BIOENG-420

Single-cell biology

Week 1. Cell-to-Cell heterogeneity

About me…

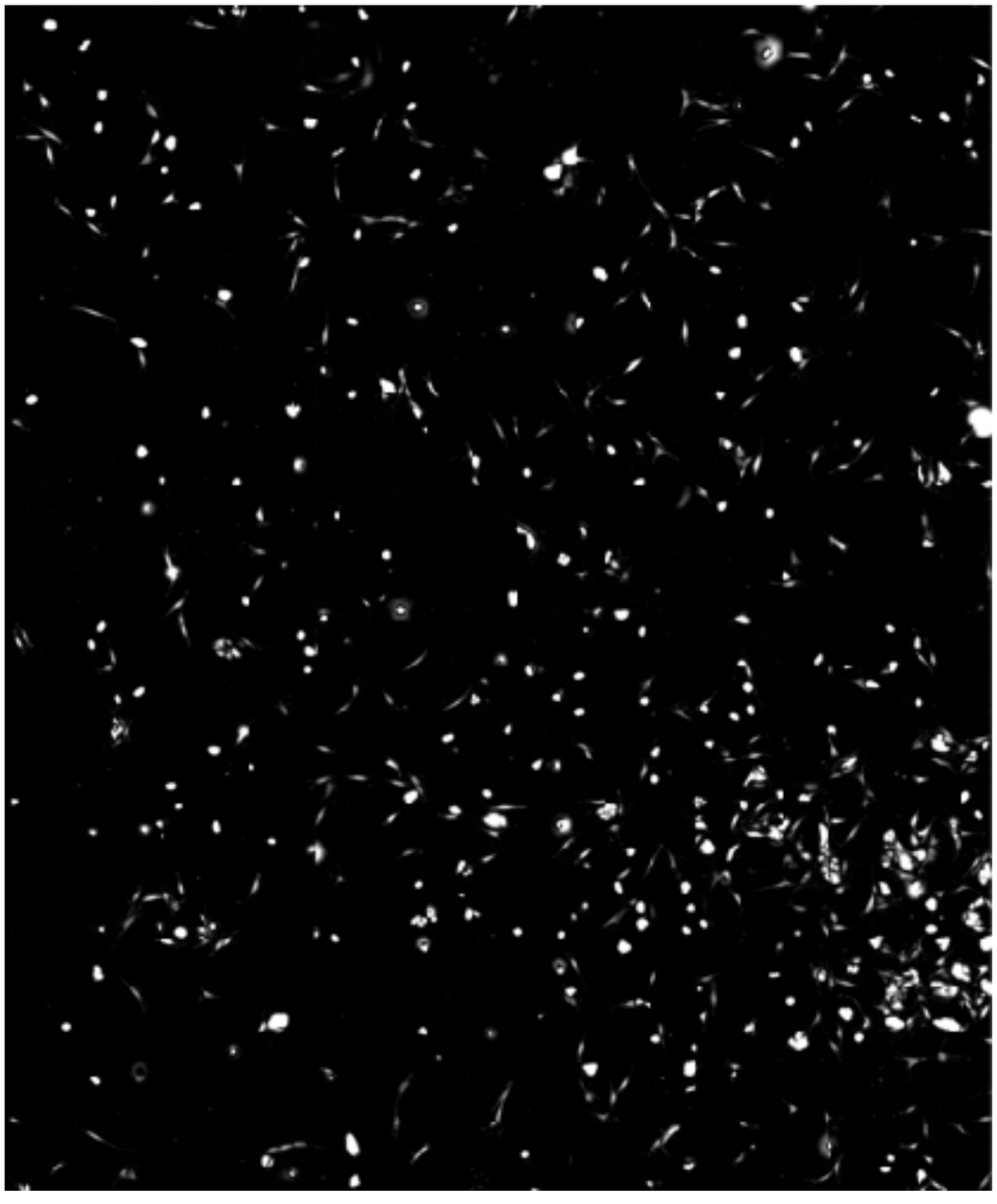
1998-2003 M.S. in Medical Biotechnology, University of Naples, School of Medicine, Italy

2004- 2008 PhD in Life Sciences, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy

2009-2012 Postdoctoral fellow. Telethon Institute for Genetics and Medicine, Naples, Italy.

2013-2018 Researcher National Research Council of Italy, Naples, Italy

2018- Professor Institute of Bioengineering and Global Health Institute EPFL



Main Interests:

Lipid Metabolism , Membrane Cell Biology

Course Structure

Giovanni D'Angelo

W1 Lecture 1: Cell-to-Cell Heterogeneity

Vincent Gardeux

W2 Lecture 2: Sc Transcriptomics

W3 Lecture 3: Sc Transcriptomics

W4 Lecture 4: Sc Transcriptomics

W5 Lecture 5: Sc Transcriptomics

TAs:
Jiayan Lin
Elisa Bugnani

1/6th of final grade

Giovanni D'Angelo

W6 Lecture 6: Sc Metabolomics

W7 Lecture 7: Sc Metabolomics

W8 Lecture 8: Sc Metabolomics

1/6th of final grade

Fides Zenk

W9 Lecture 9: Sc Epigenomics

W10 Lecture 10: Sc Epigenomics

W11 Lecture 11: Sc Epigenomics

W12 Lecture 12: Sc Epigenomics

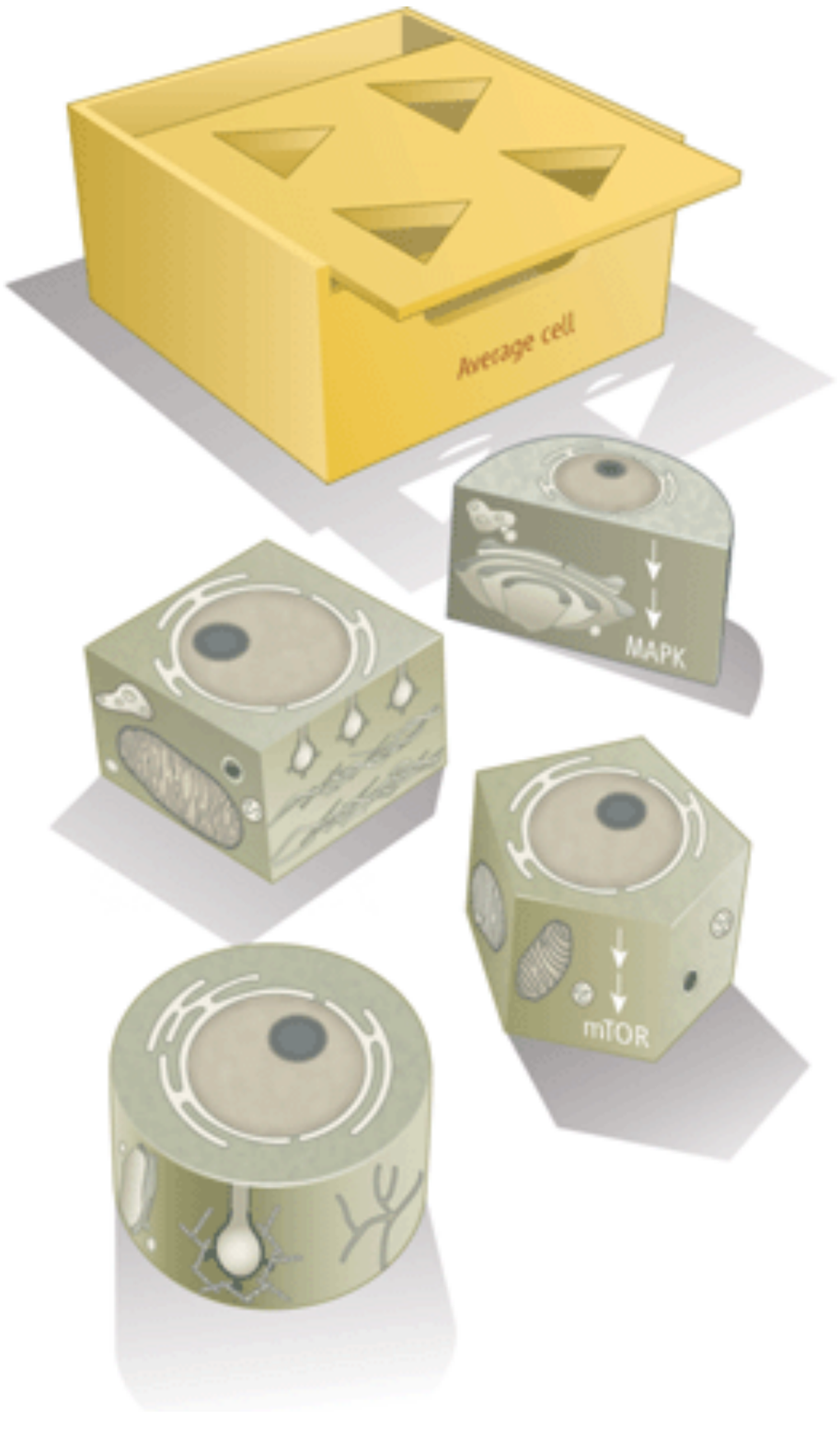
1/6th of final grade

W13 Lecture 13: mini symposium

W14 Lecture 14: Exam

50 % of final grade
written exam on a Sc_paper

Cell-to-cell heterogeneity



Single Cell Analyses have a meaning only in the presence of cell-to-cell heterogeneity.

how can we define cell-to-cell heterogeneity?

We talk about cell-to-cell heterogeneity when individual cells in a population differ in a specific parameter (cell shape - cell size… signalling… transcriptome …. metabolite etc).

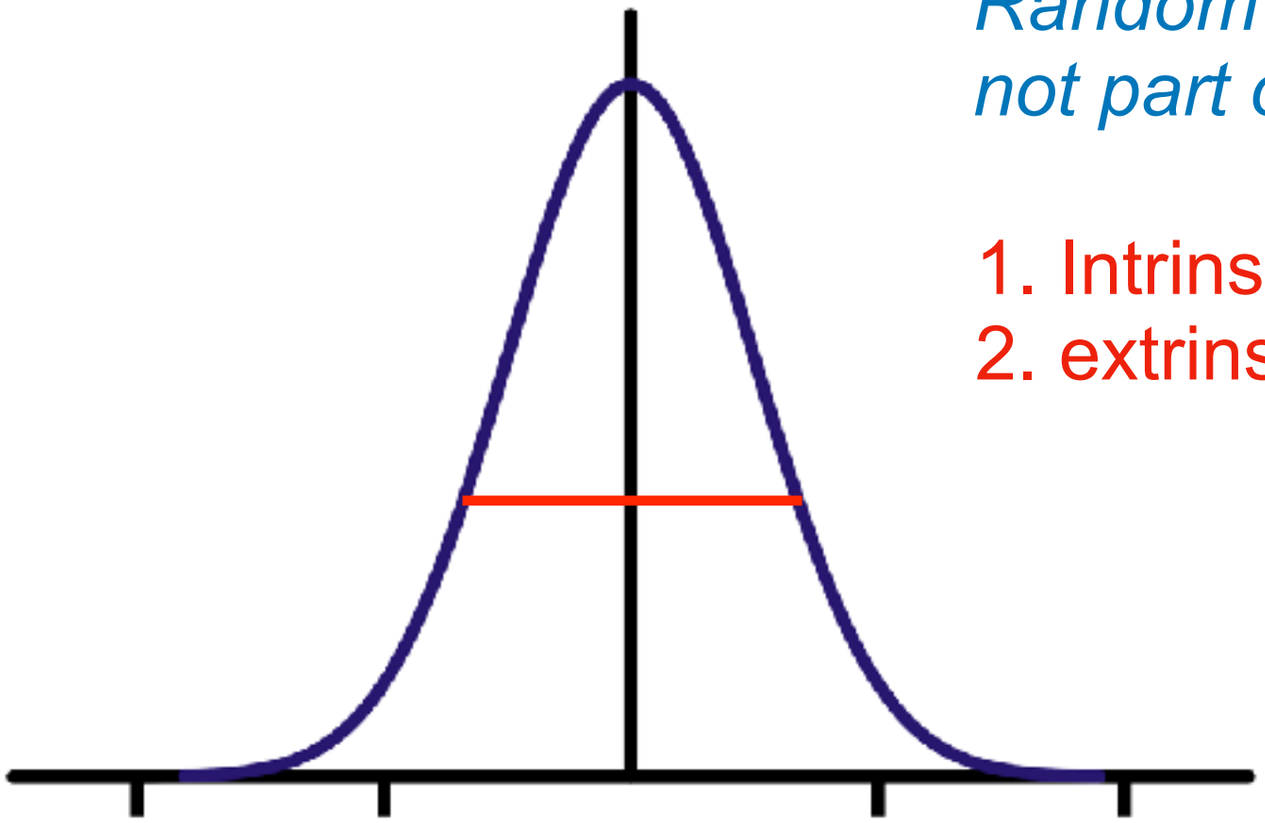
Cell-to-cell heterogeneity

What is cell-to-cell heterogeneity due to?

1. **stochastic variability**
2. deterministic variability

stochastic variability -> noise

$$\eta = \sigma / \mu$$



Random or irregular fluctuations which are not part of a signal

1. Intrinsic noise
2. extrinsic noise

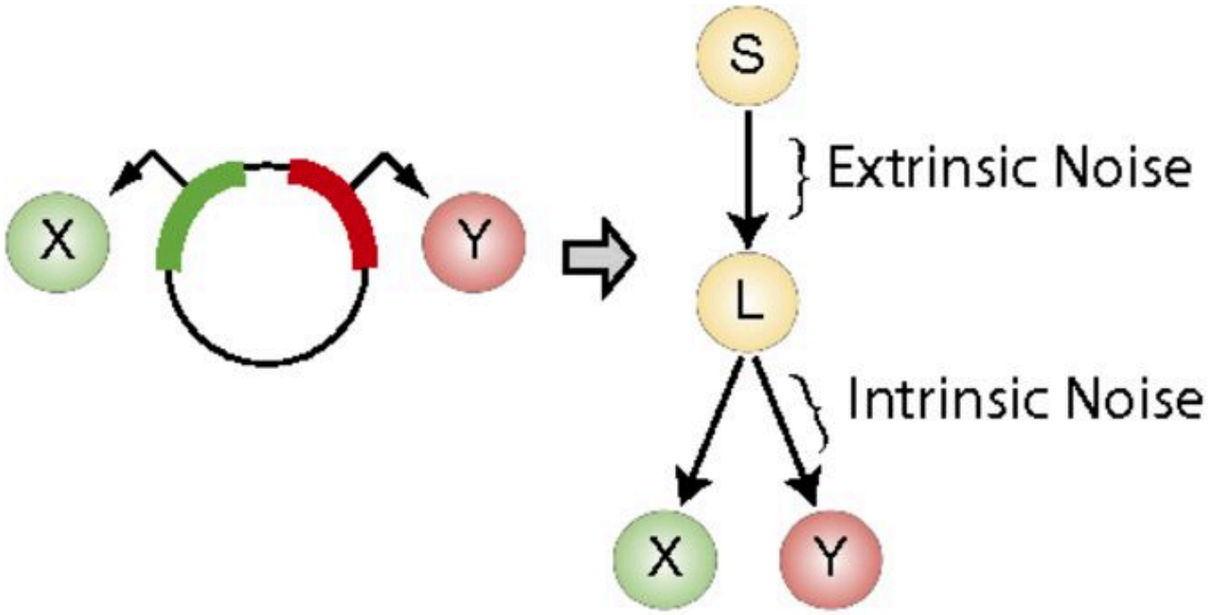
$$\eta_t = \eta_i + \eta_e$$

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$

Intrinsic noise is the variation in a parameter that derives from pure probabilistic factors. Low copy number is one of such factors

Extrinsic noise is not inherent to the measured parameter but rather derives from a noisy upstream regulator.

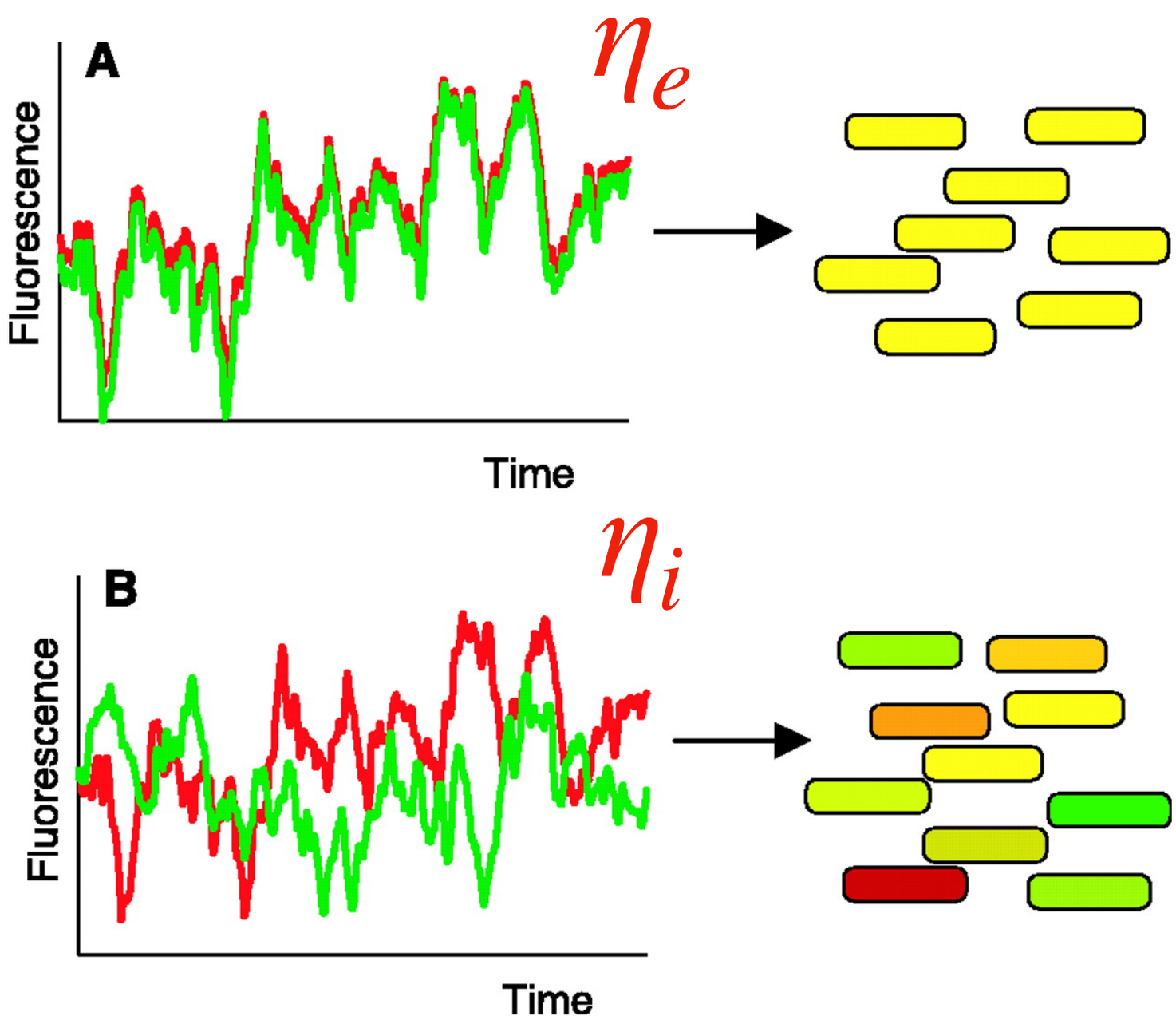


Can we discriminate intrinsic and extrinsic noise in biology?

The Elowitz experiment

Elowitz et al Science 2002

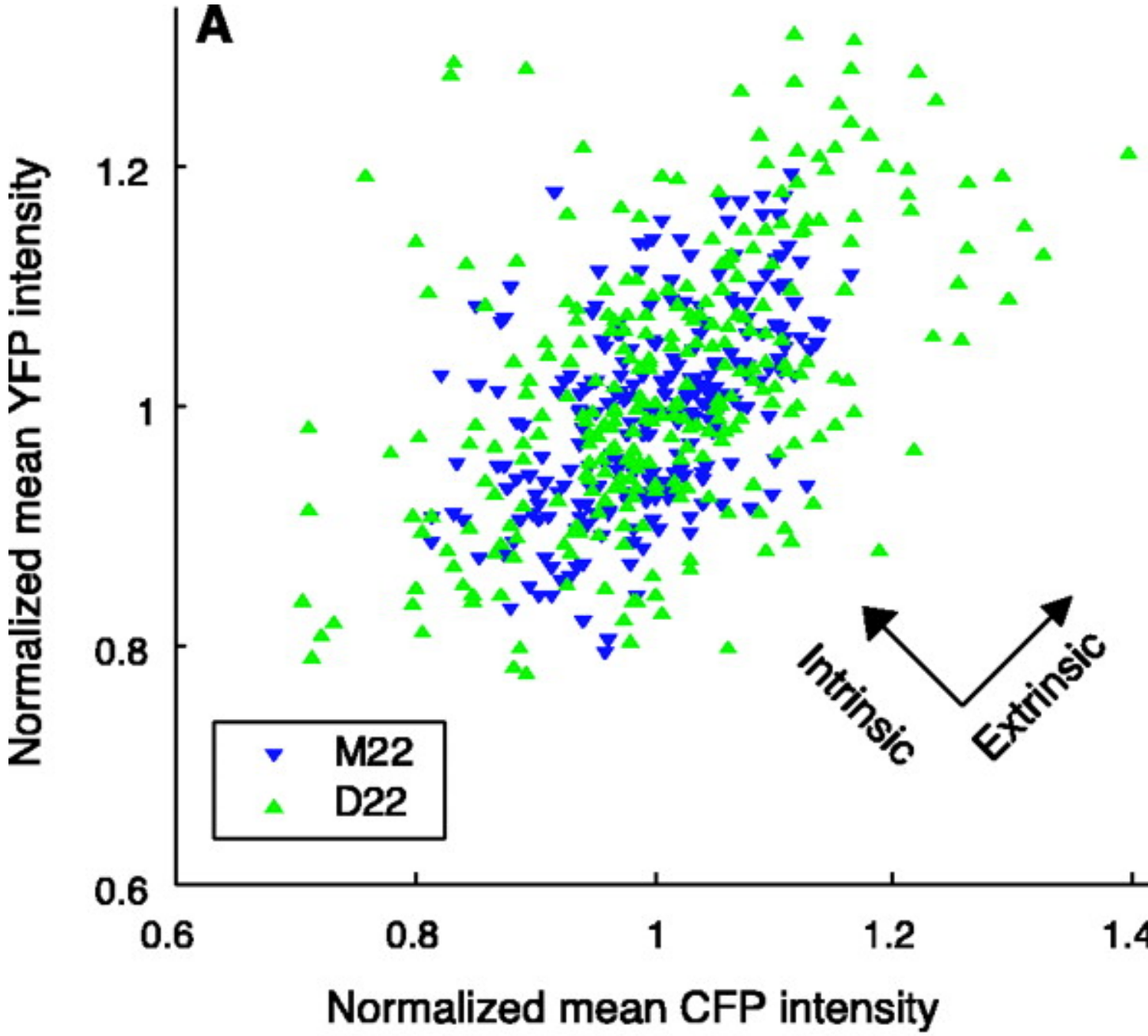
Cell-to-cell heterogeneity



Elowitz et al Science 2002

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$



Elowitz et al Science 2002

Cell-to-cell heterogeneity

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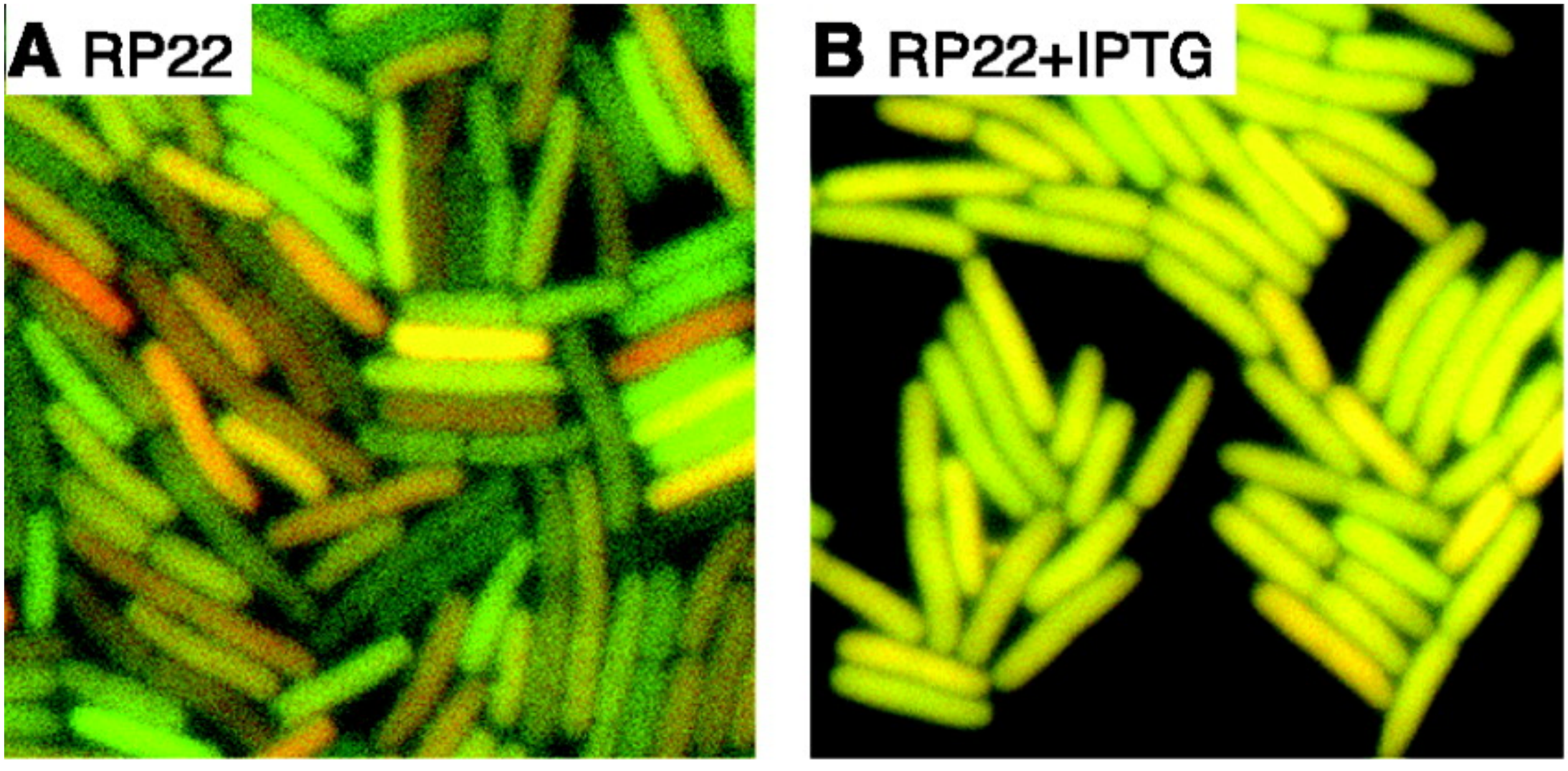

Elowitz et al Science 2002

Cell-to-cell heterogeneity

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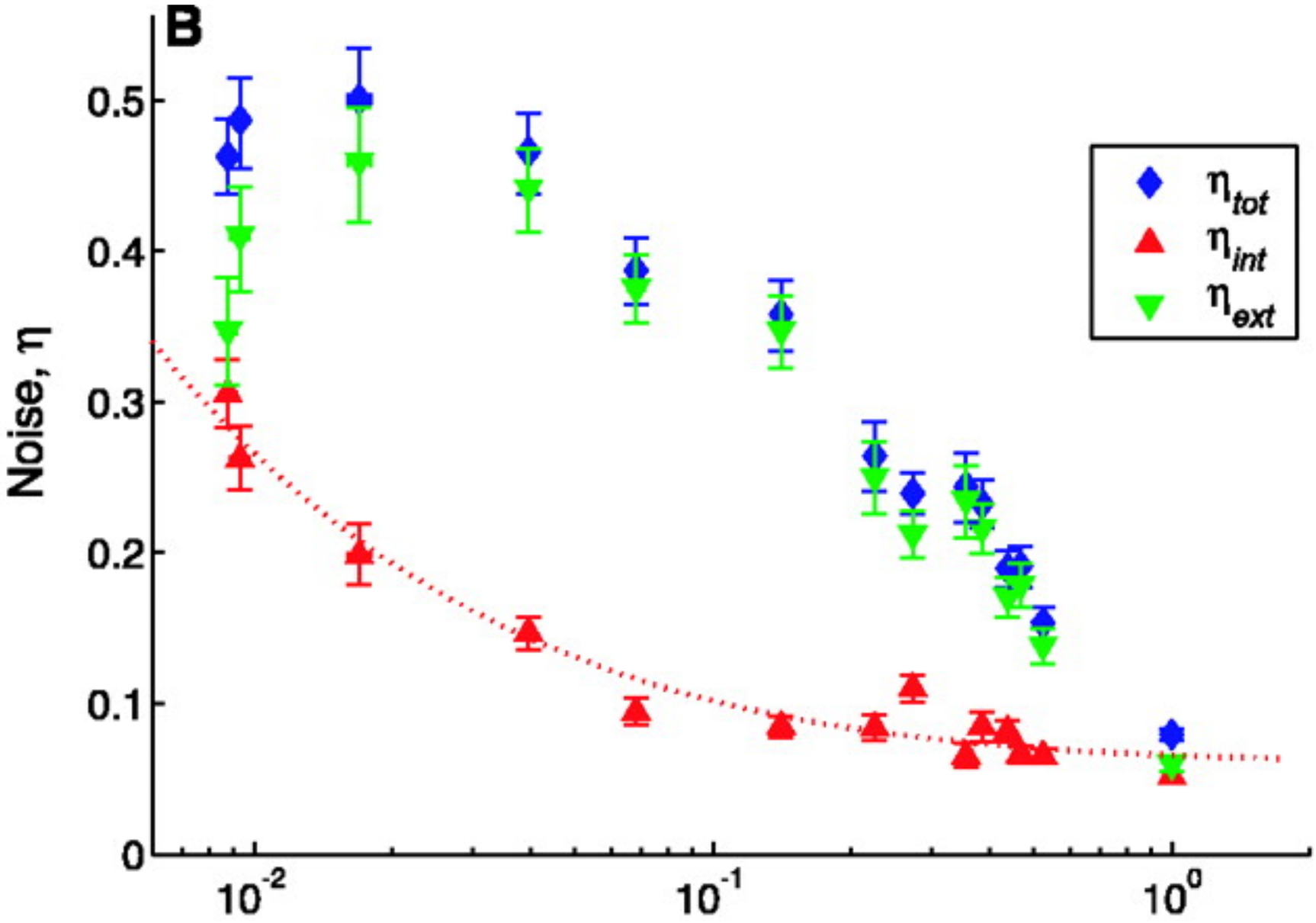
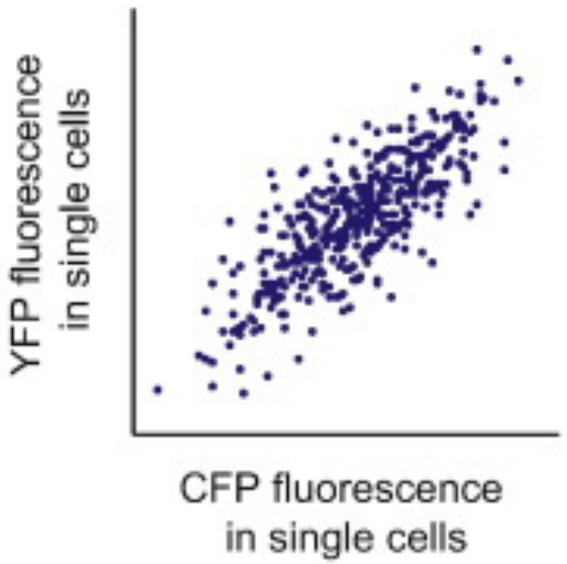


Elowitz et al Science 2002

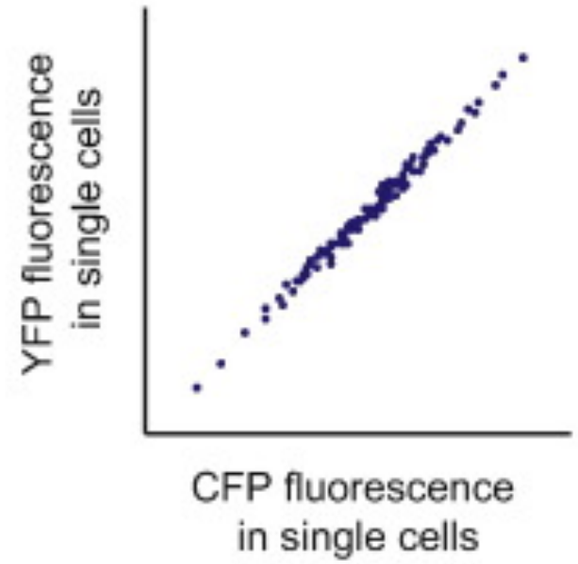
Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$

Single cell distribution

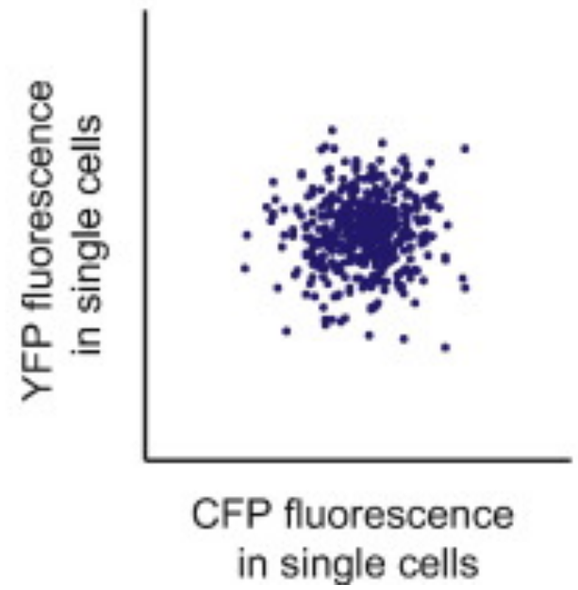


Extrinsic noise contribution

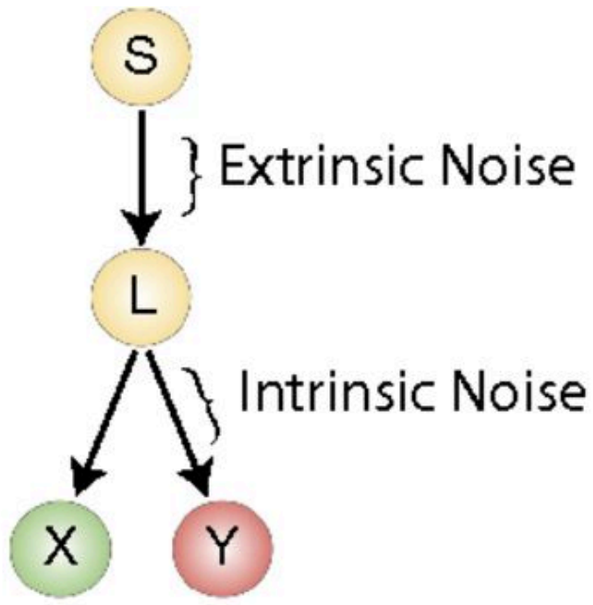


η_e non-stochastic noise?

Intrinsic noise contribution



η_i completely stochastic



Elowitz et al Science 2002

Cell-to-cell heterogeneity

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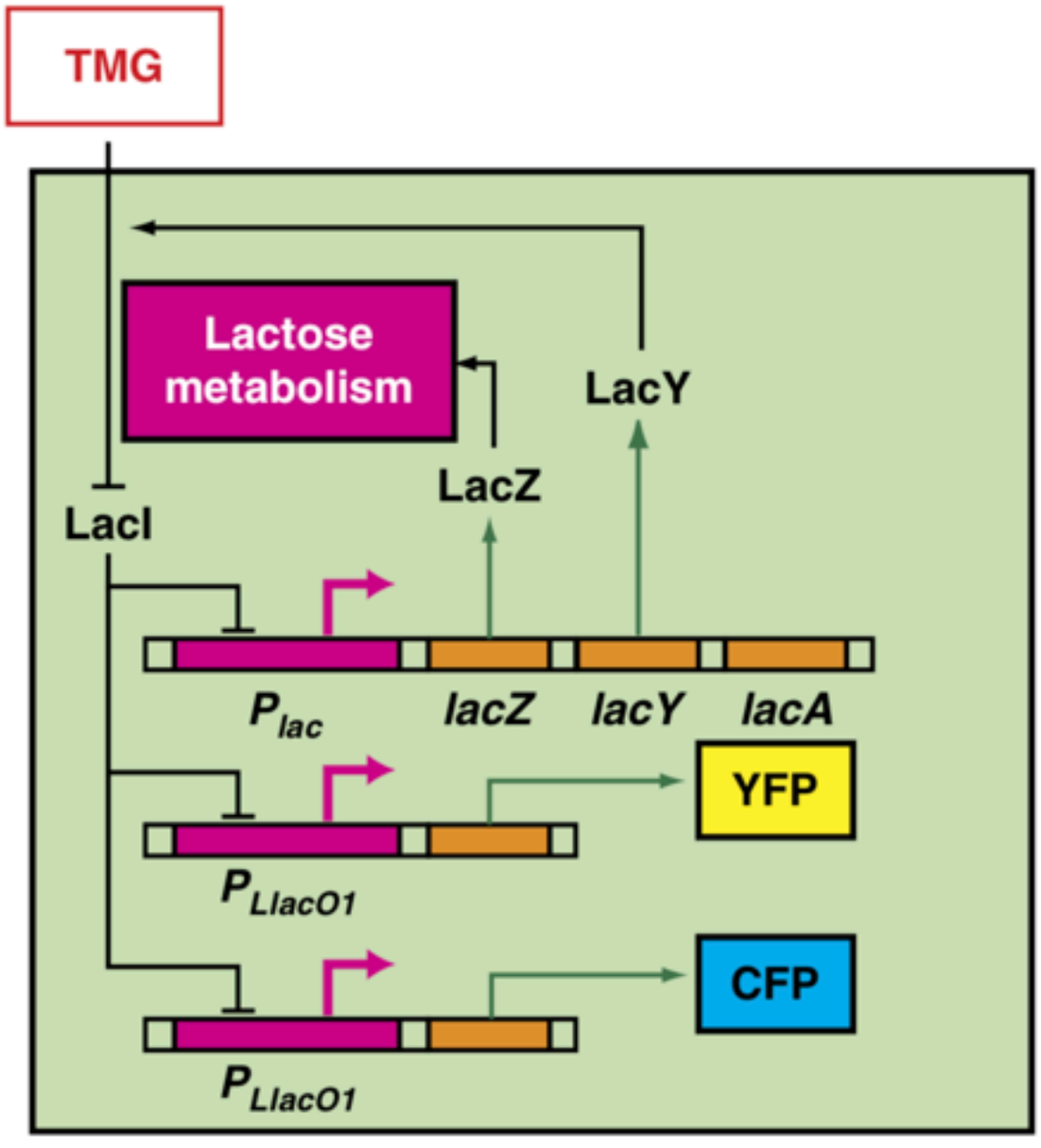
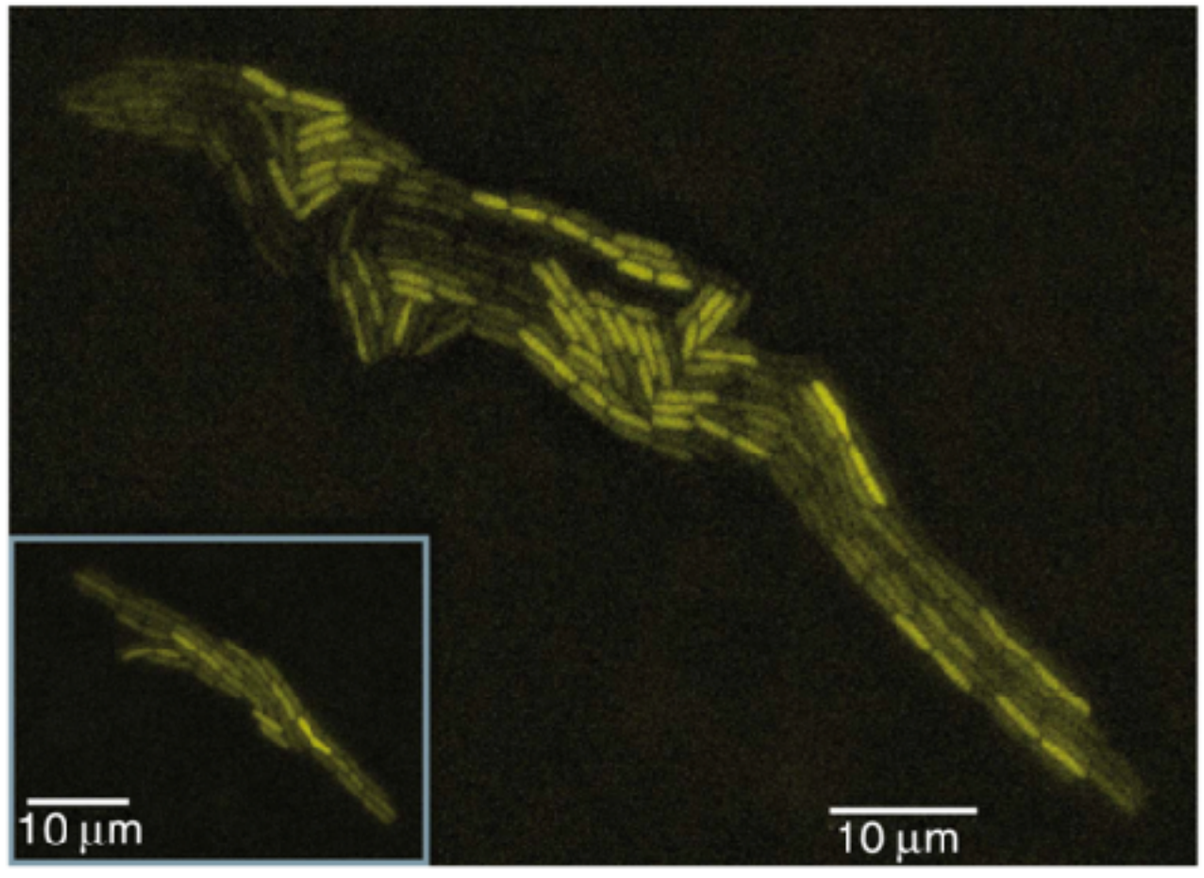
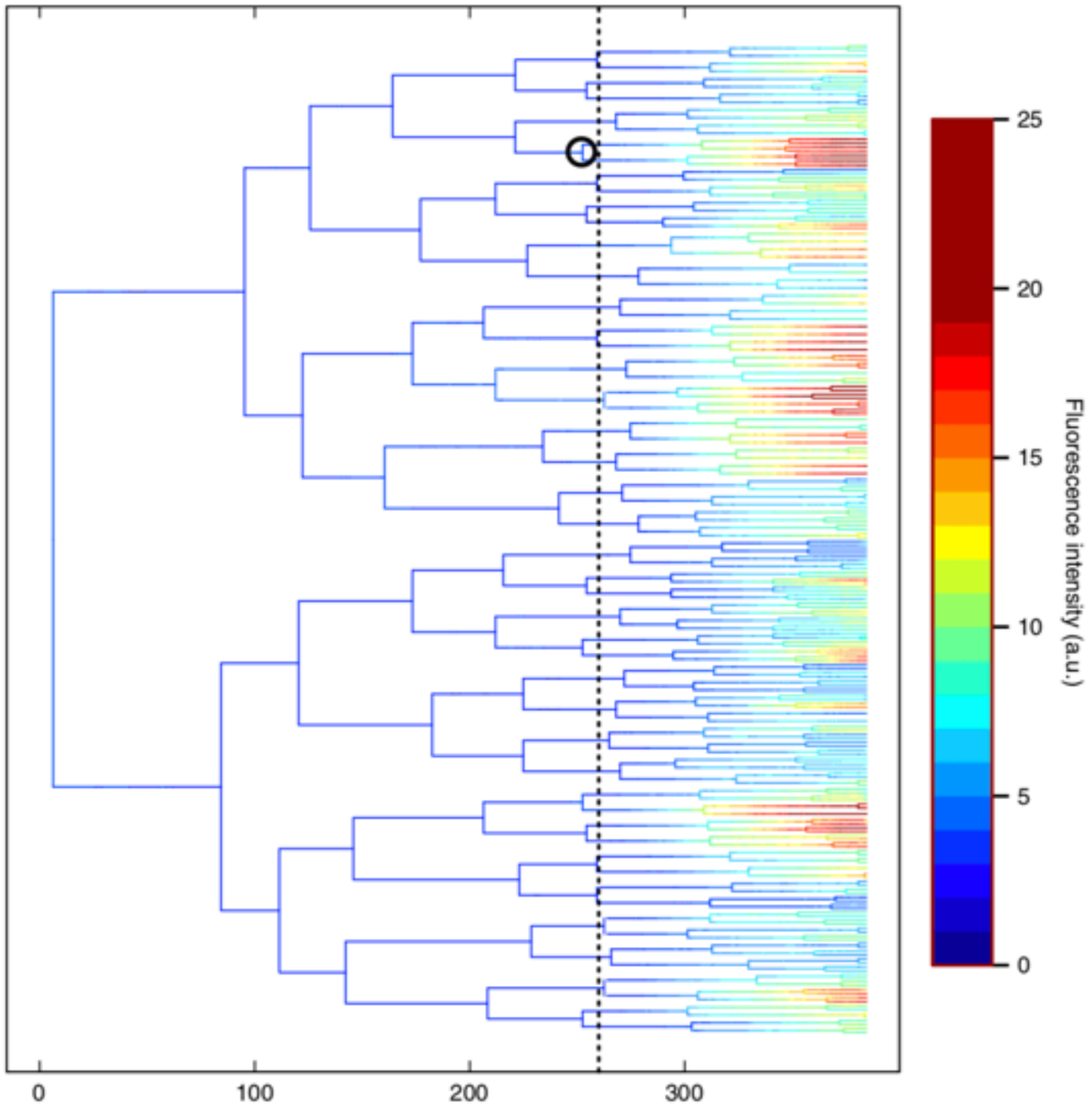




Robert et al Mol Sys Biol 2010

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$

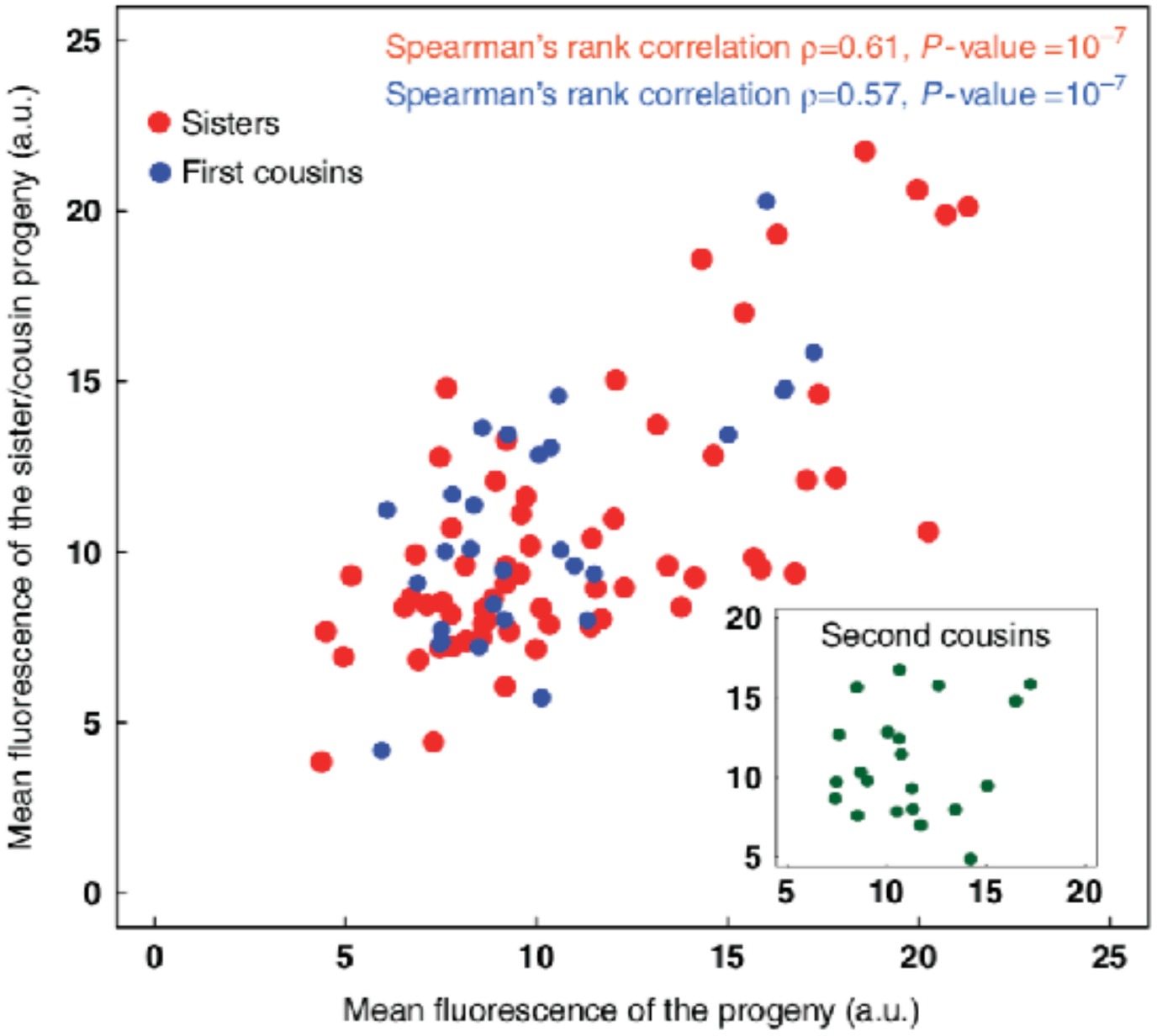


In this case the authors found that cells derived from a common progenitor have a high chance to respond similarly to TMG induction

Robert et al Mol Sys Biol 2010

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$



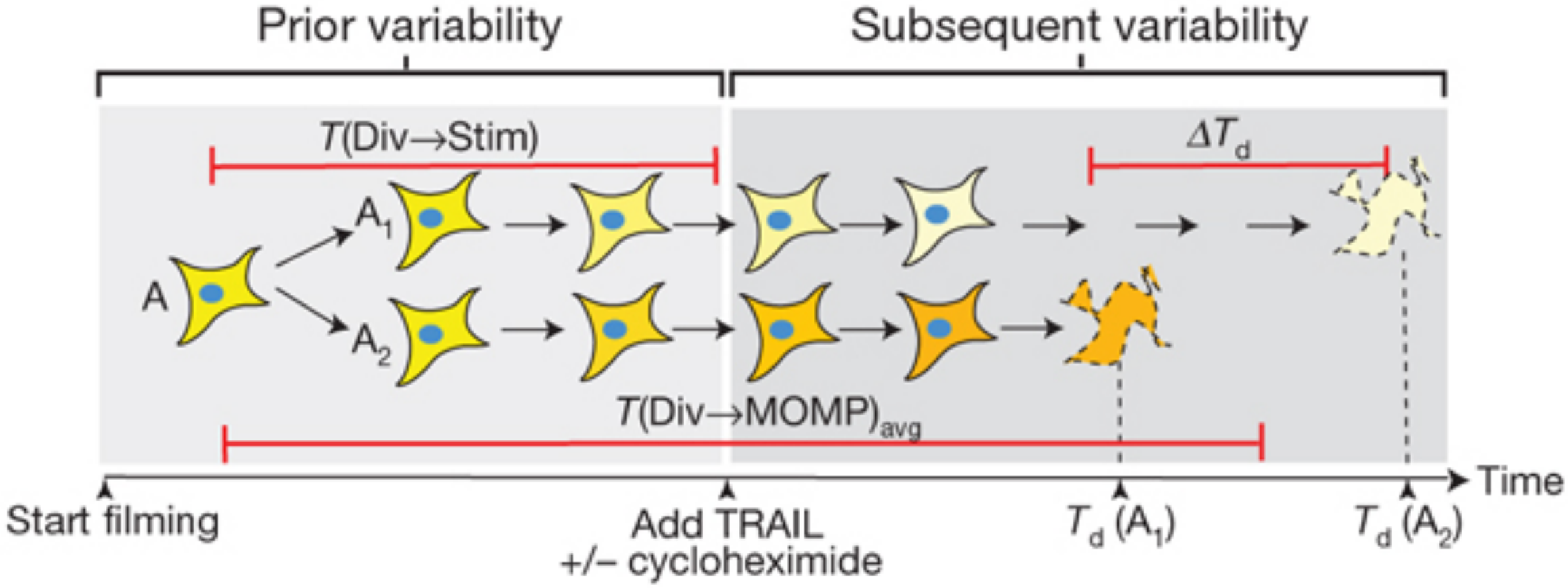
Our parameter is not completely stochastic as it can be predicted (with some precision) by evaluating the same parameter in lineage related cells.

Evaluating noise we have learnt something about biology….

Robert et al Mol Sys Biol 2010

Cell-to-cell heterogeneity

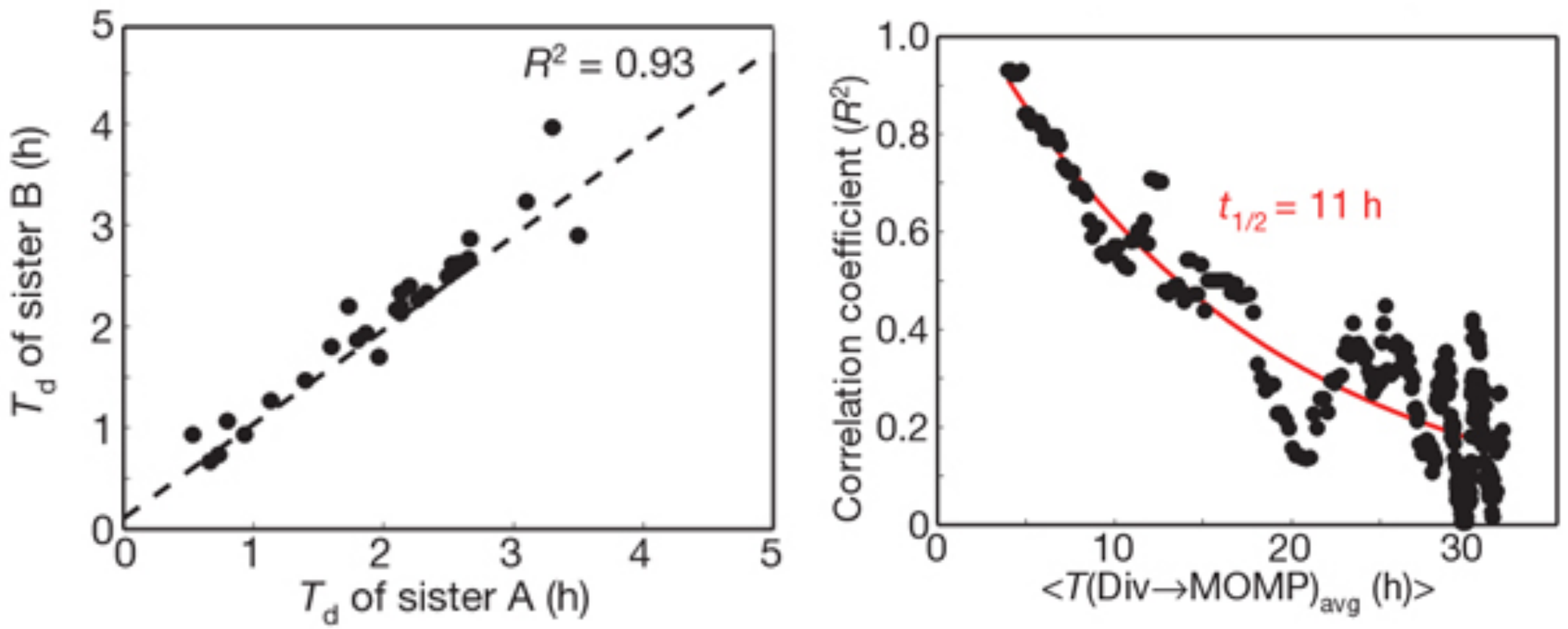
$$\eta_t = \eta_i + \eta_e$$



Spenser et al Nature 2009

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$

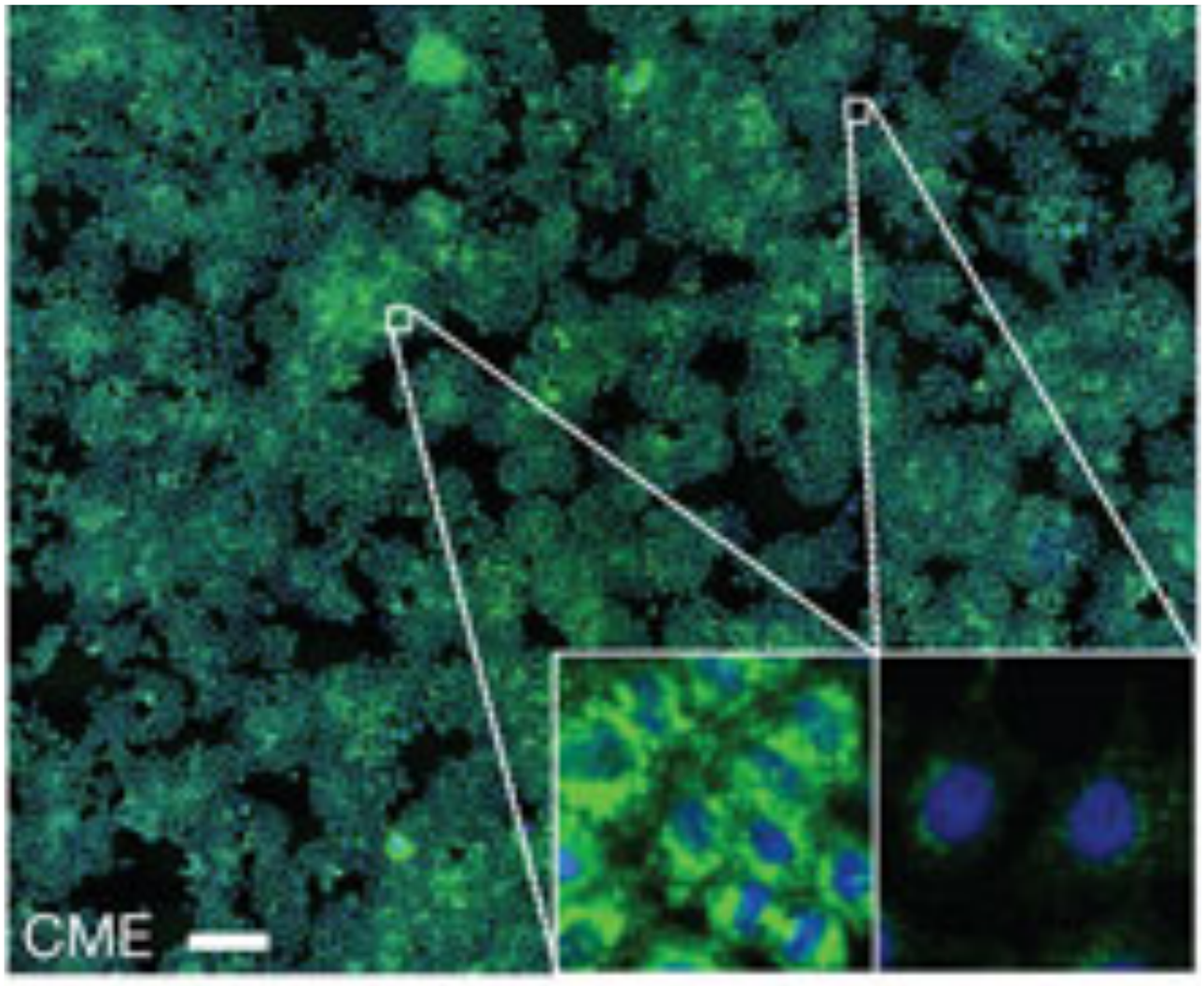


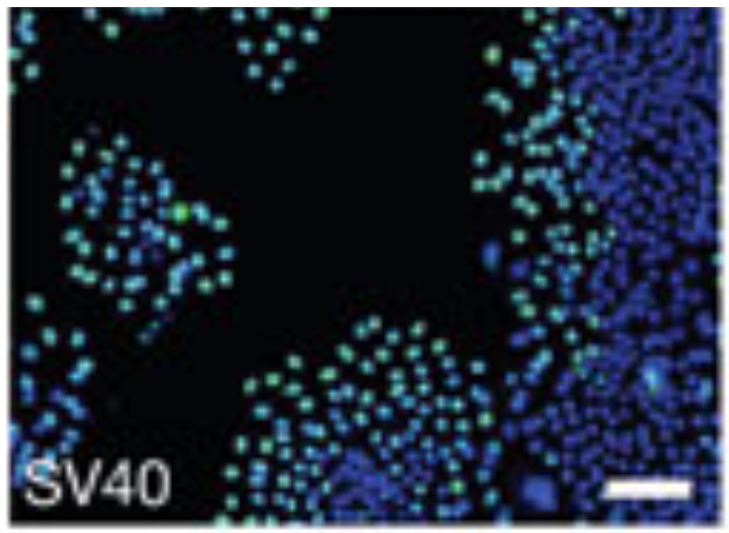
Here the heterogeneous cell response to pro-apoptotic stimuli is correlated with an inherited transient parameter.

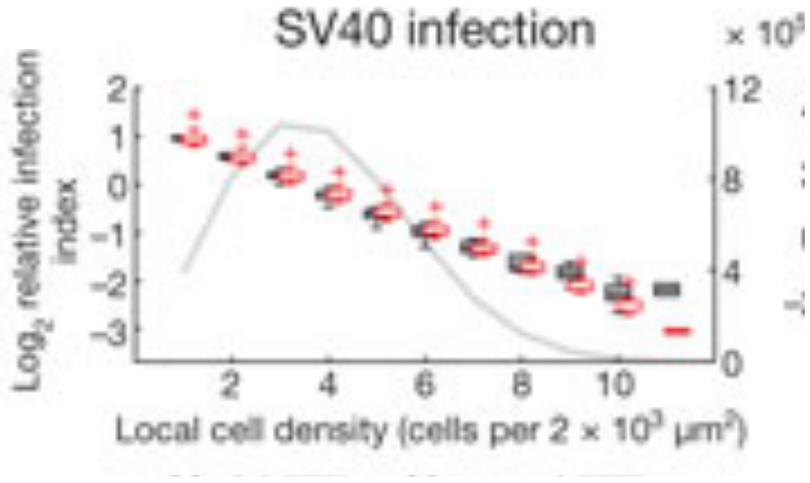
Spenser et al Nature 2009

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$





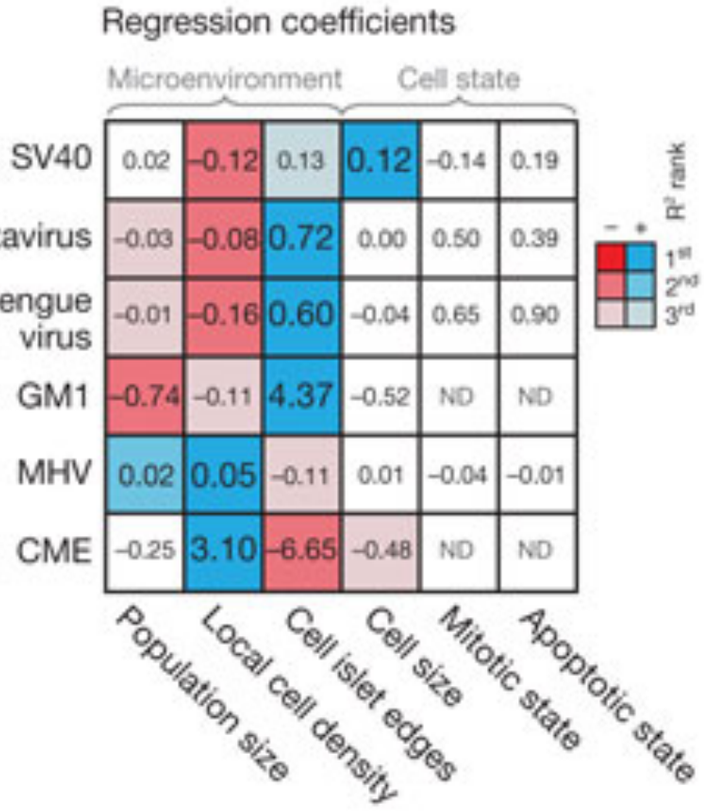


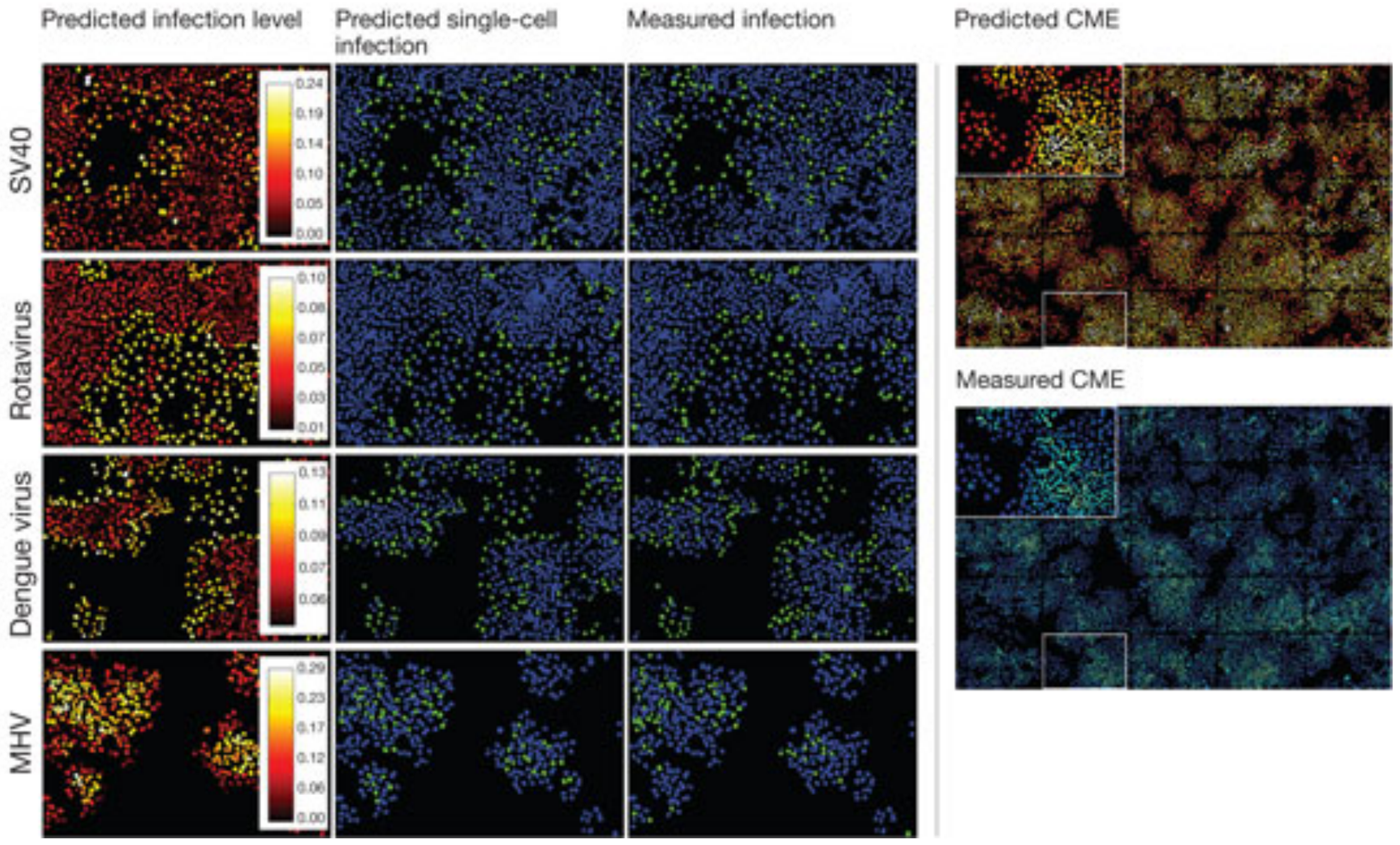
cell-to-cell variability can also derive from the microenvironmental context cells are in

Snijder et al Nature 2009

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$





Snijder et al Nature 2009

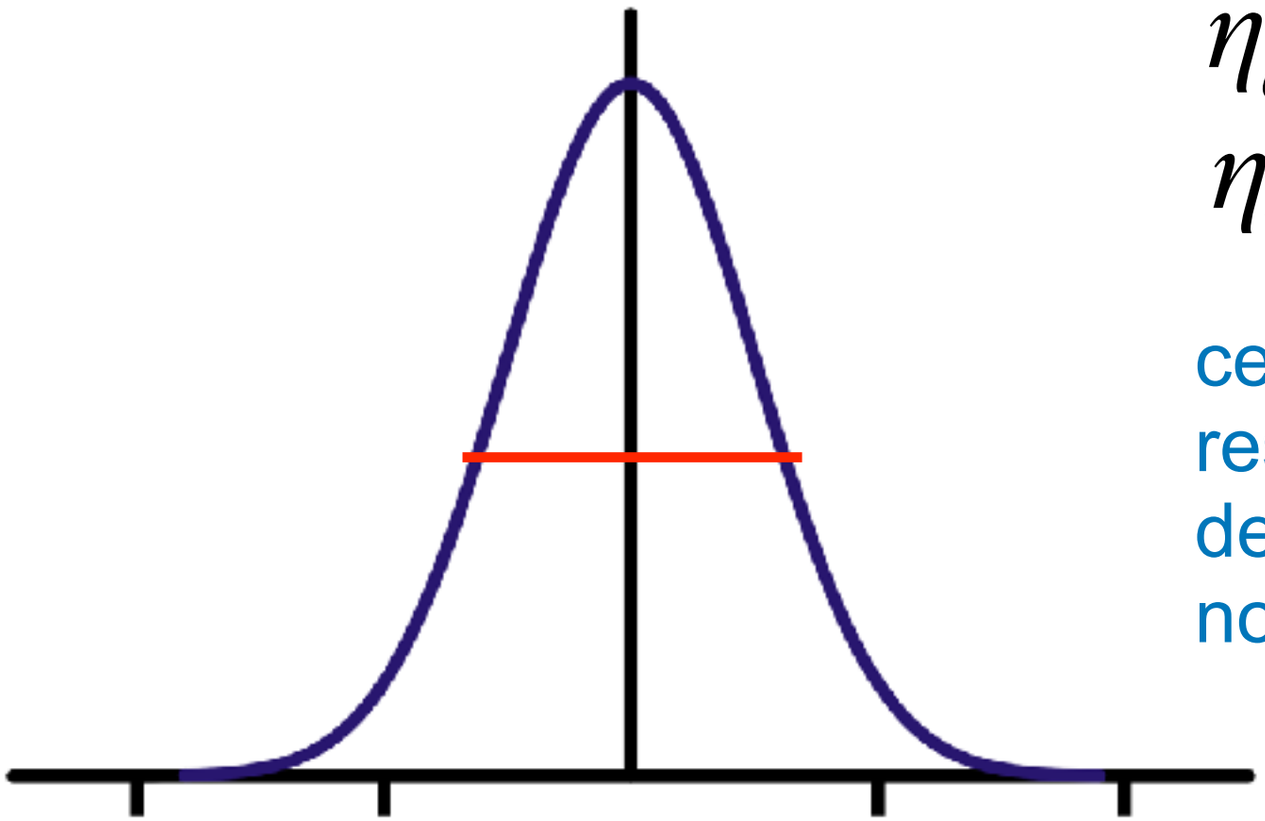
10’ Break

Cell-to-cell heterogeneity

$$\eta_t = \eta_i + \eta_e$$

$$\eta_e = \eta_d + \eta_\tau$$

$$\eta_t = \eta_i + (\eta_d + \eta_\tau)$$



η_t total cell-to-cell variation

η_i Intrinsic noise

η_e extrinsic variation

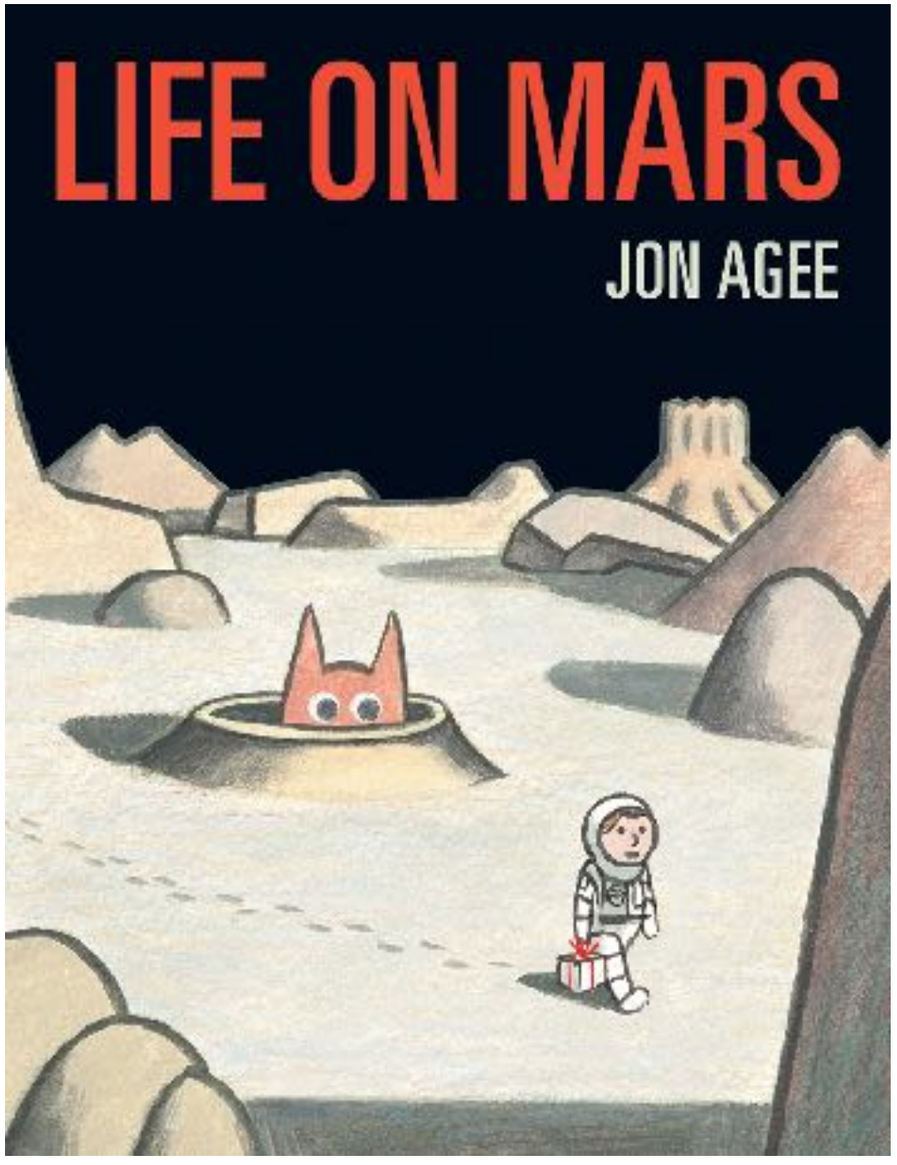
η_d deterministic variation

η_τ teleonomic variation

cell-to-cell variability is often the result of deterministic processes, despite the existence of intrinsic noise in molecular networks.

When does deterministic variability has biological meaning?

Cell-to-cell heterogeneity



Of Strange Objects

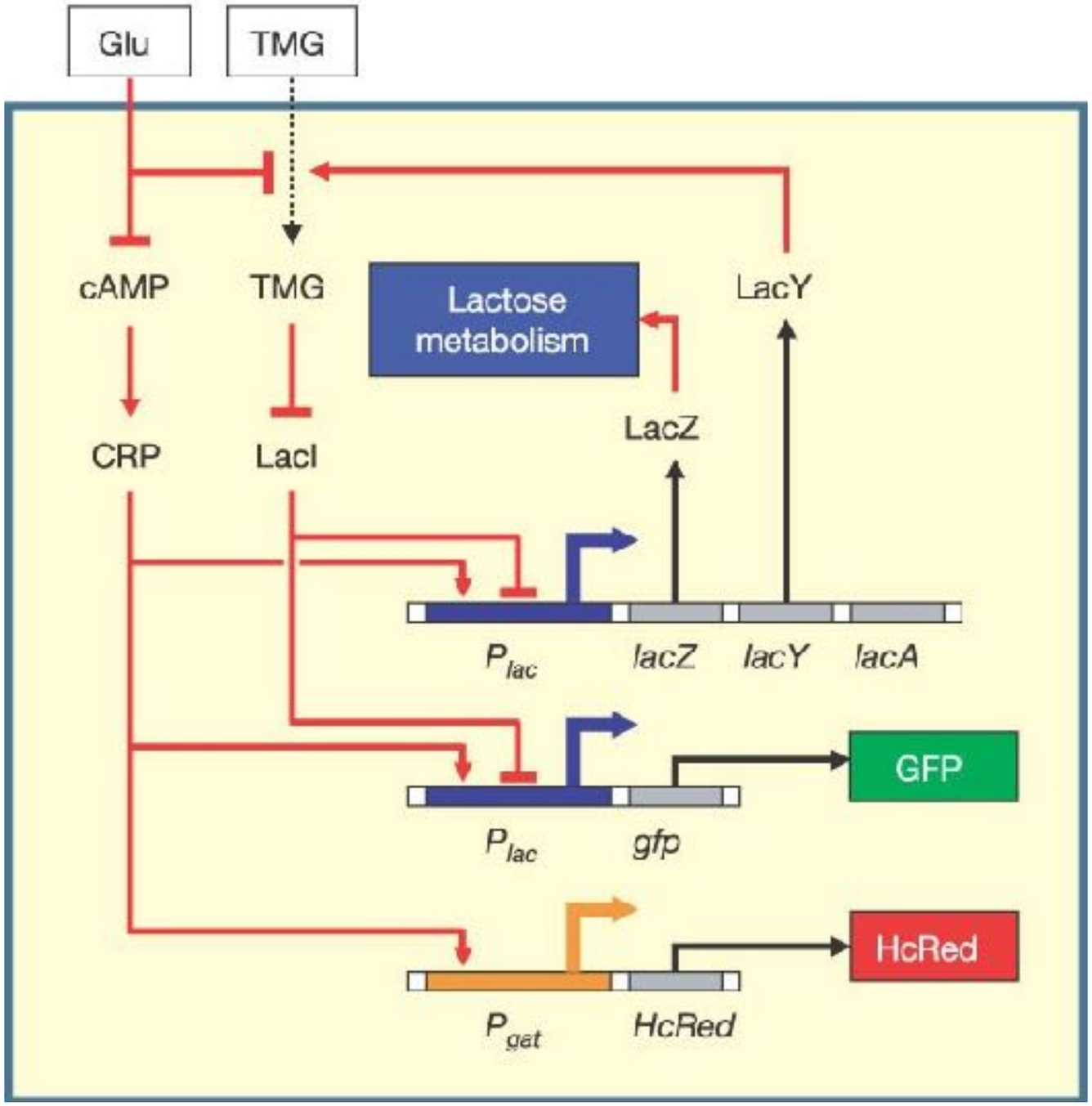
Let us suppose that a spacecraft is soon to be landed upon Venus or Mars; what more fascinating question than to find out whether our neighboring planets are, or at some earlier period have been, inhabited by intelligent beings capable of projective activity? In order to detect such present or past activity we would have to search for and be able to recognize its products, however radically unlike the fruit of human industry they might be. Wholly ignorant of the nature of such beings and of the projects they might have conceived, our program would have to utilize only very general criteria, solely based upon the examined objects' structure and form and without any reference to their eventual function.

Jacques Monod , Chance and Necessity 1970

Teleonomy is the quality of apparent purposefulness and of goal-directedness of structures and functions in living organisms brought about by natural processes like natural selection.

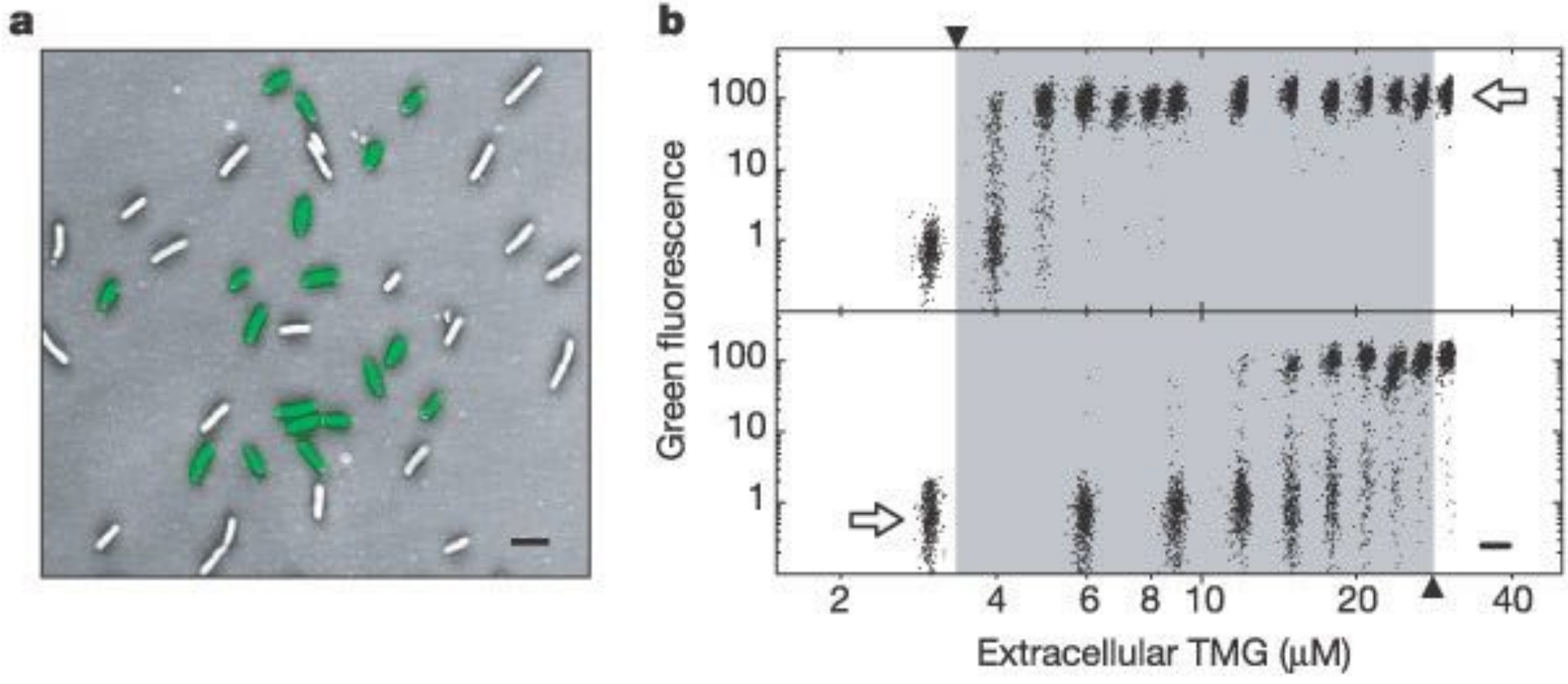
Cell-to-cell heterogeneity as a **programmed feature** of living objects

Teleonomic heterogeneity



Ozbudak et al Nature 2004

Teleonomic heterogeneity



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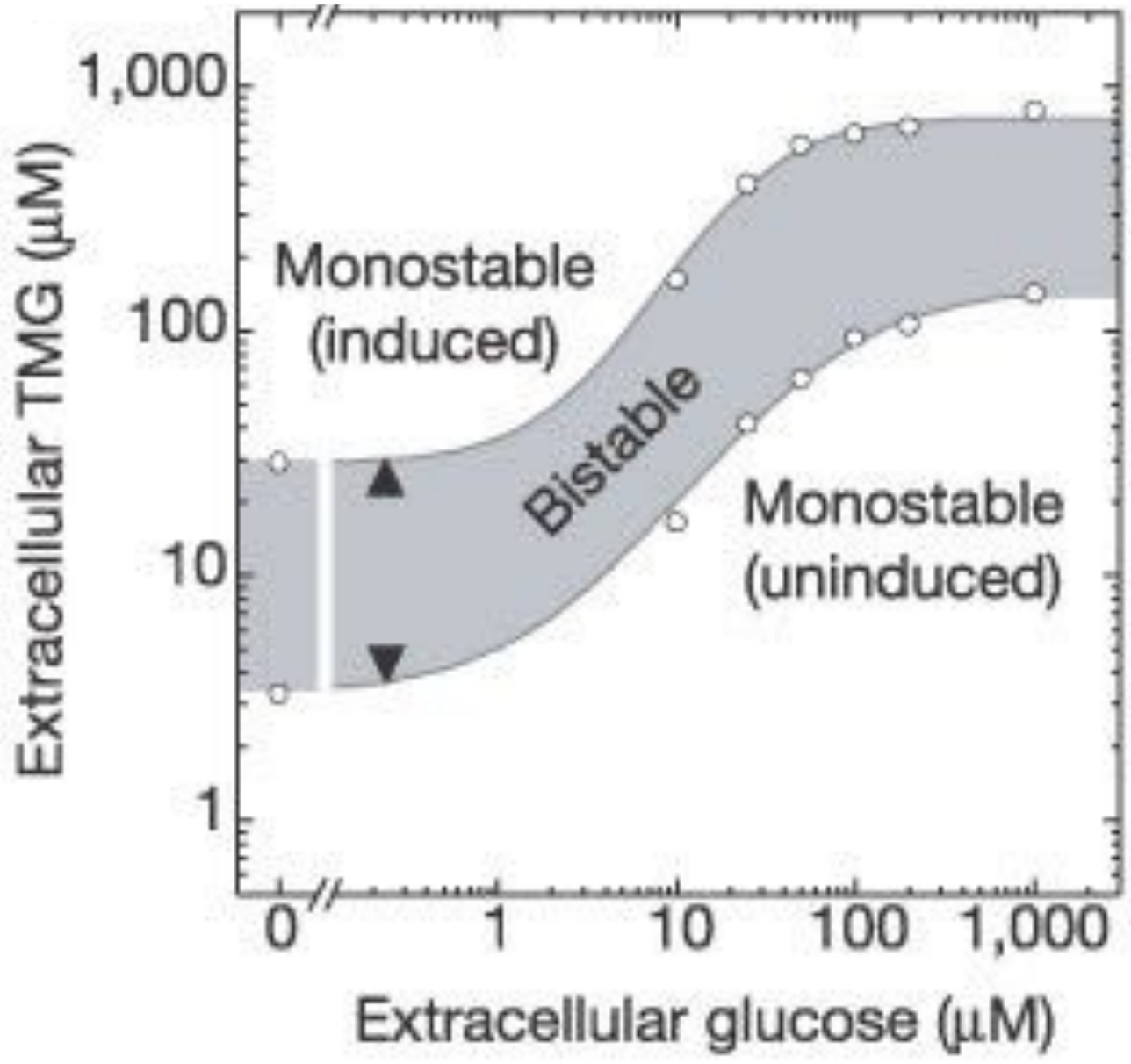
Teleonomic heterogeneity

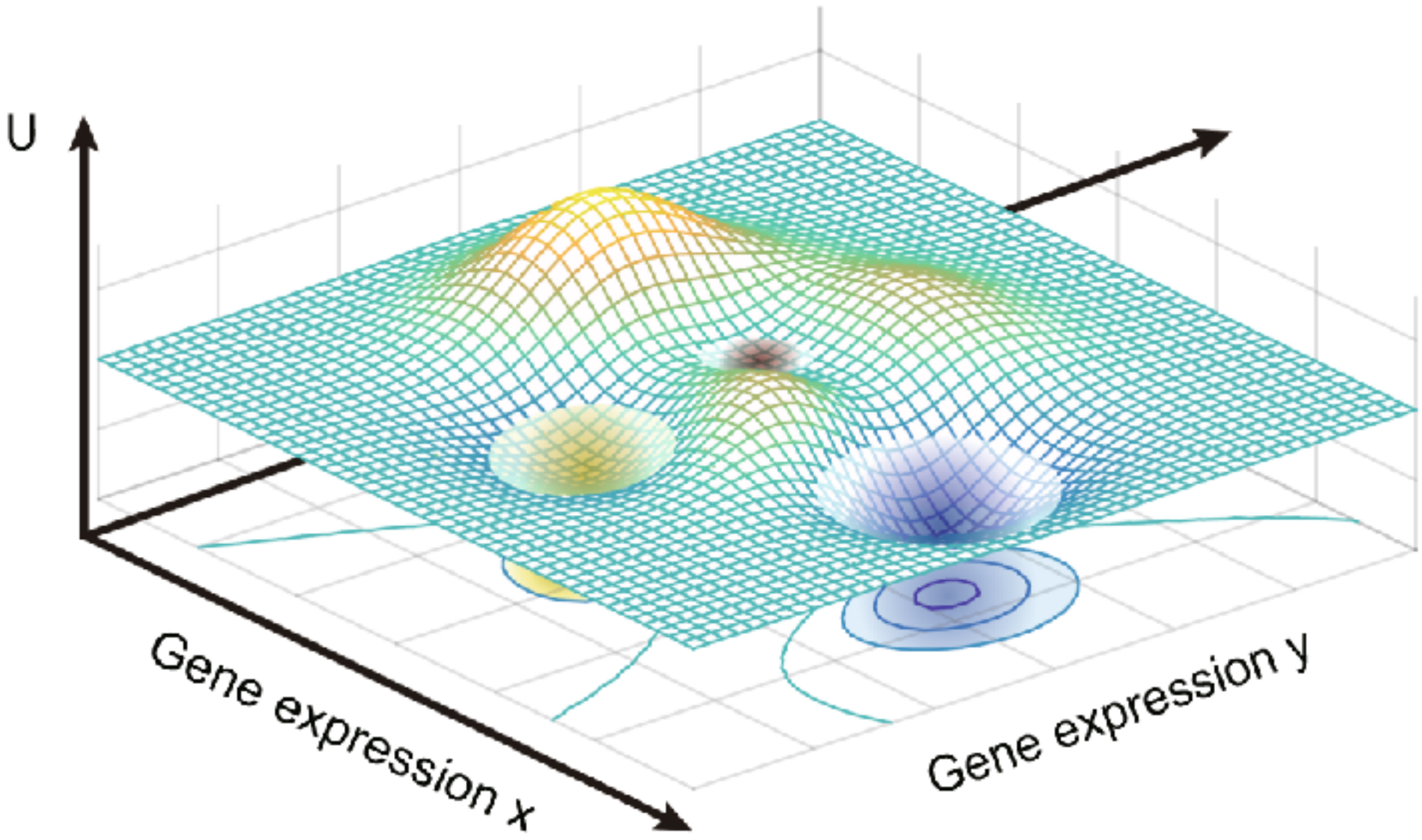


E. Coli can grow in media containing glucose or lactose. When glucose is presence in sufficient amounts the Lac operon is switched off. When Lactose (TMG here) is the the only source of energy the Lac operon is activated. In intermediate conditions *E. Coli* acquires a bistable population behaviour where some cells only use glucose and other use lactose

Here heterogeneity as a **programmed feature** of E. Coli to quickly adapt to changing environment [population dynamic] -> advantage

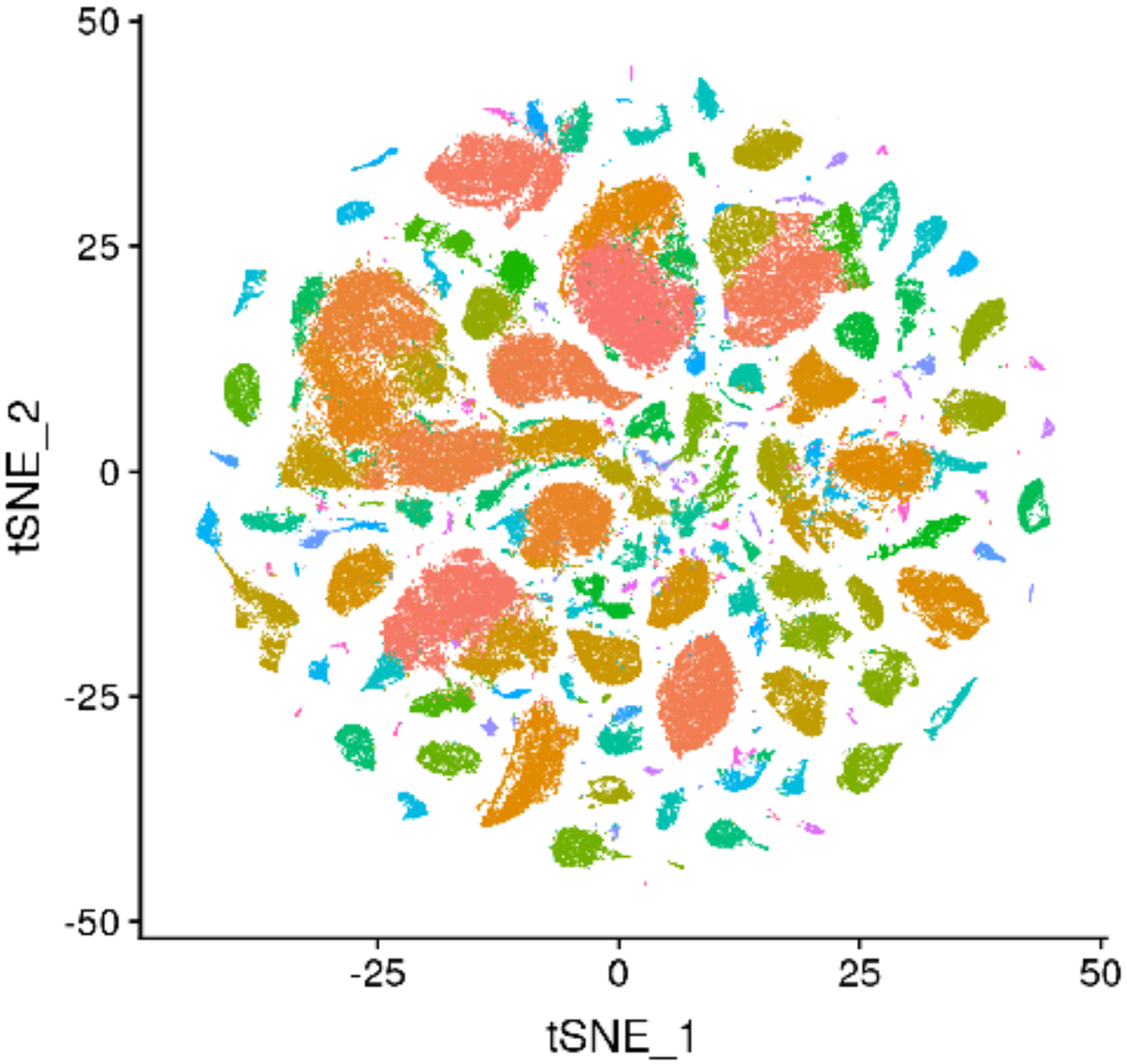
Ozbudak et al Nature 2004

Teleonomic heterogeneity



Regulatory circuits that generate stable phenotypic states have been selected by evolution to account for multicellularity

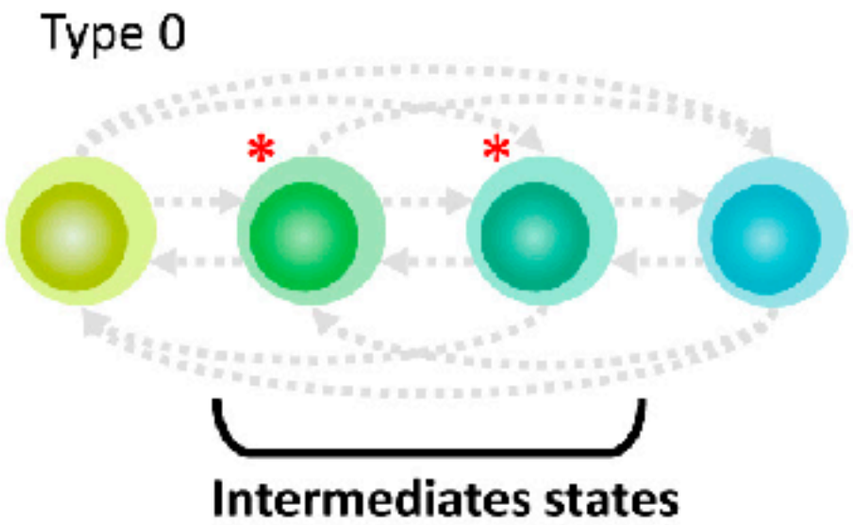
Teleonomic heterogeneity



Gene/ signalling/ or metabolic networks are integrated to produce the cell-to-cell heterogeneity associated with the existence of **cell states** and **cell types**

Cell States and Cell Types

Cell States:
conversions are largely
Heterarchical



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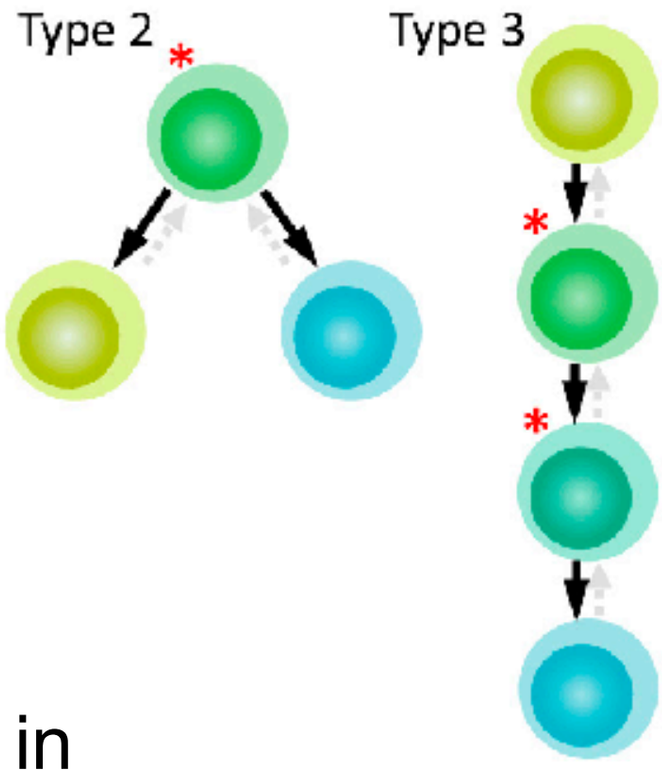
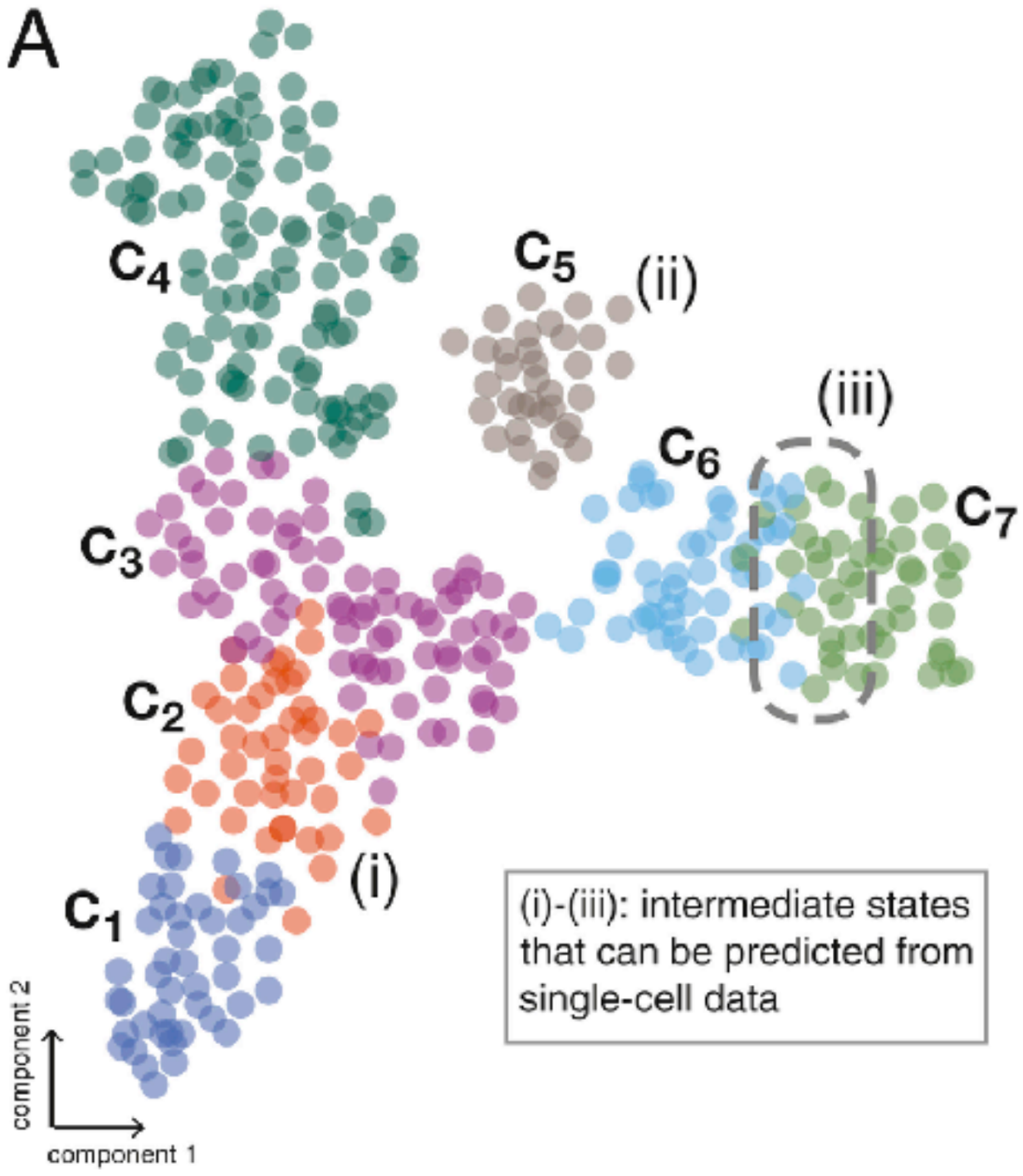
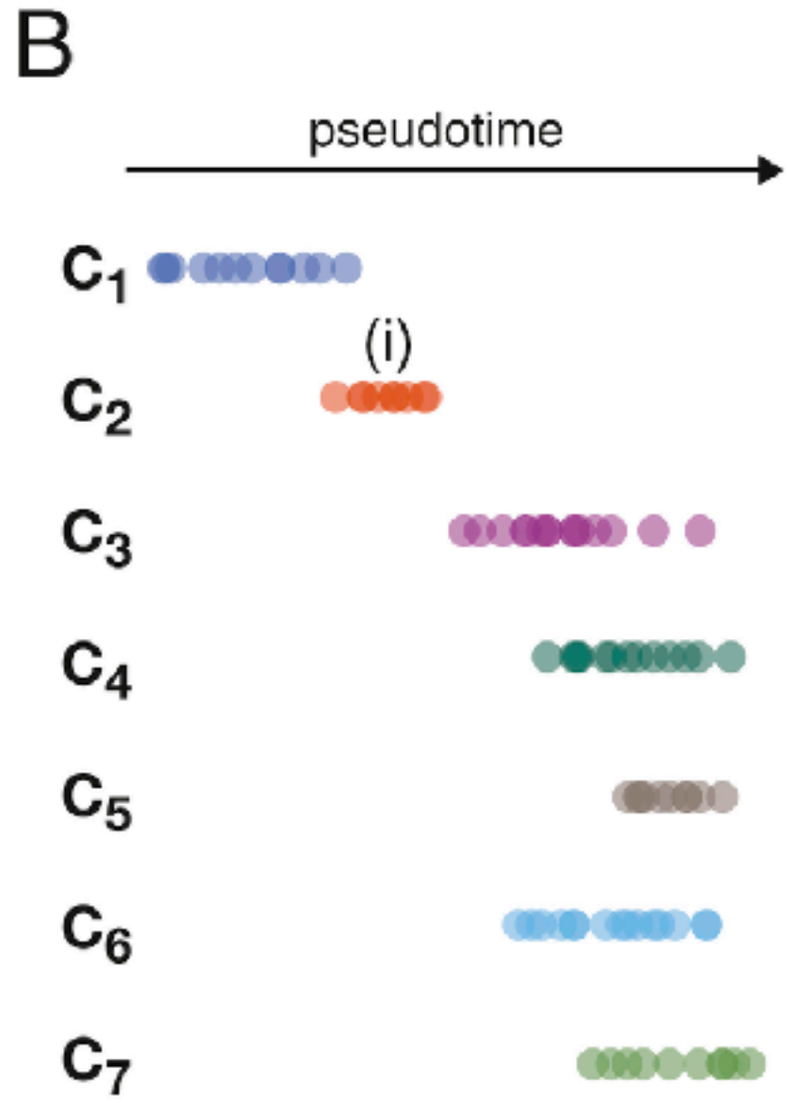


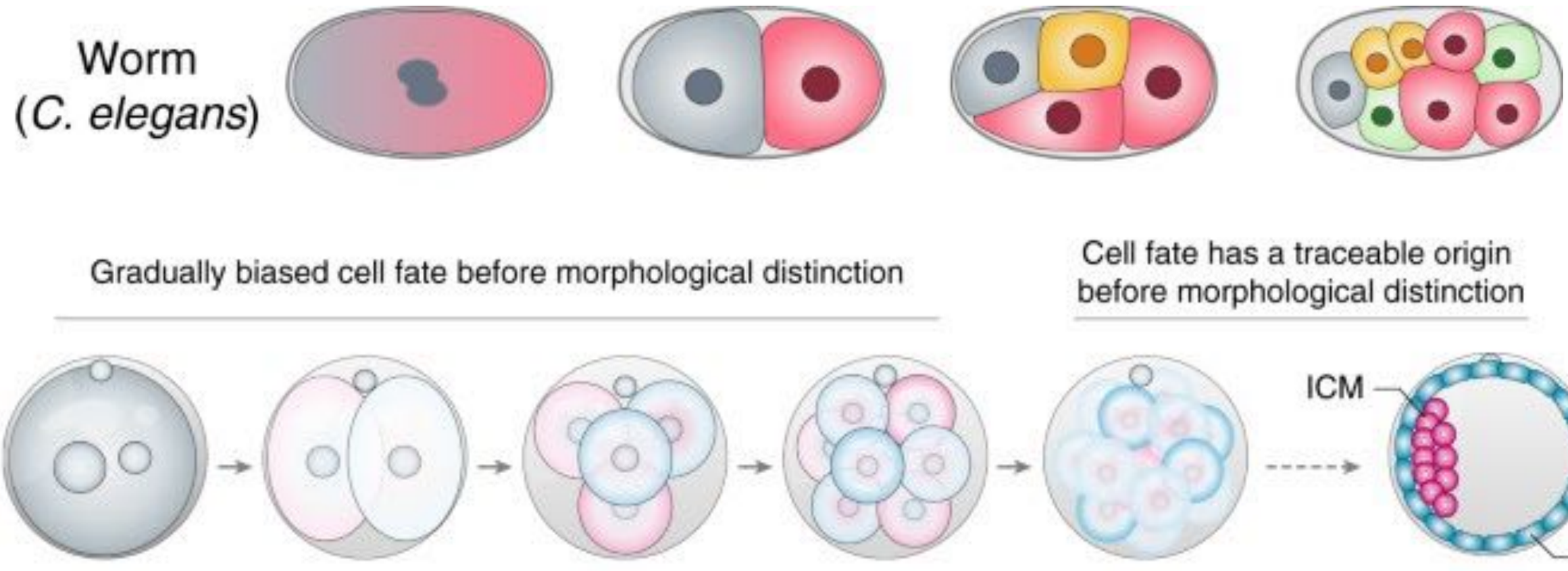
Cell States can be intermediates in the conversion between cell types

Cell States and Cell Types



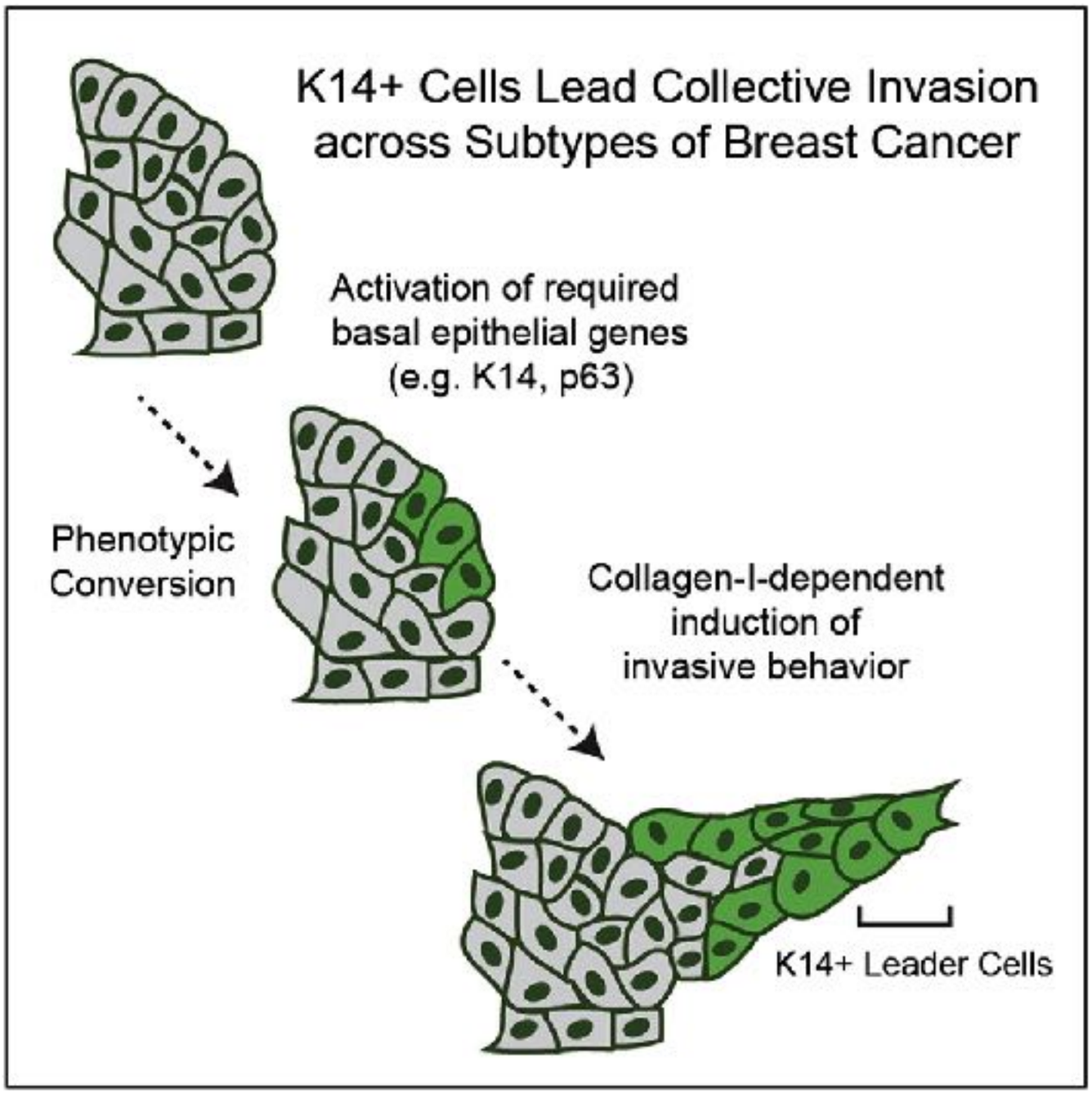


Cell States and Cell Types and symmetry breaking



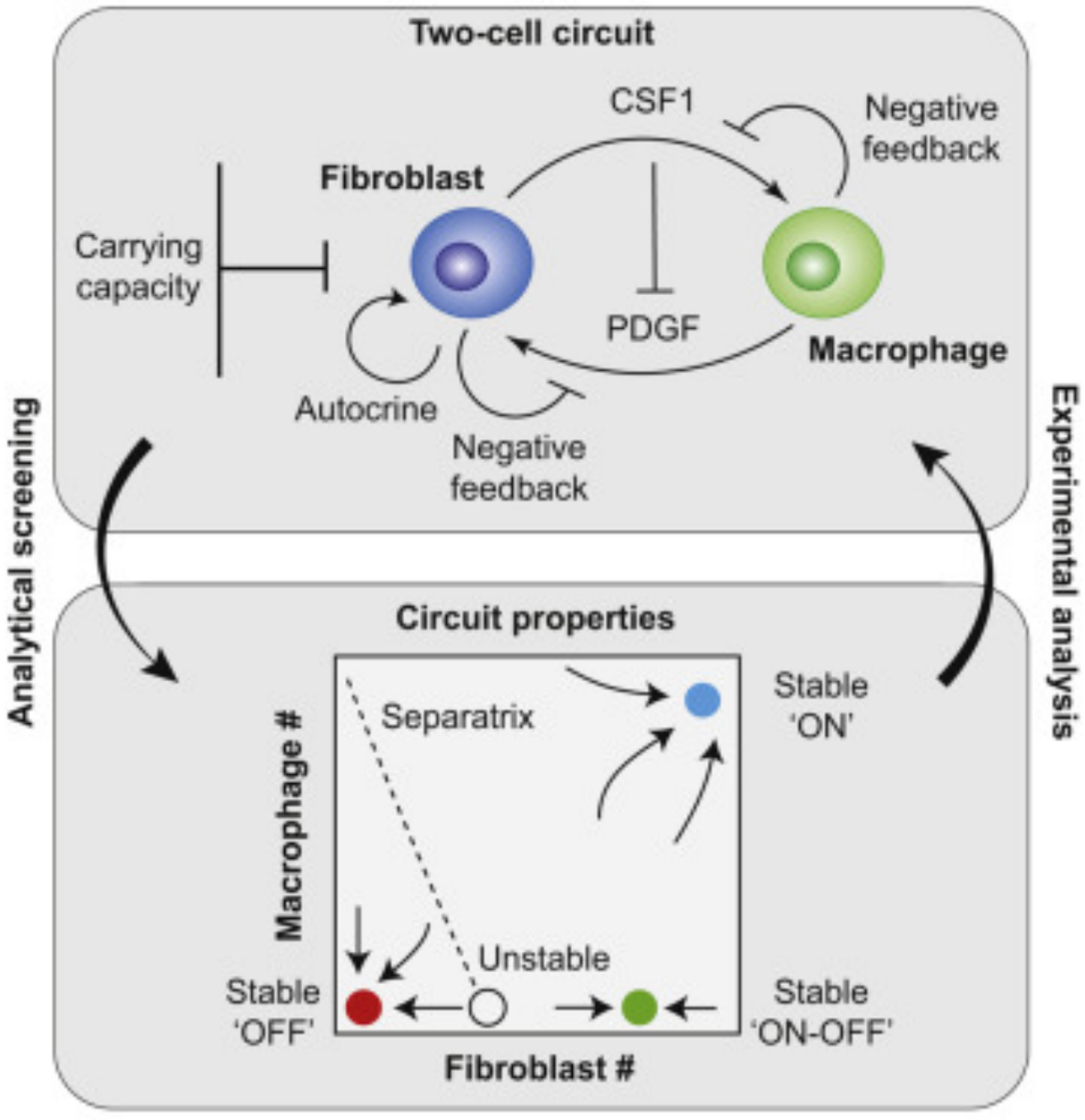
Cell States can set the background state bias on which diverging differentiation programs are triggered

Cell States and Cell Types and symmetry breaking



Cell States can trigger **collective cell behaviours**

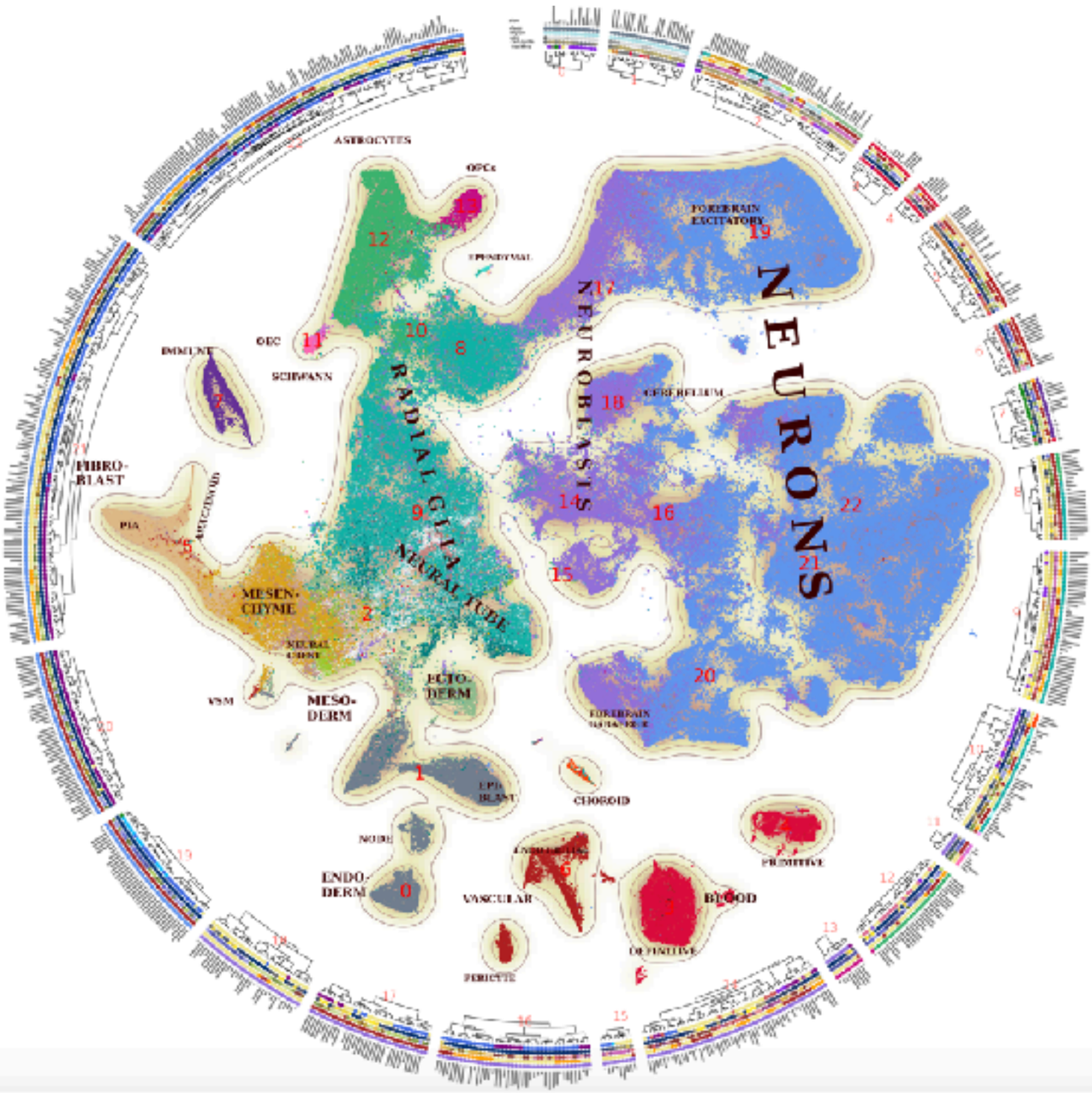
Cell Circuits



Cells of different types (states) are not isolated entities but they communicate and often control each other identity and proportions in cell populations.

In other words multicellular systems can be described as **microscopic societies** composed by different types of individuals that interact to maintain their heterogeneity

Cell Atlases



Our current challenge is to understand how the different cells that compose our tissues emerge and get organised to mediate multicellular life.

Thank you