Growing from a few cells to a population (and back)

G. Amselem, A. Barizien, C. Baroud
(LadHyX & Institut Pasteur)

T. Roget, A. Marguet, V. Bansaye, S. Méléard
(CMAP)

Prokaryotes

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 6578–6583, June 1998

Perspective

Prokaryotes: The unseen majority

*William B. Whitman**†, *David C. Coleman*‡, *and William J. Wiebe*§

10^{30} prokaryotes on Earth

10^{5}-10^{6} prokaryotes/mL water

10^{6}-10^{9} prokaryotes/gram soil

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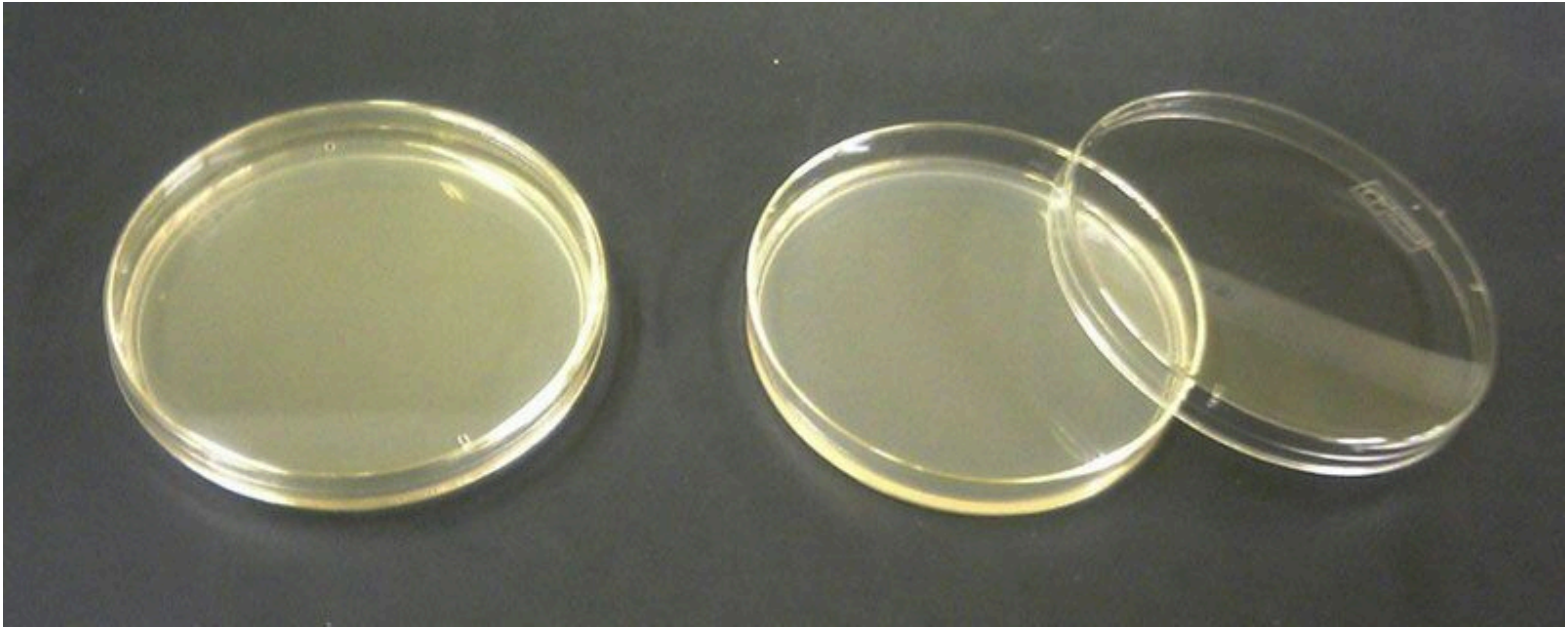
Host-Bacterial Mutualism in the Human Intestine

Fredrik Bäckhed,* Ruth E. Ley,* Justin L. Sonnenburg, Daniel A. Peterson, Jeffrey I. Gordon†

SCIENCE VOL 307 25 MARCH 2005

10^{14} bacteria/human gut (10x more than our cells)

Microbial growth 101



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Hand print on a large TSA plate from my 8 1/2 year old son after playing outside.

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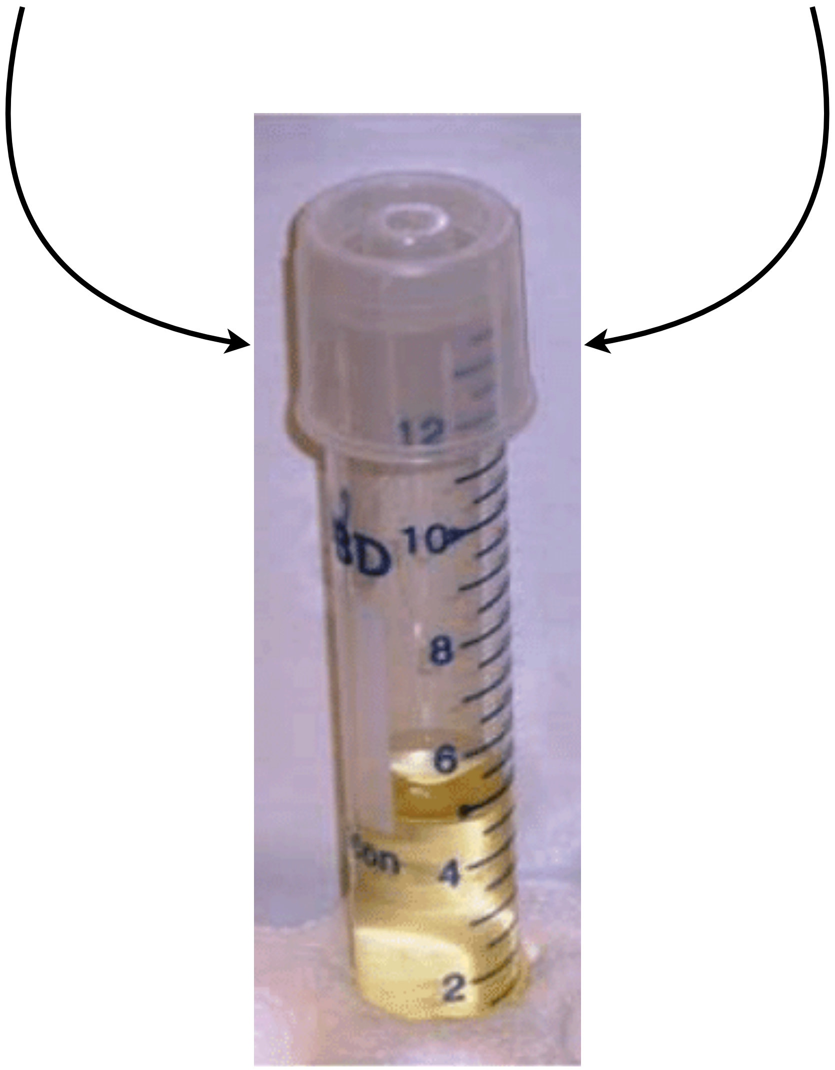

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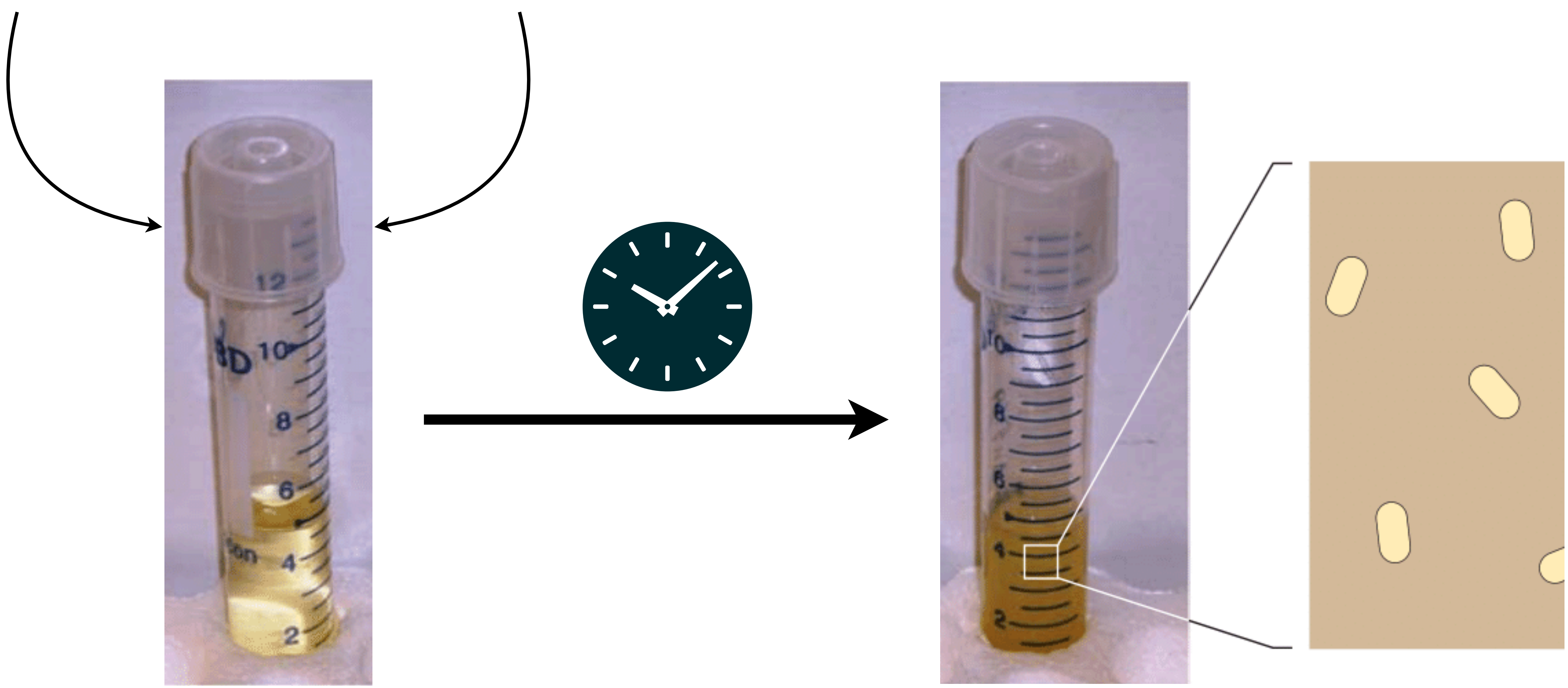
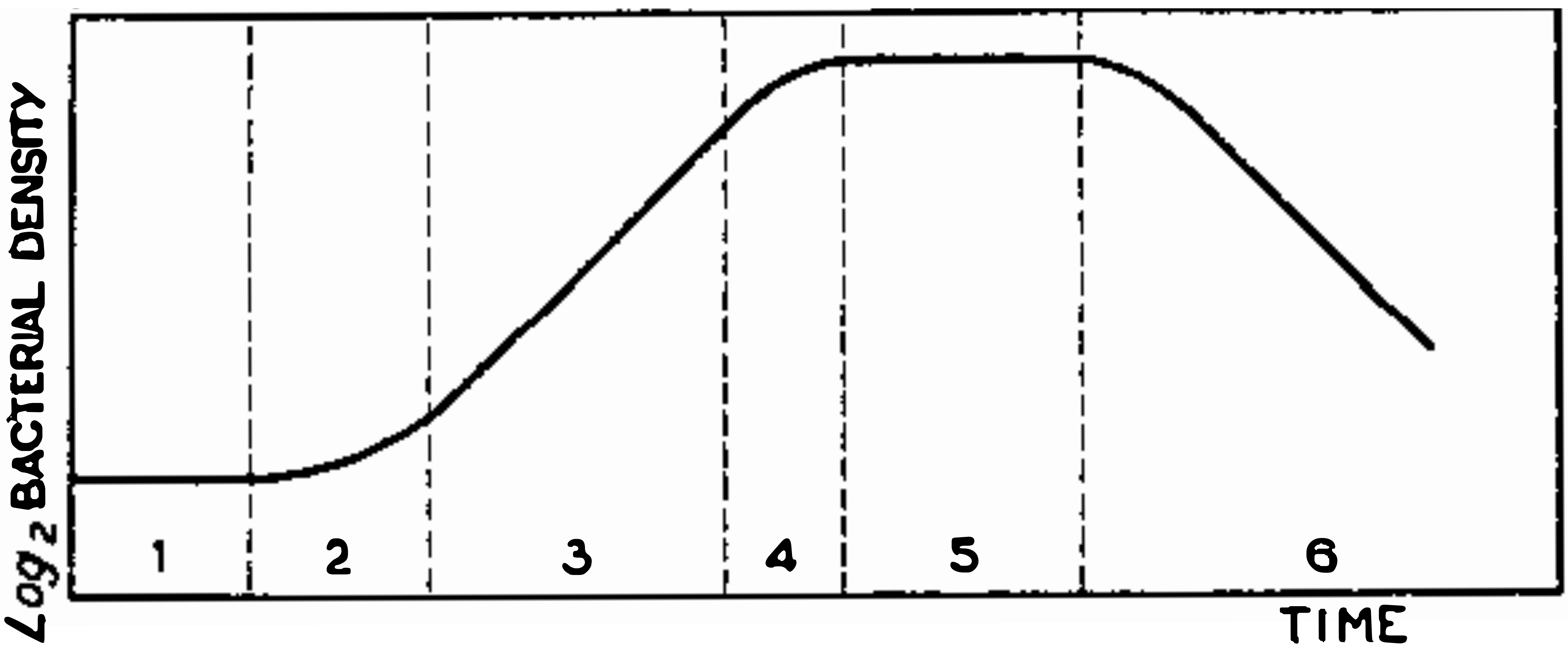
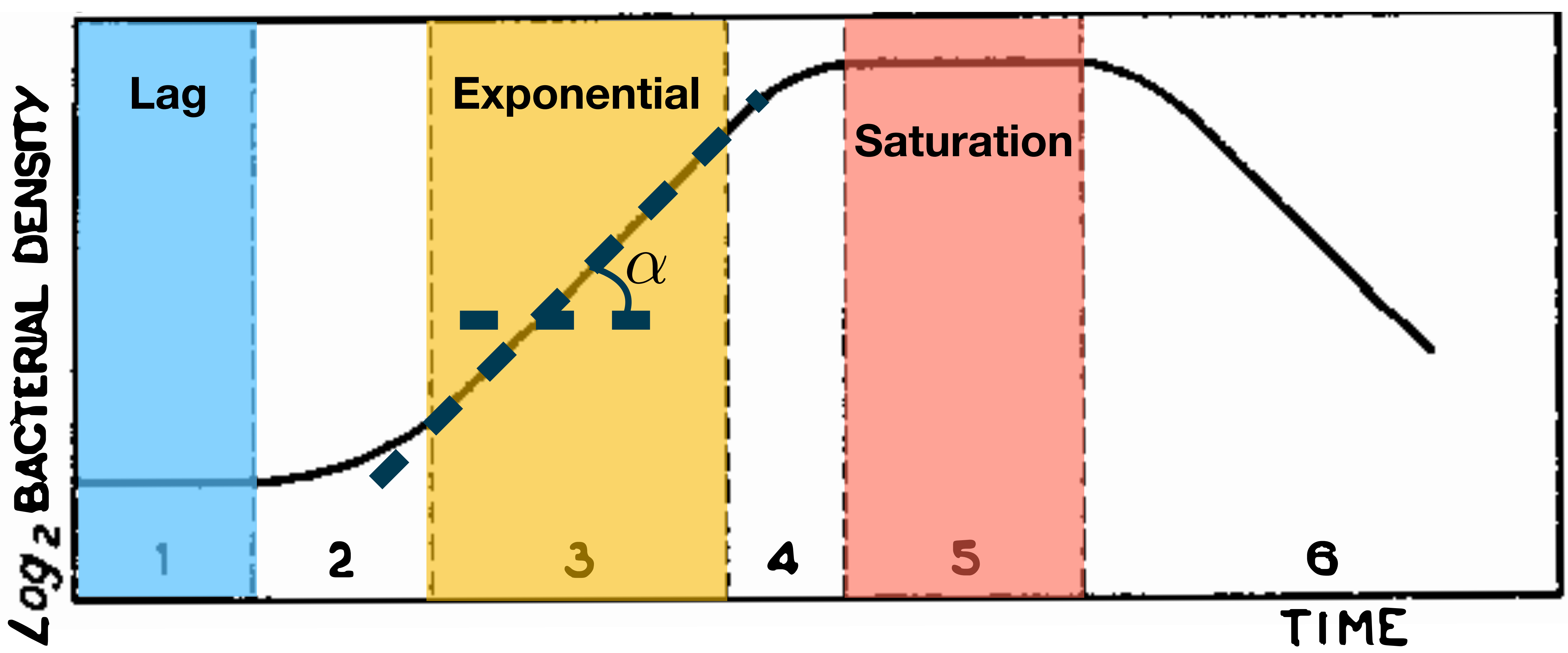


Bacterial growth: population level



Monod (1949)

Bacterial growth: population level



Monod (1949)

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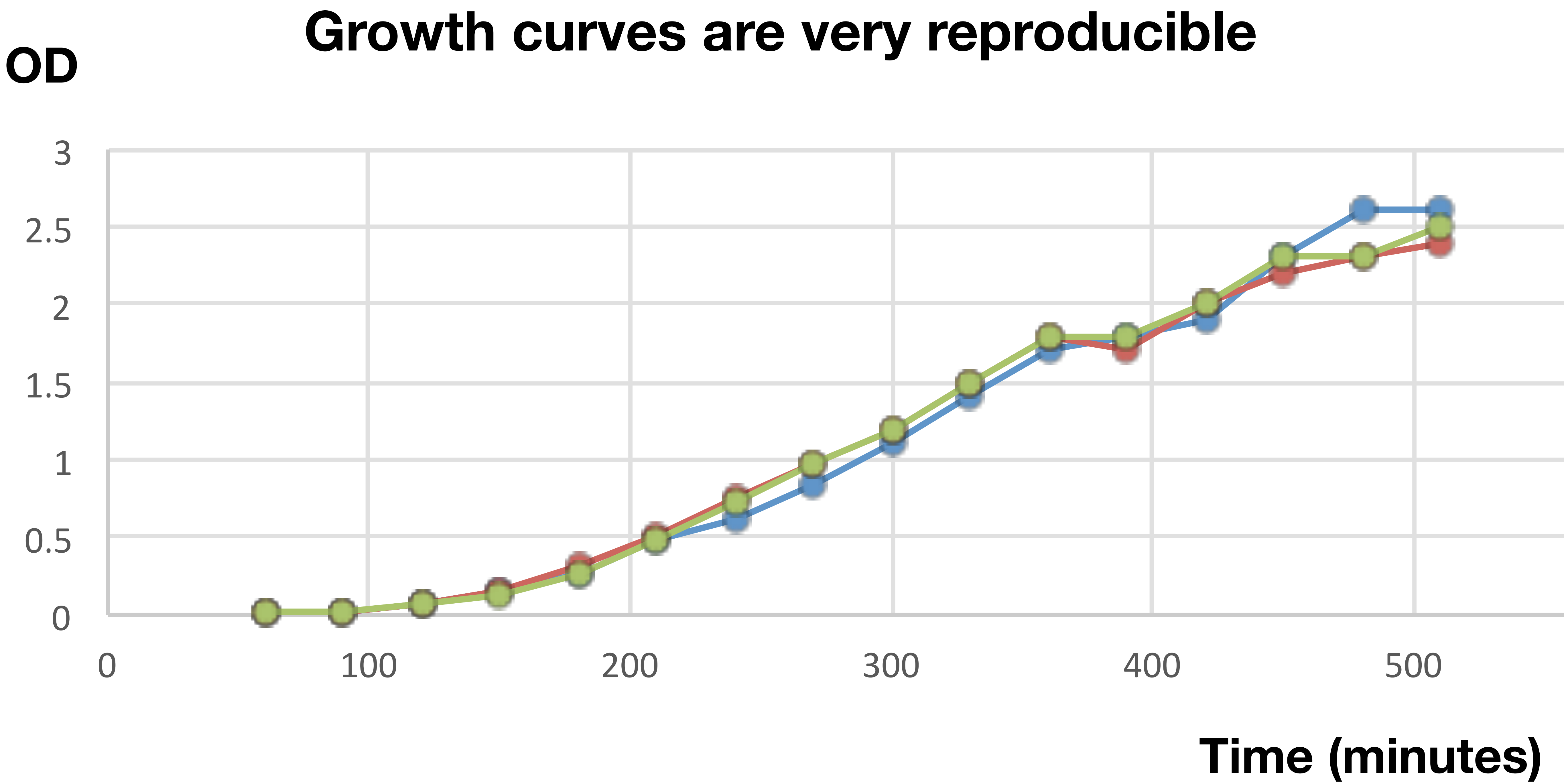
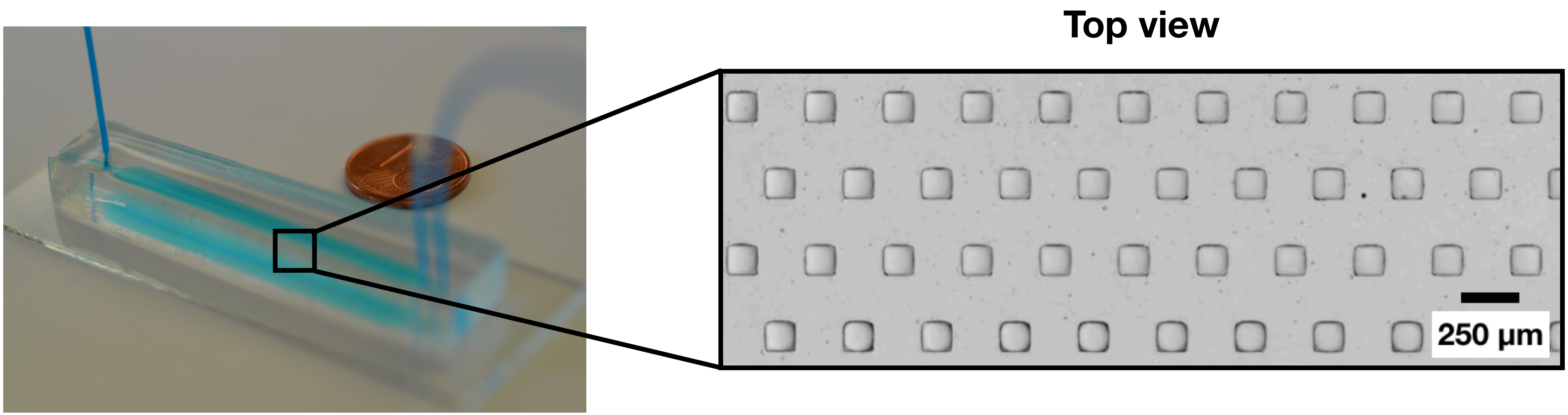
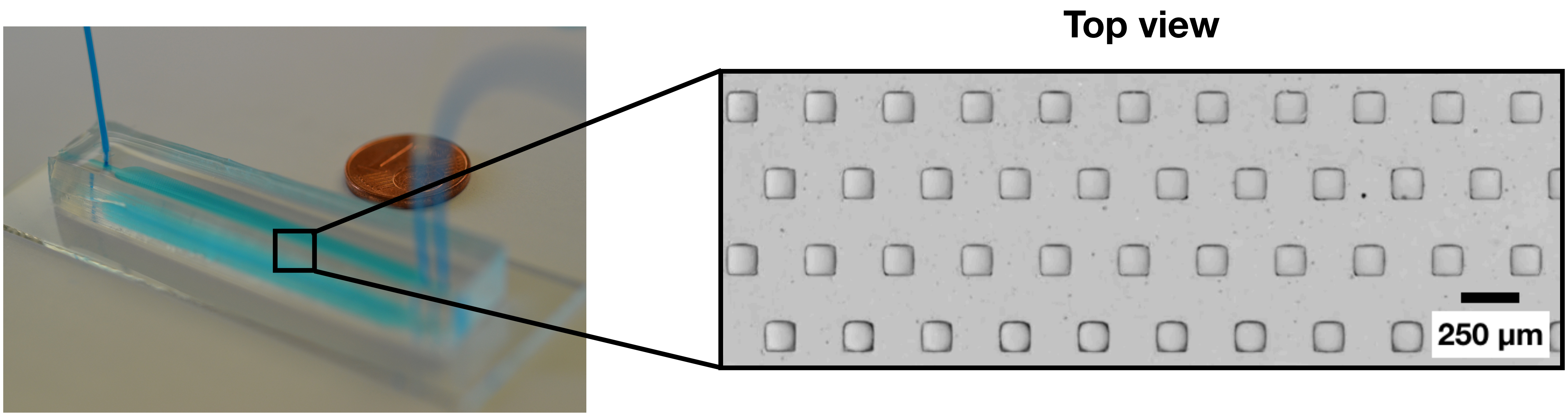
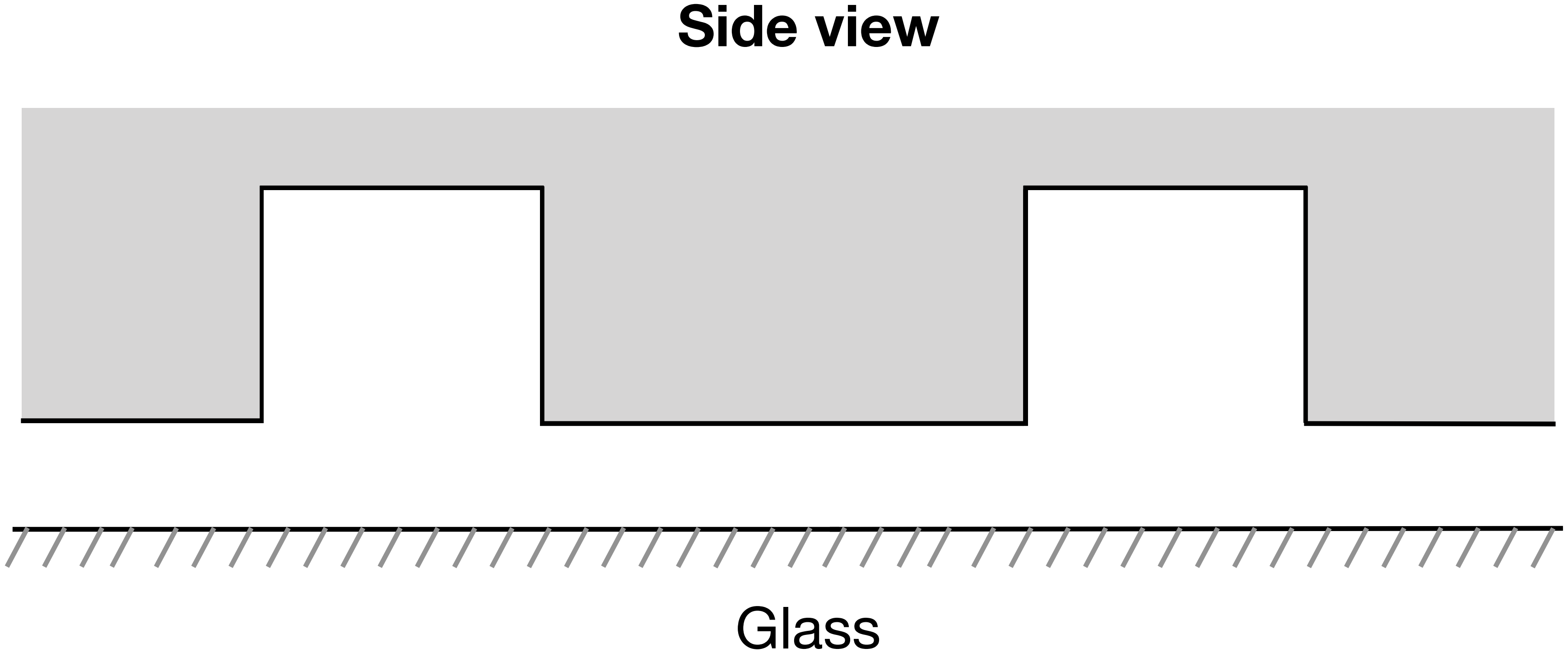


Microfluidics for bacterial growth



Microfluidics for bacterial growth





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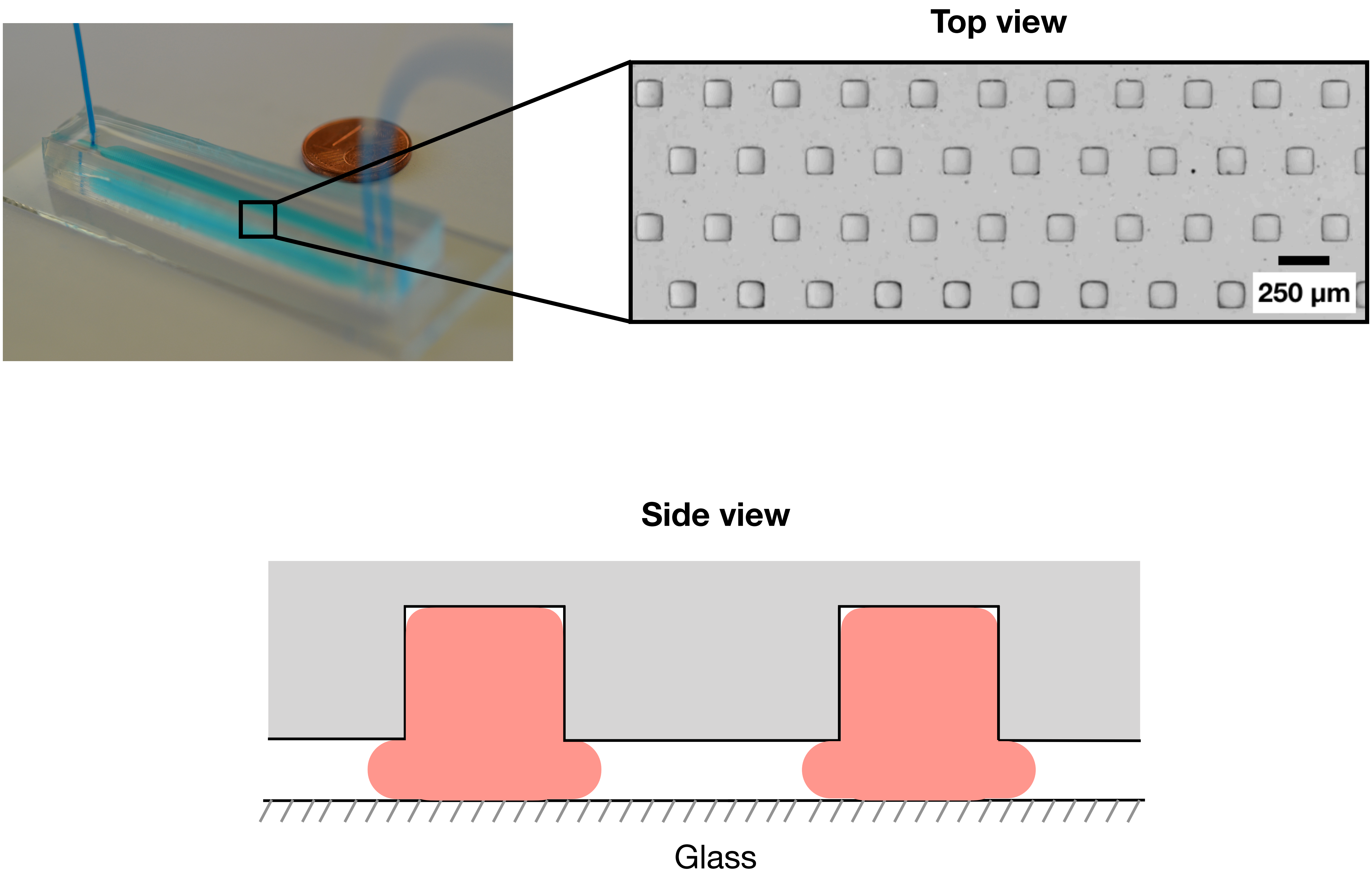

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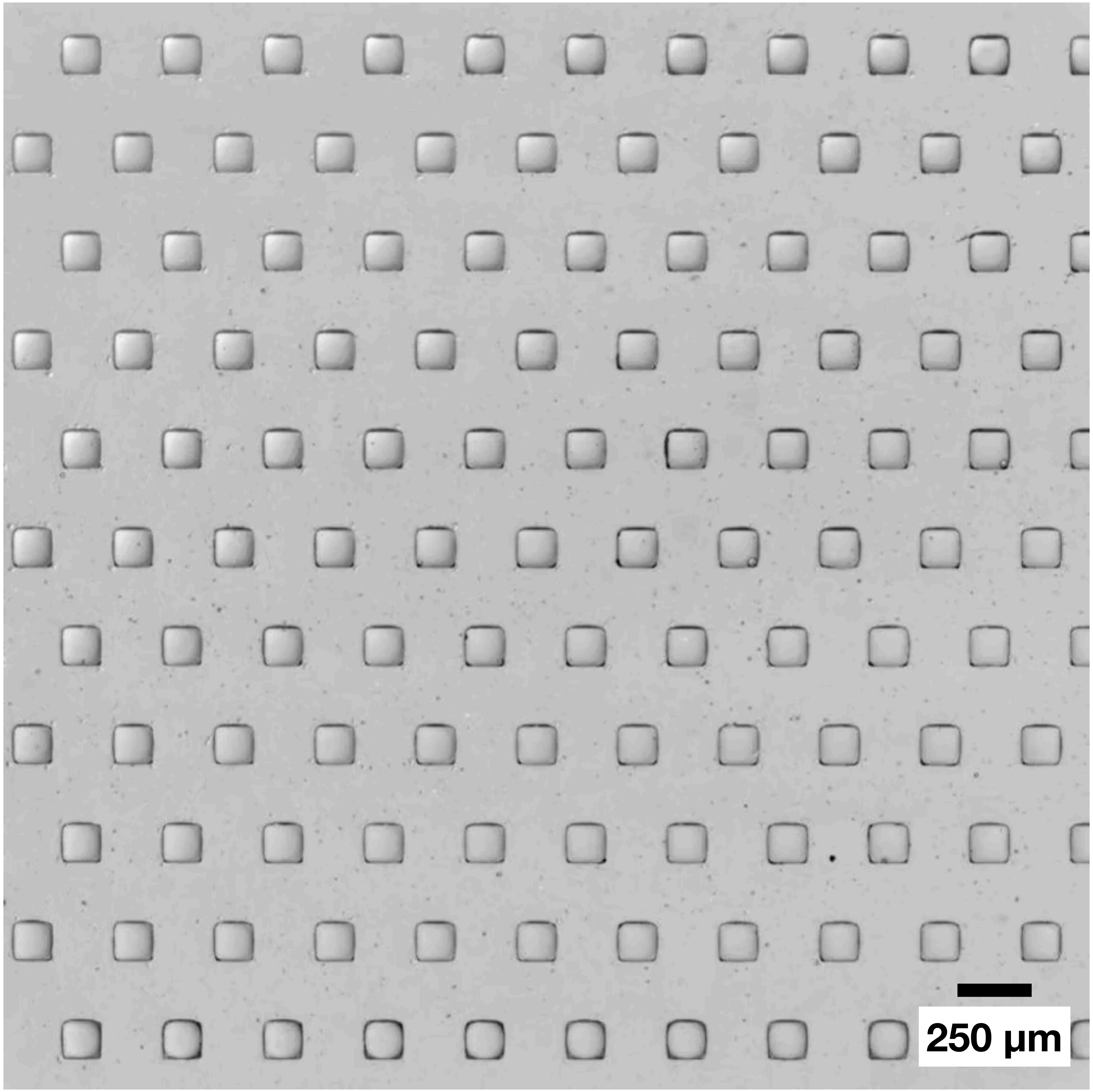


1,500 droplets/chip

1 droplet : 1 nL

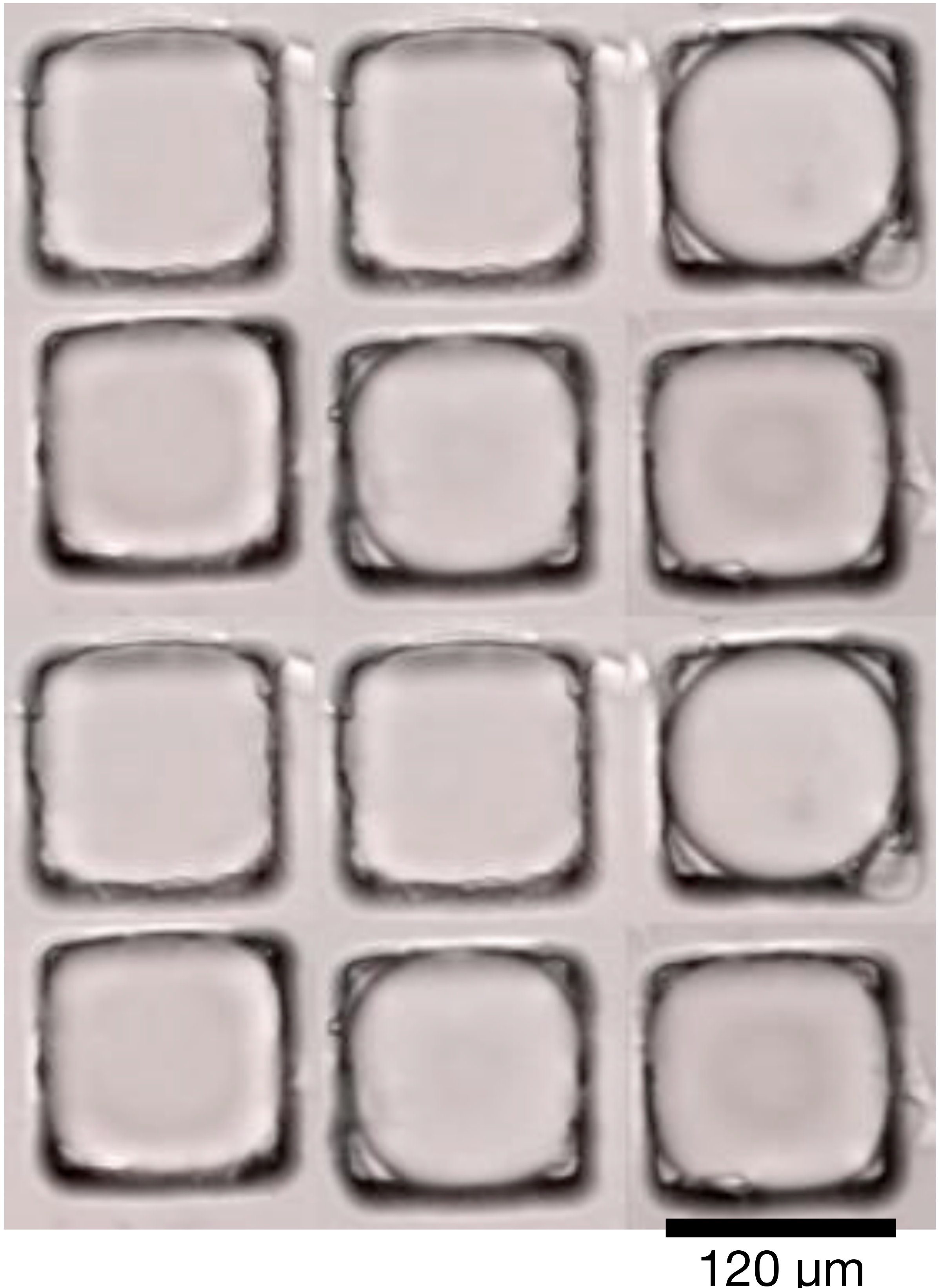
Amselem, Guermonprez et al., *Lab Chip* (2016)

Microfluidics for bacterial growth

1 second ⟷ 70 minutes

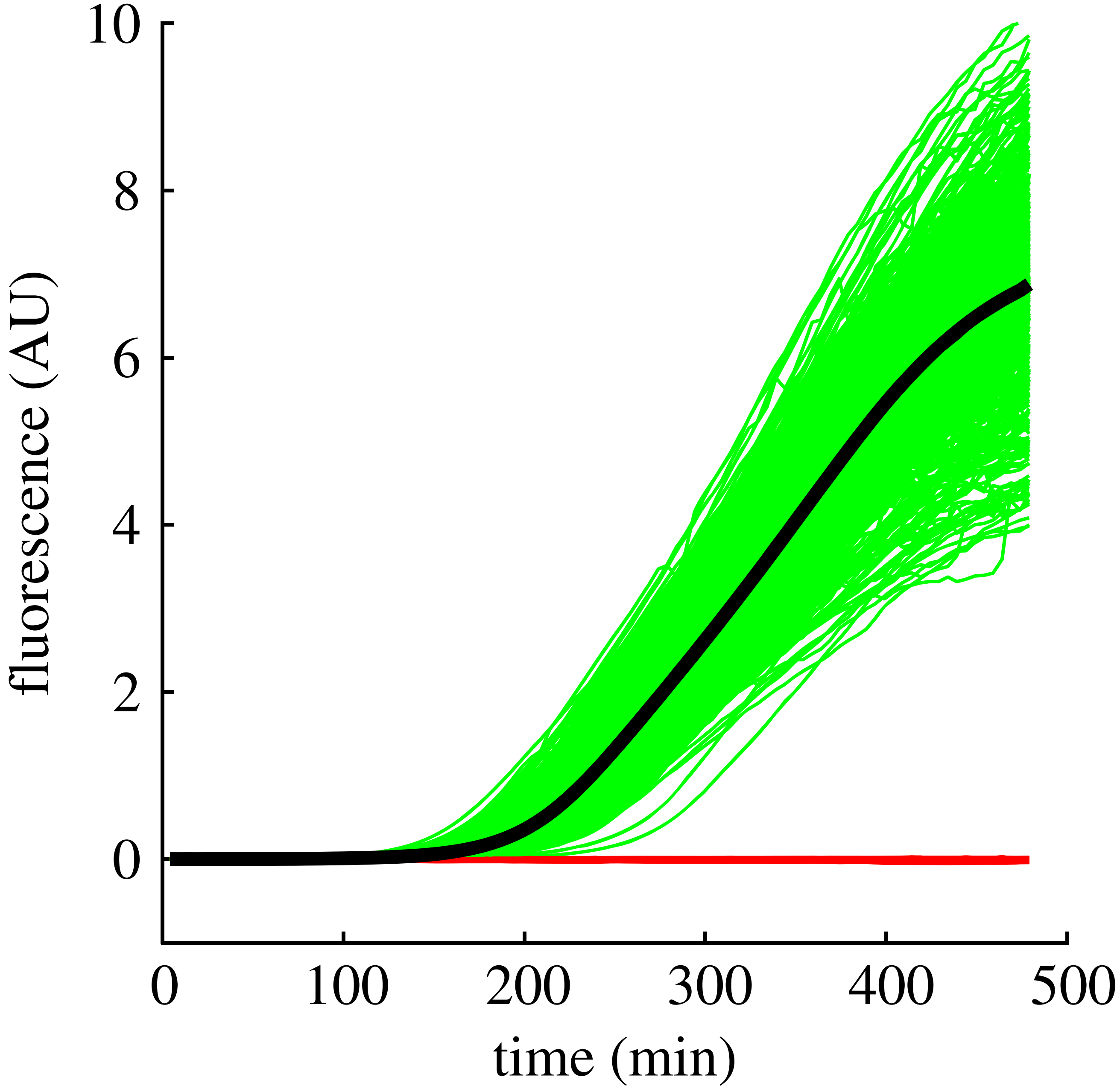
Bacillus subtilis
growing in LB

1 cell/droplet
~900 scanned
droplets per chip



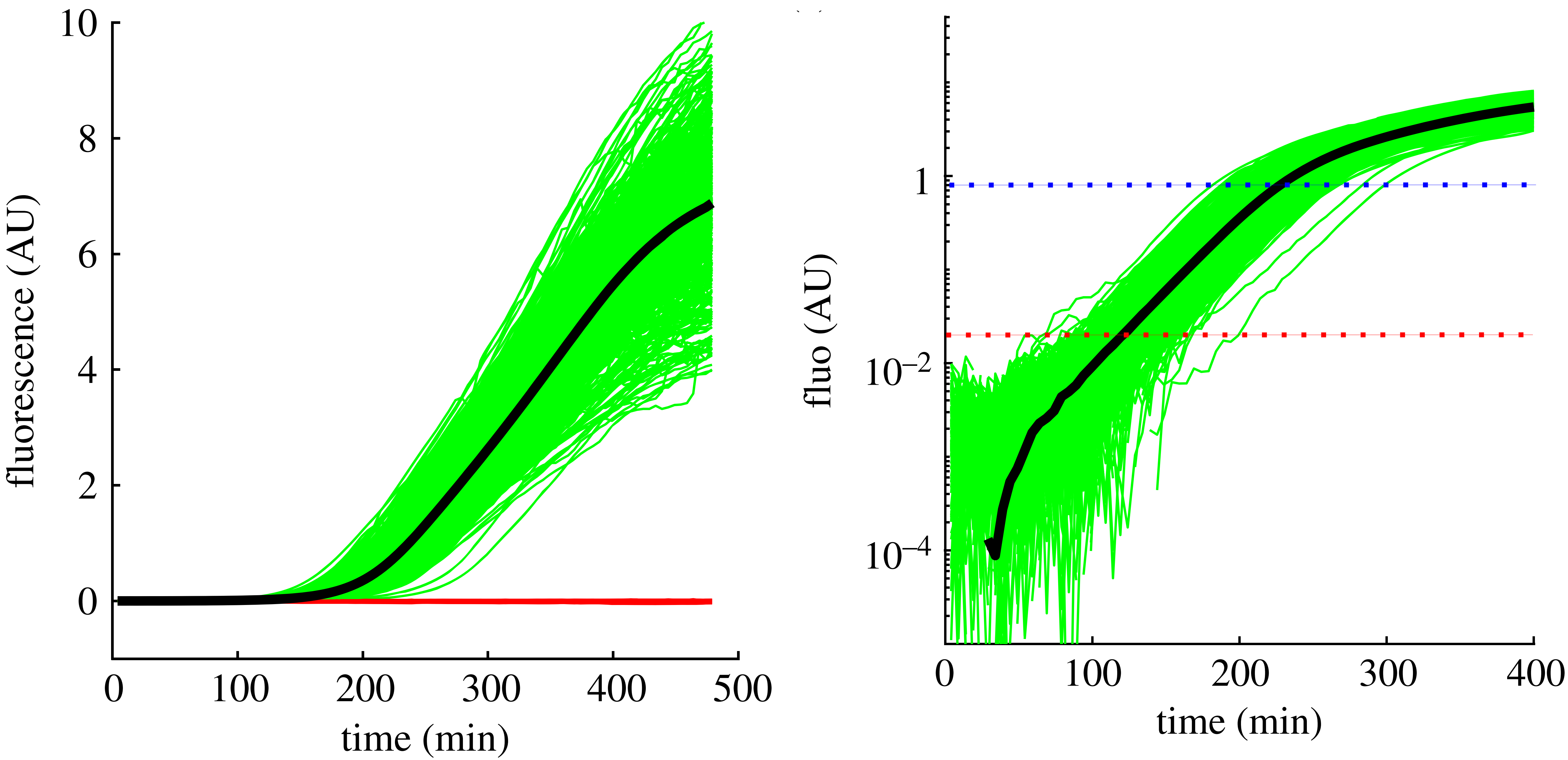
Barizien et al, *J. R. Soc. Interface*, 2019

Bacterial growth curves



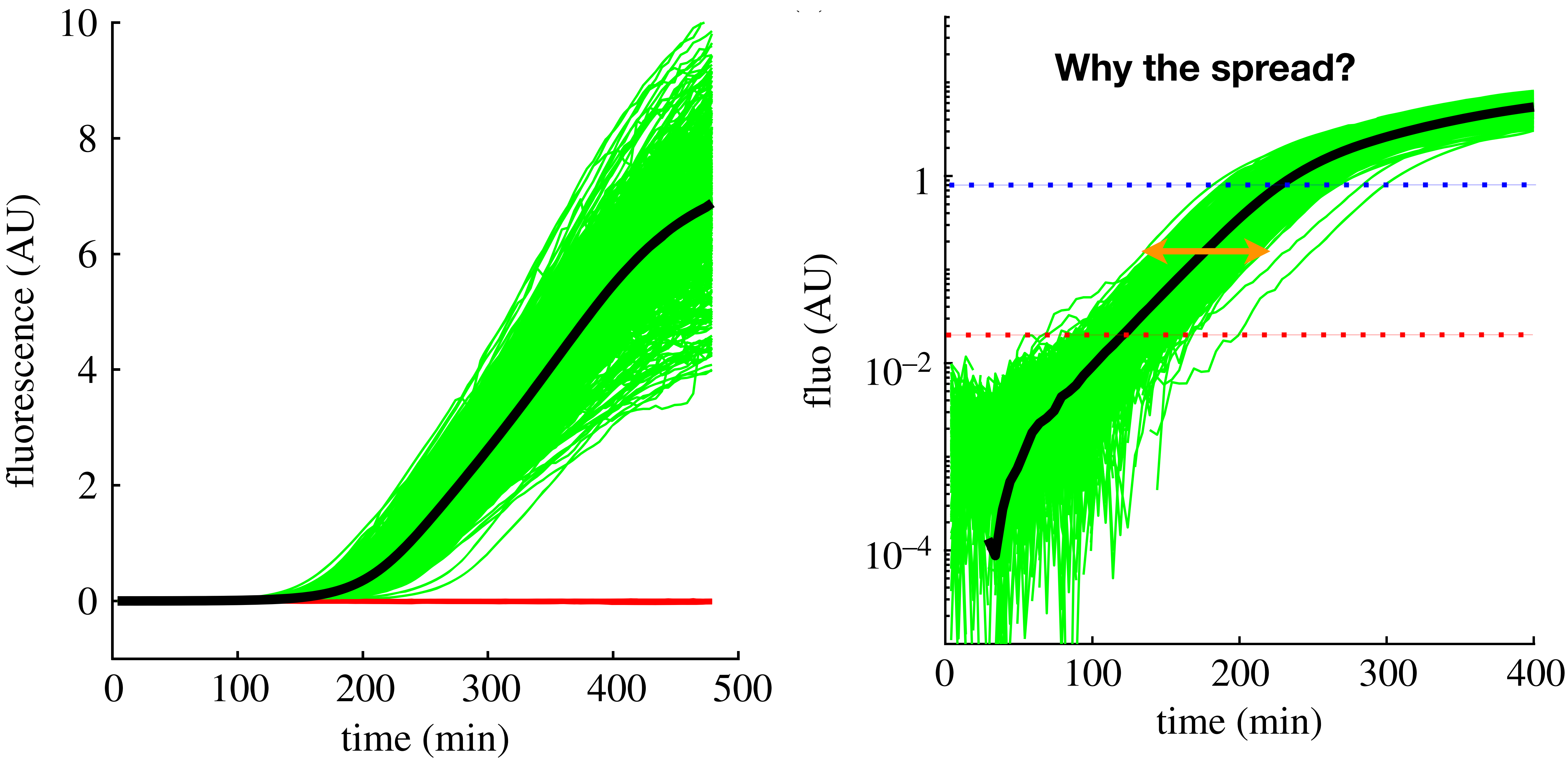
Barizien et al, *J. R. Soc. Interface*, 2019

Bacterial growth curves



Barizien et al, *J. R. Soc. Interface*, 2019

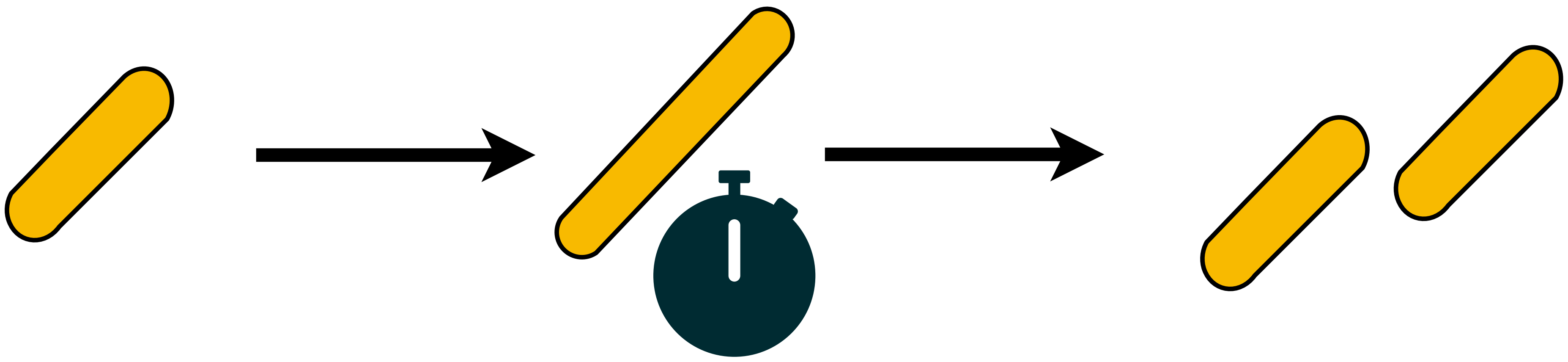
Bacterial growth curves



Barizien et al, *J. R. Soc. Interface*, 2019

Cell-division models

Timer



Cell-division models

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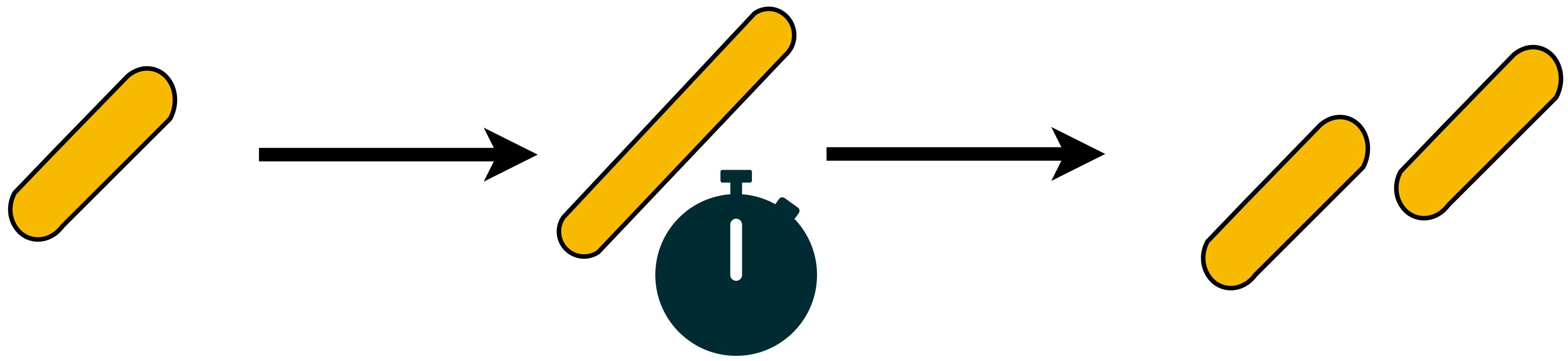
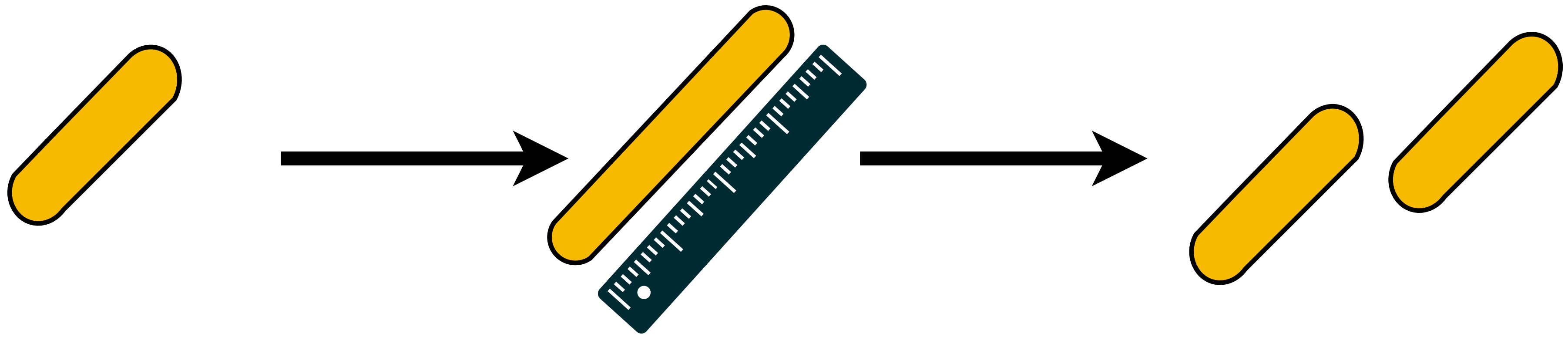


Sizer



Cell-division models

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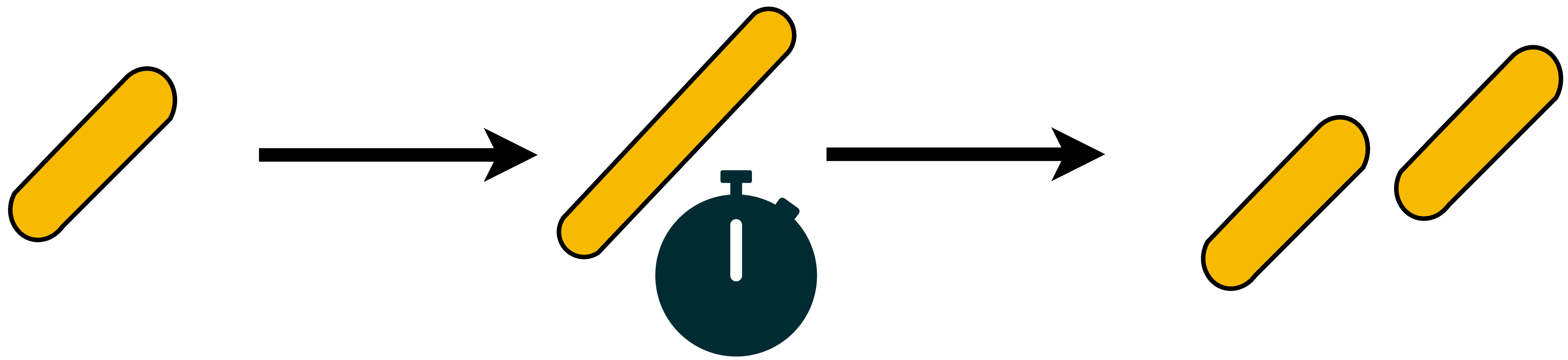

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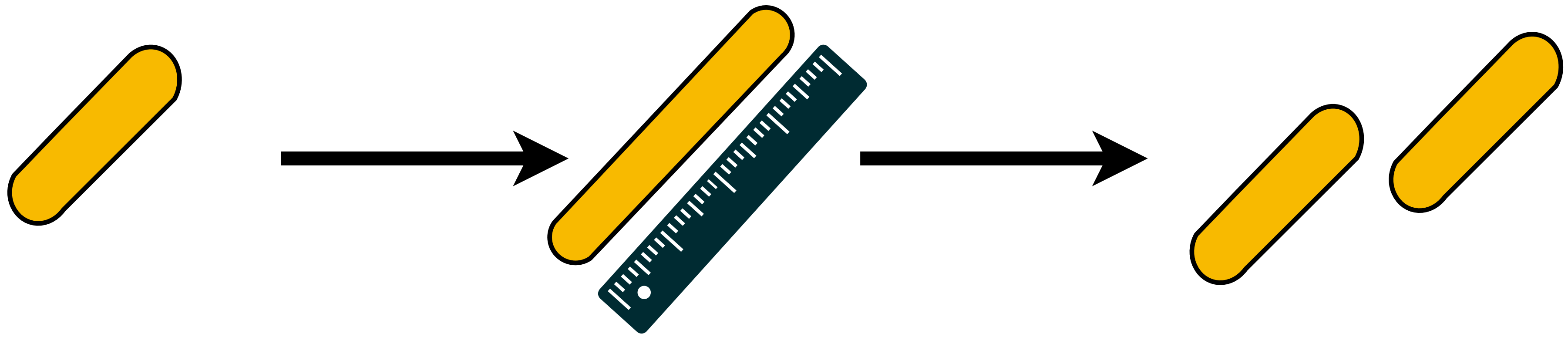
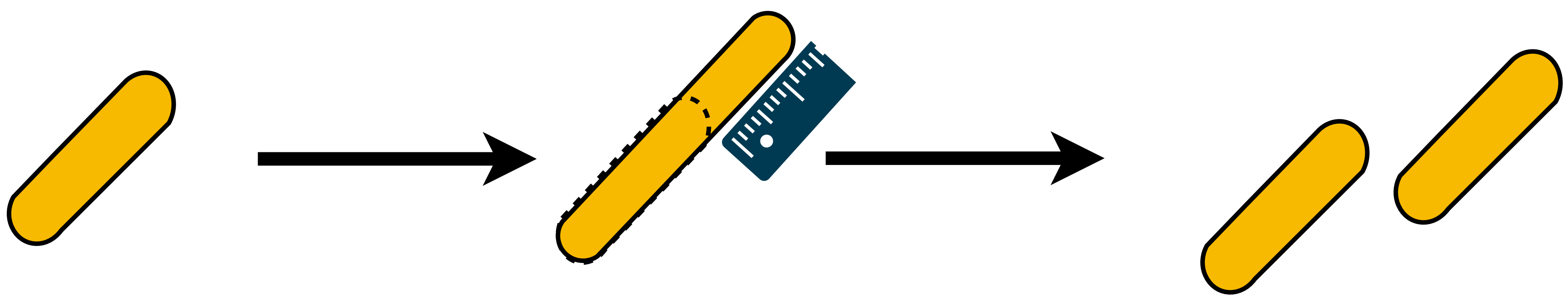


Adder

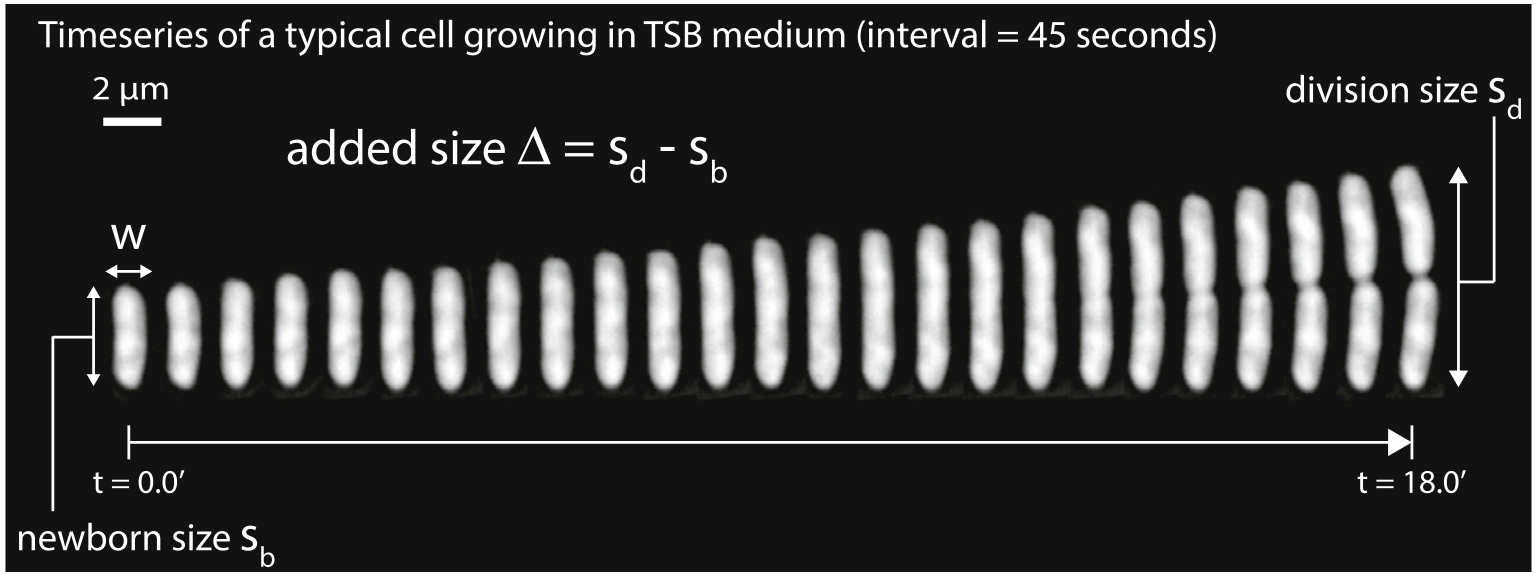


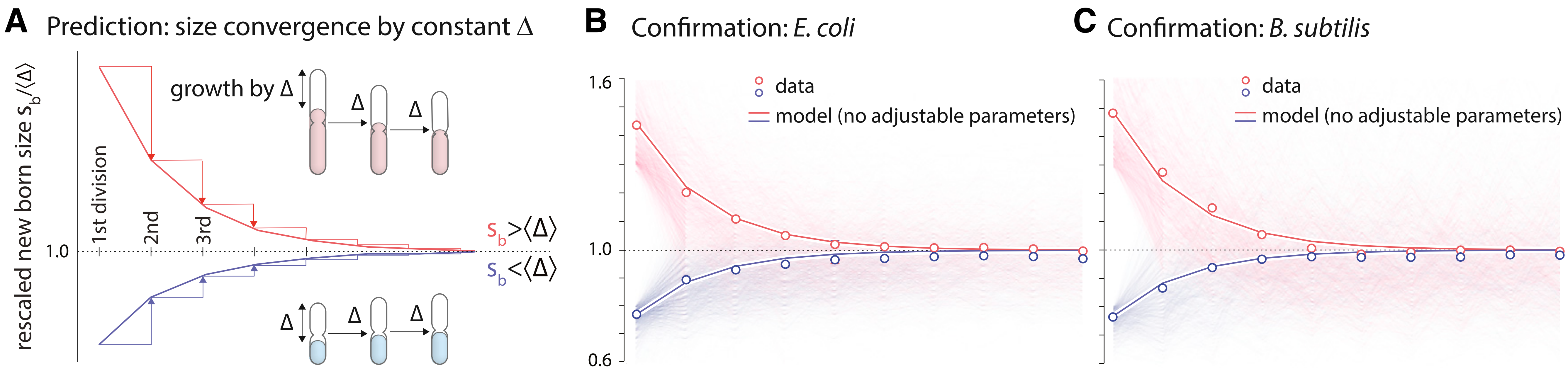
Bacteria are adders

Current Biology *25*, 385–391, February 2, 2015

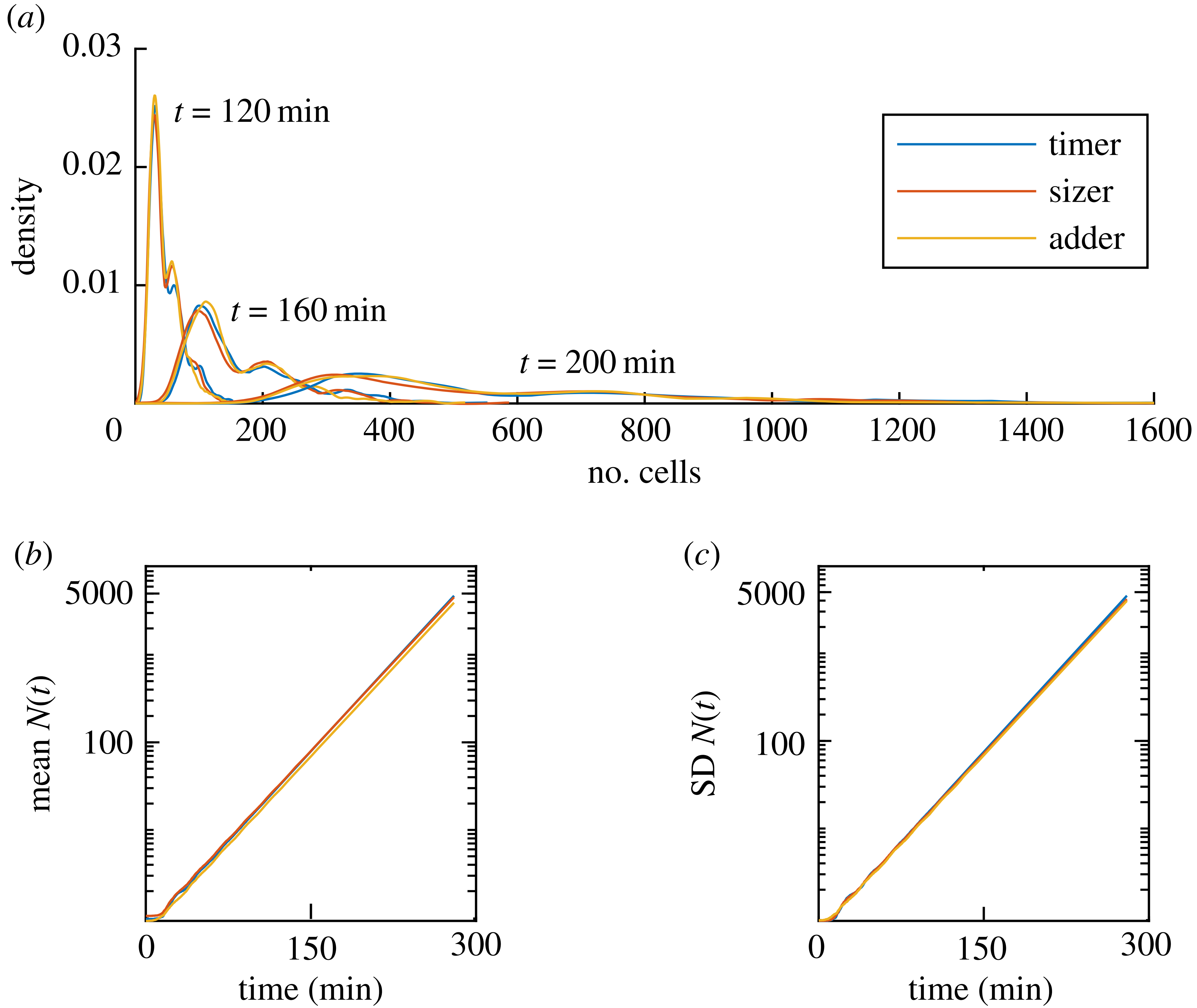
Cell-Size Control and Homeostasis in Bacteria

Sattar Taheri-Araghi,[1,7] Serena Bradde,[2,7] John T. Sauls,[1]
Norbert S. Hill,[3] Petra Anne Levin,[4] Johan Paulsson,[5]
Massimo Vergassola,[1,*] and Suckjoon Jun[1,6,*]





Differences between the models are (very) small



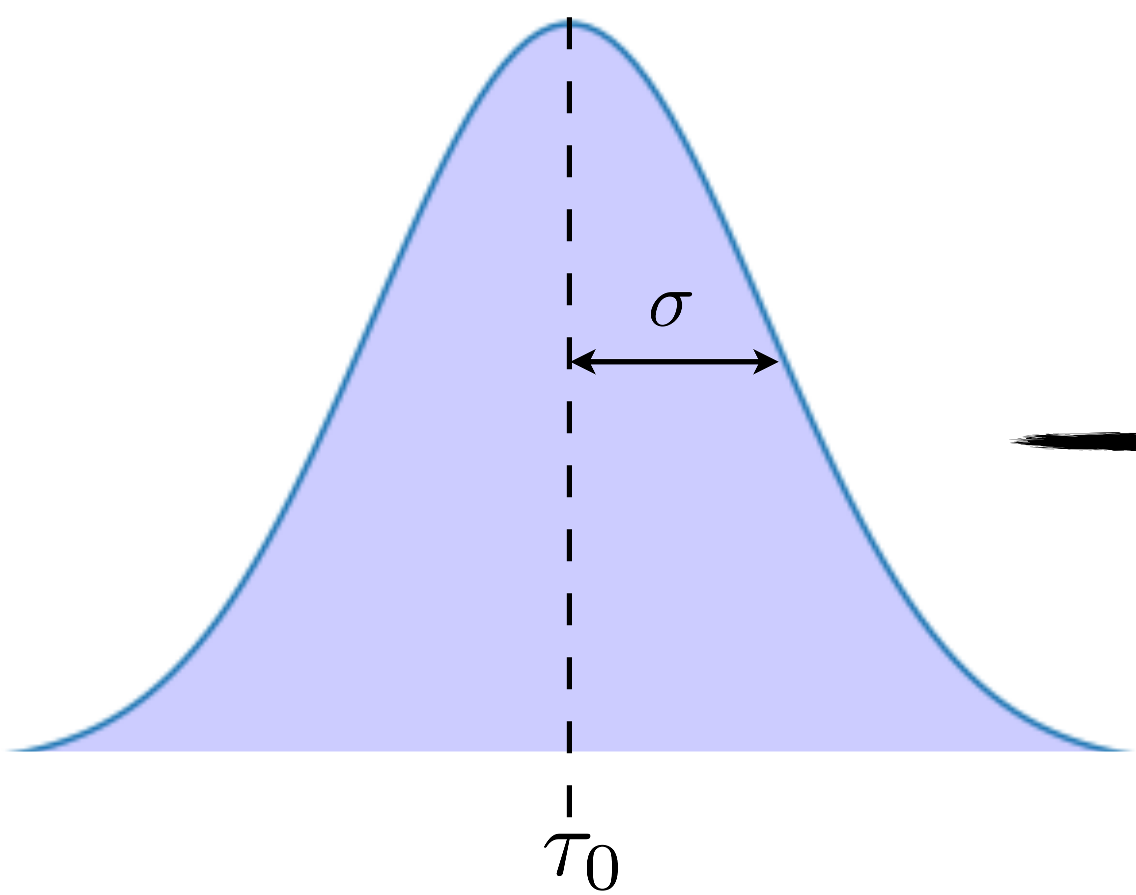
And analytically it's easier to use a timer model…

ANNALS OF MATHEMATICS
Vol. 55, No. 2, March, 1952
Printed in U.S.A.

ON AGE-DEPENDENT BINARY BRANCHING PROCESSES[1]

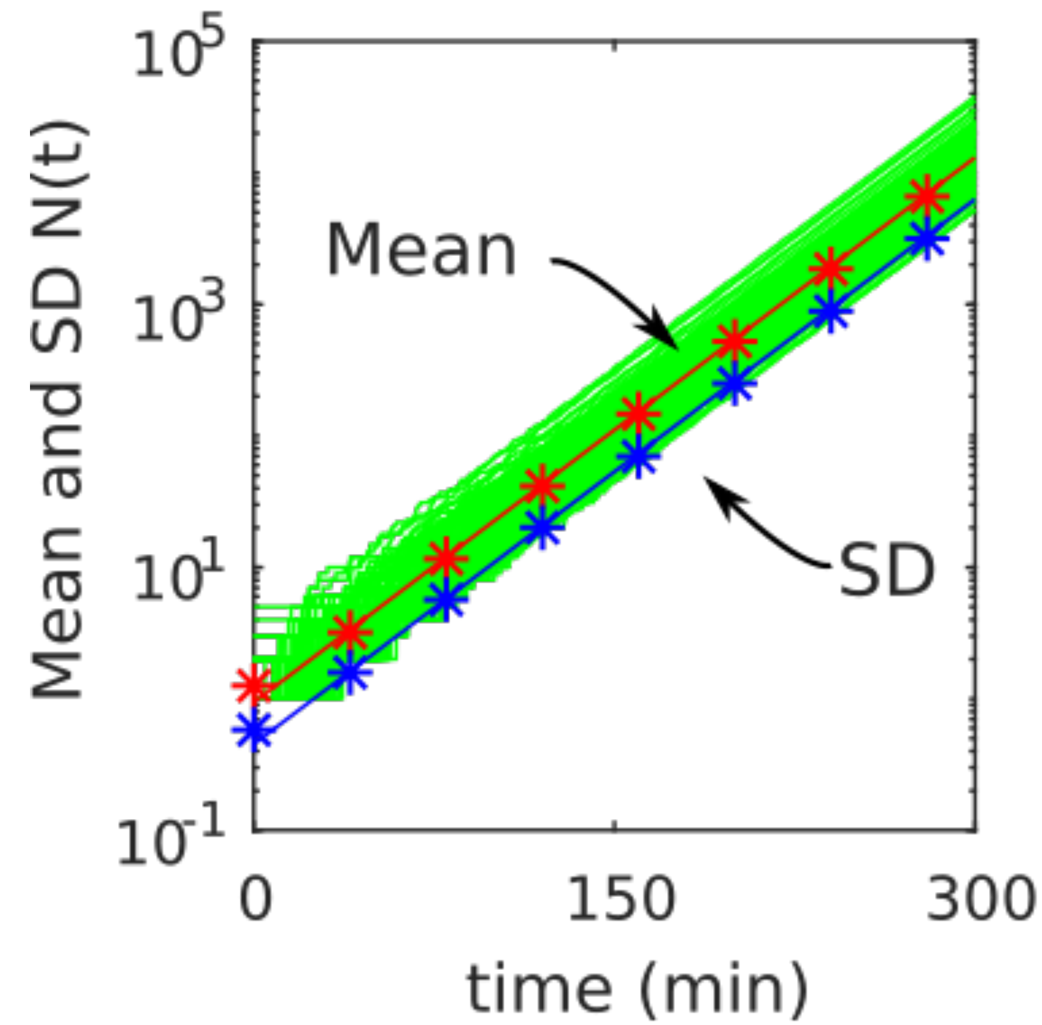
BY RICHARD BELLMAN AND THEODORE HARRIS

Microscopic variability in division times



$$\tau_d \sim \mathcal{N}(\tau_0, \sigma)$$
$$\mathrm{cv}_\mu = \sigma/\tau_0$$

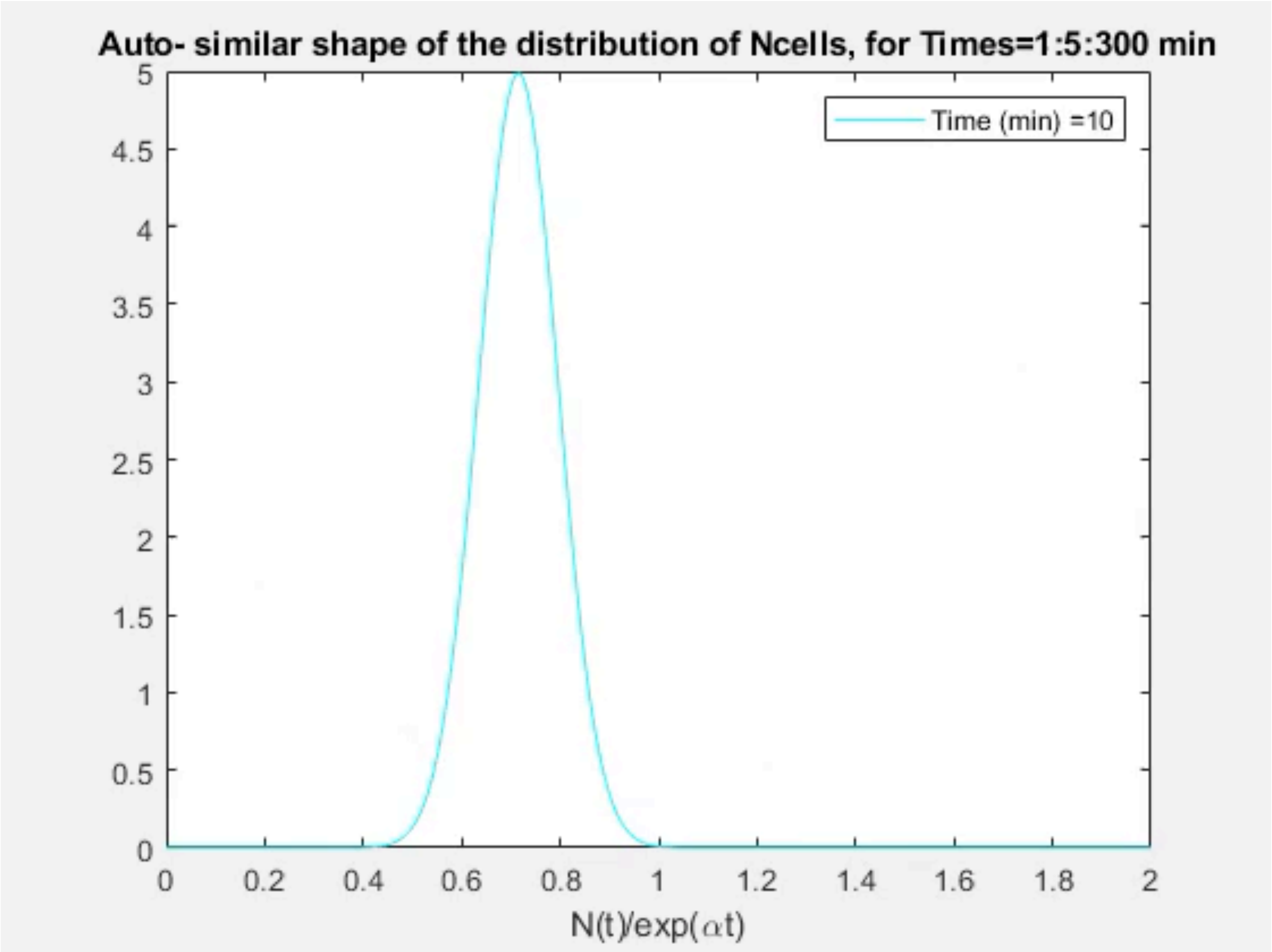
Macroscopic variability in population sizes



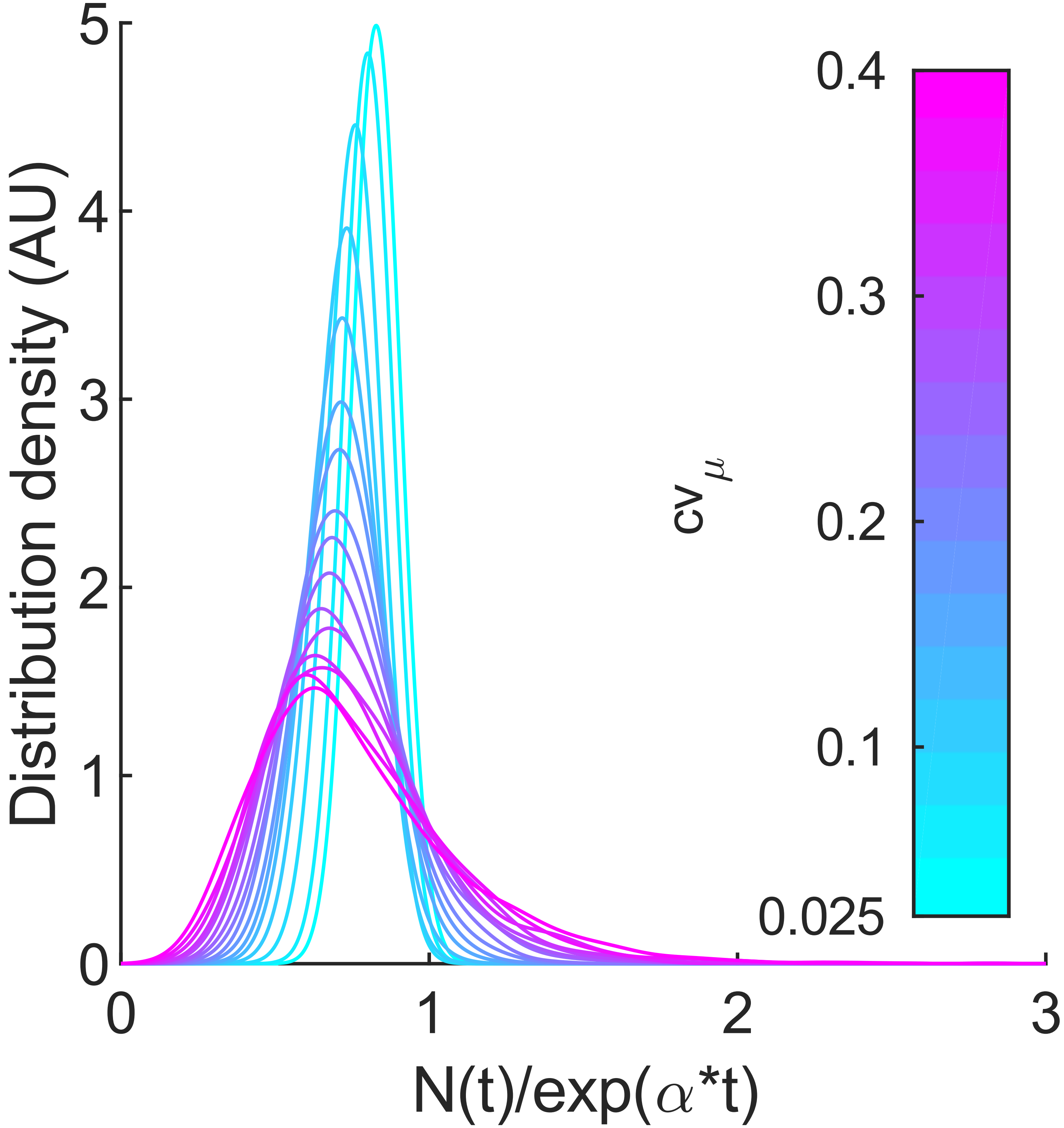
$$\mathrm{CV}_N(t) = SD_N(t)/M_N(t)$$

Distribution of population sizes as a function of time

All moments grow exponentially, with the same growth rate α



Asymptotic shape depends on cv_μ



Bellman-Harris

All moments grow exponentially, with the same growth rate α

$$M_N(t) \sim n_1 e^{\alpha t} \qquad SD_N(t) \sim n_2 e^{\alpha t}$$

$$\mathrm{CV}_N(t) = SD_N(t)/M_N(t) = n_2/n_1$$

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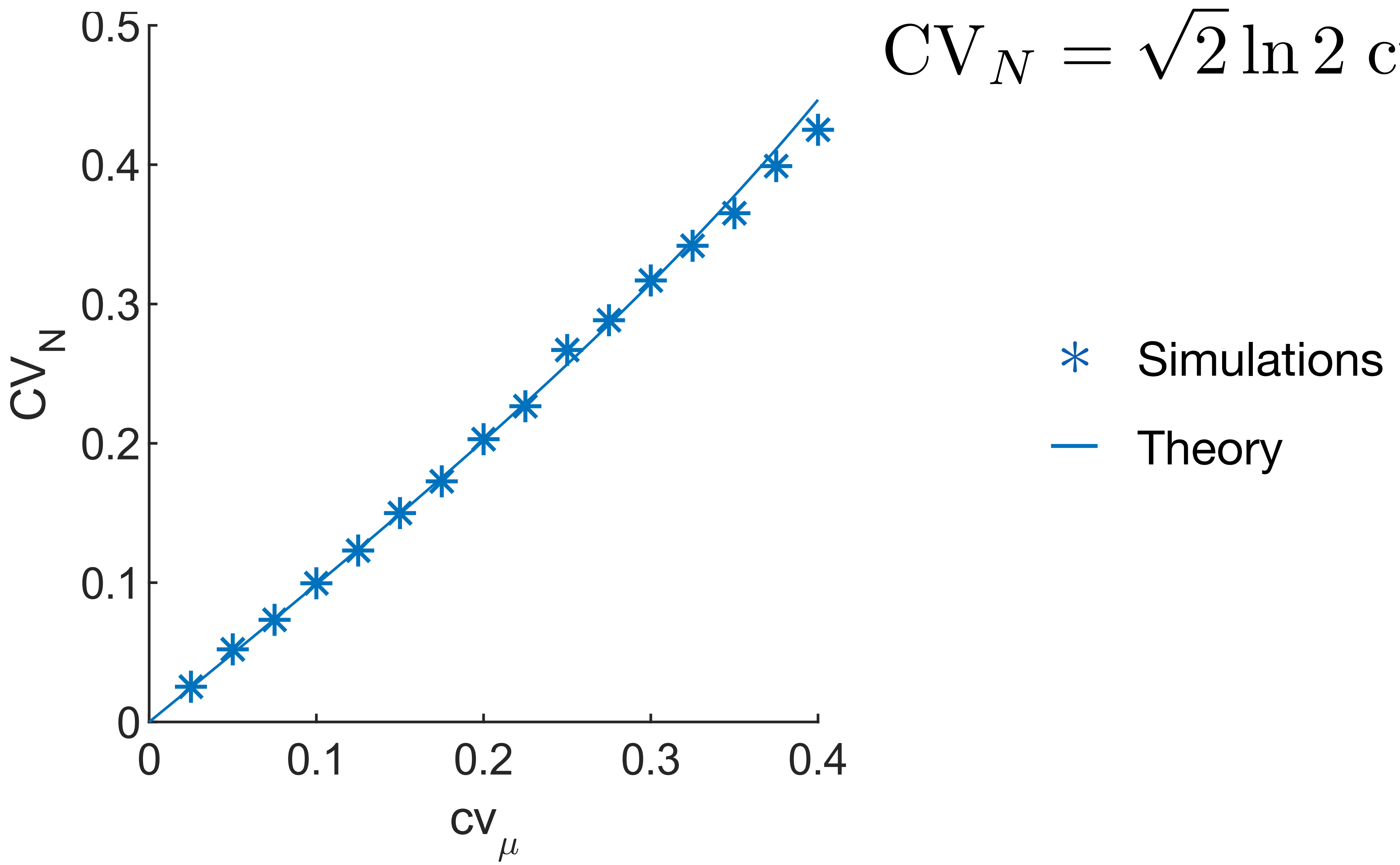
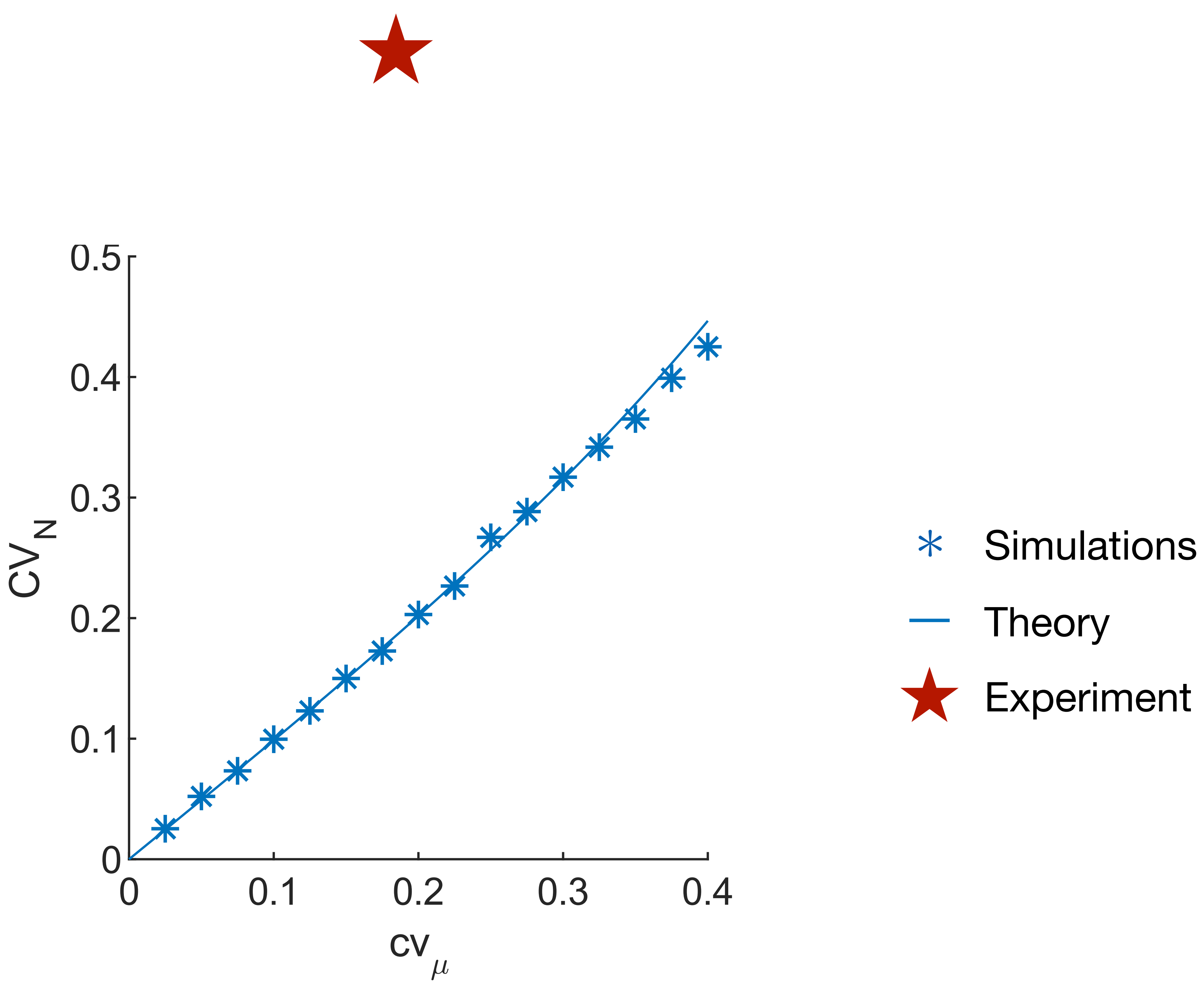
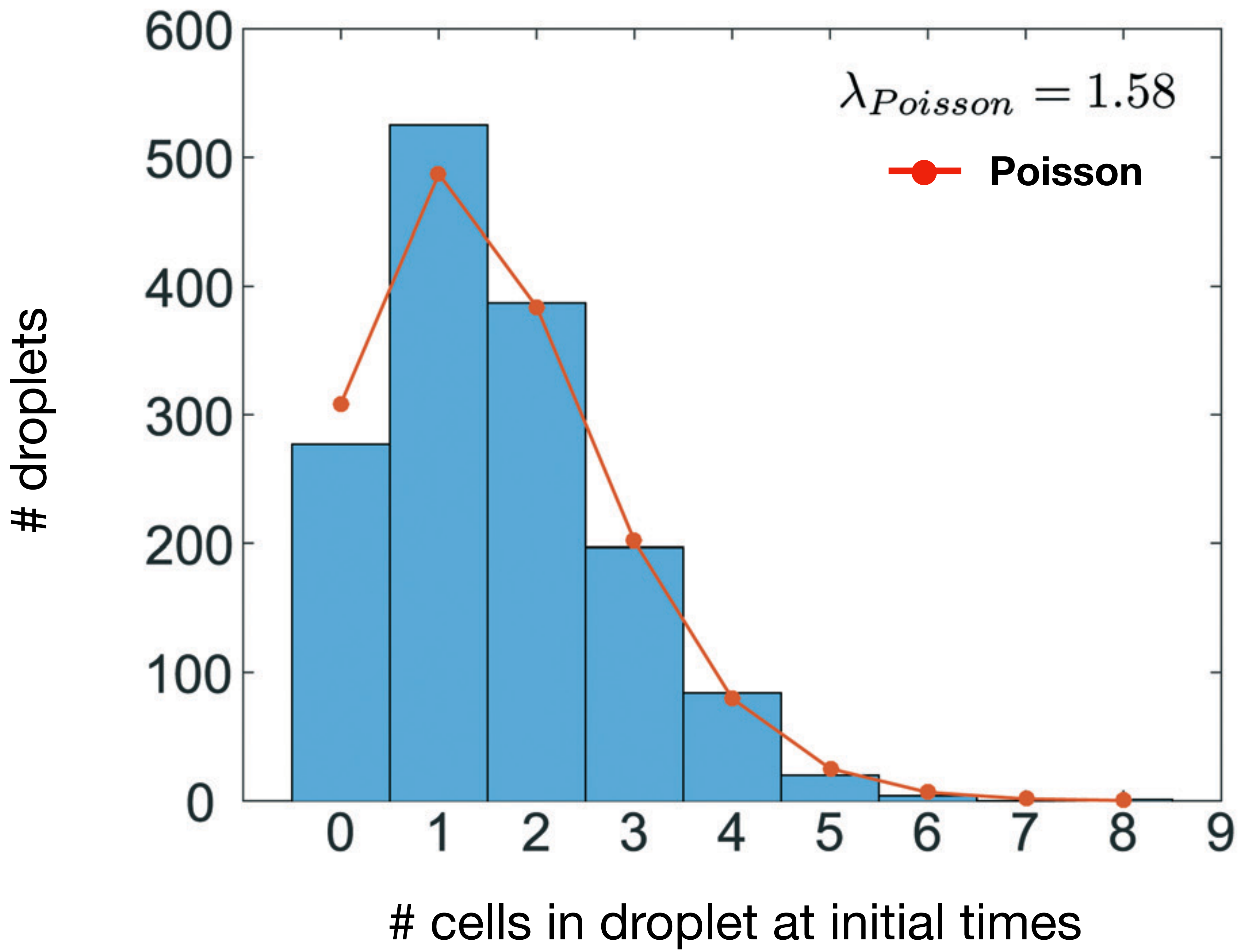


$$\mathrm{CV}_N = \sqrt{2}\ln 2\ \mathrm{cv}_\mu$$

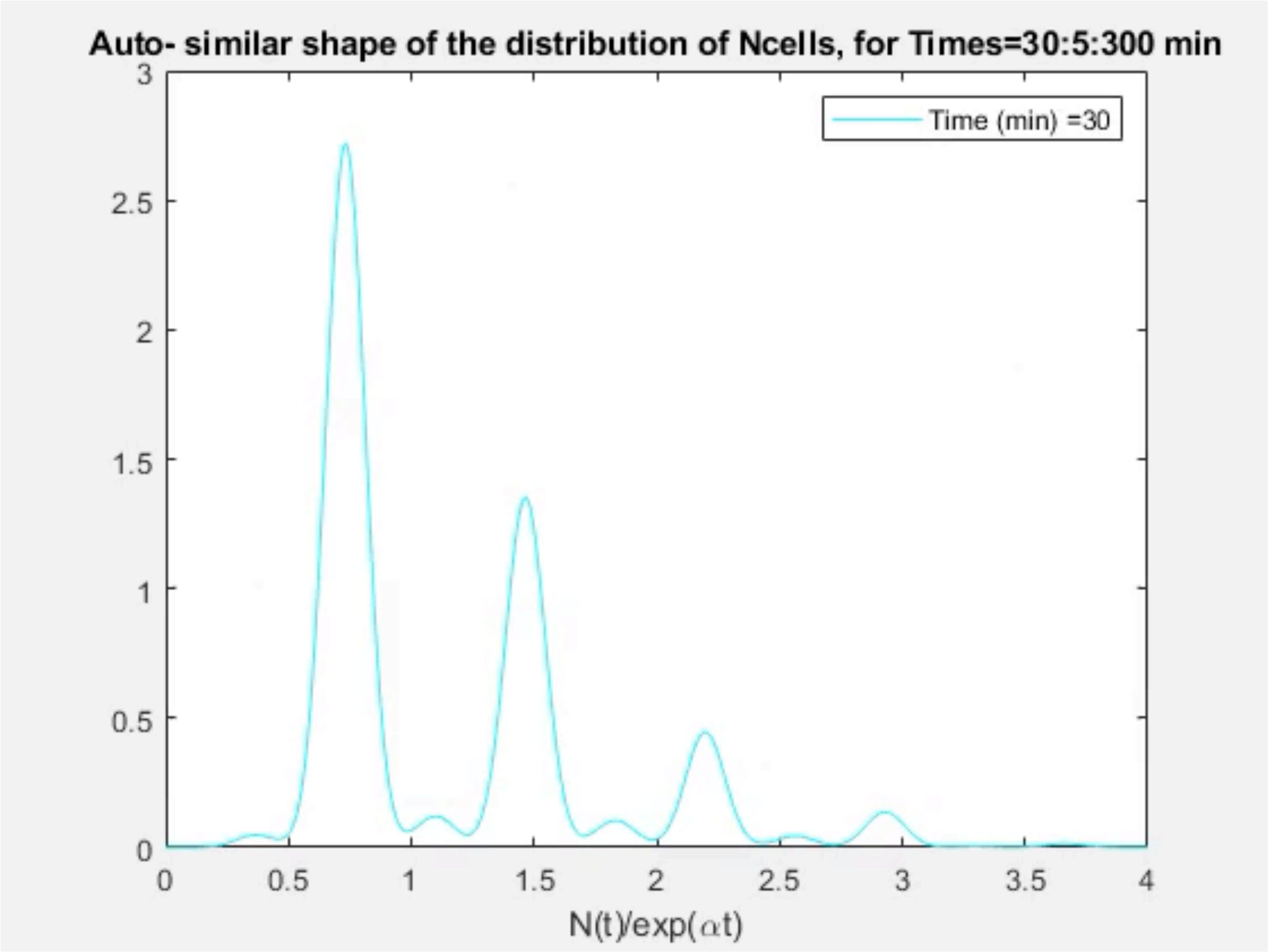
Comparison with experiment



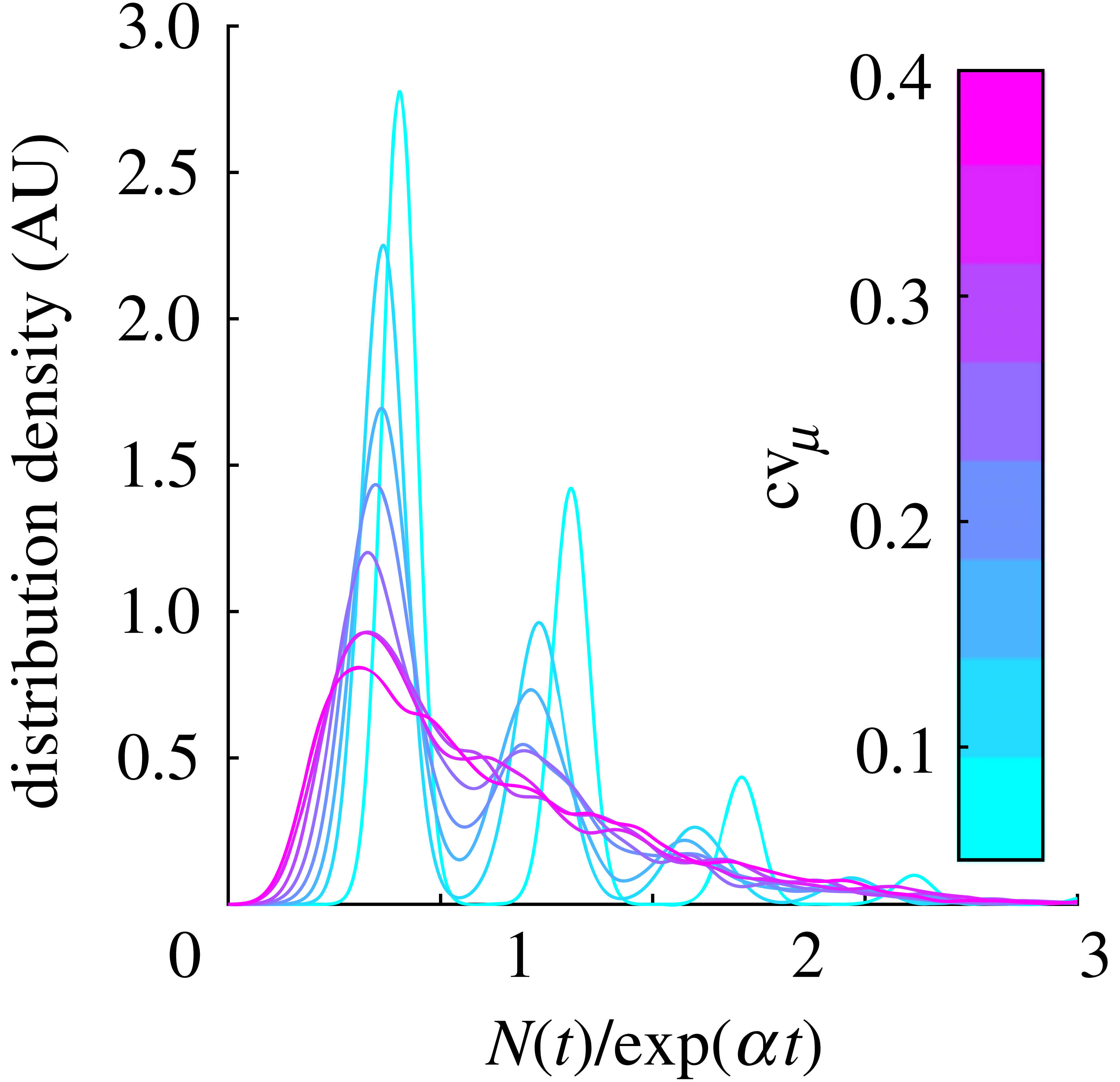
Poisson distribution of cells at initial times



Bellman-Harris + Poisson distribution



Bellman-Harris + Poisson distribution



Bellman-Harris + Poisson distribution

$$CV_{\lambda}^{2}(\infty) = \left(\frac{n_2}{n_1}\right)_{\lambda}^{2} = \underbrace{\frac{1-e^{-\lambda}}{\lambda}\left(\frac{n_2}{n_1}\right)_{BH}^{2}}_{(1)} + \underbrace{\frac{1-(\lambda+1)\,e^{-\lambda}}{\lambda}}_{(2)}.$$

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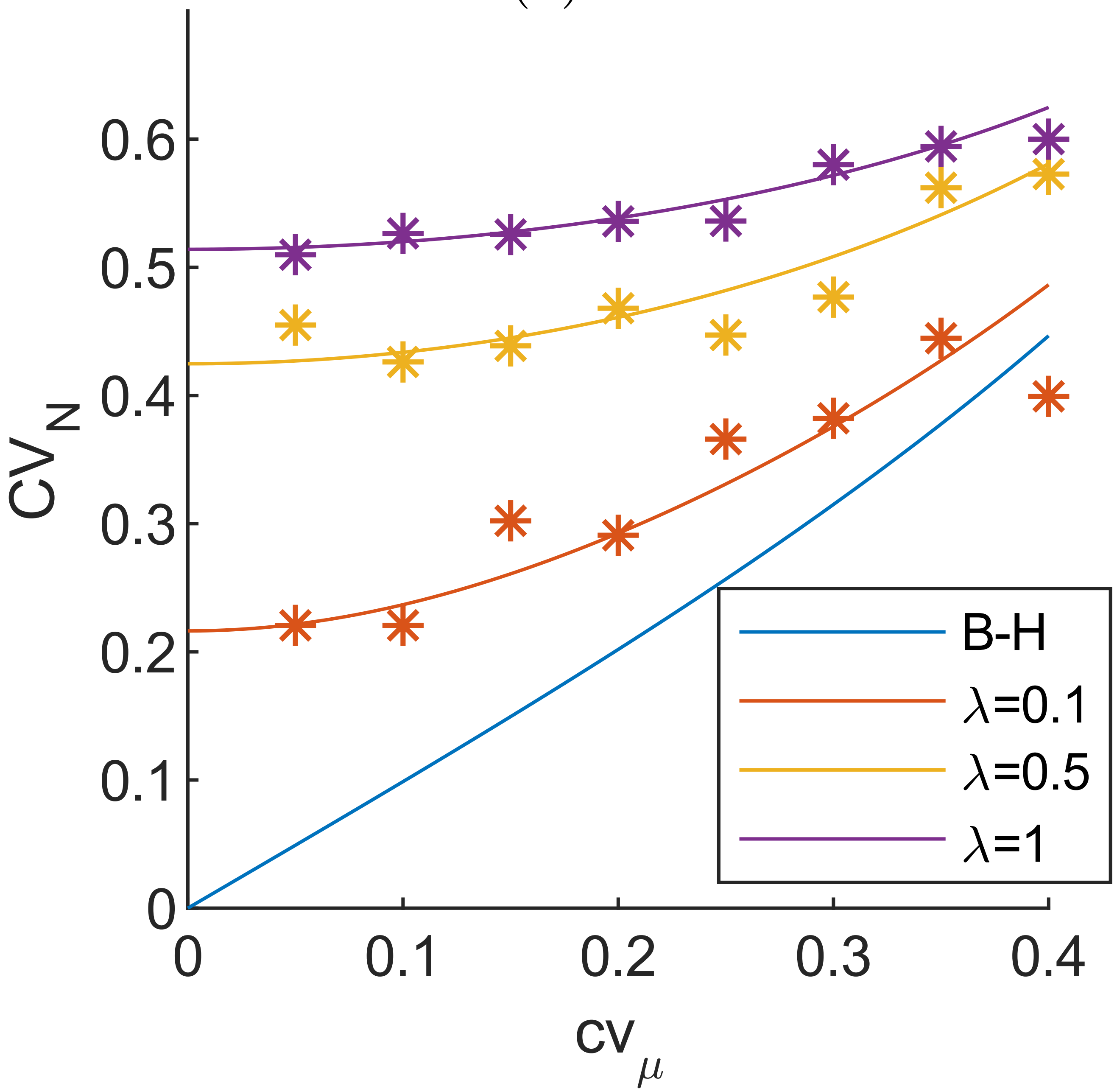

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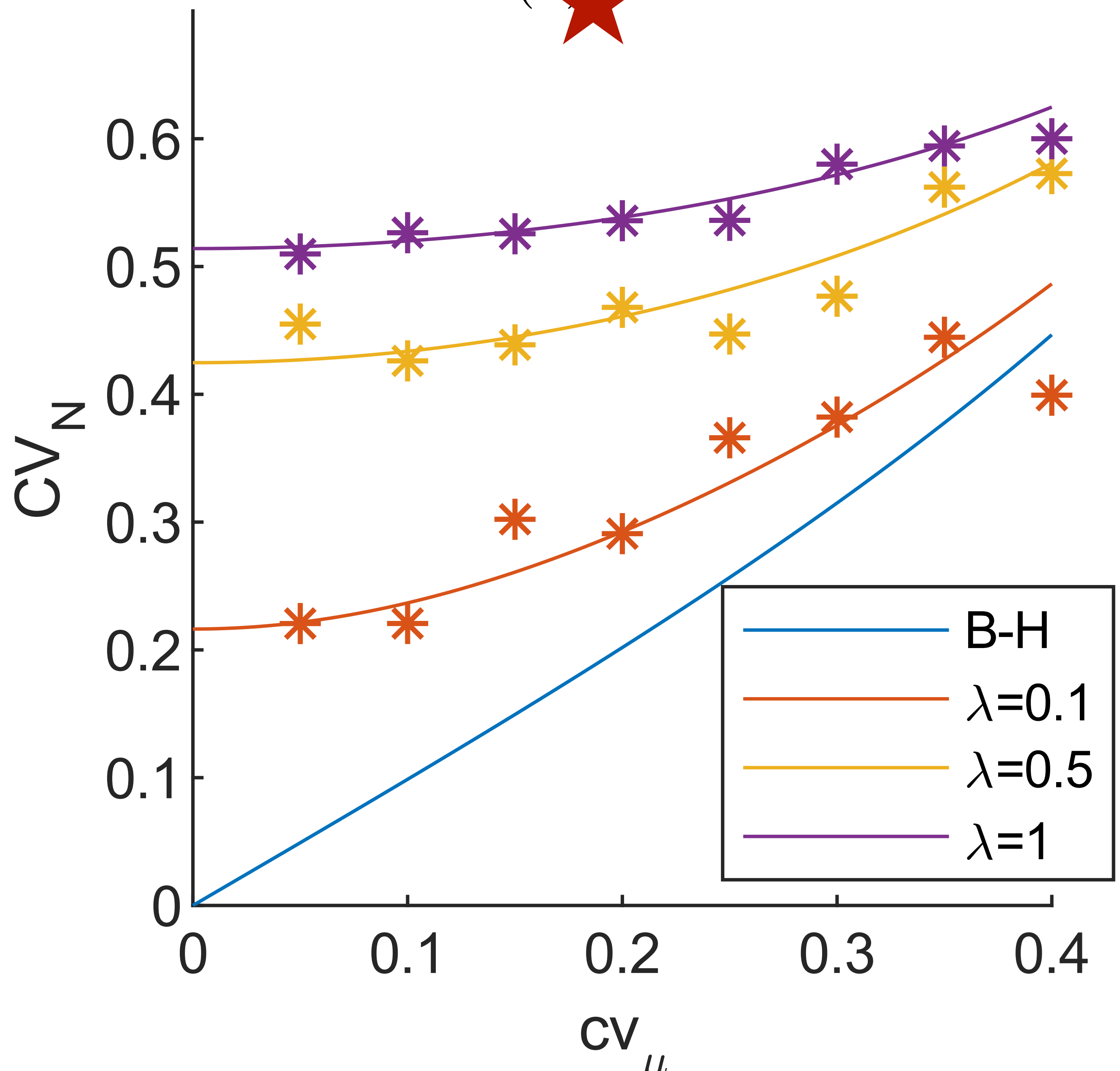
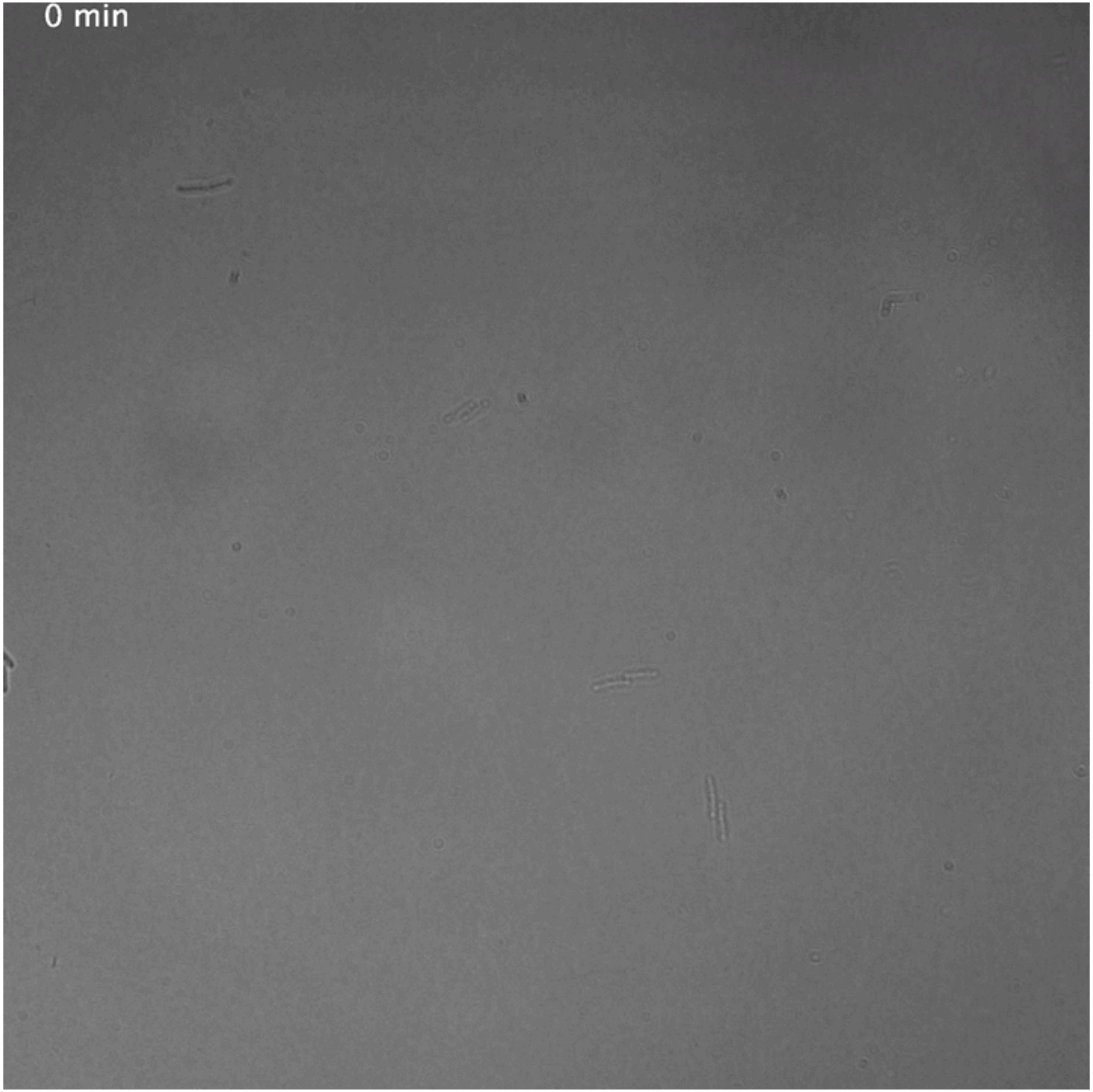


Adaptation to a new environment



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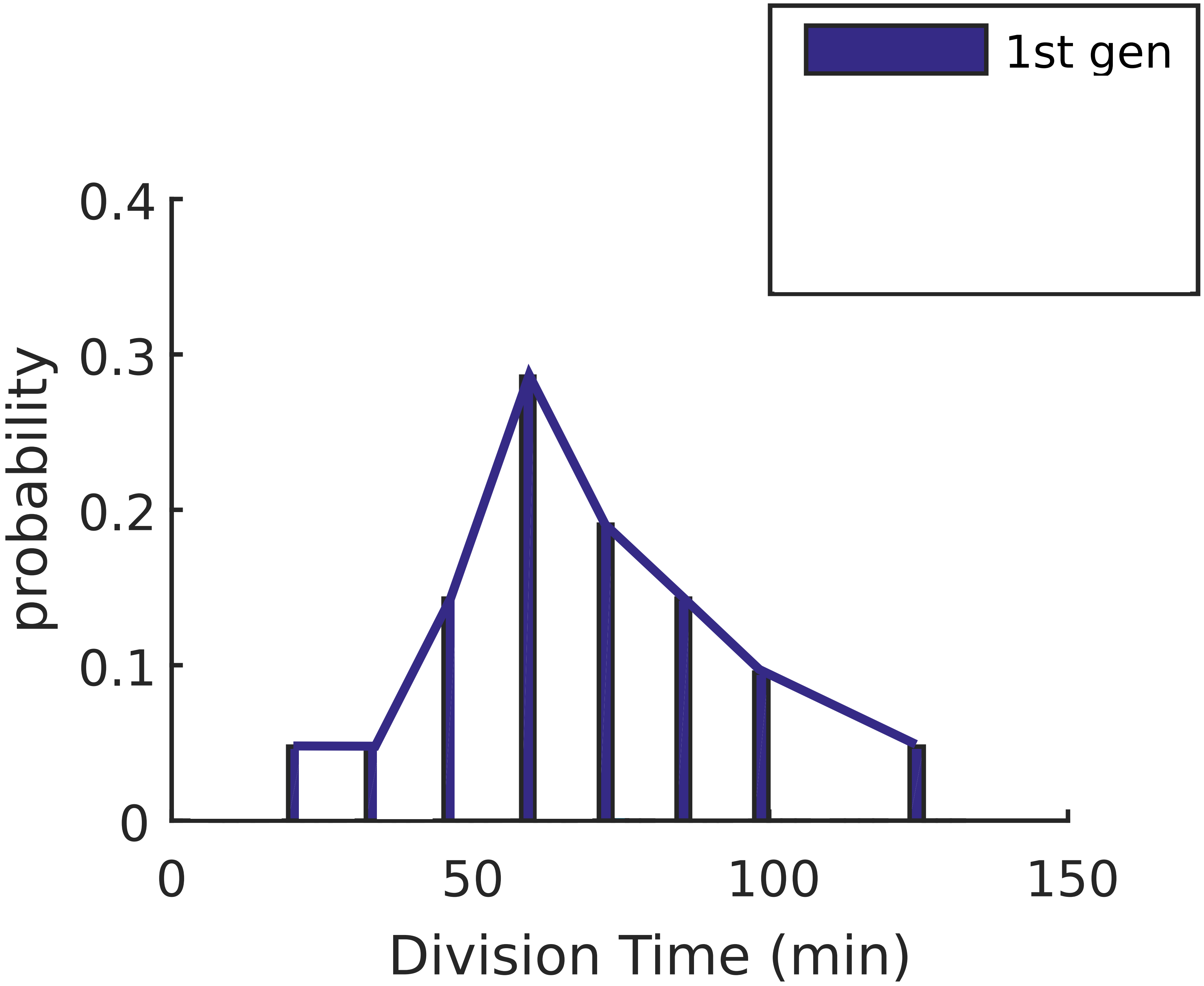

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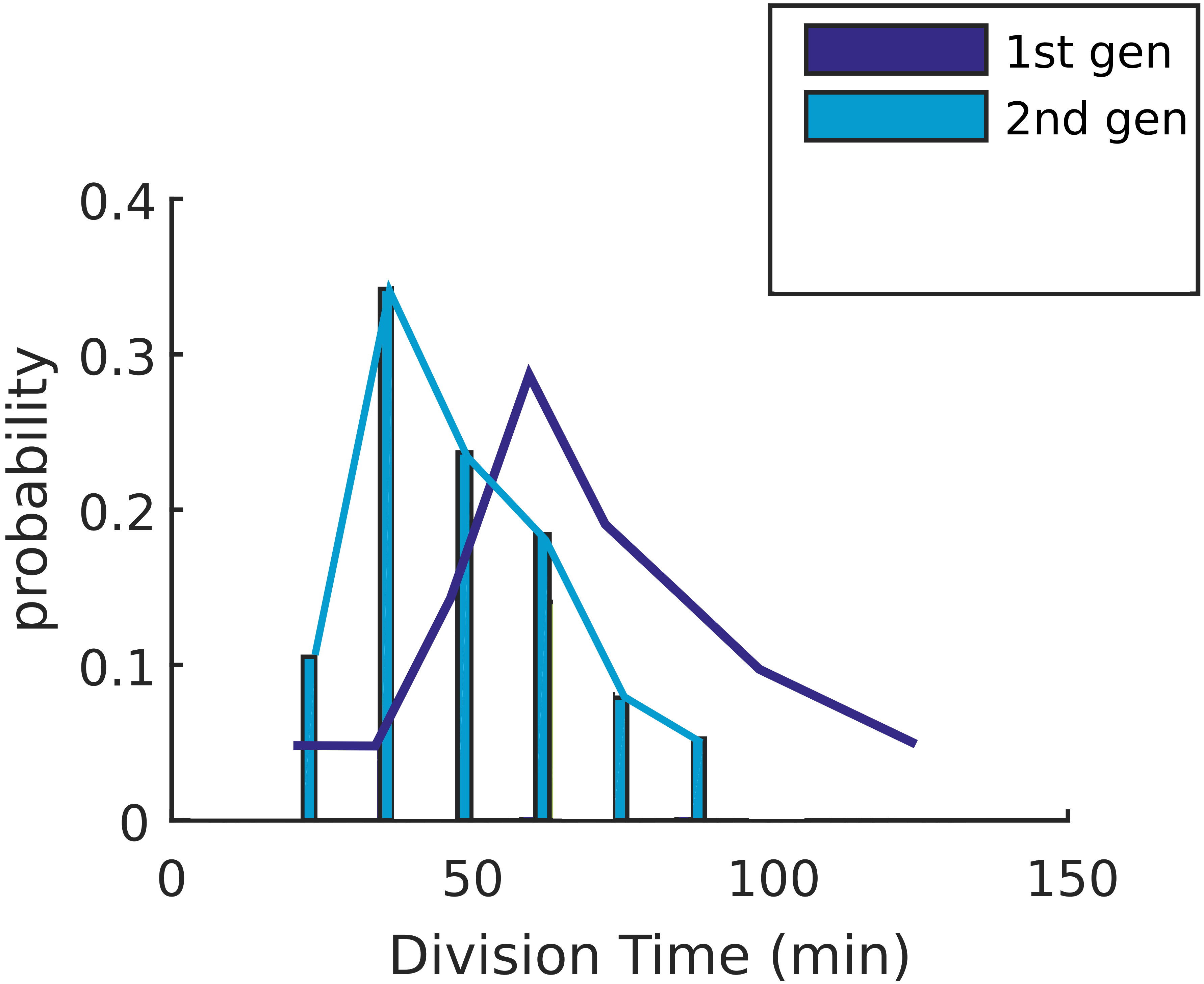

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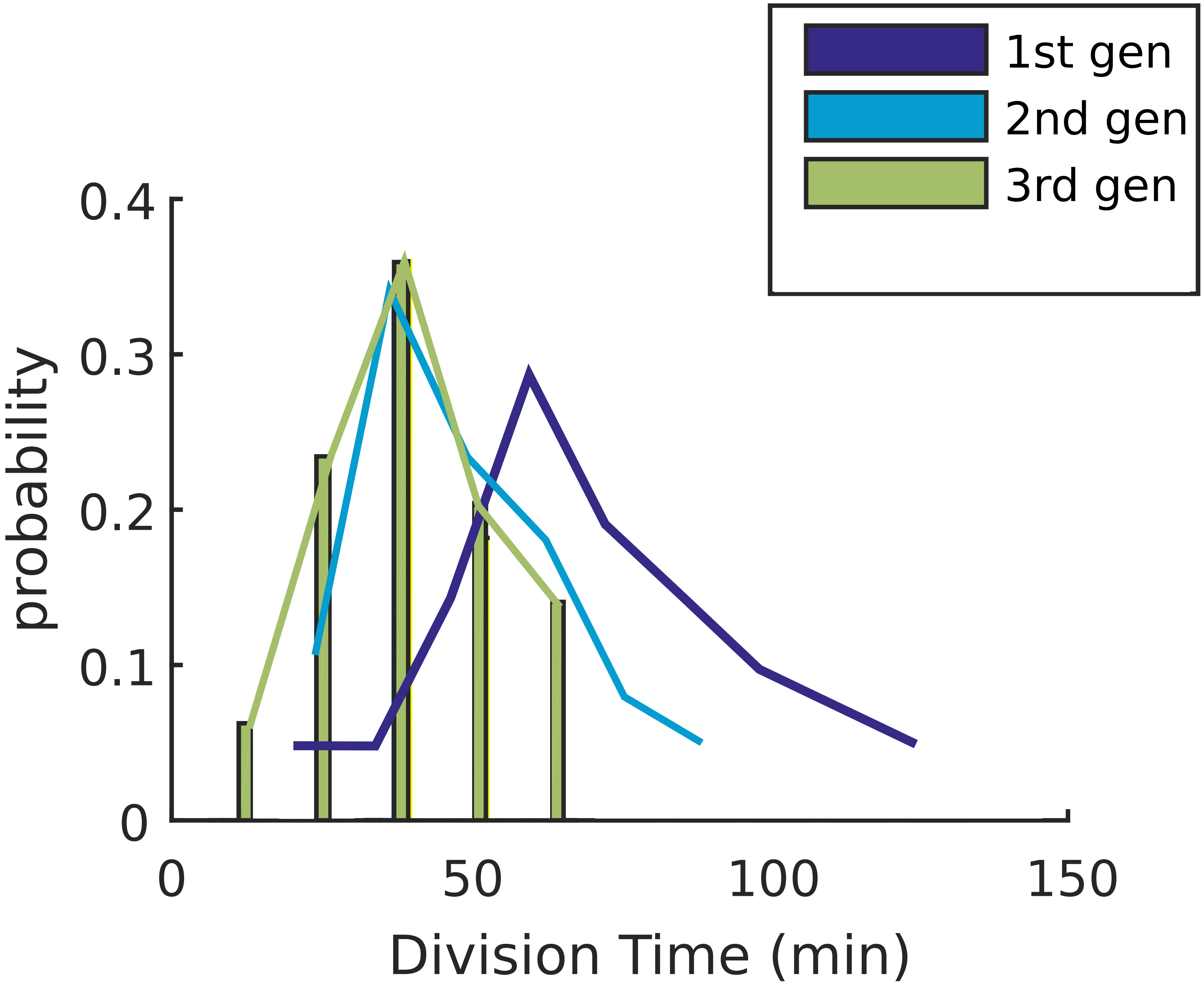

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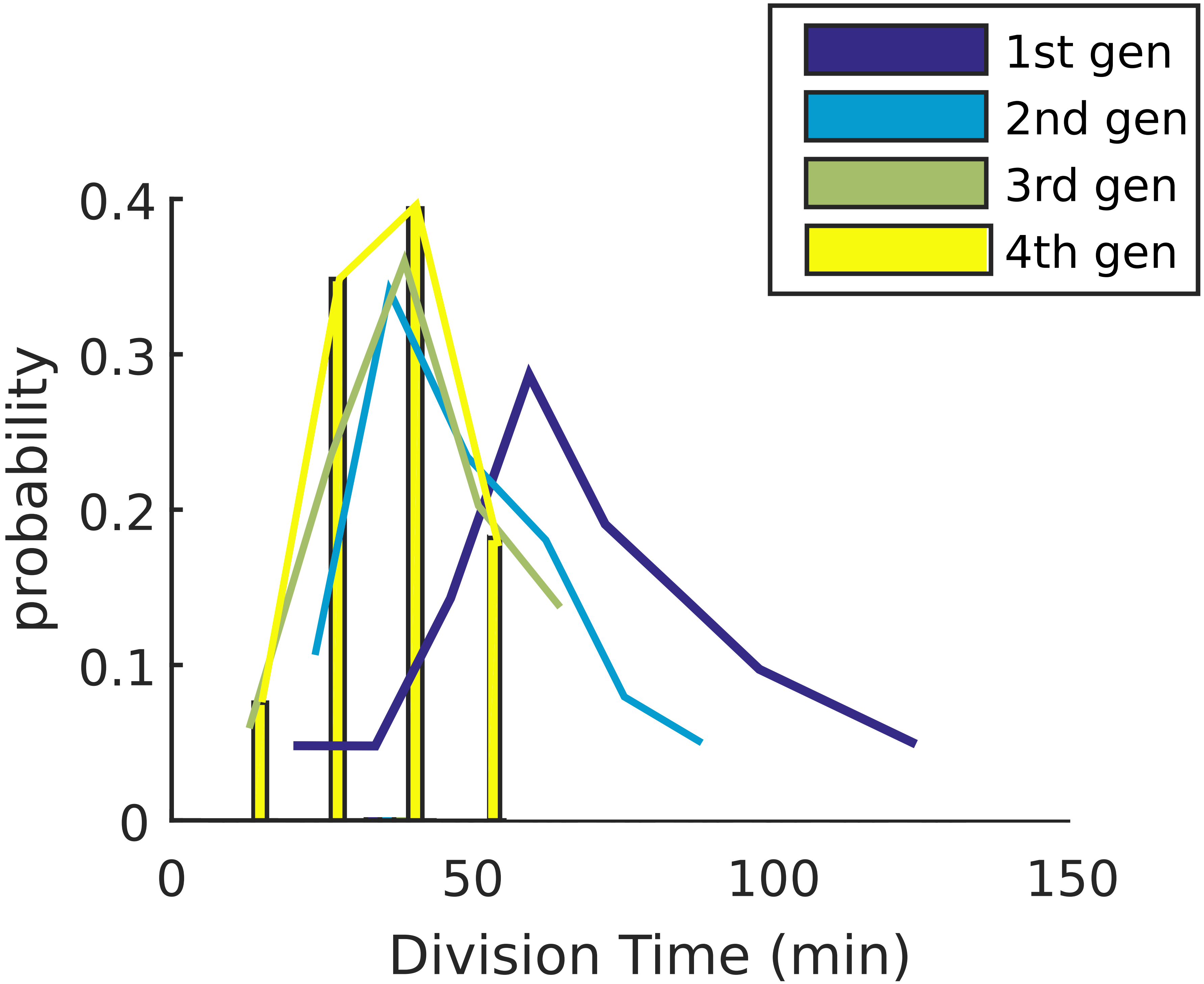

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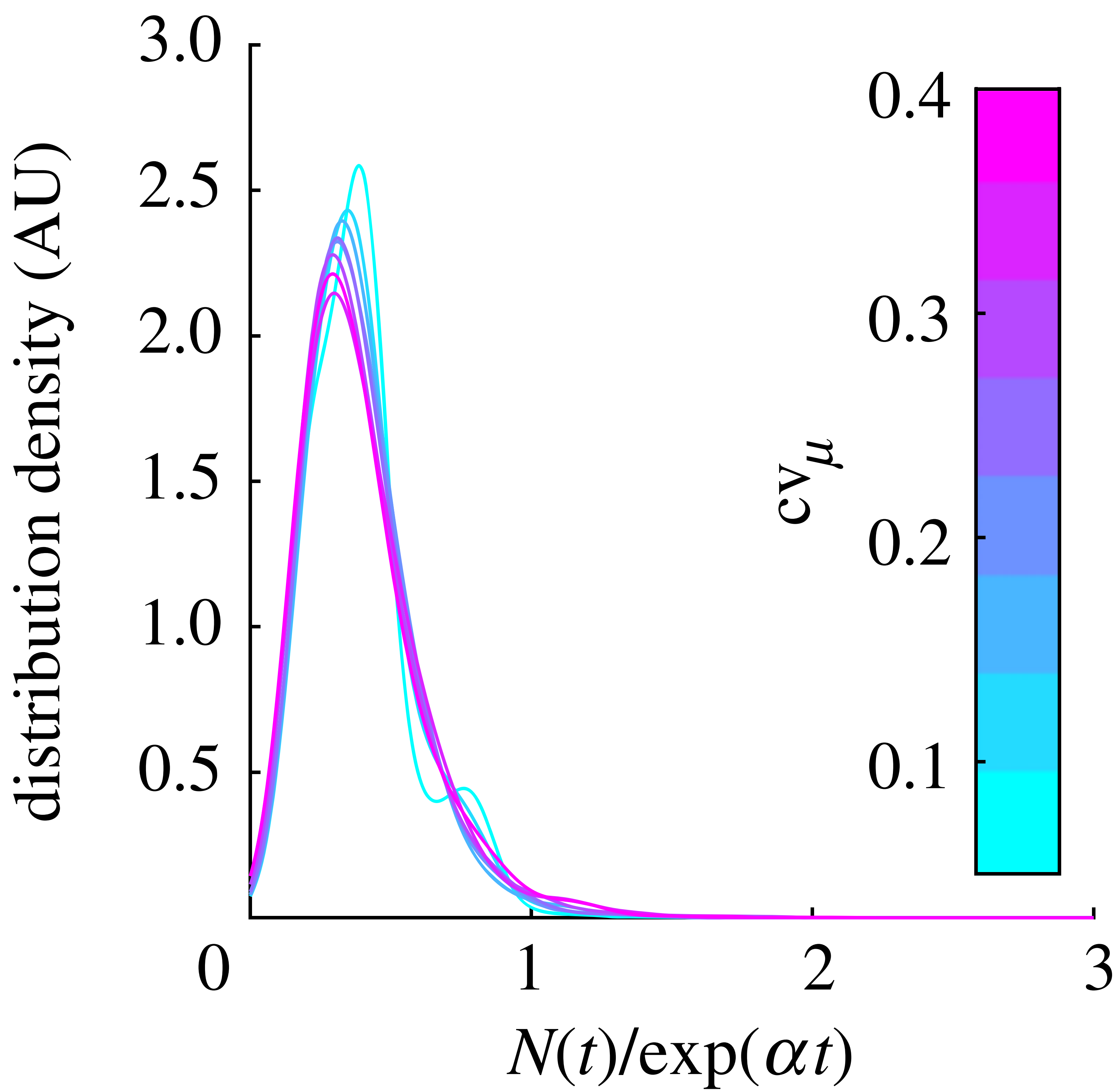
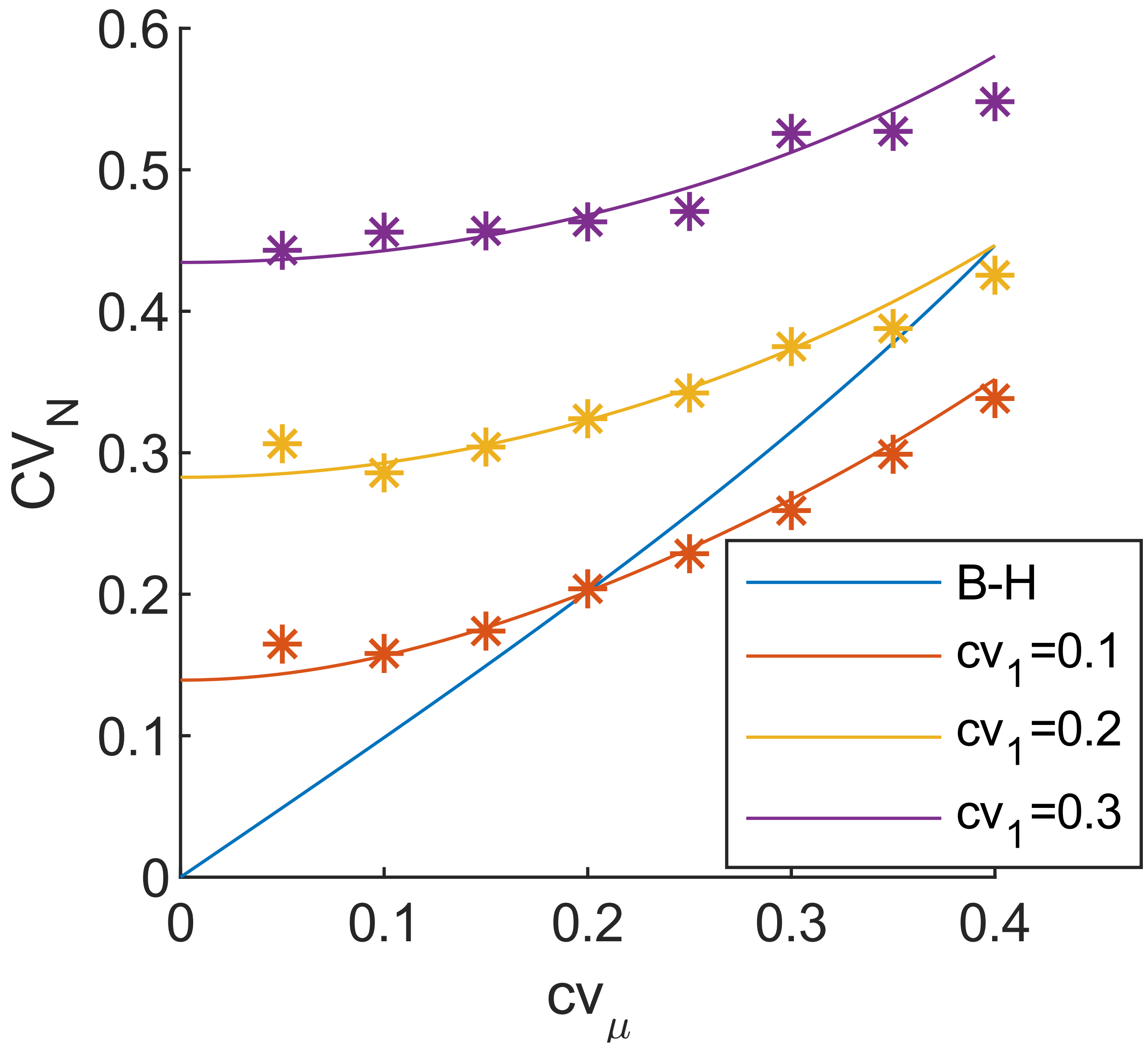


Adaptation to a new environment

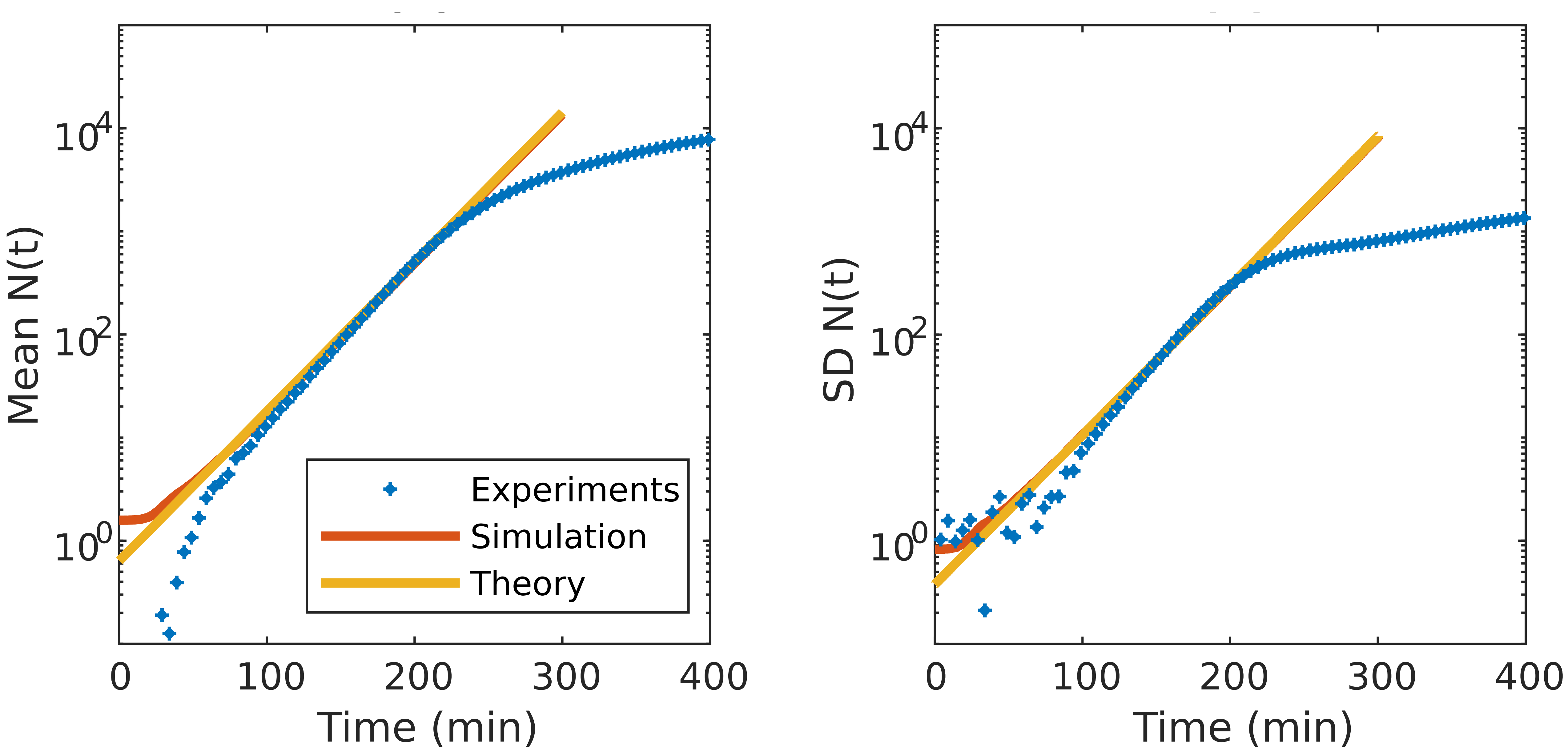
$$CV^2_{\sigma_1}(\infty) = \left(\frac{n_2}{n_1}\right)^2_{\sigma_1} = \underbrace{e^{\alpha^2\left(\sigma_1^2-\sigma^2\right)}\left(\frac{n_2}{n_1}\right)^2_{BH}}_{(1)} + \underbrace{e^{\alpha^2\left(\sigma_1^2-\sigma^2\right)}}_{(2)} - 1.$$



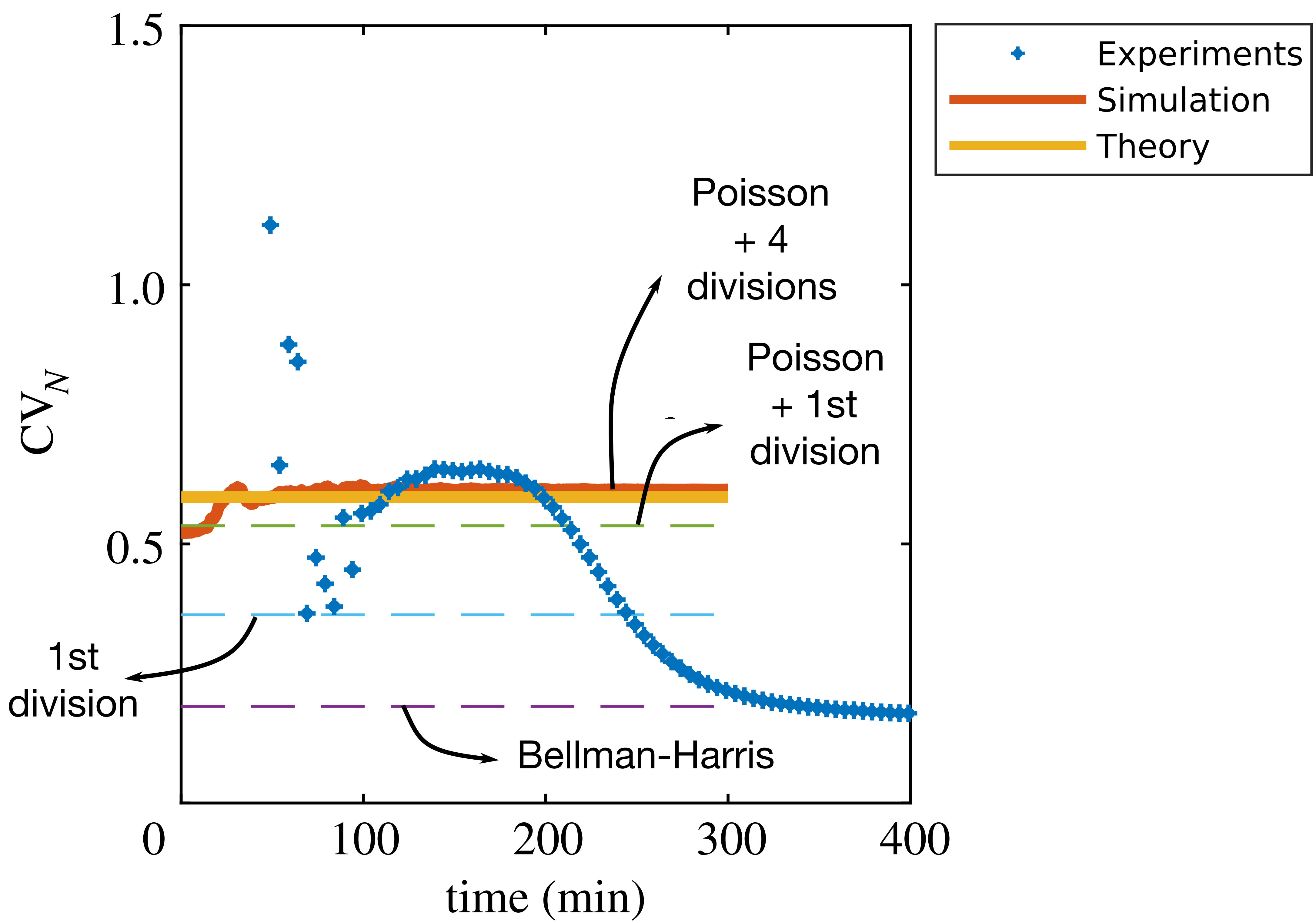
Combining all sources of stochasticity

$$CV^2_{\sigma_1,\lambda}(\infty) = \left(\frac{n_2}{n_1}\right)^2_{\sigma_1,\lambda} = \frac{1-e^{-\lambda}}{\lambda} e^{\alpha^2\left(\sigma_1^2-\sigma^2\right)} \left(\frac{n_2}{n_1}\right)^2_{BH}$$
$$+ \frac{1-e^{-\lambda}}{\lambda}\left(e^{\alpha^2\left(\sigma_1^2-\sigma^2\right)} - 1\right)$$
$$+ \frac{1-(\lambda+1)\,e^{-\lambda}}{\lambda}.$$

Comparison theory/experiments



Comparison theory/experiments



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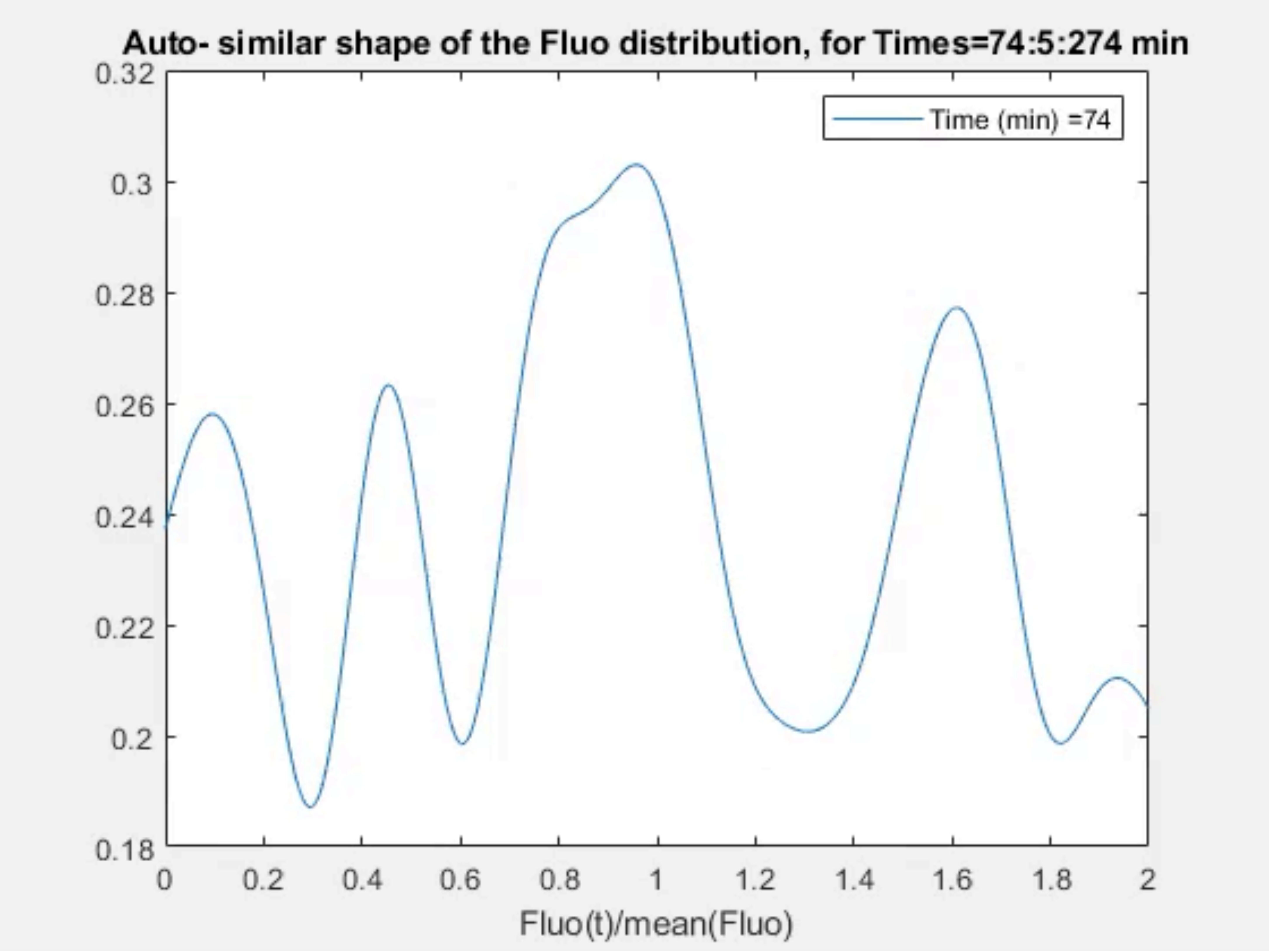

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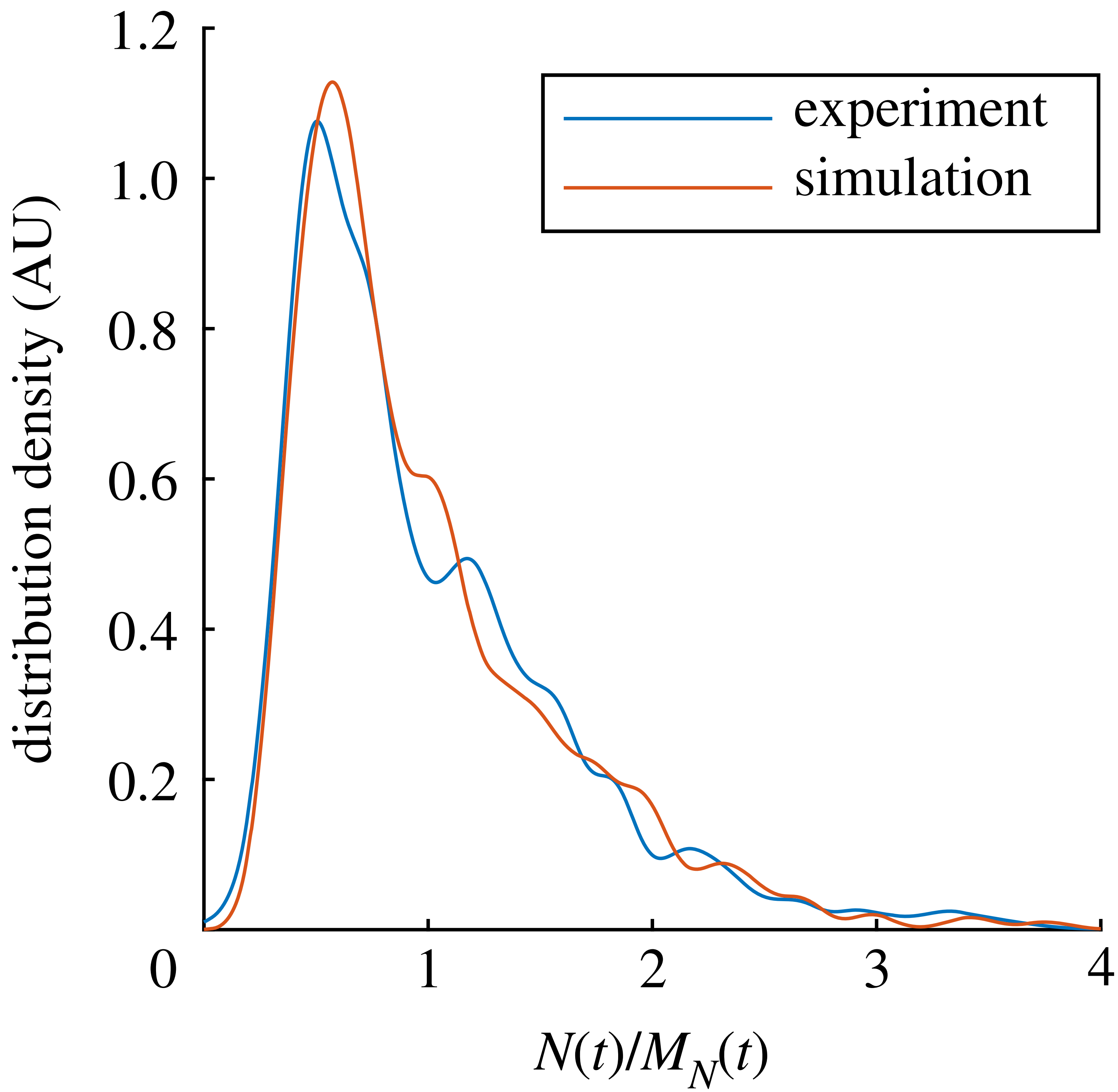
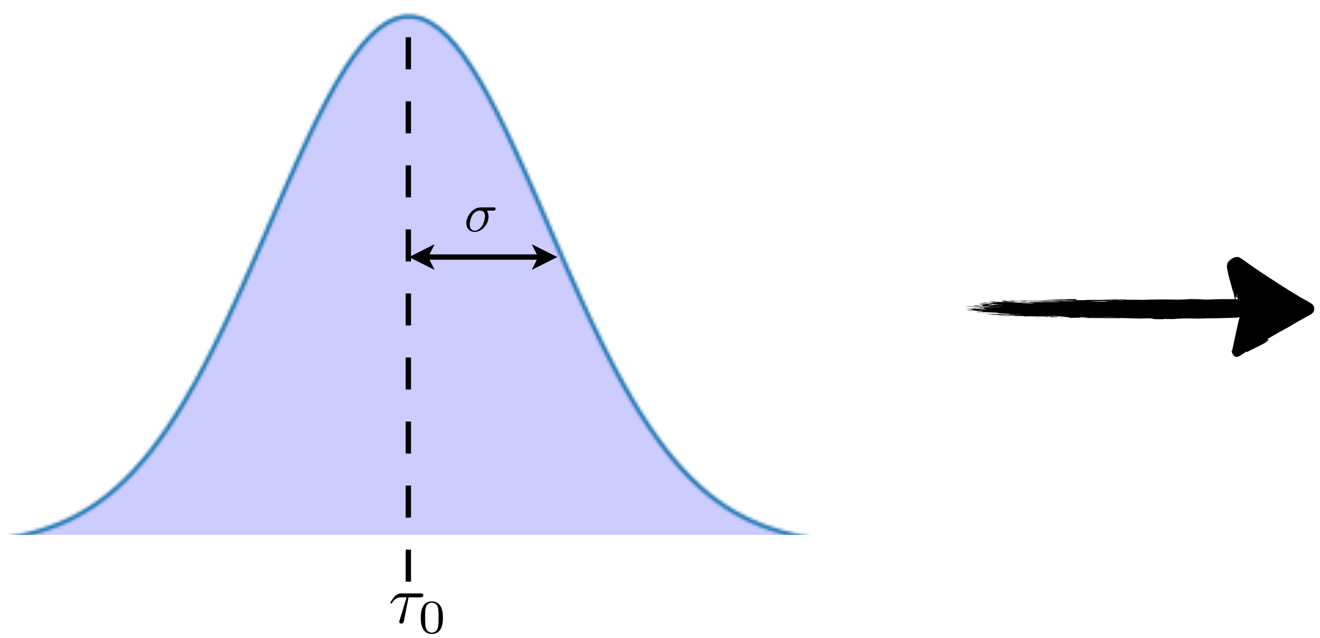
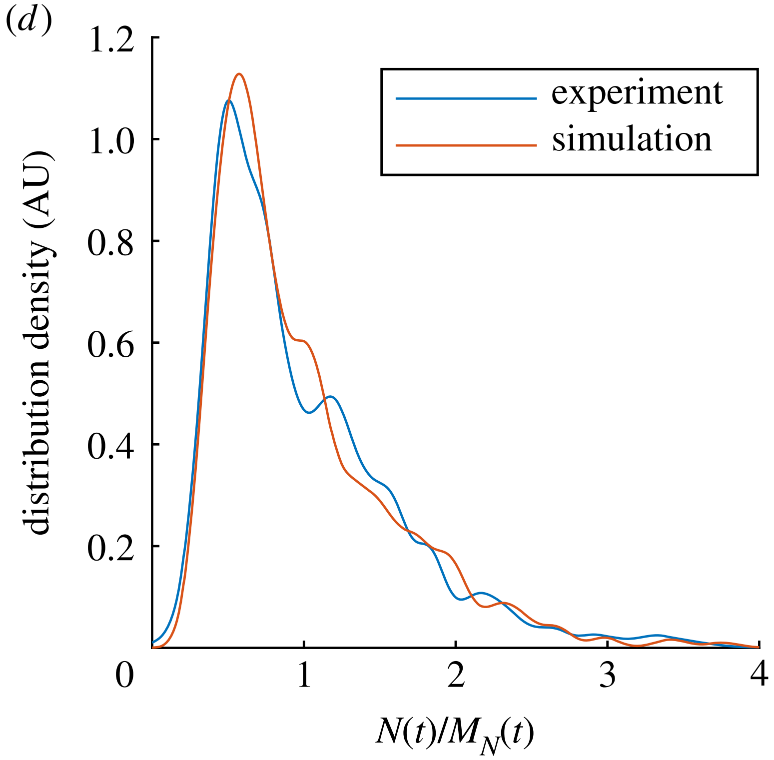


From one cell to a population





- Timer/adder/sizer give similar population distributions

- Variability comes from 3 sources:

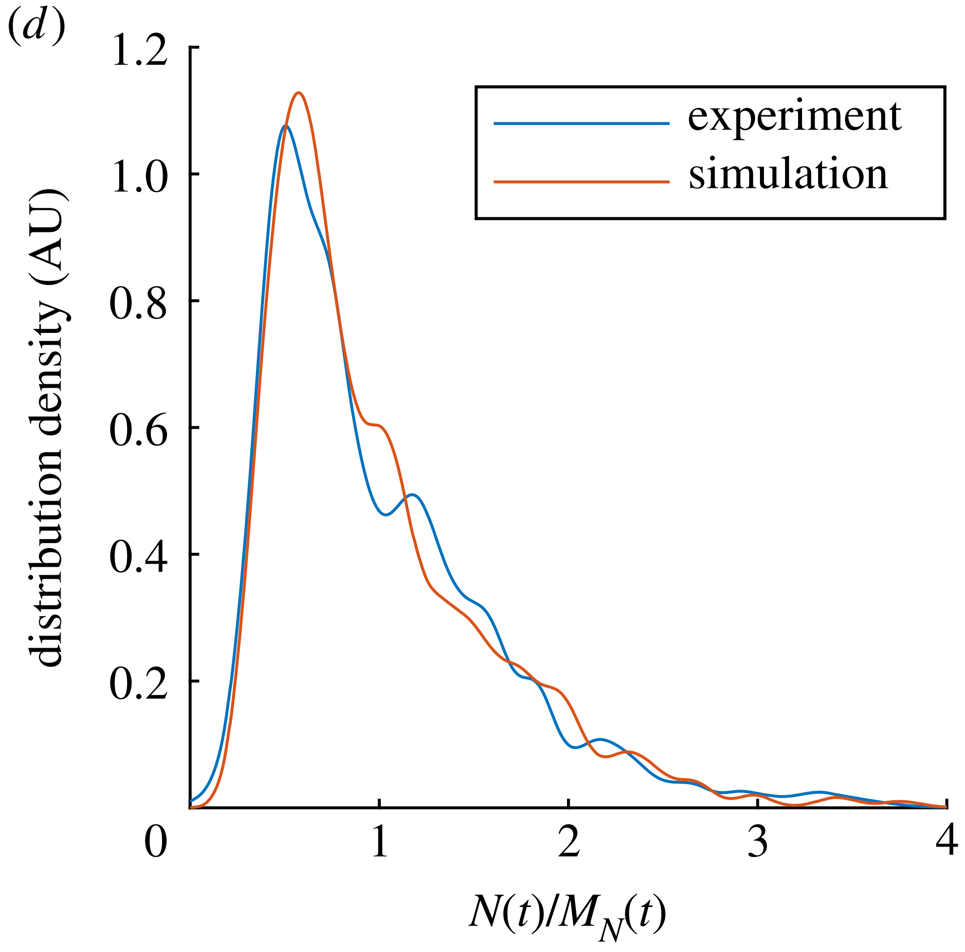
  Stochasticity in division times (classical Bellman-Harris)
  Adaptation to a new environment
  Poisson distribution of initial number of cells

- Stochasticity at initial times dominates variability in division times

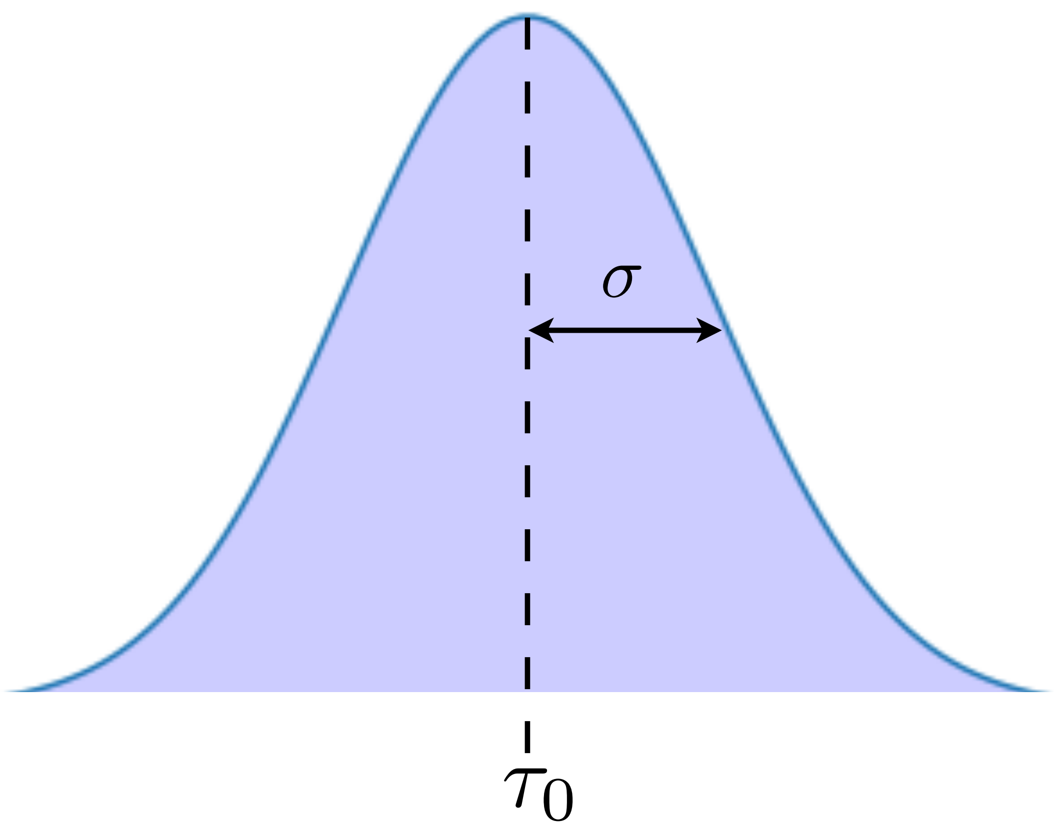
Barizien et al, *J. R. Soc. Interface*, 2019

From population to single cell stochasticity

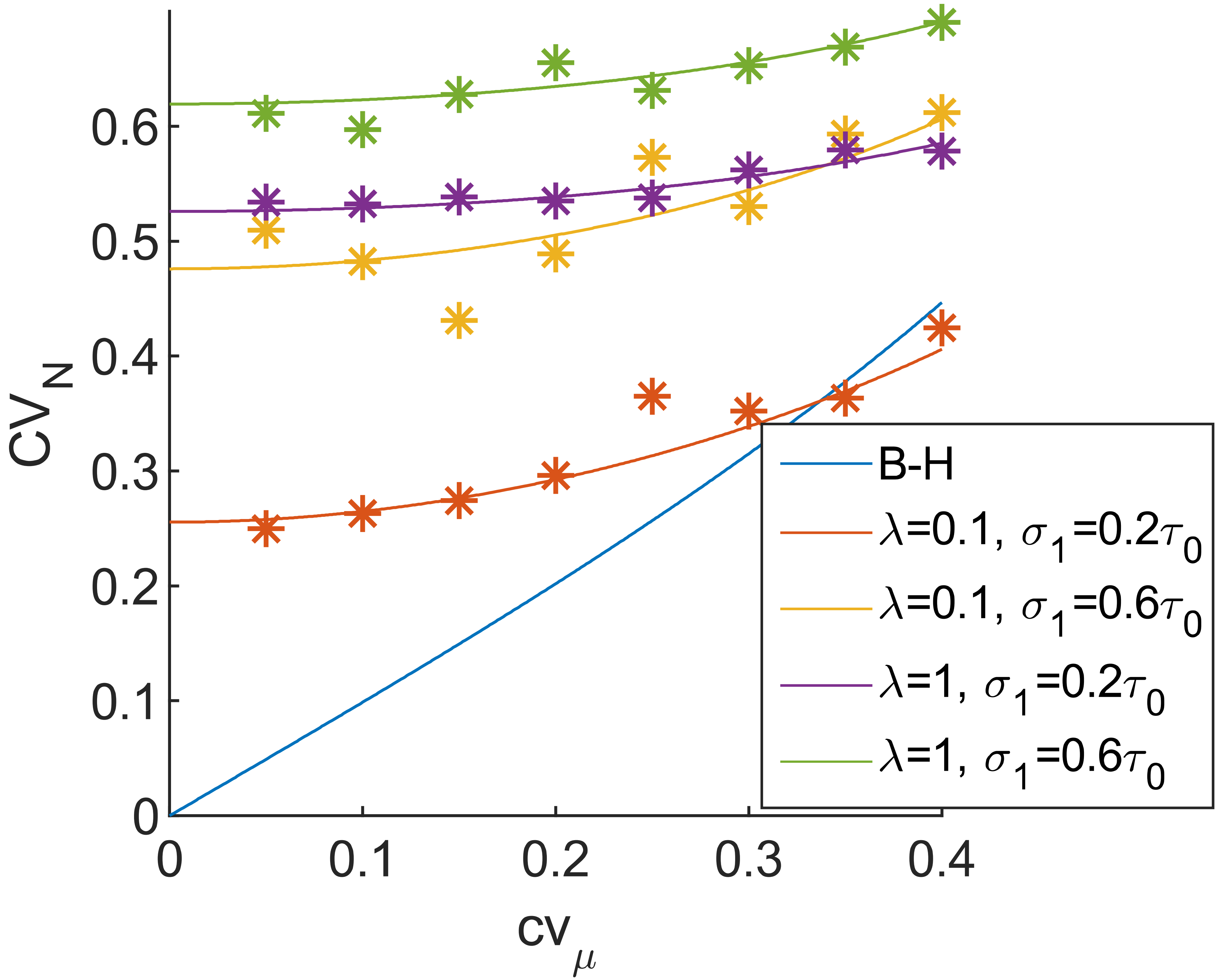
Macroscopic variability in population sizes



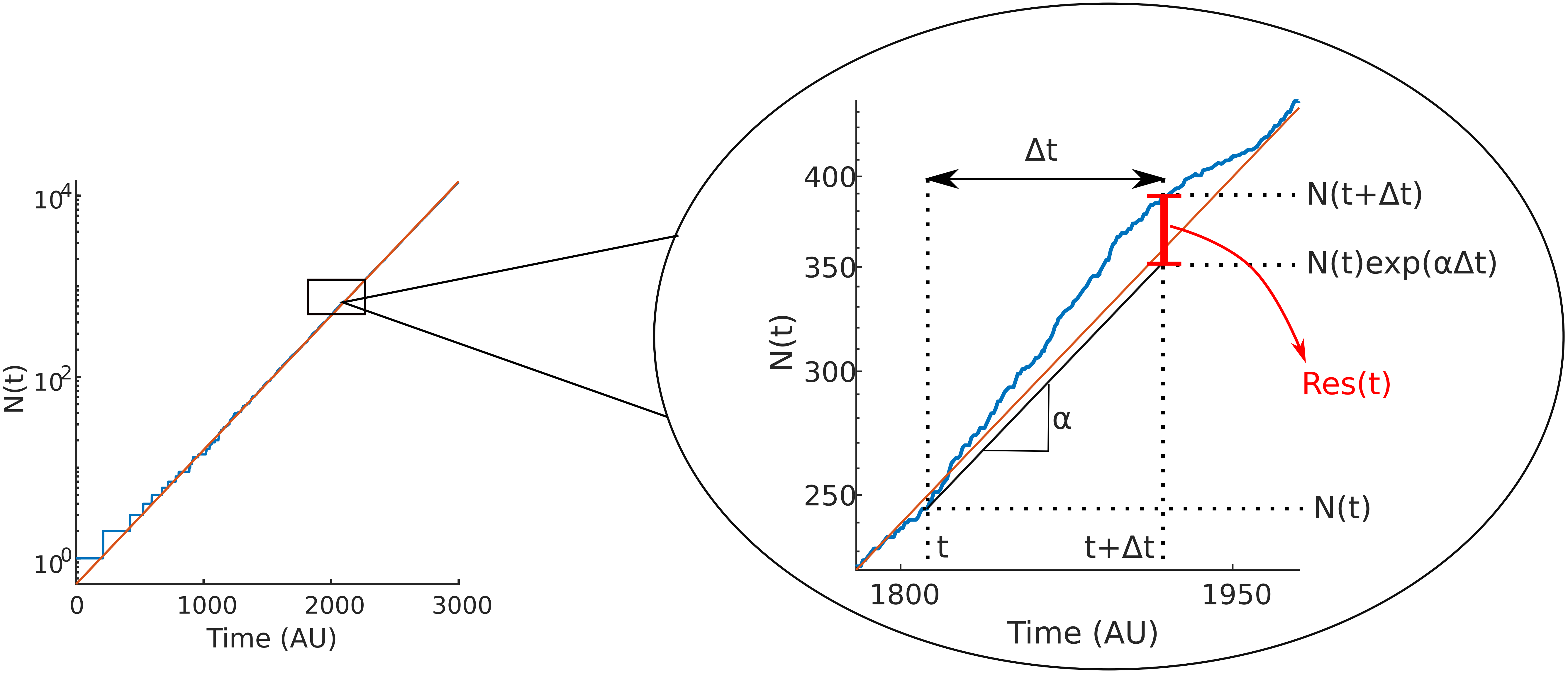
Microscopic variability in division times



Using the CV does not work

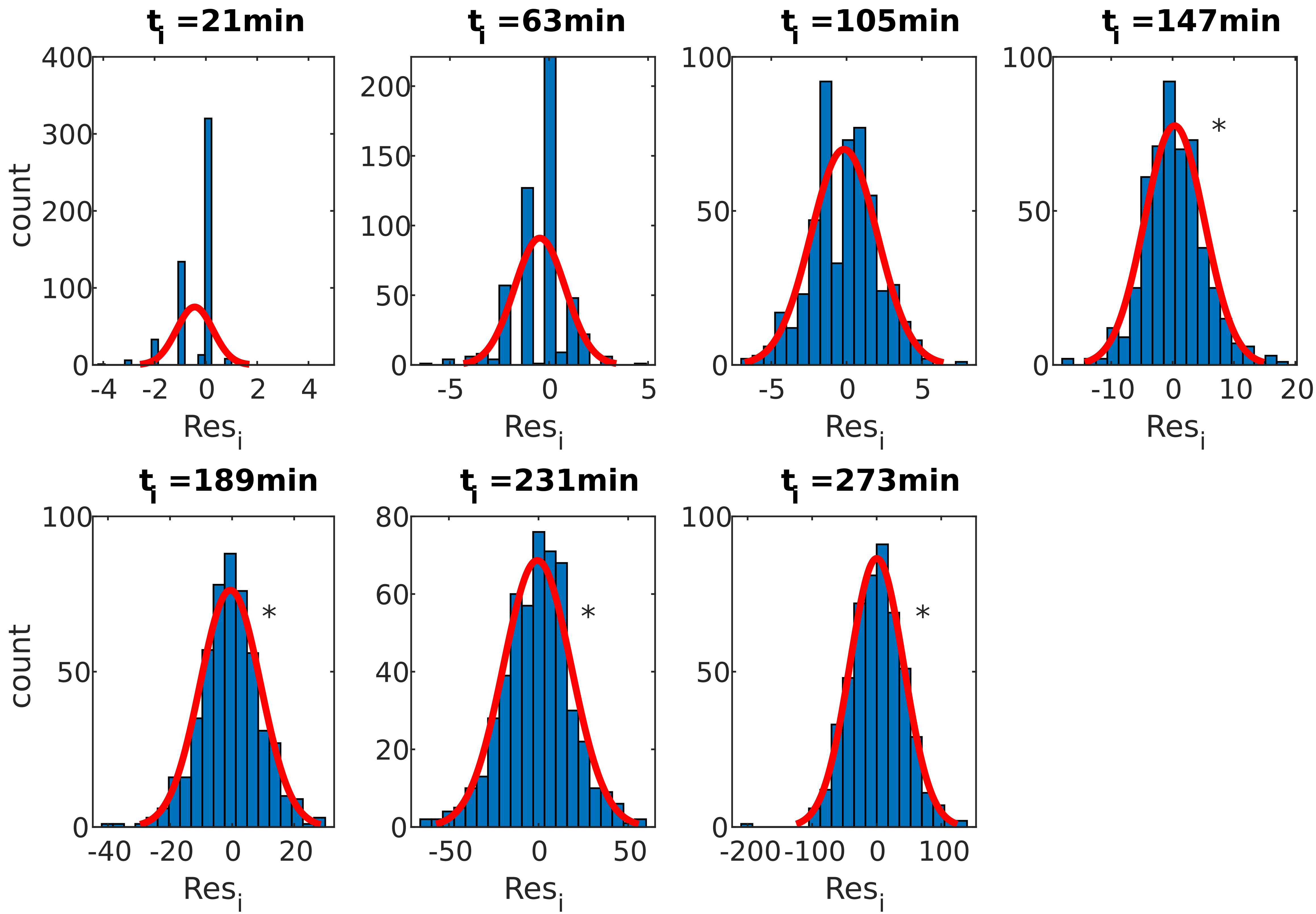


Dynamics of division



$$Res_i = Res(t_i) = N(t_{i+1}) - N(t_i)\exp\left(\alpha\Delta t\right).$$

Residuals - simulations



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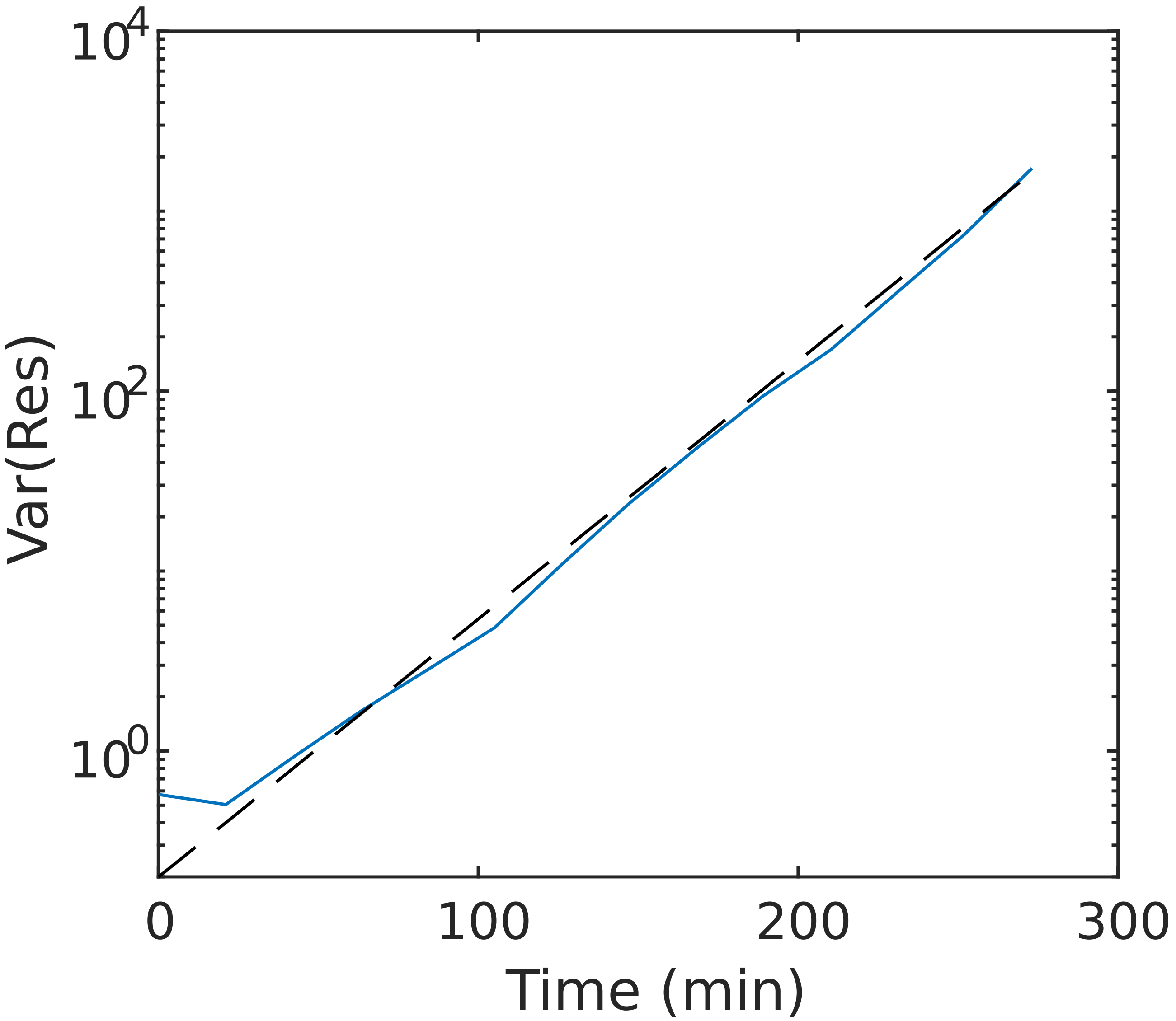
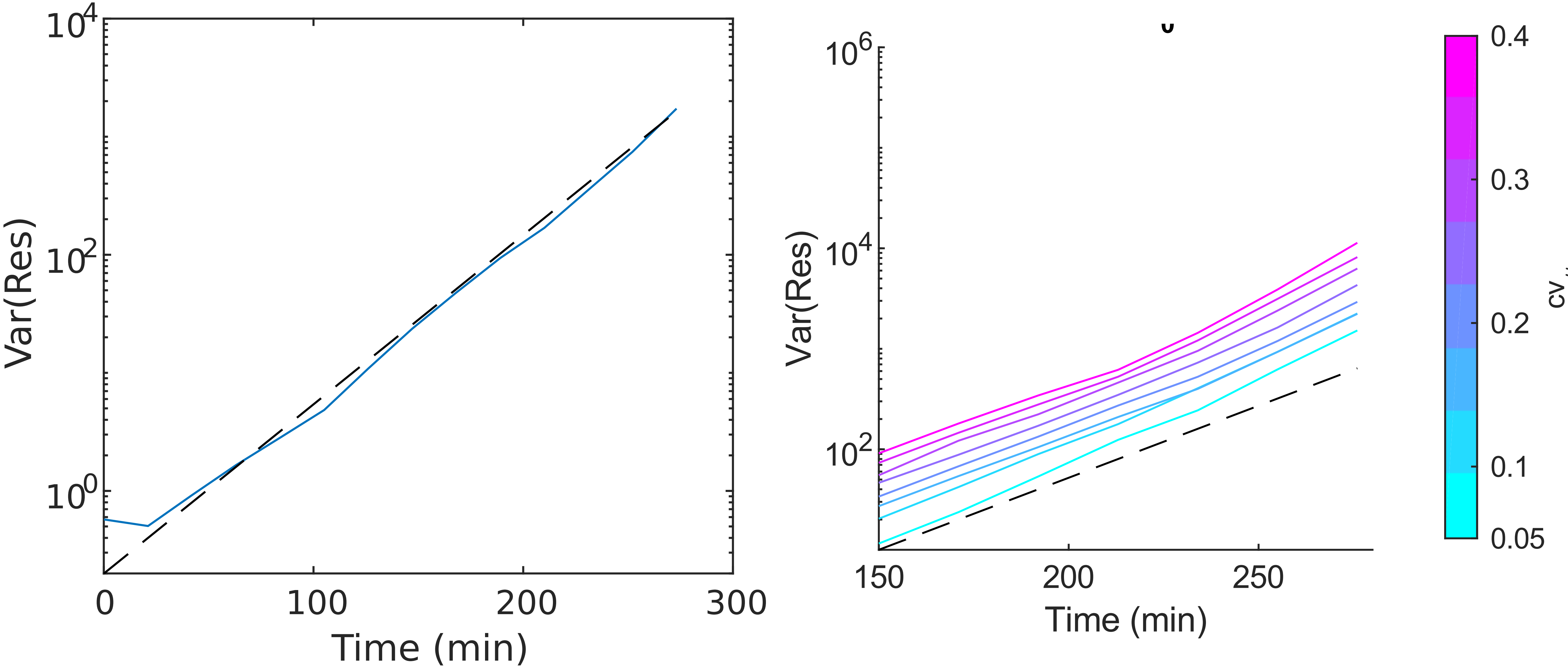
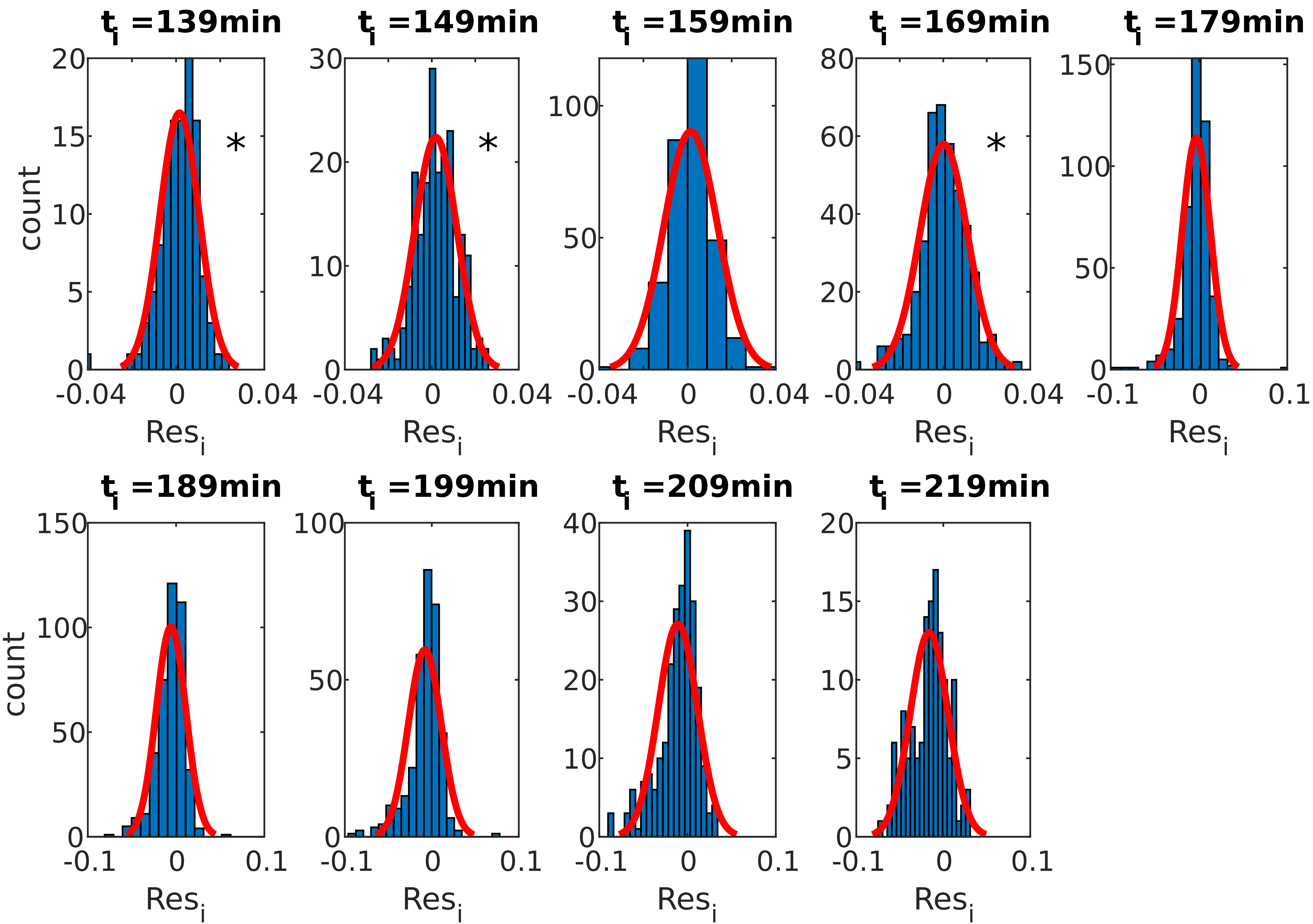


Residuals - simulations



Residuals - experiments



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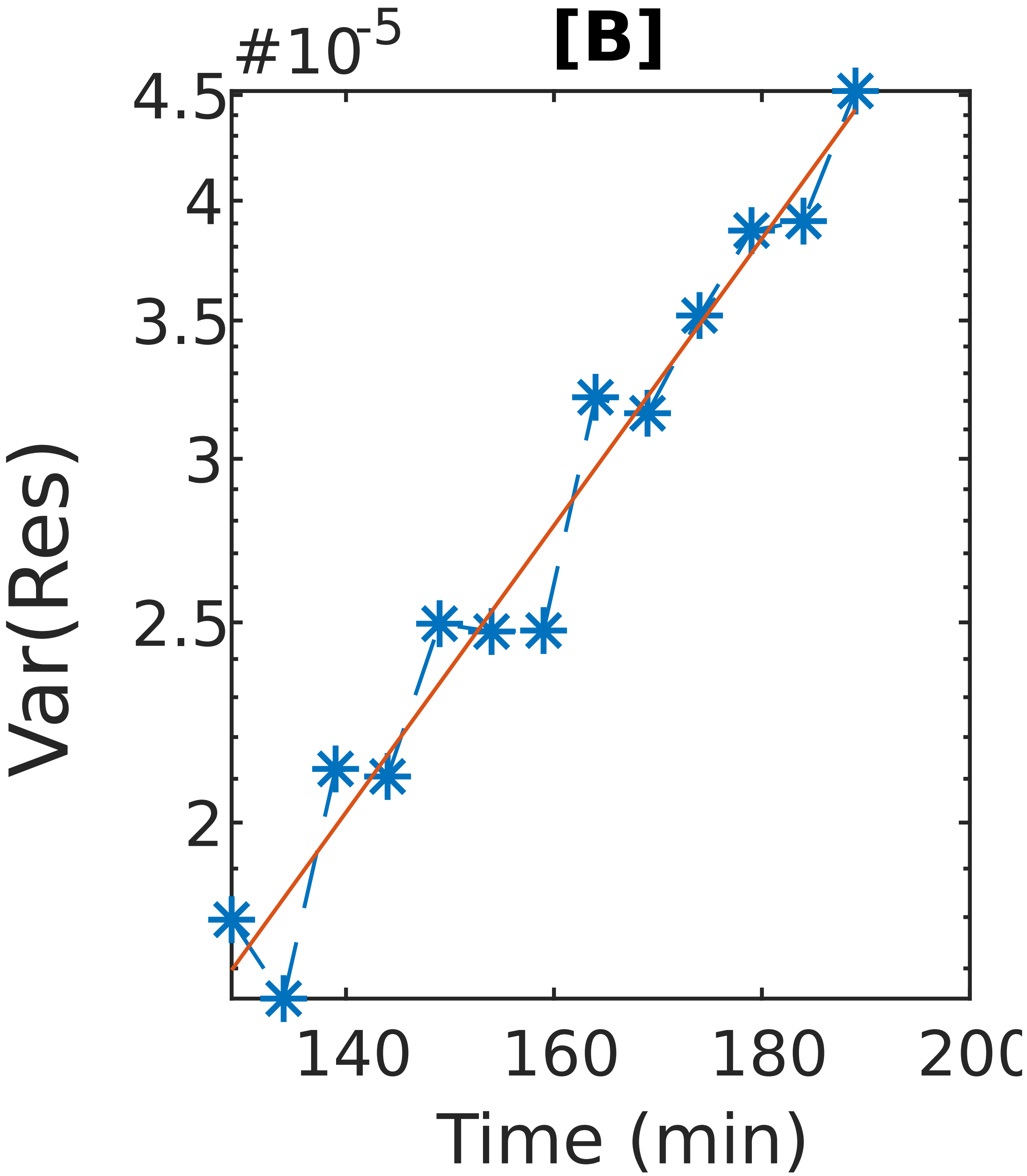
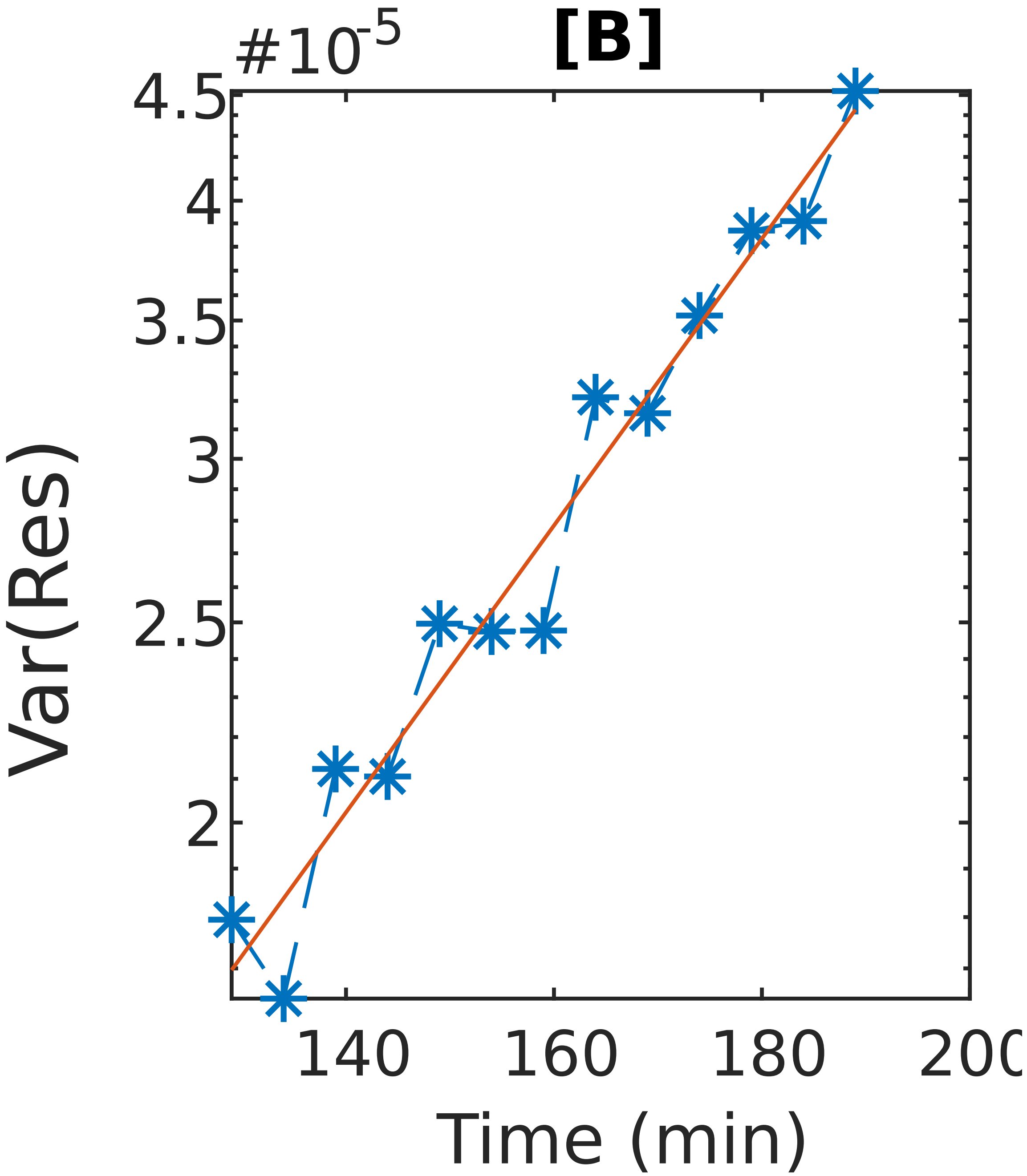
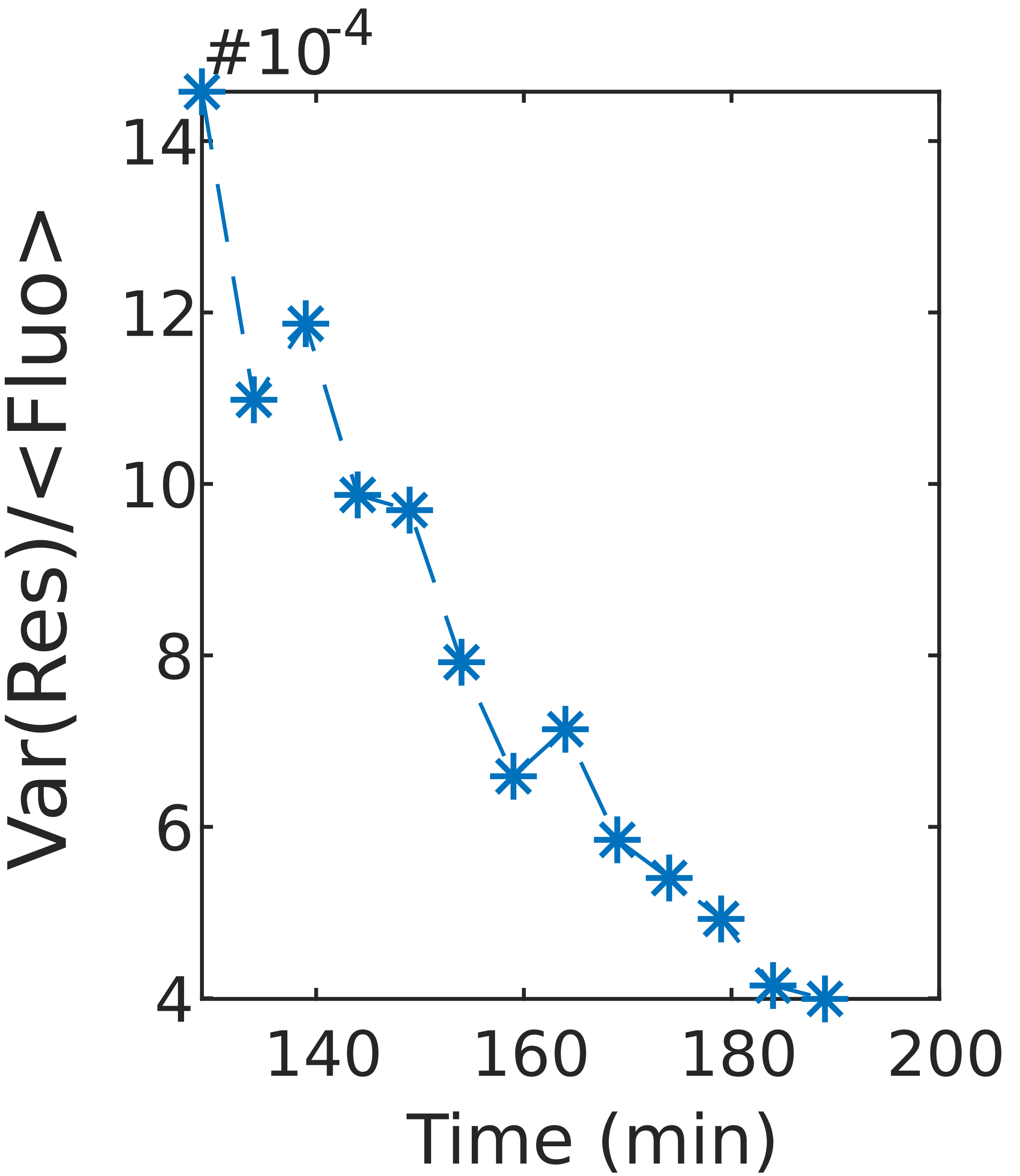
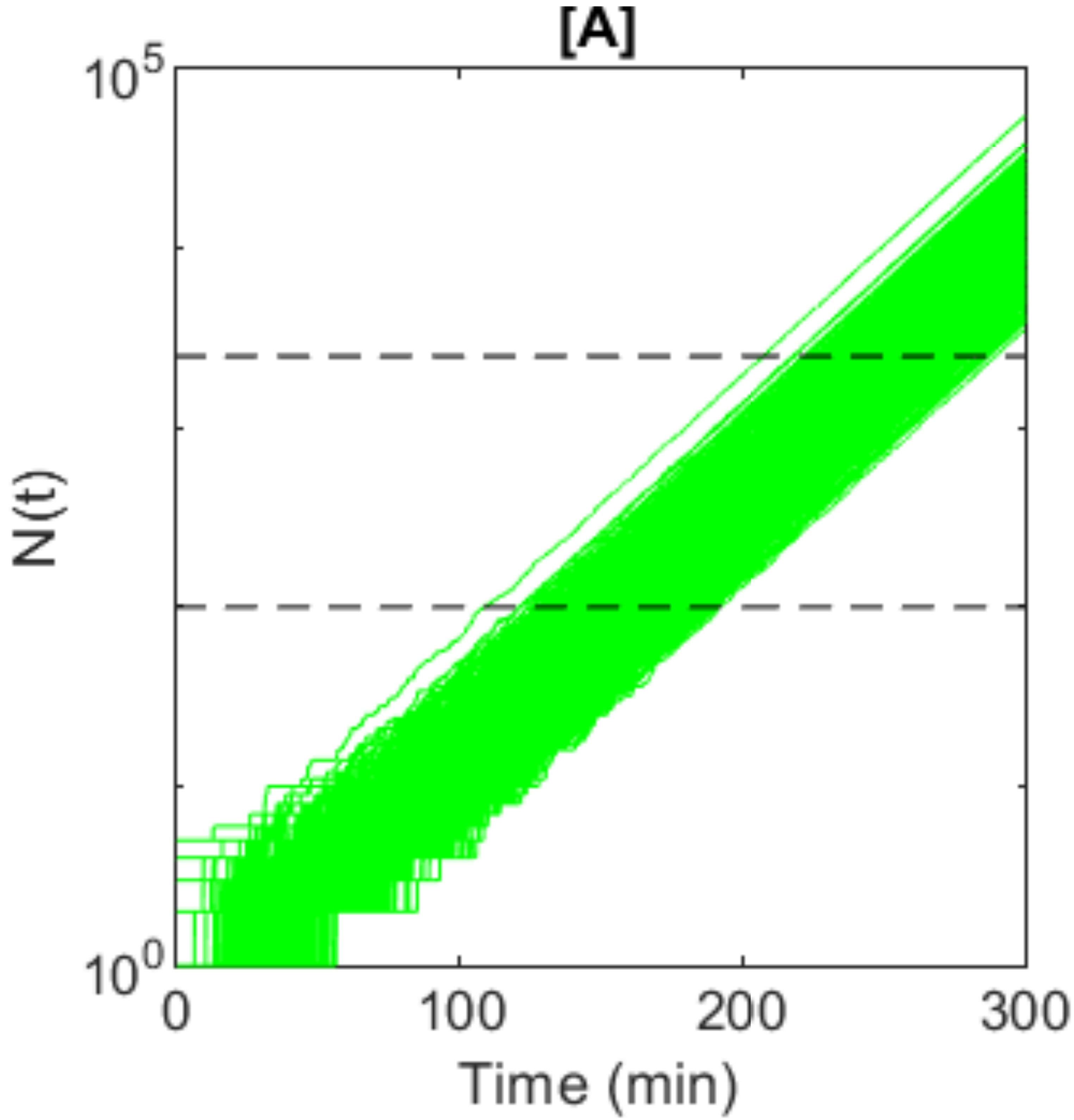


Residuals - experiments

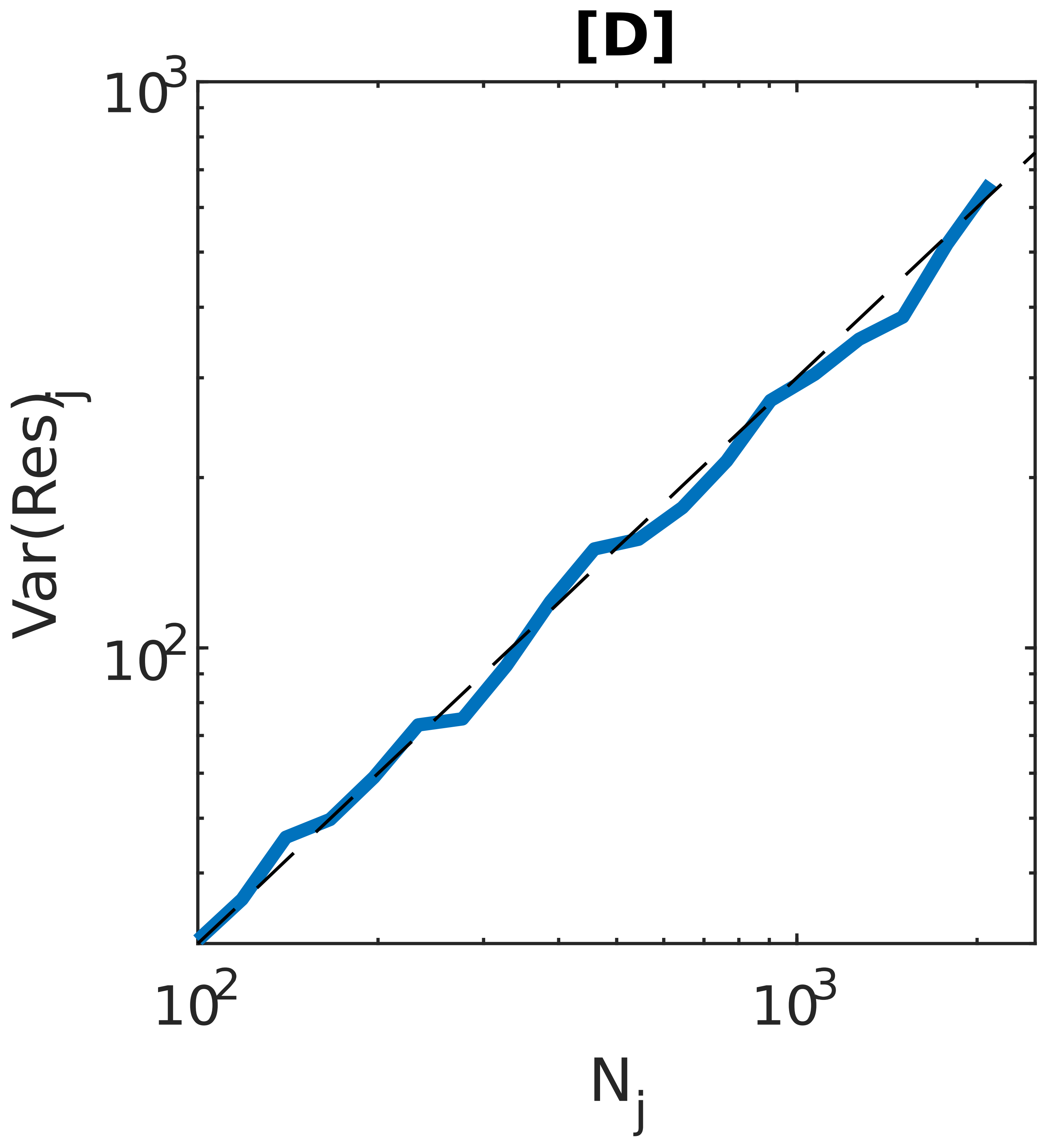




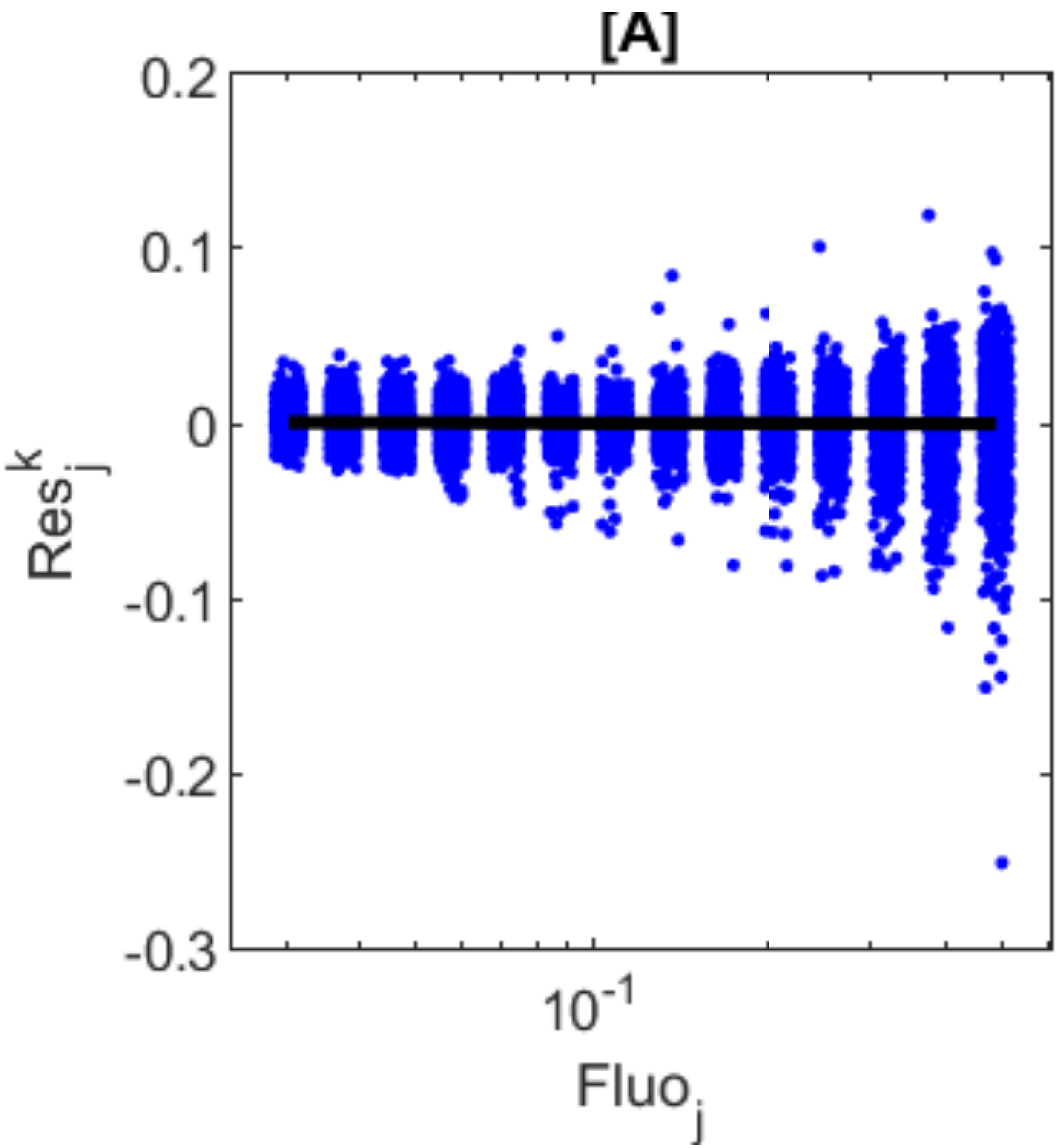
Residuals - binning by N



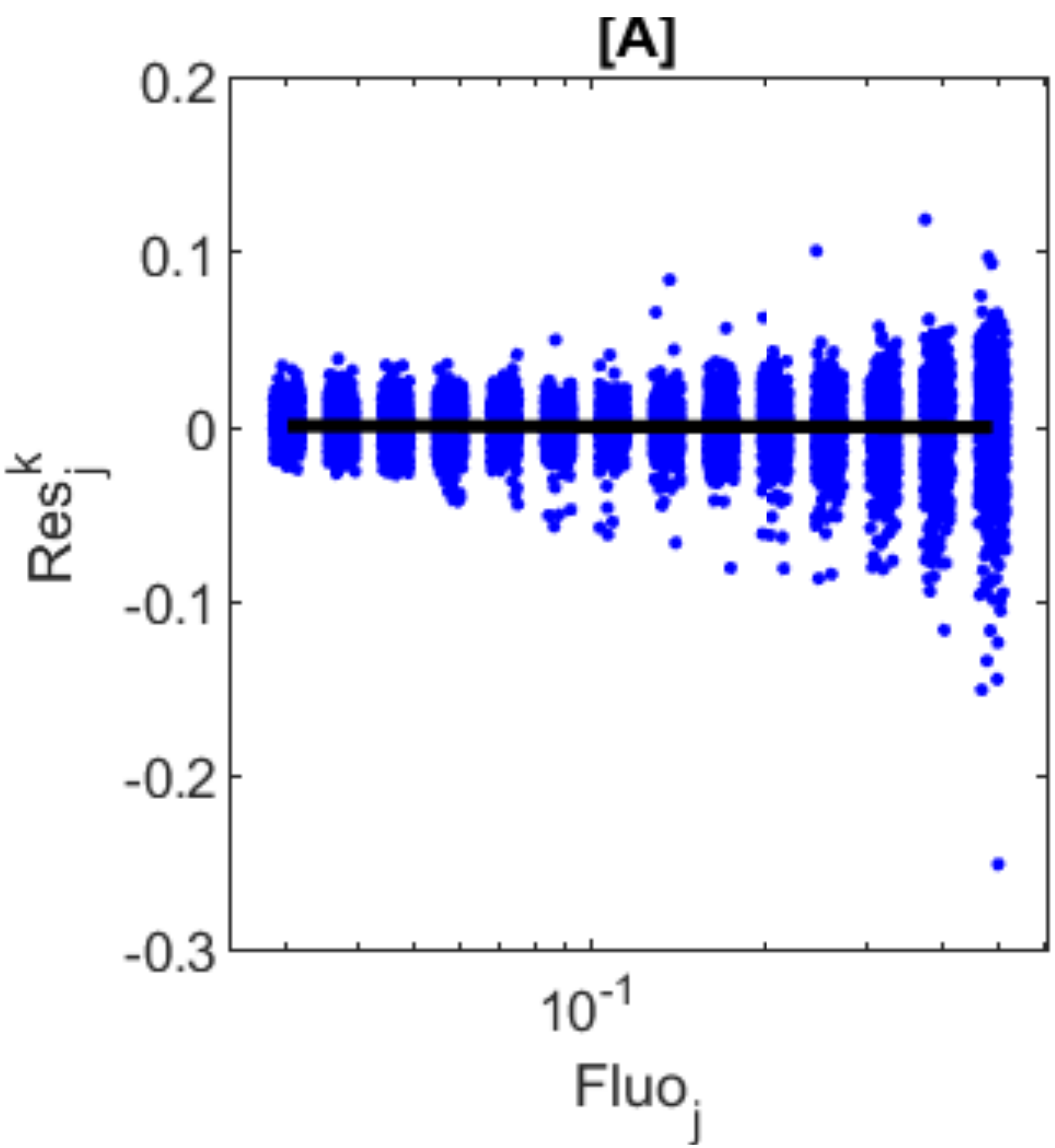
Residuals — binning by N — simulations

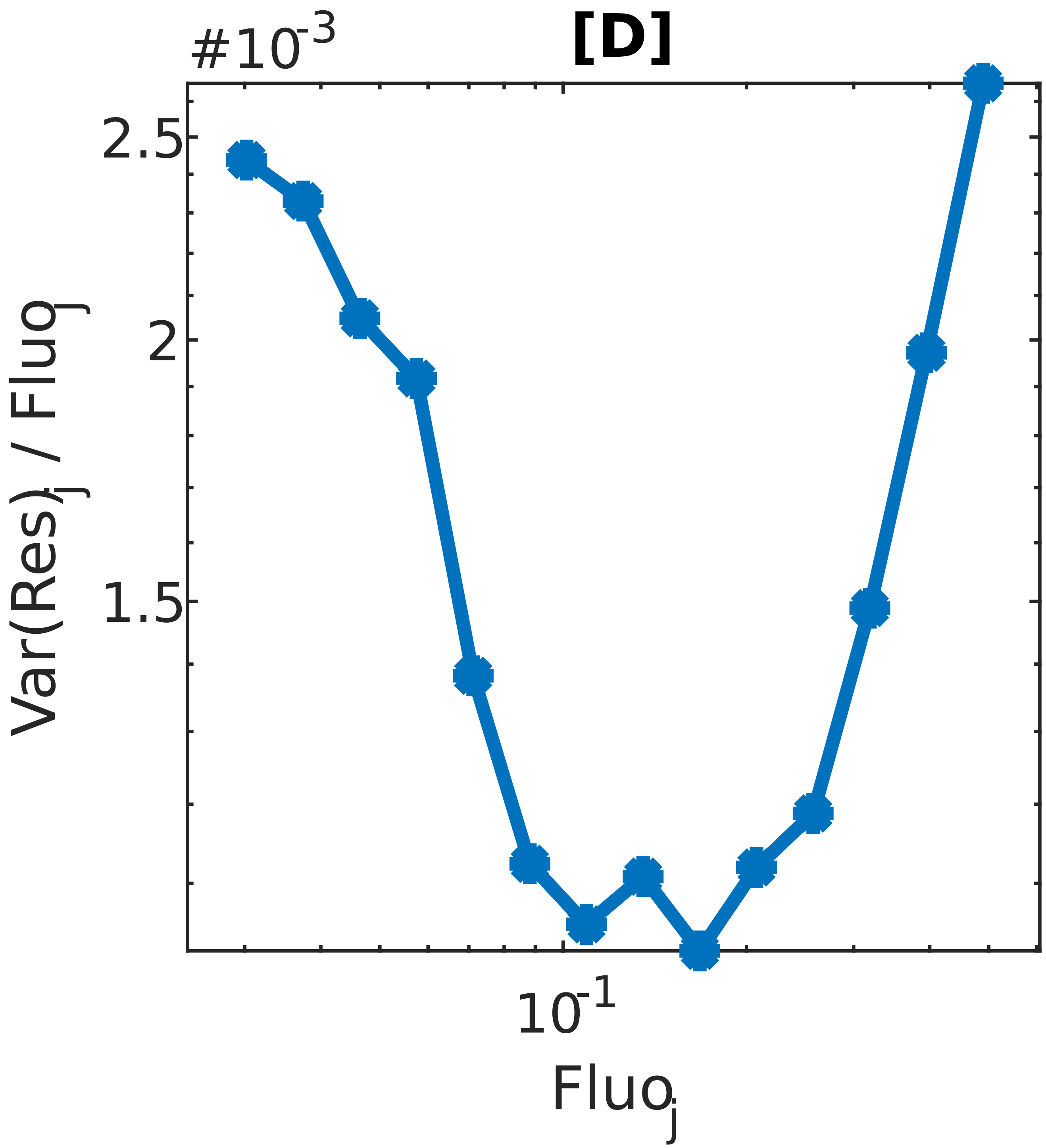


Residuals — binning by N — experiments

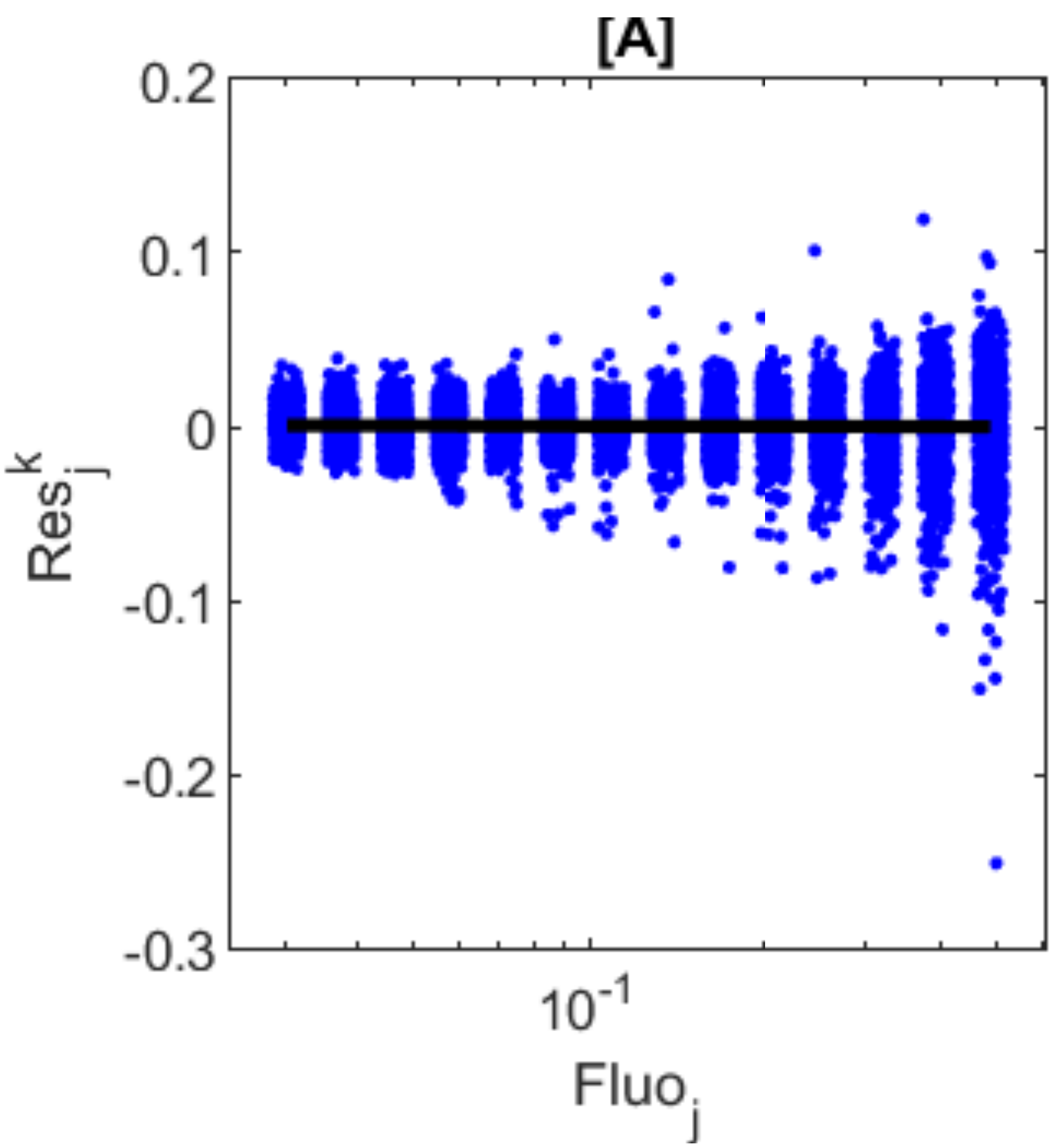


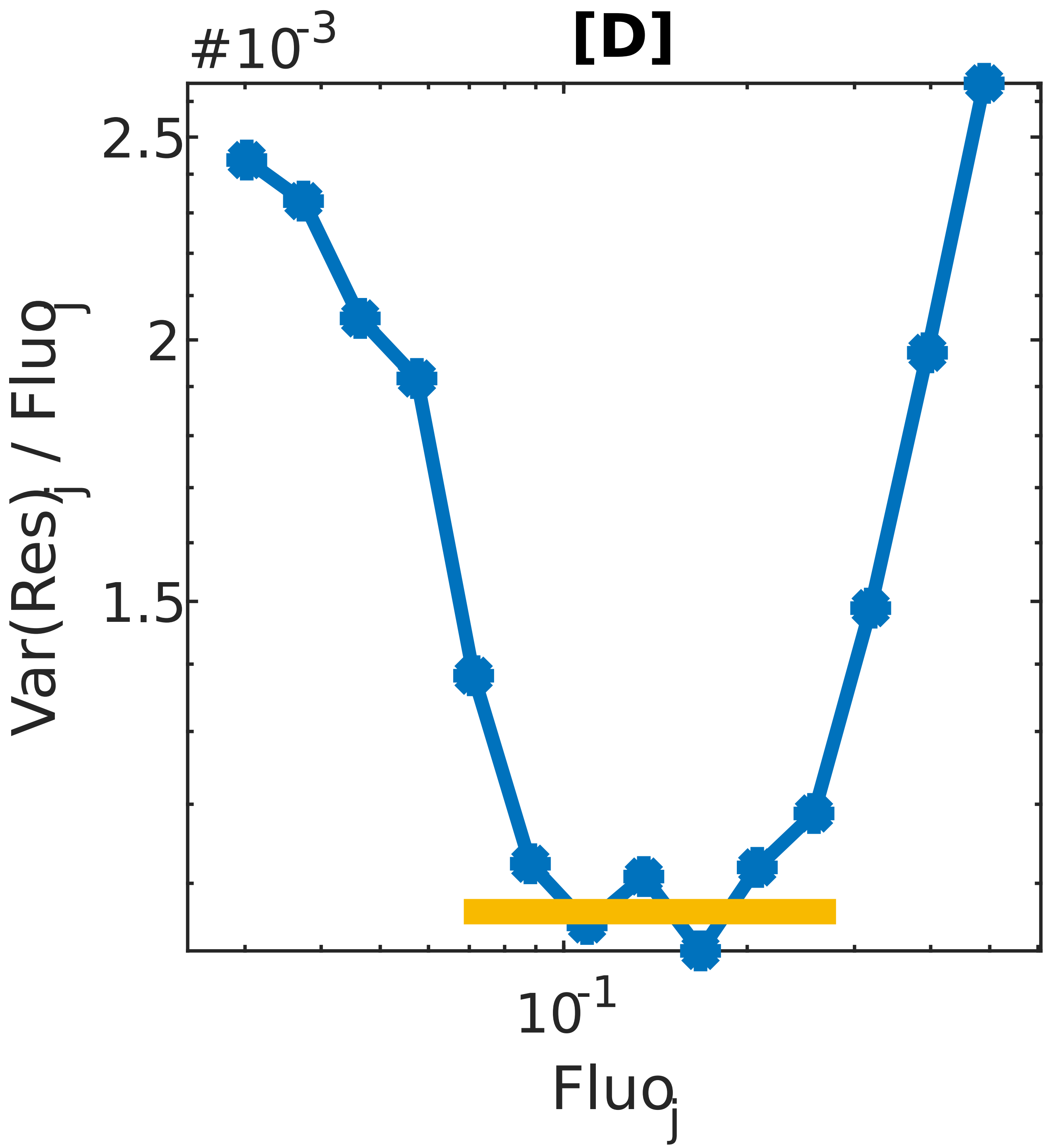
Residuals — binning by N — experiments



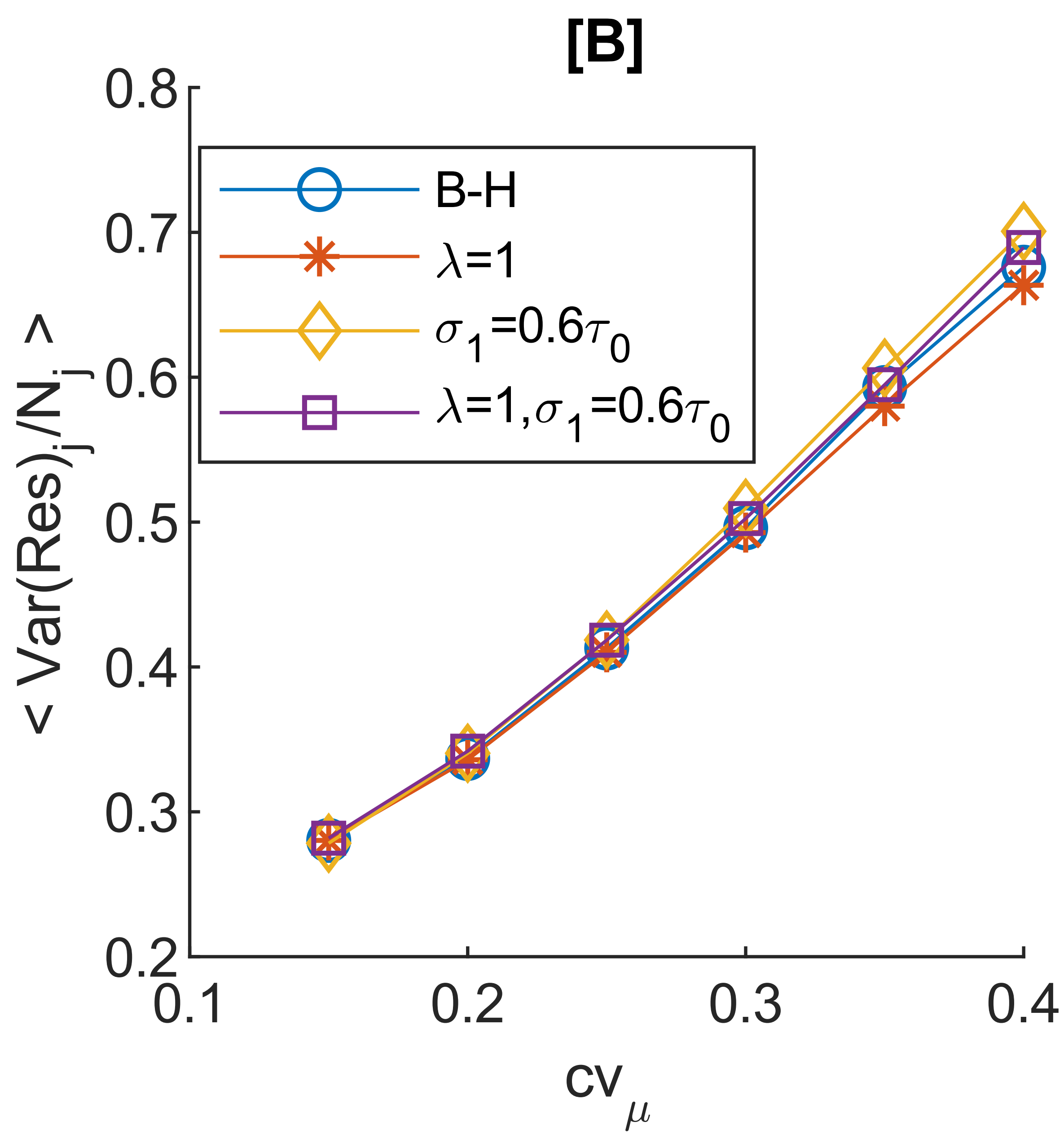


Residuals — binning by N — experiments

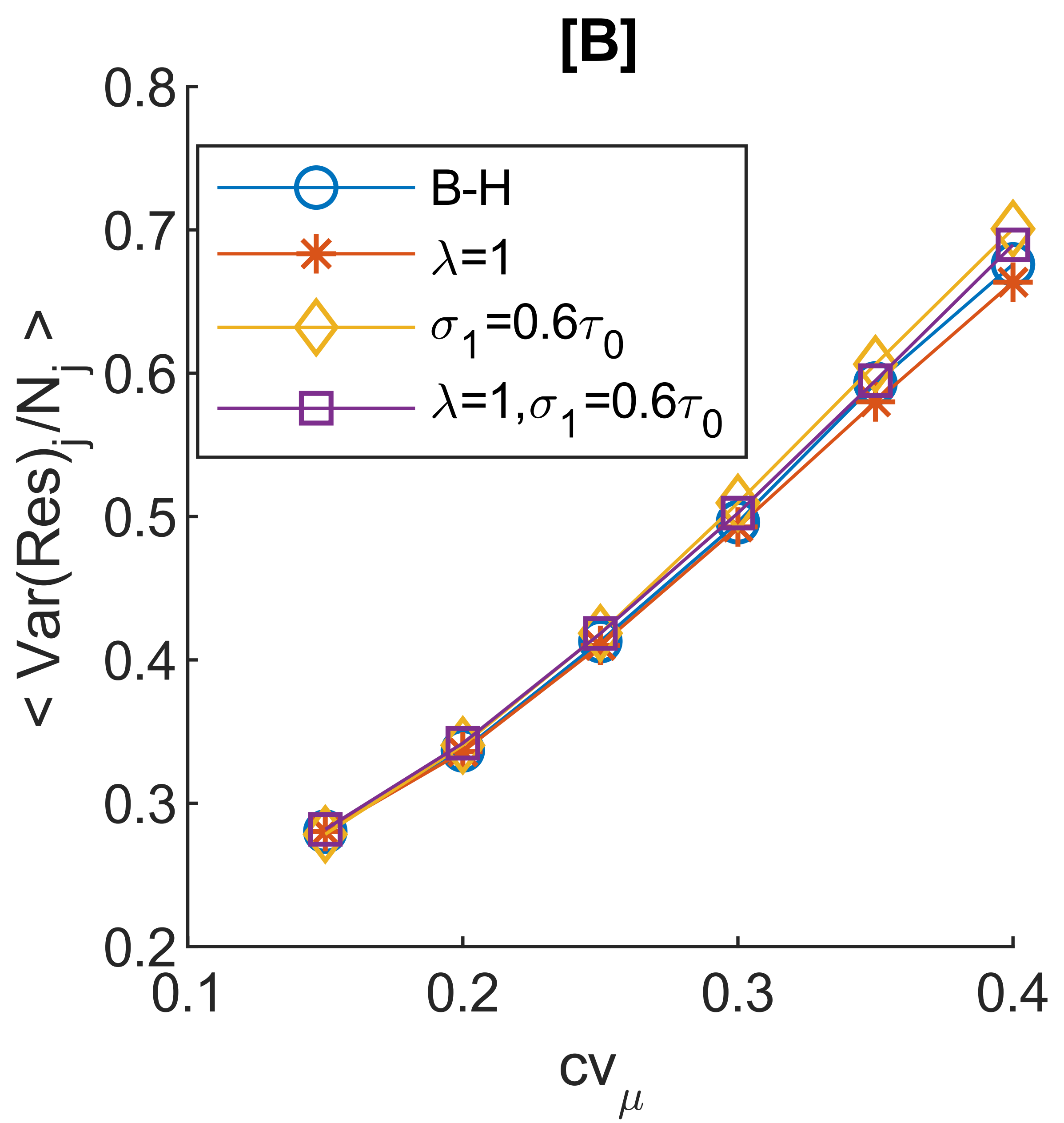




Residuals — one more problem



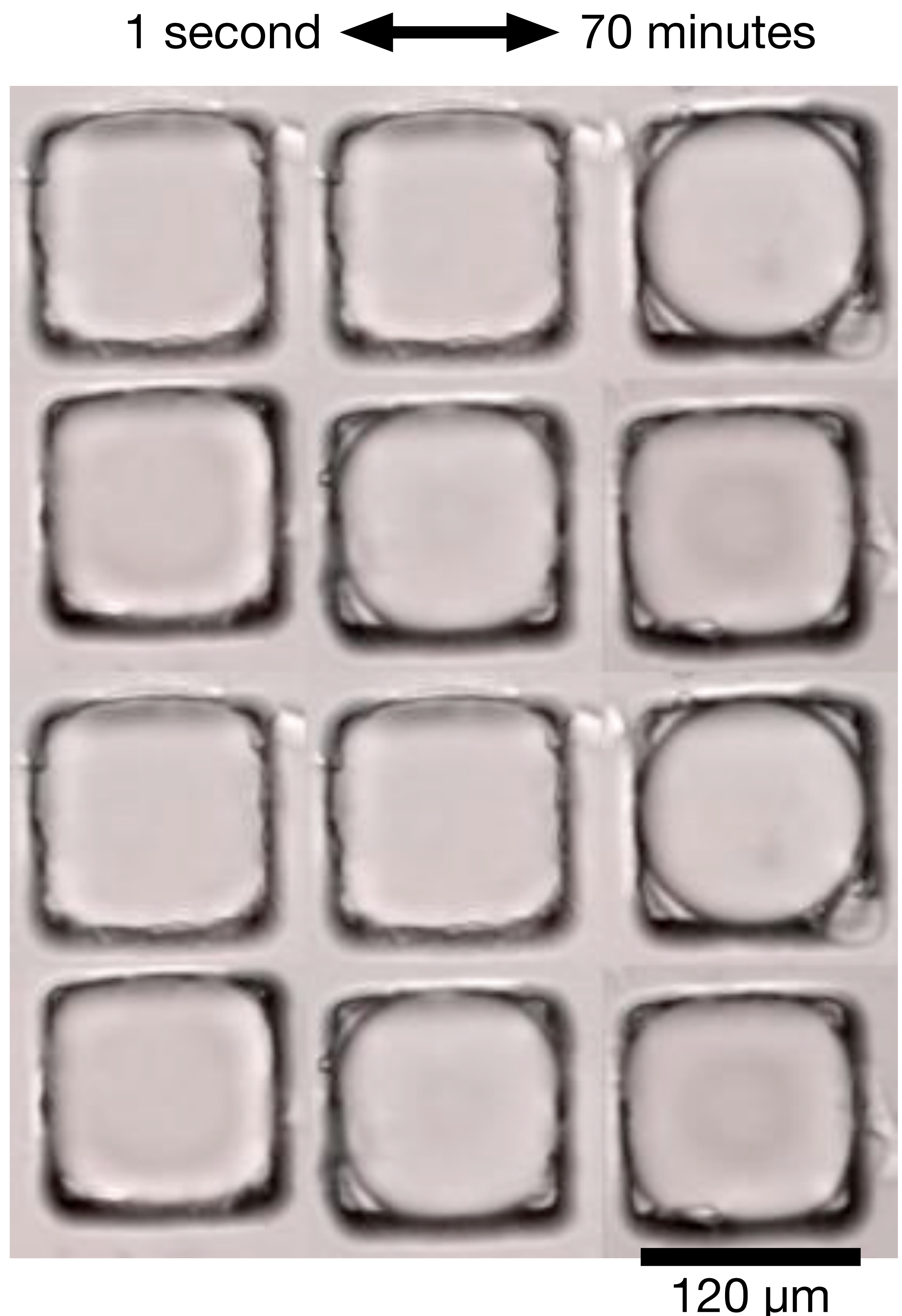
Residuals — one more problem



Residuals — one more problem

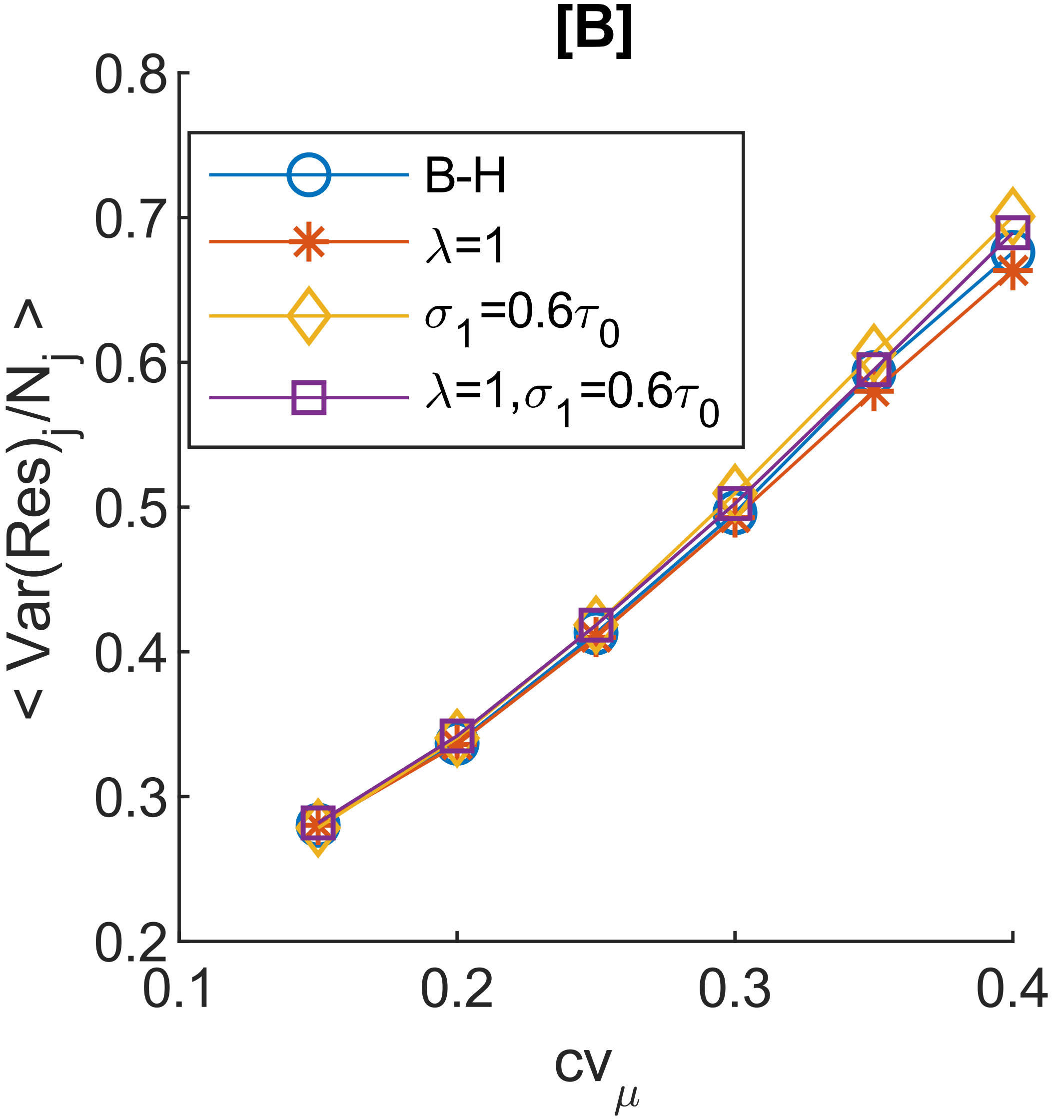
What is the proportionality coefficient between fluorescence and number of cells?

What is the variability in fluorescence between cells?



From population to single cell

- In theory, we can infer single-cell division parameters from macroscopic parameters on population sizes
- Compute the residuals
- Experimentally: work in progress



Thank you!