Max-Planck-Institut für terrestrische Mikrobiologie
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# Bacterial chemotaxis as a model for systems biology

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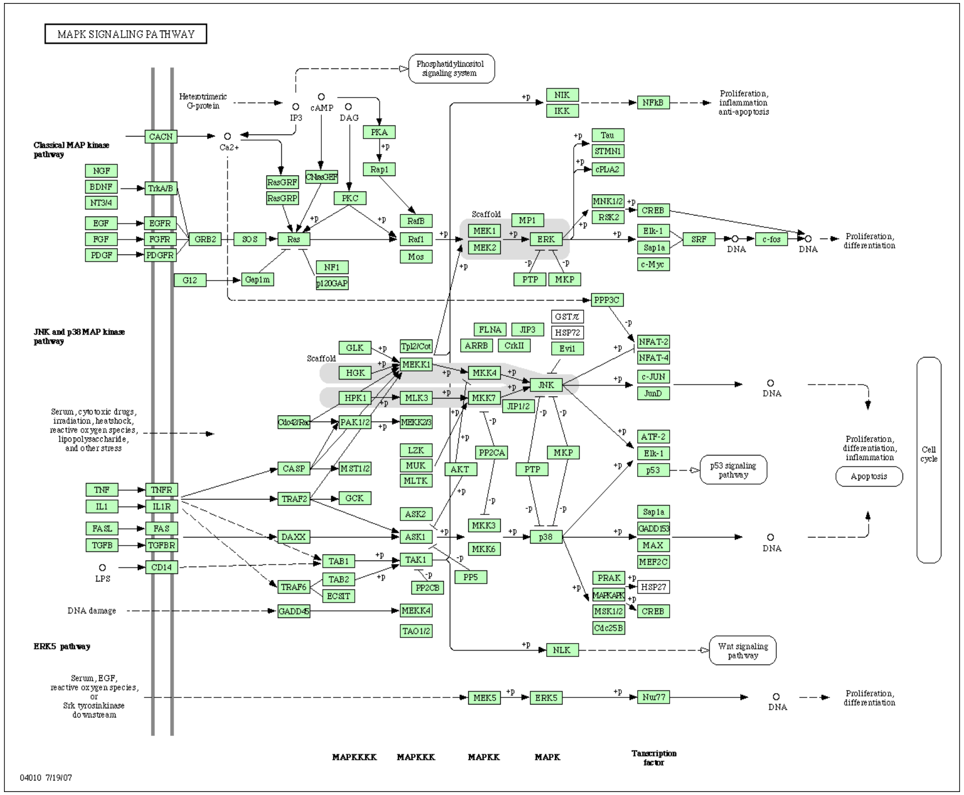
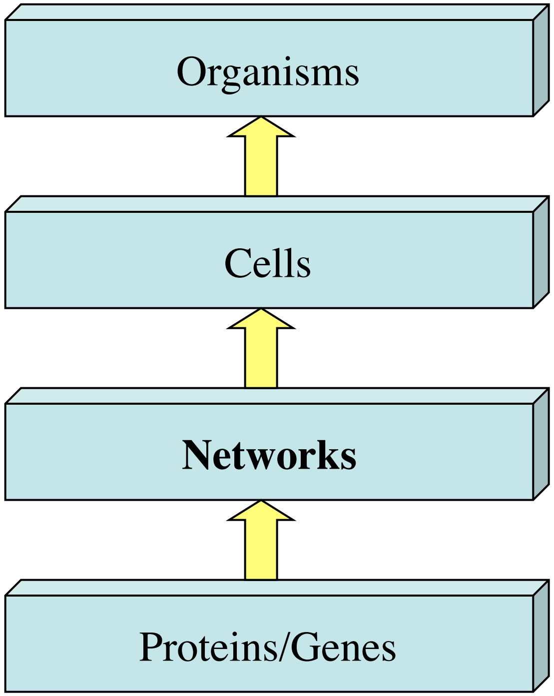
# *Systems biology:*
# Biology of cellular networks

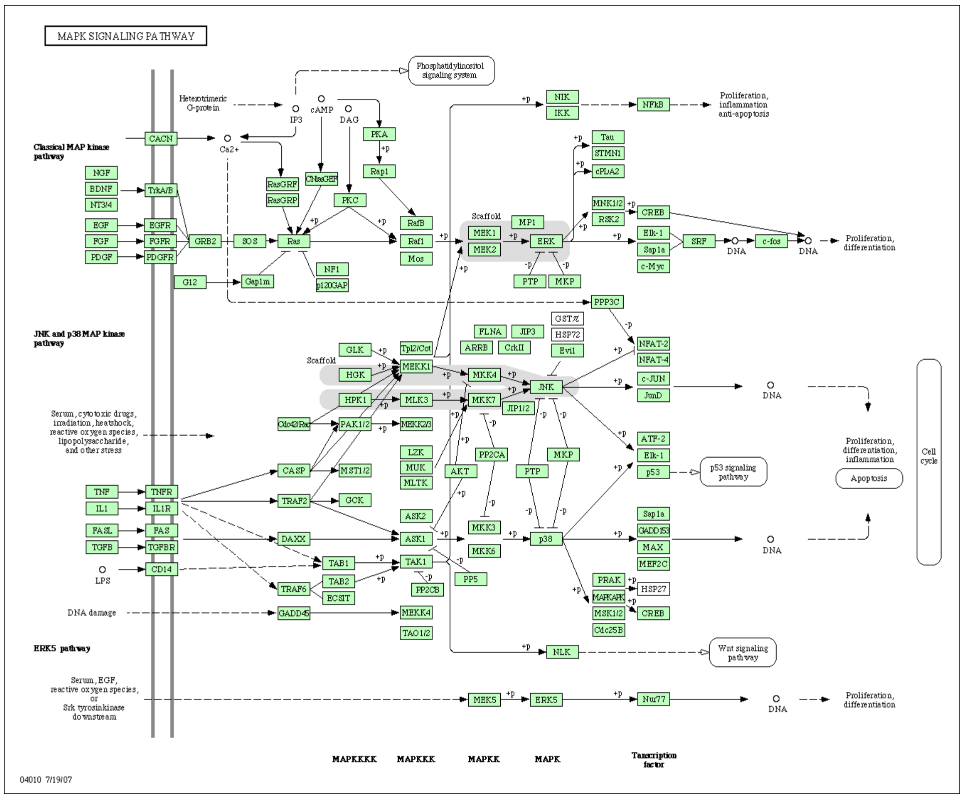
## Proteins and genes are organized in networks:
### How can we understand the operation of networks?



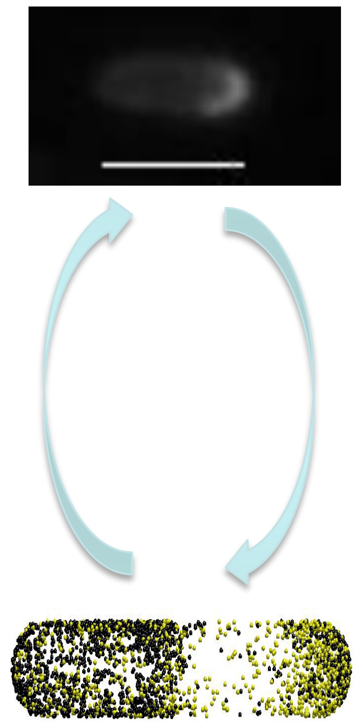



# *Systems biology:*
# Biology of cellular networks

## *Proteins and genes are organized in networks:*
## How can we understand the operation of networks?

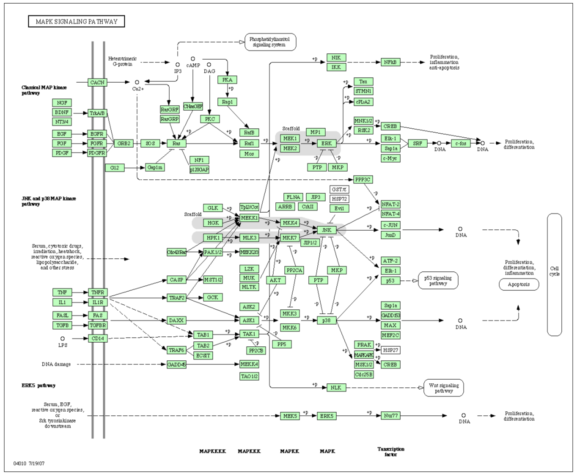



**Quantitative experiments**



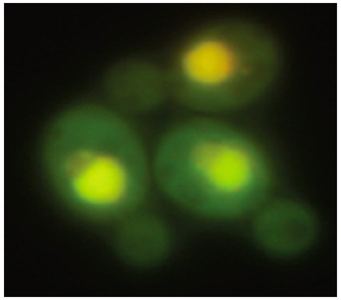
**Modeling / Simulation**

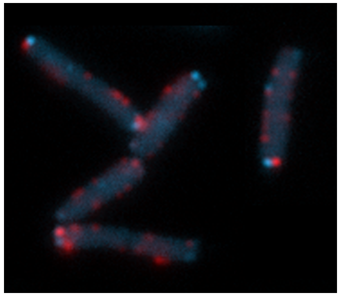
# Properties of cellular networks




## Network analysis:

- Network connectivity
- Real-time dynamics and signal processing
- Spatial organization and assembly
- Robustness to perturbations
- Regulation and micorevolution





## Model systems:

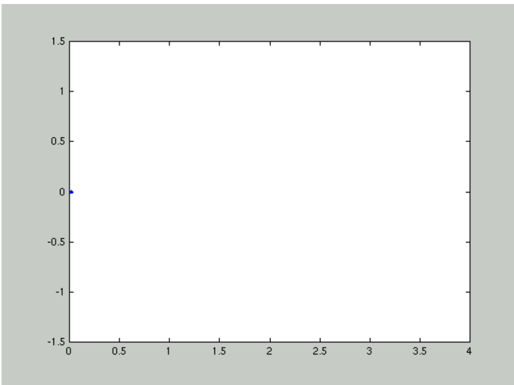
*E. coli*

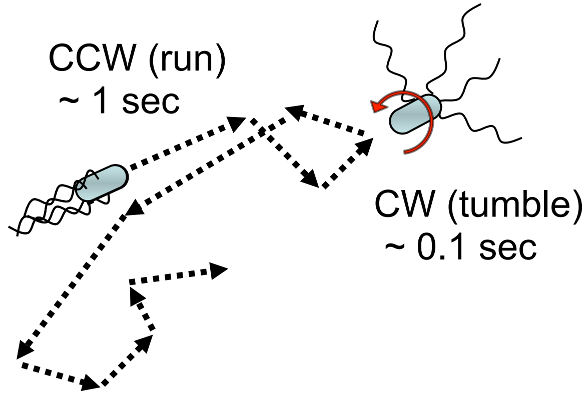
- Chemotaxis and motility
- Two-component sensors
- Sugar transport network
- Chaperone network
- Min system

*S. cerevisiae*

- Mating pathway

# *E. coli* chemotaxis as a model for simple behaviour




Adapted cells (no gradient)

Random walk

*Berg & Brown, Nature, 1972*

*Vladimirov et al., PLoS Comp Biol, 2008; 2010*

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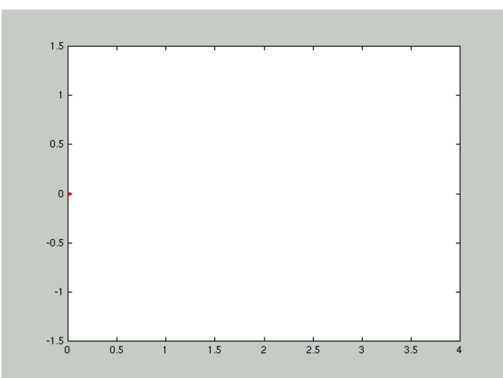
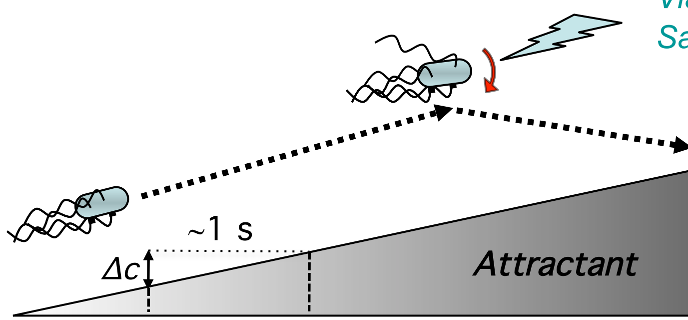
***Adjustment of tumbling angle***

*Vladimirov et al., PLoS Comp Biol, 2010*

*Saragosti et al., PNAS, 2011*




Cells in a gradient

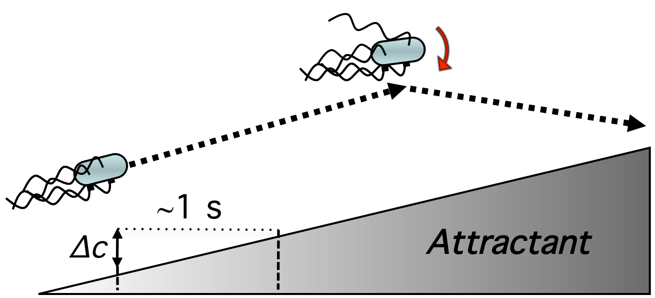
Biased random walk

***Direction-dependent adjustment of tumbling probability***

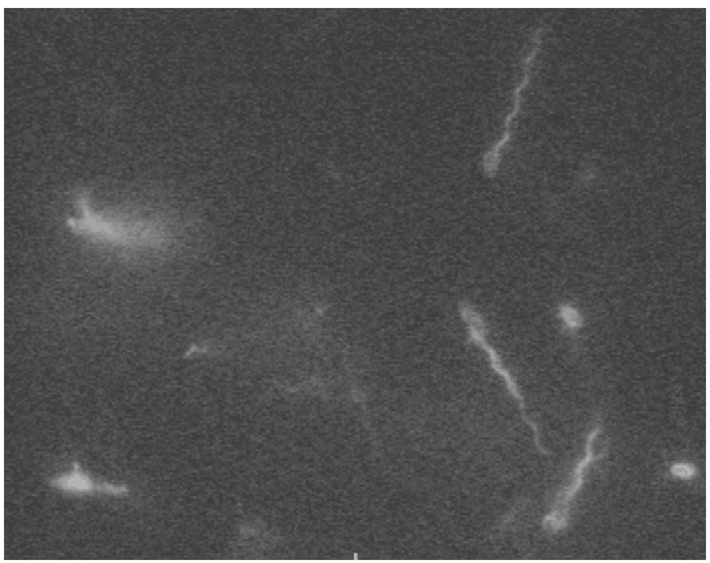
*Temporal comparison as optimal strategy for bacteria*

*Berg & Purcell, Biophys J, 1977*

# *E. coli* chemotaxis as a model for signalling



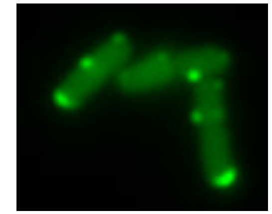

Sourjik & Wingreen, Curr Opin Cell Biol, 2012



Turner & Berg, 2000

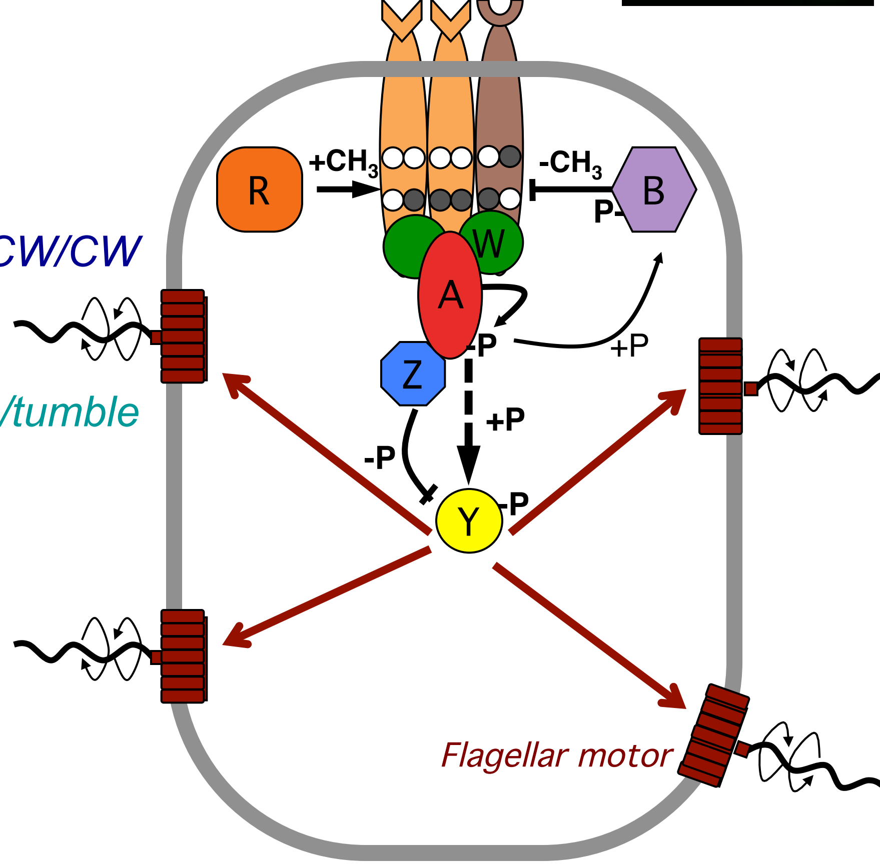
CheA: Kinase
CheY: Response regulator
CheZ: Phosphatase
CheW: Scaffold
CheR/B: Adaptation

Chemoreceptor clusters

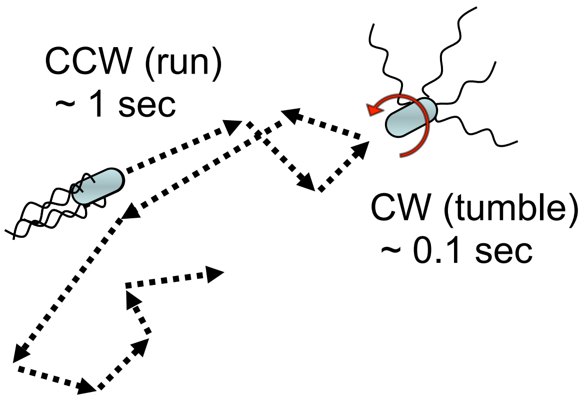


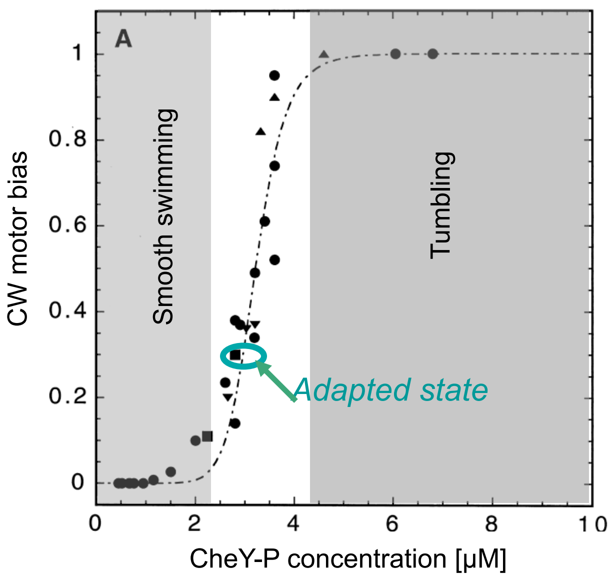
CCW/CW

Run/tumble



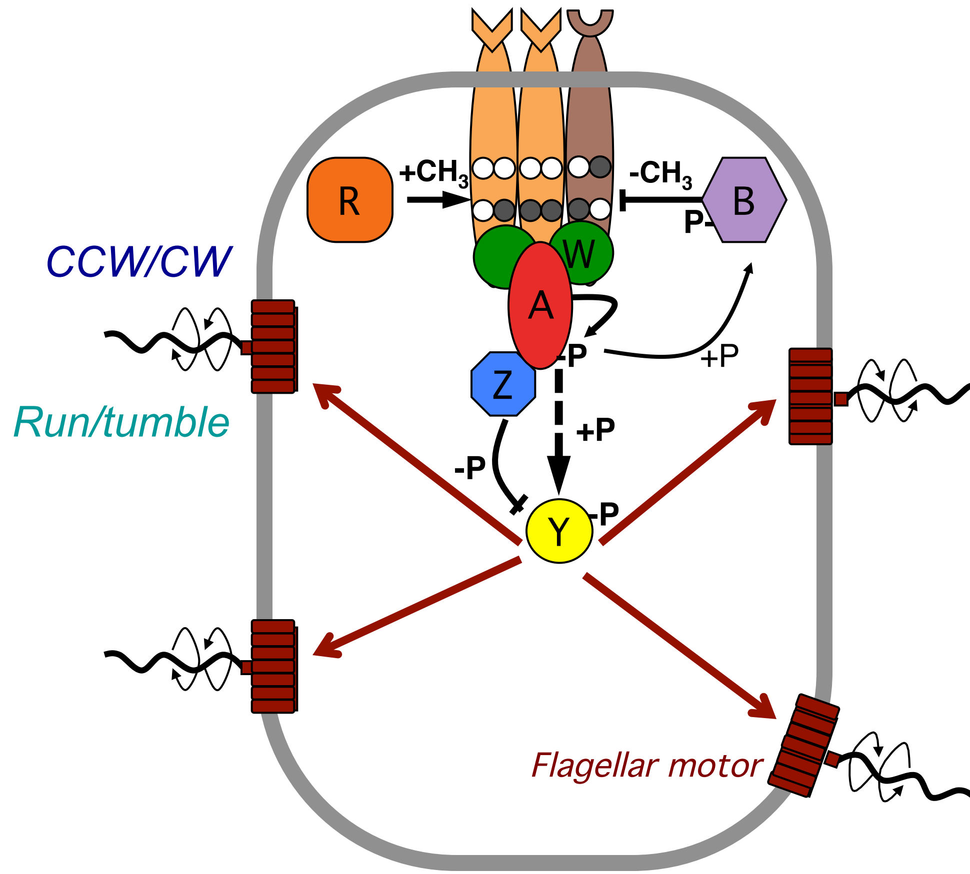
# *E. coli* chemotaxis as a model for signalling



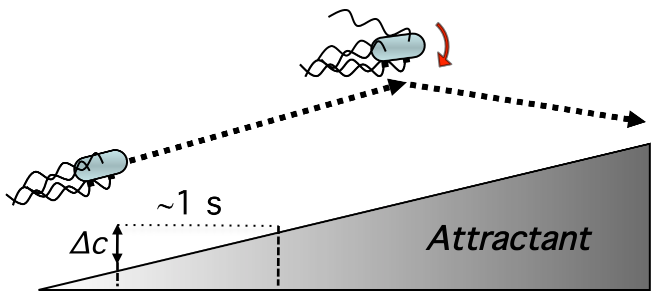



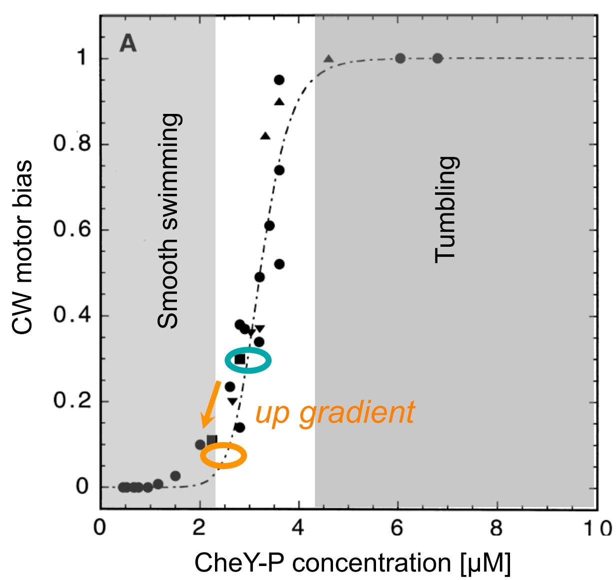

*Cluzel et al, 2000*

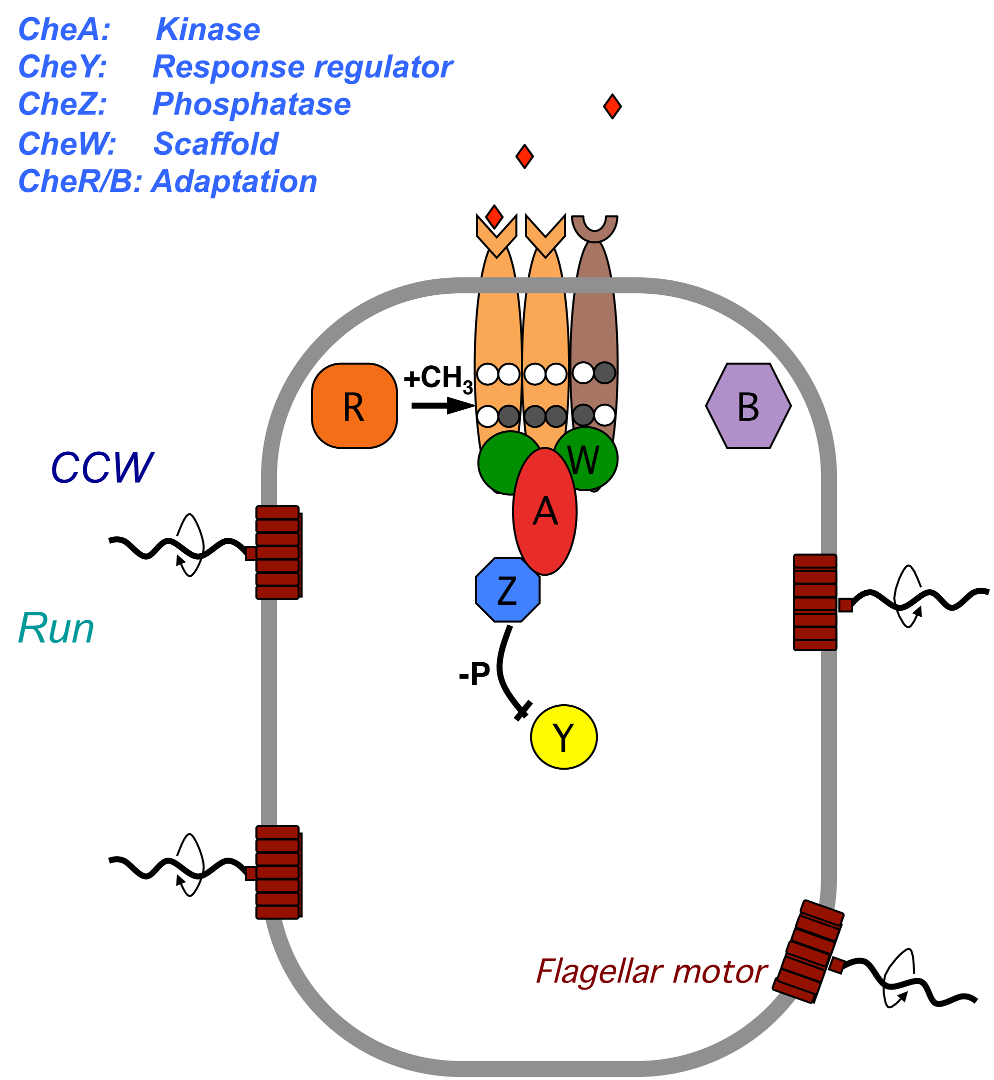
***CheA: Kinase***
***CheY: Response regulator***
***CheZ: Phosphatase***
***CheW: Scaffold***
***CheR/B: Adaptation***



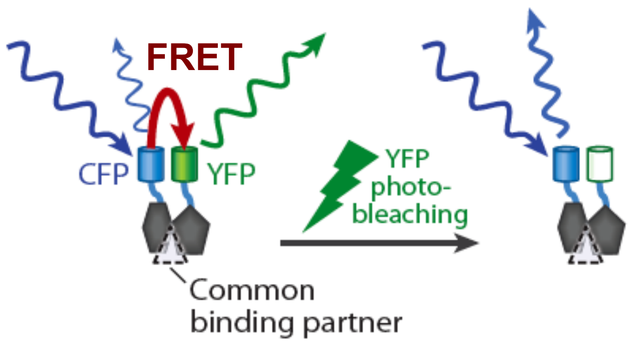
# *E. coli* chemotaxis as a model for signalling

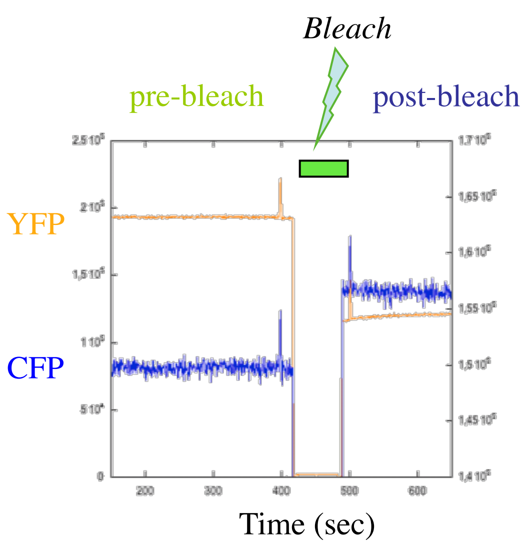


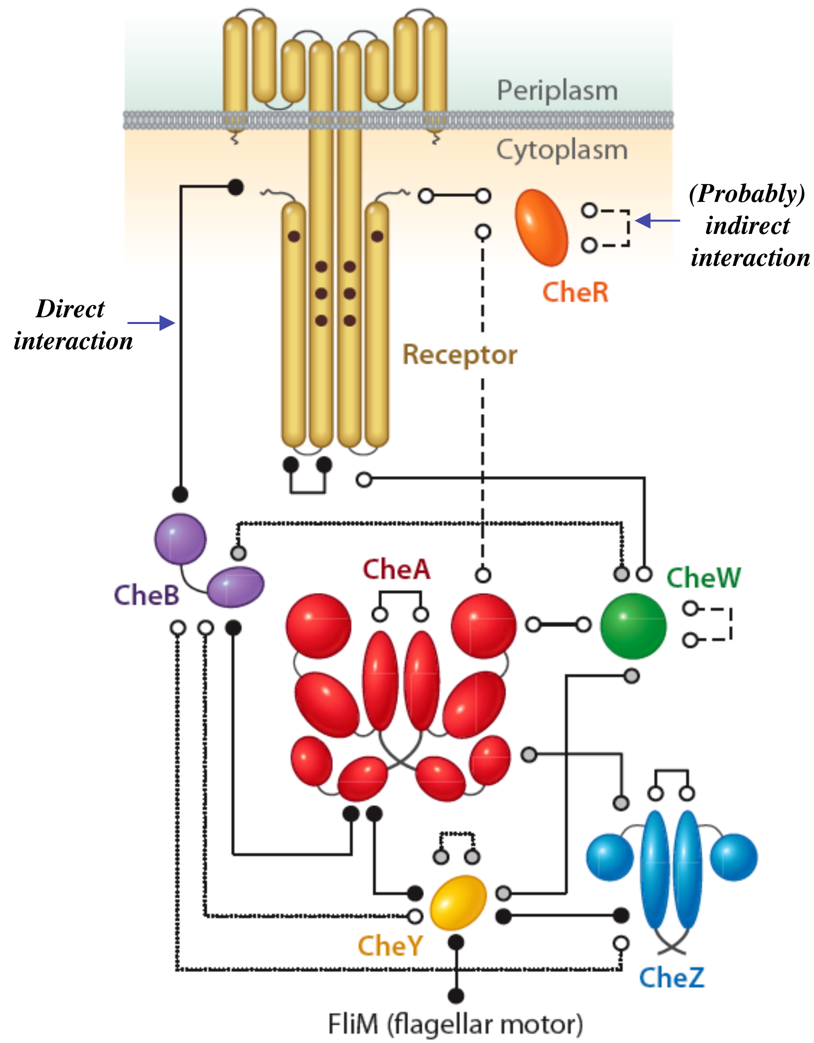



# Mapping network interactions by FRET

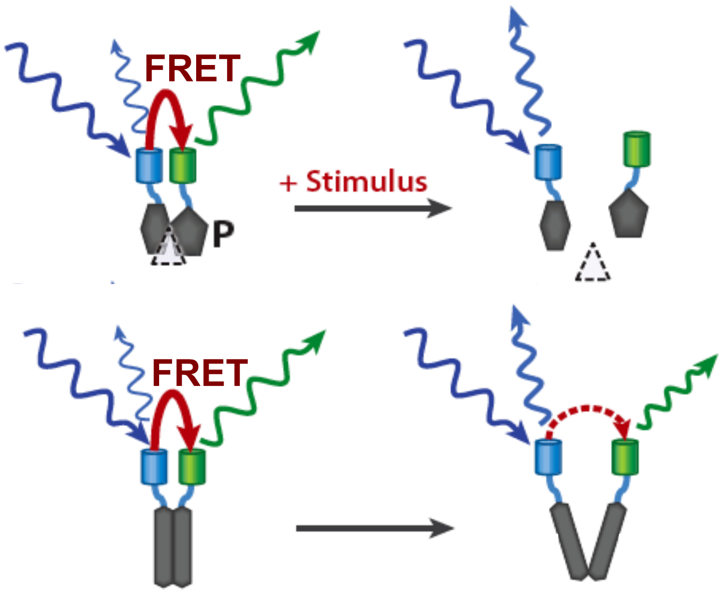


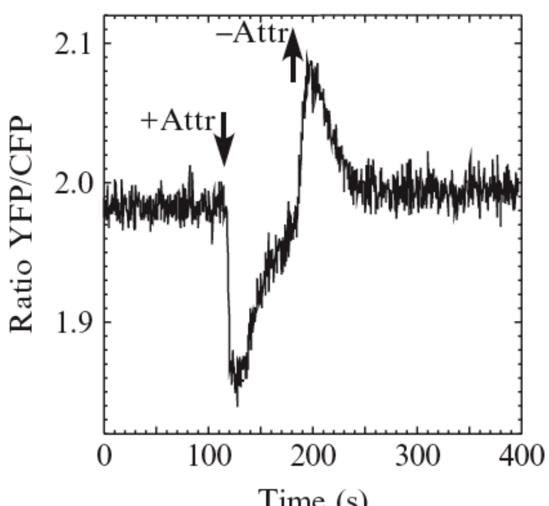



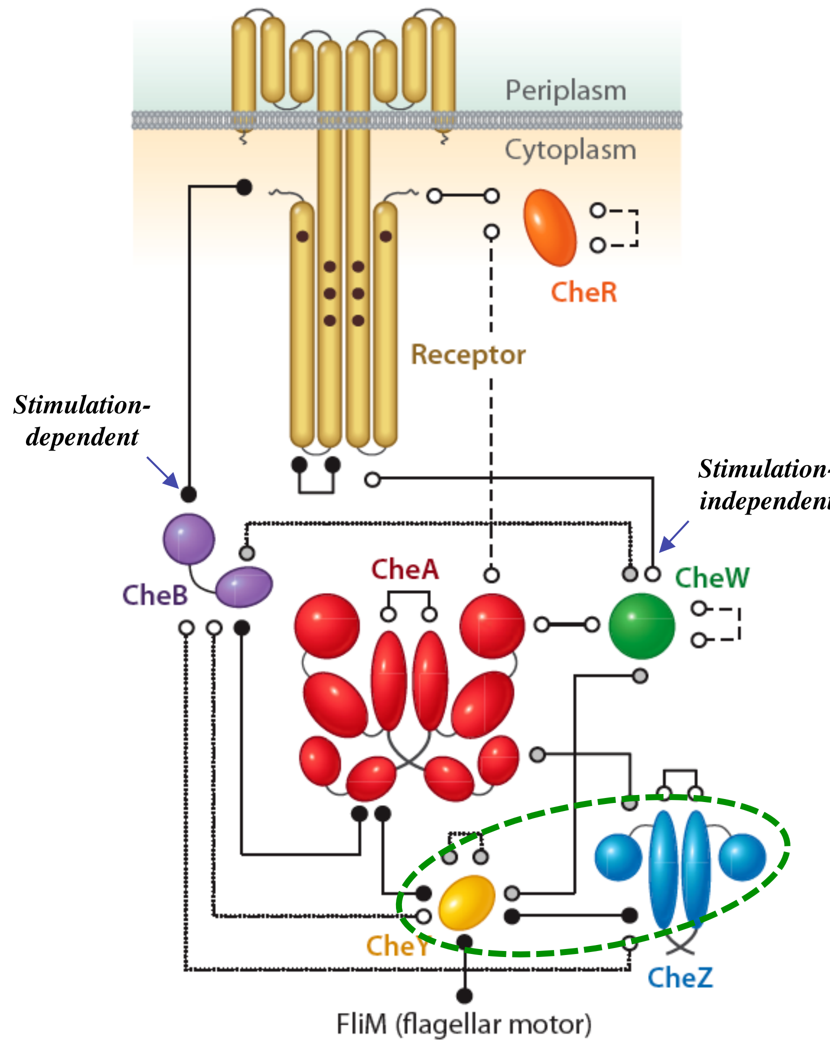

*Sourjik & Berg, PNAS, 2002a,b*
*Kentner & Sourjik, Mol Syst Biol 2009*
*Kentner & Sourjik, Annu Rev Microbiol 2010*

# Studying network dynamics by FRET




CheY/CheZ FRET



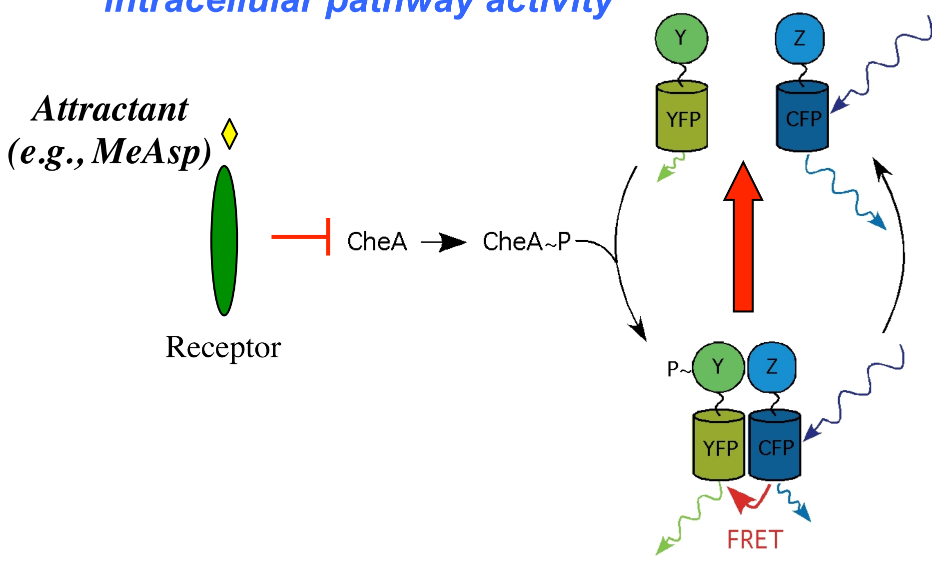

*Signal processing and response kinetics*

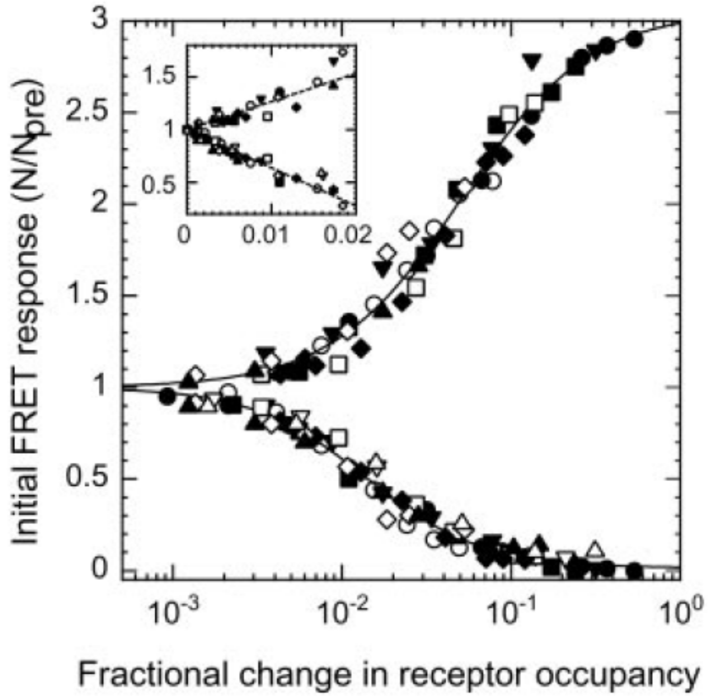
*=> Computational analysis*

# Dose-response relationship in chemotaxis

***~20-30 fold signal amplification by the cluster***

***FRET-based readout of intracellular pathway activity***

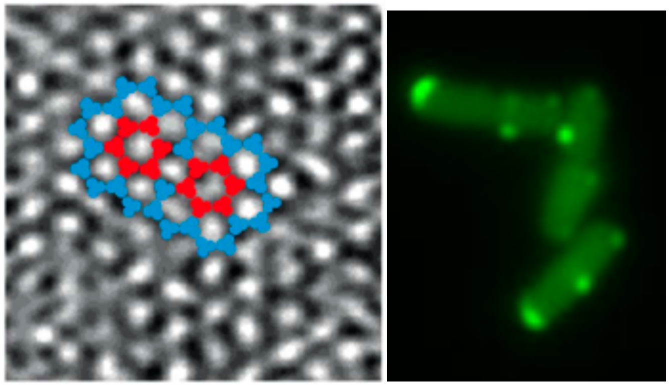


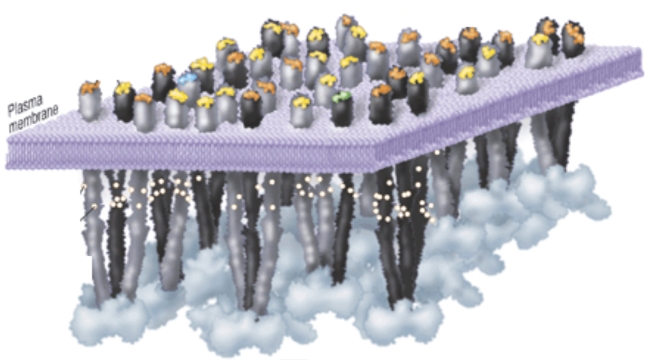

***Where does this amplification come from?***

*Sourjik & Berg, PNAS, 2002*

# Signal amplification in receptor clusters

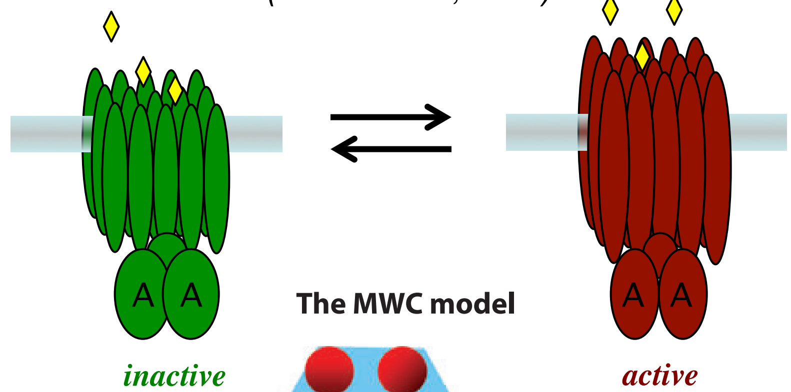


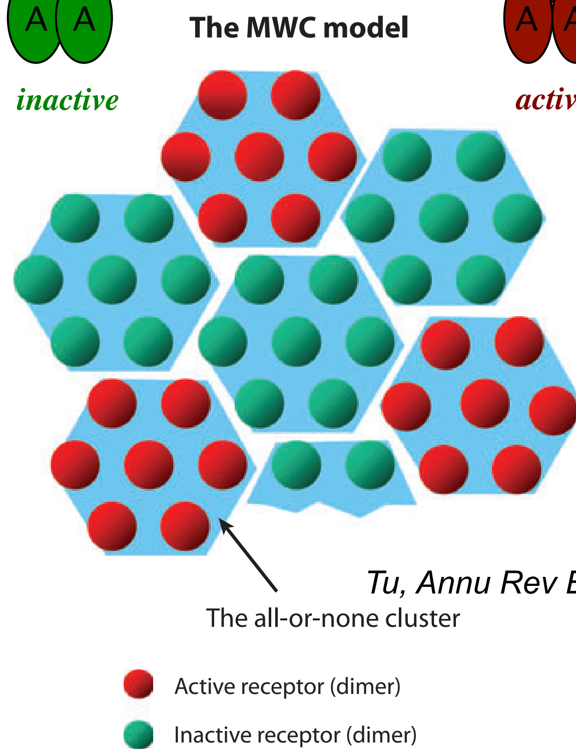
Maddock & Shapiro, Science, 1993
Sourjik & Berg, Mol Microbiol, 2000
Briegel et al., Mol Microbiol, 2009




Bray, Science, 20001

**Monod-Wyman-Changeaux (MWC) model**
(Monod et al., 1965)



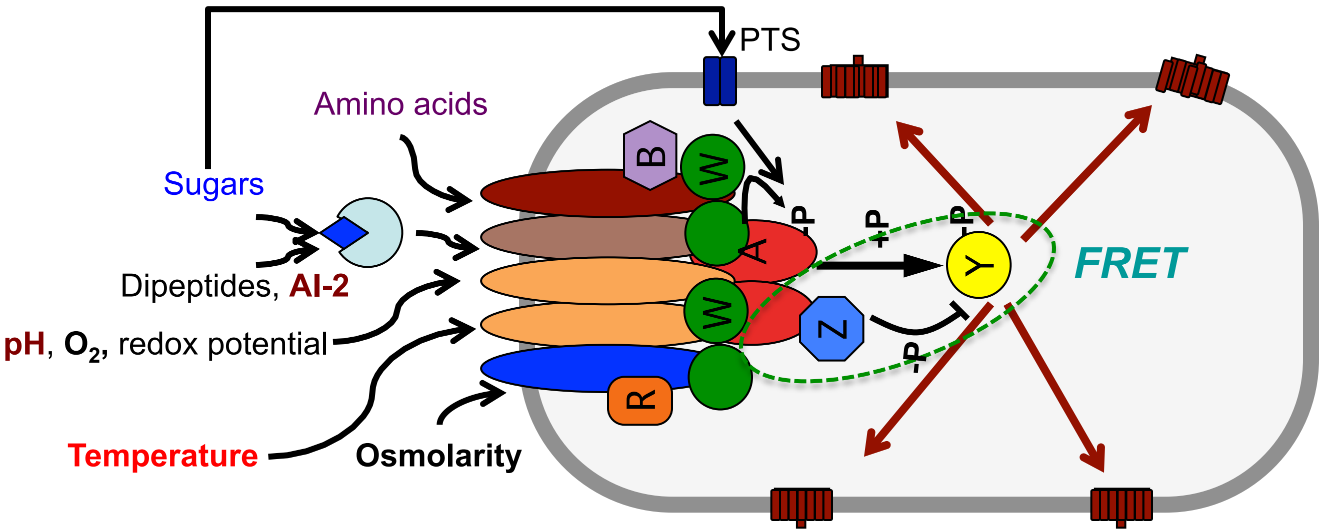



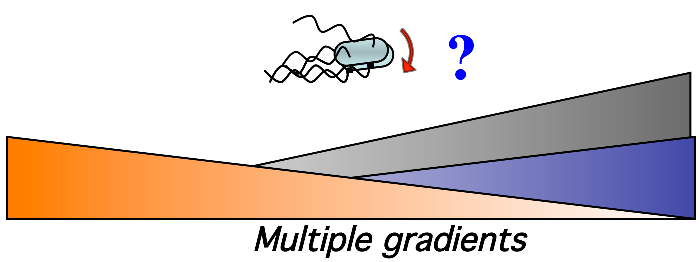

Tu, Annu Rev Biophys, 2013

**Sensitivity to small stimuli ~ N**

Sourjik & Berg, Nature, 2004; Mello & Tu, PNAS, 2005; Keymer et al., PNAS, 2006

# Integration of chemotactic stimuli




***Signal integration:***

*Net response is determined by the net energy change due to ligand binding*

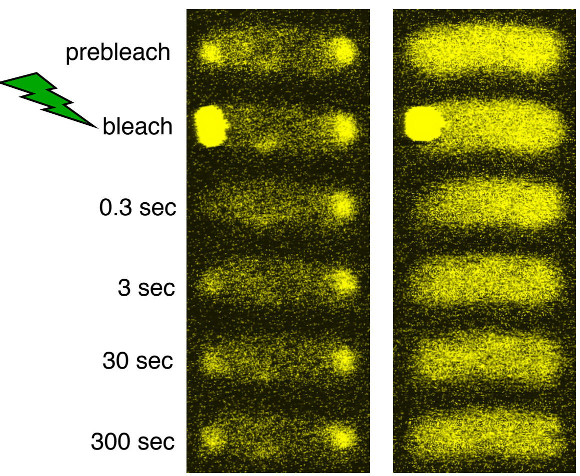
$\Sigma\delta(\Delta f_i)$

*Neumann et al., EMBO J, 2010; Kalinin et al., J Bacteriol, 2010; Neumann et al., PNAS, 2012; Yang & Sourjik, Mol Microbiol, 2012*

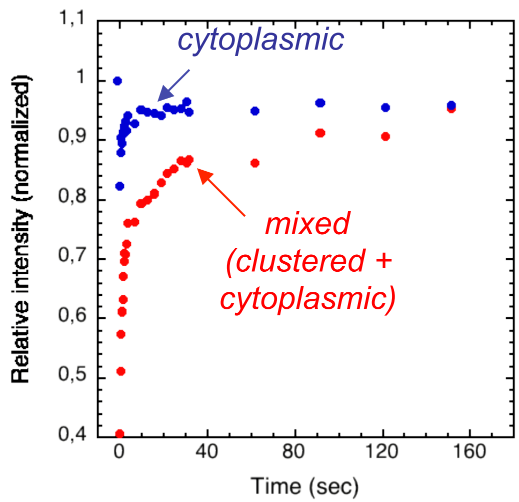
# Mapping complex stability and protein mobility by FRAP

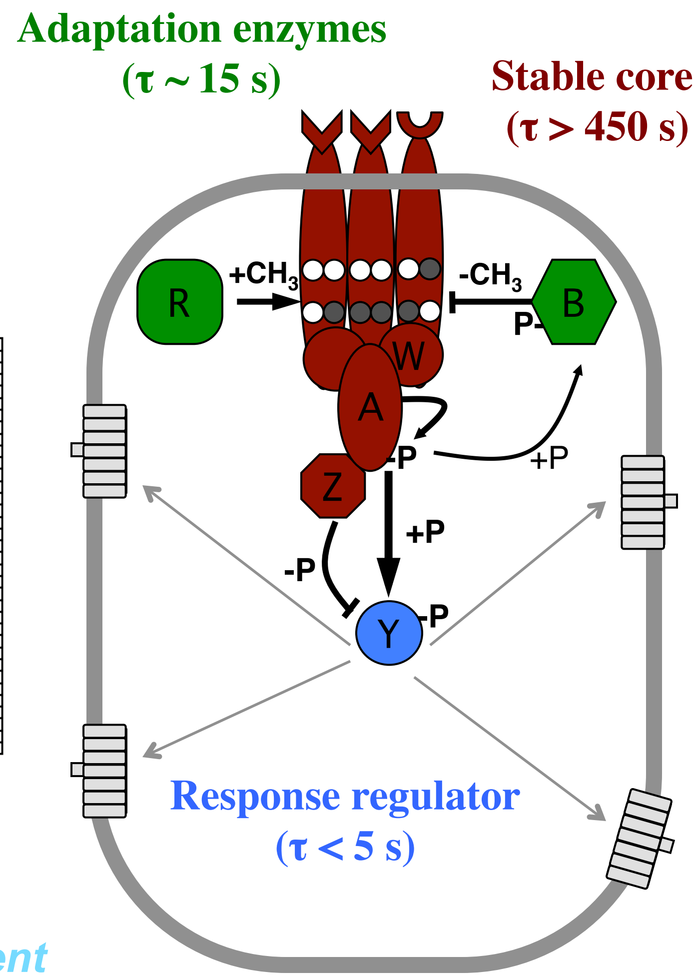
- ***Protein exchange rates***
- *Diffusion coefficients*

*FRAP*




***Recovery kinetics***

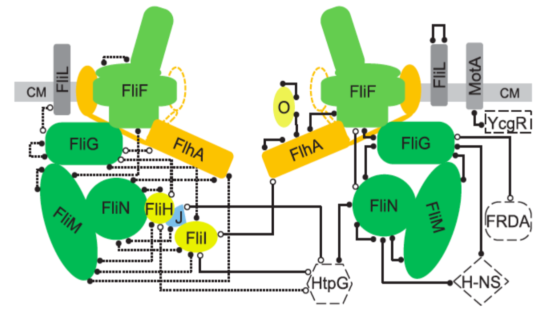



- ***Exchange times match protein function***
- ***Complex stability is tuned by the environment***

*Schulmeister et al., PNAS, 2008*
*Schulmeister et al., BMC Microbiol, 2011*

# Application of FRET and FRAP to study other cellular networks in bacteria

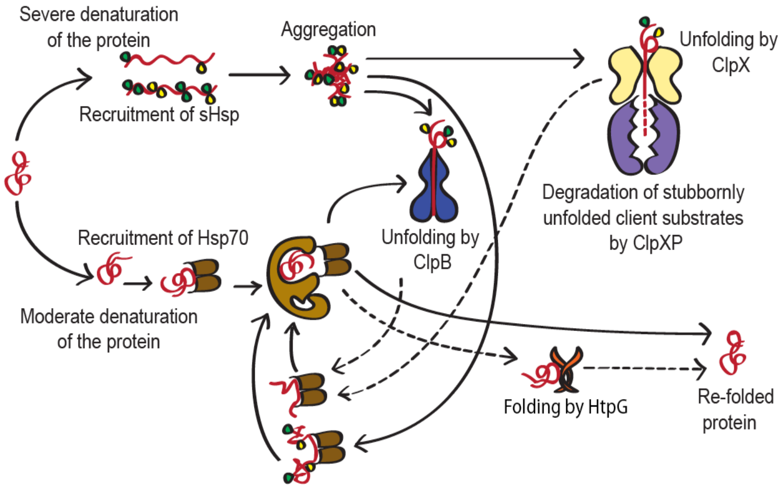



- *Assembly, dynamics and regulation of flagellar motor*

*Li & Sourjik., Mol Microbiol, 2011; Böhm et al., Cell, 2010; Zarbiv et al., J Mol Biol, 2012*
*Press et al., PLoS Pathog, 2013*

- *Assembly and dynamics of receptor clusters*

*Thiem et al., EMBO J, 2007; Schulmeister et al., PNAS, 2008; Schulmeister et al., BMC Microbiol, 2011*




- *Substrate processing by the chaperone network*

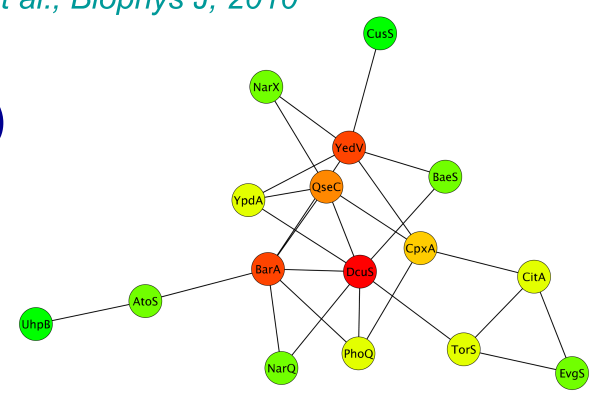
*Kumar & Sourjik, Mol Microbiol, 2012; Seyffer et al., NSMB, 2012*

- *Secretion through the Sec system*

*Kuhn et al, Traffic, 2011*

- *Size-dependence of protein mobility*

*Kumar et al., Biophys J, 2010*



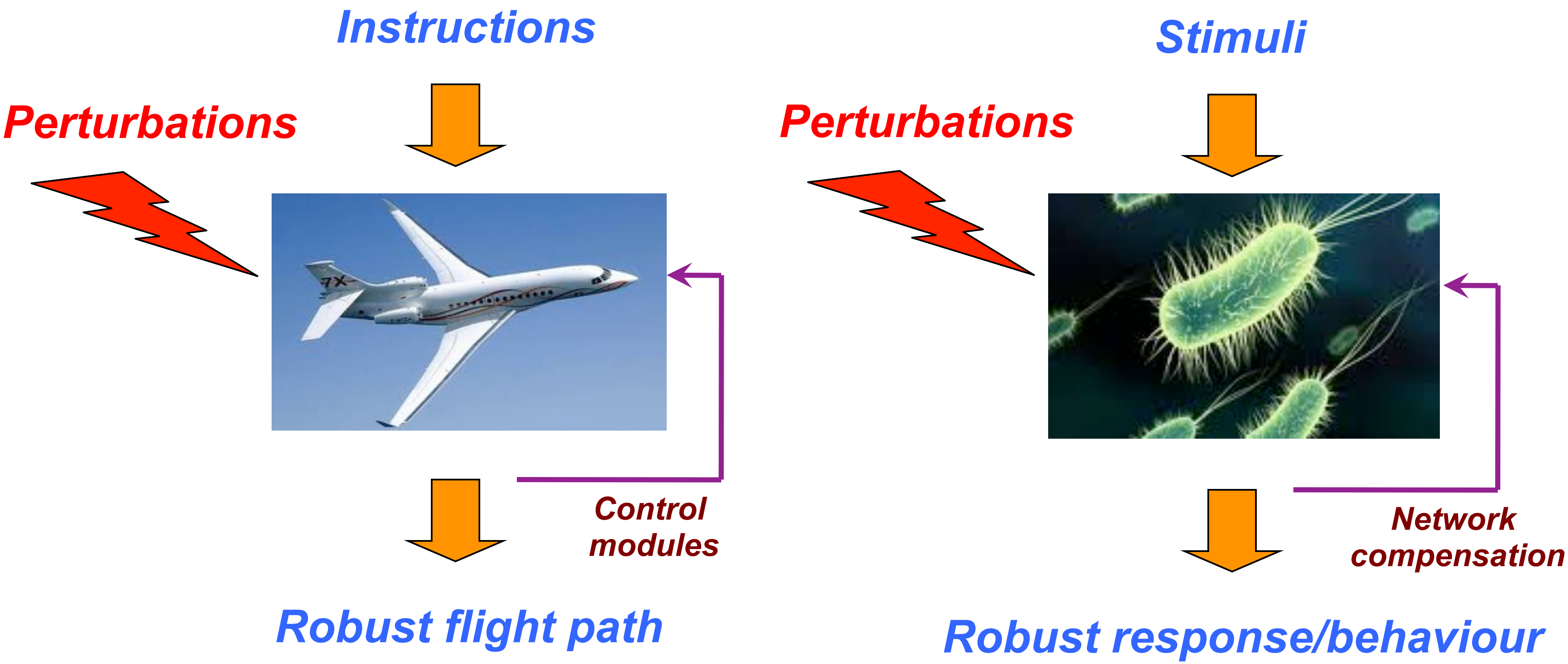

- *Network of two-component sensors (TCS)*

*Sommer et al., PLoS One, 2013; Sommer et al., in preparation*

- *Network of sugar transporters*

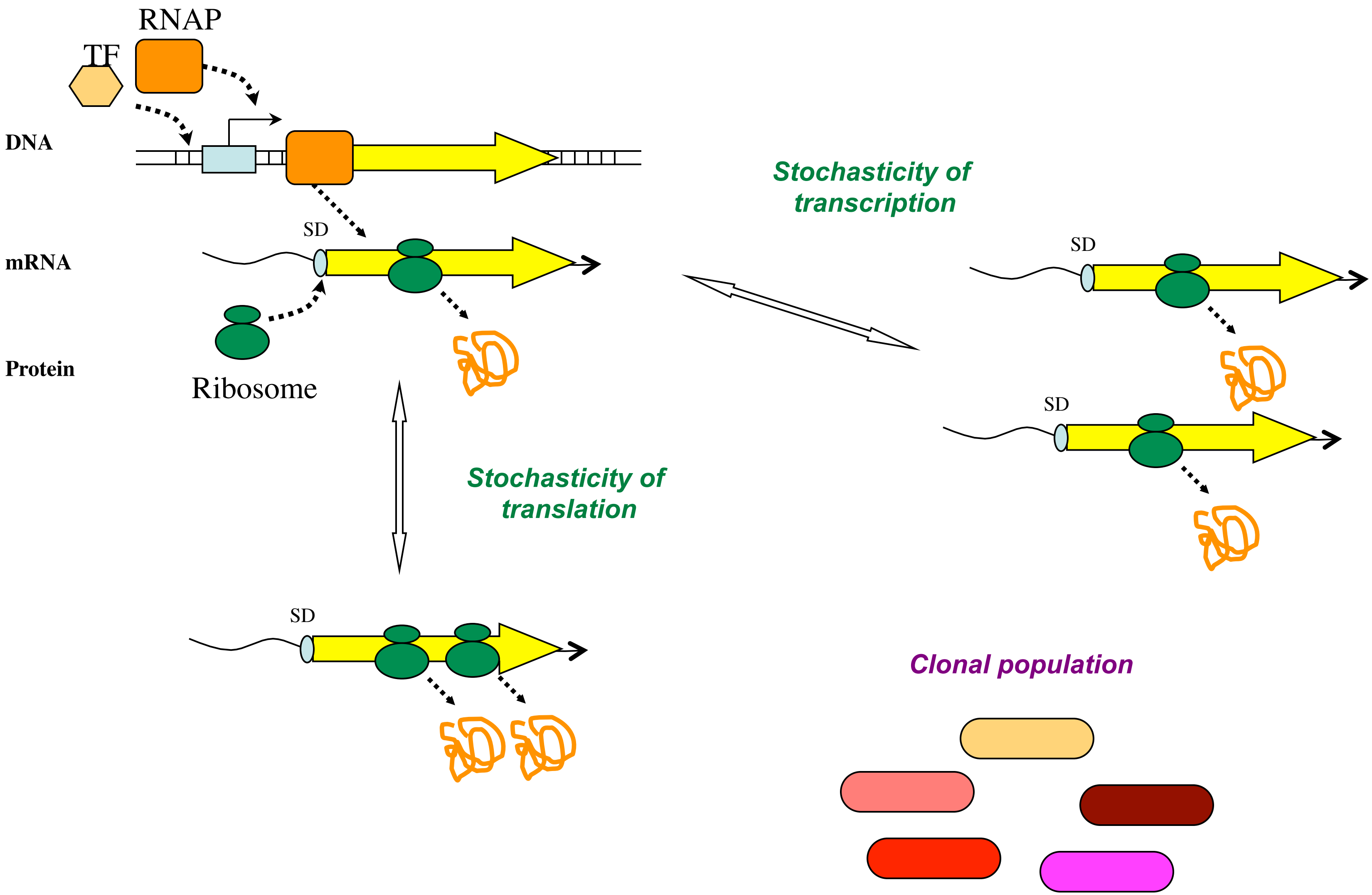
*Grosse et al., in preparation*

# Robustness as a fundamental property of both designed and evolved systems

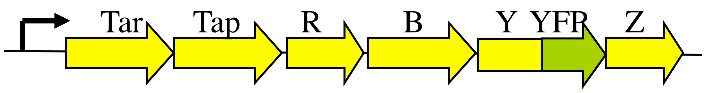


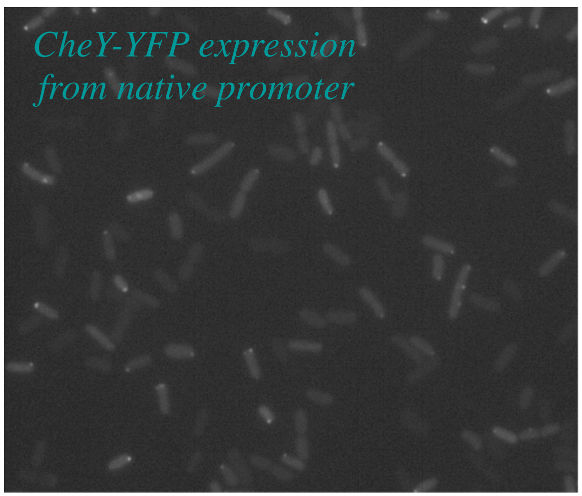

*Kitano, 2004*
*Carlson & Doyle, 2002*
*Yi et al., 2000*
*Barkai & Leibler, 1997*

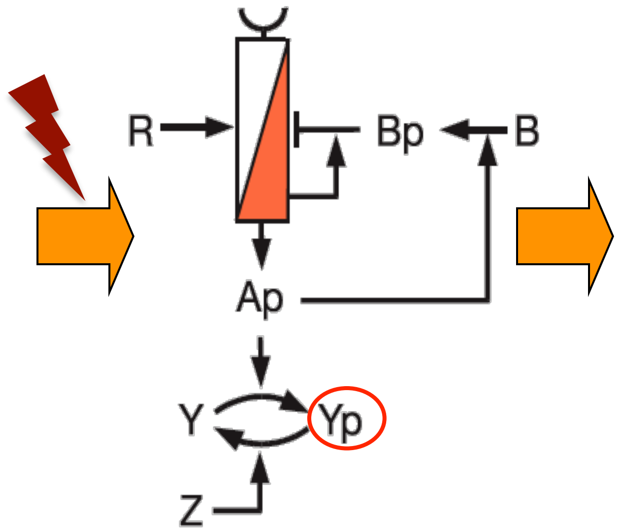
# Stochastic variations in protein levels (*gene expression noise*)



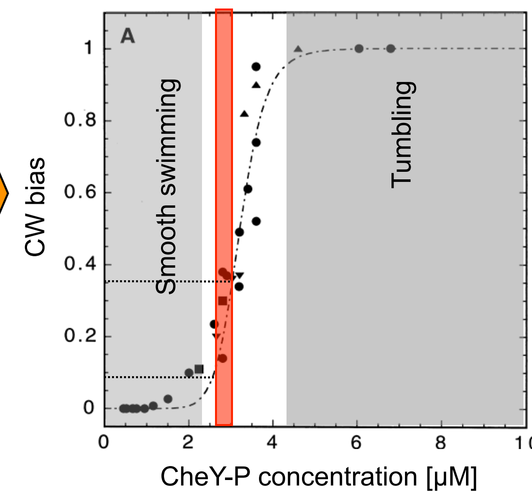
# Robustness against gene expression noise




Kollmann et al., Nature, 2005



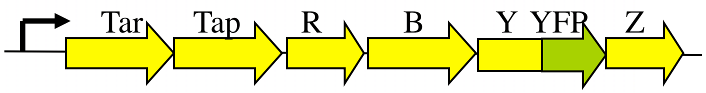

***Variable gene expression across population***

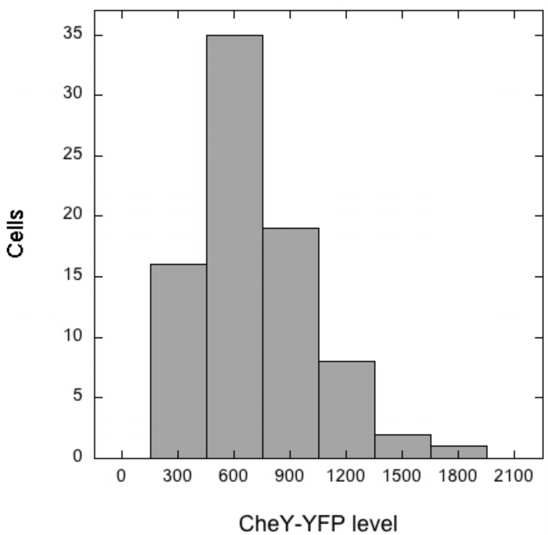
*= gene expression noise*

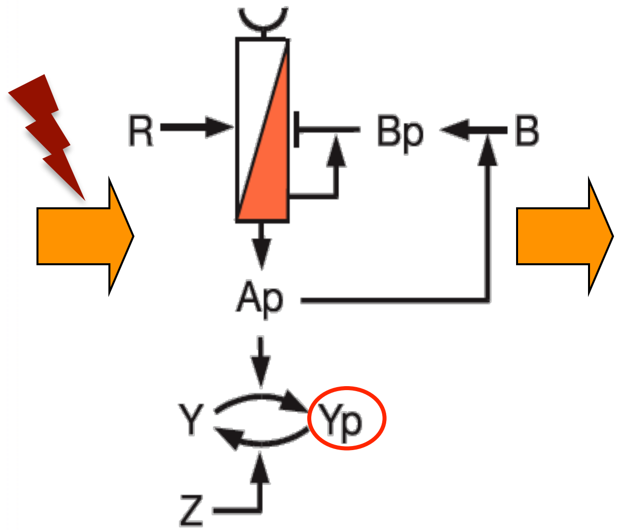
***Robust output***

# Robustness against gene expression noise

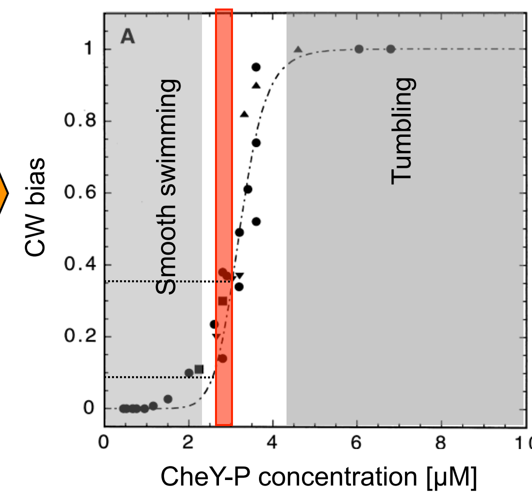
*Noise compensation mechanisms?*




*Kollmann et al., Nature, 2005*

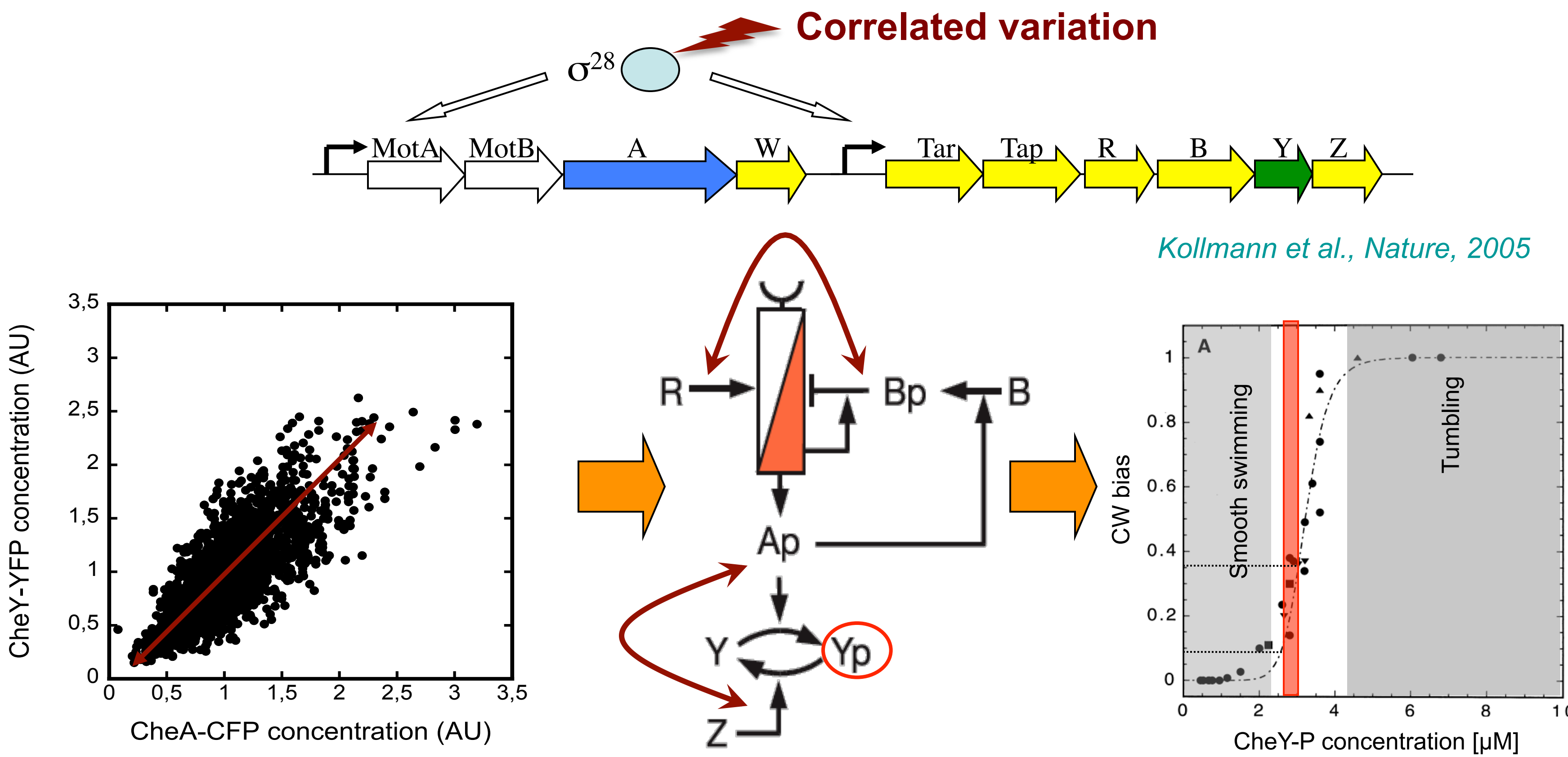



***Variable gene expression across population***

*= gene expression noise*

***Robust output***

# Noise compensation mechanisms

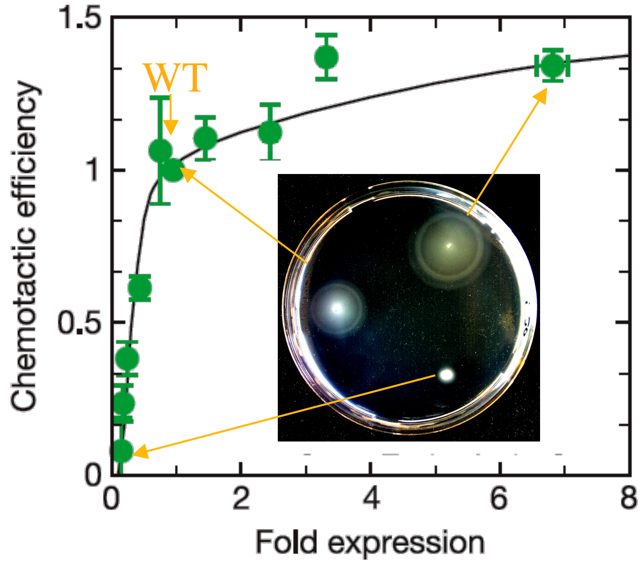



•*Coupled gene expression*

•*Opposing enzymatic activities*

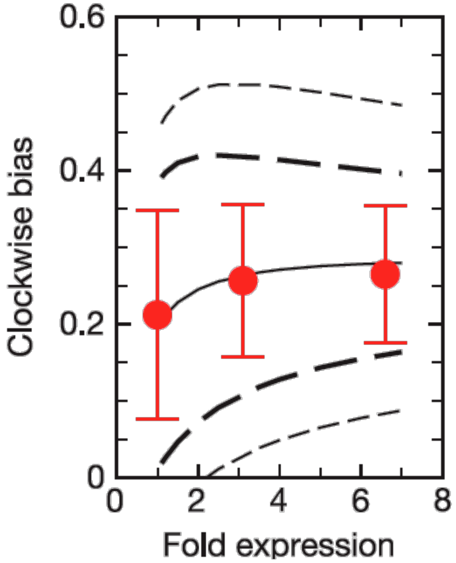
=> *Output is robust against correlated transcriptional noise*

# Steady-state output is robust against co-variation in protein levels

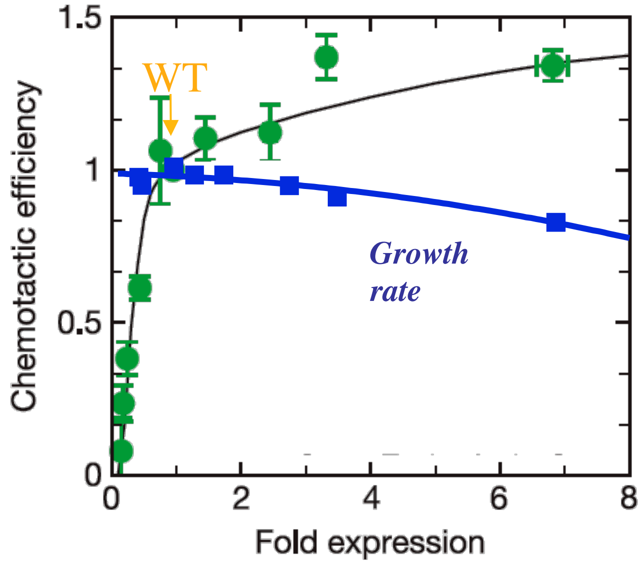



*(all chemotaxis proteins)*

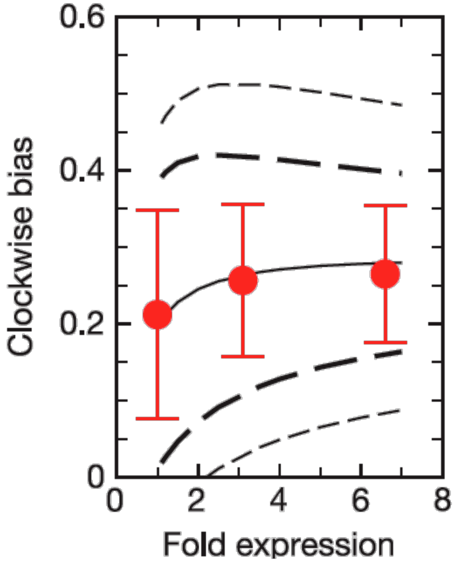
*Kollmann et al., Nature, 2005*



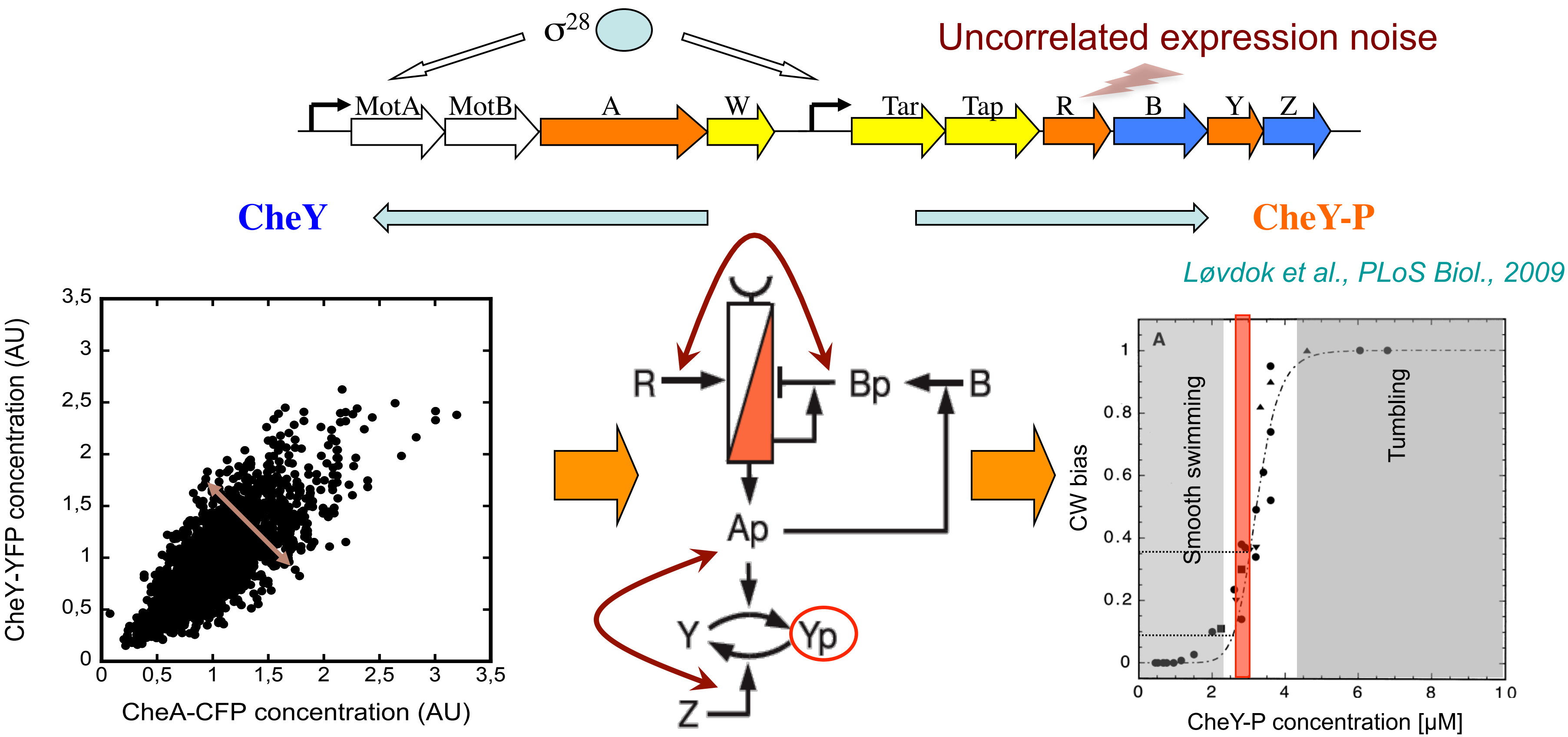
# Endogenous protein levels as a trade-off between robustness and growth




*(all chemotaxis proteins)*



# Robustness against uncorrelated variation

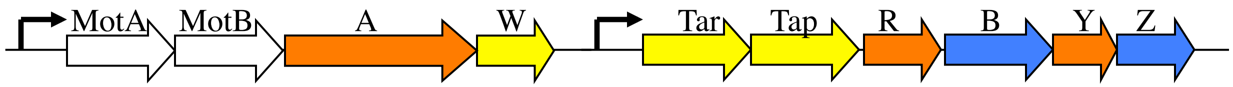



***•Translational coupling of opposing activities***

***•Evolutionary selected gene order***

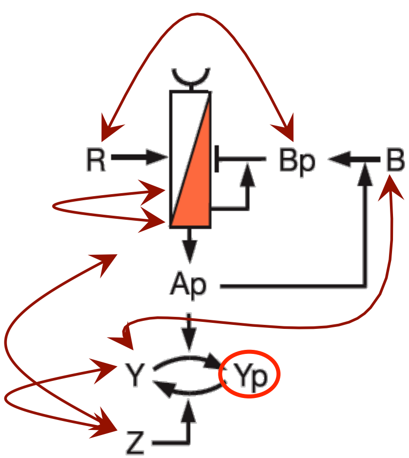
*⇒ Robustness against translational noise*

# Conserved gene order in chemotaxis operons



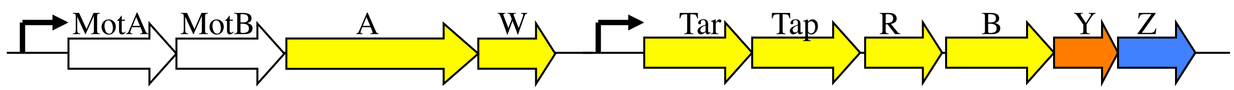

Løvdok et al., PLoS Biol., 2009

**Coupling of counteracting proteins**

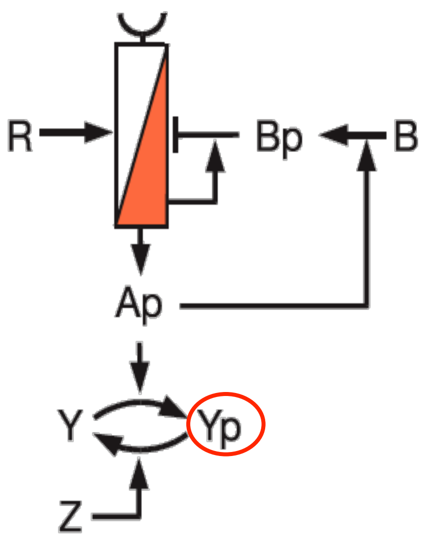


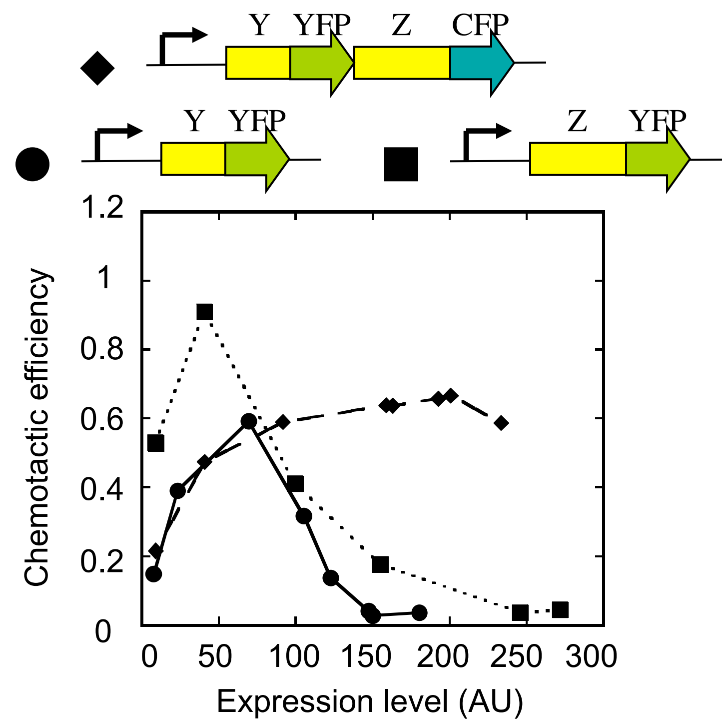

| | *cheA* (771) | | *cheW* (1232) | | *cheR* (802) | | *cheB* (656) | | *cheY* (1376) | | *cheZ* (209) | | *mcp*[b] (6521) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | left | right | left | right | left | right | left | right | left | right | left | right | left | righ |
| *cheA* | 1.0 | <1 | **19.6** | 3.2 | 2.7 | 2.2 | 14.8 | 8.6 | <1 | 7.7 | <1 | **32.5** | <1 | <1 |
| *cheW* | 7.4 | **37.8** | 5.9 | 5.6 | **20.8** | 7.2 | 5.2 | 1.4 | 2.3 | 2.8 | 0.0 | 0.0 | 4.0 | 3.0 |
| *cheR* | 2.3 | 3.9 | 4.6 | 13.7 | <1 | <1 | **28.6** | 10.7 | 1.9 | <1 | 0.0 | 0.0 | <1 | 2.0 |
| *cheB* | 5.2 | 15.1 | <1 | 2.7 | 8.6 | **26.1** | <1 | <1 | **7.2** | 2.3 | <1 | 0.0 | <1 | <1 |
| *cheY* | **15.7** | <1 | 3.4 | 2.3 | 1.4 | 3.1 | 4.9 | **15.0** | 1.9 | 1.7 | **90.0** | 0.0 | <1 | <1 |
| *cheZ* | 8.1 | <1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | <1 | **9.6** | 0.0 | 0.0 | <1 | 0.0 |
| *mcp* | 10.5 | 6.4 | 13.0 | **16.5** | 16.8 | 2.1 | 1.1 | 2.3 | 1.9 | 1.2 | 0.0 | <1 | **5.3** | **5.1** |

# Co-expression of counteracting proteins enhances robustness

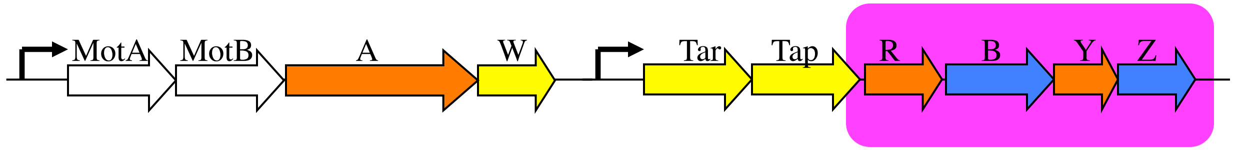



*Løvdok et al., J Biotechnol, 2007*

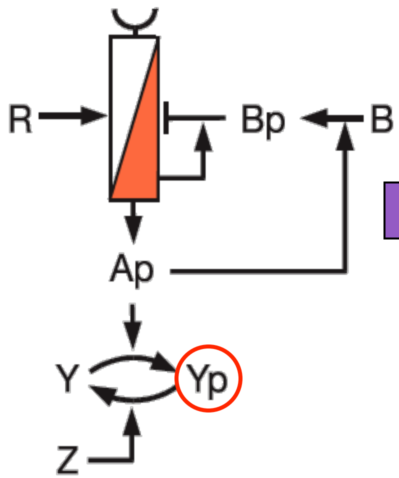


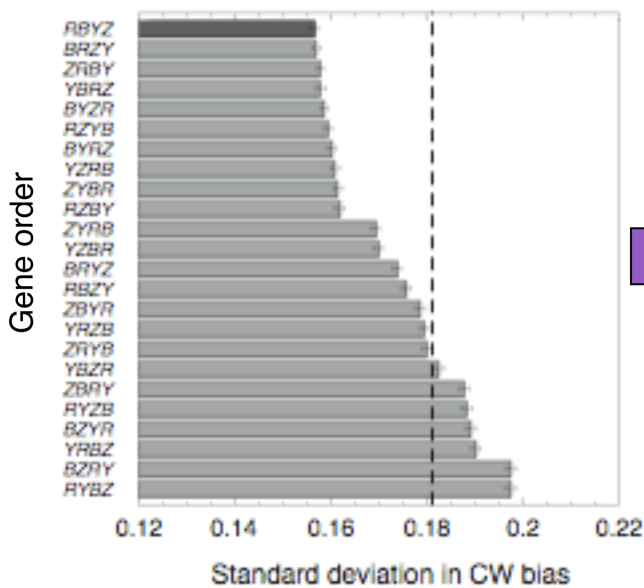



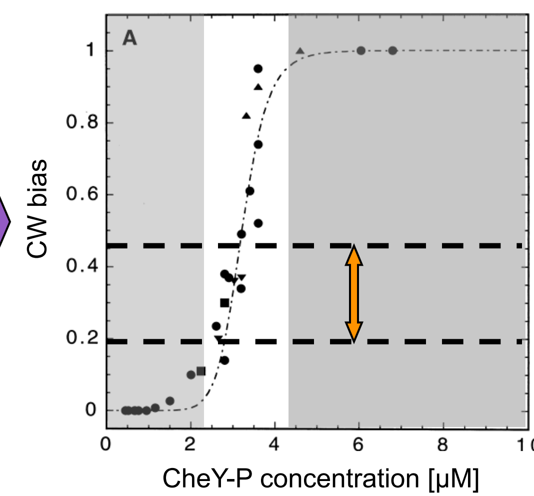
# Optimization for noise reduction can explain gene order




*Løvdok et al., PLoS Biol., 2009*



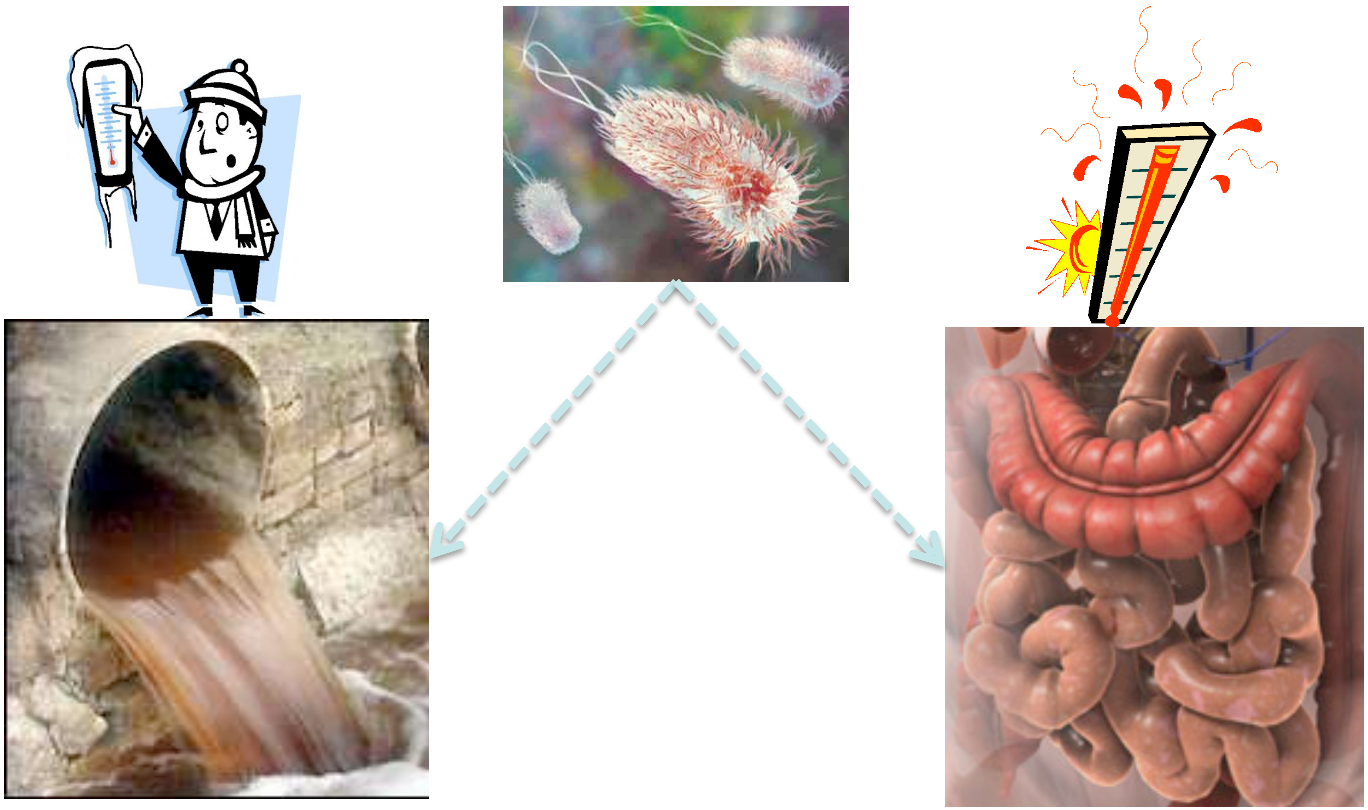




*Simulations including translational noise and translational coupling*
*(Kajetan Bentele and Markus Kollmann)*

# Thermal robustness of chemotaxis network

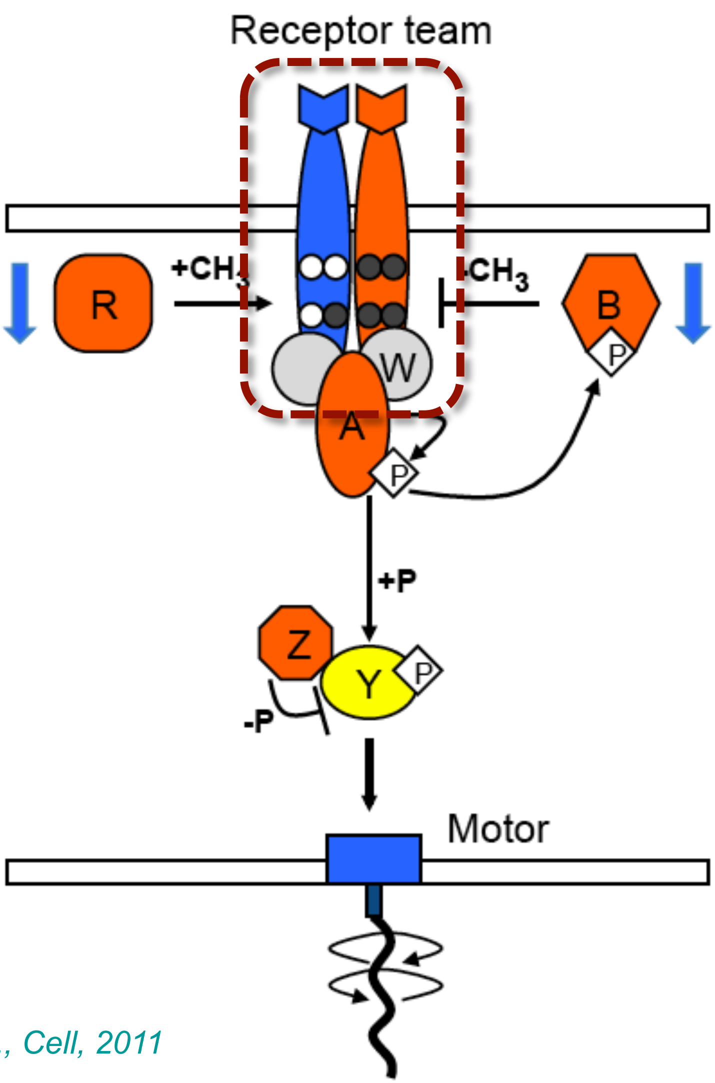
*Compensation of temperature effects on signalling?*

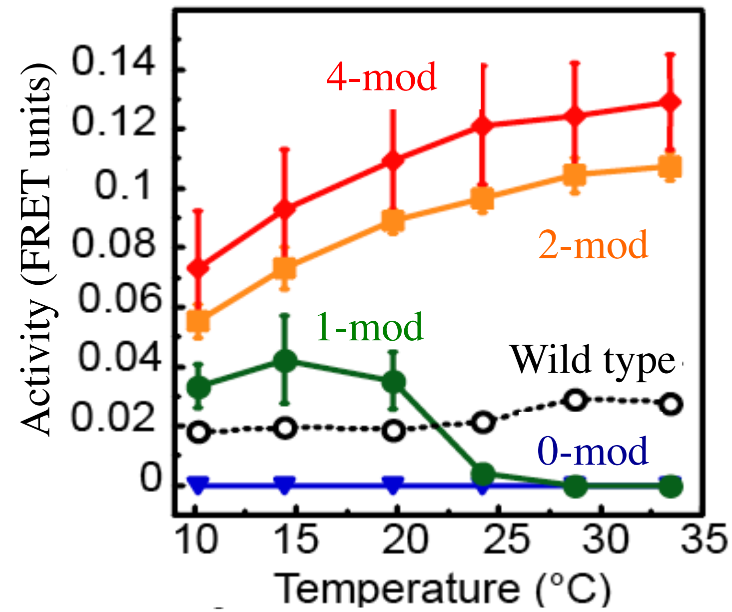


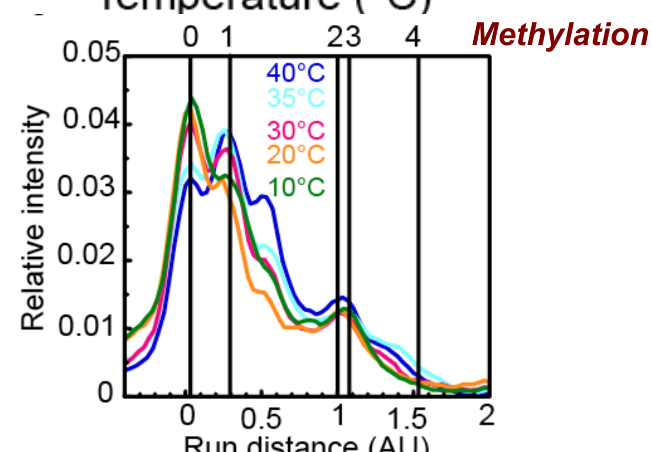
*Oleksiuk et al., Cell, 2011*

# Thermal robustness of steady-state output

*Opposing temperature effects on activities of individual receptors*



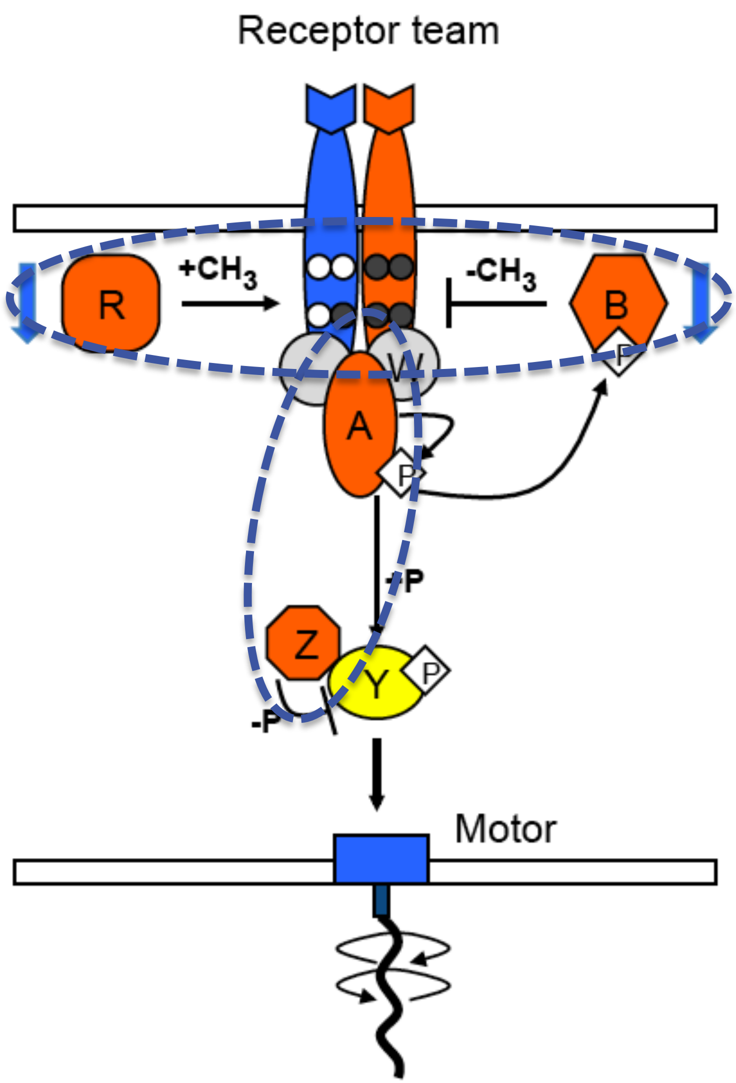



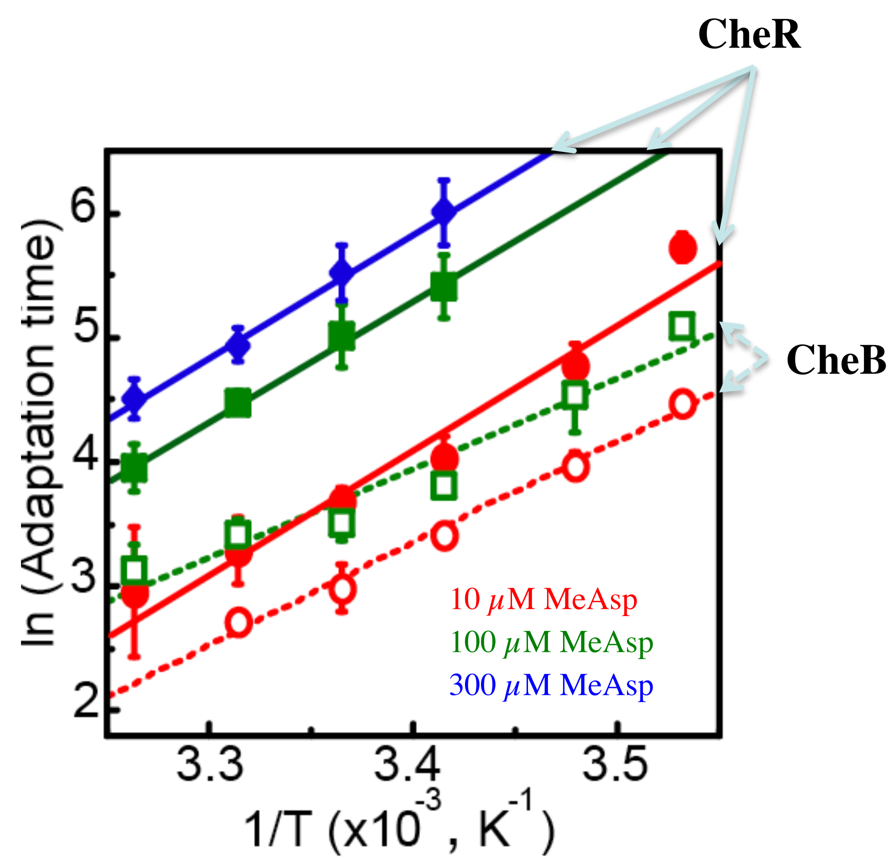




*Oleksiuk et al., Cell, 2011*

# Thermal robustness of steady-state output

*Similar temperature effects on kinetics of opposing enzymes*

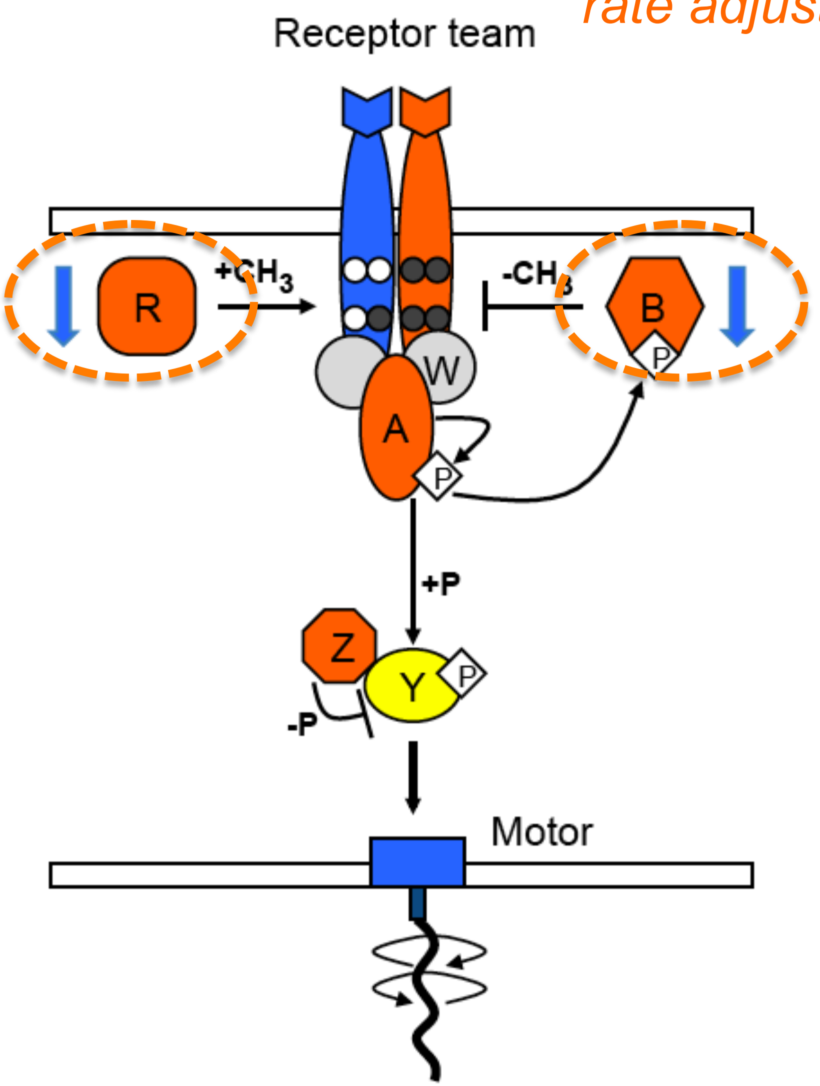


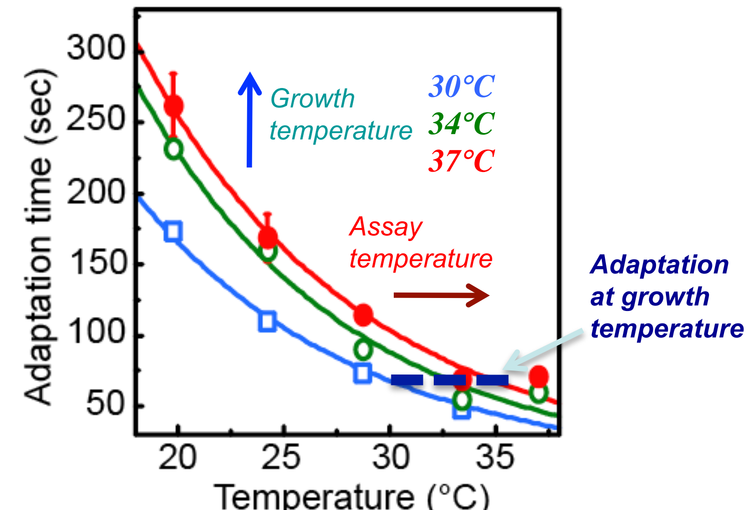



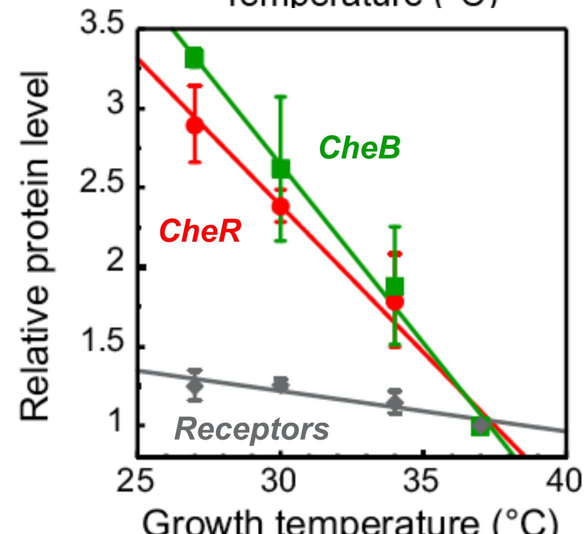

*Oleksiuk et al., Cell, 2011*

# Thermal robustness of adaptation kinetics

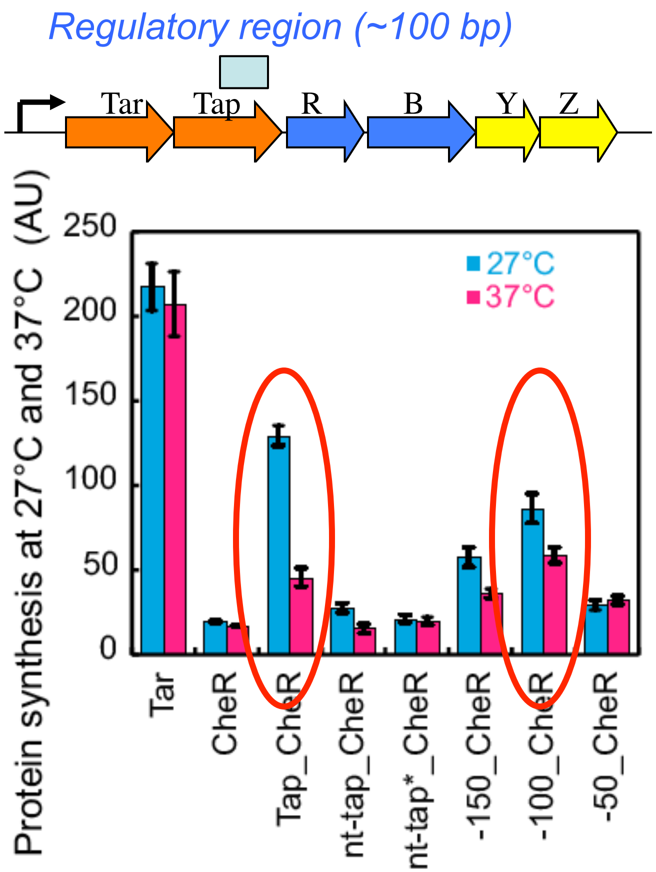
*Effects on kinetics are compensated by growth-temperature dependent rate adjustment*

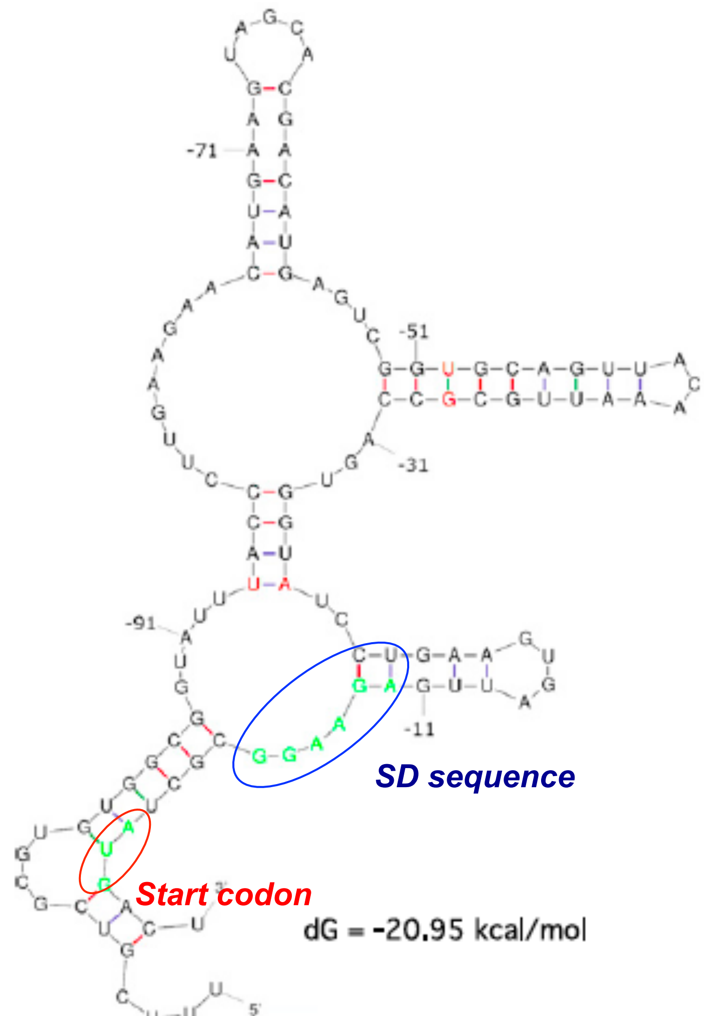


# Temperature-dependent translational regulation of CheR

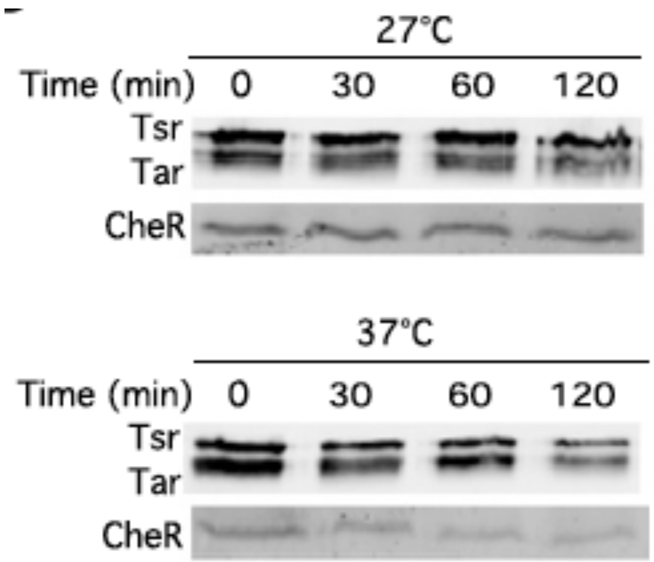


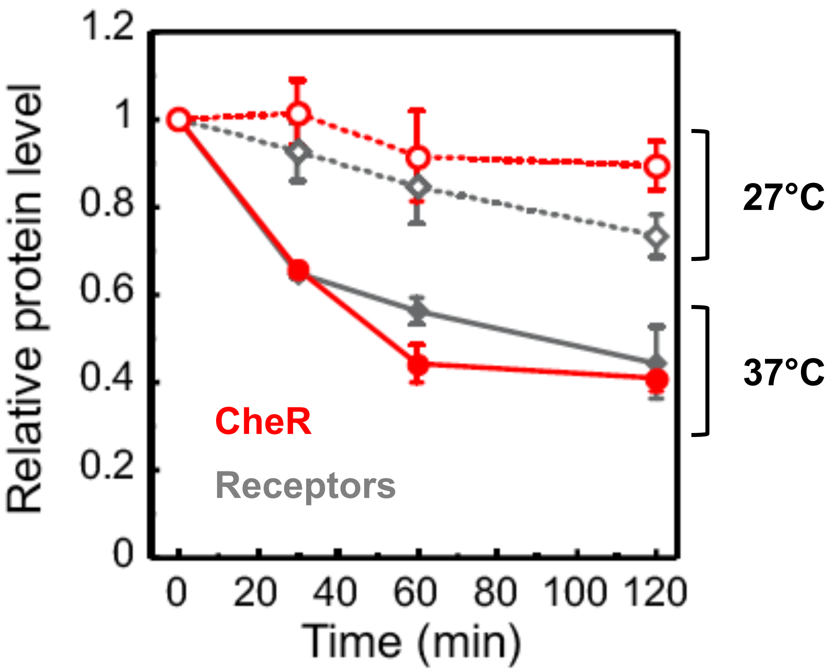




*Secondary mRNA sructure apparently enhances CheR translation at low temperatures*

*Oleksiuk et al., Cell, 2011*

# Temperature-dependent enhancement of CheR proteolysis



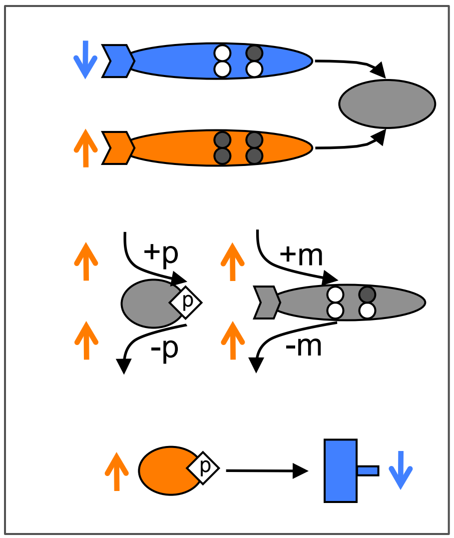

*High temperature disproportionally increases CheR proteolysis*

*Oleksiuk et al., Cell, 2011*

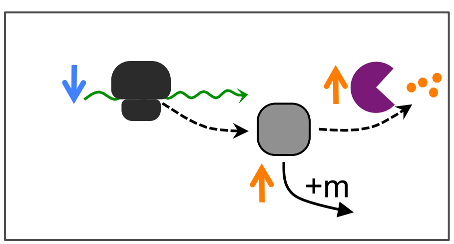
# Thermal robustness in biological and man-made systems

**Compensatory motifs in chemotaxis**

*Steady state output*




*Kinetics*

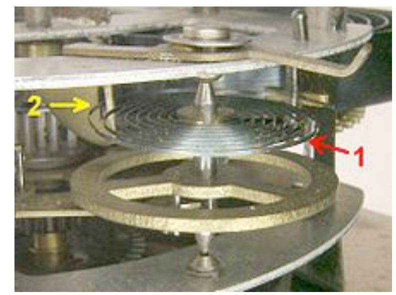



***Thermal compensation***

***Anticipatory optimal adjustment of function***

**Compensation in mechanical systems**

*Balance spring in clocks*

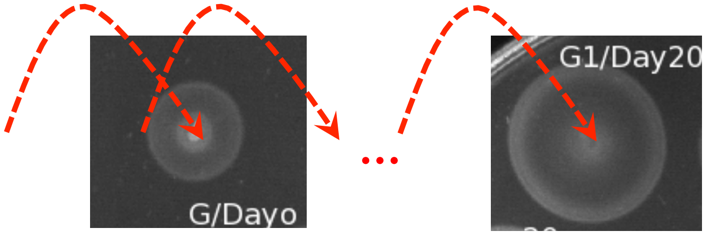


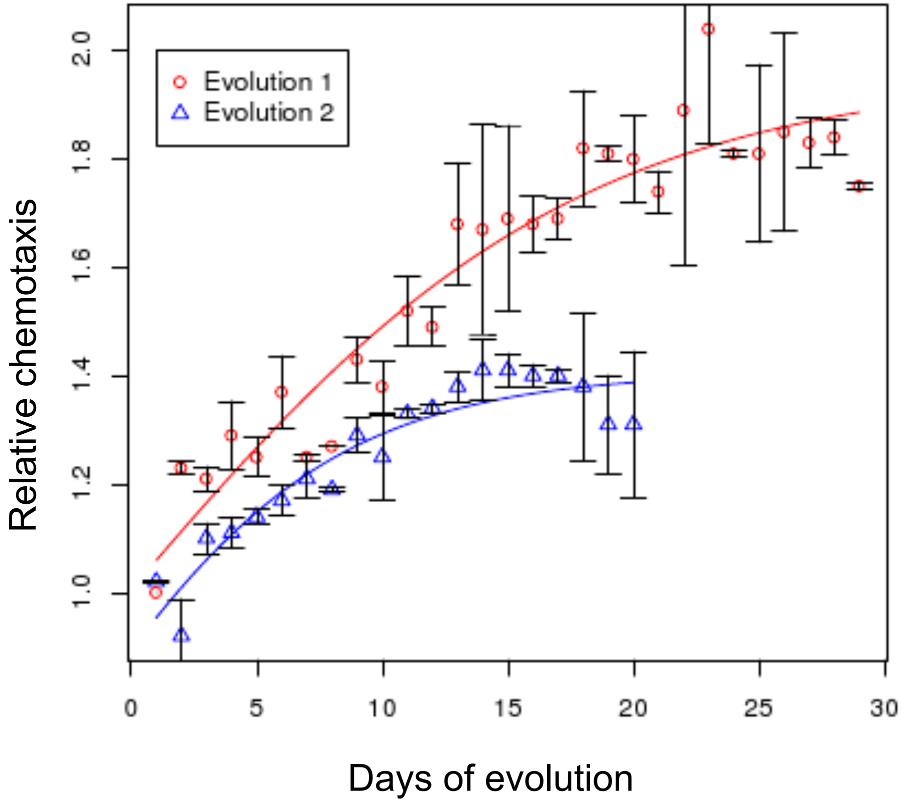

***2 Metals: Expanding / contracting***

*Car engine*

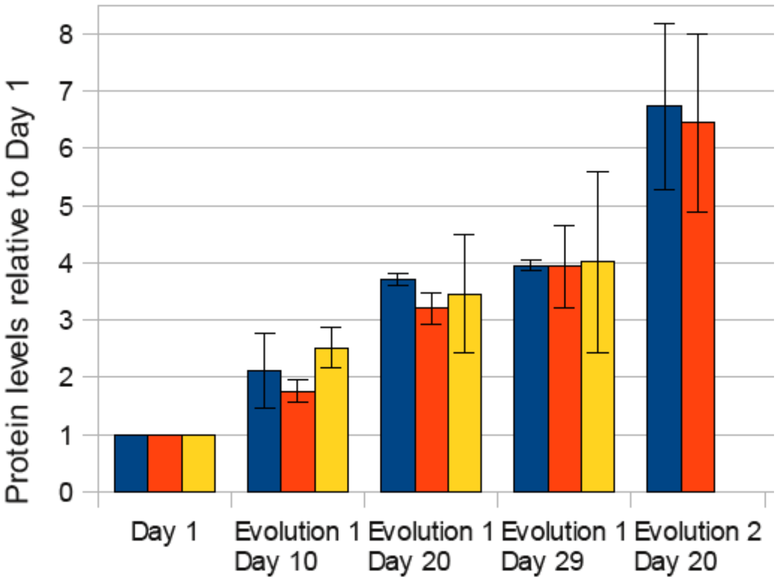
***Adjustment of ignition***

# Can chemotaxis be improved by experimental microevolution?



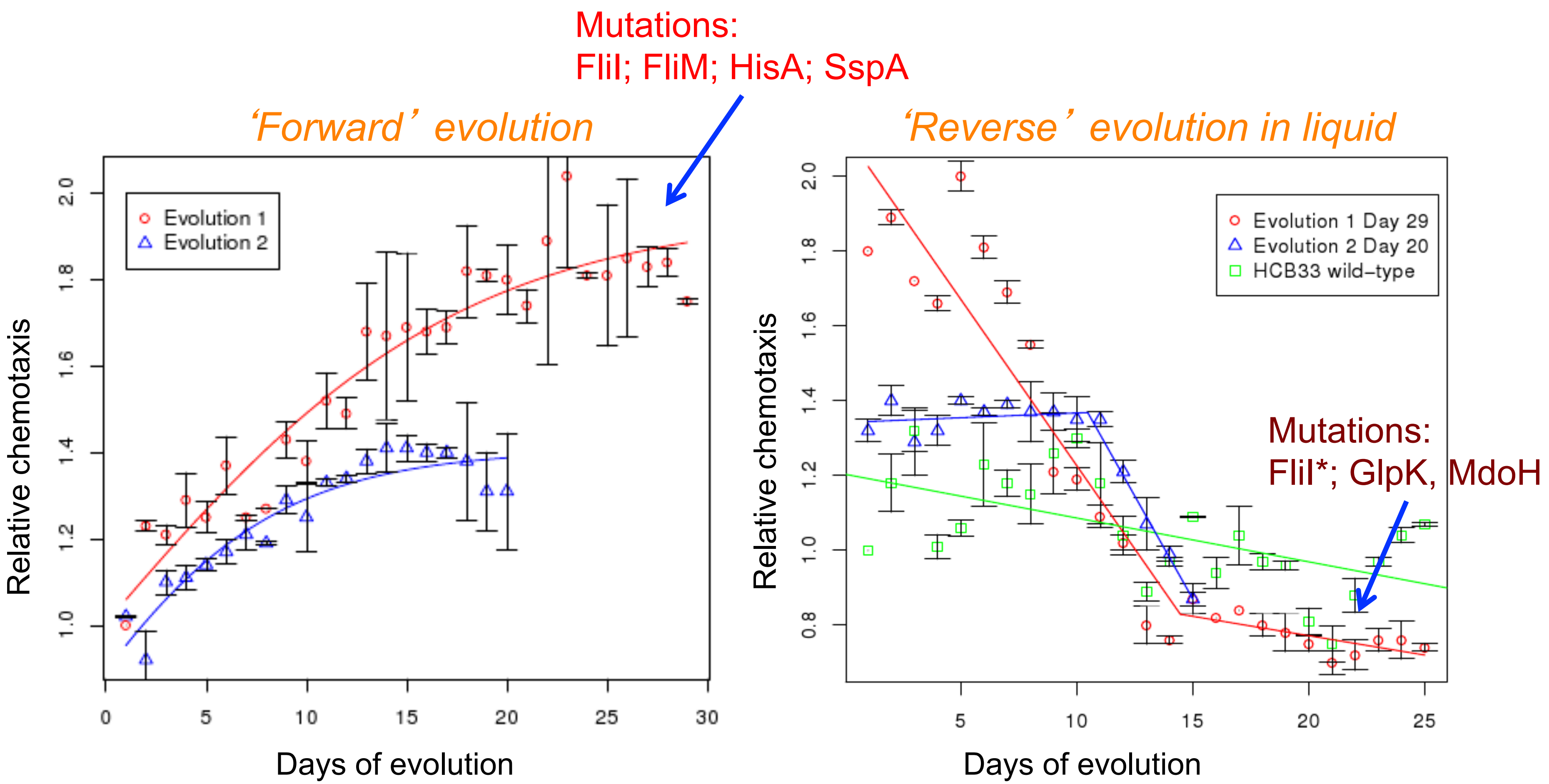




**Chemotaxis proteins are upregulated in evolved strains**




**Higher protein expression -> lower noise -> better chemotaxis**

# Evolution for better chemotaxis is reversible



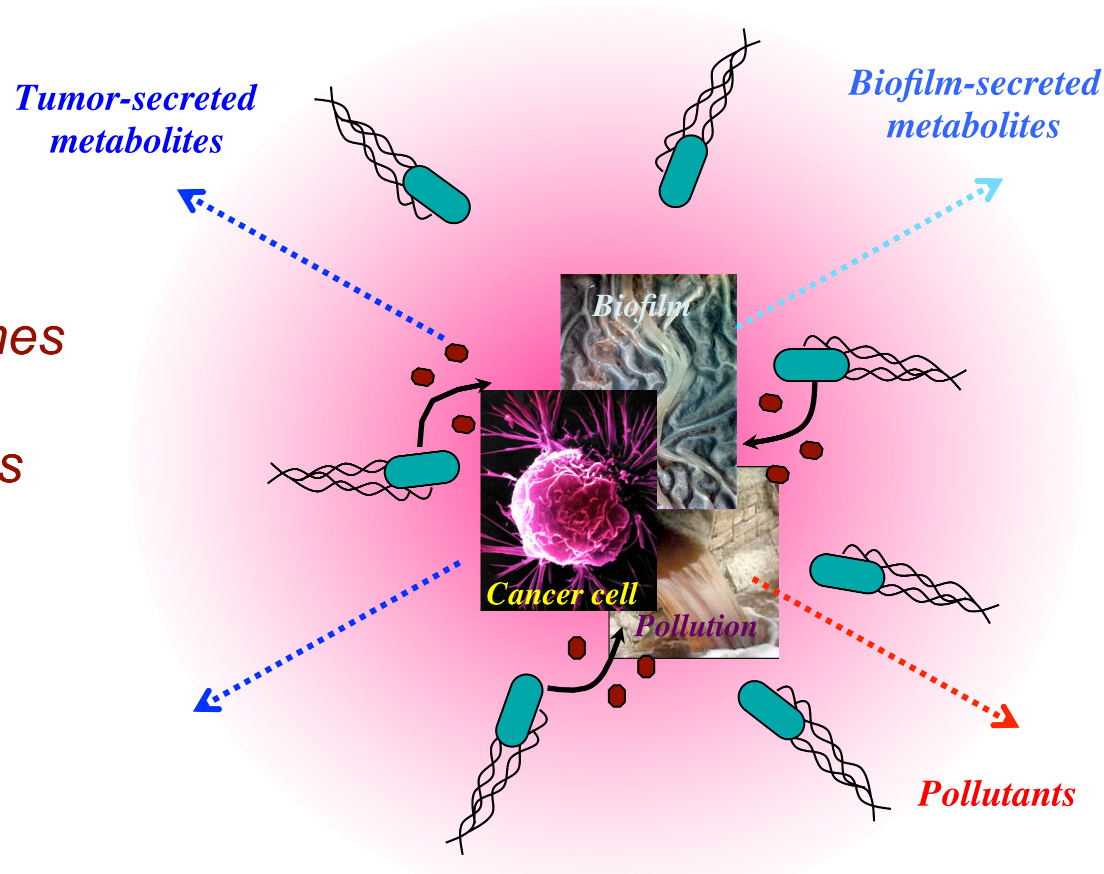
# *E. coli* chemotaxis as a biosensor

***Utilizing bacterial chemotaxis to locate sources of***

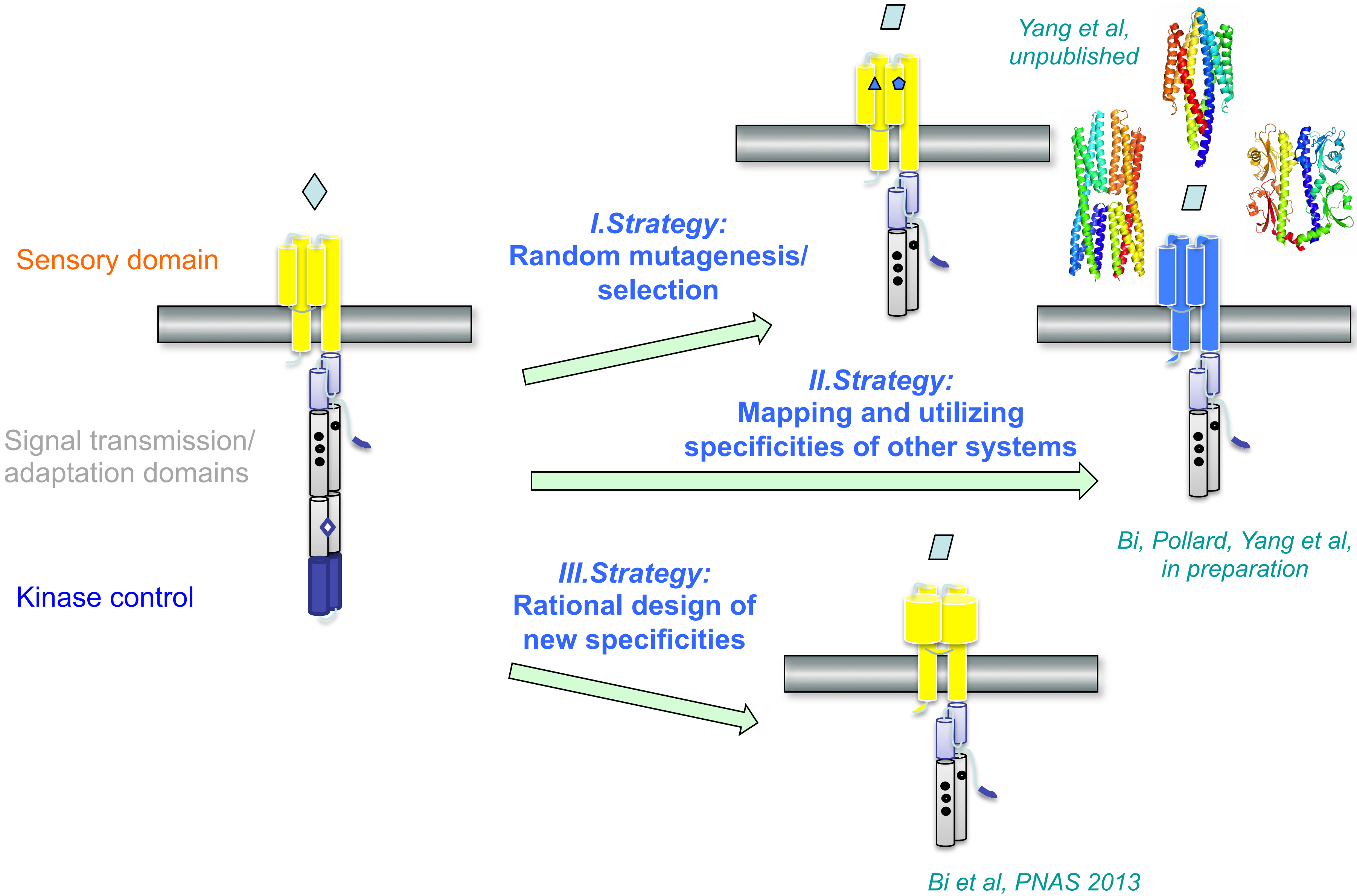
- *Environmental pollutants*
- *Bacterial biofilms*
- *Tumors*

***Equip bacteria with tools for bioremediation***

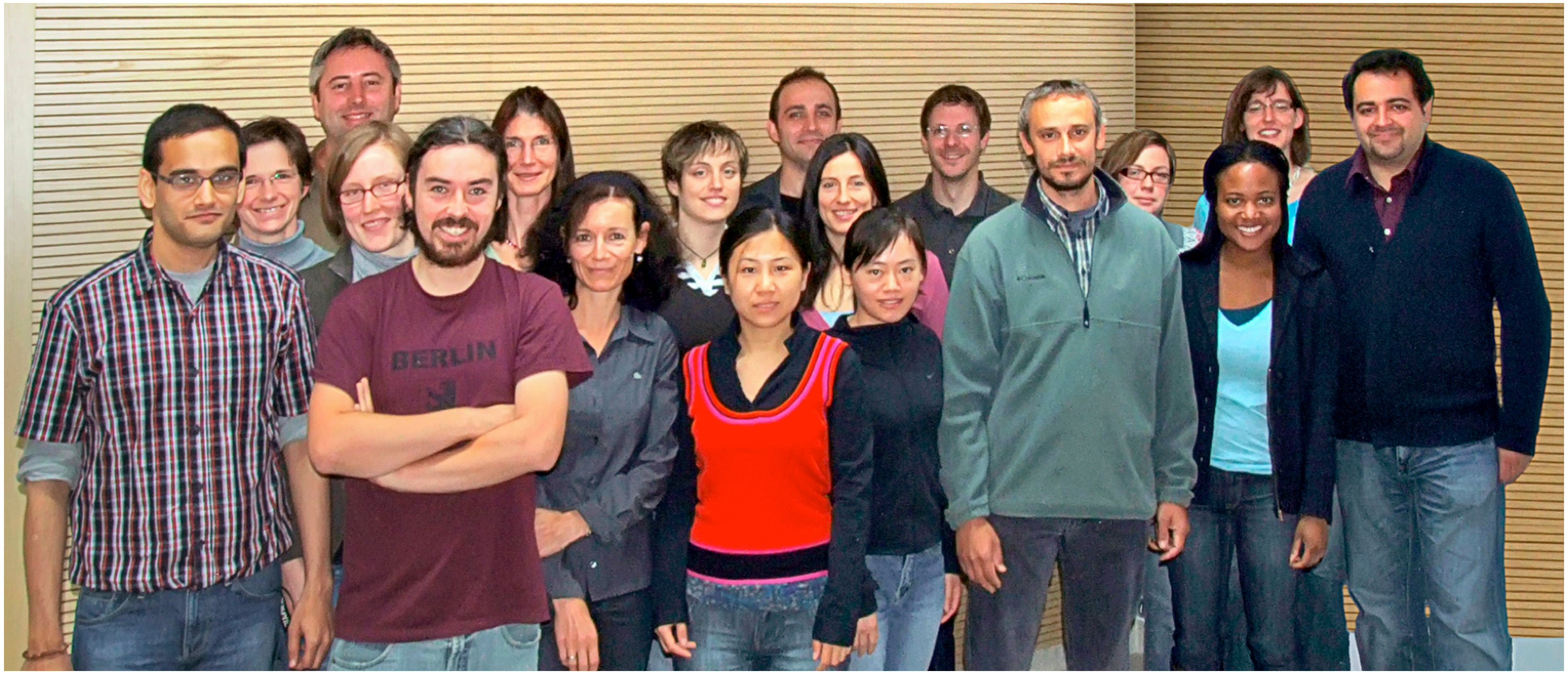
- *Pollutant-degrading enzymes*
- *Anticancer peptides*
- *Biofilm-dispersing enzymes*



# Modifying specificity of *E. coli* chemotaxis



# Acknowledgements



**Collaborations**

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*Markus Kollmann (University of Düsseldorf)*
*Ady Vaknin (Hebrew University, Israel)*
*Yuhai Tu (IBM Research, USA)*
*Robert Endres (Imperial College, London)*
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