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A perspective on early detection systems models for COVID-19 spreading

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ABSTRACT

The ongoing COVID-19 epidemic highlights the need for effective tools capable of predicting the onset of infection outbreaks at their early stages. The tracing of confirmed cases and the prediction of the local dynamics of contagion through early indicators are crucial measures to a successful fight against emerging infectious diseases (EID).

The proposed framework is model-free and applies Early Warning Detection Systems (EWDS) techniques to detect changes in the territorial spread of infections in the very early stages of onset. This study uses publicly available raw data on the spread of SARS-CoV-2 mainly sourced from the database of the Italian Civil Protection Department.

Two distinct EWDS approaches, the Hub-Jones (H&J) and Strozzi-Zaldivar (S&Z), are adapted and applied to the current SARS-CoV-2 outbreak. They promptly generate warning signals and detect the onset of an epidemic at early surveillance stages even if working on the limited daily available, open-source data.

Additionally, EWDS S&Z criterion is theoretically validated on the basis of the epidemiological SIR.

Discussed EWDS successfully analyze self-accelerating systems, like the SARS-CoV-2 scenario, to precociously identify an epidemic spread through the calculation of onset parameters. This approach can also facilitate early clustering detection, further supporting common fight strategies against the spread of EIDs. Overall, we are presenting an effective tool based on solid scientific and methodological foundations to be used to complement medical actions to contrast the spread of infections such as COVID-19.

1. Introduction

The ongoing outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), propagated in more than 215 countries, claimed more than 1,000,000 lives and over 44,000,000 confirmed cases worldwide since early December 2019 [1]; numbers that are probably underestimated. The outbreak was defined a public international health emergency on January 31st, 2020 and the pandemic scenario was declared on March 11th, 2020 [2]. Since then, governments took unprecedented measures to reduce its spread including travel restrictions, physical distancing and extended closures [3–5]. Research leaps forward brought cures and vaccines closer to the population, but key mitigation strategies must still be based upon urgent community interventions. Such early mitigative measures can delay exponential outbreaks and prevent emerging infectious diseases (EID) spread [6–8].

Notwithstanding an erroneous initial low risk perception in SARS-CoV-2, several governments mobilized to minimize the virus transmission. In Italy, the alert level spiked when Veneto and Lombardy regions experienced a rapid infection growth at the endo of February. This prompted Italian Authorities to enforce a total lockdown (March 9th) to avoid the collapse of the health system. Besides China, and although to different extents, other countries faced analogous challenges [9,10].

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Despite countries adopting risk mitigation measures at unprecedented levels, SARS-CoV-2 brought out the weaknesses of the current systems, mainly ascribed to their unpreparedness and delayed actions. Starting from the concept of sociotechnical systems, the resilient capability failed at least partially in the three relevant phases: avoidance, survival and recovery. The focus of this paper is on sensing early warnings based on weak signals, which, together with error tolerant design, plasticity and recoverability, are the key elements of system resilience.

Preparedness is a key condition to effectively control EIDs outbreaks, and in SARS-CoV-2 scientific warnings were not detected quickly enough [9], as evidenced by the study of control measures in different Countries [11]. Delayed risk mitigation measures may trigger local outbreaks, leading to a full pandemic scenario, especially with new biological agents characterized by high infectivity, high morbidity and even lethality. The window of intervention for full containment may be very narrow, and an early detection and identification of abnormal increases of epidemic data is pivotal.

Early warning systems for EIDs are therefore an essential requirement for a robust public health emergency work, quickly and robustly translating warnings into a structured response strategy. They are challenged to quantitatively analyze surveillance data with specialized early detection approaches on data aberrations, to send out signals related to EID outbreak. Early detection and interpretation of abnormal rises in surveillance data are essential for the incisive control of infectious diseases and a rapid response to potential uncontrolled spreads [12], thus representing an up-to-date research topic still not fully explored in the scientific literature.

This approach is here proposed for the first time in the given context and relies on a conceptual similarity between the early trend of the SARS-CoV-2 data and a self-accelerating system that may rapidly escalate to uncontrolled conditions. Such systems are well-documented in the field of chemical engineering within the framework of runaway mechanisms, where EWDS methodologies apply. EWDS are targeted to monitor evolving systems and to detect suitable early-warning conditions for uncontrolled runaway. We here discuss the applicability and adaptability of two EWDS criteria to EIDs outbreaks: the Hub-Jones (H&J) [13] and the Strozzi-Zaldivar (S&Z) [14] approaches. They can work on available, daily real-time, open-source SARS-CoV-2 data at early surveillance stages, even if limited, to promptly generate warning signals and detect the onset of a potential epidemic. These signals are produced upon detection of a specific indicator and depend on the adopted approach. The H&J and S&Z EWDS are here exemplified using the dynamics of Lombardy and Sardinia, although methodologies are of general applicability and model-free, requiring only dynamics data and no previous model training. We demonstrate how these approaches enable the prompt detection of onset conditions and abnormal changes of disease trends, within a perspective of surveillance-based early warning monitoring. The simplicity of the approach is a must when limitations in the quality and quantity of data impede building more complex versions [7].

This research aims at providing methodologies greatly advancing the detection of clustering and early spread of EIDs. This strategy may enhance the community resilience against new EIDs outbreaks by lowering the intervention time, and supporting policy makers to rapidly detect aberrations and put appropriate actions in place [15]. Improved prediction and prevention science supports building defenses against biological threats, and can be used to assess and manage risks upstream of outbreaks [16,17]. A more integrated and transdisciplinary approach can anticipate and reduce risk from the onset in a prevent-detect-respond-recover strategic virtuous loop.

The following sections are structured as follows: section 2 outlines the methodology for early warning detection; section 3 illustrates the data collection strategy for modeling, introducing the issue of data uncertainties and possible consequences on model estimates; section 4 presents the EWDS framework, adapted from the H&J and S&Z models, proving its successful use in two detailed Italian case studies and upon theoretical validation against a simple epidemiological model. Section 5 finally discusses the main findings and limitations of the study, and draws conclusions.

2. Early warning detection system methodology

Several criteria for the prediction of onset conditions in runaway systems have been published over the past 50 years. EWDS methodologies can be classified into geometry- or sensitivity-based. In geometry-based approaches, the runaway behavior is described according to the geometrical features of a system variable such as dimensionless temperature or heat release rate. The further adoption of innovative criteria based on parametric sensitivity allows surpassing the limiting factor of not quantifying the runaway magnitude. The key observation is that approaching the runaway point the system becomes very sensitive to perturbations, and experiences dramatic changes in response to little variations of the system parameters. The identification of this “sensitivity region” provides the alert conditions for the thermal runaway.

This class of reliable and validated methodologies includes the H&J [13] and S&Z [14] approaches.

The H&J criterion [13] states that runaway occurs when the first and the second mathematical derivatives of a system variable s (usually temperature, T) with respect to time t are simultaneously positive, i.e.:

$$\begin{cases} \dfrac{ds}{dt} > 0 \\ \dfrac{d^2s}{dt^2} > 0 \end{cases} \tag{1}$$

In a typical reaction engineering system, as a reactor temperature increases so that $dT/dt > 0$, the runaway occurs if also the second condition of Eqn. (1) holds. The boundary between a stable and an unstable (runaway) behavior is represented by the temperature vs. time trajectory where the maximum value of (d^2T/dt^2) is zero while the reactor temperature is increasing.

A different approach is the divergence criterion of S&Z [18,19], which finds its basis on chaos theory [14]. This generalized approach can operate under complex systems and does not require specific mathematical models of the process investigated, thus making it suitable for on-line detection of runaway deviations. When applied to a batch reactor as $t \to \infty$, the trajectory of the system in the space of phase tends to a specific point; as an example, we can see it in the reactor temperature equaling the ambient or jacket temperature while the reactant conversion is maximized. Generalizing, the trajectories of two variables meet at the same final point, when the reaction is complete. However, the individual paths can diverge on their way to the final state. If the system parameters are close to the runaway boundary, a small position change results in a wide perturbation of the trajectories. The runaway condition is detected with the evaluation of the divergence of the mathematical system composed of balance differential equations. Once a local positive divergence occurs along the trajectory, the process operates under runaway conditions. In the approach by S&Z, the Lyapunov exponents are used to define the sensitivity and the phase space volume elements are expressed in terms of temperature differences [14].

3. Epidemiological history and data

This study is based on publicly available raw data mainly sourced from the database of Dipartimento della Protezione Civile (Italian Civil Protection Department) GitHub repository [20], where daily updates related to the COVID-19 emergency are posted.

Considered data cover 241 days from February 24th, 2020 (day 1) to October 22nd, 2020 (day 241) and the trend of the Italian epidemiological scenario based on real data is reported in Fig. 1.

It is important to emphasize that the proposed approach is model-free, and entirely based on available real data. These distinctive features make the foundation and the approach validation, directly related to "pure" datasets without the need for any modelling-related background.

The proposed methodology is applied to the real data of two Italian regions, selected based on their peculiar characteristics relevant to COVID 19 spread, being very different by their typical territorial, social, economic, environmental and cultural features. Lombardy was thus selected as representative of the most critical context in the Italian scenario due to its demographic and industrial concentration, while Sardinia as an isolated domain, characterized by two different flows of people over time: very high flow rates during summer vacations and reduced transfers across the borders for the rest of the year.

Lombardy claimed the first Italian SARS-CoV-2 patient in Italy, while Sardinia registered its first case on March 3rd.

Fig. 2 shows the trend of the epidemiological curves according to real data till September 8th, 2020 for Lombardy and Sardinia.

4. Results and discussion on the framework for early warning detection system

EWDS techniques discussed in section 2 were tested on available epidemic data. Their performance was assessed with respect to the capability of early alerting on epidemic outbreaks. A timeline of the main relevant events is given in Table 1.

Additionally, EWDS S&Z criterion is firstly theoretically validated on the basis of the epidemiological SIR (Susceptible, Infectious, and Recovered) model [21] simulated data, to compare results with those based on the reproductive number R_0, a widely-known epidemiologic metric used to describe the contagiousness or transmissibility of infectious agents.

4.1. H&J approach

The application of the H&J approach requires the calculation of the first and second derivative of a generic system variable *s*. Here, *s* stands for the total reported cases of infection and the number of deceased patients. As of Fig. 3, the first and second derivatives calculated from raw data for Lombardy show some noise, mainly derived from the collection system. Nonetheless, the reported profiles show the overlapping effect on the epidemic curve of multiple subsequent outbreaks. Specifically, the outbreaks of Lodi, Brescia - Bergamo and Milan are detected (highlighted by arrows) according to historical evidences.

Based on the runaway criterion, the epidemic trend is self-accelerating when both first and second derivative are positive, allowing to identify the local development trend of the epidemic scenario and the start of the regression phase, when the derivatives have opposite sign.

The same criteria was then applied to the epidemiological curves of Sardinia, Fig. 4, were a delayed and reduced SARS-CoV-2 contagion was recorded and potentially correlated to its geographical isolation, and reduced in/out flux of people.

The strength of the proposed methods is in the early prediction of the onset point of an emerging epidemic outbreak. From the

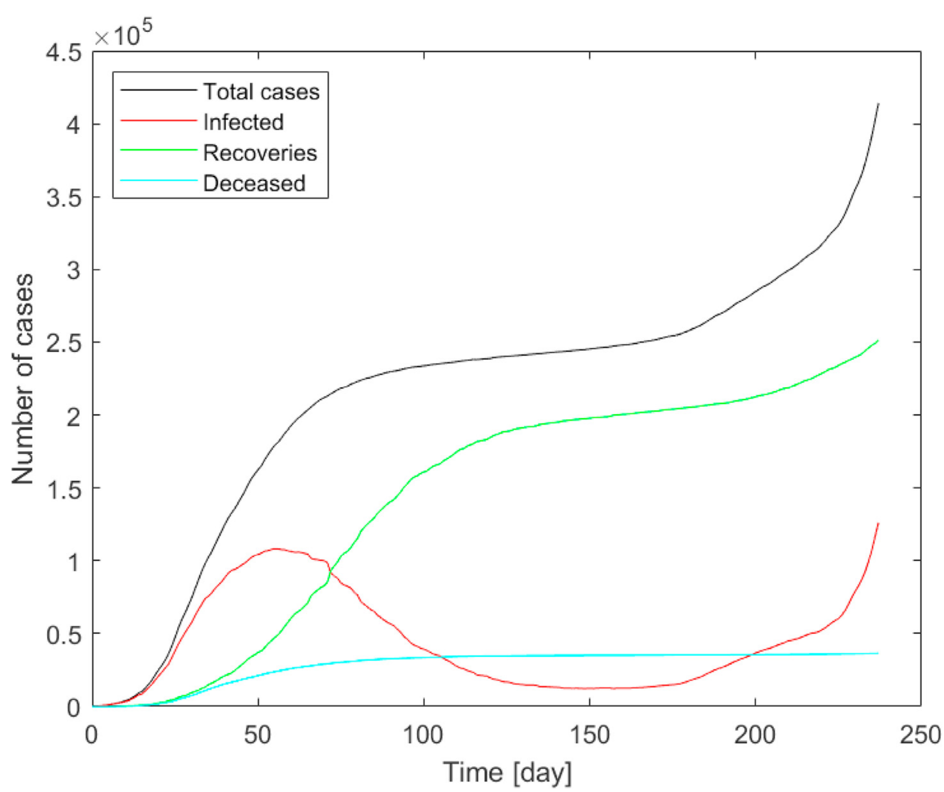

Fig. 1. Epidemiological curve of Italy in the period February 24th – October 22nd, 2020.

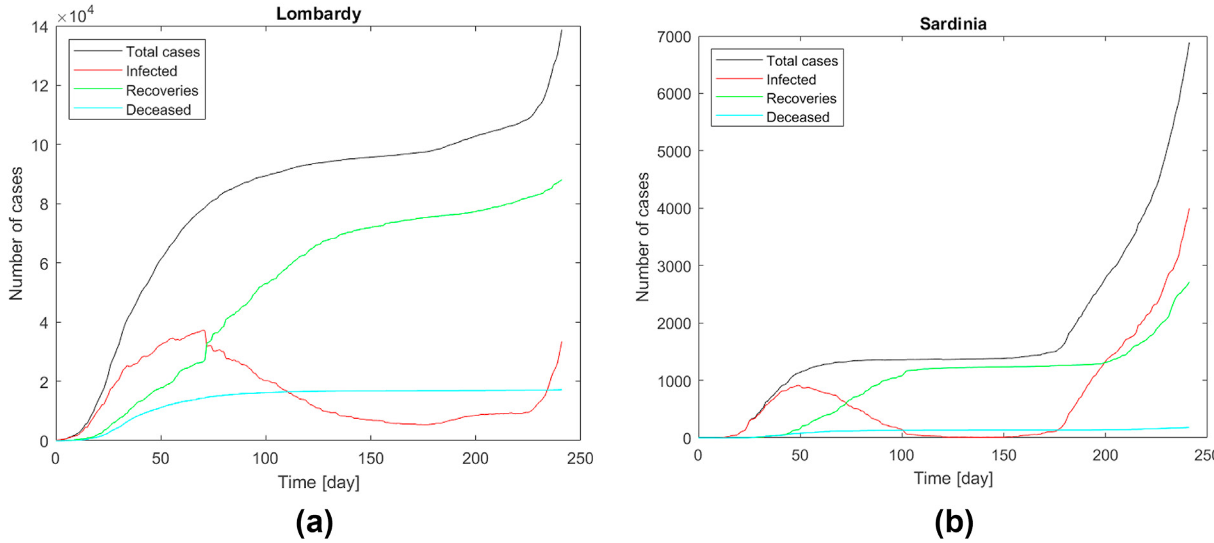

Fig. 2. Real data trends of Lombardy and Sardinia until September 8th, 2020.

Table 1
Main events in the timeline of the considered epidemic real data.

Event	Date	Reference sample	Sampled Day
Lodi outbreak	Feb 24th, 2020	Lombardy	0
Brescia-Bergamo outbreak	Mar 14th, 2020		19
Milano outbreak	Mar 26th, 2020		31
Sardinia first recorded case	Mar 3rd, 2020	Sardinia	8
National lockdown (President of the Council of Ministers decree)	Mar 22nd, 2020	All	27
Reopening of production activities	May 4th, 2020		70

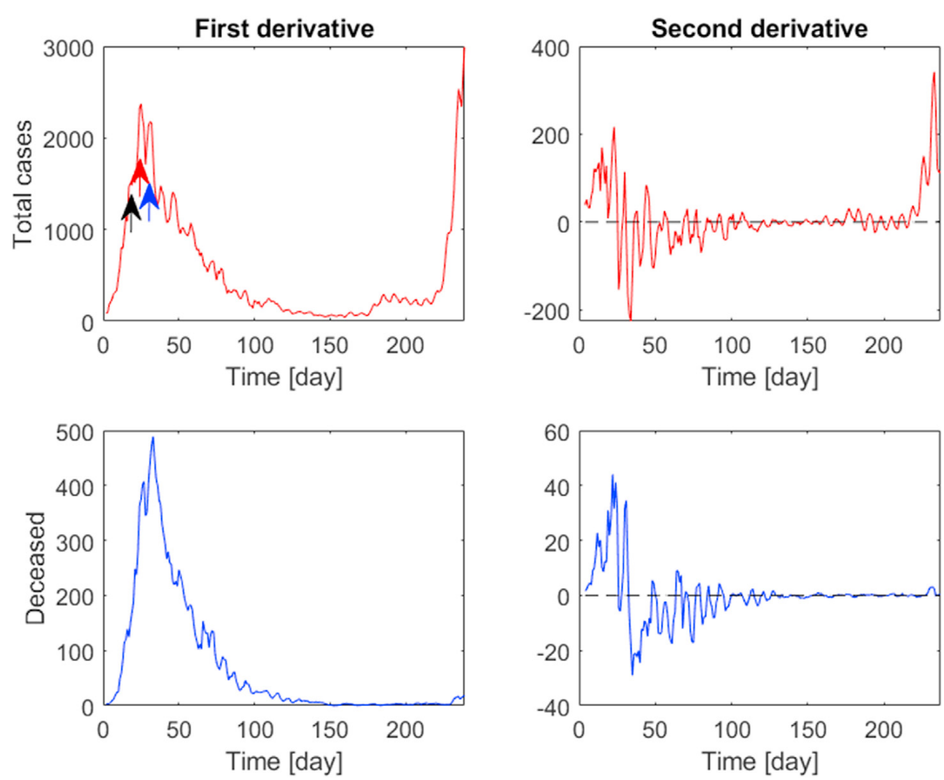

Fig. 3. First and second derivative profiles of epidemiological real data trends in Lombardy (Italy), related to total and deaths reported cases. The timeline is evaluated from the first reported case. Black arrow denotes the outbreaks of Lodi, red arrow Brescia - Bergamo and the blue arrow that of Milan. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

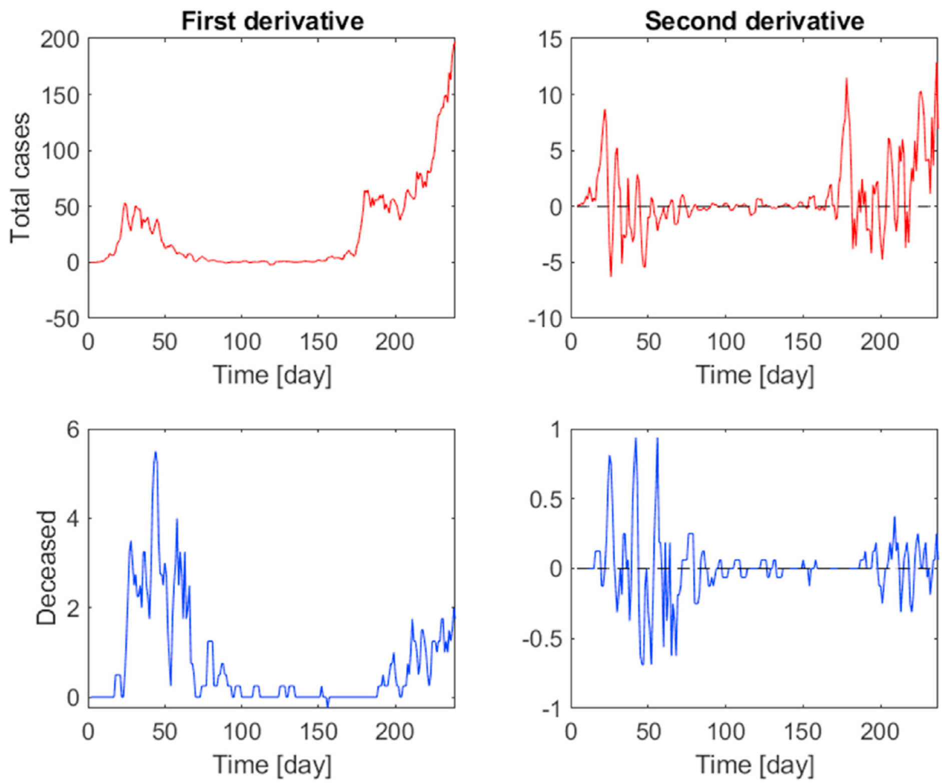

Fig. 4. Derivatives profile of epidemiological trends in Sardinia (Italy) related to total and deaths reported cases. Abscissa denotes time in days since case 1 was recorded.

sample geographic area and monitoring data, the point matching the onset of the self-accelerating trend can be detected well in advance. Fig. 5 refers to Lombardy data and details the application of the method in detecting the onset by evaluating variation of the first derivative near the spike for the first 60 days.

Fig. 6 shows the determination of the onset based on Lombardy and Sardinia data (Fig. 6a and 6. b).

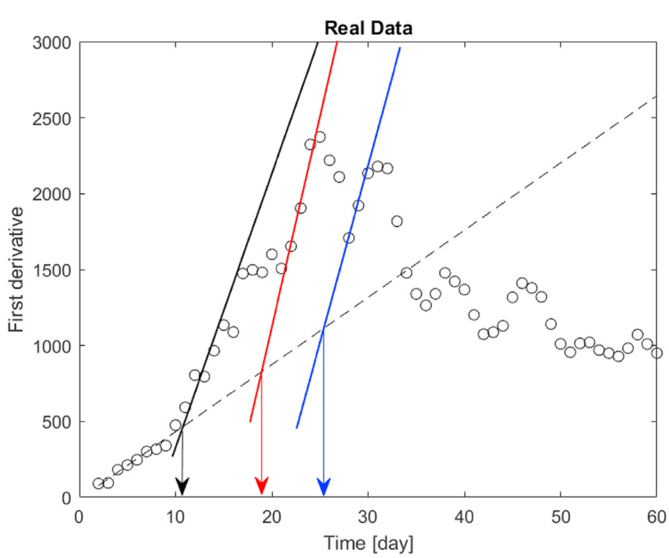

Fig. 5. Application of the EWDS of Hub and Jones in Lombardy region. Identification of the onset date based on the trend of total cases. Real data are black dotted, the base line is black dashed, black line denotes the onset of Lodi, red line Brescia - Bergamo and blue line Milan. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2 shows the results related to the onset of Lombardy and Sardinia regions.

Data from Table 2 prove that the H&J approach is suitable for the early detection of self-accelerating trends of the epidemiological dynamics. The onset identification allows for the determination of the threshold day after which there's an escalation to a critical scenario. Calculated values via H&J approach are in line with the real epidemiological history.

This approach thus has a strong potential for an early fight against the onset of self-accelerated drifts of the epidemic scenario. EWDS H&J strategy is intended as a complementary crucial tool to anticipate an epidemic uncontrolled spreading on both local and regional scales. In this way, appropriate and effective actions can be put in place to ensure a successful preventive and mitigative complete strategy.

4.2. S&Z approach applied to real data from Lombardy and Sardinia regions

Figs. 7–8 show the behavior of the divergence calculated for the total cases and number of deaths for the real data in Lombardy and Sardinia.

The divergence calculated on Lombardy data (Fig. 7) is positive but with a decreasing trend from day one (February 24th) until day 40 (April 4th -reopening of production activities). Divergence then stabilizes around zero until day 158 (30 July), when another increase ensues probably as an effect of circulation and contacts among people during the summer, but without reaching the high levels of February.

The behavior of the divergence for Sardinia (Fig. 8) shares similarities with Lombardy, but also shows a few differences. Again, the method's prediction perfectly fits the real situation: the divergence goes below zero a few days later than in Lombardy. Moreover, being

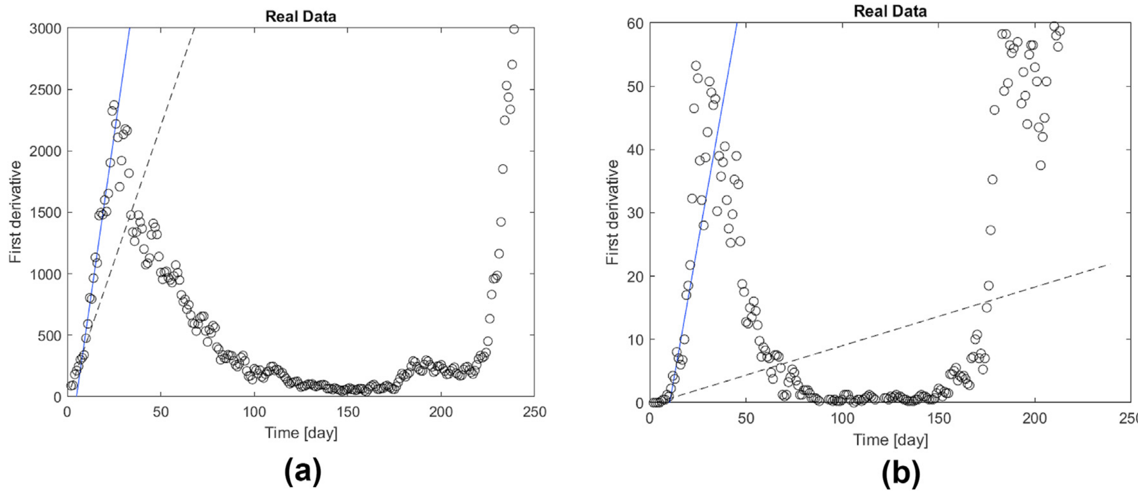

Fig. 6. Application of the EWDS of Hub and Jones in a) Lombardy region; b) Sardinia region.

Table 2
Calculation of onset for Lombardy and Sardinia scenarios via H&J approach.

	Lombardy	Sardinia
Real data	8.2	10.7

Sardinia a typical summer holydays destination, the divergence resumes positive values near the sampled point 120 (end of June), way before Lombardy, which records new positive divergence at sampled point 160 (end of July). This is an important finding, and confirms the ability of the divergence operator to promptly detect unexpected trends of the epidemics.

The divergence criterion, upon proper refinement, can be applied using any variables, i.e. total cases and deceased, thus making it possible to choose easiest to measure and/or cleaner one. Another clear advantage is use of series of raw data to measure the divergence, without the need of complex mathematical models, thus reducing the sources of error. Last but not least, this indicator's ability to act as an amplifier of the trigger moment of the runaway reaction, makes it possible to rapidly detect the appearance of exponential accelerations in the number of infected or deceased as it happens, for example, after the summer holydays or the deceleration in response to mitigation strategies.

4.3. *S&Z approach applied to the epidemiologic susceptible infected recovered (SIR) model*

In this section, the S&Z criterion is applied to the SIR model [22] to provide a theoretical validation by analytically calculating the divergence from the basic equations of the model. According to the model, it is relatively simple to verify what happens when the reproduction number R_0 exceeds the critical value of 1 and the epidemic spreads exponentially.

The SIR is the most widely accepted mathematical models for the spread of a pandemic, and has been used in several studies analyzing COVID-19 [23–26].

Letting s be the percentage of individuals susceptible to infection, i the infected, r the dead or recovered, b the probability of contracting the disease and n the probability of healing, the SIR model can be expressed as:

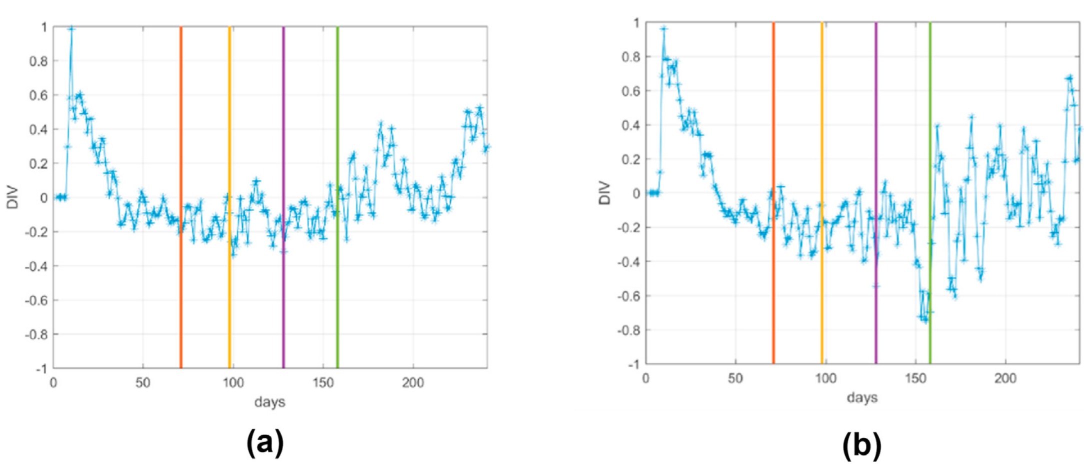

Fig. 7. Divergence calculated in Lombardy region for: (a) Total cases (infected + deceased); (b) Deceased. The vertical lines represent, from left to right, production activities reopened on 4th of May (Sampled point 70), 31st of May (Sampled point 97), 30th of June (sampled point 127) and 31st of July (sampled point 158).

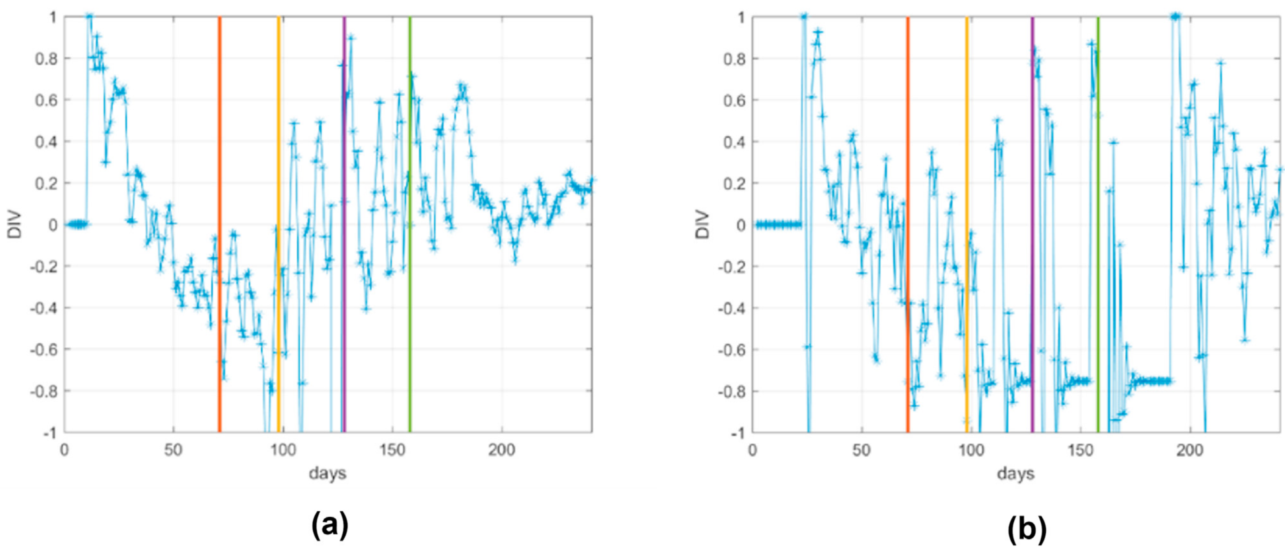

Fig. 8. Divergence calculated in Sardinia region for: (a) Total cases (infected + deceased); (b) Deceased. The vertical lines represent, from left to right, production activities reopened on 4th of May (Sampled point 70), 31st of May (Sampled point 97), 30th of June (sampled point 127) and 31st of July (sampled point 158).

$$\begin{cases} \dfrac{ds}{dt} = -bsi \\ \dfrac{di}{dt} = bsi - ni \\ \dfrac{dr}{dt} = ni \end{cases} \quad (2)$$

The condition for outbreak spread is $\frac{di}{dt} = bsi - ni > 0$, where bs is the number of individuals who may be infected in the given population s and $1/n$ is the average length of the period of infectivity.

Under the conservative hypothesis that, at the onset, the entire population is susceptible (i.e. $S_0 = 1$), by imposing $R_0 = b/n$, the condition for the spread of the epidemic is $R_0 > 1$. Conversely, the condition for epidemic extinction is:

$$bsi - ni < 0 \quad (3)$$

Based on the S&Z criterion, the epidemic does not spread if the divergence of the system is lower than zero. The divergence is the sum of the diagonal elements of the Jacobian matrix, that for the SIR system (2) in a given state is:

$$J = \begin{bmatrix} -bi & -bs & 0 \\ bi & bs - n & 0 \\ 0 & n & 0 \end{bmatrix} \quad (4)$$

The not propagating condition is therefore:

$$b(s - i)n < 0 \quad (5)$$

When $i = 0$ (i.e. at the beginning or at the end of the outbreak), conditions (3) and (5) coincide.

The divergence during the whole evolution of the contagion can be easily simulated with Matlab® and the results are shown in Fig. 9. During the simulation, at time t = 40, the value of R0 is varied from 0.7 to 2.2, and the divergence increases and becomes positive indicating a restart of the outbreak.

Moreover, even if R0>1, just after t = 80, when the infected decrease below the susceptible, the divergence becomes <0, indicating a contraction of the epidemic. The divergence thus seems a better indicator of the epidemic expansion than the reproduction number.

5. Conclusions

The characteristics of the Covid-19 epidemic, combined with the high population density and intense movements on the territory in the North Italian area, has required and still requires an intense scientific and technological effort to support the control and prevention of the virus spread.

An effective fight against similar future scenarios must be a rapid, integrated, and proactive intervention based on the ability to aggregate large datasets from different sources with the tracing of confirmed cases and the prediction of the local dynamics of contagion through early indicators.

These elements are part of a “quick learn” strategy, where rapid interpretation of evolving data is crucial to identify the best actions to prevent and contain infection outbreaks, thus enabling Governments to implement timely mitigating strategies. Additionally, the rapid enforcement of preventive measures may avoid resorting to drastic and prolonged lockdowns, which carry dramatic financial implications.

To support this strategy, we proved that EWDS algorithms developed and tested on the basis of ongoing epidemic dynamics, can be validly used to monitor the evolution of EIDs. This approach can be useful even if an EID is latent for medium to long periods in a specified area, giving early warnings to detect the onset of new outbreaks or the disease spread resumption.

Both discussed and adopted EWDS systems allow robust monitoring of the development status of the epidemic, and to predict early on-set peaks even in case of overlapping outbreaks. The main advantage of the EWDS is the fact of being Model Free, thus simply requiring series of data and not consolidated mathematical models, thus greatly reducing the sources of error and increasing their versatility.

The results of the two methodologies show that the H&J method can predict well in advance the set point of the exponential growth of the epidemic. The S&Z method relying on the divergence, highlights in advance the impact of the effects due to the mitigation decrees. The measures adopted in March in Italy influenced the trend of the divergence, by decreasing it. On the contrary, when the

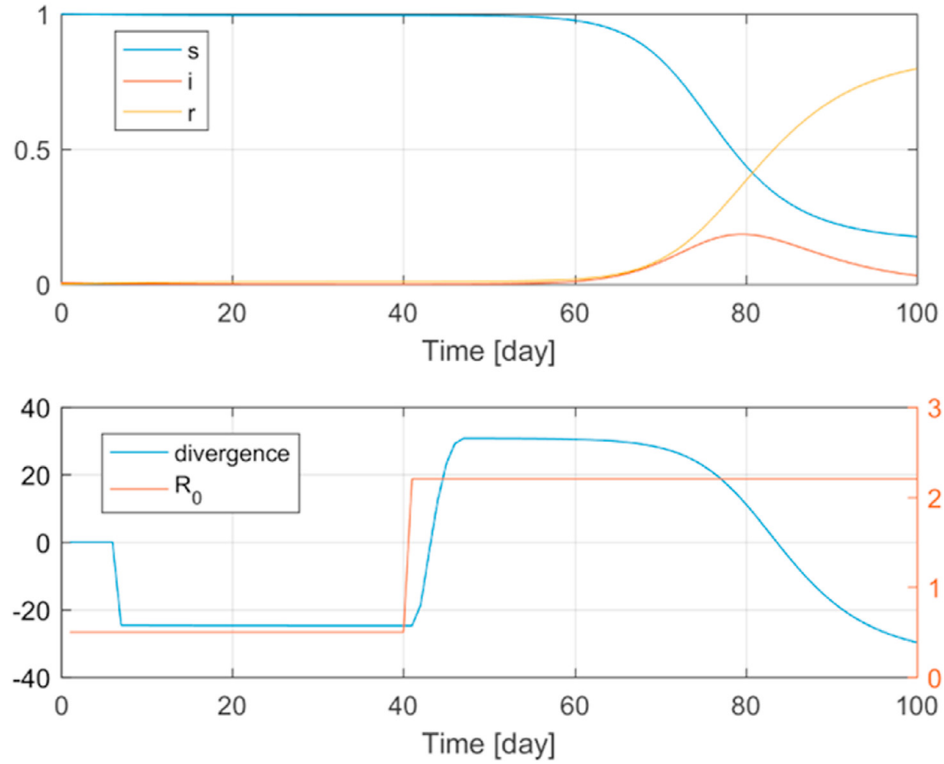

Fig. 9. In the upper part there is the evolution of the variables of the SIR model for $(s_0, i_0, r_0) = (1, 0.005, 0.00)$. At the bottom the divergence reconstructed using the simulated data of the recovered (r) when the basic reproduction number R0 changes from 0.7 to 2.2 at t = 41.

epidemic restarts the divergence again increases becoming higher than zero and it can be used as an early warning system. The trend is clearly highlighted for example during the summer holidays in Italy, where Sardinia region represents an appealing and renowned tourist resort (Fig. 8).

The results achieved with the combination of the two developed EWDS systems, can represent an early alerting tool for tracking the epidemic. This combined approach can robustly support decision makers to best define switches between phases (tightening and/or untightening of restriction measures), also differentiated in the national territory, and it can mainly be used as an early warning tool for future epidemic outbreaks to be rapidly detected, confined and recovered.

In perspective, the EWDS criteria may also be coupled with the monitoring of other relevant data that will be identified by decision makers on the basis of the fundamental scientific contribution of the medical community. Even considering the limitations of the combined approach, as commented by Thomas [7] “the knowledge about the main modes of the epidemic’s behaviour and the orders of magnitude of the numbers of people affected under the various options can regarded as good enough to guide policy decisions”.

The proposed framework therefore lends itself easily to being extended and applied to an increasingly evolved, exhaustive and accurate context of available information.In this way, upon proper refinement and possible connection with advanced epidemiological data, a predictive tool based on solid scientific and methodological foundations will be made available to decision makers which, coupled with medical and epidemiological studies suitable for understanding the mechanisms of replication and spread of the virus, can provide an integrated method for contrasting its spread.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Johns Hopkins Resource Center, COVID-19 Map, Johns Hopkins Coronavirus Resour. Cent, 2020.
[2] World Health Organization, WHO Coronavirus Disease (COVID-19) Dashboard, World Heal. Organ., 2020.
[3] S.H. Ebrahim, Q.A. Ahmed, E. Gozzer, P. Schlagenhauf, Z.A. Memish, Covid-19 and community mitigation strategies in a pandemic, BMJ 368 (2020), https://doi.org/10.1136/bmj.m1066.
[4] R.M. Anderson, H. Heesterbeek, D. Klinkenberg, T.D. Hollingsworth, How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet (2020) https://doi.org/10.1016/S0140-6736(20)30567-5.
[5] K. Prem, Y. Liu, T.W. Russell, A.J. Kucharski, R.M. Eggo, N. Davies, S. Flasche, S. Clifford, C.A.B. Pearson, J.D. Munday, S. Abbott, H. Gibbs, A. Rosello, B.J. Quilty, T. Jombart, F. Sun, C. Diamond, A. Gimma, K. van Zandvoort, S. Funk, C.I. Jarvis, W.J. Edmunds, N.I. Bosse, J. Hellewell, M. Jit, P. Klepac, The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study, Lancet Public Heal (2020), https://doi.org/10.1016/S2468-2667(20)30073-6.
[6] H. Tian, Y. Li, Y. Liu, M.U.G. Kraemer, B. Chen, J. Cai, B. Li, B. Xu, Q. Yang, P. Yang, Y. Cui, Y. Song, P. Zheng, Q. Wang, O.N. Bjornstad, R. Yang, O. Pybus, B. Grenfell, C. Dye, Early Evaluation of the Wuhan City Travel Restrictions in Response to the 2019 Novel Coronavirus Outbreak, MedRxiv, 2020.
[7] S. Flaxman, S. Mishra, A. Gandy, H.T. Juliette Unwin, T.A. Mellan, H. Coupland, C. Whittaker, H. Zhu, T. Berah, J.W. Eaton, C.A. Donnelly, S. Riley, M.A. C Vollmer, N.M. Ferguson, L.C. Okell, S. Bhatt, Estimating the effects of non-pharmaceutical interventions on COVID-19 in europe mélodie monod 1, imperial college COVID-19 response team*, azra C, Nature (2020).
[8] H. Tian, Y. Liu, Y. Li, C.-H. Wu, B. Chen, M.U.G. Kraemer, B. Li, J. Cai, B. Xu, Q. Yang, B. Wang, P. Yang, Y. Cui, Y. Song, P. Zheng, Q. Wang, O.N. Bjornstad, R. Yang, B. Grenfell, O. Pybus, C. Dye, The impact of transmission control measures during the first 50 days of the COVID-19 epidemic in China, MedRxiv (2020) 2020, https://doi.org/10.1101/2020.01.30.20019844.
[9] Y. Bruinen de Bruin, A.S. Lequarre, J. McCourt, P. Clevestig, F. Pigazzani, M. Zare Jeddi, C. Colosio, M. Goulart, Initial impacts of global risk mitigation measures

taken during the combatting of the COVID-19 pandemic, Saf. Sci. (2020), https://doi.org/10.1016/j.ssci.2020.104773.
[10] M. Gatto, E. Bertuzzo, L. Mari, S. Miccoli, L. Carraro, R. Casagrandi, A. Rinaldo, Spread and dynamics of the COVID-19 epidemic in Italy: effects of emergency containment measures, Proc. Natl. Acad. Sci. U. S. A. (2020), https://doi.org/10.1073/pnas.2004978117.
[11] A. Tomar, N. Gupta, Prediction for the spread of COVID-19 in India and effectiveness of preventive measures, Sci. Total Environ. (2020), https://doi.org/10.1016/j.scitotenv.2020.138762.
[12] Y. Weizhong, Early warning for infectious disease outbreak. Acad. Press, Academic Press, London (UK), 2017, p. iv, https://doi.org/10.1016/B978-0-12-812343-0.09991-4.
[13] L. Hub, J.D. Jones, Early on-line detection of exothermic reactions, Plant/Operations Prog. 5 (1986) 221–224, https://doi.org/10.1002/prsb.720050408.
[14] F. Strozzi, J.M. Zaldívar, A.E. Kronberg, K.R. Westerterp, On-Line runaway detection in batch reactors using chaos theory techniques, AIChE J 45 (1999) 2429–2443, https://doi.org/10.1002/aic.690451116.
[15] European Centre for Disease Prevention and Control, Infection prevention and control for COVID-19 in healthcare settings, Elsevier's Nov, Coronavirus Inf. Cent. (2020).
[16] E. Massaro, A. Ganin, N. Perra, I. Linkov, A. Vespignani, Resilience management during large-scale epidemic outbreaks, Sci. Rep. (2018), https://doi.org/10.1038/s41598-018-19706-2.
[17] Y. Liao, B. Xu, J. Wang, X. Liu, A new method for assessing the risk of infectious disease outbreak, Sci. Rep. (2017), https://doi.org/10.1038/srep40084.
[18] A. Varma, M. Morbidelli, H. Wu, Parametric Sensitivity in Chemical Systems:, Cambridge University Press, Cambridge, 1999 https://doi.org/10.1017/CBO9780511721779.
[19] F. Strozzi, J.M. Zaldívar, A general method for assessing the thermal stability of batch chemical reactors by sensitivity calculation based on Lyapunov exponents, Chem. Eng. Sci. 49 (1994) 2681–2688, https://doi.org/10.1016/0009-2509(94)E0067-Z.
[20] Dipartimento della Protezione Civile, COVID-19 Monitoring Italy Database, 2020. https://github.com/pcm-dpc/COVID-19.
[21] H.W. Hethcote, Mathematics of infectious diseases, SIAM Rev., 2000, https://doi.org/10.1137/S0036144500371907.
[22] W.O. Kermack, A.G. McKendrick, A contribution to the mathematical theory of epidemics, Proc. R. Soc. London. Ser. A, Contain. Pap. a Math. Phys. Character. (1927), https://doi.org/10.1098/rspa.1927.0118.
[23] S. Zhao, H. Chen, Modeling the epidemic dynamics and control of COVID-19 outbreak in China, Quant. Biol. (2020), https://doi.org/10.1007/s40484-020-0199-0.
[24] S. Zimeras, M. Diomidous, Computer virus models - the susceptible infected removed (SIR) model, Stud. Health Technol. Inform. 251 (2018) 75–77.
[25] T. Hasegawa, K. Nemoto, Efficiency of prompt quarantine measures on a susceptible-infected-removed model in networks, Phys. Rev. E. (2017), https://doi.org/10.1103/PhysRevE.96.022311.
[26] K. Sasaki, COVID-19 Dynamics with SIR Model, 2020. https://www.lewuathe.com/covid-19-dynamics-with-sir-model.html.