Deterministic Reaction-Diffusion Simulators

Definition

A deterministic reaction-diffusion simulator is software designed to approximate the dynamics of a system governed by the diffusion and interaction of species within a domain in a deterministic fashion.

Detailed Description

In neuroscience, these species can be one of many classes of molecules: ions, enzymes, polypeptides, globular proteins, microRNAs, etc. The interactions are chemical reactions, such as phosphorylation or binding, the synthesis of a new molecule out of substrates, or the breakdown of a molecule. Unlike stochastic simulators, which approximate these dynamics using pseudorandom processes, deterministic simulators solve a system of partial differential equations (PDEs) . Thus, while stochastic simulators need to be run many times to identify the range of likely outcomes, deterministic simulators need only be run once, as the result is unique.

Theory

Deterministic simulators are most appropriate when they can rely on the law of large numbers (Kotelenez 1986), which implies that noise variation of concentration becomes small as the number of molecules in the population increases. That is, when a large number of molecules are present, the dynamics of the population becomes well approximated by the mean dynamics. This assumption underlies a key trade-off between deterministic and stochastic simulators. Deterministic simulations allow the use of a single number to represent the concentration in a given volume over a relatively large time step in the setting of large numbers of particles. Stochastic simulations are needed when the number of molecules is small, but exact stochastic methods generally require either a state variable for each molecule (which is inefficient if the number of molecules is large) and/or small time steps (Rathinam et al. 2003; Kerr et al. 2008).
Fick's second law of diffusion states that the diffusion of a species with concentration u (x,t) at position x (in 1, 2, or 3 dimensions) at time t within a domain is governed by

$$u_t = D\,\nabla^2 u$$

which states that the rate of change of concentration at a given point and time is proportional (with proportionality constant D, the diffusion constant) to the Laplacian of the concentration u, a measure of its unevenness. A reaction-diffusion equation for a single species is the diffusion equation except with an additional term f (u,t) added to the right-hand side to account for the net effects of the reactions:

$$u_t = D\nabla^2 u + f(u,t)$$

When multiple species are present, the system of PDEs consists of many equations of this form, where the reaction term may depend on all species present. Initial and boundary conditions complete the mathematical description (Fife 1979). In neuroscience, Neumann boundary conditions are common, as they describe the flux across the boundary, such as occurs through ion channels.

Practice

Since every deterministic reaction-diffusion simulator must provide tools to fully specify the PDE, existing tools require the same conceptual steps, although the order may vary: 1. the domain is specified (whole cell or part of cell) and discretized, 2. the species are specified, 3. the reactions are specified, and 4. the equations are integrated. Results may then be analyzed, either within the simulator or with external tools.
NEURON (Carnevale and Hines 2006), STEPS (Hepburn et al. 2012), and Virtual Cell (Loew and Schaff 2001) - widely used tools in the computational neuroscience community that support deterministic reaction-diffusion - illustrate much of the variation possible within the shared conceptual framework. NEURON and STEPS are primarily targeted at

computational neuroscientists, while Virtual Cell is primarily targeted at cell biologists but supports the spatial variation and membrane-associated ion channels essential for computational neuroscience (Brown et al. 2011). Other simulators also provide facilities for deterministic diffusion, including Chemesis (Blackwell and Kotaleski 2003) and MOOSE (Ray and Bhalla 2008).

The domain may be specified and discretized in a variety of ways. Discretization is the process of choosing finitely many locations to represent the infinitely many points in a domain. Virtual Cell simulates on 1-, 2-, or 3-dimensional domains specified either analytically or via segmented images. It then discretizes the domain using a regular Cartesian mesh. A variation on this approach would be to use unequally sized cubes chosen at either the beginning or repeatedly throughout a simulation to focus computational effort as needed. STEPS works with (possibly unequally sized) tetrahedra, but the discretization must be done using another tool. NEURON works on 1-dimensional branching geometries either described programmatically or imported from tracing programs such as Neurolucida (Glaser and Glaser 1990). This one-dimensional branched geometry is then discretized into short segments.

Reaction dynamics are typically specified as either kinetic schemes directly linked to the biology or directly as terms in the underlying PDEs. Simulators that support kinetic schemes typically internally translate them into PDEs so that they can be integrated.

Multiple integration options are possible. The STEPS solver uses "Wmrk4," an explicit Runge-Kutta method (Kutta 1901). NEURON supports first- and second-order implicit fixed-step integration via implicit Euler and Crank-Nicholson (Crank and Nicolson 1947), respectively. NEURON also supports variable-step variable-order implicit methods from the SUNDIALS (Hindmarsh et al. 2005) library. Virtual Cell supports a variety of explicit, implicit, and semi-implicit finite volume methods. Finite elements are an alternative strategy.

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