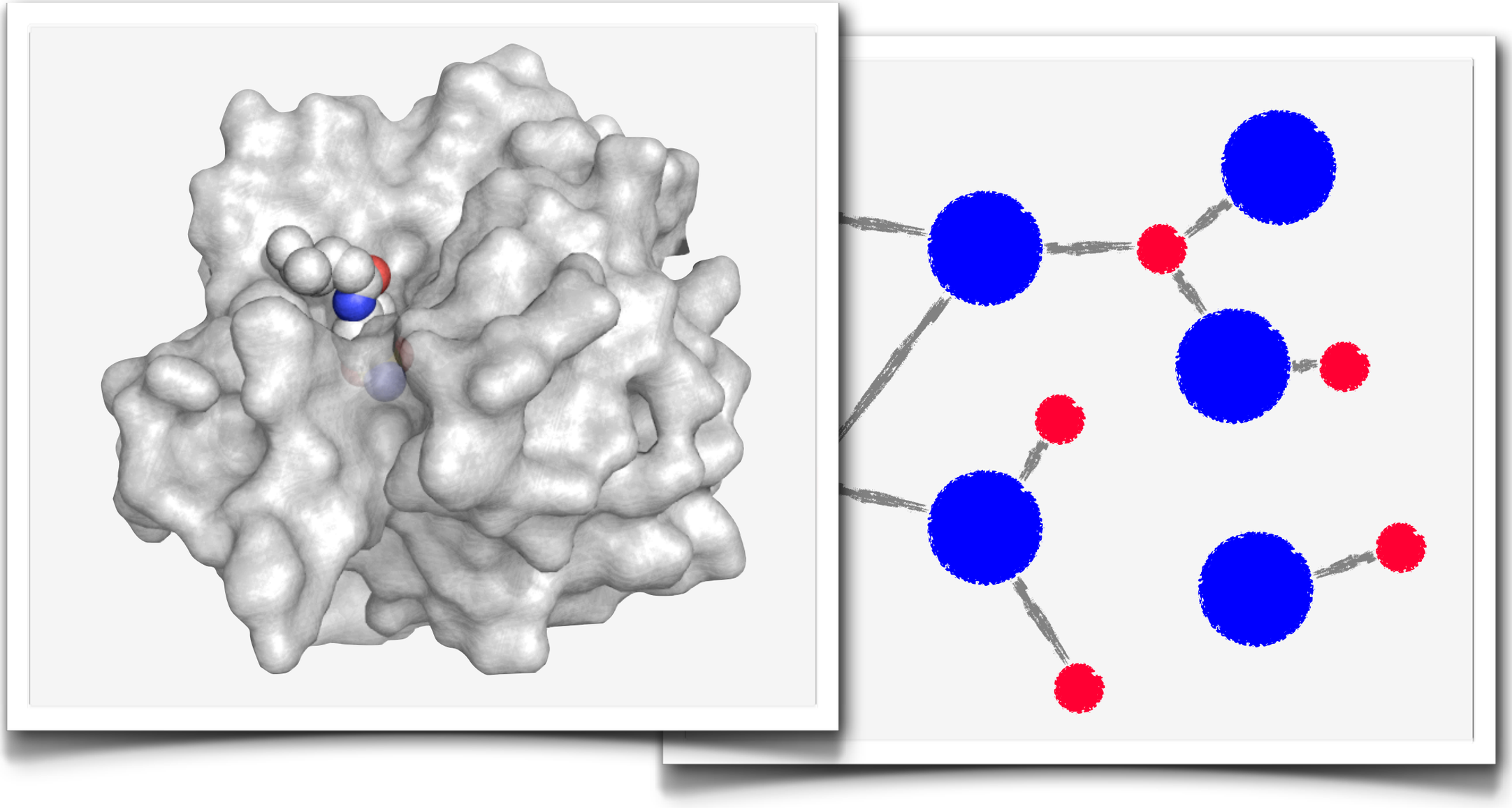
Reposicionamiento de fármacos promiscuos



Aurelio Moya García
Universidad de Málaga

Systems Microscopy
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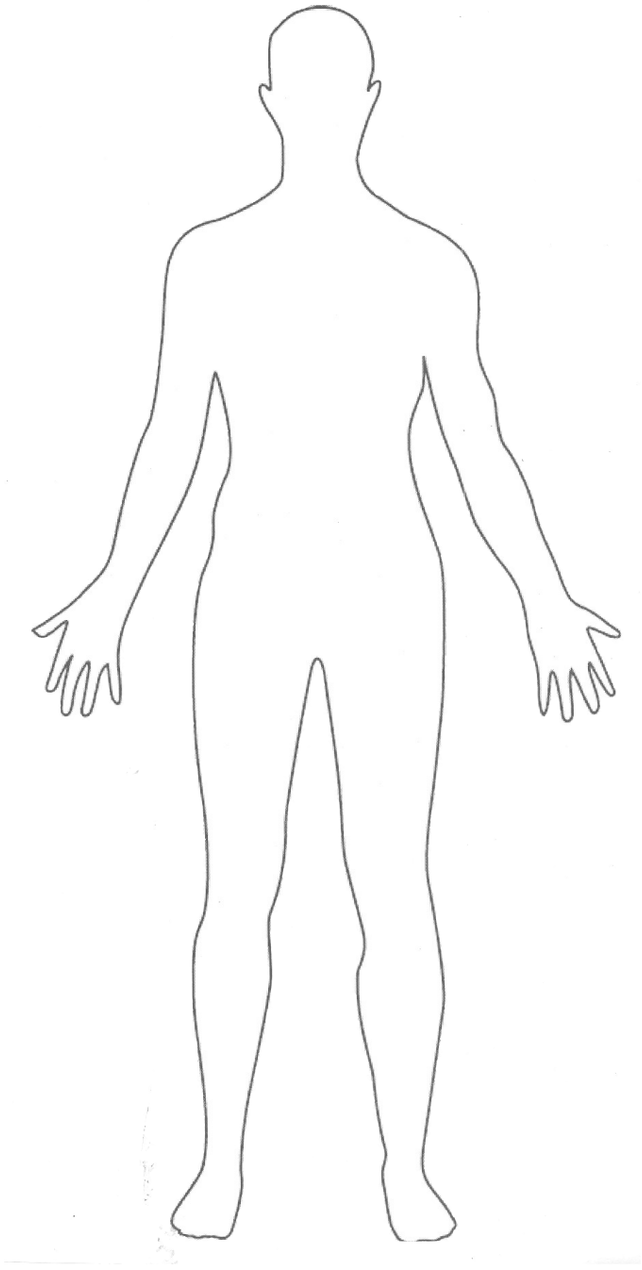
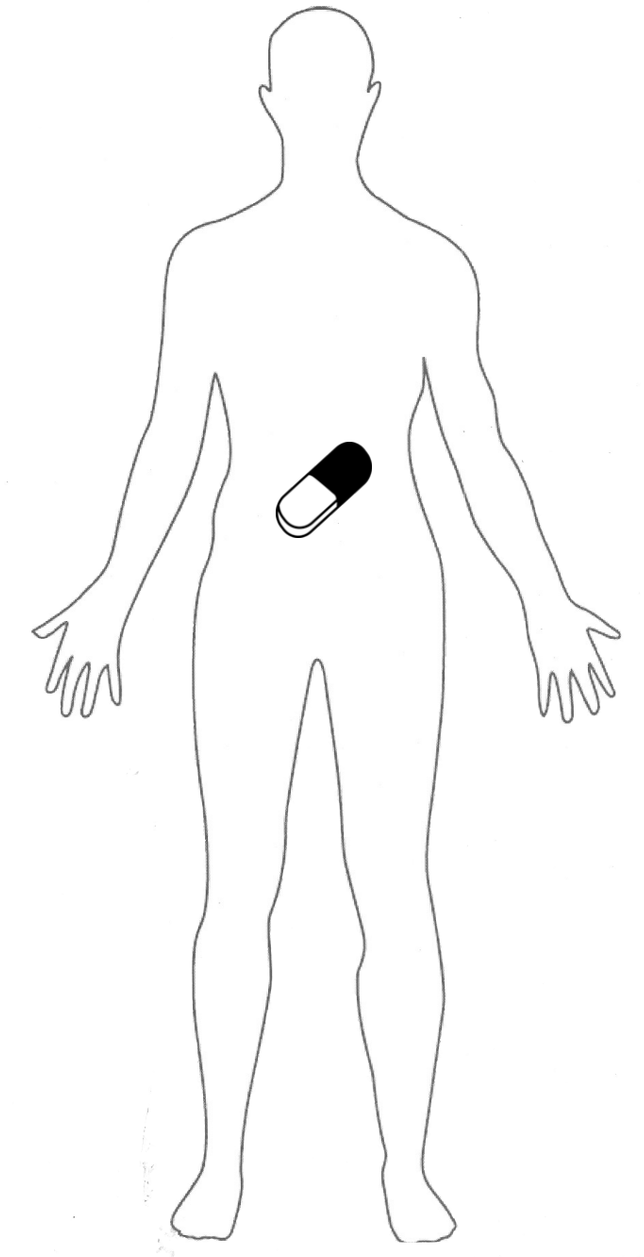
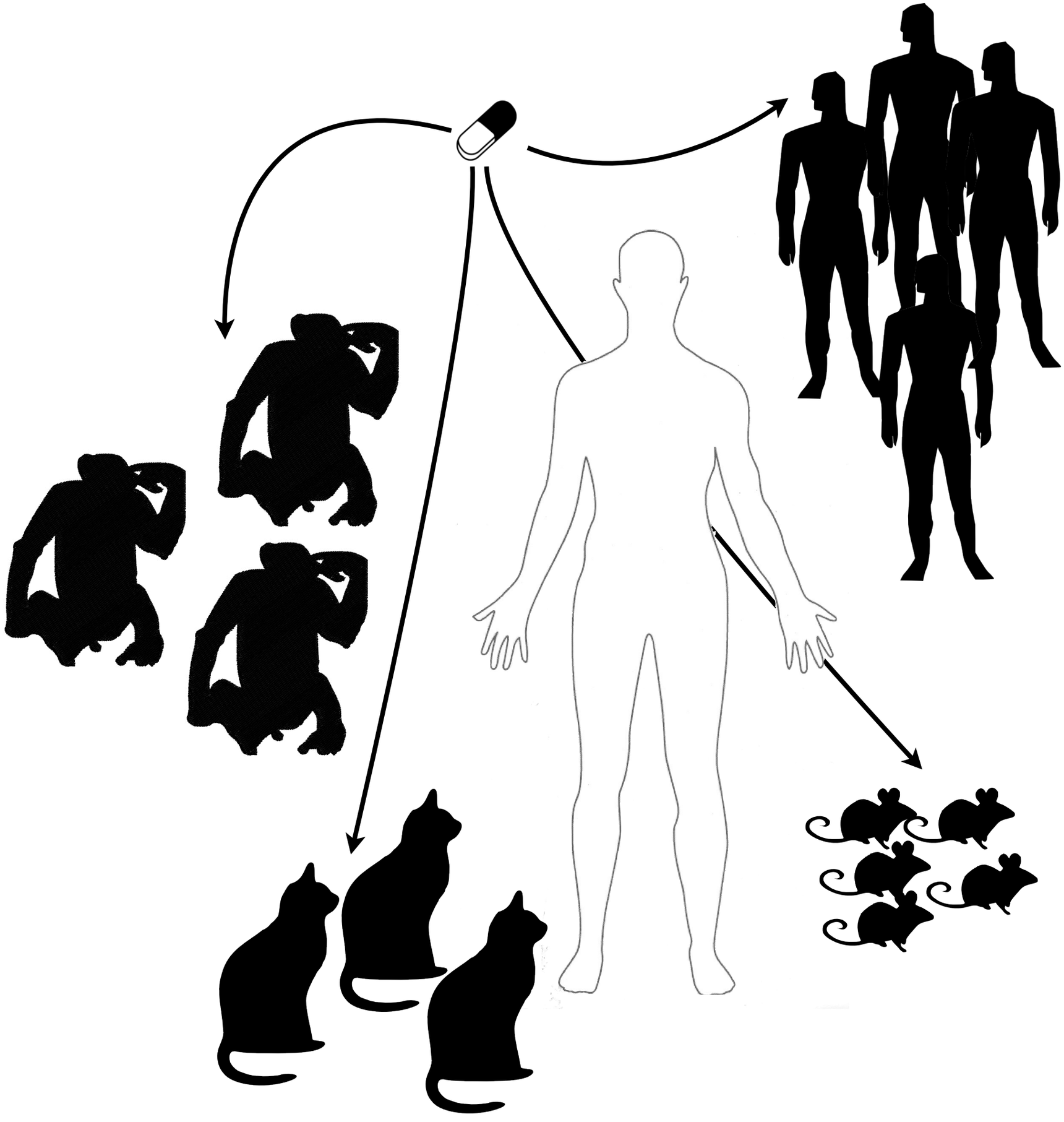
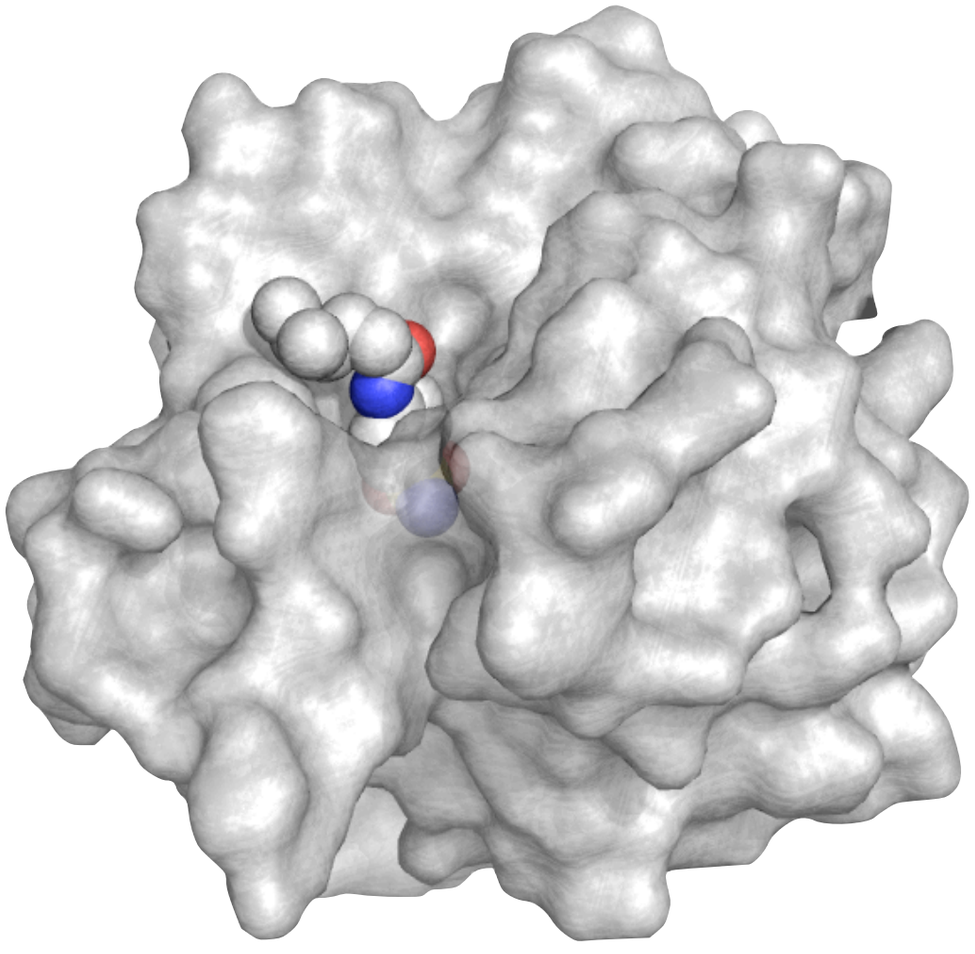
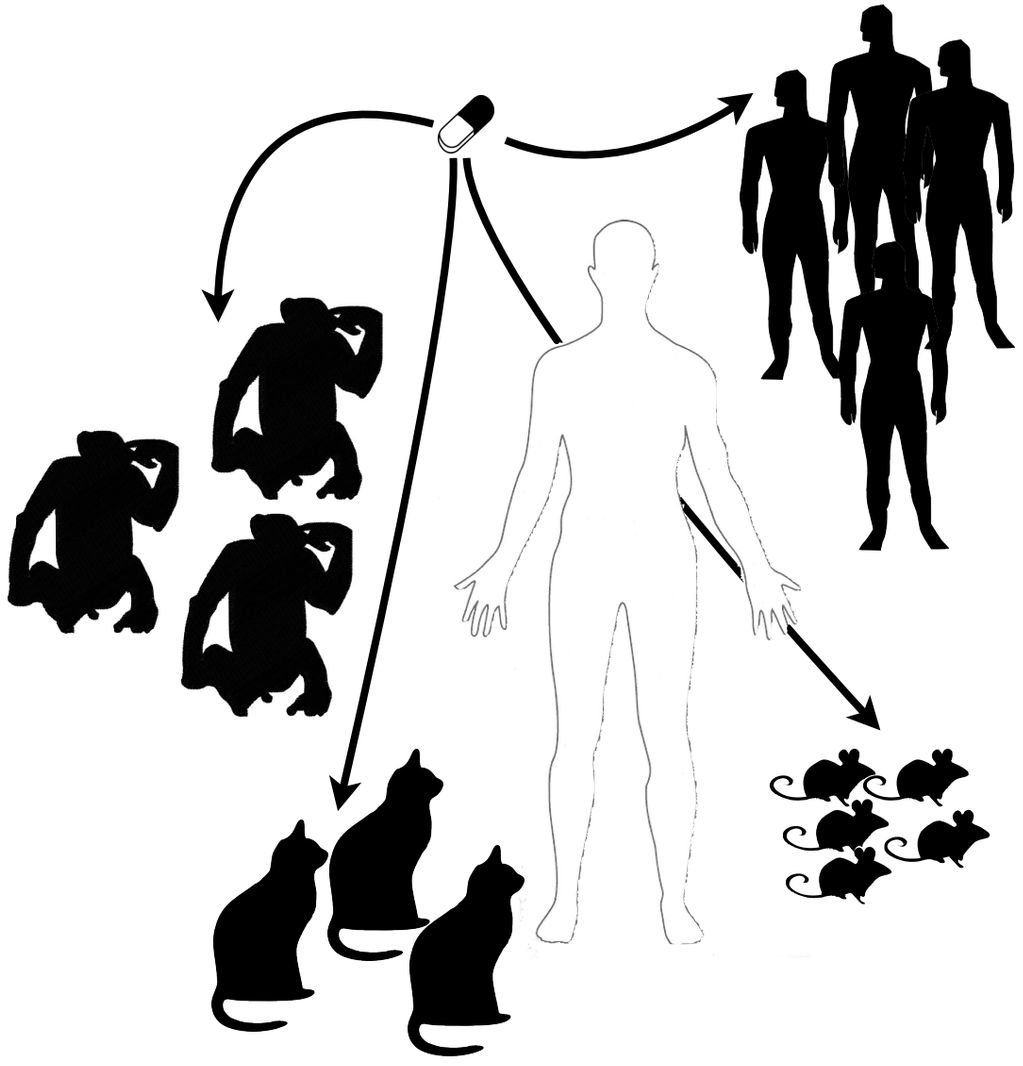


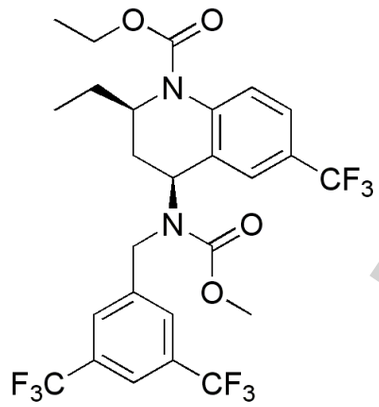




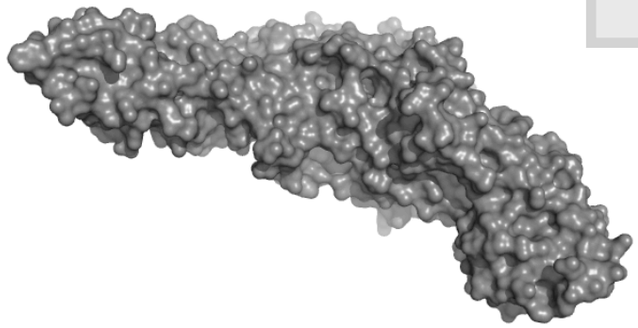




The low hanging fruit is gone. We are in the world of complex nonlinear systems (e.g. the human body...)



Torcetrapib (Pfizer)



cholesterylester transfer protein (CETP)

HDL

LDL

Pfizer gives the first dose of torcetrapib to patients.

Phase II trials begin

Phase III trials begin

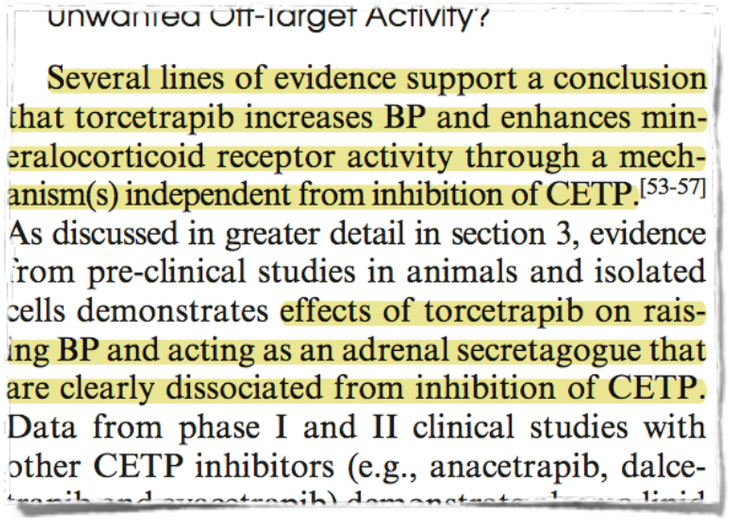
NEJM Study

Pfizer halts torcetrapib

1999 2000 2003 2004 2006

Timeline of Pfizer's Torcetrapib

Not long after torcetrapib demise, Pfizer announced that it was **cutting 10,000 jobs**. The company spent **$800 million** developing the drug.



unwanted Off-Target Activity?

Several lines of evidence support a conclusion that torcetrapib increases BP and enhances mineralocorticoid receptor activity through a mechanism(s) independent from inhibition of CETP.[53-57] As discussed in greater detail in section 3, evidence from pre-clinical studies in animals and isolated cells demonstrates effects of torcetrapib on raising BP and acting as an adrenal secretagogue that are clearly dissociated from inhibition of CETP. Data from phase I and II clinical studies with other CETP inhibitors (e.g., anacetrapib, dalce-

Johns et al. On-and Off-Target Pharmacology of Torcetrapib: Current Understanding and Implications for the Structure Activity Relationships (SAR), Discovery and Development of Cholesteryl Ester-Transfer Protein (CETP) Inhibitors. Drugs (2012) 72 491–507

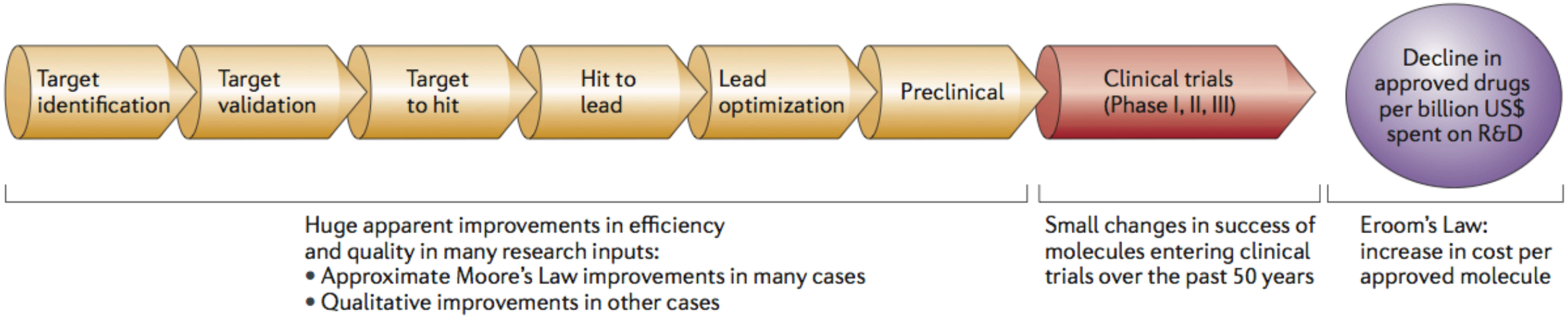


Figure 2 | **How can some parts of the R&D process improve, yet the overall efficiency decline?** Dramatic improvements in brute force screening methods and basic science should have tended to increase the efficiency of the research process (more leads tested against more targets, at a lower cost; shown in gold) and raised its quality (better targets as disease pathways and mechanisms are understood, better leads that avoid old mistakes surrounding ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics, and so on). This, in turn, should have increased the probability that molecules would succeed in the clinic (shown in red), which in turn should have increased overall efficiency, as research and development (R&D) costs are dominated by the cost of failure. However, the probability that a small molecule successfully completes clinical trials has remained more or less constant for 50 years[21], whereas overall R&D efficiency has declined[24]. One possible explanation for this is that much of the industry industrialized and 'optimized' the wrong set of R&D activities.

The 'basic research–brute force' bias. The 'basic research–brute force' bias is the tendency to overestimate the ability of advances in basic research (particularly in molecular biology) and brute force screening methods (embodied in the first few steps of the standard discovery and preclinical research process) to increase the probability that a molecule will be safe and effective in clinical trials (FIG. 2). We suspect that this has been the intellectual basis for a move away from

There have been several interesting critiques of modern research[33,48,55], but here we highlight two potential problems. First, much of the pharmaceutical industry's R&D is now based on the idea that high-affinity binding to a single biological target linked to a disease will lead to medical benefit in humans[39]. However, if the causal link between single targets and disease states is weaker than commonly thought[38,56], or if drugs rarely act on a single target, one can

periods.

Indeed, drug-like small molecules tend to bind promiscuously, and this sometimes turns out to have an important role in their efficacy[47,57] as well as their so-called off-target effects[39]. Targets are parts of complex networks leading to unpredictable effects[58], and biological systems show a high degree of

Scannell JW, Blanckley A, Boldon H, et al. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 2012; 11:191–200

Target-based approaches may not be optimal

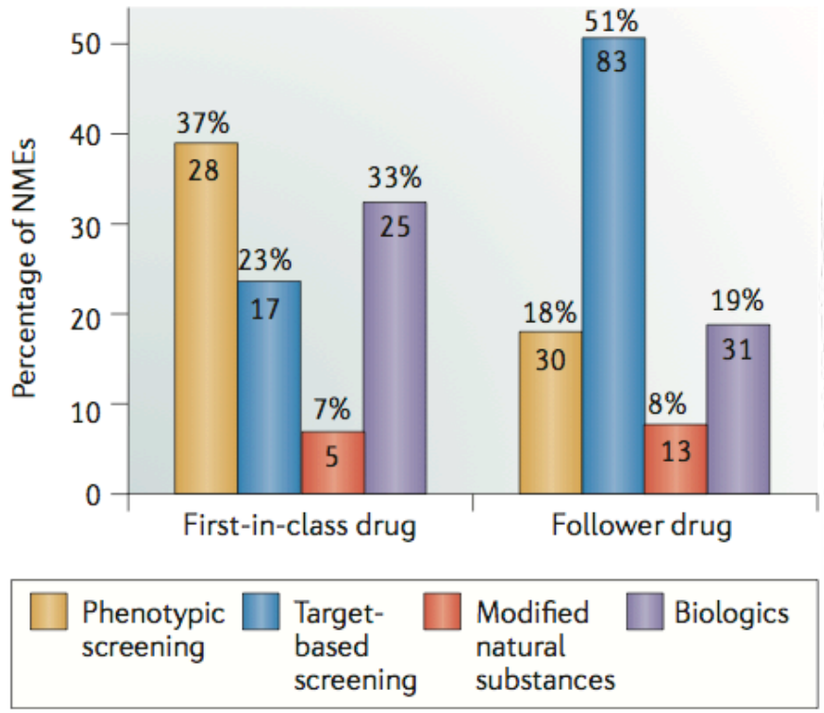


Figure 2 | **The distribution of new drugs discovered between 1999 and 2008, according to the discovery strategy.** The graph illustrates the number of new molecular entities (NMEs) in each category. Phenotypic screening was the most successful approach for first-in-class drugs, whereas target-based screening was the most successful for follower drugs during the period of this analysis. The total number of medicines that were discovered via phenotypic assays was similar for first-in-class and follower drugs — 28 and 30, respectively — whereas the total number of medicines that were discovered via target-based screening was nearly five times higher for follower drugs versus first-in-class drugs (83 to 17, respectively).

From Swinney and Anthony. How were new medicines discovered? Nat Rev Drug Discov (2011) 10 507–519

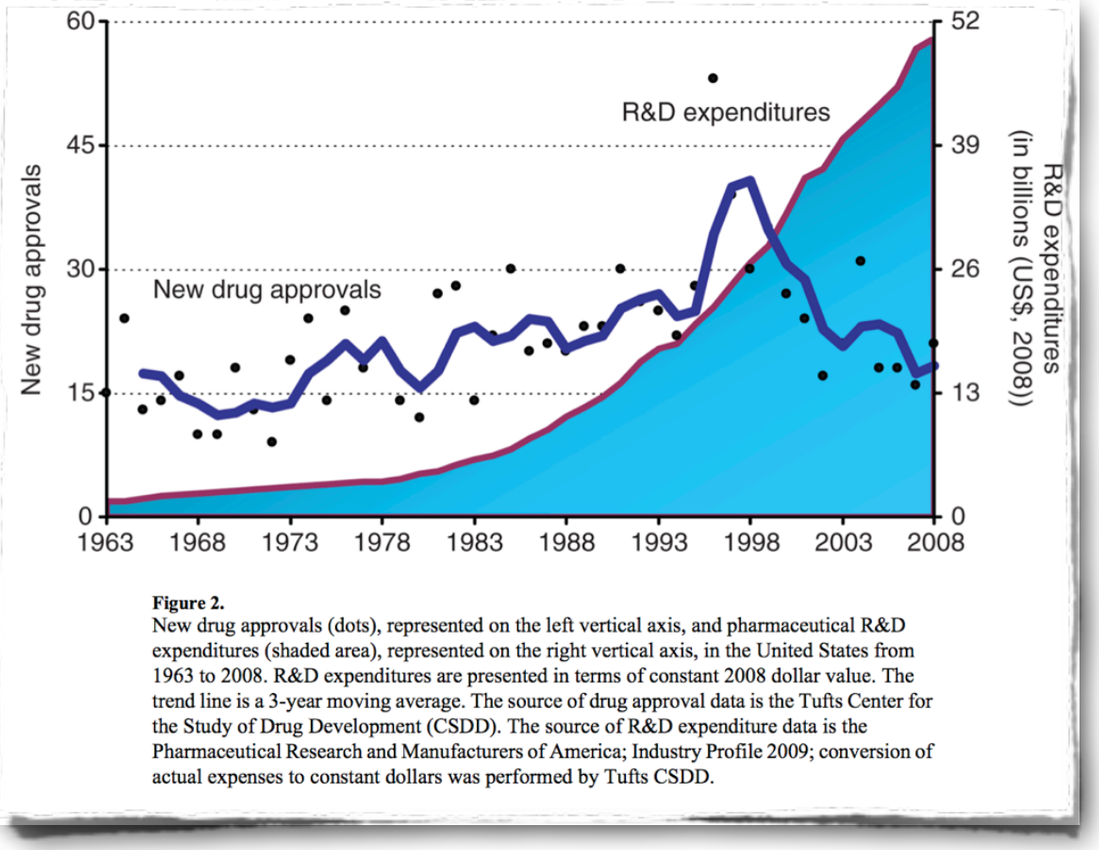


Figure 2.
New drug approvals (dots), represented on the left vertical axis, and pharmaceutical R&D expenditures (shaded area), represented on the right vertical axis, in the United States from 1963 to 2008. R&D expenditures are presented in terms of constant 2008 dollar value. The trend line is a 3-year moving average. The source of drug approval data is the Tufts Center for the Study of Drug Development (CSDD). The source of R&D expenditure data is the Pharmaceutical Research and Manufacturers of America; Industry Profile 2009; conversion of actual expenses to constant dollars was performed by Tufts CSDD.

From Kaitin. Deconstructing the drug development process: the new face of innovation. Clin. Pharmacol. Ther (2010) 87 356 361

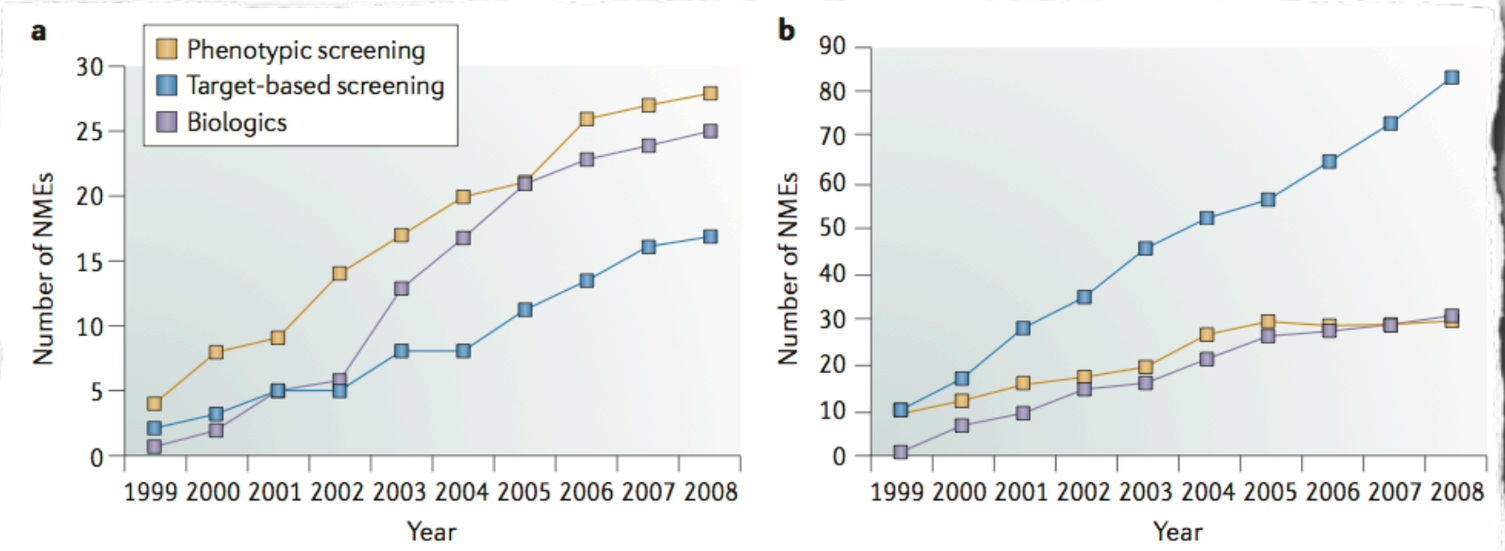


Figure 3 | **Cumulative distribution of new drugs by discovery strategy. a** | First-in-class drugs. A lag is not strongly apparent in a comparison of the cumulative number of small-molecule new molecular entities (NMEs) that were discovered from the different approaches during the period analysed. **b** | Follower drugs. For follower drugs, the ratio of small-molecule NMEs discovered through target-based screening to those discovered through phenotypic screening appears to increase in the second half of the time period.

Finding new uses for old drugs

TABLE 1

Examples of approved drug molecules identified using low-throughput screening methods as having effects against diseases other than the original target[a]

Molecule	Original use	New use	Method of discovery	Refs
Aprepitant	Nausea: NK-1 receptor antagonist	Drug-resistant HIV-1 infection: downregulates CCR5 in macrophages Cryptosporidiosis in immunosuppressed hosts	Initial hypothesis tested with another NK-1 receptor antagonist *in vitro* Tested *in vivo* in immunosuppressed mice infected with *Cryptosporidium parvum*; decreased substance P levels	[99,100] [101]
Amiodarone	Class III anti-arrhythmic	Chagas disease: blocks ergosterol biosynthesis	Literature search	[102]
Glybenclamide	Antidiabetic	Antithrombotic activity in mouse models IC_{50} 9.6 μM	Common pharmacophore with an experimental TP receptor antagonist SQ29,548	[103]
Tamoxifen	Antiestrogen	Anti-protozoal: *Leishmania amazonensis* IC_{50} 11.1–16.4 μM	Focused screening to test hypothesis and *in vivo* mice studies	[104,105]
Trimetrexate	Antifolate used in *Pneumocystis carinii* infection in patients with AIDS	Inhibitor of *Trypanosoma cruzi* DHFR IC_{50} 6.6 nM	Enzyme activity and antiparasite activity assays for one compound	[106]
Riluzole	Amyotrophic lateral sclerosis: inhibits glutamate release and reuptake	Currently in clinical trials for treating melanoma, but might have activity against other cancers	Treatment of GRM1-positive human melanoma cells reduced levels of released glutamate, suppressed melanoma cell growth and also suppressed tumor growth in xenograft model; induced cell cycle arrest, leading to apoptosis	[107]
Sertraline	Antidepressant (selective serotonin reuptake inhibitor)	Neuroprotective, prolongs survival, improves motor performance and ameliorates brain atrophy in the R6/2 HD model	Previously shown that another SSRI was neuroprotective	[108]

[a] Abbreviations: CCR5, chemokine receptor 5; DHFR, dihydrofolate reductase; GRM1, glutamate receptor, metabotropic 1; NK-1, neurokinin-1 receptor; SSRI, selective serotonin reuptake inhibitors.

Ekins S, Williams AJ, Krasowski MD, et al. In silico repositioning of approved drugs for rare and neglected diseases. Drug Discov Today 2011; 16:298–310

TABLE 2

Examples of approved drug molecules identified using HTS or *in silico* screening methods as having effects against diseases other than original target[a]

Molecule	Original use	New use	Method of discovery	Refs
Itraconazole	Antifungal: lanosterol 14α-demethylase inhibitor	Inhibition of angiogenesis by inhibiting human lanosterol 14α-demethylase; IC_{50} 160 nM	*In vitro* HUVEC proliferation screen against FDA-approved drugs (JHCCL)	[109]
Astemizole	Non-sedating antihistamine (removed from US market by FDA in 1999)	Antimalarial IC_{50} 227 nM against *Plasmodium falciparum* 3D7	*In vitro* screen for *P. falciparum* growth of 1937 FDA-approved drugs (JHCCL)	[110]
Mycophenolic acid	Immunosuppressive drug: inhibits guanine nucleotide biosynthesis	Inhibition of angiogenesis by targeting type 1 inosine monophosphate dehydrogenase; IC_{50} 99.2 nM	*In vitro* HUVEC proliferation screen of 2450 FDA- and foreign-approved drugs (JHCCL)	[111]
Entacapone and tolcapone	Parkinson's Disease: catechol-*O*-methyltransferase inhibitors	Antitubercular: entacapone inhibits InhA; IC_{50} 80 μM	Used a chemical systems biology approach	[77]
Nitazoxanide	Infections caused by *Giardia* and *Cryptosporidium* spp.	Antitubercular: multiple potential targets	Screens against replicating and non-replicating Mtb	[112]
(±)-2-amino-3-phosphonopropionic acid	Human metabolite, mGluR agonist	Antimalarial: inhibits HSP-90; IC_{50} 0.06 μM against *P. falciparum* 3D7	HTS screening of 4000 compounds	[113]
Acrisorcin	Antifungal	Antimalarial: inhibits HSP-90; IC_{50} 0.05 μM against *P. falciparum* 3D7	HTS screening of 4000 compounds	[113]
Harmine	Anticancer	Antimalarial: inhibits HSP-90; IC_{50} 0.05 μM against *P. falciparum* 3D7	HTS screening of 4000 compounds	[113]
Acetophenazine, fluphenazine and periciazine	Antipsychotics–D2 and 5-HT_2 inhibitors	Human androgen receptor antagonists acetophenazine (K_i 0.8 μM), fluphenazine(K_i 0.8 μM), periciazine (K_i 3.0 μM)	Docking of known drugs into androgen receptor followed by *in vitro* screening	[96]
Levofloxacin, gatifloxacin, sarafloxacin, moxifloxacin and gemifloxacin	DNA gyrase	Active against ATCC17978; inactive against BAA-1605 MIC ≤0.03–0.04 (mg/l)	Screening of 1040 drugs from microsource drugs library versus *Acinetobacter baumannii*	[114]
Bithional, bortezomib, cantharidin, chromomycin A3, duanorubicin, digitoxin, ectinascidin 743, emetine, fluorosalen, manidipine HCl, narasin, lestaurtinib, ouabain, sorafenib tosylate, sunitinib malate, tioconazole, tribromsalen, triclabendazolum and zafirlukast	Various	NF-κB inhibitors; IC_{50} 0.02–39.8 μM	Screening of NCGC pharmaceutical collection of 2816 small molecules *in vitro*	[115]
Pyrvinium pamoate	Anthelmintic	Antitubercular: Alamar blue assay	*In vitro* screen against 1514 known	[10]

Ekins S, Williams AJ, Krasowski MD, et al. In silico repositioning of approved drugs for rare and neglected diseases. Drug Discov Today 2011; 16:298–310

What is Systems Biology?

Cartesian rationalism, the essence of **reductionism**:

1. Analysis Break down complex problem in simpler problems
2. Solve simpler, partial problems were solved
3. Synthesis allows the comprehension and resolution of the initial complex problems as a result of the combination of the partial results.

Aristotle (Metaphysics, book 8, 1045a, 8-10) "The whole is something over and above its parts, and not just the sum of them all."

Jan Smuts coined the term holism to refer to this principle, according to which the comprehension of systems as a whole is irreducible.

Ursus Wehrli *Tidying Up Art 2003*
http://www.ted.com/talks/ursus_wehrli_tidies_up_art.html

Keit Haring, *Untitled 1986*

Omics produce partlists

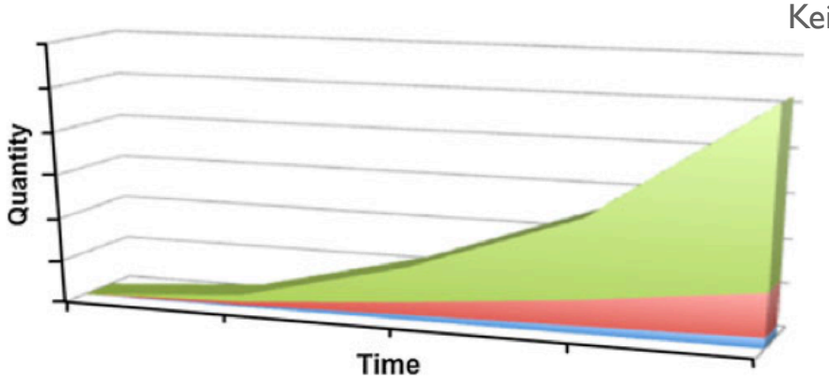


Fig. 2 The growing gap between the amount of available scientific data and the actual new knowledge generated from these data. Axis *X* time; axis *Y* relative accumulated quantity of scientific data (*green*), information (*reddish*) and knowledge (*blue*).

From Medina MA. Systems biology for molecular life sciences and its impact in biomedicine. Cell Mol Life Sci 2012; 70:103

System

network of interconnected and mutually dependent components that constitute a unified whole

hierarchical structure

structure maintained through interrelationship between its components

dynamic, thermodynamically open system

ical system can be derived from insight into four key properties:

1) System structures. These include the network of gene interactions and biochemical pathways, as well as the mechanisms by which such interactions modulate the physical properties of intracellular and multicellular structures.

2) System dynamics. How a system behaves over time under various conditions can be understood through metabolic analysis, sensitivity analysis, dynamic analysis methods such as phase portrait and bifurcation analysis, and by identifying essential mechanisms underlying specific behaviors. Bifurcation analysis traces time-varying change(s) in the state of the system in a multidimensional space where each dimension represents a particular concentration of the biochemical factor involved.

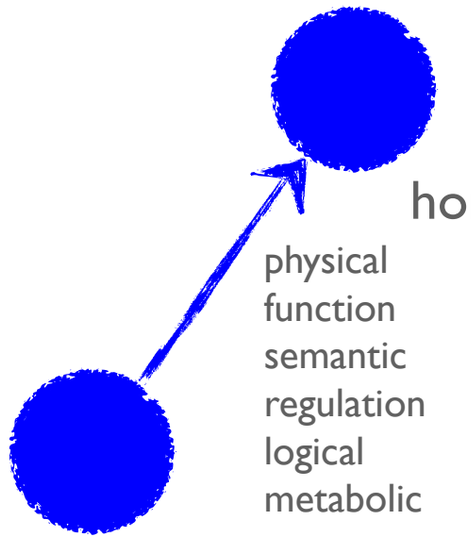
3) The control method. Mechanisms that systematically control the state of the cell can be modulated to minimize malfunctions and provide potential therapeutic targets for treatment of disease.

4) The design method. Strategies to modify and construct biological systems having desired properties can be devised based on definite design principles and simulations, instead of blind trial-and-error.

Kitano H. Systems biology: a brief overview. Science 2002; 295:1662

gene
RNA
protein
drug/ligand
disease
patient
process

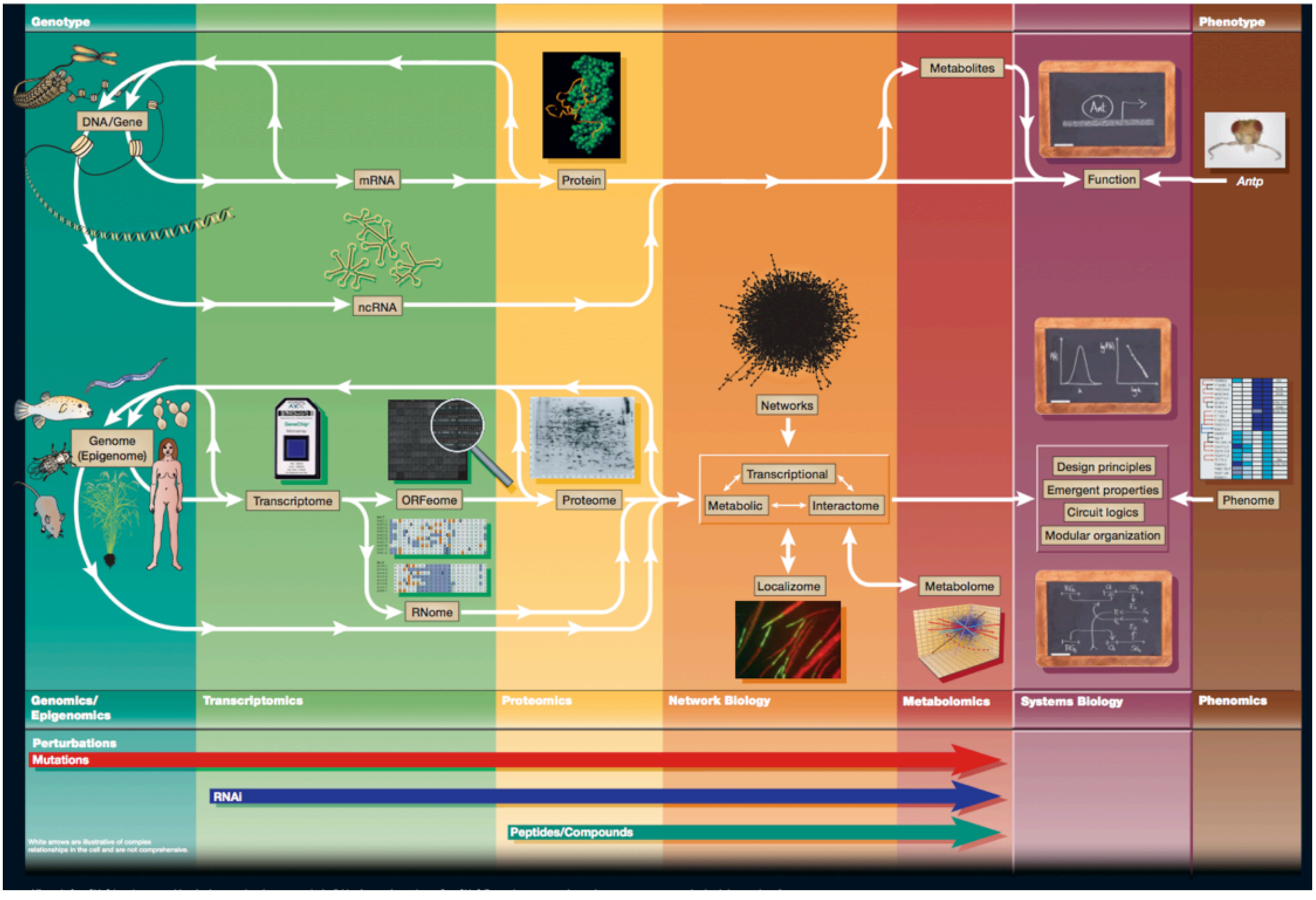
heterogeneous/bipartite



homogeneous

physical
function
semantic
regulation
logical
metabolic

Complex Networks



Marc Vidal and Eileen E. M. Furlong From OMICS to systems biology. Nature Reviews Genetic 2004; 5:10

Drug repositioning strategies

large-scale computational approach that simulates three-dimensional binding between existing drugs and target proteins to predict novel drug-target interactions

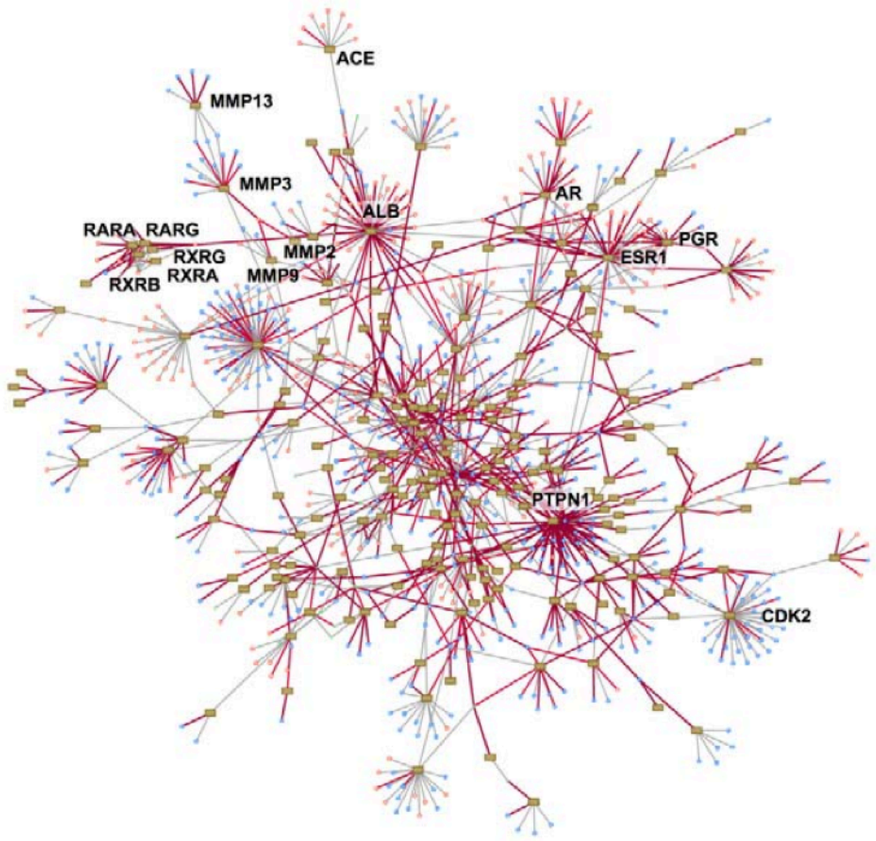


Figure 3. Network of known protein-drug interactions. Proteins are shown as rectangular boxes (nodes), drugs are shown as pink (approved) and blue (experimental) circles, and edges represent known interactions annotated by DrugBank. Edges colored red denote known interactions that were docked with a good icm-score. Here we show only the 252 proteins for which at least one known drug docked well – the 'reliable-for-docking' set. The proteins at the bottom of the graph are not connected to other proteins through shared binding drugs.
doi:10.1371/journal.pcbi.1002139.g003

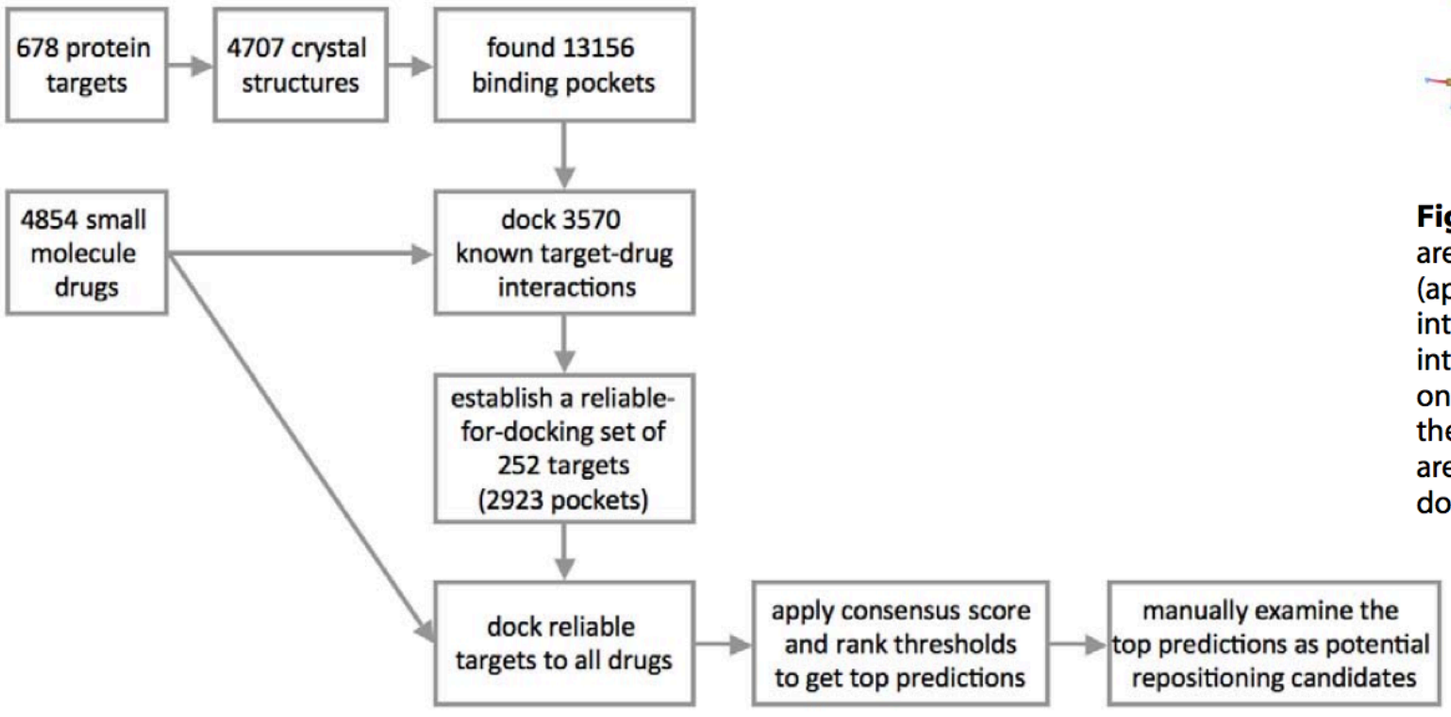


Figure 1. The computational molecular-docking pipeline.
doi:10.1371/journal.pcbi.1002139.g001

Li Y, An J, Jones S. A Computational Approach to Finding Novel Targets for Existing Drugs. PLoS Computational Biology 7:e1002139

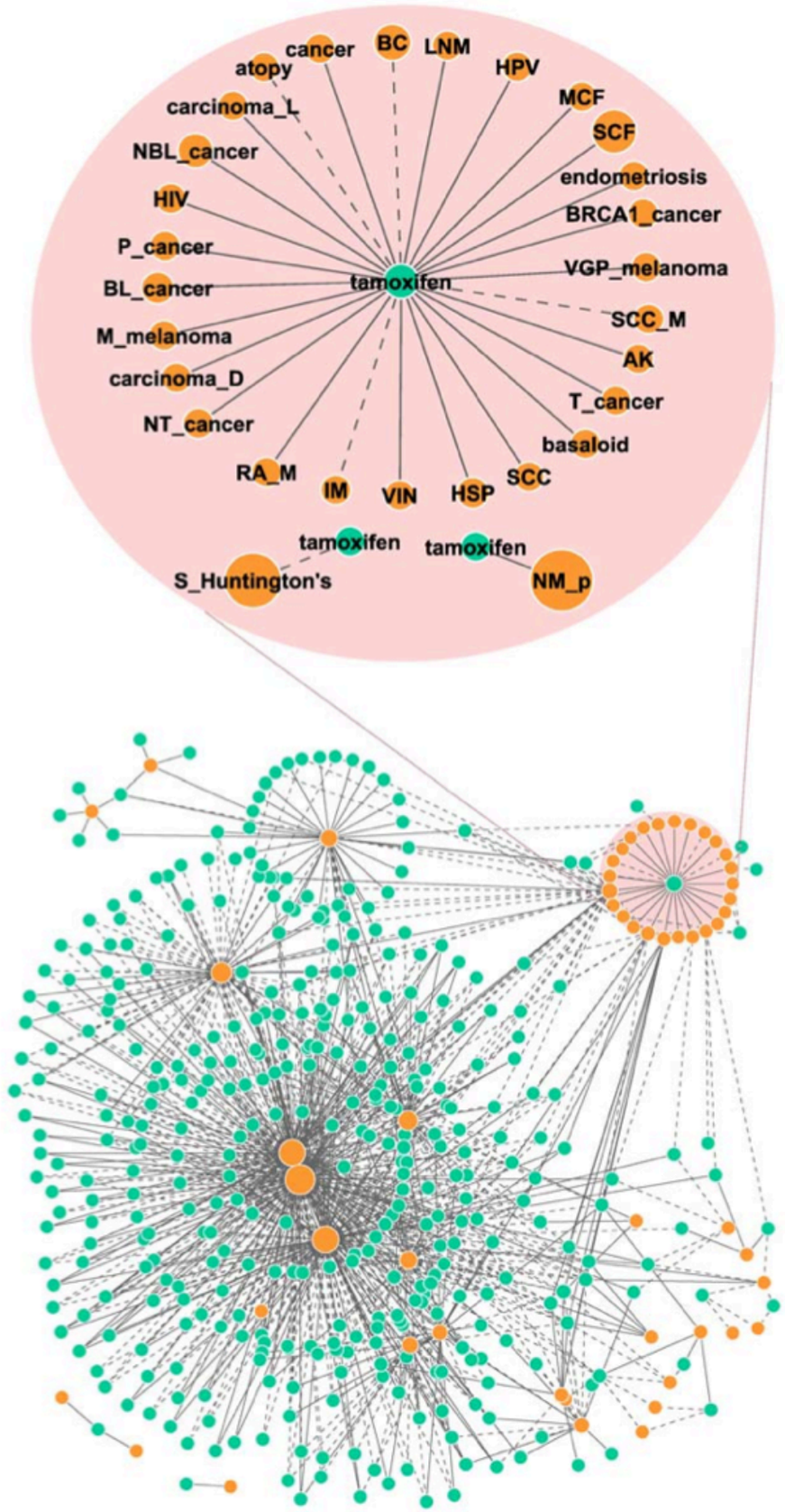


Figure 2. Disease-drug network. This disease-drug network contains a total of 49 diseases in dark cyan nodes, 213 drugs in gold, and 906 connections. The size of the nodes is proportional to the number of links. Positive matches are shown by solid lines and negative relationships by dotted lines. Multiple nodes with the same descriptive name exist because the corresponding profiles were generated under different conditions or

Here we generate a large-scale disease-disease, drug-drug and disease-drug network by directly matching their molecular profiles; in particular, their transcriptomic profiles thanks to the accumulation of whole-genome gene expression data available in the public domain. The main assumption of our approach is that gene expression profiles of many (but not all) diseases and drugs can characterize to some extent the effects of disease and drugs; therefore, these diseases and drugs can be related based on the similarity/dissimilarity of their induced expression profiles. This assumption, though not without caveats and limitations, has been

Hu G, Agarwal P. Human disease-drug network based on genomic expression profiles. PLoS ONE 2009; 4:e6536

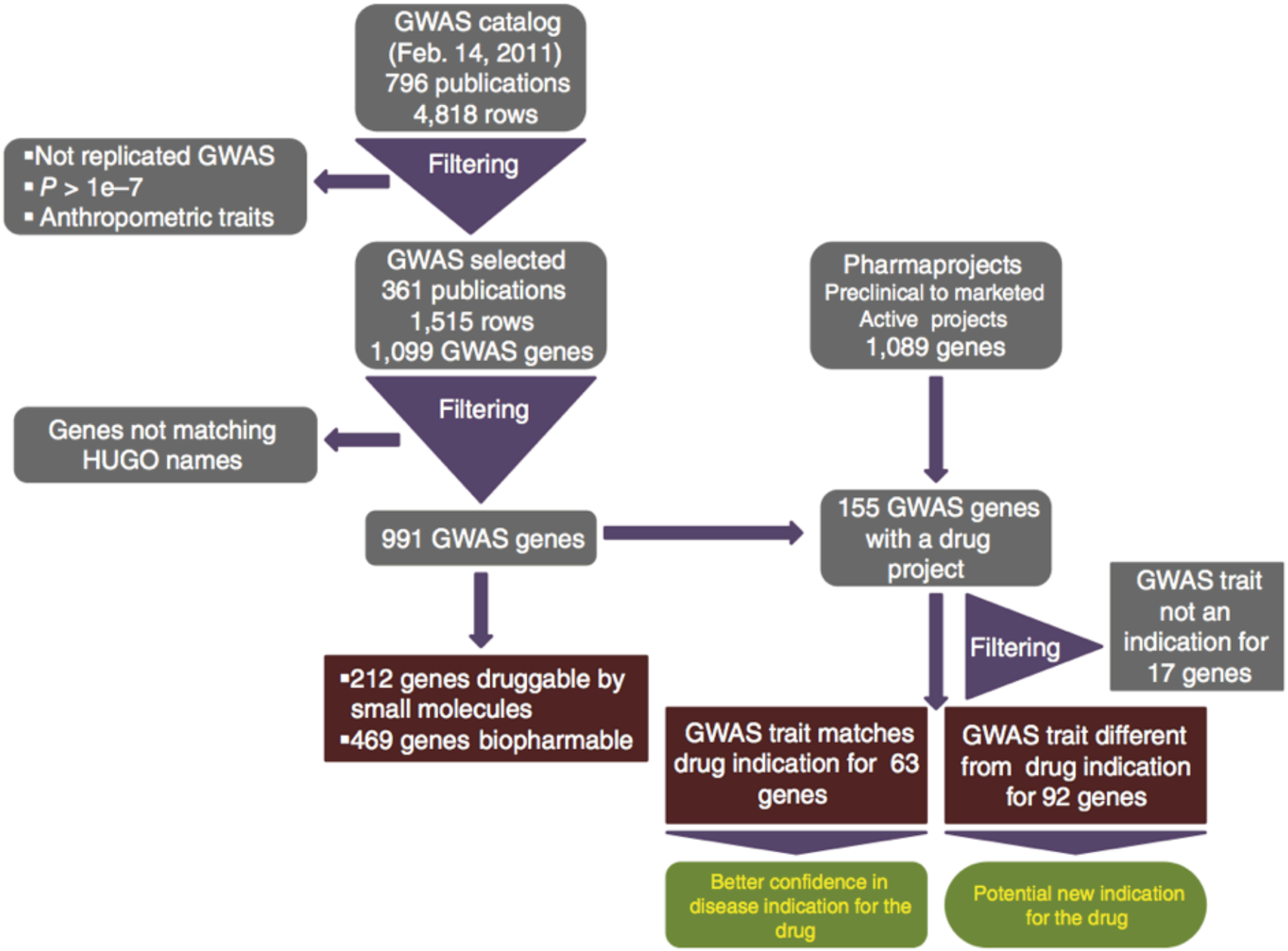


Figure 1 Analysis pipeline. Nine hundred ninety-one GWAS-associated genes were selected from the GWAS catalog after two filtering steps (**Supplementary Methods**). These genes were evaluated as potential drug targets for small molecules and biopharmaceuticals. One hundred fifty-five of these 991 genes were also targeted by drugs currently in pharmaceutical pipelines, as listed on the Pharmaprojects database, which has a total of 1,089 genes targeted by pipeline drugs. A total of 63 individual genes mapped to 52 different GWAS traits and drugs with the same or closely related indication to the GWAS traits (considered as matches). Conversely, 92 individual genes map to 51 GWAS traits and drugs with indications different from the GWAS traits (considered mismatches or potential drug-repositioning opportunities). Some genes are in both lists as they have multiple GWAS phenotypes that resulted in both a match to an existing indication and also a potentially novel indication.

Sanseau P, Agarwal P, Barnes MR, et al. Use of genome-wide association studies for drug repositioning. Nat Biotechnol 2012; 30:317–320

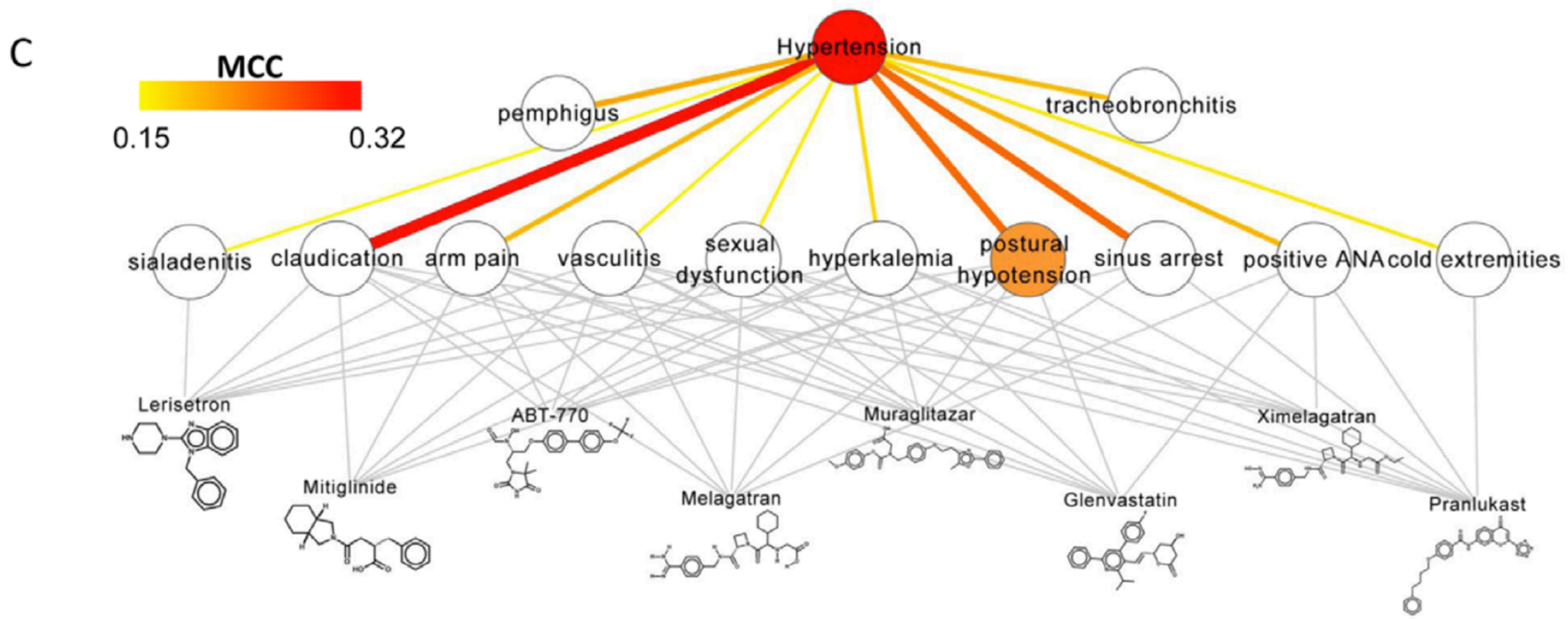


Figure 3. Predict drugs' repositioning potential for hypertension via DRoSEf. a) The distribution of the Θ score for the positive (red) and negative (blue) set for hypertension. The molecules with high Θ score in negative set (red square bracket) were chosen as the candidates for treating hypertension. b) The ROC curve of using Θ score to predict hypertension. The AUC is 0.74. c) Predicted relationships of the top molecules with the 12 SEs and the association of these SEs with the hypertension. The binary association among molecules and SEs is in grey lines. The association strength between SE and disease is reflected in the color and the width of the edge. *Postural hypotension* is highlighted as the SE explicitly linked to hypertension.

Drug repositioning helps fully explore indications for marketed drugs and clinical candidates. Here we show that the clinical side-effects (SEs) provide a human phenotypic profile for the drug, and this profile can suggest additional disease indications. We extracted 3,175 SE-disease relationships by combining the SE-drug relationships from drug labels and the drug-disease relationships from PharmGKB. Many relationships provide explicit repositioning hypotheses, such as drugs causing hypoglycemia are potential candidates for diabetes. We built Naïve Bayes models to predict indications for 145

Yang L, Agarwal P. Systematic drug repositioning based on clinical side-effects. PLoS ONE 2011; 6:e28025

Modeling complex systems through networks

1. INTRODUCTION

Networks have become a pervasive abstraction with which many different types of complex system are modeled [1]. They provide an intuitive way of defining a set of components or agents and the interactions that take place between them; the main ingredients of any complex system. Examples range from cell populations communicating via quorum sensing in biology [2] to power grids and the

Correspondence to: T. E. Gorochowski, Bristol

Gorochowski et al. Evolving dynamical networks: A formalism for describing complex systems. Complexity (2012) 17 3 18-25

Drug Discovery Today • Volume 00, Number 00 • May 2012 REVIEWS

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Science Signaling AAAS

Network-Based Tools for the Identification of Novel Drug Targets
Illés J. Farkas, Tamás Korcsmáros, István A. Kovács, Ágoston Mihalik, Robin Palotai, Gábor I. Simkó, Kristóf Z. Szalay, Máté Szalay-Beko, Tibor Vellai, Shijun Wang and Peter Csermely (17 May 2011)
Science Signaling **4** (173), pt3. [DOI: 10.1126/scisignal.2001950]

Network analysis has diverse roles in drug discovery

Samiul Hasan, Bhushan K. Bonde, Natalie S. Buchan and Matthew D. Hall

GlaxoSmithKline, Computational

Reviews • INFORMA

Opinion

Cell PRESS

Allo-network drugs: harnessing allostery in cellular networks

Ruth Nussinov[1,2], Chung-Jung Tsai[1] and Peter Csermely[3]

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Cancer Ins
[2] Sackler I
Tel Aviv U
[3] Departm

REVIEW

nature chemical biology

Network pharmacology: the next paradigm in drug discovery

Andrew L Hopkins

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FEBS Letters

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Minireview

A network medicine approach to human disease

Andreas Zanzoni [a], Montserrat Soler-López [a], Patrick Aloy [a,b,*]

[a] *Institute for Research in Biomedicine (IRB) and Barcelona Supercomputing Center (BSC), c/ Baldiri i Reixac 10-12, 08028 Barcelona, Spain*
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EDITORIAL

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Network pharmacology for cancer drug discovery: are we there yet?

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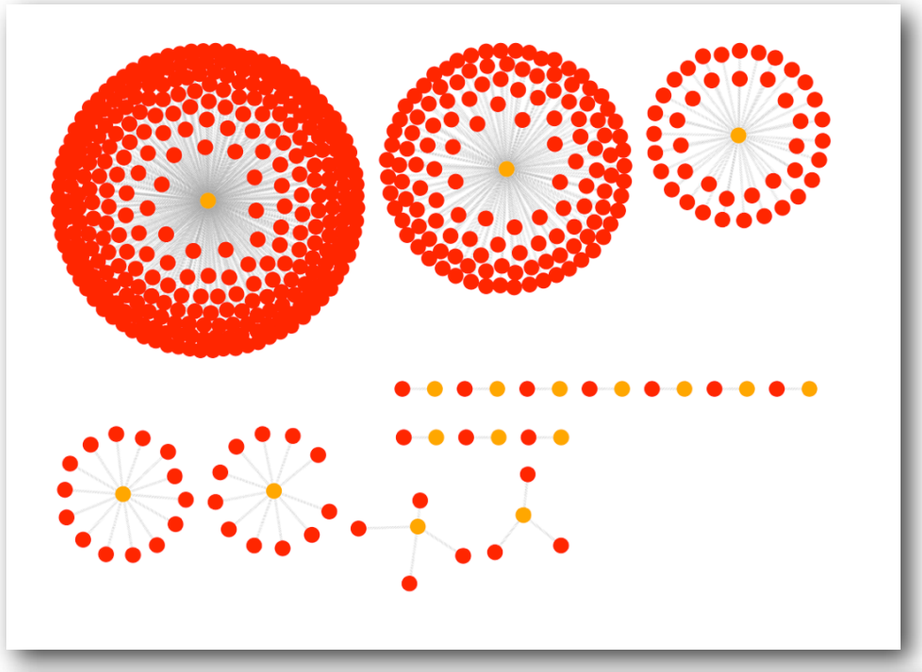
Multiscale Mechanisms of Drug Action

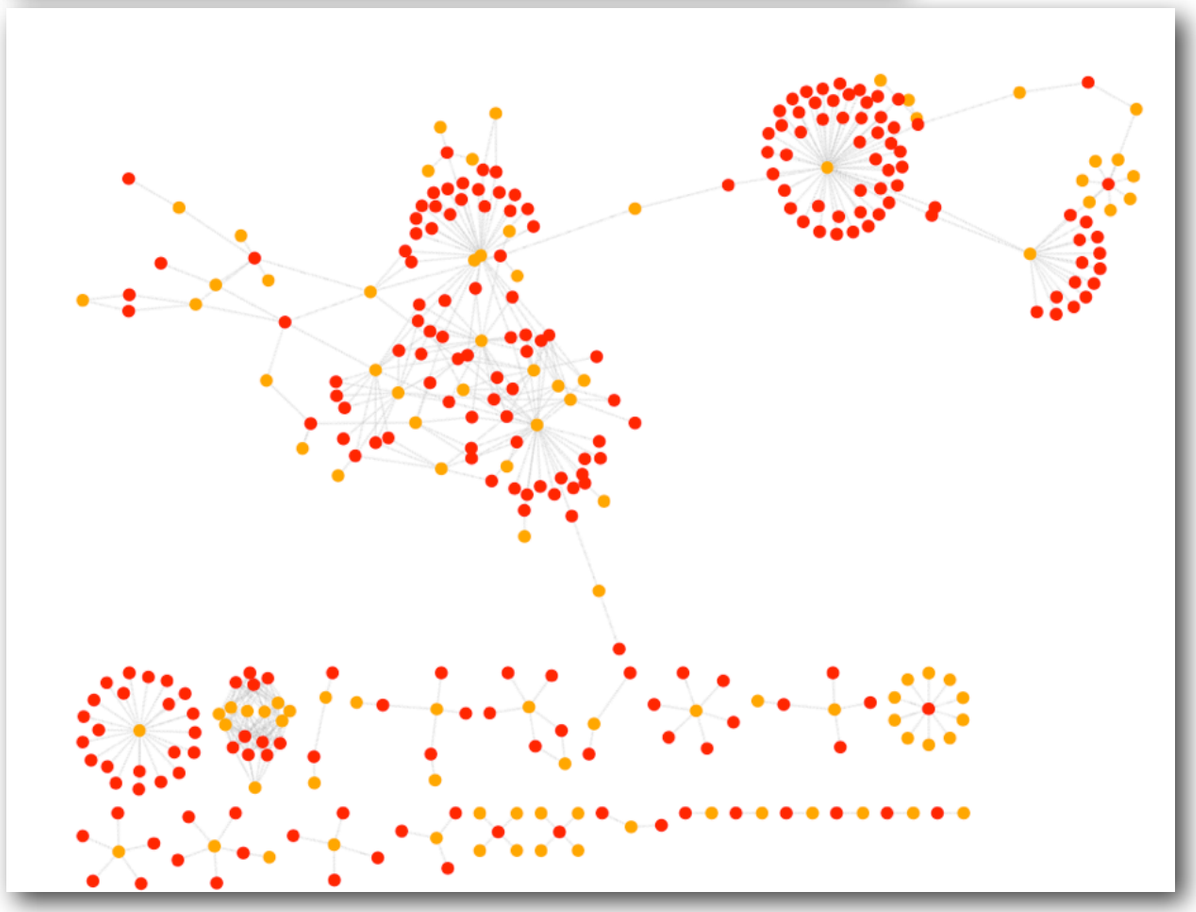
Shan Zhao and Ravi Iyengar

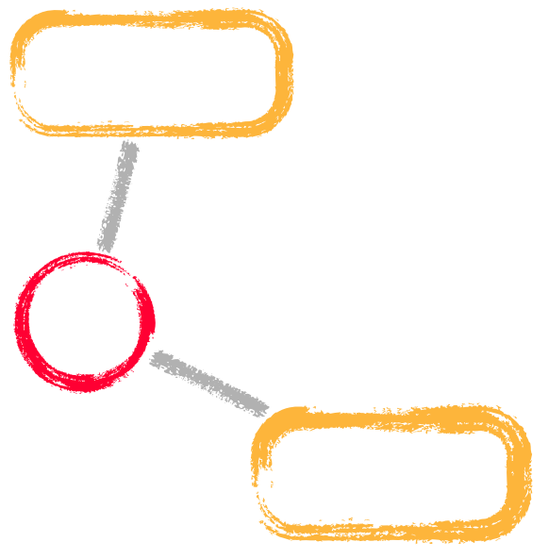
Department of Pharmacology and Systems Therapeutics, and Systems Biology Center New York, Mount Sinai School of Medicine, New York, New York 10029;
email: ravi.iyengar@mssm.edu

Clean drugs or dirty drugs?



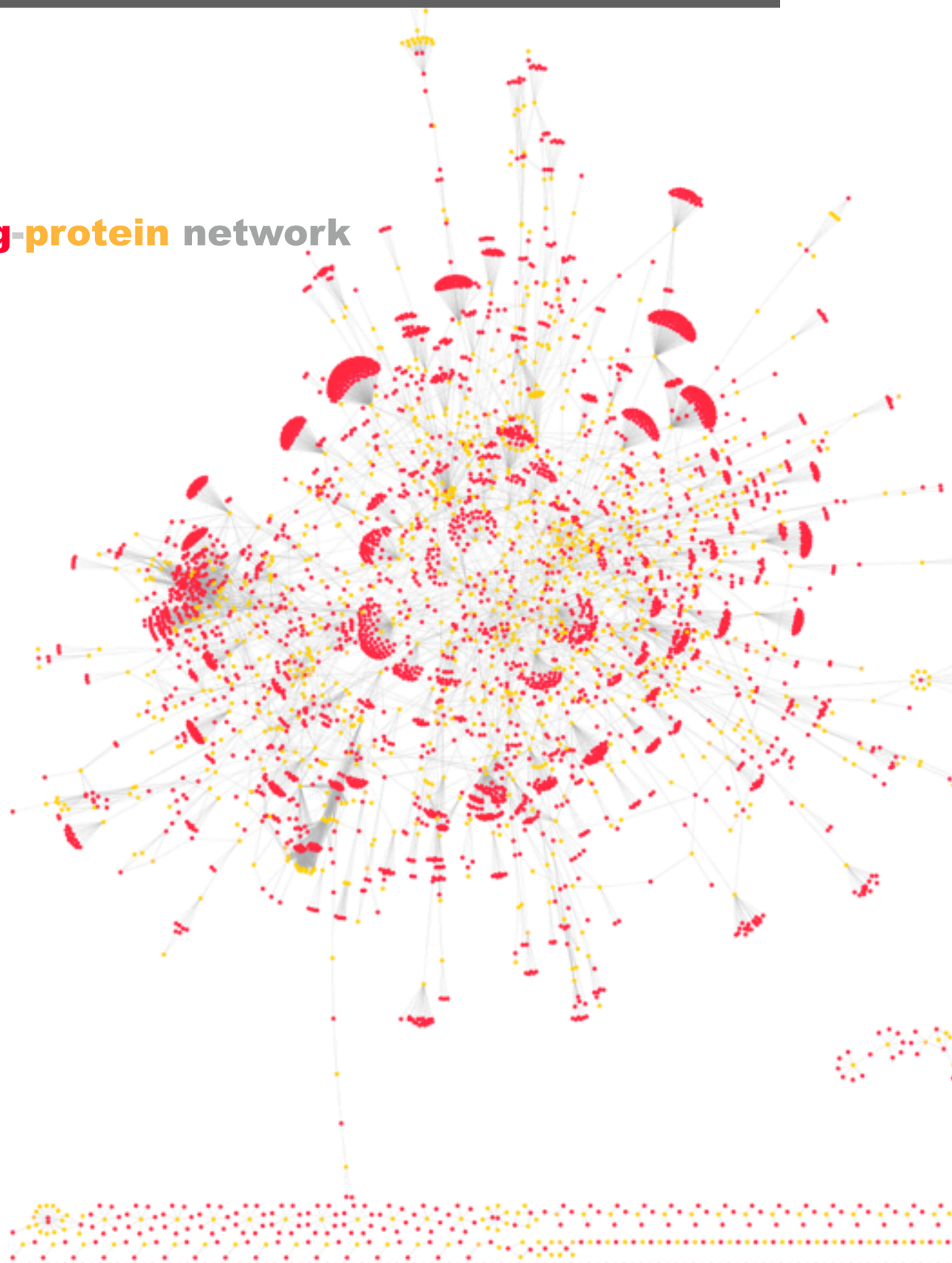
selective drug (clean drug)





promiscuous (dirty) drug

Not a bug but a feature



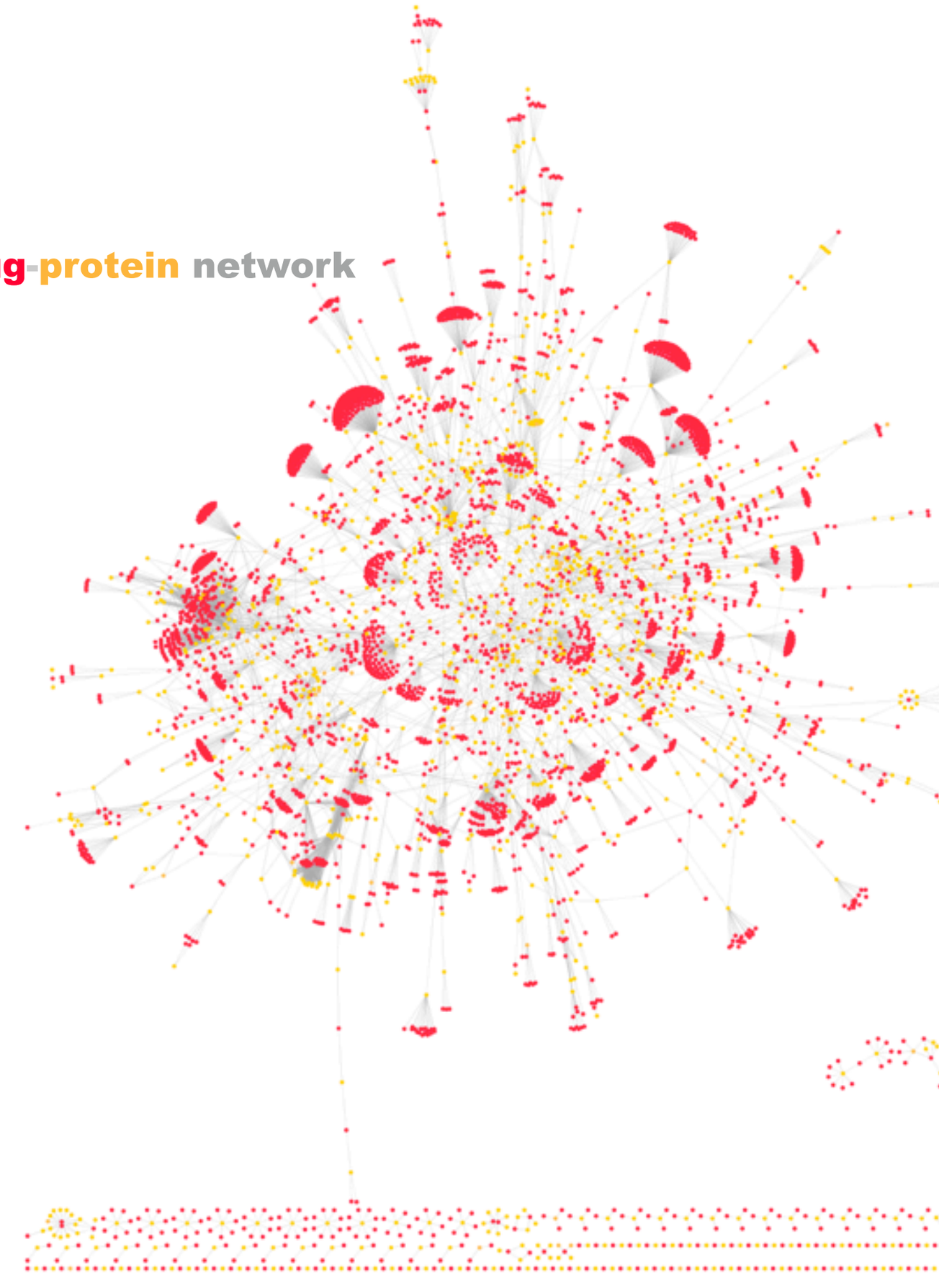
Polypharmacology: Drugs are not specific, they target more than one entity. This is not the exception but the rule

network-based drug design

"magic shotgun" drug able to bind multiple targets with low specificity

Zanzoni et al. Network medicine approach to human disease. FEBS Lett (2009) 583 1759–1765

drug-protein network



Exploit polypharmacology to:

- the identification new drug targets
- find new potential drugs with selective polypharmacology profiles
- elucidate optimal strategies of direct interference with several points in the same pathway, that can assist new therapeutical approaches

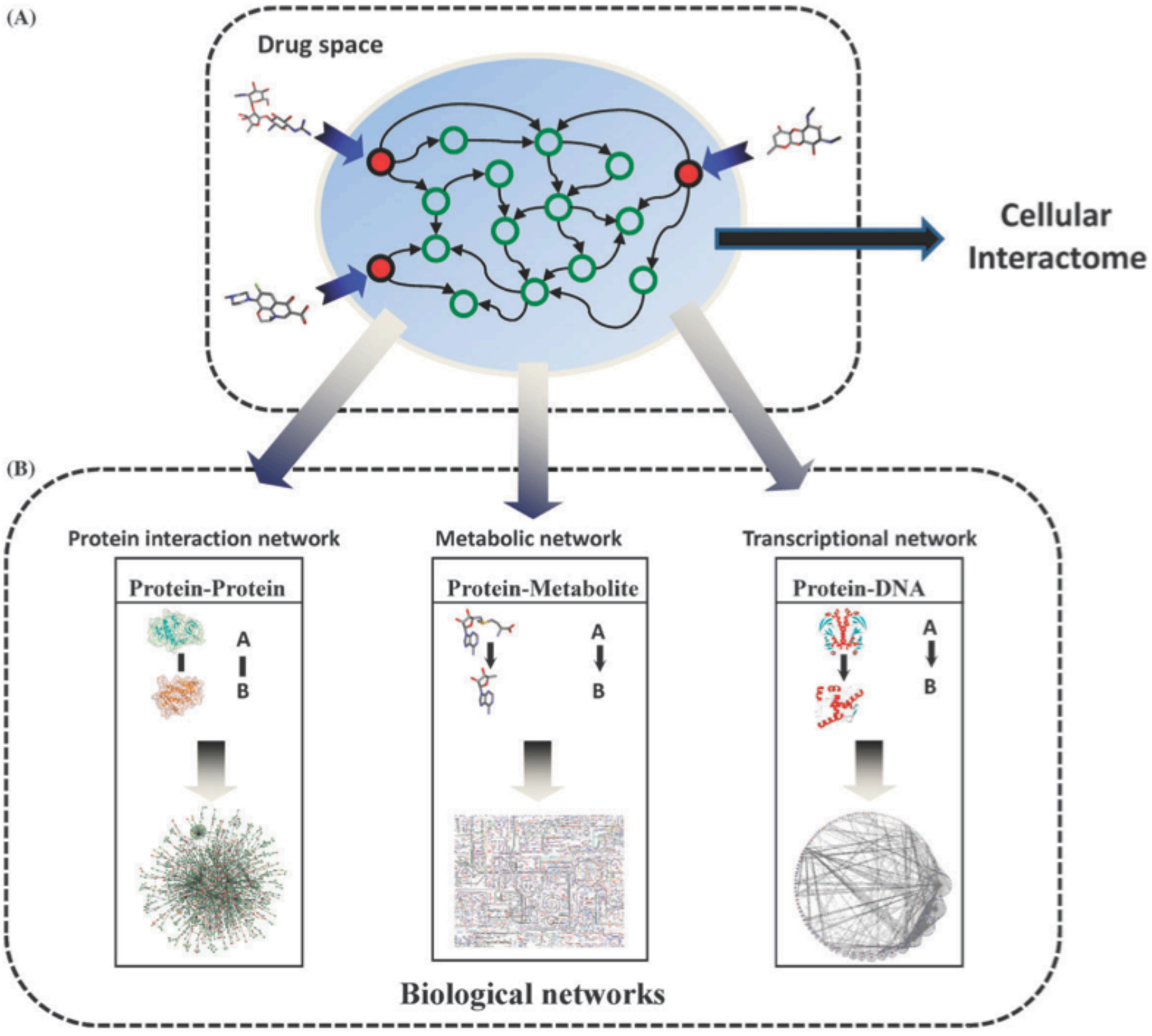


Fig. 3 Different components of the drug-target network. (A) Drug space (marked with the outer box) consists of the small-molecules which can potentially bind entities with-in the cell (marked as drug targets in red spheres). In turn cellular interactions between different components (marked with red spheres and green circles) form cellular interactome comprising the target space. (B) Target space comprises of different components namely protein–protein interactions, metabolic pathways and transcriptional circuits which together form the biological network or the cellular interactome.

From Janga and Tzakos. Structure and organization of drug-target networks: insights from genomic approaches for drug discovery. Mol Biosyst (2009) 5 1536–1548

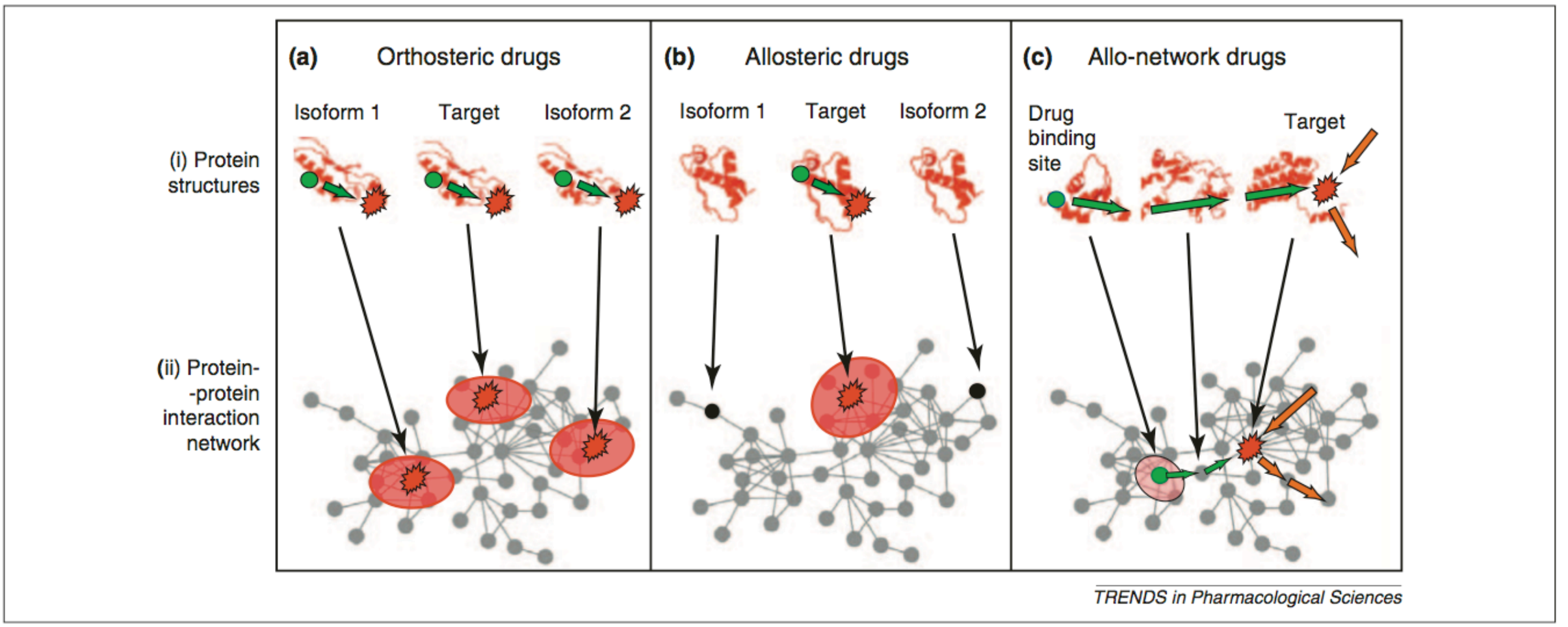
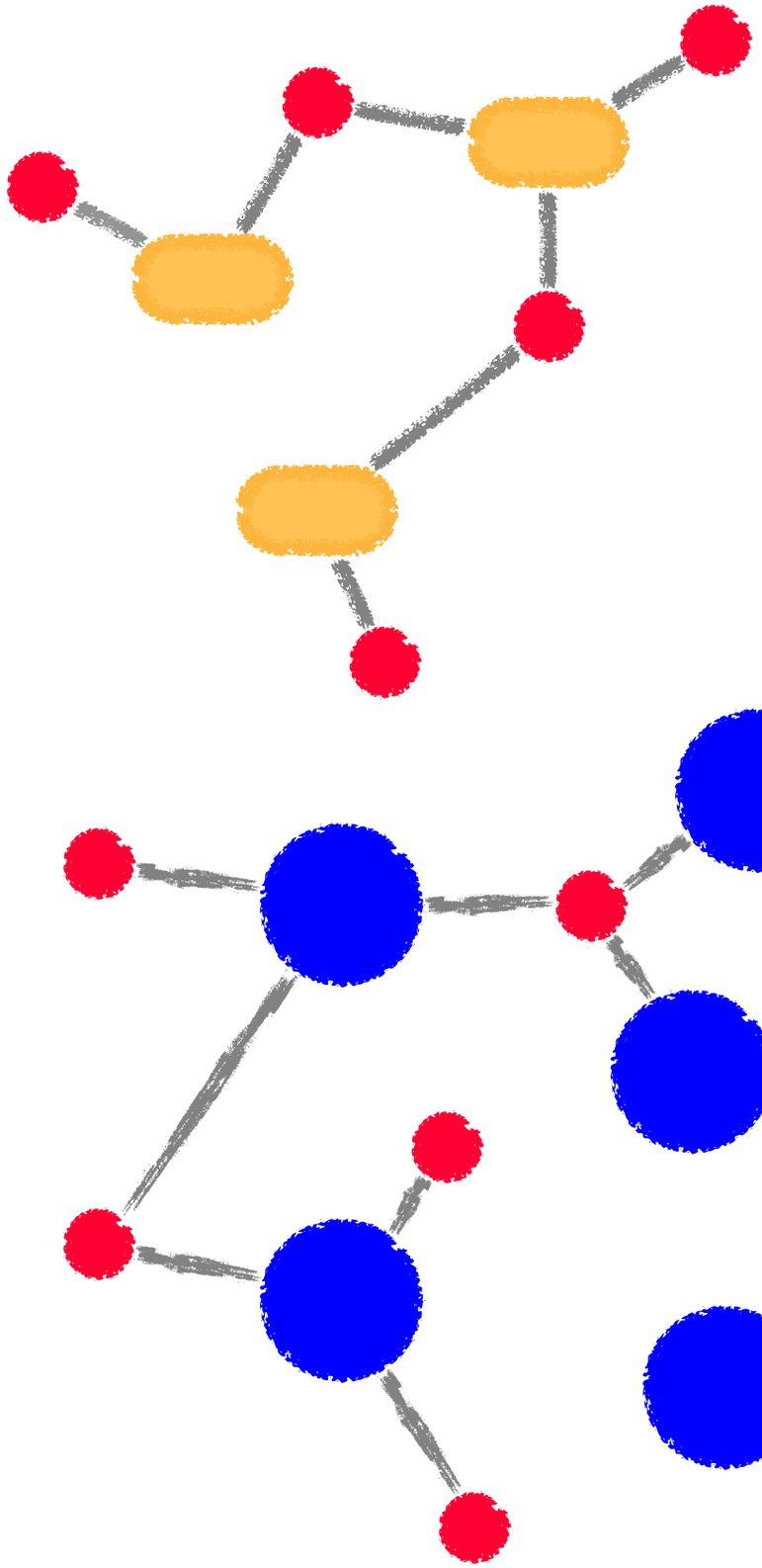
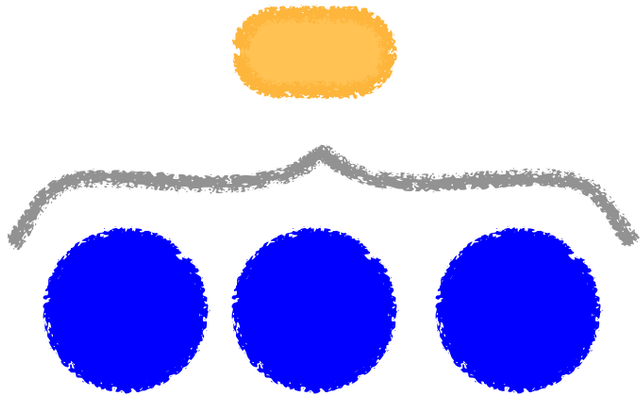


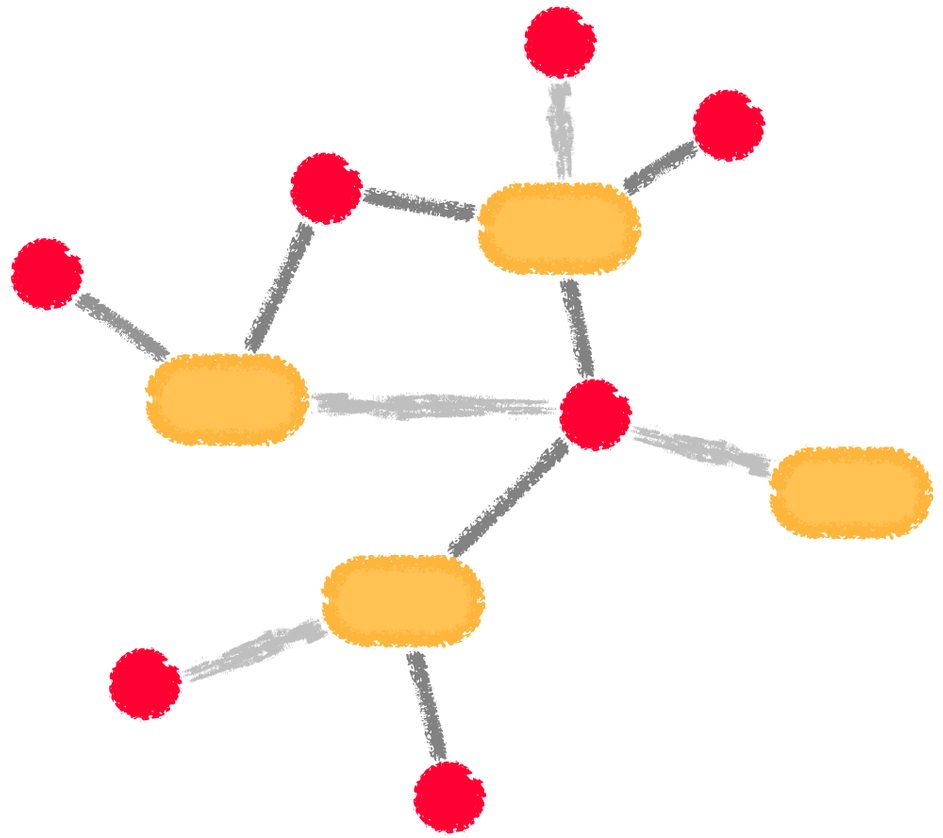
Figure 2. Comparison of orthosteric, allosteric and allo-network drugs. Here, in all cases the effect of the drug on the target site is via an allosteric propagation. Intra-protein propagation of drug-induced conformational changes is represented by dark green arrows. Conformational changes propagating through multiple proteins are marked with light green arrows. Drug binding sites are depicted by green circles; target sites are highlighted by red asterisks. **(a)** Orthosteric drugs. Here the inhibition (or activation, illustrated by light red ellipsoids at the bottom row) is via an allosteric effect which is elicited by active site (orthosteric) binding and propagates to a target site (dark-green arrow). Because protein families often share similar binding pockets, orthosteric drugs can bind to multiple proteins (named here 'isoform 1' and 'isoform 2'), which can lead to side effects. **(b)** Allosteric drugs. Drug binding is in an allosteric site. Allosteric drugs are more specific than orthosteric drugs, because they usually do not bind to isoforms of the target. **(c)** Allo-network drugs. Here, drug binding is at an allosteric site; however, the target site is on a different protein in the cellular network. The pathway of allo-network drug-induced conformational changes (marked by light green arrows) may be highly specific and (or) specifically enhance (inhibit) an intracellular pathway of propagating conformational changes (marked by orange arrows) at the target site. In promising allo-network drugs these intracellular pathways are disease-specific.

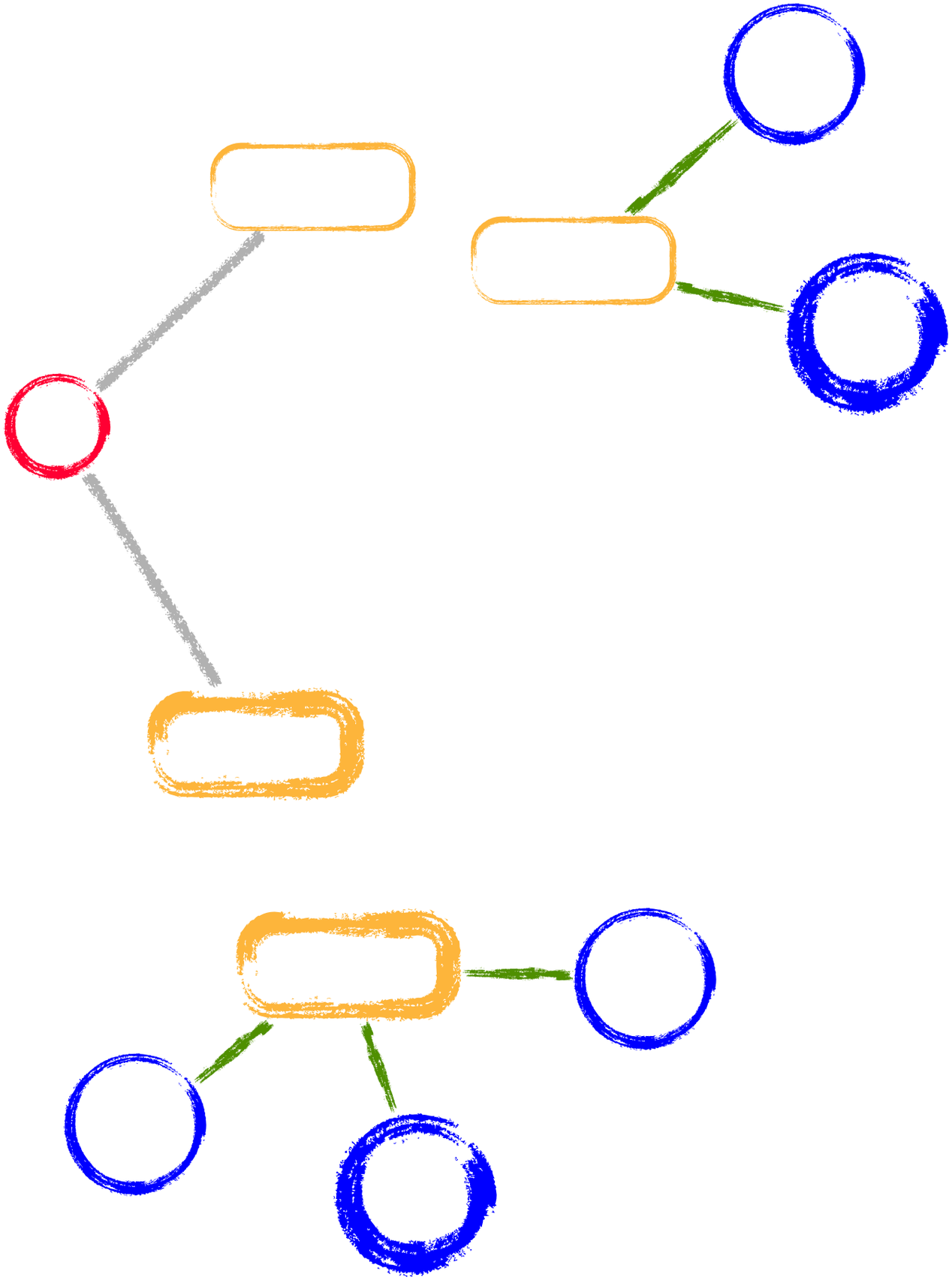
From Nussinov R, Tsai C-J, Csermely P. Allo-network drugs: harnessing allostery in cellular networks. Trends Pharmacol Sci 2011; 32:686–693

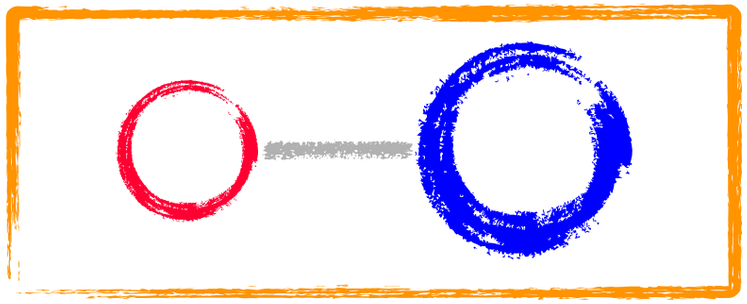
Can domains be drug targets?

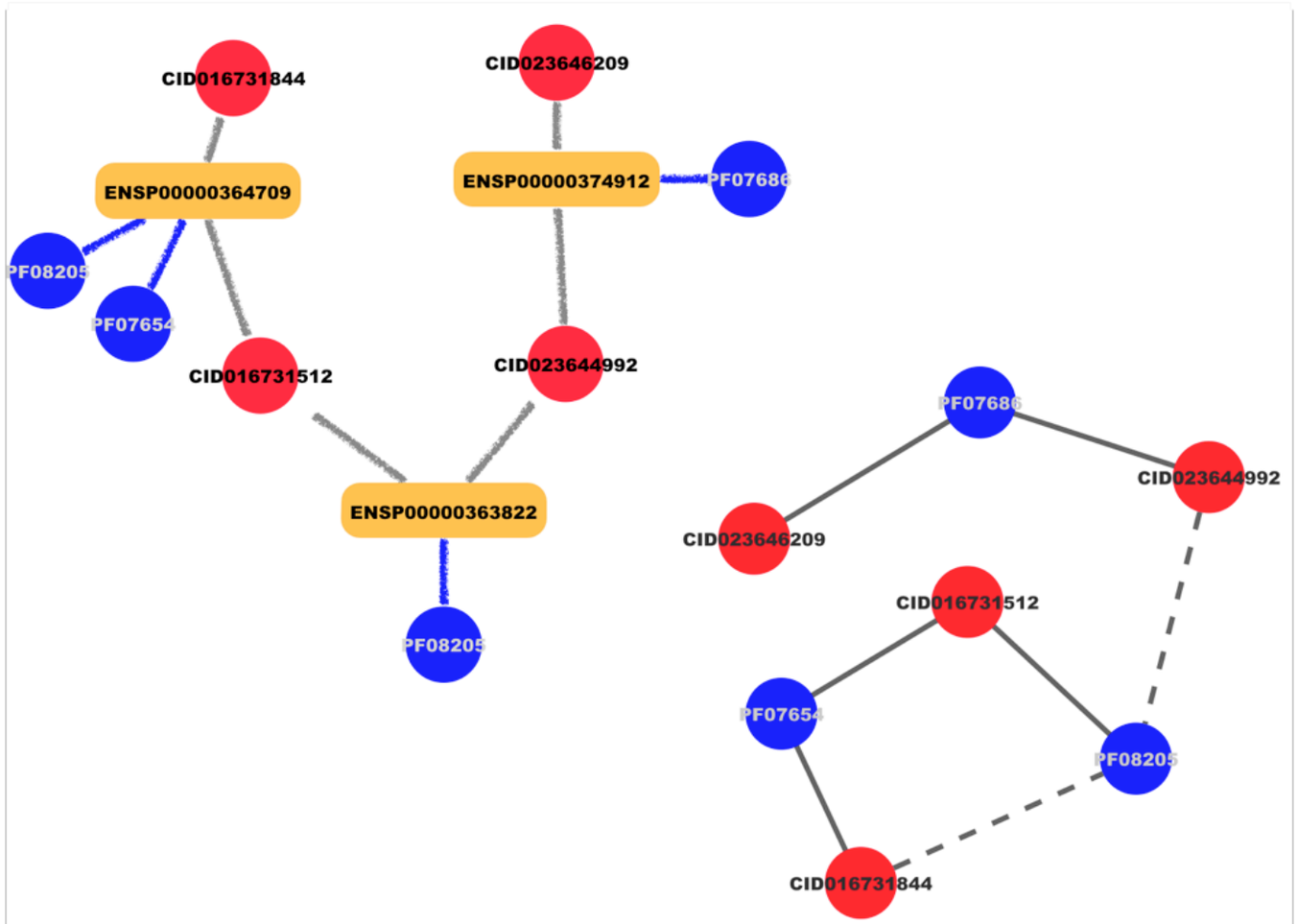












$$Score(dD) = N(dD) \cdot I(dD)$$

número de veces que aparece dD

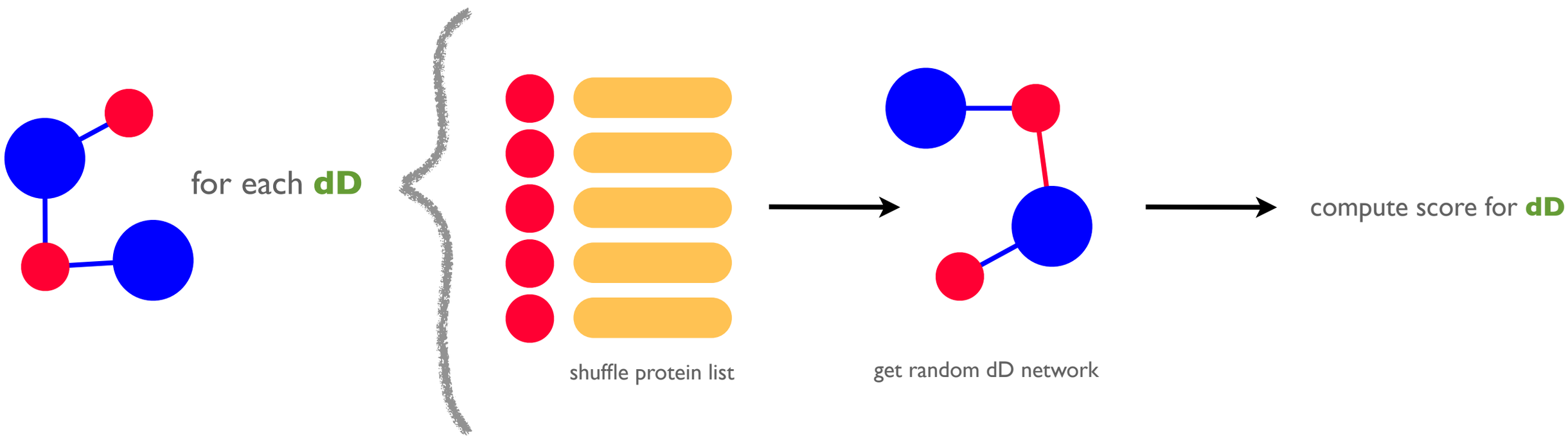
I(dD) es la información asociada a que aparezca dD

$$I(dD) = -\log_2 P(d,D)$$

probabilidad de que d y D aparezcan asociados

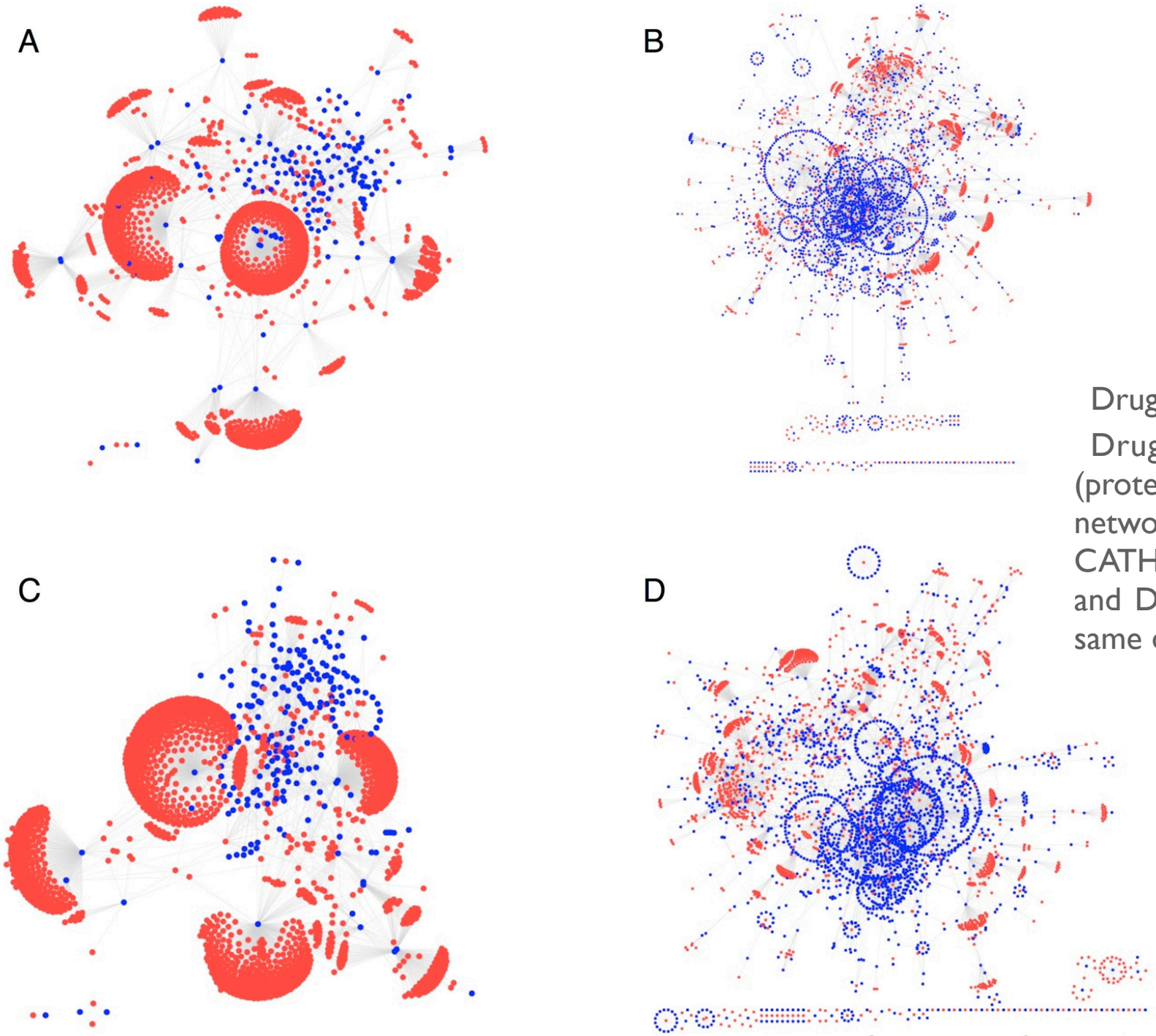
$$P(d,D) = p(d) \cdot p(D) = (nd/\sum d) \cdot (nD/\sum D)$$

nd y nD son el número de veces que aparece cada d y cada D respectivamente



dD score {random score$_1$,...,random score$_{25}$} average random score stdev p-val

t-test.
Null hypothesis: score belongs to random scores distribution

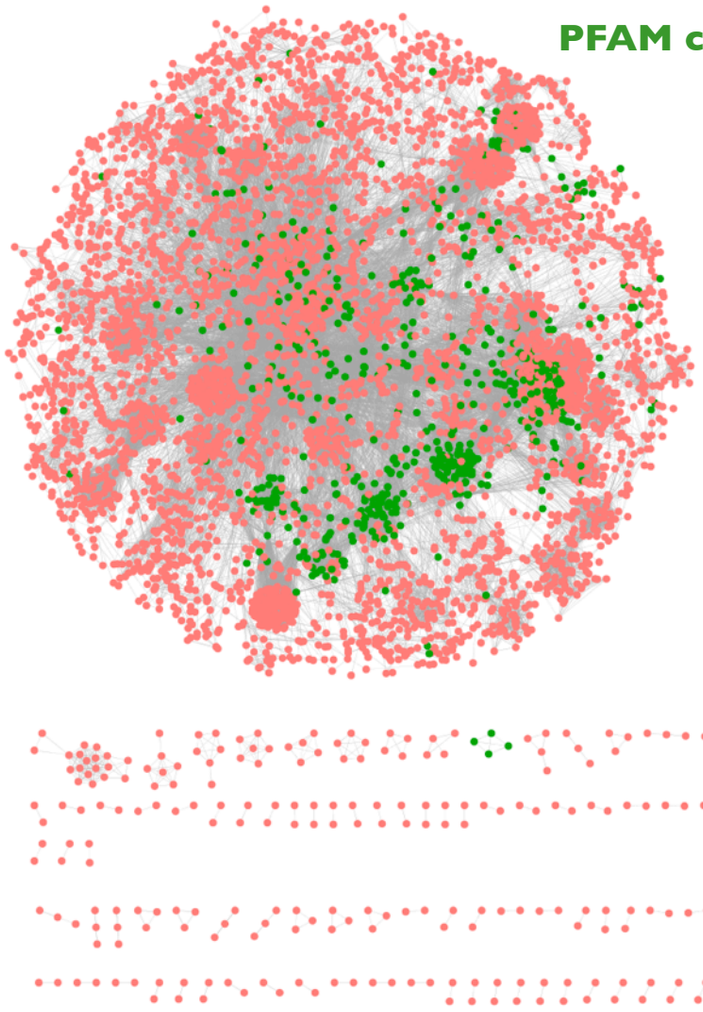


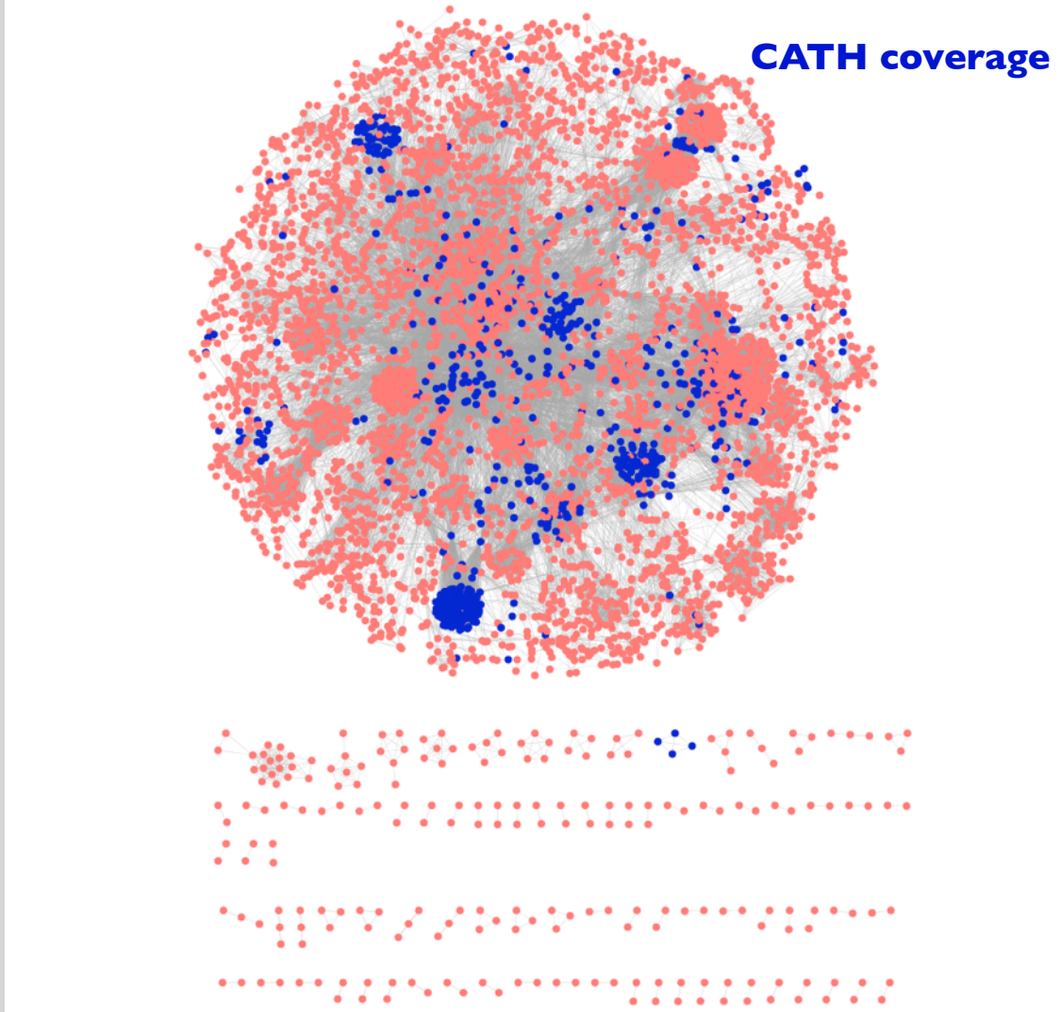
Drug-target bipartite networks.

Drugs are colored in red, and targets (proteins in dP networks or domains in dD networks) are colored in blue. A and C are the CATH and PFAM dD networks, respectively. B and D are the dP subnetworks containing the same drugs as A and C, respectively.

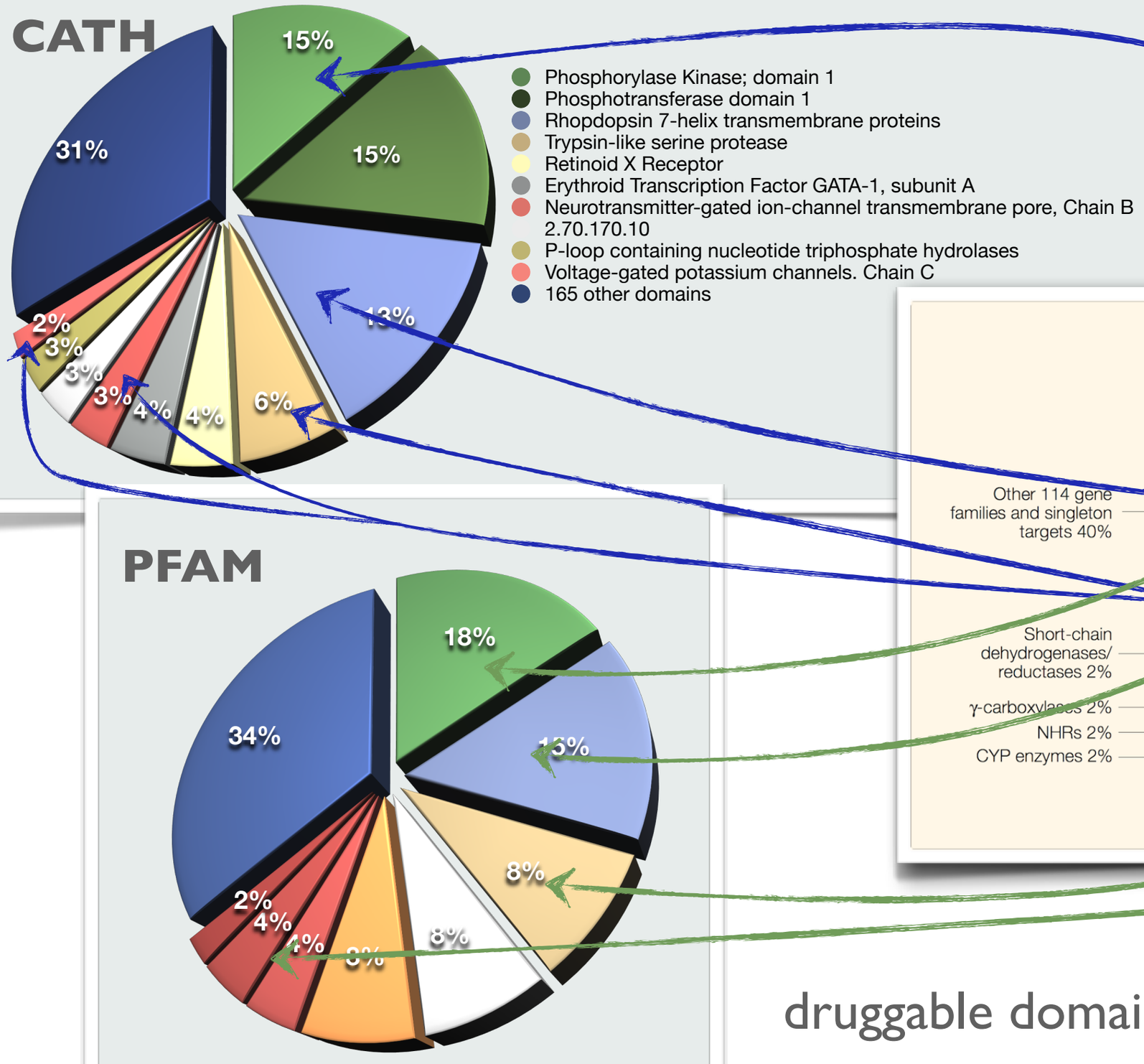
	drugs	targets	pairs	drug average degree	target average degree
dDPFAM	1535	223	2846	1.85	12.76
dDCATH	1441	175	2829	1.96	16.17
dP subnet PFAM	1535	2236	6562	4.27	2.93
dP subnet CATH	1441	2309	6673	4.63	2.89
dP	5531	3580	12754	2.30	3.56

drug-drug projections

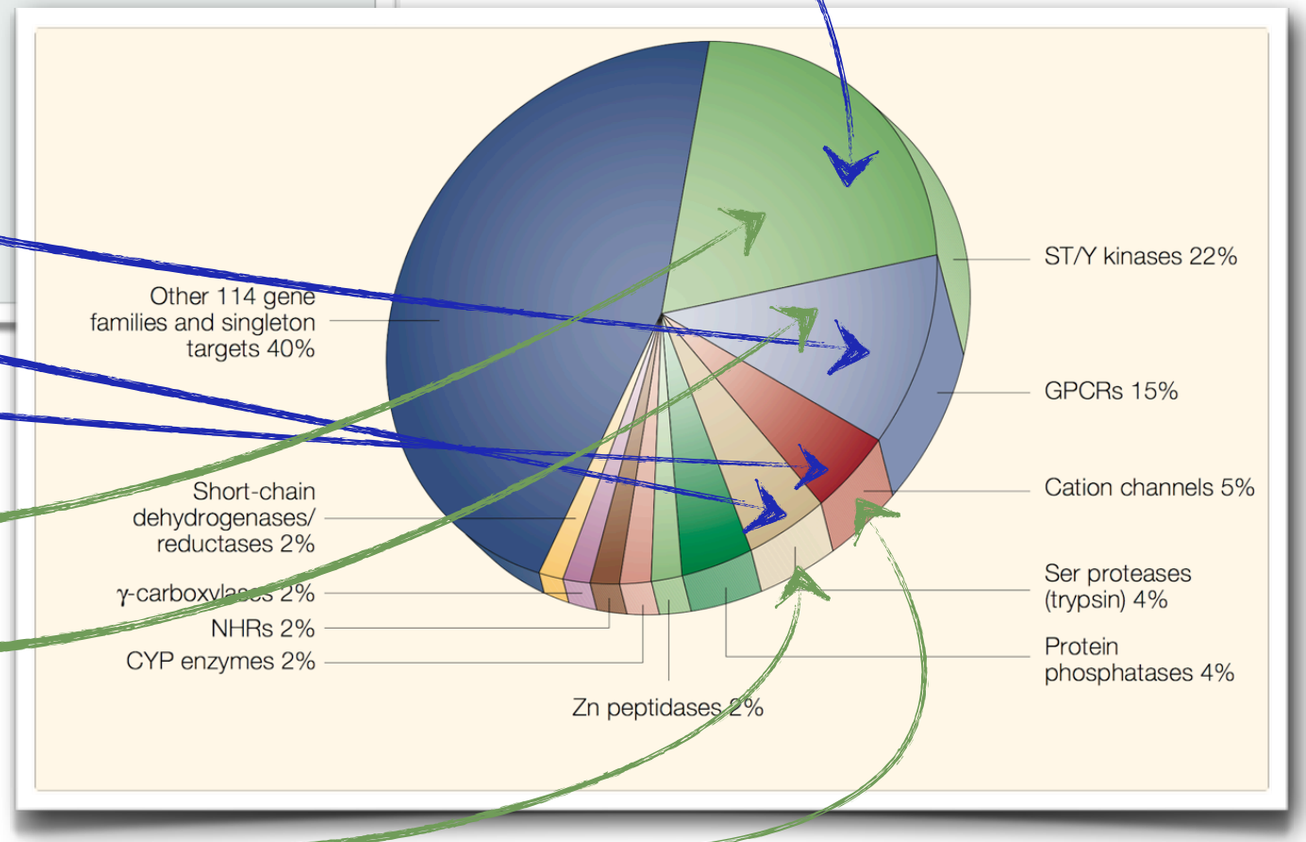




	dD CATH	dP CATH	dD PFAM	dP PFAM
Heterogeneity	0.61	0.89	0.46	0.84
Cluster coefficient	0.96	0.83	0.97	0.85

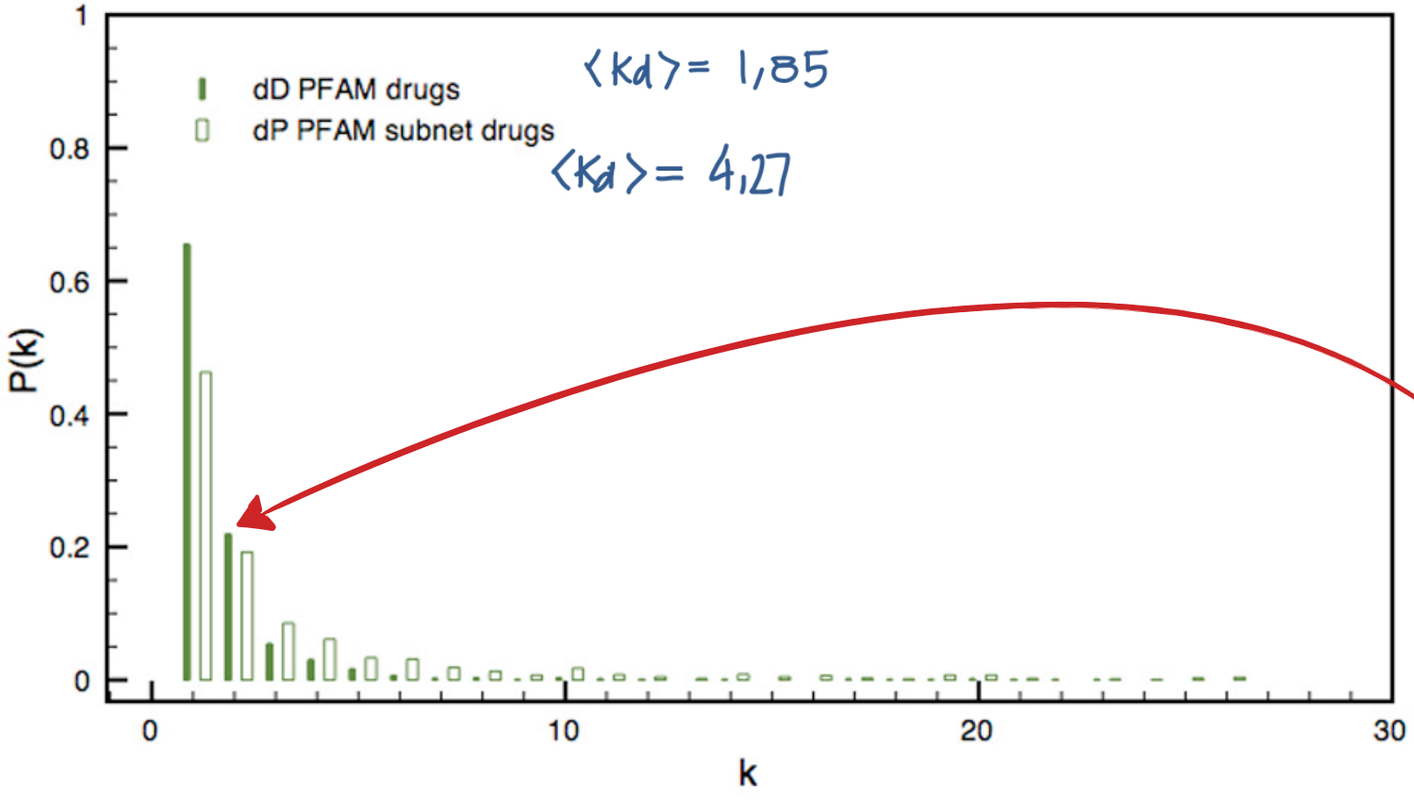


From Hopkins & Groom. The druggable genome Nat. Rev. Drug Discov. (2002) 1 727–730.

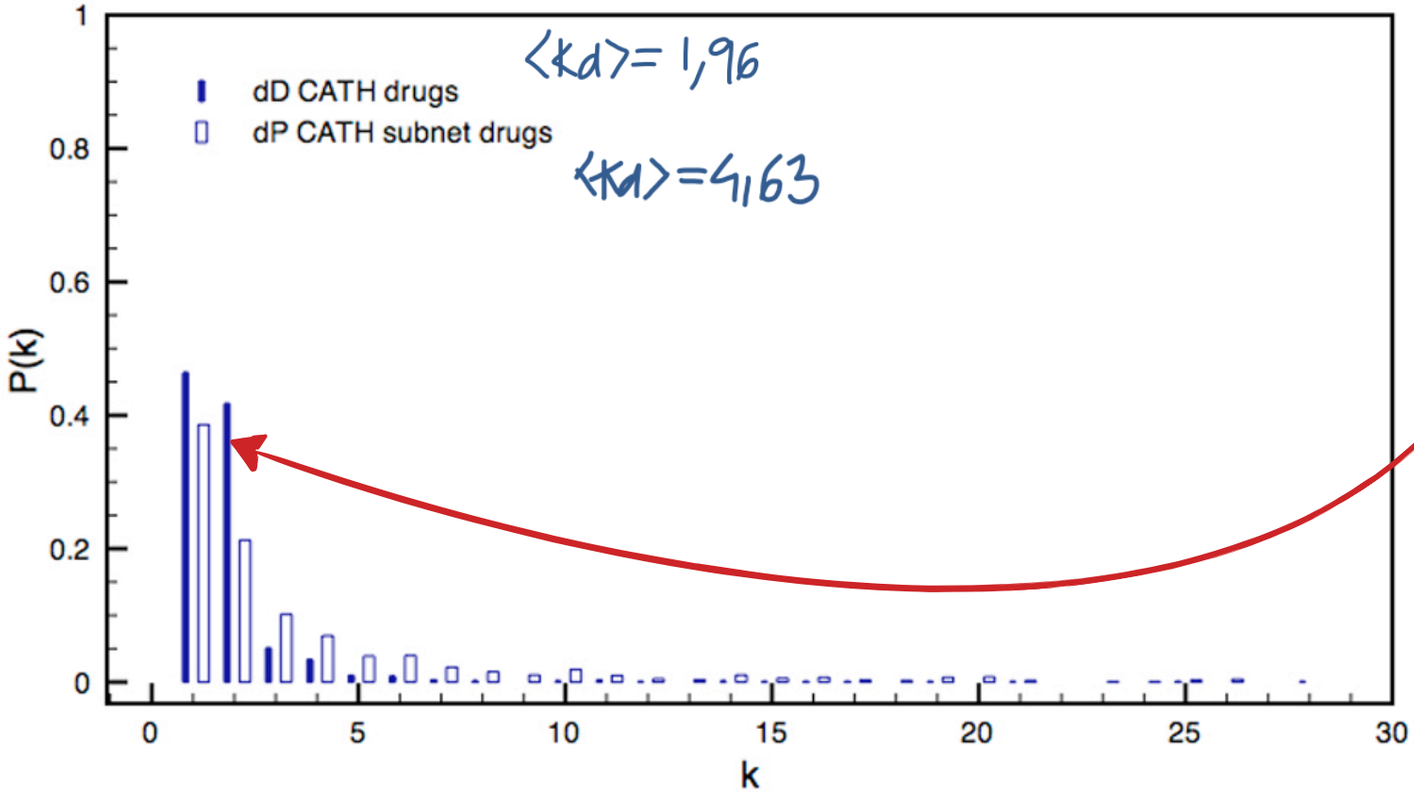


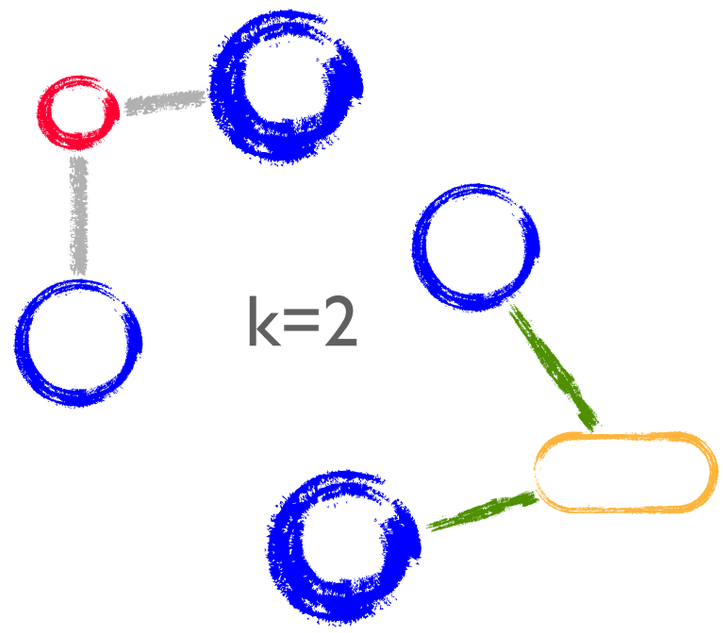
druggable domains

Domain definition at protein families level identify druggable targets



these domains are in the same proteins





Drug degree distributions in the dD (filled bars) and dP (empty bars) bipartite networks. PFAM, upper panel. CATH, lower panel.

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