S2. Macrophages

S2.1 Scope and schedule

This submodel specifies macrophage behaviour: state transitions, bacterial uptake and killing, the three intracellular signalling pathways, death routes and their bacteriological consequences, exposure memory, suppression by regulatory T cells, and the activated-macrophage sweep over the neighbourhood.

Block	Macrophage activity	Specified in
Split half-step, twice per diffusion step	Secretion of TNF, IL-10 and chemokines; oxygen consumption	S6, S7
Molecular substeps	Coarse receptor sink on TNF when TNFR dynamics are off, and on IL-10 when IL-10R dynamics are off	S6, M3
Movement block	Movement attempt, state-dependent cadence	S1
Next-state block	All state transitions, uptake, killing, death, pathway updates	This document
State commitment	Next state committed; dead cells removed	Spine 3

Macrophages are the first type processed in movement and in next-state computation (spine 3). Their next-state computation follows all movement and recruitment, so it reads occupancy after both, including newly recruited cells. STAT1 stimulation applied by a Tgam on the previous timestep remains available, subject to the expiry rules of S2.4. T cells, processed later, see macrophages' current states, immediate signalling changes and immediate deaths, but not deferred self-transitions (spine 2.3).

Reads:

- own state, pathway flags and counters, intracellular container, exposure flag and timer, age;
- TNF and IL-10 at the own compartment, and own surface receptor counts;
- live extracellular bacterial counts at the own compartment and in the periodic Moore neighbourhood;
- live and dead extracellular bacteria in the boundary-clipped neighbourhood, and the intracellular counts of neighbouring macrophages (S2.10);
- caseation status of neighbouring compartments.

Writes:

- own next state, pathway flags and counters, exposure flag and timer, death time and activation time;
- TNF and IL-10 fields, through the coarse sink terms (S6);
- extracellular bacterial containers at the own compartment and, when activated, in caseous neighbours;
- compartment killing counts, on its own death and on killing others (S5);
- healing clocks of neighbouring caseous compartments (S2.8);
- own intracellular container.

S2.2 States and transitions

States

A macrophage occupies one of five states: resting (R), infected (I), chronically infected (C), activated (A) and dead (D). Dead is absorbing.

A dead macrophage stays in the agent list and on the grid until the removal pass at the end of the cellular timestep, and every rule that tests for death skips it. Removal, not the transition to dead, increments the compartment death counter and frees the slot (spine 2.3).

The activated state is not a function of infection. An activated macrophage may hold intracellular bacteria, which the activated handler then kills (S2.8); there is no activated-and-infected state.

Infected and chronically infected differ only by a threshold on the live intracellular count. The change is irreversible: nothing returns a chronically infected macrophage to the infected state, even if its load later falls.

Transition edges

Edge labels are stable identifiers.

Edge	From	To	Condition	Evaluated in
E1	R, I, C, A	D	$t \geq$ death time	Dispatch, before any handler
E2	R, I, C, A	D	TNF-induced apoptosis test succeeds (S6)	Dispatch, before any handler
E3	R	A	Discrete STAT1 and NF-κB both set	Resting handler
E4	R	I	Bacteria present, not killed, taken up instead	Killing-versus-uptake routine
E5	R	R	Neither E3 nor E4	Resting handler
E6	I	C	Live intracellular count $\geq$ `Core_Mac_nrIntMtbCInf`	Chronic-infection check
E7	I	A	Not E6, and discrete STAT1 and NF-κB both set	Infected handler
E8	I	I	Neither E6 nor E7	Infected handler
E9	I	R	Live intracellular count is zero, pending state is I, exposure memory has lapsed	Infected handler, after E6 to E8
E10	C	D	Live intracellular count $\geq$ `Core_Mac_nrIntMtbBurstCInf`	Burst check
E11	C	C	Not E10	Chronically infected handler
E12	A	A	Unconditional	Activated handler

Edge	From	To	Condition	Evaluated in
E13	R, A	R	Suppression, no live intracellular bacteria	Suppression routine
E14	R, A	I	Suppression, live intracellular bacteria present	Suppression routine
E15	I	I	Suppression with a pending state of I or A; pending A is overwritten with I	Suppression routine
E16	R, I, C, A	D	Killed by another agent (S3), by caseation or by entrapment (S5)	External to this document

E1 and E2 are tested first, as the opening branches of an else-if chain, so a macrophage dying by either runs no handler and no further rule that timestep (S2.3).

E6 is tested before E7 and short-circuits it. A macrophage whose load crosses the chronic threshold on a timestep when both pro-inflammatory flags are set becomes chronically infected, not activated.

E9 is conditioned on the pending state, not the current state. A macrophage that cleared its bacteria and activated on the same timestep does not revert; it becomes an activated macrophage carrying no bacteria.

E16 deaths are written by the killing agent or by the grid, and apply at once to both the current and the pending state.

Chronically infected is absorbing among the live states: it can be left only by death (E1, E2, E10, E16). Activated is left only by death or by suppression (E13 to E15). Suppression therefore permits loss of activation but not reversal of chronic infection.

Death-time rewrites

Only these transitions change the death time after construction.

Transition	Death time written	Effect
E3, E7	t + `Core_Mac_maxAgeAct`	At most 1440 timesteps, 10 days, from the moment of activation
E13 and E14, and suppression of an infected cell whose pending state is resting (S2.11)	birth time + `Core_Mac_maxAge`	14400 timesteps, 100 days, measured from birth

Activation measures the death time from the activation timestep, so it can shorten or extend the remaining life. With the tabulated values every newly activated macrophage receives 10 days from activation, even if its ordinary deadline was nearer.

If a macrophage is suppressed after its ordinary deadline has passed, the restored death time lies in the past, and it senesces at its next next-state computation. A macrophage cannot first activate after its ordinary death time, because senescence is checked before activation.

How state is written

Macrophage self-transitions are written to the pending state only. Pending-state assignment is monotone toward death (spine 2.3).

The routine that increments a compartment's killing count on behalf of a named agent kills that agent first, writing its current and pending state (S5). A self-inflicted death that increments the killing count is therefore immediate. These deaths are TNF-induced apoptosis, bursting and activated senescence. Non-activated senescence changes only the pending state.

External killing (E16) changes both states at once. Suppression changes signalling variables and the suppression timer at once, but any state reassignment it makes changes only the pending state; it never writes the current state.

Construction invariants

Each invariant raises an exception and terminates the run if violated at creation.

Invariant	Condition
C1	A macrophage in a state other than infected or chronically infected may not be created with a positive intracellular count
C2	An infected or chronically infected macrophage must be created with a positive intracellular count
C3	A chronically infected macrophage must be created with the NF-κB flag set

C1 and C2 hold only at creation. An infected macrophage that loses all its bacteria stays infected until its exposure memory lapses (E9), and may stay infected indefinitely if exposure is refreshed. The invariant that does hold throughout, asserted at the end of the rule sequence, is that a positive live intracellular count implies the exposure flag is set. The converse does not hold.

Exposure is set at creation if and only if the creation state is infected or chronically infected. The exposure timer and the activation timestamp start at -1. The constructor permits an activated macrophage with no bacteria, but then sets no activation-relative death time and does not require the flags; such construction differs from activation through E3 or E7. No route uses it by default.

Macrophages are created by seeding (infected, one bacterium; spine 5.4), as the initial population (resting; spine 5.3), by recruitment (resting; S8) and by deserialization (spine 5). No route creates a chronically infected or activated macrophage by default, so C3 is never exercised. M8 reinfection would create a further infected macrophage.

S2.3 Dispatch

A macrophage's next-state computation is a guarded else-if chain. The senescence and apoptosis branches are terminal.

```
nextStateComputation(macrophage m, timestep t):
    if m is dead or dead-next:
        pending state <- dead; return
```

```
if t >= death time:                                    // senescence
    update the outside-granuloma release statistics (S9.8)
    release all intracellular bacteria into the own compartment (S4)
    bank the residence time
    if state == activated:
        increment the killing count at m's compartment, naming m
    set pending state dead

else if TNF-induced apoptosis test succeeds (S6):    // apoptosis
    apoptosis: set pending state dead;
               disperse half the intracellular bacteria (S4)
    increment the killing count at m's compartment, naming m
    bank the residence time

else:                                                  // survival
    exposure check, then exposure-expiry rewrite (S2.10)
    [M4 secretion-reduction check; M3 MHC class II action]
    if suppression has expired: clear the suppression timer
    if not suppressed:
        run the state handler (S2.5 to S2.8)
    else if state is infected or chronically infected:
        grow and decay the intracellular bacteria (S4)
        infected: chronic-infection check; chronic: burst check

// every path, terminal branches included
assert(live intracellular count == 0 or exposed)
if live intracellular count > 0: increment the holding statistic (S9.15)
```

The entry guard repeats the test the scheduler makes just before the call.

Activity	Senescence	Apoptosis	Survival
Bacterial fate	All released locally	Half dispersed, remainder destroyed	Determined by handler
Killing count incremented	Only if activated	Always	Only if the handler kills
Residence time banked	Yes	Yes	Only on clearing the container
Exposure memory updated	No	No	Yes
Suppression expiry checked	No	No	Yes
Pathways updated	No	No	Yes, unless suppressed
State handler called	No	No	Yes, unless suppressed

A macrophage dying in a terminal branch does not update its exposure memory. It presents its previous timestep's exposure flag to any T cell evaluating proliferation later in the same pass. It also does not check suppression expiry, so it is recorded as suppressed at death even if its interval elapses that timestep.

Senescence contributes to caseation only when activated. A resting, infected or chronically infected macrophage reaching its death time releases its bacteria without incrementing the killing count. Baseline turnover of the resting population therefore causes no caseation. The deaths that count are activated senescence, TNF-induced apoptosis, bursting, killing by T cells, and the cascades of caseation itself (S2.9, S5).

Apoptosis order. Apoptosis disperses half the bacteria and empties the container before the killing-count increment, and the residence time is banked last. A cascade triggered by the increment therefore meets an empty container. Dispersal can place bacteria in the own compartment. The cascade kills immune-cell occupants, not extracellular bacteria.

The suppressed branch

A suppressed macrophage bypasses its handler but is not inert. If infected or chronically infected, its bacteria grow and decay and are tested against the chronic and burst thresholds, so it can become chronically infected, or burst, while suppressed.

Suppression stops neither movement (S1), nor the coarse receptor sink (S6), nor oxygen consumption (S7). A suppressed macrophage does not secrete (S2.11), update any pathway, take up or kill bacteria, activate, revert or heal caseation.

The expiry test is non-strict, suppression start + `Core_Mac_maxTimeReg` $\leq t$, and is evaluated before the branch on suppression status. A macrophage whose suppression elapses on timestep t runs its handler on timestep t.

Pending death and target selection

A non-activated macrophage that senesced keeps a live current state while its pending state is dead. It can still be picked as a target by T cells (S3). Fas-mediated and cytotoxic killing reject a target whose pending state is dead, so neither kills it again. Exposure-based proliferation and interaction counting apply no such guard. Entrapment tests only the current state (S5.4).

S2.4 Signalling pathways

STAT1 and NF-κB are pro-inflammatory; STAT3 is anti-inflammatory. Each pathway has a discrete flag with an expiry timestep, a graded counter with its own expiry, and a gene index.

Activation is gated by the conjunction of the discrete STAT1 and NF-κB flags, and by nothing else. The counters and gene indices feed only the polarization index, which gates nothing (spine 2.3, S9.15). The discrete STAT3 flag governs no macrophage transition, but M8 Treg induction reads it: a selected STAT3-positive macrophage increments the Tgam's ICOS-associated counter (M8).

Discrete update

```
discreteUpdate(pathway, t, stimulated):
    if stimulated:
        flag <- true
        intervalEnd <- t + activation interval of the pathway
    if intervalEnd != -1 and intervalEnd < t:
        intervalEnd <- -1
        flag <- false
```

Repeated stimulation extends the interval rather than accumulating it. Expiry is strict: the flag survives through the timestep equal to its expiry value and clears on the next. The STAT1 interval is about 29 times the NF-κB interval, so a STAT1 flag can persist across several NF-κB cycles. Which flag limits activation depends on the local stimulation history.

Graded update

```
gradedUpdate(pathway, t, stimulated):
    if stimulated:
        counterIntervalEnd <- t + counter interval of the pathway
        counter <- min(counter + 1, counter cap)
    elapsed <- counterIntervalEnd != -1 and counterIntervalEnd < t
    if elapsed and not stimulated:
        if counter > 0:
            counter <- counter - 1
            counterIntervalEnd <- t + counter interval
        else:
            counter <- 0; counterIntervalEnd <- -1
    update the gene index
```

The macrophage's own graded STAT1 routine has no stimulation branch and only decrements. STAT1 increments occur in the stimulation routine called by the Tgam (S3.7).

Each gene index updates as $G \leftarrow \max(G + c\beta - G\delta, 1)$, with c the current counter value and β, δ the pathway's amplification and decay factors (S2.12). The floor at 1 makes the polarization index exactly 1 for an unstimulated macrophage (spine 2.3).

Stimulation conditions

STAT1 is stimulated only by the IFN-γ action of an IFN-γ-producing Tgam within Moore distance 2. The Tgam sets the flag, extends the interval and increments the counter in one operation. Targets, exclusions and draws are specified in S3.7.

NF-κB is stimulated if the TNF-induced NF-κB test of S6 succeeds, or if the live extracellular count summed over the periodic Moore neighbourhood exceeds `Core_Mac_nrExtMtbNFkB` (strict).

In the discrete NF-κB routine, either stimulation or a current state of chronically infected or activated sets the flag and refreshes its expiry to t + `Core_Mac_nfkbActivationTime`. The chronically infected and activated handlers do not call that routine, so this forcing is not reached from them. The chronically infected handler writes the flag directly (S2.7); the activated handler keeps it without evaluating its expiry (S2.8).

STAT3 is stimulated by the IL-10-induced STAT3 test of S6.

Which updates run in which state

Routine	STAT1 discrete	STAT1 graded	NF-κB discrete	NF-κB graded	STAT3 discrete	STAT3 graded	Called by
Full	Yes	Yes	Yes	Yes	Yes	Yes	Resting, infected handlers
Partial	No	Yes	No	Yes	Yes	Yes	Chronically infected, activated handlers

Neither routine runs for a dead or suppressed macrophage. In the partial routine, discrete STAT1 and NF-κB expiry is not evaluated. Each routine evaluates the NF-κB and STAT3 conditions once and passes the result to both the discrete and the graded update, so the flag and the counter cannot disagree about whether stimulation occurred.

Suppression resets the gene indices, flags and counters as tabulated in S2.11.

S2.5 Resting macrophage

```
restingHandler(m, t):
    full pathway routine (S2.4)
    if STAT1 and NF-kB:
        activation timestamp <- t
        death time <- t + Core_Mac_maxAgeAct
        pending state <- activated
        increment the activation statistic, indexed by the current state
    else:
        p_kill <- Core_Mac_probKillExtMtbRest * phi
        if STAT1 or NF-kB:
            p_kill <- (1 + Core_Mac_fKillExtMtbRest) * p_kill
        p_kill <- min(p_kill, 1)
        killingVersusUptake(m, t, p_kill)
```

The pathway routine runs first, so a resting macrophage whose second flag is set this timestep activates this timestep. Activation and the killing-versus-uptake decision are exclusive.

No bacterial load, cytokine concentration or cell contact enters activation except through the flags. With no initial STAT1-positive macrophage and no Tgam, activation is impossible until Tgams arrive; this follows from initialization and recruitment, not from the constructor.

ϕ is the TGF-β adjustment factor of M4. It is computed here with no module gate, and equals 1 when M4 is off.

The boost applies only with exactly one flag set, since both set is the activation condition. Before adaptive onset STAT1 is unreachable, so the boost is reached only through NF-κB, in compartments where TNF or bacteria are already high. Across the sampled ranges the base probability lies in [0.0971, 0.1528] and the boosted one in about [0.111, 0.192], so the cap never binds.

Killing versus uptake

```
killingVersusUptake(m, t, p_kill):
    E <- extracellular container at m's compartment
    if E.liveCount == 0:
        return                                          // no draw
    increment the caseation-associated uptake statistic (S9.13)
    u <- Core_Mac_nrExtMtbUptakeRest
    if E.liveBiomass < u:                               // Outcome A, no draw
        kill all live bacteria of E
        pending state <- current state
    else if U(0,1) < p_kill:                            // Outcome B
        kill u live bacteria of E
        pending state <- current state
    else:                                               // Outcome C
        transfer u live bacteria from E to m (S4.12)
        grow m's intracellular bacteria at once (S4)
        pending state <- infected
        increment the infected count statistic
```

Outcome A compares the total live extracellular biomass with `Core_Mac_nrExtMtbUptakeRest`, not the count, and the comparison is strict. Killing all moves the bacteria to the dead list and arms their decay clocks; it deletes nothing (S4).

Division multiplies the pre-division biomass by `Mtb_Agents_divisionFraction` and its complement. Dividing at biomass 2 with fraction 0.43 gives products of about 0.86 and 1.14. Growth precedes the division test, so the actual pre-division biomass can exceed the threshold, and the products are then correspondingly larger.

Contents	Total live biomass	Outcome A with uptake amount 1
One smaller division product	0.86	Satisfied
One larger division product	1.14	Not satisfied
Both products	2	Not satisfied
One newly constructed bacterium	1	Not satisfied (strict)

`Core_Mac_nrExtMtbUptakeRest` is an integer count of bacteria killed in Outcome B or taken up in Outcome C. The bacterium taken is chosen uniformly from the live list (S4.10). A request above the available count is the subject of S4.12.

Outcome C grows the uptaken bacterium at once, at the intracellular rate. The extracellular pass runs after all agents, so without this call the bacterium would miss growth on its uptake timestep. It can divide that timestep, so a newly infected macrophage may end the timestep holding two.

S2.6 Infected macrophage

```
infectedHandler(m, t):
    n <- live intracellular count
    p_uptake <- (1 - Core_Mac_probKillExtMtbRest) / 2 * (1 - n / Core_Mac_nrIntMtbCInf)
    if live extracellular count at m's compartment > 0 and U(0,1) < p_uptake:
        increment the caseation-associated uptake statistic (S9.13)
        transfer Core_Mac_nrExtMtbUptakeRest live bacteria into m (S4.12)
    grow and decay the intracellular bacteria (S4)          [M6 drug steps]
    residence accumulator <- residence accumulator + 1
    if live intracellular count < 1: kill all intracellular bacteria
    if not chronicCheck(m):                                 // E6
        full pathway routine (S2.4)
        if STAT1 and NF-kB:                                 // E7
            activation timestamp <- t
            death time <- t + Core_Mac_maxAgeAct
            pending state <- activated
            increment the activation statistic, indexed by the current state
        else:
            pending state <- infected
    if live intracellular count == 0:
        bank and reset the residence accumulator
        if pending state == infected and not exposed:       // E9
            pending state <- resting
```

Uptake. n is the live count at the start of the handler, before uptake and growth. Uptake is attempted only if live extracellular bacteria are present. n is always below the chronic threshold on entry, so p_uptake is positive. Its base, half the complement of the resting kill probability, lies in [0.424, 0.451] across the sampled range, and it falls linearly to 0 at the threshold. The final approach to the threshold is therefore driven mainly by replication.

An infected macrophage never kills extracellular bacteria. Its only outcomes are uptake or nothing. Only activation restores killing.

Uptake precedes the single growth call, so newly taken bacteria grow that timestep, and uptake can raise the load by two.

Chronic transition. The chronic test is live count $\geq$ `Core_Mac_nrIntMtbCInf`, after growth. It is the enclosing condition, so it pre-empts the pathway routine and activation. A macrophage becoming chronically infected updates no pathway that timestep: its discrete STAT3 flag, counters and gene indices are frozen for one timestep. The transition sets the NF-κB flag at once, not through the pending state. This satisfies C3 and governs the cell's secretion in the next timestep's diffusion block.

Activation from infected uses the same condition and death-time rewrite as from resting. The activation statistic is indexed by prior state (S9.15). Activation from infected is the principal route by which intracellular bacteria are killed rather than contained (S2.8).

Reversion requires a live count of 0, a pending state of infected and exposure clear. A macrophage that cleared its bacteria while becoming chronic or activated does not revert; it can be activated with an empty container.

The reversion lock. The exposure check runs before the handler (S2.3). While the cell holds live bacteria it re-arms its own 5-day timer (S2.10). If its bacteria die during the handler, the reversion test that timestep fails. **A macrophage that clears its bacteria therefore stays infected for at least 5 days**, and only if no further exposure occurs in that interval. Throughout, it secretes at infected rates, is a Fas and cytotoxic target (both

select on state), and can activate. "Infected" does not mean "carrying bacteria".

Starvation is not a clearance route at the default values (S4).

Residence time. The residence accumulator is incremented unconditionally once per timestep in this handler, and banked and reset whenever the live count is 0. The consequence for the residence-time statistics is specified in S9.15.

S2.7 Chronically infected macrophage

```
chronicallyInfectedHandler(m, t):
    partial pathway routine (S2.4)
    grow and decay the intracellular bacteria (S4)          [M6 drug steps]
    residence accumulator <- residence accumulator + 1
    if not burstCheck(m):
        pending state <- chronically infected
        NF-kB <- true

burstCheck(m):
    if live intracellular count >= Core_Mac_nrIntMtbBurstCInf:     // E10
        disperse all intracellular bacteria, live and dead, at fraction 1.0 (S4.13)
        bank the residence time
        set pending state dead
        increment the killing count at m's compartment, naming m   // immediate
        increment the burst statistic
        return true
    return false
```

There is no uptake, no discrete STAT1 or NF-κB update and no reversion. A chronically infected macrophage always holds bacteria, so the residence increment counts only timesteps on which it holds them.

The burst threshold must strictly exceed the chronic threshold, checked at startup (S2.12), so no macrophage bursts on its entry timestep.

Time to burst. Intracellular growth alone sets it. At the default rate one doubling takes 155 timesteps, about 25.8 hours (S4). From a load of 10 the count reaches 24 in about 1.3 doublings (196 timesteps) and 41 in about 2 (316 timesteps), about 1.4 to 2.2 days. Across the sampled thresholds the residence is about 0.7 to 2.2 days. A chronically infected macrophage therefore almost always bursts rather than senescing.

Immobility. Chronically infected macrophages never move (S1).

Suppression. Suppression of a chronically infected macrophage is an empty case (S2.11). The suppressed branch's chronic handling is reachable only by a cell suppressed while infected that then became chronically infected.

The NF-κB flag. The flag is written true at the chronic transition (S2.6), by the discrete routine's state forcing (S2.4), and at the end of every non-bursting timestep here. The partial routine does not call the discrete update, so in this state the end-of-handler write is the only mechanism maintaining the flag. The graded NF-κB counter is not forced: it decays while the flag stays true. A fully pro-inflammatory chronic macrophage in a quiet neighbourhood can therefore report a polarization index near 1.

Secretion. A chronically infected macrophage is an immobile source of both TNF and IL-10 until death (S6). With its residence of at most about 2.2 days, it is a fixed, short-lived signalling source at the centre of the lesion.

S2.8 Activated macrophage

```
activatedHandler(m, t):
    partial pathway routine (S2.4)
    if live intracellular count > 0:
        residence accumulator <- residence accumulator + 1
        kill 1 intracellular bacterium                      [M6 drug killing]
    if live extracellular count at m's compartment > 0:
        kill up to Core_Mac_nrExtMtbUptakeAct live bacteria there
    heal <- U(0,1) < Core_Mac_probHealCaseation             // one draw for all nine
    for each compartment p of the periodic Moore neighbourhood, own included:
        if caseous(p) and heal and healing clock of p == 0:
            healing clock of p <- t
            increment the healing statistic (S9.13)
        else if caseous(p) and live extracellular count at p > 0:
            if U(0,1) < 0.1:
                kill up to Core_Mac_nrExtMtbUptakeAct live bacteria at p
    if live intracellular count == 0:
        bank and reset the residence accumulator
    pending state <- activated
```

No transition other than death is reachable from this handler. The activated state is left only by the death routes of S2.9 or by suppression (S2.11).

Intracellular killing

An activated macrophage kills exactly one intracellular bacterium per timestep, a fixed constant. It calls no intracellular growth, so n bacteria are cleared in exactly n executions; a load of 10 is cleared in 10 timesteps.

The handler also makes no decay call on the intracellular container. Bacteria killed here stay in the dead list, undecayed, until the cell dies; every death route then releases or disperses them with the live list (S2.9). The dead list holds at most the load at activation, which is below `Core_Mac_nrIntMtbCInf`, since activated macrophages take up and grow nothing. The resting handler likewise makes no decay call.

Own-compartment killing

The macrophage kills up to `Core_Mac_nrExtMtbUptakeAct` bacteria in its own compartment, with certainty. The counted kill routine kills the whole live list when the request equals or exceeds it (S4.10), so fewer are killed when fewer are present. An activated macrophage has no uptake branch and never becomes infected by its own action.

The neighbourhood sweep

The sweep covers the periodic Moore neighbourhood, own compartment included, in fixed ordinal order. The own compartment cannot satisfy either branch, since a compartment holding a live macrophage is not caseous.

The branches are exclusive, and healing is tested first. A caseous neighbour that is healed is not also depleted that timestep.

Healing initiation. Healing is initiated, not performed, here. The conditions are: the neighbour is caseous, the macrophage's heal draw succeeded, and no healing is already in progress there (healing clock = 0). The macrophage stamps the neighbour's healing clock with t. The halving of the killing count follows later, when the delay has elapsed (S5).

One heal draw per macrophage per timestep covers all nine compartments. Healing initiations within one neighbourhood are therefore all-or-none: a macrophage with three eligible neighbours heals all three or none. The mean rate is unaffected, but variance is higher and the spatial pattern is clustered.

With the sampled `Core_Mac_probHealCaseation`, an activated macrophage beside caseum initiates healing on about one timestep in 200. The healing delay, about 9.6 to 11.4 days (S5), is comparable to the activated lifespan of 10 days.

Killing within caseum. For each caseous neighbour holding live bacteria, a separate draw against the fixed probability 0.1 decides whether the macrophage kills up to `Core_Mac_nrExtMtbUptakeAct` bacteria there. Unlike the heal draw, this draw is per compartment. It is the only immune killing of bacteria inside caseum.

Lifespan, pathways and residence

Activation sets the death time 10 days ahead (S2.2). Activation is self-limiting, and activated senescence feeds caseation where the immune response is strongest (spine 4.1, 4.2).

The partial routine never evaluates discrete STAT1 or NF-κB expiry, so both flags stay true for the rest of the activated life. The full routine would expire STAT1. The flags are re-evaluated only after suppression, which clears both (S2.11).

The residence increment is guarded on a positive live count. Once the container is empty the banking block runs every timestep but adds 0.

Activated IL-10 secretion depends on local TNF (S6).

S2.9 Death routes

Route	Inflicted by	Condition	Specified in
Senescence	Self	$t \geq$ death time	S2.3
TNF-induced apoptosis	Self	Threshold-and-probability test on TNF receptor occupancy	S2.3, S6
Bursting	Self	Live intracellular count $\geq$ `Core_Mac_nrIntMtbBurstCInf`	S2.7
Fas-mediated killing	Tgam	Target infected or chronically infected	S3
Cytotoxic killing	Tcyt	Target infected or chronically infected	S3

Route	Inflicted by	Condition	Specified in
Caseation or entrapment	Grid	Caseation cascade, or the compartment becomes caseous by entrapment	S5

Bacterial fate

Local release and fractional dispersal are specified in S4.13, under survival of Mtb after macrophage death. Senescence alone uses local release: the whole container goes to the own compartment's extracellular container, and nothing is destroyed. Every other route except the clean cytotoxic kill uses fractional dispersal.

A route dispersing at fraction 0.5 destroys a lone bacterium, so it sterilizes a macrophage holding one (S4.13). Dispersed dead bacteria keep their decay clocks and still confer exposure (S2.10).

Route	Fate	Fraction
Senescence, any state	Local release	—
TNF-induced apoptosis	Fractional dispersal	0.5
Bursting	Fractional dispersal	1.0
Fas-mediated killing	Fractional dispersal	0.5
Cytotoxic killing, clean	Kill in place	—
Cytotoxic killing, dispersing	Fractional dispersal	0.5
Caseation or entrapment	Fractional dispersal	1.0

The clean cytotoxic kill marks every live intracellular bacterium dead without dispersing. They are destroyed with the cell at removal, and confer no exposure, since neighbours read the live count. Which cytotoxic outcome occurs is decided by the T cell (S3).

Killing count and immediacy

Route	Killing count incremented	Current state written at once
Senescence, not activated	No	No
Senescence, activated	Yes	Yes
TNF-induced apoptosis	Yes	Yes
Bursting	Yes	Yes
Fas-mediated or cytotoxic killing	Yes, by the T cell	Yes
Caseation or entrapment	Yes, once per occupant killed	Yes

The table follows from S2.2 (how state is written). The re-kill by entrapment, on the same timestep, of a macrophage that senesced while not activated is specified in S5.4. Increments from cascade kills mean the count is not bounded by the caseation threshold (S5).

Residence time and statistics

Senescence, TNF-induced apoptosis, bursting, Fas-mediated killing and cytotoxic killing bank and reset the residence accumulator, as do the infected and activated handlers whenever their live count is 0. Caseation and entrapment discard it.

The statistics each route credits, and the residence-time statistics and their denominator, are specified in S9.15. The outside-granuloma release counters, which count senescence releases only, are specified in S9.8.

S2.10 Exposure memory

Exposure memory is a flag paired with an expiry timestep. It licenses T cell proliferation nearby (S3), and it gates reversion of an infected macrophage (S2.6); it has no other consequence.

```
exposureCheck(m, t):
    if live intracellular count of m > 0:
        exposed <- true; exposure expiry <- t + Core_Mac_maxExposureTime
        return
    for each compartment p of the boundary-clipped Moore neighbourhood:
        if live or dead extracellular count at p > 0:
            exposed <- true; exposure expiry <- t + Core_Mac_maxExposureTime
            stop
        if some macrophage occupant of p has live intracellular count > 0:
            exposed <- true; exposure expiry <- t + Core_Mac_maxExposureTime
            stop

exposureExpiryRewrite(m, t):
    exposed <- (t <= exposure expiry)
```

Both routines run in the survival branch, before the handler (S2.3). The second rewrites the flag from the timer in both directions every timestep, so the flag is a function of the timer. The timer is set, not incremented; expiry is strict; and a timer of -1 means unexposed.

Dead bacteria count. The extracellular test reads the live and the dead list. A dead bacterium is deleted at the end of the fifth decay call after its death (S4.14). One killed in the extracellular pass on timestep t is therefore visible to exposure checks on timesteps t + 1 to t + 4. One killed earlier in the next-state block on timestep t is also visible, later that timestep, to macrophages processed after it.

Neighbours are read through their live intracellular count, not their state. An infected macrophage that has cleared its bacteria confers no exposure; a resting or activated macrophage holding bacteria does.

Only macrophages are read. A non-macrophage occupant is skipped, so a neighbouring neutrophil holding bacteria confers no exposure (M9.6). Dendritic cells, which share the macrophage type, would be read (S2.13).

The neighbourhood is boundary-clipped, unlike most agent sensing, which is periodic (spine 2.2). A macrophage at the domain edge examines 6 compartments, and one at a corner 4. The other clipped helpers are the M4 secretion-reduction check and the M8 reinfection fallback.

Proliferation licence. A cognate T cell is licensed by any exposed macrophage in its Moore neighbourhood (S3). The effective radius from bacterium to licensed T cell is therefore 2, and the licence persists 5 days after the last contact.

Exposure does not affect secretion, killing, uptake, activation, recruitment or any field, and it confers no immunological memory. The exposed-macrophage statistic is defined in S9.15.

S2.11 Suppression

Suppression is a contact action of an active regulatory T cell on a macrophage in its Moore neighbourhood. Targeting and the per-target draw are specified in S3. The T cell applies suppression at once to the target. It resets the macrophage's signalling state and, in most cases, arms a timer during which the macrophage runs no state handler.

```
suppress(m, t):
    if suppression start != -1 or pending state == dead or state == dead:
        return
    dispatch on current state, then on pending state (table)
```

A suppressed macrophage cannot be suppressed again, so the duration is fixed at `Core_Mac_maxTimeReg`, with no extension by repeated contact. The pending state read is the one the macrophage wrote earlier in the same timestep, since macrophages are processed before T cells.

Resets go through one routine that assigns its arguments unconditionally. It never writes the discrete STAT3 flag or the NF-κB counter interval end. Gene indices are reset to 1 beforehand in every live case except chronically infected.

Current state	Pending state	STAT1	NF-κB	STAT1, STAT3 counters	NF-κB counter	STAT1, STAT3 flag and counter interval ends	NF-κB flag interval end	Timer armed	Pending written	Death time
Chronically infected	any	unchanged	unchanged	unchanged	unchanged	unchanged	unchanged	No	No	unchanged
Resting or activated	Infected	false	false	0	0	-1	-1	No	No	unchanged
Resting or activated	any other	false	false	0	0	-1	-1	Yes	Resting or infected	reverted
Infected	Chronically infected	false	preserved	0	preserved	-1	preserved	No	No	unchanged
Infected	Resting	false	false	0	0	-1	-1	Yes	No	reverted
Infected	Activated or infected	false	false	0	0	-1	-1	No	Infected	unchanged

"Reverted" means death time ← birth time + `Core_Mac_maxAge`.

The chronically infected, resting-or-activated-with-pending-infected and infected-with-pending-chronic or -activated-or-infected rows arm no timer. They reset signalling without suspension, and the cell runs its handler normally next timestep. The rationale is that silencing the secretion of a cell heading toward infection can cause the early granuloma to break up and reform.

The infected-to-chronically-infected row preserves the NF-κB flag, its interval end and its counter, which C3 requires; STAT1 is still cleared.

For a macrophage suppressed from activated, reverting the death time undoes the activated lifespan. For one suppressed from resting the write is a no-op: its death time already has this value, or, if it was previously activated and suppressed, has this value again.

Resting or activated branch

```
case resting or activated:
    reset gene indices; increment the suppression statistic
    if pending state == infected:
        reset flags, counters and interval ends; timer not armed
    else:
        reset flags, counters and interval ends; suppression start <- t
        death time <- birth time + Core_Mac_maxAge
        if live intracellular count > 0: pending state <- infected
        else: pending state <- resting
```

An activated macrophage holding bacteria has pending state activated, written by its own handler. It therefore takes the arming branch: the timer is armed, and the pending state is written as infected. The suppressed cell then grows its bacteria in the suppressed branch without killing them, and can become chronically infected while suppressed. An activated macrophage holding bacteria is not a Fas or cytotoxic target, since those select on state.

Infected branch

```
case infected:
    reset gene indices; increment the suppression statistic
    pending chronically infected: reset, preserving the NF-kB flag,
        its interval end and its counter; timer not armed
    pending resting: reset; suppression start <- t;
        death time <- birth time + Core_Mac_maxAge
    pending activated or infected: reset; timer not armed;
        pending state <- infected
```

The pending-resting case is the only one in this branch that arms the timer. It is reached only when the cell's exposure lapsed this timestep, at least 5 days after it cleared its bacteria (S2.6).

The pending-activated case cancels an activation before it takes effect. The activation statistic keeps its increment, and the cell keeps the 10-day death time written by its handler.

Expiry and what suppression leaves

Expiry is non-strict and is tested before the branch on suppression status (S2.3). Recovery clears the timer and restores nothing else: cleared STAT1 and NF-κB must be stimulated again before activation.

Suppression does not touch the discrete STAT3 flag. It sets the STAT3 interval end to -1, so a retained flag has no armed expiry until stimulation re-arms it. It also leaves the intracellular container, the exposure flag and timer, receptor counts, position and the activation timestamp unchanged.

Secretion. The secretion routine returns early for a macrophage whose timer is armed (S6). Secretion precedes the next-state block, so silencing begins in the diffusion block of the next timestep. On the timestep suppression expires, secretion is still silenced, because it runs before the expiry check; it resumes the timestep after.

S2.12 Parameters

LU marks log-uniform sampling; the rest are uniform, integers over inclusive bounds. `Core_Mac_dIL10Act`, `Core_Mac_dIL10Inf`, `Core_Mac_thresholdNFkBTNF`, `Core_Mac_kNFkB`, `Core_Mac_thresholdSTAT3IL10` and `Core_Mac_kSTAT3IL10` are tabled in S6.16.

Identifier	Value or range	Range	Units	Meaning
`Core_Mac_nrExtMtbNFkB`	—	[144.95, 255.69]	bacteria	NF-κB bacterial threshold (S2.4)[1]
`Core_Mac_probKillExtMtbRest`	—	[0.0971, 0.1528]	probability	Resting kill probability (S2.5, S2.6)
`Core_Mac_fKillExtMtbRest`	—	[0.1436, 0.2571]	fraction	Single-flag kill boost (S2.5)
`Core_Mac_nrIntMtbCInf`	—	[10, 15]	bacteria	Chronic threshold (S2.6)[2]
`Core_Mac_nrIntMtbBurstCInf`	—	[24, 41]	bacteria	Burst threshold (S2.7)[2]
`Core_Mac_nrExtMtbUptakeAct`	—	[3, 10]	bacteria	Activated kill amount (S2.8)
`Core_Mac_probHealCaseation`	—	[0.003898, 0.006992]	probability	Heal draw (S2.8)
`Core_Mac_maxAge`	14400		timesteps	Ordinary lifespan, 100 days (S2.2)
`Core_Mac_maxAgeAct`	1440		timesteps	Activated lifespan from activation, 10 days (S2.2)
`Core_Mac_maxTimeReg`	144		timesteps	Suppression interval, 1 day (S2.11)
`Core_Mac_maxExposureTime`	720		timesteps	Exposure interval, 5 days (S2.10)
`Core_Mac_nrExtMtbUptakeRest`	1		bacteria	Resting uptake and kill amount; Outcome A biomass threshold; infected uptake amount (S2.5, S2.6)
`Core_Mac_stat1ActivationTime`	430		timesteps	STAT1 flag interval[3]

Identifier	Value or range	Range	Units	Meaning
`Core_Mac_nfkbActivationTime`	15		timesteps	NF-κB flag interval[3]
`Core_Mac_stat3ActivationTime`	100		timesteps	STAT3 flag interval[3]
`Core_Mac_stat1CounterTimeInterval`, `Core_Mac_stat3CounterTimeInterval`	120		timesteps	STAT1 and STAT3 counter intervals[3] [4]
`Core_Mac_nfkbCounterTimeInterval`	15		timesteps	NF-κB counter interval[3] [4]
`Core_Mac_stat1CounterMaxLevel`, `Core_Mac_nfkbCounterMaxLevel`, `Core_Mac_stat3CounterMaxLevel`	10		none	Counter caps
`Core_Mac_stat1Beta`, `Core_Mac_stat1GeneDeg`	1, 0.05		none	STAT1 gene-index β, δ
`Core_Mac_nfkbBeta`, `Core_Mac_nfkbGeneDeg`	1, 0.005		none	NF-κB gene-index β, δ
`Core_Mac_stat3Beta`, `Core_Mac_stat3GeneDeg`	5, 0.2		none	STAT3 gene-index β, δ

[1] A real-valued threshold compared strictly with an integer sum: 144.95 requires at least 145 bacteria, 145 at least 146. It applies in every live state that calls a pathway routine.
[2] Checked at startup: `Core_Mac_nrIntMtbBurstCInf` > `Core_Mac_nrIntMtbCInf`, strictly. A violation aborts the run before the first timestep. The sampled ranges satisfy it for every combination.
[3] The interval parameters are real-valued but interval ends are integers, so t + interval truncates toward zero. This matters only for non-integer intervals.
[4] Strict expiry and re-arming at the decrement timestep space successive decrements I + 1 timesteps apart. With no intervening stimulation or suppression, a counter falls from 10 to 0 in 10(I + 1) timesteps: 1210 for STAT1 and STAT3, 160 for NF-κB.

Validity. `Core_Mac_probKillExtMtbRest`, `Core_Mac_fKillExtMtbRest` and `Core_Mac_probHealCaseation` are declared on [0, 1] and checked at startup; a value outside aborts the run. `Core_Mac_dIL10Act`, `Core_Mac_dIL10Inf`, `Core_Mac_maxAge`, `Core_Mac_maxAgeAct`, `Core_Mac_maxTimeReg`, `Core_Mac_maxExposureTime`, `Core_Mac_stat1ActivationTime`, the counter intervals and the counter caps are declared with a minimum of 0 only, which is not checked (spine 7.0, "Validity ranges"). The other parameters in the table have no declared range.

Signalling timescales. The flag intervals are compared in S2.4. The STAT1 and STAT3 counter intervals are eight times the NF-κB interval, so the NF-κB counter rises and falls faster. The NF-κB counter interval equals its flag interval, but the two are independent: the flag clears after one interval, whereas the counter takes up to ten. The gene-index relaxation timescales $1/\delta$ are 20, 200 and 5 timesteps for STAT1, NF-κB and STAT3. The index is dominated by NF-κB, whose ceiling is an order of magnitude above the others. STAT3 relaxes first and NF-κB last, so the index drifts toward M1 as stimulation subsides before relaxing to 1. The NF-κB index relaxes

more slowly than its counter empties in 160 timesteps, so the two are not in quasi-equilibrium. The counter and gene-index parameters affect only the polarization index.

Fixed structural constants. Intracellular kill of 1 bacterium per timestep (S2.8). Caseum kill probability 0.1 (S2.8). Dispersal fraction 0.5 for apoptosis, and 1.0 for bursting, caseation and entrapment (S2.9); the general kill routine takes the fraction from its caller, T cells passing 0.5 and the grid 1.0.

Read but without effect by default: `Core_Mac_TGFBmax` (read; no effect by default; must be non-zero, M4.4), `Core_Mac_tgfbBindingRate` and `Core_Mac_dTGFBInactive` (read only inside M4-gated calls), and `Molecular_IL10_Mac_halfSatIL10mRNA` (its result is consumed only by M3).

Parameters owned elsewhere are linked in S2.13: movement intervals and the movement bonus factor (S1), the initial density and count (spine 5.3, S8), secretion rates, receptor complements, dissociation constants and `Core_Mac_saturationFracNFkBTNF` (S6.16), healing time and caseation threshold (S5).

S2.13 Interfaces

With	Provides or receives	See
Spine 2.3	Receives occupancy, the hybrid update, monotone pending death and removal; provides the macrophage state inventory and polarization index	Spine 2.3
Spine 3	Receives the type order: macrophages first in movement and next-state computation	Spine 3
Spine 5	Seeding macrophage, initial population, birth times, deserialization	Spine 5.3, 5.4
S1	Movement intervals and bonus factor; chronically infected macrophages never move; suppression does not stop movement	S1
S3	STAT1 stimulation by Tgam; Fas-mediated and cytotoxic killing; suppression targeting; proliferation licence read from exposure memory	S3
S4	Intracellular growth and decay; the container operations (kill, kill all, transfer, release, dispersal) and survival of Mtb after macrophage death	S4
S5	Killing count, caseation cascade, entrapment and its re-kill of senesced macrophages; healing delay and halving	S5
S6	Receptor complements and occupancy; TNF-induced apoptosis and NF-κB tests, IL-10-induced STAT3 test; secretion and the coarse receptor sink	S6
S7	Oxygen consumption	S7
S8	Recruitment of resting macrophages; recruitment floor	S8
S9	Macrophage statistics, residence-time statistics, outside-granuloma release counters, polarization index reporting	S9.8, S9.13, S9.15

With	Provides or receives	See
M1	No macrophage code affected; fields read and written through solver-independent accessors	M1
M2	No macrophage code affected; recruitment creates macrophages but does not alter their behaviour	M2
M3	Four decision routines branch on module flags; molecular state carried and serialized; MHC class II action before the suppression test; IL-10 synthesis rescaling	M3
M4	Binding and latent secretion and the secretion-reduction check, gated; the TGF-β factor in resting killing, ungated, equal to 1 when off	M4
M5	Every neighbourhood operation of this document scales from 9 to 27 compartments	M5
M6	Drug concentration, killing, efflux and dispersal touchpoints	M6
M7	Anti-TNF species carried; statistics zero	M7
M8	Growth-rate randomization of intracellular bacteria; cytokine depletion of macrophage secretion; reinfection; Treg induction reads the STAT3 flag	M8
M9	Neutrophils are not read by the exposure rule; neutrophil receptor parameter groups	M9.6, M9.10.2
Appendix B	Disabled-module parameter groups and toggles	Appendix B

Default option: Under the coarse option used by default, receptor occupancy is computed in closed form from local fields and own receptor counts (S6).

The dendritic cell is a subclass of the macrophage sharing its type tag. Every neighbourhood type test for a macrophage would therefore also return a dendritic cell, including the exposure rule (S2.10) and T cell target selection (S3). None is created in the default configuration.