Programming hierarchical self-assembly of colloids: matching stability and accessibility

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Encoding hierarchical self-assembly in colloidal building blocks is a promising bottom-up route to high-level structural complexity often observed in biological materials. However, harnessing this promise faces the grand challenge of bridging hierarchies of multiple length- and time-scales, associated with structure and dynamics respectively along the self-assembly pathway. Here we report on a case study, which examines the kinetic accessibility of a series of hollow spherical structures with a two-level structural hierarchy self-assembled from charge-stabilized colloidal magnetic particles. By means of a variety of computational methods, we find that for a staged assembly pathway, the structure, which derives the strongest energetic stability from the first stage of assembly and the weakest from the second stage, is most kinetically accessible. Such a striking correspondence between energetics and kinetics for optimal design principles should have general implications for programming hierarchical self-assembly pathways for nano- and micro-particles, while matching stability and accessibility.

Self-assembly of colloidal particles offers tremendous opportunities for fabricating three-dimensional structures in a bottom-up approach due to the scope for tuning the interparticle interactions.1,2 Recent advances in the synthesis of complex colloidal particles have made a wide variety of nano- and micro-scale building blocks available. Many of these colloidal building blocks involve anisotropic interparticle interactions, often due to either anisotropic shape or heterogeneous surface chemistry.2–5 These novel colloidal particles offer rich avenues for programming colloidal self-assembly.6,7

Hierarchical self-assembly of nano- and micro-particles is emerging as an attractive route to structural organization at a higher level, spanning multiple length scales.8,9 Notably, the hierarchical self-assembly of mono-disperse colloidal octapod-shaped nanocrystals resulted in a three-dimensional superlattice via the formation of linear chains of interlocked octapods.10 The assembly of binary and ternary patchy nano-particles produced supracolloidal ordered structures in a hierarchical scheme.11 The ‘patchiness’ of colloidal triblock spherical particles was exploited to encode staged self-assembly triggered by stepwise changes of the ionic strength of the medium.12 A computational study demonstrated an alternative scheme for patchiness without engineered surfaces en route to a variety of complex superstructures via hierarchical self-assembly.13 A theoretical analysis was presented for programming self-assembly of octopus nanoparticles, which themselves may be self-assembled, into a target nanostructure.14 Recent work also demonstrated how the self-assembly of colloidal particles in confinement could lead to a complex hierarchical geometry that exhibited a rich variety of optical effects including structural coloration due to the interaction of light with the structural features at different length scales.15 We recently followed a biomimetic design route to hollow spherical structures, exploiting a hierarchical self-assembly scheme for charge-stabilized colloidal magnetic particles with an off-centered magnetic dipole.16,17 While a growing body of work in recent years has demonstrated the great promise of hierarchical colloidal self-assembly,16–18 a conceptual framework to reliably program hierarchical self-assembly of colloidal building blocks has proved to be elusive. Such a framework is crucially important to address the challenges of a multiscale design problem, arising from the requirement of bridging hierarchies of multiple length- and time-scales, associated with structure and dynamics respectively, along the self-assembly pathway.19

Harnessing the enormous potential for colloidal self-assembly to offer a bottom-up route to structure fabrication critically hinges on our ability to manipulate the interactions between the colloidal particles such that a target structure is not only thermodynamically favorable, but also kinetically accessible on experimental time scales.6,14,20 This task becomes even more formidable in the context of hierarchical self-assembly. In this case, a pertinent question is whether the pathway is staged – that is to say, whether the assembly itself follows a hierarchical pathway.17,21 Such a pathway for colloidal self-assembly would involve concerted movements of colloidal par-
articles over the course of the assembly. In fact, the requirement
of matching stability and accessibility draws a parallel between
the target structure for programmed self-assembly and the
native structure of a protein.22

In particular, hollow spherical structures at the nano- and
micro-scale are attractive targets for a range of practical
applications,23–25 especially as nanocapsules resembling viral
capsids and microvesicles for drug delivery.26,27 Viral capsids
of icosahedral symmetry are in fact marvelous examples of
molecular self-assembly in nature, resulting in a remarkable
structural hierarchy in terms of repeating subunits.28
While the structures of viral capsids are now known in great
detail, the pathways for capsid assembly still remain poorly
understood largely due to limitations on experimental
characterization.29,30

In this contribution, we report on a case study where we
employed a variety of computational methods to examine the
kinetic accessibility of a series of hollow spherical structures
self-assembled from charge-stabilized colloidal magnetic par-
ticles. The structures each show a fascinating two-level struc-
tural hierarchy. We demonstrate how an optimal design rule
for hierarchical self-assembly in this case can be derived while
satisfying both the thermodynamic and kinetic criteria. We
find a striking correspondence between the energetics and
kinetics, which we account for a staged assembly pathway.
While our designer building blocks closely resemble recently
synthesized colloidal magnetic particles,31 our results suggest
design principles, which should have general implications for
programming hierarchical self-assembly of nano- and micro-
particles.19

While magnetic colloidal particles are classic examples of
microscale building blocks with anisotropic interactions,72
recent years have experienced a surge in the synthesis of exotic
colloidal magnetic particles.31,33 Having drawn motivation
from these research activities, a number of computational
studies have focused on spherical magnetic colloids with an
additional anisotropy attribute in terms of an off-centered
point-dipole.16,34,35 We considered charge-stabilized colloidal
magnetic particles, which included a permanent point-dipole
shifted away from the center,16 closely resembling those syn-
thesized using a single-domain hematite cube inclusion
underneath the surface of organopolymer spheres.31 However,
there was uncertainty in the direction of the dipole moment
within the magnetic cube in this experimental system.35 It was
most likely that the direction of the dipole was not parallel to
the radial shift vector to the position of the dipole.35 We intro-
duced an additional model parameter θ, denoting the angle at
which the direction of the point-dipole is inclined to the radial
shift vector (see Fig. 1a).17

We employed the basin-hopping global optimization
method to identify the global minima on the potential energy
landscapes for size-selected clusters.36,37 In the case of a
cluster of \(N = 24\) particles, a polyhedron of octahedral sym-
metry topologically equivalent to the snub cube was found to
be the most favored structure on the potential energy land-
scape for a range of \(θ\) values from 0° to 10° (see Fig. 1), the rest

![Fig. 1](image)
trimmers. Hereafter, we refer to this structure as the snub cube structure or the hollow spherical structure. For \( \theta = 15^\circ \), the snub cube structure was no longer the global minimum on the energy landscape. It is of interest to note that an analysis of the energetics for the snub cube structure revealed that an energetically favorable nearly anti-parallel arrangement of the dipoles in neighboring trimers, as apparent in Fig. 1d, was the key factor driving the second level of assembly into this hollow spherical structure.\(^{17}\) In the present study, we compared the kinetic accessibility of the snub cube structure for three different \( \theta \) values over the range from 0\(^\circ\) to 10\(^\circ\), in which this structure is the global minimum on the energy landscape.

Although the basin-hopping global optimization method relies upon a hypersurface deformation,\(^{36,37}\) which removes the barriers on the potential energy landscape, the success rate of this method in finding the global minimum reflects the complexity of the landscape, which would have some impact on the kinetics. It is noteworthy that a series of basin-hopping steps do not correspond to a physical dynamical process. As \( \theta \) assumed a non-zero value, an indication for reduced complexity and improved kinetics was apparent in a significant enhancement of the success rate for the basin-hopping global optimization method to find the snub cube structure as the global minimum on the potential energy landscape within a certain pre-fixed number of basin-hopping steps. When identical sets of 20 random starting configurations were considered for half a million basin-hopping steps, the success of finding the global minimum was only 5\% for \( \theta = 0^\circ \) as opposed to 100\% for both \( \theta = 5^\circ \) and \( \theta = 10^\circ \). The mean first encounter times differed only by approximately 4\% between \( \theta = 5^\circ \) and \( \theta = 10^\circ \) – not significant enough for comparing their kinetic accessibility conclusively.

In order to draw a comparison of the hollow spherical structures for different \( \theta \) values in terms of their kinetic accessibility when the underlying energy landscape is sampled at a non-zero temperature, we carried out Monte Carlo (MC) simulations. In a given MC run, the reduced temperature \( T^* \), defined by \( T^* = k_BT_\text{YM} / r_\text{YM} \) being the Yukawa contact potential chosen as the unit of energy, was gradually lowered. In the context of emerging structural hierarchy, single-particle Monte Carlo moves for the elementary building blocks were known to be inadequate.\(^{16}\) The dominant pathway for the hierarchical self-assembly into a structure topologically equivalent to the snub tetrahedron for \( N = 12 \) and \( \theta = 10^\circ \) was found by means of a rare event simulation technique to proceed stagewise via the formation of trimers.\(^{17}\) It was therefore reasonable to anticipate that a staged assembly pathway would most likely be followed for the emergence of structural hierarchy in this case. We thus performed Monte Carlo simulations with the trimers formed at the first level of the assembly, and carried out single-particle moves treating these secondary units as rigid bodies. The secondary units with dipoles in planar flux-closure arrangements, as shown in Fig. 1(b), were distinct for each value of \( \theta \). The distinct structural features are tabulated in Table 1. 10 independent Monte Carlo simulations were carried out with \( N_t = 8 \) rigid secondary units for all three \( \theta \) values, each within an identical spherical container. The data shown in Fig. 2 are corresponding to the spherical container of radius 2.5 in the reduced unit, while the radius of gyration is 1.405 for the snub cube structure corresponding to the value of \( \theta = 10^\circ \). The formation of a hollow spherical structure was monitored with the relative shape anisotropy parameter \( \kappa^2 \) as shown in Fig. 2, and was also confirmed by visual inspection.

<table>
<thead>
<tr>
<th>( \theta )</th>
<th>0(^\circ)</th>
<th>5(^\circ)</th>
<th>10(^\circ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_{cc} )</td>
<td>0.963</td>
<td>0.955</td>
<td>0.949</td>
</tr>
<tr>
<td>( r_{dd} )</td>
<td>0.667</td>
<td>0.637</td>
<td>0.612</td>
</tr>
<tr>
<td>( \varphi )</td>
<td>30.92(^\circ)</td>
<td>30.42(^\circ)</td>
<td>29.67(^\circ)</td>
</tr>
</tbody>
</table>

![Fig. 2](View Article Online)
reasonable range; we indeed observed the formation of the snub cube structure up to a radius of 5 in the reduced unit.

The free-energy profiles for the formation of the hollow spherical structures, as shown in Fig. 3, were found to be consistent with the gradual increase in their kinetic accessibility as \( \theta \) was varied from 0° to 10°. The free-energy profiles were obtained by the umbrella sampling technique, where the order parameter \( \kappa^2 \) was used as the reaction coordinate. For each order parameter value, the umbrella sampling simulations were undertaken around the respective temperatures at which the formation of the hollow spherical structures was first observed upon cooling. The biased Monte Carlo simulations were carried out with rigid secondary units, distinct for each order parameter value, with single-particle moves. The self-assembly of the colloidal particles into the snub cube structure, which is of octahedral symmetry, is expected to incur an entropy cost. Fig. 3 shows that the snub cube structure was indeed the global minimum on the free energy profile for all three \( \theta \) values, despite the entropy cost. It is also evident in Fig. 3 that the free energy barrier to the formation of the snub cube structure gradually decreased as the model parameter \( \theta \) was increased from 0°, thus leading to increased kinetic accessibility.

Since the aforementioned series of Monte Carlo simulations were performed with the rigid secondary units, these simulations could capture only the second stage of assembly. In order to garner a complete picture, we also performed Monte Carlo simulations of the primary building blocks for all three \( \theta \) values. Using the virtual-move Monte Carlo (VMMC) algorithm, we carried out 10 independent VMMC simulations of \( N = 24 \) colloidal magnetic particles within a fixed spherical container for each of the three \( \theta \) values. As the temperature \( T^* \) was gradually decreased for the VMMC simulations, the formation of the snub cube structure demonstrating a remarkable two-level structural hierarchy was observed for \( \theta = 5° \) and 10°, as revealed by the evolution of the order parameter \( \kappa^2 \) (Fig. 4). The desired snub cube structure was formed with a 30% success rate for \( \theta = 5° \) and with a 60% success rate for \( \theta = 10° \). However, for \( \theta = 0° \), the snub cube structure was not obtained in any of these simulation runs. In fact, we did not observe even the formation of the requisite number of trimers (i.e. 8 trimers for a 24-particle system) in a single instance for \( \theta = 0° \), implying that the first stage of the assembly was not completed correctly in this case. The results of the VMMC simulations thus unequivocally provided evidence that the hollow spherical structure was most kinetically accessible for \( \theta = 10° \). A spherical container of radius 25 in the reduced unit was used for the data in Fig. 4. For the representative case of \( \theta = 10° \), additional data, not shown here, confirmed the formation of the snub cube structure with spherical containers up to the radius of 4 in the reduced unit. It is apparent that upon cooling the systems the relative shape anisotropy \( \kappa^2 \) undergoes a rise before it falls rather sharply to values close to zero corresponding to the formation of the snub cube structure. It is plausible that entropically favorable open bowl-like structures, which are also stabilized by anti-parallel arrangements of the dipoles in the neighboring trimers, tend to form first upon gradual cooling before the closed snub cube structure was formed, resulting in such a non-monotonic behavior of \( \kappa^2 \).

The hollow spherical structure, despite being thermodynamically favorable, proved elusive for \( \theta = 0° \). While a staged pathway was most likely, it was striking that the first stage of

![Fig. 3](image-url) The free energy profiles as a function of the order parameter \( \kappa^2 \) for finite-size clusters of \( N_1 = 8 \) rigid trimers for three different \( \theta \) values. The free energy profiles were obtained by performing umbrella sampling simulations at different reduced temperatures: \( T^* = 0.11 \) for \( \theta = 0° \) (black), \( T^* = 0.08 \) for \( \theta = 5° \) (blue), and \( T^* = 0.07 \) for \( \theta = 10° \) (red). Colored rings highlight metastable minima on the free energy profiles; the corresponding structures are shown.

![Fig. 4](image-url) The relative shape anisotropy \( \kappa^2 \) as a function of the reduced temperature \( T^* \) in virtual-move Monte Carlo simulations of \( N = 24 \) colloidal magnetic particles for two different \( \theta \) values. The data presented are average values calculated from the simulation runs for which the hollow spherical structures are successfully formed.
the self-assembly into the trimers could not be completed in terms of forming requisite number of trimers in our VMMC simulations. This observation, in particular, led us to analyze the energetics of the snub cube structure, which shows a two-level structural hierarchy, and compare the energetic stabilities gained at each level of the assembly for all three $\theta$ values, as shown in Table 2. The analysis revealed a remarkable correspondence between the relative energetic stabilities gained at successive levels of the assembly, as shown schematically in Fig. 5, and the kinetic accessibility of the hollow spherical structure as the model parameter $\theta$ was varied. It is clearly evident that the thermodynamic driving forces arising from the energetic stability gained through the formation of a trimer at the first level of the assembly increased as $\theta$ increased from $\theta = 0^\circ$ to $\theta = 10^\circ$. This resulted in the formation of increasingly more stable secondary building units. The second stage of assembly brought together eight such secondary building units to form the snub cube structure. The difference in the potential energy between the snub cube structure and eight independent trimers, which appears in the column denoted by $\Delta E_{12}$ in Table 2, accounts for the energetic driving force behind the second stage of the assembly. It thus follows that the energetic driving force for the second stage of the assembly gradually decreased as $\theta$ was varied from $\theta = 0^\circ$ to $\theta = 10^\circ$. The energetic stability was drawn from nearly antiparallel arrangements for pairs of dipoles in neighboring secondary units emerging from the second stage of the assembly.

Table 2. The energetics of the two-level hierarchical self-assembly for three different values of the model parameter $\theta$. In each case, $E_1$ stands for the potential energy of the global minimum for $N = 3$ colloidal magnetic particles, $E_2$ is the potential energy of the global minimum corresponding to the hollow spherical structure, and $\Delta E_{12}$ the difference in potential energy: $\Delta E_{12} = E_2 - 8E_1$ denoting the energetic stability gained from the second stage of assembly.

<table>
<thead>
<tr>
<th>$\theta$</th>
<th>$E_1$</th>
<th>$E_2$</th>
<th>$\Delta E_{12}$</th>
</tr>
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<tbody>
<tr>
<td>$0^\circ$</td>
<td>-31.294</td>
<td>-275.225</td>
<td>-24.873</td>
</tr>
<tr>
<td>$5^\circ$</td>
<td>-33.761</td>
<td>-304.189</td>
<td>-18.101</td>
</tr>
<tr>
<td>$10^\circ$</td>
<td>-40.395</td>
<td>-336.721</td>
<td>-13.361</td>
</tr>
</tbody>
</table>

Note that the formation of the closed snub cube structure would incur a reduction in entropy. The decrease in energetic driving force for the second stage of assembly as the parameter $\theta$ increases therefore also accounts for the corresponding decrease in the temperature at which the formation of the snub cube structure was first observed as the finite system was gradually cooled in both MC (Fig. 2) and VMMC (Fig. 4) simulations.

The striking correspondence between the energetics and kinetics of the self-assembly into a two-level structural hierarchy, as revealed here, called for an explanation. For the success of programmed self-assembly into a target structure, the microscale colloidal particles need to negotiate the so-called kinetic traps, which arise from the presence of metastable “wrong” structures in the free-energy landscape. Reversible association allows for facile annealing of defects, and hence removal of kinetic traps. Such reversibility is best achieved here at the expense of relatively weak thermodynamic driving forces for the second stage of assembly. In the present case, the hierarchical self-assembly followed a staged pathway, in which the trimers formed in the first stage of assembly served as the secondary building blocks in the course of the second stage of assembly while retaining their integrity. Such a pathway involved concerted movements of the colloidal particles over the course of the second stage of assembly, incurring an entropy contribution to the free energy barrier. The more energetically stable the secondary building blocks, the higher would be the energy penalty for any alternative pathway involving the loss of integrity of the secondary building blocks once they are formed, making such a pathway highly unlikely. A strong energetic driving force for the first stage of assembly therefore not only facilitates this stage from a thermodynamic consideration, but also promotes concerted movements in the next stage despite the entropy cost involved, and thus favor a staged assembly pathway from the perspective of the free energy barrier.

It follows from the results presented here that a hierarchy of interactions is crucial for a staged assembly pathway to structural hierarchy. Such a hierarchy of interactions allows us to consider also a staged disassembly into the secondary building blocks and their reassembly, as shown in Fig. 6 for the case of $\theta = 10^\circ$, by the application of a weak external magnetic field in the first place and then turning it off. The strength of the magnetic field was so chosen that it could open up the snub cube structure while retaining the integrity of the trimers. For the data shown in Fig. 6, $B = 0.25$ at $T^* = 0.07$. This demonstration suggests that a weak magnetic field could, in principle, be also
exploited to induce staged disassembly of any “wrong” structure obtained from the second stage of assembly. The ease of disassembly that such an operational hierarchy of interactions implies may have implications for disassembly observed for viral capsids.

In the present study we employed a variety of computational methods to examine the kinetic accessibility of a series of hollow spherical structures, each displaying a remarkable two-level structural hierarchy, self-assembled from charge-stabilized colloidal magnetic particles. For these designer building blocks, which were modeled after recently synthesized colloidal magnetic particles, a model parameter was varied across the series, resulting in a gradual change in the energetics. We found that for a staged assembly pathway, the structure, which derived the strongest energetic stability from the first stage of the assembly and the weakest from the second stage, was most kinetically accessible. We accounted for such a striking correspondence and the weakest from the second stage, was most kinetically stable from the first stage of the assembly for a staged assembly pathway, the structure, which derived the pathway leading to it has the lowest free energy barrier.39

We further note that it is quite likely that an experimental scenario should be distinguished from those, where thermodynamic control or kinetic control prevails so that a structure is observed either because it is the most stable state or because the pathway leading to it has the lowest free energy barrier.39

Global optimization

We used the basin-hopping (BH) global optimization method,36,37 as implemented in GLOSP, a program for Global Optimization for Structure Prediction developed-in-house, to identify the global minimum of potential energy landscape and to calculate mean first-encounter times. A hypersurface deformation, which results in a reduced configuration space spanned by all the local minima of original landscape, underlies this method. This reduced configuration space is then explored by proposing random steps, followed by local geometry optimization to a minimum. The limited-memory Broyden–Fletcher–Goldfarb–Shanno algorithm was employed for local minimization.42 The proposed step from the current minimum is accepted or rejected by the application of the Metropolis criterion, using the relative energies of the two minima and a fictitious temperature. In our implementation of the method, the local minimization was performed using analytical gradients; an angle-axis representation was used for the rigid-body rotational coordinates due to certain numerical advantages associated with such a representation in the context of geometry optimization.42

For each set of model parameters with a distinct value of \( \theta \), twenty independent BH global optimization runs were performed, undertaking \( 0.5 \times 10^6 \) basin-hopping steps from an identical set of random initial configurations. The BH step at
which the global minimum was first identified for each run, the first-encounter time, was recorded to calculate a mean first-encounter time for each \( \theta \).

Monte Carlo sampling

Monte Carlo simulations of a number of systems, each containing \( N = 8 \) rigid building blocks, were performed in the canonical ensemble, employing a constraining radius to avoid evaporation especially at high temperatures. For each set of model parameters with a distinct value for \( \theta \), 10 independent MC runs were undertaken. In a given run, starting from a random initial configuration, the system was gradually cooled. The number of MC steps carried out increased from \( 10^7 \) at high temperatures to \( 2 \times 10^8 \) at low temperatures; the first half of the MC run at every temperature was used for the system to equilibrate. Each MC step involved \( N \) single-particle moves in both translational and rotational coordinates, where the step sizes were adapted to achieve a target acceptance ratio of 0.45. For the MC simulations, the reduced temperature \( T^* \) was used.

The formation of the spherical structure was monitored by calculating the relative shape anisotropy \( \kappa^2 \) for the distribution of the particles in the system, which is given by: \( \kappa^2 = \frac{b^2 + (3/4)c^2}{R_g^2} \).

where \( R_g \) is the radius of gyration, \( b \) the asphericity, and \( c \) the acylindricity: \( R_g^2 = \lambda_2^2 + \lambda_y^2 + \lambda_z^2 \), \( b = (3/2)\lambda_2^2 - (1/2)R_g^2 \) and \( c = \lambda_y^2 - \lambda_z^2; \lambda_2^2 \leq \lambda_y^2 \leq \lambda_z^2 \) are the principle moments of the gyration tensor \( S \).

In order to compute the free energy profiles, we employed umbrella sampling, using the relative shape anisotropy \( \kappa^2 \) as the order parameter. To this end, a series of Monte Carlo simulations of 8 rigid trimers were carried out employing additional biasing potentials, which were harmonic functions, centered on successive values of the order parameter. The biasing potentials ensured efficient sampling over several partially overlapping windows, spanning the range of the order parameter of interest. The unbiased probability distribution was then obtained using the weighted histogram analysis method. Finally, the free energy difference along the chosen order parameter was evaluated from this unbiased probability distribution, taking the hollow spherical structure, corresponding to \( \kappa^2 \approx 0 \), as the reference.

Virtual move Monte Carlo

We employed the virtual move Monte Carlo (VMMC) algorithm, as implemented in PaSSion, a Package for Soft Matter Simulation developed in-house, following a recent prescription. The VMMC algorithm prescribes cluster moves. It is necessary to consider cluster moves in the context of emergent structural hierarchy. Such an algorithm helps to overcome the non-physical kinetic traps that are encountered during MC simulations employing single-particle moves, leading to an enhanced sampling of the equilibrium distribution.

We carried out VMMC simulations in the canonical ensemble for finite-size clusters of \( N = 24 \) particles, mostly contained within a spherical volume of radius 2.5 in the reduced unit. For each set of model parameters with a distinct value for \( \theta \), 10 independent VMMC simulations were performed starting from random initial configurations. For a given run, the system was gradually cooled. As the reduced temperature \( T^* \) was decreased, the number of VMMC cycles undertaken was increased from \( 10^8 \) at high temperatures to \( 10^9 \) at low temperatures. Each VMMC cycle involved \( N \) translational moves or \( N \) collective rotational moves; the first half of the run at every temperature studied was used for equilibration. The step sizes proposed within the translational and collective rotational VMMC moves were adjusted to secure an average acceptance ratio of 0.45. For the VMMC simulations, the reduced temperature \( T^* \) was also given by \( T^* = \frac{k_B T \epsilon V}{\kappa_g} \).

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council of the UK via EP/M506461/1 and the University of Birmingham. The datasets presented here are available from the corresponding author on request.

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