

Supplementary Information

Mathematical characterization of population dynamics in breast cancer cells treated with doxorubicin

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Abbreviations

NRMSE: Normalized root mean square error

R^2 : Coefficient of determination

PCC: Pearson correlation coefficient

CCC: Concordance correlation coefficient

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Supplementary Tables

Parameter	Definition	Units
N_0	Initial number of tumor cells	cells
g_0	Baseline proliferation rate	h^{-1}
θ_u	Untreated carrying capacity	cells
θ_{Dox}	Treated carrying capacity	cells
f_r	Fraction of resistant cells	-
g_r	Proliferation rate of drug-resistant tumor cells	h^{-1}
g_s	Proliferation rate of drug-sensitive tumor cells	h^{-1}
k_d	Doxorubicin-induced death rate of drug-sensitive tumor cells	h^{-1}
γ_d	Doxorubicin-induced death delay rate of drug-sensitive tumor cells	h^{-1}

Supplementary Table S1. Definition and units of the model parameters.

Dose [nM]	Initial guess and bounds							
	N_0 [cells]	g_0 [h^{-1}]	θ_{Dox} [cells]	f_r [-]	g_r [h^{-1}]	g_s [h^{-1}]	k_d [h^{-1}]	$\gamma_d s$ [h^{-1}]
0	$N_{0,obs}$ [700, 2000]	0.025 [0.0075, 0.035]	60000 [40000, 70000]*	-	-	-	-	-
10	$N_{0,obs}$ [1200, 3000]	0.03 [0.02, 0.035]	60000 [15000, 90000]	0.75 [0, 1]	0.02 [0.001, 0.05]	0.05 [0.001, 0.065]	-0.001 [-0.01, 0]	0.01 [1/120, 1/10]
20	„	„	„	„	„	„	„	„
35	„	„	50000 [15000, 90000]	0.5 [0, 1]	„	„	„	0.015 [1/120, 1/10]
50	„	„	60000 [15000, 90000]	„	„	„	„	„
75	„	„	„	„	„	„	„	0.02 [1/120, 1/10]
100	„	„	„	„	„	„	„	0.035 [1/120, 1/10]
125	„	„	„	„	„	0.01 [0.001, 0.065]	„	0.04 [1/120, 1/10]
150	„	„	80000 [15000, 90000]	0.25 [0, 1]	„	„	„	0.05 [1/120, 1/10]
300	„	„	60000 [15000, 90000]	„	„	0.005 [0.001, 0.065]	-0.0025 [-0.01, 0]	„

Supplementary Table S2. Parameter initial guesses and bounds used for fitting the single-dose model to time courses resulting from cells treated with a single dose of doxorubicin at varying concentrations (n = 6 per tested concentration; Experiment 1 in Table 1 of the main text). A ditto mark („) indicates that the initial guess and bounds are identical to the values in the cells above. *For 0 nM, we report the initial guess and bounds for θ_u instead of θ_{Dox} .

Dose [nM]	Parameter values							
	N_0 [cells]	g_0 [h ⁻¹]	θ_{Dox} [cells]	f_r [-]	g_r [h ⁻¹]	g_s [h ⁻¹]	k_d [h ⁻¹]	γ_d [h ⁻¹]
0	1276 [1120, 1409]	0.028 [0.027, 0.028]	54640 [51414, 55769]*	-	-	-	-	-
10	1400 [1346, 1482]	0.026 [0.026, 0.027]	63579 [61403, 66880]	0.82 [0.80, 0.85]	0.019 [0.019, 0.021]	0.045 [0.04, 0.05]	-7.6×10^{-4} [-9.3×10^{-4} , -2.4×10^{-4}]	0.01 [0.0084, 0.012]
20	1444 [1283, 1475]	0.026 [0.025, 0.027]	77484 [71701, 83936]	0.54 [0.50, 0.58]	0.015 [0.014, 0.015]	0.037 [0.031, 0.039]	-0.0054 [-0.0091, -0.0038]	0.018 [0.015, 0.022]
35	1346 [1248, 1386]	0.024 [0.023, 0.024]	63576 [48622, 73338]	0.071 [0.049, 0.18]	0.018 [0.013, 0.021]	0.031 [0.029, 0.035]	-0.0072 [-0.008, -0.0059]	0.02 [0.019, 0.027]
50	1370 [1305, 1499]	0.024 [0.023, 0.025]	68827 [61904, 71593]	0.051 [0.036, 0.091]	0.014 [0.011, 0.021]	0.027 [0.025, 0.035]	-0.008 [-0.009, -0.0067]	0.025 [0.021, 0.031]
75	1469 [1326, 1563]	0.024 [0.022, 0.025]	68569 [52398, 77716]	0.031 [0.012, 0.036]	0.011 [0.0081, 0.016]	0.021 [0.015, 0.031]	-0.007 [-0.0077, -0.0061]	0.028 [0.023, 0.033]
100	1480 [1323, 1564]	0.023 [0.022, 0.025]	68167 [66466, 79285]	0.02 [0.015, 0.057]	0.0079 [0.0024, 0.0091]	0.026 [0.011, 0.032]	-0.0055 [-0.0078, -0.0042]	0.038 [0.025, 0.046]
125	1435 [1352, 1505]	0.026 [0.024, 0.028]	68167 [20746, 68167]	0.0095 [9×10^{-5} , 0.057]	0.0031 [0.001, 0.011]	0.013 [0.0058, 0.018]	-0.0049 [-0.0086, -0.0041]	0.024 [0.021, 0.046]
150	1444 [1234, 1562]	0.024 [0.022, 0.025]	68167 [68167, 88076]	0.0092 [4×10^{-5} , 0.02]	0.0035 [0.002, 0.015]	0.012 [0.009, 0.024]	-0.0047 [-0.0068, -0.0043]	0.031 [0.024, 0.033]
300	1482 [1381, 1546]	0.025 [0.024, 0.025]	68167 [68167, 68167]	0.0072 [5×10^{-4} , 0.014]	0.0028 [0.0018, 0.0063]	0.014 [0.0096, 0.022]	-0.0046 [-0.0051, -0.0043]	0.043 [0.033, 0.06]

Supplementary Table S3. Median and range of the single-dose model parameters obtained from the fits to the time courses resulting from cells treated with a single dose of doxorubicin at varying concentrations (n = 6 per tested concentration; Experiment 1 in Table 1 of the main text). *For 0 nM, we report the mean and range for θ_u instead of θ_{Dox} .

Dose [nM]	Quality of fit metrics			
	NRMSE [%]	R^2	PCC	CCC
0	1.11 [0.76, 1.40]	>0.999 [>0.999, >0.999]	>0.999 [>0.999, >0.999]	0.986 [0.985, 0.986]
10	1.13 [0.804, 1.2]	>0.999 [>0.999, >0.999]	>0.99 [>0.999, >0.999]	0.984 [0.984, 0.985]
20	1.46 [1.23, 2.29]	0.999 [0.999, >0.999]	>0.99 [0.999, >0.999]	0.986 [0.986, 0.986]
35	2.58 [0.804, 2.87]	0.999 [0.999, 0.999]	0.999 [0.999, >0.999]	0.991 [0.990, 0.991]
50	3.07 [0.804, 4.37]	0.998 [0.998, >0.999]	0.999 [0.999, >0.999]	0.991 [0.991, 0.992]
75	2.75 [0.804, 4.61]	0.999 [0.995, >0.999]	0.999 [0.997, >0.999]	0.994 [0.992, 0.994]
100	5.19 [0.804, 10.2]	0.993 [0.959, 0.997]	0.996 [0.980, 0.998]	0.991 [0.973, 0.993]
125	4.53 [0.804, 8.48]	0.996 [0.972, 0.997]	0.998 [0.986, 0.999]	0.993 [0.981, 0.994]
150	8.48 [0.804, 12.2]	0.990 [0.985, 0.999]	0.995 [0.993, >0.999]	0.991 [0.989, 0.996]
300	9.06 [0.804, 12]	0.990 [0.981, 0.996]	0.995 [0.991, 0.998]	0.992 [0.987, 0.994]

Supplementary Table S4. Median and range of the quality of fit metrics for the single-dose model fits to the time courses resulting from cells treated with a single dose of doxorubicin at varying concentrations (n = 6 per tested concentration; Experiment 1 in Table 1 of the main text).

Dose [nM]	0	10	20	35	50	75	100	125	150	300
0	-	0.9372	0.0022	0.0087	0.0022	0.0022	0.0022	0.0022	0.0043	0.0022
10	-	-	0.0022	0.0022	0.0022	0.0022	0.0022	0.0022	0.0022	0.0022
20	-	-	-	0.1797	0.0931	0.0022	0.0022	0.0022	0.0649	0.0022
35	-	-	-	-	0.0931	0.0043	0.0022	0.0022	0.0649	0.0022
50	-	-	-	-	-	0.0649	0.0043	0.0022	0.0931	0.0022
75	-	-	-	-	-	-	0.1797	0.0152	0.1797	0.0022
100	-	-	-	-	-	-	-	0.0931	0.3939	0.0022
125	-	-	-	-	-	-	-	-	0.3939	0.9372
150	-	-	-	-	-	-	-	-	-	0.2403
300	-	-	-	-	-	-	-	-	-	-

Supplementary Table S5. P-values from two-sided Wilcoxon rank sum tests comparing the observed final tumor cell numbers for every distinct combination of the varying doxorubicin concentration datasets (n = 6 per tested concentration; Experiment 1 in Table 1 of the main text). Values bolded in red indicate $p < 0.05$.

Parameter formula	Parameter values			
	α_1	α_2	α_3	α_4
$f_r(D) = \alpha_1 e^{-(\alpha_2 D)} + \alpha_3$	1.63 [1.05, 2.20]	0.065 [0.038, 0.093]	0.0032 [-0.061, 0.068]	-
$g_r(D) = \alpha_1 e^{-(\alpha_2 D)}$	0.022 [0.017, 0.026]	0.010 [0.0061, 0.015]	-	-
$g_s(D) = \alpha_1 e^{-(\alpha_2 D)}$	0.043 [0.033, 0.053]	0.0074 [0.0036, 0.011]	-	-
$k_d(D) = \alpha_1(1 - e^{-(\alpha_2(D-\alpha_3))})^2 - \alpha_4$	0.0033 [0.0023, 0.0044]	0.028 [0.02, 0.035]	41.92 [35.24, 48.60]	0.0078 [0.0072, 0.0084]
$\gamma_d(D) = \alpha_1 - \alpha_2 e^{-(\alpha_3 D)}$	0.035 [0.027, 0.043]	0.026 [0.006, 0.047]	0.0104 [-0.0062, 0.0270]	-

Supplementary Table S6. Fitted empirical parameter values and the corresponding 95% confidence intervals for the empirical parameter formulas derived from the single-dose model fits to the varying doxorubicin concentration datasets (n = 6 per tested concentration; Experiment 1 in Table 1 of the main text).

Parameter formula	Quality of fit metrics			
	NRMSE [%]	R^2	PCC	CCC
$f_r(D) = \alpha_1 e^{-(\alpha_2 D)} + \alpha_3$	153.64*	0.977	0.985	0.876
$g_r(D) = \alpha_1 e^{-(\alpha_2 D)}$	16.73	0.909	0.953	0.845
$g_s(D) = \alpha_1 e^{-(\alpha_2 D)}$	17.65	0.818	0.912	0.810
$k_d(D) = \alpha_1(1 - e^{-(\alpha_2(D-\alpha_3))})^2 - \alpha_4$	5.45	0.978	0.992	0.879
$\gamma_d(D) = \alpha_1 - \alpha_2 e^{-(\alpha_3 D)}$	17.94	0.784	0.883	0.779

Supplementary Table S7. Quality of fit metrics for the empirical parameter formulas derived from the single-dose model fits to the varying doxorubicin concentration datasets (n = 6 per tested concentration; Experiment 1 in Table 1 of the main text). *For larger drug concentrations, f_r takes on values on the order of 10^{-5} , such that natural variations of f_r across replicates may result in NRMSE values greater than 100%. However, these variations have a negligible impact on model outcome.

Interval [d]	Initial guess and bounds										
	N_0 [cells]	g_0 [h ⁻¹]	θ_{Dox} [cells]	f_r^1 [-]	f_r^2 [-]	g_r [h ⁻¹]	g_s [h ⁻¹]	k_d [h ⁻¹]	γ_d^1 [h ⁻¹]	γ_d^2 [h ⁻¹]	
Multiple-dose model with constant parameters											
0	$N_{0,obs}$ [1000, 2500]	0.0234 [0.02, 0.035]	60000 [30000, 90000]	0.0337 [0, 1]		0.0101 [0.001, 0.05]	0.0277 [0.001, 0.05]	-0.0069 [-0.01, 0]		0.0325 [0, 1/15]	
2	//	//	//	//		//	//	//		//	
4	//	//	//	//		//	//	//		//	
6	//	//	//	//		//	//	//		//	
Multiple-dose model with varying f_r and γ_d											
8	$N_{0,obs}$ [1200, 2500]	0.0234 [0.02, 0.035]	60000 [15000, 90000]	0.0337 [0, 0.1]	0.005 [0, 1]	0.0101 [0.001, 0.05]	0.0277 [0.001, 0.055]	-5×10 ⁻⁴ [-0.01, 0]		0.0325 [0, 1/15]	1/75 [0, 1/15]
10	//	//	//	//	//	//	//	//		//	//
12	//	//	//	//	//	//	//	//		//	//
14	//	//	//	//	//	//	//	//		//	//
16	//	//	//	//	//	//	//	//		//	//

Supplementary Table S8. Parameter initial guesses and bounds used for fitting the multiple-dose model to the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals (n = 12 per tested interval; Experiment 2 in Table 1 of the main text). A ditto mark (//) indicates that the initial guess and bounds are identical to the values in the cells above.

Interval [d]	Parameter values									
	N_0 [cells]	g_0 [h ⁻¹]	θ_{Dox} [cells]	f_r^1 [-]	f_r^2 [-]	g_r [h ⁻¹]	g_s [h ⁻¹]	k_d [h ⁻¹]	γ_d^1 [h ⁻¹]	γ_d^2 [h ⁻¹]
Multiple-dose model with constant parameters										
0	1468 [1354, 1542]	0.024 [0.023, 0.025]	53376 [42605, 80016]	0.0019 [7×10 ⁻⁵ , 0.017]		0.002 [0.001, 0.014]	0.022 [0.012, 0.026]	-0.0035 [-0.0047, -0.002]		0.046 [0.027, 0.057]
2	1468 [1381, 1591]	0.024 [0.024, 0.025]	53376 [53376, 53376]	0.012 [0.0069, 0.23]		0.0045 [0.0028, 0.0069]	0.026 [0.023, 0.038]	-0.0035 [-0.0047, -0.0032]		0.048 [0.042, 0.063]
4	1514 [1396, 1572]	0.024 [0.023, 0.025]	53376 [53376, 53376]	0.018 [0.016, 0.084]		0.0067 [0.0054, 0.0079]	0.022 [0.021, 0.025]	-0.0037 [-0.0042, -0.0034]		0.04 [0.035, 0.05]
6	1411 [1312, 1591]	0.024 [0.023, 0.025]	53376 [30690, 53376]	0.031 [0.011, 0.09]		0.0086 [0.0063, 0.011]	0.019 [0.017, 0.022]	-0.0042 [-0.0061, -0.0033]		0.031 [0.027, 0.04]
Multiple-dose model with varying f_r and γ_d										
8	1572 [1289, 1676]	0.021 [0.02, 0.024]	53376 [36130, 56316]	0.0170 [0.0009, 0.0310]	0.1100 [0.029, 0.20]	0.0093 [0.0010, 0.0160]	0.0020 [0.0160, 0.0230]	-0.0036 [-0.0043, -0.0027]	0.0340 [0.0280, 0.0440]	0.0300 [0.0120, 0.0440]
10	1573 [1382, 1687]	0.022 [0.02, 0.025]	53376 [36130, 56316]	0.021 [0.0055, 0.037]	0.13 [0.051, 0.23]	0.0094 [0.0077, 0.015]	0.019 [0.015, 0.022]	-0.0034 [-0.0046, -0.0027]	0.032 [0.024, 0.039]	0.024 [0.014, 0.034]
12	1372 [1209, 1479]	0.022 [0.020, 0.025]	53376 [46045, 67004]	0.016 [0.0083, 0.033]	0.16 [0.079, 0.24]	0.0098 [0.0084, 0.012]	0.02 [0.017, 0.024]	-0.0031 [-0.0036, -0.0021]	0.041 [0.035, 0.051]	0.016 [0.0089, 0.032]
14	1428 [1327, 1850]	0.022 [0.020, 0.025]	58091 [37433, 73197]	0.025 [0.0066, 0.042]	0.082 [0.046, 0.26]	0.01 [0.0078, 0.012]	0.019 [0.0038, 0.024]	-0.0031 [-0.0048, -0.0017]	0.042 [0.025, 0.065]	0.014 [0.011, 0.026]
16	1560 [1350, 1684]	0.023 [0.021, 0.025]	53376 [42964, 81236]	0.032 [0.016, 0.04]	0.13 [0.075, 0.25]	0.01 [0.007, 0.012]	0.019 [0.013, 0.021]	-0.0039 [-0.0049, -0.0031]	0.04 [0.028, 0.047]	0.018 [0.012, 0.038]

Supplementary Table S9. Median and range of the multiple-dose model parameters obtained from the fits to the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals (n = 12 per tested interval; Experiment 2 in Table 1 of the main text).

Interval [d]	Quality of fit metrics			
	NRMSE [%]	R^2	PCC	CCC
Multiple-dose model with constant parameters				
0	4.9 [3.2, 13.5]	0.995 [0.948, 0.998]	0.998 [0.974, 0.999]	0.994 [0.969, 0.995]
2	4.39 [3.26, 4.76]	0.996 [0.992, 0.998]	0.998 [0.996, 0.999]	0.994 [0.992, 0.995]
4	6.12 [5.03, 7.27]	0.991 [0.979, 0.994]	0.995 [0.990, 0.997]	0.991 [0.986, 0.993]
6	5.27 [2.74, 9.47]	0.992 [0.971, 0.999]	0.996 [0.986, >0.999]	0.992 [0.982, 0.996]
Multiple-dose model with varying f_r and γ_d				
8	4.57 [3.59, 6.32]	0.993 [0.983, 0.997]	0.997 [0.992, 0.999]	0.992 [0.988, 0.995]
10	4.08 [3.59, 6.57]	0.992 [0.974, 0.998]	0.996 [0.988, 0.999]	0.992 [0.983, 0.995]
12	4.54 [3.44, 10.2]	0.995 [0.963, 0.998]	0.998 [0.982, 0.999]	0.994 [0.977, 0.995]
14	4.39 [2.79, 14.3]	0.996 [0.769, 0.999]	0.998 [0.911, >0.999]	0.994 [0.898, 0.996]
16	4.38 [3.12, 7.04]	0.996 [0.971, 0.998]	0.998 [0.986, 0.999]	0.994 [0.981, 0.995]

Supplementary Table S10. Median and range of the quality of fit metrics for the multiple-dose model fits to the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals (n = 12 per tested interval; Experiment 2 in Table 1 of the main text).

Interval [d]	0	2	4	6	8	10	12	14	16
0	-	0.2145	0.4705	0.0999	0.0783	0.0226	0.0166	0.0102	0.0061
2	-	-	0.0029	1.96×10⁻⁴	1.55×10⁻⁴	3.66×10⁻⁵	3.66×10⁻⁵	3.66×10⁻⁵	3.66×10⁻⁵
4	-	-	-	0.0102	0.0029	3.66×10⁻⁵	3.66×10⁻⁵	3.66×10⁻⁵	3.66×10⁻⁵
6	-	-	-	-	0.5067	0.0262	0.0035	0.0120	0.0011
8	-	-	-	-	-	0.1749	0.0783	0.0404	0.0024
10	-	-	-	-	-	-	0.5834	0.4705	0.0690
12	-	-	-	-	-	-	-	0.5444	0.1124
14	-	-	-	-	-	-	-	-	0.5444
16	-	-	-	-	-	-	-	-	-

Supplementary Table S11. P-values from two-sided Wilcoxon rank sum tests comparing the observed final tumor cell numbers for every distinct combination of the varying inter-treatment interval datasets (n = 12 per tested interval; Experiment 2 in Table 1 of the main text). Values bolded in red indicate $p < 0.05$.

Number of doses	Initial guess and bounds: 2-day inter-treatment interval							
	N_0 [cells]	g_0 [h^{-1}]	θ_{Dox} [cells]	f_r [-]	g_r [h^{-1}]	g_s [h^{-1}]	k_d [h^{-1}]	γ_d [h^{-1}]
1	$N_{0,obs}$ [1000, 2500]	0.0234 [0.0225, 0.05]	60000 [20000, 90000]	0.0337 [0, 0.05]	0.0101 [1×10^{-4} , 0.05]	0.0277 [1×10^{-4} , 0.05]	-1×10^{-5} [-0.05, 0]	0.0325 [0, 1]
2	"	"	"	0.01 [0, 0.05]	0.0025 [1×10^{-4} , 0.05]	0.0025 [1×10^{-4} , 0.05]	-0.015 [-0.05, 0]	"
3	"	"	"	0.001 [0, 0.05]	"	"	"	0.05 [0, 1]
4	"	"	"	1×10^{-5} [0, 0.05]	"	"	"	0.08 [0, 1]
5	"	"	"	1×10^{-9} [0, 0.05]	1.5×10^{-4} [1×10^{-4} , 0.05]	1.5×10^{-4} [1×10^{-4} , 0.05]	-0.035 [-0.05, 0]	0.75 [0, 1]

Supplementary Table S12. Parameter initial guesses and bounds used for fitting the multiple-dose model to the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-day inter-treatment intervals ($n = 12$ per tested number of doses; Experiment 3 in Table 1 of the main text). A ditto mark (") indicates that the initial guess and bounds are identical to the values in the cells above.

Number of Doses	Parameter values: 2-day inter-treatment interval							
	N_0 [cells]	g_0 [h^{-1}]	θ_{Dox} [cells]	f_r [-]	g_r [h^{-1}]	g_s [h^{-1}]	k_d [h^{-1}]	γ_d [h^{-1}]
1	1477 [1276, 1712]	0.024 [0.023, 0.028]	59448 [34132, 87537]	0.02 [0.004, 0.029]	0.01 [0.0084, 0.015]	0.021 [0.0088, 0.03]	-0.006 [-0.0089, -0.003]	0.037 [0.014, 0.064]
2	1313 [1194, 1503]	0.028 [0.027, 0.029]	59448 [59448, 59448]	0.0088 [1×10^{-7} , 0.05]	0.0062 [0.0047, 0.0079]	0.019 [0.012, 0.039]	-0.004 [-0.0042, -0.0034]	0.08 [0.059, 0.2]
3	1278 [1081, 1456]	0.028 [0.026, 0.029]	59448 [59448, 59448]	0.0066 [1×10^{-7} , 0.016]	0.013 [0.0099, 0.016]	0.029 [0.017, 0.038]	-0.005 [-0.005, -0.0041]	0.13 [0.088, 0.15]
4	1196 [1032, 1380]	0.028 [0.026, 0.029]	59448 [59448, 59448]	6×10^{-5} [2×10^{-14} , 0.0086]	1×10^{-4} [1×10^{-4} , 0.017]	0.027 [0.023, 0.033]	-0.005 [-0.0058, -0.0045]	0.11 [0.074, 0.15]
5	1140 [1051, 1305]	0.028 [0.026, 0.029]	59448 [59448, 59448]	0.031 [0.023, 0.047]	0.015 [0.013, 0.017]	0.035 [0.028, 0.05]	-0.006 [-0.0068, -0.0061]	0.11 [0.086, 0.18]

Supplementary Table S13. Median and range of the multiple-dose model parameters obtained from the fits to the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-day inter-treatment intervals ($n = 12$ per tested number of doses; Experiment 3 in Table 1 of the main text).

Number of doses	Quality of fit metrics: 2-day inter-treatment interval			
	NRMSE [%]	R^2	PCC	CCC
1	3.5 [2.72, 5.79]	0.998 [0.992, 0.999]	0.999 [0.996, >0.999]	0.993 [0.99, 0.994]
2	4.72 [4.14, 19.1]	0.997 [0.992, 0.999]	0.998 [0.934, 0.999]	0.994 [0.928, 0.995]
3	12.1 [10.1, 13.7]	0.985 [0.992, 0.999]	0.993 [0.991, 0.995]	0.988 [0.987, 0.991]
4	16.2 [15.1, 17.5]	0.975 [0.992, 0.999]	0.989 [0.987, 0.991]	0.984 [0.981, 0.986]
5	14.8 [13, 16.4]	0.983 [0.992, 0.999]	0.993 [0.991, 0.995]	0.988 [0.986, 0.99]

Supplementary Table S14. Median and range of the quality of fit metrics for the multiple-dose model fits to the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-day inter-treatment intervals (n = 12 per tested number of doses; Experiment 3 in Table 1 of the main text).

Number of doses	1	2	3	4	5
1	-	3.66×10^{-5}	3.64×10^{-5}	3.64×10^{-5}	3.64×10^{-5}
2	-	-	0.0165	0.0110	4.68×10^{-5}
3	-	-	-	0.7289	1.08×10^{-4}
4	-	-	-	-	0.0079
5	-	-	-	-	-

Supplementary Table S15. P-values from 2-sided Wilcoxon rank sum tests comparing the final tumor cell numbers for every distinct combination of the varying dose number datasets with a 2-day inter-treatment interval. (n = 12 per tested number of doses; Experiment 3 in Table 1 of the main text). Values bolded in red indicate $p < 0.05$.

Number of Doses	Initial guess and bounds: 2-week inter-treatment interval					
	N_0 [cells]	g_0 [h^{-1}]	θ_{Dox} [cells]	g_r [h^{-1}]	g_s [h^{-1}]	k_d [h^{-1}]
1	$N_{0,obs}$ [900, 3000]	0.0275 [0.02, 0.05]	80000 [15000, 90000]	0.02 [0.001, 0.05]	0.0275 [0.0125, 0.075]	-0.0075 [-0.01, -0.001]
2	„	„	„	„	„	„
3	„	„	„	„	„	„
4	„	„	„	„	„	„
5	„	„	„	„	„	„

Supplementary Table S16. Initial guesses and bounds of the constant parameters used for fitting the multiple-dose model to the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals ($n = 12$ per tested number of doses; Experiment 3 in Table 1 of the main text). A ditto mark („) indicates that the initial guess and bounds are identical to the values in the cells above.

Initial guess & bounds: 2-week inter-treatment interval				
f_r^1 [-]	f_r^2 [-]	f_r^3 [-]	f_r^4 [-]	f_r^5 [-]
0.001 [0, 1]	0.005 [0, 0.5]	0.005 [0, 0.5]	0.005 [0, 0.5]	0.005 [0, 0.5]
γ_d^1 [h^{-1}]	γ_d^2 [h^{-1}]	γ_d^3 [h^{-1}]	γ_d^4 [h^{-1}]	γ_d^5 [h^{-1}]
1/50 [0, 1/15]	1/50 [0, 1/15]	1/50 [0, 1/15]	1/50 [0, 1/15]	1/50 [0, 1/15]

Supplementary Table S17. Initial guesses and bounds of f_r and γ_d for each doxorubicin dose used for fitting the multiple-dose model to the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals ($n = 12$ per tested number of doses; Experiment 3 in Table 1 of the main text). A ditto mark („) indicates that the initial guess and bounds are identical to the values in the cells above.

Number of doses	Parameter values: 2-week inter-treatment interval					
	N_0 [cells]	g_0 [h^{-1}]	θ_{Dox} [cells]	g_r [h^{-1}]	g_s [h^{-1}]	k_d [h^{-1}]
1	1626 [1437, 1791]	0.024 [0.023, 0.025]	52460 [41191, 73604]	0.013 [0.011, 0.015]	0.02 [0.014, 0.023]	-0.0053 [-0.0073, -0.0032]
2	1322 [1066, 1568]	0.026 [0.024, 0.027]	55086 [32671, 62376]	0.015 [0.013, 0.018]	0.014 [0.013, 0.016]	-0.0026 [-0.0037, -0.0023]
3	1345 [1051, 1553]	0.025 [0.022, 0.027]	68390 [62376, 78206]	0.018 [0.016, 0.019]	0.014 [0.013, 0.023]	-0.0023 [-0.0029, -0.001]
4	1182 [1017, 1417]	0.024 [0.021, 0.026]	71551 [54867, 77778]	0.018 [0.016, 0.02]	0.013 [0.013, 0.018]	-0.0014 [-0.0021, -0.001]
5	1114 [901, 1287]	0.024 [0.021, 0.025]	70227 [57909, 78940]	0.019 [0.016, 0.019]	0.015 [0.013, 0.019]	-0.0014 [-0.003, -0.001]

Supplementary Table S18. Median and range of the constant model parameters from the multiple-dose model fits to the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals ($n = 12$ per tested number of doses; Experiment 3 in Table 1 of the main text).

Parameter values: 2-week inter-treatment interval				
f_r^1 [-]	f_r^2 [-]	f_r^3 [-]	f_r^4 [-]	f_r^5 [-]
0.003 [2×10^{-4} , 0.057]	0.0076 [0.0032, 0.07]	0.0076 [0.0032, 0.07]	0.0076 [0.0032, 0.07]	0.0076 [0.0032, 0.07]
γ_d^1 [h^{-1}]	γ_d^2 [h^{-1}]	γ_d^3 [h^{-1}]	γ_d^4 [h^{-1}]	γ_d^5 [h^{-1}]
0.039 [0.02, 0.067]	0.0097 [0.0049, 0.017]	0.0097 [0.0049, 0.017]	0.0097 [0.0049, 0.017]	0.0097 [0.0049, 0.017]

Supplementary Table S19. Median and range of f_r and γ_d for each doxorubicin dose from the multiple-dose model fits to the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals ($n = 12$ per tested number of doses; Experiment 3 in Table 1 of the main text).

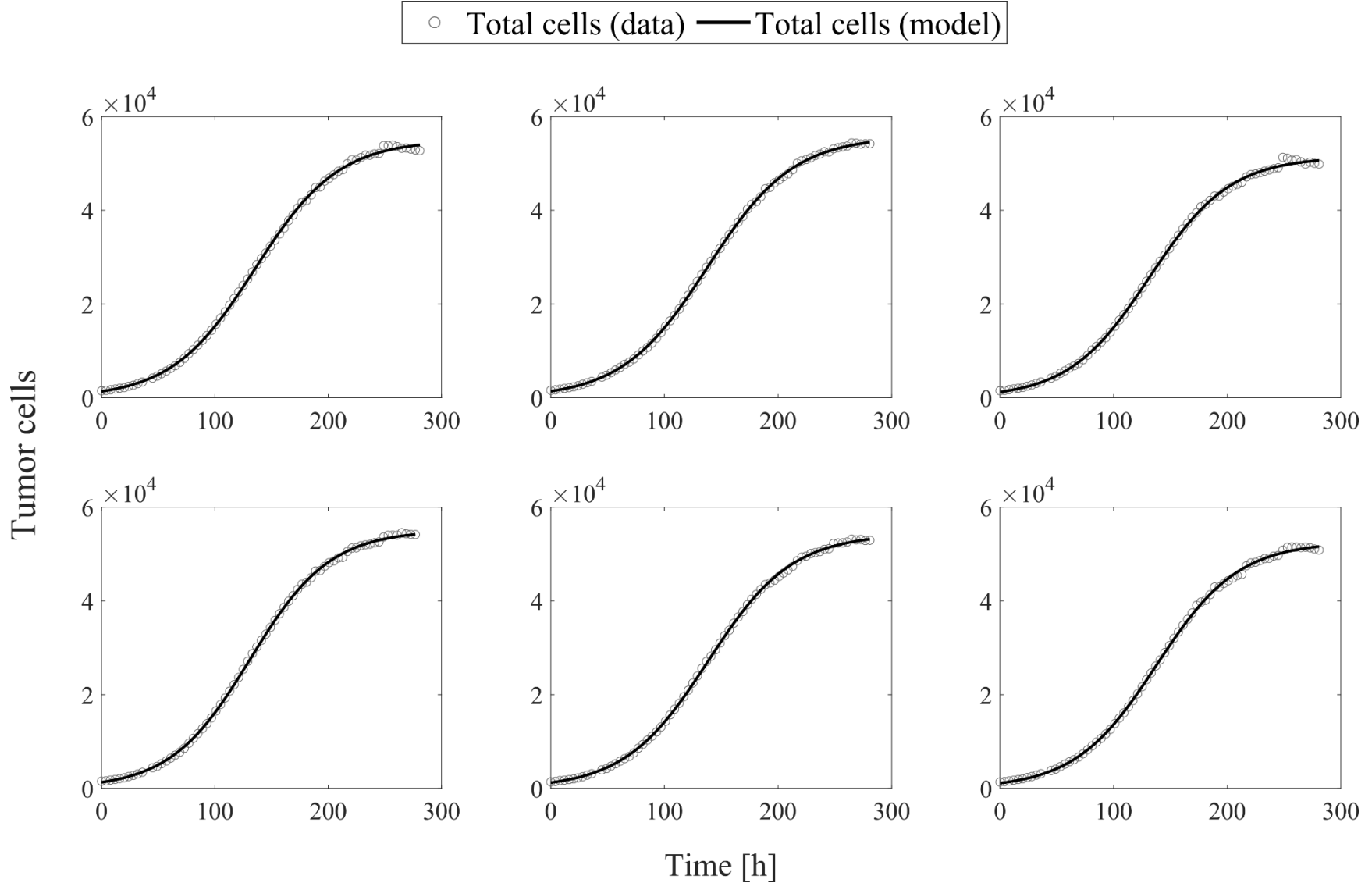
Number of doses	Quality of fit metrics: 2-week inter-treatment interval			
	NRMSE [%]	R^2	PCC	CCC
1	2.38 [2.05, 3.11]	0.999 [0.998, >0.999]	>0.999 [0.999, >0.999]	0.993 [0.993, 0.994]
2	3.45 [2.13, 8.57]	0.996 [0.932, 0.999]	0.998 [0.969, 0.999]	0.993 [0.959, 0.995]
3	3.69 [2.90, 6.80]	0.993 [0.952, 0.997]	0.997 [0.978, 0.999]	0.992 [0.971, 0.995]
4	3.51 [1.91, 7.02]	0.996 [0.975, 0.999]	0.998 [0.988, >0.999]	0.995 [0.984, 0.997]
5	3.10 [1.99, 6.40]	0.996 [0.934, 0.999]	0.998 [0.969, 0.999]	0.995 [0.963, 0.997]

Supplementary Table S20. Median and range of the quality of fit metrics for the multiple-dose model fits to time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals (n = 12 per tested number of doses; Experiment 3 in Table 1 of the main text).

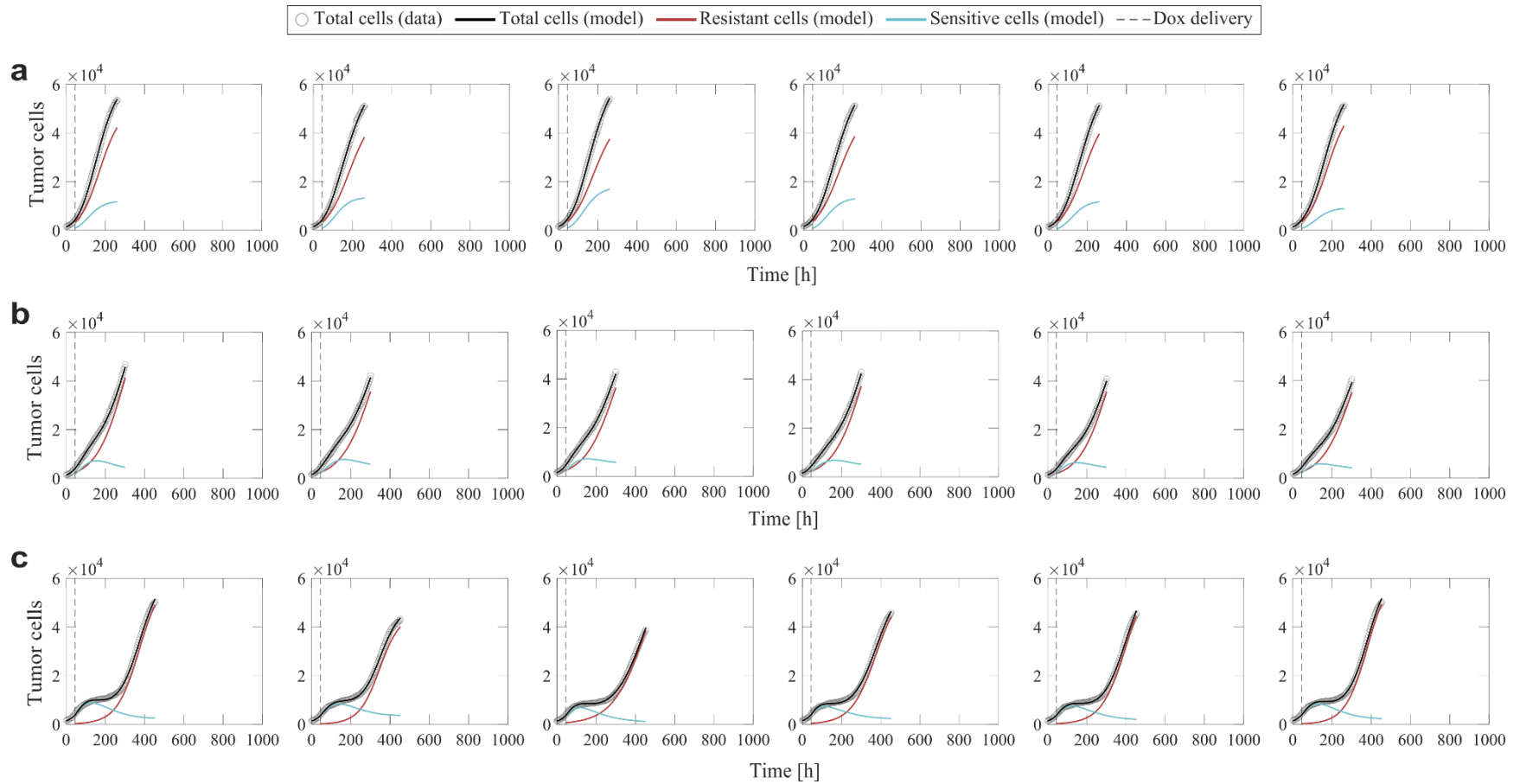
Number of doses	1	2	3	4	5
1	-	9.73×10^{-5}	4.69×10^{-5}	2.46×10^{-5}	7.66×10^{-5}
2	-	-	0.4357	0.7508	0.5444
3	-	-	-	0.1572	0.4025
4	-	-	-	-	0.3708
5	-	-	-	-	-

Supplementary Table S21. P-values from 2-sided Wilcoxon rank sum tests comparing the final tumor cell numbers for every distinct combination of the varying dose number datasets with a 2-week treatment interval. (n = 12 per tested number of doses; Experiment 3 in Table 1 of the main text). Values bolded in red indicate $p < 0.05$.

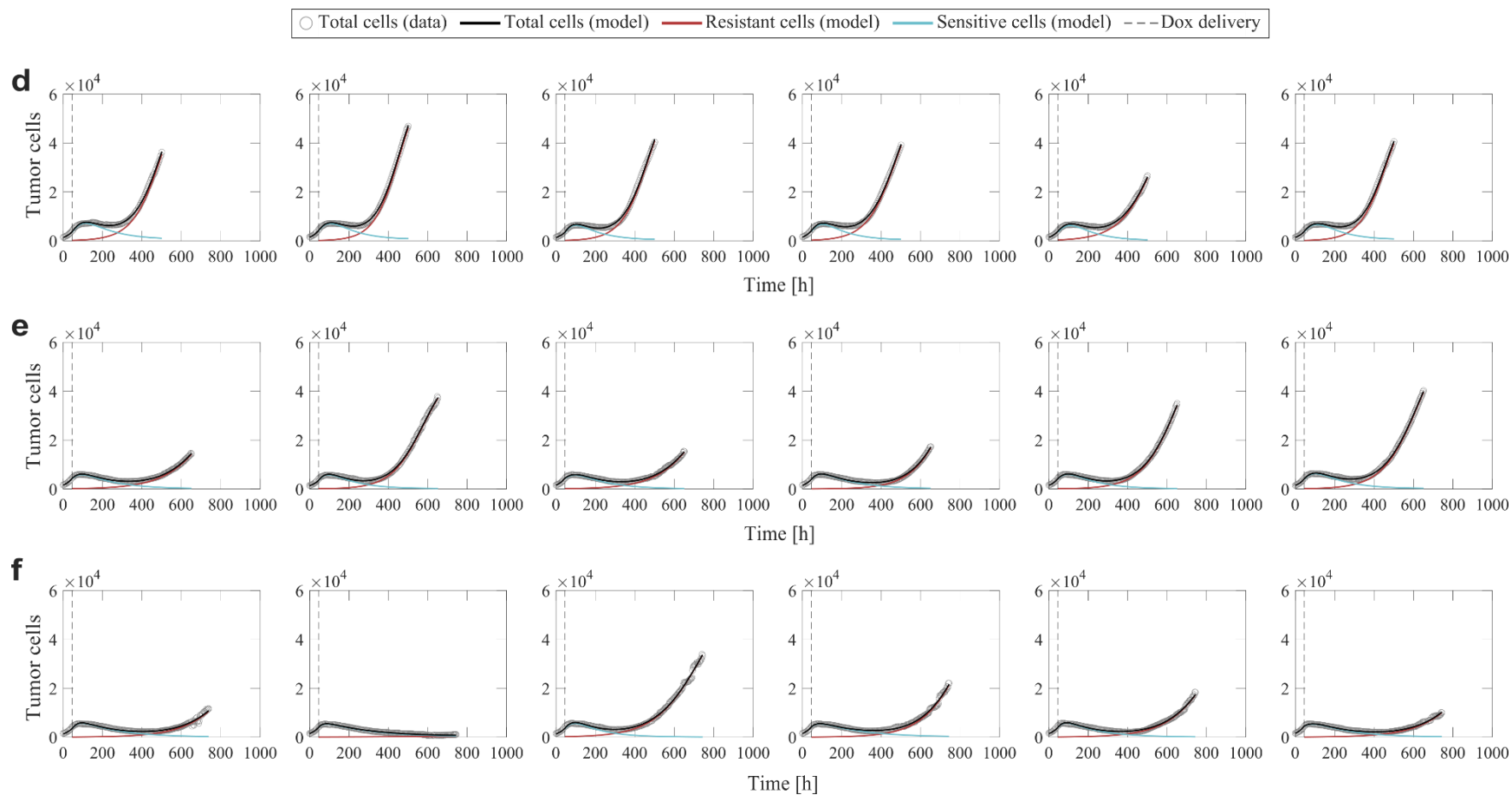
Supplementary Figures



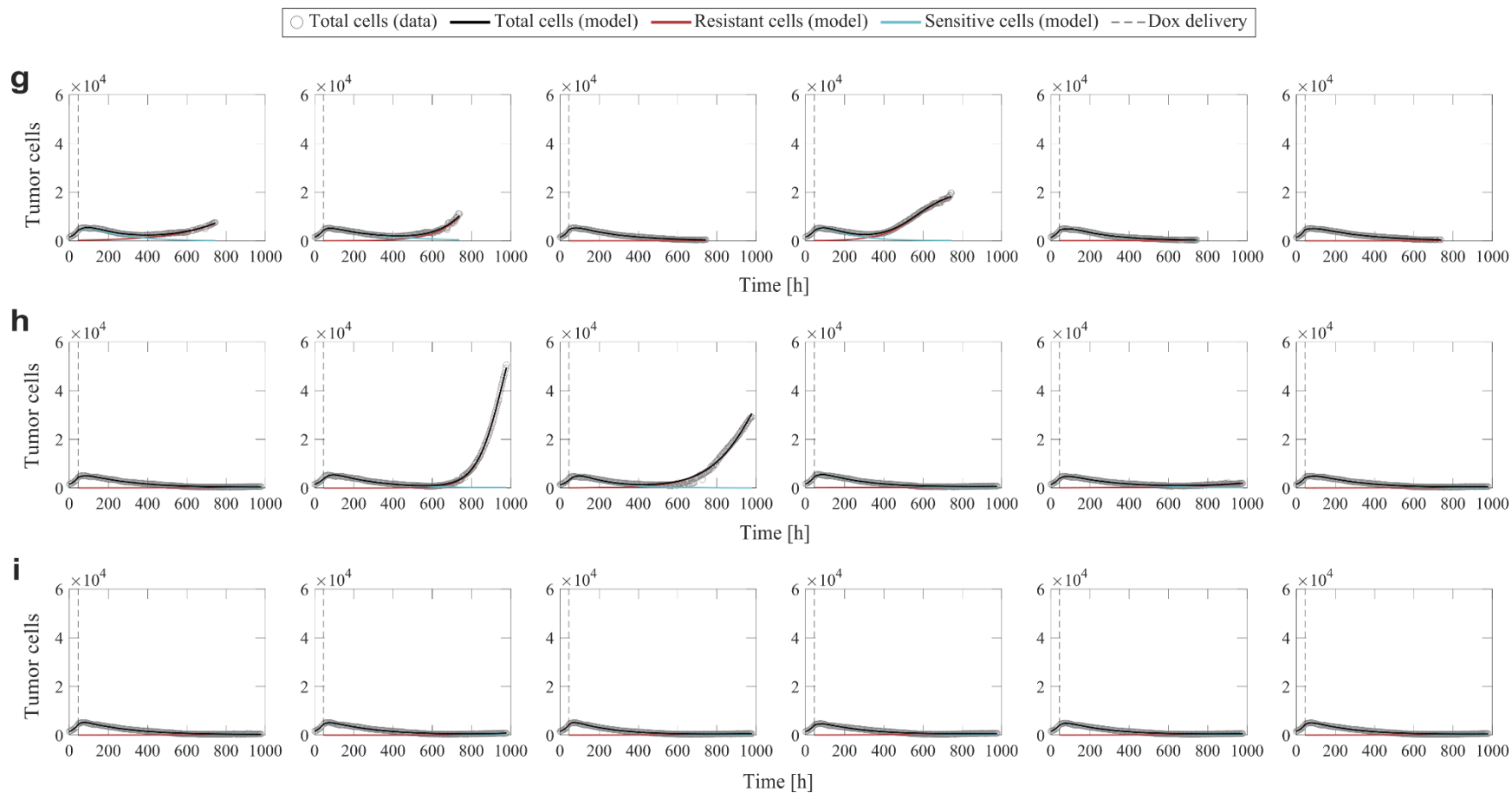
Supplementary Figure S1. Logistic growth model fits for all of the untreated tumor cell time courses (i.e., for a doxorubicin concentration of 0 nM in Experiment 1 in Table 1 of the main text; $n = 6$).



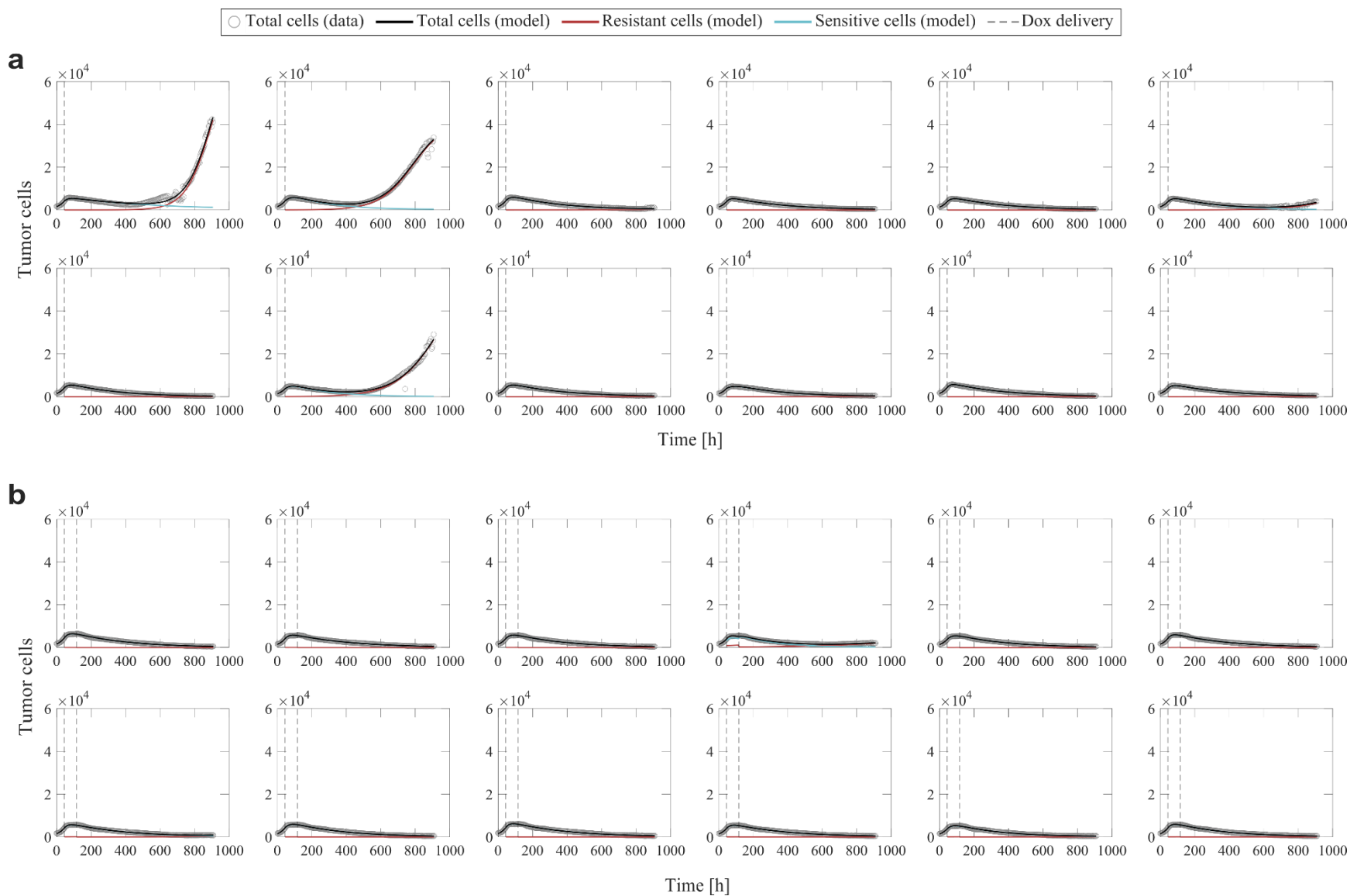
Supplementary Figure S2. Single-dose model fits for all of the time courses resulting from cells treated with a single dose of doxorubicin at concentrations ranging from 10 to 300 nM ($n = 6$ for each concentration; Experiment 1 in Table 1 of the main text). **(a)** 10 nM; **(b)** 20 nM; **(c)** 35 nM.



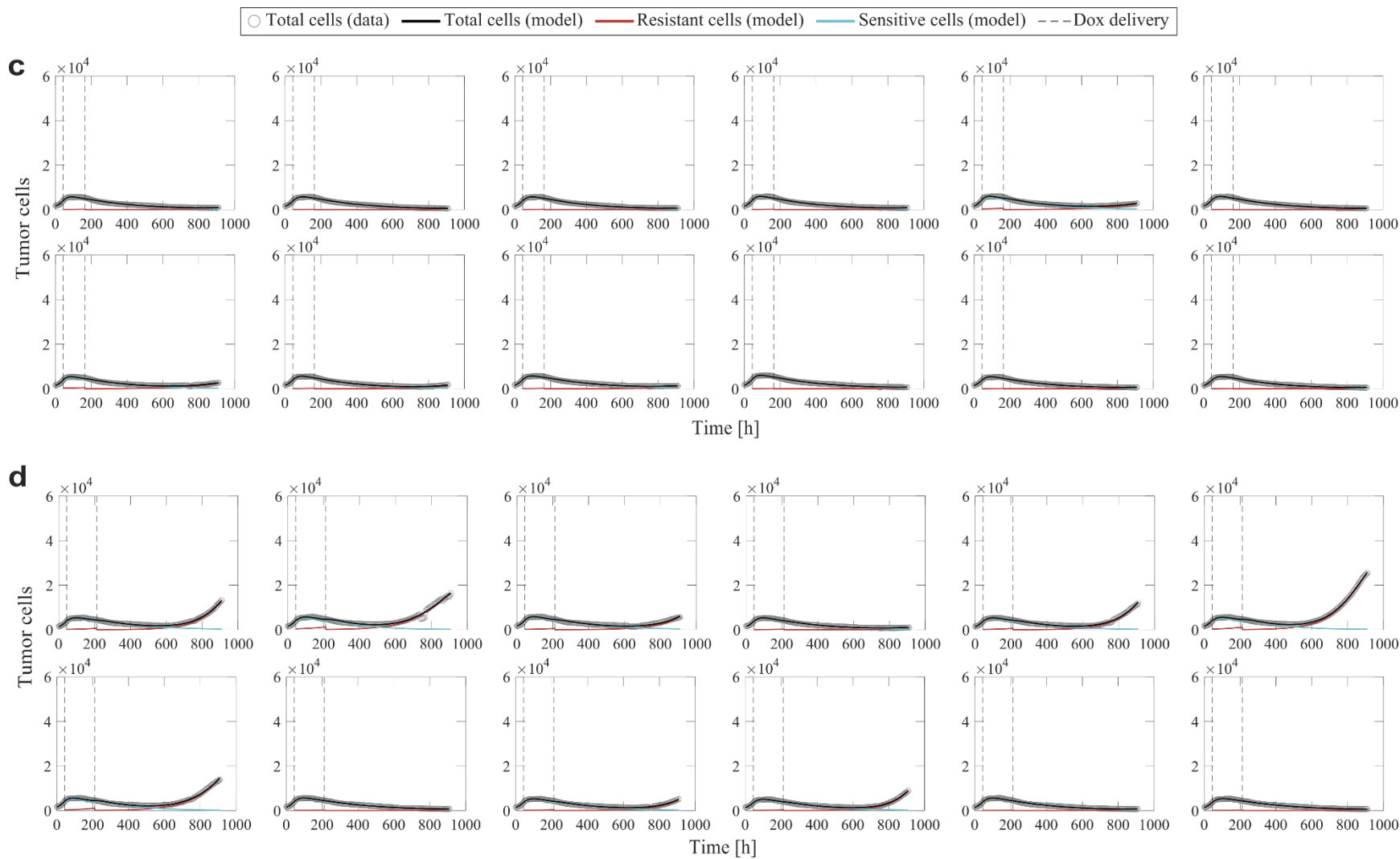
Supplementary Figure S2 (continued). Single-dose model fits for all of the time courses resulting from cells treated with a single dose of doxorubicin at concentrations ranging from 10 to 300 nM ($n = 6$ for each concentration; Experiment 1 in Table 1 of the main text). **(d)** 50nM; **(e)** 75nM; **(f)** 100 nM.



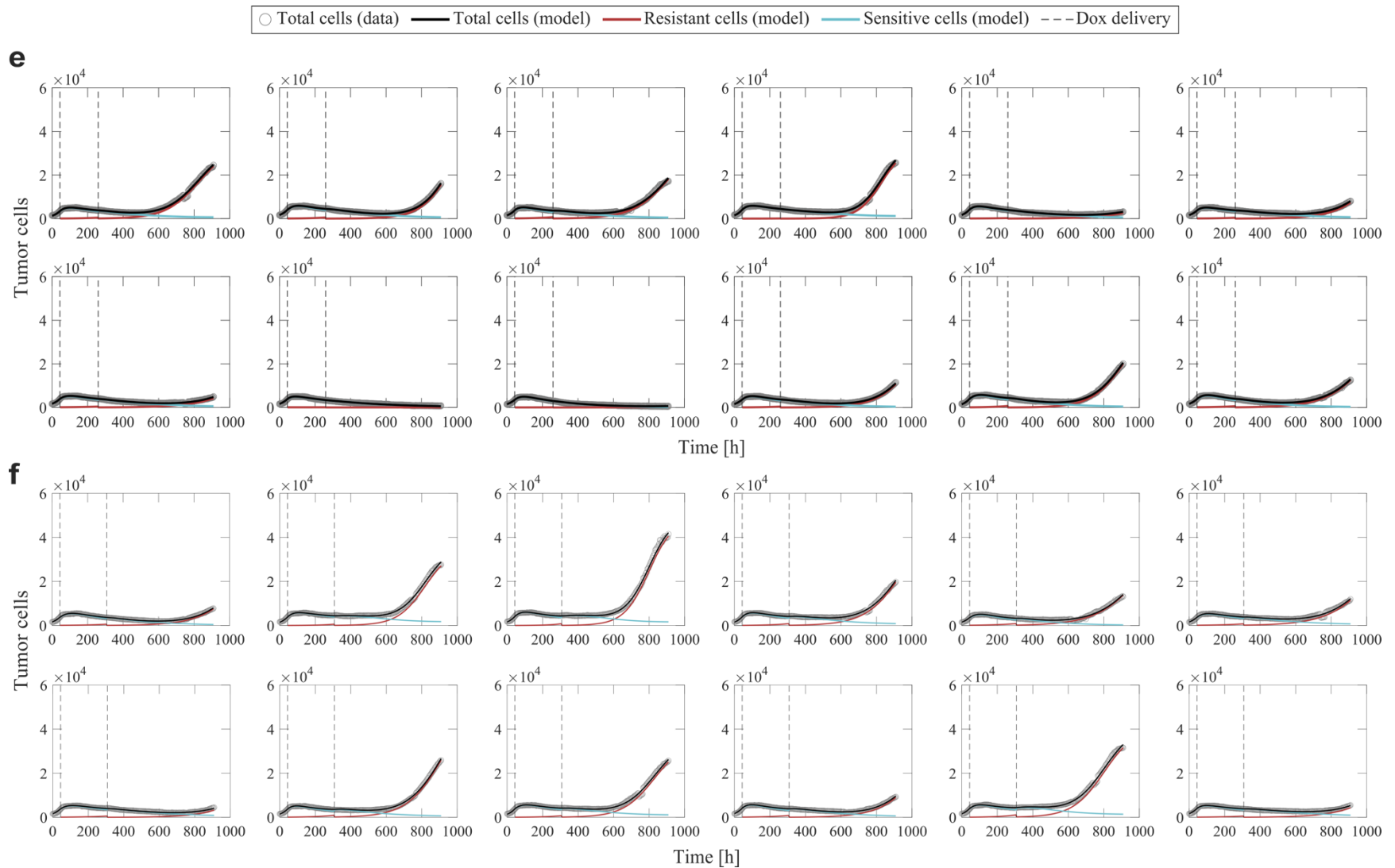
Supplementary Figure S2 (continued). Single-dose model fits for all of the time courses resulting from cells treated with a single dose of doxorubicin at concentrations ranging from 10 to 300 nM ($n = 6$ for each concentration; Experiment 1 in Table 1 of the main text). **(g)** 125 nM; **(h)** 150 nM; **(i)** 300 nM.



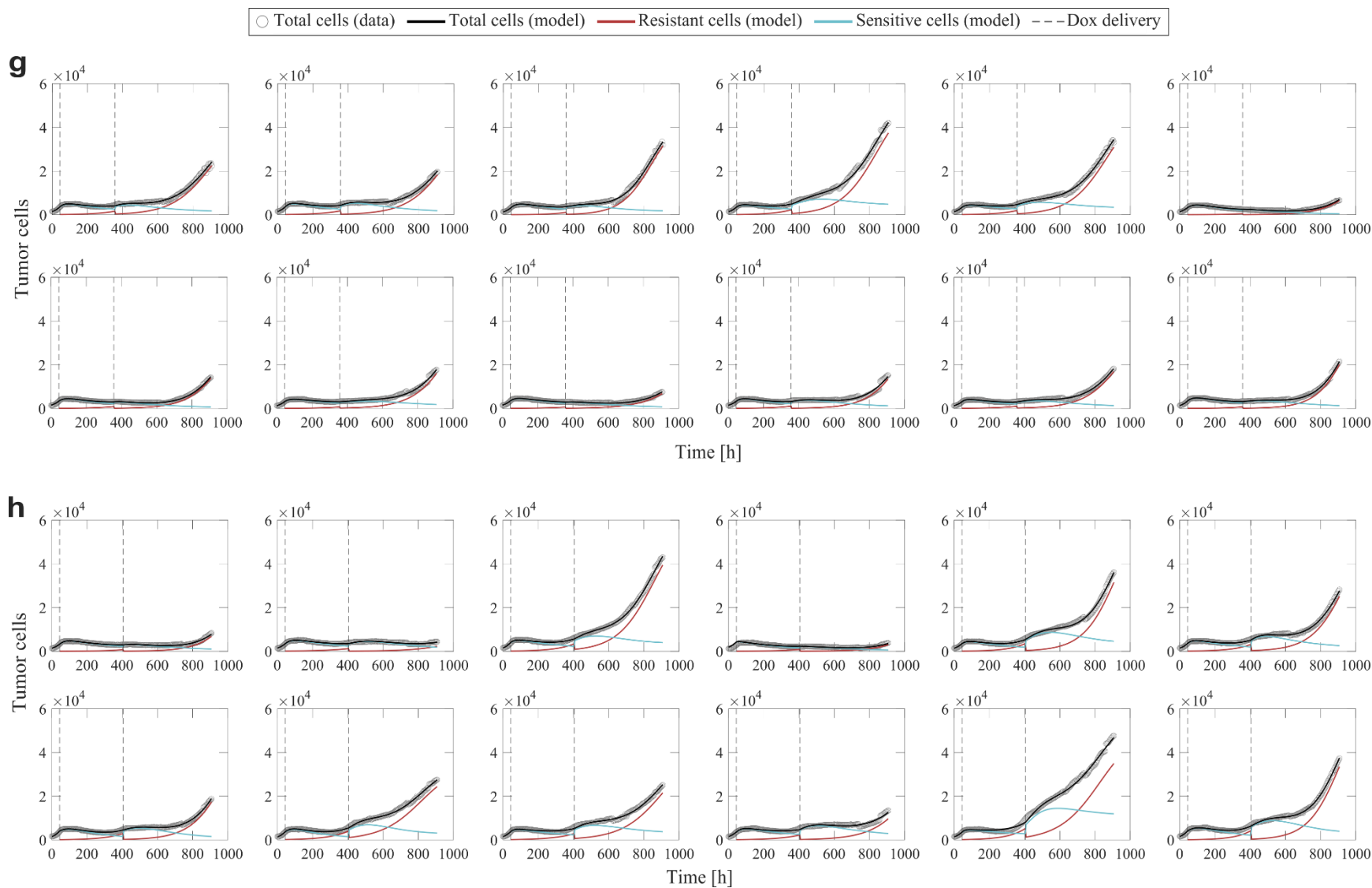
Supplementary Figure S3. Multiple-dose model fits for all of the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals ($n = 12$ for each interval; Experiment 2 in Table 1 of the main text). **(a)** 0 days; **(b)** 2 days. For **(a)-(d)**, the multiple-dose model with constant parameters was used to fit the datasets, while for **(e)-(i)**, the multiple-dose model with varying f_r and γ_d was used.



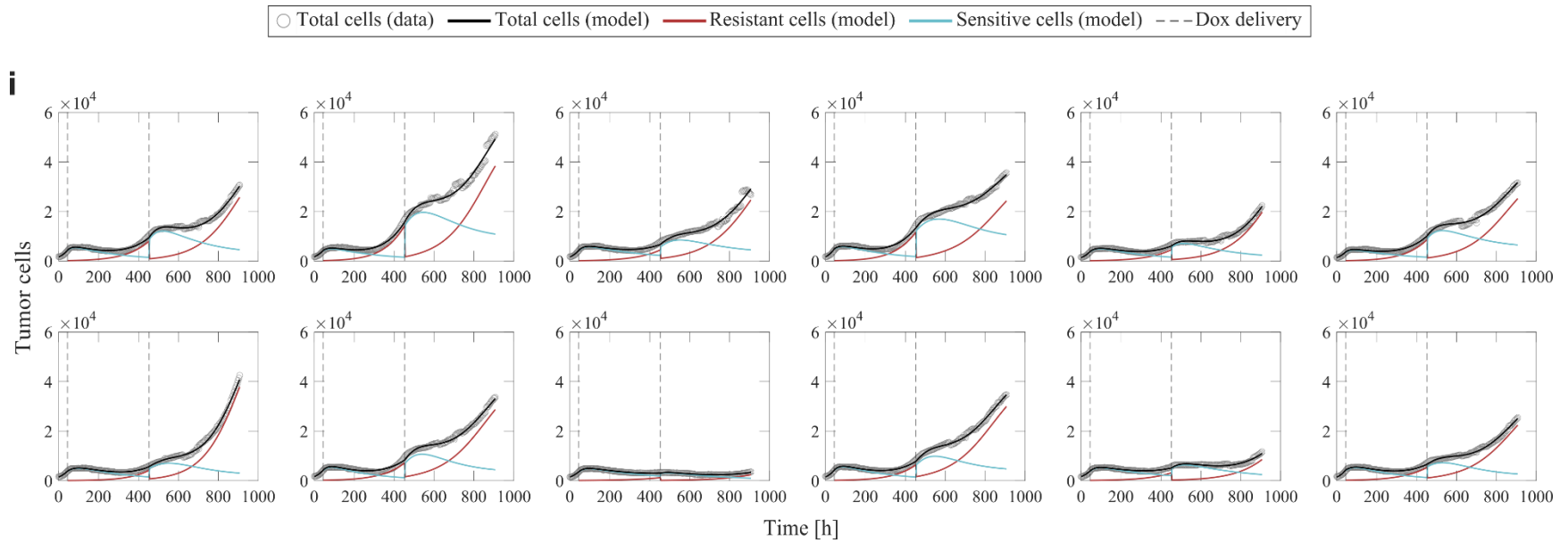
Supplementary Figure S3 (continued). Multiple-dose model fits for all of the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals ($n = 12$ for each interval; Experiment 2 in Table 1 of the main text). (c) 4 days; (d) 6 days. For (a)-(d), the multiple-dose model with constant parameters was used to fit the datasets, while for (e)-(i), the multiple-dose model with varying f_r and γ_d was used.



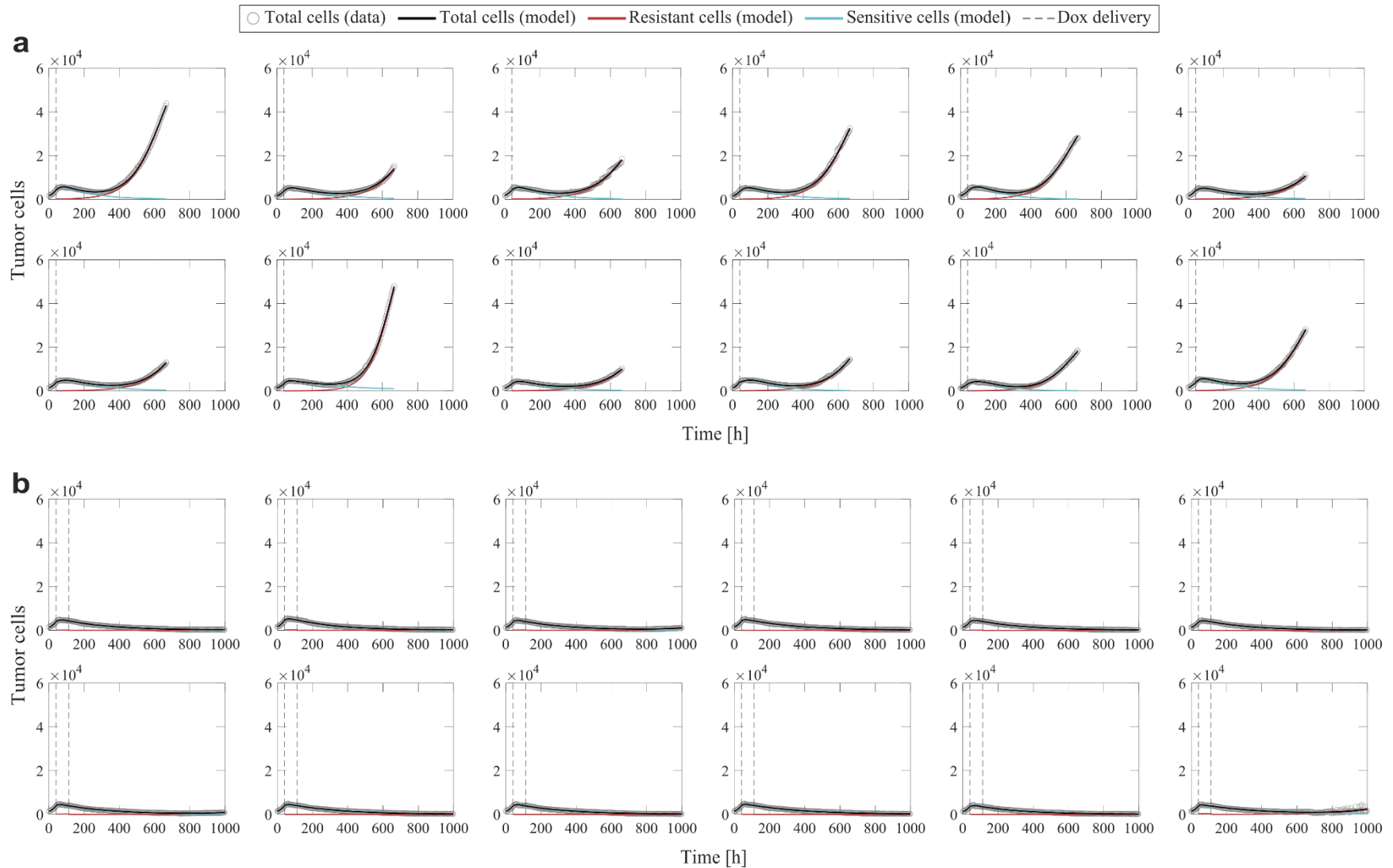
Supplementary Figure S3 (continued). Multiple-dose model fits for all of the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals ($n = 12$ for each interval; Experiment 2 in Table 1 of the main text). (e) 8 days; (f) 10 days. For (a)-(d), the multiple-dose model with constant parameters was used to fit the datasets, while for (e)-(i), the multiple-dose model with varying f_r and γ_d was used.



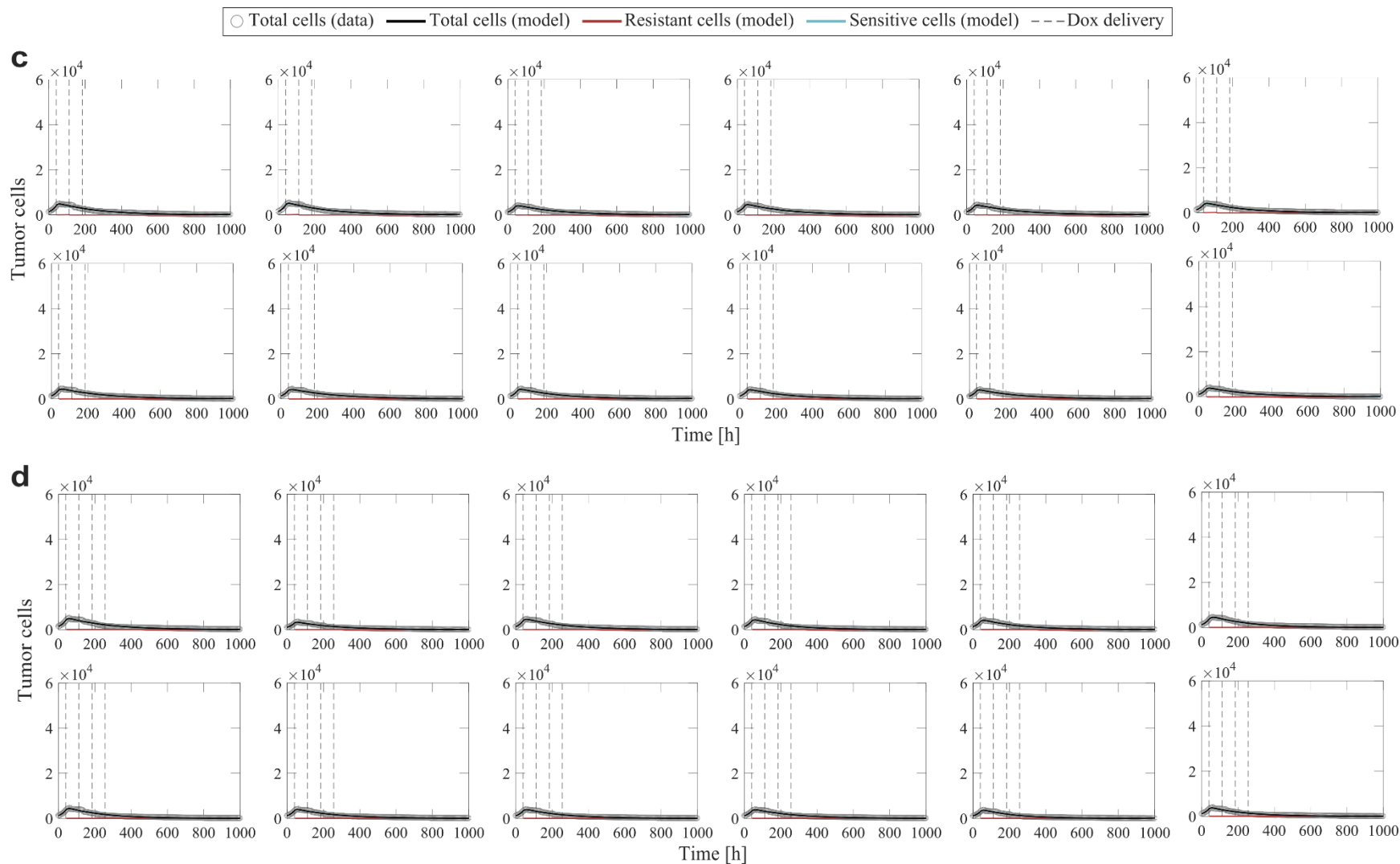
Supplementary Figure S3 (continued). Multiple-dose model fits for all of the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals ($n=12$ for each interval; Experiment 2 in Table 1 of the main text). **(g)** 12 days; **(h)** 14 days. For **(a)-(d)**, the multiple-dose model with constant parameters was used to fit the datasets, while for **(e)-(i)**, the multiple-dose model with varying f_r and γ_d was used.



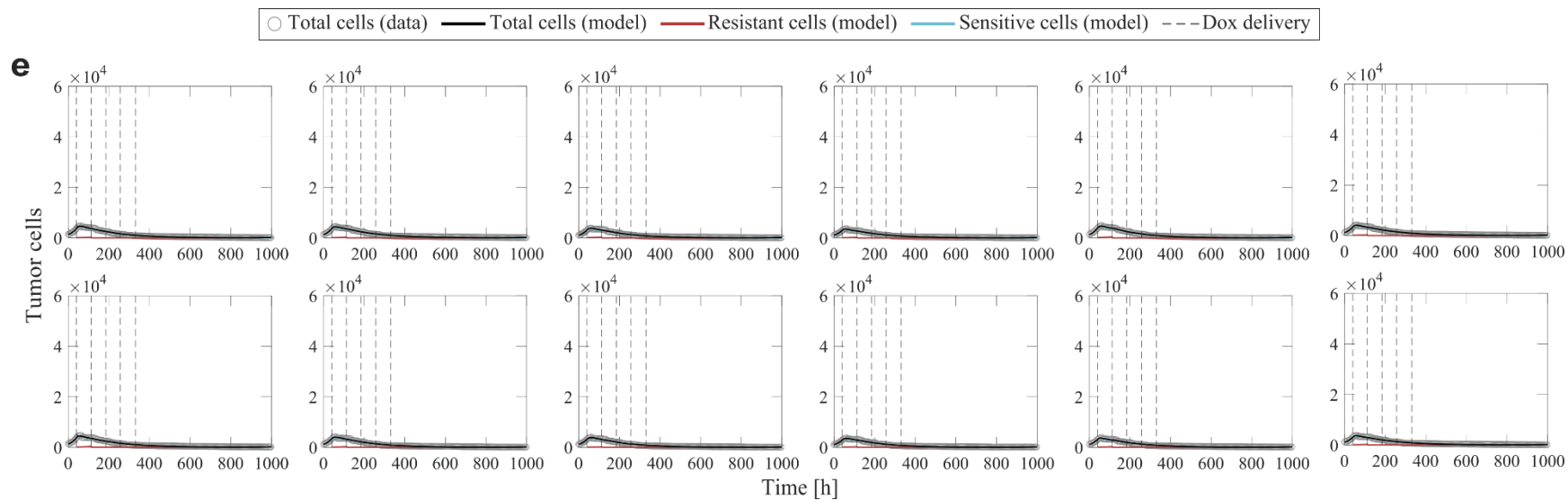
Supplementary Figure S3 (continued). Multiple-dose model fits for all of the time courses resulting from cells treated with two consecutive doses of 75 nM doxorubicin delivered at varying inter-treatment intervals ($n=12$ for each interval; Experiment 2 in Table 1 of the main text). **(i)** 16 days. For **(a)-(d)**, the multiple-dose model with constant parameters was used to fit the datasets, while for **(e)-(i)**, the multiple-dose model with varying f_r and γ_d was used.



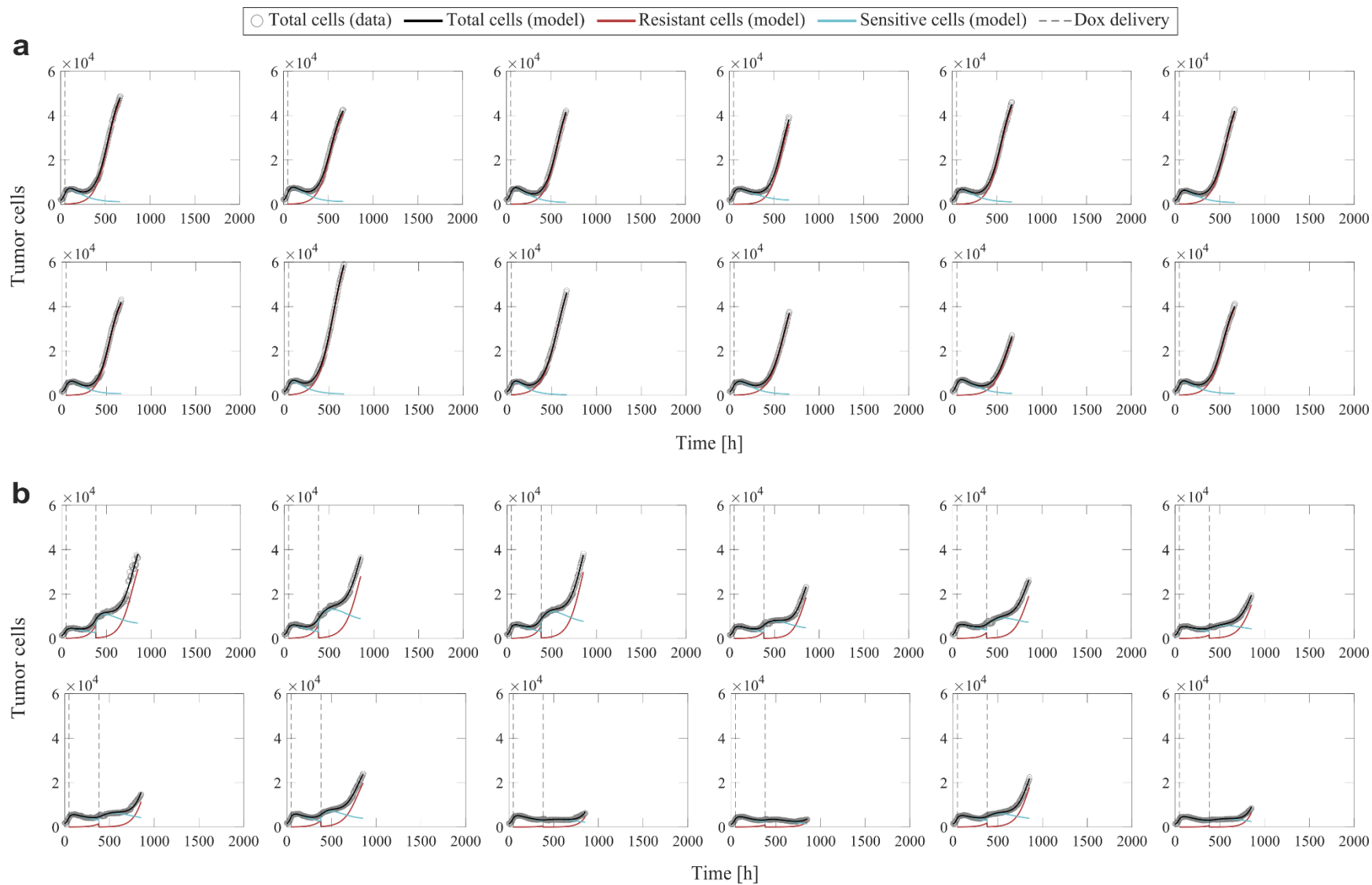
Supplementary Figure S4. Multiple-dose model fits for all of the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-day inter-treatment intervals ($n = 12$ for each total dose number; Experiment 3 in Table 1 of the main text). **(a)** 1 dose; **(b)** 2 doses. The multiple-dose model with constant parameters was used to fit the datasets.



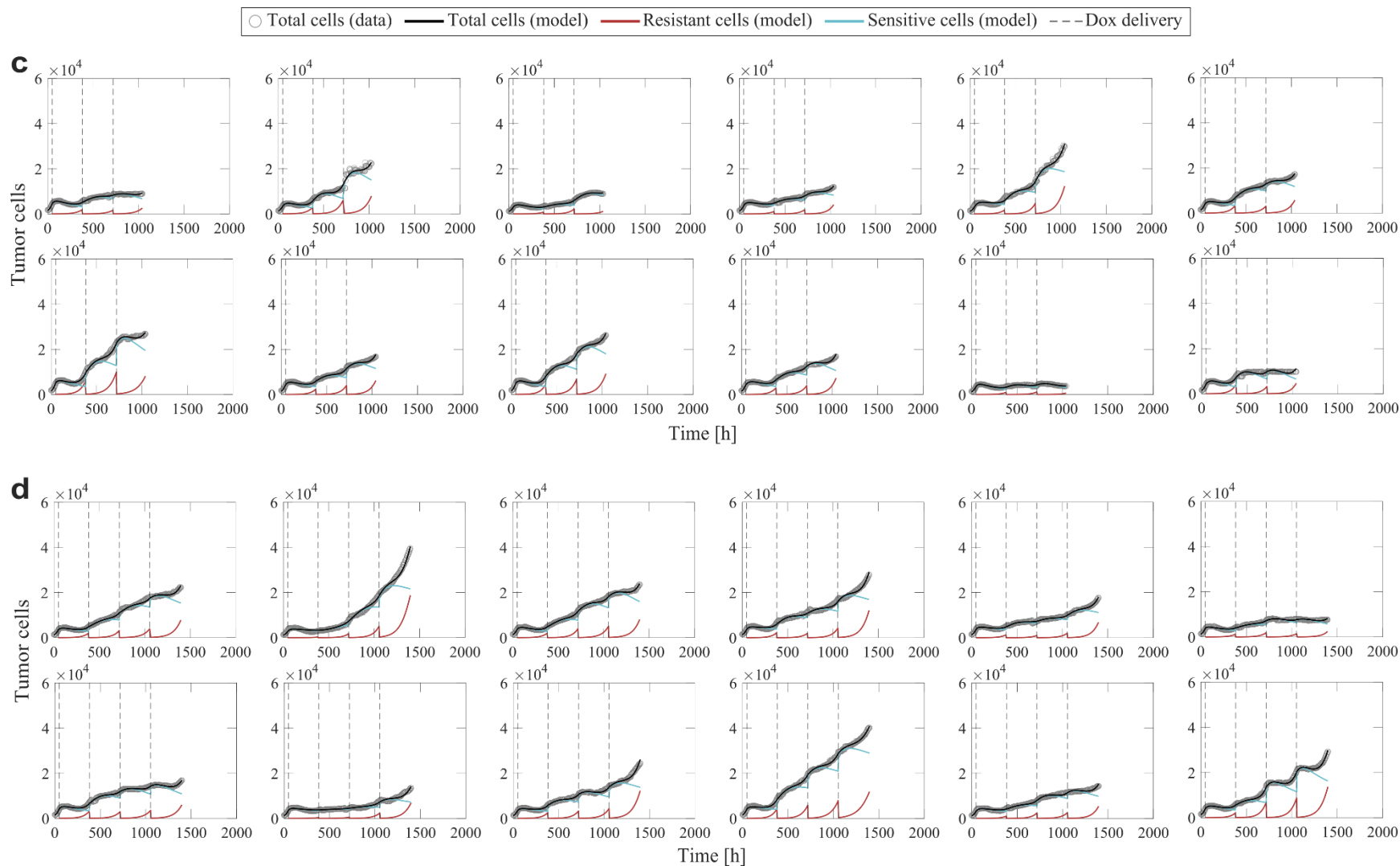
Supplementary Figure S4 (continued). Multiple-dose model fits for all of the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-day inter-treatment intervals ($n = 12$ for each total dose number; Experiment 3 in Table 1 of the main text). (c) 3 doses; (d) 4 doses. The multiple-dose model with constant parameters was used to fit the datasets.



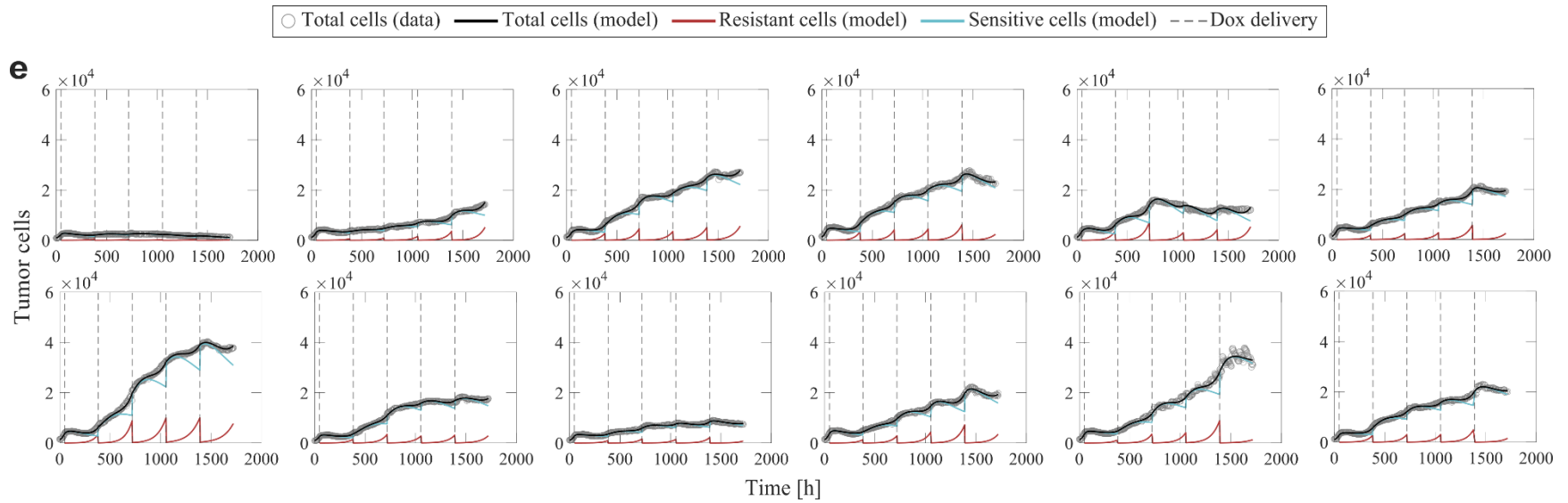
Supplementary Figure S4 (continued). Multiple-dose model for all of the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-day inter-treatment intervals ($n = 12$ for each total dose number; Experiment 3 in Table 1 of the main text). **(e)** 5 doses. The multiple-dose model with constant parameters was used to fit the datasets.



Supplementary Figure S5. Multiple-dose model fits for all of the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals ($n = 12$ for each total dose number; Experiment 3 in Table 1 of the main text). **(a)** 1 dose; **(b)** 2 doses. The multiple-dose model with varying f_r and γ_d was used to fit the datasets.



Supplementary Figure S5 (continued). Multiple-dose model fits for all of the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals ($n = 12$ for each total dose number; Experiment 3 in Table 1 of the main text). (c) 3 doses; (d) 4 doses. The multiple-dose model with varying f_r and γ_d was used to fit the datasets.



Supplementary Figure S5 (continued). Multiple-dose model fits for all of the time courses resulting from cells treated with a varying number of 75 nM doxorubicin doses delivered at 2-week inter-treatment intervals ($n = 12$ for each total dose number; Experiment 3 in Table 1 of the main text). (e) 5 doses. The multiple-dose model with varying f_r and γ_d was used to fit the datasets.