From local to global changes in proteins: a network view

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To fulfill the biological activities in living organisms, proteins are endowed with dynamics, robustness and adaptability. The three properties co-exist because they allow global changes in structure to arise from local perturbations (dynamics). Robustness refers to the ability of the protein to incur such changes without suffering loss of function; adaptability is the emergence of a new biological activity. Since loss of function may jeopardize the survival of the organism and lead to disease, adaptability may occur through the combination of two local perturbations that together rescue the initial function. The review highlights the relevancy of computational network analysis to understand how a local change produces global changes.

Introduction

The folding of a protein (Box 1) and its biological activity depend on the dynamics of the atomic interactions between the amino acids of the protein. Every amino acid interacts with every other amino acid, through interactions that weaken with distance. To create a simplified picture for tractability, we define 'a chemical link' as at least one atom of residue *i* being closer than 5 Å to an atom of residue *j* (Box 1). Above that distance, there is no “chemical” link. Thus a protein can be represented as a network (Box 1) of interacting amino acids.

Proteins present ample dynamics, well-illustrated by protein allostery where a perturbation at one site (binding) affects another (active) site which is distant both in the sequence and in space [1,2]. The question is: how do two sites distant within the protein communicate? This issue involves understanding how a local perturbation (e.g. amino acid mutation, ligand binding) produces the dynamics that leads to global effects, i.e. manifest far beyond the site of the perturbation. The science of networks has produced numerous methods to tackle this question because networks mediate communications from local to global scale. Some applications of such methods to protein dynamics are briefly described in the first part of the review. Yet, the mechanisms underlying local-to-global changes in proteins still escape us and the transfer of "technology" remains a difficult exercise. To motivate it, the second part of the review prospectively visits other real networks.

Amino acid networks (Box 1)

Evidence of local-to-global changes in proteins

Local perturbations of proteins may produce global changes that result in (i) robustness (maintenance of the function), (ii) diseases (harmful loss of the function) or (iii) adaptability (new/combined/recovered function) (Fig. 1). The latter often involves a combination of two local perturbations. Protein evolution and diseases related to protein changes are examples [3-8].

p53 is a transcription factor (DNA binding protein) regulating cell death, acting thus as a tumor suppressor by preventing cancers. In most tumors robust, lethal or adapted local perturbations are found in p53 [9,10]. It is therefore a suitable prototype to consider local-to-global changes in proteins.

Such changes in p53 have been observed using molecular dynamic (MD) simulations and computational network analysis [8]. Robust, lethal and adaptive mutations found in [8] are Y239N, G245S and G245S-N239Y, respectively. MD simulations performed on the X-ray structures of wild-type and mutant p53 were analyzed by building networks of amino acids (nodes) linked by Root-Mean-Square Deviation (RMSD)-distances across the simulation. Clustering methods were applied to group amino acids according to ΔRSMD. Roughly, if all amino acids were moving concomitantly there would be one cluster. The number of clusters (NOC) reports the extent of independent amino acid motions: many clusters indicate a lack of rigidity and a destabilized protein. The p53 cancerous G245S mutant of p53 has 32 NOCs, against 21 for the wild-type (WT), consistent with a large global change that agrees with the loss of function of the protein. N239Y has 19 NOCs suggesting small global changes compatible with maintenance of function. The G245S-N239Y has 15 NOCs, which is less than the WT, indicating global changes leading to a more rigid conformation, perhaps countering the G245S changes and rescuing protein function. Network clustering is also used for identifying allosteric sites and protein sectors evolutionary units of three-dimensional structure [1,2,6,7,11,12].

Mutations that lead to loss of function and cancer are also found in the tetrameric domain of the p53 [13,14]. Topological amino acid networks built from the X-ray structures of wild-type and mutants, considering amino acid as nodes and distances between the atoms of the amino acids as links, indicated that amino-acid contacts (referred to as signatures), changed upon mutation [15-17]. Because the signatures capture contacts beyond chemical ones, these results showed that the local perturbation had global effects. Graph signatures are also used to predict enzyme promiscuity [18]. Likewise, we reported changes of links and nodes in the entire p53 network upon a single mutation [19]. Here the links in the networks are chemical bonds, possibly monitored by different measures (distance, accessible surface area, etc.) such that different networks can be constructed from the same X-ray structure [20,21]. Note that topological amino acid networks are called several names in the literature: contact networks/graphs, protein structure network, residue interaction graphs (RIG) or amino acid networks, used here.

What about the mechanism underlying local to global communication in proteins?

Assuming the changes are discrete atomic interaction modifications rather than an overall reduction of the protein dynamics, the next question is how the change on a local site is carried out elsewhere.

Is it a question of finding a path? Classically in networks, shortest paths are measured (e.g. using Floyd Warshall algorithm, Girvan−Newman algorithm) to identify nodes or links which are central to the communication in the network (betweenness, closeness, etc.). Such measures are used in protein allostery [22-29]. They are relevant only to networks whose communication seeks the shortest available routes (e.g. goods/metabolite transports).

It is also a question of network architecture which designs communication avenues (Fig. 2A). The classic 'scale-free' network provides communication through 'hubs', nodes with many links [30,31]. Such networks have a power law degree distribution (Box 1), namely few hubs and a majority of nodes with few links. By definition, hubs are in contact with many nodes and so every one of them is close to others through them (small world effect) (Fig. 2A). Under well-defined conditions on the degree distribution, the mean path length (Box 1) and the clustering coefficient, hubs control the communication within the network [30]. Since the majority of nodes are poorly connected, perturbation (i.e. the removal of a node and its links) usually has little effect on the network; however perturbing hubs is particularly damaging (Fig 2A) [31]. This mirrors the behaviour seen in protein mutation: most amino acid mutations are robust to loss of function, with the minority being dangerous. Indeed, proteins have been described as small worlds [24,32,33]. Nevertheless, this description does not provide a natural platform for understanding adaptability through the combination of two perturbations, which requires that both positions communicate and that the changes are reversible. In such framework, perturbation over two hubs would be necessary and the damages of one would need to compensate the damages of the other instead of cumulating damages.

Moreover, the two hubs would need to communicate, which raises the issue of correlation of degrees: a measure of the global architecture of networks [34] (Fig. 2A). A network is assortative when nodes preferentially attach to nodes with similar degree and disassortative when the preference is for nodes of different degree [35-37]. Knowing the level of assortativity aids prediction of the number of changes between connecting hubs in an amino acid network [38,39]. In model and real networks, nodes that regulate the network (driver node) avoid high degree nodes probably to keep the network under control [40]. Robustness and adaptability in terms of correlation of degrees is a complex problem beyond the scope of the review; see for example [41-43].

Let us explore amino acid hubs as communication devices in proteins. First, there are few statistics on amino acid networks that report simultaneous measures of degree distributions, mean path length and clustering coefficients [33]. Second, amino acid networks have random, exponential or power law degree distribution [19,21,33,44]. In other networks, hubs have hundred or more times as many connections as non-hubs; in proteins however the difference in connectedness is much smaller. Out of twenty-two amino acids only R, W, Y, F and H are frequently observed with a degree above three or four, arguing against the existence of hubs in proteins, at least if we define them as nodes with a degree exceeding significantly the average degree [19,21]. Thus, there is no log scale differences in the degree of amino acids in contrast, for example to a web network, e.g. 300 000 nodes and hubs ranging from degree 100 to 1000 [45]. Such ratios are impossible in proteins because the contacts between amino acids are based on Euclidian distances, so the surface of contacts grows with $\sim r^2$ (r is the amino acid radius). A degree ratio of 100 would imply an amino acid with a 10 Å radius. Thus amino acid hubs must have a degree moderately higher than the average network degree, as reported [19,21,33]. Whether moderate degree hubs can control the communication in proteins is still unknown.

What can be learned from other real networks?

Peer to peer communications [46,47].

However, communications mediated by high versus moderate degree hubs have been studied in other real networks such as epidemic risk and computer communications (Fig. 2B). Nowadays computer-to-computer communications are based on peer-to-peer (P2P) or GOSSIP networks where information circulates step by step from one computer to the next (Fig. 2B). P2P networks have nodes of similar degree and hubs of moderate degree. The P2P architecture is robust to node failures (i.e. removal of nodes and links) and would be a satisfactory model of amino acid networks, where most nodes/amino acids are resistant to mutation. P2P networks are resilient: they use more resources (links) than the minimum necessary and organize them to have alternative/back-up paths between nodes to avoid failures [48]. In fact, resilience and combinatorial interactions are common mechanisms for robustness in biological networks [49-51].

Let us explore P2P communication in amino acid networks. Amino acids communicate via chemical links between their atoms, which have by our definition a limited spatial reach. It is therefore reasonable to assume that communication beyond that point involves a step by step mechanism. Quite simply, amino acid *i* chemically interacts with amino acids *j* (distance 1), amino acid *j* chemically interacts with amino acids *k*, which makes a communication path between *i* and *k* at distance 2, and this process can be iterated. We have looked at the changes in the atomic interactions of the p53 tumor suppressor upon the local perturbations N239Y and N239Y-G245S, respectively. Unweighted and weighted networks are built from the X-rays structures (Fig. 2C). For the former, two amino acids which have at least one pair of atoms at a distance below 5 Å are defined to have one link; for the latter, the number of links (weighted degree) between two amino acids is equal to the number of pairs of atoms they have which are closer than 5 Å. The weighted degree measures how strongly two residues are connected while the unweighted degree simply keeps track of the fact that they are connected. The mutation of Asn^{239} (residue *i*) introduces a new link between residues Pro^{177} (residue *k*) and Gly^{245} (residue *l*) (Fig. 2C). Thus, this local perturbation leads to changes at distance 3, far beyond the residue's chemical reach. It also alters the weighted links between Asn^{239} and His^{179} (residue *j*) and between His^{179} and Pro^{177}. A P2P mechanism rationalizes the change at distance 3 when considering the changes over the weighted network: the perturbation of Asn^{239} modifies the weighed degree of His^{179}, which modifies the weighted degree of Pro^{177}, which modifies the weighted and unweighted degrees of Gly^{245}. The double mutation creates a chemical link between Asn^{239} and Gly^{245} showing that the two sites of perturbation communicate. The weighted graph provides a more reliable geometrical description of the amino acids which is important to design new paths. A P2P mechanism is one possible alternative to small world communication to explain how a local perturbation can produce global changes.

Mechanisms underlying local to global changes: quality versus quantity

Very recently financial networks were found to be weaken more by influences between financial partners than by their degree of connectivity [52]. Feedback centrality, which identifies nodes whose perturbation affects not only their direct contacts (distance 1) but also the direct contacts of their direct contacts (distance 2, etc.) in a domino effect, was measured. Basically, the risk of failures depended on the sphere of influence of the nodes (how far the damages spread in the network) and not of their degrees [52,53]. This illustrates how the total amount of change (global change) upon a perturbation does not solely relate to the quantity of links of the disturbed node. Along these lines, we have found that the *in silico* mutation of the highest degree node in the network of the cholera toxin B pentamer interface had a lower impact on the stability of the interface than the mutation of a node of degree one [54]. Moreover, the changes observed for the N239Y p53 mutant resemble a domino effect. We have observed a similar domino effect upon the single mutation G334V in the p53 tetramerization domain [19].

Influence effects are referred to as cascades and are used to measure epidemic risks [55,56]. There are many flow algorithms, feedback centrality and influential algorithms worth considering. For example, the Dijkstra algorithm applied on P2P networks allows one to calculate best itineraries or fastest internet routing [57,58]. Influential algorithms are developed essentially to analyze social behavior from human decisions to flocks of birds, but may also apply to protein-protein interaction networks [59]. In particular Hegselmann-Krause's and French-de Groot's models look at how a node is influenced by and influences its direct contacts [60-63].

Besides influences, what other changes can be expected upon an amino acid mutation? Altogether, a mutation can either add or remove nodes/links, or conserve the wild-type connectivity. The real problem is to anticipate the consequences of the local change. Again, this question arises in other real networks and can be discussed in terms of quality and quantity of changes [64]. In social sciences, it is known that weak ties between two nodes of two different communities otherwise unconnected introduce a risk in the network (Fig 2A) [65-67]. This is typically a low quantity/high quality change. Likewise in proteins, weak ties, if any, can be expected to create at least structural changes upon mutation. In fact, the N239Y-G245S p53 mutant is a good example of how little (low quantity) changes can prevent large impact. Now the high quantity of links also creates risk, such as for the p53 tetramerization and the financial networks, whose high connectivity promotes fragility because of the domino effect [19] [52]. In contrast, amino acid networks of protein interfaces, issued from "healthy" proteins (Box 1) are disconnected/sparse [19].

This warns us that there is no *stricto sensu* correlation between connectivity, density of contacts and robustness or lack of robustness. The consequences of changes depend on whether they provide or remove 'back-up' interactions [50,68].

The complex relationship between connectivity and robustness/sensitivity to changes, observed in networks, is mirrored in proteins [69]. Schematically, proteins with high (globular) and low (disordered) density of contacts are stable enough to exist.

Conclusion: A combination of network measures is essential to capture changes underlying local to global changes in proteins: local measures on the nodes and links as well as influential/flow measures along the paths of communication (architecture and diffusion). Complex networks are often systems whose properties are not just the sum of the properties of their individual components they are nonlinear systems. This also applies to amino acid networks and proteins. This concept is explored further in the review [70] on the complexity of systemic risk in networks.

Box 1. Definitions

Protein: a chain of amino acids covalently linked, whose unique sequence encodes the shape and the function of the protein. Amino acids are also called residues.

Protein folding: acquisition of the protein's three-dimensional shape, also called fold or conformation.

Network: a network represents interactions between elements. The elements of the network are the **nodes, also called vertices,** and the interactions between two distinct nodes are the **links, also called edges**. A network is particularly well suited to model complex systems in which many elements interact with many others.

Amino acid networks: network built using amino acid as nodes and interactions between amino acid as links.

Robustness: the property of a system allowing it to maintain its functions despite external and internal perturbations.

Local perturbation: the change of a single node, e.g. a single amino acid mutation.

Degree: the number of links of a node.

Path length: the number of links, called distance, one passes through travelling from one node to another.

Cascade effect: an avalanche or a domino effect, in which one change produces other changes which in turn produce other changes etc.

Healthy proteins: proteins which do not undergo shape or functional changes that lead to a disease or reduced lifespan.

Figure legend

Figure 1. Complexity and dynamics of proteins. To cope with local perturbations, proteins rely on dynamics as outlined here. For the sake of clarity, a protein is schematized by simple shapes made of balls and sticks representing its amino acids and their links, respectively. In the central black box, the protein has a shape S_1 suitable to a function F_1. The local perturbation 1 (p1, blue lightning) on one amino acid modifies the shape S_1 enough to prevent the protein from functioning (blue arrows). Such a global change is lethal and underlies the development of some diseases. The local perturbation 2 (p2, red lightning) on an amino acid at a different position, also modifies the shape S_1 but in such a way that the protein maintains its function (red arrows). This is referred to as robustness to change, the local perturbation p2 being neutral. The combination of the two local perturbations p1 and p2 creates a global change (purple arrows) that is a solution of the protein to adapt either by taking a new function F_2 or by combining two functions F_1 and F_2 or by rescuing the function F_1 and preventing p1 lethal changes. The mechanism common to these dynamics is that a global change is triggered by a local perturbation.

Figure 2. Network architecture. A. Theoretical networks. The nodes and links are represented by circles and lines, respectively. *Left panel.* Network with high degree hubs connected to one another (assortative network). Red circles are hubs and dotted lines are weak ties. The lightning represents perturbation. The potential paths of changes subsequent to the perturbation are indicated by black and green arrows. The spread of perturbation to a node of degree one (green arrow) is weaker than to a hub (black arrows) because the hub has many links. *Right panel.* Network with moderate degree hubs connected to lower degree nodes (dissassortativity). Paths of changes upon local perturbation appear less obvious in such architecture. **B. Computer networks.** Schematics illustrate a served based network (left panel) and a Peer-to-Peer network (right panel). In the former, the communications between computers rely on a “hub” central computer. **C. Real networks: from local to global changes in the tumor suppressor p53.** The wild-type tumor suppressor p53 and two mutated versions (N239Y and N239Y-G245S) are taken as examples to illustrate the mechanism of changes upon a local perturbation. The top panels represent a close up of the X-ray crystallography structures of the proteins, focusing around the site of the mutations. The wild-type (yellow), N239Y (blue) and N239Y-G245S (green) PDBs are 1TSR, 1UOL and 2J1Y, respectively. The side chains of the amino acids are shown with their type and position along the protein sequence. Atomic distances are indicated in Angström and highlighted by black lines. Continuous and dotted lines are for distances below and above 5 Å, respectively. Changes in

the atomic distances upon mutation are indicated in red as well as the mutation. The middle panels are unweighted network representations of the respective atomic close ups of wild-type, N239Y and N239Y-G245S. Nodes and links are represented by black dots and lines. A link between two amino acids signifies that the amino acids have at least one pair of atoms at a distance below 5 Å (unweighted graph). Residues Asn^{239}, His^{179}, Pro^{177} and Gly^{245} are nodes *i*, *j*, *k* and *l*, respectively. The bottom panels are weighted network representations of the respective atomic close ups of wild-type, N239Y and N239Y-G245S. In the weighted networks, the number of links between two amino acids equals the number of pairs of atoms at distances below 5 Å they share. The weight is indicated on the link. The local perturbation (i.e. mutation) is illustrated by a lightning bolt.

Figure 3. Double site perturbations and protein adaptability. One possible solution to adaptability through the combination of two local perturbations is explained by a straightforward example, using a simple rigid shape maintained by a set of links (sticks) between atoms (balls). A first local perturbation on one site (lightning) removes one link (red stick). The shape relaxes; the protein becomes dynamic and flexible, able to explore new shapes. A second local perturbation on a distinct site introduces a new link (red stick), and yields a new rigid shape. This mechanism applies as much to more complex shape/system (e.g. snow coat/snow flake). Likewise, if the sticks are secondary structure elements and the balls are amino acids. We have used this roadmap to explore the transition from a fully folded protein to a protein fiber [71].

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The authors discuss the relation between fold, function and innovability and highlight a variety of relations which underlies the multiple mechanisms providing robustness and plasticity to a complex system. The authors propose a polar model in which two distinct parts of the protein are dedicated to robustness and plasticity, respectively.

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The authors propose a new approach based on tiling to explore protein conformational changes. The transition from protein oligomers to protein fibers is analyzed but the method apply more generally. The important result is that little local changes are necessary to trigger significant global conformational changes.

Figure 1

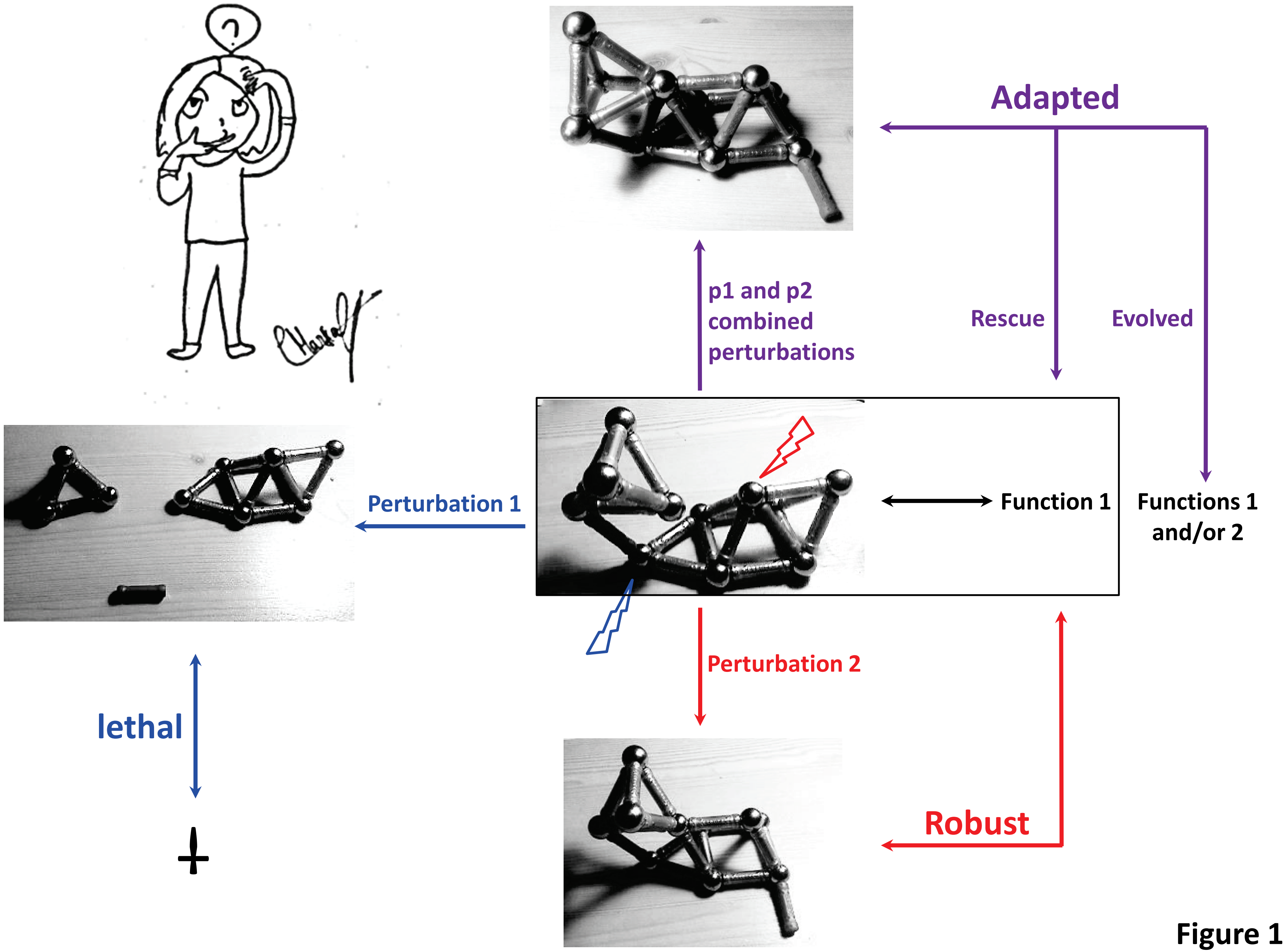

Figure 1

Figure 2

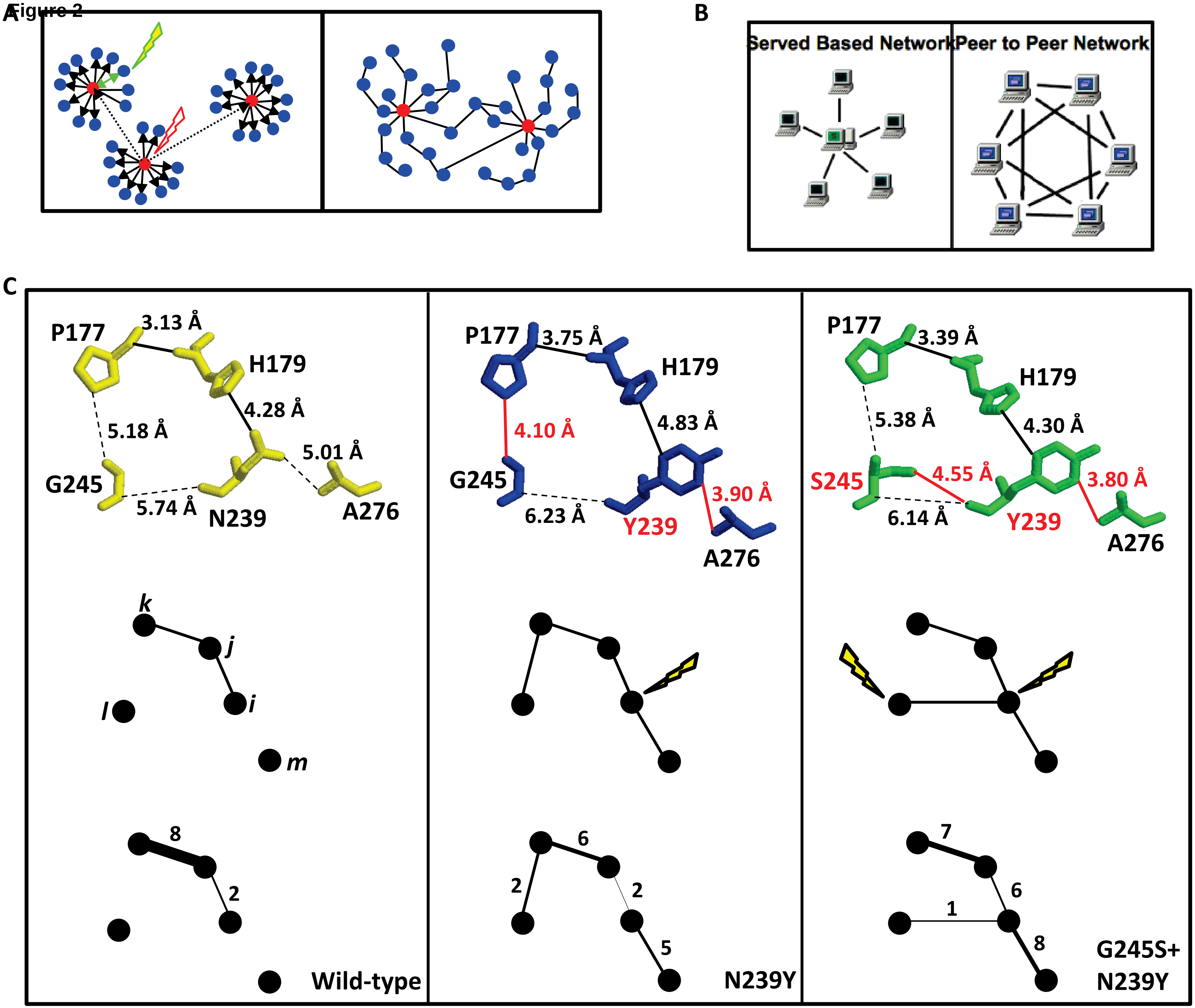

Figure 2

Figure 3