Haptic Rendering of Molecular Conformations

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Abstract—**Current computational simulation are capable of producing enromous amounts of data. Complete understanding of their features presents a challenge even if very sophisticated visualization techniques are deployed. Computational analysis of conformational behaviour of biologically active compounds represents such simulation. We investigate methods how haptic rendering may contribute to better and faster understanding of the simulation results. This paper presents current progress in our research.**

I. Molecular Flexibility and Conformational Behaviour

Many molecules exhibit an important chemical property — flexibility. Biological activity of large molecules is directly related to their flexibility. The flexibility can be described in terms of *conformational behaviour* of the molecule. Undergoing the behaviour, the molecule changes its shape (*configuration*) only, no chemical bonds are either created or broken, as well as the absolute configuration on atoms (or other chiral centres) does not change. Roughly speaking, internal potential energy of the molecule is a function of the configuration, therefore, in general, not all the configurations are favoured equally. By *conformations* we mean local potential energy minima, i. e. the configurations that are more stable than the others. Then the conformational behaviour is the process of traversing among conformations via transition states.

Various computational methods of discovering conformations of a molecule and describing its conformational behaviour were proposed. It is beyond the scope and purpose of this article to provide even an overview. In our application we use results of the Cicada family of programs performing heuristic search of conformational space [1]. They produce a graph of interconnected conformations and *transition states*, i. e. saddle points in terms of potential energy. Two edges of the graph that share a common transition state represent a traversal path of minimal energy barrier between a pair of conformations.

II. Haptic Model

In this section we focus on the description of the model being deployed in our application and its mathematical aspects. Various implementation issues like program structure, performing exhaustive computation off-line etc. are discussed in detail in Sect. III.

A. Virtual Energy and Haptic Steering

We build the model on the principle of *haptic steering,* i. e. the user is provided with a virtual tool bound to the haptic device. With the tool she is able to interact with the virtual model. The interaction enforces changes in the virtual world that incorporate changes of the potential energy of the model. According to well-known physical laws the work, i. e. the energy produced or consumed by a system, can be computed by integrating force interaction along a path. Hence, the force feedback can be computed as a spatial gradient of the energy.

The model, despite depicting a micro-world scene, should behave intuitively in terms of macro-world physical laws in order to be convincing. In our everyday life we witness consequences of the second thermodynamic law — spontaneous energy minimization. Any natural system without an external intervention does not stay in an instable state, it follows its potential energy gradient until reaching a local minimum. Therefore, in order to achieve an intuitive, convincing behaviour of the virtual model, we have to simulate the energy minimization. For this purpose we introduce a concept of *virtual energy* that covers both the properties of the model we intend to render as well as physical properties that resemble a real-world object.

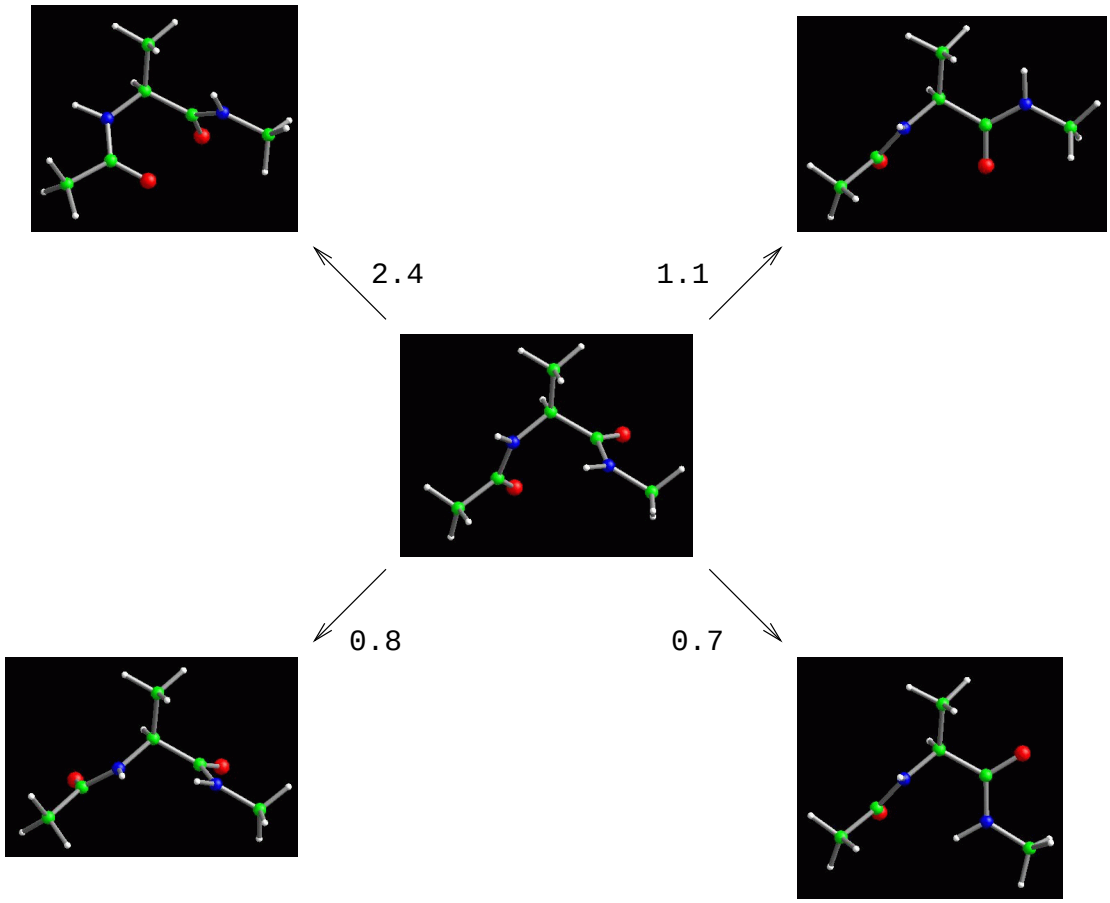

Fig. 1. Example conformation and four transition states of the alanine amino acid. The numbers show energy barriers (in kcal/mol)

B. Molecular Model Setup

The current implementation restricts the model to a chosen conformation and its surroundings, i. e. it spans upto the set of enclosing transition states. An example is shown in Fig. 1. We are able to compute an arbitrary point on a path between the conformation and a transition state. However, for the purpose of haptic interface, we have to cover the intermediate configuration as well. It is generally acceped as an affordable simplification that the conformational paths can be expressed in terms of *torsions*, i. e. twisting the molecule along a particular bond (or more bonds simultaneously) — this can be seen in Fig. 1.

Therefore, given position on the paths, we are able to construct a merged configuration[1] by averaging those twist angles.

The user is presented a van der Waals molecular surface (atoms are represented by spheres, overlapping in general, see Fig. 2) both in the haptic and graphical interface. A 3-DOF haptic device is attached to a virtual *probe*, an approximately water-sized sphere.

C. Energy and Force Computation

Virtual energy of this model depends on the probe position and the actual configuration of the molecule, and obeys the following rules:

- *Penetration of the surface by the probe is strongly penalized but not completely forbidden.* The interaction of the probe with the surface is the only way of enforcing a shape change, therefore the configuration change should be favoured. On the other hand, the amount of penetration is a direct and proven clue to the computation of force feedback, e. g. [2], [3], [4].

[1]It has to be emphasized that this merge is artificial, with no direct background in chemistry. Its purpose is building a continuous state space that has to be present in a haptic model. However, we are really interested in the precomputed conformational paths only.

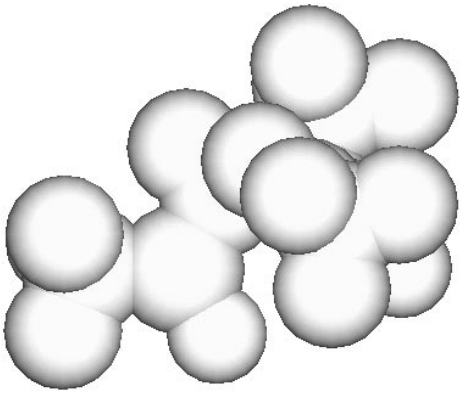

Fig. 2. Van der Waals surface of the alanine amino acid

- The configuration paths between the central conformation and the transition states are supposed to go through "valleys" of the true potential energy. Therefore *the precomputed paths are favoured in comparison to other configurations.* In addition, according to the input data structure we are given direct information on the potential energy on those paths only.
- Auxiliary terms that selectively penalize shift of atoms from their initial position (see [5]) are included. As a consequence *shape modifications close to the probe are easy to do* while the molecule is still fixed in space.

In each iteration of the interface driving loop we are given current coordinates of the probe. For the purpose of energy minimization, we treat it as a configuration constraint on the model.

The degrees of freedom of the model are expressed in terms of its free variables. Basically, there are two classes of them: positions on the precomputed conformation–transition state paths which represent the actual shape of the molecular model, and overall shift and rotation of the molecule defining an absolute position of the model in 3D space.

Given values of the free variables the shape of the molecule can be computed. The virtual energy follows the results of chemical calculation in case of paths between the central conformation and transition states, and is raised artificially (but coincidently with chemical expectations) to form barriers in areas between those paths. Then the molecule is located in 3D according to the second class variables. Now the probe-penetration and position-stabilizing terms can be computed as well.

The minimization starts from the last known state, i. e. free variable values. The energy minimization outputs a favoured shape and position. Those are shown directly by the graphical interface. As the energy contribution of the probe interaction with the surface is proportional to the resulting amount of penetration only, the force interaction can be derived from it directly.

From the user's point of view the molecular model resembles a slippery flexible object. It is possible to modify its shape by pushing the probe against it. Certain shape changes (those corresponding to the energy "valleys") are strongly prefered to others.

III. Implementation Issues

Let's focus on the computational requirements of the above model now. The computations can be classified as follows:

- *shape and position from the free variables*, (hence the force interaction) — fast enough to be computed inside the haptic interface loop (i. e., at 1–5 kHz rate),
- *energy minimization* — typically several hundreds shape computations, cannot be done inside the haptic loop.

Therefore we perform all the energy minimizations offline, on a regular grid of the probe positions. For the PHANToM device we use $200\times260\times85$ grid covering most of the device workspace. Moreover, different states (i. e., free variables vector) can be reached if the same probe position was approached from different previous states. Therefore we have to introduce another dimension (a *level*) to the grid, and keep track of transitions between the levels as well. Fortunately, level transitions are quite rare,

the grid size is usually increased by factor less than 2. With the given resolution the grid size is less than 10 M points. We do not need high resolution of the free variables (1 byte is enough), and a typical conformation of molecules we work with can be described with upto 20 variables. As the state space is continuous we can traverse the grid in 6 orthogonal directions only, keeping the information on level transition in 4 bits. Therefore we end up with maximal grid file size 250 MB, which is generally affordable.

At run time, we compute trilinear interpolation of free variables' values according to the probe position in the grid. The force interaction is computed from the interpolated values.

The prototype application consists of three programs: offline grid computation, force feedback device (PHANToM) driving, and visualization. The current implementation of the energy minimization uses the NAG numerical library, restricting us to the SGI platform by our license terms, but this is not a general concern. The PHANToM driving runs on a RT-Linux machine using a driver developed at our site[2]. The driver allows high refresh rates (over 10 kHz) of the haptic device as well as loading critical parts of the code into the Linux kernel. In this way a guaranteed response time of the device driving is achieved.

We use VMD — a publicly available chemical visualization tool[3] for the visual rendering of the scene. VMD is a complex tool, besides different visual representations of the molecular model it allows real-time measure of geometry properties (distances, angles, ...) etc. The system defines a network communication protocol (originally designed for interaction with the NAMD molecular dynamics program) that is used to feed it with geometry data from the force feedback driving.

IV. Conclusions and Future Work

We build a haptic model of a molecule and its behaviour in surroundings of a chosen conformation. The model is realistic in the means that it strictly follows results of chemical calculation in "valleys" of potential energy, i. e. the areas that are interesting to the user. The information on energy of the current state of the model is delivered via the force feedback. This proves to be a natural and intuitive representation of the quantity. As the model is highly interactive it provides an immediate insight on the behaviour.

The work presented in this article is a continuation of recent research [6], [5]. There are two principal improvements in the current implementation:

- The model follows real precomputed conformational paths instead of relying on bond flexibility.
- Most of the exhaustive calculation is performed offline. Therefore the interactivity of the model improved significantly.

In the future we are going to focus on two extensions of the current model. The first one is overcoming the restriction of the user's workspace to a single conformation. Once the user delivers sufficient force in a proper direction to overcome an energy barrier of a particular conformational path, the molecular model should "flip" to the other conformation. We believe this is a technical problem only as the energy function as defined in this article overlaps near transitions states not regarding from where the state is approached.

The second possible extension we can see is more challenging. In order to explore more complex molecules in their full features more haptic devices (maybe more DOF's per device) are required. However, straightforward increasing the number of DOF's increases the dimension of the precomputed grid file which is not affordable generally. Therefore we shall have to look for a smarter solution.

[2] `http://decibel.fi.muni.cz/phantom/`
[3] `http://www.ks.uiuc.edu/Research/vmd/`

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