Rational Design of Antibiotic Treatment Plans

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Joint paper with Portia Mira, Kristina Crona,
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Our Abstract

"The development of reliable methods for restoring susceptibility after antibiotic resistance arises has proven elusive. A greater understanding of the relationship between antibiotic administration and the evolution of resistance is key to overcoming this challenge.

Here we present a data-driven mathematical approach for developing antibiotic treatment plans that can reverse the evolution of antibiotic resistance determinants.

We have generated adaptive landscapes for 16 genotypes of the TEM β-lactamase that vary from the wild type genotype TEM-1 through all combinations of four amino acid substitutions . . . . . .

. . . . . .

Overall this study shows that there is promise for **reversing the evolution of resistance through antibiotic treatment plans**."

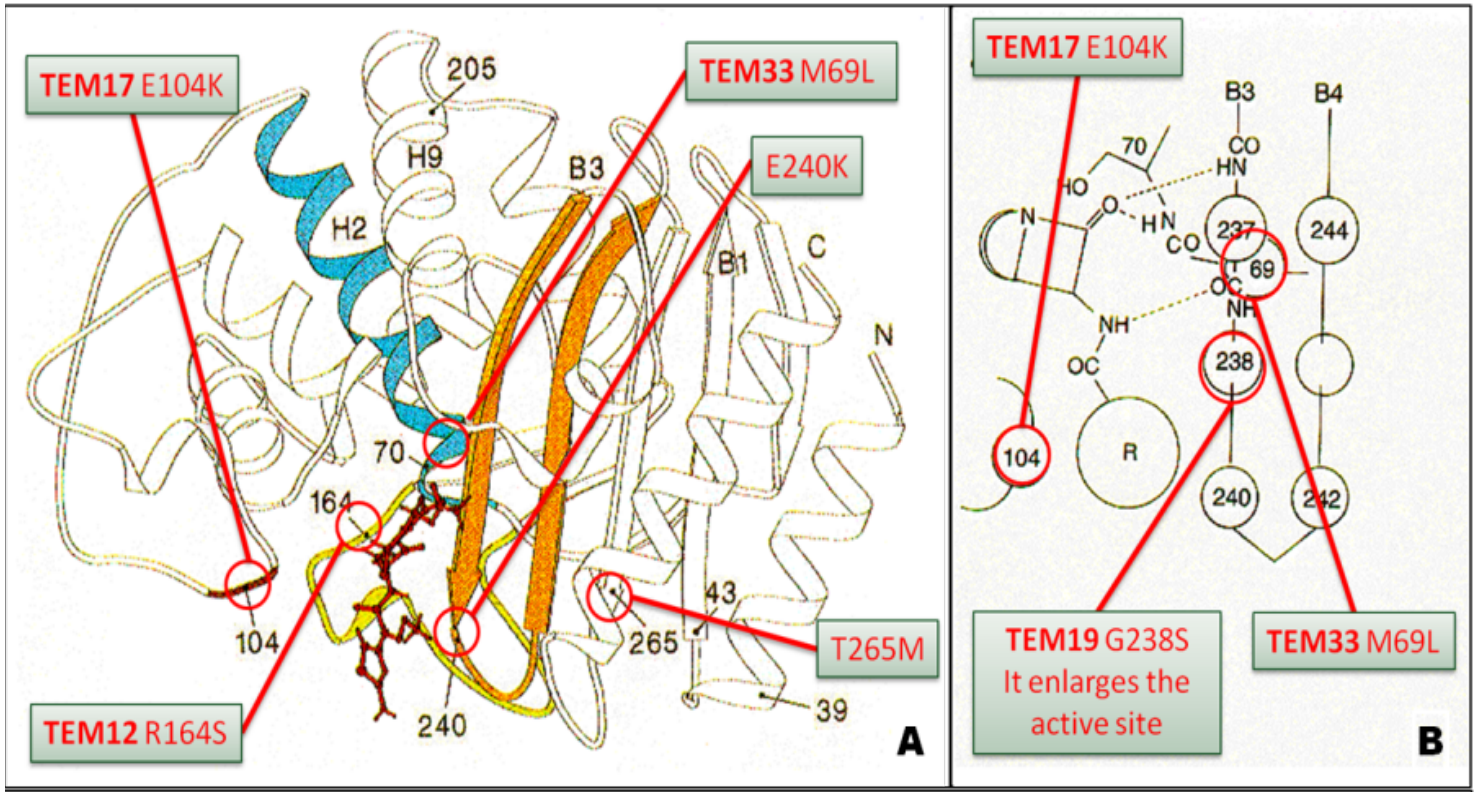
Time Machine

Think of reversing the evolution as traveling back in time.

Chemistry

Our time traveler is the resistance gene TEM β-lactamase.

Identified by Naomi Datta in 1963; named after patient Temoneira.



Wiki: Beta-lactamases are enzymes produced by some bacteria that provide resistance to ... antibiotics like penicillins, cephamycins, ...

Beta-lactamase provides antibiotic resistance by breaking the antibiotics' structure. These antibiotics all have a common element in their molecular structure: a four-atom ring known as a β-lactam ...

Evolution Observed

Of 190 clinically identified TEM genotypes, 174 differ from the wild type TEM-1 by at most four amino acid substitutions:

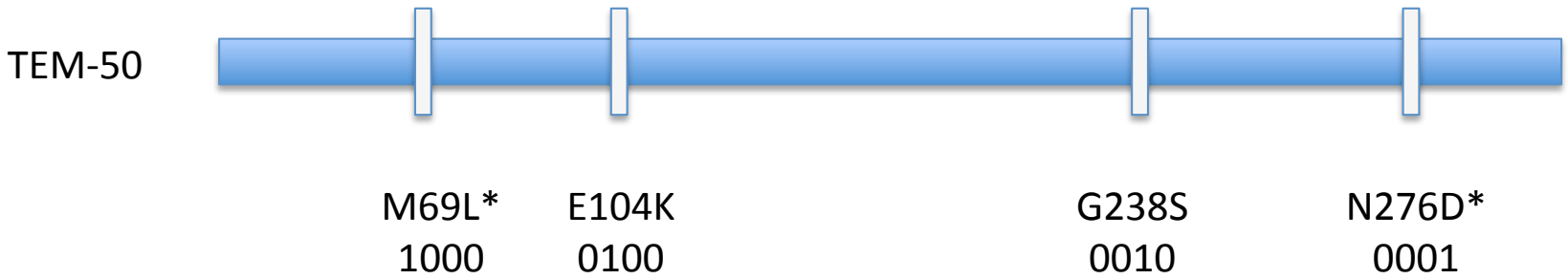
Number of amino acid substitutions	Number of TEM enzymes
1	53
2	53
3	37
4	31
5	10
6	2
7	2
8	0
9	0
10	1
11	1

The Barlow lab studies a system with four amino acid substitutions.

TEM-50 system

The TEM-50 genotyope is highly evolved.

It differs from the TEM-1 in four amino acid substitutions:



Experiments: The Barlow lab

- created all 16 genotypes between TEM-1 and TEM-50
- measured the growth rates of 12 replicates of E.coli DH5α-E
- repeated in the presence of each of 15 β-lactam antibiotics

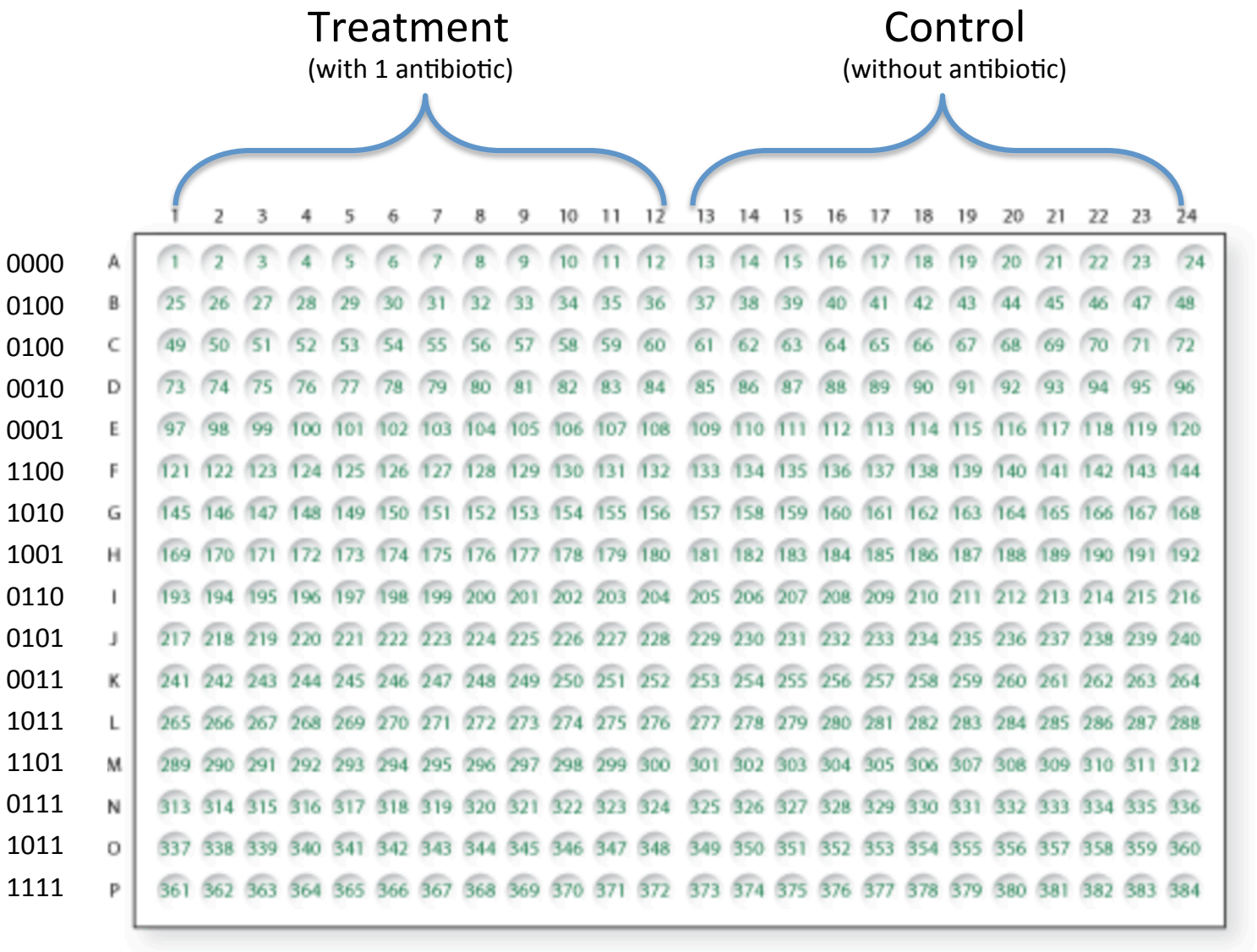
  AMP, AM, CEC, CTX, ZOX, CXM, CRO, AMC, CAZ, CTT, SAM, CPR, CPD, TZP, FEP

The 4-dimensional cube

Mutant	Isolated	Binary Allele Code
Wild Type	TEM-1	0000
M69L	TEM-33	1000
E104K	TEM-17	0100
G238S	TEM-19	0010
N276D	TEM-84	0001
M69L/E104K	-	1100
M69L/G238S	-	1010
M69L/N276D	TEM-35	1001
G238S/E104K	TEM-15	0110
G238S/N276D	-	0011
N276D/E104K	-	0101
M69L/E104K/ N276D	-	1101
M69L/E104K/ G238S	-	1110
G238S/N276D/ E104K	-	0111
G238S/N276D/ M69L	-	1011
TEM-50	TEM-50	1111

The data

Measure the fitness of each of the 16 genotypes



... in the presence of each of 15 antibiotics.

Fitness landscapes

For each of the 15 **antibiotics** AMP, AM, CEC, CTX, ZOX, CXM, CRO, AMC, CAZ, CTT, SAM, CPR, CPD, TZP, FEP we have a

$$2\times2\times2\times2\text{-table } \mathbf{f} = (f_{ijkl}) \text{ with entries in } \mathbb{R}$$

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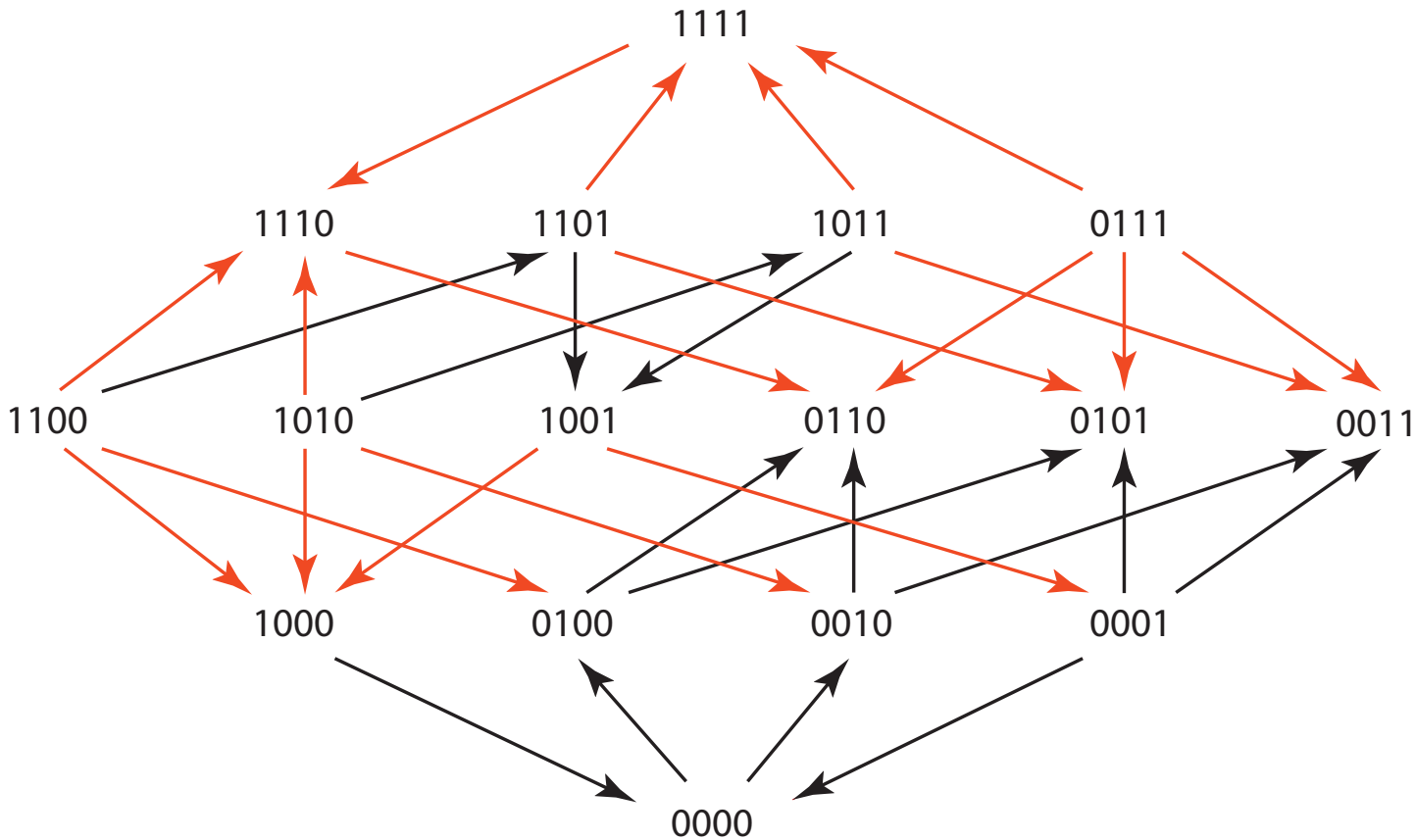
We care about the dynamics on such fitness landscapes:



Population genetics

A *substitution model* is a function

$$M : \mathbb{R}^{16} \longrightarrow \mathbb{R}^{16\times 16}$$

that assigns to each fitness landscape $\mathbf{f}$ a transition matrix $M(\mathbf{f})$.

We use two simple models:

- The Equal Probability Model (EPM)

  $$M_{uv} = 1/k$$

  if $u \to v$ and genotype u has k outgoing arrows.

- The Correlated Probability Model (CPM)

  $$M_{uv} = \frac{f_v - f_u}{\sum_w (f_w - f_u)}$$

  if $u \to v$ and the sum is over all genotypes w with $u \to w$.

Data yield matrices $M^{XPM}(\mathbf{f}_\star)$ of format 16×16, where $X = E, C$ and $\star =$ AMP, AM, CEC, CTX, ZOX, CXM, CRO, AMC, CAZ, CTT, SAM, CPR, CPD, TZP, FEP

Matrix algebra

Fix EPM or CPM, and consider the matrix product

$$M(\mathbf{f}_{a_1}) \cdot M(\mathbf{f}_{a_2}) \cdot M(\mathbf{f}_{a_3}) \ \cdots \ M(\mathbf{f}_{a_k})$$

where $a_1, a_2, a_3, \ldots, a_k$ is any sequence of antibiotics.

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There are 15^k *such sequences!*

Which ones should the doctors try?

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Fix two genotypes $u, v \in \{0,1\}^4$.

The entry of this matrix in row u and column v is the fixation probability of genotype u mutating to genotype v.

Combinatorial optimization

Let $v =$ TEM-1 and u any other genotype.

Time Machine Problem: Maximize the (u, v) entry of the matrix

$$M(\mathbf{f}_{a_1}) \cdot M(\mathbf{f}_{a_2}) \cdot M(\mathbf{f}_{a_3}) \cdots M(\mathbf{f}_{a_k})$$

over all 15^k antibiotic sequences of length k.

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Idea: Travel back in time to 1963

Just do it

Time Machine Problem: Given 15 transition matrices of format 16×16, consider all products of length k, and maximize a particular entry in the first row.

We implemented a brute-force approach for $k = 2, \ldots, 6$ in `maple`, and we computed optimal solutions for both substitution models.

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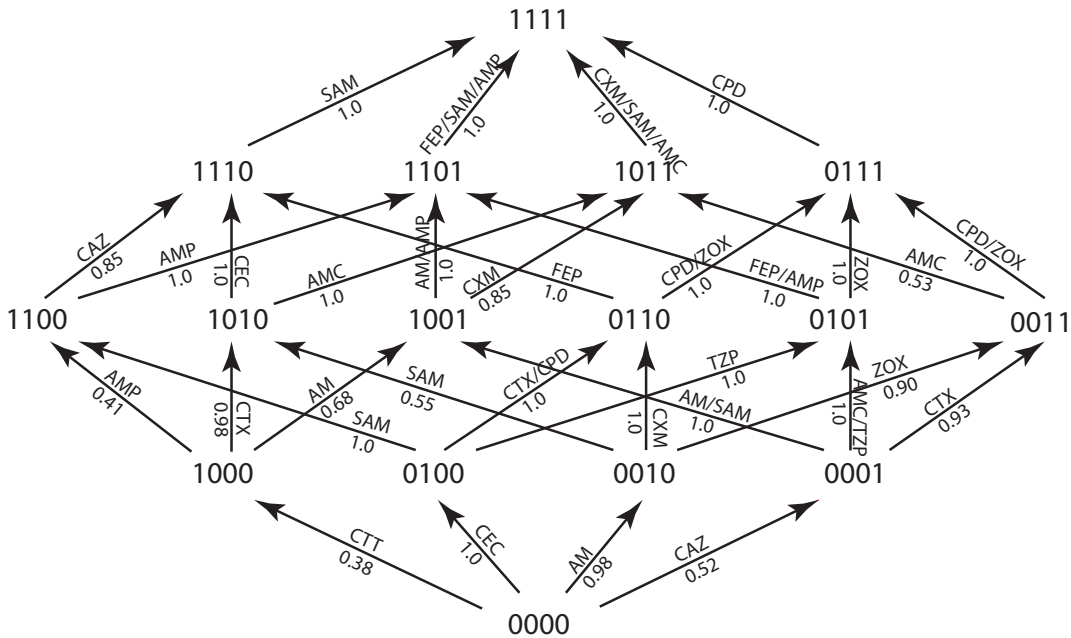
Results:

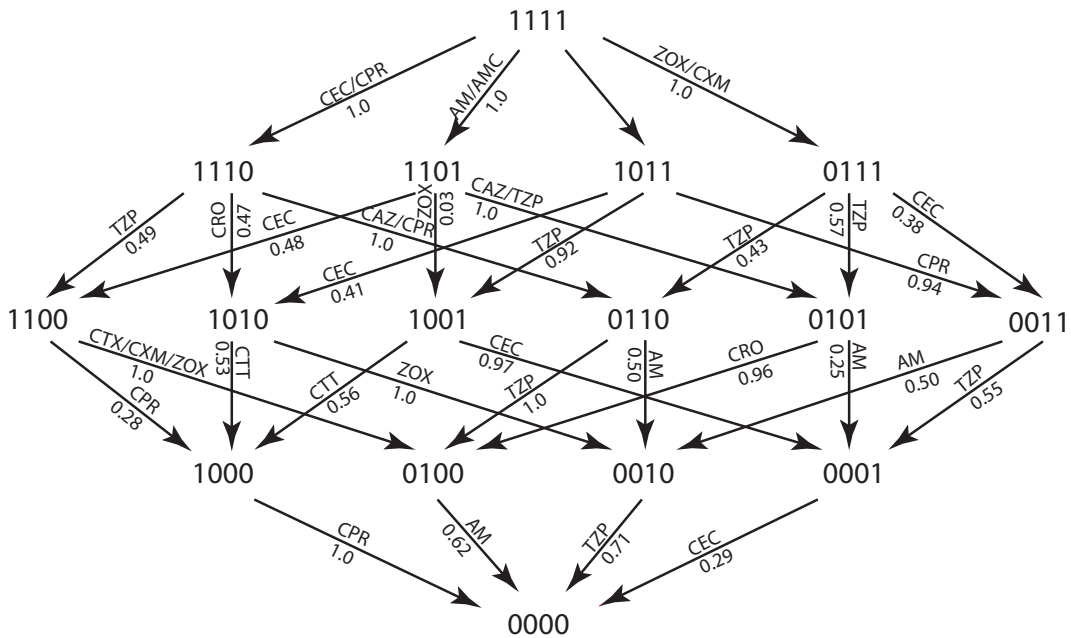
Starting Genotype	1 Step	#	2 Step	#	3 Step	#	4 Step	#	5 Step	#
1000	1.0	1	1.0	3	1.0	7	1.0	15	1.0	31
0100	0.617	1	0.617	6	0.617	36	0.617	219	0.617	1360
0010	0.714	1	0.714	2	0.714	3	0.714	4	0.714	5
0001	0.287	1	0.287	1	0.592	2	0.592	18	0.726	2
1100			0.617	3	0.617	18	0.617	108	0.617	657
1010			0.715	1	0.715	6	0.715	27	0.715	112
1001			0.559	1	0.559	4	0.726	1	0.726	2
0110			0.617	1	0.617	10	0.617	78	0.617	555
0101			0.592	1	0.592	9	0.612	1	0.612	9
0011			0.361	1	0.361	9	0.586	1	0.599	2
1110			-		0.617	2	0.617	24	0.617	215
1101			-		0.592	2	0.592	24	0.617	12
1011			-		0.532	1	0.532	1	0.684	1
0111			-		0.586	1	0.600	1	0.617	4
1111			-		-		0.617	4	0.617	72

Biomedical interpretation

Since 1963:



Back to wild type:



Press Coverage

examiner.com

NEWS / SCIENCE & SPACE

See also: science & space, antibiotic resistant bacteria

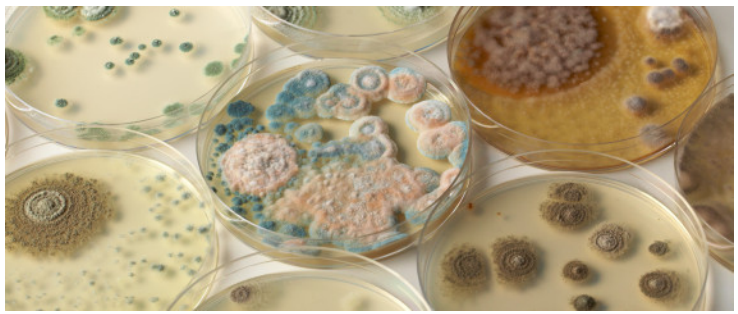
Researchers find a way to reverse antibiotic resistance in bacteria

May 6, 2015

Scientists May Have Just Found A Solution For Deadly Superbugs

The Huffington Post | By Anna Almendrala (/anna-almendrala/) (/usehttp://twitter.com/annaalmendrala)

Posted: 05/07/2015 5:06 pm EDT | Updated: 05/07/2015 6:59 pm EDT



THE SCOTSMAN

SCOTLAND on SUNDAY

Drug-resistant superbugs beaten by 'time machine'

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Biology leads to New Mathematics

Time Machine Problem: Given square matrices $M_1, \ldots, M_n$, maximize a particular matrix entry over all n^ℓ words $M_{i_1} M_{i_2} \cdots M_{i_\ell}$ of length ℓ in these matrices.

What is the computational complexity of this problem ?
Does there exists an efficient dynamic programming approach?

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The answer is **no**. It can be reduced to k-SAT.

Theorem (Ngoc Tran & Jed Yang, `arXiv`: May 11, 2015)
"Antibiotics Time Machine Problem is NP-hard".

Tran and Yang also show that a certain natural convex relaxation can be solved in polynomial time.

Biology leads to New Mathematics[1]

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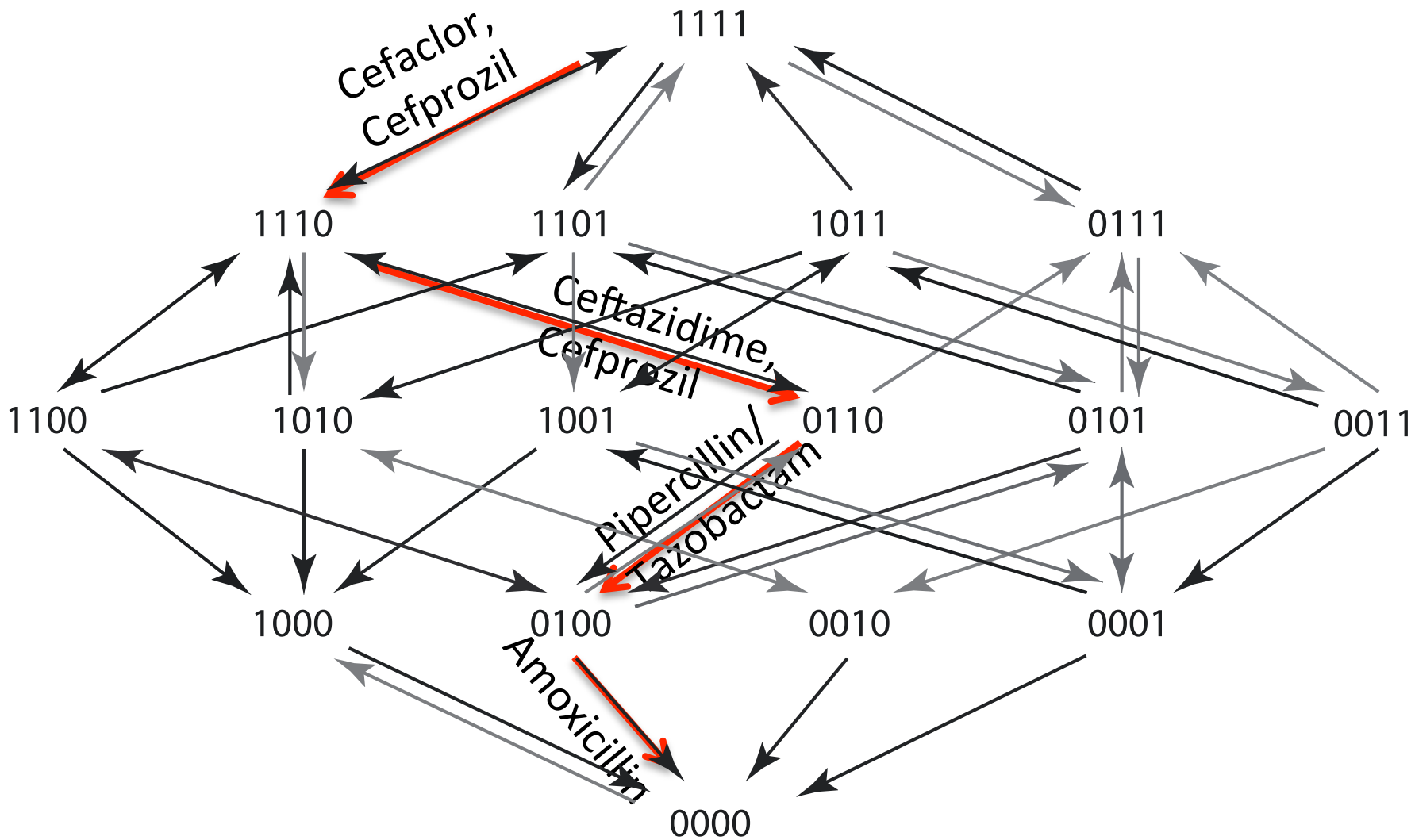
[1] Is Theoretical Computer Science Part of Mathematics?

Conclusion: Optimal Treatment Plans Can Be Designed



.... by solving the Time Machine Problem

Press Coverage

Computer Scientists May Have Just Found A Solution For Deadly Superbugs

May 7, 2015

Diário da SAÚDE

15/05/2015

Resistência de bactérias aos antibióticos é revertida

Redação do Diário da Saúde

Evolução às avessas

A proliferação das bactérias resistentes aos antibióticos é um problema crescente em nível mundial.

A boa notícia é que esse problema talvez seja reversível.

Miriam Barlow (Universidade da Califórnia) e Kristina Crona (Universidade Americana) descobriram uma maneira de fazer com que as bactérias retornem a um estado pré-resistente.

As duas pequisadoras demonstraram essa "evolução às avessas" usando uma família de 15 antibióticos disponíveis para combater infecções comuns, incluindo a penicilina.

Ciclagem de antibióticos

Para anular o processo r a aos antibióticos, as pesquisadoras as expus Com esses dados, elas calcularam a probabilida de ao medicamento.

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May 6, 2015

Reverse Resistance by Rewinding Evolution

Antibiotic drug-resistance continues to be one of the toughest global issues that clinicians face today.