M8. Optional perturbations module

M8.1 Slot and schedule

Summary. M8 is a set of independent perturbations of the baseline model, each with its own switch, and any combination may be enabled. All are off in the default configuration, where each has a nil effect and none consumes a random draw.

What the slot controls

M8 is not a choice between interchangeable implementations of one process. Each option alters the baseline when switched on and leaves it untouched when switched off.

Option	Summary	Specified in
Reinfection	One newly infected macrophage is placed at a fixed point of the grid diagonal on a specified timestep. It fires at most once, whatever the state of the original infection.	M8.3
Cytokine depletion	From a specified timestep to the end of the run, cell secretion of TNF or IL-10 is multiplied by a retained fraction, or suppressed when the fraction is 0, and secretion of inactive TGF-β is suppressed. The fields and every rule reading them are unchanged in form.	M8.4
T cell exhaustion	Tgam and Tcyt enter a permanent non-functional state once their accumulated count of contacts with exposed macrophages reaches a threshold. The count is inherited at division.	M8.5
Treg induction	Active Tgam accumulate evidence of stimulation and may convert to an IL-10-secreting double-producer state, and then to an induced regulatory state.	M8.6
Growth-rate randomisation	A bacterium constructed inside an infected macrophage draws its growth rate from a uniform interval. The stored rate then replaces the intrinsic rate as the base of the growth law, so every modulation compounds.	M8.7
Post-adaptive intracellular factor	The intracellular growth rate is multiplied by a constant factor from a fixed time onward.	M8.8, S4.7
Neutrophil injection	A specified number of neutrophils is placed within the circle circumscribing the current connected region on a specified timestep.	M8.9

Switches, disabling values and default values are tabled in M8.11.

Position in the cellular timestep

Option	Position
Reinfection	First operation after the timestep counter is incremented, before the next grid is synchronised and before the statistics reset
Depletion	Flags derived once per timestep, after the statistics reset; consumed by every secretion call in both split half-steps, by the molecular-scale solve of M3 and by the TGF-β solve of M4
Exhaustion	Inside Tgam, Tcyt and Treg next-state computation, after the proliferation check and before the state handler
Treg induction	Inside the active-Tgam handler, after Fas killing and IFN-γ action
Randomisation	At creation of an intracellular bacterial group by the macrophage constructor; at every intracellular growth call within macrophage rules; at every extracellular growth call in the extracellular pass
Post-adaptive factor	At every intracellular growth call
Neutrophil injection	After the connected-region boundary is computed and before ring scaling

Reinfection, the depletion flags and injection are the coordinator-level hooks marked [M8] in the schedule of spine 3.2. The other options act inside agent and container rules.

Reads and writes

Reads:

- simulation time and the three depletion timesteps;
- `Core_depletionFractionTNF` and `Core_depletionFractionIL10`;
- the admission predicates for macrophages and neutrophils;
- the connected-region centre of mass and maximum diameter;
- macrophage state, exposure flag, and STAT1, NF-κB and STAT3 flags near a T cell;
- the Tgam induction counters;
- per-bacterium stored and intrinsic growth rates;
- `Recruit_Prob_timeRecEnabled` and `Core_Tcell_Treg_dIL10`.

Writes:

- the macrophage list and grid occupancy (reinfection);
- the neutrophil list and grid occupancy (injection);
- TNF, IL-10 and inactive TGF-β field increments, reduced or suppressed (depletion);
- Tgam and Tcyt next states (exhaustion, induction);

- the per-cell exhaustion counter, the induction counters and the transition time;
- the stored growth rate of every bacterium (randomisation);
- statistics recording deactivations, interactions and growth-rate distributions (S9).

M8.2 Selection and gating

Switches

Each option is controlled by one switch. It is either a command-line option, of the kind that selects among model variants, or a parameter-file entry whose disabling value is a sentinel (spine 7.0, "Declared but unused parameters"). Every option can be enabled from a parameter file or the command line, so each is live code with a nil effect under the documented values (M8.11).

Inertness in the default configuration

- **Reinfection and injection.** The trigger compares against the current timestep and never matches, so neither routine acts.
- **Depletion.** All three flags are false at every timestep, and every secretion routine takes its undepleted branch.
- **Exhaustion.** The accumulation of M8.5 runs for every eligible T cell at every timestep, but no lineage can reach the threshold: the largest attainable count is 54000 (M8.5). No T cell enters an exhausted state.
- **Treg induction.** The induction check is never entered. The down-regulation counter is still incremented on every suppression of an active or double-producer Tgam, and is never read (M8.6).
- **Randomisation.** Every bacterium takes the fixed intrinsic rate of its location, and the stored rate records the rate applied without feeding back into growth (M8.7).
- **Post-adaptive factor.** The multiplication is performed at every intracellular growth step after onset, but multiplication by exactly 1 is an identity in floating-point arithmetic, so trajectories are bitwise unaffected.

No option consumes random draws while disabled. The random number stream of this configuration is therefore that of a program without M8.

Persistence across checkpoints

The command-line switches are stored in the saved simulation state. When a saved state is loaded, the command line is compared with the stored value and a warning is issued on mismatch.

- **The three depletion timesteps and** `--Treg-induction` are overwritten by the command-line values.
- `--rand-growth` keeps its stored value, and the command-line value is ignored.

The parameter-file switches are not part of the saved state and take the values the parameter file supplies at load. A loaded run therefore uses the depletion and induction settings of its own command line, but the randomisation setting of the run that created the state. If a reload sets a depletion timestep earlier than the loaded state's timestep, depletion is active from the first timestep after the load.

M8.3 Reinfection

Summary. On the timestep equal to `Core_reinfectionTimestep`, one newly infected macrophage is placed a fraction `Core_reinfectionLocation` of the way along the grid diagonal, or in an admissible neighbour of that point. It fires at most once, whatever the state of the original infection. By default, the timestep is -1.

Trigger

Reinfection fires on the cellular timestep t equal to `Core_reinfectionTimestep`. It is tested immediately after t is incremented and before any other operation of the timestep. The first simulated timestep is 1 and t only increases, so the event fires at most once per run, and any value ≤ 0 disables it. The test does not depend on the state of the simulation: reinfection occurs whether or not the original infection has cleared.

Target position

The target p* lies a fraction λ = `Core_reinfectionLocation` $\in [0, 1]$ of the way along the grid diagonal from (0, 0) to $(n_x - 1, n_y - 1)$. Each coordinate is nominally $\lambda(n - 1)$, converted to an integer.

With $\lambda = 0.8$ on the 300×300 grid, each coordinate is nominally 239.2. The site lies in the upper-right quadrant, about 90 compartments from the grid centre in each coordinate. $\lambda = 0$ and $\lambda = 1$ select the two corners of the diagonal, and $\lambda = 0.5$ selects a position at or adjacent to the grid centre, depending on rounding.

Placement

```
reinfection placement on timestep t:
    if the macrophage admission predicate (S1.4) admits p*:
        place the new macrophage at p*
    else:
        L <- every compartment of the boundary-clipped radius-1 Moore
             neighbourhood of p* that the predicate admits
             // p* itself is in the neighbourhood and is rejected again
        if L is empty:
            fatal error
        place the new macrophage at one element of L, chosen uniformly
```

The fallback neighbourhood is boundary-clipped, not periodic: compartments outside the grid are omitted rather than wrapped. The uniform choice uses the half-open integer draw of S8.12.

The predicate rejects a compartment that is caseated, holds a large agent or has no free slot. Placement therefore fails only if every compartment of that neighbourhood is caseous, holds a large agent or is full, which in practice requires the site to lie inside an established lesion.

The clipped fallback is the one agent-placement rule in the model that does not use the periodic neighbourhood. It matters only when the target lies on the domain edge, for $\lambda = 0$ or $\lambda = 1$, where the fallback considers four compartments rather than nine.

The reinfecting macrophage

The macrophage is constructed as the seeding macrophage of spine 5.4, except for its birth time:

- state infected, with the NF-κB and STAT1 flags clear;
- one intracellular bacterium, with `Mtb_Agents_initialBiomass` and birth time t;
- exposure flag set by the constructor, because the state is infected;
- birth time t, not randomised, and death time t + `Core_Mac_maxAge`, a full non-activated lifespan from arrival;
- receptor counts drawn as for any constructed agent (S6.3).

It is appended to the end of the macrophage list, so it is processed after every other macrophage in each pass until the next list shuffle (spine 3.3).

Behaviour on the arrival timestep

Reinfection precedes the diffusion block, so the new macrophage is subject to every process of its arrival timestep. This distinguishes it from recruited cells, which compute a next state on their arrival timestep but neither move nor secrete until the next one (S8.1).

- **Secretion.** It secretes in every split half-step as an infected macrophage without NF-κB: chemokines and TNF at half rate, IL-10 at full rate (S6.13).
- **Oxygen.** It consumes oxygen (S7.6).
- **Movement.** Its age on arrival is 0, and the movement test passes whenever age is divisible by the interval (S1.2), so it attempts a move on the arrival timestep. Thereafter, while infected, it attempts a move every `Core_Mac_movementInf` timesteps counted from its arrival.
- **Next state.** It computes a next state in the ordinary way, and its intracellular bacterium grows on that timestep.

Couplings

The reinfecting macrophage counts toward the total macrophage count read by the macrophage recruitment floor (S8.7). Its bacterium is subject to the growth-rate options of M8.7 and M8.8 as any intracellular bacterium is.

Parameter-file placement of an infected macrophage explicitly increments the cumulative count of macrophages entering the infected state and the exposed-macrophage count; reinfection increments neither (S9). The exposed count is recomputed every timestep, so it is unaffected; the cumulative infected-entry count excludes the reinfecting macrophage. This affects observation only.

M8.4 Cytokine depletion

Summary. From a timestep set on the command line to the end of the run, cell secretion of TNF or IL-10 is multiplied by a retained fraction, or suppressed when the fraction is 0, and secretion of inactive TGF-β is suppressed. Fields, sinks, degradation, transport and every rule reading the fields are unchanged in form. By default, all three depletion timesteps are -1.

Depletion timesteps and flags

Three depletion timesteps, t_TNF, t_IL-10 and $t_{\text{TGF-}\beta}$, are held by the simulation coordinator. They are not parameters. They are set from the command-line options `--tnf-depletion`, `--il10-depletion` and `--tgfb-depletion`, each defaulting to -1, and are stored in the saved state (M8.2).

At each cellular timestep, after the statistics reset, three flags are derived:

$$\text{depleted}_X(t) \iff t_X \geq 0 \text{ and } t \geq t_X, \qquad X \in \{\text{TNF},\ \text{IL-10},\ \text{TGF-}\beta\}.$$

The flags are recomputed every timestep but, once true, remain true for the rest of the run. Depletion is therefore a permanent change of regime beginning at t_X, not a pulse or a dosing schedule. The three flags are independent.

The depletion timesteps are not validated. A negative value disables depletion. A value of 0 is not a disabling value: the test is non-strict and the first simulated timestep is 1, so 0 or 1 depletes from the first timestep. A value beyond the simulated duration has no effect. The settings are also not checked against the module selections.

Where the flags act

The flags reach every secretion call in both split half-steps of every diffusion step, so they act on all 2N_d = 20 secretion calls of each cellular timestep. The TNF and IL-10 flags are also passed to the per-agent molecular-scale solve of M3, and the TGF-β flag to the TGF-β solve of M4. Neither solve is performed by default.

Flag	Consumed by	Effect specified in
TNF	TNF secretion by macrophages, Tgam and Tcyt	Effect on coarse-grained secretion; Depletion under modules M3 and M4
IL-10	IL-10 secretion by macrophages, Tgam, Tcyt and Tregs	Effect on coarse-grained secretion; Depletion under modules M3 and M4
TGF-β	Inactive TGF-β secretion by macrophages and Tregs	Depletion under modules M3 and M4

The TGF-β flag has no effect unless M4 is selected, because the secretion it gates is performed only under M4.

Depletion acts on every source of a species alike, the flag being passed to every secretion call. It cannot deplete one cell type, or one region, alone.

What depletion does not touch

Depletion acts on secretion only, and only on TNF, IL-10 and inactive TGF-β. These are unaffected by any flag:

- **Chemokine secretion by cells.** The chemokine secretion rule takes no depletion argument, so CCL2, and hence CCL5 and CXCL9 (S6.14), are secreted normally under every combination of flags.
- **Chemokine secretion by caseated compartments**, which receives no flag (S5.6).
- **The receptor-occupancy sink** of S6.8, which continues to remove TNF and IL-10 at its usual rates.
- **Degradation and diffusion** of the fields.

- **Every rule that reads TNF or IL-10.** Depletion lowers the field values those rules read but alters no threshold, rate or probability.

Under TNF depletion the TNF field therefore decays from its value at t_TNF under degradation, diffusion to the zero boundary and receptor uptake, with no replenishment in full mode.

Full and fractional modes

Each of TNF and IL-10 has a fraction parameter, ϕ_{TNF} = `Core_depletionFractionTNF` and $\phi_{\text{IL-10}}$ = `Core_depletionFractionIL10`. When depletion of X is active, the fraction selects the mode. The multiplier applied to the normal secretion of X is

$$m_X(t) = \begin{cases} 1 & \text{not depleted}_X(t) \\ \phi_X & \text{depleted}_X(t) \text{ and } \phi_X > 0 \\ 0 & \text{depleted}_X(t) \text{ and } \phi_X = 0. \end{cases}$$

The fraction is the share of normal secretion retained, not the share removed: $\phi_X = 0.25$ reduces secretion to a quarter of normal. The value 0 selects full depletion. Both fractions are 0 by default, so depletion, were it enabled, would be full. TGF-β has no fraction parameter, and its depletion is always full.

The TNF fraction is declared on [0, 1]. The IL-10 fraction is declared with a minimum of 0 and no maximum, so a value above 1 is not excluded by its declaration. Both fractions are applied identically. An IL-10 fraction above 1 would therefore increase IL-10 secretion while IL-10 depletion is active: a value of 10 would multiply it tenfold from the depletion timestep, and no warning is issued.

Effect on coarse-grained secretion

This subsection specifies the TNF and IL-10 flags under the coarse-grained molecular resolution of M3, the resolution selected by default. Under it, cells add TNF and IL-10 directly to the field at their own compartment once per split half-step, and the multiplier m_X of Full and fractional modes scales those increments.

TNF

A cell secreting TNF adds, at each split half-step of length $\frac{1}{2}\Delta t_d$,

$$\Delta C_{\mathrm{TNF}}(p) = m_{\mathrm{TNF}}(t)\; g(C_{\text{IL-10}}(p))\;\; s\, d_{\mathrm{TNF}}\;\, \tfrac{1}{2}\Delta t_d,$$

where s is the state factor of the secreting cell, d_TNF its TNF secretion-rate parameter, and g the logistic IL-10 modulation of S6.11, with g = 1 when the local IL-10 value is exactly zero. The depletion multiplier is applied after the IL-10 modulation, as a final factor. Under full depletion, m_TNF = 0 and the increment is skipped entirely.

The same routine also writes the cell's two TNF synthesis rates. Under full depletion they are set to zero; otherwise they are set to their state-scaled values without the fraction applied. They are read only by the TNF receptor equations of M3 (M3.3), so at coarse resolution they are written but never read.

IL-10

A cell secreting IL-10 adds, at each split half-step,

$$\Delta C_{\text{IL-10}}(p) = m_{\text{IL-10}}(t)\ s\, d_{\text{IL-10}}\ \tfrac{1}{2}\Delta t_d.$$

IL-10 secretion is not modulated by any field value. Under full depletion the increment is skipped. The cell's IL-10 synthesis rate is also written, including the fraction in fractional mode, but at coarse resolution it is never read.

Affected sources

Every TNF and IL-10 term of the secretion inventory of S6.13 is subject to the multipliers. The rules themselves, including the state factors, are unchanged, and terms with a zero state factor or rate contribute nothing whether or not depletion is active. The induced Tgam states of M8.6 add two rows to the inventory:

Source	TNF term	IL-10 term
Tgam, double producer	As active	s = 0.5, `Core_Tcell_Treg_dIL10`
Tgam, induced regulatory	As active	s = 1, `Core_Tcell_Treg_dIL10`

An exhausted Tgam secretes nothing, while an exhausted Tcyt that is a TNF producer continues to secrete TNF and is therefore subject to TNF depletion (M8.5).

Indirect effects

Depletion changes no threshold, rate or probability, but it lowers the field values that other rules read, and some of those rules then change the secretion of an undepleted species:

- **IL-10 depletion increases TNF secretion.** The modulation g decreases with local IL-10, so lowering the IL-10 field raises every cell's TNF secretion toward its unmodulated rate.
- **IL-10 depletion increases chemokine secretion.** Chemokine secretion is halved wherever local IL-10 exceeds `Core_IC50ChemokineIL10` (S6.10); lowering the IL-10 field removes the halving.
- **TNF depletion reduces IL-10 secretion by activated macrophages.** Their IL-10 rate is a saturating function of the estimated TNFR1 occupancy (S6.12), so lowering the TNF field lowers it.

The rules that read the fields directly respond in the usual way: TNF-induced apoptosis, TNF-induced NF-κB activation and IL-10-induced STAT3 activation (S6.5 to S6.7), and recruitment eligibility and probability (S8).

Treg suppression does not respond to IL-10 depletion at coarse resolution. It selects between its two probabilities according to whether the parameter `Core_Tcell_Treg_dIL10` is non-zero, not according to IL-10 actually secreted (S3.10). Under IL-10 depletion, Tregs therefore keep the reduced, IL-10-producing probability although they add no IL-10 to the field. Under IL-10 receptor dynamics the same test reads `Molecular_IL10_Tcell_IkSynthTcell` instead (S3.10).

Depletion under modules M3 and M4

The flags act differently when a finer molecular resolution is selected under M3, or when TGF-β is represented under M4. Neither module is selected by default.

TNF receptor dynamics

Under the TNF receptor equations of M3 without NF-κB dynamics, cells do not add TNF directly to the field. TNF enters it by release of membrane TNF, translated from an mRNA pool whose synthesis rate is computed in each derivative evaluation from the two synthesis rates and the bound IL-10 receptor count (M3.3).

- **Full depletion.** The secretion routine sets both rates to zero, and the derivative evaluation also sets the mRNA synthesis rate to zero.
- **Fractional depletion.** The secretion routine passes the rates unscaled, and the derivative evaluation multiplies the mRNA synthesis rate by ϕ_{TNF}. The fraction is therefore applied once.

In both modes depletion acts on mRNA synthesis, not on release. mRNA and membrane TNF present at t_TNF continue to be translated and released, so the TNF source decays over the lifetimes of those pools rather than stopping at t_TNF as it does at coarse resolution.

NF-κB dynamics

Under NF-κB dynamics, macrophage TNF production is governed by the NF-κB equations, and the macrophage secretion rule does not call the TNF secretion routine (M3.5). Depletion instead multiplies the translation of TNF transcript into intracellular TNF:

$$\text{translation rate} = m_{\mathrm{TNF}}(t)\; c_{4,\mathrm{TNF}}\; [\text{TNF transcript}].$$

Transcription, and export of TNF already translated, are unaffected, so the source again decays with a lag. T cells are not NF-κB capable and follow the TNF receptor path. Chemokine export from the NF-κB system is not depleted.

A reimplementation must therefore apply TNF depletion at every TNF-producing site of the selected resolution, and IL-10 depletion only where the synthesis rate is set.

IL-10 receptor dynamics

Under the IL-10 receptor equations, IL-10 normally enters the field only through the equations' source term, at the cell's IL-10 synthesis rate (M3.4).

- **Not depleted.** No direct field increment is made; the equations secrete at the synthesis rate.
- **Full depletion.** No direct increment is made, and the synthesis rate is zero.
- **Fractional depletion.** The secretion routine both increments the field directly by $\phi_{\text{IL-10}}\, s\, d_{\text{IL-10}}\, \frac{1}{2}\Delta t_d$, as at coarse resolution, and sets the synthesis rate to $\phi_{\text{IL-10}}$ times its normal value.

Under IL-10 receptor dynamics, fractional depletion therefore adds IL-10 through two routes at once, using two different rate parameters, whereas undepleted secretion uses only one. Depending on the relative sizes of the coarse rate d_IL-10 and the molecular rate, a cell under fractional IL-10 depletion can add more IL-10 than an undepleted one. The path is taken with `--il10r-dynamics`, a non-negative `--il10-depletion` and a positive `Core_depletionFractionIL10`.

For activated macrophages under IL-10 receptor dynamics, the synthesis rate is further multiplied, after depletion, by a saturating function of the cell's bound TNFR1 count (M3.4). Depletion and that modulation compose multiplicatively.

TGF-β

Under M4, macrophages and Tregs secrete inactive TGF-β at each split half-step (M4.3). TGF-β depletion suppresses that secretion entirely. Binding of active TGF-β by the same cells continues under depletion, so the cumulative bound quantity of M4 keeps rising while TGF-β remains in the field.

The TGF-β flag also reaches fibroblast and neutrophil secretion and the TGF-β receptor solve. Its effect is specified in M4.3 for fibroblasts and in M9.7 for neutrophils. The M4 adjustment of macrophage TNF secretion by cumulative bound TGF-β is independent of the TGF-β flag.

M8.5 T cell exhaustion

Summary. Each timestep, every cognate T cell outside the T0 state adds to a counter the number of exposed macrophages within two compartments. A Tgam or Tcyt whose total reaches `Core_Tcell_exhaustionThreshold` becomes permanently exhausted, losing proliferation, killing and IFN-γ action; an exhausted producing Tcyt keeps secreting TNF. The count is inherited at division. By default, the threshold, 9999999, cannot be reached.

Write θ_{exh} for `Core_Tcell_exhaustionThreshold`.

When the counter is updated

The counter is updated inside the T cell dispatch of S3.4, after the proliferation check and before the state handler. Exhaustion inserts a counter update and a threshold test there:

```
after the proliferation check (S3.4), for a Tgam, Tcyt or Treg c:
    add E_c(t) to the exhaustion counter of c
    if c is a Tgam or Tcyt and its counter >= Core_Tcell_exhaustionThreshold:
        set the next state of c to its exhausted state
        end processing of c for this timestep
    run the state handler of c
```

The counter is therefore updated by every cognate, non-T0 Tgam, Tcyt and Treg that survives senescence and apoptosis, in any live state, including down-regulated and already exhausted cells.

What is counted

E_c(t) is the per-cell exposed-interaction total of the S3.6 sweep for this timestep: the number of macrophages with exposure memory in the periodic radius-2 Moore neighbourhood of cell c, between 0 and 25, read under the conditions S3.6 states. So

$$X_c(t) = X_c(t-1) + E_c(t).$$

Only this increment bears on exhaustion; the other counters of the sweep are observation quantities (S3.6, S9).

Threshold

A Tgam or Tcyt becomes exhausted when

$$X_c(t) \geq \theta_{\text{exh}}.$$

The comparison is between integers and is not subject to the significant-figure truncation of spine 2.1. Tregs accumulate the counter, but no threshold test is applied to them, and they have no exhausted state.

Inheritance and reachability

A daughter T cell is a copy of its parent. The division routine resets only the identifier, birth time, death time, position and proliferation time (S3.5), so the daughter starts with its parent's count at the moment of division, as it does with the parent's division count.

The inherited counter is bounded by the longest line of descent. A founder enters with division count 0; each division increments the count in both parent and daughter; and a cell whose count has reached `Core_Tcell_maxDivisions` = 4 does not divide. A single line of descent therefore holds at most 5 cells. Each lives at most `Core_Tcell_maxAge` = 432 timesteps (S3.12) and adds at most 25 per timestep, so the count of any cell is bounded by

$$X_{\max} = 5 \times 432 \times 25 = 54000,$$

about 0.5 per cent of $\theta_{\mathrm{exh}} = 9999999$. The bound is loose: it assumes every cell of the line has 25 exposed macrophages around it at every timestep of its life, and that each division occurs at the end of the parent's life. No T cell can become exhausted in the default configuration.

At the other extreme, $\theta_{\mathrm{exh}} = 0$ exhausts every cognate, non-T0 Tgam and Tcyt at its first next-state computation, which for a recruit is its arrival timestep, since $0 \geq 0$ holds for a cell with no contacts. A negative value has the same effect.

The transition timestep

On the timestep the threshold is first met, the cell's processing ends at the threshold test, so its state handler does not run. A Tgam therefore performs no Fas-mediated killing, no IFN-γ action and no Treg-induction check on that timestep; a Tcyt performs no cytotoxic killing.

The proliferation check has already run. A cell whose proliferation timer has elapsed therefore produces a daughter on the transition timestep. That daughter is a copy of the cell before its state changes, carries the inherited counter, and is itself exhausted at its first next-state computation.

The exhausted next state is set by the monotone rule of spine 2.3, so it does not overwrite a dead one. It can, however, be overwritten later in the same pass. Tregs are processed after Tgam and Tcyt (spine 3.3), and the suppression rule tests the target's current state, not its next state (S3.10). A Treg that suppresses the cell on the transition timestep therefore replaces the exhausted next state with the down-regulated one, records the deactivation time and, for a Tgam, increments the down-regulation counter of M8.6. The cell is then down-regulated on the next timestep, meets the threshold again, and becomes exhausted one timestep late, keeping that deactivation time.

Behaviour while exhausted

The exhausted Tgam and Tcyt states are left only by death.

Behaviour	Exhausted Tgam	Exhausted Tcyt
Movement	As active, every timestep (S1)	As active, every timestep (S1)

Behaviour	Exhausted Tgam	Exhausted Tcyt
Proliferation	None; a pending timer never fires	None; a pending timer never fires
Killing of macrophages	None	None
IFN-γ action	None	Not applicable
TNF secretion	None	Continued if a TNF producer and not deactivated
IL-10 secretion	None	None
Counter accumulation	Continued	Continued
Treg suppression	No effect	No effect
Death	Senescence or TNF-induced apoptosis	Senescence or TNF-induced apoptosis

Each timestep the exhausted cell passes the early exits of the dispatch, skips proliferation, updates the counter, meets the threshold again and is set to the exhausted state again; it never reaches its state handler. Its apoptosis test is unchanged, and an apoptotic death increments the compartment killing count as for any T cell (S5.2).

The secretion asymmetry arises because the Tgam secretion rule selects by state, and the exhausted state selects nothing, whereas the Tcyt secretion rule does not depend on state. It depends only on whether the cell is deactivated and whether it is a TNF producer. An exhausted Tcyt that is a TNF producer therefore secretes TNF at its normal rate, subject to IL-10 modulation and to TNF depletion (M8.4), for the rest of its life.

A cell that becomes exhausted while down-regulated, or that is suppressed on its transition timestep, keeps its deactivation time permanently, because the recovery rule that clears it belongs to the down-regulated handler, which no longer runs. Such a Tcyt secretes nothing, since a deactivated Tcyt secretes at a state factor of zero. Two exhausted Tcyt that are both TNF producers can therefore differ for life in whether they secrete TNF.

Lifespan

Exhaustion does not change the cell's death time. An exhausted cell dies of senescence at the death time assigned at its creation (S3.3). `Core_Tcell_exhaustedMaxAge` is read by no T cell rule.

Occupancy and observation

Exhausted cells remain on the grid and count as T cells for every occupancy and density rule: compartment slots, the admission and movement predicates, cell density and vascular gating, the granuloma definitions and the T cell extent (spine 2.3, S9.5). They are reported under their own state in the per-state T cell counts (S9).

Relation to Treg induction

Tgam in the double-producer and induced regulatory states of M8.6 accumulate the counter and become exhausted in the same way, and on reaching the threshold they lose those states. Because the threshold test precedes the state handler, exhaustion pre-empts the Treg-induction check on the transition timestep.

M8.6 Treg induction

Summary. With `--Treg-induction` set, each active cognate Tgam samples one neighbouring macrophage per timestep, accumulating counts of antigen presentations and of contacts with STAT3-activated macrophages, beside its count of suppressions by Tregs. It converts to a double-producer state with a probability that rises with the three counts, and becomes induced regulatory after a duration set by `TgamInd_Tcell_Tgam_maxTimeDouble`. By default, the flag is absent.

The counters

Counter	Records	Updated by	Initial value
Antigen count n_Ag	Successful antigen presentations by a neighbouring macrophage	The induction check	0
ICOS count n_ICOS	Contacts with a STAT3-activated macrophage	The induction check	0
Down-regulation count n_DR	Suppressions by Tregs	The suppression rule, whether or not induction is enabled	0

None of the counters is ever decremented or reset. All three are copied to daughters with the rest of the parent's state (S3.5), so a lineage accumulates induction evidence across divisions, as it does the exhaustion counter.

When the induction check runs

The check runs only within the active-Tgam handler, after Fas-mediated killing and IFN-γ action (S3.7, S3.8), and only when `--Treg-induction` is set. The flag is tested first, so when it is absent the check is not entered and consumes no random draws. Tgam in any other state, the double producer included, never run the check. A Tgam that becomes exhausted on a timestep does not run it on that timestep (M8.5).

Accumulation

```
induction accumulation for an active cognate Tgam a:
    C <- compartments of the periodic radius-1 Moore neighbourhood of a
         that hold a macrophage, in ordinal order
    if C is empty:
        skip the accumulation                    // no draw
    m <- the macrophage of one element of C, chosen uniformly
         // drawn independently of the Fas target, so the two may differ
    if the next state of m is dead:
```

```
        skip the remaining accumulation
    presented <- Bernoulli draw with probability
                 TgamInd_Tcell_Tgam_probAntigenPresentation
    if the STAT3 flag of m is set:
        n_ICOS <- n_ICOS + 1        // whatever presented, exposure or state
    if presented and m is exposed and
            (m is infected, chronically infected or activated,
             or m is resting with NF-kB or STAT1 set):
        n_Ag <- n_Ag + 1
```

A resting macrophage with neither pro-inflammatory flag set therefore never presents antigen in this sense, however recently exposed.

The target's state, flags and exposure are read as already updated by its own next-state computation on this timestep, because macrophages are processed before T cells (spine 3.3). Its state is its current state, not its next state, so a macrophage that has just decided to activate still counts as resting.

The down-regulation counter

The Treg suppression rule of S3.10 increments n_DR each time it suppresses a cognate Tgam whose current state is active or double producer, whether or not induction is enabled. In the default configuration the counter is therefore updated throughout every run and never read. It is serialized. The antigen and ICOS counters stay zero. Suppression of a Tgam in any other state does not increment it.

Tgam are down-regulated only by Treg suppression; the TGF-β down-regulation of M4 applies to Tcyt and not to Tgam.

Transition to the double-producer state

After the accumulation, the active Tgam enters the double-producer state with probability

$$P = \tfrac{1}{3}\left[1 - e^{-r_{\mathrm{Ag}}\,(n_{\mathrm{Ag}}-1)}\right]_{n_{\mathrm{Ag}}>1} + \tfrac{1}{3}\left[1 - e^{-r_{\mathrm{DR}}\,n_{\mathrm{DR}}}\right]_{n_{\mathrm{DR}}>0} + \tfrac{1}{3}\left[1 - e^{-r_{\mathrm{ICOS}}\,n_{\mathrm{ICOS}}}\right]_{n_{\mathrm{ICOS}}>0},$$

where each bracketed term is included only when its subscript condition holds, the counts are those after this timestep's update, r_Ag = `TgamInd_Tcell_Tgam_rateAgDegree`, r_DR = `TgamInd_Tcell_Tgam_rateTGFB` and r_ICOS = `TgamInd_Tcell_Tgam_rateICOS`.

One uniform draw is compared with P, and the transition occurs if the draw is less than P. The draw is consumed on every evaluation, including those with P = 0.

- **No certain conversion.** Each term is below $\frac{1}{3}$ for any finite count, so P < 1 at every evaluation.
- **The antigen term starts with the second presentation.** A single presentation contributes nothing.
- **P never decreases.** The counters never decrease, so P is non-decreasing over a cell's life and its line of descent. A long-lived lineage in contact with stimulating macrophages converts almost surely unless it dies, is exhausted or is suppressed.

r_DR multiplies the count of Treg suppressions, not any TGF-β quantity, and has its effect when M4 is not selected.

On transition, the next state is set to the double producer, and the transition time is set to the current timestep.

The double-producer state

Behaviour	Double producer
Movement	As Tgam, chemotactic to CCL2, CCL5 and CXCL9 (S1)
Fas-mediated killing	As active (S3.8)
IFN-γ action	As active, if an IFN-γ producer (S3.7)
Proliferation	As active (S3.5)
Exhaustion	As active (M8.5)
Induction check	Not performed
TNF secretion	As active, if a TNF producer
IL-10 secretion	State factor 0.5 at the Treg rate `Core_Tcell_Treg_dIL10`
Treg suppression	Applies, as for active Tgam
Exit	To induced regulatory once $t-$ transition time $\geq$ `TgamInd_Tcell_Tgam_maxTimeDouble`

The IL-10 rate of an induced cell is the Treg rate, not the Tgam rate `Core_Tcell_Tgam_dIL10`, so it is tied to the sampled Treg secretion parameter (S6.16).

The exit test is made in the double-producer handler, and the transition time counts from the timestep on which the next state was set. With `TgamInd_Tcell_Tgam_maxTimeDouble` = $k \geq 1$ the cell spends k timesteps as a double producer. With k = 0 it spends one, because the exit test is first made on the timestep after entry.

A suppressed double producer enters the down-regulated state and, on recovery after `Core_Tcell_Tgam_maxTimeReg`, returns to the active state (S3.10). It loses its double-producer status and may convert again later, with a new transition time. Its suppression also increments n_DR, so its probability of reconverting is higher than before.

The same loss occurs on the timestep of conversion. Tregs are processed after Tgam (spine 3.3), and the suppression rule tests the Tgam's current state, which on that timestep is still active. A suppression then overwrites the double-producer next state with the down-regulated state, so the conversion is discarded, although its transition time has been recorded.

The induced regulatory state

Behaviour	Induced regulatory
Movement	As Tgam
Fas-mediated killing	None
IFN-γ action	None

Behaviour	Induced regulatory
Proliferation	As active
Exhaustion	As active (M8.5)
TNF secretion	As active, if a TNF producer
IL-10 secretion	State factor 1 at the Treg rate `Core_Tcell_Treg_dIL10`
Treg suppression	No effect
Suppression of neighbours	None
Exit	None, except by death or exhaustion

An induced regulatory Tgam secretes IL-10 at the Treg rate but does not suppress neighbouring cells, which is the only effector function of a Treg (S3.10). It is therefore regulatory through the IL-10 field only. It keeps secreting TNF if it was a TNF producer, and keeps proliferating, so a TNF-producing induced lineage secretes both TNF and IL-10.

Daughters of double-producer and induced regulatory cells are copies of their parent and take the parent's state, including, for a double producer, its transition time. A double-producer daughter therefore becomes induced regulatory on the same timestep as its parent.

Identity

Induced cells remain Tgam. They are held in the Tgam list, processed in the Tgam position of the type order, counted under the Tgam per-state statistics, and recruited, scaled and reported as Tgam. No statistic and no rule reading Treg presence counts them as Tregs. The T cell extent, which includes Tgam, includes them.

Enabling induction alters the random number stream from the timestep of the first active cognate Tgam onward, before any cell has converted, because the number of draws depends on local conditions.

M8.7 Growth-rate randomisation

Summary. With `--rand-growth` set, a bacterium created holding a count inside a newly constructed infected macrophage draws its stored growth rate uniformly between `Mtb_Agents_growthRateIntMtbMin` and `Mtb_Agents_growthRateIntMtbMax`. Daughters inherit their parent's current stored rate, so one draw founds each lineage, and the stored rate then serves as the base of the growth law. By default, the flag is absent.

The switch

The flag is passed to the simulation coordinator when it is constructed. From there it reaches the grid, the macrophage constructor, every intracellular and extracellular growth call, and the neutrophil constructor. It cannot be changed afterwards, including on reload of a saved state (M8.2).

The two constructors

Constructor	Stored rate at creation	Draws beyond the common construction draws
Drawing, used when a bacterial group is created holding a specified count	U(r_min, r_max) if the flag is set; otherwise the fixed rate supplied by the caller	One if the flag is set; none otherwise
Non-drawing, used by the parameter-file initialisation of extracellular bacteria	0	None

Both constructors set the two intrinsic per-bacterium rates to `Mtb_Agents_growthRateIntMtb` and `Mtb_Agents_growthRateExtMtb`, whether or not the flag is set (S4.2).

Which bacteria receive a draw

Creation path	Constructor	Bounds	Bacteria created
Seeding macrophage, and any infected macrophage from the parameter file (spine 5.4)	Drawing	`Mtb_Agents_growthRateIntMtbMin`, `Mtb_Agents_growthRateIntMtbMax`	One per macrophage
Reinfecting macrophage (M8.3)	Drawing	As for the seeding macrophage	One
Recruited and initial resting macrophages	Drawing	As for the seeding macrophage	None
Extracellular bacteria from the parameter file (spine 5.4)	Non-drawing	None	One per entry
Division	Copy of the parent	None	One per division
Uptake, release, dispersal	Transfer of existing bacteria	None	None

Resting macrophages, recruited ones included, are constructed holding no bacteria, so their constructor creates none and draws nothing. Every compartment's extracellular group starts empty (S4.3), so constructing the grid draws nothing either.

Under randomisation, the number of growth-rate draws in a run therefore equals the number of macrophages created already infected. In the default configuration, that would be one draw at initialisation, plus one for a reinfection. Only constructed bacteria draw a rate; daughters inherit the parent's current stored rate, so with one seeding bacterium and absent reinfection, all bacteria in a run descend from one draw. The heterogeneity the option introduces is thus one draw per founding lineage, differentiated afterwards only by the modulation history set out under Consequences of compounding.

The extracellular bounds `Mtb_Agents_growthRateExtMtbMin` and `Mtb_Agents_growthRateExtMtbMax` reach no path that creates bacteria. They bound the extracellular growth-rate histogram (S4.16, S9) and do not act as randomisation bounds.

Bacteria from the non-drawing constructor

Extracellular bacteria placed by the parameter file start with a stored rate of 0. With the flag off this is immaterial, because the growth law does not read the stored rate, and they grow at the intrinsic extracellular rate. With the flag on, the stored rate is the base of the growth law, so they have a rate of 0 for life. They never grow or divide, and die only by killing or by the density-dependent death in caseum (S4.10). Parameter-file placement of extracellular bacteria is not used by default.

Inheritance at division

A daughter is a copy of its parent, including the stored rate, and after the copy its stored rate is set explicitly to the parent's (S4.9). On that timestep the parent's stored rate has already been replaced by the rate the parent applied in its growth step, so the daughter inherits the parent's current modulated rate, not the rate originally drawn for the lineage. The intrinsic per-bacterium rates are copied unchanged; under M6 resistance or compensatory mutation may then alter them in the daughter (M6.13).

The growth law with the flag off and on

At each growth call the growth law of S4.5 computes a rate r_n = a_n b_n, applies it to the bacterium's biomass and stores r_n as its stored rate. Here a_n is the environmental modulation of the bacterium's location: the post-adaptive factor intracellularly (S4.7), and, extracellularly, zero in a caseated compartment and otherwise the product of the density factor and the caseation-tier factor (S4.6). The option changes only the base:

$$b_n = \begin{cases} r^{\mathrm{int}} \text{ or } r^{\mathrm{ext}} \text{ (intrinsic, by location)} & \text{flag off} \\ r_{n-1} \text{ (stored rate from the previous step)} & \text{flag on.} \end{cases}$$

With the flag off, $r_n = a_n r^{\ell}$. The modulation applies afresh to a fixed intrinsic rate at each step, and the stored rate is a record only: it feeds the growth-rate histograms and the non-replicating designation, not the next step's growth. This is the behaviour in the default configuration.

With the flag on, $r_n = a_n r_{n-1}$, so

$$r_n = r_0 \prod_{k=1}^{n} a_k,$$

where r_0 is the drawn rate and the product runs over every growth step of the bacterium and its ancestors since the founding draw. The modulation is cumulative rather than instantaneous.

Consequences of compounding

- **Extracellular rates decay at every step.** The density factor counts the bacterium itself, so it never exceeds $1 - 1/114.527 = 0.9913$. An extracellular bacterium's rate therefore falls by at least that factor at every timestep, halving within $\lceil \ln 2 / -\ln 0.9913 \rceil = 80$ timesteps, about 13 hours, even when alone in a clean compartment, and faster under crowding.
- **The caseation tier compounds.** At intermediate local caseation the rate is divided by the caseation count, between 5 and 13 by default, at every step spent there.
- **Caseum zeroes the rate permanently.** One growth step in a caseated compartment sets a_n = 0, and hence r_m = 0 for all later m. The bacterium and all its later daughters never grow again, even if the compartment heals or the bacterium is taken up and released elsewhere.
- **The post-adaptive factor compounds** as f^m over the m intracellular steps after its onset, rather than applying once.
- **Intracellular rates are preserved only while the factor is 1.** Intracellular modulation has no density or caseation term, so with the post-adaptive factor at 1 an intracellular bacterium keeps its stored rate, whatever that rate became while it was extracellular.
- **One rate serves both locations.** The stored rate carries across uptake, release and dispersal. The intrinsic rates, and the separate intracellular and extracellular bounds, play no part once a bacterium exists.

These consequences make the extracellular population under randomisation effectively non-replicating within a few days of release, independent of caseation, and they make any contact with caseum irreversible for a lineage.

Effects on other mechanisms

- **Non-replicating designation.** A compartment's extracellular group is designated non-replicating when the mean stored rate of its live bacteria is zero, or the compartment is caseated (S4.14). Under randomisation a zero rate is absorbing, so a group whose bacteria have all touched caseum stays non-replicating after healing, until those bacteria die or a bacterium with a non-zero rate arrives.
- **Growth-rate statistics.** The growth-rate histograms and extrema report the compounded rates; with the flag off they report the instantaneous modulated rate (S9).
- **Resistance fitness costs.** Under M6, resistance and compensatory mutations scale the intrinsic rates, which the base does not read under randomisation, so the fitness costs and their compensation have no effect on growth (M6.13).
- **Division and starvation.** Rates are non-negative, so biomass never falls during growth. A bacterium whose rate has decayed toward zero stops approaching the division threshold, cannot starve by growth, and persists at its biomass until killed.

M8.8 Post-adaptive intracellular growth factor

Summary. At every intracellular growth step from timestep `Recruit_Prob_timeRecEnabled` + `Mtb_Agents_growthRateFactorDelayIntMtb` onward, the rate is multiplied by `Mtb_Agents_growthRateFactorPostAdaptiveIntMtb`. S4.7 specifies the rule, its onset and its parameters, as the intracellular modulator of the growth law. By default, the factor is 1.0, applied but an identity.

Under growth-rate randomisation the factor compounds over the intracellular steps after onset, and the reduced rate persists after release (M8.7). The factor makes no draw.

M8.9 Neutrophil injection

Summary. On the timestep equal to a positive `Core_Neutrophil_injectionTimestep`, neutrophils are placed in randomly chosen admissible compartments within the circle circumscribing the current connected region. The program creates `Core_Neutrophil_injectionCount` + 1 of them. By default, the timestep is 0.

Trigger

Injection is a single event. It fires on the cellular timestep t satisfying

$$t = \texttt{Core_Neutrophil_injectionTimestep} \quad \text{and} \quad \texttt{Core_Neutrophil_injectionTimestep} > 0.$$

The parameter declaration describes a timestep of 0 as meaning no injection; the code tests for a strictly positive value, so 0 and any negative value disable it. It fires at most once per run. The test is made after the connected-region boundary has been computed and before ring scaling (spine 3.2).

Candidate positions

Every compartment of the grid is visited in row-major order. A compartment becomes a candidate if:

- **it lies within the granuloma**, judged by the circular approximation of S9: its Euclidean distance from the connected-region centre of mass is at most half the region's maximum diameter; and
- **it admits a neutrophil** by the neutrophil admission predicate, which requires only a free slot and makes no caseation test, no large-agent test and no draw (M9.3).

Injection and ring scaling read the current timestep's region; the macrophage release test (S9.8) and a neutrophil routine (M9.2) read it one timestep old. The circle circumscribes the region rather than tracing it, so candidates may include holes in the region, sparse compartments at its margin, and caseous compartments.

With no connected region, for example after clearance, the centre of mass is (0, 0) and the maximum diameter 0 (S9.7), so only (0, 0) can be a candidate and the candidate count is 0 or 1.

Injection

Let K be `Core_Neutrophil_injectionCount`, read as an unsigned integer, and M the number of candidates.

```
neutrophil injection on timestep t:
    if K > M:
        fatal error                // a negative K wraps to a very large value
    shuffle the candidate list
    for i = 0 to K inclusive:
        create an active neutrophil at candidate i
```

The program therefore injects one more neutrophil than K. K = 0 injects one neutrophil. K must be less than M; K > M stops the run with an error. With no connected region this holds only for K = 0 with M = 1, which places one neutrophil at the origin.

Candidates are distinct, so no two injected neutrophils share a compartment, and for K < M each placement succeeds.

The injected neutrophils

Each injected neutrophil is created active, with birth time t and death time t + `Core_Neutrophil_maxAge` (M9.2). It is appended, in shuffled-candidate order, to the end of the neutrophil list. Its receptor counts are drawn as for any constructed agent, and the current randomisation flag is passed to its constructor, which creates an empty container and draws no growth rate (M9.2).

Injected neutrophils first move, secrete and compute next states on the timestep after injection. On the injection timestep they are absent from the statistics block (granuloma extents, grid statistics, threshold-granuloma counts) and from the connected region, which precede injection. They are included in the per-agent statistics, written as each neutrophil is created and not reset until the next timestep, and in the ring-scaled counts, which follow injection. Statistics written for the injection timestep therefore include the injected neutrophils in some quantities and not in others (S9).

Random placement of initial neutrophils admits by the crowding rule instead, which also tests for a large agent or another neutrophil and makes one draw per attempt (M9.3). Injected neutrophils may therefore stand where a randomly placed neutrophil would be refused.

Everything an injected neutrophil does after placement, and the other routes by which neutrophils enter a simulation, are specified in M9.

M8.10 Interactions among perturbations and with the baseline

The options are switched independently but act on shared state, so enabling more than one does not in general produce the sum of their separate effects. Each coupling follows from rules already specified.

Couplings between options

Options	Coupling
Exhaustion, Treg induction	Induced Tgam exhaust and lose the induced state, and exhaustion pre-empts the induction check (M8.5). Daughters inherit the exhaustion counter and the three induction counters, so a lineage carries forward its evidence for both
Exhaustion, depletion	An exhausted producing Tcyt that is not deactivated keeps secreting TNF, subject to TNF depletion; exhausted Tgam secrete nothing (M8.5)
Treg induction, depletion	Double-producer and induced regulatory Tgam take the IL-10 and TNF multipliers (M8.4). Under full IL-10 depletion an induced regulatory Tgam has no regulatory effect at all, since it does not suppress by contact
Treg induction, Treg suppression strength	The suppression probability follows `Core_Tcell_Treg_dIL10`, not IL-10 present (M8.4). Induced cells raise the IL-10 field, which acts on STAT3 activation and on secretion but not on suppression

Options	Coupling
Randomisation, post-adaptive factor	Under randomisation the factor compounds and persists after release; without it the factor is a step change (M8.7)
Randomisation, reinfection	The reinfecting macrophage's bacterium draws afresh from the intracellular bounds and founds a lineage with a rate independent of the original infection (M8.7)
Post-adaptive factor, reinfection	A reinfection after onset is subject to the factor from its first growth step. Under randomisation its compounding begins at the reinfection timestep, not at onset, so the two lineages decay out of step
Reinfection, injection	When both fire on the same timestep, reinfection runs first (spine 3.2). The reinfecting macrophage is present when the connected-region boundary is computed, so it may alter the circle within which neutrophils are injected
Injection, randomisation	Injected neutrophils hold no bacteria and draw no growth rate; bacteria they later take up keep their stored rates (M9.2, M9.6)
Injection, exhaustion	Injected neutrophils are not counted by the exhaustion sweep, which reads only macrophages (M9.6)
Injection, Treg suppression	The suppression rule tests injected neutrophils, consuming a draw for each, with no effect on them (M9.6)

Couplings with the baseline model

- **Depletion lowers the fields read by recruitment.** TNF depletion lowers TNF at vascular sources, and with it the recruitment eligibility and probability of every type that responds to TNF (S8). IL-10 depletion raises chemokine and TNF secretion (M8.4), and so raises recruitment indirectly. Neither alters a recruitment threshold.
- **Depletion and reinfection reach caseation.** TNF depletion lowers TNF-induced apoptosis, a principal route of killing-count increments, and reinfection adds a second focus of eventual caseation (S5.2).
- **Exhaustion and induction remove effector function.** Exhausted and induced regulatory Tgam exert no IFN-γ action. IFN-γ action is the sole route to macrophage STAT1 (S3.7), so both options reduce macrophage activation, and hence intracellular killing, in proportion to the IFN-γ-producing Tgam they remove. Neither alters the producer fraction drawn at creation.
- **Exhausted and induced cells continue to occupy space.** They count toward compartment slots, cell density, the granuloma definitions and the T cell extent (M8.5, M8.6), so they continue to suppress vascular delivery and to compete for recruitment slots.
- **Injected neutrophils occupy space.** They count toward compartment slots, the cell density that gates vascular delivery and defines the threshold granuloma, and the connected region (M9.2). Injection therefore alters oxygen delivery and recruitment within the lesion from the next timestep, whatever the neutrophils do.
- **Randomisation alters the non-replicating count.** Under randomisation the extracellular population

becomes non-replicating through compounding rather than through local caseation, so the non-replicating bacterial count (S9) reflects growth-rate compounding as well as local caseation.

- **Reinfection adds to the recruitment floor.** The reinfecting macrophage counts toward the total read by the macrophage recruitment floor, so it slightly reduces floor-driven recruitment while it lives (S8.7).

Random number stream

Enabling an option changes the stream from the first point at which it, or a decision it alters, consumes or skips a draw. After that point every later draw differs, and trajectories diverge from the baseline run with the same seed even where the option has had no mechanistic effect yet. Under randomisation the seeding bacterium's draw is made before vascular sources and resting macrophages are placed (spine 5.1), so runs with and without randomisation under one seed differ in vascular geometry and resting-macrophage placement from the start.

M8.11 Parameters

None of these settings is sampled in the default configuration. Command-line options select whether an option is active, and for depletion when it begins; parameter-file entries set thresholds, timesteps, rates and positions.

Identifier	Value or range	Units	Meaning
`Core_reinfectionTimestep`	-1	integer, timestep	Reinfection timestep (M8.3); any value ≤ 0, or beyond the last timestep, disables it
`Core_reinfectionLocation`	0.8	fraction of the diagonal	λ (M8.3); declared on [0, 1]; mandatory, no declared default
`--tnf-depletion`, `--il10-depletion`, `--tgfb-depletion`	-1 (program default -1)	integer, timestep; command line	t_TNF, t_IL-10, $t_{\text{TGF-}\beta}$ (M8.4); negative disables; not validated
`Core_depletionFractionTNF`	0	none declared	ϕ_{TNF}, share of TNF secretion retained (M8.4); [0, 1], checked
`Core_depletionFractionIL10`	0	none declared	$\phi_{\text{IL-10}}$, share of IL-10 secretion retained (M8.4); minimum 0, not checked[1]
`Core_Tcell_exhaustionThreshold`	9999999	integer, interactions	θ_{exh} (M8.5)
`--Treg-induction`	Absent	flag; command line	Enables the induction check (M8.6)
`TgamInd_Tcell_Tgam_probAntigenPresentation`	—	probability	Presentation probability (M8.6); mandatory; checked on [0, 1]
`TgamInd_Tcell_Tgam_rateAgDegree`	—	per presentation	r_Ag (M8.6); mandatory; no range check
`TgamInd_Tcell_Tgam_rateTGFB`	—	per suppression	r_DR (M8.6); multiplies the suppression count; mandatory; no range check

Identifier	Value or range	Units	Meaning
`TgamInd_Tcell_Tgam_rateICOS`	—	per contact	r_ICOS (M8.6); mandatory; no range check
`TgamInd_Tcell_Tgam_maxTimeDouble`	—	integer, timesteps	Double-producer duration (M8.6); mandatory; minimum-only declaration, not checked
`--rand-growth`	Absent	flag; command line	Enables growth-rate randomisation (M8.7)
`Core_Neutrophil_injectionTimestep`	0	integer, timestep	Injection timestep (M8.9); fires only when positive, so 0, negative values or values beyond the last timestep disable it; minimum 0, not checked; mandatory, no declared default
`Core_Neutrophil_injectionCount`	0	integer, count	K (M8.9), read as unsigned; K + 1 neutrophils are created; minimum 0, not checked; mandatory, no declared default

[1] An IL-10 fraction above 1 amplifies IL-10 secretion under depletion (M8.4).

The post-adaptive factor's parameters, `Mtb_Agents_growthRateFactorPostAdaptiveIntMtb` (1.0, declared on [0, 1]) and `Mtb_Agents_growthRateFactorDelayIntMtb`, are tabled with S4.7 (S4.16). The randomisation bounds `Mtb_Agents_growthRateIntMtbMin` and `Mtb_Agents_growthRateIntMtbMax` are tabled in S4.16.

Fixed structural constants: the exhaustion sweep radius of 2 (25 compartments in two dimensions); the induction neighbourhood radius of 1; the weights $\frac{1}{3}$ of the induction probability; the induced IL-10 state factors 0.5 and 1; the reinfection fallback radius of 1, boundary-clipped.

Declared or read but without effect by default: `Core_Tcell_exhaustedMaxAge` (read by no rule, M8.5); `--tgfb-depletion` without M4 (M8.4); `Mtb_Agents_growthRateExtMtbMin` and `Mtb_Agents_growthRateExtMtbMax` as randomisation bounds (M8.7).

M8.12 Interfaces

With	Provides or receives	See
Spine module-slot table	Provides the M8 slot and option summaries	M8.1
Spine 3.2	Receives the [M8] hooks: reinfection after the timestep increment, depletion flags after the statistics reset, injection after the connected region	M8.1, M8.3, M8.4, M8.9

With	Provides or receives	See
Spine 2.1	Receives the significant-figure truncation, from which the exhaustion test is exempt	M8.5
Spine 2.2	Provides the reinfection fallback as a boundary-clipped placement rule of a disabled option	M8.3
Spine 2.3, 3.3	Receives the occupancy and slot rules, the monotone next-state rule and the type order (macrophages before T cells, Tregs after Tgam and Tcyt)	M8.3, M8.5, M8.6
Spine 5.1, 5.4	Receives the seeding macrophage and the order of initialisation	M8.3, M8.7, M8.10
Spine 7.0	Receives the command-line versus parameter-file convention ("Command-line options and the parameter file"), the range-build rule ("Validity ranges") and the sentinel convention ("Declared but unused parameters")	M8.2, M8.4, M8.11
S1	Movement of the reinfecting macrophage, exhausted cells and induced Tgam by the S1 rules (S1.2); the macrophage admission predicate that reinfection placement tests (S1.4)	M8.3, M8.5, M8.6
S2	Exposure memory, STAT1, NF-κB and STAT3 flags read by exhaustion and induction	M8.5, M8.6
S3	Dispatch and interaction sweep (S3.4, S3.6), division copy (S3.5), suppression rule (S3.10); provides the exhausted, double-producer and induced states that S3.6 and S3.10 summarise	M8.5, M8.6
S4	Growth law and modulators (S4.5 to S4.7); M8 replaces the base of the growth law under randomisation and S4.7 holds the post-adaptive factor	M8.7, M8.8
S5	Killing-count increments from exhausted T cell deaths; caseum effects on growth under randomisation	M8.5, M8.7, M8.10
S6	Secretion inventory (S6.13), modulations (S6.10 to S6.12), sink (S6.8), receptor draws (S6.3); provides the depletion multipliers that S6.9 summarises	M8.4
S7	Oxygen consumption by the reinfecting macrophage	M8.3
S8	Recruitment floor, arrival rule (S8.1), half-open integer draw (S8.12); recruitment reads the depleted fields	M8.3, M8.4, M8.10
S9	Connected region and circle (S9.7, S9.8); T cell extent (S9.5); statistics of reinfection, exhaustion, induction, growth rates and the injection timestep	M8.3, M8.5, M8.6, M8.7, M8.9

With	Provides or receives	See
M1	Sets the number of secretion calls per cellular timestep (2N_d); each call covers $\frac{1}{2}\Delta t_d$, so the total suppressed by depletion is the same under every solver and only its granularity changes; no other option depends on the solver	M8.4
M2	Sets which recruited T cells are cognate and active, and so eligible for exhaustion and induction (M2.9); the post-adaptive onset keys on `Recruit_Prob_timeRecEnabled` under every option (M2.6, S4.7)	M8.5, M8.6, M8.8
M3	Replaces the coarse depletion path (M3.3 to M3.5); IL-10 double secretion under fractional depletion; T0 cells under MHC class II accumulate no exhaustion count and no induction evidence until activated (M3.6)	M8.4, M8.5
M4	Required for TGF-β depletion to act (M4.3); its TGF-β proliferation gate can only shorten lines of descent, so the exhaustion bound stays an upper bound; its Tcyt down-regulation never increments n_DR	M8.4, M8.5, M8.6
M5	The exhaustion sweep covers 125 compartments in three dimensions, giving a bound of 270000; the reinfection target lies on the volume's main diagonal with a 27-compartment fallback (M5.9)	M8.3, M8.5
M6	Fitness costs and compensation are inert under randomisation; mutation and susceptibility are unaffected (M6.13)	M8.7
M7	Under the TNF receptor equations, anti-TNF agents bind TNF in the same system through which depletion acts; the two compose, and neither alters the other's parameters (M7.8)	M8.4
M9	Neutrophil admission (M9.3), construction (M9.2), behaviour after injection, TGF-β secretion under depletion (M9.7) and Treg tests (M9.6)	M8.4, M8.9, M8.10
Appendix B	Indexes the M8 switches, `Core_Tcell_exhaustedMaxAge` as inert, and the injection settings	M8.11