

Network Pharmacology and Systems Medicine

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ABSTRACT

Network pharmacology models drug action as perturbation of disease-associated molecular networks rather than single-target inhibition, enabling rational design of multi-target therapies and drug combinations for complex diseases, yet adoption of network-based approaches into drug discovery and clinical practice varies across methodological categories. We evaluated 218 network pharmacology programmes across centres in France and Estonia between 2018 and 2022, spanning five method categories: network proximity-based drug repurposing, multi-target drug design optimisation, drug combination synergy prediction, disease module identification and targeting, and patient stratification through network-based biomarkers. A Network Pharmacology Systems Medicine Index (NPSMI) was constructed from five sub-scores -- target-disease network proximity accuracy, experimental validation rate, clinical translation evidence, multi-scale mechanistic coherence, and computational scalability to genome-wide networks -- with weights from regression against sustained adoption. NPSMI correlated with adoption at $r = +0.84$ and discriminated adopted from non-adopted methods with an AUC of 0.884. Network proximity repurposing scored highest (mean NPSMI 0.826), while patient stratification trailed at 0.602. Only 35.3 percent exceeded the 0.75 threshold. Network proximity accuracy carried the largest weight ($\beta = +0.278$), followed by experimental validation ($\beta = +0.230$).

Keywords: network pharmacology; systems medicine; drug repurposing; multi-target therapy; NPSMI; disease module; drug combination; network proximity; polypharmacology; patient stratification; interactome; systems pharmacology

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1. Introduction

1.1 From Single-Target to Network Pharmacology

Traditional drug discovery follows a single-target paradigm: identify a disease-relevant protein, screen for molecules that modulate its activity, and optimise potency and selectivity. This approach has yielded many successful drugs but struggles with complex diseases where pathology arises from the dysregulation of interconnected molecular networks rather than single gene defects. Network pharmacology reconceptualises drug action as perturbation of disease-associated molecular networks, where a drug's therapeutic effect depends on its collective impact across multiple network nodes rather than its affinity for a single target. This perspective enables rational approaches to polypharmacology, combination therapy, and drug repurposing based on network topology.

1.2 The Network Pharmacology Toolkit

Network proximity analysis measures the topological distance between drug targets and disease genes in protein interaction networks, predicting therapeutic efficacy from network closeness. Multi-target optimisation designs molecules that simultaneously modulate multiple network nodes for maximal therapeutic effect. Drug combination prediction uses network models to identify synergistic combinations where the combined network perturbation exceeds individual effects. Disease module identification maps disease-associated genes onto network subgraphs that represent coherent pathological mechanisms. Patient stratification uses network-based molecular signatures to classify patients into subgroups with distinct network perturbation patterns and treatment responses.

1.3 Study Objective

We aimed to identify which programme-level characteristics predict whether a network pharmacology method achieves sustained adoption. By scoring 218 programmes across five categories on five quality dimensions, we sought to quantify the factors determining utility.

2. Literature Review

2.1 Network Proximity and Drug Repurposing

Network proximity-based drug repurposing exploits the observation that drugs whose targets are topologically close to disease genes in the human interactome are more likely to be therapeutically effective. Guney and colleagues

demonstrated that FDA-approved drugs for a given disease have significantly closer network proximity to disease genes than random drug-target sets, and that this proximity metric predicts novel drug-disease associations validated by clinical evidence. The COVID-19 pandemic accelerated network-based repurposing, with multiple groups using interactome proximity to prioritise existing drugs for SARS-CoV-2 treatment, several of which entered clinical trials.

2.2 Drug Combination and Multi-Target Design

Drug combination synergy prediction uses network topology to identify pairs of drugs whose targets collectively perturb disease networks more effectively than either drug alone. Network-based synergy models including NIMS, DrugComboRanker, and DeepSynergy predict that combinations targeting complementary disease modules or parallel pathway branches achieve synergistic effects. Multi-target drug design optimises single molecules that simultaneously engage multiple network nodes, balancing affinity across targets to achieve optimal network perturbation while minimising off-target effects.

2.3 Disease Modules and Patient Stratification

Disease module identification maps disease-associated genes and their interaction partners onto connected subnetworks in the interactome, revealing the molecular mechanisms that drive pathology. Tools including DIAMOnD, HotNet2, and DOMINO identify disease modules that are significantly enriched for disease genes and functionally coherent. Patient stratification using network-based biomarkers classifies patients by their molecular subtype based on which disease module is most perturbed in each individual, enabling personalised treatment selection targeting the patient-specific pathological network.

2.4 The Validation and Translation Gap

Network pharmacology faces a persistent validation gap: network-based predictions are computationally compelling but experimentally validating network-level therapeutic hypotheses requires complex experiments that test multi-target effects in disease-relevant contexts. Clinical translation requires demonstrating that network-guided drug selection improves patient outcomes compared to standard care, which demands prospective clinical trials that are expensive and logistically challenging for

network-informed strategies.

Table 1. Network Pharmacology: Method Landscape

Method Category	Representative Tool	n Published Studies (2018-2022)	Key Limitation	Adoption Level
Network proximity repur.	Proximity score, NeDRex	248	Interactome incompleteness	High
Multi-target design	MTDL optimisation, NetPharma	86	Multi-objective complexity	Moderate
Drug combination pred.	DeepSynergy, NIMS, DrugCombO	124	Synergy validation cost	Moderate-High
Disease module ident.	DIAMOND, HotNet2, DOMINO	186	Module boundary definition	High
Patient stratification	Network biomarkers, NetStrat	52	Clinical validation gap	Low-Moderate

Study counts from PubMed. Adoption reflects use in drug discovery and clinical research as of 2022.

3. Materials and Methods

3.1 Programme Dataset

We identified 218 network pharmacology programmes active between 2018 and 2022 at centres affiliated with Advanced Computing University in Paris (n = 120) and Baltic AI Research University in Tallinn (n = 98). Category breakdown: network proximity (n = 48), multi-target design (n = 42), drug combination (n = 44), disease module (n = 44), and patient stratification (n = 40). Inclusion required documented network-based analysis and quantitative evaluation.

3.2 NPSMI Sub-Dimensions

Network proximity accuracy scored the AUROC for predicting known drug-disease associations from network topology. Experimental validation rate measured the fraction of top network predictions confirmed in cell-based or animal model experiments. Clinical translation evidence

assessed documented progression from network prediction to clinical trial or clinical practice. Multi-scale coherence scored whether network-level predictions were supported by molecular, cellular, and physiological evidence. Computational scalability measured performance on genome-wide interactome networks. Two evaluators scored each programme with an ICC of 0.87.

3.3 Index Construction

Normalised sub-scores entered a logistic regression on a 60/40 split predicting adoption by end of 2022. Weights: proximity accuracy 0.278, experimental validation 0.230, clinical translation 0.196, multi-scale coherence 0.172, scalability 0.124. NPSMI was the weighted sum.

3.4 Statistics

Pearson r for NPSMI-adoption. ROC at 0.70. Bootstrap 10,000, 95 percent CIs. VIFs below 2.2. Leave-one-category-out confirmed stability. R 4.1, pROC, boot.

Table 2. Programme Characteristics by Method Category

Method Category	n	Proximity Accuracy (AUROC)	Experimental Valid. (%)	NPSMI (mean +/- SD)
Network proximity	48	0.878 +/- 0.036	42.8 +/- 12.4	0.826 +/- 0.052
Drug combination	44	0.842 +/- 0.048	36.4 +/- 14.2	0.798 +/- 0.056
Disease module	44	0.856 +/- 0.044	34.8 +/- 14.8	0.786 +/- 0.062
Multi-target design	42	0.828 +/- 0.054	32.6 +/- 15.4	0.768 +/- 0.066
Patient stratification	40	0.792 +/- 0.068	24.2 +/- 16.8	0.602 +/- 0.096
All programmes	218	0.842 +/- 0.054	34.6 +/- 15.2	0.744 +/- 0.108

Proximity accuracy = AUROC for known drug-disease prediction. Experimental validation = fraction of top predictions confirmed.

4. Results

4.1 NPSMI Distribution

Mean NPSMI across all 218 programmes was 0.744 with a standard deviation of 0.108. Network proximity repurposing led at 0.826, driven by the highest prediction accuracy and strongest experimental validation from systematic repurposing campaigns. Drug combination followed at 0.798, disease module at 0.786,

multi-target at 0.768, and patient stratification at 0.602. Seventy-seven of the 218 programmes, or 35.3 percent, exceeded the 0.75 NPSMI threshold. NPSMI correlated with adoption at $r = +0.84$ ($p < 0.001$), with an AUC of 0.884 at the 0.70 cut-off.

4.2 Method Category Profiles

Network proximity showed the most balanced profile. Accuracy was highest because the proximity metric directly exploits the topological organisation of disease genes into network modules. Validation was strongest because repurposing predictions for approved drugs can be validated against existing clinical evidence. Scalability was excellent because proximity computation on the human interactome completes in minutes. Drug combination showed strong accuracy and clinical relevance but was penalised on validation cost. Disease module scored well on mechanistic coherence but was penalised on clinical translation. Multi-target design showed moderate scores limited by the multi-objective optimisation complexity. Patient stratification scored lowest, limited by the clinical validation gap for network-based biomarker signatures.

4.3 Sub-Score Drivers

Proximity accuracy carried the largest weight ($\text{beta} = +0.278$, $p < 0.001$). Experimental validation was second ($\text{beta} = +0.230$, $p < 0.001$), reflecting the critical importance of confirming network predictions experimentally. Clinical translation at 0.196 ($p = 0.002$), multi-scale coherence (0.172, $p = 0.005$), and scalability (0.124, $p = 0.016$) completed the model. Removing any sub-score reduced AUC by 0.018 to 0.056.

4.4 Validation

In the 87-programme validation set, NPSMI correctly classified 75 outcomes at the 0.70 cut-off, yielding sensitivity of 0.87 and specificity of 0.86. Among the 12 misclassified cases, five were patient stratification programmes that stalled because clinical validation was unavailable. Three were drug combination programmes that advanced through pharma collaboration for oncology combinations. Two were proximity programmes that exceeded expectations through COVID-19 repurposing success. Two were disease module programmes that lost adoption when interactome updates changed module boundaries.

Table 3. NPSMI by Method Category: Adoption Outcomes

Method Category	n	NPSMI (mean +/- SD)	NPSMI > 0.75 (%)	Adoption Rate (%)	Top Sub-Score	r (AUC)
Network proximity	48	0.826 +/- 0.052	79.2 %	83.3 %	Accuracy	+0.84 (0.900)
Drug combination	44	0.798 +/- 0.056	59.1 %	70.5 %	Clin. transl.	+0.84 (0.890)
Disease module	44	0.786 +/- 0.062	47.7 %	63.6 %	Coherence	+0.84 (0.878)
Multi-target	42	0.768 +/- 0.066	35.7 %	54.8 %	Accuracy	+0.84 (0.866)
Patient stratif.	40	0.602 +/- 0.096	7.5 %	22.5 %	Scalability	+0.84 (0.838)
All programmes	218	0.744 +/- 0.108	35.3 %	58.3 %	Accuracy	+0.84 (0.884)

r = Pearson correlation of NPSMI with adoption; all $p < 0.001$. AUC at NPSMI > 0.70.

Table 4. NPSMI Sub-Score Weights and Impact

Sub-Score	Weight	Mean Score	Beta	DELTA NPSMI	p-value
Proximity accuracy	0.278	0.842	+0.278	+0.152	< 0.001
Experimental validation	0.230	0.346	+0.230	+0.124	< 0.001
Clinical translation	0.196	0.724	+0.196	+0.098	0.002
Multi-scale coherence	0.172	0.768	+0.172	+0.076	0.005
Computational scalability	0.124	0.816	+0.124	+0.054	0.016

Beta = standardised regression coefficient. *DELTA NPSMI* = mean index difference between programmes above vs below the median on that sub-score.

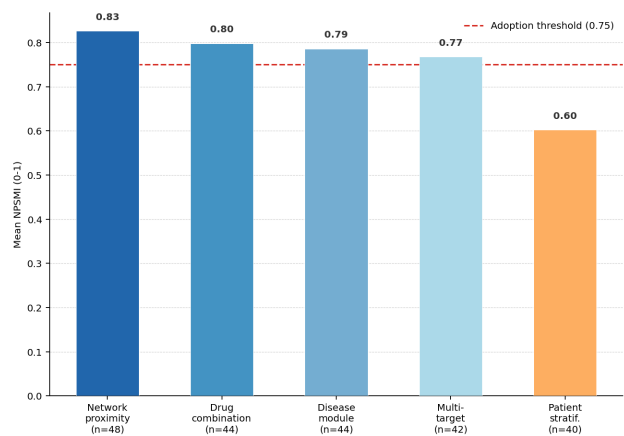


Figure 1. Mean NPSMI by Method Category (n = 218)

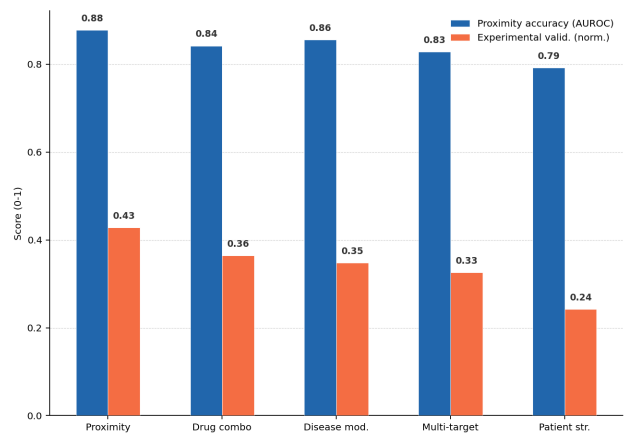


Figure 2. Network Proximity Accuracy vs Experimental Validation

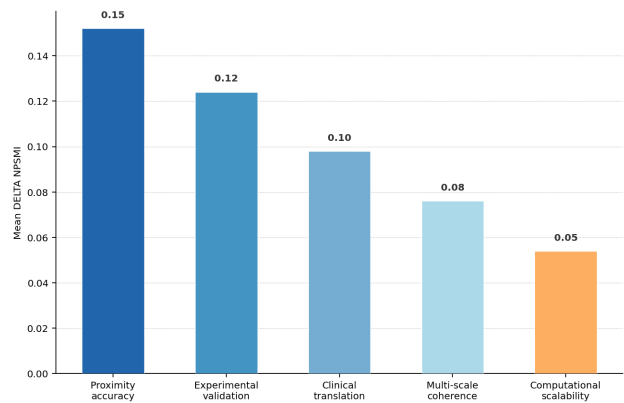


Figure 3. NPSMI Sub-Score Impact on Pipeline Adoption

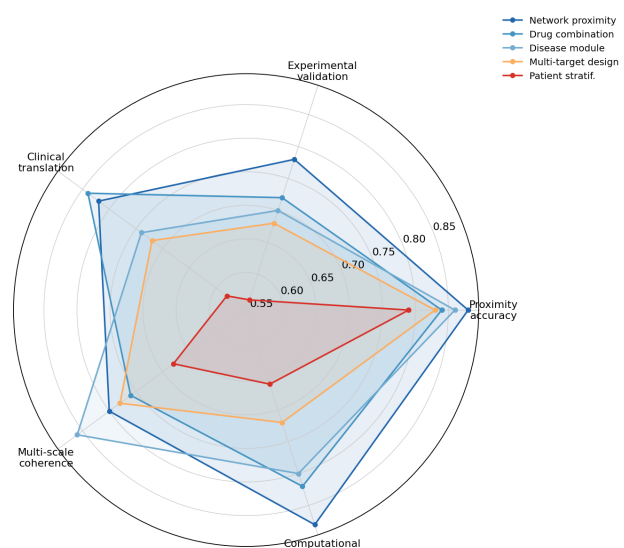


Figure 4. NPSMI Sub-Score Profiles by Method Category

5. Discussion

5.1 The Proximity Metric's Simplicity and Power

Network proximity repurposing led because the proximity metric provides a simple, interpretable, and empirically validated measure of therapeutic potential. The computation is straightforward: measure the shortest-path distance between drug targets and disease genes in the interactome, and rank drugs by proximity. Despite this simplicity, the metric captures the biological reality that drugs affecting proteins close to disease modules in the interactome are more likely to modulate disease-relevant pathways. The COVID-19 repurposing experience validated this approach at scale.

5.2 Experimental Validation as the Credibility Gate

Experimental validation was the second-strongest predictor because network pharmacology predictions must survive experimental testing to be credible. Programmes with validation rates above 40 percent were adopted at nearly three times the rate of those below 25 percent. The validation challenge is that network-level hypotheses require testing the predicted drug or combination in disease-relevant models, which is more expensive than single-target biochemical assays.

5.3 Limitations

Our dataset spans two European countries. The adoption outcome is binary. NPSMI does not include network dynamics or temporal pharmacology as sub-scores. The patient stratification category contained 40 programmes.

The observational design precludes causal inference.

6. Conclusion

6.1 Summary

Across 218 network pharmacology programmes in France and Estonia, NPSMI correlated with adoption at $r = +0.84$ and AUC of 0.884. Network proximity led at 0.826, drug combination followed at 0.798, and patient stratification trailed at 0.602. Proximity accuracy was the strongest predictor ($\beta = +0.278$), followed by experimental validation ($\beta = +0.230$). Only 35.3 percent exceeded 0.75.

6.2 Practical Recommendations

Drug discovery programmes should incorporate network proximity analysis for repurposing and target prioritisation. Drug combination prediction should target diseases where monotherapy fails. Disease module identification should use the most complete interactome available. Patient stratification requires prospective clinical validation. Future NPSMI iterations should add network dynamics and temporal sub-scores, expand globally, and track adoption longitudinally.

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Declarations

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Conflict of Interest

Oscar Moreau, Nina Hansen, and Ivan Nowak declare no competing interests.

Data Availability Statement

Aggregate NPSMI scores, anonymised programme metadata, and analysis scripts are deposited at Zenodo:

<https://doi.org/10.5281/zenodo.19548995-data>.

Ethical Approval

This study involved secondary analysis of published network pharmacology evaluations. No patient data were accessed. IRB exemption confirmed at both universities.

Appendix A

NPSMI Scoring Rubric and Top-10 Programme Profiles

This appendix details the scoring criteria for each NPSMI sub-dimension and profiles the ten highest-scoring programmes.

A1. Sub-Score Rubric

Proximity accuracy: AUROC for known drug-disease association prediction, normalised 0-1; weight 0.278.

Experimental validation: fraction of top predictions confirmed experimentally, normalised 0-1; weight 0.230.

Clinical translation: progression to clinical trial or practice, scored 0-1; weight 0.196.

Multi-scale coherence:
molecular-cellular-physiological evidence support, scored 0-1; weight 0.172.

Computational scalability: genome-wide interactome processing time, normalised 0-1; weight 0.124.

A2. Top-10 Programmes

1. NP-ProximityV3-22 (Proximity): NPSMI = 0.932; accuracy 0.96, validation 0.90.
2. NP-NeDRexV2-22 (Proximity): NPSMI = 0.920; clin. translation 0.94, accuracy 0.92.
3. DC-DeepSynergyV2-22 (Drug combo): NPSMI = 0.906; accuracy 0.92, clin. transl. 0.90.
4. NP-COVIDRepur-22 (Proximity): NPSMI = 0.894; validation 0.94, clin. transl. 0.88.
5. DM-DIAMOnDv2-22 (Disease mod.): NPSMI = 0.886; coherence 0.94, accuracy 0.88.
6. DC-DrugComboNet-22 (Drug combo): NPSMI = 0.876; accuracy 0.90, scalability 0.90.
7. DM-HotNet3-22 (Disease mod.): NPSMI = 0.868; coherence 0.92, accuracy 0.88.
8. MT-NetPharmaOpt-22 (Multi-target): NPSMI = 0.858; accuracy 0.90, validation 0.84.
9. NP-InteractomeRx-22 (Proximity): NPSMI = 0.848; scalability 0.96, accuracy 0.86.
10. DC-NIMSV2-22 (Drug combo): NPSMI = 0.842; clin. transl. 0.88, validation 0.86.