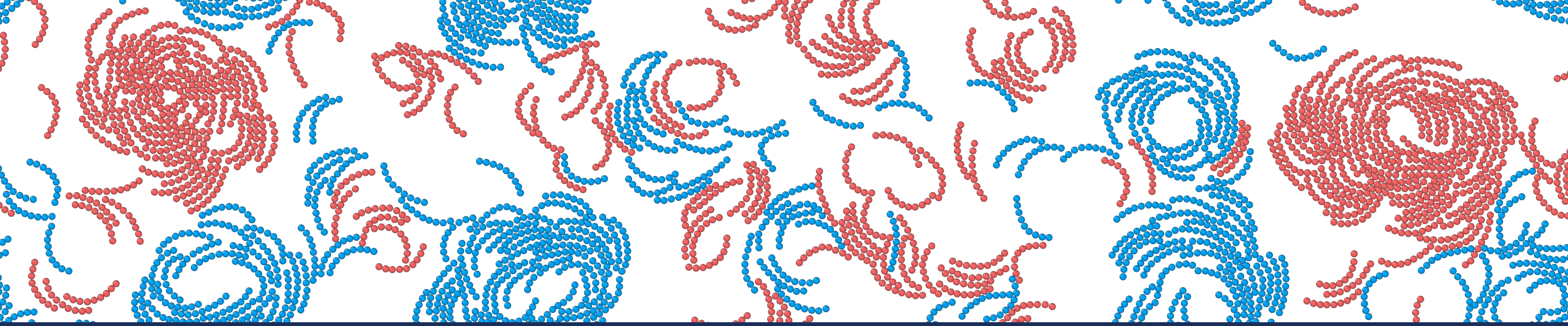

# 2D Simulation of FtsZ Filaments

University of Strathclyde Science

THE CARNEGIE TRUST FOR THE UNIVERSITIES OF SCOTLAND

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## General Background

The topic for research in this Proposal was one of interdisciplinary investigation, and lay within the realms of biophysics. Specifically, the aim was to develop a mathematical framework and preliminary simulation model to study the behaviour of FtsZ (Filamenting temperature-sensitive mutant Z) – a protein that exists amongst many bacteria types and is present during the initial stages of cell division [1].

Whilst biological research has been conducted into FtsZ mechanics over the past five years, a decisive framework behind FtsZ's physical role in bacteria division and cell wall synthesis remains unclear [2]. In simpler terms, what it does has been determined, but not how it does this; FtsZ filaments are involved in initiating the division process, and allow for other enzymes to synthesis new membrane, although the complete mechanics involved here are still undefined.

It was only recently discovered that FtsZ are subject to interesting "treadmilling" dynamics [3], where one end of the filament grows and the other shrinks, therefore creating a form of motion within the division plane. This is only part of the dynamics picture, and goes to show the lack of complete insight into FtsZ properties.

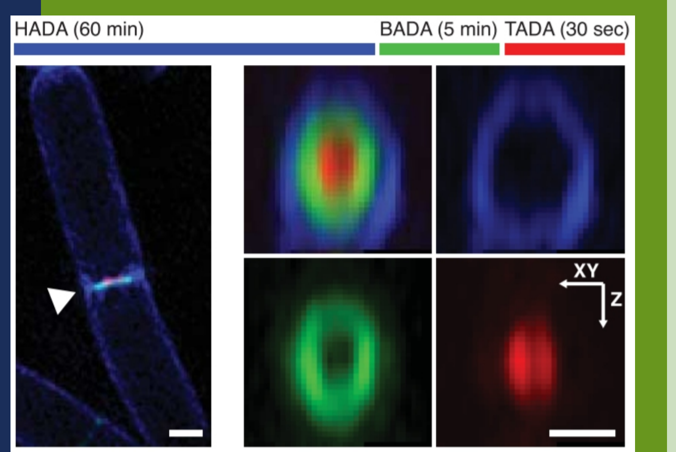



**Fig 1** | Outside-in synthesis of division septa, ultimately driven by FtsZ protein. (From Fig1A of Source [2]).

Since the presence of FtsZ filaments is so fundamental to the reproduction of many bacteria species, understanding their dynamics and collective behaviour in detail is of utmost importance, as it may lead to future development of medical cures largely unaffected by antibiotic-resistance.

## Project Objectives

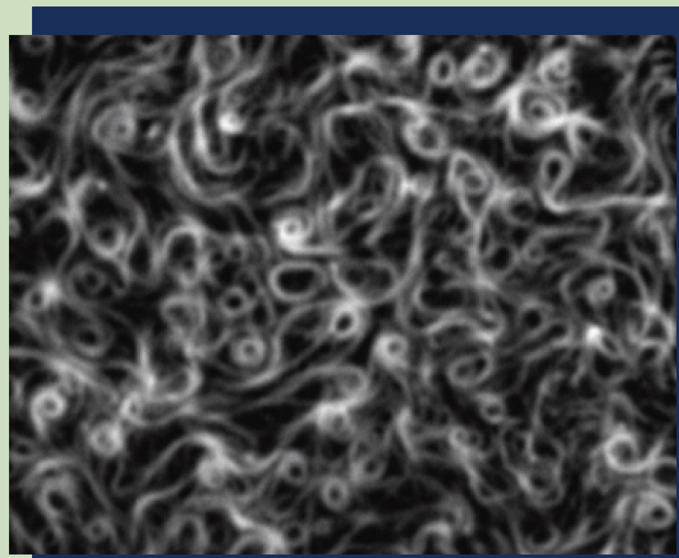


**Fig 2** | Experimental evidence of intrinsic vortex formation of FtsZ (From Fig3 of Source [3]). The success of the simulator developed in this Project ultimately relied on its ability to computationally replicate similar vortex emergence.

The aim for this project was to develop a 2D model of simplified FtsZ dynamics. This involved C/C++ source file adaptation and extension of the open-source package *"**LAMMPS**"*.

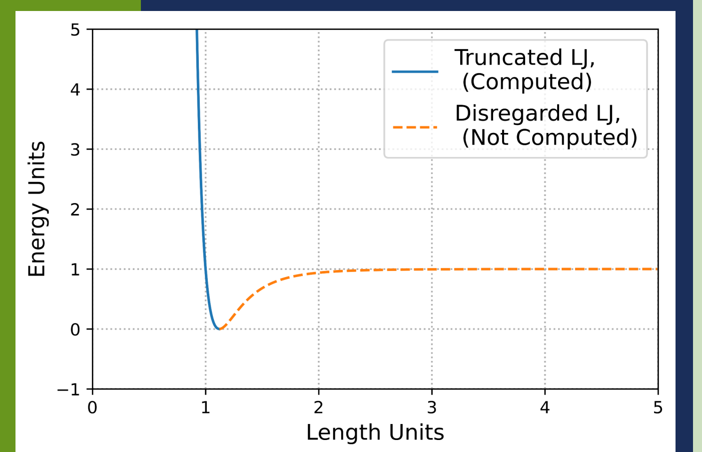
The acronym describes the package well – "**L**arge-scale **A**tomic/**M**olecular **M**assively **P**arallel **S**imulator".

Drawing upon a previously published, simplified model [4] for reference, a 2D model centred around LAMMPS was created.

The filaments where to be modelled as a chain of beads, forming a polymer. Properties, such as the polymers' radius of curvature and interaction potentials would have to be appropriately determined in order to observe previously reported vortex formation [4,5]. Other changes of variable included:

- Temperature
- Filament Densities
- Treadmilling Velocities

**Fig 3** | An example of the purely repulsive Lennard-Jones (LJ12-6) Interaction Potential used.

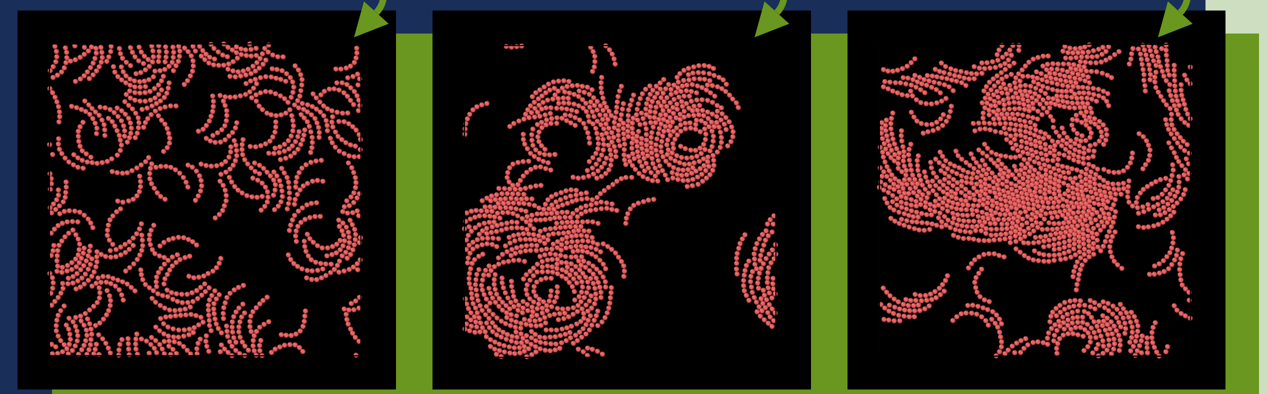



All Appropriate References Shown on Final Page

## Overall Conclusions

Results where summarised into three visually distinct states:

**Disorder** **Vortexes** **Trains**



**Disorder** | Found to generally occur at higher temperatures and/or lower FtsZ densities. No self-arrangement between polymers.

**Vortexes** | The desired pattern that mimics FtsZ self-arrangement at the formation of division septa.

**Trains** | At lower temperatures and higher FtsZ densities, the polymers where found to cluster together, transverse across the membrane, although without the necessary formation to initiate cell division conditions.

**Phase Portraits** | A noise ratio (sigma) between thermal fluctuations and frictional forces was plotted against FtsZ density (rho). This provided a test range by which to compare different versions of the code during development, as well as investigating polymer sets with various distributions of anti-clockwise (right-handed) and clockwise (left-handed) self-propulsion orientation.

**Statistical Analysis** | Radial Distribution Functions (RDFs) where taken for the centre of radii between polymers, taking a temporal average across frames. In the case of mixed left-right-handedness simulations, an additional and unconventional cross-correlated RDF was also developed.

# Phase Portraits

Shown here are two complete phase portraits, plotting thermal noise level within the FtsZ simulation against the system density. The top diagram represents a typical single-handed polymer collection; and the bottom, a mixed-handed polymer collection (as experimentally investigated in vitro [6]).

## Single-Handed State

| sigma | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.25 | A10 - 1.235 | A20 | A30 | A40 | A50 | A60 | A70 | A80 | A90 | A100 | A110 - 1.235 | A120 | A130 | A140 | A150 | A160 | A170 | A180 | A190 | A200 | |
| 1.125 | A9 - 1.111 | A19 | A29 | A39 | A49 | A59 | A69 | A79 | A89 | A99 | A109 - 1.111 | A119 | A129 | A139 | A149 | A159 | A169 | A179 | A189 | A199 | |
| 1 | A8 - 0.988 | A18 | A28 | A38 | A48 | A58 | A68 | A78 | A88 | A98 | A108 - 0.988 | A118 | A128 | A138 | A148 | A158 | A168 | A178 | A188 | A198 | |
| 0.875 | A7 - 0.864 | A17 | A27 | A37 | A47 | A57 | A67 | A77 | A87 | A97 | A107 - 0.864 | A117 | A127 | A137 | A147 | A157 | A167 | A177 | A187 | A197 | |
| 0.75 | A6 - 0.741 | A16 | A26 | A36 | A46 | A56 | A66 | A76 | A86 | A96 | A106 - 0.741 | A116 | A126 | A136 | A146 | A156 | A166 | A176 | A186 | A196 | |
| 0.625 | A5 - 0.617 | A15 | A25 | A35 | A45 | A55 | A65 | A75 | A85 | A95 | A105 - 0.617 | A115 | A125 | A135 | A145 | A155 | A165 | A175 | A185 | A195 | |
| 0.5 | A4 - 0.494 | A14 | A24 | A34 | A44 | A54 | A64 | A74 | A84 | A94 | A104 - 0.494 | A114 | A124 | A134 | A144 | A154 | A164 | A174 | A184 | A194 | |
| 0.375 | A3 - 0.370 | A13 | A23 | A33 | A43 | A53 | A63 | A73 | A83 | A93 | A103 - 0.370 | A113 | A123 | A133 | A143 | A153 | A163 | A173 | A183 | A193 | |
| 0.25 | A2 - 0.247 | A12 | A22 | A32 | A42 | A52 | A62 | A72 | A82 | A92 | A102 - 0.247 | A112 | A122 | A132 | A142 | A152 | A162 | A172 | A182 | A192 | |
| 0.125 | A1 - 0.123 | A11 | A21 | A31 | A41 | A51 | A61 | A71 | A81 | A91 | A101 - 0.123 | A111 | A121 | A131 | A141 | A151 | A161 | A171 | A181 | A191 | |
| 0 | 0.069 | 0.15 | 0.243 | 0.313 | 0.39 | 0.444 | 0.5 | 0.556 | 0.625 | 0.694 | 0.764 | 0.833 | 0.903 | 0.972 | 1.042 | 1.111 | 1.18 | 1.25 | 1.319 | 1.389 | rho |
| | 0.07 | 0.15 | 0.245 | 0.315 | 0.39 | 0.45 | 0.5 | 0.557 | 0.625 | 0.7 | 0.77 | 0.84 | 0.905 | 0.975 | 1.045 | 1.115 | 1.185 | 1.255 | 1.325 | 1.389 | typed |
| | | | | | | | | | | | | | | | | | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | |

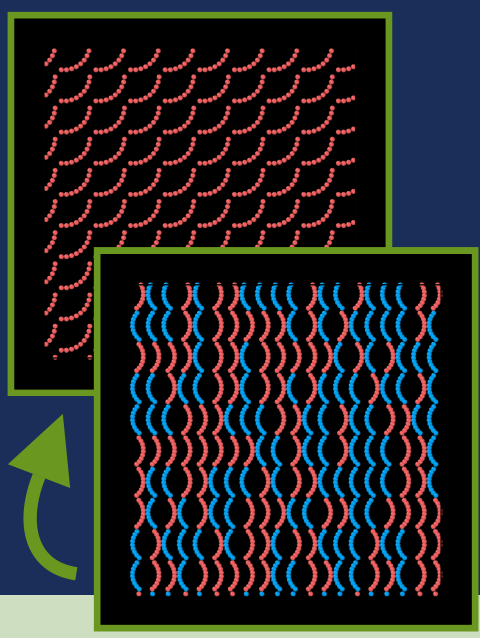
**Disorder =** **Vortexes =** **Trains =**

## Mixed State (50:50, L:R)

| sigma | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.25 | 10 - 1.235 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | 110 - 1.235 | 120 | 130 | 140 | 150 | 160 | 170 | 180 | 190 | 200 | |
| 1.125 | 9 - 1.111 | 19 | 29 | 39 | 49 | 59 | 69 | 79 | 89 | 99 | 109 - 1.111 | 119 | 129 | 139 | 149 | 159 | 169 | 179 | 189 | 199 | |
| 1 | 8 - 0.988 | 18 | 28 | 38 | 48 | 58 | 68 | 78 | 88 | 98 | 108 - 0.988 | 118 | 128 | 138 | 148 | 158 | 168 | 178 | 188 | 198 | |
| 0.875 | 7 - 0.864 | 17 | 27 | 37 | 47 | 57 | 67 | 77 | 87 | 97 | 107 - 0.864 | 117 | 127 | 137 | 147 | 157 | 167 | 177 | 187 | 197 | |
| 0.75 | 6 - 0.741 | 16 | 26 | 36 | 46 | 56 | 66 | 76 | 86 | 96 | 106 - 0.741 | 116 | 126 | 136 | 146 | 156 | 166 | 176 | 186 | 196 | |
| 0.625 | 5 - 0.617 | 15 | 25 | 35 | 45 | 55 | 65 | 75 | 85 | 95 | 105 - 0.617 | 115 | 125 | 135 | 145 | 155 | 165 | 175 | 185 | 195 | |
| 0.5 | 4 - 0.494 | 14 | 24 | 34 | 44 | 54 | 64 | 74 | 84 | 94 | 104 - 0.494 | 114 | 124 | 134 | 144 | 154 | 164 | 174 | 184 | 194 | |
| 0.375 | 3 - 0.370 | 13 | 23 | 33 | 43 | 53 | 63 | 73 | 83 | 93 | 103 - 0.370 | 113 | 123 | 133 | 143 | 153 | 163 | 173 | 183 | 193 | |
| 0.25 | 2 - 0.247 | 12 | 22 | 32 | 42 | 52 | 62 | 72 | 82 | 92 | 102 - 0.247 | 112 | 122 | 132 | 142 | 152 | 162 | 172 | 182 | 192 | |
| 0.125 | 1 - 0.123 | 11 | 21 | 31 | 41 | 51 | 61 | 71 | 81 | 91 | 101 - 0.123 | 111 | 121 | 131 | 141 | 151 | 161 | 171 | 181 | 191 | |
| 0 | 0.069 | 0.15 | 0.243 | 0.313 | 0.39 | 0.444 | 0.5 | 0.556 | 0.625 | 0.694 | 0.764 | 0.833 | 0.903 | 0.972 | 1.042 | 1.111 | 1.18 | 1.25 | 1.319 | 1.389 | rho |
| | 0.07 | 0.15 | 0.245 | 0.315 | 0.39 | 0.45 | 0.5 | 0.557 | 0.625 | 0.7 | 0.77 | 0.84 | 0.905 | 0.975 | 1.045 | 1.115 | 1.185 | 1.255 | 1.325 | 1.389 | typed |
| | | | | | | | | | | | | | | | | | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | |

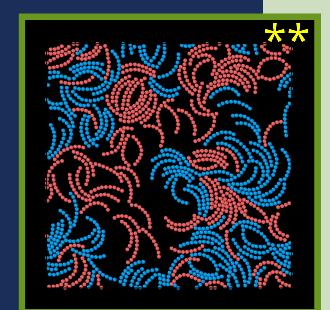
**Thermal Noise (Sigma)** | This parameter could be varied in two ways. The first, by increasing the temperature of the system (achieved in LAMMPS through an increase in the size of the “fix langevin” command); or secondly, by altering the velocity of the FtsZ self-propulsion, effectively signifying an alteration to the FtsZ treadmilling rate.

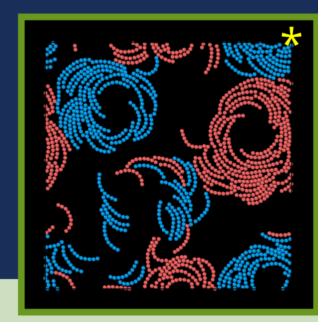
Both methods yield the same phases portrait results when ran across the same range of sigma values.

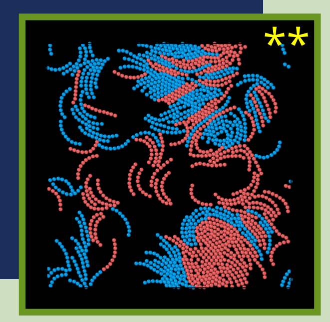


**Polymer Density (Rho)** | A script - written in C - was developed that allowed a desired density value to be inputted, and finished with writing to file a corresponding data input file for LAMMPS. Total polymer count was rounded to the closest *MxN* array size, hence the “typed” value and actual rho value. This worked for both single-handed states and mixed-states.

**Mixed States** | Inspired by in vitro research searching for the source of FtsZ force production [6], mixed state systems where also ran across the same phase portrait ranges as standard single-handed runs. In the developed 2D simulator, it was found that within this 2D plane, mixed states did not interact when within vortex formation*, though did cross-mix in disordered and train states**.



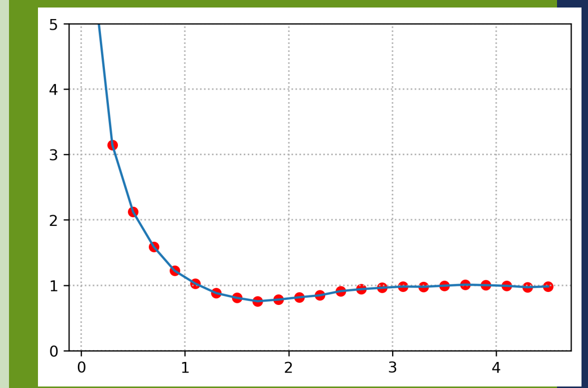



# 2D Simulation of FtsZ Filaments

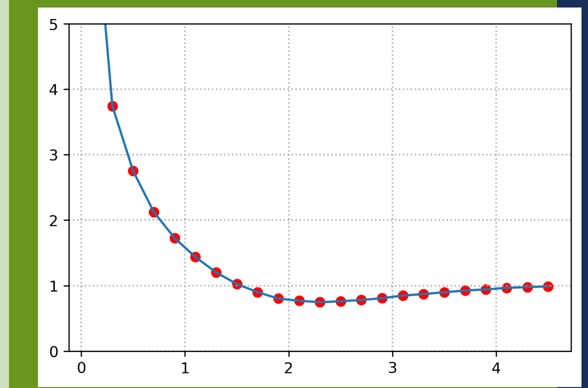
## Standard RDFs

The standard *Radial Distribution Function, "g(r)"*, also referred to as a *Pair Correlation Function*, counts the number of particles found within a given radial distance range, and is a common method for describing how system density varies across radial distance away from a reference point.

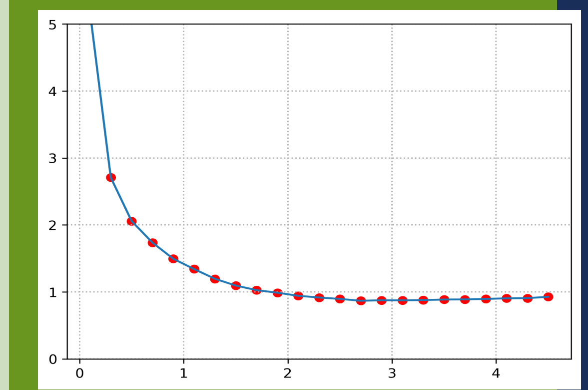
When applied to the FtsZ simulations, results where categorised into the three visual states through the location of the minimum of *g(r)*, similar to Source [4]. The states where:



- **Disordered** | If $g(r)_{min}$ was around or less than twice the polymer radius of curvature.

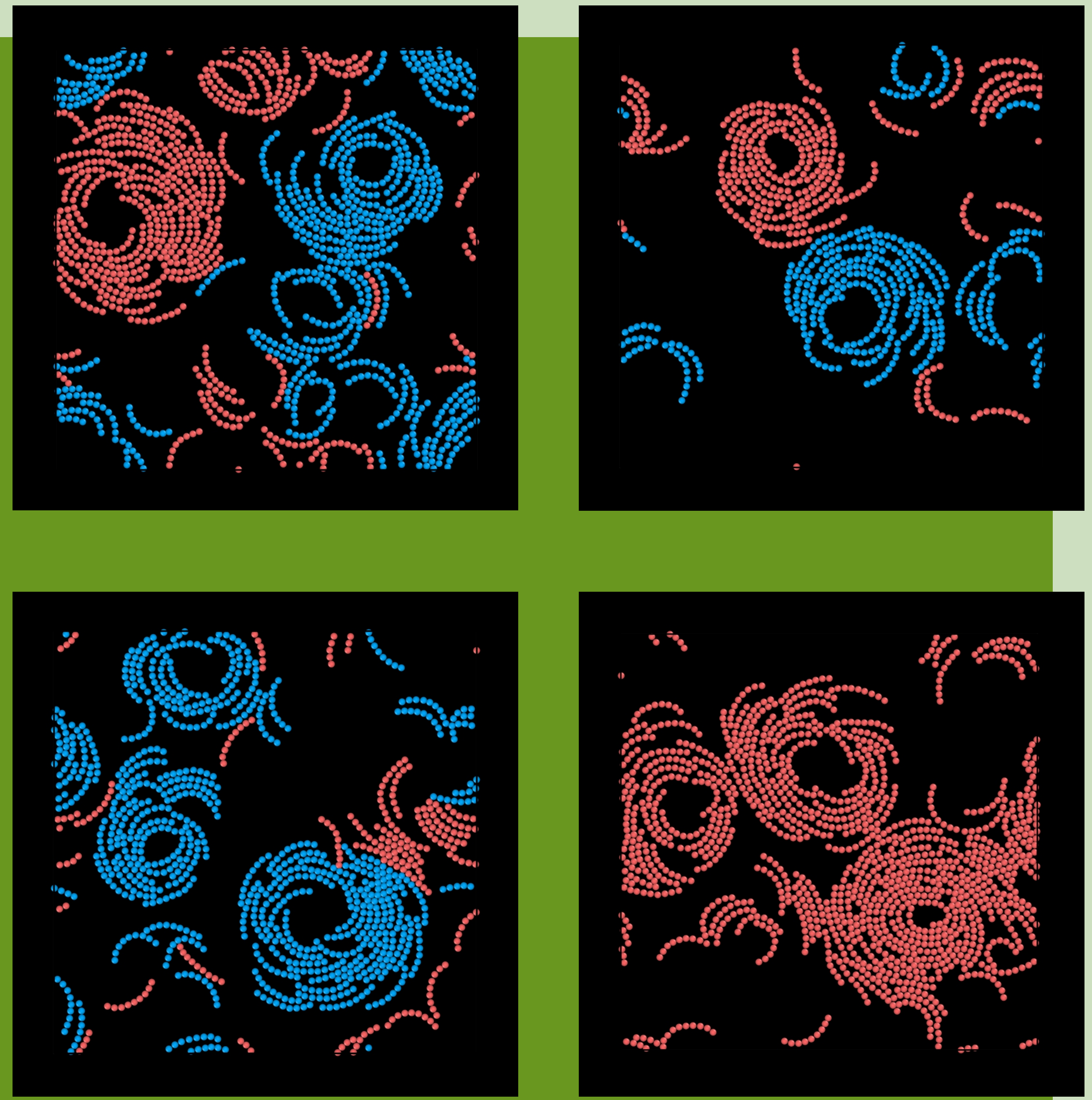


- **Vortex** | If $g(r)_{min}$ was greater than twice the polymer radius of curvature.



- **Train** | If *g(r)* did not have a significant minimum turning point.

This RDF criterion was utilised across all handedness distributions, and was used to determined the states found within the previously shown phase portraits.



A Selection of Frames Showcasing Vortex States

## References


[1] W. Margolin, "FtsZ and the division of prokaryotic cells and organelles," Nat. Rev. Mol. Cell Biol., vol. 6, p. 862–871, 14 October 2005.

[2] A. Bisson-Filho, Y. Hsu, G. Squyres, et al., "Treadmilling by FtsZ filaments drives peptidoglycan synthesis and bacterial cell division," Science 355, p. 739–743, 17 February 2017.

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[4] J. Denk, L. Huber, E. Reithmann, et al., "Active Curved Polymers Form Vortex Patterns on Membranes," Phys. Rev. Lett., vol. 116, p. 178301, 25 April 2016.

[5] M. Loose, T. Mitchison, "The bacterial cell division proteins FtsA and FtsZ self-organize into dynamic cytoskeletal patterns", Nat. Cell Biol., vol 16, no. 1, p. 38, January 2014.

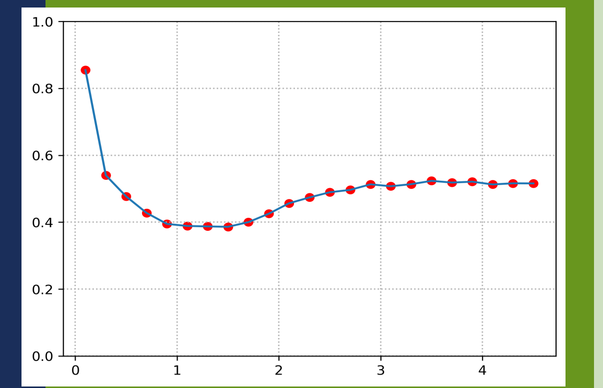
[6] Ramirez-Diaz, D.A., Merino-Salomón, A., Meyer, F. et al. "FtsZ induces membrane deformations via torsional stress upon GTP hydrolysis". Nat Commun 12, 3310 (2021). https://doi.org/10.1038/s41467-021-23387-3


## Cross-Correlated RDFs

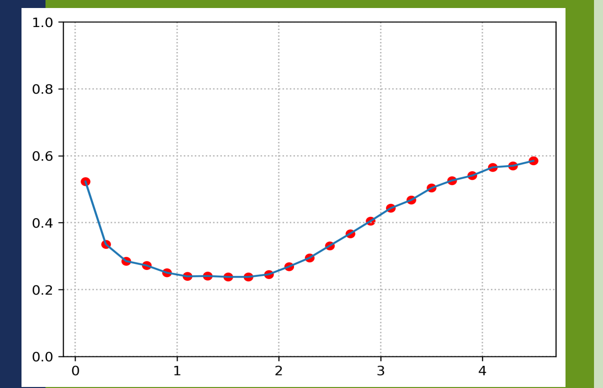
This alternative and unconventional cross-correlated RDF compared unmatched filaments, using the same algorithm as the standard RDF, though with adapted loop structure. Here, the loop sits on a centre of radii for a polymer of *x*-handedness, and loops through all *y*-handedness polymers' centre of radii to calculate distances. This is repeated across all *x*-handed polymers.

The three distinct states featured different cross-correlated RDF patterns:

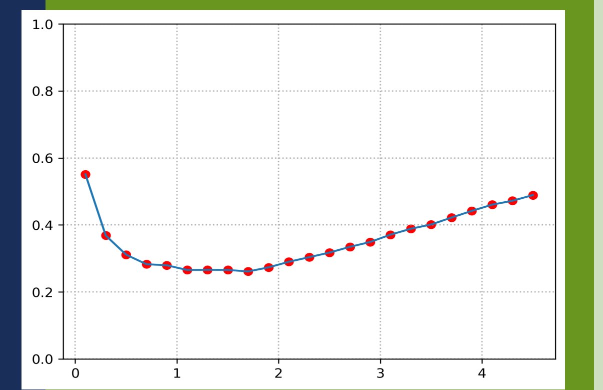
- **Disordered** | If, after $g(r)_{min}$, *g(r)* quickly flattened off into a homogeneous state.



- **Vortex** | If, after $g(r)_{min}$, *g(r)* curved to a point of inflection.



- **Train** | If, after $g(r)_{min}$, *g(r)* formed a straight line (constant gradient).



All RDFs, both Standard and Cross-Correlated, where developed and generated through post-processing methods in *Python*.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