```
39c39
< use of a bounding-box construct.  This is a box in which a group of points are contained
---
> use of a bounding-box construct.  This is a box in which a group of points is contained
56c56
< they too are elongated.   In this work, the original method based on sphere’s is
---
> they too are elongated.   In this work, the original method based on spheres is
87,90c87,89
< straight section of pipe with hemi-spherical end-caps).   The use of the original box
< registered on the coordinate frame was avoided for reasons mentioned above and without
< this registration, any advantage is lost in calculating the overlap between arbitrarily
< orientated rectangular boxes.
---
> straight section of pipe with hemi-spherical end-caps).  Both spheres and tubes have been
> used widely in coarse-grainned modelling, with the latter being a good representation
> for an RNA stem-loop or an \AH\ or even a general peptide \cite{VachaRet14}.
139c138,143
< dependent on the displacement of the children as in high speed collisions, any
---
> dependent on the displacement of the children as in high speed\footnote{
> The term "speed" is used throught to refer to the step size per cycle of any
> geometric transformation.   As the stepsize is not related to any physical
> process, it does not have any implications for biological macromolecules.
> }
> collisions, any
208c212
< was accommodated in the refinement of ideal distances and angles.
---
> was accommodated in the choice of ideal distances and angles.
18c18
< the high-level objects are the bounding-volvumes for their children.
---
> the high-level objects are the bounding-volumes for their children.
166c166
< is itself recursive and id called on the children of any clashing children that it encoun
ters.
---
> is itself recursive and is called on the children of any clashing children that it encoun
ters.
171c171
< which are dealt with by the {\tt touch()} routine.i (Box 3).
---
> which are dealt with by the {\tt touch()} routine (Box 3).
423c423
< The error is typically less than 0.001\%.
---
> The error is typically less than 0.1\%.
0a1,46
> \section{Bonds and links}
>
> The maintenance of bond and link lengths is very similar and the two routines,
> \TT{bonder} and \TT{linker}, that implement this task will be considered together.
> Both recursively traverse the object tree looking for things to fix.
>
> \subsection{\TT{bonder}}
>
> \subsubsection{Bond lengths}
>
> The \TT{bonder} simply checks if an object has any assigned bonds and if so, uses
> the utility {\tt part2cells()} to push them towards their assigned bond length.
>
> \subsubsection{Nucleic acid exceptions}
>
> Exceptions need to be made when bonding tubes in nucleic acids, which occur both at
> the secondary structure level as basepairs and the domain level
> as segments of double helix.
>
```

```
> For basepairs, if these are part of a double helix, their 'bond-length' is the distance
> between their mid-points (object centre) which is refined to an ideal base-stacking separ
ation.
> Outside a base-pair, say in a loop region, the 'secondary structure', like a loop in a pr
otein,
> can contain multiple nucleotides and no bond length is refined.
>
> At the domain level, double-stranded DNA segments will always be bonded end-to-end
> at a specific distance that allows the helix to run continuously from one segment to
> the next.   On the other hand, when the segment is an RNA stem-loop, the chain can enter
> and exit the same end of the tube or, with an insertion, even through the side.
>
>
> \subsection{\TT{linker}}
>
> \subsubsection{Breaking links}
>
> The \TT{linker} follows the same basic outline as the \TT{bonder} but with the main
> difference that links can be made and broken during the simulation.   The dynamic creatio
n
> of links is not a built-in feature of \NAME\ and must be provided through the user-suppli
ed
> \TT{driver} routine.   However, if a link becomes over stretched, it is automatically des
troyed in
> the \TT{linker}.    The default length of a link is the bump diameter and the default ext
ension
> is 50\%, beyond which the link breaks.
>
> \subsubsection{Preset link lengths}
>
> Local links are automatically created for standard secondary structures,  not only betwee
n the H-bonded
> connections in the \AH, i---i+3 and i---i+4, but also between the i-1---i+1 separation al
ong a \Bs.
> However, the non-local links between strands in a \BS\ must be user defined.
17c17
< motion to propel two identical objects into each other.   To avoid a direct "head-on"
---
> displacement to propel two identical objects into each other.   To avoid a direct "head-o
n"
25c25,30
< To investigate the the contribution of the soft repulsion component of higher level objec
ts,
---
> The model was initially tested with only a hard repulsion at the atomic level.
> However, without the protective shell of their parent, the bonds between atoms were flexi
ble enough
> to allow bonded pairs to transiently pass through each other resulting
> in interpenetrating chains, even though these still preserved their steric and average bo
nd lengths.
>
> To investigate the contribution of the soft repulsion component of higher level objects,
116c121
< Collisions between these constructs was engineered as above with the coordinates
---
> Collisions between these constructs were engineered as above, with the coordinates
126c131
< for the equivalent sized "cubic" chains of the previous subsection ($hard = 1.0$, $soft =
 0.1$).
---
> for the equivalent sized Hilbert chains of the previous subsection ($hard = 1.0$, $soft =
 0.1$).
11c11
< mutations.  (See \cite{TaylorWRet13} for a review).
---
> mutations.  (See ref.\cite{TaylorWRet13} for a review).
43,45d42
< The method was also applied to a protein of unknown structure, FlhA, which is
```

```
< a component in the type-III secretion system and thought to form a ring
< of nine proteins (\Fig{flhA-model}).
47c44
< As an exercise in structure prediction, the helices were allowed to move
---
> As an exercise in structure refinement, the helices were allowed to move
55a53,56
> The method was also applied to a protein of unknown structure, FlhA: which is
> a core component in the bacterial flagellum motor (in its type-III secretion
> sub-system) and thought to form a ring of nine proteins (\Fig{flhA-model}).
>
94c95
< $b$) The highest scoring rhodopsin model is superposed on the native structure.
---
> $b$) The highest scoring rhodopsin model is superposed on the native structure (PDB code
{\tt 1GZM}).
106c107
< prediction methods produce a "clover-leaf" structure reminiscent of tRNA, and like that m
olecule, its
---
> prediction methods \cite{HofackerIL03} produce a "clover-leaf" structure reminiscent of t
RNA, and like that molecule, its
197a199,201
> The blue dots mark models that started from the ’default’ secondary structure layout
> (Figure 6a) and the red dots started from the alternative arrangement with two stemloops
> (top and right) in swapped positions.
2a3,10
> The behaviour of the current method has been investigated using two distinct
> approaches: in the examples involving collisions, a constant driving displacement
> was applied to a single high-level object (to force it to make contact with
> another object), by contrast,  in the examples involving constraint satisfaction the
> displacements were instead applied to the lowest level objects ("atoms").  In the first
> case, the response of the lower level objects to maintain structural integrity was monito
red
> whereas in the second, the resulting rearrangement of the higher levels objects was of in
terest.
>
57c65
< a binding event would stil rely on external knowledge of the residues involved.
---
> a binding event would still rely on external knowledge of the residues involved.
79c87
< be transfered to another assembly or a large multi-domain chain may be cleaved.
---
> be transferred to another assembly or a large multi-domain chain may be cleaved.
82a91,123
>
> \subsection{Relationship to other methods}
>
> Given a model in which all the constraints have been chosen well to avoid bond
> or bump violations at all levels, then in the absence of any user applied displacements,
> the behaviour of the current method is to do nothing.
> It is left entirely up to the user how things should move, which is done by implementing
> custom code in what is called the "driver" routine.    This code can be either very
> simple, such as the few lines of code needed to implement the collision displacement or
> quite complicated such as the code to apply the distance constraints described in the
> Results section.
>
> Extrapolating this progression, the constraints could be applied in the form of a potenti
al and
> indeed a potential could even be applied to many pairs of atoms \cite{PerioleXet09}.   Th
e next
> obvious step would be to implement full molecular dynamics, Lagrangian mechanics or Monte
 Carlo.
> However, the problem with implementing anything complicated in the driver routine is that
 at some
> point, the current method will start to act on the (common) coordinates and if the
> driver code requires consistency in terms of distances and derived potentials, forces and
```

> velocities, then a multitude of problems will arise.
>
> The simplest approach to this problem is to attach a warning notice stating that \NAME\ cannot
> be used in combination with any method that requires global internal consistency. The only
> route that might avoid this incompatibility would be through a more stochastic 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 problem might be through a variation of Gaussian elastic
> networks, However, elastic
> networks require a fixed topology that cannot be expected to remain intact across the
> large (driven) displacements envisaged for the current method.
>
> These possible developments will be reconsidered at a later time as it is currently
> unclear, not only how a consistent potential could be applied but also how potentials
> on different levels should interact.