Creative elements: network-based predictions of active centres in proteins and cellular and social networks

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Active centres and hot spots of proteins have a paramount importance in enzyme action, protein-complex formation and drug design. Recently, several publications successfully applied the analysis of residue networks to predict active centres in proteins. Most real-world networks show several properties, such as small-worldness or scale-free degree distribution, which are rather general features of networks, from molecules to society at large. Using analogy, I propose that existing findings and methodology already enable us to detect active centres in cells and can be expanded to social networks and ecosystems. Members of these active centres are termed here as 'creative elements' of their respective networks, which can help them to survive unprecedented, novel challenges and play a key part in the development, survival and evolvability of complex systems.

Introduction: various approaches to determine key elements of protein structures

Active centres of proteins have been first identified by their function, for example, by their participation in enzyme catalysis and substrate binding. The well-known 'lock-and-key model', whereby the conformation of the active centre (see Glossary) of a protein (the lock) was only matched by its unique ligand(s) (the key), was proposed by Emil Fischer in the 19th century [1] and was used to describe the mechanism of enzyme action for a long time. It wasn't until fifty years ago that Daniel Koshland challenged this view and proposed the 'induced-fit mechanism', whereby the binding of the correct ligand(s) led to the protein changing its shape and adopting its active conformation, a concept that became a centrepiece of our biochemical understanding of enzyme function [2]. More recent developments emphasize the importance of atomic vibrations of the protein structure and the partner-driven selection of the binding-compatible conformation from an ensemble of alternating conformations of the original protein. This mechanism was first outlined in 1964 by Bruno Straub, who called it 'fluctuation fit' and, more recently, by Nussinov and colleagues as a modern day interpretation called the 'pre-existing equilibrium or conformational selection model' [3,4]. Another way to achieve 'fluctuation' is structural disorder in a large number of protein complexes, termed as 'fuzziness' by Peter Tompa

Glossary

Active centre: in the traditional sense we call a protein segment an active centre if it plays a key part in the catalytic action of the enzyme function displayed by the respective protein. In the network sense, an active centre of the protein contains a cluster of amino acids that have a high centrality in the amino acid network of the hosting protein. With the exception of the introduction, throughout this paper I use the term 'active centre' in this novel, network sense.

Centrality: centrality of a network element or link defines the relative importance of the element or link within the network. There are various measures of centrality using the local network topology, global properties of the whole network, or both.

Degree: the number of links of a given element in a network. The degree distribution is an important property of the network showing whether the network is a random network (with binomial degree distribution), a scale-free network (with a power law degree distribution) or different from both.

Elastic network model: in the elastic network model the protein is modelled as an ensemble of its amino acids occupying the equilibrium positions of the α carbon atoms, as found in the experimental three-dimensional structure. Each amino acid interacts with its neighbours, as specified by a cut-off distance, and is modelled as an oscillator linked by springs to all interacting amino acids. The model calculates the most probable modes of oscillation of each amino acid.

Element: the element is a single building block of a network. The element is also called a vertex in graph theory, a node or a site in physics, or an actor in sociology. Most of the time, the element itself can be perceived as a complex network. Like the elements of protein–protein interaction networks, the individual protein molecules can be perceived as networks of their constituting amino acids or atoms.

Fractal: fractal objects are generated by a recursive process, in which self-similar objects of different size are repeated and repeated again. In nature we are often talking about fractal-like behaviour, in which the extent of self-similarity is not as complete as in pure (and many times extremely beautiful) mathematical fractals.

Hierarchy: a hierarchical organization arises in a network when an element has a 'parent' and this 'parent' also has a 'grandparent', like in a family tree. Network hierarchy might arise at the level of modules, which might be considered as elements of a higher level network. Modules of this higher level network might be considered again as elements of an even higher level, and so on.

Hot spots: amino acid residues of protein-binding surfaces having an extraordinarily high level of binding free energy.

Hub: a hub is a highly connected element of the network. Usually a hub has >1% of total interactions.

Module: modules are groups of network elements that are relatively isolated from the rest of the network and where the elements inside the module are functionally linked to each other and have denser contacts with each other than the group with outside groups. Modules are also called network communities.

Network topology: the topology of a network is the precise description of the links between the elements of the network. Many special topologies are discriminated by their degree distribution.

Scale-free: scale-free topology denotes a degree distribution of network elements that follows a power law (algebraic decay instead of, for example, exponential). These networks have many nodes with a low degree (i.e. few connected links); however, they also have a non-zero number of hubs (i.e. nodes with an unusually high number of links).

Small-worlds: we call a network a small-world when the average number of steps we need to reach any element of the network from any other element grows only logarithmically with the number of elements in the network. In smaller networks this means that the elements are less than six steps apart from each other.

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Box 1. Active centres and hot spots

The terminology of important protein residues and regions is rather complex owing to the various approaches identifying these crucial segments of protein structure. Here, I outline the various approaches and the related terms.

Functional terms: active centres and binding sites
In the traditional sense we call a protein segment an active centre if it plays a key part in the catalytic action of the enzyme function displayed by the respective protein. Similarly, amino acid side chains located at the binding interface are called the binding site. However, in both cases the protein segments, which functionally participate in either the catalytic or the binding action, are much broader than those identified by the traditional terms of the active centre or binding site.

Energy terms: hot spots and hot regions
A small number of crucial amino acid residues of protein-binding surfaces can be discriminated by an extraordinarily high binding free energy and have been termed as 'hot spots' [7]. Hot spots often cluster to densely packed 'hot regions' [8].

Structural terms: central residues, active centres and creative elements
Description of protein structures as amino acid networks enabled the identification of central network residues. These residues are often clustered and form active centres in the structural, network sense. With the exception of the introduction, throughout this paper I use the term 'active centre' in this novel, network sense. A highly specific subset of these central residues has been described in this paper as creative elements. For the discriminatory features of creative elements, see the main text.

The terminologies defined by the three approaches overlap each other. Hot spots and hot regions are parts of binding sites. Central residues often contain catalytic residues (active centres in the traditional sense) in addition to segments of binding sites including hot spots. However, central amino acid network residues including creative elements often go beyond the traditionally identified key segments and highlight novel crucial residues governing conformational changes. The above terms are often compared with and extended by mutational studies and by evolutionary analysis. As expected, mutations inducing more damage in protein function in addition to evolutionary conserved residues are often (but, by far, not always) overlapping with the active centres, binding sites, hot spots and central residues.

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[5]. Here, it is worth emphasizing that, from the point of the general elements of the binding mechanism of a protein, the binding partner can be not only a substrate but also any other small ligand, drug or even a macromolecule, such as another protein, DNA or RNA. An increase in the size and binding strength of the partner was proposed to shift the preferred binding mechanism from the fluctuation fit towards the induced fit [6]. Owing to the concentration of binding free energy to a small number of crucial amino acid residues of protein-binding surfaces, these residues were termed as 'hot spots' [7] (for further elaboration on the terminology of active centres and hot spots, see Box 1). Hot spots often cluster to densely packed 'hot regions' [8]. Active centres are, thus, not just binding pockets acting as baits waiting for their prey but must also have a special position in the protein structure to trigger a set of concerted conformational changes.

How can we predict active centres and hot spots? During the past decades several methods have been developed that are able to predict active centres and their key residues with high accuracy such as SCOTCH, MAPPIS, KFC-server and CS-Map (for many more freely available pro-grams, see Tables 6 and 7 of Ref. [9]). These methods use the evolutionary conservation of physico-chemical properties, energy-optimization, neural networks or machine learning. However, most of these approaches are dependent on structural and energy-based information, which is local, or need the extensive comparison of evolutionary variants [9–12]. The special position of active centres in the overall structure of the hosting protein might enable the use of global structural determinants to identify additional discriminatory features helping their prediction from a single protein structure.

Here, in the first section, I summarize our knowledge on protein structure networks (residue networks), which is followed by the description of network-based prediction of active centres. I show that amino acids of active centres have several discriminatory features at their own network element level. Because (i) all these discriminatory features are independent from the functional identification of active centres using the properties of the whole network together (thus, a system one level higher in the hierarchical organization of nature), (ii) they identify a broader set of crucially important amino acids than the amino acids of traditional active centres (Box 1) and (iii) they correspond to the network behaviour of creative persons, I propose that it is worth to discriminate key residues of protein structure networks and call them 'creative elements'. In the concluding parts of the paper I give several examples to show that in other networks, such as in protein–protein interaction networks, signalling networks, social networks and ecosystems, we can also identify highly similar creative elements, thus their existence seems to be a widespread feature of evolving systems. The examples here show that creative elements help the survival of unprecedented challenges and play a key part in the development and evolvability of complex systems.

Protein structure networks

The role of a certain amino acid at a certain position in the protein structure can be assessed by the network approach. Networks help us to understand complex system behaviour by reducing the system to a set of interacting elements that are bound together by links [13–15]. In protein structure networks (also known as residue networks) the interacting elements are the amino acids of protein molecules, whereas the links represent their neighbouring position in space if the inter-element distance is below a cut-off of usually between 0.45 and 0.85 nm. Protein structure networks might use weights instead of the cut-off, might be restricted to hydrogen bonds only and might also define each individual atom of the protein structure as an element [16,17]. Proteins are small-worlds. In the small-worlds of protein structure networks any two elements are connected to each other via only a few other elements represented by amino acids. Small-worldness determines folding probability (proteins with denser protein structure networks fold more easily) and increases during the folding process as the protein structure becomes more and more compact [18].

Protein structure networks contain the constraints of the protein backbone only as indirect information. The neglect of the backbone-related confinement of potential

amino acid motions doesn't cause any problems if we restrict our analysis to the topology of these networks and do not want to examine their dynamics. However, for a more complete understanding of protein dynamics, different methods are also needed. The majority of the elastic network model approaches use the atomic coordinates of the α carbon atoms and a harmonic potential to account for the pair-wise interactions between them. Other elastic network representations include all atoms, forming a spring network [19–23]. As I show later, these elastic network models can accommodate the recent knowledge on atomic vibrations in the protein structure and enable a better understanding of the conformational selection process.

Network-based prediction of active centres in proteins

How can we find discriminatory features of active centres by analyzing the topology of protein structure networks? Owing to the constraints imposed by the protein structure, local topological extremities do not seem to answer this question. As an example of this, 'stars' or 'mega-hubs' (i.e. elements with an extremely large number of neighbours) cannot be observed in protein structure networks because the surface area and binding properties of a single amino acid side chain do not enable the continuous binding of a large number of neighbours owing to steric hindrance. The trick of partner change (used for the expansion of partners in other networks, for example in protein–protein interaction networks or in human relationships) is hindered by the protein backbone [16,17]. If searching for discriminatory features of active centres, we should consider the complexity of the whole network.

Centrality is a key measure of long-range network topology. According to an often-used version of the multitude of centrality definitions called 'betweenness centrality', an element is central if it is needed for a large number of shortest paths, where the term 'shortest path' means the shortest possible route between two elements of the network [13–15]. Ruth Nussinov and colleagues pruned the protein structure networks of seven large protein families, removing those segments that did not affect the average path-length greatly [24]. With this method they constructed a network skeleton containing only those side chains that were central enough to have an important role in the information flow (conformational relaxation) of the whole protein. Indeed, they found that these conserved interconnectivity determinants were key elements of communication between the allosteric site(s) and the active sites (e.g. catalytic sites). It is of particular interest that in the case of the HIV-1 protease the remaining residues outside the active sites were sites the mutations of which led to drug resistance [24]. Central residues with small average shortest path lengths were found to coincide with the catalytic site or ligand-binding site(s). This, together with surface accessibility, proved to be a good predictor of active sites in 70% of 178 protein chains. Interestingly, not all active-site residues had a high degree (i.e. a large number of neighbours) in the network [25]. These studies showed that active sites are, indeed, preferentially centred within the protein structure network. The catalytic centre of the rRNA also occupies a central position in the rRNA

nucleotide network, and an additional central nucleotide, A2439, lies in the middle of the information flow (conformational changes) of the rRNA molecule, which extends the these statements to ribozymes [26].

However, the residue networks mentioned so far are static and reflect only a single conformation of the entire conformational ensemble of the protein. Changes in protein conformation might rearrange the centrality of individual residues. Indeed, shifts in residue centrality ranks were observed when the active and inactive conformations of hemoglobin and nitrogen regulatory protein C were compared [24]. Moreover, network centrality, when applied alone, might identify additional key residues besides active centres, such as allosteric sites, hinge elements and so on. A better prediction, thus, requires additional information, which might come from protein dynamics. Indeed, central amino acids have a more restricted motion [27], raising the possibility that elastic network models might reveal additional discriminatory features of active centres.

Using the structural perturbations of the elastic network model, a set of sparsely connected, highly conserved residues were identified that are key elements for the transmission of allosteric signals in three nanomachines: DNA polymerase, myosin and the GroEL chaperonin [28]. The combination of the elastic network model with information diffusion revealed that active centres are endowed with fast and precise communication [29]. A perturbation study of the conformational ensemble of dihydrofolate reductase [30] showed that the binding sites have a greater impact on the cooperation of residue pairs than any other segments of the protein. These findings indicate that active centres are not only structurally central in protein structure networks but also have a central position to affect protein dynamics.

Recently, the elastic network model has been extended by adding anharmonic, nonlinear terms and by taking into account the fact that the energy of the surface amino acids is dissipated by the surrounding water. This approach identified active centres as special, energy-preserving protein segments in 833 enzymes. The active centres collecting and harbouring long-lived, localized vibrations, called 'discrete breathers', were located on the stiffest parts of the proteins and had many neighbours that were not preferentially connected to each other [31,32]. The uniquely high local energy of active sites is in agreement with the preferential local unfolding of these sites [33] in addition to their high local 'frustration', that is, low contribution to the stabilization energy of the protein [34].

The network analysis showed that active centres: (i) occupy a central position in protein structure networks; (ii) most of the time, but not always, are hubs (i.e. have many neighbours); (iii) give non-redundant, unique connections in their neighbourhood; (iv) integrate the communication of the entire network; (v) are individual and do not take part in the dissipative motions of 'ordinary' residues; and (vi) collect and accommodate most of the energy of the whole network (Figure 1). Let me note here that these features are not only characteristic to the *bona fide* active sites of enzymes but also to the binding sites of ligands, drugs, proteins, DNA or RNA. In summary, active centres
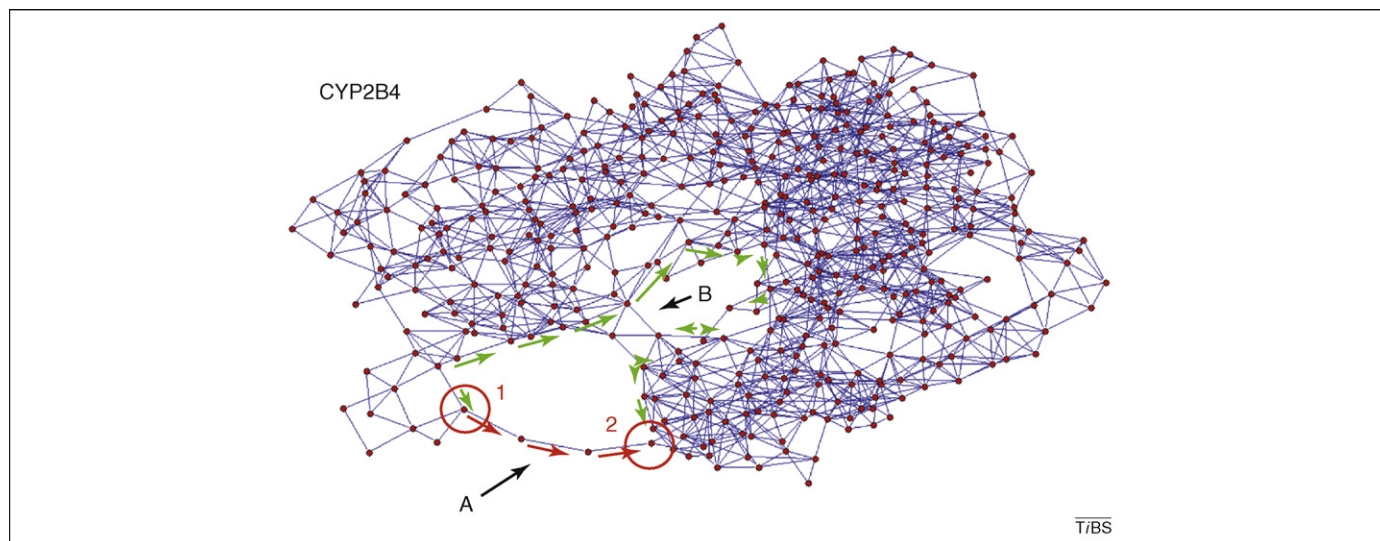
Figure 1. Active centres of protein structural networks. The figure illustrates the key role of active centres of protein structural networks in the communication of the protein molecule using the example of the hydrogen-bond network (made by the HBPlus program of Ref. [58] and the Pajek program with the Kamada-Kawai algorithm) of the open conformation of the cytochrome P450 protein, CYP2B4 (pdb file: 1po5; www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1po5) leaving out the hydrogen bonds of the haem and water molecules. The black arrows point to two active centres of the hydrogen bond structural network (marked with A and B). These active centres have a key role in the communication of the network as it is shown by the red arrows, which highlight a three-steps-long communication path between sites 1 and 2 (marked with the red circles), whereas in the absence of active centres A and B the alternative communication pathways (exemplified by the one marked with the green arrows) would provide a much longer (in this particular case 21 steps long) communication path. The active centre A of the network contains Ile114 and corresponds to the substrate recognition site, whereas the active centre B, containing Arg98 and Arg133, forms the haem binding site illustrating the overlap of structurally important segments of protein networks with functionally important sites of the protein molecule.

are different: they have unique properties (being stiff when the rest of the protein is flexible, being frustrated, etc.) and they influence the communication of all other network elements while maintaining their individuality. In analogous terms, this summary might sound like the characterization of a mastermind, broker, innovator or network entrepreneur. Indeed, as we proposed in preliminary forms before [35,36] and as I show in the next section, elements with a similar network position and features can also be found in networks of proteins, signal transduction and neurons, and in social networks and ecosystems.

Active centres, creative elements of cells, ecosystems and social networks

Networks have several properties that are typical to most of them. The already-mentioned small-worldness of protein structure networks is an example of one of these usually valid properties of most complex systems ensuring the fast and undistorted propagation of information in the whole network. Many real-world networks have a scale-free degree distribution, that is, a highly uneven distribution of connections resulting in the presence of hubs and elements with many more neighbours than the average [13,14,37]. Most networks are modular and have a well-developed hierarchical structure of overlapping groups. The module hierarchy often leads to a fractal-like structure where the individual structures of the different hierarchical levels resemble each other [35,38]. The hierarchical modularity enables easy navigation in the network and (together with the presence of hubs) the filtering out of unwanted information and noise. Moreover, several pieces of evidence indicate that networks are usually stabilized by low-affinity, low-intensity, weak links [15,39].

The aforementioned list of ubiquitous network properties (which is far from complete) prompts me to think that the concept of active centres can be extended to networks other than protein structures. In protein–protein interaction networks a good analogue of an active centre is a date hub, the definition of which in this context is a protein with one or two interaction surfaces that forms complexes with different subsets of its partners at different times and at different cellular locations. Date hubs are enriched for intrinsic disorder and structural flexibility, which makes them different from other proteins that are structurally more defined [40]. Date hubs are preferentially located in the overlaps of multiple modules, thus their connections are non-redundant and unique [35]. As an example, molecular chaperones have an inter-modular localization and are among those date hubs that constitute the true central coordinators of the cellular network [41,42]. Several chaperones are also called stress proteins or heat-shock proteins, and their centrality increases in protein–protein interaction networks after stress [41]. In other words, chaperones become key integrators when the cell experiences an unexpected situation (i.e. a stress). As an additional example, central elements of signal-transduction networks, exemplified by the phosphatidylinostiol-3-kinase, the AKT/PKB-kinase or the insulin-receptor substrate families, have been termed as 'critical nodes' by Ronald C. Kahn and colleagues [43]. Critical nodes often have many isoforms, which shows the importance of the need for 'back-ups' for active centres in addition to the need to extend the variability of these key elements of signal transduction further. It is of substantial interest how the signalling mediators of various membranes [44] can be included to this picture.

Going several levels of integration higher to the level of mammalian networks, top predators act as couplers of distinct and dissimilar energy channels and, by integrating the ecosystem network, increase its stability [45]. Dolphins

occupying inter-modular positions in dolphin communities were shown to act as brokers of social cohesion for the whole group [46]. In social networks the archetype of the aforementioned unique, inter-modular element is the 'stranger' described by one of the forefathers of sociology, George Simmel, a hundred years ago [47]. The stranger is different from anyone else. The stranger belongs to all groups, but at the same time does not belong to any of them. A later, well-known example came from Ronald S. Burt [48], who proved that innovators and successful managers occupy 'structural holes', which are exactly the non-redundant, centrally connecting positions of the active centres in protein structure networks. People bridging structural holes have 'weak links', for example they often change their contacts [48]. Malcolm Gladwell describes several 'active centre figures' in his best-seller book 'Tipping point' [49]. These 'connectors' (including the famous Boston citizen of the American history, Paul Revere, who alarmed his fellows during the 'Midnight Ride' to combat the coming danger at the beginning of the American Revolution) are interested in a large number of dissimilar persons and information. This wide and unbiased interest propels these boundary-spanning individuals to an integrative, central position in the social and information networks. Such a person can also be imported from outside. For example, consultants typically span otherwise-isolating intra-organization boundaries [50].

Going one level higher in the hierarchy again, having a central position also offers a great advantage to groups. As an example of this, biotech companies with diverse portfolios of well-connected collaborators were found to have the fastest access to novel information and directed the evolution of the field. This was only possible in the long run if most of these connections were transient [51]. Their transient, far-reaching, exploratory contact structure helps performance only in those cases when the tasks are novel (e.g. those emerging in uncertain environments or in crisis) and require creative thinking to solve. Conversely, if the task is one that is typical and the expertise that is already present within the group is enough to solve it, the maintenance of exploratory contacts is costly and hinders performance [52,53].

These analogies enrich the characteristics of active centres further. Active centres of networks at higher levels than proteins are not only central elements having a unique set of properties and integrating the communication of the entire network but they also perform a partially random sampling of the whole network and connect distant modules. Active centres (especially those of less-constrained networks than proteins) have transient, weak links leading to important positions (often hubs) in the network and become especially important when the whole system experiences an atypical situation requiring a novel, creative solution. Owing to this crucial property of active centres, I propose the term 'creative elements' for the network elements participating in active centres (Figure 2).

Creative elements have an integrated property set

After completing the description of creative elements in a large variety of evolving networks, here I show that the
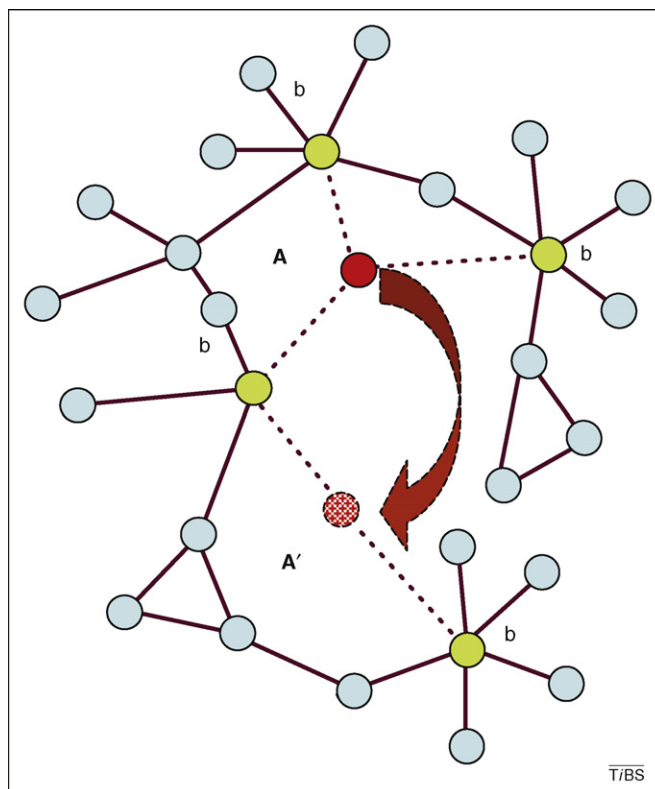

Figure 2. Creative elements. The figure illustrates the integrative network position of creative elements integrating network communication, performing a partially random sampling of the network and connecting distant network modules. Creative elements often have transient, weak links leading to hubs. Creative elements (A and A′) and hubs (b) are marked with red and green circles, respectively. Solid lines denote strong links, whereas dotted lines show weak, transient links. It is of key importance that the figure is a snapshot only and that the position of creative elements in real-world, dynamic networks will change to a similarly integrative position elsewhere in the network at the very next moment. This is illustrated by the jump of the creative element from position A to A′.

properties of creative elements require and predict each other and, therefore, make an integrated set of assumptions.

Autonomy and transient links
Creative elements are the least specialized and are the best among all network elements to conduct an individual, autonomous life independent from the rest of the network; this independence explains why they might, and should, continuously rearrange their contacts.

Transient links and structural holes
Creative elements must connect elements that are not directly connected to each other. If creative elements introduced their new and unexpected content to multiple sites of a densely connected region, they would make an extremely large cumulative disorder that would be either intolerable or would lead to a permanent change instead of a transient change. Owing to the same reason, creative elements must connect to hubs to enable either the dismissal or the fast dissipation of their novel content.

Structural holes and network integration
If an element connects distant modules (with transient weak links leading to the generation of important positions of the modules involved), this element performs a

Box 2. Possible proofs of principle

In this section, I suggest several methods to test or refute the existence of creative elements. Because the properties of creative elements are linked to each other, the ideas below not only describe individual tests but also offer a system for cross-checks, cross-correlations and for the sequential selection of creative elements [35].

Autonomy

- The internal properties of creative elements differ from the rest of the network (the number of dimensions – degrees of freedom – of this difference increase as the complexity of the element grows).
- Creative elements mostly act as sources in directed networks.

Network topology

- Creative elements are preferentially connected to hubs with large centrality.
- Creative elements provide short cuts (decrease maximal shortest paths).
- Creative elements are in the overlaps of multiple modules maintaining approximately equal contact(s) with all modules.
- Insertion of a creative element to a network structure is predominantly occurring at positions where it induces a large decrease in the structural entropy of the network (in other words, usually, but not always, the position of creative elements is the least random position of all network elements giving them the most information content).

Network dynamics

- The internal structure of creative elements is flexible (the flexibility increases as the complexity of the element grows).
- Creative elements have more weak links than the average of the network (similarly to date hubs [40,42], they have a small number of links at a given time).
- Creative elements might be found among those elements that have a large dynamical importance as defined by Restrepo *et al.* [59].
- The behaviour of creative elements is the least predictable if compared with the predictability of other network elements (this is also related to their extremely large autonomy).

Crisis management

- Creative elements have a maximal influence on the development and maintenance of cooperation in the network by mediating the conflicts of network elements and modules (as a similar finding we recently proved that innovativity helps cooperation in spatial games of social conflict [60]).
- The number and importance (centrality) of creative elements transiently increase if the network experiences unexpected situations regulating the evolvability of the system.

continuous sampling of key information of the entire network and, therefore, has a central and integrating role in network function.

Network integration and creativity

If an element is accommodating key and representative information of a whole network it (i) might easily invent novel means to dissipate an unexpected, novel perturbation or (ii) might connect distant elements of the network with ease and elegance helping them to combine their existing knowledge to cope with the novel situation. The re-formulation of the original problem (by translating it from one distant element to another) and the generation of novel associations and novel solutions, flexibility, diver-

gence and originality are all well-known hallmarks of creativity.

Creative elements are the luxury of a network operating in 'business as usual' situations. Therefore, the number of creative elements is usually very small. This situation might be characteristic of most man-made networks, such as the internet, traffic networks or power-grids. However, creative elements are the 'life insurance' of complex systems helping their survival during any unexpected damage. Therefore, the number and importance of creative elements should increase if the complex organism experiences a fluctuating environment [35,41]. The adaptation of a large group of competing organisms to fluctuating environments can be described by the process of evolution. The capacity of an organism to generate heritable phenotypic variation is called evolvability [54]. Evolvability is a selectable trait, which assumes that it is modulated by specific mechanisms [15]. Summarizing the ideas here, I propose that creative elements have a crucial role in the development, inheritance and regulation of evolvability. Based on all the properties of creative elements outlined so far, several methods can be designed to test or refute their existence (Box 2).

Concluding remarks

In conclusion, I have provided here a description of creative elements as the network representation of active centres and showed that their properties are consistent with each other, with our common knowledge on creativity and with their suggested role to invent novel solutions, which integrates the knowledge of the whole network in response to unexpected situations. In addition, I note that in most networks the status of the creative element is, by itself, transient. Creative elements might be transformed into task-distributing party hubs [40,42] or bridges, which preferentially connect two modules with strong links or into problem-solving specialized elements. These transformations of creative elements usually happen after repeated stress, showing that the network 'learned' the novel response by re-organizing its topology and providing the first unusual, creative solution in a regular, reliable and highly efficient manner [55]. This 'commercialization of creativity' might explain why signalling networks have isoforms of their critical nodes [48], which might replace each other in a redundant manner when one became engaged continuously with a specific task.

Creative elements add random elements to network behaviour inducing an increase of noise. This is highly beneficial to a certain extent, but becomes intolerable if it exceeds a certain threshold. This threshold is high if the hosting network lives an individual life and often meets unexpected situations. However, the same threshold becomes low if the hosting network is part of a higher level organization that provides a stable environment. As examples of this, 'creative cells' (e.g. ones that occur after malignant transformation) might substantially disturb the regular functions of the hosting network and finally cause its disintegration then death; symbiotic organisms that became engulfed by another shed off a large section of their network variability [56], probably including most of their creative elements.

Here, so far, I have only mentioned creative elements. I note that the same concept might also apply to links. I hope that the description of creative elements and links will stimulate the long-range inter-modular connections [57] within, and the creative links between, many brains and will prompt further discussion and work in the field. Creativity, if combined with efficient learning, information processing and perseverance, leads to giftedness and talent – features that we certainly need in order to understand the evolution of complexity in the network context.
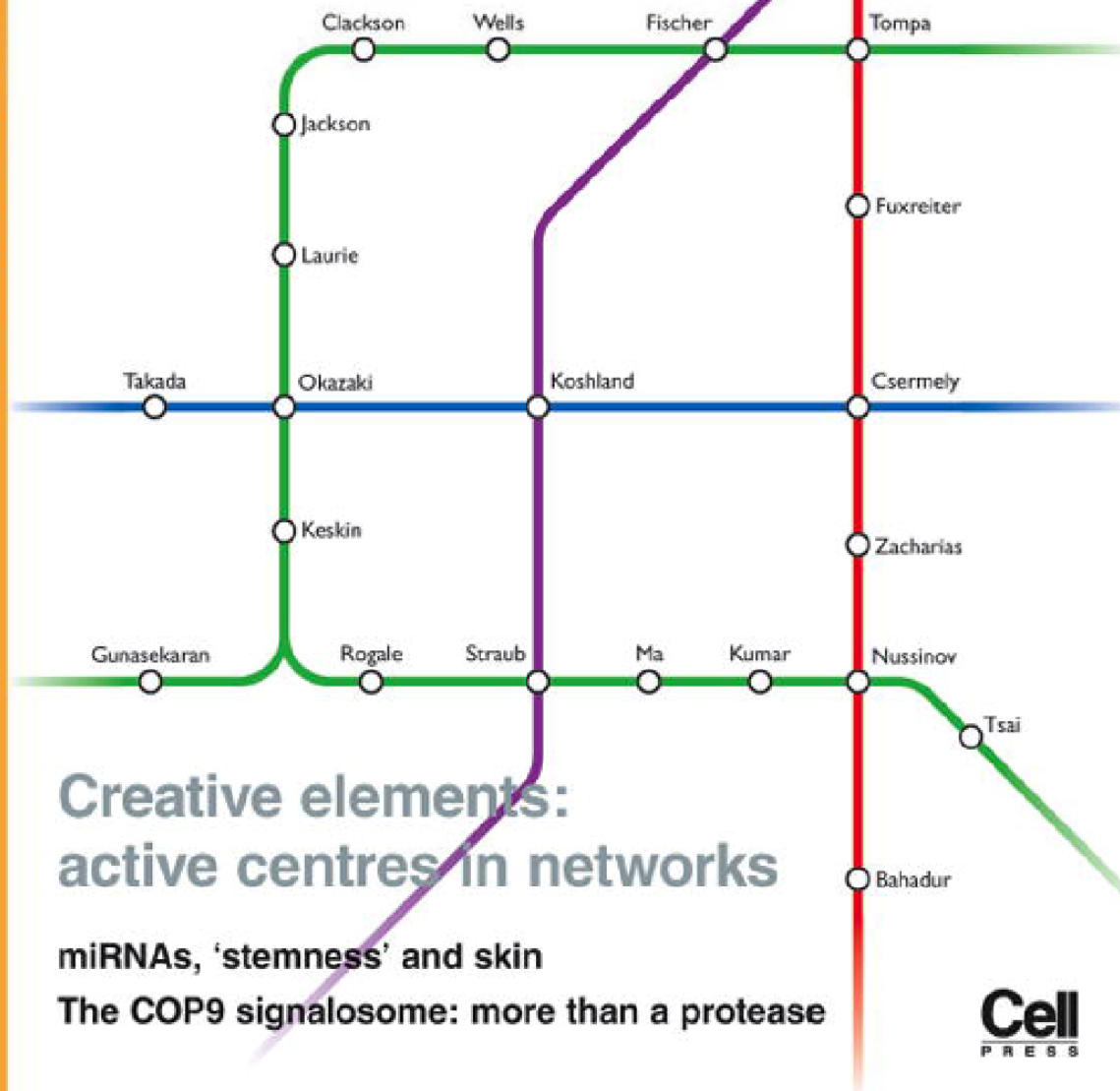
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