Multi-Scale Spatially Distributed Simulations of Microbial Ecosystems

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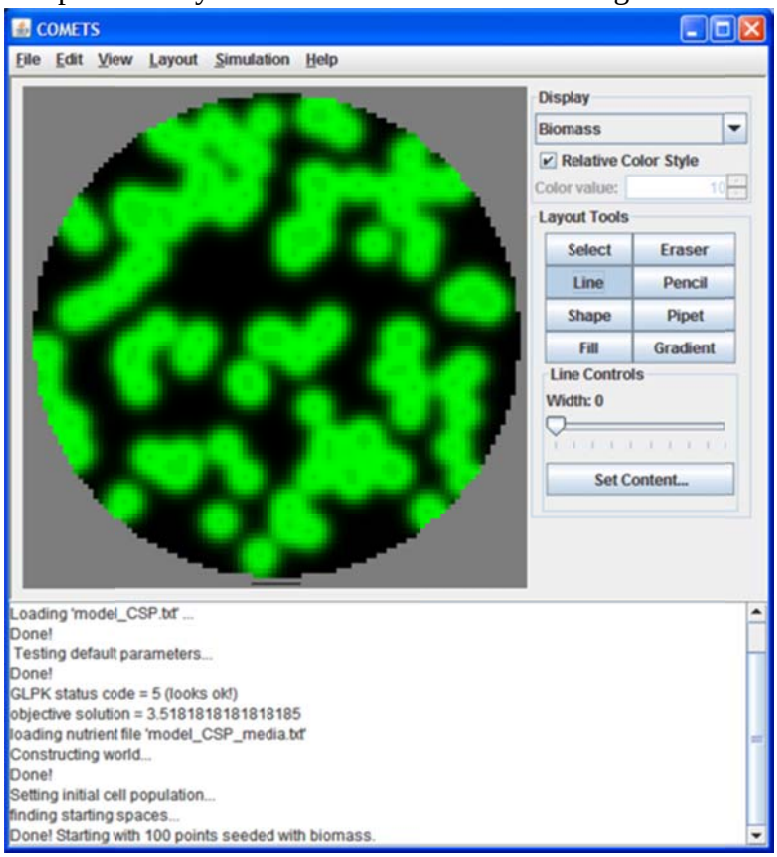
Project Goals: The goal of this project is to develop a tool for facilitating simulation, validation and discovery of multiscale dynamical processes in microbial ecosystems. Our Computation Of Microbial Ecosystems in Time and Space (COMETS) is a an open-source platform for performing spatially distributed time-dependent flux balance based simulations of microbial metabolism. Our plan involves building the software platform itself, calibrating and testing it through comparison with experimental data, and integrating simulations and experiments to address important open questions on the evolution and dynamics of cross-feeding interactions between microbial species.

COMETS (Computation Of Microbial Ecosystems in Time and Space) is a broadly applicable and user-friendly platform for modeling metabolic interactions between microbial species. This platform builds on dynamic flux balance analysis (dFBA [1]) to perform time-dependent metabolic simulations of microbial ecosystems, bridging the gap between stoichiometric and environmental modeling. Simulations occur on a spatially structured lattice of interacting metabolic subsystems, representing a level of detail that is intermediate between fine-grained single-cell modeling and a global population modeling approach.

The current version of COMETS incorporates three fundamental steps: *(i)* Implementation of cellular growth (increase of biomass), using a hybrid kinetic-dFBA solver for every point in the 2D lattice. Upper bounds on uptake fluxes for the dFBA calculation are estimated based on a concentration-dependent saturating function, in analogy with Michaelis-Menten kinetics. Each grid point may contain biomass for an arbitrary number of different species; *(ii)* Advance of the front of biomass, which we treat as an incompressible fluid (in analogy to [2]). This step involves the solution of the Laplace equation, followed by a calculation of the new biomass front using a level set method; *(iii)* Implementation of a finite differences approximation of the diffusion equation for modeling the diffusion of extracellular small molecules, i.e. environmentally available nutrients and secreted byproducts.

To correctly perform this last part of the simulation, we exploit the natural separation of time scales between growth and diffusion of small molecules. The typical time scale associated with growth, t_{growth}, is set by cell doubling times and is of order 10^3 seconds. The dependence of

growth rates on the external nutrients is incorporated by solving a spatially dependent FBA on a time scale $t_{FBA} << t_{growth}$, and is typically of order 10^2 seconds. Diffusion is then performed on time scales $t_D \sim 10$ seconds, an order of magnitude smaller than the FBA update times. This separation of time scales allows us to efficiently model the complex dynamics in a computationally tractable manner while ensuring that our scheme is physically consistent. An important consequence of this scheme is that it associates a length scale l with each point in our lattice. The scale is set by the smallest diffusion constant, D_{min}, and is given by $l^2 \sim D_{min}/t_D$. Typically, for small metabolites $D_{min} \sim 10^{-5}$ cm^2s, implying that we have a spatial resolution of about 10^{-2} cm per grid point.



Our prototype of COMETS uses the open-source GNU Linear Programming Kit (GLPK) for performing the dFBA calculations, and a Java platform for coordinating the simulations and for rapid visualization. Several microbial species have been imported into COMETS, including *Escherichia coli*, *Salmonella typhimurium*, *Shewanella oneidensis*, *Lactococcus lactis*, and *Saccharomyces cerevisiae*. New species and new environmental settings can be easily incorporated through a macro language, or using a custom graphical user interface (see Figure). COMETS is being tested by comparing computational simulations to available and newly measured spatial distributions of biomass in individual *E. coli* colonies on agar [3]. In addition, we are applying this platform to study the population dynamics of two syntrophic bacteria [4], with special attention to the effects of initial density in a diverse spatially organized system that contains a population of cheaters.

References

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