Generalized Topological Spaces in Evolutionary Theory and Combinatorial Chemistry

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Outline

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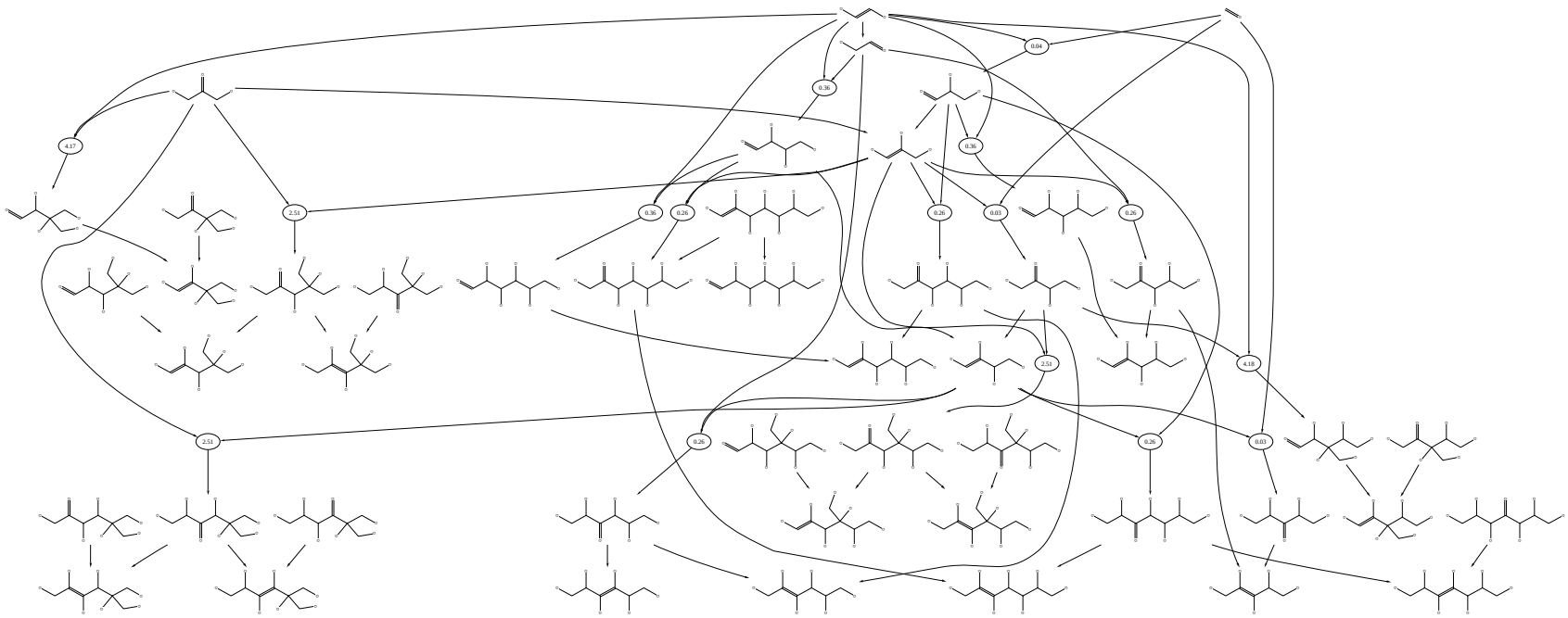
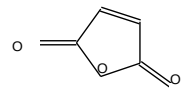
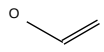
  - A Theory of Characters (Merkmale)
- Fitness Landscapes
  - Local Minima
  - Connectedness
  - Barrier Trees
- Chemical Organizations
  - Chemical Reactions and Stationary Fluxes
  - Dittrich's Theory
  - Chemical Organization as Topology

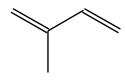
Chemical Reaction Networks

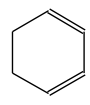


A Growing Chemical Network



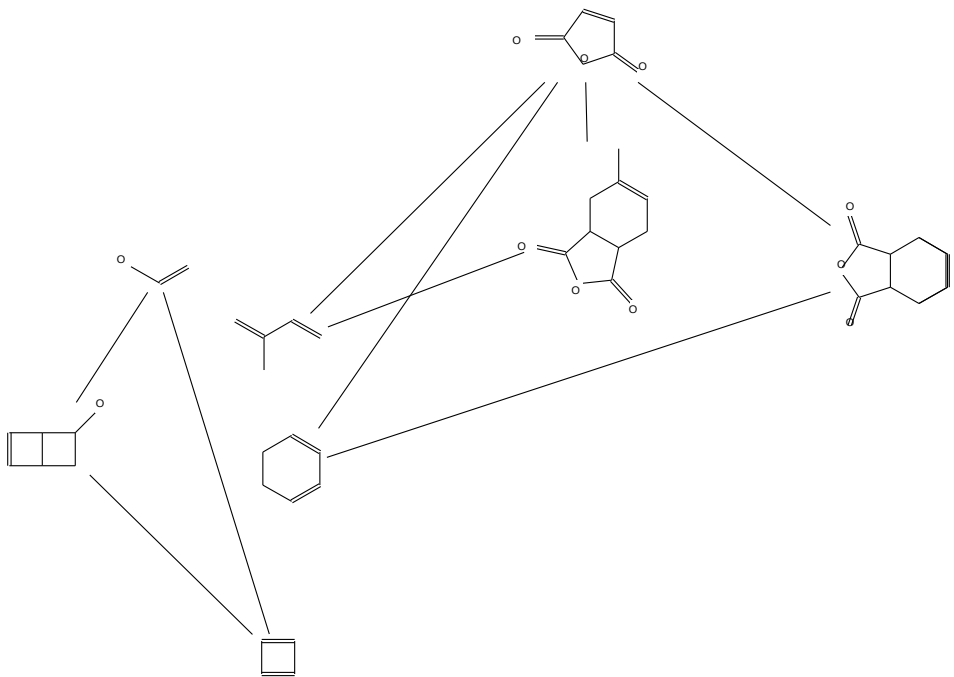






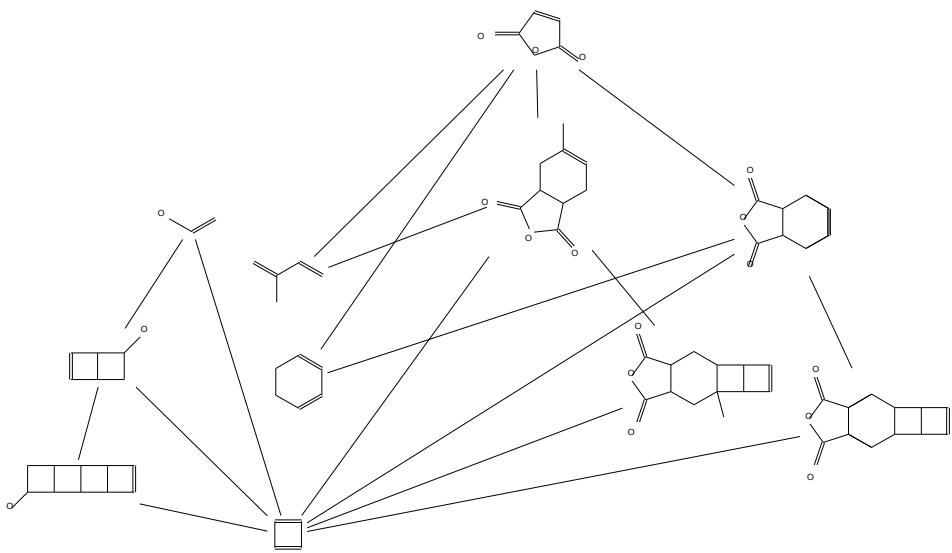
A

A Growing Chemical Network



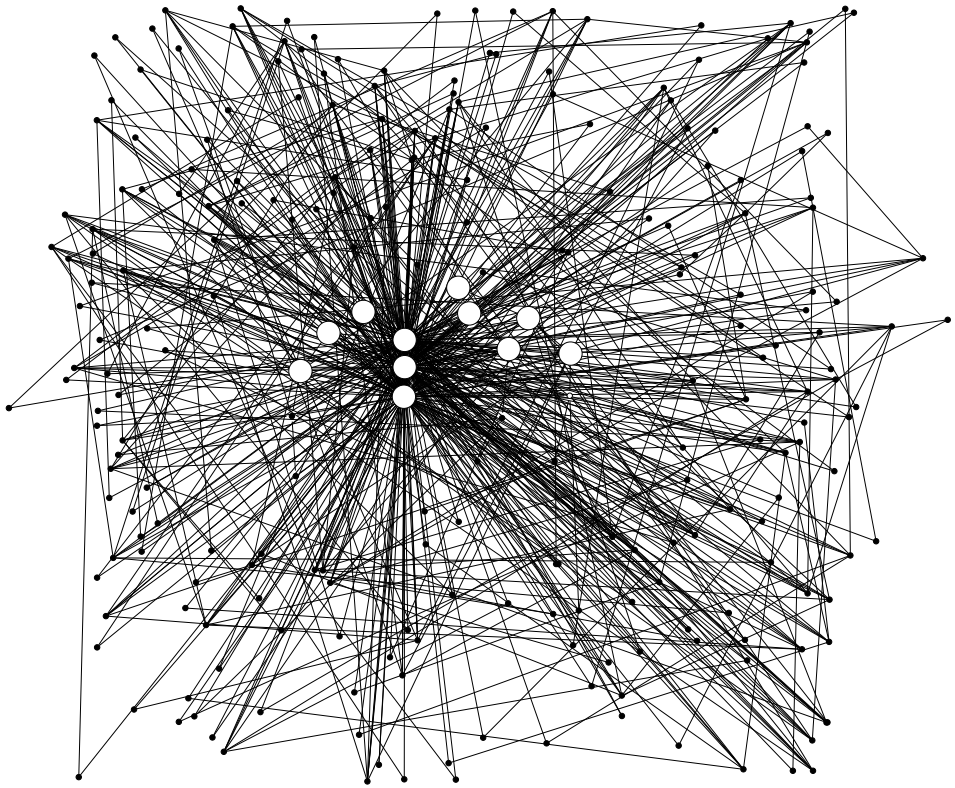
$\mathrm{cl}(A)$

A Growing Chemical Network



$\mathrm{cl}(\mathrm{cl}(A))$

A Growing Chemical Network



$\mathrm{cl}(\mathrm{cl}(\mathrm{cl}(A)))$

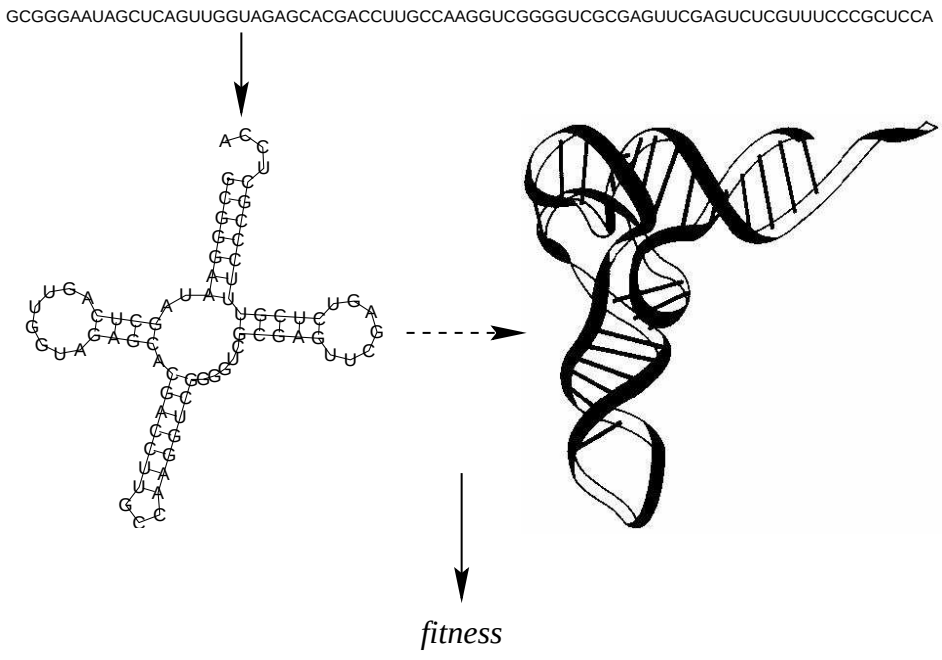
“Chemical Space”

* Chemical Reactions define a mathematical structure of “accessibility” on the set of molecules

?? What is the (mathematical) structure of the operator cl?

Before we get to this . . .
. . . let’s have a look at a very different topic!

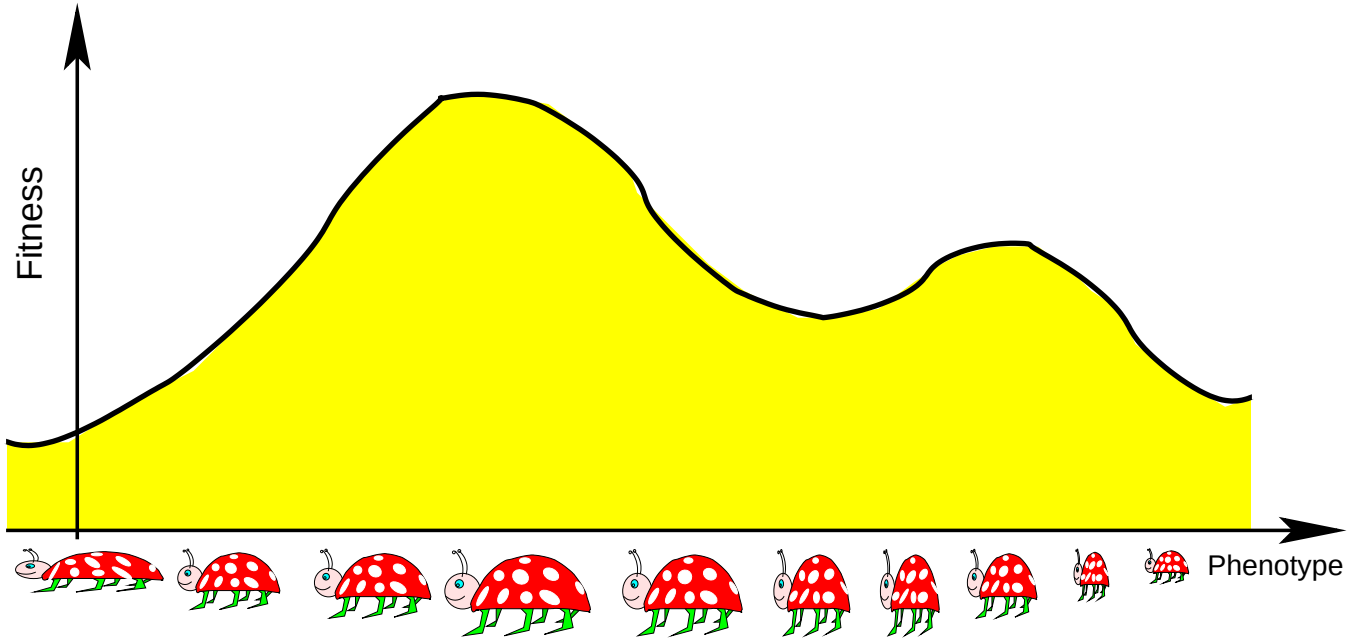
Evolutionary Biology: Genotype-Phenotype Maps



Given:

- A **set** X of genotypes (sequences)
- Genetic Operators (mutation and/or recombination ...)
- A **set** Y of (potential) phenotypes (structures)
- A **function** $f : X \longrightarrow Y$ assigning a phenotype to each genotype.

The "usual" view

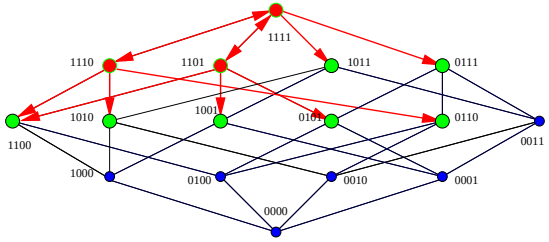


- Phenotypes are "somehow" numbers or *vectors*
- Accessible phenotypes are within a small (Euclidean) distance (in this vector space)
- Fitness is a (more or less) smooth function

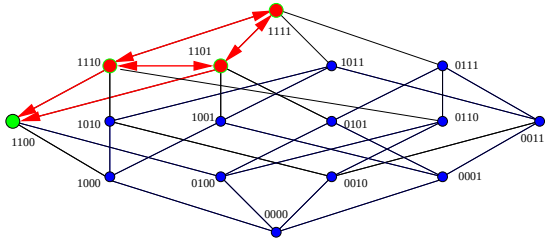
Population Genetics is perfectly happy . . .

So, what is wrong with this picture?

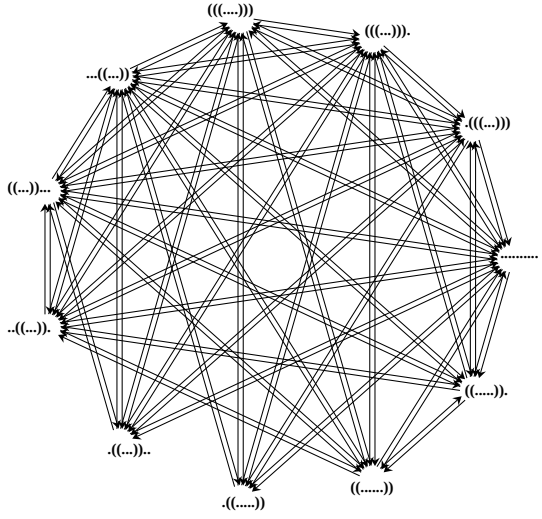
(1) Genotype space is **discrete**



(2) Its structure depends on the **genetic operator**



(3) Phenotype space inherits its structure from genotype space



Accessibility at genotypic levels **implies** accessibility at phenotypic level

Does Evolution really "live" on an Euclidean space????

Goal: A "Relative" Theory

We want a theory of phenotypes that can deal with concepts such as

- Continuity and Discontinuity
- Character
- Homology
- Innovation

WITHOUT recourse to a

specific representation of the phenotype

Genotype Spaces

Given:

a set X of possible genotypes

a set A of realized genotypes

a fixed collection of genetic operators

[such as mutation, recombination, gene-rearrangement]

define the set A' of genotypes accessible from A.

Properties

(i) No spontaneous creation, i.e, $\emptyset' = \emptyset$.

(ii) A more diverse population produces more diverse offsprings: $A \subseteq B$ implies $A' \subseteq B'$

(iii) All parental genotypes are also accessible in the next time step $A \subseteq A'$.

This is the same as the C-operator for the chemical network!

In the case of mutation as the only source of diversity:

haploid populations, no sex, no recombination, etc

(iv) Diversity of offsprings depends only on the parent: $A' = \bigcup_{x \in A} \{x\}'$

Generalized Closure Spaces

... instead of vector spaces ...
Set X, closure function $\mathrm{cl} : \mathcal{P}(X) \to \mathcal{P}(X)$
Equivalent formulations:

$$\mathrm{int}(A) = X \setminus \mathrm{cl}(X \setminus A)$$

The interior is the dual of the closure function
A set N is a neigbhorhood of x if and only if $x \in \mathrm{int}(N)$.
Let $\mathcal{N}(x)$ be the set of all neighborhood of x.
$\mathcal{N} : X \to \mathcal{P}(\mathcal{P}(X))$.
Closure, interior and neighborhood functions are equivalent.

Generalized Closure Spaces

	closure	neighborhood
K0	$\mathrm{cl}(\emptyset) = \emptyset$	$X \in \mathcal{N}(x)$
K1	$A \subseteq B \implies \mathrm{cl}(A) \subseteq \mathrm{cl}(B)$ $\mathrm{cl}(A \cap B) \subseteq \mathrm{cl}(A) \cap \mathrm{cl}(B)$ $\mathrm{cl}(A) \cup \mathrm{cl}(B) \subseteq \mathrm{cl}(A \cup B)$	$N \in \mathcal{N}(x),\ N \subseteq N'$ $\implies$ $N' \in \mathcal{N}(x)$
K2	$A \subseteq \mathrm{cl}(A)$	$N \in \mathcal{N}(x) \Rightarrow x \in N$
K3	$\mathrm{cl}(A \cup B) \subseteq \mathrm{cl}(A) \cup \mathrm{cl}(B)$	$N', N'' \in \mathcal{N}(x) \implies$ $N' \cap N'' \in \mathcal{N}(x)$
K4	$\mathrm{cl}(\mathrm{cl}(A)) = \mathrm{cl}(A)$	$N \in \mathcal{N}(x) \iff$ $\mathrm{int}(N) \in \mathcal{N}(x)$
K5	$\bigcup_{i \in I} \mathrm{cl}(A_i) = \mathrm{cl}\left(\bigcup_{i \in I} A_i\right)$	$\mathcal{N}(x) = \emptyset$ or $\exists N(x) : N(x) \subseteq N$ iff $N \in \mathcal{N}(x)$

In general: only (K0), (K1), (K2) hold: **neighborhood space** For mutation in haploid populations: (K0), (K1), (K2), (K5) [and thus (K3)]: **additive pretopological space**

For comparison: (K0), (K1), (K2), (K3), and (K4) are equivalent to the axioms of a **topology**.

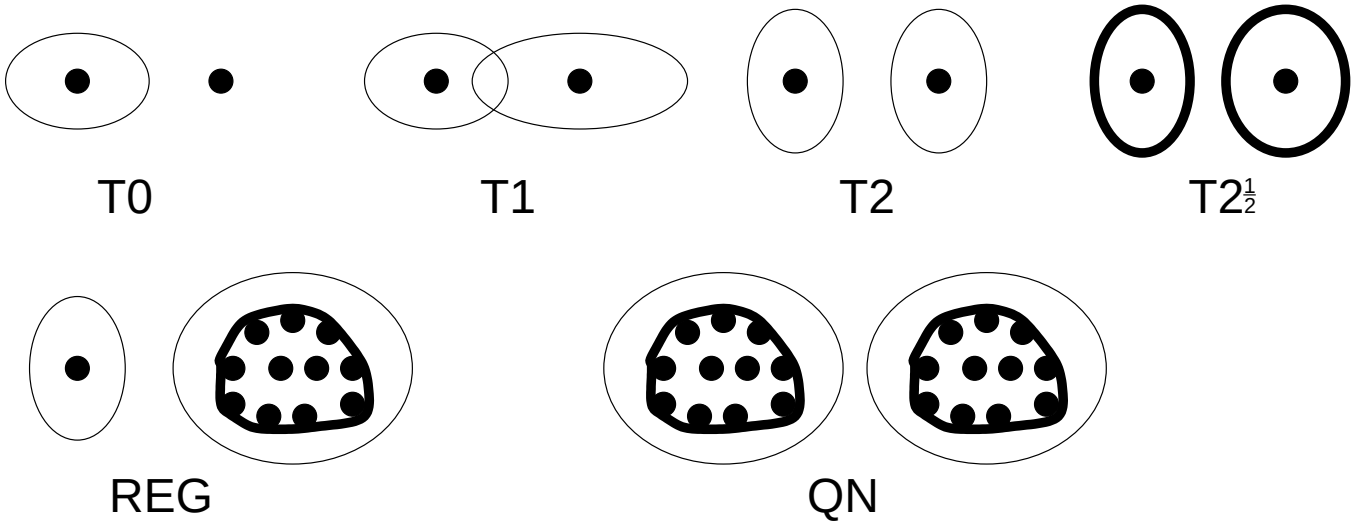
Cool!

. . . so, real evolution, genetic algorithms, evolution strategies, multi-objective optimization heuristics, genetic programming, etc., etc., live on a neighborhood space.
. . . for mutation only, it is even a pretopology.
Thus:
Directed graphs and finite pretopological spaces are the same thing

Should we care that our closure function is NOT idempotent?
NO, Eduard Čech in the 1960s wrote a big, fat textbook on point set topology, where he showed that pretty much everything works in pretopologies — thus you can do topology without every talking about open or closed sets. (Just the proofs get a bit more tedious without this convenience.)

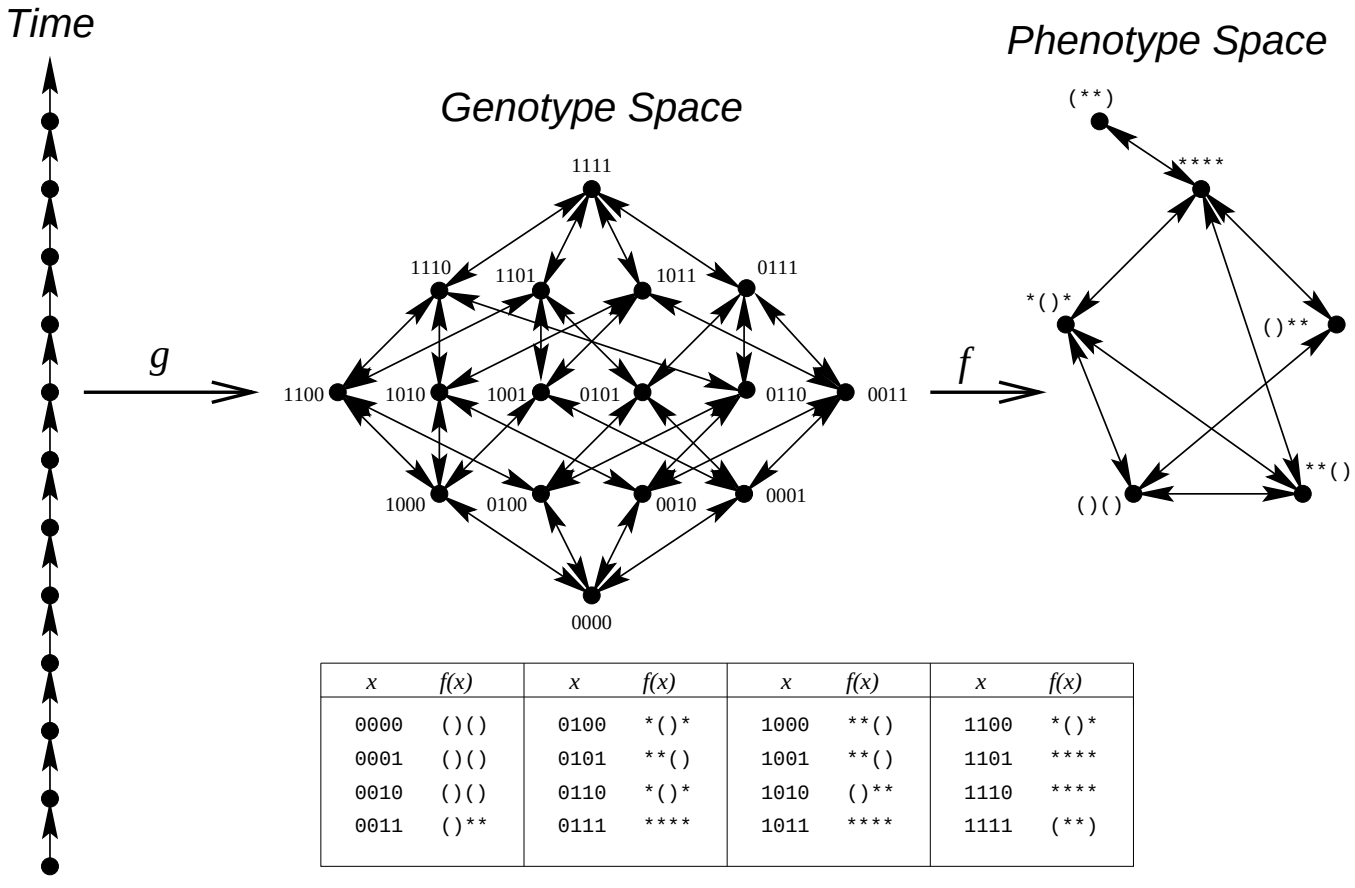
What can we prove about closure spaces?

For example: Implications between *Separation Axioms*



$$(\text{T4}{=}\text{T0}{+}\text{R0}{+}\text{QN}) \implies (\text{T3}{=}\text{T0}{+}\text{REG}) \implies \text{T2}\tfrac{1}{2} \implies \text{T2}$$
$$\implies \text{T1} \implies \text{T0}$$

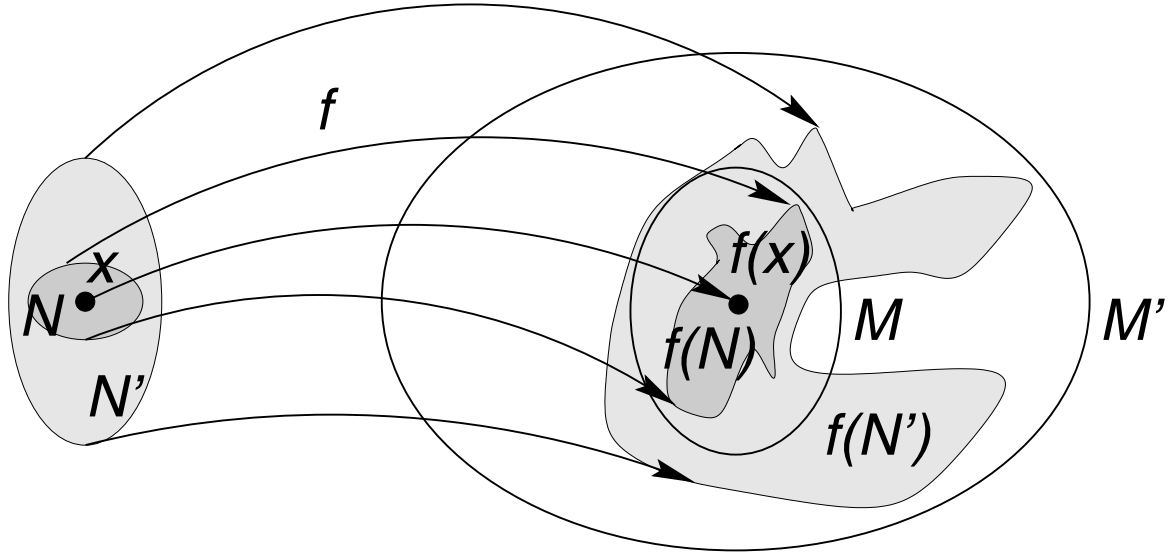
Evolutionary Trajectories



x	f(x)	x	f(x)	x	f(x)	x	f(x)
0000	()()	0100	*()*	1000	**()	1100	*()*
0001	()()	0101	**()	1001	**()	1101	****
0010	()()	0110	*()*	1010	()**	1110	****
0011	()**	0111	****	1011	****	1111	(**)

Continuity

Genotype-Phenotype map: $(X, \mathrm{cl}) \to (Y, \mathrm{cl})$



Equivalent: **closure preservation**: $f(\mathrm{cl}(A)) \subseteq \mathrm{cl}(f(A))$.

BUT: What is closure in phenotype space?
$y' \in \mathrm{cl}(B)$ ... y' is "readily accessible" from B
i.e., there are "enough" genotypes that fold into members of B who can mutate or recombine into an offspring with phenotype y'.
$\Rightarrow$ Notion of continuous versus discontinuous trajectories

Product Spaces

Let (X_1, c_1) and (X_2, c_2) be two general closure spaces, with neighborhood systems $\mathcal{N}_1$ on X_1 and $\mathcal{N}_2$ on X_2.

Product space: Point set $X_1 \times X_2$.

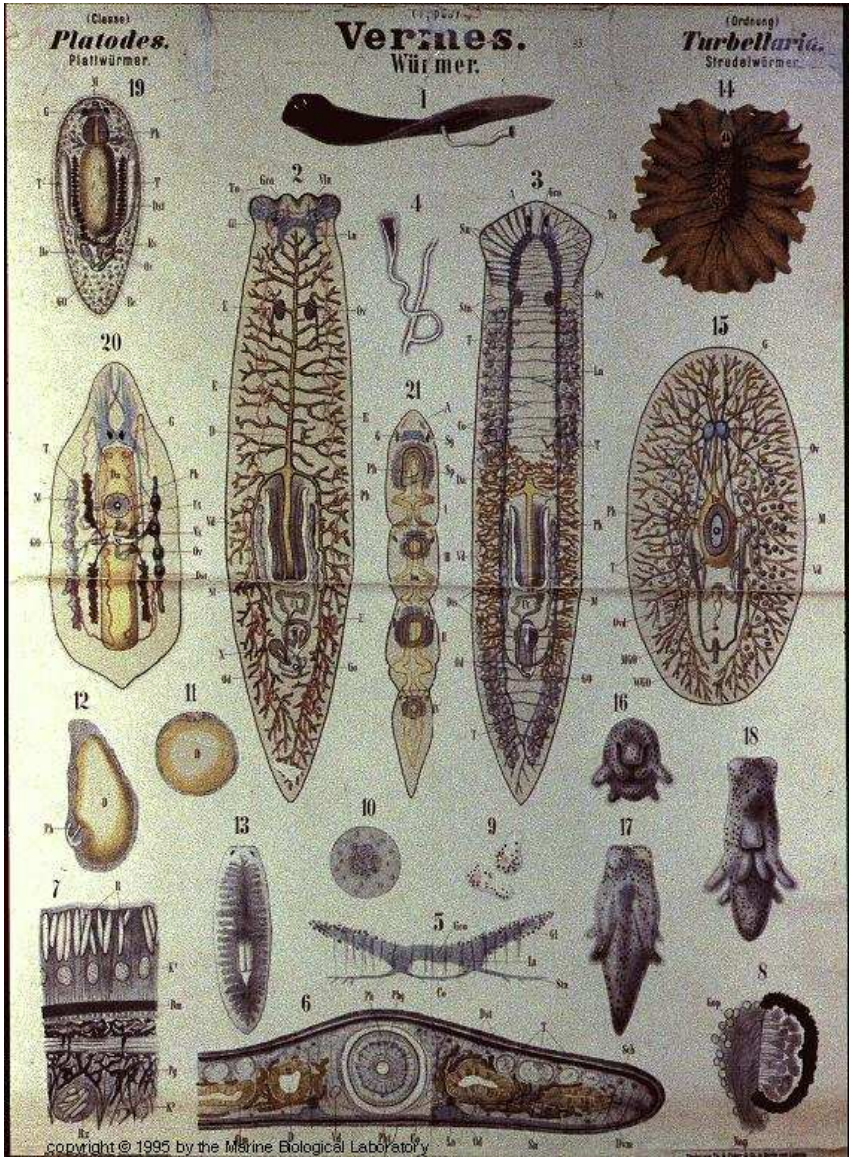
The neighborhoods of the product space satisfy:

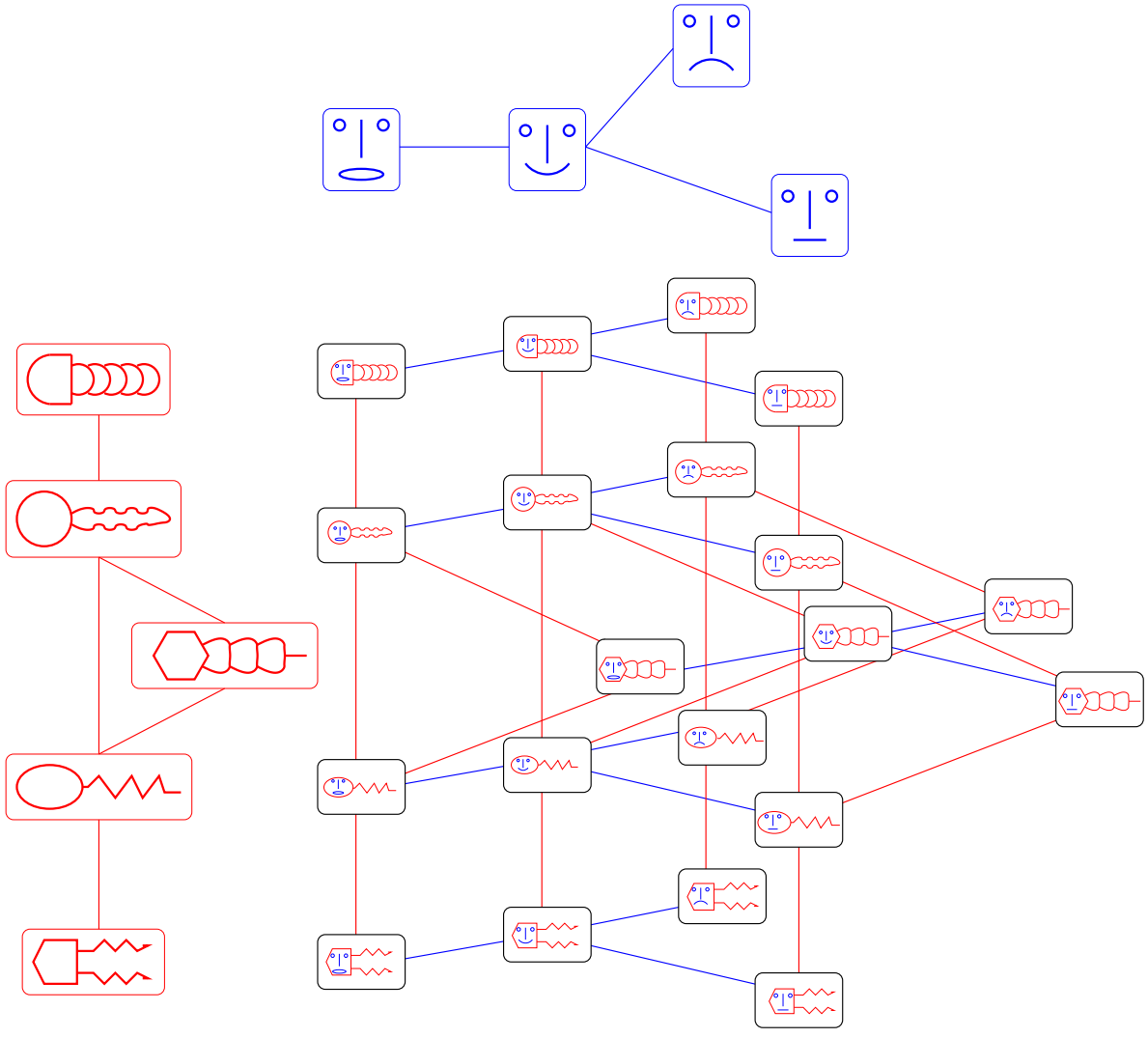
N is a neighborbood of (x_1, x_2) iff there are neighborhoods $N_1 \in \mathcal{N}_1(x_1)$ and $N_2 \in \mathcal{N}_2(x_2)$ such that $N_1 \times N_2 \subseteq N$.

The projections $\pi_i : (X_1 \times X_2, \mathcal{N}) \to (X_i, \mathcal{N}_i) : \ (x_1, x_2) \mapsto x_i$ are continuous functions for $i = 1, 2$.

(as in topological spaces)

What is a Phenotypic Character (Merkmal)?





Characters

Idea:

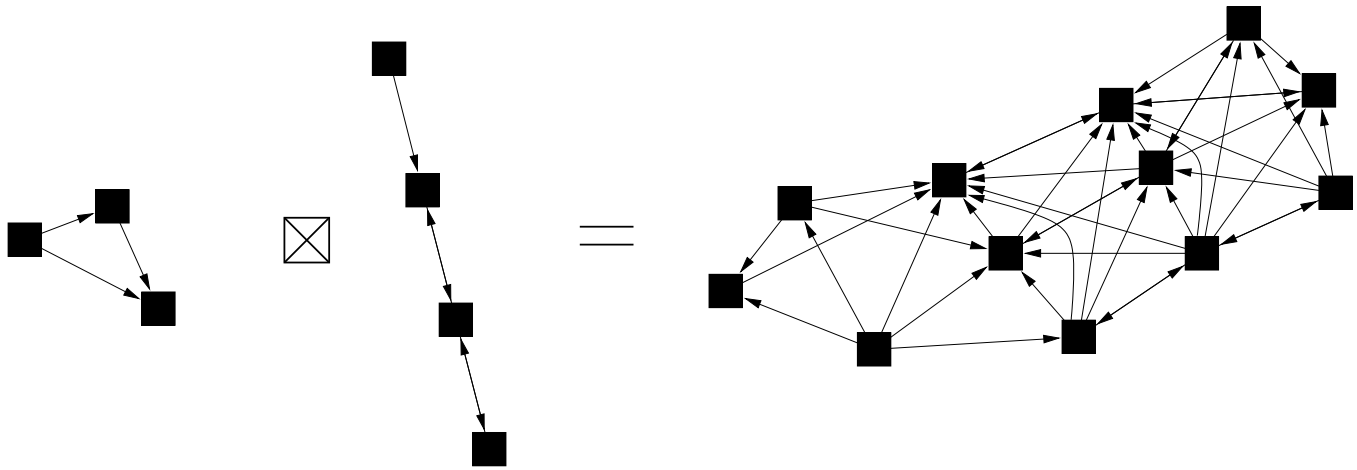
Characters **can** vary independently

$\Longleftrightarrow$

Factors of phenotype space

Mutation only: Directed Graphs

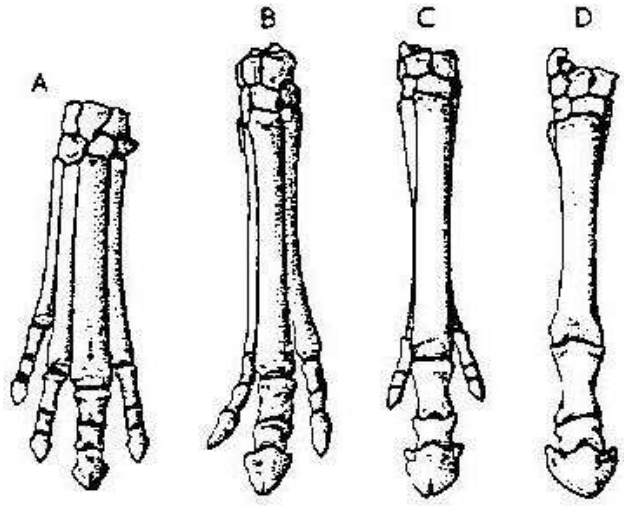
topological product $\Longleftrightarrow$ strong product of graphs



Unique prime factor decomposition of connected graphs and digraphs.

Allows identification of global characters.

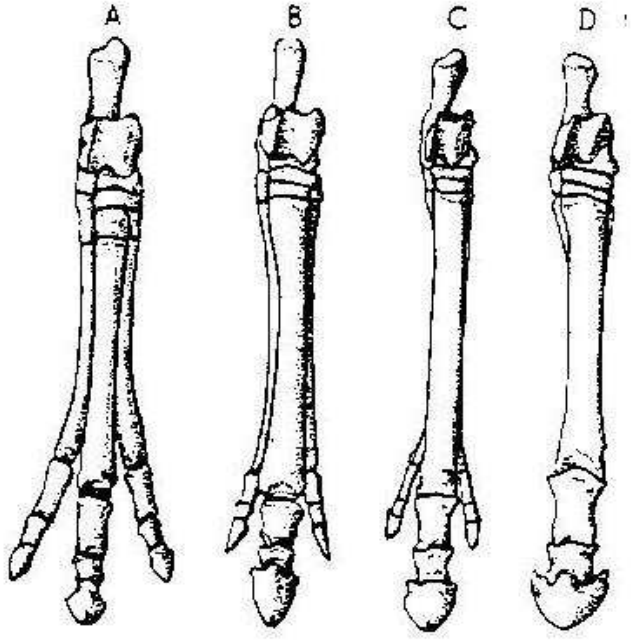
Homologous Characters



Horse Leg Evolution

A Hyracotherium
B Miohippus
C Merychippus
D Equus

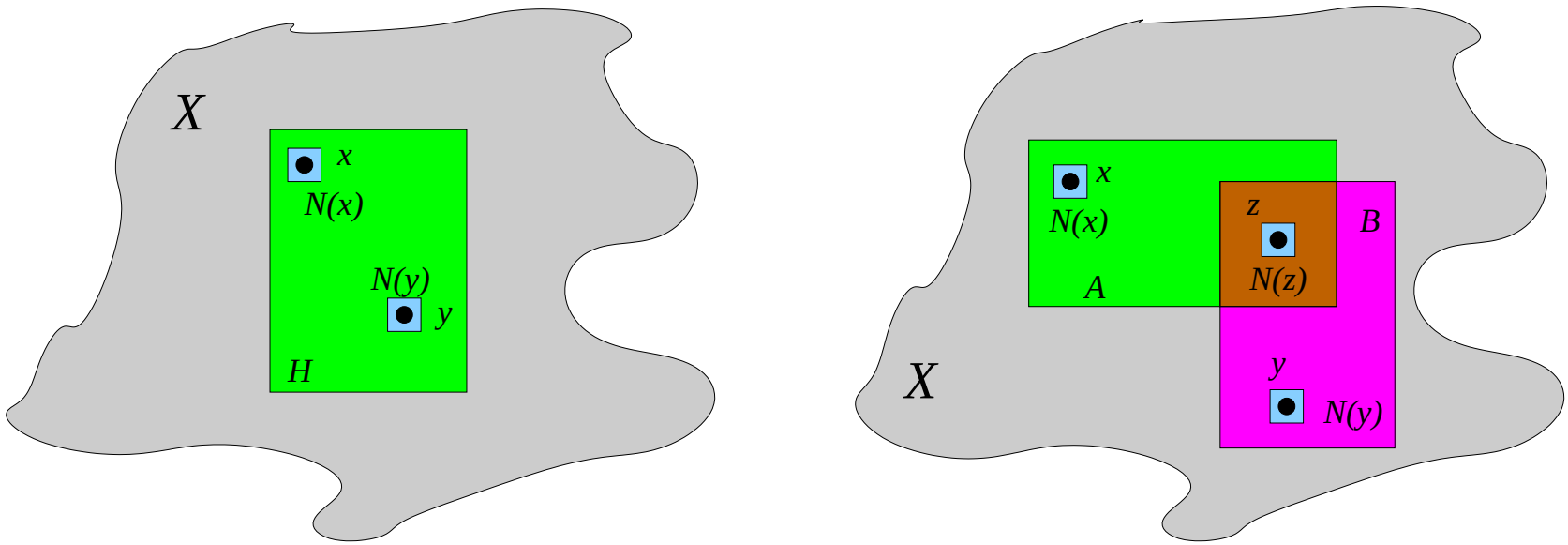
Forefeet



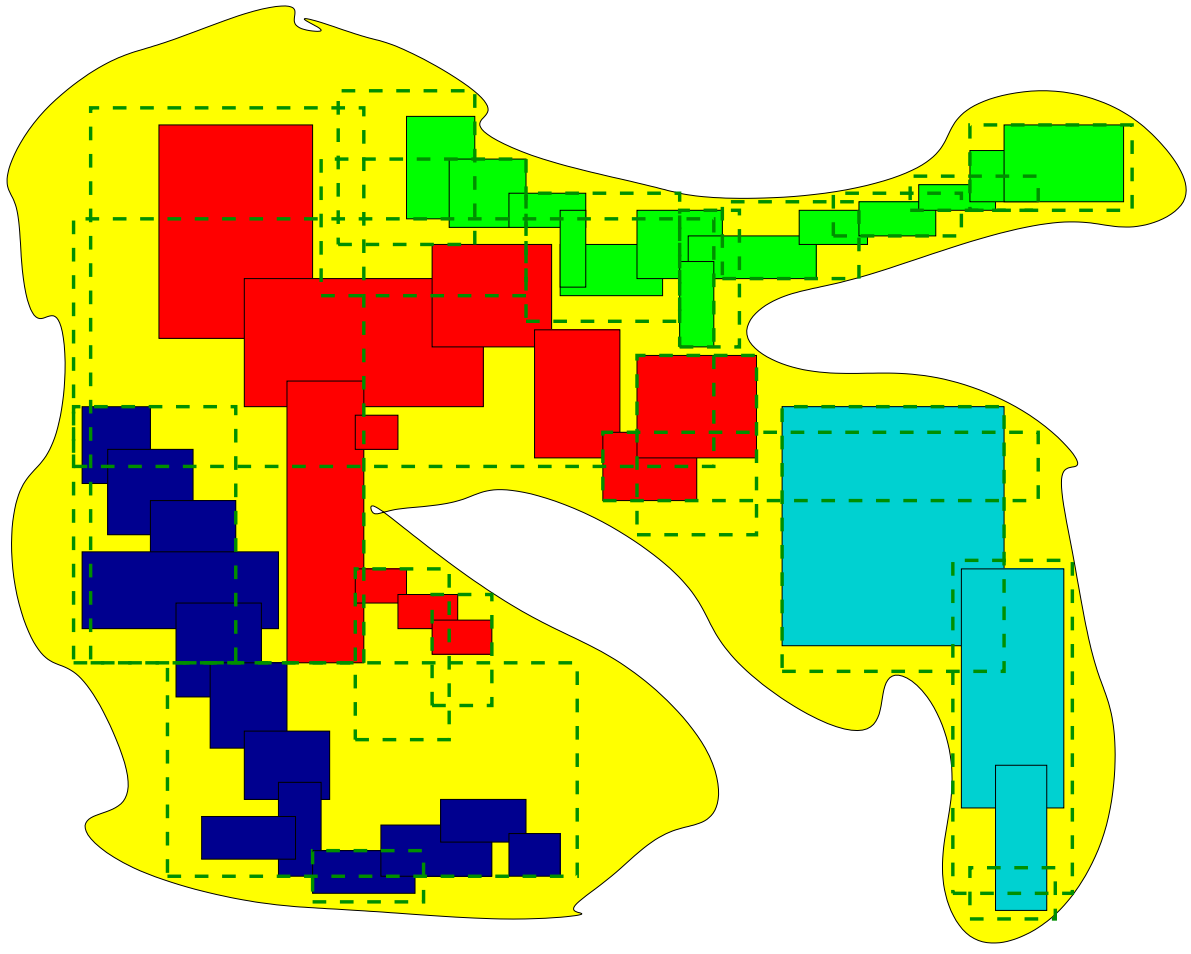
Hindfeet

Homology

If characters "are" just factors of the phenotype space, how do we know which factors are "the same" in different places of phenotype space??



A factorizable region H established the identity of characters between two points $x, y \in \text{int}(H)$. In a second step overlapping factorizable regions A and B can mediate character identity via points in their common interior $z \in \text{int}(A) \cap \text{int}(B)$.



The identity of characters can be extended wherever the colored rectangles overlap. The four types of factorizations (different colors) all may have one “highlevel”-factor (character) in common (green dashed outline) which can be made up of different combinations of “sub-characters”.

Summary on Molecular Evolution

We have developed here a **framework** (or a **language**) for formalizing evolution at large scales that can deal with:

- Continuous and discontinuous evolutionary transitions
- the concept of a **character**
- the concept of **homology**
- different notions of **innovation**
- & suggests (at least some) testable hypotheses

Of course, it is only a first step ...

Fitness Landscapes (again ...)

Fitness Landscapes: Optimization by Local Search

Given:

- A set X of configurations
- A set Z of (partially) ordered values
- A fitness function $f : X \to Z$
- Some collection $\mathfrak{M}$ of rules that transform subsets of X into other subsets of X. (For technical convenience we assume that $\mathfrak{M}$ contains an identity operator that simply leaves the subset unchanged.)

So: all structure on X is implied *somehow* by $\mathfrak{M}$.

A closure function

How does $\mathfrak{M}$ "explore" / "search" X?
Define $c : \mathcal{P}(X) \to \mathcal{P}(X)$ such that for each subset $A \subseteq X$ holds:
$c(A) =$
$\{x \in X | x$ can be generated instantaneously from (a subset of) A by means of $\mathfrak{M}\}$
"instantaneous" means a **single** application of an operator from $\mathfrak{M}$
Properties of c:

- $c(\emptyset) = \emptyset$
- $A \subseteq A'$ implies $c(A) \subseteq c(A')$
- $A \subseteq c(A)$

So (X, c) is a neighborhood space. This is nice.

Local Minima

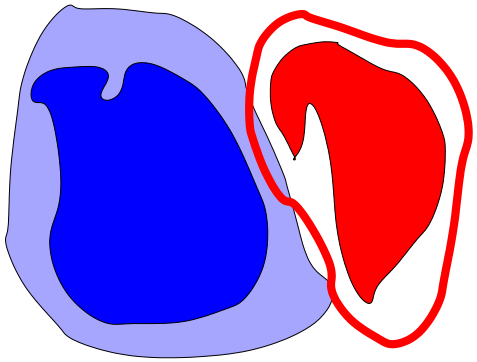
x is a local minimum of $f : X \to Z$ if there is a neighborhood $N \in \mathcal{N}(x)$ such that there is no $y \in N$ with $y < x$.

If Z is a po-set instead of ordered, these are the local Pareto points!

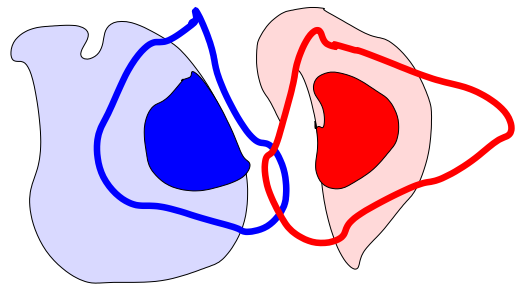
Maybe a stricter definition is desirable sometimes:
x is a local minimum of $f : X \to Z$ if every neighborhood of x contains a neighborhood $N \in \mathcal{N}(x)$ such that there is no $y \in N$ with $y < x$.

Connectedness in Neighborhood Spaces

"Separation" defines what is NOT connected.



semi−separated sets



equivalently: all pairs of subsets are semiseparated

Additional requirement for separation: If A and B are "separated" then combining subsets $A' \subseteq A$ and $B' \subseteq B$ does not generate anything novel, i.e.: $c(A' \cup B') = c(A') \cup c(B')$.

Connectedness in Neighborhood Spaces

Definition. Two sets A and B are productively separated if for any subset $U \subseteq A \cup B$ holds:

- $c(U \cap A) \cap B = \emptyset$,
- $c(U \cap B) \cap A = \emptyset$, and
- $c(U) = c(U \cap A) \cup c(U \cap B)$.

Definition. A subset A of X is *connected* if it cannot be decomposed into two non-empty productively separated sets.

Hawai‘i Theorem

Theorem. Connected sets in neighborhood spaces have the "usual" properties.

Hawai'i Theorem

- Individual points $\{x\}$ are always connected.
- If U' and U'' are connected and $U' \cap U'' \neq \emptyset$, then $U' \cup U''$ is connected
- If U is connected then $c(U)$ is connected.
- Let $\{U_\imath\}$ be a collection of connected sets with $x \in U_\imath$ for all $\imath$, then $\bigcup_\imath U_\imath$ is also connected.

Thus: For each set $A \subseteq X$ and each $x \in A$ the connected component

$$A[x] = \bigcup \{A' \subseteq A | x \in A' \text{ and } A' \text{ connected}\} \tag{1}$$

is well-defined.

Level Sets

For each $\eta \in Z$ define the level sets

$$\Lambda_\eta = \{z \in X | f(z) < \eta\}$$

For each $x \in X$ and each $\eta in Z$ define $\Lambda^*_\eta(x)$ as the connected component containing x, provided $f(x) < \eta$.
We set $\Lambda^*_\eta(x) = \{x\}$ if $f(x) = \eta$ and $\Lambda^*_\eta(x) = \emptyset$ otherwise.

$$\eta[x, y] = \inf\{\eta \in Z | \Lambda^*_\eta(x) \cap \Lambda^*_\eta(y) \neq \emptyset\}$$

Then x and y belong to the same connected component of the levelset at heights above $\eta[x, y]$ and to different components below $\eta[x, y]$.
THUS: $\eta[x, y]$ is the height of the saddle between x and y.
So what are saddle points?
... we need an appropriate notion of compactness to talk about this ...

So What?

- We can think about topological/geometric features of landscapes without making the distinction between discrete, continuum, low- or high dimensional
- We don't need symmetries of the move set, additivity (i.e., a graph structure), or a distance between points.
- It seems that the language for the most part does not care if we use integers, reals, vectors, or any arbitrary poset as value set.
- We can define barrier trees completely naturally for arbitrary problems with ARBITRARY genetic operators
- It was fun working on it.

And in Chemistry?

Peter Dittrich (U. Jena) constructed a theory of *Chemical Organizations* based on Walter Fontana's the notions of a

- "closed" sets of molecules
- "self-maintaining" set of molecules

Chemical Reactions

X . . . set of molecular types
$\mathfrak{R}$ . . . set of reactions:

$$\sum_x \bar{\alpha}_{x,\rho} \to \sum_x \alpha_{x,\rho}$$

Stochiometric coefficients: $\bar{\alpha}_{x,\rho}$ (l.h.s.) $\alpha_{x,\rho}$ (r.h.s.)
Domain and image of a reaction ρ:

$$\mathrm{dom}\rho = \{x \in X | \bar{\alpha}_{x,\rho} > 0\}$$
$$\mathrm{img}\rho = \{x \in X | \alpha_{x,\rho} > 0\}$$

Production Function

Consider a reaction mixture composed of molecules of types $A \subseteq X$.
The reaction ρ can take place in this medium if and only if $\mathrm{dom}\rho \subseteq A$.
Define the collection of all possible reactions that can start from A:

$$\mathfrak{R}_A = \{\rho \in \mathfrak{R} | \mathrm{dom}\rho \subseteq A\}$$

The products of all these reactions will have non-zero concentration after infinitesimal time.

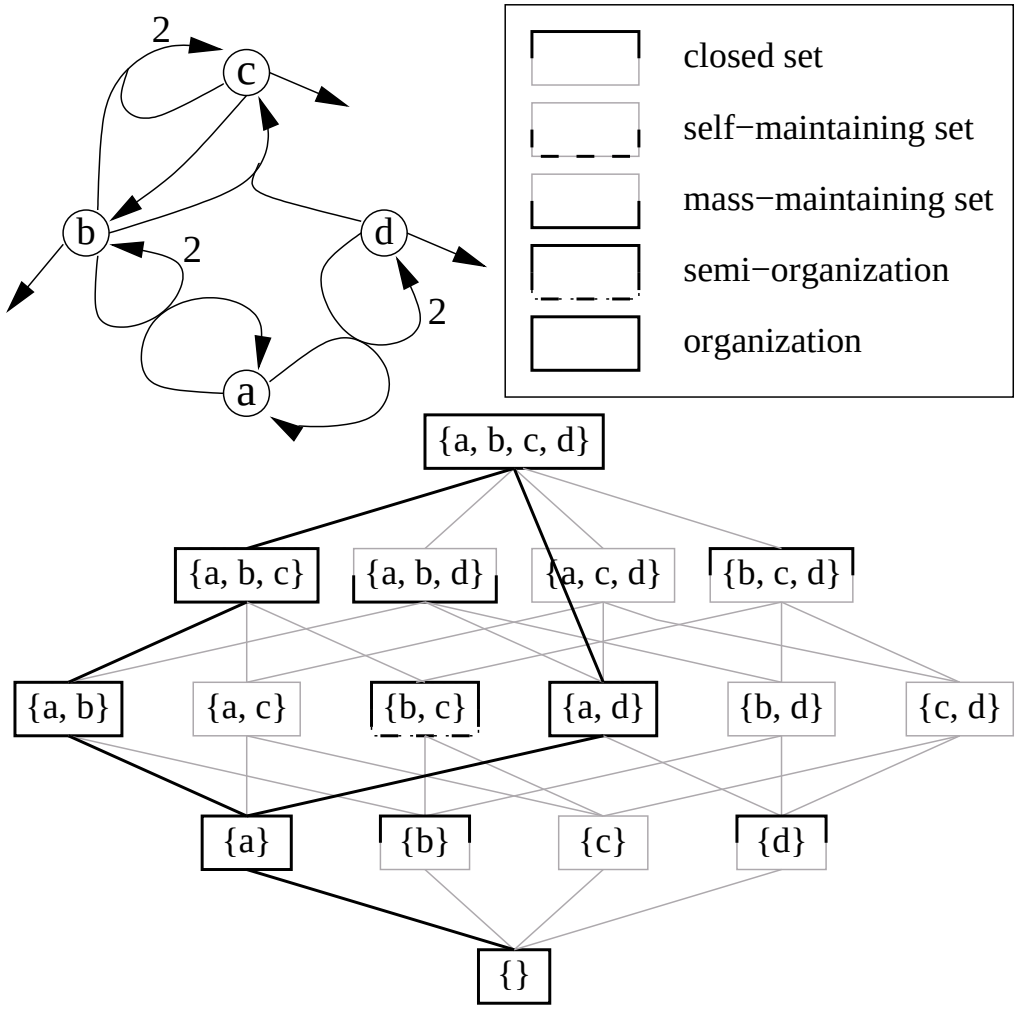
$$p(A) = \bigcup_{\rho:\mathrm{dom}\rho\subseteq A} \mathrm{img}\rho$$

We call $p : \mathcal{P}(X) \to \mathcal{P}(X)$ the production function of $(X, \mathcal{R})$.
Open question: To what extent is $(X, \mathcal{R})$ determined by p?

Refined Model

Stochiometric matrix of net reaction: $s_{x,\rho} = \alpha_{x,\rho} - \bar{\alpha}_{x,\rho}$
Stationary Fluxes J satisfy $\mathbf{S}J = 0$ and $J_\rho \geq 0$ (Clarke, Fell, . . .)
"outflux reactions" ψ_x for each species x
"influx reactions" ϕ_x for *some* species that are supplied from outside.
The flux vector J is said to produce x from A if $J_{\psi_x} > 0$ and $J_\rho > 0$ implies $\mathrm{dom}\rho \subseteq A$ for all non-outflux reactions ρ.
The species x is *maintainable* from A if there is a stationary flux vector J that produces x from A.
Let $s(A)$ denote the set of all species maintainable from A.
Then there is always a stationary flux vector that simultaneously produces all $x \in s(A)$ from A.
Theorem. $s(A) \subseteq p(A)$.
Furthermore, both $s(A)$ and $p(A)$ are isotonic.

Dittrich's Lattice of Organizations



P.Dittrich et al., archive/q-bio 0501016

Stationary state $\Rightarrow$ support is closed set w.r.t. s.

Chemical Organization Dictionary

The following works in the absence of inhibitory interactions:

Set functions	P. Dittrich's theory
$s(A) \subseteq p(A) \subseteq A$	"closed"
$A \subseteq p(A)$	self-maintaining
$A \subseteq s(A)$	mass-maintaining
$A = p(A)$	semi-organization
$A = s(A) = p(A)$	organization

THUS:Chemical organizations thus can be understood as topological constructs

Summary

- Large Chemical Reaction Networks can be understood as generalized topological spaces
- Chemical Organization Theory has a topological interpretation.
  Whether this correspondence is fruitful is a subject of current research
- Many basic results and constructions from classical point set theory still work for generalized closure spaces.
- Agende: explore whether other topological concepts such as denseness, connectedness, convergence, separation can be interpreted in chemical terms. After all, these concepts come for free with the topological interpretation of $(X, \mathfrak{R})$.

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