S6. Cytokines and chemokines at coarse resolution

S6.1 Scope and schedule

S6 specifies the coarse-grained representation of soluble signalling. It covers the receptor-occupancy proxy from which every cytokine effect is computed, the effector tests built on it, and the receptor sink by which cells deplete local TNF and IL-10. It also covers the secretion helpers with their two IL-10 inhibitions, the per-type secretion inventory, the derived chemokine fields and the degradation constants. S1, S2, S3 and S8 read from this layer.

Coarse resolution (default): cytokine effects are computed from the algebraic occupancy proxy of S6.2, and no per-agent receptor, transcription-factor or MHC class II equations are solved (M3).

Signalling has no spatial reach

Every quantity in S6 is computed from the field values at the acting agent's own compartment and from that agent's own receptor counts. No S6 rule reads a neighbourhood or any other compartment.

- **Spatial structure comes from the diffusion solver alone (M1).** Secretion is a point source and sensing a point measurement. Where another rule reads a neighbourhood sum of a field, as the MHC class II inputs do, the summation belongs to that rule (M3).
- **Heterogeneity is per agent, not per compartment.** It comes from the receptor draws (S6.3).
- **S6 reads no compartment state.** Caseation, the killing count, occupancy, oxygen and granuloma membership are invisible to it. Caseum secretes chemokines by a direct grid write that bypasses every S6 helper (S5.6), so a sensed field does not distinguish cell sources from caseum.

Blocks of the cellular timestep

The cadences are those of spine 2.2: $\Delta t_d = 60$ s, $\Delta t_m = 6$ s, $N_d = N_m = 10$.

Block	Activity	Calls per cellular timestep	Interval	See
Split half-step	Secretion: macrophages, then T cells in the order Tgam, Tcyt, Treg, then fibroblasts (M4) and neutrophils (M9.7)	2N_d = 20	$\Delta t_d/2 = 30$ s	S6.9–S6.13
Split half-step	Caseum chemokine sweep, at one quarter of the macrophage rates, after the cellular secretion	20	30 s	S5.6
Molecular substep loop	Receptor sink, over the macrophage list, then the Tgam, Tcyt and Treg lists	N_d N_m = 100	$\Delta t_m = 6$ s	S6.8
Diffusion solve	Transport, decay folded into the scheme, the concentration cutoff, the derived-field assignment	N_d = 10	Δt_d	M1, S6.14, S6.15
Next-state block, all four agent types	Apoptosis test, once per live agent, after the senescence test	Once per agent	—	S6.6
Next-state block, macrophages	NF-κB test (through the stimulus routine) and STAT3 test, in all four live states, for a macrophage not suppressed	Once per surviving macrophage	—	S6.5, S6.7

Block	Activity	Calls per cellular timestep	Interval	See
Statistics block	Field totals, maxima, normalised concentrations, the TNF area count and the apoptosis and NF-κB counters	Once	—	S9

Over one cellular timestep, at the default cadences, secretion is applied for $20 \times 30 = 600$ s and the sink for $100 \times 6 = 600$ s, each equal to Δt_a. Each increment is linear in its interval, so the totals secreted and consumed are module-independent to first order. They are not so exactly: the sink compounds over N_d N_m substeps, so its total depends on Δt_m, and the IL-10 modulation of secretion reads a field that changes between half-steps. Oxygen consumption differs, since it receives the full diffusion timestep in a routine called twice (S7.6).

Placement in the schedule. These properties change outcomes:

- **The diffusion and molecular block precedes all agent behaviour.** Every effector test reads a field that includes this timestep's secretion, transport and decay. The sink in that block was computed from the previous timestep's agent configuration.
- **Secretion uses the agent's current state, not its pending state.** A macrophage that becomes activated on a timestep secretes at its prior state's factor for that whole timestep, and at the activated factor from the next. A macrophage killed in the next-state block has already secreted twenty times on that timestep.
- **Within a half-step, all secretion completes before the first molecular substep.** The sink therefore always acts on a field that includes that half-step's secretion. A reimplementation that interleaved the two would differ.
- **The sink routine is called whenever either fine-grained receptor option of M3 is off.** Its TNF and IL-10 terms are guarded separately on their own options, so with exactly one option on, the sink applies to the other species alone. Both are off by default, so both terms apply.

The molecular-scale solve is gated on any M3 component and never runs by default; no agent ordinary differential equation is solved (M3).

Reads and writes

Reads:

- the TNF and IL-10 fields at the agent's own compartment;
- the agent's own receptor counts R_1 (TNFR1), R_2 (TNFR2) and R_IL10, drawn at construction (S6.3);
- the bound-receptor quantities of M3, identically zero by default, read only by the M3 branches and by a factor on an M3 rate variable that has no effect by default;
- the agent's current state, for the state factor, and its suppression timer, for the early return in every secretion routine;
- for T cells, the cognate and TNF-producer flags, which gate secretion;
- the cumulative bound TGF-β of M4, zero by default, for the TGF-β adjustment of TNF secretion;
- the parameters of S6.16, the M8 depletion flags and the current timestep.

Writes:

- the TNF and IL-10 fields at the agent's own compartment, incremented by secretion and decremented by the sink;
- the CCL2, CCL5 and CXCL9 fields at a macrophage's own compartment;
- the secretion counter, by macrophages only (S9);
- one draw on the random number stream per effector test evaluated.

The three effector tests write no state. A reimplementation may treat each as a pure function of the agent and the local field values, plus one draw.

Agent types outside the signalling blocks

The secretion block iterates the macrophage, Tgam, Tcyt, Treg, fibroblast and neutrophil lists. It has no dendritic-cell routine, and the macrophage routine iterates the macrophage list only, so a dendritic cell secretes nothing, although it inherits the macrophage secretion routine. The sink iterates the macrophage and three T cell lists only. Dendritic cells therefore neither secrete nor consume. Fibroblast sinks and receptor draws are specified in M4.5. Neutrophils secrete TNF but take no sink (M9.7). The M3 molecular loop also omits dendritic cells (M3.2). No dendritic cell, fibroblast or neutrophil exists in the default configuration. The secretion helpers and the sink make no draws, so iterating further lists would change field values but not the random number stream.

IFN-γ and TGF-β

IFN-γ is not a field in any configuration: it has no grid entry, diffusivity, decay constant or secretion helper. Its action is a proximity effect of IFN-γ-producing Tgam on macrophage STAT1 within two compartments (S3.7, S2.4), so no occupancy proxy applies to it. Under the MHC class II component of M3, agents carry an IFN-γ molar quantity computed from Tgam counts, still not transported (M3).

TGF-β is absent by default: the M4 option in force is none (M4). The TGF-β fields stay zero and no cell binds TGF-β. The TNF helper's TGF-β adjustment is therefore 1 (S6.11); the resting-macrophage killing adjustment, computed outside the M4 guard, reads `Core_Mac_TGFBmax` and is 1 (S2.5); and the M4 activation routine that reads the signalling quantity is not called (S6.4).

Couplings

The only field reads away from the reading agent's own compartment are the chemotactic weighting, over the Moore neighbourhood (S1.3), and the neutrophil neighbourhood sums (M9.4, M9.5). Every other cytokine or chemokine read is at the agent's own compartment or at a vascular source (S8).

- **STAT1 is not set by S6.** Its only source is the IFN-γ action (S3.7). Activation needs STAT1 and NF-κB jointly (S2.4), so S6 supplies a necessary but not sufficient condition for macrophage activation.
- **Bacteria reach the fields only through secretion.** No secretion rate has a bacterial term. Bacteria raise TNF and chemokine levels by infecting macrophages, which secrete at higher state factors, and through the NF-κB stimulus (S6.5). Bacteria without a cell secrete nothing.
- **IL-10 does not reach Treg suppression.** The suppression probability is selected by a branch on a parameter, the Treg's IL-10 secretion rate; the local IL-10 field is not read (S3.10). That rate is sampled on [0.7, 0.8], so it is non-zero in every sample, the divided branch is always taken, and the probability is `Core_Tcell_Treg_probTregDeactivate` / `Core_Tcell_Treg_factorDeactIL10`, about 1.9×10^{-3} to 1.0×10^{-2}: a constant of the sample. IL-10's reach is therefore confined to the STAT3 test and the two secretion inhibitions. S3.10 specifies the rule.

S6.2 The receptor-occupancy proxy

Every cytokine effect here is computed from one algebraic form. The result is compared with a threshold, used in an exponential, or multiplied by a consumption rate.

Canonical form

$$B(C, R; K_D, f) = \frac{C\,R}{K_D N_A V + C}\, f,$$

where C is the field value at the agent's compartment, in molecules per compartment; R is the agent's surface receptor count, in molecules per cell; K_D is a dissociation constant in mol/L; N_A = `NAV` = 6.02×10^{23}; V = `VOL` = 8.0×10^{-12} L; and f is a dimensionless correction factor (spine 2.1 for the constants).

This is the Langmuir isotherm written with total rather than free receptor, scaled by f. It is zero at C = 0, increasing and concave in C, half-maximal at C = K_D N_A V, and has supremum f R. A threshold above f R can never be crossed. The apoptosis and STAT3 tests have thresholds below their suprema (S6.6, S6.7).

Field units

All five cytokine and chemokine fields are carried in molecules per compartment, a count rather than a concentration; `VOL` enters only where a conversion is made. Secretion rates are in molecules per second, the effector-test thresholds are receptor counts, and mass units appear only at a conversion: the chemokine step (S6.10) and the observation layer (S9). Oxygen is the exception; its unit is specified in S7.

The unit conversion

The product K_D N_A V converts a molar dissociation constant into molecules per compartment.

Receptor	Parameter	K_D	K_D N_A V, molecules per compartment
TNFR1	`Molecular_TNF_KD1`	1.9×10^{-11} M	91.5
TNFR2	`Molecular_TNF_KD2`	4.2×10^{-10} M	2022.7
IL-10R	`Molecular_IL10_IkD`	4.56×10^{-10} M	2196.1

The three dissociation constants are declared in M3 parameter groups but are read by the coarse code and are active by default. With the receptor-complement parameters of S6.3, they are the fine-grained-group parameters the coarse code reads; group membership does not imply inertness.

TNFR1 half-saturates near 90 molecules per compartment; TNFR2 and IL-10R need over twenty times more. At the TNF levels near the effector thresholds (tens of molecules), the TNFR1 proxy operates near half-saturation, while the TNFR2 and IL-10 terms are near-linear, $B \approx CRf/(K_D N_A V)$.

Instantiations

Site	K_D	R	f	Further multiplier	See
Signalling quantity	`Molecular_TNF_KD1`	R_1	`Core_estBoundFactorTNF`	None	S6.4
Apoptosis test	`Molecular_TNF_KD1`	R_1	`Core_estBoundFactorTNF`	`Core_estIntPartitionTNF`	S6.6
STAT3 test	`Molecular_IL10_IkD`	R_IL10	`Core_estBoundFactorIL10`	None	S6.7
Sink, TNF term	`Molecular_TNF_KD1` and `Molecular_TNF_KD2`, summed	R_1 and R_2	`Core_estBoundFactorTNF` on both	`Core_estConsRateTNF`	S6.8
Sink, IL-10 term	`Molecular_IL10_IkD`	R_IL10	`Core_estBoundFactorIL10`	`Core_estConsRateIL10`	S6.8
Activated-macrophage IL-10 rate	`Molecular_TNF_KD1`	R_1	`Core_estBoundFactorTNF`	Enters a Michaelis function	S6.12

No chemokine proxy. CCL2, CCL5 and CXCL9 have no dissociation constant, no receptor count and no occupancy. They act by direct threshold comparison of the field value (S1, S8) and are never consumed. No oxygen proxy exists either; oxygen consumption is Michaelis–Menten in the field value (S7). IFN-γ is not a field (S6.1).

The proxy is an equilibrium quantity with no state

- **It is recomputed at every evaluation and stored nowhere.** Two evaluations in one timestep agree because the next-state block writes no field.
- **It has no memory.** Persistence of the TNF response comes from the pathway timers and counters of S2.4.
- **It uses total receptor, so ligand never depletes free receptor.** This is the central simplification relative to M3.
- **There is no mass balance.** The sink removes ligand in proportion to occupancy, the occupancy is not reduced by that

removal, and no bound species accumulates. A reimplementation that conserved ligand in a bound pool would not reproduce the model.

S6.3 Per-agent receptor complements

Receptor counts are drawn when an agent is built by the constructor and never revised. A division daughter copies its parent's counts and makes no draw (S3.5). They are the only source of variation in the signalling response within a type: two agents of one type in one compartment read the same field but generally compute different occupancies.

The draws

Each count is drawn uniformly on $[\text{mean} - w, \text{mean} + w]$, where w is the parameter named `std…`. The draws are not normal with that standard deviation. A fourth construction draw gives the log-normal initial value of one NF-κB species, which no active rule reads; its arguments are taken as the parameters of the underlying normal (M3.5).

Agent type	TNFR1	TNFR2	IL-10R
Macrophage (and dendritic cell)	U(1100, 1900)	U(400, 800)	U(1150, 1850)
Tgam, Tcyt, Treg	U(400, 1200)	U(600, 800)	U(250, 550)

S6.16 gives the parameter for each mean and half-width. Neutrophils have their own receptor parameters (M9.2).

On average a macrophage has about twice the TNFR1 of a T cell and two to seven times the IL-10R, so its occupancy at a given field value is correspondingly larger. The apoptosis test is the only effector test applied to T cells. Both types share `Core_thresholdApoptosisTNF` and `Core_kApoptosis`, so the macrophage's greater susceptibility comes entirely from the receptor draw (S6.6).

Values fixed at construction for M3

Receptor synthesis rates ($R_1 \times$ `Molecular_TNF_kT1`, $R_2 \times$ `Molecular_TNF_kT2` and $R_{\mathrm{IL10}} \times$ `Molecular_IL10_IkT`), a type-mean IL-10R count, and the membrane-TNF synthesis and TACE rates are fixed at construction and read only by M3. The T cell TACE rate is `Molecular_TNF_Tcell_kTaceTcell`. The coarse sink is passed the drawn IL-10R count, not the type mean, so coarse IL-10 consumption is heterogeneous across agents (S6.8).

S6.4 The TNF signalling quantity

The NF-κB test reads the signalling quantity specified here. The apoptosis test computes its own quantity inline (S6.6). The two differ by a factor and a ceiling: the model's representation of surface versus internalised signalling.

The rule

At coarse resolution, with C the local TNF:

$$s = \min\left(\frac{C\,R_1}{K_{D1} N_A V + C}\,\texttt{Core_estBoundFactorTNF},\ \ \texttt{Core_Mac_saturationFracNFkBTNF} \cdot R_1 \right),$$

with K_D1 = `Molecular_TNF_KD1`. The quantity is in molecules per cell. Under the TNF receptor option of M3 the same routine returns the integrated bound-receptor count instead, clamped against free plus bound receptor (M3). At coarse resolution the ceiling's denominator is R_1 because no depletion occurs.

The quantity is read by the NF-κB test, through the macrophage stimulus routine, and by the TGF-β activation routine of M4, which is not reached by default. No T cell reads it.

The ceiling never binds

With `Core_estBoundFactorTNF` = 0.45 and `Core_Mac_saturationFracNFkBTNF` = 0.541, the supremum $0.45 R_1$ is below the ceiling $0.541 R_1$ at every concentration and receptor count. The quantity is therefore

$$s = \frac{0.45\,C\,R_1}{91.5 + C},$$

with supremum between 495 and 855 molecules per cell across the macrophage draw.

The ceiling is live code with no effect at the values in force. `Core_Mac_saturationFracNFkBTNF` is declared on [0, 1], and any value below `Core_estBoundFactorTNF` would make it bind. A reimplementation must keep it: whether it acts depends on the ordering of the two parameters, not on either value alone.

The coarse and fine branches read distinct parameters with the same leaf name, `Core_Mac_saturationFracNFkBTNF` and `Molecular_TNF_Mac_saturationFracNFkBTNF`. The same holds for the thresholds and rate constants of all three effector tests: selecting an M3 option selects which is read.

S6.5 TNF-induced NF-κB activation

The NF-κB test is the route by which local TNF contributes to a macrophage's NF-κB flag, one of the two activation conditions (S2.4).

The rule

At coarse resolution, with s the signalling quantity of S6.4, θ = `Core_Mac_thresholdNFkBTNF` and k = `Core_Mac_kNFkB`:

```
NF-kB test, coarse branch:
    s <- signalling quantity (S6.4)
    threshold   <- s > theta                              // seven-figure comparison
    probability <- 1 - exp(-k (s - theta)) > U(0,1)       // seven-figure comparison
    return threshold and probability
```

The test fires if and only if $s > \theta$ and $U(0,1) < 1 - \exp[-k(s-\theta)]$. Both comparisons are strict and use the significant-figure comparison of spine 2.1. Both operands are evaluated before the conjunction, so a draw is consumed on every evaluation, whether or not the threshold is met. The M3 branches are specified in M3.

θ is in molecules per cell. k is dimensionless as used: it multiplies a receptor count, with no time factor, and is calibrated to a per-evaluation (per-cellular-timestep) probability.

Redundancy of the threshold condition

For $s \le \theta$ the probability argument is non-positive, and a draw on [0, 1) cannot be below it. In the coarse branch the probability condition therefore implies the threshold condition. The threshold test is not removable from the code, because in the M3 receptor branch the two conditions read different quantities.

Magnitudes

- **Threshold concentration.** $s = \theta$ at $C = 91.5\theta/(0.45R_1 - \theta)$: about 9 to 19 molecules per compartment across the receptor draw and the sampled θ.
- **Maximum probability.** The exponent is at most $1.01 \times 10^{-5} \times (855 - 74.52) = 7.88 \times 10^{-3}$, a maximum per-evaluation probability of 0.785 %; at the low end of k and R_1, with θ at the top of its range (85.42), the maximum is 0.276 %.
- **Near-linearity.** Across the reachable range $p \approx k(s-\theta)$, with relative error about x/2 (up to about 0.4 %). The linear form describes the response but is not a permissible substitute when reproducing trajectories, since the difference far exceeds the seven-figure resolution.

Where the test is reached

The macrophage stimulus routine sets the NF-κB stimulus to the TNF test OR a live extracellular count in the Moore neighbourhood above `Core_Mac_nrExtMtbNFkB` (S2.4). The TNF result is also returned separately, and only increments the TNF-attributed NF-κB statistic (S9).

The test is evaluated once per surviving macrophage per timestep, through the full pathway routine (resting and infected states: flag and counter) or the partial routine (chronically infected and activated states: counter only) of S2.4. Both consume a draw. In the chronically infected and activated states the flag is already held, so the result reaches only the graded counter, which feeds the polarisation index and gates nothing. A suppressed macrophage reaches neither routine, so no NF-κB or STAT3 draw is consumed (S2.3).

No upper bound is declared for θ, so a threshold above the supremum would make the test unsatisfiable. At the ranges in force the largest threshold, 85.42, is below the smallest supremum, 495.

S6.6 TNF-induced apoptosis

The apoptosis test is the only effector test applied to every agent type. It is how TNF kills.

The rule

At coarse resolution, with C the local TNF, ϕ = `Core_estIntPartitionTNF`, f = `Core_estBoundFactorTNF`, x_sat = `Core_saturationApoptosisTNF`, θ = `Core_thresholdApoptosisTNF` and k = `Core_kApoptosis`:

```
apoptosis test, coarse branch:
    x <- C R1 / (91.5 + C) * phi * f
    x <- min(x, x_sat)                                  // clamp precedes both conditions
    threshold   <- x > theta                                // seven-figure comparison
    probability <- 1 - exp(-k (x - theta)) > U(0,1)         // seven-figure comparison
    return threshold and probability
```

As in S6.5, both comparisons are strict, a draw is consumed on every evaluation, and the probability condition implies the threshold condition. The M3 branches are specified in M3; in the M3 receptor branch the threshold is tested against the unclamped quantity. The two arrangements agree because x_sat exceeds θ by a factor of five to six, an ordering no validation enforces.

The internalisation factor

ϕ is the coarse counterpart of the M3 distinction between internalised complex, which drives apoptosis, and surface complex, which drives NF-κB activation. Here both derive from one surface occupancy. Because $\phi = 11.3$ the apoptosis quantity is 11.3 times the signalling quantity at every concentration, so its threshold (about 1200 to 1330) is an order of magnitude above the NF-κB threshold at comparable local TNF. The product $\phi f = 5.085$ scales the occupancy.

The ceiling binds for most macrophages and for no T cell

The supremum is $5.085R_1$, so the ceiling binds at high concentration if and only if $R_1 > 1376.6$. It does so for about 65.4 % of macrophage draws (supremum 5594 to 9662) and for no T cell (supremum 2034 to 6102). Unlike the S6.4 ceiling, its relevance is a per-agent property. It engages at $C_{\text{sat}} = 91.5 \times 7000/(5.085R_1 - 7000)$: about 5380 molecules per compartment at $R_1 = 1400$, 1020 at 1500 and 240 at 1900. So it is reached at attainable concentrations only for macrophages in the upper part of the draw.

Magnitudes

- **Threshold concentration.** $x = \theta$ at $C = 91.5\theta/(5.085R_1 - \theta)$: 12.9 to 28.5 molecules per compartment for a macrophage, 22.3 to 172.1 for a T cell.
- **Macrophage NF-κB and apoptosis thresholds are close.** In a macrophage the local TNF at the NF-κB threshold (about 9 to 19 molecules) and at the apoptosis threshold (about 13 to 29) lie within a factor of two. No concentration activates a macrophage by TNF without a risk of killing it.
- **T cells are more resistant.** By about 1.5 to 5 times in threshold concentration, purely through the receptor draw; a T cell at the bottom of its draw needs over five times the TNF of an average macrophage.
- **Maximum probability.** The exponent is at most $7.5 \times 10^{-6} \times (7000 - 1194.85) = 4.35 \times 10^{-2}$, or 4.26 % per

evaluation, for a macrophage whose ceiling binds. For a T cell the maximum is 3.61 % at the top of the draw and 0.63 % at the bottom. All fall fivefold at the low end of k.

Apoptosis increments the killing count, whereas senescence of a non-activated macrophage or of a T cell does not (S5.2); this is the coupling through which TNF drives caseation (spine 4.2).

Call sites

The test is evaluated once per agent per timestep, immediately after the senescence test and before any other behaviour, in all four agent types. A positive result sets the agent dead and increments the killing count; for a macrophage it also disperses half the intracellular bacteria (S2.3, S2.9, S3.4, S5.2).

- **T cells pass the NF-κB option as false.** So they take the coarse branch even with the NF-κB option of M3 alone on; under the TNF receptor option they take the receptor branch (M3).
- **Non-cognate and T0 T cells are tested.** Their early return follows this test, so they can die by TNF apoptosis, and such a death increments the killing count.
- **In the macrophage the test precedes the suppression check.** A suppressed macrophage can die by TNF apoptosis, although it reaches neither pathway test.

No upper bound is declared for θ, k or x_sat, and no cross-parameter check enforces $\theta < x_{\mathrm{sat}}$ or $\theta < \phi f R_1$. Both hold at the values in force. No sample makes the test unsatisfiable for a macrophage: the smallest supremum, 5594, exceeds the largest threshold.

For a T cell at the bottom of its receptor draw ($R_1 = 400$) the supremum is 2034, so with θ at the top of its range (1327.87), at the low end of k the maximum probability is 0.106 % per timestep, a mean wait of 944 timesteps against a T cell lifespan of 432; at the top of the draw in the same sample it is 0.71 %. T cell susceptibility thus spreads by about sevenfold within a sample and a further fivefold across samples.

S6.7 IL-10-induced STAT3 activation

The STAT3 test is the only route by which IL-10 acts on macrophage signalling state, and the only effector test that reads IL-10. Its sampled parameters span the widest range, and it is the only test whose probability can approach 1.

The rule

At coarse resolution, with C the local IL-10, f = `Core_estBoundFactorIL10`, θ = `Core_Mac_thresholdSTAT3IL10` and k = `Core_Mac_kSTAT3IL10`:

```
STAT3 test, coarse branch:
    y <- C R_IL10 / (2196.1 + C) * f
    threshold   <- y > theta                                  // seven-figure comparison
    probability <- 1 - exp(-k (y - theta)) > U(0,1)           // seven-figure comparison
    return threshold and probability
```

As in S6.5, both comparisons are strict, a draw is consumed on every evaluation, and the probability condition implies the threshold condition. The M3 branch, which clamps against `Molecular_IL10_Mac_saturationFracSTAT3IL10`, is specified in M3. Each of the three effector tests ends in a branch that throws when no option combination matches; it is unreachable under every configuration.

No saturation ceiling

The coarse branch applies no ceiling, and no `Core_` saturation parameter exists for this test. The quantity is bounded only by f R_IL10, which spans 230 to 1850 across the sampled f and the macrophage draw, an eightfold range of which fivefold comes from f. Of the bound-factor and consumption-rate parameters, the IL-10 pair is sampled and the TNF pair fixed, so the IL-10 supremum varies across samples.

Magnitudes

- **Threshold condition.** The threshold is reached at $C = 2196.1\theta/(fR_{\mathrm{IL10}} - \theta)$, defined only when $\theta < fR_{\mathrm{IL10}}$.
- **Probability.** At the supremum, the probability per evaluation ranges from indistinguishable from 1 ($k = 10^{-1}$) to 2.26 % ($k = 10^{-4}$).
- **Regimes.** The probability reaches one half at a margin ln 2 / k above threshold: 6.9 at $k = 10^{-1}$, 6931 at $k = 10^{-4}$. At high k the test is a hard switch; at low k it never reaches one half at an attainable concentration. Only in the intermediate case does the exponential's shape matter. The STAT3 test is the only effector test that reaches the saturating form.

Where the test is reached

The test is evaluated once per surviving, non-suppressed macrophage per timestep, through the full or partial pathway routine of S2.4. Unlike the NF-κB result, its discrete consequence is processed in all four live states: in the chronically infected and activated states both pro-inflammatory flags are already held, so only discrete STAT3 is processed. The STAT3 flag therefore keeps setting and lapsing in states where the pro-inflammatory flags are fixed. The flag gates no transition by default; it is read only by M8 Treg induction, and its counter feeds the polarisation index (S2.4). A suppressed macrophage does not reach the test (S2.3).

Joint satisfiability

The test can fire only if $\theta < fR_{\mathrm{IL10}}$. θ is sampled up to 1000 while f R_IL10 spans 230 to 1850. At $\theta = 1000$ the test is unsatisfiable for every macrophage when f < 0.541, and satisfiable for every macrophage only when f > 0.870. In such a sample IL-10 acts only through its secretion effects (S6.10, S6.11). The macrophage STAT3 pathway is then silent: the STAT3 gene index stays at its floor of 1, so the polarisation index cannot fall below 1. Neither parameter is individually out of range.

S6.8 Receptor-mediated depletion of TNF and IL-10

Cells remove TNF and IL-10 at their own compartment in proportion to their receptor occupancy. This is the coarse stand-in for receptor-mediated internalisation, accounted for as extra degradation.

The rule

```
sink for agent a, interval dt = dt_m:
    if the TNF receptor option of M3 is off:
        C  <- TNF at a.pos
        B1 <- C R1 / (Molecular_TNF_KD1 N_A V + C) * Core_estBoundFactorTNF
        B2 <- C R2 / (Molecular_TNF_KD2 N_A V + C) * Core_estBoundFactorTNF
        TNF at a.pos -= Core_estConsRateTNF * (B1 + B2) * dt
    if the IL-10 receptor option of M3 is off:
        D  <- IL-10 at a.pos
        Bi <- D R_IL10 / (Molecular_IL10_IkD N_A V + D) * Core_estBoundFactorIL10
        IL-10 at a.pos -= Core_estConsRateIL10 * Bi * dt
```

The macrophage and T cell routines pass each agent's own drawn receptor counts (S6.3), not the type means. `Molecular_TNF_KD2` is therefore active at coarse resolution: it converts the TNFR2 occupancy added to the TNF sink. The sink consumes no draw and makes no decision; it and the secretion helpers are the deterministic parts of S6.

What is consumed

- **TNF through both receptors, IL-10 through one.** At low concentration $B_1/B_2 \approx (R_1/R_2) \times 22.1$, which is 55 for mean macrophage draws. TNFR2 contributes under 2 % of the TNF sink there, rising toward $R_2/(R_1 + R_2)$, about 29 %, only at several thousand molecules. In practice the TNF sink is a TNFR1 sink.
- **No chemokine is consumed anywhere.** Chemokines are removed only by first-order decay and boundary loss (M1, S6.15).

- **Oxygen is consumed by its own Michaelis–Menten rule and cadence (S7).**

Functional form

With κ the consumption rate, f the correction factor and K = K_D N_A V, the single-receptor sink is $\Delta C = -\kappa f C R/(K + C)\Delta t_m$, Michaelis–Menten in C.

- For $C \ll K$ the field decays geometrically, with fractional removal $\alpha = \kappa f R \Delta t_m / K$ per substep.
- For $C \gg K$ the removal is constant at $\kappa f R \Delta t_m$ molecules per substep.

α decreases with C, so its low-concentration value bounds stability. For TNF, $\alpha = \kappa f (R_1/K_1 + R_2/K_2)\Delta t_m$.

Both consumption rates are rates in s^{-1} as used; neither declaration states a unit.

Magnitudes

- **TNF.** α is 2.5 % to 4.4 % per substep for a macrophage, and about 0.97 % to 2.8 % for a T cell. A mean macrophage would remove 97 % of its compartment's TNF per cellular timestep at low concentration, against 61 % for bulk decay at `Core_kDeg`: one macrophage is a stronger TNF sink than bulk degradation.
- **IL-10.** Across the sampled `Core_estConsRateIL10` and `Core_estBoundFactorIL10`, α spans 0.0025 % to 20.2 % per substep, from 0.25 % per cellular timestep to effectively complete removal: about four orders of magnitude. The span straddles bulk IL-10 decay at `Core_Ikdeg` (about 25 % per cellular timestep), so the sink ranges from negligible, through comparable, to overwhelming.

Order of application within a compartment

The sink iterates the macrophage list to completion, then Tgam, Tcyt and Treg. Each agent reads the field afresh, so removals by agents sharing a compartment compound multiplicatively. In the linear regime the total does not depend on the order; elsewhere it depends on it weakly. The type order is part of the specification. No statistic attributes consumption to an agent (S9).

Stability

The field cannot go negative by default. The largest single-agent fractional removal is 20.2 % (IL-10, at the sampled extreme) and 4.4 % (TNF), with at most two agents per compartment. The increment accessors have no clamp or sign test. The concentration cutoff of M1 zeroes any value at or below 10^{-12} after each solve, negatives included; it is a backstop, not part of this rule.

IL-10 would go negative within one substep if $\kappa f R \Delta t_m > K$, that is $\Delta t_m > 2196.1/(\kappa f R)$. At the sampled extreme ($\kappa = 4 \times 10^{-2}$, f = 1.0, R = 1850) this is $\Delta t_m > 29.7$ s. The molecular timestep may be set up to and including 30 s, which the ceiling check on it admits (M1.2). A negative value would persist until the next cutoff.

S6.9 Secretion architecture and the state-factor convention

All agent secretion passes through helper functions on the agent base class. Each type's secretion routine selects a state factor and rate parameters and calls the helpers; the helpers apply the modulation and write the field. No agent writes a cytokine or chemokine field directly, and the helpers hold no state logic.

The helpers

Helper	Fields written	Modulation
Chemokine helper	CCL2, CCL5, CXCL9	Step function in local IL-10 (S6.10)
TNF helper	TNF	Logistic in local IL-10 (S6.11); TGF-β adjustment of the state factor under M4
IL-10 helper	IL-10	None (S6.12)
NF-κB helper	None	None; sets transcription rates read only by M3

IL-10 inhibits chemokine and TNF secretion by different functional forms and does not inhibit its own secretion. TNF inhibits nothing: the pro-inflammatory axis acts on secretion only through macrophage state.

Common pattern

Each helper computes the secreted rate as state factor $\times$ rate + bonus, stores it in a rate variable for M3, and, only when the species' M3 option is off, increments the field by modulation $\times$ (state factor $\times$ rate + bonus) $\times$ interval. By default every increment occurs, and the rate variables are read by no rule. Under M3 the rate variable feeds the derivative and the increment ceases (M3).

The bonus argument is a literal zero at every call site in the macrophage, Tgam, Tcyt and Treg secretion routines, so every secretion by default reduces to

$$\Delta C = m \cdot \sigma \cdot d \cdot \Delta t,$$

with m the modulation factor, σ the state factor, d the rate parameter and $\Delta t = 30$ s. The bonus is inert, not dead: any call site could pass a non-zero value with a code change.

The suppressed early return

Every secretion routine except the Treg's begins with the suppression test. If the agent is suppressed it calls the TNF and IL-10 helpers with zero state factor and rates, and returns; the macrophage also calls the NF-κB helper. The chemokine helper is not called on that path, so suppression silences chemokines by not calling their helper and TNF and IL-10 by zero increments. The zero-argument calls are how suppression stops secretion under M3, and a reimplementation should keep the arrangement (M3).

Gates that precede the state factor

Gate	Macrophage	Tgam	Tcyt	Treg
Suppressed	Early return	Early return	Early return	Not tested
Non-cognate	—	Early return, all species	Early return, all species	Early return, all species
T0 state	—	Early return	Early return	Early return
TNF producer status	—	Gates TNF only	Gates TNF only	—

The Treg lacks the suppression gate because Treg suppression has an empty body (S3.10).

State factor and rate

A secretion quantity is a pair: a rate parameter, a property of species and cell type, and a dimensionless state factor selected by the cell's current state at the call site. The state factors in use are 0.0, 0.1, 0.5, 1.0 and 1.5: the chronically infected macrophage uses 1.5, and several call sites use 0.0, one of them against a non-zero sampled rate. S6.13 holds the inventory. These rates have no effect:

Call site	Rate parameter	Value	Factor	Effect
Tgam active, IL-10	`Core_Tcell_Tgam_dIL10`	0	0.0	Doubly inert
Tcyt, IL-10	`Core_Tcell_Tcyt_dIL10`	U(0.07, 0.08)	0.0	Sampled (S6.16)
Resting macrophage without NF-κB, TNF and IL-10	Zero literals	—	0.0	Nothing secreted

Order of secretion

Within a half-step the secretion order is macrophages, Tgam, Tcyt, Treg, fibroblasts, neutrophils, then caseum (S6.1). The order has no compounding effect on the increments themselves, but it changes outcomes through the modulation. The TNF and chemokine helpers read the local IL-10, which the IL-10 helper writes. A macrophage sharing a compartment with a Treg secretes before the Treg's IL-10 of that half-step. Reversing the type order would change the macrophage's TNF output.

Depletion

Depletion (default: none scheduled): from a specified timestep onward, multiplies cell secretion of TNF or IL-10 by a retained fraction, or suppresses it when the fraction is 0, and suppresses secretion of inactive TGF-β (M8).

Depletion is an option of M8, which specifies its flags, fractions and sites. In the default configuration no depletion is scheduled and both depletion fractions are 0, so the depletion branches of the TNF and IL-10 helpers are live code with no effect. Chemokines cannot be depleted.

S6.10 Chemokine secretion

Chemokines have sources and no sink. They are secreted by macrophages and by caseum (S5.6), transported, decayed in bulk and consumed by nothing (S6.8). No T cell secretes a chemokine: no T cell calls the chemokine helper.

The rule

```
chemokine helper, state factor sigma, interval dt = 30 s:
    I <- IL-10 at pos * MW_IL10 * 1e6 / (N_A V)       // ng/mL
    if I > Core_IC50ChemokineIL10:
        m <- 1/2
    else:
        m <- 1
    CCL2  at pos += m sigma Core_Mac_dCCL2  dt
    CCL5  at pos += m sigma Core_Mac_dCCL5  dt
    CXCL9 at pos += m sigma Core_Mac_dCXCL9 dt
```

The comparison is strict. The helper has no module guard and sets no rate variable. Under the NF-κB option of M3 the macrophage takes another branch and does not call it (M3).

The inhibition is a step. Above the threshold all three increments are halved; below it none is reduced, however far the threshold is exceeded. IL-10 inhibits TNF secretion by a continuous logistic with no floor (S6.11), so the two inhibitions differ in form and in maximum strength: a factor of two here, arbitrarily close to zero for TNF.

The unit conversion. With `MW_IL10` = 18600 g/mol, the coefficient is $18600 \times 10^6/(N_A V) = 3.862 \times 10^{-3}$ ng/mL per molecule per compartment, so 1 ng/mL is 259 molecules per compartment. This is the only mass-unit conversion in the rules of this submodel. `Core_IC50ChemokineIL10` is therefore in ng/mL. Over its sampled range of 1 to 500 ng/mL it corresponds to 259 to 129 000 molecules per compartment.

The modulation is uniform across the three species. The same factor multiplies all three increments, preserving the ratio of the rates and hence the derived-field relation (S6.14). A reimplementation must preserve this.

Call sites

All call sites are in the macrophage secretion routine; S6.13 gives the state factors. The rate arguments are `Core_Mac_dCCL2`, `Core_Mac_dCCL5` and `Core_Mac_dCXCL9` at every call site, so the macrophage secretes the three chemokines in fixed proportion in every state. A resting macrophage without the NF-κB flag is the only live macrophage that secretes no chemokine. The initial population is resting with flags clear (spine 5.3), so at time zero only the seeding macrophage, which is infected, secretes chemokine, at factor 0.5.

The three rates set macrophage secretion, the caseum rate (S5.6) and the derived-field ratios r_5 and r_9 (S6.14).

S6.11 TNF secretion

TNF is secreted by macrophages and by cognate TNF-producer T cells (S6.13). Its secretion is modulated continuously by local IL-10.

The rule

```
TNF helper, state factor sigma, rate d_TNF, interval dt = 30 s:
    if TGF-beta dynamics (M4) is selected:            // not by default
        sigma <- sigma * max((Core_Mac_TGFBmax - Gamma) / Core_Mac_TGFBmax, 0.5)
    if the TNF receptor option of M3 is off and TNF is not fully depleted (M8):
        D <- IL-10 at pos                          // molecules, unconverted
        if D == 0:
            tnfMOD <- 1
        else:
            tnfMOD <- 1 / (1 + exp((log10(D) + Core_LinkLogAlpha) / Core_LinkLogBeta))
        dC <- tnfMOD * sigma * d_TNF * dt
        if fractional TNF depletion is in force:    // M8; not by default
            dC <- dC * Core_depletionFractionTNF
        TNF at pos += dC
```

Γ is the agent's cumulative bound TGF-β. By default the TGF-β branch is not taken and no depletion is scheduled, so $\Delta C = \mathrm{tnfMOD}(D)\,\sigma\,d_{\mathrm{TNF}}\,\Delta t$, with D the local IL-10 in molecules per compartment. The exact-zero branch is reachable because the M1 cutoff sets IL-10 at or below 10^{-12} to exactly zero (S6.15).

The logistic inhibition

With α = `Core_LinkLogAlpha` = -1.93 and β = `Core_LinkLogBeta` = 0.181, tnfMOD decreases in D and is one half at $\log_{10} D = 1.93$, that is D = 85.1 molecules per compartment. It falls from 0.9 to 0.1 over $\log_{10} D$ from 1.532 to 2.328, about 34 to 213 molecules: a factor of six.

Local IL-10, molecules per compartment	tnfMOD
0	1 (special case)
10	0.994
34	0.9
85.1	0.5
213	0.1
500	0.014
2000	5.1×10^{-4}
10^4	1.1×10^{-5}

The inhibition has no floor. At 10^4 IL-10 molecules an activated macrophage secretes about 0.01 TNF molecules per cellular timestep. `Core_MaxIL10Inhibition` = 0.14 is read by no rule, and the inhibition has no lower bound.

The logistic reads IL-10 in molecules. The TNF helper takes the logarithm of the IL-10 molecule count per compartment; the chemokine helper converts IL-10 to ng/mL first (S6.10). Expressed in ng/mL, the logistic midpoint is 0.329 ng/mL.

TGF-β adjustment and depletion

Under M4 the macrophage state factor is scaled by max((`Core_Mac_TGFBmax` $-\Gamma$)/`Core_Mac_TGFBmax`, 0.5). The three T cell routines pass "no TGF-β" explicitly and the macrophage passes the live selection, so even under M4 the adjustment applies to macrophages only (M4).

Depletion is specified with its option (S6.9, M8). In the TNF helper, fractional depletion is nested inside the non-depletion guard, whereas in the IL-10 helper the cases are exclusive branches; a reimplementation copying one onto the other would differ (M8).

Rates

S6.13 gives the call sites and state factors. A producing Tcyt secretes 0.9 TNF molecules per cellular timestep, against 900 for an activated macrophage. `Core_Tcell_Treg_dTNF` = 0 is declared and read by nothing, since the Treg calls only the IL-10 helper.

S6.12 IL-10 secretion

IL-10 is secreted by three macrophage states and by active cognate Tregs. It is not inhibited, and at one call site its rate depends on another field.

The rule

With no depletion scheduled, the IL-10 helper adds $\Delta C = \sigma\, d_{\mathrm{IL10}}\, \Delta t$ at the agent's compartment, $\Delta t = 30$ s, when the IL-10 receptor option of M3 is off. There is no modulation factor. The helper reads no field: IL-10 has no negative feedback on its own sources, and its local level is limited only by decay, transport and the sink (S6.8). TNF does not inhibit IL-10 secretion; the one cross-dependence is positive, through the activated-macrophage rate.

The depletion branches of the helper are specified with the depletion option (M8). Full depletion zeroes both the field increment and the rate variable.

The IL-10 sources by default are exactly infected, chronically infected and activated macrophages, and active cognate Tregs. The two Tgam states of M8 Treg induction would also secrete IL-10, using `Core_Tcell_Treg_dIL10` (M8).

The activated-macrophage rate depends on local TNF

Immediately before the activated-state call, the macrophage computes

$$d_{\mathrm{IL10}}^{\mathrm{act}} = \texttt{Core_Mac_dIL10Act} \cdot \frac{B}{B+H}, \qquad B = \frac{C\,R_1}{K_{D1} N_A V + C}\,\texttt{Core_estBoundFactorTNF}, \qquad H = \texttt{Core_Mac_halfSatIL10},$$

with C the local TNF. B is the unclamped proxy, equal by default to the signalling quantity of S6.4. With H = 190, the factor is half-maximal at $C = 91.5H/(0.45R_1 - H)$, 26.1 to 57.0 molecules across the macrophage draw. Its supremum is $0.45R_1/(0.45R_1 + H)$, 0.723 to 0.818. An activated macrophage therefore secretes IL-10 at most at about 72 % to 82 % of `Core_Mac_dIL10Act`, depending on its receptor draw.

The arrangement closes a negative feedback loop through the shared compartment: TNF raises IL-10 secretion, and IL-10 suppresses TNF secretion (S6.11). A neighbour's TNF drives it equally.

S6.13 Per-type secretion inventory

S6.13 states the state factors and rates by cell type and state. S6.10 to S6.12 give the helpers and their modulation.

Macrophages

The switch is on state, with the NF-κB flag tested within the resting and infected cases. Under the NF-κB option of M3 the macrophage takes a different branch (M3).

State	Condition	Chemokine helper	TNF helper	IL-10 helper
Suppressed, any state	Suppression timer set	Not called	0.0, zero rates	0.0, zero rates
Resting	Flag clear	Not called	0.0, zero rates	0.0, zero rates
Resting	Flag set	0.5	0.5, `Core_Mac_dTNF`	0.0, zero rates
Infected	Flag clear	0.5	0.5, `Core_Mac_dTNF`	1.0, `Core_Mac_dIL10Inf`
Infected	Flag set	1.0	1.0, `Core_Mac_dTNF`	1.0, `Core_Mac_dIL10Inf`
Chronically infected	Flag held by the state	1.0	1.0, `Core_Mac_dTNF`	1.5, `Core_Mac_dIL10Inf`
Activated	Both flags held by the state	1.0	1.0, `Core_Mac_dTNF`	1.0, activated rate (S6.12)
Dead	—	Nothing	Nothing	Nothing

A dead macrophage is never reached, because dead agents are removed before the next secretion (spine 3). The NF-κB flag governs secretion only in the resting state (secrete or not) and the infected state (half or full chemokine and TNF); it has no effect on IL-10. An infected macrophage secretes IL-10 at full factor whether or not the flag is set, so the flag shifts the balance rather than scaling all secretion. Resting macrophages secrete no IL-10. Every secreting macrophage branch increments the secretion counter; T cells and caseum do not (S9).

T cells

All three types return early for non-cognate cells and for the T0 state before any state factor is selected; Tgam and Tcyt also return early when suppressed (S6.9).

Type and state	TNF helper	IL-10 helper	Reached by default
Tgam, suppressed	0.0, zero rates	0.0, zero rates	Yes
Tgam, active	1.0, `Core_Tcell_Tgam_dTNF`, producers only	0.0, `Core_Tcell_Tgam_dIL10`	Yes
Tgam, down-regulated	0.0, zero rates, producers only	0.0, zero rates	No: the suppression early return precedes it
Tgam, two Treg-induction states	1.0, `Core_Tcell_Tgam_dTNF`, producers only	0.5 or 1.0, `Core_Tcell_Treg_dIL10`	Under M8 only
Tgam, exhausted	Nothing	Nothing	Under M8 only
Tcyt, suppressed	0.0, zero rates	0.0, zero rates	Yes
Tcyt, any other live state	0.1, `Core_Tcell_Tcyt_dTNF`, producers only	0.0, `Core_Tcell_Tcyt_dIL10`	Yes
Treg, active	Not called	1.0, `Core_Tcell_Treg_dIL10`	Yes

- **Tcyt has no state switch.** Down-regulation silences a Tcyt only through the suppression timer, which is set together with the down-regulated state, so the early return is taken (S3).
- **The producer gate wraps only the TNF call.** A cognate non-producer Tgam or Tcyt reaches the IL-10 helper but not the TNF helper.
- **The Treg makes no TNF call.** Its single call is at full factor.

Secretion per cellular timestep

In molecules per compartment per cellular timestep ($\Delta t_a = 600$ s), at the default rates, before modulation.

Source	CCL2	CCL5	CXCL9	TNF	IL-10
Macrophage, resting, flag set	1800	1800	3600	450	0
Macrophage, infected, flag clear	1800	1800	3600	450	4.2–42
Macrophage, infected, flag set	3600	3600	7200	900	4.2–42
Macrophage, chronically infected	3600	3600	7200	900	6.3–63
Macrophage, activated	3600	3600	7200	900	at most 34–3436
Tgam, active, TNF producer	0	0	0	90	0
Tcyt, TNF producer	0	0	0	0.9	0
Treg, active	0	0	0	0	420–480
Caseous compartment (S5.6)	900	900	1800	0	0

The chemokine columns are halved above the IL-10 step threshold, and the TNF column is multiplied by the logistic, except for caseum, which receives neither. The activated IL-10 figure is an upper bound, since the Michaelis factor reaches at most 0.72 to 0.82 (S6.12).

Because caseum is never inhibited, where the IL-10 inhibition is in force a caseous compartment equals an inhibited NF-κB-positive resting macrophage, and half an inhibited full secretor. With at most one macrophage per compartment (spine 2.3) and no second chemokine source able to share a compartment with it, the chemokine maxima of a single macrophage cannot be exceeded.

S6.14 The derived chemokine fields

Three chemokines are secreted, sensed and reported, but only CCL2 is transported. After each diffusion solve, CCL5 and CXCL9 are assigned pointwise from CCL2. M1 specifies the mechanism; S6.14 states the relation, the conditions under which it holds, and its consequences.

The assignment

At every compartment p,

$$C_{\mathrm{CCL5}}(p) = r_5\, C_{\mathrm{CCL2}}(p), \qquad C_{\mathrm{CXCL9}}(p) = r_9\, C_{\mathrm{CCL2}}(p),$$

with r_5 = `Core_Mac_dCCL5` / `Core_Mac_dCCL2` = 1.0 and r_9 = `Core_Mac_dCXCL9` / `Core_Mac_dCCL2` = 2.0. The ratios are not parameters: they are quotients of the three macrophage secretion rates, which also set macrophage and caseum output (S6.10, S5.6). The solve recomputes them on every call (M1.3). Varying one rate changes r_5 or r_9 with it; the coarse assignment stays exact, and only the M3 path's literal 1 : 1 : 2 would then disagree. This rests on a simplifying assumption: in GranSim, macrophages secrete CCL5 and CXCL9 under the same conditions as CCL2, differing only in rate.

The assignment relies on all three chemokines sharing a diffusivity, `Core_diffusivityChemokines`, and a decay constant, `Core_ChemokinekDeg`, and on fixed proportions of secretion. It saves two of the spectral transforms per step (M1.3, "Derived assignment of CCL5 and CXCL9").

Conditions under which the relation is exact

- **Identical transport.** The three fields share the diffusivity and decay constant, so the solver applies the same linear operator to each.

- **Identical boundary condition.** All three take the same condition under the selected solver (M1).
- **Proportional sources.** Every source adds the three species in the proportion $1 : r_5 : r_9$. The macrophage passes the three rate parameters at every call site (S6.10); caseum writes one quarter of the same three (S5.6); no other source exists.
- **Uniform modulation.** The IL-10 step multiplies all three increments by the same factor (S6.10).

Given these conditions, the assignment is an identity, not an approximation, up to rounding: the derived fields are redundant state.

One half-step of direct writes survives

Each diffusion step runs secretion, the solve, then secretion again, so the loop ends with a secretion half-step. Agents therefore read the derived assignment from the tenth solve plus one half-step of direct additions; at the default cadences and rates, these are 45 CCL5 and 90 CXCL9 molecules for a caseous compartment, 180 and 360 for a fully secreting macrophage. These surviving additions are proportional by the proportional-sources and uniform-modulation conditions, so the relation holds exactly as agents read it. A configuration violating either condition would leave the derived fields inconsistent by one half-step.

The writers of CCL5 and CXCL9, the fate of their direct writes and of parameter-file initialisation, and where a reimplementation may perform the assignment are specified with the assignment (M1.3, "Derived assignment of CCL5 and CXCL9").

Consequences for readers

Every chemokine reader reads CCL2 at one of three scalings.

- **Chemotaxis.** The weight sums are a type-dependent constant times CCL2, so every motile type draws from the same destination distribution; sensitivities matter only for the per-species window (S1.3).
- **Recruitment.** Per-type chemokine sums are constants times CCL2, so the per-type thresholds reparameterise a single response (S8).
- **Observation.** Several chemokine statistics carry no information beyond the CCL2 total and the two ratios (S9).

The per-species window gating, and the distinction between the species in the parameter set, are not redundant. The model cannot represent differential chemokine regulation: no state, cell type or parameter setting gives the three chemokines distinct spatial distributions, and any ratio-based pattern is fixed at r_5 or r_9.

Nothing enforces the proportion of the three rates. Under M3 the path's literal 1 : 1 : 2 agrees with r_5 and r_9 only while the three rates stand in that proportion, and changing `Core_Mac_dCXCL9` relative to `Core_Mac_dCCL2` would break it (M3).

S6.15 Degradation and the division of labour with M1

S6 supplies the source and sink terms and the decay constants of the diffused species. It does not transport them or apply the decay.

The field equations

Each diffused species obeys $\partial C/\partial t = D\nabla^2 C - kC + S - U$, with D the diffusivity, k the decay constant, S secretion and U the receptor sink. For CCL5 and CXCL9 the equation is replaced by the assignment of S6.14, so it is solved for CCL2, TNF and IL-10 only.

Term	Supplied by	Applied by	Cadence
$D\nabla^2 C$	M1.6 (diffusivities)	M1	Once per Δt_d
$-kC$	S6.15 (decay constants)	M1, folded into the solve	Once per Δt_d
S	S6.9–S6.13; S5.6 for caseum	S6, as direct increments	Twice per Δt_d

Term	Supplied by	Applied by	Cadence
$-U$	S6.8	S6, as direct decrements	N_m times per Δt_d, N_m/2 in each split half-step (spine 2.2)

Oxygen has no spatial operator or decay here; its terms belong to S7.

The decay constants

Species	Parameter	Value	Half-life	Removed per Δt_a, decay alone
TNF	`Core_kDeg`	1.58×10^{-3} s^{-1}	439 s	61.2 %
CCL2, CCL5, CXCL9	`Core_ChemokinekDeg`	1.58×10^{-3} s^{-1}	439 s	61.2 %
IL-10	`Core_Ikdeg`	4.85113×10^{-4} s^{-1}	1429 s	25.3 %

TNF and the chemokines share a decay value, as distinct declarations, and a diffusivity (M1.6). TNF and CCL2 thus share one transport operator, and differ in their sources, their IL-10 modulation and the TNF receptor sink.

IL-10 persists about 3.26 times as long as TNF. The decay length $\sqrt{D/k}$ is 57.4 μm for TNF and the chemokines. For IL-10, with `Core_diffusivityIL10` uniform on $[4 \times 10^{-8}, 6 \times 10^{-8}]$ cm^2/s (M1.6), it is about 91 to 111 μm. With compartments 20 μm across, that is about three compartments for TNF and five for IL-10. Every species is short-ranged relative to the 300×300 grid.

How the decay is applied

Decay is folded into the spectral solve, and no routine applies $-kC$ explicitly (M1).

- **Cadence.** Decay acts once per diffusion step (ten times per cellular timestep), while the sink acts a hundred times. A reimplementation combining them into one first-order removal would have to reconcile the cadences.
- **Order within a diffusion step.** Secrete, sink, solve with decay, secrete, sink. Secretion in the first half-step decays within the same diffusion step; secretion in the second does not decay until the next.
- **The cutoff.** M1 sets every value at or below 10^{-12} to zero after each solve. This is the only guard against negative values, and it makes the exact-zero branch of the TNF logistic reachable (S6.11).

The constants are biological

The decay constants are model properties and take the same values under any solver. The timesteps, boundary condition, planning strategy and smoother belong to M1. The Δt_d accuracy check reads `Core_diffusivityTNF` alone, so no IL-10 parameter enters it, and neither selected solver is affected (M1.2).

S6.16 Parameters

Range marks sampled parameters, one value per run; LU marks log-uniform sampling. `Core_Tcell_Tcyt_dIL10` is sampled, and its only call site multiplies it by a state factor of 0.0, so it does not change secretion (S6.9). S2.12, S3.12 and M3.9 refer to this table.

Identifier	Value or range	Range	Units	Meaning
`Core_Mac_thresholdNFkBTNF`	74.52 to 85.42	Sampled	molecules per cell	NF-κB test threshold θ (S6.5)[1]
`Core_Mac_kNFkB`	6.76×10^{-6} to 1.01×10^{-5}	Sampled	unstated	NF-κB test rate constant (S6.5)
`Core_Mac_saturationFracNFkBTNF`	0.541	—	fraction of R_1	Ceiling on the signalling quantity; never binds by default (S6.4)[2]

Identifier	Value or range	Range	Units	Meaning
`Core_thresholdApoptosisTNF`	1194.85 to 1327.87	Sampled	molecules per cell	Apoptosis test threshold (S6.6)[3] [4]
`Core_kApoptosis`	1.5×10^{-6} to 7.5×10^{-6}	Sampled	dimensionless, per evaluation	Apoptosis test rate constant (S6.6)
`Core_saturationApoptosisTNF`	7000	—	molecules	Apoptosis ceiling; binds for about 65 % of macrophages, no T cell (S6.6)
`Core_estIntPartitionTNF`	11.3	—	—	Internalisation factor ϕ (S6.6)
`Core_estBoundFactorTNF`	0.45	—	—	TNF correction factor f: signalling quantity, apoptosis quantity, both TNF sink terms, activated IL-10 rate (S6.4, S6.6, S6.8, S6.12)
`Core_estConsRateTNF`	7.7×10^{-4}	—	s^{-1}	TNF sink rate κ (S6.8)
`Core_Mac_thresholdSTAT3IL10`	1 to 1000	Sampled, LU	unstated	STAT3 test threshold (S6.7)[5]
`Core_Mac_kSTAT3IL10`	10^{-4} to 10^{-1}	Sampled, LU	unstated	STAT3 test rate constant (S6.7)
`Core_estBoundFactorIL10`	0.2 to 1.0	Sampled	—	IL-10 correction factor f: STAT3 test and IL-10 sink (S6.7, S6.8)
`Core_estConsRateIL10`	4×10^{-5} to 4×10^{-2}	Sampled, LU	s^{-1}	IL-10 sink rate κ (S6.8)[6]
`Core_IC50ChemokineIL10`	1 to 500	Sampled, LU	ng/mL	Chemokine step threshold (S6.10)
`Core_LinkLogAlpha`	-1.93	—	$\log_{10}$ of molecules per compartment, as used	TNF logistic midpoint α (S6.11)
`Core_LinkLogBeta`	0.181	—	$\log_{10}$ units	TNF logistic width β (S6.11)
`Core_Mac_halfSatIL10`	190	—	molecules per cell	Half-saturation H of the activated IL-10 rate (S6.12)
`Core_Mac_dCCL2`	6	—	molecules/s	Macrophage CCL2 rate; denominator of r_5, r_9 (S6.10, S6.14)[7]
`Core_Mac_dCCL5`	6	—	molecules/s	Macrophage CCL5 rate; numerator of r_5 (S6.10, S6.14)
`Core_Mac_dCXCL9`	12	—	molecules/s	Macrophage CXCL9 rate; numerator of r_9 (S6.10, S6.14)
`Core_Mac_dTNF`	1.5	—	molecules/s	Macrophage TNF rate (S6.13)
`Core_Tcell_Tgam_dTNF`	0.15	—	molecules/s	Tgam TNF rate, producers only (S6.13)
`Core_Tcell_Tcyt_dTNF`	0.015	—	molecules/s	Tcyt TNF rate, producers only (S6.13)
`Core_Mac_dIL10Inf`	0.007 to 0.07	Sampled	molecules/s	Infected and chronically infected IL-10 rate (S6.13)
`Core_Mac_dIL10Act`	0.07 to 7	Sampled	molecules/s	Activated IL-10 rate, before the Michaelis factor (S6.12)
`Core_Tcell_Treg_dIL10`	0.7 to 0.8	Sampled	molecules/s	Treg IL-10 rate; also the two M8 Tgam states (S6.12, S6.13)
`Core_Tcell_Tcyt_dIL10`	0.07 to 0.08	Sampled	molecules/s	Multiplied by 0 (S6.9)
`Core_kDeg`	1.58×10^{-3}	—	s^{-1}	TNF decay (S6.15)
`Core_ChemokinekDeg`	1.58×10^{-3}	—	s^{-1}	Decay of all three chemokines (S6.15)
`Core_Ikdeg`	4.85113×10^{-4}	—	s^{-1}	IL-10 decay (S6.15)

Identifier	Value or range	Range	Units	Meaning
`Molecular_TNF_KD1`	1.9×10^{-11}	—	M	TNFR1 dissociation constant (S6.2)
`Molecular_TNF_KD2`	4.2×10^{-10}	—	M	TNFR2 dissociation constant; TNF sink (S6.2, S6.8)
`Molecular_IL10_IkD`	4.56×10^{-10}	—	M	IL-10R dissociation constant (S6.2)
`Molecular_TNF_Mac_meanTNFR1Mac`, `…_stdTNFR1Mac`	1500, 400	—	per cell	Macrophage TNFR1 mean and half-width (S6.3)
`Molecular_TNF_Mac_meanTNFR2Mac`, `…_stdTNFR2Mac`	600, 200	—	per cell	Macrophage TNFR2 mean and half-width (S6.3)
`Molecular_IL10_Mac_meanIL10RMac`, `…_stdIL10RMac`	1500, 350	—	per cell	Macrophage IL-10R mean and half-width (S6.3)
`Molecular_TNF_Tcell_meanTNFR1Tcell`, `…_stdTNFR1Tcell`	800, 400	—	per cell	T cell TNFR1 mean and half-width (S6.3)
`Molecular_TNF_Tcell_meanTNFR2Tcell`, `…_stdTNFR2Tcell`	700, 100	—	per cell	T cell TNFR2 mean and half-width (S6.3)
`Molecular_IL10_Tcell_meanIL10RTcell`, `…_stdIL10RTcell`	400, 150	—	per cell	T cell IL-10R mean and half-width (S6.3)

Cross-parameter relations. None is checked at startup, and no sampled parameter of S6 has a checked upper bound.

[1] `Core_Mac_thresholdNFkBTNF` $< 0.45R_1$ is needed for the NF-κB test to be satisfiable; it holds by a factor of about six.

[2] The NF-κB ceiling acts only if `Core_Mac_saturationFracNFkBTNF` < `Core_estBoundFactorTNF`.

[3] `Core_thresholdApoptosisTNF` $< \min(5.085R_1, 7000)$ is needed for the apoptosis test to be satisfiable; it holds for every macrophage and T cell draw.

[4] `Core_thresholdApoptosisTNF` < `Core_saturationApoptosisTNF` is needed for the coarse and M3 receptor branches of the apoptosis test to agree; it holds by a factor of five to six.

[5] `Core_Mac_thresholdSTAT3IL10` < `Core_estBoundFactorIL10` $\times R_{\mathrm{IL10}}$ is needed for the STAT3 test to be satisfiable; part of the sampled space does not satisfy it (S6.7).

[6] `Core_estConsRateIL10` $\times$ `Core_estBoundFactorIL10` $\times R_{\mathrm{IL10}} \times \Delta t_m < 2196.1$ is needed for the IL-10 sink to stay non-negative; it holds at $\Delta t_m = 6$ s and fails near 30 s (S6.8).

[7] `Core_Mac_dCCL5` = `Core_Mac_dCCL2` and `Core_Mac_dCXCL9` = 2 `Core_Mac_dCCL2` are needed only for the M3 chemokine path to agree with r_5 and r_9 (S6.14).

The logistic is narrow because β is small: its 90 %-to-10 % transition spans $4.394\beta = 0.795$ in $\log_{10} D$, a factor of 6.2. A β of order unity would spread the same transition over about four orders of magnitude.

The dissociation constants and the receptor mean and half-width parameters sit in M3 parameter groups but are read here; a parameter file stripped of the `Molecular` groups would not run.

Fixed structural constants: the chemokine step factor 1/2; the state factors 0.0, 0.1, 0.5, 1.0 and 1.5; `NAV` and `VOL` (spine 2.1); `MW_IL10` = 18600 g/mol; `INITIAL_NFKB_FACTOR` = 0.64872; the Tcyt membrane-TNF synthesis divisor 10 and the macrophage and Treg synthesis rates 0, read only by M3; the factor 2 on CXCL9 in the M3 chemokine write-back; the secretion bonus 0. The caseum secretion factor 0.25 is specified in S5.6, and the concentration cutoff 10^{-12} in M1.

Read but without effect by default: `Core_Tcell_Tcyt_dIL10` and `Core_Tcell_Tgam_dIL10` (state factor 0); `Core_Tcell_Treg_dTNF` (no call site); `Core_MaxIL10Inhibition` (read by no rule); `Molecular_IL10_LinkRNAGamma` and `Molecular_IL10_LinkRNADelta` (read only by an uncalled routine and by M3); `Molecular_TNF_kT1`, `Molecular_TNF_kT2`, `Molecular_IL10_IkT`, `Molecular_TNF_Mac_kTaceMac`, `Molecular_TNF_Tcell_kTaceTcell`, `Molecular_TNF_Tcell_kSynthTcell`,

`Molecular_TNF_Mac_kSynthMac`, `Molecular_TNF_Mac_kRNAMac`, `Molecular_TNF_Tcell_kRNATcell`, `Molecular_IL10_Mac_IkSynthMacInf`, `Molecular_IL10_Mac_IkSynthMacAct`, `Molecular_IL10_Tcell_IkSynthTcell`, `NFkB_KNN` (stored for M3); `NFkB_meanNFkB` (stored for M3, but gates a construction draw); the M3-branch test parameters `Molecular_TNF_Mac_thresholdNFkBTNF`, `Molecular_TNF_Mac_kNFkB`, `Molecular_TNF_Mac_saturationFracNFkBTNF`, `Molecular_TNF_thresholdApoptosisTNF`, `Molecular_TNF_kApoptosis`, `Molecular_TNF_saturationApoptosisTNF`, `NFkB_kApoptosis`, `NFkB_kIAP`, `NFkB_actThreshold`, `NFkB_activationRate`, `Molecular_IL10_Mac_thresholdSTAT3IL10`, `Molecular_IL10_Mac_kSTAT3IL10`, `Molecular_IL10_Mac_saturationFracSTAT3IL10`; `Molecular_IL10_Mac_halfSatIL10mRNA` (read, multiplied by zero); `NFkB_c1r`, `NFkB_epsilon1`, `NFkB_epsilon2`, `NFkB_e3Chem` (NF-κB branch of M3); `Core_Mac_TGFBmax` (read; adjustments equal 1, S6.1); `Core_depletionFractionTNF`, `Core_depletionFractionIL10` (M8).

Some declared units and descriptions differ from the use stated here; the units column states how each parameter is used. In the units column "—" means dimensionless; "unstated" marks the three rows whose units are not stated.

S6.17 Interfaces

With	Provides or receives	See
Spine Element 7	S6 expands the coarse-grained cytokine and chemokine submodel listed there	—
Spine 2.1	Receives `NAV`, `VOL` and the significant-figure comparison used by every effector test; the molecular weights are in S6.16, S7.2 and S9	S6.2, S6.5
Spine 2.2	Receives the cadences Δt_d, Δt_m, N_d and N_m and the split half-step	S6.1
Spine 2.3	Receives the occupancy rules (at most one macrophage per compartment) and the hybrid update	S6.13
Spine 2.4	Provides the five field definitions' units, the IL-10 producer list and the derived-field relation	S6.12, S6.14, S6.2
Spine Element 3	Receives the block order: secretion and sink before agent behaviour; dead agents removed before the next secretion	S6.1, S6.13
Spine Element 4	Provides the TNF apoptosis–caseation coupling (4.2) and the absence of IL-10 modulation of Treg suppression (4.1, 4.3)	S6.6, S6.1
Spine 5.3	Receives the initial resting population with flags clear	S6.10
Spine 7.13	Provides the absences: oxygen gates no S6 rule; no bacterial secretion term; no chemokine receptor	S6.2, S6.1
S1	Provides the chemokine fields and their derived relation; S1.3 owns the chemotactic window, the sensitivities and the identical-distribution result	S1.3, S6.14
S2	Provides the NF-κB, STAT3 and apoptosis test results and the secretion inventory; receives the pathway routines, the stimulus routine, suppression and the death routes	S2.3, S2.4, S2.9, S6.5–S6.7, S6.13
S3	Provides the apoptosis test and the T cell secretion factor and rate tables; receives the specificity and producer flags, the IFN-γ action that sets STAT1, and Treg suppression	S3.4, S3.7, S3.10, S6.6, S6.13
S4	Receives the construction-draw rule for bacteria	S3.5
S5	Provides apoptosis as a killing-count route; receives the caseum chemokine secretion and its 0.25 factor, which bypass every S6 helper	S5.2, S5.6

With	Provides or receives	See
S7	Oxygen is not an S6 field: its consumption and units are specified in S7	S7.2, S7.6
S8	Provides the TNF and chemokine fields read at sources; receives the recruited T cells' specificity	S8
S9	Provides the field totals, maxima, normalised concentrations, the TNF area count, the apoptosis and NF-κB counters and the macrophage secretion counter	S9
M1	Applies transport, folded decay, the 10^{-12} cutoff and the derived-field assignment; owns the diffusivities, timesteps and accuracy check. Secretion and sink totals are module-independent to first order under every solver	M1.2, M1.3, M1.6
M2	No effect on S6 mechanics; under option B the cognate fraction is a model output, which changes the secreting T cell fraction	M2.9
M3	Replaces the occupancy proxy and the effector tests (S6.2–S6.7), the sink (S6.8) and the macrophage TNF and chemokine secretion paths with receptor and pathway equations; under the NF-κB pathway option, IL-10 secretion is still written coarsely, since its guard is on the IL-10 receptor option. Default: coarse resolution	S6.1 slot; M3
M4	Would activate the TNF adjustment, TGF-β binding and secretion, and the activation routine that reads the signalling quantity. Default: none	S6.11, S6.1; M4
M5	No direct effect, since S6 reads no neighbourhood; consuming rules use larger neighbourhoods in three dimensions	M5
M6	None: the drug sink is separate from the cytokine sink. Default: off	M6
M7	Anti-TNF antibodies add a sequestration pathway for TNF competing with the sink and decay; the effector thresholds stay in free TNF. Default: off	M7
M8	Depletion slot (S6.9); Treg induction reads the STAT3 flag and its two Tgam states secrete IL-10 at `Core_Tcell_Treg_dIL10`; an exhausted Tgam secretes nothing, while an exhausted producing Tcyt keeps secreting TNF. Default: all options off	S6.9; M8
M9	Neutrophils secrete TNF at their own rate, take no TNF or IL-10 sink, draw their own receptor counts and read CCL5 over their neighbourhood	M9.2, M9.4, M9.5, M9.7
Appendix B	Indexes the read-but-inert parameters and the depletion options	S6.16