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SARS-CoV-2 mutational cascades and the risk of hyper-exponential growth

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A B S T R A C T

The emergence of novel SARS-CoV-2 variants of concern (VOC), in late 2020, with selective transmission advantage and partial immunity escape potential, has been driving further evolution in the pandemic. The timing of mutational evolution and its limits are thus of paramount importance in preparedness planning. Here, we present a model predicting the pattern of epidemic growth including the emergence of variants through mutation. It is based on the SEIR (Susceptible, Exposed, Infected, Removed) model, but its equations are modified according to the transmission parameters of novel variants. Since more transmissible strains will drive a further increase in the number of cases, they will also lead to further novel mutations. As one cannot predict whether there is a viral mutational evolutionary limit, we model a cascade that could lead to hyper-exponential growth (HEG) involving the emergence of even more transmissible mutants that could overwhelm any systematic response. Our results are consistent with the timing, since the beginning of the pandemic, of the concurrent and independent emergence of the VOCs. The current dominance of the Delta variant and the need for additional public health measures indicates some of the risks of a possible HEG. We examine conditions that favor the expected appearance of similar variants, thus enabling better preparedness and more targeted research.

1. Introduction

The SARS-CoV-2 pandemic entered a novel phase in 2021 with the gradual dominance of the variants of concern (VOC). Since, apart from theoretical projections, there is no blueprint about the ways a coronavirus pandemic will evolve (in space, time, and number of cases), and since we cannot ascertain whether there is a limit in the viral transmission, virulence, and immune escape potential, public authorities need to evaluate a range of possible trajectories in order to preemptively design public health response measures.

VOCs are defined as variants that possess important novel characteristics in terms of high virulence, transmission potential, reproduction number (R0), ability to infect previously low-risk groups like children, and resistance to the neutralizing effect of both serum from convalescent individuals and antibodies emerging post vaccination. As of August 2021, the World Health Organization has defined four SARS-CoV-2 variants as VOCs. Variant Alpha (PANGO lineage B.1.1.7/, formerly also known as 501Y.V1) was first isolated in the United Kingdom and exhibits markedly higher transmission potential as well as increased virulence. Variant Beta (PANGO lineage B.1.351/, formerly also known as 501Y.V2) was first isolated in patients from South Africa and is the most potent escape variant, reducing severalfold convalescent and vaccinated sera neutralizing potential. Gamma variant (PANGO lineage P.1/, formerly also known as 501Y.V3) was first isolated in patients originating from Brazil and possesses marked immunity resistance. Both Beta and Gamma exhibit moderately higher transmissibility. These three variants emerged independently but possess a common mutation, N501Y, conferring stronger adherence of the viral receptor binding domain (RBD) to host receptors. The fourth VOC, Delta variant (PANGO lineage B.1.617.2), does not possess such a mutation. Delta was first isolated in India and rapidly spread to dominance; it is characterized by a major increase in transmissibility (that could be attributed to the P681R mutation, neighboring the furin cleavage site and thus potentially inducing rapid cleavage) and possibly partial immune escape and vaccine breakthrough [1–4] (Fig. 1). Other variants under surveillance are termed Variants of Interest.

It is well known that coronaviruses exhibit a lower mutation rate than other major viral pathogens, such as Influenza A. It has recently been demonstrated that coronavirus 229E, a cause of the common cold, needs roughly a decade in order to achieve adequate therapeutic escape...
which has spawned in turn several successful variants with a higher reproductive number \( R_0^{(1)} \). This is the current evolution of the pandemic. Future developments (to the right of the red broken line) could include the emergence of more variants (‘X’, ‘Y’ etc.), with even greater reproductive numbers \( R_0^{(2)}, R_0^{(3)} \) etc.

There are three types of outcome. If the probability of a successful mutation is very small \((p < 10^{-6})\), there is a strong cascade of more variants (\( R_0^{(1)} \)); this is the case when the virus becomes less infectious. In the second case, \( p \) is so large \((p > 10^{-3})\), there is a strong cascade effect, leading to a hyper-exponential growth pattern, with an increasing exponent. This is seen in the growth of the SARS-CoV-2 during the pandemic. In the third case, \( p \) is of intermediate value, which implies sequential accelerations and hyper-exponential growth, with even greater reproductive numbers \( R_0^{(2)}, R_0^{(3)} \) etc.

The distribution of times for the first emergence of an order-\( k \) variant, estimated using a Monte-Carlo approach, is shown in Fig. 3. This figure is based on the results of 10,000 runs of the model. In general, order 1–3 variants always emerge, but order-4 variants have a low probability of developing because the epidemic burns out. The observed times of emergence of the first four VOCs fall within the pattern of order-2 emergence times. However, emergence of the variant of interest D614G was rare compared with the average time of 217 days for order-1 variants in the model.

### 3. Discussion

Since SARS-CoV-2 is constantly evolving, as evidenced by the continuing emergence of novel variants, the future dynamics of the pandemic remain uncertain. This uncertainty is accentuated by the increasing but unevenly distributed vaccination coverage and by vaccine resistance. It is not clear how the virulence of SARS-CoV-2 will evolve. The prevailing dogma for most of the 20th century was that disease organisms would always evolve toward benign coexistence with their hosts [15]. This view dominated both the academic [16] and popular literature [17] and so it is often argued that SARS-CoV-2 will follow a trajectory of diminishing virulence. However, as argued by Ewald 2004 [15] and as shown by the variants of SARS-CoV-2, this need not be the case. From the original variant to the currently advancing Delta variant, there has been a notable decline in the relative fatality rate. However, infectiousness has been increasing. For example,
according to Ref. [18], the Alpha, Beta and Gamma variants are up to 50% more transmissible than the original (Wuhan), while the Delta variant may be twice as transmissible. Thus, through the course of the pandemic, a prevailing feature is the growth of transmission coefficient in the variants, as expected from our analysis. With the rise of the percentage of vaccinated humans, we expect the virus to shift its evolutionary preferences towards escape mutations. A major unanswered question is whether there is a limit in viral fitness [19].

The probability of a successful mutation, \( p \), is crucial because it determines which of the possible outcomes (no change in the system, cascade effect or a few dominant variants) will happen. For a mutational cascade to develop, a probability greater than \( 10^{-5} \) per infected person is required. Such large values seem unlikely for SARS-CoV-2. A more likely outcome is that a single mutation increases the \( R_0 \) but without developing into a cascade of increasing \( R_0 \). This happens because there is enough time for the first variant to infect most of the susceptible population but not enough time for the faster strains to reach high numbers and spawn further successful new strains. The new strain D614G that went on to replace the original Wuhan variant globally was first identified in February 2020 [20], when the total cumulative number of infected individuals was below 100,000; this would be consistent with a value of \( p > 10^{-5} \), i.e., the value that we used.

The COVID-19 pandemic represents an inadvertent experiment involving viral infection and mutation. Similar dynamics would not have been seen in other pandemics either because their expansion happened prior to the age of scientific observation or because they have
been limited in their expansion (SARS-CoV-1). Interestingly, all the previously recognized RNA viral epidemic diseases with higher $R_0$ concern viruses with smaller genomes than SARS-CoV-2. As SARS-CoV-2 has been established in the human population, in contrast to SARS-CoV-1 and MERS, the question then arises whether the accumulation of mutations associated with its larger genome might confer a greater potential for infectiousness compared to previous RNA viral diseases. Selection on the basis of growth rate alone can happen in the expansion phase of any invasive organism; this type of selection may be very different to that in an established population. For example, in the expansion of the cane toad (*Rhinella marina*), individuals tend to have longer legs on the invasion front [21], but once the population is established, short legs return [22]. Likewise, once the “frontier” closes for SARS-CoV-2, its evolution may join the more familiar pattern in other epidemics, optimizing for long-term coexistence with its hosts.

Hyper-exponential growth, which can be understood as an accelerating exponential curve, is of interest for a number of reasons. In addition to the current concern, HEG does not arise in most biological systems but in systems involving some sort of innovation and adaptation [23]. In contrast to exponential-type processes, such explosions reach a population singularity in finite time [11, 23]. This model follows, as a single pair of differential equations, from the modified SEIR or related SIR (Susceptible, Infected, Removed) system, if mutation is included.

Our model is by necessity a simple one. We have not included spatial effects in it, nor the effects of age structure in the human population. These factors that need to be incorporated when considering the worrying possibilities of uneven lockdown or non-homogenous vaccine coverage that might allow intense localized viral circulation. Our model of evolution is simplified and linear: while we consider different values for mutation probability, in any simulation, the probability of successful mutation (per infected person) is constant. We have assumed that mutations of viral traits are all independent, although, in reality, they may include trade-offs. We further have not considered the potential future effects of non-linear, epistatic mutations, as well as the effect of multiple sequential nucleotide mutations. In presenting our model, we have focused on the basic patterns we are likely to see when successful mutations arise in an expanding pandemic.

Following the emergence of D614G from the original Wuhan variant in February, the arrival of the three VOCs that emerged in late 2020 may be seen as the evolution of order-2 variants from an order-1 variant. Assuming there is no maximal viral advantage embodied in that configuration, our model predicts the timing of emergence of even more problematic higher-order variants (Fig. 3). This does not take into account the increased infectiousness of Delta variant, which also seems to be order-2, since Delta essentially appeared in late 2020 but was slower in its eventual successful introduction and dominance. In all runs of this model, large numbers of new strains emerged. The probability that the events will unfold similarly to Fig. 2b is hard to predict because these depend on factors not included in the model, such as spatial configuration and human responses. Our findings underline the need to minimize inhomogeneous vaccine coverage, since failure to do so along with other factors, like “social distancing fatigue” [14] and vaccination resistance, could contribute to pandemic resurgence and the possibility of HEG developing.

### 4. Materials and methods

Several authors have modeled the current pandemic in various places by a system of SEIR equations [13, 14]. We use this model without age or spatial structure. We assume individuals who get infected spend on average $D = 14$ days upon becoming infectious before death or recovery [13,14], although the actual infectious period may be far shorter. In 2020, the global pandemic increased from a weekly average of 26 cases day$^{-1}$ (20th January) to one of 579,000 day$^{-1}$ (5th December), equivalent to an exponential growth rate of 0.031 day$^{-1}$, which we take as the basic growth rate. With each new infection, there is a fixed probability of a mutation causing a significantly higher growth rate (Fig. 2a). Such successful mutations happen according to a Poisson process, with fixed rate per infected person. We assume that this enters through the transmission parameter $\beta$ in the equations, so that only the growth rate is affected. A virus with a transmission parameter $\beta_0$ evolves into one with a parameter $\beta_0 + \Delta \beta$ and an associated reproductive number $R_0^{(1)}$ (order-1). Further successful mutations (order-2, order-3, etc.), with transmission rates $\beta_0 + 2\Delta \beta$, $\beta_0 + 3\Delta \beta$, and so on, lead to still higher reproductive numbers $R_0^{(2)}$, $R_0^{(3)}$…, respectively. This is typical for RNA viruses that are causative agents of major diseases throughout human history and which are transmitted via respiratory droplets or aerosols, including the measles virus with a $R_0$ about 12–18, mumps ($R_0 \approx 10–12$) and rubella ($R_0 \approx 6–7$) [24]. We assume a limit for $R_0$ to be 20, close to the highest known $R_0$ (measles) for such viruses. We can associate these additive increments with successively adapting traits (spike protein, infectious period [25]), heat resistance, etc). Our model follows each new strain that emerges from a significant mutation. We ignore strains that mutate to the same or lower $R_0$. We do not include in the model complex mutations like blooms or super-spreaders variants, and we do not make specific provisions for immuno-compromised populations that may harbor viral persistence, potentially initiating a novel variant.

In order to obtain results from our model, via simulation, we set up a series of difference equations to approximate the differential equations and solved it recursively, using the Euler method, following the standard approach [13, 14]. Model time covers two years beginning with the start of the pandemic. We used the parameters above. In simulations, we kept track of all state variables for each of the strains created representing populations of cases for each of the strains in the pandemic. The only random element is the time of emergence of each new mutation. All calculations were performed in R [26].

#### 4.1. Simulation model: the SEIR with evolving transmission rate

We begin with the standard SEIR model for a single strain [24] that contains equations for the number of susceptible people ($S$), the infected hosts ($I_0$) and the number recovered or dead ($R$), plus an equation for the number of pre-infectious people ($E_0$), so we have:

$$
\begin{align*}
\frac{dS}{dt} &= -\beta SI \\
\frac{dE_0}{dt} &= +\beta SI - fE_0 \\
\frac{dI_0}{dt} &= +fE_0 - \gamma I_0 \\
\frac{dR}{dt} &= +\gamma I_0 
\end{align*}
$$

Here, $f = 1/D'$, where $D'$ is the latency period, $\beta$ is the per capita transmission rate and $\gamma$ is the recovery rate. In Eq. (1), the infected stages have a subscript ‘$0$’ because they refer to the original strain. There may be several strains but the susceptible and recovered/removed subpopulations are common to all strains.

In our model, each subsequent strain, $k$, has its own subpopulation of pre-infectious and infectious individuals ($E_k$ and $I_k$, respectively). Thus, if the total number of strains is $K+1$, we have $K+1$ pre-infectious ($E_0, E_1, E_2, \ldots, E_K$) and K+1 infectious ($I_0, I_1, I_2, \ldots, I_K$) subpopulations. Thus, we now have $2K + 4$ equations in the system:
\[
\frac{dS}{dt} = -S \sum_{k=0}^{K} \beta_k I_k
\]
\[
\frac{dE_k}{dt} = +S \beta_k I_k - f E_k + \delta_k \text{ for } k = 0, 1, 2, \ldots, K
\]
\[
\frac{dI_k}{dt} = +f E_k - \gamma I_k \text{ for } k = 0, 1, 2, \ldots, K
\]
\[
\frac{dR}{dt} = +\gamma \sum_{k=0}^{K} I_k
\]

We assume that the latency time and the recovery rate are the same for all \(K+1\) variants, but the transmission coefficient is assumed to change for each strain. This system of equations is solved by the Euler method using a time step of \(\Delta t\).

The term \(\delta_k\) is a random variable associated with the creation of strain \(k\) from strain \(k-1\). For a system with strains 0, 1, 2, \ldots, \(K\) already in circulation, the creation of the new strain “\(k\)” proceeds as follows: For each host-pathogen interaction, we assume a probability \(p\) of a successful mutation establishing a new strain. There are \(\beta_k I_k(\delta_k)\) such interactions in the time step of length \(\Delta t\), based on Eq. (1). Thus, for a successful new mutation (one for which the infectiousness is at least as great as \(\beta_k\)), there is a large number of successful or neutral mutations independent of each other and each leading to the same increase in \(I_k\), i.e., \(\Delta I = \beta_k \Delta \beta\).

Suppose \(\Delta \beta = 0.9\beta_0\) and four variants existing, variant-0 with transmission coefficient \(\beta_0\) and three others, variant-1, variant-2 and variant-3, each with transmission coefficient \(1.9\beta_0\). If a mutation happens in variant-0, the result is the creation of a new strain, variant-4, again with \(1.9\beta_0\). If, however, the mutation happens in one of the other strains, we have a new strain with transmission coefficient \(\beta_4 = 2.8\beta_0\).

We assume that an important mutation, one that increases transmission rate by at least \(\Delta \beta\), has a probability \(p\), which is typically very small for an individual. For such a mutation to happen somewhere in the population, when \(R\) individuals have had the disease after a time \(\Delta t\), then \(pR\) should have reached at least unity. \(R\) is found by integrating Eq. (1d) for a variant that initially grows exponentially from a single infection:

\[
R(t) = \int_0^t I(t) \, dt = \frac{e^{\gamma t} - 1}{\lambda} \approx \frac{t}{\lambda} \text{ for small } t
\]

Using the requirement that \(R(t) = 1/p\), we can invert this to get the time-interval for the appearance of the new variant,

\[
t_1 = \frac{1}{\lambda} \ln[D \alpha / p]
\]

Thus, if \(D = 14\) days, and we assume a doubling time of 3 weeks (\(\lambda = 0.031\)), using these numbers in Eq. (5), we get the first successful mutation appearing after \(t_1 = 270\) days if \(p = 10^{-4}\), or after \(t_1 = 493\) days if \(p = 10^{-5}\). Subsequent variants of the same order will occur more quickly because of the higher abundance, given the exponential growth (see Fig. 2b). However, the time for these new strains to reach sufficient abundance and start generating their own mutations may be substantial. For achieving parity with an exponentially growing variant of initial abundance \(I_0\), the new mutant with \(\Delta \lambda\) greater growth rate still needs time:

\[
t_1 = \frac{\ln(I_0(t_1))}{\Delta \lambda}
\]

For example, the D614G variant, appearing around 20\(^{th}\) February 2020 (very early, according to Eq. (5)), took three months to attain dominance over the D614C form [20]. If we use a figure of 52,000 (the sum of new cases over the previous 14 days) as an estimate of the number of infected people \(I(t)\), then a difference of \(\Delta \lambda = 0.12\) per day would bring about parity within 90 days.

4.2. The differential equations of hyper-exponential growth

The SIR equations, based on a simpler model that assumes that the latency period is small, may be written as follows [27]:

\[
\frac{dI}{dt} = -\beta SI
\]
\[
\frac{dI}{dt} = +\beta SI - \gamma I
\]
\[
\frac{dR}{dt} = +\gamma I
\]

In the earliest stages of the epidemic, the number of infections is small relative to the total population, so \(S \approx N\). We can then solve Eq. (7b) by solving the equation \(dI/dt=(\beta N-I)I = \lambda I\). Since \(\lambda\) is constant, the solution of this is exponential growth with rate \(\lambda\). Note that, in the SIR model, \(\lambda\) is related to the reproductive number by \(k=(R_0-1)/\gamma\).

We assume that the per capita transmission coefficient, \(\beta\), can be altered by successful mutations. If these are plentiful, we assume that there is a large number of successful or neutral mutations independent of each other and each leading to the same increase in \(\beta\) and, correspondingly, in growth rate, \(\lambda\). We refer to the incremental increase in \(\lambda\) as \(\Delta \lambda\). If the number of people who have had the disease is \(R\), using Eq. (7c) and the fact that the probability of a successful mutation is \(p\), then the change in the number of successful mutations is proportional to \(R\), i.e., \(\Delta \lambda \propto \Delta R\), so we can submit this into the third equation to get:

\[
\frac{dI}{dt} = \lambda(t)I(t)
\]
\[
\frac{dI}{dt} = \rho I(t)
\]

where the constant \(\rho \propto p/D\).

Author contributions

John Halley: Conceptualization, Formal analysis, Visualization, Writing-Original draft preparation, Writing-Reviewing and Editing; Despoina Vokou: Investigation; Writing-Reviewing and Editing; Georgios Pappas: Investigation, Visualization, Writing-Original draft preparation, Writing-Reviewing and Editing; Ioannis Sainis: Investigation, Writing-Reviewing and Editing

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.

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Appendix A. Supplementary data

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