Memory Formation in Driven Disordered Systems – Dead or Alive

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Driven Disordered Systems Approach to Biological Evolution in Changing Environments, PRX 2022

Grenoble 2022

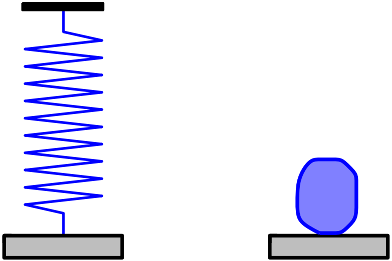
Scope

- Cross-fertilization between statistical mechanics of disordered systems and adaptive evolution in biology.
- Key concept: fitness landscape of a biological population.
- Fitness landscape describes growth rates of different genotypes in a fixed environment.
- **fitness landscape** $\leftrightarrow$ **energy landscape** of disordered systems.
- **BUT: environments change!**
- Adaptive evolution in **changing fitness landscapes** *as* **driven disordered systems**.

THEME: Can adaptive evolution of a bacterial population retain a memory of its past environments?

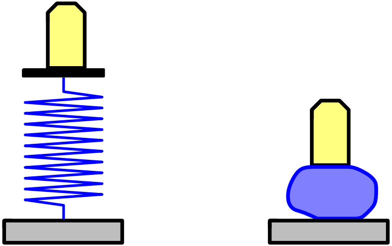
Reversible *vs.* irreversibe deformations and memory

- Suppose we load a spring and a sand bag with varying loads ...



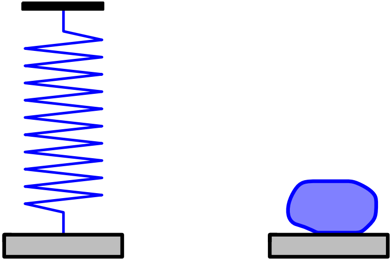
Reversible *vs.* irreversibe deformations and memory

- Place two identical **medium** loads on each ...



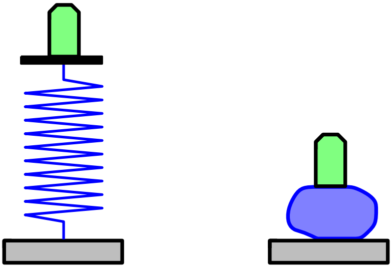
Reversible *vs.* irreversibe deformations and memory

- Remove loads.
- Spring **restores** initial position, sand bag **remains** deformed.



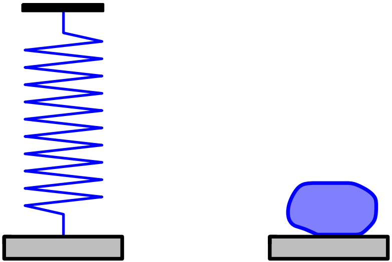
Reversible *vs.* irreversibe deformations and memory

- Next place identical **lighter** loads on spring and bag.
- Spring compresses less, while sand bag **retains** deformed state.



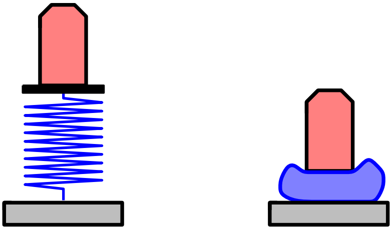
Reversible *vs.* irreversibe deformations and memory

- Removing the lighter load, spring returns to initial position.
- Sand bag **retains** initial deformation:
- Sand bag keeps a **memory** of initial loading.



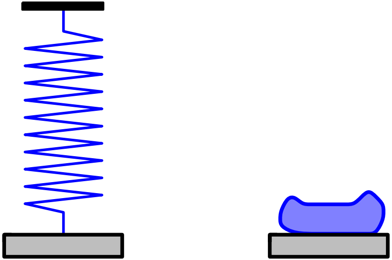
Reversible *vs.* irreversibe deformations and memory

- Place next identical **heavier** loads.
- Spring compresses more than before.
- Sand bag also **deforms** further.



Reversible *vs.* irreversibe deformations and memory

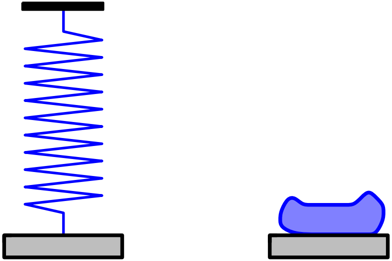
- Remove heavy loads.
- Spring **restores** its uncompressed state.
- Sand bag remains in **further deformed** state.



Reversible *vs.* irreversibe deformations and memory

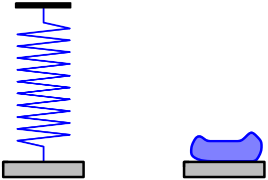
Sand bag:

- Retains **memory** of past deformations.
- Placing **heavier** load on sand bag, $\Rightarrow$ **memory** of previous load is **lost**.
- Memory is **overwritten** by **heavier** load.



Reversible *vs.* irreversibe deformations and memory

Two "devices", two different responses:



- Spring: **perfectly elastic**: returns to **same** position when unloaded. **No memory of its loading history.**
- Sand bag: **plastic**: **retains memory of loading history:** memory of **largest load**.
- **Spring:** "records" instantaneous state of loading, *e.g.* like a kitchen scale.
- **Sand bag:** "records" extreme loading event in its history $\Rightarrow$ future response is **history-dependent**.

Recap – Memory Formation

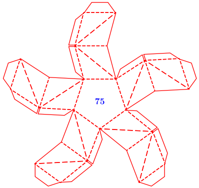
- Example of system that can record the largest applied load.
- Simple prototype of a system interacting with a changing environment:
  - **System:** sand bag,
  - **Changing Environment:** various loads placed on sand bag,
  - **Effect on system:** altering shape of sand bag.
- Main ingredients:
  - **Disorder**
  - **Large number of degrees of freedom**

Q: How do we characterize systems that retain a memory of their past environments?

Outline of this talk

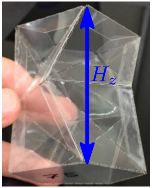
- **Memory formation** in **driven soft-matter systems.**
- Focus on **athermal, quasi-static (AQS)** response to driving.
- Response to AQS driving can be captured via **state transition graphs**: $\Rightarrow$ **Dynamical features are encoded in graph topology**
- Demonstrate how these ideas can be used to **understand and utilize** memory formation.
- Show that these ideas can be used to analyze a model for **adaptive evolution in changing environments**.

Origami-bellows as mechanical memory device

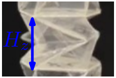


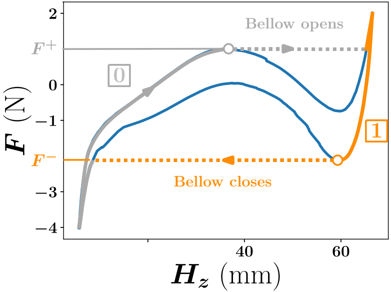
Folding

Bellow open 1

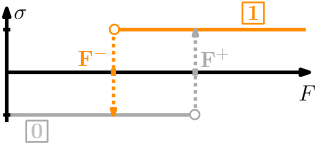


Bellow closed 0

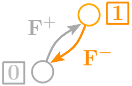




Preisach Element (Hysteron)



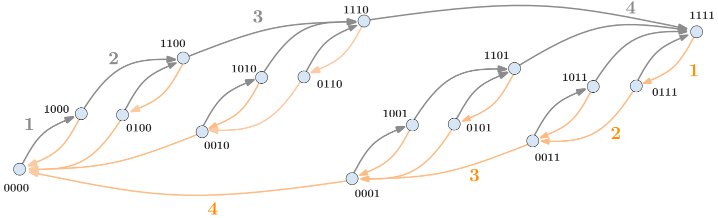
Graph representation

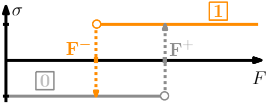


Hysteresis:
$F^- < F^+$

(Jules, Reed, Daniels, **MM**, & Lechenault Phys. Rev. Res. (2022))

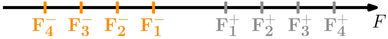
A stack of four bellows – The Preisach Model





Switching Sequence:

Down: 1 → 2 → 3 → 4 Up: 1 → 2 → 3 → 4



Preisach Model:

Each hysteron changes state:

- **based on F,**
- **its current state (history)**

INDEPENDENTLY

By INDEPENDENCE label hysterons s.t.

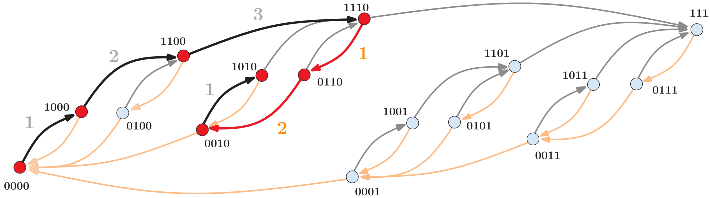
Up: 1 → 2 → 3 → 4

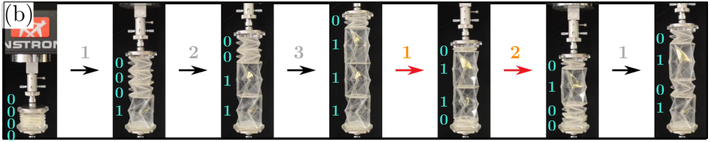
Using different bellows we can alter down sequence (call it ρ)

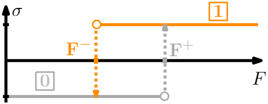
$$\rho = 1\,2\,3\,4$$

(Jules, Reed, Daniels, **MM**, & Lechenault Phys. Rev. Res. (2022))

A stack of four bellows – The Preisach Model







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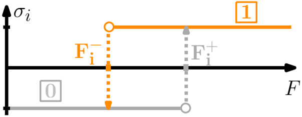
(Jules, Reed, Daniels, **MM**, & Lechenault Phys. Rev. Res. (2022))

The (discrete) Preisach Model in a nutshell

Suppose we have a system with N hysterons: $\boldsymbol{\sigma} = (\sigma_1, \sigma_2, \ldots, \sigma_N)$ **is a state,**
$\sigma_i = 0, 1$



Switching fields: $F_1^{\pm}, F_2^{\pm}, \ldots, F_N^{\pm}$

$F_i^- < F_i^+$

$\sigma_i = 1$ **requires** $F > F_i^-$

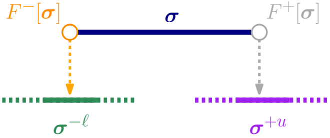
$\sigma_j = 0$ **requires** $F < F_j^+$

POSSIBLE ONLY IF $\boldsymbol{\sigma}$ such that:

$$F^-[\boldsymbol{\sigma}] \equiv \max_{\{i : \sigma_i = 1\}} F_i^- < \min_{\{j : \sigma_j = 0\}} F_j^+ \equiv F^+[\boldsymbol{\sigma}]$$

(Stability condition, determines the set of states)

Let ℓ and u be the sites were the max **and** min **are attained**



$\Rightarrow$ **Single site flips suffice to regain stability**
NO AVALANCHES!

(M.M. Terzi & **MM** PRE **102** (2021) 012122)

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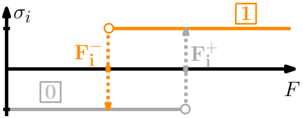

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By INDEPENDENCE label hysterons s.t.

Up: $1 \to 2 \to \ldots \to N$

Down: $\rho_1 \to \rho_2 \to \ldots \to \rho_N$

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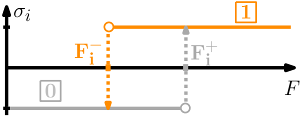

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Switching Sequence $\boldsymbol{\rho}$ determines transition graph between $(00\ldots0)$ and $(11\ldots1)$!

(M.M. Terzi & **MM** PRE **102** (2021) 012122)

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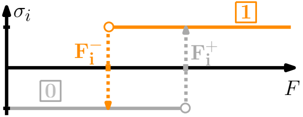

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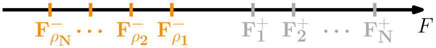

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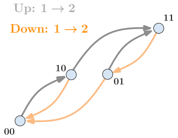

$\boldsymbol{\rho} = 1\,2$

(M.M. Terzi & **MM** PRE **102** (2021) 012122)

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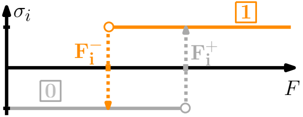

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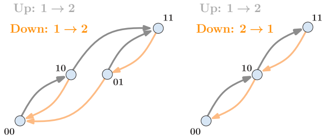
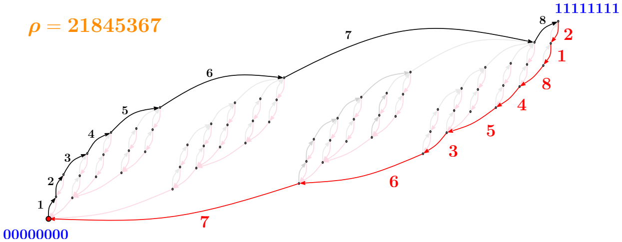


$\boldsymbol{\rho} = 1\,2$ $\boldsymbol{\rho} = 2\,1$

(M.M. Terzi & **MM** PRE **102** (2021) 012122)

The Preisach Model and Return Point Memory (RPM)



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Up: $1 \to 2 \to 3 \to 4 \to 5 \to 6 \to 7 \to 8$

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Switching Sequence ρ COMPLETELY determines the transition graph between $(00\ldots0)$ and $(11\ldots1)$!

(**MM** & M.M. Terzi AHP **20** (2019) 2819 – 2872)

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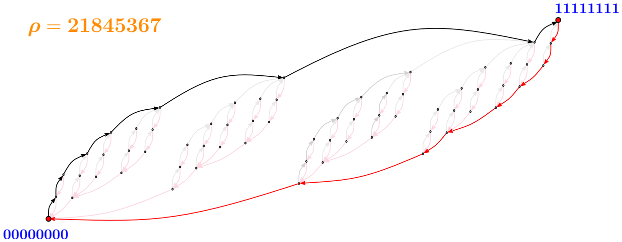

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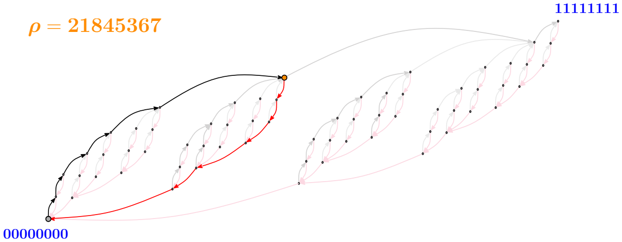

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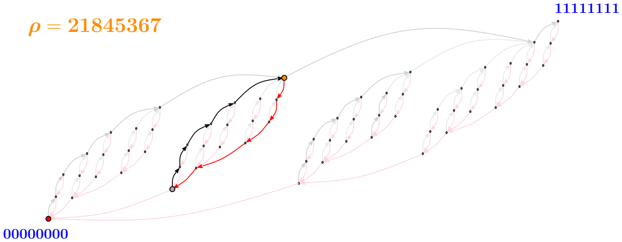

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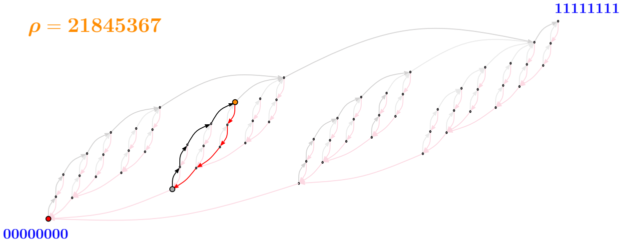

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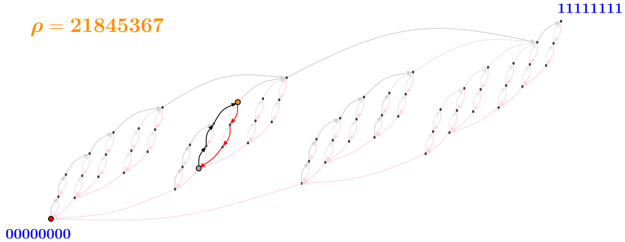

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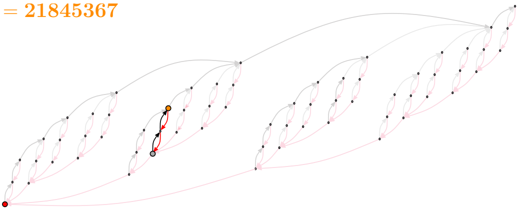
(**MM** & M.M. Terzi AHP **20** (2019) 2819 – 2872)

The Preisach Model and Return Point Memory (RPM)

$\rho = 21845367$



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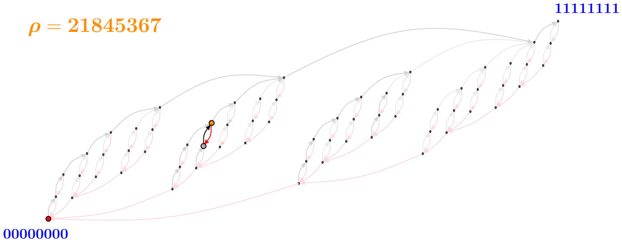

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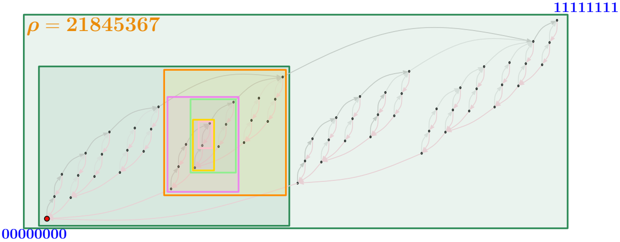

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loop Return Point Memory (ℓRPM) as topological feature of transition graph

$\Rightarrow$ Hierarchical Structure of loops nested within loops

"Every loop is existed from its end points!"

(**MM** & M.M. Terzi AHP **20** (2019) 2819 – 2872)

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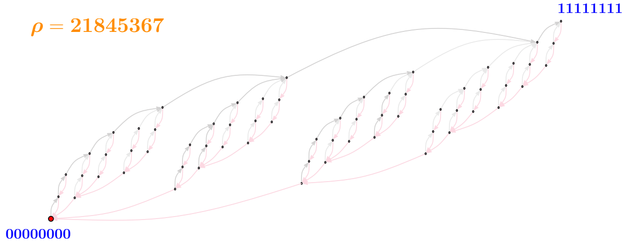

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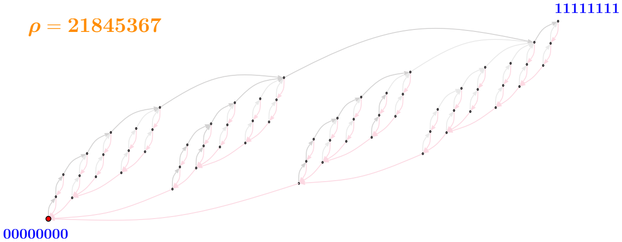
Given ρ what is the number of vertices in the main loop?

M.M. Terzi & **MM** PRE **102** (2021) 012122,
P. L. Ferrari, **MM** & M.M. Terzi AIHPD 2022

The Preisach Model and Return Point Memory (RPM)



Switching Sequence:

Up: $1 \to 2 \to 3 \to 4 \to 5 \to 6 \to 7 \to 8$

Down: $2 \to 1 \to 8 \to 4 \to 5 \to 3 \to 6 \to 7$

Given ρ what is the number of vertices in the main loop?
ANSWER: It is equal to the # of increasing subsequences contained in ρ

M.M. Terzi & **MM** PRE **102** (2021) 012122,
P. L. Ferrari, **MM** & M.M. Terzi AIHPD 2022

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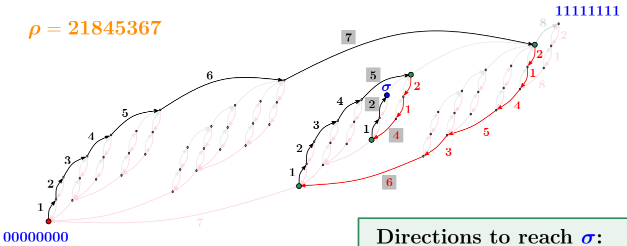

Directions to reach σ:
00000000 $\longrightarrow$ 7 $\longrightarrow$ 6 $\longrightarrow$ 5 $\longrightarrow$ 4 $\longrightarrow$ 2 : σ

2 4 5 6 7 is an increasing subsequence of $\rho = 21845367$

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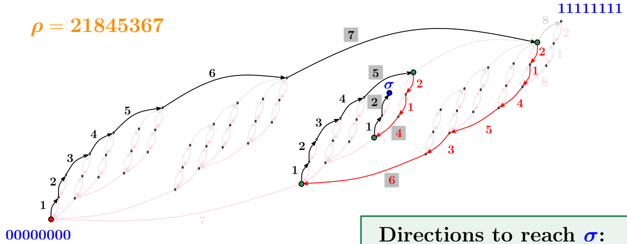

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Histories are mapped into states

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Recap: Memory formation in driven disordered systems

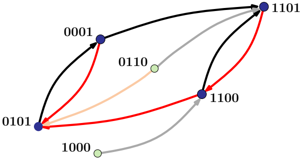
- **Return point memory (RPM)** is one way of **encoding memory of deformation history**.
- **Memory and history-dependence** become **topological features** of transition graph (***t*-graph**) $\Rightarrow$ **loop return point memory (ℓRPM)**, **MM** & Terzi, AHP (2019).
- Preisach model: **simplest model with ℓRPM**.
- More **complicated ℓRPM systems**: Random field Ising model with ferromagnetic interactions, models of depinning, i.e. elastic manifolds in random media.
- Systems that exhibit **ℓRPM approximately**: the sheared amorphous solids (**MM**, S. Sastry, K. Dahmen & I. Regev, PRL (2019)).

A fitness landscape model describing the evolution of antibiotic drug resistance

- The **trade-off induced fitness landscape model (TIL)** (S.G. Das, S.O.L. Direito, B. Waclaw, R. Allen & J. Krug, eLife **9** (2020) e55155):
  - Bacteria in environment of **varying antibiotic drug concentration** x.
  - L possible loci where mutations can occur.
  - Binary vector $\boldsymbol{\sigma} = (\sigma_1, \ldots, \sigma_L)$ encodes whether mutation at i is present ($\sigma_i = 1$) or absent ($\sigma_i = 0$).
- Environment characterized by **single parameter:** antibiotic concentration x.
- For each x: a mapping that assigns to each genotype $\boldsymbol{\sigma}$ a fitness $f_{\boldsymbol{\sigma}}$.

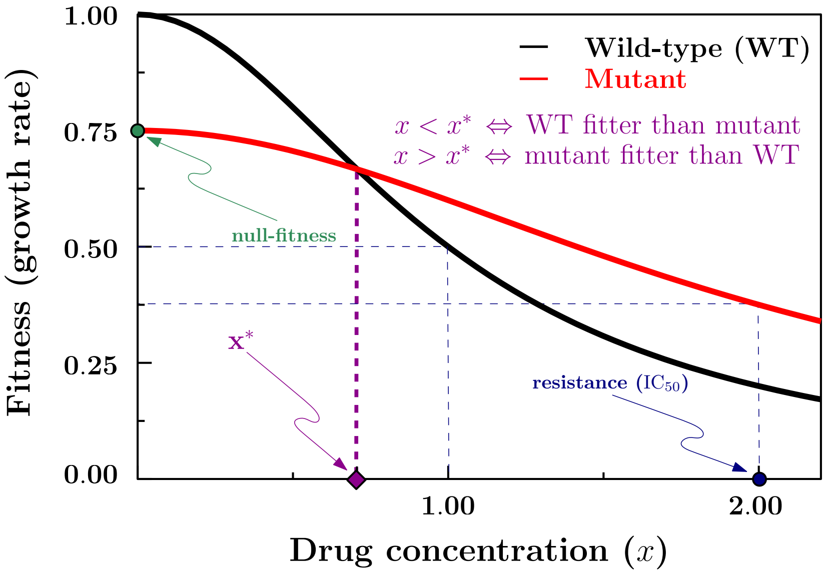
A fitness landscape model describing the evolution of antibiotic drug resistance

- Das *et al.* focus on **topography of fitness landscape:** local fitness maxima, adaptive paths leading to them.
- **Goal:** Characterize the transition between genotypes as x is changed and fitness maxima change.
- **Motivation:**



- $L = 4$ mutation sites in antibiotic resistance enzyme TEM-50 β-lactamase for antibiotic piperacilin at three concentrations.
- Black/Gray and Red/Orange arrows indicate transitions to new fitness peaks under incease and decease of concentration.
- Data compiled from M. Mira *et al.* Mol. Bio. Evol. **32** (2015) 2707.

Dose response (DR) curves, phenotypes & trade-off

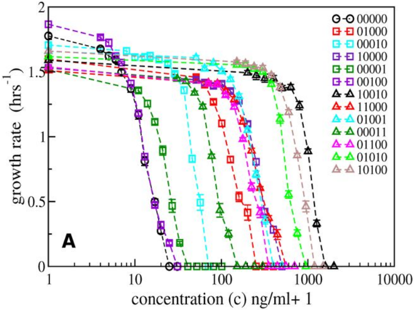


TIL adaptive trade-off: Empirical Evidence I

DR curves of E-coli in the presence of ciprofloxacin.

$L = 5$ **loci**
5 **single mutants**
8 **double mutants**
genotype $\boldsymbol{\sigma}$**:**

- $f_{\boldsymbol{\sigma}}(x)$ **fitness**
- $\boldsymbol{r_{\sigma}}$ **null-fitness**
- $\boldsymbol{m_{\sigma}}$ IC_{50}



(S.G. Das, S.O.L Direito, B. Waclaw, R.J Allen & J. Krug, eLife **9** (2020) e55155)

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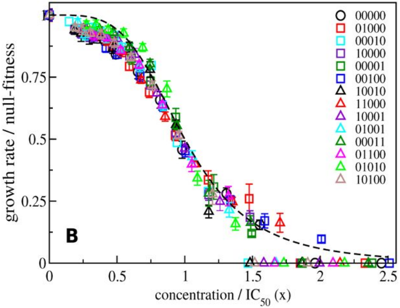


Plotting $\frac{f_{\boldsymbol{\sigma}}(x)}{\boldsymbol{r_{\sigma}}}$ **vs.** $\frac{x}{\boldsymbol{m_{\sigma}}}$ **falls onto a single curve** $w(x)$ **(almost)!**

$$\frac{f_{\boldsymbol{\sigma}}(x)}{\boldsymbol{r_{\sigma}}} = w\left(\frac{x}{\boldsymbol{m_{\sigma}}}\right) \qquad \textbf{fit:} \quad w(x) = \frac{1}{1+x^4}$$

(S.G. Das, S.O.L Direito, B. Waclaw, R.J Allen & J. Krug, eLife **9** (2020) e55155)

TIL adaptive trade-off: Empirical Evidence II

E-coli in the presence of ciprofloxacin (data by Marcusson *et al.* 2009)

Given $\boldsymbol{\sigma}$,

$I^{+}[\boldsymbol{\sigma}] = \{i : \sigma_i = 1\}$

$I^{-}[\boldsymbol{\sigma}] = \{i : \sigma_i = 0\}$

r_i **null-fitness of single mutation at locus** i

m_i **IC$_{50}$ of single mutation at locus** i

Strain	String	log null-fitness	Non-epistatic	log MIC	Non-epistatic
MG1655	00000	0.00 (± .004)	NA	0.00 (± .35)	NA
LM378	10000	0.01 (± .016)	NA	3.17 (± .70)	NA
LM534	01000	-0.01 (± .018)	NA	2.75 (± .70)	NA
LM202	00010	-0.19 (± .020)	NA	0.69 (± .70)	NA
LM351	00001	-0.094 (± .014)	NA	1.08 (± .70)	NA
LM625	11000	-0.030 (± .011)	0.0 (± .038)	3.17 (± .70)	5.92 (± 1.1)
LM421	10010	-0.15 (± .019)	-0.18 (±.040)	4.13 (± .70)	3.56 (± 1.1)
LM647	10001	-0.051 (± .013)	-0.084 (± .034)	3.44 (± .70)	4.65 (± 1.1)
LM538	01010	-0.19 (± .020)	-0.20 (± .042)	4.13 (± .70)	3.46 (± 1.1)
LM592	01001	-0.083 (± .015)	-0.10 (± .036)	3.16 (± .70)	3.83 (± 1.1)
LM367	00011	-0.20 (± .026)	-0.28 (± .038)	2.06 (± .70)	1.77 (± 1.1)
LM695	11010	-0.24 (± .017)	-0.19 (± .058)	3.85 (±. 70)	6.61 (± 1.1)
LM691	11001	-0.073 (± .013)	-0.094 (± .052)	3.85 (±. 70)	7.00 (± 1.4)
LM709	10011	-0.24 (± .027)	-0.274 (± .054)	4.54 (±. 70)	4.94 (± 1.4)
LM595	01011	-0.51 (± .051)	-0.294 (± .056)	4.54 (±. 70)	4.52 (± 1.4)
LM701	11011	-0.42 (± .037)	-0.284 (±.072)	4.83 (±. 70)	7.69 (± 1.8)

non-epistatic combination of single mutations:
(Das *et al.* (2020))

$$r_{\boldsymbol{\sigma}} = \prod_{i \in I^{+}[\boldsymbol{\sigma}]} r_i \, , m_{\boldsymbol{\sigma}} = \prod_{i \in I^{+}[\boldsymbol{\sigma}]} m_i$$

TIL Model – Ingredients

- L loci, $i = 1, 2, \ldots L$, $\boldsymbol{\sigma} = (\sigma_1, \sigma_2, \ldots, \sigma_L)$.
- $\sigma_i = 0, 1$ mutation is absent/present at i.

$$I^+[\boldsymbol{\sigma}] = \{i : \sigma_i = 1\}, \quad I^-[\boldsymbol{\sigma}] = \{i : \sigma_i = 0\}.$$

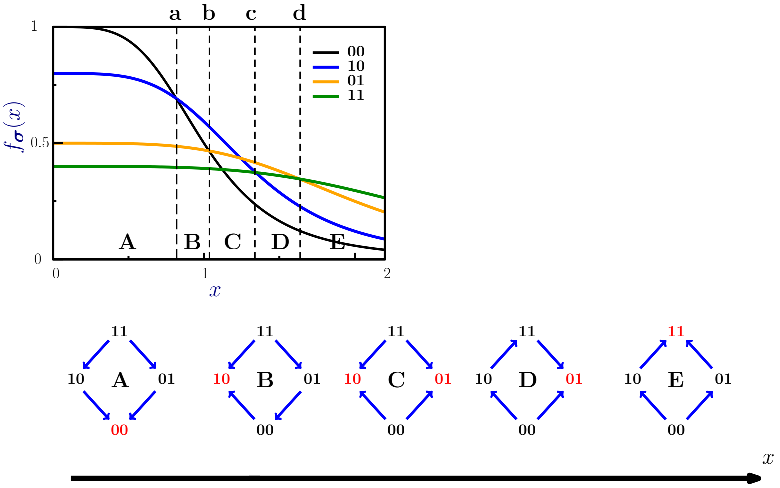
- r_i and m_i are the null-fitness and IC_{50} of a single mutation at locus i
- Adaptive trade-off: $r_i < 1$ **and** $m_i > 1$.
- **General $\boldsymbol{\sigma}$:** DR-curve given by

$$f_{\boldsymbol{\sigma}}(x) = \boldsymbol{r}_{\boldsymbol{\sigma}}\, w\left(\frac{x}{\boldsymbol{m}_{\boldsymbol{\sigma}}}\right), \quad \text{where} \quad \boldsymbol{r}_{\boldsymbol{\sigma}} = \prod_{i \in I^+[\boldsymbol{\sigma}]} r_i, \ \boldsymbol{m}_{\boldsymbol{\sigma}} = \prod_{i \in I^+[\boldsymbol{\sigma}]} m_i$$

- $w(x)$ continuous and decreasing, s.t. fitness curves of WT $\boldsymbol{\sigma} = 0$ and single point mutations $\boldsymbol{\sigma} = 0^{+i}$ intersect once:

$$w(x) = r_i w\left(\frac{x}{m_i}\right) \quad \Rightarrow \quad x = x_i.$$

TIL Model – $L = 2$ Example – Evolving Fitness Landscape



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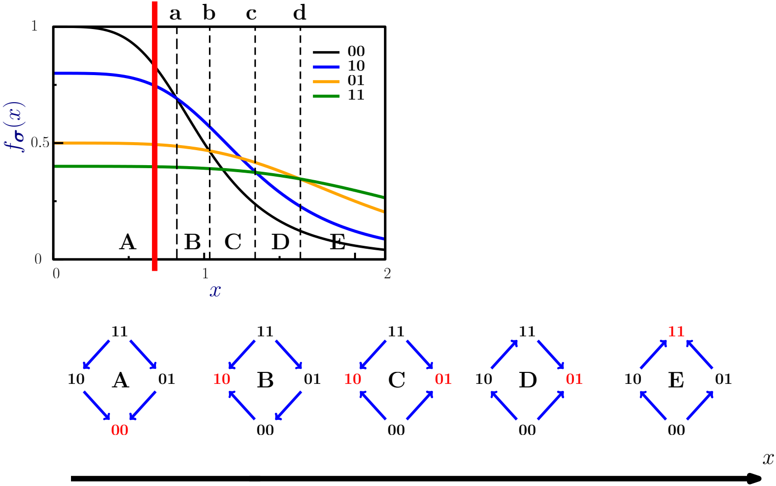

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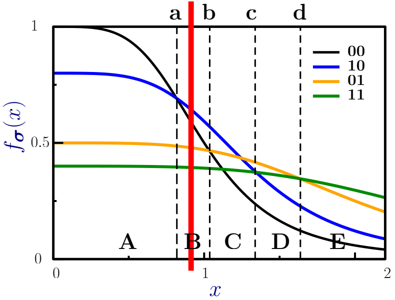

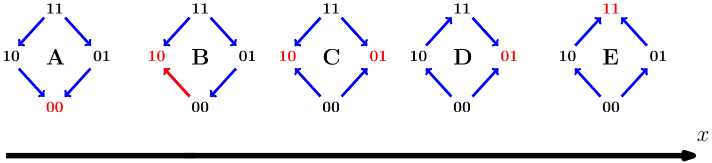

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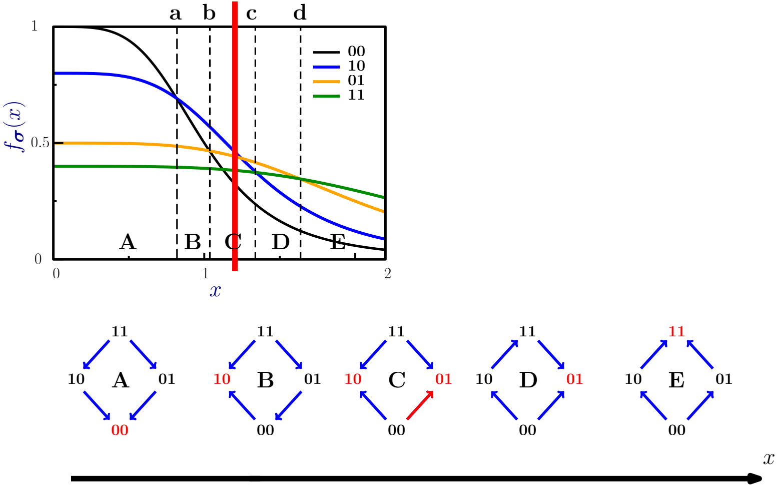

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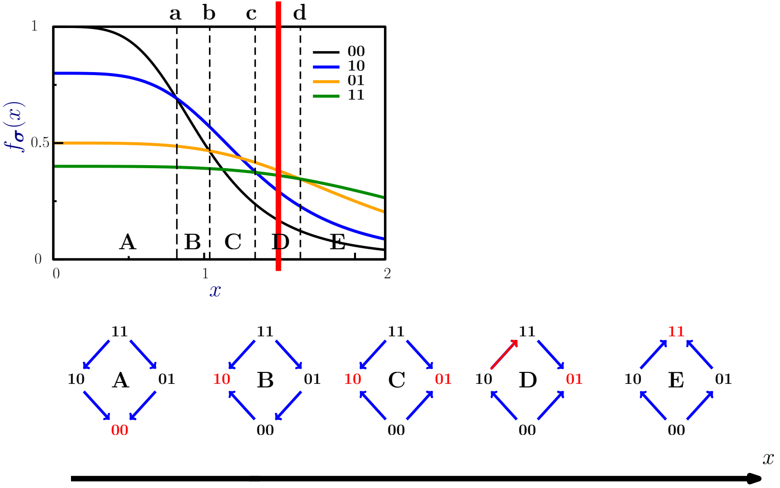

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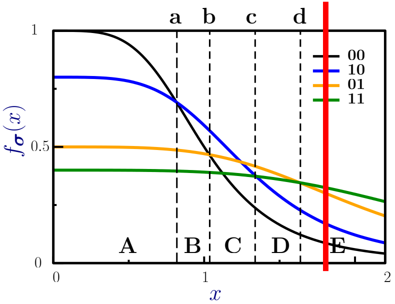

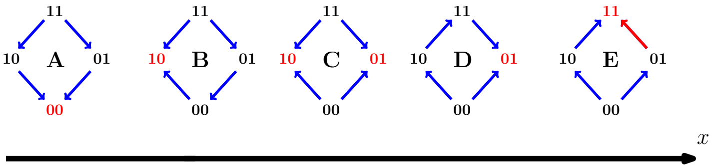

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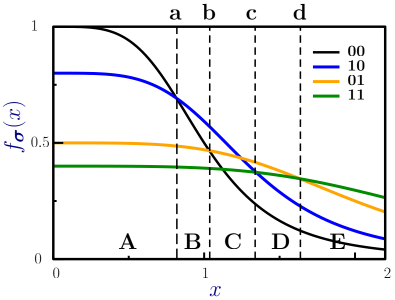

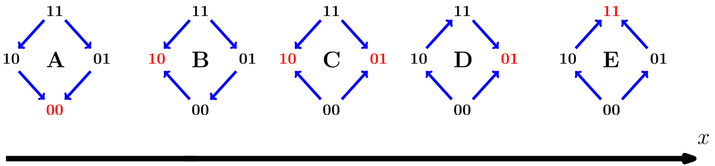

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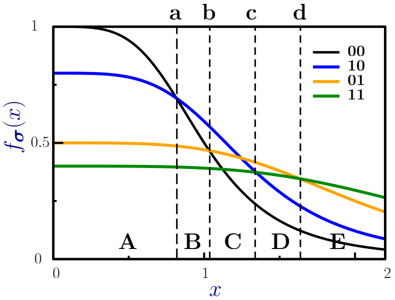

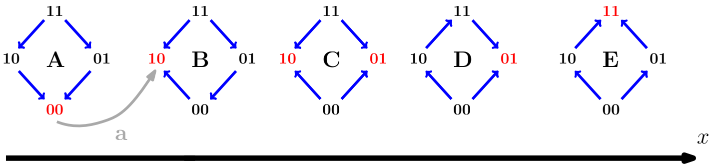

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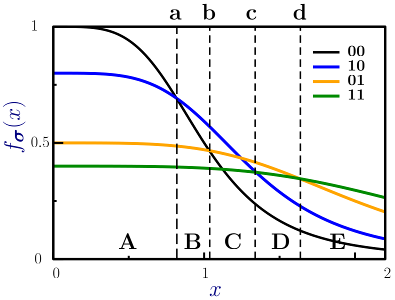

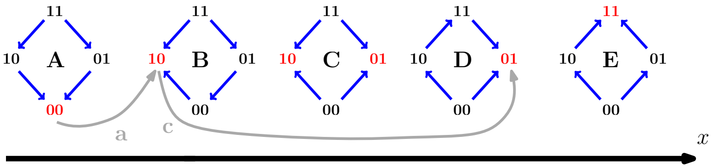

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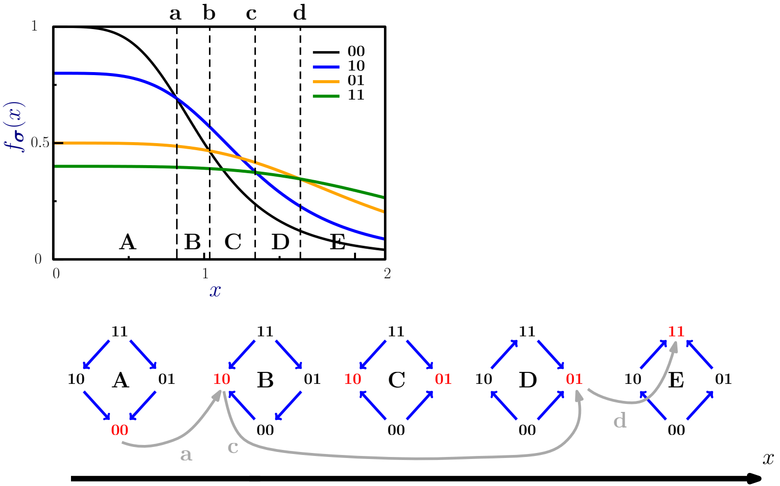

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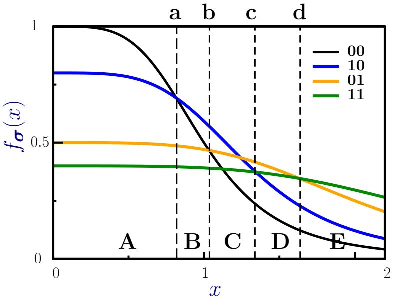

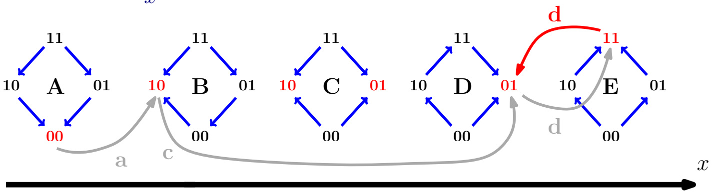

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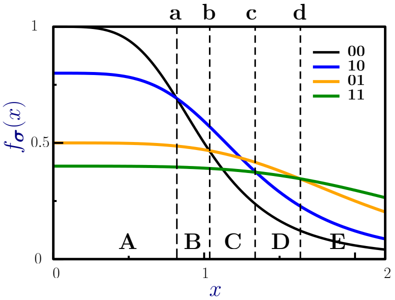

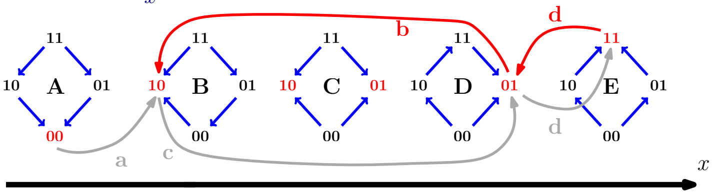

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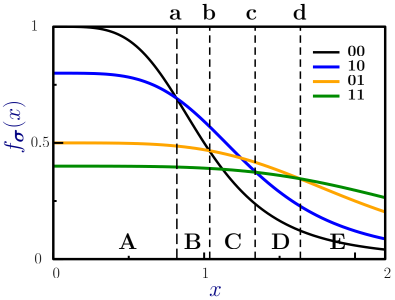

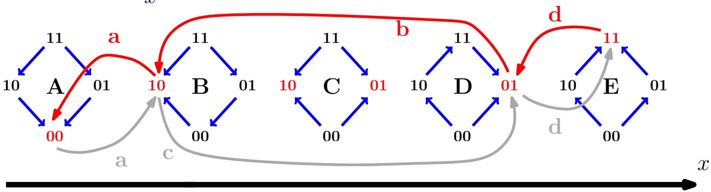

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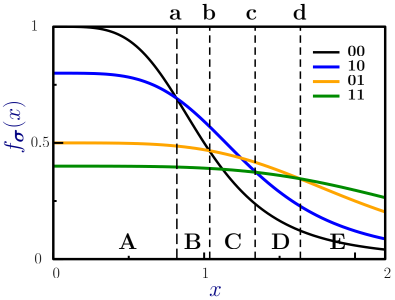

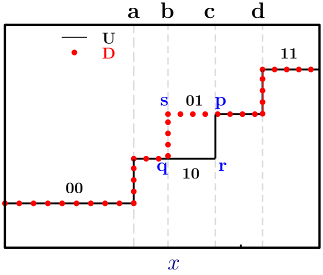

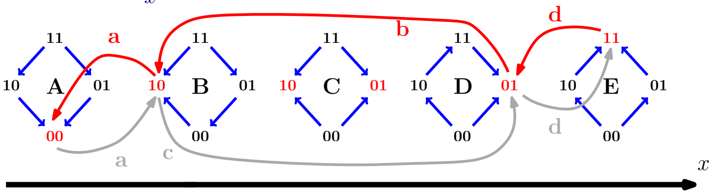

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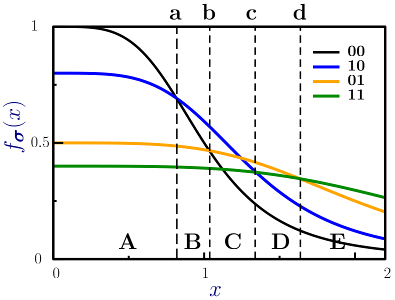

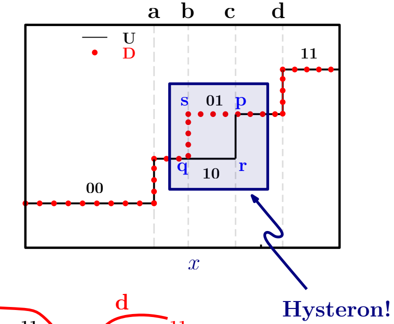

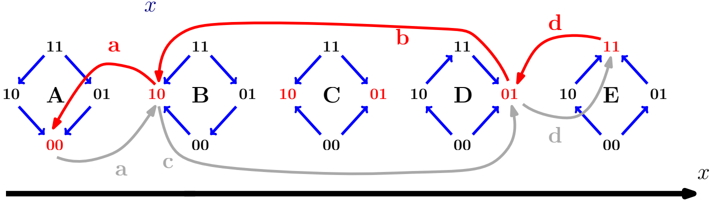

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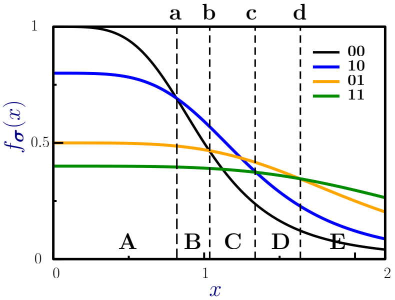

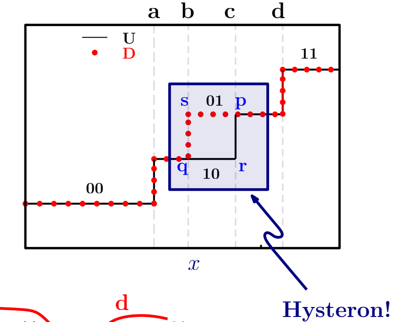

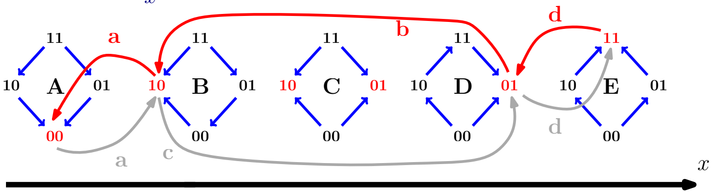

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TIL fitness maxima

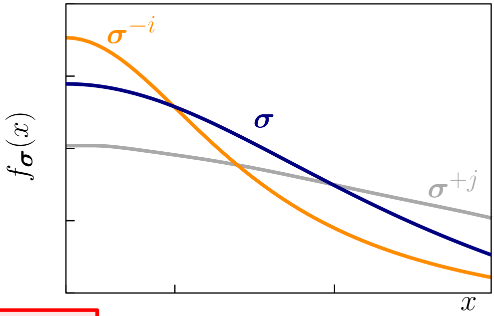
Single mutation loci of $\boldsymbol{\sigma}$:

$$I^- = \{j : \sigma_j = 0\} \Rightarrow \boldsymbol{\sigma} \to \boldsymbol{\sigma}^{+j}$$

mutation at locus j

$$I^+ = \{i : \sigma_i = 1\} \Rightarrow \boldsymbol{\sigma} \to \boldsymbol{\sigma}^{-i}$$

reversion of mutation at i



$\boldsymbol{\sigma}$ is a fitness maximum at x if:

$$f_{\boldsymbol{\sigma}^{+j}}(x) < f_{\boldsymbol{\sigma}}(x) \quad \text{for all } j \in I^-$$

$$f_{\boldsymbol{\sigma}^{-i}}(x) < f_{\boldsymbol{\sigma}}(x) \quad \text{for all } i \in I^+$$

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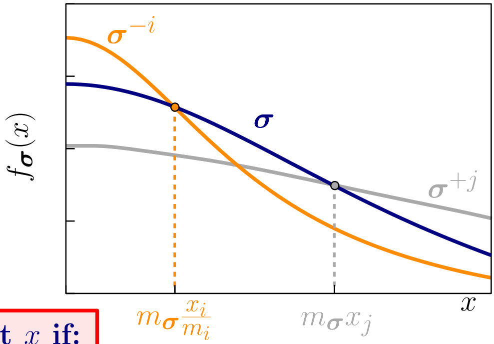

$\boldsymbol{\sigma}$ is a fitness maximum at x if:

$$x < \boldsymbol{m}_{\boldsymbol{\sigma}} x_j \quad \text{for all } j \in I^-$$

$$x > \boldsymbol{m}_{\boldsymbol{\sigma}} \frac{x_i}{m_i} \quad \text{for all } i \in I^+$$

requires $$\max_{i \in I^+} \frac{x_i}{m_i} < \min_{j \in I^-} x_j$$

TIL fitness maxima

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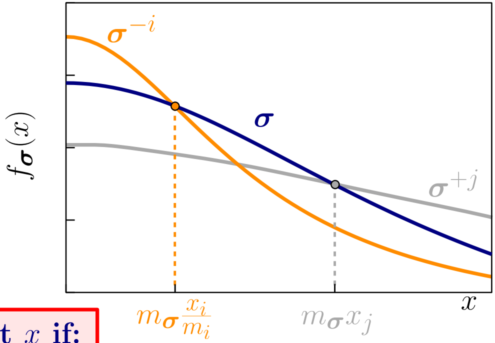

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$$x < \boldsymbol{m}_{\boldsymbol{\sigma}} x_j \quad \text{for all } j \in I^-$$

$$x > \boldsymbol{m}_{\boldsymbol{\sigma}} \frac{x_i}{m_i} \quad \text{for all } i \in I^+$$

requires $\max\limits_{i \in I^+} \frac{x_i}{m_i} < \min\limits_{j \in I^-} x_j$

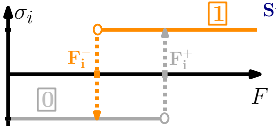
Like Preisach!

$F_i^- \leftrightarrow \frac{x_i}{m_i}$ **and** $F_i^+ \leftrightarrow x_i$

fitness range of $\boldsymbol{\sigma}$:

$$\boldsymbol{m}_{\boldsymbol{\sigma}} \frac{x_\ell}{m_\ell} < x < \boldsymbol{m}_{\boldsymbol{\sigma}} x_u$$

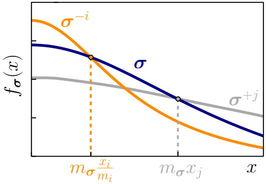
$$\boldsymbol{\sigma} = (\sigma_1, \sigma_2, \ldots, \sigma_L), \qquad \sigma_i = 0, 1$$



Switching fields:

$F_1^\pm, F_2^\pm, \ldots, F_L^\pm$

$F_i^- < F_i^+$



Switching concentrations of single mutations of wild-type:

$x_1, x_2, \ldots, x_L$

$\frac{x_1}{m_1}, \frac{x_2}{m_2}, \ldots, \frac{x_L}{m_L}$

$m_i > 1$

$\frac{x_i}{m_i} < x_i$

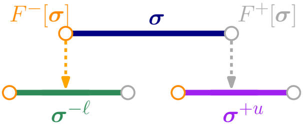
$\boldsymbol{\sigma}$ is POSSIBLE ONLY IF:

$$F^-[\boldsymbol{\sigma}] \equiv \max_{\{i:\sigma_i=1\}} F_i^- < \min_{\{j:\sigma_j=0\}} F_j^+ \equiv F^+[\boldsymbol{\sigma}]$$

$$x^-[\boldsymbol{\sigma}] \equiv m_{\boldsymbol{\sigma}} \max_{\{i:\sigma_i=1\}} \frac{x_i}{m_i} < m_{\boldsymbol{\sigma}} \min_{\{j:\sigma_j=0\}} x_j \equiv x^+[\boldsymbol{\sigma}]$$

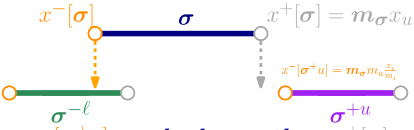
(determines the SAME set of states/fitness maxima)

Let ℓ and u be the sites were the max and min are attained



$\Rightarrow$ **Single site flips suffice**

NO AVALANCHES!

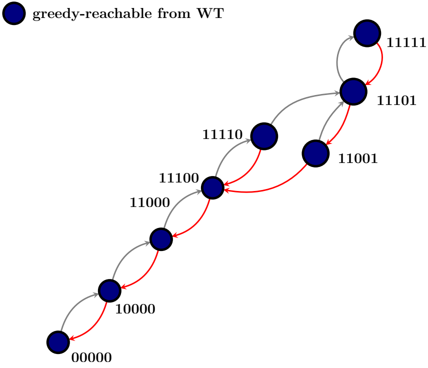


$x^-[\boldsymbol{\sigma}^+u]$ **can be larger than** $x^+[\boldsymbol{\sigma}]$

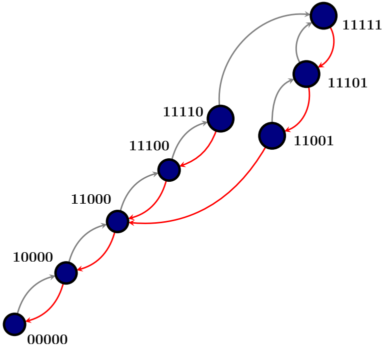
additional (complementary) mutations!

The Preisach – TIL equivalence

TIL Dynamics

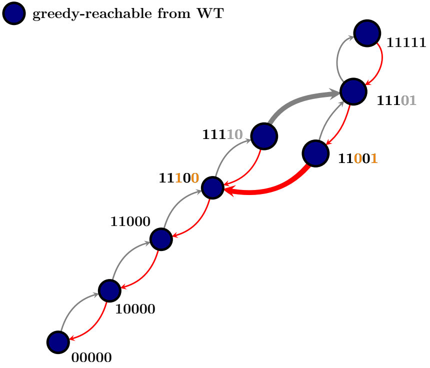


Preisach Dynamics

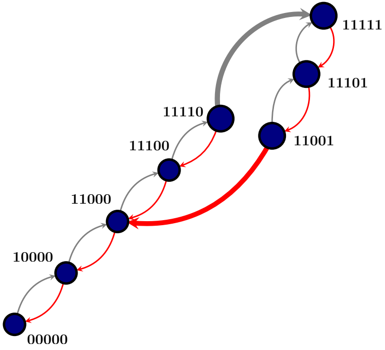


The Preisach – TIL equivalence

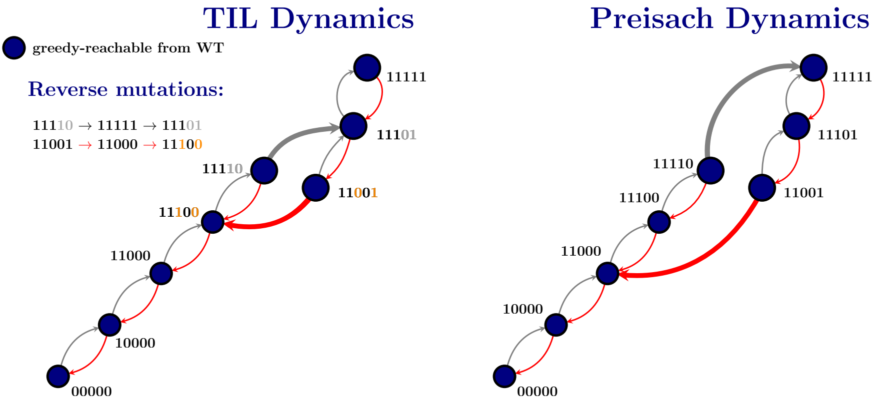
TIL Dynamics



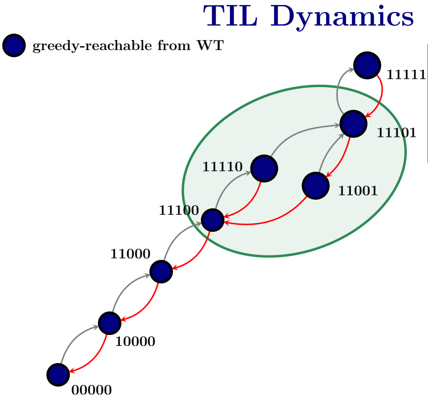
Preisach Dynamics



The Preisach – TIL equivalence



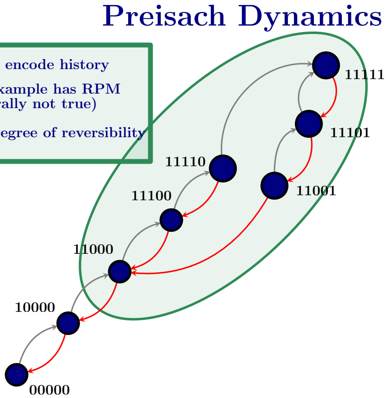
The Preisach – TIL equivalence



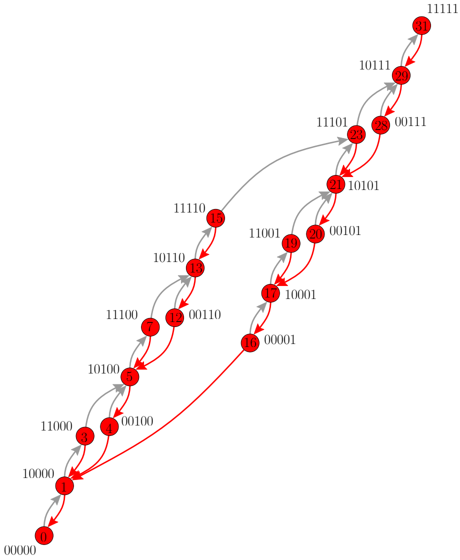
States encode history

TIL example has RPM (generally not true)

High degree of reversibility

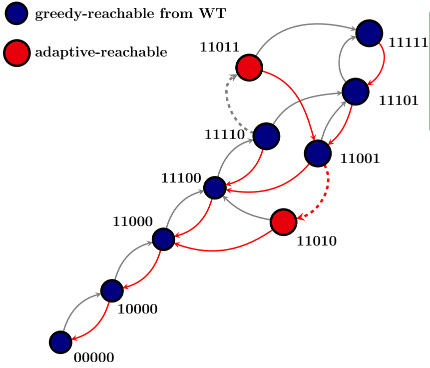


TIL nested cycles



The Preisach – TIL equivalence

TIL Dynamics

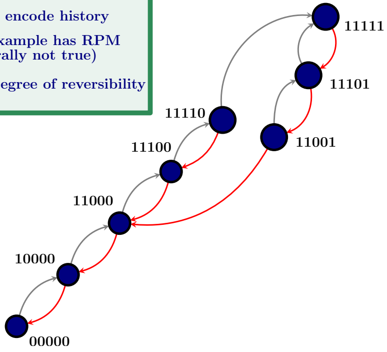


States encode history

TIL example has RPM (generally not true)

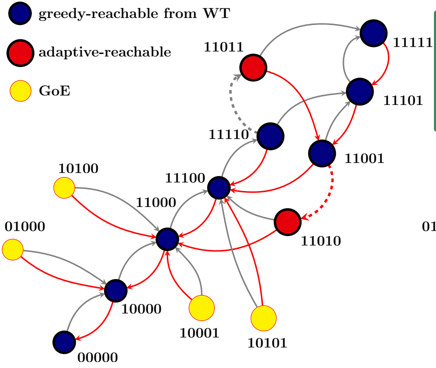
High degree of reversibility

Preisach Dynamics



The Preisach – TIL equivalence

TIL Dynamics

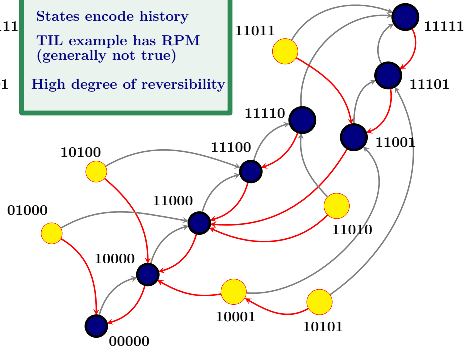


States encode history

TIL example has RPM
(generally not true)

High degree of reversibility

Preisach Dynamics



TIL Dynamics – Summary

- Introduced a simple **model of adaptive evolution** of drug resistance **in a changing environment.**
- Established a **connection with the Preisach model:**
- However, in general the **dynamics is different:**
  - Cascades of mutations in the TIL model vs. single site changes in Preisach dynamics
  - In the biological setting one can have adaptive pathways that are biologically meaningful but not necessarily greedy.
- **Nevertheless:**
  - TIL dynamics has **history dependence**,
  - **Genotypes encode information on past environmental changes.**

What's next?

- **Connection with experiments:** Search of hysteresis, reversibility and memory in the adaptive evolution of bacterial populations
- **Explicitly add epistatic interactions:** e.g. relax the assumptions that single site mutations act independently in combination.
- **More complicated environments:** e.g. multiple drugs, incorporating explicit time dependence.
- **Beyond greedy adaptive walks:** characterize the **evolution of fitness landscapes**, i.e. how the full landscape evolves under concentration changes, how its "shape" changes.

THANK YOU!