

title: [nearly] Rate Independent Synthesis of Stochastic Biochemical Computation
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Randomness is inherent to biochemistry: at each instant, the sequence of reactions that fires is a matter of chance. Some biological systems exploit such randomness, choosing between different outcomes stochastically. We have developed a computer-aided design tool called BAMB I (Brian's Automated Modular Biochemical Instantiator) that synthesizes biochemical reactions with stochastic behavior. Given a library of parts, such as MIT's BioBricks, it selects biochemical reactions that produce different combinations of molecular types according to a specified probability distribution. The response is precise and robust to perturbations. Furthermore, it is programmable: the probability distribution is a function of the quantities of input types. The method is modular and extensible. We discuss strategies for implementing various functional dependencies: linear, logarithmic, exponential, etc.

An important constraint is the timing, captured in the relative rates of the biochemical reactions: all the outputs of a given phase must be produced before the next phase can begin consuming them as inputs. To achieve this synchronization, the reaction rates must sometimes be separated by orders of magnitude: some much faster than others, some much slower. This might be costly or infeasible given a specific library of biochemical reactions. We describe a novel mechanism for locking the computation of biochemical modules -- analogous to handshaking mechanisms in asynchronous circuit design. With locking, our method synthesizes robust computation that is nearly rate independent, requiring at most two speeds ("fast" and "slow").

We present a general compilation strategy for synthesizing biochemical reactions that perform sequential arithmetic computation on protein quantities, analogous to register-based computations in digital systems. This algorithm is implemented as a compiler called VERB (Verilog Elements for Register-Based Biochemistry). From a Verilog file, VERB generates biochemical reactions that produce output quantities as a function of input quantities, performing operations such as addition, subtraction, and multiplication. Sequential operations are implemented by transferring quantities between protein types, based on a clocking mechanism. We demonstrate the algorithm on the synthesis of simple circuits. The designs are validated through transient stochastic simulation of the chemical kinetics.

