Fluctuations of Complex Networks:

Electrical Properties of Single Protein Nanodevices

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Abstract

We present for the first time a complex network approach to the study of the electrical properties of single protein devices. In particular, we consider an electronic nanobiosensor based on a G-protein coupled receptor. By adopting a coarse grain description, the protein is modeled as a complex network of elementary impedances. The positions of the alpha-carbon atoms of each amino acid are taken as the nodes of the network. The amino acids are assumed to interact electrically among them. Consequently, a link is drawn between any pair of nodes neighboring in space within a given distance and an elementary impedance is associated with each link. The value of this impedance can be related to the physical and chemical properties of the amino acid pair and to their relative distance. Accordingly, the conformational changes of the receptor induced by the capture of the ligand, are translated into a variation of its electrical properties. Stochastic fluctuations in the value of the elementary impedances of the network, which mimic different physical effects, have
also been considered. Preliminary results concerning the impedance spectrum of the network and its fluctuations are presented and discussed for different values of the model parameters.

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I. INTRODUCTION

Originated as an evolution of the Erdös and Rény theory of random graphs, the study of complex networks has started in ’98-’99 with the seminal works of Watts and Strogatz [1] and Barabasi and Albert [2]. Thenceforth, it has fastly grown, becoming one of the most lively research fields [3–10]. The reasons of this boom rely on the fact that the concepts and techniques which are introduced and developed in the theory of complex networks offer very powerful tools for the study of many real-life systems like: communication networks, social behaviors, metabolic and cellular networks, electric power grids, etc [3–10].

On the other hand, the attention to develop new hybrid molecular electronic devices and, in particular, of ultra miniaturized single-molecule devices, has also grown tumultuously, since the first single-molecule experiment performed 30 years ago on biomolecules [11], in view of a huge amount of technological applications [8,12–15]. Therefore, nowadays a very large number of experimental and computational works are devoted to this mandatory issue [8,10,12–21]. However, in many cases, the atomic complexity of bioelectronic systems makes arduous the task of performing a microscopic study of their electrical properties.

Here we present for the first time a complex network approach to the study of the electrical properties of a two terminal device that is a promising candidate for the realization of single protein nanobiosensors [22]. The device under consideration consists of a G protein-coupled receptor (GPCR) [18,23,19–21] embedded in a lipid bilayer and contacted to two ideal electrodes. In particular, we will show results for bovine rhodopsin [13,27–30] (a photonic receptor) although the results can be easily extended to other receptors belonging to the GPCR family, as for instance olfactory receptors (ORs) [12,14,15,24–26]. In fact,
all GPCRs share the seven helices trans-membrane structure, shown schematically in Fig. 1. The seven trans-membrane helices (TH), are interconnected by extracellular (EC) and intracellular (IC) loops. Additionally, there are an extracellular terminal chain (N terminus) and an intracellular terminal chain (C terminus) [18,23,19–21,27,28]. We note that the understanding of the electrical properties of GPCRs is crucial to the purpose of developing single-protein electronic biosensors. However, the information about their structure at atomic level is generally missing. By contrast, this information is available for rhodopsin [27,28,20,31]. Indeed, in this case it is possible to pack together the molecules in a crystal structure and to determine the atomic coordinates by diffraction experiments [27,28].

Therefore, by taking advantage of the common topology of the peptidic chain of rhodopsin and other GPCRs, we have developed the following "coarse grain" approach to the electrical properties of these kind of receptors. The receptor is modeled as a complex network of elementary impedances. The positions of the alpha-carbon atoms, $C_\alpha$, of each amino acid (residue) are taken as the reference positions of the network nodes. The amino acids are assumed to interact electrically among them. Charge transfers between neighboring residues [16,32] and/or changes of their electronic polarization [33] are taken to affect the state of these interactions. Therefore, a link is drawn between any pair of nodes neighboring in space within a given a distance and an elementary impedance is associated with each link. This elementary impedance is taken as the impedance of a parallel RC circuit. Its value can be related to the physical and chemical properties of the amino acid pair [33] and to their relative distance. The conformational changes of the receptor induced by the photons or by the capture of a ligand [15,34,35,32], are then translated into a variation of its electrical properties. Stochastic fluctuations in the value of the elementary impedances of the network, which mimic different physical effects, can be also accounted for. The impedance spectrum of the network and its fluctuations are studied and analyzed for different values of the parameters introduced in the model.
II. MODEL AND RESULTS

In the following we will focus on the modelization of the electrical properties of bovine rhodopsin, the best known GPCR [18,23,19–21,27–30]. To this purpose, we consider a two terminal device made by a single molecule of rhodopsin embedded in a small portion of membrane, placed within a suitable environment (physiological buffer solution) and inserted between two metallic contacts, to which an AC voltage can be applied. The device is sketched in Fig. 2, where, without loss of generality, a vertical configuration has been assumed for the electrodes (other configurations can also be considered). The left and right hand side of Fig. 2, refer to the basic state and to the most stable light-activated state of rhodopsin, respectively. Rhodopsin in the last state is referred to as metarhodopsin II [29]. The atomic coordinates of bovine rhodopsin have been taken from Protein Data Bank (PDB) [31] where data of several independent experiments are present as standard PDB files (we have used PDB IDs: 1F88 [27] and 1JFP [28]). There is also an engineered data for metarhodopsin II (PDB ID 1LN6) [29].

The device is then modeled as a complex network of elementary impedances that is constructed according to the following procedure. First, from the PDB file we extract the spatial coordinates of the $C_{\alpha}$ atom of each amino acid (348 for bovine rhodopsin). The positions of these atoms are taken to coincide with the nodes of the network. We assume that the amino acids interact electrically among them through charge transfer processes between neighboring residues [16,32] and/or changes of their electronic polarization [33]. Accordingly, as illustrated in Fig. 3(a), a link is drawn between any pair of nodes which are neighboring in space within a given distance $d \equiv 2R_{a}$, where $R_{a}$ represents an interaction radius. Moreover, we introduce two extra nodes that are associated with the electrodes (contact-nodes), as shown in Fig. 3(b). These contact-nodes are linked to a given set of amino acids, depending on the particular geometry of the contacts in the real device (each electrode is linked at least to one amino acid). The environment is not taken into account at this preliminary stage of the model. Then, an impedance is assigned to each
link. We take this elementary impedance as the impedance of a RC parallel circuit (the most usual equivalent passive AC circuit). Then, we denote as \( Z_{i,j} \), \( R_{i,j} \), \( C_{i,j} \), respectively the impedance, the resistance and the capacitance associated with the link between the \( i \)-th and \( j \)-th nodes (see Fig. 4).

Different expressions can be adopted for the determination of \( Z_{i,j} \). Here, we have considered three possibilities corresponding to an increasing level of complexity. The first possibility, model (i), is the simplest one: all the impedances are taken to be equal: \( Z_{i,j} = Z_0 \).

The second possibility, model (ii), consists in assuming that \( R_{i,j} \) is a simple ohmic resistor and \( C_{i,j} \) a planar homogeneous capacitor, therefore: \( R_{i,j} \propto l_{i,j} \) and \( C_{i,j} \propto 1/l_{i,j} \), where \( l_{i,j} \) is the distance between the nodes \( i \) and \( j \). Consequently, \( Z_{i,j} \) takes the expression:

\[
Z_{i,j} = \left( \frac{l_{i,j}}{A} \right) \left( \frac{1}{\rho^{-1} + i\epsilon\epsilon_0\omega} \right)
\]  

where \( A \) is the cross-sectional area of the capacitor, \( \rho \) the resistivity of the resistor, \( \epsilon \) the relative dielectric constant, \( \epsilon_0 \) the dielectric constant of vacuum and \( \omega \) the frequency of the external AC voltage. The third choice, model (iii), consists in taking the cross-sectional area of the resistor and of the capacitor equal to the area of the cross-section defined by the overlap of the two spheres in Fig. 4. In this case, \( Z_{i,j} \) becomes:

\[
Z_{i,j} = \frac{l_{i,j}}{(R_a^2 - l_{i,j}^2/4)} \left( \frac{1}{\rho^{-1} + i\epsilon\epsilon_0\omega} \right)
\]  

where \( A \) is the cross-sectional area of the capacitor, \( R_a \) the radius of the sphere, \( \rho \) the resistivity of the resistor, \( \epsilon \) the relative dielectric constant, \( \epsilon_0 \) the dielectric constant of vacuum and \( \omega \) the frequency of the external AC voltage.

Of course, an improvement in the description of the receptor is expected if the physical and chemical properties of the different amino acids are accounted for in the expression of \( Z_{i,j} \). At a simplest level, this can be done by taking \( \epsilon \) and/or \( \rho \) dependent on the indices \( i \) and \( j \). To this purpose, here, we have assumed the following expression for the dielectric constant of the capacitor associated with the pair of amino acid \( i \) and \( j \): \( \epsilon_{i,j} = 1 + g[(\alpha_i + \alpha_j)/2 - 1] \), where \( \alpha_i \) and \( \alpha_j \) are the intrinsic polarizabilities of the corresponding amino acids, given in Ref. [33] The factor \( g = 4.647 \) in the previous expression of \( \epsilon_{i,j} \) has been introduced to the purpose of obtaining values of \( \epsilon_{i,j} \) distributed between 1 and 80 (vacuum and water) proportionally to \((\alpha_i + \alpha_j)/2\).
A comparison of the three models previously introduced has been carried out by taking $\epsilon_{i,j}$ independent of the indices $i$ and $j$ and it concerns with the dependence of the network impedance, $Z$, on the interaction radius. The network impedance is calculated by solving Kirchhoff’s node equations, as in Ref. [36]. We note that in the present case of an irregular network with complex topology, the use of node equations is particularly convenient with respect to the use of loop equations. Figure 5 shows the modulus of the network impedance $|Z|$, calculated by using models (i), (ii) and (iii), as a function of the interaction radius. The systematic decrease of $|Z|$ at increasing values of $R_a$ reflects the increasing importance of parallel with respect to series connections. One can see that the curves of the first two models show a step-like behavior related to the sharp discontinuity in the value of $|Z|$ when $R_a$ becomes equal to $l_{i,j}$. On the contrary, by removing the impedance value discontinuity, the curve obtained by using model (iii) shows a continuous behavior. Furthermore, model (iii) appears to be more sensitive to a variation of the number of links in the networks. Therefore, in the following we will discuss results obtained by using model (iii).

Figure 6 shows the degree distribution, i.e. the distribution function of the node connectivities, for different values of the interaction radius, ranging from 2 ÷ 6 Å. The degree distribution is found to be Poissonian-like for all values of $R_a$. This is a signature of a random network [5,3]. We note that the width of the distribution becomes progressively larger at increasing values of $R_a$. This trend will saturate at a certain value $R_{a,\text{max}}$ of the interaction radius, which corresponds to a network where each nodes is connected with all the other nodes. At saturation, for values of $R_a > R_{a,\text{max}}$, the degree of a node (number of neighbors of a node) becomes equals to $(N_a - 1)/2$, where $N_a$ is the number of amino acids, independently of $R_a$.

Figure 7 reports the total number of links in the network, $N$, as a function of the interaction radius, for the basic state of rhodopsin (black dashed curve) and for the activated state metarhodopsin II (gray dotted curve). We can see that for an arbitrary value of $R_a$, $N$ is different in the two states. In fact, even if the primary structure of the protein remains the same, the conformational change induced by the photon modifies the distances
between $C_\alpha$ atoms. As a consequence, for a given value of the interaction radius, the network changes: in the activated configuration of the receptor some new links will arise and some other will disappear. Furthermore, Fig. 7 displays the relative increment of the number of links, $\Delta N/\Delta R_a$, as a function of $R_a$: the solid curves, black and gray, show this quantity respectively in the basic and in the activated states of rhodopsin. Overall, from the behavior of $N$ and of $\Delta N/\Delta R_a$, we conclude that the sensitivity of the network to conformational changes is maximum when $R_a \approx 10 - 18$ Å. It must be noted that this dependence of the total network impedance on conformational changes is further emphasized by the fact that the elementary impedances $Z_{i,j}$ are taken to be dependent on the distances $l_{i,j}$.

Impedance spectroscopy measurements are frequently used to investigate the electrical properties of self-assembled layers of biomolecules lying on functionalized metallic supports [13]. Even in the case under consideration, a single-molecule device, we expect useful information from this kind of technique. Therefore, we have calculated the impedance of the network as a function of the frequency of the applied AC voltage. Figure 8 shows the Nyquist plot of the impedance corresponding to the rhodopsin network. Precisely, the figure displays the minus imaginary part of the network impedance versus the real part, where both these quantities are calculated in the frequency range $0 \div 1$ KHz. The two curves reported in the figure are obtained by taking $R_a = 2$ Å (dashed curve) and $R_a = 12.5$ Å (solid curve). In both cases it is $\rho = 10^9$ Ωm while the amplitude of the applied voltage, $V_0$, is $V_0 = 1$ V. Moreover, the real and the imaginary part of the impedance have been normalized to the static value of the real part, $Re[Z(\omega = 0)]$, which takes the values $Re[Z(\omega = 0)] = 302$ GΩ and $Re[Z(\omega = 0)] = 1.67$ MΩ, respectively for $R_a = 2$ Å and $R_a = 12.5$ Å. As a general trend, when $R_a \geq 5$ Å, the shape of the Nyquist plot is indistinguishable from that corresponding to a single RC parallel circuit (semi-circle). By contrast, when $R_a \leq 5$ Å the Nyquist plot deviates from this behavior. In particular, when $R_a = 2$ Å, the degree of most of the nodes of the network is 2 (see Fig. 6) and the series combination of elementary impedances $Z_{i,j}$ becomes predominant in the network structure. In other terms, changes in the shape of the Nyquist plot are only detected in the sequential limit. Of course, the value of $Re[Z(\omega = 0)]$
depends on both $R_a$ and $\rho$. Therefore, impedance spectroscopy measurements will allow the identification of the values of the parameters to be used in the modelization of the receptor. Furthermore, the Nyquist plot is a convenient tool to detect the presence of series resistances in the contacts and other spurious phenomena.

Figure 9 displays a comparison between the Nyquist plot corresponding to the rhodopsin network and that corresponding to the metarhodopsin II network. Precisely, the solid curve is obtained for rhodopsin while the dot-dashed curve for metarhodopsin II. In both cases we have taken $R_a = 12.5 \, \text{Å}$, $\rho = 10^9 \, \Omega \text{m}$, and $V_0 = 1 \, \text{V}$. The real and the imaginary part of the impedance are normalized to the static value of the real part of the network impedance in the metarhodopsin state: $Re[Z(\omega = 0)] = 2.04 \, \text{MΩ}$. The figure shows that the conformational change of the receptor due to the photon implies a significant variation in the Nyquist curve, in principle detectable by impedance spectroscopy measurements. This result, is of particular relevance in view of the application of the model to ORs.

As a next step we have considered the possibility of introducing stochastic fluctuations in the interaction network. In fact, fluctuations of the number of links or fluctuations of the elementary impedances $Z_{i,j}$, must be allowed to account for the fluctuations of the electrical properties of the receptor. These last can arise from different mechanisms, like thermal fluctuations of the atomic positions, fluctuations in the charge transport and/or in the polarization state of the amino acids, etc. As a starting level, we have extended the approach already developed for the case of regular-lattice networks [37] to the case of the rhodopsin interaction network. Therefore, starting from the rhodopsin network previously constructed, that can be called perfect network, we have assumed the existence of two random processes, consisting in the breaking and in the recovery of the links. The impedance of a broken link is taken greater than that an active link for a factor of $10^8$. By defining $W_b$ and $W_r$ as the probabilities of occurrence of the two processes, the network either reaches a steady state or breaks, depending on the values of $W_b$ and $W_r$. In the first case, the fraction of broken links, $p$, and the network impedance, $Z$, fluctuate around their respective average values $< p >$ and $< Z >$. In the second case, a path of broken links spans the network. This second
possibility occurs when $p$ reaches a characteristic value, percolation threshold, that depends on the network structure [38].

By Monte Carlo simulation we have calculated the evolution of the rhodopsin interaction network when the two random processes described above are present. Figure 10 reports the results obtained for different values of $W_b$ and $W_r$ and which correspond to steady states of the network. Precisely, Fig. 10 shows the modulus of the network impedance versus time (measured in units of iteration steps). In this case we have used the following values of the parameters: $R_a = 5 \, \text{Å}$, $\rho = 10^6 \, \Omega \text{m}$, $V_0 = 1 \, \text{V}$, while the frequency is $\omega = 8 \, \text{Hz}$. The short dashed curve, the solid gray and the solid black curves are obtained by taking: $W_b = 2 \times 10^{-3}, 5 \times 10^{-3}, 6 \times 10^{-3}$, respectively. The different curves evidence that at increasing value of $W_b$, the fluctuations become more and more relevant, denoting an increasing instability of the network.

III. CONCLUSIONS

We have presented a complex network approach to the study of the electrical properties of single protein devices. In particular, we have considered a two terminal device consisting of a G protein coupled receptor (rhodopsin) embedded in a lipid bilayer and contacted to two ideal electrodes. A coarse grain description has been developed for the description of the electrical properties of the receptor, which is modeled as a network of elementary impedances. The conformational changes of the receptor induced by the capture of the ligand (photon), are then translated into a variation of the network impedance. The role played by the different parameters of the model on the network structure and on the impedance spectral properties has been studied. Furthermore, stochastic fluctuations in the value of the elementary impedances of the network, which mimic different physical effects, have been considered.
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FIGURE CAPTIONS

Fig. 1. Schematic representation of a G protein coupled receptor in its environment. The gray snake-like curve represents the seven helices trans-membrane receptor, which is embedded in the cellular membrane (lipid bilayer), shown as the black double lines, which separates the extracellular region from the intracellular region (cytoplasm). The ligand captured by the receptor is shown as the gray triangle. The N and C terminus represent respectively the extracellular and the intracellular terminal chains.

Fig. 2. Receptor contacted between two electrodes in a vertical configuration. On the left, schematic representation of the basic state of the rhodopsin, on the right of the activated state. The meaning of the letter is the following: 1, N-terminus; 2, trans-membrane core; 3, C-terminus.

Fig. 3. a) Interaction network associated with a hypothetical protein made of 11 residues: the circles show the nodes positioned at the alpha carbon atom of each amino acid, the lines represent the links arising from electrical interactions; b) addition of two extra nodes associated with the electrodes.

Fig. 4. A link is drawn between two nodes, associated with the amino acids i and j, when the distance between their respective alpha carbon atoms is less than twice the interaction radius. An elementary impedance taken as the impedance of a parallel RC circuit, is attributed to each link.

Fig. 5. Modulus of the network impedance as a function of the interaction radius: the dashed-dotted curve is obtained from model (i), the solid curve from model (ii) and the long-dashed curve from model (iii). The impedance is expressed in arbitrary units, the interaction radius is in Å.
Fig. 6. Degree distribution (distribution function of the node connectivities) for different values of the interaction radius. Precisely, the radius is: 2, 3, 4, 5, 6 Å.

Fig. 7. Total number of links in the network, N, and its relative increment as a function of the interaction radius. The black dashed curve shows N in the basic state of rhodopsin and the gray dotted curve in the activated state (metarhodopsin II). The solid curves, black and gray, shows the relative increment of N respectively in the basic state and in the activated states of rhodopsin. The interaction radius is expressed in Å.

Fig. 8. Nyquist plot of the network impedance: the dashed curve corresponds to a value of the interaction radius equals to 2 Å and the solid one to a value of 12.5 Å. The real and the imaginary part of the impedance are normalized to the static value of the real part, which takes the values 302 G Ohm and 1.67 M Ohm, respectively when the interaction radius is 2 and 12.5 Å. Both curves correspond to the basic state of rhodopsin and are obtained by taking a resistivity of 1 G Ohm m.

Fig. 9. Nyquist plot of the network impedance: the solid curve is obtained for rhodopsin by taking the interaction radius equals to 12.5 Å and a resistivity of 1 G Ohm m, the dot-dashed curve is obtained for metarhodopsin by taking the same values of the parameters. The real and the imaginary part of the impedance are normalized to the static value of the real part of the network impedance in the metarhodopsin state which takes the value 2.04 M Ohm.

Fig. 10. Fluctuations of the modulus of the impedance versus times for different values of the breaking and recovery probabilities, as specified in the figure. The impedance is expressed in Ohm, the time in simulation steps.
a) Contact nodes

b) Contact nodes
Amino acid $i$  

Amino acid $j$  

$C_{\alpha i}$  

$R_a$  

$l_{i,j} < 2 \ R_a$  

$C_{\alpha j}$  

$Z_{i,j}$  

$C_{\alpha i}$  

$C_{\alpha j}$
Degree distribution for Rhodopsin IN

$N(k)$

$R_a = 6\text{A}$

$R_a = 5\text{A}$

$R_a = 4\text{A}$

$R_a = 3\text{A}$

$R_a = 2\text{A}$
N (links), \( \Delta N/\Delta R_a \), N

Rhodopsin in the dark

\( \Delta N/\Delta R_a \)

Metarhodopsin II

\( \Delta N/\Delta R_a \)

N
solid: $\rho = 10^9 \, \Omega m, \, R_a = 12.5 \, A$

dotted: $\rho = 10^9 \, \Omega m, \, R_a = 2 \, A$
solid: $\rho=10^9 \Omega m$, $R_a=12.5$ A, rhodopsin
dot–dashed: $\rho=10^9 \Omega m$, $R_a=12.5$ A, metarhodopsin
Probabilities $W_b$, $W_r$:

- $2 \times 10^{-3}$, $8 \times 10^{-3}$
- $5 \times 10^{-3}$, $6 \times 10^{-3}$, $4 \times 10^{-3}$

Steps vs. $|Z|$ and $\Omega \times 10^{15}$