Proceedings of the
International School of Physics
"Enrico Fermi," Varenna, Italy

course **16** DIRECTOR: N. Rashevsky

PHYSICOMATHEMATICAL ASPECTS OF BIOLOGY

ACADEMIC PRESS New York and London

Introduction to the Course.

N. RASHEVSKY

Direttore del Corso

This year marks a significant departure from the usual programs of the International Summer School of the Italian Physical Society. This time the program includes a field which lies on the border-line of physics and biology. This is a particularly important innovation because frequently the most important milestones in the development of Science have been characterized by the discovery of close relations between what appeared at first as unrelated fields. In pure physics we may mention as examples the establishment by Maxwell of the close relation between electromagnetism and light, which made the latter a part of the former; or the discovery of such phenomena as the Zeeman effect which introduced the new branch of physics—magneto-optics.

The existence of physical aspects of biology has been apparent for a very long time. The very existence of biological phenomena can be perceived by us only through their *physical* manifestations. The locomotion of organisms, the circulation of blood, the movement of an organism under the influence of light, sound, or heat, are basically physical phenomena. Attempts at *explaining* these and similar phenomena in terms of known physical laws are almost as old as biology itself. It must be remembered, however, that compared to physics, biology is still a very young science. Unfortunately either due to the complexity of some biological phenomena or due to insufficient knowledge of physics by some of the older biologists, explanation of some biological phenomena in terms of physics was not found in spite of assiduous efforts. This has led to a school of thought amongst the biologists that life is essentially a non-physical, or extra-physical phenomenon, and is not reducible to physics. However, with the development of physical techniques in biology as well as with the increased training of biologists in physics, the number of such « pessimists » has appreciably decreased. Moreover many

investigators feel, that it is possible to study fruitfully the physical mechanisms of separate biological phenomena without touching upon the dangerous question of whether the ultimate basic processes of life can be reduced to physics.

Of course everybody will agree with me that we cannot postulate *a priori* that *all biological phenomena* can be explained in terms of *the contemporary* (1960) *physics*. Classical physics, in particular classical electrodynamics, did give an excellent quantitative explanation of a very vast array of physical facts. Yet it failed in explaining such phenomena as the Michelson experiment or as the Trouton-Noble experiment, and had to be generalized into the present relativistic form. Similarly a number of spectroscopic phenomena proved refractory to an explanation in terms of classical physics and quantum mechanics had to be introduced. But does this make the above mentioned phenomena unphysical or extraphysical? Certainly not. It is perfectly possible that in order to explain *all* the known biological phenomena as well as those still to be discovered, we shall have to generalize and extend contemporary physics, in particular quantum mechanics. And if we have to do so, this will not make the biological phenomena in any way extraphysical. However, until the necessity for such a generalization of physics becomes quite evident, there is no use to worry about it. On this interesting point I shall touch in my last lecture.

As we said, biology is still a relatively young science. Much younger is the borderline field of biophysics. Still younger is a branch called mathematical biophysics, or mathematical biology, which stands in the same relation to experimental biophysics or biology as mathematical physics stands to experimental physics. As you possibly know, I happen to be a representative of this youngest of all branches.

When I received the gracious invitation from the Italian Physical Society to organize a course in biophysics, I was faced with more than a dilemma: either I could choose as a subject of the course some special branch of experimental biophysics and invite leading scientists in this field to discuss it. Or I could devote the whole course to some branch of mathematical biophysics which is much closer to my heart and which I feel much more qualified to handle. Or, finally, I could choose to present a general view of experimental and mathematical biophysics, properly blended, as any mathematical and experimental science should be. I chose the latter course. I felt that inasmuch as this is the first International Course in this borderline field, it is preferable to give our students and listeners a general survey of the field, rather than a detailed cross-section of a specialized branch. I am also deeply convinced that the successful development of any science is contingent upon a harmonious co-operation between experiment and theory.

On our distinguished panel of lecturers we have both theoreticians, like

Professor LANDAHL, or Professor BARTHOLOMAY, as well as experimental scientists, like Professor BOERI, Professor POLISSAR and Professor DEFARES, and Doctors BOUMAN and WISE. But the experimentalists have also been engaged in some important theoretical work, while at least some of the theoreticians have been very closely connected in their work with experimental problems.

Although the science of biophysics, both experimental or theoretical, is very young, yet it already has developed to a very large extent. To cover the whole field in the short period of three weeks is impossible. The general course in mathematical biology given at the University of Chicago, takes nine months. Therefore we had to limit ourseves to selected topics. Professor BOERI will discuss enzyme reactions which offer many interesting physical aspects. He will conclude with the discussion of the challenging problem of the DNA molecule, which thrills equally biologists and physicists. Professor BARTHOLOMAY will discuss reaction rates, a problem closely connected with Professor BOERI's. Dr. BOUMAN will discuss the physics of sensory phenomena, while Professor DEFARES, Dr. WISE, and Professor LANDAHL will discuss some physico-mathematical aspects of the functions of the respiratory tract. Dr. WISE will also devote some lectures to problem of radiation hazards. Professor POLISSAR will discuss his work on some physico-mathematical aspects of cardiac functions. Professor LANDAHL will also discuss some theoretical aspects of sensory phenomena, as well as the phenomena of diffusion, which are so vital in biology, and the general theory of the central nervous system. A number of other important phenomena, such as for example circulation, the function of the digestive tract, etc., will have to be left out for lack of time. Perhaps future courses could be devoted to them.

Insofar as their theoretical aspects are concerned all the above mentioned discussions will deal basically with what may be called physico-mathematical models of different biological phenomena. Mathematical biology should, however, attempt more than that. Like mathematical physics it should attempt to establish general mathematical principles. Such principles *per se* do not explain any given complex phenomenon, just as Newton's principles of motion do not explain *alone* let us say the behavior of an ideal gas. But in conjunction with specific assumptions or models of given phenomena, such general principle should be applicable to any case. In my four lectures I shall present a still very tentative formulation of two such principles.

At this time it is appropriate to record with feelings of deepest sorrow the untimely death of Professor H. DE VRIES, who was one of the first to accept my invitation to this course. I also regret to inform you that Professor THORSEN TEORELL, who expressed a great interest in the course and hoped to be able to join the panel of lecturers, was prevented from doing so by other assignments.

* * *

Nel concludere questa breve introduzione, sono certo di esprimere i sentimenti di tutti noi porgendo i sensi della nostra gratitudine all'Amministrazione della Villa Monastero per la sua cordialissima ospitalità. In particolare, vorrei ringraziare la Società Italiana di Fisica, il suo Presidente, Professor POLVANI, il suo Vice-Presidente, Professor CALDIROLA, ed il suo Segretario Professor GERMANÀ, per aver reso possibile questo Corso di lezioni ed avere così aiutato il progresso di una scienza nuova e importante, una scienza che congiunge la Fisica con la Biologia e da entrambe deriva i suoi fondamenti. Questo nuovo ramo dello scibile — ne sono fermamente convinto — è destinato a fornire nel futuro un importante contributo per il benessere del genere umano.

Physico-Mathematical Foundations of Reaction Rate Theory.

A. F. BARTHOLOMAY

Harvard Medical School - Boston, Mass.

1. – Introduction.

When chemical substances react, either alone or in co-operation with other « reactants » to produce new « product » compounds, two important aspects of the reaction are 1) its detailed mechanism and 2) the rates of the various processes involved. The elucidation of both of these factors comprises the branch of chemistry called « chemical kinetics ».

A whole theory of reaction rates has evolved, particularly during the first half of the present century. It is the purpose of these lectures to present the foundations of this theory, with particular emphasis on the physical principles involved and on the related mathematical models constructed from these principles.

The importance to the chemist of reaction rate theory may in fact be said to lie in these mathematical models which provide a mathematical framework with reference to which proposed mechanisms may be analyzed and checked. From a broader scientific point of view this subject has also served as a prototype for the construction of kinetic theories in various branches of biology and points the way to a generalized kinetics theory or theory of material transformations [1-3].

It will be seen that advances in physics immediately prior to and during this fifty year period of development of rate theory have been responsible for the passage of rate theory through a succession of various distinct stages, each stage consisting of a refinement and extension of the former one. In particular, direct applications of such physical theories as molecular gas kinetics, Maxwell-Boltzmann statistics, Brownian motion, and Maxwellian velocity distributions have been used extensively in the course of this development. The influence of physics may be seen most explicitly in the most recent « collision » and « transition-state » theories. It appears completely enmeshed with

chemical theory in the most recent critical examinations of the fundamental bases of these theories which will be found in the chemical literature during the past ten years.

Mathematical models appearing in the theory have the form, usually, of ordinary differential equations or systems of such equations joining the rate of change of the concentration of one chemical species to the concentrations of the other reactants and products present in the reaction mixture. Such models are suggestive of the Lagrangian equations of motion in classical physical mechanics. Despite its discrete nature, the « concentration variable » (in the final analysis the unit is the number of molecules per cubic centimeter, say) is treated as an ordinary differentiable function of time. Thus, as in the mechanical analogues, the deterministic requirement made is to the effect that, given the initial concentrations and parameters (such as temperature, pressure, pH), the integration of such equations leads to analytic expressions for the concentrations of all the chemical species involved which allow one to predict precisely their magnitudes at any subsequent instant of time.

This pattern remains even to the present day, despite the evidence of random fluctuation in the concentration-time data produced in the course of a given reaction run and the quantum and statistical mechanical assumptions of a probabilistic kind particularly in the most modern form of the theory. While such considerations point to stochastic process representations which are being advocated by a few investigators [4-6], the adoption of such representations as general procedure would mean a real mathematical departure from even the most current theory. It is a remarkable fact that the transition from one theory to the next over the entire 50 year period from 1900 to 1950, as we shall see, has always amounted to a further decomposition of the « rate constant » into factors which result from the new probabilistic and physical considerations. Thus, the mathematical representation undergoes little change in form in passing from one theory to the next, say, the predicted values of rate constants reflecting almost entirely the new ideas which have been added.

A shift to stochastic models would bring about changes even in the related statistical analysis of kinetic data and provide a rationale, possibly, for separating some of the factors responsible for fluctuation of data about projected smooth time courses. Aside from assigning as the cause of such fluctuation, simply random errors and uncontrollable factors, the current deterministic theory cannot predict the occurrence of such fluctuation about the expected smooth time course as a function of mechanism. On the other hand, the stochastic point-of-view emphasizes that the occurrence of random irregularities in data is at least partly an inherent characteristic of the mechanism of reaction and provides a mathematical basis for analyzing such fluctuations. According to the stochastic theory the ultimate transformation of a given molecule is a relatively « rare event » when considered as the culmination of a

long sequence of random « ineffective » collisions with other reactant molecules.

The tremendous speed of most reactions, the great number of molecules involved, upwards of 10^{23}, usually, the relative insensitivity to individual events of currently employed kinetic apparatus, combined with predictable quantum-mechanical limits of resolution, and the mathematical complexities of the young stochastic theory, all point to the greater practicability of pursuing a deterministic approach. On the other hand, a stochastic theory based on discrete events appears to be a more fundamental and ultimate objective, if certain of the practical disadvantages can be overcome, particularly in view of the identity of the stochastic « mean values » with the deterministic time courses (*). Certainly this way of thinking would pave the way for the introduction of Monte Carlo methods (*), and, in conjunction with high-speed computers, could lead to a useful new kind of « paper chemistry ».

Because of the current lack of a complete stochastic rate theory, these lectures will emphasize the classical deterministic rate theory development. Thus, in keeping with the main line of development up to the present time, the function of the mathematical reaction rate model will be thought of as the prediction of the concentration variable precisely at a given time (**).

2. – Early origins.

■ The beginnings of a whole theory of chemical reaction rates may be traced to the much older and persistent doctrine of « chemical affinity », originally introduced as a qualitative notion by ALBERTUS MAGNUS seven centuries ago. Much later BERGMANN [7] postulated that there was a « force », called « affinity » operating between certain interactive chemical substances, which is an invariant under identical conditions of reaction and which is independent of the masses of these substances. The universal force of gravity was held responsible for this force. Variations in affinity would therefore be observed by changing the form and positions of the small particles of the reacting substances.

Many of his predictions and speculations based on this hypothesis were attacked and shown to be erroneous. A leading opponent in these matters was BERTHOLLET [8] who was responsible for introducing the « concentration » (*i.e.*, the amount of chemical reactant per unit volume of reaction mixture)

(*) See reference [6].
(**) As opposed to obtaining the probability distributions of such concentrations at any time, in the stochastic sense.

as an additional factor in control of the course of a chemical reaction. In 1803 he concluded [8] « the chemical affinity of a substance depends on the force of its affinity, and on the mass which is present in a given volume ». His conclusion was in turn rejected *in toto* by his contemporaries because he had incorrectly deduced that, given the same reactant chemical species, the final products were not always predictable and would be, in fact, a function of the amounts of reactants present. However, the relationship of affinity to concentration was restudied in subsequent years. The work of ROSE [9] about forty years later, on the decomposition of alkaline-earth sulfides by water and on the reversible action between a soluble carbonate and insoluble sulfate once more centered attention on the concentration factor.

In the meanwhile WENZEL [10] had begun identifying affinity with the rate of reaction, pointing out, for example that the « rate of solution » of certain salts was proportional to the concentration of acid. WILHELMY [11] is generally credited (*) with having made the first kinetic measurements. In 1850 he published the results of his measurements of the rate of sucrose inversion, calling attention to the influence of concentration on rates. A few years later BERTHELOT and ST. GILLES [13] published similar data on the rate of combination of acid and alcohol in the maintenance of an equilibrium between ethanol, acetic acid, ethyl acetate and water. They observed that the rate of the forward reaction was directly proportional to the acid and alcohol concentrations. At about this time A. N. WILLIAMSON [14] made studies of the esterification of alcohol by concentrated sulfuric acid, pointing out that though the reaction appeared to become stationary, this was because of the simultaneity of forward and reverse reactions and that equilibirum was really a dynamic condition.

In 1867 C. M. GULDBERG and P. WAAGE [15] formulated the celebrated Law of Mass Action: the rate of chemical reaction is proportional to the active masses of the reacting substances, the molecular concentrations of the substances in solution or in the gas phase being the usual measure of active mass. The constant of proportionality was first referred to by them as the « affinity constant » and later [16] changed to « coefficient of velocity. » The mathematical interpretation and applications of this law to various mechanisms of reaction constituted the very beginning of a theory of the rates of chemical reactions and rate processes in general. The mathematical model which it generated is discussed in the next section and referred to as the « classical deterministic model. »

(*) See LAIDLER [12].

3. – The classical deterministic model.

Before discussing the mathematical models for various basic mechanisms that arise by application of the Law of Mass Action, it may be of interest to draw an analogy between this law and the physical law of attraction between two masses. While this represents a retrospective view it seems likely, in view of the applications made subsequently, that this physical analogy may have been a working hypothesis.

For the purpose of this analogy, identifying reaction *rate* with a *force F* (of affinity, for example) the Law of Mass Action applied to two reactant species, say A_1 and A_2, which combine in equal proportions to form new products, can be represented by the equation

$$(1) \qquad F = k \, \frac{m_1}{V} \cdot \frac{m_2}{V} \, .$$

Here m_1 and m_2 are the amounts of substances A_1 and A_2 present and V is the total constant volume. Referring back to Bergmann's affinity hypothesis in which F is regarded as an effect of the force of gravity; and identifying m_1 and m_2 with the masses of two particles located a « distance V » apart; and the rate constant k, with a « universal constant » k, the analogy with the physical law of mutual attraction between two particles is obvious. If the analogy is valid, then, we would expect rates in complicated mechanisms to be combined in a fashion similar to the combination of vectors in a mechanical system. This, indeed, turns out to be the case (*v.i.*).

The reduction of equation (1) to the more usual form is accomplished by the following reasoning. Since m_1 and m_2 are changing over the entire course of the reaction mixture, m_1 and m_2 are really functions of time; and because of the great numbers of molecules being transformed over small periods of time it has become customary to regard m_1 and m_2 as continuous, in fact, differentiable functions of time. Accordingly, the rate of change is expressed as the instantaneous rate, or the derivative and eq. (1) is therefore rewritten as

$$(2) \qquad \frac{1}{V} \, \frac{\mathrm{d}m_1}{\mathrm{d}t} = - \, k \, \frac{m_1}{V} \cdot \frac{m_2}{V} \, ,$$

the negative sign before the positive constant indicating that as the reaction proceeds, species A_1 decreases at the rate shown. (In this case $\mathrm{d}m_1/\mathrm{d}t$ may be replaced by $\mathrm{d}m_2/\mathrm{d}t$ to give the rate of change of species A_2).

One further refinement of notation is necessary to obtain this rate expression in the customary form. Since that notation relates the rate equation to

the « stoichiometric equation » of the reaction, it is necessary first to discuss the dual role of such equations in chemical kinetics. Stoichiometric equations are algebraic-like expressions (*) for balancing the atomic composition of re-actants and final products; or looked at, from another point of view, the weights of the substances involved. Choosing a simple example,

$$(3) \qquad\qquad 2\,H_2 + O_2 = 2\,H_2O$$

is a stoichiometric equation expressing the condition that 2 weights of hydro-gen gas must combine with 1 of oxygen to obtain 2 weights of the product, water; or that the total of 4 hydrogen atoms and 2 of oxygen occurring in each hydrogen-oxygen combination must be accounted for fully in the liberated products—via 2 molecules of water. If this « overall » stoichiometric expres-sion were obtained by direct transition (say, irreversibly) from the reactants to the products then it would also represent the « mechanism » (**) of reaction. To indicate mechanism, often, an arrow is used in place of the « equality » sign, with the corresponding rate constant written over the arrow.

$$(4) \qquad a_1 A_1 + a_2 A_2 + \ldots + a_M A_M \xrightarrow{k} b_1 B_1 + b_2 B_2 + \ldots + b_N B_N$$
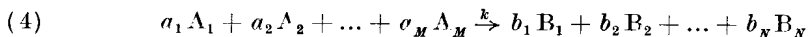
i
s an example of a more general stoichiometric expression, where a_m mole-cules of chemical reactant species A_m $(m = 1, 2, \ldots, M)$ interact with a_j mo-lecules of A_j $(j \neq m, \ j = 1, 2, \ldots, M)$ to produce the products on the right in the proportions shown by the b-coefficients. The bracketed chemical symbols, $[A_m]$ $(m = 1, 2, \ldots, M)$ and $[B_n]$ $(n = 1, 2, \ldots, N)$ represent the « concentrations of » the corresponding chemical species. Thus, *e.g.* in the simple bimolecular reaction discussed above, the implied mechanism is represented by

$$(5) \qquad\qquad A_1 + A_2 \xrightarrow{k} B \ ,$$

say, and corresponding to eq. (2) the rate expression, or « mathematical rate model » (*v.i.*) becomes

$$(6) \qquad \begin{cases} \dfrac{d[A_1]}{dt} = -k[A_1][A_2] \ , \\[2mm] \text{initial conditions: } [A_1] = A_{10}, \quad [A_2] = A_{20}, \quad [B] = 0 \ . \end{cases}$$

The term « bimolecular » used in connection with (6) refers to the necessity for the successful co-operation of 2 molecules of reactant (in this case, of dif-

---

(*) See BARTHOLOMAY [17b] for a discussion of the very special mathematical context of such expressions.

(**) This point will be discussed at greater length below.

ferent kinds) for a single chemical transformation. « Equation » (3) is an example of a termolecular mechanism, requiring a triplet of 2 reactant molecules of one kind and one of another kind for reaction. The simplest « elementary » reaction is the « unimolecular decomposition » $A \rightarrow B$. The « order of molecularity » in general refers to the total number of reactant molecules, either of the same or of different kinds, for reaction to occur. Expression (4) has for its molecular order, the integer $\sum\limits_{m=1}^{M} a_m$.

It is assumed in this discussion that the mechanisms are « complete » or « elementary » in the sense that there are no intervening steps separating reactants from products as in the stoichiometric expression. Rate theory makes contact with experimental considerations at precisely such a point: if the mechanism is complete, then the concentration-time data should fit the form of the expression predicted by the mathematical model corresponding to that mechanism. An indication that this is not so would come from the fact that the « kinetic order » of the data does not agree with the *molecular order*. *Kinetic order* is an empirical concept, which should not be confused with « molecular order ». It is defined in cases where the rate estimated from data by regression or curve-fitting appears to be of the type (*) $\prod\limits_{m=1}^{M} [A_m]^{a'_m}$, where a'_m is not necessarily an integer, in which case the kinetic order is $\sum\limits_{m=1}^{M} a'_m$.

Clearly if a step of a reaction (or the complete reaction) is of molecular order $\sum\limits_{m=1}^{M} a_m$, it will generate rate data which have for their kinetic order the same number, partitioned in the same way. Where there is a disparity between the two numbers, then the mechanism proposed does not account for the kinetic expression obtained and a different mechanism must be hypothesized. Good examples of this are furnished by the following reactions. Hydrogen iodide is known to be formed in a bimolecular reaction between hydrogen and iodine:

$$(7) \qquad\qquad H_2 + I_2 \rightarrow 2\,HI \ .$$
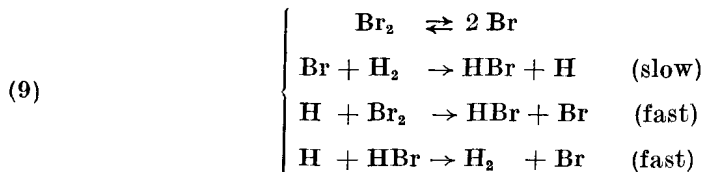
It would therefore seem reasonable to expect that the formation of hydrogen bromide follows a similar elementary mechanism:

$$(8) \qquad\qquad H_2 + Br_2 \rightarrow 2\,HBr \ .$$

However the kinetic data obtained have been shown not to be of the second order: they do not agree with the second order molecularity property

(*) See eq. (23) below.

of the proposed bimolecular reaction. The finally accepted mechanism for this reaction has been shown to consist of a sequence of several steps, the first of which is « reversible » as indicated by the double arrow:

(9)

$$
\begin{cases}
\mathrm{Br_2} & \rightleftarrows 2\,\mathrm{Br} \\
\mathrm{Br + H_2} & \rightarrow \mathrm{HBr + H} & \text{(slow)} \\
\mathrm{H\ + Br_2} & \rightarrow \mathrm{HBr + Br} & \text{(fast)} \\
\mathrm{H\ + HBr} & \rightarrow \mathrm{H_2\ + Br} & \text{(fast)}
\end{cases}
$$

And in the case of the formation of water from its component gases, equation (3) is correct for the overall stoichiometry, but does not actually elucidate the whole mechanism. In fact, the whole mechanism of this deceivingly simple reaction is so complicated that it has not as yet been completely worked out.

Throughout the remainder of these lectures we shall be discussing only basic, elementary reaction types, unless otherwise indicated, *i.e.*, mechanisms or steps of mechanisms which are complete in the sense that the molecular and kinetic order are assumed to agree. There is no loss of generality in this, for in non-elementary complex reactions, the mathematical models will be synthesized from those corresponding to the individual steps in the whole mechanism formally (in much the same way that the resultant forces on mechanical systems are calculated by composition of individual, independent component forces).

1) *The unimolecular decomposition*:

(10)
$$ \mathrm{A} \xrightarrow{k} \mathrm{B}\,. $$

The corresponding differential equation with initial condition in this case is

(11)
$$
\begin{cases}
\dfrac{d[\mathrm{A}]}{dt} = -\,k[\mathrm{A}], \\
[\mathrm{A}]\ \ = A_0 \text{ initially}\,.
\end{cases}
$$

Integration yields directly

(12)
$$ [\mathrm{A}] = A_0 \exp\left[-\,kt\right] $$

expressing the concentration of reactant A to be expected at time t as an exponential function of time. Thus, to test whether a specific reaction, suspected of being first order molecularly, is unimolecular in fact, one would expect the points $(t, [\mathrm{A}])$ to exhibit « first order kinetics »; *i.e.*, to define a

negative exponential curve. The usual way of testing this hypothesis graphically and of estimating the rate constant as a linear regression coefficient (or slope) is to transform (12) into the form

$$\text{(13)} \qquad \ln (^*) [A] = \ln A_0 - kt$$

and accordingly to plot the natural logarithms of observed concentrations as the ordinate against time t as abscissa (**).

2) *The M-molecular reaction mechanism with unit coefficients*:

$$A_1 + A_2 + ... + A_M \xrightarrow{k} B .$$
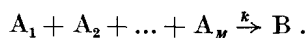
The same differential expression may be written down for each of the reactants (or product **B**, with sign changed):

$$\text{(14)} \qquad \begin{cases} \dfrac{d[A_m]}{dt} = - k \prod_{m=1}^{M} [A_m] , \\ \text{initially, } [A_m] = A_{m0} , \qquad (m = 1, 2, ..., M), \\ [B] = 0 . \end{cases}$$

This of course follows directly from the Law of Mass Action which states that the rate is directly proportional to the concentration of reactive species. If, *e.g.*,

$$\text{(15)} \qquad A_{10} < A_{m0} \qquad\qquad (m > 1),$$

then, since

$$\text{(16)} \qquad A_{10} - [A_1] = A_{20} - [A_2] = ... = A_{M0} - [A_M] ,$$

$$\text{(17)} \qquad \begin{cases} [A_2] = [A_1] + (A_{20} - A_{10}) = [A_1] + c_2 , \\ [A_3] = [A_1] + (A_{30} - A_{10}) = [A_1] + c_3 , \\ \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; , \\ \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; , \\ \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; \cdot \;\; , \\ [A_M] = [A_1] + (A_{M0} - A_{10}) = [A_1] + c_M . \end{cases}$$

(*) Natural logarithms, base e understood, will be used throughout.
(**) For a discussion of first order rate constants and a new rational and for their calculations see BARTHOLOMAY [17a].

With these substitutions into (14) the resulting differential equations in $[A_1]$ has the solution:

$$(18) \qquad \ln\left[\left(\frac{A_1}{A_{10}}\right)^{d_1}\cdot\left(\frac{A_1+c_2}{A_{20}}\right)^{d_2}\cdot\ldots\cdot\left(\frac{A_1+c_M}{A_{M0}}\right)^{d_M}\right] = -kt\ ,$$

in which $d_1,\ d_2,\ \ldots,\ d_M$ are determined by the partial fraction expansion of

$$[A_1]^{-1}\prod_{m=2}^{M}\left([A_1]+c_m\right)^{-1}\ .$$

In the bimolecular case $(M=2)$ this leads to the expression for $[A_1]$ as a function of time:

$$(19) \qquad [A_1] = \frac{A_{10}(A_{10}-A_{20})}{A_{10}-A_{20}\exp\left[(A_{20}-A_{10})kt\right]}\ ,$$

which is monotonically decreasing, reversed sigmoid curve going from A_{10} at $t=0$ to 0 as $t\to\infty$. From the relation $[A_2]=(A_{20}-A_{10})+[A_1]$ one obtains the expression

$$(20) \quad [A_2] = \frac{-A_{20}(A_{20}-A_{10})\exp\left[(A_{20}-A_{10})kt\right]}{A_{10}-A_{20}\exp\left[(A_{20}-A_{10})kt\right]} = \frac{A_{20}(A_{20}-A_{10})}{A_{20}-A_{10}\exp\left[(A_{10}-A_{20})kt\right]}\ ,$$

which shows $[A_2]$ going from A_{20} at $t=0$, to $(A_{20}-A_{10})$ as $t\to\infty$.

The $[B]$ function may be obtained separately by integration of the differential equation

$$(21) \qquad \frac{d[B]}{dt} = k[A_1]\cdot[A_2]\ .$$

Combining the condition

$$(22) \qquad [A_1]+[A_2]+[B] = A_{10}+A_{20}$$

with the additional constraint $A_{10}-[A_1]=A_{20}-[A_2]$, yields

$$(23) \qquad [A_1] = A_{10}-\tfrac{1}{2}[B] \qquad \text{or} \qquad [A_2] = A_{20}-\tfrac{1}{2}[B]\ .$$

The substitution into (21) gives

$$(24) \qquad \frac{d[B]}{dt} = \frac{k}{2}\left(2A_{10}-[B]\right)\left(2A_{20}-[B]\right)\ ,$$

which leads to the integrals

$$(25) \qquad \frac{1}{2(A_{20} - A_{10})} \int_0^{[B]} \frac{dx}{2A_{10} - x} + \frac{1}{2(A_{10} - A_{20})} \int_0^{[B]} \frac{dx}{2A_{20} - x} = \frac{k}{2} \int_0^t d\theta \, .$$

Now since $A_{10} < A_{20}$, it can be assumed that $[B] < 2A_{10}$ and certainly $[B] < 2A_{20}$, so that singularities are avoided in the integration, giving simply

$$(26) \qquad -\frac{1}{2(A_{20} - A_{10})} \ln (2A_{10} - x) \Big|_0^{[B]} - \frac{1}{2(A_{10} - A_{20})} \ln (2A_{20} - x) \Big|_0^{[B]} = \frac{k}{2} t \, ,$$

$$(27) \qquad [B] = 2A_{10}A_{20} \frac{1 - \exp [(A_{20} - A_{10})kt]}{A_{10} - A_{20} \exp [(A_{20} - A_{10})kt]} \, .$$

Alternatively, (27) may be derived algebraically from the expression for $[A_1]$ or $[A_2]$ by noting that (22) may be solved for $[B]$ to give

$$(28) \qquad [B] = (A_{10} - [A_1]) + (A_{20} - [A_2]) \, ;$$

and since

$$A_{10} - [A_1] = A_{20} - [A_2] \, ,$$

$$(29) \qquad [B] = 2 (A_{10} - [A_1]) \, .$$

Substituting from (19) into (29),

$$(30) \qquad [B] = 2 \left\{ A_{10} - \frac{A_{10}(A_{10} - A_{20})}{A_{10} - A_{20} \exp [(A_{20} - A_{10})kt]} \right\} ,$$

which reduces to (27).

The analytic expressions for $[A_1]$, $[A_2]$ and $[B]$ all involve logistic shaped curves or components to which the various special methods for estimating rate constants of logistic curves may be applied (*). It is interesting to note the universality of the logistic curve which is at the heart of biological growth theory. Such curves also arise in connection with autocatalytic processes in chemistry.

While we shall not go into details in other examples, the mathematical details of this case have been worked out completely in order to illustrate the combination of algebra with the integration process which is so characteristic of the mathematical mechanics of this subject. Thus, the complete deterministic mathematical model corresponding to a given chemical reaction

(*) See KEMPTHORNE et al. [18], chap. 8 by K. R. NAIR.

mechanism consists of a differential equation (or set of equations) together with initial conditions and algebraic concentration interdependencies (« material balance conditions »). Of course, to obtain such a rate theory boundary value problem it is necessary to assume that the reaction system is a homogeneous closed system (in the usual physical sense). These lectures are confined entirely to this simplest case. Open systems result in differential equations with additional diffusion terms and constants due to the material exchange of the reaction system with its environment.

3) *The general $\sum\limits_{m=1}^{M} a_m$ molecular case with coefficients greater than unity*:

(31) $$a_1 A_1 + a_2 A_2 + ... + a_M A_M \rightarrow B .$$

The complete mathematical model in this case will be

(32)
$$
\begin{cases}
\dfrac{d[A_m]}{dt} = - k_m \prod_{m=1}^{M} [A_m]^{a_m}, \qquad (m = 1, 2, ..., M), \\[2ex]
\left.\begin{array}{l} [A_m] = A_{m0}, \qquad B_0 = 0 \\ A_{10} = \min\limits_{m}\{A_m\} \end{array}\right\} \text{ initial conditions} \\[3ex]
\left.\begin{array}{l} \sum\limits_{m=1}^{M} [A_m] + [B] = \sum\limits_{m=1}^{M} A_{m0} \\[1ex] A_{m0} - [A_m] = \dfrac{a_m}{a_j} (A_{j0} - [A_j]) \end{array}\right\} \begin{array}{l} \text{material balance} \\ \text{conditions} \\[1ex] (m \neq j) \end{array}
\end{cases}
$$

Noting that $k_m/k_j = a_m/a_j$ $(m, j = 1, 2, ..., M)$, a unique rate constant k may be defined by the relation: $k_m \equiv a_m k$. Another observation to be made is that the initial conditions given are entirely arbitrary; in a particular reaction system, they will be arrived at by experimental considerations.

All of the mechanisms so far discussed have been of the « irreversible type » The simplest « reversible » mechanism would be:

4) *The reversible unimolecular reaction mechanism*:

(33) $$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B .$$

The mathematical model in this case is obtained by considering, *e.g.*, that acting on [A] are two reaction velocity forces

(34) $$\left.\frac{d[A]}{dt}\right|_1 = - k_1 [A] \qquad \text{(forward reaction velocity component)} ,$$

(35) $$\left.\frac{d[A]}{dt}\right|_2 = k_2 [B] \qquad \text{(reverse reaction velocity component)} ,$$