Epidemics from the Eye of the Pathogen

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Abstract

While a common trend in disease modeling is to develop models of increasing complexity, it was recently pointed out that outbreaks appear remarkably simple when viewed in the incidence vs. cumulative cases (ICC) plane. This article details the theory behind this phenomenon by analyzing the stochastic SIR (Susceptible, Infected, Recovered) model in the cumulative cases domain. We prove that the Markov chain associated with this model reduces, in the ICC plane, to a pure birth chain for the cumulative number of cases, whose limit leads to an independent increments Gaussian process that fluctuates about a deterministic ICC curve. We calculate the associated variance and quantify the additional variability due to estimating incidence over a finite period of time. We also illustrate the universality brought forth by the ICC concept on real-world data for Influenza A and for the COVID-19 outbreak in Arizona.

1 Introduction: Outbreaks beyond the time domain and the ICC perspective

As evidenced by the COVID-19 pandemic, societies throughout the world are highly vulnerable to disease outbreaks [13]. To understand the mechanism involved in disease spread and eventually provide a framework for effective public health guidance, scientists have developed numerous mathematical, statistical, and computational models of infectious disease dynamics [10, 23]. But a dilemma quickly emerges: because disease

spread is inherently complex, realistic descriptions commonly rely on a large number of parameters that are often unidentifiable or difficult to estimate, thereby leading to huge uncertainty in associated forecasts [5]. As is typically the case with nonlinear systems, reducing the dynamics to a core nonlinear model and quantifying the associated uncertainty should provide a viable compromise between complexity and simplicity. The ICC approach [12, 11] introduces such a framework and, as illustrated in Figure 1, uncovers what appears to be a generic property of outbreak data.

In most instances, the independent variable underlying the course of an epidemic is time: health authorities report numbers of new cases and deaths per day or week, forming what is commonly called an epidemiological (EPI) curve (see examples in the top left panel of Figure 1); and modelers fit their models to this same EPI curve. However, time – as we measure it – is not intrinsic to the spread dynamics of the pathogen. As such, focusing on temporal aspects obscure relevant properties of these dynamics, thereby making it more difficult to fit models to data. The ICC viewpoint [12, 11] suggests replacing time with a monotonic, nonlinear function thereof: cumulative cases. Therefore, in contrast to EPI curves, which describe how humans perceive outbreaks as time unfolds, ICC curves emphasize the pathogen's perspective centered on the number of people infected (i.e. the resources that have been consumed so far).

Figure 1 illustrates how these ideas can reveal important traits shared by different outbreaks associated with the same pathogen. The left plot of the top row shows the EPI curves of the 24 Inluenza A (H3N2) outbreaks that took place in US HHS regions between 1998 and 2019 and led to more than 3000 confirmed cases. No specific properties of these curves are readily observable, because the peak timing and peak height vary between seasons. However, when the same curves are plotted in the incidence vs. cumulative cases (ICC) plane, a structure emerges (top right panel), revealing similarities between each season that, as we will see, are characteristic of the disease itself. To emphasize that such properties are generic, the bottom row of Figure 1 shows similar results for multiple realizations of a stochastic SIR (Susceptible, Infected, Recovered) model via simulations on a complete graph. Again, the universality normally hidden behind classical EPI curves (Figure 1 bottom row, left) becomes evident once time is removed from the picture and the independent variable is replaced with cumulative cases (Figure 1 bottom row, right). Incidence is defined as βIS , which for the deterministic SIR model equals dC/dt. Here, β is the microscopic contact rate of the disease, I is the number of infected individuals, S is the number of susceptible individuals, and C is the cumulative number of cases. The parameter β represents the probability that a given susceptible individual will encounter a specific infected individual in a population of size n and therefore scales like 1/n. Below we will introduce the population-level contact rate, $\beta_P = \beta n$, which remains finite as $n \to \infty$. For deterministic systems, an ICC curve is therefore the graph of dC/dt as a function of C. In a discrete setting, the reported incidence is the number of new cases ΔC that occurred over a fixed period of time Δ and the incidence per unit of time is $\Delta C/\Delta$. Because disease incidence is a function of time and cumulative cases are monotonically

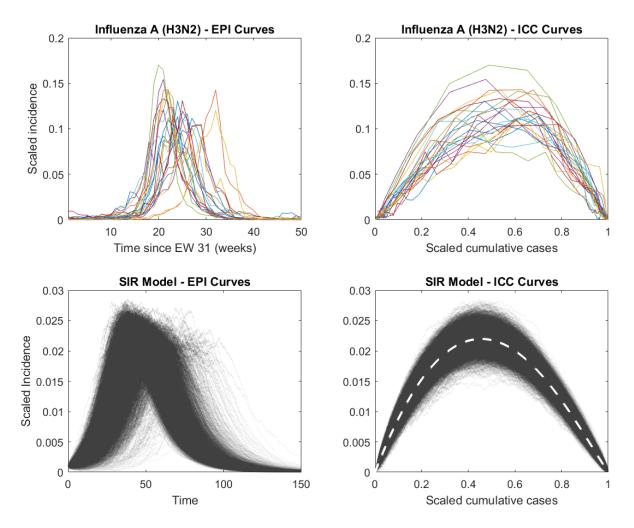


Figure 1: **Top Row**, **left:** weekly incidence $\mathcal{I}/\hat{C}_{\infty}$ plotted as a function of time, for influenza A (H3N2) outbreaks that took place in the US between 1998 and 2019, and were of final size $\hat{C}_{\infty} > 3000$ cases. Each curve corresponds to one flu season in an HHS region. Time is measured in weeks from epidemiological week (EW) 31 of each year. The data were downloaded from the CDC Fluview database using the R cdcfluview package [15]. **Top row**, **right:** the same curves plotted in the ICC plane, showing $\mathcal{I}/\hat{C}_{\infty}$ as a function of scaled cumulative cases C/\hat{C}_{∞} . **Bottom row**, **left:** EPI curves for 5997 runs of a stochastic SIR model with size N=2500 and $R_0=2$. **Bottom row**, **right:** Corresponding ICC curves, showing $\mathcal{I}/\hat{C}_{\infty}$ as a function of C/\hat{C}_{∞} . The white dashed curve corresponds to Equation 1, scaled to the expected final size C_{∞} of the outbreak (C_{∞}/N) is the non-zero root of the right-hand side of Eq. 1 with c_0 set to 0). For the stochastic SIR model, \mathcal{I} is defined as the random variable βIS (see text for details).

increasing with time, the ICC curve, like the EPI curve, is always the graph of a function defined on integer values of C. In addition, because incidence decreases to zero between separate waves of disease spread, and consequently the cumulative cases plateau during the same periods of time, each wave of an outbreak corresponds to one "hump" (as shown in the right column of Figure 1) of the ICC curve. One of the results of the present work is that the ICC curve of an outbreak described by the stochastic SIR model (corresponding to any of the black curves in the bottom right panel of Figure 1) fluctuates about a mean ICC curve given by the deterministic SIR model (leading to the white dashed line in the same panel).

Dynamical systems theory has long promoted such a phase portrait perspective as displayed in the right panels of Figure 1, since it can provide both intuitive insights and analytical approaches not easily identified under the time domain description. In [12], Lega & Brown advocated for the relevance of this viewpoint in disease modeling; they pointed out that in many instances epidemiological data appear to follow a parabolic ICC curve, thereby suggesting that the logistic equation is a good model for the overall dynamics of C as a function of time. This provided context to earlier works, in which the relevance of the logistic equation to the spread of Ebola in Africa had been noted [4, 14]. In [11], Lega proved that the deterministic SIR compartmental model [10] has an exact ICC curve, whose shape is almost parabolic. The present work goes beyond the macroscopic picture provided by deterministic approaches. We analyze the statistical properties of the stochastic SIR model and explain the origins of the ICC curve from microscopic stochastic interactions.

The rest of this article is organized as follows. Section 2 introduces the stochastic SIR model and establishes that, in the limit of large populations, a single realization of this model fluctuates about the deterministic SIR ICC curve. Section 3 builds on these results to prove that the stochastic SIR model defines a Gaussian process with independent increments in the ICC plane. We quantify the associated variance, provide an elegant way of recovering a known formula for the distribution of the final size of an outbreak, find the distribution of incidence at expected disease peak, and discuss the added variability due to the difference quotient nature of the reported incidence. Section 4 illustrates what some of the ideas discussed in this manuscript mean for real outbreak data. Section 5 summarizes our results and reviews their potential applications to the analysis of outbreak data.

2 The Stochastic SIR model and a Functional Law of Large Numbers

The SIR model consists of three compartments representing individuals susceptible of catching the disease (S), those who have the disease and are infectious (I), and those who have recovered (R) and can not longer infect others. In the stochastic version, the

size of each compartment evolves according to a continuous time Markov process [2] involving the two transitions described in Table 1. Here, n is the number of individuals in the population, n_S , n_I , and n_R are the number of susceptible, infective, and recovered individuals respectively, and $n_C = n_I + n_R = n - n_S$ is the number of cases. The parameters β and γ are the individual contact and recovery rates of the disease, respectively. As mentioned above, β scales like 1/n.

event	transition	rate
	$(n_S, n_I, n_R) \to (n_S - 1, n_I + 1, n_R)$	
recovery	$(n_S, n_I, n_R) \to (n_S, n_I - 1, n_R + 1)$	γn_I

Table 1: Continuous-time Markov process associated with the SIR model. The parameter β scales like 1/n, where $n = n_S + n_I + n_R$ is the total population size, whereas the recovery rate γ is independent of n.

The ICC curve was developed to determine a direct relationship between incidence and the number of cases. For the deterministic SIR model, it reads [11]

$$\frac{dc}{dt} = \beta_P \left(c + \frac{1}{R_0} \ln(1 - c) - \frac{1}{R_0} \ln(1 - c_0) \right) (1 - c) = G(c, c_0), \tag{1}$$

where $c = n_C/n$. The **population-level contact rate** β_P is the **individual-level contact rate** β times the population size n. R_0 is the basic reproductive number, and c_0 , the initial condition for c, is positive and small. Both β_P and $R_0 = \beta_P/\gamma$ are independent of n and therefore remain finite in the limit of large population sizes. The goal of this section is to prove that a relationship analogous to (1) can be found by representing the stochastic SIR model as a multiparameter random time change (see [6], Section 6.2).

2.1 Multiparameter Random Time Change Representation

A time homogeneous pure jump Markov process on a finite state space can be represented using an appropriate number of independent rate one Poisson processes, one for each type of jump. The rate associated to any given Poisson process is random and based on the current state of the process. Consequently, the multiparameter time change representation for the stochastic SIR model requires two Poisson processes, Y_i , i = 1, 2, one for **infection**

and one for **recovery**. Thus, we write the stochastic SIR model (N_S, N_I, N_R) as

$$N_{S}(t) = N_{S}(0) - Y_{1} \left(\int_{0}^{t} \beta N_{S}(u) N_{I}(u) du \right),$$

$$N_{I}(t) = N_{I}(0) + Y_{1} \left(\int_{0}^{t} \beta N_{S}(u) N_{I}(u) du \right) - Y_{2} \left(\int_{0}^{t} \gamma N_{I}(u) du \right),$$

$$N_{R}(t) = N_{R}(0) + Y_{2} \left(\int_{0}^{t} \gamma N_{I}(u) du \right).$$
(2)

As is shown in Section 6.4 of [6], the system of equations in (2) has a unique solution and is the SIR model introduced in Table 1. The cumulative number of cases $N_C(t) = N_I(t) + N_R(t)$ satisfies

$$N_{C}(t) = N_{C}(0) + Y_{1} \left(\int_{0}^{t} \beta N_{S}(u) N_{I}(u) du \right)$$
$$= N_{C}(0) + Y_{1} \left(\int_{0}^{t} \beta (n - N_{C}(u)) N_{I}(u) du \right).$$

Now, taking advantage of the independent increments of the Poisson process, we may write

$$N_{C}(t + \Delta) - N_{C}(t)$$

$$= Y_{1} \left(\int_{0}^{t+\Delta} \beta(n - N_{C}(u)) N_{I}(u) du \right) - Y_{1} \left(\int_{0}^{t} \beta(n - N_{C}(u)) N_{I}(u) du \right)$$

$$= \tilde{Y}_{1} \left(\int_{t}^{t+\Delta} \beta(n - N_{C}(u)) N_{I}(u) du \right), \tag{3}$$

where \tilde{Y}_1 is also a unit rate Poisson process. As a consequence, we have the following lemma.

Lemma 1. The rate of increase in the expected number of cases

$$\dot{C}(n_C) = \frac{d}{d\Delta} E[N_C(t+\Delta) - N_C(t)|N_C(t) = n_C]\Big|_{\Delta=0}$$

satisfies the equation

$$\dot{C}(n_C) = E[\beta N_I(t)(n - n_C)|N_C(t) = n_C] = \beta E[N_I(t)|N_C(t) = n_C](n - n_C). \tag{4}$$

Proof. The conditional mean of the increment in (3) is given by

$$E[N_C(t+\Delta) - N_C(t)|N_C(t) = n_C]$$

$$= E\left[\tilde{Y}_1\left(\int_t^{t+\Delta} \beta(n - N_C(u))N_I(u)du\right) \middle| N_C(t) = n_C\right]$$

$$= \int_t^{t+\Delta} \beta E[(n - N_C(u))N_I(u)|N_C(t) = n_C] du$$

Now divide by Δ and let $\Delta \to 0$.

Lemma 1 relates $\dot{C}(n_C)$ to the conditional expectation of $\beta n_I(n-n_C) = \beta n_I n_S$. We call the random variable $\mathcal{I} = \beta n_I n_S$ the "macroscopic incidence." Our next step is to find a formula for $E[N_I(t)|N_C(t)=n_C]$, the mean number of infective individuals given the number of cases. This relationship can be understood by examining the underlying discrete time Markov chain.

2.2 Underlying discrete time Markov chain

By the Doob-Gillespie algorithm [8] and [3] Section 15.6, a time-homogeneous pure-jump Markov process consists of two independent parts.

- 1. The length of time that the process remains in its current state is exponentially distributed with parameter value depending only on the current state, equal to the sum of the rates listed in the above table.
- 2. The jumps form an underlying time-homogeneous discrete time Markov chain.

For the SIR model, the underlying discrete time Markov chain has two transitions, with probabilities listed in the table below.

event	transition	probability
infection	$(n_S, n_I, n_R) \to (n_S - 1, n_I + 1, n_R)$	$\beta n_S n_I / (\beta n_S n_I + \gamma n_I)$
		$= \beta n_S / (\beta n_S + \gamma)$
recovery	$(n_S, n_I, n_R) \to (n_S, n_I - 1, n_R + 1)$	$ \gamma n_I/(\beta n_S n_I + \gamma n_I) $
		$= \gamma/(\beta n_S + \gamma)$

Note that the probabilities in the last column do not depend on n_I when $n_I > 0$. Choosing state space variables n_C and n_I , we recast the Markov chain transitions in terms of the total population n and the number of cases n_C , leading to the following table.

eventtransitionprobabilityinfection
$$(n_C, n_I) \rightarrow (n_C + 1, n_I + 1)$$
 $p(n_C) = \beta(n - n_C)/(\beta(n - n_C) + \gamma)$ recovery $(n_C, n_I) \rightarrow (n_C, n_I - 1)$ $1 - p(n_C) = \gamma/(\beta(n - n_C) + \gamma)$

Since n is given, the above probabilities only depend on n_C , the number of cases that have occurred since the beginning of the outbreak. Using the expression for the basic reproduction number, $R_0 = n\beta/\gamma = \beta_P/\gamma$, we can also write

$$p(n_C) = \frac{R_0(n - n_C)/n}{R_0(n - n_C)/n + 1}.$$

Consequently, we can denote the underlying Markov chain by C_j , j = 0, 1, ... for the total number of cases at the j-th event. The ability to cast the Markov chain for cases alone with the number of infectives playing no role mirrors the property that the dynamics of the deterministic SIR model is completely described by a first-order differential equations for C(t) [11]. Note that C_j is a pure birth chain with a jump up with each new infection. This Markov chain has a single parameter, namely R_0 , which is a characteristic of the outbreak and independent of the population size n. In terms of statistical inference, the ratio that leads to the probabilities $p(n_C)$ shows that the parameter β is **ancillary** to the dynamics (see [7] for the properties of ancillary statistics).

2.3 The mean for the number of infected individuals

We are now prepared to investigate properties of the distribution of I_j , the number of infected individuals at the jth event, when the number of cases is known. To this end, note that with $C_j = n_C$

$$I_{j} = n_{C} - (j - n_{C}) = 2n_{C} - j \tag{5}$$

since there have been n_C infections in j steps, and thus $j - n_C$ recoveries. Also note that the nature of the chain is such that $C_0 = 0$ and $C_1 = 1$. Next, let

$$\tau_{n_C} = \min\{j; C_j = n_C\}$$

denote the number of steps in the discrete Markov chain needed to reach n_C cases, which is also known as a hitting time of the Markov chain. Then,

$$I_{\tau_{n_C}} = 2n_C - \tau_{n_C}.$$

This shows that if we can determine the distribution of τ_{n_C} , then we can also determine the distribution of $I_{\tau_{n_C}}$.

Theorem 2. The expectation of τ_{n_C} satisfies

$$\lim_{n \to \infty} \frac{1}{n} E \tau_{n_C} = c - \frac{1}{R_0} \ln(1 - c)$$

and consequently,

$$\lim_{n \to \infty} \frac{1}{n} E I_{\tau_{n_C}} = c + \frac{1}{R_0} \ln(1 - c),$$

where $c = n_C/n$.

Proof. A pure-birth Markov chain remains in a given state m for a geometric number of steps before making the transition to the state m+1. With this in mind, we can write

$$\tau_{n_C} = \sigma_1 + \dots + \sigma_{n_C - 1} \tag{6}$$

as the sum of independent random variables $\sigma_m \sim Geom_1(p(m))$, where the subscript 1 in $Geom_1(p(m))$ indicates that the state space is $\{1, 2, \ldots\}$ (rather than $\{0, 1, 2, \ldots\}$). Thus, $E\sigma_m = 1/p(m)$. Write

$$E\tau_{n_C} = \sum_{m=1}^{n_C-1} \frac{1}{p(m)} = \sum_{m=1}^{n_C-1} \frac{R_0(n-m)/n+1}{R_0(n-m)/n} = (n_C-1) + \frac{n}{R_0} \sum_{m=1}^{n_C-1} \frac{1}{n-m}.$$

Then,

$$\frac{1}{n}E\tau_{n_C} = c - \frac{1}{n} + \frac{1}{R_0} \sum_{m=1}^{n_{c-1}} \frac{1}{1 - m/n} \frac{1}{n}$$

$$\to c + \frac{1}{R_0} \int_0^c \frac{1}{1 - q} dq = c - \frac{1}{R_0} \ln(1 - c) \quad \text{as } n \to \infty.$$

Corollary 3. The scaled rate of increase in the expected number of cases, \dot{c} (see Lemma 1), satisfies

$$\dot{c} = \lim_{n \to \infty} \frac{1}{n} \dot{C}([nc]) = \beta_P \left(c + \frac{1}{R_0} \ln(1 - c) \right) (1 - c). \tag{7}$$

Proof. The theorem above shows that

$$\lim_{n \to \infty} \frac{1}{n} E[N_I(t)|N_C(t) = n c] = c + \frac{1}{R_0} \ln(1 - c) = m_I(c),$$

where the last inequality defines $m_I(c)$. Now substitute into (4) and recall that $\beta_P = n\beta$.

We therefore have recovered the ICC curve (1) as the mean of the macroscopic incidence \mathcal{I} in the limit as $n \to \infty$. We now turn to a description of how individual realizations of \mathcal{I} in the stochastic SIR model fluctuate about the mean ICC curve.

3 The statistics of fluctuations about the ICC curve

In this section, we establish a functional central limit theorem in which the limit is an independent increments Gaussian process.

The ingredients for a Gaussian process are a mean function and a variance-covariance function. Thus, the next task is to determine the variance structure that arises as a limit for the pure-birth Markov chain C_j . Recall that we set $\sigma_m \sim Geom_1(p(m))$, the number of steps that the chain remains in a given state m. Because the σ_m are independent, we can use (6) and write the variance of τ_{n_C} as follows.

$$\operatorname{Var}(\tau_{n_{C}}) = \sum_{m=1}^{n_{C}-1} \operatorname{Var}(\sigma_{m}) = \sum_{m=1}^{n_{C}-1} \frac{1 - p(m)}{p(m)^{2}}$$

$$= \sum_{m=1}^{n_{C}-1} \frac{1/(R_{0}(n-m)/n+1)}{((R_{0}(n-m)/n)/(R_{0}(n-m)/n+1))^{2}}$$

$$= \sum_{m=1}^{n_{C}-1} \frac{R_{0}(n-m)/n+1}{R_{0}^{2}(n-m)^{2}/n^{2}} = \frac{n}{R_{0}} \sum_{m=1}^{n_{C}-1} \frac{1}{n-m} + \frac{n^{2}}{R_{0}^{2}} \sum_{m=1}^{n_{C}-1} \frac{1}{(n-m)^{2}}.$$
(8)

Consequently, using the relationship in (5).

$$\operatorname{Var}(I_{\tau_{n_C}}) = \operatorname{Var}(\tau_{n_C}) = \frac{n}{R_0} \sum_{m=1}^{n_C - 1} \frac{1}{n - m} + \frac{n^2}{R_0^2} \sum_{m=1}^{n_C - 1} \frac{1}{(n - m)^2}.$$

Theorem 4. Set $c_0 = n_{C_0}/n$ and $c = n_C/n$,

$$\lim_{n \to \infty} \frac{1}{n} (Var(I_{\tau_{n_C}}) - Var(I_{\tau_{n_{C_0}}})) = \frac{1}{R_0} \ln \left(\frac{1 - c_0}{1 - c} \right) + \frac{1}{R_0^2} \frac{c - c_0}{(1 - c)(1 - c_0)}.$$

Proof. Take the expression (8), divide by n and notice that the two sums are Riemann sums. Take the limit to obtain the corresponding integral, which can be evaluated explicitly.

3.1 Functional central limit theorem

We can turn the calculations above into a functional central limit theorem. To start, define

$$\bar{I}_c = \frac{1}{n} I_{\tau_{n_C}}, \qquad \bar{\tau}_c = \frac{1}{n} \tau_{n_C}.$$

Due to the fact that they are derived from sums of independent geometric random variables, both \bar{I}_c and $\bar{\tau}_c$ have independent increments. In particular, set $c = n_C/n$ and define \mathcal{F}_c to be the σ -algebra generated by $\{C_j; j \leq \tau_{n_C}\}$. Then for $c_0 < c_1$, $\bar{\tau}_{c_1} - \bar{\tau}_{c_0}$ and \mathcal{F}_{c_0} are independent and by the basic properties of conditional expectation

$$E[\bar{\tau}_{c_1} - \bar{\tau}_{c_0}|\mathcal{F}_{c_0}] = E[\bar{\tau}_{c_1} - \bar{\tau}_{c_0}] = E\bar{\tau}_{c_1} - E\bar{\tau}_{c_0}.$$

Rearranging terms,

$$E[\bar{\tau}_{c_1} - E\bar{\tau}_{c_1}|\mathcal{F}_{c_0}] = \bar{\tau}_{c_0} - E\bar{\tau}_{c_0},\tag{9}$$

where we have used $E[E\bar{\tau}_{c_1}|\mathcal{F}_{c_0}] = E\bar{\tau}_{c_1}$ and $E[\bar{\tau}_{c_0}|\mathcal{F}_{c_0}] = \bar{\tau}_{c_0}$.

Theorem 5. Define

$$M_c^n = \sqrt{n}(\bar{I}_c - E\bar{I}_c) = -\sqrt{n}(\bar{\tau}_c - E\bar{\tau}_c).$$

and

$$A_c^n = n \operatorname{Var}(\bar{I}_c) = n \operatorname{Var}(\bar{\tau}_c) = \operatorname{Var}(M_c^n).$$

Then, M_c^n and $(M_c^n)^2 - A_c^n$ are mean zero martingales.

Proof. The fact $E[M_{c_1}^n|\mathcal{F}_{c_0}] = M_{c_0}^n$ follows directory from (9), showing that M_c^n is a mean zero martingale.

Using the mean zero and independent increments properties again, we find

$$E[(M_{c_1}^n - M_{c_0}^n)^2 | \mathcal{F}_{c_0}] = Var(M_{c_1}^n - M_{c_0}^n | \mathcal{F}_{c_0}) = Var(M_{c_1}^n - M_{c_0}^n) = A_{c_1}^n - A_{c_0}^n.$$

Also,

$$E[(M_{c_1}^n - M_{c_0}^n)^2 | \mathcal{F}_{c_0}] = E[(M_{c_1}^n)^2 | \mathcal{F}_{c_0}] - 2M_{c_0}^n E[M_{c_1}^n | \mathcal{F}_{c_0}] + (M_{c_0}^n)^2$$
$$= E[(M_{c_1}^n)^2 | \mathcal{F}_{c_0}] - (M_{c_0}^n)^2.$$

Combining,

$$E[(M_{c_1}^n)^2|\mathcal{F}_{c_0}] - (M_{c_0}^n)^2 = A_{c_1}^n - A_{c_0}^n, \text{ and } E[(M_{c_1}^n)^2 - A_{c_1}^n|\mathcal{F}_{c_0}] = (M_{c_0}^n)^2 - A_{c_0}^n,$$

showing that

$$(M_c^n)^2 - A_c^n$$

is also a martingale.

We may therefore state the following theorem.

Theorem 6. M_c^n converges in distribution as $n \to \infty$ to a continuous independent increments Gaussian process with mean zero and variance function $\sigma_I^2(c)$.

Proof. The martingale central limit theorem has three ingredients:

- 1. A sequence of martingales, here the sequence of stochastic processes M_c^n .
- 2. A sequence of positive processes A_c^n that compensate for $(M_c^n)^2$ so that $(M_c^n)^2 A_c^n$ is a martingale.
- 3. A_c^n converges to a deterministic function continuous in c. Here the A_c^n are themselves deterministic and converge to $\sigma_I^2(c)$ as $n \to \infty$, where

$$\sigma_I^2(c) = -\frac{1}{R_0} \ln(1-c) + \frac{1}{R_0^2} \frac{c}{1-c}.$$

We have set $c_0 = 0$ in the asymptotic expansions derived in Theorem 4 to obtain an expression in terms of c only.

Since 1, 2, and 3 hold, then the sequence of martingales converges to a mean-zero independent increments Gaussian process (see [6] Section 7.1). \Box

Remark 7. As a consequence of Theorem 6, the mean of the scaled infected satisfies

$$E\bar{I}_c \simeq m_I(c) = c + \frac{1}{R_0} \ln(1 - c)$$

and the variance

$$n \operatorname{Var}(\bar{I}_c) \simeq \sigma_I^2(c),$$

with equality in the limit as $n \to \infty$.

Remark 8. Because $Var(\bar{I}_c) \to 0$ as $n \to \infty$, the convergence of expectations in Theorem 2 can, by Theorem 6, be replaced by convergence in mean square.

Remark 9. We can recover the number of recovered at the hitting time τ_{n_C} by noting that

$$R_{\tau_{n_C}} - R_{\tau_{n_0}} = (\tau_{n_C} - \tau_{n_0}) - (n_C - n_0) = -(I_{\tau_{n_C}} - I_{\tau_{n_0}}) + (n_C - n_0)$$

and thus

$$\frac{1}{n}(R_{\tau_{n_C}} - R_{\tau_{n_0}}) = -\frac{1}{n}(I_{\tau_{n_C}} - I_{\tau_{n_0}}) + (c - c_0) = -(\bar{I}_c - \bar{I}_{c_0}) + (c - c_0).$$

Corollary 10. The scaled limit of $\bar{R}_c = R_{\tau_{n_C}}/n$ converges to an independent increments Gaussian process. The mean of the increment from c_0 to c is

$$m_R(c) - m_R(c_0) = \frac{1}{R_0} \ln \left(\frac{1 - c_0}{1 - c} \right).$$

The variance satisfies $\sigma_R^2(c) = \sigma_I^2(c)$. The limiting processes for the scaled infective and recovered individuals have correlation -1.

Remark 11. For large n and $c_0 > 0$, the distribution of increment $\bar{I}_c - \bar{I}_{c_0}$ can be approximated using a deterministic time change of standard Brownian motion, B.

$$\bar{I}_c - \bar{I}_{c_0} \approx m_I(c) - m_I(c_0) + \frac{1}{\sqrt{n}} (B(\sigma_I(c)) - B(\sigma_I(c_0))).$$

This allow for easy and very accurate simulation of the independent increments Gaussian process.

3.2 Functional central limit theorem for the macroscopic incidence

We now turn to the macroscopic incidence scaled to the population size n, defined as

$$\frac{\mathcal{I}}{n} = \mathcal{I}_n = (\beta n)\bar{I}_c(1-c), \qquad \mathcal{I} = \beta n_I n_S,$$

where \mathcal{I} was introduced at the end of Section 2. Note that as $n \to \infty$, the population contact rate $\beta_P = \beta n$ remains constant for fixed $R_0 = (\beta n)/\gamma = \beta_P/\gamma$. A central limit theorem similar to the one established in the previous section applies to \mathcal{I}_n . The mean scaled macroscopic incidence is obtained from the scaled number of infections

$$m_{\mathcal{I}}(c) = (\beta n) m_I(c) (1 - c),$$

and so is its variance, as stated below.

Corollary 12. The scaled limit of \mathcal{I}_n converges to an independent increments Gaussian process, of mean

$$G(c,0) = G(c) = (\beta n) \left(c + \frac{1}{R_0} \ln(1-c) \right) (1-c)$$

$$= \beta_P \left(c + \frac{1}{R_0} \ln(1-c) \right) (1-c)$$
(10)

and variance $\frac{1}{n}\sigma_{\mathcal{I}}^{2}(c)$, where

$$\sigma_{\mathcal{I}}^{2}(c) = (\beta n)^{2} \sigma_{I}^{2}(c) (1 - c)^{2} = \beta_{P}^{2} \left(-\frac{1}{R_{0}} \ln(1 - c) + \frac{1}{R_{0}^{2}} \frac{c}{1 - c} \right) (1 - c)^{2}.$$
 (11)

The expression for G in (10) is the same as in Equation (1) with c_0/n set to 0, showing agreement between the deterministic result and the mean of the stochastic model in the limit of large populations. This is the reason why we called $\mathcal{I} = \beta n_I n_S$ the macroscopic incidence. The above calculations have immediate consequences for the distribution of two quantities relevant to public health: the fraction of the population infected at peak incidence, and the final size of the outbreak. We state these results in the next section.

3.3 Final population size and peak incidence

Important properties of a disease outbreak are given at critical values c_* of the fraction of cumulative cases $c = n_C/n$. Two particularly relevant examples of c_* are

1. c_{\wedge} , the fraction of the population that will have been infected at expected peak incidence, i.e. when $G'(c_{\wedge}) = 0$, and

2. c_{∞} , the expected final size of the outbreak, i.e. the mean fraction of the population that will have been infected by the time the outbreak ends.

The first may be obtained implicitly by solving $G'(c_{\wedge}) = 0$ for c_{\wedge} .

$$0 = G'(c_{\wedge}) = (\beta n)((m'_{I}(c_{\wedge})(1 - c_{\wedge}) - m_{I}(c_{\wedge}))$$

$$= (\beta n) \left(\left(1 - \frac{1}{R_{0}} \frac{1}{1 - c_{\wedge}} \right) (1 - c_{\wedge}) - \left(c_{\wedge} + \frac{1}{R_{0}} \ln(1 - c_{\wedge}) \right) \right)$$

$$= (\beta n) \left(\left((1 - c_{\wedge}) - \frac{1}{R_{0}} \right) - \left(c_{\wedge} + \frac{1}{R_{0}} \ln(1 - c_{\wedge}) \right) \right)$$

$$= (\beta n) \left(1 - 2c_{\wedge} - \frac{1}{R_{0}} (1 + \ln(1 - c_{\wedge})) \right)$$

$$\implies c_{\wedge} = \frac{-1}{2R_{0}} (1 + \ln(1 - c_{\wedge})) + \frac{1}{2}.$$

The value of c_{\wedge} may then be found numerically for specific values of R_0 . In addition, the expression for $\sigma_{\mathcal{I}}(c_{\wedge})$ may be applied to estimate the distribution of the scaled macroscopic incidence when $c = c_{\wedge}$. The bottom row of Figure 2 shows c_{\wedge} (left) and $\sigma_{\wedge} = \sigma_{\mathcal{I}}/(\beta n)$ (right) as functions of R_0 , whereas Table 2 displays their numerical values for typical values of R_0 .

The second requires the variant of the delta method applied to hitting times (see [6], Section 11.4). This approach uses propagation of error to give a valuable extension of the central limit theorem. We state the result in the form of a theorem below.

Theorem 13. Define

$$\hat{c}_{\infty} = \inf\{c > 0; \bar{I}_c = 0\}.$$

Then, \hat{c}_{∞} is approximately normally distributed, with mean c_{∞} such that $m_I(c_{\infty}) = 0$ and standard deviation

$$\sigma(\hat{c}_{\infty}) \approx \frac{1}{|m'(c_{\infty})|} \frac{\sigma_I(c_{\infty})}{\sqrt{n}} = \frac{\sigma_{\infty}}{\sqrt{n}}.$$

Proof. Because $\bar{I}_c \to m_I(c)$ in L^2 as $n \to \infty$ and m_I is continuous, we have $\hat{c}_\infty \to c_\infty$. By the central limit theorem (Theorem 6 of the previous section),

$$\sqrt{n}(\bar{I}_{\hat{c}_{\infty}} - m_I(\hat{c}_{\infty})) \to W,$$

where $W \sim N(0, \sigma_I^2(c_\infty))$, a normal random variable with mean 0 and variance $\sigma_I^2(c_\infty)$. Next, recall that $m_I(c_\infty) = \bar{I}_{\hat{c}_\infty} = 0$, thus

$$\sqrt{n}(\bar{I}_{\hat{c}_{\infty}} - m_I(\hat{c}_{\infty})) = \sqrt{n}(m_I(c_{\infty}) - m_I(\hat{c}_{\infty})) \simeq \sqrt{n} \, m_I'(c_{\infty})(c_{\infty} - \hat{c}_{\infty}).$$

Consequently, \hat{c}_{∞} is approximately normally distributed, with mean c_{∞} and standard deviation

$$\sigma(\hat{c}_{\infty}) \simeq \frac{1}{|m'(c_{\infty})|} \frac{\sigma_I(c_{\infty})}{\sqrt{n}} = \frac{\sigma_{\infty}}{\sqrt{n}}.$$

Thus, the standard deviation is multiplied by a propagation of error which is inversely proportional to the slope of $m_I(c_\infty)$. The error is expanded when the slope is shallow and contracted when the slope is steep. An expression for c_∞ may be found implicitly as a function of R_0 .

$$0 = m_I(c_\infty) = c_\infty + \frac{1}{R_0} \ln(1 - c_\infty),$$
 i.e. $c_\infty = -\frac{1}{R_0} \ln(1 - c_\infty).$

Substituting into the variance formula, we have

$$\sigma_I^2(c_\infty) = -\frac{1}{R_0} \ln(1 - c_\infty) + \frac{1}{R_0^2} \frac{c_\infty}{1 - c_\infty} = c_\infty + \frac{1}{R_0^2} \frac{c_\infty}{1 - c_\infty}.$$

In addition, the derivative

$$m_I'(c_\infty) = 1 - \frac{1}{R_0} \frac{1}{1 - c_\infty}$$

leads to

$$\frac{\sigma_I^2(c_\infty)}{m_I'(c_\infty)^2} = \frac{c_\infty + \frac{1}{R_0^2} \frac{c_\infty}{1 - c_\infty}}{\left(1 - \frac{1}{R_0} \frac{1}{1 - c_\infty}\right)^2} = \frac{R_0^2 c_\infty (1 - c_\infty)^2 + c_\infty (1 - c_\infty)}{(R_0(1 - c_\infty) - 1)^2}$$

$$= \frac{c_\infty (1 - c_\infty)(R_0^2 (1 - c_\infty) + 1)}{(R_0(1 - c_\infty) - 1)^2}.$$

The square root of this expression gives σ_{∞} , from which one can calculate $\sigma(\hat{c}_{\infty})$ for specific values of n. The top row of Figure 2 shows c_{∞} (left) and σ_{∞} (right) as functions of R_0 . Selected numerical values are displayed in Table 2.

Remark 14. The central limit theorem for c_{∞} is known (see [16, 17]) but the proof presented here is new.

As the graphs associated to c_{∞} show, the course of the pandemic looks more and more deterministic as R_0 grows, with an increase in cases and reduction in the standard deviation σ_{∞} . The value of c_{\wedge} increases with R_0 from 0.152 to 0.462 as R_0 increases from 1.2 to 5.0 while the standard deviation σ_{\wedge} decreases for $R_0 > 1.5$. Notably, the ratio c_{\wedge}/c_{∞} is nearly stable between 0.45 and 0.49 over a large range of values for R_0 , reflecting the universal properties of the shape of the ICC curve.

3.4 The stochastic ICC curve

Section 3.1 focused on the relationship between the fraction of infective individuals and the fraction of cumulative cases. This casting of the question has been shown to remove time from the analysis and with it the parameter β , the **time** rate of infections.

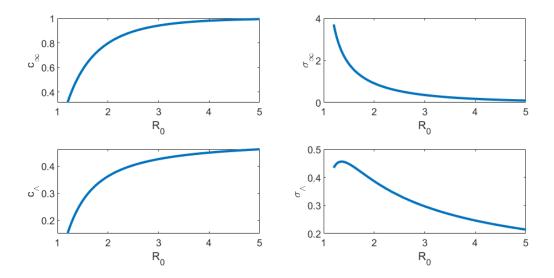


Figure 2: Functional dependence of select outbreak characteristics on the basic reproduction number R_0 . Top row, left: Mean c_{∞} of the fraction of population that eventually become cases, \hat{c}_{∞} . Top row, right: Behavior of σ_{∞} , where \hat{c}_{∞} has standard deviation σ_{∞}/\sqrt{n} . Bottom row, left: Fraction of cumulative cases at expected peak infection c_{\wedge} . Bottom row, right: Behavior of σ_{\wedge} , where $\mathcal{I}_n(c_{\wedge})$ has standard deviation $(\beta n)\sigma_{\wedge}/\sqrt{n}$.

R_0	$\mu_{\hat{c}_{\infty}} = c_{\infty}$	σ_{∞}	$\mu_{\hat{c}_{\wedge}} = c_{\wedge}$	σ_{\wedge}	c_{\wedge}/c_{∞}
1.2	0.314	3.708	0.152	0.434	0.485
1.5	0.583	1.835	0.273	0.448	0.468
2.0	0.797	0.913	0.363	0.386	0.455
2.5	0.893	0.547	0.403	0.335	0.452
3.0	0.941	0.357	0.426	0.297	0.453
3.5	0.966	0.245	0.440	0.268	0.455
4.0	0.980	0.174	0.450	0.246	0.459
4.5	0.988	0.126	0.457	0.229	0.462
5.0	0.993	0.094	0.462	0.214	0.465

Table 2: Values for the means of the fraction of population that eventually become cases $\mu_{\hat{c}_{\infty}} = c_{\infty}$, and the fraction of cases at peak infection $\mu_{\hat{c}_{\wedge}} = c_{\wedge}$. For a population of size n, the standard deviation for \hat{c}_{∞} is σ_{∞}/\sqrt{n} . The standard deviation of \mathcal{I}/n at $c = c_{\wedge}$ is $(\beta n) \sigma_{\wedge}/\sqrt{n}$. The final column gives the ratio of means and shows the universality of the ICC curve over a range of values for R_0 .

We know bring time back into the picture by examining discrete incidence as a function of cases. Discrete, or reported, incidence \mathcal{I}_{Δ} is the number of new cases that occur over a given period of time Δ . We shall see how the variance for \mathcal{I}_{Δ} depends on Δ in a nontrivial manner. To understand this dependence, we return to Equation (3) and continue our analysis by computing the variance of the increment of the number of cases from time t to time $t + \Delta$.

$$\operatorname{Var}(N_C(t+\Delta) - N_C(t)|N_C(t) = n_C)$$

$$= \operatorname{Var}\left(\tilde{Y}_1\left(\int_t^{t+\Delta} \beta(n - N_C(u))N_I(u)du\right) \middle| N_C(t) = n_C\right).$$

where \tilde{Y}_1 is a rate-1 Poisson process.

To simplify notation, denote the conditional expectation $E_{n_C} = E[\cdot|N_C(t) = n_C]$ and conditional variance $\text{Var}_{n_C} = \text{Var}(\cdot|N_C(t) = n_C)$. Define the random variables

$$\zeta = \int_{t}^{t+\Delta} \beta(n - N_{C}(u)) N_{I}(u) du \quad \text{and} \quad \eta = \tilde{Y}_{1}(\zeta).$$

Then, $\eta \sim Pois(\zeta)$. Because the parameter in a Poisson random variable is both its mean and its variance, $E_{n_C}[\eta|\zeta] = \operatorname{Var}_{n_C}(\eta|\zeta) = \zeta$. By the law of total variance,

$$\operatorname{Var}_{n_C}(\eta) = E_{n_C}[\operatorname{Var}_{n_C}(\eta|\zeta)] + \operatorname{Var}_{n_C}(E_{n_C}[\eta|\zeta]) = E_{n_C}[\zeta] + \operatorname{Var}_{n_C}(\zeta). \tag{12}$$

The first term of (12) has order Δ . Corollary 3 shows, that after dividing by Δ , its limit as $\Delta \to 0$ is

$$\beta(n - n_C)E[N_I(t)|N_C(t) = n_C]. \tag{13}$$

Expression (13) is the ICC curve. The second term is $O(\Delta^2)$. So, dividing by Δ^2 ,

$$\frac{1}{\Delta^2} \operatorname{Var}_{n_C}(\zeta) = \operatorname{Var}_{n_C} \left(\frac{1}{\Delta} \int_t^{t+\Delta} \beta(n - N_C(u)) N_I(u) du \right)
\to \operatorname{Var}_{n_C}(\beta(n - n_C) N_I(t)) = \beta^2 (n - n_C)^2 \operatorname{Var}(N_I(t) | N_C(t) = n_C). (14)$$

as $\Delta \to 0$. In the limit of large populations, expression (14) is the variance of the macroscopic incidence given by $Var(\mathcal{I}) = n \sigma_{\mathcal{I}}^2$, where $\sigma_{\mathcal{I}}^2$ is defined in Equation (11).

Because the second term in the law of total variance is $O(\Delta^2)$, we will need to determine the second order term for $E_{n_C}[\zeta]$ to complete our analysis. To this end, we first rewrite the continuous time Markov SIR model with the number of cases n_C and the number of infective individuals n_I as state variables.

The information in Table 3 is also conveyed using the generator G of the Markov process,

$$Gh(n_C, n_I) = \beta(n - n_C)n_I (h(n_C + 1, n_I + 1) - h(n_C, n_I)) + \gamma n_I (h(n_C, n_I - 1) - h(n_C, n_I))$$

event	transition	rate
infection	$(n_C, n_I) \to (n_C + 1, n_I + 1)$	$\beta(n-n_C)n_I$
recovery	$(n_C, n_I) \to (n_C, n_I - 1)$	γn_I

Table 3: Continuous-time SIR Markov process model with number of cases and number of infective as state variables.

Proposition 15. The $O(\Delta^2)$ term in the expansion of $E_{n_C}[\zeta]$ is

$$\frac{1}{2}\beta^2(n-n_C)\left(\left(n-n_C-1-\frac{n}{R_0}\right)E_{n_C}[N_I(t)]-E_{n_C}[N_I(t)^2]\right). \tag{15}$$

Proof. Set $g(n_C, n_I) = \beta(n - n_C)n_I$. Then subtract the $O(\Delta)$ term (13) from $E_{n_C}[\zeta]$ as defined in Equation (12).

$$E_{n_C} \left[\tilde{Y}_1 \left(\int_t^{t+\Delta} g(N_C(u), N_I(u)) du \right) - g(n_C, N_I(t)) \Delta \right]$$

$$= E_{n_C} \left[\int_t^{t+\Delta} g(N_C(u), N_I(u)) du - g(n_C, N_I(t)) \Delta \right]$$

$$= E_{n_C} \left[\int_t^{t+\Delta} \left(g(N_C(u), N_I(u)) - g(n_C, N_I(t)) \right) du \right]$$

$$= \int_t^{t+\Delta} E_{n_C} \left[g(N_C(u), N_I(u)) - g(n_C, N_I(t)) \right] du.$$

Divide by Δ^2 and take a limit using, successively, l'Hôpital's rule and the definition of the generator.

$$\lim_{\Delta \to 0} \frac{1}{\Delta^{2}} \int_{t}^{t+\Delta} E_{n_{C}} \left[g(N_{C}(u), N_{I}(u)) - g(n_{C}, N_{I}(t)) \right] du$$

$$= \lim_{\Delta \to 0} \frac{1}{2\Delta} E_{n_{C}} \left[g(N_{C}(t+\Delta), N_{I}(t+\Delta)) - g(n_{C}, N_{I}(t)) \right]$$

$$= \frac{1}{2} E_{n_{C}} \left[Gg(n_{C}, N_{I}(t)) \right] = \frac{1}{2} E \left[Gg(n_{C}, N_{I}(t)) \middle| N_{C}(t) = n_{C} \right]$$
(16)

To evaluate the generator G on g, note that

$$g(n_C + 1, n_I + 1) - g(n_C, n_I) = \beta(n - n_C - n_I - 1)$$

$$g(n_C, n_I - 1) - g(n_C, n_I) = -\beta(n - n_C)$$

So,

$$Gg(n_{C}, n_{I}) = \beta(n - n_{C})n_{I}\beta(n - n_{C} - n_{I} - 1) - \gamma n_{I}\beta(n - n_{C})$$

$$= \beta(n - n_{C})n_{I}(\beta(n - n_{C} - n_{I} - 1) - \gamma)$$

$$= \beta(n - n_{C})((\beta(n - n_{C} - 1) - \gamma)n_{I} - \beta n_{I}^{2})$$

$$= \beta(n - n_{C})(\beta((n - n_{C} - 1) - n_{I} - \beta n_{I}^{2})$$

Now, put this in the expression for the limit in Equation (16).

Theorem 16. The variance of the incidence over a time interval Δ is to order Δ^2 ,

$$\frac{1}{n} Var(N_C(t + \Delta) - N_C(t)|N_C(t) = n_C)$$

$$\simeq \beta_P(1 - c)m_I(c)\Delta$$

$$+ \beta_P^2(1 - c) \left(\frac{1}{2} \left(\left(1 - c - \frac{1}{R_0}\right) m_I(c) - m_I(c)^2\right) + (1 - c)\sigma_I^2(c)\right) \Delta^2$$

$$+ O(\Delta^3)$$

as $\Delta \to 0$, with equality in the limit as $n \to \infty$.

Proof. Recall that $\beta_P = n\beta$, $R_0 = \beta_P/\gamma$, and $c = n_C/n$. We take the three expressions (13), (15), and (14) arising from Equation 12 in order.

1. $O(\Delta)$ for $E_{n_C}[\zeta]$.

$$\frac{1}{n}\beta(n-n_C)E[N_I(t)|N_C(t) = n_C]$$

$$=\beta_P(1-c)E\left[\frac{1}{n}N_I(t)|N_C(t) = n_C\right] \to \beta_P(1-c)m_I(c)$$

as $n \to \infty$ by the proof of Corollary 3.

2. $O(\Delta^2)$ for $E_{n_C}[\zeta]$.

$$\frac{1}{2n}\beta^{2}(n-n_{C})\left(\left(n-n_{C}-1-\frac{n}{R_{0}}\right)E_{n_{C}}[N_{I}(t)]-E_{n_{C}}[N_{I}(t)^{2}]\right)$$

$$=\frac{1}{2}\beta_{P}^{2}(1-c)\left(\left(1-c-\frac{1}{n}-\frac{1}{R_{0}}\right)E_{n_{C}}[N_{I}(t)/n]-E_{n_{C}}[(N_{I}(t)/n)^{2}]\right)$$

$$=\frac{1}{2}\beta_{P}^{2}(1-c)\left(\left(1-c-\frac{1}{n}-\frac{1}{R_{0}}\right)E_{n_{C}}[N_{I}(t)/n]\right)$$

$$-\left(\left(E_{n_{C}}[N_{I}(t)/n]\right)^{2}+\operatorname{Var}_{n_{C}}\left(N_{I}(t)/n\right)\right)\right)$$

$$\simeq\frac{1}{2}\beta_{P}^{2}(1-c)\left(\left(1-c-\frac{1}{n}-\frac{1}{R_{0}}\right)m_{I}(c)-\left(m_{I}(c)^{2}+\frac{\sigma_{I}^{2}(c)}{n}\right)\right)$$

$$\to\frac{1}{2}\beta_{P}^{2}(1-c)\left(\left(1-c-\frac{1}{R_{0}}\right)m_{I}(c)-m_{I}(c)^{2}\right)$$

where the last two lines stem from Remark 7.

3. $O(\Delta^2)$ for $Var_{n_C}(\zeta)$.

$$\frac{1}{n}\beta^2(n-n_C)^2 \operatorname{Var}(N_I(t)|N_C(t)=n_C) = \beta_P^2(1-c)^2 n \operatorname{Var}_{n_C}(N_I(t)/n)$$
$$\to \beta_P^2(1-c)^2 \sigma_I^2(c),$$

as $n \to \infty$, by Theorem 6.

Remark 17. Let's examine the implications for these terms.

- 1. The first order term in Δ for $E_{n_C}[\zeta]$ (shown in dashed blue in Figure 3, left) indicates that over a short time interval, the incidence is dominated by the Poisson arrival of new cases and thus the variance is Δ times the ICC curve.
- 2. The second order term in Δ arising from $Var_{n_C}(\zeta)$ reflects the uncertainty in the number of infected over the time interval under consideration (shown in dash-dotted red in Figure 3, left). It corresponds to the variance of the macroscopic incidence \mathcal{I} .
- 3. The second order term in Δ for $E_{n_C}[\zeta]$ (shown in dotted yellow in Figure 3, left) is a small perturbation of the second order term in $Var_{n_C}(\zeta)$.

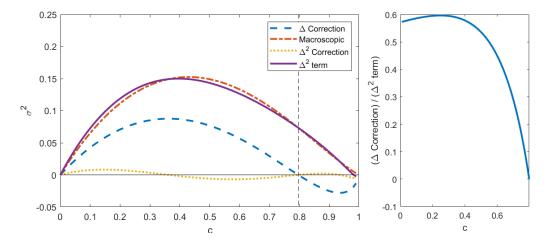


Figure 3: Left: Graphs for the terms in the variance in the stochastic ICC curve $(R_0 = 2)$. Dashed blue curve times $\beta_P \Delta$ is the first order term from $E_{n_C}[\zeta]$. Dash-dotted red curve times $(\beta_P \Delta)^2$ is the second order term from $\operatorname{Var}_{n_C}(\zeta)$. Dotted yellow curve times $(\beta_P \Delta)^2$ is the second order term from $E_{n_C}[\zeta]$. Sum of second order terms shown in solid violet. Right: The graph times $\beta_p \Delta$ is the ratio of the second to the first order terms.

- 4. The first order term depends on β_P and Δ through their product, the dimensionless term $\beta_P\Delta$. Correspondingly the second order terms depend on these quantities through $\beta_P^2\Delta^2$, the square of their product.
- 5. The ratio of the first and second order terms (shown Figure 3, right with $R_0 = 2$) is relatively constant over a large range of values for c. For example, for $R_0 = 2$, this ratio lies between 0.5 and 0.6 for $c \in [0, 0.5]$.
- 6. Thus, the first order terms dominates the variance when $\beta_P \Delta \gg \beta_P^2 \Delta^2$ or for short time intervals for which $\Delta \ll 1/\beta_P$. The second order term dominates for longer time intervals when these inequalities are reversed. Both terms play a significant role for values of Δ between these two extremes.

Figure 4 summarizes these results for 20,000 Markov chain simulations, analogous to the results of the complete graph networked simulations of Figure 1. The ℓ_2 norm of $\sigma^2 = \text{Var}(\mathcal{I}_{\Delta}/n)$, where $\mathcal{I}_{\Delta} = (N_C(t+\Delta) - N_C(t)|N_C(t) = n_C)/\Delta$, is calculated numerically and compared to the expressions shown in Theorem 16 for different values of Δ . This is a discrete norm since it is estimated at discrete values of c. Good agreement is observed for a range of values of Δ , with the macroscopic term, $\text{Var}(\mathcal{I}_n)$, becoming dominant for larger values of Δ .

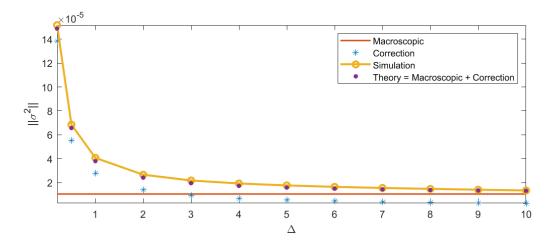


Figure 4: Norms of the numerically evaluated variance $\sigma^2 = \text{Var}(\mathcal{I}_{\Delta}/n)$ (yellow circles), of the macroscopic variance $\text{Var}(\mathcal{I}_n)$ (solid red curve), and of the correction term to order Δ^2 (blue stars), for 20,000 simulations with N = 10,000 and different values of Δ . The theoretical estimate described in Theorem 16 (dots) matches the numerical simulations (yellow circles) over a broad range of values of Δ .

4 Relevance of the stochastic SIR model to outbreak data

The relevance of the SIR model to outbreaks is illustrated in Figure 5, which shows the daily COVID-19 incidence in the state of Arizona for the 2020 calendar year, both in the time domain (top row: standard EPI curve) and in the cumulative cases domain (bottom row: ICC curve). The first arrow marks the end of the initial stay at home period (03/19/2020 - 05/15/2020) ordered by the Governor of Arizona [19, 20, 18]; the second arrow, on August 31st, indicates the end of the first six months of the outbreak (the first two cases were reported in Arizona on 03/04/2020); the third arrow marks the last day the number of cumulative cases in the state was below 300,000. Whereas the spacing between consecutive dates (108 and 83 days respectively) is similar in the time domain (top plot), this is no longer true in the cumulative case domain (bottom plot), which reveals that about twice as many cases were reported between 05/15/2020 and 08/31/2020 than between 08/31/2020 and 11/22/2020.

The inset displays an enlargement of the ICC curve for the first 30,000 cases (in the time domain, from 03/04/2020 to 06/10/2020). Three different waves are visible in the bottom panel of Figure 5, each of which is locally well approximated by an ICC curve (in black) of the form $\bar{\mathcal{I}} = N G(c, c_0)$, where c = C/N, $c_0 = C_0/N$, and G is defined in Equation (1). Recall that β_P is the population contact rate of the disease, R_0 is the basic reproductive number, and C_0 represents initial conditions. In addition,

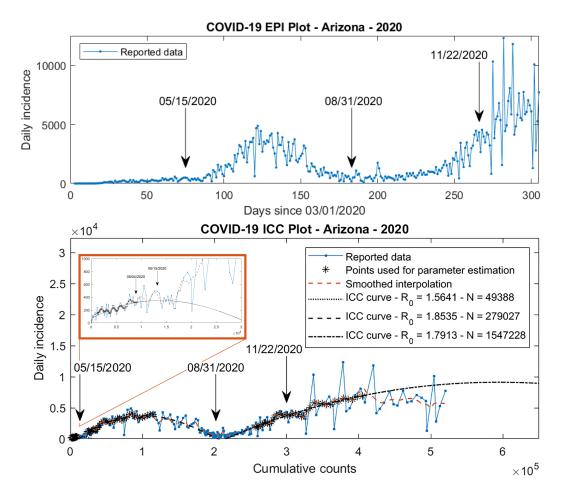


Figure 5: COVID-19 outbreak in the state of Arizona in 2020, from March 1st to December 31st. **Top:** Daily incidence as a function of time. **Bottom:** Daily incidence as a function of cumulative cases. The inset magnifies the region with less than 30,000 cumulative cases. The first arrow corresponds to 05/04/2020, when it was announced that the stay at home order would end [22, 21] before 05/15/2020 (second arrow). The three waves are well approximated by ICC curves for the SIR model (black solid lines), whose parameters were found using a range (stars) of smoothed incidence values (yellow). The nonlinear relationship between cumulative counts C and time is reflected by the change in spacing between the arrows in the top and bottom plots. COVID-19 case data provided by The COVID Tracking Project at *The Atlantic* under a CC BY-4.0 license [1].

N should be thought of as an effective population size. The parameters used to fit each wave vary, indicating an increase in the effective size N (estimated at 49,388 individuals for the first wave, 279,027 for the second, and 1,547,228 for the third) as the outbreak unfolds, while the basic reproduction number R_0 fluctuates between 1.5 and 2 (respective estimates are 1.56, 1.85, and 1.79). The corresponding values of β_P and $\gamma = \beta_P/R_0$ are $(\beta_P, \gamma) \simeq (0.12, 0.08), (0.21, 0.11), and (0.16, 0.09)$ respectively.

Figure 5 suggests that each wave of the COVID-19 outbreak in Arizona is, in trend, well captured by the deterministic SIR model: the black curves, of equation $\bar{\mathcal{I}} = N G(c, c_0)$ where G is defined in (1), are the exact relationship between incidence $\bar{\mathcal{I}}$ and cumulative cases C for the deterministic SIR model [11]. In addition, consistent with the results of this manuscript for the stochastic SIR model, each of the three waves appears to be independent from the others, and the daily incidence \mathcal{I}_{Δ} , $\Delta = 1$, fluctuates about one of the three mean ICC curves.

5 Conclusions

Although not surprising from a dynamical systems point of view, the ICC perspective [12, 11] presents a fundamentally new way of thinking about epidemics. This article develops the corresponding theory for stochastic outbreaks and explains how they relate to deterministic ICC curves. The analysis is done for the stochastic SIR model, which captures the basic tenets of disease spread. We prove that, in the limit of large populations, the dynamics of this model in the ICC plane results from a Gaussian process with independent increments, whose distribution is concentrated about the deterministic ICC curve (1). The variance of \mathcal{I}_{Δ} , the incidence over a period of time Δ , is equal to the variance of the macroscopic incidence \mathcal{I} plus a correction term that depends on Δ , as described in Theorem 16. In addition, the relevance of the ICC approach becomes apparent in the nature of the dynamics: the Markov chain and its limit involve a single parameter R_0 , and the contact rate β_P for infections is an ancillary parameter. Both R_0 and β_P are independent of the population size. In other words, shifting from the human time-centric perspective (in terms of EPI curves) to the pathogen's resource-centric perspective (in terms of ICC curves), isolates ancillary parameters from the statistical analysis of single outbreaks.

The ability to describe outbreaks as realizations of a Gaussian process with independent increments presents many advantages. First, any outbreak can easily be simulated in the ICC plane as a deterministic time change of Brownian motion, as suggested by Remark 11. The discrete equivalent consists in looking at the current number of cumulative cases C(t), drawing the new number of cases \mathcal{I}_{Δ} from the appropriate Gaussian distribution, adding this number to C(t), and repeating these steps until no new infection occurs. Second, parameter estimation is simplified: likelihoods naturally factorize into a product of normal densities, leading to a weighted least-square minimization problem in

the ICC domain. This is much simpler than the typical MCMC methods used for parameter estimation in the time domain. In addition, Fisher information can be computed explicitly to give confidence regions for model parameters, in contrast to computationally intensive simulation-based approaches. Third, the property of independent increments guarantees that estimates do not depend on the past history of the epidemic, thereby making it possible, in the case of evolving outbreaks, to infer time-dependent parameters from local data in the ICC plane.

Although the stochastic SIR model provides a simplified description of contagion, we show in Section 4 that in the ICC plane, COVID-19 incidence data fluctuate about a finite number of mean ICC curves, each having the same functional form as G(c), obtained from the SIR model. Each of these mean ICC curves corresponds to one wave of the pandemic. We use Arizona as an example, but similar behaviors are observed in other states and other countries. Moreover, the independent increment nature of the process is dramatically illustrated by these data (see Figure 5). Estimates of R_0 and N are entirely informed by the local dynamics of the portion of the epidemic under a given ICC curve. Data associated to the other ICC curves cannot and do not play any role.

The present analysis also shows that ICC curves can address recent challenges raised in the literature regarding time-based analysis of epidemics. In 2020, Juul et al. [9] reported on the issues associated with fixed time statistics and the underestimation of extremes in epidemic curve ensembles. ICC curves circumvent many of the shortcomings of fixed time statistics because the stochastic ICC process has independent increments and thus obviates the issues of long-term correlations. In addition, the call for "curve based" statistics made in [9] is integral to the characterization of the epidemic as a realization of a Gaussian process. This makes it possible to incorporate the entire ICC curve in the likelihood associated with any estimation, including for parameter inference, or for detecting the impact of changes – for instance in people's behavior or due to the introduction of a vaccine, and for forecasting.

In summary, the probabilistic analysis described in the present article equips us with more powerful approaches to understand epidemic dynamics. With a change of perspective from the human to the pathogen, this article shows that the nearly century-old Kermack-McKendrick [10] mathematical model is again the foundation for modern, even more powerful, analytical tools that yield clearer insights into the nature of an outbreak.

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Author contributions

FDS and JL conceived of the project. JCW led in deriving the mathematical results. JL and WF coordinated the simulations and numerical results and generated figures. All authors contributed to the writing of the manuscript and approved the final version.

Competing interests

All authors declare that they have no competing interests.

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