S7. Oxygen and Vascular Sources

S7.1 Scope and schedule

This document specifies the oxygen field: its unit, its storage, its uniform initialization, its supply at vascular sources and its consumption by macrophages. The number and placement of sources are initialization (spine 5.2). Recruitment at sources is a separate submodel (S8). Antibiotics and immunomodulators are delivered at the same sources in other configurations (M6, M7; S7.10).

No rule here sets an agent state variable, and no rule here depends on recruitment. Consumption reads the macrophage list and each macrophage's position.

Position in the cellular timestep

Both mechanisms run inside the split half-step of the diffusion and molecular block, and so before any movement, recruitment or next-state computation. The enclosing sequence is in spine 3.2.

Block	Activity	Time argument	Position within the split half-step
Consumption	Each macrophage consumes at its own compartment	Δt_d	After all secretion calls, before the drug-uptake block
Supply	Each source exchanges with blood at its own compartment	$\Delta t_d/2$	After the molecular substep loop and the drug and immunomodulator vascular calls, immediately before the smoother

The split half-step runs twice per diffusion step, and there are N_d = 10 diffusion steps per cellular timestep, so each routine is entered twenty times per cellular timestep. Supply receives the half-step and consumption the full diffusion timestep. The consequences are specified in S7.6.

Nothing here runs on the cellular timestep proper or on the molecular substep.

Which grid object is written

The grid is double-buffered (M1.3, Non-transformed fields and grid buffering; spine 2.2). The next grid object is reset to a copy of the current one once per cellular timestep, before the diffusion block (spine 3.2). Both mechanisms write to the grid object that is current at the moment of the call. The objects are exchanged between the two split half-steps of each diffusion step, so consecutive oxygen writes alternate between them, and each object receives ten of the twenty applications of each routine. N_d is even, so the object current at the end of the diffusion loop is the one that was current at its start, and it survives into the next synchronization.

Neither the spectral nor the explicit solver advances or copies oxygen (M1.3, Fields presented; M1.3, Non-transformed fields and grid buffering; M1.4). Each grid object therefore keeps its own oxygen history between synchronizations, and only the history of the object current at the end of the diffusion loop survives. That history holds one application of each routine per diffusion step: ten applications of each oxygen routine per cellular timestep under the spectral option, twenty under the explicit option. Every per-timestep figure in this document counts surviving applications.

A reimplementation with a single grid, or one that carries oxygen forward between the two grid objects, does not reproduce this model.

Reads and writes

All reads and writes are against the current grid object.

Reads:

- oxygen at the acting macrophage's own compartment;
- oxygen, cell density and caseation status at each source's own compartment;
- the source list and the macrophage list;
- the five active parameters of the `O2` group (S7.9), and the constants `MW_O2`, `VOL` and the two-dimensional compartment lateral area (S7.2).

Writes:

- oxygen at the acting macrophage's own compartment, as an absolute value;
- oxygen at each source compartment, as an increment;
- the two auxiliary arrays of the oxygen field, implicitly, by both writes (S7.2).

The writes are exhaustive. No compartment counter, agent state variable or statistic is written here. The oxygen statistic is accumulated later in the timestep by the statistics sweep (S9).

A macrophage reads oxygen at its own compartment only, not across a neighbourhood. A source reads oxygen at its own compartment only, not as a mean over neighbours.

S7.2 Representation and units

Oxygen is carried in mg/L. This is an exception to the molecules-per-compartment convention of spine 2.1. The unit follows from the arithmetic of the flux term (S7.5), whose result is in mg/L with the molecular weight in mg/mol.

`MW_O2` is 32000 mg/mol. The header's other molecular weights, of the five cytokines and chemokines and the two anti-TNF agents, are in g/mol. 32 g/mol is 32000 mg/mol, and with the molecular weight in mg/mol the flux (S7.5) yields mg/L. The per-drug molecular weights `Drugs_*_MW`, which use the same flux routine, are also declared in mg/mol.

The supply routine divides the field by `MW_O2` to obtain mol/L and adds the returned change to the field without conversion.

The exchange area A is the lateral surface of a compartment in two dimensions, excluding its top and bottom faces:

```
A = 4 * (20 * 10^-4 cm)^2 = 1.6 * 10^-5 cm^2
```

It equals the lateral surface A_{cmpt} of spine 2.1. The whole perimeter of the source compartment exchanges with blood, not a single vessel wall.

Storage

Oxygen is declared as a padded field, like the diffusing fields, so it has a one-compartment halo and two auxiliary arrays maintained by its accessors. The halo exists for the stencil of a spatial operator, and the auxiliary arrays for the alternating-direction explicit solver. Neither is read in the default configuration, and a reimplementation may omit both.

S7.3 Initialization

When the grid is constructed, every compartment, source or not, is set to

```
O2_bloodConcentration * MW_O2 = 0.004 * 32000 = 128 mg/L
```

This converts the blood concentration from mol/L to mg/L. Oxygen is the only field initialized to a non-zero value (spine 5.5).

The initial value is the unique fixed point of the flux term: 128/32000 = 0.004, which equals the blood concentration with $\kappa = 1$. No source delivers or withdraws anything on the first half-step. The first non-zero flux occurs only after a macrophage has consumed oxygen in a source compartment, or after a source's delivery gate has closed and reopened around a compartment whose value has since changed.

The field is in mg/L. Initialization and supply operate in that unit; the conversions the consumption routine applies are given in S7.6.

The parameter-file field initialization of spine 5.4 can target oxygen, since oxygen is in the field inventory. It runs at the end of initialization, after the uniform value, and overrides it. It is not used by default, and the spine 5.4 caveat on dependent statistics applies.

S7.4 Vascular sources and the delivery gate

The source list

Sources are grid positions held by the grid; they are not agents and carry no state (spine 2.3). The supply routine visits them in list order. Each source reads and writes only its own compartment, so the order has no effect on oxygen.

The list is shuffled once per cellular timestep, immediately before recruitment, because the macrophage floor reads a count updated within the source loop (S8.2, S8.7); sources do not compete for slots. The shuffle follows the diffusion block, and it has no effect on oxygen.

The delivery gate

Delivery occurs at a source p if and only if $\delta(p) < 0.8$ (strict) and p is not caseated:

```
for each source p, in list order:
    if cell density delta(p) < 0.8 and p is not caseated:
        local <- oxygen(p) / MW_O2            # mol/L
        oxygen(p) <- oxygen(p) + flux(local)   # S7.5
    # no else branch
```

There is no else branch. Above the threshold, or in caseum, the flux is omitted rather than attenuated, and the compartment's oxygen is unchanged. The oxygen gate is therefore binary, where the drug gate is graded by a per-drug vessel activity (M6.4). A closed gate also blocks back-flux from a compartment above equilibrium; this never arises, because no mechanism raises a compartment above 128 mg/L.

The density is computed directly at each call; it is not read from the cache that M6 fills.

What the density measures

$\delta(p)$ is the cell density of S9.3: the fraction of the periodic Moore neighbourhood of p, centre included, that holds an immune cell, holds live extracellular bacteria, or is caseated. Density uses the periodic neighbourhood, so every source is evaluated against nine compartments.

The criterion measures tissue involvement, not viable cellularity: a wholly destroyed region has density 1. The rationale is that vascular structures are not visible in macrophage-rich regions or caseum in the reference imaging.

Densities are ninths, so 0.8 falls between 7/9 = 0.778 and 8/9 = 0.889. Delivery stops when eight or more of the nine compartments are occupied. Any threshold in (7/9, 8/9] gives identical behaviour in two dimensions.

The threshold 0.8 is a literal, with no parameter. It affects only the oxygen statistic by default, since no behavioural rule reads oxygen (S7.8). It also gates delivery under M6 and M7.

S7.5 The vascular flux term

With the gate open, the change added to the source compartment is

```
dC = P A dt MW / (10^3 V) * (kappa C_blood - C(p)/MW)
```

Symbol	Identifier or constant	Value
P	`O2_vascularPermeabilityO2`	1.28×10^{-5} cm/s
A	two-dimensional compartment lateral area	1.6×10^{-5} cm^2
κ	`O2_permCoeffO2`	1
C_blood	`O2_bloodConcentration`	0.004 mol/L
MW	`MW_O2`	32000 mg/mol
V	`VOL`	8×10^{-12} L
Δt	$\Delta t_d/2$	30 s

The routine is shared with the antibiotic path. The term is signed: a compartment below equilibrium gains oxygen, and one above it loses oxygen. With $\kappa = 1$ the equilibrium is the initial value of S7.3.

Magnitude

Writing $g = 128 - C(p)$ for the gap in mg/L, the term reduces to

```
dC = P A dt / (10^3 V) * g = 0.768 g
```

Each application closes 76.8 % of the gap, and the residual factor is 0.232. At full depletion $\Delta C = 98.3$ mg/L. A fully depleted compartment reaches 99 % of equilibrium in four applications, which is 0.4 cellular timestep of the surviving history. The coefficient 0.768 is also the ratio that governs the overshoot guard.

The oxygen caller applies neither the drug path's clamp of the change against the current value nor its cutoff truncation. The change is negative only above equilibrium, and the field is clamped at zero on the consumption side (S7.6), so adding either step leaves every trajectory unchanged.

The overshoot guard

The flux routine aborts the run if

```
|dC| > |kappa C_blood - C(p)/MW| * MW
```

Both sides share the bracket, so the guard fires if and only if $PA\Delta t/(10^3 V) > 1$, that is $\Delta t > 39.1$ s, independent of the field. The realized ratio is 0.768, so the guard never fires by default; the margin is 23 %. Because the argument is the half-step, the constraint is $\Delta t_d < 78.1$ s. Every diffusion option satisfies it: $\Delta t_d = 60$ s gives 0.768, and 30 s gives 0.384 (M1.2). Another option, or a recalibrated permeability, could violate it.

The constraint is enforced only at run time. Each drug's permeability is tested against the same bound, strictly, when the drug is created and on a regular reload. The non-strict check in timestep synchronization runs only on a load or restart, against saved values (M6.4). The oxygen permeability is not tested at startup. With a larger Δt_d the run passes startup and stops on the first half-step at which an open-gated source compartment stands below equilibrium.

What the term represents

The flux represents exchange across the whole lateral surface, driven by a fixed blood concentration. Vessel geometry, calibre, flow and oxygen binding are not represented. The blood concentration is a constant, never depleted by delivery; there is no systemic compartment for oxygen. Supply is therefore unlimited in aggregate and limited only per compartment, by the gate and the equilibrium ceiling.

S7.6 Consumption by macrophages

Who consumes

Only macrophages consume, because the consumption routine iterates the macrophage list alone. Dendritic cells, held in their own list, do not consume although they inherit the method; neutrophils (M9.6) and T cells never do. No dendritic cell or neutrophil exists in the default configuration. The restriction comes from the iteration, not from the configuration: dispatching consumption over all agents would not reproduce the model where other types exist.

A compartment holds at most one macrophage, as a large agent (spine 2.3). The routine writes an absolute value, which would be order-sensitive only with two consumers in one compartment.

Every macrophage alive at the end of the previous timestep consumes throughout this one, since the diffusion block precedes next-state computation and the removal of dead agents. A macrophage that dies later in the timestep has already made all its applications. A macrophage recruited this timestep makes none, since recruitment follows the diffusion block. A daughter is never a macrophage.

The rate

```
R = V_max C / (C + k_m)
C <- max(C - R dt_d, 0)
```

The zero clamp is the only clamp on the oxygen field. Both constants are converted before use:

- V_max = `O2_VMAO2` $/10^{-15} = 0.0625$;
- k_m = `O2_KMAO2` $/10^{3} \times$ `VOL` $/10^{-15} = 0.0168$.

The program applies both conversions to the field in mg/L (S7.2), so V_max acts as 0.0625 mg/L per second and k_m as 0.0168 mg/L. Oxygen rates differ from their nominal values (spine 1.3). Per cellular timestep, consumption acts for 600 s at these rates and supply for 300 s (S7.1).

k_m is about four orders of magnitude below the field, so consumption is zero-order until the clamp.

Realized consumption

Each application removes $0.0625 \times 60 = 3.75$ mg/L. With ten surviving applications per cellular timestep, a macrophage removes up to 37.5 mg/L per cellular timestep. Supply acts over 300 s of surviving time per timestep, half the cellular timestep.

A non-source compartment is exhausted after $\lceil 128/3.75 \rceil = 35$ surviving applications, one per diffusion step: the fifth of the fourth timestep of residence, about 35 minutes. An exhausted non-source compartment stays at zero, since oxygen is never transported laterally (S7.8).

Within each half-step consumption precedes supply. An occupied open-gated source is therefore depleted and partly refilled once per surviving diffusion step, and the two compose into a map with a fixed point (S7.7).

S7.7 Supply, demand and hypoxia

Quantities in this section are per surviving application unless stated otherwise. Consumption removes a fixed amount per application; supply closes a fixed fraction of the gap. They cannot be compared as rates.

An occupied open-gated source

Consumption precedes supply, so the two compose into the map

```
C |-> (C - 3.75) + 0.768 [128 - (C - 3.75)]
```

whose fixed point is 126.9 mg/L. An occupied open-gated source oscillates between 123.1 and 126.9 mg/L, 96–99 % of equilibrium. A macrophage depresses an open-gated source by a few per cent only.

A non-source compartment

A non-source compartment has no supply term, so any resident macrophage drives it monotonically to zero. k_m is reached only on the last application, and the clamp disposes of the remainder without extending the time.

An exhausted compartment stays at zero unless it is a source whose gate later opens. A gate reopens if density falls, as when the lesion recedes, or if healing clears caseation: an adjacent activated macrophage starts healing, and after `Core_caseationHealingTime` the killing count halves and may fall below threshold (S2.8, S5.8). A caseous source in a sparse neighbourhood can therefore resume delivery; a dense neighbourhood blocks it regardless of caseation.

Structure of the field

Each compartment is in one of these conditions:

Condition	Oxygen
Source, gate open	At or near 128 mg/L
No source, never visited by a macrophage	Exactly 128 mg/L
No open-gated source, visited by a macrophage	Zero within four cellular timesteps of the first full residence; occasionally an intermediate residue

There is almost no intermediate regime and no gradient. Transitions run only toward depletion. The contrast between the source and non-source cases, not a balance of rates, produces this structure.

Exhaustion needs 3.5 timesteps of continuous residence. A residence can be shorter, because movement opportunity is tested on age modulo the movement interval, not on time since arrival (S1.2). A recruited resting macrophage has its first opportunity between one timestep and one full interval after arrival, roughly uniformly, since recruits are given randomized birth times (S8.12). With `Core_Mac_movementRest` in [4, 6], a one-timestep first residence has probability 1/4 to 1/6. A change of state can also bring the next opportunity forward (S1.2).

A one-timestep residence, ended when the chosen destination admits the macrophage, removes 37.5 mg/L and leaves 90.5 mg/L. A residence of a full interval at the resting rate or slower always exhausts the compartment. Intermediate residues are sparse and persist until another macrophage resides there.

The field therefore superimposes two binary patterns: the positions of open-gated sources, and cumulative macrophage residence. It records where macrophages have been, not where they are.

What produces hypoxia

The gate is not the binding constraint. Sources are about 8.8 % of compartments (spine 5.2). The other 91.2 % are never supplied, and the first macrophage to rest in one depletes it. Hypoxia results from the absence of lateral transport; the gate only extends it to the sources once the lesion is dense.

Extracellular bacterial growth is modulated instead by the radius-2 count of caseous compartments and chronically infected macrophages, which parameter names describe as a hypoxia proxy (S4.6, S5.5). The oxygen field is not that proxy and is not read by it. The model therefore holds two independent representations of local hypoxia, which need not agree. They need not coincide in space either: the proxy follows death and chronic infection, while the field follows residence of any state and source geometry.

S7.8 Oxygen as an output

No behavioural rule is gated on oxygen. The only reads that bear on output are a macrophage's own consumption, the flux, and the observation sum. The submodel is a pure output: removing it leaves every agent and bacterial trajectory identical, and changes only the oxygen statistic, field dumps and saved state. It consumes no random draws, so removing it does not perturb the random stream.

No solver transports oxygen in any configuration: the oxygen diffusion path is compiled out in every solver (M1.3, Fields presented). `O2_diffusivityO2` and `O2_degRateConstO2` are therefore read and have no effect (M1.5).

The oxygen statistic is a plain sum of mg/L values over all compartments. Unlike the cytokine totals, from which S9 forms concentrations, the oxygen total has no concentration counterpart. Its properties are specified in S9.11.

S7.9 Parameters

All parameters are in group `O2`. None is sampled.

Identifier	Value or range	Units	Meaning
`O2_bloodConcentration`	0.004	mol/L	C_blood in the flux term (S7.5); times `MW_O2`, the uniform initial value (S7.3)[1]
`O2_vascularPermeabilityO2`	1.28×10^{-5}	cm/s	Permeability P (S7.5)[2]
`O2_permCoeffO2`	1	—	Multiplier κ on C_blood; at 1 the equilibrium is C_blood itself
`O2_VmaO2`	6.25×10^{-17}	mol/cell/s (declared)	Maximum consumption rate; acts as 0.0625 mg/L per second (S7.6)[1]
`O2_kmaO2`	2.1×10^{-3}	mM (declared)	Half-saturation for consumption; acts as 0.0168 mg/L (S7.6)[1]
`O2_diffusivityO2`	1.75×10^{-5}	cm^2/s	Read; no effect (S7.8)
`O2_degRateConstO2`	0	—	Read; no effect (S7.8)

[1] The consumption parameters are converted before use as stated in S7.6. `O2_bloodConcentration` enters the flux in mol/L, its declared unit, and is converted to mg/L at initialization.

[2] With the present permeability, $\Delta t_d < 78.1$ s is required; it is checked only at run time (S7.5).

No `O2` parameter declares a minimum or maximum, so none is range-checked. Negative values pass startup; they reverse the flux or make consumption add oxygen. Two parameters carry declared defaults, `O2_VmaO2` and `O2_kmaO2`. The other five have no declared default, so a parameter file that omits any of them fails at startup (spine 7.0, Resolution).

Fixed structural constants. The density gate threshold 0.8 (S7.4); the area $A = 1.6 \times 10^{-5}$ cm^2; `VOL` = 8×10^{-12} L; `MW_O2` = 32000 mg/mol; the factor 10^3 in the flux; the factor 10^{-15}, twice, in consumption; and the guard bound implied by the flux routine (S7.5).

Read here, owned elsewhere. The gate reads caseation, whose threshold `Core_nrKillingsCaseation` is sampled over [12, 18] (S5), so gate closure varies across the library although no `O2` parameter does. Δt_d and N_d belong to the diffusion option (M1).

Read but without effect by default. `O2_diffusivityO2`, `O2_degRateConstO2`.

S7.10 Interfaces

With	Provides or receives	See
Spine Element 7	S7 specifies the oxygen and vascular-source submodel listed there	Spine Element 7
Spine 2.1, 2.3	Unit convention, of which oxygen is the exception; one large agent per compartment	S7.2, S7.6
Spine 2.2, 2.4	Double buffering; padded storage of oxygen	S7.1, S7.2
Spine 3.2	Enclosing sequence of the split half-step	S7.1
Spine 4.2	Hypoxia results from the absence of lateral transport; bacteria read the caseation proxy	S7.7
Spine 5.2, 5.4, 5.5	Source count and placement; parameter-file field initialization; oxygen as the only non-zero initial field	S7.3, S7.4
Spine 7.0	Omitted-parameter rule (Resolution) and range rule (Validity ranges)	S7.9
S1	Movement opportunity on age modulo the interval, which sets residence times	S1.2
S2, S5	Caseation predicate and threshold read by the gate; healing reopens gates	S2.8, S5.8
S4, S5	The caseation proxy for hypoxia, independent of this field	S4.6, S5.5
S8	Shares the source list; shuffles it before recruitment; recruitment applies no density gate	S8.1, S8.2

With	Provides or receives	See
S9	Cell density and occupancy predicates read by the gate; the oxygen statistic	S9.3, S9.11
M1	Δt_d is the argument of both mechanisms and N_d sets how often each applies; neither the spectral nor the explicit solver advances or copies oxygen	M1.3, M1.4
M2, M3	No effect. M2 shares the source list but does not alter it	M2, M3
M4	Fibroblasts do not consume oxygen but count toward cell density, so can close a gate	M4
M5	Three-dimensional build	M5.5, M5.11
M6	Adds drug species to the source loop and shares the flux routine; attenuates instead of omitting	M6.3, M6.4
M7	Adds immunomodulator species through a different flux routine; does not interact with oxygen	M7.4, M7.5
M8	Reinfection creates a consuming macrophage; not enabled	M8.3
M9	Neutrophils do not consume oxygen but count toward cell density; injection (M8.9) would add density; not enabled	M9.2, M9.6
Appendix B	Indexes the `O2` parameters read without effect	Appendix B

M1 options. Under the explicit option $\Delta t_d = 30$ s and $N_d = 20$, so each routine is entered forty times per cellular timestep and twenty applications survive. Accumulated consumption (one cellular timestep) and supply (half of one) are identical under both options, though the substep size differs. Occupied-source steady states differ only in the third significant figure (126.9 against 125.0 mg/L). The molecular timestep does not enter this submodel.

M5, three dimensions. The flux and the run-time guard (S7.5) use the two-dimensional area constant, shared by both builds, so the exchange surface and the guard bound are the same in three dimensions (M5.11). The three-dimensional area constant is held by M5.5. `VOL` is the same in both builds; a two-dimensional compartment is a cube one compartment thick (M5.5). In three dimensions the gate admits at most 21 of 27 occupied compartments, the same fraction as in two dimensions. The S9 scaling of counts is not applied to the oxygen statistic.

M6 and M7, other species at vascular sources. The vascular machinery also delivers antibiotics and immunomodulators at the same sources. Both are inactive by default. Antibiotic delivery, its plasma pharmacokinetics, its attenuated density branch and its neighbour-mean local concentration are specified in M6.3 and M6.4. Immunomodulator delivery, its flux routine and its guard are specified in M7.4 and M7.5. The vascular object is still constructed, serialized and cloned (M7.4).