

Supplementary Material

1 SUPPLEMENTARY TABLES AND FIGURES

1.1 Lotka-Volterra model (M1)

Time point (min)	x_1	x_2
1.1	1.8823	0.5214
2.4	1.5510	1.2471
3.9	0.4007	0.9858
5.6	0.0454	0.2924
7.5	1.8881	0.6133
9.6	0.1839	1.3163
11.9	-0.1940	0.8171
14.4	1.6015	1.7212

Table S1. Model M1: *in silico* noisy dataset used for calibration.

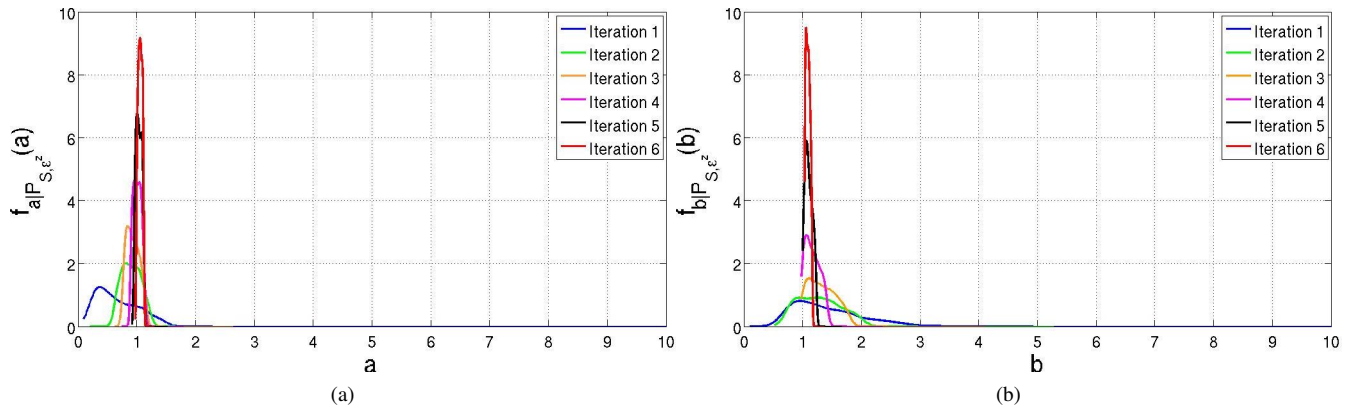


Figure S1: Model M1-CRC: S1a, S1b Evolution of the conditional pdfs of parameter a and b respectively, in all iterations.

Iteration (z)	Mean		Variance	
	$f_{D_{x_1}}(d_{x_1,p})$	$f_{D_{x_2}}(d_{x_2,p})$	$f_{D_{x_1}}(d_{x_1,p})$	$f_{D_{x_2}}(d_{x_2,p})$
1	$2.4610 * 10^{42}$	16.8570	$1.3097 * 10^{84}$	295.8022
2	7.0325	6.2825	2.3915	8.4197
3	6.8387	9.1485	3.3102	27.3043
4	5.6736	5.3518	2.8713	6.1758
5	4.6699	4.3444	1.5612	2.0294
6	3.6127	3.3814	0.3309	0.5885

Table S2. Model M1-CRC: summary statistics for the distance functions.

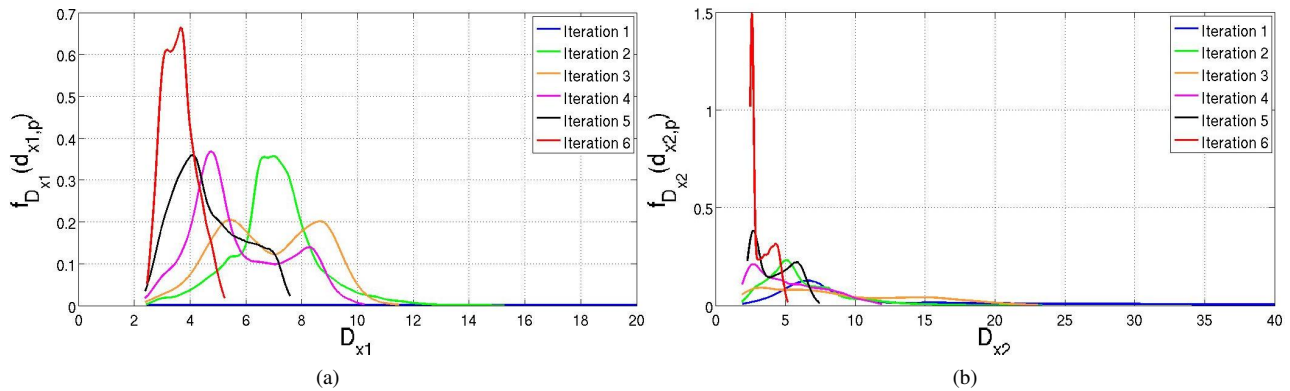


Figure S2: Model M1-CRC: S2a, S2b evolution of the distance functions $f_{D_{x_1}}(d_{x_1,p})$ and $f_{D_{x_2}}(d_{x_2,p})$ over the six iterations.

Iteration (z)	Mean		Variance	
	$f_{a P_{S,\epsilon z}}(a)$	$f_{b P_{S,\epsilon z}}(b)$	$f_{a P_{S,\epsilon z}}(a)$	$f_{b P_{S,\epsilon z}}(b)$
1	0.6740	1.4020	8.1871	8.1881
2	0.9071	1.2816	0.2773	1.8854
3	0.9376	1.3430	0.3364	0.8124
4	1.0097	1.1821	0.0913	0.1576
5	1.0360	1.1099	0.0305	0.0363
6	1.0583	1.0946	0.0081	0.0091

Table S3. Model M1-CRC: summary statistics of $f_{a|P_{S,\epsilon z}}(a)$ and $f_{b|P_{S,\epsilon z}}(b)$.

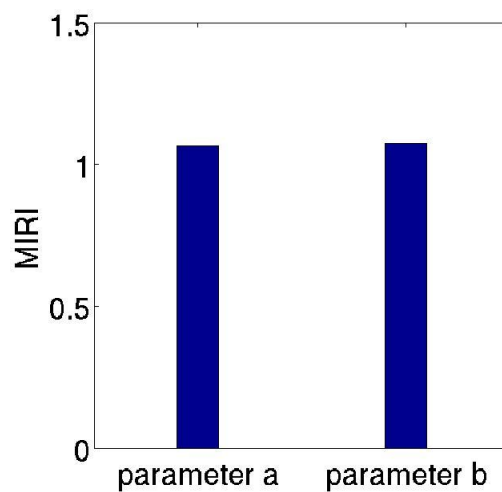


Figure S3: Model M1-CRC: values of the MIRI for parameter a and b , obtained through robustness analysis.

Parameter	\hat{p}	σ^-	σ^+
a	+1.066	+0.937	+1.162
b	+1.046	+0.872	+1.340

Table S4. Model M1-PL: results of the Profile Likelihood. \hat{p} is the parameter value estimated by *lsqnonlin*, σ^- and σ^+ are the 95% point-wise confidence intervals.

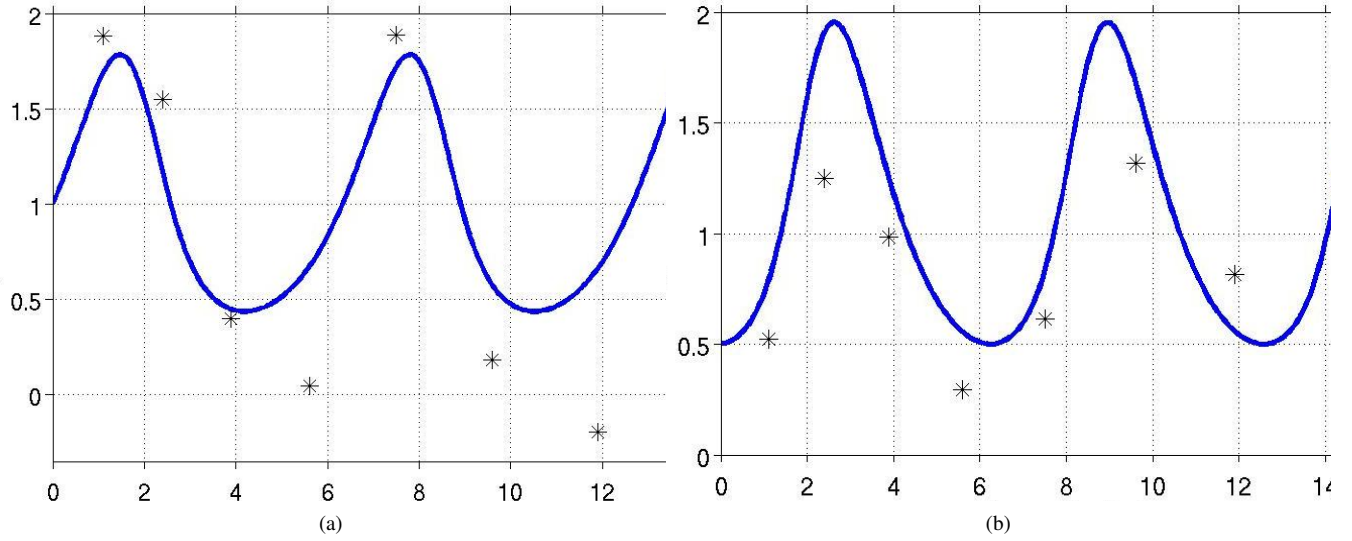


Figure S4: Model M1-PL: time behavior of output variables x_1 (S4a) and x_2 (S4b) using best fit parameters estimated by *lsqnonlin* in D2D (see Table S4). Asterisks represent the experimental dataset.

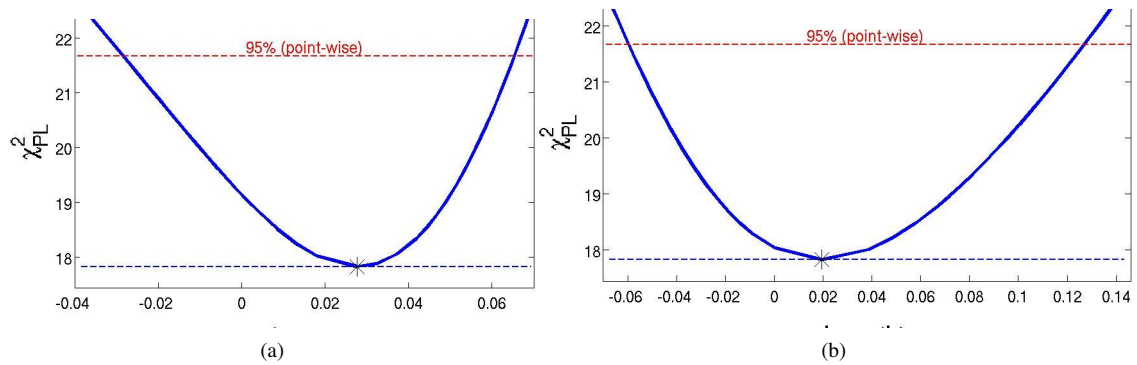
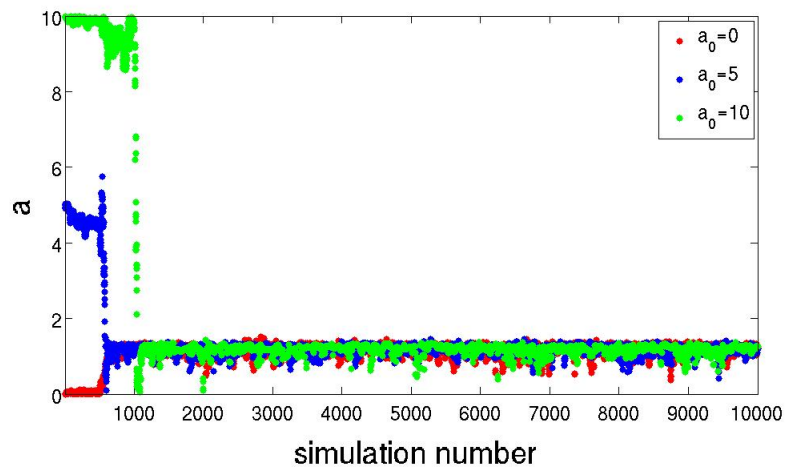


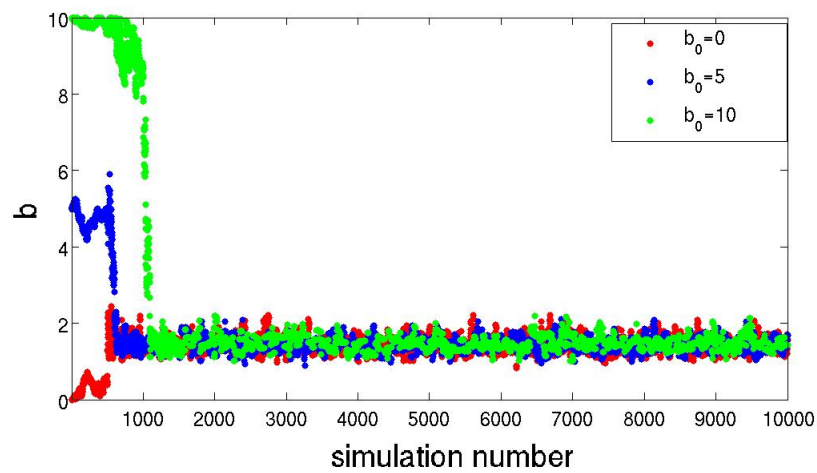
Figure S5: Model M1-PL: Profile Likelihood (denoted by χ^2_{PL}) of parameter a (S5a) and parameter b (S5b). The solid lines indicate the PL; the broken lines indicate the threshold to assess confidence intervals; the asterisks indicate the optimal parameter values.

Iteration	Number of generated particles	Tolerance
1	26228	30
2	36667	16
3	46989	6
4	49271	5
5	52194	4.3

Table S5. Model M1-ABC SMC: results of ABC-SMC algorithm Toni et al. (2009).

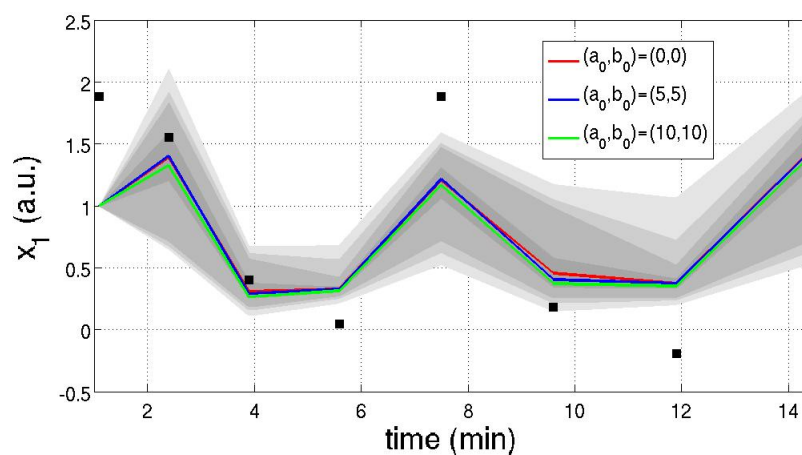


(a)

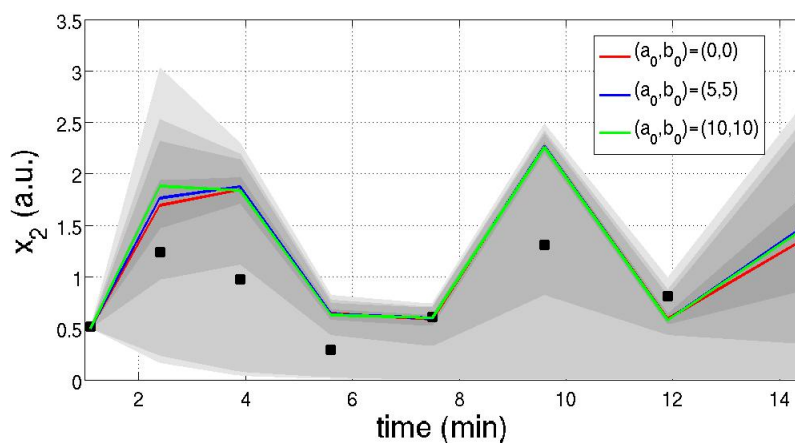


(b)

Figure S6: Model M1-DRAM: DRAM chain for parameter a (S6a) and b (S6b) when the initial error variance is set to 0.1 and the corresponding prior weight is set to 3. The red, blue and green chains correspond to initial parameter values equal to 0, 5 and 10, respectively. The x-axis represents the length of the DRAM chain.



(a)



(b)

Figure S7: Model M1-DRAM: the red, blue and green line represents the time behavior of x_1 (S7a) and x_2 (S7b) when parameters are equal to the mean values of the chains returned by DRAM when initial parameter values are both equal to 0, 5 and 10, respectively. Black squares are the experimental data. The gray regions represent the 50%, 90%, 95%, and 99% predictive probability limits due parameter uncertainty.

1.2 EpoR System model (M2)

$$\begin{aligned}
 \dot{E} &= -k_1 \cdot E \cdot L \\
 \dot{E}^* &= k_1 \cdot E \cdot L - k_2 \cdot E^* \\
 \dot{E}^{**} &= k_2 \cdot E^* \\
 \dot{S} &= -k_3 \cdot E^{**} \cdot S \\
 \dot{P} &= k_3 \cdot E^{**} \cdot S
 \end{aligned} \tag{S1}$$

$$\begin{aligned}
 E(0) &= init_E \\
 E^*(0) &= 0 \\
 E^{**}(0) &= 0 \\
 S(0) &= init_S \\
 P(0) &= 0
 \end{aligned} \tag{S2}$$

$$\begin{aligned}
 y_1(t_i) &= scale_E \cdot E(t_i) \\
 y_2(t_i) &= scale_S \cdot S(t_i)
 \end{aligned} \tag{S3}$$

Time (min)	Noiseless dataset		Noisy dataset	
	y_1	y_2	y_1	y_2
0	40	10	39.24	10.24
3.33	-	9.4909	-	10.61
6.66	-	6.9968	-	7.23
10	14.7152	3.5448	21.89	5.47
13.33	-	1.2052	-	1.43
16.66	-	0.2768	-	0.53
20	5.4134	0.0446	3.08	1.08
23.33	-	0.0054	-	0.38
26.66	-	$5.0042 \cdot 10^{-4}$	-	0.11
30	1.9915	$3.8284 \cdot 10^{-5}$	0.12	0.08
40	0.732	-	1.37	-

Table S6. Model M2: noiseless and noisy datasets used for parameter estimation and robustness analysis Raue et al. (2011).

Iteration	$f_{D_{y_1}}(d_{y_1,p})$		$f_{D_{y_2}}(d_{y_2,p})$	
	Mean value	Variance	Mean value	Variance
1	217.4148	919.7	465.0677	2692.3
2	220.0488	834.4704	108.8659	372.1710
3	127.0054	325.2496	84.1557	209.9309
4	93.1872	159.6009	48.5669	61.8872
5	67.1666	63.0651	38.2407	22.3253
6	48.9377	21.3781	32.6934	5.5355
7	27.7286	9.1382	26.1496	2.9610
8	18.6834	4.8059	13.6144	2.9206
9	15.2435	2.0665	7.3401	1.5109

Table S7. Model M2-CRC: summary statistics for $f_{D_{y_1}}(d_{y_1,p})$ and $f_{D_{y_2}}(d_{y_2,p})$ over the nine iterations. Values are averaged over the 10 independent realizations.

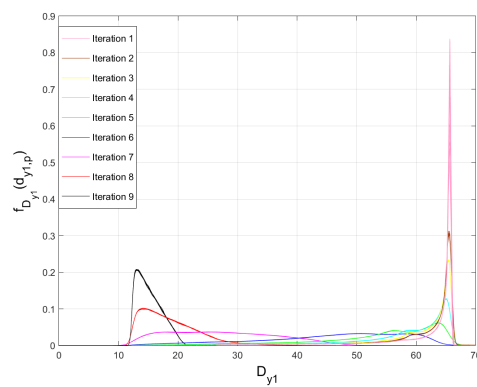


Figure S8: Model M2-CRC: pdf of y_1 distance function.

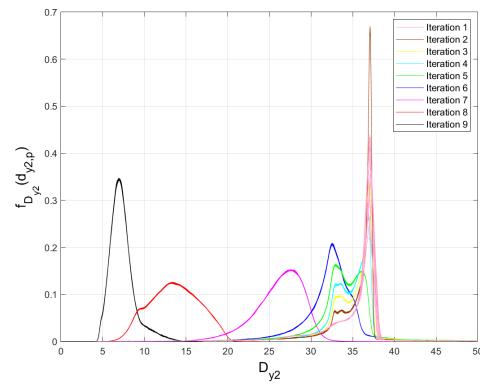


Figure S9: Model M2-CRC: pdf of y_2 distance function.

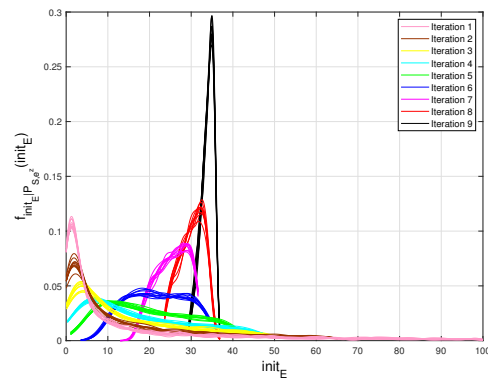


Figure S10: Model M2-CRC: conditional pdfs of the $init_E$ parameter.

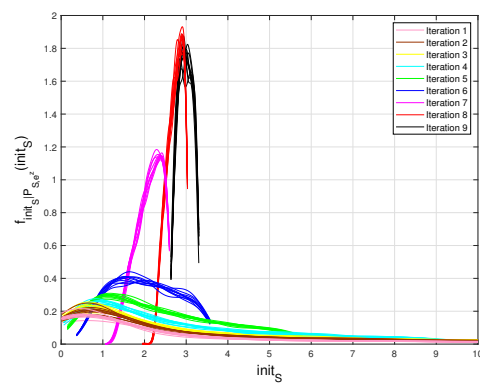


Figure S11: Model M2-CRC: conditional pdfs of the $init_S$ parameter.

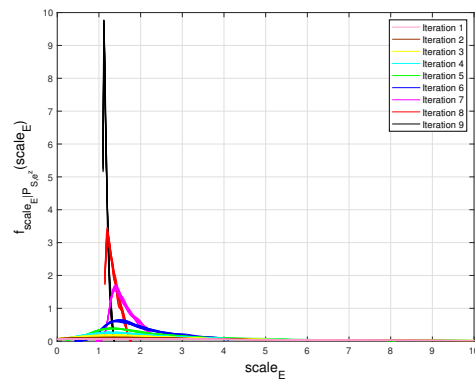


Figure S12: Model M2-CRC: conditional pdfs of the $scale_E$ parameter.

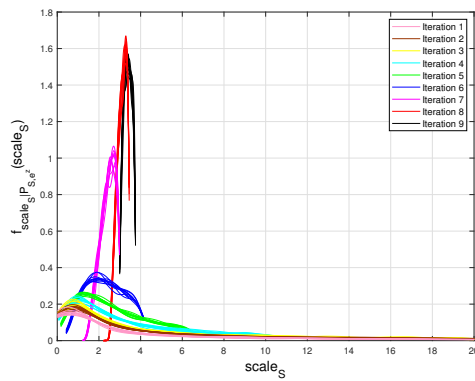


Figure S13: Model M2-CRC: conditional pdfs of the $init_S$ parameter.

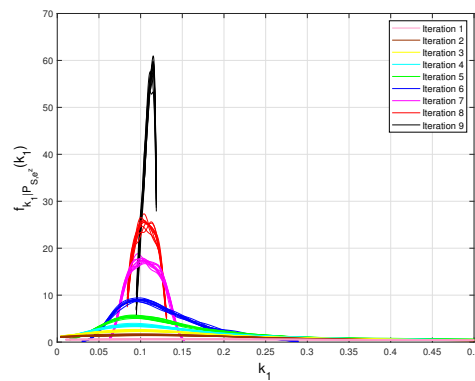


Figure S14: Model M2-CRC: conditional pdfs of the k_1 parameter.

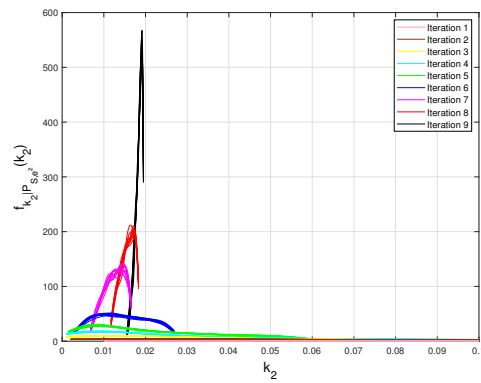


Figure S15: Model M2-CRC: conditional pdfs of the k_2 parameter.

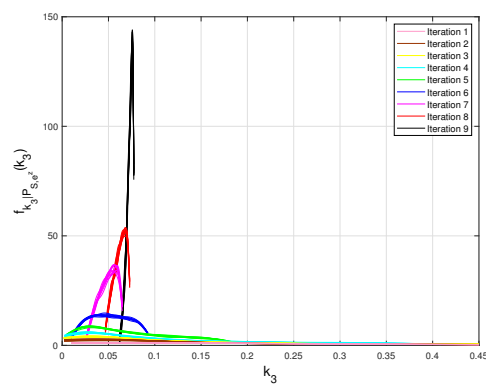


Figure S16: Model M2-CRC: conditional pdfs of the k_3 parameter.

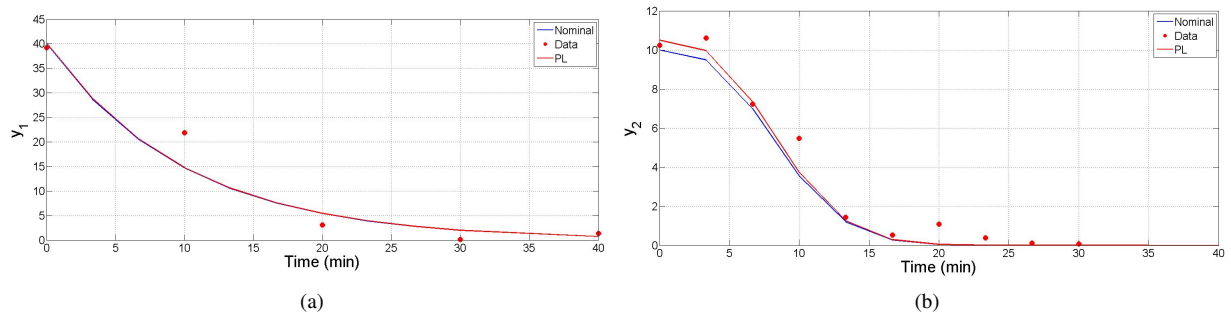


Figure S17: Model M2-PL: S17a S17b show the temporal behavior of y_1 and y_2 returned by PL approach.

Parameter	Iteration	Mean value	Variance	Mode
k_1	1	11.6207	19.9535	0.1676
	2	1.4223	1.9153	0.1057
	3	0.5564	0.6338	0.0955
	4	0.3016	0.2861	0.0928
	5	0.1828	0.1280	0.0925
	6	0.1254	0.0490	0.0976
	7	0.1058	0.0183	0.1024
	8	0.1096	0.0122	0.1042
	9	0.1092	0.0062	0.1143
k_2	1	11.3579	18.8793	0.1031
	2	0.7662	1.1162	0.0248
	3	0.1360	0.1512	0.0128
	4	0.0480	0.0425	0.0095
	5	0.0237	0.0161	0.0086
	6	0.0145	0.0065	0.0106
	7	0.0124	0.0025	0.0143
	8	0.0156	0.0017	0.0171
	9	0.0183	0.0009	0.0191
k_3	1	8.7008	17.8986	0.1031
	2	0.8074	1.1006	0.0422
	3	0.2615	0.2676	0.0327
	4	0.1316	0.1108	0.0292
	5	0.0758	0.0497	0.0296
	6	0.0514	0.0223	0.0415
	7	0.0491	0.0098	0.0569
	8	0.0623	0.0068	0.0678
	9	0.0728	0.0033	0.0758

Table S8. Model M2-CRC: summary statistics of the three kinetic parameters.

Parameter	Iteration	Mean value	Variance	Mode
$init_E$	1	16.6944	22.0296	1.3032
	2	15.6962	16.4395	1.9840
	3	15.8885	13.4175	3.8127
	4	18.3333	12.9594	6.6465
	5	19.8313	10.6221	10.9966
	6	21.4556	7.0448	20.2614
	7	25.1709	3.8984	28.8037
	8	30.1755	2.9611	32.2857
	9	33.9041	1.5291	34.9329
$init_S$	1	15.6737	22.0031	0.5592
	2	6.1501	6.8975	0.7217
	3	4.5241	4.5694	0.7536
	4	3.0397	2.4375	0.9278
	5	2.3863	1.4694	1.1437
	6	1.9944	0.8117	1.6620
	7	2.0976	0.3166	2.3654
	8	2.7230	0.1935	2.8951
	9	2.9790	0.1756	2.9554

Table S9. Model M2-CRC: summary statistics of the parameters of the two initial conditions.

Parameter	Iteration	Mean value	Variance	Mode
s_1	1	19.6923	23.2733	1.7029
	2	14.2438	18.3015	1.4727
	3	6.9718	7.9647	1.3845
	4	4.0516	3.8055	1.3002
	5	2.6284	1.7600	1.3185
	6	2.0039	0.7726	1.4515
	7	1.5910	0.2682	1.3950
	8	1.3388	0.1368	1.2086
	9	1.1705	0.0535	1.1224
s_2	1	16.3713	22.4893	0.6056
	2	6.7946	7.4791	0.8120
	3	5.0803	5.1099	0.8483
	4	3.4347	2.7596	1.0551
	5	2.7124	1.6798	1.3281
	6	2.3114	0.9483	1.9099
	7	2.4076	0.3647	2.6942
	8	3.0965	0.2210	3.2922
	9	3.3867	0.2018	3.3674

Table S10. Model M2-CRC: summary statistics of the two scale factor parameters.

Parameter name	p^*	\hat{p}	σ^-	σ^+
k_1	0.1	0.087	0.04	0.2
k_2	0.1	0.019	-Inf	+Inf
k_3	0.1	0.37	0.015	+Inf
$init_E$	10	10.05	9.66	10.42
$init_S$	5	4.97	4.78	5.15
$scale_E$	4	4.027	2.57	5.5
$scale_S$	2	2.1	1.59	2.79

Table S11. Model M2-PL: results of parameter estimation and identifiability analysis achieved through the PL approach. p^* is the nominal parameter value, \hat{p} is the estimated value, σ^- and σ^+ are, respectively, the lower and upper boundary of the confidence interval.

Population	Threshold	N.particles	Acceptance rate	Time simulation (s)
1	82	389908	0.0025	41934
2	81	104151	0.0096	11122
3	76.9	100485	0.0099	10894
4	70.3	106418	0.0093	11833
5	62.6	117310	0.0085	14267
6	52.5	176936	0.0056	18106
7	37.5	349409	0.0028	46656

Table S12. Model M2-ABC SMC: results of ABC-SMC algorithm.

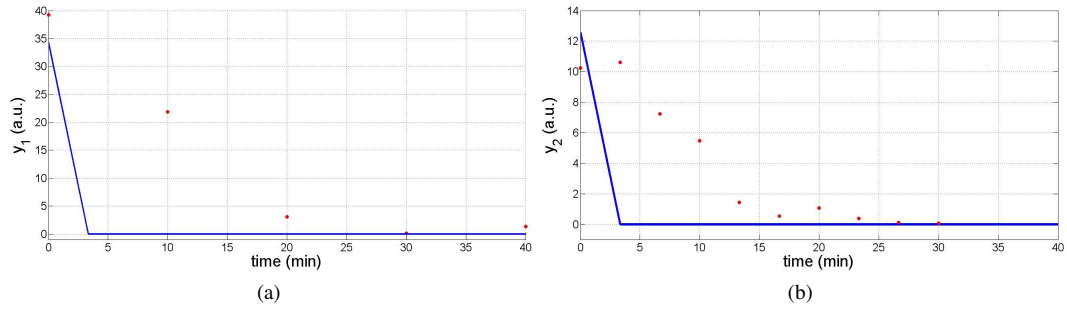


Figure S18: Model M2-ABC SMC: S18a and S18b show the temporal behavior of y_1 and y_2 . The blue lines are the time simulations using the median parameter vector returned by ABC-SMC. Red dots are the *in silico* noisy data.

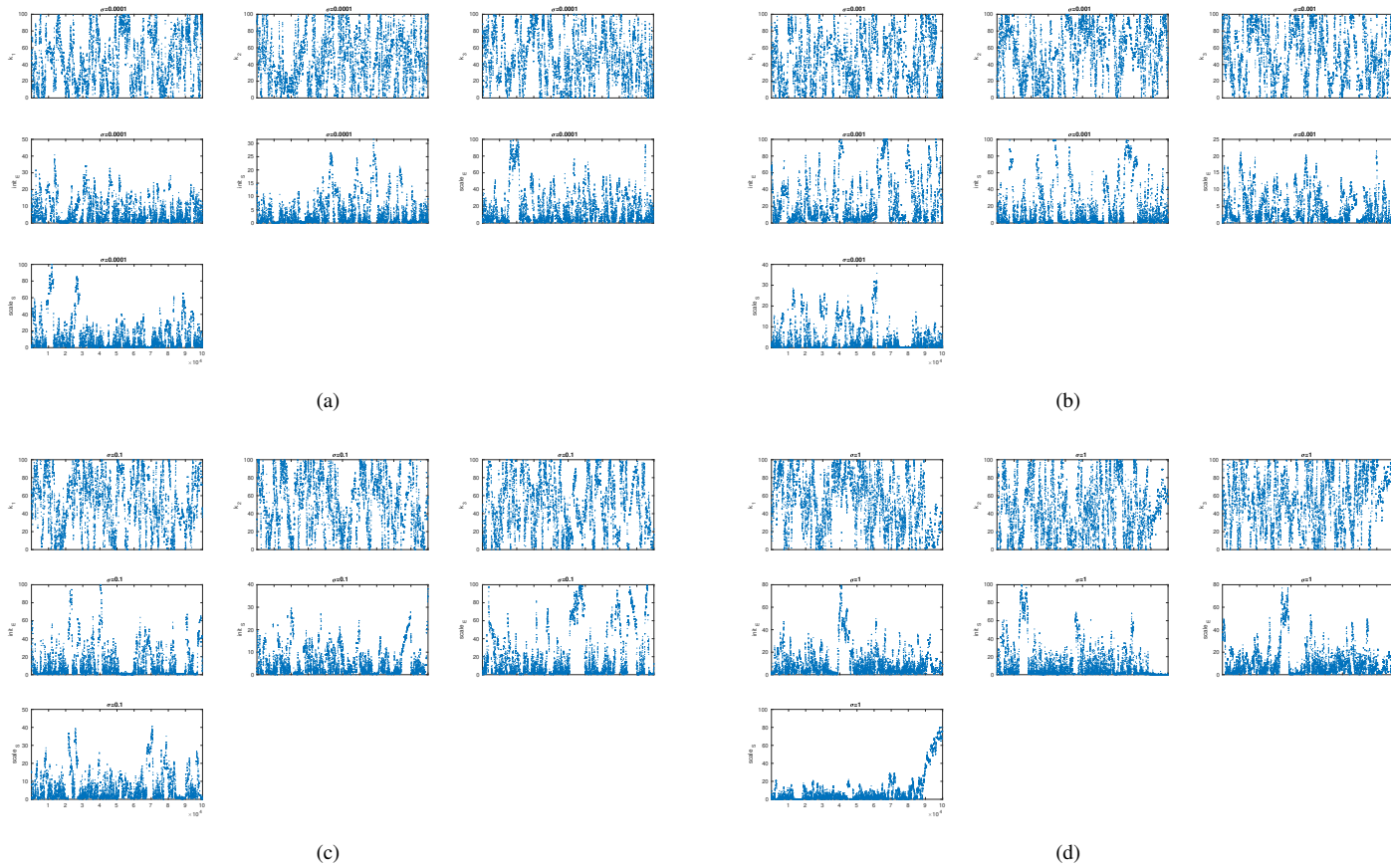


Figure S19: Model M2-DRAM: chains of all the parameters returned by DRAM in the 9th iteration. The x-axis represents the length of the chain. The vector of the initial conditions is $[0.5, 0.5, 0.5, 8, 7, 5, 3]$. The initial error variance σ is set equal to 0.001 (S19a), 0.01 (S19b), 0.1 (S19c) and 1 (S19d).

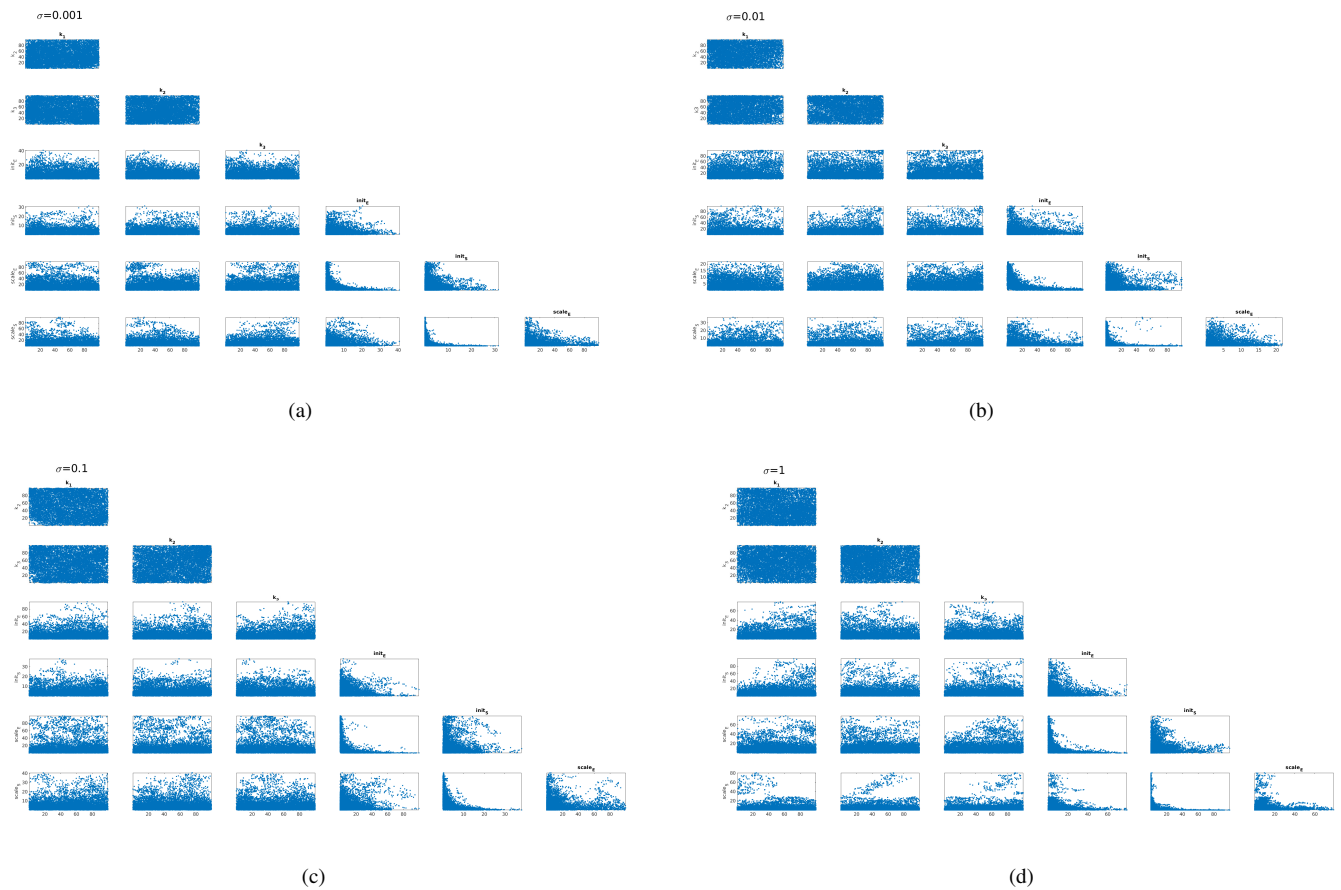


Figure S20: Model M2-DRAM: pairplot of the chains of all the parameters in the 9th iteration. The x-axis and y-axis represent the different model parameters. The vector of the initial conditions is $[0.5, 0.5, 0.5, 8, 7, 5, 3]$. The initial error variance σ is set equal to 0.001 (S20a), 0.01 (S20b), 0.1 (S20c) and 1 (S20d).

Parameter name	$\sigma = 0.001$	$\sigma = 0.01$	$\sigma = 0.1$	$\sigma = 1$
k_1	44.5	45	52.82	52.07
k_2	44.27	56.01	51.04	44.85
k_3	48.33	51.6	49.25	54.70
$init_E$	7.54	27.2	13.55	10.81
$init_S$	4.54	21.06	5.75	13.11
$scale_E$	18.42	4.52	24.23	11.64
$scale_S$	14.51	4.93	6.99	10.13

Table S13. Model M2-DRAM: mean values of parameter chains returned by DRAM in the 9th iteration with different values of the error variance σ .

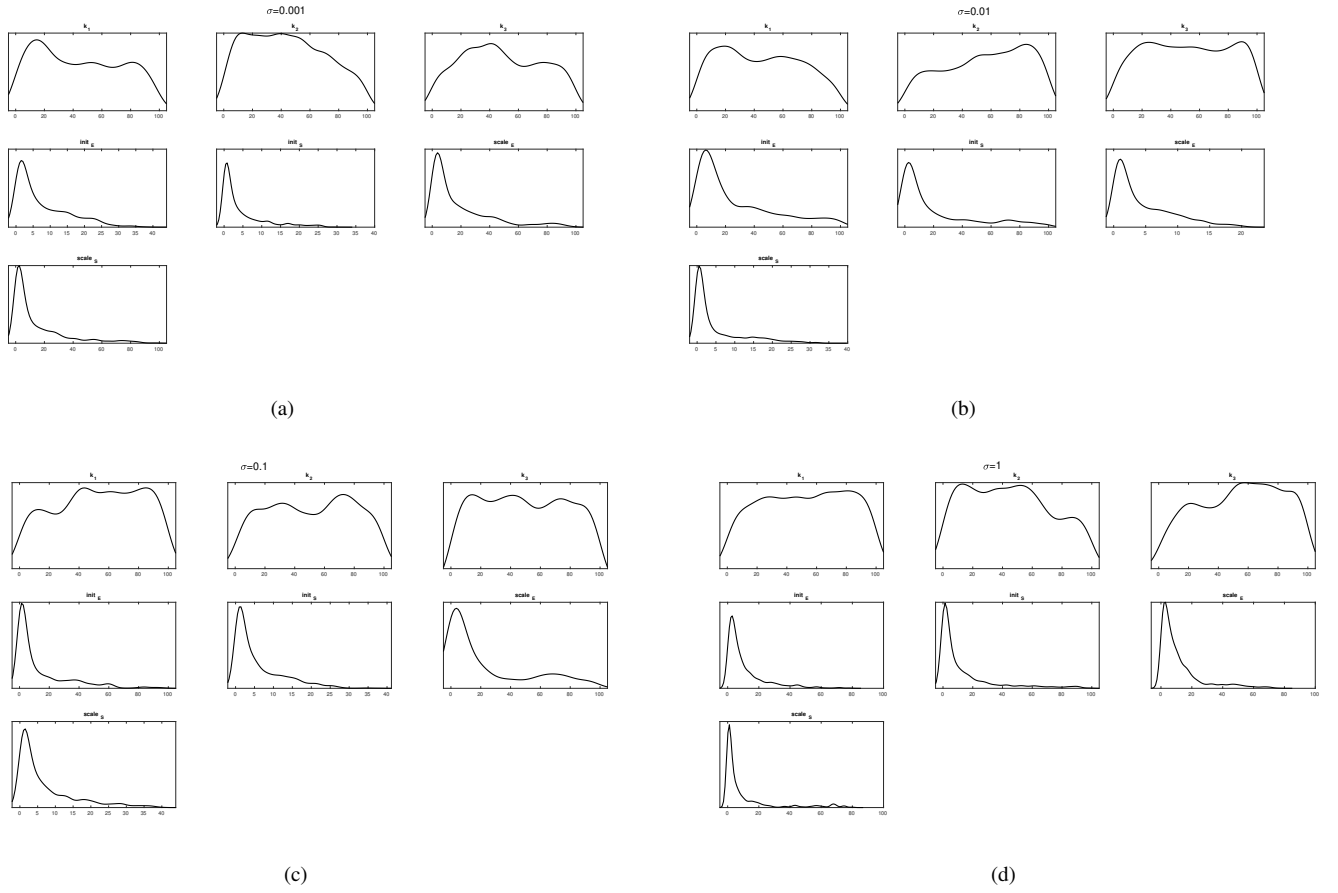


Figure S21: Model M2-DRAM: pdfs of all the parameters in the 9th iteration. The vector of the initial conditions is $[0.5, 0.5, 0.5, 8, 7, 5, 3]$. The initial error variance σ is set equal to 0.001 (S21a), 0.01(S21b), 0.1(S21c) and 1(S21d).

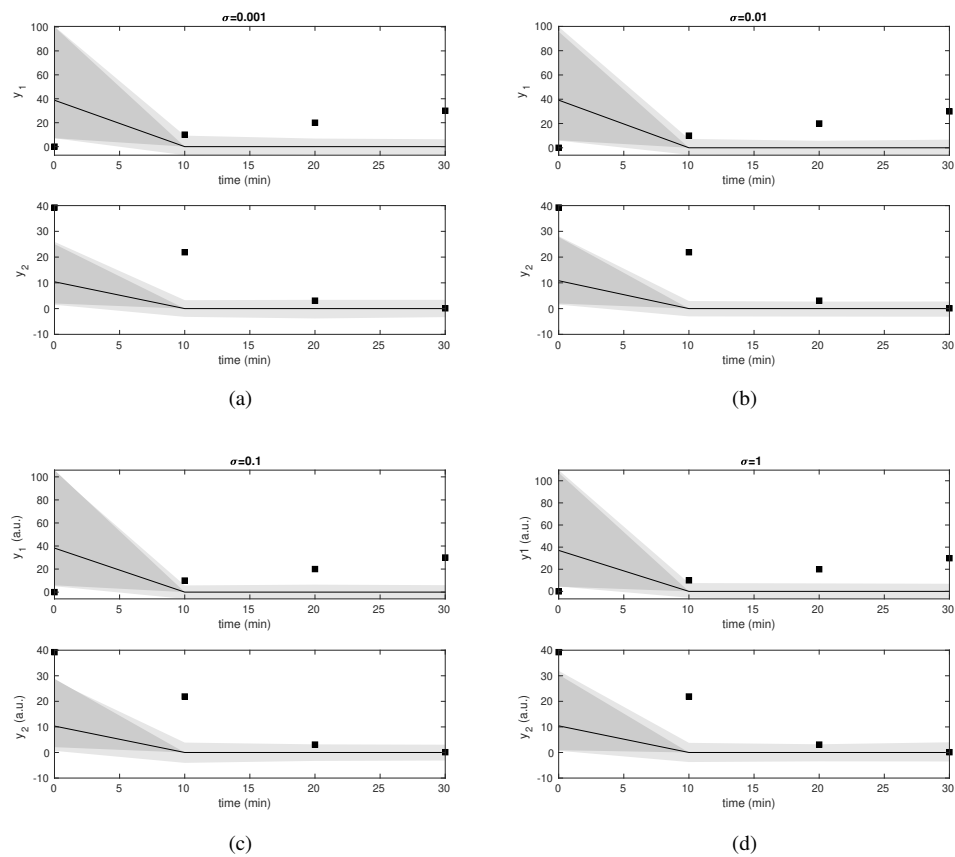


Figure S22: Model M2-DRAM: time behavior of the output variables when parameters are set equal to the mean of corresponding chains (see Table S13) returned by DRAM in the 9th iteration. The black squares are the experimental data used to calibrate the model. The vector of the initial conditions is $[0.5, 0.5, 0.5, 8, 7, 5, 3]$. The initial error variance σ is set equal to 0.001 (S22a), 0.01 (S22b), 0.1 (S22c) and 1 (S22d).

1.3 Multiple Myeloma model (M3)

		Time points (min)					
		0	5	10	30	60	90
Proteins	Shc Y317	1.000	1.029	1.139	1.113	1.124	1.108
	Pras40 T246	1.000	0.889	0.779	0.813	0.916	0.906
	PI3K p85	1.000	0.844	0.773	0.805	0.800	0.814
	p38 T180-182	1.000	1.065	0.930	1.123	1.010	0.834
	PDK1 S241	1.000	0.826	0.860	0.807	0.894	0.834
	AKT S473	1.000	1.111	1.502	1.408	1.254	1.489
	mTOR S2248	1.000	1.082	1.383	1.440	1.219	1.440
	Rafc S388	1.000	1.087	0.960	0.954	0.897	0.858
	MEK1 S217	1.000	0.908	0.847	0.777	0.822	0.790
	MAPK T202	1.000	0.959	1.069	0.991	1.036	0.992
	p70S6K T389	1.000	1.080	1.191	1.124	1.332	1.033
	CJUN S73	1.000	1.000	0.994	1.134	1.165	1.559
	Bclxl	1.000	1.087	1.013	0.992	1.089	1.058
	BAX	1.000	1.075	0.993	0.984	1.050	1.007
	NFKB S65	1.000	1.201	1.008	1.281	1.023	0.706
	PARP-cleaved	1.000	0.983	1.039	0.908	0.912	0.980

Table S14. Model M3: dataset of RPPA values used for calibration Peng et al. (2014).

The equations of Model M3 are reported below:

$$\dot{GFR} = -k_{GFR} * GFR + k_{pGFR} * pGFR$$

$$p\dot{GFR} = k_{GFR} * GFR - k_{pGFR} * pGFR$$

$$\dot{Shc} = -k_{Shc.pGFR} * Shc * pGFR + k_{pShc} * pShc$$

$$p\dot{Shc} = k_{Shc.pGFR} * Shc * pGFR - k_{pShc} * pShc$$

$$\dot{RasGDP} = -k_{RasGDP.pShc} * RasGDP * pShc + k_{RasGTP.pERK12} * RasGTP * pERK12$$

$$Ras\dot{GTP} = k_{RasGDP.pShc} * RasGDP * pShc - k_{RasGTP.pERK12} * RasGTP * pERK12$$

$$\dot{IRS1} = -k_{IRS1.pGFR} * IRS1 * pGFR + k_{pIRS1.pERK12} * pIRS1 * pERK12 +$$

$$+ k_{pIRS1.pAKT} * pIRS1 * pAKT$$

$$p\dot{IRS1} = k_{IRS1.pGFR} * IRS1 * pGFR - k_{pIRS1.pERK12} * pIRS1 * pERK12 -$$

$$- k_{pIRS1.pAKT} * pIRS1 * pAKT$$

$$\dot{PI3K} = -k_{PI3K.pIRS1} * PI3K * pIRS1 + k_{pPI3K} * pPI3K$$

$$p\dot{PI3K} = k_{PI3K.pIRS1} * PI3K * pIRS1 - k_{pPI3K} * pPI3K$$

$$\dot{MKK47} = -k_{MKK47.RasGTP} * MKK47 * RasGTP + k_{MKK47.pPI3K} * MKK47 * pPI3K +$$

$$+ k_{pMKK47} * pMKK47$$

$$p\dot{MKK47} = k_{MKK47.RasGTP} * MKK47 * RasGTP - k_{MKK47.pPI3K} * MKK47 * pPI3K -$$

$$- k_{pMKK47} * pMKK47$$

$$\dot{p38} = -k_{p38.pMKK47} * p38 * pMKK47 + k_{pp38} * pp38$$

$$pp\dot{38} = k_{p38.pMKK47} * p38 * pMKK47 - k_{pp38} * pp38$$

$$\dot{PDK1} = -k_{PDK1.pPI3K} * PDK1 * pPI3K + k_{pPDK1} * pPDK1$$

$$p\dot{PDK1} = k_{PDK1.pPI3K} * PDK1 * pPI3K - k_{pPDK1} * pPDK1$$

$$\dot{AKT} = -k_{AKT.pPDK1} * AKT * pPDK1 - k_{AKT.pPI3K} * AKT * pPI3K -$$

$$- k_{AKT.RasGTP} * AKT * RasGTP + k_{pAKT} * pAKT$$

$$\begin{aligned}
p\dot{A}KT &= k_{AKT_pPDK1} * AKT * pPDK1 + k_{AKT_pPI3K} * AKT * pPI3K + \\
&+ k_{AKT_RasGTP} * AKT * RasGTP - k_{pAKT} * pAKT \\
m\dot{T}OR &= -k_{mTOR_pAKT} * mTOR * pAKT + k_{pmTOR} * pmTOR \\
pm\dot{T}OR &= k_{mTOR_pAKT} * mTOR * pAKT - k_{pmTOR} * pmTOR \\
R\dot{a}f1 &= -k_{Raf1_RasGTP} * Raf1 * RasGTP - k_{Raf1_pPI3K} * Raf1 * pPI3K + \\
&+ k_{pRaf1_pAKT} * pRaf1 * pAKT \\
pR\dot{a}f1 &= k_{Raf1_RasGTP} * Raf1 * RasGTP + k_{Raf1_pPI3K} * Raf1 * pPI3K - \\
&- k_{pRaf1_pAKT} * pRaf1 * pAKT \\
ME\dot{K}12 &= -k_{MEK12_pRaf1} * MEK12 * pRaf1 + k_{pMEK12} * pMEK12 \\
pME\dot{K}12 &= k_{MEK12_pRaf1} * MEK12 * pRaf1 - k_{pMEK12} * pMEK12 \\
ER\dot{K}12 &= -k_{ERK12_MEK12} * ERK12 * MEK12 - k_{ERK12_pp38} * ERK12 * pp38 + k_{pERK12} * pERK12 \\
pER\dot{K}12 &= k_{ERK12_MEK12} * ERK12 + MEK12 + k_{ERK12_pp38} * ERK12 * pp38 - k_{pERK12} * pERK12 \\
P70\dot{S}6K &= -k_{P70S6K_pERK12} * P70S6K * pERK12 - k_{P70S6K_pmTOR} * P70S6K * pmTOR + \\
&+ k_{pP70S6K} * pP70S6K \\
pP70\dot{S}6K &= k_{P70S6K_pERK12} * P70S6K * pERK12 + k_{P70S6K_pmTOR} * P70S6K * pmTOR - \\
&- k_{pP70S6K} * pP70S6K \\
J\dot{N}K &= -k_{JNK_pMKK47} * JNK * pMKK47 + k_{pJNK} * pJNK \\
pJ\dot{N}K &= k_{JNK_pMKK47} * JNK * pMKK47 - k_{pJNK} * pJNK \\
cJ\dot{U}N &= -k_{cJUN_pJNK} * cJUN * pJNK + k_{pcJUN} * pcJUN \\
pcJ\dot{U}N &= k_{cJUN_pJNK} * cJUN * pJNK - k_{pcJUN} * pcJUN \\
BCL\dot{X}L &= k_{BCLXL_pp38} * BCLXL * pp38 - k_{BCLXL_pJNK} * BCLXL * pJNK \\
B\dot{A}X &= k_{BAX_pp38} * BAX * pp38 - k_{BAX_pJNK} * BAX * pJNK - k_{BAX} * BAX \\
I\dot{K}K &= -k_{IKK_pMKK47} * IKK * pMKK47 - k_{IKK_pAKT} * IKK * pAKT + k_{pIKK} * pIKK \\
pI\dot{K}K &= k_{IKK_pMKK47} * IKK * pMKK47 + k_{IKK_pAKT} * IKK * pAKT - k_{pIKK} * pIKK \\
NF\dot{k}B &= -k_{NFkB_pIKK} * NFkB * pIKK + k_{pNFkB} * pNFkB \\
pNF\dot{k}B &= k_{NFkB_pIKK} * NFkB * pIKK - k_{pNFkB} * pNFkB \\
PAR\dot{P} &= -k_{PARP_pcJUN} * PARP * pcJUN - k_{PARP_BAX} * PARP * BAX + \\
&+ k_{cPARP_BCLXL} * cPARP * BCLXL + k_{cPARP_pNFkB} * cPARP * pNFkB \\
cPAR\dot{P} &= k_{PARP_pcJUN} * PARP * pcJUN + k_{PARP_BAX} * PARP * BAX - \\
&- k_{cPARP_BCLXL} * cPARP * BCLXL - k_{cPARP_pNFkB} * cPARP * pNFkB
\end{aligned}$$

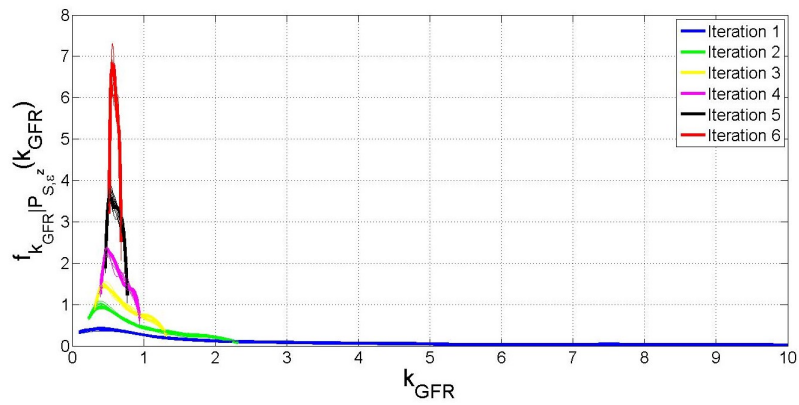


Figure S23: Model M3-CRC: conditional pdfs of the k_{GFR} parameter.

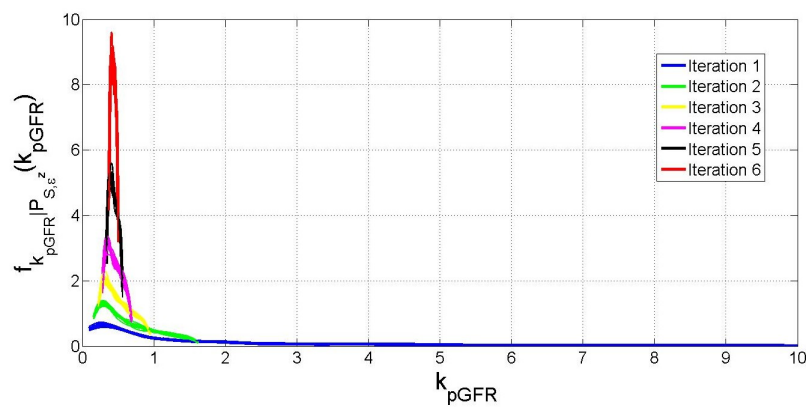


Figure S24: Model M3-CRC: conditional pdfs of the k_{pGFR} parameter.

Iteration (z)	Time (min)
1	110
2	80
3	70
4	60
5	60
6	60

Table S15. Model M3-CRC: computational time for performing each iteration of CRC.

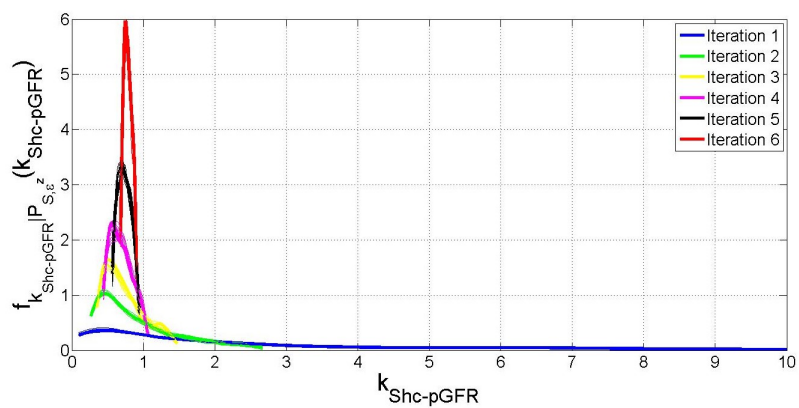


Figure S25: Model M3-CRC: conditional pdfs of the $k_{Shc-pGFR}$ parameter.

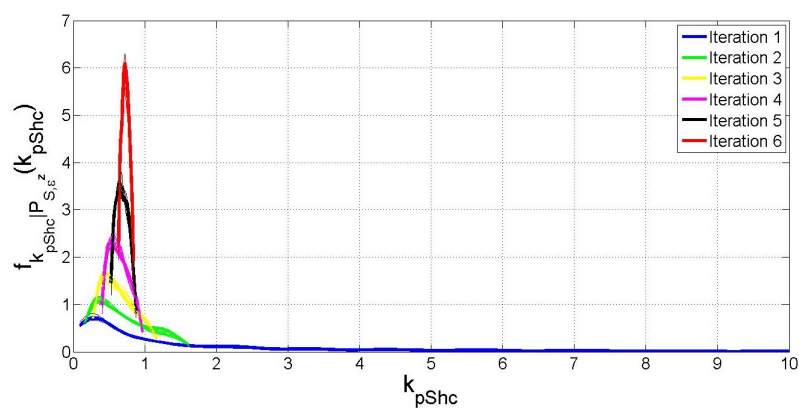


Figure S26: Model M3-CRC: conditional pdfs of the k_{pShc} parameter.

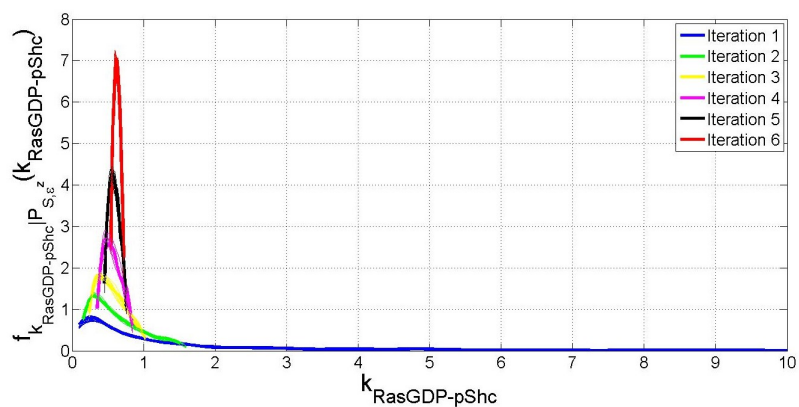


Figure S27: Model M3-CRC: conditional pdfs of the $k_{RasGDP-pShc}$ parameter.

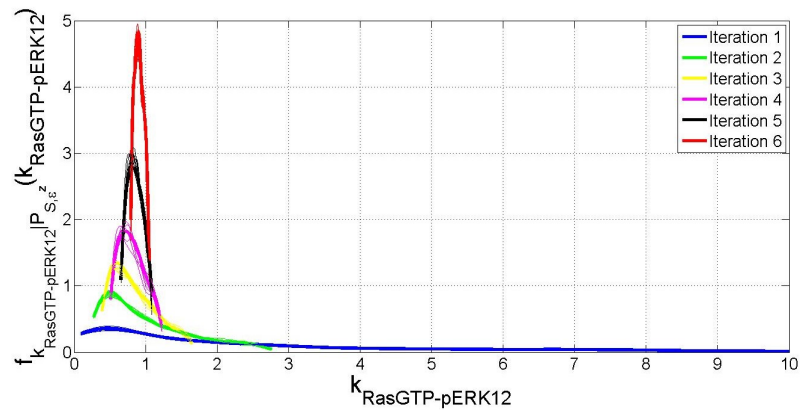


Figure S28: Model M3-CRC: conditional pdfs of the $k_{RasGTP-pERK12}$ parameter.

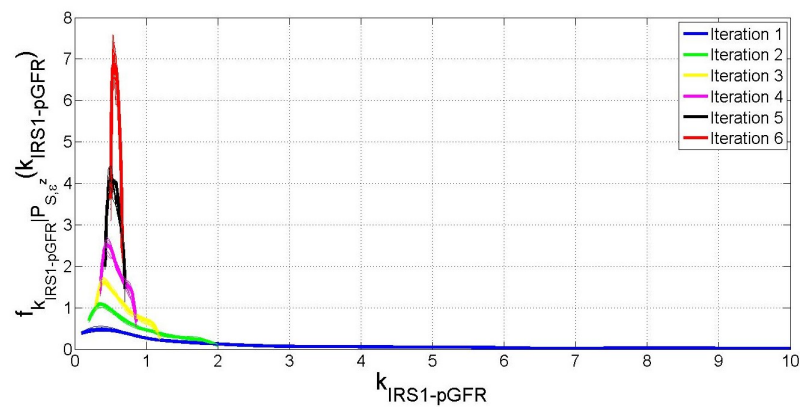


Figure S29: Model M3-CRC: conditional pdfs of the $k_{IRS1-pGFR}$ parameter.

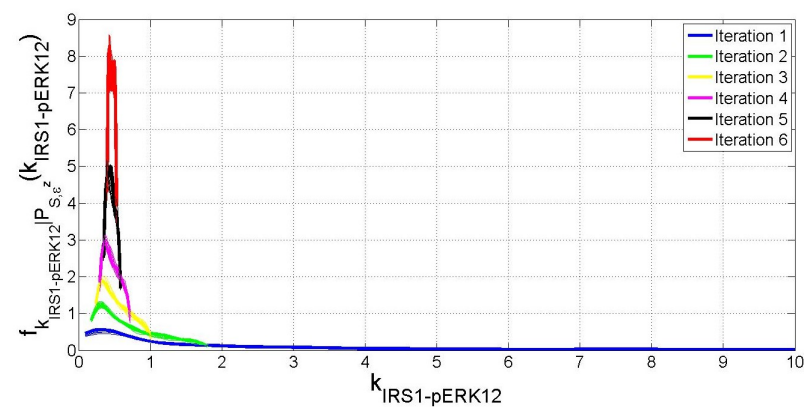


Figure S30: Model M3-CRC: conditional pdfs of the $k_{pIRS1-pERK12}$ parameter.

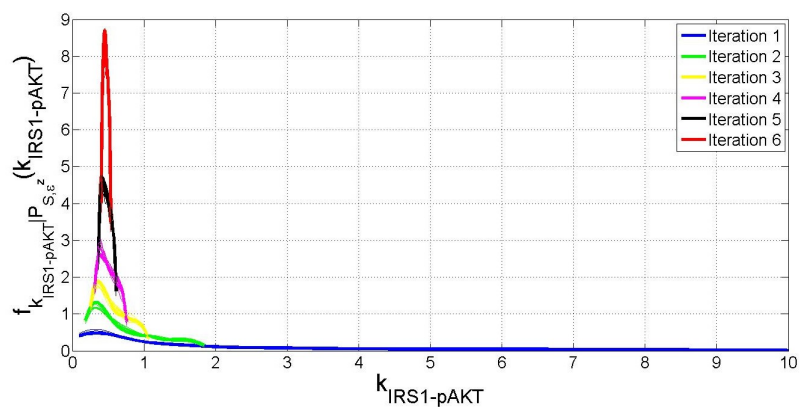


Figure S31: Model M3-CRC: conditional pdfs of the $k_{pIRS1-pAKT}$ parameter.

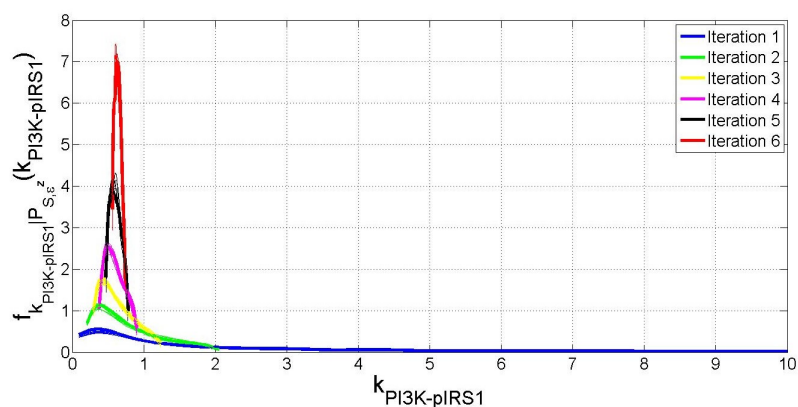


Figure S32: Model M3-CRC: conditional pdfs of the $k_{pPI3K-pIRS1}$ parameter.

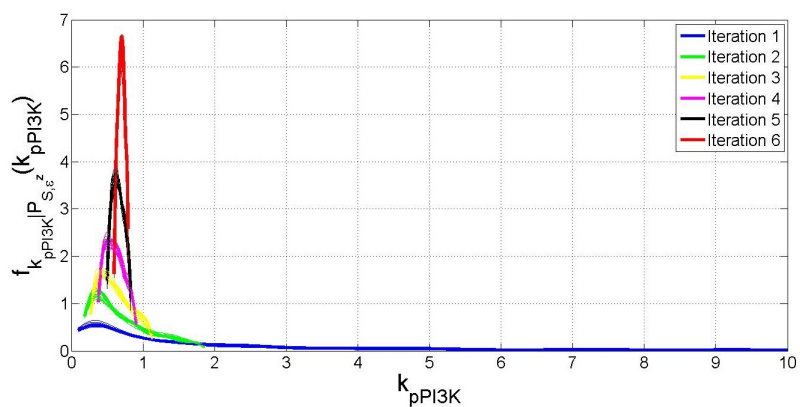


Figure S33: Model M3-CRC: conditional pdfs of the k_{pPI3K} parameter.

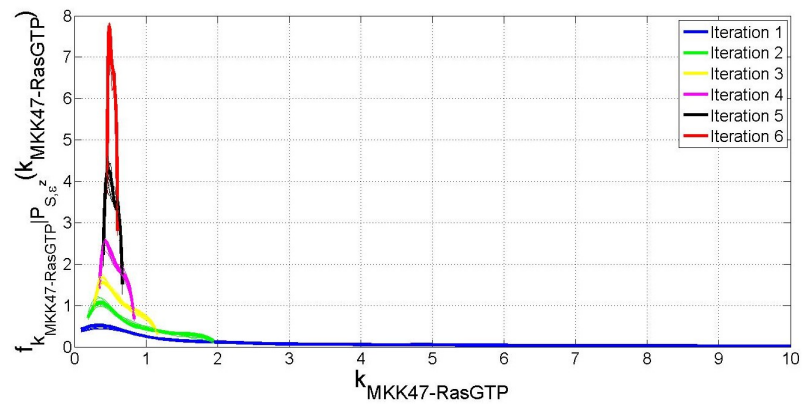


Figure S34: Model M3-CRC: conditional pdfs of the $k_{MKK47-RasGTP}$ parameter.

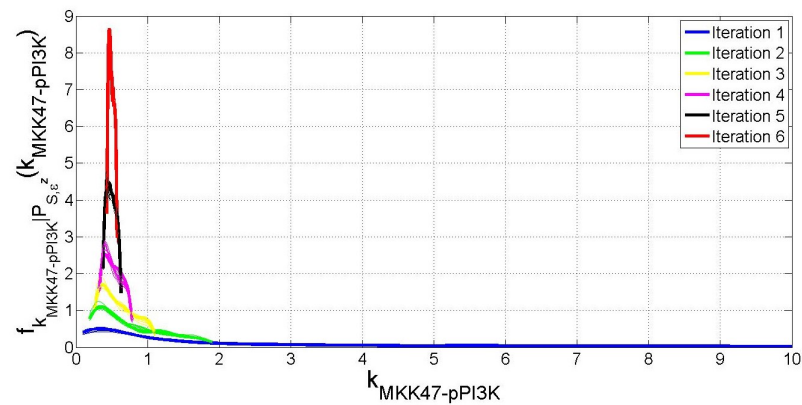


Figure S35: Model M3-CRC: conditional pdfs of the $k_{MKK47-pPI3K}$ parameter.

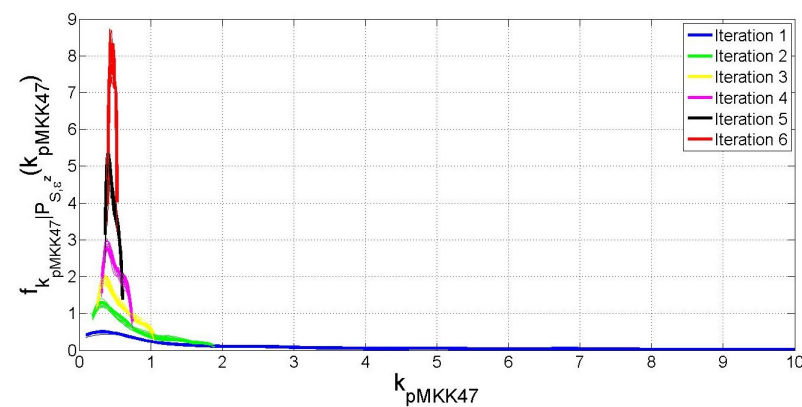


Figure S36: Model M3-CRC: conditional pdfs of the k_{pMKK47} parameter.

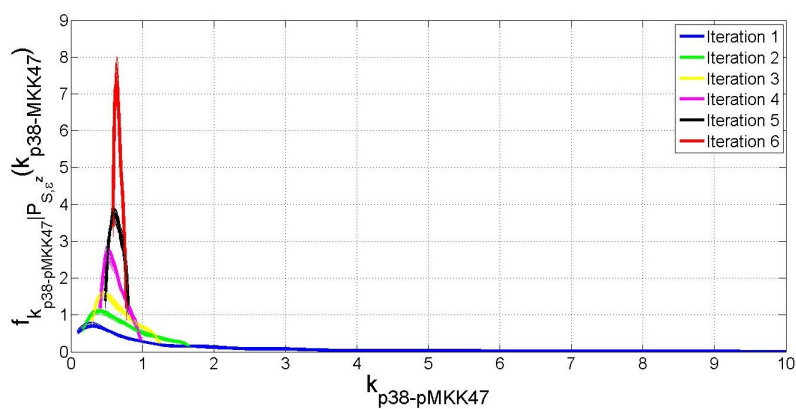


Figure S37: Model M3-CRC: conditional pdfs of the $k_{p38-pMKK47}$ parameter.

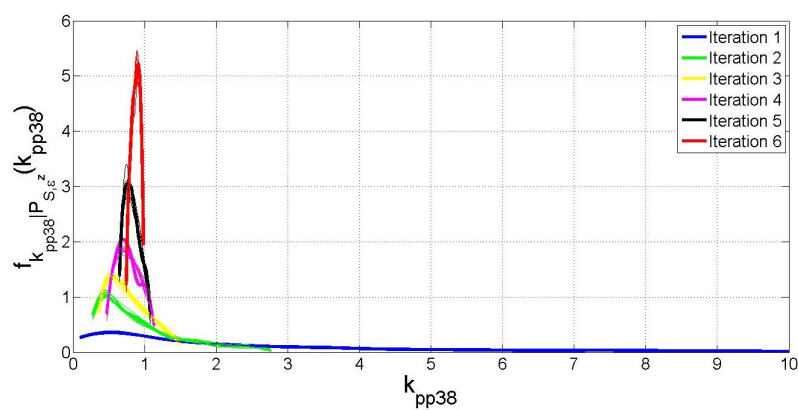


Figure S38: Model M3-CRC: conditional pdfs of the k_{pp38} parameter.

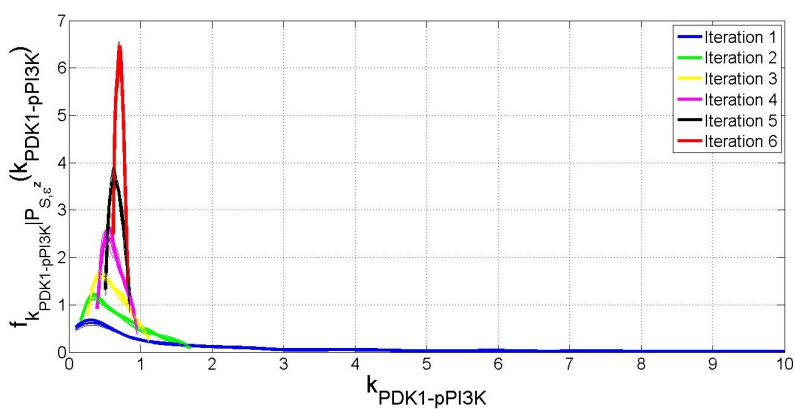


Figure S39: Model M3-CRC: conditional pdfs of the $k_{PDK1-pPI3K}$ parameter.

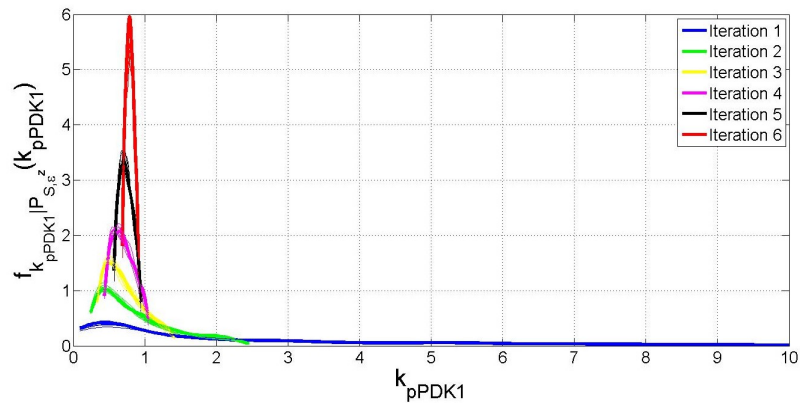


Figure S40: Model M3-CRC: conditional pdfs of the k_{pPDK1} parameter.

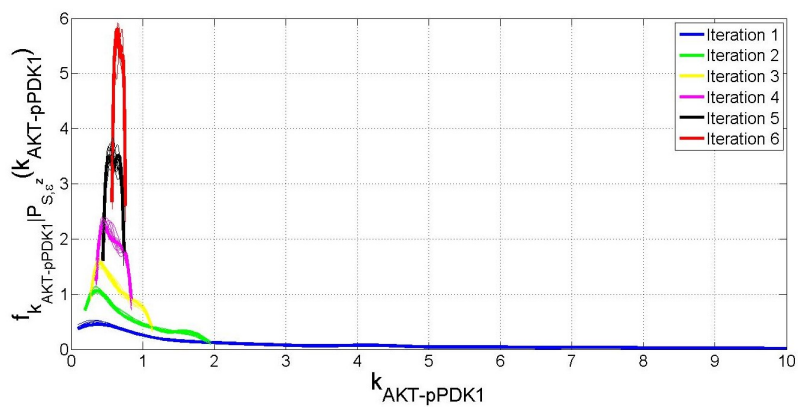


Figure S41: Model M3-CRC: conditional pdfs of the $k_{AKT-pPDK1}$ parameter.

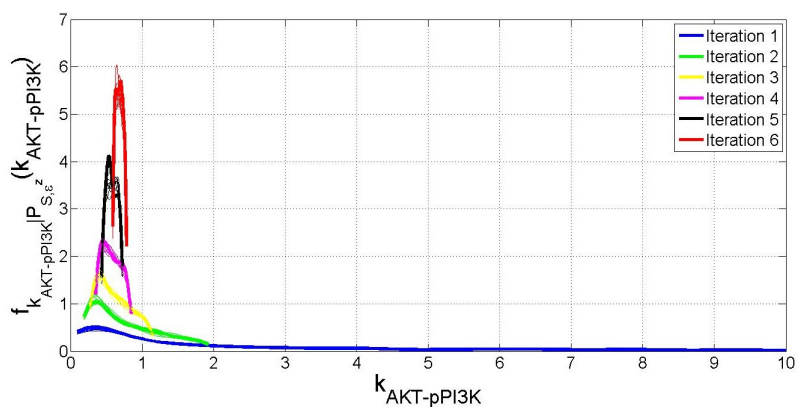


Figure S42: Model M3-CRC: conditional pdfs of the $k_{AKT-pPI3K}$ parameter.

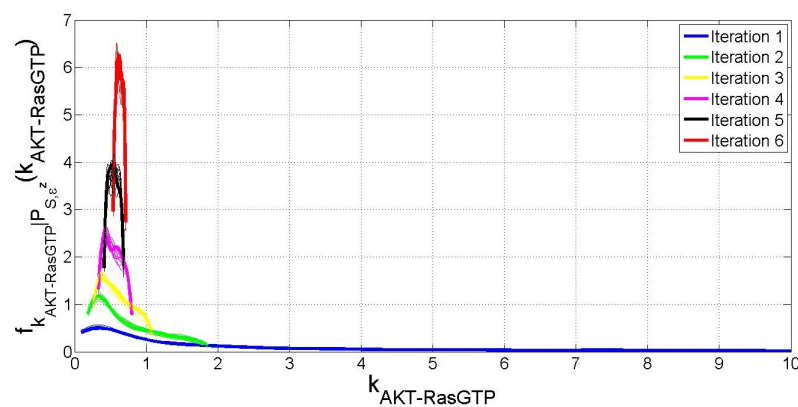


Figure S43: Model M3-CRC: conditional pdfs of the $k_{AKT-RasGTP}$ parameter.

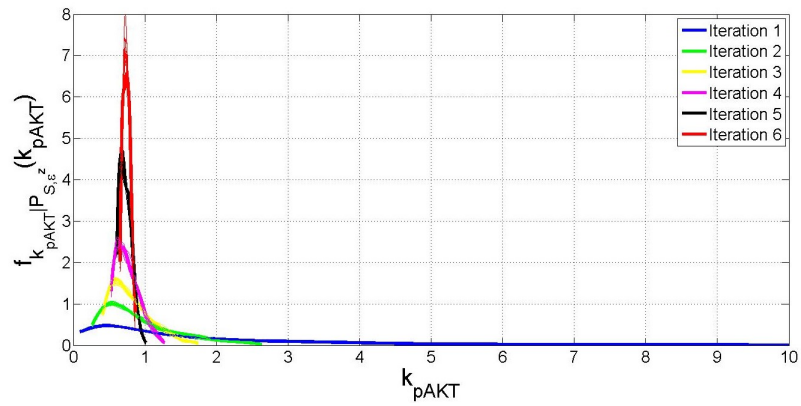


Figure S44: Model M3-CRC: conditional pdfs of the k_{pAKT} parameter.

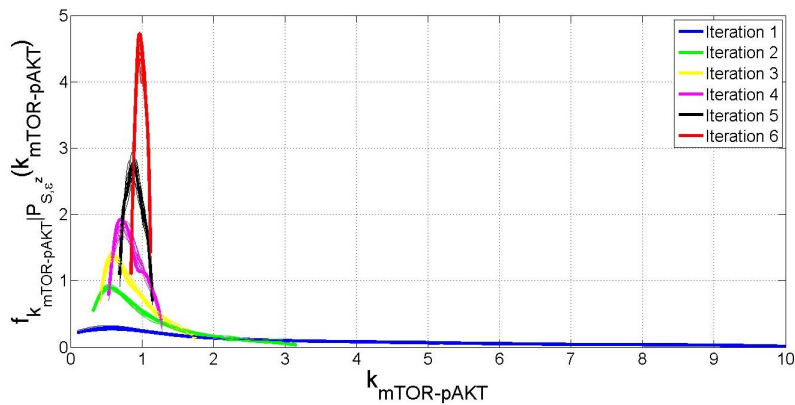


Figure S45: Model M3-CRC: conditional pdfs of the $k_{mTOR-pAKT}$ parameter.

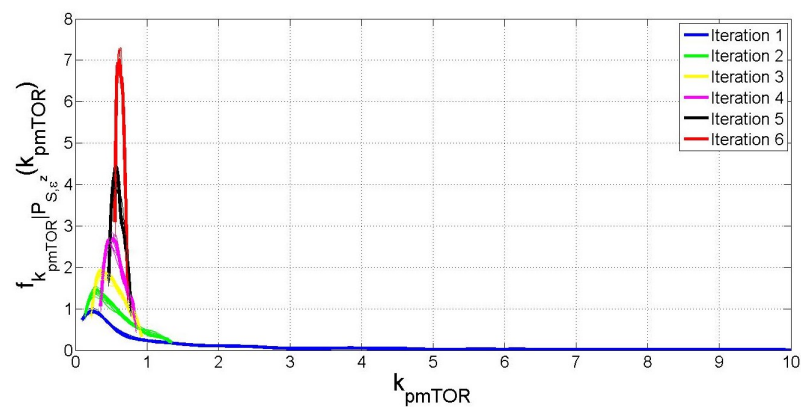


Figure S46: Model M3-CRC: conditional pdfs of the k_{pmTOR} parameter.

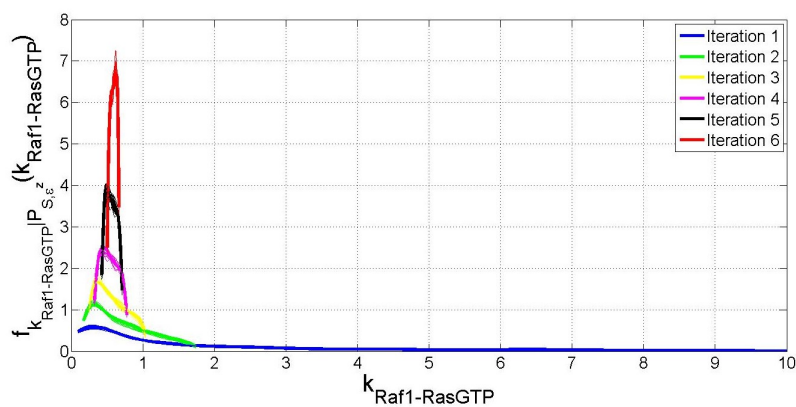


Figure S47: Model M3-CRC: conditional pdfs of the $k_{Raf1-RasGTP}$ parameter.

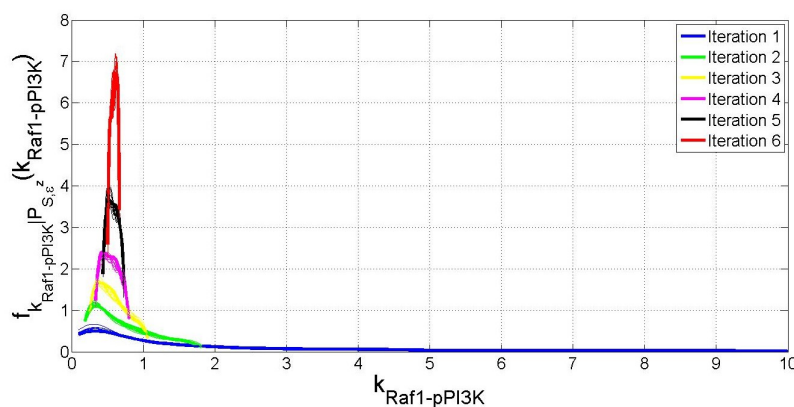


Figure S48: Model M3-CRC: conditional pdfs of the $k_{Raf1-pI3K}$ parameter.

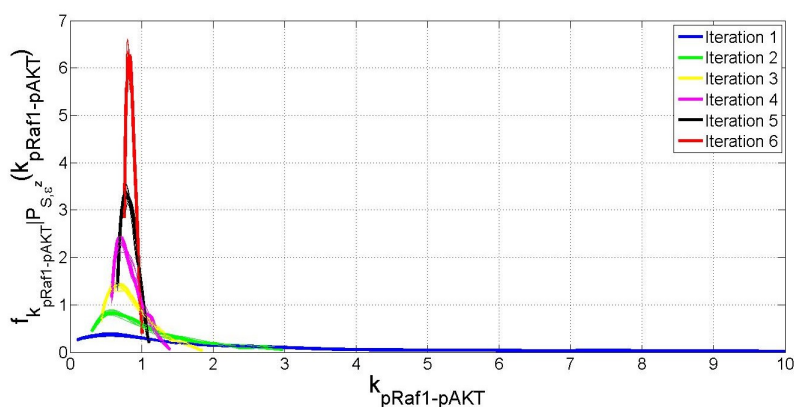


Figure S49: Model M3-CRC: conditional pdfs of the $k_{pRaf1-pAKT}$ parameter.

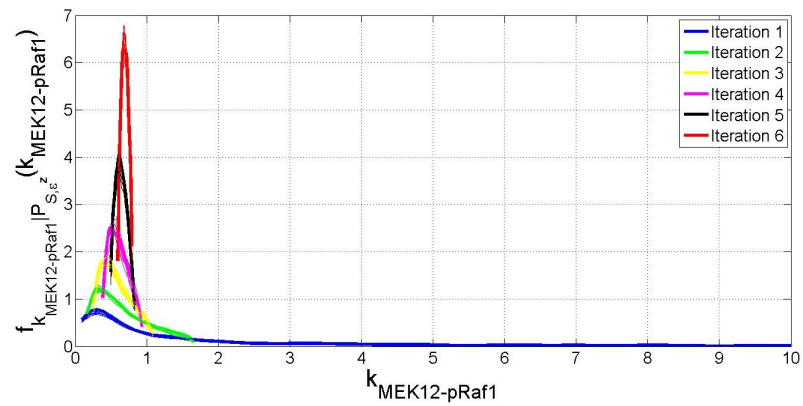


Figure S50: Model M3-CRC: conditional pdfs of the $k_{MEK12-pRaf1}$ parameter.

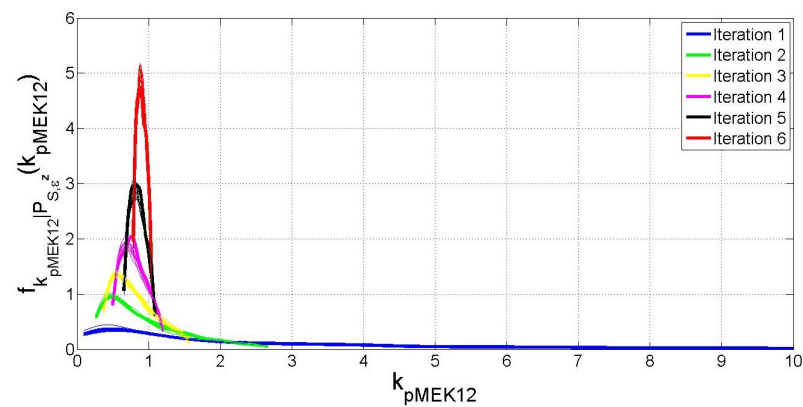


Figure S51: Model M3-CRC: conditional pdfs of the k_{pMEK12} parameter.

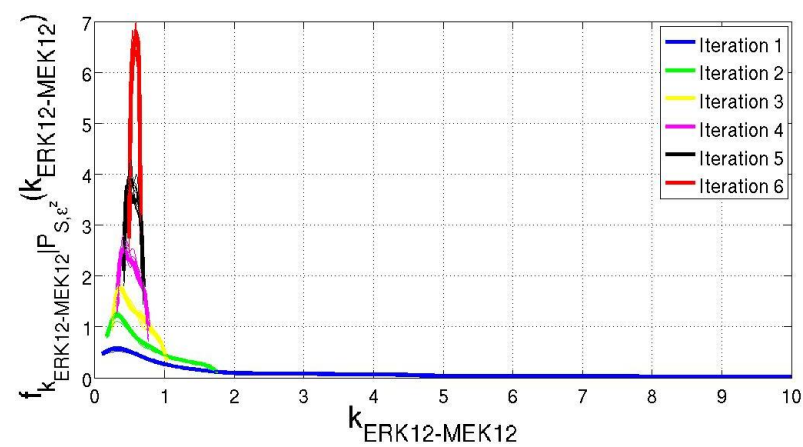


Figure S52: Model M3-CRC: conditional pdfs of the $k_{ERK12-MEK12}$ parameter.

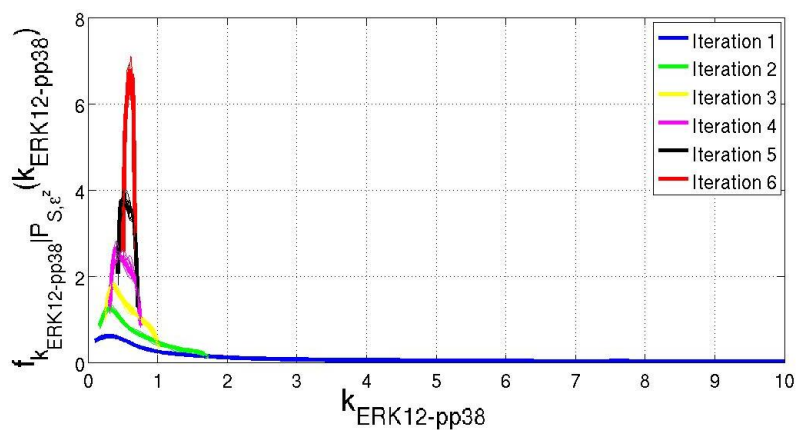


Figure S53: Model M3-CRC: conditional pdfs of the $k_{ERK12-pp38}$ parameter.

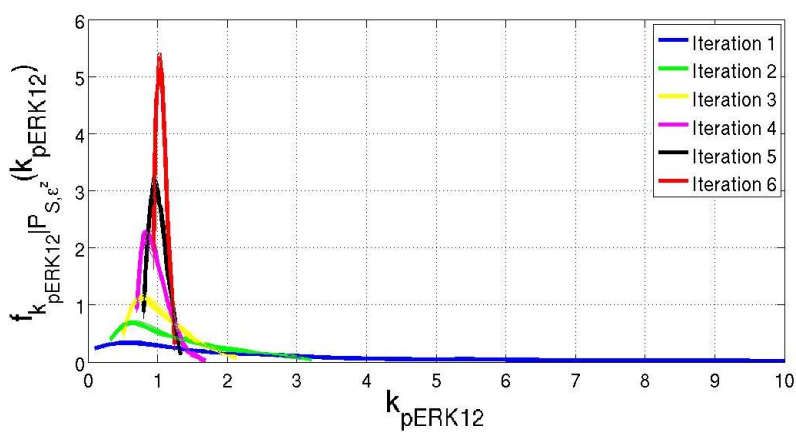


Figure S54: Model M3-CRC: conditional pdfs of the k_{pERK12} parameter.

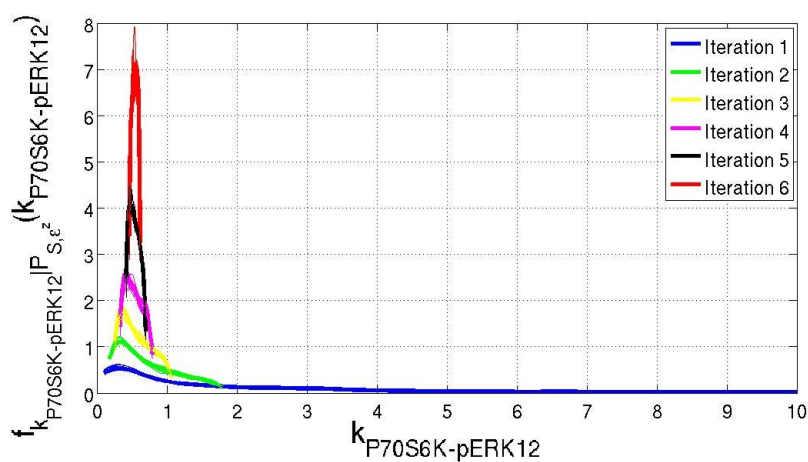


Figure S55: Model M3-CRC: conditional pdfs of the $k_{P70S6K-pERK12}$ parameter.

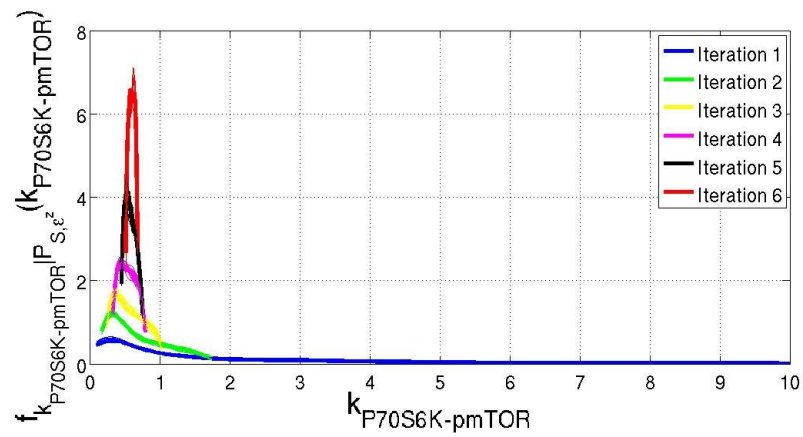


Figure S56: Model M3-CRC: conditional pdfs of the $k_{P70S6K-pmTOR}$ parameter.

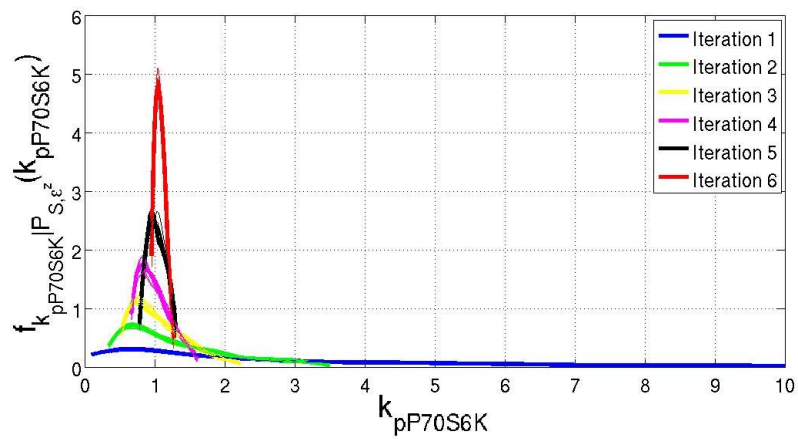


Figure S57: Model M3-CRC: conditional pdfs of the $k_{pP70S6K}$ parameter.

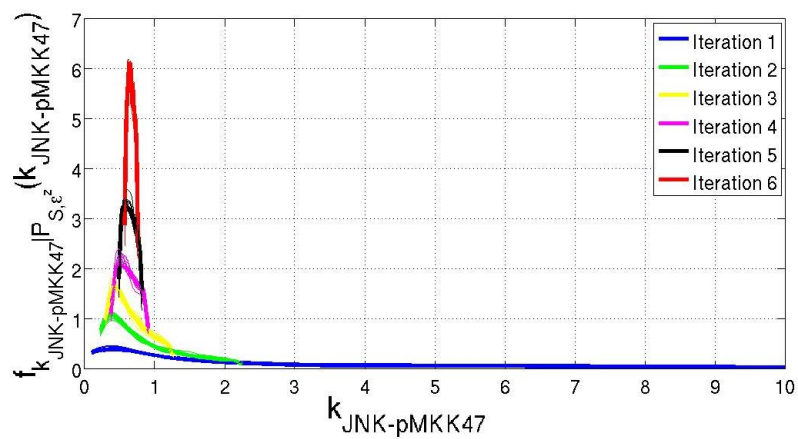


Figure S58: Model M3-CRC: conditional pdfs of the $k_{JNK-pMKK47}$ parameter.

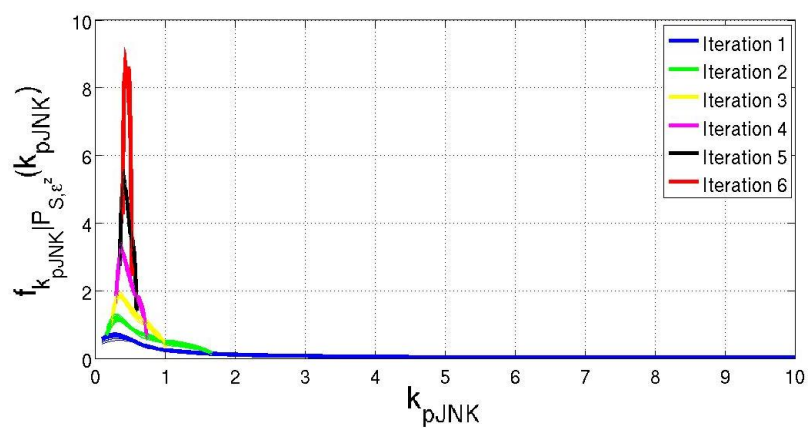


Figure S59: Model M3-CRC: conditional pdfs of the k_{pJNK} parameter.

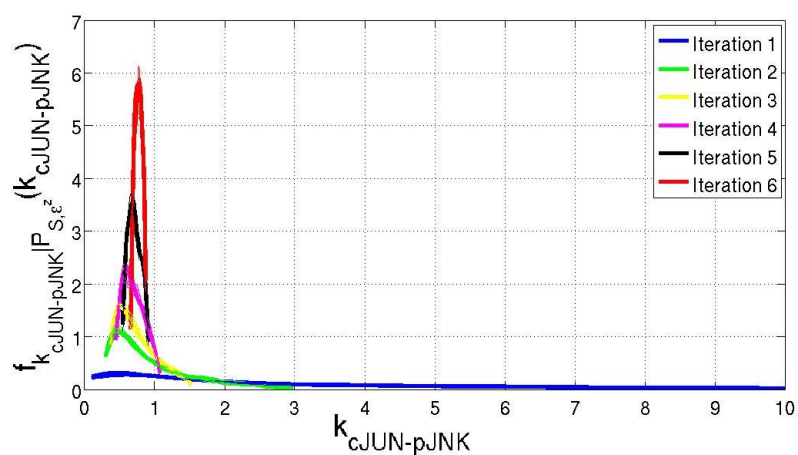


Figure S60: Model M3-CRC: conditional pdfs of the $k_{cJUN-pJNK}$ parameter.

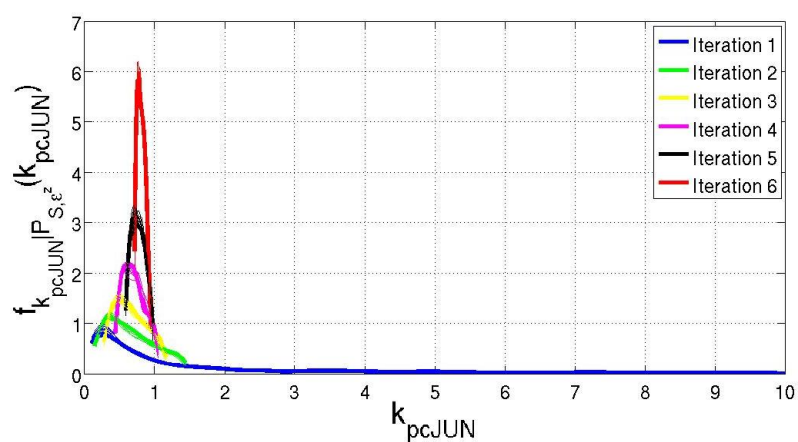


Figure S61: Model M3-CRC: conditional pdfs of the k_{pcJUN} parameter.

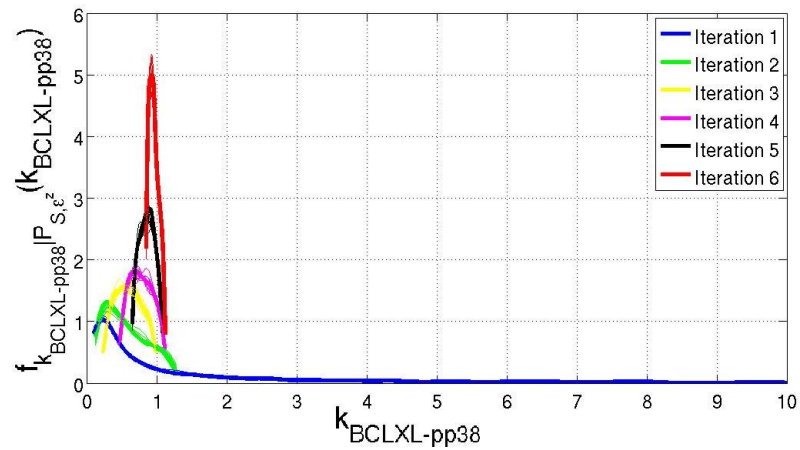


Figure S62: Model M3-CRC: conditional pdfs of the $k_{BCLXL-pp38}$ parameter.

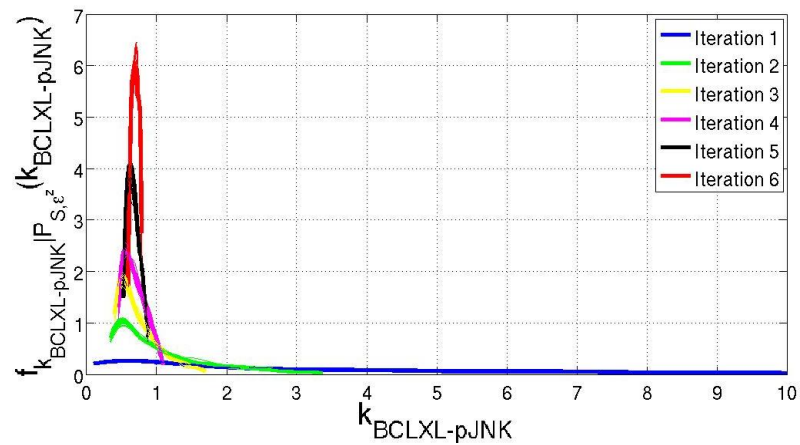


Figure S63: Model M3-CRC: conditional pdfs of the $k_{BCLXL-pJNK}$ parameter.

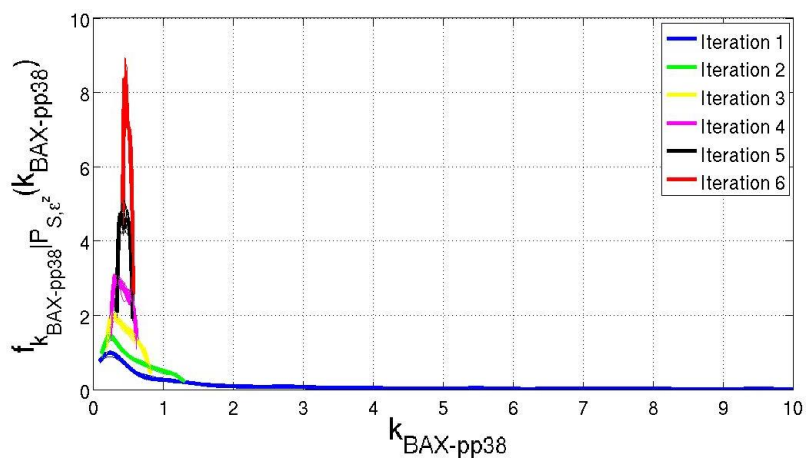


Figure S64: Model M3-CRC: conditional pdfs of the $k_{BAX-pp38}$ parameter.

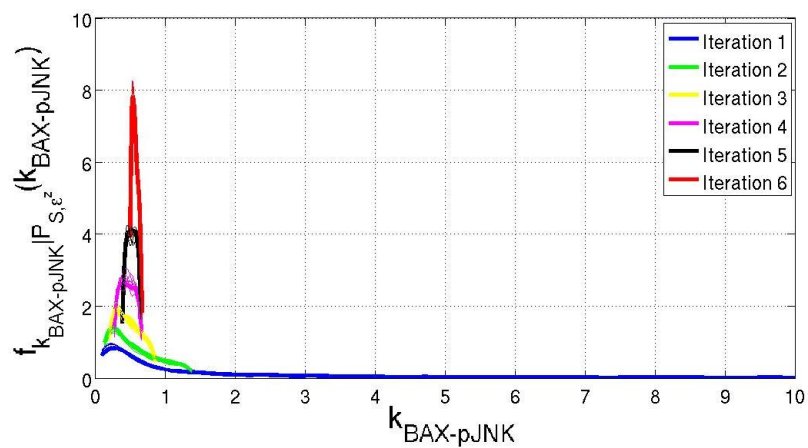


Figure S65: Model M3-CRC: conditional pdfs of the $k_{BAX-pJNK}$ parameter.

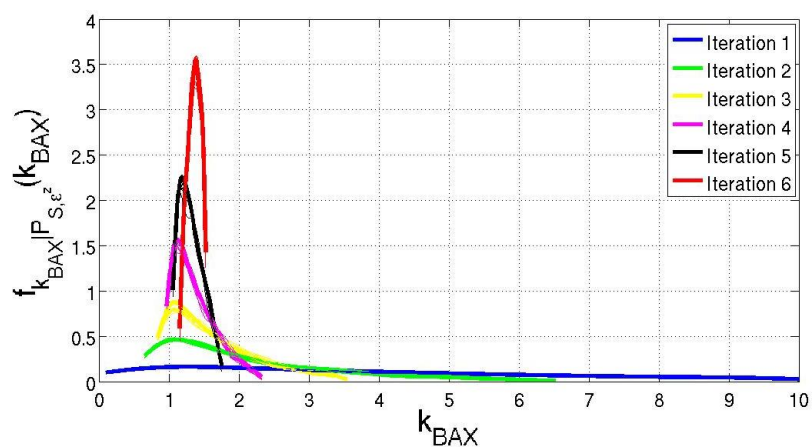


Figure S66: Model M3-CRC: conditional pdfs of the k_{BAX} parameter.

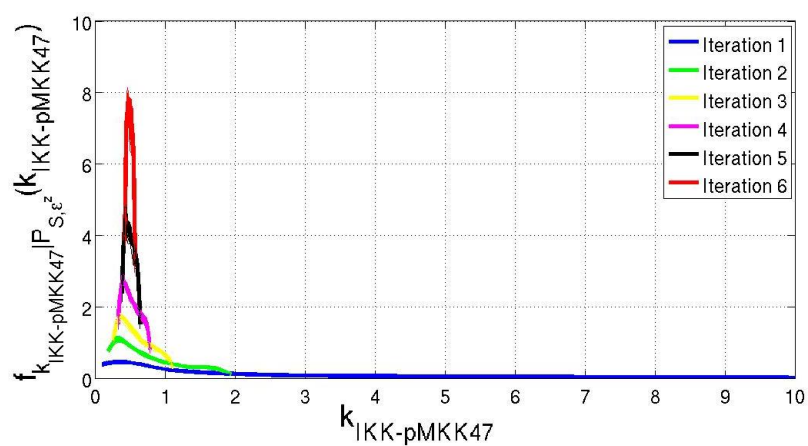


Figure S67: Model M3-CRC: conditional pdfs of the $k_{IKK-pMKK47}$ parameter.

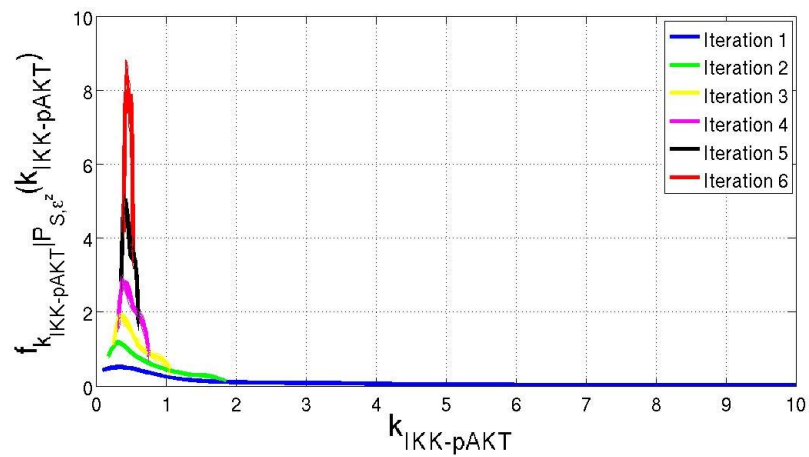


Figure S68: Model M3-CRC: conditional pdfs of the $k_{IKK-pAKT}$ parameter.

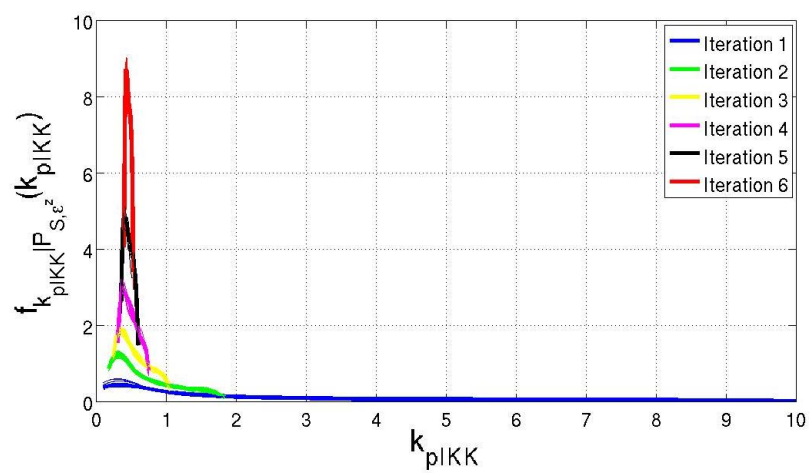


Figure S69: Model M3-CRC: conditional pdfs of the k_{pIKK} parameter.

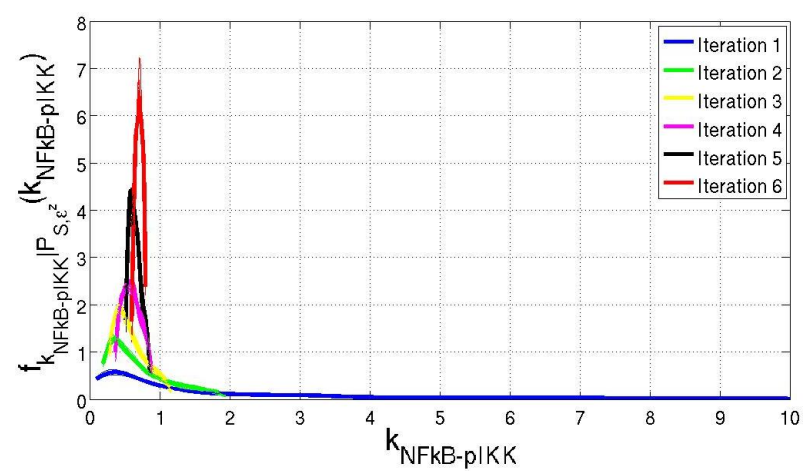


Figure S70: Model M3-CRC: conditional pdfs of the $k_{NFkB-pIKK}$ parameter.

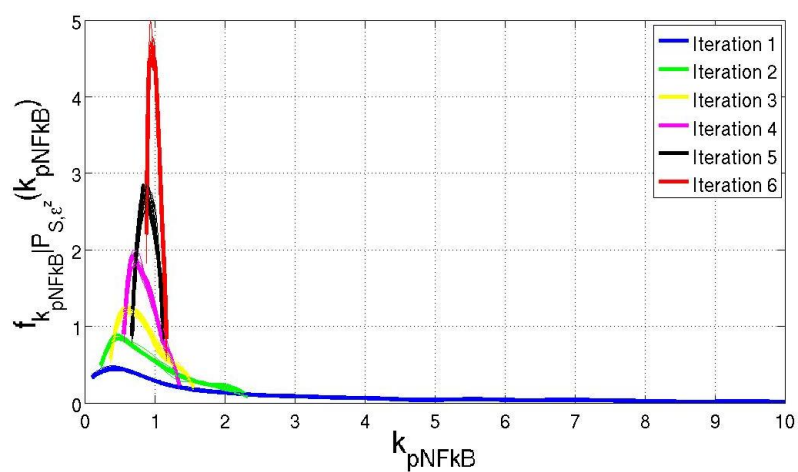


Figure S71: Model M3-CRC: conditional pdfs of the k_{pNFkB} parameter.

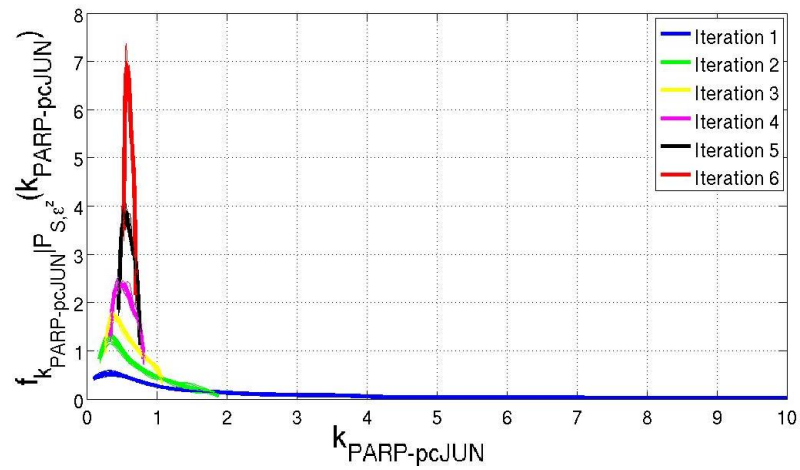


Figure S72: Model M3-CRC: conditional pdfs of the $k_{PARP-pcJUN}$ parameter.

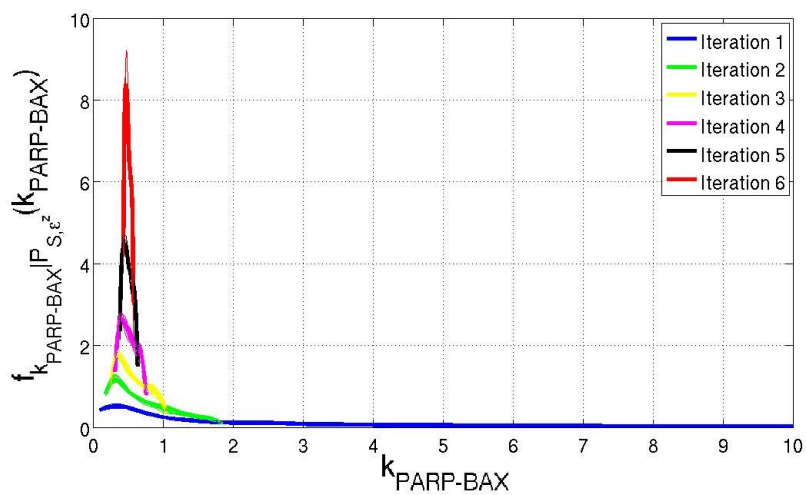


Figure S73: Model M3-CRC: conditional pdfs of the $k_{PARP-BAX}$ parameter.

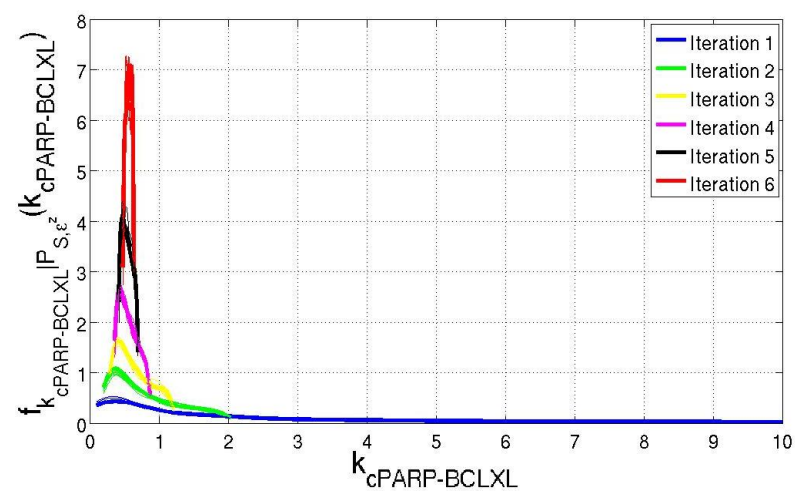


Figure S74: Model M3-CRC: conditional pdfs of the $k_{cPARP-BCLXL}$ parameter.

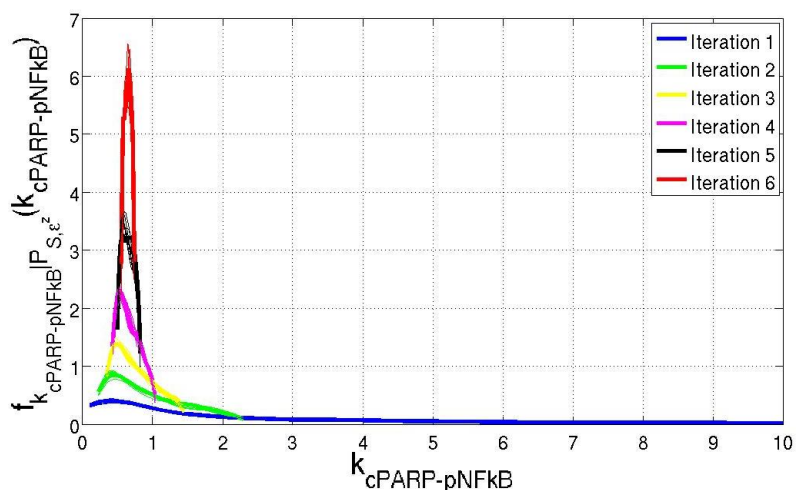


Figure S75: Model M3-CRC: conditional pdfs of the $k_{cPARP-pNFkB}$ parameter.

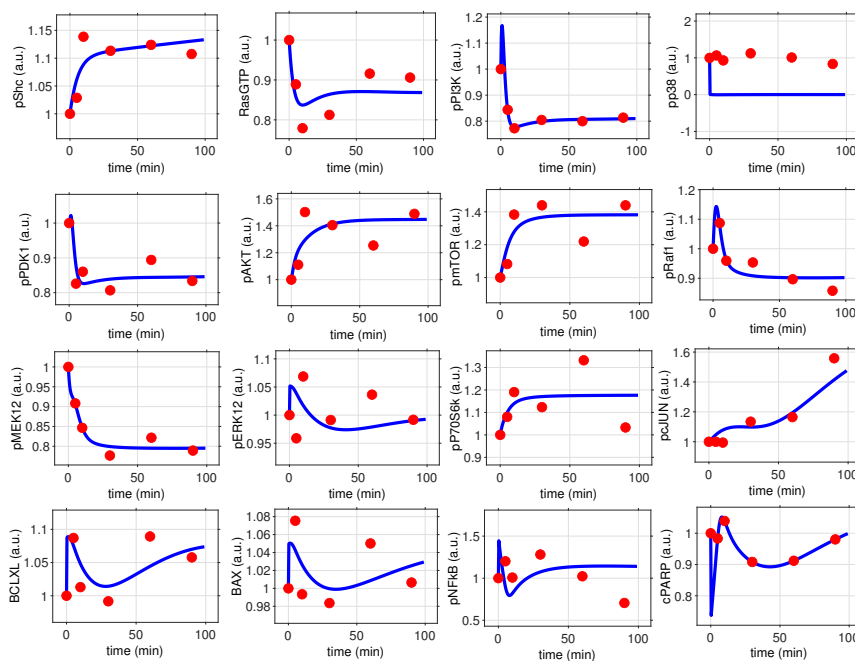


Figure S76: Model M3-PL: simulated output variables (blue lines) using best fit parameters returned by *lsqnonlin* in D2D software, in comparison with RPPA data (red dots).

Parameter name	Iteration 1		
	Mean	Mode	Variance
k_{GFR}	2.6428	0.4222	8.1891
k_{pGFR}	2.0697	0.2948	8.1891
$k_{Shc.pGFR}$	2.5742	0.4850	8.1891
k_{pShc}	1.8307	0.2938	8.1891
$k_{RasGDP.pShc}$	1.7006	0.2893	8.1891
$k_{RasGTP.pERK12}$	2.6164	0.5023	8.1891
$k_{IRS1.pGFR}$	2.4432	0.3646	8.1891
$k_{pIRS1.pERK12}$	2.3077	0.3273	8.1891
$k_{pIRS1.pAKT}$	2.3970	0.3356	8.1891
$k_{PI3K.pIRS1}$	2.2818	0.3732	8.1891
k_{pPI3K}	2.1015	0.3375	8.1891
$k_{MKK47.RasGTP}$	2.4564	0.3533	8.1891
$k_{MKK47.pPI3K}$	2.4854	0.3456	8.1891
k_{pMKK47}	2.3878	0.3444	8.1891
$k_{p38.pMKK47}$	1.7639	0.3035	8.1891
k_{pp38}	2.5979	0.5035	8.1891
$k_{PDK1.pPI3K}$	1.9777	0.3087	8.1891
k_{pPDK1}	2.4943	0.4460	8.1891
$k_{AKT.pPDK1}$	2.4556	0.3542	8.1891
$k_{AKT.pPI3K}$	2.4602	0.3506	8.1891
$k_{AKT.RasGTP}$	2.3608	0.3383	8.1891
k_{pAKT}	2.0209	0.4781	8.1891
$k_{mTOR.pAKT}$	2.9470	0.5752	8.1891
k_{pmTOR}	1.5913	0.2450	8.1891
$k_{Raf1.RasGTP}$	2.1298	0.3174	8.1891
$k_{Raf1.pPI3K}$	2.2175	0.3306	8.1891
$k_{pRaf1.pAKT}$	2.6456	0.5410	8.1891
$k_{MEK12.pRaf1}$	1.7806	0.3008	8.1891
k_{pMEK12}	2.5954	0.4842	8.1891
$k_{ERK12.MEK12}$	2.1513	0.3192	8.1891
$k_{ERK12.pp38}$	2.1174	0.3138	8.1891
k_{pERK12}	2.6293	0.5823	8.1891
$k_{P70S6K.pERK12}$	2.1589	0.3245	8.1891
$k_{P70S6K.pmTOR}$	2.0891	0.3159	8.1891
$k_{pP70S6K}$	2.6831	0.6373	8.1891
$k_{JNK.pMKK47}$	2.5811	0.4082	8.1891
k_{pJNK}	2.0664	0.3026	8.1891
$k_{cJUN.pJNK}$	2.8219	0.5409	8.1891
k_{pcJUN}	1.6580	0.2624	8.1891
$k_{BCLXL.pp38}$	1.4953	0.2318	8.1891
$k_{BCLXL.pJNK}$	3.0574	0.6130	8.1891
$k_{BAX.pp38}$	1.4828	0.2371	8.1891
$k_{BAX.pJNK}$	1.6553	0.2510	8.1891
k_{BAX}	3.8068	1.1849	8.1891
$k_{IKK.pMKK47}$	2.4871	0.3540	8.1891
$k_{IKK.pAKT}$	2.4250	0.3367	8.1891
k_{pIKK}	2.3950	0.3349	8.1891
$k_{NFkB.pIKK}$	2.0127	0.3531	8.1891
k_{pNFkB}	2.2628	0.4230	8.1891
$k_{PARP.pcJUN}$	2.1648	0.3428	8.1891
$k_{PARP.BAX}$	2.3078	0.3375	8.1891
$k_{cPARP.BCLXL}$	2.4996	0.3720	8.1891
$k_{cPARP.pNFkB}$	2.5531	0.4158	8.1891

Table S16. Model M3-CRC: summary statistics of parameter pdfs in iteration 1 of CRC algorithm.

Protein name	Iteration 1	
	Mean	Variance
pShc	0.4518	0.0560
RasGTP	0.5741	0.0835
pPI3K	0.5875	0.0840
pp38	0.4935	0.0591
pPDK1	0.5841	0.0774
pAKT	0.3139	0.0315
pmTOR	0.3840	0.0504
pRaf1	0.5019	0.0670
pMEK12	0.5829	0.0986
pERK12	0.4661	0.0565
pP70S6K	0.3911	0.0367
pcJUN	0.4571	0.0511
BCLXL	5.8866	356.7352
BAX	6.3346	217.1105
pNFkB	0.4851	0.0496
cPARP	0.5472	0.0660

Table S17. Model M3-CRC: summary statistics of distance function pdfs in iteration 1 of CRC algorithm.

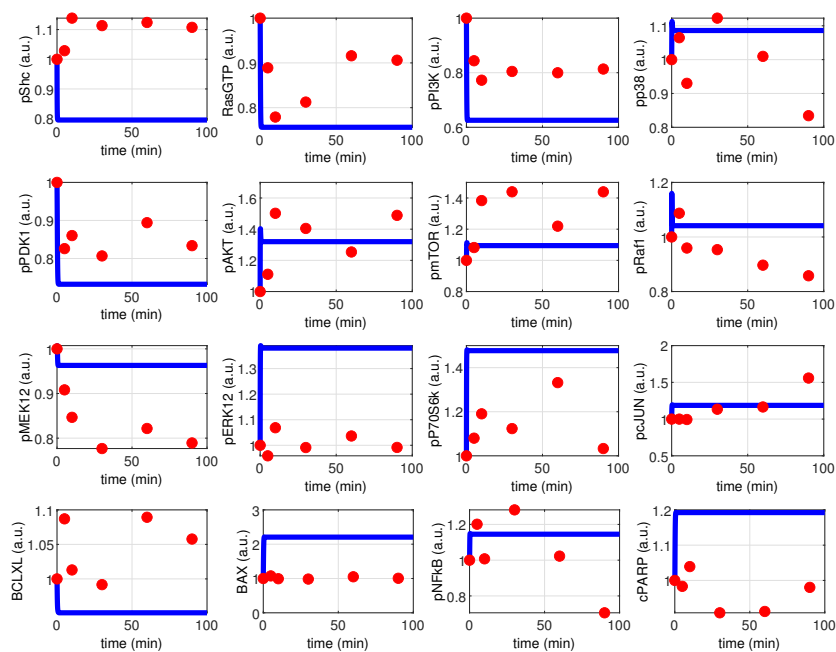


Figure S77: Model M3-ABC SMC: simulated output variables (blue lines) using the median parameter vector returned by the standard ABC-SMC in the 4 – *th* iteration, in comparison with the experimental dataset (red dots).

Parameter name	Iteration 2		
	Mean	Mode	Variance
k_{GFR}	0.9400	0.4066	0.3651
k_{pGFR}	0.6730	0.2915	0.1779
$k_{Shc.pGFR}$	0.9480	0.4528	0.4816
k_{pShc}	0.7122	0.3578	0.1767
$k_{RasGDP.pShc}$	0.6454	0.3139	0.1713
$k_{RasGTP.pERK12}$	1.0606	0.5070	0.5165
$k_{IRS1.pGFR}$	0.8248	0.3673	0.2721
$k_{pIRS1.pERK12}$	0.7309	0.3120	0.2193
$k_{pIRS1.pAKT}$	0.7576	0.3268	0.2306
$k_{PI3K.pIRS1}$	0.8138	0.3816	0.2852
k_{pPI3K}	0.7423	0.3480	0.2332
$k_{MKK47.RasGTP}$	0.8158	0.3576	0.2555
$k_{MKK47.pPI3K}$	0.7981	0.3388	0.2446
k_{pMKK47}	0.7479	0.3222	0.2429
$k_{p38.pMKK47}$	0.7295	0.3825	0.1886
k_{pp38}	0.9674	0.4591	0.5189
$k_{PDK1.pPI3K}$	0.7105	0.3436	0.1951
k_{pPDK1}	0.9080	0.4357	0.4072
$k_{AKT.pPDK1}$	0.8172	0.3505	0.2569
$k_{AKT.pPI3K}$	0.8064	0.3542	0.2516
$k_{AKT.RasGTP}$	0.7703	0.3357	0.2343
k_{pAKT}	0.9379	0.5354	0.4680
$k_{mTOR.pAKT}$	1.1185	0.5393	0.6772
k_{pmTOR}	0.5768	0.2855	0.1229
$k_{Raf1.RasGTP}$	0.7369	0.3196	0.2062
$k_{Raf1.pPI3K}$	0.7552	0.3277	0.2238
$k_{pRaf1.pAKT}$	1.1049	0.5696	0.5993
$k_{MEK12.pRaf1}$	0.6846	0.3356	0.1853
k_{pMEK12}	0.9864	0.4811	0.4800
$k_{ERK12.MEK12}$	0.7237	0.3167	0.2086
$k_{ERK12.pp38}$	0.7009	0.3138	0.2015
k_{pERK12}	1.2731	0.6529	0.6941
$k_{P70S6K.pERK12}$	0.7503	0.3271	0.2156
$k_{P70S6K.pmTOR}$	0.7196	0.3180	0.2043
$k_{pP70S6K}$	1.3212	0.6863	0.8315
$k_{JNK.pMKK47}$	0.8994	0.3906	0.3411
k_{pJNK}	0.6966	0.3114	0.1875
$k_{cJUN.pJNK}$	0.9664	0.4668	0.5990
k_{pcJUN}	0.6670	0.3582	0.1410
$k_{BCLXL.pp38}$	0.5981	0.3037	0.1100
$k_{BCLXL.pJNK}$	1.1118	0.5225	0.7693
$k_{BAX.pp38}$	0.5718	0.2531	0.1151
$k_{BAX.pJNK}$	0.6005	0.2658	0.1289
k_{BAX}	2.1943	1.0903	2.8743
$k_{IKK.pMKK47}$	0.8084	0.3423	0.2565
$k_{IKK.pAKT}$	0.7630	0.3268	0.2321
k_{pIKK}	0.7581	0.3240	0.2296
$k_{NFkB.pIKK}$	0.7320	0.3555	0.2553
k_{pNFkB}	0.9606	0.4769	0.3664
$k_{PARP.pcJUN}$	0.7438	0.3329	0.2406
$k_{PARP.BAX}$	0.7523	0.3218	0.2332
$k_{cPARP.BCLXL}$	0.8593	0.3741	0.2827
$k_{cPARP.pNFkB}$	0.9754	0.4438	0.3540

Table S18. Model M3-CRC: summary statistics of parameter pdfs in iteration 2 of CRC algorithm.

Protein name	Iteration 2	
	Mean	Variance
pShc	0.2847	0.0282
RasGTP	0.3806	0.0538
pPI3K	0.3841	0.0594
pp38	0.3218	0.0342
pPDK1	0.3809	0.05
pAKT	0.2001	0.0136
pmTOR	0.2226	0.0128
pRaf1	0.3002	0.0332
pMEK12	0.3645	0.0483
pERK12	0.2811	0.0303
pP70S6K	0.2449	0.0205
pcJUN	0.2974	0.0199
BCLXL	0.6064	0.1093
BAX	0.5338	0.1219
pNfkb	0.3239	0.0241
cPARP	0.3220	0.0399

Table S19. Model M3-CRC: summary statistics of distance function pdfs in iteration 2 of CRC algorithm.

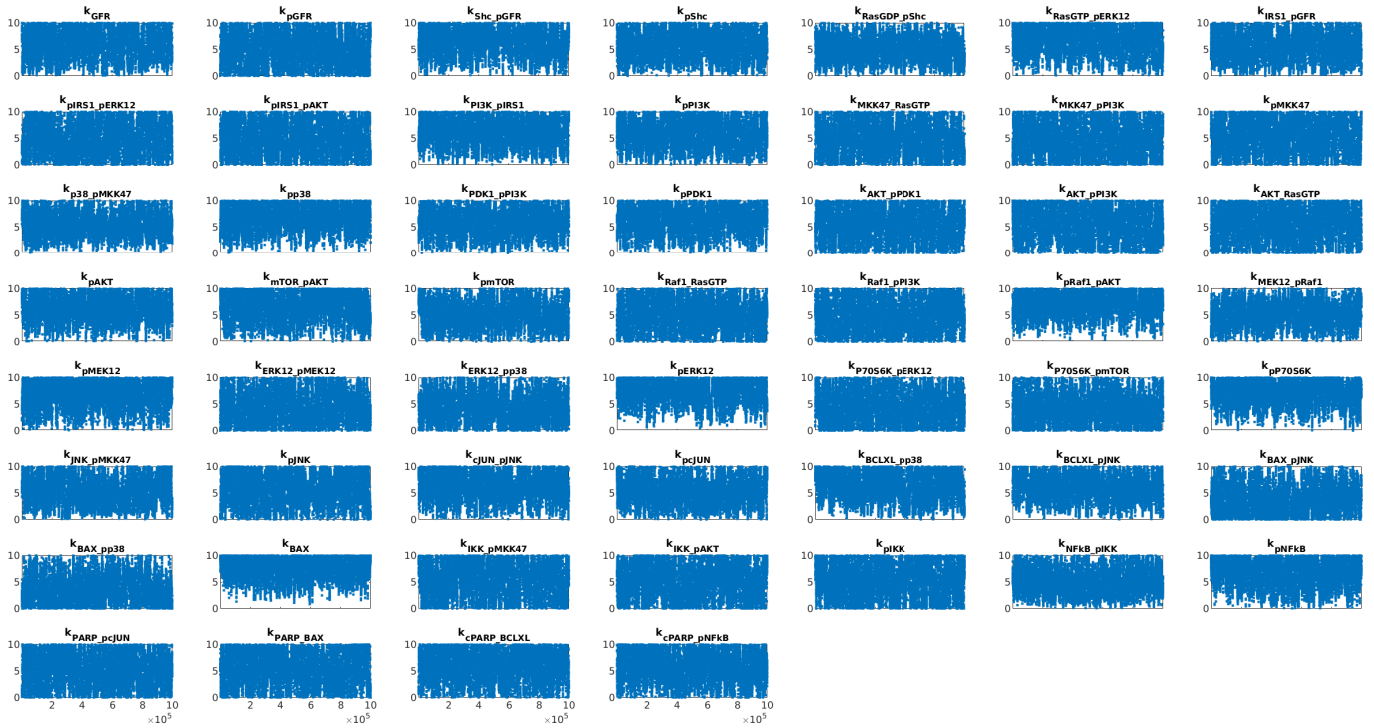


Figure S78: Model M3-DRAM: chains of model parameters computed by DRAM after six run using a lognormal prior. The initial error variance σ is set equal to 0.1 and the corresponding prior weight is set to 10.

Parameter name	Iteration 3		
	Mean	Mode	Variance
k_{GFR}	0.7173	0.4462	0.0846
k_{pGFR}	0.5167	0.3234	0.0435
$k_{Shc.pGFR}$	0.7539	0.5005	0.1049
k_{pShc}	0.6480	0.4553	0.0655
$k_{RasGDP.pShc}$	0.5620	0.3970	0.0504
$k_{RasGTP.pERK12}$	0.8594	0.5776	0.1316
$k_{IRS1.pGFR}$	0.6419	0.4042	0.0690
$k_{pIRS1.pERK12}$	0.5519	0.3376	0.0498
$k_{pIRS1.pAKT}$	0.5811	0.3575	0.0547
$k_{PI3K.pIRS1}$	0.6498	0.4255	0.0745
k_{pPI3K}	0.6177	0.4264	0.0620
$k_{MKK47.RasGTP}$	0.6367	0.3936	0.0655
$k_{MKK47.pPI3K}$	0.6041	0.3688	0.0588
k_{pMKK47}	0.5663	0.3505	0.0531
$k_{p38.pMKK47}$	0.6742	0.4633	0.0749
k_{pp38}	0.7870	0.5318	0.1079
$k_{PDK1.pPI3K}$	0.6154	0.4482	0.0604
k_{pPDK1}	0.7316	0.4947	0.0971
$k_{AKT.pPDK1}$	0.6363	0.3959	0.0629
$k_{AKT.pPI3K}$	0.6408	0.3983	0.0642
$k_{AKT.RasGTP}$	0.6091	0.3758	0.0577
k_{pAKT}	0.8243	0.5979	0.1467
$k_{mTOR.pAKT}$	0.8835	0.6035	0.1489
k_{pmTOR}	0.5252	0.4002	0.0417
$k_{Raf1.RasGTP}$	0.5820	0.3651	0.0523
$k_{Raf1.pPI3K}$	0.5921	0.3776	0.0550
$k_{pRaf1.pAKT}$	0.8853	0.6581	0.1661
$k_{MEK12.pRaf1}$	0.5910	0.4387	0.0577
k_{pMEK12}	0.8156	0.5632	0.1184
$k_{ERK12.MEK12}$	0.5718	0.3593	0.0513
$k_{ERK12.pp38}$	0.5635	0.3560	0.0504
k_{pERK12}	1.0647	0.7933	0.2182
$k_{P70S6K.pERK12}$	0.5939	0.3725	0.0547
$k_{P70S6K.pmTOR}$	0.5794	0.3748	0.0518
$k_{pP70S6K}$	1.0858	0.7552	0.2411
$k_{JNK.pMKK47}$	0.6770	0.4263	0.0781
k_{pJNK}	0.5542	0.3510	0.0496
$k_{cJUN.pJNK}$	0.7566	0.5045	0.1115
k_{pcJUN}	0.6630	0.4944	0.0657
$k_{BCLXL.pp38}$	0.6011	0.5268	0.0472
$k_{BCLXL.pJNK}$	0.7737	0.5144	0.1397
$k_{BAX.pp38}$	0.4713	0.2934	0.0328
$k_{BAX.pJNK}$	0.4926	0.3117	0.0362
k_{BAX}	1.6607	1.0950	0.6084
$k_{IKK.pMKK47}$	0.6080	0.3722	0.0600
$k_{IKK.pAKT}$	0.5761	0.3565	0.0547
k_{pIKK}	0.5713	0.3534	0.0537
$k_{NFkB.pIKK}$	0.5997	0.4189	0.0647
k_{pNFkB}	0.8499	0.6348	0.1164
$k_{PARP.pcJUN}$	0.5946	0.3830	0.0567
$k_{PARP.BAX}$	0.5766	0.3577	0.0530
$k_{cPARP.BCLXL}$	0.6595	0.4107	0.0716
$k_{cPARP.pNFkB}$	0.7713	0.4864	0.1008

Table S20. Model M3-CRC: summary statistics of parameter pdfs in iteration 3 of CRC algorithm.

Protein name	Iteration 3	
	Mean	Variance
pShc	0.19	0.0147
RasGTP	0.2628	0.0280
pPI3K	0.2656	0.0336
pp38	0.2150	0.0155
pPDK1	0.2565	0.0275
pAKT	0.1499	0.0058
pmTOR	0.1601	0.0056
pRaf1	0.2035	0.0155
pMEK12	0.2492	0.0256
pERK12	0.1881	0.0149
pP70S6K	0.1759	0.0106
pcJUN	0.2115	0.009
BCLXL	0.4484	0.0498
BAX	0.3834	0.0430
pNFkB	0.2394	0.0088
cPARP	0.2122	0.0194

Table S21. Model M3-CRC: summary statistics of distance functions pdfs in iteration 3 of CRC algorithm.

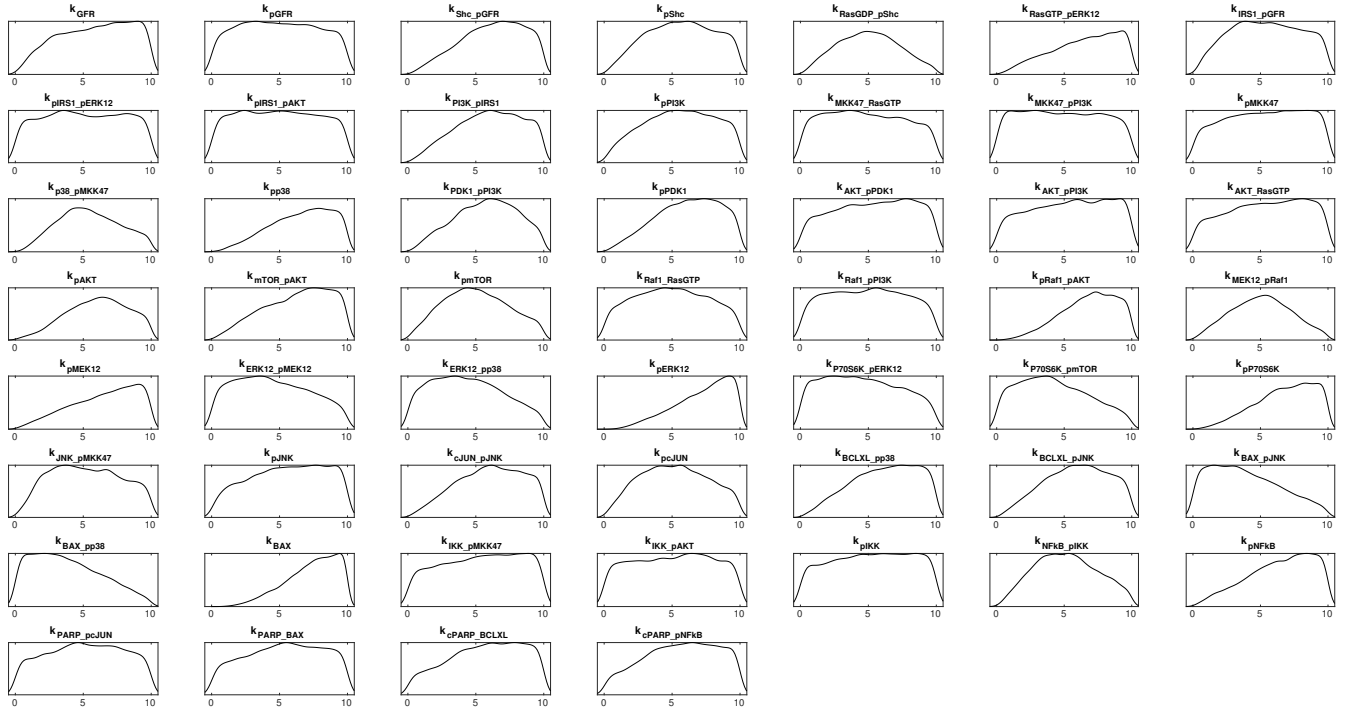


Figure S79: Model M3-DRAM: pdf of model parameters computed by DRAM after six run using a lognormal prior. The initial error variance σ is set equal to 0.1 and the corresponding prior weight is set to 10.

Parameter name	Iteration 4		
	Mean	Mode	Variance
k_{GFR}	0.6371	0.4930	0.0255
k_{pGFR}	0.4632	0.3578	0.0134
$k_{Shc.pGFR}$	0.7047	0.6026	0.0321
k_{pShc}	0.6491	0.5628	0.0265
$k_{RasGDP.pShc}$	0.5661	0.4847	0.0202
$k_{RasGTP.pERK12}$	0.8195	0.6964	0.430
$k_{IRS1.pGFR}$	0.5781	0.4511	0.0209
$k_{pIRS1.pERK12}$	0.4833	0.3729	0.0146
$k_{pIRS1.pAKT}$	0.5130	0.3898	0.0164
$k_{PI3K.pIRS1}$	0.6032	0.4996	0.0232
k_{pPI3K}	0.6141	0.5614	0.0233
$k_{MKK47.RasGTP}$	0.5652	0.4298	0.0198
$k_{MKK47.pPI3K}$	0.5281	0.4023	0.0174
k_{pMKK47}	0.5021	0.3880	0.0157
$k_{p38.pMKK47}$	0.6334	0.5116	0.0275
k_{pp38}	0.7775	0.6908	0.0362
$k_{PDK1.pPI3K}$	0.6347	0.5424	0.0257
k_{pPDK1}	0.7065	0.6060	0.0313
$k_{AKT.pPDK1}$	0.5800	0.4729	0.0201
$k_{AKT.pPI3K}$	0.5829	0.4623	0.0203
$k_{AKT.RasGTP}$	0.5490	0.4372	0.0181
k_{pAKT}	0.7711	0.6460	0.0458
$k_{mTOR.pAKT}$	0.8547	0.7333	0.466
k_{pmTOR}	0.5705	0.4969	0.0205
$k_{Raf1.RasGTP}$	0.5396	0.4534	0.0171
$k_{Raf1.pPI3K}$	0.5563	0.4663	0.0182
$k_{pRaf1.pAKT}$	0.8485	0.7048	0.0554
$k_{MEK12.pRaf1}$	0.6209	0.5300	0.0246
k_{pMEK12}	0.7998	0.6971	0.0406
$k_{ERK12.MEK12}$	0.5261	0.4425	0.0165
$k_{ERK12.pp38}$	0.5247	0.4592	0.0162
k_{pERK12}	0.9879	0.8497	0.0805
$k_{P70S6K.pERK12}$	0.5460	0.4444	0.0178
$k_{P70S6K.pmTOR}$	0.5511	0.4837	0.0180
$k_{pP70S6K}$	1.0138	0.8337	0.0730
$k_{JNK.pMKK47}$	0.6243	0.5215	0.0233
k_{pJNK}	0.4900	0.3806	0.0158
$k_{cJUN.pJNK}$	0.7100	0.5804	0.0326
k_{pcJUN}	0.7070	0.6248	0.0313
$k_{BCLXL.pp38}$	0.7825	0.6939	0.0355
$k_{BCLXL.pJNK}$	0.7029	0.55586	0.0339
$k_{BAX.pp38}$	0.4354	0.3634	0.0110
$k_{BAX.pJNK}$	0.4669	0.4168	0.0124
k_{BAX}	1.3900	1.1227	0.1535
$k_{IKK.pMKK47}$	0.5348	0.4133	0.0177
$k_{IKK.pAKT}$	0.5116	0.3878	0.0163
k_{pIKK}	0.5019	0.3846	0.0160
$k_{NFkB.pIKK}$	0.6113	0.5496	0.0225
k_{pNFkB}	0.8763	0.7189	0.0516
$k_{PARP.pcJUN}$	0.5595	0.4879	0.0188
$k_{PARP.BAX}$	0.5188	0.4083	0.0164
$k_{cPARP.BCLXL}$	0.5800	0.44476	0.0216
$k_{cPARP.pNFkB}$	0.6814	0.5274	0.0303

Table S22. Model M3-CRC: summary statistics of parameter pdfs in iteration 4 of CRC algorithm.

Iteration 4		
Protein name	Mean	Variance
pShc	0.1202	0.0061
RasGTP	0.1775	0.0128
pPI3K	0.1675	0.0138
pp38	0.1535	0.0064
pPDK1	0.1673	0.0126
pAKT	0.1157	0.0016
pmTOR	0.1160	0.0016
pRaf1	0.1391	0.0062
pMEK12	0.1621	0.0107
pERK12	0.1293	0.0071
pP70S6K	0.1259	0.0044
pcJUN	0.1546	0.0035
BCLXL	0.2775	0.0379
BAX	0.2796	0.0235
pNFkB	0.1895	0.0021
cPARP	0.1492	0.0097

Table S23. Model M3-CRC: summary statistics of distance function pdfs in iteration 4 of CRC algorithm.

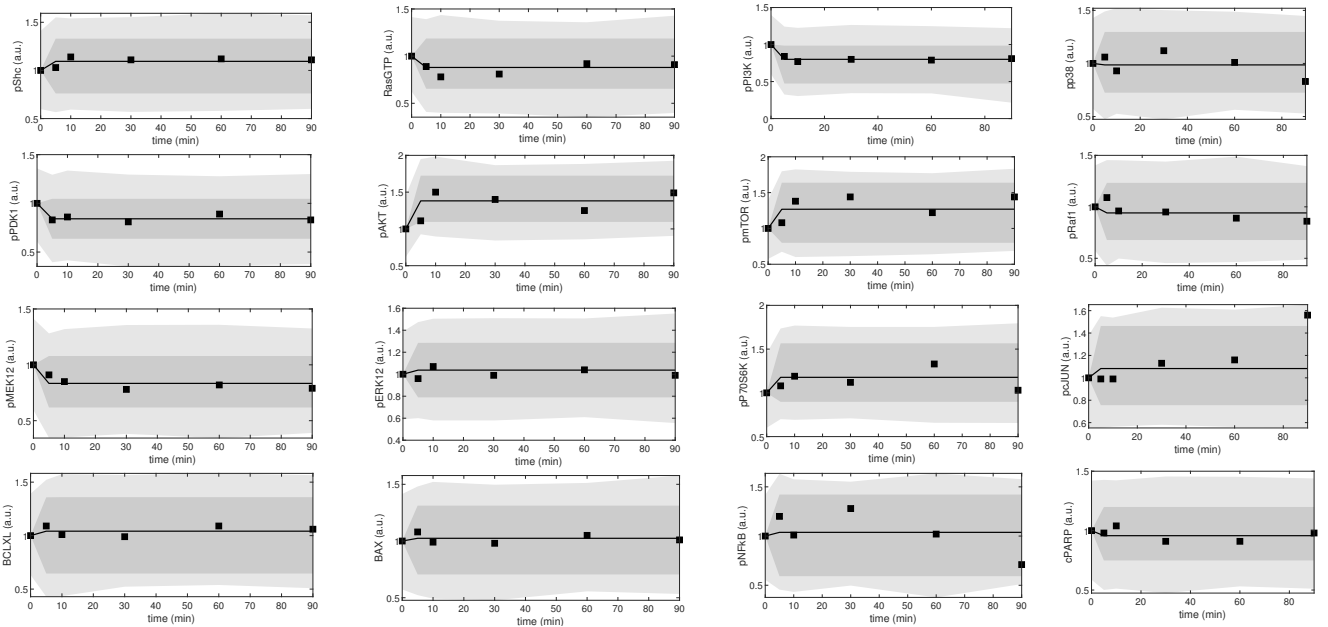


Figure S80: Model M3-DRAM: simulated output variables (blue lines) using mean values of the chains returned by DRAM at the 6th run, in comparison with RPPA data (red squares). The initial prior is lognormal.

Parameter name	Iteration 5		
	Mean	Mode	Variance
k_{GFR}	0.6079	0.5338	0.0078
k_{pGFR}	0.4396	0.3878	0.0041
$k_{Shc.pGFR}$	0.7391	0.7046	0.0116
k_{pShc}	0.6926	0.6553	0.0101
$k_{RasGDP.pShc}$	0.5937	0.5611	0.0075
$k_{RasGTP.pERK12}$	0.8554	0.8184	0.0155
$k_{IRS1.pGFR}$	0.5548	0.5183	0.0065
$k_{pIRS1.pERK12}$	0.4598	0.4117	0.0045
$k_{pIRS1.pAKT}$	0.4804	0.4175	0.0049
$k_{PI3K.pIRS1}$	0.6125	0.5789	0.0080
k_{pPI3K}	0.6547	0.6168	0.0090
$k_{MKK47.RasGTP}$	0.5319	0.4712	0.0059
$k_{MKK47.pPI3K}$	0.4981	0.4465	0.0052
k_{pMKK47}	0.4745	0.4130	0.0048
$k_{p38.pMKK47}$	0.6369	0.6076	0.0084
k_{pp38}	0.8368	0.7680	0.0153
$k_{PDK1.pPI3K}$	0.6678	0.6402	0.0094
k_{pPDK1}	0.7426	0.7091	0.0118
$k_{AKT.pPDK1}$	0.5910	0.5917	0.0072
$k_{AKT.pPI3K}$	0.5799	0.6109	0.0068
$k_{AKT.RasGTP}$	0.5472	0.5571	0.0061
k_{pAKT}	0.7398	0.6738	0.0134
$k_{mTOR.pAKT}$	0.9066	0.8733	0.0172
k_{pmTOR}	0.6078	0.5711	0.0079
$k_{Raf1.RasGTP}$	0.5639	0.5187	0.0066
$k_{Raf1.pPI3K}$	0.5786	0.5208	0.0070
$k_{pRaf1.pAKT}$	0.8410	0.7850	0.0159
$k_{MEK12.pRaf1}$	0.6502	0.6176	0.0090
k_{pMEK12}	0.8563	0.8108	0.0155
$k_{ERK12.MEK12}$	0.5497	0.5087	0.0063
$k_{ERK12.pp38}$	0.5700	0.5233	0.0067
k_{pERK12}	1.0114	0.9727	0.0231
$k_{P70S6K.pERK12}$	0.5459	0.4793	0.0063
$k_{P70S6K.pmTOR}$	0.5926	0.5326	0.0075
$k_{pP70S6K}$	1.0291	0.9889	0.0222
$k_{JNK.pMKK47}$	0.6475	0.5921	0.0087
k_{pJNK}	0.4638	0.4119	0.0046
$k_{cJUN.pJNK}$	0.7145	0.6780	0.0108
k_{pcJUN}	0.7696	0.7356	0.0125
$k_{BCLXL.pp38}$	0.8670	0.8766	0.0154
$k_{BCLXL.pJNK}$	0.6746	0.6111	0.0100
$k_{BAX.pp38}$	0.4538	0.4444	0.0042
$k_{BAX.pJNK}$	0.5222	0.5237	0.0056
k_{BAX}	1.3260	1.1884	0.0403
$k_{IKK.pMKK47}$	0.5089	0.4454	0.0055
$k_{IKK.pAKT}$	0.4758	0.4120	0.0048
k_{pIKK}	0.4743	0.4147	0.0047
$k_{NFkB.pIKK}$	0.6637	0.6208	0.0097
k_{pNFkB}	0.9004	0.9110	0.0165
$k_{PARP.pcJUN}$	0.6005	0.5482	0.0076
$k_{PARP.BAX}$	0.5032	0.4498	0.0053
$k_{cPARP.BCLXL}$	0.5514	0.4968	0.0064
$k_{cPARP.pNFkB}$	0.6494	0.5725	0.0089

Table S24. Model M3-CRC: summary statistics of parameter pdfs in iteration 5 of CRC algorithm.

Protein name	Iteration 5	
	Mean	Variance
pShc	0.0729	0.0019
RasGTP	0.1065	0.0036
pPI3K	0.0982	0.0044
pp38	0.1026	$9.82 * 10^{-4}$
pPDK1	0.1001	0.0042
pAKT	0.0978	$2.31 * 10^{-4}$
pmTOR	0.0937	$1.89 * 10^{-4}$
pRaf1	0.0896	0.0014
pMEK12	0.0997	0.0033
pERK12	0.0726	0.0019
pP70S6K	0.0809	$6.25 * 10^{-4}$
pcJUN	0.1190	$8.46 * 10^{-4}$
BCLXL	0.1688	0.0121
BAX	0.1583	0.0094
pNFkB	0.1638	$4.74 * 10^{-4}$
cPARP	0.0853	0.0025

Table S25. Model M3-CRC: summary statistics of distance functions pdfs in iteration 5 of CRC algorithm.

Parameter name	Iteration 6		
	Mean	Mode	Variance
k_{GFR}	0.5971	0.5625	0.0023
k_{pGFR}	0.4348	0.4127	0.0012
$k_{Shc.pGFR}$	0.7868	0.7663	0.0040
k_{pShc}	0.7355	0.7292	0.0034
$k_{RasGDP.pShc}$	0.6289	0.6197	0.0025
$k_{RasGTP.pERK12}$	0.9150	0.8897	0.0054
$k_{IRS1.pGFR}$	0.5785	0.5476	0.0022
$k_{pIRS1.pERK12}$	0.4621	0.4334	0.0014
$k_{pIRS1.pAKT}$	0.4689	0.4495	0.0014
$k_{PI3K.pIRS1}$	0.6418	0.6195	0.0027
k_{pPI3K}	0.6984	0.7116	0.0030
$k_{MKK47.RasGTP}$	0.5272	0.4906	0.0018
$k_{MKK47.pPI3K}$	0.4993	0.4671	0.0016
k_{pMKK47}	0.4638	0.4526	0.0014
$k_{p38.pMKK47}$	0.6686	0.6382	0.0030
k_{pp38}	0.8753	0.8986	0.0047
$k_{PDK1.pPI3K}$	0.7155	0.7076	0.0033
k_{pPDK1}	0.7963	0.7976	0.0040
$k_{AKT.pPDK1}$	0.6653	0.6471	0.0028
$k_{AKT.pPI3K}$	0.6866	0.6833	0.0030
$k_{AKT.RasGTP}$	0.6258	0.6030	0.0025
k_{pAKT}	0.7443	0.7289	0.0036
$k_{mTOR.pAKT}$	0.9853	0.9623	0.0061
k_{pmTOR}	0.6340	0.6089	0.0026
$k_{Raf1.RasGTP}$	0.5884	0.6227	0.0022
$k_{Raf1.pPI3K}$	0.5901	0.6132	0.0022
$k_{pRaf1.pAKT}$	0.8548	0.8112	0.0049
$k_{MEK12.pRaf1}$	0.6934	0.6799	0.0031
k_{pMEK12}	0.9060	0.8875	0.0053
$k_{ERK12.MEK12}$	0.5742	0.5843	0.0021
$k_{ERK12.pp38}$	0.5911	0.5982	0.0022
k_{pERK12}	1.0606	1.0261	0.0076
$k_{P70S6K.pERK12}$	0.5402	0.5474	0.0018
$k_{P70S6K.pmTOR}$	0.6025	0.6221	0.0023
$k_{pP70S6K}$	1.0856	1.0499	0.0078
$k_{JNK.pMKK47}$	0.6645	0.6491	0.0028
k_{pJNK}	0.4604	0.4391	0.0014
$k_{cJUN.pJNK}$	0.7680	0.7849	0.0037
k_{pcJUN}	0.8138	0.7797	0.0043
$k_{BCLXL.pp38}$	0.9683	0.9244	0.0061
$k_{BCLXL.pJNK}$	0.6929	0.6924	0.0030
$k_{BAX.pp38}$	0.4949	0.4607	0.0016
$k_{BAX.pJNK}$	0.5805	0.5428	0.0022
k_{BAX}	1.3567	1.3858	0.0113
$k_{IKK.pMKK47}$	0.5001	0.4766	0.0016
$k_{IKK.pAKT}$	0.4620	0.4377	0.0014
k_{pIKK}	0.4638	0.4357	0.0014
$k_{NFkB.pIKK}$	0.7048	0.7049	0.0031
k_{pNFkB}	1.0055	0.9598	0.0066
$k_{PARP.pcJUN}$	0.6107	0.5709	0.0024
$k_{PARP.BAX}$	0.5013	0.4730	0.0016
$k_{cPARP.BCLXL}$	0.5596	0.5497	0.0020
$k_{cPARP.pNFkB}$	0.6454	0.6628	0.0026

Table S26. Model M3-CRC: summary statistics of parameter pdfs in iteration 6 of CRC algorithm.

Protein name	Iteration 6	
	Mean	Variance
pShc	0.0447	4.6508×10^{-4}
RasGTP	0.0686	6.6274×10^{-4}
pPI3K	0.0598	0.0014
pp38	0.0861	1.7727×10^{-4}
pPDK1	0.0595	0.0012
pAKT	0.0877	6.88×10^{-6}
pmTOR	0.0862	1.81×10^{-5}
pRaf1	0.0706	4.57×10^{-4}
pMEK12	0.0631	7.32×10^{-4}
pERK12	0.0459	4.44×10^{-4}
pP70S6K	0.0680	1.68×10^{-4}
pcJUN	0.1023	6.77×10^{-5}
BCLXL	0.1132	0.0064
BAX	0.0919	0.0040
pNFkB	0.1508	1.43×10^{-4}
cPARP	0.0567	5.68×10^{-4}

Table S27. Model M3-CRC: summary statistics of distance function pdfs in iteration 6 of CRC algorithm.

Protein name	MSE
pShc	$6.85 \cdot 10^{-4}$
RasGTP	0.0015
pPI3K	$2.50 \cdot 10^{-4}$
pp38	0.83
pPDK1	0.0012
pAKT	0.0157
pmTOR	0.0093
pRaf1	$8.64 \cdot 10^{-4}$
pMEK12	$2.07 \cdot 10^{-4}$
pERK12	0.0046
pP70S6K	0.0084
pcJUN	0.005
BCLXL	$6.84 \cdot 10^{-4}$
BAX	$7.62 \cdot 10^{-4}$
pNFkB	0.0639
cPARP	$1.05 \cdot 10^{-6}$

Table S28. Model M3-PL: MSE of each output variable when using best fit parameters estimated by *lsqnonlin* in D2D software.

Parameter name	\hat{p}	σ^-	σ^+
k_{AKT_RasGTP}	$7.59 \cdot 10^{-04}$	$7.30 \cdot 10^{-04}$	$8.12 \cdot 10^{-04}$
k_{AKT_pPDK1}	$1.56 \cdot 10^{-04}$	$1.69 \cdot 10^{-04}$	$2.72 \cdot 10^{-04}$
k_{AKT_pPI3K}	0.0781	0.0781	0.0781
k_{BAX}	$5.45 \cdot 10^{-04}$	$5.46 \cdot 10^{-04}$	$6.41 \cdot 10^{-04}$
k_{BAX_pJNK}	$1.77 \cdot 10^{-04}$	$1.79 \cdot 10^{-04}$	$2.55 \cdot 10^{-04}$
k_{BAX_pp38}	0.7519	0.7324	0.7589
k_{BCLXL_pJNK}	$1.5 \cdot 10^{-3}$	$9 \cdot 10^{-3}$	$9.1 \cdot 10^{-3}$
k_{BCLXL_pp38}	1.3002	0.5888	1.4624
k_{ERK12_MEK12}	$2.98 \cdot 10^{-3}$	$2.9 \cdot 10^{-3}$	$3 \cdot 10^{-3}$
k_{ERK12_pp38}	0.8292	0.8325	0.8504
k_{GFR}	$7.03 \cdot 10^{-04}$	$6.96 \cdot 10^{-04}$	$7.06 \cdot 10^{-04}$
k_{IKK_pAKT}	0.0903	0.0903	0.0903
k_{IKK_pMKK47}	0.0311	0.0311	0.0311
k_{IRS1_pGFR}	0.1228	0.1228	0.1228
k_{JNK_pMKK47}	0.03	0.03	0.03
k_{MEK12_pRaf1}	0.195	0.2470	0.2966
k_{MKK47_RasGTP}	1.5523	1.5521	1.5526
k_{MKK47_pPI3K}	1.6429	1.6427	1.6431
k_{NFkB_pIKK}	30.6549	30.6548	30.6567
k_{P70S6K_pERK12}	0.0688	0	0.1192
k_{P70S6K_pmTOR}	0.3765	0.3128	0.4554
k_{PARP_BAX}	19.8215	19.8201	19.8216
k_{PARP_pcJUN}	62.2501	62.2496	62.2503
k_{PDK1_pPI3K}	1.1727	1.3660	2.3007
k_{PI3K_pIRS1}	0.9584	0.9584	0.9589
k_{Raf1_RasGTP}	$4.95 \cdot 10^{-03}$	0.0998	0.1011
k_{Raf1_pPI3K}	0.282	0.267	0.3647
k_{RasGDP_pShc}	0.0973	0.0973	0.0973
k_{RasGTP_pERK12}	0.1447	0.1447	0.1447
k_{Shc_pGFR}	0.0941	0.0941	0.0942
k_{cJUN_pJNK}	0.0122	0.0122	0.0122
k_{cPARP_BCLXL}	$1.61 \cdot 10^{-05}$	0.0049	$+\infty$
k_{cPARP_pNFkB}	98.6713	92.1351	100.8602
k_{mTOR_pAKT}	0.1198	0.0997	0.1459
k_{p38_pMKK47}	0.0164	0.0164	0.0165
$k_{pP70S6K}$	0.412	0.3478	0.4862
k_{pAKT}	0.0244	0.0244	0.0244
k_{pERK12}	$4.81 \cdot 10^{-03}$	$6.2 \cdot 10^{-03}$	$6.9 \cdot 10^{-03}$
k_{pGFR}	$7.81 \cdot 10^{-05}$	$4.54 \cdot 10^{-05}$	$9.93 \cdot 10^{-05}$
k_{pIKK}	0.5302	0.5302	0.5302
k_{pIRS1_pAKT}	$2.52 \cdot 10^{-05}$	0	$+\infty$
k_{pIRS1_pERK12}	0.7824	0.7824	0.7824
k_{pJNK}	$1.00 \cdot 10^{-05}$	$4.23 \cdot 10^{-05}$	$+\infty$
k_{pMEK12}	0.2669	0.1769	0.2109
k_{pMKK47}	0.0322	0.0321	0.0322
k_{pNFkB}	10.4550	10.4547	10.4551
k_{pPDK1}	1.2962	0.5833	1.2624
k_{pPI3K}	0.4037	0.4036	0.4037
k_{pRaf1_pAKT}	0.1959	0.195	0.1624
k_{pShc}	0.0761	0.076	0.0761
k_{pcJUN}	$2.58 \cdot 10^{-3}$	$2.58 \cdot 10^{-3}$	$2.6 \cdot 10^{-3}$
k_{pmTOR}	0.0776	0.0622	0.0945
k_{pp38}	15.4404	15.3488	15.5264

Table S29. Model M3-PL: results of parameter estimation and Profile Likelihood for model M3. \hat{p} indicates the estimated optimal parameter value. σ^- and σ^+ indicate the 95% point-wise confidence intervals. Structural non-identifiable parameters are highlighted in blue while practical non-identifiable parameters highlighted in red.

Iteration	Tolerance
1	10.5
2	6.4
3	4.4
4	2.9
5	1.875
6	1.496

Table S30. Model M3-ABC SMC: threshold schedule of ABC-SMC. The threshold in each iteration is equal to the sum of all thresholds fixed in CRC in the same corresponding iteration.

Iteration	Number of particles	Acceptance rate	Time to complete (s)
1	1460	0.6849	1362
2	1549	0.6455	1333
3	3734	0.2678	3064
4	85993	0.0116	70710

Table S31. Model M3-ABC SMC: results of ABC-SMC algorithm until the 4 – *th* iteration: number of particles generated, acceptance rate and time employed for each iteration using the ABC-SysBio software Liepe et al. (2014).

Protein name	MSE
pShc	0.0798
RasGTP	0.0115
pPI3K	0.0278
pp38	0.0159
pPDK1	0.0112
pAKT	0.0195
pmTOR	0.0562
pRaf1	0.0118
pMEK12	0.0169
pERK12	0.1157
pP70S6K	0.0971
pcJUN	0.0356
BCLXL	0.0091
BAX	1.1693
pNFkB	0.0415
cPARP	0.0452

Table S32. Model M3-ABC SMC: MSE of each output variable using the median parameter vector returned by the standard ABC-SMC in the 4 – *th* iteration.

REFERENCES

- Toni T, Welch D, Strelkowa N, Ipsen A, Stumpf MPH. Approximate Bayesian computation scheme for parameter inference and model selection in dynamical systems. *Journal of the Royal Society, Interface* **6** (2009) 187–202. doi:10.1098/RSIF.2008.0172.
- Raue A, Kreutz C, Maiwald T, Klingmüller U, Timmer J. Addressing parameter identifiability by model-based experimentation. *IET systems biology* **5** (2011) 120–130.
- Peng H, Peng T, Wen J, Engler DA, Matsunami RK, Su J, et al. Characterization of p38 MAPK isoforms for drug resistance study using systems biology approach. *Bioinformatics* **30** (2014) 1899–1907. doi:10.1093/bioinformatics/btu133.
- Liepe J, Kirk P, Filippi S, Toni T, Barnes CP, Stumpf MPH. A framework for parameter estimation and model selection from experimental data in systems biology using approximate Bayesian computation. *Nature Protocols* **9** (2014) 439–456. doi:10.1038/nprot.2014.025.