S1. Movement and chemotaxis

S1.1 Scope and schedule

This submodel specifies how motile agents change position: the movement opportunity test (S1.2), the choice of a destination compartment (S1.3) and the admission test at that destination (S1.4). S2 and S3 specify the agents that move.

Block	Activity	Interval
Movement, after the diffusion and molecular block and before recruitment (spine 3.2)	Opportunity test, destination draw and admission, for each agent on an agent list, one type at a time	Every cellular timestep; a macrophage attempts only at the ages set in S1.2

Type order. All agents of one type move before any agent of the next type, in the order macrophage, dendritic cell, neutrophil, Tgam, Tcyt, Treg, fibroblast. The dendritic-cell and neutrophil routines run every timestep, over lists that are empty by default. The fibroblast routine runs only when TGF-β dynamics is selected (M4; Appendix B). This movement order differs from the next-state and commitment order (spine 3.3), in which neutrophils come last. In the default configuration the agents that move are macrophages, then Tgam, Tcyt and Treg.

Fields read. Movement reads the chemokine fields left at the end of the diffusion and molecular block. That block ends with the second split half-step of the final diffusion step (spine 3.2), so the values include secretion applied after the last diffusion solve. Movement writes no field, so every agent in the block reads the same field values, whatever its place in the processing order.

Reads.

- CCL2, CCL5 and CXCL9 at the nine compartments of the agent's periodic Moore neighbourhood, including its own compartment, where the sensitivity gate is evaluated.
- At the drawn destination: caseation status, occupant count, whether a large agent is present and, for T cells, whether the occupant is a macrophage or a T cell.
- The agent's committed current state and, for macrophages, its birth time.
- The random number generator.

Writes.

- The agent's position.
- Slot occupancy of the origin and destination compartments.
- For macrophages, the blocked-by-large-agent statistic (S9.15).

Movement alters no field, no compartment counter other than occupancy, and no agent's state. An agent that fails to move is not penalised and does not retry within the timestep.

Agents that do not move. Bacteria have no position of their own (spine 2.3). Vascular sources are immovable. Chronically infected macrophages never pass the opportunity test (S1.2); this is the only macrophage state that never moves. Every other agent on an agent list attempts movement, irrespective of suppression, down-regulation, T0 state or antigen specificity, and moves by exactly the same rule as its counterparts; for a macrophage the suppression timer is not consulted.

No dead agent is met in the movement block in the default configuration. Dead agents are removed at the end of the previous timestep, and no rule executed between that removal and the movement block kills an agent (spine 3.2).

S1.2 Movement opportunity

The opportunity test is evaluated first. An agent that fails it does no further movement processing.

A macrophage with birth time b may attempt to move at timestep t if and only if

$$(t - b) \bmod I(\text{state}) = 0,$$

where I is the interval for its committed current state (spine 2.3):

State	Interval I (S1.6)
Resting	`Core_Mac_movementRest`
Activated	`Core_Mac_movementAct`
Infected	`Core_Mac_movementInf`
Chronically infected	None: never attempts

Because the test is on age, not on absolute time:

- **Macrophages are not synchronised.** Initial and recruited macrophages are given randomised birth times (spine 5.3, S8.12).
- **A state change does not restart the cadence.** The next attempt is at the next age divisible by the new interval, which may be anywhere from one timestep to a full interval away.
- **Cadence is shared within a state.** The interval is fixed within a simulation, so all macrophages in one state share one cadence and differ only in phase.

T cells have no opportunity test: all three types attempt movement on every timestep. They therefore attempt movement 4 to 6 times as often as resting macrophages, and over 100 times as often as infected ones.

S1.3 Destination selection

Candidate set

The candidates are the nine compartments of the periodic Moore neighbourhood of the agent's position, $N_8(\text{pos})$, addressed by the ordinal convention of spine 2.1. Weight k is sensed at the k-th position of the periodic Moore iterator, and the agent moves to ordinal k; these coincide in two dimensions (M5 for three).

Because the neighbourhood is periodic, an agent at the domain edge also has nine candidates. Candidates beyond the boundary are wrapped to the opposite side of the domain, and their weights are read from the wrapped compartments. Under the selected diffusion option the fields are held at zero at the domain boundary (M1), so values at and across an edge are depressed on both sides of it.

The agent's own compartment, ordinal 4, is a candidate and is weighted like any other. Drawing it does not by itself keep the agent in place. It is passed to the admission test of S1.4 exactly as any other destination would be, with the agent counted among its occupants.

Chemotactic sensitivity gate

One concentration window, shared by all three chemokines and all agent types, gates each chemokine's contribution. The gate for chemokine m is open if and only if

$$C_{\min} < C_m(\mathrm{pos}) < C_{\max},$$

with $C_{\min}$ = `Core_minChemotaxis` and $C_{\max}$ = `Core_maxChemotaxis` (S1.6). Both inequalities are strict, so a concentration equal to either bound closes the gate.

The gates are evaluated on every movement attempt from the values at the agent's own compartment. The gate of a chemokine the agent's type does not sense has no effect. A closed gate removes that chemokine's contribution from every candidate, including candidates at which its concentration lies inside the window. Chemotaxis for that chemokine switches off; it does not saturate or clamp.

An agent moves chemotactically if any of its sensed gates is open. When every sensed gate is closed, the destination is drawn uniformly (Weighting and draw). At the ends of the window:

- **Below the lower edge** an agent detects no gradient, even if a neighbouring compartment holds a concentration inside the window. It must first reach the window by undirected movement.
- **At or above** $C_{\max}$ an agent loses directional information and moves without bias. This disperses agents within the most chemokine-rich part of a lesion rather than concentrating them further.

Per-type sensitivities

Each agent type passes a fixed set of chemokine flags to destination selection.

Agent type	CCL2	CCL5	CXCL9
Macrophage	Yes	Yes	No
Tgam	Yes	Yes	Yes
Tcyt	No	Yes	Yes
Treg	No	Yes	No

CCL5 and CXCL9 are derived from CCL2 with ratios $r_5 = 1$ and $r_9 = 2$ (S6.14). Writing c for the CCL2 concentration at the agent's own compartment, the gates open on these intervals of c:

Chemokine	Gate open when
CCL2	$C_{\min} < c < C_{\max}$
CCL5	$C_{\min} < r_5 c < C_{\max}$, that is $C_{\min} < c < C_{\max}$
CXCL9	$C_{\min} < r_9 c < C_{\max}$, that is $C_{\min}/2 < c < C_{\max}/2$

The weight at candidate q is therefore a multiple of $C_{\mathrm{CCL2}}(q)$, set by the type and by the band holding c. A multiple of zero means that every sensed gate is closed and the destination is drawn uniformly. For $c \leq C_{\min}/2$ or $c \geq C_{\max}$ the multiple is zero for every type.

Agent type	$C_{\min}/2 < c \leq C_{\min}$	$C_{\min} < c < C_{\max}/2$	$C_{\max}/2 \leq c < C_{\max}$
Macrophage	0	2	2
Tgam	2	4	2
Tcyt	2	3	1
Treg	0	1	1

In every non-zero case the multiple is set at the agent's own compartment, so it is common to all nine candidates and cancels on normalisation. The bonus of the weighting step goes to the largest weight, so it selects the same candidate under any positive multiple. Within a chemotactic regime, therefore, every agent type has the same destination distribution.

The types differ only in the lower edge of the CCL2 window in which they are chemotactic: Tgam and Tcyt above $C_{\min}/2$, macrophages and Tregs above $C_{\min}$. All four become undirected at $C_{\max}$. With the sampled ranges the lower edge is [0.197, 0.253] molecules of CCL2 for Tgam and Tcyt, and [0.393, 0.506] for macrophages and Tregs. By default, the cell types therefore share one chemotactic steering rule and differ only in where it applies.

The result requires CCL5 and CXCL9 to equal r_5 and r_9 times CCL2 when movement is evaluated, not only immediately after each diffusion solve, since the final half-step's secretion persists until movement (S1.1). In the default configuration every chemokine source keeps the proportion $1 : r_5 : r_9$: the three macrophage secretion rates are in the proportion 1 : 1 : 2 and IL-10 suppression halves all three together; caseum adds a quarter of each macrophage rate (S5.6); T cells secrete no chemokine. The relation therefore also holds for the fields movement reads (S6.14).

Weighting and draw

For each candidate ordinal k with compartment q_k, the weight is the sum of the sensed chemokine concentrations whose gates are open:

$$w_k = \sum_{m \in M(\mathrm{type})} \mathbb{1}[g_m]\, C_m(q_k),$$

where $M(\mathrm{type})$ is the sensitivity set of the agent's type. Every weight is non-negative, since the chemokine fields are never negative.

A bonus is then applied to a single candidate k^*. It is found by scanning the weights from ordinal 0 to 8, keeping the current maximum and replacing it only when a strictly larger weight is found, so ties go to the lowest ordinal attaining the maximum. With β the bonus factor of the agent's type, `Core_Mac_movementBonusFactor` for macrophages and `Core_Tcell_movementBonusFactor` for all three T cell types,

$$S = \sum_k w_k + (\beta - 1)\, w_{k^*}, \qquad w_{k^*} \leftarrow \beta\, w_{k^*}.$$

If $S > 0$, the weights are normalised and one uniform draw u on [0, 1) is taken. The destination is the first ordinal, scanning from 0, whose cumulative probability is not less than u:

$$p_k = \frac{w_k}{S}, \qquad F_k = \sum_{j \le k} p_j, \qquad k \leftarrow \min\{k : F_k \ge u\}.$$

If $S = 0$, the destination is drawn uniformly over the nine ordinals:

$$k \sim U\{0, \dots, 8\}.$$

$S = 0$ holds exactly when every gate the agent's type senses is closed. If any sensed gate is open, that chemokine's concentration at the agent's own compartment exceeds $C_{\min} > 0$. That compartment is candidate 4, so $w_4 > 0$ and $S > 0$.

Edge cases of the search, each with a probability per draw of the order of floating-point rounding:

- A draw of exactly $u = 0$ selects ordinal 0 whatever its weight, since $F_0 \ge 0$.
- If rounding in the normalisation and summation leaves $F_8 < u$, the agent is sent to the lower-left neighbour, offset $(-1, -1)$, rather than to ordinal 8.

The uniform fallback is part of the same routine as the weighted draw, not a separate movement mode, and no agent keeps any memory of previous directions. An agent with no usable signal therefore performs an unbiased single-step random walk over its Moore neighbourhood. It draws its own compartment with probability 1/9, which does not move it (S1.4). It also stays in place whenever the drawn destination is not admitted, so its probability of staying in place on an attempt is at least 1/9.

Status of the bonus factor

Both bonus factors default to 1 and are absent from the default parameter file, so

$$\beta = 1 \implies S = \sum_k w_k, \quad w_{k^*} \text{ unchanged},$$

and the bonus term vanishes identically. Movement in the default configuration is a plain concentration-proportional draw with no gradient sharpening.

S1.4 Admission at the destination

Drawing a destination does not move the agent. A type-specific test is applied to the drawn compartment q, as it stands when the agent is processed (S1.5). The agent's position changes only if the test passes and q differs from its current position. If q is the agent's own compartment, the agent is counted among its occupants. The occupant count n(q) is that of spine 2.3; by default the only possible occupants are macrophages and T cells.

At the movement block no compartment holds a dead agent. Agents killed in the previous timestep, including those killed when their compartment caseated, were removed at its end (spine 3.2). Every caseated compartment is therefore empty when movement is evaluated in the default configuration.

Macrophages

The macrophage procedure is deterministic.

```
q <- drawn destination
if n(q) < 2 and q holds a large agent:
    increment the blocked-by-large-agent statistic (S9.15)
if not caseated(q) and n(q) < 2 and q holds no large agent:
    place the macrophage in the first free slot of q
    remove it from its slot in the origin compartment
    pos <- q
```

Macrophages are the only large agents in the default configuration, so the large-agent condition excludes any compartment already holding a macrophage. A macrophage may enter an empty compartment or one holding a single T cell. It may not enter a compartment holding another macrophage, one holding two T cells, or a caseated compartment.

When the drawn destination is the macrophage's own compartment, the macrophage is itself the large agent present. Admission therefore always fails, and the macrophage stays where it is.

T cells

All three T cell types use the same procedure.

```
q <- drawn destination
admit <- false
if not caseated(q) and n(q) < 2:
    if n(q) == 0:
        admit <- true
    else if q holds a macrophage and U(0,1) < p_mac:
        admit <- true
    else if q holds a T cell and U(0,1) < p_tcell:
        admit <- true
if admit:
    remove the T cell from its slot in the origin compartment
    place it in the first free slot of q
    pos <- q
```

Here p_{mac} = `Core_Tcell_probMoveToMac` and p_{tcell} = `Core_Tcell_probMoveToTcell` (S1.6). Both comparisons are strict.

No large-agent exclusion applies to T cells: a T cell may enter a compartment holding a macrophage, with probability p_{mac}.

Destination contents	**Admission**
Caseated	Rejected
Two occupants	Rejected
Empty	Certain
One macrophage	With probability p_{mac}
One T cell	With probability p_{tcell}

Destination contents	Admission
One occupant of another type	Rejected, with no draw

The occupant of another type is a neutrophil (M9) or a fibroblast (M4), both absent by default. Its refusal lies in the T cell movement routine. The grid's test for adding a T cell (not caseated, n(q) < 2) does not refuse such a compartment (M9.6).

T cell self-destination

When the drawn destination is the T cell's own compartment, the outcome depends on what else the compartment holds.

- **With another agent,** n(q) = 2. The attempt is rejected and no draw is consumed.
- **Alone,** n(q) = 1, and the sole occupant is a T cell: the cell itself. One draw is made against p_{tcell}. On success the T cell is removed from its slot and placed in the first free slot of the same compartment. Its position does not change, but its slot index may.

S1.5 Sequential evaluation

Movement is sequential, not simultaneous. Agents act one at a time in list order, and each addition to and removal from grid slots takes effect at once. Every agent therefore sees the occupancy left by all agents processed before it in the block. Each agent makes at most one attempt per block, moves at most one compartment, and is not revisited.

- **Displacement chains.** An agent may enter a compartment vacated earlier in the block by another agent, of the same type or of a type processed earlier. Chains of displacement through a congested region can therefore advance within one timestep, one compartment per agent.
- **Contests for space.** When two agents draw the same destination and only one can be admitted, the one processed first takes the slot. Within a type the processing order is the agent-list order, permuted only by the periodic shuffle of spine 3.3. Between shuffles it is carried forward, with newly recruited agents and committed daughters appended at the end of their lists and dead agents removed.
- **Type asymmetry.** All macrophages move before any T cell (S1.1). T cells therefore see the post-movement macrophage configuration, and macrophages the pre-movement T cell configuration. The type order (S1.1) is never shuffled.
- **New agents.** Agents recruited, or committed as daughters, on a timestep are placed after the movement block (spine 3.2). They make no attempt until the next timestep, and they are not occupants when the agents already on the grid move. The reinfecting macrophage of M8 differs (S1.7).

S1.6 Parameters

Identifier	Value or range	Units	Meaning	Range
`Core_Mac_movementRest`	Sampled	timesteps	Movement interval of a resting macrophage (S1.2)	[4, 6]

Identifier	Value or range	Units	Meaning	Range
`Core_Mac_movementAct`	Sampled	timesteps	Movement interval of an activated macrophage	[21, 23]
`Core_Mac_movementInf`	Sampled	timesteps	Movement interval of an infected macrophage	[133, 172]
`Core_minChemotaxis`	Sampled	molecules	Lower bound $C_{\min}$ of the shared sensitivity window (S1.3)	[0.393, 0.506]
`Core_maxChemotaxis`	Sampled	molecules	Upper bound $C_{\max}$ of the shared sensitivity window	[397.0, 504.3]
`Core_Tcell_probMoveToMac`	Sampled	probability	p_{mac}: T cell admission into a compartment holding one macrophage (S1.4)	[0.03404, 0.05548]
`Core_Tcell_probMoveToTcell`	0.08	probability	p_{tcell}: T cell admission into a compartment holding one T cell, including the T cell itself; also read by recruitment (S8.9)	—
`Core_Mac_movementBonusFactor`	1.0, default; absent from the file	—	Bonus factor β for macrophages[1]	—
`Core_Tcell_movementBonusFactor`	1.0, default; absent from the file	—	Bonus factor β for all T cell types[1]	—

[1] Startup fails if either bonus factor is below 1, which would penalise rather than reward the strongest direction.

Fixed structural constant. The candidate count is 9: the Moore neighbourhood of radius 1, including the agent's own compartment, which is also the range of the uniform fallback. It is not a parameter-file entry. The two slots per compartment and the single large agent per compartment are fixed by spine 2.3.

Read but without effect by default: both bonus factors (inert at $\beta = 1$).

S1.7 Interfaces

With	Provides or receives	See
Spine Element 7	S1 expands the movement submodel listed there	Spine 7.1
Spine 2.1	Ordinal convention and offset decoding	Spine 2.1
Spine 2.3	Occupant count, slots, size classes, committed state	Spine 2.3

With	Provides or receives	See
Spine 3.2, 3.3	Block position; next-state and commitment order; agent-list shuffle; removal of dead agents; placement of recruits and daughters after movement	Spine 3.2, 3.3
Spine 5.3	Randomised birth times of initial macrophages	Spine 5.3
S2	Macrophage states; S2 links S1 for the movement intervals, the bonus factor and the immobility of chronically infected macrophages	S2.13
S3	T cell types, cognate status, down-regulation and T0 states; all T cells move by the same rule (S1.1)	S3
S5	Caseation status read at the destination	S5
S6	Derived chemokine fields, and secretion by every source in the proportion $1 : r_5 : r_9$	S6.14
S8	Randomised birth times of recruits; recruitment reads `Core_Tcell_probMoveToTcell`	S8.9, S8.12
S9	Definition of the blocked-by-large-agent statistic, including its counting of macrophage self-draws	S9.15
M1	Advances the chemokine fields read here; zero-concentration boundary under the selected option. The identical-distribution result assumes CCL5 and CXCL9 are reassigned from CCL2 after each solve; a solver diffusing them independently would invalidate it	M1.3
M2	No change to the movement rule. Under the lymph-node option, the cognate fraction is a model output (M2), set by the relative blood concentrations of the cognate and non-cognate effector compartments; the `Recruit_Prob_Tcell_<type>_probCognate` parameters are not read. All T cells move by the same rule	M2.9
M3	No change to the movement rule. Under the fine-grained option the NF-κB system's chemokine output is added in a literal proportion 1 : 1 : 2, which matches the reference ratios and so preserves the proportionality S1.3 needs	S6.14
M4	Fibroblasts move after Tregs, only when TGF-β dynamics is selected. Fibroblast admission is the macrophage test of S1.4, so a fibroblast cannot enter a compartment holding a macrophage. Myofibroblasts use the S1.3 routine with all three chemokine flags and $\beta = 1$. Movement rule and size class in M4; no TGF-β quantity enters any other type's movement	M4.5
M5	27 candidates and a uniform fallback of 1/27; gate intervals unchanged. In three dimensions the iterator position and the ordinal differ (M5.4)	M5.3, M5.4
M6	No change to the movement rule. Intracellular drug moves with the macrophage	M6.8

With	Provides or receives	See
M7	No effect on movement	—
M8	A reinfecting macrophage has birth time t and is added before the movement block, so it is at age 0 and may attempt movement on its arrival timestep, unlike recruits. No other M8 option alters movement	M8.3
M9	Neutrophils do not use the S1.3 weighting. They choose destinations by their own rule (M9.4), decoded as in S1.3, including its rounding case, and admit by the crowding rule, which makes no caseation test, so they may enter caseated compartments (M9.3)	M9.3, M9.4