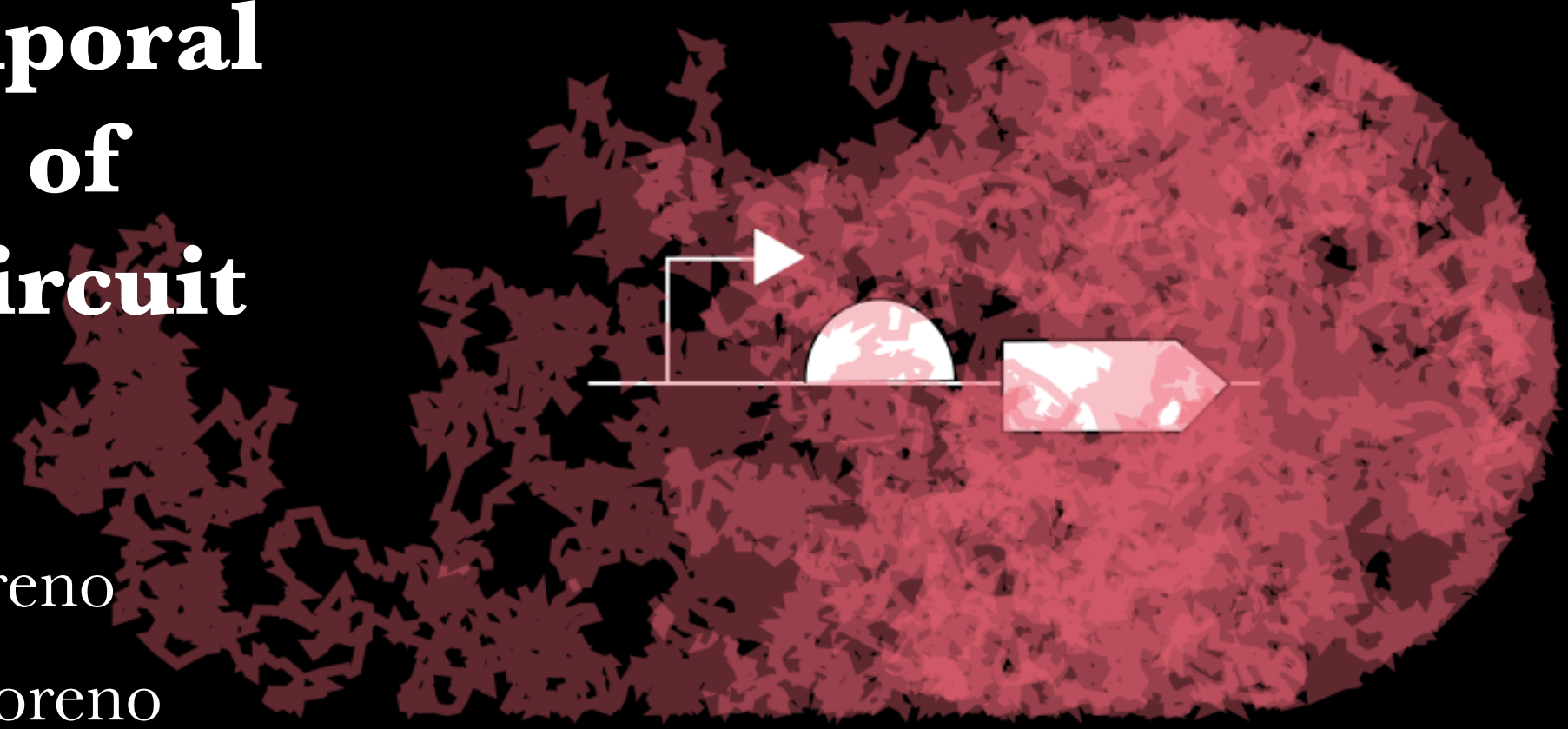
# Spatiotemporal Principles of Genetic Circuit Design



Angel Goñi Moreno

@AngelGMoreno

angel.goni-moreno@ncl.ac.uk

I(C$_2$)S

Syn 3D Bio

Newcastle University

London, November 2018

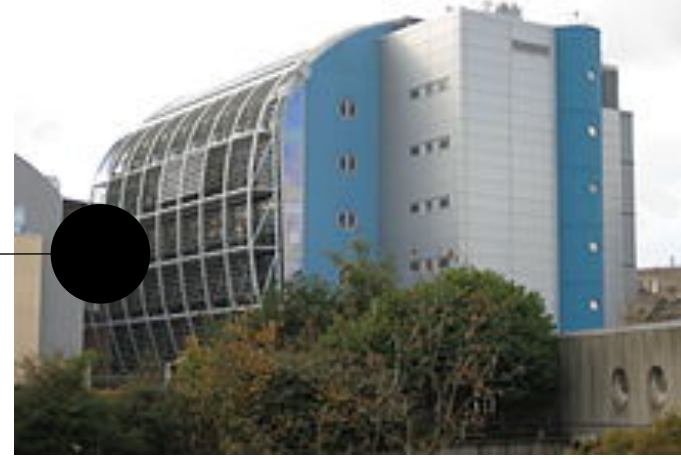
I(C)$_2$S

Newcastle University

# Interdisciplinary Computing & Complex BioSystems (ICOS) research group

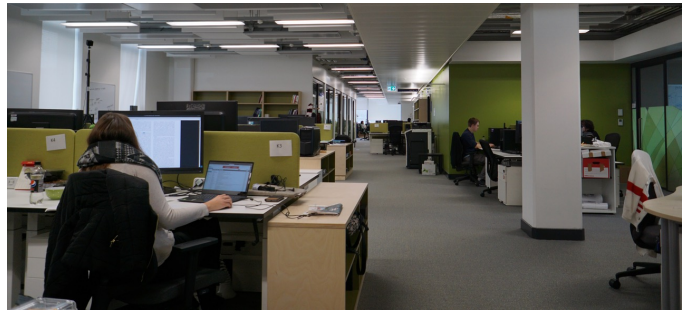
School of Computing

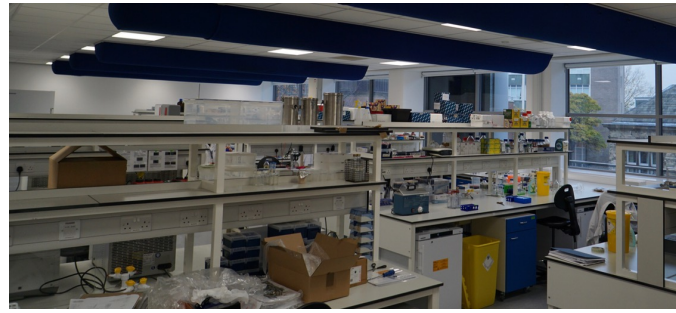
ICOS in-silico Lab



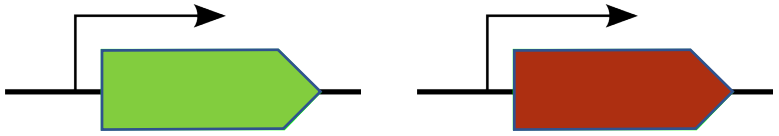
Centre for Biosystems Science and Engineering

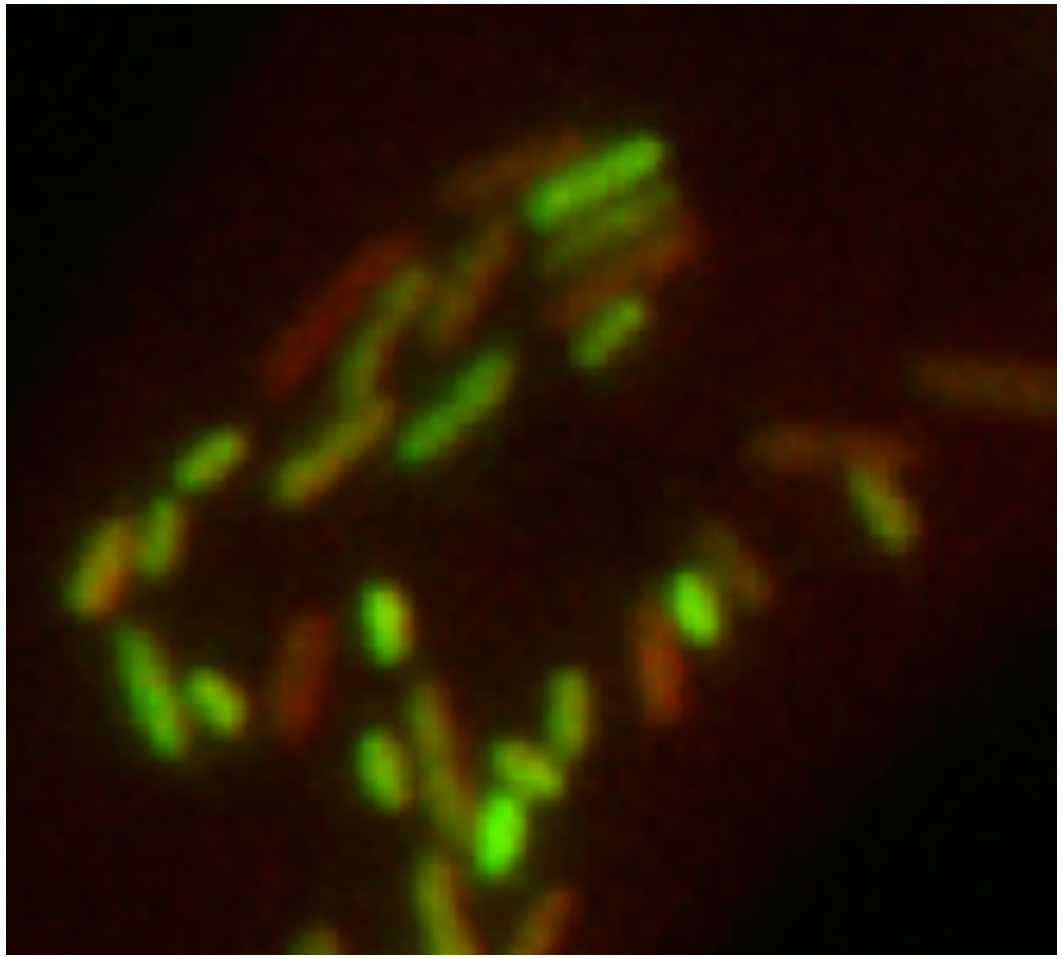
ICOS wet Lab



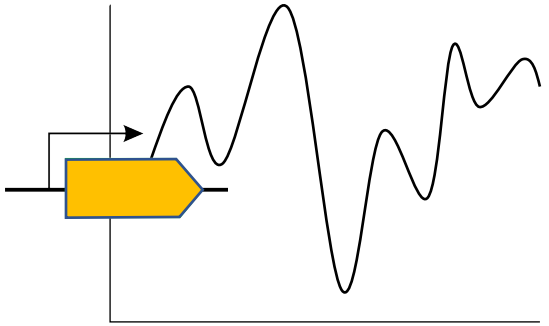


# Noise – Space – Compartments

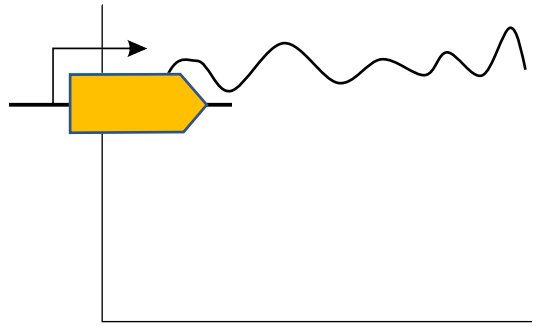




Noisy promoter



Noise-less promoter



- Fluctuations in gene expression over time due to the so-called bursting effect.
- Noise is a problem considering the electric engineering framework.
- Is noise noisy?

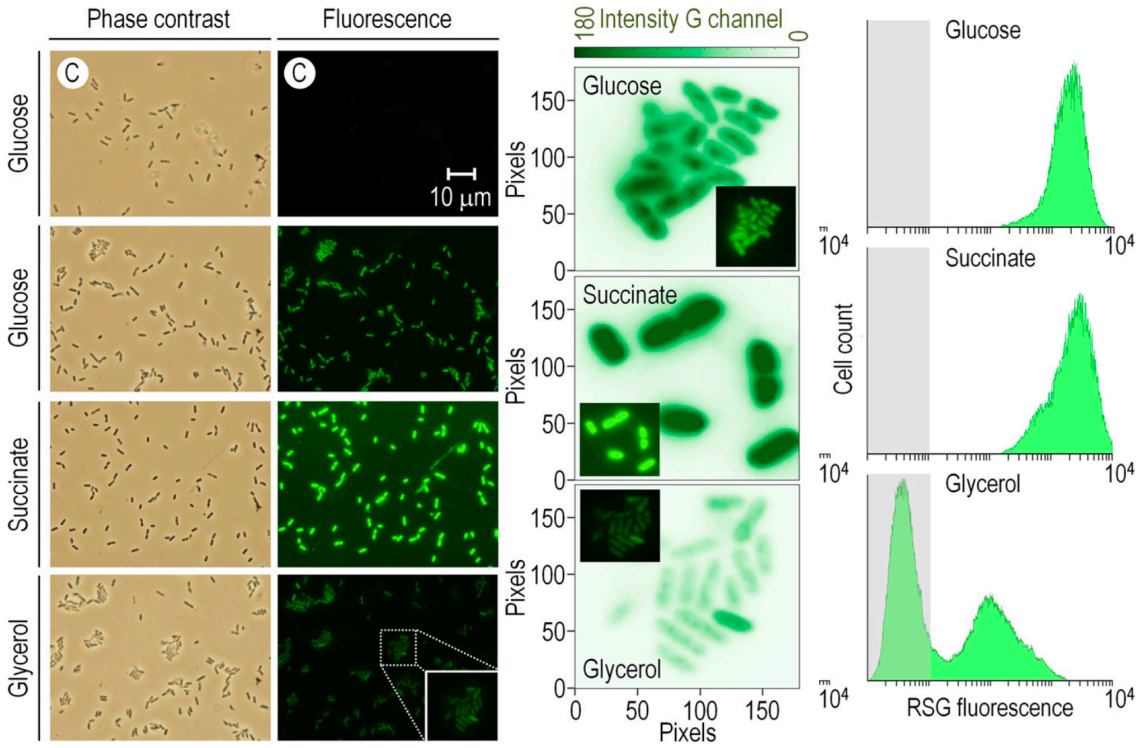
# Noise – Space – Compartments

## The Glycerol-Dependent Metabolic Persistence of *Pseudomonas putida* KT2440 Reflects the Regulatory Logic of the GlpR Repressor

**Pablo I. Nikel,[a] Francisco J. Romero-Campero,[b] Joshua A. Zeidman,[c] Ángel Goñi-Moreno,[a] Víctor de Lorenzo[a]**

Systems and Synthetic Biology Program, Centro Nacional de Biotecnología (CNB-CSIC), Madrid, Spain[a]; Department of Computer Science an Universidad de Sevilla, Seville, Spain[b]; Massachusetts Institute of Technology, Cambridge, Massachusetts, USA[c]

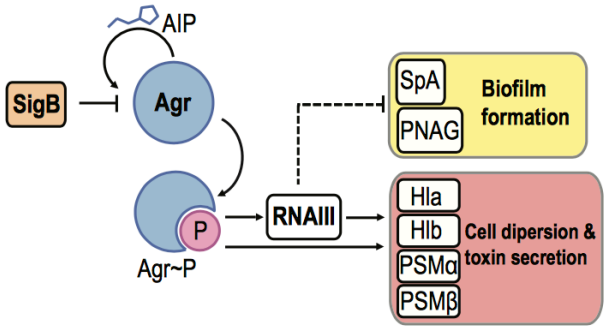
mBio®
AN OPEN ACCESS JOURNAL PUBLISHED BY THE AMERICAN SOCIETY FOR MICROBIOLOGY

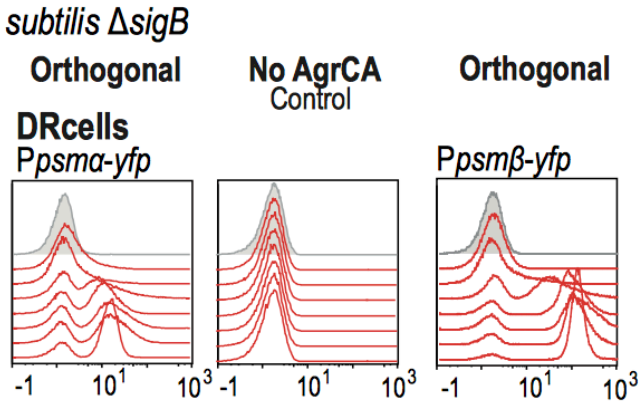



## Cell differentiation defines acute and chronic infection cell types in *Staphylococcus aureus*

eLIFE
elifesciences.org

**Juan-Carlos García-Betancur[1,2], Angel Goñi-Moreno[3], Thomas Horger[4], Melanie Schott[5], Malvika Sharan[1], Julian Eikmeier[1,2], Barbara Wohlmuth[4], Alma Zernecke[5], Knut Ohlsen[1], Christina Kuttler[4], Daniel Lopez[1,2,6]***



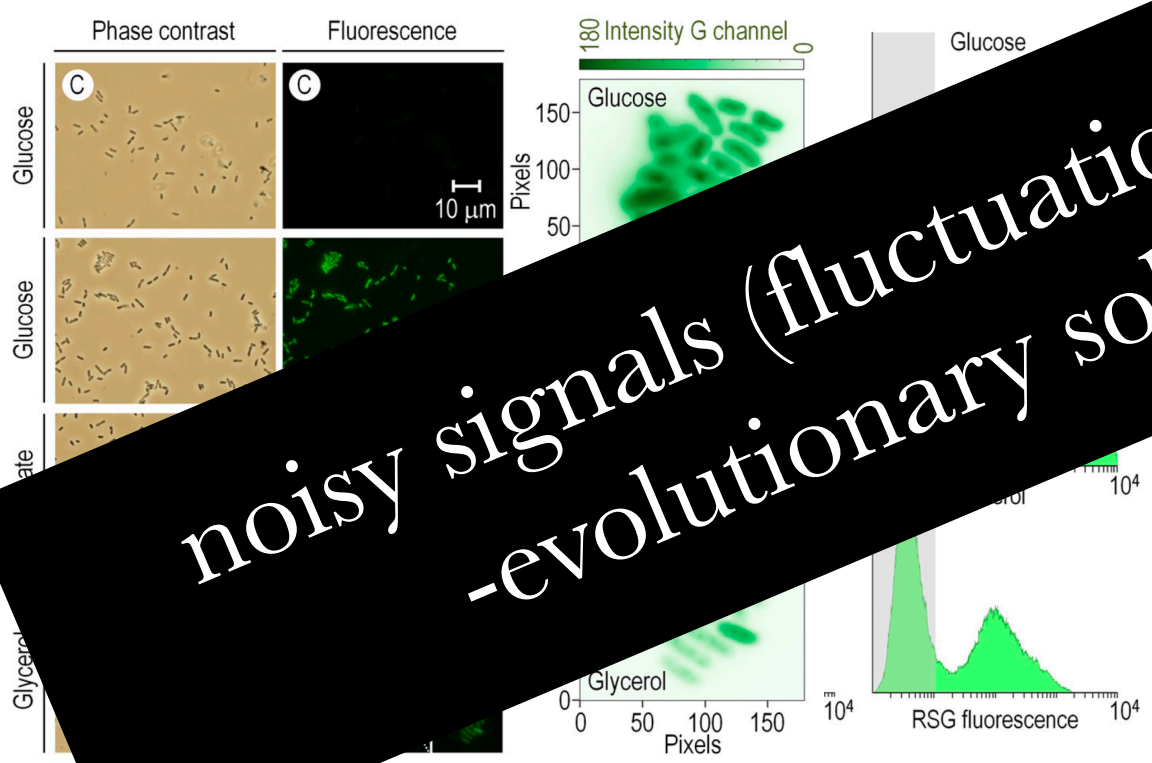
# Noise – Space – Compartments

## The Glycerol-Dependent Metabolic Persistence of *Pseudomonas putida* KT2440 Reflects the Regulatory Logic of the GlpR Repressor

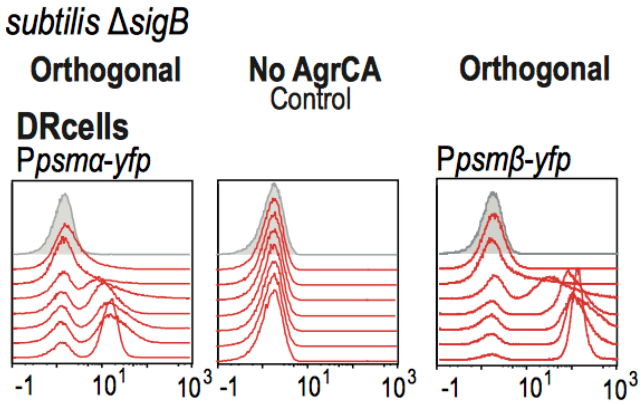
**Pablo I. Nikel,[a] Francisco J. Romero-Campero,[b] Joshua A. Zeidman,[c] Ángel Goñi-Moreno,[a] Víctor de Lorenzo[a]**

Systems and Synthetic Biology Program, Centro Nacional de Biotecnología (CNB-CSIC), Madrid, Spain[a]; Department of Computer Science an Universidad de Sevilla, Seville, Spain[b]; Massachusetts Institute of Technology, Cambridge, Massachusetts, USA[c]

mBio®
AN OPEN ACCESS JOURNAL PUBLISHED BY THE AMERICAN SOCIETY FOR MICROBIOLOGY




**Cell differentiati**
**chronic inf**
***Staph***



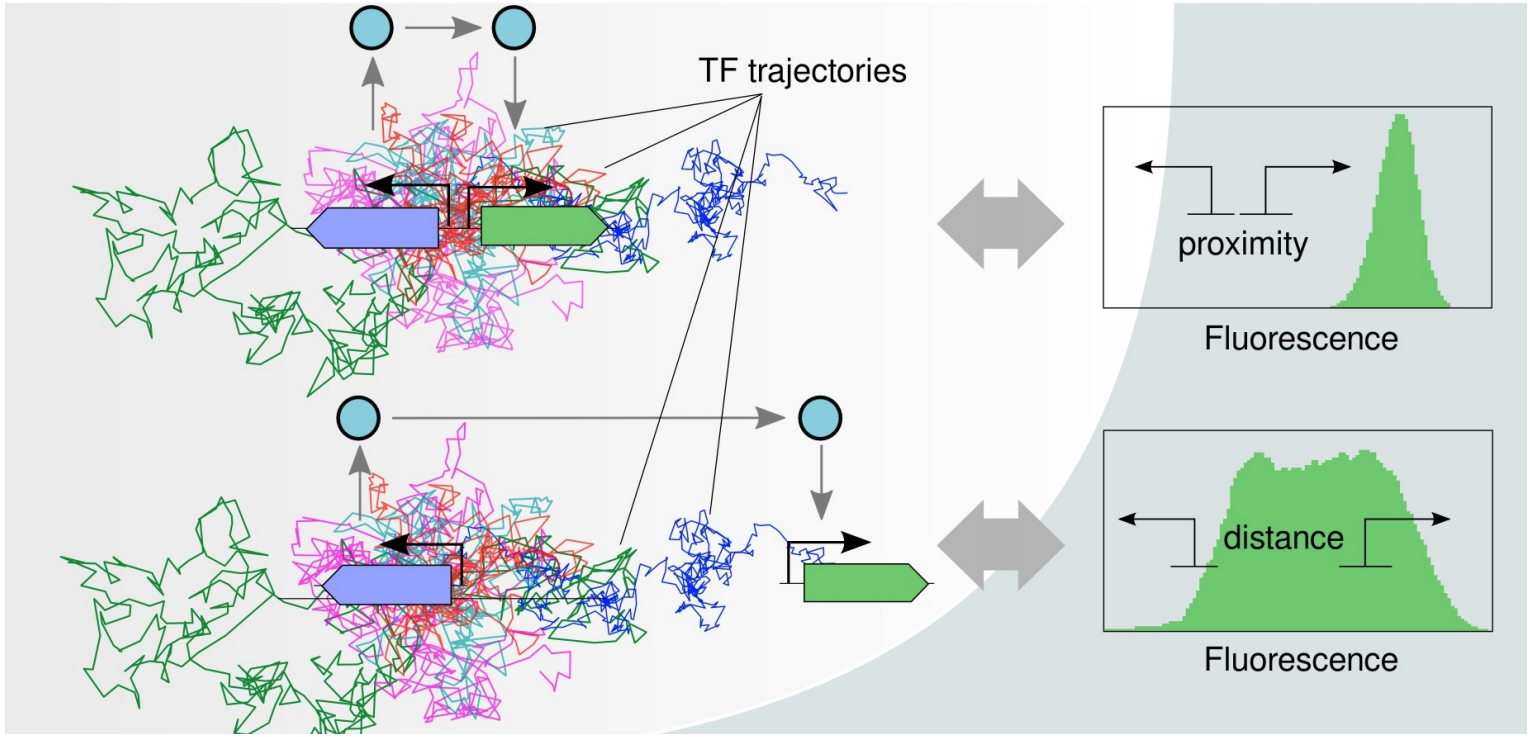

noisy signals (fluctuations) are useful to the cell
-evolutionary solution to a problem-

# Noise – Space – Compartments

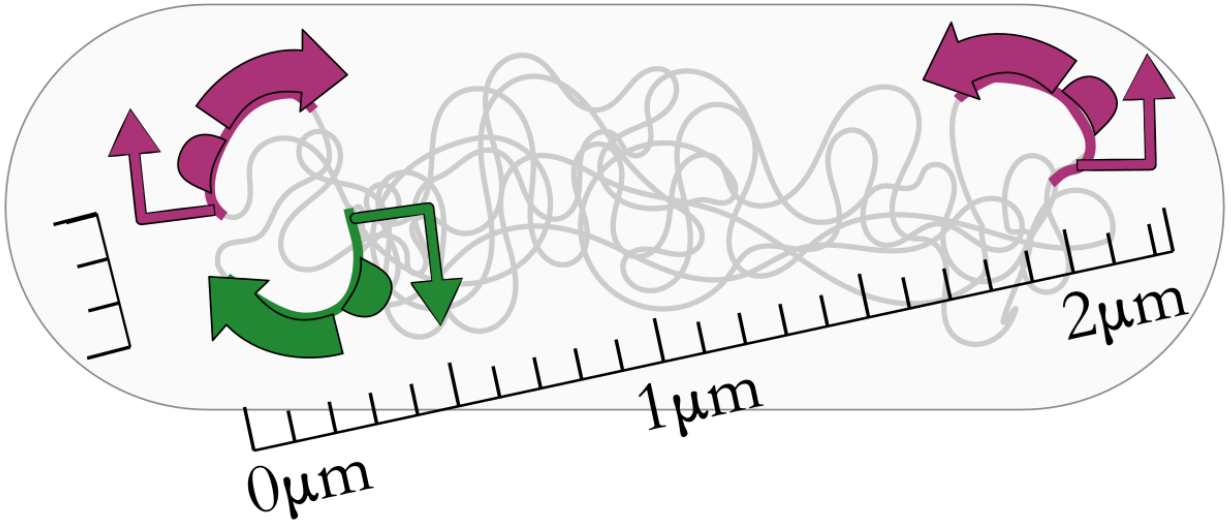
ACS SyntheticBiology
Research Article
pubs.acs.org/synthbio

## Deconvolution of Gene Expression Noise into Spatial Dynamics of Transcription Factor–Promoter Interplay

Ángel Goñi-Moreno,† Ilaria Benedetti, Juhyun Kim, and Víctor de Lorenzo*



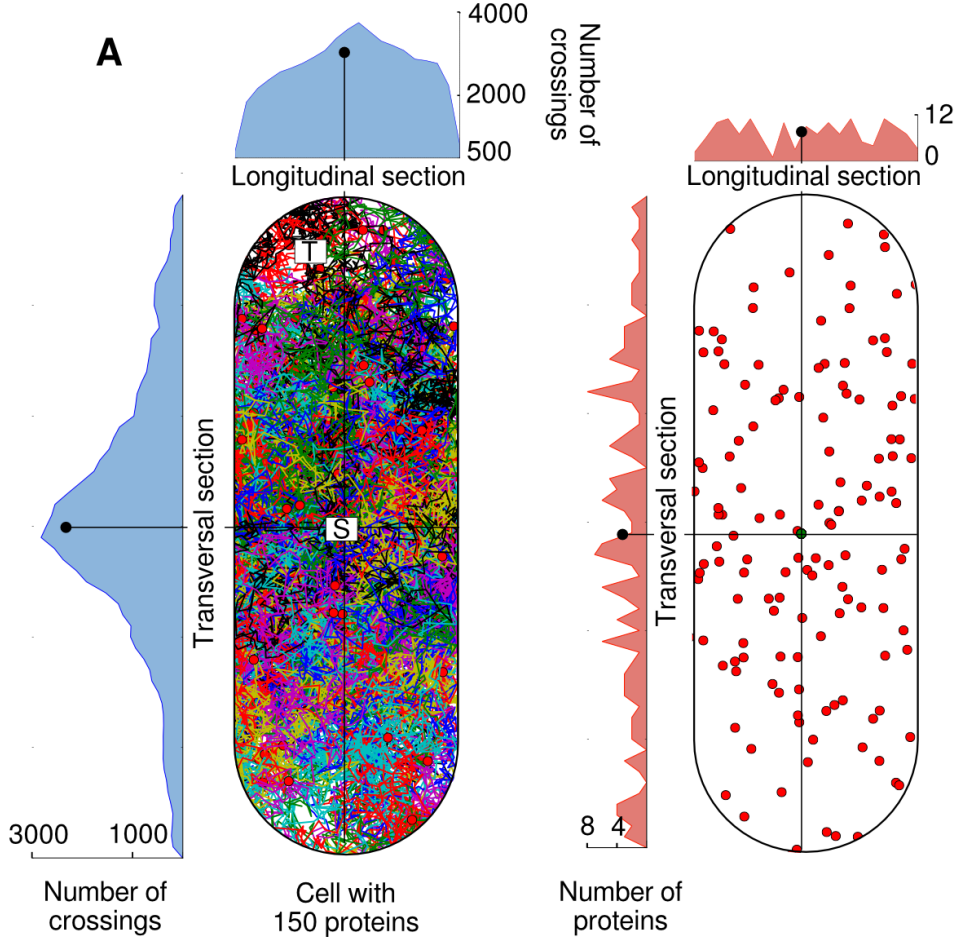

- Gene expression noise correlated to intracellular distance.
- Expression sharp when components close.
- Expression noisy when promoters far.
- Reusability of designs!



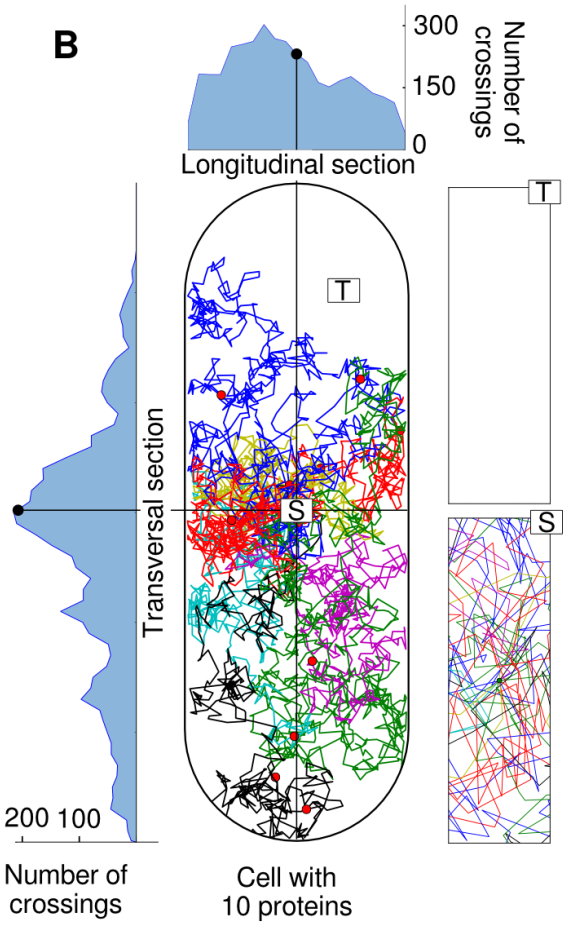

"An intriguing question is whether inter-genetic distance has been exploited as a tool by evolution to fine tune systems to deploy beneficial phenotypes. The corresponding challenge is then to embed spatial constraints as engineering principles to improve the design-build-test-learn lifecycle."

# Noise – Space – Compartments

- Mathematical models **were** not ready to embed spatial constraints.
- Low TF numbers are needed to maximize fluctuations at longer distances.
- TF time-point distribution vs. time-lapse trajectories.

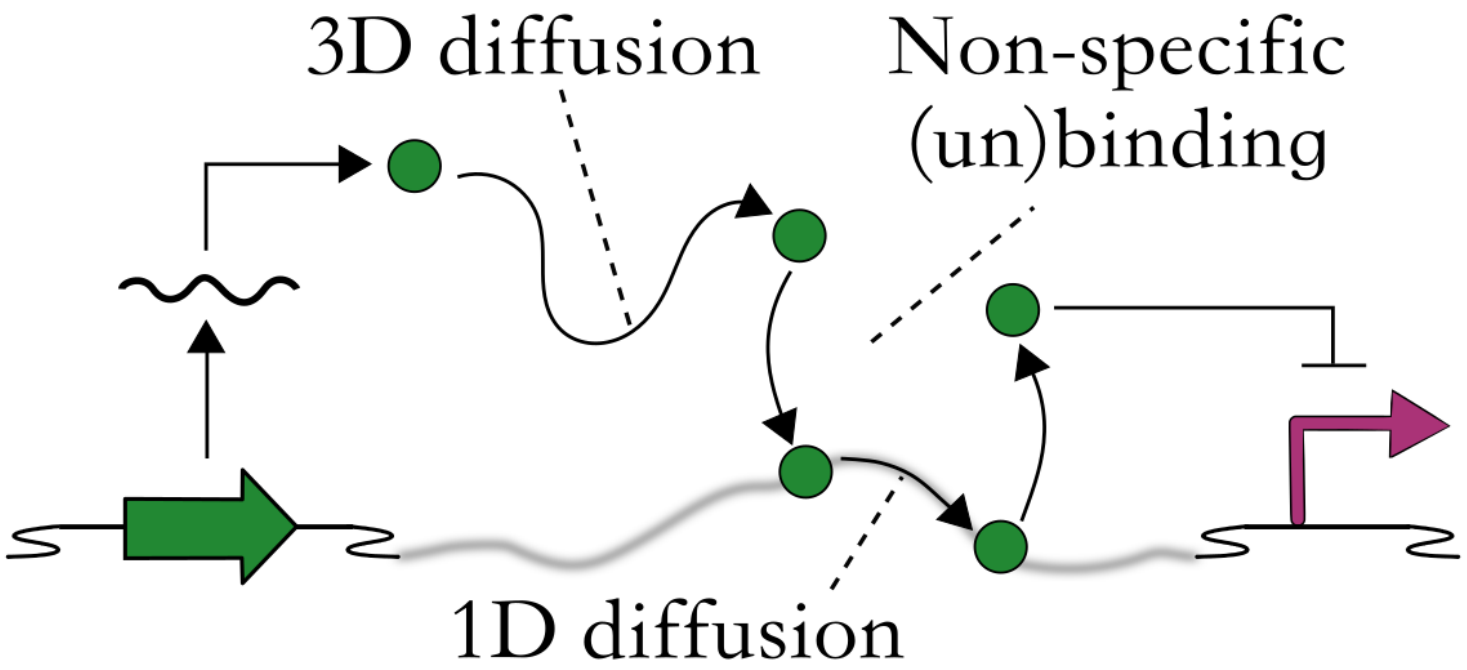



High TF numbers




Low TF numbers

# Noise – Space – Compartments



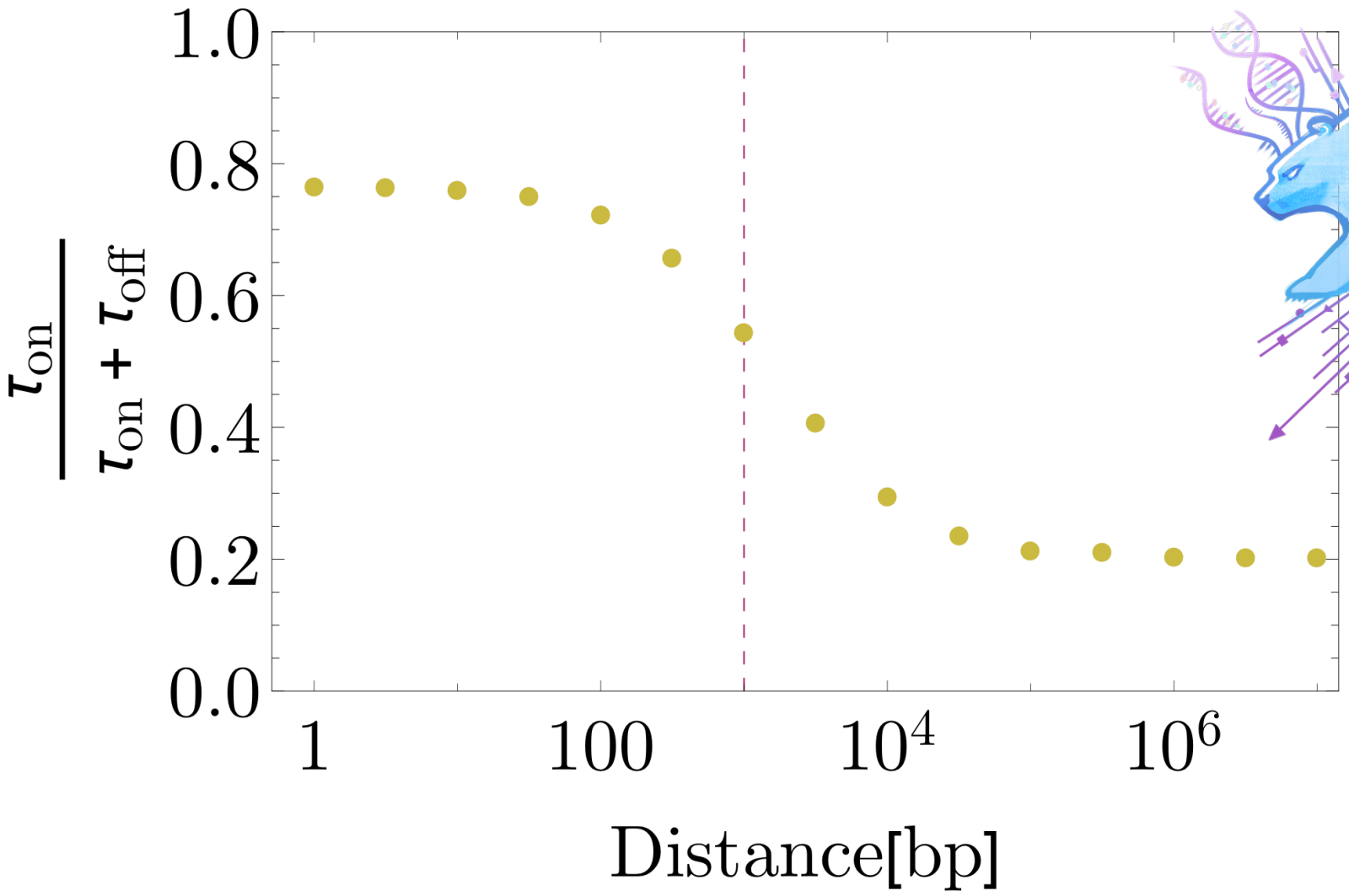

**TF remains bound:**

- 1D sliding
- Low searching time
- Unlikely at long distances

**TF unbinds into bulk:**

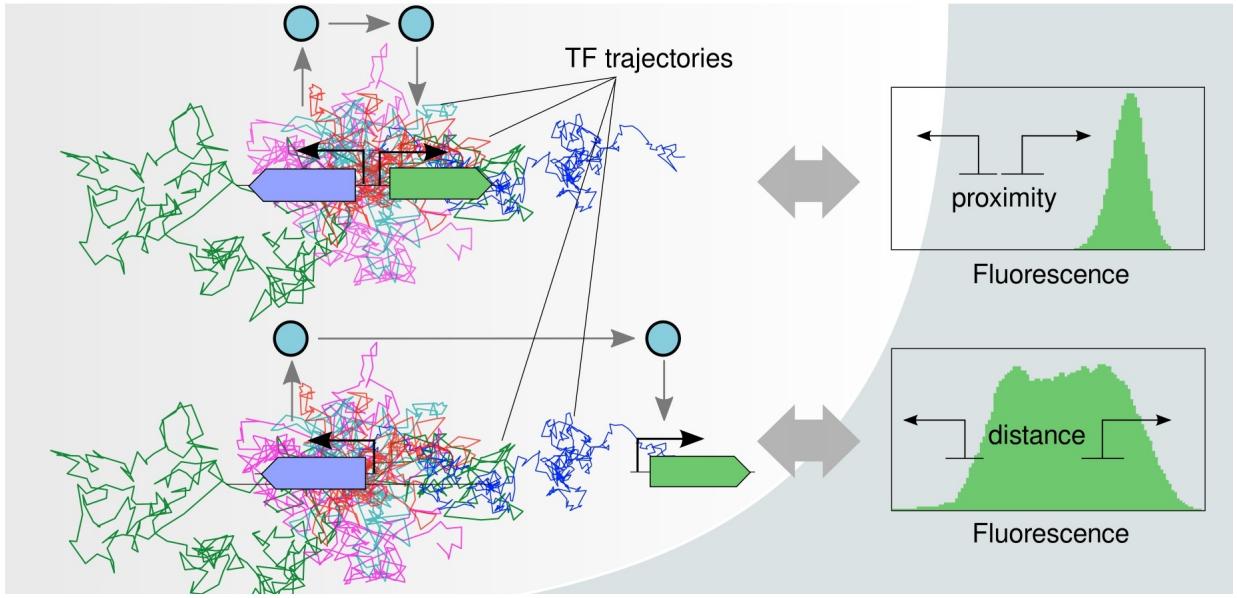
- 3D diffusion
- Slow(er) searching time
- Reach long distances

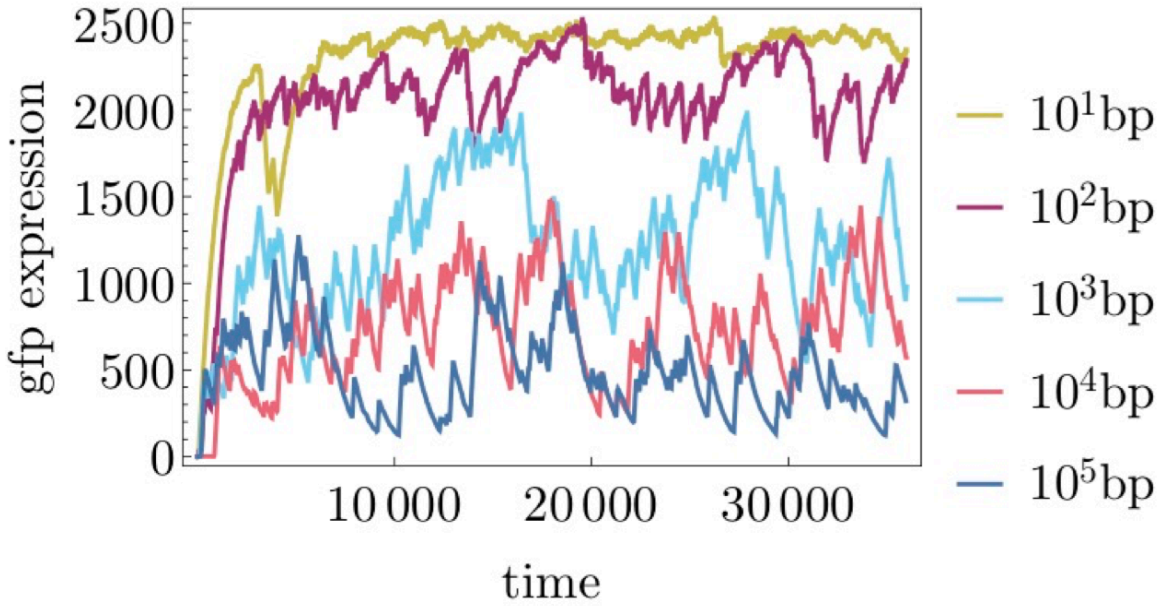
# Noise – Space – Compartments



- Promoter activity (inducible promoter): the further, the less.
- Performance switches relatively quickly at specific intervals.

# Noise – Space – Compartments




- The model can now reproduce the experiments by changing ONLY space between components. All other rates untouched.
- Noise patterns are not just random fluctuations!

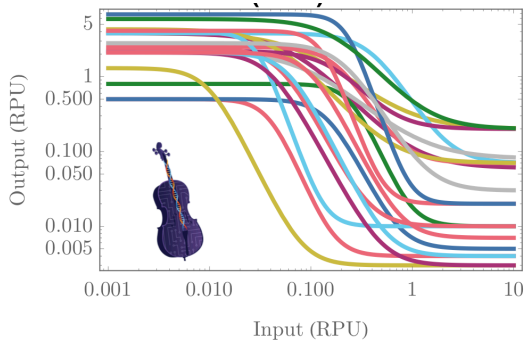
# Noise – Space – Compartments

SYNTHETIC BIOLOGY

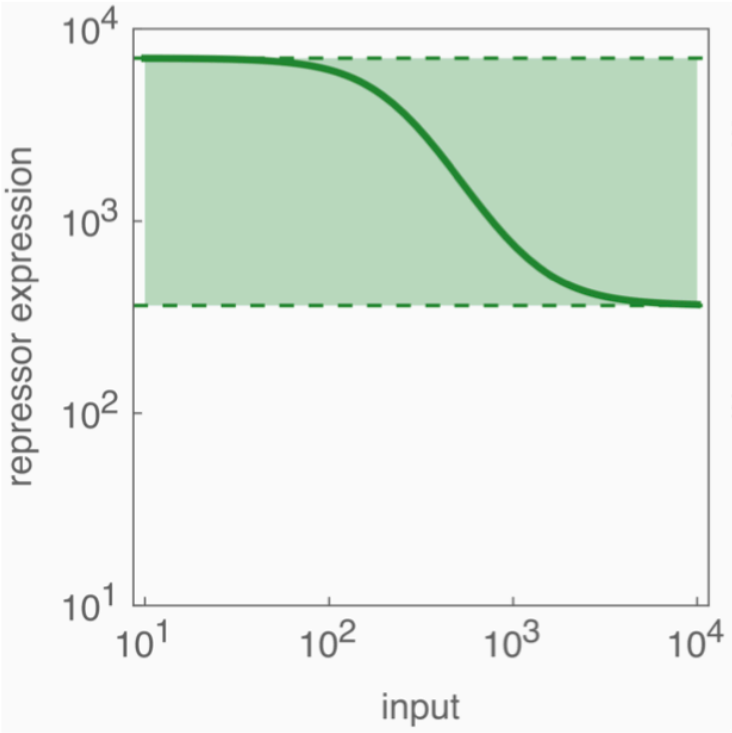
## Genetic circuit design automation

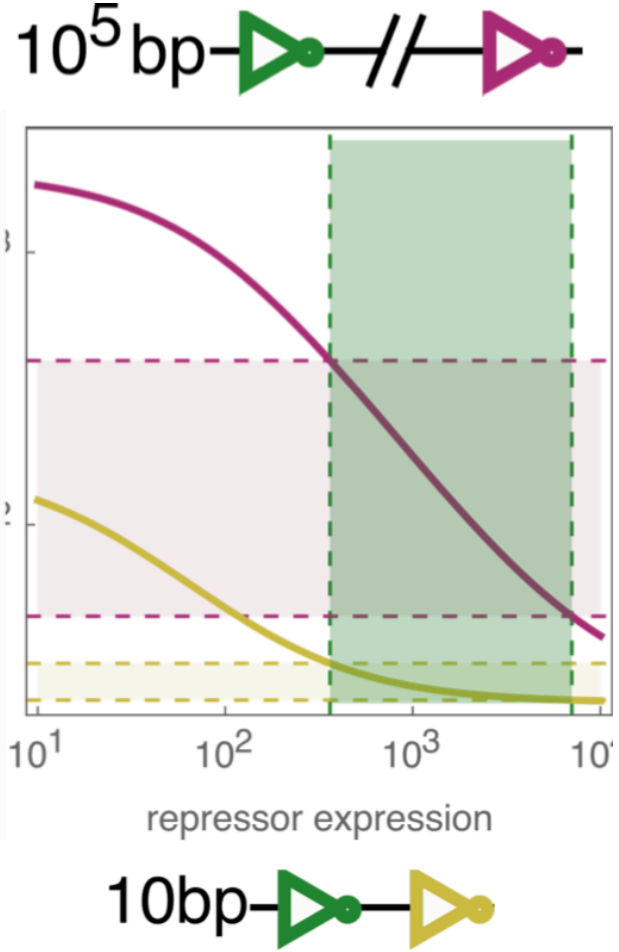
Alec A. K. Nielsen,[1] Bryan S. Der,[1,2] Jonghyeon Shin,[1] Prashant Vaidyanathan,[2] Vanya Paralanov,[3] Elizabeth A. Strychalski,[3] David Ross,[3] Douglas Densmore,[2] Christopher A. Voigt[1]*

Nielsen *et al.* Science 352 (2016)



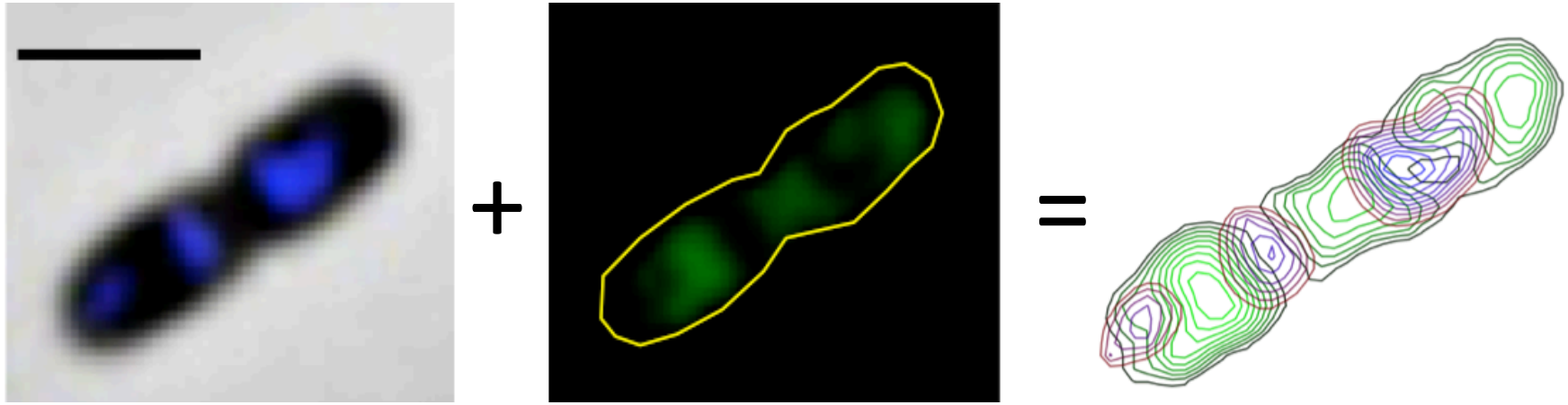

- Engineer performance through spatial constraints.
- Flexible dataset! Make compatible pairs by moving parts around.



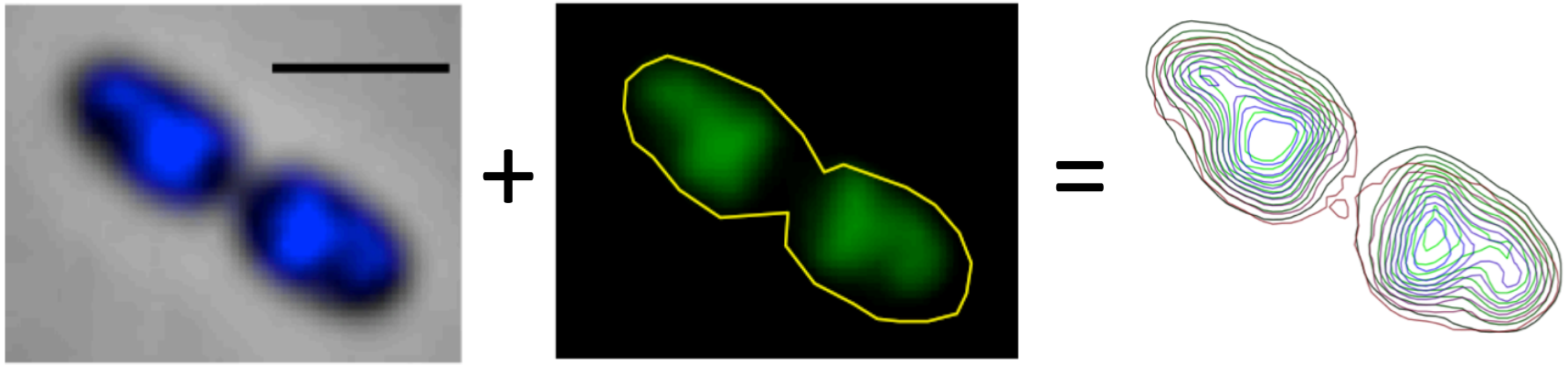



# Noise – Space – Compartments

Nucleoid + Ribosomes =



Nucleoid + RNAP =

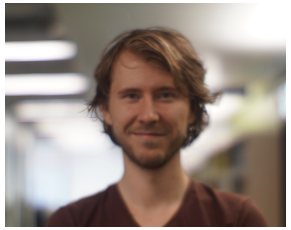


- Are transcription and translation coupled?
- How this affects the 1D vs 3D movement of the TFs?
- Is RNA diffusion a relevant factor?

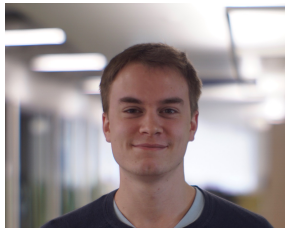
# The team:

Angel Goni-Moreno

Alexander Wood



Ruud Stoof



Lewis Grozinger

Connor Barker

Syn3D Bio

I(CO)2S

Newcastle University

EPSRC
Engineering and Physical Sciences Research Council

European Commission

Horizon 2020
European Union funding for Research & Innovation

# The collaborators:

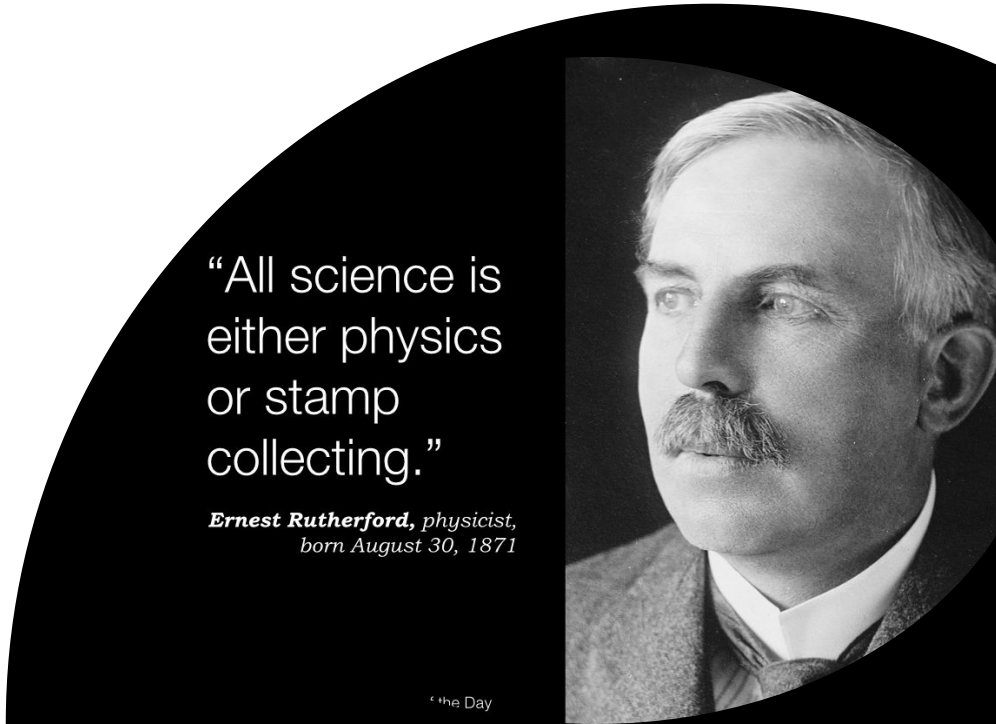
Victor de Lorenzo (CNB, Spain)

Yuhjun Kim (Surrey, UK)

Daniel Lopez (CNB, Spain)

# Contact:


@AngelGMoreno

@SynBio3D

angel.goni-moreno@ncl.ac.uk