M4. TGF-β and fibrosis module

M4.1 Slot, options and selection

Summary. M4 adds a latent and an active TGF-β field, a collagen field and a fibroblast agent that can differentiate into a collagen-secreting myofibroblast. Bound TGF-β reduces macrophage killing and TNF secretion, gates T cell proliferation and down-regulates cytotoxic T cells. The module is not selected by default, where its only executed expressions leave the trajectory unchanged (M4.1, "Behaviour under the none option").

M4 specifies the module in full, including the fibroblast agent, which exists only when the module is selected. The mechanism sections describe the module as it behaves when selected.

Schedule

Block	Operations	Cadence	Section
Split half-step	Latent TGF-β secretion by macrophages, regulatory T cells, fibroblasts and neutrophils; binding of active TGF-β; collagen secretion by myofibroblasts	$\Delta t_d/2$ per call, twice per diffusion step	M4.3, M4.6
Molecular substep loop, within the split half-step	The fibroblast receptor ODE system, ODE option only	Δt_m per substep, N_m substeps per diffusion step	M4.7
Diffusion solve	Transform of the active field; copy-forward and decay of the inactive field	Once per diffusion step	M4.2
After the diffusion loop, before any movement	Activation of latent TGF-β in macrophage compartments	Once per cellular timestep	M4.3
After T cell movement	Fibroblast movement	Once per cellular timestep	M4.5
Next-state pass and daughter commitment	Fibroblast state machine, proliferation, differentiation and IL-10 binding; effects on macrophage killing, macrophage TNF secretion, and T cell proliferation and down-regulation	Once per agent per cellular timestep	M4.4 to M4.6

The effector couplings have no block of their own. They are expressions inside the macrophage and T cell rules, so they run in the type order of spine 3.3. The fibroblast's place in the movement order is owned by S1.1.

Reads and writes

Reads:

- active and inactive TGF-β, IL-10 and TNF at the agent's own compartment;
- caseation and occupancy of the Moore neighbourhood;
- cumulative bound TGF-β on macrophages, T cells and fibroblasts;
- the macrophage's signalling-bound and free surface TNFR1 counts (S6.4);
- presence of a Tgam in the boundary-clipped Moore neighbourhood of a macrophage;
- the current timestep, the TGF-β depletion schedule (M8) and the parameters of M4.9.

Writes:

- active TGF-β, decremented by binding and incremented by activation;
- inactive TGF-β, incremented by latent secretion and decremented by activation;
- IL-10, decremented by fibroblast binding and, under the ODE option, by the ODE sink;
- collagen, incremented by myofibroblasts;
- cumulative bound TGF-β on every agent type;
- on fibroblasts: cumulative bound IL-10, cumulative aSMA, the free surface and internalized receptor counts, the surface and internalized complex counts, the internalization record and internalized IL-10;
- the macrophage secretion-reduction end timestep;
- the fibroblast state, differentiation time and proliferation time;
- the fibroblast proliferation list and the proliferation-location map;
- the fibroblast-proliferation-begun flag, and through it the stored granuloma membership flag (M4.8);
- the cytotoxic T cell state and deactivation time;
- the statistics of M4.8.

The killing-reduction factor and the TNF secretion factor (M4.4) are computed and consumed within one rule and are stored on no agent.

Options and selection

The module is selected by a three-valued command-line option, not a parameter-file entry (Appendix B). The simulation constructor sets it to the none option, so a run that omits the option has the module off.

Option	Value	Summary
None	0	No TGF-β mechanism and no fibroblast. Selected by default
Coarse	1	Latent secretion and binding at fixed per-type rates, with no receptor representation. Fibroblasts exist, proliferate, move and bind, but no fibroblast differentiates, so no collagen is secreted (M4.6)
ODE	2	A twelve-variable per-fibroblast receptor and ligand ODE system replaces the coarse fibroblast binding and secretion

Any integer outside {0, 1, 2} is rejected at startup. The selection is saved with the simulation state; on reload a differing command-line value takes precedence, with a warning (Appendix B).

Gates

The two active values are not nested. Most mechanisms are gated on the selection not being none, and each active value gates one mechanism of its own. Appendix B refers to this table for the gates.

Mechanism	Gate
Fibroblast and myofibroblast initialization, deterministic and random	Not none
Activation of latent TGF-β	Not none
Fibroblast movement	Not none
Macrophage binding of active TGF-β and latent secretion	Not none
Reduction of macrophage TNF secretion	Not none
Macrophage secretion-reduction interval on Tgam proximity	Not none
T cell binding of active TGF-β; latent secretion by regulatory T cells	Not none
Probabilistic gating of T cell proliferation	Not none
Cytotoxic T cell down-regulation	Not none
Fibroblast binding and latent secretion	Coarse only
The fibroblast receptor ODE system	ODE only
Reduction of resting macrophage killing	Ungated (M4.4)
Allocation, serialization, diffusion, degradation and observation of the three fields	Ungated (M4.2; M4.1, "Behaviour under the none option")
The call to the fibroblast secretion routine from the split half-step	Ungated; the list is empty when the module is off

Fibroblast latent secretion therefore occurs under the coarse option only. Under the ODE option the latent pool is fed instead by the synthesis term `TGFB1ksynth` and the feedback term `TGFB1kis` of the ODE system, and the fibroblast secretion routine does nothing. Macrophage, Treg and neutrophil latent secretion run under both active options.

A fibroblast's cumulative bound TGF-β is written by different mechanisms, in different units, under the two active options, while the thresholds compared with it are the same (M4.3).

The killing reduction of M4.4 is evaluated under every selection. Under the none option it equals exactly 1, but its parameter is read, and the expression is not a number if that parameter is zero.

Behaviour under the none option

Under the "none" option the module contributes nothing to the trajectory. This section records what nonetheless executes, so that parameter files, grid dumps and saved states are not misread.

- **Fields.** All three fields are allocated, saved with the simulation state, included in the field inventory and the grid-dump name map, and summed every timestep into `TotTGFBActive`, `TotTGFBInactive` and `collagen` (S9). All three start at zero and stay zero.
- **Field operations.** On every diffusion step the active field is transformed and propagated, and the inactive field is copied forward and decayed (M4.2). Both propagators are built when the diffusion object is constructed. All of this acts on zero.
- **Fibroblast secretion.** The routine is called from each half-step without a module guard, unlike fibroblast movement and activation, and iterates an empty list.
- **No fibroblast.** Init-section fibroblast and myofibroblast entries are ignored with a warning, and random placement is skipped by the same guard (M4.5). `Core_Fibroblast_initNumber`, computed from `Core_Fibroblast_initDensity` during parameter resolution, is 0.
- **Agent variables.** Every agent, bacteria included, carries a cumulative bound TGF-β that starts at zero and is never written. Every macrophage carries a secretion-reduction end timestep of -1, never written, because the reduction routine returns at once.
- **Killing reduction.** It evaluates to exactly 1, leaving `Core_Mac_probKillExtMtbRest` unchanged (M4.4).
- **Draws.** The module consumes no random draw: every module draw lies in a guarded block or in a rule of an agent type that is never created.
- **Observation.** Every fibroblast statistic is zero. The fibroblast-proliferation-begun flag stays false, so the stored granuloma membership flag is recomputed every timestep (M4.8).

M4.2 The TGF-β and collagen fields

Field	Transport	Degradation	Written by
Active TGF-β	Diffused by the selected solver under a zero-concentration boundary (M1)	`Core_degRateTGFBActive`, folded into the solver	Activation (M4.3); decremented by binding (M4.3)
Inactive (latent) TGF-β	None	`Core_degRateTGFBInactive`, applied as a separate pointwise step	Latent secretion (M4.3); decremented by activation
Collagen	None	None	Myofibroblasts only (M4.6)

Active TGF-β

The active field is advanced like the other diffused cytokines. For it, the diffusivity is `Core_diffusivityTGFBActive` and the degradation rate is `Core_degRateTGFBActive`. The transform, propagator, normalization, concentration cutoff and the alternating-direction treatment are specified in M1.3 ("The propagator and incorporation of decay"; "Normalisation and the cutoff") and M1.4. M1.3, "The propagator and incorporation of decay", also holds the zero-diffusivity case, which applies to this field in every configuration because the field is transformed with no module gate.

Inactive TGF-β

The inactive field is never transformed or swept. On each diffusion step its main array is copied whole to the next grid, carrying forward the secretion of the earlier half-step, and is then multiplied in place by

$$\exp(-\texttt{Core_degRateTGFBInactive} \cdot \Delta t_d)\,.$$

No concentration cutoff is applied, so the field can hold arbitrarily small positive values, unlike every diffused species. The field has no boundary condition. Latent TGF-β stays in the compartment where it was secreted until it is activated or decays, so the latent pool maps the positions of its secreting cells.

Collagen

Collagen is neither transported nor decayed, and it is not copied forward by the field advance. Each grid object holds its own copy, so only the writes made to the buffer current at the end of the diffusion loop survive, those of ten of the twenty secretion half-steps per timestep (M1.3, "Non-transformed fields and grid buffering"). Collagen is read only by the whole-grid statistic. No rule reads it, so it has no mechanistic consequence and serves as the module's output measure of fibrosis.

Initialization

All three fields start at zero. Each can be set by name from the parameter-file Init section, at one compartment or uniformly (spine 5.5). This is the only route to a non-zero value under the none option. A non-zero active field there would diffuse and decay, with no cell to bind it and no source to replenish it.

M4.3 The TGF-β cycle

Summary. TGF-β enters only as latent TGF-β, secreted by macrophages, regulatory T cells, neutrophils (M9.7) and, under the coarse option, active fibroblasts; under the ODE option the fibroblast receptor system also synthesizes and activates it (M4.7). Macrophages activate it in their own compartments, in part in proportion to TNF signalling. Cells bind the active form into a cumulative bound quantity that never falls.

Secretion of latent TGF-β

TGF-β enters the model only as the latent species. No cell secretes the active form. The active field is fed only by activation (Activation of latent TGF-β) and, under the ODE option, by the conversion term of the ODE system (M4.7).

Latent secretion runs in the split half-step with duration $\Delta t_d/2$. A cell secreting at rate r therefore adds $r\Delta t_a$ to the latent field at its compartment over one cellular timestep.

Secreting entity	Latent rate	Condition
Macrophage, any live state	`Core_Mac_dTGFBInactive`	Not suppressed
Treg	`Core_Tcell_Treg_dTGFBtreg`	Cognate and not in T0
Active fibroblast	`Core_Fibroblast_dTGFBInactive`	Coarse option only
Neutrophil	M9.7	—
Suppressed macrophage, myofibroblast, Tgam, Tcyt, non-cognate T cell	None	—

Macrophage secretion is state-independent. It is written before the state switch of the macrophage secretion routine and carries no state factor. A resting macrophage secretes latent TGF-β at exactly the rate of an activated one. The other macrophage secretions are scaled by a state factor (S6.13).

A suppressed macrophage neither secretes nor binds. The TGF-β block follows the early return taken by a macrophage suppressed by a regulatory T cell. A down-regulated Tgam or Tcyt, by contrast, keeps binding active TGF-β, because its binding call precedes its deactivation check (Binding of active TGF-β by cells).

Only Tregs secrete among T cells, and only when cognate and out of T0. The cognate fraction is set by the `probCognate` parameters (S8.13).

Reduction of macrophage secretion near a Tgam

A macrophage's latent secretion rate is halved while a reduction interval is in force. The interval is managed once per macrophage per cellular timestep, in the next-state pass, gated on the module:

```
if no reduction interval is in force:
    if any Tgam is in the boundary-clipped Moore neighbourhood:
        interval end <- t + Core_tgfbSecretionReductionInterval
else if t >= interval end:
    clear the interval
```

This is a proxy for IFN-γ suppressing macrophage TGF-β production, IFN-γ not being a field.

- The trigger is any Tgam, whatever its state, cognate status or producer status. The IFN-γ action of S3.7, by contrast, requires an active cognate producer.
- The search uses the boundary-clipped Moore neighbourhood and stops at the first Tgam, so the reduction is binary in the number of Tgams.
- The interval is not extended while in force. No Tgam test is made on the timestep it lapses, so the earliest a new interval can begin is the next timestep.
- The factor of one half is hard-coded.

Depletion

M8 owns the TGF-β depletion schedule, which holds from a command-line timestep to the end of the run. While it holds, every latent secretion term in the secretion table is suppressed, and under the ODE option `TGFB1ksynth` and `TGFB1kis` are set to zero in the derivative (M4.7). Neutrophil secretion under depletion is specified in M9.7.

Binding is not suppressed. Cells keep removing active TGF-β, so both fields drain and every cell's cumulative bound quantity freezes at the value it has reached. TGF-β has no fractional depletion; depletion is all or nothing (M8).

Activation of latent TGF-β

Activation is performed by a simulation-level routine once per cellular timestep, after the diffusion loop and before any agent moves, guarded on the module.

For each macrophage in the macrophage list, the routine transfers

$$A = [f + (1 - f)\, s]\, C_{\mathrm{lat}}(p), \qquad s = \frac{\text{signalling-bound TNFR1}}{\text{free surface TNFR1}},$$

from the latent to the active field at the macrophage's compartment p. Here f = `Core_Mac_tgfbActivationFraction` and C_lat(p) is the latent concentration before the transfer. The latent field loses A and the active field gains A, so total TGF-β is conserved. The signalling quantity is that of S6.4.

f is the fraction of the local latent pool activated in the absence of any TNF signal; the rest, $1 - f$, is recruited in proportion to TNF signalling.

Under the coarse option of M3, $s < 0.45$ (S6.4). The activated fraction therefore lies in $[f, f + 0.45(1 - f))$, within [0, 1] for any admissible f.

- **Only macrophage compartments activate.** Latent TGF-β secreted where no macrophage stands decays without becoming active, unless a macrophage later moves in.
- **At most one activation per compartment.** Macrophages are large, so no two share a compartment. Dendritic cells are held in a separate list that the routine does not iterate, so they never activate TGF-β.
- **Activation lags binding by one timestep.** Binding runs inside the diffusion loop and activation after it. Active TGF-β bound during timestep t was activated at the end of $t - 1$. Nothing secreted, activated and bound within one timestep reaches a cell.
- **Activation reads the post-diffusion TNF field** for the timestep, not the value at its start.

Under the ODE option a second activation term, `TGFB1kact`, acts in every fibroblast compartment on the molecular timestep (M4.7). It acts on the same two fields.

Under the fine-grained option of M3 the activated fraction is not clamped and can exceed 1. The transfer then leaves the latent field negative, and the inactive field has no cutoff (M4.2).

Binding of active TGF-β by cells

Binding is one routine shared by all agent types. It is called from each type's secretion routine in the split half-step. For a binding rate r and half-step dt it computes

$$b = \min(r\,dt,\ C_{\text{act}}(p))\ ,$$

decrements the active field at the agent's compartment by b, and adds b to the agent's cumulative bound TGF-β. Only the active species is bound. The rule is a zeroth-order flux capped by local availability, not a fractional uptake.

Binding entity	Rate parameter	Gate
Macrophage, not suppressed	`Core_Mac_tgfbBindingRate`	Module active
Tgam and Tcyt, cognate, not T0, any state including down-regulated	`Core_Tcell_tgfbBindingRate`	Module active
Treg, cognate, active	`Core_Tcell_tgfbBindingRate`	Module active
Active fibroblast	`Core_Fibroblast_tgfbBindingRate`	Coarse option only
Neutrophil	M9.7	—
Myofibroblast	None	—

Binding runs twenty times per cellular timestep (ten diffusion steps by two half-steps), each call capped separately. A compartment replenished between calls can therefore yield more over a timestep than one capped call would allow. Where two agents share a compartment, the macrophage binds before the T cell (spine 3.3), so it has priority on a depleted compartment.

The cumulative bound quantity

Every agent's cumulative bound TGF-β starts at zero and rises by binding. It is never decremented and never reset, on any transition. Daughters inherit it by cloning. Every threshold placed on it is therefore one-way: once crossed, it stays crossed. The thresholds are those of the macrophage factors (M4.4), the T cell proliferation gate and the Tcyt down-regulation (M4.4), and fibroblast proliferation and differentiation (M4.5, M4.6).

The macrophage and T cell binding rates are used as fluxes in molecules per second and are range-checked on [0, 1], which caps them at 1 molecule/s, 600 per cellular timestep (M4.9). Under the ODE option a fibroblast's cumulative quantity is written by the ODE system in other units (M4.7), while macrophages and T cells still accumulate in molecules. The neutrophil binding rate is range-checked the same way (M9.10.1).

M4.4 Effects on macrophages and T cells

Summary. Cumulative bound TGF-β lowers a resting macrophage's killing probability and every macrophage's TNF secretion, each to a floor of one half. In T cells it gates proliferation, with a floor of zero, and down-regulates a cytotoxic T cell once it exceeds a threshold.

Macrophage bacterial killing

The module lowers a resting macrophage's probability of killing, rather than taking up, the extracellular bacteria in its own compartment. The factor is computed in the resting handler, on the branch taken when the cell is not becoming activated, just before the killing decision of S2.5:

$$\phi_{\text{kill}} = \max\left(\frac{\texttt{Core_Mac_TGFBmax} - B}{\texttt{Core_Mac_TGFBmax}},\ 0.5\right),$$

with B the macrophage's cumulative bound TGF-β. S2.5 multiplies the base probability and its pro-inflammatory bonus alike by ϕ_{kill}. A failed killing draw means uptake and infection, so the reduction converts clearance into infection one for one.

- **It is ungated.** It is evaluated under every selection. Under the none option B is zero and ϕ_{kill} is exactly 1, but `Core_Mac_TGFBmax` is read on every resting call (S2.12). A zero value gives 0/0 and a killing probability that is not a number.
- **The floor is one half.** The module can halve innate clearance but not abolish it.
- **Only the resting state is affected.** Activated intracellular, own-compartment and caseum killing, and infected uptake, are unchanged.

Because B never falls, a macrophage's killing probability declines monotonically over its life toward the floor and never recovers.

Macrophage TNF secretion

Inside the shared TNF secretion helper, on the module-active branch, the state factor σ is replaced by

$$\sigma' = \max\big(\sigma\,\phi_{\text{TNF}},\ 0\big), \qquad \phi_{\text{TNF}} = \max\left(\frac{\texttt{Core_Mac_TGFBmax} - B}{\texttt{Core_Mac_TGFBmax}},\ 0.5\right).$$

σ is the S6.13 TNF state factor (0, 0.5 or 1.0).

σ' feeds the TNF field increment and the synthesis and messenger rates handed to M3. This coupling is gated: under the none option the factor passes through unchanged and the parameter is not read here.

T cells are exempt. Every T cell caller passes the none option to the shared helper in place of the actual selection. The rationale is that TGF-β does not affect T cell TNF secretion. A reimplementation should preserve this asymmetry.

The two macrophage couplings move together but are computed separately. They share parameter and form, so a macrophage that has lost half its killing probability has also lost half its TNF secretion. The killing factor is computed once per timestep in the next-state pass; the secretion factor twenty times per timestep in the half-step. Binding changes B between the secretion calls, so a reimplementation may not compute one factor per timestep and reuse it.

T cells

Gating of proliferation

With the module active, the T cell proliferation check opens with a draw. The routine returns at once unless U(0,1) < p, with

$$p = \max\left(\frac{\texttt{Core_Tcell_TGFBmax} - B}{\texttt{Core_Tcell_TGFBmax}},\ 0\right).$$

The floor is zero, so proliferation can be blocked entirely. A zero `Core_Tcell_TGFBmax` divides by zero.

The gate precedes both branches of S3.5, division and stimulation. A failed draw therefore stops a stimulated cell from dividing and an unstimulated cell from becoming stimulated. The probability falls over a cell's life, and daughters inherit B, so a lineage founded by an exposed cell starts suppressed.

`Core_Tcell_TGFBmax` is read nowhere else.

Down-regulation of cytotoxic T cells

At the end of the active Tcyt handler, after the cytotoxic killing attempt of S3.9:

```
if module active and cumulative bound TGF-beta > Core_Tcell_Tcyt_tgfbDownRegThreshold:
    next state <- down-regulated
    deactivation time <- t
```

The comparison is strict. The transition is deterministic once the threshold is crossed, unlike Treg suppression. Both routes use the same state, timer and recovery rule (S3.10).

Because the quantity tested never falls, the result is a cycle. The cell recovers after the suppression interval, spends one timestep active, is re-tested at the end of that timestep and is down-regulated again. With the interval at 36 timesteps, a cell that crosses the threshold early spends 36 of every 37 timesteps, over 97 per cent of its remaining life, down-regulated. Each recovery allows one killing attempt at full probability, since the attempt precedes the test.

While down-regulated the cell neither kills nor secretes TNF, and its proliferation timer is paused; it still moves, ages, binds TGF-β and can die by TNF-induced apoptosis (S3).

Tgam and Treg have no such threshold.

M4.5 Fibroblasts

Summary. Fibroblasts are large agents placed at initialization and never recruited. Active fibroblasts have no death route except caseation, and they multiply by proliferation gated on bound TGF-β, bound IL-10 and local TNF. Active fibroblasts move by an unbiased random walk, and fibroblasts of both states bind IL-10 by a rule of their own.

The fibroblast entity

States

A single fibroblast class has the states active, myofibroblast and dead, and one agent type. A myofibroblast is a fibroblast in the myofibroblast state. There is no separate class, list, type or size class. Every per-type facility treats the two states as one type; the in-granuloma counts distinguish them by state (M4.8).

Size and admission

Fibroblasts are large agents. Their admission predicate is that of the macrophage: not caseous, fewer than two occupants, and no large agent present. Movement and admission use the same test. A fibroblast and a macrophage therefore exclude each other, and a fibroblast may share a compartment with one T cell.

State variables

Beyond the common agent variables (spine 2.3), a fibroblast carries:

Variable	Initial value	Meaning
State, next state	As created	Hybrid update (spine 2.3)
Differentiation time	0	Timestep of differentiation; reference for myofibroblast death
Proliferation time	|birth time|, or -1 if created as a myofibroblast	Timestep at or after which a daughter may be produced; -1 means never
Division count	0	Divisions accrued; never capped or read
Cumulative bound IL-10	0	IL-10 bound since entry (IL-10 binding)
Cumulative aSMA	0	Drives differentiation (M4.6)
Free surface receptors R	`Molecular_TGFB_Fibroblast_initTGFB1R`	ODE (M4.7)
Internalized free receptors R_i	`Molecular_TGFB_Fibroblast_initTGFB1Rint`	ODE
Surface complexes C	`Molecular_TGFB_Fibroblast_initTGFB1R_TGFB1A`	ODE
Internalized complexes C_i	`Molecular_TGFB_Fibroblast_initTGFB1R_TGFB1Aint`	ODE
Internalization record N	0	ODE
Internalized IL-10 I_i	0	ODE

The four ODE initial conditions are read at the construction of every fibroblast, under either active option (no fibroblast exists under the none option), so a fibroblast created under the coarse option carries receptor counts it never uses.

Construction

The common agent constructor receives the macrophage TNFR1, TNFR2 and IL-10 receptor parameters and a TNF synthesis rate of zero. Each fibroblast therefore makes the construction draws of S6.3 from the macrophage distributions; the values are never read.

`Core_Fibroblast_maxAge` sets a stored death time that is never tested.

The coarse receptor-sink routine and the deactivation routine are no-ops for a fibroblast, so Treg suppression has no effect on it. Fibroblasts are absent from the receptor-sink loop of S6.8, so they take no TNF or IL-10 receptor sink. Their only chemical sinks are TGF-β binding (M4.3) and IL-10 binding.

Death routes

An active fibroblast has no intrinsic death route. Its next-state computation tests neither the death time nor TNF-induced apoptosis, and its handler never sets dead. Only caseation removes it.

Route	Applies to	Increments the killing count
Senescence, TNF-induced apoptosis	Neither state	—
Treg suppression	Neither state; no-op	—
Fas-mediated or cytotoxic killing	Neither state; T cells target macrophages only	—
Caseation, threshold and entrapment sweeps (S5.3, S5.4)	Both states	Yes, once per agent killed
Apoptosis proxy (M4.6)	Myofibroblast only	No

Fibroblasts are exempt from neither caseation sweep.

Initialization

Fibroblasts are never recruited. During a run, only proliferation adds them (Proliferation). At initialization they enter by two routes, both gated on the module; under the none option Init-section fibroblast and myofibroblast entries are ignored with a warning and make no draw.

- **Init-section entries.** `Fibroblast` and `Myofibroblast` entries take a position in the usual forms (spine 5.4), and each creates one cell in the corresponding state.
- **Random placement.** It follows the resting macrophages, the initial cognate Tgam and the dendritic cells, and precedes the neutrophils (spine 5.4). `Core_Fibroblast_initNumber` active fibroblasts are placed by rejection sampling under the admission predicate. The count is computed from `Core_Fibroblast_initDensity` (spine 7.0, "Computed parameters"). Startup fails if it exceeds the compartments left.

By either route the birth time is drawn uniformly from $\{-144, \dots, 0\}$, to desynchronize the population. This differs from the macrophage convention (spine 5.3) and does not read the lifespan parameter.

Initial proliferation time

The constructor sets the proliferation time to the absolute value of the birth time. An initial cell born at -100 cannot proliferate until timestep 100, about 17 hours into the run. One born at -144 waits until timestep 144, one day. One born at 0 may proliferate at once. The initial population thus enters the proliferative programme staggered by a delay equal to each cell's initial age, so the oldest cells wait longest.

A fibroblast constructed during a run, with a positive birth time, would be eligible at once. None is constructed in a run: daughters are clones (Cloning). A cell created as a myofibroblast gets proliferation time -1.

Cloning

Cloning is a plain copy. A daughter inherits every cumulative quantity, the receptor state and the division count, and gets a new identifier, birth time and position.

Movement

Fibroblasts move once per cellular timestep, after the T cells, gated on the module (S1.1). Movement is limited by a per-timestep probability, not by an age interval, and the two states move by different rules:

```
draw r
if r >= Core_Fibroblast_probMove:
    return
if active:
    destination <- uniformly random periodic Moore ordinal
else if myofibroblast:
    destination <- chemotactic destination (S1.3), all three chemokines, bonus factor 1
if the fibroblast admission predicate admits the destination:
    move there
```

Active fibroblasts do not chemotax. An active fibroblast picks one of the nine ordinals uniformly, its own included, reading no field. Its movement is an unbiased random walk slowed by the probability gate.

Myofibroblasts chemotax on all three chemokines, through the S1.3 routine with all three sensitivities set and a bonus factor of 1, so the gradient-sharpening term is inactive. The rationale is that fibrosis is late, so chemotaxis waits for differentiation. S1.3 states how this compares with sensing CCL2 alone.

Movement and proliferation use different predicates. Movement tests caseation, the slot count and a large agent. Daughter placement uses the shared helper, which tests caseation and free slots (Destination and deferred placement). They agree for a two-slot request, but they are different tests.

Proliferation

Only active fibroblasts proliferate. The check opens the next-state computation, before the state switch. Its outcome is passed to the active handler, because a cell that proliferates on a timestep cannot differentiate on it (M4.6).

The gate

A daughter is produced only if all of these hold:

Condition	Form
Not barred	Proliferation time $\neq -1$
Timer elapsed	$t \geq$ proliferation time
TGF-β sufficient	Cumulative bound TGF-$\beta \geq$ `Core_Fibroblast_TgfbProlifThreshold`
IL-10 not excessive	Cumulative bound IL-10 < `Core_Fibroblast_IL10ProlifMax`
TNF sufficient	TNF(p) $\geq$ `Core_Fibroblast_TNFThreshold`
Draw succeeds	U(0,1) < p_prolif
Destination available	A periodic Moore compartment with two free slots, not caseous

with

$$p_{\text{prolif}} = \frac{\texttt{Core_Fibroblast_IL10ProlifMax} - \text{cumulative bound IL-10}}{\texttt{Core_Fibroblast_IL10ProlifMax}}.$$

p_prolif is not clamped, but the IL-10 condition makes the numerator positive and the cumulative quantity is non-negative, so p_prolif lies in (0, 1] whenever the draw is reached. The program does not check the denominator; a zero ceiling makes proliferation impossible and is accepted.

The TGF-β and IL-10 conditions are on cumulative quantities and are one-way: a cell that has bound enough TGF-β satisfies its condition for good, and one that has bound too much IL-10 can never proliferate again. The TNF condition reads the current field and can flip. A daughter inherits both cumulative quantities.

When the draw fails, the fibroblast entry of the deferred-proliferation statistic is incremented. When the draw succeeds but no destination is found, it is not (M4.8).

Destination and deferred placement

The destination comes from the shared placement helper of S3.5, asked for two free slots. Two slots means a wholly empty compartment, so the parent's own compartment never qualifies.

The daughter is appended to the fibroblast proliferation list, which is drained after all next states, under the commitment rule of spine 3.3 and S5. A daughter promised to a compartment that has since become caseous is discarded, with an increment of the killing count; otherwise it is placed. A daughter does not act on its creation timestep.

The daughter gets a new identifier, birth time t and the chosen position. It inherits the active state, the division count including this division, the death time, the cumulative quantities, the receptor state, and the parent's proliferation time as just reset.

Proliferation is unlimited

On success the parent sets its proliferation time to t + `Core_Fibroblast_proliferationTime` and increments its division count. The count is never capped, unlike the T cell rule of S3.5. It is inherited, so it records lineage depth, but no rule reads it and no statistic reports it. With no death route for an active fibroblast (Death routes), the active population is bounded only by space and caseation.

The first successful proliferation sets a simulation flag that is never cleared (M4.8).

IL-10 binding

Fibroblasts and myofibroblasts remove IL-10 by a rule of their own, outside the receptor sink of S6.8. Under the coarse option it is their only effect on IL-10.

The rule

Once per cellular timestep, in the state handler, a fibroblast computes

$$b = \min(\texttt{Core_il10BindingRate} \cdot \Delta t_a,\ C_{\text{IL-10}}(p))\,,$$

with $\Delta t_a = 600$ s. It decrements the IL-10 field at its compartment by b and adds b to its cumulative bound IL-10. Like TGF-β binding, this is a zeroth-order flux capped by availability. `Core_il10BindingRate` is read by this rule alone.

Cadence and placement

The rule runs in the next-state pass, once per timestep with the full timestep as its duration. It is the only chemical sink in the model applied at cellular cadence.

- It acts after the diffusion loop. It is first felt by the next timestep's secretion, suppression and STAT3 rules; within the current pass, only agents processed later see it (other fibroblasts, and neutrophils, M9.1).
- Where supply is ample it removes the same total as a half-step sink. In a depleted compartment it removes only what is present after the loop, whereas a half-step sink would share each replenishment.

State	Placement	Consequence
Active	First action of the active handler, after the proliferation check and before the differentiation gate	Proliferation reads cumulative IL-10 as it stood at the end of the previous timestep; the differentiation gate does not read it at all
Myofibroblast	After the death test	A myofibroblast dying on a timestep does not bind on it
Dead	Not called	—

A myofibroblast keeps binding IL-10, although nothing reads its cumulative value.

Under the ODE option

The rule still runs, gated on state only. The ODE system also depletes IL-10 through its variable I and accumulates bound IL-10 into the same cumulative quantity through B_I (M4.7).

M4.6 Differentiation and myofibroblasts

Summary. An active fibroblast differentiates irreversibly into a myofibroblast with a probability proportional to its cumulative aSMA, which only the ODE option writes. Myofibroblasts chemotax, secrete collagen up to a ceiling, and die by an age-and-probability rule that does not increment the killing count.

Differentiation

Differentiation is the module's one irreversible transition. It is evaluated in the active handler, after the proliferation check.

The gate

The next state defaults to active. Differentiation is attempted only if all of these hold:

Condition	Form
Did not proliferate this timestep	—
TGF-β sufficient	Cumulative bound TGF-$\beta \geq$ `Core_Fibroblast_myoBoundTGFBThreshold`

Condition	Form
TGF-β dominant over IL-10	$\rho(p) \geq$ `Core_Fibroblast_myoTGFBIL10Threshold`
TNF sufficient	TNF(p) $\geq$ `Core_Fibroblast_TNFThreshold`

A draw is then made against p_diff. On success the cell sets its differentiation time to t, its proliferation time to -1 and its next state to myofibroblast.

Proliferation takes precedence: a cell that divides cannot differentiate on the same timestep. Both processes use the same TNF threshold. The TGF-β condition is one-way; the ratio and TNF conditions read current fields and can flip.

The ratio

$$\rho(p) = \begin{cases} C_{\text{act}}(p) \,/\, C_{\text{IL-10}}(p) & C_{\text{IL-10}}(p) \neq 0 \\ C_{\text{act}}(p) & C_{\text{IL-10}}(p) = 0 \end{cases}$$

At exactly zero IL-10, ρ is the raw active TGF-β count rather than a ratio, and the threshold is compared with whichever it is. The test is exact equality, and the concentration cutoff sets IL-10 to exactly zero wherever it falls to 10^{-12} or below (M1.3, "Normalisation and the cutoff"), so the count branch is the common one.

The probability

$$p_{\text{diff}} = \texttt{Core_Myofibroblast_differentiation_Slope} \cdot \frac{\text{cumulative aSMA}}{\texttt{Core_Fibroblast_maxASMA}}.$$

The expression is not clamped to [0, 1]. Under the ODE option, the only option under which cumulative aSMA is written at all, aSMA is an ODE variable with no ceiling (M4.7). Its ratio to `Core_Fibroblast_maxASMA` can therefore exceed 1, and the probability is bounded only by the slope and the steady state of the aSMA equation. A product above 1 makes differentiation certain on every timestep on which the gate holds; a slope of zero makes it impossible. The slope has no declared unit or range.

The aSMA quantity

Cumulative aSMA is written only by variable S of the ODE system (M4.7), on every molecular substep under the ODE option. The source also holds an algebraic aSMA routine, which nothing calls.

Under the coarse option, therefore, nothing writes aSMA. It starts at zero and is inherited as zero, so p_diff is identically zero. No fibroblast differentiates, no collagen is secreted, and fibroblasts die only by caseation. Differentiation, myofibroblast behaviour and collagen are reachable only under the ODE option.

Myofibroblast behaviour and death

A myofibroblast chemotaxes (M4.5), secretes collagen and may die. It neither proliferates nor reverts.

Collagen secretion

In the split half-step, with dt the half-step and C_col(p) the local collagen,

$$\Delta = \min(\texttt{Core_Myofibroblast_maxCollagen} - C_{\mathrm{col}}(p),\ \ \texttt{Core_Myofibroblast_dCollagen} \cdot dt)\,.$$

Local collagen therefore rises at the nominal rate until it reaches the ceiling exactly, in a finite number of steps.

Collagen undergoes neither transport nor decay, but only the writes to the buffer current at the end of the diffusion loop survive (M4.2). The surviving value therefore accumulates at half the nominal rate, reads its headroom from that buffer, and never falls; it records myofibroblast occupancy. Two myofibroblasts cannot share a compartment, so the ceiling is approached by successive occupants.

No TGF-β secretion or binding

A myofibroblast neither secretes latent nor binds active TGF-β. Its secretion branch writes collagen only, and its cumulative bound TGF-β is frozen at its value on differentiation. `Core_Myofibroblast_tgfbBindingRate` is read by no live code.

Death

At the start of the myofibroblast handler:

```
age <- t - differentiation time
draw r
if age >= Core_Myofibroblast_deathAgeThreshold and r <= Core_Myofibroblast_deathProb:
    next state <- dead
    return
```

Age is measured from differentiation, not birth. Once eligible, a myofibroblast dies with constant probability per timestep, so its residual life is geometric with mean 1/`Core_Myofibroblast_deathProb` timesteps. This is the lineage's only death route besides caseation.

Like non-activated macrophage senescence and T cell senescence (S5.2), this death does not increment the count. As with them, entrapment on the same timestep re-kills the cell and charges one increment (S5.4).

M4.7 The ODE option: fibroblast receptor system

Summary. Under the ODE option each fibroblast integrates a twelve-variable system of TGF-β receptor binding, internalization, aSMA production and IL-10 uptake. It replaces coarse fibroblast binding and secretion, adds a second activation route in fibroblast compartments, and is the only writer of aSMA.

It is the only per-agent ODE system outside M3. No agent ODE is solved in the default configuration (spine 2.2).

Invocation

The system is solved in the molecular substep loop of the split half-step, after the S6.8 sink, once per fibroblast per substep, with step Δt_m. Each fibroblast is advanced through $N_d N_m \Delta t_m = \Delta t_a$ per cellular timestep ($10 \times 10 \times 6$ s). The loop covers every listed fibroblast: myofibroblasts and dead-flagged cells are integrated too, since the system tests no state.

Each call loads the state from the agent and from three fields at its compartment, takes one step of the global ODE method shared with M3 (M3.2), and writes every variable back, the three fields by assignment.

The fibroblast uses the base-class stepper, shared with T cells. Under the fine-grained option of M3 with the ODE option, both use work arrays sized for whichever system first creates the stepper (M3.2).

State vector

Variable	Loaded from and written to	Meaning
L	Inactive TGF-β field	Latent ligand
A	Active TGF-β field	Active ligand
R	Fibroblast	Free surface receptor
R_i	Fibroblast	Internalized free receptor
C	Fibroblast	Surface receptor–ligand complex
C_i	Fibroblast	Internalized complex, current
N	Fibroblast	Internalization record
S	Cumulative aSMA	Alpha smooth muscle actin
I	IL-10 field	Soluble IL-10
I_i	Fibroblast	Internalized IL-10
B_T	Cumulative bound TGF-β	Bound TGF-β
B_I	Cumulative bound IL-10	Bound IL-10

Right-hand sides

The constants are in group `Molecular_TGFB_Fibroblast`: k_s `TGFB1ksynth`, k_a `TGFB1kact`, k_is `TGFB1kis`, k_on `TGFB1kon`, k_d `TGFB1kdis`, v_R `TGFB1Rsynth`, k_Ri `TGFB1Rint`, k_Ci `TGFB1RAint`, k_r `TGFB1rec`, k_Rd `TGFB1Rdeg`, k_ℓ `TGFB1Rlid`, k_N `tgfbintdeg`, a `adact`, σ `stiff`, α_1 `alpha1`, α_2 `alpha2`, k_S `complexdeg`, k_I `IL10bind`, k_Ii `IL10complexdeg`. V and N_A are the compartment volume and Avogadro's number (spine 2.1).

$$
\begin{aligned}
\dot{L} &= \frac{k_s}{V} - k_a L + \frac{k_{is}\, C_i}{N_A V} \\
\dot{A} &= k_a L - \frac{k_{on} A R}{N_A} + \frac{k_d\, C}{N_A V} \\
\dot{R} &= v_R - k_{on} A R V + k_d C - k_{Ri} R + k_r (R_i + C_i) \\
\dot{R}_i &= k_{Ri} R - (k_r + k_{Rd}) R_i \\
\dot{C} &= k_{on} A R V - (k_d + k_{Ci}) C \\
\dot{C}_i &= k_{Ci} C - (k_r + k_\ell + k_{Rd}) C_i \\
\dot{N} &= k_{Ci} C - k_N N \\
\dot{S} &= a\, \sigma\, \frac{\alpha_1}{I_i + \alpha_2}\, N - k_S S \\
\dot{I} &= -k_I I \\
\dot{I}_i &= k_I I\, N_A V - k_{Ii} I_i \\
\dot{B}_T &= \frac{k_{on} A R}{N_A} \\
\dot{B}_I &= k_I I
\end{aligned}
$$

While TGF-β depletion holds, k_s and k_is are set to zero for the call. The receptor, actin and IL-10 equations are unchanged.

Units and bookkeeping

The soluble variables are loaded from and written to fields stored in molecules per compartment, with no conversion; the cell variables are counts per cell (M4.9).

Ligand bookkeeping is not conservative. Recycling returns receptor to R, but internalized ligand returns to neither soluble pool and is lost. Ligand re-enters only through the synthesis term k_is C_i.

Neither soluble TGF-β species degrades within the system, only in the M4.2 step. `TGFB1kdegl` and `TGFB1kdega` have no effect.

Properties

- **Concurrent activation.** k_a L activates latent TGF-β in every fibroblast compartment on every substep. These compartments are disjoint from the macrophage compartments of M4.3. A compartment holding neither activates nothing.
- **N is not cumulative.** It decays at rate k_N, so it is a leaky integrator of the internalization flux, relaxing toward k_Ci C/k_N. Differentiation therefore follows recent, not lifetime, receptor engagement.
- **aSMA is uncapped** under this option (M4.6).
- **IL-10 inhibits actin** through $\alpha_1/(I_i + \alpha_2)$. This and the ratio test of M4.6 are its only routes to differentiation under this option.
- **Field writes.** Each call assigns three fields at the fibroblast's compartment. At most one fibroblast stands in a compartment, so list order does not matter.
- **Accumulators.** B_T is the integral of k_on A R / N_A on fields held in molecules, and B_I the integral of k_I I, with I in molecules per compartment; the coarse accumulation of M4.3 is in molecules.

M4.8 Granuloma definition and observation

The fibroblast-proliferation flag and the membership freeze

The module carries one simulation flag recording that fibroblast proliferation has begun. It starts false, is set by the next-state computation of the first fibroblast to proliferate successfully, is never cleared, and is saved with the simulation state. It is set when the placement helper finds a destination, even if the daughter is later discarded (M4.5). Deterministic placement never sets it.

What the flag does

In the per-compartment sweep of the statistics block, the stored granuloma membership flag is written only while the flag is false:

```
for each compartment p:
    member <- cell density(p) >= threshold or caseous(p)
    if fibroblast proliferation has not begun:
        stored membership(p) <- member
```

Once the flag is set, every compartment's stored membership is frozen at its last value. The statistics block follows the next-state pass in which the flag is raised, so the timestep of the first proliferation is already frozen. Nothing is added or removed afterwards. The rationale is that density from fibroblast proliferation is fibrosis, not granuloma.

What the flag does not do

Only the pre-fibrosis counts read the stored membership (What the flag does). The in-granuloma counts, the M6 partition of drug totals and the cell-density extent behind the lesion volume evaluate the membership predicate afresh (S9.4). They are not frozen, and they grow with fibroblast density. No agent rule reads the stored membership, so the freeze is observation only.

In the default configuration the flag is never set. The pre-fibrosis counts equal the unrestricted ones, and `NrOfMacsInPreFibrosisGran` is populated and equal to `NrOfMacsInGran`.

Statistics

The module populates these statistics. Reset codes are those of S9: 0 cumulative, 1 reset each timestep, 2 rebuilt in the agent pass. All are zero in the default configuration except where marked.

Statistic	Reset	Content
`NrOfAgents`, fibroblast entry	2	Live fibroblasts of both states
`NrOfFibroblasts`, per state	2	Counts in each state
`NrOfFibrosUnscaled`, per state	2	Within the connected-region bounding circle

Statistic	Reset	Content
`NrOfFibrosScaledRing`, `FibrosScaledRingFactor`, per state	2	Ring-scaled count and realized factor (S9)
`NrOfFibrosScaledExtent`, per state	2	Scaled by the fibroblast extent factor (S9)
`FibroblastCaseationRec`	1	Fibroblasts in caseous neighbourhoods
`Proliferated`, fibroblast entry	2	Daughters produced this timestep
`DeferredProliferation`, fibroblast entry	2	Failed proliferation draws (M4.5)
`TotTGFBActive`, `TotTGFBInactive`, `collagen`	1	Whole-grid field totals
`NrOfFibroblastsInGran`, `NrOfMyoFibroblastsInGran`	1	By state, in compartments meeting the membership predicate
`NrOfFibroblastsInPreFibrosisGran`, `NrOfMyoFibroblastsInPreFibrosisGran`	1	By state, in the frozen region
`NrOfMacsInPreFibrosisGran`	1	Macrophages in the frozen region; populated in the default configuration, equal to `NrOfMacsInGran`

The fibroblast extent, its diameter and its scaling factor are specified in S9.

Not populated. The cumulative proliferation, maximum-division, blocked-movement and recruitment entries exist for fibroblasts but are never incremented, and there is no cumulative fibroblast count. No statistic records differentiations or myofibroblast deaths. Differencing the per-state counts at the daily output cadence confounds them with proliferation and caseation.

M4.9 Parameters

The module's parameters are in five groups: `Core`, the existing cell-type groups, `Core_Fibroblast`, `Core_Myofibroblast` and `Molecular_TGFB_Fibroblast`. None is sampled by default and none has a declared default, so each must be supplied (spine 7.0, "Resolution"). Values are not reported, except the three field constants, since the module is not selected by default; a study selecting it reports its own.

Only the parameters declared on [0, 1] are range-checked: `Core_Mac_tgfbActivationFraction`, `Core_Mac_tgfbBindingRate`, `Core_Tcell_tgfbBindingRate`, `Core_Neutrophil_tgfbBindingRate` (M9.10.1), `Core_Fibroblast_initDensity`, `Core_Fibroblast_probMove` and `Core_Myofibroblast_deathProb`. A declaration with minimum 0 and no maximum is not checked (spine 7.0, "Validity ranges"). Several declared units differ from the units in which the program uses the values (M4.3, M4.7); the Units columns give the declared units verbatim, with the units of use noted where they differ.

General and effector parameters

M1.6 refers to this table for `Core_diffusivityTGFBActive`, `Core_degRateTGFBActive` and `Core_degRateTGFBInactive`.

Identifier	Value or range	Units	Meaning
`Core_diffusivityTGFBActive`	5.2×10^{-8}	cm^2/s	Diffusivity of active TGF-β (M4.2), and of the unused inactive propagator (M1.3); read under every selection
`Core_degRateTGFBActive`	1.58×10^{-3}	1/s	Degradation of active TGF-β, folded into the solver; read under every selection
`Core_degRateTGFBInactive`	1.58×10^{-5}	1/s	Pointwise decay of inactive TGF-β (M4.2); read under every selection
`Core_tgfbSecretionReductionInterval`	—	timesteps	Duration of halved macrophage latent secretion after Tgam proximity (M4.3)
`Core_il10BindingRate`	—	molecules/s	Fibroblast IL-10 binding flux (M4.5)
`Core_Mac_dTGFBInactive`	—	molecules/s	Macrophage latent secretion (M4.3)
`Core_Mac_tgfbActivationFraction`	—	none declared	f, the activation floor (M4.3)
`Core_Mac_tgfbBindingRate`	—	declared fraction; used as molecules/s	Macrophage binding flux (M4.3)
`Core_Tcell_tgfbBindingRate`	—	declared fraction; used as molecules/s	T cell binding flux, all three types (M4.3)
`Core_Tcell_TGFBmax`	—	none declared	Ceiling of the T cell proliferation gate (M4.4)[1]
`Core_Tcell_Tcyt_tgfbDownRegThreshold`	—	none declared	Tcyt down-regulation threshold, strict (M4.4)
`Core_Tcell_Treg_dTGFBtreg`	—	molecules/s	Treg latent secretion (M4.3)

A "—" in the Value column marks a value not reported: the module is not selected by default, and a study selecting it reports its own.

`Core_Mac_TGFBmax`, the ceiling of both macrophage factors (M4.4), is tabled in S2.12, being read in every configuration. The neutrophil secretion and binding rates are tabled in M9.10.1.

Fibroblast and myofibroblast parameters

Identifier	Value or range	Units	Meaning
`Core_Fibroblast_maxAge`	—	timesteps	Sets a death time that is never tested (M4.5)
`Core_Fibroblast_initDensity`	—	none declared	Initial density (M4.5)
`Core_Fibroblast_initNumber`	0, computed	none declared	Initial count, computed from the density, overwriting any file value (M4.5)
`Core_Fibroblast_probMove`	—	none declared	Per-timestep movement probability, both states (M4.5)
`Core_Fibroblast_dTGFBInactive`	—	molecules/s	Latent secretion, coarse option only (M4.3)
`Core_Fibroblast_tgfbBindingRate`	—	molecules/s	Binding flux, coarse option only (M4.3)
`Core_Fibroblast_proliferationTime`	—	timesteps	Interval between divisions (M4.5)
`Core_Fibroblast_TgfbProlifThreshold`	—	none declared	Proliferation threshold on cumulative bound TGF-β (M4.5)
`Core_Fibroblast_IL10ProlifMax`	—	declared moles; compared with molecules	IL-10 ceiling and denominator of p_prolif (M4.5)[1]
`Core_Fibroblast_TNFThreshold`	—	molecules per compartment	TNF threshold for proliferation and differentiation (M4.5, M4.6)
`Core_Fibroblast_myoBoundTGFBThreshold`	—	none declared	Differentiation threshold on cumulative bound TGF-β (M4.6)
`Core_Fibroblast_myoTGFBIL10Threshold`	—	none declared	Threshold on ρ, a ratio or a count by branch (M4.6)
`Core_Fibroblast_maxASMA`	—	none declared	Denominator of p_diff; ODE option only (M4.6)[1]
`Core_Fibroblast_aSMAFactor`	—	molecules/cell	Read by no live code (M4.6)
`Core_Fibroblast_myoActivationThreshold`	—	molecules/cell	Read by no live code (M4.6)
`Core_Myofibroblast_dCollagen`	—	declared molecules/hour; multiplied by a step in seconds	Collagen secretion rate (M4.6)
`Core_Myofibroblast_maxCollagen`	—	molecules	Per-compartment collagen ceiling (M4.6)[2]
`Core_Myofibroblast_deathAgeThreshold`	—	timesteps; declared real	Minimum age since differentiation for death (M4.6)[3]

Identifier	Value or range	Units	Meaning
`Core_Myofibroblast_deathProb`	—	none declared	Per-timestep death probability once eligible (M4.6)
`Core_Myofibroblast_differentiation_Slope`	—	none declared; no range	Scale of p_diff; ODE option only (M4.6)[4]
`Core_Myofibroblast_tgfbBindingRate`	—	molecules/s	Read by no live code (M4.6)

A "—" in the Value column marks a value not reported: the module is not selected by default, and a study selecting it reports its own.

Under the coarse option every differentiation, myofibroblast and collagen parameter is without effect (M4.6).

Fibroblast receptor ODE parameters

The group `Molecular_TGFB_Fibroblast` has 26 entries and belongs to this module, not M3: no M3 routine reads it. Every entry is declared with minimum 0 and no maximum, so none is range-checked and a negative value is accepted. The four initial conditions are read under either active option; the rest only under the ODE option.

Identifier	Value	Declared units	Meaning (M4.7)
`initTGFB1R`	—	#/cell	R(0)
`initTGFB1Rint`	—	#/cell	R_i(0)
`initTGFB1R_TGFB1A`	—	#/cell	C(0)
`initTGFB1R_TGFB1Aint`	—	#/cell	C_i(0)
`TGFB1ksynth`	—	picoMoles	k_s, latent synthesis; enters as a rate; zeroed under depletion
`TGFB1kact`	—	picoMoles/min	k_a, latent-to-active conversion; first order
`TGFB1kon`	—	1/(picoMoles·min)	k_on, binding
`TGFB1kdis`	—	picoMoles/min	k_d, complex dissociation; first order
`TGFB1Rsynth`	—	Number/cell·min	v_R, receptor synthesis
`TGFB1Rint`	—	Number/cell·min	k_Ri, free-receptor internalization; first order
`TGFB1RAint`	—	Number/cell·min	k_Ci, complex internalization; first order

Identifier	Value	Declared units	Meaning (M4.7)
`TGFB1rec`	—	Number/cell·min	k_r, recycling; first order
`TGFB1Rdeg`	—	Number/cell·min	k_Rd, constitutive receptor degradation; first order
`TGFB1Rlid`	—	Number/cell·min	k_ℓ, ligand-induced degradation; first order
`TGFB1kis`	—	picoMoles/min	k_is, ligand-induced latent synthesis; first order on C_i; zeroed under depletion
`TGFB1kdegl`	—	picoMoles/min	No effect (M4.7)
`TGFB1kdega`	—	picoMoles/min	No effect (M4.7)
`tgfbintdeg`	—	number/cell·min	k_N, decay of N; first order
`adact`	—	no units	a, actin production scale
`stiff`	—	no units	σ, actin production scale
`alpha1`	—	no units	α_1, numerator of the IL-10 inhibition
`alpha2`	—	no units	α_2, its half-inhibition constant
`complexdeg`	—	number/cell·min	k_S, decay of S; first order
`IL10bind`	—	picoMoles/min	k_I, IL-10 uptake; first order
`IL10complexdeg`	—	number/cell·min	k_Ii, decay of I_i; first order
`IL10synth`	—	Number/cell·min	Read by nothing; the soluble IL-10 equation has no synthesis term (M4.7)

A "—" in the Value column marks a value not reported: the module is not selected by default, and a study selecting it reports its own.

Every time-dependent entry is declared per minute, and the system is integrated per second with no rescaling. `adact` and `stiff` enter only as their product, so they are not separately identifiable.

Constraints, constants and inert parameters

The startup consistency check imposes nothing on this module. None of these constraints is checked:

[1] `Core_Tcell_TGFBmax`, `Core_Fibroblast_IL10ProlifMax` and `Core_Fibroblast_maxASMA`, like `Core_Mac_TGFBmax`, must be strictly positive. Zero makes the T cell gate or p_diff divide by zero, or proliferation impossible.

[2] `Core_Myofibroblast_maxCollagen` must be non-negative; a negative ceiling makes the first collagen increment negative.

[3] `Core_Myofibroblast_deathAgeThreshold` is compared with an integer age, so a non-integral value acts as its ceiling.

[4] `Core_Myofibroblast_differentiation_Slope` must lie in [0, 1] for p_diff to stay a probability while aSMA stays below `Core_Fibroblast_maxASMA`; under the ODE option, with aSMA uncapped, no finite slope guarantees it. A negative slope makes p_diff negative.

Negative `Molecular_TGFB_Fibroblast` rates reverse the sign of their terms. With the fine-grained option of M3, the ODE option runs with the unclamped activation fraction (M4.3) and the shared stepper (M4.7).

The derivation of `Core_Fibroblast_initNumber` from `Core_Fibroblast_initDensity`, and the reverse derivation, follow spine 7.0, "Computed parameters".

Fixed structural constants: the macrophage secretion-reduction factor of one half (M4.3); the floors of one half on both macrophage factors and of zero on the T cell gate (M4.4); the IL-10 binding duration of 600 s (M4.5).

Read but without effect under every selection: `Core_Fibroblast_aSMAFactor`, `Core_Fibroblast_myoActivationThreshold`, `Core_Myofibroblast_tgfbBindingRate`, `TGFB1kdegl`, `TGFB1kdega`, `IL10synth`, and `Core_Fibroblast_maxAge`, which sets an untested death time. Appendix B indexes them.

M4.10 Interfaces

With	Provides or receives	See
Spine module-slot table	Provides the M4 summary and option summaries	M4.1
Spine 2.3	Receives the occupancy rules and the hybrid update; provides the fibroblast entity (one type, two live states, large)	M4.5
Spine 3.3	Receives the type order in which the effector couplings run, and the daughter-commitment rule	M4.1, M4.5
Spine 5.3, 5.4, 5.5	Receives the Init-section element order, position forms, placement-loop order and the field Init facility	M4.2, M4.5
Spine 7.0	Receives the omitted-entry rule (Resolution), the range-check rule (Validity ranges) and the computed-parameter rule (Computed parameters)	M4.9
S1	Receives the fibroblast's place in the movement order and the chemotactic routine with its gate, sensitivities and identical-distribution result	M4.5

With	Provides or receives	See
S2	Ungated killing reduction (S2.5, `Core_Mac_TGFBmax` in S2.12); gated TNF secretion reduction; latent secretion after the suppression early return; the Tgam-proximity halving	M4.3, M4.4
S3	Proliferation gate before stimulation and division (S3.5); Tcyt down-regulation sharing the S3.10 recovery rule; T cell TNF exemption; the shared placement helper; Treg suppression has no effect on fibroblasts	M4.4, M4.5
S5	Fibroblasts of both states die in both caseation sweeps and increment the count. The myofibroblast proxy death writes only the pending state, does not increment, and is re-killed by entrapment (S5.2, S5.4)	M4.5, M4.6
S6	Receives the signalling quantity (S6.4) and the TNF state factor (S6.13); fibroblasts take no receptor sink but bind TGF-β and IL-10 by their own rules; their receptor draws use the macrophage distributions	M4.3, M4.4, M4.5
S7	Fibroblasts do not consume oxygen but count toward cell density, so can close a source's oxygen gate (S7.4, S7.6)	M4.5
S8	No direct coupling; the TNF reduction lowers the field every recruitment probability reads. Fibroblasts are not recruitable. Receives the `probCognate` parameters	M4.3, M4.4
S9	Receives the statistic definitions, reset codes, extents and the membership predicate; provides the fibroblast statistics and the membership freeze	M4.8
M1	Advances the active field; copies forward and decays the inactive field; specifies the zero-diffusivity case and the unused inactive propagator (M1.3, "The propagator and incorporation of decay") and the buffering that collagen shares with oxygen (M1.3, "Non-transformed fields and grid buffering"). The smoother acts on the active field when its step count is non-zero (zero by default)	M4.2
M2	Fibroblasts are not recruitable under either option	M4.5
M3	Supplies the TNF signalling quantity: activation is bounded under the coarse option and unbounded under the fine-grained one. The ODE option shares M3's global ODE method and the base-class stepper	M4.3, M4.7
M5	Sets occupancy limits and Moore neighbourhood sizes. The three-dimensional fibroblast and diffusion paths are not specified in this document	M4.5
M6	The drug-total partition reads the membership predicate, not the frozen flag	M4.8
M7	No coupling	—
M8	Supplies TGF-β depletion, which suppresses latent secretion and ODE synthesis but not binding	M4.3, M4.7

With	Provides or receives	See
M9	Neutrophil TGF-β secretion, binding and depletion (M9.7); neutrophils in caseation (M9.8); the neutrophil binding-rate declaration (M9.10.1)	M4.3, M4.5
Appendix B	Indexes the selection option, the gate rows (linking M4.1) and the inert parameters	M4.1, M4.9