Supplementary Information

Supplementary Table S1. Parameters of the mathematical model

The values of the parameters of the model were either taken from the literature (References are listed) or optimized to obtain the best possible fit to the experimental data.

Notation	Parameter	Value	Units	Description	Refs.
1	$k_{ATG\ int}$	0.25	1/min	Rate of production of ATG	[1]
2	$k_{MADG\ int}$	90	1/min	Rate of production of MADG	[1]
3	k_{DMAG}	0.0122	1/min	Rate of production of DMAG	[1]
4	k_{oxd}	33.254	1/min	Rate of oxidation of DMA^{III}	[1]
5	k_{oxm}	0.2375	1/min	Rate of oxidation of MMA^{III}	[1]
6	$k_{iAs^{III}\ int}$	320	1/min	Rate of production of iAs^{III}	[1]
7	$k_{MMA^{III}\ int}$	1200	1/min	Rate of production of MMA^{III}	[1]
8	n_3	8	-	Hill coefficient of inhibition of MMA^{III}	[1]
9	Kd_3	12.94	μM	Dissociation constant of inhibition of MMA^{III}	[1]
10	f_{GSHm}	0.992	-	Coefficient of inhibition of MADG hydrolysis	[1]
11	$k_{dec\ ROS}$	99.55	1/min	Rate of ROS production decrease	fitted
12	$k_{DMA^{III}\ int}$	0.8472	1/min	Rate of production of DMA^{III}	[1]
13	f_{GSHd}	0.9988	-	Coefficient of inhibition of DMAG hydrolysis	[1]
14	$Vmax_{t2}$	1.237	pmol/min	Maximal rate of MADG efflux	[1]
15	Km_{t2}	19.47	μM	Half saturation constant of MADG efflux	[1]
16	$k_{in\ ROS}$	6.26	1/min	Rate of ROS production increase	fitted
17	k_{ss}	4.26	1/min	Steady state rate of efflux of iAs^{III}	[1]
18	τ_e	10	min	Time constant of AQP9 inactivation	[1]
19	k_0	4.2	1/min	Initial rate of efflux of iAs^{III}	[1]
20	k_{inf}	1.613	1/min	Influx of iAs^{III}	[1]
21	k_{MMAext}	0.0006	1/min	Rate of efflux of MMA	[1]
22	f_m	0.2	-	Coefficient of efflux of MMA	[1]
23	$Vmax_{t1}$	0.35	pmol/min	Maximal rate of ATG efflux	[1]
24	Km_{t1}	2.3	μM	Half saturation constant of ATG efflux	[1]
25	k_{DMAext}	0.002	1/min	Rate of efflux of DMA	[1]
26	f_d	3	-	Coefficient of efflux of DMA	[1]
27	$Vmax_m$	50	pmol/min	Maximal rate of ATG methylation	[1]
28	Km_m	9.32	μM	Half saturation constant of ATG methylation	[1]
29	n_1	1.22	-	Hill coefficient of ATG methylation	[1]
30	Kd_1	0.315	μM	Dissociation constant of ATG methylation	[1]
31	K_{im}	1.53	μM	Inhibition constant of ATG methylation	[1]
32	K_{id}	1	μM	Inhibition constant of MADG methylation	[1]
33	$Vmax_d$	8	pmol/min	Maximal rate of MADG methylation	[1]
34	Km_d	0.034	μM	Half saturation constant of MADG methylation	[1]
35	n_2	1.83	-	Hill coefficient of MADG methylation	[1]
36	Kd_2	2.33	μM	Dissociation constant of MADG methylation	[1]
37	ka_{in}	1.64	1/min	Rate of AS3MT efficiency increase	[1]
38	f_A	50	-	Coefficient of MADG methylation inactivation	[1]
39	k_{TR}	0.99	1/min	Rate of TR signaling	[1]
40	$k_{TRinact}$	987.13	1/min	Rate of TR inactivation	[1]
41	TR_C	15	-	Constant of TR inactivation	[1]
42	N	1.75	-	Hill coefficient of TR inactivation	[1]
43	TR_0	9.27	-	Steady state value of TR activity	[1]

Notation	Parameter	Value	Units	Description	Refs.
44	$k_{syn\ NF}$	994.53	μM^{-1} / min	Rate of increase of Nrf2 activity	fitted
45	$k_{deg\ NF}$	0.38	1/min	Rate of decrease of Nrf2 activity	fitted
46	k_{mGC}	0.06	1/min	Rate of transcriptional activity of GCLC	fitted
47	k_{synGC}	1.9	1/min	Rate of translational activity of GCLC	fitted
48	k_{mMRP}	5.78	1/min	Rate of transcriptional activity of MRP	fitted
49	k_{MRP}	99.96	1/min	Rate of translational activity of MRP	fitted
50	k_{synG}	98.43	-	Coefficient of transcriptional activity of GCLC	fitted
51	k_{synP}	993.2	-	Coefficient of transcriptional activity of MRP	fitted
52	Kd_4	1000	μM	Dissociation constant of GCLC upregulation	fitted
53	n_4	1.3	-	Hill coefficient of GCLC upregulation	fitted
54	k_{DNA}	69,994	1/min	Rate of production of DNA lesions	fitted
55	k_1	0.45	1/min	Rate of Ogg1 glycosylase	[2,3,4]
56	k_2	184.8	1/min	Rate of Ape1 AP endonuclease	[2,3,4]
57	k_3	37.5	1/min	Rate of Polβ gap-filling	[2,3,4]
58	k_4	4.5	1/min	Rate of Polβ dRp lyase	[2,3,4]
59	k_5	2.4	1/min	Rate of Lig1 ligation	[2,3,4]
60	k_6	0.13	1/min	Rate of Polδ gap-filling	[2,3,4]
61	k_7	46.8	1/min	Rate of Fen1 5’-endo	[2,3,4]
62	e_1	0.048	μM	Concentration of Ogg1	[2,3,4]
63	e_2	0.119	μM	Concentration of Ape1	[2,3,4]
64	e_3	0.019	μM	Concentration of Polβ	[2,3,4]
65	e_4	0.019	μM	Concentration of Polδ	[2,3,4]
66	e_5	0.019	μM	Concentration of Fen1	[2,3,4]
67	e_6	0.127	μM	Concentration of Lig1	[2,3,4]
68	K_1	0.0089	μM	Half saturation constant of Ogg1 glycosylase	[2,3,4]
69	K_2	0.0325	μM	Half saturation constant of Ape1 AP endonuclease	[2,3,4]
70	K_3	0.3	μM	Half saturation constant of Polβ gap-filling	[2,3,4]
71	K_4	0.5	μM	Half saturation constant of Polβ dRp lyase	[2,3,4]
72	K_5	0.1	μM	Half saturation constant of Lig1 ligation	[2,3,4]
73	K_6	0.067	μM	Half saturation constant of Polδ gap-filling	[2,3,4]
74	K_7	0.039	μM	Half saturation constant of Fen1 5’-endo	[2,3,4]

Supplementary Figures. Sensitivity analysis and robustness to parameter perturbations

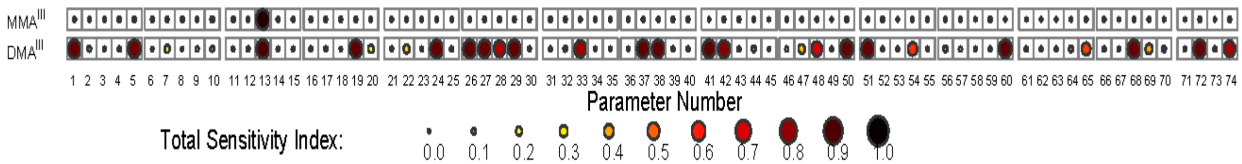

Figure S1. Sensitivity analysis of intracellular levels of MMA^{III} and DMA^{III}.

Total Sensitivity Indices (TSI) of the cellular-level TK/TD model parameters for exposure to iAs^{III}. The parameters are listed in Table S1.

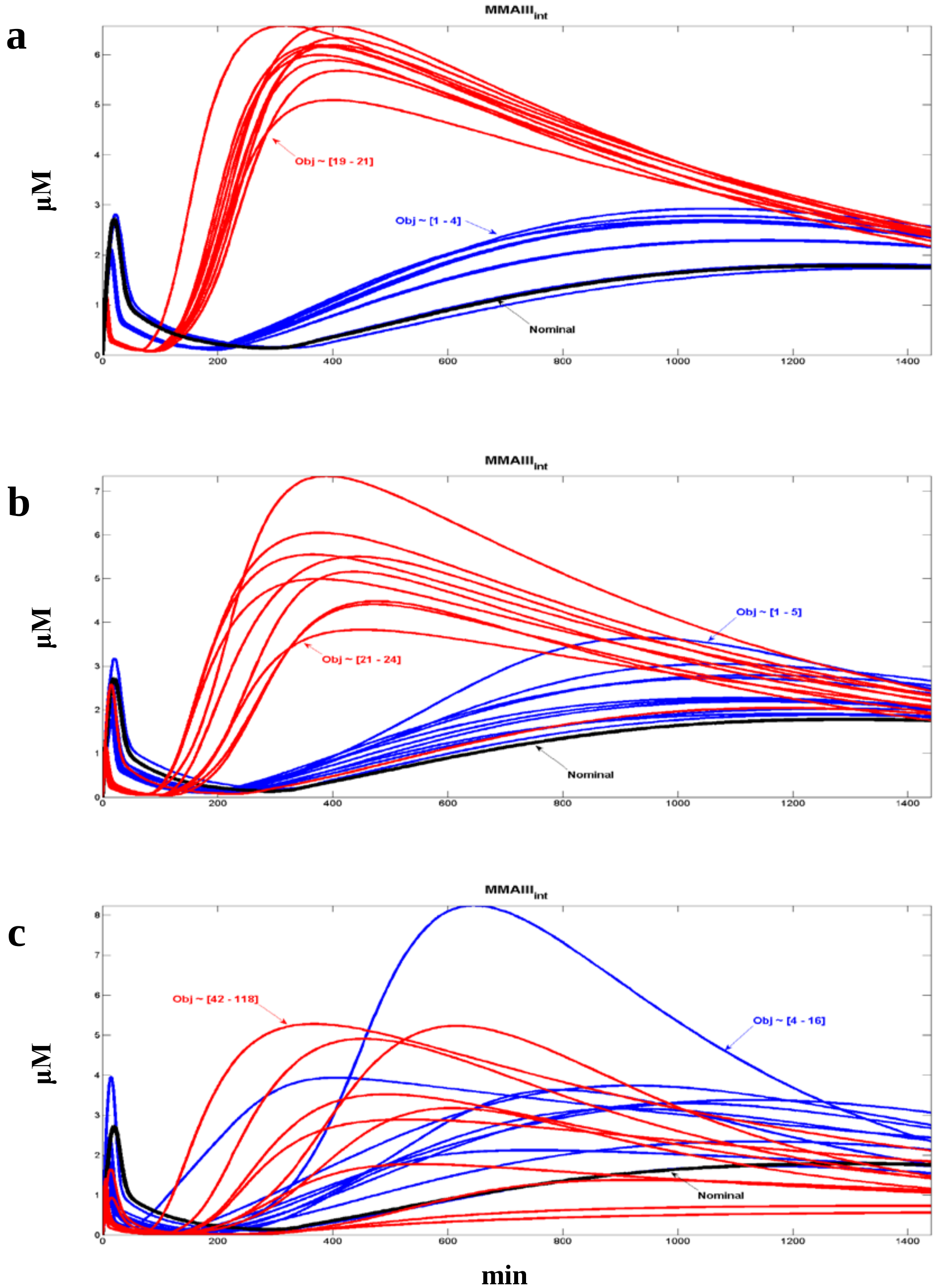

Figure S2. Robustness of time course profiles of intracellular MMA^{III} (µM) in hepatocytes due to perturbations in the parameter set.

Black line corresponds to the nominal parameter set. Blue lines correspond to simulations with normalized objective cost function that spans up to 16-fold increase. The red lines correspond to simulations with normalized cost function which is over 19-fold elevated. a) 5%, b) 10%, c) 20%, standard deviation of the nominal parameter value.

Supplementary Text. Mathematical formulation of the TK model of arsenite (iAs^{III}) in human hepatocytes [1]

$$\frac{d(iAs^{III})_{int}}{dt} = k_{inf} \times (iAs^{III})_{ext} - AQP9 \times (iAs^{III})_{int} - k_{ATG_{int}} \times (iAs^{III})_{int} + k_{iAs^{III}_{int}} \times (ATG)_{int} \quad (A.1a)$$

$$AQP9 = [k_0 + (k_{SS} - k_0) \times (1 - e^{-\frac{t}{\tau_e}})] \quad (A.1b)$$

$$\frac{d(iAs^{III})_{ext}}{dt} = AQP9 \times (iAs^{III})_{int} - k_{inf} \times (iAs^{III})_{ext} \quad (A.2)$$

$$\frac{dTR}{dt} = k_{TR} \times (TR_0 - TR) - \frac{S}{TR_C} \times k_{TR_{inact}} \times H_{TR} \quad (A.3a)$$

$$H_{TR} = \frac{[MMA^{III}]^N}{(IC_{TR})^N + [MMA^{III}]^N} \quad (A.3b)$$

$$\frac{dGSH}{dt} = k_{g_{in}} \times \frac{1}{TR} - k_{g_{deg}} \times GSH \quad (A.4a)$$

$$k_{g_{deg}} = \frac{k_{g_{in}}}{TR_0} \quad (A.4b)$$

$$\frac{dMRP}{dt} = k_{m_{in}} \times \frac{1}{TR} - k_{m_{deg}} \times MRP \quad (A.5a)$$

$$k_{m_{deg}} = \frac{k_{m_{in}}}{TR_0} \quad (A.5b)$$

$$\frac{dAS3MT}{dt} = k_{a_{in}} \times TR - k_{a_{dec}} \times AS3MT \quad (A.6a)$$

$$k_{a_{dec}} = k_{a_{in}} \times TR_0 \quad (A.6b)$$

$$MADG_{ui} = MT_1 \times \frac{[ATG]_{int}}{1 + \frac{[ATG]_{int}}{Km_m} \times (1 + \frac{[ATG]_{int}}{K_{im}})} \quad (A.7a)$$

$$MT_1 = \frac{([ATG]_{int} + [ATG]_{ext})^{n_1}}{(Kd_1)^{n_1} + ([ATG]_{int} + [ATG]_{ext})^{n_1}} \times \frac{V_{max_m}}{Km_m} \quad (A.7b)$$

$$DMAG_{ui} = MT_2 \times \frac{[MADG]_{int}}{1 + \frac{[MADG]_{int}}{Km_d} \times (1 + \frac{[ATG]_{int}}{K_{id}})} \quad (A.8a)$$

$$MT_2 = \frac{AS3MT}{f_A \times \tanh(S) + 1} \times \frac{([ATG]_{int} + [ATG]_{ext})^{n_2}}{(Kd_2)^{n_2} + ([ATG]_{int} + [ATG]_{ext})^{n_2}} \times \frac{V_{max_d}}{Km_d} \quad (A.8b)$$

$$HD_m = [1 - f_{GSH_m} \times \tanh(S)] \times (1 - H_{GSH} + \tanh(S) \times H_{GSH}) \times GS\text{-}P_m \times (MADG)_{int} \quad (A.9a)$$

$$GS\text{-}P_m = \frac{k_{MMA^{III}_{int}}}{GSH} \quad (A.9b)$$

$$H_{GSH} = \frac{([ATG]_{int} + [ATG]_{ext})^{n_3}}{(Kd_3)^{n_3} + ([ATG]_{int} + [ATG]_{ext})^{n_3}} \quad (A.9c)$$

$$HD_d = [1 - f_{GSH_d} \times \tanh(S)] \times GS\text{-}P_d \times (DMAG)_{int} \quad (A.10a)$$

$$GS\text{-}P_d = \frac{k_{DMA^{III}_{int}}}{GSH} \quad (A.10b)$$

$$\frac{d(ATG)_{ext}}{dt} = MRP_a \times \frac{[ATG]_{int}}{1 + \frac{[ATG]_{int}}{Km_{t_1}}} \quad \text{(A.11a)}$$

$$MRP_a = \frac{Vmax_{t_1}}{Km_{t_1}} \quad \text{(A.11b)}$$

$$\frac{d(MADG)_{ext}}{dt} = MRP_m \times \frac{[MADG]_{int}}{1+ \frac{[MADG]_{int}}{Km_{t_2}}} \quad \text{(A.12a)}$$

$$MRP_m = MRP \times \frac{Vmax_{t_2}}{Km_{t_2}} \quad \text{(A.12b)}$$

$$\frac{d(MMA^{V})_{ext}}{dt} = [(f_m - 1) \times \tanh(S) + 1] \times k_{MMA_{ext}} \times (MMA^{V})_{int} \quad \text{(A.13)}$$

$$\frac{d(MMA^{III})_{ext}}{dt} = [(f_m - 1) \times \tanh(S) + 1] \times k_{MMA_{ext}} \times (MMA^{III})_{int} \quad \text{(A.14)}$$

$$\frac{d(DMA)^{V}_{ext}}{dt} = [(f_d - 1) \times \tanh(S) + 1] \times k_{DMA_{ext}} \times (DMA^{V})_{int} \quad \text{(A.15)}$$

$$\frac{d(DMA)^{III}_{ext}}{dt} = [(f_d - 1) \times \tanh(S) + 1] \times k_{DMA_{ext}} \times (DMA^{III})_{int} \quad \text{(A.16)}$$

$$\frac{d(ATG)_{int}}{dt} = k_{ATG_{int}} \times (iAs^{III})_{int} - k_{iAs^{III}_{int}} \times (ATG)_{int} - MADG_{ui} - \frac{d(ATG)_{ext}}{dt} \quad \text{(A.17)}$$

$$\frac{d(MADG)_{int}}{dt} = MADG_{ui} + k_{MADG_{int}} \times (MMA^{III})_{int} - DMAG_{ui} - HD_m - \frac{d(MADG)_{ext}}{dt} \quad \text{(A.18)}$$

$$\frac{d(MMA^{III})_{int}}{dt} = HD_m - (k_{MADG_{int}} + k_{oxm}) \times (MMA^{III})_{int} - \frac{d(MMA^{III})_{ext}}{dt} \qquad (A.19)$$

$$\frac{d(MMA^{V})_{int}}{dt} = k_{oxm} \times (MMA^{III})_{int} - \frac{d(MMA^{V})_{ext}}{dt} \qquad (A.20)$$

$$\frac{d(DMAG)}{dt} = DMAG_{ui} + k_{DMAG} \times (DMA^{III})_{int} - HD_d \qquad (A.21)$$

$$\frac{d(DMA^{III})_{int}}{dt} = HD_d - (k_{DMAG} + k_{oxd}) \times (DMA^{III})_{int} - \frac{d(DMA)^{III}_{ext}}{dt} \qquad (A.22)$$

$$\frac{d(DMA^{V})_{int}}{dt} = k_{oxd} \times (DMA^{III})_{int} - \frac{d(DMA)^{V}_{ext}}{dt} \qquad (A.23)$$

References

1. Stamatelos SK, Brinkerhoff CJ, Isukapalli SS, Georgopoulos PG (2011) Mathematical model of uptake and metabolism of arsenicals in human hepatocytes – Incorporation of cellular antioxidant response and threshold-dependent behavior. BMC Systems Biology 5: 16.
2. Sokhansanj BA, Rodrigue GR, Fitch JP, Wilson DM (2002) A quantitative model of human DNA base excision repair. I. mechanistic insights. Nucleic Acids Research 30: 1817-1825.
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