**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).

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| 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 |
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| N10000\_subpopOnly1.2  Contains two simulations:  N10000\_subpopOnly1  N10000\_subpopOnly2 | Tumor populations given (from simulation results in *N10000*)  N10000 results were first processed to remove any weak Pareto optimal solutions (see *anlyz.N10000 postsim\_process* in ./analyses/ folder)  10,000 heterogeneous tumor populations  Symmetric toxicitydrug optimized based on only predominant (subpopOnly1) or second largest (subpopOnly2) subpopulation |
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| N10000\_sametox0 | Monte Carlo simulation  10,000 heterogeneous tumor populations  Asymmetric toxicity  Drug optimized based on all subpopulations |
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| 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 *bcN1*)  *bcN1* results were combined and processed to remove any weak Pareto optimal solutions (see *anlyz.bcN1 postsim\_process* 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.

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| Simulation results | Working copy in |
| *N10000*, *N10000\_ subpopOnly1*, *N10000\_ subpopOnly2*, *N10000\_ sametox0* | ./analyses/output/ |
| *bcN1*, *bcN1\_subpopOnly1*, *bcN1\_subpopOnly2* | ./analyses/outputs\_bc/ |
| *rho\_selection* | ./analyses/anlyz.rho\_selection/ |
| *noToxMaxConstraint* | ./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.

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| Analysis (folder name) | Description | Used to generate figure… |
| anlyz.dataset | Generates summary figures (heatmaps/clustergrams) of datasets | Fig. S1, Fig. 7A |
| anlyz.rho\_selection | Analyzes *rho\_selection* results | Fig. S3 |
| anlyz.noToxMaxConstraint | Analyzes *noToxMaxConstraint* results | Fig. 2, Fig. S4 |
| anlyz.N10000 postsim\_process | Removes weak Pareto optimal solutions from *N10000* results  Newly generated results (.mat) copied to ./analyses/outputs | N/A |
| anlyz.N10000\_sametox0 | Analyzes *N10000\_sametox0* simulation results | Fig. S14, Fig. S15,  Fig. 7B, 7C |
| anlyz.N10000\_sametox1 | Performs general statistical and sensitivity analyses on *N10000* results | Fig. 3, Fig. 6, Fig. S8 |
| anlyz.N10000\_sametox1\_subpopOnly1 | Performs general statistical and sensitivity analyses on *N10000\_subpopOnly1* results | Fig. 4, Fig. S9 |
| anlyz.N10000\_sametox1 vs\_subpopOnly1 | Compares *N10000* and *N10000\_subpopOnly1* results | Fig. 5 |
| anlyz.N10000\_sametox1 vs\_subpopOnly1.2 | Compares *N10000* and (*N10000\_subpopOnly1* & *N10000\_subpopOnly2*) results | Fig S10 |
| anlyz.N10000\_sametox1 partial\_corr | Matthews correlation and partial spearman correlation analysis of *N10000* and *N10000\_subpopOnly1* results | Fig. S5, Fig. S6, Fig. S7 |
| anlyz.N10000\_sametox1 drug\_distribution | Analyzes *N10000* versus *N10000\_subpopOnly1*; *N10000* versus *N10000\_subpopOnly1* and *N10000\_subpopOnly2* results, decomposed based on predominant and second largest subpopulation proportions | Fig. S11, Fig. S12 |
| anlyz.bcN1 postsim\_process | Combines *bcN1* simulation results  Removes weak Pareto optimal solutions from combined *bcN1* results  Newly generated results (.mat) copied to ./analyses/outputs\_bc/ | N/A |
| anlyz.bcN1 drug\_distribution | Analyzes *bcN1* versus *bcN1\_subpopOnly1*; *bcN1* versus *bcN1\_subpopOnly1* and *bcN1\_subpopOnly2* results, decomposed based on predominant and second largest subpopulation proportions | Fig. S13 |