Appendix

A. Sobol sequences for non-uniformly distributed parameters

The main issue of concern with Sobol sequencing is convergence for non-uniformly distributed parameters. Sobol sequences create quasi-Monte Carlo sequences, also called quasi-random low-discrepancy sequences. Discrepancy refers to a measure of the maximum deviation of a point set from a uniform distribution (Niederreiter, 1992; Drmota & Tichy, 1997). Discrepancy is especially important in numerical integration, as the bound of the integration error is the variation of the function multiplied by the discrepancy. This is demonstrated by the Koksma-Hlawka inequality and gives a convergence criterion for the integration (Kuipers & Niederreiter, 2006). Low-discrepancy sequences are preferable to Monte Carlo methods for numerical integration, as their error order is $O\left(\frac{(loglog\ N\ )^p}{N}\right)$ as compared to $\frac{1}{\sqrt{N}}$ for Monte Carlo integration, where p is the number of parameters and N is the number of points in the sequence.

For non-uniformly distributed parameters, H-discrepancy is a commonly used measure of discrepancy (Chelson, 1976). H-discrepancy measures distribution properties with respect to the measure H (a non-uniform distribution) on a uniform distribution. Going about generating the H-distributed low-discrepancy sequences can be difficult. For a single dimension, we might be able to solve for this if we know the inverse of the distribution, but this is often not explicit. If the parameter space is multidimensional with dependencies, discrepancy is not preserved.

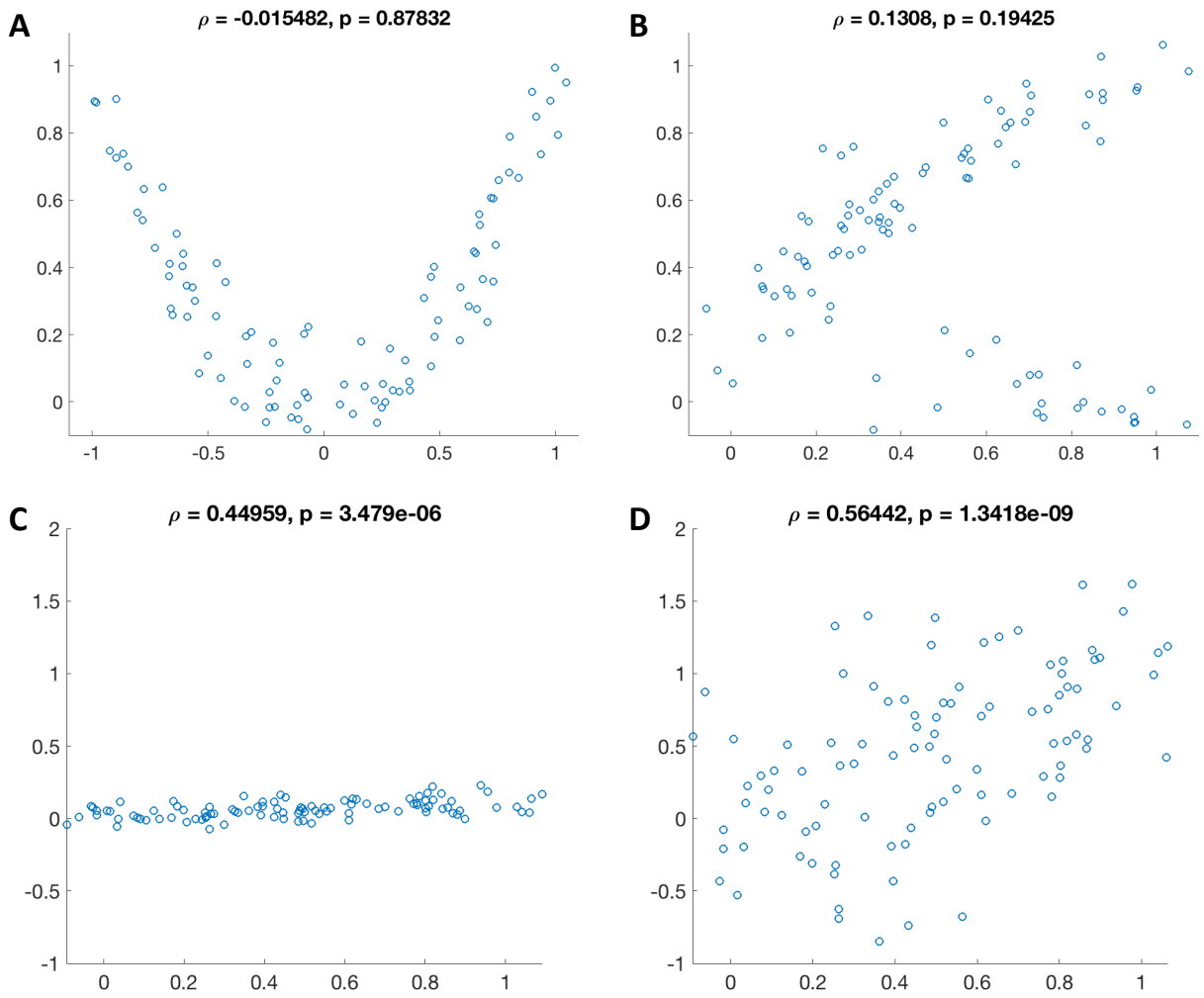
One way that has shown promise to get around this is a modification of the Hlawka-Muck transformation (Hlawka & Muck, 1972). Numerical approximation of the integral is done and the transformed values are assigned onto the new distribution, corresponding to where its relative position is in the new distribution based on its relative position in the previous distribution. This was later expanded to using one-dimensional marginal distributions instead of conditional distributions (Hlawka, 1997) and Hartinger and Kainhofer added on an interpolation step between jumps to avoid the lattice structure and improve the approximation of the inverse distribution function. (Hartinger & Kainhofer, 2005).

There are some issues with such modifications for low-discrepancy sequences. First, if we have dependent marginals (i.e. not all of our parameters are independent from each other), the upper band on discrepancy becomes higher. To get around this, dependencies can be hidden in the integrand through a copula (Nelsen, 2006). Second, spacing in the parameter space is dependent on the number of points chosen N. N has to be fixed before calculation and the set generated by it heavily depends on it. To add more points to the sequence, everything has to be regenerated. To get around this, one can set the N for our newly distributed points to be $\widetilde{N} = i^N$. New points can then be added until $\widetilde{N} > N$ (Hartinger & Kainhofer, 2005). Third, it is possible for several transformed data points to have identical coordinates. This is especially true for highly peaked distributions, such as the log-normal. Finally, it is computational expensive, as each point involves summing up all other points. The distribution function also needs to be evaluated pN times.

This method only applies for distributions supported on the unit hypercube, which assumes variation is finite. Therefore, singularity on the boundaries poses a problem. Sobol was able to prove a convergence theorem, but only for uniformly distributed low-discrepancy sequences (Sobol 1973). This newer method has been shown to converge under certain origin- or corner-avoidance conditions (Hartinger & Kainhofer, 2005). A method to get around these issues is transforming between the real line and unit interval given by the double exponential distribution, along with a zero shift by $\frac{1}{N}$ (Kainhofer, 2003).

B. PRCC limitations

PRCC analysis relies on the assumption that relationships between model inputs and outputs are monotone, i.e., that the trends are either increasing or decreasing (but not both) over the full parameter range. When this assumption is violated, PRCC may result in small and possibly insignificant correlations even when there is a strong relationship between input and output. Non-monotonicity can take different forms, demonstrated in panels A and B below. One possibility is that the input-output data follows a single non-monotonic function, such as that shown in panel A. Another possibility is that the data separates and follows two or more distinct trends, possibly due to a bifurcation, such as that shown in panel B. In both of these cases, the PRCC value (denoted by ρ) is quite small and the p-value indicates insignificance, despite a clear relationship between input (x) and output (y). A further limitation of PRCC, as explored in Section 5.3.2, is that it does not quantify effect size. This is demonstrated in panels C and D, where there is a ten-fold difference in the range of outputs (y) which is not reflected in the PRCC values or significance.



C. ODE granuloma model (Example 2)

1. Model equations

$$\frac{dB_E}{dt} = \alpha_{20}B_E + k_{17}NM_I\left(\frac{B_I^2}{B_I^2 + N^2M_I^2}\right) + k_{14a}N_{fracc}\frac{B_I}{M_I}M_I\left(\frac{\left(\frac{T_C + w_3T_1}{M_I}\right)}{\left(\frac{T_C + w_3T_1}{M_I}\right) + c_4}\right)$$
$$+ k_{14b}N_{fraca}\frac{B_I}{M_I}M_I\left(\frac{F_\alpha}{F_\alpha + f_9I_{10} + s_{4b}}\right) - k_2\frac{N}{2}M_R\left(\frac{B_E}{B_E + c_9}\right) - k_{15}M_AB_E - k_{18}M_RB_E$$
$$- \mu_{B_E}B_E + \mu_{M_I}N_{fracd}\frac{B_I}{M_I}M_I$$

$$\frac{dB_I}{dt} = \alpha_{19}B_I(NM_I - B_I) + k_2\frac{N}{2}M_R\left(\frac{B_E}{B_E + c_9}\right) - k_{17}NM_I\left(\frac{B_I^2}{B_I^2 + N^2M_I^2}\right)$$
$$- k_{14a}\frac{B_I}{M_I}M_I\left(\frac{\left(\frac{T_C + w_3T_1}{M_I}\right)}{\left(\frac{T_C + w_3T_1}{M_I}\right) + c_4}\right) - k_{14b}\frac{B_I}{M_I}M_I\left(\frac{F_\alpha}{F_\alpha + f_9I_{10} + s_{4b}}\right)$$
$$- k_{52}\frac{B_I}{M_I}M_I\left(\frac{\left(\frac{T_C\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1T_1}{M_I}\right)}{\left(\frac{T_C\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1T_1}{M_I}\right) + c_{52}}\right) - \mu_{B_I}B_I + \mu_{M_I}\frac{B_I}{M_I}M_I$$

$$\frac{dM_R}{dt} = Sr_M + \alpha_{4a}(M_A + w_2M_I) + Sr_{4b}\left(\frac{F_\alpha}{F_\alpha + f_8I_{10} + s_{4b}}\right) - k_2M_R\left(\frac{B_E}{B_E + c_9}\right)$$
$$- k_3M_R\left(\frac{B_E + wB_I + \beta F_\alpha}{B_E + wB_I + \beta F_\alpha + c_8}\right)\left(\frac{I_\gamma}{I_\gamma + f_1I_4 + f_7I_{10} + s_1}\right) - \mu_{M_R}M_R$$

$$\frac{dM_I}{dt} = k_2M_R\left(\frac{B_E}{B_E + c_9}\right) - k_{17}M_I\left(\frac{B_I^2}{B_I^2 + N^2M_I^2}\right) - k_{14a}M_I\left(\frac{\left(\frac{T_C + w_3T_1}{M_I}\right)}{\left(\frac{T_C + w_3T_1}{M_I}\right) + c_4}\right)$$
$$- k_{14b}M_I\left(\frac{F_\alpha}{F_\alpha + f_9I_{10} + s_{4b}}\right) - k_{52}M_I\left(\frac{\left(\frac{T_C\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1T_1}{M_I}\right)}{\left(\frac{T_C\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1T_1}{M_I}\right) + c_{52}}\right) - \mu_{M_I}M_I$$

$$\frac{dM_A}{dt} = k_3M_R\left(\frac{B_E + wB_I + \beta F_\alpha}{B_E + wB_I + \beta F_\alpha + c_8}\right)\left(\frac{I_\gamma}{I_\gamma + f_1I_4 + f_7I_{10} + s_1}\right) - k_4M_A\left(\frac{I_{10}}{I_{10} + s_8}\right) - \mu_{M_A}M_A$$

$$\frac{dT_0}{dt} = \alpha_{1a}(M_A + w_2M_I) + Sr_{1b}\left(\frac{F_\alpha}{F_\alpha + f_8I_{10} + s_{4b2}}\right) + \alpha_2T_0\left(\frac{M_A}{M_A + c_{15}}\right)$$
$$- k_6I_{12}T_0\left(\frac{I_\gamma}{I_\gamma + f_1I_4 + f_7I_{10} + s_1}\right) - k_7T_0\left(\frac{I_4}{I_4 + f_2I_\gamma + s_2}\right) - \mu_{T_0}T_0$$

$$\frac{dT_1}{dt} = \alpha_{3a}(M_A + w_2M_I) + Sr_{3b}\left(\frac{F_\alpha}{F_\alpha + f_8I_{10} + s_{4b1}}\right) + k_6I_{12}T_0\left(\frac{I_\gamma}{I_\gamma + f_1I_4 + f_7I_{10} + s_1}\right) + k_{31}T_{4EM}M_I$$
$$- \mu_{T_\gamma}\left(\frac{I_\gamma}{I_\gamma + c}\right)T_1M_A - \mu_{T_1}T_1$$

$$\frac{dT_2}{dt} = \alpha_{3a2}(M_A + w_2M_I) + Sr_{3b2}\left(\frac{F_\alpha}{F_\alpha + f_8I_{10} + s_{4b1}}\right) + k_7T_0\left(\frac{I_4}{I_4 + f_2I_\gamma + s_2}\right) + k_{32}T_{4EM}M_A - \mu_{T_2}T_2$$

$$\frac{dT_{80}}{dt} = \alpha_{1a}(M_A + w_2M_I) + Sr_{1b}\left(\frac{F_\alpha}{F_\alpha + f_8I_{10} + s_{4b2}}\right) + \alpha_2T_{80}\left(\frac{M_A}{M_A + c_{15}}\right)$$
$$- k_6I_{12}T_{80}\left(\frac{I_\gamma}{I_\gamma + f_1I_4 + f_7I_{10} + s_1}\right) - \mu_{T_{80}}T_{80}$$

$$\frac{dT_8}{dt} = m\alpha_{3ac}(M_A + w_2M_I) + mSr_{3bc}\left(\frac{F_\alpha}{F_\alpha + f_8I_{10} + s_{4b1}}\right) + mk_6I_{12}T_{80}\left(\frac{I_\gamma}{I_\gamma + f_1I_4 + f_7I_{10} + s_1}\right)$$
$$+ k_{34}T_{8EM}M_I - \mu_{T_{c\gamma}}\left(\frac{I_\gamma}{I_\gamma + c_c}\right)T_8M_A - \mu_{T_C}T_8$$

$$\frac{dT_C}{dt} = m\alpha_{3ac}(M_A + w_2 M_I) + mSr_{3bc}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right) + mk_6 I_{12} T_{80}\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) + k_{33} T_{8EM} M_I - \mu_{T_{c\gamma}}\left(\frac{I_\gamma}{I_\gamma + c_c}\right) T_C M_A - \mu_{T_C} T_C$$

$$\frac{dT_{4EM}}{dt} = Sr_{4EM}\left(\frac{F_\alpha}{F_\alpha + hs_{4EM}}\right) - k_{31} T_{4EM} M_I - k_{32} T_{4EM} M_A - \mu_{T_{4EM}} T_{4EM}$$

$$\frac{dT_{8EM}}{dt} = Sr_{8EM}\left(\frac{F_\alpha}{F_\alpha + hs_{8EM}}\right) - k_{33} T_{8EM} M_I - k_{34} T_{8EM} M_I - \mu_{T_{8EM}} T_{8EM}$$

$$\frac{dT_{4N\,on}}{dt} = Sr_{4N\,on}\left(\frac{F_\alpha}{F_\alpha + hs_{4N\,on}}\right) - \mu_{T_{4N\,on}} T_{4N\,on}$$

$$\frac{dT_{8N\,on}}{dt} = Sr_{8N\,on}\left(\frac{F_\alpha}{F_\alpha + hs_{8N\,on}}\right) - \mu_{T_{8N\,on}} T_{8N\,on}$$

$$\frac{dF_\alpha}{dt} = \alpha_{30} M_I + \alpha_{31} M_A\left(\frac{I_\gamma + \beta_2(B_E + wB_I)}{I_\gamma + \beta_2(B_E + wB_I) + f_1 I_4 + f_7 I_{10} + s_{10}}\right) + \alpha_{32} T_1 + \alpha_{33}\left(\frac{T_C + T_8}{2m}\right) - \mu_{F_\alpha} F_\alpha$$

$$\frac{dI_\gamma}{dt} = s_g\left(\frac{B_E + wB_I}{B_E + wB_I + c_{10}}\right)\left(\frac{I_{12}}{I_{12} + s_7}\right) + \alpha_{5a} T_1\left(\frac{M_A}{M_A + c_{5a}}\right) + \alpha_{5b} T_8\left(\frac{M_A}{M_A + c_{5b}}\right) + \alpha_{5c} M_I + \alpha_7 T_0\left(\frac{I_{12}}{I_{12} + f_4 I_{10} + s_4}\right) + \alpha_7 T_{80}\left(\frac{I_{12}}{I_{12} + f_4 I_{10} + s_4}\right) - \mu_{I_\gamma} I_\gamma$$

$$\frac{dI_{12}}{dt} = s_{12}\left(\frac{B_E + wB_I}{B_E + wB_I + c_{230}}\right) + \alpha_{23} M_R\left(\frac{B_E + wB_I}{B_E + wB_I + c_{23}}\right) + \alpha_8 M_A\left(\frac{s}{s + I_{10}}\right) - \mu_{I_{12}} I_{12}$$

$$\frac{dI_{10}}{dt} = \delta_7(M_I + M_A)\left(\frac{s_6}{I_{10} + f_6 I_\gamma + s_6}\right) + \alpha_{16} T_1 + \alpha_{17} T_2 + \alpha_{18}\left(\frac{T_C + T_8}{2m}\right) - \mu_{I_{10}} I_{10}$$

$$\frac{dI_4}{dt} = \alpha_{11} T_0 + \alpha_{12} T_2 - \mu_{I_4} I_4$$

2. Parameters

Name	min	max	Name	min	max
Srm	0	0	cc	355	592
alpha4a	0.574	0.834	nuTC	0.319	0.319
w	0.285	0.329	sg	2370	7350
w3	0.233	0.369	c10	544000	6370000
w2	1	1	s7	593	823
Sr4b	655	750	alpha5a	0.634	0.836
f8	0.00164	0.00164	c5a	316	627
f9	0.6	0.6	alpha5b	0.159	0.590
s4b	3210	4860	alpha5c	0.0806	0.356
s4b1	6780	9420	c5b	160	795
s4b2	5340	9420	alpha7	0.0125	0.161
k4	0.0744	0.171	f4	1.5	1.5
s8	195	945	s4	273	894
k2	0.431	2.24	nuIG	6.36	9.26
c9	1190	7450	alpha23	0.00438	0.00438
k3	0.0391	0.0391	c23	138	526
f1	151	151	alpha8	0.376	0.7871
s1	53.4	453	s12	2330	3660

beta	10000000	10000000	c230	390	708
c8	175000	363000	nuI12	1.1	1.1
nuMR	0.005	0.005	s	170	657
k17	0.112	0.312	s6	683	772
N	22.3	24.9	f6	0.355	0.355
k14a	0.0617	0.342	delta7	0.406	0.839
c4	406	878	alpha16	0.331	0.830
k14b	0.627	0.864	alpha17	0.400	0.595
k52	0.596	0.694	alpha18	0.536	0.750
w1	0.186	0.685	nuI10	1.81	4.14
c52	103000	247000	alpha11	0.00324	0.0729
cT1	35.8	35.9	alpha12	0.0189	0.0658
nuMI	0.00330	0.00330	nuI4	2.7	2.7
nuMA	0.174	0.174	alpha30	0.0466	0.0902
alpha1a	0.0264	0.566	alpha31	0.156	0.787
Sr1b	23200	54200	beta2	12000	12000
alpha2	0.122	0.364	s10	109	290
c15	2750000	4100000	alpha32	0.187	0.289
k6	0.098	0.209	alpha33	0.221	0.332
f7	7.21	30.8	nuTNF	1.14	1.14
k7	0.249	0.644	alpha19	0.874	1.28
f2	0.209	0.409	alpha20	0.311	0.395
s2	404	908	Nfracc	0.06	0.06
nuT0	0.217	0.217	Nfraca	0.06	0.06
m	0.8	0.8	k15	0.000166	0.000166
alpha3a	0.427	0.807	k18	0.000120	0.000803
Sr3b	13.9	77.3	nI	6.26E-05	8.29E-05
alpha3a2	0.216	0.762	nE	4.37E-09	6.65E-09
Sr3b2	53.2	89.2	Nfracd	0.00132	0.00132
nuTg	0.238	0.747	power	2	2
c	271	687	Sr4Non	3.63	50.0
nuT1	0.33	0.33	hs4Non	32.3	84.6
nuT2	0.33	0.33	mui4Non	0.310	0.323
alpha3ac	0.256	0.763	Sr8Non	17.6	42.1
Sr3bc	14.4	26.1	hs8Non	6.64	35.0
nuTCg	0.453	0.830	mui8Non	0.321	0.326

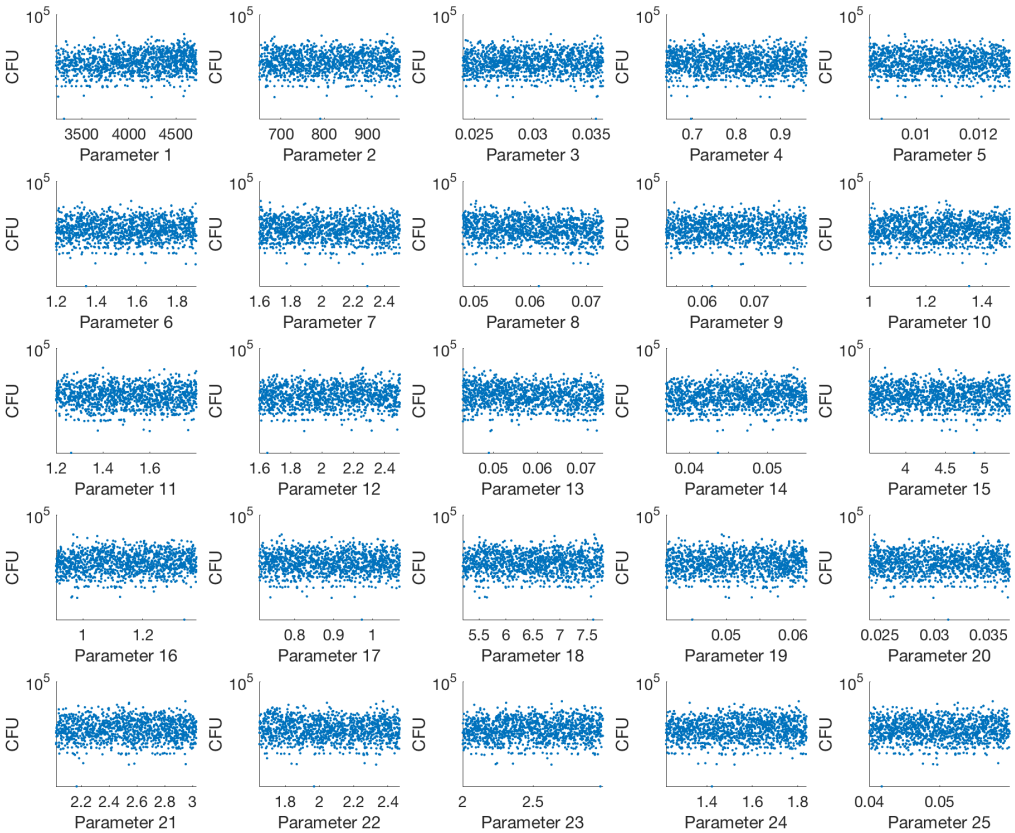
D. *GranSim* – Agent-based model (Example 3)

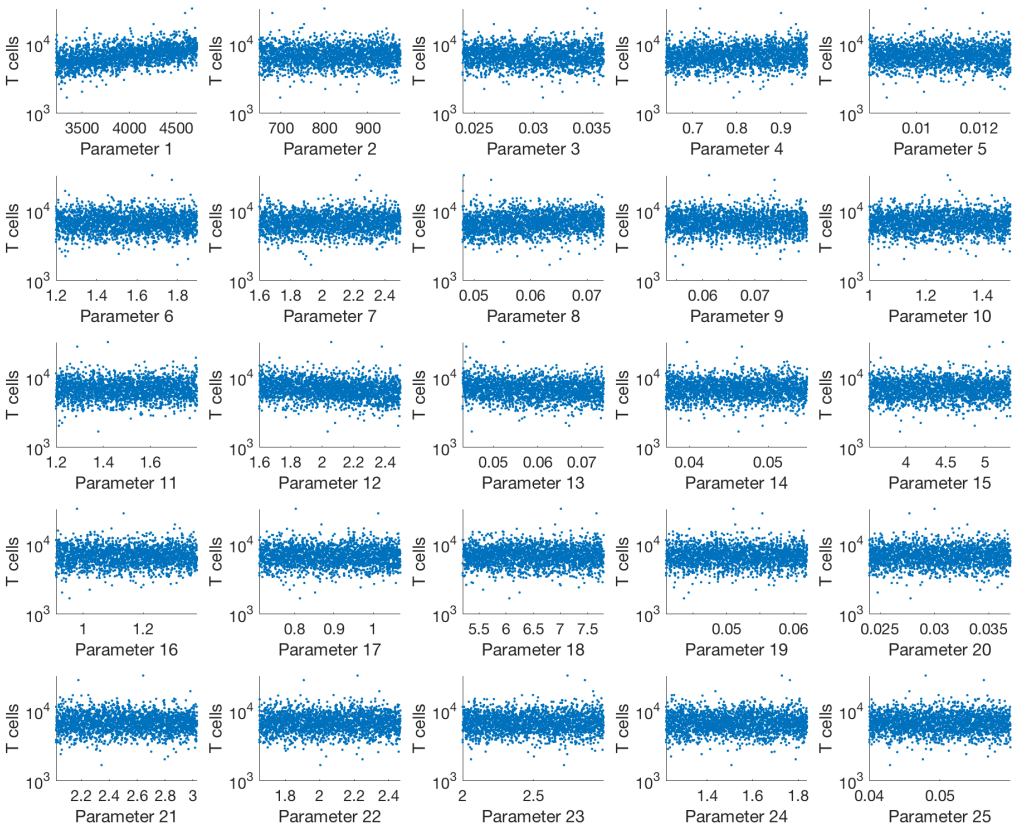
1. Model parameters

Index	Parameter name	Description (units)	Range
1	GR_Recruit_Prob__timeRecEnabled	Time after which T cell recruitment is enabled (10-minute time steps)	[3225, 4722]
2	GR_Recruit_Prob__timeMaxRecDelay	Time after which maximum T cell recruitment is enabled (10-minute time steps)	[650, 976]
3	GR_Recruit_Prob_Mac__maxRecProb	Max probability of recruiting a macrophage	[0.024, 0.036]
4	GR_Recruit_Prob_Mac__thresholdRecChemokine	Threshold of Mac recruitment for chemokines	[0.64, 0.96]
5	GR_Recruit_Prob_Mac__thresholdRecTNF	Threshold of Mac recruitment for TNF	[0.0085, 0.013]
6	GR_Recruit_Prob_Mac__recruitmentHalfSatTNF	Half-saturation parameter for Mac TNF-dependent recruitment	[1.2, 1.9]
7	GR_Recruit_Prob_Mac__recruitmentHalfSatChemokine	Half-saturation parameter for Mac chemokine-dependent recruitment	[1.6, 2.5]
8	GR_Recruit_Prob_Tcell_Tgam__maxRecProb	Max probability of recruiting a Tgam	[0.048, 0.073]
9	GR_Recruit_Prob_Tcell_Tgam__thresholdRecChemokine	Threshold of Tgam recruitment for chemokines	[0.053, 0.08]
10	GR_Recruit_Prob_Tcell_Tgam__thresholdRecTNF	Threshold of Tgam recruitment for TNF	[1, 1.5]
11	GR_Recruit_Prob_Tcell_Tgam__recruitmentHalfSatTNF	Half-saturation parameter for Tgam TNF-dependent recruitment	[1.2, 1.8]
12	GR_Recruit_Prob_Tcell_Tgam__recruitmentHalfSatChemokine	Half-saturation parameter for Tgam chemokine-dependent recruitment	[1.6, 2.5]
13	GR_Recruit_Prob_Tcell_Tgam__probCognate	Probability Tgam will be cognate when recruited through recruitment by probability	[0.043, 0.075]
14	GR_Recruit_Prob_Tcell_Tcyt__maxRecProb	Max probability of recruiting a Tcyt	[0.037, 0.055]
15	GR_Recruit_Prob_Tcell_Tcyt__thresholdRecChemokine	Threshold of Tcyt recruitment for chemokines	[3.54, 5.32]

16	GR_Recruit_Prob_Tcell_Tcyt__thresholdRecTNF	Threshold of Tcyt recruitment for TNF	[0.91, 1.38]
17	GR_Recruit_Prob_Tcell_Tcyt__recruitmentHalfSatTNF	Half-saturation parameter for Tcyt TNF-dependent recruitment	[0.71, 1.07]
18	GR_Recruit_Prob_Tcell_Tcyt__recruitmentHalfSatChemokine	Half-saturation parameter for Tcyt chemokine-dependent recruitment	[5.2, 7.8]
19	GR_Recruit_Prob_Tcell_Tcyt__probCognate	Probability Tcyt will be cognate when recruited through recruitment by probability	[0.041, 0.062]
20	GR_Recruit_Prob_Tcell_Treg__maxRecProb	Max probability of recruiting a Treg	[0.024, 0.037]
21	GR_Recruit_Prob_Tcell_Treg__thresholdRecChemokine	Threshold of Treg recruitment for chemokines	[2.02, 3.03]
22	GR_Recruit_Prob_Tcell_Treg__thresholdRecTNF	Threshold of Treg recruitment for TNF	[1.65, 2.47]
23	GR_Recruit_Prob_Tcell_Treg__recruitmentHalfSatTNF	Half-saturation parameter for Treg TNF-dependent recruitment	[2, 3]
24	GR_Recruit_Prob_Tcell_Treg__recruitmentHalfSatChemokine	Half-saturation parameter for Treg chemokine-dependent recruitment	[1.22, 1.84]
25	GR_Recruit_Prob_Tcell_Treg__probCognate	Probability Treg will be cognate when recruited through recruitment by probability	[0.04, 0.06]

2. Scatterplots of parameters vs. outputs


CFU
10^5
3500 4000 4500
Parameter 1
700 800 900
Parameter 2
0.025 0.03 0.035
Parameter 3
0.7 0.8 0.9
Parameter 4
0.01 0.012
Parameter 5
1.2 1.4 1.6 1.8
Parameter 6
1.6 1.8 2 2.2 2.4
Parameter 7
0.05 0.06 0.07
Parameter 8
0.06 0.07
Parameter 9
1 1.2 1.4
Parameter 10
1.2 1.4 1.6
Parameter 11
1.6 1.8 2 2.2 2.4
Parameter 12
0.05 0.06 0.07
Parameter 13
0.04 0.05
Parameter 14
4 4.5 5
Parameter 15
1 1.2
Parameter 16
0.8 0.9 1
Parameter 17
5.5 6 6.5 7 7.5
Parameter 18
0.05 0.06
Parameter 19
0.025 0.03 0.035
Parameter 20
2.2 2.4 2.6 2.8 3
Parameter 21
1.8 2 2.2 2.4
Parameter 22
2 2.5
Parameter 23
1.4 1.6 1.8
Parameter 24
0.04 0.05
Parameter 25



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