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An improved cellular automata model of enzyme kinetics based on genetic algorithm

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HIGHLIGHTS

- Cellular automata are used to model enzymatic reaction kinetics on a 2D torus.
- Fine-tuning the probabilities of reactions and movement is challenging.
- A multi-objective genetic algorithm obtains the probabilities in feasible time.
- A validation study indicates the applicability of the cellular automata model.

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ABSTRACT

Based on a generalized Cellular Automata (CA) model which has the flexibility of reaction interactions between all possible two-agent combinations on both reactant and product side, in previous studies by the authors, probabilistic reaction events were combined in a multiplicative order and an exploratory study of the variability analysis was performed. However it was found that the probabilistic parameter values are extremely sensitive to the final model output. As such, NSGA-II based on a Multi-objective Genetic Algorithm (MOGA) is used in this study to obtain optimum sets of these probability parameter values within a feasible computational time. For each generation of the MOGA, the probability rules parameter values are updated (improved) based on the objective functions. Finally, a validation study is performed to indicate the applicability of the CA model to represent specific enzymatic reactions when coupled with the multi-objective optimization algorithm.

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1. Introduction

Natural processes from population dynamics (Soarse-Filho et al., 2002; Lauf et al., 2012) to fluid dynamics (Somers, 1993; Chopard and Masselot, 1999), from biofilm growth (Pizarro et al., 2005; Fagerlind et al., 2012) to tumor growth (Kansal et al., 2002; Alemani et al., 2012) all occur in discrete space and time so that a probabilistic nature of representation is needed to understand precisely the dynamics of such processes. Stochasticity is an intrinsic property of any natural system, more specifically at a microscopic scale (Deutsch and Dormann, 2005). Several studies have observed occurrence of stochastic fluctuations in living systems (Abkowitz et al., 1996; Meng et al., 2004; Wu and Higgs 2012). Most biological events are triggered as network of chemical reactions which pose larger challenges due to computational representation and requirements (Kier et al., 2005). The noise of one event can alter the outcomes of the succeeding event and simultaneously affect the final outcome (Blake et al., 2003). When concentrations of species in an enzymatic reaction are high, the reaction can be mathematically modeled using deterministic approaches, like Michaelis–Menten kinetics. But, at lower concentrations, it is advisable to use modeling tools which have some stochastic property within the rule structure. Such models shall evolve to show certain global properties and are also unpredictable until the event actually occurs to completion. Thus an accurate mathematical model can help clarify the roles of individual components within a process and generate specific, testable hypotheses and predictions (Apte et al., 2008). Cellular Automata (CA) is one such stochastic approach in which a natural event can be successfully simulated. Using probabilistic rule application, CA can capture the properties that evolve from the stochastic nature present in microscopic scale in natural systems assuming both time and space to be discrete. In our earlier studies (Kar et al., 2010; Dutta et al., 2011), a generalized two-dimensional (2D) interaction model was created to represent two-agent kinetic

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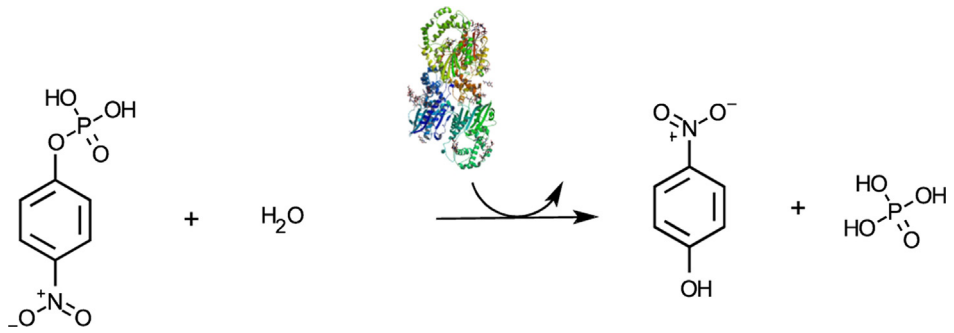

Fig. 1. Molecular reaction structure of P-nitrophenylphosphate and water reacting in presence of acid phosphatase enzyme to form P-nitrophenols and phosphoric acid.

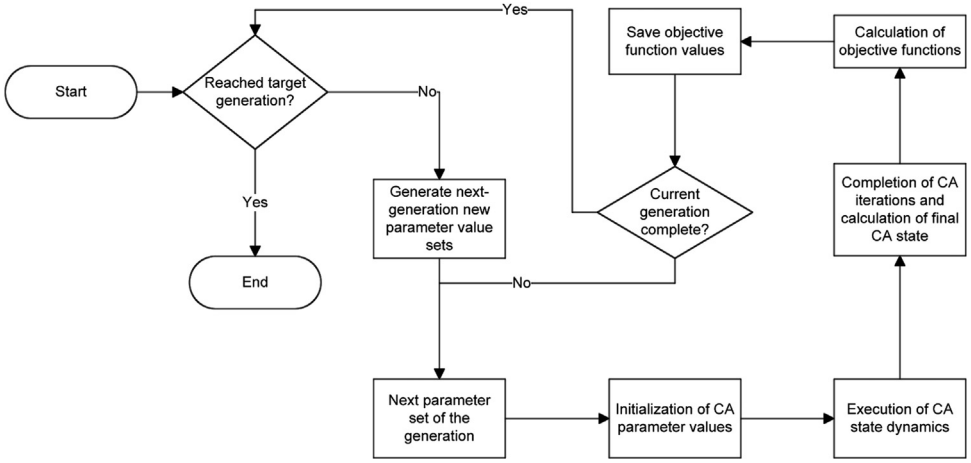

Fig. 2. A simplified flowchart for the Genetic Algorithm (GA) coupled with Cellular Automata (CA) model system implemented in this study.

interactions of an enzymatic reaction. From the sensitivity analysis study of Dutta et al. (submitted for publication) based on several input parameters, it was realized that there cannot be any specific mathematical relationship between the input parameters and the model output. It is also not feasible to define a strict mathematical relation between the chemical kinetic constants and the CA model parameters as the model is an abstract representation of a realistic reaction. This makes repeated trial-and-error interactions of random parameter values the only way to capture specifically the resulting state of a model system. When there are multiple objective functions of a model to be satisfied, useful combinations of parameter values become rarer in the infinite pool of solutions (Konak et al., 2006). If the problem is NP-hard, finding the optimal solutions by exhaustive search may be too costly or practically impossible. Genetic Algorithm (GA) is a popular meta-heuristic tool frequently used for solving optimization problems (Holland, 1975).

Acid phosphatases (APs) are a family of enzymes that are widespread in nature, that non-specifically catalyze the hydrolysis of orthophosphate monoesters to produce inorganic phosphate and can be found in many animal and plant species (Bull et al., 2002). These enzymes are competitively inhibited by inorganic phosphate (Odds and Hierholzer, 1973). Alvarez (1961) was the first to characterize the kinetics and mechanism of the hydrolysis of phosphoric acid esters by potato acid phosphatase. He found that the enzymatic activity depended on three ionizable groups. Based on these findings, a reaction mechanism was proposed (see Fig. 1). After the nucleophilic attack of one of the ionizable groups on the phosphorous atom of p-nitrophenyl phosphate, the enzyme–substrate complex is formed. After releasing p-nitrophenol, the enzyme–phosphate complex gets hydrolyzed, resulting in the formation of inorganic phosphate and recycled acid phosphatase.

$$S + E \rightleftharpoons ES \rightleftharpoons EP \rightleftharpoons E + P$$
$$E + I \rightleftharpoons EI$$
$$S + W \rightleftharpoons SW$$
$$W + W \rightleftharpoons WW$$

Fig. 3. Reaction steps for the pseudo-artificial competitive enzyme inhibition reaction representation in the CA model. The symbols indicate Substrate (S), Enzyme (E), Product (P), Inhibitor (I) and Water (W).

In this study, an NSGA-II based Multi-Objective Genetic Algorithm (MOGA) approach is implemented for a stepwise improvement of the CA model. Finally, this approach is validated using the enzymatic hydrolysis of p-nitrophenyl phosphate by acid phosphatase with inhibition reaction.

2. Cellular automata model

In accordance with our previous studies, the CA model is framed on a two-dimensional grid. Extended von-Neumann neighborhoods are considered for application of local rules. To represent the boundary as virtually infinite, periodic boundary condition are implemented. This facilitates the boundary molecules to interact with the molecules present in the boundary of opposite direction, as on the surface of toroid. Also, such a neighborhood implementation facilitates the application of probability rules in a combinatorial fashion without any exception due to edge restrictions (Dutta et al., 2011). Each of the reaction compound molecules is considered as a single agent in the model. Each cross section of the grid represents a single lattice

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