Non linear genotype-phenotype mapping: RNA landscapes
UPTO NOW

Classical Population Dynamic replicator models

+ Space or vesiccles
  emergent or predefines mesoscale pattern)

+ invasion OR ongoing PHENOTYPIC Mutations
  (parameters of the model)

Who persists/invades; outcompete/outevolve;

multilevel evolution: replicators and “above”

Evolution of complexity as conflict resolution
HOWEVER....... 

*what whe did “wrong” so far*

“Defining property of biotic systems”:

**Very high dimensional genotype space**

**complex genotype - phenotype mapping**

Therefore use of phenotypic mutations in few dimensions not appropriate

*no RNA in RNA world*

*RNA-like Replicators dimensionless points without physical/chemical properties*
Constructive Darwinian Evolution

Darwinian evolution as efficient design (optimization) tool

*Genetic Algorithms (Holland), evolutionary computation*

- population of (coded) structures/solutions/'cases'
- mutational operators
- fitness criterion
- reproduce/decay according to fitness

**e.g.**

- computer network design/job scheduling
- robotic control/body design
- protein design

*in vitro evolution* **Ribozymes** *(RNA world)*
in vitro RNA evolution - ligase
search space ca $4^{120}$ - pop size $10^{10}$

**WHY do we find it??**

All positions essential!
Landscape important in hill climbing
(and evolution of finite population(?))

**Fitness Landscape**

- **genotype** \(\rightarrow\) **phenotype** \(\rightarrow\) **fitness**

**coding structure**!

- Smooth - no epistasis
- Rugged epistasis
RNA secondary structure as paradigm for 'natural' coding structure
genotype-phenotype (GP) map

- computable 'natural' genotype-phenotype map
- RNA world
- in vitro evolution efficient

assume fitness depends on distance to predefined target secondary structure

Fontana, Schuster, Hoffacker, Ancel, Flamm etc. (Vienna)
Huynen, van Nimwegen, Takeuchi, Hogeweg (Utrecht)
RNA Structure (tRNA-phe yeast)

Sequence (2D)

2D Structure

2D Structure (Mountain range representation)

3D Structure
Computation of RNA genotype-phenotype mapping

- Secondary structure is planer

![Secondary structure diagram]

- Base pairs
  
  \[
  \begin{align*}
  e(C, G) &= -3 \\
  e(A, U) &= -2 \\
  e(G, U) &= -1 \\
  e(\text{others}) &= 0
  \end{align*}
  \]

- Minimum energy

  If \( j - i < 4 \) (i.e., length < 5),
  
  \[ E_{i,j} = 0 \]

  Otherwise,

  \[
  E_{i,j} = \min \begin{cases} 
  E_{i+1,j}, & E_{i,j-1} \\
  e(i, j) + E_{i+1,j-1} \\
  \min_{i' = i+1}^{i'-1}(E_{i,i'} + E_{i'+1,j}) 
  \end{cases}
  \]

  \[(1) \quad (2) \quad (3)\]

(Zuker & Stiegler '81!)
RNA secondary structure as paradigm for genotype-phenotype mapping computable??

16SRNA
Min. Energy folding vs Conserved folding

23S RNA

A. globiformis, Anabaena sp., A. tumefaciens, B. japonicum, E. coli B. subtilis, T. thermoph, Pir. marina, Rb. sphaero

RNA-landscape: multi-one genotype-phenotype mapping

Almost all sequences fold in 'typical shape'

but

Only small fraction of shapes is typical

Example: GC strings length 30:

<table>
<thead>
<tr>
<th>1.07 * 10^9 sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>218830 shapes</td>
</tr>
<tr>
<td>22718 &quot;typical&quot;</td>
</tr>
<tr>
<td>93.4% seqs in typical shape</td>
</tr>
</tbody>
</table>


Nevertheless...

GCAU seqs. length 70: 999919 different structures in 1 million seqs
RNA Landscape: average phenotypic change by mutations
(local) RNA Landscape
relation distance in genotype and distance in phenotype

- single mutation: often NO change
  *ca 30% for length 70; saturates at 20% for longer seq.*
- single mutation: sometimes NO similarity (max. distance)
- distance distribution of phenotypes independent of genotype distance for moderate to large genotype distances
  *(small correlation length)*

RUGGED

*True for different measures of phenotypic distance*
*Hamming distance on string representation*
*# bond changes*
Folding of Eukaryotic mRNA: major change by point mutation (5' vs 3' end)
2 different functional ribozymes
1 point mutation NO similarity in secondary structure

EA Schultes, DP Bartel - Science
found by "evolutionary" search