Temperature-based inputs for molecular reservoir computers

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Abstract

We design and implement a temperature-based input mechanism for molecular reservoir computing. Using temperature allows us to interact with the system while keeping it chemically closed, a crucial step to use the reservoir computing approach with standard laboratory equipment. We implement the reservoir with a robust molecular oscillator, subjecting it to sudden temperature variations and monitoring its response with fluorescent reporters. We then train *in-silico* neural networks on the fluorescence traces to predict the inputted temperature profiles. We reach an average of 87% accuracy for a single layer and 91% for two layers, showing the potential of such reservoir.

Introduction

Molecular programming approaches have allowed researcher to harness the potential of chemical systems to explore the emergence of complex behaviors *in-vitro*. Those approaches provide programming tools to design chemical reaction networks in a systematic way, with applications ranging from programmable reaction-diffusion systems (Padirac et al., 2013; Abe et al., 2019) to the implementation of artificial neural networks (Qian et al., 2011; Cherry and Qian, 2018) and swarming behaviors (Zadorin et al., 2017; Aubert-Kato et al., 2017; Keya et al., 2018).

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. Reservoir Computing is an efficient approach for that purpose (Yahiro et al., 2018). That approach (Jaeger, 2001) was originally designed to train recurrent neural networks despite the non-linearities inherent to those systems. Their intermediate layers (the reservoir) are randomly initialized and do not update with training. Only the last layer (called read-out) is updated, resulting in a very fast process.

Reservoir Computing has been applied to other types of black-box non-linear systems (Tanaka et al., 2019), including molecular programming systems (Goudarzi et al., 2013). However, proposed molecular approaches rely on a chemically open system, which prevents several potential applications, *e.g.*, exploring the behavioral landscape of a molecular system (Genot et al., 2016) or implementing a controller for molecular robots (Sato et al., 2017).

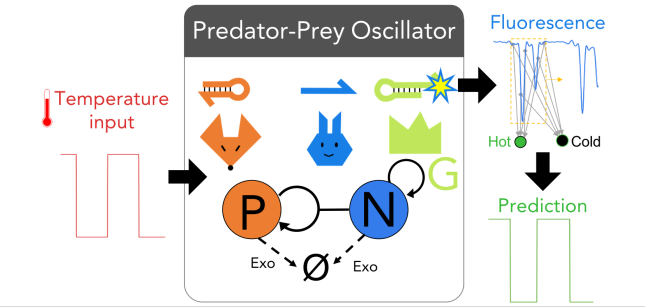

Figure 1: Reservoir computing scheme: temperature is set externally, impacting the behavior of the reservoir made of a predator-prey oscillator. As sliding window of fluorescence, capturing the state of the system, is fed into the output layer of the reservoir.

Here, we solve that issue by introducing an input scheme relying on the interface of real-time PCR machines, a very common piece of equipment. We use temperature as input: 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 Rondelez and Fujii (Fujii and Rondelez, 2013), 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. The full system is summarized in Fig. 1.

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.

Methods

Molecular system: the predator-prey oscillator relies on the interactions between DNA molecules and enzymes to

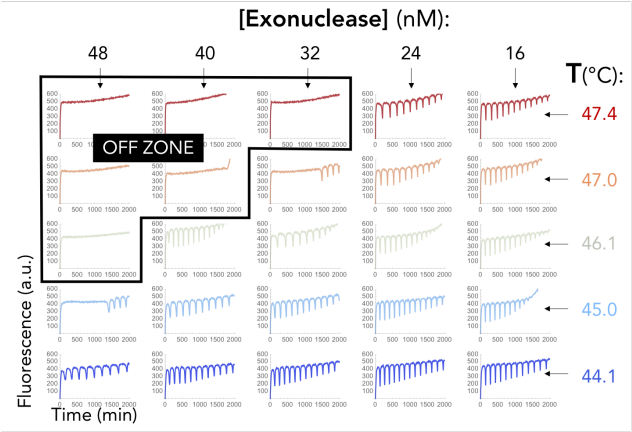

Figure 2: Behavior of the predator-prey oscillator according to temperature and exonuclease concentration.

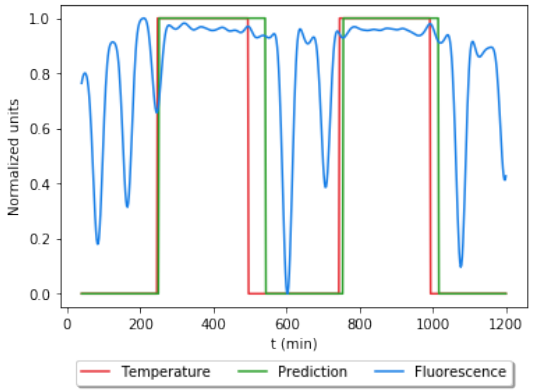

Figure 3: Normalized temperature, prediction and fluorescence over time from the re-evaluation.

dynamically produce and degrade DNA signal. The prey molecule catalyses its own production by the "grass" DNA strands and enzymes. It is consumed by the predator species to produce more predators. Finally, both preys and predators are degraded over time by the exonuclease enzyme (Fig. 1).

Temperature input: We use the built-in temperature variation function of a BioRad CFX96 real-time PCR machine. Enzymatic activity is enhanced at different temperature ranges, giving higher degradation or higher production. Similarly, DNA double-strand stability decreases with temperature, thus impacting production. Thus, the behavior of the system is highly dependent on the temperature.

Fluorescence output: The system is monitored by one fluorescent signal, corresponding to the amount of double-stranded "grass" (correlated to the concentration of prey). It is smoothed with a second order Butterworth filter. Background fluorescence is impacted by the temperature of the system. As the underlying concentration signal is continuous, we shift the fluorescence signal to recover a continuous function; the signal is then normalized between 0 and 1.

Reservoir performance: We train a neural network (with Keras (Chollet et al., 2015)) to predict the temperature from the fluorescence signal. We consider two setups. First, a single layer perceptron with two outputs using softmax, predicting either high or low temperature levels, taking the past 40 normalized fluorescence levels to capture oscillations. That design is chosen to be equivalent to the standard output layer of a reservoir. Second, a multilayer perceptron (MLP) with an additional hidden layer of 10 neurons, to check if better performance can be achieved with more expressivity.

Results

The behavior of the predator-prey oscillator in function of the temperature and exonuclease concentration is shown in Fig. 2. The system can sharply transition from the oscillatory state to the stable state for exonuclease concentrations above 32nM. Next, we selected a concentration of 48nM and made the system switch back and forth between both states by alternating low and high temperatures (Fig. 3).

We performed two repeats of the experiment: One to train the neural network predicting the temperature from the fluorescence, and one to evaluate its performance. Training was run 100 times, with an average accuracy of 87.4 ± 1.1 for the perceptron and $91.7 \pm 0.1\%$ for the MLP. Performance evaluation was done on an experimental replicate of the predator-prey system, with an average accuracy of 90.0 ± 5.0 for the perceptron and $91.6 \pm 0.5\%$ for the MLP. The normalized fluorescence and the temperature predicted by a typical MLP are shown in Fig. 3. The excellent performance on an independent experiment shows the robustness of the approach.

The system can accurately predict the transition toward high temperatures, but displays a delay in the transition toward low temperatures. At high temperature, the increase in exonuclease activity causes the concentration of prey to decrease exponentially, providing a sharp transition. When switching to a low temperature, the system first enters a transient phase where the prey species has to first load the autocatalytic templates before the concentration starts increasing. During that phase, fluorescence remains constant, preventing the system from accurately predicting the shift.

Conclusion

We showed that we could implement a simple molecular reservoir *in vitro* while keeping the system chemically closed. Moreover, interactions with the system rely only on standard laboratory equipment, and can allow feedback loops through the computer controlling said equipment.

While the current setup only has a binary input, additional predator-prey oscillators can be added to the system (Fujii and Rondelez, 2013), providing multiple temperature thresholds, or other types of signals, such as UV light (Asanuma et al., 2007), could provide additional inputs.

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References

Abe, K., Kawamata, I., Shin-ichiro, M. N., and Murata, S. (2019). Programmable reactions and diffusion using DNA for pattern formation in hydrogel medium. *Molecular Systems Design & Engineering*, 4(3):639–643.

Asanuma, H., Liang, X., Nishioka, H., Matsunaga, D., Liu, M., and Komiyama, M. (2007). Synthesis of azobenzene-tethered DNA for reversible photo-regulation of DNA functions: hybridization and transcription. *Nature protocols*, 2(1):203.

Aubert-Kato, N., Fosseprez, C., Gines, G., Kawamata, I., Dinh, H., Cazenille, L., Estevez-Torres, A., Hagiya, M., Rondelez, Y., and Bredeche, N. (2017). Evolutionary optimization of self-assembly in a swarm of bio-micro-robots. In *Proceedings of the Genetic and Evolutionary Computation Conference*, pages 59–66.

Cherry, K. M. and Qian, L. (2018). Scaling up molecular pattern recognition with DNA-based winner-take-all neural networks. *Nature*, 559(7714):370–376.

Chollet, F. et al. (2015). Keras. `https://keras.io`.

Fujii, T. and Rondelez, Y. (2013). Predator–prey molecular ecosystems. *ACS nano*, 7(1):27–34.

Genot, A., Baccouche, A., Sieskind, R., Aubert-Kato, N., Bredeche, N., Bartolo, J., Taly, V., Fujii, T., and Rondelez, Y. (2016). High-resolution mapping of bifurcations in nonlinear biochemical circuits. *Nature Chemistry*, pages 760–767.

Goudarzi, A., Lakin, M. R., and Stefanovic, D. (2013). DNA reservoir computing: a novel molecular computing approach. In *International Workshop on DNA-Based Computers*, pages 76–89. Springer.

Jaeger, H. (2001). The "echo state" approach to analysing and training recurrent neural networks-with an erratum note. *Bonn, Germany: German National Research Center for Information Technology GMD Technical Report*, 148(34):13.

Keya, J. J., Suzuki, R., Kabir, A. M. R., Inoue, D., Asanuma, H., Sada, K., Hess, H., Kuzuya, A., and Kakugo, A. (2018). DNA-assisted swarm control in a biomolecular motor system. *Nature communications*, 9(1):1–8.

Padirac, A., Fujii, T., Estevez-Torres, A., and Rondelez, Y. (2013). Spatial waves in synthetic biochemical networks. *Journal of the American Chemical Society*, 135(39):14586–14592.

Qian, L., Winfree, E., and Bruck, J. (2011). Neural network computation with DNA strand displacement cascades. *Nature*, 475(7356):368–372.

Sato, Y., Hiratsuka, Y., Kawamata, I., Murata, S., and Nomura, S.-i. M. (2017). Micrometer-sized molecular robot changes its shape in response to signal molecules. *Science Robotics*, 2(4).

Tanaka, G., Yamane, T., Héroux, J. B., Nakane, R., Kanazawa, N., Takeda, S., Numata, H., Nakano, D., and Hirose, A. (2019). Recent advances in physical reservoir computing: A review. *Neural Networks*.

Yahiro, W., Aubert-Kato, N., and Hagiya, M. (2018). A reservoir computing approach for molecular computing. In *Artificial Life Conference Proceedings*, pages 31–38. MIT Press.

Zadorin, A. S., Rondelez, Y., Gines, G., Dilhas, V., Urtel, G., Zambrano, A., Galas, J.-C., and Estevez-Torres, A. (2017). Synthesis and materialization of a reaction–diffusion french flag pattern. *Nature chemistry*, 9(10):990.