Discrete Mathematical Models in Synthetic Biology

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SIAM 2017 Minisymposium: Discrete Methods in Molecular Biology
#SIAM2017

Davidson - Missouri Western Synthetic Biology Research Collaboration

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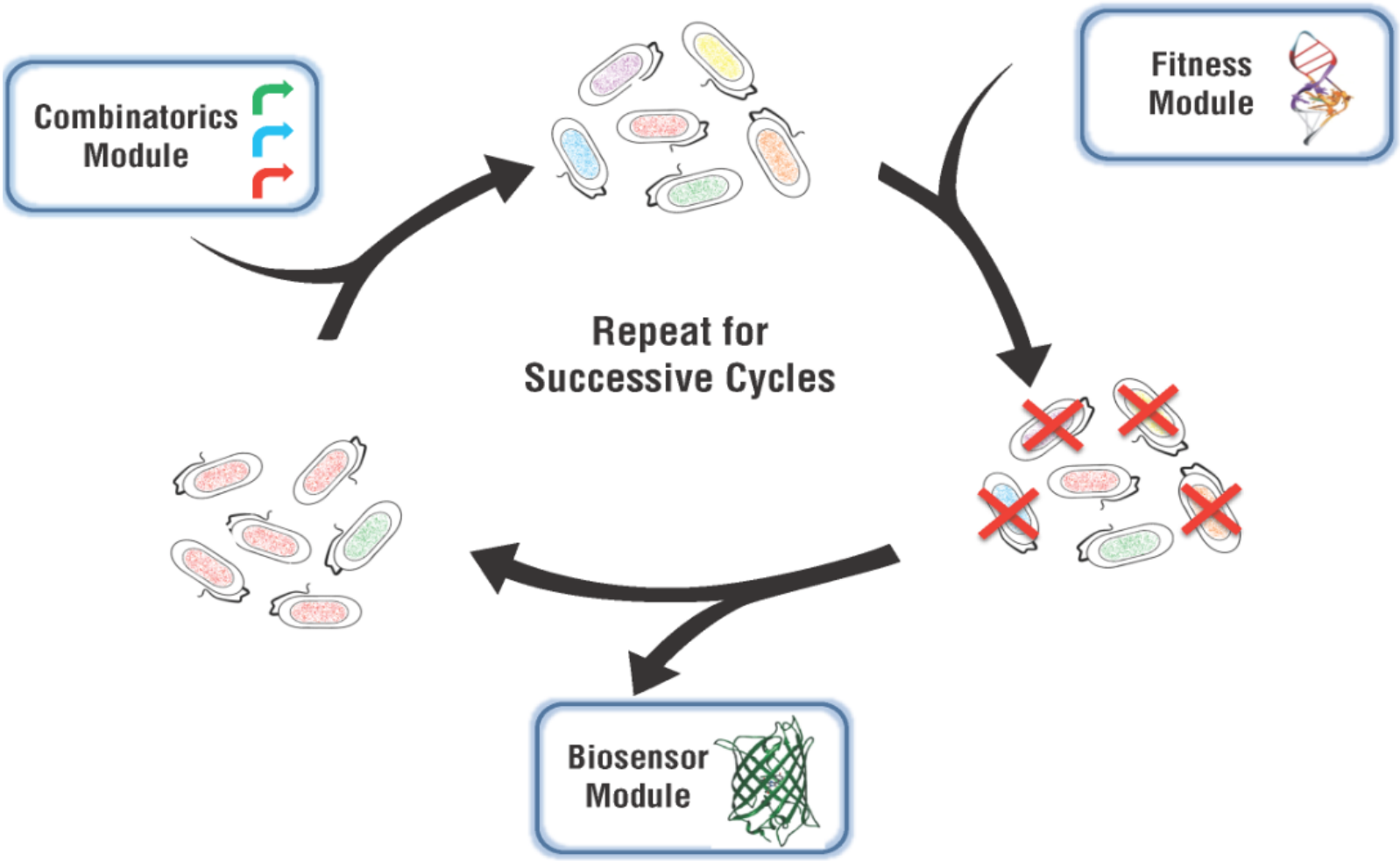
- Design and construction of biological devices and systems
- Engineering principles and mathematical modeling
- Applications in energy, environment, medicine, technology

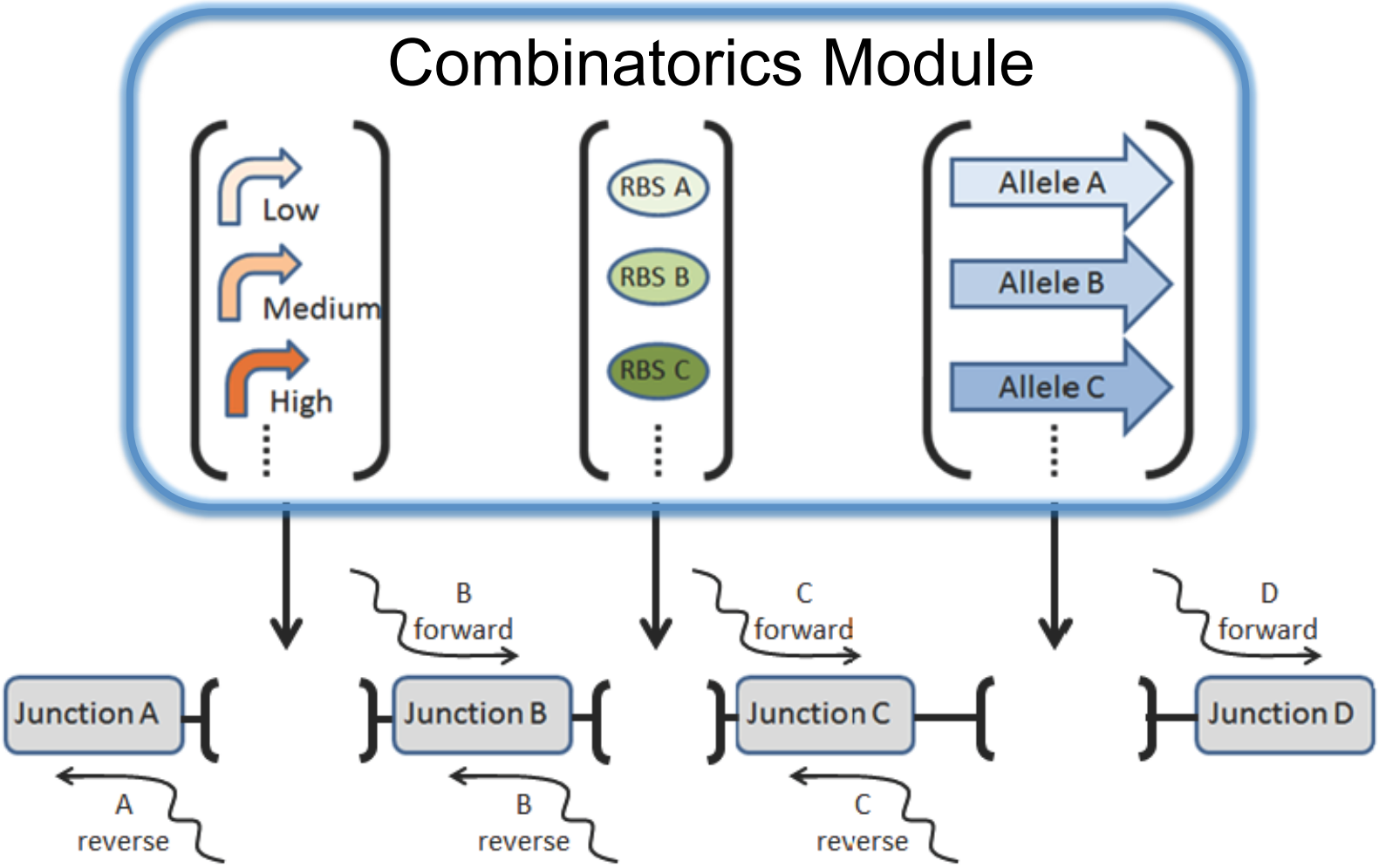
Davidson - Missouri Western Synthetic Biology Research Collaboration

- Focus on undergraduate education
- Pooling human resources
- Built on previous collaborations
- BioMath connections
- Common prioritized goals
  - Learn every day
  - Have fun
  - Contribute to science

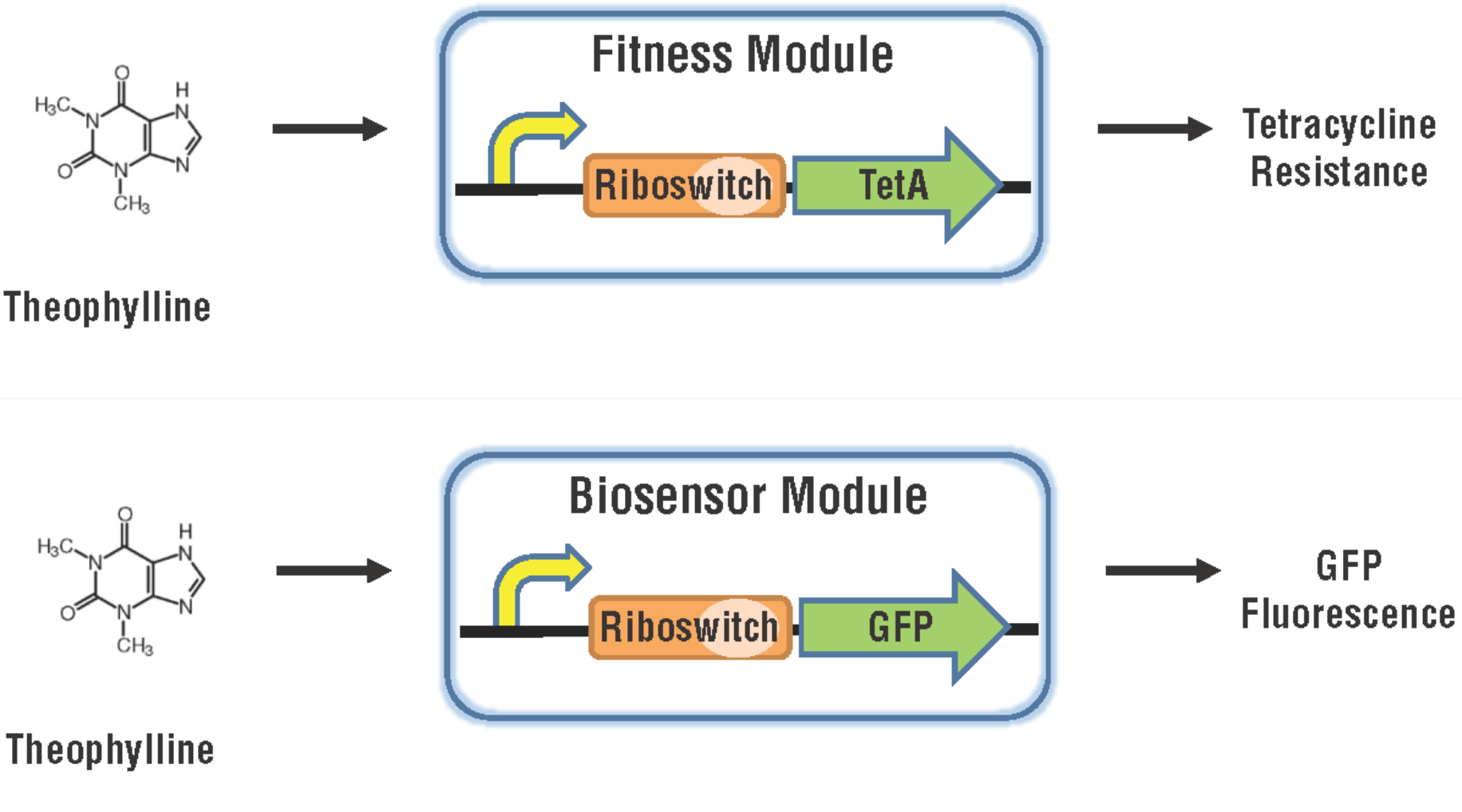
Programmed Evolution



Uniform Random Starting Population

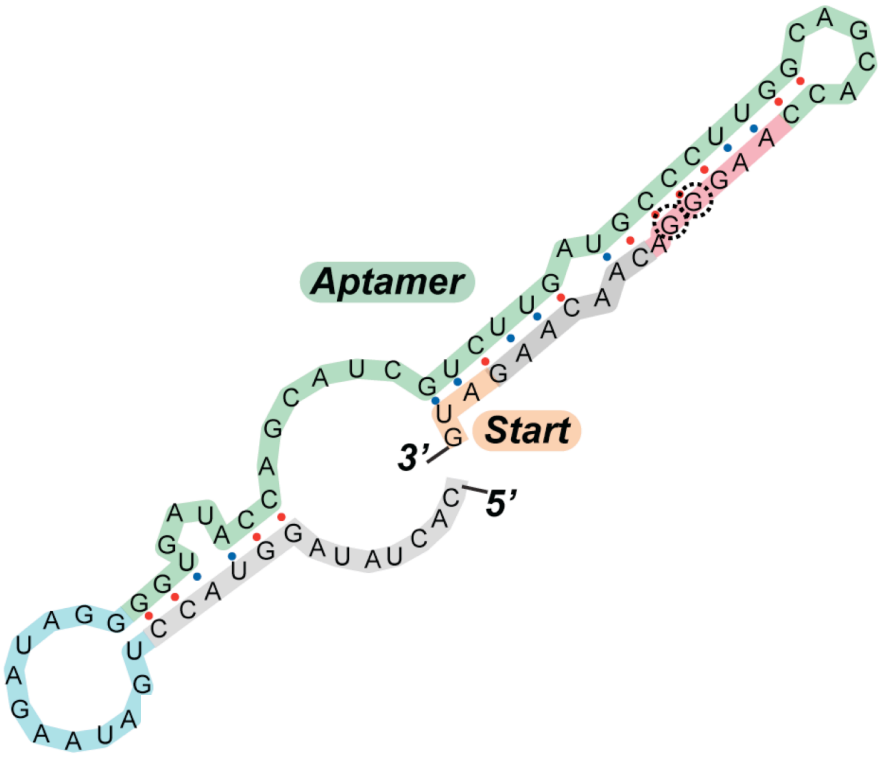


Driving (and Measuring) Evolution

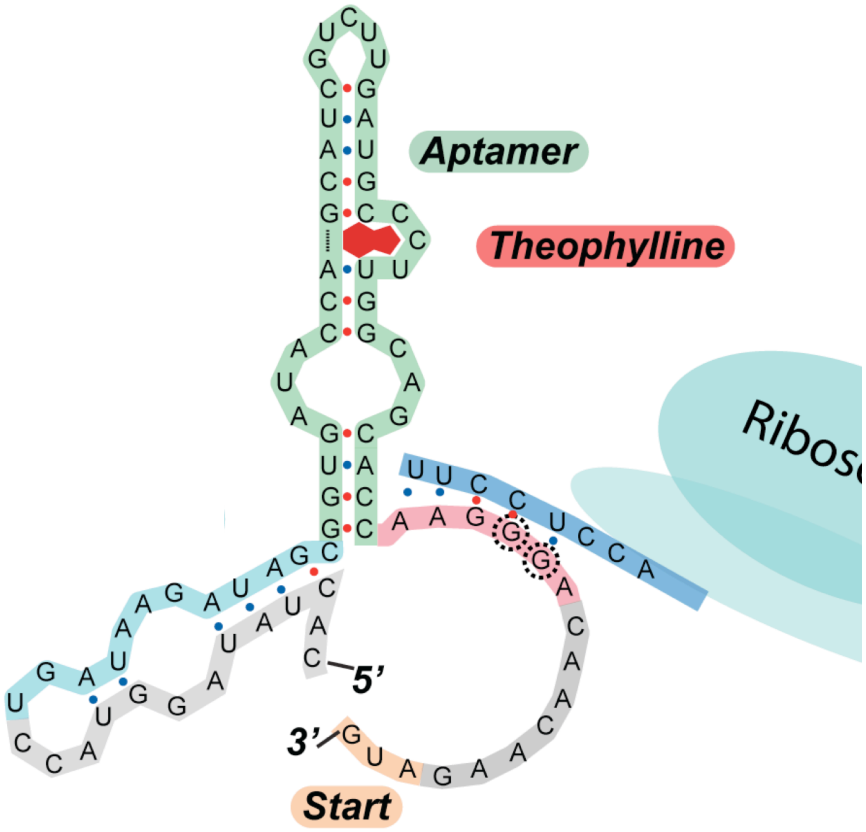


Riboswitch Function

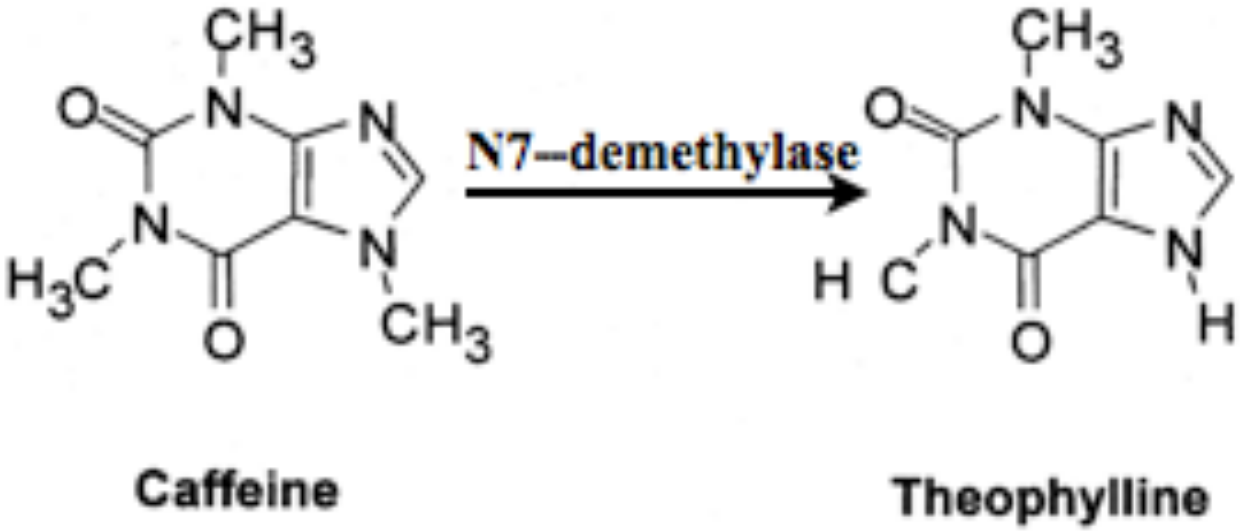
Without theophylline



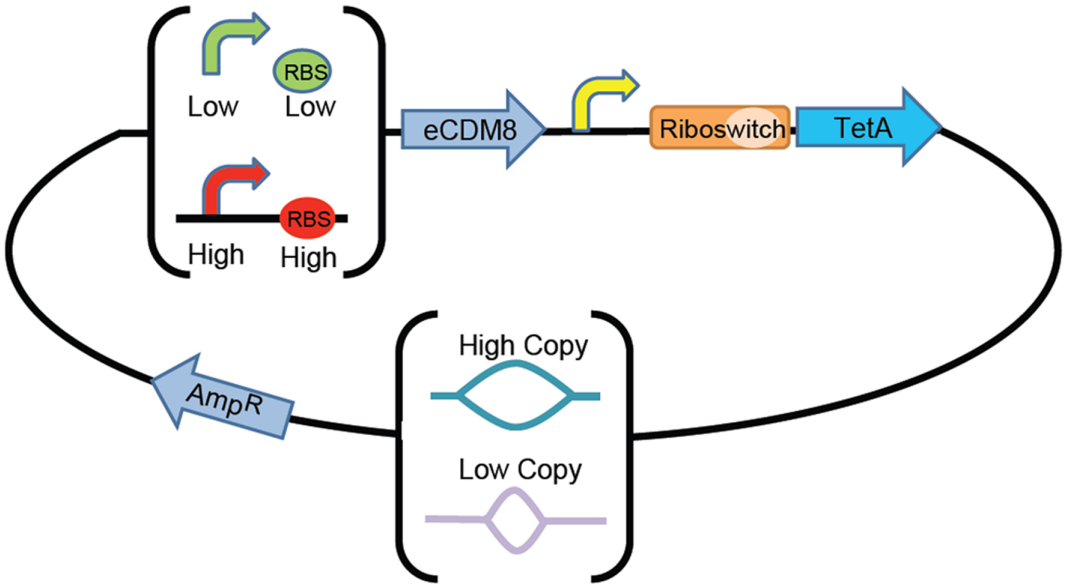
With theophylline

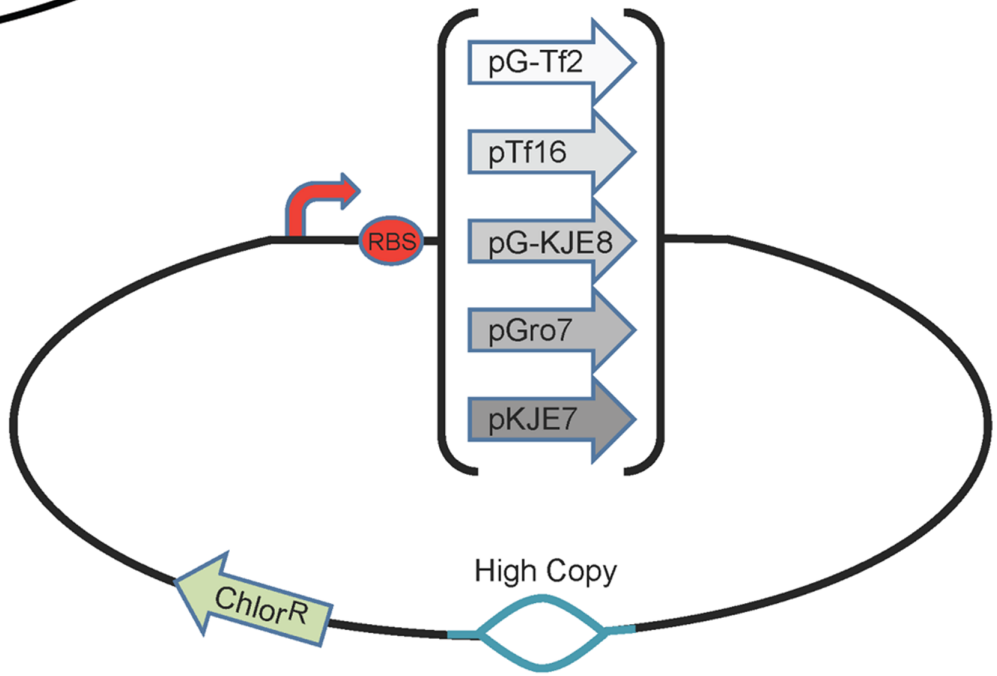


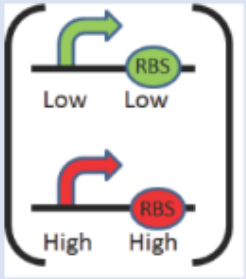
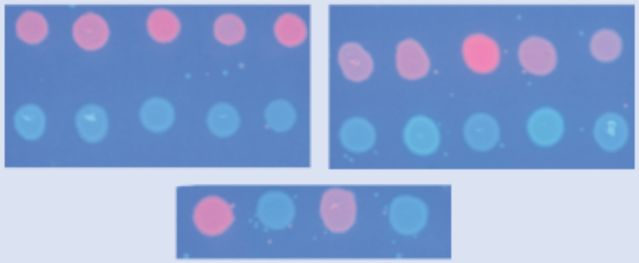
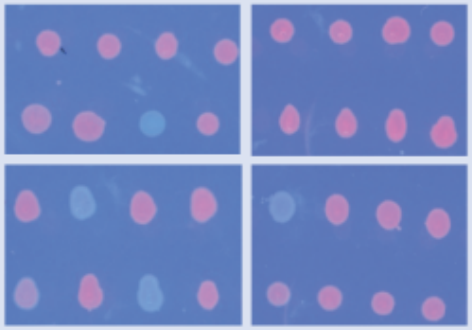
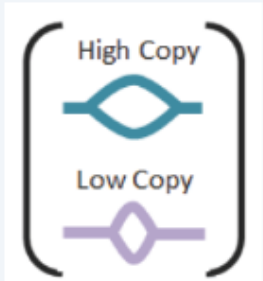
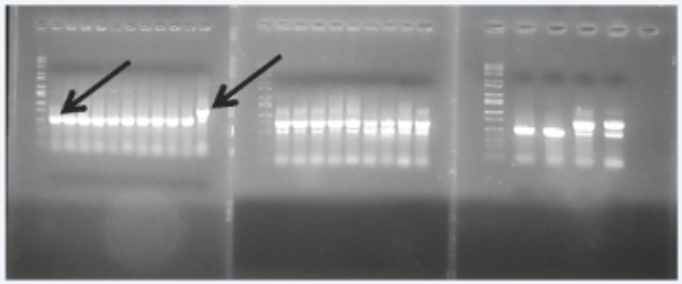
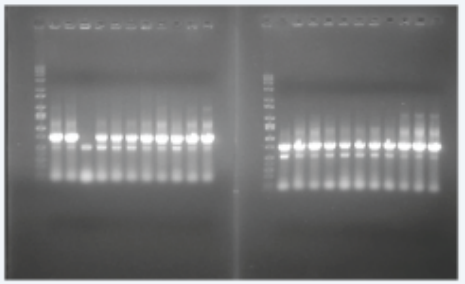
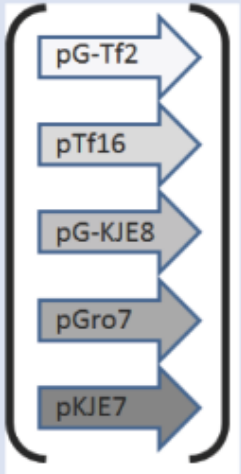
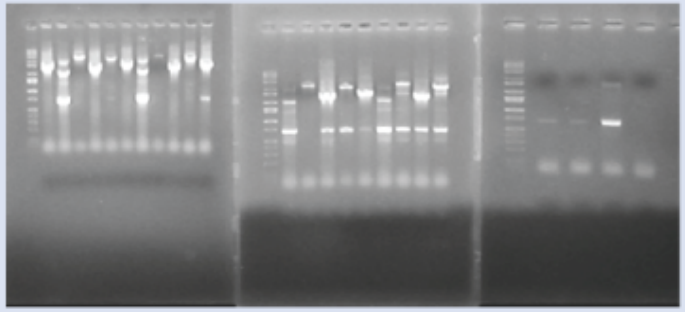
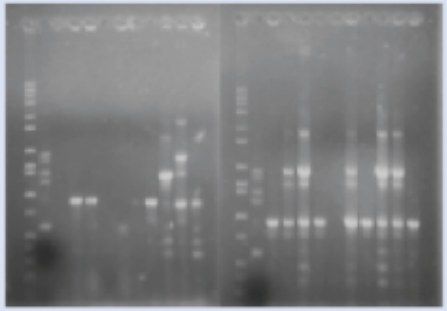
Evolution Target



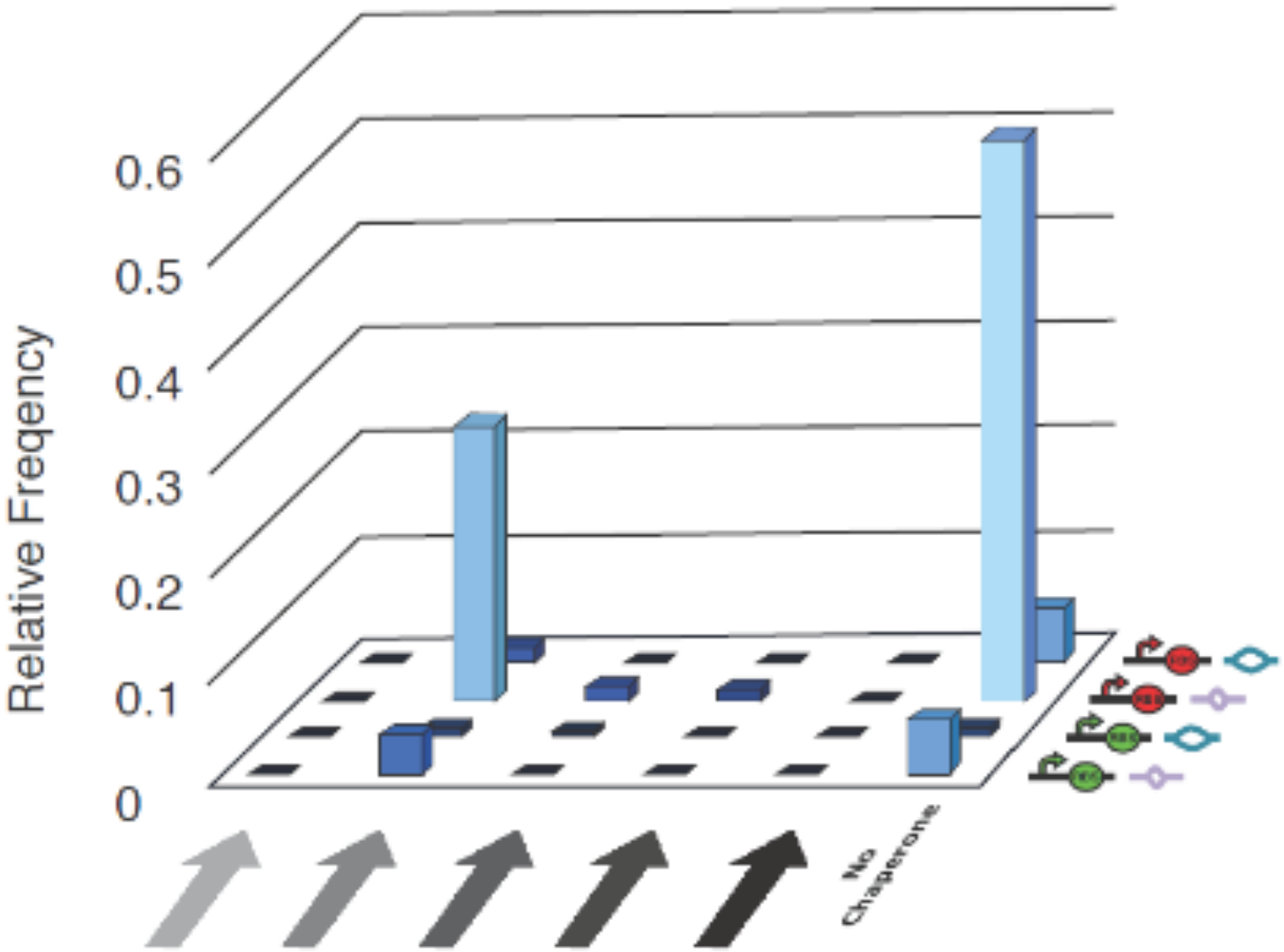
Programmed Evolution, v1.0





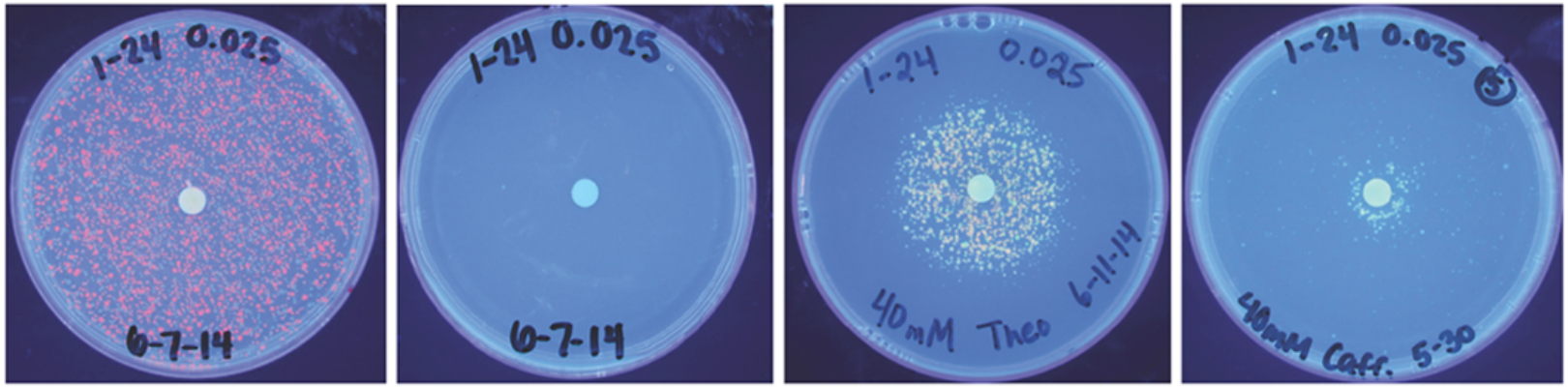
Genotype Element	Genotypes of Starting Population	Genotypes of Population after Programmed Evolution
		
		
		

Population after Programmed Evolution



Tracking the Input

- A disk soaked in caffeine is placed in the dish
  - what is the concentration of caffeine at each point of the plate as a function of time?
- Caffeine Diffusion Model



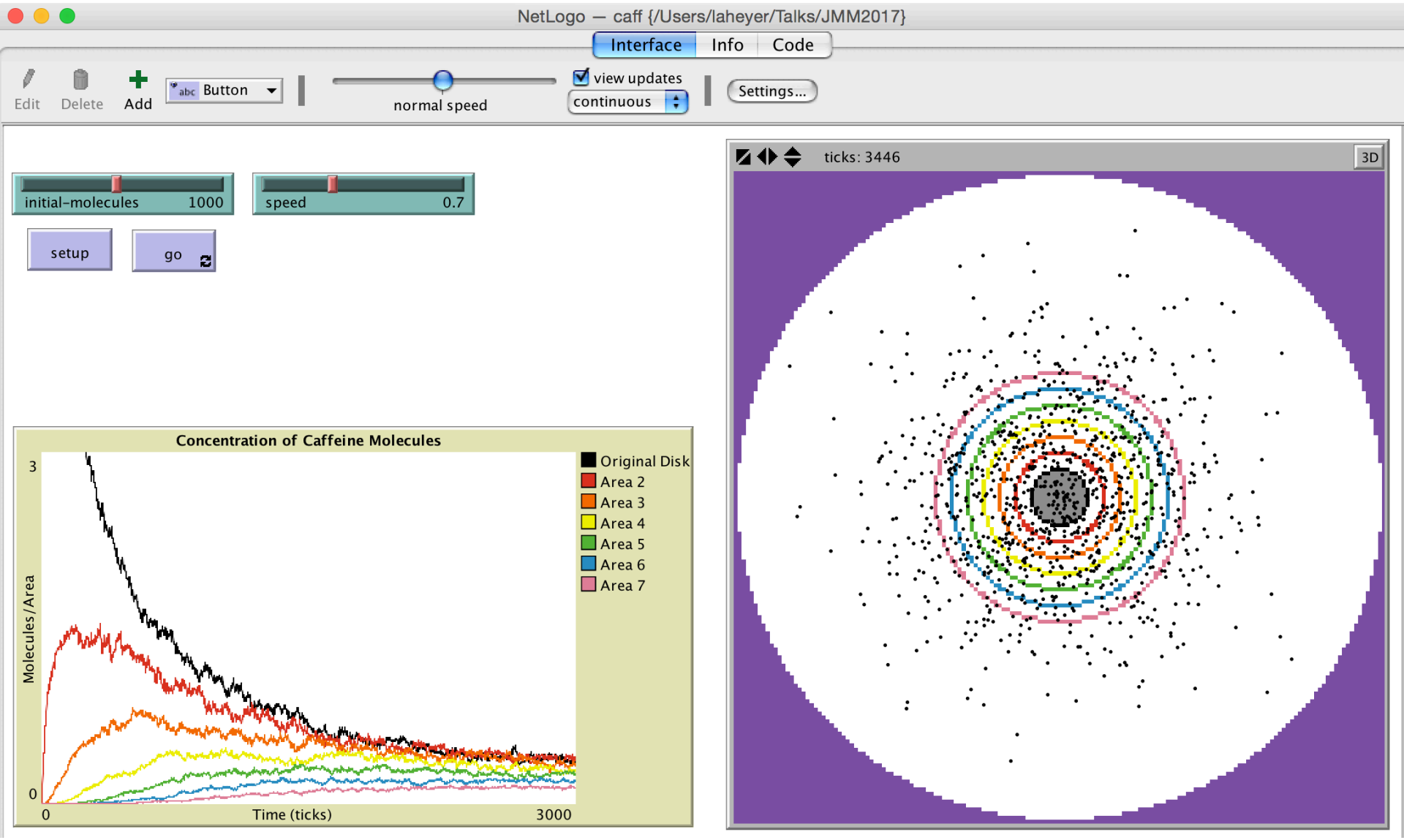
LB + Amp
H_20
Disk

LB + Tet
H_20
Disk

LB + Tet
40 mM Theophylline
Disk

LB + Tet
40 mM Caffeine
Disk

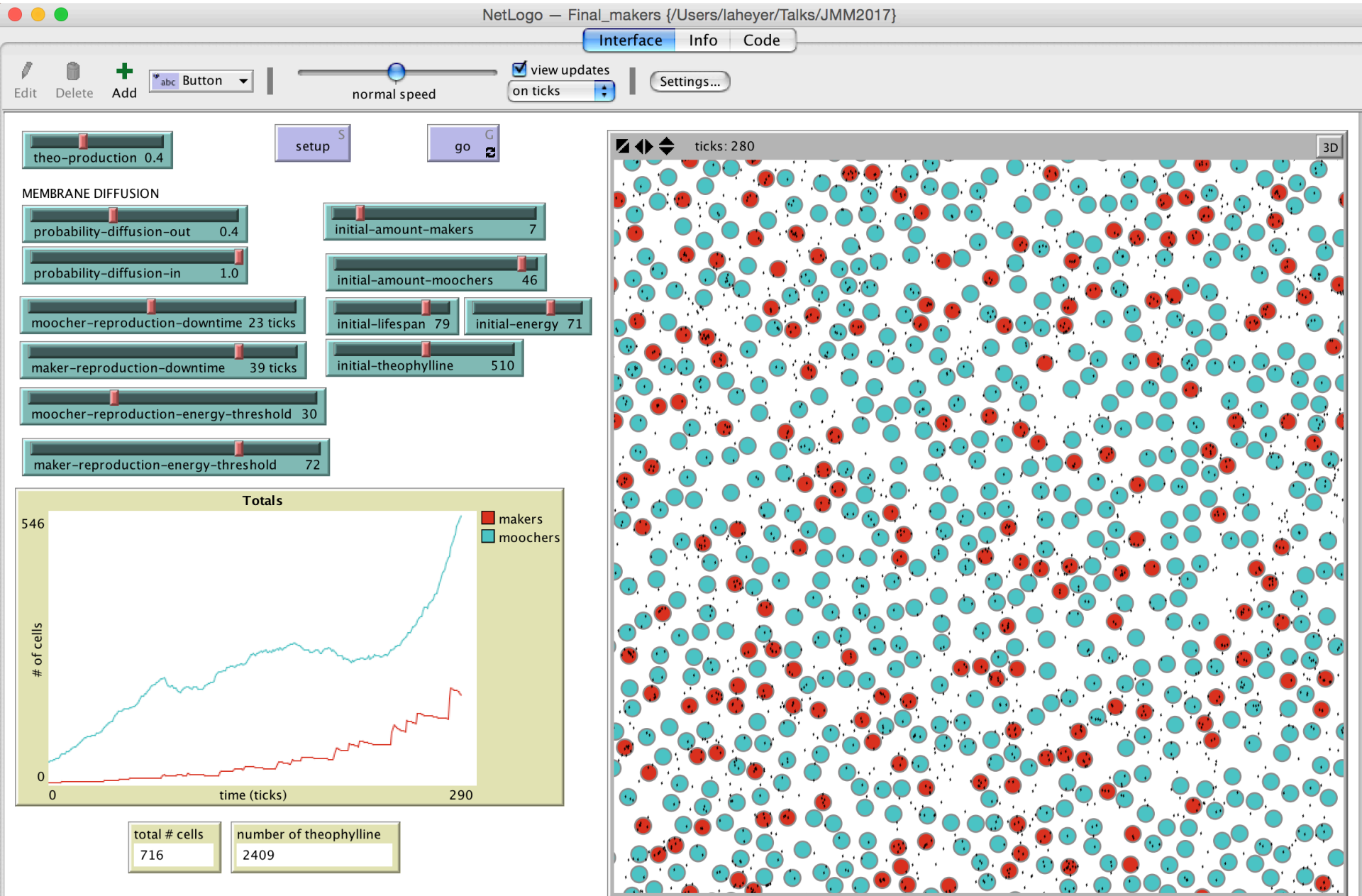
Agent-Based Diffusion Model



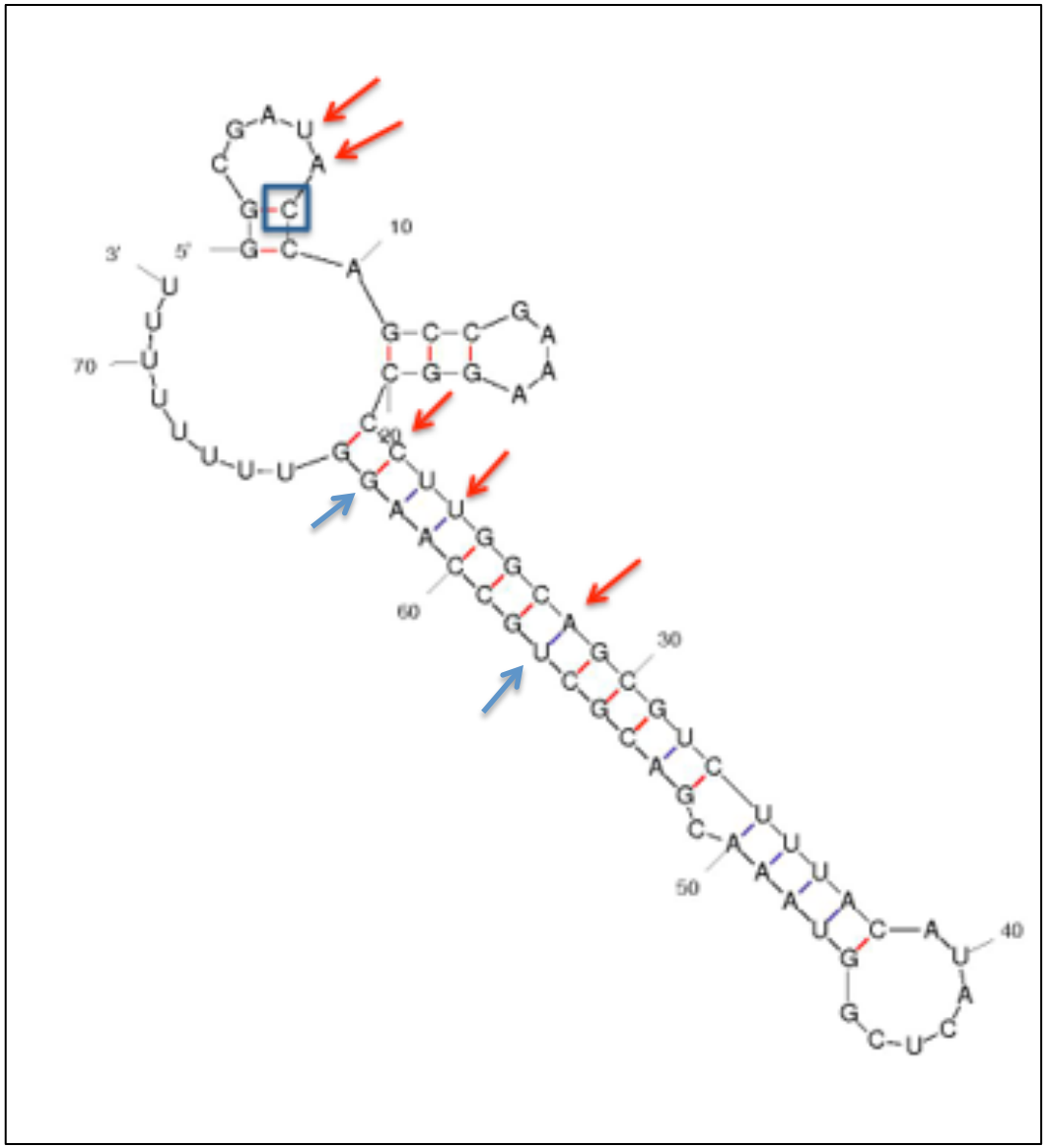
Tracking the Output

- Some cells evolve to be good at converting caffeine to theophylline
  - Do other cells benefit by theophylline diffusing across cellular membranes?
  - Under what conditions might these cells dominate the ending population?
- "Makers and Moochers" model

“Makers” and “Moochers”



Riboswitch Design: Beyond Theophyline



Theophylline-binding bases targeted for mutation

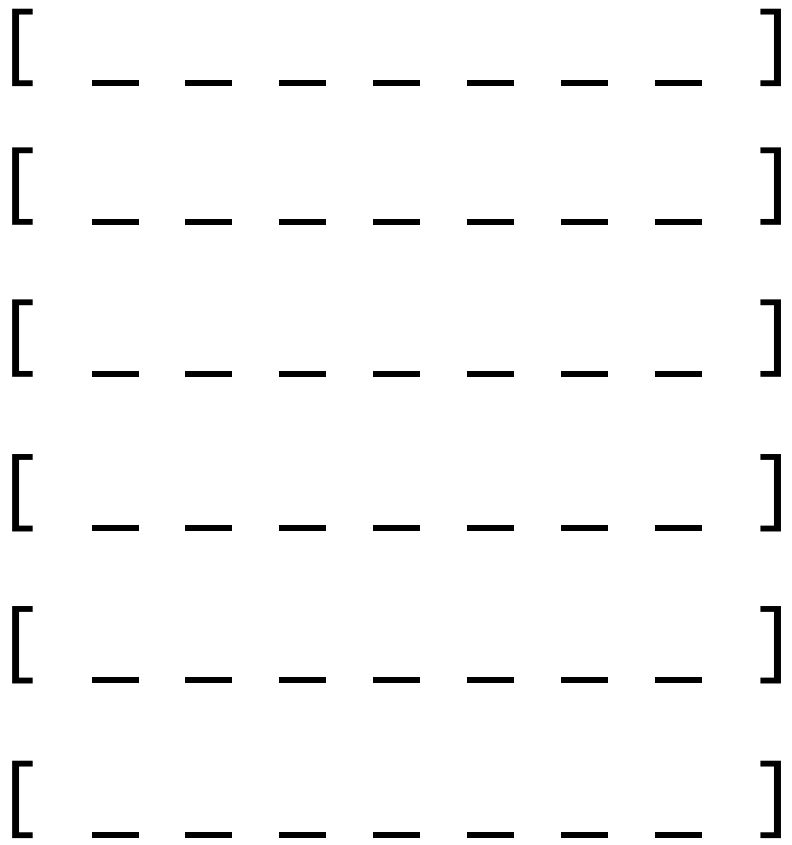
Other candidates for mutation

Theophylline-binding base, unmutated

Optimizing Mutations

Mutate sets of seven mutation sites to all four possible bases. Repeat six times.

$6 \times 4^7 = 98{,}304$ total variants



Optimizing Mutations

Mutate sets of seven mutation sites to all four possible bases. Repeat six times.

$6 \times 4^7 = 98{,}304$ total variants

[1 2 3 4 5 6 7]

[1 2 3 4 5 8 9]

[1 2 3 4 6 8 10]

[1 2 3 5 7 9 10]

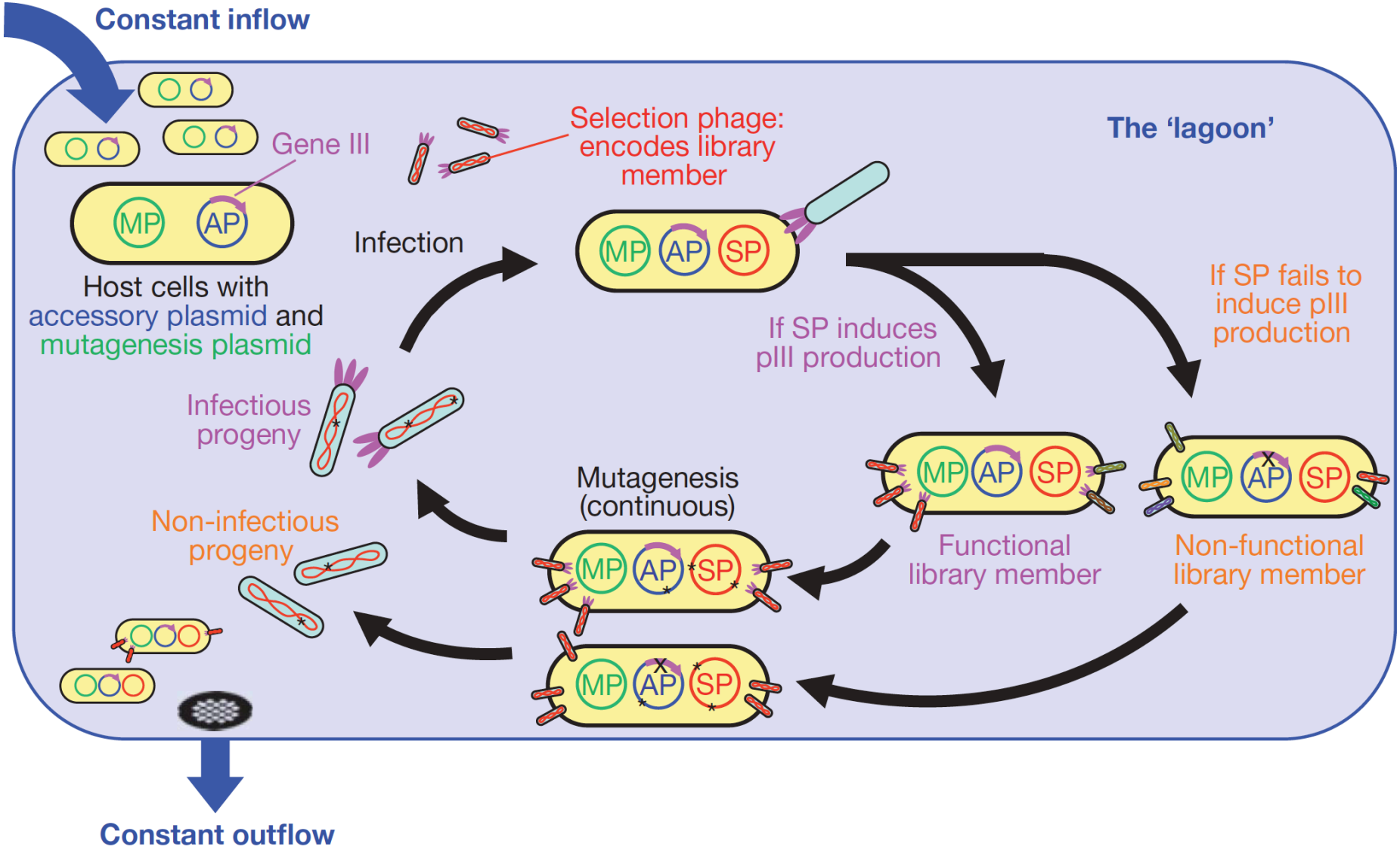
[1 2 6 7 8 9 10]

[4 5 6 7 8 9 10]

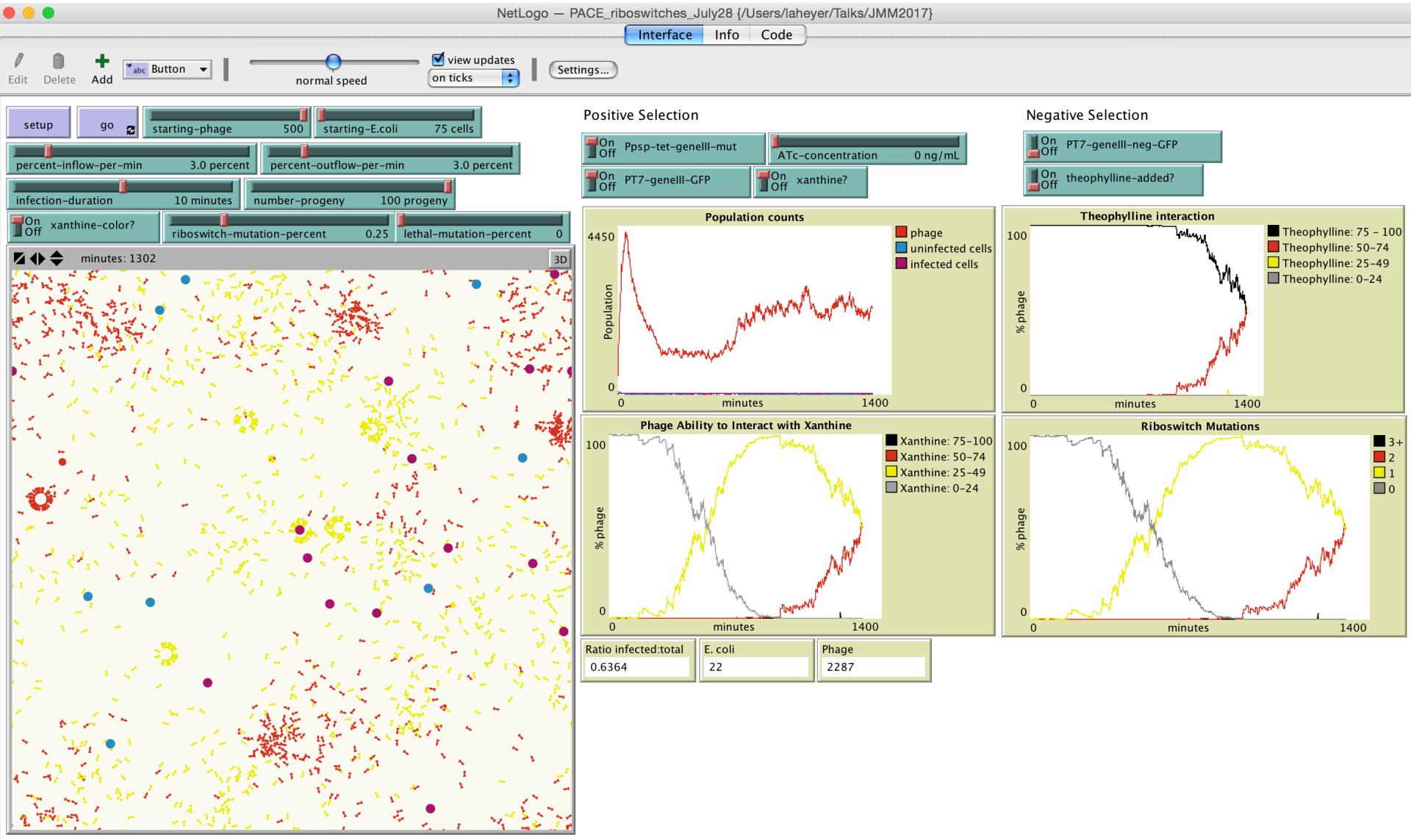
Pair Frequencies

SITE	1	2	3	4	5	6	7	8	9	10
1	5	5	4	3	3	3	3	3	3	3
2	5	5	4	3	3	3	3	3	3	3
3	4	4	4	3	3	2	2	2	2	2
4	3	3	3	4	3	3	2	3	2	2
5	3	3	3	3	4	2	3	2	3	2
6	3	3	2	3	2	4	3	3	2	3
7	3	3	2	2	3	3	4	2	3	3
8	3	3	2	3	2	3	2	4	3	3
9	3	3	2	2	3	2	3	3	4	3
10	3	3	2	2	2	3	3	3	3	4

PACE: A New Combinatorics Module



Agent-Based Model of PACE



```
to go  ;; each tick
  if not any? turtles [ stop ]
  move-turtles
  check-washout  ;; randomly washes out portion of phage and cells
  check-inflow  ;; flows cells into lagoon
  ask phage [
    ifelse xanthine-color? [assign-color-phage] [set color 2]

    ;; if incubating and host is washed out, die
    if host = nobody
      [if incubating < infection-duration
        [die]
      ]

    ;; tracks time that progeny has been incubating
    if incubating < infection-duration
      [set incubating incubating + 1
        move-to host  ;; follow host cell (stay inside)
      ]

    if not has-infected?
      [if incubating >= infection-duration  ;; if not incubating
        [infect-cells]
      ]

    ;; create progeny after infecting
    if has-infected? [
```

The Coupon-Collecting Problem

The Phage-Collecting Problem

Q: In 24 hours of PACE, will we see all possible riboswitches (~40 nt)?

$(5 \times 10^{-5}$ mutations/nt) x (40 nt) x $(5 \times 10^{10}$ phage)
$= 1 \times 10^{8}$ mutations

$np = (1 \times 10^{8}) \times (5 \times 10^{-10}) = 0.05$

$P(\text{double mutant}) = 1 - e^{-0.05} - 0.05\, e^{-0.05} = 2 \times 10^{-6}$

Expected number of double mutants = 1×10^{5}

Applying (an approximation for) the expected number of coupons required to see all 2700 double mutants:

$E(X) \approx n \log n = 2700 \log 2700 \approx 2 \times 10^{4}$

For Further Reading

- [with 49 undergraduate students] Programmed Evolution for Optimization of Orthogonal Metabolic Output in Bacteria. *PLoS ONE* (2015) 10(2): e0118322. doi:10.1371/journal.pone.0118322.
- Engineering bacteria to solve the burnt pancake problem. *Journal of Biological Engineering* (2008) **2**:8.
- Solving a Hamiltonian Path Problem with a Bacterial Computer. *Journal of Biological Engineering* (2007) **3**:11
- Synthetic Biology: A New Frontier. *American Mathematical Monthly*. **121**:857-867

Acknowledgments

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