CATALYSIS RESEARCH

Review Article

Gibbs Free Energy and Epidemic Models: A Framework for Control Strategies

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ABSTRACT

This work introduces a novel thermodynamic framework for epidemic modeling by establishing a direct relationship between the effective reproductive number R_t and the Gibbs free energy, $\Delta G = -E ln(R_t)$. We explore how epidemic transitions can be interpreted as phase transitions, drawing a formal analogy with spontaneous and catalyzed chemical reactions. Building on the analytical structure of SIR and SEIR models, we estimate (R_t) for SARS-CoV-2 using confirmed case data from a regional health authority, applying both the serial interval distribution (log-normal) and an alternative linear regression approach based on doubling time. This thermodynamic perspective provides a deeper physical interpretation of epidemic dynamics and opens new avenues for predicting and controlling community transmission.

Keywords: Deterministic Compartmental Models, Dynamics of Social Systems, Collective Phenomena, Spontaneous and Catalytic Chemical Reactions, Data Analysis, Thermodynamics

INTRODUCTION

As is well known, dynamical systems have broad applicability in describing collective phenomena in physical systems, biological processes, and social dynamics [1-8], and within this branch of mathematics are deterministic models and the study of the dynamics of infectious diseases [9-12]. In this context, the simplest systems of differential equations that can describe the transmission dynamics of a virus within a community are the SIR (Susceptible, Infected, Recovered) and SEIR (Susceptible, Exposed, Infected, Recovered) models, along with their variations [13-26]. Within this study of transmission dynamics, the concept of the reproductive number (basic/effective) naturally arises as a measure of transmissibility, making it a crucial quantity for understanding the spread. Several methods have been developed to estimate the average number of

secondary cases caused by a single infected individual during their infectious period over the course of an epidemic (R_t), and some of these tools deserve our attention [27-29].

The average time it takes for an infecting individual (primary case) to transmit the infection to a secondary case, expressed in terms of a distribution, can be used to calculate the effective or instantaneous reproductive number R_t. This distribution is built from data collected by health agents through interviews conducted at the onset and during the course of the outbreak. It informs us about the speed of cycles in the transmission chain and is generally approximated (proxy) by the serial interval [30]. The serial interval is defined as the duration between the onset of symptoms in a primary case (infector) and the onset of symptoms in a secondary case (infected). Finally, as an alternative yet complementary approach, we can also obtain R_t using local behavior involving exponential growth, linear interpolation, and the relationship between the reproductive number (basic/instantaneous) and the doubling time [31,32].

The theoretical foundations involving the reproductive number and its relationship with reality—considering that many key characteristics of disease transmission cannot be directly observed—are currently an active area of research [33]. Thus, our goal is to present in a solid manner the concepts involving this elusive number R and how understanding it from different perspectives leads to a deeper view of the study of virus transmission dynamics in a community.

Thermodynamic and physical approaches to complex systems have been extensively explored in the literature, particularly in the context of epidemics and pandemics [34,35]. By analyzing the SIR model as a chemical reaction involving both spontaneous and catalytic processes, and applying the law of mass action, it is possible to establish a relationship between the Gibbs free energy and the chemical equilibrium constant. In this article, we propose a novel connection between the reproductive number and the Gibbs free energy, expressed as [36,37].

$$\Delta G = -Eln(R_t), \left(E > 0\right)$$

and thus we have the classification:

$\Delta G < 0$ (favorable reaction)

$\Delta G = 0$ (equilibrium)

$\Delta G > 0$ (unfavorable reaction).

Therefore, for the reaction to be favorable, it is required that $R_t > 1$. This condition opens the pathway for exploring analogies with phase transitions in thermodynamics, providing a new framework to investigate collective phenomena through the lens of free energy. Although we derive the favorable reaction condition $R_t > 1$ from the dimensionless Gibbs free energy $\ln(R_t)$, the physical meaning of the energy scale E is profound and intrinsically related to the second law of thermodynamics and entropy S. Given the relation between entropy and Gibbs free energy, $S = -\frac{\partial G}{\partial T^1}$ in which T denotes the temperature, we obtain $\Delta S = kln(R_t)$,

wherein we employ the condition from chemical equilibrium E = kT. Here, k denotes the Boltzmann constant. So the entropy of the system never decreases.

As is well known, entropy has proven to be a fundamental tool for the analysis of some biosystems [38-40]. Entropy-based metrics also provide insights into control strategies, as reducing entropy can be associated with effective interventions. The modern interpretation of entropy in the context of SIR epidemiological models general use Shannon information-theoretic perspective [41-43]. The distribution of individuals among compartments can be treated as a probabilistic state, allowing the use of Shannon entropy to quantify the uncertainty and disorder in the population. Moreover, the epidemic dynamics can be understood as an irreversible process characterized by entropy production, which often peaks near the turning points of the infection curve.

In this work, we present an interdisciplinary review that bridges classical epidemiological models, such as SIR and SEIR, with concepts from statistical physics and thermodynamics, particularly through a novel connection between the effective reproductive number R_t and the Gibbs free energy. By proposing the relation $\Delta G = Eln(R_t)$, we reinterpret epidemic transitions as phase transitions, offering a fresh physical perspective on the dynamics of viral spread within populations. Beyond the theoretical framework, we apply this approach to real-world epidemiological data, analyzing COVID-19 transmission in a specific region of Brazil using the EpiEstim tool. This synthesis of mathematical modeling, physical analogy, and empirical analysis provides new insights into how physical methodologies can enrich our understanding of collective epidemiological phenomena and the effectiveness of control measures. The article is organized as follows. In Sec.2, we present the simplest model that can describe virus transmission dynamics (SIR). In Sec.3, we refine

the SIR model considering intervention measures (social distancing, mask usage, quarantine, and vaccines). In Sec.4, we investigate a more realistic model (SEIR), taking into account the incubation period. We also summarize how all the previous investigations of the SIR and SEIR models—considering the vast number of variables—influence the spread of a virus within a population. In Sec.5, we derive the relationship between the reproductive number and the Gibbs free energy, and we present the phase transition diagram. In Sec.6, we calculate the reproductive number of a specific macro-region monitored by a regional health authority, using the serial interval. We place this investigation within the context of a phase transition by defining an average variation of the Gibbs free energy and studying the transition using appropriate variables. Finally, in Sec.7, we present our conclusions.

EPIDEMIC DYNAMICS DESCRIBED BY THE SIR MODEL

The simplest mathematical framework capable of describing the transmission dynamics of a virus is given by the following set of equations

$$\frac{ds}{dt} = -\beta is$$

$$\frac{ds}{dt} = \beta is - \gamma i$$

$$\frac{ds}{dt} = \beta is - \gamma i \qquad (1)$$

where s represents the fraction of susceptible individuals, i the fraction of infected individuals, and r the fraction of recovered individuals (s +i+r = 1). Lowercase letters represent fractions or densities in terms of the total population N (S + I + R = N). We can understand the transmission of a contagious disease as a catalytic chemical reaction, in which infected individuals convert susceptible individuals into new infected ones, as illustrated in Figure 1 through a flow diagram.

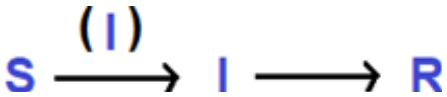

Figure 1: Representation of the processes involved in the SIR model of epidemic spread.

The classes of individuals are: susceptible (S), infected (I), recovered (R). An I in parentheses indicates that the process is catalytic, with I acting as the catalyst. The other processes are spontaneous.

Note that the system has the following disease-free equilibrium point: (s, i, r) = (1, 0, 0). The inverse of the rates has the dimension of time, with the transmission rate given by $\beta = Cp$, where C is the average number of daily contacts (network), p is the probability of infection per contact, and $\frac{1}{\gamma}$ is the average recovery time for an infected individual.

The variation of the fraction of infected individuals i is given by:

$$\frac{di}{dt} = (\beta s - \gamma)1 \qquad (2)$$

Thus, in order to have a contagion outbreak that affects a portion of the population, the following condition must be met:

$$\frac{\beta}{\gamma} s > 1 \qquad (3)$$

Therefore, we observe that the quantity:

$$R_0 = \frac{\beta}{v} = \frac{C_\rho}{\gamma} = \frac{recovery\ time\ of\ an\ infected\ individual}{time\ for\ an\ infected\ individual\ to\ infect\ another\ person} \qquad (4)$$

indicates that at the beginning of the outbreak (s = 1), the infection rate exceeds the recovery rate.

Suppose that on average a person meets 5 others per day, with an infection probability of 0.05. Thus, an infected individual infects 0.25 people per day, and in 4 days, infects one person. If the recovery time is approximately 12 days (about 2 weeks), the basic reproduction number R0 would be 3, which can be visualized in Figure 2 in terms of generation chains.

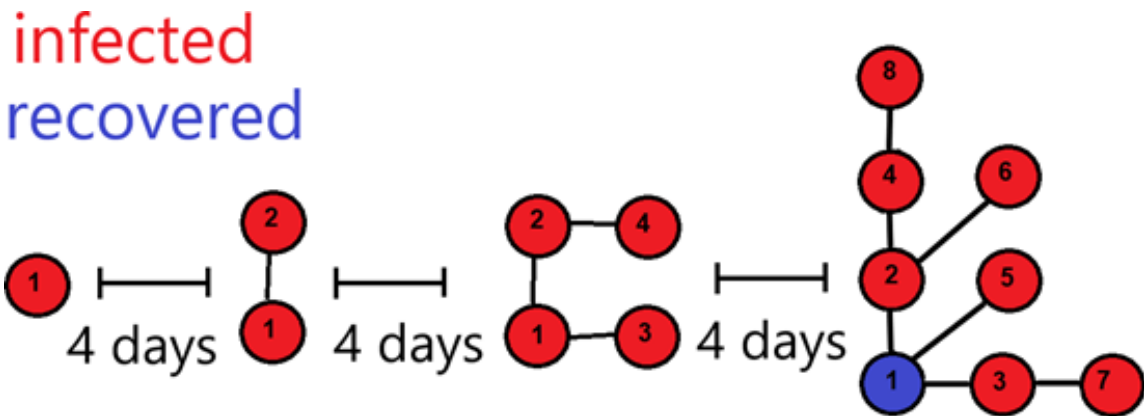

Figure 2: The basic reproduction number R_o and the chain of generations.

Thus, the basic reproduction number R_0 represents a threshold for the transmission dynamics: $R_0 > 1$ implies that there will be no significant transmission and spread of the virus within a community. The interpretation of the reproduction number is the average number of people that an infected individual will infect before recovering, as clearly seen in Eq. (4).

The epidemic spreads when the reaction rate β reaches a critical value ($\beta = \gamma$), leading to a phase transition analogous to what occurs in thermodynamics with a critical temperature. Therefore, the number of individuals that an infected person infects on average is given, from Eq. (2), by the definition of an effective reproduction number Reff:

$$\mathrm{R}_{eff} = \left(\frac{\beta}{\gamma}\right) \qquad (5)$$

where the basic reproduction number is the effective reproduction number evaluated at the disease- free equilibrium point (s, i, r) = (1, 0, 0).

The system of equations in Eq. (1) has very useful properties when applying the SIR model to describe the transmission dynamics of a disease within a community.

The first property relates to the initial behavior of the transmission dynamics. Since at the beginning of the outbreak s ≈ 1, from the second equation in the system (1) we obtain:

$$\frac{di}{i} = [R_o - 1]\gamma dt, \qquad (6)$$

which can be solved by integrating both sides:

$$i = i(0)exp[(R_o - 1)\gamma t] \qquad (7)$$

where γ=(R_o 1)γ is the growth rate. We can fit the exponential behavior above to data associated with the number of confirmed cases at the onset of the epidemic in a population, thereby estimating the basic reproduction number:

$$R_o = 1 + \frac{\gamma}{v} \qquad (8)$$

The second property concerns the final behavior $t \to \infty$ of the transmission dynamics. By dividing the second equation of the system (1) by the first, we obtain:

$$\frac{di}{ds} = -1 + \frac{1}{R_o s} \qquad (9)$$

which can be immediately solved by integrating both sides:

$$i + s = i(0) + s(o) + \frac{1}{R_o}\ln\frac{s}{s(o)} \qquad (10)$$

Since i(∞) = 0 and s(∞) = 1 − r(∞), it follows that:

$$R_o = \frac{1}{r(\infty)}\ln\frac{1}{1-r(\infty)} \qquad (11)$$

Thus, the basic reproduction number can be expressed in terms of the fraction of the population that was infected and recovered (r), and vice versa. By conducting serological (antibody) surveys within a population, we can estimate this fraction (prevalence) and consequently the basic reproduction number.

By numerically solving Eq. (11), we can determine the percentage of the population that would be infected by a disease for a given basic reproduction number (attack rate), as shown in Figure 3.

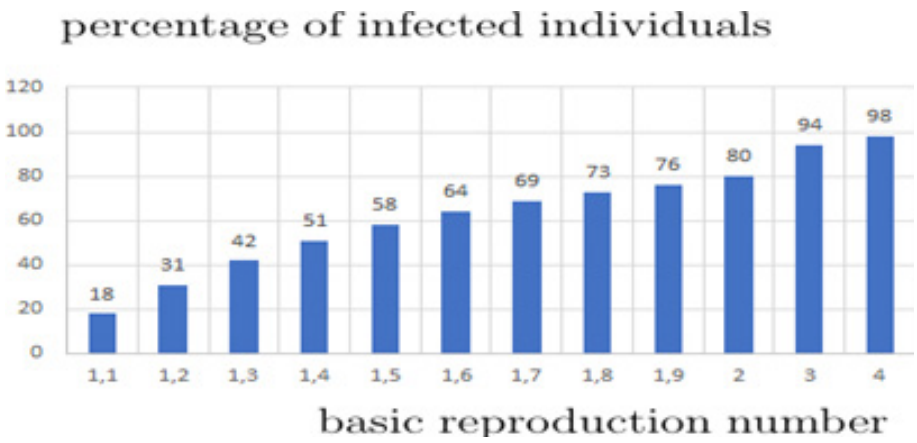

Figure 3: Total percentage of infected individuals as a function of the basic reproduction number.

Now let us suppose that a fraction of the infected individuals die due to the infection's mortality rate. In this case, by introducing a new class representing deaths (m), the system of equations becomes (SIRM):

$$\frac{ds}{dt} = \beta 1 s$$

$$\frac{di}{dt} = \beta 1 s - \gamma 1 - \Theta 1$$

$$\frac{\mathrm{dr}}{\mathrm{dt}} = \gamma \mathrm{i}$$

$$\frac{\mathrm{dm}}{\mathrm{dt}} = \theta 1, \qquad (12)$$

where 1/θ is the average time until death for an infected individual. The system of Eqs. (12) is represented by the diagram in Figure 4.

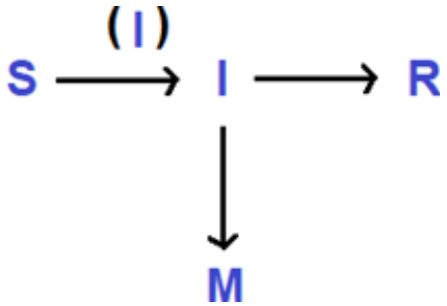

Figure 4: Representation of the processes involved in the SIRM model of epidemic spread. The classes of individuals are: susceptible (S), infected (I), recovered (R), and deceased (M).

We can organize the above system as follows:

$$\frac{ds}{dt} = -\beta 1 s$$

$$\frac{di}{dt} = \beta 1 s - (\gamma + \theta) 1$$

$$\frac{\mathrm{d(r+m)}}{\mathrm{dt}} = (\gamma + \theta)\mathrm{I} \qquad (13)$$

Thus, the entire previous discussion for the SIR model holds with the following transformations:

$$r \to r' = r + m$$

$$\gamma \to \gamma' = \gamma + \theta. \qquad (14)$$

Hence, we define the following basic reproduction number:

$$R_o = \frac{\beta}{\gamma+\theta} = \frac{R_o}{1+\frac{\upsilon}{\gamma}} \qquad (15)$$

If the mortality rate θ increases, the basic reproduction number decreases. Consequently, in diseases with a high mortality rate, an infected individual may not have enough time to infect others, thus preventing the spread of the disease.

Moreover, the equations describing the initial and final behavior of an epidemic are given by:

$$\frac{R_o}{1+\frac{\vartheta}{\gamma}} = 1 + \frac{\lambda}{\gamma'}$$

$$\frac{R_o}{1+\frac{\vartheta}{\lambda}} = \frac{1}{r(\infty)+m(\infty)} \ln \frac{1}{1-r(\infty)-m(\infty)}, \qquad (16)$$

respectively. If the infection fatality rate is very low, we recover the SIR model.

Finally, let us introduce a vital dynamic into the SIRM model, through the daily birth rate λ and death rate κ:

$$\frac{ds}{dt} = \lambda - \kappa s - \beta is$$

$$\frac{di}{dt} = \beta is - \gamma i - \theta i - \kappa i$$

$$\frac{dr}{dt} = \gamma i - \kappa r$$

$$\frac{dm}{dt} = \theta i + \kappa(s + i + r) \qquad (17)$$

The system of Eqs. (17) is represented by the diagram in Figure 5.

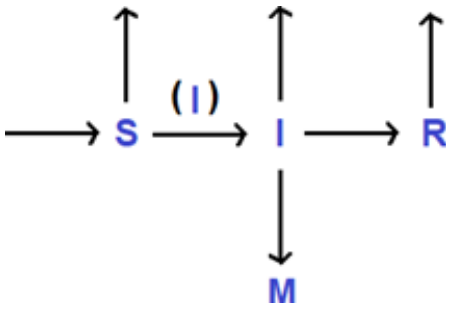

Figure 5: Representation of the processes involved in the SIRM model with vital dynamics. The classes of individuals are: susceptible (S), infected (I), recovered (R), and deceased due to viral infection (M). The arrows entering and exiting the diagram represent the fluxes associated with the population's birth and death rates, respectively.

We can organize the above system as follows:

$$\frac{dN}{dt} = \Lambda - \kappa N - \theta 1$$

$$\frac{dM}{dt} = \theta 1 + \kappa N, \qquad (18)$$

where N = S + I + R and Λ = Nλ. In this case, N + M = N(0) + M(0) + Λt, and if the birth rate far exceeds the death rate, we have a linear population growth: $N(t)\mathrm{N}(0) + \Lambda t$.

Finally, from Eq. (12), we obtain the following effective reproduction number:

$$R_{eff} = \frac{\beta s}{\gamma + \theta + \kappa} \qquad (19)$$

which leads to the basic reproduction number when evaluated at the disease-free equilibrium point (*s,i,r,m*)= $\frac{\lambda}{\kappa}0,0,0$:

$$R_o = \frac{\lambda}{\kappa}\frac{\beta}{\gamma + \theta + \kappa} \qquad (20)$$

(EXTERNAL/INTERNAL) INFLUENCES ON EPIDEMIC DYNAMICS AND INTERVENTION MEASURES

We are now prepared to refine the previous discussion by implementing how intervention measures could affect the previous equations and their respective consequences [19-26].

Social Distancing or Herd Immunity

Let us suppose that a virus encounters a population in which a certain fraction is already immune or practices social distancing (mitigation), with s1=(1-x)s representing the fraction of the population that does not practice social distancing or is not immune, and s2 = xs representing the fraction that does practice social distancing or is immune (s = s1 + s2). Considering the SIR model discussed earlier, the transmission dynamics would be given by the following equations:

$$\frac{ds}{dt} = -\beta_1 is_1 - \beta_2 is_2$$

$$\frac{di}{dt} = \beta_1 is_1 - \beta_2 is_2 - \gamma\iota$$

$$\frac{\mathrm{dr}}{\mathrm{dt}} = \gamma\mathrm{i}. \qquad (21)$$

We represent Eqs. (21) with the diagram in Figure 6.

Since the transmission of the virus to people practicing social distancing or with immunity is practically null (β1 = β, β2 = 0), we have:

$$\frac{\mathrm{ds}}{\mathrm{dt}} = -(1 - \mathrm{x})\beta\mathrm{is}$$

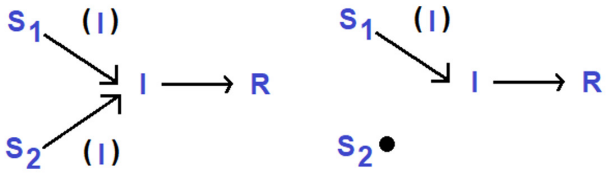

Figure 6: Representation of the processes involved in the SIR epidemic spread model with herd immunity or an equivalent control measure. The classes of individuals are: susceptible (S1) without immunity, susceptible (S2) with immunity, infected (I), and recovered (R). Infected individuals (catalysts) react differently with susceptible individuals. When β1 = β2 = β or

one of the transmission rates is null, we recover the classic SIR model. Immunity or social distancing suppresses the reaction $S_2 \xrightarrow{(I)} I$, disabling this type of interaction between susceptible and infected individuals, represented by the disappearance of the arrow indicating the flow of individuals from one class to another.

$$\frac{di}{dt} = (1-x)\beta is - \gamma i$$

$$\frac{dr}{dt} = \gamma i. \qquad (22)$$

Thus, we can write the following effective reproductive number:

$$R_{eff=(1-x)R_o}\frac{S}{N}, R_o = \frac{\beta}{\gamma'} \qquad (23)$$

so that increasing the fraction x reduces the reproductive number. To control the epidemic:

$$(1-x)R_o < 1 \Rightarrow x > 1 - \frac{1}{R_o}. \qquad (24)$$

Therefore, to control an epidemic, a certain percentage of the population must be immunized, or the control measure must be equally effective, as shown in Figure 7.

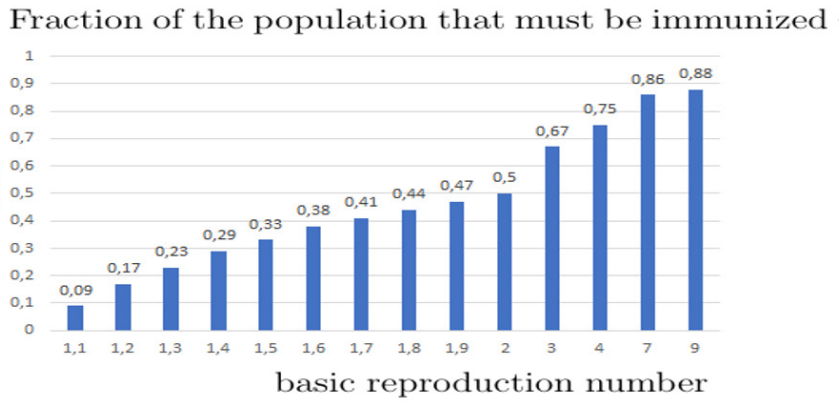

Figure 7: Fraction of the population that must be immunized as a function of the basic reproductive number.

Use of Masks and Hand Washing

Let us consider a population N divided between individuals who use masks and those who do not, with s_1 representing the fraction of individuals who use masks, s_2 the fraction who do not, i_1 the fraction of infected individuals who use masks, and i_2 the fraction of infected individuals who do not use masks. Considering the SIR model discussed previously and also that:

$$s + i + r = 1$$

$$s = s_1 + s_2$$

$$i = i_1 + i_2 \qquad (25)$$

and assuming that mask-wearing, along with hand washing or an equivalent control measure, reduces the transmission probability of infected individuals to $\beta(1-\epsilon_1)$, where $\in_1$ is the efficiency (e.g., of the mask) in reducing transmissibility between infected and susceptible individuals, we obtain the following:

Contact Probability	Infected with Mask	Susceptible with Mask	Transmission Chance
$i_1 s_1$	Yes	Yes	$\beta(1-\epsilon 1)$
$i_1(s-s_1)$	Yes	No	$\beta(1-\epsilon 1)$
$(i-i_1)s_1$	No	Yes	β
$(i-i_1)(s-s_1)$	No	No	β

In this case, we would have the following system of differential equations describing the transmission dynamics of the virus in a heterogeneous population composed of individuals who use and do not use masks:

$$\frac{ds}{dt} = -\beta_1 i_1 s_1 - \beta_2 i_2 s_1 - \beta_3 i_1 s_2 - \beta_4 i_2 s_2$$

$$\frac{di}{dt} = -\beta_1 i_1 s_1 + \beta_2 i_2 s_1 + \beta_3 i_1 s_2 + \beta_4 i_2 s_2 - \gamma i$$

$$\frac{dr}{dt} = \gamma i, \qquad (26)$$

$$\beta_1 = \beta(1-\epsilon_1), \beta_2 = \beta, \beta_3 = \beta(1-\epsilon_1), \text{and and } \beta_{4=}\beta$$

Thus, we obtain:

$$\beta_1 i_1 s_1 + \beta_2 i_2 s_1 + \beta_3 i_1 s_2 + \beta_4 i_2 s_2 = \beta(1-\epsilon_1) i_1 s_1 + \beta(i-i_1) s_1 + \beta(1-\epsilon_1) i_1 (s-s_1) + \beta(i-i_1)(s-s_1) = i[s-s_1] = i[s\left(1-\bar{\epsilon}_1 \frac{i_1}{i}\right)] \qquad (27)$$

Therefore, defining the effective reproductive number as:

$$R_{eff} = \frac{\beta}{\gamma}[s\left(1-\bar{\epsilon}_1 \frac{i_1}{i}\right)] \qquad (28)$$

we conclude that increasing either the fraction of infected individuals who use masks (i_1/i) or the efficacy $\in_1$ of the mask reduces the transmission rate and consequently the reproductive number. In general, assuming also that masks, hand washing, or equivalent control measures protect susceptibles with an efficiency $\in_2$, then β_1=β(1-$\in_1$) (1-$\in_2$), β_2= β(1-$\in_2$), β_3= β(1-$\in_1$) e β_4 = β. We represent Eqs. (26) with the diagram in Figure 8. Thus, from the system of equations in Eq. (27), we obtain the following effective reproductive number:

$$R_{eff} = \frac{\beta}{\gamma}[s(1-\bar{\epsilon}_1 \frac{i_1}{i} - \bar{\epsilon}_2 \frac{s_1}{s} + \frac{s_1 i_1}{s\, i}\epsilon_1\epsilon_2)] = \frac{\beta}{\gamma}[s(1-\frac{i_1}{i}\epsilon_1)(1-\frac{s_1}{s}\epsilon_2)]. \qquad (29)$$

In this case, if we increase the fraction of infected individuals (i_1) or susceptible individuals (s_1) who use masks, and also the efficacy of the mask in reducing the transmission from infected individuals ($\in_1$) or preventing contagion of susceptibles ($\in_2$), we reduce the effective reproductive number and possibly control an epidemic.

For simplification, assuming that $\in_1 = \in_2 = \in$ and $i_1/i = s_1/s = \rho$, we have the following (effective/basic) reproductive number:

$$R_{eff=(1-\rho\epsilon)^2 R_o},\ R_o = \frac{\beta}{\gamma} \qquad (30)$$

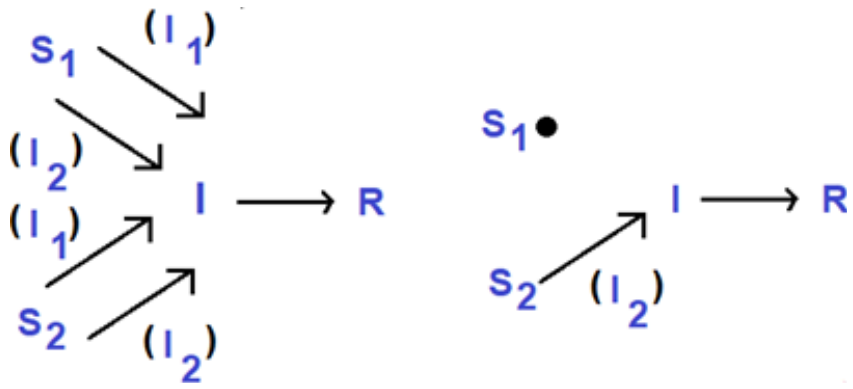

Figure 8: Representation of the processes involved in the SIR epidemic spread model with mask usage, hand washing, or equivalent control measures. The classes of individuals are: susceptible (s_1) who use masks, susceptible (s_2) who do not use masks, infected (i_1) who use masks, infected (i_2) who do not use masks, and recovered (R). Infected individuals (catalysts) react differently with susceptible individuals. When $\beta_1 = \beta_2 = \beta_3 = \beta_4 = \beta$, we recover the classic SIR model.

The control measures of mask-wearing and hand washing suppress the reactions $s_1 \xrightarrow{i_2} I$, $s_1 \xrightarrow{i_2} i_2$, and $s_2 \xrightarrow{i_2} I$. disabling these types of interactions between susceptibles and infected, represented by the disappearance of the arrows indicating the flow of individuals from one class to another.

Finally, in Figure 9, we consider two scenarios: a pessimistic one in blue, considering that masks are not very effective ($\in$ = 0.6), and an optimistic one in orange, considering that masks are highly effective ($\in$ = 0.9), in the attempt to contain an epidemic R_{eff}<1. Note that in the pessimistic scenario it is not possible to contain an epidemic with a reproductive number (R_o>6) using masks alone, even if 100% of the population uses masks. In both the pessimistic and optimistic scenarios, if facing an epidemic with R_o=3, more than 50% of the population should use masks in order to control transmission.

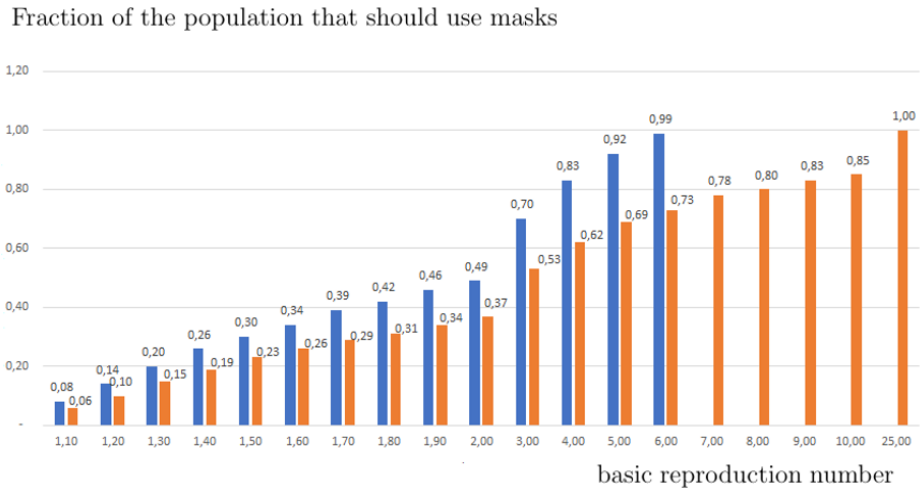

Figure 9: Fraction of the population that should use masks as a function of the basic reproductive number. In blue, we consider masks that are not very effective ($\in_o$=0.6), and in orange, masks that are highly effective ($\in_o$=0.9)

$$\frac{ds}{dt} = -\beta 1 s$$

$$\frac{di}{dt} = \beta 1 s - (\gamma + \delta) 1$$

$$\frac{dq}{dt} = \delta 1 - cq$$

$$\frac{dr}{dt} = \gamma 1 + cq \qquad (31)$$

where 1/δ is the average time it takes to place infected individuals into quarantine, and 1/ς is the average duration that infected individuals remain in quarantine. The set of equations (31) of the SIQR model is represented by the diagram in Figure 10.

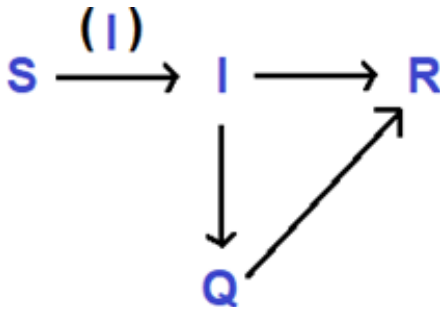

Figure 10: Representation of the processes involved in the SIQR epidemic spread model. The individual classes are: susceptible (S), infected (I), individuals in quarantine (Q), and recovered (R). Quarantine increases the outflow of infected individuals from class (I) to class (Q), thus reducing the number of infectious catalysts and consequently decreasing the reaction $S \xrightarrow{(1)} I$.

In this case, the effective reproductive number is given by:

$$R_{eff} = \frac{\beta}{\gamma+\delta} s. \qquad (32)$$

By reducing the time interval required to place infected individuals into quarantine, we decrease the reproductive number, thereby contributing to the control of the epidemic.

Let T_R=1/γ be the time an infected individual takes to recover and TQ = 1/δ the time required to place an infected individual into quarantine. To control an epidemic solely through quarantine (Reff < 1), we must satisfy the following condition:

$$T_Q = \frac{1}{R_0 - 1} T_R \qquad (33)$$

We represent the above equation for different basic reproductive numbers R_0, considering T_R = 12, in Figure 11. For R_0 = 3, the infected individual must be quarantined before half of their infectious period. When R_0 > 7, it becomes very difficult to quarantine the infected individual within one day or less.

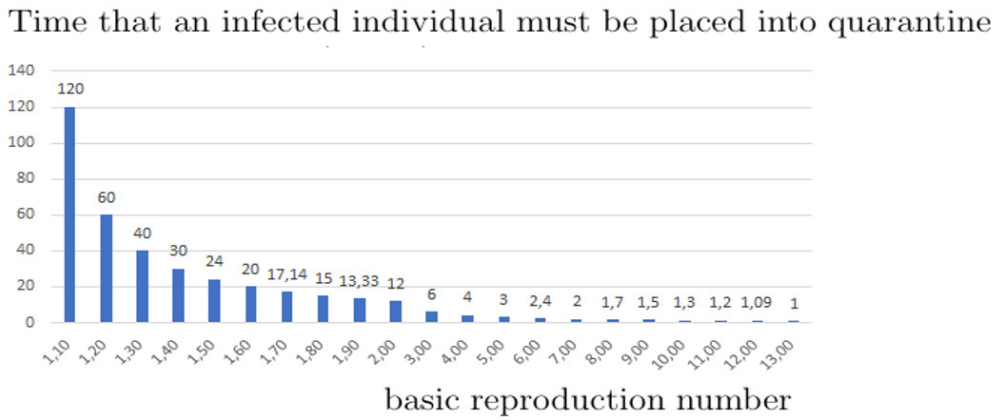

Figure 11: Time that an infected individual must be placed into quarantine (y-axis) as a function of the basic reproductive number (x-axis).

It is also possible to rewrite the system of equations in (31) as follows:

$$\frac{ds}{dt} = -\beta 1 s$$

$$\frac{di}{dt} = \beta 1 s - (\gamma + \delta) 1$$

$$\frac{dq}{dt} = \delta 1 - cq$$

$$\frac{dr_c}{dt} = \gamma 1 + cq$$

$$\frac{dr_\gamma}{dt} = \gamma i, \qquad (34)$$

where we describe the initial behavior of the transmission dynamics (s ~ 1) through the following equations:

$$\frac{d(q + r_c)}{dt} = \delta 1$$

$$i(t) = i(0)\, exp\{[\beta - (\gamma + \delta)]t\}, \qquad (35)$$

whose solution is given by:

$$(q + r_c)(t) = \frac{\delta i(0)}{[\beta - (\gamma+\delta)]} [exp\{[\beta - (\gamma + \delta)]t\} - 1]. \qquad (36)$$

Thus, we could fit the number of quarantined and recovered-from-quarantine cases (q + rç) to empirical data.

Vaccination

To investigate how vaccination influences the transmission dynamics of a virus within a community, let us first consider the following set of equations:

$$\frac{ds}{dt} = \kappa(1 - \upsilon) - \beta i s - \kappa s$$

$$\frac{di}{dt} = \beta i s - \gamma i - \kappa i$$

$$\frac{dr}{dt} = \kappa \upsilon + \gamma i - \kappa r \qquad (37)$$

which represents a vital dynamics system with λ = κ, following eq. (12), where (*s*+*i*+*r*)=1 and υ is the fraction of vaccinated and immunized individuals. The basic reproductive number R_o is evaluated at the disease-free equilibrium point (*s*,*i*,*r*,*m*)=((1-υ),0,0,0) and is immediately given by:

$$R_o^- = (1-\upsilon)R_o$$

$$R_o = \frac{\beta}{\gamma+\kappa'} \qquad (38)$$

Thus, by increasing the fraction of vaccinated individuals υ, the reproductive number is reduced. The fraction of the population that must be vaccinated to control the epidemic is given by the condition $R_0^-=1$:

$$\upsilon = 1 - \frac{1}{R_o} \qquad (39)$$

Alternatively, we can perform the following transformation in eqs. (37):

$$s = (1-\upsilon)s_1$$

$$i = (1-\upsilon)i_1$$

$$r = (1-\upsilon)r_1 + \upsilon, \qquad (40)$$

leading to:

$$\frac{ds_1}{dt} = \kappa - (1-\upsilon)\beta i1 s_1$$

$$\frac{di_1}{dt} = (1-\upsilon)\beta i1 s_1 - \gamma i1$$

$$\frac{dr_1}{dt} = \kappa\upsilon + \gamma i1 - \kappa r1, \qquad (41)$$

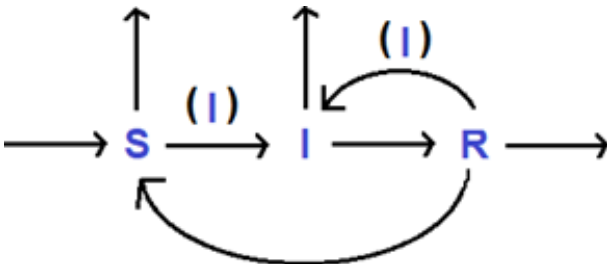

Figure 12: Representation of the processes involved in the SIR model with vital dynamics and population vaccination. The classes of individuals are: susceptible (S), infected (I), and recovered (R).

The reaction $(R\text{-}\rightarrow I)$ is associated with vaccine efficacy, with infected individuals as catalysts, while the reaction $(R\text{-}\rightarrow S)$ represents spontaneous immunity waning.

In this case, the effective reproductive number is given by the second equation as:

$$R_{eff} = \frac{\beta}{\gamma+\kappa}[s + (1-\alpha)r]. \qquad (43)$$

To find the basic reproductive number, we evaluate the effective reproductive number at the disease-free equilibrium where we observe a system of equations similar to eq. (22), but with a reduced transmission rate (1-υ)β.

Now let us incorporate into eq. (37) the concept of partial vaccine protection (efficacy α) and immunity waning at rate ϑ:

$$\frac{ds}{dt} = \kappa(1-\upsilon) - \beta i s - \kappa s + \vartheta r$$

$$\frac{di}{dt} = \beta i s + (1-\alpha)\beta i r_{\gamma i} - \kappa i$$

$$\frac{dr}{dt} = \kappa\upsilon + \gamma i - (1-\alpha)\beta i r - \kappa r - \upsilon r, \qquad (42)$$

where $1/\vartheta$ is the average time for a vaccinated individual to become susceptible again. The system of equations (42), representing the SIR model with vital dynamics and vaccination, is depicted in Figure 12.

(I = 0), which is determined by the following equations:

$$\kappa(1-\upsilon) - \kappa s + \vartheta r = 0$$

$$\kappa\upsilon - \kappa r - \theta r = 0. \qquad (44)$$

Thus, evaluating R_{eff} at the disease-free equilibrium $s, i, r = \frac{(1-\upsilon)(\kappa+\vartheta)+\upsilon\vartheta}{\kappa+\vartheta}, 0, \frac{\kappa\upsilon}{\kappa+\vartheta'}$, we obtain:

$$\bar{R}_0 = R_0\left[\frac{(\kappa+\vartheta) - \alpha\kappa\upsilon}{(\kappa+\vartheta)}\right], \qquad (45)$$

In this case, the fraction of the population that must be vaccinated to contain the disease (R_o=1) is given by:

$$\upsilon = 1 - \frac{1}{R_o}\frac{\kappa+\vartheta}{\kappa\alpha} \qquad (46)$$

Note that if the vaccine provides lifelong immunity ($\vartheta = 0$), the fraction of the population that must be vaccinated to contain the epidemic depends on the vaccine's efficacy α. Conversely, even if the vaccine is perfectly effective (α = 1), it may not always be possible to eradicate the disease due to the inequality (υ < 1):

$$\frac{\kappa}{\kappa+\vartheta} > 1 - \frac{1}{R_o} \qquad (47)$$

thus necessitating booster vaccination.

Epidemic Dynamics Described by the SEIR Model

Considering that when infected by a virus there is generally an incubation period during which the individual does not transmit the virus, the mathematical model describing the transmission dynamics within a population is given by the SIR model with the addition of a class associated with the incubation period. Thus, we have the following equations [26]:

$$\frac{ds}{dt} = \beta is$$

$$\frac{de}{dt} = \beta is - \omega e$$

$$\frac{di}{dt} = \omega e - \gamma i$$

$$\frac{dr}{dt} = \gamma i \qquad (48)$$

Here, s represents the fraction of susceptibles, e the fraction of exposed individuals, i the fraction of infected individuals, and r the fraction of recovered individuals. The parameter 1/ω corresponds to the incubation period and 1/γ to the infectious period. We can understand the transmission of a contagious disease as a catalytic chemical reaction, where infected individuals transform susceptible individuals into exposed and consequently into new infected individuals, as shown in Figure 13 through a flow diagram of the classes.

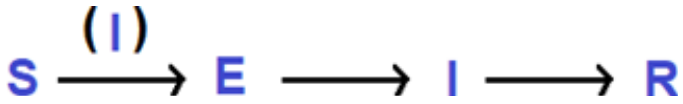

Figure 13: Representation of the processes involved in the SEIR model of epidemic spread. The classes of individuals are: susceptibles (S), exposed (E), infectious (I), recovered (R). An I in parentheses indicates that the process is catalytic and I is the catalyst. Other processes are spontaneous.

As we have two classes associated with infecteds (e, i), how do we define the reproductive number? Writing the classes in matrix form, we have:

$$X_i = [B]_{ij}X_j - [A]_{ij}X_j = ([B]_{ik}[A]_{\kappa 1}^{-1} - \delta_{il})[A]_{lj}X_j \qquad (49)$$

$$X = (e, i)^T, [B] = [[0, \beta\, s], [0.1]], [A] = [[\omega, 0], [-\omega, \gamma]] \qquad (50)$$

We define the matrix [R_eff] = [B][A]$^{-1}$ associated with the reproductive number (effective/basic):

$$[R\_eff] = [[\beta/\gamma\ s, \beta/\gamma s], [0,0]] \qquad (51)$$

We now introduce the concept of the next-generation matrix [45]. Suppose there are two types of infected in a population: those wearing masks (C) and those not wearing masks (S). We define the recurrence relation:

$$X_{n+1} = [R_o]\, X_n, [R_o] = [[0,1], [2,3]] \quad (52)$$

In this case:

$$[c_{n+1}, s_{n+1}]^T = [[0,2], [1,3]]\ [C_n, S_n]^T = [[0,2], [1,3]]^n [C_o, S_o]^T \quad (53)$$

Thus, the basic reproductive number R_0 is associated with the sequence:

$$\{(c_{n+1}+s_{n+1})\}/(c_n+s_n)\} = \{5,17/5,61/17,217/61,\ldots\} \qquad (54)$$

Alternatively, we can diagonalize the matrix $[R_0]$ through eigenvalues and eigenvectors:

$$[R_o]x = \lambda x, \det([R_o] - \lambda I) = 0, \lambda\pm = (3 \pm \sqrt{17})/2 \qquad (55)$$

$$[V]^{-1}[R_o]\ [V] = [[\lambda + ,0], [0, \lambda -]], [V] = [[-3 + \sqrt{17}, -3 - \sqrt{17}], [2,2]] \qquad (56)$$

Thus, the recurrence relation becomes:

$$X_{n+1} = [V]([V]^{-1}[R_o][V])^n\ V^{-1}X_o \qquad (57)$$

Hence, as $n \to \infty$:

$$[C_{n+1}, S_{n+1}]^T = [(3 + \sqrt{17/2}]^n [C_o, 0]^T \quad (58)$$

and consequently we define the basic reproductive number as:

$$R_o = \frac{\lim\ (n\to\infty)(C_{n+1}+S_{n+1})}{C_n+S_n} = \lambda_+ = (3 + \sqrt{17)/2} \approx 3.56 \quad (59)$$

Applying the same methodology to the SEIR model with matrix [R_eff]:

$$[R_{eff}]\ x = \lambda\ x, \det([R\_eff] - \lambda I) = 0, \lambda = \beta/\gamma s, \lambda = 0 \quad (60)$$

$$R\_eff = \beta/\gamma\ s \quad (61)$$

Thus, the basic reproductive number $R_O = \frac{\beta}{\gamma}$ is given by evaluating at the disease-free equilibrium (s,e,i,r) = (1,0,0,0).

Continuing the discussion, near the disease-free equilibrium we obtain:

$$\frac{dX}{dt} = [\lambda]\ X, [\lambda] = [[-\omega, \beta], [\omega, -\gamma]] \quad (62)$$

Diagonalizing [λ] via eigenvalues and eigenvectors:

$$\lambda\pm = (-(\omega + \gamma) \pm \sqrt{((\omega + \gamma)^2 - 4(\gamma - \beta)\omega))/2} \quad (63)$$

$$[U][\lambda][U]^{-1=}[[\lambda_+, 0], [0, \lambda_-]] \quad (64)$$

Thus, the system becomes with solution:

$$X = [[exp(\lambda_+ t),0], [0, exp(\lambda - t)]]X_o \sim [[exp(\lambda_+ t),0], [0,0]]X_0(t \to \infty) \quad (65)$$

Therefore, we relate λ_+ with R_0:

$$\lambda_+ = (-(\omega + \gamma) + \sqrt{((\omega + \gamma)^2 - 4(\gamma - \beta)\omega))/2} \quad (66)$$

$$R_o = \beta/\gamma \quad (67)$$

Thus, the relation between the growth rate λ+ and the basic reproductive number R_0 is:

$$R_o = (\lambda + +\gamma)(\lambda + +\omega)/(\gamma\omega) \quad (68)$$

Finally, for the long-term behavior $(t \to \infty)$, dividing the fourth equation of (48) by the first yields:

$$dr/_{ds} = -1/_{R_o} . 1/_s \quad (69)$$

Integrating this equation, we obtain the same result as in the SIR model.

Lastly, synthesizing all previous investigations of SIR and SEIR models, considering various factors influencing viral propagation such as control measures (social distancing, mask usage, quarantine), vital dynamics, or population immunity (vaccination), we construct the SEIQRM model:

$$\frac{ds}{dt} = \kappa(1 - \upsilon) - (1 - x)(1 - \rho\epsilon)^2\ i\beta s - \kappa s + \vartheta r$$

$$\frac{de}{dt} = (1 - x)(1 - \rho\epsilon)^2\beta i[s + (1 - \alpha)r] - \omega e - \kappa e$$

$$\frac{di}{dt} = \omega e - \gamma i - \delta i - \theta i - \kappa i$$

$$\frac{dq}{dt} = \delta i - \varsigma q - \kappa q$$

$$\frac{dr}{dt} = \kappa\upsilon + \gamma i - (1 - x)(1 - \rho\epsilon)^2(1 - \alpha)\beta ir + \varsigma q - \kappa r - \vartheta r$$

$$\frac{dm}{dt} = \theta i + \kappa(s + e + i + q + r) \quad (70)$$

These equations are represented in Figure 14.

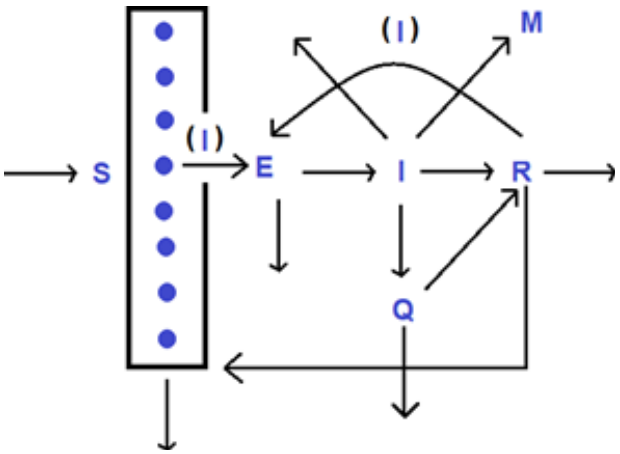

Figure 14: Representation of the processes involved in the SEIQRM epidemic dissemination model, considering control measures (social distancing, mask use, quarantine), vital dynamics, or population immunity (vaccination). The classes are: susceptible (S), exposed (E), infected (I), quarantined (Q), recovered (R), and deceased due to infection (M). Within the susceptible class, there are

8 subclasses related to whether individuals practice social distancing, have been vaccinated, and wear masks. Arrows represent flows associated with birth and death rates. Infected individuals are the catalysts for $S \xrightarrow{(I)} E$, and $R \xrightarrow{(I)} E$, transitions; other transitions are spontaneous. Control measures discourage catalytic reactions.

There always exists an effective reproductive number:

$$R_{eff} = \frac{(1-x)(1-\rho\epsilon)^2\beta}{\gamma+\delta+\theta+\kappa)}[s + (1-\alpha)ir] \qquad (71)$$

which will indicate whether or not community transmission will occur and also how efficient pharma- ceutical or non-pharmaceutical intervention measures must be to halt the spread of the virus within a community R_{eff}<1. As we can see, the reproductive number is a quantity that is highly sensitive to various external or even internal influences, making it difficult to quantify.

Given the control actions and the heterogeneous behavior of a population, the dynamic inter- actions associated with transitions between compartments, which occur behind the scenes of virus transmission within a community, constitute a complex system. In such a system, the design associated with the flow diagrams of individuals moving from one compartment to another becomes increasingly sophisticated.

Interestingly, these backstage interactions between compartments transform the basic reproduction number R_o (a bare quantity) into the effective reproduction number R_eff (a dressed quantity), drawing a parallel between dynamics and the concept of renormalization.

In the following investigations, we will present some ways to quantify the reproductive number, using recent data related to the transmission of SARS-CoV-2 in a given region of southern Mi- nas Gerais. The goal is to investigate the phase transition associated with the transformation of susceptible individuals into recovered or deceased due to infection by a virus in an ongoing epidemic.

Reproductive Number and Gibbs Free Energy in the Context of Chemistry

We finally converge on a topic of great importance for this work: the description of equilibrium in chemical reactions through free energy. The SIR epidemiological model and its derivatives can be analyzed analogously to chemical reactions. Given the Lotka-Volterra equations in Eq. (1), we can write them in reaction notation as:

$$S + I \rightarrow 2I$$

$$I \rightarrow R, \qquad (72)$$

where we define the free energies of each reaction inspired by the law of mass action to describe chemical equilibrium:

$$\Delta G_1 = -E\, ln\, \kappa_1 = \frac{di}{i}$$

$$\Delta G_2 = -E\, ln\, \kappa_2 = \frac{dr}{i} \qquad (73)$$

Here, the rates are interpreted with the aid of the concept of chemical equilibrium constants. Thus, we have:

$$\Delta G = \Delta G_1 - \Delta G_2 = -E\, ln\, \frac{\kappa_1}{\kappa_2} = -E\, ln \frac{\beta}{\gamma} s \qquad (74)$$

where E is a quantity with units of energy, introduced to balance the physical dimensions of the above equations (dimensional analysis). Note that we are considering the variations of individuals in the infected class: di = βsidt and dr = γidt.

Since R_o=β/γ we obtain:

$$\Delta G = -E \ln (R_{eff}), R_{eff} = \frac{\beta}{\gamma} s \qquad (75)$$

Thus, we arrive at the following classification:

ΔG < 0 Spontaneous reaction (exergonic)

ΔG = 0 Equilibrium

ΔG > 0 Non-spontaneous reaction (endergonic)

Therefore, for the reaction to be favorable, R_t>1. Graphically, we have a phase transition described by the SIR model, as shown in Figure 15.

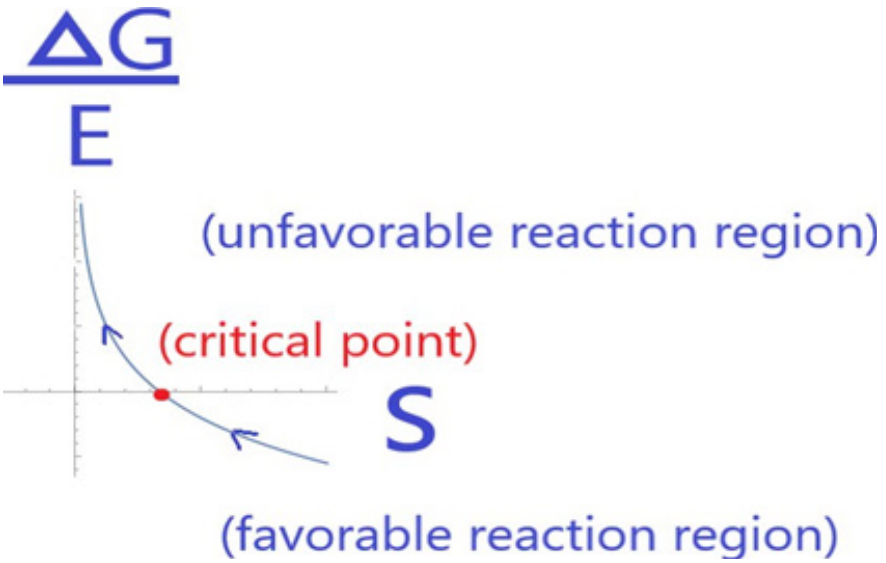

Figure 15: Variation of the dimensionless Gibbs free energy ln (R_o s) as a function of the susceptible fraction s. The critical point is given by $s = \frac{1}{R_0}$

In general, we can investigate how the control measures proposed in this work affect the critical point and the phase transition, bearing in mind Eq. (71) and its various parameters and functions. The investigation of how control measures affect the equilibrium constants and, consequently, the variation of Gibbs energy has been detailed in the work. The relations between the constants are given by

$$R_{eff} = \frac{\kappa_1}{\kappa_2} \qquad (76)$$

The expressions for κ_1 and κ_2 under different control strategies are summarized in the Table. 1 below.

Control Strategy	K_1	K_2
SIR (no control)	$\beta\, s\, dt$	$\gamma\, dt$
Social distancing	$(1-x)\,\beta\, s\, dt$	$\gamma\, dt$
Masks	$\left(1-\frac{i_1}{i}\epsilon_1\right)\left(1-\frac{s_1}{s}\epsilon_2\right)\beta s\, dt$	$\gamma\, dt$
Quarantine	$\beta\, s\, dt$	$(\gamma+\delta)\, dt$
Vaccination	$\beta\, i[s+(1-\alpha)r]\, dt$	$(\gamma+\kappa)\, i\, dt$
SEIQRM	$(1-x)(1-\rho\varepsilon)^2\,\beta[s+(1-\alpha)r]\, dt$	$(\gamma+\delta+\theta+\kappa)\, dt$

Table 1: Equilibrium constants K_1 and K_2 for different control strategies.

Reproductive number and Gibbs free energy in the con- text of epidemiology: R_t methodology

Taking into account all the previous analytical investigation about the reproductive number (basic/effective), we see that we have all the conceptual background to extract this number from the histogram associated with the number of confirmed cases reported by the health system. To calculate the effective or instantaneous reproductive number (R_t) we will use the R software (focused on data manipulation, analysis, and visualization) with the EpiEstim tool. For more details on how to use this tool, see the articles [28,29]. The methodology of

R_t has been developed and improved recently in the scientific literature, considering the SARS epidemics and control measures.

Let the number of confirmed cases on day i be given by I_i; these are related to the numbers of previously confirmed cases (Is,s<i)through the distribution W_s

$$I_{i=R_t} \sum_{s=1}^{s=i-1} W_s \, I_{i-s} \qquad (77)$$

where W_s represents the average time that an infector (primary case) takes to infect (secondary case), and in this case Ri would be the effective reproductive number. To clarify the previous argument, suppose that the distribution W_s is given by a Kronecker delta $W_s = \delta_{sg}$

$$\mathrm{I_i} = \mathrm{R_i I_{i-g}}, \ (78)$$

thus the number of cases on day (i-g) would generate cases on day i. This relationship is represented in Figure 16.

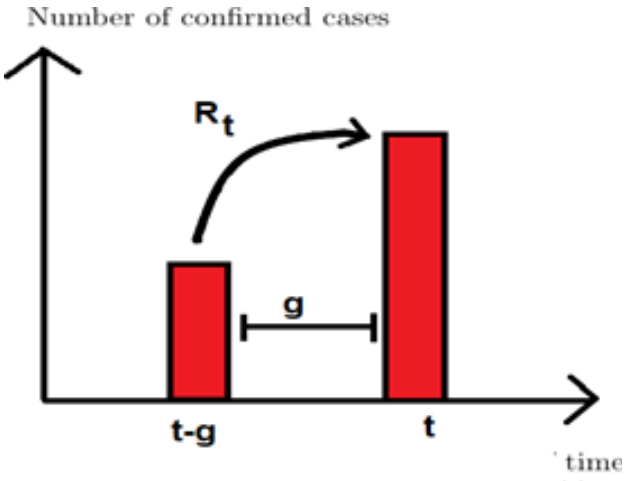

Figure 16: Number of confirmed cases as a function of time. The interval g represents the time that primary cases at (t-g) generate secondary cases at (t) and R_t is the fraction of secondary cases generated by the primary cases.

The distribution W_s is constructed from data collected by health agents during interviews at the beginning and during the outbreak, informing us about the speed of the cycles in the transmission chain. It can be approximately represented by the serial interval. The serial interval is defined as the duration between the symptom onset of a primary case (infector) and the symptom onset of a secondary case (infected). One of the main aspects of the transmission dynamics of a disease is the knowledge of the serial interval.

In the case of SARS-COV-2, we can use a log-normal distribution with mean (4.8) and standard deviation (2.3) to describe the serial interval [30]. Graphically, the serial interval is shown in Figure17. From Figure 17, we can conclude that, on average, the infector (primary case) transmits the disease to the infected (secondary case) in approximately 4.8 days. After 10 days, it is very unlikely to have secondary cases derived from the primary case. Since SARS-COV-2 transmission occurs during the asymptomatic period, isolating the infected individual before transmitting the virus to another person presents a significant challenge.

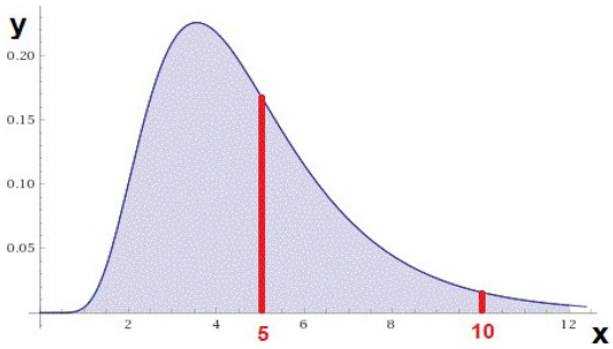

Figure 17: Log-normal distribution associated with the serial interval of SARS-COV-2, where y is the probability of a primary case transmitting the disease to a secondary case as a function of time x.

Considering that after 10 days it is very unlikely to have secondary cases from the primary case, we can, as an approximation, a truncation effect occurs starting on the 10^{th} $(W_{i\sim 0, i>10})$ such that $(\sum_{i=1}^{i=10} w_i \sim 1)$. Thus, we obtain a histogram associated with the serial interval, represented in Figure 18.

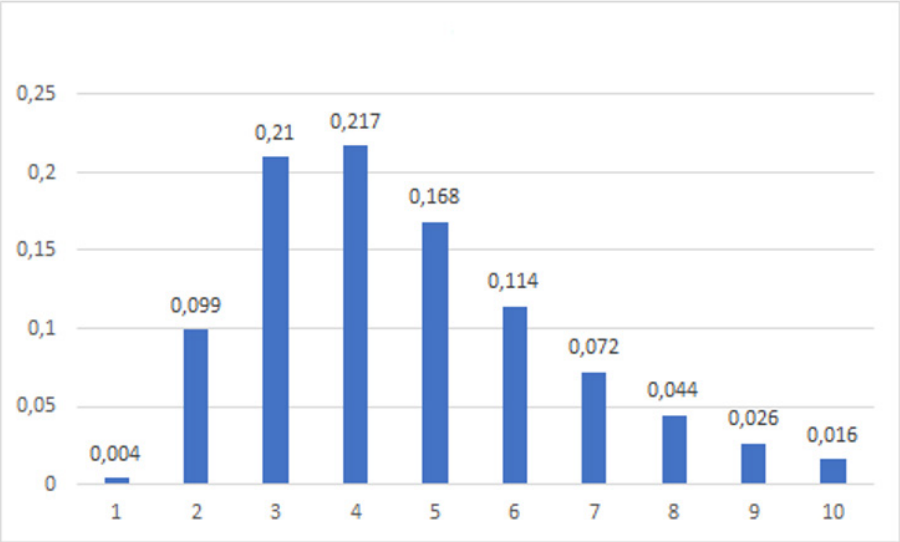

Figure 18: Histogram associated with the serial interval of SARS-COV-2.

Now, the number of daily confirmed infected cases for the region associated with the Varginha Health Regional (50 cities, approximately 854,442 inhabitants) was obtained from the website of the Minas Gerais State Health Department during the initial months of COVID-19 transmission in this region. The distribution of cases starts on 03/25/2020 and ends on 05/25/2020, totaling 62 days.

The distribution of cases (infected) by notification date is shown in Figure 19.

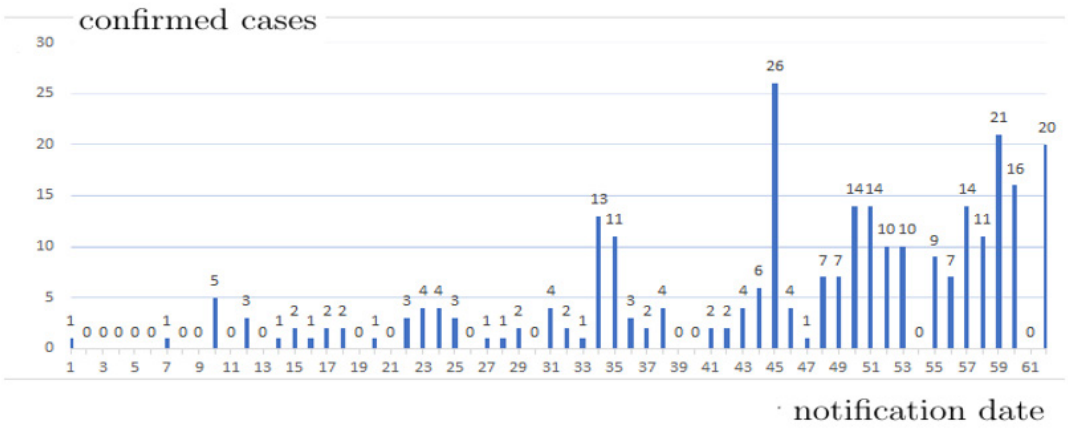

Figure 19: Histogram of confirmed cases by notification date.

In summary, since we have the distributions (histograms) associated with the serial interval and the number of confirmed cases per day, shown in Figures 18 and 19 respectively, we can input them into CSV tables (Excel) in the R software following the example below

Serial interval	Confirmed cases
0	1
0.004	0
0.099	0
0.21	0
0.217	0
0.168	0
0.114	1
0.072	0
0.044	0
0.026	5
0.016	0
0.01	3
0.01	0
0.005	1
0.005	2
0	1

Table 2: Format of the tables to be entered into the EpiEstim platform, representing the histogram associated with the serial interval and confirmed cases, respectively. og-normal distribution associated with the serial interval of SARS-COV-2, where y is the probability of a primary case transmitting the disease to a secondary case as a function of time x.

As an output we will obtain the effective reproductive number (R_t) represented in Figure 20, using a 12-day window to estimate R_t.

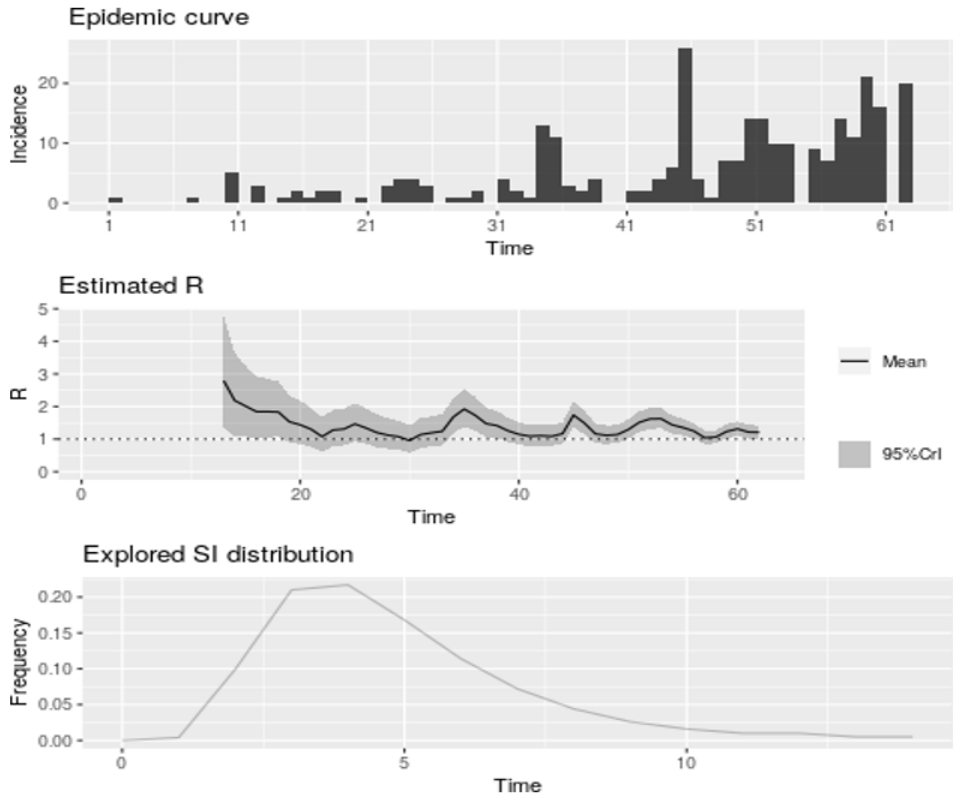

Figure 20: Estimate of the effective reproductive number R_t, visually generated online by the Epi- Estim tool, considering the histograms associated with the confirmed cases and serial interval investigated in the text. The shaded region around the R_t estimate (mean) represents a 95% confidence interval. All information about mean, standard deviation, and confidence intervals are provided in tables by the platform.

An interesting number to discuss is the mean of the effective reproductive number <R_t> (trend), since R_t fluctuates greatly. As in an SIR model the effective reproductive number is given by the expression $R_t=R_O$ s, where R_O is the basic reproductive number and s the fraction of susceptibles, when we take the average of R_t at the beginning of the outbreak we obtain:

$$< R_t >= R_o \frac{s_1+s_2+\ldots+s_i}{j} \sim R_o \qquad (79)$$

that is, the mean of the effective reproductive number at the start of the outbreak could possibly more appropriately represent the basic reproductive number characteristic of the region. The trend of the effective reproductive number and its mean can be seen in Figures 21 and 22, respectively.

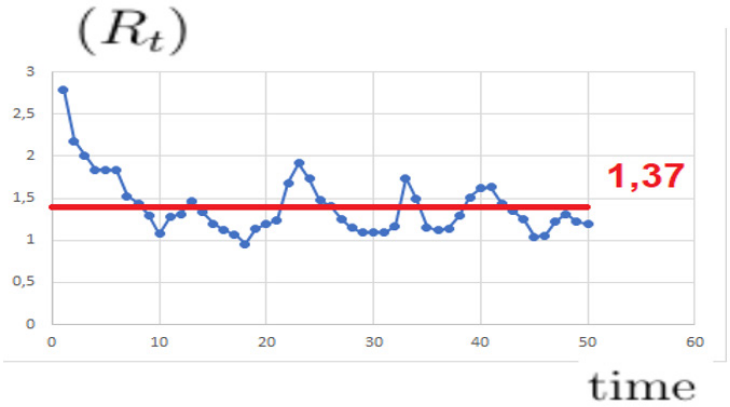

Figure 21: Mean number of infected per contaminant (R_t) as a function of time (days), with the trend of the effective reproductive number given by R_t = 1.37 ± 0.07. We used 2 significant digits and propagated uncertainties considering a 95% confidence interval for R_t.

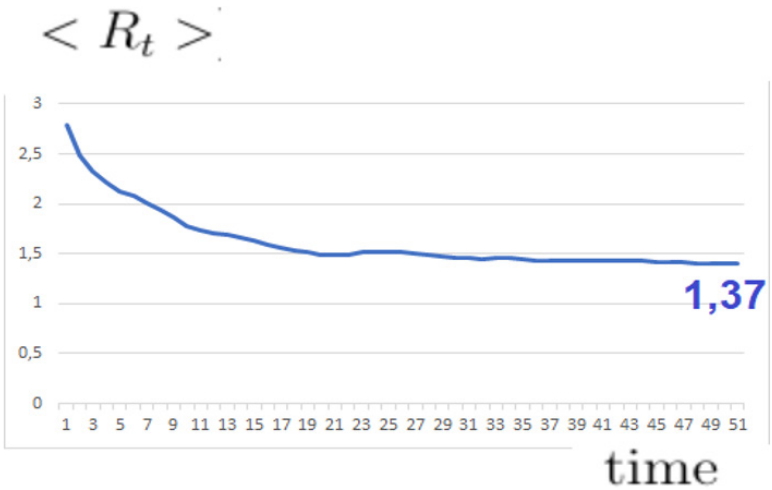

Figure 22: Mean of the effective reproductive number <R_t> as a function of time x (days).

Considering the previous analyses, we conclude that possibly the effective reproductive number R_t^{RV} of the region monitored by the Varginha Health Regional (50 cities) is within the range [0.96- 2.79] with a downward trend, fluctuating around 1.50 in the first month (30 days) and 1.37 in the second month. Consequently, we could argue that at the beginning of the disease spread in the region R_{t-0}^{RV}=2.79 ~ 3 (close to the value widely reported by the media) but possibly due to the characteristic behavior of the population in the region, there was a natural difficulty in virus propagation.

$$R_o^{RV} \sim 1.5 \pm 0.11. \qquad (80)$$

Thus, considering the SIR model with a recovery time of 12 days (approximately 2 weeks), one contaminant infects a person within 8 days. On the other hand, considering a more realistic SEIR model with an infectious period of 3 days, after an incubation period of approximately 5 days, one contaminant infects a person within 5 hours (0.22 days) after the incubation period.

Following the methodology for the basic reproductive number presented in a methodology involving linear regression, we can also obtain the effective reproductive number R_t by exploring its relation with the doubling time Δ_t, which is calculated through the slope parameter of a linear interpolation of the logarithm of the daily confirmed case numbers, over a certain time interval [32]. Estimates of the infection rate and predictions about the spread of a virus in a community can be based on initial data [23,24,46].

Now, with the aim of placing the investigation in the context of a phase transition, and similarly to eq. (75), we propose the following average variation of Gibbs free energy:

$$< \Delta G >= -E < ln(R_t) >= -E\,(\Sigma\_\{i = 1\}\^N\, ln[R\_i]/N) = -E\, ln[R^-_{-eff}] = -E\, ln[R^- s^-] \quad (81)$$

where the variables $\mathrm{R}^-_{\text{-eff}}$, R^- and s^- are given by geometric means:

$$R^-_{eff} = (\Pi\_\{j = 1\}\^N(R^-_{eff})\_j)\^(1/N)$$

$$R^- = (\Pi\_\{j = 1\}\^N(R^-_{eff})\_j)\^(1/N) = \{\Pi\_\{j = 1\} \wedge N[(1 - \rho\epsilon)2\beta/(\gamma + \delta + \theta + \kappa)]\_j\} \wedge (1/N) \quad (82)$$

$$s^- = (\Pi\_\{j = 1\} \wedge Ns^-\_j)\^(1/N) = \{\Pi\_\{j = 1\}\^N[s + (1 - \alpha)r]\_j\}\^(1/N)$$

Note that we have the relation $\mathrm{R}^-_{\text{-eff}} = R^- S^-$

$$(R^-_{eff})j = [\tfrac{(1-x)(1-\rho\epsilon)^2\beta}{\nu+\delta+\theta+\kappa)}]j[s + (1 - \alpha)r]j \quad (83)$$

considering the entire theoretical discussion about the influence of control measures, synthesized in eq. (71). We could implement more variables in the study of the effective reproductive number, making the problem more sophisticated than presented here. Since at the beginning of the virus spread in a community $\mathrm{R}^-_j \sim R_0 S^-$ and $\mathrm{S}^-_j \sim S$, we have $< \Delta G >\sim -E\, ln(R_o s).< \Delta G >\sim -E\, ln(R_o s).$

Graphically, a phase transition given by eq. (81) can be described by Figure 23. On the surface $z = ln(xy)$ we highlight the critical transition points xy 1, separating favorable regions (xy)>1 and unfavorable ones (xy)<1, and highlight the critical point of a particular trajectory x=1.5 and z=ln(1.5 y) described by the red color (phase transition of the SIR model with R_o=1.5). In general, finding the trajectory of the phase transition in an ongoing pandemic is a numerical endeavor.

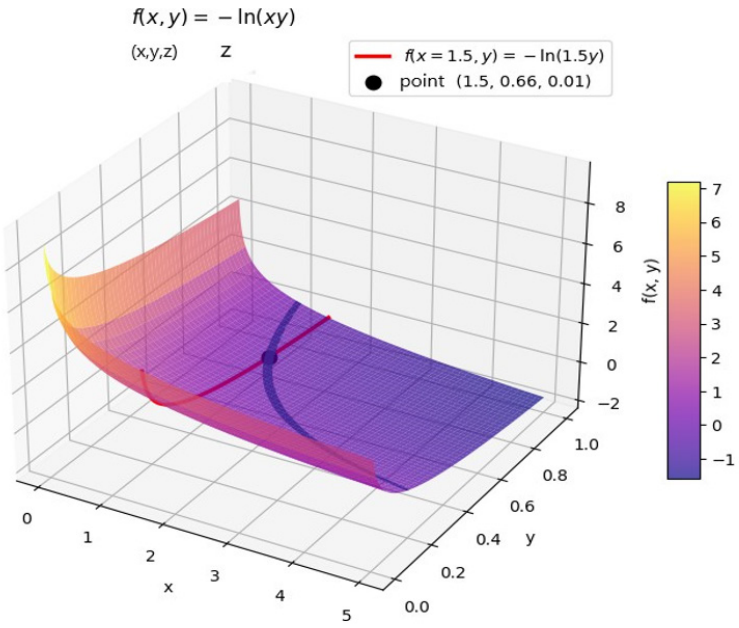

Figure 23: Variation of the dimensionless Gibbs free energy z=-1n(xy) as a function of the variable representing the reproductive number x=R^- and the variable representing the fraction of susceptibles y=s^-. The red line represents a SIR pandemic model with R_o=1.5.

Final Remarks

As we have shown, we investigated not only analytical but also numerical aspects related to the study of the transmission dynamics of a virus within a population, specifically SARS-CoV-2. This study led us to define an essential quantity for understanding epidemic dynamics, known as the reproductive number (the average number of individuals that one infected person transmits the virus to before the end of their infectious period). With this quantity, it is possible to have an idea of the type of phase transition occurring in a given region or city, from an initial state of susceptible individuals to a final state of recovered or deceased individuals.

The infection dynamics catalyzed by infected individuals, which occur behind the scenes of viral transmission in a community, can constitute an extremely complex system due to a vast number of variables and classes. These are necessary not only to describe how control measures can discourage the transmission by catalyst individuals but also because of the natural behavioral heterogeneity of a population. On the other hand, by relating the reproductive number to the Gibbs free energy, given its similarity with chemical reactions, it was possible to select appropriate variables to highlight a phase transition, thus establishing a parallel between epidemic models and the underlying physics.

Initially, we worked with the simplest system of differential equations that can describe the transmission dynamics of a virus in a community—the SIR model—as presented in Eq. (1). We introduced the concepts of the effective and basic reproductive numbers in Eq. (4) and explored some properties of epidemic dynamics associated with their initial and final behaviors, in Eqs. (8) and (11), respectively. An interesting relationship is the total percentage of the population that would become infected by a given disease as a function of the basic reproductive number R0, illustrated in Fig. 3. The discussion continued with the implementation of a class associated with the mortality rate due to infection, where we reasoned that if a disease is highly lethal, the infected individual may not have sufficient time to transmit it to others, as suggested by Eq. (15). Finally, we incorporated into the SIR model a vital dynamics, Eq. (12), associated with birth and death rates in a population. Subsequently, we explored how intervention measures affect the dynamics of the SIR model.

We showed that if a fraction x of the population is immunized or practices social distancing, the reproductive number in Eq. (23) decreases. The percentage of the population that should practice social distancing or be immunized to control an epidemic, given the basic reproductive number of a transmissible disease, is shown in Fig. 7. Next, we investigated how the use of masks and handwashing affects the reproductive number, as in Eq. (29), and presented the fraction of the population that should use masks to contain an epidemic under both pessimistic and optimistic scenarios, illustrated in Fig. 9. We then analyzed how quarantine could control an epidemic, based on Eq. (32) and Fig. 11. Given that COVID-19 is a highly transmissible respiratory syndrome, an educated guess would be to study the possibility of implementing all three control measures simultaneously (social distancing, masks, and quarantine). Lastly, we explored how vaccination impacts the reproductive number in Eq. (45), determining the fraction of the population that needs to be vaccinated to contain transmission, and also the necessity of booster vaccinations to eradicate a disease.

Following the same steps as with the SIR model, we presented the SEIR model in Eq. (48), describing virus transmission involving both an incubation and an infectious period. The calculation of the reproductive number (effective/basic) became more sophisticated through Eq. (50), due to the presence of two compartments associated with viral transmission (Exposed and Infectious), requiring the introduction of the next-generation matrix concept. Nevertheless, in the end, the reproductive number is defined similarly to the SIR model, in Eq. (61). Furthermore, we established the relationship between the basic reproductive number and the growth rate in Eq. (68), as well as the relationship between the basic reproductive number and the total number of individuals ultimately infected by the virus in Eq. (69). Finally, we synthesized all investigations from the SIR and SEIR models into the SEIQRM model, presented in Eq. (70), where we generally observed the sensitivity of the reproductive number to both internal and external influences.

With the goal of quantifying the reproductive number (effective/basic) in a dynamic epidemic, we presented two methodologies and the relationship between them. First, using the histogram as- sociated with the number of confirmed cases in a specific macro-region of southern Minas Gerais (Figure 19), monitored by the Varginha Health Regional Office (approximately 854,442 inhabitants), and a histogram of the serial interval representing the average time an infectious individual takes to infect others (Fig. 18), we calculated the instantaneous reproductive number R_t (Figs. 21 and 22). We concluded that the effective reproductive number R_t^{RV} ranged

between [0.96, 2.79] with a declining trend, oscillating around 1.5±0.11in the first month and 1.37±0.07 in the second month. Consequently, we could argue that at the beginning of the disease spread in the region, R_t^{RV}=2.79 ~ 3 (close to the widely reported value in the media); however, possibly due to characteristic behavioral patterns of the population in the region, there was a natural difficulty in the virus's spread, with R_0^{RV} ~ 1.5. In an SIR model considering a recovery time of 12 days, with R_0^{RV} ~ 1.5, an infected individual would transmit the virus to another within 8 days, leading to the infection of two individuals within 16 days, consistent with the observed doubling time. Similarly, in an SEIR model, we would reach the same result if we consider an incubation period of 5 days and an infectious period of 7 days.

Proceeding, we established a formal analogy between epidemic models and chemical reaction dynamics through the concept of Gibbs free energy. By interpreting the SIR model reactions in terms of mass action laws, we derived an expression relating the effective reproductive number R_{eff} to the Gibbs free energy variation:

$$\Delta G = -E ln(R_{eff}). \qquad (84)$$

This thermodynamic framework allows classifying epidemic propagation similarly to chemical reactions: spontaneous when R_{eff} >1, equilibrium at R_{eff} =1, and non-spontaneous for R_{eff} <1, highlighting a phase transition at s=(1/ R_{eff})

Building on this, we applied the methodology for estimating the time-dependent effective reproductive number R_t using real epidemiological data from the Varginha Health Regional (Minas Gerais, Brazil), via the EpiEstim tool. Considering the serial interval of SARS-CoV-2, we constructed the Rt dynamics, obtaining a decreasing trend with values ranging from approximately 2.79 to 0.96, stabilizing around 1.37 ± 0.07 in the second month. This suggested an initial reproductive number around R_0^{RV}≈1.5, likely influenced by behavioral and demographic factors in the region.

Finally, we extended the thermodynamic analogy by defining an average Gibbs free energy variation,

$$< \Delta G >= -E < ln(R_t) >, \qquad (85)$$

associated with the ongoing epidemic dynamics. This framework allows interpreting the epidemic trajectory as a phase transition surface in the (R^-, s^-) plane in eq. (82), delineating favorable and unfavorable regions of viral spread. These results reinforce the usefulness of combining epidemiological modeling with thermodynamic concepts to deepen the understanding of epidemic transitions and inform control strategies.

A Chemical Equilibrium and Gibbs Free Energy

By introducing the concept of chemical potential proposed by Gibbs [47-50], we allow the number of particles in a thermodynamic system to vary, and we write the internal energy U as follows:

$$dU = T\,ds - P\,dV + \mu\,dn \qquad (86)$$

If the physical system gains or loses particles to the thermal reservoir, its internal energy increases or decreases, respectively. We can then rewrite the variations of the thermodynamic functions:

$$dH = T\,dS + V\,dP + \mu\,dN \qquad (87)$$

$$dA = -P\,dV - S\,dT + \mu\,dN \qquad (88)$$

$$dG = S\,dT + V\,dP + \mu\,dN \qquad (89)$$

where we define the chemical potential μ as:

$$\mu = (\delta G/\delta N)\_(P, T) \quad (90)$$

Consider an isolated system divided into two parts:

$$U = U_1 + U_2 \qquad (91)$$

$$S = S_1 + S_2 \qquad (92)$$

$$V = V_1 + V_2 \qquad (93)$$

$$N = N_1 + N_2 \qquad (94)$$

According to the First Law of Thermodynamics:

$$dU_1 = T_1\,dS_1 - P_1\,dV_1 + \mu_1\,dN_1 \qquad (95)$$

$$dU_2 = T_2 dS_2 - P_2 dV_2 + \mu_2 dN_2 \qquad (96)$$

Thus:

$$dU_1 + dU_2 = 0 = (T_1 - T_2)\,dS_1 - (P_1 - P_2)\,dV_1 + (\mu_1 - \mu_2)\,dN_1 \quad (97)$$

At thermodynamic equilibrium:

$$T_1 = T_2, P_1 = P_2, \mu_1 = \mu_2 \quad (98)$$

Consider the chemical reaction:

$$xA + yB \rightleftarrows zC \qquad (99)$$

with consumption of n_A of reagent A:

$$N'\_A = N\_A - n\_A \qquad (100)$$

$$N'\_B = N\_B - n\_B \qquad (101)$$

$$N'\_C = N\_C - n\_C \qquad (102)$$

with the constraint:

$$n\_A/x = n\_B/y = n\_C/z \qquad (103)$$

The condition for equilibrium is:

$$\Sigma_i \mu_i \nu\_i = 0 \qquad (104)$$

wherein we define the equilibrium constant:

$$K = \Pi\_\{i = 1\}^\wedge q\ [A\_i]^\wedge(\nu\_i) \qquad (105)$$

with:

$$\ln K = \Sigma\_\{i =\}^\wedge q\ \nu_i ln\ [A\_i], [A\_i] = N\_i/V \qquad (106)$$

The entropy of mixing for ideal gases leads to:

$$\Delta S = -k\ \Sigma_i N_i ln\ (N\_i/N) \qquad (107)$$

With ΔH=0, the Gibbs free energy changes as:

$$\Delta G = -T\Delta S = kT\ \Sigma_i N_i ln\ (N\_i/N) \qquad (108)$$

$$G = \Sigma_i N_i\ [g_i(TP) + kT\ ln\ (N\_i/N)] \qquad (109)$$

$$\mu_i = g_i\ (TP) + kT\ ln\left(\frac{N_i}{N}\right) + kT \qquad (110)$$

From the Law of Mass Action:

$$\Sigma\_i \nu\_i g_i(T, P) = -kT\ ln\ K - kT\ [1 + ln\ (N/V)]\ \Sigma\_i\ \nu\_i \qquad (111)$$

Therefore:

$$\Delta G\_reaction = G_o - kT\ ln\ K \qquad (112)$$

$$\Delta G\_reaction = -kT\ ln\ K \qquad (113)$$

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