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EXCELLENCE

UNIVERSITÄT
HEIDELBERG
ZUKUNFT
SEIT 1386

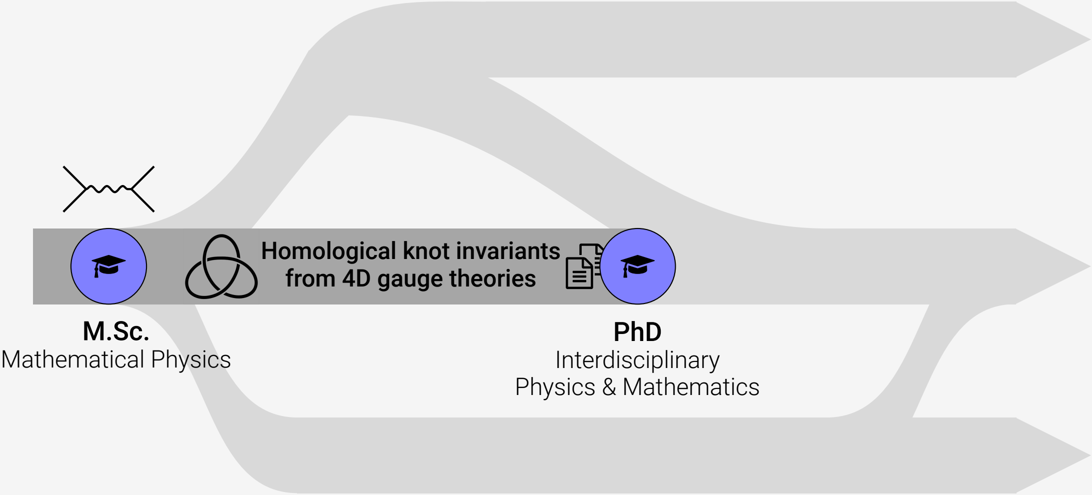
Michael Bleher

Institute for Mathematics, Heidelberg University

– 12 December 2024, MPI-MCG –

Persistence and Coarse-Graining in Dynamical Biological Systems

A Vision for Research at MPI-MCG



Homological knot invariants from 4D gauge theories

M.Sc.
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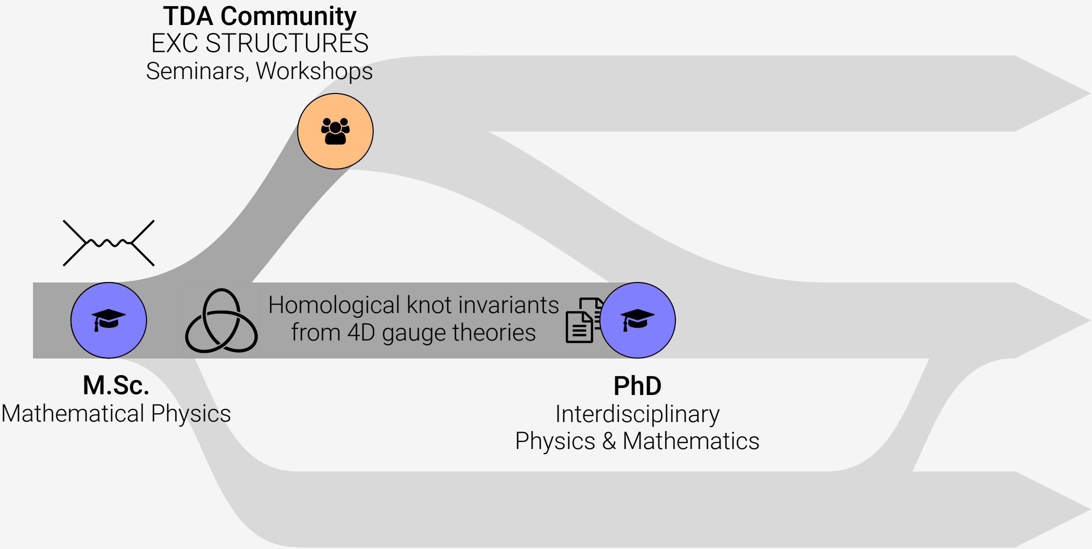

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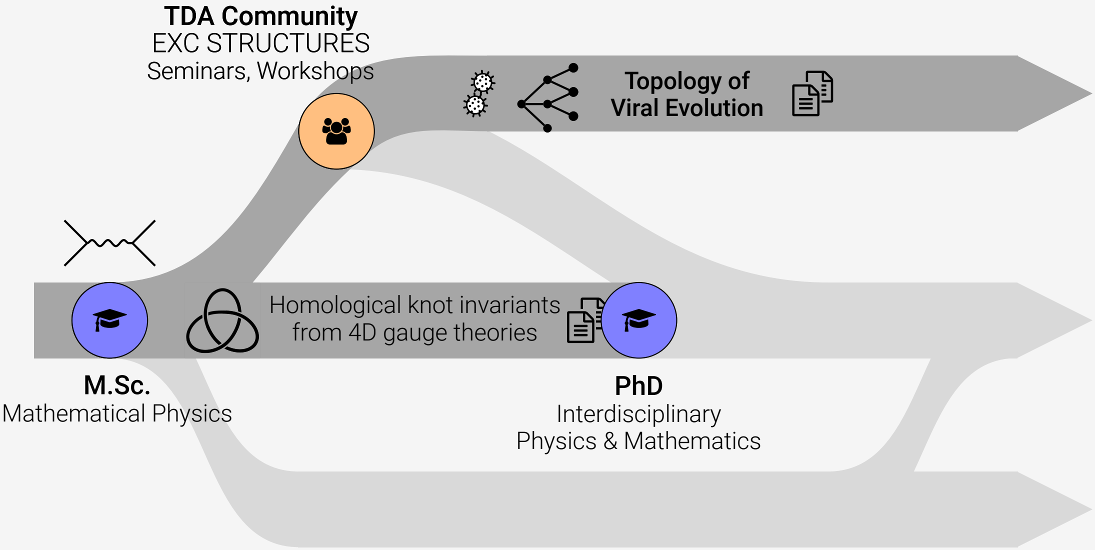

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Viral Evolution - a topologists's perspective

```
>seq0|date|location   >seq3|date|location
ATGAAGAGCTTAGTCCTAG   ATGAAGAGCTTAGTCGTAG
>seq1|date|location   >seq4|date|location
ATGAAGAGCTTTGTCCTAG   ATGAAGCGCTTTGTCGTAG
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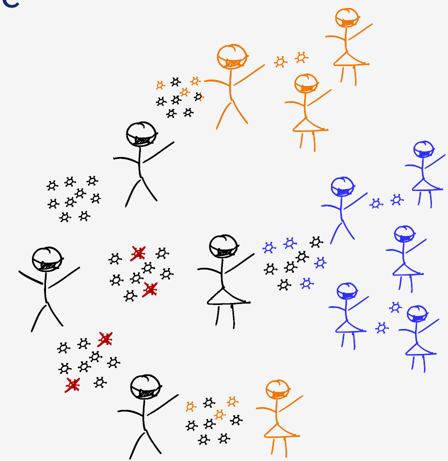
Transmission modulates observed mutation frequencies

- not every mutation is beneficial
- wide-spread mutations are not necessarily beneficial (founder effects)
- not every beneficial mutation catches on
- BUT: beneficial mutations tend to **appear repeatedly** (and may then spread more widely)



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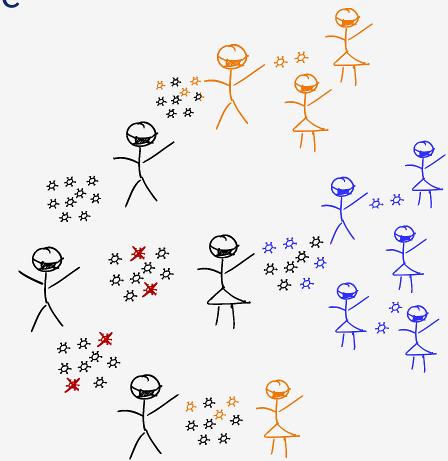

Recurrence is a hallmark of increased fitness.

Example: evolution of wings (birds, bats, insects)

Viral Evolution - a topologists's perspective

```
>seq0       >seq3
..A..C..    ..A..G..
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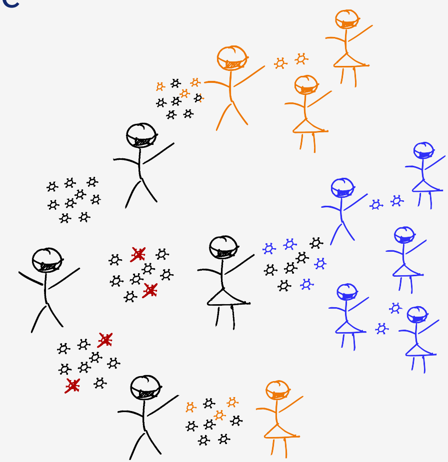

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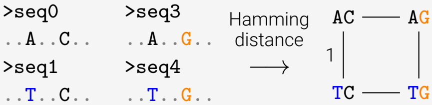

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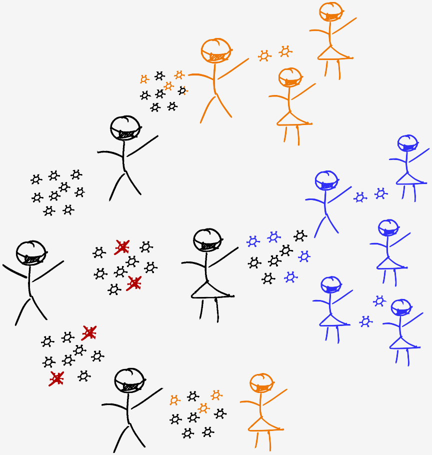

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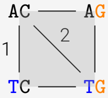
Hamming distance ⟶



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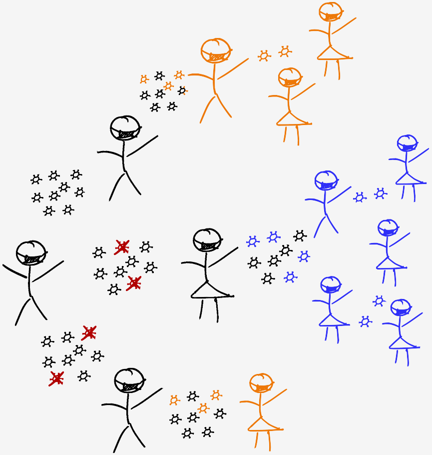

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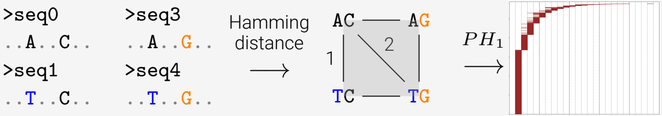

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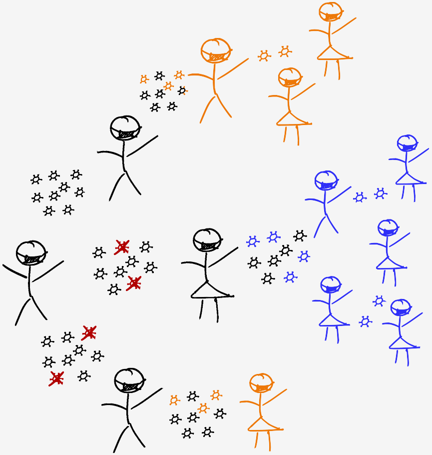

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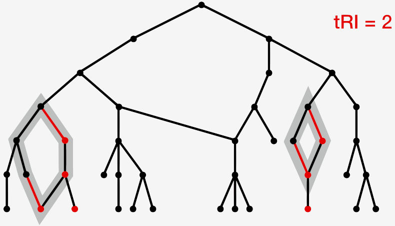
Topological Recurrence Index (tRI)

`arxiv: 2106.07292`

M.B., Lukas Hahn, Maximilian Neumann, Juan Angel Patino-Galindo,
Mathieu Carriere, Ulrich Bauer, Raul Rabadan, Andreas Ott.

Def.

The **topological Recurrence Index (tRI)** of a mutation is the number of $[1, d)$-cycles in which it appears.



$\Longrightarrow$ **tRI counts small scale recurrence**

- rare events
- non-homologous $\Longrightarrow$ independent acquicistion
- either high mutation rate or fitness advantage

Topological Recurrence Index (tRI)

`arxiv: 2207.03394`

Maximilian Neumann, **M.B.**, Lukas Hahn, Samuel Braun,
Holger Obermaier, Mehmet Soysal, René Caspart, Andreas Ott.

Data include time series information

→ **2-parameter persistence**

All tRI counts appear in 1d subfiltration.

"Thm"

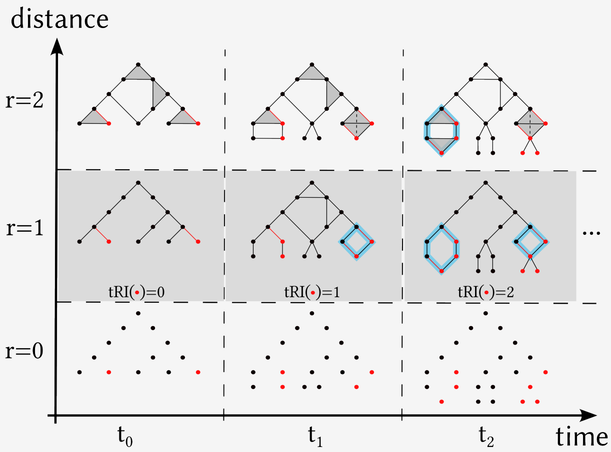
For any multi-filtered flag complex, get 1d submodules from a deformed metric.

Multiparameter persistence via Rips Transformations (`MuRiT`)

Ripser "Add-on":

- distance matrix
- pointwise poset filtration
- discrete path in product poset

⟶ 1d persistence submodule



Topological Recurrence Index (tRI)

`on-going`
Zachary Ardern, **M.B.**, Maximilian Neumann, Andreas Ott.

Data include time series information

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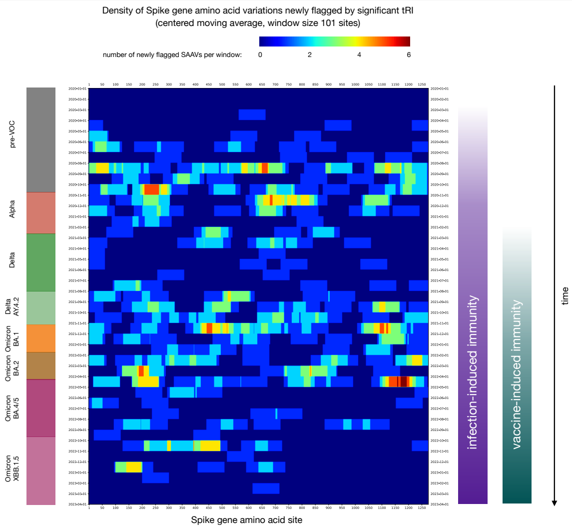
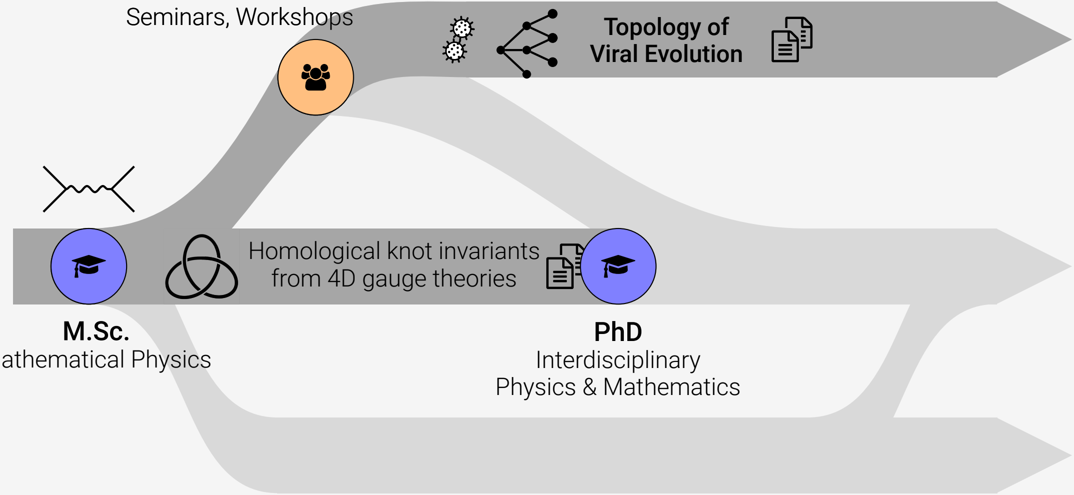


Density of Spike gene amino acid variations newly flagged by significant tRI
(centered moving average, window size 101 sites)



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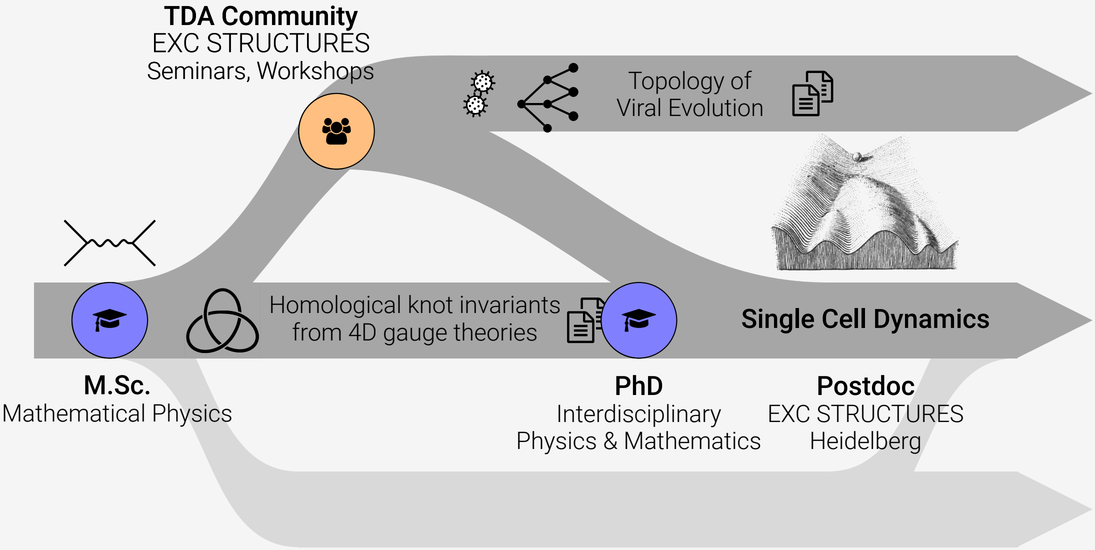

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Single Cell Dynamics

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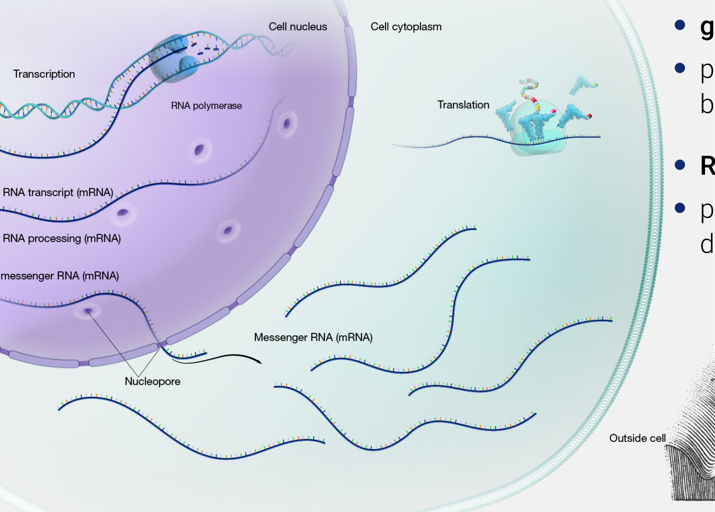
Single Cell Dynamics – a geometer's perspective

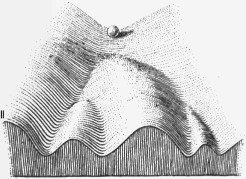
`on-going`
M.B., Fred Hamprecht,
Anna Marciniak-Czochra, Anna Wienhard.

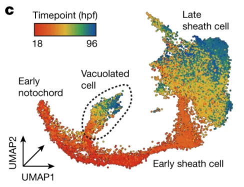


- **gene expression** = # mRNA
- proxy for cell's current biological state $x_i \in \mathbb{R}^{\#\text{genes}}$

- **RNA velocity** = rate of change in # mRNA
- proxy for cell's current development direction $v_i \in \mathbb{R}^{\#\text{genes}}$

Epigenetic Landscape





Single Cell Dynamics – a geometer's perspective

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Time evolution of individual points $p_i = (x_i, v_i) \in TM$ follows a Hamiltonian flow

$$\dot{\gamma} = X_H \ , \ \gamma(0) = p$$

Here H is some Hamiltonian ($\simeq$ energy) and X_H is the associated Hamiltonian vector field defined by

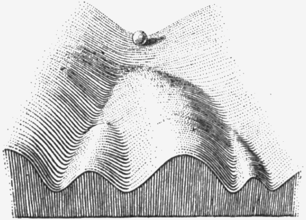
$$\omega(X_H, \cdot) = dH$$

Key Property

Model complex dynamics with few parameters.

Examples

- $H(x,v) = \frac{1}{2}\|v\|^2 \rightsquigarrow$ Geodesics (shortest paths)
- $H(x,v) = V(x) \rightsquigarrow$ Epigenetic Landscape



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Challenges

- High-dimensional data (# genes)
- Noise, batch effects
- destructive sampling

Manifold Learning

Hypothesis: Processes take place on low-dimensional submanifold.

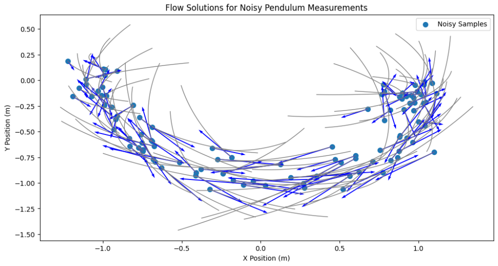
Goal: "Effective Hamiltonian Dynamics"

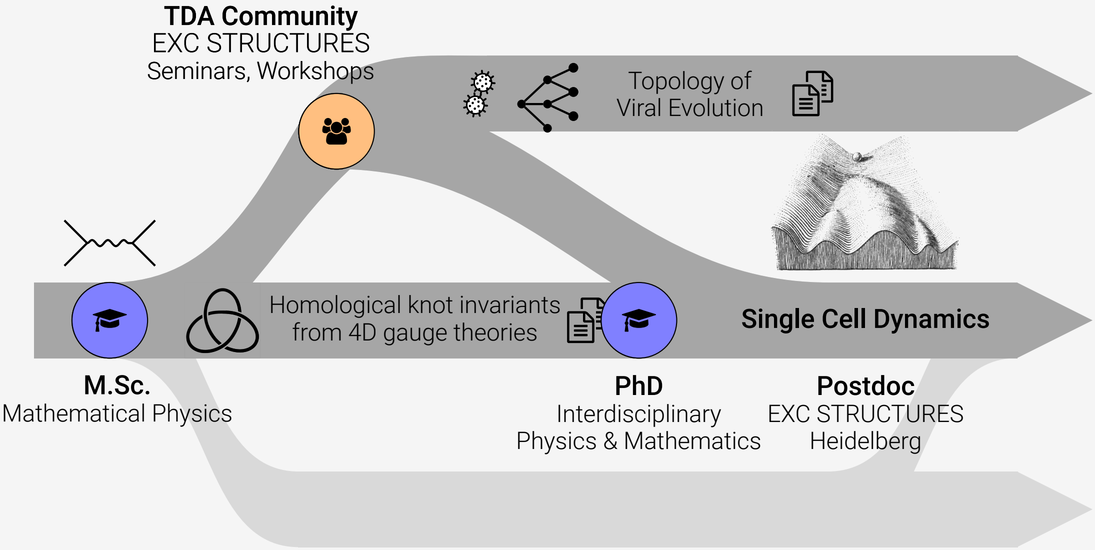
Investigate development and disease through latent space models of differentiation.

Python Package: `gNE`

(geometric Neighbour Embeddings)

RNA velocity embeddings in low-dimensions and learning Hamiltonian dynamics.


Flow Solutions for Noisy Pendulum Measurements



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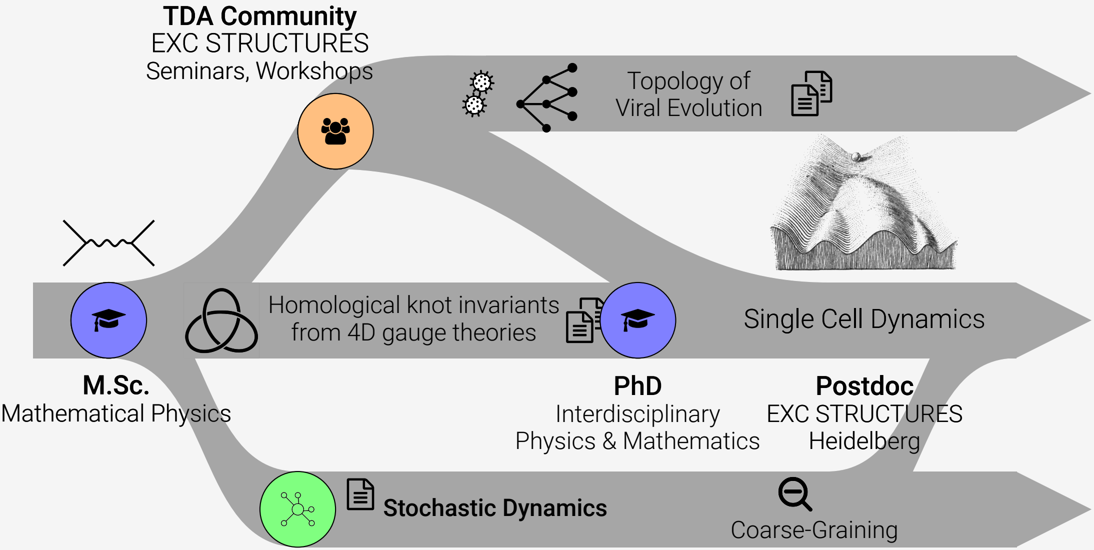

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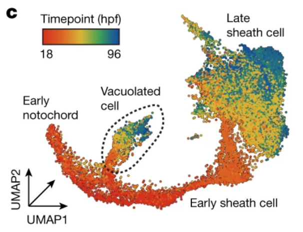
Stochastic Dynamics

Coarse-Graining

From Single Cells to Populations

`on-going`
M.B., Diana-Patricia Danciu, Carolin Lindow,
Anna Marciniak-Czochra, Ana Martin-Vilalba.

Zebrafish Embryogenesis (notochord)



Saunders, L.M., Srivatsan, S.R., Duran, M. et al. *Nature* **623**, 782–791 (2023).

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Mouse Neurogenesis (quasi-stationary)

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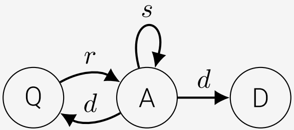
Population Dynamics



Q: quiescent
A: active
D: differentiated

$$\frac{d}{dt}Q = -rQ + sA$$
$$\frac{d}{dt}A = rQ - 2dA$$
$$\frac{d}{dt}D = dA$$

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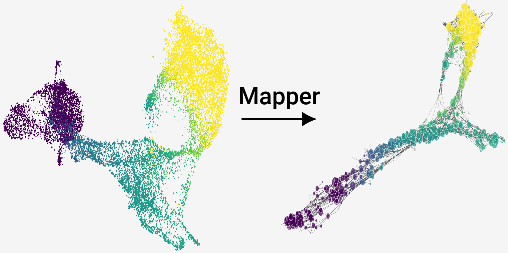


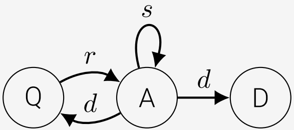
From single cells to population dynamics?

Describe position probability of individual cells by continuous time Markov chain

$$\frac{d}{dt}p_i(t) = \sum_j H_{ij}p_j(t)$$

Deduce transition probabilities H_{ij} from data.

Population Dynamics



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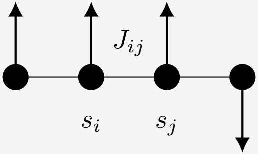
From Single Cells to Populations - a physicist’s perspective



Renormalization, aka Coarse-Graining

Ising model: $s_i \in \{-1, 1\}$, $J_{ij} \in \mathbb{R}$

$$E(J) = \sum_{\langle i,j \rangle} J_{ij} s_i s_j$$

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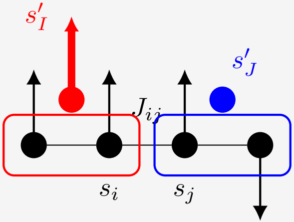
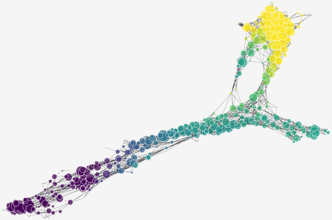


Renormalization, aka Coarse-Graining

Ising model: $s_i \in \{-1,1\}$, $J_{ij} \in \mathbb{R}$, $s'_I \in \{-1,0,1\}$

$$E(J) = \sum_{\langle i,j \rangle} J_{ij} s_i s_j \xRightarrow{s'_I = \frac{1}{|I|} \sum_{i \in I} s_I} E'(J') = \sum_{\langle I,J \rangle} J'_{IJ} s'_I s'_J .$$

From Single Cells to Populations - a physicist's perspective



Renormalization, aka Coarse-Graining

Continuous time Markov chain: $p_i \in [0,1]$, $H_{ij} \in \mathbb{R}$

$$\frac{d}{dt} p_i(t) = \sum_j H_{ij} p_j(t)$$

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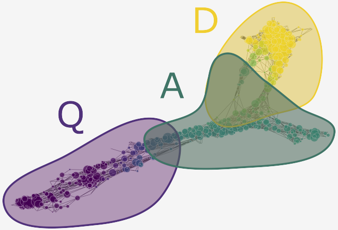

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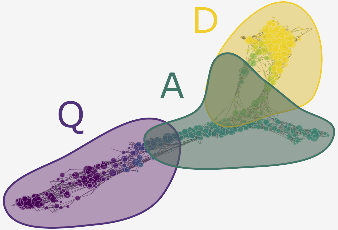

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Persistence and coarse-graining in dynamical biological systems?

Small scale
diffusion-drift model
of scRNA-seq

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Large scale
population models
of bulk RNA-seq

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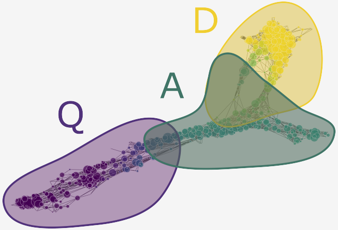

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Persistence and coarse-graining in dynamical biological systems?

Small scale
diffusion-drift model
of scRNA-seq

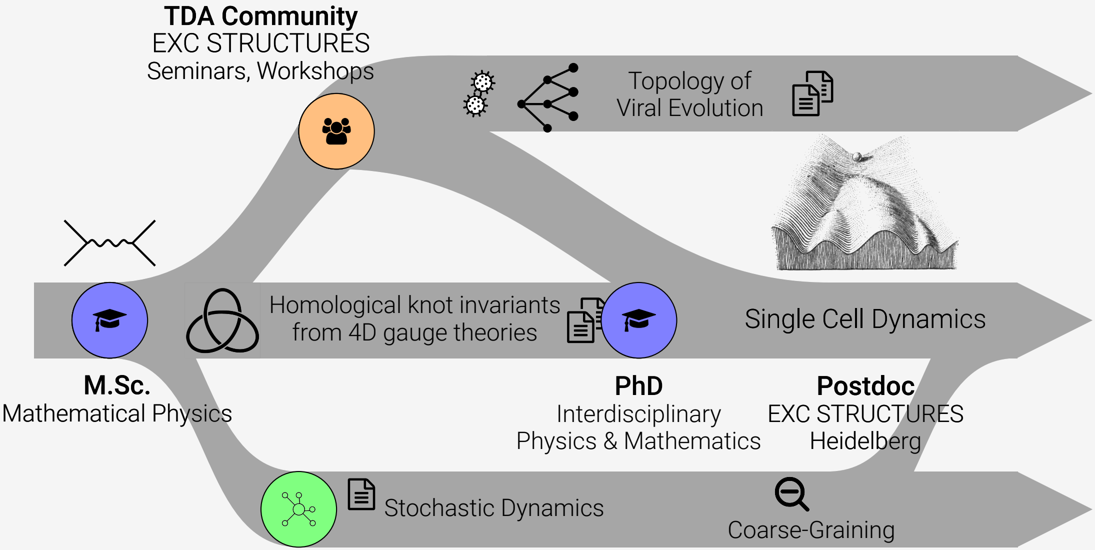
$\xrightarrow{\text{TDA, ML}}$

Effective Dynamics
e.g. continuous time
Markov chain

$\xrightarrow{\text{RG}}$

Large scale
population models
of bulk RNA-seq

persistence tracks **topological** features across scales
renormalization tracks **dynamical** features across scales



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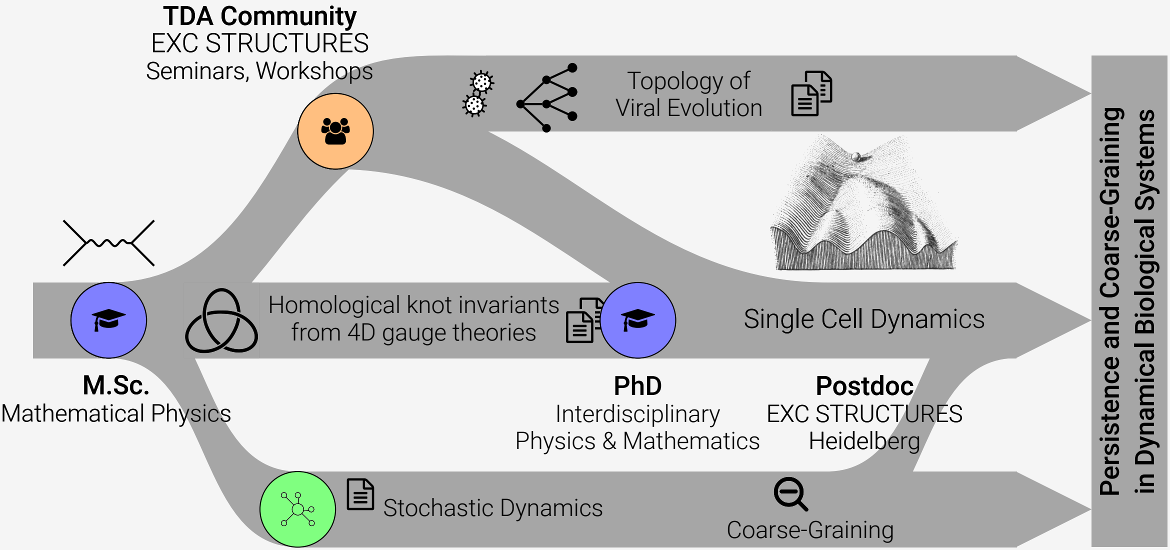

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