מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

Compositional Assemblies Behave Similarly to Quasispecies Model

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Group meeting, 01/10/2013

Introduction

Quasispecies are a cloud of genotypes that appear in a population at mutation-selection balance.

(J.J Bull et al, *PLoS 2005)*

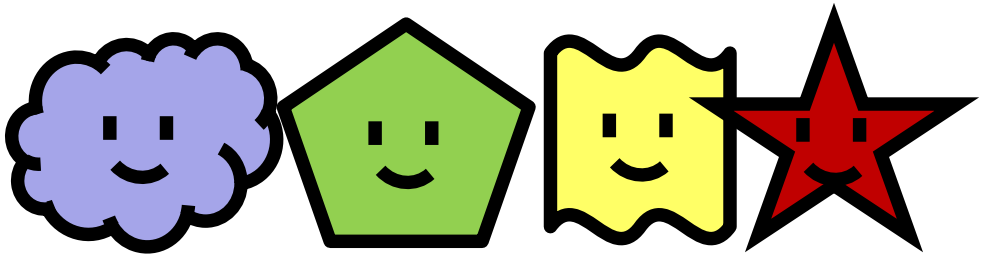
- Theoretical model (equations and assumptions), with experimental support by RNA viruses.
- Usually applied when mutation rates are high.

- GARD composomes replicate with relatively low fidelity (high mutation rate).

Could they show similar dynamic behavior?

Quasispecies model

- Basically a population model
- *n* different genotypes / identities



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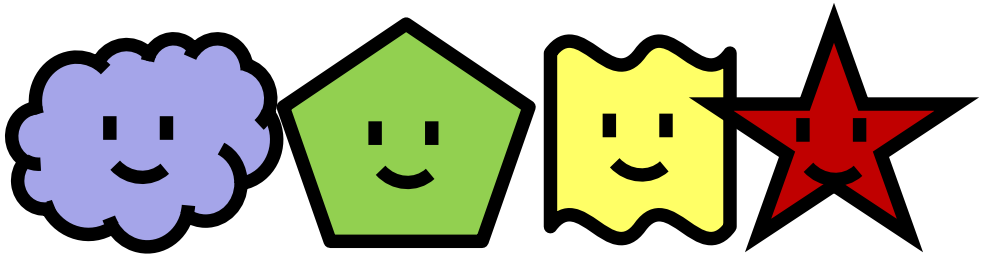

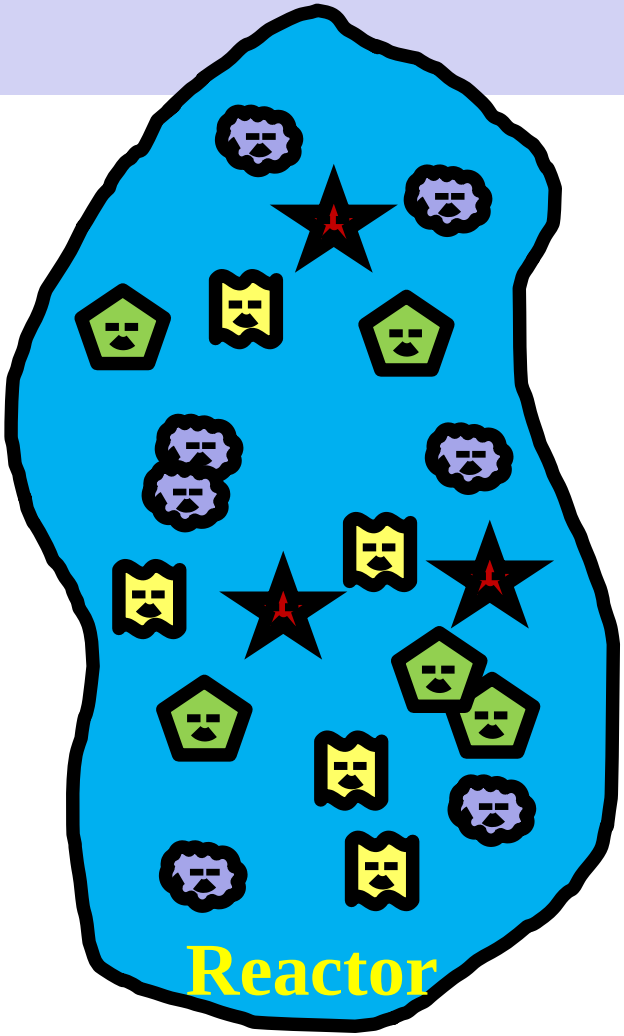

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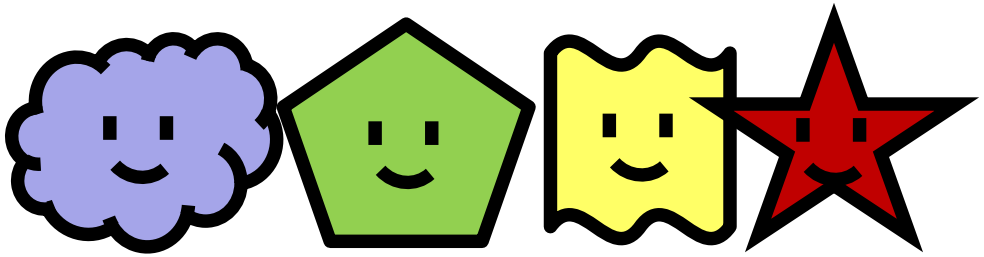
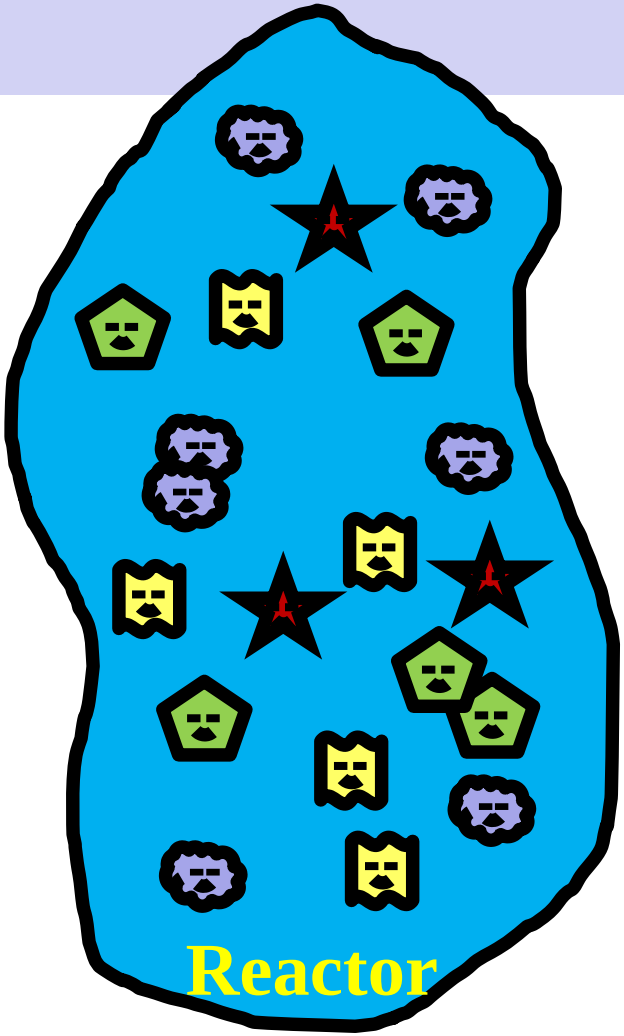


- Their relative **concentration** in the environment is denoted by the fraction x_i.



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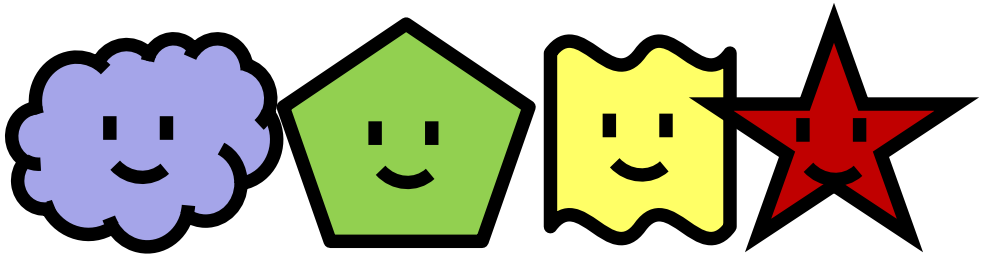
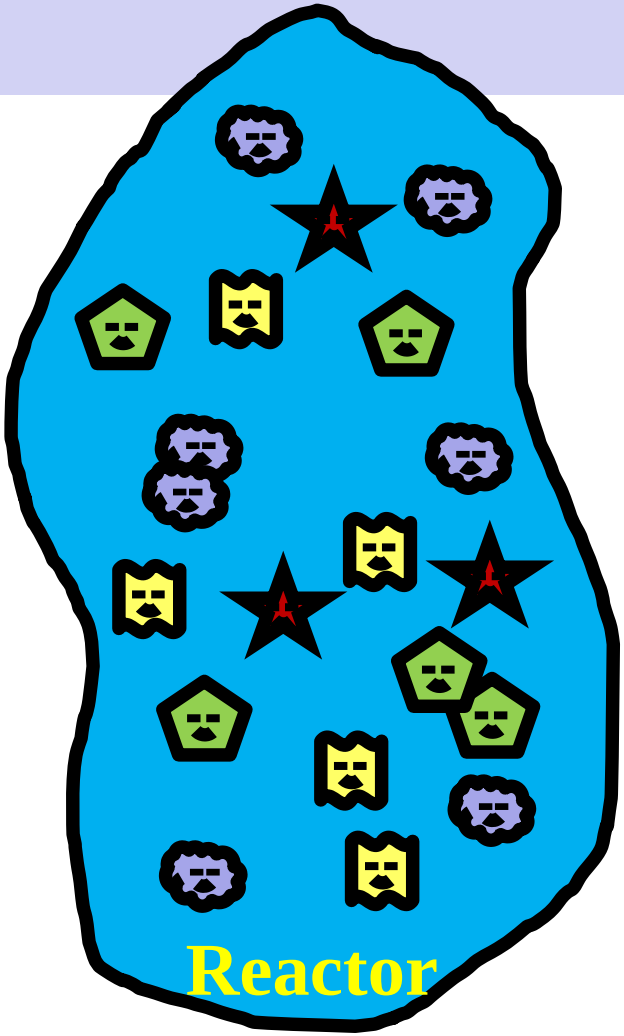


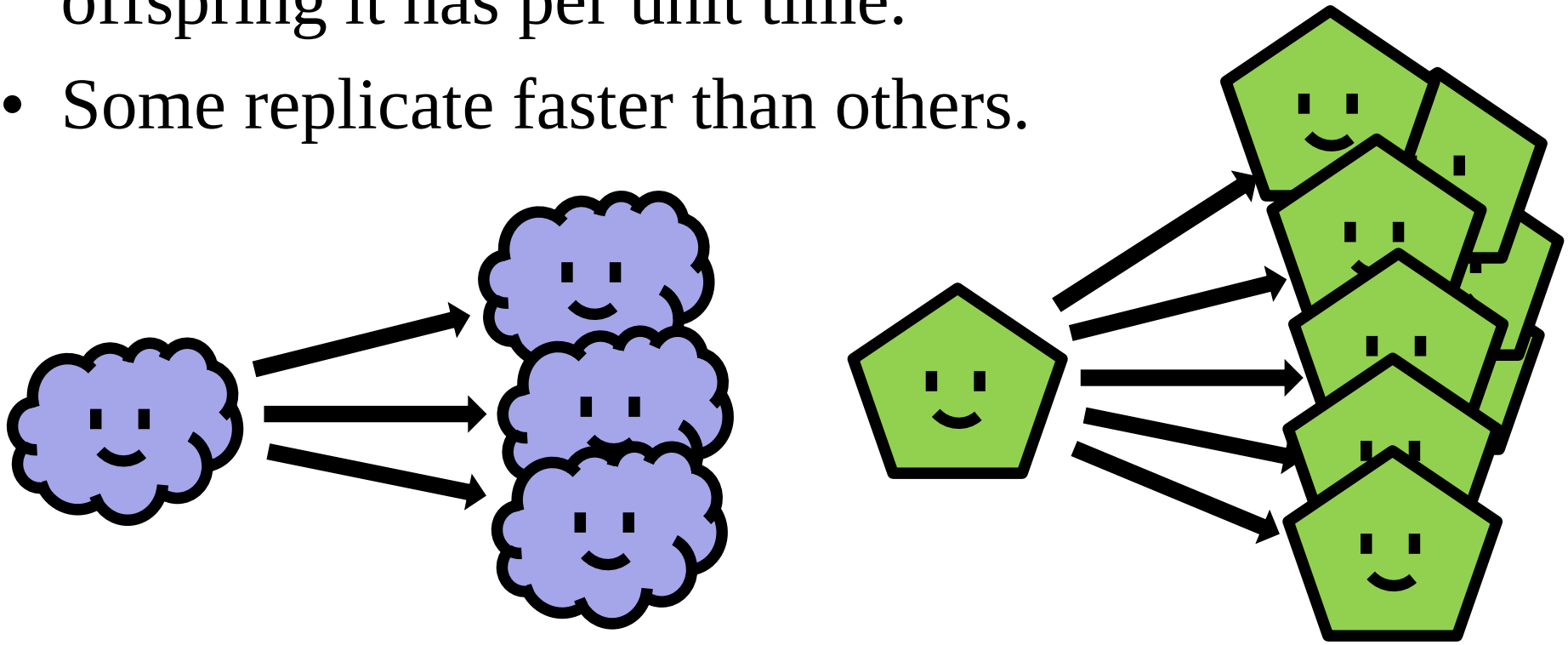


- Their relative **concentration** in the environment is denoted by the fraction x_i.
- **Goal: To find out how x_i behave as a function of time.**

$$\sum_{i=1}^{n} x_i = 1$$

Quasispecies model

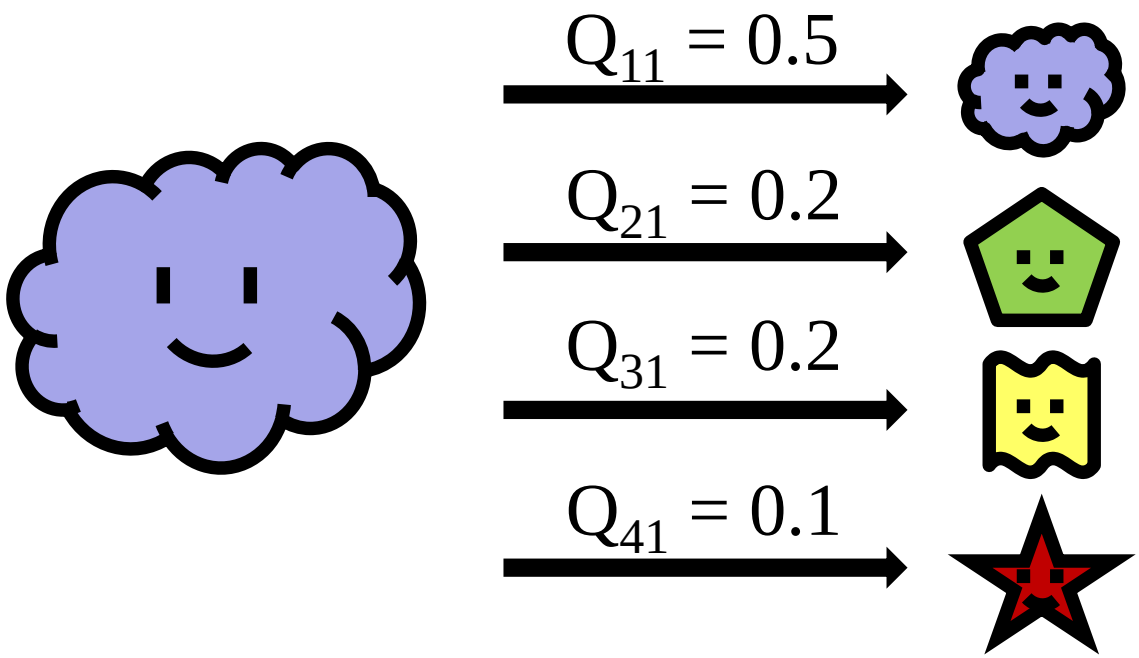
- Each one replicates at a certain rate – how many offspring it has per unit time.
- Some replicate faster than others.



- This is called the **replication rate**, denoted A_i
- $A_i = \frac{number\ of\ offspring}{time}$

Quasispecies model

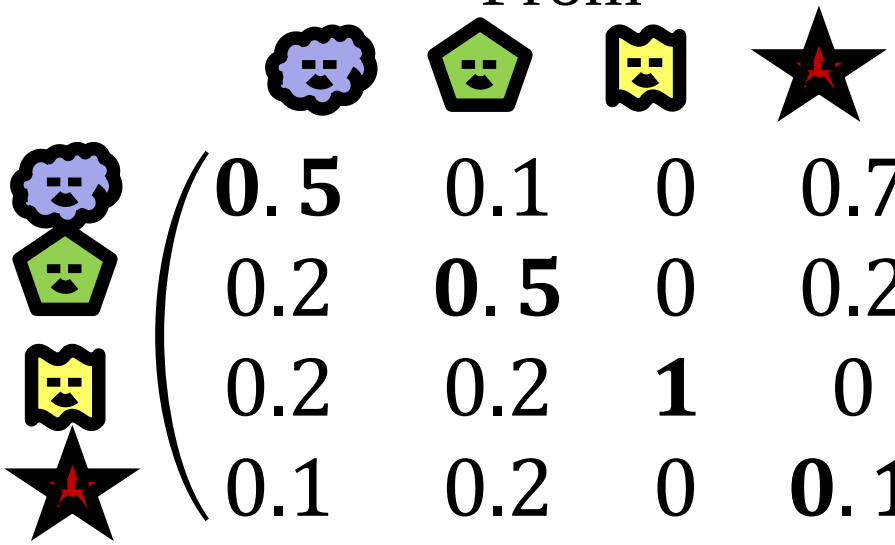
- However, replication is not exact. Sometimes, the offspring is of another genotype.
- The chance that a genotype *j* replicates into genotype *i* is denoted Q_{ij}.



Quasispecies model

- We can put everything in a matrix, called the **transition matrix, Q.**

From



To

$$\begin{pmatrix} \mathbf{0.5} & 0.1 & 0 & 0.7 \\ 0.2 & \mathbf{0.5} & 0 & 0.2 \\ 0.2 & 0.2 & \mathbf{1} & 0 \\ 0.1 & 0.2 & 0 & \mathbf{0.1} \end{pmatrix}$$

- The main diagonal is faithful self replication.

Quasispecies model

- How can we find out **Q** and **A**?
- Assume that we are dealing with RNA sequences of length *v*:
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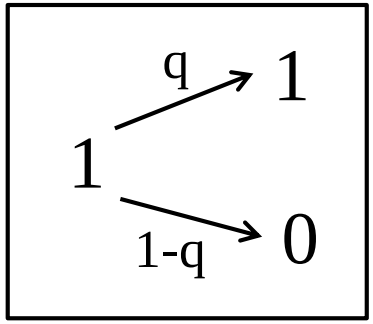

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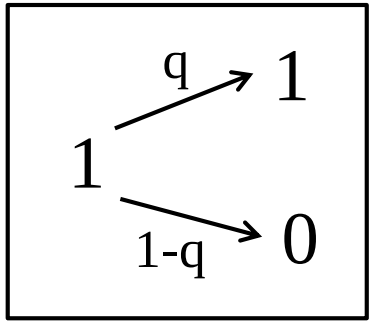
    - What is the chance for error-less replication?
  - All mutations of the master sequence replicate slower according to the Hamming distance.
    - Effectively, many genotypes are grouped together.
    - **Q** and **A** are built only from *q* and *v*.



Quasispecies model

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- $q = 1$ ➔

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Quasispecies model

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- Starting at $q = 1$, lowering it results in loss of the master sequence as the most frequent genotype.
  - (requires lack of back mutation)

ERROR CATASTROPHE

- RNA viruses may be fought by bringing them to error catastrophe.

Quasispecies model

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- The *Eigen* equation (after Manfred Eigen):

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- Where E is the "**average excess rate**"

$$\tilde{E}(t) = \sum_{i=1}^{n} A_i x_i$$

Quasispecies model

- **Q** and **A** can be combined into one matrix **W**, which tells how much of each genotype is produced per unit time.

$$\boldsymbol{W} = \boldsymbol{Q} \cdot diag(\boldsymbol{A})$$

Examples:

$$\boldsymbol{W} = \begin{pmatrix} 1 & 0.001 & 0.001 & 0.01 \\ 0.1 & 2 & 0.01 & 0.01 \\ 0.001 & 0.1 & 3 & 0.01 \\ 0.001 & 0.001 & 0.001 & 4 \end{pmatrix}$$

- Initial conditions: $x_1 = 1$, all others are 0.

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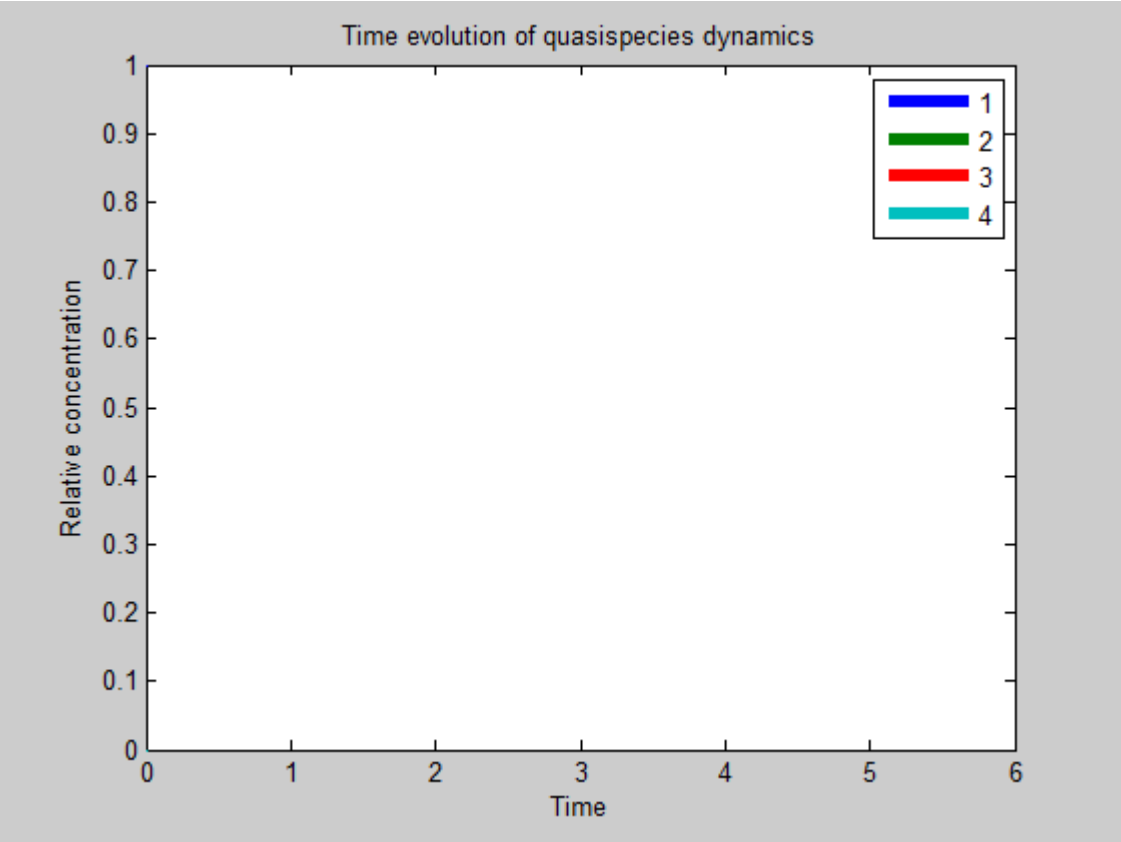

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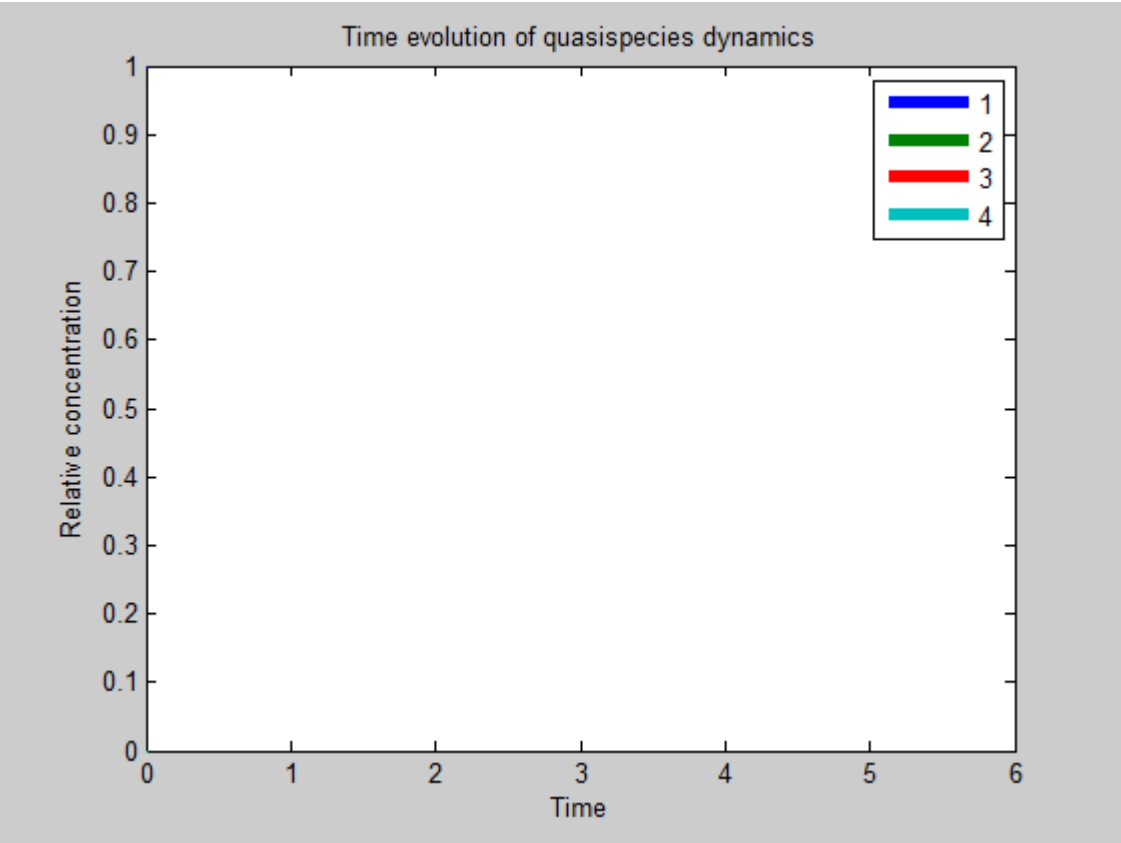
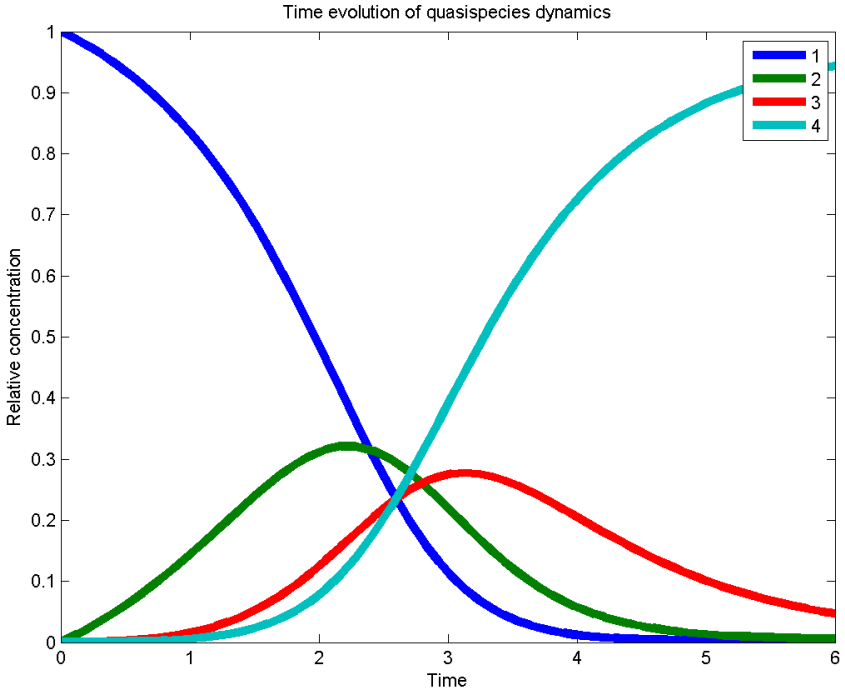
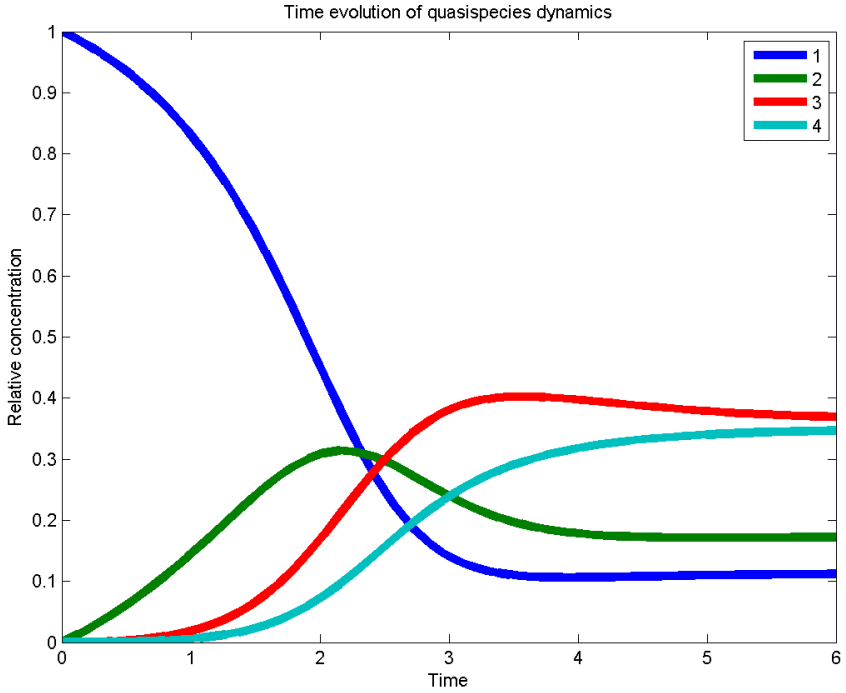




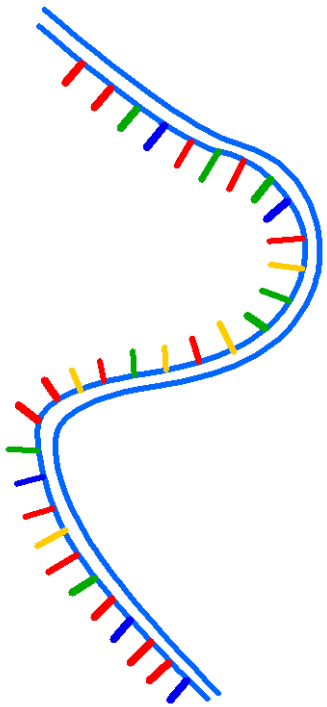


- The most frequent genotype is not necessarily the one with highest A_i.
- The steady state population distribution is called the **quasispecies.**
  - That means, a vertical slice

GARD model (Graded Autocatalysis Replication Domain)

RNA world

Lipid world



DNA / RNA / Polymers →

<u>Sequence</u>

covalent bonds

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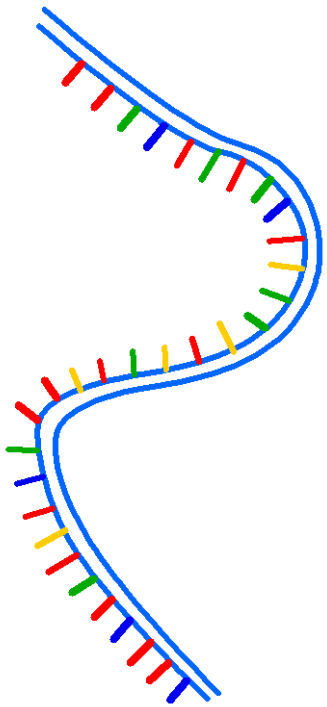

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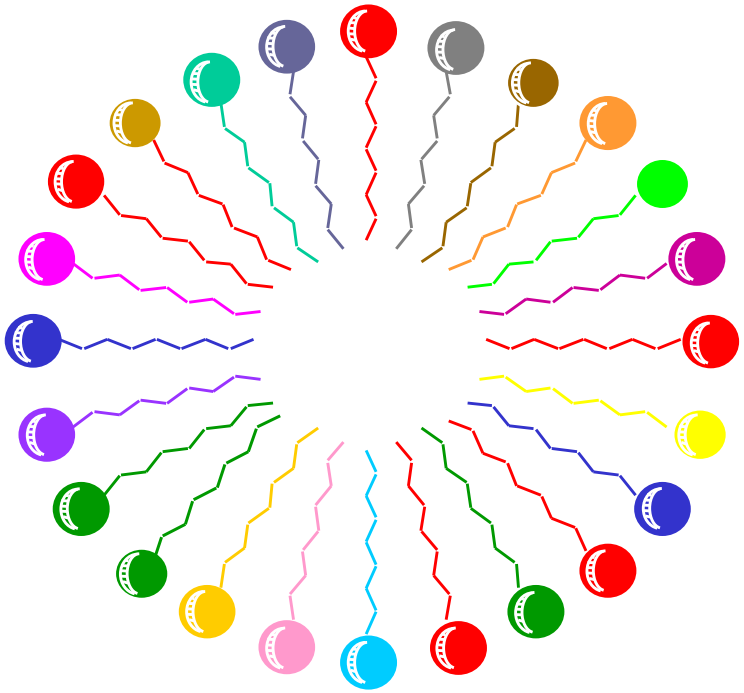

DNA / RNA / Polymers →
<u>Sequence</u>
covalent bonds

Assemblies / Clusters / Vesicles / Membranes →
<u>Composition</u>
non-covalent bonds

Segre and Lancet, EMBO Reports 1 (2000)

GARD model (Graded Autocatalysis Replication Domain)

- Synthetic chemistry
- Kinetic model
- Catalytic network (β) of rate-enhancement values

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Rate enhancement

$$\frac{dn_i}{dt} = \left(k_f \rho_i N - k_b n_i\right)\left(1 + \sum_{j=1}^{N_G} \beta_{ij} \frac{n_j}{N}\right) \qquad (i = 1..N_G)$$

Molecular repertoire

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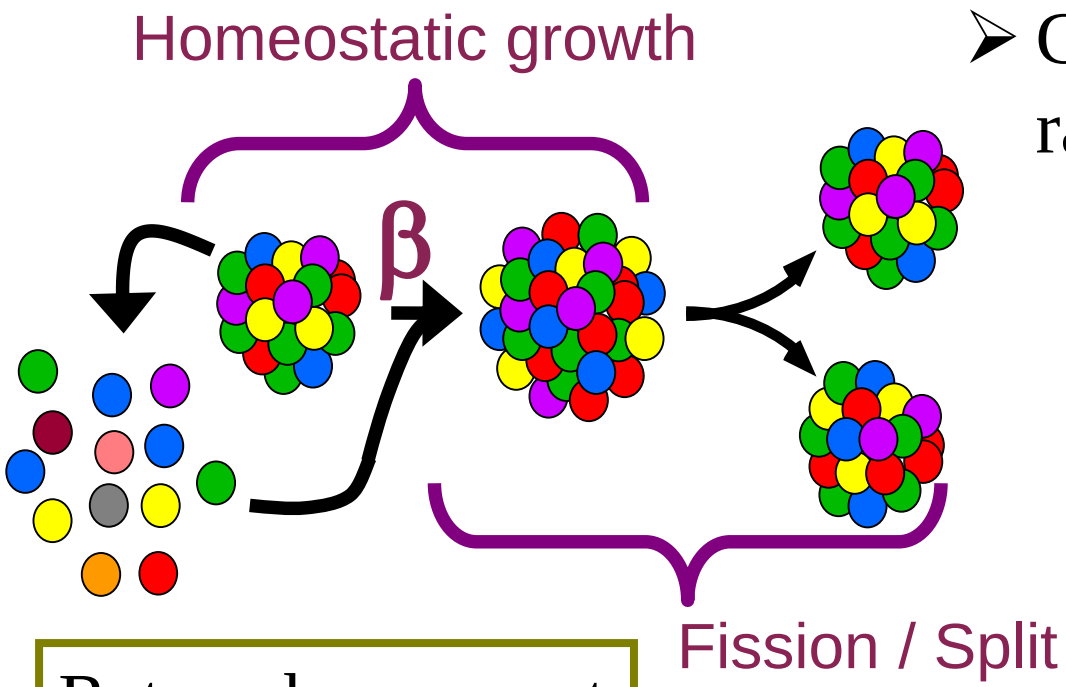

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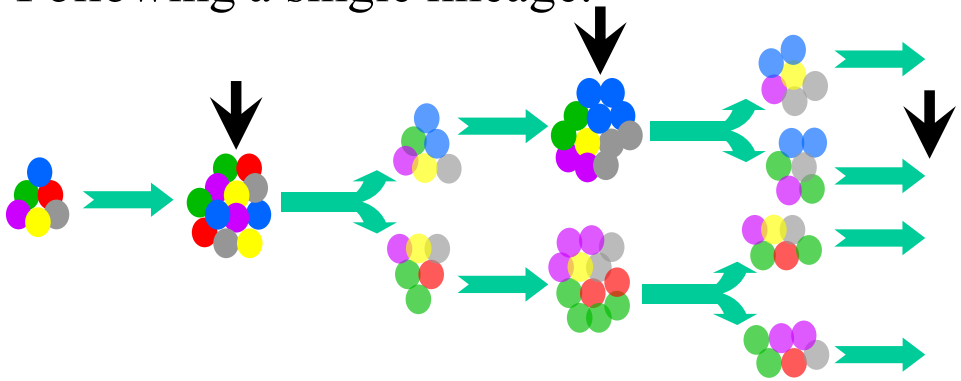

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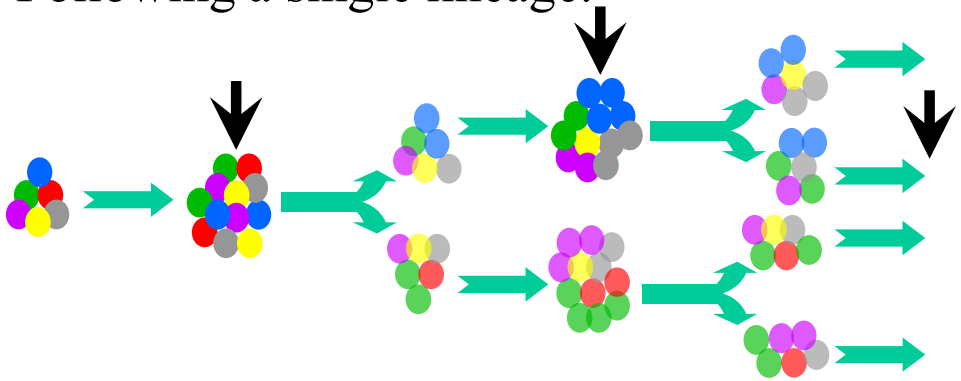
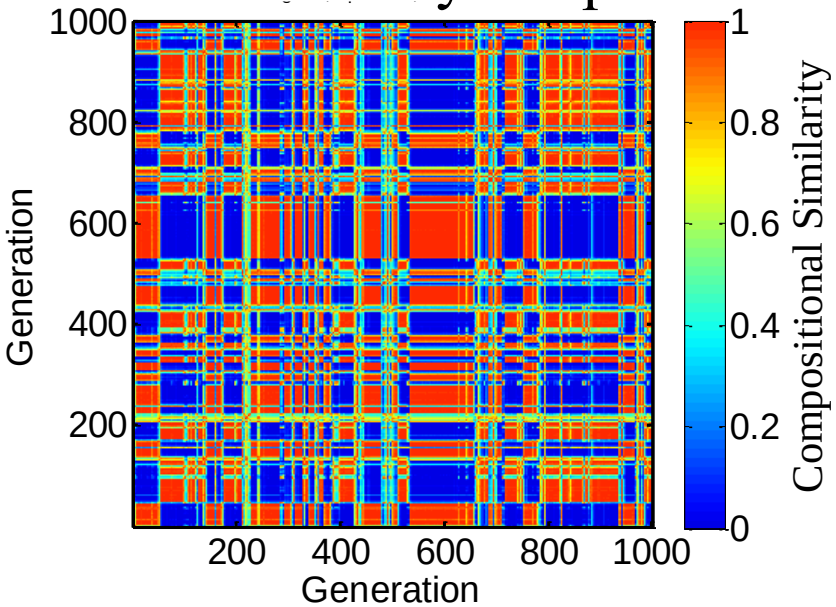


Similarity 'carpet'



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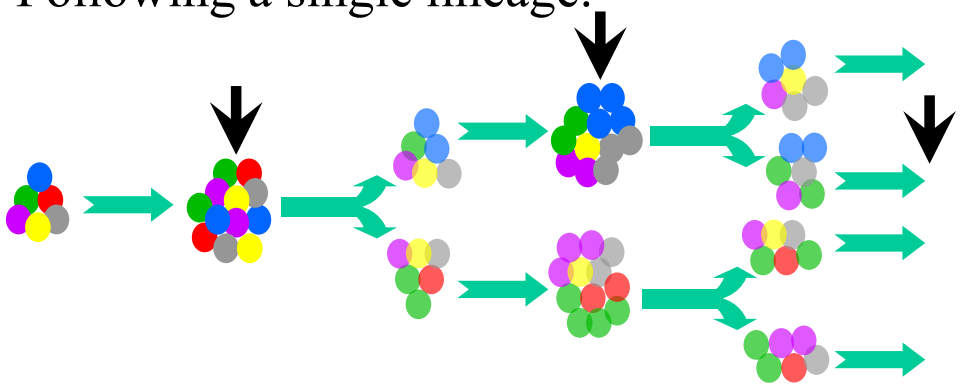

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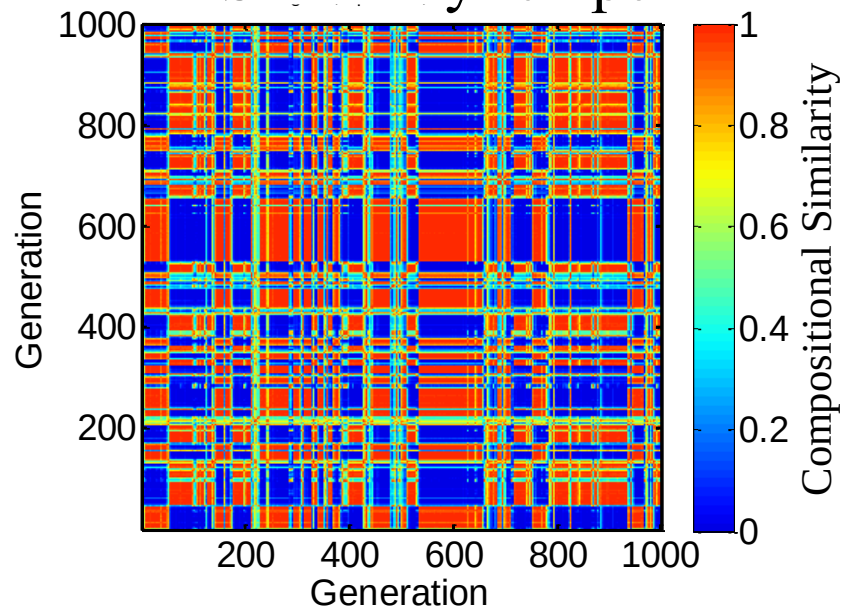

Composome (compositional genome): a faithfully replicating composition/assembly.

Compotype (composome type): a collection of similar composomes.

Molecular Compotype: the center of mass of the compotype cloud, treated as a molecular assembly.

GARD model (Graded Autocatalysis Replication Domain)

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- Idea: if we ignore the stochasticity inherent in the model, then errorless-replication occurs according to beta matrix eigenvectors.

Moment Algebraux

- Multiplying a matrix by a vector gives another vector
- $\boldsymbol{A} \cdot \vec{x} = \vec{y}$
- $\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \cdot \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} a_{11}x_1 + a_{12}x_2 \\ a_{21}x_1 + a_{22}x_2 \end{pmatrix} = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$

- An **eigenvector** is a vector $\vec{x}$ such that:
- $\boldsymbol{A} \cdot \vec{x} = \lambda \vec{x}$
  - λ is called the **eigenvalue**.
  - λ may be complex, and so may the eigenvector.

Moment Algebraux

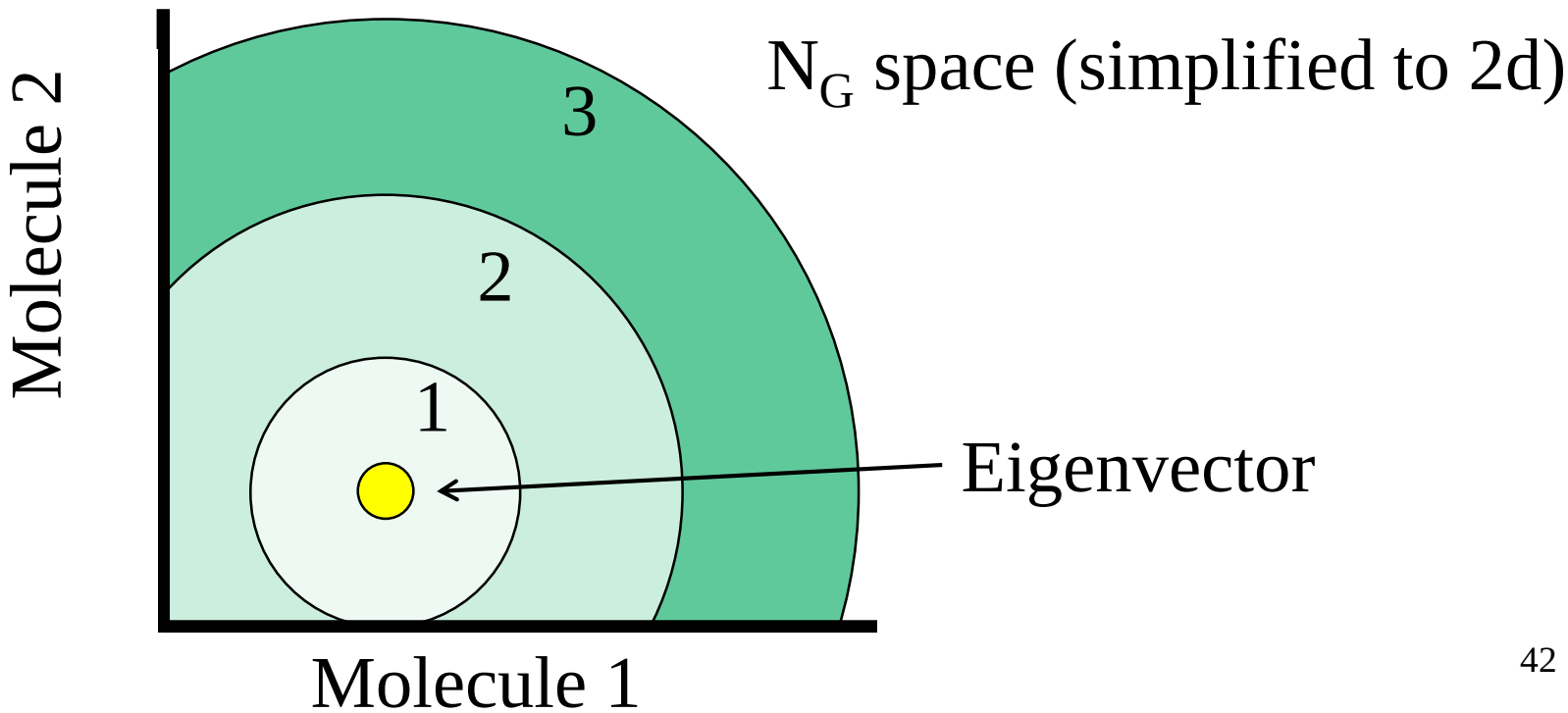
- The Perron-Frobenius Theorem:
  - A matrix with strictly positive entries contains a maximal **real** eigenvalue.
  - Its eigenvector is real and non-negative. In fact, it's the only one with this property.
- As molecular assemblies must contain real non-negative number of molecules, this looks interesting.

GARD and Quasispecies

- Do GARD population dynamics behave like the quasispecies model?
- What we would like to do:
  - For each assembly, experimentally find out the transition frequencies and replication rates
  - In other words: find **Q** and **A.**
- Problem:
  - $N_G = 100$, $n_{max} = 100$ ➔ There are $\binom{199}{100}$ possible assemblies ($\sim 4 \cdot 10^{58}$)

GARD and Quasispecies

- Solution: group some assemblies together and treat them as one genotype.
- We decided to group together by distances from the eigenvector.



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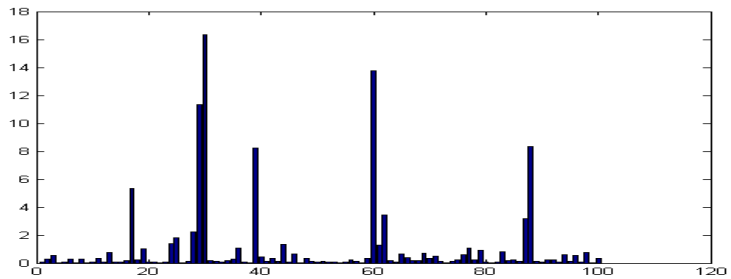

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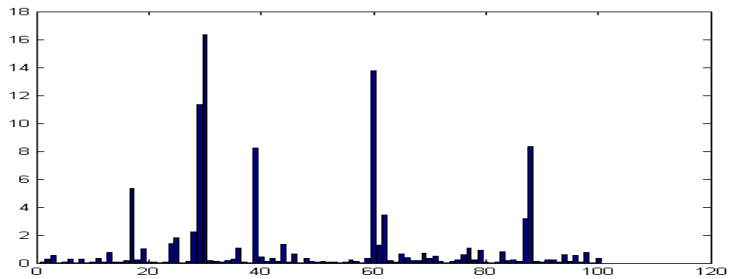

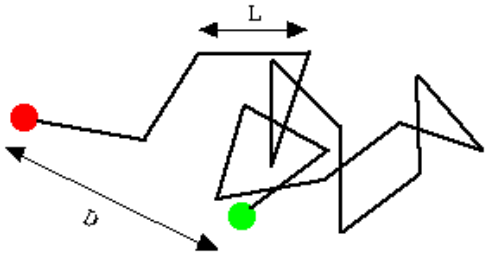

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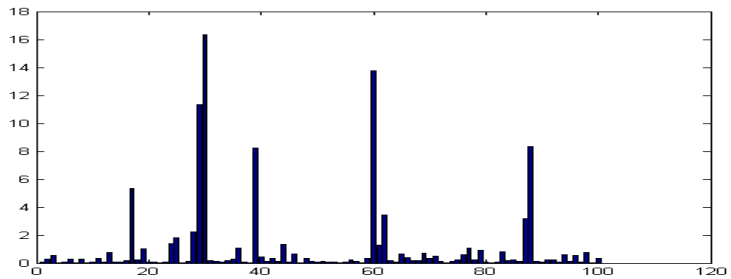
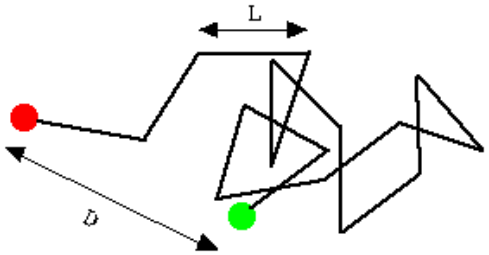


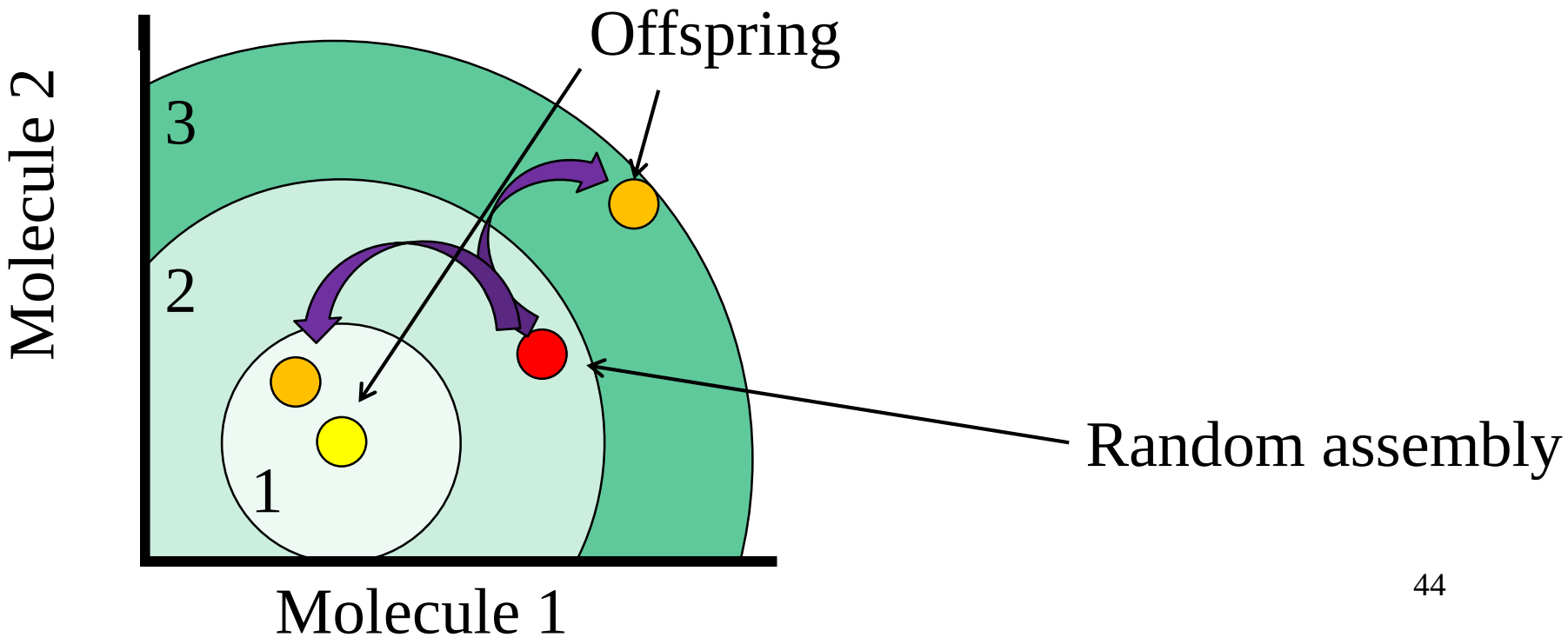


- Sampling is still a problematic issue.

- http://www2.ess.ucla.edu/~jewitt/oort2-random.html

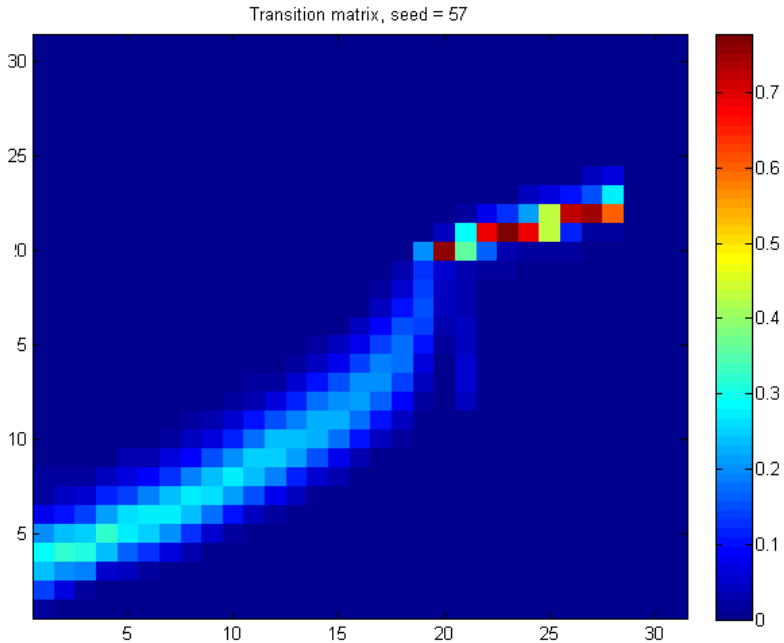
GARD and Quasispecies

- Each assembly is split and its offspring grown.
  - **Q** = to where did the assembly split?
  - **A** = how long did it take the offspring to grow?



- Example of a transition matrix:

To



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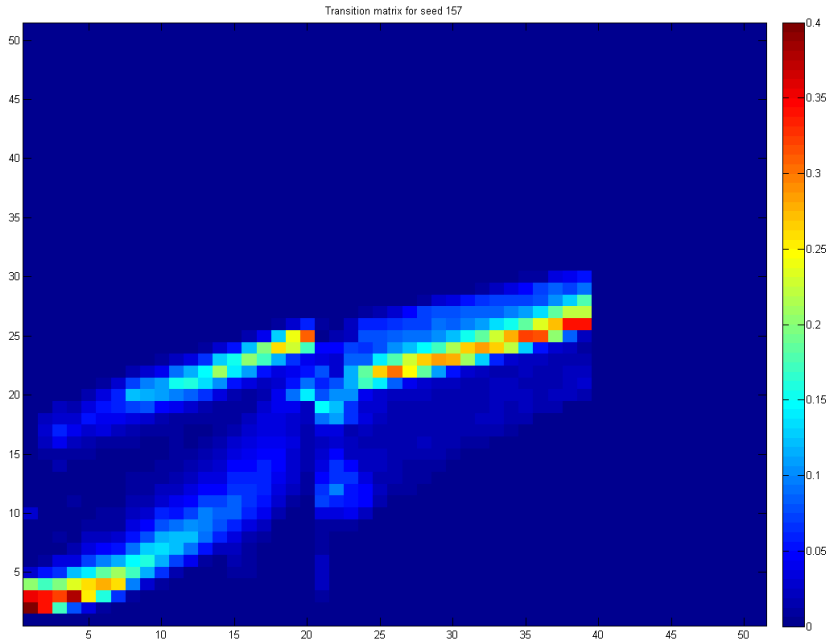


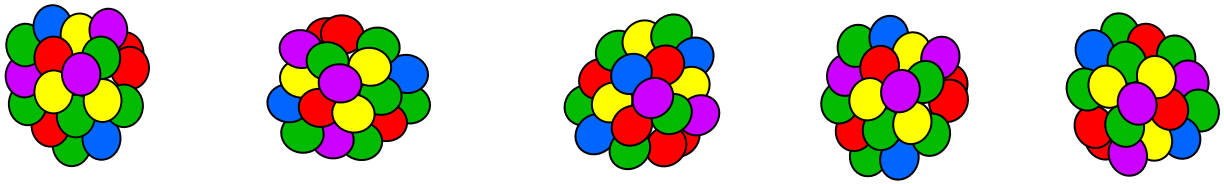
From

GARD and Quasispecies

- Now all that is left is to compare population model with quasispecies shell model.
- The population runs were already performed by Omer: a constant population Moran-process.

GARD and Quasispecies

- There is a constant number of assemblies in a population.



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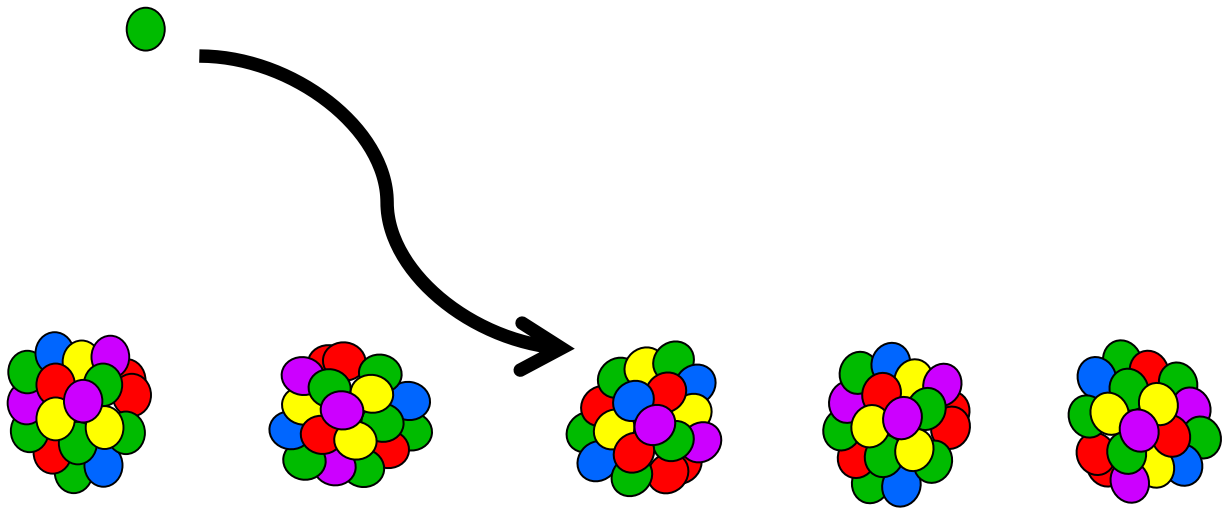

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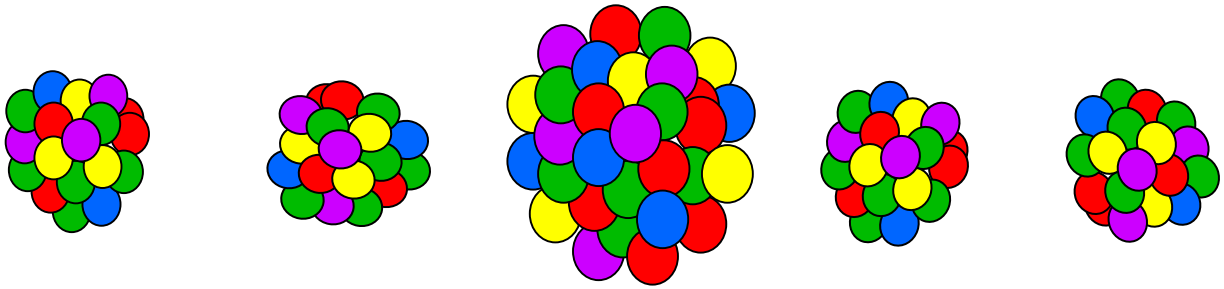

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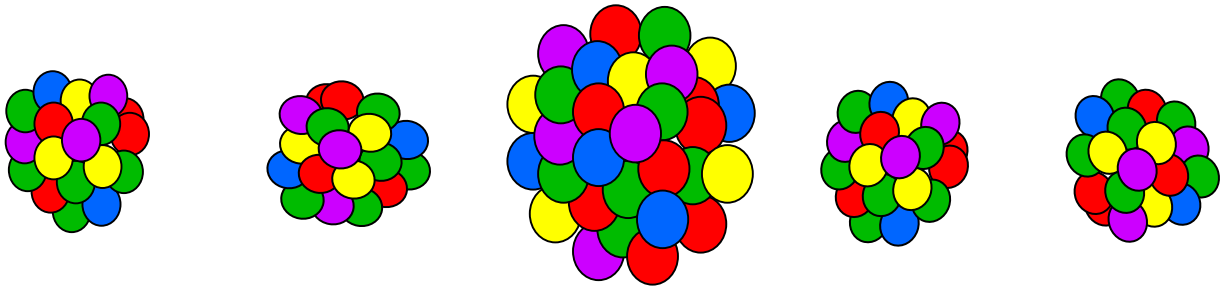

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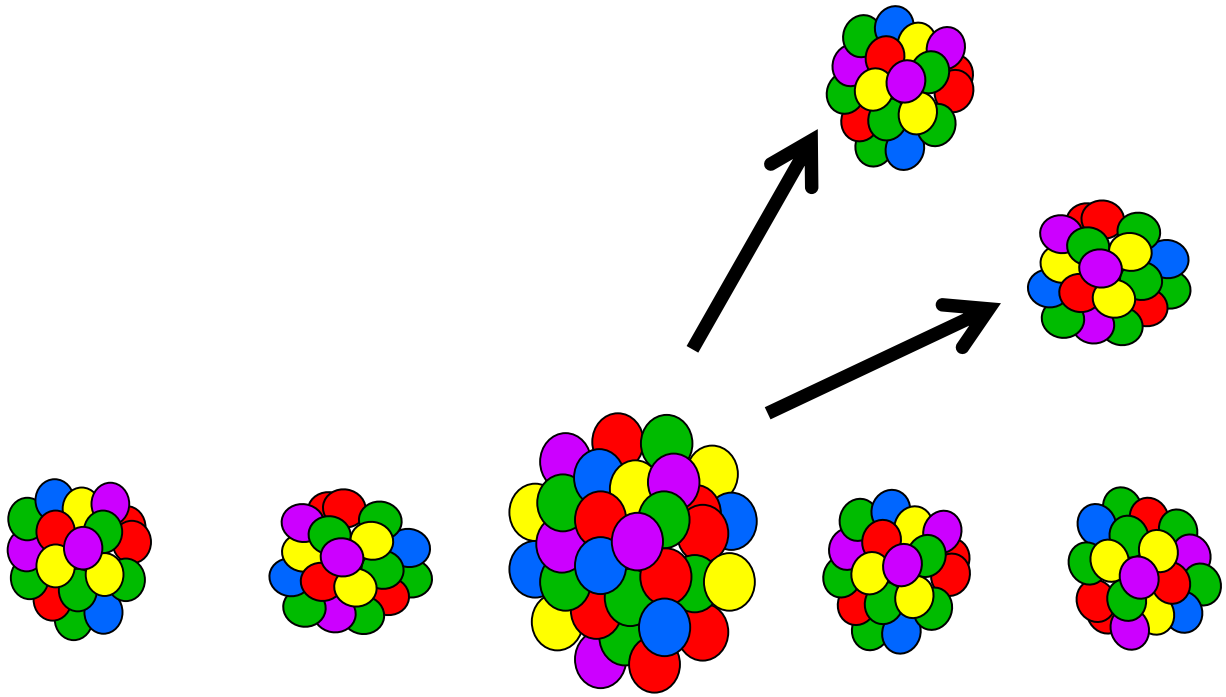

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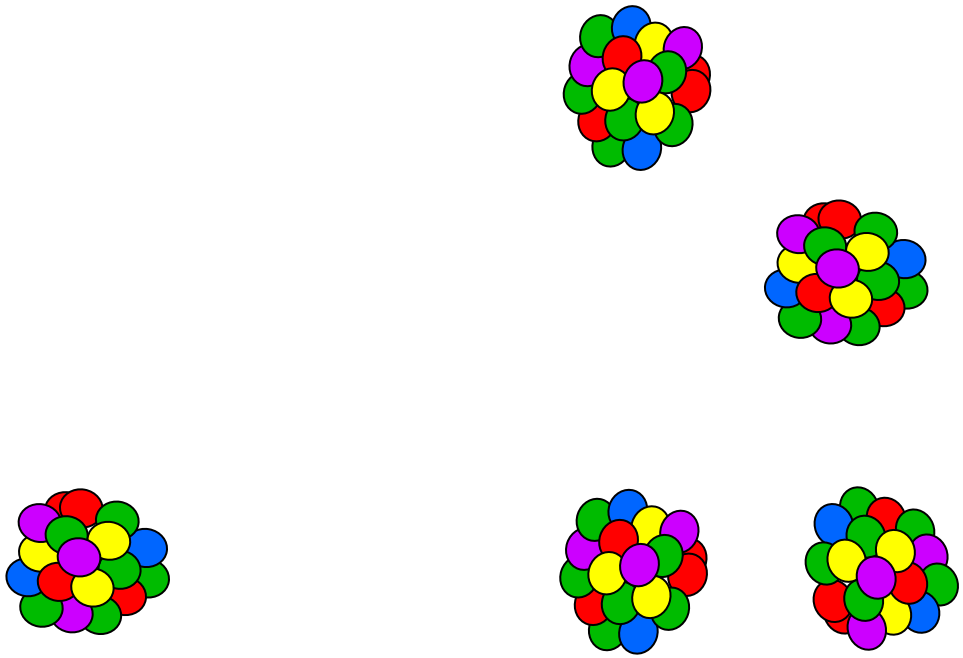

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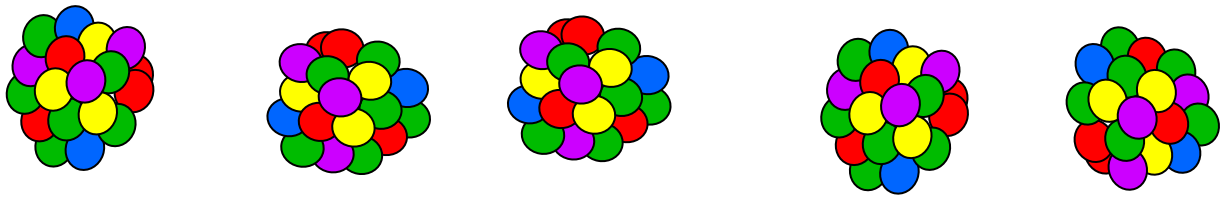
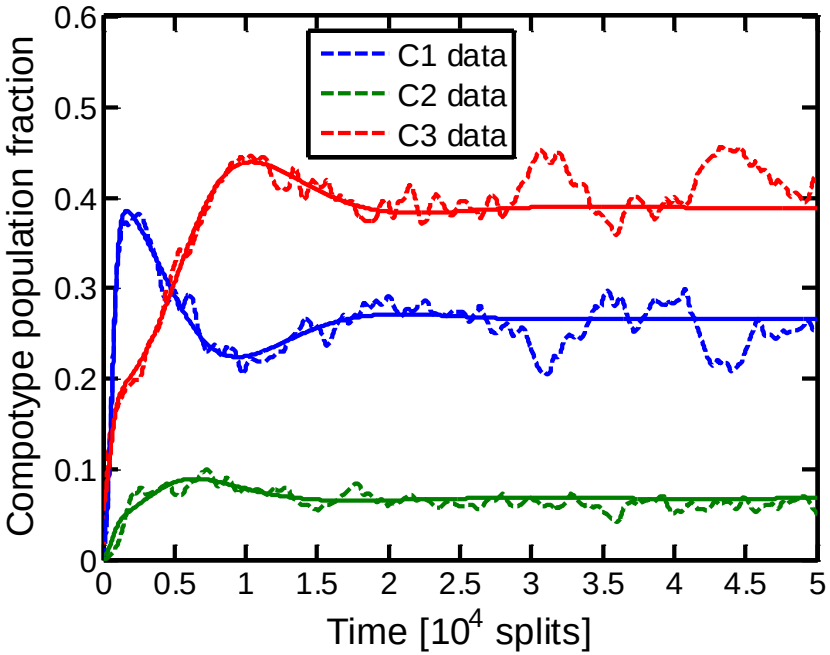


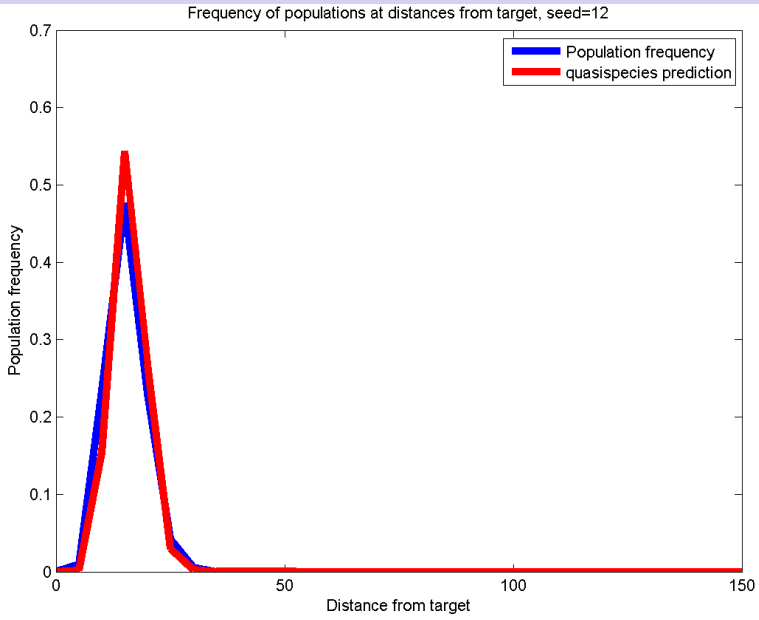
GARD and Quasispecies

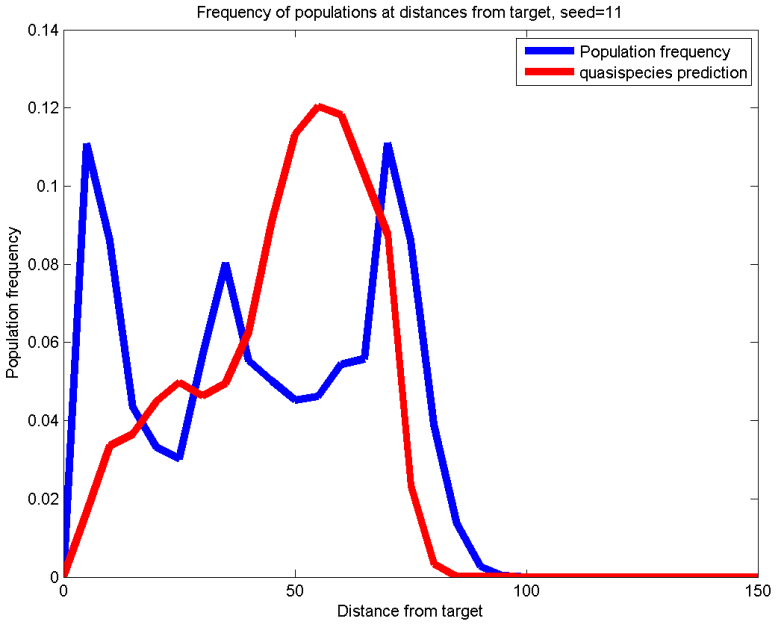
- The population simulation goes into steady state, concerning the frequencies of **compotypes** (as shown by Omer)

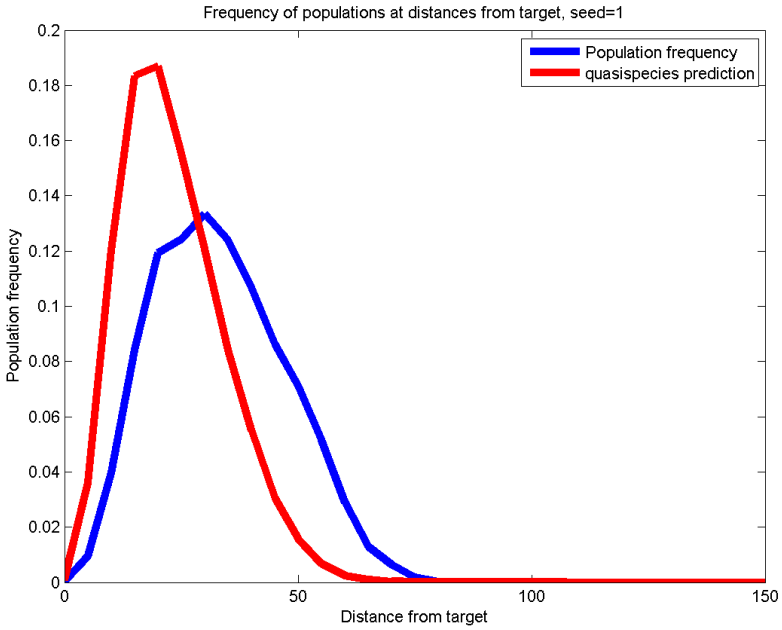


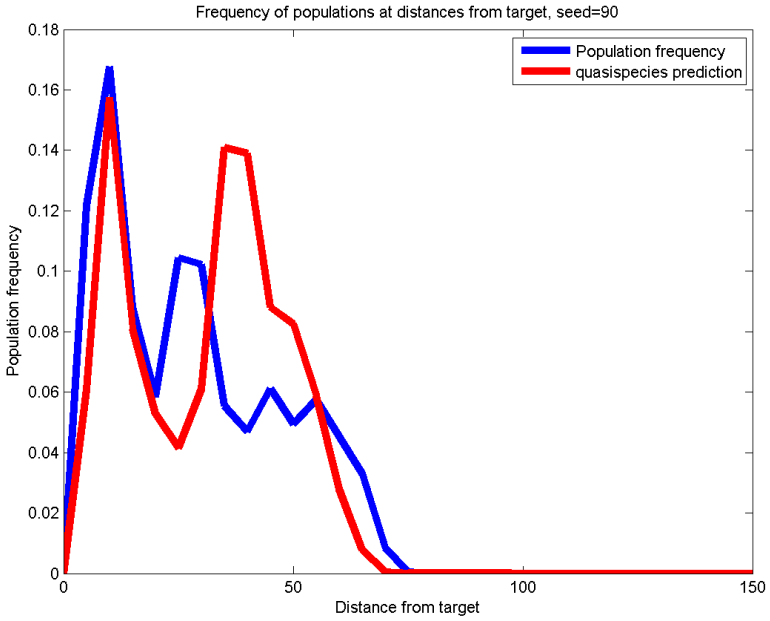
- The distribution of distances from the eigenvector was calculated for the population steady state, and compared with prediction.

GARD and Quasispecies









GARD and Quasispecies

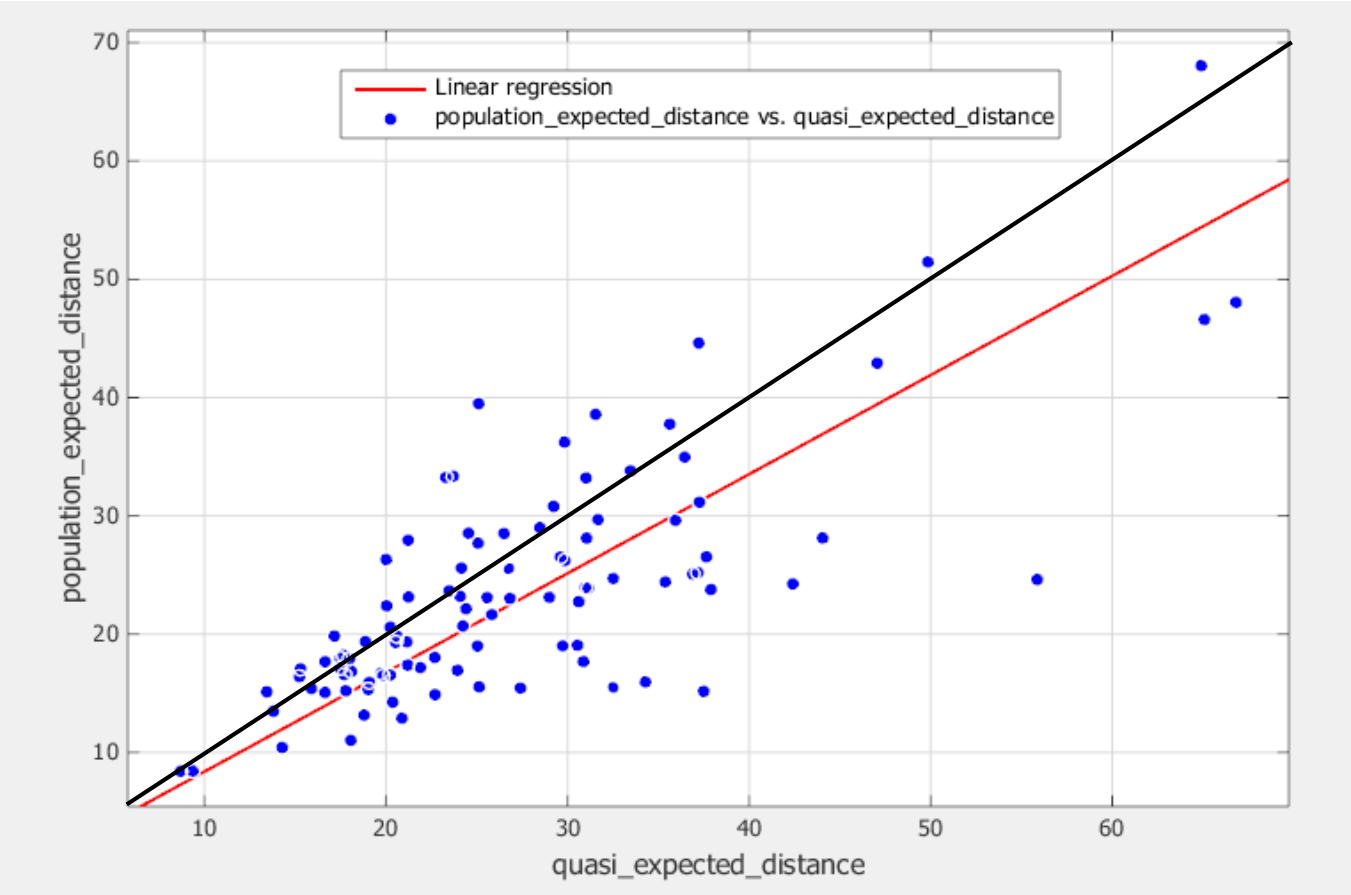
- How do we know if we got a good match?
- Two metrics were used:
  - Expected distance:

$$E = \sum_{i=1}^{n} d_i x_i$$

  - Pearson correlation – do the troughs and hills go up and down at the same time for both population and prediction?

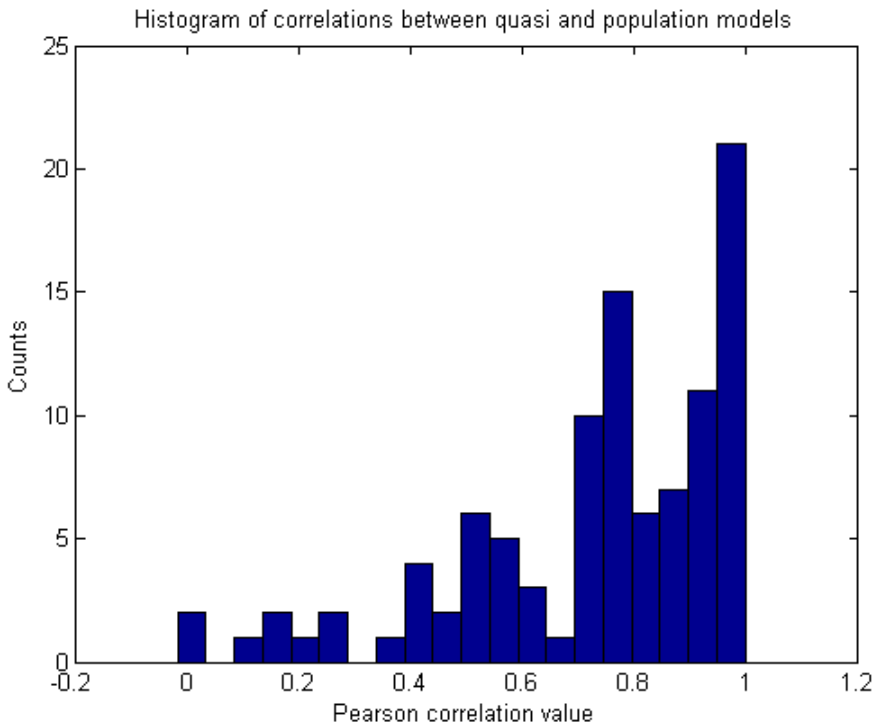
GARD and Quasispecies

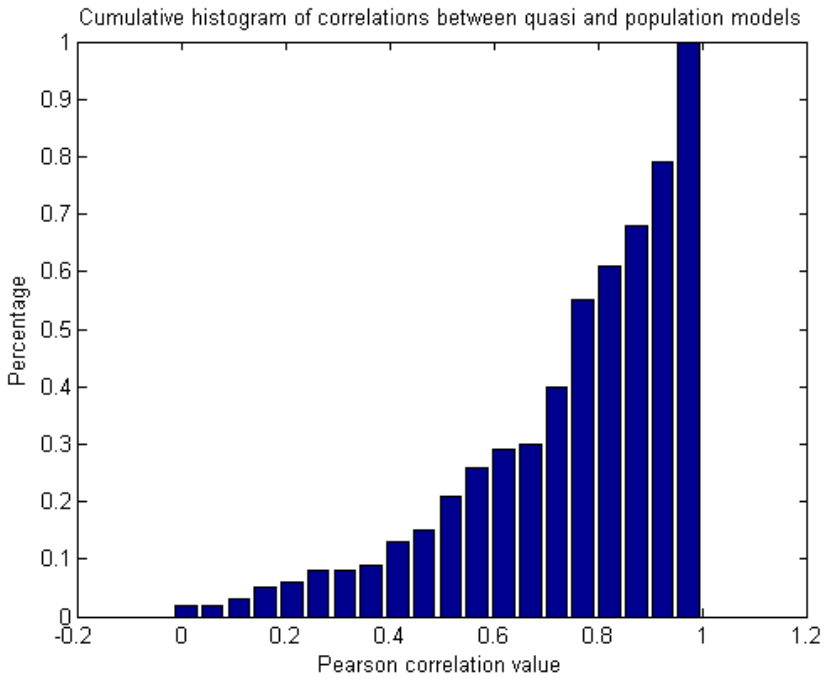
- Expected distances
- $R^2 = 0.52$, slope = 0.83



GARD and Quasispecies

- Correlations
- About half are above 0.8





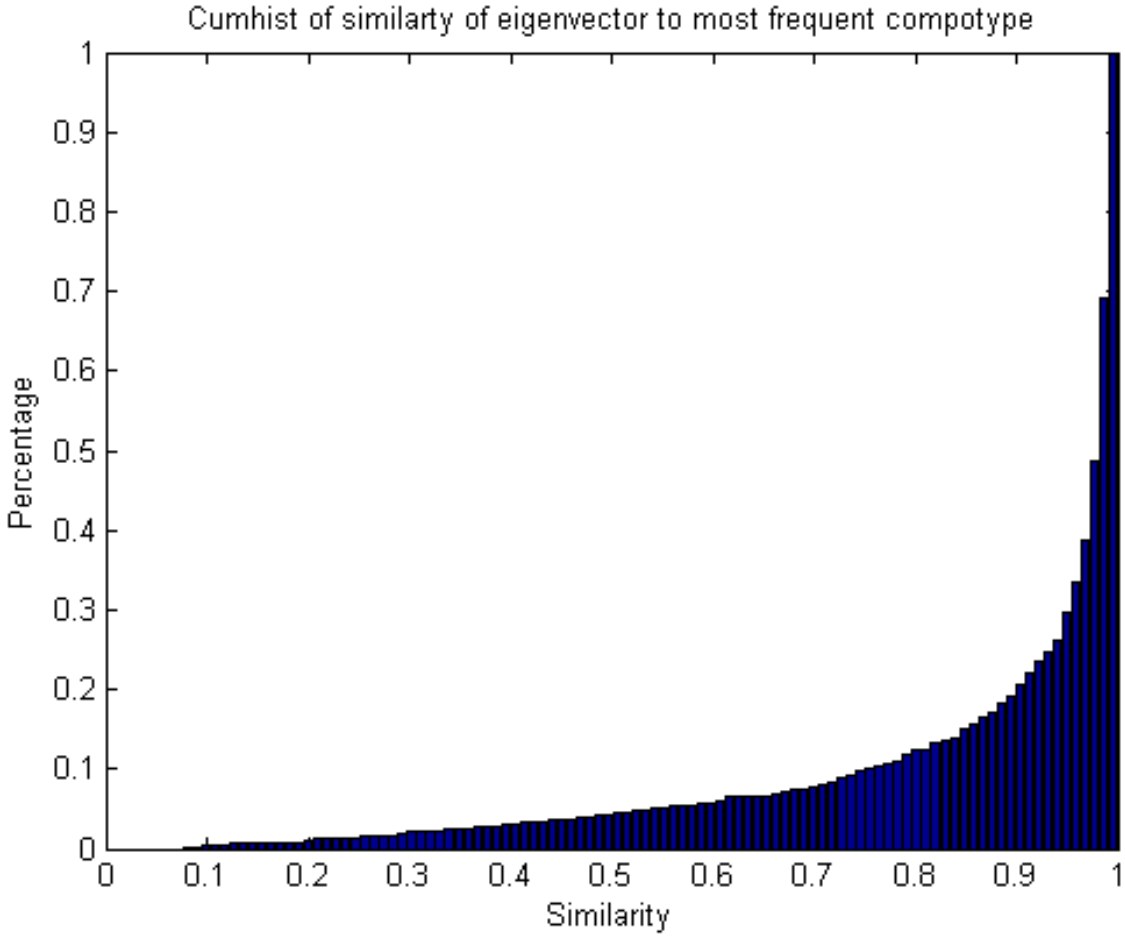
GARD and Quasispecies

- Ok, is this good?
- We can change the target of the distance measurement, to see if we get a better result.

- Two more assemblies were tried:
  - The most common compotype
  - A random assembly.

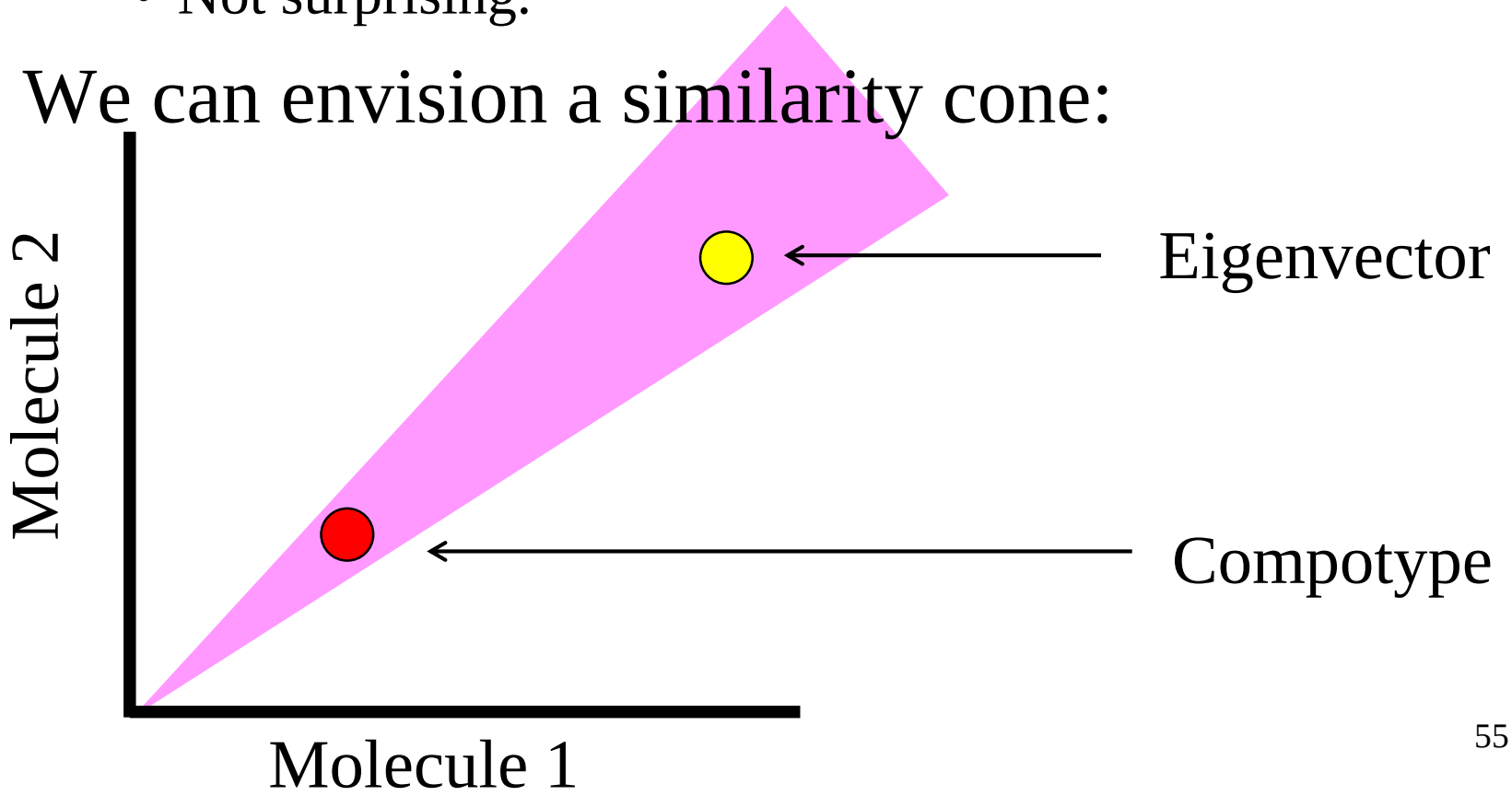
GARD and Quasispecies

- The most common compotype is very similar to the eigenvector.



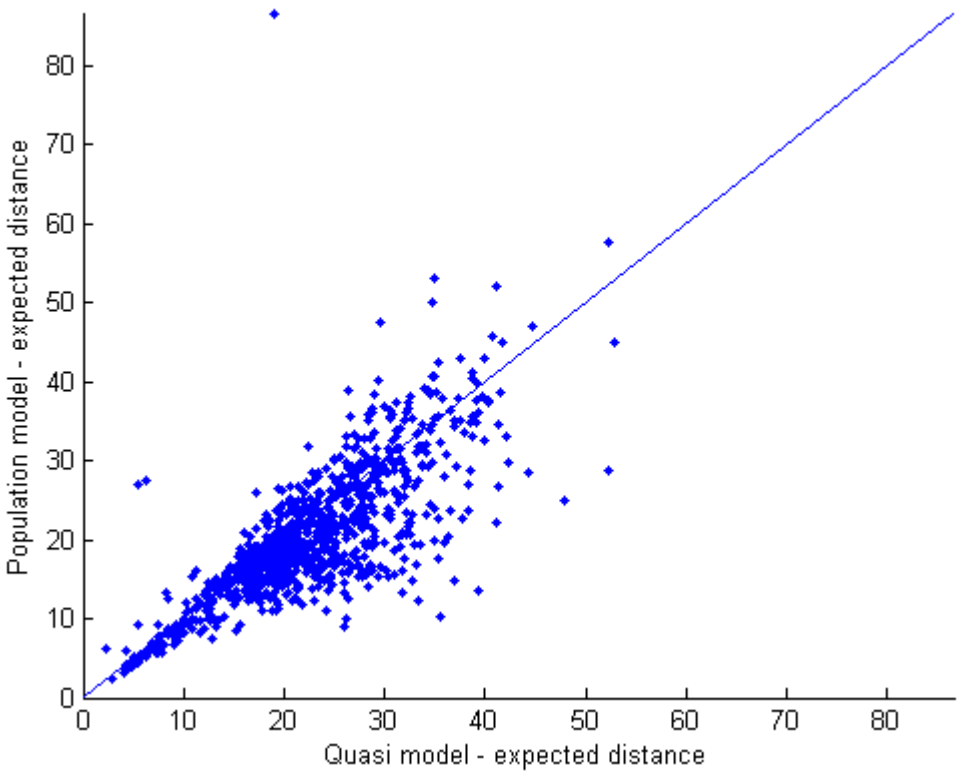
GARD and Quasispecies

- However, they are not exactly the same; often the eigenvector is larger (larger Euclidean norm)
  - This means it is less homogenous than compotypes
    - Not surprising.
- We can envision a similarity cone:



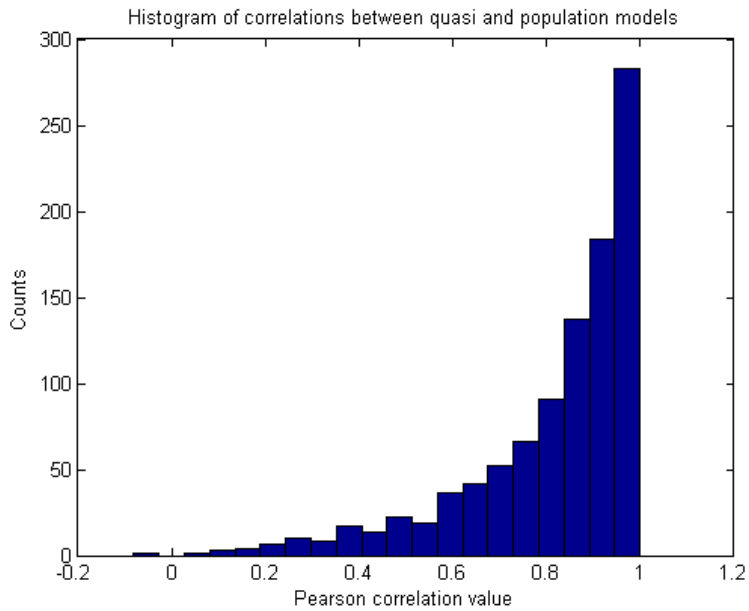
GARD and Quasispecies

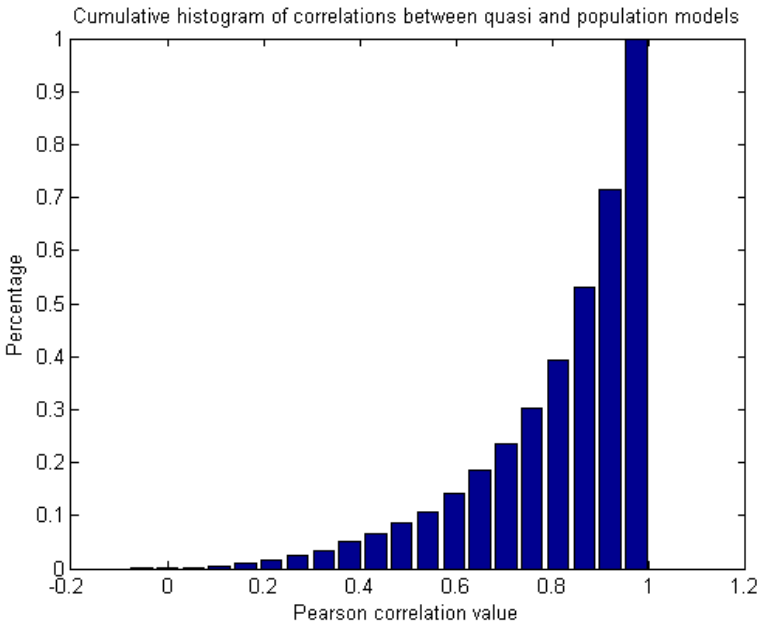
- Results are better for compotypes, and worse for random. $R^2 = 0.64$, slope = 0.89



GARD and Quasispecies

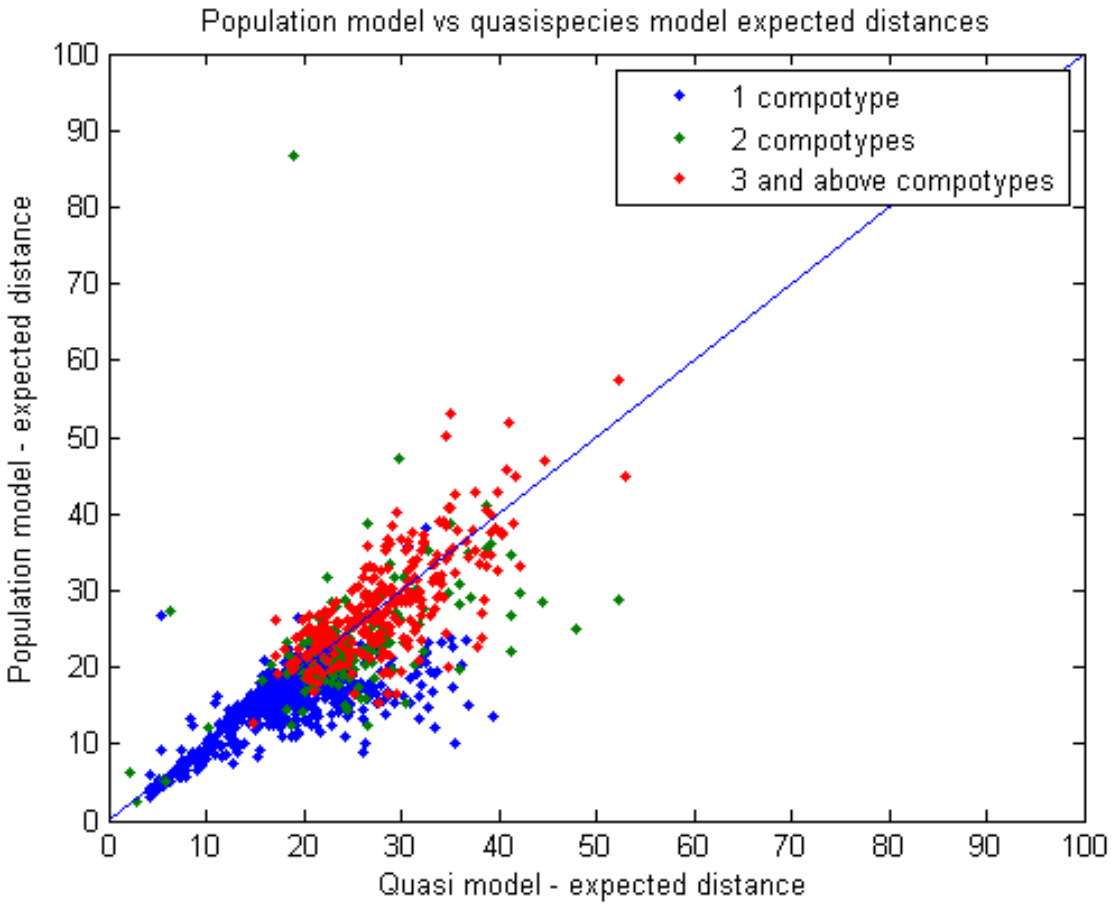
- Correlations
- About 0.7 are above 0.8





GARD and Quasispecies

- There is a dependence on the number of compotypes

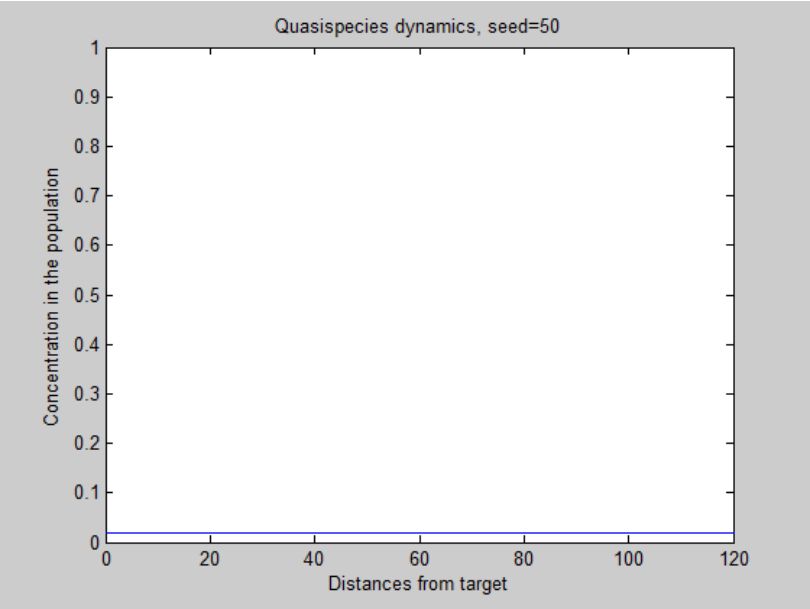


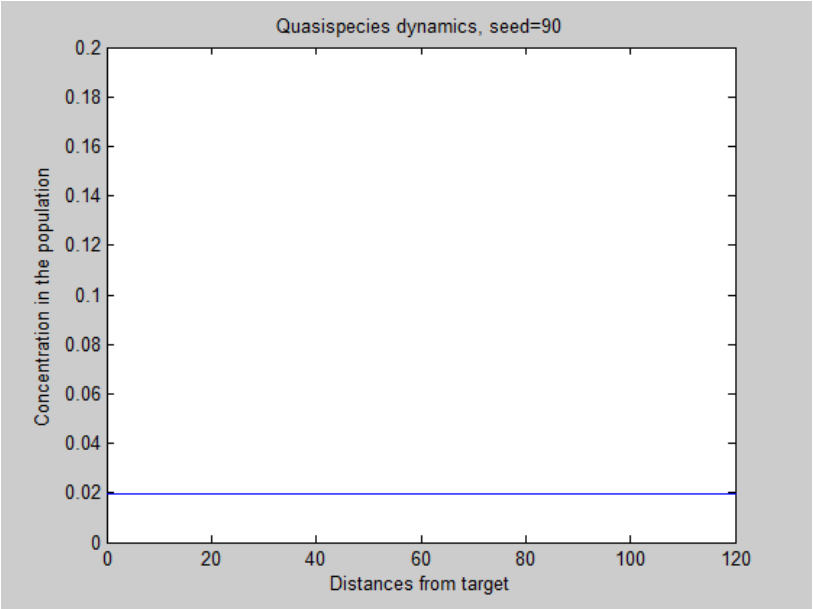
GARD and Quasispecies

- The future…?
  - Better sampling
  - More rigorous analysis of number of compotypes

GARD and Quasispecies

- The future…?
  - Better sampling
  - More rigorous analysis of number of compotypes
  - Dynamics, and not just steady state





Error Catastrophe in GARD

- For sequential information carriers, *q* acts as a "faithful replication" parameter.
- Does anything like this exist for GARD?

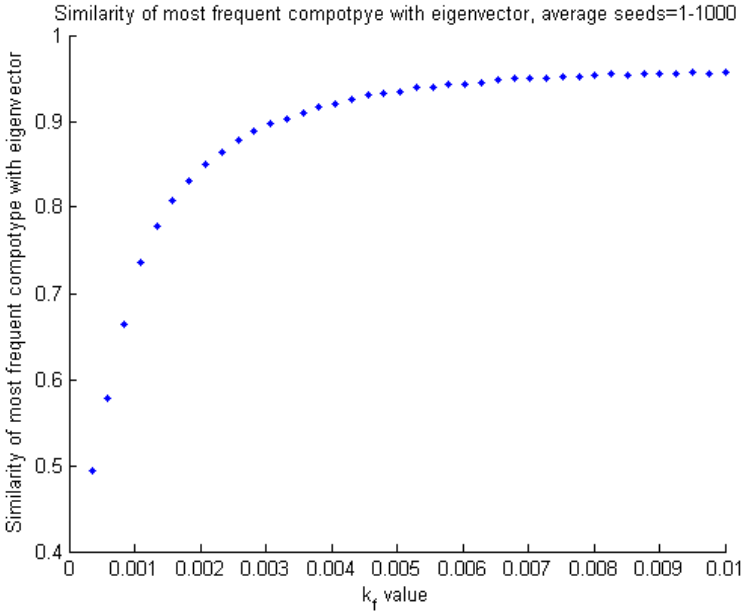
  "*Idea: if we ignore the stochasticity inherent in the model and solution, then errorless-replication occurs according to beta matrix eigenvectors.*"

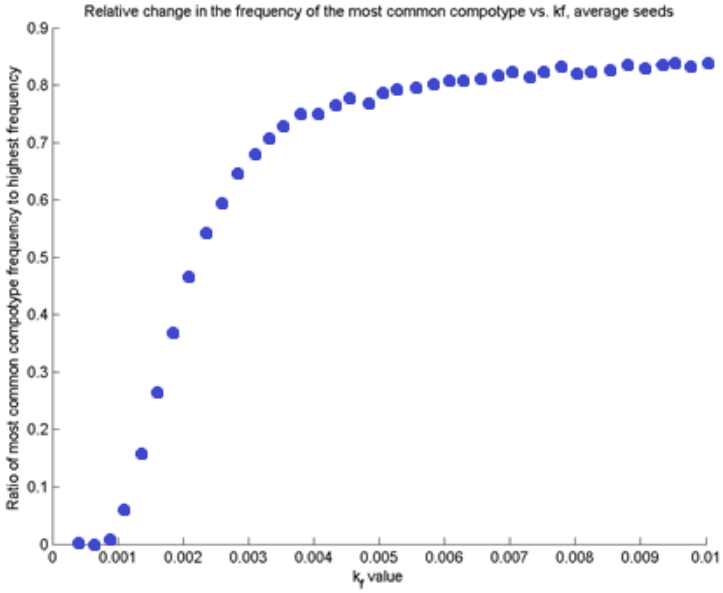
  - R.G

- Forward and backward accretion (k_f and k_b) are responsible for much of the stochasticity.

Error Catastrophe in GARD

- What happens if you lower k_f ?
- Run single lineage simulation with different k_f values.





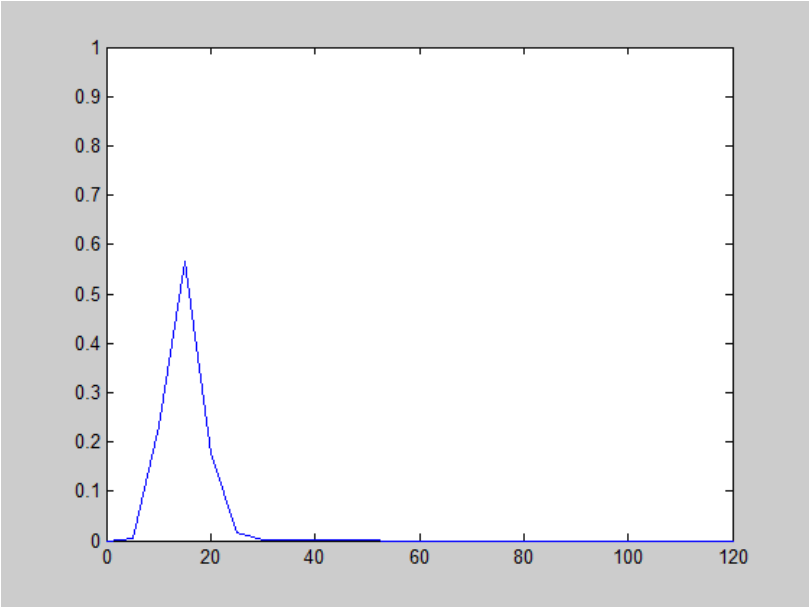
Error Catastrophe in GARD

- Since the most common compotype frequency decreases drastically, there is a high increase in drift → no composomes.

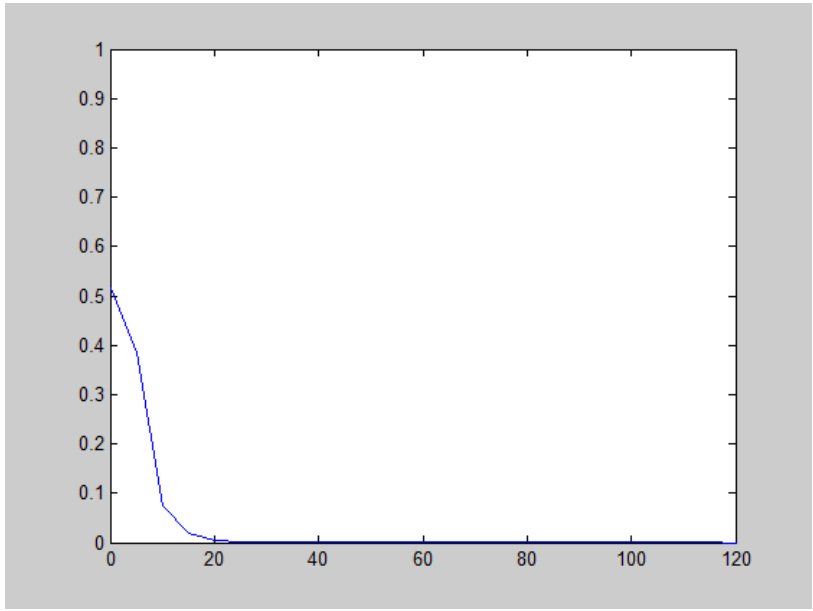
- Conclusion: k_f and k_b affect replication fidelity.

Error Catastrophe in GARD

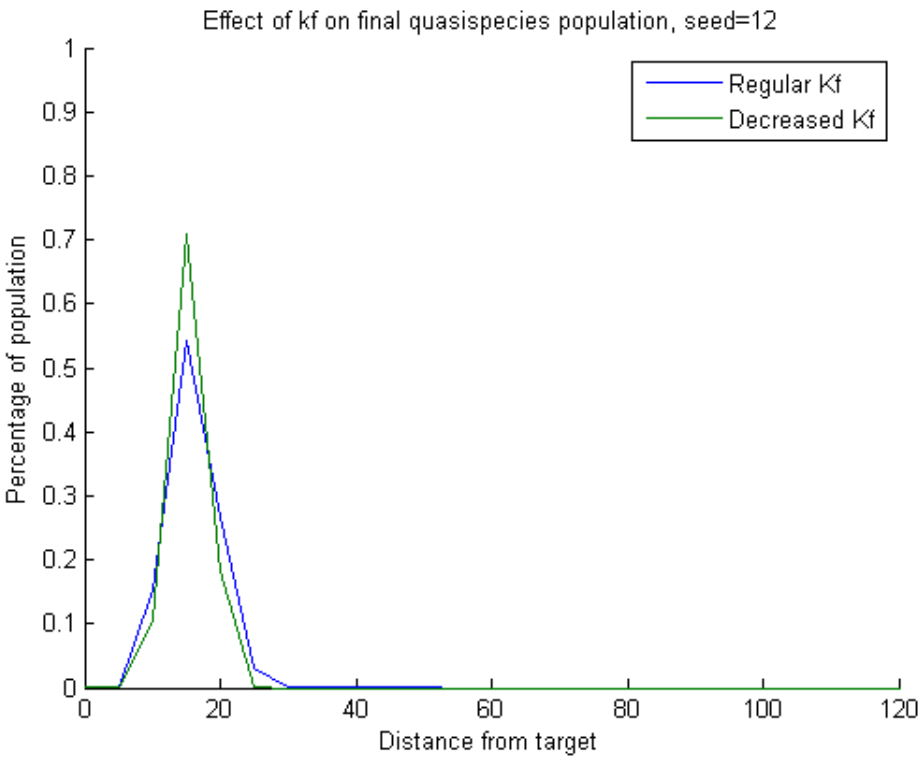
- What happens in quasispecies model?
  - We obtained **Q** and **A** for lower k_f values.
- Two types of results:
- Seed = 12

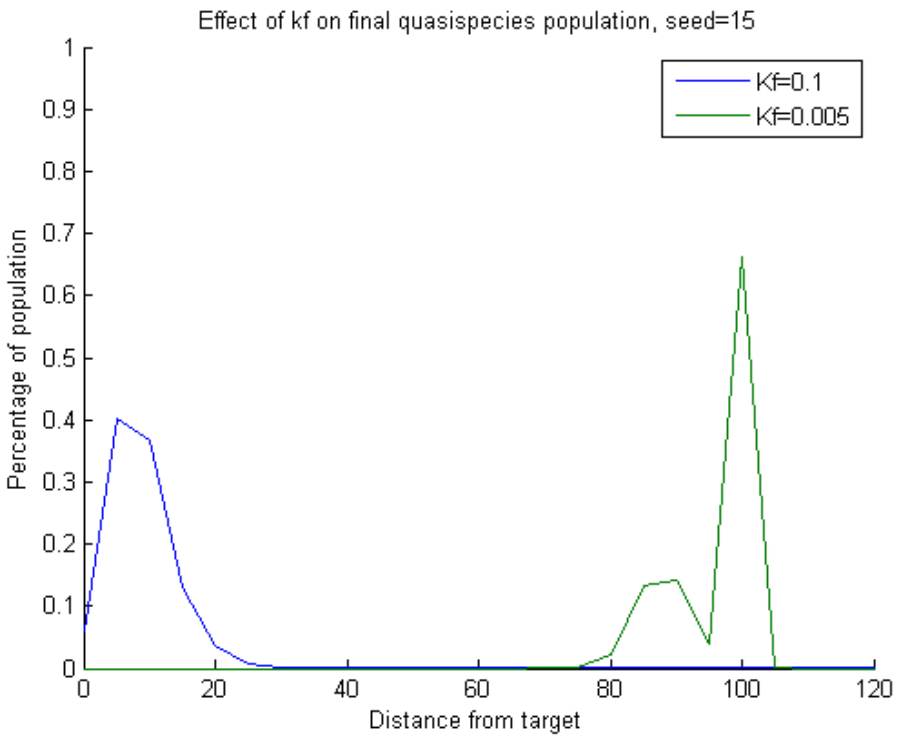


Seed = 15



Error Catastrophe in GARD





- The difference seems to relate to the **size** of the compotype.

Error Catastrophe in GARD

- Random drift assemblies are homogenous → they have small Euclidean norm.
  - **X** == [100, 0, 0, 0, 0, 0,…,0] ➔

$$|\boldsymbol{X}| = \sqrt{100^2} = 100$$

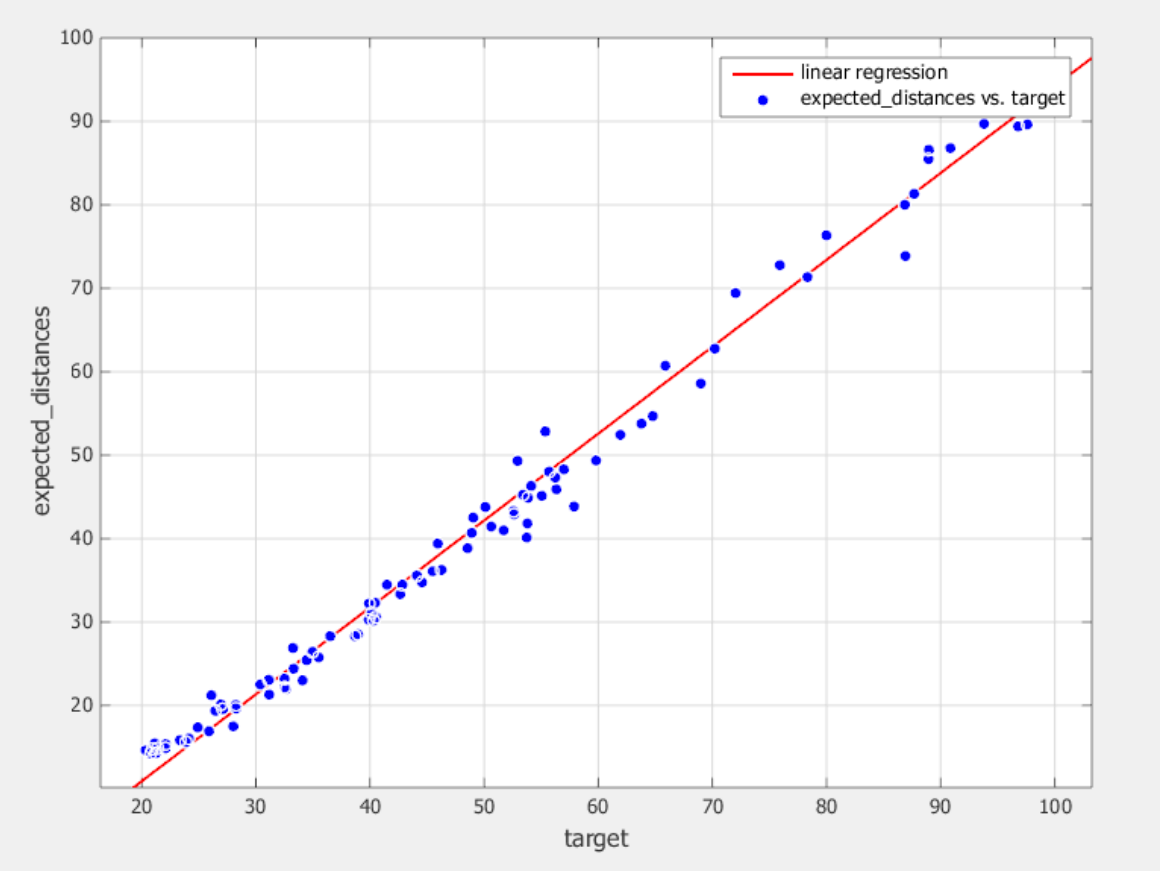
  - **X** == [1, 1, 1, 1, …, 1] ➔

$$|\boldsymbol{X}| = \sqrt{1 + 1 + 1 \ldots} = \sqrt{100} = 10$$

- Distances to compotypes / eigenvectors then depend mostly on the size of the compotype / eigenvector.

Error Catastrophe in GARD

- Indeed, not that bad correlation.
  - $y = 1.041x - 9.89$; $R^2 = 0.9899$



Error Catastrophe in GARD

- K_f and K_b are similar to q
- Of course, there are differences.
  - No complementary replication
  - In this case, what is the master sequence?
  - Back mutation?

Conclusions

- GARD constant population models give distance distributions that are similar to those generated by the quasispecies model.

- GARD replication fidelity shows sensitivity to k_f and k_b. Low k_f results in loss of compotype dominance, just like low q-0.5 results in loss of master sequence.

∴ Compotypes/composomes behave similarly to quasispecies.