SUPPLEMENTARY DOCUMENT

NP-hardness Proof

In the following we prove that the alignment problem is NP-hard even for the special case where both PPI networks in the input are simply paths. We note that NP-hardness proofs for different versions of the alignment problem have been provided previously [1, 2]. The optimization functions employed in both studies are similar to that defined in our work. However the NP-hardness results provided in these studies do not provide sufficient intuition to grasp the true computational nature of the alignment problem. The proof presented in Ay *et al.* [1] applies to one-to-many alignments of metabolic pathways which are modelled using directed graphs. Therefore the problems under consideration are in fact different. More importantly, their proof is based on constructing a reduction from maximum weight independent set (MWIS) problem to yet another version of the MWIS problem. Their algorithm to solve the alignment problem is based on creating a *conflict* graph (node-weighted graph where each node represents every possible alignment group and an edge between two nodes represents the impossibility of the existence of both alignment groups in the output alignment) and applying a MWIS solution on this graph. The NP-hardness proof does not provide a reduction that creates the pathways themselves but only such a conflict graph. Therefore in effect it is an NP-hardness proof of the solvability of the alignment problem with their suggested method rather than the alignment problem itself. The problem definition of Klau [2] is the same as our pairwise global PPI network alignment problem. The provided NP-hardness proof requires setting $\alpha = 1$ in the GNAS definition provided in the original paper and making a trivial reduction from the *maximum common subgraph* (MCS) problem. We note that a similar reduction under different names including *maximum common edge subgraph* [3], *subgraph isomorphism* [4], and *generalized graph matching* [5] is suggested in almost all previous network alignment studies. However such a reduction from a subgraph isomorphism type problem misses an important detail; the network alignment problem as defined requires *simultaneous* optimization of two separate properties. The proof we provide below asserts that the problem with its simultaneous nature is NP-hard and is so even when the problem is restricted simply to paths. To our knowledge this is the first such result in the global PPI network alignment literature.

We provide a reduction from the 3-PARTITION problem. Given a sequence of nonnegative integers $A = (a_1, a_2.....a_{3n})$ such that for each $a_k \in A$ we have $b/4 < a_k < b/2$ and $\sum_{1 \leq k \leq 3n} a_k = nb$, the problem is to determine whether there exists a partition of the given integers into n disjoint groups of three such that each group sums exactly to b. The 3-PARTITION problem is NP-complete in the strong sense [6]. Our reduction is similar in spirit to that employed in [7] for the NP-hardness proof of the largest common subtrees problem.

THEOREM 1. *The pairwise global PPI network alignment problem is NP-hard for a pair of paths.*

PROOF. Given a 3-PARTITION instance, we construct the input graphs G_1, G_2 and the sequence similarity matrix seq. Let G_1 be the path $u_1, \ldots, u_{nb+6n}$ and G_2 be the path $v_1, \ldots, v_{nb+n}$. The r^{th} row of the seq matrix corresponds to the r^{th} vertex u_r in the first path, whereas the c^{th} column corresponds to the c^{th} vertex v_c in the second path. Let x be a positive integer greater than $\frac{(nb+n-1)\alpha}{1-\alpha}$. Let $a_0 = 0$. We call a vertex u_r of the first path a *partition vertex* if $\sum_{0 \leq t \leq k_1 - 1} a_t < r - 2(k_1 - 1) \leq \sum_{0 \leq t \leq k_1} a_t$ for some integer k_1, such that $1 \leq k_1 \leq 3n$. The rest of the vertices of G_1 are *nonpartition vertices*. For each row corresponding to a partition vertex, the entry at column $k_2 b + k_2$, where $1 \leq k_2 \leq n$, is assigned to 0 and the entries in all the rest of the columns are assigned to x. For each row corresponding to a nonpartition vertex the sequence similarity score assignment is exactly the opposite, that is each entry at column $k_2 b + k_2$ is assigned to x, and the rest are assigned to 0; see Figure 1. Intuitively, if there exists a partition, all the vertices of a group in the partition plus a single vertex can be aligned with a $(b+1)$ group in G_2. For the other direction, providing maximum alignment score entails aligning each vertex of G_2 with a vertex of G_1 with which it has a sequence similarity of x. The problem of maximizing alignment score then turns into that of maximizing number of conserved interactions with the provided constraint. This is achieved only if the b vertices of each $(b+1)$ group in G_2 are aligned with all the vertices of a group in a partition, which further implies resolving the 3-partition problem. We now formally prove that there exists a 3-partition if and only if there exists an alignment with score at least $(bn - 2n)\alpha + x(bn + n)(1 - \alpha)$.

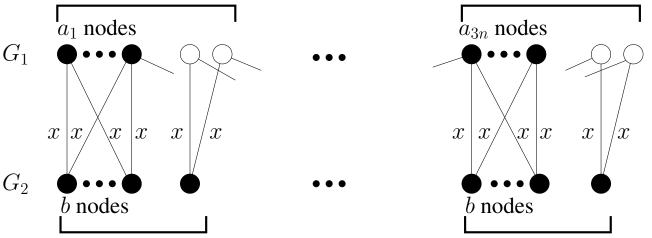

Fig. 1. Constructing the gadgets for the NP-hardness proof. Both G_1, G_2 are paths with the depicted left to right order of the nodes. Nodes of G_1 are shown using two colors: Black nodes are *partition* nodes and white nodes are *nonpartition* nodes. Edge weights of x indicate the sequence similarity score between a pair of nodes. Each partition node in G_1 has an edge of weight x to only each and every one of the b nodes. Each nonpartition node has edges of weight x with only the rest of the nodes of G_2.

Assume there is a 3-partition. We consider each disjoint group of the partition one by one. Let (a_p, a_q, a_w) be the m^{th} group we consider. Starting at index $2p - 1 + \sum_{0 \leq t \leq p-1} a_t$ (inclusive), the a_p consecutive vertices in G_1 are aligned with consecutive vertices of G_2 starting at index $s_1 = (m-1)(b+1)+1$ (inclusive). Starting at index $2q - 1 + \sum_{0 \leq t \leq q-1} a_t$ (inclusive), the a_q consecutive vertices in G_1 are aligned with consecutive vertices of G_2 starting at index $s_2 = s_1 + a_p$ (inclusive). Finally, starting at index $2w - 1 + \sum_{0 \leq t \leq w-1} a_t$ (inclusive), the $a_w + 1$ consecutive vertices in G_1 are aligned with consecutive vertices of G_2 starting at index $s_3 = s_2 + a_q$ (inclusive). Each of the $a_p, a_q, a_w + 1$ vertices is aligned with a vertex such that the similarity score is x. Thus the total sequence similarity scores is $x(bn + n)(1 - \alpha)$. Starting from the beginning of the second path G_2, divide the path into n disjoint subpaths each with $b + 1$ consecutive vertices. At each subpath exactly two conserved interactions that are incident only on the first b vertices are missed. Thus each subpath by itself provides $b - 2$ conserved interactions. There is no conserved interaction between

Table 1. GNAS evaluations for SPINAL including extreme α values. *ce* stands for *C. Elegans*, *dm* for *D. Melanogaster*, *hs* for *H. Sapiens*, and *sc* for *S. Cerevisiae*. For each species pair, first row lists $|E_{12}|$, whereas the second lists $GNAS(A_{12})$ for the alignment output by the corresponding algorithm provided in the columns.

Dataset	SPINAL										
	$\alpha = 0.01$	$\alpha = 0.05$	$\alpha = 0.10$	$\alpha = 0.3$	$\alpha = 0.4$	$\alpha = 0.5$	$\alpha = 0.6$	$\alpha = 0.7$	$\alpha = 0.90$	$\alpha = 0.95$	$\alpha = 0.99$
ce-dm	2205	2215	2213	2343	2320	2300	2237	2258	2240	2278	2287
	44.99	131.34	240.76	717.99	941.19	1159.93	1350.59	1586.87	2018.04	2165.02	2264.30
ce-hs	2326	2298	2316	2370	2446	2437	2487	2512	2443	2440	2473
	49.51	139.56	255.01	728.26	993.07	1229.95	1501.61	1764.93	2200.88	2319.18	2448.47
ce-sc	2274	2296	2288	2326	2384	2323	2361	2398	2426	2430	2385
	40.40	131.66	244.90	709.12	963.28	1168.95	1422.74	1683.13	2184.97	2309.19	2361.30
dm-hs	6119	6183	6176	6189	6235	6282	6291	6344	6254	6383	6211
	101.62	347.10	652.83	1883.22	2517.23	3160.48	3790.79	4451.60	5632.26	6065.59	6149.26
dm-sc	5081	5142	5137	5203	5150	5311	5283	5360	5367	5211	5255
	78.92	282.42	536.77	1579.06	2075.14	2668.65	3180.27	3759.07	4832.32	4951.33	5202.64
hs-sc	5567	5636	5681	5703	5593	5651	5706	5798	5707	5709	5818
	90.30	313.72	596.03	1731.81	2253.66	2839.00	3434.54	4066.22	5138.76	5424.74	5760.08

any two consecutive subpaths. This gives rise to exactly $bn - 2n$ conserved interactions.

For the other direction assume there is an alignment with score at least $(bn-2n)\alpha + x(bn+n)(1-\alpha)$. Even if all edges of G_2 were conserved, the total contribution of these conserved interactions to the alignment score would at most be $(bn + n - 1)\alpha$. Note that the contribution of a single aligned pair with sequence similarity x is greater than this amount. Thus in order to achieve the desired score, every node in G_2 must be aligned with a node from G_1 such that the sequence similarity score of the pair is x. This has two implications. Firstly, considering again each disjoint subpath of G_2, the first b vertices of the subpath must be aligned with partition vertices of G_1 and the last vertex must be aligned with a nonpartition vertex of G_1. Secondly, there must be at least $bn - 2n$ conserved interactions in the alignment. Now each subpath in G_2 must be missing *at least* two conserved interactions that are incident only on the first b vertices of the subpath, since each one of the first b vertices must be aligned with a partition vertex from G_1 and for each a_k we have $a_k < b/2$. Furthermore the last vertex of each subpath in G_2 other than the last one, must be incident to *at least* one nonconserved edge. Since there are at least $bn-2n$ conserved interactions in total, the lowerbounds for the numbers of missing conserved interactions mentioned in the previous two statements must be exact. This further implies that there is a 3-partition. □

We note that the above proof works when α is not fixed to 0 or 1. Otherwise in both cases the problem is solvable in polynomial time. In the former case the conserved interactions do not contribute to the alignment score and the problem becomes that of finding a maximum weight matching in bipartite graphs. In the latter the sequence similarity scores do not contribute to the score and a trivial optimum alignment simply aligns every u_r with v_r.

Implementation Details and Running Time Analysis

We provide a discussion of SPINAL in terms of its running time and its *stability*. A separate running time analysis is made for each phase of the algorithm and necessary implementation details are discussed.

In our implementation of the initial *coarse-grained* phase of the SPINAL algorithm we do not use an exact maximum matching algorithm for computing the constructors set C of $\mathcal{NBG}$. It is rather computed using a simple greedy matching based on sorting the weights and greedily selecting the largest nonconflicting edge iteratively. Employing the greedy strategy as opposed to maximum matching, there is no noticable difference in the accuracy of results, whereas the gain in running time is quite large. We executed both versions on the largest network instances H.Sapiens vs S.Cerevisiae. The version with the greedy matching for the first phase is four times faster than the version with the optimum matching (the greedy matching version completed in almost half an hour). The number of conserved interactions produced with the greedy version is 5798 and the GNAS score is 4066.22. For the optimum matching version the number of conserved interactions is 5771 and the GNAS core is 4047.20. We note that although it is not recommended to employ the optimum matching in this phase, we still provide a parameter setting that allows the user to do so if necessary.

Denoting the maximum degrees of G_1, G_2 with Δ_1, Δ_2 respectively and denoting the number of iterations of the main loop with k, the running time of the algorithm with this implementation is $O(k|V_1||V_2|\Delta_1\Delta_2 \log(\Delta_1\Delta_2))$. As noted in the paper, the algorithm converges around 10-15 iterations even for the largest networks experimented. A second implementation detail worth mentioning is that among all $N(u_i) \times N(v_j)$ only those with confidence scores larger than a threshold contribute to the score of (u_i, v_j). Therefore the factor $\Delta_1\Delta_2 \log(\Delta_1\Delta_2)$ in the running time is actually an overestimated upperbound.

As for the analysis of the *fine-grained* phase of SPINAL, there are three main steps within this phase: *Construction of* $\mathcal{NBG}$, *construction of the contributors set* and *improvements via swaps*. The construction of $\mathcal{NBG}$s throughout all iterations requires $O(|V_1|V_2|\Delta_1\Delta_2)$ time. For the rest of the analysis we make an observation. An edge in the edge set of $\mathcal{NBG}$ exists in only one of the bipartite graphs of all iterations, since once it is in the edge set, that is it becomes a contributor, at least one incident node of it is aligned at the end of that iteration. This is true even when the original contributor is replaced as part of swap improvements. Since each alignment node can be neighbors with at most $\Delta_1\Delta_2$ pairs from all $\mathcal{NBG}$s, the total number of edges in all the $\mathcal{NBG}$s is bounded by $O(|A_{12}|\Delta_1\Delta_2)$. Assuming $|V_1|>|V_2|$, we have $|A_{12}| = |V_2|$. Note that the maximum weight matching of a bipartite graph with n nodes and m edges requires $O(n \times (m +$

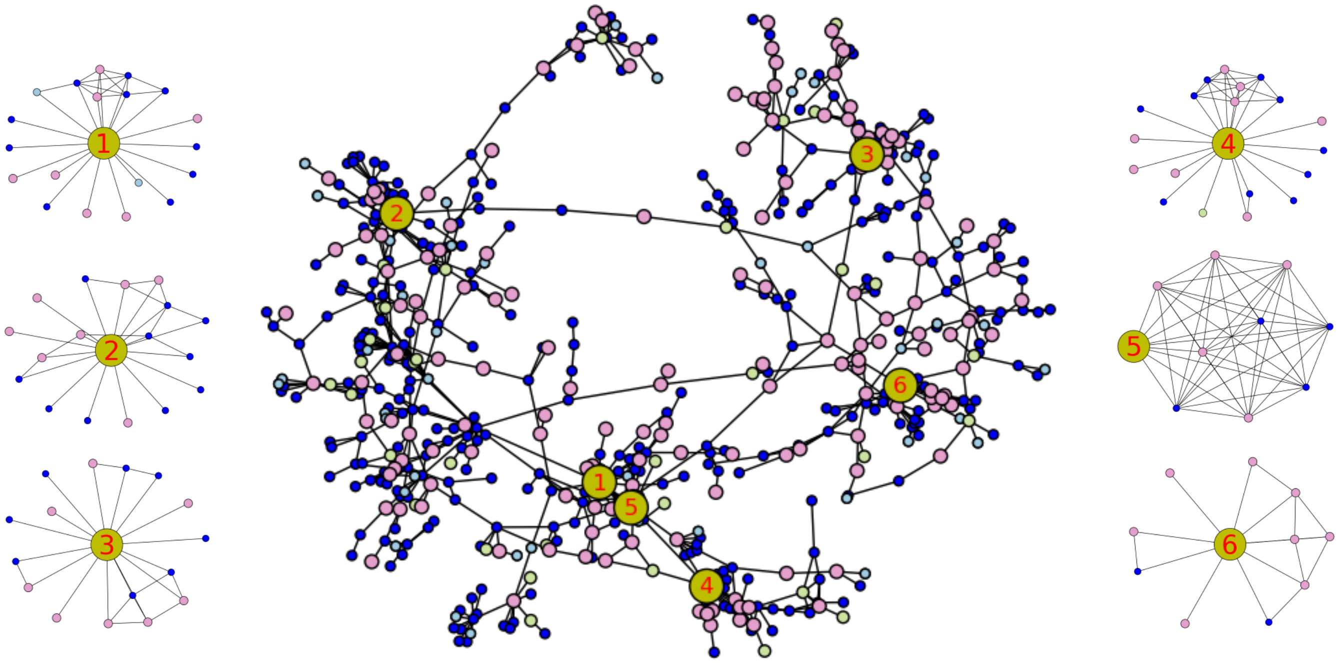

Fig. 2. The largest connected component of the Human-Yeast alignment network. Going from the smallest to the largest nodes, a blue node is a match that does not contain any annotation overlaps of its proteins, a light blue node is one with a single GO annotation overlap, a green node is one with two GO annotations overlap, and a pink node is one with at least three GO annotations overlap. Labels, corresponding matches, and the dominating categories are respectively as follows: 1- TBP|YER148W GO:0006355 (regulation of transcription, DNA-dependent), 2- RAN|YLR293C GO:0006810 (transport), 3- LOC392454|YBR088C GO:0003677 (DNA binding), 4- POLR2A|YDL140C GO:0006351 (transcription, DNA-dependent), 5- TAF7|YPL011C GO:0051123 (RNA polymerase II transciptional preinitiation complex assembly), 6- MCM2|YBL023C GO:0006260 (DNA replication).

$n \log n))$ time. The time required by maximum weight bipartite matchings throughout all iterations is therefore $O(|V_1||V_2|\Delta_1\Delta_2 + |V_1|^2 \log |V_1|)$. We note that in the construction of $\mathcal{NBG}$, for each edge in the edge set of $\mathcal{NBG}$, we can store the number of its neighbors in V_{12} without any extra cost. Therefore, again making use of the observation, the running time of the swaps throughout all iterations becomes $O(|A_{12}|\Delta_1\Delta_2)$. Combining all three together with the time required for initial sorting, we get $O(|V_1||V_2|\Delta_1\Delta_2 + |V_1|^2 \log |V_1|)$. We note that the running time cost of the fine-grained phase is much less than that of the coarse-grained phase. This is also verified by our experimental evaluations; in almost all cases more than 95% of the execution time is spent by the initial phase of SPINAL.

We finally note that SPINAL is a *stable* algorithm, in the sense that executions on the same instance with the same parameters provides the same alignment. None of the primitive opeartions requires randomization. The only tie-breaking situations may arise only for the steps requiring sorting and the maximum weight bipartite matching primitives. Since both implementations are stable [8], the algorithm overall is stable.

Global Network Alignment for Extreme α Values

The GNAS evaluations in the original manuscript provide results based on values of $\alpha = 0.3$ to 0.7 at the increments of 0.1. Although these are the instances commonly used in previous related work with similar problem definitions, it is also useful to repeat the evaluations for extreme α values as well. We tested the SPINAL algorithm employing marginal α values of $0.01, 0.05, 0.10$ at the $0 - extreme$, and $0.9, 0.95, 0.99$ at the $1 - extreme$; see Table 1. The provided scores indicate that even for marginal values, SPINAL performs very well. In terms of edge conservation the scores of SPINAL under α settings at the 0-extreme are slightly lower, whereas those at the 1-extreme are slightly larger than the scores attained under popular α settings of $0.3 - 0.7$. However the differences between the scores are quite low. In terms of the GNAS scors themselves, the 0-extreme scores are low whereas the 1-extreme scores are quite high. This is expected, since the edge conservations are almost the same and the GNAS score is proportional to the α values.

Alignment Network Employed in Annotation Transfers

We provide details of the alignment network employed in the section regarding the functional annotation transfers of the S. Cerevisiae-H. Sapiens networks; see Figure 2. There are 5298 nodes and 2209 edges in the alignment network. The largest connected component of the network shown in Figure 2 contains 569 nodes and 757 edges. The GO overlap induced subgraph of the alignment network, that is the subgraph that contains only the nodes with at least one GO annotation overlap, contains 1781 nodes and 433 edges. We note that each node in this induced subgraph contributes to the score

Table 2. Experiments on NAPAbench data.

Dataset	Algorithm	CN	MNE	COV	SPE
DMC dataset	SPINAL$_I$	4144	0.249	2758	75.127
	IsoRank	3588	0.347	2747	65.308
	IsoRank$_{HSP}$	3844	0.301	2750	69.891
DMR dataset	SPINAL$_I$	4096	0.254	2744	74.636
	IsoRank	3598	0.339	2721	66.115
	IsoRank$_{HSP}$	3846	0.296	2730	70.440
CG dataset	SPINAL$_I$	4330	0.225	2794	77.49
	IsoRank	3334	0.394	2750	60.618
	IsoRank$_{HSP}$	3946	0.290	2778	71.022

shown in Table 2 of the paper. The neighborhood graphs of potential regulating hubs are shown in the peripheral graphs in Figure 2. Neighborhood of node 5 gives rise to a *single-component hub*.

Extended Experimental Evaluations

We extend the experimental evaluations provided in the original paper in three major directions; firstly by introducing additional evaluation parameters, secondly by introducing a new dataset, the NAPAbench, and finally by considering the IsoBase data as in the original manuscript but this time limiting the set of GO categories under consideration and employing new evaluation metrics.

Regarding additional evaluation parameters, we have five measures in total: *GO Consistency (GOC), correct nodes (CN), mean normalized entropy (MNE), coverage (COV),* and *specificity (SPE)*. The first one is defined in the original paper. Note that the *GOC* score computes the sum, over all alignment pairs, of the size of the intersection set of the FO (*functional orthology*) groups annotating the protein pair normalized by the size of the union of the groups. The rest of the scores are defined in [9]. Hereinafter the set of alignment pairs refer to those with both proteins annotated to some FO group, that is we exclude all those pairs where at least one of the proteins do not contain any annotation. An alignment pair is *correct* if both proteins are annotated with at least *threshold* FO groups that are the same. Given an alignment output, *CN* measures the total number of nodes that constitute correct alignment pairs. In a sense this is a measure to reflect the sensitivity of the produced alignment. For a given alignment pair, the *normalized entropy* is defined as $\frac{-1}{\log d}\sum_{i=1}^{d} p_i \log p_i$, where p_i denotes the fraction of proteins in the alignment with the FO annotation F_i and d is the number of different FO groups. We note that lower entropy implies higher functional consistency. Finally, we define *COV* as the total number of alignment pairs and *SPE* as the percentage of correct alignment pairs.

For the second direction, The *Network Alignment Performance Assessment Benchmark* (NAPAbench) has been suggested recently as a benchmark for evaluating network alignment algorithms [9]. The NAPAbench includes a dataset applicable to pairwise global one-to-one network alignment. Three different network growth heuristics, namely *DMC, DMR,* and *CG* have been suggested to simulate properties of PPI networks. Corresponding sequence data mimicking BLAST bit scores are provided accordingly. Since the comparisons in [9] indicate the superiority of IsoRank over MI-GRAAL on this dataset, in this subsection following the same methodology we compare the performances of SPINAL and the two versions of IsoRank under the measures defined previously. The results are presented in Table 2. Note that in the NAPAbench data each protein is annotated with a single FO. Therefore *threshold* is 1. Since the *GOC* values are proportional to *CN* under these settings, we do not provide the *GOC* values in this case. It can be easily verified that under all metrics SPINAL provides better results than both versions of IsoRank (the IsoRank as presented in the original paper in [10] and the IsoRank$_{HSP}$ version which is claimed to provide better results in terms of functional consistency evaluations).

Finally for the last direction we extend the experimental evaluations on the IsoBase data which are presented in the original manuscript. Let FO groups indicate the set of GO categories under consideration. Since GO category organization is hierarchical, there might be very specific categories at levels further away from the root of the GO DAG. Therefore expecting exact category overlaps may in some cases be a strong requirement for alignment evaluations. For our first definition of the FO groups, similar to the evaluation method suggested in [10], we annotate each protein to a standardized set of GO categories. Let $GO(u_i)$ be the set of GO terms annotating a protein u_i. We retrieve GO annotations from the Gene Ontology Consortium [11]. The FO group of u_i consists of the terms that are both at a distance of 5 from the root node and are ancestors of each term in $GO(u_i)$. Terms that are closer than distance 5 to the root are discarded since they are not considered specific enough. Hereinafter the resulting FO groups are simply referred to as *standardized*. We further limit this *standardized* definition of FO groups, to create a second group of tests that emphasize GO annotations obtained using experimental techniques with evidence codes IPI, IGI, IMP, IDA, IEP, TAS, and IC. In this case the original GO annotations are first filtered according to these evidence codes before applying standardizations. The resulting FO groups are referred to as *experimental*.

The results of the *standardized* tests on SPINAL$_I$, IsoRank, IsoRank$_{HSP}$, and MI-GRAAL (*Alignment3* version) are provided in Figure 3. In the figure the depicted values for the SPINAL and IsoRank versions are the averages of the scores obtained under the settings of $\alpha = 0.3$ through $\alpha = 0.7$ for each pair of species in the IsoBase data. We note that the Alignment3 version of MI-GRAAL is the favored version over other versions of MI-GRAAL since it is stable and is tested to provide the best results in evaluations [4]. It is also the version we employed in our tests, except for the H. Sapiens vs S. Cerevisiae runs, in which case Alignment3 did not execute until completion and the Alignment1 results are provided instead. Other than the C. Elegans vs H. Sapiens instance, among all thirty instances, SPINAL$_I$ provides the best *GOC* scores. The next best performer is IsoRank$_{HSP}$. It is followed by IsoRank and the worst performer for this measure is MI-GRAAL. The trend is similar for the *MNE* evaluations; SPINAL$_I$ and IsoRank$_{HSP}$ perform the best. In almost half of the instances SPINAL$_I$ is better than IsoRank$_{HSP}$ whereas for the other half IsoRank$_{HSP}$ performs better. Nevertheless in almost all instances the differences between their scores are almost negligible. IsoRank is the next best performer and finally MI-GRAAL performs the worst. In terms of correct nodes measure *CN*, SPINAL performs the best in almost all the instances. IsoRank$_{HSP}$ comes second, followed by IsoRank and MI-GRAAL. As far as the *SPE* scores are concerned IsoRank$_{HSP}$ seems to perform better than SPINAL although the scores are quite close in most cases. We note that this performance of IsoRank$_{HSP}$ comes at the expense of coverage *COV*. The number of output alignment pairs produced by IsoRank$_{HSP}$ is quite low, especially for larger network pairs such as the *dm-hs*, *dm-sc*, or the *hs-sc* pairs. In almost all instances SPINAL provides the highest coverage. Therefore considering the fact that *SPE* scores are normalized by coverage, the specificity scores of SPINAL are quite impressive. Repeating the same evaluations for the *experimental* FO groups, very similar results are obtained and the arguments above apply in most instances; see Figure 4.

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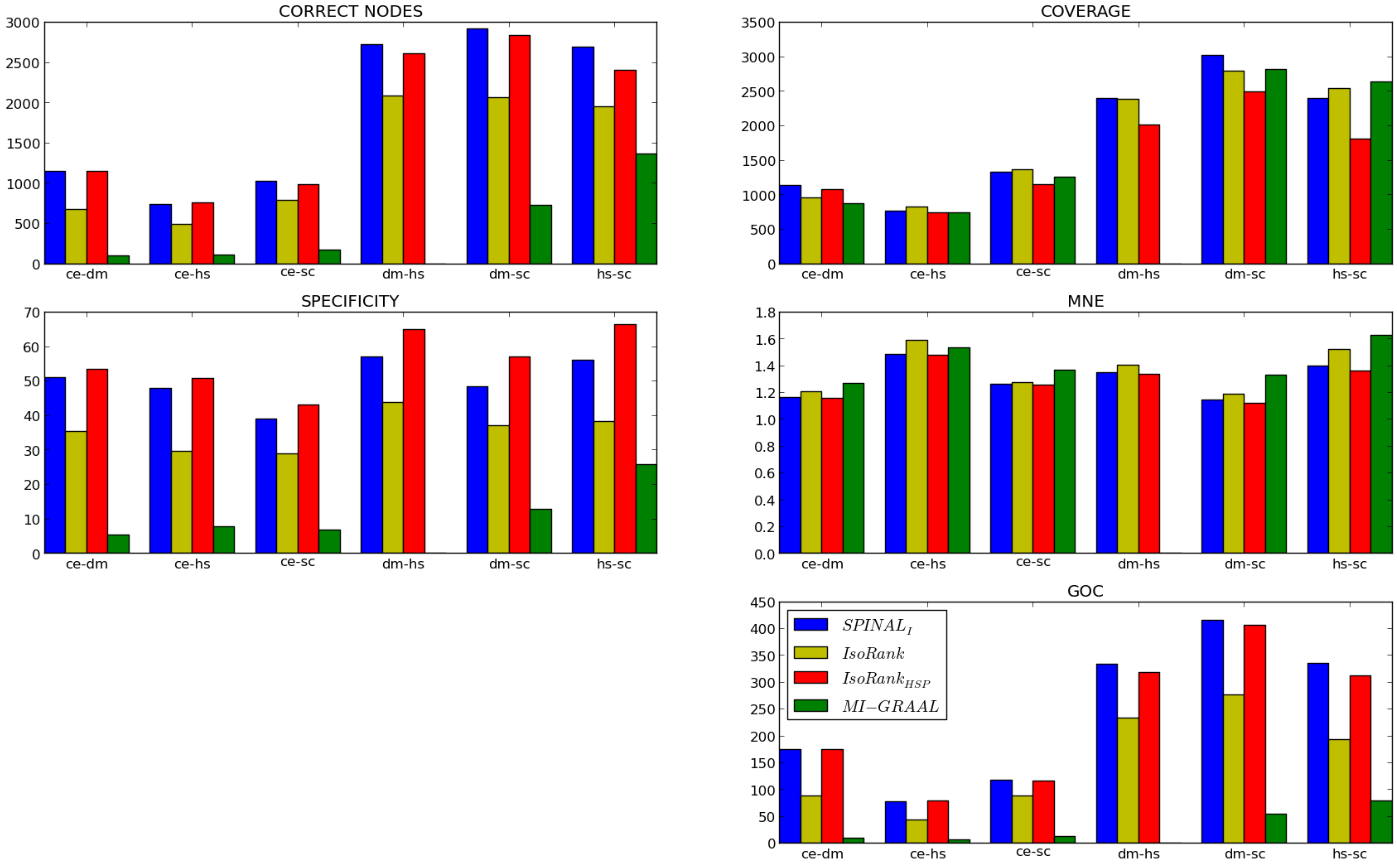

Fig. 3. Results of the standardized tests. For SPINAL and IsoRank versions, the values are averages of those obtained under settings of $\alpha = 0.3$ through $\alpha = 0.7$. At each plot the order of the pairs of species from left to right are as ce-dm, ce-hs, ce-sc, dm-hs, dm-sc, hs-sc.

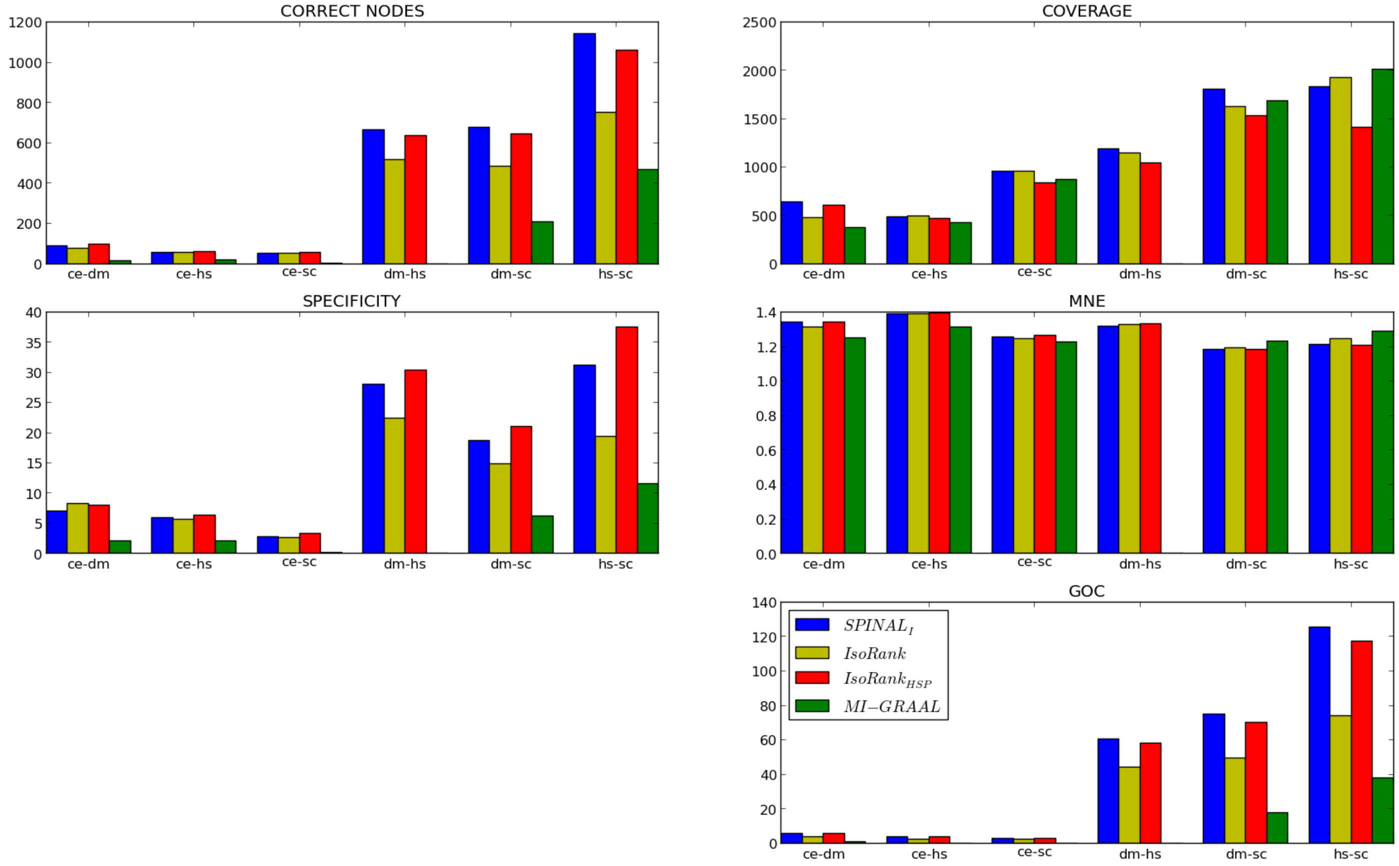

Fig. 4. Results of the experimental tests. For SPINAL and IsoRank versions, the values are averages of those obtained under settings of $\alpha = 0.3$ through $\alpha = 0.7$. At each plot the order of the pairs of species from left to right are as ce-dm, ce-hs, ce-sc, dm-hs, dm-sc, hs-sc.