**Integrating Models to Quantify Environment-Mediated Drug Resistance**

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**Supplemental Materials and Methods**

**Analytical solution of ODE model**

All parameter estimation routines involve data fitting to the analytical solution of the relevant set of ODEs (Table 1).

**Parameter Estimation with Approximate Bayesian Computation**

Let $y⊂R\_{>0}^{N}$ be a dataset of $N$ temporal observations and $M=M(ζ )$ a model that we chose to explain the observed data, where $ζ$ is the vector of model parameters, taking values in $Ω⊂R^{q}$. We want to estimate values of parameters $ζ$ that best explain the data $y$, with the given model $M$. The Approximate Bayesian Computation (ABC) rejection algorithm allows us to build a discrete approximation of the posterior distribution of $ζ$. Specifically, the algorithm iteratively draws a proposed q-tuple of values for $ζ$ from a uniform prior on some region $\overbar{Ω}⊂Ω$. If the model, simulated with the proposed parameter set, falls close to the data within tolerance $ε$, the q-tuple is accepted, otherwise rejected. The collection of all accepted q-tuples constitutes an approximation of the posterior distribution. We chose the sum of squared distances as distance metric, and the temporal sequence of tumor size ($S\left(t\right)+R(t)$) as summary statistic for $M$. The smaller the tolerance $ε$, the more reliable is the approximated posterior distribution. However, too small an $ε$ will result in zero acceptance ratio (defined as number of accepted q-tuples over J). The value of $ε$ giving satisfying results has to be tweaked for every set of data and model. In order to obtain consistent results across estimates, we fix the desired acceptance ratio to $\overbar{π}= 0.0002$, and iteratively run the ABC rejection algorithm with increased or decreased $ε$, until the targeted acceptance ratio is reached.

The pseudo-algorithm reads as follows.

Note that for each experimental condition the *in vitro* data consist of three replicates. We obtained one estimate that best fits all of the replicates at the same time (i.e. in the algorithm the norm-2 is calculated on the vector of concatenated data of length $3N$). On the other hand, *in vivo* replicates display significant qualitative and quantitative variability. Therefore, the estimation routine for these data is run individually for each mouse replicate, obtaining the set of estimates reported in Table 2.

**Simulation of ODE model**

Solutions of the ODE systems are obtained using Matlab routine *ode45*.