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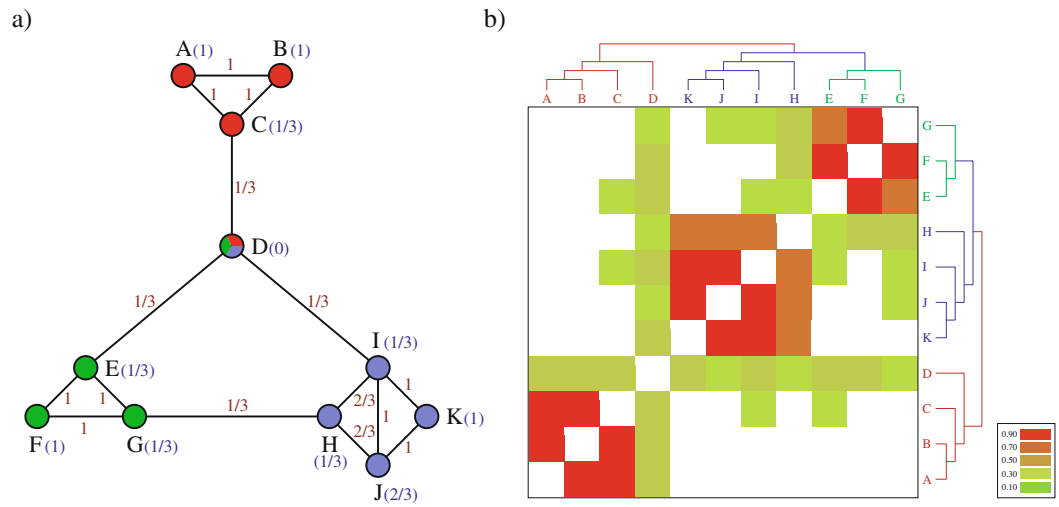
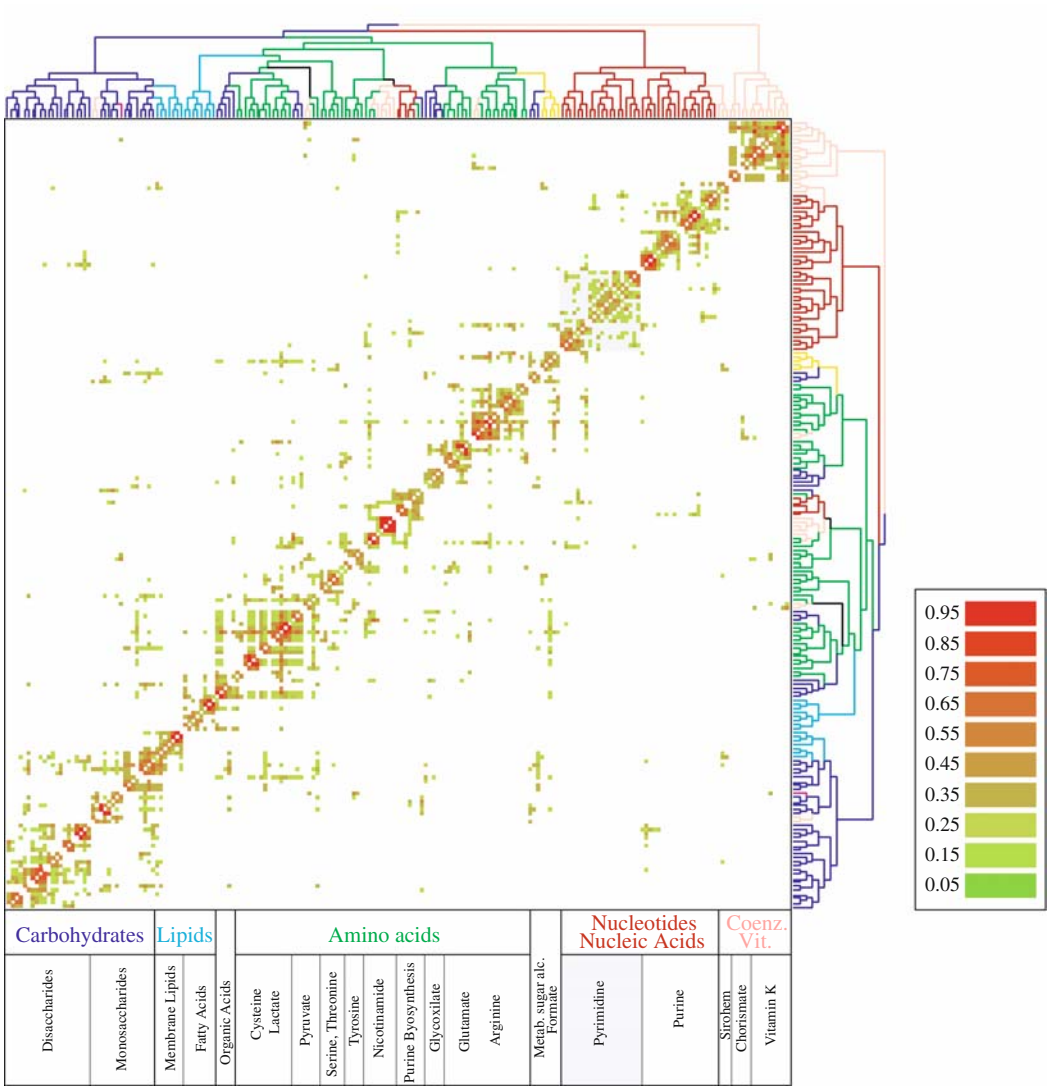
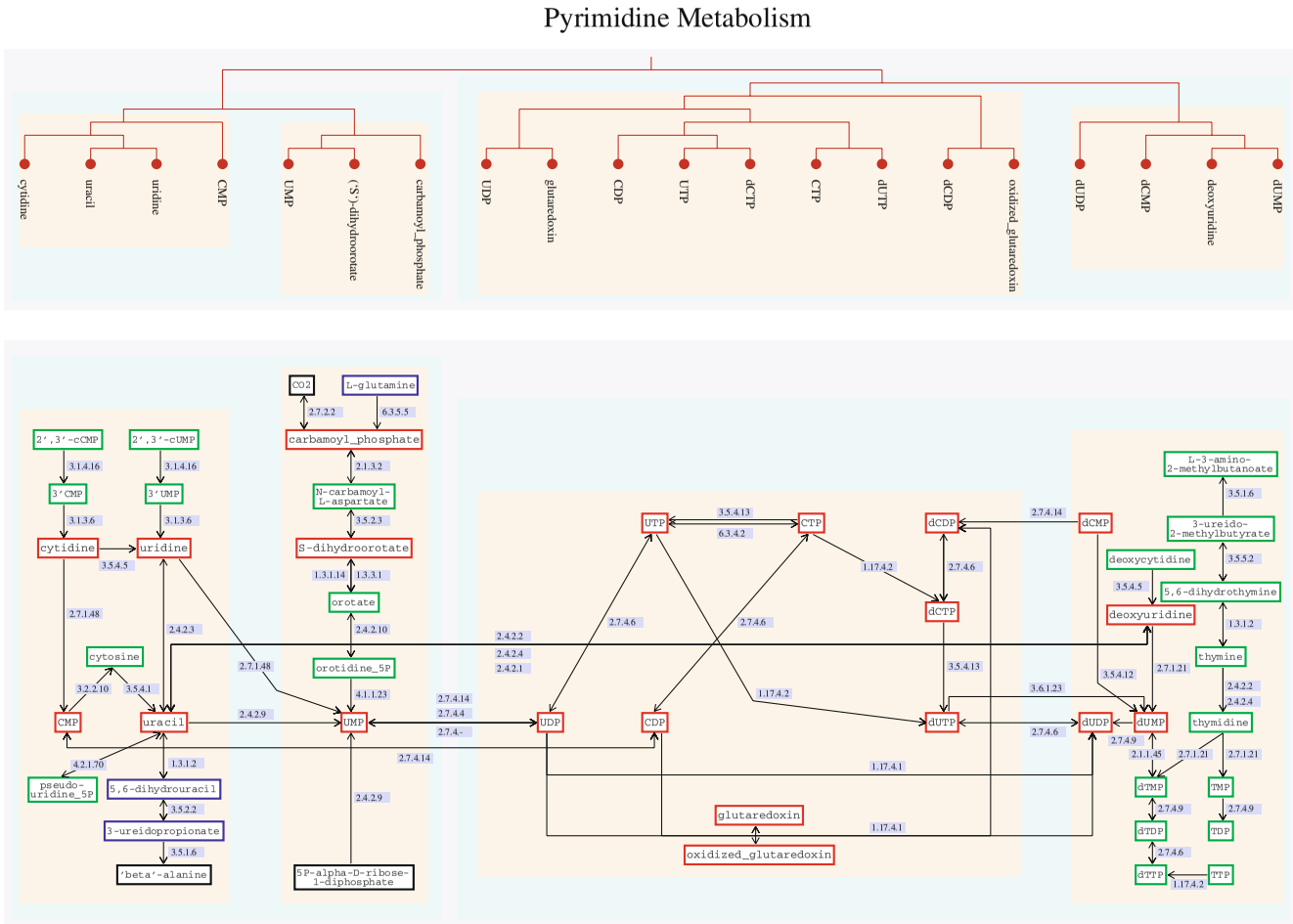


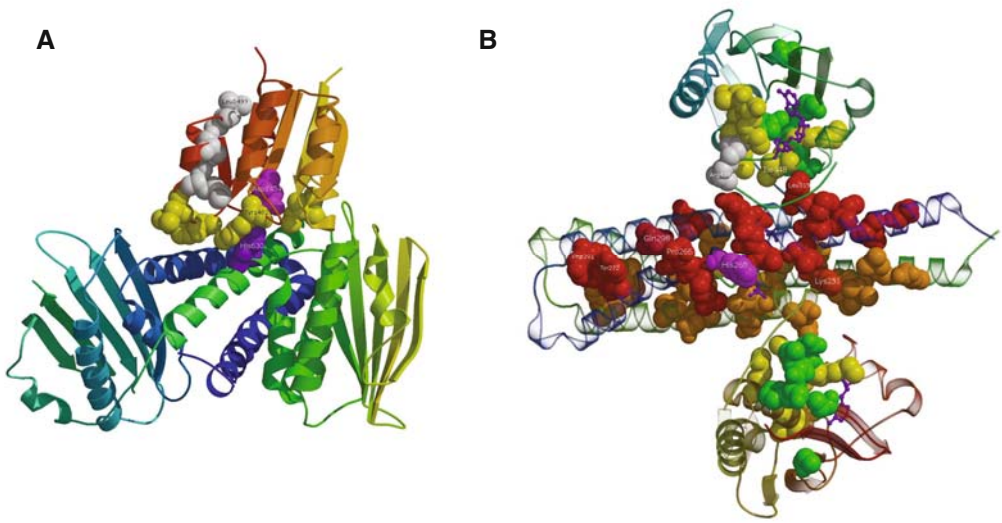

**Color Plate 1.** Uncovering the underlying modularity of a complex network. **(a)** Topological overlap illustrated on a small hypothetical network. On each link, we indicate the topological overlap for the connected nodes; and in parentheses next to each node, we indicate the node's clustering coefficient. **(b)** The topological overlap matrix corresponding to the small network shown in (**a**). The *rows and columns* of the matrix were reordered by the application of an average linkage clustering method to its elements, allowing us to identify and place close to each other those nodes that have high topological overlap. The *color code* denotes the degree of topological overlap between the nodes. The associated tree reflects the three distinct modules built into the model, as well as the fact that the EFG and HIJK modules are closer to each other in the topological sense than to the ABC module (Chapter 7, Fig. 3; *see* discussion on p. 151).



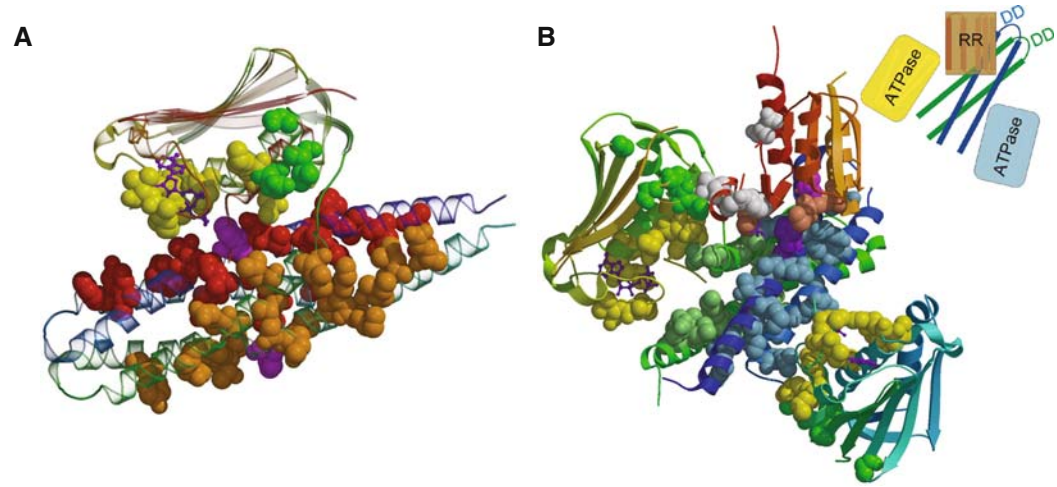

**Color Plate 2.** Topological modules in the *Escherichia coli* metabolism: the topologic overlap matrix, together with the corresponding hierarchical tree (*top and right*) that quantifies the relation between the different modules. The branches of the tree are *color-coded* to reflect the predominant biochemical classification of their substrates. The *color code* of the matrix denotes the degree of topological overlap shown in the matrix. The large-scale functional map of the metabolism, as suggested by the hierarchical tree, is also shown (*bottom*) (Chapter 7, Fig. 5; *see* discussion on p. 153).



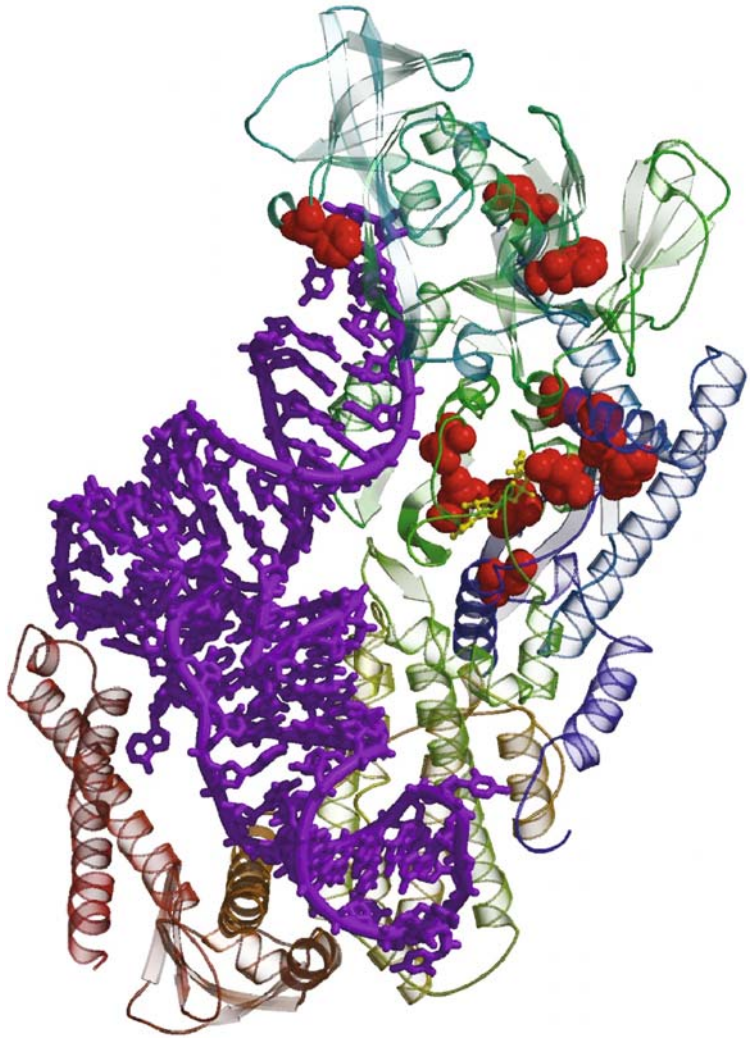

**Color Plate 3.** Enlarged view of the substrate module of pyrimidine metabolism, along with a detailed diagram of the metabolic reactions that surround and incorporate it. The *colored boxes* in the background denote the first two levels of the three levels of nested modularity suggested by the hierarchical tree. *Red-outlined boxes* denote the substrates directly appearing in the reduced metabolism and thus on the tree (Chapter 7, Fig. 6; *see* discussion on p. 154 and full caption on p. 155).




**Color Plate 4.** Structural localization of putative SDRs and CERs in two-component system domains. (**a**) RR Spo0F (*red-brown ribbon*) bound to structural analog of the DD in Spo0B protein. The conserved His is shown in *purple*, the conserved Asp in RR in *magenta*. SDRs and CERs are shown in *yellow* or, when located on the $\alpha$4 helix, in *white* (PDB entry *1F51*). (b) The non-catalytic conformation of HK homodimer. ADP is shown as a *purple* wireframe, the phosphate-accepting conserved His residue in *magenta spacefill*. SDRs and CERs on the ATPase are shown in *yellow*, or in *white* if located on the unresolved ATP-lid loop that was superimposed from PhoQ kinase (PDB entry *1ID0*), or in *green* in the RR-specific CERs side patch. SDRs and CERs on the DD are shown in *red* on one homodimer and *orange* on another (PDB entry *2C2A*) (Chapter 18, Fig. 6; *see* discussion on p. 435).




**Color Plate 5.** Localization of putative SDRs and CERs on computationally obtained models (models provided by Marina et al *(27)*). (**a**) HK in the active conformation, the ATPase is docked on the DD so that transfer of the phosphoryl group is possible. SDRs and CERs on the ATPase domain are shown in *yellow* or *green* when located in the RR-specific CERs side patch. SDRs and CERs on the DD are shown in *red* on one homodimer and orange on another. (**b**) Spo0F computationally docked on HK and subsequently superimposed with RR from OmpR. RR (*brown-red ribbon*) (PDB entry *1KGS*) with its $\alpha$4 helix swung $\sim$90°: the phosphorylated Asp in the RR is shown in *magenta*, SDR and CERs are shown in *light red* or, when located the $\alpha$4 helix in *white*. DD (*dark blue* and *dark green ribbon*): SDRs and CERs are shown in *light blue* on one dimer and in *light green* on another. ATPase (*yellow-green ribbon* on the *left* and *light-blue* on the *right*): the colors are the same as in (**a**) (Chapter 18, Fig. 7; *see* discussion on p. 439).



**Color Plate 6.** Valine aminoacyl-tRNA synthetase (PDB entry *1GAX*). The tRNA is shown as a *purple* wireframe structure, SDRs and CERs are *red* balls, and amino acid (valyl-adenylate analog) is in *yellow* wireframe (Chapter 18, Fig. 8; *see* discussion on p. 443).