

Chapter 2

The Role of Fragmentation on the Formation of Homomeric Protein Complexes

2.1 Introduction

The synthesis of larger structures by the assembly of several basic building blocks is a general principle in biology. We can see this reflected in the fact that, for example, many proteins are actually complexes formed from several subunits, which spontaneously organize and come together. In a more general way, we could define self-assembly as a process by which ordered aggregates are formed, as a result of the interplay of tightly tuned attractive and repulsive forces in a stochastic environment, with random thermal fluctuations. As such, self-assembly is a widely studied phenomenon in the areas of chemistry, biology and physics [28]. There are many different examples of self-assembly systems, such as crystals, lipid bilayers and many biological structures, such as the aforementioned example of proteins complexes. In this chapter we elaborate a theory of protein assembly, using the Smoluchowski coagulation equation as a simple model. The central objective is to determine the most important parameters which affect the efficiency of the complex formation process. We directly apply the concepts introduced to homomeric membrane complexes of the bacteria *E. coli*.

In chemistry and biology the process of self-assembly is usually reversible and characterized by weak interactions, such as hydrogen bonds. The formed structures are often, therefore, in thermodynamic equilibrium. In this work we analyse the role of reversibility on the formation of proteins complexes, focusing more specifically on role exerted by fragmentation on the final aggregate.

This chapter is organized as follows. At first, in [Sect. 2.2](#) we introduce the biological system we will use as an example, which are the homomeric protein complexes. In [Sect. 2.3](#) we provide a description of the theoretical tools that we employ in this chapter. The important estimations in our study are the time scales of aggregation and of fragmentation. In order to obtain these quantities we consider the relevant stochastic processes, and analyse them using the first-passage time approach. We end the literature review in [Sect. 2.4](#) with an introduction on the Smoluchowski coagulation equation, which is the mean-field approximation in the core of our theory. Then we

turn in [Sect. 2.5.1](#) to the development of our approach which employs a truncated form of the previously described Smoluchowski equation. We introduce the definition of efficiency of the process, which is simply the ratio of subunits forming the complete protein complex. Then we analyse the irreversible aggregation process, which is highly inefficient when the goal is the formation of large complexes. We follow by extensive studies of the system with fragmentation, which behaves very differently from the irreversible case, with significantly greater efficiency. We have found that the minimisation of the fragmentation rate is a certain way to increase the efficiency of the process, but it cannot vanish such that aggregation becomes irreversible. Furthermore, the contextualisation of our findings for the proposed biological problem shows that the minimisation of the fragmentation rate is not always possible. For the biological system, the total time available to the oligomerisation of proteins is limited by the life time cycle, since a required number of protein complexes should be ready to be transferred to the daughter cells. By imposing such a time constraint, we find the existence of an optimum fragmentation rate, for which the final product is formed with the highest possible efficiency. However for very large complexes, the existence of this optimum fragmentation rate does not imply a large production of final complexes. For this reason we speculate that for a biological system this can consist in an additional evolutionary pressure to keep the complexes small, and to tune the fragmentation rate to correspond to the optimum peaks in efficiency.

2.2 Homomeric Protein Complexes

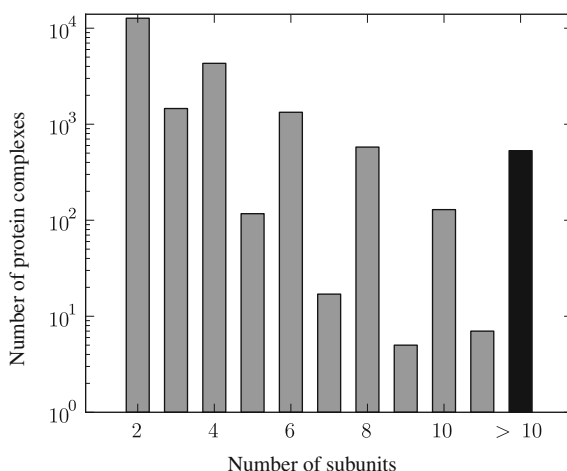
The past few decades provided a large amount of knowledge about the structure of many proteins. The construction of large data banks of such crystal structures, like protein data bank (PDB)¹ or PISA² allowed comparative and evolutionary studies [7, 11, 12, 19]. These analyses characterized a large number of proteins as being composed by several distinct units combined into complexes. They are produced as separate polypeptide chains and assembled into protein complexes as diverse as enzymes, ion channels, receptors, chaperones and transcription factors. These complexes can be either composed by identical subunits, called homo-oligomers (homomers) or they can be formed by distinct interacting parts called hetero-oligomers [1]. As we have described in the [Introduction](#) of this chapter we are interested in the process of self-assembly of the first type: the homomeric proteins.

Because these complexes are highly abundant in nature it is speculated that they present evolutionary advantages. Possibly, the most important benefit is that the formation of complexes permits the production of large structures without increasing the genome size. Furthermore, additional advantages include the introduction of an additional level of control, as they can be allosterically regulated; more reliability in transcription, since shorter sequences are more likely to be error-free; the

¹ <http://www.pdb.org>

² http://www.ebi.ac.uk/msd-srv/prot_int/pistart.html

Fig. 2.1 Number of known homomeric proteins complexes (data from PISA)



amplification of evolutionary pressures, since both deleterious and beneficial mutations are more evident; the resistance of larger proteins to degradation and denaturation; the ability to support more complex functions; and finally the larger binding-site specificity of enzymes [1, 7].

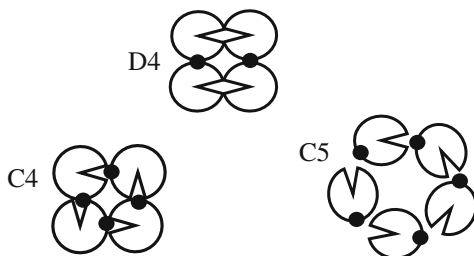
The homomeric proteins are particularly abundant among protein complexes and constitute 50–70% of the proteins with resolved quaternary structure³ [12]. A large fraction of 62% associate only in dimers and the number of proteins decreases exponentially with the number of subunits (see Fig. 2.1). Also it is easy to notice that the number of complexes with odd number of subunits is much smaller than those with an even number (see Fig. 2.1). The preference for the formation of homomeric complexes is due to a strong attraction between identical surfaces. A study from Lukatsky et al. [15] demonstrated theoretically this fact. Their research analysed the energy of interaction between surfaces with random patterns, and they showed numerically that identical random surfaces have always an average minimum energy shifted towards the lower energies, compared with distinct random surfaces.

Another important property of homomeric proteins is their symmetry [1]. Because symmetry confers stability, the homomeric proteins are usually symmetric and have predominantly: cyclical (C_n),⁴ dihedral (D_n) or cubic symmetries [3]. The cyclic symmetries involve only one type of interaction, and contain a single axis of rotational symmetry, forming a ring of symmetrically arranged subunits (see Fig. 2.2). Typically, they are involved in functions that require directionality or rotational motion. They usually form tubes and can interact with membranes forming complexes such as ion channels. On the other hand, protein complexes with dihedral symmetry have

³ The primary structure of a protein is its amino acid sequence. The secondary structure the α -helices and β -sheets. The tertiary represents the chain fold. The quaternary structure is the assembly of those folded polypeptide chains.

⁴ In this notation C represents the cyclical symmetry of the protein and n the number of subunits that compose this protein. For example: C_6 is a cyclic hexamer.

Fig. 2.2 Examples of the two possible symmetries of homomeric complexes: a dihedral complex of four subunits, showing two types of interactions; and cyclic tetramer and pentamer



at least two distinct interactions, and they appear to have evolved from cyclic dimers (see Fig. 2.2). They require an even number of subunits, and are mostly cytoplasmic proteins, therefore they can not be incorporated in polar biological membranes. The dihedral complexes are by far more abundant than cyclical ones (it was estimated that they are at least 10 times more abundant [12]). There are several recent works on the constraints imposed by the symmetry on the evolution of protein complexes [11]. Here we highlight the work of Villar et al. [25], which focused on the role played by the relative strengths of the two interactions in dihedral complexes. The authors used a molecular dynamic approach and showed that there are advantages in the production of assembled proteins using a two step process, which can explain why the even number of subunits and the dihedral symmetries are more abundant in nature. However, since membrane proteins have cylindrical symmetry, they could not have evolved to tune the efficiency of their productions by the strategy described in [25].

As we mentioned previously the cyclic symmetry is predominant in the membrane protein complexes. In the next subsections we show some examples of such complexes for bacteria and describe their main properties, such as the interaction strength between subunits and the diffusion coefficient on the cell membrane.

2.2.1 Homomeric Membrane Proteins

The structure of all membrane proteins is constrained by the lipid bilayer. There are over 200 unique structures of membrane proteins available in the PDB. The understanding of their function is a challenge in the drug development field since they are key components for signaling and cell growth control [26]. It has been reported so far that essential structural themes for the membrane proteins are both the α -helices and β -barrels. The first ones are predominant in cytoplasmic and cellular components and the second ones on the outer membrane of bacteria, mitochondria and chloroplasts [26].

Membrane homomeric proteins can be either channels, pores or receptors with cyclical symmetry (C_n). As examples we can name: bacterio-rhodopsin (C_3), AmtB—ammonia transporter *E. coli* (C_3), potassium channels (C_4), acetylcholine receptors (C_5), FocA—formate transporter *E. coli* (C_5), MscL mechanosensitive

Table 2.1 Stability of the complexes estimated by PISA

	PDB code	Size of the complex	H-bonds	Salt-bridges	BSA
AmtB	1U7G	3 subunits	~4	~3	~17 nm ²
MscL	2OAR	5 subunits	~7	~5	~18 nm ²
FocA	3KCU	5 subunits	~6	~1	~15 nm ²
MscS	2OAU	7 subunits	~25	~8	~26 nm ²

**Fig. 2.3** FocA and MscL channels have 5, and MscS has 7 identical subunits

channel of large conductance *E. coli* (C_5), MscS mechanosensitive channel of small conductance *E. coli* (C_7). In Table 2.1 we list some of the proteins from *E. coli* with some of their important characteristics (they all play fundamental roles in the cell survival⁵), for resolved crystal structures see Fig. 2.3.

Since the aim of this work is to study dynamics and the efficiency of their assembly, we will focus on the rate of diffusion and the interaction strength between subunits, which are described in the following two subsections; these two concepts are the ones we will need for modelling the dynamics of the assembly process later on.

2.2.2 Interactions Responsible for the Formation of Quaternary Structures

The quaternary structure of proteins depends on the interactions among the subunits. In general terms, we can summarize all the aspects of the stability of macromolecular complexes and their compatibility of assembly as follows: hydrogen bonds, salt bridges, hydrophobic specificity, interface area; also it is important to take into account the free energy of the complex formation and solvation energy gain. All these aspects are treated in detail with different available software. In this work we use the data available from PISA. Although we do not discuss all of them in detail, in the next part we discuss the buried surface area concept followed by the analysis of hydrogen bonds, which are fundamental for the stability of membrane proteins.

⁵ The mechanosensitive channels are described in detail in this chapter.

2.2.2.1 Buried Surface Area

The specificity of recognition is estimated from the geometry and chemical properties of the interfaces between subunits. One of the widely used parameters is the interface area, which is the accessible surface area of the subunits that becomes inaccessible to solvent due to protein–protein contacts. This is usually denominated as the buried surface area (BSA) between the macromolecules [9]. It is usual to have the antigen–antibody interaction as a reference measure, which is characterised to be in the range of 12–20 nm². Many other protein–protein interfaces are also found to have BSA in this range and have what is considered to be a standard interface area [5, 8].

The BSA is characterised by its topology and the number of hydrogen bonds found on it. Early studies suggested that there is about one hydrogen bond per 2 nm² of subunit interface [9]. As we explain in the next subsection, hydrogen bonds are very important for protein stability.

2.2.2.2 Hydrogen Bonds

Hydrogen bonds are known to be one of the main interactions responsible for the stabilization of the secondary structure of proteins and of the formation of protein complexes. In non-polar environments such as biological membranes, these bonds provide enough energy for the establishment of the protein conformation and its tertiary interactions. They are widely considered to be an important force in the membrane environment because of the low dielectric constant of membranes and a lack of competition from water. Indeed, polar residue substitutions are the most common disease-causing mutations in membrane proteins [4]. The strength of the hydrogen bonds can be estimated from the structure of the protein. The strength of the hydrogen bonds in the biological membranes is evaluated to be similar to the strength in vacuum. For N–H···O this corresponds to ~12 kJ/mol. However for an aqueous environment the hydrogen bond energy is lower, around ~6 kJ/mol.

Apart from the interactions which govern the formation of protein complexes, it is necessary to understand how they diffuse on the membrane, if one is to model their efficiency. In the following subsection we provide an estimation of the diffusion coefficient of membrane proteins, based on the Saffman–Delbruck approach [22] and the experimental results of Ramdurai et al. [20].

2.2.3 *Diffusion Coefficient of Membrane Proteins*

The remaining parameter relevant for the assembly of proteins on the membrane is their diffusion coefficient. More specifically, it is necessary to relate the size of the protein with its diffusion constant on the membrane surface. There are two models used in the literature: in the first one the diffusion constant scales with $1/r$, where r is the radius of the protein; the second model (which is recently gaining credibility)

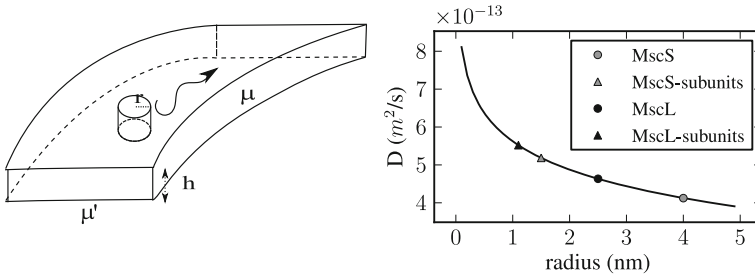


Fig. 2.4 On the *left* a protein of a radius r diffusing on a membrane of thickness h , and viscosity μ . The membrane is surrounded by a liquid of viscosity μ' . On the *right* the diffusion coefficient in an uncrowded membrane as a function of the protein radius according to the Saffman–Delbruck law

considers a logarithmic relation between these two quantities. The relation is given by the Saffman–Delbruck equation [22],

$$D = \frac{k_b T}{4\pi \mu h} \left(\ln \left(\frac{\mu h}{\mu' r} \right) - \gamma \right), \quad (2.1)$$

where k_b is the Boltzmann constant, T is the absolute temperature, h is the thickness of the bilayer, μ is viscosity of the membrane, μ' is viscosity of the outer liquid and γ is the Euler constant. This model was elaborated by Saffman and Delbruck in 1970 to describe the diffusion in highly anisotropic environments such as biological membranes. The diffusion of membrane proteins in *E. coli* was finally analysed in [20], and the results show the validity of the Saffman–Delbruck equation. In Fig. 2.4 we show the prediction, according to this model, for the diffusion of the subunits of mechanosensitive channels, as well as for the assembled functional channel.

2.3 The First Passage Time Processes: An Estimation of the Aggregation Time Scale

It is possible to approach the random walk problem with two types of questions: 1. How far from the starting position x_0 is a particle that moves by Brownian motion after a time t ?; 2. Starting from the position x_0 how long it takes for the particle to arrive for the first time at a point x ? The second question is very relevant in the context of transport in disordered media, neuron firing, spread of diseases, target search processes, and diffusion-limited reactions. Understanding the first time approach is essential to derive the main theoretical tool which we use in this part, which is the Smoluchowski theory of coagulation. We will start by giving a short introduction to this topic applied to the problem in question. A very good review of first passage time processes can also be found in Sidney Redner’s book [21].

2.3.1 The First Passage Time on a Sphere

Since our objective is to describe the diffusion on a surface of a cell we need to describe the first passage time process on a closed surface. We will solve the problem for a particle in Brownian motion on a surface of a sphere of radius R . The particle moves randomly, until it reaches a small absorbent cap, of radius r ($r/R \sim \sin(\delta/2)$), on the north pole of the sphere, in a mean time W . Considering x the particle position, and an infinitesimal time step δt , the mean time is given by the recursion formula

$$W(x) = \frac{1}{2} ((W(x + \delta x) + \delta t) + (W(x - \delta x) + \delta t)), \quad (2.2)$$

which can easily be rewritten as

$$W(x - \delta x) - 2W(x) + W(x + \delta x) = -2\delta t. \quad (2.3)$$

This turns to

$$DW''(x) = -1 \quad (2.4)$$

with $D = \frac{1}{2\delta t}$. This equation can be generalised to a Poisson equation for a d -dimensional space,

$$D\nabla^2 W(r) = -1, \quad (2.5)$$

where ∇^2 is the Laplace–Bertrami operator of the 2-sphere.⁶ With this formalism is possible to obtain the average first passage time on a domain with defined boundaries. The problem, therefore, is reduced to a solution of the well-known Poisson equation from electrostatics. Considering a description with spherical coordinates, this system then can be simplified due to its symmetry, since W is independent of the coordinate ϕ ,

$$\nabla^2 W(\theta) = \frac{1}{R^2} \left(\frac{d^2 W}{d\theta^2} + \cot \theta \frac{dW}{d\theta} \right) = -\frac{1}{D}, \quad (2.6)$$

with the boundary conditions given by

$$\frac{dW(\pi)}{d\theta} = 0 \quad W(\delta) = 0. \quad (2.7)$$

The solution of the equation is⁷

$$W(\theta) = \frac{2R^2}{D} \ln \frac{\sin \theta/2}{\sin \delta/2}. \quad (2.8)$$

⁶ This operator corresponds to the Laplace operator on a curved surface.

⁷ The maximum time that it takes for the particle to find the cap corresponds to the starting point $\theta = \pi$ $W(\pi) = \frac{2R^2}{D} \ln \left(\frac{R}{r} \right)$.

It is also possible to find the average time τ for the particle to reach the absorbing cap from any initial position on the sphere:

$$\langle \tau \rangle = \frac{\int_{\delta}^{\pi} W(\theta) \sin(\theta) d\theta}{\int_{\delta}^{\pi} \sin(\theta) d\theta} = \frac{2R^2}{D} \ln \left(\frac{R}{r} \right). \quad (2.9)$$

With the theory developed in this section it is possible to estimate the time of formation of the assemblies on the cell surface. It is important to point out that the assembly time will be dependent on the size of the cell and on the diffusion coefficient. The dependence on the radius of the particle, as given by the Saffman–Delbruck model of diffusion discussed previously, is $\tau \sim \ln(R/r) \frac{1}{\ln(1/r)}$. As such, we have a complete approximation of the time scale of the rate of assembly on a spherical surface, which we can use as a parameter in our Smoluchowski-based approach, described in the following sections.

2.4 The Smoluchowski Coagulation Equation

Growth by aggregation is a common natural phenomena found in several different fields, such as astrophysics, colloidal chemistry, polymer science, graph theory and biology [13]. In all these areas, the main process can be described as a dynamics in which complexes of diverse sizes diffuse in the system, and when they approach each other they coalesce in complexes with larger size, which correspond to the sum of the masses of the two originating parts,

$$A_m + A_n \rightarrow A_{m+n}. \quad (2.10)$$

The most studied process in the literature, which we describe in this section, is that of *unbounded* aggregation, where the assembly process proceeds to form infinitely large aggregates. Such situation applies well to systems such as aerosol and liquid droplet coalescence. However, for the study of the assembly of homomeric proteins we use a different approach, which will be described in detail in [Sect. 2.5](#), which imposes an upper bound for the assembly dynamics. This bound for aggregation convey properties to the system which are very distinct from the unbounded variant.

The time evolution of the coagulation process can be described with a master equation approach, where the system is represented by an infinite set of differential equations, which describe the evolution in time of the concentration of each complex size. The main assumptions which need to be made are as follows [10],

1. *The mean-field hypotheses.* It is assumed that there are no spatial correlations of the aggregation reactions, and the particles have a homogeneous distribution in space. Although it is a very strong assumption it is proved to be valid for many physical systems.
2. *Binary collisions.* The reactions happen only between pairs of bodies.

3. *Shape independence.* The aggregation process does not depend on the shape of the aggregate. However it can depend on the aggregate size.

This type of approach to describe the coagulation phenomena was first developed by Marian Smoluchowski in 1917 [23], when he introduced the approach in its continuous form, which can be written as

$$\frac{dn_j}{dt} = \frac{1}{2} \sum_{i=1}^{j-1} K_{i,j-i} n_i n_{j-i} - n_j \sum_{i=1}^{\infty} K_{ij} n_i \quad (2.11)$$

The members and parameters of these equations are the following:

1. j is the agglomerate size, or units of mass. We define a particle of unit mass as a monomer. Therefore j represents the number of monomers inside a cluster and is also denominated as a j -mer. The number of monomers can vary in the range $[0, \infty]$.
2. n_j is the concentration of particles with size j in the system. It varies in the range $[0, 1]$.
3. K_{ij} is the rate of a specific reaction, called the agglomeration *kernel* and reflects the main dynamical properties of the system. A common assumption is to have symmetric reactions, $K_{ij} = K_{ji}$.
4. M is the total number of units of mass, i.e. monomers, present in the system.

$$M = \sum_{i=0}^{\infty} i n_i(t) \quad (2.12)$$

It is a conserved parameter during the process. It is possible to verify from Eq. 2.11 that $\frac{dM}{dt} = 0$.

This system was extensively studied for simple kernels such as: $K_{ij} = \text{const.}$, $K_{ij} = ij$, and $K_{ij} = i + j$. For most other kernels, an analytical solution has not yet been found. For example, for the kernel representing the rate of collision for particles moving in Brownian motion, with diffusion rates D_u and radius R_u of a complex of size u , which is given by $K_{ij} = (D_i + D_j)(R_i + R_j)$, a general analytical solution has not yet been obtained.

It was shown that the important parameter for this system is not the initial conditions, but only the total mass M . Therefore, it is usual to study the system starting with the simple initial condition

$$n_j(t = 0) = M \delta_{j1} \quad (2.13)$$

where the system starts only with monomers. The exact solution can be calculated for simple kernels. For the constant kernel, Eq. 2.11, using Eq. 2.12 can be rewritten as

$$\frac{dn_j}{dt} = \frac{1}{2} \sum_{i=1}^{j-1} n_i n_{j-i} - n_j N(t), \quad (2.14)$$

where $N(t) = \sum_i n_i$ and be solved by a recursive approach, leading to the solution

$$n_j = \frac{t^{j-1}}{(1+t)^{(j+1)}} \quad (2.15)$$

For both the sum and product kernels, an exact solution can be obtained by using generating functions [10]. A very interesting alternative was developed recently by Lushnikov [16], where the system is described as discrete states, with operators of annihilation and creation which act on them. Another alternative is to consider a combined system

$$K_{ij} = \frac{1}{2}(i^\alpha j^\beta + j^\alpha i^\beta) \quad (2.16)$$

where the properties can be analysed in terms of the coefficients α and β [17, 27]. In these systems there is the emergence of very interesting phenomena, such as gelation, which is characterized by the condensation of a non zero fraction of the total mass in a single cluster [10]. The system can be in one of two phases: the gel phase (large cluster) and sol phase (small clusters that disappear with time).

2.4.1 System with Fragmentation

There are many ways to introduce fragmentation in the system, according to the different dynamics that can be in the core of this process, such as random fracture, shattering or homogeneous break-outs. In its simplest form, this process is commonly approached as aggregation running backwards in time (compare with Eq. 2.10) [10]:

$$A_{m+n} \rightarrow A_m + A_n \quad (2.17)$$

The system with aggregation and fragmentation can be represented as

$$\frac{dn_j}{dt} = A(n_1, n_2 \dots) + \mu' F_j(n_1, n_2 \dots), \quad (2.18)$$

where $A(n_1, n_2 \dots)$ is the agglomeration part which can be represented as before by a Smoluchowski coagulation equation. $F_j(n_1, n_2 \dots)$ is the part that accounts for the fragmentation, and its rate is given by a constant μ' . The first work on coagulation–fragmentation systems was done by Blatz et al. [2] and the fragmentation process was considered as

$$F_j(n_1, n_2 \dots) = -\frac{n_j}{2}(j-1) + \sum_{i=j+1}^{\infty} n_i \quad (2.19)$$

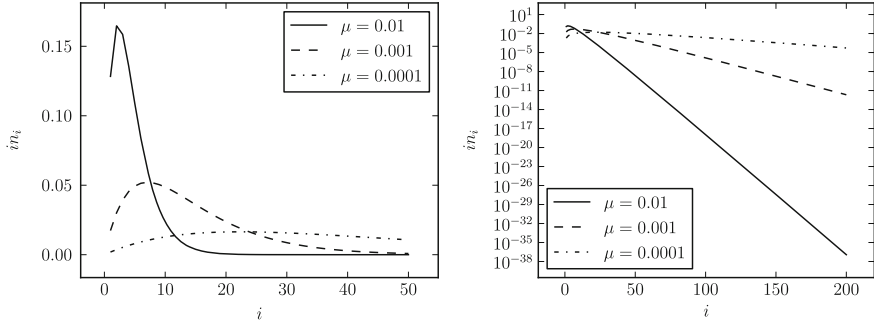


Fig.2.5 Mass (number of monomers) as a function of size of the cluster i for different fragmentation rates μ

A fragmentation of this type means that larger complexes have more ways to fragment. Here we consider a rescaled version of the parameter $\mu = \frac{\mu'}{K}$, such that we have only one free parameter. The solution of this system is given by [2]

$$n_j = (p)^{j-1} (1-p)^2 \propto e^{(j-1) \ln p} \quad (2.20)$$

where

$$p = \frac{1}{1 + \mu/2 + \sqrt{\mu^2/4 + \mu}} \quad (2.21)$$

An example for the mass distribution in this system is represented in Fig.2.5. We can see that for a strong fragmentation rate, such as $\mu = 0.01$, the distribution is concentrated in the range of smaller clusters. However for small fragmentation rate ($\mu = 0.0001$), larger aggregates form and the mass is spread on a larger range of aggregate sizes. The decay is always exponential, with exponent $\ln p$.

2.5 The Efficiency of Formation of Protein Complexes

In the following part we present a general theoretical approach for the assembly of protein subunits into oligomeric complexes. Although little is known about the steps of this process, the consensus is that the subunits after production are incorporated in apparently non-correlated locations in the lipid bilayer. They diffuse and by chance approach each other. The short range interactions promote their assembly, and linking bonds between subparts are created. In the case of homomeric proteins, there is a geometrical constrain for the coalescence process. The bounds between subunits are specific, and they establish angles between monomers, which determine the shape of the final structure. This works as a physical barrier for the assembly.

Because we describe an aggregation process, we use the Smoluchowski coagulation approach. As we described previously, the entire reaction dynamics is defined by the coagulation kernel. This approach is equivalent, but largely simpler computationally, to the average calculation of simulations based on individual particle trajectories. Therefore, we highlight that all the numerical solutions presented in this chapter are only numerical solutions of the Smoluchowski coagulation equation. The kernel that we use in the following sections is the constant kernel, which comes from the assumption that every collision leads to an agglomeration event. Therefore, the rate of coagulation reflects directly the dynamics of particle encounters on an approximately spherical surface. As we explained in Sect. 2.3 the first passage time on a sphere is proportional to the radius of the sphere and the diffusion coefficient. The dependence on the radius of the particle, as obtained with the Saffman–Delbruck model of diffusion discussed previously, is $\tau \sim \ln(R/r) \frac{1}{\ln(1/r)}$. Such a logarithmic dependence on the complex size is very weak, especially if the size of the complexes formed do not vary by many orders of magnitude. Therefore it is justifiable to use a constant kernel as a first approximation, since it simplifies the analysis considerably.

We are interested in the situation where the complexes cannot exceed a maximum size N , as is the case of many protein complexes. This will result in a truncated form of the master equation of Eq. 2.11, proposed by McLeod [18].

$$\frac{dn_j}{dt} = \frac{1}{2} \sum_{i=1}^{j-1} K_{i,j-i} n_i n_{j-i} - n_j \sum_{i=1}^{N-j} K_{ij} n_i \quad (2.22)$$

This is the equation that we will employ in our further studies of protein complexes. Equation 2.11 is its formal limit for $N \rightarrow \infty$ [14, 18] and for $M \ll N$. Equation 2.22 has one and only one solution for each set of initial conditions, such that $n_i \geq 0$ (see [18]).

We are particularly interested in the calculation of the ratio of total monomers which are incorporated into the complexes of maximum size. Our objective is to analyse in which conditions this quantity reaches its largest possible value. To quantify this ratio, we use the term *efficiency*, which has the following meaning throughout this chapter.

Definition The efficiency E of formation of particles of maximum possible size N , is the fraction of monomers (n_N) belonging to complexes of size N in the steady state:

$$E = n_N N. \quad (2.23)$$

We start with the irreversible process and follow with the addition of a fragmentation. We analyse the steady state distribution of the particle sizes.

2.5.1 Steady State Size Distribution with Irreversible Dynamics

In this section we analyse numerically the truncated Eq. 2.22 with a constant kernel, $K_{ij} = 1$. We start the analysis with the study of the steady state ($\frac{dn_j}{dt} = 0$ for all j). As we can see from the Eq. 2.22 a general characteristic of the steady of the system is that all $n_i = 0$ for $i < \frac{N}{2}$. This fact is easy to prove by induction and it does not depend on the initial conditions. On the other hand the values of n_i for $i > \frac{N}{2}$ will all depend on the initial conditions, and any final distribution of n_i , $i > \frac{N}{2}$ is possible. For example, trivially, a set of any initial conditions which has only $n_i > 0$ ($\forall i > \frac{N}{2}$) will not evolve further in time and will be a fixed point. This is a direct consequence of the size constraint that we impose on the system, since particles of sizes larger than N can not be formed, i.e. a collision between two particles, for which the summed mass exceeds N , does not lead to aggregation.

However we are interested in a specific set of initial condition, where only monomers are present, because this is how we expect to find the protein subunits in the beginning of our process. Therefore we start with mono-disperse initial conditions, $n_j(t = 0) = 1\delta_{j1}$. Subunits assemble into complexes through the evolution of time and the processes stops when subunits of small sizes ($i < \frac{N}{2}$) are completely consumed (see Fig. 2.6), since larger complexes with number of particles $i > \frac{N}{2}$ cannot coalesce. An example of a final size distribution can be seen in Fig. 2.7. It is possible to identify three regions in the distribution as follows, for convenience, we assume that N is odd,

$$n_j = 0 \quad \text{for } j < \frac{N}{2} \quad (2.24)$$

$$\frac{dn_j}{dt} = \sum_{i=1}^{N-j} n_i \left(\frac{n_{j-i}}{\delta} - n_j \right) \quad \text{for } \frac{N}{2} < j \leq \frac{2N}{3} \quad (2.25)$$

$$\frac{dn_j}{dt} = \sum_{i=1}^{N-j} n_i \left(\frac{n_{j-i}}{\delta} - n_j \right) + \sum_{i=N-j+1}^{i \leq N/2} n_i n_{j-i} \quad \text{for } \frac{2N}{3} < j \quad (2.26)$$

where

$$\delta = \begin{cases} 2 & \text{if } i < 2j - N \\ 1 & \text{otherwise.} \end{cases} \quad (2.27)$$

The case for N even can be obtained by including the appropriate terms proportional to $N^2/2$. The two solutions should converge to each other for $N \gg 1$. The particles of size $j < N/2$ are always consumed, and for the larger sizes there are two accumulation behaviours depending on how strong is the effect of the size constraint imposed.

It is also possible to see the effect of the system truncation from the approach introduced by Davies et al. [6]. It is possible to see the evolution in time of the

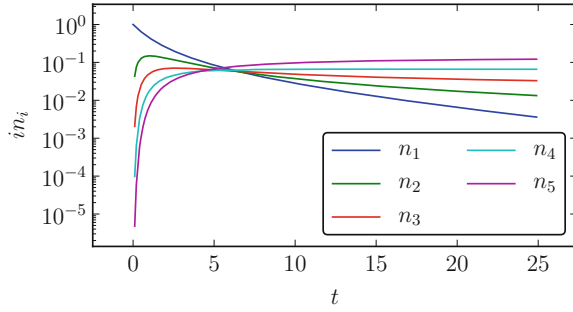


Fig. 2.6 Time evolution of the concentration of j -mers in an aggregation process with a truncation limit $N = 5$, starting with monodisperse initial conditions

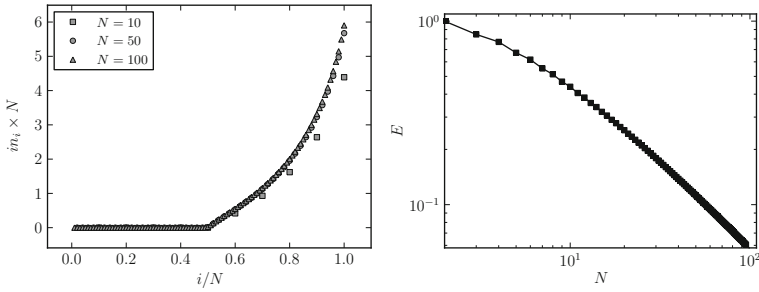


Fig. 2.7 On the left the equilibrium distribution for $N = 100$ starting from monodisperse initial conditions. in_i the total mass of i -mers in the system as a function of particle size i . On the right is the efficiency of the process as a function of truncation size N

process as a flux of mass (monomers) on a lattice with, in our case, N sites. The site r represents the total mass of the particles of size r (rn_r). In this case we introduce J_r which is the mass flux from the cluster at maximum size r to clusters of size larger than r (see Fig. 2.8).

$$J_r = \sum_{j=1}^r \sum_{i=r+1-j}^{N-r} j K_{ij} c_j c_i \quad (2.28)$$

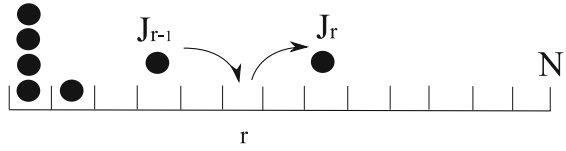
The variation of the mass of particles with size r is therefore

$$\frac{d(rc_r)}{dt} = J_{r-1} - J_r \quad (2.29)$$

As we can see in Eq. 2.28 the flux J_r decreases as r approaches N . The flux of mass is larger for smaller r and decrease progressively until the site N .

However, the most important thing is to see how this effect is reflected on the efficiency of the process. The efficiency of the process decreases with the increase of

Fig. 2.8 We can also represent the system by a mass flux through different states of agglomeration using the concept of a flux J_r



the maximum size N , as can be seen in Fig. 2.7. With the increase of N the number of the intermediate states $N > i > \frac{N}{2}$, in which a subunit can get trapped increases as well. If the total mass of the system is spread through a larger number of intermediates, not many complete complexes are formed at the end of the process.

As we can see, the efficiency of the process is constrained by the assembly dynamics, more specifically by its irreversibility. An alternative therefore is to consider a reversible process, which we do by the introduction of a fragmentation rate in the next section.

2.5.2 Role of the Fragmentation

In this section we introduce a fragmentation rate μ into the process. The system therefore acquires reversible dynamics and in the steady state there is an equilibrium between the assembly of the still incomplete complexes and the fragmentation. The fragmented particles therefore function as a additional inflow of subunits into the system. The dynamics of the system can be represented by Eq. 2.18. However here we use a truncated version of $F_j(n_1, n_2 \dots)$

$$\frac{dn_j}{dt} = \frac{1}{2} \sum_{i=1}^{j-1} K_{i,j-i} n_i n_{j-i} - n_j \sum_{i=1}^{N-j} K_{ij} n_i - \mu \left(\frac{n_j}{2} (j-1) + \sum_{i=j+1}^N n_i \right). \quad (2.30)$$

Similarly to the case of the aggregation kernel, we adopt simple forms of the fragmentation rate. We consider two cases: open and closed chains. For open chains we consider a constant fragmentation rate independent on the size of the complex. In the second case we consider a constant fragmentation rate for all intermediate complexes except for the last one, which is considered to be more stable. This reflects the formation of circular chains of proteins, where the fragmentation of a complete chain implies in breaking not only one, but two links.

2.5.2.1 Uniform Fragmentation Rate (Open Chain)

In this part we analyse the steady state solution of the system with uniform fragmentation. It is possible to find the solution of the steady state, which is given by the expression

$$n_j = \frac{n_1^j}{\mu^{j-1}}, \quad (2.31)$$

for $j > 1$, which can be verified by substitution in Eq. 2.30. The remaining value n_1 can be determined from the relation of conservation of monomers with time

$$M = \sum_{j=1}^N \frac{j n_1^j}{\mu^{j-1}}. \quad (2.32)$$

We can see that the distribution depends strongly on the fragmentation rate μ (see Fig. 2.9). In this case we also produce intermediates and the proportion of these intermediates is related to μ . As the fragmentation rate increases, the predominant size of intermediate complexes changes from the maximum size N to smaller values. In order to obtain this dependence on μ more precisely, we differentiate Eq. 2.31 in respect to μ ,

$$\frac{dn_j}{d\mu} = \frac{n_1^{j-1}}{\mu^{j-1}} \left(j \frac{dn_1}{d\mu} - (j-1) \frac{n_1}{\mu} \right). \quad (2.33)$$

On the other hand, the differentiation of Eq. 2.31 gives us

$$\frac{dn_1}{d\mu} = \frac{n_1}{\mu} \left(1 - \frac{M}{M_1(\mu, n_1(\mu))} \right), \quad (2.34)$$

where

$$M_1(\mu, n_1(\mu)) = \sum_{i=1}^N \frac{i^2 n_1^i}{\mu^{i-1}}, \quad M_1(\mu, n_1(\mu)) = n_1 \frac{dM}{dn_1}. \quad (2.35)$$

Using Eq. 2.33 we obtain

$$\frac{dn_j}{d\mu} = \frac{n_j}{\mu} \left(1 - \frac{jM}{M_1(\mu, n_1)} \right). \quad (2.36)$$

The equation above shows us that $n_N(\mu)$ is a strictly decreasing function, since $NM > M_1$ always holds, as can be seen in Fig. 2.9. This equation also shows that n_1 is always an increasing function with μ , since $M < M_1$. However it is not as easy to obtain the behaviour of other intermediates, n_j with μ . We can calculate the maximum of the function, in other words the value of μ for which n_j is the largest, by solving the polynomial

$$\sum_{i=1}^N (i^2 - ji) \frac{n_1^i}{\mu^{i-1}} = 0. \quad (2.37)$$

This analysis shows how different is the behaviour of the system with the introduction of fragmentation. The efficiency of the process increases for $\mu \rightarrow 0$, however at the

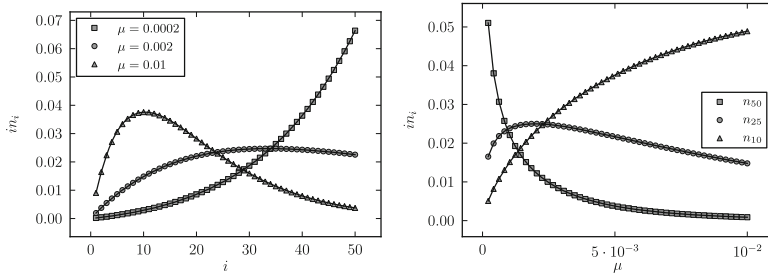


Fig. 2.9 Distribution of mass $i n_i$ as a function of particle size i (left) and μ (right) for $N = 50$. The dots are results from numerical solutions of Eq. 2.30, and the solid lines are the analytical results given by Eqs. 2.31 and 2.32

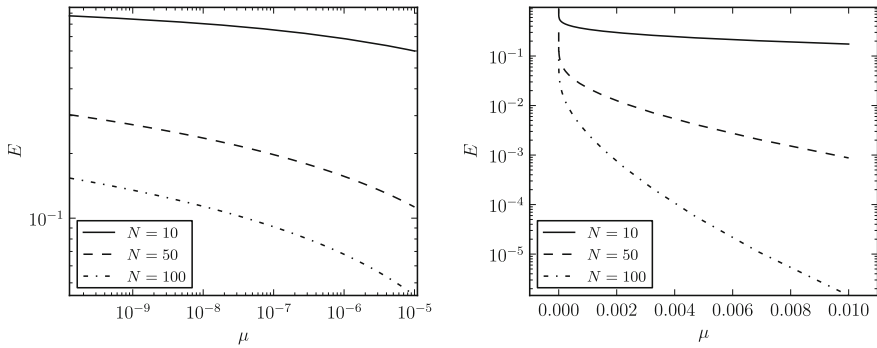


Fig. 2.10 The efficiency E as a function of μ , for different values of N . The graph on the left is close up of the graph on the right, for small values of μ

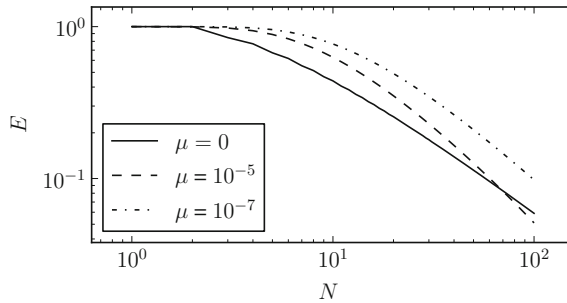


Fig. 2.11 The efficiency of formation of complexes of maximum size as a function of truncation size N , for the system without the fragmentation rate (solid line) and for the system with fragmentation (dashed line). There are a small increase in the efficiency of the process for small fragmentation rate. However the efficiency still strongly decreases as we increase N equivalently to the case with irreversible dynamics

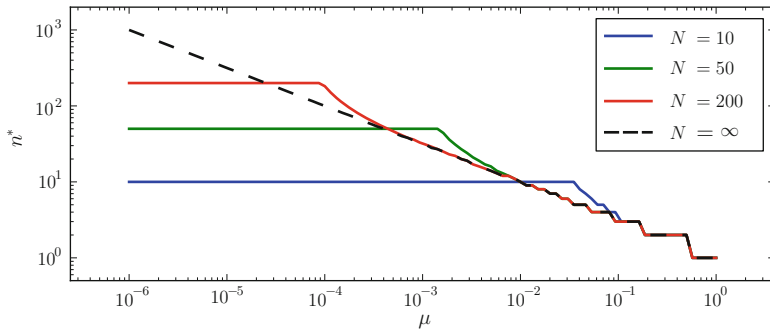


Fig. 2.12 The n^* is the size of particles present in larger concentration in the steady state distribution of the system. The complete complex size is the most formed j -mer for a wide range of μ . The distribution approaches the non-truncated Smoluchowski coagulation equation for large fragmentation rates

point $\mu = 0$ the system is again irreversible and the efficiency drops discontinuously (see Figs. 2.9, 2.10, 2.11).

The behaviour of the system changes in important ways as the value of μ is varied: For small values of μ , the constraint of the maximum size will be the main factor to determine the steady state distribution. However in a system with large values of μ , the constraint stops influencing the dynamics, since the fragmentation does not permit the mass flow in the system to reach the maximum size. In this situation the dynamics is identical to a traditional Smoluchowski coagulation with $N = \infty$. This fact is illustrated in Fig. 2.12, where it is shown the size n^* of the particles that dominates in the distribution of the mass of the steady state, $n^* n_{n^*} \geq j n_j \forall j$, as of function of μ . For small values of μ the predominant size is the maximum possible size N . However as the μ increases the fragmentation does not allow the mass flow to distribute significantly further a certain j -mer ($j < N$). In this case the predominant size that captures the larger number of monomers in the steady state is an intermediate size. A similar message is shown in Fig. 2.13, where the system is divided in two regions, as a function of the parameters μ and N : the black region represents the system with the steady state mass belonging predominantly to particles of maximum size ($E > 0.5$), and the white region it is the intermediate particles which dominate ($E < 0.5$).

We now turn to a relevant aspect of aggregation of protein complexes which is the time necessary for their formation. We have obtained so far that smaller fragmentation leads to higher efficiency. However, an aggregation process which relies on a very small fragmentation rate will also tend to be very slow, and in some cases there will be a limitation for the time of aggregation. Such a time limit is present, for example, in a living organism which is expected to duplicate the number of all its arsenal of proteins during a replication cycle. Therefore it is interesting to analyse the assembly product after a given time, in a stage before the system achieves the steady state. The simplest consequence of this limitation is that very small fragmentation rates will

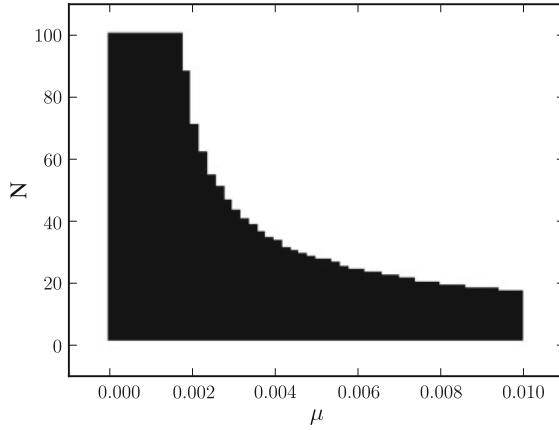


Fig.2.13 In *black* the region of parameters (N -maximum of the size grow and μ -fragmentation rate) where the aggregates of maximum size N have the larger total mass, $Nn_N > in_i \forall i \neq N$

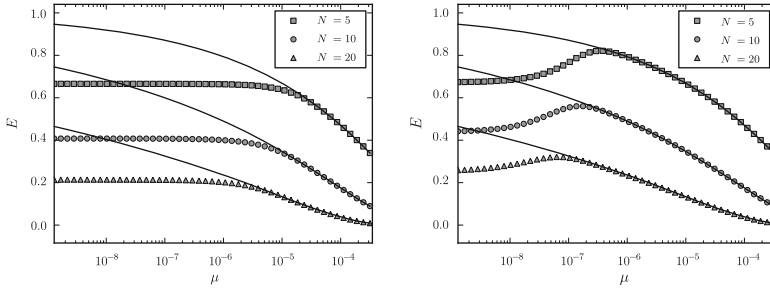


Fig.2.14 The efficiency E of the assembly process as a function of μ different values of N for a system in a transient state (*points*) and in the steady state (*solid lines*). On the *left* the iteration time is equivalent to 1,000 sec and on the *right* to 10,000 sec

not have any effect. Our observation is that with this limitation there is an optimum fragmentation rate (see Fig. 2.14), and that this optimum decreases with the maximum complex size. For a *E. coli* bacteria the replication time is 20 min. The association kernel can be estimated from the Eq.2.9 to be $\sim 0.01 \text{ s}^{-1}$. Figure 2.14 shows how the efficiency of the assembly changes with the protein size for the estimated time. From this estimation we see that very large complexes with this limitation can not be formed efficiently, even if the fragmentation rate is very low.

2.5.2.2 Fragmentation Rate for Rings (Closed Chains)

In this part we consider a system where the complex of maximum size has a higher stability then its intermediates. In this case the monomers assemble in to a circular

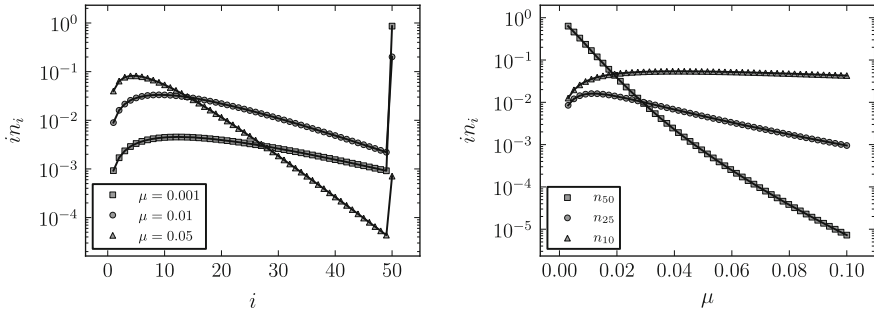


Fig. 2.15 Distribution of particle mass in_i as a function of particle size i , for *closed rings* with $N = 50$. On the *left* we show the final distribution for three fragmentation rates μ . On the *right* we show how the efficiency of formation of i -mers changes with μ , for different values of i

geometry that closes into a ring when the final size complex is achieved. All the intermediate complexes will have a fragmentation rate μ . However due to the circular geometry, two links have to break in order to fragment a complex with maximum size, and therefore the fragmentation rate for it will correspond to μ^2 ,

$$F_j(n_1, n_2 \dots) = -\frac{n_j}{2}(j-1) + \sum_{i=j+1}^{N-1} n_i + \mu n_N \quad j \neq N \quad (2.38)$$

$$F_N(n_1, n_2 \dots) = -\mu \frac{n_N}{2}(N-1) \quad (2.39)$$

Similarly to the case of open chains, we can find the steady state distribution. In the case of $n_j > 0$, the steady state solution is

$$n_j = \frac{n_1^j}{\mu^{j-1}} \quad 1 < j < N, \quad (2.40)$$

$$n_N = \frac{n_1^N}{\mu^N}, \quad (2.41)$$

where n_1 can be determined from the relation of conservation of monomers with time

$$M = \sum_{j=1}^{N-1} \frac{j n_1^j}{\mu^{j-1}} + \frac{n_1^N}{\mu^N}. \quad (2.42)$$

As we can see from the Fig. 2.15 by the decrease in the fragmentation rate of the complete complexes strongly favors their concentration, as expected. As for the previous case we analyse the dependence of n_N on μ .

$$\frac{dn_N}{d\mu} = \frac{Nn_1^{N-1}}{\mu^N} \left(\frac{dn_1}{d\mu} - \frac{n_1}{\mu} \right) \quad (2.43)$$

Also differentiation of the conservation relation gives us:

$$\frac{d}{d\mu} \left(\sum_{j=1}^{N-1} \frac{jn_1^j}{\mu^{j-1}} \right) + N \frac{dn_N}{d\mu} = 0 \quad (2.44)$$

$$\frac{d}{d\mu} \left(\sum_{j=1}^{N-1} \frac{jn_1^j}{\mu^{j-1}} \right) = \sum_{j=1}^{N-1} \frac{j^2 n_1^{j-1}}{\mu^{j-1}} \left(\frac{dn_1}{d\mu} - \frac{n_1}{\mu} \right) + \frac{n_1}{\mu} \sum_{j=1}^{N-1} \frac{n_1^{j-1}}{\mu^{j-1}} \quad (2.45)$$

A substitution in Eq. 2.44 results in:

$$\frac{1}{n_1} \left(\sum_{j=1}^{N-1} \frac{j^2 n_1^j}{\mu^{j-1}} + \frac{N^2 n_1^N}{\mu^N} \right) \left(\frac{dn_1}{d\mu} - \frac{n_1}{\mu} \right) + \frac{1}{\mu} \sum_{j=1}^{N-1} \frac{n_1^j}{\mu^{j-1}} = 0 \quad (2.46)$$

Defining M_1 as:

$$M_1(\mu, n_1(\mu)) = \sum_{i=1}^N \frac{i^2 n_1^i}{\mu^{i-1}} + \frac{N^2 n_1^N}{\mu^N}, \quad M_1(\mu, n_1(\mu)) = \frac{1}{n_1} \frac{dM}{dn_1} = 0 \quad (2.47)$$

We end up with the expression

$$\frac{dn_1}{d\mu} = \frac{n_1}{\mu} \left(1 - \frac{(M - Nn_N)}{M_1} \right). \quad (2.48)$$

This expression shows that n_N is always a decreasing function with μ , since

$$\frac{dn_N}{d\mu} = -\frac{MNn_N}{M_1\mu} \left(1 - \frac{Nn_N}{M} \right) < 0. \quad (2.49)$$

The efficiency of this process is higher (Fig. 2.16) compared to the system with an open chain (Fig. 2.11), however it has also the same qualitative behaviour with $\mu \rightarrow 0$ (Fig. 2.15). The formation of the complexes with the maximum size is still predominant even for relatively large μ , compared to the open chain system.

As it possible to see from Fig. 2.15, this system has two local maxima, one for the particle of maximum size and another determined by the fragmentation rate. A predominant fraction of the system's mass often corresponds to the particles with maximum size N , until the stage when it ceases to be affected by the truncation completely. At this point the system behaves analogously to the system without truncation (see Fig. 2.17). This result is very similar to the case of an open chain analysed before.

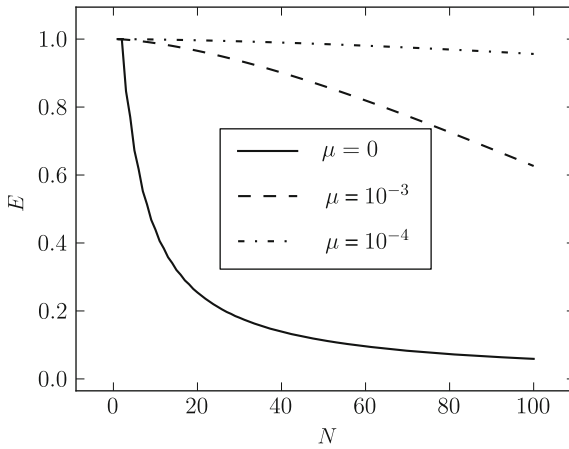


Fig. 2.16 The efficiency of formation of complexes of maximum size as a function of truncation size N , for the system without the fragmentation rate (*solid line*) and for the system with fragmentation (*dashed lines*)

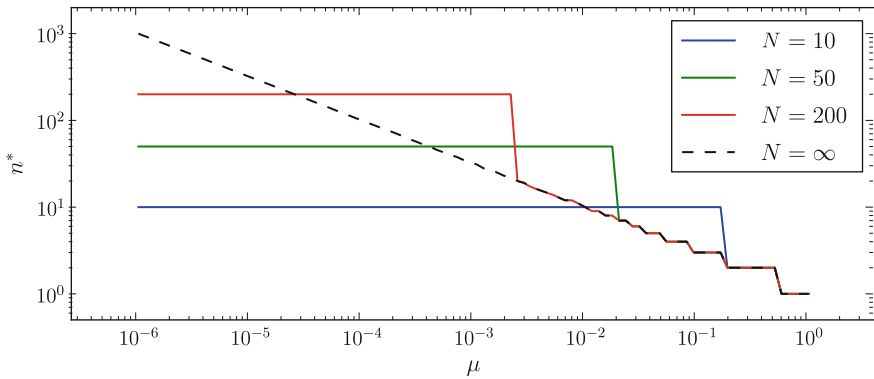


Fig. 2.17 The n^* is the size of particles present in larger concentration in the steady state distribution of the system. The complete complex size is the most formed j -mer for a wide range of μ . The distribution approaches the non-truncated Smoluchowski coagulation equation for large fragmentation rates (*dashed lines*)

It is also possible to analyse this system for a time-limited dynamics, similarly as done in the case for open chains. In this case the system is strongly robust to strong fragmentation rates, however with the imposition of a time limit, lower values of fragmentation also do not lead to higher efficiency, as can be seen in Fig. 2.18. It can be observed that there are optimum values of fragmentation, for which the value of E is maximum. From Fig. 2.18, we can see that the formation of large complexes is strongly constrained by the time limitation. For a time of 1,000 sec, most complexes cannot be formed with maximum efficiency, regardless of the value of μ . For a biological system, this can imply an extra evolutionary pressure to keep

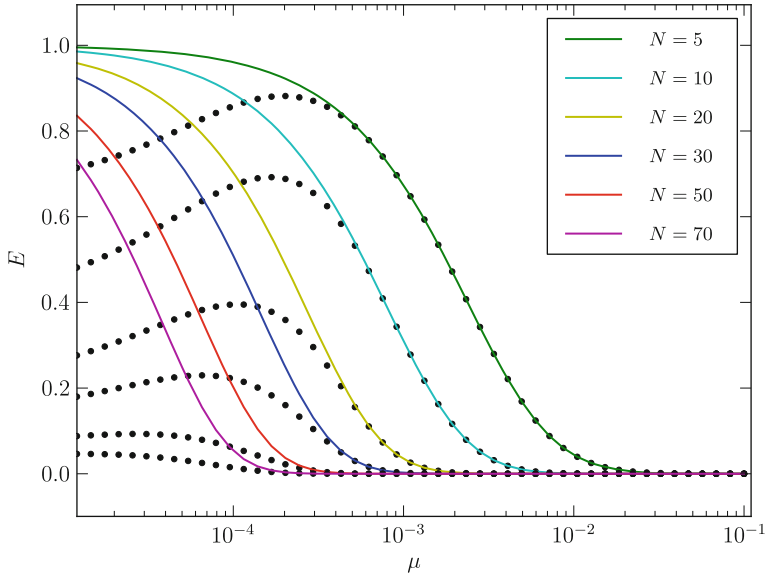


Fig.2.18 The efficiency E of the assembly process for closed chains as a function of μ different values of N for a system in a transient state after 1,000 sec (*points*) and in the steady state (*solid lines*)

the complexes small, and to tune the fragmentation rate to correspond to the optimum peaks in efficiency.

2.6 Discussion

In this chapter we analysed the formation of protein complexes on the cell membrane with the use of a truncated form of the Smoluchowski coagulation equation. Our aim was to understand the role of fragmentation on the efficiency of the process. In the case of zero fragmentation rate, the irreversibility of the process leads to low efficiency, because the steady state is characterized by a large amount of incomplete intermediates that fail to achieve the maximum size. This is a consequence of the fact that as the small particles are consumed, the growth of the particles of large size is constrained. This effect gets stronger for larger complexes, due to the larger number of intermediate states in which the complexes can be trapped before achieving its final size. The introduction of fragmentation changes this behaviour, because it allows the system to reverse the dynamics with a rate μ . The equilibrium between aggregation and fragmentation results in several possible types of final distributions depending on the parameter μ . Some of these distributions are far more efficient than the irreversible process alone. Furthermore we were able to prove that a dynamic

with infinitesimally small but non-zero fragmentation ($\mu \rightarrow 0$) is the most efficient, independently on how large is the final size that is necessary.

The application of these results to the formation of homomeric protein complexes suggests possible pressures to which their evolution was subjected: larger complexes (those with a larger number of subunits) must have smaller fragmentation rates, which implies more specific interactions between their subunits, to allow for an efficient assembly process. This requires larger interaction surfaces and a larger number of bonds between subunits. We compare the data presented in Table 2.1, where it is possible to see how the number of hydrogen bonds and BSA increases with the number of subunits that form the complete complex. As more protein structures become available we suggest a systematic continuation of this comparative study.

A decrease of the fragmentation rate necessarily implies a longer time to achieve equilibrium. Therefore the most efficient assembly processes would have to take a longer time. For *E. coli* bacteria the replication time is of approximately 20 min. During this time the bacteria doubles in size and the number of proteins received by the two daughter cells should be identical to the original. Therefore there is an upper bound for the available time for protein formation. For the aggregation kernel equivalent to 0.01 s^{-1} , the fragmentation below $\sim 10^{-5} \text{ s}^{-1}$ will not be relevant for the process. This implies that each organism will have an upper bound for the larger possible complex size that it can form efficiently, and that for each limited time of formation and protein size there is an optimum fragmentation rate.

We propose as a possible continuation of this theoretical study the introduction of distinct aggregation kernels and fragmentation rates. One of the possible alterations is to introduce a diffusion rate which changes with the size of the complex and see how that would alter the dynamics. Also a fragmentation rate that decreases with the complex size or corresponds to certain empirical data would be of interest. Additionally, as an application of the theory, one could investigate the pore forming toxins of bacteria, which also consist of subunits that assemble on the infected membrane, and form holes causing host cell leakage. Since “bacteria toxins are some of the most potent poisons to man” [24], the understanding of their process of assembly can be relevant for pharmaceutical applications.

References

1. Ali, M.H., Imperiali, B.: Protein oligomerization: how and why. *Bioorg. Med. Chem.* **13**(17), 5013–5020 (2005)
2. Blatz, P.J., Tobolsky, A.V.: Note on the kinetics of systems manifesting simultaneous polymerization-depolymerization phenomena. *J. Phys. Chem.* **49**(2), 77–80 (1945)
3. Blundell, T.L., Srinivasan, N.: Symmetry, stability, and dynamics of multidomain and multi-component protein systems. *Proc. Natl. Acad. Sci. U. S. A.* **93**(25), 14243–14248 (1996)
4. Bowie, J.U.: Membrane protein folding: how important are hydrogen bonds? *Curr. Opin. Struct. Biol.* (2010, in press, corrected proof)
5. Lo Conte, L., Chothia, C., Janin, J.: The atomic structure of protein-protein recognition sites. *J. Mol. Biol.* **285**(5), 2177–2198 (1999)

6. Davies, S.C.: Self-similar behaviour in the coagulation equations. *J. Eng. Math.* **36**, 57–88 (1999)
7. Dayhoff, J.E., Shoemaker, B.A., Bryant, S.H., Panchenko, A.R.: Evolution of protein binding modes in homooligomers. *J. Mol. Biol.* **395**(4), 860–870 (2010)
8. Hwang, H., Pierce, B., Mintseris, J., Janin, J., Weng, Z.: Protein-protein docking benchmark version 3.0. *Proteins* **73**(3), 705–709 (2008)
9. Janin, J., Bahadur, R.P., Chakrabarti, P.: Protein-protein interaction and quaternary structure. *Q. Rev. Biophys.* **41**(2), 133–180 (2008)
10. Krapivsky, P.L., Redner, S., Ben-Naim, E.: *A Kinetic View of Statistical Physics*. Cambridge University Press, Cambridge (2010)
11. Levy, E.D., Pereira-Leal, J.B.: Evolution and dynamics of protein interactions and networks. *Curr. Opin. Struct. Biol.* **18**(3), 349–357 (2008)
12. Levy, E.D., Erba, E.B., Robinson, C.V.: Assembly reflects evolution of protein complexes. *Nature* **453**(7199), 1262–1265 (2008)
13. Leyvraz, F.: Scaling theory and exactly solved models in the kinetics of irreversible aggregation. *Phys. Rep.* **383**(2–3), 95–212 (2003)
14. Leyvraz, F., Tschudi, H.R.: Singularities in the kinetics of coagulation processes. *J. Phys. A. Math. Gen.* **14**(12), 3389–3405 (1981)
15. Lukatsky, D.B., Zeldovich, K.B., Shakhnovich, E.I.: Statistically enhanced self-attraction of random patterns. *Phys. Rev. Lett.* **97**(17), 178101 (2006)
16. Lushnikov, A.A.: Exact kinetics of the sol-gel transition. *Phys. Rev. E* **71**(4), 046129 (2005)
17. Lushnikov, A.A.: Critical behaviour of the particle mass spectra in a family of gelling systems. *Phys. Rev. E* **76**(1), 011120 (2007)
18. McLeod, J.B.: On an infinite set of non-linear differential equations. *Q. J. Math.* **13**(1), 119 (1962)
19. Pereira-Leal, J.B., Levy, E.D., Kamp, C., Teichmann, S.A.: Evolution of protein complexes by duplication of homomeric interactions. *Genome Biol.* **8**(4), R51 (2007)
20. Ramadurai, S., Holt, V.K.A., van den Bogaart, G., Killian, J.A., Poolman, B.: Lateral diffusion of membrane proteins. *J. Am. Chem. Soc.* **131**(35), 12650–12656 (2009)
21. Redner, S.: *A Guide to First-Passage Processes*. Cambridge University Press, Cambridge (2001)
22. Saffman, P.G., Delbrück, M.: Brownian motion in biological membranes. *Proc. Natl. Acad. Sci. U. S. A.* **72**(8), 3111–3113 (1975)
23. von Smoluchowski, M.: Versuch einer mathematischen Theorie der Koagulationskinetik kolloider Lösungen. *Z. Phys. Chem.* **92**, 124–168 (1917)
24. Tilley, S.J., Saibil, H.R.: The mechanism of pore formation by bacterial toxins. *Curr. Opin. Struct. Biol.* **16**(2), 230–236 (2006)
25. Villar, G., Wilber, A.W., Williamson, A.J., Thiara, P., Doye, J.P.K., Louis, A.A., Jochum, M.N., Louis, A.C.F., Levy, E.D.: Self-assembly and evolution of homomeric protein complexes. *Phys. Rev. Lett.* **101**(11), 118106 (2009)
26. Vinothkumar, K.R., Henderson, R.: Structures of membrane proteins. *Q. Rev. Biophys.* **43**(1), 65–158 (2010)
27. Wattis, J.A.D.: An introduction to mathematical models of coagulation-fragmentation processes: a discrete deterministic mean-field approach. *Phys. D Nonlinear Phenom.* **222**(1–2), 1–20 (2006)
28. Whitesides, G.M., Boncheva, M.: Beyond molecules: self-assembly of mesoscopic and macroscopic components. *Proc. Natl. Acad. Sci. U. S. A.* **99**(8), 4769–4774 (2002)

Formation and Cooperative Behaviour of Protein
Complexes on the Cell Membrane

Guseva, K.

2012, XII, 80 p., Hardcover

ISBN: 978-3-642-23987-8