

Origin of directional epistasis in RNA folding

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-1-

Decay Functions

- Investigate fitness decay functions $w(d)$.
- Decay functions give change in average fitness with genetic distance d from some reference sequence.
- In RNA case: $w(d)$ is the number of neutral folds divided by the total number of sequences at distance d .

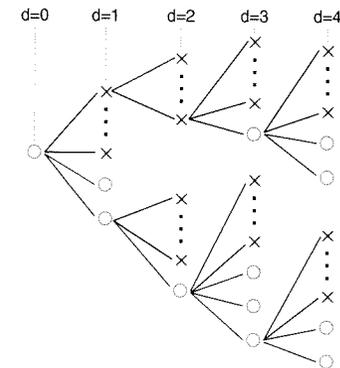
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Fitness Landscape

Null hypothesis
(no epistasis):
 $w(d) \approx \exp(-\alpha d)$

With epistasis:
 $w(d) \approx \exp(-\alpha d^\beta)$

$\beta > 1$: synergism
 $\beta < 1$: antagonism



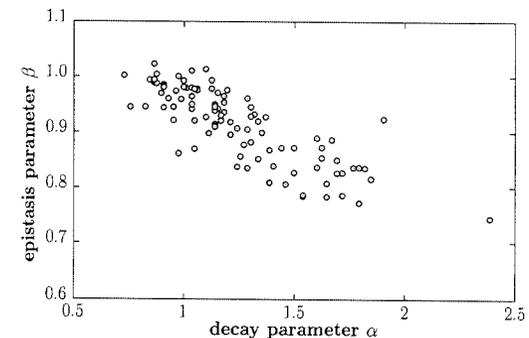
Exponential decay is caused by the treelike structure of the genotype space (circles: viable sequences, crosses: inviable sequences).

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Correlation between α and β

Measured α and β for 100 random RNA sequences of length 76 (RNA folding done with Vienna package).

Result:
 α and β are strongly correlated.



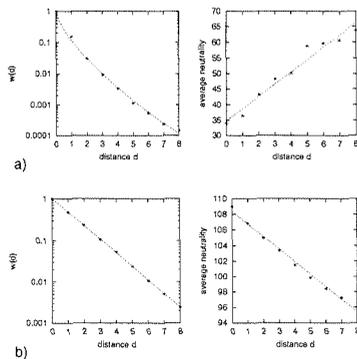
→ Sequences for which single mutations have a large effect are strongly antagonistic, sequences for which single mutations have a small effect are only slightly antagonistic or even synergistic.

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Origin of correlation

high $\alpha \rightarrow$
 high density of neutral
 sequences \rightarrow
 density decreases as d
 increases \rightarrow high β

likewise:
 low $\alpha \rightarrow$ low β .



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Origin of shift in β

Hypothesis: background of compensatory mutations shifts distribution of β .

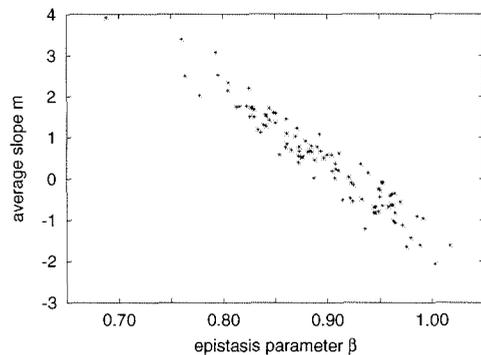
Here, compensatory mutations are defined as those that lead from an inviable sequence to a viable one that is not part of the original neutral network.

Knowledge of neutrality at distance d allows us to disentangle compensatory mutations from other mutations.

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Distribution of Density Changes

The parameter m measures the change in neutrality with distance d from the reference sequence.

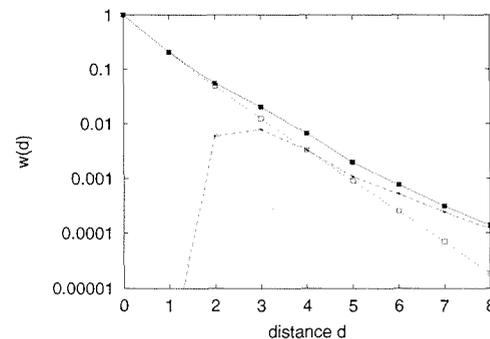


Why is β always $\lesssim 1$, when neutrality changes (m) go both ways?

-6-

Adjusting for Compensatory Mutations

We can separate $w(d)$ (solid line) into contributions from original neutral network (dashed line) and contribution from compensatory mutations (dot-dashed line).

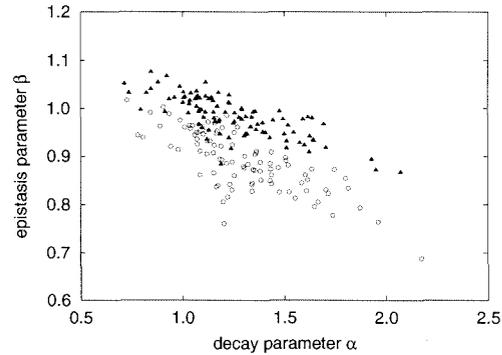


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Adjusted α and β

The adjustment results in an upwards shift of β .

The epistasis parameter α is almost unaltered after the adjustment.



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Conclusions

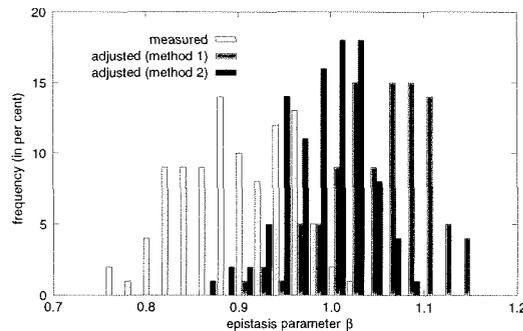
- Strength and direction of epistasis depend on position of chosen reference sequence in genotype space.
- Synergistic epistasis: reference sequence is in center of a dense cluster of viable sequences.
- Antagonistic epistasis: reference sequence is outside of a dense cluster of viable sequences.
- Background of compensatory mutations leads to excess of antagonistic epistasis.

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Distribution of β

We use two different methods of adjustment

In both cases, a significant percentage of cases has $\beta > 1$.



(Measured: $\langle\beta\rangle = 0.89 \pm 0.01$, Adjusted M1: $\langle\beta\rangle = 1.05 \pm 0.01$, Adjusted M2: $\langle\beta\rangle = 0.98 \pm 0.01$)

-10-

References

- I. L. Hofacker *et al.* Fast folding and comparison of RNA secondary structures. *Monatshefte f. Chemie*, 125:167–188 (1994).
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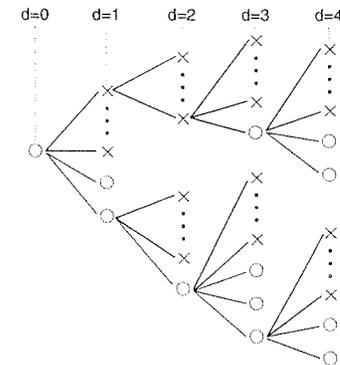
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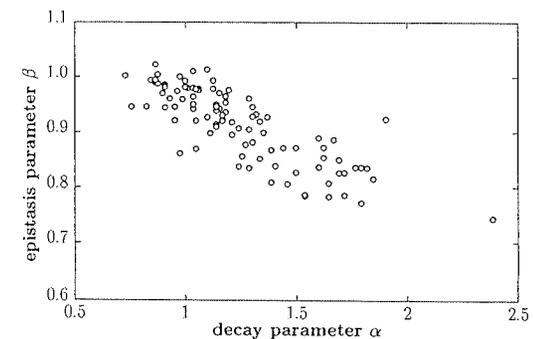
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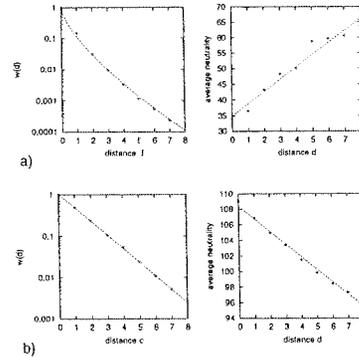
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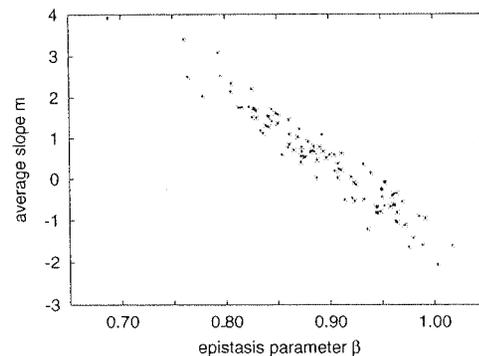
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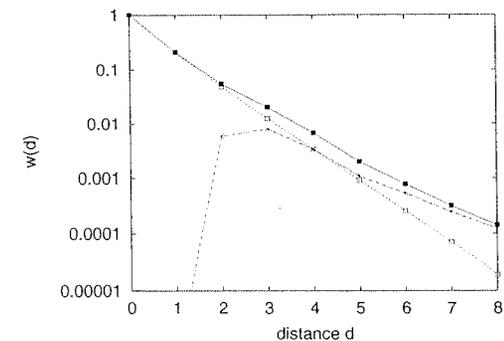


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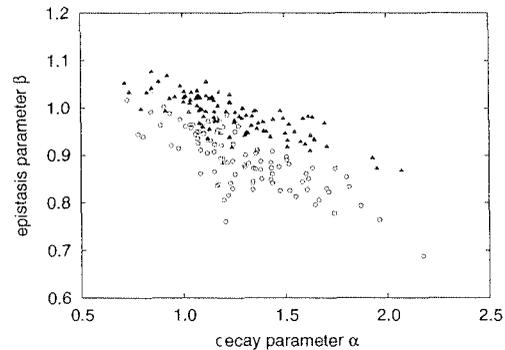


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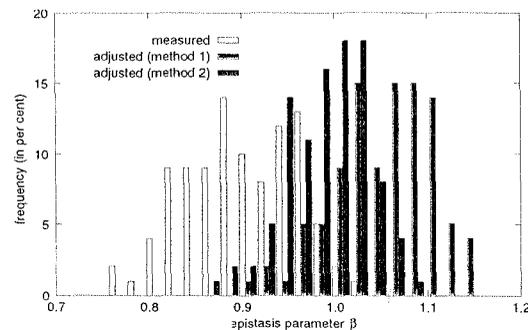
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