SUPPLEMENTARY MATERIAL TO THE MANUSCRIPT

A multi-compartment agent-based model of TB granuloma formation and T cell priming

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Supplementary Text S1: The scaling factor Υ

Table S2 shows how the scaling factor Υ, is consistently negatively correlated to bacterial burden and granuloma size. Υ is a proxy for multiple LN sources of precursor and effector T cells. Again, more effector T cells at the granuloma site are beneficial to the host (lower bacterial burden). Υ is positively correlated to $T\gamma$ and CTL cells, early during infection (<3 weeks). The same parameter is negatively correlated to both $T\gamma$ and CTL later during infection**.** The scaling factor Υ applies to both precursor and effector $T\gamma$ and CTL cells (it is the same for all these cell types). These results on Υ are apparently contradictory. The switch from positive to negative correlation of $T\gamma$ and CTL cell levels to Υ during infection may suggest that the number of effector Ts at the site initially (at the onset of infection) has the most beneficial impact on infection progression (as shown by the PRCCs related to bacterial load). Later during infection, the same scaling mechanism lowers the total number of effector T cells at the granuloma site, because less T cells are likely needed to maintain containment. This strongly suggests that a few more effector T cells can make a difference early during infection rather than once the granuloma has been established. The *Vaccination and Immunotherapy* section in the main text investigates some of these hypotheses.

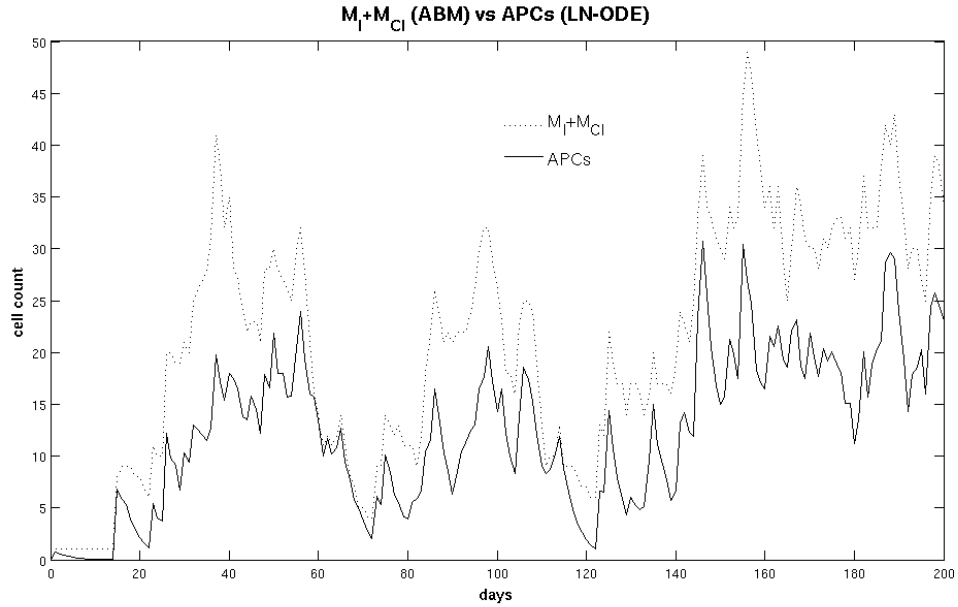


Figure S1: comparison of the sum $[M_I(t)+M_{CI}(t)]$ generated by the ABM (dashed line) in a containment scenario and the corresponding MDC dynamics (dotted line) generated by the LN-ODE module (seeded by *scalingMDC* x $[M_I(t)+M_{CI}(t)]$). The parameter *scalingAPC* is set to 1.

Table S1: projection factors to scale the 2D granuloma predictions (cell and bacterial numbers) to a 3D spherical granuloma of equivalent diameter. List of diameter lesions and corresponding 2D and 3D volumes (assuming a microcompartment volume of 0.08 mm^3). The percentage of volume occupied by the 2D volume in the 3D sphere is obtained dividing the 3D by the 2D volume. The projection factor column lists the scaling needed to project cell and bacterial numbers into a 3D spherical granuloma.

	Diameter lesion (mm)	Volume 2D (mm^3)	Volume 3D (mm^3)	% of volume occupied by the 2D disk	Projection factor
	0.1	0.00015708	0.000524	30	3.333333
	0.2	0.000628319	0.004189	15	6.666667
Containment	0.3	0.001413717	0.014137	10	10
	0.4	0.002513274	0.03351	7.5	13.33333
	0.5	0.003926991	0.06545	6	16.66667
	0.6	0.005654867	0.113097	5	20
Dissemination	0.7	0.007696902	0.179594	4.285714	23.33333
	0.8	0.010053096	0.268083	3.75	26.66667
	0.9	0.01272345	0.381704	3.333333	30
	1	0.015707963	0.523599	3	33.33333
	1.1	0.019006636	0.69691	2.727273	36.66667
	1.2	0.022619467	0.904779	2.5	40
	1.3	0.026546458	1.150347	2.307692	43.33333
	1.4	0.030787608	1.436755	2.142857	46.66667
	1.5	0.035342917	1.767146	2	50
	1.6	0.040212386	2.144661	1.875	53.33333
	1.7	0.045396014	2.572441	1.764706	56.66667
	1.8	0.050893801	3.053628	1.666667	60
	1.9	0.056705747	3.591364	1.578947	63.33333
	2	0.062831853	4.18879	1.5	66.66667

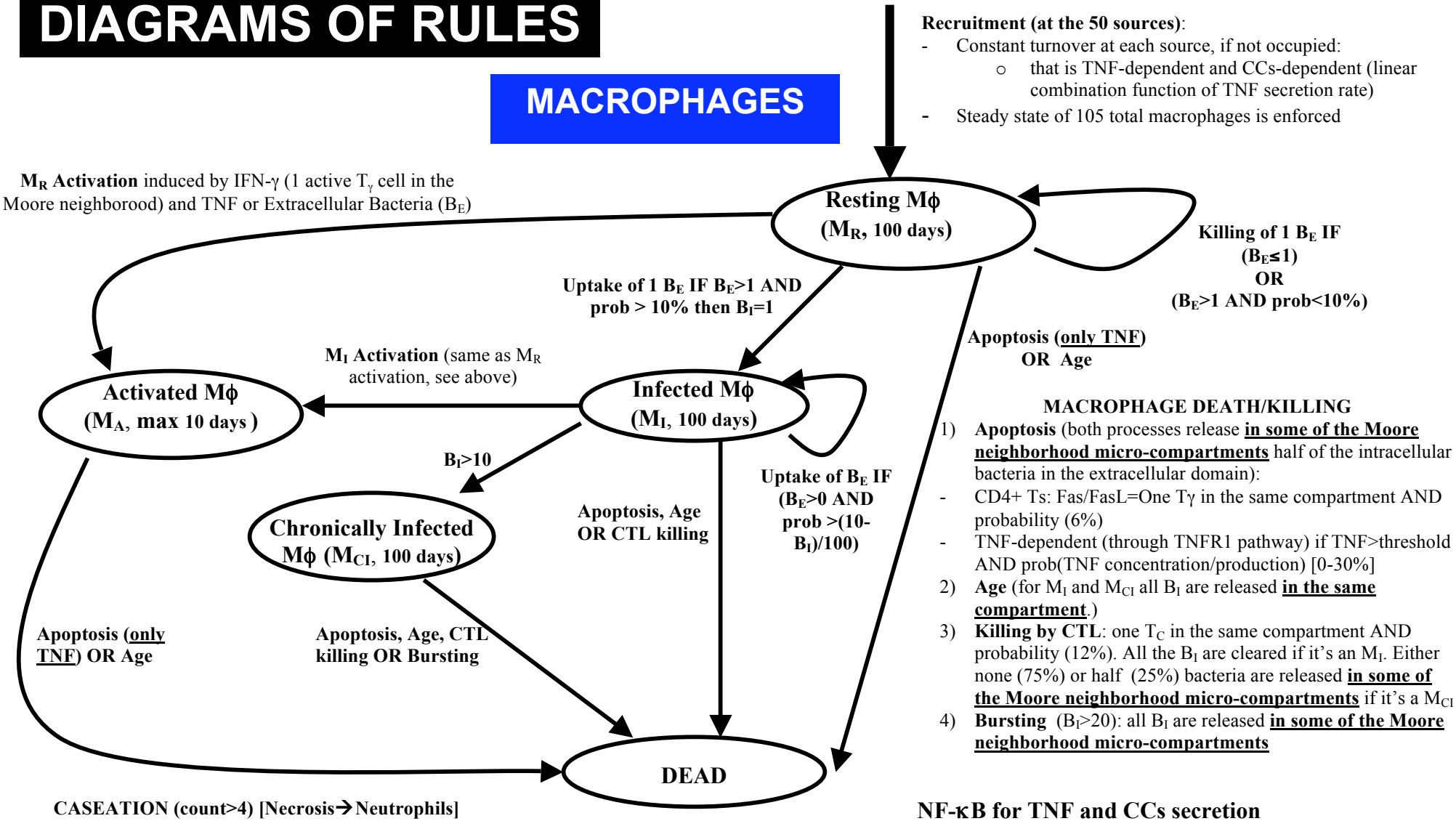
Table S2: detailed PRCC results based on LHS ranges defined in Table 1. We only show the parameters with significant PRCCs ($p<0.05$).

OUTPUT	POSITIVE CORRELATION			NEGATIVE CORRELATION		
	ALWAYS	*EARLY*	*LATE*	*ALWAYS*	*EARLY*	*LATE*
$B_I+B_E=B_T$		ξ_1 , ξ_2	τ_{NFkb}	*scalingAPC*, Υ	k_{14}, k_{15}, k_{20a}	k_{16}
$T\gamma$		k_{14}, k_{15}, k_{20a}, Υ	τ_{NFkb} (>day 20)		ξ_1 , ξ_2 μ_{MDC}, μ_{N4}	Υ
T_C		k_{17}	τ_{NFkb} , ξ_1 (>day 20)		k_{15}, ξ_2	Υ
T_{reg}		k_{14}, k_{15}, k_{20a}, Υ	τ_{NFkb} (>day 20)		ξ_1 , ξ_2 , μ_{MDC}, μ_{N4} (day 21)	k_{16}
M_I+M_{CI}	ξ_1 *(till 150 days),* ξ_2 *(>day 7)*		τ_{NFkb}	*scalingAPC,* Υ *(>day 7)*	k_{20a}	k_{16}
Granuloma size	ξ_1		μ_{MDC} , ξ_2	*scalingAPC*	τ_{NFkb} k_{17}	Υ , k_{20a},
M_A	ξ_1 *(>20 days)*		ξ_2	τ_{NFkb} (till day 150)	k_{15}, k_{24a}	Υ

DIAGRAMS OF RULES

MACROPHAGES

Recruitment (at the 50 sources):
- Constant turnover at each source, if not occupied:
  - that is TNF-dependent and CCs-dependent (linear combination function of TNF secretion rate)
- Steady state of 105 total macrophages is enforced



MACROPHAGE DEATH/KILLING

1) **Apoptosis** (both processes release **in some of the Moore neighborhood micro-compartments** half of the intracellular bacteria in the extracellular domain):
   - CD4+ Ts: Fas/FasL=One Tγ in the same compartment AND probability (6%)
   - TNF-dependent (through TNFR1 pathway) if TNF>threshold AND prob(TNF concentration/production) [0-30%]
2) **Age** (for M_I and M_{CI} all B_I are released **in the same compartment**.)
3) **Killing by CTL**: one T_C in the same compartment AND probability (12%). All the B_I are cleared if it's an M_I. Either none (75%) or half (25%) bacteria are released **in some of the Moore neighborhood micro-compartments** if it's a M_{CI}
4) **Bursting** ($B_I>20$): all B_I are released **in some of the Moore neighborhood micro-compartments**

CASEATION (count>4) [Necrosis→Neutrophils]

1) M_A death (just AGE)
2) M_I and M_{CI} killing by CTL contribute to caseation
3) M_I and M_{CI} killing by apoptosis (CD4+ Ts / Fas)
4) M_{CI} bursting

Mϕ ACTIVATION

1) *STAT1* is activated (proxy for IFN-γ) for M_R and M_I with prob<0.03*(# Tγ cell in the Moore neighborhood)
2) AND *NF-κB* is activated (biologically means that either (TNF>(*threshold_1*) AND prob(TNF concentration/production) [0-60%]) OR Bacteria (B_E>100, total in the Moore neighborhood)

NF-κB for TNF and CCs secretion

NF-κB is activated IF
1) (TNF>*threshold_1*) AND prob(TNF concentration/production)) OR
2) IF B_E>100 in the Moore neighborhood OR
3) IF macrophage state is ACTIVE or CHRONICALLY INFECTED

IF *NF-κB* is activated
- All Macs secrete TNF and CCs at max rate

IF *NF-κB* is deactivated
- M_R DO NOT secrete TNF and CCs AND M_I secretes TNF and CCs at half rate

➢ **NF-κB and STAT-1 are deactivated** (for K time steps) IF at least 1 Treg is in the Moore Neighborood

➢ **NF-κB and STAT-1 cannot be deactivated in Chronically Infected macrophages**

T CELLS

Treg action

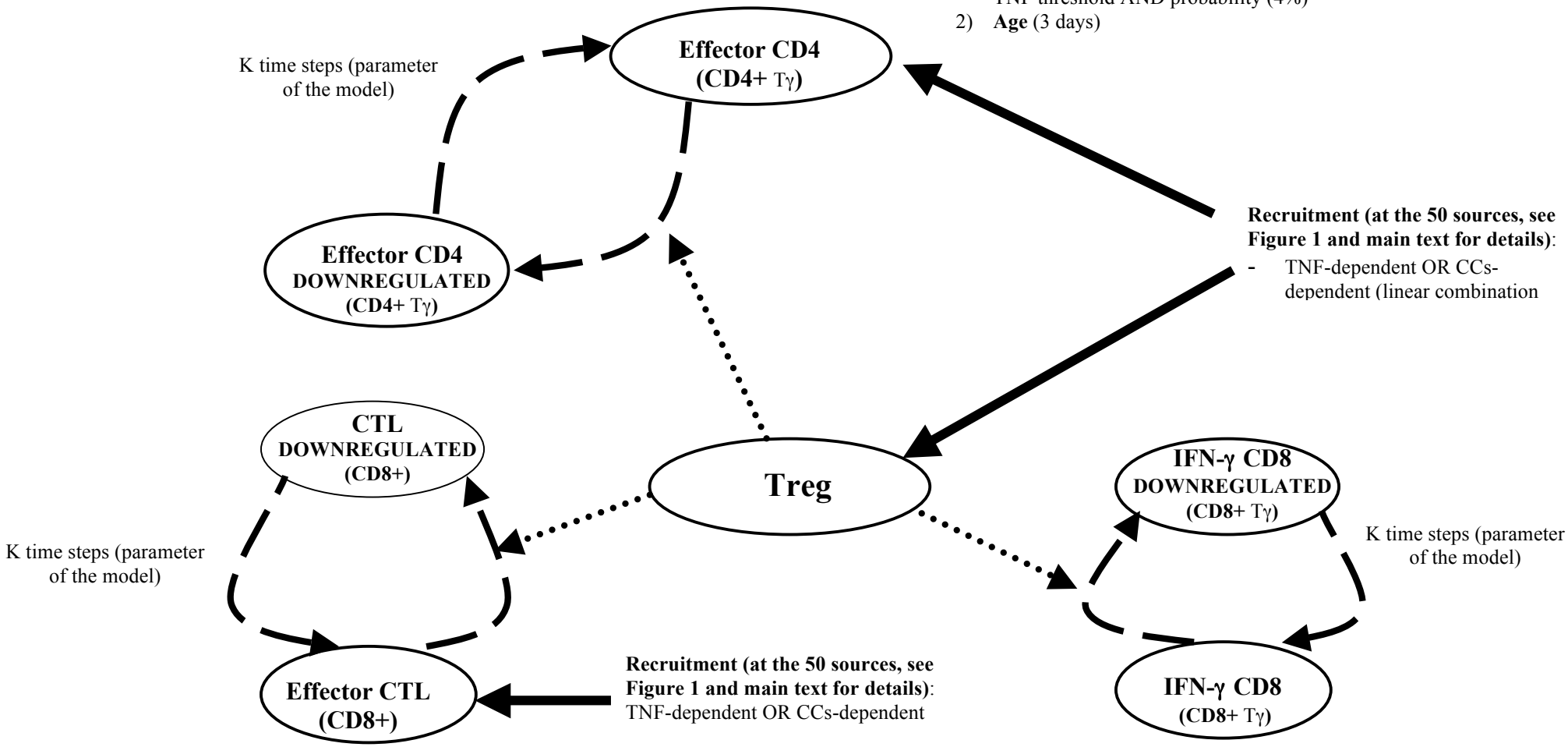
1 Treg in the Moore neighborood of the T cell is sufficient to stop **(for K time steps)** either IFN-γ production, CTL killing or proliferation**]**.

T CELL DEATH

ALL T cell die by TNF-induced apoptosis or Age

1) **Apoptosis**:
- TNF-dependent (through TNFR1 pathway)=above a TNF threshold AND probability (4%)

2) **Age** (3 days)



DIFFUSION

Finite difference approximation for discrete-time discrete-space diffusion on the grid:

$$C_{i,j}(t+dt) = (1-\delta\, dt)\, C_{i,j}(t) + \frac{\lambda}{4}\{C_{i-1,j}(t) + C_{i+1,j}(t) + C_{i,j-1}(t) + C_{i,j+1}(t) - 4\,C_{i,j}(t)\}$$

where $C_{i,j}(t)$ is the concentration of the diffusing molecule in the micro-compartment (i,j) at time t and λ is a function of D (diffusion coeff.), diffusion time-step (dt = 6 s), and lattice spacing through which diffusion occurs (dx = 20 μm): $\lambda = 4Ddt/(dx)^2$. Solution to Equation 5 is stable if $\lambda < 1$. Thus, $d\,t$ and dx must be picked accordingly.

MOVEMENT RULES (Macs, Ts)

1) Sensitivity ranges for CCs ([min,max])
2) Chemokine gradient define the probabilities (i.e., proportional) of moving into different micro-compartment
3) CCL2, CCL5 and CXCL9 have different effect for different cell types

CROWDING RULES (Macs, Ts)

1) 2 agents per micro-compartment
   a. 1 mac
   b. 1 T cell
   c. 1 mac + 1 T cell
   d. 2 T cells