M7. Immunomodulation module

M7.1 Slot

Module slot M7 represents systemic administration of four agents: exogenous TNF, exogenous IL-10, and the anti-TNF antibodies Etanercept and Infliximab. The slot has two options, selected on the command line (M7.2).

Option	Selected by	Summary
Off	`--immuno-mod` absent	No dose, delivery, transport or membrane binding takes place. The module's state is carried and, unless a drug field is initialized from the parameter file, stays zero, so host behaviour is identical to a build without the module (M7.11).
On	`--immuno-mod` present; each agent selected by a nonzero dosage	Each dosed agent has a scalar blood concentration, subject to dosing and first-order clearance, and is delivered from blood to tissue at eligible vascular sources. Exogenous TNF and IL-10 are added to the host TNF and IL-10 fields. The antibodies have six grid fields of their own, are transported and decayed, and bind soluble TNF in tissue and, under some M3 configurations, membrane TNF on cells.

The default configuration does not select the module (spine 7.14, module-slot table). The rest of this document specifies the "on" option for a study that selects it.

Exogenous TNF and IL-10 have no grid state of their own. They are delivered into the existing TNF and IL-10 fields (spine 2.4), after which no rule and no statistic can distinguish them from secreted cytokine. The two antibodies carry six fields of their own (M7.3).

Position in the cellular timestep

The module occupies these blocks, in the order in which they execute within one diffusion step.

Block	Location	Specified in
Membrane binding	Molecular substeps of each split half-step, inside the per-agent ODE solve	M7.8; M3.2
Dosing, clearance and vascular delivery	Each split half-step, after antibiotic delivery and before oxygen delivery	M7.4, M7.5; spine 3.2
Smoothing of drug fields	End of each split half-step, spectral solver only	M7.6; M1.3
Transport and decay of drug fields	Diffusion solve, after all host fields	M7.6; M1
Soluble binding	Diffusion solve, after every field has been advanced and before the grids are exchanged	M7.7
Observation	After each vascular delivery, and in the statistics block	M7.10; S9

The skeleton places these blocks within the diffusion loop. It shows only the operations that M7 adds or depends on; spine 3.2 gives the full loop.

```
for diffusionStep k = 0 .. N_d - 1:

    first split half-step (k, substeps 0 .. N_m/2 - 1)

    diffusion solve:                                        // M1
        advance host fields
        advance antibiotic fields if drugs are active       // M6
        if switch on and t >= Mod_dosageStartTime:
            advance the six drug fields                     // M7.6
        soluble binding on the next grid                    // M7.7
        exchange current and next grids

    second split half-step (k, substeps N_m/2 .. N_m - 1)

split half-step (k, substeps):
    secretion, oxygen consumption, antibiotic uptake
    for each substep:
        per-agent ODE solve if any M3 ODE is enabled,
            with membrane binding terms if the antibody is added   // M7.8
        receptor-occupancy sink terms
    antibiotic delivery if drugs are active                 // M6
    if switch on and t >= Mod_dosageStartTime:
        dosing, delivery, clearance (dt_d / 2, t, k)        // M7.4, M7.5
        record blood concentrations                         // M7.10
    oxygen delivery                                         // S7
    smoother                                                // M1.3, M7.6
```

Soluble binding lies inside the diffusion solve, so spine 3.2 shows no separate line for it. It operates on the next grid after transport has been applied to every field in that diffusion step, and therefore sees TNF already diffused and degraded for the full Δt_d.

Reads and writes

- **Reads:** t and k; the four blood concentrations; the vascular source list in its current order; cell density and caseation at each source; TNF, IL-10, Etanercept and Infliximab on the boundary-clipped Von Neumann neighbourhood of each source; TNF and the six drug fields at every compartment; per-agent membrane TNF, TACE rate and membrane-complex variables; the `Mod` parameters, `Core_kDeg`, the selected solver's Δt_d, and the master switch.
- **Writes:** the four blood concentrations; TNF and IL-10 at sources (delivery); Etanercept and Infliximab at sources (delivery); the six drug fields (transport, decay, soluble binding; free-drug and soluble-complex fields at an agent's compartment by membrane binding); TNF at every compartment (soluble binding); per-agent membrane TNF and membrane-complex variables; the anti-TNF statistics group.

No component needs a nested description in the sense of Grimm et al., paragraph 4.10: the blood compartment is four scalars advanced by an explicit update (M7.4), and the membrane terms add at most ten variables to the per-agent ODE system of M3 (M7.8).

M7.2 Selection and gating

Master switch

The module is selected by the command-line option `--immuno-mod`, which takes no value. Its presence sets a Boolean held by the simulation object and written with the saved state. No parameter-file entry controls it. On resumption the command-line value replaces the saved value, with a warning if they differ (spine 7.0).

Agent selection

Beneath the switch, each agent is selected by its own dosage parameter: `Mod_TNF_dosage`, `Mod_IL10_dosage`, `Mod_Etanercept_dosage` and `Mod_Infliximab_dosage`. Any combination may be selected. Dosing begins at `Mod_dosageStartTime`, common to all four agents; M7.12 gives the first-dose timing when it is zero.

The dosage tests are not uniform. Some hooks test for a nonzero dosage and others for a positive one. The two coincide for any non-negative value and differ only for a negative dosage. Negative dosages are not rejected: each dosage is declared with a minimum of zero and no maximum, which builds no range check (spine 7.0, Validity ranges).

Gates by hook

"Switch" means the master switch; "started" means $t \geq$ `Mod_dosageStartTime`.

Hook	Gate	Remarks
Dose addition and blood clearance	Switch and started	Executed for all four agents whether selected or not; an unselected agent receives a dose of zero
Vascular delivery of one agent	Switch, started, and that agent's dosage nonzero	Tested separately at each source
Transport and decay of the six drug fields	Switch and started	Same gate in all three solvers and in the spectral smoother
Soluble binding, Etanercept	`Mod_Etanercept_dosage` nonzero	Every diffusion step from the first, independent of the switch and of time
Soluble binding, Infliximab	`Mod_Infliximab_dosage` nonzero	As for Etanercept
Membrane binding, each antibody	Switch, that antibody's dosage positive, and the per-agent ODE solve running	No time gate; effective only under the M3 configurations of M7.8
Drug-field statistics, each antibody	Switch and that antibody's dosage positive	Every timestep; no time gate

Hook	Gate	Remarks
Blood-concentration statistics	Any call of the vascular statistics routine	Called after each M7 delivery call, and also after each antibiotic delivery call under M6
Membrane-complex statistics	None	Accumulated for every macrophage at every timestep

Consequences of the gate structure

Binding can execute when nothing can be bound. Before `Mod_dosageStartTime` no drug is delivered and the drug fields are not transported, yet soluble and membrane binding are evaluated whenever their own tests pass. The drug fields are initialized to zero (spine 5.5) and nothing else writes them before delivery begins. Every binding rate is then exactly zero, and the steps leave every quantity unchanged.

Soluble binding does not depend on the switch. Without `--immuno-mod`, soluble binding is still evaluated at every diffusion step for any antibody with a nonzero dosage. The effect is nil because the fields are zero, with one exception: if the parameter file initializes a drug field directly (spine 5.4), binding acts on that field with no transport and no solver decay.

Changing the switch on resumption has asymmetric effects, because drug fields and blood concentrations are carried in the saved state. If the switch is removed when a run resumes:

- drug already in tissue is no longer transported, degraded by the solver or replenished, and writes to the drug fields follow the grid-exchange behaviour of M7.6;
- soluble binding continues for any antibody with a nonzero dosage, and its `Core_kDeg` route still degrades complex-bound TNF and returns drug to the free pool (M7.7);
- membrane binding and the drug-field statistics stop.

M7.3 Dosed agents and molecular species

Dosed agents

Agent	Selected by	Tissue state	Molecular weight
Exogenous TNF	`Mod_TNF_dosage`	The host TNF field (spine 2.4)	`MW_TNF` $= 17400$ g/mol
Exogenous IL-10	`Mod_IL10_dosage`	The host IL-10 field (spine 2.4)	`MW_IL10` $= 18600$ g/mol
Etanercept	`Mod_Etanercept_dosage`	`Etanercept` and `EtanTNF`	`MW_Etanercept` $= 150000$ g/mol
Infliximab	`Mod_Infliximab_dosage`	`Infliximab` and `Ifx1TNF` to `Ifx3TNF`	`MW_Infliximab` $= 149100$ g/mol

The molecular weights are compiled constants, not parameters. Within the module they are used only in delivery: to convert blood concentrations to molar concentrations in the flux, and in the abort condition (M7.5).

Drug fields

Field	Species	Composition assumed when the complex decays
`Etanercept`	Free Etanercept	n/a
`Infliximab`	Free Infliximab	n/a
`EtanTNF`	Soluble TNF bound by Etanercept	One TNF, one Etanercept
`Ifx1TNF`	Soluble TNF bound by one Infliximab	One TNF, one Infliximab
`Ifx2TNF`	Soluble TNF bound by two Infliximab	One TNF, two Infliximab
`Ifx3TNF`	Soluble TNF bound by three Infliximab	One TNF, three Infliximab

The decay step of M7.7 assumes these compositions: each complex returns one TNF to degradation and its antibody molecules to the free pool. In the binding step, forming a higher Infliximab complex does not decrement the lower one; M7.7 gives the ledger as implemented.

Each drug field is a padded field of the same kind as the host cytokine fields (spine 2.4), holding one value per compartment in molecules per compartment, and double-buffered like them (spine 2.2). The drug fields are always allocated, initialized to zero (spine 5.5), written with the saved state, and selectable by name for grid dumps. There are no separate fields for complexes released from cell membranes: shed membrane complexes enter the same soluble complex fields (M7.8).

Per-agent variables

The common agent state (spine 2.3) includes ten variables belonging to this module.

Variables	Meaning	Status
Membrane TNF bound by Etanercept	Per-cell count	Integrated in the per-agent ODE system (M7.8)
Membrane TNF bound by one, two or three Infliximab	Per-cell counts	Integrated in the per-agent ODE system (M7.8)
Free Etanercept and Etanercept soluble complex, per agent	—	Written by no rule; zero throughout
Free Infliximab and the three Infliximab soluble complexes, per agent	—	Written by no rule; zero throughout

The membrane terms also read and write the agent's membrane TNF, which belongs to the TNF receptor block of M3, and read its TACE rate.

The six unassigned variables are initialized to zero at construction and written with the saved state; no rule reads or writes them. Free drug and soluble complex are represented by the grid fields instead: the per-agent ODE system loads its free-drug and soluble-complex entries from the fields at the agent's compartment and writes them back there.

All ten variables belong to the common agent state, so every agent carries them, bacteria and neutrophils included. Only agents that perform the per-agent ODE solve, macrophages and T cells, can change them.

M7.4 Blood compartment and dosing

State

A single vascular object holds the blood state. Four scalar blood concentrations are used, one per dosed agent. They are carried in ug/kg, a dose per unit body mass rather than an amount per unit volume; the conversion to molar concentration happens in the delivery flux, through each agent's volume of distribution (M7.5). All four start at zero and are written with the saved state. Before `Mod_dosageStartTime` no rule touches them, so they remain zero unless a saved state supplies other values.

The vascular object also carries four blood concentrations for the antibody–TNF complexes, one for each complex field. They are initialized to zero and written with the saved state, and accessor functions exist for them, but no rule assigns them and no statistic reads them, so they are identically zero. The vascular object, with all eight blood variables, is constructed, serialized and cloned even when the module is off.

Sequence within one call

The blood state is advanced inside the delivery routine, called once in each split half-step (twice per diffusion step) under the gate of M7.2. Each call receives the half-step duration $\frac{1}{2}\Delta t_d$, the cellular timestep t and the diffusion step index k, and performs, in order:

1. **Elapsed time:** compute the time since the start of dosing.
2. **Dosing:** apply the dosing rule to each agent, in the order TNF, IL-10, Etanercept, Infliximab.
3. **Delivery:** deliver to tissue at every eligible source (M7.5).
4. **Clearance:** apply clearance to each agent, in the same order.

Delivery in a call therefore sees the blood concentration after that call's dose and before its clearance.

Dosing

Elapsed time is computed in whole seconds,

$$s = 600\,t + k\,\Delta t_d - 600\,t_0,$$

where $t_0 = $ `Mod_dosageStartTime`. The first two terms are truncated to an integer before $600\,t_0$ is subtracted; the truncation is exact whenever Δt_d is a whole number of seconds, as under every solver of M1.

For each agent, with dosage $D = $ `Mod_*_dosage` and interval $I = $ `Mod_*_dosageInterval` in timesteps, the blood concentration c receives half a dose when the elapsed time falls on a dosing boundary:

$$c \leftarrow c + \tfrac{1}{2} D \qquad \text{if} \qquad (s + 600\, I) \bmod (600\, I) = 0.$$

The dose is added in its declared units, ug/kg, directly to the blood concentration.

Within the gate $s \geq 0$, and $0 \leq k\, \Delta t_d < 600$ for every diffusion step. The condition therefore holds if and only if $k = 0$ and $t - t_0$ is a multiple of I. Both calls in diffusion step 0 satisfy it, one before and one after the diffusion solve, and each adds $\frac{1}{2} D$.

Each agent therefore receives exactly one full dose D per dosing timestep, at t_0, $t_0 + I$, $t_0 + 2I$, and so on. The first dose falls on the start timestep itself when `Mod_dosageStartTime` is at least one; when it is zero, the first dose falls at $t = I$ (M7.12). The schedule does not depend on the solver's diffusion timestep.

Splitting the dose has an effect that a reimplementation must reproduce: the first delivery of each dosing timestep sees only half the new dose, and the second sees the full dose less one clearance step. Adding D once at the first call would produce a different tissue exposure.

The dosing rule is applied to all four agents on every call. An unselected agent has $D = 0$ and is unchanged, but its interval is still used: an interval of zero for any agent makes the modulus zero. The integer modulo by zero terminates the run on the first call after dosing begins. A negative interval behaves as its absolute value, because the remainder test is unaffected by the sign of the divisor. Neither zero nor negative intervals are rejected at startup, since the declaration builds no range check (spine 7.0, Validity ranges).

Clearance

After delivery, each blood concentration is advanced by one forward-Euler step of first-order elimination over the half-step:

$$c \leftarrow c \left(1 - k_{cl}\, \tfrac{1}{2} \Delta t_d\right),$$

with $k_{cl} = $ `Mod_*_clearanceRate`. There are $2N_d$ calls per cellular timestep, each of duration $\frac{1}{2} \Delta t_d$, so clearance is applied for exactly 600 s per cellular timestep. Over one cellular timestep with no dose, the concentration is multiplied by the clearance factor

$$\left(1 - k_{cl}\, \tfrac{1}{2} \Delta t_d\right)^{2N_d},$$

a first-order approximation to $\exp(-600\, k_{cl})$. Because the factor depends on Δt_d, the blood trajectory for given parameters differs slightly between solvers.

The time argument is in seconds, so the parameter is applied as a rate constant per second.

No guard limits the step. If $k_{cl}\, \frac{1}{2} \Delta t_d > 1$, the concentration becomes negative after one call and alternates in sign thereafter; if the product exceeds 2, it also grows in magnitude. No startup check tests this.

Blood is not depleted by tissue

Delivery transfers drug and cytokine into tissue without reducing the blood concentration, and outward flux from tissue does not increase it (M7.5). Each agent's blood concentration is therefore a function of its dosing schedule and clearance alone: it is independent of the number and state of vascular sources, of the amount delivered, and of any quantity in tissue. Between doses it decays by the clearance factor, and at each dosing timestep it rises by D in two halves.

M7.5 Vascular delivery

Eligible sources

The delivery routine visits every vascular source in the current order of the source list. That list is shuffled immediately before recruitment (spine 3.2; S8), and delivery precedes recruitment within a cellular timestep, so delivery uses the order produced by the previous timestep's shuffle, or the order of initialization at the first timestep.

A source p delivers only if

$$\delta(p) < 0.8 \qquad \text{and} \qquad \text{not caseated}(p),$$

where δ is the cell density of S9.3. The density threshold is a compiled constant. The same rule gates oxygen delivery (S7.4). Cell density is a multiple of $1/9$, so the condition admits sources with at most seven of nine occupied compartments in their periodic Moore neighbourhood ($7/9 \approx 0.78$, $8/9 \approx 0.89$).

There is no partial delivery at dense sources. Unlike the antibiotics of M6, which deliver at reduced activity at or above the density threshold (M6.4), an ineligible source delivers nothing.

Order within a source

At each eligible source the four agents are processed in the order TNF, IL-10, Etanercept, Infliximab, each only if its dosage is nonzero. Each agent reads and writes only its own field, so the order among agents at one source has no effect.

Agent	Field written	Molecular weight	Permeability	Volume of distribution
TNF	TNF	`MW_TNF`	`Mod_TNF_vascularPermeability`	`Mod_TNF_volumeDist`
IL-10	IL-10	`MW_IL10`	`Mod_IL10_vascularPermeability`	`Mod_IL10_volumeDist`
Etanercept	`Etanercept`	`MW_Etanercept`	`Mod_Etanercept_vascularPermeability`	`Mod_Etanercept_volumeDist`
Infliximab	`Infliximab`	`MW_Infliximab`	`Mod_Infliximab_vascularPermeability`	`Mod_Infliximab_volumeDist`

Only free antibody is delivered; no complex is delivered.

Local concentration

The tissue concentration seen by a source is the mean of the field over the boundary-clipped Von Neumann neighbourhood of the source, excluding the source compartment,

$$\bar{n}(p) = \frac{1}{\left|N_4^{\text{clip}}(p)\right|} \sum_{q \in N_4^{\text{clip}}(p)} n(q),$$

in molecules per compartment. This is the local term of antibiotic delivery (M6.4); oxygen delivery instead reads the source compartment itself (S7.4). In three dimensions the neighbour set is that of M5.3. The divisor is the number of neighbours found, so a source on the domain edge averages over three neighbours and a corner source over two. When the border exclusion (spine 5.2) is at least one compartment, every randomly placed

source has four neighbours; with no border, or for a source placed explicitly from the parameter file, a source may lie on the edge.

Flux

The increment, in molecules, written to the source compartment over one call is

$$\Delta n(p) = N_A\, P\, A_{\mathrm{cmpt}}\, \tfrac{1}{2}\Delta t_d \left[\frac{c_b}{10^9\, V_d\, \mathrm{MW}} - \frac{\bar{n}(p)}{10^3\, N_A\, V} \right],$$

where c_b is the blood concentration in ug/kg after this call's dose (M7.4); P the permeability in cm/s; A_{cmpt} the compartment lateral area (spine 2.1) in cm^2; V_d the volume of distribution in L/kg; MW in g/mol; and V the compartment volume in litres. Both bracketed terms are in mol/cm^3 (c_b/V_d is in ug/L, and 10^9 converts ug to g and litres to cm^3); the prefactor $P\, A_{\mathrm{cmpt}}\, \frac{1}{2}\Delta t_d$ is a volume in cm^3; and N_A converts moles to molecules.

Equivalently, with the blood-equivalent count

$$n_b = \frac{N_A\, V\, c_b}{10^6\, V_d\, \mathrm{MW}},$$

the number of molecules a compartment would hold at the molar concentration of blood,

$$\Delta n(p) = \alpha\, (n_b - \bar{n}(p))\,, \qquad \alpha = \frac{P\, A_{\mathrm{cmpt}}\, \frac{1}{2}\Delta t_d}{10^3\, V} = 2000\, P\, \tfrac{1}{2}\Delta t_d,$$

for P in cm/s and Δt_d in seconds, with $A_{\mathrm{cmpt}} = 1.6 \times 10^{-5}$ cm^2 and $10^3 V = 8 \times 10^{-9}$ cm^3.

Each call covers half a diffusion step, so delivery is applied for exactly Δt_d per diffusion step.

Properties of the flux

The source compartment is not self-limiting. The driving difference uses the neighbourhood mean, not the source value, so delivery keeps raising the source compartment while its neighbours stay below n_b, and the source can exceed n_b. Accumulation at the source is limited only by transport away from it, by decay and, for the antibodies, by binding.

Outward flux is permitted and not bounded. If $\bar{n}(p) > n_b$ the increment is negative and is applied with no floor; because it is proportional to the neighbours, not to the source, the source value can be driven below zero. No cutoff follows delivery. Outward flux removes material from tissue without adding it to blood.

Delivery depends on source order. A source writes only its own compartment but reads four neighbours. Where two eligible sources are Von Neumann neighbours, the source visited later sees a neighbour already incremented by the earlier one in the same call. Because the list is shuffled each timestep, this dependence varies between timesteps.

The update is explicit with no stability check. α is not tested at startup. For $\alpha > 1$ a single call moves the source by more than the whole driving difference.

Abort condition

After computing the flux, the routine terminates the run with a fatal error if

$$\left|\frac{\Delta n(p)}{N_A}\right| > \left|c_b - \frac{\bar{n}(p)}{N_A}\right| \mathrm{MW}.$$

The left side is in moles; the right side combines ug/kg with moles, so the two sides are in different units (M7.12, Constraints).

M7.6 Transport and decay of drug fields

Fields and equation

Within each diffusion solve, under the transport gate of M7.2, the six drug fields are transported together, after every host field and after the antibiotic fields of M6, each with its own diffusivity and degradation rate constant.

Field	Diffusivity	Degradation rate constant
`Etanercept`	`Mod_Etanercept_diffusivity`	`Mod_Etanercept_degRateConst`
`Infliximab`	`Mod_Infliximab_diffusivity`	`Mod_Infliximab_degRateConst`
`EtanTNF`	`Mod_EtanTNF_diffusivity`	`Mod_EtanTNF_degRateConst`
`Ifx1TNF`	`Mod_Ifx1TNF_diffusivity`	`Mod_Ifx1TNF_degRateConst`
`Ifx2TNF`	`Mod_Ifx2TNF_diffusivity`	`Mod_Ifx2TNF_degRateConst`
`Ifx3TNF`	`Mod_Ifx3TNF_diffusivity`	`Mod_Ifx3TNF_degRateConst`

Each field obeys

$$\frac{\partial C}{\partial t} = D\nabla^2 C - kC$$

over Δt_d, with a zero-flux (Neumann) boundary on every edge. This differs from the host cytokine fields, which have a zero-concentration boundary (M1). Drug therefore cannot leave through the domain boundary. It leaves tissue only by decay, by outward flux at sources (M7.5), by the concentration cutoff and, as membrane-bound complex, with a dying agent (M7.8).

Diffusivity is uniform in space and constant in time; it does not depend on cell density or caseation. The degradation rate constant is applied as a rate per second, because it multiplies a duration in seconds; its declared unit is blank. Here k is the solver decay of the whole species: for a complex it removes the complex together with its bound antibody. The binding step of M7.7 applies a second, separate decay to the TNF component of each complex.

Scheme by solver

The selected solver of M1 determines how the equation is advanced; each solver reads its own diffusion timestep (M1.2).

Solver	Transport	Decay	Cutoff
Spectral (M1.3)	Cosine transform with no-flux propagation factors	Folded into the factor of every mode; $\exp(-k\,\Delta t_d)$ in the zero mode	Values $\leq 10^{-12}$ set to zero on writing back
Alternating-direction explicit (M1.4)	Two directional sweeps with no-flux treatment, then averaged	Each sweep result multiplied by $\exp(-k\,\Delta t_d)$ before averaging	Within each sweep, before decay
Crank-Nicolson ADI (M1.5)	Two implicit directional solves with no-flux matrices	Result multiplied by $\exp(-k\,\Delta t_d)$ after the solves, when $k > 0$	After decay

Under the spectral solver the zero-mode factor is exactly $\exp(-k\,\Delta t_d)$, so transport leaves the domain total unchanged and the total decays at exactly the degradation rate, apart from the cutoff. The cutoff removes values at or below 10^{-12} and sets negative values to zero. Negative values can arise from outward delivery flux (M7.5) or from binding (M7.7), so the cutoff can increase the total.

The Crank-Nicolson ADI solver requires a square grid, and the dimensionality module restricts it to two dimensions (M1.5).

Smoothing

Under the spectral solver only, the smoothing pass at the end of each split half-step (M1.3) acts on the drug fields, under the transport gate. It applies no decay and no cutoff to them, and its stability bound $\mathrm{Fo} \leq 1/4$, with $\mathrm{Fo} = D\,\Delta t_s/\Delta x^2$, is not checked. With `Diffusion_FFT_numSmootherSteps` zero the pass has no effect on the drug fields. The other two solvers have no smoother.

Fields not advanced

When the gate is closed, the solver writes nothing into the drug fields of the next grid, and those fields are not copied between the grid objects during the diffusion loop. Each grid object then carries its own copy of each drug field, and every exchange alternates which copy is current. The next grid is overwritten with a copy of the current grid only at the start of each cellular timestep (spine 2.2).

Consequently, while the gate is closed, a value written into the current grid during a split half-step, as by membrane binding (M7.8), is not visible after the next exchange; it becomes visible again two exchanges later unless overwritten. Soluble binding reads and writes the next grid (M7.7), so its result becomes current at the following exchange. Whatever the other copy holds at the end of the loop is discarded at the start of the next cellular timestep; with N_d even, the copy retained is the one current at the start of the loop. In a run started afresh without direct field initialization both copies are zero whenever the gate is closed, so this has no effect. It becomes observable on resumption with the switch removed, or with drug fields initialized from the parameter file.

Startup checks

The startup timestep checks of M1.2 do not include this module's diffusivities. No transport scheme has a stability limit for these fields: the spectral and Crank-Nicolson ADI schemes are implicit in effect, and the alternating-direction explicit scheme is unconditionally stable but loses accuracy at large Fourier numbers. The spectral smoother is explicit, and its stability bound for these fields is not checked (Smoothing).

The six `Mod_*_minDiffusivity` parameters are read and stored, and their descriptions refer to a reduced diffusivity in compartments with many cells. No rule reads them, and no density-dependent diffusivity exists for the drug fields.

M7.7 Soluble-phase TNF binding

Placement and gate

Binding between the antibodies and soluble TNF is evaluated once per diffusion step inside the diffusion solve, after every field has been transported and degraded and before the grids are exchanged (M7.1). It acts on the next grid. Each solver of M1 implements the step separately; the implementations differ only in the sign of the Etanercept term for free TNF, and each uses its own group's diffusion timestep, which equals the one in force. The gates are those of M7.2: neither part tests the master switch or the start time.

The step is evaluated at every compartment, with no test of occupancy, caseation or source status. Each compartment reads and writes only its own values, so compartment order has no effect. Within a compartment the order is fixed: the Etanercept part, then the Infliximab part, then, when M3 enables TNF receptor dynamics, the unbinding of TNF from shed TNFR2 (M3.3). Each later part reads the free TNF left by the earlier ones.

Notation

At a compartment, let T be free TNF, E free Etanercept, C_E the Etanercept complex, I free Infliximab, and C_1, C_2, C_3 the Infliximab complexes of M7.3, all in molecules per compartment, read from the next grid. Let $\kappa = 1/(N_A V)$, which converts a count in one compartment to a molar concentration, and k_{deg} = `Core_kDeg`, *the degradation rate constant of free TNF (S6). The association and dissociation constants are* `Mod_Etanercept_kOn` *and* `Mod_Etanercept_kOff`, *written* k_{on}^E and k_{off}^E, and `Mod_Infliximab_kOn` and `Mod_Infliximab_kOff`, written k_{on}^I and k_{off}^I. One pair serves all three Infliximab binding steps. With k_{on} in 1/(M s), each rate is in molecules per second.

Etanercept

$$\beta_E = \left(k_{\text{on}}^E \, \kappa \, E \, T - k_{\text{off}}^E \, C_E\right) \Delta t_d, \qquad \delta_E = k_{\text{deg}} \, C_E \, \Delta t_d,$$

both from the values at the start of the step; then

$$C_E \leftarrow C_E + \beta_E - \delta_E, \qquad E \leftarrow E + \delta_E - \beta_E, \qquad T \leftarrow T + s \, \beta_E,$$

with $s = +1$ under the spectral solver and $s = -1$ under the alternating-direction explicit and Crank-Nicolson ADI solvers.

δ_E is degradation of the TNF held in the complex: it removes the complex and returns its antibody to the free pool. Under the alternating-direction explicit and Crank-Nicolson ADI solvers, binding removes free TNF in the amount added to the complex. Under the spectral solver it adds that amount instead, so each net binding event raises free TNF while also forming a complex.

Infliximab

Infliximab binds in three successive steps, free TNF to C_1, C_1 to C_2 and C_2 to C_3, each by one further antibody. With T' the free TNF after the Etanercept part,

$$\beta_1 = \left(k^I_{\text{on}}\,\kappa\,I\,T' - k^I_{\text{off}}\,C_1\right)\Delta t_d, \quad \beta_2 = \left(k^I_{\text{on}}\,\kappa\,I\,C_1 - k^I_{\text{off}}\,C_2\right)\Delta t_d, \quad \beta_3 = \left(k^I_{\text{on}}\,\kappa\,I\,C_2 - k^I_{\text{off}}\,C_3\right)\Delta t_d,$$

and $\delta_j = k_{\text{deg}}\,C_j\,\Delta t_d$ for $j = 1, 2, 3$, all from the values at the start of the Infliximab part; then

$$C_j \leftarrow C_j + \beta_j - \delta_j, \qquad I \leftarrow I + \delta_1 + 2\delta_2 + 3\delta_3 - \beta_1 - \beta_2 - \beta_3, \qquad T \leftarrow T' - \beta_1.$$

The sign of the TNF term is the same in all three solvers. Forming C_2 does not decrement C_1, and forming C_3 does not decrement C_2. On decay, by contrast, C_j returns j antibodies to the free pool, consistent with the compositions of M7.3.

Ledger

Per step and compartment, the implemented updates change the totals as follows. A positive β is net binding; a negative β is net unbinding, in which case the same expressions describe destruction rather than creation. The step does not conserve total Infliximab or Infliximab-associated TNF, nor, under the spectral solver, Etanercept-associated TNF; M7.8 gives the membrane chain.

Total	Implemented change per step
Etanercept, $E + C_E$	0
Etanercept-associated TNF, $T + C_E$, spectral solver	$2\beta_E - \delta_E$
Etanercept-associated TNF, $T + C_E$, other solvers	$-\delta_E$
Infliximab, $I + C_1 + 2C_2 + 3C_3$	$\beta_2 + 2\beta_3$
Infliximab-associated TNF, $T + C_1 + C_2 + C_3$	$\beta_2 + \beta_3 - \delta_1 - \delta_2 - \delta_3$

Decay of complexes by two routes

Each complex decays by two independent routes in every diffusion step: in transport (M7.6), the whole complex, antibody included, decays at `Mod_*TNF_degRateConst`; in this step, the TNF component decays at `Core_kDeg` and the antibody returns to the free pool. Both apply. A complex therefore loses antibody only through whole-complex decay in transport, and TNF through both routes.

Integration and positivity

The step is a single explicit Euler step of length Δt_d, with no subdivision and no bound on the dimensionless rates $k_{\mathrm{on}}\,\kappa\,E\,\Delta t_d$, $k_{\mathrm{on}}\,\kappa\,I\,\Delta t_d$, $k_{\mathrm{off}}\,\Delta t_d$ and $k_{\mathrm{deg}}\,\Delta t_d$. When any exceeds one, a step removes more of a species than is present. No floor is applied, and the result can be negative, most likely near vascular sources, where free antibody is highest.

Negative values are not removed until the next transport writes the field back through the cutoff (M7.6). Until then they persist through the following split half-step and, after the last diffusion step of a cellular timestep, through all agent behaviour of that timestep; agents reading free TNF in that interval read the negative value.

M7.8 Membrane-phase TNF binding

Mechanism

Each antibody also binds the membrane TNF of individual cells, through extra variables and terms added to the per-agent ODE system of M3. The terms run in every molecular substep of every split half-step, so N_m times per diffusion step, for every agent that performs the per-agent ODE solve. The system is integrated over Δt_m with the stepper selected by `--odesolver`, whose program default is 4, fourth-order Runge–Kutta (M3.2). The per-agent solve gates, the stepper, the per-class derivative function and the NF-κB substep subdivision are specified in M3.2.

When the terms act

Within the solve, the Etanercept variables are added when the switch is on and `Mod_Etanercept_dosage` is positive, and the Infliximab variables likewise with `Mod_Infliximab_dosage`. There is no time gate (M7.2).

The variables can be added without being acted on. Their derivatives are written only by the TNF receptor derivative routine, which is evaluated only when the derivative function contains a TNF receptor block and no NF-κB block. Agents of a class share one stepper, whose derivative buffer keeps its values between evaluations (M3.2), so the antibody entries keep zero derivative only where no evaluation in that class writes them. This holds in every configuration the table marks inert: under NF-κB dynamics the macrophage stepper's NF-κB derivative never writes them, and without a TNF receptor block no derivative does. There the variables are loaded, integrated with zero derivative and written back unchanged.

Macrophages build their derivative function from the M3 flags as given; T cells use one built with NF-κB and MHC class II dynamics forced off (M3.2). The macrophage derivative function always carries the TNF receptor block under NF-κB dynamics (M3.2); a T cell's carries it only when TNF receptor dynamics is selected. The terms therefore act as follows.

M3 configuration	Macrophages	T cells
TNF receptor dynamics, without NF-κB	Act	Act
NF-κB dynamics, with TNF receptor dynamics	Carried, inert	Act
NF-κB dynamics, without TNF receptor dynamics	Carried, inert	Carried, inert

M3 configuration	Macrophages	T cells
IL-10 receptor dynamics without TNF receptor dynamics, with or without MHC class II	Carried, inert	Carried, inert
MHC class II dynamics only, without TNF receptor dynamics	Carried, inert	Not solved
Coarse-grained throughout	Not solved	Not solved

When M3 is coarse-grained throughout, no per-agent solve runs and the membrane variables stay zero for the whole run. In the default configuration, membrane binding would therefore have no effect even if the module were selected.

Variables

For an agent at compartment p, write m for its membrane TNF, M_E for its Etanercept-bound membrane TNF, M_1, M_2, M_3 for its membrane TNF bound by one, two or three Infliximab, and τ for its TACE rate. These are per-cell counts. Write E, C_E, I and C_1 to C_3 for the drug fields at p in the current grid, in molecules per compartment, and κ as in M7.7.

At the start of each substep the field values at p are copied into the agent's ODE vector, together with its membrane variables. After the step the fields are set at p through the field accessor, preserving the membrane variables stored in the agent.

Etanercept

With $\gamma_E = k_{\text{on}}^E \, \kappa \, E \, m - k_{\text{off}}^E \, M_E$, the terms added are

$$\frac{dE}{dt} = -\rho \, \gamma_E, \qquad \frac{dM_E}{dt} = \gamma_E - \tau M_E, \qquad \frac{dC_E}{dt} = \rho \, \tau M_E, \qquad \frac{dm}{dt} \mathrel{+}= -\gamma_E,$$

the dm/dt term being added to the membrane TNF equation of the M3 TNF receptor block. Here $\rho = $ `DENSITY` $\cdot V = 1.25 \times 10^{11} \times 8 \times 10^{-12} = 1$ exactly. It converts a per-cell rate into a per-compartment change, assuming one cell per compartment volume; because it equals one, a per-cell event changes the field by exactly one molecule.

Membrane-bound complex is shed by the same TACE activity that sheds free membrane TNF, into the soluble complex field, where transport, decay and soluble binding act on it (M7.6, M7.7).

Infliximab

With

$$\gamma_1 = k_{\text{on}}^I \, \kappa \, I \, m - k_{\text{off}}^I \, M_1, \quad \gamma_2 = k_{\text{on}}^I \, \kappa \, I \, M_1 - k_{\text{off}}^I \, M_2, \quad \gamma_3 = k_{\text{on}}^I \, \kappa \, I \, M_2 - k_{\text{off}}^I \, M_3,$$

the terms added are

$$\frac{dI}{dt} = \rho \, k_{\text{off}}^I M_1 - k_{\text{on}}^I \, \kappa \, I \, m, \qquad \frac{dM_1}{dt} = \gamma_1 - \gamma_2 - \tau M_1, \qquad \frac{dM_2}{dt} = \gamma_2 - \gamma_3 - \tau M_2,$$

$$\frac{dM_3}{dt} = \gamma_3 - \tau M_3, \qquad \frac{dC_j}{dt} = \rho \, \tau M_j \quad (j = 1, 2, 3), \qquad \frac{dm}{dt} \mathrel{+}= -\gamma_1.$$

In the free-antibody equation ρ multiplies only the dissociation term; since $\rho = 1$, the equation equals $-\gamma_1$ numerically. Unlike the soluble chain, the membrane chain decrements each complex as the next forms, but it does not debit free antibody for the second and third binding steps, nor credit it when they reverse.

Ledger

Total	Rate of change from these terms
Etanercept, $E + M_E + C_E$	0
Etanercept-associated TNF, $m + M_E + C_E$	0
Infliximab, $I + (M_1 + C_1) + 2(M_2 + C_2) + 3(M_3 + C_3)$	$\gamma_2 + \gamma_3$
Infliximab-associated TNF, $m + \sum_j (M_j + C_j)$	0

Membrane TNF is conserved across binding and shedding. Higher-order Infliximab binding on membranes creates antibody at rate $\gamma_2 + \gamma_3$, one antibody for each binding step that is not debited from free antibody.

Order and co-location

The per-agent solves are performed agent by agent, macrophages first, then Tgam, Tcyt and Treg, each in current list order. Each agent reads the drug fields at its compartment as left by the previous agent and writes its result back before the next. A compartment can hold a macrophage and a T cell, or two T cells (spine 2.3); the agent processed second binds against free antibody already depleted, and sheds into complex fields already incremented, by the first.

The writes go to the current grid, which transport reads in the next diffusion solve when the gate is open; M7.6 gives the consequences when it is closed.

Positivity, death and division

No floor is applied to the integrated values, and no cutoff on writing back. A negative value written into a drug field persists until transport removes it (M7.6).

When an agent dies, its membrane complexes and membrane TNF are removed with it. No rule releases them to the grid, so the antibody and TNF they hold leave the system.

A daughter T cell is created as a copy of its parent and begins with the parent's membrane-complex values (S3.5). The parent keeps its own, so division duplicates the membrane-bound antibody and TNF of the parent.

M7.9 Coupling to host submodels

Channels

The module affects the rest of the model through three channels, and through no others:

- **Delivery:** exogenous TNF and IL-10 are added to the host TNF and IL-10 fields at vascular sources (M7.5).
- **Soluble binding:** the host TNF field changes at every compartment where antibody or complex is present (M7.7).
- **Membrane binding:** per-agent membrane TNF changes, and with it the TNF the agent sheds, under the

M3 configurations of M7.8.

No host rule reads any drug field, complex field, blood concentration or per-agent complex variable. Antibody and complex act on cells only through the free TNF they remove from the TNF field or, under the spectral solver, add to it (M7.7).

Host rules reached

Every host rule that reads the TNF or IL-10 field responds to the module.

Host rule	Field read	Channels	Specified in
TNF-induced apoptosis of macrophages and T cells	TNF at the agent's compartment	Delivery, soluble, membrane	S6, S2, S3
NF-κB activation of macrophages	TNF at the agent's compartment	Delivery, soluble, membrane	S6, S2
TNF modulation of IL-10 secretion by activated macrophages	TNF at the agent's compartment	Delivery, soluble, membrane	S6.12
Receptor-occupancy sink terms	TNF and IL-10 at the agent's compartment	Delivery, soluble	S6
Recruitment eligibility and probability	TNF at the source compartment	Delivery, soluble, membrane	S8
STAT3 activation of macrophages	IL-10 at the agent's compartment	Delivery	S6, S2
IL-10 suppression of TNF and chemokine secretion	IL-10 at the agent's compartment	Delivery	S6
TGF-β activation, under M4	TNF at the macrophage's compartment	Delivery, soluble, membrane	M4
Fine-grained receptor dynamics, under M3	TNF and IL-10 at the agent's compartment	Delivery, soluble, membrane	M3

The membrane channel reaches the soluble field only through TNF shed by agents performing the per-agent ODE solve, so it is absent wherever M7.8 records the terms as inert or not solved, in particular whenever M3 is coarse-grained throughout. It requires TNF receptor dynamics, under which the TNF sink term is not applied (S6), so the sink terms are reached by delivery and soluble binding only. Recruitment reads the field at the source compartment, which shed TNF reaches by diffusion, or directly when a shedding agent occupies the source.

Chemotaxis reads only the chemokine fields (S1) and is reached by no channel. Oxygen is not reached either; it shares only the source eligibility rule with delivery (S7.4).

Exogenous cytokine

Delivery is the only route by which TNF or IL-10 can enter the grid other than cellular secretion. Exogenous cytokine enters tissue only at eligible sources, those with cell density below 0.8 and no caseation, so dense or caseous regions receive it only by diffusion from surrounding tissue. Once delivered it is diffused, degraded and consumed by the sink terms exactly as secreted cytokine is.

Delivery writes the source compartment, which is also the compartment recruitment reads (S8), so exogenous TNF raises the recruitment signal at the very compartment where it is delivered. The last delivery of a cellular timestep occurs in the second split half-step of the last diffusion step, after the final diffusion solve and before recruitment (spine 3.2), so recruitment reads TNF that includes one half-step of delivery not yet diffused. That final delivery also precedes the first soluble binding of the next cellular timestep, so antibody delivered then has bound no TNF when recruitment reads the field.

The TNF and IL-10 depletion settings of M8 suppress secretion only; under depletion, exogenous cytokine is still delivered at the dosed rate.

Antibody

Complex-bound TNF has no activity. It does not enter the occupancy proxies of S6, so it contributes nothing to apoptosis, NF-κB activation, secretion modulation or recruitment. It is not consumed by the receptor-occupancy sink terms, which act on free TNF only, so complexes are removed only by the two decay routes of M7.7. When a complex dissociates, its TNF returns to the free field and is active again. Neither antibody affects the IL-10 field, and neither binds shed TNFR2 or any other species.

Caseation does not affect the antibodies in tissue: drug fields are transported through caseous compartments and soluble binding is evaluated there as elsewhere. Only delivery is excluded at caseous sources.

M7.10 Observation

Anti-TNF statistics group

Every statistic of the group has reset code 1 (S9): it is cleared at the start of each cellular timestep and records that timestep only. None is cumulative.

Statistic	Quantity	Computed in	Condition
`BloodConcEtan`	Etanercept blood concentration, ug/kg	Vascular statistics routine	Each call
`BloodConcIfx`	Infliximab blood concentration, ug/kg	Vascular statistics routine	Each call
`freeEtan`	Sum of `Etanercept` over the grid	Grid statistics sweep	Switch and positive Etanercept dosage
`EtansTNF`	Sum of `EtanTNF` over the grid	Grid statistics sweep	Switch and positive Etanercept dosage

Statistic	Quantity	Computed in	Condition
`freeIfx`	Sum of `Infliximab` over the grid	Grid statistics sweep	Switch and positive Infliximab dosage
`Ifx1sTNF`, `Ifx2sTNF`, `Ifx3sTNF`	Sums of `Ifx1TNF` to `Ifx3TNF` over the grid	Grid statistics sweep	Switch and positive Infliximab dosage
`TotmTNF`	Sum of membrane TNF over macrophages	Per-agent statistics	None
`EtanmTNF`	Sum of Etanercept-bound membrane TNF over macrophages	Per-agent statistics	None
`Ifx1mTNF`, `Ifx2mTNF`, `Ifx3mTNF`	Sums of Infliximab-bound membrane TNF over macrophages	Per-agent statistics	None

Timing

The grid sums are taken in the statistics block at the end of the timestep, from the current grid after the full diffusion loop. They include any negative values left by delivery or binding since the last transport cutoff (M7.5, M7.7).

The blood statistics are written by the vascular statistics routine, called after every immunomodulation delivery call and after every antibiotic delivery call under M6. The recorded value is therefore the blood concentration after the clearance step of the last such call in the timestep. The statistic is zero on any timestep without a call, in particular before `Mod_dosageStartTime` when M6 is not selected, whatever the blood state.

The membrane statistics are accumulated as each macrophage's statistics are updated, at its creation and again at state commitment (spine 3.2). Every macrophage present at commitment is included, including those that die in that timestep. A macrophage created during the timestep has zero values at creation and contributes nothing extra.

`TotmTNF` is accumulated whether or not the module is selected. It reports macrophage membrane TNF, an M3 quantity, nonzero only under fine-grained TNF receptor dynamics.

What is not reported

- Membrane-bound complexes and membrane TNF of T cells: the membrane statistics are taken from macrophages only, although T cells carry and, under some M3 configurations, integrate the same variables (M7.8).
- The blood concentrations of exogenous TNF and IL-10.
- The contribution of exogenous cytokine to tissue: it is inside the host TNF and IL-10 totals and the pg/mL concentration estimates (S9.11), and cannot be separated from secreted cytokine.
- Complex-bound TNF in any host TNF statistic: the TNF total and the granuloma TNF concentration report free TNF only.
- Any partition of drug or complex between granuloma and normal tissue.

The six drug fields can be named for grid dumps, written as for every padded field (S9).

M7.11 Behaviour when the module is not selected

With `--immuno-mod` absent, as in the default configuration, the gates of M7.2 close dosing, clearance, delivery, transport, smoothing, membrane binding and the drug-field statistics. The four blood concentrations stay zero, and the blood statistics are written only if M6 calls the vascular statistics routine, in which case they record zero.

The module's state is nevertheless present. The six drug fields are allocated, with their halo and auxiliary arrays, copied from the current to the next grid at the start of every cellular timestep, and written with the saved state. The ten per-agent variables of M7.3 are carried by every agent and saved, and the vascular object with its eight blood variables is constructed, serialized and cloned (M7.4). All remain zero throughout a run started afresh, unless the parameter file initializes a drug field directly (spine 5.4).

Soluble binding still runs for each antibody whose dosage is nonzero (M7.2). With the default parameter values, `Mod_Etanercept_dosage` is 500 and the other three dosages are 0, so the Etanercept part is evaluated at every compartment on every diffusion step; every rate is exactly zero and no field changes. The macrophage membrane statistics, `TotmTNF` included, are also accumulated every timestep.

Host behaviour is therefore identical, timestep by timestep, to a build without the module. Appendix B indexes the controlling option and the gating logic.

M7.12 Parameters

The parameters belong to the group `Mod` and its subgroups. Default values are not tabulated, since the default configuration does not select the module; M7.11 and M7.12 cite the ones that matter with the module off, and a study that selects the module supplies the rest. Every parameter of the group is read and stored whether or not the module is selected.

No parameter of the group declares a default, so omitting one is fatal at startup (spine 7.0). Every numeric parameter declares a minimum of zero and no maximum, which builds no range, so negative values are accepted. The behaviours at zero listed in the table are those of an explicit zero.

In the table, `<agent>` is `TNF`, `IL10`, `Etanercept` or `Infliximab`; `<field>` is one of the six drug fields of M7.6; and `<antibody>` is `Etanercept` or `Infliximab`.

Identifier	Value or range	Units (declared; as applied)	Meaning
`Mod_dosageStartTime`	—	Timesteps; integer	First timestep at which dosing, clearance, delivery and transport run (M7.2, M7.4)[a]
`Mod_<agent>_dosage`	500 for Etanercept; 0 for the other three (M7.11)	ug/kg; added directly to the blood concentration in two halves	Selects the agent and sets the dose size (M7.4). At zero the agent is not selected: no dose, delivery, binding or drug-field statistics; its blood statistic, where it has one, is still written (M7.10)

Identifier	Value or range	Units (declared; as applied)	Meaning
`Mod_<agent>_dosageInterval`	—	Timesteps; integer	Interval between doses (M7.4). At zero, an integer modulo by zero on the first call after dosing starts, for any agent, selected or not
`Mod_<agent>_clearanceRate`	—	Declared 1/min; applied 1/s in a forward-Euler step over $\frac{1}{2}\Delta t_d$	First-order elimination from blood (M7.4). At zero, no clearance: the blood concentration rises by one dose per dosing timestep without bound
`Mod_<agent>_volumeDist`	—	L/kg	Divides the blood concentration in the delivery flux (M7.5). At zero, a division by zero in the delivery flux of a selected agent
`Mod_<agent>_vascularPermeability`	—	cm/s	Enters the delivery coefficient α (M7.5). At zero, no delivery; the blood state is still advanced
`Mod_<field>_diffusivity`	—	cm^2/s	Diffusivity of the field, in the selected solver's transport and the spectral smoother (M7.6). At zero: under the spectral solver the field becomes not a number; under the other solvers it is not transported
`Mod_<field>_degRateConst`	—	None declared; applied 1/s, multiplying Δt_d	Whole-species decay in transport (M7.6). At zero, no solver decay; complexes still lose TNF by the route of M7.7
`Mod_<antibody>_kOn`	—	1/(M s), multiplied by κ	Association rate of antibody with TNF, soluble and membrane (M7.7, M7.8). At zero, no binding; existing complex still dissociates and decays
`Mod_<antibody>_kOff`	—	1/s	Dissociation rate of the complex. At zero, binding is irreversible; complex is removed only by decay and, on membranes, by shedding

A "—" in the Value or range column marks a value that is read but has no effect while the module is not selected.

[a] The simulation clock is incremented before each timestep is processed, so the first processed timestep is $t = 1$ (spine 3.2). For $t_0 \geq 1$ the first dose falls at t_0. For $t_0 = 0$ the gate is open from the first timestep, but the first dose falls at $t = I$, with clearance and delivery performed from $t = 1$.

One pair of binding constants serves every binding step of an antibody: for Infliximab all three steps of the chain, and for both antibodies soluble and membrane TNF alike. No parameter distinguishes affinity for membrane TNF from affinity for soluble TNF, or one binding step from another.

The declared units differ from the units applied: the clearance rate is applied per second; the dose and blood concentration are in ug/kg, an amount per body mass until the volume of distribution is applied in the flux; and the unused blood-concentration parameters are declared molar, while blood is held in ug/kg.

Read but without effect: `Mod_Etanercept_bloodConc`, `Mod_Infliximab_bloodConc` (declared M) and the six `Mod_<field>_minDiffusivity` (declared cm^2/s). `Drugs_bloodVolume` (M6) is read by no rule of this module.

When the tissue parameters are read

- Under the spectral solver, the propagation factors are computed from `diffusivity` and `degRateConst` once, when the solver is constructed, whether or not the module is selected. The smoother reads `diffusivity` at each call.
- Under the Crank-Nicolson ADI solver, the implicit matrices are computed from `diffusivity` once, at construction; `degRateConst` is read at each solve (M1.5).
- Under the alternating-direction explicit solver, both are read at each transport step.
- The binding constants are read at every evaluation of the binding terms.

Zero diffusivity under the spectral solver

Under the spectral solver the propagation factor for each mode is

$$\exp\left(-\frac{2D}{\Delta x^2}\left[2 + \frac{k\,\Delta x^2}{2D} - \cos\theta_j - \cos\theta_i\right]\Delta t_d\right),$$

with D the diffusivity, k the degradation rate constant and θ_i, θ_j the mode angles (M1.3). The degradation term enters only as k/D multiplied back by D. For $D = 0$ the product is undefined ($0 \cdot \infty$ when $k > 0$, $0 \cdot (0/0)$ when $k = 0$), so every factor is not-a-number whatever k. M1.3 (The propagator and incorporation of decay) specifies this construction for host and drug fields.

On the first transport of the field after the gate opens, every value of the field becomes not-a-number, because the transform mixes all modes; the cutoff does not remove such values, since the comparison with 10^{-12} is false. If the field belongs to an antibody whose dosage is nonzero, soluble binding reads it and free TNF becomes not-a-number at every compartment, so every host rule reading TNF reads a value that is not a number. If the antibody's dosage is zero, no rule reads the field, and the not-a-number values appear only in grid dumps. This arises under the spectral solver only, and only once the module is selected and dosing has started. The other two solvers do not transport the field at $D = 0$; decay still applies. The default values do not trigger it: every drug-field diffusivity is non-zero.

Sign and magnitude

Negative values are accepted and none is detected. A negative `degRateConst` makes the field grow exponentially in transport; a negative `kOn` or `kOff` reverses the corresponding process; and a negative `diffusivity` makes the spectral propagation factors exceed one at high wavenumber, so transport amplifies small-scale variation. Large values are accepted without the checks that apply to host and antibiotic fields.

Fixed structural constants

These values are compiled and cannot be set from a parameter file or the command line. A reimplementation must use them exactly, including those that differ from standard physical constants.

- Delivery density threshold 0.8: sources at or above it do not deliver. The same rule gates oxygen delivery (S7.4).
- `NAV` $= 6.02 \times 10^{23}$ per mol, truncated to three significant figures; `VOL` $= 8 \times 10^{-12}$ L (spine 2.1). With these, $\kappa = 1/(N_A V) = 1/(4.816 \times 10^{12}) = 2.0764 \times 10^{-13}$ M per molecule.
- `DENSITY` $= 1.25 \times 10^{11}$ per L, so $\rho = $ `DENSITY` · `VOL` $= 1$ (M7.8).
- Compartment lateral area 1.6×10^{-5} cm^2 (delivery flux); compartment face area 4×10^{-6} cm^2, used as Δx^2 in the smoother (spine 2.1).
- `MW_TNF` $= 17400$, `MW_IL1O` $= 18600$ (S9), `MW_Etanercept` $= 150000$ and `MW_Infliximab` $= 149100$ g/mol.
- Transport cutoff 10^{-12} molecules (M1); no cutoff is applied after delivery, soluble binding or membrane binding.
- 600 s per cellular timestep, in the dosing rule.

Constraints

No startup check covers any parameter of the module. The table gives the conditions under which the module's updates behave as described, and the values that end the run or produce non-numbers, each in terms of the parameters alone.

Condition	Required for	Consequence if violated	See
$1000\,P\,\Delta t_d \le 1$ for each selected agent (P in cm/s, Δt_d in s)	Delivery that does not overshoot the driving difference	A call moves the source past the blood-equivalent count; outward flux can make it negative	M7.5
$k_{cl}\,\frac{1}{2}\Delta t_d \le 1$ for each agent, k_{cl} as applied, per second	Non-negative blood concentration	The concentration changes sign each call; above 2 it also grows	M7.4
$k_{on}\,\kappa\,E\,\Delta t_d \le 1$ and $k_{on}\,\kappa\,I\,\Delta t_d \le 1$ at every compartment	Soluble binding that does not overdraw free TNF or a lower complex	Negative free TNF or complex, persisting until the next transport cutoff and read by agents	M7.7

Condition	Required for	Consequence if violated	See
$k_{off}\,\Delta t_d \le 1$ and `Core_kDeg` $\Delta t_d \le 1$	Soluble dissociation and complex decay that do not overdraw a complex	Negative complex; for decay, more antibody returned than the complex held	M7.7
$k_{on}\,\kappa\,E\,\Delta t_m$, $k_{off}\,\Delta t_m$ and $\tau\,\Delta t_m$ within the stability region of the selected stepper	Stable integration of membrane binding	Oscillating or divergent membrane variables, written back into the drug fields	M7.8
$D\,\Delta t_s/(4\times10^{-6}) \le 1/4$ for each drug field, when the smoother step count is positive	Stable spectral smoothing	Growing grid-scale oscillation in the drug field	M7.6
`dosageInterval` $\neq 0$ for all four agents	Any run with the module selected and dosing started	Integer modulo by zero; the run normally terminates	M7.4
`volumeDist` $\neq 0$ for each selected agent	Delivery	The blood term is infinite or not a number: with nonzero permeability and blood concentration, the abort condition of M7.5 is met and the run terminates; otherwise the source compartment becomes not-a-number	M7.5
`diffusivity` $\neq 0$ for each drug field, spectral solver	Transport	The field becomes not-a-number everywhere, and free TNF with it if the antibody is dosed	M7.12
Non-negative values for every parameter of the group	Every rule	Sign reversal of the corresponding process, accepted without error	M7.12

The binding conditions depend on free antibody, which is largest at vascular sources, so they are most likely violated there, immediately after delivery. There are no constraints between parameters of different agents: dosing schedules, clearances and permeabilities are independent, and the agents may be dosed in any combination.

M7.13 Interfaces

With	Provides or receives	See
Spine 2.2, 2.4, 5.5	The six drug fields are padded, double-buffered fields of the field inventory, initialized to zero	M7.3

With	Provides or receives	See
Spine 3.2	Places the dosing and delivery block, the transport and soluble-binding steps, and the membrane terms in the schedule	M7.1
Spine 7.0	Omitted-parameter, range-check and resume-override rules	M7.2, M7.12
S1	Chemotaxis reads only chemokines; no channel reaches it	M7.9
S2, S3	Every TNF- and IL-10-dependent macrophage and T cell rule is reached; a daughter T cell inherits its parent's membrane-complex values (S3.5)	M7.8, M7.9
S6	Occupancy proxies, sink terms and secretion modulation read free TNF and IL-10 only; complex-bound TNF is invisible to them. The module adds a TNF-sequestration pathway in competition with the sink (S6.8) and decay. `Core_kDeg` is shared with the free-TNF decay	M7.7, M7.9
S7	Delivery uses the oxygen source-eligibility rule and its 0.8 literal (S7.4); oxygen reads the source compartment, not the neighbour mean	M7.5
S8	Delivery and recruitment both act on the source compartment; delivery precedes recruitment and uses the previous shuffle order	M7.5, M7.9
S9	Cell density (S9.3); reset codes and grid-dump format; the anti-TNF statistics belong to the inventory	M7.5, M7.10
M1	The selected solver sets the transport scheme, the placement of decay and cutoff, the smoother, the Etanercept sign, and Δt_d in dosing, clearance, delivery and soluble binding. The two spectral planning variants use identical equations. M1.3 specifies the zero-diffusivity construction (The propagator and incorporation of decay) and the smoother (The smoother), and M1.5 the Crank-Nicolson facts	M7.6, M7.7, M7.12
M2	Under the probabilistic option, delivery, soluble binding and shed TNF reach recruitment through TNF at each source compartment; under the alternative option, as M2 specifies	M7.9
M3	Membrane binding exists only within the per-agent ODE solve (M3.2: solve gates, stepper, `--odesolver`, shared stepper, per-class derivative function, subdivision). Membrane TNF and the TACE rate are M3's. Under coarse M3 throughout, the module acts by delivery and soluble binding only. The shed TNFR2 unbinding (M3.3) follows the antibody parts at each compartment	M7.7, M7.8
M4	TGF-β activation reads TNF at macrophage compartments and is reached by every channel; the module reads and writes no TGF-β field	M7.9
M5	The solvers described are those of the two-dimensional executable; the Crank-Nicolson ADI solver exists only there. M5.3 gives the 3D neighbour set of the local mean; a cloned three-dimensional solver uses no-flux plans with a sine transform on z, which affects its drug fields (M5.10)	M7.5, M7.6

With	Provides or receives	See
M6	Shared vascular object and vascular statistics routine; neither module reads the other's state; antibiotic delivery precedes immunomodulation delivery in each half-step, and the two write different fields; blood statistics are also written after antibiotic calls. Delivery computes cell density when called and does not use M6's density cache. M6.3: plasma is a forcing function for antibiotics. Unlike this module's permeabilities, antibiotic permeabilities are tested at each drug's creation and on a regular reload (M6.4)	M7.4, M7.5, M7.10
M8	TNF and IL-10 depletion suppress secretion only and do not affect delivery; no other perturbation interacts	M7.9
M9	Neutrophils carry the ten agent variables but never run the per-agent solve (M9.7), so they stay zero; no neutrophil rule depends on the module	M7.3
Appendix B	Indexes `--immuno-mod`, the dosages as agent selectors, the gating locations, and the inert parameters, fields and agent variables	M7.11
Parameters of other groups	`Core_kDeg` (S6); the diffusion and molecular timesteps and the smoother parameters (M1); the TACE rates (M3, S6.3)	M7.4–M7.8