Mathematical modelling for determining COVID-19 incidence from testing data

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Joint work with Christian Berrig and Viggo Andreasen

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Göteborg, October 23rd, 2023

Introduction to the problem

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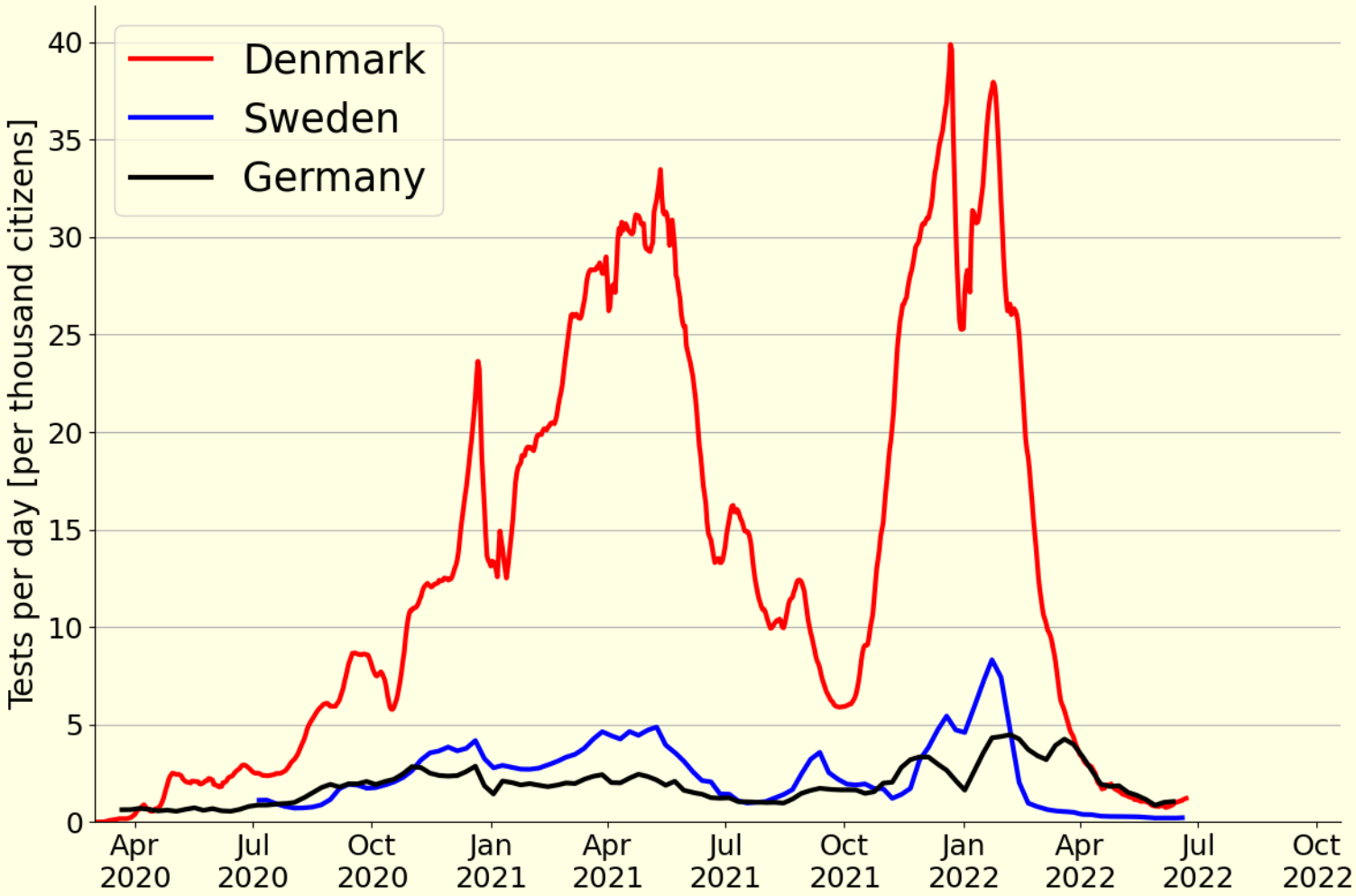
- **How do we compare case-counts between periods and places where testing activity was different?**

Let's look at some data...



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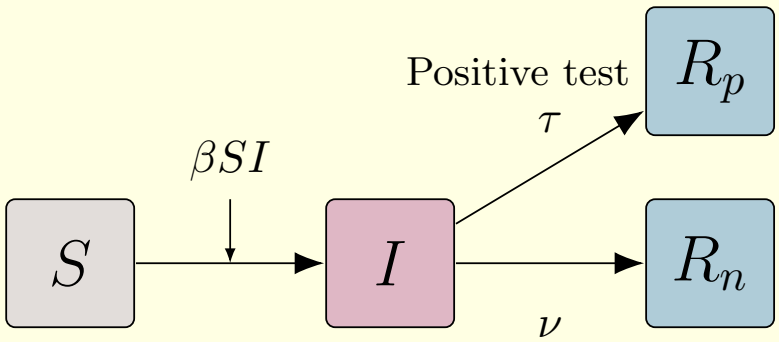
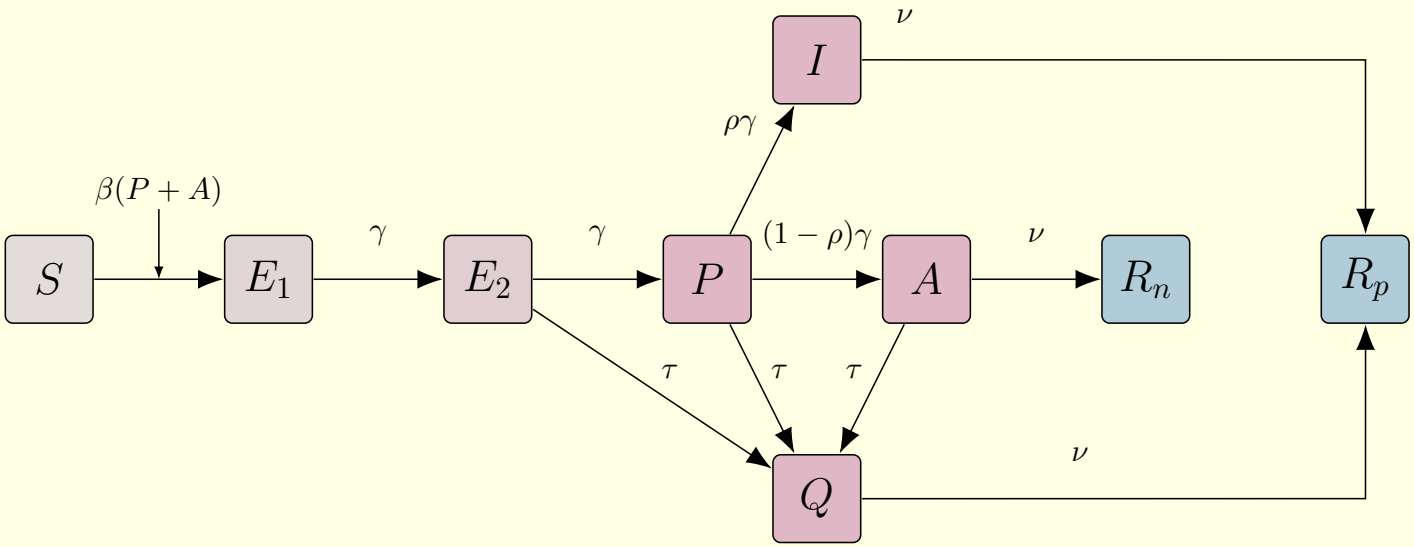
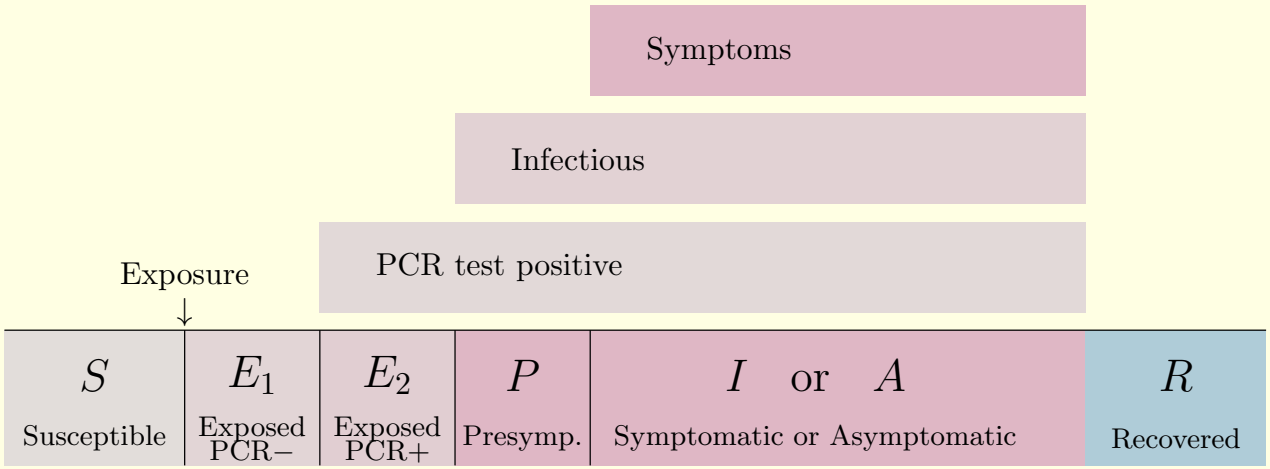
- Approach: Extend the classic SIR-model to include testing.

The conceptual idea

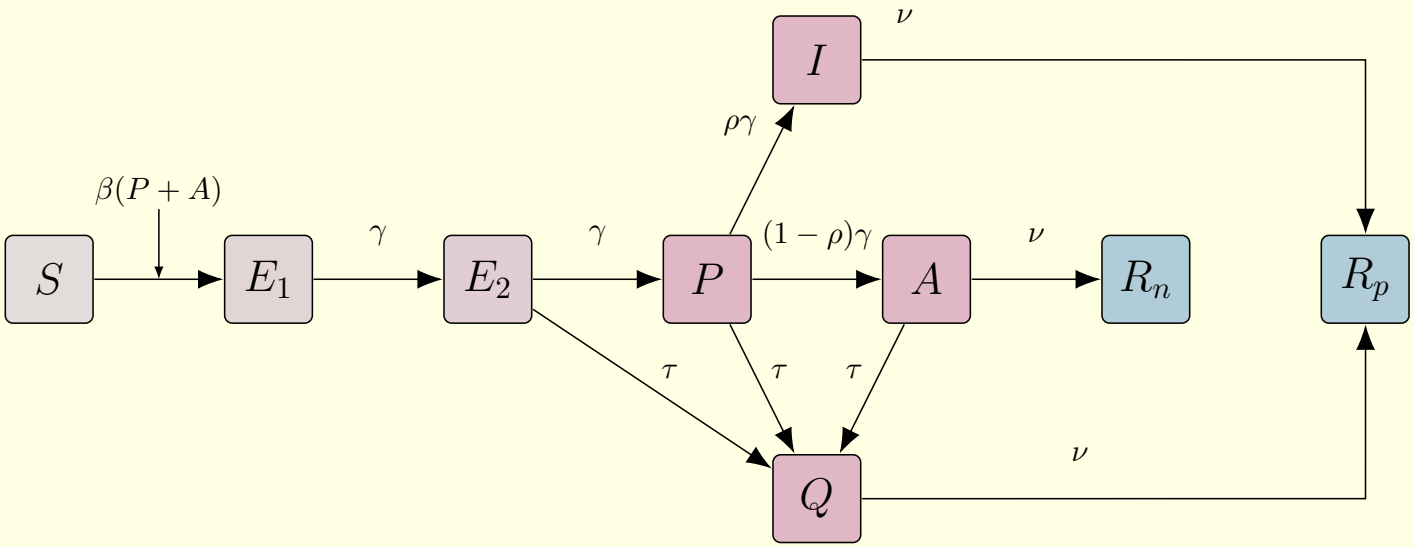


The model


ν
I
$\rho\gamma$
$\beta(P+A)$
S
γ
E_1
γ
E_2
P
$(1-\rho)\gamma$
A
ν
R_n
R_p
τ
τ
τ
ν
Q


Symptoms
Infectious
PCR test positive
Exposure
S
Susceptible
E_1
Exposed PCR−
E_2
Exposed PCR+
P
Presymp.
I or A
Symptomatic or Asymptomatic
R
Recovered

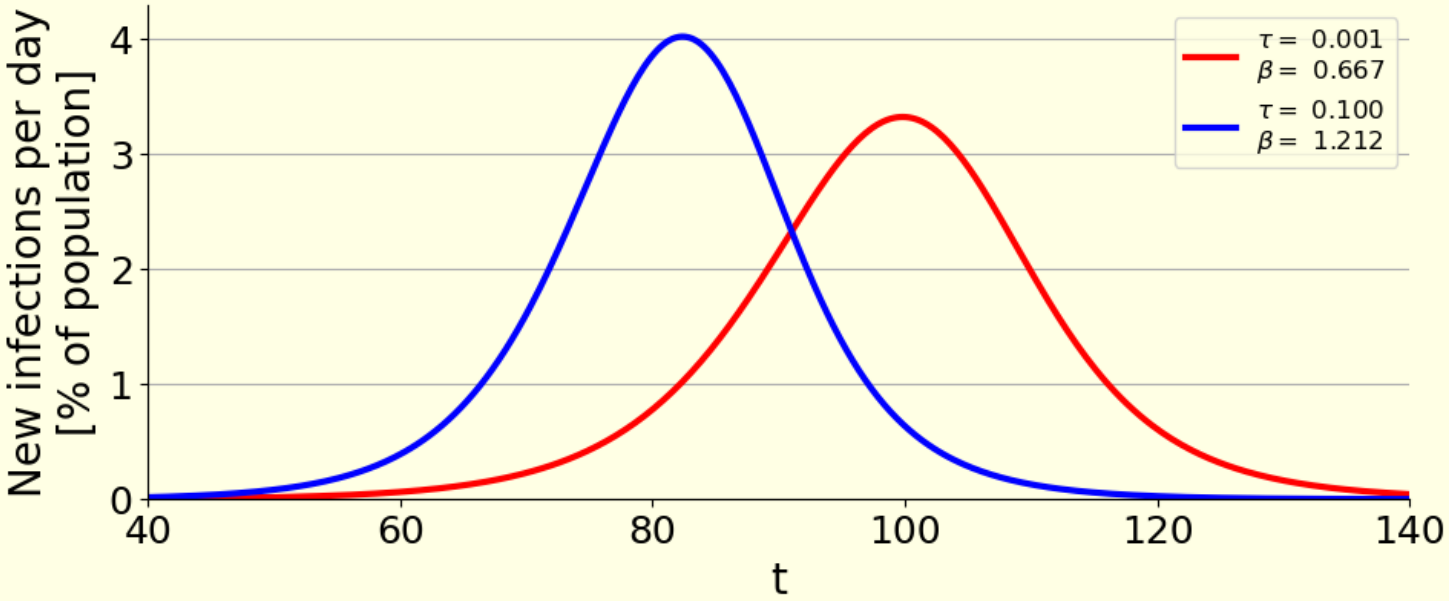
The model

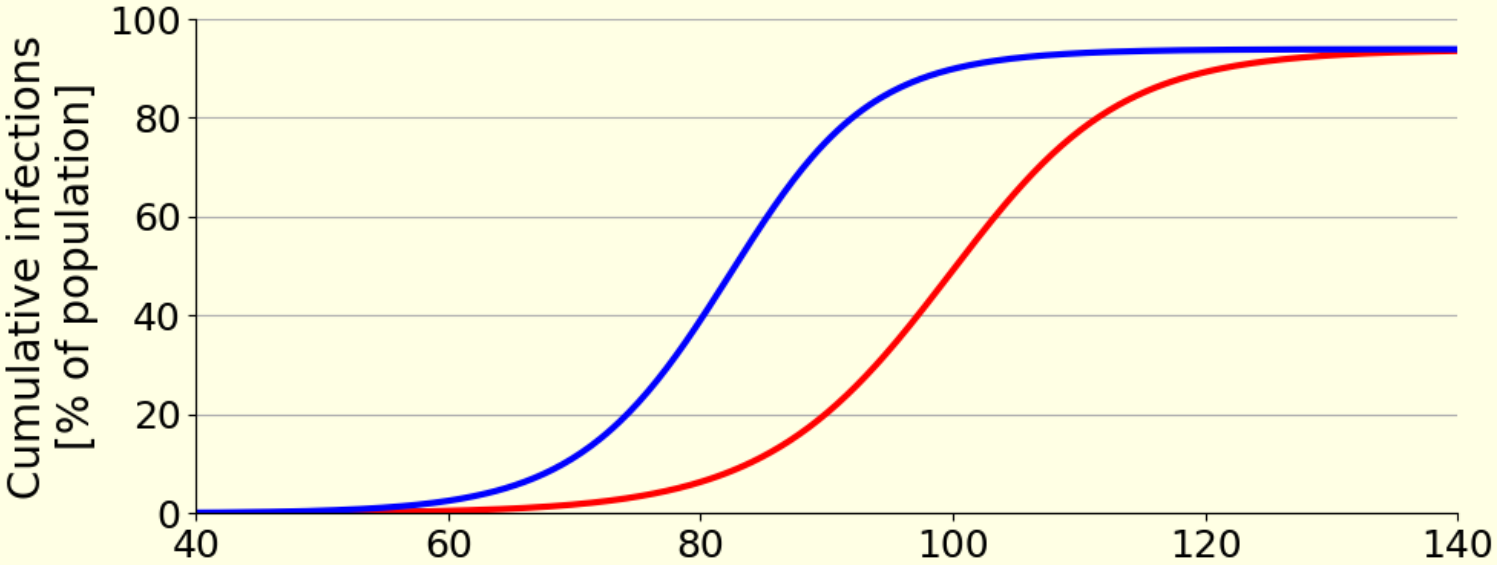


$$\dot{S} = -\beta S(P+A)$$
$$\dot{E}_1 = \beta S(P+A) - \gamma E_1$$
$$\dot{E}_2 = \gamma E_1 - (\gamma+\tau)E_2$$
$$\dot{P} = \gamma E_2 - (\gamma+\tau)P$$
$$\dot{I} = \gamma\rho P - \nu I$$
$$\dot{A} = \gamma(1-\rho)P - (\nu+\tau)A$$
$$\dot{Q} = \tau(E_2+P+A) - \nu Q$$
$$\dot{R}_p = \nu Q + \nu I$$
$$\dot{R}_n = \nu A$$

τ: Testing-rate. β: Infectivity.

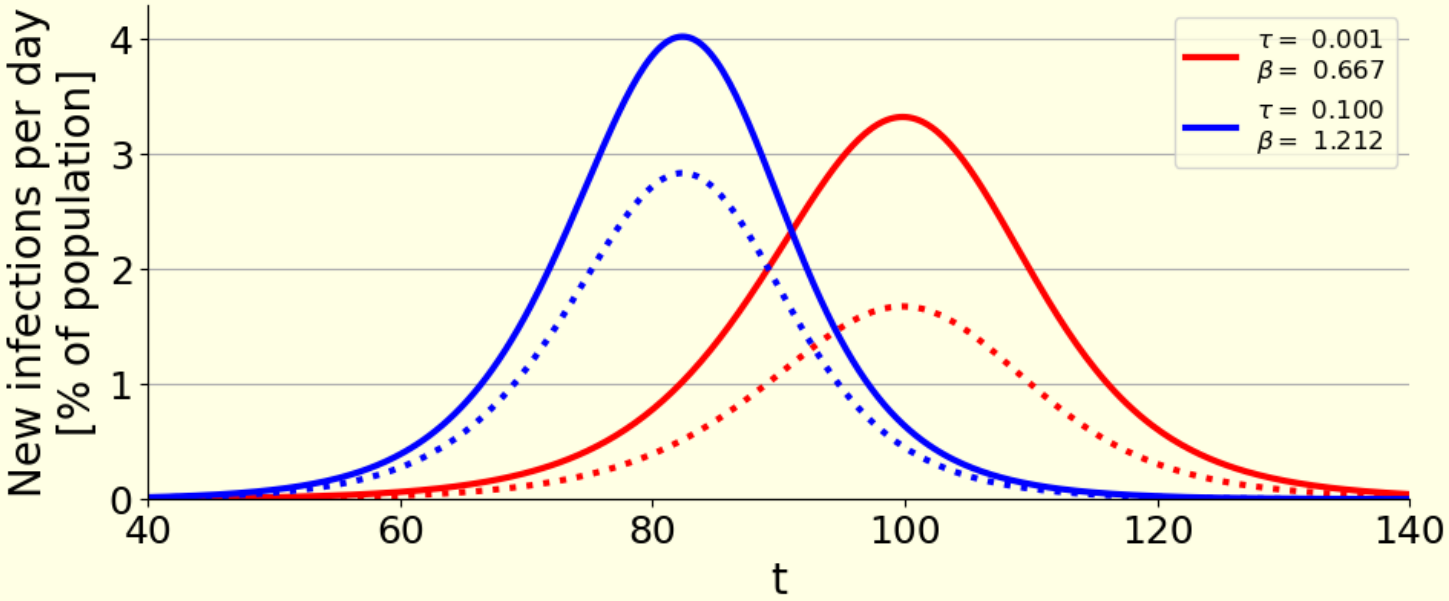
General model dynamics

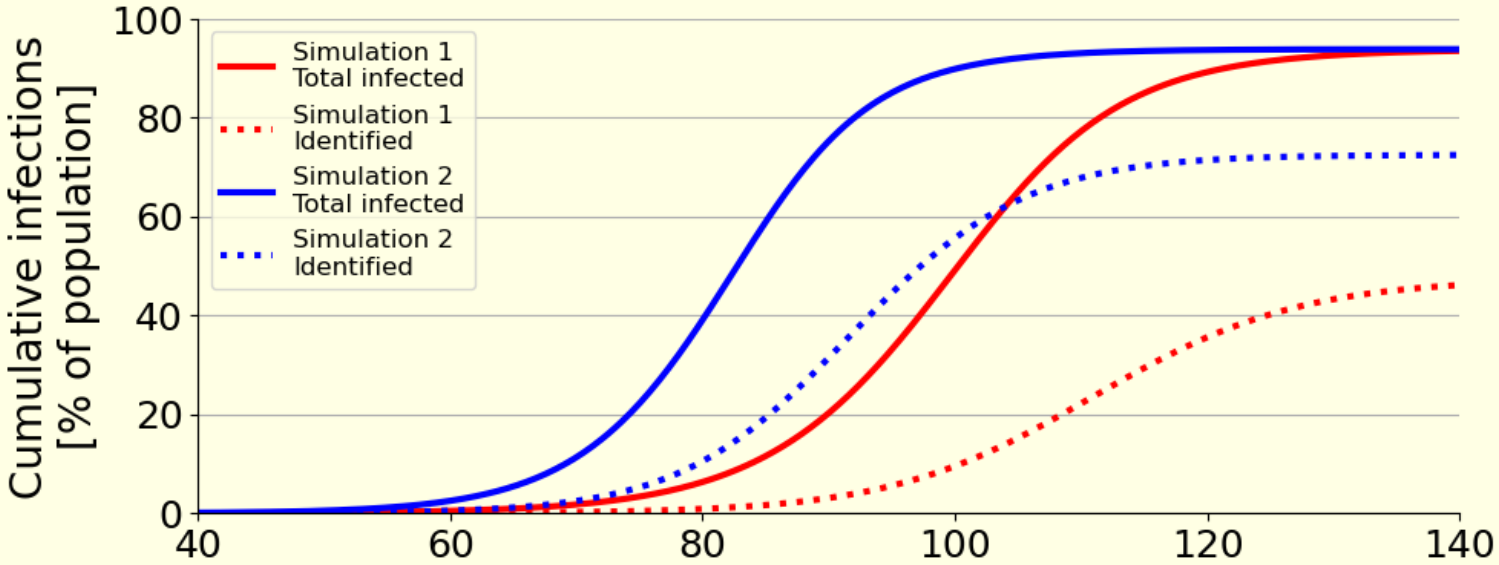




Other parameters: $\gamma = \nu = \frac{1}{3}$ and $\rho = \frac{1}{2}$.

General model dynamics





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Model analysis and correction ratio

We describe the correction factor as ratio between all cases and cases identified:

$$\frac{R_n(t) + R_p(t)}{R_p(t)} \tag{1}$$

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Inspired by previous work on epidemic final size[1] (and after a lot of analysis and calculation), we find that as $t \to \infty$

$$\frac{R_p}{R_n + R_p} = 1 - \left(1 - \frac{\tau}{\gamma + \tau}\right)\left(1 - \frac{\gamma\rho + \tau}{\gamma + \tau}\right)\left(\frac{\nu}{\nu + \tau}\right) \tag{2}$$

[1] (Andreasen, 2018, *Bull. Math. Biol.*)

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Note that this is independent of β.

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Calculating the correction-factor

$$\frac{R_p}{R_n + R_p} = 1 - \left(1 - \frac{\tau}{\gamma + \tau}\right)\left(1 - \frac{\gamma\rho + \tau}{\gamma + \tau}\right)\left(\frac{\nu}{\nu + \tau}\right)$$

With parameters: $\gamma = \nu = \frac{1}{3}$ and $\rho = \frac{1}{2}$.

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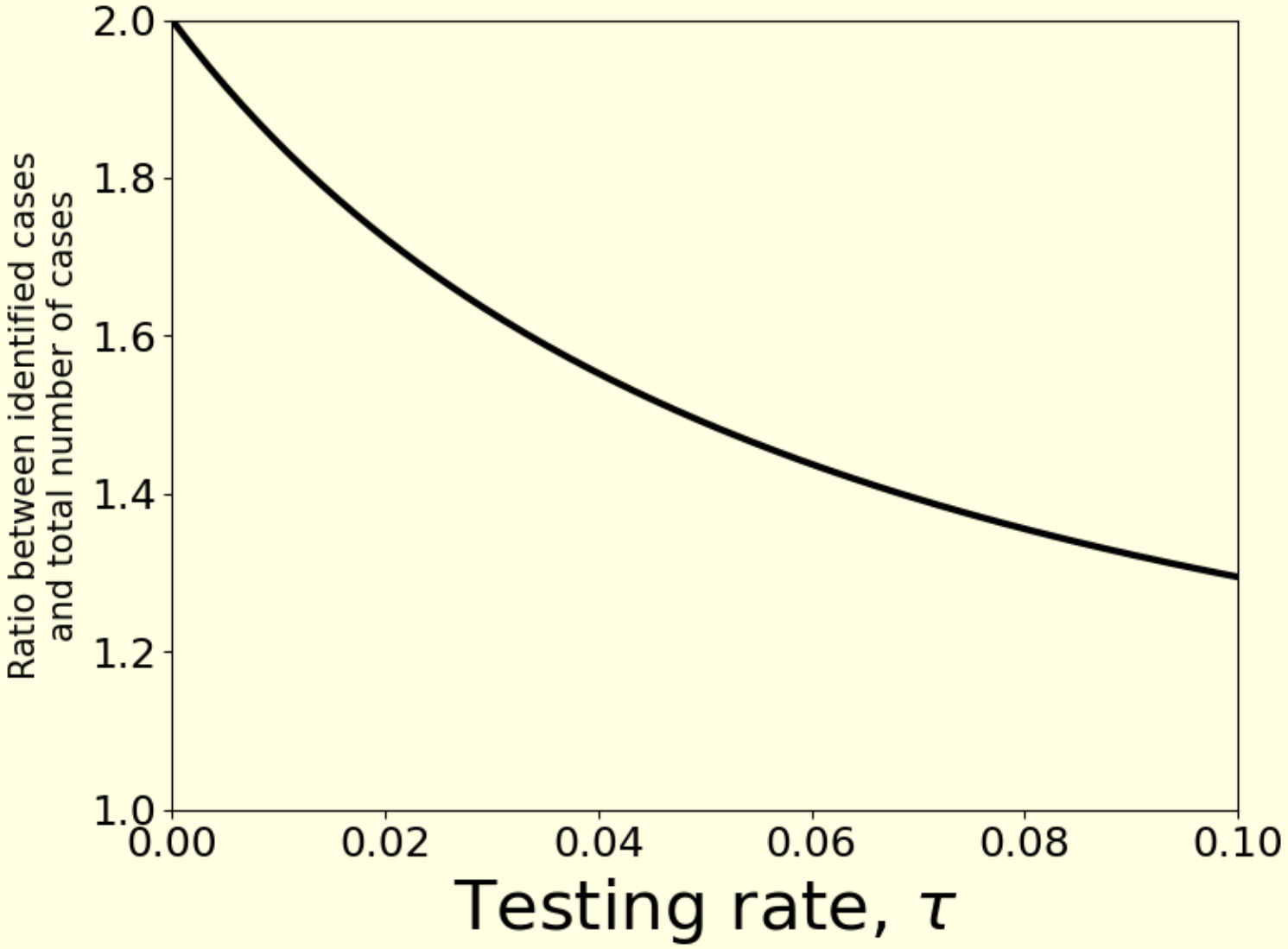
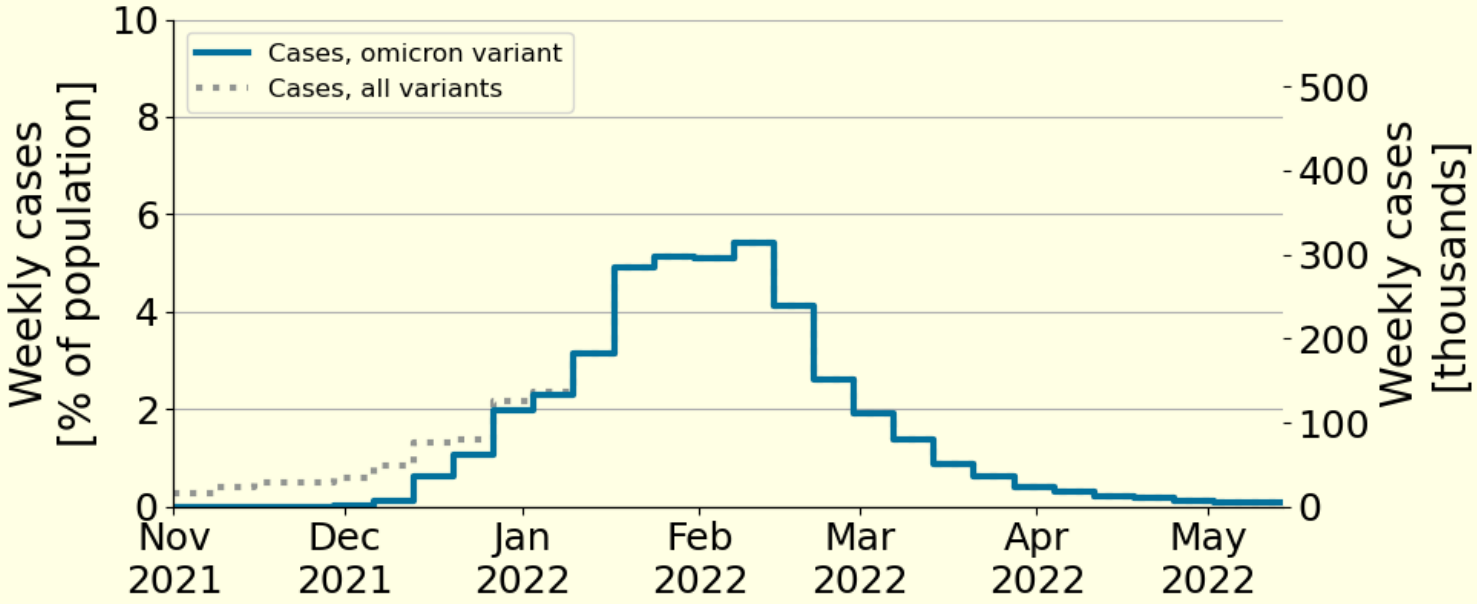
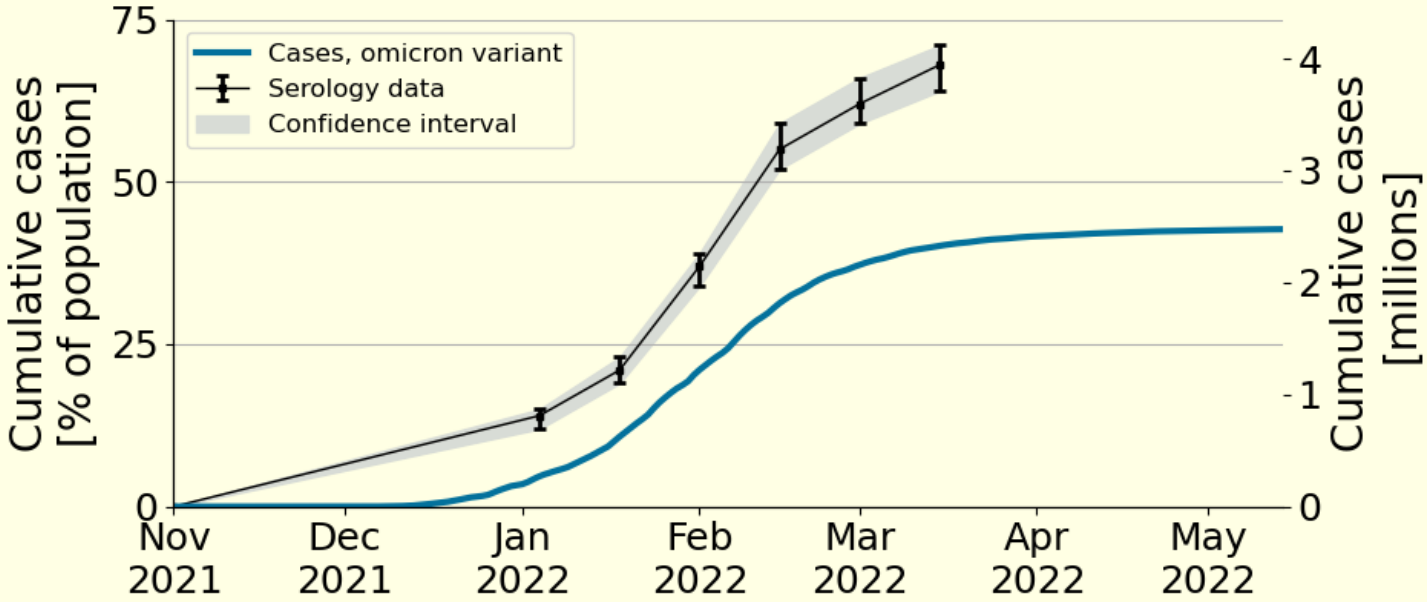
Calculating the correction-factor



With parameters: $\gamma = \nu = \frac{1}{3}$ and $\rho = \frac{1}{2}$.

The Danish data





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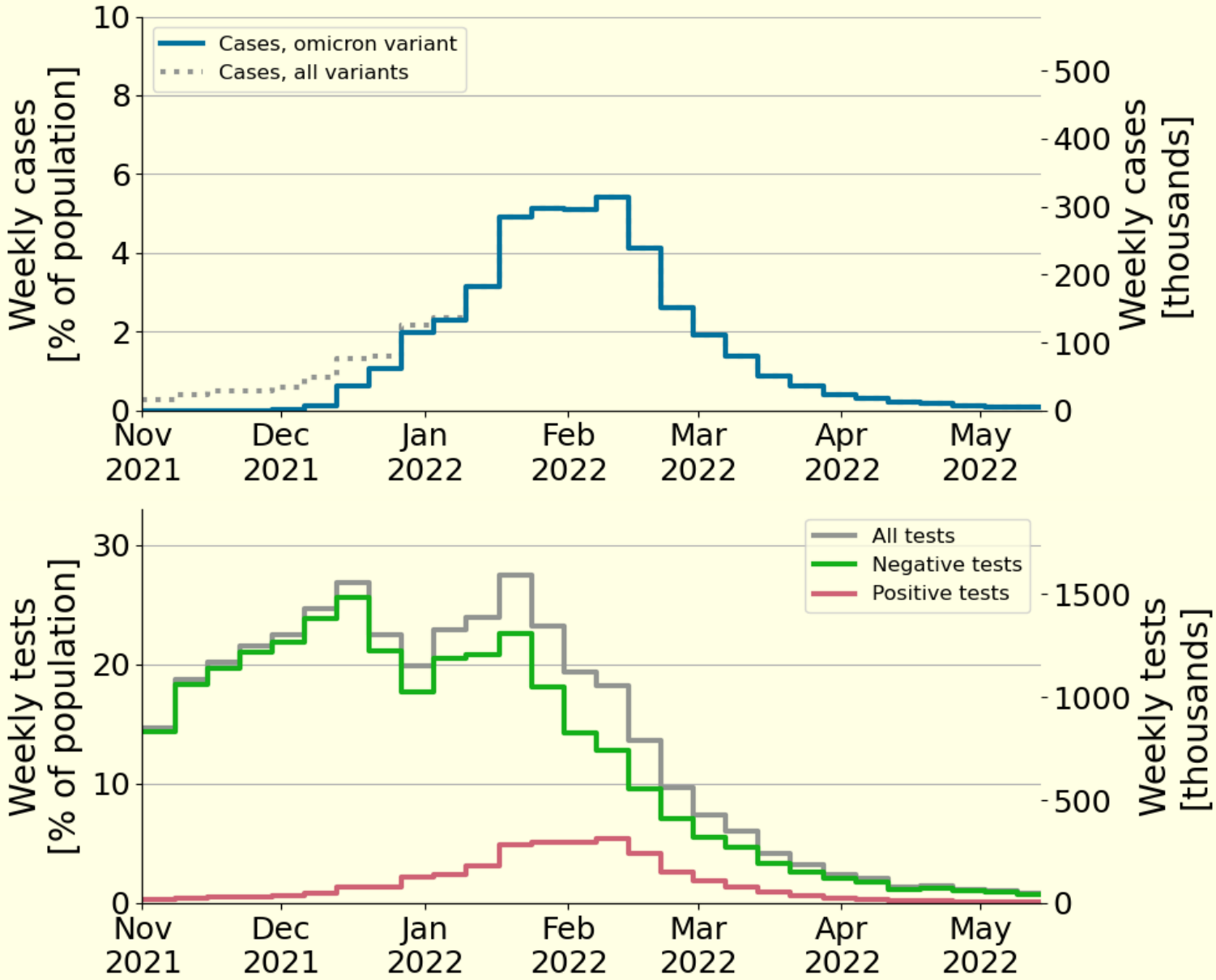
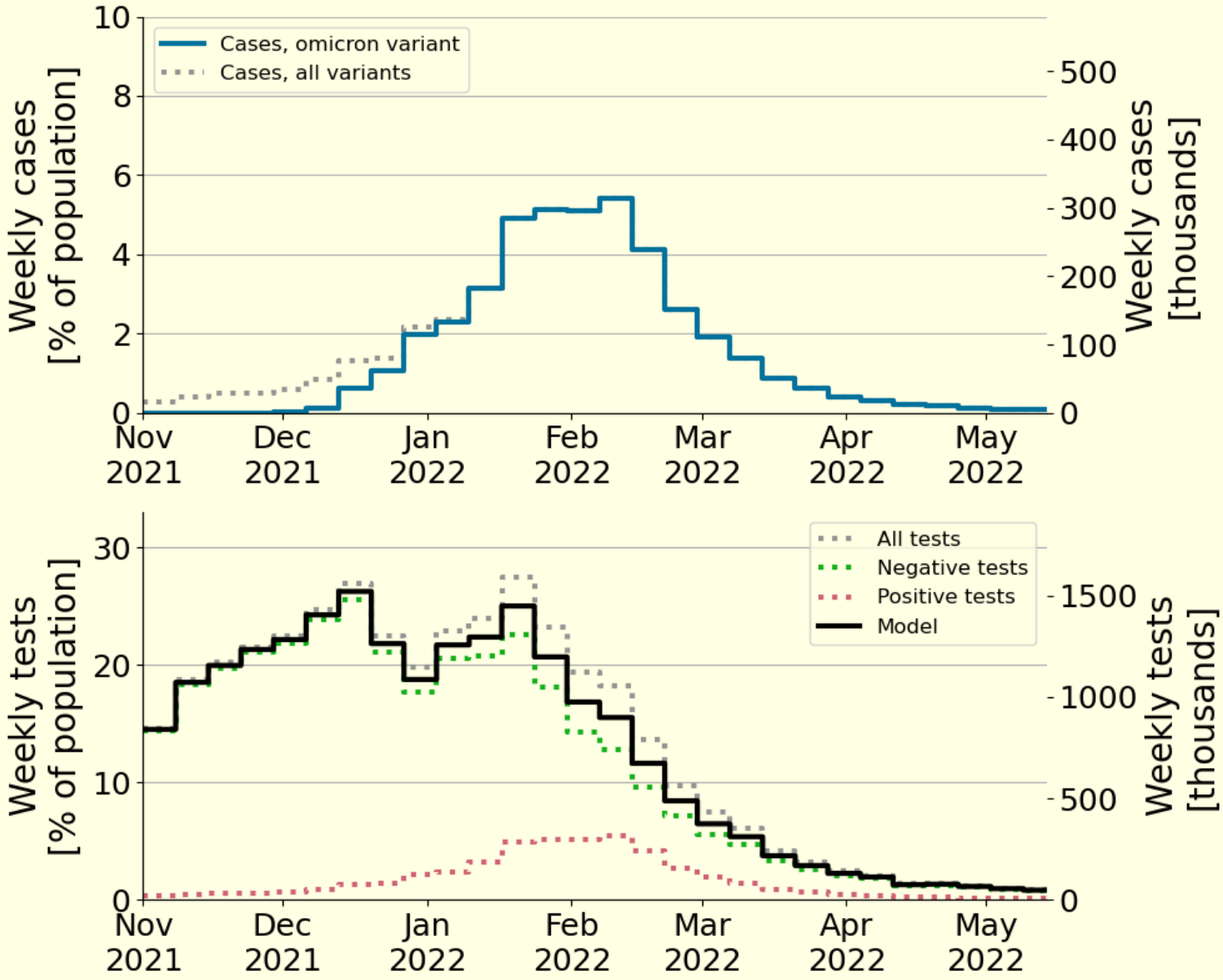


Relating our results to data



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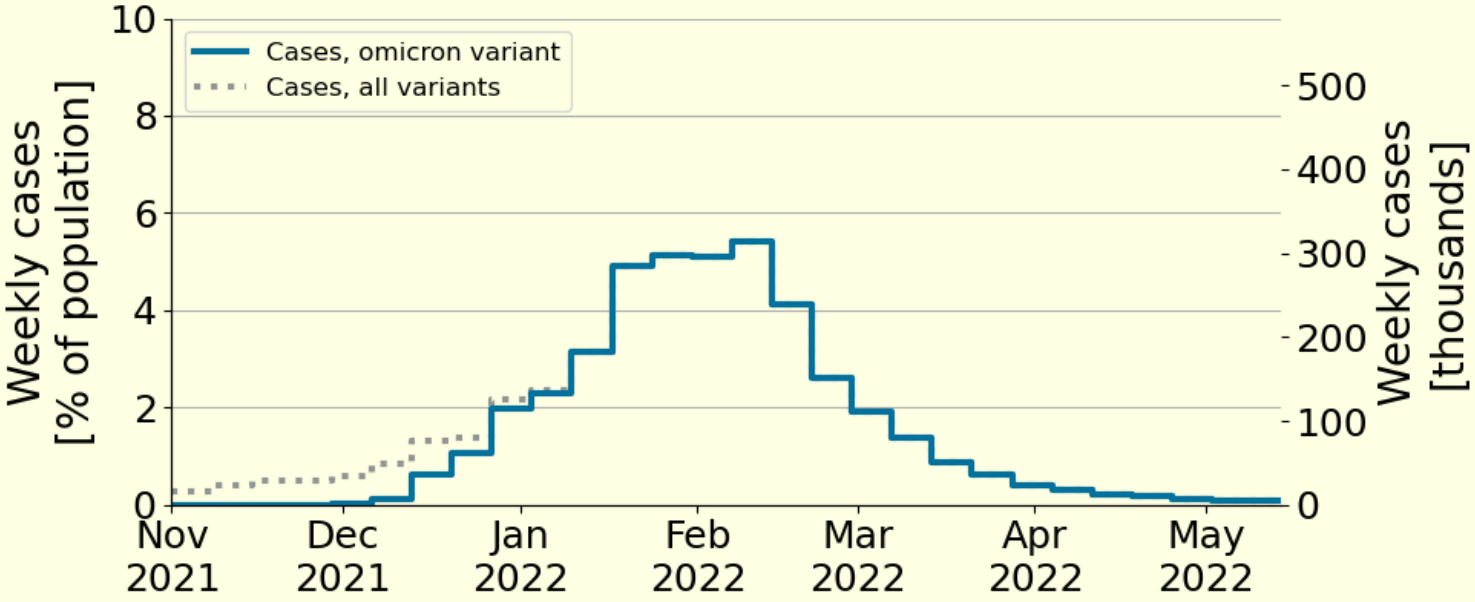

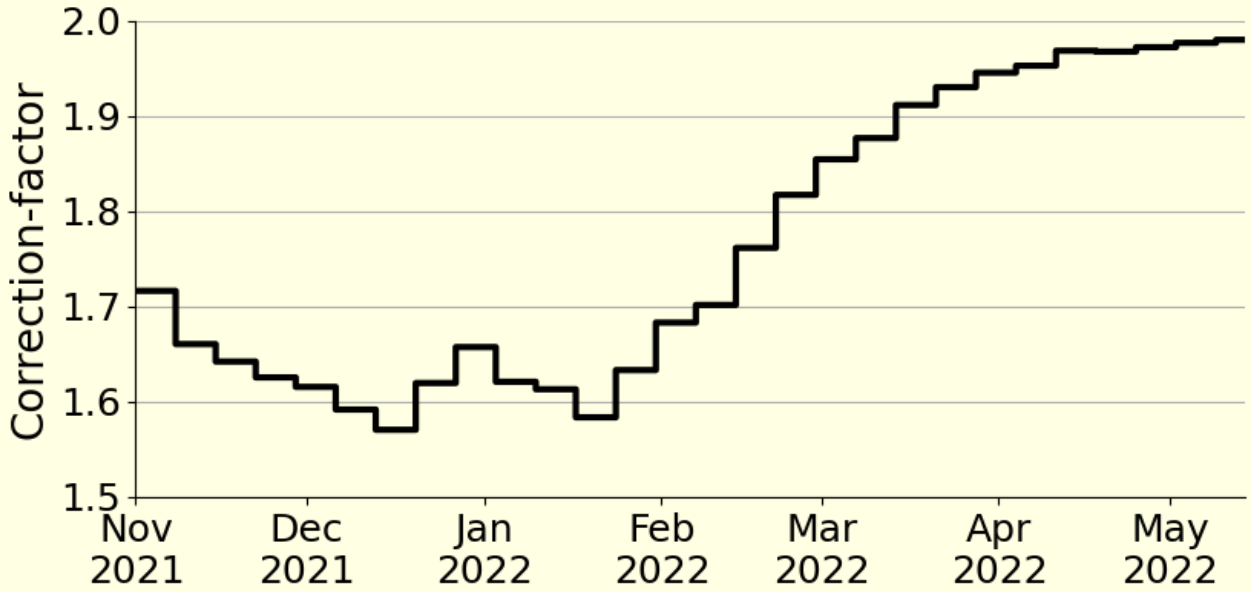

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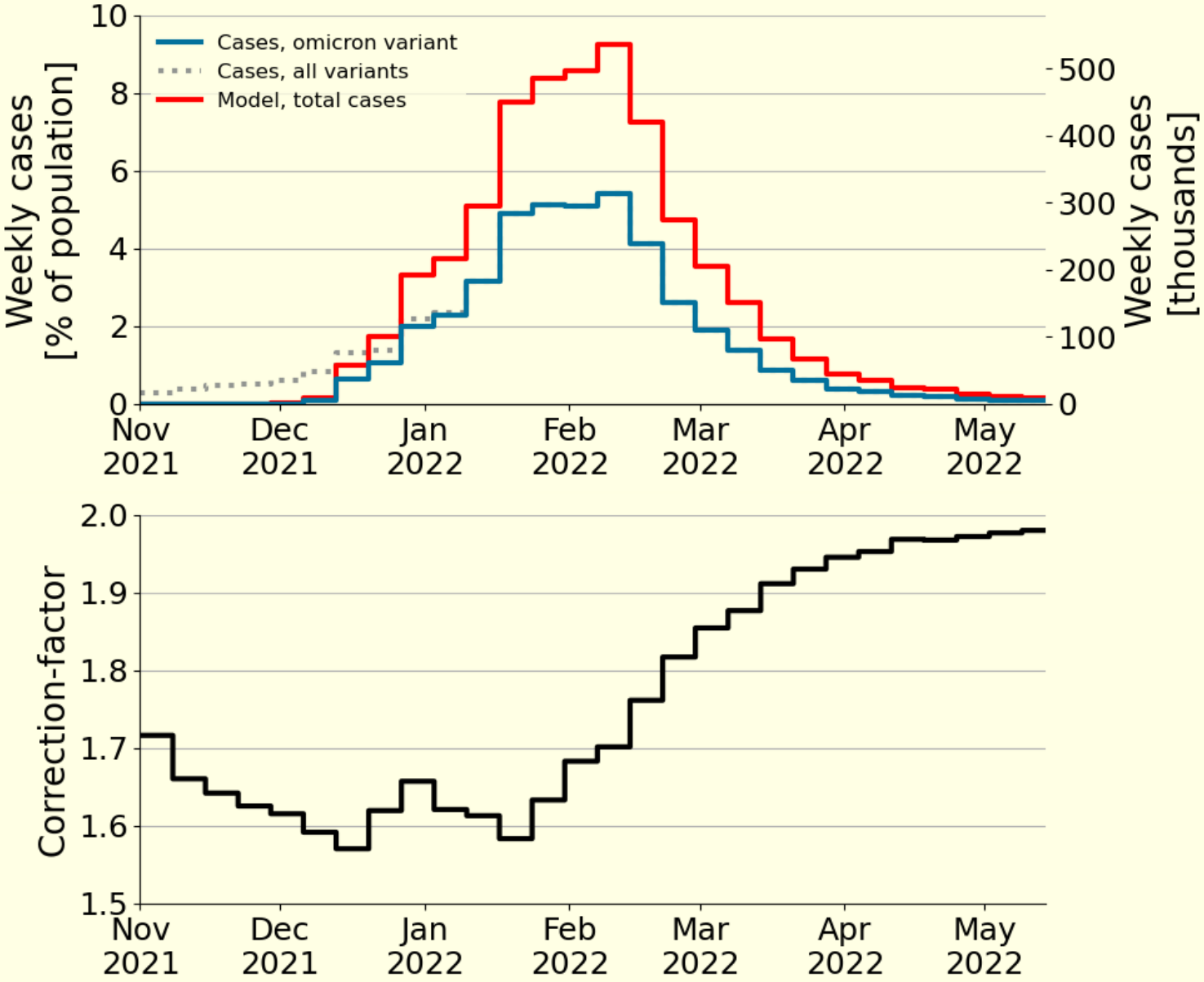

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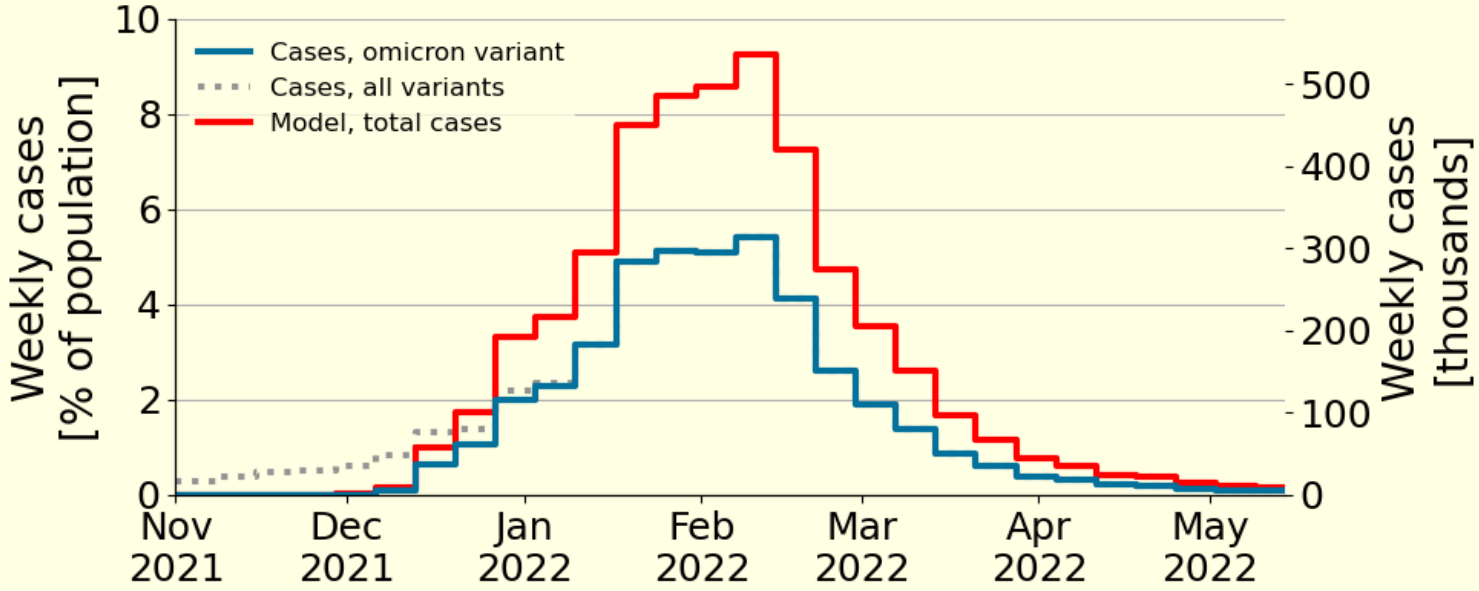
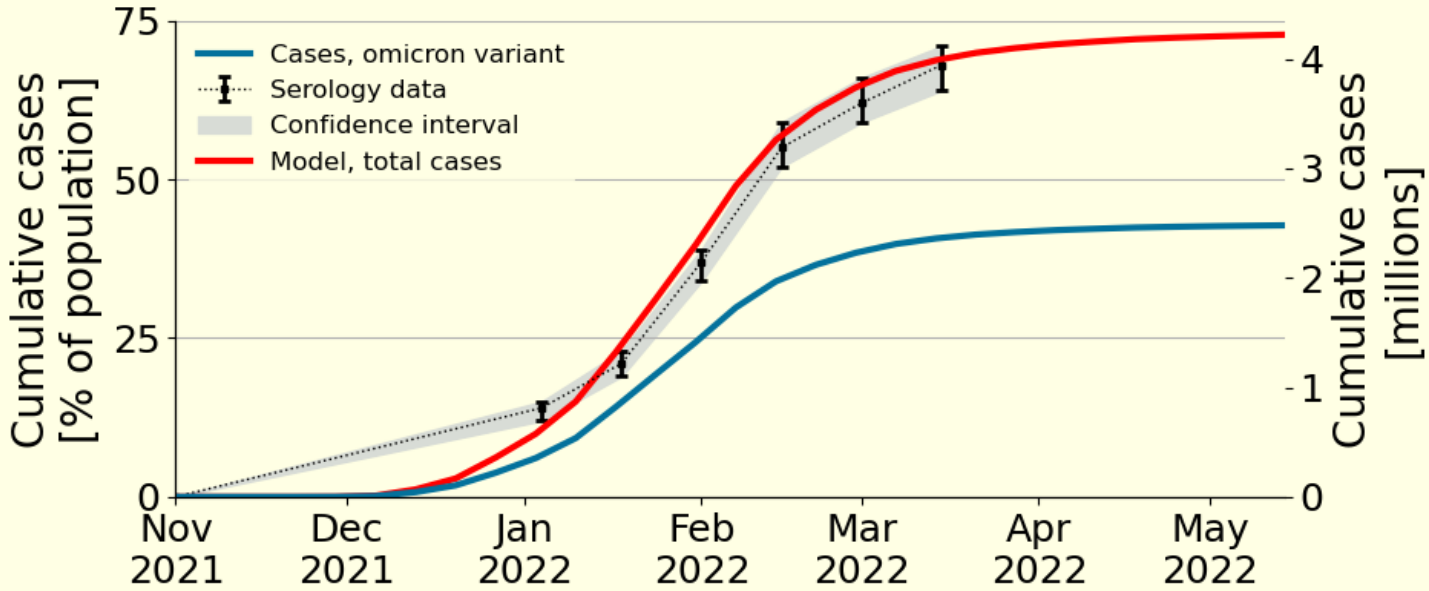




Calculation of assertion ratio

A.3 Final Size Calculations

As $t \to \infty$, the model system approaches a steady state without any active cases. In this section, we derive an analytic expression for the value that the fraction of cases identified, $K(t)$, approaches as $t \to \infty$.

To obtain an expression for K_F, we follow the methodology previously considered by **?**.

For notational purposes, we define for each variable x, the integral over the full epidemic as $T_x = \int_0^\infty x dt$.

From the system of differential equations given in equations (1), we write up the following quantities:

$$\dot{S}/S = -\beta(P + A) \tag{3a}$$
$$\dot{S} + \dot{E}_1 + \dot{E}_2 = -(\gamma + \tau)E_2 \tag{3b}$$
$$\dot{S} + \dot{E}_1 + \dot{E}_2 + \dot{P} = -(\gamma + \tau)P - \tau E_2 \tag{3c}$$
$$\dot{S} + \dot{E}_1 + \dot{E}_2 + \dot{P} + \dot{A} = -(\nu + \tau)A - (\gamma\rho + \tau)P - \tau E_2 \tag{3d}$$

As t approaches infinity, the stability of the systems implies that all variables apart from S, R_p and R_n are zero. We denote that final size of these variables as $S(t) \underset{t\to\infty}{\longrightarrow} \sigma$, $R_p(t) \underset{t\to\infty}{\longrightarrow} r_p$ and $R_n(t) \underset{t\to\infty}{\longrightarrow} r_n$

Integrating equations (3) from $t = 0$ to $t = \infty$ yields:

$$\log\sigma = -\beta(T_P - T_A) \tag{4a}$$
$$\sigma - S_0 - E_{1,0} - E_{2,0} = -(\gamma + \tau)T_{E_2} \tag{4b}$$
$$\sigma - S_0 - E_{1,0} - E_{2,0} - P_0 = -(\gamma + \tau)T_P - \tau T_{E_2} \tag{4c}$$
$$\sigma - S_0 - E_{1,0} - E_{2,0} - P_0 - A_0 = -(\nu + \tau)T_A - (\gamma\rho + \tau)T_P - \tau T_{E_2} \tag{4d}$$

Where X_0 denote the initial condition for variable X.

Furthermore, observe that the equations for $\dot{R}_n$ and $\dot{R}_p$, equations (1i) and (1h) respectively, when integrated from $t = 0$ to $t = \infty$ yields:

$$r_p - R_{p,0} = \nu T_Q + \nu T_I \tag{5}$$
$$r_n - R_{n,0} = \nu T_A \tag{6}$$

In general, we consider initial conditions such that the vast majority of the population is initially susceptible, $S_0 \approx 1$, and the initial number of cases is low, $0 < E_{1,0} \ll 1$. In the limit where $S_0 \to 1$, with $E_{1,0} \to 0$, $E_{2,0} \to 0$, $P_0 \to 0$ and $A_0 \to 0$, equations (4) become:

$$\log\sigma = -\beta(T_P - T_A) \tag{7a}$$
$$\sigma = 1 - (\gamma + \tau)T_{E_2} \tag{7b}$$
$$\sigma = 1 - (\gamma + \tau)T_P - \tau T_{E_2} \tag{7c}$$
$$\sigma = 1 - (\nu + \tau)T_A - (\gamma\rho + \tau)T_P - \tau T_{E_2} \tag{7d}$$

Assuming $T_P + T_A \neq 0$, this can be written as:

$$\beta = \frac{-\log\sigma}{T_P + T_A} \tag{8a}$$
$$T_{E_2} = \frac{1}{\gamma + \tau}(1 - \sigma) \tag{8b}$$
$$T_P = \frac{1}{\gamma + \tau}(1 - \sigma - \tau T_{E_2}) \tag{8c}$$
$$T_A = \frac{1}{\nu + \tau}(1 - \sigma - (\gamma\rho + \tau)T_P - \tau T_{E_2}) \tag{8d}$$

We define $K_F = \frac{r_p}{r_p + r_n}$ and note that at steady state $\sigma = 1 - r_p - r_n$ must hold. This implies that $K_F = \frac{r_p}{1-\sigma}$. Combining equations (8) with equations (5) and (6) under the assumptions $R_{p,0} = 0$ and $R_{n,0} = 0$ and simplifying yields:

$$K_F = \frac{r_p}{r_p + r_n} = \frac{r_p + r_n - r_n}{r_p + r_n} = 1 - \frac{r_n}{r_p + r_n} = 1 - \frac{r_n}{1-\sigma} = 1 - \frac{\nu}{1-\sigma}T_A \tag{9}$$
$$K_F = 1 - \left(\frac{\nu}{\nu + \tau}\right)\left(1 - \frac{\tau}{\gamma + \tau}\right)\left(1 - \frac{\gamma\rho + \tau}{\gamma + \tau}\right) \tag{10}$$

For initial conditions sufficiently close to the case where $S_0 = 1$ and all other variables are zero, K_F is an approximation of the final size of $K(t)$ as $t \to \infty$.

Note that the expression for K_F, equation (10) is independent of σ and β.

Furthermore, in the absence of tests, i.e. for $\tau = 0$, we have $K_F = 1 - 1(1-0)(1-\rho) = \rho$. This is expected, as only the symptomatic cases, I, are found in the situation where $\tau = 0$, and the symptomatic cases make up exactly ρ of all cases.

In the situation where all cases are symptomatic, $\rho = 1$, we obtain $K_F = 1$, that is, all cases are identified.

We note that equation (8a) describes a relation between β and σ. Since T_P and T_A are described in terms of γ, τ, ν and σ, it is possible to use equation (8a) to determine a value of β that yields a particular σ.

$$\frac{R_p}{R_n + R_p} = 1 - \left(1 - \frac{\tau}{\gamma + \tau}\right)\left(1 - \frac{\gamma\rho + \tau}{\gamma + \tau}\right)\left(\frac{\nu}{\nu + \tau}\right)$$

Simplified method, Flow-considerations

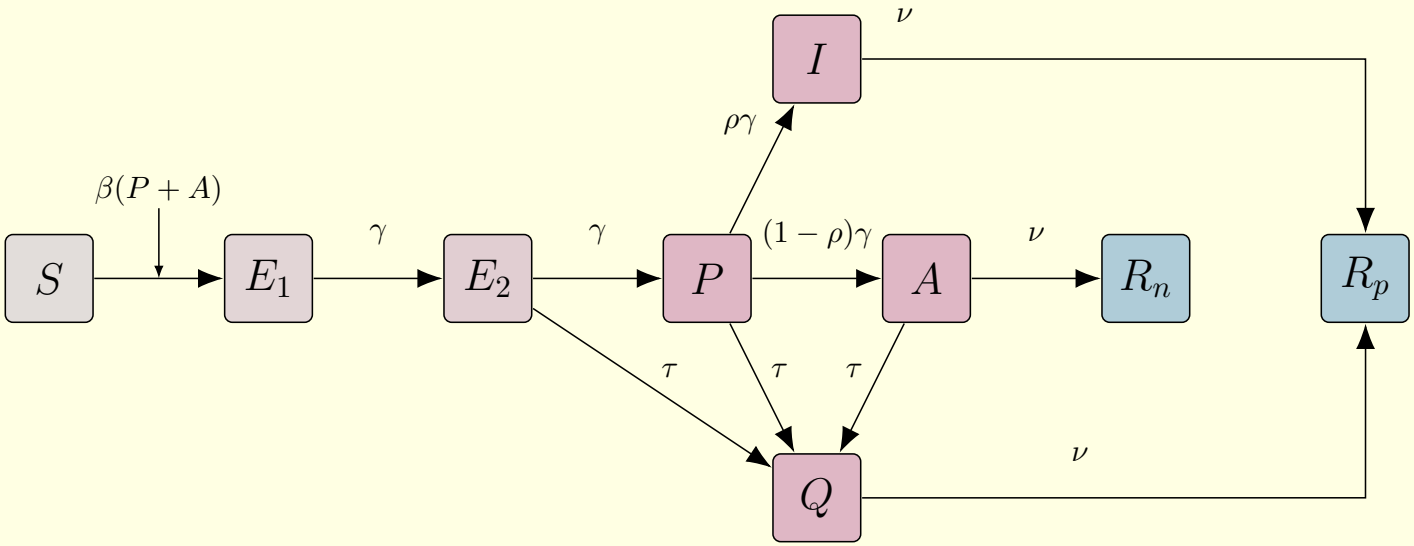
$$\frac{R_p}{R_n + R_p} = 1 - \left(1 - \frac{\tau}{\gamma + \tau}\right)\left(1 - \frac{\gamma\rho + \tau}{\gamma + \tau}\right)\left(\frac{\nu}{\nu + \tau}\right)$$

can be rewritten as:

$$1 - \frac{R_p}{R_n + R_p} =$$

$$\frac{R_n}{R_n + R_p} = \left(\frac{\gamma}{\gamma + \tau}\right)\left(\frac{(1-\rho)\gamma}{\gamma + \tau}\right)\left(\frac{\nu}{\nu + \tau}\right)$$

Simplified method, Flow-considerations



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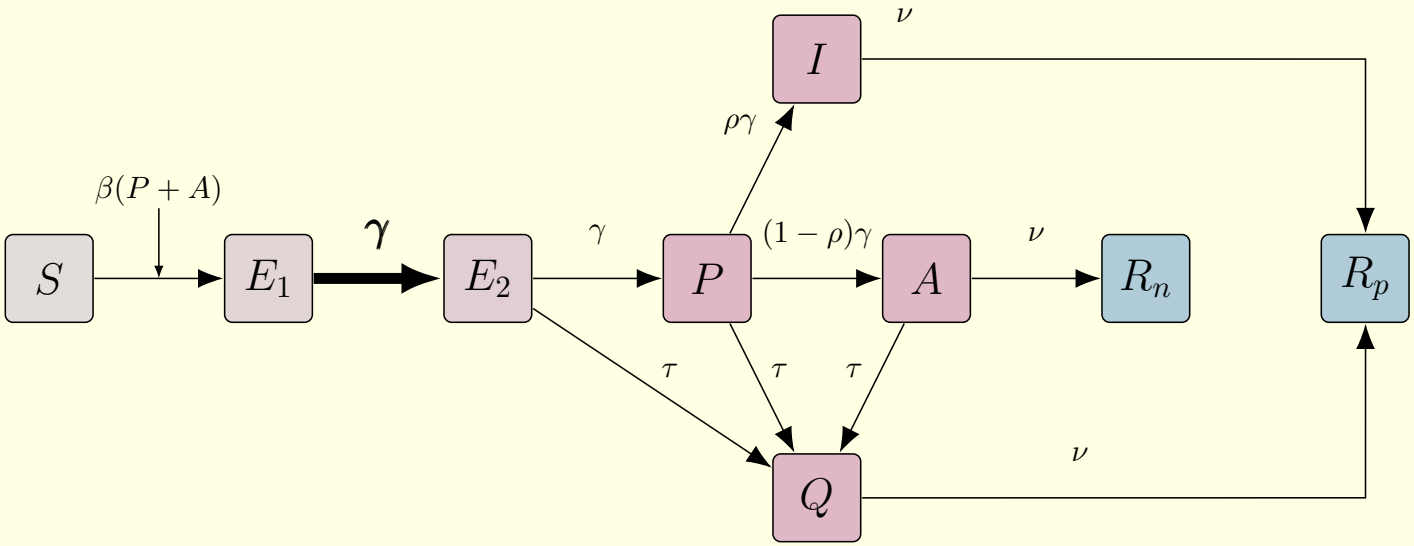
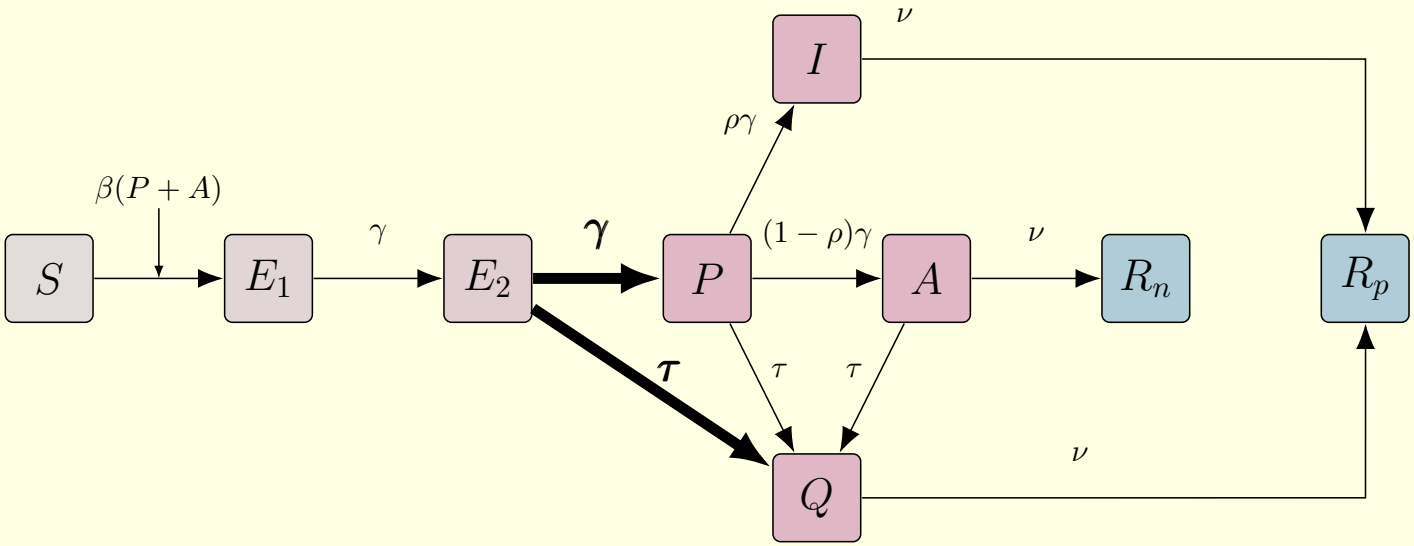


$$\begin{pmatrix} \gamma \\ \hline \gamma \end{pmatrix}$$

Simplified method, Flow-considerations



$$\left(\frac{\gamma}{\gamma}\right) \left(\frac{\gamma}{\gamma+\tau}\right)$$

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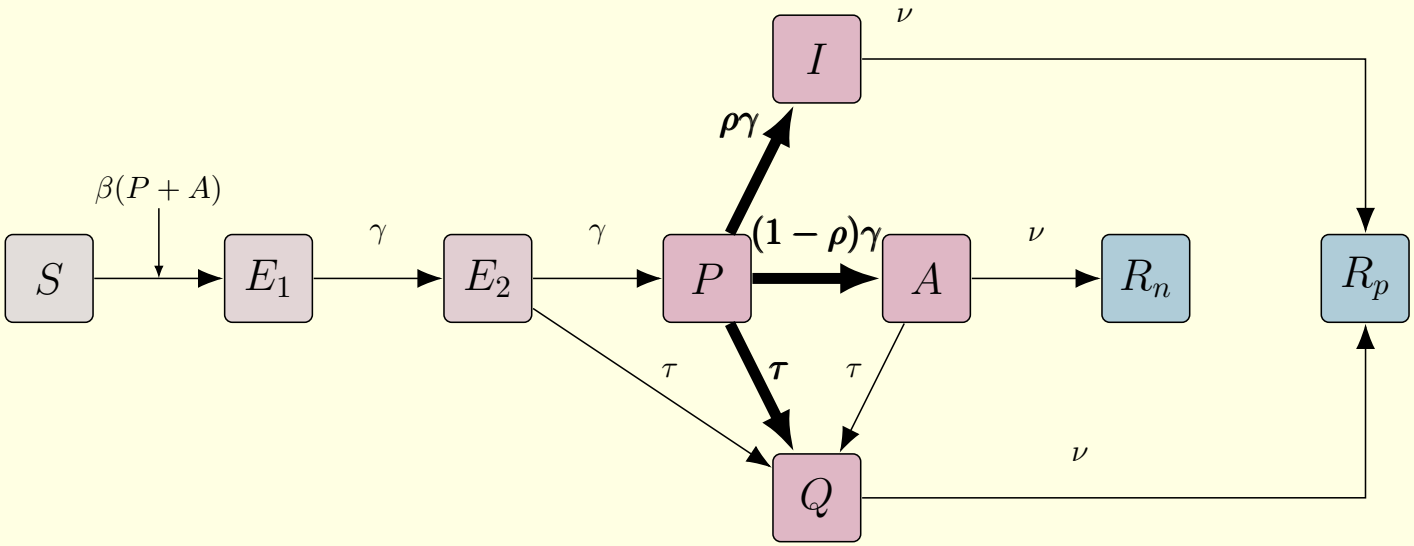
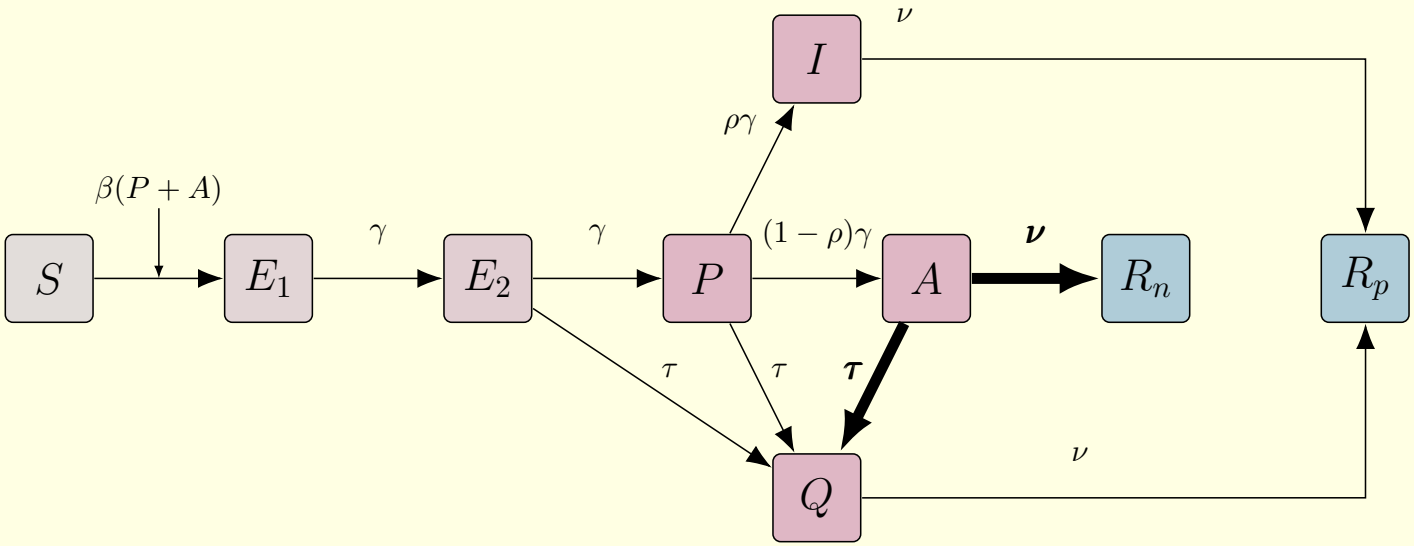


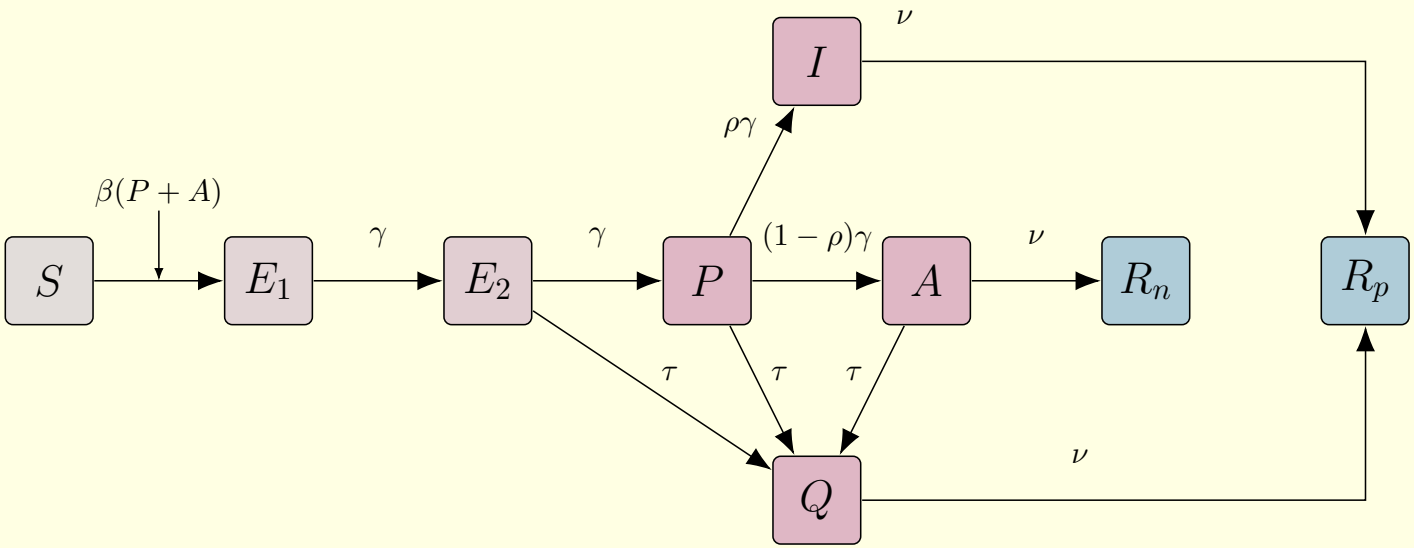
$$\left(\frac{\gamma}{\gamma}\right)\ \left(\frac{\gamma}{\gamma+\tau}\right)\ \left(\frac{(1-\rho)\gamma}{\gamma+\tau}\right)$$

Simplified method, Flow-considerations



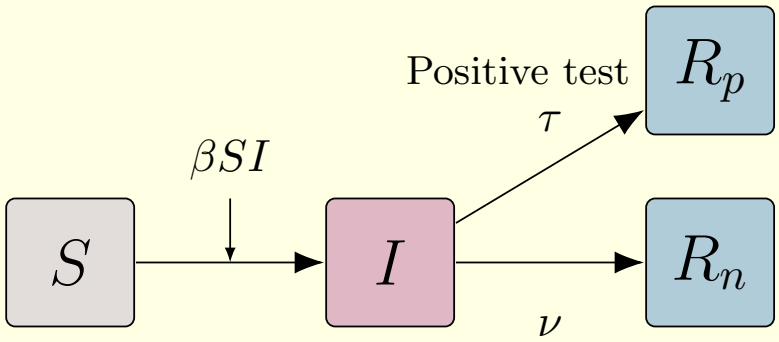
$$\left(\frac{\gamma}{\gamma}\right)\ \left(\frac{\gamma}{\gamma+\tau}\right)\ \left(\frac{(1-\rho)\gamma}{\gamma+\tau}\right)\ \left(\frac{\nu}{\nu+\tau}\right)$$

Simplified method, Flow-considerations



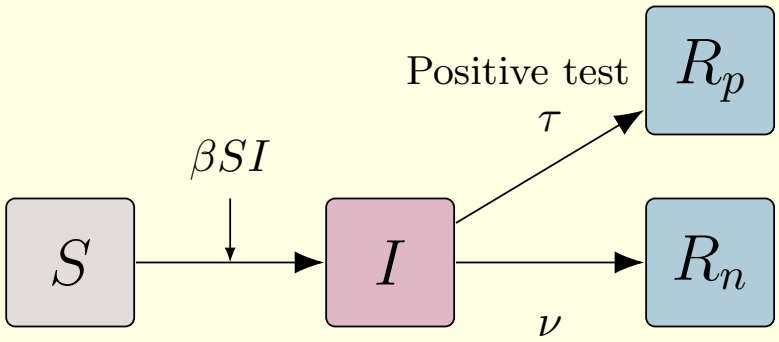
$$\frac{R_n}{R_n + R_p} = \left(\frac{\gamma}{\gamma+\tau}\right)\left(\frac{\gamma(1-\rho)}{\gamma+\tau}\right)\left(\frac{\nu}{\nu+\tau}\right)$$

Extension to other models, example 1



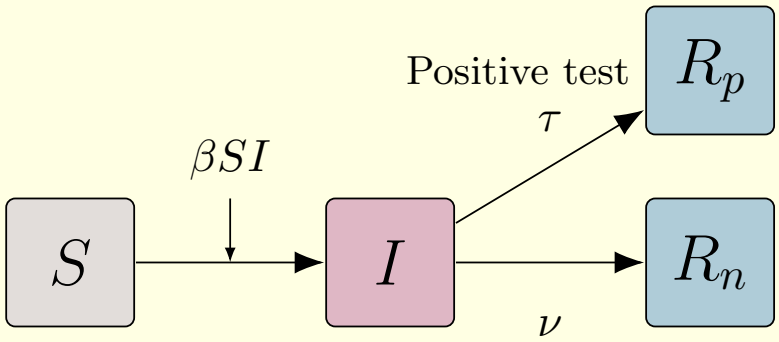
Flow-considerations:

Extension to other models, example 1



Flow-considerations: $\frac{R_n}{R_n + R_p} = \frac{\nu}{\nu + \tau}$

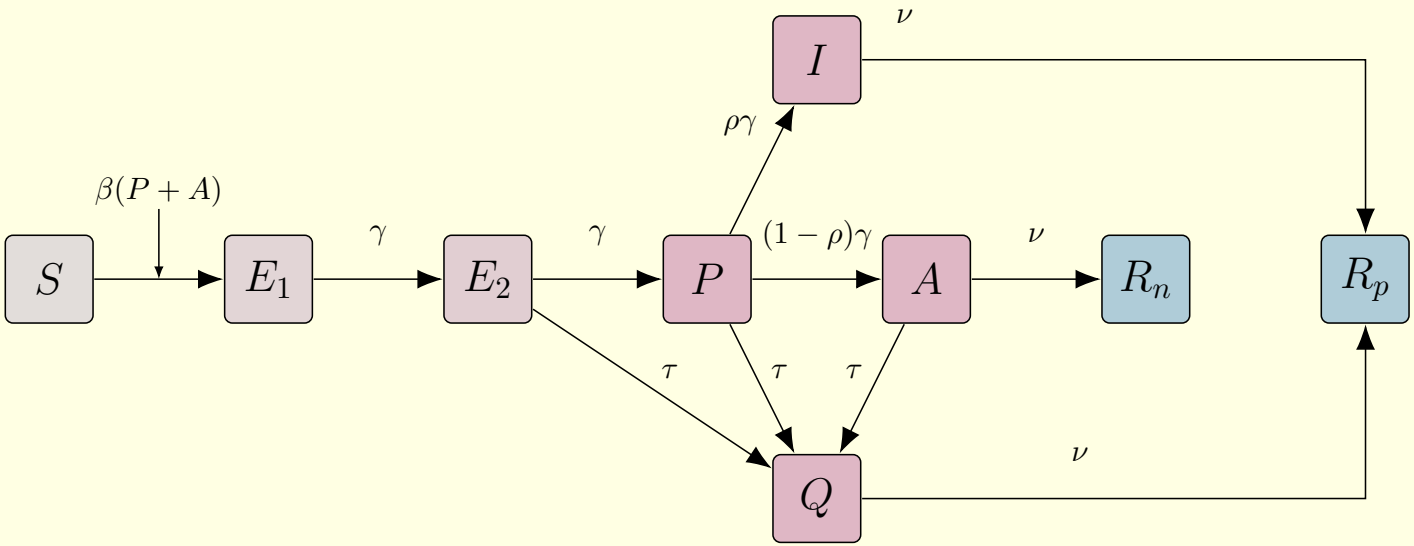
Extension to other models, example 1



Flow-considerations: $\frac{R_n}{R_n + R_p} = \frac{\nu}{\nu + \tau}$

Correction factor: $\frac{\nu + \tau}{\tau}$

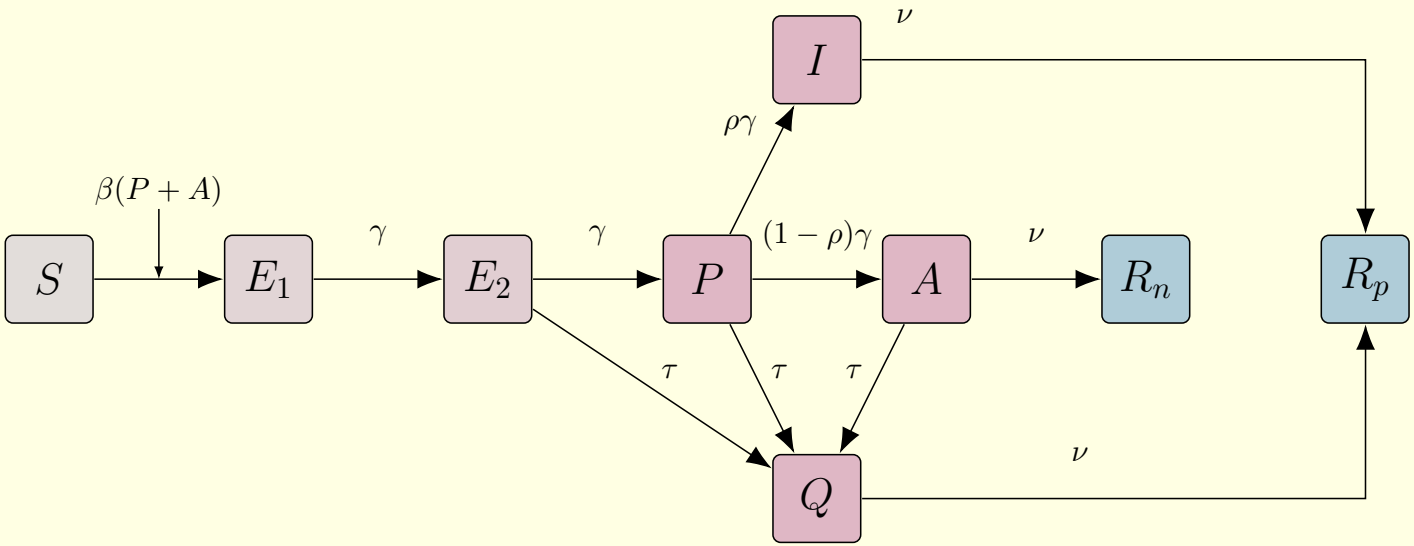
Simplified method, Matrix-form



For SIR-type models[2], the inverse of a matrix V describing flows in the "infected sub-system" is typically computed to determine the reproduction number $\mathcal{R}_0$.

[1] See (van den Drische and Watmough, 2002) for definition and derivation.

Simplified method, Matrix-form

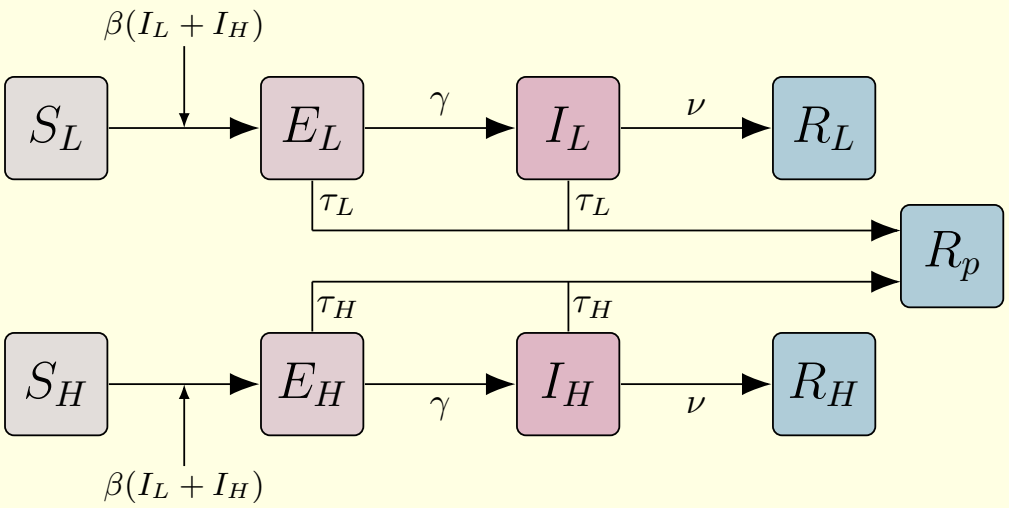


For SIR-type models[2], the inverse of a matrix V describing flows in the "infected sub-system" is typically computed to determine the reproduction number $\mathcal{R}_0$.
With sub-system $x = (E_1, E_2, P, I, A)$ and matrix V, we consider "inputs" $\alpha = (1, 0, 0, 0, 0)$ and "outputs" $\omega = (0, 0, 0, 0, \nu)$, and find that:

$$\frac{R_n}{R_n + R_p} = \omega V^{-1} \alpha^T$$

[1] See (van den Drische and Watmough, 2002) for definition and derivation.

Extension to other models, example 2



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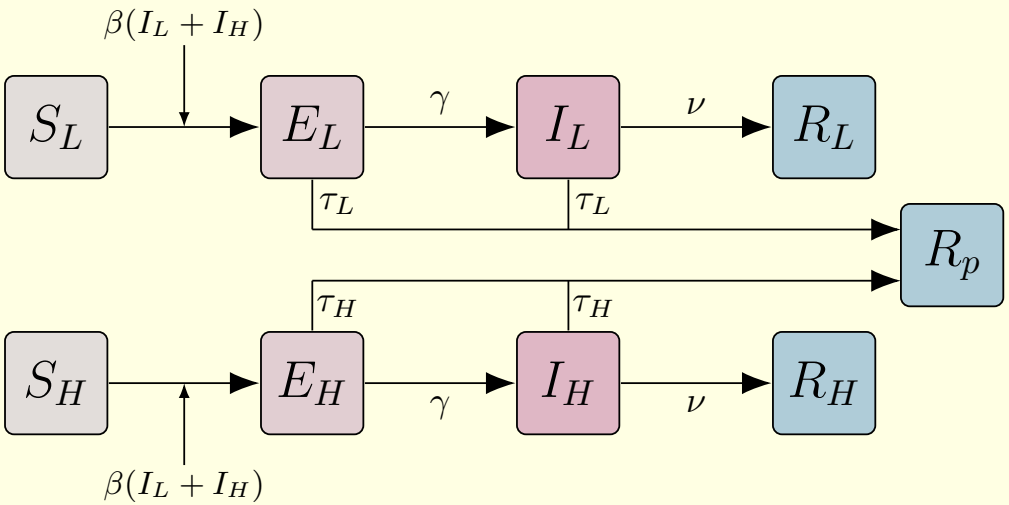

$$x = (E_H, E_L, I_H, I_L), \quad V = \begin{pmatrix} \gamma + \tau_H & 0 & 0 & 0 \\ 0 & \gamma + \tau_L & 0 & 0 \\ \gamma & 0 & \nu + \tau_H & 0 \\ 0 & \gamma & 0 & \nu + \tau_L \end{pmatrix}$$

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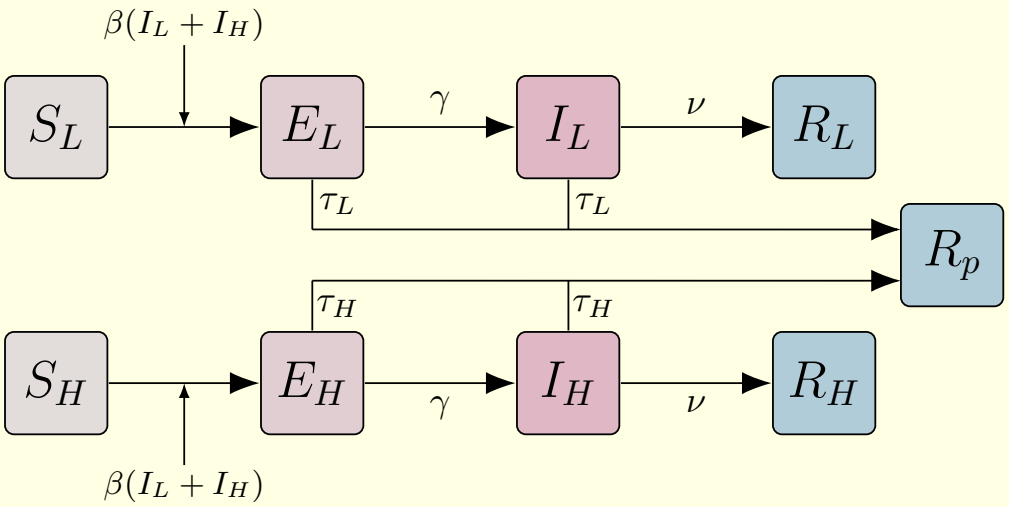

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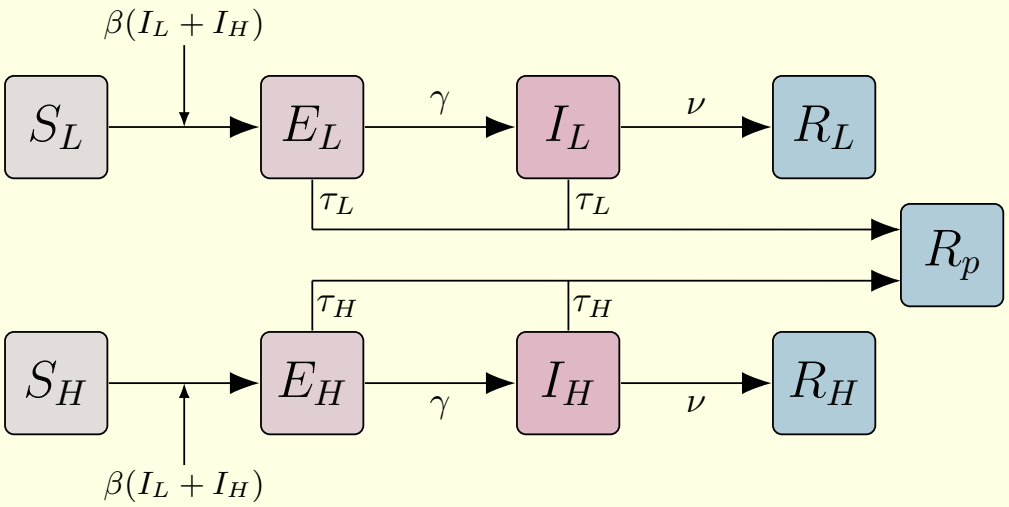

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Hence: $\omega V^{-1} \alpha^T = \frac{\nu\gamma}{S_H + S_L} \left(\frac{S_H}{(\nu + \tau_H)(\gamma + \tau_H)} + \frac{S_L}{(\nu + \tau_L)(\gamma + \tau_L)} \right)$

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Thank you for your attention.

Feel free to email me
with questions or comments

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