The rate laws of mathematical epidemiology are historically related to the rate laws of chemistry [1]. However, the infection rate law in epidemic models involves a product of the number of infected persons by the number of noninfected persons, which in chemistry would translate into the unusual multiplication of the concentrations of reactants by the concentration of products in the rate law. Indeed, the first mass-action law introduced in 1864 by Guldberg and Waage [2] linked the rate of a chemical reaction to the concentration of reactants but not to the concentration of products. A main idea that quickly followed was that a reaction can occur in two opposite directions and that equilibrium corresponds to the point where the speeds of the forward and backward reaction cancel each other but still involves only the concentration of reactants for each direction of reaction [3]. Chemical thermodynamics established a long time ago that rate constants depend on the reaction activation energy [4] and that mass-action rate laws in their simplest form are compatible with the thermodynamic constant of equilibrium of a chemical reaction [5]. However, the general kinetic form of mass-action rate laws still currently does not follow from first principles in thermodynamics [6]. These rate laws remain phenomenological relations requiring experimental validation [7].

Prigogine et al. have shown that close to equilibrium, the speed of a chemical reaction should be proportional to affinity [8], the thermodynamic driving force of a chemical reaction that varies with entropy during the reaction. At equilibrium, affinity is zero, and the reaction quotient equals the constant of equilibrium. Prigogine and Defay derived an equation of evolution for affinity, leading to an exponential relaxation towards equilibrium when the rate of variation of the other state parameters (pressure, temperature) is small [9], but assumed that the linear dependence of the reaction rate on affinity was valid only close to equilibrium [8]. Predicting the reaction rate from the time evolution of affinity was once attempted but using an empirical decay rate law [9]. We present here a kinetic theory based on the idea that an exponential relaxation of affinity towards equilibrium determines the rate of chemical reactions. This convergence mechanism is analogous to stress relaxation in a simple liquid suddenly put out-of-equilibrium [10]. In affinity relaxation theory (ART), the reaction rate depends linearly on affinity, even far away from equilibrium. The theory removes the need to consider separate forward and backward reactions and remarkably predicts a significant time delay in the peak reaction rate that is nonexistent in conventional chemical rate laws. Strikingly, the thermodynamic rate laws obtained in the ART model involve both the concentration of reactants and products, similar to the infection rate law of epidemic models.

Looking at actual epidemic data, we found an even closer analogy between this kinetic theory of chemical reactions and epidemic dynamics. Considering the analog of affinity for an epidemic wave, an epidemic appears, since the start of the outbreak, as an exponentially slowing down process. In this analogy, the epidemic would converge towards an equilibrium state where the total number of infections has the highest probability of occurring for a given population size. The entropy of mixing between noninfected and infected people is a measure of this probability. The exponential relaxation of the epidemic ‘affinity’ nevertheless leads to an epidemic wave that rises until reaching a peak and falls beyond. Interestingly, the shape of the epidemic wave directly follows the parameters controlling the initial exponential relaxation, which opens the possibility to make early projections of an epidemic outbreak evolution and anticipate the time and amplitude of the epidemic wave peak. An iconic example of these relaxation dynamics is the first COVID-19 wave in the United Kingdom, where we find an exponential relaxation of the epidemic affinity lasting more than four months. Furthermore, we find that deviations from a pure exponential relaxation process can be reproduced by linear superimposition of a series of independent subwaves, adding together to produce the main wave shape. Through a detailed analysis of the fourth COVID-19 wave in France and the first half of the fifth wave, we find that the starting time of each subwave matches changes in social behavior due to public health decisions or major holiday travel times, showing the sensitivity of the relaxation process to perturbations.
To illustrate the new predictions of the ART model, we consider here the simplest chemical reaction \( A \rightleftharpoons B \). \( x_A \) and \( x_B \) are the number fractions of molecules \( A \) and \( B \). The equilibrium reaction constant is \( K_e = x_B/e/x_A/e \). We note \( K = x_B/x_A \) the reaction quotient corresponding to the out-of-equilibrium value and the value at an initial reference time \( K_o = x_B/o/x_A/o \). For an ideal solution, the affinity of the chemical reaction at any time is \( A = k_B T \ln(K_e/K) \). Assuming an exponential relaxation of affinity towards equilibrium \( A_e = A_e^{-x/T} \) [3], the reaction quotient \( K \) verifies:

\[
K(t) = K_o e^{-x/T} K_e^{1-x/T} \tag{1}
\]

This prediction has a mathematical form that falls into the family of Gompertz functions [11][13]. To find the corresponding reaction rate, we express the link between the extent of reaction \( \xi \) and the reaction quotient \( K \). In the simple chemical reaction considered here, the number of molecules are \( N_A = N_A/o - \xi \) and \( N_B = N_B/o + \xi \), and the number fractions \( x_A = N_A/N_o \) and \( x_B = N_B/N_o \), where \( N_o = N_A/o + N_B/o \). The reaction rate is then:

\[
\frac{d\xi}{dt} = \frac{N_o}{\tau k_B T} x_A x_B A \tag{2}
\]

This relation is valid for all values of \( A_o \), however small or large. Thus, the reaction rate varies linearly with affinity even far from equilibrium. Second, there are no forward or backward reactions in this expression. The reaction direction depends only on the sign of affinity. If \( K_o < K \) (resp. \( K_o > K \)), affinity is positive (resp. negative), and the reaction will proceed in the forward (resp. backward) direction. In this approach, there is no longer a need for the concept of forward and backward reactions that cancel each other at equilibrium [3]. Third, the mass-action rate law appears to be an approximation of this theoretical prediction. The usual mass-action rate law states that \( d\xi/dt = k_+/N_o x_A - k_-/N_o x_B \), where \( k_+ \) and \( k_- \) are the kinetic constants of the forward and backward reactions, leading to an exponential evolution of \( \xi \) and \( d\xi/dt \). In the case of a complete forward reaction \((k_+ \gg k_-)\), Eq. \( 2 \) shows that \( k_- \) is not a constant but evolves as the product of affinity and fraction of \( B \) molecules \( x_B A \), which has a bell-shaped variation.

Here, we consider the time evolution of the rate law Eq. (2) (Fig. 1(a-c)) for various equilibrium fractions \( x_e \) and initial fractions \( x_o < x_e \) of molecules \( B \). When the initial fraction is small enough, a peak in the reaction rate occurs at a fraction \( x_p \) that depends only on the equilibrium fraction \( x_e \) (Fig. 1(d)). The peak reaction rate is then (Fig. 1(e)):

\[
\frac{d\xi}{dt} \bigg|_p = \frac{N_o x_p (1-x_p)}{\tau (1-2x_p)} \tag{3}
\]

and occurs at time (Fig. 1(f)):

\[
t_p = \tau \ln \left( \frac{A_o}{A_p} \right) \tag{4}
\]

where \( A_p \) is the value of affinity at fraction \( x_p \). The overall shape of the reaction rate depends on the equilibrium fraction (Fig. 1(g)). Eq. (4) shows that a peak time exists only if \( A_o > A_p \) (here, \( A > 0 \)), which means \( x_o < x_p \). This is a necessary condition for the appearance of a delayed peak rate. The time delay increases with smaller initial fractions of \( B \) molecules (Fig. 1(f)). In the opposite case where \( x_o > x_p \), the maximum reaction rate occurs at the initial time and decreases almost purely exponentially with time. In that case, the classical mass-action rate law remains a very good approximation.

From a theoretical perspective, rate laws proportional to both the amount of reactant and product exist in the distant field of mathematical epidemiology [11]. A central assumption in most epidemic models is indeed that the rate of infection grows with the product of the number of susceptible persons by the number of infected persons, which is analogous to the product of the \( A \) and \( B \) molecule fraction that appears in Eq. (2). As an example of epidemic data observations, we show in Fig. 2(a-b) the daily rate of COVID-19 mortality in the UK [13]. We observe that the shape is very close to the reaction rate predicted by Eq. (2) when the equilibrium fraction is \( x_e = 0.5 \) (i.e. \( K_e = 1 \)), and the initial fraction of \( B \) molecules is \( x_o \sim 1.2110^{-7} \). Other values of equilibrium fractions \( x_e \) would produce a different shape (Fig. 1(g)). In this analogy between chemical reactions and epidemics, an epidemic would converge towards an
FIG. 2. (a) The reaction rate of a simple chemical reaction with an equilibrium fraction close to 0.5 very well describes the shape of an epidemic wave, here the daily mortality rate in the United Kingdom (19). (b), Same data as in (a), shown in logarithmic scale. (c) The daily rate of the logarithm of total mortality displays almost purely exponential behavior for more than 4 months. See Supplementary Materials for details on the fitting procedure of the ART model.

equilibrium where the entropy of mixing between noninfected and infected persons is close to its maximum value. This would happen when the number of possibilities for choosing a given number of infected people among a given population size is highest, which is equivalent to choosing \( N_i \) so that the binomial coefficient \( N_0! / [(N_0 - N_i)! N_i!] \) reaches its maximum value (for large populations \( N_0 \) and \( N_i \), the logarithm of the binomial coefficient and the entropy of mixing are proportional). As the binomial distribution function strongly peaks at \( N_i = N_0/2 \) when \( N_0 \) is large, fractions of the infected population above 50 percent are increasingly and rapidly less likely to occur and would lead to a decrease in the entropy of mixing. Such entropic considerations help understand why Herd immunity would happen mostly when at least 50 percent of a population is immune [16, 17].

Furthermore, we found that the rate of the logarithm of total mortality in the UK was almost purely exponential for more than four months (Fig. 2(c)). In the ART model, this quantity is related to the rate of change in the chemical potential of molecules \( B \) which contributes to the exponential relaxation of affinity. This would mean that an epidemic tends to converge towards an equilibrium state since the early instants of the epidemic outbreak. The fluctuations observed in the exponential decrease may be a sign of changes in the conditions in which the epidemic is spreading. We illustrate possible origins of such fluctuations by considering the number of cases that occurred during the more recent fourth COVID-19 wave in France [15]. In Fig. 3(a), we observe a globally decreasing quantity but not a pure exponential quantity. We decompose this behavior into several linearly superimposed waves, or subwaves, leading to a very good description of the daily rate of cases (Fig. 3(b-c)). For the first subwave, we proceeded by choosing the date range that agrees best with the ART model, exploring many different possibilities for the first and last date of the date range considered (Supplementary Material). For the following subwaves, we added data until a date that is also optimum for the ART model.

FIG. 3. (a) The daily rate of the logarithmic case number during the Fourth wave in France is not a simple exponential. It can be decomposed into several superimposed waves or subwaves. (b) The corresponding daily rate of cases on a logarithmic scale allows visualization of each subwave’s starting time. (c) Same as (b) shown on the more usual linear scale. The time range of data used for each subwave is shown in (d) as a vertical bar. The corresponding model parameters are shown in (d), (e) and (f). The starting time of each subwave relates to social behavior changes (deconfinement steps on June 9 and June 30, major summer holiday crossover around national holiday July 14 and July 31-Aug. 1 week-end, or end of free COVID-19 tests on Oct. 15). See Supplementary Materials for details on the fitting procedure of the ART model.
following subwave. For each subwave, the corresponding date range of analyzed data is shown in Fig. 3(d) (vertical bars). The initial time to of each subwave occurs between 2 and 6 weeks before the first date added to the newly analyzed data (except for subwave 2). Remarkably, subwave 1 starts on June 13, 4 days after France relaxed social restriction, allowing, for instance, inside dining with half capacity. Subwave 2 starts on July 4, 4 days after the end of most restrictions, allowing, for instance, inside dining with full capacity. Subwave 3 starts on July 14, a national holiday and 4 days after the first major summer holiday crossover during the weekend of July 10-11. Subwaves 4 and 5 both start after the biggest week-end of summer holiday departure of July 31-Aug. 1, respectively 5 and 9 days after. Subwave 6 starts on Oct. 15, at the same time the end of free COVID-19 tests in France started. Thus, all subwaves detected by the ART model seem to correlate with important event dates related to public health policy changes or major travel times. Moreover, for subwave 6, the optimum value has just been reached at the time this article was written (see Supplementary Material), indicating that a new subwave may have been triggered and is competing with the current subwave. A sign of this is the departure of the ART model convergence for subwave 6 from the peak observed on Fig. 3(d). Also, the slow-downing of the ART model leads to a new formulation of mass-action law kinetics. How microscopic kinetic laws of interaction between species translate into a macroscopic evolution of entropy towards its equilibrium value remains an open issue.

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