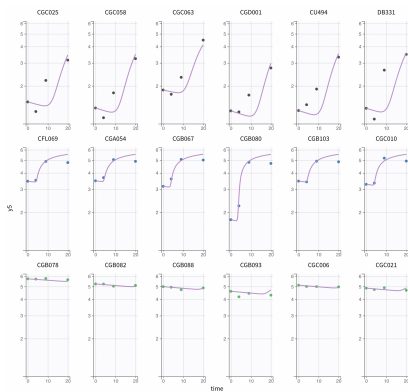
Results

Individual plots

Figure: Individual plots for the starting and the previous model.



(a) Starting model.
BIC_c=768



(b) New model.
BIC_c = 823

Results

Differences between studied models

The starting model :

$$\left\{ \begin{array}{l} \dot{T}^X = -(1 - \varepsilon_{Ab})\beta V_i^X T^X - \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X \\ \dot{I}_1^X = (1 - \varepsilon_{Ab})\beta V_i^X T^X + \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X - k I_1^X \\ \dot{I}_2^X = k I_1^X - \delta I_2^X - \xi A b_2 I_2^X \\ \dot{V}_i^X = P^X \mu I_2^X - c V_i^X - (1 - \varepsilon_{Ab})\beta V_i^X T^X \\ \dot{V}_{ni}^X = P^X (1 - \mu) I_2^X - c V_{ni}^X \\ \dot{V}_S^X = -c_I V_S^X - \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X \\ \dot{A}b_1 = \gamma V + r_A \left(1 - \frac{A b_1}{A b_{max}}\right) A b_1 - k_{Ab} A b_1 \\ \dot{A}b_2 = k_{Ab} A b_1 - \xi A b_2 I_2 - \delta_{Ab} A b_2 \end{array} \right.$$

The new model :

$$\left\{ \begin{array}{l} \dot{T}^X = -(1 - \varepsilon_{Ab})\beta V_i^X T^X - \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X \\ \dot{I}_1^X = (1 - \varepsilon_{Ab})\beta V_i^X T^X + \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X - k I_1^X \\ \dot{I}_2^X = k I_1^X - \delta (I_2^X)^H I_2^X \\ \dot{V}_i^X = P^X \mu I_2^X - c V_i^X - (1 - \varepsilon_{Ab})\beta V_i^X T^X \\ \dot{V}_{ni}^X = P^X (1 - \mu) I_2^X - c V_{ni}^X \\ \dot{V}_S^X = -c_I V_S^X - \mu(1 - \varepsilon_{Ab})\beta V_S^X T^X \\ \dot{M}_1 = \gamma I_2 + r_A \left(1 - \frac{M_1}{A b_{max}}\right) M_1 - k_{Ab} M_1 \\ \dot{M}_2 = k_{Ab} M_1 - k_{Ab} M_2 \\ \dot{A}b = k_{Ab} M_2 - \delta_{Ab} A b \end{array} \right.$$

Results

Model comparison

$$BICc = -2\mathcal{L}\mathcal{L}_y(\theta) + \dim(\theta_R) \log(N) + \dim(\theta_F) \log(n_{tot})$$

Basic model	Modification	BICc
The starting model	None	768
	$\dot{A}b_1 = \gamma l_2 + r_A \left(1 - \frac{Ab_1}{Ab_{max}}\right) Ab_1 - k_{Ab} Ab_1$	800
	$i_2^X = k l_1^X - \delta (l_2^X)^H l_2^X$	≥ 1000
The new model	None	823
	$\dot{M}_1 = \gamma V + r_A \left(1 - \frac{M_1}{Ab_{max}}\right) M_1 - k_{Ab} M_1$	789
	$i_2^X = k l_1^X - \delta l_2^X$	964

Conclusion

- After a review of the literature, the starting model is the best one among those that we have estimated.
- Finalize the implementation of sequential approach, apply simulation scheme and compare results with those of the variational approach.

Thanks for listening !

Any questions ?