# Laplace-filter enhanced haptic rendering of macromolecules

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## Abstract

The modeling of large biomolecular assemblies frequently requires a combination of multi-resolution data from a variety of biophysical sources. Several algorithmic solutions to this docking problem have been proposed which are usually based on the spatial cross correlation. In [1] it was shown that Laplace-filtering techniques can improve the docking performance of these algorithms. This note presents the implementation and first results of the Laplace-filter enhanced fitting into the interactive SenSitus program, which supports the docking by virtual reality (VR) techniques (3D-stereoscopic view and haptic rendering). This implementation has to consider the special needs of the interactive rendering strategy. We employ reduced models using vector quantization to achieve the required force update rate.

## 1 Introduction

Future advances in modern biology and medicine will depend on an understanding of fundamental cellular processes, most of which involve the actions and interactions of large bio-molecular assemblies [2]. To this end it is essential to determine their structure on an atomic level of detail, i.e. at a resolution of a few Å (=$10^{-10}m$). However, typically these complexes are solved by means of electron microscopy (EM) at medium- to low-resolution (10-30Å). Fortunately, their subunits (e.g. specific proteins) are usually known at atomic detail using X-ray crystallography. To infer the atomic structure of the large complexes one can build them from their subunits, i.e., by combining multi-resolution data from a variety of biophysical sources.

Several algorithmic solutions to this problem have been proposed [3]. The majority of the matching algorithms is based on the correlation coefficient [4, 5, 6] as a fitting criterion. Although successful, this approach of fitting the probe to the target suffers from the ambiguity of the correlation coefficient and is thereby not applicable to all problem settings [3]. The multi-resolution docking can also be done visually [7] by exploiting the shape similarity of the two objects. This approach allows an expert to take advantage of biochemical knowledge and it can be used even with very noisy experimental data. However, the docking by eye is inherently subjective and not fully reproducible.

The SenSitus [8, 9] program uses VR techniques to combine the advantages of both approaches while avoiding their shortcomings. It augments the interactive visual information with real-time force-feedback. This feedback force corresponds to the gradient of the cross-correlation coefficient and is exerted by a haptic device (see Fig. 1). While the force-feedback guides the user towards a better fitting location, the 3D visualization does allow for a simultaneous maximization of the shape similarity criterion by visual docking. Thereby the ambiguity problem of the correlation coefficient is alleviated. In Sec. 2 we briefly review the feedback-force calculation of SenSitus which involves vector quantization to speed up the calculation and to meet the real-time requirements of the interactive haptic rendering.

It is known that the simple correlation-based docking yields poor results when the resolution of the EM-data falls below ≈15Å [3]. In [1] it has been shown that the docking performance improves significantly when the correlation is not calculated from the spatial distribution but from the image un-

der the Laplace-filter. The Laplace-filter provides edge information i.e. introduces the distinction between interior and contour region. Again, a straightforward implementation of this idea into SenSitus is prohibited by the force-update rate required for a high quality haptic rendering (0.5-1kHz [10]). Therefore the vector quantization method has to be extended to Laplace-filtered maps, as discussed in Sec. 3. In Sec. 4 first results are presented.

## 2 Correlation based fitting and vector quantization

To fit the high-resolution structure into the low-resolution data the original SenSitus version performs the following steps:

- The high-resolution data are transformed into a density distribution $\rho_c$ by means of a Gaussian blurring. The resolution is lowered to match with the low-resolution EM-distribution $\rho_{\mathrm{EM}}$.
- To speed up the subsequent calculations the distribution $\rho_c$ is vector-quantized, i.e. a number $k$ of so-called code-book vectors, $w_i$, are calculated. Each code-book vector represents a region of the original data (the corresponding "Voronoi cell"). This is done using the Topology Representing Networks (TRN)-algorithm [11] [1]. Thus the distribution can be approximated by:

$$\rho_c(r) \approx \sum_{i=1}^{k} \delta(r - w_i) \qquad (1)$$

- Finally the quality of the fit is judged by means of the cross-correlation $C^\rho$. For a given rotation $R$ and translation $T$ the correlation is given by the following expression:

$$\begin{aligned} C^\rho(R,T) &= \int \rho_c(R,T,r) \cdot \rho_{\mathrm{EM}}(r) \mathrm{d}^3 r \\ &= \sum_{i=1}^{k} \rho_{\mathrm{EM}}(w_i(R,T)) \end{aligned}$$

The last line follows when substituting Equ. 1 into the definition of the correlation.

SenSitus uses the gradient of the correlation $C^\rho$ as a feedback-force which drives the user into the closest maximum of the correlation. Fig. 1 shows a haptic device which exerts this force on the user.

Figure 1: Force-feedback device "Phantom 1.5/6DOF", manufactured by SensAble Technologies.

Fig. 2 displays an example of an atomic structure fitted into a low-resolution density.

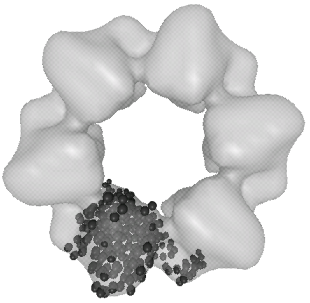

Figure 2: Atomic structure of the RecA monomer fitted into the low-resolution density of the RecA hexamer (displayed as an iso-surface) [17].

## 3 Laplace-filter enhanced fitting

It is known that for resolutions below 15Å the spatial cross-correlation loses its discrimination power [3]. In [1] it has been shown that the docking performance improves significantly when the correla-

[1] The search for a partition of a given space by Voronoi cells is mathematically related to the identification of "receptive fields" in the theory of artificial neural networks (ANN) and the code-book vectors, $w_i$, can be viewed as the analog to "synaptic weight vectors" [12, p.227]. The TRN method takes advantage of this similarity and applies a technique which was originally designed in the context of ANN to the problem of vector-quantization [11, 13, 14].

$$= \underbrace{\sum_{i=1}^{r} \rho^L_{\mathrm{EM}}(w^C_i(R,T))}_{\text{contour-match}} - \underbrace{\sum_{i=1}^{s} \rho^L_{\mathrm{EM}}(w^I_i(R,T))}_{\text{interior-match}}$$

The second term is negative to increase the correlation when evaluated for the interior region of $\rho_{\mathrm{EM}}$ i.e. when the interior of the atomic-structure data matches the interior of the low-resolution data.

# 4 Results

## 4.1 Laplace-filter

Fig. 4 illustrates the effect of the Laplace filter for the RecA hexamer.

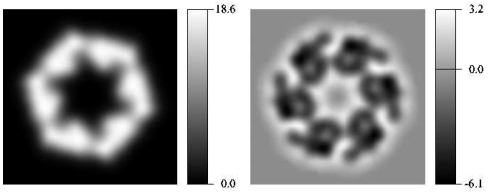


Figure 4: Cross-section of the spatial density map (left) and the same cross-section after application of the Laplace-filter for the RecA hexamer.

## 4.2 Vector quantization

Fig. 5 shows an atomic structure (tube representation) together with the code-book vectors of the contour-region (dark balls) and the interior-region (light balls). It can be seen that the code-book vectors are indeed located in the corresponding region.

## 4.3 Comparison with the spatial correlation

We now turn to the comparison between the Laplace-correlation based docking with the original spatial-correlation based approach. We investigate

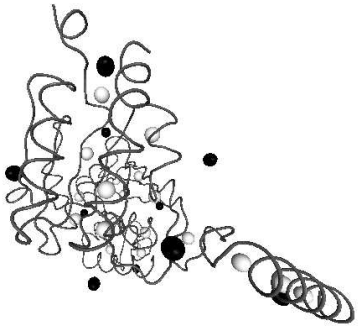

Figure 5: RecA monomer (tube representation) with 10 code-book vectors of the contour-region (dark balls) and 20 code-book vectors for the interior-region (light balls).

for which resolutions the Laplace-correlation outperforms the spatial-correlation. However, this task is related to the question how the total number of code-book vectors as well as the ratio between interior and contour code-book vectors needs to be adjusted to yield optimal results. Finally we analyze the impact of the vector quantization method on the Laplace-filter enhanced fitting.

All tests are based on the docking of the atomic structure of the RecA-monomer [17] into a low-resolution map which was obtained from blurring the atomic structure data of the RecA hexamer (see Fig. 2). This use of pseudo-data has the advantage that a well defined best-docking position exists, with which the performance of the algorithm can be compared.

### 4.3.1 Dependence on the resolution

To investigate the dependence of the docking performance on the resolution of the target map we have blurred the RecA hexamer to resolutions of 15, 20 and 25Å. The position of the RecA monomer was varied in 1Å steps in a range of $\pm$10Å around the optimal docking position along a given axis. For each position the correlation was calculated[4]. Fig. 6 shows the results for this analysis. Compared is the docking-performance for spatial- and Laplace-correlation when the RecA monomer is approxi-

[4] In addition at each position the rotation was chosen which maximizes the correlation.

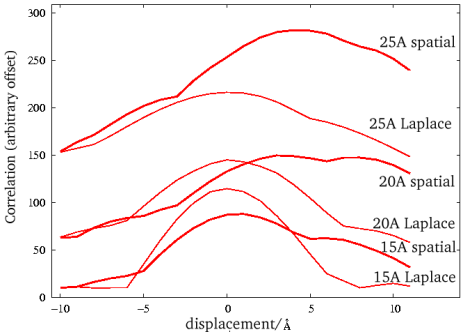


Figure 6: Comparison of the docking performance for different resolutions of the target map. The plot shows the correlation as a function of the displacement around the optimal docking at 0. The monomer was approximated with 70 code-book vectors. In the Laplace case these were distributed in equal shares to interior and contour region. The Laplace method shows a more pronounced maximum of the correlation in all cases. This results into a stronger feedback force which drives the system into the original docking position.

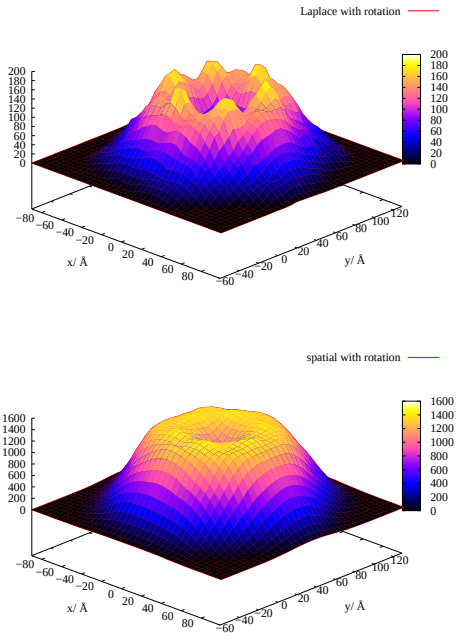


Figure 7: Docking of the RecA monomer into the hexamer at 25Å resolution. Displayed is the correlation in the $xy$-plane. Top: Laplace-filter method, bottom: spatial correlation. The Laplace method leads to well defined maxima for the monomer while the spatial correlation ranks the whole RecA structure high.

mated with 70 code-book vectors (the monomer consists of 443 atoms). For the Laplace-filtered data an equal number of code-book vectors assigned to the interior and contour region was chosen.

The study confirms the expectation that with dropping resolution the Laplace method outperforms the spatial correlation i.e. the Laplace-correlation displays a better defined maximum with steeper edges, resulting into a stronger feed-back force which drives the system into the best docking position. Fig. 7 compares the performance of Laplace and spatial correlation for 25Å data in the $xy$-plane. For every position the optimal rotation was calculated. It can be clearly seen that the Laplace method (top) distinguishes the 6 possible docking positions while the spatial correlation ranks the whole RecA structure high.

Finally, Fig. 2 in the appendix compares the docking based on the spatial correlation and the Laplace correlation in terms of the resulting positions for the 3D structure. Fig. 2a in the appendix shows that for the spatial correlation based method the best fit is shifted from the optimal position by $\approx$ 1Å. The Laplace method can reproduce the optimal position within a small fraction of 1Å, at least if a proper choice for the fraction of interior and contour code-book vectors is made (see Fig. 2b and Fig. 2c in the appendix). The next section is devoted to the question how the performance of the Laplace docking depends on the fraction of interior and contour code-book vectors.

#### 4.3.2 Dependence on the ratio between interior and contour region

Clearly the performance of both algorithms (spatial- and Laplace-correlation) depends on the number of code-book vectors i.e. improves with a larger number of code-book vectors. However, the Laplace method introduces an other degree of freedom into

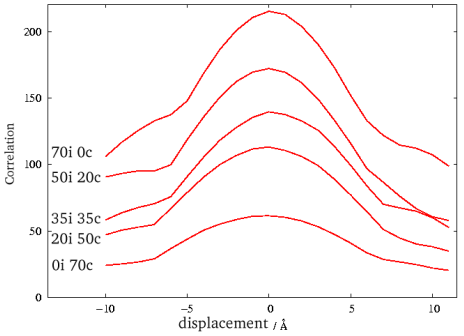


Figure 8: Correlation as a function of the displacement for different ratios of the number of code-book vectors for interior (i) and contour region (c). The position 0 corresponds to perfect docking of the RecA monomer into the hexamer. For each displacement the optimal rotation has been calculated. It can be seen that the performance of the Laplace method increases with the fraction of interior code-book vectors.

the analysis, namely the ratio between the number of code-book vectors assigned to the interior and contour region respectively. To investigate the impact of this choice we have repeated the monomer docking for different ratios of interior and contour code-book vectors.

Fig. 8 shows the corresponding results for the 20Å case. It can be clearly seen that the performance of the algorithm improves with the fraction of interior code-book vectors until all code-book vectors are assigned to the interior region. That the docking is strongly driven by the interior code-book vectors seems to be particularly surprising since the interior amounts only to ≈30% of the total volume. The reason for this unexpected behavior lies presumably in the fact, that the compact inner region is easier to approximate than the "thin-walled" contour region. Furthermore the contour of the single monomer is certainly not expected to match perfectly to the contour of a monomer within the full hexamer. However, one should note that this result does not indicate, that the distinction between interior and contour becomes irrelevant. First, the interior code-book vectors do confine the boundary region "from inside" i.e. carry indirect information about the contour region likewise. Second, and more important, even in the absence of any contour code-book vector does the low-resolution data carry the sign-information about the contour-interior distinction. Hence, it still plays a role in the algorithm.

Finally, Fig. 1 in the appendix compares spatial- and Laplace-based docking at 15Å resolution. For the Laplace method the monomer was approximated by 70 code-book vectors, *all* assigned to the interior region. Displayed is the absolute value of the feedback-force. The Laplace-filter method shows a much better pronounced minimum at the original docking position (0,0).

### 4.3.3 Impact of the vector-quantization

The vector-quantization approximates the original atomic structure by a small set of code-book vectors. In our example the number of code-book vectors corresponds to only 16% of the total number of atoms. To examine the impact of this approximation on Laplace filtered maps and the subsequent determination of the correlation one need to compare the performance of our docking with a Laplace-filter algorithm which does not use any data compression [5]

Fig. 2 in the appendix compares the results of these two algorithms for the docking of the RecA monomer. In all plots does the green tube correspond to the optimal position, the blue tube to the Laplace docking result *without* vector-quantization and the red tube to a result *with* vector-quantization. In plot 2b the red tube is based on the Laplace correlation with 70 interior code-book vectors while for plot 2c 35 interior and 35 contour code-book vectors were employed. Again, the Laplace-docking with vector quantization improves with the fraction of interior code-book vectors. Moreover, plot 2b shows an excellent agreement between the two Laplace-filter based methods and the optimal docking position.

## 5 Summary

We have successfully implemented the Laplace-filter method into SenSitus for the docking of atomic structures into low-resolution data. The Laplace filter gives edge information i.e. introduces the distinction between interior and contour region.

[5] Such a method is implemented into the algorithmic docking tool CoLoRes (Contour-based Low-Resolution docking) which is part of the Situs [16] package.

Tests show that this method significantly improves the docking for resolution of 15Å and below.

SenSitus supports the docking by VR techniques which are especially well suited for the analysis of these highly complex macro-molecules. To allow for force update rates of 1kHZ and above, as required in VR-environments [10], SenSitus employs the vector-quantization method to approximate the structure data. The application of this method for Laplace-filtered maps introduces the question of how to deal with the sign-information of the Laplace filter and how to share the code-book vectors between interior and contour region. Our investigation shows that the docking is strongly driven by the interior code-book vectors. However, even in the absence of any contour code-book vector for the structure data does the low-resolution data carry the sign-information of contour and interior regions. Hence, the contour information is retained by the algorithm.

## Acknowledgment

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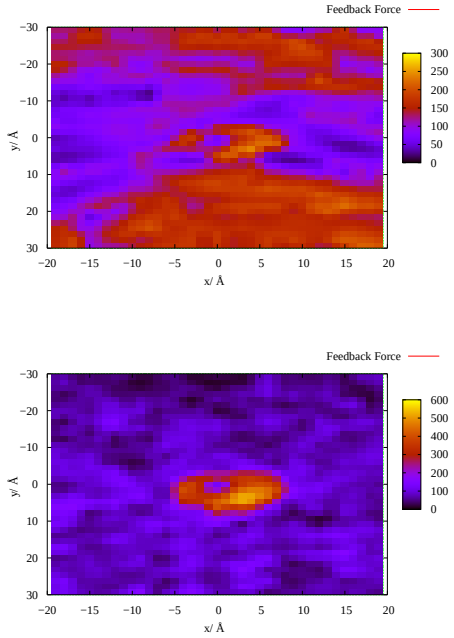


Figure 9: Docking of the RecA monomer into the hexamer at 15Å resolution. Displayed is the absolute value of the feedback-force in a cutout of the $xy$-plane around the optimal docking position (0,0). Shown are the results for the method based on the spatial correlation (top) and for the Laplace-filter method (bottom). Again, the Laplace method yields the more pronounced maximum of the correlation which results in a well defined local minimum of the feedback force.

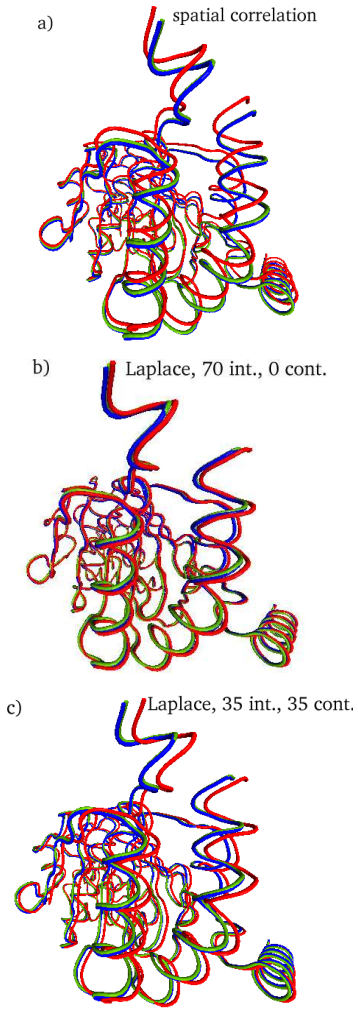


Figure 10: Docking of the RecA monomer into the hexamer at a resolution of 15Å. In all three plots does the green tube correspond to the optimal position, the blue tube to the Laplace result *without* vector-quantization (these two curves are almost indistinguishable) and the red tube to a result *with* vector-quantization. a) The red tube is based on the spatial correlation with 70 code-book vectors. b) The red tube is based on the Laplace correlation with 70 interior code-book vectors. c) The red tube is based on the Laplace correlation with 35 interior and 35 contour code-book vectors. While for a) and c) the vector-quatization result is shifted by $\approx$ 1Å from the optimal position, does plot b) show an excellent agreement.