Evolutionary construction of synthetic biochemical systems

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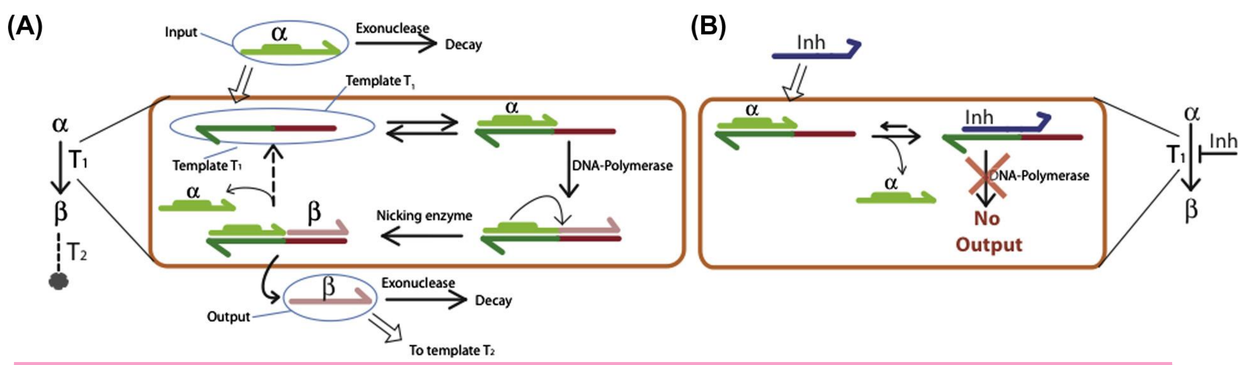
1. Introduction

■ **Goal**: use Evolutionary Computations to design analog dynamic biochemical systems, starting from the desired behavior to the actual sequence and concentration of each chemical compound. Apply to cases where there is no clues about the relevant network structure.

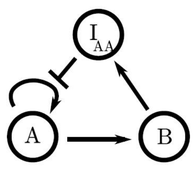
- Generally, *trial-and-error* procedures are applied in parallel with the use of mathematical models → not efficient for optimization and implementation of complex systems.
- The DNA Toolbox [1] – an experimental molecular programming scheme coupled with quantitative mathematical models – could theoretically permit the automation of the full design of biochemical circuits.
- This work uses the combination of an effective technique called ERNe [2] and Differential Evolution to discover feasible and robust solutions to a challenging information processing problem: mathematical calculations – which could be used as filters or integrators in molecular circuits.
- This work also tests the possibility of completely automated function-to-test tube design process.

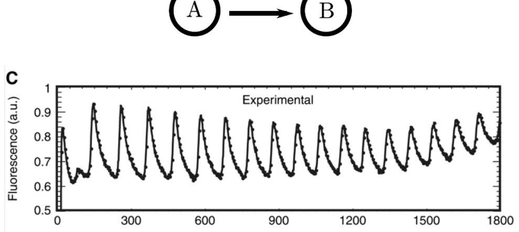
2. Models and Methods

2.1 Building molecular networks: the PEN DNA Toolbox



(A) Activation link between two species (B) Inhibition of activation links



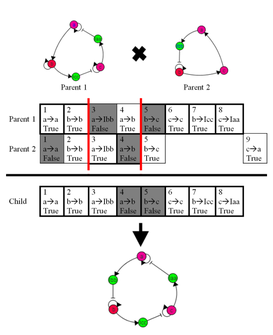


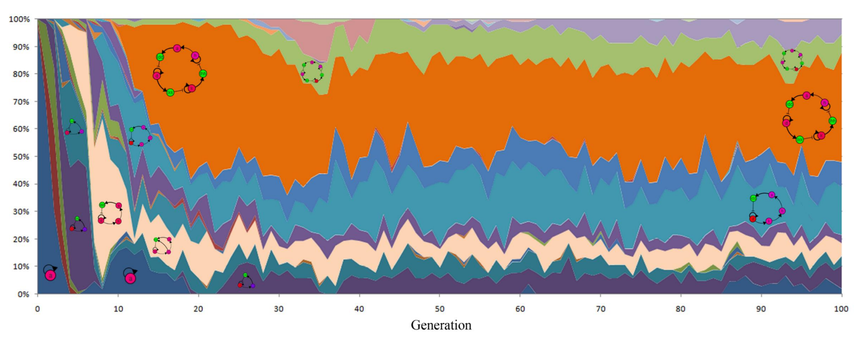
Oscillator's graphical representation and its equivalent equations [1]

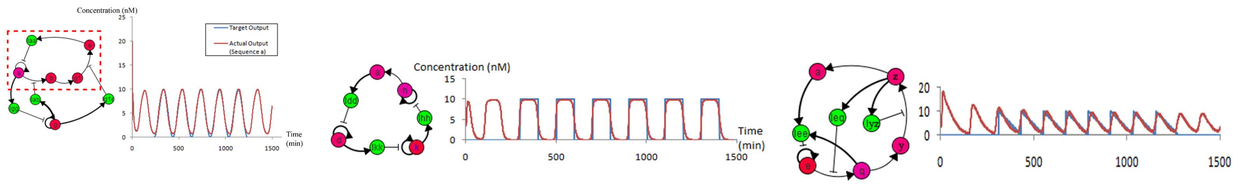
2.2 Searching through topology/parameter space efficiently – ERNe Algorithm

An efficient derivative of the NeuroEvolution of Augmenting Topologies (NEAT) algorithm [3] directed at the evolution of biochemical systems or molecular programs.

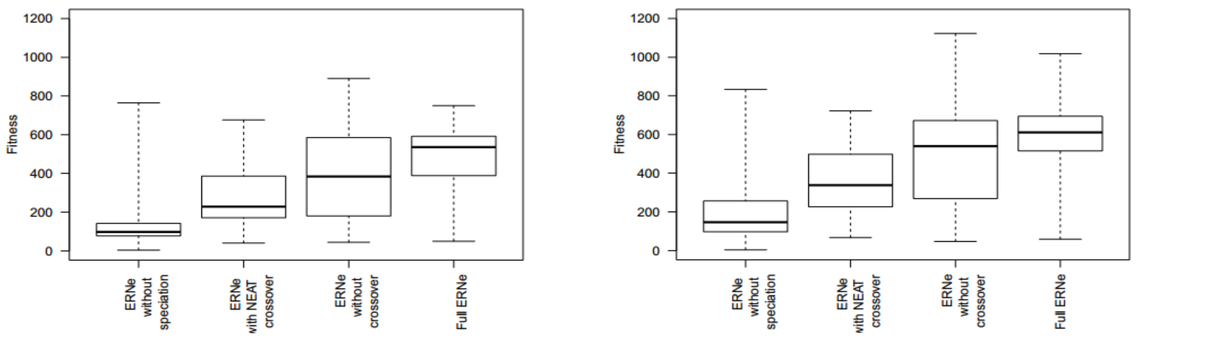
- meaningful crossovers between two chemical reaction networks of different topologies.
- preserving topological innovations through speciation.







ERNe crossover, speciation, and various types of discovered oscillations

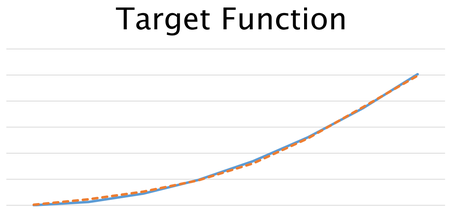


ERNe performance. Left: at generation 50, Right: at generation 100

2.3 Construction of square function calculator

Information Encoding:

- Input: Input sequence's initial concentration.
- Output: Output sequence's concentration at stable state.



- Square function
  $$output \propto input^2$$
- Input range: from 1μM to 50μM.
- Fitness measured by MSE.

Topologies discovered by ERNe

The discovered topologies clearly shows that there must be an autocatalysis inhibiting the activation from input node to output node.

Minimal topologies obtained by manual pruning

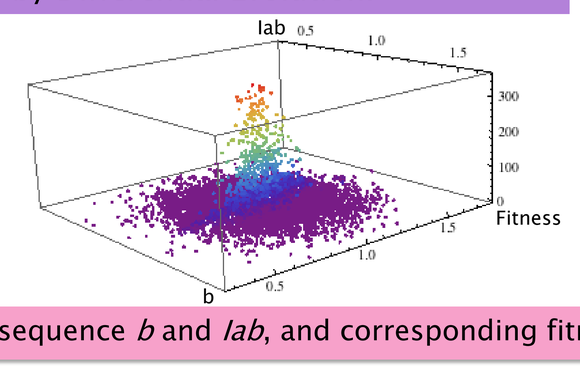
Pruning process:
- Remove irrelevant parts.
- Simplify indirect connections.

Parameters optimized by Differential Evolution

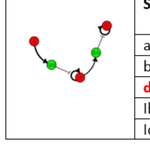
Usually, after pruning, fitness reduces significantly. We keep the topologies, and have their parameters optimized by Differential Evolution.

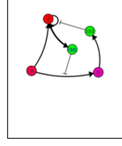
Robustness Evaluation

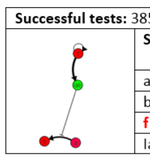
5,000 tests: multiplicative noise is given to sequences' kinetic parameters.



Plot of multiplicative noise given to sequence *b* and *Iab*, and corresponding fitness

Successful tests: 12 (0.24%)		
	Sequence	Acceptable standard deviation
	a	±20.08%
	b	±14.93%
	d	**±14.49%**
	Ibb	±19.54%
	Idd	±15.06%

Successful tests: 2137 (42.74%)		
	Sequence	Acceptable standard deviation
	a	**±11.21%**
	b	±18.44%
	d	±16.73%
	Iab	±16.08%
	Idd	±20.18%

Successful tests: 385 (7.7%)		
	Sequence	Acceptable standard deviation
	a	±13.72%
	b	±14.96%
	f	**±4.21%**
	Iab	±16.10%

Successful tests: 2067 (41.34%)		
	Sequence	Acceptable standard deviation
	a	±19.56%
	b	±16.30%
	d	±19.43%
	Iab	**±13.85%**

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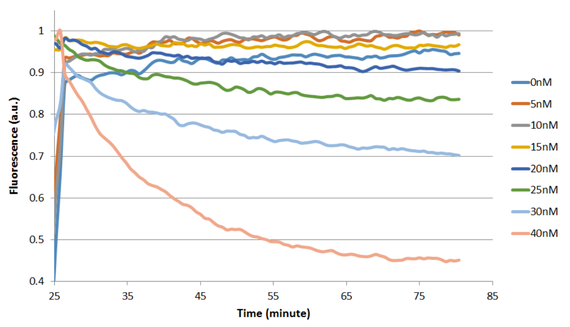
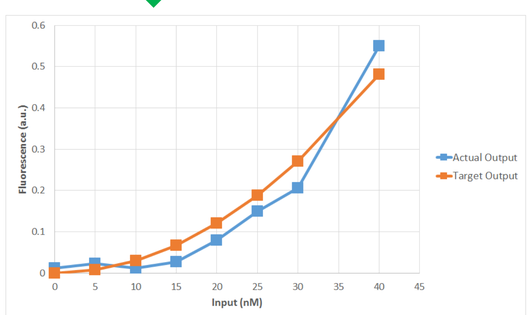
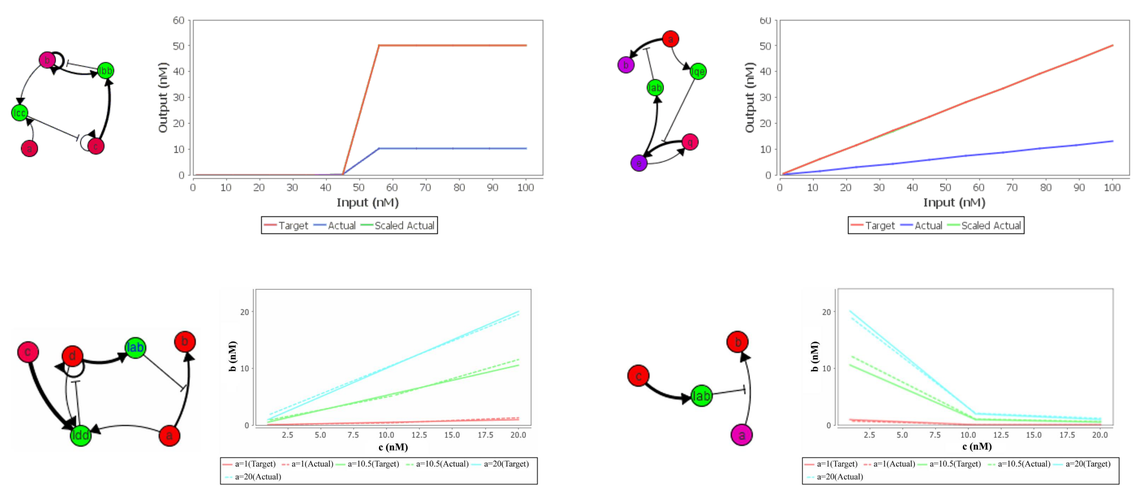
In vitro implementation





2.3 Designs of other mathematical functions



References

[1] Montagne, Kevin, *et al.* "Programming an in vitro DNA oscillator using a molecular networking strategy." Molecular systems biology, 7(466), 2011.
[2] Quang Huy, Dinh, *et al.* "An Effective Method for Evolving Reaction Networks in Synthetic Biochemical Systems." IEEE Transactions on Evolutionary Computations. (in press).
[3] Kenneth O., Stanley and Risto Miikkulainen. "Evolving neural networks through augmenting topologies." Evolutionary Computation, 10(2), 2002.