Appendix B. Index of configuration toggles

B.1 Scope and conventions

Purpose

This appendix indexes every setting that does any of these:

- switches a mechanism on or off;
- selects among variants of a mechanism;
- holds a mechanism at nil effect.

For each setting it gives the controlling identifier and its options, the program default, the default-configuration value, and the source file and function holding the gate. Grimm et al. (paragraph 4.22) recommend a table locating each element of a model description in the code; this appendix provides that linkage for configuration. Source locations refer to revision r9959 (spine 1.4).

The rules of a mechanism that a switch gates are specified by the mechanism's owner, which each section links. This appendix keeps the switch, its gate, what holds it at nil, and how settings interact.

The default configuration

The default configuration is the set of settings used for the study reported in the main text. Its module selections are listed in the spine's module-slot table, and its invocation is given in B.3.

The default configuration is a documented starting point, not a prescription. A study may change any setting indexed here. Many mechanisms that contribute nothing in the default configuration are fully implemented, although some need two settings changed together (B.11, conjunctive gates).

The appendix describes the configuration space, not individual runs. It excludes run-specific values:

- the parameter file path;
- the output directory;
- the random seed;
- the flags used by batch-management scripts;
- the sampled parameter values of any individual simulation.

The ranges of sampled parameters are given in the owning S# and M# parameter tables.

Terms

Term	Meaning
Program default	The value used when a setting is not supplied: for a command-line option, the default declared in `grmain.cpp`; for a parameter-file entry, the default declared in `params.def`

Term	Meaning
Default-configuration value	The value used in the default configuration
Selected	The option chosen for a module slot
Gate	The test in the source that decides whether a mechanism executes
Inert	Live code that executes but whose effect on model state is nil in the default configuration; inert code may still consume random draws
Sentinel	A value of an ordinary parameter that disables the mechanism reading it, by its sign or magnitude rather than by a dedicated switch
Defaulted	A parameter whose value was not read from the parameter file and was taken from its declared default
Mandatory	A parameter declared without a default; omitting it from the parameter file is fatal at startup

Program defaults and default-configuration values coincide for most settings, but not all. A setting omitted from an invocation takes its program default, not its default-configuration value, so every switch table reports both.

A component is absent when no instance of it is ever created. Every absence is held by a live gate (B.5), not by removal of code, so configuration alone can make the component present.

Notation

Command-line options are written with their leading double hyphen, as `--diffusion`. Parameters are written as `Group_name` (spine 2.1), as `Core_Mac_dCCL2`. Source functions are written as `Class::function`.

Identifiers are quoted verbatim, including spellings that are part of the interface, such as `mtbStopppingTimeStep`. A parameter file must use the declared spelling.

B.2 Toggle mechanisms and resolution order

Mechanisms

Configuration enters the program by four mechanisms, tabulated here. They differ in where they are set, when they are resolved, and whether they survive the loading of a saved state.

Mechanism	Read by	Resolved	Effect on a loaded state	Examples
Compile-time macro	Preprocessor	At build time; fixed for the executable	Not applicable	`DIMENSION`, `DEBUG` or `NDEBUG`, `STATE_VERSION`
Command-line option	`main` and `buildSim` in `grmain.cpp`	Once at startup	Overrides the setting stored in the state, with a warning; `--rand-growth` and the histogram sample counts are the exceptions (B.11)	`--diffusion`, `--recr`, `--tgfbr-dynamics`, `--dim`

Mechanism	Read by	Resolved	Effect on a loaded state	Examples
Parameter-file attribute	`ParamFileHandler::visit`, then `Params::computeParams` and `Params::validate`	Once at startup, before the simulation object is constructed	Parameters are not part of a saved state; the parameter file of the run that loads the state is in force	`Recruit_Prob_mtbRecEnabled`, `Core_reinfectionTimestep`, `Diffusion_FFT_numSmootherSteps`
Parameter-file Init-section element	`GrSimulation::initSectionInit` and `GrGrid::initNonAgentGrids`	During `GrSimulation::init`, for a new run only	Ignored	`Mac`, `DC`, `ExtMtb`, `Source`, `Fibroblast`, `Myofibroblast`, `Neutrophil`, and any grid name

Module selections, the domain and the duration are command-line options; quantities entering model equations are parameter-file entries (spine 7.0, "Command-line options and the parameter file"). Some parameter-file entries nevertheless act as switches: several by their value (B.6), and others by controlling whether a cell type is ever created (B.5).

Startup sequence for a new run

The order in which settings are resolved determines which settings can influence which. For a run that does not load a saved state, `main` resolves settings in this order. The rules of the parameter-loading step are specified in spine 7.0.

```
1.  Set the significant-figure comparison precision.
2.  Parse the command line. An unparseable option is fatal.
3.  Check the output directory, and any restart-completion markers.
4.  Set the duration: --timesteps if given, otherwise 144 x --days.
5.  Load parameters, through LungParam::getInstance(pdim)->load:
      a. resolve every declared parameter from the file or its
         declared default, recording a missing-parameter error
         where neither exists;
      b. check each value against its declared range, where one exists;
      c. Params::computeParams: derive counts or densities and the
         caseation growth thresholds, and check the neutrophil
         depletion window and injection count;
      d. Params::validate: repeat the range checks, then apply the
         cross-parameter checks of Params::checkParams.
     Any error recorded in a to d is fatal.
6.  Fix the agent slot count at 2 (spine 2.3).
7.  Seed the global generator from -s, or from the clock if absent.
8.  Construct GrSimulation:
      a. construct both grid buffers, each compartment's empty
         extracellular container, and the uniform oxygen field;
      b. construct the vascular and lymphatics objects;
      c. construct the ADE diffusion solver, reading the ADE timestep
         pair and enforcing its 60 s ceiling.
9.  buildSim:
      a. select the recruitment scheme from --recr;
      b. postConstructionOrLoadPreInit:
           - replace the solver with the one selected by --diffusion,
             taking that solver's timestep pair;
           - GrSimulation::timestepSync: synchronization and
             accuracy checks;
           - GrSimulation::computeParams: rescale the MHC class II
             rates to the molecular timestep (M3.6);
```

```
      c. set the granuloma area thresholds;
      d. check the antibiotic option combination;
      e. set the molecular-resolution switches, the TGF-beta method,
         the ODE solver, Treg induction, and the three depletion
         timesteps;
      f. create the antibiotic objects, if any are named;
      g. set immunomodulation and MHC class II dynamics.
10. GrSimulation::init:
      a. defineTCellRecTime: fix the T cell recruitment onset (S8.10);
      b. initSectionInit: Init-section entries, random vascular
         sources, resting macrophages, initial cognate Tgam,
         dendritic cells, fibroblasts and neutrophils, then
         Init-section grid values and statistics, in the order
         of spine 5.1.
11. Set up tracking, the seed file, the output streams, and the
    timespecs; then enter the timestep loop.
```

The MHC class II rescaling in `postConstructionOrLoadPreInit` uses the molecular timestep of the solver selected there (M3.6). The antibiotic objects are created later in `buildSim`, after the synchronization checks; M6.4 states which drug checks run when.

Startup sequence for a loaded state

When a state is loaded, either by `--load` or automatically from a restart checkpoint (B.8.6), every step up to and including seeding is unchanged. The later steps differ in these ways.

1. The simulation object is constructed with placeholder arguments. The ADE solver is therefore still constructed, and its ceiling is enforced on a load as on a new run.
2. The state is deserialized. This includes the global random number generator, whose restored state replaces the seed set at the seeding step.
3. `buildSim` runs in full, and `GrSimulation::init` is not called; command-line settings and the Init section are treated as in the mechanisms table.
4. If `--new-seed-on-load` is given, the generator is reseeded from `-s` after `buildSim`. Without a seed, this option is fatal.

Consequences of the order

- **Parameters are fixed before any module is selected.** No computed parameter can depend on a command-line module selection. Dimensionality is the exception in effect: it reaches `Params::computeParams` through the compile-time constant `GridSpec::GRID_DIM_COUNT` (B.4.5).
- **The domain size enters parameter resolution.** `--dim` is supplied to the parameter singleton when parameters are loaded, so the density-derived counts depend on it (spine 7.0, "Computed parameters"; B.7).
- **The molecular timestep is known before the MHC class II rescaling.** The rescaling uses the selected solver's molecular timestep, not the ADE one.
- **The TGF-beta method is set before initialization.** It is set in `buildSim`, before `initSectionInit`, so fibroblast and myofibroblast placement can be gated on it (B.4.4, B.5).

B.3 The default configuration

Invocation

The default configuration is obtained by running the two-dimensional executable with these options.

```
./gr -i PARAM_FILE -o OUTPUT_DIR -s SEED --lhs \
     --dim 300 --days 154 --diffusion 6 \
     --restart-interval 7200 \
     --stats-timespec 0/144/22176 \
     --agent-dump-timespec 0/1008/22176 --agent-dump-file agents \
     --grid-dump-timespec 0/1008/22176 --grids-to-dump TNF,nKillings
```

The operational options (`-i`, `-o`, `-s`, `--lhs`) are run-specific. Each run supplies its own values, and they are not part of the configuration:

- `-i` names the parameter file;
- `-o` names an output directory, which must already exist;
- `-s` supplies the seed of the global random number generator;
- `--lhs` marks the run as one of a batch and suppresses console statistics.

`--dim`, `--days` and `--diffusion` fix the domain, the duration and the diffusion solver. With `--days 154` the run lasts $144 \times 154 = 22176$ timesteps. `--restart-interval` and the timespec and dump options configure restart checkpoints and the output streams of S9.18. Every option not shown takes its program default.

Reading the switch tables

The module slot table covers the slots of the spine's module-slot table. The other-switches table covers entity presence, sentinels, the domain and duration, granuloma thresholds, seeding, output and batch execution. Each row gives one switch, or a group of related switches, with:

- its kind: CT for a compile-time macro, CL for a command-line option, PF for a parameter-file entry;
- its options;
- its program default, where "Mandatory" means a parameter with no declared default;
- its default-configuration value;
- what it controls;
- the section where it is indexed in detail.

A slot is often governed by more than one switch. In several slots a parameter-file entry, not the command-line option, holds the mechanism at nil in the default configuration; such entries are listed under the slot they govern.

Module slot switches

Slot	Switch	Kind	Options	Program default	Default configuration	Controls	Detail
M1	`--diffusion`	CL	4 alternating-direction explicit; 5 spectral (FFT), default; 6 spectral with estimate planning, giving identical transforms in every run; 7 Crank-Nicolson ADI, two-dimensional builds only	5	6	The diffusion solver, and with it the diffusion and molecular timesteps	B.4.1
M1	`Diffusion_FFT_numSmootherSteps`	PF	Integer, 0 or more	Mandatory	0	Explicit smoothing iterations after each split half-step under the spectral solver; 0 makes the smoother a no-op	B.4.1
M2	`--recr`	CL	0 probabilistic from local signals; 1 lymph node and blood compartment model	0	0	The recruitment scheme	B.4.2
M2	`Recruit_Prob_mtbRecEnabled`	PF	Positive selects the bacterial-load criterion; zero or negative selects the time criterion	Mandatory	0	The criterion for the onset of T cell recruitment	B.4.2
M3	`--tnfr-dynamics`	CL	Flag	Off	Off	Per-agent TNF and TNFR ordinary differential equations	B.4.3
M3	`--il10r-dynamics`	CL	Flag	Off	Off	Per-agent IL-10 and IL-10R ordinary differential equations	B.4.3
M3	`--NFkB-dynamics`	CL	Flag	Off	Off	Intracellular NF-κB ordinary differential equations; also switches on TNFR dynamics	B.4.3
M3	`--mhc-dynamics`	CL	Flag	Off	Off	MHC class II ordinary differential equations; recruited T cells then enter the T0 state, under either recruitment scheme	B.4.3
M3	`Molecular_MHCII_mhcMtbDownReg1` to `4`	PF	0 or 1 each	Mandatory	0	Four alternative hypotheses of bacterial down-regulation of MHC class II processing	B.4.3
M3	`NFkB_meanNFkB`	PF	Positive makes the draw; zero or negative does not	0	10^5	Whether each agent built by a constructor makes a log-normal NF-κB draw; division daughters make none. Under coarse resolution the value is unused but the draw consumes random numbers	B.4.3
M3	`--odesolver`	CL	Stepper index	4	4	The stepper for per-agent, TGF-β and pharmacokinetic ordinary differential equations; inert unless one of these is in use	B.4.3
M4	`--tgfbr-dynamics`	CL	0 none; 1 coarse-grained; 2 receptor ODEs	0	0	TGF-β activation, the fibroblast lineage and fibroblast placement	B.4.4
M5	`DIMENSION`	CT	2; 3	Set by the build	2	Spatial dimensionality of the executable	B.4.5
M6	`--antibiotics-to-include`	CL	Drug codes, comma- or whitespace-separated for a new run	Empty	Empty	Creates one set of antibiotic fields per named drug; empty disables the module	B.4.6
M6	`--drug-interaction-method`	CL	0 none; 1 INDIGO; 2 Loewe; 3 Bliss	0	0	The model of combined drug killing; non-zero requires named drugs and an interaction file	B.4.6
M6	`--drug-interaction-file`	CL	Path	Empty	Empty	Interaction data for methods 1 to 3	B.4.6
M6	`Drugs_dosageStartTime`	PF	Timestep	Mandatory	28801	Start of dosing; with drugs named, gates every drug process; the default value lies beyond the end of the run	B.4.6
M7	`--immuno-mod`	CL	Flag	Off	Off	Vascular dosing of TNF, IL-10 and the anti-TNF agents, and diffusion of the anti-TNF fields	B.4.7
M7	`Mod_dosageStartTime`	PF	Timestep	Mandatory	1	Start of dosing under `--immuno-mod`	B.4.7
M7	`Mod_Etanercept_dosage`; `Mod_Infliximab_dosage`	PF	Non-negative; 0 disables the agent	Mandatory	500; 0	Per-agent dosage; the anti-TNF binding step tests the dosage independently of `--immuno-mod`	B.4.7
M8	`--Treg-induction`	CL	Flag	Off	Off	Induction of regulatory T cells from Tgam	B.4.8
M8	`Core_Tcell_exhaustionThreshold`	PF	Integer	Mandatory	9999999	Interaction count at which an effector T cell becomes exhausted; the default value cannot be reached along a lineage	B.4.8
M8	`--rand-growth`	CL	Flag	Off	Off	A growth rate drawn for each constructed bacterium within the `Mtb_Agents_growthRateIntMtbMin` to `Max` and `Mtb_Agents_growthRateExtMtbMin` to `Max` bounds	B.4.8
M8	`Core_reinfectionTimestep`	PF	Timestep; -1 disables	Mandatory	-1	One-time placement of a further infected macrophage	B.4.8

Slot	Switch	Kind	Options	Program default	Default configuration	Controls	Detail
M8	`--tnf-depletion`; `--il10-depletion`; `--tgfb-depletion`	CL	Timestep; -1 disables	-1	-1	Suppression of the named secretion from that timestep onward	B.4.8
M8	`Core_depletionFractionTNF`; `Core_depletionFractionIL10`	PF	Fraction; 0 means not applied	Mandatory	0.0; 0.0	Fractional depletion applied when the corresponding depletion is active	B.4.8
M8	`Core_Neutrophil_injectionTimestep`; `Core_Neutrophil_injectionCount`	PF	Positive timestep enables; the count must then be positive	Mandatory	0; 0	One-time injection of neutrophils within the granuloma bounding circle	B.4.8

Other switches

Group	Switch	Kind	Options	Program default	Default configuration	Controls	Detail
Entity presence	`Core_Mac_initDensity`; `Core_Mac_initNumber`	PF	Density in [0, 1], or a count; at least one of the pair must appear in the file, and a density, if read, takes precedence	0.0; 0	Sampled density; count derived	The initial resting macrophage population, and the floor below which macrophages are recruited unconditionally (S8.7)	B.5
Entity presence	`Core_sourceDensity`; `Core_nrSources`	PF	As for the macrophage pair; zero sources, with no Init-section `Source` element, disables recruitment and vascular oxygen delivery	0.2; 0	0.08762770113823116; count derived as 7886	The number of vascular sources	B.5
Entity presence	`Core_Neutrophil_initDensity`; `Core_Neutrophil_initNumber`	PF	As for the macrophage pair	0.0; 0	0.0; count derived as 0	Neutrophils placed at initialization	B.5
Entity presence	`Recruit_Prob_Neutrophil_depletionTimestep`; `Recruit_Prob_Neutrophil_depletionEndTimestep`	PF	A window of timesteps in which neutrophil recruitment is suppressed; a negative end means no end; a non-negative end must exceed the start	Mandatory	0; -1	Holds neutrophil recruitment at nil for the whole run	B.5, B.6
Entity presence	`Core_DCellLung_percentOfMacInitNumber`	PF	Fraction in [0, 1] of the initial macrophage count	Mandatory	0.0	Dendritic cells placed at initialization	B.5
Entity presence	`Core_Fibroblast_initDensity`; `Core_Fibroblast_initNumber`	PF	As for the macrophage pair; placement also requires `--tgfbr-dynamics` non-zero	0.0; 0	0; count derived as 0	Fibroblasts placed at initialization	B.5
Entity presence	`Core_Tcell_Tgam_initCognateNumber`	PF	Count	Mandatory	0	Cognate Tgam placed at initialization	B.5
Entity presence	Init-section `Mac`, `DC`, `ExtMtb`, `Source`, `Fibroblast`, `Myofibroblast`, `Neutrophil`	PF Init	Any number of elements, each with a position	None	One `Mac` at `center`	Deterministically placed entities, including the seeding infected macrophage	B.5
Entity presence	Init-section elements named after a grid field	PF Init	A value at one position, or at `all`	None	None	Direct initialization of compartment fields and counters; intended for testing	B.5
Onset	`Recruit_Prob_timeRecEnabledRange`	PF	Half-width; 0 makes the onset deterministic and consumes no draw	Mandatory	0	Randomization of the T cell recruitment onset about `Recruit_Prob_timeRecEnabled`	B.4.2, B.6
Onset	`Recruit_Prob_timeMaxRecDelay`	PF	Timesteps; zero or negative removes the ramp	Mandatory	Sampled	Duration of the ramp to full T cell recruitment	B.4.2, B.6
Sentinel	`Mtb_Agents_growthRateFactorPostAdaptiveIntMtb`	PF	Multiplier; 1 disables	Mandatory	1.0	Change in intracellular bacterial growth after the nominal adaptive onset (S4.7; M8.8)	B.6
Sentinel	`Core_Mac_movementBonusFactor`; `Core_Tcell_movementBonusFactor`	PF	Multiplier of at least 1; 1 disables	1.0; 1.0	Defaulted, 1.0; 1.0	Additional weight on the strongest chemotactic direction (S1.3)	B.6
Sentinel	`Drugs_*_minEffluxInduction`	PF	Fraction of the MIC; -1 means efflux pumps are not used	Mandatory	-1 for every drug	Efflux pump induction under module M6	B.6
Sentinel	`Recruit_ODE_Ag2ConvertTime`	PF	Timestep; 0 means no conversion	Mandatory	0	Conversion to a second antigen specificity under `--recr 1`	B.6
Domain and duration	`--dim`	CL	Compartments per side	200	300	Domain size; enters parameter resolution	B.8.2
Domain and duration	`--days`; `--timesteps`	CL	Days, or timesteps; `--timesteps` takes precedence	200; none	154; not given	Simulated duration	B.8.2
Stopping	`--stop-on-clearance`	CL	Flag	Off	Off	Ends the run when total bacterial load reaches zero	B.8.2
Stopping	`mtbStopppingTimeStep`, `mtbStopppingTimeStep2`, `areaCellDensityStopppingTimeStep`, `areaCellDensityStopppingTimeStep2`, with their thresholds	PF	Timestep at which to test; 0 disables	0 for each timestep	0 for each timestep	Early termination on low or high bacterial load or granuloma area (S9.20)	B.8.2, B.6
Granuloma thresholds	`--area-cell-density-threshold`	CL	[0, 1]	0.5	0.5	The threshold of the threshold granuloma (S9.4), and hence the lesion volume used for concentration conversion	B.8.3
Granuloma thresholds	`--area-tnf-threshold`	CL	[0, 1]	0.5	0.5	The TNF-based granuloma area statistic	B.8.3
Granuloma thresholds	`occupiedNeighborFraction`	PF	[0, 1]	Mandatory	0.66	Eligibility for the connected-region granuloma (S9.6)	B.8.3
Seeding and loading	`-s`	CL	Unsigned integer	Derived from the clock	Supplied per run	Seed of the global random number generator	B.8.4
Seeding and loading	`--load`; `--new-seed-on-load`	CL	Path; flag	None; off	Not given	Starting from a saved state, optionally with a new seed	B.8.4

Group	Switch	Kind	Options	Program default	Default configuration	Controls	Detail
Output	`--stats-timespec`, `--agent-dump-timespec`, `--grid-dump-timespec`, `--state-timespec`, `--moi-timespec`, `--molecular-track-timespec`, `--mtb-track-timespec`, `--tcell-mac-interaction-timespec`	CL	Timespec; empty disables the stream	Empty	The first three every 144, 1008 and 1008 timesteps; the rest empty	Which output streams are written, and when	B.8.5
Output	`--grids-to-dump`; `--agent-dump-file`; `--walltime`; `--dump-antibiotics`	CL	Grid names; file stem; flags	None; none; off; off	`TNF,nKillings`; `agents`; off; off	Contents of the dump streams	B.8.5
Output	`--molecular-track-radius`; `--molecular-track-ids`; `--trackAll`	CL	Radius; identifiers; flag	0; none; off	0; none; off	Agents selected for molecular tracking	B.8.5
Output	`--rand-growth-samples`; `--biomass-samples`; `--reserve-samples`	CL	Bin counts	10; 10; 10	10; 10; 10	Resolution of the bacterial histogram statistics; `--reserve-samples` has no effect, since the reserve count is replaced by zero	B.8.5
Batch execution	`--restart-interval`	CL	Timesteps; non-positive disables	-1	7200	Checkpoint interval for automatic restart	B.8.6
Batch execution	`--chunk`; `--last-chunk`; `--append-stats`; `--lhs`; `--quiet`	CL	Integer; flags	-1; off; off; off; off	Not given; off; off; on; off	Running a simulation in chunks, appending to existing statistics, and console output	B.8.6

Settings whose program default differs from the default-configuration value

These settings change the program's behaviour from its defaults in the invocation of the default configuration. Omitting any of them yields a different configuration, and no warning is issued.

`--diffusion`. The program default, 5, selects the spectral solver with exhaustive transform planning, which does not guarantee identical results across runs. The reference value, 6, selects the same scheme with estimate planning, which does (M1.3, "Planning strategy and determinism"). Only the reference value supports the reproducibility guarantee of spine 3.4. A run that omits `--diffusion 6` is not reproducible from its executable, parameter file and seed alone.

`--dim`. The program default, 200, gives a $4\ \mathrm{mm} \times 4\ \mathrm{mm}$ domain of 40000 compartments. Because the initial macrophage and vascular source counts are derived from densities and the number of compartments, the same parameter file then gives different populations: $\lfloor 0.08762770113823116 \times 40000 \rfloor = 3505$ sources instead of 7886, and an initial macrophage count of 191 to 410 across the sampled density range instead of 431 to 923.

`--days`. The program default, 200, gives 28800 timesteps instead of 22176. The default output timespecs end at timestep 22176, so later timesteps would be written only by the final-timestep rule of S9.18. The default value of `Drugs_dosageStartTime`, 28801, lies beyond both durations, so dosing does not begin under either.

B.4 Module slot switches

B.4.1 M1 Diffusion solver

Switches

Switch	Kind	Options	Program default	Default configuration	Gate location
`--diffusion`	CL	4, 5, 6, 7	5	6	Parsed in `buildSim`, `grmain.cpp`; applied by `GrSimulation::setDiffusionMethod`
`Diffusion_ADE_timestepDiffusion`, `Diffusion_ADE_timestepMolecular`	PF	Seconds	Mandatory	30, 5	Read by `setDiffusionMethod` for code 4, and by the constructor in every configuration
`Diffusion_FFT_timestepDiffusion`, `Diffusion_FFT_timestepMolecular`	PF	Seconds	Mandatory	60, 6	Read by `setDiffusionMethod` for codes 5 and 6, and directly by `GrDiffusionFFT`
`Diffusion_CNADI_timestepDiffusion`, `Diffusion_CNADI_timestepMolecular`	PF	Seconds	Mandatory	60, 3	Read by `setDiffusionMethod` for code 7
`Diffusion_FFT_numSmoootherSteps`	PF	Integer	Mandatory	0	Loop bound in `GrDiffusionFFT::smoother`

Switch	Kind	Options	Program default	Default configuration	Gate location
`Diffusion_FFT_timestepDiffusionSmoother`	PF	Seconds	Mandatory	1.2	Fourier number in the smoother; unused when the step count is 0

All three timestep pairs and both smoother parameters are mandatory whichever solver is selected, because each is declared without a default; codes 5 and 6 share the FFT pair. A parameter file prepared for one solver must therefore still contain the entries of the others.

Options

Code	Solver	Timestep pair	N_d	N_m	Notes
4	Alternating-direction explicit	30 s, 5 s	20	6	Uses the auxiliary `u` and `v` arrays; hard ceiling of 60 s on the diffusion timestep
5	Spectral (FFT), default	60 s, 6 s	10	10	—
6	Spectral with estimate planning	60 s, 6 s	10	10	Identical transforms in every run; selected
7	Crank-Nicolson alternating-direction implicit	60 s, 3 s	10	20	Two-dimensional builds only

The iteration counts and the synchronization conditions are specified in M1.2. Every default timestep pair passes them. Codes 5 and 6 construct the same solver and run the same scheme; they differ only in the planning flag passed when the transform plans are built. Code 7 is accepted only when `DIMENSION == 2`: in a three-dimensional build the option parser and `setDiffusionMethod` omit it, the command-line help lists codes 4 to 6 only, and supplying 7 is fatal.

Gate sequence

The solver is constructed and checked at these points, in order.

1. **Constructor default.** The `GrSimulation` constructor calls `setDiffusionMethod` for the explicit solver before any option is processed, so that a saved state can be deserialized into a valid object. This reads the ADE timestep pair and throws if `Diffusion_ADE_timestepDiffusion` exceeds 60 s. The ceiling is therefore enforced in every configuration, including those that never use the explicit solver.
2. **Selection.** `postConstructionOrLoadPreInit` calls `setDiffusionMethod` with the parsed code. If it differs from the current method, the explicit solver is deleted, the selected solver constructed, and its timestep pair replaces the ADE pair.
3. **Synchronization.** `GrSimulation::timestepSync` applies the synchronization conditions and the accuracy limit of M1.2. Only `Core_diffusivityTNF` enters the cytokine accuracy limit; no IL-10 parameter is read. The sampled `Core_diffusivityIL10` is uniform on $[4 \times 10^{-8}, 6 \times 10^{-8}]$ cm^2/s, and a limit computed from it would be 66.7 s under code 4 and about 3.3×10^5 s under the spectral solver, so neither default timestep would be affected. The oxygen flux routine imposes a separate ceiling on Δt_d, outside these checks, which applies under every solver (B.11).

4. **Diffusion.** `GrSimulation::solve` calls the solver once per diffusion step, between the two split half-steps (spine Element 3).
5. **Smoother.** At the end of each half-step, `GrSimulation::strangStep` calls `smoother` only under codes 5 and 6. The smoother performs `Diffusion_FFT_numSmootherSteps` iterations; with the default value of 0 the call returns at once (M1.3, "The smoother").

Field gates under the spectral solver

Each field is advanced, degraded or skipped by its own gate, which decides whether it is inert or absent in a given configuration. Treatment and boundary are specified in M1.3.

Field	Gate
TNF, CCL2, IL-10	None; always advanced
CCL5, CXCL9	None; set from CCL2 after each solve (S6.14)
Active TGF-β	None; diffused and degraded in every configuration, and inert on a zero field when M4 is not selected
Inactive TGF-β	None; copied forward and degraded, not diffused, in every configuration; inert on a zero field when M4 is not selected
Shed TNFR2	`--tnfr-dynamics`
Antibiotic fields	`doDrugs` (B.4.6); absent unless a drug is named
Etanercept, Infliximab and their TNF complexes	`--immuno-mod` and $t \geq$ `Mod_dosageStartTime`
Oxygen	Not advanced under any solver (M1.3, "Fields presented to the solver")

After the field solves, the post-solve binding step runs on every diffusion step. Its anti-TNF blocks are gated on the agent dosages alone (B.4.7), and its shed TNFR2 block on `--tnfr-dynamics`. Propagation matrices, including one for inactive TGF-β that is never applied, are built once in the solver constructor (M1.3, "The propagator and incorporation of decay").

The Crank-Nicolson solver builds an oxygen system from `O2_diffusivityO2` in its constructor, so that parameter is read under code 7, but the system is never applied (M1.5). `O2_degRateConstO2` has no live consumer under any solver.

Dependencies

The solver choice fixes Δt_d and Δt_m, and through them the molecular substep count, the MHC class II rescaling factor (M3.6) and the oxygen flux limit (B.11). The algorithms are specified in M1.

B.4.2 M2 Recruitment scheme

Switches

Switch	Kind	Options	Program default	Default configuration	Gate location
`--recr`	CL	0 probabilistic; 1 lymph node and blood compartment model	0	0	Parsed in `buildSim`, `grmain.cpp`; applied by `GrSimulation::setRecruitmentMethod`
`Recruit_Prob_mtbRecEnabled`	PF	Positive selects the bacterial criterion; otherwise the time criterion	Mandatory	0	`GrSimulation::checkTCellRecruitmentStart`
`Recruit_Prob_timeRecEnabled`	PF	Timestep	Mandatory	Sampled (S8.13)	`GrSimulation::defineTCellRecTime`
`Recruit_Prob_timeRecEnabledRange`	PF	Half-width in timesteps; 0 disables randomization	Mandatory	0	`GrSimulation::defineTCellRecTime`
`Recruit_Prob_timeMaxRecDelay`	PF	Timesteps; zero or negative removes the ramp	Mandatory	Sampled (S8.13)	`RecruitmentProb::getTcellRecruitmentFraction`

Options

Code 0, the probabilistic scheme, is selected; it is specified in S8. Code 1 couples recruitment to a lymph node and blood compartment model of T cell priming (M2.9). Any other code is fatal.

The recruitment object is serialized. On load, `setRecruitmentMethod` keeps the deserialized object if its method matches the command line; otherwise it deletes it and constructs the requested type, discarding any internal state of the replaced object, such as the lymph node compartment populations.

`Recruit_OLD_Mac_probRec` is read only by the lymph node scheme. It is mandatory under either code and has no effect under code 0. The other `Recruit_OLD` entries are indexed in B.10.

The lymphatics object is constructed in the `GrSimulation` constructor and serialized under both codes. No dendritic cell exists in the default configuration (B.5); under code 1 the scheme advances the lymphatics and converts recruited monocytes to dendritic cells (M2.9, M2.10).

The command-line help for `--mhc-dynamics` states that it requires the lymph node scheme. The program does not require it. Under either code with `--mhc-dynamics`, recruited T cells are created in their T0 state rather than active (B.4.3; S8.12; M2.9).

Onset gates

The onset of T cell recruitment under code 0 is governed by a latched onset flag, a fixed onset time and a ramp factor, specified in S8.10. As switches:

- `defineTCellRecTime` runs once, at the start of `GrSimulation::init`. With a zero range it makes no draw. Because `init` is not called for a loaded state, the onset time is restored from the state, and changing either onset parameter before a load has no effect on it.
- `checkTCellRecruitmentStart` sets the flag by the bacterial criterion when `Recruit_Prob_mtbRecEnabled` is positive, and by the time criterion otherwise. The flag is never cleared and is serialized.
- The ramp is anchored to the onset time under both criteria, so the bacterial criterion can delay recruitment but not advance it (S8.10).
- Macrophage recruitment is not ramped.

The onset flag is applied in `RecruitmentProb::recruit` as a conjunction with each T cell candidacy test. Each candidacy test is evaluated first, and consumes its draws, whether or not the flag is set (S8.11).

Dependencies

Recruitment occurs only at vascular sources, so the scheme depends on the source switches of B.5. Its thresholds read the CCL5 and CXCL9 fields, derived from CCL2 (S6.14). The macrophage recruitment floor is a rule of the scheme, not a switch (S8.7). In the default configuration neutrophil candidacy is always false, so the cascade divides between macrophages and T cells (S8.11; M9.5).

B.4.3 M3 Molecular resolution

Switches

Switch	Kind	Options	Program default	Default configuration	Gate location
`--tnfr-dynamics`	CL	Flag	Off	Off	`buildSim`; `GrSimulation::setTnfrDynamics`
`--il10r-dynamics`	CL	Flag	Off	Off	`buildSim`; `GrSimulation::setIl10rDynamics`
`--NFkB-dynamics`	CL	Flag; also sets TNFR dynamics	Off	Off	`buildSim`; `GrSimulation::setNfkbDynamics` and `setTnfrDynamics`
`--mhc-dynamics`	CL	Flag	Off	Off	`buildSim`; `GrSimulation::setMhcDynamics`
`--odesolver`	CL	Stepper index, validated by `ODESolvers::isValidOdeMethod`	4	4	`buildSim`; `GrSimulation::setODESolverMethod`
`NFkB_meanNFkB`	PF	Positive makes the construction draw; zero or negative does not	0	10^5	`Agent::Agent`
`Molecular_MHCII_mhcMtbDownReg1` to `4`	PF	0 or 1 each	Mandatory	0	Read under MHC class II dynamics, through `LungFunc::mhcMtbDownReg`

The coarse-grained resolution of S6 is not a separate option. It is what results when all four flags are off, which is the default configuration. The flags are independent except that `--NFkB-dynamics` switches on TNFR dynamics, because the NF-κB system consumes the receptor species. The resolution can therefore be raised pathway by pathway, and mixed configurations are permitted (M3.1, M3.8).

Gate sites

Site	Gate	Effect when the gate passes
`GrSimulation::strangStep`, each molecular substep	Any of the four flags	`solveMolecularScale` integrates the per-agent systems over Δt_m (M3.2)
`GrSimulation::strangStep`, each molecular substep	TNFR dynamics or IL-10R dynamics is off	`adjustFauxDegradation` applies the receptor-occupancy sink terms of S6.8 to the pathway not resolved
`GrSimulation::solveMolecularScale`, T cells	NF-κB, TNFR or IL-10R dynamics	T cells integrate their systems; MHC class II dynamics alone does not include T cells (M3.2)
End of `GrSimulation::solve`	MHC class II dynamics	The MHC class II spatial statistics (M3.6)
`Treg::checkDeactivation`	IL-10R dynamics	The test of whether a Treg is making IL-10 reads `Molecular_IL10_Tcell_IkSynthTcell` instead of `Core_Tcell_Treg_dIL10` (S3.10)

The two substep gates are not exclusive: with exactly one of TNFR and IL-10R dynamics on, both run in each substep (S6.8, M3.1).

Computations that do not depend on the flags

These execute in every configuration and are inert in the default configuration:

- **MHC class II rescaling.** `GrSimulation::computeParams` rescales the MHC class II rates to the molecular timestep and derives dependent quantities (M3.6). The results are not read when MHC class II dynamics is off.
- **MHC class II statistics.** `GrSimulation::updateMhcIIStats` and the MHC class II input statistics of `GrSimulation::updateGridStats` affect output columns only (M3.6; B.9). The input statistics count compartments holding at least one Tgam of any state, including dead Tgam not yet removed.
- **Construction draw.** While `NFkB_meanNFkB` is positive, each agent built by a constructor makes a log-normal NF-κB draw (S6.3; M3.5). Under coarse resolution the value is never read, but the draw changes the random stream. A value of zero is dynamically equivalent under coarse resolution but follows a different stream.
- **Receptor turnover products.** `Agent::Agent` stores the drawn TNFR1, TNFR2 and IL-10R counts multiplied by `Molecular_TNF_kT1`, `Molecular_TNF_kT2` and `Molecular_IL10_IkT`. These consume no draws and are read only by the receptor systems.

The significant-figure precision is set in `main` from the solution accuracy of the ODE stepper interface. It applies to every threshold comparison in the model, whether or not any ODE is integrated.

The ODE stepper

`--odesolver` selects the stepper used by every ordinary differential equation system in the platform:

- the per-agent systems of this slot (M3.2);
- the fibroblast TGF-β receptor system of M4 (M4.7);
- the drug pharmacokinetic systems of M6 (M6.3);
- the drug partitioning step of M6 (M6.7).

In the default configuration none of these runs, and the option is inert. An invalid index is fatal. The setter runs on every run and every load, restarts included, so the method in force is always the option's value. Index 4 selects the classic fourth-order Runge-Kutta stepper; the indices are 0 forward Euler, 1 Euler predictor-corrector, and 2 to 4 Runge-Kutta of orders 2 to 4.

Each enabled down-regulation hypothesis multiplies its target rate by $1 - R\,n/(K + n)$, where n is the intracellular bacterial count (M3.6). The switches have no effect without `--mhc-dynamics`.

Parameter groups

The groups `Molecular_TNF`, `Molecular_TNF_Mac`, `Molecular_TNF_Tcell`, `Molecular_IL10`, `Molecular_IL10_Mac`, `Molecular_IL10_Tcell`, `NFkB` and `Molecular_MHCII` belong to this slot. Most of their entries are mandatory under every setting of the flags. The entries read with effect under coarse resolution are the receptor means and half-widths, the dissociation constants `Molecular_TNF_KD1`, `Molecular_TNF_KD2` and

`Molecular_IL10_IkD`, and `NFkB_meanNFkB`, through the construction draw alone (S6.16; M3.9). The rest are indexed in B.10.

Dependencies

The molecular timestep, and with it the substep count and the MHC class II rescaling factor, is set by the solver choice of B.4.1. The coarse-grained algorithms are specified in S6, and the receptor, NF-κB and MHC class II systems in M3.

B.4.4 M4 TGF-β and fibrosis

Switches

Switch	Kind	Options	Program default	Default configuration	Gate location
`--tgfbr-dynamics`	CL	0 none; 1 coarse-grained; 2 receptor ODEs	0	0	Parsed in `buildSim`, `grmain.cpp`; applied by `GrSimulation::setTgfbrDynamicsMethod`
`Core_Fibroblast_initDensity`; `Core_Fibroblast_initNumber`	PF	Density or count, resolved as for the macrophage pair (B.7)	0.0; 0	0; 0, both read, so the count is derived from the density as 0	`Params::computeParams`; placement in `GrSimulation::initSectionInit`
Init-section `Fibroblast` and `Myofibroblast` elements	PF Init	Positions	None	None	`GrSimulation::initSectionInit`
`--tgfb-depletion`	CL	Timestep; -1 disables	-1	-1	`GrSimulation::solve`; consumed only by TGF-β secretion (B.4.8)

Any other value of `--tgfbr-dynamics` is fatal. The method is serialized; on load the command-line value replaces the stored one, with a warning.

Options

Most gates test that the method is not none, so they pass under both other options; one gate tests for the receptor ODE option alone. Which fibroblast rules run under the coarse-grained option is specified in M4.1.

Behaviour	None	Coarse-grained	Receptor ODEs
Activation of inactive TGF-β by macrophages	No	Yes	Yes
Fibroblast movement pass, after the T cell movement pass	No	Yes	Yes
Fibroblast placement at initialization	Ignored, with a warning	Yes	Yes
Treg binding of active TGF-β and secretion of inactive TGF-β	No	Yes	Yes
Per-fibroblast TGF-β receptor ODEs, each molecular substep	No	No	Yes

Further branch points on the method lie in macrophage secretion and in the fibroblast class (M4).

Gate sites

Site	Gate	Effect when the gate passes
`GrSimulation::solve`, after the diffusion loop	Not none	TGF-β activation in compartments holding a macrophage (M4.3)
`GrSimulation::solve`, movement block	Not none	Fibroblast movement, after the T cell movement pass
`GrSimulation::strangStep`, each molecular substep	Receptor ODEs	`solveMolecularScaleTgfb` integrates each fibroblast's receptor system over Δt_m
`Treg::secrete`	Not none	TGF-β binding and, unless TGF-β depletion is active, inactive TGF-β secretion (M4.3)
`GrSimulation::initSectionInit`, Init-section elements	Not none	Each `Fibroblast` element creates an active fibroblast and each `Myofibroblast` element a myofibroblast; otherwise each element is reported and ignored
`GrSimulation::initSectionInit`, random placement	Not none, and a positive derived count	Fibroblasts are placed by rejection sampling under the fibroblast admission predicate (M4.5); otherwise a positive count is reported and ignored
`GrSimulation::updateGridStats`	The latched fibroblast-proliferation flag	While the flag is false, the threshold-granuloma membership flag is recomputed each timestep; once it is true, the membership flag is frozen (S9.4; M4.8)

The fibroblast-proliferation flag is set when the first fibroblast proliferates. It is never cleared and is serialized. It can become true only if a fibroblast exists, and so only when the method is not none. When placement is ignored, no draw is made for the ignored entity.

Computations that do not depend on the switch

These execute in every configuration. In the default configuration each operates on zero fields or empty lists and is inert.

- **Field updates.** The active TGF-β field is diffused and degraded each diffusion step, and the inactive field copied forward and degraded (B.4.1). Their propagation factors are built from `Core_diffusivityTGFBActive`, `Core_degRateTGFBActive` and `Core_degRateTGFBInactive`, which are therefore read with effect on these fields in every configuration (M1.6).
- **Fibroblast list passes.** Fibroblast secretion in each split half-step, and the fibroblast passes of next-state computation, proliferation, state commitment, shuffling and caseation statistics, run over the fibroblast list.
- **Statistics.** The TGF-β and collagen totals, the fibroblast counts within the threshold and pre-fibrosis granulomas, and the fibroblast extent are computed, and are zero (S9; M4.8).

- **Depletion flag.** The TGF-β depletion flag is computed each timestep from `--tgfb-depletion` and passed to every secretion call. Only TGF-β secretion consumes it, so `--tgfb-depletion` has no effect unless M4 is selected.

Parameter groups

These belong to this slot and are mandatory under every setting of the switch:

- the TGF-β entries of `Core`: `diffusivityTGFBActive`, `degRateTGFBActive`, `degRateTGFBInactive`, `tgfbSecretionReductionInterval` and `il10BindingRate`;
- the TGF-β entries of `Core_Mac`, `Core_Tcell`, `Core_Tcell_Tcyt` and `Core_Tcell_Treg`;
- the whole of `Core_Myofibroblast` and `Molecular_TGFB_Fibroblast`, and every entry of `Core_Fibroblast` except `initNumber` and `initDensity`, which are defaulted.

`Core_il10BindingRate` is consumed by the fibroblast IL-10 binding rule (M4.5). Apart from the three field parameters named under field updates, none of these is read with effect in the default configuration; they are indexed in B.10.

Dependencies

TGF-β activation reads the macrophage signalling TNFR1 occupancy, computed under whichever TNFR resolution is selected in B.4.3. The receptor ODE option uses the stepper selected by `--odesolver` and the molecular timestep of B.4.1. Fibroblast placement depends on the entity switches of B.5. The fibroblast lineage, collagen deposition and the remaining branch points are specified in M4.

B.4.5 M5 Dimensionality

Switch

Switch	Kind	Options	Program default	Default configuration	Gate location
`DIMENSION`	CT	2; 3	None declared; set by the build	2	Tested in `grmain.cpp`, `grsimulation.cpp` and the grid headers, including the selector headers `grid-selector.h` and `pos-selector.h`

Dimensionality is the only module slot selected at compile time. The two-dimensional and three-dimensional configurations are separate executables, and no option, parameter or loaded state can change the dimensionality of a running program. Only the values 2 and 3 produce an executable; the option declarations in `main` branch on `DIMENSION == 2` and `DIMENSION == 3`, and any other value reaches an `#error` directive (M5.1). The reference simulations were run with a two-dimensional build.

The value is written at the start of every run on the line beginning `DIM:`, and is embedded in the executable as `EXECUTABLE_INFO_DIM`, so it can be recovered without running the program. This is the reliable way to confirm which M5 option produced a set of results (M5.1).

Consequences that bear on configuration

The macro reaches the model through the source files compiled, through preprocessor tests in the coordinator and option parser, and through the compile-time grid constants `GridSpec::GRID_DIM_COUNT` and `GridSpec::MOORE_COUNT`. Only the grid and diffusion solver sources differ between the two builds.

Aspect	Two-dimensional, selected	Three-dimensional	Detail
Diffusion codes accepted	4, 5, 6, 7	4, 5, 6	B.4.1
Solver sources	`grdiffusionFFT.cpp`, `grdiffusionadeswap.cpp`, `grdiffusion-crank-nicolson-adi.cpp`	`grdiffusionFFT3d.cpp`, `grdiffusionadeswap3d.cpp`	M5.10
`Diffusion_CNADI_*` pair	Read; used under code 7	Read and checked as mandatory, never used	B.4.1
Neighbourhood sizes, thresholds and scaling	Specified in the owners	Specified in M5	M5.3, M5.8, M5.12
Domain from `--dim 300`	$300^2 = 90000$ compartments	300^3 compartments	M5.6

A parameter file runs unchanged in either executable, but its meaning changes: fraction-valued thresholds, density-derived populations and Moore-count fractions take different values (M5.13).

Dependencies

Dimensionality constrains the choice of diffusion solver (B.4.1) and determines the computed parameters of spine 7.0, "Computed parameters", and the scaling procedure of S9. The three-dimensional configuration is specified in M5.

B.4.6 M6 Antibiotics and pharmacology

Switches

Switch	Kind	Options	Program default	Default configuration	Gate location
`--antibiotics-to-include`	CL	Drug codes; comma- or whitespace-separated for a new run	Empty	Empty	`GrSimulation::createAntibiotics` (parsing); `abxCmdLineOptionsAndLoadedState`; `GrSimulation::antibioticInit`
`--drug-interaction-method`	CL	0 none; 1 INDIGO; 2 Loewe; 3 Bliss	0	0	`abxCmdLineOptions`; `GrGrid::defineDrugKill`
`--drug-interaction-file`	CL	Path	Empty	Empty	`abxCmdLineOptions`; `GrGrid::defineDrugKill`
`--dump-antibiotics`	CL	Flag	Off	Off	`getAntibioticDumpStreams` in `grmain.cpp`
`Drugs_dosageStartTime`	PF	Timestep	Mandatory	28801	`GrSimulation::doDrugs`, `atTreatmentStart`, `noMtbDeathInCaseum`, `updateDrugConcentrationStats`; `Vascular::isDoseStartTime`
`Drugs_numberOfRandomMultiResistantBugsToAdd`; `Drugs_*_numberOfRandomMonoResistantBugsToAdd`	PF	Counts; 0 adds none	Mandatory	0; 0 for every drug	`GrSimulation::addRandomResistantBugs`

The module is selected by naming at least one drug. No other switch creates antibiotic objects, and with the list empty every gate of the module fails.

The command-line help describes the drug list as comma-separated with no spaces; for a new run the parser also accepts whitespace as a separator. On a regular load of a state that holds drugs, the command-line string has its spaces removed and must equal the loaded drug names joined by commas, in order; a space-only list then fails fatally.

Option consistency

`abxCmdLineOptions` checks the three antibiotic options against one another before any simulation object is configured. A combination marked fatal ends the run at startup.

Drug codes	Interaction method	Interaction file	Result
Empty	0	Empty	Accepted; module not selected
Empty	1, 2 or 3	Any	Fatal
Empty	0	Given	Fatal
Given	0	Empty	Accepted; the drug with the highest kill rate is used
Given	0	Given	Fatal
Given	1, 2 or 3	Empty	Fatal
Given	1, 2 or 3	Given	Accepted
Any	4 or more	Any	Fatal

`--dump-antibiotics` is fatal unless drug codes are given and a grid-dump timespec is supplied.

Each named drug constructs its own set of fields and pharmacokinetic state (M6.2); with no drug named, no antibiotic field exists. The order of codes on the command line fixes the order of all per-drug loops (M6). An unrecognized code is fatal after the list has been scanned.

Activation in time

Naming drugs creates the module; its dynamics are gated in time by three predicates.

Predicate	True when	Used for
Dosing	The antibiotic list is non-empty and $t \geq$ `Drugs_dosageStartTime`	Every drug process in the timestep
Treatment start	The list is non-empty and $t =$ `Drugs_dosageStartTime`	One-time conversion of bacteria to resistant
Fluoroquinolone suppression	MXF, LVX or GFX is named and $t \geq$ `Drugs_dosageStartTime`	Suppression of density-dependent bacterial death in caseum

Naming a fluoroquinolone therefore changes a core submodel: from the start of dosing, the caseum death rule of S4 and S5 no longer applies in any compartment (M6.14). In the default configuration the antibiotic list is empty, so all three predicates are false throughout. The default `Drugs_dosageStartTime`, 28801, also lies beyond the end of the run, so they would stay false even if drugs were named.

Gate sites

Site	Gate	Effect when the gate passes
`GrSimulation::solve`, prologue	Treatment start	Random resistant bacteria are seeded (M6.13)
`GrSimulation::solve`, prologue	Dosing	The cell-density grid is computed for every compartment; no rule reads it (M6)
`GrSimulation::strangStep`	Dosing	Drug consumption, partitioning, and vascular dosing and flux at sources (M6.4 to M6.7)
`GrDiffusionFFT::diffuse`	Dosing	Diffusion of the free drug fields and degradation of the bound fields (M6.5)
`GrDiffusionFFT::smoother`	Dosing, evaluated in `strangStep` and passed as an argument	Smoothing of the drug fields; the smoother itself tests only the immunomodulation gate
`GrSimulation::timestepSync`	Non-empty list at the time of the check	The drug accuracy and permeability limits (M6.4)
`GrSimulation::reallyHandleExtMtb`	Dosing, passed as an argument	Extracellular drug killing and efflux induction (M6.11, M6.12)
`GrSimulation::reallyHandleExtMtb`	Fluoroquinolone suppression	Caseum death skipped (M6.14)
`GrSimulation::updateGridStats`	Dosing	Drug statistics (M6.15)
`GrSimulation::updateDrugConcentrationStats`	$t \geq$ `Drugs_dosageStartTime` only, not the list	Concentration time-series statistics per drug

Computations that do not depend on the switch

These execute in every configuration and are inert in the default configuration:

- **Empty-list loops.** Per-drug statistic resets, intracellular and total grid updates, and per-drug average concentrations iterate over the empty list, as do the mutation trials performed at each division; none consumes a random draw.
- **Per-bacterium calls.** The extracellular pass calls the drug killing and efflux routines on every compartment holding live bacteria, passing the dosing predicate, and updates the resistant and efflux counts unconditionally. With dosing false and no bacterium resistant, these have nil effect.
- **Per-agent lists.** Every macrophage and bacterium carries an antibiotic concentration list, filled at construction from the grid's list; by default every list is empty.
- **Parameters.** The `Drugs` group and the per-drug groups are declared, read and stored in every configuration (B.10).

The grids `nCells`, `ExtFIC` and `IntFIC` remain zero, the three interaction-factor averages are zero at every timestep, and no per-drug statistic exists. The documented status of the module is set out in M6.1.

Saved states

The antibiotic objects and the drug interaction object are part of the serialized grid. On load, `abxCmdLineOptionsAndLoadedState` reconciles them with the command line.

Load type	State has drugs	Codes given	Result
Either	No	Yes	Warning; for a regular load, the drugs are then created and every agent and bacterium given its concentration list
Either	Yes	No	Warning; the stored drugs remain
Either	Yes	Yes, method differs	Warning
Regular	Yes	Yes	The codes must match the stored list exactly and in the same order, or the run is fatal; the drug parameters are then reloaded from the parameter file
Restart	No	Yes	Warning only; no drugs are created
Restart	Yes	Yes	The stored drugs remain; their parameters are not reloaded

A restart run whose command line names drugs absent from its restart state therefore continues without them, after a warning. A restart run whose parameter file has changed keeps the stored drug parameters.

Dependencies

Drug delivery occurs only at vascular sources, is suppressed in caseated compartments, and is scaled by `Drugs_*_vesselActivity` where cell density is at least 0.8 (M6.4); it therefore depends on the source switches of B.5. The pharmacokinetic and partitioning systems use the stepper selected by `--odesolver` (B.4.3). Drug diffusion uses the solver of B.4.1. The interaction methods, resistance, efflux and drug killing are specified in M6.

B.4.7 M7 Immunomodulation

Switches

Switch	Kind	Options	Program default	Default configuration	Gate location
`--immuno-mod`	CL	Flag	Off	Off	Passed to the `GrSimulation` constructor by `getRegularSimulation`, and set again by `GrSimulation::setImmunoMod` in `buildSim`

Switch	Kind	Options	Program default	Default configuration	Gate location
`Mod_dosageStartTime`	PF	Timestep	Mandatory	1	`GrSimulation::strangStep`; `GrDiffusionFFT::diffuse` and `smoother`; `Vascular::isDoseStartTimeMod`
`Mod_TNF_dosage`; `Mod_IL10_dosage`	PF	Non-negative; 0 disables	Mandatory	0; 0	`Vascular::solveVascularSourcesMod`
`Mod_Etanercept_dosage`; `Mod_Infliximab_dosage`	PF	Non-negative; 0 disables	Mandatory	500; 0	`Vascular::solveVascularSourcesMod`; `GrSimulation::addEtan` and `addIfx`; the post-solve binding step of `GrDiffusionFFT`
`Mod_TNF_dosageInterval`, `Mod_IL10_dosageInterval`, `Mod_Etanercept_dosageInterval`, `Mod_Infliximab_dosageInterval`	PF	Timesteps	Mandatory	72, 72, 1008, 999999	`Vascular::addDose`

The module is selected by `--immuno-mod`. Within it, each of the four agents (TNF, IL-10, Etanercept and Infliximab) is enabled by a non-zero dosage. The setting is serialized; on load the command-line value replaces the stored one, with a warning.

In the default parameter file the Etanercept dosage is 500 and the other three are 0. The module is therefore held at nil by the absence of `--immuno-mod` alone. With that flag and the default parameter file, Etanercept is administered from timestep 1, every 1008 timesteps (M7.11).

Gate sites

Site	Gate	Effect when the gate passes
`GrSimulation::strangStep`, each half-step	`--immuno-mod` and $t \geq$ `Mod_dosageStartTime`	Vascular dosing and exchange at sources, then the blood-concentration statistics (M7.4, M7.5)
`GrDiffusionFFT::smoother`	`--immuno-mod` and $t \geq$ `Mod_dosageStartTime`, as for diffusion (B.4.1); the smoother reads `Mod_dosageStartTime` only when immunomodulation is on	Smoothing of the same six fields; no iterations under the default smoother setting
`GrSimulation::addEtan`, `addIfx`	`--immuno-mod` and the agent's dosage positive	Passed to every agent's molecular-scale solve; used to sum the free agent and complex fields in the statistics

The post-solve binding step (B.4.1; M7.7) is the one gate of this slot that does not test `--immuno-mod`. In the default configuration its Etanercept block therefore executes in every compartment on every diffusion step, because the Etanercept dosage is 500. Its effect is nil, because the Etanercept and Etanercept-TNF fields are zero. The Infliximab block does not execute, since its dosage is 0.

`addEtan` and `addIfx` reach agents only through the molecular-scale solve, which is called only when at least one M3 flag is on (B.4.3). Under coarse-grained molecular resolution the module therefore acts on cells only through the grid fields, by binding TNF.

Dose timing, blood updates and the neighbourhood used for the tissue concentration are specified in M7.4 and M7.5.

Computations that do not depend on the switch

These execute in every configuration and are inert in the default configuration; none consumes random draws:

- **Fields.** The Etanercept, Infliximab and four complex fields are allocated as padded fields with auxiliary arrays, serialized, and remain zero.
- **Propagation matrices.** The solver constructor builds the no-flux matrices of the six fields, reading `Mod_*_diffusivity` and `Mod_*_degRateConst`, whether or not the module is selected.
- **Vascular state.** The vascular object carries and serializes eight blood concentrations, all zero; the four complex concentrations among them are never assigned (M7.4). The commented-out `modulateBlood` calls are recorded at M6.3.
- **Agent state.** Every agent carries and serializes the ten per-agent variables of the module. Six of them, the free drug and soluble complexes per agent, are never assigned; with the module off, all ten stay zero (M7.8, M7.11).

Dependencies

Delivery occurs only at vascular sources, so the slot depends on the source switches of B.5. The fields are advanced by the solver of B.4.1. Effects within cells require one of the M3 flags of B.4.3. The pharmacology of the four agents is specified in M7.

B.4.8 M8 Optional perturbations

Switches

Perturbation	Switch	Kind	Options	Program default	Default configuration	Gate location
Treg induction	`--Treg-induction`	CL	Flag	Off	Off	`buildSim`; `GrSimulation::setTgammaTransition`; consumed in the Tgam class
T cell exhaustion	`Core_Tcell_exhaustionThreshold`	PF	Integer count	Mandatory	9999999	Effector T cell interaction counting
T cell exhaustion	`Core_Tcell_exhaustedMaxAge`	PF	Timesteps	Mandatory	432	Read by no rule (M8.5)
Growth-rate randomization	`--rand-growth`	CL	Flag	Off	Off	Passed to the `GrSimulation`, grid and container constructors; consumed in the `Mtb` constructor
Reinfection	`Core_reinfectionTimestep`	PF	Timestep	Mandatory	-1	`GrSimulation::solve`, before the grid copy
Reinfection	`Core_reinfectionLocation`	PF	Fraction in [0, 1]	Mandatory	0.8	`GrSimulation::reinfect`
Cytokine depletion	`--tnf-depletion`; `--il10-depletion`; `--tgfb-depletion`	CL	Timestep; negative disables	-1; -1; -1	-1; -1; -1	`GrSimulation::solve`, prologue
Cytokine depletion	`Core_depletionFractionTNF`; `Core_depletionFractionIL10`	PF	Fraction; 0 means not applied	Mandatory	0.0; 0.0	Secretion routines of the agent classes
Neutrophil injection	`Core_Neutrophil_injectionTimestep`; `Core_Neutrophil_injectionCount`	PF	Positive timestep enables; the count must then be positive	Mandatory	0; 0	`GrSimulation::injectNeutrophils`; checked in `Params::computeParams`

The perturbations are independent of one another. Each is held at nil in the default configuration, and none requires a change of executable:

- Treg induction, growth-rate randomization and cytokine depletion by command-line options left at their defaults;
- T cell exhaustion, reinfection and neutrophil injection by parameter values.

Treg induction

`--Treg-induction` permits the Tgam transitions from the active state to the double-producer state and from there to the induced regulatory state. With the flag off, the supporting state variables are not updated and the two states are unreachable. The transition rule is specified in M8.6.

Growth-rate randomization

With `--rand-growth`, each bacterium built by a constructor through a container draws its growth rate within the bounds of its location; division daughters inherit the parent's stored rate. The rule and its consequences are specified in M8.7. Each construction with the flag on consumes one additional uniform draw, so the flag changes the random stream as well as the dynamics.

The flag is read once, at construction of the simulation object, and propagated to the grid, to every extracellular container, and to every macrophage and neutrophil intracellular container. On load, a differing command-line setting is reported and ignored, because changing it would require redrawing the rate of every existing bacterium. This is the one dynamical exception to the precedence of the command line over a loaded state (B.11).

The four bound parameters are mandatory in every configuration. They are also read as the limits of the growth-rate histogram statistics, so they affect output even when the flag is off (B.10).

Reinfection

`GrSimulation::solve` increments the timestep and then tests it for equality with `Core_reinfectionTimestep`. Since the first tested timestep is 1, any value below 1, or beyond the last timestep, disables reinfection, including the declared minimum 0 and the default value -1. The default value lies below the declared minimum (B.6). Placement of the reinfecting macrophage is specified in M8.3.

Cytokine depletion

Each depletion option names the timestep from which the corresponding secretion is suppressed. The flags are computed afresh each timestep, each true when its option is non-negative and the current timestep has reached it, so a value of 0 enables depletion from the first timestep. Depletion acts on secretion and, for TNF and IL-10, on synthesis under the M3 receptor options (M8.4). The fractions `Core_depletionFractionTNF` and `Core_depletionFractionIL10` qualify active TNF and IL-10 depletion; with the default value 0 they are not applied.

T cell exhaustion

Each active cognate Tgam and Tcyt accumulates interactions with exposed macrophages in its radius-two neighbourhood on every behaviour update (S3.6). When the count reaches `Core_Tcell_exhaustionThreshold` the cell becomes exhausted (M8.5).

The default threshold cannot be reached. A T cell accrues at most 25 interactions per timestep and lives at most `Core_Tcell_maxAge` = 432 timesteps. The count is inherited at division, so the bound applies along a lineage: at most $25 \times 432 \times 5 = 54000$ with the default values (M8.5). Any threshold above this disables exhaustion, and the default value 9999999 does so. The threshold is therefore a sentinel (B.6), and the exhausted states are unreachable.

The counting itself runs in the default configuration as live code. It consumes no random draws, and feeds the T cell interaction statistics, whose exhausted-cell counts are zero (S9.16).

Neutrophil injection

`GrSimulation::injectNeutrophils` is called at the end of every timestep and acts only when `Core_Neutrophil_injectionTimestep` is positive and equal to the current timestep. `Params::computeParams` makes a positive injection timestep with a non-positive count fatal at startup. With the default value 0 the routine returns at once on every timestep. Injection is independent of the neutrophil recruitment window of B.5: injected neutrophils persist for their lifespan though none is recruited. The injection algorithm and its timing are specified in M8.9, and the behaviour of an injected neutrophil in M9.

Post-adaptive intracellular growth factor

`Mtb_Agents_growthRateFactorPostAdaptiveIntMtb` is indexed as a sentinel (B.6). Its rule is specified in S4.7 and summarized in M8.8.

Dependencies

Treg induction changes the composition of the T cell population recruited under B.4.2. TNF and IL-10 depletion act on synthesis under the receptor options of B.4.3 as well as on coarse-grained secretion. TGF-β depletion acts only under B.4.4. Growth-rate randomization alters the bacterial submodel of S4 and the random stream. Neutrophil injection depends on the connected-region construction of S9 and on the neutrophil admission predicate (M9.3). The perturbations are specified in M8.

B.5 Entity presence switches

Several cell types implemented in the platform never appear in the default configuration. Each absence is held by the value of a live switch, not by removal or exclusion of code, and every creation path remains executable. This section lists, for each entity, every path by which an instance can be created, the switch controlling it, and its default value. A reader enabling an entity must close or open every path listed, not only the most obvious one.

Neutrophils

Path	Switch	Default configuration	Gate location	Draws when the path is closed
Init-section `Neutrophil` elements	Presence of the element	None	`GrSimulation::initSectionInit`	None
Random placement at initialization	`Core_Neutrophil_initDensity`, or `Core_Neutrophil_initNumber` if the density is not read	0.0, giving a count of 0	`GrSimulation::initSectionInit`	None
Recruitment at vascular sources	`Recruit_Prob_Neutrophil_depletionTimestep` and `Recruit_Prob_Neutrophil_depletionEndTimestep`	0 and -1	`RecruitmentProb::PossibleRecruitNeutrophil`	One uniform per open slot per timestep
Injection	Indexed in B.4.8			

No neutrophil path tests a module switch. An Init-section `Neutrophil` element creates an active neutrophil at the stated position in every configuration, whatever the command line; it is not ignored with a warning, as fibroblast elements are under `--tgfbr-dynamics 0`. Placing one where it cannot be admitted is fatal. Random placement admits by the neutrophil crowding rule, with one draw per attempt; with a count of 0 the placement loop is not entered and no draw is made. Neutrophil construction, birth times and admission are specified in M9.2 and M9.3.

The recruitment window

Neutrophil recruitment is the path held closed by a sentinel rather than a zero count. Under `--recr 0` the neutrophil predicate is evaluated for every open slot of every source on every timestep. It refuses recruitment when

$$d_0 \geq 0 \quad \text{and} \quad t \geq d_0 \quad \text{and} \quad (d_1 < 0 \text{ or } t \leq d_1)\,,$$

where d_0 is `Recruit_Prob_Neutrophil_depletionTimestep` and d_1 is `Recruit_Prob_Neutrophil_depletionEndTimestep`. The window is closed at both ends, and a negative end means it never closes (M9.5). With the default values $d_0 = 0$ and $d_1 = -1$ the condition holds on every timestep, so recruitment is refused for the whole run. A non-negative end that does not exceed the start is fatal at startup, in `Params::computeParams`. The default value -1 lies below the declared minimum of 0 (B.6).

To enable neutrophil recruitment, set d_0 negative, or set d_1 to the last timestep of a finite depletion window.

Work done by the closed recruitment path

The window is tested last. Before it, on every open slot in the default configuration, the predicate computes the neutrophil recruitment signal, with its fatal consistency checks; evaluates the crowding rule, which consumes one uniform draw whatever its outcome; and increments the neutrophil source statistics (M9.5, M9.9). The crowding draw is part of the random stream of the default configuration.

The neutrophil source statistics are written and are not zero, although no neutrophil ever exists. A non-zero neutrophil source count is not evidence of neutrophil recruitment.

Dendritic cells

Path	Switch	Default configuration	Gate location	Draws when the path is closed
Init-section `DC` elements	Presence of the element	None	`GrSimulation::initSectionInit`	None
Random placement at initialization	`Core_DCellLung_percentOfMacInitNumber`	0.0	`GrSimulation::initSectionInit`	None
Recruitment	None under `--recr 0`; under `--recr 1`, conversion of recruited monocytes (M2.9)	Not applicable	`RecruitmentProb` has no dendritic cell path	None

No dendritic cell path tests a module switch: a `DC` element creates a dendritic cell in every configuration. The count, placement and birth times are specified in spine 5.4, and the count parameter is tabled in M2.13. Despite its name, the parameter is a fraction in [0, 1], not a percentage. With the default value 0.0 the count is 0, the placement block is skipped, and no draw is made.

Before placement, the count is compared with the number of compartments remaining after the earlier placements.

With no dendritic cell present, the dendritic cell passes of movement, next-state computation, state commitment, shuffling and the dendritic cell extent run over an empty list and are inert.

Fibroblasts and myofibroblasts

Path	Switch	Default configuration	Gate location	Draws when the path is closed
Init-section `Fibroblast` elements	Presence of the element, and `--tgfbr-dynamics` not 0	None; 0	`GrSimulation::initSectionInit`	None
Init-section `Myofibroblast` elements	As for `Fibroblast` elements	None; 0	`GrSimulation::initSectionInit`	None
Random placement at initialization	`Core_Fibroblast_initDensity`, or `Core_Fibroblast_initNumber` if the density is not read, and `--tgfbr-dynamics` not 0	0, giving a count of 0; 0	`GrSimulation::initSectionInit`	None
Proliferation	An existing fibroblast	None exists	Fibroblast class (M4)	None

These are the only cell types whose initial placement is gated on a module switch. Placement under `--tgfbr-dynamics 0` is indexed in B.4.4. Birth times and admission under the other options are specified in M4.5. Fibroblasts are not recruited under `--recr 0`; once present they increase only by proliferation, which sets the latched flag that freezes the threshold-granuloma membership flag (B.4.4).

Initial cognate Tgam

Path	Switch	Default configuration	Gate location
Random placement at initialization	`Core_Tcell_Tgam_initCognateNumber`	0	`GrSimulation::initSectionInit`

The path is not gated on a module switch. With the default value 0 the placement loop is not entered. Placement of initial cognate Tgam is specified in spine 5.4.

Init-section seeds

The Init section of the parameter file can place agents and sources at stated positions, for a new run only (B.2). Positions, processing order and admission are specified in spine 5.2 and 5.4.

Element	Gated on a module switch	Default configuration
`Mac`	No	One, at `center`
`ExtMtb`	No	None
`Source`	No	None
`DC`	No	None

Element	Gated on a module switch	Default configuration
`Neutrophil`	No	None
`Fibroblast`, `Myofibroblast`	`--tgfbr-dynamics` not 0	None

The `Mac` element is the means by which the default configuration is infected. Removing it gives a run with no bacteria, unless `ExtMtb` elements are supplied. Each `Mac` element always creates an infected macrophage holding one live bacterium; its state and bacterial count are not configurable from the element.

Deterministic sources add to the random ones, so recruitment and vascular oxygen delivery stop entirely only when there is neither a random nor a `Source` element source (spine 5.2).

Non-agent grid initialization

After all agents and sources are placed, `GrGrid::initNonAgentGrids` reads, for every grid field (spine 2.4, 2.6), any Init-section element of that name. Each element must carry a non-negative `value` and either a position or `pos="all"`, and sets the field there or everywhere. The facility applies in every configuration, is intended for testing, and is not used in the default configuration.

It writes the fields directly and triggers none of the rules that would normally accompany a change:

- a value written to `nKillings` at or above the caseation threshold makes the compartment caseated without killing its occupants, so an agent placed earlier remains in a caseated compartment until it dies or the compartment is tested by the entrapment rule;
- the extracellular container of such a compartment keeps the replicating designation given at grid construction until the first extracellular pass reclassifies it;
- a value written to `O2` replaces the uniform initial value of spine 5.5 at that position;
- the statistics computed at the end of initialization do not fully reflect the written values.

Resting macrophages and vascular sources

The initial resting macrophage population and the vascular sources are always present in the default configuration. They are listed because their switches are density and count pairs whose direction of derivation depends on which member is read (B.7).

Entity	Switch pair	Default parameter file	Value in force
Resting macrophages	`Core_Mac_initDensity`; `Core_Mac_initNumber`	Sampled density; 105	Count derived from the density, 431 to 923; the file count is overwritten
Vascular sources	`Core_sourceDensity`; `Core_nrSources`	0.08762770113823116; 50	7886, derived from the density; the file count is overwritten

The derived macrophage count also sets the recruitment floor (S8.7), so changing the initial density changes the population maintained throughout the run, not only the starting population. Placement of resting macrophages and sources is specified in spine 5.2 and 5.3.

B.6 Sentinel conventions

A sentinel is defined in B.1. The parameters of the sentinel table are those through which the default configuration holds a mechanism at nil, together with those whose default value is a sentinel although the mechanism is not otherwise relevant in the default configuration. Zero counts that simply create no instances, such as initial densities, are not sentinels; they are indexed in B.5.

Sentinel table

The column "Disabling values" gives every value that disables the mechanism under the test as implemented, which is often wider than the default value.

Parameter	Test as implemented	Disabling values	Default configuration	Test site
`mtbStopppingTimeStep`; `mtbStopppingTimeStep2`	Positive and equal to the current timestep	Any value ≤ 0, or beyond the last timestep	0; 0	`shouldStop` in `grmain.cpp`
`areaCellDensityStopppingTimeStep`; `areaCellDensityStopppingTimeStep2`	Non-zero and equal to the current timestep	Any value ≤ 0, or beyond the last timestep	0; 0	`shouldStop`
`Mtb_Agents_growthRateFactorPostAdaptiveIntMtb`	Multiplies intracellular growth after the nominal onset plus `Mtb_Agents_growthRateFactorDelayIntMtb` (S4.7)	1	1.0	Intracellular growth (S4)
`Core_Mac_movementBonusFactor`; `Core_Tcell_movementBonusFactor`	Multiplies the weight of the strongest chemotactic direction	1; values below 1 are fatal	Defaulted, 1.0; 1.0	`Agent::getDestinationOrdinal` (S1.3); checked in `Params::checkParams`
`Core_Tcell_exhaustionThreshold`	Accumulated interactions reach the value	Any value above the lineage bound of 54000 (B.4.8; M8.5)	9999999	Effector T cell interaction counting
`Recruit_Prob_Neutrophil_depletionTimestep`; `Recruit_Prob_Neutrophil_depletionEndTimestep`	Recruitment refused while $t \geq d_0 \geq 0$ and either $d_1 < 0$ or $t \leq d_1$	Depletion is disabled by $d_0 < 0$, or by d_0 beyond the last timestep; the default values (0, -1) make it permanent	0; -1	`RecruitmentProb::PossibleRecruitNeutrophil` (B.5)

The other sentinels are indexed with their switches, which give the test and the disabling value: `Recruit_Prob_mtbRecEnabled`, `Recruit_Prob_timeRecEnabledRange`, `Recruit_Prob_timeMaxRecDelay` and `Recruit_ODE_Ag2ConvertTime` (B.3, B.4.2); `Diffusion_FFT_numSmoootherSteps` (B.4.1); `Drugs_*_minEffluxInduction` and the resistant-bacterium counts (B.3, B.4.6); the four `Mod_*_dosage` entries (B.4.7); `Core_reinfectionTimestep`, `Core_Neutrophil_injectionTimestep` and the depletion fractions (B.4.8).

Other entries disable a mechanism in the default configuration by magnitude, although they are not designed as sentinels:

- `Drugs_dosageStartTime` = 28801 lies beyond the run, so drug dosing would not begin even if drugs were named (B.4.6);
- `Core_nrSources` = 0 would disable random source placement, but in the default configuration it is overwritten by the value derived from the source density (B.5);
- the command-line depletion options use -1 in the same way as the parameter sentinels (B.4.8).

Testing conventions

The tests are not uniform. Some test equality with the current timestep, some test sign, some test for zero, and `Drugs_*_minEffluxInduction` is tested for the exact value -1. As a result:

- **Timestep sentinels.** A timestep sentinel beyond the last timestep of the run also disables its mechanism, because the equality is never met. The value that disables a mechanism therefore depends on the duration in force (B.8.2).
- **Equality and sign tests.** A sentinel tested by equality with the current timestep, such as the reinfection

timestep, also disables at 0, the declared minimum, since the first tested timestep is 1. A sentinel tested by sign, such as the injection timestep, disables at 0 by design.

- **Magnitude sentinels.** The exhaustion threshold and the drug dosage start time hold their mechanisms at nil only relative to the lifespan and duration in force. A configuration that lengthens either may bring the mechanism into play without any change to the sentinel.

Sentinels below a declared minimum

Some default values lie below their declared minimum; minimum-only declarations are not range-checked (spine 7.0, "Validity ranges"). In the default parameter file these are the sentinels `Core_reinfectionTimestep` = -1, `Recruit_Prob_Neutrophil_depletionEndTimestep` = -1 and `Drugs_*_minEffluxInduction` = -1 for every drug, each declared with a minimum of 0 and no maximum, and `Core_LinkLogAlpha` = -1.93, an active parameter of the coarse-grained IL-10 submodel (S6), declared with a minimum of 0.

`Recruit_Prob_timeRecEnabledRange` is also declared with a minimum of 0 and no maximum, so a negative value is accepted. `defineTCellRecTime` then draws on an interval whose lower bound exceeds its upper bound. The default value is 0.

B.7 Parameter-file mechanics

The parameter-file mechanics (addressing, resolution, the omitted-parameter and range-check rules, undeclared entries and the computed parameters, including the count and density pairs) are specified in spine 7.0. The sentinels of B.6 depend on its range-check rule, and the inert parameters a file must still supply are indexed in B.10.

Defaulted parameters in the default configuration

Few parameters have defaults, and few of those are defaulted in the default parameter file.

Parameter	Declared default	In the default parameter file	Value in force
`Core_Mac_movementBonusFactor`	1.0	Absent	1.0
`Core_Tcell_movementBonusFactor`	1.0	Absent	1.0
`Drugs_interactThreshold`	0.1	Present, 0.1	0.1
The count and density pairs of B.5	0 or 0.0, except `Core_sourceDensity`, 0.2	Present	Derived

Undeclared entries

The default parameter file contains these undeclared entries, which the reader ignores, and no warning is issued (spine 7.0, "Declaration and addressing"):

Entry	Note
`Core_diffusivityPGE2`, `Core_degRatePGE2`, written with a leading underscore	Their declarations are commented out (B.10)

Entry	Note
`Core_Fibroblast_initNumber`, written with a leading underscore, beside the declared `initNumber`	An alternative value disabled by renaming
`Core_Neutrophil_dTNF`, written with a leading underscore, beside the declared `dTNF`	An alternative value disabled by renaming
`O2_minDiffusivityO2`	No declaration
`Molecular_TNF_TranscriptionFraction`	No declaration; unused (M3.9)
`Molecular_TGFB_Fibroblast_Nav`, `Molecular_TGFB_Fibroblast_vol`	No declaration
`Core_Myofibroblast_maxAge`	No declaration in that group
`TgamInd_Mac_thresholdICOS`, `TgamInd_Mac_icosActivationTime`	No declaration

B.8 Other build and run-time settings

B.8.1 Build settings

Besides `DIMENSION` (B.4.5), the compile-time settings in this table affect the executable. None selects a model variant.

Macro	Options	Effect	Location
`DEBUG`; `NDEBUG`	Exactly one must be defined	Selects debug or release compilation. Under `NDEBUG` the standard assertions are removed, and `assert_res` evaluates its argument without checking it. The setting is recorded as the `Debug status:` line of the version output and in the executable strings. If neither is defined, compilation of `grmain.cpp` fails	`grmain.cpp`, `gr.h`
`STATE_VERSION`	Integer	Version number written into saved states. A state whose version differs is loaded with a warning, not refused. The custom version declaration admits values above 255	`grsimulation.h`

The assertions removed under `NDEBUG` include the preconditions of the recruitment functions, which state that the source is not caseated and has room. In a release build a violated precondition is not detected at that point. The build mode of the reference simulations is recorded in the `Debug status:` line of each run's console output.

B.8.2 Domain, duration and stopping

`--dim` (B.3) is read by `main`, by `LungParam::getInstance(pdim)` and by the `GrSimulation` constructor. It gives a single integer, from which a square domain is constructed (spine 2.2).

When a saved state is loaded, the grid dimensions are restored from the state, but the computed parameters were derived from `--dim` during parameter loading, and the program does not compare the two. A load with a `--dim` differing from the stored grid therefore runs on the stored grid with initial counts and a macrophage recruitment floor derived for the other size; `buildSim` checks only the agent slot count. Inert for new runs, including the default configuration.

The duration (B.3; B.2) is not part of a saved state: a run that loads a state continues from the stored timestep to the final timestep of its own command line. A duration of 0 timesteps is accepted and performs no timestep; it writes the outputs of the loaded or initialized state once, which supports post-processing of saved states.

`--stop-on-clearance` and the four parameter-file stopping criteria (B.3) are tested in `shouldStop` in `grmain.cpp`. Their tests and thresholds are specified in S9.20; all four parameter-file criteria are disabled in the default configuration. Stopping does not alter dynamics; it truncates the trajectory.

B.8.3 Granuloma area thresholds

The two command-line thresholds (B.3) are consumed by `GrSimulation::updateGridStats`. Their validation, storage and every use, and those of `occupiedNeighborFraction`, are specified in S9.4, S9.6 and S9.20; their precedence on load is indexed in B.11. In the default configuration all three affect output only. The meaning of `occupiedNeighborFraction` changes with dimensionality (M5.13).

B.8.4 Seeding and loading

`-s` (also `--seed`) is read by `main` and `Rand::setSeed`; without it the seed is derived from the clock by `createTimeSeed`. `--load` (also `-l`) names a saved state, decompressing a name ending in `.gz`, and is read by `getRegularSimulation` and `getSimulationFromSavedState`, as is `--new-seed-on-load`.

The global generator is seeded once, at the seeding step of the startup sequence (B.2), after parameter loading. With `-s` the run is fully determined by the executable, the parameter file, the command line and the seed, subject to the solver choice of B.3. Without it the seed is taken from the clock, and the run can be reproduced only from the seed recorded afterwards (S9.18).

A saved state contains the complete simulation state, including the generator. Loading it replaces the seed set from `-s` or the clock, so a run continued from a state follows the draw sequence of the run that saved it. `--new-seed-on-load` reseeds the generator from `-s` after the state is loaded and configured, so that several runs can start from one saved state with distinct random streams. It applies only to `--load`: a state loaded automatically for restart (B.8.6) always keeps its stored generator. A file named by `--load` that does not exist, or cannot be deserialized, is fatal.

B.8.5 Output and statistics

Every statistic is computed on every timestep, whatever output is requested. The output options select which quantities are written, and when. None of them changes model state or consumes random draws. The output streams, their file names and their cadences are specified in S9.18; the options are indexed in B.3.

Grid dumps of padded fields, which include the default TNF dumps, are written at six significant digits.

The histogram sample counts `--rand-growth-samples`, `--biomass-samples` and `--reserve-samples` give the number of bins of the bacterial growth-rate, biomass and reserve histograms. They are fixed when the statistics object is constructed and stored in a saved state; on load a differing command-line value is reported and the stored value kept. The growth-rate histogram bounds are the four randomization parameters of B.4.8. `--reserve-samples` and `Mtb_Agents_maxReserve` have no effect: the sample count is replaced by zero on the statistics object, and the output writers emit reserve columns only when it is positive (S9.20).

B.8.6 Batch execution and restart

The batch options (B.3) support running large numbers of simulations on shared computing resources, where a run may be interrupted and must resume without corrupting its output. None changes model dynamics, but restart and chunking decide whether an interrupted run's output equals that of an uninterrupted one.

A resumed run keeps the generator stored in its checkpoint (B.8.4). The constructors used during deserialization make no random draws, so the generator remains synchronized; with the estimate planning strategy of B.3, a resumed run is intended to reproduce the trajectory of an uninterrupted one. The parameter file and command line in force are those of the resuming invocation, so a change made between interruption and resumption takes effect from the resumption timestep, subject to the precedence rules of B.11.

B.9 Inert computations and random-draw consumption

This section gathers the live code that executes in the default configuration with nil effect on model state. Each item is described where its switch is indexed. Inert code may still consume random draws (B.1); the draws and their order are part of the specification. Some inert code writes statistics, whose columns are not zero and are not evidence that the mechanism is active.

Inert computations that consume draws

- the construction draws of each agent built by a constructor (S6.3; B.4.3);
- the neutrophil crowding draw on every open source slot (B.5; M9.5);
- the T cell candidacy draws before the onset flag is set (B.4.2; S8.11);
- Treg suppression draws on agents for which suppression has no effect (S3.10).

Inert computations that consume no draws

Computation	Held at nil by	Detail
Maintenance of the auxiliary `u` and `v` arrays of every padded field	Read only by the explicit solver	M1
Construction of the explicit solver, and its 60 s ceiling	Replaced by the selected solver	B.4.1
Diffusion of active TGF-β; degradation of inactive TGF-β	Both fields zero	B.4.4

Computation	Held at nil by	Detail
Propagation matrix for inactive TGF-β	Computed, never applied	M1.3, "The propagator and incorporation of decay"
Propagation matrices of the six anti-TNF fields	Applied only under `--immuno-mod`	B.4.7
Etanercept binding block	Etanercept and complex fields zero	B.4.7
Smoother call	`Diffusion_FFT_numSmootherSteps` = 0	B.4.1
MHC class II rate rescaling and derivations	Rates read only under MHC class II dynamics	B.4.3
Receptor turnover products	Read only by the receptor systems	B.4.3
Passes over the empty dendritic cell, fibroblast and neutrophil lists	No instance exists	B.4.4; B.5
Lymphatics object	No dendritic cell exists	B.4.2
Antibiotic loops, per-agent concentration lists, and resistance and efflux counting	Antibiotic list empty	B.4.6
Exhaustion interaction counting	Threshold unreachable	B.4.8
Shed TNFR2, collagen and the six anti-TNF fields: allocation, serialization, statistics	Fields zero	Spine 2.4

The antibiotic fields are not in this table: they exist only for named drugs, so with none named they are absent, not zero (B.4.6).

Inert computations that write statistics

These execute with nil effect on model state but produce non-zero output columns in the default configuration:

Statistic	Detail
Neutrophil source counts: candidacy passed, recruitment blocked, blocked by a large agent, and extracellular bacteria above the neighbourhood maximum	B.5; M9.9
MHC class II input statistics around compartments holding a macrophage	M3.6
MHC class II summary statistics	Constant values; M3.6
T cell interaction counts	Exhausted-cell counts remain zero; B.4.8

The four growth-rate randomization bounds of B.4.8 are inert as dynamics but are read as the growth-rate histogram limits, so they affect output in every configuration.

B.10 Parameters without effect in the default configuration

Every parameter declared in `params.def` is read, range-checked where a range exists, and stored in every configuration (B.7). Most are mandatory, so a parameter file must contain them whether or not the mechanism they serve is selected. This section indexes the parameters whose values have no effect on model state in the default configuration, in these classes:

- **Module groups.** Whole groups that serve a module or entity not selected or not present, given with the switch that would bring them into effect.
- **Individually inert parameters.** Parameters in active groups whose value has no effect, because it is multiplied by a zero term, selects a branch not taken, or is overwritten.
- **Unused parameters.** Parameters that no code reads with effect in any configuration.

A parameter listed here may still be read during execution, several every timestep by inert code (B.9), and some affect output columns. "Without effect" refers to model state only. Counts are of entries declared in `params.def` at revision r9959; an entry is mandatory unless the "Defaulted entries" column names it.

Module groups

Group	Declared entries	Defaulted entries	Brought into effect by	Entries with effect in the default configuration
`Drugs`	6	`interactThreshold`	Named drugs (B.4.6)	None
`Drugs_*`, one group per drug: INH, RIF, MXF, LVX, GFX, EMB, PZA, BDQ, PTM, LZD, RPT	50 per drug; 550 in all	`epitheliumBindingRateConst` and `cellularKout` in every drug; also `epitheliumBindingKa` in INH and RIF	Naming the drug (B.4.6)	None
`Mod` and its sub-groups `TNF`, `IL10`, `Etanercept`, `EtanTNF`, `Infliximab`, `Ifx1TNF`, `Ifx2TNF`, `Ifx3TNF`	45	None	`--immuno-mod`, with a non-zero dosage (B.4.7)	None; the anti-TNF diffusivities and degradation rates are read into inert propagation matrices, and `Mod_Etanercept_dosage` gates an inert binding block
`Recruit_ODE`	71	None	`--recr 1` (B.4.2)	None
`Recruit_OLD_Mac`, `probRec` only	1	None	`--recr 1`	None
`TgamInd_Tcell_Tgam`	5	None	`--Treg-induction` (B.4.8)	None
`NFkB`	53	All except `kApoptosis` and `NFkBTimeCoefficient`, defaulting to 0	`--NFkB-dynamics` (B.4.3)	`meanNFkB`, through the construction draw only
`Molecular_TNF`	18	None	`--tnfr-dynamics` or `--NFkB-dynamics`	`KD1` and `KD2`; `diffusivityShedTNFR2` is read into an inert propagation matrix
`Molecular_TNF_Mac`	10	None	As for `Molecular_TNF`	The four receptor means and half-widths
`Molecular_TNF_Tcell`	7	None	As for `Molecular_TNF`	The four receptor means and half-widths
`Molecular_TNF_Neutrophil`	10	None	TNFR dynamics with neutrophils present	None (M9.10.2)
`Molecular_IL10`	6	None	`--il10r-dynamics`	`IkD`
`Molecular_IL10_Mac`	8	None	As for `Molecular_IL10`	The receptor mean and half-width

Group	Declared entries	Defaulted entries	Brought into effect by	Entries with effect in the default configuration
`Molecular_IL10_Tcell`	3	None	As for `Molecular_IL10`	The receptor mean and half-width; `IkSynthTcell` is read by the Treg suppression rule only under IL-10R dynamics
`Molecular_IL10_Neutrophil`	7	None	IL-10R dynamics with neutrophils present	None (M9.10.2)
`Molecular_MHCII`	59	Seven computed initial conditions, defaulting to 0.0: `recOut`, `mrna`, `selfPepIn`, `mhcIn`, `mhcOut`, `mhcSelfPepIn`, `mhcSelfPepOut`	`--mhc-dynamics`	None; the rates are rescaled and further values derived every run (B.4.3), and `mhcIIBindingThreshold` enters an output statistic
`Molecular_TGFB_Fibroblast`	26	None	`--tgfbr-dynamics 2` with fibroblasts present	None
`Core_Fibroblast`	15	`initNumber`, `initDensity`	`--tgfbr-dynamics` 1 or 2 (B.4.4)	`initNumber` and `initDensity`, as presence switches (B.5)
`Core_Myofibroblast`	6	None	As for `Core_Fibroblast`	None
`Core_Neutrophil`	21	`initNumber`, `initDensity`	Any neutrophil creation path (B.5)	The presence switches of B.5; `probMoveToBigOrNeut` is read by the inert crowding test on every open source slot (M9.10.1)
`Recruit_Prob_Neutrophil`	10	None	An open recruitment window (B.5)	The window bounds, as the switch holding recruitment at nil; the probability bounds, the two used weights and the chemokine bounds are read on every open source slot to compute a probability that is discarded (M9.10.2)
`Core_DCellLung`	3	None	Any dendritic cell creation path (B.5)	`percentOfMacInitNumber`, as a presence switch

For the per-drug groups, the declared defaults reach only the general loader's copies. The per-drug reader requires every attribute and treats a missing attribute or drug node as fatal, so no default reaches a drug object (M6.17).

The `Recruit_ODE` numbering is non-contiguous. The nine half-saturation parameters are numbered 1, 4, 5, 8, 10, 11, 13, 14 and 17; the sixteen rate constants run 1 to 8 and 10 to 17; the eight efflux rates are numbered 2, 3, 5, 6, 8, 9, 11 and 12. Only the death rates, 1 to 9, are contiguous. Of the 71 entries, 66 have no declared range. Only the four second-antigen conversion quantities and the conversion latency carry a minimum, none carries a maximum, and a minimum-only declaration builds a range only when that minimum is not 0 (spine 7.0, "Validity ranges"). Startup therefore range-checks almost none of the group: a negative rate constant, a blood concentration exceeding any physiological value, or a carrying capacity of zero is accepted (M2).

The TGF-β entries of the active groups `Core`, `Core_Mac`, `Core_Tcell`, `Core_Tcell_Tcyt` and `Core_Tcell_Treg` also belong to slot M4 and are without effect by default, except the three field parameters that enter inert propagation factors (B.4.4).

In all, about 1000 of the declared entries have no effect on model state in the default configuration, of which the eleven drug groups account for more than half. The bulk of a parameter file is therefore configuration for modules not selected. A study selecting none of them must still supply every mandatory entry, and may supply any value that passes the range checks, without effect on its results.

Individually inert parameters

These belong to groups that are active in the default configuration, but their own values have no effect on model state there.

The following are also inert in the default configuration and are indexed with their switches: the count members of the macrophage and source pairs and the two caseated-growth thresholds, overwritten by computed values (B.5; S4.6); `Molecular_IL10_Tcell_IkSynthTcell` (B.4.3); `Molecular_TNF_kT1`, `kT2` and `Molecular_IL10_IkT` (B.4.3); the depletion fractions, `Core_reinfectionLocation` and `Core_Tcell_exhaustedMaxAge` (B.4.8); the ADE and Crank-Nicolson timestep pairs and the smoother Fourier number (B.4.1); `O2_diffusivityO2` and `O2_degRateConstO2`, which no live code reads with effect under any solver (B.4.1; S7.8).

Parameter	Default configuration	Inert because	Detail
`Mtb_Agents_growthRateFactorDelayIntMtb`	0.0	Qualifies a multiplier held at the sentinel 1	B.6
`Mtb_Agents_growthRateIntMtbMin`, `Max`; `Mtb_Agents_growthRateExtMtbMin`, `Max`	0.001, 0.005; 0.0005, 0.00325	Read as growth rates only when `--rand-growth` is given; the extracellular pair is passed to every container constructor regardless. The four bounds are also read as the growth-rate histogram limits whether or not `--rand-growth` is given, so they affect output	B.4.8
`Mtb_Agents_degRateBiomass`; `Mtb_Agents_degRateBiomassMin`	0.001; 0	Read by no rule	S4.16
`Mtb_Agents_initialReserve`	0	Sets each bacterium's starting reserve, one of the five variables read by no rule (S4.3); it enters only the reserve totals `TotExtRes` and `TotIntRes`	S4.16; S9.14
`Mtb_Agents_maxReserve`	—	Labels reserve histogram bins that are never written	B.8.5
`Mtb_Agents_perBasePairMutationRate`	2×10^{-12}	Read only by resistance mutation under module M6	M6.13
`Core_Tcell_Tgam_dIL10`	0	Zero, and multiplied by a state factor of zero	S6.13
`Core_Tcell_Tcyt_dIL10`	Sampled, [0.07, 0.08]	Multiplied by a state factor of zero	S6.13
`Core_Tcell_Treg_dTNF`	0	Not read by Treg secretion, which secretes IL-10 only	S3.11
The four stopping thresholds	50; 10^9; 1.8×10^7; 3×10^8	Their timesteps are 0	B.6; S9.20

Parameter	Default configuration	Inert because	Detail
`Molecular_TNF_kOn2`; `Molecular_TNF_diffusivityShedTNFR2`	—	M3 disabled; `Molecular_TNF_KD2` is not inert, entering the coarse TNFR2 sink	M1.6
The `Mod_*_diffusivity` and `Mod_*_degRateConst` entries of the six anti-TNF species; the Etanercept and Infliximab `kOn` and `kOff`; `Mod_dosageStartTime`	—	M7 disabled	M1.6; M7.12
`Mod_Etanercept_minDiffusivity`, `Mod_Infliximab_minDiffusivity`, `Mod_EtanTNF_minDiffusivity`, `Mod_Ifx1TNF_minDiffusivity`, `Mod_Ifx2TNF_minDiffusivity`, `Mod_Ifx3TNF_minDiffusivity`	—	Declared and not read by the solver	M7.6
`Drugs_*_minDiffusivity`; `Drugs_bloodVolume`; `Drugs_*_volDistLung`; the five observation attributes `resistRiskIndicatorFlag`, `aucRiskLB`, `aucRiskUP`, `cmaxRiskLB`, `cmaxRiskUP`; the general-loader values of every per-drug attribute	—	Stored and never read; read only by a routine with no live call site; scales a lung compartment never advanced; affect observation only; validated but never consulted	M6.17
`Core_MaxIL10Inhibition`	0.14	No read anywhere	S6.11
`Molecular_IL10_LinkRNAGamma`, `Molecular_IL10_LinkRNADelta`	—	Read by an uncalled routine, and by the fine-grained TNF derivative under M3	S6.11
The M3-branch parameters of the coarse-grained effector tests: `Molecular_TNF_Mac_thresholdNFkBTNF`, `kNFkB`, `saturationFracNFkBTNF`; `Molecular_TNF_thresholdApoptosisTNF`, `kApoptosis`, `saturationApoptosisTNF`; `NFkB_kApoptosis`, `kIAP`, `actThreshold`, `activationRate`; `Molecular_IL10_Mac_thresholdSTAT3IL10`, `kSTAT3IL10`, `saturationFracSTAT3IL10`	—	Read by a live function in a branch taken only under M3	S6.16; M3.7
`Molecular_IL10_Mac_halfSatIL10mRNA`	—	Read on the coarse path, in a factor whose numerator is identically zero	S6.12
`Molecular_MHCII_numCells`; `Molecular_MHCII_rxnVol`; `Molecular_MHCII_kdegIfng`	10^5; 0.001; 4.9015×10^{-5} in force	Read by no live code path; `kdegIfng` is rescaled at load but consumed only by an unreachable branch	M3.6; M3.9
`Molecular_MHCII_ifng`; `Molecular_MHCII_exAgOut`	10^{-9} M; 10^{-4} M	Read at agent construction and overwritten before use	M3.6
`Core_Fibroblast_aSMAFactor`; `Core_Fibroblast_myoActivationThreshold`; `Core_Myofibroblast_tgfbBindingRate`; `Molecular_TGFB_Fibroblast_TGFB1kdegl`, `TGFB1kdega`, `IL10synth`	—	Read by no live code, under every M4 option	M4.9

Parameter	Default configuration	Inert because	Detail
`Core_Fibroblast_maxAge`	—	Sets a death time that is never tested	M4.5
`Core_Tcell_TGFBmax`	—	Read only under M4; a disabled-module parameter by default	M4.4

`Core_Tcell_Treg_dIL10` is conditionally inert in a way that bears on sampling. It serves both as the Treg IL-10 secretion rate and, under coarse IL-10 resolution, as the test of whether `Core_Tcell_Treg_factorDeactIL10` divides the suppression probability. Any non-zero value selects the divided form; a value of 0 would remove Treg IL-10 secretion and also make `factorDeactIL10` inert. The parameter is sampled uniformly on [0.7, 0.8] molecules/s, so the divided form applies throughout. Its declaration (mandatory, minimum 0, no maximum) would admit 0, so "non-zero throughout" rests on the sampling design. Treg suppression strength therefore depends on `factorDeactIL10` and `probTregDeactivate` only, and on no IL-10 concentration (S3.10).

Unused parameters

These are read from the parameter file but no code reads them with effect in any configuration.

Parameter	Entries	Mandatory	Basis
`Recruit_OLD_Mac_thresholdRec`	1	Yes	Read by no code; only `Recruit_OLD_Mac_probRec` is read, by the lymph node scheme
`Recruit_OLD_Tcell_Tgam_thresholdRec`, `probRec`; likewise for `Tcyt` and `Treg`	6	Yes	Read by no code
`Recruit_OLD_effectRecTNF`, `effectRecCCL2`, `effectRecCCL5`, `effectRecCXCL9`	4	No; defaults 1.0, 0.0, 0.0, 0.0	Read by no code
`Core_Tcell_Treg_deactivateSlope`; `Core_Tcell_Treg_deactivateIntercept`	2	Yes	Read only by a routine called only from the five-argument Treg suppression overload, which is never called (S3.10)
`Recruit_Prob_Neutrophil_Mi_RecWeight`; `Recruit_Prob_Neutrophil_CCL5_RecWeight`	2	Yes	Not read; the neutrophil recruitment signal derives both weights from the other two (M9.5)
`Core_Neutrophil_nKillings_MovWeight`; `Core_Neutrophil_CCL5_MovWeight`	2	Yes	Not read; neutrophil movement derives both weights from `liveCount_MovWeight` (M9.4)
`Core_Neutrophil_probHealCaseation`	1	Yes	Read by no rule (M9.8)
`Mod_Etanercept_bloodConc`; `Mod_Infliximab_bloodConc`	2	Yes	Not read; the only reference is commented out (M7.12)
`Mtb_minGrowthBin`; `Mtb_maxGrowthBin`	2	—	Read by nothing; the growth-rate histogram bounds are the four randomization parameters (S9.20)

The `Recruit_OLD` groups are not wholly without a reader: the lymph node scheme reads `Recruit_OLD_Mac_probRec` (B.4.2). The mandatory entries among these must appear in every parameter file, although no value can affect a run. For a mandatory parameter that no code reads, the declaration requires an entry that is never used (B.7).

B.11 Switch interactions, constraints and precedence

The switches of B.4 to B.8 are largely independent, but not entirely. This section collects implications, conjunctive gates, exclusions and requirements, and the precedence rules that decide which setting is in force when a saved state is loaded, followed by the startup and run-time checks.

Implications

Most implications between switches are indexed with the switch that carries them: `--NFkB-dynamics` switches on TNFR dynamics, and the coarse receptor-occupancy sinks apply whenever TNFR or IL-10R dynamics is off (B.4.3); under coarse resolution `addEtan` and `addIfx` do not reach agents (B.4.7); `--tgfbr-dynamics` 1 or 2 permits fibroblast placement, movement and proliferation, and under 0 `--tgfb-depletion` has no effect (B.4.4); a named fluoroquinolone suppresses caseum death from the dosage start (B.4.6); under coarse IL-10 resolution a non-zero `Core_Tcell_Treg_dIL10` selects the divided Treg suppression probability (B.10; S3.10).

Setting	Implies	Enforced	Site
`--mhc-dynamics`	Recruited T cells enter the T0 state	Yes, under either recruitment scheme	`RecruitmentProb::recruitCellTgam`, `Tcyt`, `Treg`; `RecruitmentLn::recruit*`

The help text of `--mhc-dynamics` states that it requires the lymph node recruitment scheme; the program does not require it (B.4.2). Under `--recr 0` with `--mhc-dynamics`, recruited T cells enter T0 and become active only through activation by a macrophage, which the MHC class II system provides. The combination therefore runs, and differs from the default configuration in T cell activation as well as in molecular resolution.

Conjunctive gates

Several mechanisms require two settings together. Setting only one leaves the mechanism at nil, and no warning is issued. The conjunctions for antibiotic dynamics (B.4.6), immunomodulation dosing and the dosage-only anti-TNF binding gate (B.4.7), fibroblast placement (B.4.4), neutrophil injection (B.4.8) and T cell recruitment (B.4.2; S8.10) are indexed with those switches. The output conjunctions are:

Mechanism	Requires	Detail
Agent dump	`--agent-dump-timespec` and `--agent-dump-file`; either alone writes nothing	S9.18
Grid dump	`--grid-dump-timespec` and `--grids-to-dump`; a timespec with no valid grid name produces a warning	S9.18

Exclusions and requirements

The fatal option values and combinations are indexed with their switches: `--diffusion 7` in a three-dimensional build (B.4.1), invalid `--recr`, `--tgfbr-dynamics` and `--odesolver` values (B.4.2 to B.4.4), the antibiotic option combinations and `--dump-antibiotics` (B.4.6), `--new-seed-on-load` without `-s` (B.8.4) and area thresholds outside [0, 1] (B.8.3). The smoother parameters have no effect under a solver other than 5 or 6 (B.4.1). In addition:

Combination	Result	Site
A `--diffusion` code outside 4 to 7	Fatal	`buildSim`
`--rand-growth` on a new run	Accepted, with a warning	`buildSim` (B.4.8)

Precedence when a state is loaded

A saved state stores the simulation object, including most command-line settings. When a state is loaded, by `--load` or for restart, each setting is resolved by these rules.

Setting	Stored in the state	In force after loading
Recruitment scheme, diffusion method, the four molecular-resolution flags, TGF-β method, ODE solver, Treg induction, the three depletion timesteps, immunomodulation, area thresholds	Yes	The command-line value; a differing value is reported
Output streams, tracking selection, restart and chunk options	No	The command line of the loading run

The other settings are resolved as indexed with their switches: `--rand-growth` keeps its stored value (B.4.8); the histogram sample counts keep their stored values (B.8.5); the drug list and interaction method depend on whether the load is regular or restart (B.4.6); the grid dimensions are those stored, and `--dim` is not compared (B.8.2); the T cell recruitment onset time and flag are those stored (B.4.2); the generator is the stored one unless `--new-seed-on-load` is given with a regular load (B.8.4); parameters, the Init section and the duration are not stored, so those of the loading run apply, the Init section having no effect (B.2; B.8.2).

The command line therefore overrides the stored configuration, with one exception for a dynamical setting and one for an output setting. Parameters are never stored, so a state can be continued under a changed parameter file without any warning, and the change takes effect from the loaded timestep. This applies equally to restart, so a parameter file edited between interruption and resumption alters the remainder of the run (B.8.6).

Settings stored in agents rather than in the simulation object are not revised by the command line. Examples are the receptor counts and growth rates drawn at construction, antigen specificity and producer status. These keep the values drawn under the configuration in which each agent was created.

Startup and run-time checks

Several settings are checked against one another, either at startup or when the code that uses them first executes. A failed check is fatal. The parameter-load checks (declared ranges, count and density pairs, cross-parameter constraints) are specified in spine 7.0; the neutrophil window and injection checks are indexed in B.5 and B.4.8; the explicit-solver ceiling at construction in B.2 and B.4.1; the intracellular-bacteria check of the neutrophil recruitment signal in B.5 (M9.5).

Stage	Check	Fails when	Default configuration	Site
Solver selection	Explicit-solver ceiling, again	`Diffusion_ADE_timestepDiffusion` above 60 s, under code 4	Not selected	`setDiffusionMethod`
Synchronization	Synchronization conditions and cytokine accuracy limit	As specified in M1.2	All pass	`GrSimulation::timestepSync`
Synchronization	Drug accuracy and permeability limits	Antibiotic list non-empty at the check, and the limit exceeded (M6.4)	List empty	`timestepSync`
Option processing	Option combinations	As listed under exclusions	All valid	`buildSim`; `abxCmdLineOptions`
Initialization	Entity capacity	A requested count exceeds the total number of compartments (resting macrophages) or the compartments remaining after earlier placements (dendritic cells)	All within capacity	`GrSimulation::initSectionInit`; `GrGrid::initSources` (B.5)
First half-step onwards	Oxygen flux	The flux limit of S7.5 is exceeded	Passes at 60 s	`Vascular::calculateFluxChangeDrugs` (S7.5)

Only the timestep pair of the selected solver is checked for synchronization. The pairs of the other solvers are read but not checked, except the ADE diffusion timestep, which is checked against its ceiling in every configuration. A parameter file whose ADE or Crank-Nicolson pair fails to divide 600 s therefore runs without complaint under the spectral solver.

The oxygen flux limit

The vascular oxygen flux routine imposes an upper limit on Δt_d (S7.5), which applies under every solver, since oxygen delivery runs in every configuration. `timestepSync` does not test this limit; a configuration exceeding it stops with a fatal error during the run, at the first eligible source whose oxygen value differs from the blood value.

Checks that run during the timestep

Two fatal checks run within the timestep in every configuration, independently of the switches that would normally make them relevant: the intracellular-bacteria check of the neutrophil recruitment signal (M9.5) and the oxygen flux check. Other in-timestep checks are confined to modules not selected: the drug flux check, the immunomodulation flux check, the T cell recruitment consistency check in `RecruitmentProb::recruit`, and the admission failures raised when a created agent cannot be placed. A reimplementation need not reproduce the failures themselves, but it must respect the conditions under which the default configuration avoids them.

B.12 Interfaces

With	Provides or receives	See
Spine 1.4	Source revision r9959 cited by every gate location	B.1

With	Provides or receives	See
Spine 2.1	Identifier convention	B.1
Spine 2.2, 2.3, 2.4, 2.6	Domain shape; agent slots; field inventory; grid fields named by Init-section elements	B.5, B.8.2, B.9
Spine Element 3	Schedule positions of the gate sites	B.4
Spine 5.2 to 5.5	Init-section positions, processing order and placement of sources, resting macrophages, initial cognate Tgam and seeds	B.2, B.5
Spine 7.0	Parameter resolution, the omitted-parameter and range-check rules, computed parameters	B.2, B.6, B.7
Spine module-slot table	Default module selections	B.1, B.3
S1	Movement bonus factors as sentinels	B.6; S1.3
S3	Exhaustion sweep (S3.6); Treg suppression rule, its parameter test and the unreachable five-argument overload (S3.10)	B.4.8, B.10
S4	Caseation growth thresholds; post-adaptive factor (S4.7); growth-rate and reserve parameters (S4.16)	B.6, B.7, B.10
S5	Caseum death rule suspended under fluoroquinolone dosing	B.4.6
S6	Coarse-grained resolution when all M3 flags are off; sink gating (S6.8); construction draws (S6.3); read-but-inert parameters (S6.16)	B.4.3, B.10
S7	Oxygen flux limit (S7.5); oxygen parameters read without effect (S7.8)	B.10, B.11
S8	Onset, ramp, floor and cascade (S8.7, S8.10, S8.11); recruit construction and T0 states (S8.12)	B.4.2, B.5
S9	Threshold and connected-region granulomas, output streams, histogram bins and stopping criteria (S9.4, S9.6, S9.18, S9.20)	B.8.3, B.8.5
M1	`--diffusion` (program default 5, default-configuration value 6), solver gates and inert solver parameters	B.4.1, B.10; M1.1, M1.2, M1.3, M1.6
M2	`--recr`; lymph node scheme, dendritic cell conversion and the `Recruit_ODE` and `Recruit_OLD` groups	B.4.2, B.10; M2.9, M2.13
M3	Molecular-resolution flags, `--odesolver`, NF-κB construction draw, MHC class II rescaling and statistics	B.4.3; M3.1, M3.2, M3.5, M3.6, M3.9
M4	`--tgfbr-dynamics` and the fibroblast presence gates	B.4.4, B.5; M4.1, M4.9

With	Provides or receives	See
M5	`DIMENSION` and its consequences for configuration	B.4.5; M5.1, M5.13
M6	Drug options, time predicates, load reconciliation, inert drug parameters	B.4.6, B.10; M6.1, M6.4, M6.17
M7	`--immuno-mod`, dosage selectors, gate sites; dose timing and blood updates	B.4.7, B.10; M7.4, M7.7, M7.12
M8	Perturbation switches and sentinels	B.4.8, B.6; M8.3 to M8.11
M9	Neutrophil creation paths, the recruitment window and the closed-path work; neutrophil inert parameters	B.5, B.10; M9.1 to M9.5, M9.10