Analysis: An intrinsic viral cycle

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The COVID-19 pandemic is one of the most significant events in modern human history. It is ongoing and any means that can be used to understand its dynamics is critical for mitigating its harmful effects. Most COVID-19 studies are justifiably biologically oriented. Nonetheless, given the wealth of data that are available, COVID-19 can also be studied from a mere signal processing perspective. Recent reports in the news have discussed a putative 2-month cycle in COVID-19 cases, which prompted us to conduct a rigorous time series analysis. Our analysis indeed finds strong evidence for cyclicity, but the period is more like 4 months and a long-term modulation of its amplitude is also present. These quantitative results imply that "waves" in pandemics are controlled by an intrinsic viral cycle and knowing this can be used to predict and prepare for them.

Time series analysis of COVID-19 cases

We conduct time series analysis on COVID-19 case data. Two datasets were used, the number of new COVID cases per million people in the United States of America (USA) and the World. USA was selected for their accuracy of case reporting as well as the high number of cases per million people as compared to other countries. The World dataset was selected to explore whether the observations made from one country were applicable to a majority of countries or not. The datasets starting from January 22, 2020 were downloaded from http://ourworldindata.org on October 10th, 2021, yielding a time series length of 626 days. Multiple standard time series analysis methods were used to confirm the results: the periodogram, the fast-Fourier transform (FFT), and the multi-taper method (MTM). Gaussian filters were used to characterize the cycles associated with spectral peaks with dominant spectral power. For the signals identified with notable amplitude modulation, their envelopes were also defined. All methods were conducted using freely available AnalySeries software[1]. In preparation for time series analysis, both datasets were detrended, the USA data with a simple linear regression and the World data with a degree-3 polynomial (Fig. 1B). After the linear detrend, the USA data has strong ~330 day (i.e., annual cycle) that was notch filtered in order to more accurately assess putative cycles with more repetitions.

Multiple cycles are present in the COVID-19 datasets. The highest frequency cycle identified is 7 days, i.e., weekly, where cases are lowest on Sunday and highest on Wednesday/Thursday. Presumably this is due to the efficacy of quarantine (on the weekend) for mitigating the spread of new cases, which occurs less often during the work week. Interestingly, the filtered weekly signals in both datasets exhibit systematic amplitude modulations that reflect the longest wavelength features in the datasets. For example, the envelope of the weekly World cycle is identical to its degree-3 polynomial trend. The dominant cycle in both the USA and the World has a ~4-month period (Fig. 1A, C). The 4-month cycles in both datasets exhibits amplitude modulations (Fig. 1A, C) that are similar to the degree-3 polynomial trend of the World data (Fig. 1B). Thus, the long-term modulation appears to control both the amplitudes of the high-frequency weekly cycle and the low-frequency 4-month cycle. Amplitude modulation implies that the long-term and short-term variations not only exist in the same system, but they are related to each other.

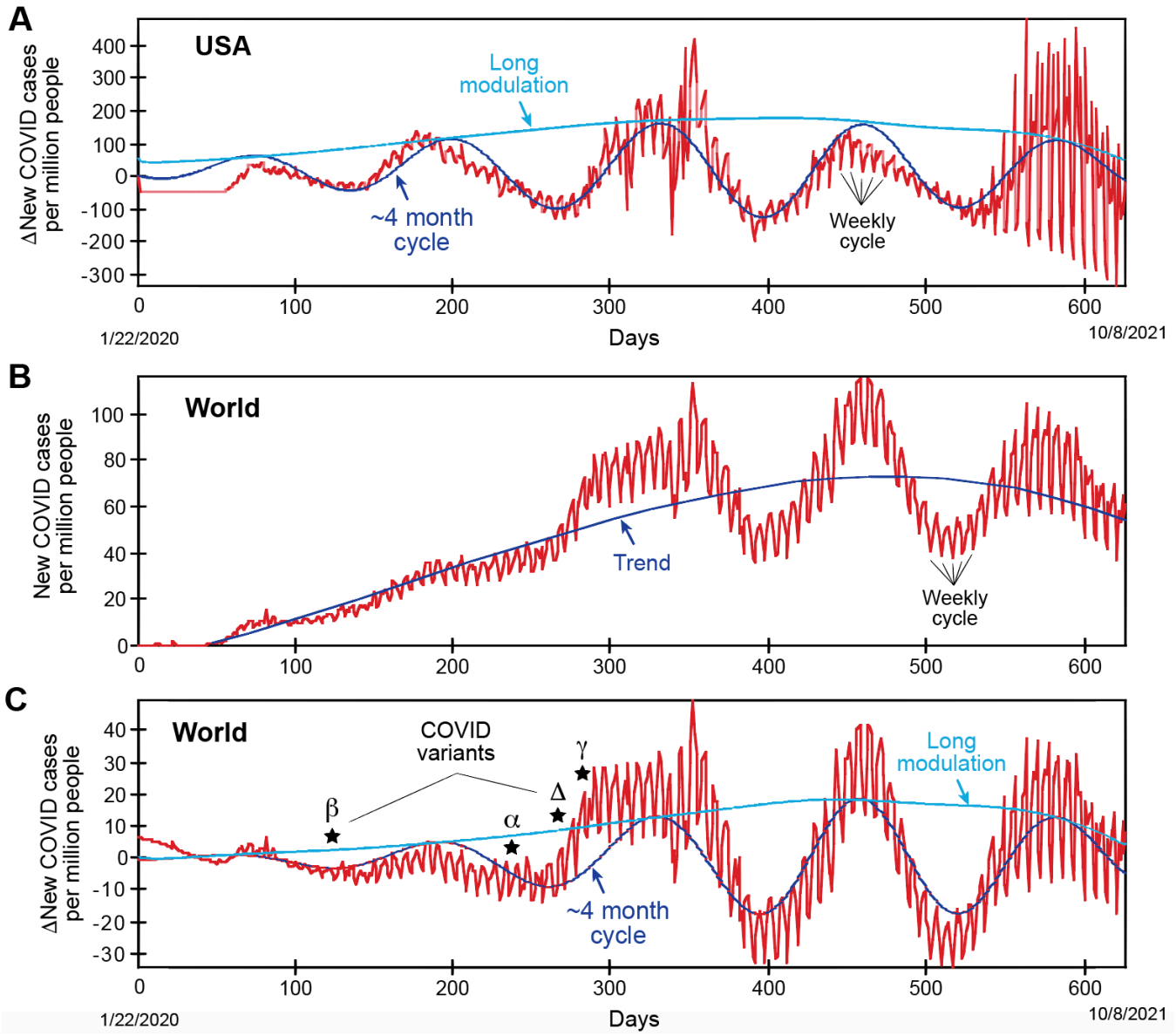

Figure 1. Cycles in COVID-19 cases (A) Detrended United States of America (USA) data. (B) Raw World data with long-term trend. (C) Detrended World data. COVID variant origination dates of α, β, γ, and Δ are indicated in (C). Three identical cycles are identified in both datasets: a long term modulation, a ~4-month cycle, and a weekly cycle.

Intrinsic pandemic cyclicity

A natural next question to ask is whether other pandemics also exhibited characteristic cyclicity. Unfortunately, datasets as complete as those of COVID-19 are not available. The Spanish Flu of 1918 (caused by an H1N1 influenza) is the most analogous to COVID-19 in terms of duration and lethality, although there are also many differences between the two pandemics[2]. Antibiotics and influenza vaccines, for example, were not available at that time and mitigation mainly relied on quarantine. One striking similarity between the two severe pandemics is that they are both characterized by multiple "waves". The Spanish Flu of 1918 spread in three waves over a one year period[3,4], thus 365 days ÷ 3 waves = 122 days ÷ 30.45 days/month = 4 months/wave, i.e., identical to the COVID-19 cycle. Furthermore, the amplitude of the three waves of the Spanish flu were also modulated by a longer cycle, with the second wave being in fact an order of magnitude higher in mortality than the waves before and after it[4].

Although "waves" of pandemics are common knowledge, the idea of an intrinsic viral cycle is new. In the wake of the Spanish Flu, Eichel[5] argued that the rise and fall of pandemic epochs over the last four centuries was shortening in recurrence intervals from 172, 95, 65, to 26 years. But a cyclic response to an individual virus is novel. The next natural question is why. There is no obvious human behavioral or environmental cycle that may explain the origin of the 4-month cycle. It is too long for the seasonal cycle, which has been discredited as a first-order control on cases[6]. The appearance of multiple COVID-19 variants may be related to the cycle. Plotting the dates for the earliest samples identified for the four variants (α, β, γ, and Δ; ordered for their designation as a virus of concern [VOC]) shows they all originated during phases of the 4-month cycle when cases were low (Fig. 1C), consistent with the notion that mutation takes place as an adaptive response to rising population immunity. Thus, variants appear to be a response to the cycle as opposed to a forcing for it.

Without a better explanation, we assume the presence of an intrinsic viral cycle. Although this is speculative, we argue that it is quite reasonable. Perhaps the most compelling argument is that the cycle appears to operate independently of containment measures taken. These measures have notably varied significantly (i) over time (from initially social distancing, masking, personal hygiene, travel restrictions, and curfews, to later vaccines and other pharmaceutical measures), (ii) from country to country, and (iii) within countries over time. The regular cyclicity observed in both datasets of a single country and all countries is thus hard to explain if such measures have any first-order control of the cyclicity. To be clear, such containment measures are likely *critical* for keeping the average number of cases down, even though they appear to have no control of the 4-month cycle.

Forecast

The systematic cycles identified here can be used to anticipate the natural fluctuations in viral pandemics. The high-frequency weekly cycle illustrates that the inherent social distancing and quarantine on weekends compared to work days should emphasize the importance of virtual meetings and working from home if possible. The long-term amplitude modulation of the 4-month cycle would appear to possibly indicate that the worst is over. However, two words of caution should be mentioned. First, although this may be the case globally, some countries like USA (with a linear increasing long-term trend) have not yet turned the corner. Second, the lesson of the Spanish Flu of 1918 is that two seasonal recurrences of the H1N1 influenza occurred during the three winters following the first year of three waves[4]; although these recurrences were less severe, they prolonged the pandemic considerably. It

remains to be seen whether containment measures, in light of the identification of the strong 4-month cycle, can be modified appropriately to mitigate the amplitude of the viral cycle.

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