

Supplementary material (MATLAB codes and simulation results) for “*Intratumor Heterogeneity Alters Most Effective Drugs in Designed Combinations*”

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This supplementary package contains three folders: ./matlab/, ./simulations/, and ./analyses/

MATLAB classes/datasets (./matlab/)

./matlab/lib: contains all classes for performing Monte Carlo sampling and optimizing drug combinations;
 MATLAB codes in the other two folders create instances of class for simulations and analyses
 ./matlab/datasets: contains D21H30.m and D21H30.mat, the dataset with 21 drugs and 30 subpopulations (shRNAs).

IMPORTANT NOTE: CPLEX libraries are required to solve the optimization problems – to derive optimal drug combinations. CPLEX libraries for MATLAB need to be placed inside a ./matlab/cplex folder (or on path). The libraries are not included in this supplementary package due to license restrictions.

Simulations (./simulations/)

All simulations were run on a computing cluster. Jobs were written in shell scripts (.sh files).

Simulation (folder name)	Description (brief summary of input parameter values for each simulation run)
N10000	Monte Carlo simulation 10,000 heterogeneous tumor populations Symmetric toxicity Drug optimized based on all subpopulations
N10000_subpopOnly1.2 Contains two simulations: N10000_subpopOnly1 N10000_subpopOnly2	Tumor populations given (from simulation results in <i>N10000</i>) N10000 results were first processed to remove any weak Pareto optimal solutions (see <i>anlyz.N10000_postsims_process</i> in ./analyses/ folder) 10,000 heterogeneous tumor populations Symmetric toxicity drug optimized based on only predominant (subpopOnly1) or second largest (subpopOnly2) subpopulation
N10000_sametox0	Monte Carlo simulation 10,000 heterogeneous tumor populations Asymmetric toxicity Drug optimized based on all subpopulations
bcN1 Contains multiple simulations that are subsequently combined	Monte Carlo simulation with first two largest subpopulations fixed (see methods in paper for details) 13,050 heterogeneous tumor populations Symmetric toxicity Drug optimized based on all subpopulations
bcN1_subpopOnly1.2 Contains two simulations: bcN1_subpopOnly1 bcN1_subpopOnly2	Tumor populations given (from simulation results in <i>bcN1</i>) <i>bcN1</i> results were combined and processed to remove any weak Pareto optimal solutions (see <i>anlyz.bcN1_postsims_process</i> in ./analyses/ folder) 13,050 heterogeneous tumor populations Symmetric toxicity Drug optimized based on only predominant (subpopOnly1) or second largest (subpopOnly2) subpopulation
rho_selection Contains multiple simulations (different rho values; modified manually in OptimizationModels.m; see comments in code)	Tumor population given (single homogeneous shATM population) 1 homogeneous tumor population Symmetric toxicity Drug optimized based on all subpopulations (i.e. in this case just the one) Maximum toxicity constraint value set to generate all solutions along Pareto frontier
noToxMaxConstraint Contains four simulations (modified manually in code; see comments in code)	Tumor population given 1 homogeneous tumor population Symmetric toxicity Drug optimized based on all subpopulations Maximum toxicity constraint value set to generate all solutions along Pareto frontier

Analyses (./analyses/)

Simulation results (from above, saved as .mat files) were copied into ./analyses/ as working copies for analyses.

Simulation results	Working copy in
<i>N10000</i> , <i>N10000_subpopOnly1</i> , <i>N10000_subpopOnly2</i> , <i>N10000_sametox0</i>	./analyses/output/
<i>bcN1</i> , <i>bcN1_subpopOnly1</i> , <i>bcN1_subpopOnly2</i>	./analyses/outputs_bc/
<i>rho_selection</i>	./analyses/anlyz.rho_selection/
<i>noToxMaxConstraint</i>	./analyses/anlyz.noToxMaxConstraint/

Some MATLAB codes in ./analyses/ may require varying the parameter values manually to generate all figures (e.g. in specifying which regimen to analyze). These were commented accordingly in codes.

Analysis (folder name)	Description	Used to generate figure...
anlyz.dataset	Generates summary figures (heatmaps/clustergrams) of datasets	Fig. S1, Fig. S15A
anlyz.rho_selection	Analyzes <i>rho_selection</i> results	Fig. S3
anlyz.noToxMaxConstraint	Analyzes <i>noToxMaxConstraint</i> results	Fig. 2, Fig. S4
anlyz.N10000 postsim_process	Removes weak Pareto optimal solutions from <i>N10000</i> results Newly generated results (.mat) copied to ./analyses/outputs	N/A
anlyz.N10000_sametox0	Analyzes <i>N10000_sametox0</i> simulation results	Fig. S14, Fig. S16, Fig. S15B, S15C
anlyz.N10000_sametox1	Performs general statistical and sensitivity analyses on <i>N10000</i> results	Fig. 3, Fig. 6, Fig. S8
anlyz.N10000_sametox1_subpopOnly1	Performs general statistical and sensitivity analyses on <i>N10000_subpopOnly1</i> results	Fig. 4, Fig. S9
anlyz.N10000_sametox1 vs_subpopOnly1	Compares <i>N10000</i> and <i>N10000_subpopOnly1</i> results	Fig. 5
anlyz.N10000_sametox1 vs_subpopOnly1.2	Compares <i>N10000</i> and (<i>N10000_subpopOnly1</i> & <i>N10000_subpopOnly2</i>) results	Fig S10
anlyz.N10000_sametox1 partial_corr	Matthews correlation and partial spearman correlation analysis of <i>N10000</i> and <i>N10000_subpopOnly1</i> results	Fig. S5, Fig. S6, Fig. S7
anlyz.N10000_sametox1 drug_distribution	Analyzes <i>N10000</i> versus <i>N10000_subpopOnly1</i> ; <i>N10000</i> versus <i>N10000_subpopOnly1</i> and <i>N10000_subpopOnly2</i> results, decomposed based on predominant and second largest subpopulation proportions	Fig. S11, Fig. S12
anlyz.bcN1 postsim_process	Combines <i>bcN1</i> simulation results Removes weak Pareto optimal solutions from combined <i>bcN1</i> results Newly generated results (.mat) copied to ./analyses/outputs_bc/	N/A
anlyz.bcN1 drug_distribution	Analyzes <i>bcN1</i> versus <i>bcN1_subpopOnly1</i> ; <i>bcN1</i> versus <i>bcN1_subpopOnly1</i> and <i>bcN1_subpopOnly2</i> results, decomposed based on predominant and second largest subpopulation proportions	Fig. S13