Modelling stochastic biological systems

BAMC mini-symposium 2019

Thursday PM

1. Modelling stochastic biological systems – C.A. Smith
2. Particle-based simulations of stochastic reaction-diffusion processes with Aboria – M. Robinson
3. Equilibration times within heterogeneous crowded environments – D. Wilson
4. Stochastic amplification of oscillatory gene expression underlies cell differentiation during embryonic neurogenesis – J. Kursawe

Friday AM

1. Homogenization approximations for advection-dominated solute transport in a spatially disordered domain – G. Price
2. Modelling molecular diffusion in the intracellular environment – R. Stana
3. Stochastic dynamics and regulation of filopodia-like structures – U. Dobramysl

Modelling stochastic biological systems

British Applied Mathematics Colloquium 2019

Mini-symposium

Kit Yates, Enrico Gavagnin, Jennifer Owen, **Cameron Smith**

CMB
Centre for Mathematical Biology
University of Bath

Centre for Mathematical Biology,
University of Bath

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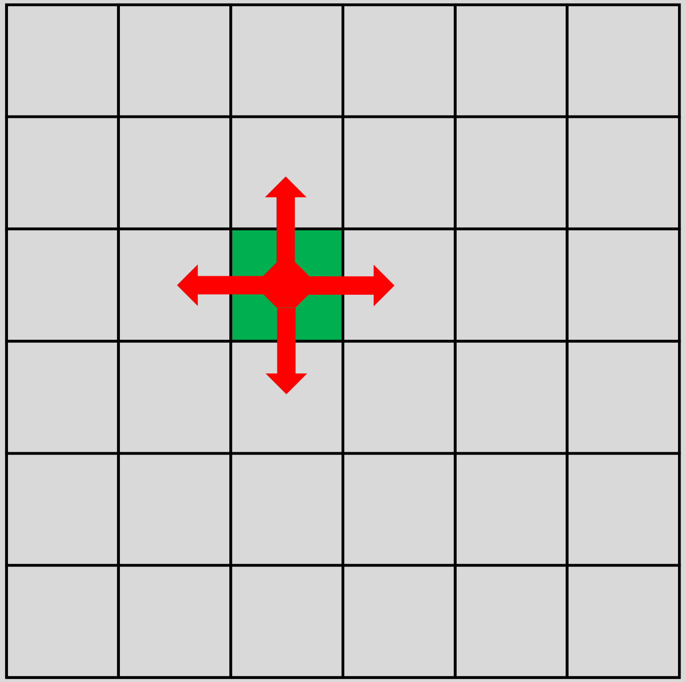
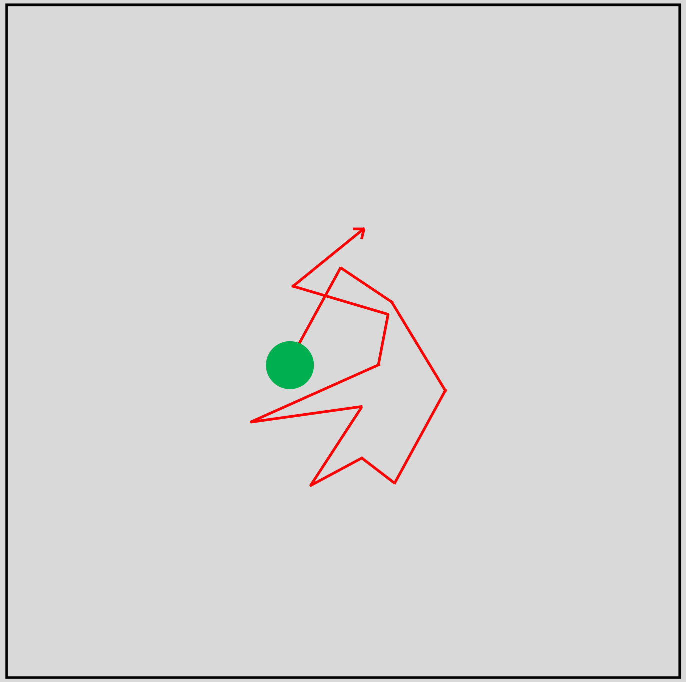
Stochastic methods: movement

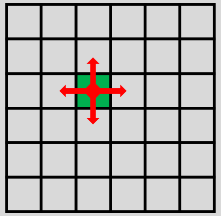
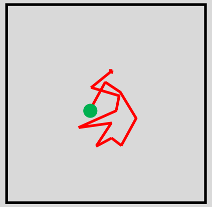
On-lattice



Off-lattice



Stochastic methods: movement

	On-lattice	Off-lattice
		
Advantages	Quick to simulate. All processes use the same algorithm.	Retention of individual particle paths. Knowledge of particle distributions.
Disadvantages	Lose precise particle locations. Assumes well-mixed particles.	Can be very computationally expensive for large particle numbers.
Simulation	Spatial Gillespie algorithm, [Gillespie, 1977].	Unbiased: Standard Brownian motion. Biased: Stochastic differential equations.

D.T. Gillespie, Exact stochastic simulation of coupled chemical reactions, *J. Phys. Chem.,* 1977.

Stochastic methods: movement

1. Assign each jump event an exponential waiting time.
2. Calculate the first event to occur.
3. Enact the event with probability proportional to their rates.

1. Draw an independent normal variable with zero mean and $2D\delta t$ variance for each dimension of space
2. Update each coordinate by adding this random variables to them.

Simulation	Spatial Gillespie algorithm, [Gillespie, 1977].	Unbiased: Standard Brownian motion. Biased: Stochastic differential equations.

D.T. Gillespie, Exact stochastic simulation of coupled chemical reactions, *J. Phys. Chem.,* 1977.

The Yates group




Kit Yates – Senior Lecturer c.yates@bath.ac.uk

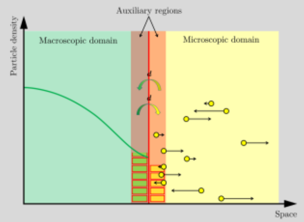
Enrico Gavagnin – PhD student e.gavagnin@bath.ac.uk

Jennifer Owen – PhD student j.owen@bath.ac.uk

Cameron Smith – PhD Student c.smith3@bath.ac.uk

Outline

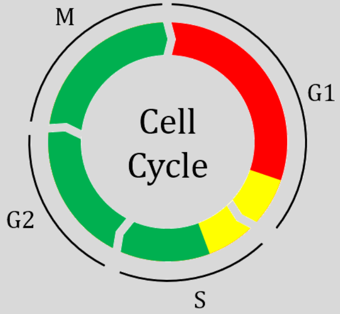
Hybrid methods: "Spatially extended hybrid methods: a review" – C.A. Smith and C.A. Yates, 2018.

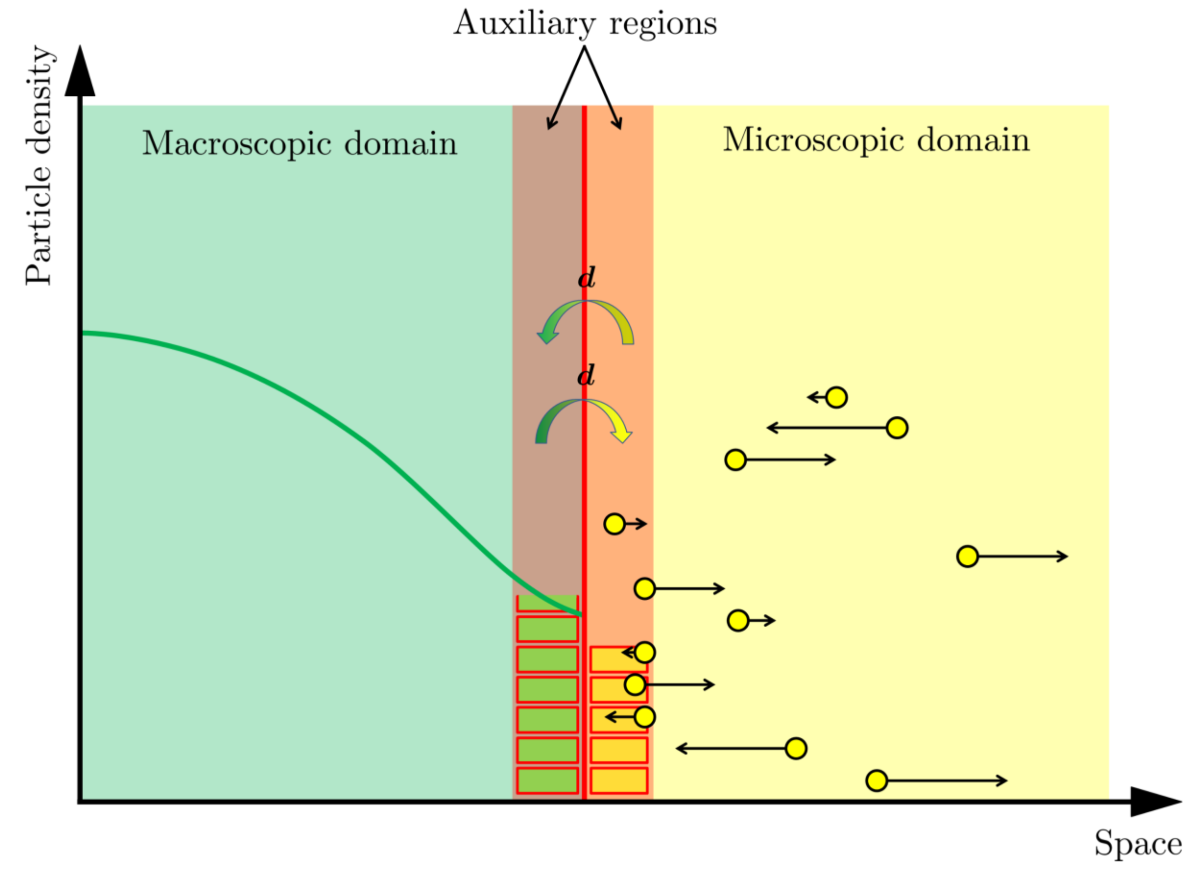


On-lattice domain growth: "From microscopic to macroscopic descriptions of cell migration on growing domains" – R.E. Baker, C.A. Yates & R. Erban, 2010.

Zebrafish pigment patterns: "A quantitative modelling approach to zebrafish pigment pattern formation" – J.P. Owen, R.N. Kelsh and C.A. Yates, 2019.

Cell migration models: "The invasion speed of cell migration models with realistic cell cycle time distributions " – Gavagnin *et al.*, 2018.





Hybrid methods

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C.A. Smith & C.A. Yates, Spatially extended hybrid methods: a review. *J. Royal Soc. Interface,* 2018.

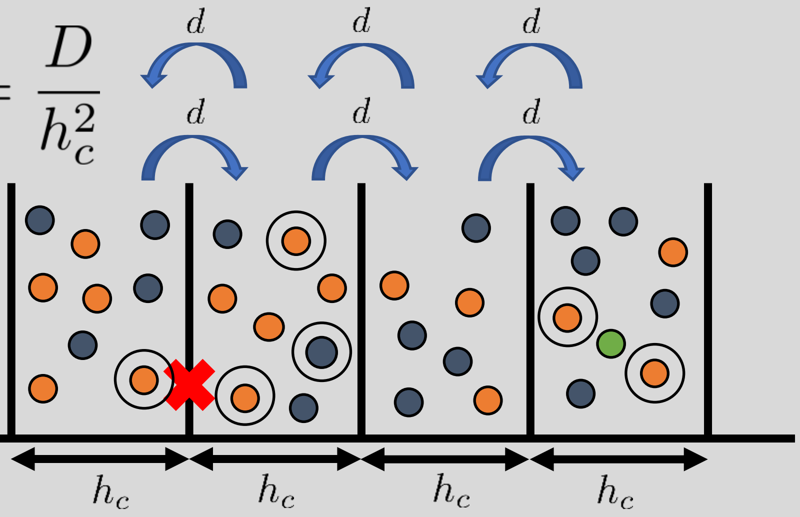
Reaction-diffusion systems




We look at modelling at three levels:

Mesoscale – compartment-based modelling

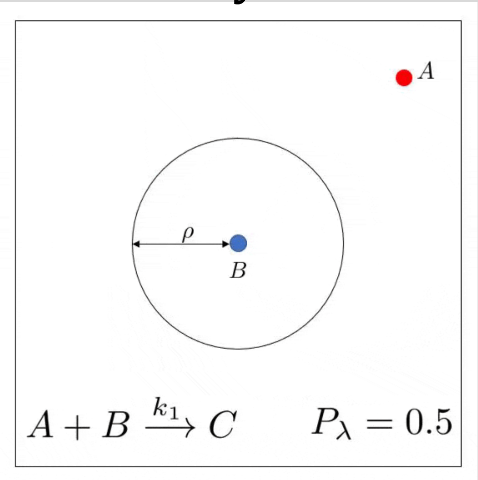
$$d = \frac{D}{h_c^2}$$



Macroscale – PDEs and SPDEs

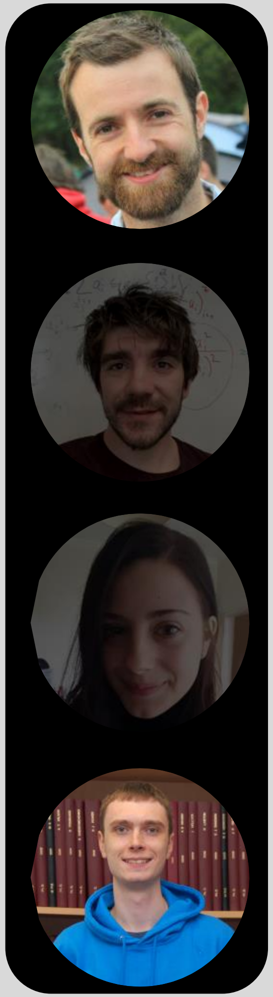
$$\frac{\partial u}{\partial t} = D\nabla^2 u + \mathcal{R}(u)$$

Microscale – Brownian-based dynamics

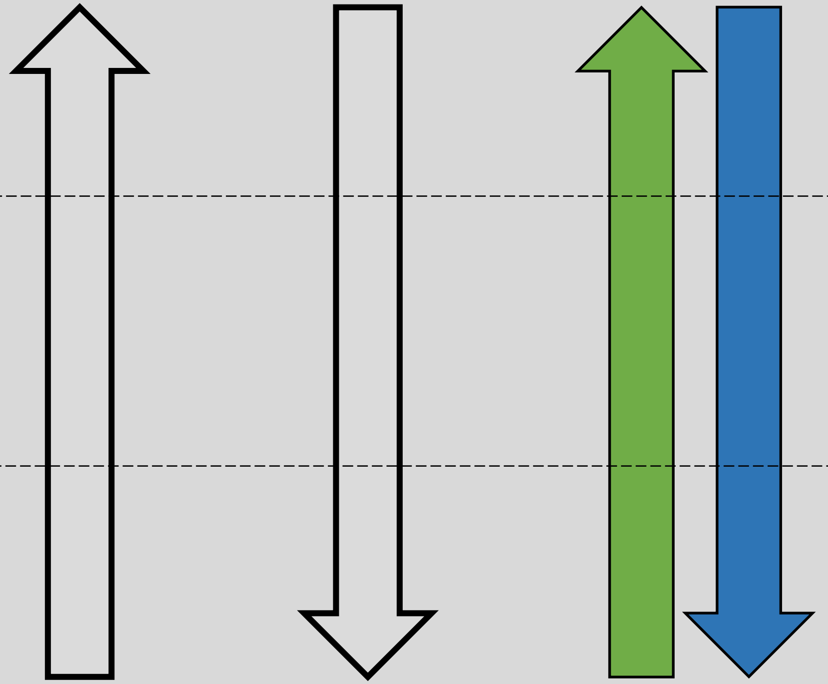


H.G. Othmer and A. Stevens, Aggregation, blowup, and collapse: the ABC's of taxis in reinforced random walks, *SIAM J. Appl. Math.,* 1997.
R. Erban and S.J. Chapman, Stochastic modelling of reaction-diffusion processes: algorithms for bimolecular reactions, *Phys. Biol.,* 2009.

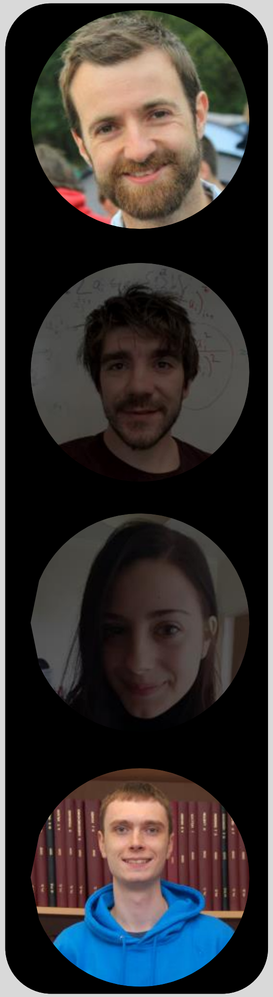
Summary of models

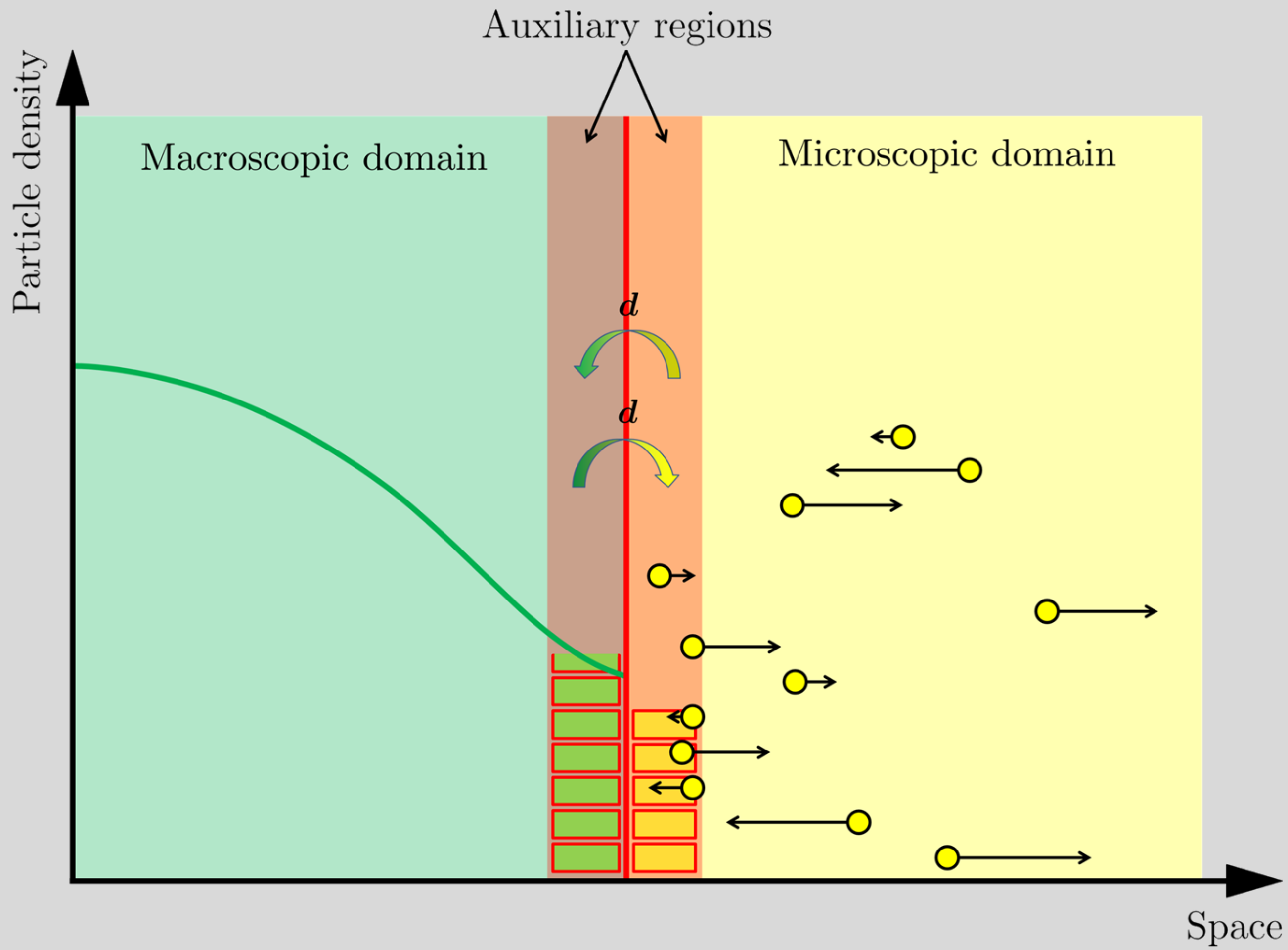


	Speed	Accuracy	Suitability for high/low copy numbers	Other
Macroscale				Amenable to analysis.
Mesoscale				Represents the individual-level behaviour. Does not retain precise locations of particles.
Microscale				Retains precise Particles locations.



Spatially extended hybrid methods





C.A. Smith & C.A. Yates, The auxiliary region method: A hybrid method for coupling PDE- and Brownian-based dynamics for reaction-diffusion systems, *Royal Soc. Open Sci.,* 2018.

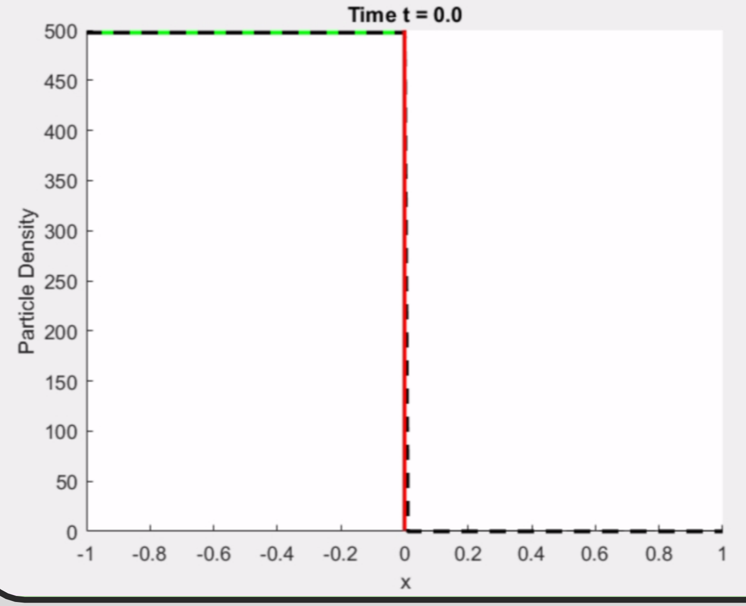
Results

Pure diffusion

$$\frac{\partial u}{\partial t} = D\nabla^2 u$$

$$\left.\frac{\partial u}{\partial x}\right|_{x=-1} = 0 \text{ and } \left.\frac{\partial u}{\partial x}\right|_{x=1} = 0$$

$$u(x,0) = \begin{cases} 500 & x \in [-1,0) \\ 0 & x \in [0,1] \end{cases}$$

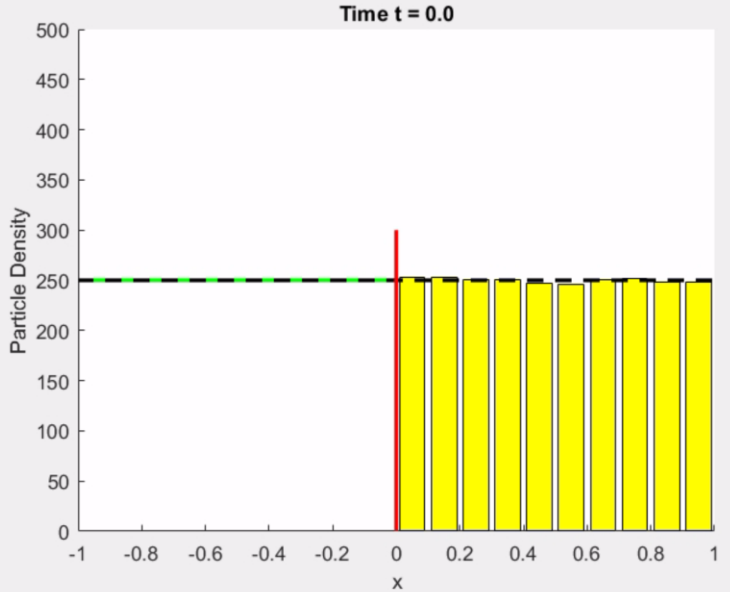


Morphogen gradient

$$\frac{\partial u}{\partial t} = D\nabla^2 u - \mu u$$

$$\left.\frac{\partial u}{\partial x}\right|_{x=-1} = -\lambda \text{ and } \left.\frac{\partial u}{\partial x}\right|_{x=1} = 0$$

$$u(x,0) = 250 \; \forall x \in [-1,1]$$



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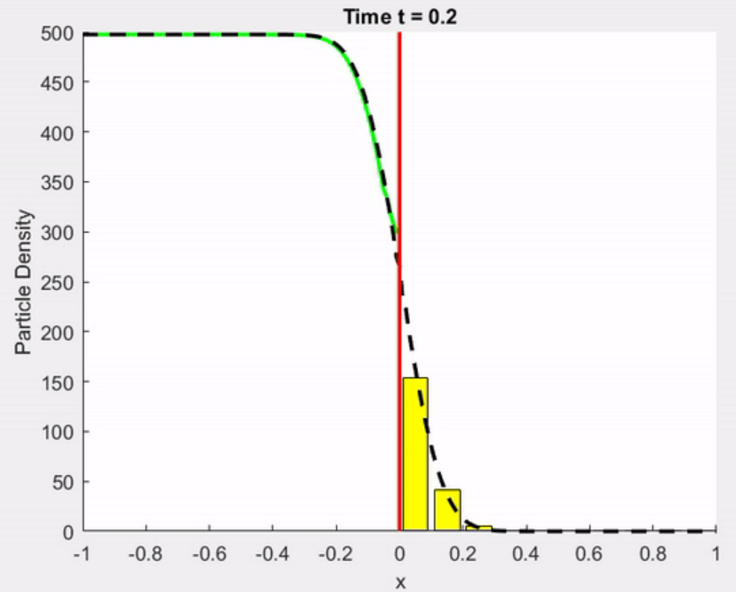

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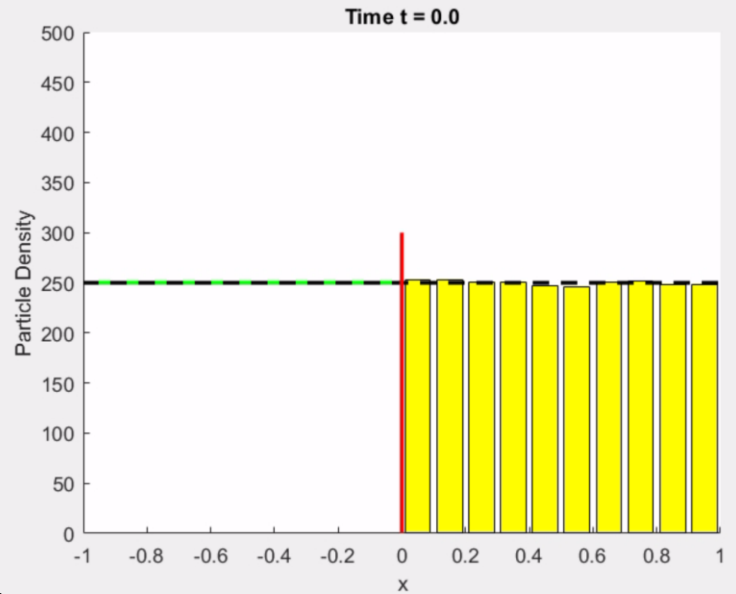

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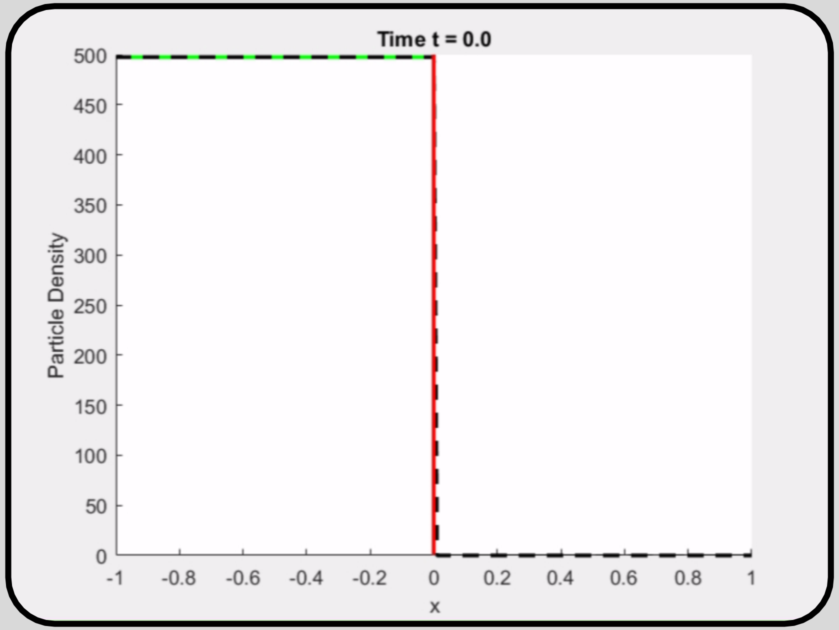

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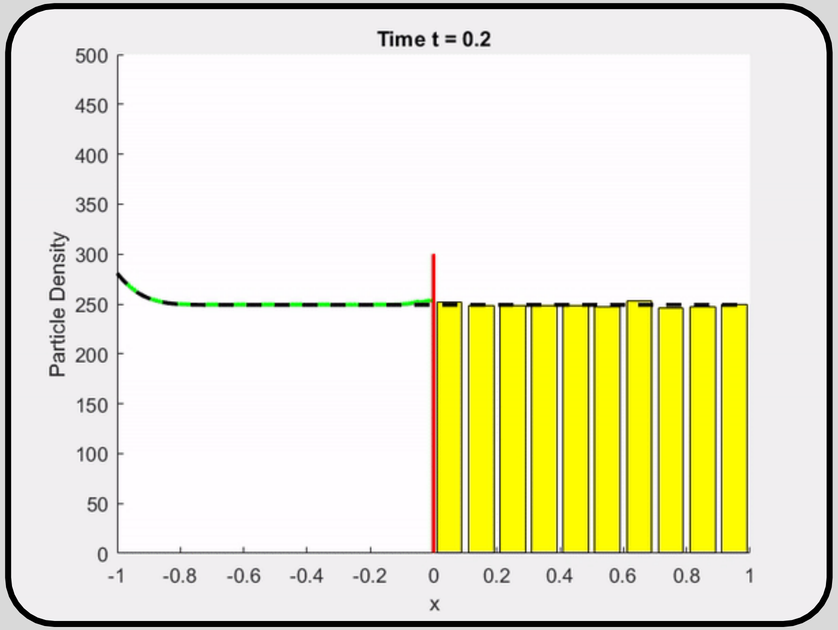
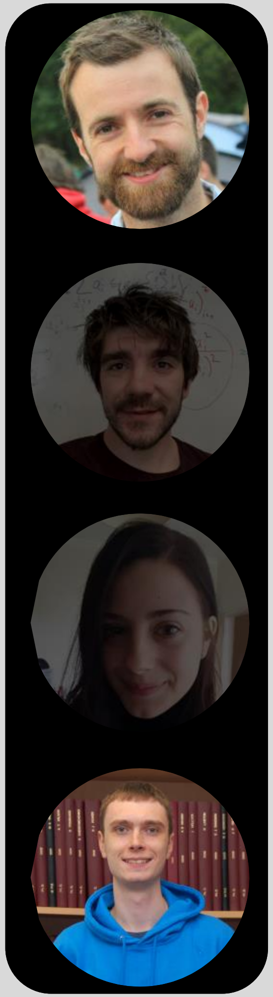


Summary: Hybrid methods



Aim

To utilise the strengths and weaknesses of different modelling techniques.

Model

ARM: Off-lattice to PDE coupling. Auxiliary regions use on-lattice approach.

Conclusions

Combining different modelling paradigms leads to accurate and efficient modelling.

On-lattice domain growth

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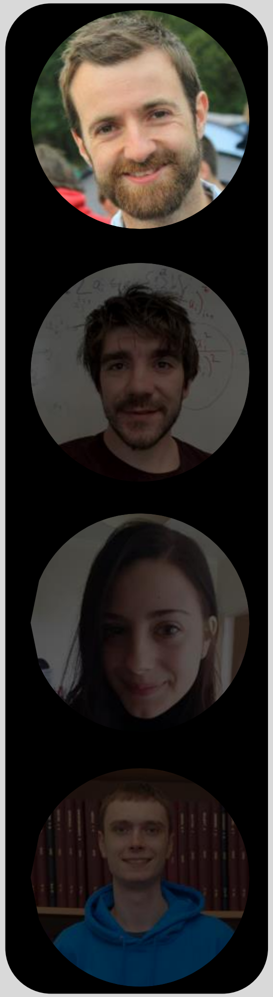
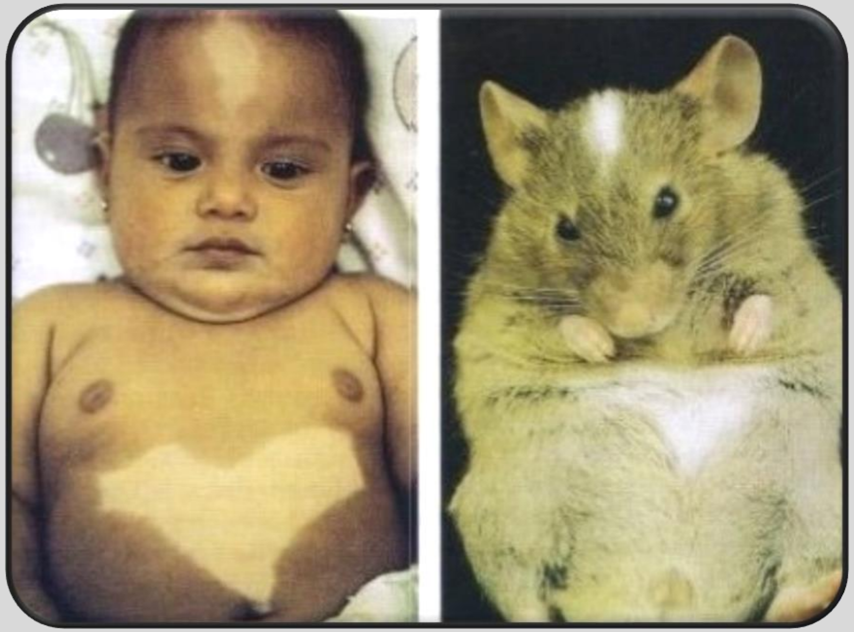
R.E. Baker, C.A. Yates & R. Erban, From microscopic to macroscopic descriptions of cell migration on growing domains, *Bull. Math. Biol.,* 2010.

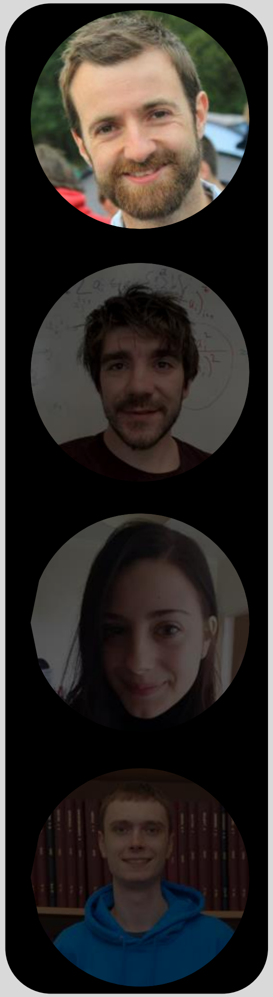
Domain growth in biology





B. Alberts *et al.,* Molecular biology of the cell: reference edition, *Garland Science*, 2007.

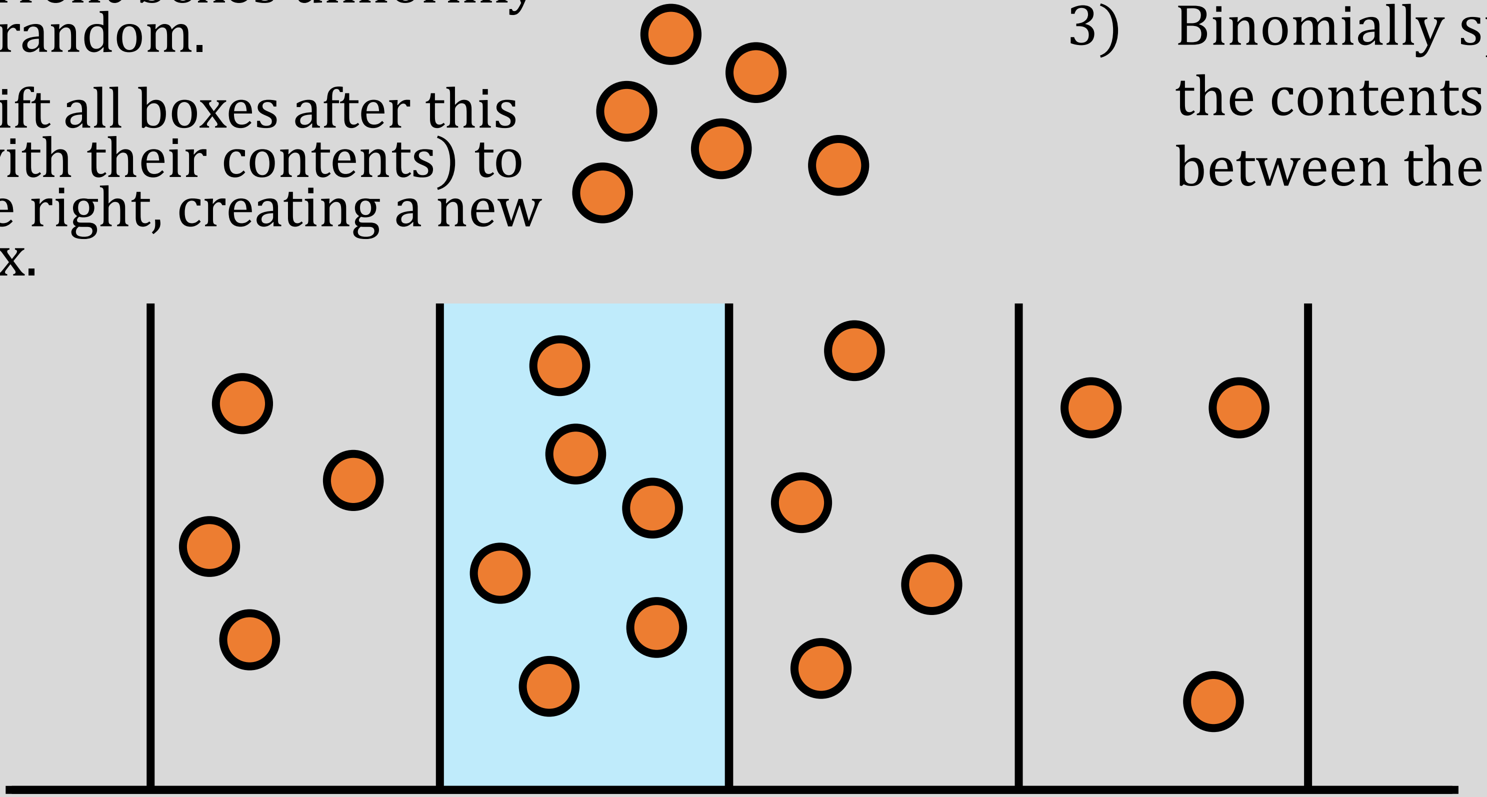
On-lattice domain growth



1) Choose one of the current boxes uniformly at random.

2) Shift all boxes after this (with their contents) to the right, creating a new box.

3) Binomially split ($p = 0.5$) the contents of the old box between the two new boxes.

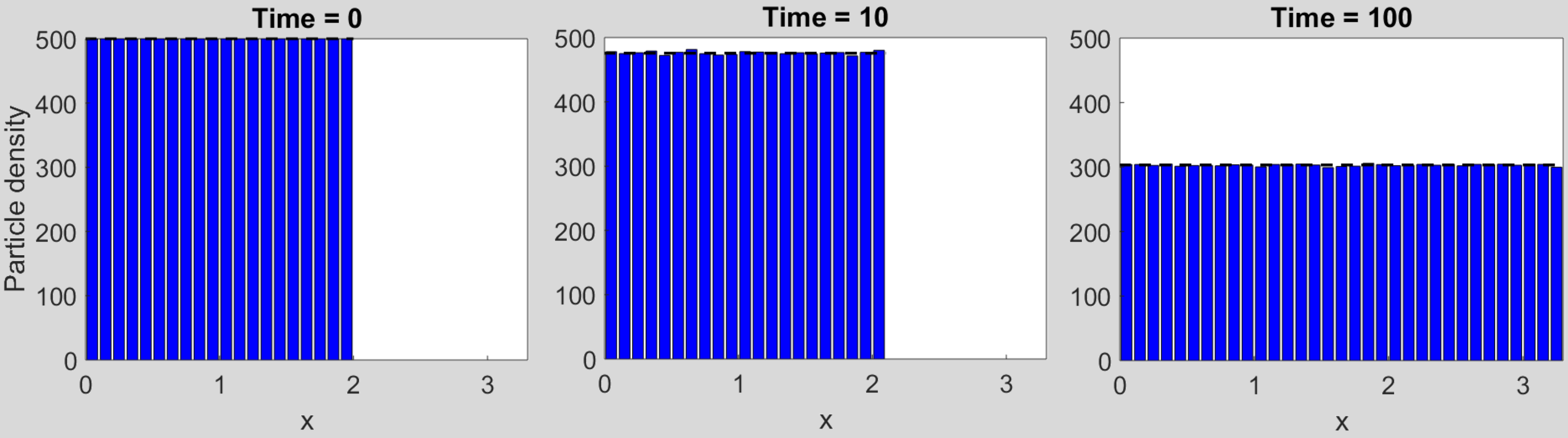


R.E. Baker, C.A. Yates & R. Erban, From microscopic to macroscopic descriptions of cell migration on growing domains, *Bull. Math. Biol.,* 2010.

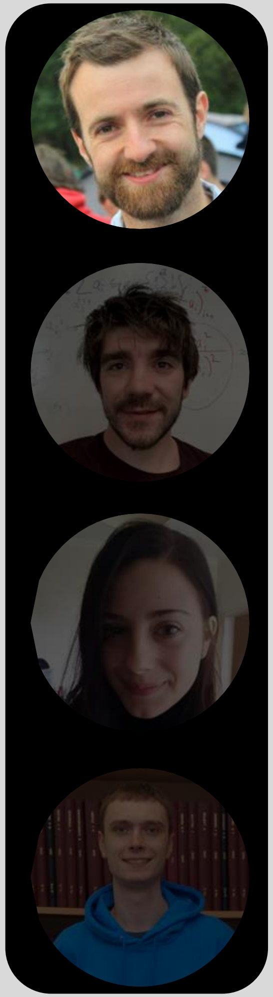
Results



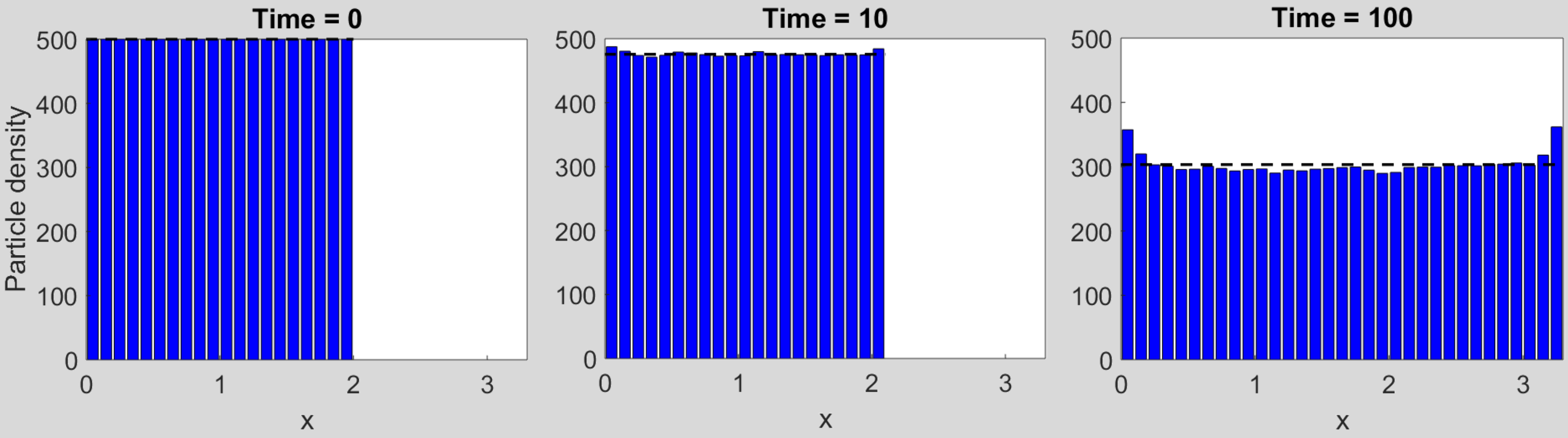

Large diffusion



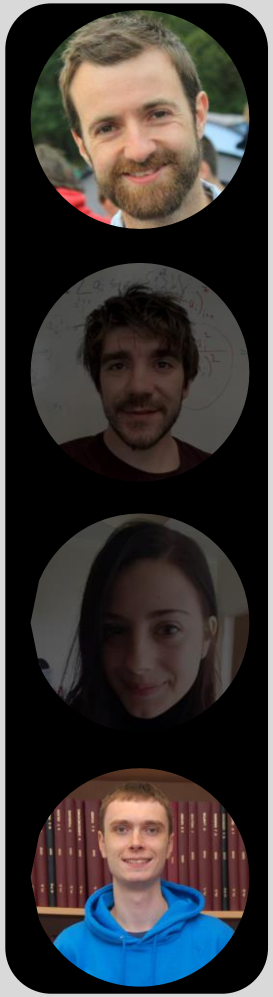
Results

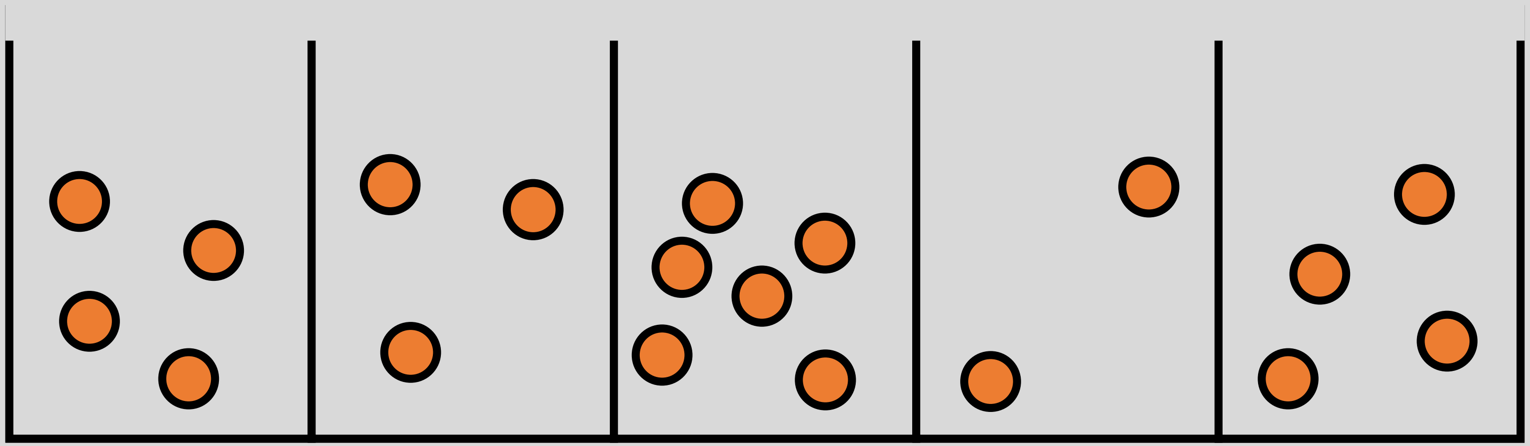


Small diffusion



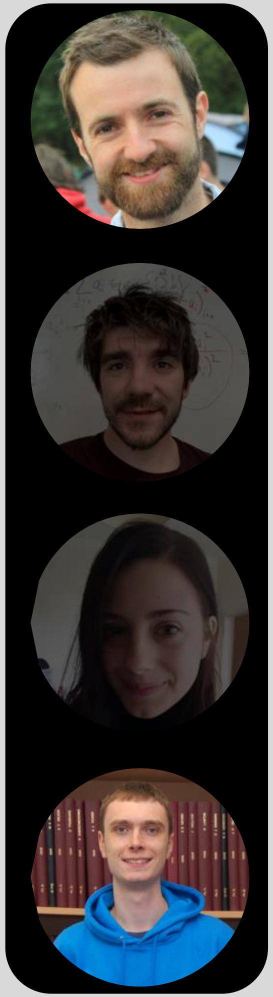
Stretching method

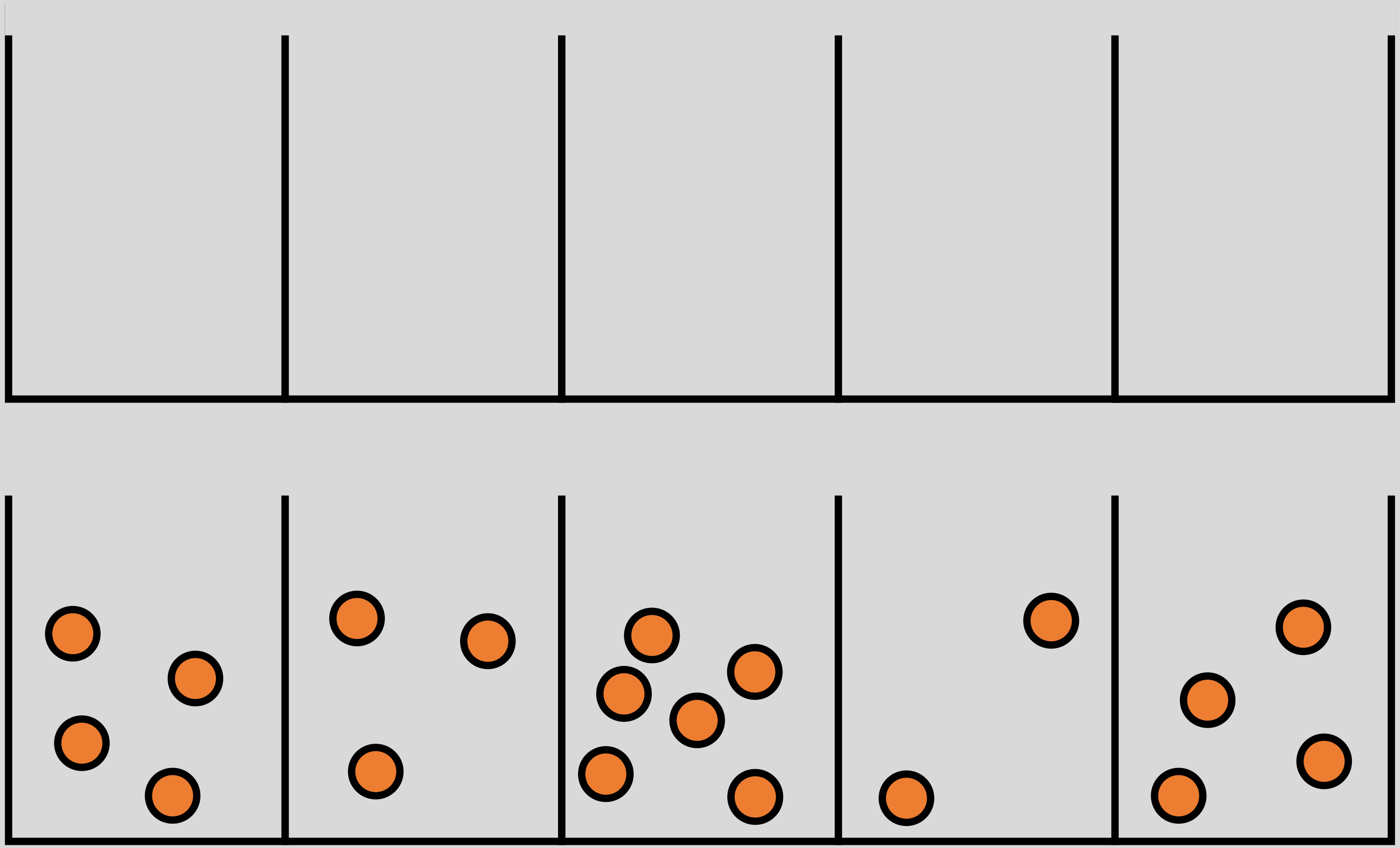




C.A. Smith, C. Mailler & C.A. Yates, Unbiased on-lattice domain growth, *arXiv: 1904.00662,* 2019.

Stretching method





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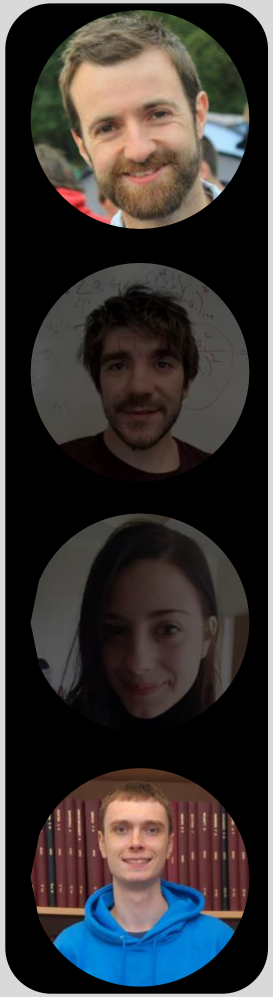

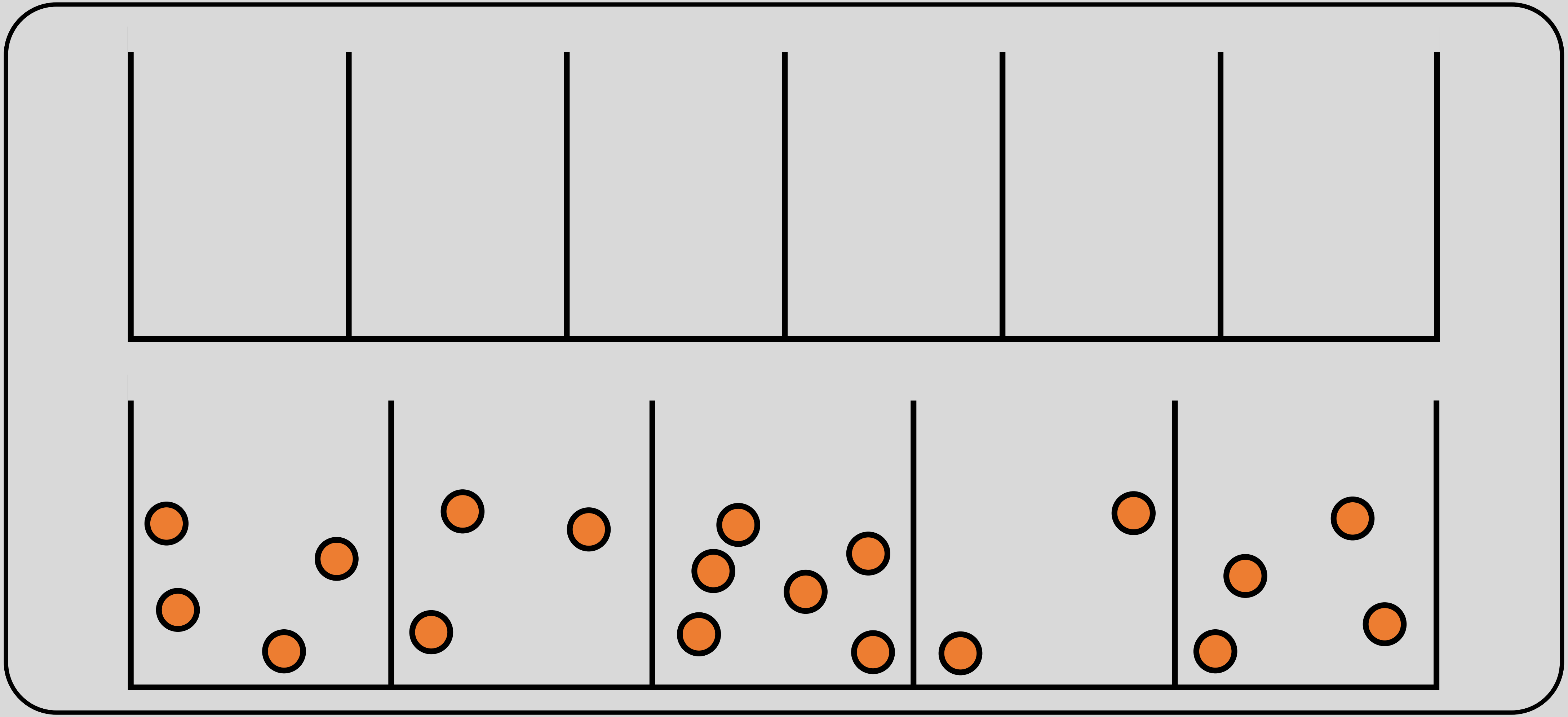

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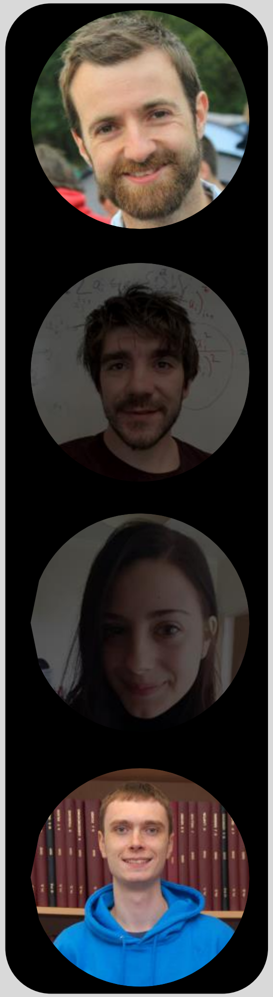

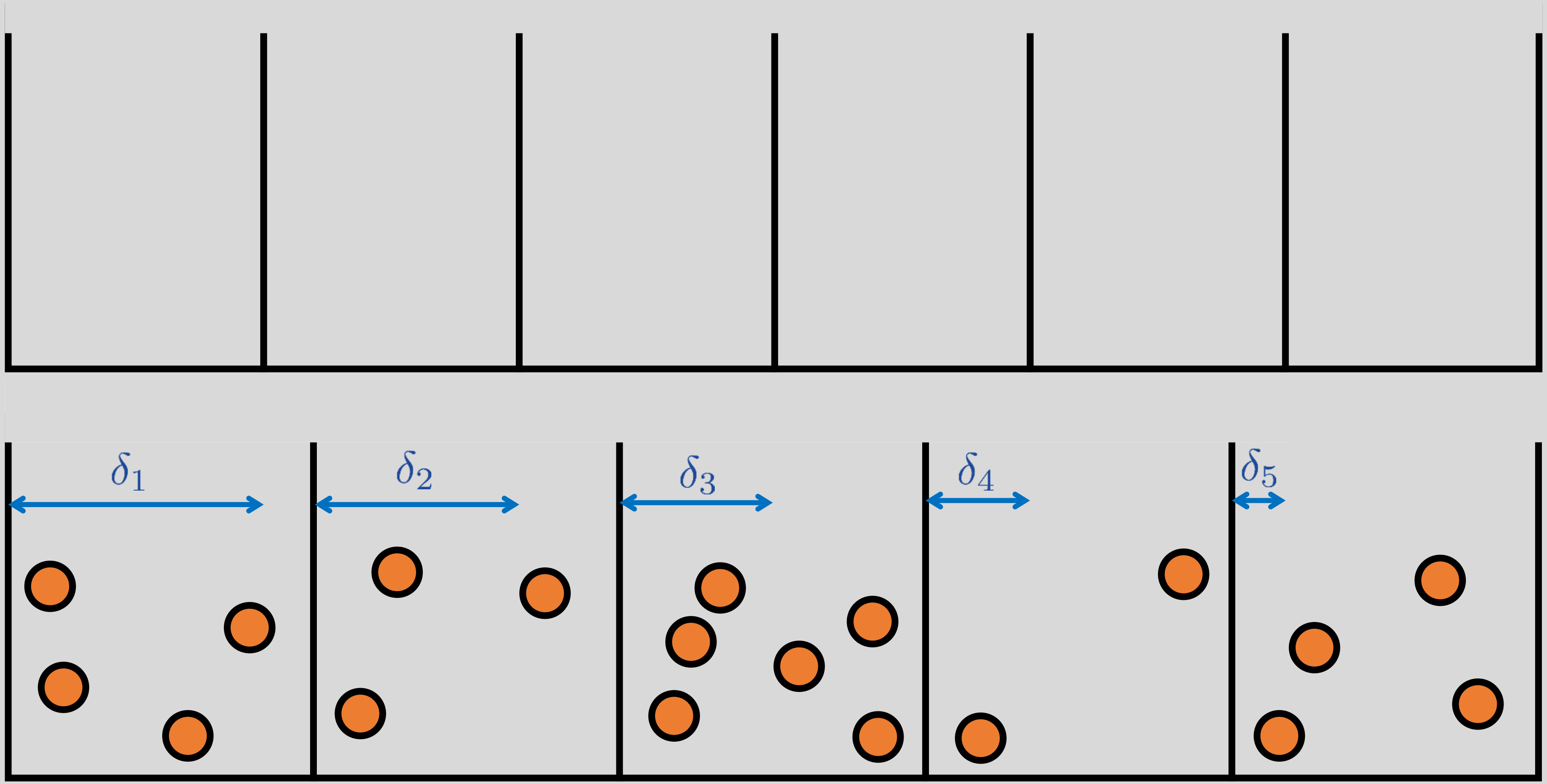

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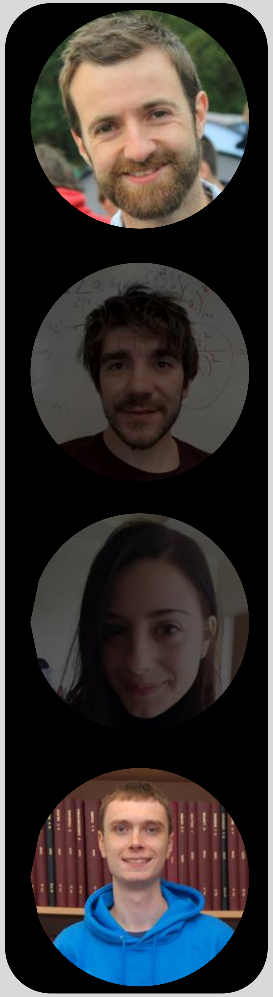

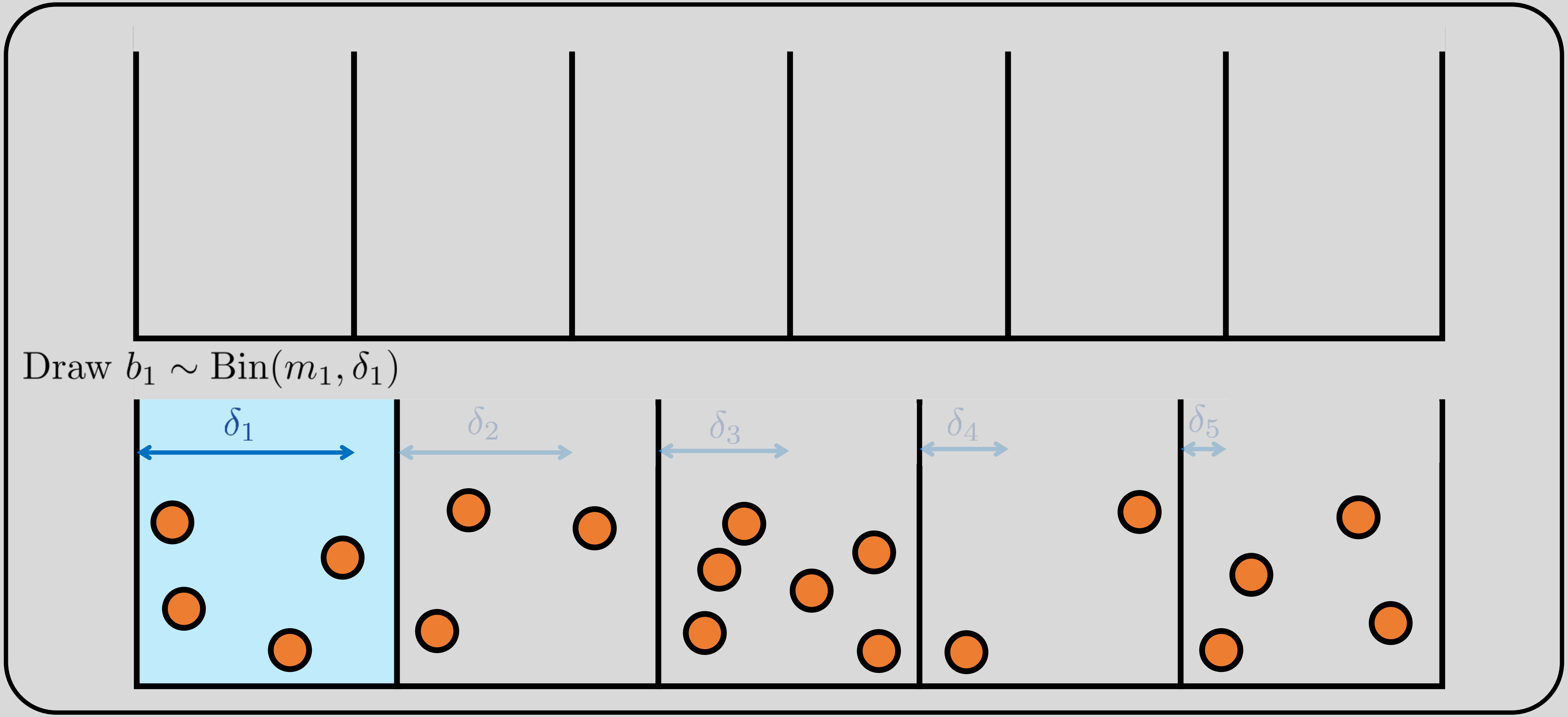

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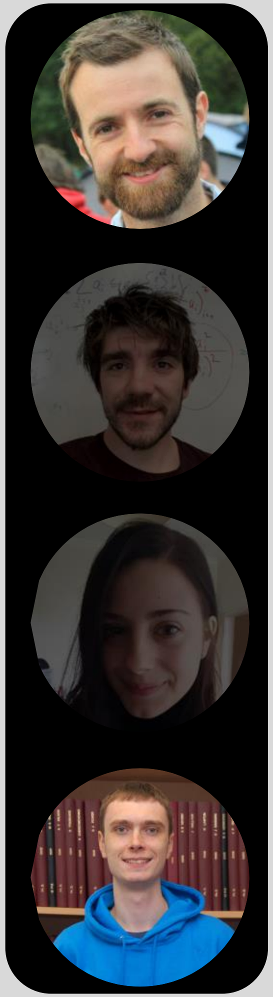

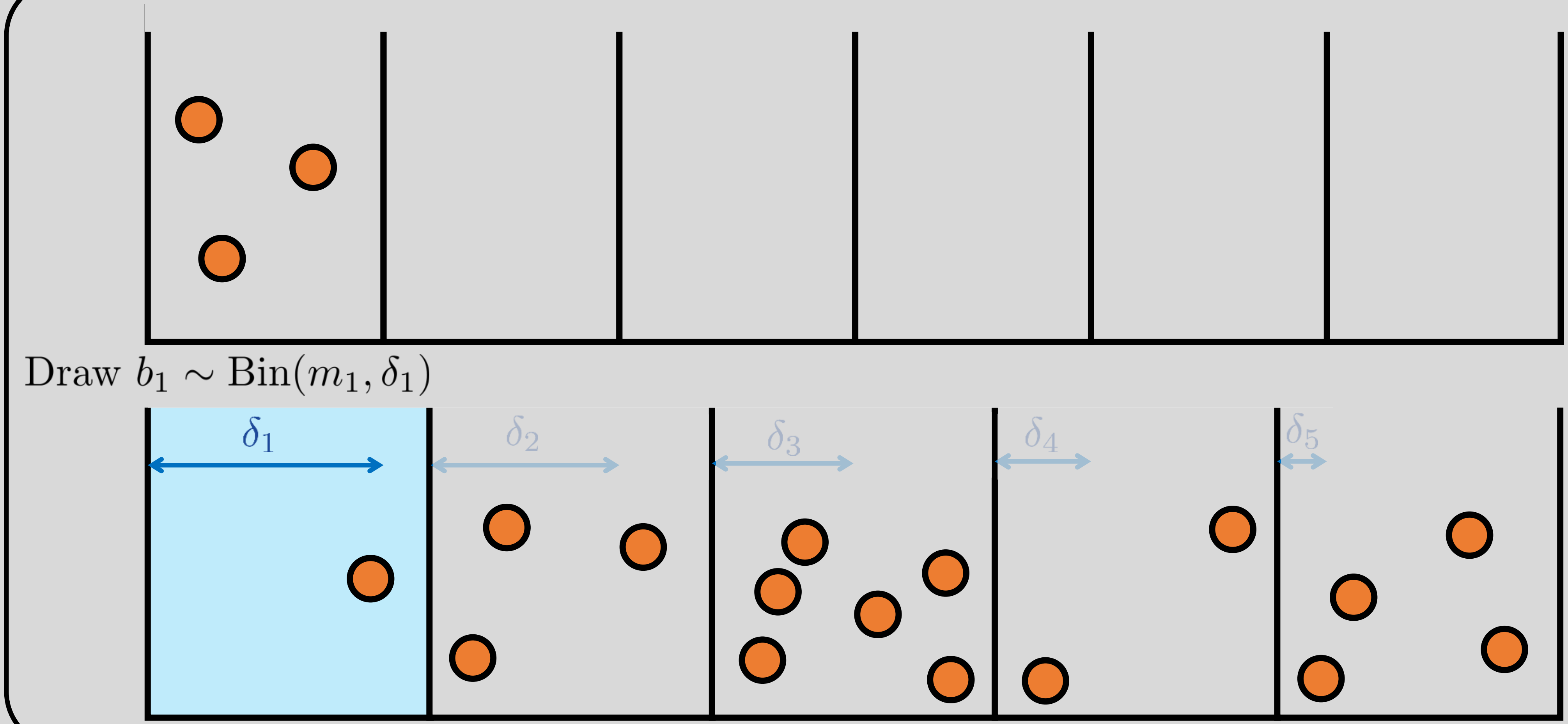

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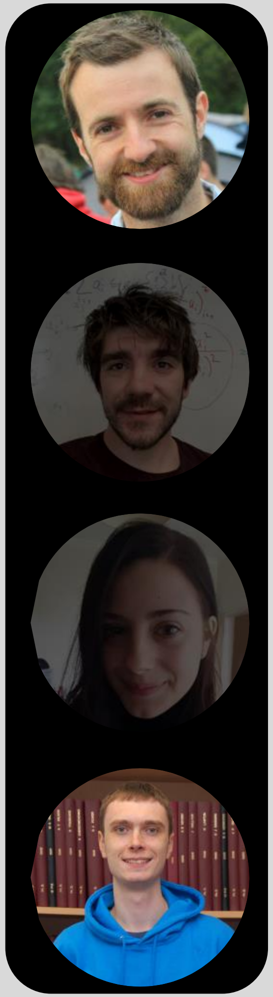

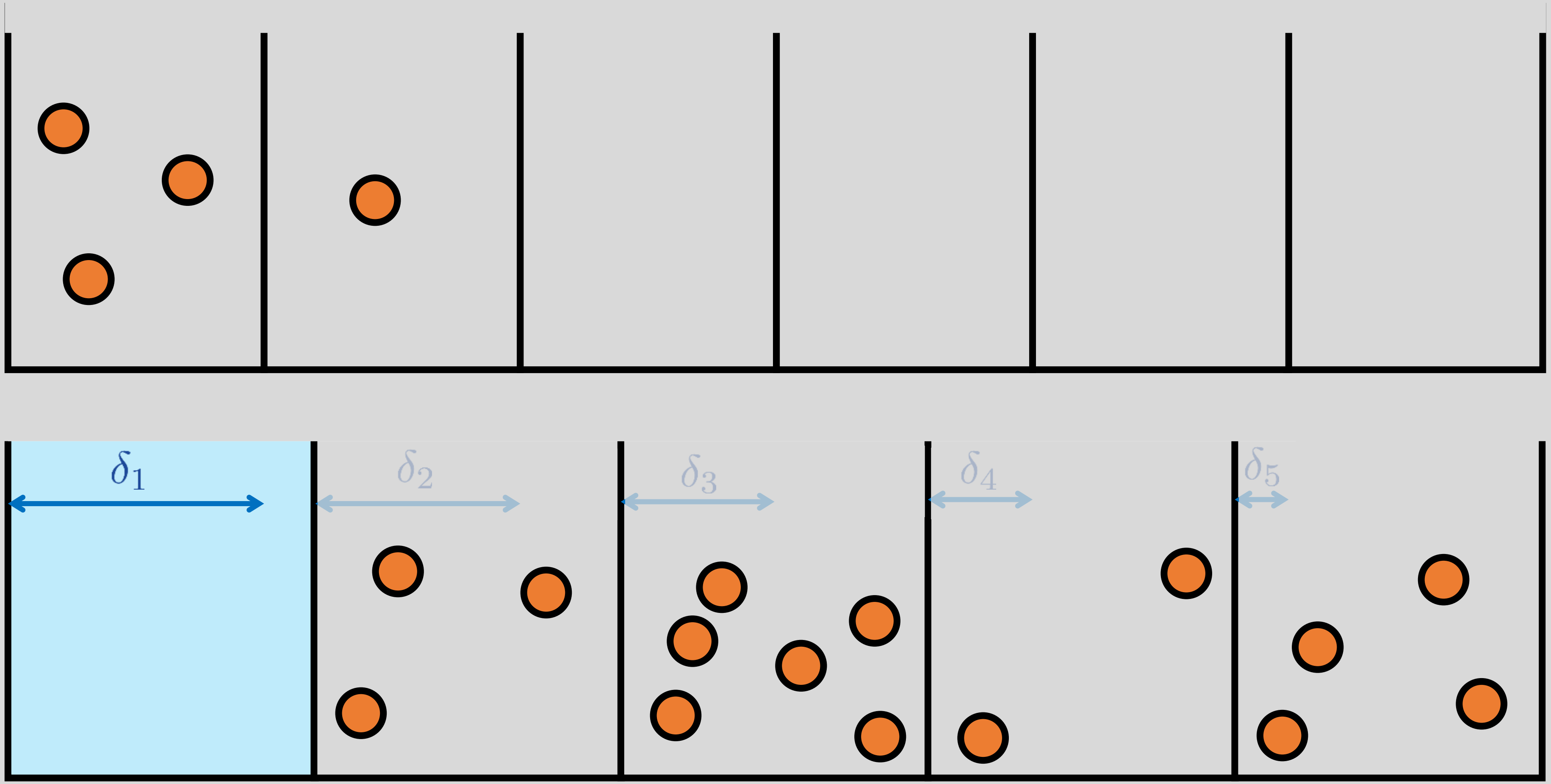

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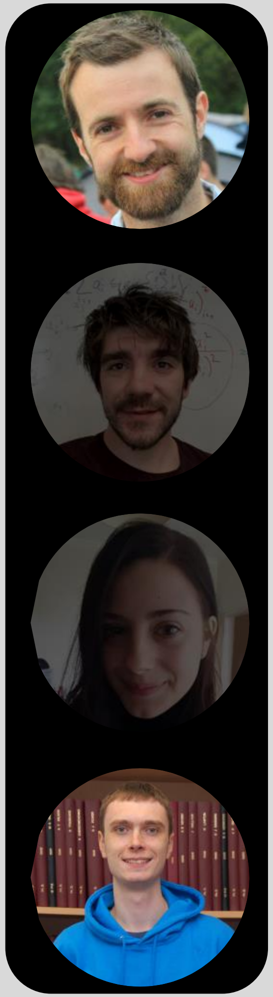

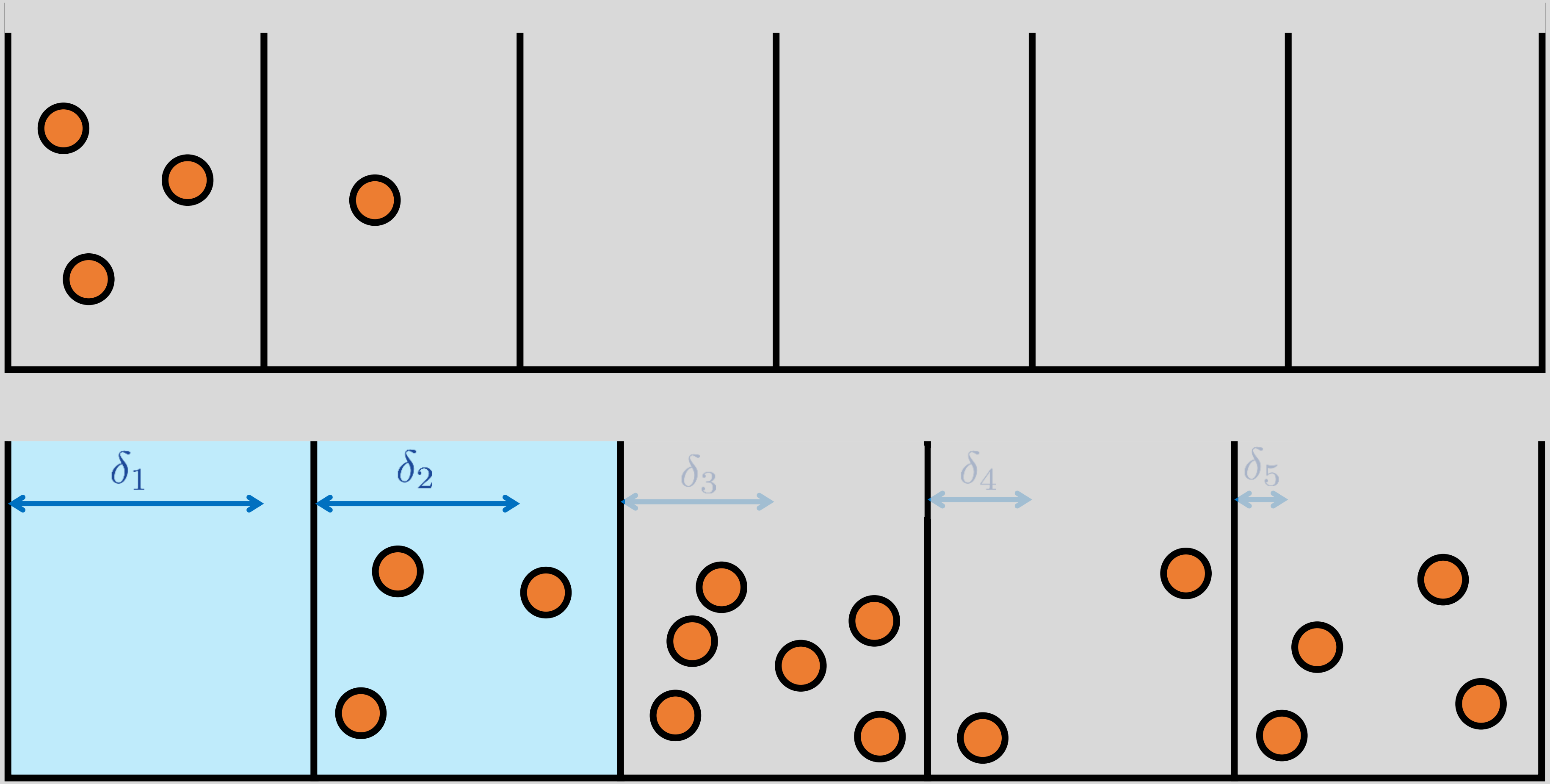

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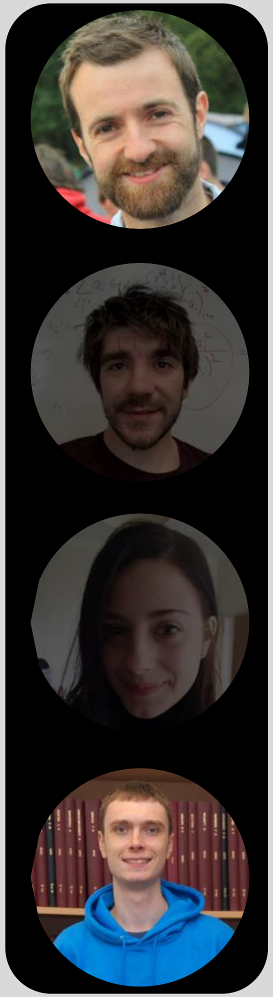

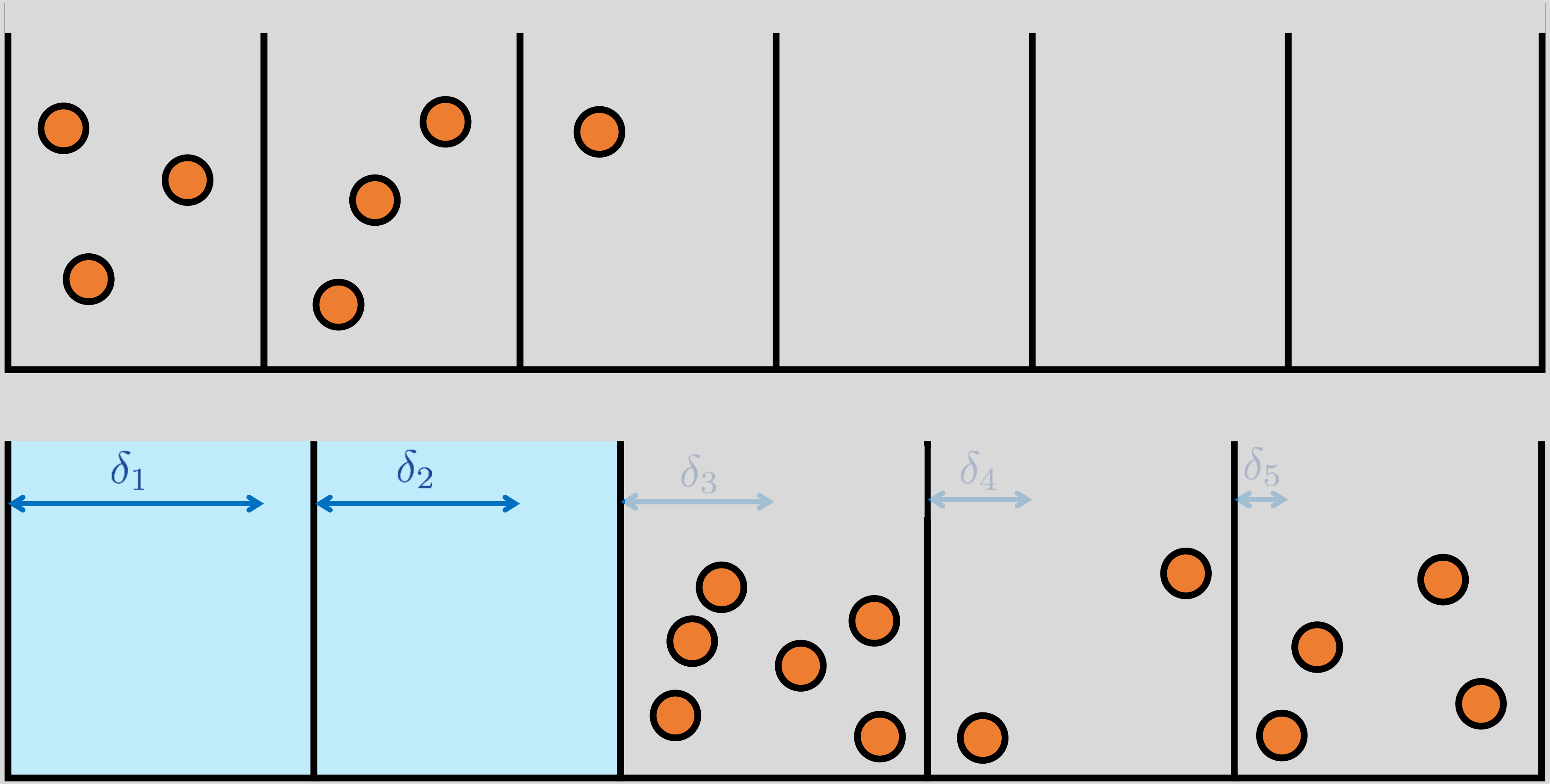

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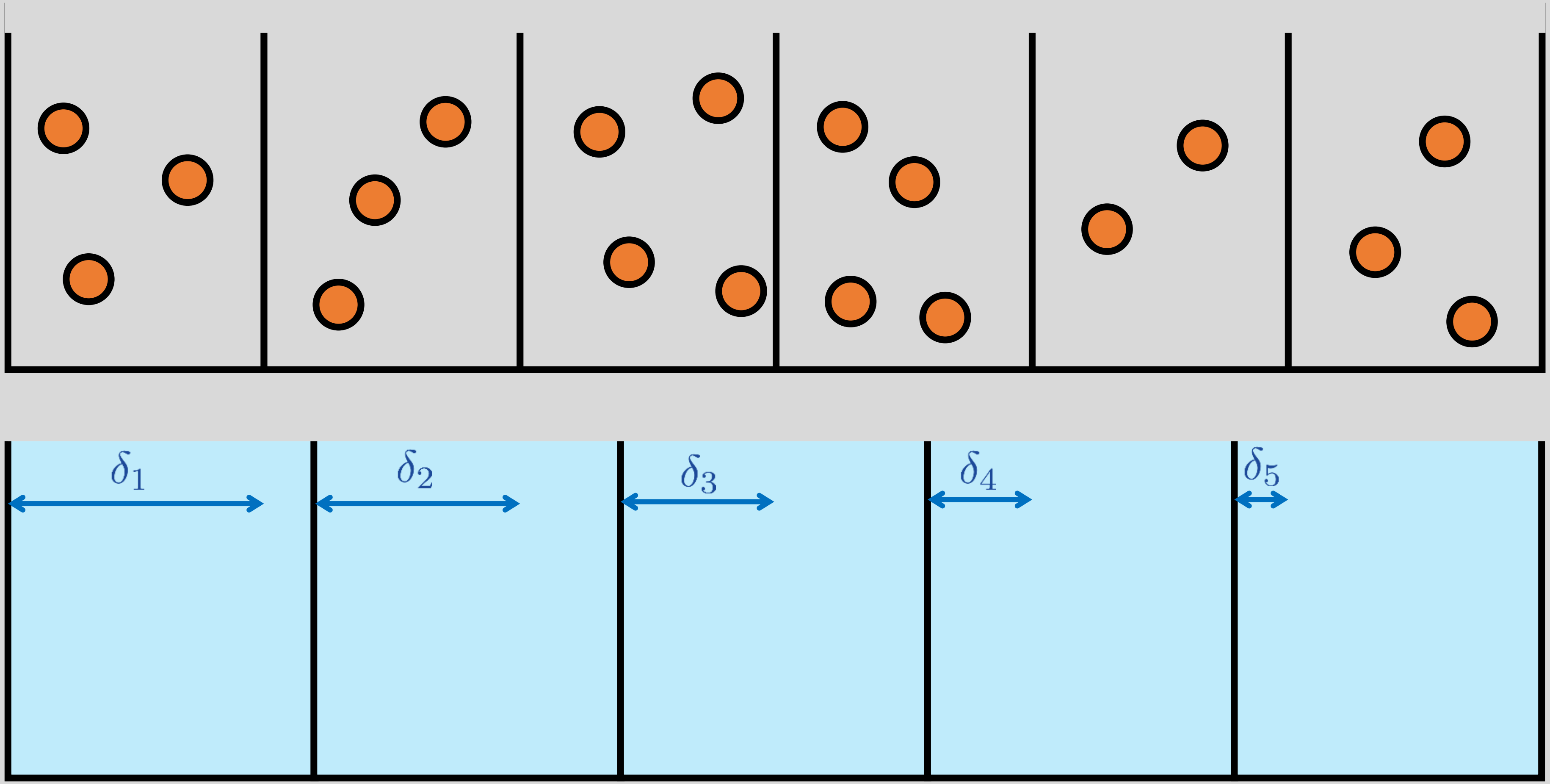

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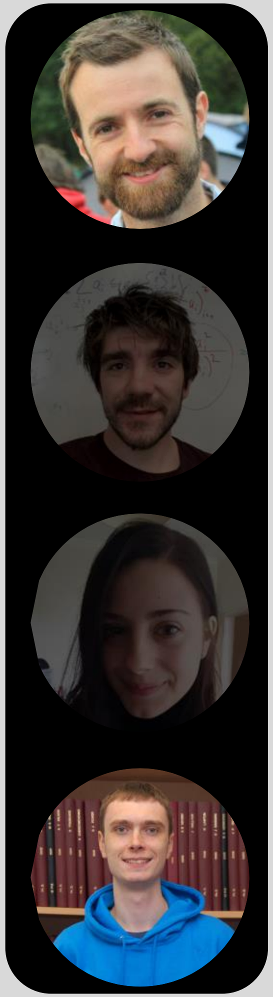

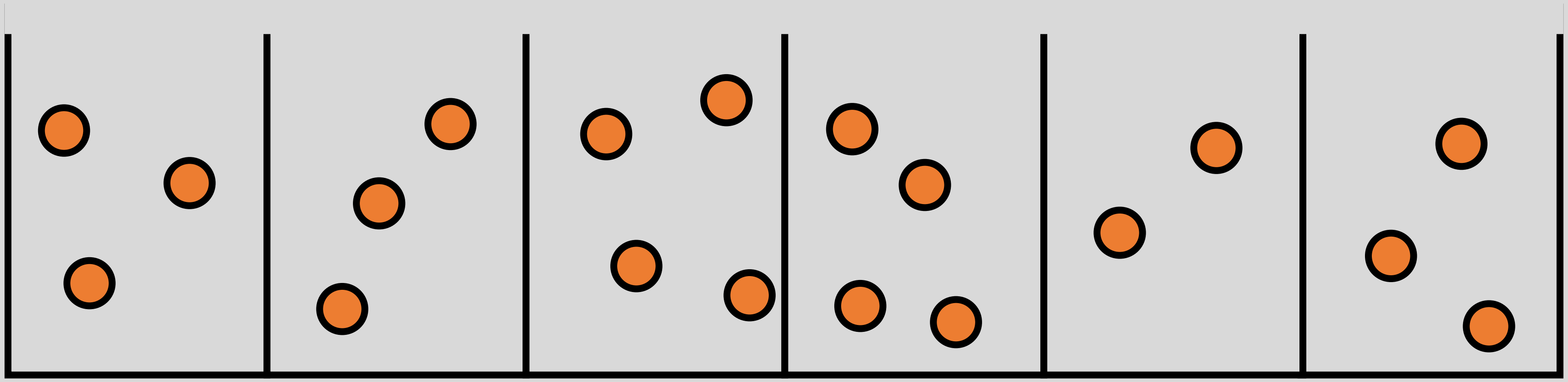

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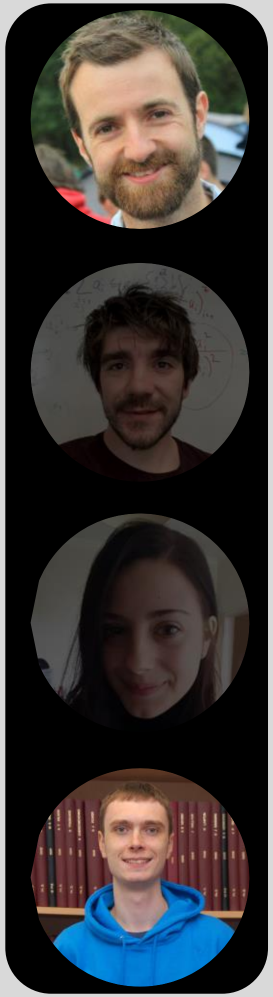

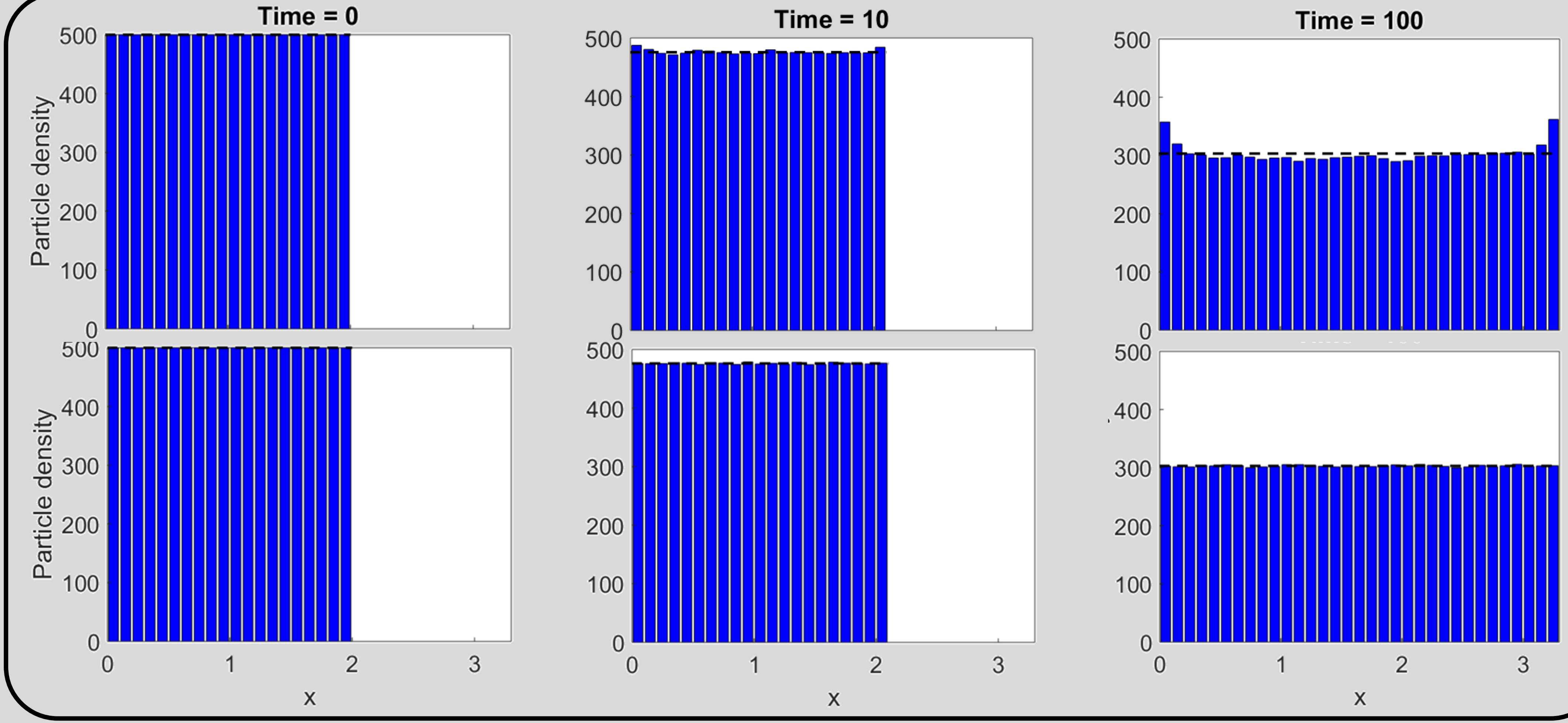

Summary: On-lattice domain growth




Aim

To create an unbiased on-lattice domain growth method.

Model

On-lattice with two domain growth mechanisms.

Conclusions

The choice of domain growth mechanism is important, especially when diffusion is low.

Zebrafish pigment patterns

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J.P. Owen, R.N. Kelsh, C.A. Yates, A quantitative modelling approach to zebrafish pigment pattern formation, *In preparation,* 2019.

Zebrafish patterns




Adult zebrafish

shady mutant
missing iridophores

The model: An overview




5 “species”

M Melanophores

I^d I^l Dense and loose S-Iridophores

X X^b Xanthophores and Xanthoblasts

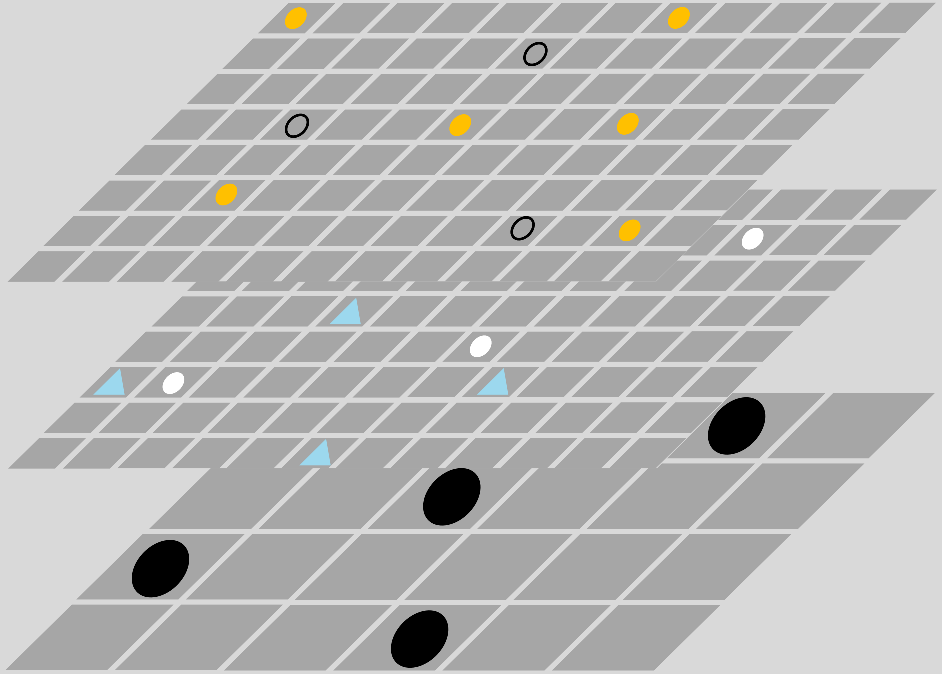
The model: An overview



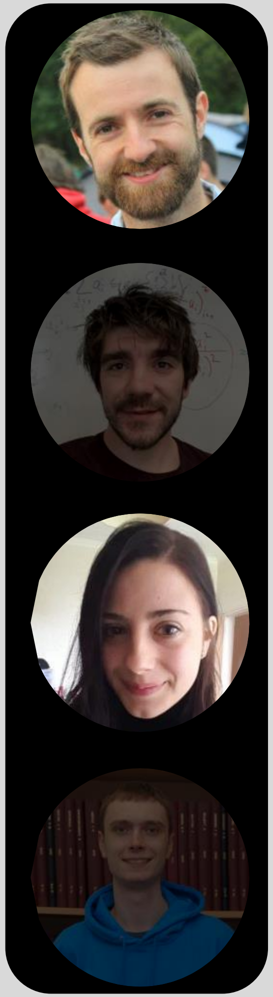

5 “species”

M I^d I^l X X^b

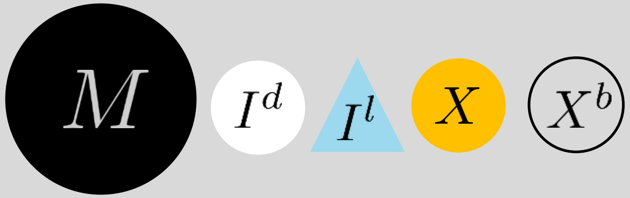
Three lattices



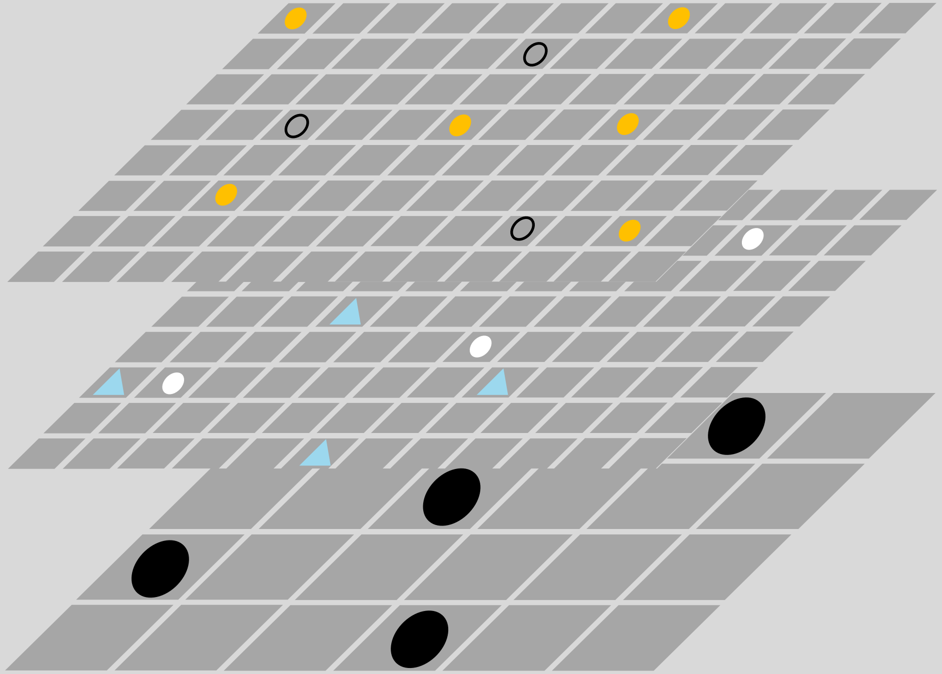
The model: An overview



5 “species”



Three lattices



The model: An overview

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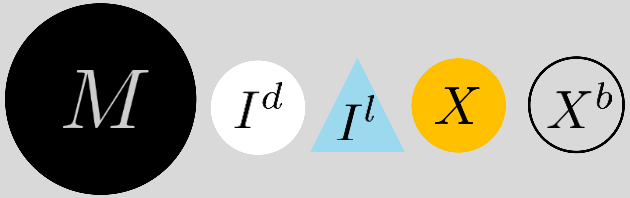
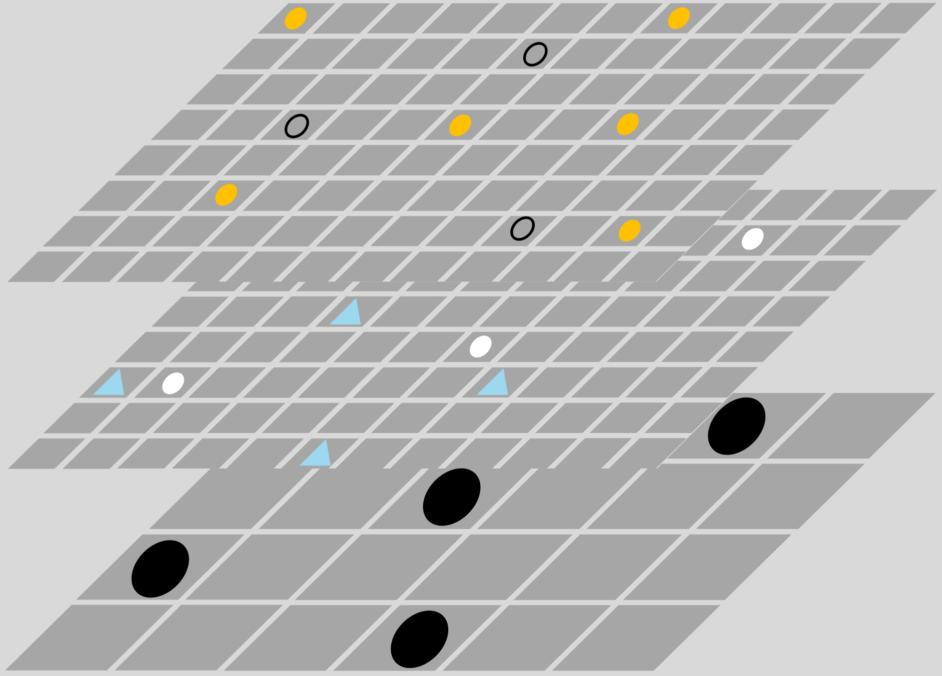
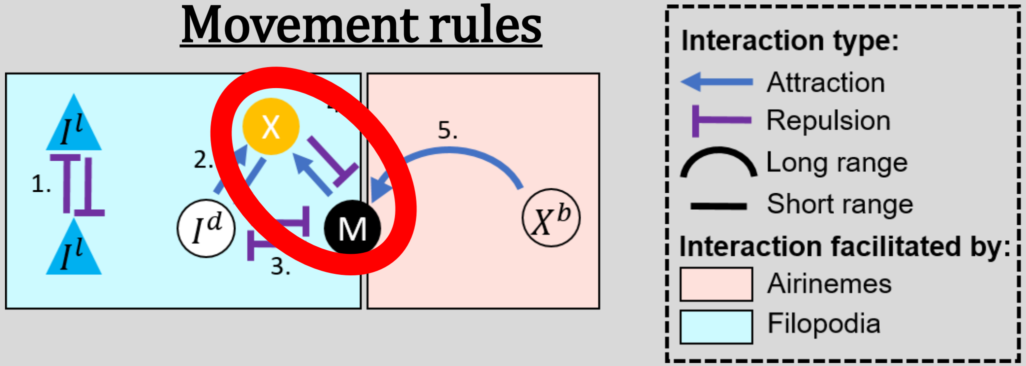


Three lattices

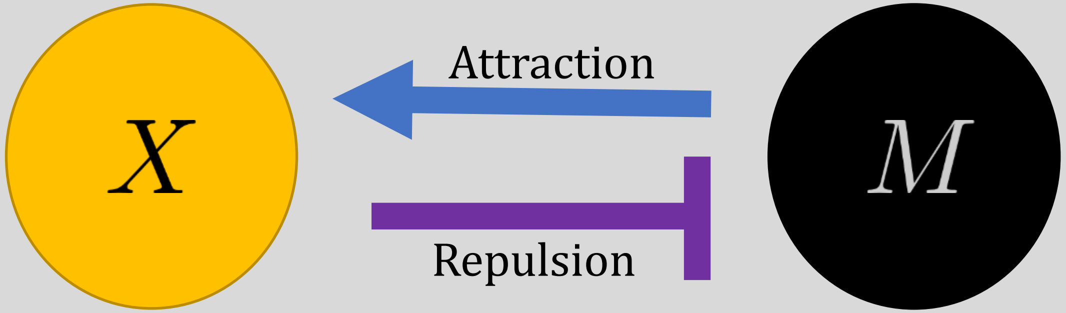


Fifteen "events"

Movement rules

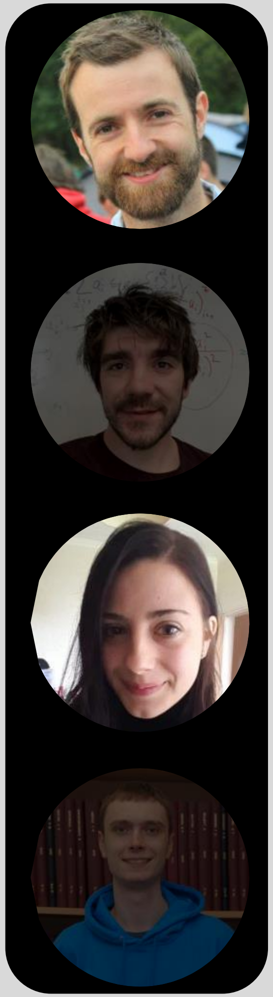


The model: example event

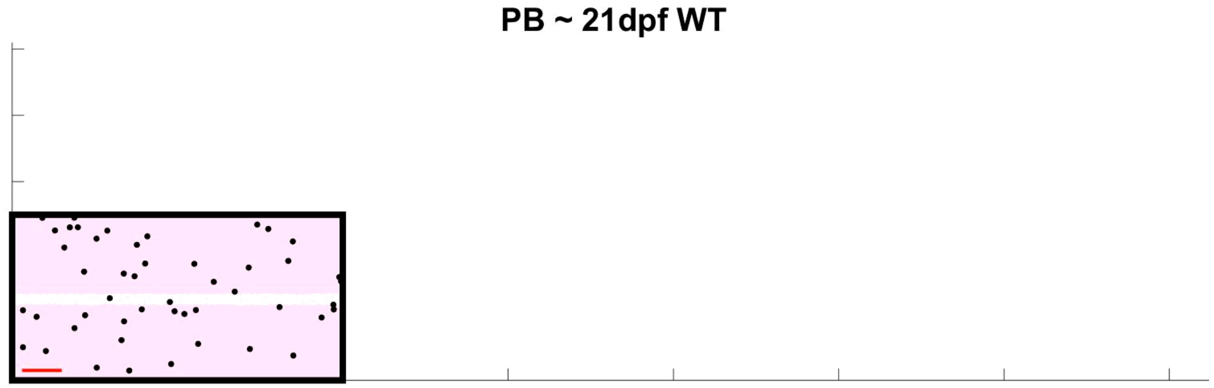


Melanophore-xanthophore interaction *in vitro*. Yamanaka *et al.*, 2014.

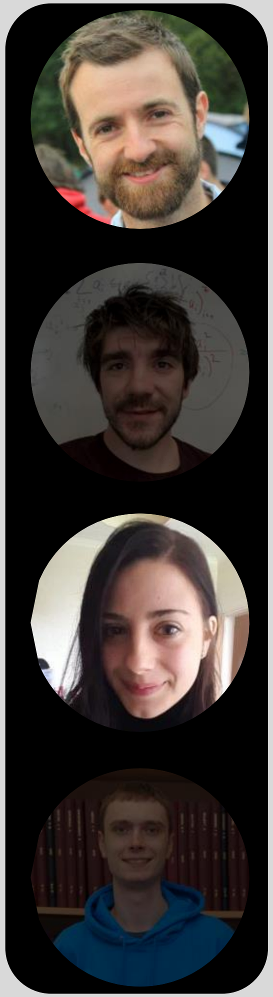
Results: wild type

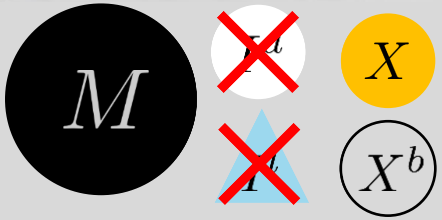


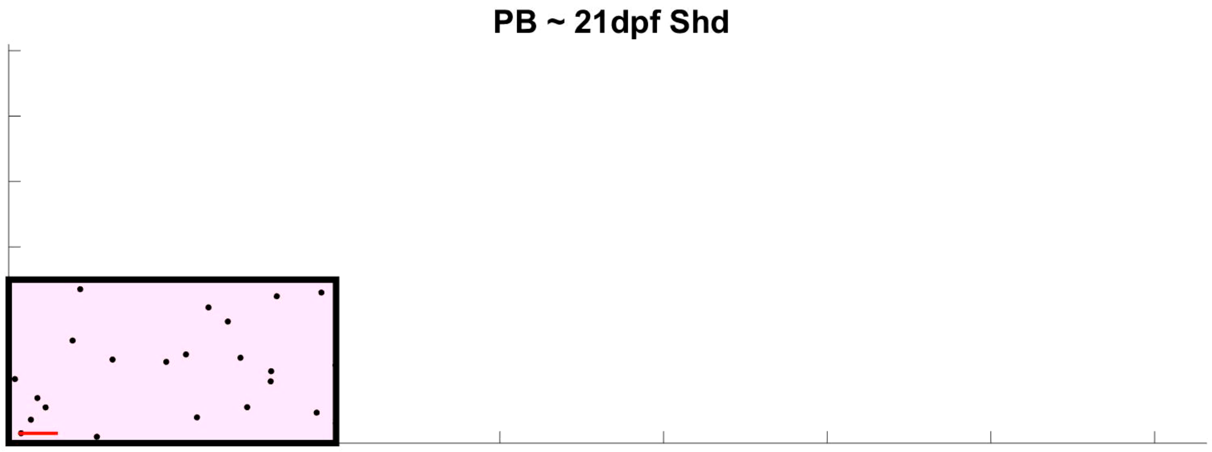
M I^d I^l X X^b



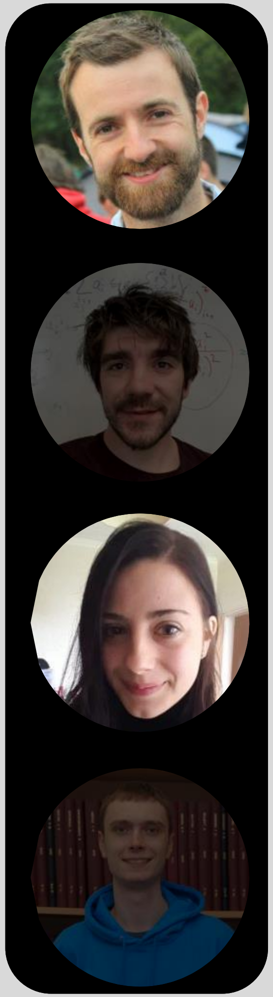
Results: *shady* mutant







Summary: Zebrafish pigment patterns



Aim

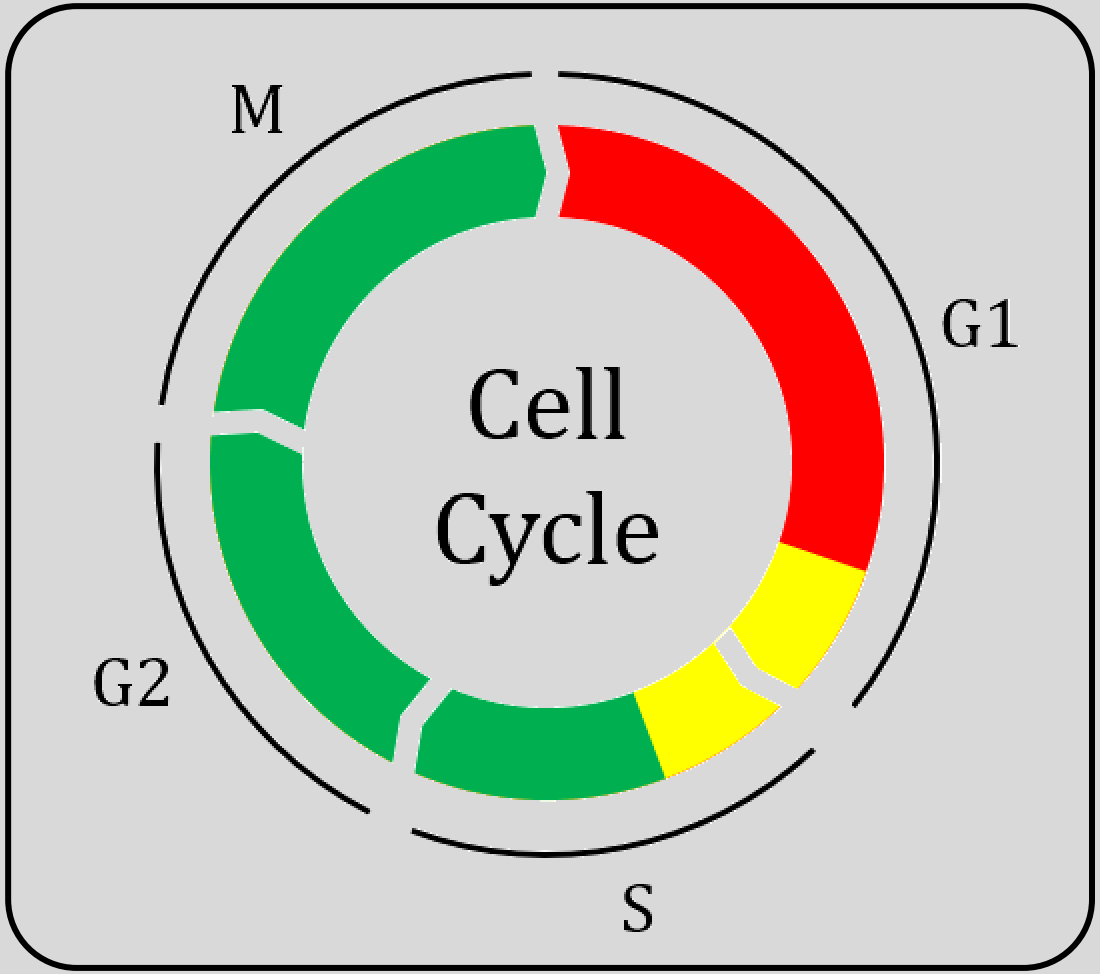
To use biologically observed or experimentally hypothesised rules to explain zebrafish pigment pattern formation.

Model

Five species, on lattice model on a growing domain with fifteen interaction events.

Conclusions

Iridiphores are an important cell type for the formation of the characteristic zebrafish pattern.

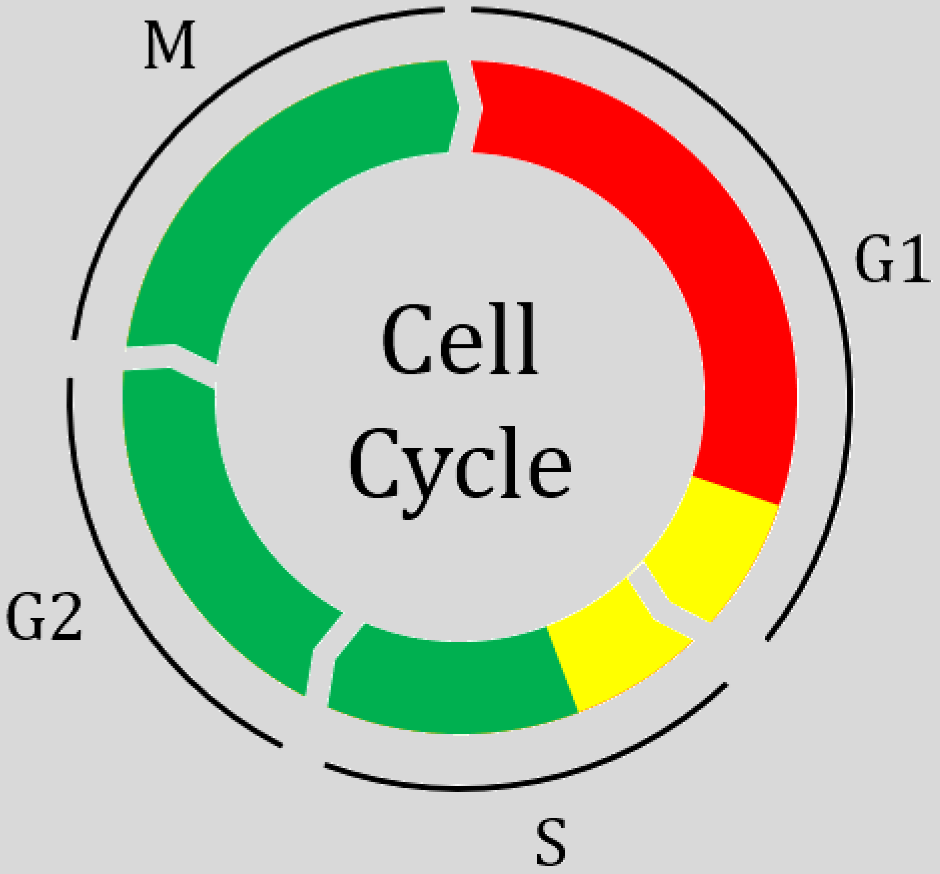


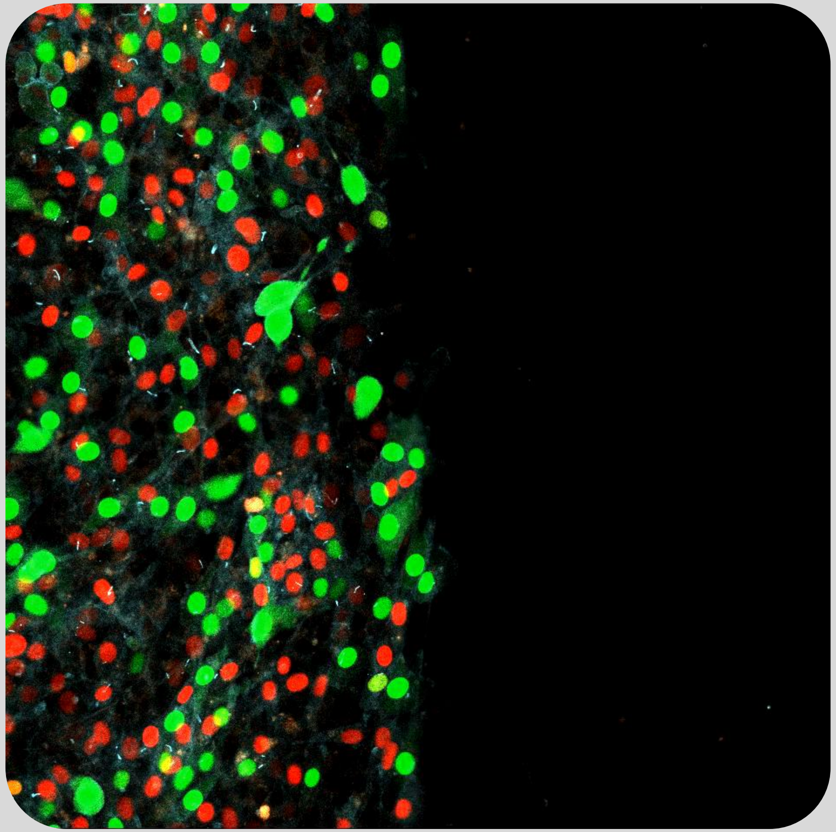
Cell migration models

UNIVERSITY OF BATH

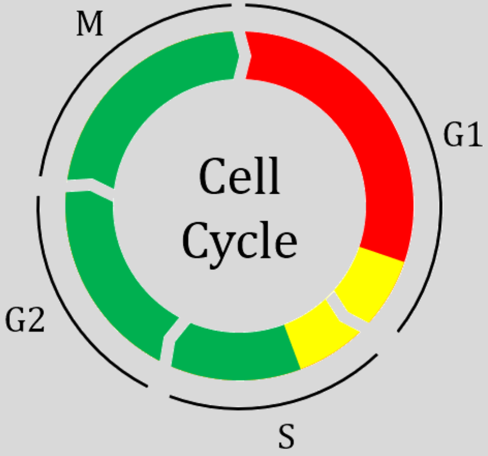
E. Gavagnin *et al.*, The invasion speed of cell migration models with realistic cell cycle time distributions, *J. Theor. Biol.,* 2018.

The cell cycle

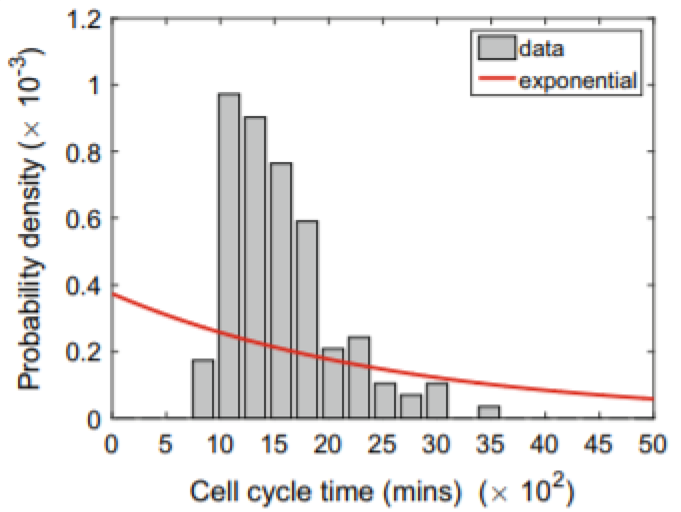




The cell cycle



Traditionally modelled using an exponential distribution…



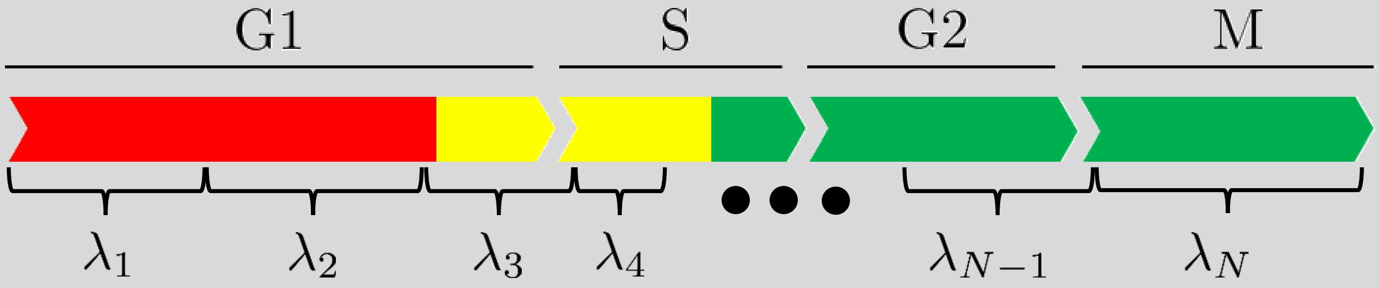
How do we accurately model the cell cycle?

C.A. Yates, M.J. Ford & R.L. Mort, A multi-stage representation of cell proliferation as a Markov process, *Bull. Math. Biol.,* 2017.

The cell cycle




How do we accurately model the cell cycle?



$$T_i \sim \text{Exp}(\lambda_i)$$

Exponentially-modified Erlang

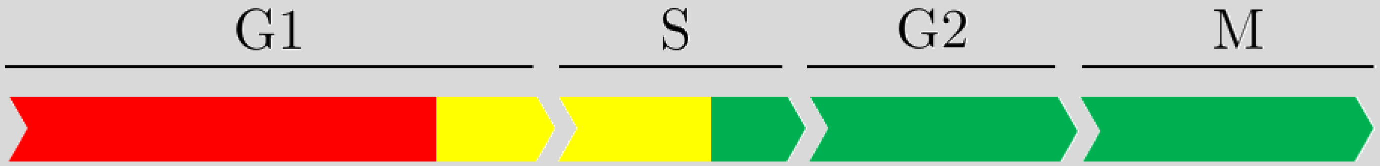
$$\lambda_i = \lambda,\ i \in \{1, \ldots, N-1\}$$
$$\lambda_N = \alpha,\ \alpha \neq \lambda$$

Erlang

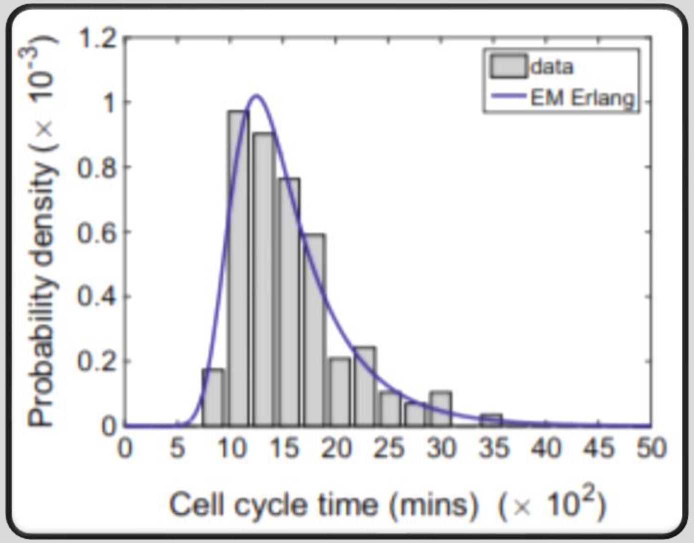
$$\lambda_i = \lambda,\ i \in \{1, \ldots, N\}$$

The cell cycle

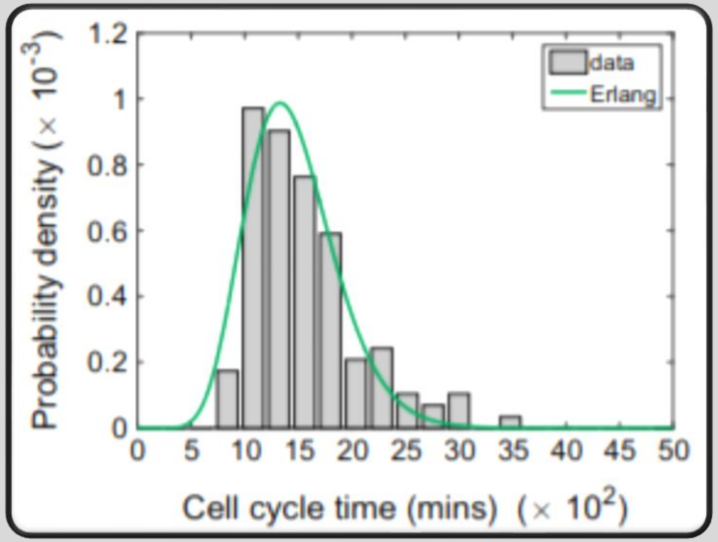
How do we accurately model the cell cycle?



Exponentially-modified Erlang

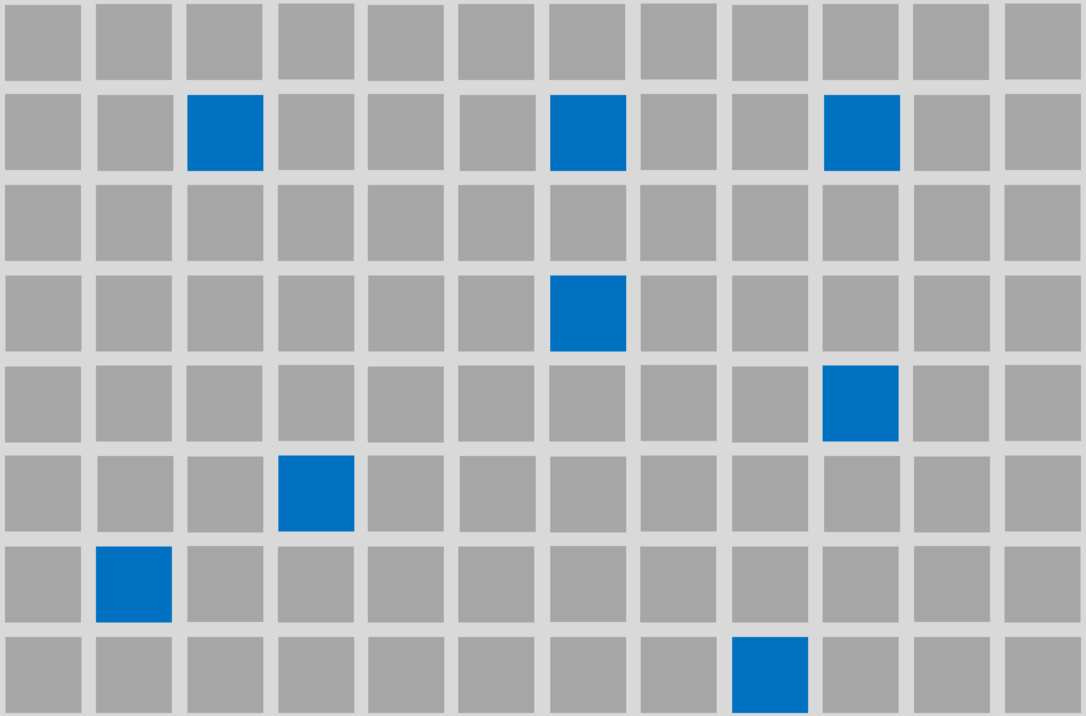


Erlang



C.A. Yates, M.J. Ford & R.L. Mort, A multi-stage representation of cell proliferation as a Markov process, *Bull. Math. Biol.,* 2017.

The model

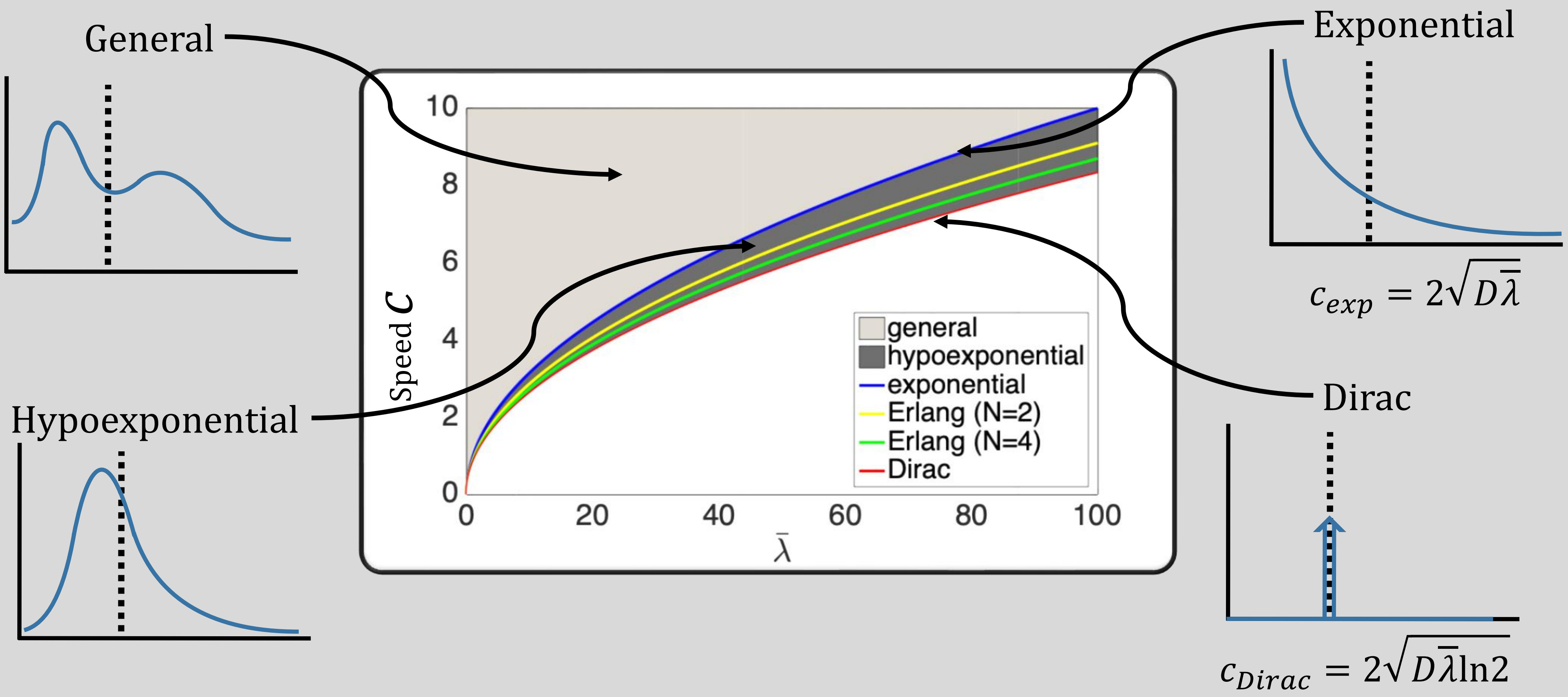


Volume exclusion.

Split cell cycle into N stages.

Proliferation only occurs at the final stage.

Results


General
Hypoexponential
Exponential
Dirac
Speed C
$\bar{\lambda}$
0
2
4
6
8
10
0
20
40
60
80
100
general
hypoexponential
exponential
Erlang (N=2)
Erlang (N=4)
Dirac
$c_{exp} = 2\sqrt{D\bar{\lambda}}$
$c_{Dirac} = 2\sqrt{D\bar{\lambda}\ln 2}$

Summary: Cell migration models




Aim

To determine how a realistic cell cycle distribution effects dynamics.

Model

On-lattice cell invasion model with different cell cycle distributions.

Conclusions

The cell cycle distribution is important in determining invasion speed.

And finally...




Reminder – Part 2 of this mini-symposium takes place tomorrow:

CB 4.16 from 11:00 – 12:30

Thank you for your attention.

I am supported by a scholarship from the EPSRC Centre for Doctoral Training in Statistical Applied Mathematics at Bath (SAMBa), under the project EP/L015684/1.

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https://people.bath.ac.uk/cs640/