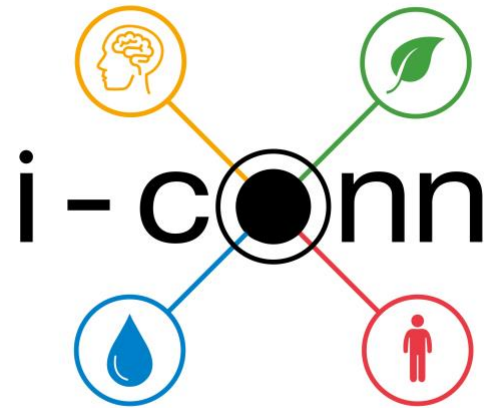


i-CONN Network



This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 859937



Deliverable D1.3 Report Evidence of SC/FC relationships

Taxonomy of structural and functional connectivities in complex systems

Deliverable D1.3

Selim Haj Ali¹, Venetia Voutsas¹, Marc-Thorsten Hütt^{1,*}, and i-CONN consortium²

¹School of Science, Constructor University, D-28759 Bremen, Germany

²<https://iconn.network>

*mhuett@constructor.university

ABSTRACT

An important branch of research on complex systems studies self-organized dynamics in networks by comparing structural and functional connectivity. Structural connectivity (SC) here is derived from the network itself, whereas functional connectivity (FC) is derived from the dynamics. This classification into SC and FC is prominent in neuroscience, but can be seen in social sciences, life sciences, geomorphology, earth systems science and many more.

Here we provide a taxonomy of different types of structural and functional connectivities, which are the results of a 'close reading' of twelve highly diverse datasets from this SC/FC perspective.

Applying all SC and FC variants to all datasets we show how this taxonomy enhances system comparison, enables systemic understanding and offers a catalog of interpretation strategies for complex systems in general.

1 Introduction

This document is Deliverable D1.3 of the i-CONN project. Eventually, it is planned to extend this document and submit it for publication to an academic journal.

An online tool, where the taxonomy elements can be applied to the datasets, is available at:

<https://connectivity-browser.onrender.com/>.

Our taxonomy is not related to 'standard' graph taxonomy, distinguishing between directed and undirected graphs, multigraphs, and other structural features.

2 The taxonomy

Figure 1 illustrate our taxonomy of structural and functional connectivities.

Within structural connectivities we distinguish between **empirical SC**, which is further divided into **relational SC** and **layout SC**, and **pragmatic SC**.

The most common usage of the SC concept is indeed relational SC, which is an SC representation directly derived from the network architecture itself without any additional information. The network's adjacency matrix is a version of relational SC. In case the system is embedded in a physical space or an abstract feature space, one can use proximity of nodes within that space to define a network architecture. This is layout SC. The only requirement is a metric being available in the embedding space. In case the system indeed has both relational information of the elements (i.e., the network) and the embedding in some space, one can compare relational SC and layout SC with each other, but also in their individual capacities to explain functional connectivity. Several of the case studies described below are built on this possibility. If the system does not have relational information, layout SC is the only possibility to study the system from a network perspective.

Pragmatic SCs are useful constructs to resort to when the real system structure is not accessible, in the cases where an exhaustive inventorying of all the interactions of the nodes (relational SC) is impossible, and in absence of an appropriate abstract features space (layout SC). Pragmatic SCs are measured functional network layers (FCs) that we assume as structural for the sake of comparison between different types of dynamics, whether these are empirically measured or simulated.

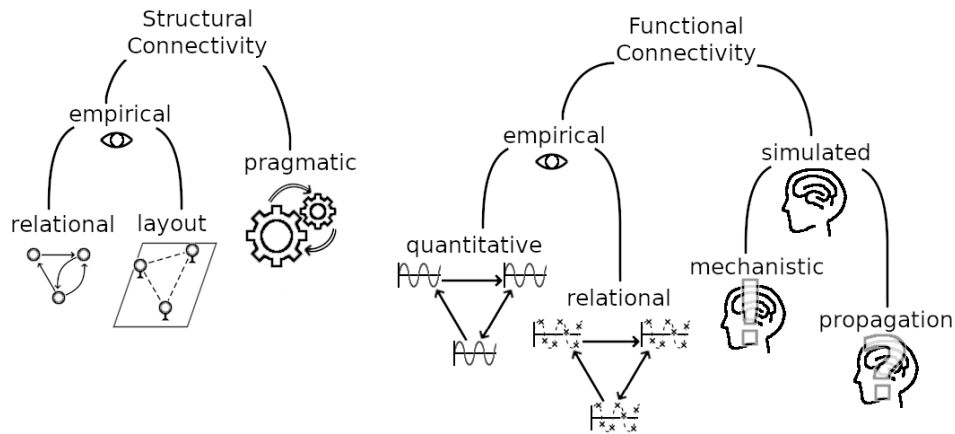


Figure 1. Structural and Functional Connectivity taxonomy dendrogram. *Structural Connectivity* is either empirical or pragmatic: *Empirical SCs* can be subdivided into two groups: (i) *Relational SCs* where network links represent relations specific to each particular pair (or group) of nodes. (ii) *Layout SCs* where network links represent similarity measures between nodes laid out on a metric space. *Pragmatic SCs* are not faithful representations of the system's structure, unlike the former category. They encapsulate instances where, in absence of an empirical SC, we consider any type of information about the relationships among system elements. As a consequence, pragmatic SCs links can be either of a relational or a layout type. *Functional Connectivity* is either empirical or simulated: *Empirical FCs* result from real-world observations where links can be of two natures: (i) *Quantitative FCs* are derived from time-refined data measured on elements of the system. (ii) *Relational FCs* evaluate dynamics in terms of relationships between elements of the systems. A *simulated FC* results from process-generating mathematical models, of which we distinguish mechanistic and propagation types: (i) A *mechanistic FC* is built from a model that requires prior assumptions about the underlying dynamical processes (i.e., a physics-informed model). (ii) A *propagation FC* is built from a model with no prior assumptions about the underlying dynamical processes (physics-free model).

Functional connectivities are classified as **empirical FC**, with subcategories **quantitative FC** and **relational FC**, and **simulated FC**, with subcategories **mechanistic FC** and **propagation FC**.

Empirical FC summarizes all cases, where empirical information on the dynamical state of the system is evaluated. Quantitative FC is the most common form of functional connectivity. It is based on time series measured at each node of the network (or, more generally speaking, each element of the system). A matrix of co-activity or pairwise synchronization indices are examples of quantitative FC (e.g. recorded correlations between different cortical brain regions).

Sometimes such detailed time-series information may not be available, but still some knowledge about functional states exists. This is the domain of relational FC. In this type of FC all relations among system elements are processed (e.g., "A takes advice from B" in a social system like a company or a research group).

Often relational FC comes in the form of a multilayer network, as different categories of relations among elements may exist. Relational FC is, hence, in most realizations a more qualitative version of FC, than quantitative FC. Sometimes, instead of time series, only snapshots of activity are available under different conditions (for example gene expression data for the regulatory network in a biological cell). Then relational FC would offer the possibility to draw conclusions from co-activation patterns and the distribution of differentially expressed genes across the regulatory network.

Given that relational FC evaluates dynamics in terms of relationships among system elements, it is more about the dynamics *of* the network than dynamics *on* the network (with the latter being the domain of the quantitative FC introduced above).

Sometimes no empirical information on dynamics or relational processes is available at all, but still one would want to explore the functional capabilities of a given SC. This is the application domain of simulated FC, which contains the remaining two types of FC as subcategories.

In the case of mechanistic FC, even though we do not have measured data on the functional level, we still have

a good mechanistic understanding or a model based on physical processes to simulate data. These simulated data based on physical laws or mechanistic systemic processes give rise to mechanistic FC (e.g. the correlated sequential evolution of river bed covers resulting a simulated sediment transports time series model¹)

If even such physical laws or mechanistic models do not exist for the system at hand, one can still explore the functional capabilities of a given SC with simulated flows (represented by random walks or diffusive processes). These simulated flows give rise to propagation FC.

Propagation FCs are derived from numerical simulations of toy models of dynamical processes on a given SC layer, in the absence of mechanistic models for the system at hand. These FCs are often tied with the concept of pragmatic SCs: by running simple models on the network constructed by the measured dynamics, we can uncover the existence of insightful substructures in the network of dynamics such as small-world effects or inter-modular communication.

3 The data

The taxonomy introduced above allows us to explore a wide range of complex systems from the perspective of structural and functional connectivities. Figure 2 introduces the 12 data sets we use to illustrate our approach. The data sets come from diverse application domains and explore a multitude of spatial and temporal scales.

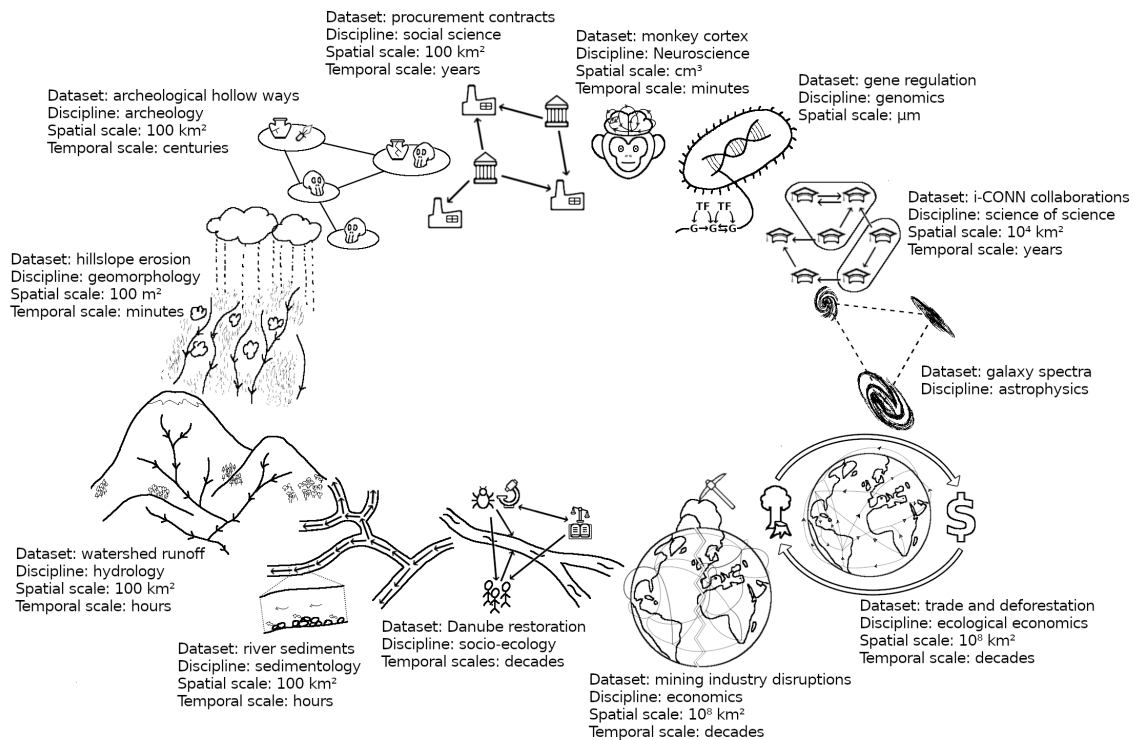


Figure 2. Datasets descriptions. Name, discipline and (available) spatio-temporal scales, when appropriate, for all the 12 datasets explored in this deliverable.

We have created a web space, where each data set can be explored on different levels of the taxonomy as illustrated in Table 1.

Archeological settlements is an undirected network of which nodes represent 723 excavated settlement sites in the Khabur Valley in ancient Mesopotamia². Links represent either physical hollow ways³ (relational FC) or inter-site geographical proximity (layout SC). These cover a time period spanning from the Early Bronze Age to the Iron Age.

Danube Restoration is a directed network of which nodes represent the 14 different actors and 12 action-situations (AS) involved in the water governance of the Danube river from the 19th century to today (relational FC). Directed AS-AS links indicate whether the outcome of the source AS affects the target AS. Undirected actor-AS links indicate

the involvement of the former in the latter.

Deforestation and trade is a directed network of which nodes represent 163 countries⁴. Links represent either the yearly embodied deforestation of all products exchanged internationally from 2000 to 2020⁵ (quantitative FC) or geographical proximity between all 163 countries' capitals (layout SC).

Economic vulnerability is a directed network of which 7987 nodes represent the 163 sectors of 44 countries and 5 'rest of the world' regions. Links are either yearly inter-sectoral international exchanges in M\$ from 1995 to 2020⁶ (quantitative FC) or the correlated commodity price surges after simulated global supply shortages⁷ (mechanistic FC).

Galaxy spectra is an undirected network of which nodes represent 200 ultraluminous infrared galaxies in the ELAIS N1 field at redshift 2⁸. Links represent the similarity of spectral energy distributions (SED) between these galaxies. SEDs are constructed according to one of four different data-fitting models: CYGNUS^{9,10}, Fritz¹¹, Siebenmorgen¹² and SKIRTOR^{13,14} (mechanistic FC).

Gene regulation is a directed signed network of which nodes are 2197 *Escherichia coli*'s genes. Links represent either co-regulation by a transcription factor¹⁵ (relational SC), spatial proximity in the bacterium's circular chromosome (layout SC) or gene co-expression patterns¹⁶ (relational FC).

Hillslope erosion is a directed network of which 1200 nodes describe a (60×20) lattice representing a $(30m \times 10m)$ field topographical data from the Sevilleta Long Term Ecological Research site in central New Mexico USA. Links represent topographically defined (steepest descent) connections between nodes¹⁷ (relational/layout SC), or the sequential evolution of discharge from one node to another from modelled spatial time series of discharge¹⁸ (mechanistic FC). The "hillslope runoff" dataset contains three modelled rainfall scenarios: (i) constant rainfall applied to the upper third of the hillslope; (ii) a gradient of rainfall over the hillslope, highest at the top of the hillslope, for a small amount of rain; and (iii) the same gradient of rainfall over the hillslope for a larger amount of rain. Each of the three scenarios is repeated 100 times with stochastic soil moisture content that preserves the spatial properties of soil moisture patterns observed under field conditions.

i-CONN collaboration network is a directed network of which nodes represent 41 scientific researchers of the i-CONN consortium. Links represent either proximity of studied topics (layout SC), geographical proximity (layout SC), prior relations (relational FC), or three 6-months apart surveyed relations of advice seeking, influence and collaboration between researchers (relational FC).

Monkey cortex is a directed network of which 29 nodes are monkey cortical regions. Links are either nervous fibers[?] (relational SC) or brain signals recorded in different frequency bands[?] (quantitative FC).

Procurement contracts is an undirected bipartite network of which nodes are 340 local municipalities and 2108 private companies in Guatemala. Links are contracts granted from the former to the latter from 2012 to 2020. We consider the network projection on municipalities where nodes represent the 340 Guatemalan municipalities. Links are either the geographical proximity between municipalities (layout SC), or contracts signed by two municipalities with a same company within a same year (quantitative FC).

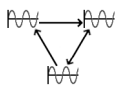
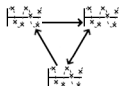
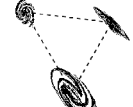
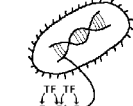
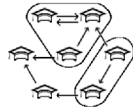
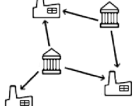
River sediments is a directed network of which nodes represent 1514 100-meter-long reaches of the River Carron in Scotland. Links represent either connections between immediate or 5th order neighboring reaches that allow sediment transport (relational SC), the difference of slopes between reaches (layout SC) or the correlated sequential evolution of bedrock and alluvial reaches resulting from simulated sediment transport/deposition time series¹ (mechanistic FC).

Watershed runoff is a directed network of which nodes represent 38 runoff measuring devices (flumes) in the 37,000-acre Walnut Gulch Experimental Watershed¹⁹. Links represent either connections between flumes allowing water flow (linking SC) or the correlation of sequential flow between flumes (quantitative FC).

4 Taxonomy applications

In the following and as a complement to this more comprehensive data exploration, we will focus on three case studies, which from our perspective illustrate best the broad applicability of the taxonomy and the interpretative power that comes along with it.

Table 1. Application array. The applicability of all taxonomy elements (columns) to all datasets (rows) is summarized as green (applicable) and red (not applicable). The numerical results for all green cases are provided by selecting the array entry in the corresponding figure on the accompanying web page.

Datasets	Structural Connectivity			Functional Connectivity			
							
							
							
							
							
							
							
							
							
							
							
							
							

4.1 Selected case study: A comparison of gene regulation and riverbed sediment cover

The two systems – bacterial gene regulation and riverbed sediment cover – offer an excellent illustration of our taxonomy of structural connectivities. In the case of gene regulation, two variants of *relational SC* (the transcriptional regulatory network and the co-regulatory network) compete with *layout SC* (via the spatial embedding of genes in the bacterium's circular chromosome) to explain gene expression patterns (gene co-activity derived from a wide range of gene expression data). In the same way, for riverbed sediment cover, *relational SC* (matrix of path lengths between reaches) competes with two types of *layout SC* (via proximity of reaches in terms of slope and width) to explain patterns of alluvial and bedrock cover across the river (sequential activity derived from simulated sediment cover fraction data that change over time).

Gene regulatory network

Bacterial gene regulation is a fascinating example of an interplay of different forms of structural and functional connectivities. The transcriptional regulatory network (TRN) senses environmental and intracellular changes to modulate gene expression of a cell and ensure the adaptation of an organism to different environmental conditions^{20–23}. The TRN can be represented as a directed network, where the nodes are genes and the directed edges represent the capability of a source gene (transcription factor) to regulate the expression of a target gene. The TRN is furthermore a signed graph, as the regulatory action can be activating or inhibitory.

There is ample evidence that the circular chromosome is a relevant regulator of gene expression and that gene expression data need to be interpreted via the interplay of chromosomal space and regulatory network^{21,24,25}.

Here, we use the signed TRN (Figure 3A) and the co-regulatory network of *E. coli* as *relational SC* and the matrix of pairwise distances of the genes on the chromosome as *layout SC*. The distance matrix was binarized such that ones indicate gene proximity in space with the threshold being $d^* = 10000$. To construct the FC matrices, we used a set of gene expression data²³, where the gene expression levels are given for diverse experimental conditions. Based on the values of the expression levels we define two categories of genes: one that exhibits very high activity (values greater than the $\mu + 2\sigma$ of the distribution of gene expression values) and one that exhibits very low activity (less than $\mu - 2\sigma$). The functional connectivity matrices were constructed as co-activity matrices when two genes both show high or low activity in the various experiments. Figures 3B and 3C show how the two categories of genes behave as we move from clear layout SC ($a = 0$) to clear relational SC ($a = 1$). When the signed TRN is used as the relational SC (Figure 1B), the active genes maintain a fairly stable behaviour up to the point where the contribution of the two SCs is equal, and then the correlation values gradually decrease until they reach zero when the TRN is only involved in the structural part. When the co-regulatory network takes the place of relational SC, the curve of highly expressed genes reaches its peak at the point where 20% of co-regulatory network and 80% of the gene proximity network compose the overall SC and then, gradually get stabilized. On the other hand, the genes that display low activity display the peak correlation value for $a = 0$ and decreases to slightly negative correlations. Overall, we notice the different role that gene proximity plays when inserted in different percentages to relational SC (TRN and co-regulatory network) to the empirical FC, which is constructed based on the gene expression data from different experimental conditions.

This analysis illustrates, how the portfolio of connectivities introduced here can yield relevant insight in the functioning of this intricate biological system. Clearly, a deeper understanding of the mechanisms, their evolutionary shaping and their functional consequences requires a dedicated set of analyses informed by prior biological knowledge (see Refs^{21,25–27} for examples).

Riverbed sediment cover

Sediment cover along river channels exhibits variations driven by grain entrainment, translation and deposition, which may be of alluvial, bedrock or a mix of both²⁸. A river network can be described by a set of nodes that represent river reaches of approximately equal length and links that connect the neighboring river segments when sediment transport between two nodes is possible. Here, we use a path length matrix among the reaches, in its binary form (threshold $l^* = 500\text{ m}$), as *relational SC* and a weighted slope and width similarity matrix as *layout SC*. The FC matrices were generated from simulated time series derived from the model¹ and they fall into the category of *mechanistic FC*. The time series characterize how the attributes of the nodes (sediment cover fraction) change over time. Based on the dynamical cover fraction values we distinguish the state of reaches as alluvial or bedrock. As the processes involve flow of sediment across the river, we included a time delay of $t^* = 100$ time steps when constructing the FC matrices. Figure 3D shows the river with the stronger positive connections when considering similarities of slope between the reaches. In Figure 3E, we can see how reaches with alluvial and bedrock cover

correlate with the slope similarity matrix. Slightly negative (for alluvial) and slightly positive (for bedrock) correlations increase and become equal when the slope matrix is not part of the total SC ($\alpha = 1$). Finally, in Figure 3F, we observe that constant correlation values between are maintained in both cases when relational activity contributes up to 60% – positive for alluvial, negative for bedrock – until they reach the same correlation value, when the contribution of the width similarity matrix is eliminated ($\alpha = 1$). In essence, this analysis highlights that river attributes (slope and width) influence channel evolution differently through the process of sediment transport and resulting sediment cover, and provides insights about their importance (additional references needed).

Discussion

We performed a parallel analysis on two datasets from two different scientific fields: biology and geomorphology. The aim is to show, how different types of underlying structural connectivities correlate with the function of systems, when their extreme responses are considered. We found that the interplay of relational and layout SC can have either a constructive or destructive effect on the SC/FC relationships, depending on the selected attributes integrated in the SC matrices. Correlations were also computed for each case using null models (shuffling the FC vectors) to indicate the high significance of the small correlation values observed for the original data. This type of analysis is suitable for cases, where a system can be meaningfully described at the SC level from a network in which there is wiring between nodes, and from a network in which we define the proximity between nodes in some metric state space. At the FC level, time series or series of data from different conditions characterising each node are required. Correlations between network architecture and dynamical information of nodes or links have been used primarily to reveal similarities between the underlying network topology and the functional network, i.e. the network constructed from experimental measurements or dynamical observations of a system. Here, we use SC/FC correlations in two case studies as an indication of how structural and spatial properties of the system influence the functional networks, rather than as a network inference method.

5 Conclusion

The taxonomy introduced here should be seen rather as a set of interpretation strategies of complex systems and not as a strict set of concepts with sharp boundaries. Often even the distinction between *structural* and *functional* connectivities is only a matter of time scales.

Still, as we illustrated with the case studies outlined above, even the debate, how a system fits into this taxonomy, can offer new, unexpected and deep insight into the functioning of the system.

Data Availability

All data analyzed during this study are publicly available via the databases referenced in the article.

Competing Interests

The Authors declare no Competing Financial or Non-Financial Interests.

Code Availability

The code used to perform the analyses presented in the current study is available in the referenced repository.

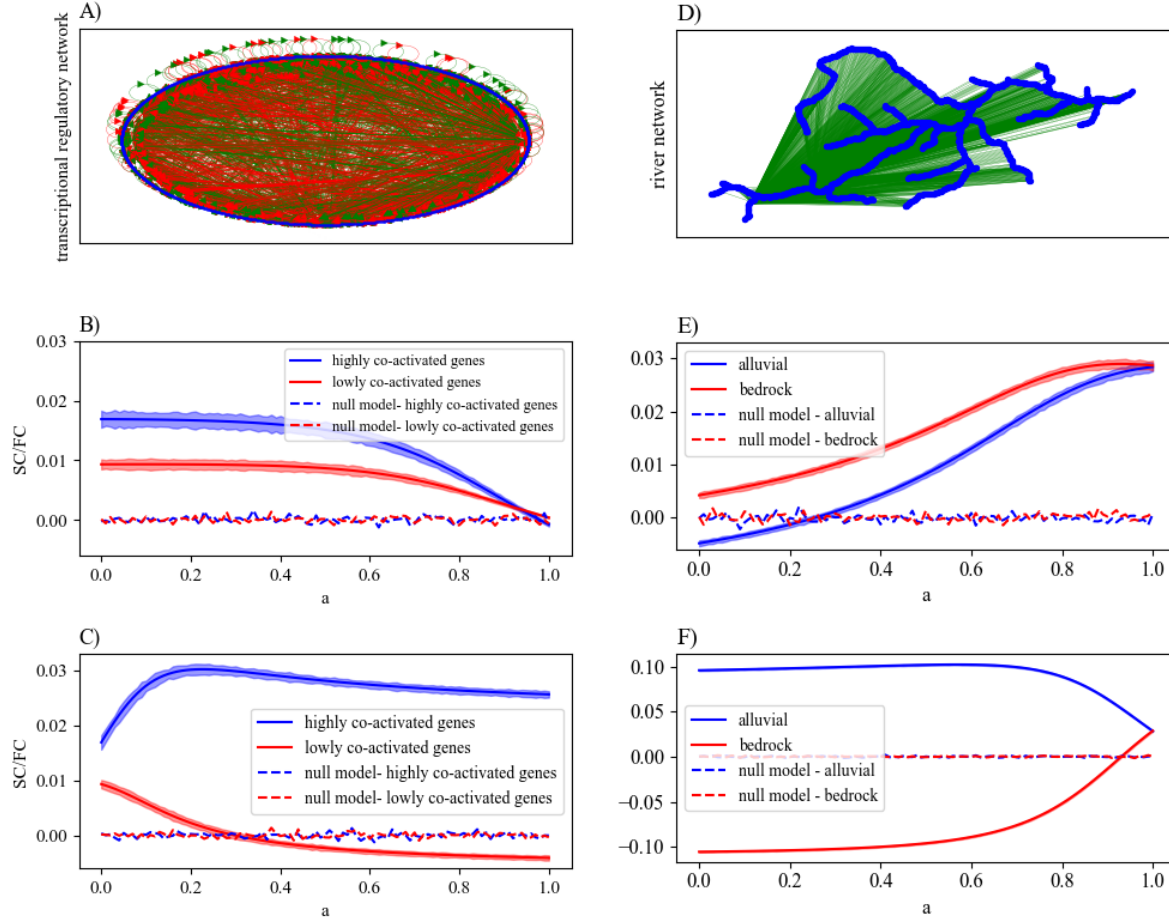


Figure 3. (A) Transcriptional regulatory network (TRN) of *E. coli*: nodes represent genes, green and red directed edges from source genes to target genes represent the gene expression regulation, i.e. activation or repression of transcriptional factors respectively. **(B)** SC/FC correlations as a function of the percentage of relational SC, where relational SC is represented from the signed TRN. Total SC is given from the sum of relational and layout SC in complementary percentages, where layout SC corresponds to the binary matrix of pairwise distances between genes embedded in space: $SC = aTRN + (1 - a)D$. The selected distance threshold is $d^* = 10000$. Distances below this threshold is represented by 1 in the binary distance matrix D and the rest by 0. The error bars of SC/FC correlations come from the standard deviation of 50 pairs bootstrap samples of the SC and FC vectors after removing the diagonal of the corresponding matrices. SC/FC of null models were computed as a mean of 50 samples after shuffling the FC vectors. **(C)** SC/FC correlations as a function of the percentage of relational SC, where relational SC is represented from the co-regulatory network. Total SC is given as $SC = aCR + (1 - a)D$. The error bars and the computation of SC/FC correlations from null models are the same as in (B). **(D)** River network (based on River Carron, Scotland): the links depict the strongest connections among the reaches in terms of slope similarity. **(E)** SC/FC correlations of alluvial and bedrock reaches as a function of the percentage of relational SC, where relational SC is given from the matrix that contains the length of river path between two reaches. The matrix was binarized with threshold $l^* = 500m$. Layout SC is given from a normalized weighted matrix that represent the similarity of slopes between the reaches. Overall SC: $SC = aL + (1 - a)S$. The error bars and the null model computations follow the same approach with the previous cases. **(F)** SC/FC correlations with the same relational SC and layout SC the normalized weighted matrix which gives the similarities in terms of the width of the reaches: $SC = aL + (1 - a)W$.

References

1. Pfeiffer, A., Barnhart, K., Czuba, J. & Hutton, E. Networksedimenttransporter: A landlab component for bed material transport through river networks. *Journal of Open Source Software* **5** (2020).
2. Galiatsatos, N., Wilkinson, T. J., Donoghue, D. N. & Philip, G. The fragile crescent project (fcp): analysis of settlement landscapes using satellite imagery (2009).
3. Menze, B. H. & Ur, J. A. Mapping patterns of long-term settlement in northern mesopotamia at a large scale. *Proceedings of the National Academy of Sciences* **109**, E778–E787 (2012).
4. Lenzen, M. *et al.* The global mrio lab—charting the world economy. *Economic Systems Research* **29**, 158–186 (2017).
5. Curtis, P. G., Slay, C. M., Harris, N. L., Tyukavina, A. & Hansen, M. C. Classifying drivers of global forest loss. *Science* **361**, 1108–1111 (2018).
6. Stadler, K. *et al.* Exiobase 3: Developing a time series of detailed environmentally extended multi-regional input-output tables. *Journal of Industrial Ecology* **22**, 502–515 (2018).
7. Kerschner, C., Prell, C., Feng, K. & Hubacek, K. Economic vulnerability to peak oil. *Global environmental change* **23**, 1424–1433 (2013).
8. Shirley, R. *et al.* Help: the herschel extragalactic legacy project. *Monthly Notices of the Royal Astronomical Society* **507**, 129–155 (2021).
9. Efstathiou, A. & Rowan-Robinson, M. Dusty discs in active galactic nuclei. *Monthly Notices of the Royal Astronomical Society* **273**, 649–661 (1995).
10. Efstathiou, A., Christopher, N., Verma, A. & Siebenmorgen, R. Active galactic nucleus torus models and the puzzling infrared spectrum of iras f10214+ 4724. *Monthly Notices of the Royal Astronomical Society* **436**, 1873–1882 (2013).
11. Fritz, J., Franceschini, A. & Hatziminaoglou, E. Revisiting the infrared spectra of active galactic nuclei with a new torus emission model. *Monthly Notices of the Royal Astronomical Society* **366**, 767–786 (2006).
12. Siebenmorgen, R., Heymann, F. & Efstathiou, A. Self-consistent two-phase agn torus models—sed library for observers. *Astronomy & Astrophysics* **583**, A120 (2015).
13. Stalevski, M., Fritz, J., Baes, M., Nakos, T. & Popović, L. Č. 3d radiative transfer modelling of the dusty tori around active galactic nuclei as a clumpy two-phase medium. *Monthly Notices of the Royal Astronomical Society* **420**, 2756–2772 (2012).
14. Stalevski, M. *et al.* The dust covering factor in active galactic nuclei. *Monthly Notices of the Royal Astronomical Society* **458**, 2288–2302 (2016).
15. Tierrafría, V. H. *et al.* Regulondb 11.0: Comprehensive high-throughput datasets on transcriptional regulation in *escherichia coli* k-12. *Microbial genomics* **8**, 000833 (2022).
16. Edgar, R., Domrachev, M. & Lash, A. E. Gene expression omnibus: Ncbi gene expression and hybridization array data repository. *Nucleic acids research* **30**, 207–210 (2002).
17. Turnbull, L., Wainwright, J., Brazier, R. E. & Bol, R. Biotic and abiotic changes in ecosystem structure over a shrub-encroachment gradient in the southwestern usa. *Ecosystems* **13**, 1239–1255 (2010).
18. Wainwright, J. *et al.* A transport-distance approach to scaling erosion rates: 1. background and model development. *Earth Surface Processes and Landforms* **33**, 813–826 (2008).
19. Nichols, M., Stone, J. & Nearing, M. Sediment database, walnut gulch experimental watershed, arizona, united states. *Water Resources Research* **44** (2008).
20. Karlebach, G. & Shamir, R. Modelling and analysis of gene regulatory networks. *Nature reviews Molecular cell biology* **9**, 770–780 (2008).
21. Marr, C., Geertz, M., Hütt, M.-T. & Muskhelishvili, G. Dissecting the logical types of network control in gene expression profiles. *BMC Systems Biology* **2**, 1–9 (2008).
22. Marr, C., Theis, F. J., Liebovitch, L. S. & Hütt, M.-T. Patterns of subnet usage reveal distinct scales of regulation in the transcriptional regulatory network of *escherichia coli*. *PLoS Computational Biology* **6**, e1000836 (2010).

23. Sastry, A. V. *et al.* The Escherichia coli transcriptome mostly consists of independently regulated modules. *Nature communications* **10**, 5536 (2019).
24. Sobetzko, P., Travers, A. & Muskhelishvili, G. Gene order and chromosome dynamics coordinate spatiotemporal gene expression during the bacterial growth cycle. *Proceedings of the National Academy of Sciences* **109**, E42–E50 (2012).
25. Kosmidis, K., Jablonski, K. P., Muskhelishvili, G. & Hütt, M.-T. Chromosomal origin of replication coordinates logically distinct types of bacterial genetic regulation. *NPJ Systems Biology and Applications* **6**, 1–9 (2020).
26. Sonnenschein, N., Geertz, M., Muskhelishvili, G. & Hütt, M.-T. Analog regulation of metabolic demand. *BMC Syst Biol* **5**, 40 (2011). URL <http://www.biomedcentral.com/1752-0509/5/40>.
27. Cakir, E., Lesne, A. & Hütt, M.-T. The economy of chromosomal distances in bacterial gene regulation. *npj Systems Biology and Applications* **7**, 49 (2021).
28. Hodge, R. A., Hoey, T. B. & Sklar, L. S. Bed load transport in bedrock rivers: The role of sediment cover in grain entrainment, translation, and deposition. *Journal of Geophysical Research: Earth Surface* **116** (2011).