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Predator prey molecular landscapes

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Abstract

This paper describes the use of molecular programming techniques to build synthetic *in vitro* and spatially distributed reactions networks with tailored topologies. The basic workflow is to use synthetic DNA strands to encode the topologies of molecular interactions of the reaction network. The actual dynamic of the system is provided by enzymatic reactions controlled and templated by these DNA strands. Here we focus on the implementation of a molecular predator-prey ecosystem. We thus create two autocatalytic DNA amplifications reactions and connect them through predation – the second DNA-species consumes the first one to fuel its growth. We also ensure that these species have a limited lifetime in the test tube. We are therefore able to detect sustained oscillations of the two molecular species, as predicted and observed for real ecosystems. This is the first time that predator prey oscillations are observed in a chemical system. We further expand the analogy between chemical and animal networks by introducing additional interactions such as symbiosis, the mutually beneficial interaction between two species. Interestingly, competition also arises quite naturally from the physical substrate that is used in the modeling process and displays remarkable dynamic consequences such as synchronization or chaos. Finally we report the construction of spatially distributed chemical ecosystems, and the observation of their spatiotemporal behaviors, in particular traveling and spirals dual waves of molecular hunts.

Introduction

Molecular programming techniques based on synthetic DNA are currently opening unprecedented opportunities for the exploration of molecular informational systems. Because DNA allows easy encoding of molecular interactions and possesses a rich biochemistry, it is possible to reproduce, in test tubes, some of the most fundamental dynamic motifs of biological regulation circuits, like oscillators, bistable switches, etc. (Montagne et al. 2011; Kim & Winfree 2011). This synthetic approach provides a unique opportunity to i) better understand the structure/function relationships at the level of biological circuits; ii) use such molecular devices (computers, controllers, memories, filters …) into informational chemical systems; and iii) design artificial molecular systems integrating more and more life-like features.

We recently went one step further by demonstrating that molecular programmers need not restrict their inspiration to cellular circuits. Other networks, such as those formed by interdependent species (ecosystems) can also be reproduced using molecular tools. Our demonstration is based on the predator-prey example, the basic motif of many ecosystems. This particular motif is well known because, somewhat disconcertingly, the simple interaction between a prey and its predator typically leads to sustained oscillations of both populations (Lotka 1920).

Results and discussion

We have encoded the topology of PP interactions in a DNA-based molecular program. The information concerning the topology of the network is genetically stored in a 20-base-long ssDNA, G (for grass), which direct the growth of complementary preys (N) as follows: N hybridizes to the 3' end of G, to form the partial duplex G:N. This duplex is extended by a polymerase and subsequently nicked by a specific nicking enzyme yielding, upon de-hybridization, two copies of N and an intact template G.

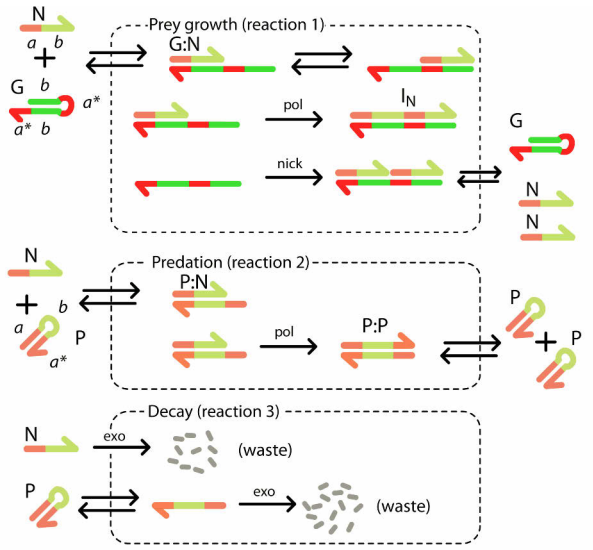

Figure 1: Molecular predator-prey network. N, P and G denote the prey, the predator and the template respectively. Harpoon-ended arrows denote DNA strands. Double-sided arrows correspond to DNA hybridization/dehybridization reactions, whereas single-sided arrows indicate irreversible enzymatic transformations. Complementary DNA domains have the same colour. Strands have different hues, light and dark, indicating if they can or cannot be degraded by the exonuclease, respectively. Pol, nick and exo stand for bst DNA polymerase, Nb.BsmI nicking enzyme and ttRecJ exonuclease.

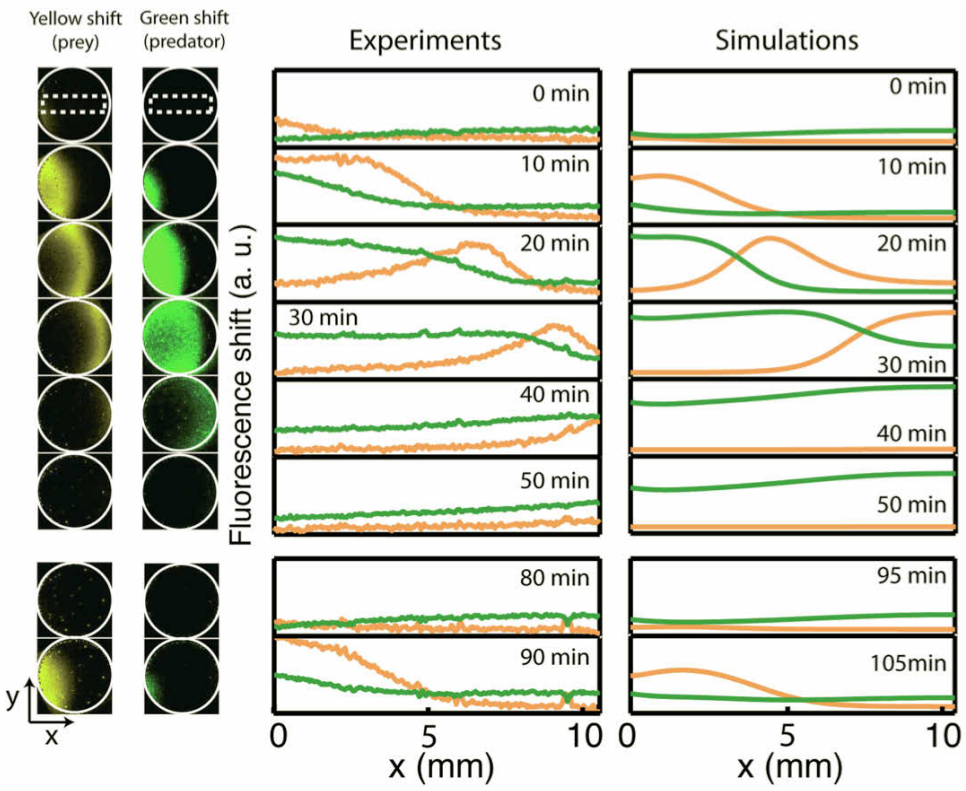

Figure 2: Waves of prey (yellow) and predators (green) in a 2D predator-prey molecular experiment. Left: Time-lapse images of the fluorescent shift in the corresponding fluorescent channels, taken every 10 min in a circular reactor 11 mm in diameter and 200 µm thick. The borders of the reactor are highlighted in white. Middle: profiles along x of the yellow (prey) and green (predator) fluorescent shifts. Right: 1D reaction-diffusion simulations of the normalized prey and predator concentrations.

Predator P is a 14 bases long palindromic ssDNA. During predation N hybridizes over P and the polymerase extends this adduct to form a double strand P:P. Upon de-hybridization, P:P yields two copies of P. Both active species N and P are degraded to unreactive dNMPs by a 5'->3', processive, ssDNA-specific exonuclease. G is not digested because it bears three protective phosphorothioate modifications in 5'.

We have then confirmed the accuracy of our experimental model by observing sustained chemical cycles in a test tube maintained at a constant temperature. The period is from one to several hours and the oscillations of the two species can be monitored in two fluorescent channels. Tens of cycles can be obtained even in the absence of any exchange of matter. This demonstrates the transposition of an agent-based non-trivial network (and its dynamic behavior) at the molecular scale.

We have further extended the approach by adding additional ecologically-relevant interactions into the molecular ecosystem: competition for shared molecular resources, such as enzymatic catalysts can lead to complex, possibly chaotic behaviors, while symbiosis at the prey level tend to stabilize the steady coexistence of the species (Fujii & Rondelez 2013). We have also integrated a spatial component into the system by moving from well-mixed to reaction-diffusion systems. This has allowed the first observation of synthetic predator-prey "waves of pursuit and evasion" (Murray 2004) under the microscope (Padirac et al. 2013).

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