Abstract

An evolvable artificial cell is a chemical or biological complex system assembled in laboratory. The system is rationally designed to show life-like properties. In order to achieve an optimal design for the emergence of minimal life, a high dimensional space of possible experimental combinations can be explored. A machine learning approach (Evo-DoE) could be applied to explore this experimental space and define optimal interactions according to a specific fitness function. Herein an implementation of an evolutionary design of experiments to optimize chemical and biochemical systems based on a machine learning process is presented. The optimization proceeds over generations of experiments in iterative loop until optimal compositions are discovered. The fitness function is experimentally measured every time the loop is closed. Two examples of complex systems, namely a liposomal drug formulation and an in vitro cell-free expression system are presented as examples of optimization of molecular interactions in high dimensional space of compositions [1,4]. These represent, for instance, the modules or subsystems that could be optimized by “mixing the protocols” to achieve the high level of sophistication that artificial cells requires. In addition a replication cycle of oil in water emulsions is presented. They represent the container for the artificial cells.

Keywords: Machine learning; experimental design; drug design; cell-free expression system; artificial cells; evolutionary programming

1. Introduction

The optimization of a liposomal drug formulation and the protein synthesis of a cell-free expression system based on a machine learning process (Evo-DoE) are demonstrations that complex systems can be engineered to obtain targeted properties. The experiments are conducted in iterative cycle, exploiting a neural network type algorithm, and the fitness function value is calculated every time the loop is closed. To start the optimization process, the experimental space is sparsely sampled with a random selection of experiments. Successively the models of the desired response from the experimental data are built followed by sparse sampling of the experimental space, and then the process repeats [1].

2. Optimization experiments

The sections bellows describe to optimization experiments conducted using highthrough-put screening methodology.
2.1. Optimization of lipids membrane composition

A lipid vesicle as the container for the artificial cell mimics some properties of the biological membranes. The minimal cell may have a great potential of technological innovation [2]. In this section the results of optimization of a liposomal drug formulation with a machine learning process are presented. The system was quickly optimized after individually testing 450 individual recipes from a space hundred of times larger. The ability of intercalating an amphiphilic drug (Amphotericin B) into the bilayers of phospholipids vesicles was measured as output to build the fitness function. The experiments were conducted in high-throughput screening and the fitness function values were measured with a spectrophotometric assay, which measured directly the amount of drug complexed in the lipid mixture.

2.2. Optimization of Cell-free expression system for in vitro protein synthesis

The cell-free expression system is a commercial E. Coli cell extract with defined sets of components used to express proteins inside the aqueous core of vesicles from DNA [3]. The fitness function was defined as the maximum in fluorescence measured at different time intervals during the expression of the green fluorescence protein (GFP). As a result a 300% improvement in protein yield was measured, compared to a benchmark recipe, was measured. Evo-DoE indentified the optimal ingredient mixture in the designed experimental space [4].

3. Life-cycles of evolvable artificial cells

The establishment of a life-cycle for artificial cells is important for extending the life time of the systems and measure their evolution over time.

3.1. Replication cycles of the artificial systems

The components are compartmentalized in order to achieve the emergence of minimal life [5]. The artificial entities could be programmed to show evolution and thereby selection could be applied during their life cycle [6]. The compartments can be based on lipid vesicles (Bioreactor) or on oil in water emulsions (Oil droplet) [7,8]. The up-take of resources needed for the metabolism and evolution can be obtained exploiting compartments dynamics, in particular fusion and fission (data not shown). The first mechanism can be used for the turnover of the building blocks constituting the complex system and the fission can be exploited to apply selection. The physical-chemical instabilities of the oil droplets are exploited to induce fusion and fission. The replication cycle is iterative, and the system dynamic properties are controlled in the laboratory.

4. ICT and artificial cells

The design and exploitation of an ICT interface for optimizing a complex system may help masses to familiarize with the interdisciplinarity beyond the modern science, which is based on technology and innovation.

4.1. The Cell-Scope interface

Two examples of experimental chemical systems optimization based on machine learning algorithms are presented. The high-throughput experiments were conducted with a robotic workstation for liquid handling. The predictive algorithm (Evo-DoE) indicated those combinations explored during the screening, thus improving the fitness functions out-put over generations of experiments. For example, this could be done inexpensively by engineering an ICT interface as a cell-scope [9]. It would provide a mobile phone platform, which integrated with imaging analysis software and learning algorithms running elsewhere, which would analyze and control the optimization of the experimental system. The remote control can be done through an automatic process, where robotic workstations are used. The oil droplets or vesicles can be used for the co-localization of the artificial cells components and since the replication-cycle is iterative; evolution could be a parameter that is measured over time.
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