

Det Kgl. Danske Videnskabernes Selskab.

Mathematisk-fysiske Meddelelser. **XVII**, 2.

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ON THE APPLICATION OF  
SMOLUCHOWSKI'S COAGULATION  
THEORY TO THE PROBLEM OF IN-  
TERCORPUSCULAR ATTRACTION

BY

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KØBENHAVN  
EJNAR MUNKSGAARD

1939

Printed in Denmark.  
Bianco Lunos Bogtrykkeri A/S.

## INTRODUCTION

**O**n microscopic examination of suspensions of human red blood cells, an "orientated" aggregation is observed, many of the corpuscles, which are disk-shaped, lying together with their flat sides against each other and forming cylindrical conglomerates. This phenomenon is termed "rouleaux formation"\* by biologists.

Owing to their enormous size in proportion to particles of ordinary hydrophobic colloids, the red blood cells possess Brownian movement only to a very slight degree; yet, in some preliminary experiments concerning the suspension stability of the blood, the writer was able to observe rouleaux within a relatively short time, even in fairly dilute suspensions.

While forces (of adhesion) with a very short range are the cause of the coagulation of most (hydrophobic) colloid solutions, we must assume that it is far-range intercorpuscular forces that bring about the rouleaux formation of the red blood cells.

\* As to studies on rouleaux formation, the reader is referred to the extensive literature on the suspension stability of the blood; comprehensive reviews by FÄHRÆUS<sup>1,2</sup>, WESTERGREN<sup>3</sup>, KATZ and LEFFKOWITZ<sup>4</sup>, and REICHEL<sup>5</sup>.

<sup>1</sup> FÄHRÆUS: *Acta med. scand.* **55**: 1, 1921.

<sup>2</sup> FÄHRÆUS: *Physiol. Rev.* **9**: 241, 1929.

<sup>3</sup> WESTERGREN: *Ergeb. d. inn. Med. u. Kinderh.* **26**: 577, 1924.

<sup>4</sup> KATZ and LEFFKOWITZ: *Ergeb. d. inn. Med. u. Kinderh.* **33**: 266, 1928.

<sup>5</sup> REICHEL: *Blutkörperchensenkung*. Wien 1936.

In hopes of being able, by the determination of such forces, to enquire into the detailed mechanism of erythrocytic aggregation, the author has attempted to generalize SMOLUCHOWSKI's<sup>1</sup> mathematical coagulation theory, so as to make it cover arbitrary attractive intermicellar forces as well.

Besides this indirect method—experiments on the kinetics of coagulation—a direct method is also given, based on a cinematographic record of the movements of the particles.

### I. Colloid Stability.

The dispersity of a colloid solution, on which many important properties depend, is the statistical result of the two antagonistic processes characteristic of colloidal chemistry: dispersion (peptisation, increase in the number of particles or decrease in the size of the particles) and condensation (flocculation, coagulation, decrease in the number of particles or increase in the size of the particles).

If the particles of the colloid solution were entirely at rest and uninfluenced by any forces, the stability would be maximal, and the system would remain unaltered indefinitely.

But the dispersed particles are subject to influences from many forces, primarily the force of gravity, which will try to drive the particles up or down (sedimentation), according to the difference in specific gravity between the particles and the suspending medium, and thus destroy the system.

With a modification of STOKES's formula as known from dispersoid analysis<sup>2</sup> the sedimentation rate for a particle

<sup>1</sup> SMOLUCHOWSKI: *Z. phys. Chem.* **92**: 129, 1917.

<sup>2</sup> GESSNER: *Die Schlämmanalyse*. Leipzig 1931. (*Kolloidforsch.* in *Einz. d. 10*).

or a spherical aggregate with the radius  $r$  and the specific gravity  $D$  is

$$v = \frac{2(D-d)g}{9\eta} r^2 = \text{constant} \times r^2$$

if the specific gravity of the suspending medium is  $d$ , and the coefficient for its internal friction is  $\eta$ , while  $g$  signifies the acceleration of gravity.

This law is valid for sedimentation in dilute suspensions only, no allowance being made for the mutual friction of the particles or other intercorporeal forces.

In case of coagulation the sedimentation rate increases rapidly, on account of the increasing radius of the aggregates, so that precipitation takes place.

As the collision of particles is a condition for coagulation, repulsive or attractive intercorporeal forces, counteracting or promoting the collisions brought about by the Brownian movements, will influence the stability of the system—and this is what the coagulation theory proper deals with.

## II. Methods of Measuring Coagulation<sup>1</sup>.

The forces interacting between the particles of a colloidal solution determine their aggregation and thus the coagulation of the colloid. Hence an ideal investigation of this process would aim at determining these forces. No such method is known, however, and generally an attempt is made therefore, to establish the quantitative course of the coagulation by measuring the "rate of coagulation" (FREUNDLICH<sup>2</sup>).

<sup>1</sup> In this work the term "coagulation" is used only in the colloidal-chemical sense—flocculation or aggregation—without reference to the reversibility or irreversibility of this process.

<sup>2</sup> FREUNDLICH: Kapillarchemie vol. II., 114. Leipzig 1932.

For this purpose various methods have been adopted, of which merely the most important principles will be mentioned here:

- 1) Counting methods, with a microscopic or ultra-microscopic estimation of the number of particles at various times.
- 2) Nephelometric methods, with observation of the transparency of the sol or the intensity of the Tyndall light.
- 3) Measuring the viscosity of the sol.
- 4) Determination of the electrical conductivity of the sol.
- 5) Measuring the flocculation by determination of the specific gravity, direct weighing, or
- 6) quantitative chemical analysis of the flocculated mass, etc.

Of these methods only the counting method ad modum ZSIGMONDY-SMOLUCHOWSKI<sup>1</sup> is of particular interest for the problems to be dealt with in the sequel.

### III. Smoluchowski's Mathematical Coagulation Theory.

On the basis of ZSIGMONDY's experimental findings, SMOLUCHOWSKI<sup>2</sup> developed the first useful theory about coagulation. Even though his theoretic-physical investigation, owing to its nature, is based upon a number of "ideal" suppositions which are hardly completely fulfilled, his theory describes almost quantitatively the coagulation of the hydrophobic colloids.

These suppositions may be summarized as follows:

- 1) that the particles and micellæ are spherical,
- 2) that the primary colloid is monodispersive, and that an approximate monodispersity prevails during the coagulation,

<sup>1</sup> SMOLUCHOWSKI: Z. phys. Chem. **92**: 129, 1917.

<sup>2</sup> Ibid. loc. cit.

3) that each particle possesses a certain sphere of action within which the attractive (adhesive) forces are so great that the particles unite "permanently", while the forces outside this sphere are put equal to zero,

4) that the frequency of the collisions of particles is determined by the Brownian movements only,

5) that other movements of the micellæ—due to sedimentation, stirring, etc.—can be disregarded,

6) that only the stationary distribution of particles round the nuclei of condensation are of significance for the coagulation,

7) that the tendency to aggregation is the same between micellæ of any multiplicity.

The third supposition—that the forces interacting between the particles can be described as such a sphere of action—means a considerable simplification of the mathematical calculation. That this assumption may lead to reasonable results will be evident from the calculations carried out by the writer concerning the dependence of the radius of action upon the intercorpular forces.

SMOLUCHOWSKI first calculates the average number of particles which, owing to their Brownian movements, in a given length of time enter the sphere of action surrounding an arbitrary particle, temporarily assumed immobile, and conceived as a nucleus of condensation.

As a diffusion process is the macroscopic expression of the Brownian movements, the problem can be solved by calculating the corresponding diffusion. If we imagine the nucleus of condensation as a completely absorbent sphere floating in the middle of an infinite medium, the solution of the diffusion equation (written according to the formula for spherical symmetry) must satisfy the following boundary conditions:

At any time the concentration of particles at the surface of the sphere of action must be zero, while outside this surface it must everywhere have a constant value at the time zero.

SMOLUCHOWSKI'S expression for the in-diffused amount consists of two components, one that is independent of the time, and one that is dependent on the time, although its influence subsides very rapidly after the commencement of coagulation.

On account of the component dependent on time, the amount coagulated will at first be a little greater per unit of time, since the concentration of particles just round the nuclei of condensation falls below the constant value which is found everywhere at the time zero.

As soon as such falls in concentration are established round the nuclei of coagulation the condition will be stationary, since now just as many particles will diffuse in as are caught up at the nucleus of condensation.

In the preliminary calculations SMOLUCHOWSKI assumed the nucleus of condensation to be immobile; but, as it is merely a random particle, performing Brownian movements just like the others, allowance has to be made for this property. Since the coagulation is determined exclusively by the relative movement of the nucleus and of the particle, which is merely a new Brownian movement, to which corresponds a diffusion constant equal to the sum of the respective diffusion constants, SMOLUCHOWSKI simply reckons with a mutual diffusion constant twice as large as that of the individual particles.

Finally the concentration of the various aggregates at any time is determined by solving a system of simultaneous differential equations. The differential equations are



highly reminiscent of those known from the kinetics of certain chemical processes or for the disintegration of radioactive substances where a number of intermediate products appear which are again transformed.

With  $\nu_0$  for the initial number of particles (per unit of volume) at the time  $t = 0$  and  $\nu_1, \nu_2, \nu_3$  etc. for the number of single, double, triple etc. particles, the total number of particles is

$$\sum \nu = \nu_1 + \nu_2 + \nu_3 + \dots$$

determined by the differential equation

$$\frac{d\sum \nu}{(\sum \nu)^2} = -\alpha dt \quad \text{where } \alpha = 4\pi DR,$$

as  $D$  is the constant of diffusion, and  $R$  the radius of the attraction sphere. If the numbers of particles are expressed as fractions of the total number,  $\alpha dt$  gives the number of particles caught up by an arbitrary condensation nucleus in the time  $dt$ .

With the initial condition  $\sum \nu = \nu_0$  for  $t = 0$  we get the solution:

$$\sum \nu = \frac{\nu_0}{1 + \alpha\nu_0 t} = \frac{\nu_0}{1 + 4\pi DR\nu_0 t} = \frac{\nu_0}{1 + \frac{t}{T}}$$

The constant  $T = \frac{1}{\alpha\nu_0}$ , which has the dimension of a time, is designated as (half) the coagulation time. For  $t = T$  we get  $\sum \nu = \frac{\nu_0}{2}$ .

By means of the result for  $\sum \nu$  SMOLUCHOWSKI is able to integrate the other differential equations, thus obtaining for the various particles:

$$\begin{aligned} \nu_1 &= \nu_0 \frac{1}{[1 + \alpha \nu_0 t]^2} & \nu_2 &= \nu_0 \frac{\alpha \nu_0 t}{[1 + \alpha \nu_0 t]^3} \\ \nu_3 &= \nu_0 \frac{[\alpha \nu_0 t]^2}{[1 + \alpha \nu_0 t]^4} & \nu_k &= \nu_0 \frac{[\alpha \nu_0 t]^{k-1}}{[1 + \alpha \nu_0 t]^{k+1}} \end{aligned}$$

The number of  $k$ -tuple particles reaches its maximum with

$$t = \frac{k-1}{2} T \text{ and this amounts to } \nu_k = 4 \nu_0 \frac{(k-1)^{k-1}}{(k+1)^{k+1}}.$$

$\nu_1$  and  $\sum \nu$  fall off, at first rapidly,  $\nu_1$  faster than  $\sum \nu$ , later slowly, while  $\nu_2, \nu_3$  etc. rise from zero and pass a maximum, at increasingly later points of time, then again falling off.

Comparison of coagulation measurements is carried out by means of "reduced" curves, obtained by plotting relative numbers of particles  $\frac{\sum \nu}{\nu_0}, \frac{\nu_1}{\nu_0}, \frac{\nu_2}{\nu_0}, \frac{\nu_3}{\nu_0}$  etc. in relation to  $\frac{t}{T}$ , the time in multiples of the coagulation time.

Whether a coagulation follows SMOLUCHOWSKI'S theory may be settled by examining:

1) whether the attraction radius is constant in the course of an experiment,

2) whether the attraction radius is constant at different initial concentrations, or, what amounts to the same thing, whether the initial concentration and the coagulation time are inversely proportional,

3) whether the coagulation probability ( $\alpha$ ) is independent of the particle radius, as

$$\alpha = \frac{1}{\nu_0 T} = 4 \pi D R = \frac{2}{3} \frac{k \theta}{\eta} \frac{R}{r}$$

since  $R$  increases proportionally to  $r$ ;  $k$  is BOLTZMANN's entropy constant;  $\theta$  is the absolute temperature; and  $\eta$  is the coefficient for the internal friction in the suspending medium,

4) whether  $\alpha$  at different temperatures is proportional to  $\frac{\theta}{\eta}$ .

The importance of the radius of attraction is most readily understood by studying the relation between the attraction radius and the particle radius,  $\frac{R}{r}$ .

If  $\frac{R}{r} = 2$  (that is,  $R = 2r$ ), it means that coagulation takes place by contact only. If  $\frac{R}{r} > 2$ , aggregation takes place, according to SMOLUCHOWSKI, if only the distance between the centres of gravity of the particles is less than  $R$ , or equal to  $R$ . With  $\frac{R}{r} < 2$  SMOLUCHOWSKI assumes that only a certain fraction  $\varepsilon$  of the collisions between the particles will result in coagulation; and on this basis he develops his theory of the "slow" coagulation, in which  $\alpha$  is merely replaced by  $\alpha\varepsilon$ .

Of the extensive literature on the measurement of coagulation (by the counting method) only a few works will here be mentioned, some classical and some more recent, for elucidation of the magnitude of  $\frac{R}{r}$ .

ZSIGMONDY<sup>1</sup> determined ultramicroscopically the decrease in the total number of particles  $\sum \nu$  in a gold sol, brought to "rapid" coagulation by the addition of electrolytes. The number of individual particles was calculated by means of the average value for  $\frac{1}{T}$  from several experiments,  $\frac{1}{T}$  being constant throughout the single experiment except for the very first moments. As the single particles showed green, and the aggregates yellow, he was able to determine the

<sup>1</sup> ZSIGMONDY: Z. phys. Chem. **92**: 600, 1917.

number of single particles, which agreed with the calculated numbers for different times. For  $\frac{R}{r}$ , values between 2 and 3 were obtained.

WESTGREN and REITSTÖTTER<sup>1</sup> who likewise examined the variation of  $\sum v$  in a gold sol found  $\frac{R}{r} = 2,3$  (average value).

EHRINGHAUS and WINTGEN<sup>2</sup> who studied the coagulation of gold particles in the borax pearl at 925° C., and determined the decrease of  $\sum v$  with the glowing time, found  $\frac{R}{r} = 2,3$ , except in one experiment where  $\frac{R}{r} = 13,7$ .

$\frac{R}{r} > 2$  may result in two essentially different ways:

1) it may be due to the form and size of the particles, for example, in

a) polydisperse suspensions of spherical particles, owing to the so-called WIEGNER-GALECKI effect<sup>3,4</sup>, when large micellæ act as germs of coagulation.

In the coagulation of polydisperse systems  $\frac{R}{r}$  rarely, even with extreme polydispersity, exceeds the value 7 (WIEGNER and TUORILA<sup>5</sup>).

b) Or in monodisperse suspensions of non-spherical particles (rod or leaf micellæ).

HANS MÜLLER<sup>6</sup> has generalized SMOLUCHOWSKI's theory for arbitrary forms of particles. For the characterization of the form and size of the particles he uses a form constant that corresponds to two times SMOLUCHOWSKI's proportion between the attraction radius and the particle radius.

<sup>1</sup> WESTGREN and REITSTÖTTER: Z. phys. Chem. **92**: 750, 1917.

<sup>2</sup> EHRINGHAUS and WINTGEN: Z. phys. Chem. **104**: 301, 1923.

<sup>3</sup> WIEGNER: Kolloid. Z. **8**: 227, 1911.

<sup>4</sup> GALECKI: Z. f. anorg. u. allg. Chem. **74**: 174, 1912.

<sup>5</sup> WIEGNER and TUORILA: Kolloid. Z. **38**: 3, 1926.

<sup>6</sup> MÜLLER: Koll. ch. Beih. **27**: 223, 1928.

For spherical particles of equal size  $\frac{R}{r} = 2$ .

For thin circular leaves  $2 < \frac{R}{r} < 3$ , i. e., the coagulation of these suspensions practically agrees with SMOLUCHOWSKI'S theory. This has been confirmed experimentally with certain clay sols (TUORILA).

For long rod micellæ, on the other hand,  $\frac{R}{r} = 2 \ln\left(\frac{a}{b}\right)$ , where  $a$  and  $b$  mean respectively half the length and half the thickness, so that considerable deviations may result.

WIEGNER and MARSHALL<sup>1</sup>, working with old sols of benzopurpurin and vanadium pentoxide in which the particles were long rods, found  $\frac{R}{r}$  values up to 100. Owing to the plumper form of the secondary particles as compared to that of the primaries,  $\frac{R}{r}$  falls off rapidly towards the value 2 in the course of an experiment. An additional proof of the significance of the rod form for a more rapid coagulation was found by measurement of the freshly prepared sols that contained very short, almost spherical, particles and therefore coagulated according to the theory of SMOLUCHOWSKI with  $\frac{R}{r}$  values 2–2.4.

2)  $\frac{R}{r} > 2$ , due to intercorpuseular forces.

The examples mentioned under 1) deal with forces of very short range, which are practically only effective when the particles touch each other, and even if the strength of these forces be increased enormously, they will not be able to accelerate the coagulation. But the far-range intermicellar forces may be able to do so, as their increase will cause a convection of the particles to be superposed on the diffusion towards the nuclei of condensation (cf. Section IV.). This fact is particularly conspicuous in experiments with

<sup>1</sup> WIEGNER and MARSHALL: Z. phys. Chem. A 140: 1, 39, 1929.

suspensions of large particles, the diffusion coefficient of which is so small that the diffusion is unable to cause coagulation within a multiple of the actual coagulation time.

In the writer's opinion, examples of such systems are found not only in different suspensions of red blood corpuscles but also in numerous other cellular suspensions (agglutination of yeast cells, protozoa and bacteria<sup>1</sup>).

ERIC PONDER<sup>2</sup> was the first who tried to employ ZSIGMONDY-SMOLUCHOWSKI'S counting method for quantitative measurements of the rouleaux formation of red blood corpuscles. Technique: Oxalated blood was centrifugalized, separating the cells from the plasma, the plasma was distributed in test tubes, and placed in an incubator. A certain small amount of blood was taken from the ear of the donor by means of a capillary pipette, and this blood was added to the tubes with plasma. During the experiment the mixing tubes were shaken "as one shakes a boiling tube".

This shaking involves the risk of some acceleration of the coagulation rate, on account of the more frequent collision of particles, whereas a more brisk shaking will cause a delay of the process, as the aggregates formed are broken up again. The sedimentation, which PONDER had probably

<sup>1</sup> The method described later in this paper is applicable to these suspensions:

Thus for a study of rouleaux formation of the red blood cells (the so-called pseudoagglutination);

for a study of the specific hæmagglutination, on which the blood-grouping is based;

for a study of erythrocyte agglutination in isotonic saccharose solution, etc.;

for a study of the bacterial agglutination involved in the Gruber-Durham-Widal reaction (agglutination of typhoid, paratyphoid, colon, dysentery and other bacilli.

<sup>2</sup> PONDER: Quartl. Journal. exp. Physiol. **16**: 173, 1926.

planned to avoid, influence the process only when the experiment is extended over some length of time or when the suspension is concentrated—a fact that may be explained as follows:

When some of the aggregates have obtained such a size that their sedimentation rate is considerably greater than that of the individual particles, the number of collisions between the particles in a vertical direction is increased, the so-called "orthokinetic" coagulation (WIEGNER and TUORILA<sup>1</sup>).

Just before a fixed period expired, a drop of the mixture was placed on a slide and walled-in with vaseline to prevent flow and evaporation. In the thin layer of fluid the red blood cells sedimented rapidly, so that the process of aggregation ceased. Then 20—30 microphotos were taken of each preparation (magnification  $\times 300$ ). The finished preparations were examined under the microscope at low magnification, and counts were made of single, double, triple etc. particles.

PONDER found that the more rapid the rouleaux formation, the greater was the attraction radius. It was not necessary, during the individual experiment, to assume any variation of the attraction radius ( $R$ ). The size of  $R$ , which was subject to great variation, was dependent upon the red cell concentration, the temperature, and "such undefined factors as the charge of the cells and the state of the red cell surface".

In his paper, unfortunately, PONDER gives no numerical values for  $R$ , nor for its variation with the concentration or with the temperature, nor for the validity of SMOLUCHOWSKI'S theory on these points. The rate of the rou-

<sup>1</sup> TUORILA: Koll. ch. Beih. **24**: 1, 1927.

leaux formation varied symbatically with the temperature, so that the aggregation proceeded more slowly at a lower temperature (15° C.), and more rapidly at a higher temperature (37° C.).

J. OLIVER and P. SMITH<sup>1</sup> studied suspensions of red blood cells in isotonic saccharose solutions, to which was added a little sodium hydroxide (till the solution was m/500) in order to stabilize the suspension. "Rapid" coagulation was brought about by the addition of aluminium chloride (till the solution was m/4000). In the counting, ZSIGMONDY'S "protective colloid method" was employed, samples being taken at intervals, and to these was added 1% gelatin; then the numbers of particles ( $\sum \nu$ ,  $\nu_1$  and  $\nu_2$ ) were determined by counting in an ordinary hæmatological counting-chamber.

The attraction radius was fairly constant in the individual experiments, and the calculated numbers of single particles agreed very well with those observed; the number of double particles was also calculated and compared with the counted number. For the different experiments, however, SMOLUCHOWSKI'S proportion  $\frac{R}{r}$  varied enormously (from 142,3 to 2513). In spite of low concentrations the rate of agglutination was found to be of the same magnitude as that for concentrated colloidal solutions.

Comparison was made with a gold sol, and this strikingly emphasized the peculiarities of the system examined. The volume of the red blood cells was about 50,000 times greater than that of the gold particles, and their Brownian movements were very small. Therefore, when the blood cells really formed aggregates, in spite of an average di-

<sup>1</sup> OLIVER and SMITH: Journ. phys. chem. **30**: 1, 1926.



stance of particles that was greater than the one for the just as rapidly coagulating gold sol, this must be due to some unknown factor.

The phenomenon of agglutination investigated by OLIVER and SMITH (*loc. cit.*) has nothing to do with the rouleaux formation of the red blood cells, even though there are points of colloido-physical resemblance between the two phenomena.

The disk-shape of the red blood cells which is necessary for the "orientated" coagulation in rouleaux formation, changes into the form of a sphere in the saccharose solution, and in keeping herewith the agglutinates are completely irregular clumps. Further, when the blood cells are transferred from their own native suspension medium (plasma) to other media, great changes take place in the electrical charge of the corpuscular membrane, the ion permeability etc.

In OLIVER and SMITH's agglutination experiment the coagulation is produced by precipitation of aluminium hydroxide on the corpuscles. The agglutination is an expression of a mutual coagulation of the hydrophilic colloid, aluminium hydroxyde, and the hydrophobic colloid, red blood cells (so-called sensibilisation). This agglutination is thus reminiscent of the rouleaux formation, where plasma proteins in principle correspond to the aluminium hydroxide.

It is strange that OLIVER and SMITH used gelatin as a protective colloid for the blood cells if gelatin causes an increased aggregation in these solutions, as in blood. Besides gelatin, gum arabic and several other viscous substances promote the rouleaux formation.

The preceding survey of the literature on SMOLUCHOWSKI'S

proportion between action radius and particle radius  $\left(\frac{R}{r}\right)$  permits a classification of the hydrophobic colloid systems into two groups:

- I. Systems with intercorpuseular forces of short range:  $\frac{R}{r} = 2$  and  $\frac{R}{r} \gg 2$ , depending upon the form and size of the particles.
- II. Systems with far-range intercorpuseular forces: the other cases with  $\frac{R}{r} \gg 2$ .

It would seem that measuring of the adhesion of colloidal particles to walls of the same substance may give us some information of coagulation forces of short range (Group I). v. BUZAGH<sup>1</sup> has studied the adhesion of quartz particles to quartz walls by means of a "Haftzahl" method and an "Abreisswinkel" method.

Some theoretical studies carried out by the writer, covering Group II. only, will be presented in the following two sections.

#### IV. An Amplification of Smoluchowski's Coagulation Theory.

(An interpretation of the attraction radius).

In order to analyse the attraction radius more thoroughly, SMOLUCHOWSKI'S coagulation theory is generalized so as to cover arbitrary intercorpuseular forces of attraction. It is likewise investigated whether it is possible by means of such a general theory physically to determine these forces on the basis of coagulation-kinetic experiments.

While SMOLUCHOWSKI assumes that the Brownian movements of the particles alone determine the frequency of

<sup>1</sup> v. BUZAGH; Kolloid. Z. **47**: 370, 1929. **51**: 105, 230, 1930. **52**: 46, 1930. Naturw. **18**: 444, 1930.

collisions (condition 4), p. 7), the forces assumed in our new theory imply an additional convection.

Since a diffusion process is merely a superposition of the Brownian movements of the individual particles, these can be calculated by solving a corresponding diffusion problem.

We now will evolve the differential equation for the present case. In case of an external force the density of current,  $\underline{i}$ , consists of two parts, one of which  $\underline{i}_D$ , which is due to diffusion, is equal to

$$\underline{i}_D = -D \text{grad } W$$

while the other  $\underline{i}_c$ , which is due to convection, is

$$\underline{i}_c = W\beta\underline{f}$$

$\beta$  signifies the hydrodynamic mobility of the particles,  $D$  is their diffusion coefficient,  $\underline{f}$  vector for the external force, and  $W$  a function of distribution, which for the macroscopic case is equal to concentration.

For the total density of current we then have:

$$\underline{i} = \underline{i}_D + \underline{i}_c = -D \text{grad } W + W\beta\underline{f}.$$

As the divergence of the vector for the density of current is equal to the decrease in the density of particles in the time

$$\text{div } \underline{i} = -\frac{\partial W}{\partial t}$$

we find (expressed as vector analysis) the differential equation:

$$\frac{\partial W}{\partial t} = D \Delta W - \beta \text{div} [W \cdot \underline{f}]$$

which the distribution function  $W$  has to satisfy.

We let SMOLUCHOWSKI'S suppositions (except 3) and 4), p. 7) remain valid.

Instead of 3) we assume:

8) that contact between the particles is necessary for aggregation, i. e., a distance between the centres equal to the diameter of the particles.

For the sake of simplicity, we further assume

9) a non-orientated coagulation, i. e., aggregation through the collision of particles, independent of the position of the particles inter se. Then the force  $\underline{f}$  will only be a function of  $r$  (the distance from the centre of the condensation nucleus):

$$\underline{f} = \underline{f}(r)$$

so that the concentration  $W$  in the sphero-symmetrical system depends solely on  $r$ :

$$W = W(r)$$

Expressing the force vector  $\underline{f}$  in the usual manner by means of a unit vector  $\frac{r}{r}$  ( $\underline{r}$  place vector), we get

$$\underline{f} = -f(r) \left( \frac{r}{r} \right)$$

where  $f(r)$  is a positive value, when

10) the force is supposed to cause attraction.

SMOLUCHOWSKI'S analysis has shown that it is only the stationary distribution of particles which determine the amount coagulated in the given time (supposition 4), p. 7). We therefore look merely for a stationary solution of the differential equation above, which is thus reduced to

$$4a) \quad D \triangle W - \beta \operatorname{div} [W \cdot \underline{f}] = 0$$

which replaces the condition

$$4) \quad D \triangle W = 0$$

in SMOLUCHOWSKI'S theory.

According to well-known propositions from vector analysis we get

$$\begin{aligned} \operatorname{div} [W \cdot \underline{f}] &= -\operatorname{div} \left[ \left( \frac{Wf}{r} \right) \cdot \underline{r} \right] = \\ &= -\frac{Wf}{r} \operatorname{div} \underline{r} - \left( \operatorname{grad} \frac{Wf}{r}, \underline{r} \right) = -3 \frac{Wf}{r} - r \frac{d}{dr} \left( \frac{Wf}{r} \right). \end{aligned}$$

By substitution of the expression obtained for

$$\operatorname{div} [W \cdot \underline{f}] \text{ and } \triangle W = \frac{d^2 W}{dr^2} + \frac{2}{r} \frac{dW}{dr}$$

in the differential equation, we have:

$$D \left\{ \frac{d^2 W}{dr^2} + \frac{2}{r} \frac{dW}{dr} \right\} + \beta \left\{ 3 \frac{Wf}{r} + r \frac{d}{dr} \left( \frac{Wf}{r} \right) \right\} = 0.$$

Since this can be written as

$$\frac{d}{dr} \left\{ r^2 \frac{dW}{dr} + \frac{\beta}{D} r^2 Wf \right\} = 0$$

integration, with  $c_1$  as an arbitrary constant, gives

$$\frac{dW}{dr} + W \frac{\beta}{D} f(r) = \frac{c_1}{r^2}.$$

By further integration, with  $c_2$  as a new arbitrary constant, we get:

$$W = e^{-\frac{\beta}{D} \int_{r_0}^r f(r) dr} \left\{ \int_{r_0}^r \frac{c_1}{r^2} e^{+\frac{\beta}{D} \int_{r_0}^r f(r) dr} dr + c_2 \right\}.$$

For the determination of the constants  $c_1$  and  $c_2$ , we have the initial conditions

$$W = 0 \text{ for } r = r_0 \text{ (contact), and}$$

$W = c$  (the constant initial concentration) for  $r \rightarrow \infty$ .  $c_2$  satisfies the first condition. Putting

$$A(\infty) = \frac{\beta}{D} \int_{r_0}^{\infty} f(r) dr$$

which is a constant, we get

$$c_1 = \frac{c}{e^{-A(\infty)} \int_{r_0}^{\infty} \frac{e^{+A(r)}}{r^2} dr}.$$

By substitution of the constants  $c_1$  and  $c_2$ , we then have:

$$W = ce^{-[A(r)-A(\infty)]} \frac{\int_{r_0}^r \frac{e^{+A(r)}}{r^2} dr}{\int_{r_0}^{\infty} \frac{e^{+A(r)}}{r^2} dr}.$$

( $W = c$  satisfied for  $r = \infty$ ), where

$$A(r) = \frac{\beta}{D} \int_{r_0}^r f(r) dr.$$

For  $r_0 = R$  (action radius) and  $f(r) = 0$  for  $r > R$  and large  $t$  (stationary state) the formula found for  $W$  passes into SMOLUCHOWSKI'S formula, since  $A(r) = 0$  for all  $r \gg r_0$ .

$$W = c \frac{\int_{r_0}^r \frac{1}{r^2} dr}{\int_{r_0}^{\infty} \frac{1}{r^2} dr} = c \frac{\left| -\frac{1}{r} \right|_R^r}{\left| -\frac{1}{r} \right|_{\infty}^R} = c \left\{ 1 - \frac{R}{r} \right\}.$$

For determination of the indiffusing amount of substance the calculation is:

$$\frac{\partial W}{\partial r} = \frac{ce^{+A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{+A(r)}}{r^2} dr} \frac{d}{dr} \left\{ e^{-A(r)} \int_{r_0}^r \frac{e^{+A(r)}}{r^2} dr \right\} =$$

$$\int_{r_0}^{\infty} \frac{e^{+A(r)}}{r^2} dr \left\{ \frac{1}{r^2} - \frac{\beta}{D} f(r) e^{-A(r)} \int_{r_0}^r \frac{e^{+A(r)}}{r^2} dr \right\}$$

the first factor being a constant. For  $r = r_0$  we have

$$\left. \frac{\partial W}{\partial r} \right|_{r=r_0} = c \frac{1}{r_0^2} \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr}.$$

So the amount diffusing through the sphere of contact (radius  $r_0$ ) per second will be

$$4 \pi r_0^2 D \left. \frac{\partial W}{\partial r} \right|_{r=r_0} = 4 \pi D c \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr},$$

and SMOLUCHOWSKI'S action radius:

$$R = \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr}.$$

By integration by parts the integral in the denominator can be transformed to

$$\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr = -\frac{1}{r} e^{A(r)} \Big|_{r_0}^{\infty} + \int_{r_0}^{\infty} \frac{1}{r} e^{A(r)} \frac{\beta}{D} f(r) dr$$

$$= \frac{1}{r_0} \left\{ 1 + r_0 \int_{r_0}^{\infty} \frac{1}{r} e^{A(r)} \frac{\beta}{D} f(r) dr \right\}.$$

Assuming small forces and evolving after  $f(r)$ , we have

$$e^{A(\infty)} = 1 + A(\infty) + \dots \quad \text{and} \quad e^{A(r)} = 1 + A(r) + \dots$$

whereafter:

$$R = r_0 \frac{1 + A(\infty) + \dots / \dots}{1 + \frac{\beta}{D} r_0 \int_{r_0}^{\infty} \frac{f(r)}{r} (1 + A(r) + \dots / \dots) dr}$$

so that employing the well-known formula

$$\frac{1}{1+x} = 1 - x + \dots$$

we have

$$R = r_0 \left( 1 + \frac{\beta}{D} \int_{r_0}^{\infty} f(r) dr \right) \left( 1 - \frac{\beta}{D} r_0 \int_{r_0}^{\infty} \frac{f(r)}{r} dr \right).$$

Through the usual discarding of the product term

$$- \left( \frac{\beta}{D} \int_{r_0}^{\infty} f(r) dr \right) \left( \frac{\beta}{D} r_0 \int_{r_0}^{\infty} \frac{f(r)}{r} dr \right)$$

we finally get

$$R = r_0 \left\{ 1 + \frac{\beta}{D} \int_{r_0}^{\infty} f(r) \frac{r - r_0}{r} dr \right\} = r_0 (1 + \text{constant}) = \text{constant}.$$

For  $f(r) = 0$  and  $r_0 = 2 r_p$  ( $r_p$  radius of the particle) SMOLUCHOWSKI's proportion  $\frac{R}{r_p} = 2$ .

If distance forces are active, i. e.,  $f(r) > 0$ , there will be a constant action radius which is greater than  $2 r_p$ .

Since the action radius is constant, all the above-cited formulæ of SMOLUCHOWSKI for calculation of the numbers of particles remain valid, so we understand why SMOLUCHOWSKI's theory can describe the coagulation in hydrophobic colloids, although the rough assumption of a simple



attraction sphere undoubtedly fails to give a correct description of the forces between the particles.

According to the formula found for  $R$ , the action radius must be a function of the absolute temperature  $\theta$ . Only if the intercorpular forces are independent of the temperature, is it possible to calculate from  $R$   $f(r)$ , which even enters implicitly in the form of an integral.

By transcription of the formula for  $R$  we get:

$$R = \frac{e^{A(\infty)}}{\int_{r_0}^{\infty} \frac{e^{A(r)}}{r^2} dr} = \frac{1}{\int_{r_0}^{\infty} \frac{e^{A(r)-A(\infty)}}{r^2} dr} = \frac{1}{\int_{r_0}^{\infty} \frac{e^{-\frac{\beta}{D} \int_{r_0}^{\infty} f(r) dr}}{r^2} dr}$$

since

$$A(r) - A(\infty) = \frac{\beta}{D} \left\{ \int_{r_0}^r f(r) dr - \int_{r_0}^{\infty} f(r) dr \right\} = -\frac{\beta}{D} \int_r^{\infty} f(r) dr = -\frac{M}{k\theta}.$$

$M$  is an abbreviated designation for the integral with the limits  $r$  and  $\infty$ . The value for  $\frac{\beta}{D}$  is derived from

$$D = \frac{H\theta}{N} \frac{1}{6\pi\eta r_p} = k\theta\beta.$$

$H$  stands for the gas constant,  $\theta$  the absolute temperature.  $N$  means AVOGADRO-LOSCHMIDT'S figure,  $\eta$  the coefficient for internal friction,  $r_p$  the particle radius, and  $k$  the entropy constant of BOLTZMANN.

The integral  $M$  is zero when  $r$  is greater than the range of the forces. The quantity  $\frac{M}{k\theta}$  being positive, we get by expansion of the  $e$  power in a MACLAURIN series and integration term by term:

$$\frac{1}{R(\theta)} = \int_{r_0}^{\infty} \frac{e^{-\frac{M}{k\theta}}}{r^2} dr = \int_{r_0}^{\infty} \sum_{n=0}^{\infty} \frac{1}{n!} \left(-\frac{M}{k\theta}\right)^n \frac{1}{\theta^n} dr = \sum_{n=0}^{\infty} A_n \frac{1}{\theta^n}$$

where  $A_n$  signifies the constant coefficients of the new series. By measuring  $R$  as a function of the temperature, the  $A$ 's can be determined and thus some information can be obtained about  $R$ .

If the force function is known, the action radius can be calculated. If the attraction takes place according to the function

$$f(r) = \alpha \frac{1}{r^2} \quad (1)$$

the corresponding action radius is calculated from

$$-\frac{\alpha}{k\theta} \int_r^\infty \frac{1}{r^2} dr = -\frac{\alpha}{k\theta} \left[ -\frac{1}{r} \right]_r^\infty = -\frac{\alpha}{k\theta} \frac{1}{r}$$

$$\int_{r_0}^\infty e^{-\frac{\alpha}{k\theta} \frac{1}{r}} \frac{1}{r^2} dr = - \int_{\frac{1}{r_0}}^0 e^{-\frac{\alpha}{k\theta} r'} dr' = \frac{k\theta}{\alpha} \left( 1 - e^{-\frac{\alpha}{k\theta} \frac{1}{r_0}} \right)$$

as we introduce  $r' = \frac{1}{r}$  as a new variable, that is,

$$R = \frac{\alpha}{k\theta \left( 1 - e^{-\frac{\alpha}{k\theta} \frac{1}{r_0}} \right)} = \frac{\alpha}{k\theta}$$

since  $\frac{\alpha}{k\theta} \frac{1}{r_0}$  is always large.

For this simple case ("square law")  $R$  and  $\theta$  will be inversely proportional, i.e., the reciprocal coagulation time  $\frac{1}{T}$  is proportional to the fluidity of the suspension medium  $\frac{1}{\eta}$ , since

$$\frac{1}{T} = 4\pi DRv_0 \quad \text{and} \quad D = k\theta \frac{1}{6\pi\eta r_p}$$

<sup>1</sup> Where the dimension  $\left[ \frac{\text{cm}^3 \text{ gram}}{\text{sec}^2} \right]$  is given to the proportionality constant as the force must have the dimension  $\left[ \frac{\text{gram cm}}{\text{sec}^2} \right]$ .

In SMOLUCHOWSKI'S case—no distance forces— $R$  is constant, and  $\frac{1}{T}$  is proportional to  $\theta \frac{1}{\eta}$ . In both cases, then,  $\frac{1}{T}$  increases with the temperature, but more rapidly in SMOLUCHOWSKI'S case.

If the force itself is dependent upon the temperature,  $f(r)$  cannot be calculated from  $R(\theta)$ , but then  $f(r)$  for a definite temperature as well as  $f(r)$ 's variation with the temperature can be determined by the following direct method.

Experiments carried out by LACHS and GOLDBERG<sup>1</sup> and by GARNER and LEWIS<sup>2</sup>, all working with gold sols brought to coagulate by the addition of barium chloride, showed approximate proportionality between  $\frac{1}{T\nu_0}$  and  $\frac{\theta}{\eta}$ .

As mentioned already (p. 13), the constant action radius (SMOLUCHOWSKI'S proportion  $\frac{R}{r_p} = 2$ ) in systems with short-range intercorpuseular forces need not necessarily express the independency of these forces upon the temperature, as considerable changes in strength do not alter the rate of coagulation if only the forces are so great that each collision of particles results in aggregation ("rapid" coagulation).

In "slow" coagulation the fraction  $\epsilon$ , which is an expression of the frequency of the effective collisions, shows distinct dependence upon the temperature.

## V. Method for Direct Determination of the Intercorpuseular Forces.

We consider two equally large spherical particles, 1 and 2 (see Fig. 1.), where the size and direction of the central line are determined by the vector  $r$ .

<sup>1</sup> LACHS and GOLDBERG: Kolloid. Z. **31**: 116, 1922.

<sup>2</sup> GARNER and LEWIS: Journ. phys. chem. **30**: 1401, 1926.

If  $\underline{r}$  is expressed by the place vectors  $\underline{x}_1$  and  $\underline{x}_2$  of the particles 1 and 2, then

$$\underline{r} = \underline{x}_2 - \underline{x}_1$$

Particle 1 is subject to the effect of the following forces:

a 1) a completely irregular influence of force  $\underline{X}_1$ , manifest in the Brownian movements of the particle.

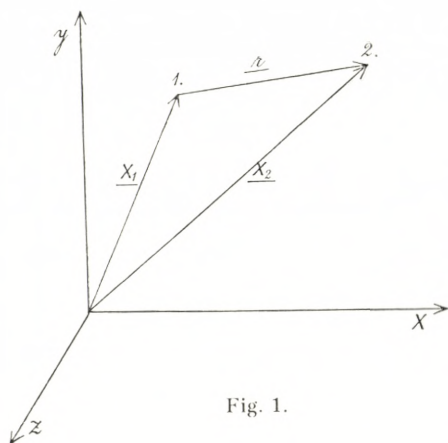


Fig. 1.

b 1) the intercorporeal attraction

$$\underline{f}_1 = f(r) \left( \frac{\underline{r}}{r} \right)$$

where  $\left( \frac{\underline{r}}{r} \right)$  is the vector of unit, and  $f(r)$  the function of force that indicates the dependence of the force upon the

position in relation to the other particle.

c 1) a force of friction

$$-\gamma \frac{dx_1}{dT}$$

the magnitude of which is directly proportional to the velocity of the particle, and the direction of which is opposite to the direction of the movement of the particle;  $\gamma$  means the hydrodynamic resistance coefficient (or reciprocal mobility), which is the same for both particles.

Particle 2 is submitted to similar forces:

a 2)  $\underline{X}_2$ , which produces the Brownian movements.

b 2)  $\underline{f}_2$ , the intercorporeal attraction which, according to the law of action and reaction, is equal to  $\underline{f}_1$ , with opposite direction, that is

$$\underline{f}_2 = -f(r) \left( \frac{r}{r} \right).$$

c 2) the force of friction

$$-\gamma \frac{dx_2}{dt}$$

Employing the definition of force, mass multiplied by acceleration, generally designated as Newton's second law, we have for particle 1:

$$m \frac{d^2 x_1}{dt^2} = -\gamma \frac{dx_1}{dt} + \underline{X}_1 + \underline{f}_1.$$

and for particle 2:

$$m \frac{d^2 x_2}{dt^2} = -\gamma \frac{dx_2}{dt} + \underline{X}_2 + \underline{f}_2$$

By subtraction we get the equation for the relative movement of the particles:

$$m \frac{d^2 r}{dt^2} = -\gamma \frac{dr}{dt} + (\underline{X}_2 - \underline{X}_1) - 2f(r) \left( \frac{r}{r} \right).$$

If, then, we imagine that from a large number of observed pairs of particles (studied in such a dilute suspension that we can pick out pairs of particles lying sufficiently far from the other particles, so that the attraction of the others can be left out of consideration) we select all those which have a distance of  $r$ , and form the average values for acceleration and velocity, we get:

$$m \left. \frac{d^2 r}{dt^2} \right|_r = -\gamma \left. \frac{dr}{dt} \right|_r - 2f(r) \left( \frac{r}{r} \right)$$

$\overline{\underline{X}_2 - \underline{X}_1} = 0$ , since the relative movement, produced by the Brownian movements of the particles, is a new Brownian movement, i. e., completely irregular.

By solving the equation with reference to  $f(r)$ , now paying no attention to the direction of the central line, we get:

$$f(r) = -\frac{\gamma}{2} \overline{\frac{dr}{dt}} \Big|_r - \frac{m}{2} \overline{\frac{d^2r}{dt^2}} \Big|_r.$$

Through direct observation by means of kinematographic records, the change in  $r$ ,  $\mathcal{A}r$  for a certain small time unit  $\mathcal{A}t$ , is measured. Now the equation for  $f(r)$  is

$$f(r) = -\frac{\gamma}{2} \overline{\frac{\mathcal{A}r}{\mathcal{A}t}} \Big|_r - \frac{m}{2} \overline{\frac{\mathcal{A}(\mathcal{A}r)}{\mathcal{A}t^2}} \Big|_r$$

( $\mathcal{A}(\mathcal{A}r)$  means the change of the change of  $r$ ).

We can now disregard the acceleration term, on account of its insignificant size. If no forces are acting between the particles we get:

$$\overline{\frac{\mathcal{A}r}{\mathcal{A}t}} \Big|_r = 0.$$

If forces are acting between the particles, we get the value of  $f(r)$  for the central distance  $r$ ; by following the phenomenon in the time, we get a complete picture of  $f(r)$ .

With the method here employed—averaging the shifts in position of numerous pairs of particles—we have eliminated the Brownian movements.

Finally, by calculation of

$$\int f(r) dr$$

and by the employment of previous formulæ, we are able to determine the action radius and compare the calculated value with values obtained by ordinary coagulation-kinetical experiments.

### Summary.

In suspensions of human red blood cells in the appertaining plasma a phenomenon of aggregation, "rouleaux formation" takes place. This phenomenon is the main cause of a decrease in the suspension stability of the blood, and manifests itself in sedimentation of the cells. The "sedimentation test" in which this sedimentation rate is determined has attained great practical and theoretical significance in medicine.

In preliminary experiments on the kinetics of rouleaux formation performed by the writer in order to investigate the mechanism of the sedimentation of the red blood cells was seen to take place in a relatively short time, in spite of the gigantic size of the cells (i. e., very small Brownian movements) and low concentration (number of particles per volume unit) in comparison with the particles of ordinary hydrophobic colloid solutions.

The rapid aggregation actually demonstrable, necessitates the assumption of attractive forces (between the corpuscles) which exert their effect far beyond the immediate vicinity of the corpuscles. In most hydrophobic colloid solutions, on the other hand, the coagulation is effected by short-range intercorpuscular forces.

Generally processes of coagulation are followed quantitatively by measuring the "rate" of coagulation, which merely expresses the total course of the process. But it seems reasonable to expect that a determination of the intercorpuscular forces—which actually constitute the main-spring of the mechanism of coagulation—may open up new roads for an investigation into the phenomena of aggregation, colloido-chemical as well as biological.

In the present work the writer has tried to give a theoretical basis for such methods, not described before.

Since the so-called "action radius" in SMOLUCHOWSKI'S mathematical coagulation theory indirectly appears to give an idea of the coagulation forces, a generalization of this theory suggested itself as the first problem to be investigated. While SMOLUCHOWSKI assumes that the Brownian movements alone are the cause of collisions between the particles, the attractive but otherwise perfectly arbitrary intercorpuseular forces introduced by the new theory imply, in addition, a convection.

As the solution of the corresponding diffusion problem SMOLUCHOWSKI'S formulæ for the numbers of particles recur with the mere modification that a new constant action radius appears. By this means it is possible to explain the good results that can be obtained with SMOLUCHOWSKI'S theory even though the rough assumption of an attraction sphere undoubtedly fails to give a correct description of the forces between the particles.

The intercorpuseular forces enter into the expression found for the action radius in the form of a force integral, so that only in a very special case (if the intercorpuseular forces are independent of the temperature) is it possible to calculate these forces from the (variation of the) action radius (with the temperature). On the other hand, it is practicable to calculate the action radius for a known function of force.

A direct method for the determination of the intercorpuseular forces could only be evolved for systems with forces acting beyond the immediate vicinity of the particles.

By a kinematographic recording of the movement of pairs of particles and measuring of the central line, the



function of force can be determined by applying the fundamental principles of mechanical physics. The influence of the Brownian movements is eliminated by studying numerous pairs of particles.

If the same suspension is used for ordinary coagulation-kinetical experiments, through which the action radius is determined, and for kinematography of pairs of particles for measuring the force function, it is possible to compare the experiments with the given theory, since then the calculated action radius should then agree with the observed.

The method here described is applicable to the study of various biological phenomena, among which may be mentioned

rouleaux formation,

specific hæmagglutination, on which the blood-grouping is based,

agglutination of red blood cells in isotonic saccharose solution etc.,

agglutination of various bacteria, especially

the Gruber-Durham-Widal reaction (agglutination of typhoid, paratyphoid, colon bacilli and others).

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I wish here to express my sincere thanks to Mr. CHR. MØLLER, Ph. D. for checking my mathematico-physical considerations and for helpful suggestions concerning these.

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