Is Antibiotic Rotation Optimal?

A mathematical approach to a medic's question.

Robert Beardmore, Dept of Maths
Imperial College, London

One idea

- October 1997, Michael Niederman's editorial...
- "The 'crop rotation' theory of antibiotic use has suggested that if we routinely vary our 'go to' antibiotic in the ICU, we can minimize the emergence of resistance ...
- selection pressure for bacteria to develop resistance to a specific antibiotic would be reduced as organisms become exposed to continually varying antimicrobials."

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Is "Crop Rotation" of Antibiotics the Solution to a "Resistant" Problem in the ICU?

Am J Respir Crit Care Med Vol. 156. pp. 1029–1031, 1997

And rotation is...?

2005, JAC, Brown & Nathwani

- "We identified 11 articles in which the authors claimed to have evaluated the efficacy of this intervention."
- "Only four were suitable for review, but, owing to multiple methodological flaws and a lack of standardization, these studies do not permit reliable conclusions ..."

Journal of Antimicrobial Chemotherapy (2005) **55**, 6–9
doi:10.1093/jac/dkh482
Advance Access publication 5 November 2004

JAC

Antibiotic cycling or rotation: a systematic review of the evidence of efficacy

A theoretical study

- October 1997, PNAS, Bonhoeffer, Lipschitz & Levin
- "When more than one antibiotic is employed, sequential use of different antibiotics in the population ('cycling') is always inferior to treatment strategies where, at any given time, equal fractions of the population receive different antibiotics."

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 12106–12111, October 1997
Medical Sciences

Evaluating treatment protocols to prevent antibiotic resistance

SEBASTIAN BONHOEFFER†‡§, MARC LIPSITCH‡, AND BRUCE R. LEVIN‡

Models

- We want to understand the 'best' way of scheduling the deployment of antibiotics into some unit of treatment (hospital, ICU, [patient])
- We need a state-space for this model, what to put in it? Apologies, Pentti, for the abstraction, but let's not worry for now.

Journal of Antimicrobial Chemotherapy (2005) **56**, 257–258
doi:10.1093/jac/dki230
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JAC

Mathematical model—tell us the future!

Pentti Huovinen*

Therefore the first comment on Magee's model concerns a lack of accurate data on antimicrobial consumption. I miss most a definition of the bacterial species that this theory concerns. Readers want to see how the model applies to the real world. It is reasonable to assume that different bacteria will behave differently. The epidemiology of *Streptococcus pneumoniae* is different from that of *Escherichia coli* or *Staphylococcus aureus*. Most of us have *E. coli*

2-drug models

One of many model structures, formulate the question as a control affine, optimal control problem:

$$\dot{x} = f(x) + A(t) \cdot \mathcal{A}x + B(t) \cdot \mathcal{B}x$$

Let A(t) be the % of A-treated patients, same for B(t), everyone is treated: A(t)+B(t) = 100%.

$x=(x_1,x_2,\ldots)$ will contain everything we think might be important, keep this abstract for now.

x contains everything we think important:

- # susceptible & infected hosts in hospital & community
- # infected or colonised by WT bacterium or SDR/MDR mutants
- # treated for infection i with drug j (some appropriate, some not)
- # treated with multi-drug combinations with drug pair (j,k)?
- drug-specific resistance mechanisms: de novo mutation or plasmid-borne?
- parameters: causes of pathogen transmission, clearance rates due to treatment, disease-induced death rates, duration of empirical treatment, pathogen mutation rates .....
- explicit spatial description or use a mass action law?

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- ~~explicit spatial description~~ or use a mass action law?

2-drug models

$$\begin{aligned}\dot{x} &= f(x) + A(t) \cdot \mathcal{A}x + (1 - A(t)) \cdot \mathcal{B}x, \\ &= f(x) + \mathcal{B}x + A(t) \cdot (\mathcal{A} - \mathcal{B})x,\end{aligned}$$

- Under the must-treat constraint, there's only one control variable: A(t).
- We now minimise 'something' wrt A(t):

$$\min \left\{ \frac{1}{T} \int_0^T (\varphi, x(t)) dt : 0 \leq A \leq 1 \right\}$$

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observable: continuous linear functional

2-drug models

optimal control problem

$$\begin{cases} \dot{x} = f(x) + \mathcal{B}x + A(t) \cdot (\mathcal{A} - \mathcal{B})x, \\ \min \left\{ \dfrac{1}{T} \displaystyle\int_0^T (\varphi, x(t)) dt : 0 \leq A \leq 1 \right\} \end{cases}$$

- symmetries lead to A-independence
- rotation: A(t) = 0 or 1: everyone is treated with the same drug at the same time
- mixing: A(t) = constant between 0 and 1: at least two patients receive different treatment for same infection

Can mixing be optimal?

- mixing strategies are used in practise & trials have implemented `maximal drug heterogeneity' policies
- random mixing (A = 1/2) has been stated as optimal when compared with strictly periodic rotation
- let's relax the assumption of strict periodicity:

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JAC

Antibiotic cycling or rotation: a systematic review of the evidence of efficacy

Erwin M. Brown[1]* and Dilip Nathwani[2]

(xi) Is the order of rotation critical?

(xii) What is the optimal duration of each cycle? If cycles are too short, changes in resistance rates may not be detected. For example, in the study carried out by Bradley *et al.*,[11] the reduction in the incidence of colonization with GRE was most marked in the latter half of the second phase of the cycling protocol. On the other hand, too long a duration may be associated with high risks of resistant strains emerging during the cycle.

(xiii) Should the duration of each cycle be the same? (Does resistance to different antibiotics develop at the same rate?)

Can mixing be optimal?

- As bang-bang (on-off) functions are weak* dense in the interval [0,1] within $L^\infty(0,T)$ and $\Phi(x(\cdot))$ is continuous wrt weak* topology, there are infimising sequences that rotate antibiotics.

The (smooth) equation

$$\dot{x} = f(x) + \mathcal{B}x + A(t) \cdot (\mathcal{A} - \mathcal{B})x, \qquad x(0) = x_0,$$

defines an operator $x : L^\infty \to W^{1,\infty}; A \mapsto x(A)$

The functional we want to minimise, then, is

$$L^\infty \to \mathbb{R}; A \mapsto \Phi(x(A))$$

where $\Phi(x) = \frac{1}{T} \int_0^T (\varphi, x(A)(t))dt$

Can mixing be optimal?

- As bang-bang (on-off) functions are weak* dense in the interval [0,1] within $L^\infty(0,T)$ and $\Phi(x(\cdot))$ is continuous wrt weak* topology, there are infimising sequences that rotate antibiotics.

a surprising consequence ? ...

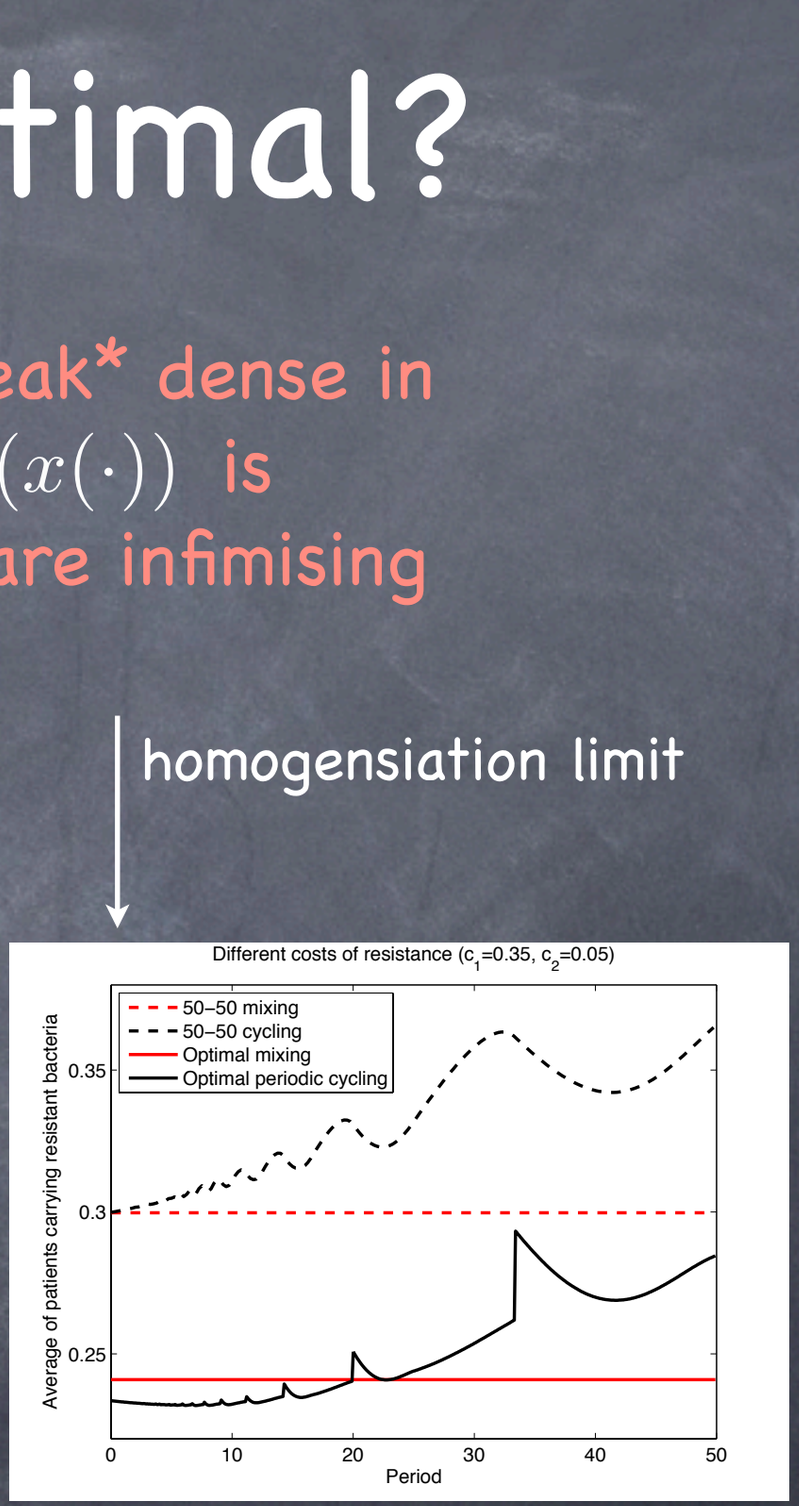
Theorem If Φ is the continuous linear functional that denotes the performance measure, then

$$\inf_{A\in\{\text{periodic cyclings}\}} \Phi(x(A)) \leq \inf_{A\in\{\text{mixings}\}} \Phi(x(A))$$

Proof. The weak* closure of the set of periodic, bang-bang functions contains all the constant functions. □

note the inf, it's not a min

homogensiation limit



Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals

Carl T. Bergstrom*†, Monique Lo‡, and Marc Lipsitch‡

*Department of Biology, University of Washington, Seattle, WA 98195; and ‡Harvard School of Public Health, Boston, MA 02115

Can mixing be optimal?

$$\begin{aligned}
\dot{x} &= f(x) + \mathcal{B}x + \omega \cdot (\mathcal{A} - \mathcal{B})x, \\
-\dot{\mu} &= \varphi + \nabla f(x)^T \mu + \mathcal{B}^T \mu + \omega \cdot (\mathcal{A}^T - \mathcal{B}^T)\mu, \\
& \qquad x(0) = x_0, \mu(T) = 0
\end{aligned}$$

- the EL equations could have a totally singular mixing control, ϖ, but under what conditions?
- there are trivial symmetries, any others?

Can mixing be optimal?

- define the Hamiltonian

$$H(x, \mu, A) = (x, \varphi) + (\mu, f(x) + \mathcal{B}x) + A(\mu, (\mathcal{A} - \mathcal{B})x)$$

Pontryagin's Maximum Principle states that

$$H(x^*, \mu^*, A^*) = \max_{0 \le A \le 1} H(x^*, \mu^*, A)$$

and so $A^*(t) = 1$ or $A^*(t) = 0$ unless

$$(\mu, (\mathcal{A} - \mathcal{B})x) \equiv 0 \qquad \text{& so} \qquad (\varphi, (\mathcal{A} - \mathcal{B})x(0)) = 0$$

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DAEs P-IC symmetries

Can mixing be optimal?

- Let's apply these symmetries to a model taken from Bergstrom, Lo, Lipschitz; PNAS 2004:

$$
\begin{aligned}
\dot{S} &= \mu(m - S) - (\tau_1 + \tau_2 + \gamma)S + \beta SX + \sigma\beta(c_1 R_1 + c_2 R_2)S, \\
\dot{R}_1 &= \mu(m_1 - R_1) - (\tau_2 + \gamma)R_1 + \beta(1 - c_1)R_1 X - \sigma\beta(c_1 S + (c_1 - c_2)R_2)R_1, \\
\dot{R}_2 &= \mu(m_2 - R_2) - (\tau_1 + \gamma)R_2 + \beta(1 - c_2)R_2 X - \sigma\beta(c_2 S + (c_2 - c_1)R_1)R_2, \\
\dot{X} &= \mu(1 - m - m_1 - m_2 - X) + (\tau_1 + \tau_2 + \gamma)S + (\tau_2 + \gamma)R_1 + (\tau_1 + \gamma)R_2 - \ldots \\
&\quad \ldots - \beta X(S + (1 - c_1)R_1 + (1 - c_2)R_2),
\end{aligned}
$$

Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals

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X uncolonised, R_1 and R_2 are infected by drug 1 and drug 2 resistant bacteria, S by drug-susceptible bacteria.

Table 1: description of model parameters

parameter	meaning
τ_1, τ_2	rate of use of drugs 1 and 2 per unit time (days)
m, m_1, m_2	patients enter hospital in states S, R_1 and R_2 at rates $\mu m, \mu m_1$ and μm_2 resp.
c_1, c_2	fitness cost of resistance to bacteria
σ	relative rate of secondary colonization to primary colonization
β	rate constant for colonization of uncolonized individuals
γ	untreated patients colonized by susceptible bacteria remain colonized $1/\gamma$ days on average
μ	rate of patient turnover in the hospital
α	represents physician compliance with cycling program

The must-treat constraint means $\tau_1 + \tau_2 = \tau_{\max}$

and we want to minimise $\int_0^T R_1(t) + R_2(t) dt$

Mixing is at least codimension-3

Theorem

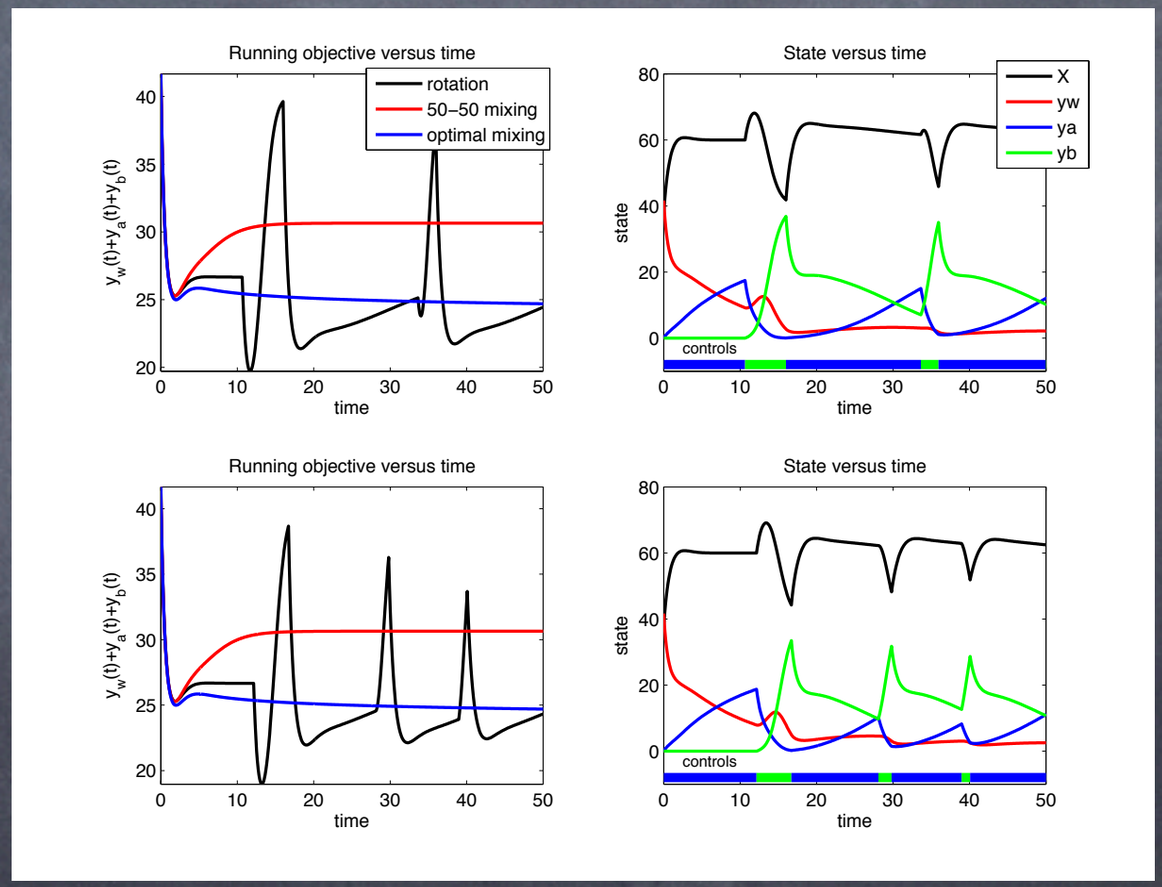
Suppose that parameters and initial conditions $(S(0), R_1(0), R_2(0), X(0)$ are non-negative and suppose there is a mixing optimal control τ_1^* that we denote by the constant $\omega^* \in (0, \tau_{\max})$. Then

$$R_1(0) = R_2(0),\ c_2 = c_1 + \frac{\tau_{\max} - 2\omega^*}{\beta(X(0) + \sigma S(0))},\ m_1 = m_2 + \frac{2(2\omega^* - \tau_{\max})\sigma R_1(0)^2}{\mu(X(0) + \sigma S(0))}.$$

As a result, if the 50-50 mixing protocol $\omega^* = \frac{\tau_{\max}}{2}$ is optimal then $c_1 = c_2$ and $m_1 = m_2$, therefore $R_1(t) = R_2(t)$ for all $t \geq 0$.

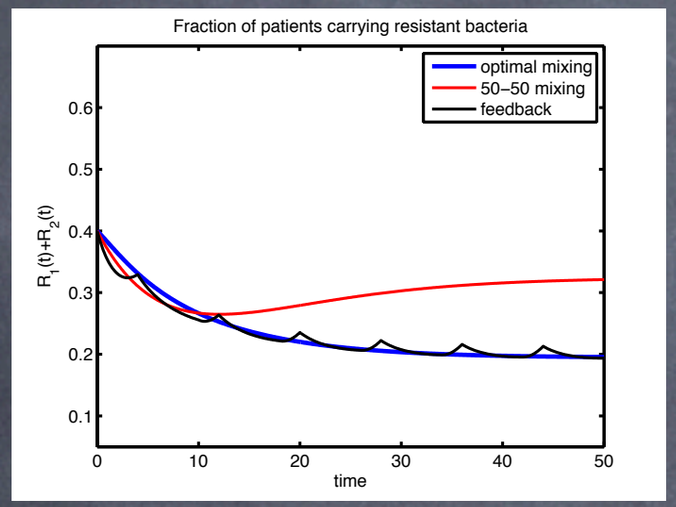
a 'universal' result

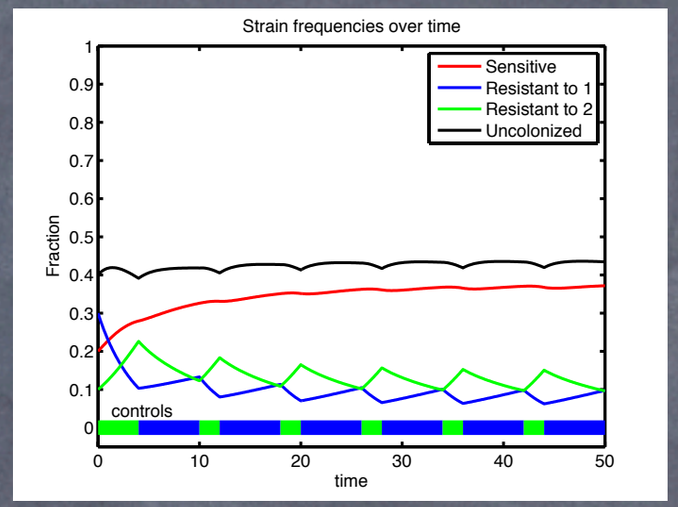
- antibiotic rotations are as good as any set of strategies
- for asymmetric models, there is a weak* nbd of ∞-many rotations all better than mixing:



a rule-based controler

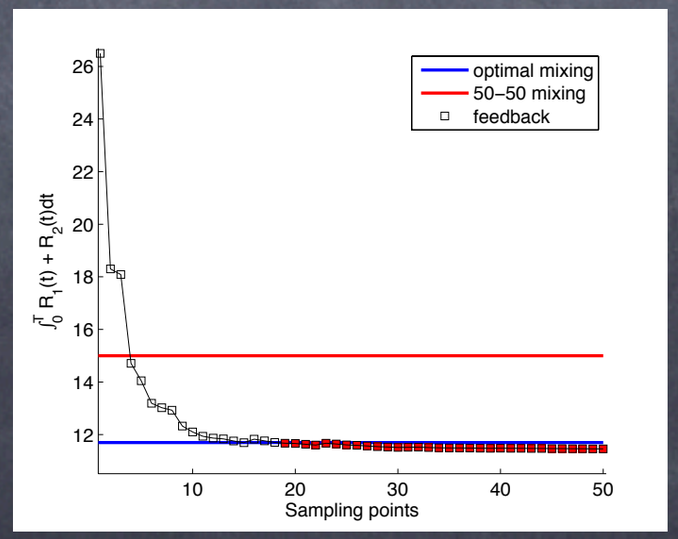
- for asymmetric models, suboptimal rotations can outperform optimal mixing:

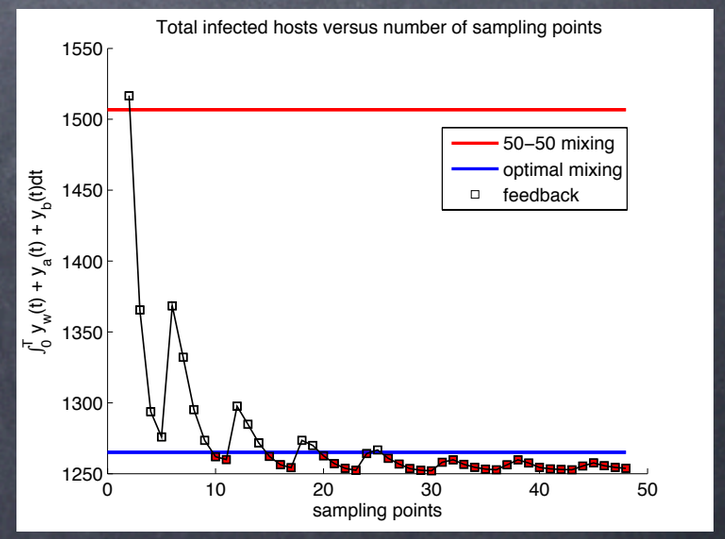




rule: if $R_1 > R_2$, use only drug 2

the controller beats mixing if information quality is high enough





So what?

- In a sense Niederman was right, but how to determine the best rotations in practise?
- Is this kind of result even relevant to current medical thinking?
- What model structures undo the veracity of this conclusion?

We developed a spatially-explicit, stochastic model to test experimental/computational proxies of protocols from recent clinical trials: based on a gradostat protocol.

protocols

(0.) *null protocol*: no patient is treated;

(1.) *random sequential treatment*: each patient receives a random drug each day (mixing);

(2.) *empirical treatment*: a random drug is allocated to the patient the moment the patient arrives at the hospital (mixing);

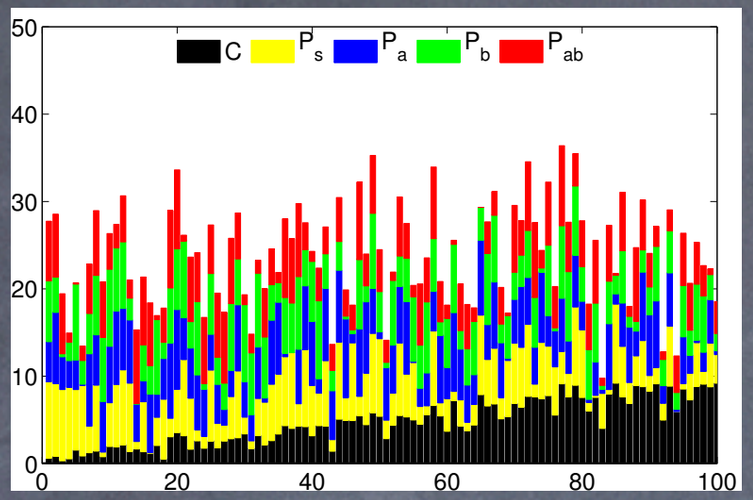
(3.) *periodic cycling*: scheduled, rotating cycles of antibiotic prioritisation and restriction are fixed before any patients have entered the hospital (rotation);

(4.) *periodic antibiotic monitoring and supervision*: the next patient to arrive at the hospital will be treated with the drug that maximises the heterogeneity of drugs currently used within the hospital (mixing);

(5.) *surveillance-based rotation*: drug-resistance phenotypic assays are regularly conducted on samples from the patient cohort and the same drug, namely the one estimated to have the currently lowest prevalence of resistance, is prescribed to all patients (rotation);

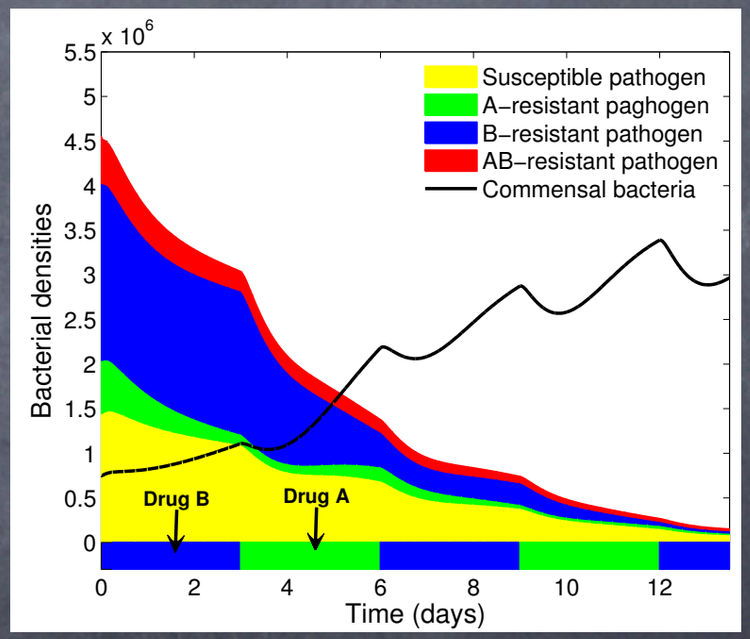
(6.) *DNA diagnosis-based dynamic treatments*: an initial and rapid assessment of the bacterial genotypes responsible for each patient's infection is made the moment a patient arrives at the hospital, a reassessment may also be conducted later during the treatment (mixing).

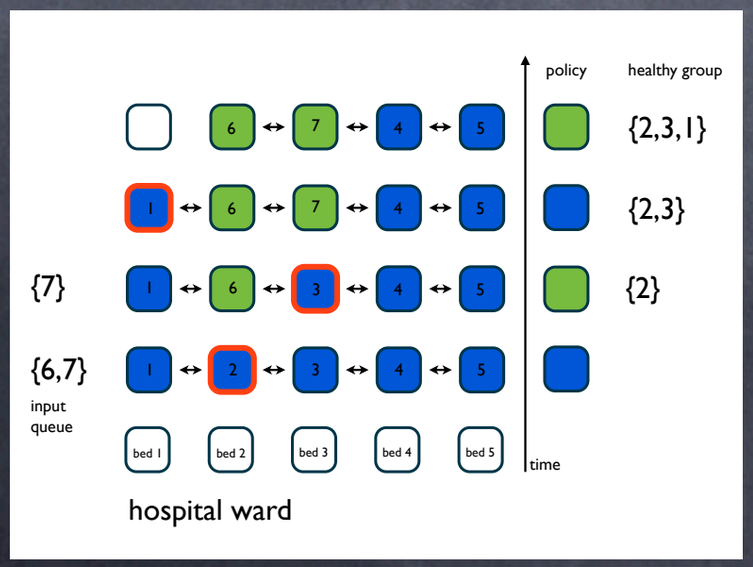
spatially-explicit model, synergistic drugs



: each of 100 'states' (the queue) is infected by SDR and MDR pathogens

therapy given until pathogens below threshold :

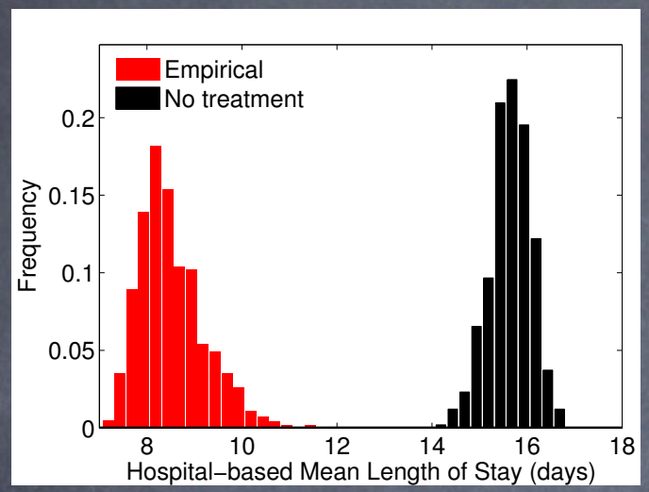


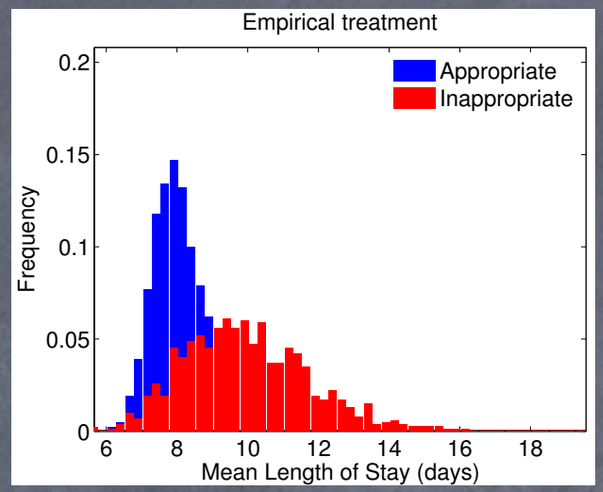


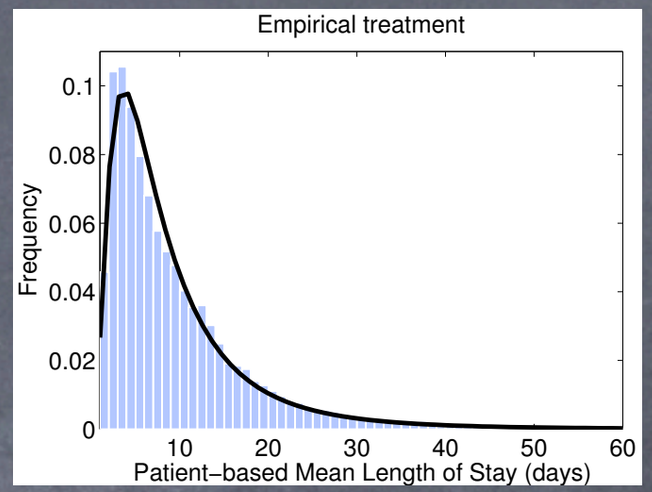
: a new state enters the simulation

spatially-explicit model, synergistic drugs

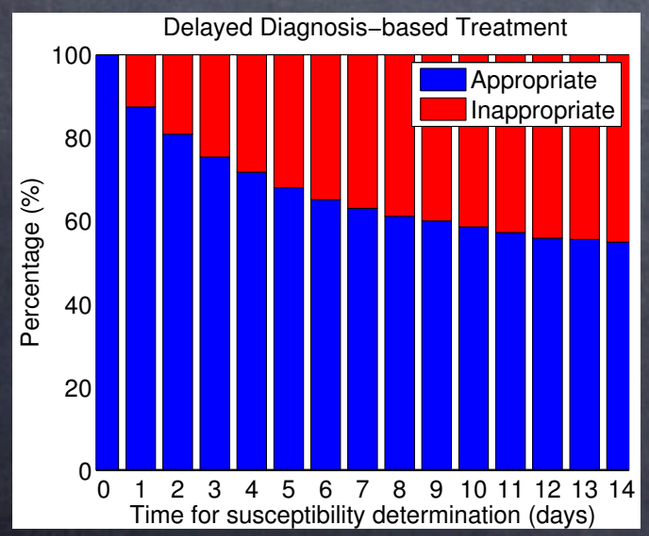
random empirical therapy is better than none:



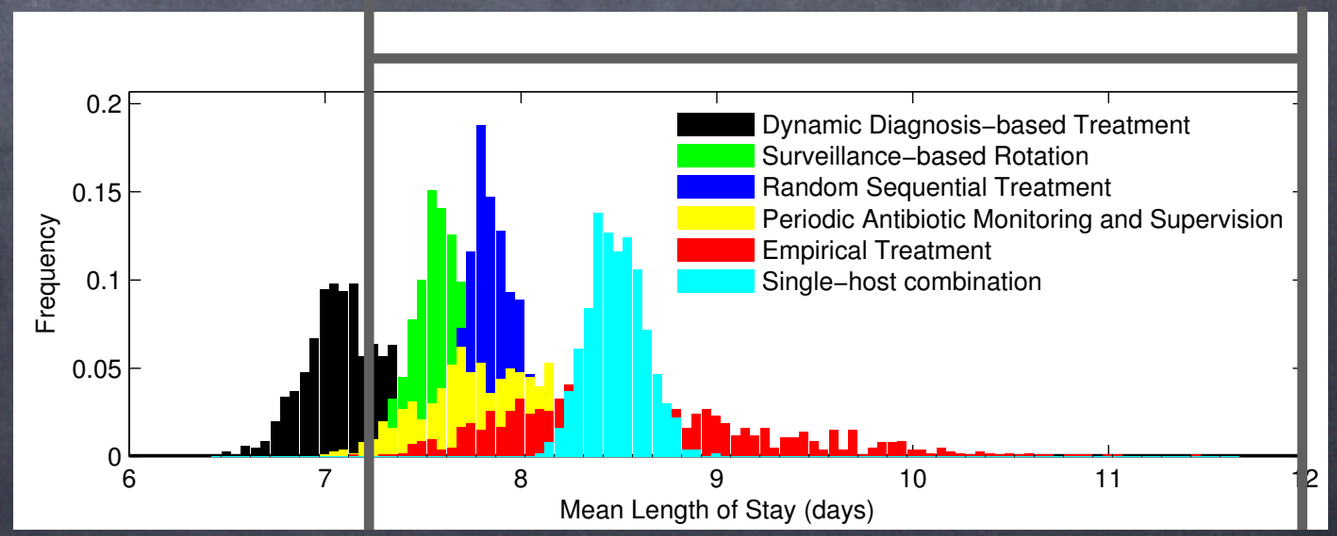




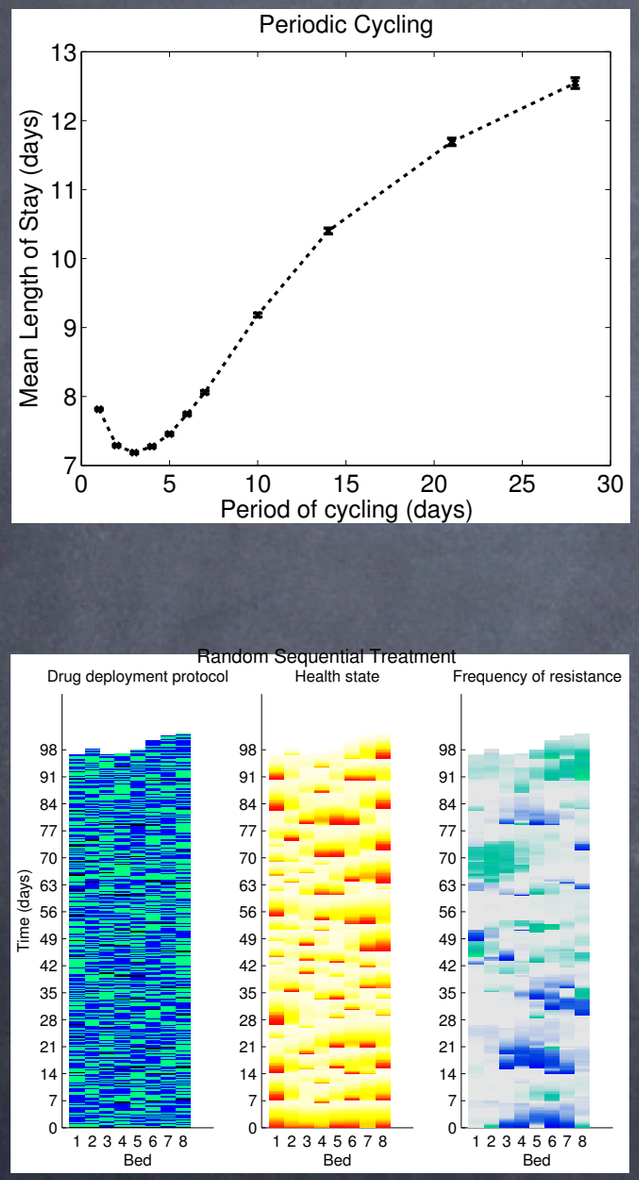
the best treatment (for this queue) gives the most appropriate therapy ASAP:



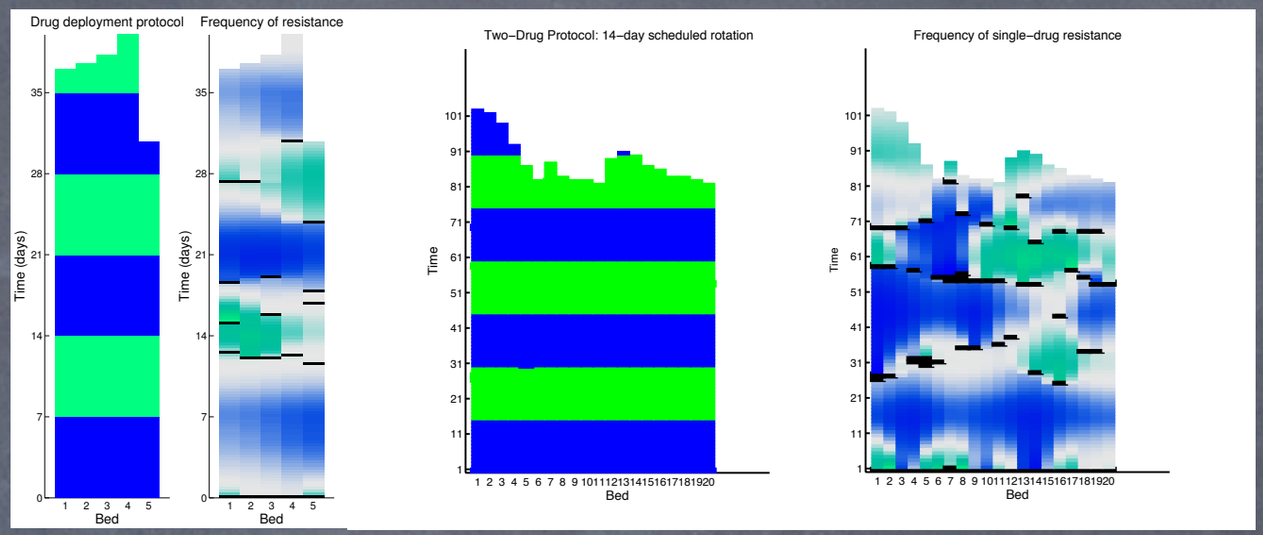
range of cycling



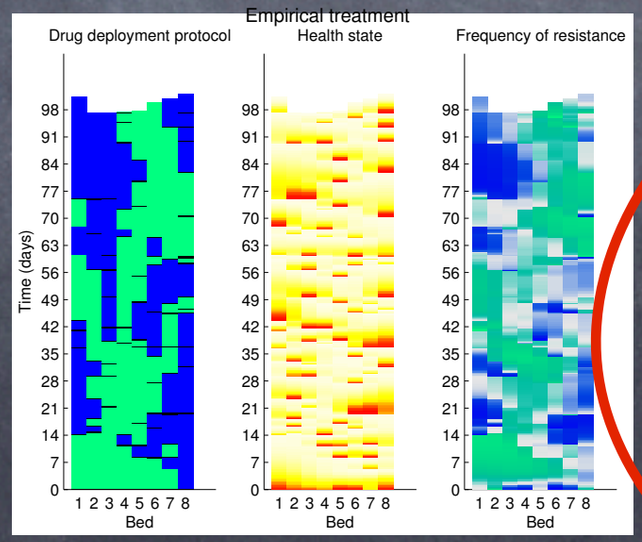
some rotations are good, many are not:

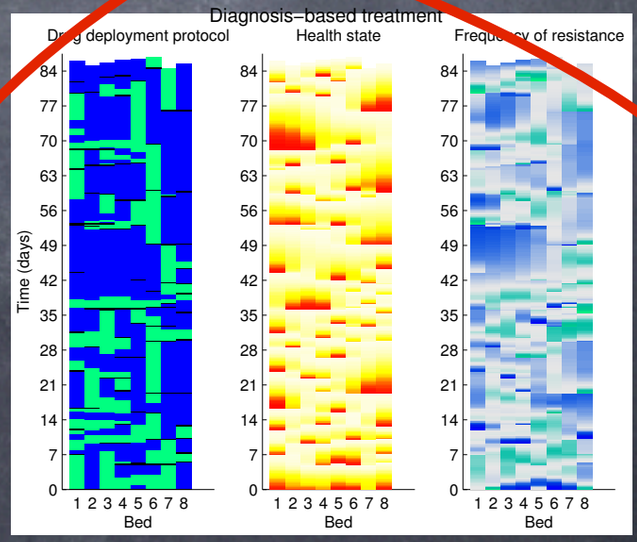


single drug resistance



: domain size effects





shortest MLoS

bang-bang controls: antibiotic mixing

many thanks

- Rafael Pena-Miller, Conacyt-funded
- Sylvain and Florence, CNRS Montpellier
- Craig Maclean, Oxford
- Martin Ackermann, ETHZ
- MRC, EPSRC, NSF - Nescent

weak* convergence

We say that $(\phi_n) \subset L^\infty$ converges weak* to $\phi \in L^\infty$ if

$$\int_0^T \phi_n(t)\psi(t)dt \to \int_0^T \phi(t)\psi(t)dt \qquad \forall \psi \in L^1.$$

This is useful because if $\|\phi_n\|_\infty$ is bounded, (ϕ_n) has a weak* convergent subsequence.