

Supplementary Material for

An Agent-Based Model of Monocyte

Differentiation into Tumour-Associated

Macrophages in Chronic Lymphocytic Leukemia

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Agent	Class	Parameters		Definition	Exploration ranges and steps	Units
		Full names	Abbreviated names			
Cancer cell	NeedSignal	Shape parameter of the Gamma distribution setting NeedSignal cell life at initialization	$ns_{\Gamma\alpha}^{life-init}$	Life expectancy at initialization, according to a Gamma distribution using this shape parameter	[0.01:1], 10^{-15}	hours
		Rate parameter of the Gamma distribution setting NeedSignal cell life at initialization	$ns_{\Gamma\beta}^{life-init}$	Life expectancy at initialization, according to a Gamma distribution using this rate parameter	[50:2500], 1	hours
		NeedSignal cell movement probability	ns_{mp}	Probability expressed as a percentage that a NeedSignal cancer cell will move at each time step	[0:100], 10	%
		NeedSignal cell sensing distance to NLCs	ns_{sd}	Perception radius within which a NeedSignal cancer cell will detect a NLC	[1:3], 1	patches
	Apoptotic	Apoptotic cell movement probability	apo_{mp}	Probability expressed as a percentage that an Apoptotic cancer cell will move at each time step	[0:100], 10	%
Myeloid cell	Monocyte	Monocyte phagocytosis efficiency	$mono_{\varphi_{eff}}$	Probability expressed as a percentage that a Monocyte will phagocytose an Apoptotic or Dead cancer cell within its perception radius	[0:100], 1	%
		Standard deviation parameter of the Normal distribution setting Monocyte differentiation status at initialization	$mono_{Nd}^{diff}$	Differentiation status of monocytes toward macrophages at initialization according to a Normal distribution with this standard deviation parameter	[0:48], 1	hours
		Monocyte differentiation threshold	$mono_{d_{threshold}}^{diff}$	Hours required for a Monocyte to differentiate into a Macrophage	[48:72], 1	hours
		Monocyte sensing distance to Dead and Apoptotic cancer cells	$mono_{sd}$	Perception radius within which a Monocyte can detect a Dead or Apoptotic cancer cell	[1:3], 1	patches
	Macrophage	Macrophage phagocytosis efficiency	$macro_{\varphi_{eff}}$	Probability expressed as a percentage that a Macrophage will phagocytose an Apoptotic or Dead cancer cell within its perception radius	[0:100], 1	%
		Macrophage killing efficiency	$macro_{k_{eff}}$	Probability expressed as a percentage that a Macrophage will kill a NeedSignal cancer cell within its perception radius	[0:5], 1	%
		Mean parameter of the Normal distribution setting Macrophage polarization status at instantiation	$macro_{N\mu}^{nlc-pol}$	Polarization status toward NLC at instantiation, according to a Normal distribution with this mean parameter	[50:100], 1	hours
		Standard deviation parameter of the Normal distribution setting Macrophage polarization status at instantiation	$macro_{Nd}^{nlc-pol}$	Polarization status toward NLC at instantiation, according to a Normal distribution with this standard deviation parameter	[0:50], 1	hours
		Macrophage sensing distance to Dead and Apoptotic cancer cells	$macro_{sd}$	Perception radius within which a Macrophage can detect a cancer cell	[1:3], 1	patches
	NLC	NLC phagocytosis efficiency	$nlc_{\varphi_{eff}}$	Probability expressed as a percentage that a NLC will phagocytose an Apoptotic or Dead cancer cell within its perception radius	[0:100], 1	%
		Level of protective effect from the anti apoptotic signals	$anti-apo_{boost}$	Life increment the cancer cells receive from NLCs when they capture the anti-apoptotic signals	[0:50], 1	hours
		Number of layers around NLCs	$layers_{nlc}$	Layers of patches of cancer cells gathered around NLCs	[1:3], 1	N/A
		NLC sensing distance to Dead and Apoptotic cancer cells	nlc_{sd}	Perception radius within which a NLC can detect a Dead or Apoptotic cancer cell	[1:3], 1	patches
		NLC threshold	$nlc_{threshold}$	Hours during which a Macrophage has been in contact with at least one NeedSignal or Apoptotic cancer cell, representing the threshold for macrophage-to-NLC conversion	[100:150], 1	hours

Table 1. ABM classes and their characteristic properties.

Patient	Initial monocyte proportion (%)	Initial apoptotic CLL cell proportion (%)
Patient 1	1.04	1.7
Patient 2	3.48	2.39
Patient 3	1.1	20.9
Patient 4	1.25	7.8
Patient 5	0.21	2.06
Patient 6	2.5	3.1
Patient 7	0.68	0.0
Patient 8	0.34	2.0
Patient 9	0.95	1.0

Table 2. Patient-specific initial monocyte and apoptotic cell proportions.

CLASS A					CLASS B				
1334	430	928	473	160	287	545	372	95	$\Delta fitness_{via}$
480	513	300	357	291	495	552	177	2113	$\Delta fitness_{conc}$
10	0	80	70	60	0	20	30	60	apo_{mp}
40	40	0	0	100	70	30	70	90	ns_{mp}
3	2	2	1	3	2	1	2	2	$layers_{nic}$
149	35	261	263	247	101	46	147	95	$anti-apo_{boost}$
55	86	89	14	46	61	55	13	77	$mono_{geff}$
52	83	52	17	89	8	1	1	3	nic_{geff}
34	60	100	78	85	3	93	3	77	$macro_{geff}$
0	0	0	0	1	2	0	0	4	$macro_{keff}$
3	1	3	2	3	2	3	3	3	ns_{sd}
3	3	3	3	3	2	1	1	2	$mono_{sd}$
3	1	3	3	3	1	1	2	2	nic_{sd}
3	1	1	2	3	1	2	3	3	$macro_{sd}$
157	184	97	165	143	128	97	100	187	$nic_{threshold}$
44	64	15	23	31	49	72	69	72	$macro_{nic-pol}_{No}$
12	20	29	19	24	16	17	14	0	$macro_{nic-pol}_{No}$
71	62	65	71	48	49	60	50	62	$mono_{diff}_{threshold}$
46	20	22	7	5	18	17	8	11	$mono_{diff}_{No}$
985	2168	2361	2472	2488	2320	2038	1288	2038	$ns_{Fe-init}_{No}$
0.6229	0.4557	0.3682	0.2312	0.3477	0.3061	0.2001	0.4114	0.3999	$ns_{Fe-init}_{No}$
Patient 8	Patient 1	Patient 5	Patient 6	Patient 3	Patient 9	Patient 4	Patient 2	Patient 7	

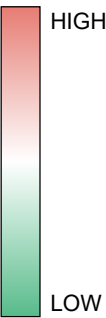
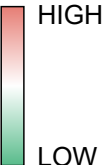


Table 3. Patient-specific knee-point parameter sets and fitness scores. Color scales were applied on each row independently.

A

patient	general model		patient-specific model	
	NRMSE_via	NRMSE_conc	NRMSE_via	NRMSE_conc
1	1.09	0.72	0.54	0.62
2	0.62	0.7	0.19	0.09
3	0.54	0.2	0.13	0.18
4	0.41	0.18	0.19	0.29
5	0.79	0.47	0.31	0.12
6	0.4	0.25	0.14	0.22
7	1.24	0.35	0.22	0.07
8	0.78	0.32	0.39	0.28
9	0.09	0.18	0.19	0.06



B

patient	general model		patient-specific model	
	R ² _via	R ² _conc	R ² _via	R ² _conc
1	-6.73	-2.64	-0.91	-1.7
2	-4.09	-4.67	0.52	0.9
3	-1.17	0.8	0.88	0.83
4	-0.48	0.71	0.68	0.24
5	-7.34	-1.68	-0.24	0.83
6	-0.25	0.58	0.85	0.68
7	-11.86	0.13	0.58	0.96
8	-4.77	0.05	-0.43	0.28
9	0.88	0.56	0.5	0.95

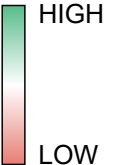


Table 4. General model and patient-specific models performance scores. A) NRMSE. B) R². Color scales are adapted to reflect good scores in green, i.e. values of R² approaching one and values of NRMSE close to zero indicating a good performance of the model. Color scales were applied on each row independently.

	Patient 9	Patient 8	Patient 5	Patient 2
CD64	1.00	0.36	0.23	0.51
CD86	0.30	1.00	0.25	0.71
CD14	0.45	0.71	1.00	0.15
CD163	0.38	0.69	1.00	0.18
Sum(M1_markers)	1.30	1.36	0.48	1.22
Sum(M2_markers)	0.83	1.40	2.00	0.33
M1/M2	1.57	0.97	0.24	3.67
molecular profiling	M1	M2	M2	M1
unsupervised profiling	M1	M2	M2	M1

Table 5. Macrophages profiling by FACS. Macrophages were sampled from PBMC autologous cultures on Day 8. CD64 and CD86 were used as M1 markers and CD14 and CD163 were used as M2 markers. Each marker expression data was scaled using the maximum absolute scaling method. Sum of M1 markers and sum M2 markers were then calculated and their ratio was used to estimate the dominant macrophage phenotype. A M1/M2 ratio higher than 1 was associated with M1-like macrophages, while a ratio less than 1 was associated with M2-like macrophages.

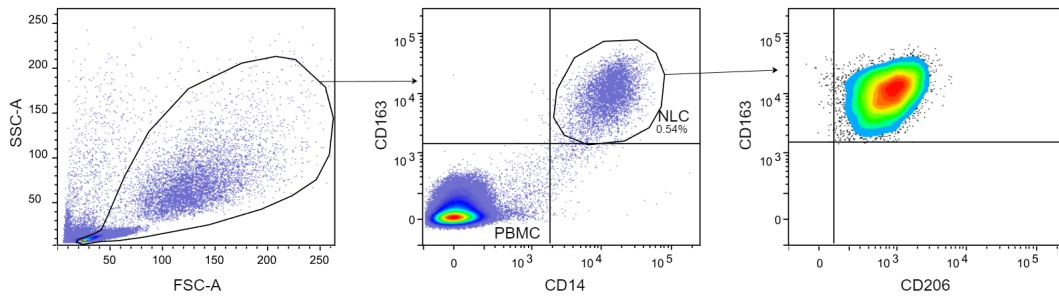
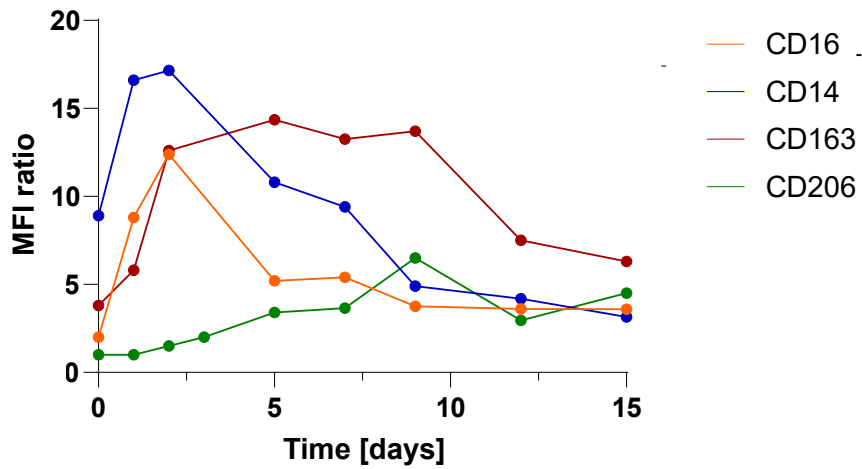
A**B**

Fig. S1. Kinetics of myeloid marker expression during monocyte-to-NLC differentiation in CLL PBMC in vitro culture. A) Gating strategy NLCs were identified based on the co-expression of CD14 and CD163 markers. **B) Evolution of myeloid marker expressions.** Expressions were represented as MFI (median fluorescence intensity) ratio between the signal of specific antibody and corresponding isotype control, as measured by flow cytometry. Graph represents mean values from 2 independent donors. CD14 and CD16 are typically used to characterize monocyte subsets (1), while CD163 and CD206 are common macrophages M2 markers (2).

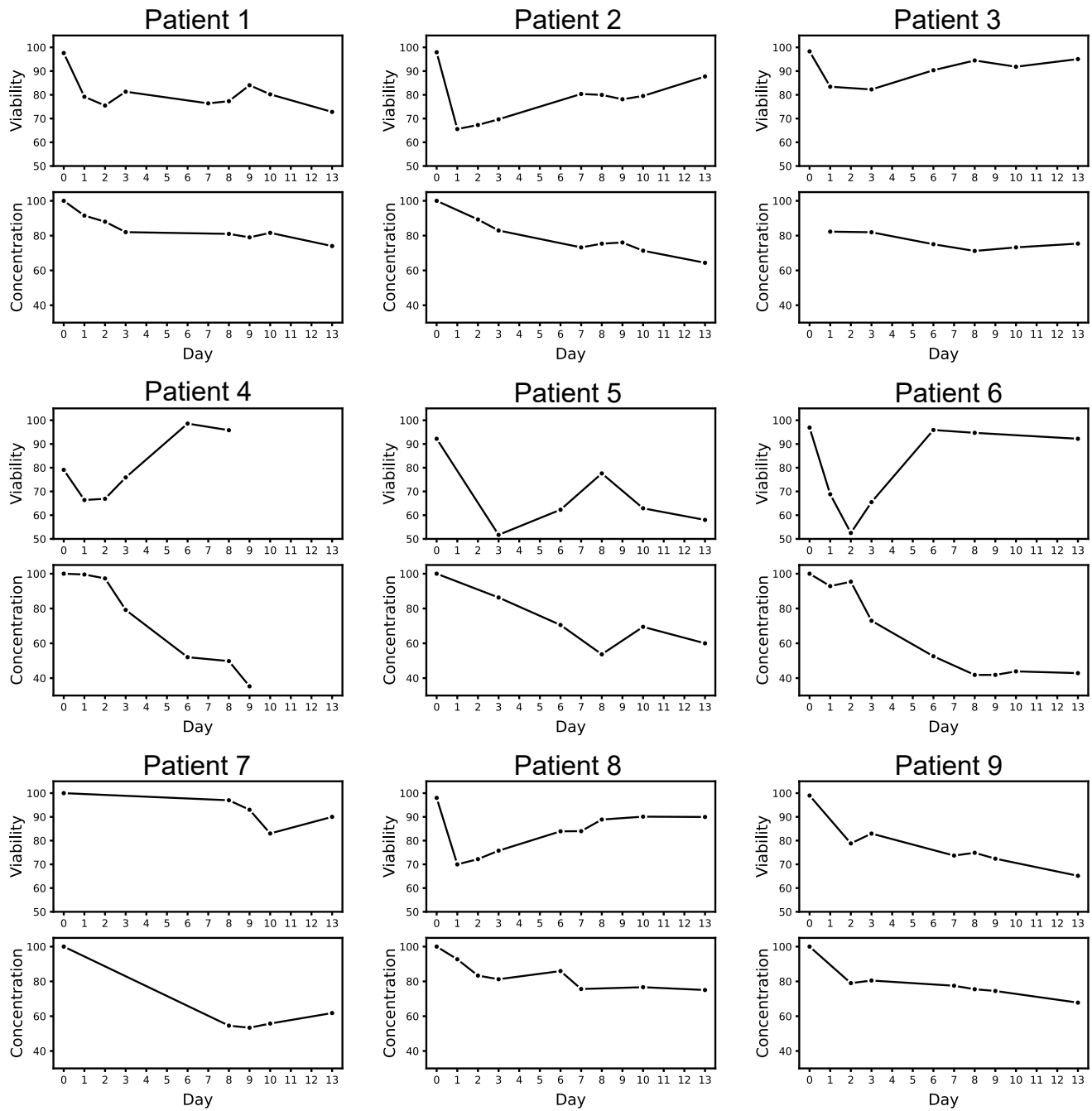


Fig. S2. Time course datasets produced from the PBMC autologous cultures. CLL cell survival was monitored by viability assay and concentration measurements at the indicated time points for each patient (dots).

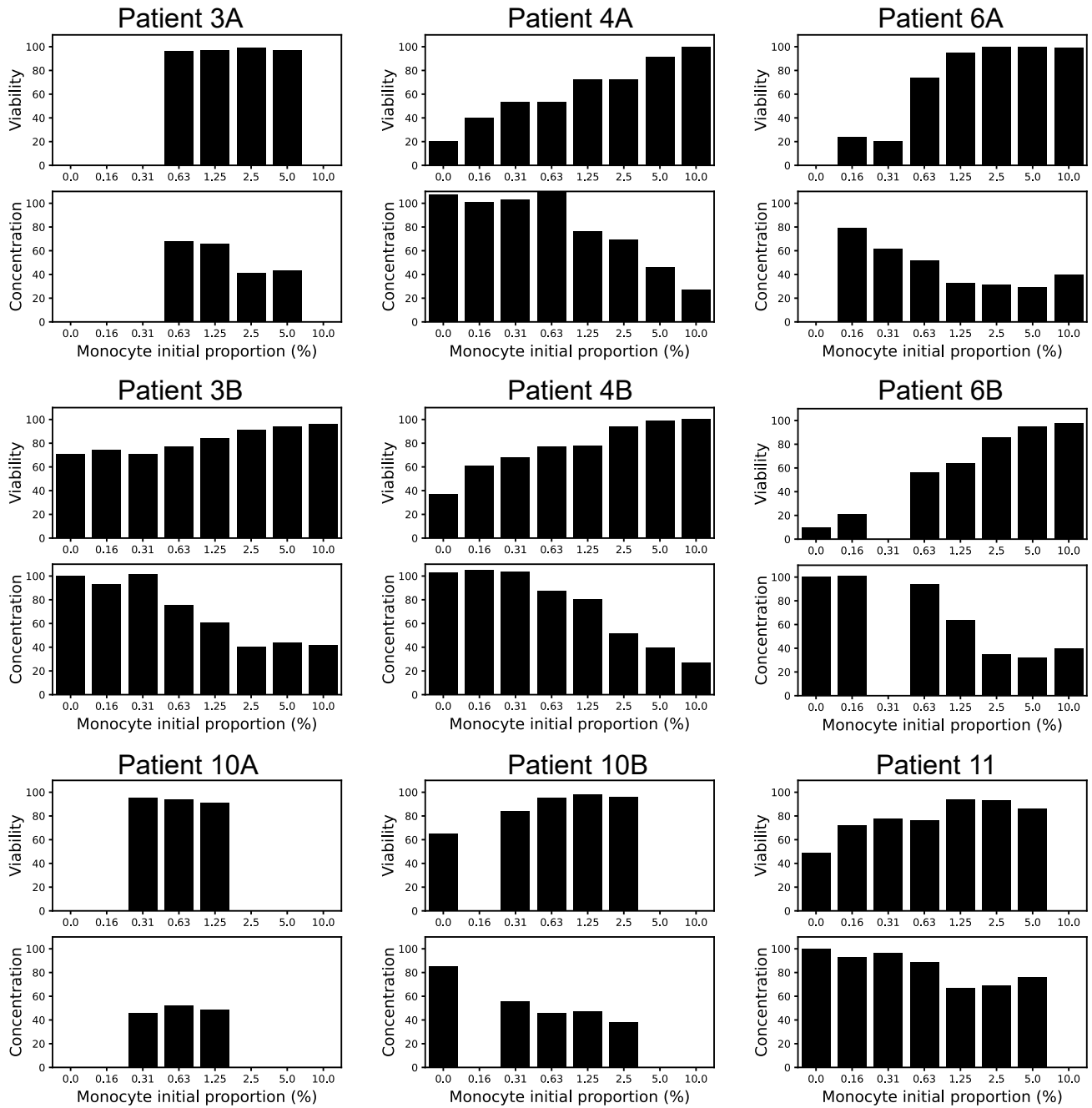


Fig. S3. Heterologous co-cultures. Monocytes from healthy donors (represented by the letters A or B) and B cells from CLL patients were co-cultured to assess the relationship between the initial density of monocytes and the level or survival of CLL cells after 9 days. The x-axis displays different monocytes initial proportions (not to scale for clarity).

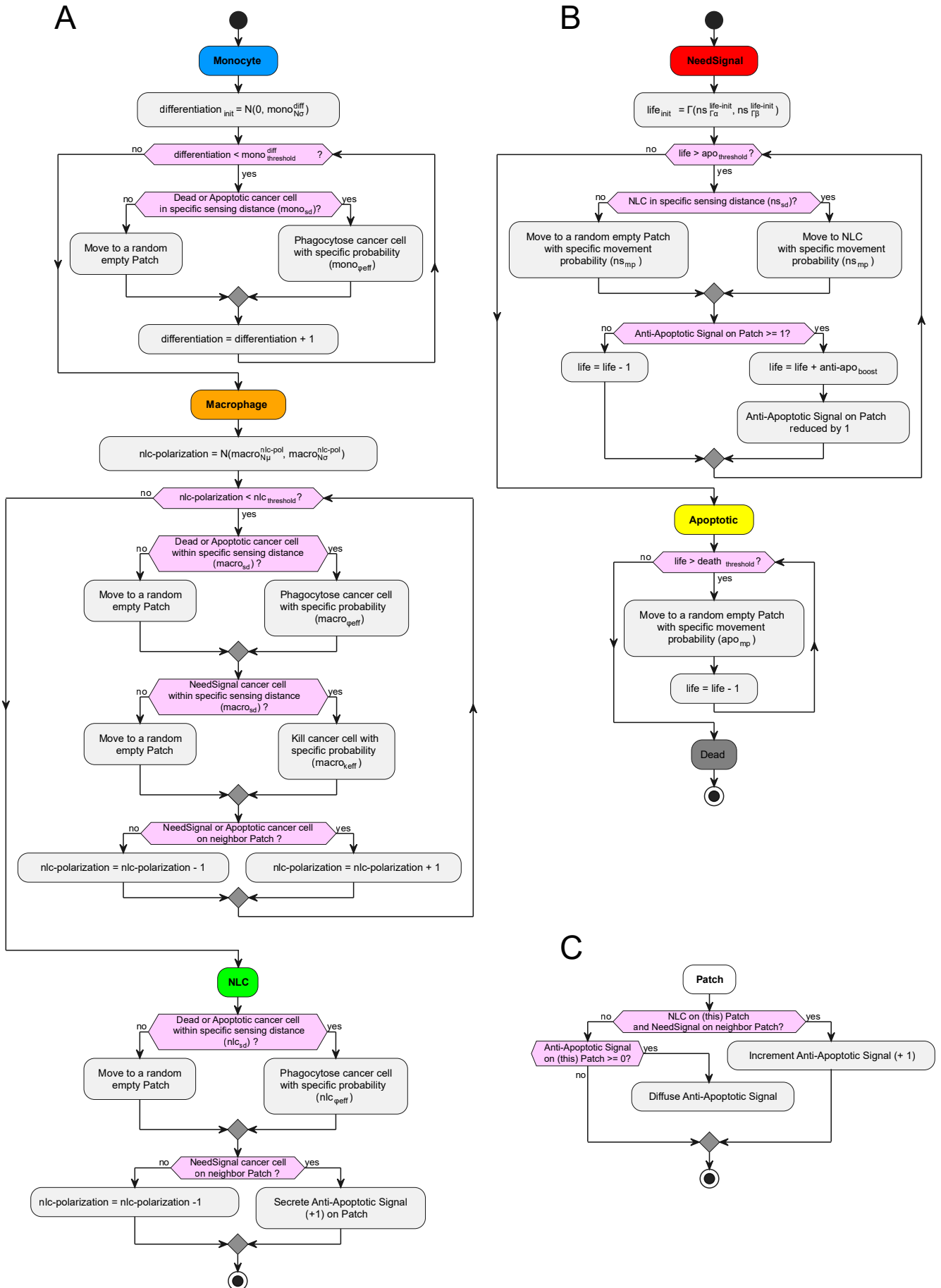


Fig. S4. UML class diagrams for A) myeloid cells, B) CLL cells, and C) patches.

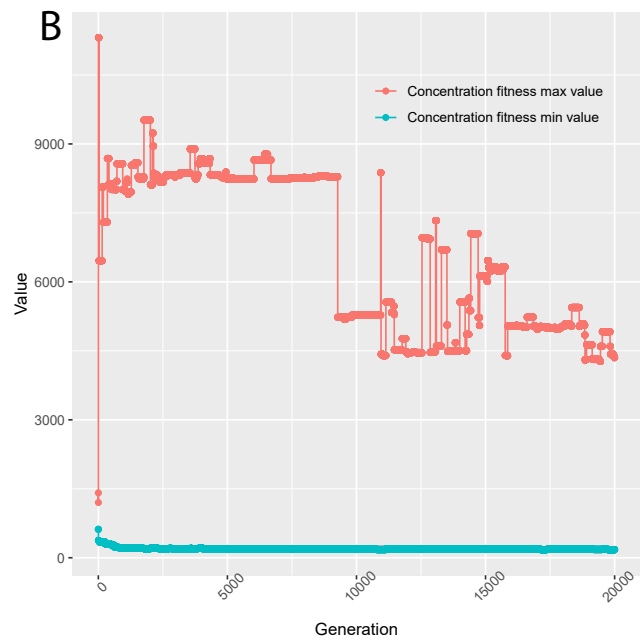
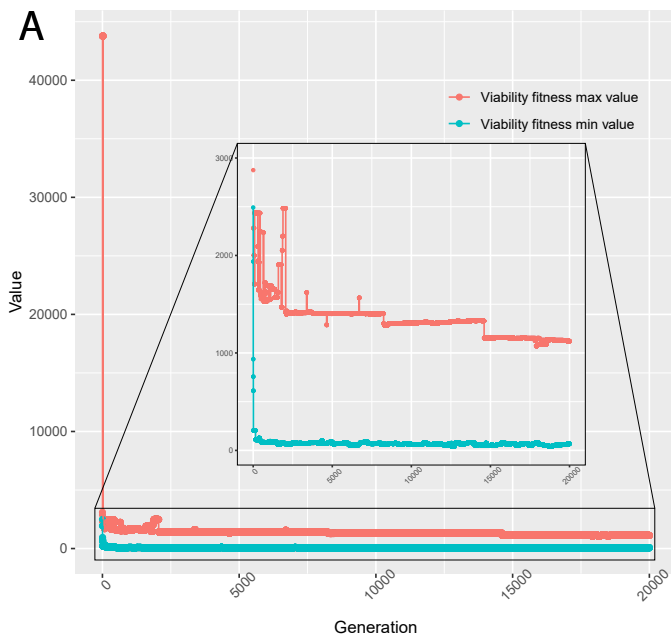


Fig. S5. Minimal and maximal values of fitnesses along 20'000 generations. A) Viability fitness evolution. B) Concentration fitness evolution.

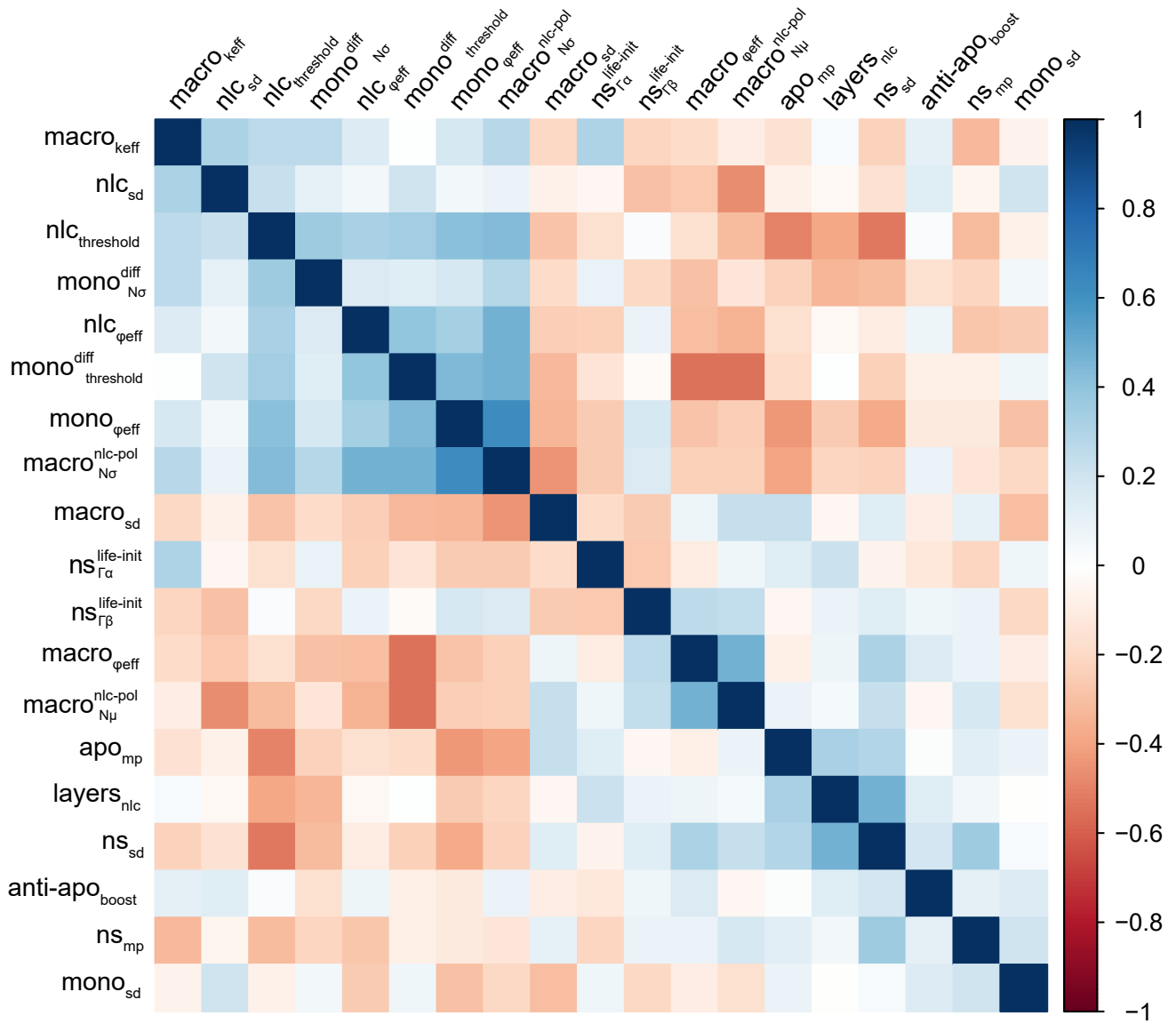


Fig. S6. Pearson correlation coefficients between model parameters. Parameters are clustered according to a complete method.

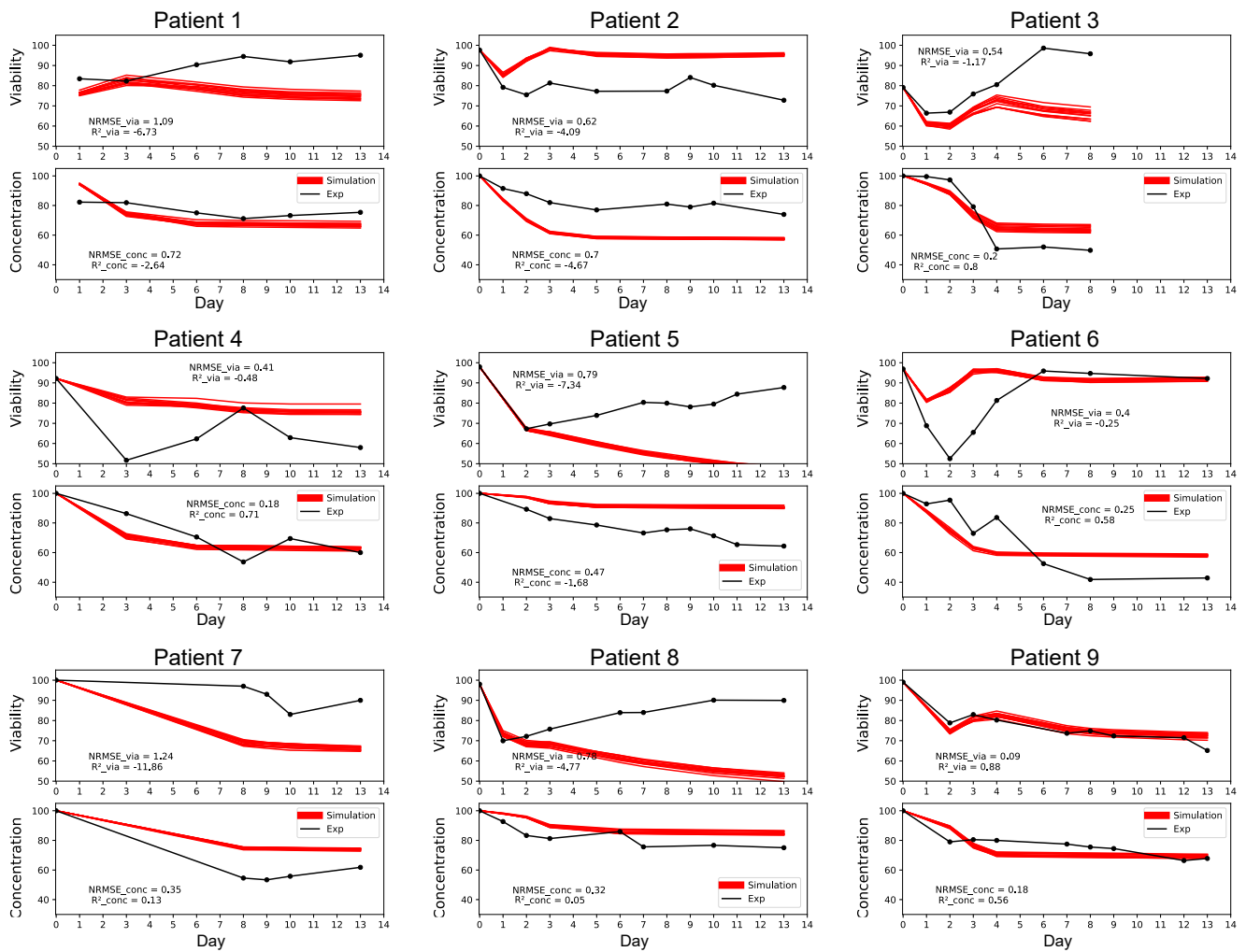


Fig. S7. General model fitting to patient-specific dynamics. 12 simulations were run with the knee-point set of parameters and compared with patient-specific viability and concentration observed experimentally setting the initial monocyte proportion to the specific percentage of monocytes and initial apoptotic cells proportions measured in each patient (Cf. Supplementary Table 2). Simulations are depicted in red and experimental data for the corresponding patient in black.

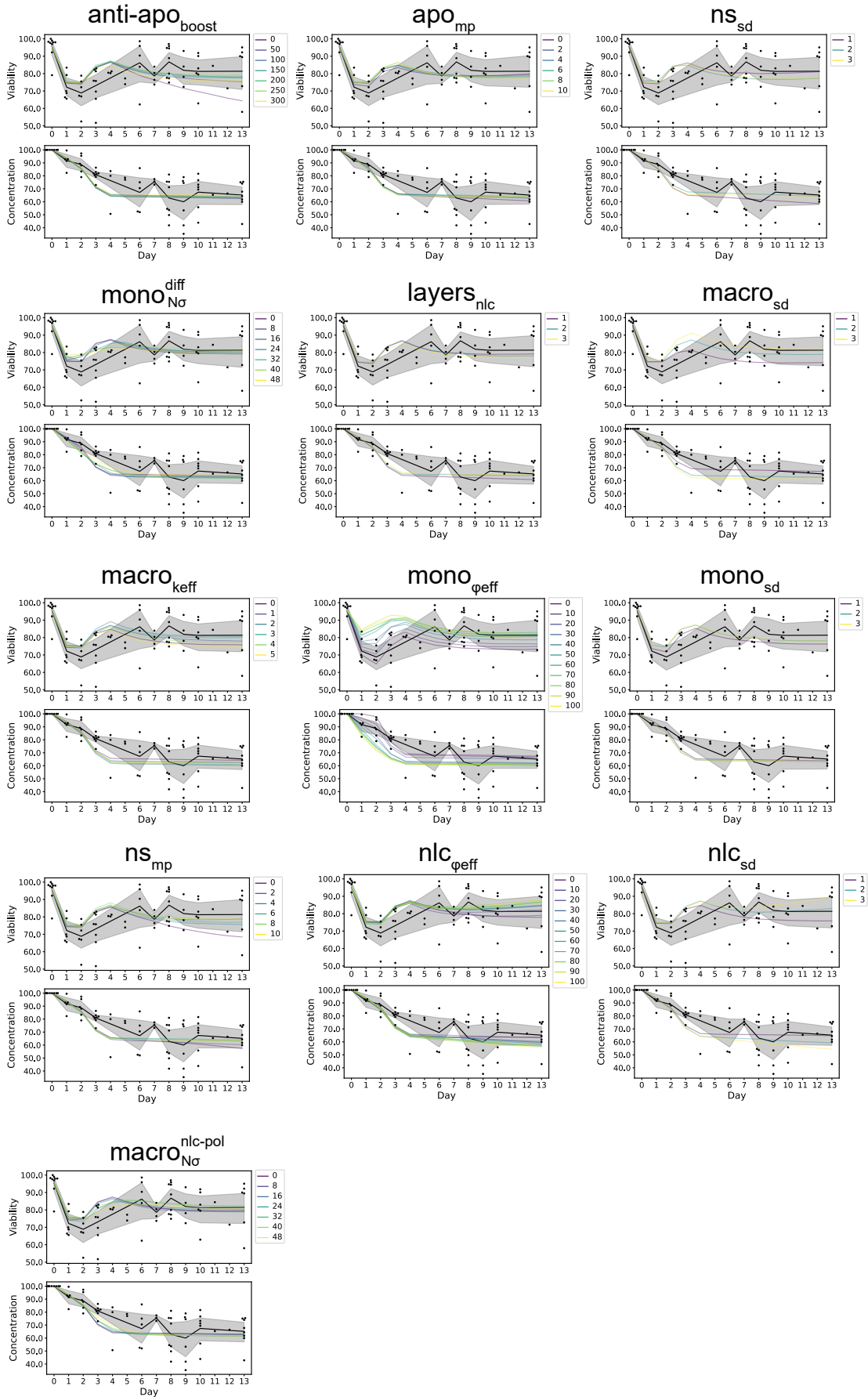


Fig. S8. Parameter sensitivity analysis. The analysis was performed on the remaining 13 parameters for which the absolute value of the correlation coefficient to the fitness on viability and fitness on concentration were below 0.4.

- 1 1. Lisa B Boyette, Camila Macedo, Kevin Hadi, Beth D Elinoff, John T Walters, Bala Ramaswami, Geetha Chalasani, Juan M Taboas, Fadi G Lakkis, and Diana M Metes. Phenotype, function, and
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