Genotype-phenotype mapping, continued
RNA genotype-phenotype mapping so far...

- “smoothness within ruggedness”
  single mutation can be neutral and can change ’everything’
- percolating and intercalating neutral networks
  from smooth-rugged towards neutral networks
- no local peaks: detours
- phenotypic vs genotypic information threshold
- diffusion on neutral networks (D prop.to $\lambda$)
- adaptive walk with majority of neutral mutations
- reconciliation neutral and adaptive evolution
- RNA landscape “ideal” for evolution
- ++++ (today)

( cf VERY efficient in vitro evolution (????))
MOREOVER: phenotype $\rightarrow$ function mapping

Alternative ligases (Ekland et al 1995)

'tyranny' of small motifs... or complex structures?
'drift' on neutral network not 'neutral':

(1) Longterm RNA evolution: fitness of mutants
(2) Evolution towards high lambda

1-q=0.039

- Total
- Master
- Mutant

\[ \lambda \]

Time
redundant genotype-phenotype mapping: choice of coding

Evolution towards 'flatter parts'

== Mutational robustness

== high connectivity of neutral network

== MAX EIGENVECTOR OF CONNECTION MATRIX
(van Nimwegen 2000)

compare blind ant (moves with prob. rel neutral NB)

\[ \rightarrow \text{same freq in each node} \]

myopic ant (moves with fixed probability)

\[ \rightarrow D = \hat{d} + \frac{\text{Var}(d)}{\hat{d}} \]
Evolution towards mutational robustness

\[ \text{largest eigenvalue of connection matrix} \]

van Nimwegen et al PNAS 1999

walk along neutral path not neutral
walk along neutral path not neutral.....
how neutral is neutral
walk along neutral path not neutral.....
how neutral is neutral

neutral if above the informatioon threshold!
Implications evolution towards higher robustness

- more robustness $\Rightarrow$ more exploration ($D\lambda$)

- evolution of evolvability

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cf Andreas Wagner e.g.

2008 Robustness and evolvability, a paradox resolved

2013 Robustness and evolvability in living systems

*high mutational load of recently evolved strains well known from traditional evolutionary experiments (Scharloo 1999: canalization)*
example of intra-molecular evolved landscape
negative epistasis

Hsp90,582-590 Effect on growth-rate of single point mutations from wild-type and from 7 (almost) neutral mutations

A systematic survey of an intragenic epistatic landscape Claudia Bank et al MBE 2014
experimental verification of evolution toward robustness ???

population level WT and evolved mutant (3 muts)


fair comparison?
Robustness, population diversity and evolutionary optimization

AVIDA: Self-replicating computer program (Adami et al)

Population variability per position (gene) $p_i \log(p_i)$
Neutrality and information accumulation (royal road)

Information accumulation up to information threshold..
Genotype-phenotype mapping: Coding structure

3 questions/answers:

**Given code** – > **which evolutionary dynamics?**
eg RNA folding: punctuated evolution etc.

**Given problem** – > **how to code?**
expectation: smooth, non-redundant;
found intertwining neutral paths

**Given evolutionary dynamics** – > **which code?**
towards robustness, hence evolvability

*reconciliation adaptive and neutral evolution*

*cf information threshold/ survival of the flattest*
RNA secondary structure as paradigm for genotype-phenotype mapping computable??

16S rRNA
Min. Energy folding vs Conserved folding

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

alternative basins of attraction: replicator in nonMFE state

FIGURE 12. Structures and base pairing density plots for the melt structure and the metastable conformation of the Gj variant S/V11. The secondary structures and their free energies are shown in the upper part. In the lower half we show the matrix of base pair probabilities as obtained from the thermodynamic partition function (McCaskill, 1990; Holacker et al., 1994) (left) and from kinetic trajectories (right).

FIGURE 13. Fraction of folding paths visiting local minima in the Gj variant S/V11. The majority of paths visits the local minima in the basin of the metastable structure where the paths get trapped. Only about 15% reach the ground state.
Derived properties
JUST RNA?
or even just by wrongly computed (and 2 D) folding?

percolating neutral path; innovations
evolution toward robustness

NO......

similar (mutatis mutandis) properties in

Gene regulatory networks (A Wagner 2007a,b)
Protein folding A Wagner 2010
Metabolic networks (A. Wagner 2012)

see also books by A. Wagner
From paradigm systems to general conclusions
vs
Studying “all” cases

NK landscapes (Kauffman):
Class of models to study impact of GP mapping on evolutionary dynamics.

N: number of properties (e.g. sequence length)
K: number of “epistatic’ interactions
most often 2 states per position

Fitness contribution of each $N \cdot 2^K$ states
chosen randomly. Fitness is sum of those

Calculate e.g. pathlength to local peak
height of optima reached (etc.)

NO percolating, intercalating neutral paths
and its evolutionary consequences

versions include neutrality BUT
Explicit model of Insuline signaling pathway

Random sampling of 15 kinetic parameters $10^{-3} - 10^3$ and evolving populations by mutating these parameters

Classifying behavior as “normal” or ”deseased” (based on glucose uptake-curve in time)

Determine sensitivity of parameters in different populations and during evolution. (log sampling of parameters)
Fig 1. Insulin signaling model, input and output. a) Molecular interactions in the signaling pathway modeled here. Briefly, extracellular insulin leads to phosphorylation of the insulin receptor, which promotes the phosphorylation of IRS1 to yield IRS1P. The latter molecule associates with PI3K in a complex that triggers production of the second messenger P34P3, which activates the protein kinases Akt and PKCZ. These kinases then promote the translocation of the glucose transporter GLUT4 to the membrane, where it helps import glucose into the cell. Mass-action parameters that determine the rates of the respective reactions are indicated by a ‘k’ followed by a subscript. Activated PKCZ and Akt exert feedback on the production of two different phosphorylated forms of IRS1 (IRS1SP and IRS1P). The strength of this feedback is encapsulated by parameters $f_{PKCZP}$ and $f_{AktP}$, respectively. See Methods for details. b)
**Fig 1. Insulin signaling model, input and output.**

a) Molecular interactions in the signaling pathway modeled here. Briefly, extracellular insulin leads to phosphorylation of the insulin receptor, which promotes the phosphorylation of IRS1 to yield IRS1P. The latter molecule associates with PI3K in a complex that triggers production of the second messenger P\_{345} P\_3, which activates the protein kinases Akt and PKCZ. These kinases then promote the translocation of the glucose transporter GLUT4 to the membrane, where it helps import glucose into the cell. Mass-action parameters that determine the rates of the respective reactions are indicated by a 'k' followed by a subscript. Activated PKCZ and Akt exert feedback on the production of two different phosphorylated forms of IRS1 (IRS1SP and IRS1P). The strength of this feedback is encapsulated by parameters f\_{PKCZP} and f\_{AMP}, respectively. See Methods for details.

b) 

![Graph showing the signal over time](image)  

**X-axis:** time (min)  
**Y-axis:** SIGNAL (nM)  
**Legend:** Blue line represents normal, pink line represents increased.

c) 

![Histogram showing glucose uptake](image)  

**X-axis:** Glucose uptake (a.u.)  
**Y-axis:** Number of parameter sets  
**Legend:** Blue bars represent normal, red bars represent increased.
very high neutrality of individual parameter changes
but very different in different parameter sets.
Rapid “Causal drift”

rapid change of sensitivity to parameter changes (mutations) due to neutral drift

“genetic background”

“cause of disease”

cf GWAS studies 50% “explained”

Mouse models
Neutrality and evolution of complexity
neutral ratchet/constructive neutral
evolution/irremediable complexity

e.g. neutral binding / increase neutrality /
accumulation of mutations / indispensibility of binding

Evolution of coding structure cont.
Evolution of multiple coding in RNA’s

*doing more with less*

Evolve towards target == set of (25) RNA structures.

ALL other structures (Shapiro) TOXIC

define possible interaction of RNA’s:

- adaptors (=single hairpin)
- can bind to other RNA
- bound (modified) nucl not ’available’
  for folding

fitness of cell: set of struct.

- cells compete in space

*How to cope with high mutation rates?*

- de Boer & H. PLOS-One 2012
high mutation rate - short genome - same functionality
one adaptor used by all sequences
many adaptors used by 1 sequence
Conclusion: multiple coding

RNA even more an “ideal evolvable molecule”

information threshold shapes coding structure
multiple coding arises and alleviates information threshold

information threshold does not (necessarily) limit functionality

(Similar effects seen with alternative (non-minimal energy) foldings)

Also in this case:
local competition in space helps!

well mixed:
Conclusions

Coding structure adapts to mutation rate
Coding length, selection strength

Result:

Evolution converges to being

Close to Information Threshold