S3. T cells

S3.1 Scope and schedule

This submodel specifies the three T cell types, Tgam, Tcyt and Treg: antigen specificity and producer status, state transitions, proliferation, the coarse-grained IFN-γ action, Fas-mediated and cytotoxic killing of macrophages, contact suppression by regulatory T cells, and the gates on T cell secretion. It expands the T cell submodel listed in spine Element 7.

Block	T cell activity	See
Split half-step, twice per diffusion step	Secretion of TNF and IL-10	S6; gates in S3.11
Molecular substep	Receptor-occupancy sink on TNF and IL-10	S6
Movement, after all macrophages	One movement attempt per timestep	S1
Next-state computation, after all macrophages	Transitions, proliferation, interaction counting, killing, IFN-γ action, suppression	S3.3 to S3.10
State commitment	Pending state committed; dead cells removed; promised daughters placed	Spine Element 3

In every block the T cell types are processed in the order Tgam, Tcyt, Treg, and always after the macrophages (spine Element 3).

Because macrophages precede T cells in movement and in next-state computation, a T cell acts on the macrophage configuration the macrophages have just produced. A macrophage sees T cell states and T cell actions from the previous timestep. A macrophage whose STAT1 flag is set by a Tgam has therefore already decided its next state, so the stimulation acts from the next timestep (S3.7).

Reads: own state, antigen specificity, producer flags, division count, proliferation timer, suppression timer and death time; TNF and IL-10 at its own compartment; the chemokine fields across its radius-1 periodic Moore neighbourhood, for movement (S1); occupant types and states in its radius-1 and radius-2 periodic Moore neighbourhoods; free-slot counts and the daughter reservation map; macrophage exposure memory; a killed macrophage's intracellular residence time.

Writes: own pending state, timers and division count; TNF and IL-10 at its own compartment, by secretion; its own position, by movement (S1); the STAT1 flag, interval and counter of macrophages within radius 2; the current and pending state and intracellular bacteria of macrophages it kills; compartment killing counts; the suppression state of agents within radius 1; the reservation map and the per-type proliferation list.

T cells do not read the oxygen field. They read caseation only in admission (S1) and in daughter placement (S3.5). They do not read a macrophage's intracellular bacterial count when selecting a target.

S3.2 Antigen specificity and producer status

Specificity

Every T cell carries a boolean antigen specificity: it is cognate or non-cognate. The specificity is supplied to the constructor, is never revised, and is inherited unchanged by daughters. The Bernoulli draw that sets it is made by the recruitment submodel (S8.12), against the per-type probabilities `Recruit_Prob_Tcell_Tgam_probCognate`, `Recruit_Prob_Tcell_Tcyt_probCognate` and `Recruit_Prob_Tcell_Treg_probCognate`, which S8.13 tables.

Treg specificity is drawn like that of the other types and is not special-cased. Non-cognate Tregs are created, are the large majority of Tregs, and are inert.

A non-cognate T cell moves, secretes nothing, and dies by senescence, TNF-induced apoptosis or caseation. It does not proliferate, kill, suppress or exert the IFN-γ action, and it cannot be suppressed; the exemption is enforced by the suppressing Treg (S3.10).

The responding population is therefore one to two orders of magnitude smaller than the total T cell count. At the lower bound of the sampled Treg cognate probability, 0.005366, about one Treg in 186 can suppress anything.

Producer status

Producer status is a binary per-cell trait, drawn once in the constructor and only for cognate cells. A non-cognate cell has every producer flag false. Daughters make no producer draw: they copy their parent's producer flags, specificity and receptor counts (S3.5), so producer status is clonal.

Type	Flags drawn, in order	Parameters
Tgam	IFN-γ producer, then TNF producer	`Core_Tcell_Tgam_probIFNProducer`, `Core_Tcell_Tgam_probTNFProducer`
Tcyt	TNF producer	`Core_Tcell_Tcyt_probTNFProducer`
Treg	None	—

A cognate Tgam either exerts the IFN-γ action of S3.7 at full strength on every eligible macrophage in range, or never exerts it. The fraction of recruited Tgam that can set a macrophage's STAT1 flag is the product of the cognate and IFN-γ producer probabilities, between $0.02645 \times 0.2889 = 7.6 \times 10^{-3}$ and $0.09421 \times 0.4591 = 4.3 \times 10^{-2}$, roughly one in 130 to one in 23.

Tregs secrete IL-10 without any producer gate, so every cognate Treg secretes. This is the only T cell cytokine production not subject to a producer draw.

S3.3 States and transitions

Declared and reachable states

Type	Declared states	Reachable by default
Tgam	T0, active, down-regulated, double-producer, induced-regulatory, exhausted, dead	Active, down-regulated, dead

Type	Declared states	Reachable by default
Tcyt	T0, active, down-regulated, exhausted, dead	Active, down-regulated, dead
Treg	T0, active, dead	Active, dead

Every T cell is created in its type's active state, by recruitment, initialization or proliferation. The T0 states are entered only under the MHC class II component of M3 (S3.3, T0 states). The double-producer and induced-regulatory states belong to M8 (S3.10, Treg induction). The exhausted states are gated on a sentinel parameter and are unreachable by default (S3.6).

The Treg state machine therefore has two live states, active and dead, with no transition between them other than death. Tgam and Tcyt each have one reversible pair, active and down-regulated.

Transitions common to all types

These edges are identical in each type and are evaluated before any type-specific rule.

Edge	From	To	Condition	Killing count
T1	Any live	Dead	$t \geq$ death time	Not incremented
T2	Any live	Dead	TNF-induced apoptosis test succeeds	Incremented at own position
T3	Any live	Dead	Compartment crosses the caseation threshold, or becomes caseous by entrapment	Incremented by the grid

T1 and T2 are the leading branches of an else-if chain, so a cell dying by either runs no further rule on that timestep. T3 is written by the grid, not by the cell, and is applied at once to both the current and the pending state.

T cells live three days against a macrophage's hundred and are sustained almost entirely by recruitment. Their large baseline turnover by senescence therefore adds nothing to caseation. A T cell death contributes to caseation by TNF-induced apoptosis, by the caseation cascade, or by entrapment. A T cell that senesces on the timestep its compartment becomes caseous by entrapment is re-killed by the entrapment sweep, and adds one increment that its senescence withheld (S5.4).

No T cell state makes senescence increment the killing count; the activated-macrophage case has no T cell analogue. No agent's effector rule kills a T cell, and Treg suppression does not kill. T1, T2 and T3 are the complete set of T cell death routes.

Tgam transitions

Edge	From	To	Condition	Evaluated in
G1	Active	Active	Unconditional, written at the end of the active handler	Active handler

Edge	From	To	Condition	Evaluated in
G2	Active	Down-regulated	Suppression by an active cognate Treg	Suppression rule (S3.10)
G3	Down-regulated	Active	$t-$ suppression timer $\geq$ `Core_Tcell_Tgam_maxTimeReg`	Down-regulated handler
G4	Down-regulated	Down-regulated	Not G3	Down-regulated handler

G3 also clears the suppression timer to the sentinel -1, so a recovered Tgam is indistinguishable from one never suppressed. With 36 timesteps (six hours) of suppression against a recruited cell's lifespan of at most 431, a Tgam can be suppressed and recover several times.

Tcyt transitions

Edge	From	To	Condition	Evaluated in
C1	Active	Active	Re-asserted only inside the cytotoxic killing routine, and only when the target's compartment did not become caseous	Cytotoxic killing (S3.9)
C2	Active	Down-regulated	Suppression by an active cognate Treg	Suppression rule (S3.10)
C3	Down-regulated	Active	$t-$ suppression timer $\geq$ `Core_Tcell_Tcyt_maxTimeReg`	Down-regulated handler
C4	Down-regulated	Down-regulated	Not C3	Down-regulated handler

The Tgam active handler writes its pending state on every path. The Tcyt active handler writes none by default except inside the killing routine it calls; its only other write belongs to M4 (S3.11).

An active Tcyt that makes no kill therefore remains active because the pending-state field already holds the active state from an earlier commitment. The field is not cleared between timesteps, and commitment copies it to the current state.

Treg transitions

Edge	From	To	Condition	Evaluated in
R1	Active	Active	No pending-state write; the state persists	Active handler

The Treg active handler performs the suppression sweep and nothing else. As for Tcyt, persistence of the pending-state field keeps the cell active.

Tregs cannot be suppressed: the Treg's suppression entry point has an empty body. A Treg is nonetheless a candidate target of its own sweep and of the sweeps of other Tregs in range (S3.10).

Lifespans

Route	Death time assigned
Recruitment	Birth time + `Core_Tcell_maxAge`; at most 431 timesteps after arrival (S8.12)
Initialization	Birth time + `Core_Tcell_maxAge` (432 timesteps); applies to initial cells only
Proliferation	t + U{`Core_Tcell_maxAge` − 144, `Core_Tcell_maxAge`}, that is t + U{288, 432}

A recruited cell arrives with a random age (S8.12), so per-lifetime figures in this document are maxima.

No T cell transition rewrites the death time; suppression and recovery leave it unchanged, unlike macrophages (S2.2). The daughter interval is integer and inclusive at both ends, so a daughter lives two to three days. The rationale for the spread is that it keeps a lineage from dying in synchrony.

T0 states (M3)

Default option: Coarse-grained molecular resolution: the MHC class II component is off, and no T cell enters a T0 state.

The T0 states, their entry at recruitment and their exit by MHC class II licensing are specified in M3.6.

S3.4 Dispatch

The common skeleton

All three types share this structure. Steps marked with a type in brackets occur only for that type.

```
next-state computation for T cell a at timestep t:

    if a is dead or dead-next:                          // entry guard
        set pending state dead; return

    if a is a TNF producer and not down-regulated:      [Tgam]
        increment the Tgam TNF-producer statistic (S9.16)
    if a is a TNF producer and its suppression timer is set:   [Tcyt]
        increment the Tcyt TNF-producer statistic (S9.16)

    if t >= death time of a:                            // T1, senescence
        set pending state dead
    else if TNF-induced apoptosis test succeeds:        // T2, apoptosis
        increment the T cell apoptosis statistic
        set pending state dead
        increment the killing count at a's compartment, naming a
                                                        // kills a at once
    else:                                               // survival
```

```
        if a is non-cognate or in T0:
            return                                      // inert return
        if state not dead, down-regulated or exhausted: [Tgam, Tcyt]
            proliferation (S3.5)
        if state not dead:
            interaction counting (S3.6)
            if exhaustion test succeeds:                [Tgam, Tcyt]
                set pending state exhausted; return
        dispatch on state:
            dead:            set pending state dead
            active:          active handler
            down-regulated:  down-regulated handler     [Tgam, Tcyt]
```

The entry guard writes the dead pending state and returns for a cell already dead or dead-next. It repeats the scheduler's immediately preceding test.

Both producer statistics are incremented before the death branches, so a dying cell is counted; only cognate cells can contribute. The Tcyt statistic counts a producer only while its suppression timer is set (S9.16).

The inert return

The return for non-cognate and T0 cells sits inside the survival branch, after both death tests. An inert cell therefore still tests senescence and apoptosis, and increments the compartment killing count if it dies by apoptosis. Non-cognate T cells take full part in the caseation dynamics of S5, and they are the large majority of T cells (S3.2).

Activity	Senescence	Apoptosis	Survival, cognate and active
Killing count incremented	No	Yes	Only if the cell kills a macrophage
Current state written at once	No	Yes, by the killing-count routine	Only for macrophages it kills
Proliferation, interaction counting, effector function	No	No	Yes; proliferation not while down-regulated

Senescence leaves a live current state

Senescence is the only T cell death that leaves a live current state for agents processed later in the pass, since it writes only the pending state. If the cell's compartment becomes caseous by entrapment on that timestep, the entrapment sweep re-kills it and adds one increment (S5.4). Treg suppression tests the pending state and so excludes a senescent cell (S3.10). As for every dying agent, the slot stays occupied until removal, and continues to block admission and daughter placement for the rest of the timestep (spine 2.3).

TNF-induced apoptosis

The test is S6's coarse-grained form, with the `Core` parameters, so a T cell and a macrophage in the same compartment are tested against the same threshold and rate. The only difference is the per-agent TNFR1 count, drawn from U(400, 1200) for T cells against U(1100, 1900) for macrophages (S6.3). T cells are therefore less susceptible on average, by a factor of about 0.53 in mean receptor count. All three types pass false for the NF-κB flag; the flag is not consulted here and matters only under M3.

S3.5 Proliferation

Proliferation applies to cognate Tgam and Tcyt only. Tregs do not proliferate: the Treg next-state routine does not call proliferation, by design.

The rule has two phases separated by a fixed delay. A cell is first stimulated, which sets a timer; when the timer elapses the cell tries to place a daughter. The phases are exclusive branches of one conditional, so a cell cannot be stimulated and divide on the same timestep, and a cell that has just divided cannot be re-stimulated until the next timestep.

Stimulation

An unstimulated cell becomes stimulated when both hold:

- division count < `Core_Tcell_maxDivisions` (strict);
- some compartment of its periodic radius-1 Moore neighbourhood, its own included, holds a macrophage whose exposure memory is set.

On success, proliferation timer $\leftarrow t +$ `Core_Tcell_proliferationTime` (144 timesteps, one day). Stimulation is deterministic.

The test returns at the first qualifying compartment, and in each compartment tests the first macrophage found, of which there is at most one. Dendritic cells would pass the macrophage type test; none exists by default.

What is tested is exposure memory, not the presence of bacteria. Exposure memory is set and expires as specified in S2.10, and persists for `Core_Mac_maxExposureTime` = 720 timesteps (five days) after the last encounter. Proliferation therefore stays licensed for up to five days after local bacteria are cleared. The licence also reaches one compartment beyond the bacteria, because a macrophage can be flagged by a neighbouring macrophage's burden. A cognate T cell can thus be stimulated two compartments (40 μm) from the nearest bacterium at the moment the flag was last refreshed. Because the flag persists and macrophages move, the distance at stimulation is not bounded by the neighbourhood geometry alone.

Exposure memory is the model's proxy for antigen availability. Under M3, MHC class II licensing gates the T0 → active transition (S3.3); stimulation still requires an exposed macrophage.

Production of a daughter

A stimulated cell whose timer has elapsed, $t \geq$ proliferation timer, searches its periodic Moore neighbourhood for a compartment q that qualifies:

- q is not caseated; and
- $\mathrm{free}(q) \geq 1$, where free(q) is the number of unclaimed slots defined under the reservation map.

The cell's own compartment is a candidate. If at least one compartment qualifies, one is drawn uniformly from the qualifying set and the daughter is produced. Otherwise a deferral statistic is incremented and nothing else happens.

The test makes no large-agent and no type test. A reimplementation may use the T cell admission predicate instead, provided the occupancy it tests includes reserved slots.

The reservation map

Daughters are placed on the grid at commitment (spine Element 3), so grid occupancy does not show promised daughters. A reservation map records, for each compartment promised at least one daughter, the number of slots still unclaimed. The map is owned by the simulation, shared by all proliferating types, and cleared at the end of each timestep.

$$\mathrm{free}(q) = \begin{cases} M(q) & q \text{ is in the map} \\ N_{\mathrm{slots}} - n(q) & \text{otherwise} \end{cases}$$

On selection, a compartment already in the map has M(q) decremented by one; one not yet in it is inserted with $N_{\mathrm{slots}} - n(q) - 1$.

Because the map is shared, Tgam and Tcyt cannot be promised the same slot. Tgam precede Tcyt, so under crowding Tgam proliferation wins contested slots.

A promised compartment that becomes caseous before commitment discards the daughter and has its killing count incremented (S5.2). A daughter is on the grid and in the statistics from its creation timestep, but has no behaviour on that timestep (spine Element 3).

Deferral

A failed placement neither clears nor advances the timer. Because the elapsed test is non-strict against a timestep already past, the attempt repeats every timestep until it succeeds or the cell dies. Proliferation is therefore space-limited in dense regions, and a cell can stay stimulated but unable to divide for the rest of its life.

Pause during suppression

Proliferation is not evaluated while a cell is down-regulated. Instead the down-regulated handler advances the timer by one on every suppressed timestep:

$$\text{proliferation timer} \leftarrow \text{proliferation timer} + 1 \quad \text{if the timer} \neq -1.$$

The rationale is that suppressed time does not count toward the delay. An unstimulated cell keeps its sentinel. The advance is performed before the recovery test in the same handler, so the timestep on which a cell recovers is also counted as suppressed and the timer advances once more. A cell suppressed for k timesteps has its division delayed by k timesteps, not $k - 1$.

One suppression of 36 timesteps extends the 144-timestep delay by a quarter, and repeated suppression may prevent division within a cell's life. Suppression thus curbs clonal expansion as well as effector function.

The division counter and lineage size

On a successful division the parent clears its timer and increments its division count. The daughter is copied after the increment, so both carry the new count, which is never reset.

Write m = `Core_Tcell_maxDivisions` = 4 and f(c) for the number of cells a lineage member with count c eventually yields, itself included. A cell with c < m divides into two cells with count c + 1, so

$$f(c) = 2f(c+1), \qquad f(m) = 1, \qquad f(0) = 2^m = 16.$$

A founder lineage can therefore yield up to 16 cells: the cap bounds the depth of the lineage tree, not its size.

In practice the cap rarely binds. Each division needs at least 145 timesteps, the 144-timestep delay plus the timestep on which re-stimulation can first occur. A recruited founder lives at most 431 timesteps (S8.12) and a daughter 288 to 432, so a founder divides at most twice, and reaching the cap takes four successive divisions over about four days. Lifespan and local space usually bind first.

Construction of the daughter

The daughter is copy-constructed from the parent, and five fields are then overwritten:

Field	Value in the daughter
Identifier	Next value of the global counter
Birth time	t
Death time	t + U{288, 432}
Position	The compartment drawn
Proliferation timer	-1, the value it already holds, the parent having cleared it before the copy

Everything else is inherited unchanged: specificity, producer flags, division count, suppression timer, interaction counters, the three receptor counts, and the anti-TNF membrane-complex variables (M7).

A daughter makes no receptor draw, an exception to the per-agent receptor draw at construction (S6.3). Receptor heterogeneity is therefore clonal: a lineage founded at the low end of the TNFR1 range is uniformly less susceptible to TNF-induced apoptosis, and apoptosis susceptibility does not vary within a lineage.

A cell cannot divide while down-regulated, so the inherited suppression timer is always at its sentinel and a daughter is always created unsuppressed.

S3.6 Macrophage interaction counting

All three types run a radius-2 proximity sweep over macrophages once per timestep, maintaining per-cell and whole-grid counters. The counters are observation quantities, except that the per-cell exposed total is the quantity the disabled exhaustion test would read (S3.6, Exhaustion).

The sweep

The neighbourhood is the periodic radius-2 Moore neighbourhood: 25 compartments, the cell's own included. The radius is hard-coded and shared with the IFN-γ action of S3.7.

For each compartment the sweep takes the macrophage present, if any; dendritic cells would be counted, and none exists by default. For each macrophage found:

- the interaction counter indexed by the macrophage's state is advanced, on the T cell and on the whole-grid statistics;
- if the macrophage's exposure memory is set, the exposed-interaction counter indexed by state is also advanced, on both, and the per-cell exposed counter advances a scalar total.

Two further grid counters count distinct T cells that met at least one macrophage, or one exposed macrophage, at most once per cell per timestep (S9.16).

What is read

The sweep applies no filter beyond the presence of a macrophage. Dead, dead-next and suppressed macrophages count, in every state. A macrophage killed earlier in the pass is still on the grid and is counted under the dead state. The state index is the current state, not the pending one, so a macrophage that decided a new state earlier in the timestep is counted under its old state.

Macrophages compute their next states before any T cell, and the exposure flag is refreshed or lapsed inside that computation, so the sweep reads the flag as already updated on the current timestep. A macrophage that died before its own next-state computation keeps the previous timestep's flag.

An interaction is proximity within two compartments, 40 μm: there is no contact requirement, no probability and no effect on the macrophage. A T cell can record up to 25 interactions per timestep, and each T cell counts a macrophage independently.

Position and accumulation

The sweep runs after proliferation and before the state handler, guarded only on the cell not being dead, so it continues while the cell is down-regulated. Tgam and Tcyt test the exhaustion predicate immediately afterwards; Treg does not (M8.5).

The per-cell counters are never reset and are inherited by daughters (S3.5). Under M8 an inherited burden would limit a lineage (M8.5).

At most 25 interactions per timestep over a lifespan of at most 431 timesteps bound the cumulative total for a recruited cell by 25 × 431 = 10775, against an exhaustion threshold of 9999999, roughly nine hundred times larger. A lineage that inherits the count can reach 54000 (M8.5).

Exhaustion (M8)

Default option: Exhaustion is disabled by a sentinel threshold, `Core_Tcell_exhaustionThreshold` = 9999999; the interaction counters of S3.6 are still maintained.

The exhausted states, their behaviour and their lifespan are specified in M8.5.

S3.7 Coarse-grained IFN-γ action

There is no IFN-γ field. An IFN-γ-producing Tgam acts directly on the STAT1 pathway of macrophages within two compartments. This action is the sole source of macrophage STAT1 (S2.4), and so the sole route to macrophage activation and to the killing of intracellular bacteria by macrophages. The clean cytotoxic kill (S3.9) is the only route that destroys an intracellular population of any size outright.

The actor

The sweep is made by a Tgam that is cognate, an IFN-γ producer, not dead or dying, not down-regulated and active; it is called only from the active handler. Tcyt and Treg have no IFN-γ action. The M8 double-producer state also makes the sweep (S3.10, Treg induction).

The sweep

The neighbourhood is the periodic radius-2 Moore neighbourhood, as in S3.6. Each macrophage present is tested in turn:

Test	On failure
Pending state is not dead	Skip the compartment
Suppression timer not set	Skip the compartment
Current state is resting or infected	No stimulation; continue

The pending-dead exclusion removes every macrophage that died earlier in the timestep, including one killed moments before by this Tgam's own Fas attempt (S3.8).

The timer exclusion tests the suppression timer, not whether a Treg has acted. The timer and Treg contact coincide for resting and activated macrophages, except where S2.11 arms no timer. An infected macrophage reset by a Treg usually acquires no timer (S2.11), so it is not excluded, and can be stimulated again by a Tgam processed after the Treg or on the next timestep.

Chronically infected and activated macrophages are not stimulated; for both the discrete flag is immaterial. Their graded STAT1 counter can only decay (S2.4).

Shell-dependent probability

$$\text{stimulate}(q) = \begin{cases} \text{always} & d(\text{pos}, q) \le 1 \\ U(0,1) < \texttt{Core_Tcell_Tgam_probIFNMooreExtend} & d(\text{pos}, q) = 2 \end{cases}$$

where d is the Chebyshev distance and the probability is 0.25. The draw is per target and is taken only after the eligibility tests pass.

The neighbourhood holds one centre compartment, 8 at distance 1 and 16 at distance 2. A Tgam surrounded entirely by eligible macrophages stimulates $9 + 0.25 \times 16 = 13$ of the 25 in expectation. The centre is at distance 0, so a Tgam sharing a compartment with an eligible macrophage stimulates it with certainty.

The distance is computed from the unwrapped position, by design. A compartment two steps beyond the domain edge is therefore treated as a distance-2 neighbour, but the stimulation is delivered to the wrapped compartment. A Tgam at one margin can thus stimulate a macrophage at the opposite margin. This is the agent-sensing periodicity of spine 2.2.

What stimulation writes

One operation on the target writes, immediately and to its live state (spine 2.3):

Field	Value written
Discrete STAT1 flag	True
STAT1 interval end	t + `Core_Mac_stat1ActivationTime` (430)
Graded STAT1 counter	min(counter + 1, `Core_Mac_stat1CounterMaxLevel`), with the cap 10
Counter interval end	t + `Core_Mac_stat1CounterTimeInterval` (120)

Repeated stimulation resets the discrete interval to a fixed offset rather than accumulating; the graded counter accumulates up to its cap. Several Tgam can stimulate one macrophage in a timestep, each raising the counter by one up to the cap, while the flag and its interval are idempotent.

One stimulation keeps STAT1 set for 430 timesteps, spanning many 15-timestep NF-κB intervals; which flag limits activation depends on stimulation history (S2.4).

Spatial consequence

The activation loop closes only if IFN-γ-producing Tgam come within two compartments of infected macrophages. With no diffusible mediator, a peripheral T cell population cannot activate a central macrophage core.

Order within the active handler

The Fas-mediated attempt of S3.8 precedes this sweep, so a Fas kill excludes its target from the sweep. The order is part of the specification.

S3.8 Fas-mediated killing

An active cognate Tgam attempts, once per timestep, to kill one infected or chronically infected macrophage in its radius-1 neighbourhood. The mechanism represents Fas–FasL engagement and is shared in targeting with Tcyt (S3.9); the two routes differ in their bacterial outcomes.

The actor and the attempt draw

The routine is called only from the Tgam active handler, so the actor is cognate, not T0, not down-regulated and alive. No producer flag is read: every active cognate Tgam can attempt, between one in 38 and one in 11 of recruited Tgam. The M8 double-producer state makes the same attempt (S3.10, Treg induction).

The attempt is gated by one Bernoulli draw, made before any target is sought:

$$U(0,1) < \texttt{Core_Tcell_Tgam_probApoptosisFasFasL}.$$

At most, a recruited cell active for 431 timesteps is expected to attempt 12.7 to 17.5 times; time spent down-regulated reduces this.

Target selection

A shared helper, also used by Tcyt, takes the nine Moore ordinals of the actor's position, wraps each periodically, and keeps those holding a macrophage. The actor's own compartment is a candidate. If no candidate remains the routine returns. Otherwise one compartment is drawn uniformly, and the target is the first macrophage in its slots. Dendritic cells would be candidates; none exists by default.

Selection is over compartments. Here that is immaterial, a compartment holding at most one macrophage, but it would not be under more than one large agent per compartment.

Selection is uniform and attends to nothing else: no preference for infected, nearer or more heavily burdened targets, and the bacterial count is not read. An unsuitable pick ends the attempt, with no retry and no second draw; beside one infected and seven uninfected macrophages the infected one is picked with probability 1/8. The effective killing rate is the attempt probability times the local susceptible fraction, which in a lesion of resting macrophages may be an order of magnitude below the attempt probability. Sensing does not confer discrimination (spine 4.7).

Exclusions and susceptible states

The selected target is tested in order:

Test	On failure
Pending state is not dead	Attempt abandoned
Current state is infected or chronically infected	Attempt abandoned

The pending-dead test prevents a second kill, and a second increment, of a macrophage already killed this timestep. The state test means resting and activated macrophages are not killed by this route; no route kills an activated macrophage (S2.9).

Suppression status is not tested. Suppression protects a resting or activated macrophage from activation but not from death; a suppressed infected macrophage usually has no timer anyway (S2.11).

Effects of a kill

A successful kill performs, in order:

1. **Event statistic:** the Fas-mediated apoptosis count is incremented.
2. **Apoptosis routine:** the target's pending state is set dead, and half its intracellular population is dispersed to its Moore neighbourhood.
3. **Residence time:** the target's intracellular residence-time counter is added to the running total and cleared.
4. **Killing-count increment:** at the target's compartment, which kills the target at once.

The increment is at the target's compartment, not the actor's. The apoptosis routine writes only the pending state; the killing-count increment makes the death immediate (S5.3), visible to every later agent in the pass, other T cells included.

Dispersal precedes the increment, so bacteria already dispersed escape a caseation that the increment triggers. Macrophage apoptosis has the same order (S2.3).

Fas-mediated killing disperses $\lfloor n/2 \rfloor$ of the target's n intracellular bacteria and destroys the rest, treating both susceptible states alike. A target holding a single bacterium is therefore sterilized. The dispersal mechanism, including how many bacteria are destroyed, is specified in S4.13. Killing a chronically infected macrophage near its burst threshold releases about half of a near-burst load.

The actor is unaffected: no state change, cost or counter. It is limited only by the attempt probability.

The Fas statistics are specified in S9.16.

S3.9 Cytotoxic killing

An active cognate Tcyt attempts, once per timestep, to kill one infected or chronically infected macrophage in its radius-1 neighbourhood. Targeting is that of S3.8; the routes differ in attempt probability and in the fate of the target's bacteria.

The actor and the attempt draw

The routine is called only from the Tcyt active handler, so the actor is cognate, not T0, not down-regulated and alive. No producer flag is read. One Bernoulli draw is made before any target is sought:

$$U(0,1) < \texttt{Core_Tcell_Tcyt_probKillMac}.$$

This is about a quarter of the Fas probability. At most, a recruited cell active for 431 timesteps is expected to attempt 2.94 to 4.39 times, and because selection is non-discriminating most attempts land on unsuitable targets. The attempt is the active handler's first operation; its only other operation is the TGF-β down-regulation branch of M4, inert by default (S3.11).

Target selection and exclusions

Selection and the pending-dead exclusion are as in S3.8. Because Tgam precede Tcyt and a Fas kill is immediate, one macrophage cannot be killed by both routes in a timestep. The susceptible states are infected and chronically infected, handled by separate branches; suppression is not tested.

Infected target

There is no second draw. The kill is always clean: the whole intracellular population is destroyed in place and nothing is released.

1. **Clean-kill routine:** all intracellular bacteria are killed; then the target's current and pending states are both set dead.
2. **Residence time:** the target's counter is added to the running total and cleared.
3. **Event statistic:** the cytotoxic kill count is incremented.
4. **Killing-count increment:** at the target's compartment.
5. **Conditional re-assertion** of the actor's active state.

The clean-kill routine writes the target's current state directly rather than through the guarded accessor, so the death is immediate independently of the increment. A cytotoxic kill of an infected macrophage is sterilizing. It is the only T cell mechanism that eliminates an intracellular population of any size outright.

Chronically infected target

A second Bernoulli draw decides the outcome:

$$U(0,1) < \texttt{Core_Tcell_Tcyt_probKillMacCleanly}.$$

On success the clean outcome applies. Otherwise the target is killed by the dispersing route, which moves half the intracellular population to the Moore neighbourhood as the Fas route does, and also disperses intracellular drug under M6. Between 8.8 and 41.6 per cent of kills on chronically infected targets therefore disperse. A chronically infected target carries from the chronic threshold, 10 to 15, up to below the burst threshold, 24 to 41 bacteria, so a dispersing kill releases about 5 to 20.

The outcome depends on the target's state, not the actor's: the same kill is sterilizing on a light burden and possibly bacteria-releasing on a heavy one.

The dispersing routine destroys the undispersed residue (S4.13). The outside-granuloma release statistics record no bacteria for this branch (S9.8).

Conditional re-assertion

Every branch ends:

```
if not (increment the killing count at the target's compartment, naming the target):
    set pending state active
```

The killing-count routine returns whether the compartment is caseous after the increment (S5.3). When a Tcyt kills in its own compartment and the increment makes that compartment caseous, the cascade kills the Tcyt itself and the re-assertion is skipped. This conditional write is the only active-state write in the Tcyt handler (S3.3).

The cytotoxic statistics are specified in S9.16.

S3.10 Suppression by regulatory T cells

An active cognate Treg tries, once per timestep, to suppress every eligible agent in its radius-1 neighbourhood. This is the Treg's only effector function. With the IFN-γ action it is one of two rules acting on many targets per actor per timestep, and it is the only rule whose targets include T cells.

The actor

The sweep is called from the Treg active handler, reached only by a cognate Treg not in T0. There is no producer flag and no attempt draw: the sweep runs on every active timestep.

Tregs are last among T cells in the next-state pass, so suppression takes effect from the next timestep. A Treg suppressing a Tgam prevents that Tgam's killing and IFN-γ action on the next timestep, not on the current one; a suppressed macrophage has already computed its next state, so the reset of S2.11 acts from the next timestep.

The sweep

The neighbourhood is the periodic radius-1 Moore neighbourhood, nine compartments with the actor's own. Both slots of each compartment are scanned, eighteen slots in all. An occupant is a candidate iff

$$\text{occupied} \wedge \neg\,\text{dead} \wedge \neg\,\text{dead-next} \wedge \neg\,\text{non-cognate T cell}.$$

No other type test is made: macrophages and cognate Tgam, Tcyt and Treg are candidates. Bacteria occupy no slot. The exclusion is by specificity, not state, so a cognate T cell in any state is a candidate, even when suppression will have no effect on it.

The probability

For each candidate one draw is taken, and the target is suppressed iff $U(0,1) \le p$, a non-strict comparison:

$$p = \begin{cases} \texttt{Core_Tcell_Treg_probTregDeactivate} \,/\, \texttt{Core_Tcell_Treg_factorDeactIL10} & \text{if Tregs secrete IL-10} \\ \texttt{Core_Tcell_Treg_probTregDeactivate} & \text{otherwise} \end{cases}$$

The branch tests whether the Treg IL-10 secretion parameter is non-zero. At coarse resolution that parameter is `Core_Tcell_Treg_dIL10`; under the IL-10 receptor dynamics of M3 it is `Molecular_IL10_Tcell_IkSynthTcell`. `Core_Tcell_Treg_dIL10` is sampled on [0.7, 0.8] molecules/s, so the divided branch is taken in every simulation. Its declaration (mandatory, minimum 0, no maximum) would admit 0, so this rests on the sampling design.

The condition is a test on a parameter, not on the actor's state or any local quantity; all Tregs use one p. The effective probability is the ratio of two sampled parameters, between 1.9×10^{-3} and 1.0×10^{-2}: the numerator varies 1.75-fold and the divisor 3-fold.

The suppression test reads no receptor constant and no IL-10 field value.

The actor as its own target

The actor is a candidate in its own sweep and in those of nearby Tregs. The Treg suppression entry point has an empty body, so this has no effect, but the draw is taken and the call is made.

Per-target effects

Target	Effect
Macrophage	As specified in S2.11
Tgam, active	Pending state down-regulated; suppression timer $\leftarrow t$; a deactivation statistic and the M8 down-regulation counter (M8.6) incremented
Tgam, down-regulated	No effect
Tcyt, active	Pending state down-regulated; suppression timer $\leftarrow t$; a deactivation statistic incremented
Tcyt, down-regulated	No effect
Treg	No effect

Chronically infected macrophages (S2.11) and Tregs are exempt. On a Tgam or Tcyt, suppression changes state only; the death time is unchanged, and recovery follows edges G3 and C3 (S3.3).

Independence and multiplicity

Draws are independent per candidate, so the number suppressed is binomial in the number of candidates (spine 4.9). With at most 17 suppressible targets besides the actor, a Treg in a saturated neighbourhood suppresses on average at most $17 \times 1.0 \times 10^{-2} \approx 0.17$ agents per timestep, and at least $17 \times 0.005823/3 \approx 0.033$.

No statistic records suppression from the actor's side; the targets increment per-state deactivation counters (S9.16, S2.11).

Treg induction (M8)

Default option: Treg induction is off: its command-line flag is not set, so the transition test never runs and the double-producer and induced-regulatory states are unreachable.

The induction counters, including the down-regulation counter that Treg suppression advances whatever the flag, are specified in M8.6.

S3.11 Secretion

T cells secrete TNF and IL-10 into the field at their own compartment. They secrete no chemokine and no IFN-γ, so they are not chemoattractant sources and affect recruitment only through TNF. TGF-β is secreted by Tregs only, and only under M4 (S3.11, TGF-β). No T cell calls the NF-κB secretion helper. A T cell infiltrate therefore does not recruit further T cells: chemokine comes from macrophages and caseous compartments.

The secretion helpers, rate formula, per-type state factors (S6.13), effective rates (S6.11) and the IL-10 modulation of TNF (S6) are specified in S6. This section states the T cell gates.

Secretion runs in the split half-step, before the next-state block (S6). It therefore reads the state committed at the end of the previous timestep: a cell down-regulated on this timestep secretes at its active rate throughout.

Gates

Two tests precede all secretion, in order:

Condition	Action
Non-cognate, or in T0	Return; nothing written
Suppression timer set	Zero-rate calls, then return

The timer test applies to Tgam and Tcyt. Treg lacks it; a Treg's timer is never set (S3.10). A suppressed cell's zero-rate calls change no field but zero the synthesis rates that M3 would read.

TNF is gated on producer status by a conditional around the call, so a non-producing Tgam or Tcyt makes no TNF call. Tgam and Tcyt IL-10 is zero by state factor: the call is made, with a non-zero rate parameter in the Tcyt case, and multiplied by zero. Tregs make no TNF call; the absence is structural. Each type therefore secretes at most one mediator: Tgam and Tcyt TNF, Treg IL-10.

Rates

A producing Tgam secretes TNF at one fifth to one tenth of the rate of a secreting macrophage. A producing Tcyt secretes at one hundredth of the Tgam rate, under one molecule per compartment per cellular timestep.

An active cognate Treg secretes IL-10 with no producer gate and a state factor of one, from 420 to 480 molecules per cellular timestep. Its rate parameter `Core_Tcell_Treg_dIL10` is distinct from the activated-macrophage rate `Core_Mac_dIL10Act` and is sampled independently. Only the macrophage rate saturates in bound TNF. Tregs are consequently a first-order contributor to the IL-10 field wherever cognate Tregs are present, limited only by the cognate fraction.

A Treg's IL-10 can reduce the TNF secretion of a co-located producing Tgam through the modulation of S6, independently of contact suppression. The field effect is continuous; the contact effect is probabilistic and lasts six hours.

`Core_Tcell_Tcyt_dIL10` is multiplied by a state factor of zero at its only call site (S6.16).

Receptor-mediated depletion

The receptor-occupancy sink of S6 acts on every T cell, whatever its specificity, producer status or suppression. A non-cognate T cell is therefore not inert toward the fields: it consumes TNF and IL-10 without producing either.

TGF-β (M4)

Default option: No TGF-β is represented: every T cell's cumulative bound TGF-β stays zero, and the T cell hooks of M4 (proliferation gate, Tcyt down-regulation, Treg binding and secretion) are inert.

The exemption of T cell TNF secretion from TGF-β modulation, in every configuration, is specified in M4.4.

S3.12 Parameters

`Core_Tcell_Tgam_dTNF`, `Core_Tcell_Tcyt_dTNF`, `Core_Tcell_Tcyt_dIL10` and `Core_Tcell_Treg_dIL10` are tabled in S6.16.

Identifier	Value or range	Range	Units	Meaning
`Core_Tcell_Tgam_probApoptosisFasFasL`	Sampled	[0.02943, 0.04050]	probability	Fas attempt probability (S3.8)
`Core_Tcell_Tgam_probIFNProducer`	Sampled	[0.2889, 0.4591]	probability	IFN-γ producer draw (S3.2)
`Core_Tcell_Tgam_probTNFProducer`	Sampled	[0.03954, 0.05037]	probability	Tgam TNF producer draw (S3.2)
`Core_Tcell_Tcyt_probKillMac`	Sampled	[0.006825, 0.010179]	probability	Cytotoxic attempt probability (S3.9)
`Core_Tcell_Tcyt_probKillMacCleanly`	Sampled	[0.5838, 0.9121]	probability	Clean outcome on a chronically infected target (S3.9)
`Core_Tcell_Tcyt_probTNFProducer`	Sampled	[0.03871, 0.06067]	probability	Tcyt TNF producer draw (S3.2)

Identifier	Value or range	Range	Units	Meaning
`Core_Tcell_Treg_probTregDeactivate`	Sampled	[0.005823, 0.010167]	probability	Numerator of the suppression probability (S3.10)
`Core_Tcell_Treg_factorDeactIL10`	Sampled	[1, 3]	dimensionless	Divisor of the suppression probability (S3.10)
`Core_Tcell_maxAge`	432	—	timesteps (3 d)	Lifespan of an initial T cell; a recruited T cell lives at most 431 timesteps (S8.12); daughter lifespan bounds (S3.3)
`Core_Tcell_proliferationTime`	144	—	timesteps (1 d)	Delay from stimulation to division (S3.5)
`Core_Tcell_maxDivisions`	4	—	divisions	Division cap (S3.5)
`Core_Tcell_Tgam_dIL10`	0	—	molecules/s	Tgam IL-10 rate; multiplied by zero (S3.11)
`Core_Tcell_Tgam_maxTimeReg`	36	—	timesteps (6 h)	Tgam recovery interval, edge G3 (S3.3)
`Core_Tcell_Tgam_probIFNMooreExtend`	0.25	—	probability	IFN-γ stimulation at Chebyshev distance 2 (S3.7)
`Core_Tcell_Tcyt_maxTimeReg`	36	—	timesteps (6 h)	Tcyt recovery interval, edge C3 (S3.3)
`Core_Tcell_Treg_dTNF`	0	—	molecules/s	Read by no rule (S3.11)

The apoptosis test's `Core` parameters, the T cell receptor complements, the dissociation constants and occupancy factors, and the IL-10 modulation constants are shared with macrophages and specified in S6 (S6.3, S6.6, S6.11). No T cell parameter modifies the apoptosis proxy or the sink.

Fixed structural constants: radius 2 for the interaction sweep (S3.6) and the IFN-γ action (S3.7), with no parameter setting either; radius 1 for proliferation, killing and suppression; 144 cellular timesteps per day, a compile-time constant setting the daughter lifespan lower bound `Core_Tcell_maxAge` − 144.

Absences: there is no per-type T cell lifespan, all types sharing `Core_Tcell_maxAge`, and no per-type receptor complement.

Read but without effect by default: `Core_Tcell_Tcyt_dIL10`, `Core_Tcell_Tgam_dIL10`, `Molecular_TNF_Tcell_kSynthTcell`, `Molecular_TNF_Tcell_kRNATcell`, `Molecular_TNF_Tcell_kTaceTcell` (S6.3), `Molecular_IL10_Tcell_IkSynthTcell` (coarse resolution), `Molecular_IL10_IkT`, `Molecular_TNF_kT1`, `Molecular_TNF_kT2`, `NFkB_meanNFkB` (a construction draw), `Core_Tcell_exhaustionThreshold`, `Core_Tcell_exhaustedMaxAge`, `Core_Tcell_movementBonusFactor` (S1), `Core_Tcell_Tgam_initCognateNumber` (spine Element 5), `Core_Tcell_Treg_deactivateSlope`, `Core_Tcell_Treg_deactivateIntercept`, `Molecular_IL10_IkOn` and `Molecular_TNF_kOn1` (read only by an uncalled overload of the Treg suppression test and, under M3, by the receptor equations), `Core_depletionFractionTNF` and `Core_depletionFractionIL10` (M8). Parameters of disabled modules are indexed in Appendix B.

S3.13 Interfaces

With	Provides or receives	See
Spine 2.2	Agent sensing is periodic while the fields are held at zero on the boundary, so a T cell at the edge sees lower TNF, IL-10 and chemokine; this lowers its apoptosis risk and chemotactic weighting, and reduces the IL-10 a Treg has itself deposited	S3.7, S3.11
Spine 2.3	Receives the occupancy rules, slot persistence until removal and the hybrid update	S3.4, S3.7
Spine Element 3	Receives the block order, the type order (macrophages, then Tgam, Tcyt, Treg) and commitment, at which promised daughters are placed	S3.1, S3.5
Spine 4.7, 4.9	Sensing without discrimination (4.7); Treg suppression draws once per target (4.9)	S3.8, S3.10
Spine Element 5	`Core_Tcell_Tgam_initCognateNumber` = 0: no cognate Tgam is placed at initialization	—
S1	Owns T cell movement, admission and its parameters (`Core_Tcell_probMoveToMac`, `Core_Tcell_probMoveToTcell`, `Core_Tcell_movementBonusFactor`)	S3.1
S2	Receives exposure memory (S2.10) and the macrophage suppression reset (S2.11); provides STAT1 stimulation, writing values of `Core_Mac_stat1ActivationTime`, `Core_Mac_stat1CounterTimeInterval` and `Core_Mac_stat1CounterMaxLevel`, which the IFN-γ action must be able to read	S3.5, S3.7, S3.10
S4	Owns dispersal and destruction of a killed macrophage's bacteria	S3.8, S3.9
S5	Receives the killing count, the cascade and its return value, discarded daughters and the entrapment re-kill of senesced T cells (S5.4)	S3.3, S3.4, S3.5, S3.9
S6	Owns the apoptosis test, receptor draws (S6.3), secretion helpers, state factors (S6.13), effective rates (S6.11), the IL-10 modulation and the sink, with their `Core` and molecular parameters	S3.4, S3.11, S3.12
S8	Draws specificity (`Recruit_Prob_Tcell_<type>_probCognate`, S8.13) and the recruited birth time (S8.12); constructs recruits	S3.2, S3.3
S9	Owns the T cell statistics: producer, apoptosis, proliferation, deferral, interaction, IFN-γ-producer, Fas, cytotoxic and deactivation counts, the outside-granuloma accounting, and the cognate split of counts (S9.16; outside-granuloma accounting S9.8; kill categories S9.14)	S3.4 to S3.10

With	Provides or receives	See
M1	Fixes the diffusion and molecular substeps, hence the number of secretion calls (20) and sink applications (100) per cellular timestep; totals are solver-independent, but granularity matters for the saturating sink	S3.11
M2	Probabilistic option: founders are recruited with drawn specificity. Under the lymph-node option, the cognate fraction is a model output (M2), set by the relative blood concentrations of the cognate and non-cognate effector compartments; `probCognate` is not read. Every Treg recruited under that option is non-cognate (M2.9), so returns before any effector function (S3.4), and no Treg suppresses	S3.2, S3.4
M3	Coarse-grained. Fine-grained options change the apoptosis test, read the synthesis rates written by secretion, solve per-agent equations, can disable the sink, and enable the T0 states and the IL-10R branch of the suppression test. T cells are excluded from the MHC class II equations and never use NF-κB dynamics	S3.3, S3.4, S3.10, S3.11
M4	Not selected. The T cell hooks: proliferation gate (M4.4), Tcyt down-regulation, Treg binding and secretion; all three types bind TGF-β, only Tregs secrete it	S3.11
M5	Two-dimensional. Under the three-dimensional option every neighbourhood grows (radius 1: 27; radius 2: 125), and with it the draw bounds and the IFN-γ shells	S3.5 to S3.10
M6	Not selected. T cells carry no drug state; Fas and dispersing cytotoxic kills disperse the target's intracellular drug	S3.8, S3.9
M7	Not selected. T cells carry the anti-TNF membrane-complex variables, inert by default and inherited by daughters	S3.5
M8	All options off. Treg induction, exhaustion and its lineage bound (M8.5), and cytokine depletion, which would zero T cell secretion or, with a positive fraction, scale it; the fractions are 0, so depletion would be total	S3.6, S3.10
M9	Treg suppression tests neutrophils, with a draw and no effect; a T cell daughter may be placed beside a lone neutrophil; Fas and cytotoxic killing never target neutrophils	M9.6
Appendix B	Indexes the disabled-module and inert T cell parameters and the controlling options	S3.12