An evolutionary paradigm favoring crosstalk between bacterial two-component signaling systems

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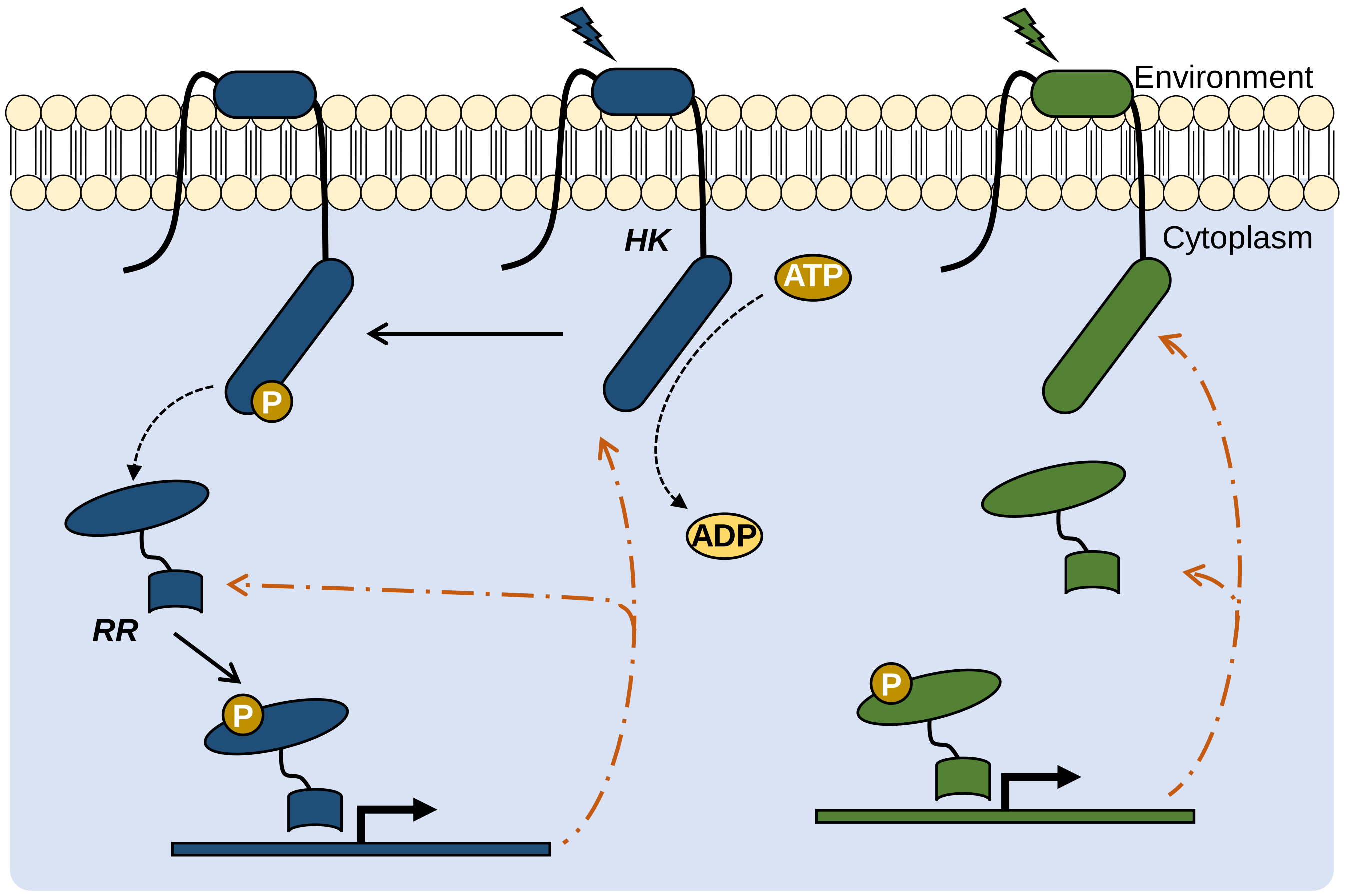
Two-component signaling systems (TCSs)

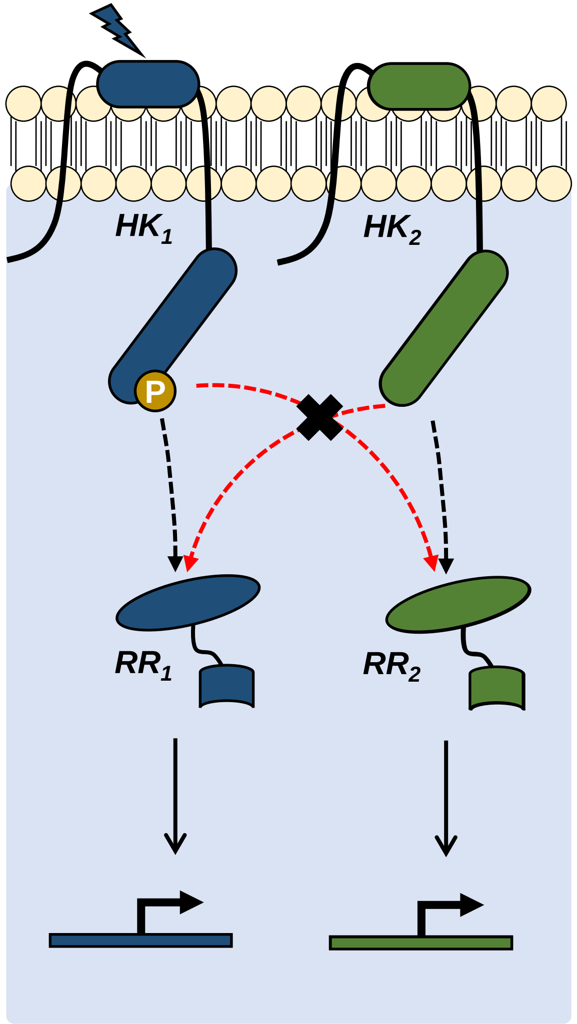


HK – Histidine kinase *RR* – Response regulator

Response for a stimulus:
(a) Production of proteins required for response
(b) Upregulation of TCS

Different TCSs sense different signals

Two component signaling systems (TCSs)



TCS proteins share significant homology

Disadvantages of crosstalk

- Signal dissipation
- Unwanted responses

HK-RR binding domains are specific to cognate partners – a few mutations abrogate binding completely

Capra et al., *Cell* 2012

During duplication, crosstalk must be eliminated before the new TCS pathway acquires novel domains

Rowland & Deeds, *PNAS* 2014

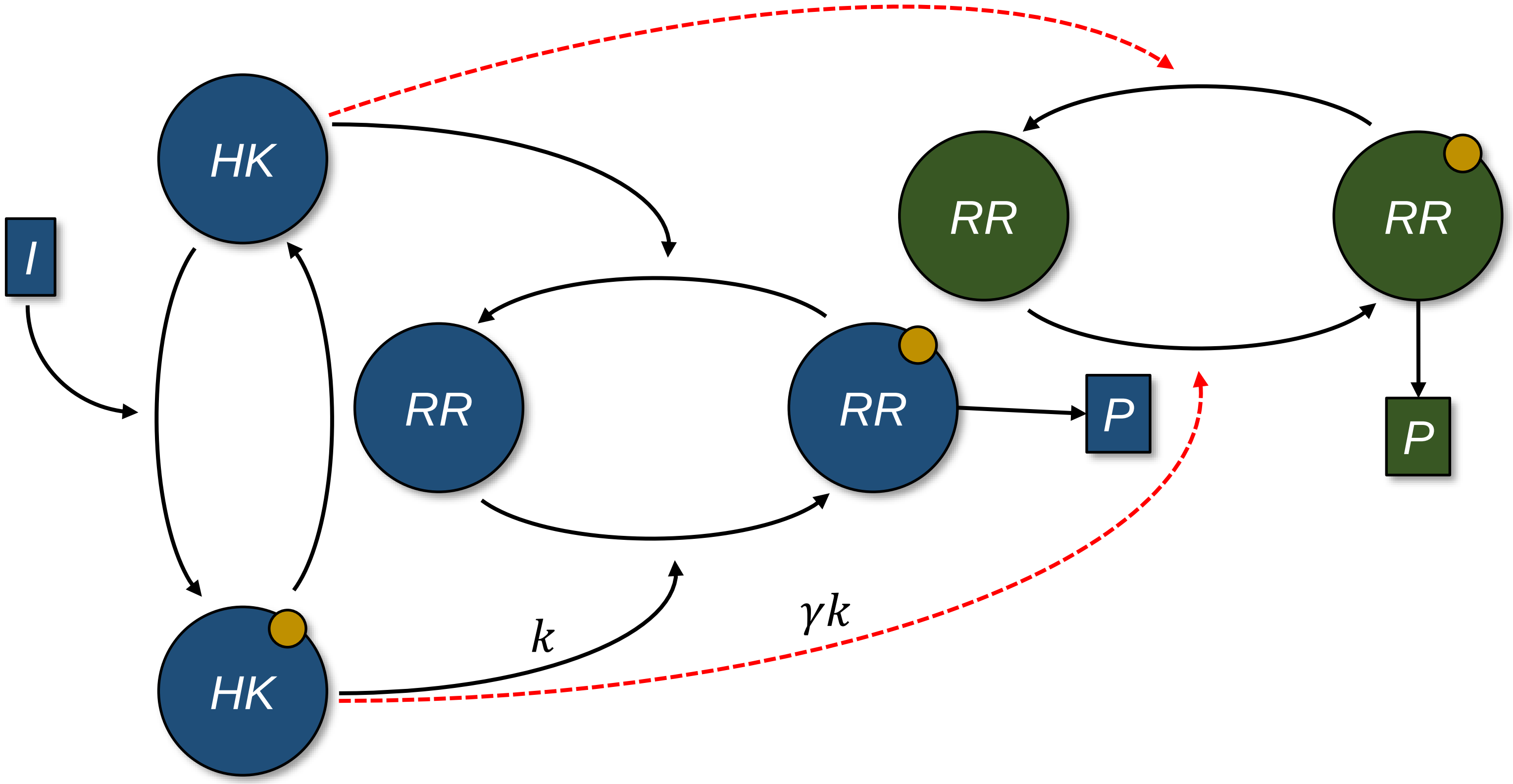
Bacterium	TCS proteins	% crosstalk interactions
E. coli	62	~3%
M. xanthus	250	0%
C. crescentus	106	0%
B. subtilis	70	~0%
M. tuberculosis	26	48%

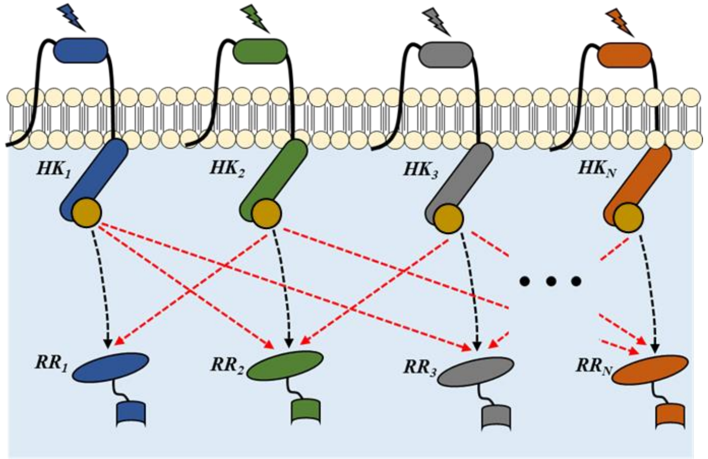
Unraveling potential evolutionary advantages of crosstalk – implications in adaptation and survival

Hypothesis

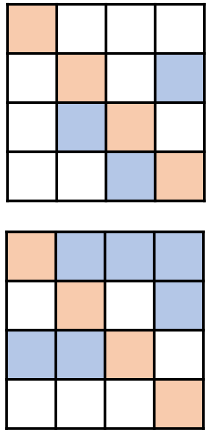
Crosstalk between TCSs might have been an evolutionary outcome of its programmed environment

Model





	RR_1	RR_2	RR_3	RR_4
HK_1	1	0	0	0
HK_2	0	1	γ	γ
HK_3	γ	γ	1	0
HK_4	γ	0	γ	1



Fitness formulation:

$$\phi_i(t) = \exp\left(-\frac{I_i(t)}{I_{max}} \times (1 - f_{bound})\right)$$

$$\Rightarrow \phi(t) = \prod_i \phi_i(t)$$

Environment:

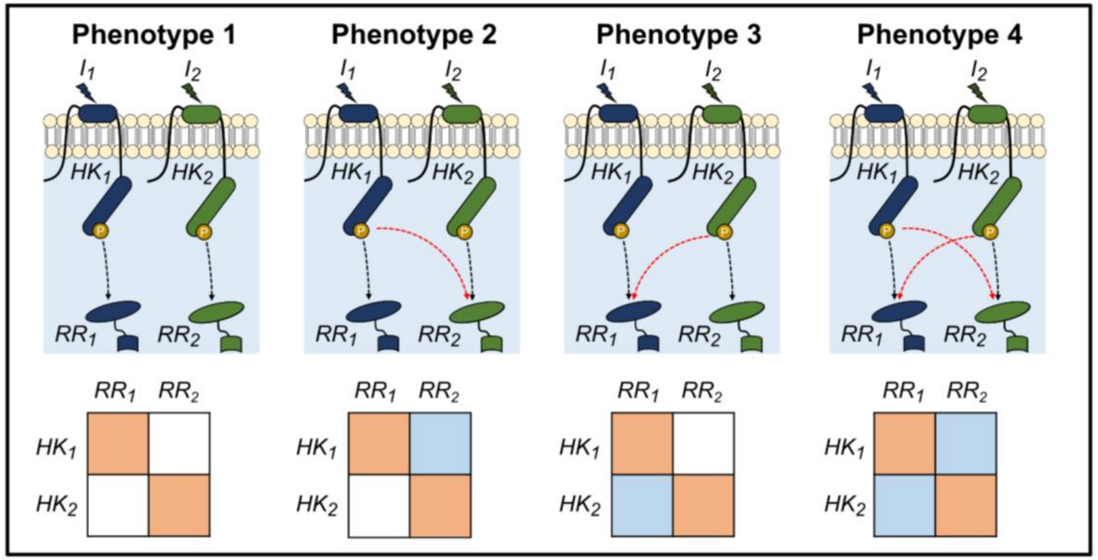
Programmed

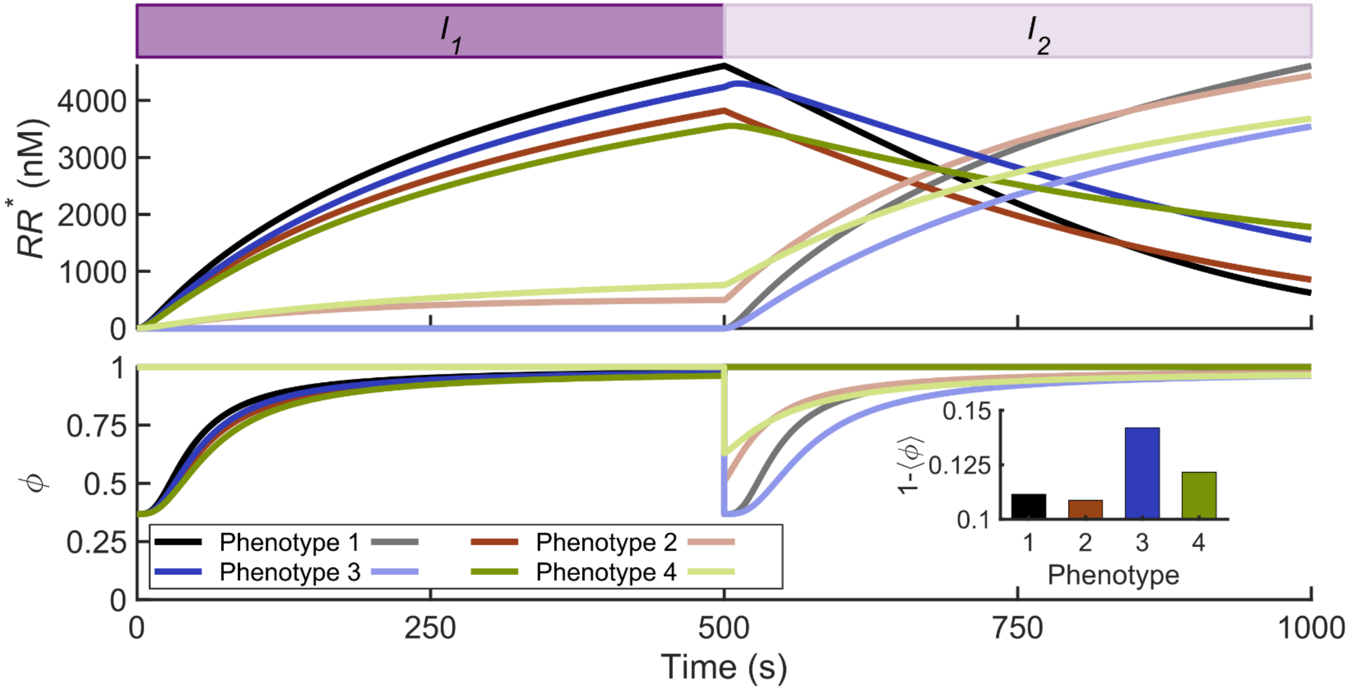
Signal pattern
1 → 2 → 3 → … N

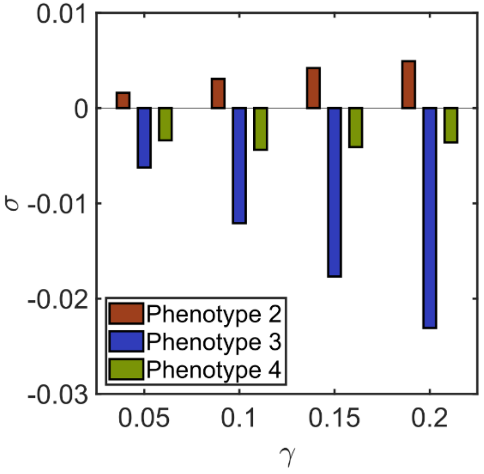
Random

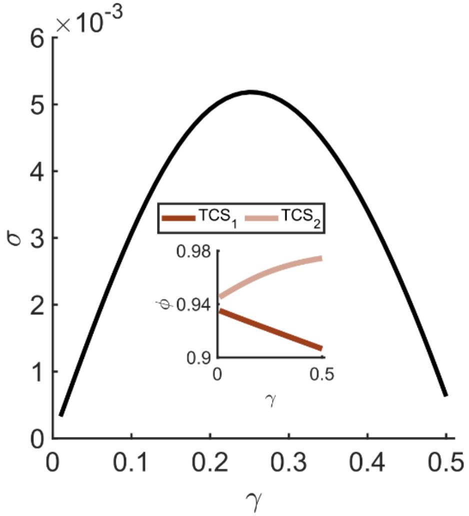
Number of possible signal sequences = N^N

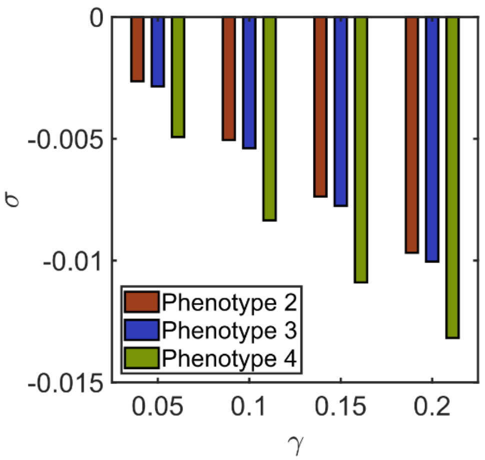
Understanding N=2 case





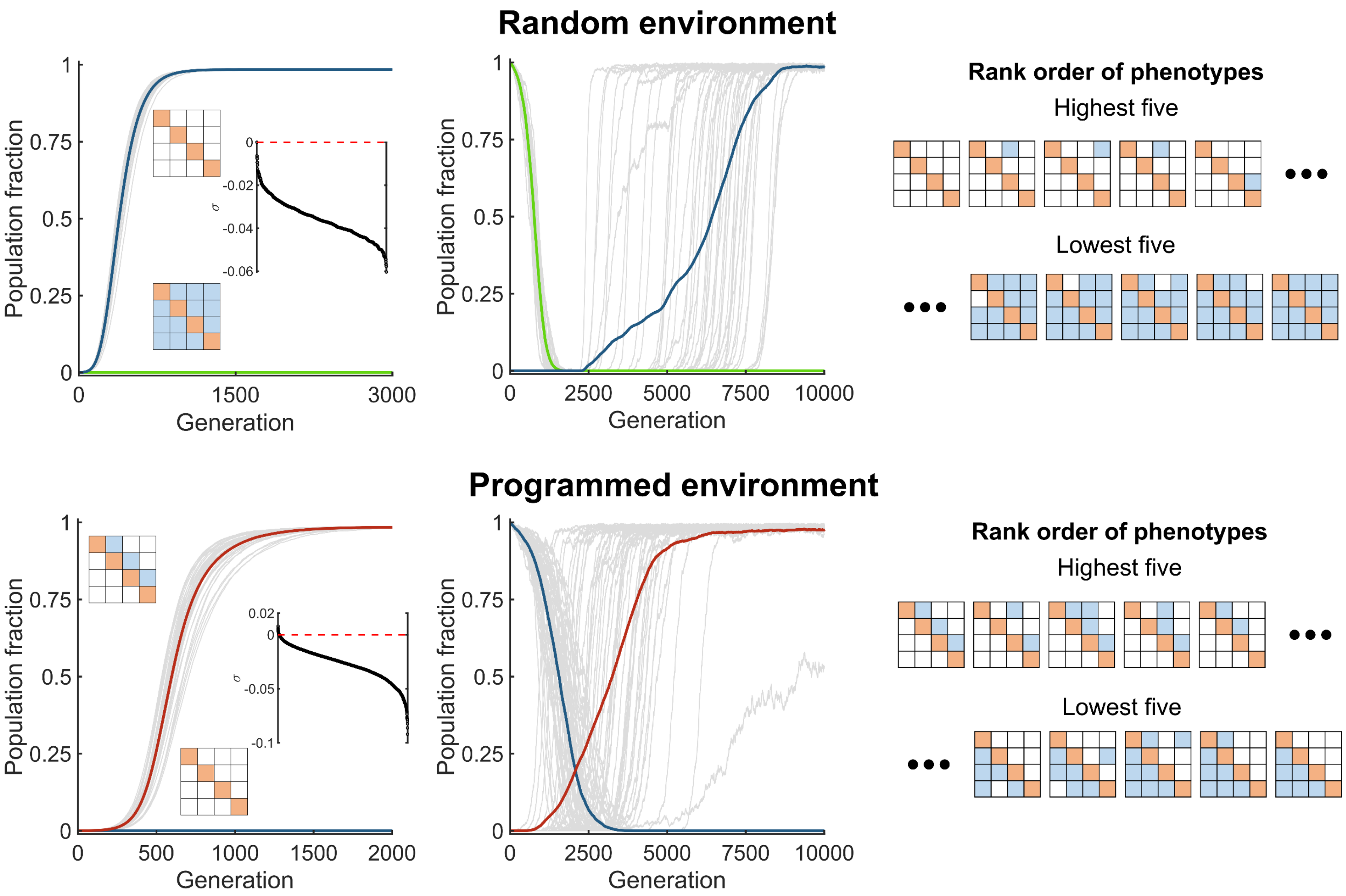






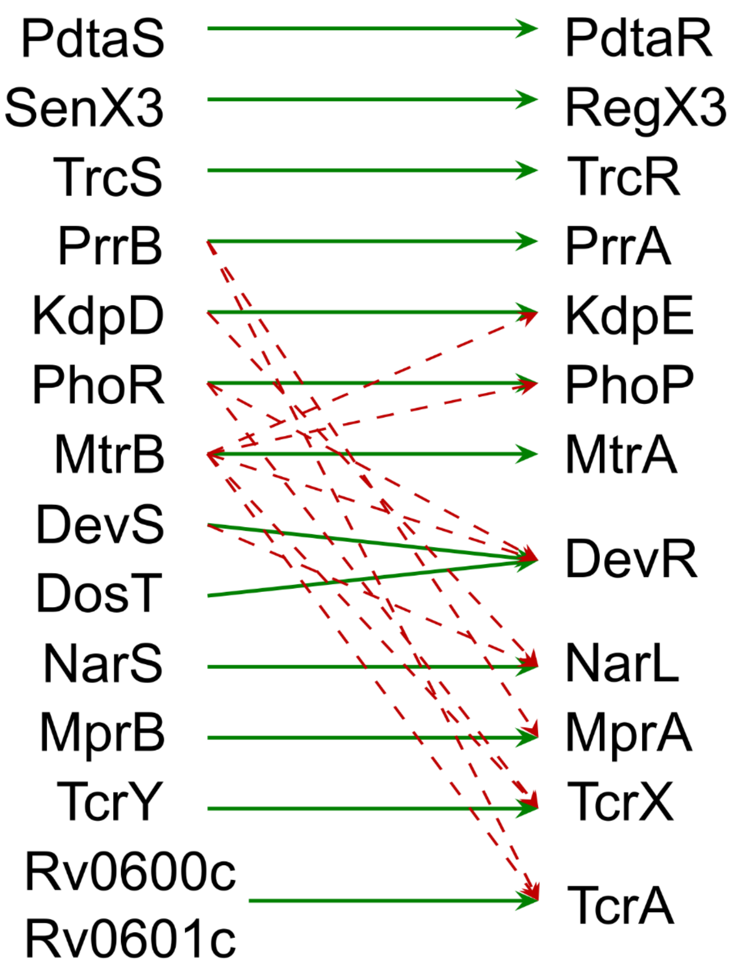
Crosstalk mirroring the signal sequence could be advantageous in programmed environments

Fitness differences are significant for evolutionary selection

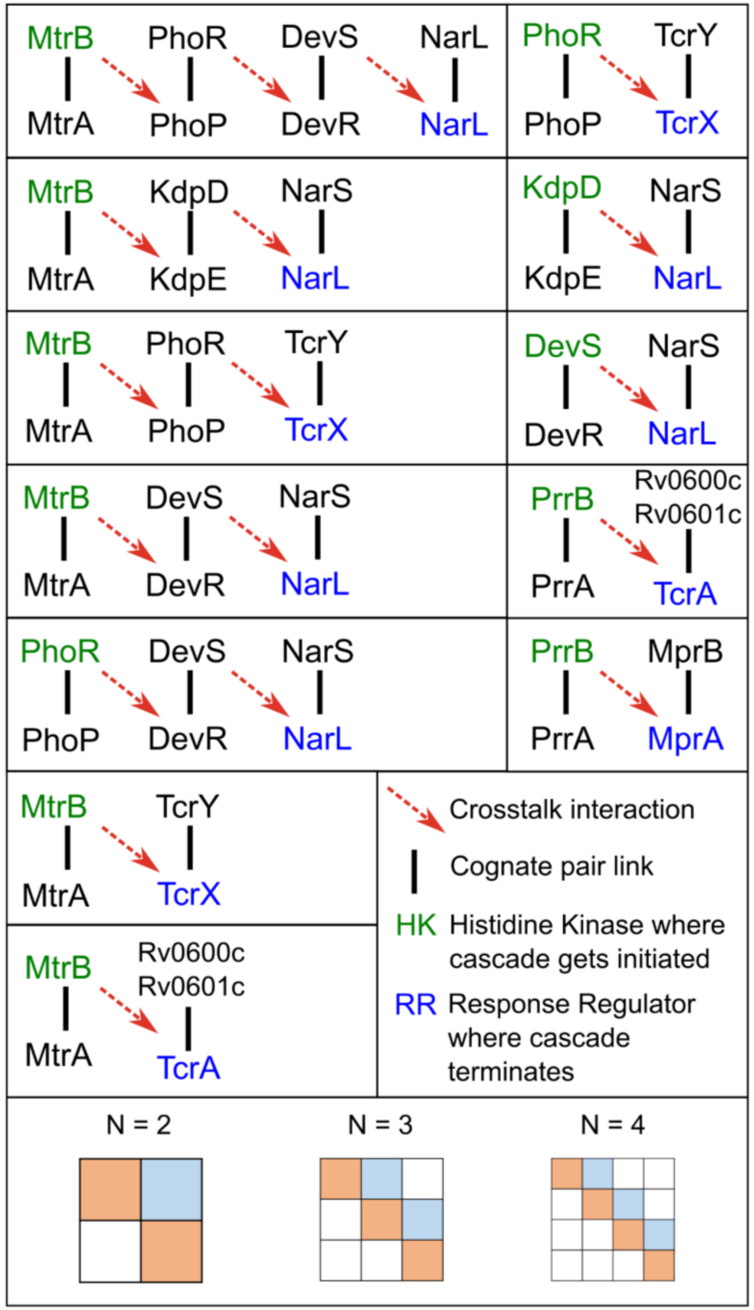


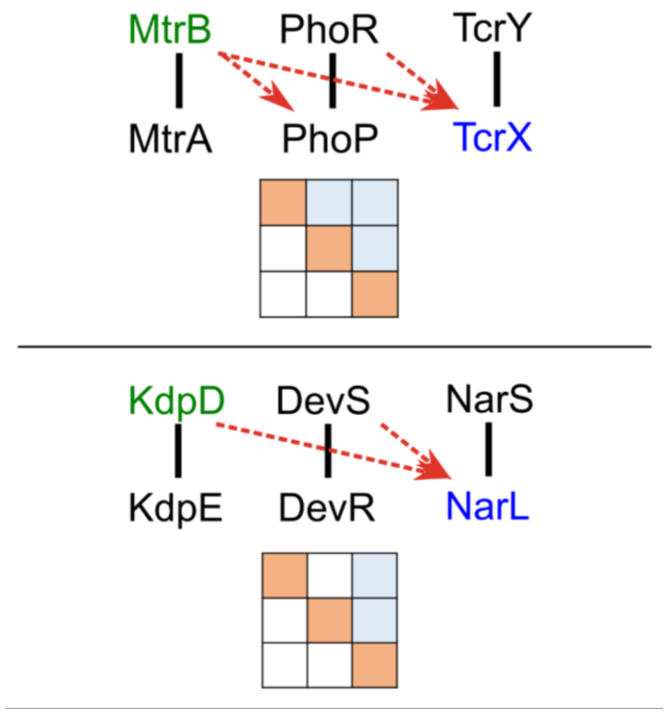
Evidences from TCS network of *M. tuberculosis*

All the crosstalk interactions were mapped for TCSs of *M. tuberculosis*



Agrawal et al., *Biochem J* 2015





These TCSs have crosstalk patterns that may have ingrained the potential signal sequences

Conclusions

1. Devised a mathematical framework to analyze crosstalk in bacterial TCSs
2. Presented alternative evolutionary paradigm where crosstalk might be advantageous
    - Crosstalk mirroring signal sequences confer advantage in programmed environments
    - Specificity is preferred when stimuli arise randomly
3. Reconciled the prevalent specificity arguments with crosstalk
4. Provided evidences for the same from experimental data

Acknowledgements

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