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More is different in real-world multilayer networks

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The constituents of many complex systems are characterized by non-trivial connectivity patterns and dynamical processes that are well captured by network models. However, most systems are coupled with each other through interdependencies, characterized by relationships among heterogeneous units, or multiplexity, characterized by the coexistence of different kinds of relationships among homogeneous units. Multilayer networks provide the framework to capture the complexity typical of systems of systems, enabling the analysis of biophysical, social and human-made networks from an integrated perspective. Here I review the most important theoretical developments in the past decade, showing how the layered structure of multilayer networks is responsible for phenomena that cannot be observed from the analysis of subsystems in isolation or from their aggregation, including enhanced diffusion, emergent mesoscale organization and phase transitions. I discuss applications spanning multiple spatial scales, from the cell to the human brain and to ecological and social systems, and offer perspectives and challenges on future research directions.

Networks are mathematical objects that are now routinely used to model the structure of complex physical, natural and artificial systems[1–3]. In contrast to regular graphs, complex networks provide a more accurate representation of the sparse and disordered interactions between units (also named nodes) that are typically observed in many systems. They are suitable for modelling either systems characterized by homogeneous connectivity, where the average number of connections is the same for all the network nodes[4], or systems exhibiting heterogeneous connectivity, characterized by a large number of units with a few connections and a few nodes (hubs) with an extraordinary number of connections, distributed in general like a power-law[5] or fat-tailed distribution. The latter class of network is rather ubiquitous[6–8], with emergent mesoscale organization into modules[9,10], hierarchies[11,12] and latent geometry[13]. Altogether, these features are responsible for a non-trivial interplay with dynamical processes on top of the units, such as synchronization[14,15], as well as for their function[16–19] and their response to internal failures and targeted attacks[20]. Some of the aforementioned dynamical processes have proven to be very useful for gaining insights about the functional organization[21] of complex networks, and about how they exchange information[22–24] and propagate signals and perturbations[25,26].

Remarkably, the framework of statistical mechanics has provided extremely powerful analytical and computational tools for studying interconnected systems, demonstrating how the structural features of empirical networks cannot be simply captured by the analysis of global properties that do not take into account information about the underlying connectivity[27–29].

Despite their success, the aforementioned methods are not suitable for dealing with the complexity of certain systems, such as those consisting of coupled or interacting subsystems. For example, this is the case for many infrastructural networks where the nodes in one system (such as stations in a communication network) depend on the activity of other nodes in another system (such as stations in a power grid) to operate. This class of interdependent networks began to attract the attention of physicists and engineers more than a decade ago[30], and efforts to understand their complexity and behaviour in response to structural perturbations have led to the discovery of unexpected critical phenomena, highlighting the emergence of fragility due to interdependence[31].

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BOX 1

Structure of a multilayer network

Illustration of the structural components of a multilayer network characterized by three distinct interacting layers (colour-coded), each representing a distinct connectivity pattern among nodes. The same node can exist in one or more layers. A state node is the unit with respect to a specific layer, whereas a physical node is the unit regardless of the layer. The state nodes of the same physical node are usually referred to as replicas. State nodes interact with other state nodes through intra-layer (within the same layer) or inter-layer (across distinct layers) edges, which can be directed or undirected.

Non-interconnected networks of networks (NoNs) are multilayer networks where state nodes are not connected by inter-layer edges. In this class of system, also known as edge-coloured multigraphs, or simply non-interconnected multiplexes, information across layers is instantaneously exchanged, without cost, from one state node to its replicas.

Interconnected NoNs are multilayer networks where state nodes are interconnected by inter-layer edges, encoding a cost for exchanging information among replicas. We have at least two classes of NoN here: (1) interconnected multiplexes, where units are homogeneous across layers (for example, all nodes are power stations), and (2) interdependent networks, also known as node-coloured graphs, where units are heterogeneous across layers (for example, nodes in one layer are power stations, nodes in another layer are autonomous systems, and so on). In interconnected NoNs, the way inter-layer edges connect layers defines a network of layers; in categorical multiplexes all layers are connected to each other, while in ordinal multiplexes, layers are connected according to some specified order (for example, temporal order, such as in the figure). Note that, in general, multilayer networks cannot be analysed as classical networks with communities (where each layer is associated to a community) without losing structural information. For non-interconnected and interconnected multiplex networks, representing a layer as a community would destroy the relationship between each physical node and its state nodes. For interdependent networks, this loss of information is mitigated, as each physical node has only one state node; nevertheless, the nature of nodes within a network with communities is the same (that is, nodes have the same colour across layers), whereas this is not the case for interdependent systems.

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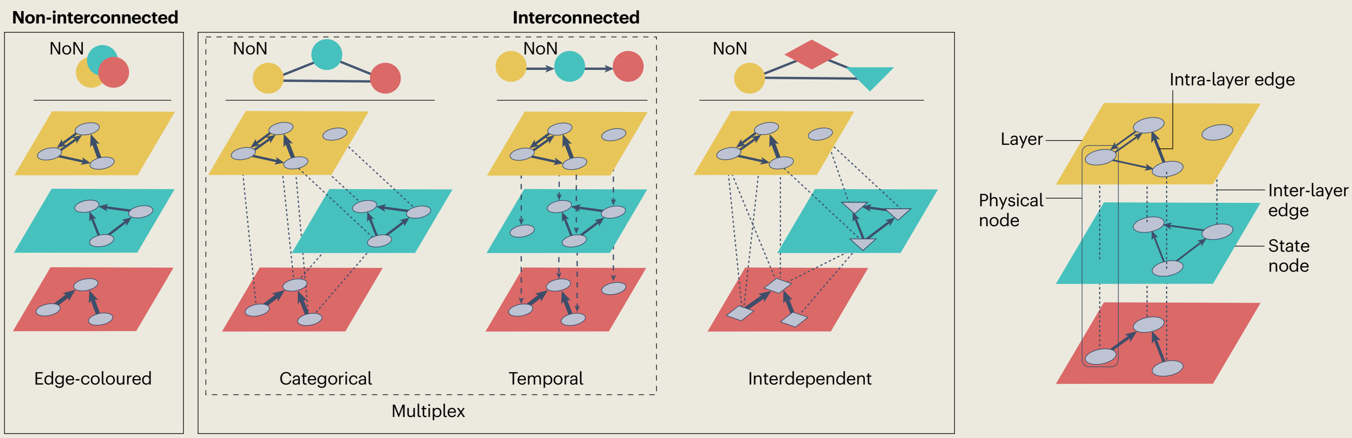

Over the same period it has been recognized that other empirical systems also do not live in isolation, but are part of a more complex web of coexisting interactions. For example, this is the case for biophysical and socio-ecological networks, where the same set of nodes—from molecules to cells and whole organisms —is often characterized by different relationships. For example, the same protein can physically interact with other proteins by means of activating or inhibitory relationships, building distinct and non-redundant connectivity patterns that coexist[32]. Similarly, neuronal connectivity can be synaptic, based on gap junctions and neuromodulators, providing multiple modes to neurons for exchanging electrochemical information[33]. Such distinct relationships among the same set of nodes define the distinct layers that characterize a multilayer network[34] (Box 1). I will describe in more detail these examples in the last part of this Review.

There are two fundamental challenges regarding the availability of data about multilayer systems[32,35–40]. The first is the necessity for a mathematical framework to cope with the new level of complexity that cannot be accounted for by the traditional models developed for classical, single-layered, networks. Such a framework should account for all the available information and use a consistent mathematical formalism. The second is the necessity to analyse the topological (for example, node centrality or mesoscale organization) and dynamical (for example, diffusion through the system or the critical response to internal failures and/or external perturbations) properties of these systems, similar in spirit to what has previously been done for classical networks.

It is thus not surprising that interest in systems of systems (or networks of networks—or multilayer networks—as they were referred to from the very beginning across distinct application domains) has increased rapidly, favouring novel, and sometimes unexpected, theoretical insights together with a plethora of practical applications. In this Review I examine the major research directions that naturally emerged in the early days of multilayer network science: modelling of the large-scale structure of coupled and time-varying systems (Large-scale structure of coupled and time-varying systems section), modelling and analysis of coupled dynamical processes and critical phenomena (Dynamical processes and critical phenomena section) and the structure and function emerging from mesoscale organization (Mesoscale organization, structure and function section). Nevertheless, it would be impossible to exhaustively review all the advances achieved during the past decade in those research directions and others. For this reason, I refer the interested reader to the first reviews[41–46] and dedicated textbooks[47–51] about these matters, as these cover in greater detail the many aspects that have had to be omitted from this short Review. I describe a broad spectrum of applications, from biomolecular to socio-ecological systems (Applications and outlook section), to demonstrate the success of the multilayer network paradigm in capturing the complexity of empirical systems spanning about eleven orders of magnitude in space, from 10^{-5} m to 10^{6} m. I conclude this Review with an outlook for the future of this fruitful research field, with the goal to emphasize its relationships with the most recent developments of network science (such as high-order mechanisms and behaviours, as well as geometry and information dynamics) as well as its impact in and beyond physics, such as in systems biology and systems medicine.

Large-scale structure of coupled and time-varying systems

Multiplexity and interdependency are two effective and ubiquitous ways to couple static subsystems with each other. When such subsystems are characterized by a disordered topology, with non-trivial connectivity patterns among their corresponding units, we have coupled complex networks, which are known as multiplex and interdependent networks, respectively. In the last section of the Review I will discuss a spectrum of empirical systems that can be suitably modelled in this way.

Context-dependent interactions characterize a specific layer where nodes interact through intra-layer edges. Often, it is useful to represent distinct types of interaction with distinct colours, with each colour identifying a unique layer. Similarly, nodes can interact with other nodes across distinct layers through inter-layer edges. Usually, a node in a specific layer is referred to as a state node to stress its dependence on the state, or context, of the interactions. The set of state nodes corresponding to the same entity is referred to as a physical node (Box 1).

Together, the units, the layers with their corresponding intra-layer connectivity patterns and inter-layer edges (which, when present, allow one to couple layers with each other according to a specific, non-trivial, network of layers) provide the fundamental constituents of a multilayer network (Box 1). Note that multilayer structures should not be confused with multilevel networks. In multilayer networks, the units can be either homogeneous (for example, proteins in a multiplex system) or heterogeneous (for example, power stations and communication servers, as in interdependent networks). In multilevel networks, units at the micro level (for example, proteins) are related to macro levels (for example, a whole cell or a population) by cross-level interactions known as the meso-level structure, with a hierarchical relationship between units that is not fully captured by multilayer networks.

The absence or presence of links between layers is the first important topological discriminator between two large classes of model: non-interconnected networks of networks (NoNs) and interconnected NoNs (Box 1).

When interconnections cannot be defined explicitly from the data, layers are implicitly interconnected. To measure topological features (such as node centrality and mesoscale organization) and to model dynamical processes (such as diffusion or synchronization), it is necessary to define vector-like objects like multilinks[52] to account for all the available structural information. Conversely, when interconnections can be defined from the data and layers are explicitly interconnected, tensor-like objects are needed[34], and additional exotic connectivity patterns are allowed (for example, links between different state nodes corresponding to distinct physical nodes). The presence of interconnectivity (either implicit or explicit) is so important to determine the behaviour of a system, for example, in terms of phase transitions in response to external perturbations or internal failures, that a different mathematical representation is required to deal with this class of system.

Given a non-interconnected multiplex system characterized by a set of networks $\{G^{(1)}, G^{(2)}, \ldots, G^{(L)}\}$ defined on the same set of N physical nodes, where each layer α ($\alpha = 1, 2, \ldots, L$) is mathematically represented by an adjacency matrix $A_{ij}^{(\alpha)}$ ($i, j = 1, 2, \ldots, N$; the entry is positive if there is a direct relationship between nodes i and j, and is zero otherwise), it is possible to describe the whole system by a three-dimensional hypermatrix, which can be imagined as an array of adjacency matrices that define coexisting interactions or multilinks[52–55]. The complexity that can be modelled by this class of models is schematically shown in the left panel of Box 1.

This representation is not sufficient to capture a higher level of complexity, such as in interconnected multiplex systems where state nodes of the same physical node are connected to each other. This case can be captured by two three-dimensional hypermatrices: one to represent intra-layer connectivity and one to represent inter-layer connectivity[35]. Remarkably, this representation is suitable for modelling either static networks that are non-trivially coupled with each other or time-varying networks where inter-layer connectivity encodes the arrow of time. In Box 1 this complexity is schematically shown by categorical and ordinal inter-layer connectivity, respectively. It is worth mentioning that this representation is sufficient also for interdependent networks[31], although it is rarely used for this purpose.

Nevertheless, the difference between non-interconnected and interconnected multiplex networks goes beyond their mathematical representation. In edge-coloured multigraphs, the information between a system's unit (that is, a node) in one layer and its replicas in other layers is exchanged instantaneously. For example, an individual in a social network who becomes aware of news through one social platform (a layer) can be considered aware of the same information across the other social platforms (the other layers). In categorical multiplex networks, the presence of inter-layer links allows us to encode physically relevant information that cannot be instantaneously spread across replicas. A typical example is a multimodal transportation system over a geographic area: connections between the same spatial patches (that is, the nodes) can be suitably used to encode the cost for switching between modes (that is, the layers). For example, the weight of inter-layer links can be used to encode the cost or the time required to switch between a bus stop and a rail station in the same geographic area, or between two different tube lines in the same station.

It has been shown that one can avoid separately specifying intra- and inter-layer connectivity with distinct hypermatrices by using rank-4 tensors[34]. Tensors are objects that are richer than hypermatrices, defined by the way they transform under a change of coordinates. In the context of complex networks, the choice of a set of coordinates is arbitrary, but if each node i is assigned to a canonical vector $\mathbf{e}(i) \in \mathbb{R}^N$, it is possible to represent the corresponding adjacency relationships by a linear combination of tensorial products of the canonical vectors. In the case of multilayer systems, a similar argument has been used to define the multilayer adjacency tensor $M_{j\beta}^{i\alpha}$ in $\mathbb{R}^{N\times L\times N\times L}$, whose entries represent interactions between node i in layer α and node j in layer β, with $i, j = 1, 2, \ldots, N$ indicating nodes and $\alpha, \beta = 1, 2, \ldots, L$ indicating layers.

This tensorial formalism allowing the development of a language turned out to be very natural and convenient for generalizing several topological indicators, such as centrality measures, from classical networks to multilayer ones[56], providing an elegant framework and complementing existing efforts in this direction[39,57–60]. Centrality, in fact, plays a special role in the microscopic analysis of a system, by measuring the importance of a node according to some criterion that can be either structural (for example, the number of outgoing connections) or functional (for example, the probability to find a walker on it that moves via the shortest paths among other nodes in the network). Remarkably, it is not possible to estimate multilayer centrality by combining the centralities calculated in each layer individually or by using the centrality calculated in the single-layer representation of the system. This has been proven rigorously[49,56].

The careful reader might wonder under which conditions the application of multilayer network models is appropriate for the analysis of empirical systems. In other words, when should one model a system as a multilayer network instead of a set of non-interacting networks? One plausible criterion is when the coupling between the layers is not strong enough with respect to intra-layer connectivity, which suggests that the properties of the whole system can be obtained from a linear combination of the properties of each layer in isolation, or from some other type of aggregation. For a specific set of interconnected multiplex random networks it has been shown that an abrupt topological transition separates two distinct regimes: one in which layers are structurally decoupled and can be treated as effective independent subsystems, and one in which multiplexity emerges and the whole system behaves as a unique network[61]. In fact, multilayer effects cannot be obtained from reduced representations of the system. However, it is not easy to quantify when this is the case, and sophisticated approaches—such as structural and functional reducibility, as discussed in the section Mesoscale organization, structure and function—have been proposed to sub-optimally solve the problem.

In the next section I will move beyond structure and describe multilayer dynamical processes. Because the function of a system depends on both its structure and its dynamics, I dedicate a separate section to mesoscale organization, which can be either structural or functional (Mesoscale organization, structure and function section).

Dynamical processes and critical phenomena

The study of the dynamics of and on complex networks is one of the most explored topics in complex systems, as it offers insights into a wide spectrum of processes, including network growth, temporal variations, diffusion and percolation. In this section I discuss how the multilayer structure is responsible for a rich landscape of complex phenomena of interest. I opt not to go through all the details, but instead provide a general overview of the dynamics that have led to novel or unexpected collective and critical behaviours during the past decade of research. Nevertheless, the careful reader should be aware that some results covered here might be obtained under specific assumptions about either the topology or the dynamics. For example, predictions from some models are obtained under mean-field approximations and can break down for non-random networks. For further details, please refer to the corresponding studies.

Another topological feature responsible for specific dynamical behaviours concerns the correlations between different layers. As a practical example, let us focus on a widely used microscopic structural indicator—the node's degree k—which accounts for the number of its connections. By indicating with k_i^{α} the degree of node i in layer α and with k_j^{β} the degree of node j in layer β, one measures (1) intra-layer correlations (or, in this specific case, degree–degree correlations within layers) if $P(k_i^{\alpha}, k_j^{\alpha}) \neq P(k_i^{\alpha})P(k_j^{\alpha})$, where $P(\cdot)$ denotes a probability measure, and (2) inter-layer correlations (or, in this specific case, degree–degree correlations across layers) if $P(k_i^{\alpha}, k_i^{\beta}) \neq P(k_i^{\alpha})P(k_i^{\beta})$ (ref. 62). Similar definitions apply to other descriptors, from the probability of a link between the same pair of node replicas across layers (that is, link overlap) to more complex indicators accounting for link weights, directionality and other topological features[63,64]. Nodes' degrees across layers can correlate positively or negatively, denoting assortative and disassortative correlations, respectively. In assortative networks, hubs in one layer are likely to be hubs in other layers, whereas disassortative systems are characterized by the opposite behaviour. Empirical multilayer networks show a rich set of layer–layer correlations, including mixed ones where both assortative and disassortative pairs of layers coexist[65], a feature that can be partially explained by their evolution dynamics[53,66]. Note that structural correlations have a non-negligible effect on the unfolding of dynamics, and the literature on this is so vast that it would deserve a separate dedicated review. For example, in a highly assortative system, the unfolding of evolutionary games leads to collective behaviour that is independent of their parameters, a phenomenon known as topological enslavement[67], whereas disassortative multiplex networks favour synchronizability[68].

In the following I will discuss (1) network growth and the time-varying structure of a multilayer system, (2) single dynamical processes unfolding on static multilayer structures, (3) coupled dynamical processes unfolding on static multilayer networks and (4) multilayer percolation and cascading processes. I refer the reader to the specific studies for further details about the limitations of a specific modelling set-up or the impact of layer–layer correlations.

System growth dynamics

One of the simplest dynamics is network growth, where an initial small core of units increases in time by adding new nodes and edge stubs to the system according to some deterministic or stochastic mechanisms, which define attachment rules. Growing networks are ubiquitous, from biomolecular interactions to transportation networks. A striking difference between monolayer and multilayer networks is that a new node has a unique arrival time in the former, whereas it has an arrival time for each layer separately in the latter, mimicking edge formation across distinct and coexisting contexts. Another distinctive factor is in the choice of the subset of nodes to which the newly arrived node will attach. Following the paradigmatic preferential attachment rule[5], where a node i is chosen with probability proportional to some function $f(k_i)$ of its degree k_i, in the multilayer context this functional dependence can be extended to the degree of replicas. For non-interconnected multiplex networks, it has been shown that navigation for earlier nodes is facilitated within a single layer, whereas later nodes have to turn to multiple layers to reach a target, with performances depending on the scaling of the growth[53,55,66].

Time-varying systems

Another class of dynamics of interest for biological, social and communication networks (for example) is represented by edges among a (fixed) set of units appearing and disappearing over time[69–71], as in the correlated activity of different areas of the human brain[72] or in face-to-face human interactions[73]. The multilayer framework is flexible enough to allow one to model the observed structural changes as follows. First, fix a time window, defining the resolution of the network model, then consider all the edge stubs that exist within a specific time interval t_k ($k = 1, 2, ..., T$) to define a monolayer network $G^{(k)} = G(t_k)$, providing a temporal snapshot of the system's structure within a specific time interval. Second, each temporal snapshot can be assumed as representing a layer: the set of all snapshots defines a multilayer network. One can use different approaches to couple the layers, either by using an edge-coloured or an interconnected multiplex representation. With the latter, it is possible to explicitly encode information about the arrow of time. A direct application of this fundamental idea has been proposed in terms of dynamical processes on top of time-varying networks, showing that it is possible to map the interplay between temporal networks and epidemic spreading dynamics into a multilayer network model, allowing one to analytically derive the epidemic threshold[74], that is, the critical population density separating the disease-free (absorbing) regime from the one where a fraction of the population is infected (active state). Several other applications have used a similar approach, either directly or indirectly, to show that node centrality in temporal networks might be very different from centrality estimated from a network obtained by aggregating all interactions[60,75], and that temporality provides advantages such as faster pathways to controlling a system's states[76]. The reader more interested in time-varying systems is referred to the dedicated review in ref. 77.

Single dynamical processes on top of the system

Instead of considering dynamical changes in a multilayer structure, a whole class of models is devoted to study the unfolding of a dynamical process on static multilayer topologies. For example, this is the case for synchronization dynamics, where nodes are oscillators[78–80] and multilayer stability can be induced even if layers, individually, induce unstable synchrony[81]. Similarly to percolation (see later), synchronization is an extensively studied dynamical process[82–84] characterized by phase transitions. In ref. 85 it has been shown that a phenomenon known as explosive synchronization—where oscillators abruptly transit from incoherence to phase-locking—can occur in adaptive and multilayer networks, even in the absence of specific microscopic correlations relating oscillators' natural frequencies with their degrees or coupling strengths. Such a behaviour (which was unexpected from existing knowledge) emerges when a fraction of nodes from each layer forms inter-layer dependency links: this fraction, for which adaptation dynamics is effective, controls the passage from a first- to a second-order transition. Moreover, it has been shown recently that even consecutive explosive transitions can be observed in multilayer systems, when a network in one layer coupled to another layer plays the role of an environmental system featuring approximate synchronization[86] (Fig. 1a–j).

Another dynamics of great interest[87] is cooperation, a collective behaviour that emerges despite the fact that the principle of Darwinian evolution (roughly speaking, the survival of the fittest) is expected to lead to competition. It is usually modelled in terms of evolutionary dynamics, where nodes are rational agents that compete or cooperate for a given payoff. In multilayer systems[44] it has been shown that cooperative behaviour can be effectively regulated by strategic incoherence in social dilemmas[88], and the enhancement of cooperation emerging only under peculiar topological correlations between layers[89] and asymmetric subpopulations[90] has also been reported.

Finally, it is also instructive to discuss another example of dynamics belonging to the class of single dynamical processes—multilayer random walks. If $\pi_{i\alpha}(t)$ indicates the probability to find a walker at time t in state node i of layer α, then the master equation accounting for jumps within layers and switch between layers reads

$$\pi_{j\beta}(t+1) = \underbrace{\tau^{j\beta}_{j\beta}\pi_{j\beta}(t)}_{\text{stay}} + \underbrace{\sum_{\substack{\alpha=1\\ \alpha\neq\beta}}^{L} \tau^{j\alpha}_{j\beta}\pi_{j\alpha}(t)}_{\text{switch}}$$
$$+ \underbrace{\sum_{\substack{i=1\\ i\neq j}}^{N} \tau^{i\beta}_{j\beta}\pi_{i\beta}(t)}_{\text{jump}} + \underbrace{\sum_{\substack{\alpha=1\\ \alpha\neq\beta}}^{L}\sum_{\substack{i=1\\ i\neq j}}^{N} \tau^{i\alpha}_{j\beta}\pi_{i\alpha}(t)}_{\text{switch and jump}},$$

where $\tau^{i\alpha}_{j\beta}$ is the transition probability to move from state node (i,α) to state node (j,β). By introducing the supra-vector $p_{i\alpha}(t)$ and the transition tensor $T^{i\alpha}_{j\beta}$, the above equation can be elegantly cast into

$$p_{j\beta}(t+1) = T^{i\alpha}_{j\beta}p_{i\alpha}(t)$$

where the Einstein summation convention is used. Using a similar approach, it is possible to write tensorial equations for more complex processes, such as epidemic spreading[91]. Diffusive processes have proven extraordinarily useful for studying properties emerging as a result of the multilayer structure. For example, it is possible to couple layers to induce a faster diffusion through the multilayer system than in each single layer separately[92,93]. If the layers are directed networks, it is possible to optimally couple them to reach a faster diffusion at an intermediate degree of coupling rather than when the layers are fully coupled, as in the undirected case[94]. Different flavours of random walks, where probabilistic rules are more sophisticated than the aforementioned example, have been used to study the navigability of multilayer networks[95] and their latent diffusion geometry[96], showing qualitative and quantitative differences from monolayer networks. Recently, Markovian dynamics has been used to reconstruct layers that could not be directly observed, and this has found application to RNA polymerases at the single-molecule level[97].

Coupled dynamical processes on top of the system

There are many empirical settings where multiple dynamical processes unfold on a multilayer network. If such processes are independent of each other, they can be reliably studied in isolation as single processes. However, they are often interdependent—that is, the unfolding of one process has a direct effect on the unfolding of the other processes—and lead to non-trivial collective phenomena.

For example, neural systems function by combining a variety of physical, chemical and electrical processes, including blood flow, oxygen and neural electrochemical exchanges. In this setting, a possible approach is to model neural activity by means of Kuramoto oscillators and the energy transport by a biased continuous-time random walk, coupling the two processes by means of a control parameter. Surprisingly, the distribution of random walkers changes from homogeneous to heterogeneous depending on the coherence of the synchronization dynamics, even if the underlying topology does not display heterogeneities. Such an emerging distribution is responsible for the appearance of a bistable phase and a tricritical point[98] (Fig. 1j).

Another class of systems requiring coupled dynamics comprises contagion processes. On the one hand, a pathogen spreads through social contacts, but on the other hand, an individual's behaviour might change depending on their awareness about a epidemic[99,100]. The interdependence between the two inhibiting spreading processes, namely information diffusion and epidemic spreading, induces non-trivial relationships between the corresponding parameters of the dynamics, which become intertwined and lead to the emergence of a metacritical point[99] separating two distinct regimes that characterize endemic and non-endemic phases of a disease (Fig. 1k). Other examples include the explicit effects of social integration or segregation coupled to epidemic spreading[101] or even interacting epidemics, where the presence of one pathogen might hinder or favour the presence of another pathogen[102], leading to emerging critical behaviour where the critical threshold of one process affects the critical threshold of the other[45].

Other dynamical processes can be coupled together in a similar manner, such as those related to distinct opinions[103], distinct evolutionary dynamics that enhance cooperation[104], or evolutionary game dynamics and social influence[105]. A general framework allowing one to understand the critical properties of a range of interdependent and competitive processes, from synchronization to epidemics, has recently been proposed in terms of heterogeneous mean-field theory, providing a unifying perspective on a variety of collective phenomena, from multistability to hysteretic behaviours with abrupt transitions that are either hybrid or explosive[106].

Finally, it is worth mentioning that even two interdependent dynamical processes, defined on top of a single network, can also be investigated in terms of two coupled dynamics unfolding on an adequately multilayer network where layers have the same structure. This approach has been used to characterize the critical behaviour of an Ashkin–Teller model in terms of two Ising spin models, unravelling rich phase-transition patterns in opinion dynamics[107]. A similar approach could provide novel insights regarding the critical behaviour observed in other complex systems, such as the one where oscillators have costly interactions[108] or where, when coupled to an evolutionary dynamics, a double explosive transition to cooperation is observed when only cooperative oscillators contribute to synchrony[109] (Fig. 1l). Another exciting perspective is that such a framework could facilitate the generalization of single-layer models of interdependent dynamics to multilayer models.

Percolation and cascading processes

The aforementioned dynamics are not the only processes exhibiting critical behaviour in multilayer systems, as this has also been widely

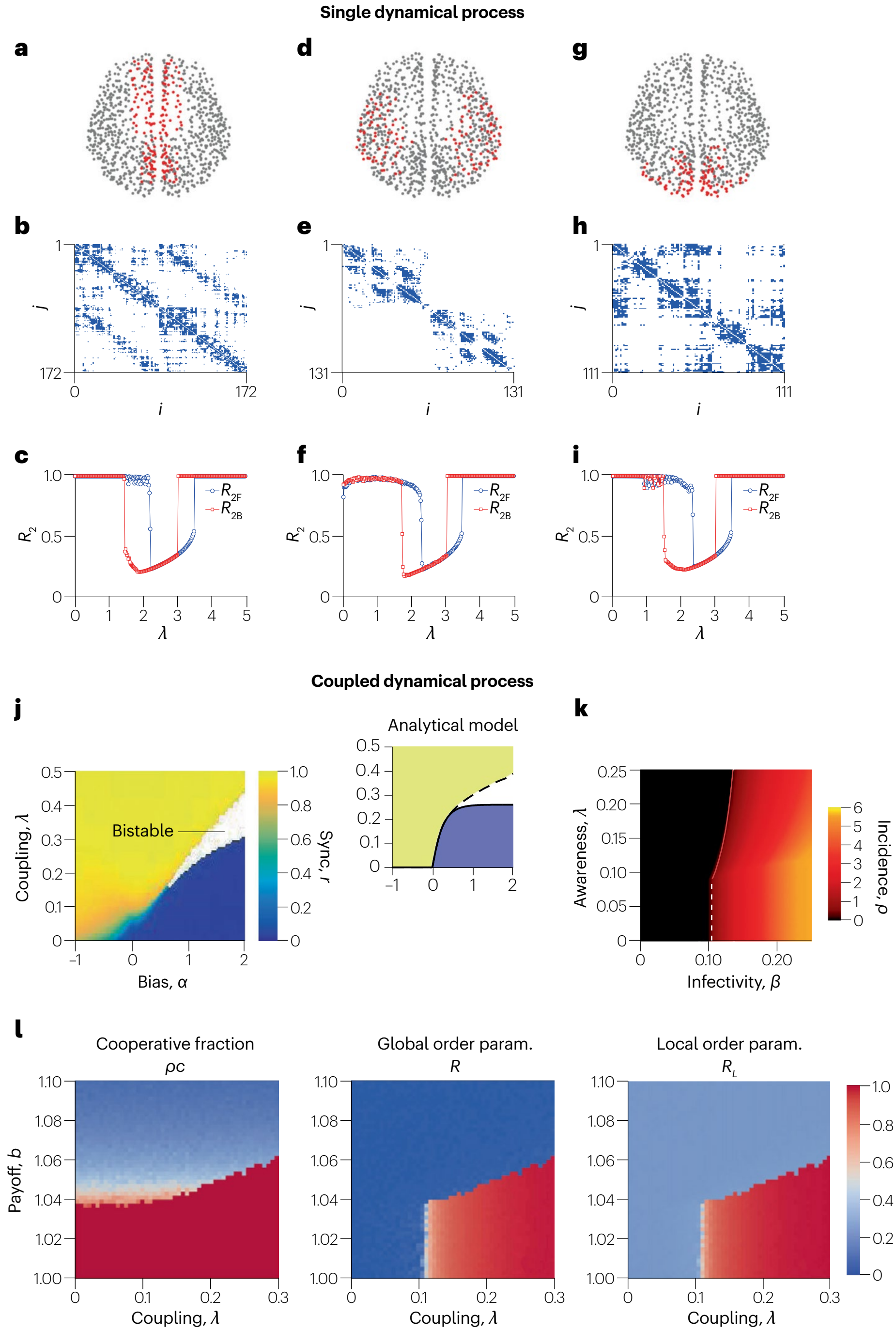

Fig. 1 | Synchronization dynamics in multilayer networks. a–i, Consecutive explosive synchronization observed on the medial default mode ($N = 172$, **a–c**), ventral temporal association ($N = 129$, **d–f**) and visual ($N = 111$, **g–i**) subsystems of a human brain network[86]. Top: visual representation of the underlying subsystem in the brain. Middle: corresponding adjacency matrices, where i and j indicate nodes. Bottom: synchronization order parameter (R_2) as a function of λ, denoting the strength of the coupling between layers, where blue circles and red squares distinguish results obtained during forward (F) and backward (B) transitions, respectively. **j**, Explosive synchronization induced by intertwining a Kuramoto dynamics, governed by coupling strength λ in one layer, with a biased random walk, governed by bias α in another layer. The collective behaviour is quantified by the order parameter r. The small inset shows the collective behaviour expected from an analytical model[98]. **k**, Interplay between disease-inhibiting processes, such as the spreading of a pathogen, governed by infectivity β in one layer, and the diffusion of awareness about it, governed by β in another layer[99], or the spreading of a disease that can impair the spreading of another one[102]. The collective behaviour is quantified by the prevalence ρ. **l**, Cooperation dynamics, governed by payoff b, coupled to Kuramoto dynamics, governed by coupling strength λ (ref. 109). Interdependent dynamical processes on a single network, such as this one, can also be understood in terms of multilayer networks where layers have the same topology and where distinct coupled dynamics unfold (see main text). Panels reproduced with permission from: **a–i**, ref. 86 under a Creative Commons license CC BY 4.0; **k**, ref. 45, Springer Nature Ltd; **l**, ref. 109, under a Creative Commons licence CC BY 4.0. Panel adapted with permission from: **j**, ref. 98, APS.

studied with respect to other classes of dynamical process, similar to what has been done for monolayers[28]. Compared to classical networks, a broader set of phenomena characterizes the critical properties of multilayer systems depending on their topology (for which there is no single-layer counterpart) in response to disruptions of the units and edges or the development of cascade failures (Fig. 2).

In monolayer networks, the removal of nodes or edges according to a specific protocol—which can be either stochastic (thus modelling

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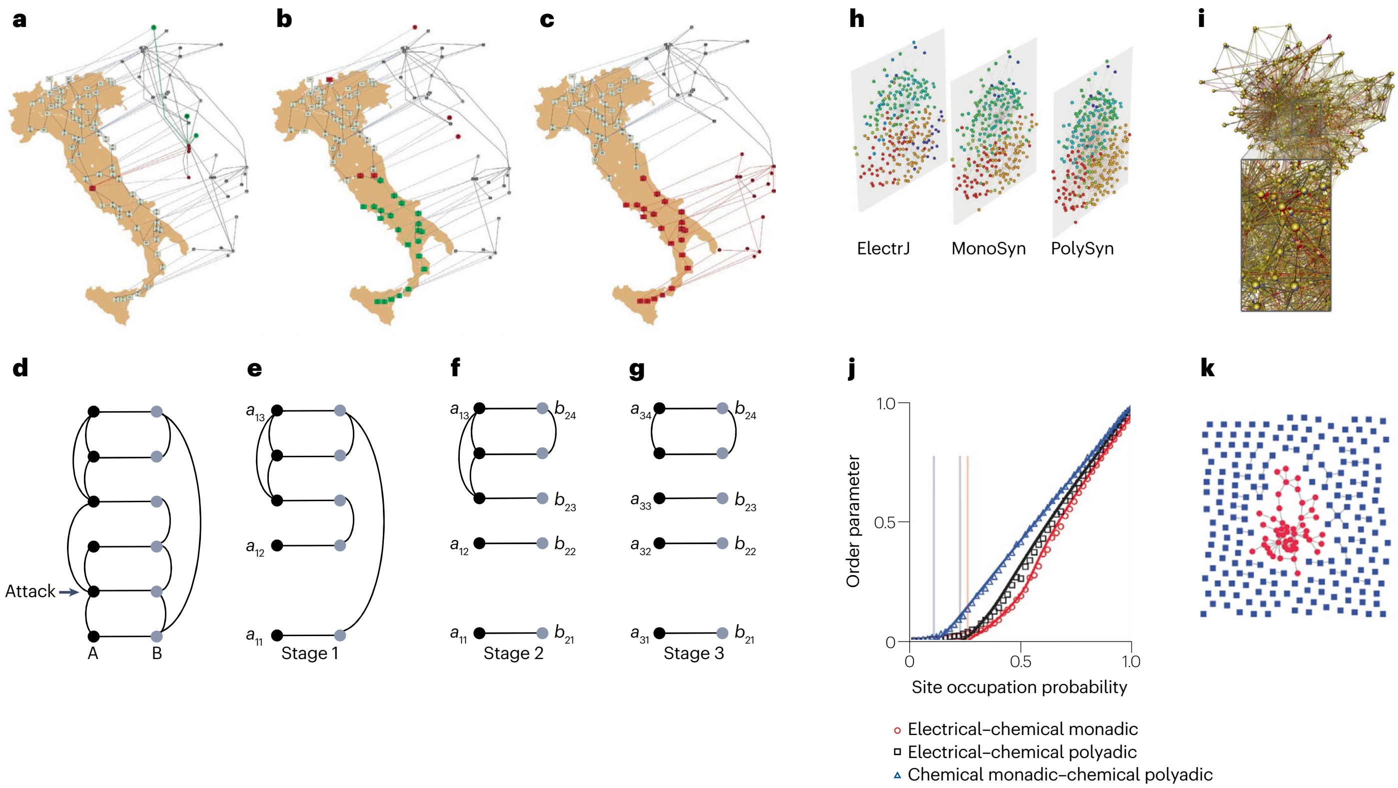

Fig. 2 | Cascade failures and percolation in multilayer networks. **a**–**c**, Evolution of a cascade of failures during a blackout in an interdependent system consisting of a power network (on the map) and an Internet network (shifted above), both spatially embedded on the Italian territory. **d**–**g**, Model sketch of the cascade failure process, from the starting configuration (**d**) and through stages 1–3 (**e**–**g**). **h**, Multiplex representation of synaptic junctions in the nematode *Caenorhabditis elegans*. Each layer represents a distinct connectivity pattern—electric (ElectrJ), chemical monadic (MonoSyn) and polyadic (PolySyn)—among the 279 neurons of the nematode. **i**, Alternative visualization of the multiplex in **h**, with edges coloured according to the type of connection they encode. **j**,**k**, Percolation diagram of the multiplex in **h** (**j**), showing how the probability that a node belongs to the largest cluster of mutually connected nodes (y axis) is affected by site occupation probability (x axis), and that the system is characterized by the existence of a core of neurons and synapses (**k**) able to hinder an abrupt percolation transition. Panels reproduced with permission from: **a**–**g**, ref. 31, Springer Nature Ltd; **j**,**k**, ref. 180, Springer Nature Ltd. Panels adapted with permission from: **h**,**i**, ref. 181 under a Creative Commons licence CC BY 4.0.

random failures) or deterministic (thus modelling targeted attacks)—defines site and bond percolation processes, respectively. Here, the control parameter is the fraction of removed nodes or edges, and the order parameter is the size of the largest connected component. At the critical threshold, the network disintegrates and a continuous phase transition is observed. Surprisingly, in multilayer systems, the presence of interdependencies between layers changes the nature of percolation to discontinuous, making mitigation and recovery strategies more difficult to implement[31,110–112] and shedding light on the fragility of such networks[113,114], which grows with increasing number of layers. The conditions required for the percolation transition to be of first order or second order have been analysed in detail[110,115], and there is evidence for the existence of a critical amount of inter-layer connectivity controlling for the chance that a system will experience a cascading failure spanning more than half the network[116]. Nevertheless, the spectrum of critical behaviours is broad, depending in some cases either on the specific topology of the layers[117] or on their spatial constraints[118].

In the case of multiplex networks (Fig. 2), the behaviour might be dramatically different, because a positive fraction of nodes existing in multiple layers simultaneously (a feature usually referred to as node multiplexity) introduces an amount of topological redundancy that should prevent abrupt transitions[95]. By studying the behaviour of the order parameter as a function of node multiplexity, it has been shown that multiplex networks must be characterized by a certain level of multiplexity to experience a discontinuous transition[119]. The average link overlap, quantifying the fraction of edge stubs that are present across layers between node replicas of the same pair of physical nodes, provides another interesting control parameter with which to study the critical behaviour of multiplex systems. It has been shown that it is possible to tune the phase transition from hybrid first order to a continuous one by adequately tuning the link overlap above or below a critical threshold[120,121]. The role of link overlap also becomes relevant in other contexts, such as optimal percolation—that is, the problem of identifying the minimal set of nodes that, once removed from the network, will lead to non-extensive disconnected clusters. This is still under active investigation[122,123].

An interesting research direction concerns the mechanisms or strategies that can make multilayer networks robust to structural or dynamical perturbations. Despite their predicted fragility, empirical interdependent networks appear rather stable. How is this possible? In fact, if network hubs are responsible for most of the inter-layer connectivity, and if the inter-layer correlations are moderately assortative (that is, nodes with similar degree connect to each other across layers), then the NoN is robust to failure[38]. After failure, it is also relevant to devise an optimal strategy for repairing the system. It has been shown that, in specific settings of two interacting networks, it is possible to identify critical points, complex hysteresis loops and forbidden transitions, with triple points playing a crucial role in optimal repairing protocols[124].

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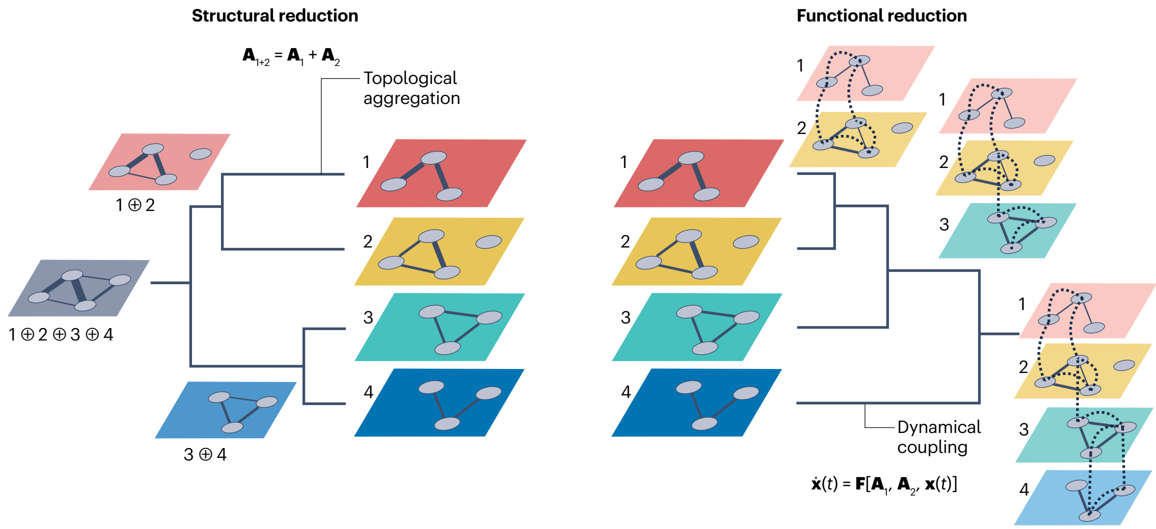

Fig. 3 | Coarse-graining a multilayer system. Finding the mesoscale structure of a system, characterized by the presence of clusters, allows one to coarse-grain it with respect to nodes. A complementary approach is to coarse-grain with respect to layers, to understand if partial or full aggregation of layers (mathematically represented by their adjacency matrices, **A**) still provides a satisfactory model without loss of information. In fact, the multilayer network representation of a complex system can have redundant layers that do not add topological or functional information. One technique used to reduce dimensionality is to aggregate the constituent layers according to similarities in connectivity (left) or dynamical (right) patterns. In the latter, the procedure depends on some dynamical process of interest, where the state of the network ($\mathbf{x}(t)$) changes over time according to some rules ($\mathbf{F}$). Such similarities have been quantified by means of network information entropies estimated from the density matrix representation of the system and the corresponding von Neumann entropy[22,32]. Figure reproduced with permission from ref. 182.

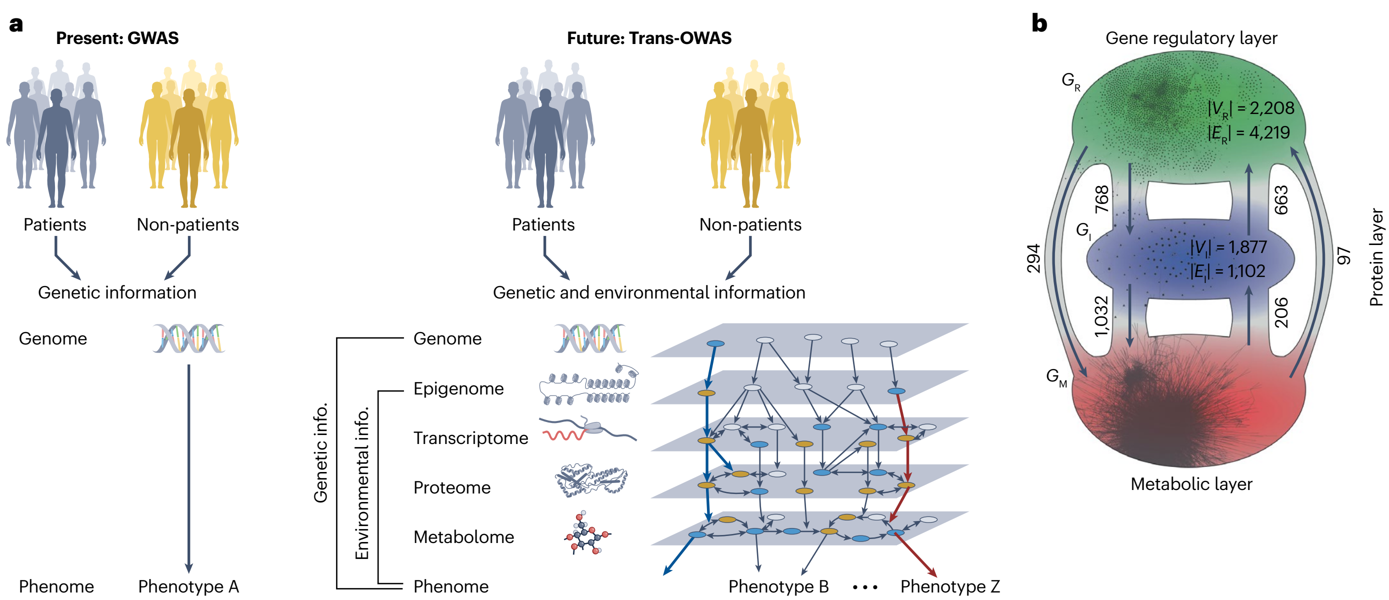

Fig. 4 | Large-scale structure of biomolecular interactions. a, Genetic information collected from healthy and unhealthy groups is generally used to capture information about macroscopic effects, such as a disease. However, multi-omics makes available richer datasets (for example, genome-wide association studies (GWAS) and openness weighted association studies (OWAS)) that can be integrated within a multilayer network, where layers also encode interactions at the scale of the transcriptome, the proteome and the metabolome[183]. **b**, An interdependent network consisting of a genetic regulatory layer connected to a metabolic layer, providing a sketch of the domain organization of the integrative *Escherichia coli* network[150].

I devote the next section to describing an emergent feature of multilayer systems—their mesoscale organization—which is responsible for how they operate and function.

Mesoscale organization, structure and function

Microscopic analysis at the level of units is crucial for understanding the detailed organization of a multilayer structure. Although it is not possible to describe in detail the many works devoted to microscopic analysis, it is worth mentioning the studies related to organization in multilayer clustering[125–127] and multilayer motifs[128–131], where the presence of multiple interactions across layers allows one to detect the non-trivial organization of nodes in triplets, quadruplets and so on, which has no counterpart in single layers in isolation, or is diluted in the aggregated representation.

Besides microscopic analysis, it is relevant to analyse the multilayer structure at larger scales. In monolayers, the corresponding

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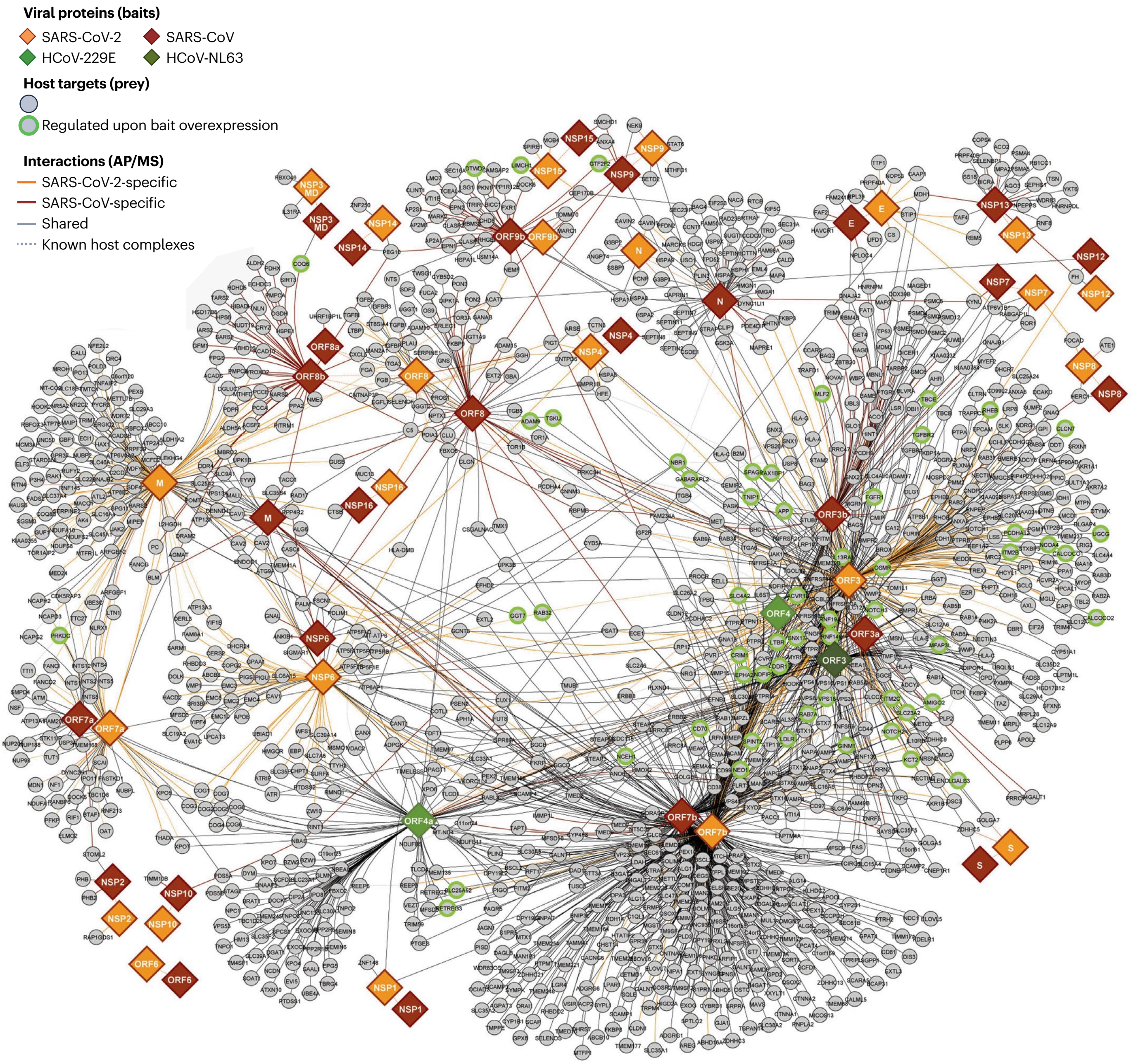

Fig. 5 | Protein–protein interactions network. Interactors are for SARS-CoV-2, SARS-CoV, HCoV-NL63 and HCoV-229E proteins or baits. Links represent virus-specific or virus-shared relationships, captured by a non-interconnected multiplex network model[184].

structures are named modules or communities[9,10]; these allow one to identify the underlying mesoscale organization and play an important role in our understanding of a system, as they may naturally correspond to its functional units. Examples include multilayer protein interaction networks, where modules often correspond to core disease-relevant pathways[132], or multilayer food networks, where modules identify food trade communities of countries that do not trivially depend on economic size or income[133].

Detecting modules in a system allows us to reduce the number of degrees of freedom to be considered for the analysis or description of a generative model. Operationally, it is necessary to define a cost function that accounts for a specific definition of what a module is and use heuristic approaches to solve a computationally complex problem. A variety of cost functions have been proposed, including considering connectivity density within and across modules[34,35,134,135], exploiting dynamical processes and information theory[136], Bayesian inference[137–139] and tensor decomposition[140]. Remarkably, modules identified by such methods can be drastically different from those identified by aggregated (with respect to layers, time or both layers and time) representations, and only approaches tailored to exploit all the available information are able to detect communities of nodes that play critical functional roles and would be otherwise invisible[141,142].

Another problem of interest, closely related to the detection of modules, is that of dimensionality reduction of a multilayer network. Detectability limitations have been investigated if layers are aggregated together, for example, by summing the corresponding adjacency matrices[141,142]. Lowering the number of layers by aggregation to reduce the complexity of a system's description is another approach to

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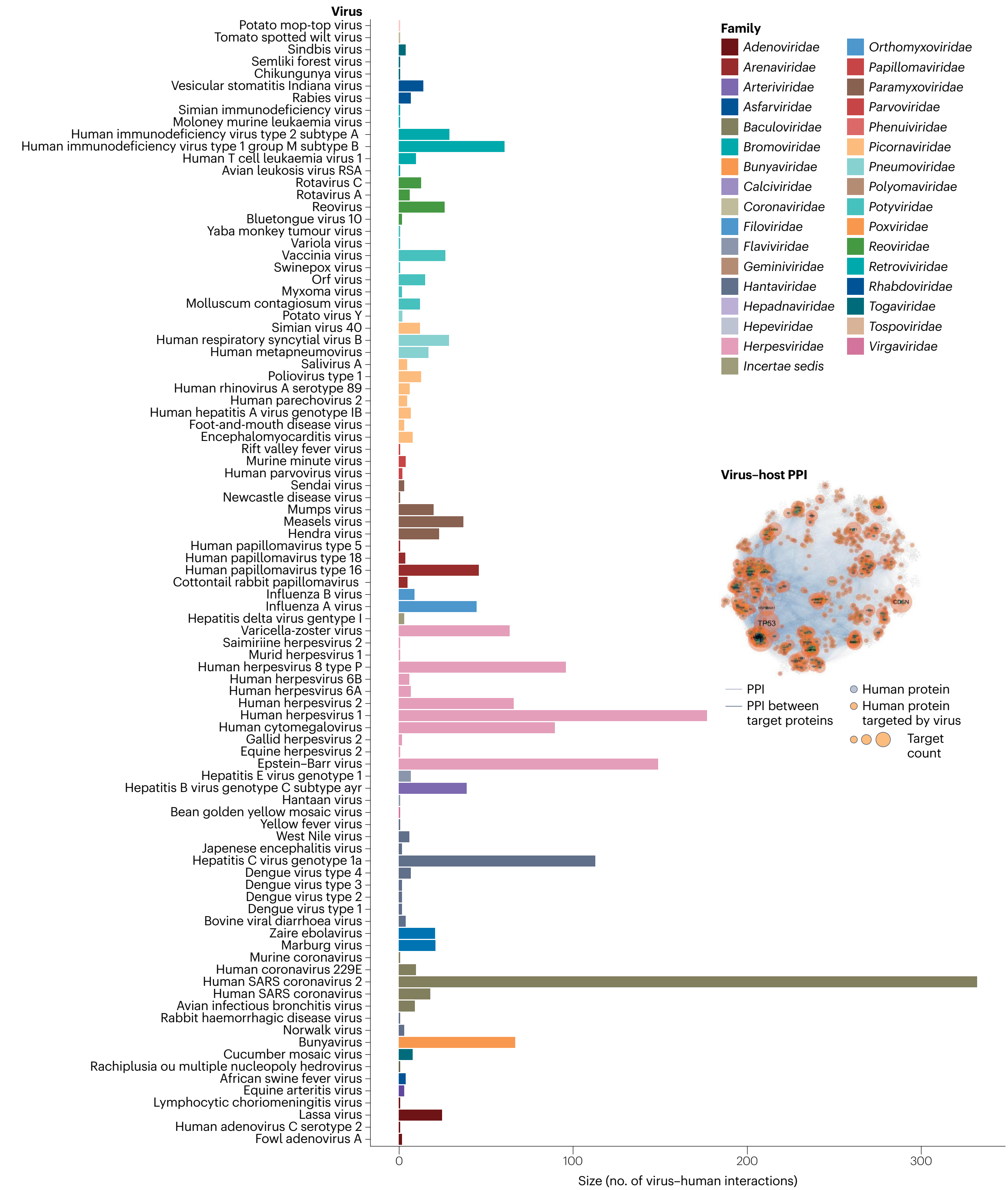

Fig. 6 | Virus-host interactions. Ninety-three families of viruses organized by the number of interactors (x axis), with interactions with proteins in the human interactome shown in the inset. Each virus represents a layer of virus–host interactions and, altogether, the structure of the system is captured by an interdependent network model[185].

coarse-grained NoNs. In fact, the number of microscopic degrees of freedom in multilayers exponentially increases with $N \times L$, instead of N as in monolayers. At the same time, finding (sub)optimal aggregation strategies with exhaustive searches would scale with e^{e^L}, whereas scaling with L or $L \log L$ would be desirable. These computational obstacles make dimensionality reduction an active research direction. There are at least two classes of approach (Fig. 3): structural ones, where layers are aggregated while controlling for redundancy in their

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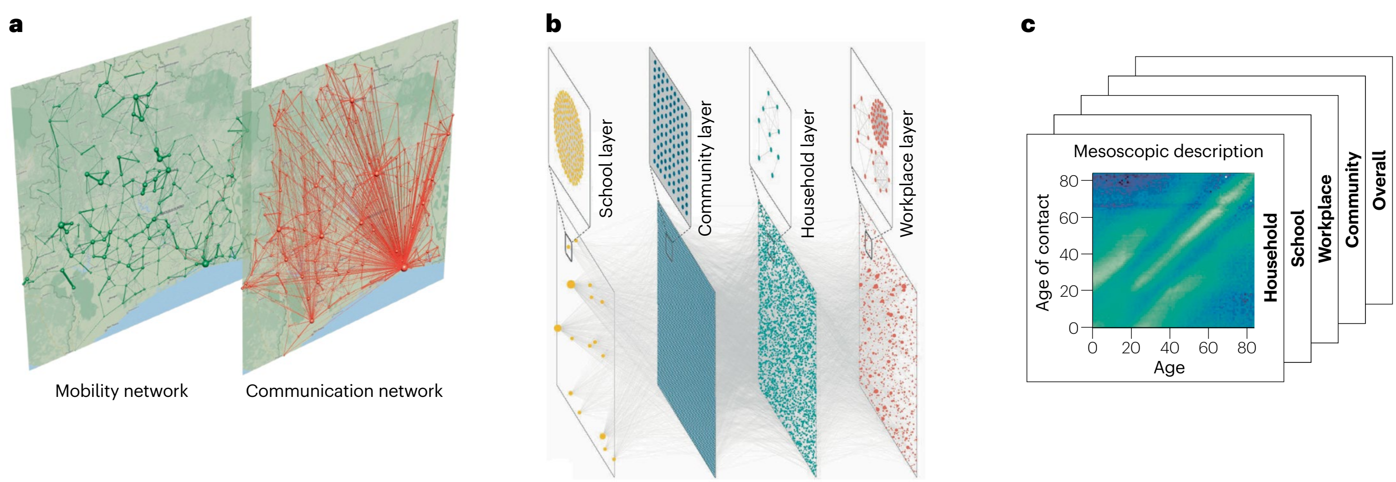

Fig. 7 | Unfolding of empirical interdependent processes. a, Non-interconnected multiplex model integrating human mobility and communication patterns, inferred from anonymized mobile phone data, in the Ivory Coast. Each node represents a subregional district, where a third dynamics, namely epidemic spreading, takes place[100]. **b**,**c**, Human mixing patterns at micro- (**b**) and mesoscopic (**c**) scales. Layers represent distinct social contexts where the transmission of a pathogen can take place[166,167]. Panels reproduced with permission from: **a**, ref. 181 under a Creative Commons license CC BY 4.0; **b**, ref. 166, National Academy of Sciences under a Creative Commons license a; **c**, ref. 167 under a Creative Commons license CC BY 4.0.

topology[32,143], and functional ones, where layers are aggregated while controlling for redundancy in some dynamical process on top[144].

In the next section I explore how the above concepts have been used to gain insights about the structure, dynamics and function of a wide spectrum of empirical multilayer systems.

Applications and outlook

To discuss successful applications of multilayer network modelling and analysis to empirical systems, I consider an example subset of networks ordered by the spatial scale at which they operate, ranging from biomolecules within a typical cell (~10 μm) to individuals moving at the urban (~10 km) or regional (~1,000 km) level.

At the cellular spatial scale, the study of biomolecular networks plays a central role in systems chemistry, systems and synthetic biology, and biological engineering. The fundamental units are molecules such as proteins, which interact, physically and chemically, to organize and preserve cellular functions. In this scenario, distinct types of interaction can be represented by distinct layers. However, this is not the only way to make sense of complex data. Multi-omics (Fig. 4)—obtained from different and complementary biochemical information, such as the interactome, the transcriptome and the metabolome, to cite a few examples—also offers insights about how cells work. For example, it has been used for network module identification across complex diseases[132] and to investigate the molecular mechanisms responsible for the pathogenesis of (non-)Mendelian diseases, such as COVID-19[145–149] (Fig. 5), as well as to quantify the robustness of coupled gene regulatory, protein–protein interaction and metabolic networks to gene perturbations in living organisms[150] (Fig. 6), cancer and metabolic diseases[151]. Furthermore, it has been shown that, by integrating information from genotype and phenotype, it is possible to better characterize disease–disease interactions[152], thus complementing empirical knowledge of existing comorbidity relationships in patients, as well as predicting new ones.

At the scale of interactions between cells, such as neurons in neuronal systems, multilayer networks allow us to integrate different types of information that was previously neglected or aggregated. Such information can be related to (1) monoamine and neuropeptide connections, as in *Caenorhabditis elegans*, a nematode widely used as a model organism[33]; (2) data acquisition set-up, as in the human brain, where structural and functional connections among regions of interest are inferred from electroencephalogram, magnetoencephalography, positron emission tomography and imaging techniques, mostly related to electro(magnetic) and haemodynamic measures, while integrated into multimodal networks[153–155]; (3) statistical relationships in the distinct windows (bands) of the temporal (frequency) domain, defining the layers of a time-varying[156] (frequency-decomposed[157]) brain network. It has been found that the multiplex core–periphery organization of the human brain consists of new areas important for brain functioning in the sensorimotor cortex[153], that in neurodegenerative diseases such as Alzheimer's the multiplex core significantly decreases[154] and that distinct neuronal areas are central to information flow in patients affected by schizophrenia with respect to healthy subjects[157]. I refer the interested reader to reviews dedicated to this class of applications[158,159].

At the scale of interaction between organisms, there are several applications related to ecological and social systems where multilayer networks play an important role for modelling. When applied to animal behaviour, multilayers can be used to map high-dimensional and heterogeneous relationships, from different habitats to distinct interactions[160], advancing animal behaviour research[161,162]. For example, it is possible to identify the species enhancing parasite spread (thus informing control strategies[163]), to quantify the role of ecological plasticity in ecosystems[40] and to use multilayer versatility to capture the importance of dispersers beyond traditional approaches, revealing the species critical to landscape functional cohesion[164,165].

When applied to human behaviour, multilayer models are routinely used to integrate multiple and complementary information about structure, such as distinct types of group contact[166,167], and dynamics, such as distinct types of human mobility flow[168], or interdependent processes such as epidemic spreading and human behaviour[100,101], especially in the field of network epidemiology[169] (Fig. 7).

Overall, multilayer network modelling has found a plethora of practical applications, from biomolecular interactions to human dynamics. Still, much work needs to be done. From a more fundamental perspective, it is desirable to explore some cornerstone problems in the physics of complex systems. These include the interplay between multiplexity or interdependency and other forms of higher-order interactions and dynamics[170,171], as well as differentiating between high-order mechanisms and behaviours[172] for a better understanding of phenomena observed in a range of complex systems. Furthermore, the latent geometry[64,173] (either structural or dependent on network-driven processes) characterizing several biological, socio-ecological and engineering systems is still an open research direction for multilayer networks. Another still poorly explored direction concerns the recovery of large-scale systems through microscopic interventions[174], which has no multilayer counterpart, despite the ubiquity of multiplexity and interdependency.

On the other hand, the impact of multilayer analysis has still not been fully exploited in a number of fields, especially in systems biology and systems medicine. Biological systems have to react quickly to perturbations originating either internally or from the external environment and, at the same time, maintain a functional organization that makes them robust to fluctuations in either their structure or the dynamics of the processes they need to survive. At a given scale, multiplex network models are suited to modelling different relationships among biomolecules, and across scales, interdependent network models are able to capture existing functional interdependencies. I also envision a great impact on network medicine[175,176], where multilayer modelling has been identified as one of the most suitable frameworks beyond reductionism[177,178], but only a few practical case studies have really been considered, and applications to realistic models that explicitly take into account the physical and biological differences between layers across multiple scales remain lacking.

Multilayer network modelling, with its solid grounding in statistical physics, builds its success on the ability to describe complex phenomena in physics and beyond physics, such as in chemistry, biology, the social sciences and engineering. The challenge for the near future is to enrich its framework to integrate information flowing across multiple coexisting scales and stretch its current application boundaries, as recently happened with the experimental physics of disordered superconductors[179], to open a new window on complex systems that are not yet well understood.

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Competing interests

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Additional information

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