PNNL-XXXXX

Biocellion 1.1 User Manual

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March 31, 2014

Prepared for the U.S. Department of Energy
under Contract DE-AC05-76RL01830

PACIFIC NORTHWEST NATIONAL LABORATORY
operated by
BATTELLE
for the
UNITED STATES DEPARTMENT OF ENERGY
under Contract DE-AC05-76RLO1830

Acknowledgments

Support for this research was provided by the Extreme Scale Computing Initiative and the Fundamental and Computational Sciences Directorate, as part of the Laboratory Directed Research and Development Program at Pacific Northwest National Laboratory (PNNL). Portions of this work were conducted using PNNL Institutional Computing at PNNL. PNNL is operated by Battelle for DOE under contract DE-ACO5-76RLO 1830.

Changes

Changes From Version 1.0

- Modify the *Biocellion* API related to file output.
  - Added the *updateFileOutputInfo* (Section 4.2.12) model routine and the FileOutputInfo class (Section 2.4.15).
  - Removed the *fileOutput* member variable from the GridPhiInfo class (Section 2.4.9). *updateFileOutputInfo* controls file output for molecular concentrations in the extracellular space.
  - Removed *num_extra* from the *output* element (Section 6.3.1). *updateFileOutputInfo* controls file output for particles.
  - Added *start_x*, *start_y*, *start_z*, *size_x*, *size_y*, and *size_z* to the *output* element (Section 6.3.1). Users can generate file output data for only a sub-region of the simulation domain.
- Modify the *Biocellion* API related to summary output.
  - Added the *updateSummaryOutputInfo* model routine (Section 4.2.13) and the SummaryOutputInfo class (Section 2.4.15).
  - Removed the *printSummary* and *summaryType* member variables from the GridPhiInfo and IfGridModelVarInfo classes (Sections 2.4.9 and 2.4.13, respectively). *updateSummaryOutputInfo* controls summary output.
  - Added the *updateSummaryVar* model routine (Section 4.6.2).
- Modify the *Biocellion* API related to setting options for partial differential equation (PDE) multigrid and ordinary differential equation (ODE) solvers.
  - Added the MGSolveInfo class (Section 2.4.10).
  - Added the mgSolveInfo member variable to the PDEInfo class (Section 2.4.12). This variable controls options for the PDE multigrid solver.
  - Added the *epsilon* and *threshold* member variables to the ODENetInfo class (Section 2.4.4).
  - Added the *odeEpsilon* and *odeThreshold* member variables to the SplittingInfo class (Section 2.4.11).
  - Removed the *mg_elliptic*, *mg_parablic*, and *ode_solve* elements (Section 6.3.2).
- Modified the syntax of the *computeForceSpAgent* (Section 4.4.2) and *computeExtraMechIn-*

trctSpAgent (Section 4.4.3) model routines. The grid attributes of the unit boxes containing an interacting discrete agent pair are passed in addition.

- Modified the syntax of the *updatePDEBufferDirichletBCVal* (Section 4.5.22) and *updatePDE-BufferNeumannBCVal* (Section 4.5.23) model routines. *a_gridPhi* is removed.

- Added the *updateFileOutputInfo*, *updateSummaryOutputInfo*, and *updateSummaryVar* model routines to Figures 4.1 and 4.2.

- Removed the *getMGEllipticNormThreshold* and *getMGParabolicNormThreshold* functions (Section 3.1).

- Added the *getSimInitType* function (Section 3.1.9).

- Removed the *disappearSpAgent* model routine (Section 4.3) and the IfGridUpdate class (Section 2.4).

- Added *getRecentSummaryRealVal* and *getRecentSummaryIntVal* functions (Sections 3.1.5 and 3.1.6, respectively) to access recent summary output values.

- Replaced *minVal* in the *ODENetInfo* and *GridPhiInfo* classes (Sections 2.4.4 and 2.4.9, respectively) with *errorThresholdVal* and *warningThresholdVal*.

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1.0 Introduction

Many biological phenomena arise as the product of complex interactions in living systems of cells. These *emergent behaviors* are evident only once these systems grow to millions to trillions of cells. Understanding and predicting emergent behaviors is crucial to solving important problems in the areas of *energy* (Ha et al. 2011, Majors et al. 2008, Melnicki et al. 2013), *environment* (Daly 2000, Singh et al. 2011), and *healthcare* (Hall-Stoodley et al. 2004, Weinberg 2007, Rubinstein et al. 2013). Computational biologists applying the scientific method iterate using modeling and simulation, refining their models until simulation results match those of experiments. *Biocellion* provides the fast simulation of living systems needed to facilitate research into emergent behaviors.

Computer simulation of biological systems requires multiple steps. Computational biologists must acquire biological knowledge or generate hypotheses on various aspects of biological system behaviors; build a mathematical model based on this biological knowledge with detail sufficient to test their hypotheses; translate the mathematical model into a computer program; run the program on computers; and visualize and analyze the simulation results.

While an ongoing challenge to this process is to gather and integrate sufficient biological knowledge to build high fidelity models, biologists have been studying the behavior of individual cells and subcellular organelles for a long time and have accumulated a great amount of knowledge about how cells and subcellular organelles behave. The most natural way to build mathematical models based on this accumulated knowledge is to treat each cell (or a subcellular organelle) as a discrete simulation entity in combination with adoption of high resolution grids to model the environment. However, simulating these models—often referred to as discrete agent-based modeling—is considered by some to be computationally intractable for the number of cells needed to study emergent behaviors of large living systems (Kim et al. 2007, Stamatakos 2010). More optimistic researchers have envisioned such simulations would be feasible *"on a supercomputer when a proper parallel implementation is used (Jiao and Torquato 2011)."*

We side with the latter researchers. *Biocellion* is a software framework implemented by high-performance computing (HPC) experts targeting large-scale systems-biology simulations and running on parallel computers ranging from laptops to supercomputers. Efficient algorithms, careful performance tuning, and exploitation of parallelism at multiple levels increases computing capability well beyond that of general simulation frameworks, enabling simulation of high-fidelity models at large scale, often several orders of magnitude faster than on other simulation platforms. *Biocellion* relieves computational biologists of the burdens posed by performance and scalability, freeing them to focus instead on the modeling task itself.

Biological systems are diverse and highly complex, and there are not yet any standards for mathematical modeling flexible enough to express the expansive biological knowledge integrated into component models. Mathematical models depend on the specifics of the biological systems, questions being answered, required level of accuracy, availability of biological knowledge, and model developer's intellectual capability and experience. Software designed for a single mathematical model will have only a short life span. Each model is unique in its design. While the need for generality in modeling is therefore paramount, we have noticed that many multicellular system models exhibit similar computational challenges. We have studied a wide range of biological systems and analyzed numerous biological system models to separate individual model specifics from common computational challenges. We have abstracted out and integrated into the *Biocellion* framework what is common to a wide spectrum of life systems, automating for example the parallel solution of partial differential equations and propagation of physical contact forces; while also providing developers easy interfaces to express model specifics, such as growth rates and adhesion properties. ***Biocellion* provides model developers with flexibility in expressing model specifics while relieving them of the burdens of parallel computation and optimization.**

Today, modelers express these model specifics as program functions that *Biocellion* invokes when it runs. This provides modelers with the flexibility of a general purpose programming language when expressing model specifics without significant loss in computational efficiency. That is, **model developers express model specifics as sequential code** (`C++` code using only basic `C++` features, Section 8 explains `C++` concepts relevant to *Biocellion*). **The *Biocellion* core framework links to this `C++` model library at runtime, invoking functions as needed to integrate the model specifics.** Realizing that most computational biologists are not `C++` experts, we envision adding a productivity layer on top of the current version of *Biocellion* once mathematical modeling of biological systems matures sufficiently. Other possibilities are enabling modelers to use other languages (eg, Python) with which they may be more comfortable, at some cost to performance but no loss in scalability.

1.1 Simulation Components

***Biocellion* simulates biological systems with a large number of cells, capturing individual cell behaviors, interactions between cells, and interactions of cells with their biotic and abiotic environment.**

The current version of *Biocellion* maps each cell to a discrete agent. In future versions, *Biocellion* will allow users to map a cell to multiple discrete agents as illustrated in (Newman 2005, Sandersius et al. 2011). Discrete agents can also represent other non-cellular biological elements—*e.g.* Xavier *et al.* represent extra-cellular matrix using discrete agents in (Xavier et al. 2005). Each discrete agent has associated variables representing its position and state. *Biocellion* users set the number of discrete agent types and the number of discrete agent state variables (or attributes) for each discrete agent type. Each agent can be placed anywhere in the simulation domain (unless restricted by the mathematical model) to within the limits of floating point precision. Individual agents move, divide, disappear, and secrete new discrete agents. *Biocellion* considers each discrete agent as a sphere by default and each discrete agent has *radius* as a state variable. Optionally, attributes may be added to a discrete agent to define a non-spherical shape. Figure 1.1 provides an example. Four attributes (three for direction and one for height) are added to treat a discrete agent as a cylinder. The *Biocellion* core framework does not use radius or other discrete agent state variables internally to update the state of a simulated biological system.

Discrete agents may interact with each other directly and indirectly. Direct interaction includes short-range physico-mechanical interaction between neighboring discrete agents such as cell-cell adhesion and shoving; or immune cells engulfing other discrete agents (*phagocytosis*). We assume the radius of direct interaction is relatively short (*e.g.* within a small multiple of cell diameter).

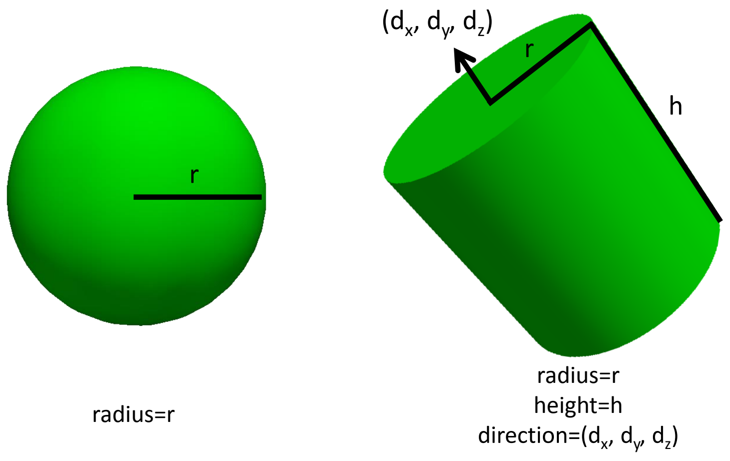


Figure 1.1. Discrete agent shapes.

Indirect interactions result from the secretion of diffusible molecules and cells uptaking the secreted diffusible molecules. Cell surface molecules (receptors) also bind to signaling molecules secreted by other cells.

Biocellion users set the maximum direct physico-mechanical interaction distance for each discrete agent type. The maximum interaction distance between two discrete agents with different types is computed by averaging the two maximum direct interaction distances for the two types. *Biocellion* invokes model routines that evaluate physico-mechanical interaction between a cell pair only for discrete agent pairs within the maximum direct interaction distance.

Physico-mechanical interactions between cell pairs often depend on past interactions. Once two cells form an adherens junction, pulling two cells apart requires stronger force. *Biocellion* users can explicitly form and break a junction between a pair of neighboring discrete agents (Figure 1.2). Each discrete agent has a set of junction ends (one for each junction), and each junction end has associated state variables. *Biocellion* asks users to set the number of junction end types and the number of attributes (or state variables) for each junction end type. Every junction automatically breaks if the distance between a pair of discrete agents exceeds the user provided maximum direct interaction distance for the pair.

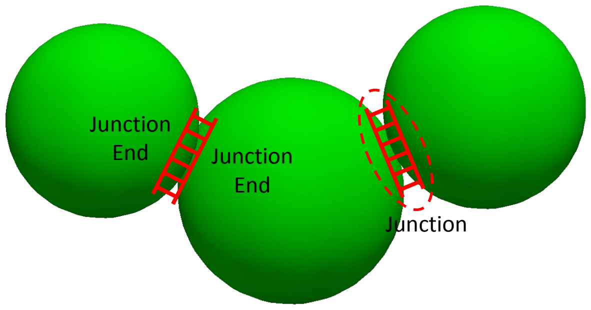


Figure 1.2. A junction between two discrete agents.

Each discrete agent has a set of variables storing its temporary mechanical interaction state (one default variable is *force*, users can add extra variables based on model requirements). Temporary mechanical interaction state variables are valid within a single *baseline time step* (time steps are explained in Section 1.3). Temporary mechanical interaction state variables are updated while evaluating physico-mechanical interactions between discrete agent pairs. These variables are used to set discrete agent displacement and to update agent state based on model specific rules.

The surrounding environment influences biological system behavior. The surrounding environment affects the transport of molecules in the extra-cellular space and promotes and limits cell movement (*e.g. chemotaxis*, cells moving towards either the upward of downward gradient of molecular concentrations, promotes cell movement, and soil aggregate structure constrains cell movement paths (Resat et al. 2011)).

Biocellion provides two different mechanisms to update environment state variables (*e.g.* molecular concentrations or other extra-cellular space attributes). One is editing state variables by model specific rules and the other is by solving partial differential equations (PDEs). *Biocellion* users also mark sub-regions of the simulation domain as uninhabitable, and discrete agents cannot penetrate into an uninhabitable region (Figure 1.3).

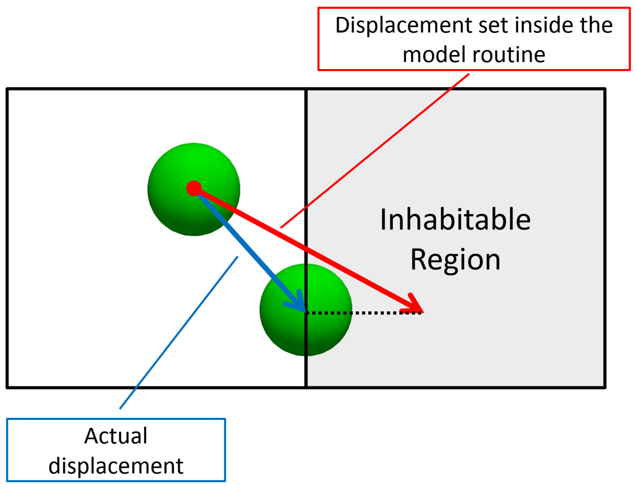


Figure 1.3. A discrete agent cannot move into an uninhabitable region. *Biocellion* considers only the position of a discrete agent in computing the displacement and does not internally use other discrete agent attributes (*e.g. radius*). By default, *Biocellion* allows any discrete agent of non-zero volume to overlap uninhabitable regions. If this is undesirable, the modeler can include code to test the agent's physical position and orientation, adjusting the displacement so as to move the agent fully out of uninhabitable regions.

Biocellion has three main computational modules to simulate the above simulation components. **The three modules 1) update the state of individual agents, 2) simulate short-range physico-mechanical interactions, and 3) update the state of the extracellular environment.** Computational modules communicate with other modules to simulate biological systems in their entirety.

1.2 Simulation Domain

Biocellion supports a three-dimensional rectangular simulation domain. *Biocellion* assumes a rectangular grid (the *interface grid*) with a fixed grid spacing (the *interface grid spacing*). **The interface grid spacing defines the resolution of extra-cellular space.** *Biocellion* users set the interface grid spacing, h. Different computational modules communicate through this interface grid (See Figures 1.4 and 1.5). For each grid aligned $h \times h \times h$-box (*unit box*) *Biocellion* maintains a list of agents located within the box. **The interface grid spacing should be equal to or larger than the maximum direct physico-mechanical interaction distance between any two discrete agents.** This assures that a discrete agent directly interacts only with discrete agents in the same box or the neighboring 26 boxes.

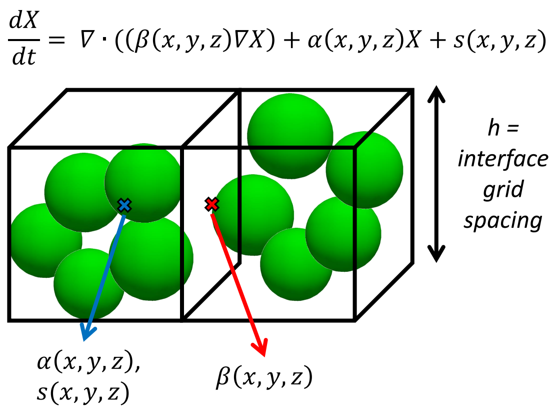

$\frac{dX}{dt} = \nabla \cdot ((\beta(x,y,z)\nabla X) + \alpha(x,y,z)X + s(x,y,z)$
h = interface grid spacing
$\alpha(x,y,z)$, $s(x,y,z)$
$\beta(x,y,z)$

Figure 1.4. *Biocellion* asks users to set partial differential equation (PDE) parameters at the granularity of a unit box. For reaction-diffusion PDEs, users set the decay rate (α) and the source term (s) for every unit box and the diffusion coefficient (β) for every face between two adjacent unit boxes sharing a face. User provided model routines set PDE parameters for a unit box based on the state of the unit box and the states of the discrete agents located in the unit box. For PDE parameters set for the face between two adjacent unit boxes, model routines set the parameters based on the states of the two adjacent unit boxes and the states of the discrete agents residing in the two boxes.

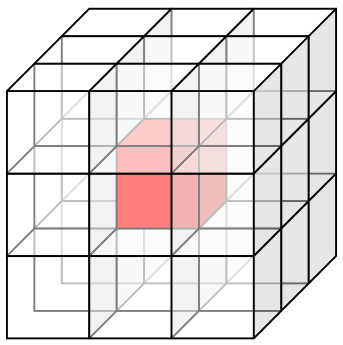


Figure 1.5. A model routine updating the state of a discrete agent can access the state of the unit box the agent belongs to (red) and its 26 neighboring unit boxes (white).

Biocellion allows users to set sub-regions of the simulation domain as a partial differential equation (PDE) buffer; the PDE buffer is relevant only when solving PDEs. No discrete agent is allowed to reside in the PDE buffer. Say we are simulating a yeast colony growing on top of a thick agarose cylinder. The agarose cylinder holds nutrients and other molecules secreted by yeast cells. The agarose cylinder region needs to be included in simulation to track molecular concentration changes in the extra-cellular space with high accuracy. However, if no cells reside in the agarose cylinder region, maintaining data structures for all three computational modules at the resolution of the interface grid spacing can waste a significant amount of computing and memory. Users can set sub-regions of the simulation domain as a PDE buffer and adopt a coarser grid spacing for the buffer—*Biocellion* supports adaptive mesh refinement (AMR, Section 1.4) and the PDE buffer grid spacing will be matched to the coarsest AMR level grid spacing. Figure 1.6 provides an example.

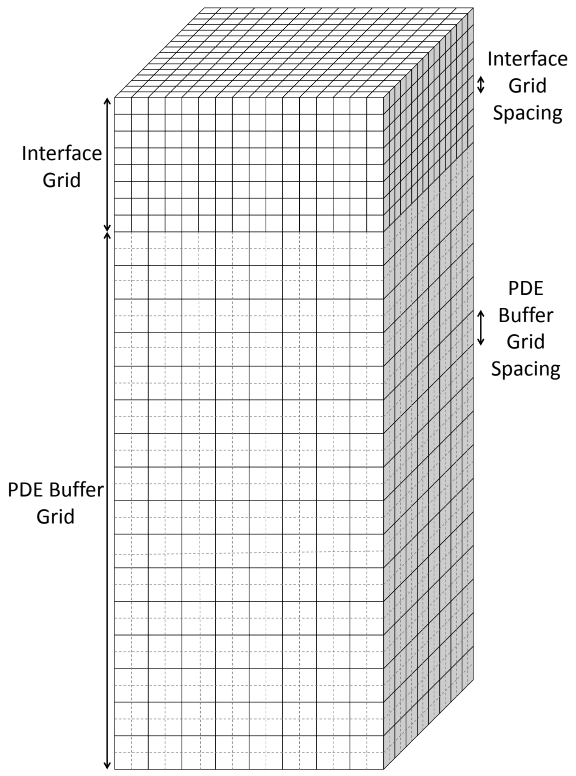


Figure 1.6. Simulation domain

The simulation domain is decomposed into multiple partitions, multiple compute processes on a cluster computer work on different sets of partitions. Note that a single multithreaded compute process can exploit multiple cores on a compute node to work on a single partition. *Biocellion* users set the partition size. *Biocellion* outputs simulation results for different partitions in different files. If *Biocellion* restarts from checkpoint data, *Biocellion* reads separate checkpoint files corresponding to distinct partitions. Users can set each partition as a normal partition or a PDE buffer partition.

1.3 Time Step Sizes

Biocellion has three main computational modules with distinct time steps. Communication intervals also vary for different pairs of computational modules.

The *baseline time step* is the largest time step used by *Biocellion*. *Biocellion* uses this time step size to simulate direct physico-mechanical interactions between discrete agent pairs and to simulate discrete agent movement, birth, death, and secretion. The computational module simulating direct short range interactions communicates with the other two modules once every *baseline time step*. Our assumption is that cells move, divide, and die at moderate rates.

Cell state changes affect the secretion and uptake rates of extra-cellular molecules. Molecular concentration changes in the extra-cellular space drive cell state changes as well. *Biocellion* allows users to couple these two processes more tightly. Users can split a *baseline time step* into one or more *state-and-grid time steps*. The cell state update module and the extra-cellular space state update module communicate once every *state-and-grid time step*.

A single *state-and-grid time step* can be further partitioned to solve partial differential equations (PDEs). The next section (Section 1.4) discusses time steps used to solve PDEs in more detail.

1.4 Partial Differential Equation (PDE) Solvers

The current version of *Biocellion* provides solvers for three different types of PDEs: steady-state linear reaction-diffusion PDEs, time-dependent linear reaction-diffusion PDEs, and time-dependent reaction-diffusion PDEs adopting the splitting scheme (Strang 1968) to update the reaction part. Future releases of *Biocellion* will support advection-reaction-diffusion PDEs.

Biocellion uses CHOMBO (Colella et al. 2012) as an internal solver for PDEs and uses the Intel ordinary differential equation (ODE) solver (Intel Corporation 2008) to solve the reaction part of the splitting PDE. We briefly describe PDE solver features relevant to *Biocellion* users in this section and refer readers to (Colella et al. 2012, Intel Corporation 2008) for additional details.

The steady-state PDE and the time-dependent linear PDE update concentrations of a single molecular species. The time-dependent PDE based on the splitting scheme update the concentrations of one or more molecular species reacting in the extra-cellular space.

Biocellion supports adaptive mesh refinement (AMR) to solve PDEs using CHOMBO (Colella et al. 2012). The grid spacing used for the interface grid is the finest spacing in the AMR hierarchy. Users can set the number of AMR levels and select either 2 or 4 as the refinement ratio between two consecutive levels. Users mark the desired AMR level for each unit box in the interface grid. The coarsest AMR level is assumed for the PDE buffer. The actual AMR grid may use a finer grid spacing than the grid spacing specfied by the user for some regions to satisfy necessary conditions to maintain numerical efficiency (*e.g.* to limit the number of boxes, because processing a large number of tiny boxes can be computationally inefficient) and correctness (*e.g.* see the proper nesting condition in the CHOMBO manual).

A variant of the second order accurate L_0 stable Runge-Kutta scheme (see the CHOMBO manual and the Twizell *et al.*'s paper (Twizell et al. 1996) for additional details) is used for time stepping. This often allows *Biocellion* users to adopt a larger time step size than explicit methods for stiff PDEs. A single *PDE time step* can be set to a smaller value than the *state-and-grid time step* by partitioning a single *state-and-grid time step* to a positive integer number of *PDE time steps*.

To solve the splitting PDE, *Biocellion* solves ODEs for the reaction part for the duration of a single *PDE time step* first and sets the PDE source term based on the changes. Then the resulting linear reaction-diffusion PDE is solved for one or more *diffusion time steps*—a single *PDE time step* can be further partitioned to multiple *diffusion time steps* when the splitting scheme is used. *Biocellion* uses a variable time step size based on error estimation to solve ODEs (following the scheme used in the Intel ODE solver), and *Biocellion* users set the minimum ODE time step size. The single *PDE time step* size becomes the maximum time step size to solve ODEs.

1.5 Future Roadmap

Over time, we plan to update *Biocellion* to accommodate an ever broadening spectrum of biological system models. In the short term, we plan to extend *Biocellion* to support mapping a single cell to multiple discrete agents and to provide advection-reaction-diffusion PDE solvers.

Mapping a cell to more than one discrete agent will allow modeling of cell shapes and mechanical interactions between cells with higher fidelity. For example, mapping a budding yeast cell to two discrete agents more realistically reproduces the shape of a real budding yeast cell (Figure 1.7).

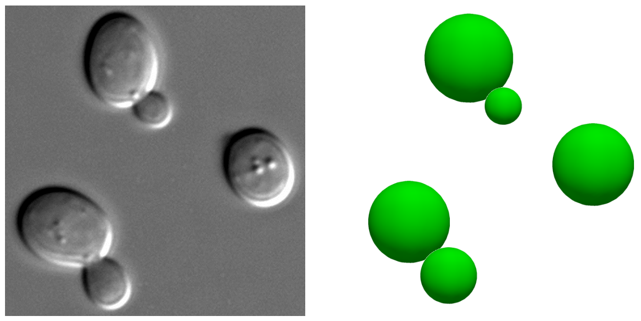


Figure 1.7. Modeling budding yeast using two discrete agents per cell. The budding yeast image (left) is reproduced from `http://en.wikipedia.org/wiki/Yeast`.

Updating individual cell states is largely a users' task at this point. *Biocellion* provides a solver for deterministic ordinary differential equation (ODE) systems, but there are many other approaches to modeling cell regulatory networks. We plan to add solvers for widely used regulatory network modeling approaches (*e.g.* boolean network, stochastic ODE systems, and hybrids). For a cell mapped to multiple discrete agents, we can consider each discrete agent as a cell compartment or a subcellular organelle. Another path to extend *Biocellion* is to provide solvers to update the state of subcellular discrete agents or to support modeling of molecular transport across subcellular compartments.

Computing the flow rate of liquid in biological systems with time varying structures (*e.g.* water flow in soil aggregate or blood flow in human tissue) is another important computational task in building high fidelity models. In computing blood flow rate, our current interest is mainly in tracking long term average flow rate changes in capillaries (which affect the delivery rate of nutrients and vessel stabilization and regression) to model tissue or vascular tumor growth rather than modeling short term dynamics (*e.g.* flow changes within a single heart beat cycle) of blood flow in arteries which is more relevant in studying cardiovascular disease.

2.0 *Biocellion* Data Types

2.1 Basic Data Types

Biocellion redefines the following basic data types to promote portability[(a)] across different platforms and to support both single-precision and double-precision floating point arithmetic without code modification.

- **REAL**: Either single or double precision floating point number (float or double) based on compile time setup.
- **U8, U16, U32, U64**: 8, 16, 32, and 64-bit unsigned integers, respectively.
- **S8, S16, S32, S64**: 8, 16, 32, and 64-bit signed integers, respectively.
- **BOOL**: Boolean data type (true or false).

BOOL replaces the `C++` bool data type. *Biocellion* uses BOOL instead of bool to prevent the `C++` standard template library (STL) vector from packing multiple boolean variables (up to 8) into a single byte. Such packing reduces memory consumption but requires additional bitwise operations to access and modify vector elements. If vector elements are concurrently updated by multiple threads, updating two different elements packed into the same byte requires locking (or using other data synchronization primitives); we expect users to write only sequential code, so data synchronization is not an issue for *Biocellion* users, but we define the BOOL type to avoid additional data type conversion overhead between user routines and the *Biocellion* framework code.

2.2 Extra Scalar Data Types

Biocellion defines additional scalar data types to maintain portability across different platforms and save memory.

- **agentType_t**: 16 bit unsigned integer by default. Every agent has an associated type. *Biocellion* users assign different numbers of model specific REAL type and S32 type variables (or discrete agent attributes) for different agent types.
- **junctionEndType_t**: 16 bit unsigned integer by default. Every junction end (Section 1.1) has an associated type. *Biocellion* users assign different numbers of model specific REAL type and S32 type variables (or junction end attributes) for different junction end types.
- **agentId_t**: 64 bit signed integer by default. Every discrete agent has a unique ID.
- **idx_t**: 16 bit signed integer by default. Three idx_t type variables are used to index a unit box (the size of a unit box is $h \times h \times h$ assuming that the grid spacing for the interface grid

(a) The current version of *Biocellion* runs only on x86 compatible architectures. This may change in the future.

is *h*).

- **ubAgentIdx_t**: 16 bit unsigned integer by default. This data type is used to access discrete agents in a single unit box.

We assume that the default sizes of the above data types are large enough for most practical applications. If this does not hold, users need to redefine the above data types and recompile the entire *Biocellion* framework and model libraries. Advanced users can redefine the above data types to a smaller integer data type to save memory if the smaller data type is sufficient for their applications.

2.3 Enumerations

Biocellion has multiple enumerated data types which are used to provide model specifics (see Section 4 for the user interface to provide model specifics).

- **domain_bdry_type_e**: Used to set the simulation domain boundary types in the x, y, and z directions.
  - `DOMAIN_BDRY_TYPE_NONPERIODIC_HARD_WALL`: Non-periodic boundary condition is assumed. In solving PDEs, users can apply either Dirichlet or Neumann boundary conditions (for the low and high sides). Discrete agents cannot pass the domain boundary.

  - `DOMAIN_BDRY_TYPE_PERIODIC`: Periodic boundary condition is assumed for PDEs. Discrete agents passing the domain boundary will appear at the other end of the simulation domain.

- **pde_buffer_bdry_type_e**: Used to set the boundary type between an interface grid region and a PDE buffer region. This boundary type is only related to discrete agent movement and irrelevant to PDE solves.
  - `PDE_BUFFER_BDRY_TYPE_HARD_WALL`: This is the only valid option at this point. Discrete agents cannot penetrate into a PDE buffer region (PDE buffer regions are automatically marked as uninhabitable).

- **pde_type_e**: Used to set PDE types.
  - `PDE_TYPE_REACTION_DIFFUSION_STEADY_STATE_LINEAR`: Used to find a (quasi) steady state solution of a reaction-diffusion linear PDE. This option assumes that the PDE reaches steady state within a single *state-and-grid time step*.

  - `PDE_TYPE_REACTION_DIFFUSION_TIME_DEPENDENT_LINEAR`: Use time-stepping to find a solution of a reaction-diffusion linear PDE.

  - `PDE_TYPE_REACTION_DIFFUSION_TIME_DEPENDENT_SPLITTING`: Use time-stepping to find a solution of a reaction-diffusion PDE. The time splitting technique (Strang 1968) is applied to simulate reactions among multiple molecular species in the extra-cellular space.

  - `PDE_TYPE_ADVECTION_REACTION_DIFFUSION_TIME_DEPENDENT_LINEAR`: Reserved for future use.

  - `PDE_TYPE_ADVECTION_REACTION_DIFFUSION_TIME_DEPENDENT_SPLITTING`: Reserved for future use.

- **bc_type_e**: Used to set PDE boundary condition types.
  - `BC_TYPE_DIRICHLET_CONST`: Apply Dirichlet boundary condition with a constant boundary value for the entire region of the domain boundary face at the low or high side in the x, y, or z direction.

  - `BC_TYPE_DIRICHLET_MODEL`: Apply Dirichlet boundary condition, and boundary values are set in the granularity of a boundary grid unit box face.

  - `BC_TYPE_NEUMANN_CONST`: Apply Neumann boundary condition with a constant boundary value for the entire region of the domain boundary face at the low or high side in the x, y, or z direction.

  - `BC_TYPE_NEUMANN_MODEL`: Apply Neumann boundary condition, and boundary values are set in the granularity of a boundary grid unit box face.

- **ode_stiff_e**: Inform the stiffness of the ODE system to solve. *Biocellion* uses different mathematical algorithms based on the provided information using the Intel ODE solver (Intel Corporation 2008).
  - `ODE_STIFF_NORMAL`: Indicate that the ODE system has low or medium stiffness. The `dodesol_rkm9st` function in the Intel ODE library (which is *"based on the fourth order Merson's method and the first order multistage method of up to and including 9 stages with stability control (Intel Corporation 2008)"*) is used to solve the ODE system.

  - `ODE_STIFF_HIGH`: Indicate that the ODE system is stiff. The `dodesol_mk52lfn` function in the Intel ODE library (which uses *"the implicit method based on L-stable(5,2)-method with the numerical Jacobi matrix, which is computed by the routine (Intel Corporation 2008)"*) is used to solve the ODE system.

- **sync_method_e**: *Biocellion* users can update temporary mechanical interaction state variables of a discrete agent in multiple function calls evaluating direct interactions between the discrete agent and the neighboring discrete agents—one function call per pair of discrete agents. *Biocellion* provides a model routine to edit grid state variables using model specific rules, and the routine is called once per unit box in the interface grid. A single invocation of the model routine can update variables associated with an interface grid unit box and its neighboring 26 unit boxes. A single variable can be updated by multiple model routine calls. This requires a mechanism to coordinate the multiple updates (often referred as *data synchronization*). sync_method_e is used to set the coordination method when a single variable is updated in multiple function calls.
  - `SYNC_METHOD_OVERWRITE`: If this option is selected, only one of the multiple up-

dates is reflected—*e.g.* if three different model routines set the value of variable *a* to 3, 5, and 9, respectively, *a* is set to either 3, 5, or 9 with equal probability.

  - `SYNC_METHOD_DELTA`: If this option is selected, the differences from the initial value are summed—*e.g.* if three different model routines set the value of variable *a* to 3, 5, and 9, respectively, then *a* is set to 3 + 5 + 9 (assuming that the initial value is 0).

  - `SYNC_METHOD_TRANSACTIONAL`: Reserved for future use.

- **if_grid_var_type_e**: Used to set the type of a variable associated with a unit box in the interface grid.
  - `IF_GRID_VAR_TYPE_PHI`: Set the type to a REAL variable storing molecular concentration which is mainly updated by solving PDEs. *Biocellion* updates variables of this type both when solving PDEs and when inside the model routine updating grid state variables based on model specific rules. Model specific REAL and S32 variables are updated only inside the model routine updating grid state variables.

  - `IF_GRID_VAR_TYPE_MODEL_REAL`: Set the type to a model specific REAL variable.

  - `IF_GRID_VAR_TYPE_MODEL_INT`: Set the type to a model specific S32 variable.

- **sim_init_type_e**: Used to set the simulation initialization method.
  - `SIM_INIT_TYPE_CODE`: Initialize inside the model routines.

  - `SIM_INIT_TYPE_BINARY`: Initialize using checkpoint data.

- **particle_output_type_e**: Used to set the output file format for discrete agents.
  - `PARTICLE_OUTPUT_TYPE_PTVU`: Set the output file format to the Paraview VTK partitioned unstructured grid file format (.ptvu). This is the only valid option at this point.

- **grid_output_type_e**: Used to set the output file format for grid values.
  - `GRID_OUTPUT_TYPE_VTM`: Set the output file format to the VTK hierarchical box data files format (.vtm). This is the only valid option at this point.

- **summary_type_e**: *Biocellion* supports a summary (reduction) mechanism for interface grid variables. Users add a fixed number of grid state variables to every unit box in the interface grid (or assign a fixed number of attributes to the interface grid), and for each attribute, users can ask *Biocellion* to visit every unit box to reduce the variables for the attribute to a single value. summary_type_e is used to set the reduction method.
  - `SUMMARY_TYPE_SUM`: Set to print the sum of the interface grid variables.

  - `SUMMARY_TYPE_AVG`: Set to print the average of the interface grid variables.

  - `SUMMARY_TYPE_MIN`: Set to print the minimum value of the interface grid variables.

  - SUMMARY_TYPE_MAX: Set to print the maximum value of the interface grid variables.

- **rng_type_e**: *Biocellion* provides random number generators—internally using Intel math kernel library (MKL). rng_type_e is used to set the random number generator type.
  - RNG_TYPE_UNIFORM: Set the random number generator to generate random numbers with the uniform distribution.
  - RNG_TYPE_GAUSSIAN: Set the random number generator to generate random numbers with the Gaussian distribution.
  - RNG_TYPE_EXPONENTIAL: Set the random number generator to generate random numbers with the exponential distribution.
  - RNG_TYPE_GAMMA: Set the random number generator to generate random numbers with the gamma distribution.

2.4 Classes

2.4.1 Vector

Vector is a wrapper class of the C++ standard template library (STL) vector—STL vector is a data type for a variable size array. We create this wrapper to perform array index bound checks (similar to CHOMBO (Colella et al. 2012)) without re-compiling both the *Biocellion* core framework and a model library. Users can enable the boundary check for a model library without enabling the check for the core framework. Visit http://www.cplusplus.com/reference/vector/vector for additional details about STL vector.

2.4.2 VIdx

VIdx is used to index a grid box in the simulation domain. VIdx has an internal array of three idx_t type variables.

Public static member variables

- VIdx ZERO: A constant three dimensional zero vector—*i.e.* (0, 0, 0).
- VIdx UNIT: A constant three dimensional unit vector—*i.e.* (1, 1, 1).
- VIdx A_BASIS[3]: A set of three dimensional basis vectors. A_BASIS[0] = (1, 0, 0), A_BASIS[1] = (0, 1, 0), and A_BASIS[2] = (0, 0, 1).

Public non-static member functions

- $+$, $-$, $\times$, $/$: Arithmetic operators.
- $==$, $!=$, $<$, $<=$, $>$, $>=$: Comparison operators.

- [*idx*]: An access operator—returns the *idx*th element of the internal array holding three idx_t type variables. *idx* should be 0, 1, or 2.

Public static member functions

- `S64 getIdx3Dto1D( const VIdx& vIdx, const VIdx& regionSize ):` Return *vIdx[0]* $\times$ *regionSize[1]* $\times$ *regionSize[2]* + *vIdx[1]* $\times$ *regionSize[2]* + *vIdx[2]*.

- `S64 getIdx3Dto1D( const VIdx& vIdx, const idx_t size ):` Return *vIdx[0]* $\times$ *size* $\times$ *size* + *vIdx[1]* $\times$ *size* + *vIdx[2]*.

- `S64 getIdx3DTo1D( const idx_t i, const idx_t j, const idx_t k, const VIdx& regionSize ):` Return *i* $\times$ *regionSize[1]* $\times$ *regionSize[2]* + *j* $\times$ *regionSize[2]* + *k*.

- `S64 getIdx3DTo1D( const idx_t i, const idx_t j, const idx_t k, const idx_t size ):` Return *i* $\times$ *size* $\times$ *size* + *j* $\times$ *size* + *k*.

- `VIdx getIdx1DTo3D( const S64 idx, const VIdx& regionSize ):` Perform the reverse operation of *getIdx3DTo1D(const VIdx& vIdx, const VIdx& regionSize)*.

- `VIdx getIdx1DTo3D( const S64 idx, const idx_t size ):` Perform the reverse operation of *getIdx3DTo1D(const VIdx& vIdx, const idx_t size)*.

2.4.3 VReal

VReal is a container for three REAL type variables.

Public static member variables

- VReal `ZERO`: A constant three dimensional zero vector—*i.e.* (0.0, 0.0, 0.0).

- VReal `UNIT`: A constant three dimensional unit vector—*i.e.* (1.0, 1.0, 1.0).

- VReal `A_BASIS[3]`: A set of three dimensional basis vectors. `A_BASIS[0]` = (1.0, 0.0, 0.0), `A_BASIS[1]` = (0.0, 1.0, 0.0), and `A_BASIS[2]` = (0.0, 0.0, 1.0).

Public non-static member functions

- $+$, $-$, $\times$, $/$: Arithmetic operators.

- [*idx*]: An access operator—returns the *idx*th element of the internal array holding three REAL type variables. *idx* should be 0, 1, or 2.

2.4.4 ODENetInfo

This class instance holds the information required to set-up a solver for a deterministic ordinary different equation (ODE) system to model a discrete agent regulatory network.

Public non-static member variables

- S32 *numVars*: Set the number of variables in the ODE system.
- ode_stiff_e *stiff*: Set the stiffness of the ODE system (*Biocellion* uses different numerical algorithms based on this information).
- REAL *h*: Set the initial step size to $h \times$ *state-and-grid time step* size. $0.0 < h \leq 1.0$.
- REAL *hm*: Set the minimum time step size to $hm \times$ *state-and-grid time step* size. $0.0 < hm \leq h$.
- REAL *epsilon*: Set the relative error tolerance. The ODE solver cannot ensure required accuracy if *epsilon* is smaller than 1e-9.
- REAL *threshold*: If the absolute value of the solution is larger than *threshold*, relative error is controlled. Otherwise, absolute error (*threshold* $\times$ *epsilon*) is controlled.
- REAL *errorThresholdVal*: If any of the ODE system variables becomes smaller than *errorThresholdVal*, *Biocellion* prints an error message and aborts the program execution. *errorThresholdVal* should be equal to or smaller than 0.0. Set *errorThresholdVal* to REAL_MAX (defined in `$BIOCELLION_ROOT/include/base_type.h`) $\times$ -1.0 to turn this check off.
- REAL *warningThresholdVal*: If any of the ODE system variables becomes smaller than *warningThresholdVal* (but still no variable is smaller than *errorThresholdVal*), *Biocellion* prints a warning message (but does not abort the program execution). *warningThresholdVal* should be equal to or smaller than 0.0 and should be equal to or larger than *errorThresholdVal*. Set *warningThresholdVal* to REAL_MAX (defined in `$BIOCELLION_ROOT/include/base_type.h`) $\times$ -1.0 to turn this check off.
- BOOL *setNegToZero*: If *setNegToZero* is set to true, *Biocellion* automatically resets negative ODE variables (equal to or larger than *errorThresholdVal*) to 0.0. Set to false to turn this feature off.

2.4.5 TimeStepInfo

This class instance holds the information required to set the sizes of *baseline time step* and *state-and-grid time step*.

Public non-static member variables

- REAL *durationBaselineTimeStep*: Set the size of *baseline time step*.

- S32 *numStateAndGridTimeStepsPerBaseline*: The *state-and-grid time step* size is set to *baseline time step* size divided by *numStateAndGridTimeStepsPerBaseline*.

2.4.6 OptModelRoutineCallInfo

Biocellion users can update the interface grid state variables based on model specific rules. *Biocellion* optionally invokes the model routine updating interface gird state variables at the beginning and at the end of every *state-and-grid time step*. This class instance controls the optional model routine invocation.

Public non-static member variables

- S32 *numUpdateIfGridVarPreStateAndGridStepRounds*: Call the model routine (once for every unit box in the interface grid) for *numUpdateIfGridVarPreStateAndGridStepRounds* rounds at the beginning of every *state-and-grid time step*. This variable should be zero or a positive integer.

- S32 *numUpdateIfGridVarPostStateAndGridStepRounds*: Call the model routine (once for every unit box in the interface grid) for *numUpdateIfGridVarPostStateAndGridStepRounds* rounds at the end of every *state-and-grid time step*. This variable should be zero or a positive integer.

2.4.7 SpAgentInfo

This class instance holds the model specifics about a discrete agent type.

Public non-static member variables

- REAL *dMax*: Set the maximum direct physico-mechanical interaction distance. The value of this variable should be equal to or smaller than the interface grid spacing. The maximum direct interaction distance between two discrete agents having different types is computed by averaging the *dMax* values for the two types. In computing direct interactions between discrete agent pairs, every pair within the maximum interaction distance is enumerated.

- S32 *numStateModelReals*: Set the number of model specific REAL type state variables for this discrete agent type.

- S32 *numStateModelInts*: Set the number of model specific S32 type state variables for this discrete agent type.

- S32 *numExtraMechIntrctModelReals*: Set the number of model specific REAL type temporary mechanical interaction state variables for this discrete agent type.

- S32 *numExtraMechIntrctModelInts*: Set the number of model specific S32 type temporary mechanical interaction state variables for this discrete agent type.

2.4.8 JunctionEndInfo

This class instance holds the model specifics about a junction end type.

Public non-static member variables

- S32 *numModelReals*: Set the number of model specific REAL type variables for this junction end type.
- S32 *numModelInts*: Set the number of model specific S32 type variables for this junction end type.

2.4.9 GridPhiInfo

This class instance holds the model specifics about the concentration values of a molecular species which are mainly updated by solving PDEs.

Public non-static member variables

- S32 *elemIdx*: Set the unique index for this molecular species. *elemIdx* should be equal to or larger than 0 and smaller than the number of molecular species in the simulation instance.
- std::string *name*: Set the name of the molecular species.
- bc_tyep_e *aa_bcType[3][2]*: Boundary condition types for the x (*aa_bcType[0][]*), y(*aa_bcType[1][]*), and z(*aa_bcType[2][]*) directions and the low (*aa_bcType[][0]*) and high (*aa_bcType[][1]*) sides. Irrelevant if periodic boundary condition is applied.
- REAL *aa_bcVal[3][2]*: Set the constant boundary value for the low and high sides in the x, y, and z directions. Relevant only when the PDE boundary type is set to `BC_TYPE_DIRCHLET_CONST` or `BC_TYPE_NEUMANN_CONST`.
- REAL *errorThresholdVal*: If any of the PDE variables becomes smaller than *errorThresholdVal*, *Biocellion* prints an error message and aborts the program execution. *errorThresholdVal* should be equal to or smaller than 0.0. Set *errorThresholdVal* to REAL_MAX (defined in `$BIOCELLION_ROOT/include/base_type.h`) × -1.0 to turn this check off.
- REAL *warningThresholdVal*: If any of the PDE variables becomes smaller than *warningThresholdVal* (but still no variable is smaller than *errorThresholdVal*), *Biocellion* prints a warning message (but does not abort the program execution). *warningThresholdVal* should be equal to or smaller than 0.0 and should be equal to or larger than *errorThresholdVal*. Set *warningThresholdVal* to REAL_MAX (defined in `$BIOCELLION_ROOT/include/base_type.h`) × -1.0 to turn this check off.

- BOOL *setNegToZero*: If *setNegToZero* is set to true, *Biocellion* automatically resets negative PDE variables (equal to or larger than *errorThresholdVal*) to 0.0. Set to false to turn this feature off.

2.4.10 MGSolveInfo

This class instance holds the model specifics about the PDE multigrid solver.

Public non-static member variables

- S32 *numPre*: Set the number of smoothing steps before averaging in the multigrid solver. Set to 3 unless you wish to tune the multgrid solver based on your specific PDE problems.

- S32 *numPre*: Set the number of smoothing steps after averaging in the multigrid solver. Set to 3 unless you wish to tune the multgrid solver based on your specific PDE problems.

- S32 *numBottom*: Set the number of smoothing steps at the bottom level. Set to 3 unless you wish to tune the multgrid solver based on your specific PDE problems.

- BOOL *vCycle*: Set to true to use V-cycle or set to false to use W-cycle in the multigrid solver. Set to true unless you wish to tune the multgrid solver based on your specific PDE problems.

- S32 *maxIters*: Set the maximum number of V-cycles (or W-cycles). Se to 30 unless you wish to tune the multigrid solver based on your specific PDE problems (*e.g.* if your PDE converges very slowly, a larger value could be more appropriate). If the PDE multigrid solver does not reach convergence within *maxIters* iterations, the solver exits prematurely and prints a warning.

- REAL *epsilon*: The PDE multigrid solver assumes solution convergence if the residual norm is equal to or smaller than the original norm multiplied by *epsilon*.

- REAL *hang*: Set the minimum required change in two consecutive V-cycles (or W-cycles). If the decrease in the norm (relative to the norm in the previous iteration) is less than *hang*, the PDE multigrid solver exits prematurely and prints a warning.

- REAL *normThreshold*: The PDE multigrid solver assumes solution convergence if the residual norm is equal to or smaller than *normThreshold*.

2.4.11 SplittingInfo

This class instance holds the information required to solve a PDE using the splitting scheme. A PDE can have multiple molecular species if the splitting scheme is used.

Public non-static member variables

- Vector<S32> *v_diffusionTimeSteps*: Set the number of diffusion time step per *PDE time step* for each molecular species in the PDE.

- ode_stiff_e *odeStiff*: Set the stiffness of the ODE system for the PDE reaction part (*Biocellion* uses different numerical algorithms based on this information).

- REAL *odeH*: Set the initial ODE time step size to *odeH* $\times$ *PDE time step* size. $0.0 < odeH \leq 1.0$.

- REAL *odeHm*: Set the minimum ODE time step size to *odeHm* $\times$ *PDE time step* size. $0.0 < odeHm \leq odeH$.

- REAL *odeEpsilon*: Set the relative error tolerance. The ODE solver cannot ensure required accuracy if *epsilon* is smaller than 1e-9.

- REAL *odeThreshold*: If the absolute value of the solution is larger than *threshold*, relative error is controlled. Otherwise, absolute error (*threshold* $\times$ *epsilon*) is controlled.

2.4.12 PDEInfo

This class instance holds the information required to solve a PDE.

Public non-static member variables

- pde_type_e *pdeType*: Set the type of the PDE.

- S32 *numLevels*: Set the number of adaptive mesh refinement (AMR) levels.

- S32 *numTimeSteps*: Set the number of *PDE time steps* per *state-and-grid time step*.

- BOOL *callAdjustRHSTimeDependentLinear*: If set to true, *Biocellion* invokes the model routines (*adjustIfGridRHSTimeDependentLinear()* and *adjustPDEBufferRHSTimeDependentLinear()*) at the beginning of every *PDE time step* to fine tune the PDE reaction term. If set to false, *Biocellion* updates the PDE reaction part only once per *state-and-grid time step*. Relevant only when *pdeType* is set to `PDE_TYPE_REACTION_DIFFUSION_TIME_DEPENDENT_LINEAR`.

- MGSolveInfo *mgSolveInfo*: Set the PDE multigrid solver options. See Section 2.4.10 for additional details.

- AdvectionInfo *advectionInfo*: Reserved for future use. Irrelevant at this point.

- SplittingInfo *splittingInfo*: Set the information required to solve the PDE using the splitting scheme. Relevant only when *pdeType* is set to `PDE_TYPE_REACTION_DIFFUSION_TIME_DEPENDENT_SPLITTING`.

- Vector<GridPhiInfo> *v_gridPhiInfo*: Provide the information about a molecular species in this PDE. If the splitting scheme is used, there can be more than one molecular species in a single PDE.

2.4.13 IfGridModelVarInfo

Biocellion allows users to assign a fixed number of model specific attributes to the interface grid (or a fixed number of REAL and S32 type state variables to every unit box in the interface grid). These variables are updated by model specific rules in the model routine called at the beginning and the end of every *state-and-grid time step*. This class instance provides the information about a model specific attribute.

Public non-static member variables

- std::string *name*: Set the name of the attribute.

2.4.14 RNGInfo

Biocellion provides random number generators with the uniform, Gaussian, exponential, and gamma distributions. We assume that the probability density functions for the exponential and gamma distributions are $\frac{1}{\beta} \times e^{-x/\beta}$ and $\beta^{\alpha} \times \frac{1}{\Gamma(\alpha)} \times x^{\alpha-1} \times e^{-\beta \times x}$, respectively.

Public non-static member variables

- rng_type_e *type*: This variable sets the random number generator type.

- REAL *param0*: The minimum value if the uniform distribution is selected, the average value if the Gaussian distribution is selected, β if the exponential distribution is selected, and α if the gamma distribution is selected.

- REAL *param1*: The maximum value if the uniform distribution is selected, the standard deviation value if the Gaussian distribution is selected, the displacement value if the exponential distribution is selected, and β if the gamma distribution is selected.

- REAL *param2*: Relevant only when the gamma distribution is selected. The displacement value for the gamma distribution.

2.4.15 FileOutputInfo

This class instance holds the information related to file output of simulation results.

Public non-static member variables

- BOOL *particleOutput*: If set to true, *Biocellion* generates output files for discrete agent data.

- S32 *particleNumExtraOutputVars*: This variable sets the number of extra output variables (in addition to the default *radius* and *color* variables) for particles representing discrete agents.

- Vector<BOOL> *v_gridPhiOutput*: Set to true to generate output files for each molecular species in the PDE.

- Vector<BOOL> *v_gridPhiOutputDivideByKappa*: Set to true to output molecular concentration values divided by κ values (Section 4.5.3) for each molecular species in the PDE.

2.4.16 SummaryOutputInfo

This class instance holds the information related to summary output of simulation results.

Public non-static member variables

- Vector<string> *v_realName*: Each vector element sets the name of the corresponding summary attribute.

- Vector<summary_type_e> *v_realType*: Each vector element sets the reduction method to print summary for the corresponding summary attribute.

2.4.17 SpAgentState

This class instance holds variables describing the state of a discrete agent and provides interface functions to access the variables. The entire set of discrete agent state variables are stored in an internal linear array. *Biocellion* does not allow direct access to the array which can be error-prone.

Public non-static member functions

- *agentType_t getType(void) const*: Return the type of the discrete agent.

- *void setType(const agentType_t type)*: Set the type of the discrete agent to *type*. **This function also resizes and resets the internal linear array.** Users need to properly initialize discrete agent state variables after this function is invoked.

- *REAL getRadius(void) const*: Return the value of the radius variable (a default discrete agent state variable).

- *void setRadius(REAL radius)*: Set the value of the radius variable (a default discrete agent state variable) to *radius*.

- *void getODEVal(const S32 odeNetIdx, const S32 varIdx) const*: Return the value of the *varIdx*th variable in the *odeNetIdx*th ordinary differential equation (ODE) system. A single discrete agent can have more than one ODE systems.

- *Vector<REAL> getODEValArray(const S32 odeNetIdx) const*: Return a Vector array holding the entire set of variable values in the *odeNetIdx*th ODE system.

- *void setODEVal(const S32 odeNetIdx, const S32 varIdx, REAL val)*: Set the value of the *varIdx*th variable in the *odeNetIdx*th ordinary differential equation (ODE) system to *val*.

- *void setODEValArray(const S32 odeNetIdx, const Vector<REAL>& v_val)*: Set the entire set of variables in the *odeNetIdx*th ODE system to *v_val*. *v_val*'s size should coincide with the number of variables in the ODE system.

- *REAL getModelReal(const S32 idx) const*: Return the value of the *idx*th model specific REAL type variable.

- *Vector<REAL> getModelRealArray(void) const*: Return a Vector array holding the entire set of model specific REAL type variable values.

- *void setModelReal(const S32 idx, const REAL val)*: Set the value of the *idx*th model specific REAL type variable to *val*.

- *void setModelRealArray(const Vector<REAL>& v_val)*: Set the entire set of model specific REAL type variables to *v_val*. *v_val*'s size should coincide with the number of model specific REAL type variables for this discrete agent type.

- *void incModelReal(const S32 idx, const REAL inc)*: Increment the value of the *idx*th model specific REAL type variable by *inc*.

- *S32 getModelInt(const S32 idx) const*: Return the value of the *idx*th model specific S32 type variable.

- *Vector<S32> getModelIntArray(void) const*: Return a Vector array holding the entire set of model specific S32 type variable values.

- *void setModelInt(const S32 idx, const S32 val)*: Set the value of the *idx*th model specific S32 type variable to *val*.

- *void setModelIntArray(const Vector<S32>& v_val)*: Set the entire set of model specific S32 type variables to *v_val*. *v_val*'s size should coincide with the number of model specific S32 type variables for this discrete agent type.

- *void incModelInt(const S32 idx, const S32 inc)*: Increment the value of the *idx*th model specific S32 type variable by *inc*.

2.4.18 JunctionEnd

This class instance holds variables describing the state of a junction end and provides interface functions to access the variables. The entire set of junction end state variables are stored in an internal linear array. *Biocellion* does not allow direct access to the array which can be error-prone.

Public non-static member functions

- *junctionEndType_t getType(void) const*: Return the type of the junction end.
- *void setType(const junctionEndType_t type)*: Set the type of the junction end to *type*. **This function also resizes and resets the internal linear array.** Users need to properly initialize junction end state variables after this function is invoked.
- *REAL getModelReal(const S32 idx) const*: Return the value of the *idx*th model specific REAL type variable.
- *Vector<REAL> getModelRealArray(void) const*: Return a Vector array holding the entire set of model specific REAL type variable values.
- *void setModelReal(const S32 idx, const REAL val)*: Set the value of the *idx*th model specific REAL type variable to *val*.
- *void setModelRealArray(const Vector<REAL>& v_val)*: Set the entire set of model specific REAL type variables to *v_val*. *v_val*'s size should coincide with the number of model specific REAL type variables for this discrete agent type.
- *void incModelReal(const S32 idx, const REAL inc)*: Increment the value of the *idx*th model specific REAL type variable by *inc*.
- *S32 getModelInt(const S32 idx) const*: Return the value of the *idx*th model specific S32 type variable.
- *Vector<S32> getModelIntArray(void) const*: Return a Vector array holding the entire set of model specific S32 type variable values.
- *void setModelInt(const S32 idx, const S32 val)*: Set the value of the *idx*th model specific S32 type variable to *val*.
- *void setModelIntArray(const Vector<S32>& v_val)*: Set the entire set of model specific S32 type variables to *v_val*. *v_val*'s size should coincide with the number of model specific S32 type variables for this discrete agent type.
- *void incModelInt(const S32 idx, const S32 inc)*: Increment the value of the *idx*th model specific S32 type variable by *inc*.

2.4.19 AgentJunctionInfo

This class instance stores a list of junctions belong to this discrete agent and the state variables of the junction ends. A unique ID is assigned to every discrete agent particle. This ID is mainly used internally, but *Biocellion* allows users to read the ID if necessary. If an agent is created in the previous *baseline time step*, this class instance also holds the ID of the mother agent (*getPrevId()* returns the ID of the mother agent). Otherwise, *getPrevId()* and *getCurId()* return the same value.

Public non-static member functions

- *S64 getPrevId(void) const*: Return the ID of the mother agent if this discrete agent is newly created. Otherwise, this function and *getCurId()* return the same value.
- *S64 getCurId(void) const*: Return the ID of this agent.
- *S32 getNumJunctions(void) const*: Return the number of junctions between this agent and other neighboring agents.
- *S64 getOtherEndId(const S32 idx) const*: Return the ID of the discrete agent at the other end of the *idx*th junction.
- *const JunctionEnd& getJunctionEndRef(const S32 idx) const*: Return a constant reference of the *idx*th junction's end at this agent's side.
- *JunctionEnd& getJunctionEndRef(const S32 idx)*: Return a modifiable reference of the *idx*th junction's end at this agent's side.
- *BOOL isLinked(const AgentJunctionInfo& otherInfo) const*: Return true if there is a valid junction between this agent and another agent assuming that *otherInfo* is the AgentJunction-Info type variable of the other discrete agent. Return false if there is no junction between the two discrete agents.
- *BOOL isLinked(const AgentJunctionInfo& otherInfo, S32& idxThis, S32& idxOther) const*: Return true if there is a valid junction between this agent and another agent assuming that *otherInfo* is the AgentJunctionInfo type variable of the other discrete agent. Return false if there is no junction between the two discrete agents. This function returns the indices to access the junction ends in addition. *idxThis* holds the index for the junction end at this discrete agent's side and *idxOther* holds the index for the junction end at the other discrete agent's side.

2.4.20 SpAgent

This class instance holds the position (offset within the interface grid unit box this agent belongs to) and the state of a cell (or a non-cellular biological entity) mapped to a single particle.

Public non-static member variables

- SpAgentState *state*: A variable holding the state of this agent.
- AgentJunctionInfo *junctionInfo*: A variable holding information about the entire set of

junctions between this agent and neighboring agents.

- VReal *vOffset*: This variable holds the offset of this discrete agent from the center of the interface grid unit box this discrete agent belongs to.

2.4.21 UBAgentData

This class instance holds a list of discrete agents in an interface grid unit box.

- Vector<SpAgent> *v_spAgent*: A collection of discrete agents in this unit box.

2.4.22 ExtraMechIntrctData

This class instance holds the extra temporary mechanical interaction state variables of a discrete agent. The entire set of extra temporary mechanical interaction state variables are stored in an internal linear array. *Biocellion* does not allow direct access to the array which can be error-prone.

Public non-static member functions

- *REAL getModelReal(const S32 idx) const*: Return the value of the *idx*th model specific REAL type variable.

- *Vector<REAL> getModelRealArray(void) const*: Return a Vector array holding the entire set of model specific REAL type variable values.

- *void setModelReal(const S32 idx, const REAL val)*: Set the value of the *idx*th model specific REAL type variable to *val*.

- *void setModelRealArray(const Vector<REAL>& v_val)*: Set the entire set of model specific REAL type variables to *v_val*. *v_val*'s size should coincide with the number of model specific REAL type variables for this discrete agent type.

- *void incModelReal(const S32 idx, const REAL inc)*: Increment the value of the *idx*th model specific REAL type variable by *inc*.

- *S32 getModelInt(const S32 idx) const*: Return the value of the *idx*th model specific S32 type variable.

- *Vector<S32> getModelIntArray(void) const*: Return a Vector array holding the entire set of model specific S32 type variable values.

- *void setModelInt(const S32 idx, const S32 val)*: Set the value of the *idx*th model specific S32 type variable to *val*.

- *void setModelIntArray(const Vector<S32>& v_val)*: Set the entire set of model specific S32 type variables to *v_val*. *v_val*'s size should coincide with the number of model specific

S32 type variables for this discrete agent type.

- *void incModelInt(const S32 idx, const S32 inc)*: Increment the value of the *idx*th model specific S32 type variable by *inc*.

2.4.23 AgentMechIntrctData

This class instance holds the sum of the forces on this discrete agent (due to direct mechanical interactions with neighboring discrete agents) and the entire set of extra temporary mechanical interaction state variables.

Public non-static member variables

- VReal *force*: The sum of the forces on this discrete agent.
- ExtraMechIntrctData *extraMechIntrctData*: This variable captures the model specific extra temporary mechanical interaction state.

2.4.24 IfGridUpdate

This class instance holds the information required to update a single state variable of a unit box in the interface grid.

- if_grid_var_type_e *type*: This variable sets the type of the interface grid state variable to update.
- S32 *elemIdx*: This variable sets the index of the interface grid state variable to update.
- union { REAL *realVal*; S32 *intVal*; } *val*: This variable stores the new value of the interface grid state variable to update.

2.4.25 NbrBox

This template class instance holds a set of 27 variables of type T (type T is given when this class instance is defined) for an interface grid unit box and its 26 neighboring boxes (one value per box). These variables are valid only for the boxes in a valid interface region. An offset variable in each dimension (*xOffset*, *yOffset*, *zOffset*, *vOffset[0]*, *vOffset[1]*, or *vOffset[2]*) should be -1, 0, or 1. (*xOffset*, *yOffset*, *zOffset*) (or alternatively (*vOffset[0]*, *vOffset[1]*, *vOffset[2]*)) = (0, 0, 0) indexes the center box.

- *BOOL getValidFlag(const S32 xOffset, const S32 yOffset, const S32 zOffset) const*: Return true if the indexed box is in a valid interface region. Return false if the box is located outside the simulation domain or in a PDE buffer region.
- *BOOL getValidFlag(const VIdx& vOffset) const*: Same to the above function. Use *vOffset* instead of (*xOffset*, *yOffset*, *zOffset*) to index the unit box.

- *const T& getVal(const S32 xOffset, const S32 yOffset, const S32 zOffset) const*: Return a constant reference of the value associated with the indexed unit box. This function should not be invoked for an invalid box.

- *const T& getVal(const VIdx& vOffset) const*: Same to the above function. Use *vOffset* instead of (*xOffset*, *yOffset*, *zOffset*) to index the unit box.

- *void setVal(const S32 xOffset, const S32 yOffset, const S32 zOffset, const T val)*: Set the variable associated with the indexed unit box to *val*. This function should not be invoked for an invalid box.

- *void setVal(const VIdx& vOffset, const T val)*: Same to the above function. Use *vOffset* instead of (*xOffset*, *yOffset*, *zOffset*) to index the unit box.

2.4.26 IfGridBoxData

This class instance holds a set of variables for a sub-region of the simulation domain (one value per one unit box in the partition). This class instance is often used to pass a set of variables for a single partition or a single partition plus the valid ghost region of the partition(a).

- *T get(const VIdx& vIdx) const*: Return the value associated with the unit box at *vIdx*. The the sub-region for this class instance should include *vIdx*.

- *void set(const VIdx& vIdx, const T val)*: Set the value associated with the unit box at *vIdx* to *val*. The the sub-region for this class instance should include *vIdx*.

- *VIdx smallEnd(void) const*: Return the grid index for the unit box at the low end corner of the sub-region for this class instance.

- *VIdx size(void) const*: Return the size of the sub-region for this class instance.

- *idx_t size(const S32 dim) const*: Return the size of the sub-region for this class instance in either x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction.

(a) The valid ghost region for a partition box can be obtained if we increase the size of the box by 1 in the $\pm$ x, y, and z directions (the box size in each direction is increased by 2) and exclude the unit boxes located in the original box, in the PDE buffer region, and outside the simulation domain

3.0 *Biocellion* Support Functions

3.1 Simulation Instance Information

3.1.1 *getCurBaselineTimeStep*

S32 getCurBaselineTimeStep(void)

Return the current *baseline time step*.

3.1.2 *getCurStateAndGridTimeStep*

S32 getCurStateAndGridTimeStep(void)

Return the current *state-and-grid time step* within the current *baseline time step*.

3.1.3 *getCurPDETimeStep*

S32 getCurPDETimeStep(const S32 pdeIdx)

Return the current *PDE time step* of the *pdeIdx*th PDE within the current *state-and-grid time step*.

3.1.4 *getGlobalDataRef*

const Vector<U8>& getGlobalDataRef(void)

Return a constant reference to the user global data. *Biocellion* invokes the model routine (*update-GlobalData()*, see Section 4.2.14) to set the global data (this data can be accessed in any model routine once the data is set) during the simulation initialization process. This function returns a constant reference to the data.

3.1.5 *getRecentSummaryRealVal*

REAL getRecentSummaryRealVal(const S32 elemidx)

Return the most recent value of the *elemIdx*th REAL type summary variable.

3.1.6 *getRecentSummaryIntVal*

REAL getRecentSummaryIntVal(const S32 elemidx)

Return the most recent value of the *elemIdx*th S32 type summary variable.

3.1.7 *getDomainSize*

idx_t getDomainSize(const S32 dim)

Return the domain size in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. The domain size is set inside the simulation configuration file (see Section 6.3).

3.1.8 *getPartSize*

idx_t getPartSize(void)

Return the partition size set inside the simulation configuration file (see Section 6.3).

3.1.9 *getSimInitType*

sim_init_type_e getSimInitType(void)

Return the simulation initialization type set inside the simulation configuration file (see Section 6.3). See the explanation about sim_init_type_e in Section 2.3 for the valid simulation initialization types.

3.1.10 *getParticleNumExtraOutputVars*

S32 getParticleNumExtraOutputVars(void)

Return the number of extra output variables (in addition to the default radius and color variables) for each particle representing a discrete agent. This value is set inside the simulation configuration file (see Section 6.3).

3.1.11 *getModelParam*

std::string getModelParam(void)

Return the model parameter string set inside the simulation configuration file (see Section 6.3).

3.1.12 *getAMRRatio*

S32 getAMRRatio(void)

Return the refinement ratio between two consecutive adaptive mesh refinement (AMR) levels. The refinement ratio is set inside the simulation configuration file (see Section 6.3).

3.2 Random Number Generator

3.2.1 *getModelRand*

REAL Util::getModelRand(const S32 idx)

Return a random number generated using the *idx*th random number generator. *Biocellion* allows users to assign a set of random number generators with different probability density functions.

3.3 Extra Support Functions

3.3.1 computeSphereUBVolOvlpRatio

void computeSphereUBVolOvlpRatio(const S32 maxLevel, const VReal& vOffset, const REAL radius, REAL aaa_ratio[3][3][3])
REAL computeSphereUBVolOvlpRatio(const S32 maxLevel, const VReal& vOffset, const REAL radius, const VIdx& ubVIdxOffset)

A discrete agent with a non-zero volume may span multiple unit boxes. Modelers may want to find the ratios of the overlapping volumes between the agent and different unit boxes over the entire volume of the agent. These functions find an approximate solution assuming that the discrete agent is a sphere (*vOffset* is the offset from the center of the unit box containing the discrete agent and points the center of the sphere, and *radius* is the radius of the sphere). The unit box containing the discrete agent and its 26 neighboring boxes are considered—the radius of a discrete agent cannot exceed one half of the interface grid spacing and the sphere can overlap with only these $3 \times 3 \times 3$ unit boxes. The first function finds the ratios for the entire set of $3 \times 3 \times 3$ unit boxes (*aaa_ratio* contains the solution), and the second function returns the ratio for only one of the $3 \times 3 \times 3$ unit boxes indexed by *ubVIdxOffset*. This function partitions the minimum bounding box of the sphere to $2^{maxLevel} \times 2^{maxLevel} \times 2^{maxLevel}$ sub-boxes. We consider that a sub-box belongs to a unit box if the sub-box center is located inside the sphere and the unit box. If the center is located exactly at the surface of the sphere, we consider the center is located inside the sphere. If the center is located exactly at the boundary of two unit boxes, we consider that the center is located at the unit box with a larger index. These functions compute the ratio by dividing the number of sub-boxes belong to a unit box by the number of sub-boxes belong to the $3 \times 3 \times 3$ boxes. *maxLevel* should be a non-negative integer equal to or smaller than 7. A larger value increases both accuracy and execution time. *vOffset* cannot point the location outside the unit box. *radius* should not exceed one half of the interface grid spacing. *ubVIdxOffset[idx]* (*idx* = 0, 1, or 2) should be -1, 0, or 1.

3.3.2 *changePosFormat2LvTo1Lv*

void changePosFormat2LvTo1Lv(const VIdx& vIdx, const VReal& vOffset, VReal& pos)

Particle position can be represented in a single level (with a single VReal varaible storing the offset from the low end corner of the simulation domain) or in two levels (with a single VIdx variable providing the unit box index the particle belongs to and a single VReal variable holding the offset from the center of the unit box). This functions changes the format from the two level format to the single level format (the updated position is stored in *pos*).

3.3.3 *changePosFormat1LvTo2Lv*

void changePosFormat1LvTo2Lv(const VReal& pos, VIdx& vIdx, VReal& vOffset)

Particle position can be represented in a single level (with a single VReal varaible storing the offset from the low end corner of the simulation domain) or in two levels (with a single VIdx variable providing the unit box index the particle belongs to and a single VReal variable holding the offset from the center of the unit box). This functions changes the format from the single level format to the two level format (the updated position is stored in *vIdx* and *vOffset*).

3.4 Macros

3.4.1 *CHECK*

CHECK(expression)

Abort if *expression* is false if this macro is enabled in compile time (Section 6.2.1).

3.4.2 *OUTPUT*

OUTPUT(minVerbosity, msg)

Print *msg* to the standard output if the standard output verbosity set inside the simulation configuration file (see Section 6.3) is equal to or larger than *minVerbosity*.

3.4.3 ***ERROR***

ERROR(msg)

Print *msg* to the standard output and abort the program.

4.0 *Biocellion* Model Routines

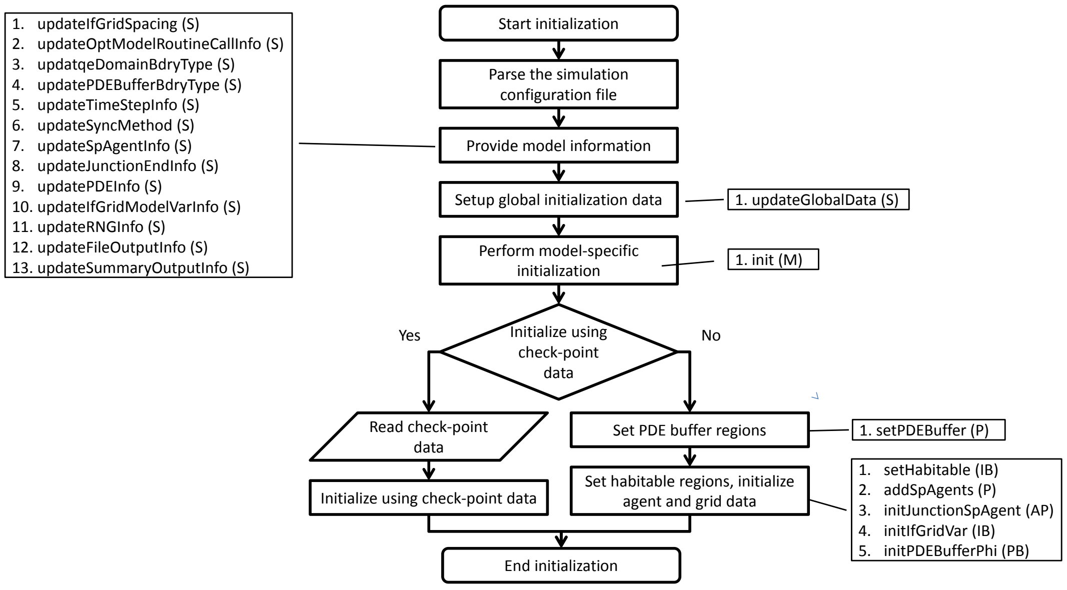
Biocellion asks users to provide their model specifics by filling the function body of a set of predefined model routines. Users write only sequential code, but the *Biocellion* framework can invoke a single model routine multiple times in parallel. Users are disallowed to use any functions that are not thread-safe—*e.g.* the C rand() function is not thread safe, use *getModelRand()* (Section 3.2.1) instead.

We also strongly discourage users to access global variables inside a model routine with few exceptions. Reading constant global variables is acceptable. If global variables are initialized at the beginning of the simulation in the *init()* model routine (Section 4.2.15), reading the initialized variables is also acceptable with one caveat. If multiple MPI processes are created to run *Biocellion* on a system with multiple shared memory nodes (*e.g.* cluster computers and supercomputers), the *init()* model routine is called once in every MPI process. Model routines executed in different MPI processes access different instances of a global variable initialized in different *init()* invocations even when the routines access a variable with the same variable name. If users need to set shared global data across the entire set of MPI processes, update the data using the *updateGlobalData()* model routine (Section 4.2.14) which is invoked exactly once by just one of the MPI processes (the MPI process having rank 0). The data is copied to the remaining MPI processes by the *Biocellion* core framework. The data cannot be modified outside the *updateGlobalData()* function, and users can access the data through *getGlobalDataRef()* (Section 3.1.4).

Section 4.1 summarizes model routine invocation timings, and the remaining of this Section explains the model routines.

4.1 Model Routine Invocation Timings

Figures 4.1, 4.2, 4.3, and 4.4 summarizes model routine invocation timings for the initialization, main computation, PDE computation, and termination, respectively. Symbols after model routine names indicate the model routine invocation granularity. **S** indicates that the model routine is called only once per simulation even when there are more than one MPI processes. **M** indicates that the model routine is called once per MPI process. If there is only one (multi-threaded) process, **S** and **M** are identical. **P** indicates that the model routine is called once per partition. **IB** indicates that the model routine is called once per interface grid unit box. **IF** indicates that the model routine is called once per relevant unit box face—*e.g.* *updateIfGridBetaDomainBdry()* is called only for the unit box faces at the domain boundary. **PB** indicates that the model routine is called once per PDE buffer grid unit box, and **PF** indicates that the model routine is called once per relevant PDE buffer grid unit box face. **A** indicates that the model routine is called once per discrete agent, and **AP** indicates that the model routine is called once per discrete agent pair within the maximum direct interaction distance.



1. updateIfGridSpacing (S)
2. updateOptModelRoutineCallInfo (S)
3. updatqeDomainBdryType (S)
4. updatePDEBufferBdryType (S)
5. updateTimeStepInfo (S)
6. updateSyncMethod (S)
7. updateSpAgentInfo (S)
8. updateJunctionEndInfo (S)
9. updatePDEInfo (S)
10. updateIfGridModelVarInfo (S)
11. updateRNGInfo (S)
12. updateFileOutputInfo (S)
13. updateSummaryOutputInfo (S)
Start initialization
Parse the simulation configuration file
Provide model information
Setup global initialization data
1. updateGlobalData (S)
Perform model-specific initialization
1. init (M)
Initialize using check-point data
Yes
No
Read check-point data
Set PDE buffer regions
1. setPDEBuffer (P)
Initialize using check-point data
Set habitable regions, initialize agent and grid data
1. setHabitable (IB)
2. addSpAgents (P)
3. initJunctionSpAgent (AP)
4. initIfGridVar (IB)
5. initPDEBufferPhi (PB)
End initialization

Figure 4.1. Initialization.

4.2 Model Configuration

4.2.1 *updateIfGridSpacing*

void updateIfGridSpacing(REAL& ifGridSpacing)

Set the interface grid spacing. This model routine sets *ifGridSpacing* to the desired interface grid spacing.

4.2.2 *updateOptModelRoutineCallInfo*

void updateOptModelRoutineCallInfo(OptModelRoutineCallInfo& callInfo)

Control the invocation of optional model routines. This model routine updates *callInfo*. See Section 2.4.6 about the OptModelRoutineCallInfo data type.

4.2.3 *updateDomainBdryType*

void updateDomainBdryType(domain_bdry_type_e a_domainBdryType[3])

Set the domain boundary types at the low and high sides in the x, y, and z directions. This model routine updates *a_domainBdryType[3]*. See the explanation about domain_bdry_type_e in Section 2.3 for the supported domain boundary types.

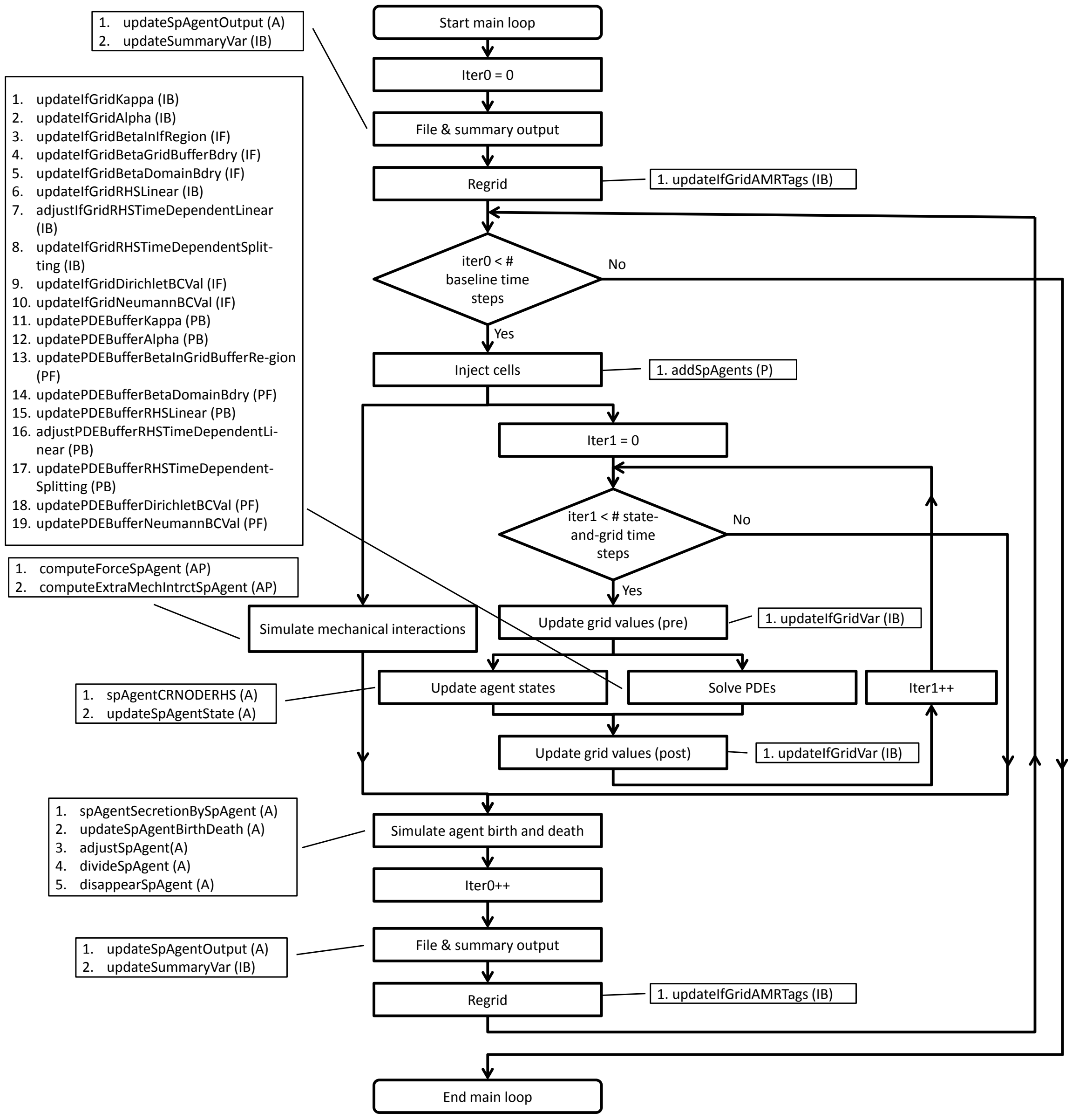
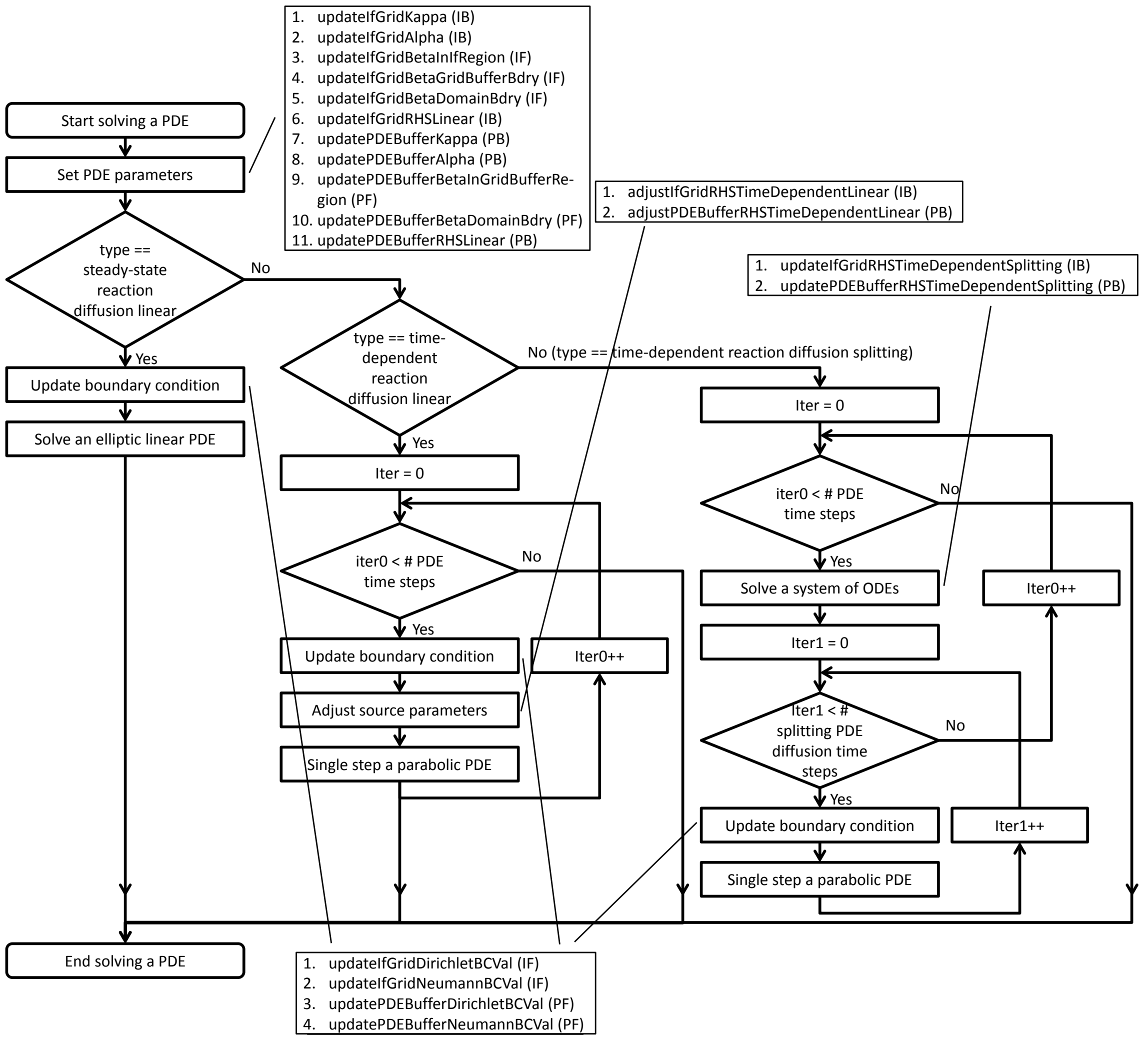

1. updateSpAgentOutput (A)
2. updateSummaryVar (IB)
Start main loop
Iter0 = 0
File & summary output
Regrid
1. updateIfGridAMRTags (IB)
1. updateIfGridKappa (IB)
2. updateIfGridAlpha (IB)
3. updateIfGridBetaInIfRegion (IF)
4. updateIfGridBetaGridBufferBdry (IF)
5. updateIfGridBetaDomainBdry (IF)
6. updateIfGridRHSLinear (IB)
7. adjustIfGridRHSTimeDependentLinear (IB)
8. updateIfGridRHSTimeDependentSplitting (IB)
9. updateIfGridDirichletBCVal (IF)
10. updateIfGridNeumannBCVal (IF)
11. updatePDEBufferKappa (PB)
12. updatePDEBufferAlpha (PB)
13. updatePDEBufferBetaInGridBufferRe-gion (PF)
14. updatePDEBufferBetaDomainBdry (PF)
15. updatePDEBufferRHSLinear (PB)
16. adjustPDEBufferRHSTimeDependentLinear (PB)
17. updatePDEBufferRHSTimeDependentSplitting (PB)
18. updatePDEBufferDirichletBCVal (PF)
19. updatePDEBufferNeumannBCVal (PF)
iter0 < # baseline time steps
No
Yes
Inject cells
1. addSpAgents (P)
Iter1 = 0
iter1 < # state-and-grid time steps
No
Yes
1. computeForceSpAgent (AP)
2. computeExtraMechIntrctSpAgent (AP)
Simulate mechanical interactions
Update grid values (pre)
1. updateIfGridVar (IB)
1. spAgentCRNODERHS (A)
2. updateSpAgentState (A)
Update agent states
Solve PDEs
Iter1++
Update grid values (post)
1. updateIfGridVar (IB)
1. spAgentSecretionBySpAgent (A)
2. updateSpAgentBirthDeath (A)
3. adjustSpAgent(A)
4. divideSpAgent (A)
5. disappearSpAgent (A)
Simulate agent birth and death
Iter0++
1. updateSpAgentOutput (A)
2. updateSummaryVar (IB)
File & summary output
Regrid
1. updateIfGridAMRTags (IB)
End main loop

Figure 4.2. Main loop.

4.2.4 *updatePDEBufferBdryType*

void updatePDEBufferBdryType(pde_buffer_bdry_type_e& pdeBufferBdryType)

Set the boundary type between an interface grid partition and a PDE buffer partition. This model routine updates *pdeBufferBdryType*. See the explanation about pde_buffer_bdry_type_e in Section 2.3 for the supported PDE buffer boundary types.



Start solving a PDE
Set PDE parameters
1. updateIfGridKappa (IB)
2. updateIfGridAlpha (IB)
3. updateIfGridBetaInIfRegion (IF)
4. updateIfGridBetaGridBufferBdry (IF)
5. updateIfGridBetaDomainBdry (IF)
6. updateIfGridRHSLinear (IB)
7. updatePDEBufferKappa (PB)
8. updatePDEBufferAlpha (PB)
9. updatePDEBufferBetaInGridBufferRegion (PF)
10. updatePDEBufferBetaDomainBdry (PF)
11. updatePDEBufferRHSLinear (PB)
type == steady-state reaction diffusion linear
No
Yes
Update boundary condition
Solve an elliptic linear PDE
type == time-dependent reaction diffusion linear
No (type == time-dependent reaction diffusion splitting)
1. adjustIfGridRHSTimeDependentLinear (IB)
2. adjustPDEBufferRHSTimeDependentLinear (PB)
1. updateIfGridRHSTimeDependentSplitting (IB)
2. updatePDEBufferRHSTimeDependentSplitting (PB)
Iter = 0
iter0 < # PDE time steps
Update boundary condition
Adjust source parameters
Single step a parabolic PDE
Iter0++
Solve a system of ODEs
Iter1 = 0
Iter1 < # splitting PDE diffusion time steps
Iter1++
End solving a PDE
1. updateIfGridDirichletBCVal (IF)
2. updateIfGridNeumannBCVal (IF)
3. updatePDEBufferDirichletBCVal (PF)
4. updatePDEBufferNeumannBCVal (PF)

Figure 4.3. Solving a PDE.

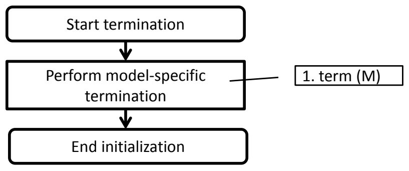


Figure 4.4. Termination.

4.2.5 *updateTimeStepInfo*

void updateTimeStepInfo(TimeStepInfo& timeStepInfo)

Set *baseline time step size* and *state-and-grid time step size*. This model routine updates *timeStepInfo*. See Section 2.4.5 to find details about the TimeStepInfo class.

4.2.6 *updateSyncMethod*

void updateSyncMethod(sync_method_e& extraMechIntrctSyncMethod, sync_method_e& adjustGridPhiAndModelVarSyncMethod)

Set the synchronization method when a single variable is updated in multiple model routine calls. This model routine updates *extraMechIntrctSyncMethod* (for extra direct mechanical interactions between agent pairs, see *computeExtraMechIntrctSpAgent()* in Section 4.4.3) and *adjustGridPhiAndModelVarSyncMethod* (to update extra-cellular space state variables based on model specific rules, see *updateIfGridVar()* in Section 4.5.2). See the explanation about sync_method_e in Section 2.3 for the supported synchronization mechanisms.

4.2.7 *updateSpAgentInfo*

void updateSpAgentInfo(Vector<SpAgentInfo>& v_spAgentInfo)

Provide the information about the discrete agent types in the user model. This model routine updates *v_spAgentInfo*. The size of *v_spAgentInfo* coincides with the number of discrete agent types. Each vector element provides the information about a single discrete agent type. See Section 2.4.7 for additional details about the SpAgentInfo class.

4.2.8 *updateJunctionEndInfo*

void updateJunctionEndInfo(Vector<JunctionEndInfo>& v_junctionEndInfo)

Provide the information about the junction end types in the user model. This model routine updates *v_junctionEndInfo*. The size of *v_junctionEndInfo* coincides with the number of junction end types. Each vector element provides the information about a single junction end type. See Section 2.4.8 for additional details about the JunctionEndInfo class.

4.2.9 *updatePDEInfo*

void updatePDEInfo(Vector<PDEInfo>& v_pdeInfo)

Provide the information about the molecular species in the user model. This model routine updates *v_pdeInfo*. The size of *v_pdeInfo* coincides with the number of molecular species. Each vector element provides the information about a single molecular species. See Section 2.4.12 for additional details about the PDEInfo class.

4.2.10 *updateIfGridModelVarInfo*

void updateIfGridModelVarInfo(Vector<IfGridModelVarInfo>& v_ifGridModelRealInfo, Vector<IfGridModelVarInfo>& v_ifGridModelIntInfo)

Provide the information about the model specific attributes for the extra-cellular space in the user model. This model routine updates *v_ifGridModelRealInfo* (for REAL type attributes) and *v_if-*

GridModelIntInfo (for S32 type variables). The sizes of *v_ifGridModelRealInfo* and *v_ifGridModelIntInfo* coincide with the number of REAL type and S32 type model specific attributes, respectively. Each vector element provides the information about a single model specific attribute. See Section 2.4.13 for additional details about the IfGridModelVarInfo class.

4.2.11 *updateRNGInfo*

void updateRNGInfo(Vector<RNGInfo>& v_rngInfo)

Provide the information about the random number generators used in the model. This model routine updates *v_rngInfo*. The size of *v_rngInfo* coincides with the number of random number generators. Each vector element provides the information about a single random number generator. See Section 2.4.14 for additional details about the RNGInfo class.

4.2.12 *updateFileOutputInfo*

void updateFileOutputInfo(FileOutputInfo& fileOutputInfo)

Provide the information about file output of simulation results. This model routine updates *fileOutputInfo*. See Section 2.4.15 for additional details about the FileOutputInfo class.

4.2.13 *updateSummaryOutputInfo*

void updateSummaryOutputInfo(SummaryOutputInfo& summaryOutputInfo)

Provide the information about summary output of simulation results. This model routine updates *summaryOutputInfo*. See Section 2.4.16 for additional details about the SummaryOutputInfo class.

4.2.14 *updateGlobalData*

void updateGlobalData(Vector<U8>& v_globalData)

Update the global data shared by every MPI process. Once *v_globalData* is updated in this model routine, the data is copied to every MPI process. *v_globalData* cannot be updated elsewhere. *getGlobalDataRef()* (Section 3.1.4) returns a constant reference to the updated data.

4.2.15 *init*

void init(void)

Users may perform model specific initialization inside this function.

4.2.16 *term*

void term(void)

Users may perform model specific clean-up inside this function.

4.2.17 ***setPDEBuffer***

void setPDEBuffer(const VIdx& startVIdx, const VIdx& regionSize, BOOL& isPDEBuffer)

Mark whether this partition is an interface grid partition (set *isPDEBuffer* to false) or a PDE buffer partition (set *isPDEBuffer* to true). *startVIdx* points the low end corner of this partition, and *regionSize* is the size of this partition assuming the interface grid spacing.

4.2.18 ***setHabitable***

void setHabitable(const VIdx& vIdx, BOOL& isHabitable)

Mark whether this unit box (indexed by *vIdx*) is habitable (set *isHabitable* to true) or not (set *isHabitable* to false). If this unit box is marked as uninhabitable, discrete agents cannot penetrate into this unit box.

4.3 Individual Agent Behavior

4.3.1 ***addSpAgents***

void addSpAgents(const BOOL init, const VIdx& startVIdx, const VIdx& regionSize, const IfGrid BoxData<BOOL>& ifGridHabitableBoxData, Vector<VIdx>& v_spAgentVIdx, Vector<SpAge ntState>& v_spAgentState, Vector<VReal>& v_spAgentOffset)

Add discrete agents to this partition at the beginning of a simulation (if *init* is true) or at the beginning of a *baseline time step* (if *init* is false). *startVIdx* points the unit box at the low end corner of this partition, and *regionSize* is the size of this partition. *ifGridHabitableBoxData* informs whether a unit box in this partition is habitable or not. It is an error to add a discrete agent to an uninhabitable unit box. This model routine updates *v_spAgentVIdx*, *v_spAgentState*, and *v_spAgentOffset*. The sizes of *v_spAgentVIdx*, *v_spAgentState*, and *v_spAgentOffset* should be same—one vector element for one newly added discrete agent. An element of *v_spAgentVIdx* locates the unit box to place a discrete agent. An element of *v_spAgentState* stores the state of a discrete agent. An element of *v_spAgentOffset* sets the discrete agent position offset within a unit box (from the center of the unit box).

4.3.2 ***spAgentCRNODERHS***

void spAgentCRNODERHS(const S32 odeNetIdx, const VIdx& vIdx, const SpAgent& spAgent, co nst Vector<NbrBox<REAL> >& v_gridPhiNbrBox, const Vector<NbrBox<REAL> >& v_grid ModelRealNbrBox, const Vector<NbrBox<S32> >& v_gridModelIntNbrBox, const Vector<dou ble>& v_y, Vector<double>& v_f)

Set the right hand side (the derivatives) of the *odeNetIdx*th ODE system for this discrete agent. *vIdx* indexes the unit box this discrete agent is located in. *spAgent* provides the information about this discrete agent. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* provide the information (molecular concentrations, model specific REAL type attributes, and model specific S32 type attributes, respectively) about the extra-cellular space for this box and the 26 neighboring boxes. *v_y* stores the current values of the ODE system variables. This model routine updates *v_f* which stores the derivatives for the variables in the ODE system. The ODE systems for a discrete agent are updated before *updateSpAgentState()* is called for the agent.

4.3.3 *updateSpAgentState*

void updateSpAgentState(const VIdx& vIdx, const AgentJunctionInfo& junctionInfo, const VReal & vOffset, const Vector<NbrBox<REAL> >& v_gridPhiNbrBox, const Vector<NbrBox<REAL > >& v_gridModelRealNbrBox, const Vector<NbrBox<S32> >& v_gridModelIntNbrBox, SpAg entState& state)

Update the state of this discrete agent. *vIdx* indexes the unit box this discrete agent is located in. *junctionInfo* stores the list of junctions between this discrete agent and its neighboring discrete agents. *vOffset* is the offset from the center of the unit box this discrete agent belongs to. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* provide the information (molecular concentrations, model specific REAL type attributes, and model specific S32 type attributes, respectively) about the extra-cellular space for this box and the 26 neighboring boxes. This model routine updates *state* based on the provided information. *state* initially holds the state of this discrete agent. *updateSpAgentState()* is called after the ODE systems for the discrete agent are updated.

4.3.4 *spAgentSecretionBySpAgent*

void spAgentSecretionBySpAgent(const VIdx& vIdx, const AgentJunctionInfo& junctionInfo, con st VReal& vOffset, const AgentMechIntrctData& mechIntrctData, const Vector<NbrBox<REAL > >& v_gridPhiNbrBox, const Vector<NbrBox<REAL> >& v_gridModelRealNbrBox, const Ve ctor<NbrBox<S32> >& v_gridModelIntNbrBox, SpAgentState& state, Vector<SpAgentState> & v_spAgentState, Vector<VReal>& v_spAgentDisp)

Secrete new discrete agents from this discrete agent. *vIdx* indexes the unit box this discrete agent is located in. *junctionInfo* stores the list of junctions between this discrete agent and its neighboring discrete agents. *vOffset* is the offset from the center of the unit box this discrete agent belongs to. *mechIntrctData* stores the temporary mechanical interaction state of this discrete agent. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* provide the information (molecular concentrations, model specific REAL type attributes, and model specific S32 type attributes, respectively) about the extra-cellular space for this box and the 26 neighboring boxes. This model routine updates this discrete agent's state (*state*) and the states (*v_spAgentState*) and the displacements (from this discrete agent, *v_spAgentDisp*) of newly secreted discrete agents. The displacement values cannot exceed the interface grid spacing. *v_spAgentState* and *v_spAgentDisp* should have same size—one element for one newly secreted discrete agent. *state* initially holds the state of this discrete agent. *spAgentSecretionBySpAgent()* is called before *updateSpAgent-BirthDeath()* within a single *baseline time step*.

4.3.5 ***updateSpAgentBirthDeath***

void updateSpAgentBirthDeath(const VIdx& vIdx, const SpAgent& spAgent, const AgentMechInt rctData& mechIntrctData, const Vector<NbrBox<REAL> >& v_gridPhiNbrBox, const Vector< NbrBox<REAL> >& v_gridModelRealNbrBox, const Vector<NbrBox<S32> >& v_gridModelI ntNbrBox, BOOL& divide, BOOL& disappear)

Mark whether this discrete agent will divide or disappear. *vIdx* indexes the unit box this discrete agent is located in. *spAgent* provides the information about this discrete agent. *mechIntrctData* stores the temporary mechanical interaction state of this discrete agent. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* provide the information (molecular concentrations, model specific REAL type attributes, and model specific S32 type attributes, respectively) about the extra-cellular space for this box and the 26 neighboring boxes. This model routine updates *divide* and *disappear*. Set *divide* to true if this discrete agent is going to divide. *divideSpAgent()* (Section 4.3.7) will be called if *divide* is set to true. Set *disappear* to true if this discrete agent is subject to disappear. If neither *divide* nor *disappear* is set to true, *adjustSpAgent()* (Section 4.3.6) is called. It is an error to set both *divide* and *disappear* to true. *updateSpAgentBirthDeath()* is called after *spAgentSecretionBySpAgent()* within a single *baseline time step*.

4.3.6 ***adjustSpAgent***

void adjustSpAgent(const VIdx& vIdx, const AgentJunctionInfo& junctionInfo, const VReal& vO ffset, const AgentMechIntrctData& mechIntrctData, const Vector<NbrBox<REAL> >& v_gridP hiNbrBox, const Vector<NbrBox<REAL> >& v_gridModelRealNbrBox, const Vector<NbrBox <S32> >& v_gridModelIntNbrBox, SpAgentState& state, VReal& disp)

Adjust the state and position of this discrete agent. *vIdx* indexes the unit box this discrete agent is located in. *junctionInfo* stores the list of junctions between this discrete agent and its neighboring discrete agents. *vOffset* is the offset from the center of the unit box this discrete agent belongs to. *mechIntrctData* stores the temporary mechanical interaction state of this discrete agent. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* provide the information (molecular concentrations, model specific REAL type attributes, and model specific S32 type attributes, respectively) about the extra-cellular space for this box and the 26 neighboring boxes. This model routine updates the state of this discrete agent (*state*) and the displacement from the original position (*disp*). *state* initially holds the state of this discrete agent. *disp* should not exceed the interface grid spacing.

4.3.7 ***divideSpAgent***

void divideSpAgent(const VIdx& vIdx, const AgentJunctionInfo& junctionInfo, const VReal& vO ffset, const AgentMechIntrctData& mechIntrctData, const Vector<NbrBox<REAL> >& v_gridP hiNbrBox, const Vector<NbrBox<REAL> >& v_gridModelRealNbrBox, const Vector<NbrBox <S32> >& v_gridModelIntNbrBox, SpAgentState& motherState, VReal& motherDisp, SpAgentS tate& daughterState, VReal& daughterDisp, Vector<BOOL>& v_junctionDivide, BOOL& moth erDaughterLinked, JunctionEnd& motherEnd, JunctionEnd& daughterEnd)

Divide this discrete agent to a mother discrete agent and a daughter discrete agent. *vIdx* indexes the unit box this discrete agent is located in. *junctionInfo* stores the list of junctions between this discrete agent and its neighboring discrete agents. *vOffset* is the offset from the center of the unit box this discrete agent belongs to. *mechIntrctData* stores the temporary mechanical interaction state of this discrete agent. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbr-Box* provide the information (molecular concentrations, model specific REAL type attributes, and model specific S32 type attributes, respectively) about the extra-cellular space for this box and the 26 neighboring boxes. This model routine updates the states of the mother discrete agent and the daughter discrete agent (*motherState* and *daughterState*, respectively), the displacements from the original position for the mother and daughter discrete agents (*motherDisp* and *daughterDisp*, respectively), and a junction between the mother and daughter discrete agents. *motherState* initially stores the state of this discrete agent. Users may overwrite the initial state. *v_junctionDivide* indicates a subset of the junctions (if the *v_junctionDivide* element for a junction is set to true, the mother agent retains the junction) the mother agent will retain—the daughter agent inherits the remaining junctions. A junction is formed between the mother and daughter discrete agents if *motherDaughterLinked* is set to true with *motherEnd* and *daughterEnd* as the junction ends for the mother and daughter sides, respectively. *motherEnd* and *daughterEnd* are irrelevant if *motherDaughterLinked* is set to false.

4.4 Physico-Mechanical Interaction Between Agents

4.4.1 *initJunctionSpAgent*

void initJunctionSpAgent(const VIdx& vIdx0, const SpAgent& spAgent0, const VIdx& vIdx1, con st SpAgent& spAgent1, const VReal& dir, const REAL& dist, BOOL& link, JunctionEnd& end0, JunctionEnd& end1)

Initialize a junction between a discrete agent pair within the maximum direct interaction distance. *vIdx0* indexes the unit box *spAgent0* is located in. *vIdx1* indexes the unit box *spAgent1* is located in. *dir* is a unit vector from the position of *spAgent1* to the position of *spAgent0*. *dist* is the distance between the positions of the two discrete agents. This model routine updates *link*, *end0*, and *end1*. Set *link* to true to form a junction between the two discrete agents. *end0* is the junction end in the *spAgent0* side and *end1* is the junction end in the *spAgent1* side. *end0* and *end1* are irrelevant if *link* is set to false.

4.4.2 *computeForceSpAgent*

void computeForceSpAgent(const VIdx& vIdx0, const SpAgent& spAgent0, const Vector<REAL >& v_gridPhi0, const Vector<REAL>& v_gridModelReal0, const Vector<S32>& v_gridModelI nt0, const VIdx& vIdx1, const SpAgent& spAgent1, const Vector<REAL>& v_gridPhi1, const Ve ctor<REAL>& v_gridModelReal1, const Vector<S32>& v_gridModelInt1, const VReal& dir, co nst REAL& dist, VReal& force)

Update force between two discrete agents. *vIdx0* indexes the unit box *spAgent0* is located in. *v_gridPhi0*, *v_gridModelReal0*, and *v_gridModelInt0* are molecular concentrations, model specific REAL type variables, and model specific S32 type variables for the unit box *spAgent0* belongs to, respectively. *vIdx1* indexes the unit box *spAgent1* is located in. *v_gridPhi1*, *v_gridModel-Real1*, and *v_gridModelInt1* are molecular concentrations, model specific REAL type variables, and model specific S32 type variables for the unit box *spAgent1* belongs to, respectively. *dir* is a unit vector from the position of *spAgent1* to the position of *spAgent0*. *dist* is the distance between the positions of the two discrete agents. This model routine updates *force*.

4.4.3 *computeExtraMechIntrctSpAgent*

void computeExtraMechIntrctSpAgent(const VIdx& vIdx0, const SpAgent& spAgent0, const Vect or<REAL>& v_gridPhi0, const Vector<REAL>& v_gridModelReal0, const Vector<S32>& v_g ridModelInt0, const VIdx& vIdx1, const SpAgent& spAgent1, const Vector<REAL>& v_gridPhi 1, const Vector<REAL>& v_gridModelReal1, const Vector<S32>& v_gridModelInt1, const VRe al& dir, const REAL& dist, ExtraMechIntrctData& extraMechIntrctData0, ExtraMechIntrctData & extraMechIntrctData1, BOOL& link, JunctionEnd& end0, JunctionEnd& end1, BOOL& unlin k)

Evaluate extra mechanical interactions between a discrete agent pair. *vIdx0* indexes the unit box *spAgent0* is located in. *v_gridPhi0*, *v_gridModelReal0*, and *v_gridModelInt0* are molecular concentrations, model specific REAL type variables, and model specific S32 type variables for the unit box *spAgent0* belongs to, respectively. *vIdx1* indexes the unit box *spAgent1* is located in. *v_gridPhi1*, *v_gridModelReal1*, and *v_gridModelInt1* are molecular concentrations, model specific REAL type variables, and model specific S32 type variables for the unit box *spAgent1* belongs to, respectively. *dir* is a unit vector from the position of *spAgent1* to the position of *spAgent0*. *dist* is the distance between the positions of the two discrete agents. This model routine updates the temporary extra mechanical interaction states for *spAgent0* and *spAgent1* which are *extraMechIn-trctData0* and *extraMechIntrctData1*, respectively. Temporary mechanical interaction state variables are reset to zero at the beginning of every *baseline time step*. Users also form and break a junction between a discrete agent pair in this model routine. If the two discrete agents are linked and *link* is set to true, the junction ends in the *spAgent0* and *spAgent1* sides are replaced with *end0* and *end1*, respectively—*isLinked* (Section 2.4.19) returns whether two discrete agents are linked or not. If *spAgent0* and *spAgent1* are linked and *unlink* is set to true, the *Biocellion* framework breaks the junction. If there is no junction between *spAgent0* and *spAgent1* and *link* is set to true, a new junction is formed with junction ends *end0* and *end1*. If there is no junction and *unlink* is set to true or both *link* and *unlink* is set to false, no change occurs. It is an error to set both *link* and *unlink* to true.

4.5 State Changes in the Extra-cellular Space

4.5.1 *initIfGridVar*

void initIfGridVar(const VIdx& vIdx, const UBAgentData& ubAgentData, Vector<REAL>& v_g ridPhi, Vector<REAL>& v_gridModelReal, Vector<S32>& v_gridModelInt)

Initialize the state variables associated with an interface grid unit box. *vIdx* indexes the unit box. *ubAgentData* holds the discrete agents located in this unit box. This model routine updates the molecular concentrations (*v_gridPhi*), the model specific REAL type attributes (*v_gridModelReal*), and the model specific S32 type attributes (*v_gridModelInt*) for this unit box.

4.5.2 *updateIfGridVar*

void updateIfGridVar(const BOOL pre, const S32 round, const VIdx& vIdx, const NbrBox<const UBAgentData>& ubAgentDataPtrNbrBox, Vector<NbrBox<REAL> >& v_gridPhiNbrBox, Vector<NbrBox<REAL> >& v_gridModelRealNbrBox, Vector<NbrBox<S32> >& v_gridModelIntNbrBox)*

Update the state variables associated with an interface grid unit box and its 26 neighboring boxes. It is an error to access or update values associated with a unit box location outside the simulation domain or a unit box location in a PDE buffer region. *pre* indicates whether this routine is called at the beginning of a *state-and-grid time step* (if *pre* is true) or at the end of a *state-and-grid time step* (if *pre* is false). *round* indicates the round in which this model routine is called—users are allowed update extra-cellular space state variables in multiple rounds (Section 2.4.6). *vIdx* indexes this unit box. *ubAgentDataPtrNbrBox* holds pointers for UBAgentData class instances for this unit box and its 26 neighboring unit boxes. This model routine updates the molecular concentrations (*v_gridPhiNbrBox*), the model specific REAL type attributes (*v_gridModelRealNbrBox*), and the model specific S32 type attributes (*v_gridModelIntNbrBox*) for this unit box and its 26 neighboring unit boxes. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* initially holds the current values associated with this box and its 26 neighboring boxes, and users may update a subset of the values based on their model specifics.

4.5.3 *updateIfGridKappa*

void updateIfGridKappa(const VIdx& vIdx, const UBAgentData& ubAgentData, const Vector< REAL>& v_gridPhi, const Vector<REAL>& v_gridModelReal, const Vector<S32>& v_gridModelInt, REAL& gridKappa)

Set the ratio of the available extra-cellular volume in computing diffusion flux. molecular concentration in *Biocellion* is the total amount of a molecular species in a unit box divided by the volume of the unit box. However, in computing diffusion, the direction and rate of diffusion is determined by the molecular concentration in the free space. If one unit box is heavily occupied by cells and another unit box has no cell, then the net amount of diffusion to the empty unit box can be positive even when the molecular concentration (ignoring cell volume exclusion) in the empty unit box is higher. This model routine sets *gridKappa* to consider cell volume exclusion in computing diffusion flux. Say there are two unit boxes (*box0* and *box1*) sharing a face. ϕ_0 and ϕ_1 are molecular concentrations for *box0* and *box1*, respectively. κ_0 and κ_1 are *gridKappa* values set for *box0* and *box1*, respectively. β is the diffusion coefficient set for the common face. Then, the diffusion flux from *box0* to *box1* becomes $\beta \times (\frac{\phi_0}{\kappa_0} - \frac{\phi_1}{\kappa_1}) \times \frac{1}{h}$. *vIdx* indexes this unit box. *ubAgentData* holds the entire set of discrete agents in this unit box. *v_gridPhi*, *v_gridModelReal*, and *v_gridModelInt* are molecular concentrations, model specific REAL type variables, and model specific S32 type variables for this unit box, respectively. $0.0 <$ *gridKappa* ≤ 1.0. Set *gridKappa* to 1.0 to ignore cell volume exclusion. *gridKappa* is assumed to be 1.0 outside the simulation domain.

4.5.4 *updateIfGridAlpha*

void updateIfGridAlpha(const S32 elemIdx, const VIdx& vIdx, const UBAgentData& ubAgentDa ta, const Vector<REAL>& v_gridPhi, const Vector<REAL>& v_gridModelReal, const Vector< S32>& v_gridModelInt, REAL& gridAlpha)

Set the decay rate for the *elemIdx*th molecular species. *vIdx* indexes this unit box. *ubAgent-Data* holds the entire set of discrete agents in this unit box. *v_gridPhi*, *v_gridModelReal*, and *v_gridModelInt* are molecular concentrations, model specific REAL type variables, and model specific S32 type variables for this unit box, respectively. This model routine updates *gridAlpha*. $-1.0 < gridAlpha \leq 0.0$. Set *gridAlpha* to 0.0 to ignore decay.

4.5.5 *updateIfGridBetaInIfRegion*

void updateIfGridBetaInIfRegion(const S32 elemIdx, const S32 dim, const VIdx& vIdx0, const VI dx& vIdx1, const UBAgentData& ubAgentData0, const UBAgentData& ubAgentData1, const Ve ctor<REAL>& v_gridPhi0, const Vector<REAL>& v_gridPhi1, const Vector<REAL>& v_grid ModelReal0, const Vector<REAL>& v_gridModelReal1, const Vector<S32>& v_gridModelInt0 , const Vector<S32>& v_gridModelInt1, REAL& gridBeta)

Set the diffusion coefficient for the *elemIdx*th molecular species for a unit box face inside the interface region. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. *vIdx0* indexes the unit box at the low side of the face and *vIdx1* indexes the unit box at the high side of the face. *ubAgentData0* and *ubAgentData1* hold discrete agents at the low and high side unit boxes, respectively. *v_gridPhi0* and *v_gridPhi1* are molecular concentrations for the low and high side unit boxes, respectively. *v_gridModelReal0* and *v_grid-ModelReal1* are the model specific REAL type variables for the unit boxes at the low and high sides. *v_gridModelInt0* and *v_gridModelInt1* are the model specific S32 type variables for the unit boxes at the low and high sides, respectively. This model routine updates *gridBeta*.

4.5.6 *updateIfGridBetaPDEBufferBdry*

void updateIfGridBetaPDEBufferBdry(const S32 elemIdx, const S32 dim, const VIdx& vIdx, cons t UBAgentData& ubAgentData, const Vector<REAL>& v_gridPhi, const Vector<REAL>& v_gr idModelReal, const Vector<S32>& v_gridModelInt, REAL& gridBeta)

Set the diffusion coefficient for the *elemIdx*th molecular species for a unit box face between an interface grid partition and a PDE buffer partition. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. *vIdx* indexes the unit box in the interface grid partition. *ubAgentData* holds the entire set of discrete agents in this unit box. *v_gridPhi*, *v_gridModelReal*, and *v_gridModelInt* are the molecular concentrations, model specific REAL type variables, and model specific S32 type variables for the unit box in the interface grid partition, respectively. This model routine updates *gridBeta*.

4.5.7 *updateIfGridBetaDomainBdry*

void updateIfGridBetaDomainBdry(const S32 elemIdx, const S32 dim, const VIdx& vIdx, const U BAgentData& ubAgentData, const Vector<REAL>& v_gridPhi, const Vector<REAL>& v_grid ModelReal, const Vector<S32>& v_gridModelInt, REAL& gridBeta)

Set the diffusion coefficient for the *elemIdx*th molecular species for a unit box face at the domain boundary. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. *vIdx* indexes the unit box in the interface grid partition. *ubAgentData* holds the entire set of discrete agents in this unit box. *v_gridPhi*, *v_gridModelReal*, and *v_gridModelInt* are the molecular concentrations, model specific REAL type variables, and model specific S32 type variables for the unit box in the interface grid partition, respectively. This model routine updates *gridBeta*.

4.5.8 *updateIfGridRHSLinear*

void updateIfGridRHSLinear(const S32 elemIdx, const VIdx& vIdx, const UBAgentData& ubAge ntData, const Vector<REAL>& v_gridPhi, const Vector<REAL>& v_gridModelReal, const Vect or<S32>& v_gridModelInt, REAL& gridRHS)

Update the source term for the *elemIdx*th molecular species. This model routine is relevant only for linear PDEs (`PDE_TYPE_REACTION_DIFFUSION_STEADY_STATE_LINEAR` and `PDE_TYPE_REACTION_DIFFUSION_TIME_DEPENDENT_LINEAR`). *vIdx* indexes this unit box. *ubAgentData* holds the entire set of discrete agents in this unit box. *v_gridPhi*, *v_gridModelReal*, and *v_gridModelInt* are molecular concentrations, model specific REAL type variables, and model specific S32 type variables for this unit box, respectively. This model routine updates *gridRHS*.

4.5.9 *adjustIfGridRHSTimeDependentLinear*

void adjustIfGridRHSTimeDependentLinear(const S32 elemIdx, const VIdx& vIdx, const REAL g ridPhi, const Vector<REAL>& v_gridModelReal, const Vector<S32>& v_gridModelInt, REAL & gridRHS)

Adjust the source term for the *elemIdx*th molecular species. This model routine is invoked in every *PDE time step* and is relevant only for time-dependent linear PDEs (`PDE_TYPE_REACTION_DIFFUSION_TIME_DEPENDENT_LINEAR`). This model routine is called only when users configure to call this function (Section 2.4.12). *vIdx* indexes this unit box. *ubAgentData* holds the entire set of discrete agents in this unit box. *gridPhi* is the concentration of the *elemIdx*th molecular species at the beginning of a *PDE time step*. *v_gridModelReal* and *v_gridModelInt* are the model specific REAL type variables and model specific S32 type variables for this unit box, respectively. *gridRHS* is initially set to the *gridRHS* value set inside the *updateIfGridRHSLinear()* function for this molecular species. Users may change the value based on model specifics.

4.5.10 ***updateIfGridRHSTimeDependentSplitting***

void updateIfGridRHSTimeDependentSplitting(const S32 pdeIdx, const VIdx& vIdx, const UBAg entData& ubAgentData, const Vector<double>& v_gridPhi, const Vector<REAL>& v_gridMod elReal, const Vector<S32>& v_gridModelInt, Vector<double>& v_gridRHS)

Set the derivative values for the reaction term of the *pdeIdx*th PDE which is solved using the splitting scheme. *vIdx* indexes this unit box. *ubAgentData* holds the entire set of discrete agents in this unit box. *v_gridPhi* holds molecular concentrations **for the molecular species in this PDE**—the size of the vector is equal to the number of molecular species in this PDE, and the first vector element holds the molecular concentration for the molecular species in this PDE with the smallest molecular species index. *v_gridModelReal* and *v_gridModelInt* are the model specific REAL type variables and model specific S32 type variables for this unit box, respectively. This model routine updates *v_gridRHS* which holds the derivative values **for the molecular species in this PDE**.

4.5.11 ***updateIfGridAMRTags***

void updateIfGridAMRTags(const VIdx& vIdx, const NbrBox<const UBAgentData>& ubAgent DataPtrNbrBox, const Vector<NbrBox<REAL> >& v_gridPhiNbrBox, const Vector<NbrBox< REAL> >& v_gridModelRealNbrBox, const Vector<NbrBox<S32> >& v_gridModelIntNbrBox , Vector<S32>& v_finestLevel)*

Set the desired adaptive mesh refinement (AMR) level for this unit box. *vIdx* indexes this unit box. *ubAgentDataPtrNbrBox* holds pointers for UBAgentData class instances for this unit box and its 26 neighboring unit boxes. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* are the molecular concentrations, model specific REAL type attributes, and model specific S32 type attributes for this unit box and its 26 neighboring unit boxes, respectively. This model routine updates *v_finestLevel* which holds the desired finest AMR level for this unit box **for the PDEs in this simulation**—index the vector using a PDE index, not a molecular species index.

4.5.12 ***updateIfGridDirichletBCVal***

void updateIfGridDirchletBCVal(const S32 elemIdx, const VReal& pos, const S32 dim, const BO OL lowSide, const REAL a_gridPhi[3], const Vector<Vector<REAL> >& vv_gridModelReal, co nst Vector<Vector<S32> >& vv_gridModelInt, REAL& bcVal)

Set the model specific Dirichlet boundary value for the *elemIdx*th molecular species for a unit box face at the domain boundary. This model routine is valid only when `BC_TYPE_DIRICHLET_MODEL` is selected. *pos* locates the center of the unit box face. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. The face is at the low side (if *lowSide* is true) or the high side (if *lowSide* is false) of the simulation domain. *a_gridPhi* holds molecular concentrations for the *elemIdx*th molecular species for the three interface grid unit boxes closest to the boundary unit box face along the direction orthogonal to the face. *vv_gridModelReal* and *vv_gridModelInt* hold model specific REAL and S32 type variables for the three boxes closest to the boundary unit box face—*e.g.* *vv_gridModelReal[elemIdx][0]* holds the value for the *elemIdx*th model specific REAL type variable for the unit box closest to the boundary face.

This model routine updates *bcVal*.

4.5.13 *updateIfGridNeumannBCVal*

void updateIfGridNeumannBCVal(const S32 elemIdx, const VReal& pos, const S32 dim, const B OOL lowSide, const REAL a_gridPhi[3], const Vector<Vector<REAL> >& vv_gridModelReal, const Vector<Vector<S32> >& vv_gridModelInt, REAL& bcVal)

Set the model specific Neumann boundary value for the *elemIdx*th molecular species for a unit box face at the domain boundary. This model routine is valid only when `BC_TYPE_NEUMANN_-MODEL` is selected. *pos* locates the center of the unit box face. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. The face is at the low side (if *lowSide* is true) or the high side (if *lowSide* is false) of the simulation domain. *a_gridPhi* holds molecular concentrations for the *elemIdx*th molecular species for the three interface grid unit boxes closest to the boundary unit box face along the direction orthogonal to the face. *vv_grid-ModelReal* and *vv_gridModelInt* hold model specific REAL and S32 type variables for the three boxes closest to the boundary unit box face. This model routine updates *bcVal*.

4.5.14 *initPDEBufferPhi*

void initPDEBufferPhi(const VIdx& startVIdx, const VIdx& pdeBufferBoxSize, Vector<REAL> & v_gridPhi)

Initialize molecular concentrations of a PDE buffer unit box. *startVIdx* points the low end corner of the PDE buffer unit box assuming the interface grid spacing (assuming that the interface grid is applied on the entire simulation domain). *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. This model routine updates *v_gridPhi*.

4.5.15 *updatePDEBufferKappa*

void updatePDEBufferKappa(const S32 pdeIdx, const VIdx& startVIdx, const VIdx& pdeBufferB oxSize, REAL& gridKappa)

Set the ratio of the available volume (used in computing diffusion flux) for a unit PDE buffer box of the *pdeIdx*th PDE. *startVIdx* points the low end corner of the PDE buffer unit box assuming the interface grid spacing. *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. This model routine updates *gridKappa*. $0.0 < gridKappa \leq 1.0$. Set *gridKappa* to 1.0 to assume that 100% of the volume is free. *gridKappa* is assumed to be 1.0 outside the simulation domain.

4.5.16 *updatePDEBufferAlpha*

void updatePDEBufferAlpha(const S32 elemIdx, const VIdx& startVIdx, const VIdx& pdeBufferB oxSize, REAL& gridAlpha)

Set the decay rate for the *elemIdx*th molecular species. *startVIdx* points the low end corner of the PDE buffer unit box assuming the interface grid spacing. *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. This model routine updates *gridAlpha*. $-1.0 < gridAlpha \leq 0.0$. Set *gridAlpha* to 0.0 to ignore decay.

4.5.17 *updatePDEBufferBetaInPDEBufferRegion*

void updatePDEBufferBetaInPDEBufferRegion(const S32 elemIdx, const S32 dim, const VIdx& s tartVIdx0, const VIdx& startVIdx1, const VIdx& pdeBufferBoxSize, REAL& gridBeta)

Set the diffusion coefficient for the *elemIdx*th molecular species for a PDE buffer grid unit box face inside a PDE buffer region. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. *startVIdx0* points the low end of the unit box at the low side of the face and *startVIdx1* points the low end of the unit box at the high side of the face assuming the interface grid spacing. *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. This model routine updates *gridBeta*.

4.5.18 *updatePDEBufferBetaDomainBdry*

void updatePDEBufferBetaDomainBdry(const S32 elemIdx, const S32 dim, const VIdx& startVId x, const VIdx& pdeBufferBoxSize, REAL& gridBeta)

Set the diffusion coefficient for the *elemIdx*th molecular species for a PDE buffer unit box face at the domain boundary. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. *startVIdx* points the low end corner of the PDE buffer unit box in the PDE buffer partition assuming the interface grid spacing. *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. This model routine updates *gridBeta*.

4.5.19 *updatePDEBufferRHSLinear*

void updatePDEBufferRHSLinear(const S32 elemIdx, const VIdx& startVIdx, const VIdx& pdeB ufferBoxSize, const REAL gridPhi, REAL& gridRHS)

Update the source term for the *elemIdx*th molecular species. This model routine is relevant only for linear PDEs (`PDE_TYPE_REACTION_DIFFUSION_STEADY_STATE_LINEAR` and `PDE_TYPE_REACTION_DIFFUSION_TIME_DEPENDENT_LINEAR`). *startVIdx* points the low end corner of the PDE buffer unit box assuming the interface grid spacing. *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. *gridPhi* holds the molecular concentration of the *elemIdx*th molecular species for this PDE buffer grid unit box. This model routine updates *gridRHS*.

4.5.20 *adjustPDEBufferRHSTimeDependentLinear*

void adjustPDEBufferRHSTimeDependentLinear(const S32 elemIdx, const VIdx& startVIdx, con st VIdx& pdeBufferBoxSize, const REAL gridPhi, REAL& gridRHS)

Adjust the source term for the *elemIdx*th molecular species. This model routine is invoked in every *PDE time step* and is relevant only for time-dependent linear PDEs (`PDE_TYPE_REACTION_-DIFFUSION_TIME_DEPENDENT_LINEAR`). This model routine is called only when users configure to call this function (Section 2.4.12). *startVIdx* points the low end corner of the PDE buffer unit box assuming the interface grid spacing. *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. *gridPhi* is the concentration of *elemIdx*th molecular species in the unit box. *gridRHS* is initially set to the *gridRHS* value set inside the *updatePDEBufferRHSLinear()* function for this molecular species. Users may change the value based on model specifics.

4.5.21 *updatePDEBufferRHSTimeDependentSplitting*

void updatePDEBufferRHSTimeDependentSplitting(const S32 pdeIdx, const VIdx& startVIdx, co nst VIdx& pdeBufferBoxSize, const Vector<double>& v_gridPhi, Vector<double>& v_gridRHS)

Set the derivative values for the reaction term for the *pdeIdx*th PDE which is solved using the splitting scheme. *startVIdx* points the low end corner of the PDE buffer unit box assuming the interface grid spacing. *pdeBufferBoxSize* is the size of a PDE buffer unit box assuming the interface grid spacing. *v_gridPhi* holds molecular concentrations **for the molecular species in this PDE**— the size of the vector is equal to the number of molecular species in this PDE, and the first vector element holds the molecular concentration for the molecular species in this PDE with the smallest molecular species index. This model routine updates *v_gridRHS* which holds the derivative values **for the molecular species in this PDE**.

4.5.22 *updatePDEBufferDirichletBCVal*

void updatePDEBufferDirichletBCVal(const S32 elemIdx, const VReal& startPos, const VReal& pdeBufferFaceSize, const S32 dim, const BOOL lowSide, REAL& bcVal)

Set the model specific Dirichlet boundary value for the *elemIdx*th molecular species for a PDE buffer unit box face at the domain boundary. This model routine is valid only when `BC_TYPE_-DIRICHLET_MODEL` is selected. *startPos* points the low end corner of the unit box face. *pdeBufferFaceSize* is the size of a PDE buffer unit box face. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. The face is at the low side (if *lowSide* is true) or the high side (if *lowSide* is false) of the simulation domain. This model routine updates *bcVal*.

4.5.23 *updatePDEBufferNeumannBCVal*

void updatePDEBufferNeumannBCVal(const S32 elemIdx, const VReal& startPos, const VReal& pdeBufferFaceSize, const S32 dim, const BOOL lowSide, REAL& bcVal)

Set model specific Neumann boundary values for the *elemIdx*th molecular species for a PDE buffer unit box face at the domain boundary. This model routine is valid only when `BC_TYPE_-NEUMANN_MODEL` is selected. *startPos* points the low end corenr of the unit box face. *pdeBufferFaceSize* is the size of a PDE buffer unit box face. The unit box face is orthogonal to a unit vector in the x (if *dim* is 0), y (if *dim* is 1), or z (if *dim* is 2) direction. The face is at the low side (if *lowSide* is true) or the high side (if *lowSide* is false) of the simulation domain. This model routine updates *bcVal*.

4.6 Simulation Output

4.6.1 *updateSpAgentOutput*

void updateSpAgentOutput(const VIdx& vIdx, const SpAgent& spAgent, REAL& color, Vector< REAL>& v_extra)

Set the output variables for a discrete agent. *vIdx* indexes the unit box this discrete agent (*spAgent*) belongs to. This model routine update the color variable (*color*) and the model specific extra output variables (*v_extra*). The number of model specific output variables for a discrete agent is set inside the simulation configuration file (see Section 6.3).

4.6.2 *updateSummaryVar*

void updateSummaryVar(const VIdx& vIdx, const NbrBox<const UBAgentData>& ubAgentDataPtrNbrBox, const Vector<NbrBox<REAL> >& v_gridPhiNbrBox, const Vector<NbrBox<REAL> >& v_gridModelRealNbrBox, cosnt Vector<NbrBox<S32> >& v_gridModelIntNbrBox , Vector<REAL>& v_realVar, Vector<S32>& v_intVar)*

Update the values of the summary variables. The entire set of summary variables (one variable per interface grid unit box) for each attribute are reduced to get a summary value (one summary value per attribute). *vIdx* indexes this unit box. *ubAgentDataPtrNbrBox* holds pointers for UBAgentData class instances for this unit box and its 26 neighboring unit boxes. *v_gridPhiNbrBox*, *v_gridModelRealNbrBox*, and *v_gridModelIntNbrBox* pass the molecular concentrations, the model specific REAL type attributes, and the model specific S32 type attributes, respectively (for this unit box and its 26 neighboring unit boxes). This model routine updates summary values for REAL type attributes (*v_realVal*) and S32 type attributes (*v_intVal*).

5.0 Sample Implementations

We provide two sample implementations porting Momeni *et al.*'s yeast patterning model (Momeni et al. 2013) and Resat *et al.*'s bacteria on soil aggregate model (Resat et al. 2011). See the cited papers for additional model details. Kang *et al.* (Kang et al. TBP) also portray the porting process of the yeast patterning model and we refer interested readers to the article.

The yeast patterning model code is located under `$BIOCELLION_ROOT/libmodel/model-yeast-pattering`, and the bacteria on soil aggregate model is located under `$BIOCELLION_ROOT/libmodel/model-soil-bacteria`. See `$BIOCELLION_ROOT/framework/main/yeast-patterning-5um.xml` and `$BIOCELLION_ROOT/framework/main/yeast-patterning-20um.xml` for simulation configuration files for the yeast patterning model with 5 *μm* and 20 *μm* interface grid spacings, respectively—see Section 6.3 for details about simulation configuration files. A sample simulation configuration file for the bacteria on soil aggregate model is in `$BIOCELLION_ROOT/framework/main/soil-bacteria.xml`. To adopt the 5 *μm* grid spacing for the yeast patterning model, `IF_GRID_SPACING_5_MICRO_METER` in `$BIOCELLION_ROOT/libmodel/model-yeast-pattering/model_define.h` should be set to 1 before compiling the model code. To adopt the 20 *μm* grid spacing, `IF_GRID_SPACING_5_MICRO_METER` needs to be set to 0.

6.0 *Biocellion* Installation and Execution

6.1 System Requirements

Biocellion runs on a spectrum of parallel computers ranging from multicore PCs and workstations to cluster computers, Cloud computers, and supercomputers—users do not need to change their model code to run on different platforms. The current version of *Biocellion* runs only on x86 compatible systems (a great majority of computers with Intel or AMD CPUs are x86 compatible). *Biocellion* runs on 64-bit Linux operating systems. Compiling *Biocellion* model code requires a `C++` compiler—we have tested using the GNU gcc compiler and the Intel icc compiler. *Biocellion* uses the Intel Thread Building Blocks library for multi-threading, and the library is freely available from the thread building blocks homepage (`http://threadingbuildingblocks.org`). *Biocellion* is pre-installed in Amazon EC2 (Section 6.6).

6.2 Compiling *Biocellion*

6.2.1 Compiling Model Code

Biocellion users first need to update directory paths in `$BIOCELLION_ROOT/Makefile.common`. `BIOCELLION_ROOT` should point the *Biocellion* root directory.

`REAL` in `$BIOCELLION_ROOT/Makefile.common` is set to "double" by default. Users can set REAL to "float" to use single-precision floating point arithmetic instead of double-precision floating point arithmetic. `MPAGENT` should be set to "no" and `SPAGENT` should be set to "yes" in the current version. Users can set `DEBUG` to "yes" for debugging support (to use GDB) or "no" for high-performance.

Users may update several variables in `$BIOCELLION_ROOT/Makefile.model` to use different compilers or different compilation flags—the default is to use GNU gcc. We strongly encourage users to enable checks on model routine outputs and input arguments of *Biocellion* support functions by setting `CHECK_FLAG` to "-DENABLE_CHECK=1" at the early stage of model development. Once the model code is well verified, users may disable the checks (set `CHECK_FLAG` to "-DENABLE_CHECK=0") to expedite simulation.

Biocellion builds a model library using the model code under `$BIOCELLION_ROOT/libmodel/model`. To test using one of the two sample models, users create a soft link (*e.g.* under `$BIOCELLION_ROOT/libmodel` type "ln -s model-yeast-patterning-updated model") and type "make" under `$BIOCELLION_ROOT/libmodel`. Once compilation completes, `libmodel.so` will be created under `$BIOCELLION_ROOT/libmodel/interface`.

6.2.2 Compiling the *Biocellion* Core Framework

Advanced users may want to recompile the *Biocellion* core framework to use a different compiler with different optimization flags or to link the *Biocellion* core framework to a different flavor of MPI library.

Compiling the core framework is more involved and requires the Intel Thread Building Block library (version 4.2 or later), Intel math kernel library (MKL), Intel ODE library, PNNL Global Arrays (`http://www.emsl.pnl.gov/docs/global`), and MPI in addition. Compiling the core framework also requires a `C++` compiler that supports `c++0x` extension—recent versions of GNU gcc and Intel icc support the extension.

Users set `DIST_MEM_PAR` in `$BIOCELLION_ROOT/Makefile.framework` to "yes" to create a *Biocellion* executable that runs using multiple MPI processes or to "no" to create a *Biocellion* version that runs using only one (multi-threaded) process. Users also need to update other directory paths in the file. Typing "make" under `$BIOCELLION_ROOT/framework` places a newly created executable under `$BIOCELLION_ROOT/framework/main`.

6.3 Simulation Configuration File

Biocellion asks users to provide specifics of a simulation instance in an XML file (sample files are located under `$BIOCELLION_ROOT/framework/main`).

6.3.1 Required Elements

- *time_step*: Set the number of baseline time steps to execute. For example, *<time_step num_baseline="60000"/>* asks *Biocellion* to run for 60,000 baseline time steps.

- *domain*: Set the domain sizes in the x, y, and z directions. For example, *<domain x="128" y="128" z="4928"/>* sets the domain size to $128 \times 128 \times 4928$ assuming the interface grid spacing. Domain sizes in the x, y, and z directions should be equal to or larger than the minimum partition size (which is 4). If adaptive mesh refinement (AMR) is used to solve PDEs, domain sizes in the x, y, and z directions should be a positive integer multiple of $AMR\ ratio^{\#\ AMR\ levels-1} \times 4$—See Section 6.3.2 for *AMR ratio* (default value is 2).

- *init_data*: Set the initialization method, partition size, and initialization file type and path. Initialization method can be either "code" or "file". If the initialization method is set to "file", *Biocellion* users need to set file type ("binary" is the only valid option at this point) and path. For example, *<init_data partition_size="32" src="file" file_type="binary" path="/data/input"/>* sets *Biocellion* to set partition size to 32 and initialize using check point data under `/data/input`. Partition size should be equal to or larger than the minimum partition size (which is 4). If adaptive mesh refinement (AMR) is used to solve PDEs, partition size should be a positive integer multiple of $AMR\ ratio^{\#\ AMR\ levels-1} \times 4$—See Section 6.3.2 for *AMR ratio* (default value is 2). Note that the number of partitions in the simulation domain should be equal to or larger than the number of MPI processes in the target system to avoid idling MPI processes—if the amount of computing in each partition varies significantly, more partitions are necessary to load-balance.

- *output*: Set the output path, interval, and file formats ("pvtu" is the only valid option for discrete agent and "vtm" is the only valid option for molecular concentrations at this point). For example, *<output path="/data/output" interval="100" particle="pvtu" grid="vtm"/>* sets the file output path to `/data/output`, the file output interval to once per every 100 baseline time steps, the particle output format to the parallel VTK unstructured grid format, and the molecular concentration output format to the VTK hierarchical box data format. Setting "interval" to 0 turns off file output.

6.3.2 Optional Elements

- *model*: Set the model specific parameter string. Model routines can access the parameter string using *getModelParam()* (Section 3.1.11). For example, *<model param="test"/>* sets the model specific parameter to "test". The model specific parameter is set to "" by default.

- *verbosity*: Set the standard output verbosity (0 to 5, 5 for the highest level of verbosity). For example, *<stdout verbosity="3"/>* sets the standard output verbosity level to 3. The default verbosity level is 1.

- *system*: Set the number of node groups, number of nodes per node group, number of sockets per node, threshold to perform load-balance, and the number of threads per MPI process. Set the number of sockets to the number of sockets per shared memory node for non-uniform memory access (NUMA) binding. Set the number of sockets per node to 1 to disable NUMA binding.
  For example, *<system num_node_groups="1" num_nodes_per_group="1" num_socket s_per_node="1" max_load_imbalance="1.05" num_threads="8"/>* sets the number of node groups, the number of nodes per group, and the number of sockets per node to 1, sets *Biocellion* to perform load balancing (in the designated interval set in the system configuration file, see the explanation about the interval element in this section) if the MPI process with the highest load has more than 1.05 times load over the average, and sets the number of threads per MPI process to 8. The default number of node groups is 1. The default value for the number of nodes per node group is equal to the number of MPI processes in the MPI communicator. The default value for the number of sockets per node is 1 (disable NUMA binding). The default threshold for load-balancing is 1.2 and the default number of threads per MPI process is the number of cores (or hardware threads in a system with hardware multi-threading support) in the target system. Note that the number of node groups × the number of nodes per group × the number of sockets per node should coincide with the number of MPI processes in the MPI communicator.

- *super_partition*: Set the super partition size in the x, y, and z directions. This is relevant when running *Biocellion* on a large cluster with a large number of nodes and hierarchical interconnection network. *Biocellion* allows users to group closely located nodes. Multiple partitions in a single super partition is processed by the MPI processes in a single node group, and this reduces communication between distant nodes and improves the performance. The sizes of a super partition in the x, y, and z directions should be a positive integer multiple of the partition size. Note that the number of super partitions in the simulation domain should be equal to or larger than the number of node groups in the target system to avoid idling node groups—if the amount of computing in each super partition varies significantly, more super partitions are necessary to load-balance. *<super_partition x="128" y="128" z=" 128"/>* sets the super partition sizes in the x, y, and z directions to 128. The default super partition size in the x, y, or z direction is the smallest positive integer multiple of the partition size that is equal to or larger than the simulation domain size in the x, y, or z direction.

- *interval*: Set the intervals for summary output, load-balancing, AMR regridding, and checkpoint data output. For example, *<interval summary=''1'' load_balance=''100'' regridding=''100'' checkpoint=''600''/>* sets *Biocellion* to print the summary every *baseline time step*, load balance once per every 100 *baseline time steps*, regrid AMR hierarchy once per every 100 *baseline time steps*, and generate checkpoint data every 600 *baseline time steps*. The load balancing interval should be a positive integer multiple of the regirdding interval. Setting the interval to 0 turns off summary, load balancing, regridding, or checkpoint data generation. Default values for summary output and checkpoint data generation are 0 and load balancing and regirdding are 100.

- *amr*: Set the refinement ratio between two consecutive AMR levels, and the desired fill ratio for AMR boxes. The fill ratio is the number of user tags in an AMR box divided by the number of unit boxes in the AMR box. If fill ratio is high, *Biocellion* tends to create a large number of tiny AMR boxes, which lowers the efficiency of computation. If fill ratio is set to a low value, *Biocellion* tends to create fewer boxes, but a larger percentage of the simulation domain is covered by fine grids. The default refinement ratio is 2, and the refinement ratio should be either 2 or 4. The default fill ratio is 0.5 and $0.0 \leq fill\ ratio \leq 1.0$.

6.4 Execution on Desktop PCs and Workstations

Biocellion usees Intel Thread Building Block (version 4.2 or later) for multi-threading, and users need to set the `LD_LIBRARY_PATH` Linux environment variable to point the TBB library directory (in TBB 4.2, this is `$TBB_ROOT/lib/intel64/gcc4.1`). *Biocellion* executables are located under `$BIOCELLION_ROOT/framework/main`. `biocellion.DP.SPAGENT.DEBUG` is a *Biocellion* executable compiled with debugging support, and `biocellion.DP.SPAGENT.OPT` is an executable that delivers high-performance (DP stands for double precision, use the executables with SP instead of DP if single-precision floating point arithmetic is sufficient). Users execute *Biocellion* by typing `./biocellion.DP.SPAGENT.OPT simulation_configuration_file`.

6.5 Execution on Clusters

Use `biocellion.DP.SPAGENT.MPI.OPT` (or `biocellion.DP.SPAGENT.MPI.DEBUG` for debugging support) to run on clusters with the Ethernet interconnect and MPICH2 (`http://www.mpich.org/`). For clusters with the InfiniBand Interconnect (or other proprietary interconnects) or different flavors of MPI libraries, users need to recompile the *Biocellion* framework using Global Arrays and MPI libraries configured for the target system. `mpiexec -n number_of_MPI_processes --machinefile machine_file_name ./biocellion.DP.SPAGNT.MPI.OPT simulation_configuration_file_name` launches multiple MPI processes to run a large simulation using multiple nodes. Refer to MPI manuals for additional details. To run *Biocellion* on a cluster with a job scheduler, refer to a job scheduler manual or contact a system administrator.

6.6 Execution on Amazon EC2

Launch EC2 instances—we use either CC1 Cluster Compute (cc1.4xlarge) or CC2 Cluster Compute (cc2.8xlarge)—using the *Biocellion* machine image (refer to the *Biocellion* homepage `http://biocellion.org` for the latest machine image name). Refer the Amazon EC2 homepage (`http://aws.amazon.com/ec2`) for instructions to launch EC2 instances. Log-in to one of the launched instances. *Biocellion* is pre-installed under `/home/ec2-user`. To run on a single EC2 instance, refer to the instructions in Section 6.4—Intel TBB is pre-installed and the `LD_LIBRARY_PATH` Linux environment variable is already set.

To run on multiple instances, update `mpd.hosts` file under `/home/ec2-user` to list the launched EC2 instance addresses. Type `mpdboot -n number_of_EC2_instances -f mpd.hosts` to launch an MPI daemon. Type `mpiexec -n number_of_MPI_processes ./biocellion.DP.SPAGNT.MPI.OPT simulation_configuration_file_name` to execute *Biocellion* using multiple instances. Note that each instance has its own `/home/ec2-user` directory. Updating a file under `/home/ec2-user` in one instance will not update the file with the same name under `/home/ec2-user` of different instances. Create an Amazon S3 storage to share files across multiple EC2 instances.

6.7 Debugging Support

Biocellion installation includes binaries with debugging support. Users can enable checks on model routine outputs and input arguments to *Biocellion* support functions by enabling the check flag on compile time as stated in Section 6.2.1.

Users can set *Biocellion* to monitor ordinary differential equation (ODE) and partial differential equation (PDE) solver outputs to assure that output values are equal to or larger than the user specified minimum valid value (Sections 2.4.4 and 2.4.9). If PDE solver output values contain a value smaller than the specified minimum value, *Biocellion* prints the PDE parameters and the molecular concentrations of the unit box with the erroneous value and the neighboring boxes in the $\pm$ x, y, and z directions at the beginning of the PDE time step along with the erroneous value after the PDE time step which produced the erroneous value. *Biocellion* aborts after printing the error message.

6.8 Visualization Using Paraview

We briefly summarize visualization instructions assuming Paraview 3.14.1. See the Paraview homepage and manual for advanced visualization.

6.8.1 Visualizing Discrete Agents

1. Click the “File” menu and select the “Open” item.

2. Open a set of files in the parallel VTK unstructured grid format(.pvtu).

3. Click the “Properties” tab at the bottom left side and click the “Apply” icon.
4. Select the “Filters” menu, the “Alphabetical” sub-menu, and the “Glyph” item.
5. Select the “Properties” tab.
6. Set “Scalars” to radius, “Glyph Type” to Sphere, “Radius” to 1.0, “Scale Mode” to Scalar, “Set Scale Factor” to 1.0, and “Maximum Number of Points” to a value larger than the number of discrete agents.
7. Click “Apply.”
8. Click the “Display” tab.
9. Set “Color by” to color.
10. Click “Zoom To Data.” This maps discrete agents to a set of spheres. Using the “Mask Points” filter instead of the “Glyph” filter maps a discrete agent to a point (instead of a sphere)—this is a computationally less expensive option to visualize discrete agent data.

6.8.2 Visualizing Molecular Concentrations

1. Click the “File” menu and select the “Open” item.
2. Open a set of files in the VTK hierarchical box data files format (.vtm).
3. When a pop-up menu appears, select the VTK Hierarchical Box Data Files format.
4. Click the “Properties” tab at the bottom left side and click the “Apply” icon.
5. Select the “Filters” menu, the “Alphabetical” sub-menu, and the “Slice” item.
6. Select the “Property” tab and adjust the plane to slice, and click the “Apply” icon.
7. Select the “Display” tab.
8. Set “Color by” to phi.
9. Click “Zoom To Data.” This displays the molecular concentrations at the slice plane.

7.0 Tips and Caveats

- We strongly encourage *Biocellion* users to enable the checks on model routine outputs and input arguments to *Biocellion* support routines (Section 6.2.1) if the simulation does not work properly. This often guides users to find errors on their model routines.

- The relative and absolute error norm thresholds for multigrid iterations (Section 2.4.10) have significant impact on the accuracy and speed of simulation. If the norm thresholds are too large, users may see no change at all in molecular concentrations even though the source terms in PDEs are set to non-zero values. Setting these values to unnecessarily small values can significantly slow down the simulation on the other hand. Be cautious when setting these parameters.

- Note that double (instead of REAL) is used in *spAgentCRNODERHS()*—this is mainly because the Intel ODE solver does not support single-precision arithmetic.

- Be cautious about setting Neumann boundary values when κ (see Sections 4.5.3 and 4.5.15) is set to a value smaller than 1.0. *Biocellion* does not consider κ in setting boundary values (κ is used only in computing diffusion flux). For example, users may expect there is no net diffusion if the Neumann boundary value for a boundary unit box face is set to 0.0. *Biocellion* sets the molecular concentration of the box outside the simulation domain to the molecular concentration of the box inside the simulation domain if the Neumann boundary value is 0.0—the gradient ignoring κ becomes 0.0. *Biocellion* assumes that κ outside the simulation domain is 1.0 and if the κ value for the box inside the simulation value is smaller than 1.0, $\frac{\phi_0}{\kappa_0} - \frac{\phi_1}{\kappa_1}$ can have a non-zero value. Users may set the diffusion coefficient at the boundary to 0.0 instead to apply the zero flux boundary condition.

8.0 C++ Basics Relevant to *Biocellion*

We provide several links for users who are new to `C++`.

- `http://www.cplusplus.com/doc/tutorial/classes/` explains `C++` class, class object (or instance), and access specifiers (`private` and `public`).

- `http://www.cplusplus.com/reference/vector/vector` explains `C++` standard template library (STL) vector.

- `http://en.wikipedia.org/wiki/Class_variable` explains static member variables and functions.

- `http://en.wikipedia.org/wiki/C%2B%2B_template` explains `C++` template

- `http://en.wikipedia.org/wiki/Reference_(C%2B%2B)` explains the concept of reference in `C++`.

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