Modeling antimicrobial cycling, mixing, and combination therapy: Why is it so difficult to draw conclusions?

Hildegard Uecker & Sebastian Bonhoeffer

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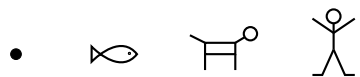
ESEB Turku 2019



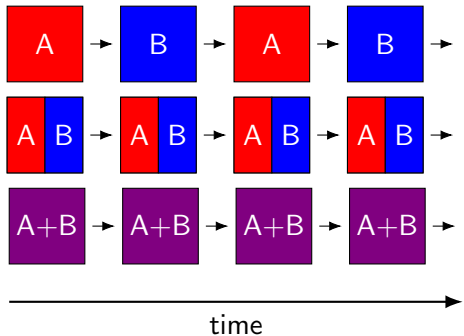
Antibiotic treatment protocols

Hospital-acquired infections:

- 30% of patients in intensive care units are affected (WHO)

To approach the resistance problem:
use two antibiotics (A and B) for the phase of empiric treatment

- antibiotic cycling
- antibiotic mixing
- combination therapy



Question:

Which strategy is best?

Bonhoeffer et al. 1997
Bergstrom et al. 2004

Literature overview

Publication	Comparison	Optimality criterion	Best strategy	Origin of resistance	Cost of resistance	Drug adjustment	R_{All} compartment	Other comments
Bonhoeffer et al. 1997	CYC, MIX, COMB	# uninfecteds in a given time interval/until resistance has reached a given frequency	COMB (MIX)	pre-existence, de novo emergence	yes	no	yes	differential efflux rates for infecteds & uninfecteds
Bergstrom et al. 2004	CYC, MIX	average # infecteds with res. strain, evol. of double resistance	MIX (CYC)	pre-existence (?), influx	yes	no	no	equal efflux rates for all patients, horizontal gene transfer leads to double resistance
Levin & Bonten 2004	CYC, MIX[1]	average # infecteds with res. strain	MIX	pre-existence (?), influx	yes	no	no	extension of Bergstrom et al. 2004 to three antibiotics
Beardmore and Pella-Miller 2010a[2]	CYC, MIX[2]	# infecteds in a given time interval, # infecteds with res. strain	CYC (MIX)	pre-existence, influx, de novo emergence	yes	no	yes	an adaptive rotation protocol (always use drug with lower resistance prevalence) is considered as well and outperforms MIX
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Beardmore and Pella-Miller 2010b[3]	CYC, MIX[2]	# infecteds in a given time interval, # infecteds with res. strain	inconclusive	pre-existence, influx, de novo emergence	yes	no	yes	
Sun et al. 2010	SINGLE, CYC, MIX, COMB	not employed	not discussed	de novo emergence	yes	no	yes	analytical treatment of the equilibria of the model in Bonhoeffer et al. 1997
Kouyos et al. 2011	CYC, MIX, ISS[3]	prevalence of res., # inappropriately treated patients	ISS	pre-existence (?), influx	yes	yes [var. 2]	yes	stochastic simulations (if deterministic: ISS ≈ MIX), status-dependent efflux rates, splits up compartments depending on applied drug
Chan et al. 2011	SINGLE, MIX, COMB, THRESH[4], DIFF[4], POC[4]	prevalence of infections in time	inconclusive (MIX)	pre-existence (?), de novo emergence	no	no	yes	no influx and efflux of patients, model specific for gonorrhea, only 1/3 of infecteds get treated
Oboloki and Hadany 2012	CYC, MIX, COMB	evol. of double resistance, #infected patients	CYC (COMB)	pre-existence (?), influx	no	no	no	equal efflux rates for all patients, stress-induced mutagenesis and horizontal gene transfer
Abel zur Wiesch et al. 2014	CYC, MIX	combination of # inappropriately treateds and # symptomatically infecteds	inconclusive (CYC at optimal frequency)	pre-existence (?), influx, de novo emergence	yes	yes [var. 1]	yes	status-dependent efflux rates; stochastic and deterministic model outcomes differ
Campbell and Chao 2014	NONE[5], CYC, "MIX"[5], COMB, MONO, CONTROL[5]	average # uninfecteds in equilibrium	COMB	pre-existence	yes	no	yes	no influx or efflux of patients, tradeoff to double-resistance, additive or antagonistic drug interaction, # uninfecteds correlates with recovery rate of infecteds (no tragedy of the commons)
Xiridou et al. 2014	SINGLE, COMB, THRESH	prevalence of infecteds	COMB	de novo emergence	yes	yes [var. 1][6]	yes	equal efflux rates for all patients, model specific for gonorrhea
Oboloki et al. 2015[7,8]	SINGLE, CYC, MIX	# incorrectly treated, evol. of double resistance	MIX (for crit. 1), inconclusive (crit. 2)	pre-existence (?), de novo emergence, influx	no	yes [var. 1]	no	equal efflux rates for all patients, focus on the effect of drug restriction
Beardmore et al. 2017	CYC, MIX, reac. CYC[9]	# correctly treateds, # infecteds with res. strain # infecteds	inconclusive (reactive CYC)	pre-existence (?), de novo, influx	yes	yes	no	several models are studied
Tepekule et al. 2017	SINGLE, CYC, MIX, COMB	gain in # uninfecteds in one year compared to no treatment	COMB (all others)	pre-existence, influx, de novo emergence	yes	no	yes	equal efflux rates for all patients, winning strategy depends on parameters but combination therapy wins most often
Uecker and Bonhoeffer 2017[9]	CYC, MIX	average # of uninfecteds, spread of double res.	inconclusive	pre-existence, influx, de novo emergence	yes	no	yes	equal efflux rates for all patients, comparison of two different model implementations

20 years of modeling

tendency:

combination therapy $>$ mixing $\gtrsim$ cycling

but not conclusive

Uecker & Bonhoeffer, bioRxiv

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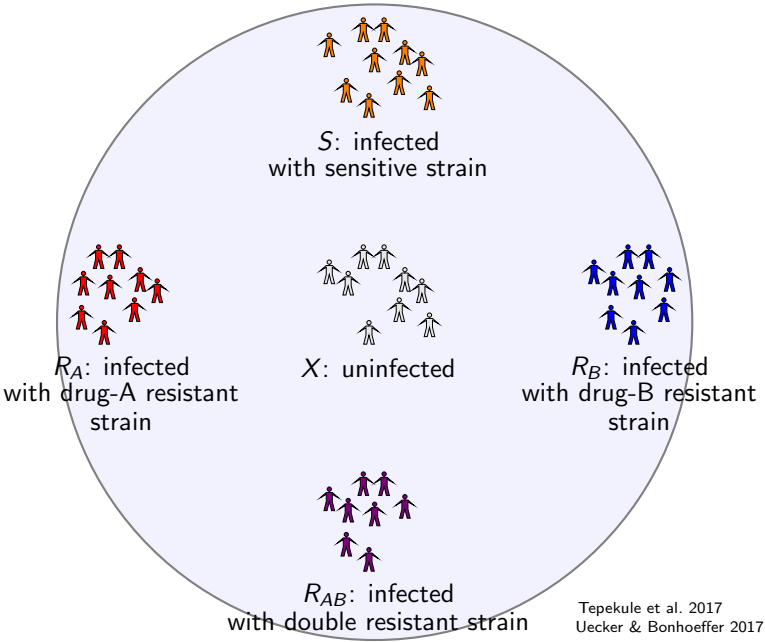
Why have mathematical models been unable to give clear answers to date?

Aim: Identify and discuss modeling aspects that influence the conclusion.

Uecker & Bonhoeffer, bioRxiv

The modeling framework

Processes:



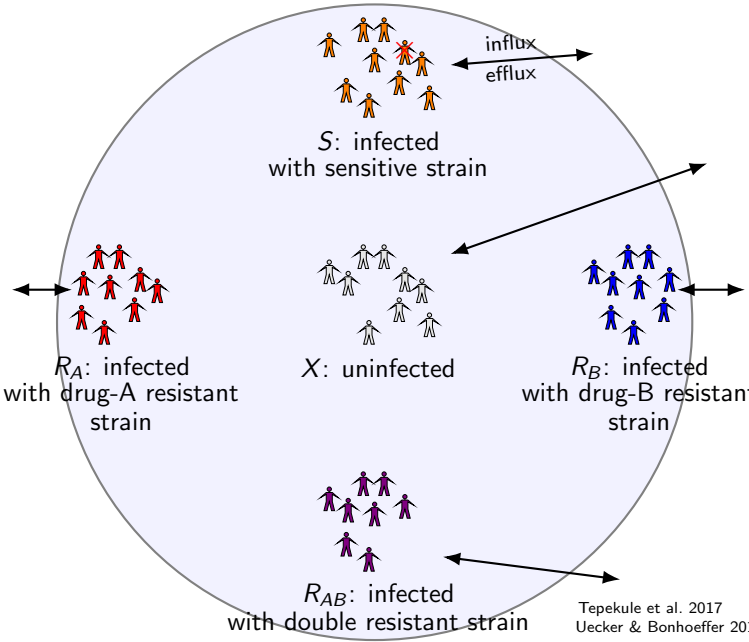
deterministic ODE system

Tepekule et al. 2017
Uecker & Bonhoeffer 2017

The modeling framework

Processes:

influx & efflux



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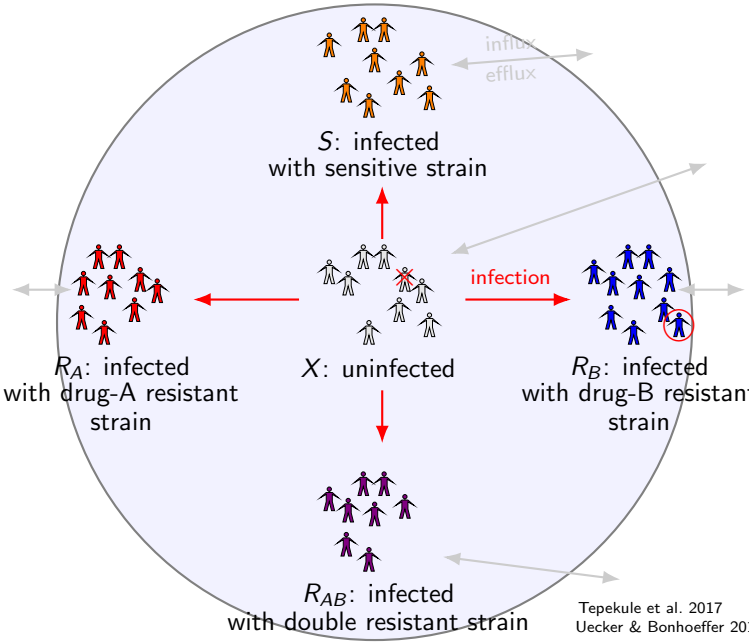
Processes:

influx & efflux

infection

mass-action kinetics,
e.g. $\beta X R_B$



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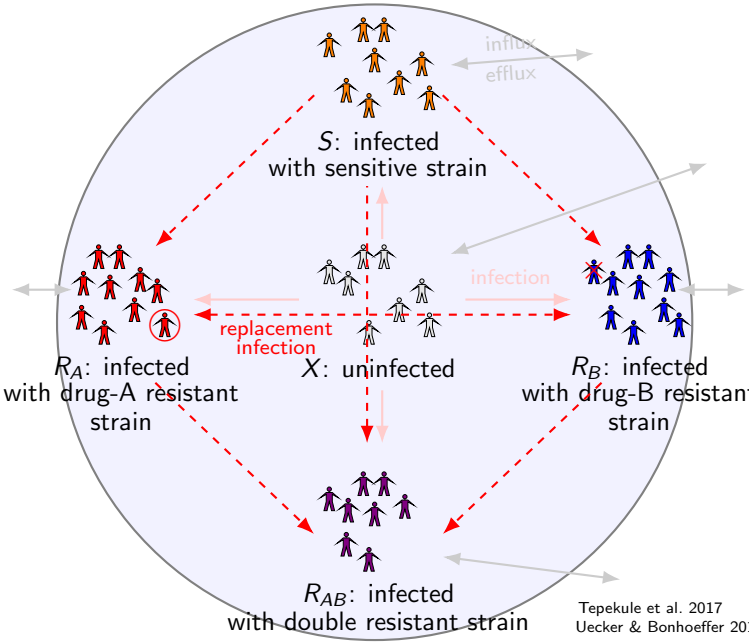
replacement infection



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replacement infection

recovery due to treatment

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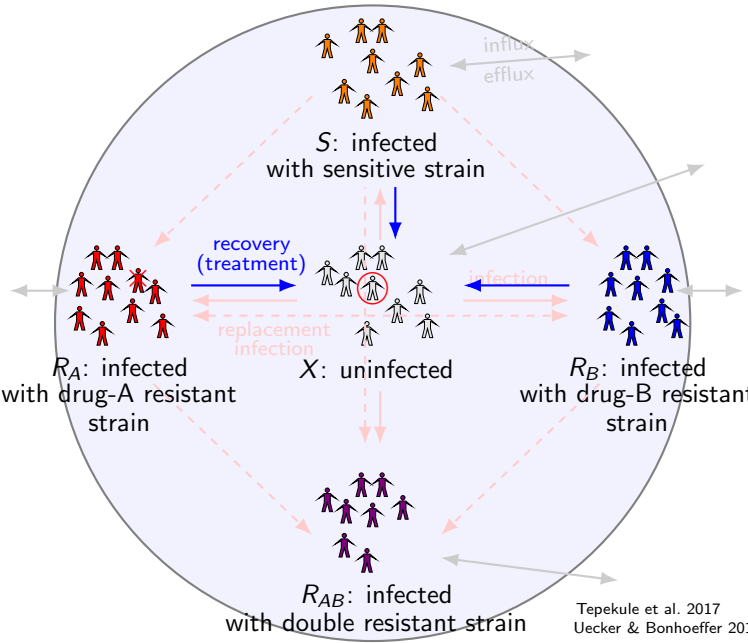

Tepekule et al. 2017
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Processes:

influx & efflux

infection

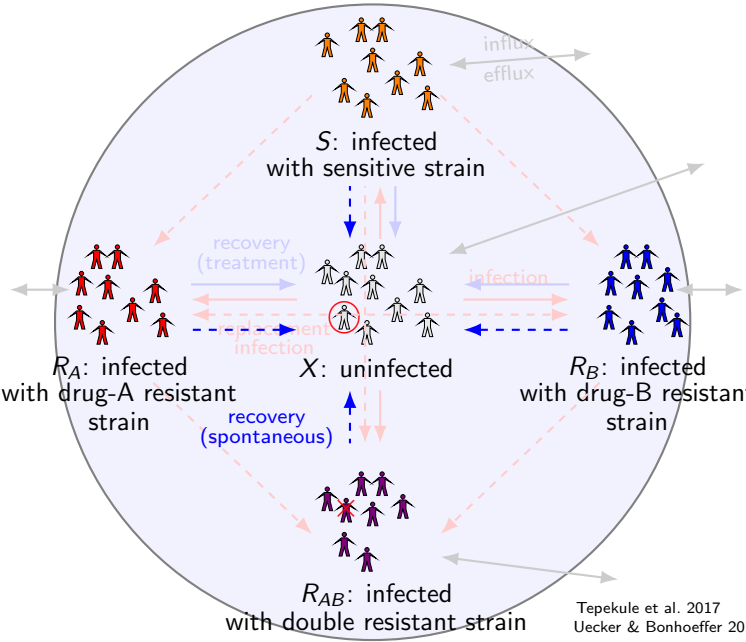
mass-action kinetics, e.g. $\beta X R_B$

replacement infection

recovery due to treatment

spontaneous recovery

deterministic ODE system



Tepekule et al. 2017
Uecker & Bonhoeffer 2017

The modeling framework

Processes:

influx & efflux

infection

mass-action kinetics, e.g. $\beta X R_B$

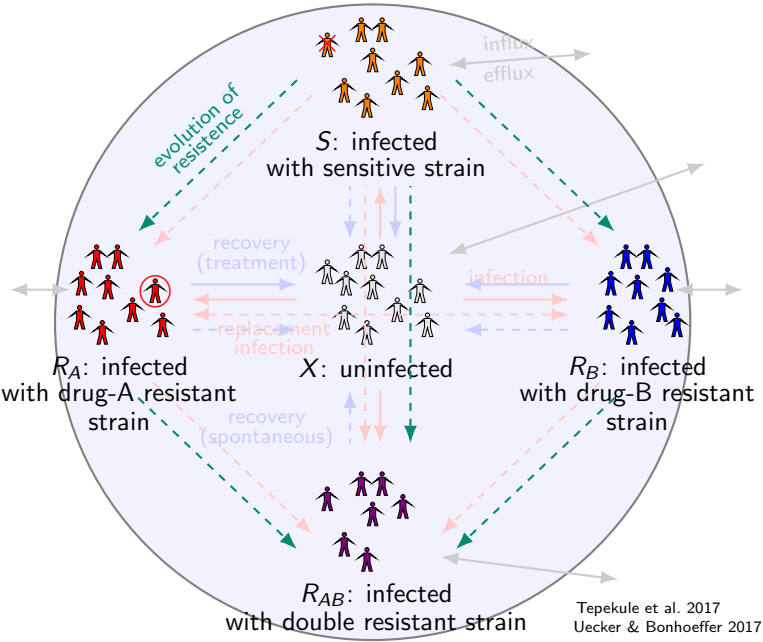
replacement infection

recovery due to treatment

spontaneous recovery

evolution of resistance

deterministic ODE system



Tepekule et al. 2017
Uecker & Bonhoeffer 2017

Optimality criteria

Two classes

Overall treatment success

- number of uninfecteds in a year
- mean number of uninfecteds in equilibrium

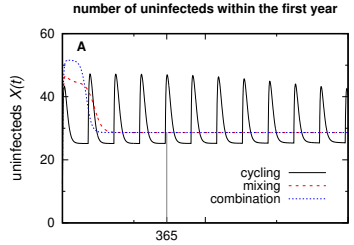
Resistance

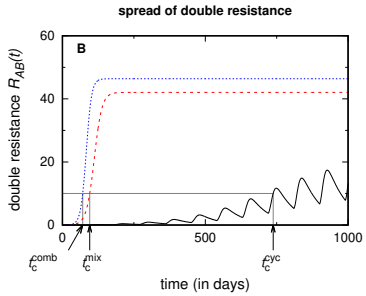
- number of infecteds with resistant strain
- rate of emergence of double resistance

Combined criterion: number of uninfecteds until resistance has reached a certain level

The optimality criterion

combination
> mixing
> cycling

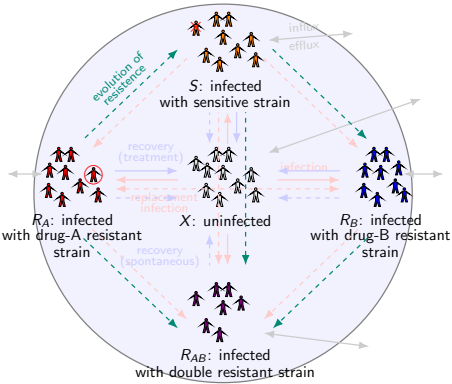


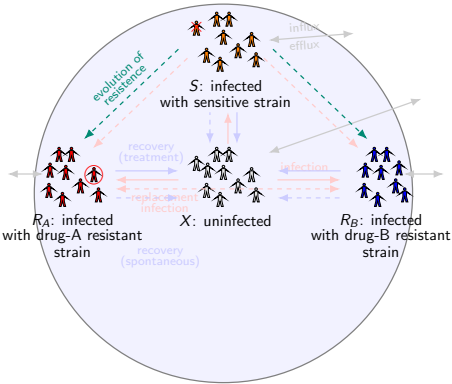


cycling
> mixing
> combination

Some other factors influencing the ranking of strategies

- Model variant without a compartment for double resistance



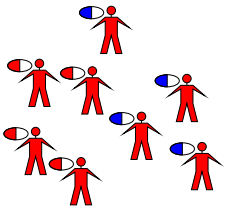


- many parameters; initial conditions
- deterministic vs stochastic implementation

Bergstrom et al. 2004

Modeling mixing and cycling

Standard model for mixing: in every compartment, 50% of all patients receive drug A *at all times*



recovery at rate $\tau \frac{R_A}{2} + \gamma R_A$

τ: treatment

γ: spontaneous

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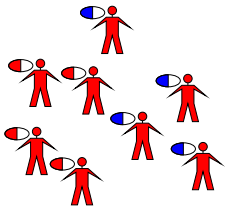

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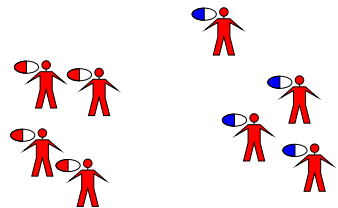
Alternative model for mixing: drug A gets assigned to 50% of all patients *at the onset of therapy*



$\gamma R_A^{(\text{drug A})}$

$(\tau + \gamma)\, R_A^{(\text{drug B})}$

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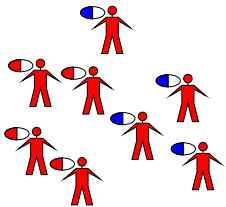

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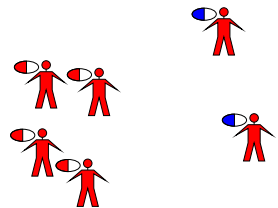

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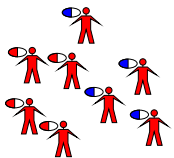
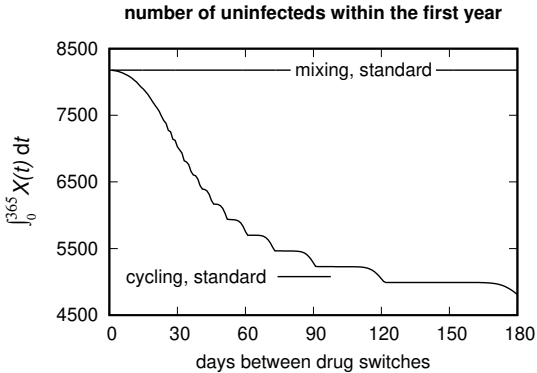
Modeling mixing and cycling (here: no double resistance)





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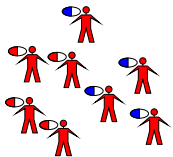

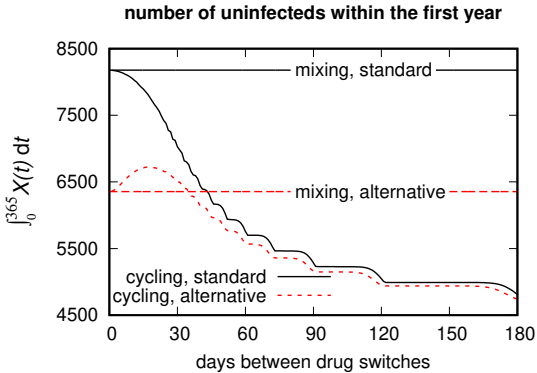

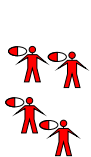

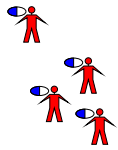

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Suggestions & Gaps & Conclusion

Optimality criterion:

- extend current modeling approaches to assess *mortality* and the *length of hospitalisation*

Further extension:

- rethink models: *commensals* as agents of infection

Conclusion:

- Can the models provide insight? – yes (but with caveats)
- *The complex picture is a result!*

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Antoine Frénoy
Burcu Tepekule
Andrew Read

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Thank you for your attention.