

Asymptotic estimates of SARS-CoV-2 infection counts and their sensitivity to stochastic perturbation

Davide Faranda, Isaac Pérez Castillo, Oliver Hulme, Aglaé Jézéquel, Jeroen Lamb, Erica Thompson

▶ To cite this version:

Davide Faranda, Isaac Pérez Castillo, Oliver Hulme, Aglaé Jézéquel, Jeroen Lamb, et al.. Asymptotic estimates of SARS-CoV-2 infection counts and their sensitivity to stochastic perturbation. Chaos: An Interdisciplinary Journal of Nonlinear Science, 2020, 30 (5), pp.051107. 10.1063/5.0008834 . hal-02668288

HAL Id: hal-02668288 https://hal.science/hal-02668288v1

Submitted on 8 Jul 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1	Asymptotic estimates of SARS-CoV-2 infection counts and their
2	sensitivity to stochastic perturbation
3	Davide Faranda [*]
4	Laboratoire des Sciences du Climat et de l'Environnement,
5	CEA Saclay l'Orme des Merisiers, UMR 8212 CEA-CNRS-UVSQ,
6	Université Paris-Saclay & IPSL, 91191 Gif-sur-Yvette, France
7	London Mathematical Laboratory, 8 Margravine Gardens, London, W6 8RH, UK and
8	LMD/IPSL, Ecole Normale Superieure,
9	PSL research University, Paris, France
10	Isaac Pérez Castillo
11	Department of Quantum Physics and Photonics, Institute of Physics,
12	UNAM, P.O. Box 20-364, 01000 Mexico City, Mexico and
13	London Mathematical Laboratory, 8 Margravine Gardens, London, W6 8RH, UK
14	Oliver Hulme
15	Danish Research Centre for Magnetic Resonance,
16	Centre for Functional and Diagnostic Imaging and Research,
17	Copenhagen University Hospital Hvidovre,
18	Kettegard Allé 30, 2650, Hvidovre, Denmark and
19	London Mathematical Laboratory, 8 Margravine Gardens, London, W6 8RH, UK
20	Aglaé Jezequel
21	LMD/IPSL, ENS, PSL Université, École Polytechnique,
22	Institut Polytechnique de Paris, Sorbonne Université, CNRS, Paris France and
23	Ecole des Ponts, Marne-la-Vallée, France
24	Jeroen S.W. Lamb
25	Department of Mathematics, Imperial College London, UK and
26	London Mathematical Laboratory, 8 Margravine Gardens, London, W6 8RH, UK
27	Yuzuru Sato

28	RIES/Department of Mathemarics, Hokkaido University,
29	N20 W10, Kita-ku, Sapporo, Hokkaido 001-0020, Japan and
30	London Mathematical Laboratory, 8 Margravine Gardens, London, W6 8RH, UK
31	Erica L. Thompson
32	Centre for the Analysis of Time Series,
33	London School of Economics and Political Science,
34	Houghton Street, London WC2A 2AE and
35	London Mathematical Laboratory, 8 Margravine Gardens, London, W6 8RH, UK
36	(Dated: March 25, 2020)

Abstract

Despite the importance of having robust estimates of the time-asymptotic total number of in-38 fections, early estimates of COVID-19 show enormous fluctuations. Using COVID-19 data for 39 different countries, we show that predictions are extremely sensitive to the reporting protocol and 40 crucially depend on the last available data-point, before the maximum number of daily infections 41 is reached. We propose a physical explanation for this sensitivity, using a Susceptible-Exposed-42 Infected-Recovered (SEIR) model where the parameters are stochastically perturbed to simulate 43 the difficulty in detecting asymptomatic patients, different confinement measures taken by differ-44 ent countries, as well as changes in the virus characteristics. Our results suggest that there are 45 physical and statistical reasons to assign low confidence to statistical and dynamical fits, despite 46 their apparently good statistical scores. These considerations are general and can be applied to 47 other epidemics. 48

49 I. LEAD PARAGRAPH

COVID-19 is currently affecting over 180 countries in the world and poses seri-50 ous threats to public health as well as economic and social stability of many coun-51 tries. Modeling and extrapolating in near real-time the evolution of COVID-19 52 epidemics is a scientific challenge, which requires a deep understanding of the 53 non-linearities undermining the dynamics of the epidemics. Here we show that 54 real-time predictions of COVID-19 infections are extremely sensitive to errors 55 in data collection and crucially depend on the last available data-point. We test 56 these ideas in both statistical (logistic) and dynamical (Susceptible-Exposed-57 Infected-Recovered) models that are currently used to forecast the evolution of 58 the COVID-19 epidemic. Our goal is to show how uncertainties arising from 59 both poor data quality and inadequate estimations of model parameters (incu-60 bation, infection and recovery rates) propagate to long term extrapolations of 61 infections count. We provide guidelines for reporting those uncertainties to the 62 scientific community and the general public. 63

^{*} Correspondence to davide.faranda@lsce.ipsl.fr

64 II. INTRODUCTION

SARS-CoV-2, a zoonotic virus of the coronavirus family [1], that provokes an infectious 65 disease known as COVID-19, has emerged in China at the end of 2019, affecting first the 66 Hubei province and quickly spreading to all Chinese provinces [2]. The failure of initial 67 containment measures caused the virus to spread internationally, and on March 11th, The 68 World Health Organization (WHO) declared COVID-19 a pandemic [3]. According to the 69 WHO Situation Report-59 released on March 19th [4], the number of countries affected by 70 the pandemic is 176, with 209 839 confirmed infections and 8778 deaths. As this report 71 also notices: the number of confirmed cases worldwide has exceeded 200 000. It took over 72 three months to reach the first 100 000 confirmed cases, and only 12 days to reach the next 73 100 000, an astonishing development, due to the highly contagious character of SARS-CoV-2. 74 75

SARS-CoV-2 causes potentially life-threatening form of pneumonia in a non-negligible patients fraction [5]. Enormous efforts to contain the virus and to not overwhelm intensive care facilities are currently taken all over the world. Following the drop in infections observed in the Hubei province, restrictive confinement measures have been taken in many countries [6]. Most of the time, those measures are taken on the basis of epidemics models, which are fitted with dynamical or statistical models on the available data.

82

88

⁸³ COVID-19 data should be provided daily, following a request of the WHO. To date, the ⁸⁴ WHO guidelines require countries to report, at each day t, the total number of infected ⁸⁵ patients I(t) as well as the number of deaths D(t). Unfortunately, there is large variability ⁸⁶ in the way both I(t) and D(t) are counted. We provide some illustrative example: on the ⁸⁷ one hand, Italy shows the highest fatality rate:

$$f = \sum_{t=1}^{\tau} D(t) / \sum_{t=1}^{\tau} I(t) \simeq 0.07$$
(1)

⁸⁹ possibly because D(t) includes all deaths who have contracted SARS-CoV-2, indepen-⁹⁰ dently on whether the virus is the first cause of death. Moreover, in a recent interview [7], ⁹¹ Italian biologist Bucci has stated that D(t) can be underestimated because it does not ⁹² include those patients who died at home without being tested. On the other hand, in ⁹³ Germany, the fatality rate is extremely low $f \simeq 0.002$. There may be several explanations for this : some query data methodology (e.g. a different method to determine D(t)) while others say high testing rates are giving a more accurate picture [8].

96

Great uncertainties also exist in the count of I(t). Whereas in the early stage of the epi-97 demic several countries tested asymptomatic individuals to track back the infection chain, 98 recent policies to estimate I(t) have changed. Most of the western countries now test only 99 patients displaying severe SARS-CoV-2 symptoms. In an effort of tracking all the chain 100 of infections, South Korea has tested many asymptomatic people. This latter strategy has 101 proven effective in supporting actions to reduce the rate of new infections. A recent study [9] 102 has estimated that an enormous part of total infections were undocumented (80% to 90%)103 and that those undetected infections were the source for 79% of documented cases in China. 104 105

The goal of this paper is to analyse the effect of those large uncertainties in real-time 106 forecasting of the long term behavior of the COVID-19 epidemic [10]. As stated by Polonsky 107 et al [11], there is a need for defining robust methods to assess both the intrinsic errors 108 inherent to fitting procedures as well as those introduced by poor data-quality. Funk et al 109 [12] give a concrete example of this applied to the Ebola epidemics in the Western Area region 110 of Sierra Leone in 2014-15. Classically, epidemiologists rely on Susceptible-Exposed-Infected-111 Recovered (SEIR) models [13]. These models consist of ordinary differential equations where 112 a population is divided into compartments, with the assumption that every individual in 113 the same compartment has the same characteristics. In SEIR, population is divided into 114 Susceptible, Exposed, Infected and Recovered individuals. Such models predict a sigmoid 115 shape of the total number of infections $C(t) = \sum_{t=1}^{\tau} I(t)$. Using the available national 116 data points I(t) one can obtain long term estimates on the total of COVID-19 infections 117 in each country. This paper focuses on the estimation of the sensitivity of these models to 118 the last available data point, before the inflection point of the I(t) curve is reached. We 119 use SEIR models to show the possible origins of this sensitivity by perturbing the relevant 120 parameters, often assumed deterministic, with a noise that mimics changes in the way the 121 virus is spreading, e.g. as a result of application of confinement measures, or the presence 122 (rate/magnitude) of super-spreaders [14]. The paper is organised as follows: in Section III 123 we discuss the various sources of data for COVID-19 and their shortcomings, and then we 124 discuss in detail the SEIR model and its statistical modelling. In Section IV we discuss the 125

results focusing on the statistical sensitivity of the modelling, and apply it to data from
France, UK and Italy. We finish, in Section V, with some remarks and point out some
potentially beneficial policy guidelines.

129 III. DATA AND MODELLING

130 A. Data

The data repository used in this paper for COVID-19 data is a Visual Dashboard operated 131 by the Johns Hopkins University Center for Systems Science and Engineering (JHU CSSE). 132 The data repository [15] is also supported by ESRI Living Atlas Team and the Johns Hopkins 133 University Applied Physics Lab (JHU APL). We used datasets of cases confirmed with 134 a laboratory test, irrespective of clinical signs and symptoms [3]. The data contains, as 135 recognized by the public authorities that dispatched them, several inhomogeneities due to 136 the different ways of testing patients with suspicious symptoms. As an example, Italy 137 announced on Feb. 26 that it relaxed testing criteria to the point that contacts linked to 138 confirmed cases or recent travelers to outbreak areas would not be tested anymore, unless 139 they show symptoms. Unlike Italy, South Korea (population of 51 million) is testing 15000 140 to 20000 individuals per day since Feb. 27 with the goal to minimize hospital pressure 141 and stop the epidemics in the early stages [16]. COVID-19 data also suffers from reporting 142 problems due to the local management of health infrastructures. In Italy, healthcare is a 143 regional task and everyday data are collected at a regional level and transmitted to the 144 Protezione Civile, who transfers the data to WHO. Many inconsistencies and delays have 145 been documented in this transfer process [17]. A similar situation occurs in Mexico, in 146 which for instance, private institutions, either hospitals or laboratories, do not possess the 147 necessary national and international certifications given by the Instituto de Diagnóstico 148 y Referencia Epidemiológicos (InDRE) and therefore their tests are not considered valid 149 and must be redone by certified institutions [18], thus unnecessarily delaying the release 150 of accurate daily reports. COVID-19 data of Mexico was collected from the daily reports 151 generated by Mexico's Secretaría de Salud [19]. Our goal is to account for these uncertainties 152 in the modelling of COVID-19 data. 153

154 B. An epidemiological Susceptible-Exposed-Infected-Recovered model

The Susceptible-Exposed-Infected-Recovered (SEIR) model [13] is an epidemiological compartmental model where a total population N is divided into susceptible individuals S, exposed individuals E, infected individuals I, and the number R of people who have had the disease and are now either recovered or dead (and assumed not to be susceptible to reinfection). The model is constructed under the assumption that the total population N = S(t) + E(t) + I(t) + R(t) does not vary. This implies:

161

169

$$0 = dN/dt = dS/dt + dE/dt + dI/dt + dR/dt, \quad \forall t \ge 0.$$
⁽²⁾

The model relies on some assumptions. First of all, susceptible individuals end up becoming infected and infected individuals can only recover or die. Individuals who are exposed (E)have had contact with an infected person, but are not themselves infectious. Furthermore, those who have recovered or died are forever immune. It is also assumed that susceptibility is equal for all and that it is proportional to the product of I(t) and S(t) at a time t. These assumptions lead us to a set of four ordinary differential equations:

$$\frac{dS}{dt} = -\lambda S(t)I(t) \tag{3}$$

$$\frac{dE}{dt} = \lambda S(t)I(t) - \alpha E(t) \tag{4}$$

$$\frac{dI}{dt} = \alpha E(t) - \gamma I(t) \tag{5}$$

$$\frac{dR}{dt} = \gamma I(t). \tag{6}$$

Here $\gamma > 0$ represents the mean recovery/death rate, or $1/\gamma$ the mean infection period, $\lambda = \lambda_0/S(0) > 0$ is considered the contact or infection rate of the disease and it is rescaled by the initial number of susceptible individuals S(0) and α is the inverse of the incubation period. These expressions satisfy (2) as required. Because data are reported only on a daily basis, we adopt the discrete SEIR model:

177 $S(t+1) = S(t) - \lambda S(t)I(t)$ (7)

$$E(t+1) = (1-\alpha)E(t) + \lambda S(t)I(t)$$
(8)

ITP
$$I(t+1) = (1-\gamma)I(t) + \alpha E(t)$$
(9)

$$R(t+1) = R(t) + \gamma I(t).$$
(10)

This model is obtained rewriting the ordinary differential equations 3-6 with an Euler 181 Scheme and fixing dt = 1 day. An important derived quantity of the model is $R_0 = \lambda_0/\gamma$, 182 the average reproduction number of the virus in a population. This quantity represents the 183 number of cases, on average, an infected person will cause during their infectious period. 184 For COVID-19 in Wuhan in January 2020, $R_0 = 2.68$ with 95% CrI 2.47–2.86 according to 185 an estimate performed with Wuhan data [20]. Dynamical modelling of COVID-19 epidemic 186 has been proposed in [21]. In that study, the authors used a Susceptible-Exposed-Infected-187 Recovered model with delays and performed a sensitivity study on the parameters. Fixing 188 $\lambda \simeq 1$ as in [21] and $\gamma = 0.37$ to recover the value of R_0 found in [20] (assuming that the 189 behavioural elements of viral transmission are consistent in other populations), we are left 190 with the choice of α . The range for incubation period of SARS-CoV-2 has been determined 191 in [22] between 2 and 11 days. As a comparison, this range is estimated to be between 2 192 and 5 days for human coronavirus, and between 2 and 10 days for severe acute respiratory 193 syndrome (SARS) coronavirus [23]. Using a trial and error procedure and a subjective 194 estimation of the quality of the fit, we obtain the best fit when we set $\alpha = 0.27$ (corresponding 195 to an incubation period between 3 and 4 days) and initial conditions S(0) = 33000, I(0) = 2, 196 E(0) = R(0) = 0. The fit against the Chinese data is reported in Figure 1. We are aware 197 that a log-likelihood method with cross-validation would provide a better fit as well as an 198 estimate of the uncertainty. However, we underline that the goal of this work is not to provide 199 the best possible model but rather to explore the sensitivity of it to perturbations. First 200 of all, we note that, despite its simplicity, the model shows qualitatively similar behaviour 201 to the published data. Note that there is a discontinuity in the dataset, which is due to a 202 change in the way infections were counted, introduced on Feb. 12, 2020 [24]. 203

This model has also evident deficiencies in representing the COVID-19 infections. First of 204 all the total population N here is to be intended as a number of people who could have been in 205 contact with infected individuals. Furthermore, the population under consideration does not 206 consist of a group of about the same age and general health level, and the the group members 207 do not mix homogeneously. The model does not have any spatial component, nor does it 208 predict the influences of policy and behavioural responses to the progress of the pandemic. 209 More complex models introducing further parameters would likely lead to overfitting and 210 over-confident predictions, due to the limited volume of data currently available. No model 211 will be sufficient to predict the outcome of this pandemic: the outcome depends on our 212

response. Models are presented here with the aim of generating some insight into the overall
behaviour and the risks entailed by inaction.

215 C. Statistical Modelling

When insight is limited and compartmental models are not suited, phenomenological sta-216 tistical models provide a starting point for estimation of key transmission parameters, such 217 as the reproduction number, and forecasts of epidemic impact [25]. One of the simplest ways 218 to model the epidemics is to observe that the function C(t) is a sigmoid function and perform 219 a statistical fit of the data to extrapolate the long-term behavior of the epidemics [26, 27]. 220 Among all the possible sigmoid functions, two have proven useful in fitting epidemic growth: 221 the generalized logistic distribution [28] and the generalized Gompertz distribution [29]. A 222 complete overview of sigmoid functions is presented in [30], although applied to in a differ-223 ent context. Since our considerations are independent of the sigmoid function used, we will 224 present results for the generalized logistic model only. The model reads: 225

226
$$C(t) = a/(1 + b \cdot \exp(-c \cdot t));$$
 (11)

where a, b and c are parameters of the model. They are linked in a non-explicit way 227 to the solution of the SEIR model. A fit to the Chinese data is presented in Figure 2. 228 Logistic fits are performed with the MATLAB Nonlinear least-squares solver constraining 229 objective function with gradient. At first sight, one can be tempted to use $R^2 \simeq 0.997$ as 230 a quality indicator of the fit. However, we stress that R^2 is not an appropriate measure 231 for nonlinear regression models: given the smoothness of data, there will be lots of models 232 (eg low-order polynomial) which could fit well (get a very good R^2) but would not make 233 credible predictions [31]. These data are however collected at a mature stage of the epidemic 234 and as such the characteristics of the logistic fit to these data can be assigned with greater 235 confidence. In the next section we will discuss the performance of the statistical model in 236 the early stage of the epidemics, where the logistic function can be used to extrapolate the 237 behavior of C(t). 238

IV. RESULTS: STATISTICAL AND DYNAMICAL MODELLING OF EARLY STAGES OF THE EPIDEMICS

A. Statistical sensitivity

We begin by showing the sensitivity of the logistic extrapolations in the early stage of 242 the epidemics by looking at French data from Mar. 04 to Mar 20. France has previously 243 recorded sporadic cases of SARS-CoV-2 infections but the exponential growth phase started 244 at the beginning of March 2020. To show the high sensitivity to the last point of the 245 datasets we first perform a logistic fit with data starting from different dates and ending 246 Mar. 20 (Figure 3a) and then do the reverse experiment by fitting data starting on Mar. 247 04 but ending at different dates (Figure 3b). Clearly, fits are more stable by removing days 248 from the beginning of the outbreak than from the most recent past. Again, we stress the 249 inadequacy of the R^2 metric as it yields values above $R^2 > 0.99$ for all cases considered in 250 Figure 3. The analysis suggests that, if a large error is presented in the last data point, the 251 extrapolation has less predictive adequacy. This implies very narrow estimates of confidence 252 intervals for C(t): for each fit, confidence intervals are as small as the thickness of the line 253 used in the plots in Figure 3. This prevents a correct evaluation of the confidence interval, 254 which is critical to assess the uncertainties around the future evolution of the epidemics, 255 and to build relevant policies to address the worst case scenario. 256

257

To further test this concept, we now assume we are uncertain about the magnitude of the last data point $C(t^*)$. To simulate this uncertainty, we replace it with a random number $\xi(t^*)$ drawn from a discrete uniform distribution with mean $C(t^*)$ and standard deviation $0.2C(t^*)$. We therefore construct an ensemble of 100 possible trajectories under this generative process. Results are presented in Figure 4 for UK (a), France (b) and Italy (c). To date, Italy is at a more mature stage of the epidemic, while France and UK face an earlier stage. This is reflected in the spread of the ensemble: for the UK, forecasting the epidemic with a logistic fit is not informative of the course of the epidemic: the ensemble spread just suggests that the current phase is an exponential growth and at best it can inform that worst case scenarios should be considered at this point. The ensemble spread reduces when the epidemics is at a more mature stage (Italy). Indeed, if we set b = 1 and we start the fit from time t_0 then the logistic distribution is written:

$$C(t) = a/(1 + \exp(-c(t - t_0))).$$

In the early growth phase, $\exp(-c(t-t_0)) \gg 1$, so:

$$C(t) \sim a \exp(c(t - t_0)) = a \exp(-c \cdot t_0) \exp(-c \cdot t) = A \exp(-c \cdot t)$$

259

Even though we can fit A and b to data, recalling that $A = a \exp(-c \cdot t_0)$ we have huge freedom over a, the upper asymptote that determines the final count of the epidemics.

B. Dynamical sensitivity in a stochastic SEIR model

Another way to understand the sensitivity in epidemics is to release the assumption 263 that incubation period α , infection rate λ and recovery rate γ are constant through the 264 epidemics [32]. Intrinsically they can vary, because of the presence of individuals with an 265 extremely high transmission rate known as super-spreaders [14], or due to the release or the 266 application of confinement measures, or changes in the SARS-CoV-2 characteristics. They 267 can also display spurious variations due to the way data are reported or collected, for the 268 problems specified above. We explore all these possibilities by considering α , λ , and γ as 269 time varying processes. The idea of using stochastic models to represent epidemics is not new 270 to the literature [33–35]. In the modelling of COVID-19 infections can be further justified 271 by the evidence that $R_0 = \lambda/\gamma$ displays spatial and temporal variability [11]. For example, 272 Wu et al. [20] show fluctuations of R_0 in different Chinese regions. These differences are 273 due to changes in the duration of contagiousness, likelihood of infection per contact and the 274 contact rate [36] which depends on demographic spatial variability [37]. There is however 275 little consensus on which variables or parameters should be perturbed in order to get a 276 realistic behavior. Our goal here is different than obtaining the best possible forecasts of the 277 epidemics as we want to understand which parameter causes a large sensitivity in the final 278 C(t) counts. Let us begin, by alternatively replacing in Equations 7-10 one of the constant 279 parameters $\kappa \in \{\alpha, \lambda, \gamma\}$ with a stochastic process: 280

281

$$\kappa(t) = \kappa_0 + \sigma \cdot \xi(t) \tag{12}$$

where σ is the intensity of the perturbation and $\xi(t)$ a random variable drawn from 282 a normal distribution N(0,1) at each time. The purpose of equation 12 is to introduce 283 instantaneous discrete jumps in the values of the daily parameters. This discrete process, 284 used in [38], is more appropriate than a continuous one (see, e.g. [39]) when observations 285 are affected by large detection errors, as in the present case. Figure 5 shows an example 286 of 30 realisations of a stochastic SEIR COVID-19 model, obtained by replacing alternately 287 α (a,b), λ (b,d) and γ with the stochastic process in Eq 12 and using $\sigma = 0.2\kappa_0$ to get 288 fluctuations of the order of 20% of each parameter values, in analogy with the statistical 289 sensitivity studies performed in the previous section. The sensitivity clearly depends on the 290 perturbed parameter: a perturbation on α mostly implies a different timing of the epidemics 291 while the final cumulative number of infections C(t) remains unchanged. Perturbations on 292 λ and γ affect the final C(t) in a deeper way, leading to a total variation in the number of 293 cases of the order of 20%. Indeed, by changing λ and γ , we also modify the basic reproduc-294 tion number R_0 . The idea of having a time-varying reproduction number has been already 295 exploited in [40], although the authors have directly modelled the dynamics of a dynamic 296 reproduction number R(t) without introducing a SEIR model. 297

298

As a further step, we add noise simultaneously to all parameters of the SEIR model via 299 Equation 12. Six realisations of the model are shown in Figure 6. Figure 6-a,b) shows the 300 evolution of S(t), R(t), E(t) and C(t). We have separated the time evolution of I(t) in 301 Figure 6-c) to compare it with that of COVID-19 data for China, South Korea and Italy 302 (Figure 6d). Despite having a quasi-smooth behavior of C(t), we observe a highly non-303 smoothness of I(t), which is reflected by the data. The sensitivity of the model is higher 304 when I(t) is large, because γ and λ directly act on I(t). Therefore, when approaching the 305 maximum of I(t) ($t \sim 50$ days) small changes in the parameters can greatly affect the final 306 total count of infections C(t). This implies that mitigation strategies based on the reduction 307 of λ by self-isolation, social distancing, are way more effective if imposed at the early stage 308 of the epidemics, as they can suppress positive fluctuations of and help reducing R_0 . 309

310 V. DISCUSSION

In this work we have discussed the statistical and dynamical sensitivity of asymptotic 311 estimates of COVID-19 infections when performed at the early stages of the epidemics. 312 First of all, we noted that SEIR model, with λ , γ and α inferred from clinical studies, 313 can fit Chinese data with a value of $N \simeq 33000$ that is very different from that of the 314 Chinese, Hubei or Wuhan populations. This enormous discrepancy can be due both to a 315 large underestimation in the number of total cases, or to the effectiveness of confinement 316 measures which results in a smaller exposed population. This estimate should be taken 317 as a first caveat in fitting a SEIR model to infer COVID-19 epidemics evolution in other 318 countries as results may be largely under/over-estimated [11]. 319

320

Then, we have shown that statistical fits often used to extrapolate the long term behav-321 ior of the epidemics are greatly affected by the magnitude of the last data point, despite 322 values of R^2 close to one, leading to unrealistic or over-confident estimates of confidence 323 intervals on the forecast of the total number of infections [41, 42]. In the early stage of the 324 epidemics, we have shown that knowing the last data point with a relative 20% error, can 325 lead to a final extrapolation of infections with an error of several orders of magnitude. In 326 order to improve the estimates of statistical models one should replace R^2 estimates by a 327 formal comparison of model-alternatives using information criteria (e.g. AIC or BIC) or 328 a log-likelihood approach with a leave-one-out cross-validation procedure. A simple cross 329 validation can follow both the approaches described in this paper: i) exclude the last data 330 points and check the stability of the estimates, ii) add noise to the last data point and 331 obtain an ensemble of estimates. Another approach could be based on evaluating every day 332 each model on the performance in predicting the new data point, and then used again with 333 the new data point for an updated estimate. 334

335

Finally, we have investigated whether this statistical sensitivity can be dynamically reproduced with a SEIR model where parameters are considered stochastic processes (Equation 12). We have found that the stochastic dynamics are more sensitive to γ and λ . Perturbations on these parameters are proportional to the number of infected patients I(t)and are therefore important in the growth phase of the epidemics. Actual data display fluc-

tuations even larger than those simulated in the stochastic models, suggesting that instead 341 of assuming observational Gaussian noise on the parameters, jump processes (e.g. Levy 342 noise) may be more appropriate [43]. Furthermore, we noticed that large fluctuations in 343 the number of detected infections is also due to changes in the testing protocols and avail-344 ability of tests. All these inconsistencies prevent the possibility of performing meaningful 345 asymptotic statistical or dynamical modelling for COVID-19, or comparing results among 346 different countries. This may be even more problematic in least developed countries, which 347 are just beginning to register cases [44–46]. 348

349

Our study suggests that dynamical and statistical modelling should focus on limited 350 stages of the epidemics and restrict the analysis to specific regions, accounting for large un-351 certainties as done in [47]. Modelling approaches should take into account both statistical 352 uncertainties as well as expert knowledge in a sort of Bayesian framework that allows to 353 guide the choice of prior probabilities [10]. In the interest of preserving the public health of 354 as many individuals as possible, once modelled the uncertainty in the data, the worst case 355 scenarios should always be taken into account very seriously as a guideline to enforce strict 356 confinement measures. 357

358

359 VI. ACKNOWLEDGMENTS

This paper is dedicated to the memory of F Molinari, who recently passed away from COVID-19. DF acknowledges A Adamou, B Dubrulle, F Pons, F Daviaud, P Yiou, M Kagayema, S Fromang and G Ramstein for useful discussions.

363 VII. DATA AVAILABILITY

The data that support the findings of this study are openly available in https:// systems.jhu.edu/research/public-health/ncov/, maintained by Johns Hopkins Uni³⁶⁶ versity Center for Systems Science.

- [1] Eleanor R Gaunt, Andrew Hardie, Eric CJ Claas, Peter Simmonds, and Kate E Templeton.
 Epidemiology and clinical presentations of the four human coronaviruses 229e, hku1, nl63, and
 oc43 detected over 3 years using a novel multiplex real-time pcr method. Journal of clinical
 microbiology, 48(8):2940–2947, 2010.
- [2] Jin Wu, Weiyi Cai, Derek Watkins, and James Glanz. How the virus got out. The New York
 Times.
- [3] World Health Organization et al. Coronavirus disease 2019 (covid-19): situation report, 51.
 2020.
- ³⁷⁵ [4] World Health Organization et al. Coronavirus disease 2019 (covid-19): situation report, 59.
 ³⁷⁶ 2020.
- [5] Chaolin Huang, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, Li Zhang,
 Guohui Fan, Jiuyang Xu, Xiaoying Gu, et al. Clinical features of patients infected with 2019
 novel coronavirus in wuhan, china. *The Lancet*, 395(10223):497–506, 2020.
- [6] Roy M Anderson, Hans Heesterbeek, Don Klinkenberg, and T Déirdre Hollingsworth. How
 will country-based mitigation measures influence the course of the covid-19 epidemic? *The Lancet*, 395(10228):931–934, 2020.
- [7] Luca Fraioli. Bucci: "dalla lombardia numeri ormai insensati. i contagiati sono di più".
 Repubblica, Mar 2020.
- [8] Philip Oltermann. Germany's low coronavirus mortality rate intrigues experts. The Guardian.
- [9] Ruiyun Li, Sen Pei, Bin Chen, Yimeng Song, Tao Zhang, Wan Yang, and Jeffrey Shaman.
 Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus
 (sars-cov2). Science, 2020.
- [10] Angel N Desai, Moritz UG Kraemer, Sangeeta Bhatia, Anne Cori, Pierre Nouvellet, Mark
 Herringer, Emily L Cohn, Malwina Carrion, John S Brownstein, Lawrence C Madoff, et al.
 Real-time epidemic forecasting: Challenges and opportunities. *Health security*, 17(4):268–275,
 2019.
- [11] Jonathan A Polonsky, Amrish Baidjoe, Zhian N Kamvar, Anne Cori, Kara Durski, W John
 Edmunds, Rosalind M Eggo, Sebastian Funk, Laurent Kaiser, Patrick Keating, et al. Out-

- ³⁹⁵ break analytics: a developing data science for informing the response to emerging pathogens.
 ³⁹⁶ Philosophical Transactions of the Royal Society B, 374(1776):20180276, 2019.
- [12] Sebastian Funk, Anton Camacho, Adam J Kucharski, Rachel Lowe, Rosalind M Eggo, and
 W John Edmunds. Assessing the performance of real-time epidemic forecasts: A case study
 of ebola in the western area region of sierra leone, 2014-15. *PLoS computational biology*,
 15(2):e1006785, 2019.
- [13] Fred Brauer. Compartmental models in epidemiology. In *Mathematical epidemiology*, pages
 19–79. Springer, 2008.
- [14] James O Lloyd-Smith, Sebastian J Schreiber, P Ekkehard Kopp, and Wayne M Getz. Superspreading and the effect of individual variation on disease emergence. *Nature*, 438(7066):355–
 359, 2005.
- 406 [15] Data last downloaded on Mar. 23 from @x https://systems.jhu.edu/research/
 407 public-health/ncov/.
- 408 [16] Kim Arin. Drive-thru clinics, drones: Korea's new weapons in virus fight. The Korea Herald.
- ⁴⁰⁹ [17] Pagella Politica AGI. Come vanno letti i dati sul coronavirus in italia. AGI Agenzia Italia.
- [18] As of 20th of March 2020 only two private hospitals in Mexico have been certified by InDRE
 to carry out tests.
- [19] There is a delay between the data reported daily by the WHO and that reported by Mexico
 health authorities.
- ⁴¹⁴ [20] Joseph T Wu, Kathy Leung, and Gabriel M Leung. Nowcasting and forecasting the potential
 ⁴¹⁵ domestic and international spread of the 2019-ncov outbreak originating in wuhan, china: a
 ⁴¹⁶ modelling study. *The Lancet*, 395(10225):689–697, 2020.
- [21] Liangrong Peng, Wuyue Yang, Dongyan Zhang, Changjing Zhuge, and Liu Hong. Epidemic
 analysis of covid-19 in china by dynamical modeling. arXiv preprint arXiv:2002.06563, 2020.
- ⁴¹⁹ [22] Stephen A Lauer, Kyra H Grantz, Qifang Bi, Forrest K Jones, Qulu Zheng, Hannah R Mered-
- ith, Andrew S Azman, Nicholas G Reich, and Justin Lessler. The incubation period of coronavirus disease 2019 (covid-19) from publicly reported confirmed cases: Estimation and application. Annals of Internal Medicine, 2020.
- ⁴²³ [23] Justin Lessler, Nicholas G Reich, Ron Brookmeyer, Trish M Perl, Kenrad E Nelson, and
 ⁴²⁴ Derek AT Cummings. Incubation periods of acute respiratory viral infections: a systematic
- $_{425}$ review. The Lancet infectious diseases, 9(5):291-300, 2009.

- ⁴²⁶ [24] Amy Gunia and Michael Zennie. China reported a huge increase in new covid-19 cases. here's
 ⁴²⁷ why it's actually a step in the right direction. *Time*.
- [25] Gerardo Chowell, Doracelly Hincapie-Palacio, Juan Ospina, Bruce Pell, Amna Tariq, Sushma
 Dahal, Seyed Moghadas, Alexandra Smirnova, Lone Simonsen, and Cécile Viboud. Using phe nomenological models to characterize transmissibility and forecast patterns and final burden
 of zika epidemics. *PLoS currents*, 8, 2016.
- [26] Gerardo Chowell. Fitting dynamic models to epidemic outbreaks with quantified uncertainty:
 a primer for parameter uncertainty, identifiability, and forecasts. *Infectious Disease Modelling*,
 2(3):379–398, 2017.
- [27] Raimund Bürger, Gerardo Chowell, and Leidy Yissedt Lara-Díaz. Comparative analysis of
 phenomenological growth models applied to epidemic outbreaks. *Mathematical biosciences* and engineering: MBE, 16(5):4250-4273, 2019.
- ⁴³⁸ [28] Pierre-François Verhulst. Notice sur la loi que la population suit dans son accroissement.
 ⁴³⁹ Corresp. Math. Phys., 10:113–126, 1838.
- [29] Benjamin Gompertz. Xxiv. on the nature of the function expressive of the law of human
 mortality, and on a new mode of determining the value of life contingencies. in a letter to
 francis baily, esq. frs &c. *Philosophical transactions of the Royal Society of London*, (115):513–
 583, 1825.
- IJ Wellock, GC Emmans, and I Kyriazakis. Describing and predicting potential growth in the
 pig. Animal Science, 78(3):379–388, 2004.
- [31] Andrej-Nikolai Spiess and Natalie Neumeyer. An evaluation of r 2 as an inadequate measure
 for nonlinear models in pharmacological and biochemical research: a monte carlo approach. *BMC pharmacology*, 10(1):6, 2010.
- [32] Hao Xiong and Huili Yan. Simulating the infected population and spread trend of 2019-ncov
 under different policy by eir model. Available at SSRN 3537083, 2020.
- [33] Lars Folke Olsen and William Morris Schaffer. Chaos versus noisy periodicity: alternative
 hypotheses for childhood epidemics. *Science*, 249(4968):499–504, 1990.
- [34] Hakan Andersson and Tom Britton. Stochastic epidemic models and their statistical analysis,
 volume 151. Springer Science & Business Media, 2012.
- [35] Joseph Dureau, Konstantinos Kalogeropoulos, and Marc Baguelin. Capturing the time-varying
- drivers of an epidemic using stochastic dynamical systems. *Biostatistics*, 14(3):541–555, 2013.

- [36] Giulio Viceconte and Nicola Petrosillo. Covid-19 r0: Magic number or conundrum? Infectious
 Disease Reports, 12(1), 2020.
- ⁴⁵⁹ [37] Ilya Kashnitsky. Covid-19 in unequally ageing european regions. 2020.
- [38] Davide Faranda and Sandro Vaienti. Extreme value laws for dynamical systems under observational noise. *Physica D: Nonlinear Phenomena*, 280:86–94, 2014.
- ⁴⁶² [39] Davide Faranda, Yuzuru Sato, Brice Saint-Michel, Cecile Wiertel, Vincent Padilla, Bérengère
- 463 Dubrulle, and François Daviaud. Stochastic chaos in a turbulent swirling flow. *Physical review* 464 *letters*, 119(1):014502, 2017.
- [40] Adam J Kucharski, Timothy W Russell, Charlie Diamond, Yang Liu, John Edmunds, Sebastian Funk, Rosalind M Eggo, Fiona Sun, Mark Jit, James D Munday, et al. Early dynamics of
 transmission and control of covid-19: a mathematical modelling study. *The Lancet Infectious Diseases*, 2020.
- ⁴⁶⁹ [41] Andrea Remuzzi and Giuseppe Remuzzi. Covid-19 and italy: what next? The Lancet, 2020.
- [42] Choujun Zhan, K Tse Chi, Zhikang Lai, Tianyong Hao, and Jingjing Su. Prediction of covid-19
 spreading profiles in south korea, italy and iran by data-driven coding. *medRxiv*, 2020.
- [43] Xianghua Zhang and Ke Wang. Stochastic seir model with jumps. Applied Mathematics and
 Computation, 239:133–143, 2014.
- ⁴⁷⁴ [44] Joost Hopman, Benedetta Allegranzi, and Shaheen Mehtar. Managing covid-19 in low-and
 ⁴⁷⁵ middle-income countries. JAMA, 2020.
- 476 [45] Marius Gilbert, Giulia Pullano, Francesco Pinotti, Eugenio Valdano, Chiara Poletto, Pierre-
- 477 Yves Boëlle, Eric D'Ortenzio, Yazdan Yazdanpanah, Serge Paul Eholie, Mathias Altmann,
 478 et al. Preparedness and vulnerability of african countries against importations of covid-19: a
 479 modelling study. *The Lancet*, 2020.
- [46] J Steenhuysen and S Nebehay. Countries rush to build diagnostic capacity as coronavirus
 spreads. *Reuters*, 2020.
- [47] Jonathan M Read, Jessica RE Bridgen, Derek AT Cummings, Antonia Ho, and Chris P
 Jewell. Novel coronavirus 2019-ncov: early estimation of epidemiological parameters and
 epidemic predictions. *MedRxiv*, 2020.



FIG. 1. Example of a Susceptible-Exposed-Infected-Recovered (SEIR) model of COVID-19 (Eqs 7-10) with $\lambda = 1./S(0)$, $\alpha = 0.27$, $\gamma = 0.37$. Initial conditions are set to I(0) = 2, S(0) = 33000, E(0) = R(0) = 0. a) Time evolution for the variables of the system, b) Time evolution for the total number of infections C(t) against the Chinese data with t=1 corresponding to Dec 19. 2019.



FIG. 2. Logistic (Eq. 11 fit of the Chinese number of infections C(t). The best fit parameters are $a = 80800 \pm 400, b = 0.225 \pm 0.005, c = 190 \pm 25.$



FIG. 3. Logistic distribution fits for the early stages of the epidemic in France. a) Logistic fits with data starting from different dates and ending Mar. 20. b) Logistic fits ending on different dates, but starting Mar. 04.



FIG. 4. Logistic distribution substituting the last data point with a random number $\xi(t^*)$ drawn from a uniform distribution with mean $C(t^*)$ and standard deviation $0.2C(t^*)$ for UK (a), France (b) and Italy (c).



FIG. 5. Example of 30 trajectories of dynamics of stochastic Susceptible-Exposed-Infected-Recovered (SEIR) model for COVID-19, obtained replacing alternatevely α (a,b), λ (b,d) and γ with the stochastic process with Eq 12. Dynamics are integrated with a fixed initial condition and 30 noise realisations. a,c,e) Time evolution for the variables of the system, b,d,f) Time evolution for the total number of infections C(t).



FIG. 6. Example of 6 trajectories of dynamics of stochastic Susceptible-Exposed-Infected-Recovered (SEIR) model for COVID-19, obtained replacing all parameters α , λ and γ with an independent stochastic process as in Eq 12. Dynamics are integrated with a fixed initial condition and 6 noise realisations. a) Time evolution for the variables of the system. b) Time evolution for the total number of infections C(t). c) Time evolution for the daily infections. d) Comparison with daily infections in China (red, starting Dec 19. 2019), South Korea (black, starting Jan 30, 2020), Italy (blue, starting Feb 20, 2020).