Workshop on the Mathematical Modelling of Variant Replacement of Infectious Diseases Pathogens

Relative Reproduction Number

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Effective Reproduction Number R_t The average number of secondary infections

When R(t) = 1

A constant number of new cases



The number of new cases declines when R(t) < 1



Estimation of Effective Reproduction Numbers

The average number of people an infected individual at time *t* could infect

Instantaneous Reproduction Number

$$R(t) = \frac{I(t)}{\sum_{j=1}^{l} g(j)I(t-j)}$$
(1)
(Fraser 2007)

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I(*t*): The number of new cases at time *t* g(j): The probability that generation time is *j* days

 $R(t) = \frac{\text{(the number of new cases of the current generation)}}{\text{(the number of new cases of the previous generation)}}$

Relative Instantaneous Reproduction Number R_{RI} (Ito et.al 2021)

- Ratio of instantaneous reproduction numbers of two variants.
- *R_{RI}* of variant *A_i* w.r.t variant *a* is defined as

$$k_i = \frac{R_{A_i}(t)}{R_a(t)} \tag{2}$$

Assumption:

 k_i is constant over time

Intuitive Meaning of R_{RI}

The average number of people an infected individual by a variant A at time t could infect

The average number of people an infected individual by a baseline variant a at time t could infect

The variant A is *k* times more transmissible than the baseline variant a.

Relative Generation Time

- We assume that the generation times of infections by *a*, *A*₁, ..., *A_n* follow the gamma distributions with a shared shape parameter of *α* and scale parameters of *θ*, *c*₁*θ*, ..., *c_nθ*, respectively.
- The generation time of A_i is c_i times longer than that of the baseline variant a.
- We call c_i the relative generation time (GT_R) of A_i w.r.t. a.

Example of GT_R



The GT_R of A_i w.r.t. a is 1.5 ($c_i = 1.5$). The generation time of A_i (mean 6 days) is 1.5 times longer than that of the baseline variant a (mean: 4 days).



Baseline virus and variant viruses

type	variant	R _{RI}	GT _R	frequency
baseline	а	1	1	$q_a(t)$
subject ₁	A_1	k_1	<i>C</i> ₁	$q_{A_1}(t)$
:	:	•	:	:
subject _n	A _n	k _n	C _n	$q_{A_n}(t)$

R(t) of Each Variant

I(t): the number of new cases at time t $g_a(j)$: the generation time distribution of baseline virus a $g_{A_i}(j)$: the generation time distribution of variant A_i $q_a(t)$: relative frequency of baseline virus a at time t $q_{A_i}(t)$: relative frequency of variant A_i at time t

Instantaneous reproduction number of a

$$R_{a}(t) = \frac{q_{a}(t)I(t)}{\sum_{j=1}^{l} g_{a}(j)q_{a}(t-j)I(t-j)}$$
(3)

Instantaneous reproduction number of A_i $R_{A_i}(t) = \frac{q_{A_i}(t)I(t)}{\sum_{j=1}^l g_{A_i}(j)q_{A_i}(t-j)I(t-j)}$ (4)

 $q_{A_{i}}(t) = \frac{\text{the numbe of new cases by } A_{i}}{\text{the numbe of new cases by } a, A_{1}, \dots, \text{ or } A_{n}}$ $q_{A_{i}}(t) = \frac{q_{A_{i}}(t)I(t)}{q_{a}(t)I(t) + \sum_{i=1}^{n} q_{A_{i}}(t)I(t)}$ Substitute $q_{a}(t)I(t) = R_{a}(t) \sum_{j=1}^{l} g_{a}(j)q_{a}(t-j)I(t-j) \quad (3)$

$$q_{A_i}(t) = \frac{q_{A_i}(t)I(t)}{R_a(t)\sum_{j=1}^l g_a(j)q_a(t-j)I(t-j) + \sum_{i=1}^n q_{A_i}(t)I(t)}$$

$$q_{A_{i}}(t) = \frac{q_{A_{i}}(t)I(t)}{R_{a}(t)\sum_{j=1}^{l}g_{a}(j)q_{a}(t-j)I(t-j) + \sum_{i=1}^{n}q_{A_{i}}(t)I(t)}$$

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Substitute
$$q_{A_i}(t)I(t) = R_{A_i}(t)\sum_{j=1}^l g_{A_i}(j)q_{A_i}(t-j)I(t-j)$$
 (4)

$$q_{A_{i}}(t) = \frac{R_{A_{i}}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}{R_{a}(t)\sum_{j=1}^{l}g_{a}(j)q_{a}(t-j)I(t-j) + \sum_{i}^{n}R_{A_{i}}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}$$

$$q_{A_{i}}(t) = \frac{R_{A_{i}}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}{R_{a}(t)\sum_{j=1}^{l}g_{a}(j)q_{a}(t-j)I(t-j) + \sum_{i}^{n}R_{A_{i}}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}$$

Substitute $R_{A_i}(t) = k_i R_a(t)$ (2)

$$q_{A_{i}}(t) = \frac{k_{i}R_{a}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}{R_{a}(t)\sum_{j=1}^{l}g_{a}(j)q_{a}(t-j)I(t-j) + \sum_{i}^{n}k_{i}R_{a}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}$$

$$q_{A_{i}}(t) = \frac{k_{i}R_{a}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}{R_{a}(t)\sum_{j=1}^{l}g_{a}(j)q_{a}(t-j)I(t-j) + \sum_{i}^{n}k_{i}R_{a}(t)\sum_{j=1}^{l}g_{A_{i}}(j)q_{A_{i}}(t-j)I(t-j)}$$

Cancel out $R_a(t)$ in the numerator and denominator

$$q_{A_i}(t) = \frac{k_i \sum_{j=1}^l g_{A_i}(j) q_{A_i}(t-j) I(t-j)}{\sum_{j=1}^l g_a(j) q_a(t-j) I(t-j) + \sum_i^n k_i \sum_{j=1}^l g_{A_i}(j) q_{A_i}(t-j) I(t-j)}$$

$$q_{A_{i}}(t) = \frac{k_{i} \sum_{j=1}^{l} g_{A_{i}}(j) q_{A_{i}}(t-j) I(t-j)}{\sum_{j=1}^{l} g_{a}(j) q_{a}(t-j) I(t-j) + \sum_{i}^{n} k_{i} \sum_{j=1}^{l} g_{A_{i}}(j) q_{A_{i}}(t-j) I(t-j)}$$

Assume
$$I(t-1) \approx I(t-2) \approx \cdots \approx I(t-l)$$
. (5)

$$q_{A_i}(t) = \frac{k_i \sum_{j=1}^l g_{A_i}(j) q_{A_i}(t-j)}{\sum_{j=1}^l g_a(j) q_a(t-j) + \sum_i^n k_i \sum_{j=1}^l g_{A_i}(j) q_{A_i}(t-j)}$$
(6)

Variant Replacement Model

The frequency of variant A_i at time t can be presented using R_{RI} of A_i w.r.t a as follows:

$$q_{A_i}(t) = \frac{k_i \sum_{j=1}^l g_{A_i}(j) q_{A_i}(t-j)}{\sum_{j=1}^l g_a(j) q_a(t-j) + \sum_i^n k_i \sum_{j=1}^l g_{A_i}(j) q_{A_i}(t-j)}$$
(6)

where $g_a(j), g_{A_1}(j), \dots, g_{A_n}(j)$ are the generation time distribution of a, A_1, \dots, A_n .

Note that the formula doesn't contain $R_a(t)$ or I(t)

Related models

 The variant replacement can be also described by the softmax model (Suzuki et al, Nature 2022)

$$q_i(t) = \frac{\exp(\mu_i(t))}{1 + \sum_{1 \le j \le n} \exp(\mu_j(t))},$$

where $\mu_i(t) = a_i + b_i t$.

- Advantage: simple and fast
- Disadvantage: doesn't consider the generation time distribution

Summary

- The relative reproduction number (*R_{RI}*) is the ratio of instantaneous reproduction numbers of two variants.
- Instantaneous reproduction numbers of variants may change over time, but the ratios among them are assumed to be constant
- The softmax model doesn't consider the generation time distribution.