TEACHING BIOPHYSICS I. THE SPECIFIC INTERACTIONS: 
THE SINE QUA NON PROCESSES OF LIFE

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Reversible molecular interactions
are the heart of the dance of life
Albert Lehninger, 1988

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Abstract. The manifestation of life, in all its aspects, is the result of an enormous number of specific biophysical and biochemical molecular interactions taking place ceaselessly into cells, in a highly ordered manner both spatially and temporally. Frequently, a product of any reaction, is not a final compound, but the initial reactant of another reaction taking place in a precise location and at right time into the intricate cellular reactions network. In this minireview, we will present, in an accessible manner, the nature and paramount importance of the specific interactions which constitute the essential basis for all life processes on the Earth.

Key words: specific interactions, steric and electric complementarity, association/dissociation constant, Gibbs free energy, electrostatic interactions, van der Waals interactions.
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1. INTRODUCTION

The structure and function of biomolecules (e.g., proteins or nucleic acids) and the dynamics of complex biological systems depend categorically on the understanding of the interactions between biomolecules and their specific ligands. The great majority of cellular biochemical reactions which form the metabolic reaction network of living organisms and driven by physical interactions, are highly specific, that is, they are favoured by the preferential non-covalent (e.g., enzyme-substrate, antigen-antibody, proteins-ligands) and/or covalent associations between partners (e.g., amino acid-amino acid coupling).

In the present paper we shall limit the analysis only to the non-covalent specific interactions, due to the huge role they play in life essential processes, such as molecular recognition, protein stabilization, and specificity of enzymatic reactions [1].
2. CHARACTERISATION OF MOLECULAR SPECIFIC INTERACTIONS

The biochemical transformations through which the reactants are transformed into products are described by the reaction mechanism, which consists of all the energy changes that take place in each step, until the reaction products are obtained. The biomolecules are not reactive under normal conditions, so that they need to receive an activation energy to allow them to proceed. Irrespective of the types of (bio)chemical reactions, they can be characterized in two ways: kinetically or thermodynamically.

2.1. KINETIC CHARACTERISATION

If we are taking into account a bimolecular reaction of the type 1:1:1, taking place in an aqueous solution, between a macromolecule, \( M \), and a ligand, \( L \), conducting to a complex, \( ML \), one can notice that, at chemical equilibrium, the concentrations \([M]\), \([L]\), and \([ML]\) remain quasi constant if the temperature, pH, and pressure remain constant, too: if by thermal collision between \( M \) and \( L \), new complexes \( ML \) are formed, then other complexes \( ML \) will be split into their components, \( M \) and \( L \), so that the chemical equilibrium is maintained:

\[
M + L \overset{k_A}{\underset{k_D}{\rightleftharpoons}} ML
\]  

(1)

where \( k_A \) and \( k_D \) are the association and dissociation rate constants of the reaction. Quantitatively, the rate of \( ML \) formation, \( r_A \), is given by the following equation:

\[
r_A = \frac{d[ML]}{dt} = k_A[M][L] \quad \text{(mol/s)}
\]

(2)

and it is equal with the rate of its dissociation rate constant, \( r_D \):

\[
r_D = \frac{d[ML]}{dt} = k_D[ML] \quad \text{(mol/s)}
\]

(3)

According to the law of mass action, \( r_A = r_D \), thus resulting:

\[
[ML] = \frac{k_A}{k_D} [M][L] \sim [M][L]
\]

(4)

This means that a great concentration of the complex, \( ML \) (i.e., a great affinity of the reaction) is depending non-specifically of the reactant concentrations, \([M]\) and \([L]\). At the limit, if \([M]\) and \([L]\) are very low, although in principle the reaction is
highly specific, the concentration of the product, $ML$, will be very low, too. Therefore, it is important that the cellular concentrations of the specific reactants to be significantly great.

From equation (4), one can define the reaction association or affinity constant, $K_A$, as follows:

$$K_A = \frac{k_A}{k_D} = \frac{[ML]}{[M][L]} \quad (M^{-1})$$

(5)

The association constant, $K_A$, characterizes the global property of binding, representing the average global behaviour of a large number of events consisting in a tremendous number of microscopic non-covalent interactions (vide infra).

The values of the rate constants of the all (bio)chemical non-covalent reactions can be extremely different. If $k_A >> k_D$ (that is, the complex concentration in solution is much greater than those of the reactants, $[ML] >> [M], [L]$), the reaction is highly specific. In other words, the two reactants manifest a high reciprocal affinity. If the concentration $[ML]$ is low, the degree of the reaction specificity is considered to be low, too. In the extreme cases in which $k_A << k_D$, the two reactants have not at all any reciprocal affinity and, consequently $[ML] << [M], [L]$. Equivalently, the high affinity of reactant partners can be characterized by a high equilibrium constant, $K_A$, or by a small dissociation constant, $K_D$ ($K_D = 1/K_A$) and also by the high lifetime, $\tau$, of the $ML$ complex: $\tau = 1/k_D$.

By analysing all the spectra of (bio)chemical reactions, it was observed that the constant affinity, $K_A$, has values in a broad domain depending of the particular reactions.

In the case of enzyme-substrate interactions, $K_A = 1/K_M \approx (10^{-5} – 10^{-10}) M^{-1}$ [2, 3]. $K_M$ is the Michaelis-Menten constant and $1/K_M$ is regarded as the binding affinity constant [4]. For instance, the enzymatic reaction between lysozyme and hexa-N-acetylgalactosamine is characterised by $K_M = 6 \times 10^{-6} M$ and therefore, $K_A \approx 1.7 \times 10^6 M^{-1}$ [2], while the interaction between Xeroderma pigmentosum group C protein is binding to the human centrin 2, with a $K_A \approx 10^9 M^{-1}$ [5].

In the case of antigen-antibody (Ag-Ab) reaction, some peculiar reactions can attain a very high affinity constant ($K_A \approx 10^{12} M^{-1}$) [6] but values of $10^9$ are commonly encountered for the interactions between some IgG antibodies and their specific antigens [7]. It is interesting to note that only a very small area of Ag and Ab molecules actually interact by complementary sites, called epitopes in Ag and paratopes in Ab [8].

An extremely high value of association constant ($K_A \approx 10^{14} M^{-1}$) is noticed in the case of streptavidin-avidin interaction, which is known as the most specific non-covalent interaction in Nature [9].

A lot of the questions are arising concerning these somehow surprising highly specific interactions which are, in fact, quite natural and therefore, ubiquitous at life global scale: How is it possible such a multitude of high specific cellular reactions to take place? Who impinges some molecules to choose their favourite partners?
There is a “molecular intelligence” at molecular level who directs and drives the specific reactants one towards another to form temporary or long lifetime complexes?

The answer is that the pair partners are not acting consciously, but are driven by their thermal agitation (a nonspecific factor), by steric and electric complementary matching between them (a specific factor), and by the synergistic action of many weak physical forces.

Indeed, during the long living matter evolution of billion years on Earth, the proteins and nucleic acids evolved in such a manner to select their favourable ligands. Some proteins even have adopted nonprotein ligands (i.e., prosthetic groups) which has become integral part of their 3D structures. It is the case of the holoproteins like myoglobin and hemoglobin (who incorporated the porphyrin cycle in their hydrophobic pockets) and of the light sensitive proteins pertaining to the rhodopsin family (e.g., rhodopsin, bacteriorhodopsin), who incorporated retinal into their structure. Therefore, the natural selection, consequence of the very long process of living matter evolution, has paved the way towards the optimized specific interactions of myriad of reactions taking place permanently and in a coordinated way into the complex reaction network of cellular metabolism.

The preferential associations of molecules is due, as already mentioned, to nonspecific thermal agitation and accomplished by the specific steric and electrostatic complementarity of the interacting partners. Therefore, the strength of the global macromolecule-ligand interaction depends on the complementarity of the physical and chemical properties of atoms from the particular pairs of protein/nucleic acid and ligand “surfaces”. The molecular pair complementarity is more precisely described as:

i) neutral atom pair matching (involved in weaker interactions mediated by many weak short-range van der Waals forces and hydrogen bonds) and

ii) electrical charge pair matching (involved in long range stronger electrostatic forces).

The estimated values of interaction energies of different kinds of bonds are given in Table 1.

<table>
<thead>
<tr>
<th>Type of interaction</th>
<th>Energy of interaction (kcal/mol)</th>
<th>Energy of interaction (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covalent bonds</td>
<td>100–150</td>
<td>419–628</td>
</tr>
<tr>
<td>Electrostatic</td>
<td>20–40</td>
<td>84–167</td>
</tr>
<tr>
<td>Hydrogen bridge</td>
<td>3–20</td>
<td>13–84</td>
</tr>
<tr>
<td>van der Waals</td>
<td>0.1–2</td>
<td>0.4–8</td>
</tr>
</tbody>
</table>

Chemical complementarity can be evaluated by the distances between atoms both on the receptors (i.e., proteins or nucleic acids) and their corresponding ligands, small differences in distances strongly influencing the reactant affinity [10].
The complexes, $ML$, are finally accomplished by these multitude of parallel and quasi simultaneous actions of hundreds or thousands of non-covalent van der Waals interactions, by many hydrogen bonds, and also by hydrophobic interactions who produce a gradual rearrangements of the 3D structure of the reactants according to the induced fit model of interactions (Fig. 1).

2.2. THERMODYNAMIC CHARACTERISATION

The specific interactions can also be approached from the thermodynamical point of view, using the main function states: Gibbs free energy ($G$), enthalpy ($H$), and entropy ($S$). We shall limit the discussion only to Gibbs free energy.

The variation of Gibbs free energy, $\Delta G$, is an indicator of the spontaneity of any process, in particular, of any (bio)chemical reaction.

If $\Delta G < 0$, the cellular reactions take place spontaneously, the liberated energy being used to drive a variety of metabolic processes which otherwise should not take place. $\Delta G < 0$ characterise all (bio)chemical reactions (called exergonic) pertaining to cellular catabolism.

On the contrary, if $\Delta G > 0$, the (bio)chemical reactions, called endergonic (e.g., synthesis of proteins from amino acids and of nucleic acids from nucleotides)
cannot take spontaneously and, therefore, must be driven by a source of energy. In cells, this needed energy comes from the exergonic reactions of catabolism. These endergonic reactions, tributary to exergonic reactions, are pertaining to the cellular anabolism. In this way, the energy liberated by exergonic reactions is not wasted, but recovered by the coupled endergonic reactions, although not in totality, a part of it being “lost” as heat. However, the heat loss is beneficial for the cells, assuring the thermal background required by the optimal functioning of the cellular machinery.

2.3. RELATION BETWEEN KINETIC AND THERMODYNAMIC PARAMETERS

The variation of this thermodynamic function (i.e., Gibbs free energy) is related to the chemical equilibrium parameters, $K_A$ and $K_D$, by the relations considered to be the most important equations in chemical thermodynamics [14]:

$$\Delta G = -RT\ln K_A = RT\ln K_D$$

(6)

One can see that equation (6) connects the kinetics formalism of a (bio)chemical reaction described by association and dissociation rate constants (included in $K_A$), with the variation of the thermodynamic function, $G$. The equation (6) predicts that, if an exergonic process involves a large negative change in the Gibbs free energy, then the process could take place spontaneously in a very easy way. On the contrary, in the case of reactants with very low association constant ($K_A \ll 1$) a positive variation of the Gibbs free energy will result, this corresponding to endergonic process which is requiring external energy in order to take place. In cellular metabolism, all the endergonic processes are coupled to the exergonic ones (e.g., the splitting of ATP into ADP and inorganic P) which supply the necessary energy. Therefore, all the anabolic endergonic processes, including all biosynthesis reactions, are coupled to and thereby driven by catabolic exergonic processes (e.g., cellular respiration).

3. THE IMPORTANT ROLE OF THERMAL MOLECULAR AGITATION

In the case of protein-protein or protein-ligand specific interaction, the complex individual movements of their atoms (e.g., stretching, bending, torsion, etc.) provoke a kind of global “breathing” of the molecules, these tending to rapidly attain their native 3D conformations, that is, global energy minima by rather „guided” pathways shortcutting many possible energetic landscape states [15, 16]. This explains why the folding of proteins is progressing very fast within a funnel-like energy landscape [17, 18]. Due to this breathing, the molecules are momentarily exposing to the exterior their ligand complementary active centres or sites of interaction. This is an absolute necessary but not sufficient condition for an interaction to be accomplished because the reciprocal spatial orientations of the two partners are not always
Specific interactions in life processes

favourable. Due to the 3D asymmetry of the reactants, one can speak of the so called anisotropic molecular collisions and interactions (Fig. 1). The favourable orientations seems to be a less probable event. However, due to the rapid thermal agitations involving both translations and rotations of the pair partners, the molecules are colliding very frequently (about 10^9/s) this substantially increasing the probability of proper and favourable collisions concluding to a progressive association.

According to induced fit model (i.e., a dynamically adaptation of the 3D molecule conformation) the two interacting particles are permanently rearranging their complementary sites (Fig. 1 Right). Therefore, the preferential associations of molecules cannot become effective in the absence of their frequent aleatory collisions of the reactants. One can say that the thermal agitations is a necessary evil for life assuring the favourable thermal background for life processes. Indeed, one can observe that the decrease of temperature is drastically slowing the rate of biochemical reactions due to the decrease of thermal agitation that involves a diminution of the collision frequency of the reactants. On the contrary, the temperature increase has an opposite effect, favouring in a non specific way, the specific interactions.

One can evaluate the temperature dependence of a (bio)chemical reaction by the so called temperature coefficient, Q_{10}, defined as the ratio between the reaction rates (R_i, i = 1, 2) at two different temperatures spaced by 10 degrees [19, 20]:

\[ Q_{10} = R_2(T_1 + 10)/R_1(T_1) \]  \hspace{1cm} (7)

where \( T_1 \) is the lower temperature.

In the particular case of biochemical reactions, the temperature coefficient, \( Q_{10} \), is approximately situatead into the interval, 2–3 [21] that is, the decrease of temperature with ten degrees induces the slowing two-three times the reaction rates.

The biochemical specific reactions having a large \( Q_{10} \) are strongly dependent on the temperature indicating a great temperature sensitivity. However, \( Q_{10} \) can correctly describes a reaction dependence of temperature only up to an optimal temperature. The reason is that if the temperature is too high (i.e., over the optimal temperature) the denaturation of biomolecules could take place, this impeding the correct associations between partner molecules.

In the case of homeothermic beings (e.g., mammals and birds), an optimal temperature (around 37–40°C) is attained assuring a proper association between molecules. In this case, it is realized a compromise between the molecular rigid compact states and the more loose flexible states of the reactants. The state rigidity is confering a high specificity to interaction, while the flexibility of partners is permitting the reciprocal adjustment during progressive docking interaction.

Observation. The extreme rigidity and flexibility are avoided by living matter: the extreme rigidity claimed for the specificity will prevent the molecule induced fit, while the extreme flexibility will prevent the preferential association.
4. SPECIFIC LIGANDS AND THE ACTIVE CENTRE OF ENZYMES

It is well known that the enzymes are excellent cellular biocatalysts, with the role of diminishing the energetic barrier, $\Delta G_1$, of the biochemical reactions (Fig. 2). However, even if the activation energy is lowered (i.e., $|\Delta G_2| < |\Delta G_1| < |\Delta G|$) by enzymes, in the case of many situations, the enzyme assisted reactions are blocked. The reason is that many enzymatic reactions, although highly specific, cannot take place because their active sites are either disorganized or hidden inside their 3D structure. One can say that these dormant enzymes are a reserve of cellular biocatalysts.

Observation. The existence of energetic barrier for biochemical reaction is another necessary evil, because otherwise, all the possible reactions will take place ceaselessly, without restrictions, resulting a rapid irreversible destruction of biological morphology of the cells and, finally, the cellular death.

Whenever necessary, many enzymes are activated by a small protein called calmodulin (CaM) which at its turn, is activated by calcium ions (Ca$^{2+}$). The Ca$^{2+}$/CaM complex controls the activity of over 120 enzymes and proteins [23, 24]. We shall mention only: cyclic nucleotide phosphodiesterases, phosphotransferases, calcineurin, plasma membrane Ca$^{2+}$-pump, phosphorilate kinases, adenylate cyclases, etc. [25].
CaM is a small protein, composed of 148 amino acids (AA) with an AA sequence surprisingly well conserved during the living matter evolution, being almost unchanged from protozoa to mammals. CaM activates such enzymes by interaction with a short specific target domain (STD) of them with a very high affinity ($K_A \sim 10^9 \text{ M}^{-1}$). For instance, the large adenylate cyclase of *Bordetella pertussis* has a STD composed only of 43 AA [26]. In spite of the large AA diversity of target protein STDs, they all have a common feature: the hydrophobic/hydrophylic profile and electric charge distribution conferring them the propensity to form similar secondary and tertiary structures complementary to CaM in its activated state ($\text{CaM}^*$) [25].

CaM, in its inactivated state, has a *structure of dumbbell* composed of two globular domains anchored by an $\alpha$-helix amino acid chain (Fig. 3a). Upon linking four Ca$^{2+}$ (two for each globular domain), the protein suffer a conformational transition in which the helical amino acid chain is obliging the two domains to be brought together (Fig. 3b). CaM* can be easily attached to specific sites of different enzymes. By CaM* coupling to the enzymes these are suffering allosteric transitions by which their hidden active centres are exposed to cellular milieu becoming thus accesible to their specific complementary substrates (Fig. 3b).

What is the role of stimuli in this sequence of chain reactions? Under the influence of an internal stimulus, the calcium ions, sequestred into cellular vesicles, are liberated into the cytosol. These ions are diffusing like a wave and encountering the inactivated molecules of CaM these ones become activated (CaMs*). In their turn, CaMs* are activating the specific enzymes, $E$. Thus, the activated enzyme, $E^*$, become able to induce a mechnano-electrical stress into the substrate, $S$, splitting it into products, $P$, according to sequential events schematically described by the relations (8)–(11):

$$\text{Stimulus} \rightarrow \text{Cellular vesicles} \rightarrow \text{Cytosol Ca}^{2+} \text{ wave} \rightarrow \text{Many Ca}^{2+} \tag{8}$$

$$\text{CaM} + 4\text{Ca}^{2+} \leftrightarrow \text{CaM}^* \tag{9}$$

$$\text{CaM}^* + E \leftrightarrow E^*\text{CaM}^* \tag{10}$$

$$S + E^*\text{CaM}^* \leftrightarrow S^*E^*\text{CaM}^* \rightarrow E + P + \text{CaM} \tag{11}$$

where $X^*$ is the notation for the activated compound, $X$.

When the activated enzymes are accomplished their role (warned by a molecular feedback) the calcium pumps (located into the vesicles membranes) are recovering the Ca ions, pumping them back into vesicles. The internal stimulus can be, for instance, in the case of miofibrils, an action potential received from the motoneurons connected synaptically to them. Upon the action of another stimulus, the sequential reactions are repeated again. The sequence of events (8)–(11) is plastically illustrated in Fig. 3b.
Another example of specific chain reaction, this time, triggered by an external stimulus (e.g., light photons), is that related to light induced catalytic reaction cascade in retina rods of the vertebrates [2, 28].

5. EXAMPLES OF SPECIFIC INTERACTIONS WITH MEDICAL APPLICATIONS

Until now we have discussed the general aspects related to naturally occurring specific biomolecular interactions. However, under the influence of external physical, chemical, and biological factors (e.g., ionising radiation, chemical pollutants, viruses, bacteria, etc.), the harmony of metabolic reaction network could be disturbed. In these cases, the anormal pathologic conditions (i.e., diseases) are installed claiming them corrections by specific natural and artificial drugs. The functioning of macromolecules (i.e., nucleic acids, proteins) involves the formation of macromolecular complexes, which mediate metabolic and signalling pathways of the cellular processes. Manifestations of normal or pathological physiological states are consequences of specific protein-protein or protein-ligand (i.e., ions, drugs) interactions. Therefore, knowledge of mechanisms of protein interaction is a key point in elucidating the molecular bases of the diseases and in choosing appropriate methods for prevention, diagnosis, and treatment [29]. As it was mentioned, many biological processes are mediated by protein interactions. For this reason, these biomolecules are the targets of
most studies on diseased biological states. Any posttranslational modification of native proteins can lead to incorrect 3D structures of the proteins and, therefore, to their unwanted interactions with pathogens.

Different factors such as temperature, pH, oxidative stress or incomplete protein-ligand complex formations can lead to protein misfolding, a common cellular event in the cell. In healthy cells, there are both correctly folded protein species, as well as intermediate or misfolded species [30]. Misfolded proteins are assisted to refold by the chaperones or are degraded by proteasomes, in order to avoid their transition into amyloid structures, known to cause neurological diseases and physiological problems [31].

It is known that many synthetic and natural drugs can be delivered to cells by protein carriers like serum proteins, such as albumins and transferrins.

Understanding the role of albumins in cardiovascular diseases, hypoalbuminemia, and autoimmune disorders should start from the specific interactions of these proteins. Albumins are the plasma proteins that bind the most endogenous and exogenous ligands. The 3D structure of serum albumins contains several drug binding sites, the main sites being Sudlow I and Sudlow II [32, 33].

The ability of albumins to bind drugs is influenced by many factors: their structure, drug and protein concentrations, and microenvironment changes [34] which, in turn, influence the rate of metabolism of the free drug. A low concentration of albumins results in a larger fraction of free drug, which may lead to unwanted adverse effects. In addition, other ligands may compete for binding to the same albumin site [35], which will influence drug binding and transport. Therefore, the interaction of serum albumins with small molecules such as dyes [36], flavonoids [37], and drugs [38–40] is of real use for the correct design of drug favouring both their interaction and transport.

Human serum transferrin, binds iron ions and transports them into those cells endowed with specific membrane receptors [41, 42]. The properties of human transferrin (e.g., biodegradability, low toxicity, non-immunogenic, ability to target specifically) have been extensively described in the literature. Iron overload of the cells occurs in most chronic and common human diseases, one of the effects being the lipid peroxidation. Most iron chelating agents have obvious harmful side effects that can be annihilated by flavonoids, a class of natural molecules. Flavonoids contain a variety of iron-binding sites and can scavenge iron. In this way, flavonoids reduce the accumulation of iron in cells and lipid peroxidation. It is assumed that, in this way, flavonoids can regulate iron metabolism and can be used to treat iron overload [43]. Recent studies [44, 45] investigated the interaction mechanism of human transferrin with flavonoids like rutin, luteolin, apigenin, and fisetin. The specific interactions of flavonoids with human transferrin take place with moderate affinities, being driven by non-covalent interactions.

The cellular iron uptake pathway (transferrin/transferrin receptors) increases the antitumour effect of some vitamins, such as vitamin C [46] which, however,
binds weakly to the transferrin site [47]. This effect can further potentiate the iron supplementation, in the form of nanoparticles. Such specific transferrin complex with iron nanoparticles [48] can be used in feeding patients with iron deficiency anaemia [49].

6. SPECIFIC INTERACTIONS INVOLVED IN DESIGN OF NEW DRUGS

The recent outbreak of the coronavirus 19 disease poses great health concerns due to the lack of approved efficient drugs. This situation urgently imposes the discovery of new therapeutic molecules, the pharmaceutical companies being under the high pressure of designing new effective drugs [50, 51].

Fortunately, the drug design is one of the intensively developing actual sciences its progress being facilitated and accelerated by artificial intelligence (AI) which predicts the 3D structure of a target (e.g., a protein), drug-target interaction, drug activity and, finally, constructs a new molecule de novo [52].

The drug design starts with the finding of a hit molecule that elicits a desired activity in a screening assay. The structure of the hit molecule is then optimized in order to improve its affinity toward the chosen target, by maximizing its specific interaction with the target exploiting the steric and electrostatic complementarity which will maximize $|\Delta G|$ given by Eq. (6).

We mention that, among the most popular AI drug design platforms, is the Swiss Drug Design System (developed by the Swiss Institute of Bioinformatics) freely accessible by the Resource Portal: https://www.expasy.org [53]. The ultimate goal of the future drug design is to synthetize a specific, non-toxic, effective and customized drugs in a very short time, in the case of emergency [52].

7. CONCLUSIONS

Almost all cellular metabolic reactions are highly selective, conferring to the biochemical reaction network a high space and time order assuring the metabolic homeostasis.

A great majority of biochemical reactions are driven by non-covalent relatively weak interactions and therefore, potentially reversible, the enzymes that assist them being cyclically recovered.

The protein interactions are dynamically docking processes, the reactants adjusting continuously their 3D structure as much as the interaction is progressing.

In the early stage of interaction process, the great affinity of molecular interactions is conferred both by the steric (spatial) and electrostatic complementarity.

Towards the final phase of docking process, the molecular associations are driven by synergistic cooperation of a great number of relatively weak physical interactions (van der Waals forces and hydrogen bonds).
Specific interactions are involved on a large scale in medicine in the case of interactions of host target macromolecules with natural ligands and/or with artificial drugs designed to cure different diseases.

Although temperature is a non specific factor, the thermal agitations of biomolecules is favouring the specific interactions by increasing the probability of efficient molecular associations by the increased frequency of reactant collisions.

In the absence of specific molecular interactions, the ordered metabolic reactions would not properly take place. In reality, the ubiquitous specific interactions make possible all the life processes and for this reason, they are considered, for good reason, of a sine qua non importance for life on Earth.

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