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PREFACE

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Preface

Preface: Marian Smoluchowski's 1916 paper—a century of inspiration

Historical context

The beginning of the 20th century was a tumultuous time in science. The strongholds of physics were shaken at several ends: Einstein's special and later general relativity questioned Newtonian mechanics for particles at high speeds; the discovery of spontaneous radioactivity by Becquerel and later the successful isolation of radium by the Curies; Rutherford, Geiger, and Marsden's gold foil scattering experiment; and the advent of quantum mechanics pushed by Bohr and his colleagues.

Another topic soaring at that time was the quest to understand the stochasticity observed in the motion of colloidal particles in liquids. Originally reported by Ingenhousz [1] and systematically investigated by Brown [2], the jittery motion was soon disproved to be due to some animate cause. Both Ingenhousz and Brown proved that the jiggling, seemingly erratic motion was not the active motion of animalcules but was due to physical principles. Yet the exact cause for this diffusive motion remained somewhat of a mystery.

It was reserved for the genius of scientists such as Einstein [3], Sutherland [4], and Smoluchowski [5], to derive the physical laws that describe diffusive motion, in particular, Fick's second law or the diffusion equation on the one hand and, on the other hand, the link between *Brownian motion* and thermodynamic and statistical mechanical laws. This established the connection of Brownian motion to the unit k_BT of thermal energy and to Avogadro's number, in turn related to the liquid's viscosity in what we now call the Einstein–Smoluchowski–Sutherland relation. Einstein, and more explicitly Smoluchowski, also achieved the connection to Pearson's random walk [6]. Building on their pioneering work, it was Langevin who then introduced the concept of a stochastic force [7].

The link between Avogadro's number and the diffusion coefficient of Brownian particles—and his close friendship with Langevin—inspired Perrin, on his quest to determine the best possible value for Avogadro's number, to pursue very detailed single trajectory measurements of microscopic putty particles [8]. Only a few years later Nordlund invented the method of stroboscopic illumination of a moving film plate to create much longer time series of single trajectories, enabling him to take single trajectory averages and significantly improve Perrin's results [9]. The subsequent race for ever better diffusive measurements was finally topped by Kappler with his torsional diffusion experiments [10]. Based on modern superresolution microscopy, experimentalists can now measure the diffusive motion of fluorescently labelled particles such as single green fluorescent proteins of some two nanometres in size in living biological cells, achieving unprecedented spatial and temporal resolution [11].

After his seminal papers on diffusion [12], Einstein's mind soon focused on other fundamental topics, the consequences of the photoelectric effect and general relativity. In contrast, Smoluchowski did not let go of the topic of diffusion. Two additional major achievements in the theory of stochastic motion bear his name. One is the Smoluchowski equation describing the motion of a diffusive particle in an external force field, in the Western literature long known as the Fokker–Planck equation [13]. The second one, maybe underlining his genius best, is Smoluchowski's theory of the diffusion limited coagulation of two colloidal particles [14]. This work may be viewed as one of the fundamental cornerstones of molecular physical chemistry and, as we will see, of cellular biochemistry. A reprint of Smoluchowski's original paper can be found at the end of this special issue collection, reproduced with permission from the Polish Academy of Science and Arts.

Smoluchowski's life: a biographic sketch

Marian Smoluchowski was born in 1872, into an upper-class family living in a town near Vienna, where Smoluchowski later studied physics. He was influenced by his teachers Exner and Stefan. After some years in Paris, Glasgow, and Berlin, Smoluchowski found his first long term faculty position in 1899, in the then Austro-Hungarian city of Lemberg, nowadays Lviv in western Ukraine. In 1913 Smoluchowski moved to the Polish city of Kraków. There, at Jagiellonian University, he worked until his untimely death in 1917. Smoluchowski regarded Boltzmann with profound admiration and was inspired by him throughout his scientific life [15]. He was even called Boltzmann's intellectual successor—'der geistige Nachfolger Boltzmanns' [16].

The best known picture of Smoluchowski shows him at his well kept desk as depicted in figure 1. In addition, a number of pictures are preserved in which Smoluchowski can be seen pursuing his favourite pastimes: skiing and hiking in the mountains, both in the Alps and the Tatra Mountains of Southern Poland. He also had a keen interest in the arts, pursuing watercolours and piano playing. Marian Smoluchowski was married to Zofia Baraniecka, with whom he had two children, Aldona and Roman.

Throughout his career Smoluchowski worked at the forefront of research at the time, at the interface of what might now be called applied mathematics and statistical physics. He had the ability to combine mathematical rigour with physical insight, a prime example being his work on the theory of diffusion, nowadays considered a start-up of the theory of stochastic processes. His unprecedented mathematical achievements were, among others, the clarification of the role of the ergodic hypothesis of Boltzmann and the probabilistic interpretation of the Second Law of thermodynamics [17]. Smoluchowski's influence on today's scientific landscape in Poland to a large extent is owed to his ability to explain science in *plain language*, an idea supported at the time by Niels Bohr, and to arrive at the physical basics of the phenomena. The legacy of Smoluchowski cannot be overrated, and it is highlighted in the annual Marian Smoluchowski Symposium on Statistical Physics organised by Jagiellonian University. The 2017 Smoluchowski meeting held in Kraków celebrating Smoluchowski's centennial is a particular witness to his tribute.

Smoluchowski's theory of coagulation

One of Smoluchowski's major achievements, then a scientific breakthrough, is the statistical description of the coagulation of two diffusing particles. The diffusional encounter of two particles—colloids or even single molecules—in a solution is the first step for any reaction occurring between these two particles. If the reaction rate itself is high, that is, if the particles

Figure 1. Marian Smoluchowski in his office in Lviv. Source: Private collection. Reproduced with permission from Mrs Teresa Jaroszewska.

react rapidly upon encounter, then the longer time it takes the particles to diffuse toward one another dominates the process. Such reactions are called diffusion-limited.

If one of the two particles is much larger (and hence usually much heavier) than the other, then the large particle can be viewed as immobile and we can straightforwardly arrive at Smoluchowski's result. The smaller, mobile particle has diffusivity D, and its target is assumed to be of 'size' b (with the notion of 'size' dependent on geometry), much larger than the size of the mobile particle. Assuming spherical geometry, consider the steady state solution of the radially symmetric diffusion equation for the volume density n of the diffusing particle,

$$\frac{\partial n}{\partial t} = D_{3\mathrm{d}} \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial n}{\partial r} \right) = 0, \tag{1}$$

with the boundary conditions of a fixed density far away from the target, $n \to n_{\mathrm{bulk}}$ as $r \to \infty$, and immediate absorbtion at the surface of the target, $n|_{r=b} = 0$. From the time-independent solution

$$n = n_{\mathrm{bulk}} \left(1 - \frac{b}{r} \right), \tag{2}$$

the Smoluchowski rate constant k_{on}^S for the coagulation reaction can be obtained from the stationary binding flux j_{stat} as

$$k_{\mathrm{on}}^S = \frac{j_{\mathrm{stat}}}{n_{\mathrm{bulk}}} = \frac{1}{n_{\mathrm{bulk}}} 4\pi b^2 D \left. \frac{\partial n}{\partial r} \right|_{r=b} = 4\pi D b. \tag{3}$$

This is exactly the famed Smoluchowski result in the limit of a static target, that is, when one particle is much larger than the other [5]. If both particles are of comparable size and mobile, a good approximate solution is to replace the size b by the combined sizes of the particles, and the diffusion coefficient by the sum of the two individual diffusion coefficients [5]. Smoluchowski's result (3) is one of the pillars of molecular physical chemistry to this day.

Note that this on-rate has physical dimension $[k_{\mathrm{on}}^S] = \mathrm{cm}^3\ \mathrm{s}^{-1}$. Consider, for instance, a typical regulatory protein, responsible for signalling in biological cells, with diameter of 5 nm.

What is the diffusion limited on-rate of this protein to its binding site on a DNA molecule, an important step in cellular signalling? By Stokes' formula we obtain $D \approx 10^2$ μm^2 s^{-1} for the protein diffusivity, and the typical target site size of one base-pair on the DNA molecule corresponds to $2b \approx 0.3$ nm. Consequently $k_{\mathrm{on}}^S \approx 10^8/((\mathrm{mol}\ \mathrm{l}^{-1}) \times \mathrm{s})$ in biochemical units. Even though this number does not include the binding of the transcription factor itself, it is much smaller than some measured on-rates: for the Lac repressor, for instance, $k_{\mathrm{on}} \approx 10^{10}/((\mathrm{mol}\ \mathrm{l}^{-1}) \times \mathrm{s})$ was found [18]. This latter observation then led scientists to the *facilitated diffusion picture*, which in some sense may be viewed as a consequence of Smoluchowski's seminal result (3). Even now, any new theory for the facilitated search of their designated binding site by signalling proteins needs to be compared to the Smoluchowski limit [19].

Smoluchowski's heritage

Smoluchowski is still one of the most revered scientists in Poland. Up until now there are numerous renowned schools following in his footsteps in statistical physics and applied mathematics. His work also inspired a large number of scientific directions worldwide, and in several disciplines. To name but a few disciplines inspired by his 1916 result for the diffusional coagulation of particles:

First passage processes in molecular context

Smoluchowski's treatment of the coagulation process helped establish the parallel of molecular first passage processes with the stochastic encounter of two particles. Especially after the invention of superresolution microscopy, extremely precise measurements of this first passage process are possible [11].

Anomalous diffusion

Smoluchowski's treatment of diffusion processes, much in the spirit of Pearson's random walk, allows the straightforward extension to random walks leading to anomalous diffusion, for instance, in the Scher–Montroll picture [20].

Facilitated diffusion

The fact that signalling proteins find their target on a DNA molecule faster than predicted by the Smoluchowski rate (3) paved the way for the facilitated diffusion model championed by Berg and von Hippel [21]. In this model the faster rates can be explained by dimensional reduction: intermittent diffusion in one dimension along the DNA chain itself switching with diffusion in three dimensions indeed leads to a speedup of the search process [21].

Random search

When systems are too complex to be described by first principles, in physics we often resort to statistical treatments. Thus, the search for food by higher animals or the motion patterns of humans are often described by direct extension of Smoluchowski's ideas. Random search in movement ecology typically uses the idea of (extensions of) the diffusional encounter. One of the generalisations relevant for the search of rare targets is based on random walks with long-tailed, Lévy stable jump lengths, leading to the celebrated Lévy foraging hypothesis [22].

In a time when tracing biochemical reaction steps in cells, one molecule at a time, is no longer science fiction, Smoluchowski's ideas of diffusional limitations of (bio)chemical processes are more timely than ever.

Centenary special issue

In this special issue we collected papers from different fields inspired by Smoluchowski's 1916 landmark publication. Roughly, these works can be categorised as follows.

First passage dynamics

The theory and applications of the first passage of stochastic particles are studied in the following contributions:

Ben-Naim and Krapivsky investigate questions of escape and the associated finite time scaling of diffusion limited annihilation reactions [23]. Related to this topic is the question of how sparse initial conditions influence the kinetics of such reactions [24].

Levernier *et al* present new results for the mean first passage time (or, in other words, the diffusion limited rate constant) of anisotropically diffusing particles [25].

The question of how sparse obstacles influence the intermittent diffusion of particles is scrutinised by Berezhkovskii and Bezrukov [26].

Following a randomly searching forager, Bénichou *et al* study how the subsequent depletion of targets (food sources) feed back on the forager [27].

Dybiec *et al* follow up on the transient behaviour of random searchers with long-tailed jump length distributions, as they may easily overshoot their target [28].

Combining short-tailed and long-tailed random walk motion, Palyulin *et al* examine the reliability and efficiency of the resulting random search [29].

The first detection time of a quantum walk is evaluated in terms of a quantum renewal approach by Friedman *et al* [30].

Facilitated diffusion and biochemical signalling

Signalling by diffusing molecules in a biochemical context is investigated by the following contributions:

Berg *et al* follow up on the question of how the molecular structure of the DNA molecule may be beneficial for the binding rate of DNA binding proteins [31].

The details of how other proteins ('roadblocks') bound to a DNA influence the motion of a specific DNA binding protein, searching for its specific binding site on this DNA chain, is studied by Koslover *et al* as well as Krepel and Levy [32, 33], highlighting different aspects of this process.

Kochugaeva *et al* concentrate on the conformational dynamics of the searching DNA binding protein itself, quantifying the resulting search efficiency [34].

Vasilyev *et al* study the binding of a diffusing molecule to a specific location on a linear antenna molecule when, in addition to three-dimensional diffusion, it may diffusively slide on the antenna molecule [35] similar to the key elements of facilitated diffusion.

An exhaustive review on the impact of Smoluchowski's work on the modelling of stochastic processes in a biochemical context is provided by Holcman and Schuss [36].

Active and collective particle motion

One of the new modern aspects considered in the context of stochastic particle motion is that of elements of active motion. This could pertain to actually moving 'particles' such as biological cells, or transport within cells by molecular motors. The following articles deal with such active motion:

Molecular signalling in linear arrangements such as long neuron cells are shown to be beneficial for signalling precision by Godec and Metzler [37].

The role of activity of stochastically moving particles in the context of chemical kinetics **is** highlighted by Oshanin *et al* [38].

What happens when a system of active particles is hindered by obstacle crowding is analysed by Huang *et al* [39].

A concrete model for active particle motion with stable noise driving for the torque of these particles is presented by Nötel *et al* [40].

Effects of collective particle motion also generalise the original Smoluchowski picture. The following works consider such effects:

Majka and Góra span the range from effective interactions to spatially correlated noise for the collective motion of colloidal particles [41].

Lizana *et al* demonstrate that collective interaction with a two-dimensional elastic network leads to logarithmically slow diffusion [42].

Fundamentals of stochastic processes

The following papers study new aspects of the fundamental nature of stochastic processes:

The Onsager coefficients for a Brownian particle are derived in the case of space-periodic and time-periodic potentials by Rosas *et al* [43].

Giuggioli *et al* consider a linear delayed Langevin equation with additive Gaussian noise and derive the associated Fokker–Planck equation [44].

As an effective description of the spatiotemporally coupled Lévy walk process, Magdziarz and Teuerle consider the formulation in terms of fractional diffusion equations with a distributed-order material derivative [45].

The higher-dimensional mathematical properties of such Lévy walks are analysed by Fuxon *et al* [46].

Fulinski considers some new concepts of fractional Brownian motion, such as the diffusion velocity and correlation functions [47].

In a continuous time random walk setting, Poloczanski *et al* study the cumulative distribution function [48].

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