**Caution coupling explains linear phase of Covid-19 curves**

John S. McCaskill and Norman H. Packard

European Centre for Living Technology, Venice, Italy

Chemelion Inc., San Francisco, USA

The understanding of epidemics through modelling is gained both through highly simplified population models such as the early SIR model [1, 2] (distinguishing Susceptible, Infective, and Recovered individuals) and its extensions: both to more stage-differentiated models like SEIR [3-6] and SIDARTHE [7, 8] and age-differentiated social mixing models [9, 10], and to include stochastic effects [11, 12] and spatial [13-15] or other network structure [16-18]. Cause and effect can also be analysed in agent models [19, 20] making use of detailed population data (big data) [21, 22]. However, certain key features of the Covid-19 pandemic data affecting us all have not been explained simply. In particular, the remarkably common extended linear phase in countries’ cumulative confirmed cases is poorly understood. While small world network effects may account for non-exponential early growth [16], they do not explain the linear saturation effect well below levels required for “herd immunity”. In this letter, we show that central features of this societal response complexity can indeed be understood using the S(E)IR(D) family of models by means of a single additional deterministic coupling, one reflecting societal introspection: *caution*. As society reacts to and endeavours to contain the strong effects of the Covid-19 virus on health, social well-being and the economy, it may appear that explanation requires every aspect of society to be modelled in detail: from the use of public transport, religious practises and child play patterns to political decision making, the media and legislature[23]. However, the prolonged near linear response both in the cumulative number of Corona cases as well as those in individual populations can be understood as a generic human response to the epidemic in the age of information. This insight may in turn help us to focus societal measures and responses more effectively.

In March 2020, a study in Oxford [24] suggested, using an SIR model, that a much larger portion of society may be infected than normally inferred from the testing data, which was biased to symptom carriers. This was in-line with standard epidemiological modelling that relates the epidemic proliferation peak and subsequent decline to the advent of a significant fraction of the population becoming immune to the disease. Contemplating the early linear global data, see Fig. 1, the author was struck by the similarities with bacterial viral proliferation kinetics inside a single cell and in evolution experiments *in vitro*, which systematically show exponential growth giving way to linear growth in the absence of immunity [25, 26]. The fundamental reason for this is specific resource limitation, for example of the Qß viral replicase enzymes responsible for copying the RNA viral genome [26]. This is, like the nesting site limitation in bird populations, a straightforward thing: when most replicase enzymes are occupied in the copying process with a particular RNA genome, they are not available for proliferation of other RNA, and the throughput of copied RNA becomes a constant, limited by the throughput of such copying enzymes. The author wondered if a related mechanism could account for the observed linear growth phase for Covid-19 in societies shown in Fig. 1.

We add an endogenous informed human cautionary response to simple compartmentalized S(E)IR models in the following way. We split the population of susceptible individuals S into two classes S and Sc, the former acting unaffectedly and hence experiencing exposure to the virus at the initial rate, the latter exercising informed caution and hence reducing their exposure to the virus by a factor c0<1. We then identify the subpopulation C in the deterministic population model most indicative of the negative impact of the disease for the population, as the trigger for this response. For example, in the case of the simple SIR model, it is the class C=I of infected individuals, and more realistically in the SEI3R model, which adds an exposed class E of not yet infectious individuals and two additional classes I2 and I3 of infectious individuals (in hospital and in intensive care respectively), it is the class C=I3. Although one may expect that the number of deaths also dramatically influences the execution of caution, it is a cumulative category which does not reflect the current situation as does I or I3. In fact, the daily number of deaths would be an appropriate indicator, but this is simply proportional to I in the SIR model and I3 in the SEI3R model.

To capture the response to this cautionary trigger, we first employ a simple reaction mechanism: a reversible caution binding mechanism. Individuals observing the pandemic can be triggered to become cautious but after a while also shed this caution. So the model involves both a forward transition of unaffected susceptible individuals S to cautious individuals Sc, with a rate proportional to the product of their densities in the population (as in the law of mass action for chemical interactions), as well as a reverse transition from cautious individuals to individuals acting unaffectedly, proportional to the density of cautious individuals (resulting in a natural single exponential decay of caution in time). The mechanism and equations of two representative endogenous caution models are shown in Fig. 2. Note that in this first approach, we do not distinguish between cautious and non-cautious exposed or infected individuals I. We have tested the impact of making this distinction in a second set of models, also shown in Fig. 2, which share the prediction of a linear phase, with a stronger impact of caution. Once in hospital, we assume naturally that all individuals are exercising (or having exercised for them by hospital staff) a significant degree of caution.

An alternative threshold trigger response replaces the product law by a threshold activation rate of the form where is the difference between the endogeneous cautionary trigger signal introduced above and a threshold value (e.g. 25% of hospital ICUs being occupied) and describes the sharpness of the transition. While this may be required to fit accurately the sudden press amplified responses to reports of rising death tolls, it is not essential to explain the observed long linear response phases.

We employed a straightforward python-based modelling strategy making use of either direct ordinary differential equation encoding and the lmfit package or the modelling package GomPy with its interface to the SciPy minimize fitting procedure via least squares. The results of our modelling are shown, firstly for representative variation of the caution parameters in Fig. 3, showing the range of response forms that the model can account for and then fitted to the country response data shown in Fig. 4.

This phenomenom is not restricted to US or Russian responses. Whereas some countries, with geographic advantages in isolation, by executing radical containment policies, have managed to reduce the daily new infection rate of the Covid-19 virus to a rather constant low level, the far more generic growth response is a transition from an exponential (or possibly power law [16]) phase to a relatively constant rate of growth, often with 100s or 1000s of cases per day, in some cases after an initial overshoot. The generic linear phases of growth are surveyed in data taken from Johns Hopkins University database, using a rolling average over 7 days to remove prominent weekly variations in reporting and some fluctuations, in Fig 2 for the 10 most affected countries (US, Brazil, Russia, India, UK, Spain, Italy, Peru, France, and Iran) and six others selected because they represent a strong variety of government responses to the pandemic (Sweden, Germany, Netherlands, Poland South Korea, Australia).

The simplest generic structure of epidemics, captured also by the SIR model, is initial exponential growth tempered by the rise of so-called herd-immunity in the population.

We briefly address a potential critique of our result arising from limitations in the testing procedure. If the number of available tests is limited in a country, then this could result in a saturation in the number of confirmed cases per day, resulting in an apparent linear growth. Although such limitations have occurred and are visible for example in the data from …, we argue that our overall conclusions are independent of this effect. Firstly, overall testing levels in a significant number of countries have exceeded by a large factor the number of positive cases. Secondly, the linear trend also occurs in the number of deaths. Thirdly, the numbers of tests have been increasing in most countries and the linear trend persists.

The implications of these results are instructive. Firstly, it is no longer herd immunity but cautionary measures that is the primary limiter of spread of the disease: the latter have effect at much lower disease frequencies than herd immunity which would only be achieved much later after an enormous societal cost. Secondly, the strongly asymmetric peak responses to the daily case statistics and the linear population responses in cumulative case indicators (and in deaths) result from an active regulation of the degree of caution exercised in the population. As evidenced by the case of Sweden this is not entirely dependent on government legislation, which itself is in response to fears of repercussions based on severity indicators like the number of deaths, but also occurs naturally in the population, for example through the ubiquitous distribution of statistics concerning ICU cases. Depending on the timescale of relaxation of caution, the response can also involve second waves and longer-term oscillation. Thirdly, the natural human response, and as we have seen also government mediation of this apart from in a few nations, is not to maintain strict caution measures up until disease eradication. The successive relaxation of measures, even close to disease eradication results in very long periods of nearly constant case frequencies, consistent with the cautionary regulation process that we describe in this paper. Examples of this include Germany, Australia, South Korea, Switzerland and many other states.

**Figures**

A

A screenshot of a cell phone

Description automatically generatedA close up of a map

Description automatically generated

B

**Fig.1 Common linear phases of growth in individual countries.** **A)** The cumulative numbers of confirmed cases of Covid-19 in the larger European countries, including Turkey (similar size, 82 million) and Sweden (minimal government control, 10 million) as interesting cases for comparison having strong and weak central intervention. **B)** Same for countries with largest population epidemics in the world for Covid-19 as of Aug 1 2020. Large countries like the US and Brazil have not had a consistent or effective communication of information about the disease, but the response is still effectively piecewise linear as expected from the cautionary model, like the more consistent Russian response. Data is taken from John Hopkins University compilation and averaged over last 7 days to remove weekly oscillations in reporting The data is fitted with a simple 3-segment piecewise linear fit. Note that second waves of infection, affecting Spain in particular in this plot, and to a lesser extent France and Germany, which depart from linearity, are also predicted in the more differentiated SC3EI3R version of the cautionary model.

|  |  |  |
| --- | --- | --- |
| SIR |  |  |
| SCIR |  |  |
| SEIR |  |  |
| SCEIR |  |  |

**Fig.2 The mechanism and equations of the two simplest endogenous caution models.** The two standard epidemic models SIR and SEIR are extended in the simplest way to self-regulating models with caution SCIR and SCEIR, by distinguishing two classes of susceptibles S and Sc with the switch to caution prompted by high observed number of infections and with caution decaying exponentially with time. Cautioned susceptibles have a reduced rate of infection. In a next step, the exposed E and infected individuals I can also be distinguished by caution (see SI Fig S1) in SC2IR and SC3EIR models. Likewise, more differentiated standard models like the SEI3R model, with three stages of infected individuals (I1 non-hospitalized, I2 hospitalized and I3 critical care) can be extended to cautionary feedback via I3 as shown SI Fig S1.

A close up of a map

Description automatically generated

**Fig. 3 Effect of caution feedback for representative variation of the caution parameters**. The two underlying models SEIR (left half) and the more realistic SEI3R (right half) with distinguished hospitalization and ICU treatment of infected individuals are extended with caution in two ways: (i) (1st and 3rd column) only adding cautioned susceptibles as in fig. 2, and (ii) (columns 2 and 4) adding cautioned susceptibles, exposed and infected S,E,I for all non-hospitalized classes (assuming hospitalized cases are always cautioned). The three rows show the variations of the response with each of the three caution parameters (c0,c1,c2) about reference values (0.2,21,0.3) corresponding to (infectivity reduction factor, caution retention time in days, and sensitivity to ICU occupation fraction or equivalently to death rate, more precisely the fraction of ICUs occupied leading to transition to caution @ 1/day). The ICU fraction relative to population is a known country dependent parameter, set to a typical western value of 0.002 in this case. The vertical axis in all plots is the daily confirmed cases as a fraction of the population (allowing application to different regions or nations).

Fig. 4 Fit to country data for caution arising from critical societal burden in SCEI3R model

# Supplementary Material

|  |  |  |
| --- | --- | --- |
| SIR |  |  |
| SCIR |  |  |
| SC2IR |  |  |
| SEIR |  |  |
| SCEIR |  |  |
| SC3EIR |  |  |
| SEI3R |  |  |
| SCEI3R |  |  |
| SC3EI3R |  |  |

**Fig. S1 Mechanism of all models analysed in this work.** The three standard models SIR, SEIR and SEI3R are each extended with cautionary feedback in two ways: (i) firstly just distinguishing cautioned susceptibles and then (ii) distinguishing also cautioned exposed and/or infected individuals (non-hospitalized ones to be more precise). In each case the reference class employed to gauge the cautionary feedback is the class of most severely affected infected individuals. We assume for simplicity that the transition to caution is independent of exposure in the differentiated models.

**Fig. S2 Piecewise linear fits to all country data for cumulative deaths.** The piecewise linear analysis is extended to include all countries (up to Aug 1) for their cumulative deaths (deemed more reliable than the cumulative infections which depend more strongly on testing rates).

A close up of a map

Description automatically generated

**Fig. S3 Effect of caution feedback for representative variation of the caution parameters**. The three underlying models SIR (left third), SEIR (middle third) and the more realistic SEI3R (right third) with distinguished hospitalization and ICU treatment of infected individuals are extended with caution in two ways: (i) (1st and 3rd column) only adding cautioned susceptibles as in fig. 2, and (ii) (columns 2 and 4) adding cautioned susceptibles, exposed and infected S,E,I for all non-hospitalized classes, (assuming hospitalized cases are always cautioned). The three rows show the variations of the response with each of the three caution parameters (c0,c1,c2) about reference values (0.2,21,0.3) corresponding to (infectivity reduction factor, caution retention time in days, and sensitivity to ICU occupation fraction or equivalently to death rate, more precisely the fraction of ICUs occupied leading to transition to caution @ 1/day). The ICU fraction relative to population is a known country dependent parameter, set to a typical western value of 0.002 in this case. The vertical axis in all plots is the daily confirmed cases as a fraction of the population (allowing application to different regions or nations).

**References**

1. Kermack, W.O., McKendrick, A.G., Walker, G.T.: A contribution to the mathematical theory of epidemics. Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character 115, 700-721 (1927) doi:10.1098/rspa.1927.0118

2. R.M., A., B., A., R.M., M.: Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford, UK (1992) 9780198540403

3. Anderson, R., May, R.: Directly transmitted infections diseases: control by vaccination. Science 215, 1053-1060 (1982) 10.1126/science.7063839

4. Hethcote, H.W.: The Mathematics of Infectious Diseases. SIAM Rev. 42, 599–653 (2000) 10.1137/s0036144500371907

5. Wu, Z., McGoogan, J.M.: Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. . JAMA 323, 1239–1242 (2020) <https://doi.org/10.1001/jama.2020.2648>

6. Lin, Q., Zhao, S., Gao, D., Lou, Y., Yang, S., Musa, S.S., Wang, M.H., Cai, Y., Wang, W., Yang, L., He, D.: A conceptual model for the coronavirus disease 2019 (COVID-19) outbreak in Wuhan, China with individual reaction and governmental action. Int. J. Infect. Dis. 93, 211-216 (2020) <https://doi.org/10.1016/j.ijid.2020.02.058>

7. Giordano, G., Blanchini, F., Bruno, R., Colaneri, P., Di Filippo, A., Di Matteo, A., Colaneri, M.: Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy. Nature Medicine (2020) <https://doi.org/10.1038/s41591-020-0883-7>

8. Gumel, A.B., Ruan, S., Day, T., Watmough, J., Brauer, F., van den Driessche, P., Gabrielson, D., Bowman, C., Alexander, M.E., Ardal, S., Wu, J., Sahai, B.M.: Modelling strategies for controlling SARS outbreaks. Proc Biol Sci 271, 2223-2232 (2004) 10.1098/rspb.2004.2800

9. Klepac, P., Kucharski, A.J., Conlan, A.J., Kissler, S., Tang, M., Fry, H., Gog, J.R.: Contacts in context: large-scale setting-specific social mixing matrices from the BBC Pandemic project. medRxiv (2020)

10. Prem, K., Liu, Y., Russell, T.W., Kucharski, A.J., Eggo, R.M., Davies, N., Flasche, S., Clifford, S., Pearson, C.A.B., Munday, J.D., Abbott, S., Gibbs, H., Rosello, A., Quilty, B.J., Jombart, T., Sun, F., Diamond, C., Gimma, A., van Zandvoort, K., Funk, S., Jarvis, C.I., Edmunds, W.J., Bosse, N.I., Hellewell, J., Jit, M., Klepac, P.: The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. The Lancet Public Health 5, e261-e270 (2020) 10.1016/S2468-2667(20)30073-6

11. Hellewell, J., Abbott, S., Gimma, A., Bosse, N.I., Jarvis, C.I., Russell, T.W., Munday, J.D., Kucharski, A.J., Edmunds, W.J., Sun, F., Flasche, S., Quilty, B.J., Davies, N., Liu, Y., Clifford, S., Klepac, P., Jit, M., Diamond, C., Gibbs, H., van Zandvoort, K., Funk, S., Eggo, R.M.: Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. The Lancet Global Health 8, e488-e496 (2020) <https://doi.org/10.1016/S2214-109X(20)30074-7>

12. Kucharski, A.J., Russell, T.W., Diamond, C., Liu, Y., Edmunds, J., Funk, S., Eggo, R.M., Sun, F., Jit, M., Munday, J.D., Davies, N., Gimma, A., van Zandvoort, K., Gibbs, H., Hellewell, J., Jarvis, C.I., Clifford, S., Quilty, B.J., Bosse, N.I., Abbott, S., Klepac, P., Flasche, S.: Early dynamics of transmission and control of COVID-19: a mathematical modelling study. The Lancet Infectious Diseases 20, 553-558 (2020) 10.1016/S1473-3099(20)30144-4

13. Angulo, J., Yu, H.-L., Langousis, A., Kolovos, A., Wang, J., Madrid, A.E., Christakos, G.: Spatiotemporal Infectious Disease Modeling: A BME-SIR Approach. PLOS ONE 8, e72168 (2013) 10.1371/journal.pone.0072168

14. Keeling, M.J.: The effects of local spatial structure on epidemiological invasions. Proc Biol Sci 266, 859-867 (1999) 10.1098/rspb.1999.0716

15. Danon, L., Brooks-Pollock, E., Bailey, M., Keeling, M.J.: A spatial model of CoVID-19 transmission in England and Wales: early spread and peak timing. medRxiv 2020.2002.2012.20022566 (2020) 10.1101/2020.02.12.20022566

16. Ziff, A.L., Ziff, R.M.: Fractal kinetics of COVID-19 pandemic. medRxiv (2020)

17. Simoes, J.M.: Spatial Epidemic Modelling in Social Networks. AIP Conference Proceedings 776, 287-297 (2005) 10.1063/1.1985395

18. Manchein, C., Brugnago, E.L., da Silva, R.M., Mendes, C.F.O., Beims, M.W.: Strong correlations between power-law growth of COVID-19 in four continents and the inefficiency of soft quarantine strategies. Chaos: An Interdisciplinary Journal of Nonlinear Science 30, 041102 (2020) 10.1063/5.0009454

19. Hunter, E., Mac Namee, B., Kelleher, J.D.: A Taxonomy for Agent-Based Models in Human Infectious Disease Epidemiology. Journal of Artificial Societies and Social Simulation 20, 2 (2017) 10.18564/jasss.3414

20. Chinazzi, M., Davis, J.T., Ajelli, M., Gioannini, C., Litvinova, M., Merler, S., Pastore y Piontti, A., Mu, K., Rossi, L., Sun, K., Viboud, C., Xiong, X., Yu, H., Halloran, M.E., Longini, I.M., Vespignani, A.: The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. Science 368, 395 (2020) 10.1126/science.aba9757

21. Wang, C.J., Ng, C.Y., Brook, R.H.: Response to COVID-19 in Taiwan: Big Data Analytics, New Technology, and Proactive Testing. JAMA 323, 1341-1342 (2020) 10.1001/jama.2020.3151

22. Zhou, C., Su, F., Pei, T., Zhang, A., Du, Y., Luo, B., Cao, Z., Wang, J., Yuan, W., Zhu, Y., Song, C., Chen, J., Xu, J., Li, F., Ma, T., Jiang, L., Yan, F., Yi, J., Hu, Y., Liao, Y., Xiao, H.: COVID-19: Challenges to GIS with Big Data. Geography and Sustainability 1, 77-87 (2020) <https://doi.org/10.1016/j.geosus.2020.03.005>

23. Bruinen de Bruin, Y., Lequarre, A.-S., McCourt, J., Clevestig, P., Pigazzani, F., Zare Jeddi, M., Colosio, C., Goulart, M.: Initial impacts of global risk mitigation measures taken during the combatting of the COVID-19 pandemic. Safety Science 128, 104773 (2020) <https://doi.org/10.1016/j.ssci.2020.104773>

24. Lourenco, J., Paton, R., Ghafari, M., Kraemer, M., Thompson, C., Simmonds, P., Klenerman, P., Gupta, S.: Fundamental principles of epidemic spread highlight the immediate need for large-scale serological surveys to assess the stage of the SARS-CoV-2 epidemic. medRxiv (2020) <https://doi.org/10.1101/2020.03.24.20042291>

25. Yin, J., Redovich, J.: Kinetic Modeling of Virus Growth in Cells. Microbiology and Molecular Biology Reviews 82, e00066-00017 (2018) 10.1128/MMBR.00066-17

26. Biebricher, C.K., Eigen, M., Gardiner, W.C.: Kinetics of ribonucleic acid replication. Biochemistry 22, 2544-2559 (1983) 10.1021/bi00279a036