Oral Presentation 6

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"Temperature-based inputs for molecular reservoir computers" Nicolas Lobato-Dauzier (Institute of Industrial Science, The University of Tokyo)

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"Exploring Self-Assembling Behaviors in a Swarm of Bio-micro-robots using Surrogate-Assisted MAP-Elites"

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<u>O3–07</u>

"Prediction of Binding of Existing Drugs to SARS-CoV-2 Main Protease Using Molecular Dynamics and Fragment Molecular Orbital Calculations" Yuma Handa

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Temperature-based inputs for molecular reservoir computers

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Keywords: DNA nanotechnology, Reservoir computing, Predator-prey oscillator, in-vitro DNA computing

We design and implement a temperature-based input mechanism for molecular reservoir computing. Reservoir computing uses a complex but fixed network which is treated as black box combined to a final readout layer which is trained to perform the desired task. This approach of exploiting the complex dynamics of the system rather than overcoming them through rational design allows us to design smaller systems, increasing the practicality of in-vitro experiments. Previously proposed molecular approaches rely on a chemically open system, which prevents several potential applications like implementing a controller for molecular robots [1]. Using temperature allows us to interact with the system while keeping it chemically closed.

The input layer of the network corresponds to the impact temperature has on the dynamics of the system. As reservoir, we use the predator-prey system from [2], a simple, but robust molecular oscillator. We tune experimentally that system to switch between oscillatory and non-oscillatory behavior based on the temperature. The state of the system is monitored in real-time by fluorescence. The read-out layer is implemented by a neural network [3]. The full system is summarized in Fig. 1.



Figure 1:

Reservoir computing scheme: temperature is set externally, impacting the behavior of the reservoir made of a predator-prey oscillator. A sliding window of fluorescence, capturing the state of the system, is fed into the output layer of the reservoir.

We first characterize the behavior of the system, provide a range of working conditions suitable for its role as reservoir and finally show that it can reliably transmit information by training the system to recover its input signal, a standard benchmark for Reservoir Computing. We reach an average of 87% accuracy for a single layer and 91% for two layers, showing the potential of such reservoir [4].

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Exploring Self-Assembling Behaviors in a Swarm of Biomicro-robots using Surrogate-Assisted MAP-Elites

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Keywords: Bio-micro-robots, swarm robotics, molecular programming, evolutionary robotics, surrogate models, quality-diversity algorithms, MAP-Elites

Swarms of molecular robots are a promising approach to create specific shapes at the microscopic scale through self-assembly [1]. However, controlling their behavior is a challenging problem as it involves complex non-linear dynamics and high experimental variability. Hand-crafting a molecular controller will often be time-consuming and give sub-optimal results. Optimization methods, like the Bioneat [1] algorithm, were previously used to partially overcome these difficulties, but they still had to cope with deceptive search spaces and computationally expensive simulations.

Here, we describe a novel approach to automatically design the chemical reaction network controllers of a large swarm (>>1000) of micro-robots, by using MAP-Elites [2], an optimization algorithm that searches for both high-performing and diverse solutions, and CMA-ES [3], a state-of-the art optimization algorithm. We apply them to a molecular robotic framework we recently introduced [1,5] that allows sensing, signaling and self-assembly at the micro-scale and show that MAP-Elites outperforms previous approaches. We propose a surrogate model of micro-robots physics and chemical reaction dynamics to reduce the computational costs of simulations. We show that this methodology is capable of optimizing controllers with similar accuracy as when using a full-fledged realistic model, with half the computational budget.



Figure 1: The micro-robots are microscopic agarose beads functionalized with CRNs that serve as robotic controllers [4]. They move through Brownian motion, can interact with their environment and aggregate into self-assembled structures. CRNs are optimized by MAP-Elites so that the swarm self-aggregates into a T-shaped pattern.

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Prediction of Binding of Existing Drugs to SARS-CoV-2 Main Protease Using Molecular Dynamics and Fragment Molecular Orbital Calculations

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Keywords: SARS-CoV-2 Main protease, Fragment molecular orbital method, Molecular dynamics

COVID-19 has become a global concern and the development of drugs to treat this disease is being urgently pursued. HIV-1 protease inhibitors such as Nelfinavir and Lopinavir have been proposed as potential inhibitors of the main protease (Mpro), which is a protein produced by the SARS-CoV-2 virus. However, the crystal structures of these inhibitors in complex with Mpro have not yet been determined. In this study, we have combined docking, molecular dynamics (MD) and fragment molecular orbital (FMO) calculations to predict the binding structures and their properties of Mpro to several inhibitors.

First, 30 docking poses were predicted by MOE using AMBER10:EHT force field. Then, FMO-MP2(PR)/6-31G* calculations using ABINIT-MP [1,2] were performed to narrow down the candidate structures to 4-6. These docking poses were used as the initial structures for 100 ns MD simulations, and 100 structures were extracted for each of the obtained trajectories. For all the extracted structures, FMO calculations were performed and statistical interaction analysis of the results was performed.

The results showed that the rankings using FMO interaction energies for the initial docking structures and those for the post-MD simulated structures were different in order. Therefore, predictions based on MD trajectories rather than docking alone were considered to be important. Furthermore, in the interaction between Mpro and the inhibitor, not only the electrostatic interaction with charged residues, but also dispersion interactions such as CH/ π interaction between hydrophobic functional groups were found to be strongly involved in the binding. In addition, Nelfinavir was found to bind more strongly to Mpro than Lopinavir. This was consistent with the results of the EC₅₀ [3].

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