A chemical engineer's take of COVID-19 epidemiology

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Abstract
SARS-CoV-2, a novel coronavirus spreading worldwide, was declared a pandemic by the World Health Organization 3 months after the outbreak. Termed as COVID-19, airborne or surface transmission occurs as droplets/aerosols and seems to be reduced by social distancing and wearing mask. Demographic and geo-temporal factors like population density, temperature, healthcare system efficiency index and lockdown stringency index also influence the COVID-19 epidemiological curve. In the present study, an attempt is made to relate these factors with curve characteristics (mean and variance) using the classical residence time distribution analysis. An analogy is drawn between the continuous stirred tank reactor and infection in a given country. The 435 days dataset for 15 countries, where the first wave of epidemic is almost ending, have been considered in this study. Using method of moments technique, dispersion coefficient has been calculated. Regression analysis has been conducted to relate parameters with the curve characteristics.

Keywords
COVID-19, dispersion coefficient, epidemiology, residence time distribution

1 | INTRODUCTION

The highly contagious coronavirus disease 19 (COVID-19), originated from China and is caused by the virus SARS-CoV-2, which is part of a family of coronaviruses that have in the past caused severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Since December 2019, COVID-19 has rapidly spread to over 200 countries worldwide, causing more than 40 million infections and 1 million deaths till November, 2020. Compared to SARS and MERS, the fatality rate of COVID-19 is lower, however as the disease is more infectious, the total number of fatalities is much higher. On March 11, COVID-19 was officially declared a pandemic by the WHO. Several models have been developed based on different approaches, with the initial attempts resulting more in confusion than clarity. Underreporting and inaccurate reporting of cases and deaths has made it difficult to fully understand the impact of the disease including ambiguity regarding spread, severity and duration of pandemic. Validity of models based on artificial intelligence has been questioned due to limitation of the training dataset. Forecasting day level data based on prior patterns has been attempted, although prediction of changes is not in its scope. Agent based models, depending on population movement, distancing and virus infectivity characteristics, have been difficult to simulate. Conventionally, differential equation models considering susceptible (S), infective (I), and recovered (R) fractions have been used for predicting pandemic dynamics. However, the efficiency of most of the SIR models developed to predict the impact was higher for short-term intervals in comparison to the long term. Modified versions of SIR models are the SEIR models, which also incorporate the exposed (E) population but demand more data for development. As a result, COVID-19 poses a distinctive difficulty in attempting to control the disease and limit the number of infections. Due to the lack of a vaccine and public health infrastructure designed to handle an outbreak of this magnitude, preventative measures have become necessary.

All over the world, governments, healthcare systems, and economic systems have implemented measures to slow the spread of the disease and minimize its impact. This includes, but is not limited to, enforcing lockdowns, closing borders, school and work closures, social distancing, increasing sanitation and hygiene, and using facemasks. As the stringency of these measures has varied by
country, the size of the outbreak has as well. A case study relating outbreak in China with government and individual action demonstrate different effect of these actions on daily cases.\textsuperscript{14} In countries such as the USA, Brazil, and India, governments have struggled with a coordinated, effective, and timely response to COVID-19, which have disproportionately affected vulnerable and economically challenged populations in these countries.\textsuperscript{15} Comparatively, the majority of Western European countries have managed to “flatten the curve,” reaching a plateau with the cumulative number of cases during the timeline considered for the analysis in this study.\textsuperscript{16} With so many components influencing the spread of COVID-19, looking at the effect of various factors on the trajectory of the outbreak can provide an insight into how the spread of the disease can be slowed down.

This article attempts to examine patterns in COVID-19 data, demographic factors, lockdown stringency, and country characteristics using residence time distribution (RTD) analysis. RTD is a theoretical modeling technique used to predict the distribution of residence times, typically in continuous flow systems. With applications in many biomedical sciences, RTD is most often used to analyze industrial units such as chemical reactors, fluidized beds, flotation cells, and mixers.\textsuperscript{17,18} One key application of RTD is in chemical engineering, where the technique is used to analyze the residence times of particles in chemical reactors. However, we demonstrate that the RTD concept can be applied toward examining the epidemiological data related to COVID-19 and new insights can be acquired.

2 | RESIDENCE TIME DISTRIBUTION (RTD)

The residence time theory deals with the particles that enter, flow and leave the system. There are situations when the reactor fluid is

![FIGURE 1](https://www.worldometers.info/coronavirus/#countries)

**FIGURE 1** Total number of infected cases and deaths for the countries considered in the study.
Source: https://www.worldometers.info/coronavirus/#countries [Color figure can be viewed at wileyonlinelibrary.com]

![FIGURE 2](https://www.worldometers.info/coronavirus/#countries)

**FIGURE 2** Illustration depicting the analogy of the present study with the residence time distribution analysis [Color figure can be viewed at wileyonlinelibrary.com]

![FIGURE 3](https://www.worldometers.info/coronavirus/#countries)

**FIGURE 3** Effect of dispersion on output concentration of tracer for different extents of back mixing (Source: Levenspiel, O., Chemical Reaction Engineering\textsuperscript{23}). Similar profiles are seen in COVID-19 daily cases trends for different countries. Also, tracer response for tank in series system follows same behavior

Curve characteristics
- Mean depicts the average time the coronavirus stayed in a particular country
- Variance tells us the degree of spread of distribution. The more the variance, the more the spread of disease.
- Method of moment relates Variance, Peclet number and Dispersion coefficient.
\[
\sigma^2 = \frac{2}{Pe} - \frac{2}{Pe^2} (1 - e^{-Pe}) \; ; \; Pe \propto \frac{1}{D}
\]
- Peclet number quantifies the flow of virus in the society (direct infection and person to person infection transmission)
- Dispersion coefficient measures the spread of the distribution around the mean value.

![FIGURE 4](https://www.worldometers.info/coronavirus/#countries)

**FIGURE 4** Illustration depicting the analogy of the present study with the residence time distribution analysis [Color figure can be viewed at wileyonlinelibrary.com]
neither perfectly mixed nor perfectly in plug flow. In such cases, RTD analysis helps in estimating the time the fluid has spent inside the reactor. Two model approaches, viz., one parameter approach and two parameter approach, are used commonly for simulating non ideal reactors. In this article, one parameter approach has been considered to deal with tank in series and axial dispersion model. RTD has been determined using the tracer injected in the reactor at time \( t = 0 \) in the form of pulse. It is assumed that the age of the particles while entering the system is zero and while leaving the system is equal to the residence time.\(^{19-21} \)

If the path of a particle is traced using a tracer with concentration, \( c(t) \), then the tracer amount, \( \Delta N \), leaving the reactor between time \( t \) and \( t + \Delta t \) is \( c(t) \nu \Delta t \); \( \nu \) is effluent volumetric flow rate.\(^{22} \)

For pulse injecting, the RTD function, \( E(t) \), is defined as

\[
E(t) = \frac{\nu c(t)}{N_0}
\]

On integrating the outlet concentration, \( N_0 \) can be obtained

\[
N_0 = \int_0^\infty \nu c(t) dt 
\]

For constant \( \nu \), the RTD then becomes,

\[
E(t) = \frac{c(t)}{\int_0^\infty c(t) dt}
\]

The base properties of the distribution function are defined by its moments. It is common to compare RTD using moments instead of full distribution. For order \( r \), the general moment is defined as Equation (4). The zeroth moment, \( r = 0 \), depicts the area under the distribution function. The first moment, \( r = 1 \), tells the centroid position indicating the mean or the expectation of residence time

\[
M_r = \int_0^\infty t^r E(t) dt
\]
The physical meaning of the mean is related to the volume/mass of the system per volumetric/mass outflow rate. Higher order moments are used to find out the experimental errors and for parameter estimation of the distribution function. Second moment \( r^{2} = \sigma^{2} \) gives the variance of the distribution \( \sigma^{2} \) and is usually calculated around the mean value that is, central moment. In order to compare residence time distributions for the different system, the dimensionless form, \( \sigma^{2} \), is used which is given as:

\[
\sigma^{2} = \frac{\sigma^{2}}{t^{2}}
\]

Method of moments technique is applied to determine the dispersion coefficients. For any closed system, the relation between the tracer concentration and the model parameter can be obtained by solving unsteady state mass balance Equation (5).

\[
D \frac{\partial^{2} c}{\partial x^{2}} - \frac{\partial (Uc)}{\partial z} = \frac{\partial c}{\partial t}
\]

where \( D \) is dispersion coefficient, \( c \) is tracer concentration, and \( U \) is superficial velocity.

For pulse input, Equation (5) is converted into dimensionless form to obtain

\[
\frac{1}{Pe} \frac{\partial^{2} \phi}{\partial \lambda^{2}} - \frac{\partial (\phi U)}{\partial \theta} = \frac{\partial \phi}{\partial \theta}
\]

where, \( \phi = \frac{c}{c_{0}}; \dot{\lambda} = \frac{L}{U} \)

Applying Danckwerts boundary conditions at \( \lambda = 0 \) and \( \lambda = 1 \), then solving numerically for mean residence time, \( t_{m} \) and \( \sigma^{2} \) can be estimated as shown in Equation (7)

\[
\sigma^{2} = \frac{\sigma^{2}}{t^{2}} = \frac{2}{Pe} \frac{2}{Pe^{2}} (1 - e^{-Pe})
\]

\[
Pe = \frac{UL}{D}
\]

The physical meaning of the mean is related to the volume/mass of the system per volumetric/mass outflow rate. Higher order moments are used to find out the experimental errors and for parameter estimation of the distribution function. Second moment \( (r = 2) \) gives the variance of the distribution \( (\sigma^{2}) \) and is usually calculated around the mean value that is, central moment. In order to compare residence time distributions for the different system, the dimensionless form, \( \sigma^{2} \), is used which is given as: \( \sigma^{2} = \frac{\sigma^{2}}{t^{2}} \). Method of moments technique is applied to determine the dispersion coefficients. For any closed system, the relation between the tracer concentration and the model parameter can be obtained by solving unsteady state mass balance Equation (5).

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where, \( u = \frac{L}{t_m} \), \( u \) is mean velocity of particle (m/s), \( L \) is length of fluidized bed (m), and \( t_m \) is mean time.

### 3 RTD ANALOGY WITH COVID-19 PANDEMIC

In the present study, the countries (Figure 1) beating the coronavirus disease 2019 (COVID-19) were considered. The countries are selected based on the fact that the number of daily cases is less than one tenth of maximum value. Analogy is drawn with RTD analysis as shown in Figure 2. Here, we consider the country as a reactor system where in virus, a tracer, is inserted into the system as a pulse with the number of people entering the country for the time till strict lockdown in implemented barring the international travel and strict self-isolation of people traveling from outside. Thus, it is assumed that the virus enters the system once during analysis. The curve becomes skewed with increase in dispersion representing the back mixing in a reactor as shown in Figure 3. For the COVID-19 spread, the spread of virus can be compared to the combination of tank in series, which is equivalent to a non-ideal plug flow reactor. In addition, it is assumed that the activity and behavior of the coronavirus is not known. The outflow from the system is the number of cases daily, indicating virus spread. Figure 4 shows the daily new cases with a 7-day average for different countries. Discrete data for 435 days (January 22, 2020 to March 31, 2021) are taken into consideration.

The trend for the countries as shown in Figure 4 seems to be Gaussian that is, bell-shaped curves with different means (first moment) and variances (second moment). For normalization, the exit age distribution curves, \( E \) curve, is obtained for all the countries (Figure 5). Then the mean, variance, Peclet number, and dispersion coefficient were calculated as listed in Table 1. The mean depicts the average time the coronavirus stayed in a particular country. Variance tells us the degree of spread of distribution. The more the variance, the more the spread of disease. Apart from these, Skewness and Kurtosis indices were also calculated. These values were indicated shift in the peak toward left or right and the presence of tail in the curve, respectively. The values were in line with curve profile. This can also be observed from visual inspection. Thus, here only first (mean) and second moment (variance) were considered. Peclet number quantifies the flow of virus in the society (direct infection and person to person infection transmission) and dispersion coefficient measures the spread of the distribution around the mean value. During calculations, \( u \) was taken as rate of cases with respect to time infection stayed in the country and \( L \) was taken as total number of infected persons.

Once the characteristic parameters (mean and median) are determined, their correlation with the factors like population, population density, and its demographic characteristics (median population age, population infected [%], infected by gender), environmental factors (Average annual temperature (°C); Average humidity (%); Average total annual rainfall (mm); Average annual wind speed (mph); Average annual Air Quality Index (AQI); PM2.5 Conc. (\( \mu g/m^3 \))), and government policies quantified using containment health index, total tests, test per million, and lockdown stringency index can be examined. For data sources, refer to Table S1 and for data refer to Tables S2–S4. For performing regression, partial least square method...
is adopted. Partial least square regression technique generalizes multilinear regression and principal component analysis wherein it reduces the number of predictors to uncorrelated components and perform regression. This technique is useful in cases when data is highly collinear and number of observations are less than predictors. The X (predictors) and Y variables are mention in Table 2.

The main objective of PLS is to explain X space, Y space and the greatest relation between the two. For the present study, PLS is performed using the JMP software. The prediction formula obtained for mean and variance are given by Equations (7) and (10).

\[ y_1 = 264.73163 + 59.26697 \times 10^{-14} x_1 - 4.80847 x_2 \\
+ 1.9651 x_3 - 1.03225 x_4 + 1.032254 e^{-2} x_5 - 5.6080078 x_6 \\
- 4.7682615 e^{-3} x_7 + 1.603318 e^{-9} x_8 - 2.25189382 e^{-7} x_9 \\
+ 7.1562 e^{-3} x_{10} - 2.19540 e^{-2} x_{11} + 2.49587 e^{-2} x_{12} \\
+ 2.40139 e^{-4} x_{13} - 0.14032033 x_{14} - 3.01809 e^{-3} x_{15} \\
+ 9.1029 e^{-2} x_{16} \]  

(9)

\[ y_2 = 18903.738728414 + 3554.7815 (-5.75194 e^{-9} x_1 \\
+ 7.498057 e^{-6} x_2 + 2.19167 e^{-7} x_3 - 0.055827 x_4 + 0.0558271 x_5 \\
+ 0.220175 x_6 - 0.172117 x_7 + 13.703774761 e^{-10} x_8 \\
+ 3.036815 e^{-6} x_9 - 0.2695 x_{10} - 0.022033 x_{11} - 0.0016909 x_{12} \\
+ 0.000338473 x_{13} + 0.085650 x_{14} + 0.00142608 x_{15} \\
- 0.00295370 x_{16}) \]

(10)

Figure 6 shows the prediction efficiency for mean and variance. Normalized root mean square value (NRMSE) of 0.7481, normalized over standard deviation, is obtained for mean whereas NRMSE of 0.4724 is obtained for variance. Residual by predicted plot was obtained by plotting individual residual values with respect to the predicted value. The residuals are randomly distributed around zero line with no specific pattern indicating that they are independent of one another. Leverage plots were used to understand the effect of individual parameters assuming that other parameters are accounted in model already. To monitor the statistical interactions between the parameters, prediction profiler was used (Box 1).

4 | PERSPECTIVE

Mathematical modeling has played a key role in shaping the policies and responses of many countries during the COVID-19 pandemic. This was observed during the strategy shift in UK’s response to the pandemic from an earlier herd-immunity based response to the current approach, which implements stringent movement controls and social distancing measures. This change was the result of a model by Ferguson et al. which projected 500,000 deaths if the herd immunity approach continued. A similar change was also implemented in the US when another model projected 2.2 million deaths without action. The success observed in countries can be attributed to implementing a wide range of different statistical modeling-based policies. Most countries in our analysis formulated policies, which included a combination of measures such as border controls, schools, or university closures, lockdowns and movement controls including restrictions on public and social gatherings and stay-home measures. In particular, two notable strategies that largely helped mitigate the pandemic spread were the proactive approach taken by Denmark and the high testing and contact tracing approach implemented by South Korea. It is also of note that Djibouti managed to control the spread despite being the only lower-middle income country in our analysis, largely due to its response plan being aligned with WHO’s four pillars (testing, isolating, early case management, and contact tracing). To summarize, the key common factors leading to mitigation in the pandemic spread were proactiveness in implementing model-based data-driven decisions in policymaking and effective communication and trust between the governments and the public. We believe that the presented regression analysis-based approach can be used to predict the curve characteristics for different country. This will help us to estimate the level of the pandemic and plan for the suitable strategies to avoid the spread.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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