I would like to thank the referees for their very careful and thoughtful evaluation of my work.
They raise mainly useful points and focus in particular on the relationship of the method to
other approaches (MD, MC, etc.) and how they can be combined and/or reconciled.

This is also a relationship that I have been considering myself for some time and although I
do not have any all-encompassing answers, there are some potential routes ahead that could
be usefully discussed as I am sure many readers from the molecular dynamics community will be
wondering the same things.

If I have understood correctly, it would appear that reviewer-1 views the method as a "wrapper"
that is to be applied over/around conventional atomistic approaches. This is indeed a possible
route along which the current work could develop but not a position that it has yet attained.
(For many of the reasons identified by the referee).

Firstly, I should clarify that if the sizes and shapes of the multi-level objects have been
chosen correctly, then, left to itself, the current method will do nothing (ie: no object will
move) and if there is motion, then that indicates that some bump-radius at some level is too
large.

It is left entirely up to the user how things should move, which is done by implementing some
custom code in what is called the "driver" routine. Now of course, this code could be
molecular dynamics, Lagrangian mechanics or Monte Carlo, or as implemented in the collision
examples, a simple displacement of a single object.

The problem with implementing anything complicated in the driver routine is that at some
point, the current method will start to interfere with the (common) coordinates and if the
driver code requires consistency in terms of distances and derived potentials, forces and
velocities, then all the problems envisaged by the referee will arise.

The simplest approach to this problem is to attach a warning notice stating that it cannot
be used in combination with any method that requires global internal consistency. The only
route I can see to avoid this incompatibility would be through a Monte Carlo like approach
in which the displacements made at all levels are treated as a (semi) random Monte Carlo
move of the system.

A second path to resolve the dilemma might be through a variation of Gaussian elastic
networks, as suggested by referee-1. This indeed is the path I am currently investigating
by using the method in conjunction with a potential based network. However, elastic
networks require a fixed topology that cannot be expected to remain intact across the
large (driven) displacements envisaged for the current method.

I hope this discussion provides some answers to the general questions raised by the referees
and on the assumption that it will be useful to others, I have expanded it into a new
section in the Discussion where I hope it will put the current method in the wider context
of other molecular simulation methods.

Reviewer #1

Recommendations:

>Define the type of simulations that may use the collision detection scheme more precisely.
Then show if the current collision detection adheres
>to the simulation model with some explicit results (e.g. for the purpose of sampling the configurational space, compare a simulation based on the child
>objects alone with one where the parental objects are used).

>
Results were presented for a range of parameters moving from a low to high weight on the hi
gher level object repulsion.
However the high level repulsion was never reduced to zero (as the referee suggests). Th
is was avoided because, without the protective
shell of the parent, the bonds between atoms are flexible enough to allow two bonded pairs
to transiently pass through each other resulting
in interpenetrating chains, even though these still preserve their steric and average bond
lengths. A comment to this effect has been added
to the text. (In the Results section describing chain collisions).

>Define more clearly if the speed up in collision detection should in principle be lossless
, in that the parameters should only affect the
>precision of the results, but not the fundamental outcomes compared to simulation of the l
owest level objects.
>
As should now be clear from the general discussion above, the addition of a repulsive term
to higher level objects
will fundamentally affect the behaviour of the lower objects. While added speed is a bene
fit, the main purpose
of the higher level objects is to ’protect’ their ’children’ from the disruptive effect of
other impinging objects.

>Add a discussion of what changes need to be made, if this technique was to be used in more
commonly used simulation techniques such as MD or
>MC with attractive potentials.
>
This should now be covered by the additional discussion section (along the lines outlined a
bove).

>Add a discussion on advantages and disadvantages of allowing parental objects to change th
e paths of the child nodes, possibly suggesting any
>alternatives to the current implementation.
>
The discussion has been extended to cover this aspect also.

>Some references that may aid the suggested discussion:
>
The suggested references have been very useful and a few have now been cited.

Minor comments:

Almost all minor comments have all been corrected or clarified. (Details below)

Minor comments:

> Page 3 â\200\230single sphereâ\200\231 - in fact some patchy colloids systems may giv
e interesting results for the behaviour of larger systems of biomol
> ecules, see for example [Vacha et. al., GÃ¶gelein et. al.]
>
Now mentioned later

> page 4 â\200\230.. on the â\200\235worldâ\200\235 coordinate frame is less relevant â
\200\231. Even though an arbitrary coordinate frame may be less relevant and is
> certainly less elegant, such an approach may be more efficient computationally due to it
s simplicity - to make any conclusion
> s, this should probably be tested.
>
As this is only a comparison to a constraint in computer games, no change was made

> page 5 - pipes with hemispherical end-caps has been used before to model parts of pr
otein structures, perhaps cite [Vacha et. al.]
>
Now cited.

> page 6 - a

> schematic drawing may help to explain the couplings of different levels of the hiera
rchy in the simulation.
>
While the levels can be represented in a diagram, I could not see any way to make a clear p
icture of their dynamic relationships.

> Section 2
> is very detailed and long - perhaps a focus on the most important advances (ellipsoi
d calculations) may show the importance
> of these results more effectively; the other parts could be available through via su
pplemental material.
>
Some or all of this material may be moved to Supplementary Material (following discussion w
ith the Editor).

> On the other hand, a description of the simulation scheme itself seems to missing [on low
est level object alone].
>
As explained in the general comments above and in the new section in the Discussion, there
is no simulation scheme, just
displacement and rotation in response to bump and bond violations.

> page 27 - typo â\200\230these constructs was engineeredâ\200\231
>
Fixed

> page 33, section 3.2 - details on how the distance constraints are added to the simul
ation are not given;
> please consider adding a section in the methods to describe this.
>
A short section has been added to the Methods covering both bonds and links which are imple
mented by the same code.

> page 34, section
> 3.2.1, last paragraph - it is unclear which protein is referred to in this last sect
ion
>
The FlhA protein has been clarified (as a bacterial flagellum protein) and is now mentioned
in a separate
paragraph from the rhodopsin application.

> page 36, caption
> figure 5 which PDB is used for the calculations?
>
PDB code added. (1GZM)

> page 39, Figure
> 7 - what do the red and blue colours mean?
>
Clarified as the models from the two different starting configurations.

> page 41 -
> â\200\234...loss of fine detailâ\200\235 - perhaps the current scheme also does not
fully solve this problem, due to the way it may inter
> fere with a simulation model (see above).
>
I only said "seeks to circumvent". I don’t think this implies a full solution.

Reviewer #2

>While I think that the structure refinement test cases are interesting, I am not entirely
sure which biological processes
>the collision simulations are supposed to mimic. Due to their interaction with an aqueous
environment, high-speed collisions
>of proteins (outside maybe some mass spectrometry techniques) seem to me unlikely to have
any biological relevance.

>
References to "speed" describe the speed of the simulation in terms of Angstroms moved per time step
but as the method does not specify any absolute time scale the correspondence to real time is arbitrary.
Although not attempted in the paper, an absolute time/speed might be estimated in terms of the diffusion
rate of proteins both in gas and aqueous phase and I would guess that the simulated collisions lie
closer to the gaseous end (as assumed by the referee). However, the purpose of the collisions was
to test how well the higher level objects were able to buffer their children (and their children, etc.),
not to mimic a biological process. A footnote to clarify this has been added at the first mention of the term

>In my opinion, few sentences could be added to the discussion as to how to model solvent interactions on a higher
>hierarchical level. Maybe a friction process corresponding to diffusion of different shapes or surface area etc.
>
As outlined above, a more general section has been added to the Discussion on the relationship of the current
work to existing dynamics methods. This mentions Brownian and Lagrangian approaches (both of which typically
incorporate a friction term) which is related to implicit solvent modelling.