University of Zurich

SIB

Wagner Lab

Jose Aguilar Rodrigues
Aditya Barve
Manuel Bichsel
Tugce Bilgin
Sinisa Bratulic
Dr. Athena Chu
Rzgar Hosseini
Debbie Leigh
Dr. Heidi Lischer
Dr. Kathleen Sprouffsky
Dr. Joshua Payne
Dr. Mariana Ricca
Annette Schmid
Dr. Yolanda Schaerli
Kasia Sluzek
Dr. Peter Szovenyi
Dr. Macarena Toll-Riera
Ali Rezaae Vahdati

Recent collaborators

Homayoun Bagheri (UZH)
Andrew Barbour (UZH)
Jaume Bertranpetit (UPF, Barcelona)
Jason Bragg (MIT)
Stefano Ciliberti (Orsay, France)
Giovanni Dall'Olio (UPF, Barcelona)
Heinz Koeppl (EPFL, Lausanne)
Thomas Jorg (Orsay, France)
Suzannah Tringe (Lawrence Berkeley Lab, California)
Olivier Martin (Orsay, France)\
Jack Pronk (TU Delft, Netherlands)
Areejit Samal (Orsay, France)
Uwe Sauer (ETH Zurich)
Kentaro Shimizu (UZH)
Joerg Stelling (ETH Zurich)

UNIVERSITÉ PARIS-SUD 11

COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

Biological evolution and innovation a complex systems approach

Overview

- Milestones of evolutionary biology
- The problem of innovation
- Metabolism: the earliest evolving systems
- Genotype networks in metabolism
- Genotype networks in other biological systems
  proteins, RNA, regulation circuits
- Where do genotype networks come from
- Reconciling neutralism and selectionism
- Robustness and innovability
- Evolvable and adaptable technologies

1859: Charles Darwin and «The origin of species»

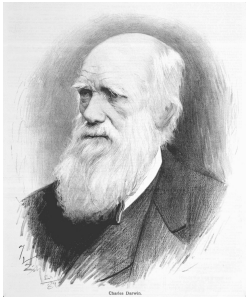
Natural selection as the cause of life's diversity

All life originated from a common ancestor

Two main areas of ignorance:

*"The **laws governing inheritance** are for the most part unknown."*

*"I have hitherto sometimes spoken as if the variations... had been due to chance. This, of course, is a wholly incorrect expression, but it serves to acknowledge plainly our ignorance of the **cause of** each particular **variation**."*

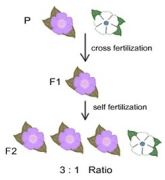


1866: Gregor Mendel

Solved part of the inheritance problem

Showed that traits can behave like particles when inherited

Forgotten and rediscovered in 1905 by de Vries



1906: Hugo de Vries

Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest.

Hugo de Vries

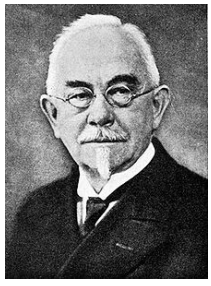
1909: Wilhelm Johannsen

Danish botanist who coined three key concepts

Gene
Mendel's particulate units of inheritance
(still completely unclear what genes were)

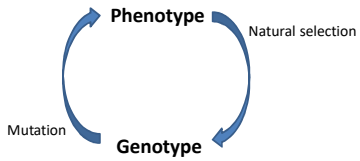
Genotype
In modern terms: all genetic material

Phenotype
All other observable traits



«*A failure to make a distinction between genotype and phenotype was at the bottom of the great controversies in the history of evolutionary biology, for instance those dealing with … the nature of mutation.*»

Mayr, The growth of biological thought (p 783)



1930-1940s: The modern synthesis

Named after a 1942 book by Julian Huxley

Main characters: R.A. Fisher, Sewall Wright, J.B.S. Haldane

Married three elements
- The importance of natural selection
- Mendel's laws of particulate inheritance
- Population thinking

Created population genetics

Quantitative and mathematical theory that predicts how selection changes allele frequencies in a population

Allele: a gene variant (humans and other diploid organisms carry two alleles of each gene)

Allele frequency: the proportion of individuals that carry that allele

1930-1940s: The modern synthesis

Powerful because of two key abstractions:

1. simple phenotypes, often represented only as a scalar quantity (fitness)

   Evolution as *"change in allele frequency within a gene pool"* (Mayr)

2. a simple relationship between genotype and phenotype

1983: The neutral theory of molecular evolution

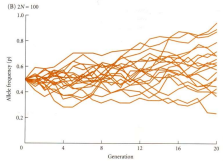
New alleles created by mutation can be *neutral* – they do not affect fitness

The fate of such mutations is determined by genetic drift – the random sampling of alleles from generation to generation.

Theory developed since the 1920s by Wright and Haldane.

Developed further with greater mathematical sophistication by Motoo Kimura

Genetic drift can be a strong force of evolutionary change in small populations.



1944-: The molecular era

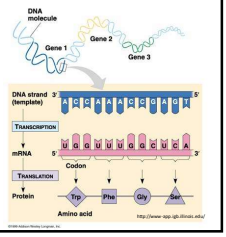
1944: Oswald Avery discovers that DNA is the material basis of inheritance

1953: James Watson and Francis Crick find the chemical structure of DNA

1950s-1960s: transcription, translation, and the genetic code

1977: Frederick Sanger describes the first efficient technique to *sequence* DNA

1995: The genome era begins with the sequencing of *Hemophilus influenzae*



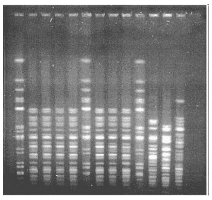
1966-: Neutralism and selectionism

1966: Lewontin and Hubby describe great amounts of *genetic variation* in fruit flies species.

"39% of loci in the genome are polymorphic over the whole [Drosophila pseudoobscura] species. The average population is polymorphic for 30% of all loci."

Populations of many other organisms, even living fossils, also contain lots of genetic variation.

Is most of this variation neutral or adaptive, that is, influenced by selection?



J. L. Hubby and R. C. Lewontin, "A Molecular Approach to the Study of Genic Heterozygosity in Natural Populations. I+II. Genetics 54 (1966)

1966-: Neutralism and selectionism

Ernst Mayr, a selectionist

"*It is altogether unlikely that two genes would have identical selective values under all the conditions under which they may coexist in a population…*
… cases of neutral polymorphisms do not exist."

Motoo Kimura, a neutralist

"*Selective elimination of definitely deleterious mutants and random fixation of selectively neutral … mutants occur far more frequently in evolution than positive Darwinian selection of definitely advantageous mutants*."

Neutralism and selectionism in a broader sense

"non-adaptationism and adaptionism"

What role might non-adaptive traits play in evolution?

Gould and Lewontin (1979):

"*We fault the adaptationist programme for its failure to distinguish current utility from reasons for origin; … for its unwillingness to consider alternatives to adaptive stories; … and for its failure to consider adequately such competing themes as random fixation of alleles,… and current utility as an epiphenomenon of non-adaptive structures.*"

Today: Population genomics

Theory of the modern synthesis combined with genome sequencing

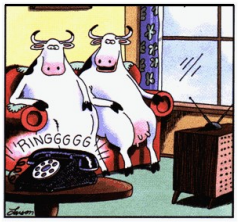
Great descriptive and explanatory power in many areas
- human history
- conservation genomics
- evolutionary origins of diseases (lactose intolerance etc.)

Focuses on data from *genotypes*

Still limited by (tacit) simplifications regading phenotypic complexity

The innovation problem

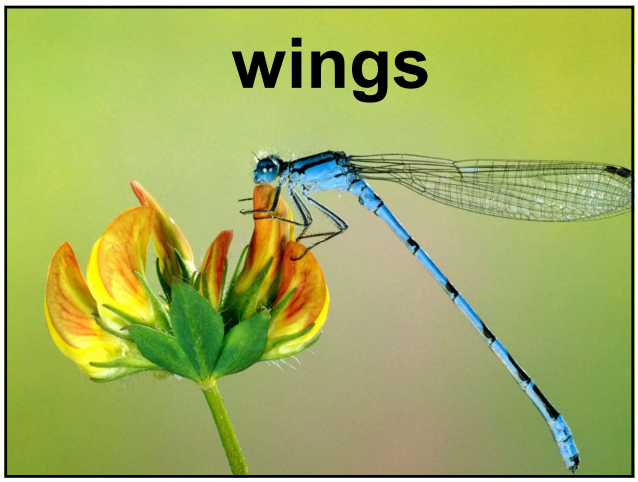
How does nature bring forth the new – evolutionary *adaptations* and *innovations,* beneficial new phenotypes?



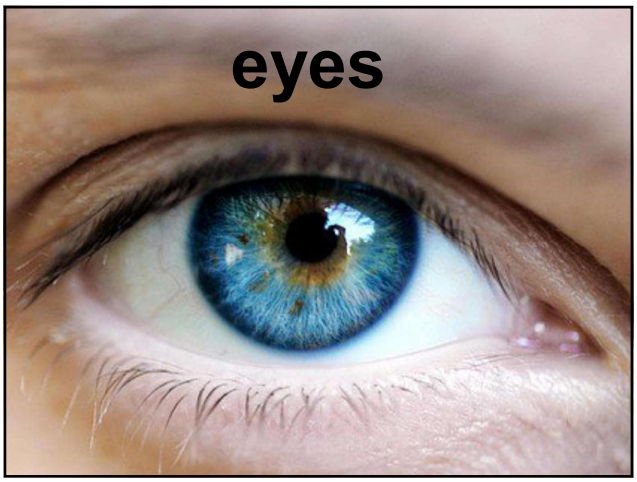
"Well, there it goes again. … And here we sit without opposable thumbs."

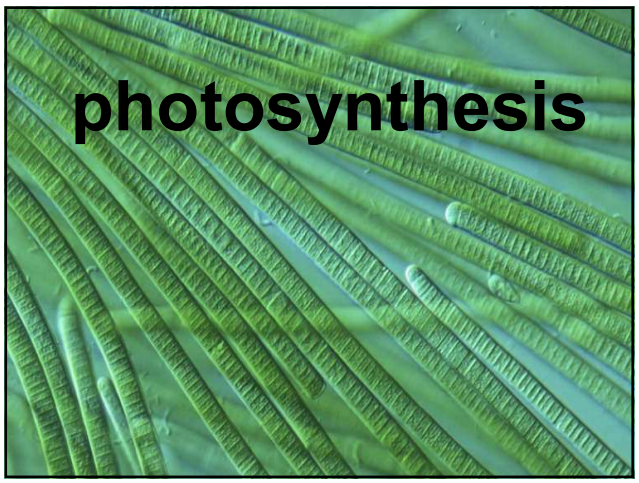
4 billion years of innovation

wings



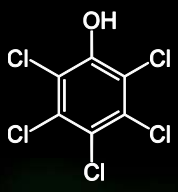
eyes



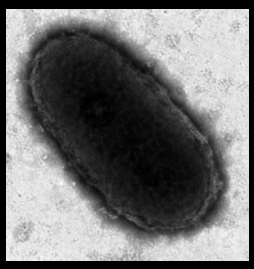


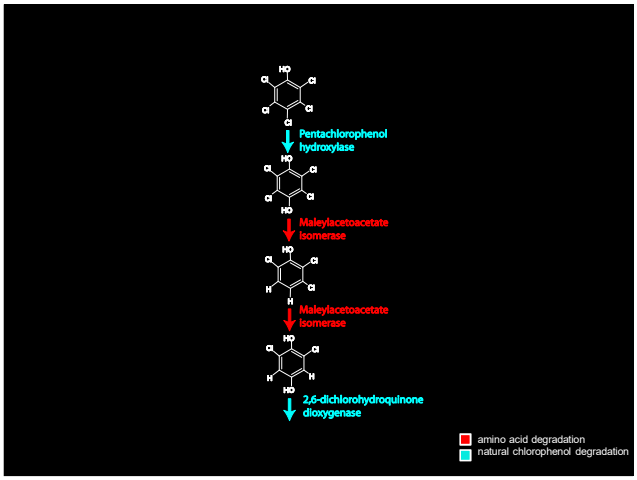
1. metabolic innovation

pentachlorophenol

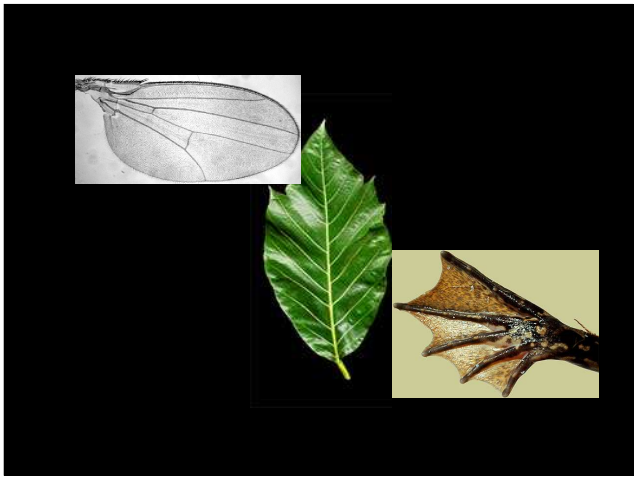


Sphingobium chlorophenolicum

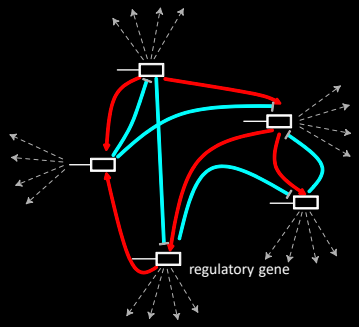


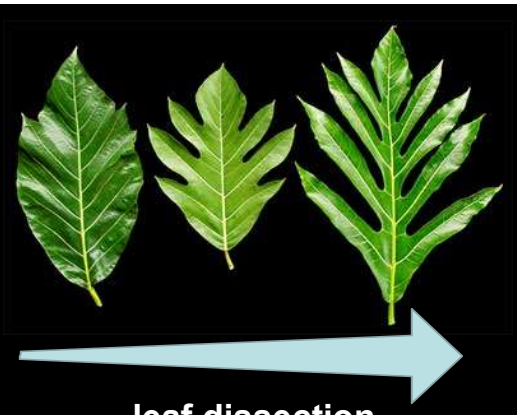


2. regulatory innovation



regulatory circuits





heat dissipation

CO_2 uptake

KNOX (KNOTTED 1-like homeobox)

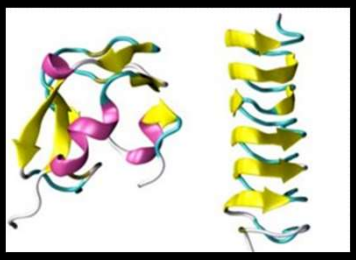
KNOX ↑ more leaflets

KNOX ↓ fewer leaflets, simple leaf

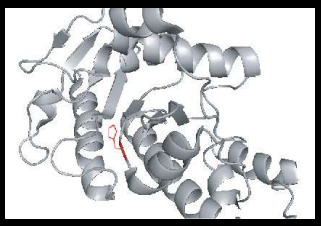
3. new macromolecules

the winter flounder

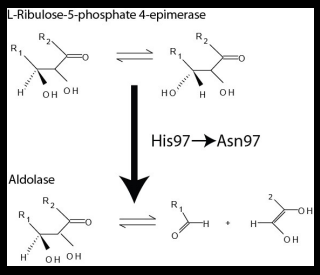
antifreeze proteins



L-ribulose-5-phosphate 4-epimerase



a minimalist innovation



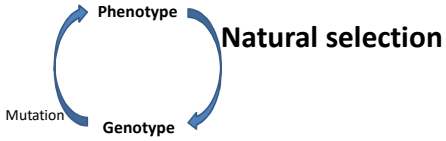
Most or all innovations involve

novel metabolic pathways
novel regulation
novel molecules

or (entangled) combinations thereof.

Are there any principles of "innovability" beyond individual examples?

We know much more about selection than about the *origins* of new and beneficial phenotypes – evolutionary *adaptations* and *innovations.*



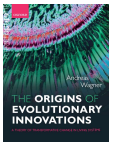
Need to study how changes in genotypes translate into changes in phenotypes

Principles of innovation should

1 **explain how biological systems can preserve existing, well adapted phenotypes while exploring (many) novel phenotypes**.

Principles of innovation should

1. **explain how biological systems can preserve existing, well adapted phenotypes while exploring (many) novel phenotypes.**
2. unify innovations that involve different levels of biological organization.
3. be able to capture the combinatorial nature of innovation.
4. enable us to study the role of environments in promoting innovations.
5. explain how the same problem can have multiple different solutions
6. be applicable to technological systems.



Innovation in complex metabolic systems

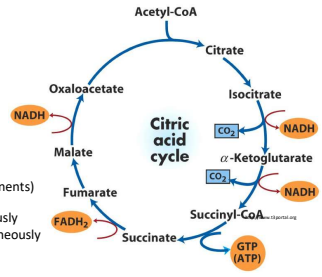
A hydrothermal vent

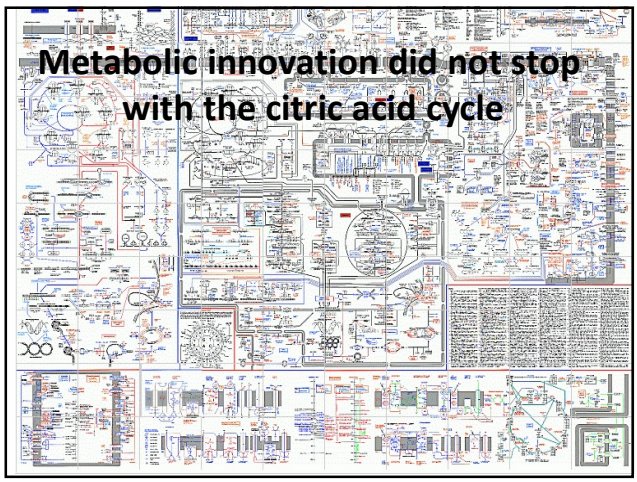
Wikimedia commons

The first metabolism?

The citric acid cycle
(Krebs cycle, tricarboxylic acid cycle)

- is ancient and ubiquitous
- produces many biomass building blocks
- can be run in two directions
  - oxidative (shown)
  - reductive (probably ancestral)
- is autocatalytic (makes more of its components)
- some of its molecules can arise spontanously and some of its reactions proceed spontaneously under vent conditions





A metabolism is a network of chemical reactions whose two main functions are to produce

chemical energy
(for maintenance of cell functions and for biosyntheses)

molecular building blocks for biosyntheses

These reactions are catalyzed by enzymes that are encoded by genes.

The metabolism of a whole organism comprises many chemical reactions

Organism	Reactions	Molecules
E. coli	2077	1039
S. cerevisiae	1412	713
A. thaliana	1567	1748
B. aphidicola	263	240

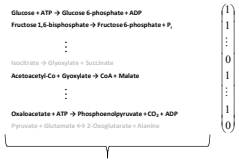
Metabolic genotype

The part of a genome that encodes metabolic enzymes

Less unwieldy:
An organism's set of (enzyme-catalyzed) metabolic reactions

These can be written as follows

A metabolic genotype



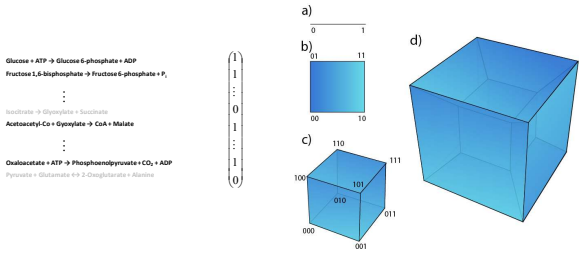
The known "universe" of metabolic reactions (>5000 reactions)

The universal library

The universe (which others call the Library) is composed of an indefinite and perhaps infinite number of hexagonal galleries…there are five shelves for each of the hexagon's walls; each shelf contains thirty-five books…The Library exists ab aeterno…there are no two identical books. The Library is total and … its shelves register all the possible combinations of the twenty-odd orthographical symbols.

Jorge Luis Borges
The library of babel

Metabolic genotypes form a vast space of possible metabolisms



This metabolic genotype space contains more than 2^{5000} metabolisms

Metabolic genotypes form a vast space of possible metabolisms

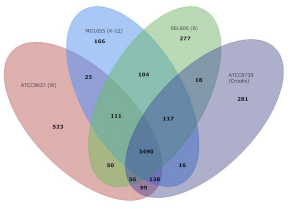
Two genotypes are neighbors if they differ in a single reaction.

A genotype's neighborhood comprises all of its neighbors.

The genotype distance D indicates the fraction of reactions at which two networks differ.

Gene content and metabolic genotypes can evolve rapidly

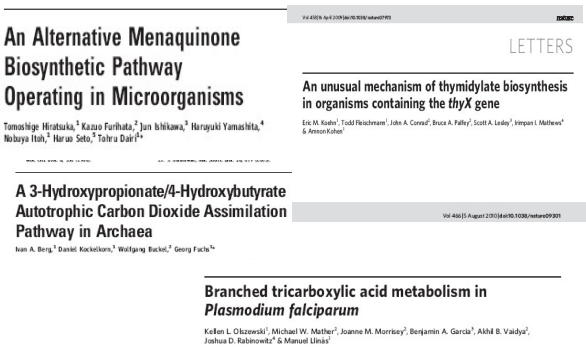
Numbers of genes in the genomes of four different Escherichia coli strains



E. coli strain	K-12	W
Genes	4493	4482
Unique Genes	403	728
Unique Reactions	**>100**	**>100**

Archer et al. BMC Genomics 2011

New metabolic pathways are being discovered continually



An Alternative Menaquinone Biosynthetic Pathway Operating in Microorganisms

Tomoshige Hiratsuka,[1] Kazuo Furihata,[2] Jun Ishikawa,[3] Haruyuki Yamashita,[4] Nobuya Itoh,[2] Haruo Seto,[2] Tohru Dairi[2]*

LETTERS

An unusual mechanism of thymidylate biosynthesis in organisms containing the *thyX* gene

Eric M. Kuhn[1], Todd Fleischmann[1], John A. Corrod[1], Bruce A. Palfey[1], Scott A. Lesley[2], Irimpan I. Mathews[3] & Amnon Kohen[1]

A 3-Hydroxypropionate/4-Hydroxybutyrate Autotrophic Carbon Dioxide Assimilation Pathway in Archaea

Ivan A. Berg,[1] Daniel Kockelkorn,[1] Wolfgang Buckel,[2] Georg Fuchs[1]*

Branched tricarboxylic acid metabolism in *Plasmodium falciparum*

Kellen L. Olszewski[1], Michael W. Mather[2], Joanne M. Morrisey[2], Benjamin A. Garcia[3], Akhil B. Vaidya[2], Joshua D. Rabinowitz[4] & Manuel Llinás[1]

Metabolic phenotype

Most important task of a metabolism:
Ensure **viability**

synthesize biomass precursor molecules (amino acids, DNA precursors etc.) from environmental nutrients

Metabolic **phenotype:** spectrum of nutrients on which a metabolism is viable

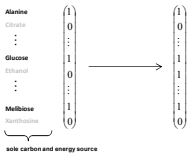
A carbon utilization phenotype

Advantages of this phenotype representation

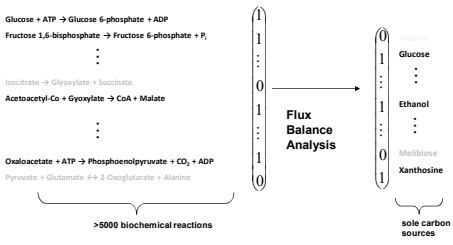
Compact

Phenotypes are complex and many (2^C for C carbon sources)

Easy to define innovation



One can predict metabolic phenotypes from metabolic genotypes



Flux balance analysis needs

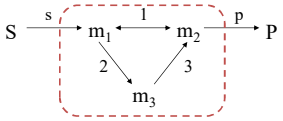
1. a list of chemical reactions known to be catalyzed by enzymes in a given organism
2. Information about nutrients in the chemical environment of a cell and their uptake rate (usually in mol/g dry weight [DW] and hour)

Flux balance analysis computes

1. allowable metabolic fluxes through a metabolic network (fluxes that do not violate the law of mass conservation)

2. within the set of allowable fluxes, those that have desirable properties (e.g., maximal rate of biomass production, maximal biomass yield per unit of carbon source.)

A simple chemical reaction network



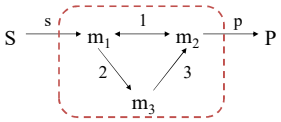
Two external metabolites
- 1 substrate (nutrient) S
- 1 product P

Two transport reactions (s,p)
- s determines the uptake rate of S
- p determines the rate at which P is excreted

Three internal metabolites (m_i)

Three internal reactions (1,2,3)

A simple chemical reaction network



Metabolite concentrations m_i change according to the equations

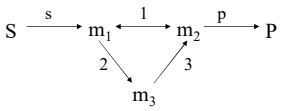
$$\frac{dm_1}{dt} = v_s - v_1 - v_2$$
$$\frac{dm_2}{dt} = v_1 + v_3 - v_p$$
$$\frac{dm_3}{dt} = v_2 - v_3$$

$$\frac{d\vec{m}}{dt} = \mathbf{S}\vec{v}$$

$$\mathbf{S} = \begin{pmatrix} 1 & -1 & -1 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 \\ 0 & 0 & 1 & -1 & 0 \end{pmatrix}$$

Stoichiometry matrix

v_i metabolic flux through reaction i



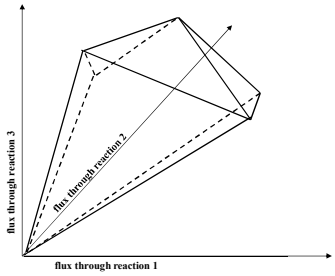
FBA assumes that metabolism is in a steady state where the concentrations of metabolites no longer change

$$\frac{d\vec{m}}{dt} = 0$$

$$\mathbf{S}\vec{v} = 0$$

The solutions of these equations are the allowable metabolic fluxes. They form the so-called <u>null space of S</u>

The null space of a complex metabolic network forms a high-dimensional "flux cone" (a convex polytope)



Several important properties of a metabolic network can be expressed as a weighted sums of fluxes

$$Z(\vec{v}) = \sum_{i=1}^{m} c_i v_i$$

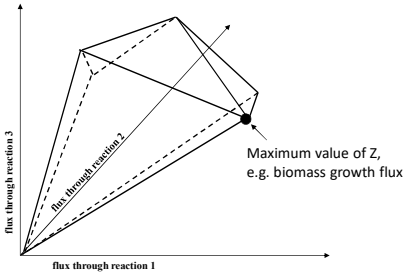
Example:

In the biomass <u>growth reaction</u>,

v_i is the rate at which essential biochemical precursor *i* is produced by a metabolic network.

c_i is a constant that reflects the relative contribution of precursor *i* to biomass (can be estimated from the biomass composition of a cell.)

FBA uses linear programming to determine regions within the flux cone where some flux or a linear function Z of multiple fluxes is maximal.



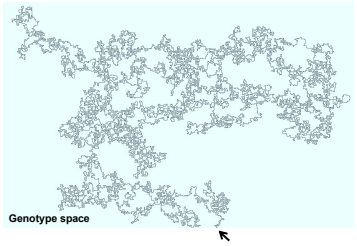
Z is also called an <u>objective function</u>

Markov Chain Monte Carlo methods can help explore and sample a space of metabolic genotypes

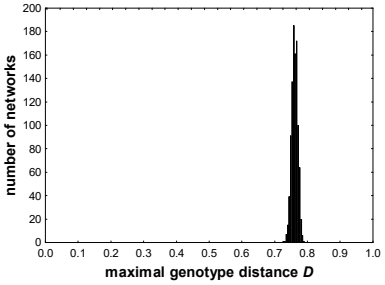
Perform random walks in genotype space

Each step must preserve
- phenotype
- number of reactions

Sample >10^3 networks
(one every 10^4 steps)



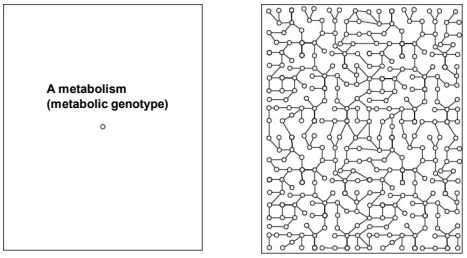
How far can you go without disrupting a phenotype?



Rodrigues and Wagner, Plos Computational Biology 2009
Samal et al., BMC Systems Biology 2010
Rodrigues and Wagner, BMC Systems Biology 2011
Barve et al., PNAS 2012

Two fundamental features of metabolic genotype space

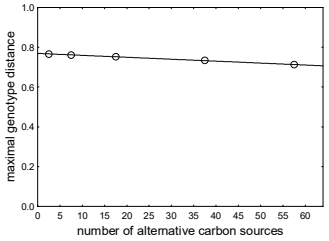
1. **Genotype networks:** Vast, far-ranging networks of metabolic genotypes with the same phenotype



Rodrigues and Wagner, Plos Computational Biology 2009
Samal et al., BMC Systems Biology 2010
Rodrigues and Wagner, BMC Systems Biology 2011
Barve et al., PNAS 2012

Two fundamental features of metabolic genotype space

1. Genotype networks

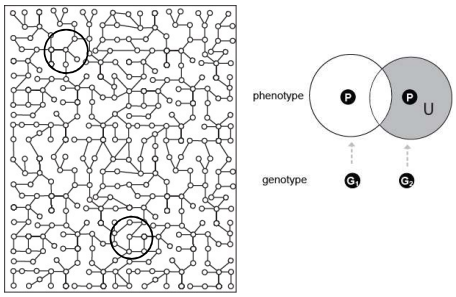


The diameter of genotype networks is not sensitive to the number of alternative carbon sources

Rodrigues and Wagner, Plos Computational Biology 2009

Two fundamental features of metabolic genotype space

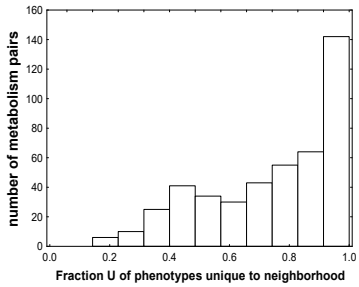
2. Phenotypically diverse neighborhoods



Rodrigues and Wagner, Plos Computational Biology 2009

Two fundamental features of metabolic genotype space

2. Phenotypically diverse neighborhoods



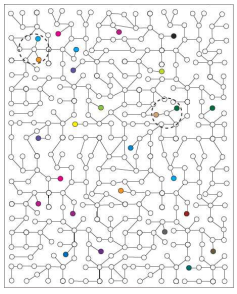
Different neighborhoods of the same genotype network contain very different novel phenotypes

Rodrigues and Wagner, Plos Computational Biology 2009

Two fundamental features of metabolic genotype space.

Metabolisms form vast phenotype-preserving genotype networks that extend far through genotype space

Different neighborhoods of these metabolisms contain very different novel phenotypes



Some resources for computational work on metabolism

The COBRA toolbox

opencobra.sourceforge.net/

BiGG database

a knowledge base of Biochemically, Genetically and Genomically structured genome-scale metabolic network reconstructions

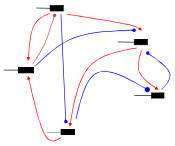
http://bigg.ucsd.edu/bigg/home.pl

A list of existing metabolic reconstructions

http://sbrg.ucsd.edu/InSilicoOrganisms/OtherOrganisms

Gene regulatory circuits create gene expression patterns that are the basis of many adaptations and innovations

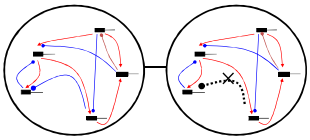
Genotype: circuit topology, a pattern of regulatory interactions



Phenotype: the activity or expression pattern of circuit genes

Gene regulatory circuits form vast genotype spaces of circuits that vary in their topologies

Neighbors: circuits that differ in exactly one (cis)-regulatory interaction



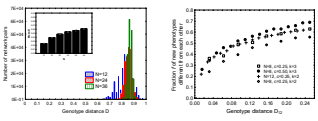
Circuit (genotype) distance: fraction of regulatory interactions in which two circuits differ.

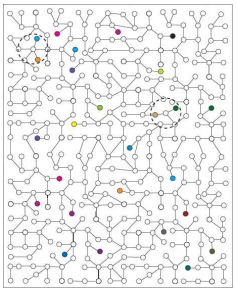
Wagner, Evolution 1996
Ciliberti, Martin, and Wagner, PNAS 2007
Ciliberti, Martin, and Wagner, PloS Comp. Bio 2007
Wagner and Martin, Genetics 2009

Two qualitative properties of regulatory circuit space.

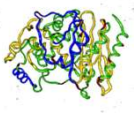
Regulatory circuits with the same gene activity phenotype form vast genotype networks that extend far through genotype space

Different neighborhoods of these networks contain very different novel phenotypes

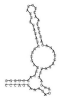




Ciliberti, Martin, and Wagner, PNAS 2007
Ciliberti, Martin, and Wagner, PloS Comp. Bio 2007



Protein and RNA molecules



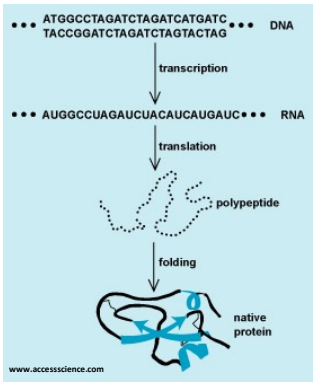
form a vast genotype space

4^L member genotypes for RNA molecules
20^L member genotypes for proteins (L…length of the molecule)

are immediate neighbors if they differ in a monomer.

A genotype's neighborhood comprises all of its neighbors.

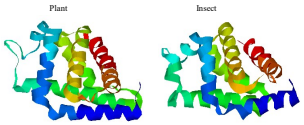
The genotype distance *D* of two molecules is the fraction of monomers at which they differ



Genotype

Phenotype

Proteins with the same structure form connected genotype networks



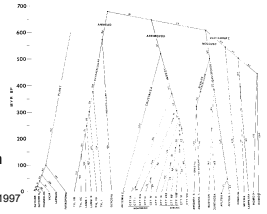
Example: oxygen-binding globins

highly divergent sequence
D>0.87 pairwise distance
only 4/97 amino acids unchanged

connected through common ancestry

preserved phenotype
oxygen-binding,
highly similar structure

Wagner (2005) Robustness and Evolvability in Living Systems, OUP

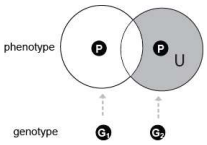


Even higher sequence divergence is common among proteins with similar structure

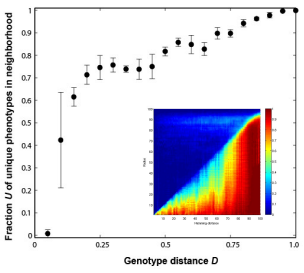
Rost, Folding and Design, 1997

Goodman et al., 1988

Different neighborhoods of protein sequence space contain very different novel phenotypes

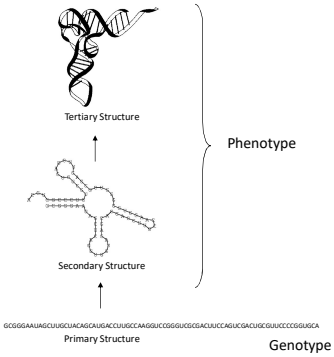


30 common protein domains
16,574 sequences
705 enzymatic (EC) functions



Ferrada and Wagner, PLoS ONE 5, 2010

Genotype and phenotype in RNA

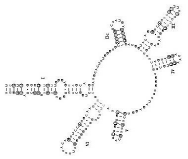


RNA secondary structures are often themselves functionally important phenotypes

Internal ribosomal entry sites (IRES) in the genome of Hepatitis C virus and other flaviviridae

TAR region of HIV-1, necessary for viral RNA replication

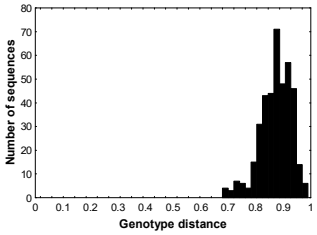
Rev responsive element (RRE) region of HIV-1, interaction with the viral Rev protein influences splicing patterns.



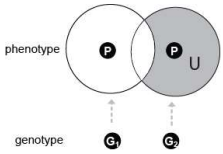
RNA sequences with the same secondary structure form vast connected genotype networks that span genotype space

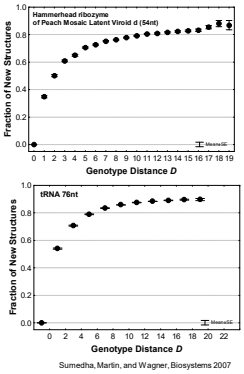
Discovered by Schuster and collaborators (Proc. Roy. Soc.1994) and called "neutral networks"

Maximal genotype distance of RNA sequence with the same structure after 5,000 single structure-preserving nucleotide changes.



Different neighborhoods of the same RNA genotype network contain very different novel secondary structure phenotypes





Sumedha, Martin, and Wagner, Biosystems 2007

Useful resources for computational RNA work

Vienna RNA WebServers

http://rna.tbi.univie.ac.at/

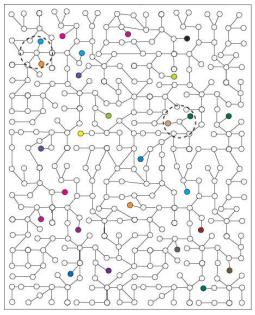
Vienna RNA Package

http://www.tbi.univie.ac.at/RNA/

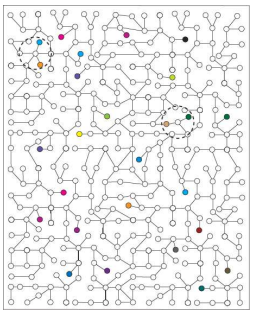
Two qualitative properties of protein and RNA genotype space

Proteins and RNA molecules form vast phenotype-preserving genotype networks that extend far through genotype space

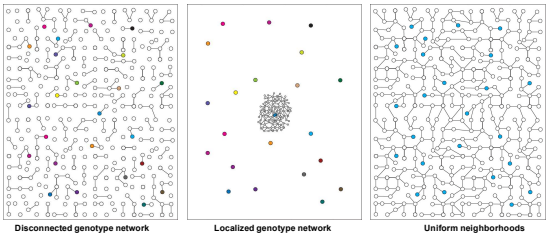
Different neighborhoods of these networks contain very different novel phenotypes



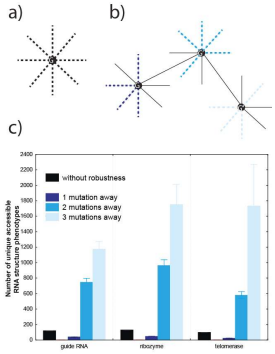
Both features of genotype spaces are necessary to explore novel phenotypes while preserving old phenotypes



Both features of genotype spaces are necessary to explore novel phenotypes while preserving old phenotypes

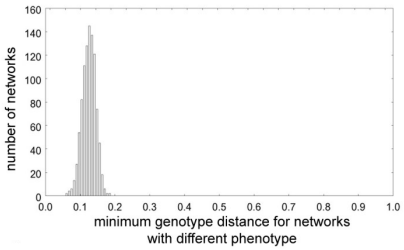


A few steps on a genotype network render many new phenotypes accessible



Genotype networks are highly interwoven

Many new phenotypes occur in a small radius around any one phenotype



Rodrigues and Wagner, PLoS Comp Bio 2009
Schuster et al., PRS B 1994

Summary (so far)

Three very different biological systems

metabolic networks
regulatory circuits
protein and RNA molecules

that are involved in most evolutionary adaptations and innovations

share two fundamental features

vast genotype networks that preserve phenotype and extend far through genotype space

different neighborhoods of any one genotype network contain many diverse phenotypes

Both features are required for the exploration of novel phenotypes while preserving old phenotypes

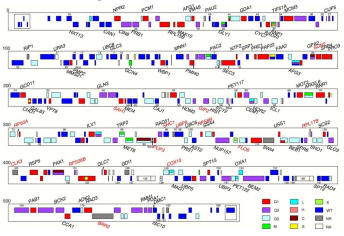
The origins of genotype networks

Robustness is a system's ability to preserve a system property (phenotype) in response to perturbations

Biological systems are to some extent robust to mutations

Example 1:

Phenotype: Rate of cell growth and division
Perturbation: Eliminations of genes from a genome



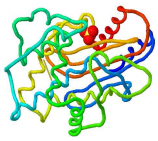
Smith *et al.* Nature 275, 464 (1997)

Biological systems are to some extent robust to mutations

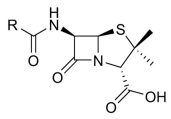
Example 2:

Phenotype: Antibiotic resistance caused by β-lactamase
Perturbation: Mutations in the amino acid sequence of the protein

More than 80 percent of random mutations in β-lactamase do not affect the function of the enzyme, which provides resistance of pathogens to antibiotics such as Penicillin



β-lactamase



Penicillin

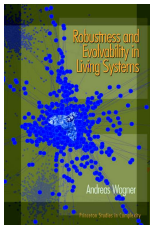
Where do genotype networks come from?

A genotype's robustness to mutations is the fraction *v* of its neighbors that have the same phenotype P.

(Typically, 0.1<*v*<0.5 for the three system classes we discussed.)

Robustness is both necessary and sufficient for genotype networks that

extend far through genotype space
are astronomically large
occupy a small fraction of this space



Where does robustness come from?

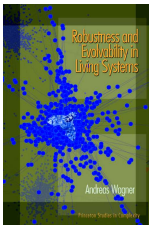
Metabolic networks must function in different external environments
nutrient availability, electron acceptors, pH…

Regulatory circuits must function in different intraorganismal environments
different embryonic regions, tissues…

Macromolecules function in different intracellular environments
temperature, ion concentrations, allosteric regulators,…

These systems are robust to environmental change.

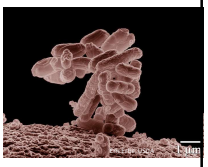
Such robustness usually entails mutational robustness.



Where does robustness come from?

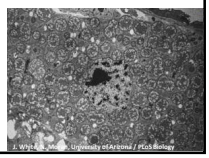
The **free-living** *E.coli* bacterium has a metabolic network with more than 900 reactions.

More than **70 percent** of these reactions are **non-essential** in a glucose-minimal environment.
Reed et al., Genome Biology 2003
Samal et al., BMC Systems Biology 2010



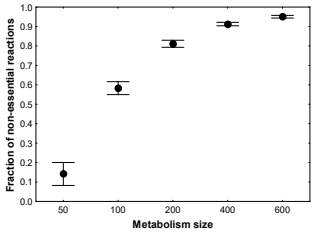
Buchnera aphidicola, an **endosymbiont** of pea aphids, has reduced its metabolic network to 263 reactions.

Only **10 percent** of these reactions are **non-essential**
Thomas et al. BMC Systems Biology 2009



Where does robustness come from?

Smaller (less complex) metabolisms with the same phenotype have lower robustness.

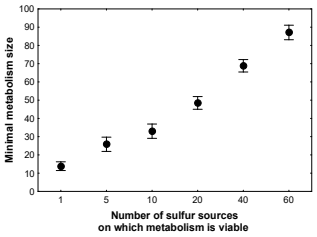


Based on 100 random metabolisms viable on 20 different sole sulfur sources.

Rodrigues and Wagner, 2010

Where does robustness come from?

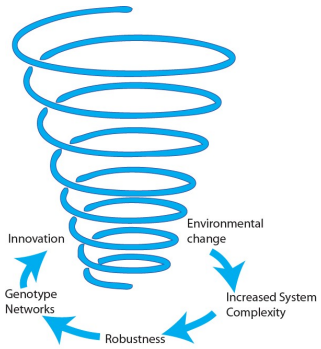
To cope with increased environmental variability metabolisms need to be more complex



Rodrigues and Wagner, 2010

Greater environmental variability requires greater system complexity

Greater complexity entails robustness to genetic change <u>in any one environment</u>



Summary of the origins of genotype networks

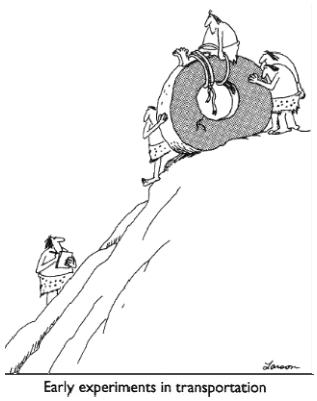
Biological systems are to some extent robust to mutations

Mutational robustness is correlated with robustness to environmental change

Much of this robustness originates from adaptation to changing environments

A robust genotype has many neighbors with the same phenotype

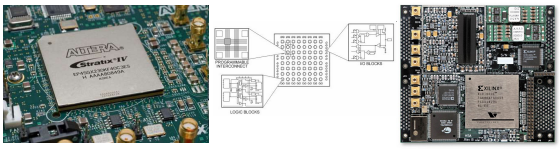
Mutational robustness is both necessary and sufficient for the existence of genotype networks



Early experiments in transportation

digital electronics

evolvable and adaptable technology



Field programmable gate arrays (FPGAs) are a kind of programmable hardware

Their logic gates compute digital logic functions (AND, OR, NOT etc.)

Logic gates and their connections are user-programmable

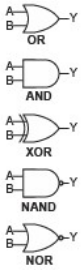
Wide ranging applications (signal processing, database searching, robotics)

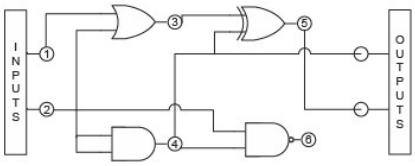
Complex (>10^6 logic gates)

World market >USD 3billion

autonomous (learning) robots

http://forum.xcitefun.net/autonomous-soccer-robots-robocup-2009-austria-t34619.html

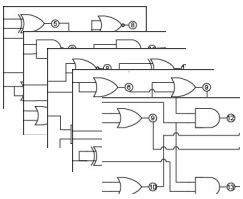




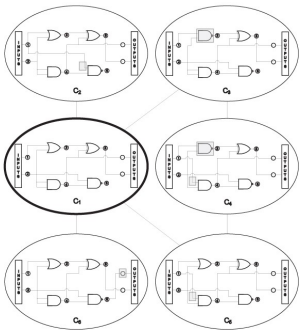
Boolean logic

011010101111010101 → 1111010101010110101

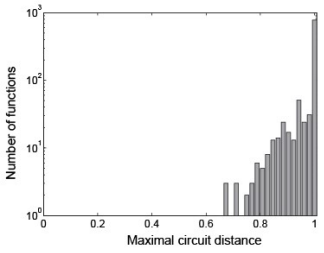
a circuit space



neighboring circuits



Circuits computing the same logic function form large connected networks that extend far through circuit space

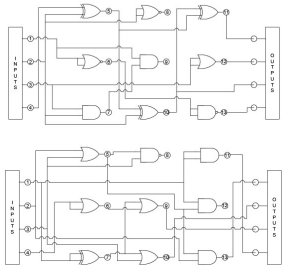


Data based on 1000 logic functions of varying frequency

Raman and Wagner, Journal of the Royal Society Interface, 2010.

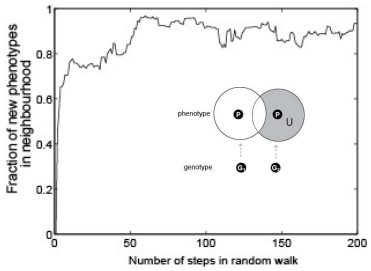
Two maximally different circuits that both compute the circular shift function.

They are two among many different solutions to the same problem.



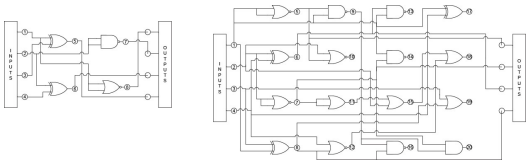
Evolvable and adaptable technology

Different neighborhoods of the same circuit (genotype) network contain very different novel logic functions



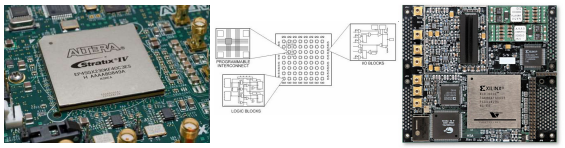
Evolvable and adaptable technology

Circuits computing the same function can have very different complexity



Complexity may be the price to pay for evolvability

Technology summary

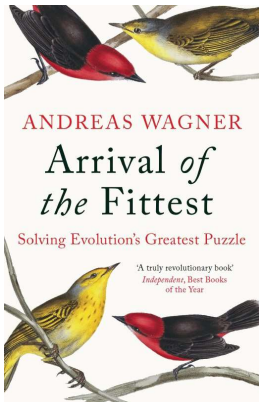


The space of programmable hardware circuits contains

extended "circuit networks"
neighborhoods whose circuits compute very different logic functions

Features that facilitate innovation in biological system exist in this technology

Such features could be designed into a technology
to create autonomous adaptive systems that reconfigure "on-the-fly"
to create evolvable technologies primed for innovation



Penguin Random House, October 2015