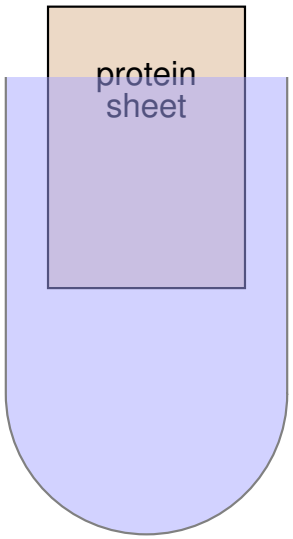
In-vitro selection algorithm

- for finding RNA strand that binds to protein

Make tube of *random* RNA strands



for t=1 to 20 do

1. Dip sheet coated with protein into tube
2. Pull out and wash off RNA that stuck
3. Multiply washed off RNA back to original amount (normalization)

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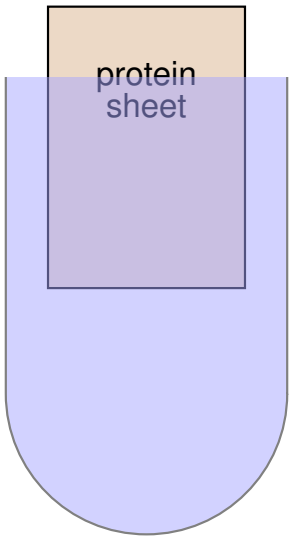

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Can't be done with computer
because 10^{15} RNA strands per liter of soup

Basic scheme

Start with unit amount of random RNA

Loop

1. Functional separation into
   good RNA and bad RNA
2. Amplify good RNA to unit amount

Duplicating DNA with PCR

needed for normalization step

- Invented by Kary Mullis 1985
- Heat - double stranded DNA comes apart
- Cool - Short primers hybridize at the ends
- Taq Polymerase runs along DNA strand and complements bases
- Back to double stranded DNA

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- Ideally all DNA strands multiplied by factor of 2

The caveat

- Not many interesting/specific functional separations found
- Need high throughput for functional separation

Mathematical description of in-vitro selection

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Strong assumption:

- Fitness W_i independent of share vector $\boldsymbol{s}$

Update

Good RNA in tube $\boldsymbol{s}$:

$$s_1 W_1 + s_2 W_2 + \cdots + s_n W_n = \boldsymbol{s} \cdot \boldsymbol{W}$$

Bad RNA:

$$s_1(1 - W_1) + s_2(1 - W_2) + \cdots + s_n(1 - W_n) = 1 - \boldsymbol{s} \cdot \boldsymbol{W}$$

- Amplification:
  - Good share of RNA i is $s_i W_i$ - multiplied by factor F
  - If precise, then all good RNA multiplied by same factor F
  - Final tube at end of loop

$$F\ \boldsymbol{s} \cdot \boldsymbol{W}$$

  - Since final tube has unit amount of RNA

$$F\ \boldsymbol{s} \cdot \boldsymbol{W} = 1 \text{ and } F = \frac{1}{\boldsymbol{s} \cdot \boldsymbol{W}}$$

  - Update in each loop

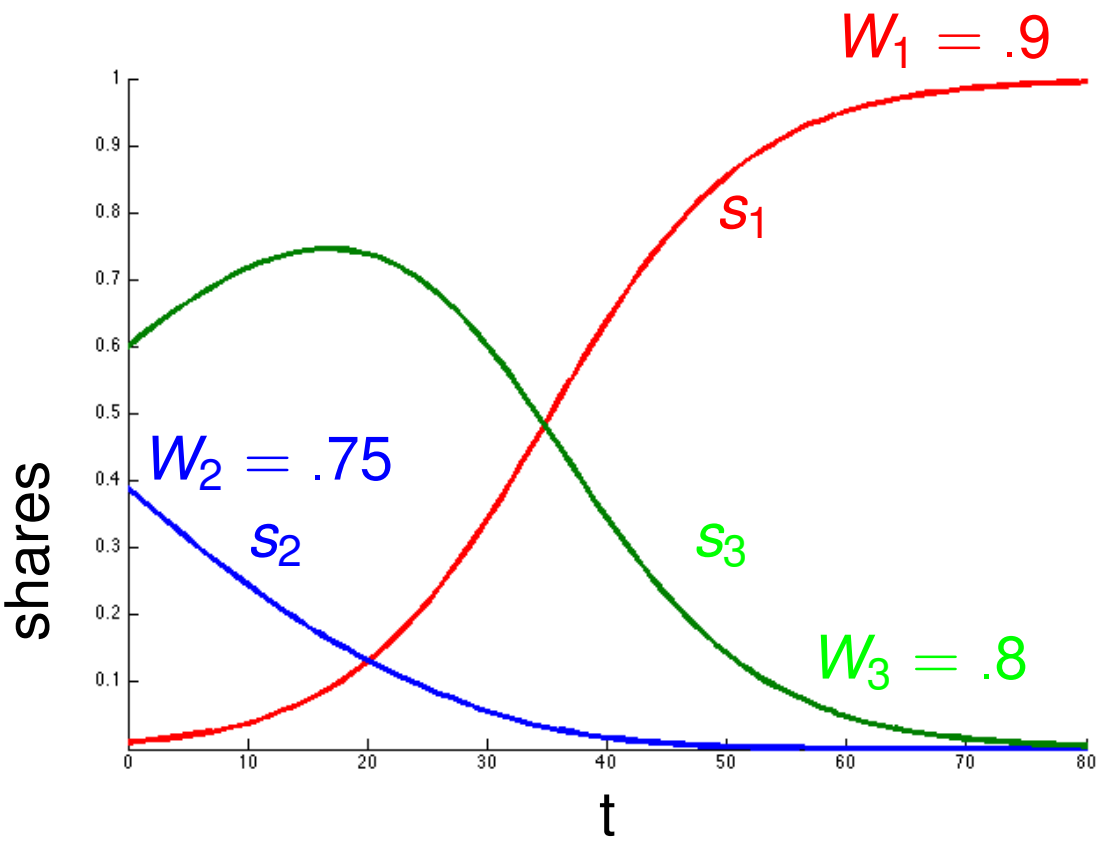
$$s_i := \frac{s_i W_i}{\boldsymbol{s} \cdot \boldsymbol{W}}$$

Implementing Bayes rule in RNA

- s_i is prior $P(i)$
- $W_i \in [0..1]$ is probability $P(Good|i)$
- $\boldsymbol{s} \cdot \boldsymbol{W}$ is probability $P(Good)$
-

$$s_i := \frac{s_i W_i}{\boldsymbol{s} \cdot \boldsymbol{W}} \quad \text{is Bayes rule} \quad \underbrace{P(i|Good)}_{\text{posterior}} = \frac{\overbrace{P(i)}^{\text{prior}} P(Good|i)}{P(Good)}$$

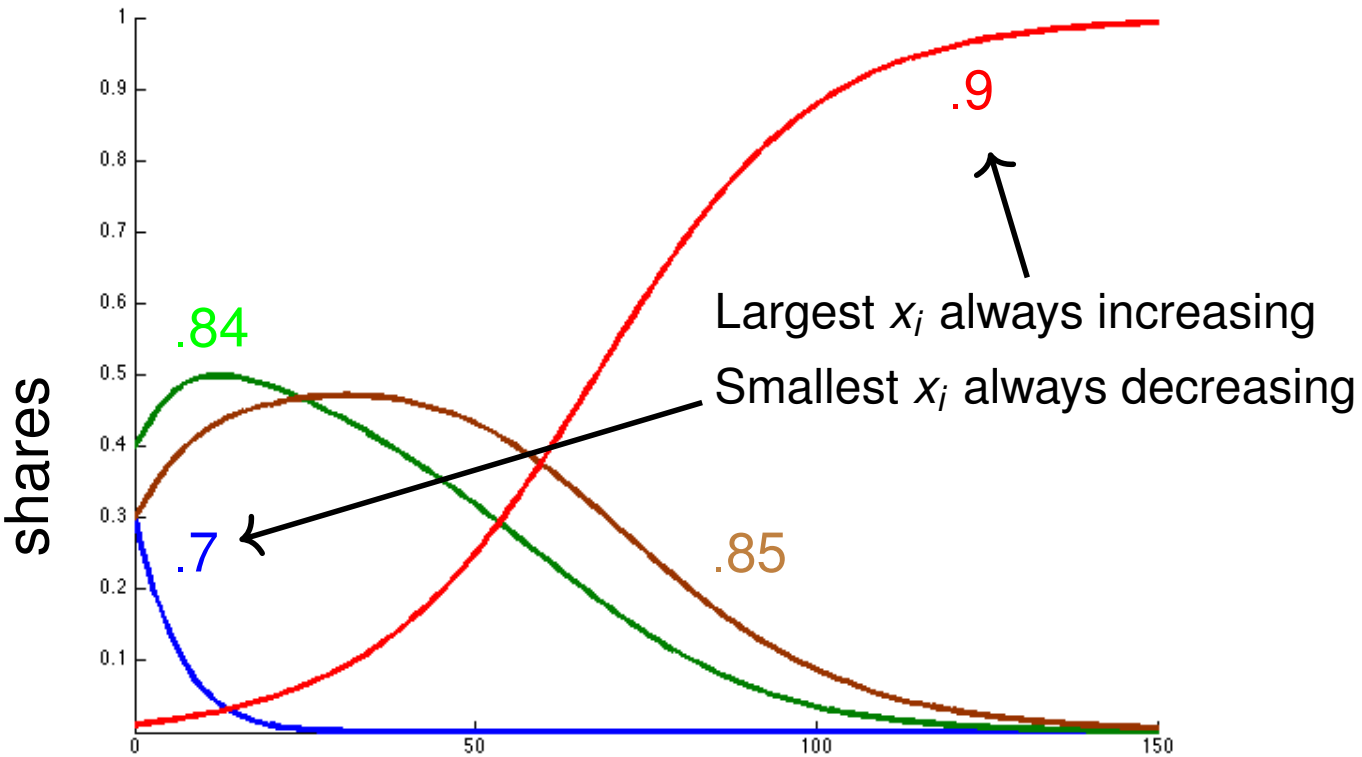
Iterating Bayes Rule with same data likelihoods



Initial $\boldsymbol{s} = (.01, .39, .6)$

$\boldsymbol{W} = (.9, .75, .8)$

$\max_i W_i$ eventually wins



$$s_{t,i} = \frac{s_{0,i} W_i^t}{\text{normalization}}$$

t is speed parameter

The best are *too* good

- Multiplicative update

$$s_i \sim s_i \underbrace{\text{fitness factor}_i}_{\geq 0}$$

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- Blessing

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- Curse

  The best wipe out the others
  Loss of diversity

View of evolution

Simple view

- Inheritance
  - mutation
  - selection for the fittest with multiplicative update