Supplementary material

How generation intervals shape the relation between growth rates and reproductive numbers

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1. MOMENT GENERATING FUNCTIONS

1.1. Mathematical properties

For a non-negative stochastic variable a that is distributed according to a probability density function $g(a)$, the moment generating function is defined as $M_{g(a)}(z) = \int_{a=0}^{\infty} \mathrm{e}^{za} g(a)\mathrm{d}a$. When the integral is finite, there is a unique relation between the probability density function and its moment generating function. The moment generating functions have a number of mathematical properties. In the main text we have exploited the following properties:

1. $M_{g(a)}(z) \geq 0$, that is, a moment generating function is never negative.
2. $M'_{g(a)}(z) = \int_{a=0}^{\infty} a\mathrm{e}^{za} g(a)\mathrm{d}a > 0$, that is, the moment generating function increases with its argument.
3. $M_{g(a)}(0) = \int_{a=0}^{\infty} g(a)\mathrm{d}a = 1$, that is, the value of a moment generating function evaluated at $z = 0$ gives the total probability mass, which is per definition equal to one.
4. $M'_{g(a)}(0) = \int_{a=0}^{\infty} ag(a)\mathrm{d}a = \mu$, that is, the slope of the moment generating function evaluated at $z = 0$ is the expected value of the stochastic variable a.
5. $\int_{a=0}^{a=\infty} \mathrm{e}^{za} g(a)da \geq \mathrm{e}^{z \int ag(a)\mathrm{d}a} \Leftrightarrow M_{g(a)}(z) \geq \mathrm{e}^{z\mu}$, that is, the average of transformed stochastic variables is at least equal to the transformed average of those variables when the transformation is convex (Jensen's inequality).
6. $\ln M_{g(a)}(z) = \mu z + \frac{1}{2!}\sigma^2 z^2 + \frac{1}{3!}\sigma^3 \gamma z^3 + \ldots$, that is, the Taylor expansion of the natural logarithm of the moment generating function around zero has as first coefficients the mean μ, the variance σ^2, and the skewness of the probability density function $g(a)$.
7. When the random variable a, distributed according to $g(a)$, can be thought of as the sum of two independent random variables a_1 and a_2, such that $a = a_1 + a_2$, with a_1 and a_2 distributed according to $f(a_1)$ and $h(a_2)$, the moment generating function for the random variable a can be composed of the moment generating function for a_1 and a_2: $M_{g(a)}(z) = M_{f(a)}(z) \times M_{h(a)}(z)$.
8. When the random variable a, distributed according to $g(a)$, can be thought of as drawn with probability p from distribution $f(a)$ and with probability $q = 1 - p$ from distribution $h(a)$, such that g is a mixture of $f$and h, then the moment generating function for $g(a)$ can be composed of the moment generating functions for $f(a)$ and $h(a)$: $M_{g(a)}(z) = pM_{f(a)}(z) + qM_{h(a)}(z)$.
9. The moment generating function $M_{g(a)}(z)$ is tabulated for many well-known statistical distributions, see Table 2.

1.2. Biological implications

To see the biological implications of these mathematical properties, we identify a with the duration of a generation interval, $g(a)$ with the generation interval distribution, and the expected value μ with the mean generation interval T_c. As derived in the main text, the reproductive number R is related to the growth rate r according to the equation $R = 1/M_{g(a)}(-r)$. The mathematical properties of the moment generating functions correspond to the following biological properties of the relationship between reproductive number R and growth rate r:

1. The reproductive number is never negative.
2. The reproductive number increases when the growth rate increases.
3. The reproductive number is one when the growth rate is zero.
4. The slope of the curve relating growth rate to reproductive number is equal to the mean generation interval T_c when growth rate is zero.
5. The reproductive number has an upper bound that is set by the exponential of growth rate and mean generation interval: $R \leq \mathrm{e}^{rT_c}$.
6. For generation intervals that are approximately normally distributed the reproductive number is approximated by $R \approx \mathrm{e}^{rT_c - \frac{1}{2}r^2\sigma^2}$.
7. The moment generating function for the generation interval can be composed from moment generating functions for the durations of successive stages in the infection cycle. For example, we consider a disease where cases are infective only after developing symptoms. We introduce two distributions for the successive stages: $f(a)$ gives the duration from infection to becoming infectious, and $h(a)$ gives the duration from becoming infectious to infection. The moment generating function for the composite generation interval is then given by $M_{g(a)} = M_{f(a)} \times M_{h(a)}$.
8. The moment generating function for the generation interval can be composed from the moment generating functions for the durations of alternative loops in the infection cycle. For example, we consider a disease where both asymptomatic and symptomatic cases can be infective, but each with a different distribution for duration of the generation interval. We introduce two distribution for the alternative loops: $f(a)$ gives the distribution of durations from secondary infection back to primary infection of asymptomatic cases, and $g(a)$ gives the distribution for symptomatic cases. We assume that a proportion p of a cohort of secondary cases is infected by asymptomatic cases, and a proportion q by symptomatic cases. The moment generating function for the composite generation interval is $M_{g(a)} = pM_{f(a)} + qM_{h(a)}$.

9. We can tabulate the relationships between growth rate r and reproductive number R for generation intervals that are distributed according to well-known statistical distributions, see Table 2.

2. EPIDEMIC MODELS

Even for a complicated infection cycle it is relatively easy to compose the moment generating function for generation intervals from moment generating functions for the duration between these successive events in an infection cycle. The composition rules are as follows: if there is only one possible sequence of events that lead back from a secondary infection to its primary infection, the moment generating function for generation intervals is simply the product of the moment generating functions for the duration between successive events. If there are several alternative sequences of events that lead back from a secondary infection to its primary infection, the moment generating function for generation intervals is a weighted sum of moment generating functions of the alternative sequences. We may expand the moment generating function expression (9) in terms of moment generating functions for duration between successive events in an infection cycle as

$$R = \frac{1}{M(-r)} = \frac{1}{\sum_{i=1}^{n} c_i M_1(-r) \times M_2(-r) \times \cdots \times M_i(-r)},$$

where M stand for the moment generating function of the entire generation interval and $M_1, M_2, \ldots, M_n$ stand for the moment generating functions for duration between successive events in the infection cycle; c_i denotes the relative contribution of the i^{th} stage to total number of secondary infections due to a typical infected individual over its entire infectious period, such that $c_1 + c_2 + \ldots + c_n = 1$.

We can use this equation as a template for deriving expressions for the reproductive number of epidemic models. Substituting the moment generating function for the exponential distribution $M_i(-r) = b_i/(b_i + r)$ into this equation for one event ($n = 1$ with $c_1 = 1$) gives equation (10). Substituting the same moment generating function into this equation for two events ($n = 2$ with $c_1 = 0$ and $c_2 = 1$) gives equation (11). Substituting the moment generating function into this equation for $x + y$ events (with $c_i = 0$ for $i = 1$ through $i = x$ and $c_i = 1/y$ for $i = x + 1$ through $i = x + y$) gives equation (12).

3. TABLES

Table 1. Notation and definition of similar concepts in ecology, demography and epidemiology

Symbol	Ecology and demography	Epidemiology	Comments
$b(t)$	birth rate at time t	rate of new cases of infection at time t	
a	age	time since infection	
$n(a)$	expected female birth rate from mother aged a $(=l(a)m(a))$	expected rate of creating secondary cases at time a since infection	
R	reproductive number, defined as expected lifetime reproductive success	reproductive number, defined as expected secondary infections created	$R = \int_{a=0}^{\infty} n(a)\mathrm{d}a$
$g(a)$	distribution of time to reproduction	generation interval distribution	$g(a) = \frac{n(a)}{\int_{a=0}^{\infty} n(a)\mathrm{d}a} = \frac{n(a)}{R}$
r	intrinsic rate of natural increase	epidemic growth rate	
T_c	cohort generation time	mean generation interval	$T_c = \int_{a=0}^{\infty} a g(a)\mathrm{d}a$
-	stable distribution of age	stable age distribution of time since infection	

Table 2. Generation interval distributions, their moment generating functions, and the resulting relationships between R and r

distribution	$g(a)$	mean	variance	$M(z)$	R	condition
Exponential	be^{-ba}	$\frac{1}{b}$	$\frac{1}{b^2}$	$\frac{b}{b-z}$	$1 + \frac{r}{b}$	$r > -b$
Gamma	$\frac{b^n}{\Gamma(n)} a^{n-1} e^{-ba}$	$\frac{n}{b}$	$\frac{n}{b^2}$	$(\frac{b}{b-z})^n$	$(1 + \frac{r}{b})^n$	$r > -b$
Normal	$\frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(a-\mu)^2}{2\sigma^2}}$	μ	σ^2	$e^{\mu z + \frac{1}{2}\sigma^2 z^2}$	$e^{\mu r - \frac{1}{2}\sigma^2 r^2}$	
Delta	1 if $a = \mu$	μ	0	$e^{\mu z}$	$e^{\mu r}$	
Uniform	$\frac{1}{b_2 - b_1}$ if $b_1 \leq a \leq b_2$	$\frac{b_1+b_2}{2}$	$\frac{(b_2-b_1)^2}{12}$	$\frac{e^{b_2 z} - e^{b_1 z}}{(b_2-b_1)z}$	$\frac{r(b_2-b_1)}{e^{-b_1 z} - e^{-b_2 z}}$	