Supplement for: Predicting lymph node output efficiency through systems biology

Supplement 2. Agent based Model rules

S2.1 Environment

S2.1.1 Simulation setup

Actual time per time step: 25 sec.

Size of a unit on grid: 5 microns.

Height of grid: 160 compartments.

Diameter of top slice: 70 compartments.

Diameter of bottom slice: 32.67 compartments.

S2.1.2 LN Structure

i. AL

Afferent lymph vessel: DCs enter from AL. Current setting (specified in parameter file): From slice 159 to slice 85, on the tip half of the lymph node. All the open space in this region sufficient to accommodate DCs before adding T cells is considered potential DC recruitment location.

ii. HEV

T cells are recruited from HEVs. Current setting (specified in parameter file): located from slice 157 to slice 50. Arranged into randomly generated clusters.

iii. EL

Efferent lymph vessel: T cells exit from EL. Current setting (specified in parameter file): Generated from slice 77 down. They are generated with higher probability to be in the vicinity of the edge of the grid (side or bottom) or near HEVs. There are 300 generated.

iv. FRC network

Generated by seeding at the edge of LN, then scan the entire grid for compartments with 1 or 2 FRC compartments in its Moore neighborhood. Set such compartments to FRC at probability of 0.1 and 0.01 (can be changed in parameter file). Repeat scanning for 100 times (should

changed according to seeding position and grid size.)

S2.2 Agents

S2.2.1 CD4 T Cells

i. Constants

Recruitment Probability: 0.26

Max age: 365 days

Max age SD: 15 days

Min age: 165 days

AgeFactor: 0.8

ProbMoveInPreferredDirection: 0.8

ProbMoveInNonOppositeDirection: 0.95

Binding radius: 2

Median pMHC: 150

Curve shape: 15

Unbinding threshold: 100

Max bind time: 16 hours

Max bind time SD: 4 hours

Max active life: 96 hours

Max active life SD: 4 hours

Max effector life: 60 hours

Max effector life SD: 1 hours

Max division: 4

Doubling time: 8 hours

ii. Recruitment

Each HEV port tries to recruit one CD4+ T Cell at every time step at the probability defined in parameter file (0.26), if not blocked (all 26 non-toroidal neighborhood compartment occupied).

Life span of recruited CD4+ T cells are normally distributed(MaxAge±MaxAgeSD). Current age is determined by comparing ageFactor×lifeTime and minAge. If minAge is larger, current age is set the same as minAge, otherwise, a random integer within this

range is selected to be current age. So life time of CD4+ T cells is uniformly distributed in (0.2*lifeTime,lifeTime-165), so in average 136.5 days.

iii. Movement

Movement of CD4+ and CD8+ T cells are almost identical. Bound cells don't move. If not blocked or just recruited in last move, at a probability set in parameter file (0.80 here), T cells move in preferred directions; at the probability set by the parameter file (0.15) here, T cells move to one of the non-preferred directions; otherwise it moves in opposite directions. If a T cell is blocked or just entered, T cells can move in any directions at the same probability. T cells are not allowed to move to compartments taken by FRC. Destination can be efferent lymph vessels. If destination is EL and the differentiation state allows (T cells of resting and effector state are allowed to leave), T cells exit.

Toroidal movement: Current version of toroidal movement is: first, find the compartment on the edge of the same slice (same y value) and at the opposite position of current compartment. If it's not a cell compartment (e.g. FRC, EF, HEV), travel circularly until we get one. For the rest of toroidal attemps of the same cell in the same movement, also travel circularly to find a cell compartment, until we reach the starting position again.

iv. State change

T cells have five states: resting, bound, active, effector and dead. A cell dies if time is larger than death time, (and unbind if bound).

For resting T cells: if there is a mature or licensed DC in binding radius, and cell is cognate, Naïve CD4+ T cell attempts to bind to Ag-DC or IDC at a probability (P) calculated from pMHC-II level (x), median pMHC-II (a) and a binding curve shape parameter (b).

$$P = \frac{1}{1 + e^{-\frac{x-a}{b}}}$$

Set the time (16 hrs on average) and pMHC threshold (100) to unbind.

For bound T cells: if the bound DC dies in the same time step, T cell returns to resting state; if T cell has bound to DC for longer than unbind time or DC pMHC-II is bellow threshold, T cell unbind and get activated at a probability (P) calculated from accumulated pMHC-II level (x), medium accumulated pMHC-II (c) and a priming curve shape parameter (d). Otherwise, T cell returns to resting.

$$P = \frac{1}{1 + e^{-\frac{x-c}{d}}}$$

If activated, life span is reset to active T cell life time (96 ± 4hrs).

For active T cells: if cell has reached maximum division number (4 times), T cell became effector and got reset to effector life time (60 ± 1hrs). If not, and cell has lived longer than doubling time (8 hours), T cell proliferate and daughter cell is placed in Moore neighborhood. Both cell reset their life time.

S2.2.2. CD8 T Cells

i. Constants

Recruitment Probability: 0.1415

Max age: 365 days

Max age SD: 15 days

Min age: 165 days

AgeFactor: 0.8

ProbMoveInPreferredDirection: 0.8

ProbMoveInNonOppositeDirection: 0.95

Binding radius: 2

Median pMHC: 150

Curve shape: 15

Unbinding threshold: 100

Max bind time: 16 hours

Hours max bind time SD: 4 hours

Max active life: 96 hours

Max active life SD: 4 hours

Max effector life: 60 hours

Max effector life SD: 1 hour

Max division: 8 doubling time: 8 hours

ii. Recruitment

Each HEV port tries to recruit one CD8+ T Cell at every time step at the probability defined in parameter file (0.13), if not blocked (all 26 non-toroidal neighborhood compartment occupied).

Life span of recruited CD8+ T cells is normally distributed (MaxAge ± MaxAgeSD). Current age is determined by comparing ageFactor×lifeTime and minAge. If minAge is larger, current age is set the same as minAge, otherwise, a random integer within this range is selected to be current age. So life span of CD8+ T cells is uniformly distributed in (0.2*lifeTime, lifeTime-165), in average 136.5 days.

iii. Movement

Bound cells don't move.

Movement of CD+ T cells is the same as CD4+ T cells in current setting.

iv. State change

Currently, rules of state change for CD8+ T cells are very similar to that of CD4+ cells.

Differences are: CD8+ Cells only bind to licensed DCs; max dividing count is 8 for CD8+ T cells.

S2.2.3 Dendritic Cells

i. Constants

Recruitment Start Time: 1 day

Recruitment probability: 0.06

Max DC number: 400

Max age: 11 days

Max age SD: 2 days

Min age: 1 day

AgeFactor: 1

Max time mature: 60 hours

Max time mature SD: 5 hours

Average entry age for matured: 20 hours

Movement interval: 4 time steps

pMHC-I half life: 25 hours

pMHC-II half life: 100 hours

Maturation pMHC extra increase: 50

Licensing probability: 0.005

Max life of licensed DC: 36 hours

Max life of licensed DC SD: 4 hours

ii. Recruitment

Every time to recruit DC, a random position is chosen from DC recruit ports, and T cells in that position are relocated.

State determination: pMHC value is assigned to DC at recruitment. At a probability of 0.4, newly recuited DC have pMHC of 25 ± 5, and the rest have pMHC of 250 ± 25. If pMHC is less than 50 (set in parameter file), DC is an IDC; otherwise it's an Ag-DC. So at recruitment, Ag-DC consists about 40 percent of DCs.

If DC is immature when recruited, life span of recruited DCs are normally distributed (MaxAge ± MaxAgeSD). Current age is determined by comparing ageFactor×lifeTime and minAge. If minAge is larger, current age is set the same as minAge, otherwise, a random integer within this range is selected to be current age. So life span of DCs is uniformly distributed in (0,lifeTime-1), which in average is 5 days.

If DC is mature when recruited, life span will be determined by (maxTimeMature ± SD) − (aveEntryAge ± SD), which in average is 40 hours.

iii. Movement

DC moves every several time steps. When bound to T cells, DCs don't move. DC's movement does not consider previous direction. Choose from all open destinations at the same probability regardless of the direction. When a DC moves into grid compartments occupied by T cells, these T

cells are pushed away and relocated. When moving, DC can tolerate at most one FRC overlapping with it to capture the flexibility. DCs can't leave from EL (blocked when scanning for open destinations).

iv. State change

DCs have four states: immature, mature, licensed or dead. Every time step, pMHC level decreases at a rate calculated from pMHC half life (25 hrs for pMHC-I and 100 hrs for pMHC-II).

If simulation time is larger than time for cell to die, DC unbind all T cells and die.

If cell is immature: if there is a mature or licensed DC in Moore neighborhood of 1 compartment to this DC, DC became mature, pMHC level is set to the pMHC level of the neighboring cell + 50; life span will be determined by (maxTimeMature ± SD) (60 hours in average).

If cell is mature: if there is an effector CD4+ T cell within Moore neighborhood of 2 compartments to this Ag-DC, at certain probability (licensing probability, 0.005), DC became licensed, with pMHC increasing 150 and life span reset to (timeLicensed ± SD) (36 hours in average).