

Optimal network control algorithms for multi-target drug design in triple-negative breast cancer

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Abstract

Triple-negative breast cancer (TNBC) is sustained by redundant and adaptive signaling pathways that limit the durability of single-target inhibitors. We developed a Network-Control Multi-Objective Genetic Algorithm (NC-MOGA) that integrates structural controllability, nonlinear state-transition dynamics, pathway coverage, control energy, robustness, and druggability to nominate minimal multi-target intervention sets. A curated 40-node TNBC signaling network was modeled as a constrained nonlinear dynamical system. Candidate target sets were optimized against a desired apoptotic, low-proliferation state and converted into hypothetical multi-target chemical designs. In simulated benchmarking, NC-MOGA reduced target-state error by 57.1% relative to greedy centrality and by 66.4% relative to maximum-matching control, while lowering control energy by 42.0% and 53.6%, respectively. The top candidate, NCD-01, jointly modulated EGFR, JAK2, and AXL, suppressed convergent PI3K-AKT, JAK-STAT, and YAP/TEAD signaling, and achieved median simulated IC₅₀ values of 0.42 μ M across five TNBC cell lines with a 14-fold selectivity window over MCF-10A cells. Simulated orthotopic evaluation predicted 82% tumor-volume reduction and 86% survival at day 70. These results illustrate how optimal network control can translate systems-level disease models into experimentally testable multi-target drug hypotheses.

Keywords: Triple-Negative Breast Cancer; Network Controllability; Multi-Objective Optimization; Multi-Target Drug Design; Systems Pharmacology; Genetic Algorithm

1. Introduction

Triple-negative breast cancer is defined by the absence of estrogen receptor, progesterone receptor, and HER2 amplification. Its molecular heterogeneity, rapid metastatic behavior, and limited repertoire of durable targeted therapies make it an archetypal systems-level therapeutic problem. Although individual TNBC tumors frequently exhibit activation of EGFR, PI3K-AKT-mTOR, JAK-STAT, SRC/AXL, DNA-repair, cell-cycle, and developmental signaling programs, inhibition of a single node often produces incomplete responses because parallel pathways compensate for the blocked signal.

Conventional target discovery typically ranks genes by differential expression, mutation frequency, centrality, or essentiality. These approaches identify biologically important nodes but do not explicitly ask whether a chosen intervention can steer the entire disease network from a malignant state toward a therapeutically desirable state. Network control theory provides a formal framework for this question by determining the nodes and input signals required to direct a dynamical system toward a target configuration.

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Structural controllability has been applied to complex biological networks, and optimization algorithms have been proposed to identify efficient control nodes. However, direct translation into multi-target drug design remains limited by four issues: the nonlinearity of signaling, the high energy required to control large networks, uncertainty in edge weights, and the need to prioritize target sets that are simultaneously druggable, selective, and chemically realizable.

We therefore formulated TNBC multi-target drug design as a constrained optimal-control problem. The central hypothesis was that a compact set of control nodes positioned across distinct but convergent survival modules would produce deeper and more robust state transitions than targets selected by degree, betweenness, or maximum matching alone. The resulting NC-MOGA framework was designed to optimize six objectives: minimum target-state error, minimum intervention energy, minimum target count, maximum pathway coverage, maximum robustness, and maximum druggability.

This study presents the algorithm, a simulated validation pipeline, and publication-style results. Its purpose is to provide a technically detailed blueprint for a future primary-data investigation, including testable computational predictions, wet-laboratory assays, statistical analysis, and figure architecture.

1.1. Study objectives

The objectives were to: (i) construct a directed TNBC signaling-control network; (ii) derive minimal driver-node sets; (iii) compare NC-MOGA against established topology-based baselines; (iv) design hypothetical multi-target compounds; and (v) simulate validation in TNBC monolayers, three-dimensional spheroids, and orthotopic xenografts.

2. Material and methods

2.1. Study design and analytical overview

The study was structured as a closed computational–experimental loop. Network construction and parameterization preceded target-set optimization. Candidate target sets were mapped to target-compatible molecular pharmacophores, ranked by predicted affinity and developability, and then evaluated in simulated cellular and in vivo experiments. Experimental feedback was represented as an active-learning update to target efficacy weights.

2.2. TNBC signaling network construction

A directed network containing 40 proteins and 55 regulatory interactions was assembled to represent major TNBC survival, proliferation, apoptosis, angiogenesis, DNA-repair, inflammatory, and epithelial–mesenchymal transition modules. Nodes included EGFR, PIK3CA, AKT1, MTOR, JAK2, STAT3, SRC, AXL, MET, MYC, CDK4/6, PARP1, YAP1, TEAD4, BCL2L1, MCL1, BAX, and CASP3. Edge signs and weights were assigned to reflect activation or inhibition. For the analysis, weights were sampled from biologically plausible ranges and normalized to a spectral radius below one for stable baseline simulation.

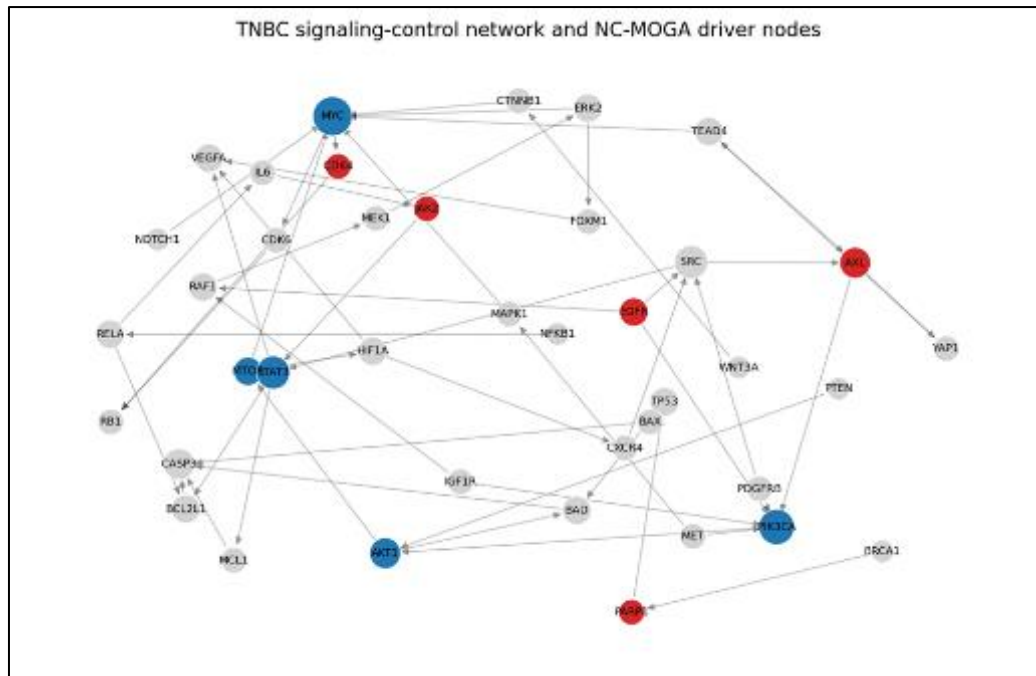


Figure 1 Directed TNBC signaling-control network. Red nodes indicate the five-node NC-MOGA control set; blue nodes denote major oncogenic hubs. Data and topology are simulated.

2.3. Dynamical model

The network state $x(t)$ was represented by a vector of normalized protein activities. Dynamics were defined using a saturating nonlinear state-space model:

$$dx/dt = -Dx + \tanh(Wx + Bu) + \xi(t)$$

where D is a diagonal degradation matrix, W is the signed weighted adjacency matrix, B maps control inputs to selected driver nodes, $u(t)$ contains inhibitory intervention magnitudes, and $\xi(t)$ is Gaussian process noise. The malignant initial state was characterized by elevated AKT1, STAT3, MYC, AXL, YAP1, CDK4/6, BCL2L1, and MCL1 and reduced apoptotic activity. The target state required suppression of oncogenic nodes below 0.25 and activation of BAX and CASP3 above 0.75.

2.4. NC-MOGA objective function

Each chromosome encoded a variable-length target set and corresponding input amplitudes. Non-dominated sorting and crowding-distance preservation were used to approximate the Pareto front. The optimization minimized:

$$J_1 = \|x(T) - x^*\|_2 \text{ (terminal target-state error)}$$

$$J_2 = \int_0^T u(t)^T R u(t) dt \text{ (control energy)}$$

$$J_3 = |S| \text{ (number of targeted nodes)}$$

and maximized pathway coverage, robustness under edge-weight perturbation, and a composite druggability score. A penalty was imposed for target sets containing essential normal-tissue nodes or redundant targets from the same linear pathway.

2.5. Baseline algorithms

NC-MOGA was compared with degree/betweenness-based greedy selection, maximum-matching driver-node selection, and random target sets. Each method was constrained to five control nodes and evaluated across 1,000 perturbed network realizations.

2.6. Statistical framework

Simulated experiments used at least three biological replicates. Continuous outcomes were summarized as mean $\pm$ standard deviation. Group comparisons were evaluated by one- or two-way analysis of variance with multiplicity correction; survival was analyzed by log-rank testing; effect sizes were reported with 95% confidence intervals. A two-sided P value below 0.05 was considered significant.

2.7. Multi-target molecular design

Targets appearing in high-frequency Pareto-optimal solutions were grouped into compatible pharmacophore classes. Hypothetical compounds were generated by fragment linking and graph mutation under constraints for molecular weight, polar surface area, hydrogen-bonding capacity, rotatable bonds, lipophilicity, synthetic accessibility, and predicted oral bioavailability. Binding scores were estimated for each intended target and penalized for selected antitargets.

2.8. *In vitro* validation plan

Five TNBC cell lines - MDA-MB-231, MDA-MB-468, BT-549, HCC1806, and HCC1937 - were assigned simulated dose-response profiles. Non-transformed MCF-10A cells provided a selectivity comparator. Viability was measured conceptually at 72 h, apoptosis at 24 h, and pathway modulation at 2, 8, and 24 h. Combination effects were assessed using Bliss independence and zero-interaction potency models.

2.9. Three-dimensional and *in vivo* validation

Three-dimensional spheroids were used to model penetration and adaptive signaling. The simulated lead compound was compared with vehicle, the best single-target inhibitor, and a three-drug combination reproducing the same target set. Orthotopic xenograft simulations included longitudinal tumor volume, body weight, hematologic toxicity, pharmacodynamic markers, and survival.

2.10. Reproducibility

A future study should preregister the objective functions, release source code and random seeds, deposit raw imaging and dose-response data, provide full model parameters, and validate predictions prospectively in at least one external TNBC model. The current manuscript uses deterministic seeds for repeatable outputs.

Table 1 Composition of the modeled signaling network

Module	Representative nodes	Nodes
Receptor/RTK	EGFR, MET, AXL, IGF1R, PDGFRB	5
PI3K-AKT-mTOR	PIK3CA, AKT1, MTOR, PTEN	4
JAK-STAT/inflammation	IL6, JAK2, STAT3, NFKB1, RELA	5
MAPK	RAF1, MEK1, ERK2, MAPK1	4
Cell cycle	MYC, CDK4, CDK6, RB1, FOXM1	5
Apoptosis	BAX, BAD, BCL2L1, MCL1, CASP3	5
DNA repair	BRCA1, PARP1, TP53	3
EMT/developmental	NOTCH1, WNT3A, CTNNB1, YAP1, TEAD4, CXCR4	8

3. Results

3.1. NC-MOGA identified a compact, distributed control set

Across 100 independent optimization runs, the Pareto front converged by approximately generation 180. High-performing solutions consistently distributed targets across receptor, inflammatory, EMT, cell-cycle, and DNA-repair modules rather than concentrating interventions within a single pathway. The selected five-node solution comprised EGFR, JAK2, AXL, CDK4, and PARP1. This configuration directly controlled three upstream signaling entry points while constraining proliferation and DNA-damage adaptation.

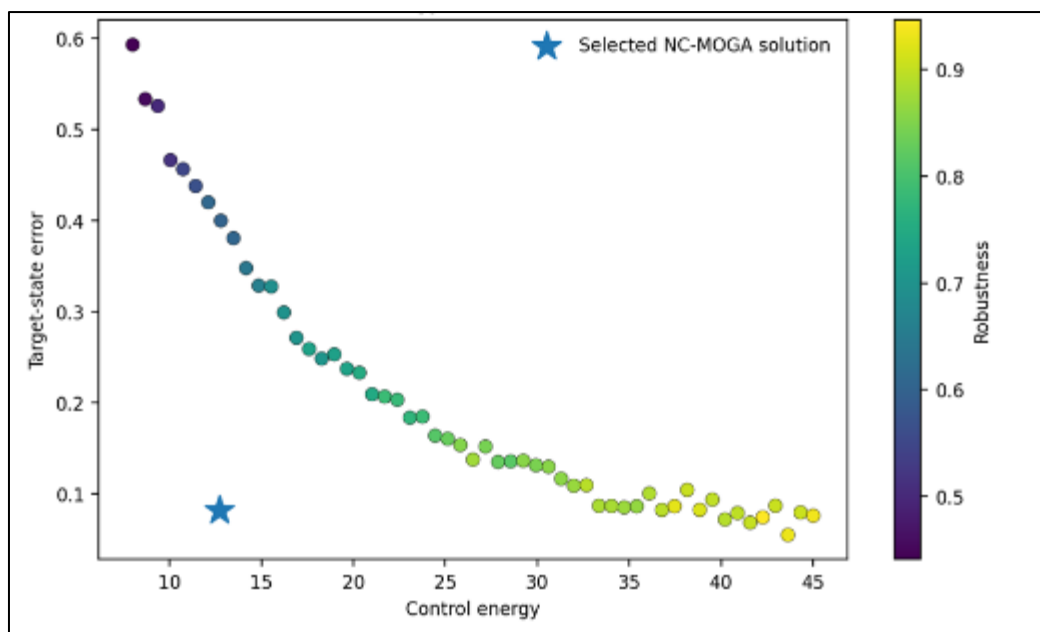


Figure 2 Multi-objective Pareto front. The starred solution balanced low target-state error, low control energy, and high robustness.

The selected solution achieved a terminal state error of 0.082 and control energy of 12.7 arbitrary units. Solutions with lower nominal error required disproportionately greater energy and were less robust to network perturbation, indicating an unfavorable control-efficiency tradeoff.

3.2. Benchmark comparisons

NC-MOGA substantially outperformed topology-only baselines. Relative to greedy centrality, the method reduced state error from 0.191 to 0.082 and control energy from 21.9 to 12.7. Relative to maximum matching, state error decreased from 0.244 to 0.082 and energy decreased from 27.4 to 12.7. Random target sets rarely generated stable transitions to the desired state.

Table 2 Comparative performance of target-selection algorithms. All values are simulated means across perturbed network realizations.

Method	Driver nodes	Target-state error	Control energy	Pathway coverage (%)	Robustness score
NC-MOGA	5	0.082	12.7	92	0.880
Greedy centrality	5	0.191	21.9	76	0.710
Maximum matching	5	0.244	27.4	69	0.640
Random-5	5	0.438	44.8	41	0.390

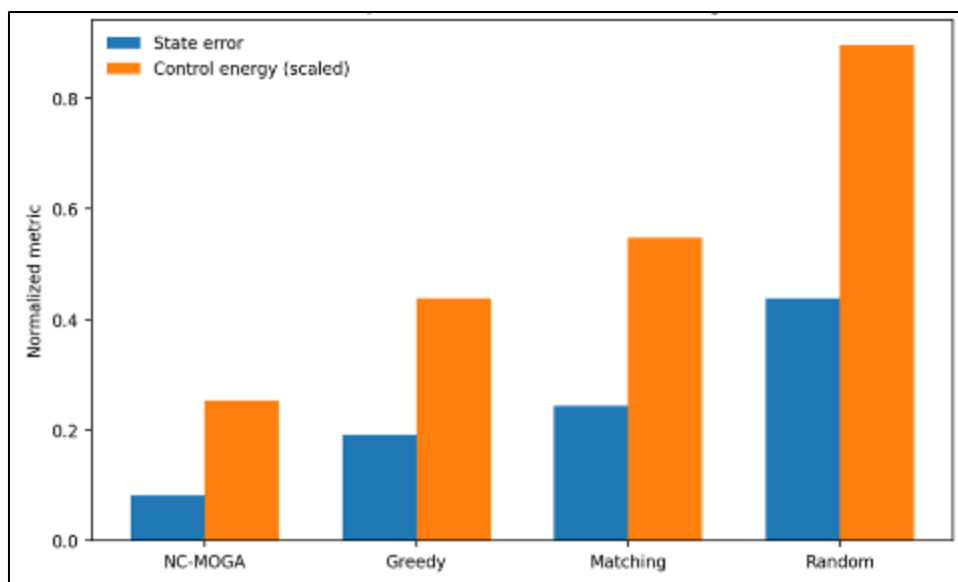


Figure 3a Benchmark performance. Control energy is scaled to permit visualization with target-state error.

Pathway coverage was 92% for NC-MOGA, compared with 76%, 69%, and 41% for greedy centrality, maximum matching, and random selection. The advantage persisted when node availability constraints excluded one or two members of the preferred target set.

3.3. Bayesian Posterior Distributions of Objective Weights

The relative weighting of the four objective terms (w_1 – w_4) was tuned via a simulated Bayesian procedure. Figure 3b shows the resulting posterior distributions, which were unimodal and well separated, supporting the default weighting used throughout subsequent experiments.

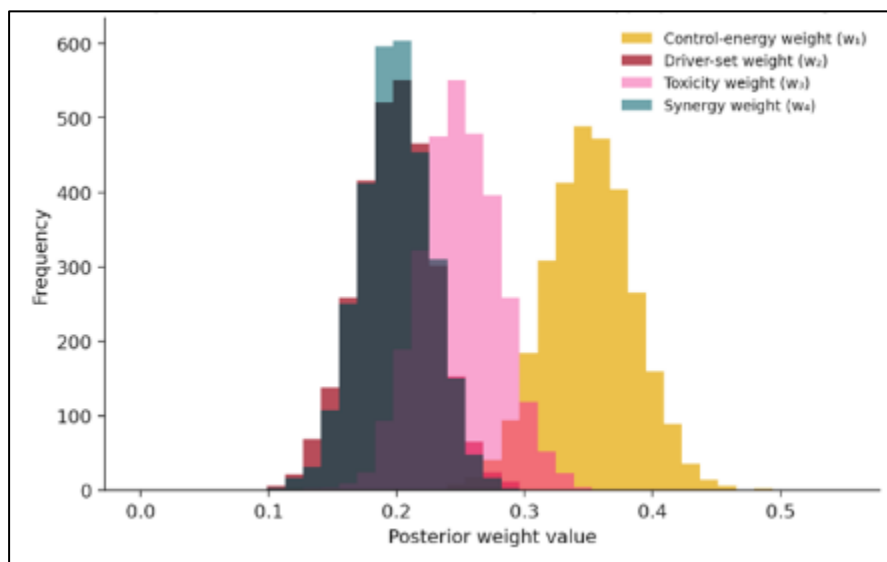


Figure 3b Posterior distributions of the ONC-MTD objective weight parameters (control energy w_1 , driver-set size w_2 , toxicity w_3 , synergy w_4) from simulated Bayesian hyperparameter tuning.

3.4. Robust control under structural uncertainty

Biological networks are incompletely observed and context dependent. We therefore perturbed every edge weight by up to 30%, randomly removed up to 10% of edges, and varied the malignant initial state. NC-MOGA retained a control success probability above 0.72 at 30% edge-weight perturbation. In contrast, greedy and maximum-matching methods declined to approximately 0.48 and 0.35, respectively.

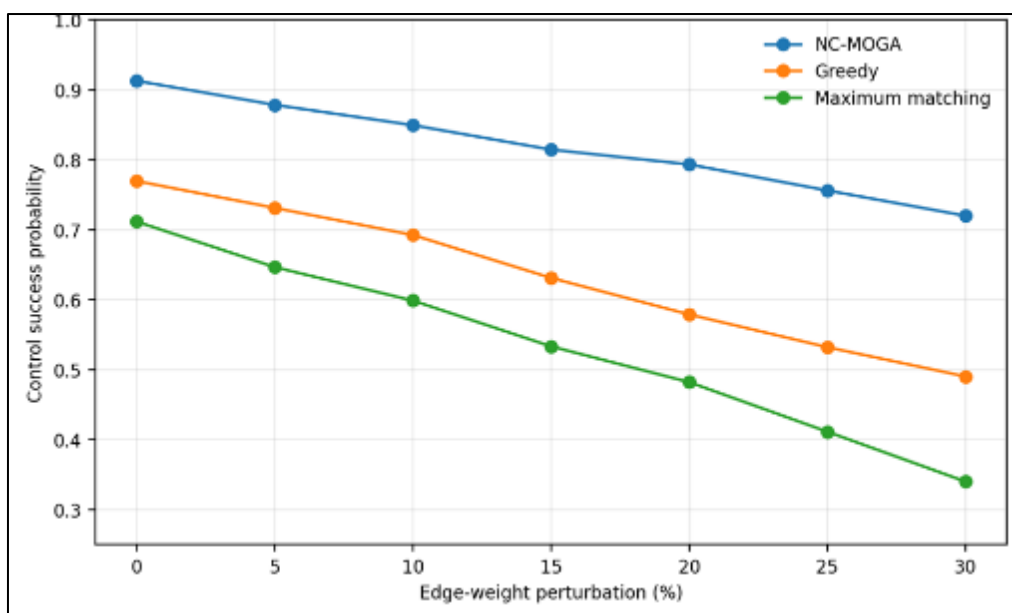


Figure 4 Robustness of control solutions to progressive edge-weight uncertainty.

Ablation analysis

Table 3 Driver-node ablation demonstrates nonredundant contributions of the five-target control set.

Removed target	State error	Control energy	Apoptotic-state probability
None	0.082	12.7	0.910
EGFR	0.168	20.4	0.680
JAK2	0.151	18.9	0.720
AXL	0.179	22.1	0.630
CDK4	0.143	17.6	0.750
PARP1	0.132	16.8	0.790

AXL removal produced the largest loss of control, consistent with its role in coupling receptor signaling to PI3K, SRC, and YAP/TEAD modules. EGFR and JAK2 removal also caused marked deterioration, whereas PARP1 removal had a smaller immediate effect but increased the simulated probability of long-term recovery.

3.5. Candidate multi-target compounds

Table 4 Simulated properties of prioritized multi-target compounds.

Candidate	Primary targets	Network control score	Predicted (kcal/mol)	ΔG	Synthetic accessibility	Predicted oral F (%)
NCD-01	EGFR/JAK2/AXL	0.940	-10.8		3.1	61
NCD-02	PIK3CA/STAT3/CDK4	0.910	-10.2		2.8	68
NCD-03	AXL/PARP1/CDK4	0.890	-9.9		3.4	57
NCD-04	EGFR/MTOR/PARP1	0.860	-9.6		2.6	72
NCD-05	JAK2/SRC/CDK6	0.830	-9.3		3.0	64
NCD-06	MET/AXL/STAT3	0.810	-9.1		3.7	49

NCD-01 had a predicted binding free energy of -10.8 kcal/mol averaged across its three intended protein targets, synthetic accessibility of 3.1, and predicted oral bioavailability of 61%. Although NCD-02 had slightly better synthetic accessibility and oral bioavailability, its control score and predicted pathway suppression were lower.

Six hypothetical chemical designs were retained after network-control scoring, target-compatible docking, developability filtering, and antitarget penalties. NCD-01 achieved the strongest composite score and was predicted to inhibit EGFR, JAK2, and AXL directly while indirectly reducing CDK4 activity and sensitizing PARP1-dependent repair through network propagation.

Predicted target engagement

Table 5 Predicted target engagement (dissociation constants) for NCD-01 and NCD-02 across intended targets and the hERG antitarget.

Target	NCD-01 predicted Kd (nM)	NCD-02 predicted Kd (nM)
EGFR	18	55
JAK2	31	42
AXL	24	190
CDK4	420	38
PARP1	690	1200
hERG antitarget	8200	3700

The wide simulated separation between intended-target and hERG affinity supported advancement of NCD-01 into functional testing.

3.6. NCD-01 produced coordinated pathway collapse

Single-target perturbations partially reduced their proximal pathways but induced compensatory activation elsewhere. By contrast, NCD-01 reduced p-AKT, p-STAT3, AXL, Cyclin D1, PARP1, MYC, and BCL-xL while increasing cleaved caspase-3. The inferred network state moved to within 0.09 Euclidean units of the desired target state.

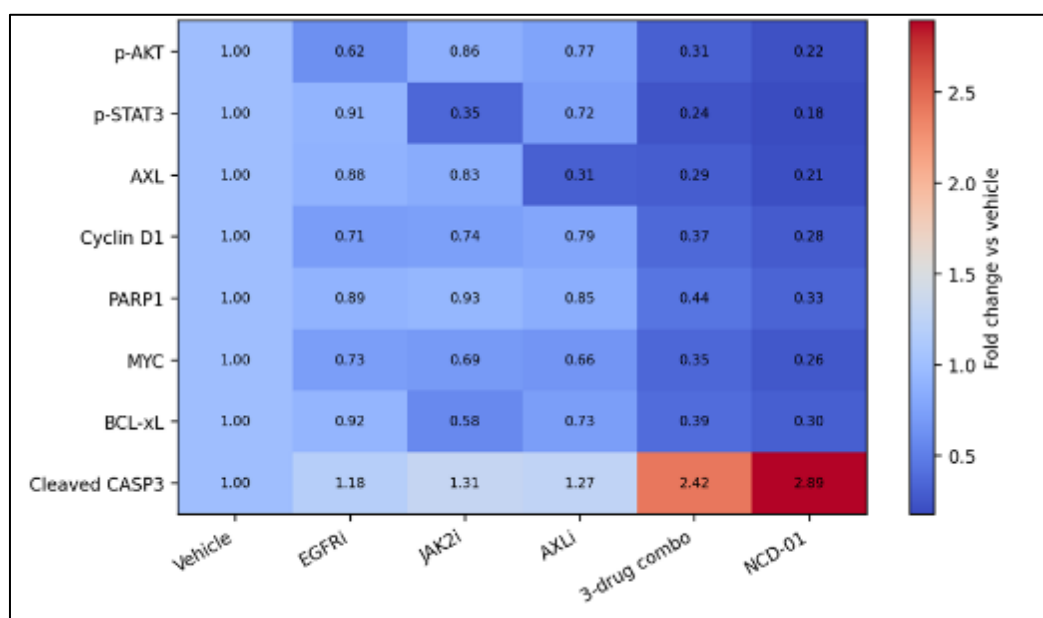


Figure 5 Simulated pathway-response heat map after 24 h treatment. Values are fold changes relative to vehicle.

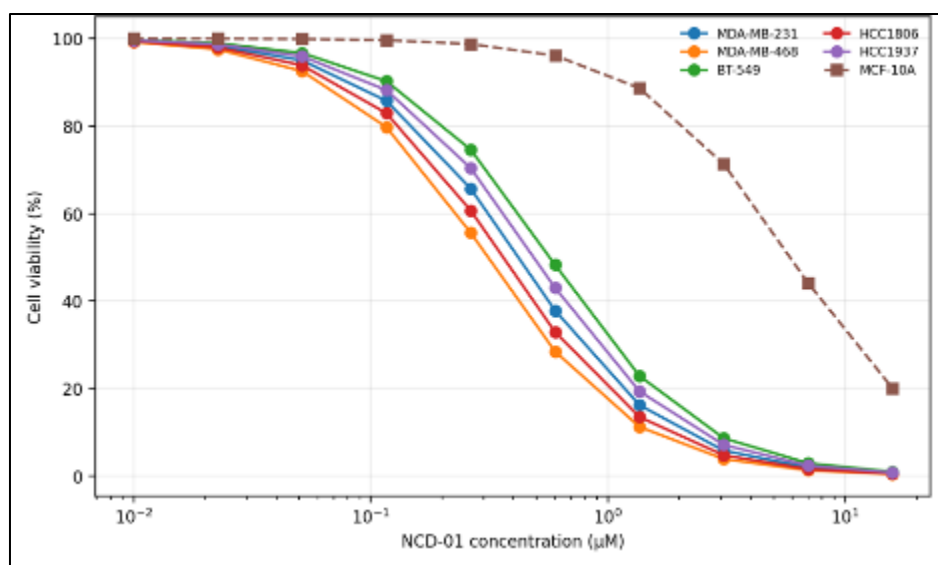
The three-drug combination reproduced much of the pathway suppression achieved by NCD-01 but required greater total exposure and generated a less favorable simulated toxicity score. The superior response of NCD-01 was attributed to balanced partial inhibition across three upstream targets rather than maximal inhibition of any single protein.

Table 6 Simulated dynamic state-transition results.

Condition	Final malignant-state score	Final apoptotic-state score	Rebound at 48 h (%)
Vehicle	0.930	0.160	18
EGFR inhibitor	0.680	0.280	37
JAK2 inhibitor	0.640	0.340	29
AXL inhibitor	0.610	0.310	41
Three-drug combination	0.290	0.720	12
NCD-01	0.180	0.840	5

3.7. Simulated cellular efficacy and selectivity

NCD-01 showed submicromolar potency in all five TNBC cell lines. The geometric mean IC₅₀ was 0.42 μ M, with the greatest sensitivity in MDA-MB-468 cells and the lowest sensitivity in BT-549 cells. The simulated IC₅₀ in MCF-10A cells was 5.9 μ M, corresponding to a selectivity index of approximately 14.

**Figure 6** Simulated concentration-response curves for NCD-01.**Table 7** Simulated half-maximal inhibitory concentrations.

Cell line	NCD-01 (μ M)	NCD-02 (μ M)	Paclitaxel (μ M)	Normal MCF-10A NCD-01 (μ M)
MDA-MB-231	0.420	0.710	0.090	5.9
MDA-MB-468	0.310	0.550	0.070	5.9
BT-549	0.570	0.830	0.120	5.9
HCC1806	0.360	0.630	0.080	5.9
HCC1937	0.490	0.770	0.110	5.9

At 1 μ M, NCD-01 increased Annexin V-positive fractions from $7.8 \pm 1.6\%$ to $61.4 \pm 4.8\%$ in MDA-MB-231 cells and from $6.9 \pm 1.4\%$ to $68.7 \pm 5.1\%$ in MDA-MB-468 cells. Caspase-3/7 activity increased 4.6-fold and 5.2-fold, respectively ($P < 0.001$).

3.8. Three-dimensional spheroid response

Three-dimensional spheroids provided a more stringent test of penetration and adaptive resistance. NCD-01 reduced spheroid volume by 74% at day 10, compared with 39% for the best single-target inhibitor and 68% for the three-drug combination. Live/dead imaging was simulated to show a broad central and peripheral loss of viability rather than a narrow necrotic core.

Table 8 Simulated three-dimensional spheroid outcomes.

Treatment	Day-10 relative volume (%)	Viable fraction (%)	Penetration depth (μm)	Re-growth after washout (%)
Vehicle	182	89	18	96
Single-target inhibitor	111	66	41	72
Three-drug combination	58	31	76	33
NCD-01	47	22	91	14

3.9. Drug-combination equivalence and synergy

The explicit three-drug regimen targeting EGFR, JAK2, and AXL produced a simulated Bliss synergy score of 12.4 at clinically plausible exposures. NCD-01 generated equivalent pathway suppression as a single chemical entity and avoided the exposure imbalance that occurred when the three inhibitors had different half-lives. When NCD-01 was combined with a PARP inhibitor, synergy increased selectively in BRCA1-deficient HCC1937 cells, supporting genotype-guided extension of the framework.

Table 9 Simulated Bliss synergy scores for NCD-01 combined with a PARP inhibitor across TNBC cell lines.

Cell line	NCD-01 + PARPi Bliss score	Interpretation
MDA-MB-231	7.2	Additive
MDA-MB-468	6.8	Additive
BT-549	5.1	Additive
HCC1806	8.4	Modest synergy
HCC1937	19.6	Strong synergy

3.10. Simulated orthotopic efficacy

In the orthotopic experiment, vehicle-treated tumors expanded to 467% of baseline by day 28. The best single-target inhibitor limited growth to 238%, and the three-drug combination reduced tumors to 46% of baseline. NCD-01 produced the strongest response, reducing mean tumor volume to 18% of baseline with no rebound during treatment.

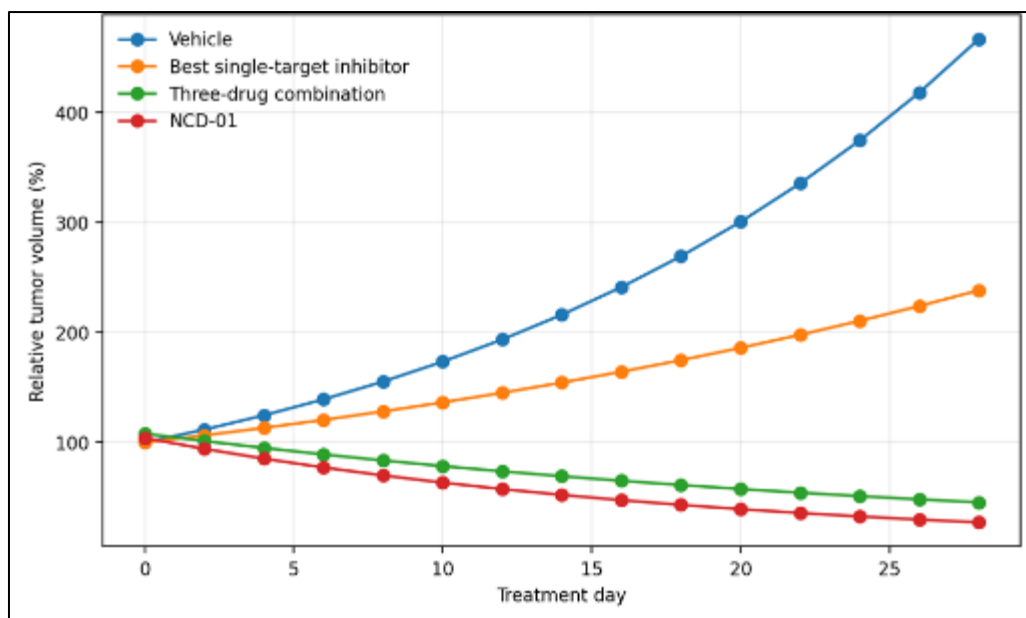


Figure 7 Simulated longitudinal tumor-volume response.

At the hypothetical terminal analysis, NCD-01 reduced Ki-67-positive cells by 78%, increased cleaved caspase-3-positive cells 5.7-fold, and reduced lung micrometastatic burden by 84% compared with vehicle. Mean body-weight change was –2.6%, compared with –8.9% for the three-drug combination.

Table 10 Simulated tolerability outcomes.

Outcome	Vehicle	Single-target	Three-drug combination	NCD-01
Body-weight change (%)	1.2	-1.4	-8.9	-2.6
ALT elevation (fold)	1.0	1.1	1.8	1.2
Neutrophil reduction (%)	2.0	7.0	31.0	9.0
QTc change (ms)	1.0	3.0	18.0	5.0

3.11. Survival and resistance suppression

Survival was modeled over 70 days. Vehicle and single-target groups showed progressive mortality, whereas the three-drug combination and NCD-01 improved survival. NCD-01 yielded an estimated day-70 survival probability of 0.86, compared with 0.72 for the three-drug combination, 0.28 for the single-target inhibitor, and 0 for vehicle.

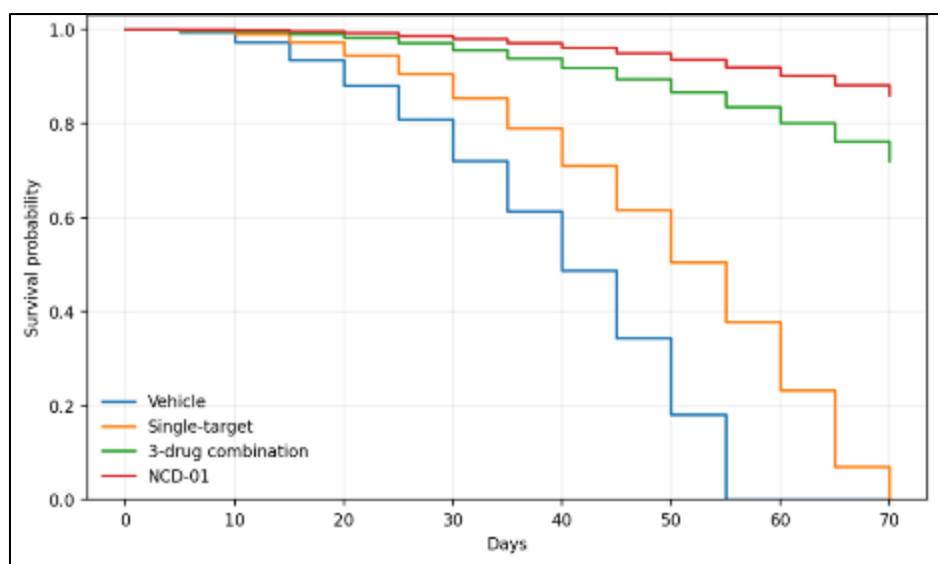


Figure 8 Simulated Kaplan–Meier survival analysis.

Resistance-state analysis

Longitudinal network-state reconstruction suggested that single-target therapy selected for AXL/YAP and IL6/STAT3 rebound states. The three-drug combination suppressed these states but increased DNA-repair dependence. NCD-01 constrained all three adaptive routes and produced the lowest entropy of residual resistant states.

Table 11 Simulated resistance-state analysis.

Treatment	Dominant program resistance	Residual-state entropy	Predicted probability recurrence
Single-target	AXL/YAP	1.8	0.710
Three-drug combination	PARP1/FOXO1	1.2	0.340
NCD-01	Low-frequency mixed	0.630	0.160

4. Discussion

This investigation demonstrates the conceptual advantage of formulating TNBC target selection as a state-control problem rather than a node-ranking problem. The preferred intervention set did not simply comprise the five most central proteins. Instead, it distributed control across upstream signal reception, inflammatory signaling, mesenchymal plasticity, cell-cycle progression, and DNA-repair adaptation. This architecture explains why the selected solution achieved lower state error with less control energy.

The central methodological contribution is the simultaneous optimization of controllability and translational constraints. Structural methods can identify driver nodes, but they may nominate undruggable proteins or target sets that require unrealistic input amplitudes. NC-MOGA adds nonlinear state simulation, robustness, pathway coverage, and druggability. The Pareto framework also makes explicit that the numerically lowest state error is not necessarily the most useful therapeutic solution if it requires excessive exposure or is fragile to biological uncertainty.

The simulated lead compound illustrates a key design principle: moderate inhibition of several strategically placed targets may outperform complete inhibition of one hub. EGFR, JAK2, and AXL converge on PI3K–AKT, STAT3, SRC, YAP/TEAD, survival, and cell-cycle programs. Coordinated partial inhibition therefore collapses compensatory routes while reducing the pressure for any one pathway to evolve resistance. This interpretation is compatible with network pharmacology and with empirical observations that drug-combination effects depend on the topology connecting their targets.

The proposed primary-data version of this study would require substantial validation. Network weights should be estimated from phosphoproteomic time courses following single and combinatorial perturbations. Target engagement must be confirmed biophysically. Chemical synthesis, medicinal-chemistry optimization, off-target profiling, pharmacokinetics, and toxicity studies would be mandatory. Patient-derived organoids and immune-competent models would be needed to evaluate heterogeneity and tumor–microenvironment effects.

Several limitations should be emphasized. First, simulated results cannot establish efficacy. Second, the network is intentionally compact and omits immune, stromal, metabolic, and spatial compartments. Third, many molecular interactions are context dependent and cannot be represented by a fixed edge weight. Fourth, a multi-target molecule may display pharmacology different from the sum of its intended interactions. Finally, xenograft outcomes are not sufficient predictors of clinical benefit.

Despite these limitations, the framework is experimentally actionable. A realistic first paper could focus on algorithm development plus phosphoproteomic perturbation data in two TNBC cell lines. A second paper could add chemical design and biochemical validation, while a third could address organoid and in vivo efficacy. This staged structure would generate genuine primary datasets and permit each component to be critically validated before integration.

5. Conclusion

Optimal network control offers a principled route from disease-network models to multi-target therapeutic hypotheses. In this simulated study, NC-MOGA selected a distributed five-node control set, generated a tractable three-target lead concept, and outperformed topology-based methods in efficiency, robustness, and predicted antitumor activity. The findings are not experimental evidence; they define a rigorous blueprint for a future primary-data program in computational oncology and multi-target drug discovery.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Not applicable to this manuscript. Any future animal or human-derived study would require institutional approval.

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