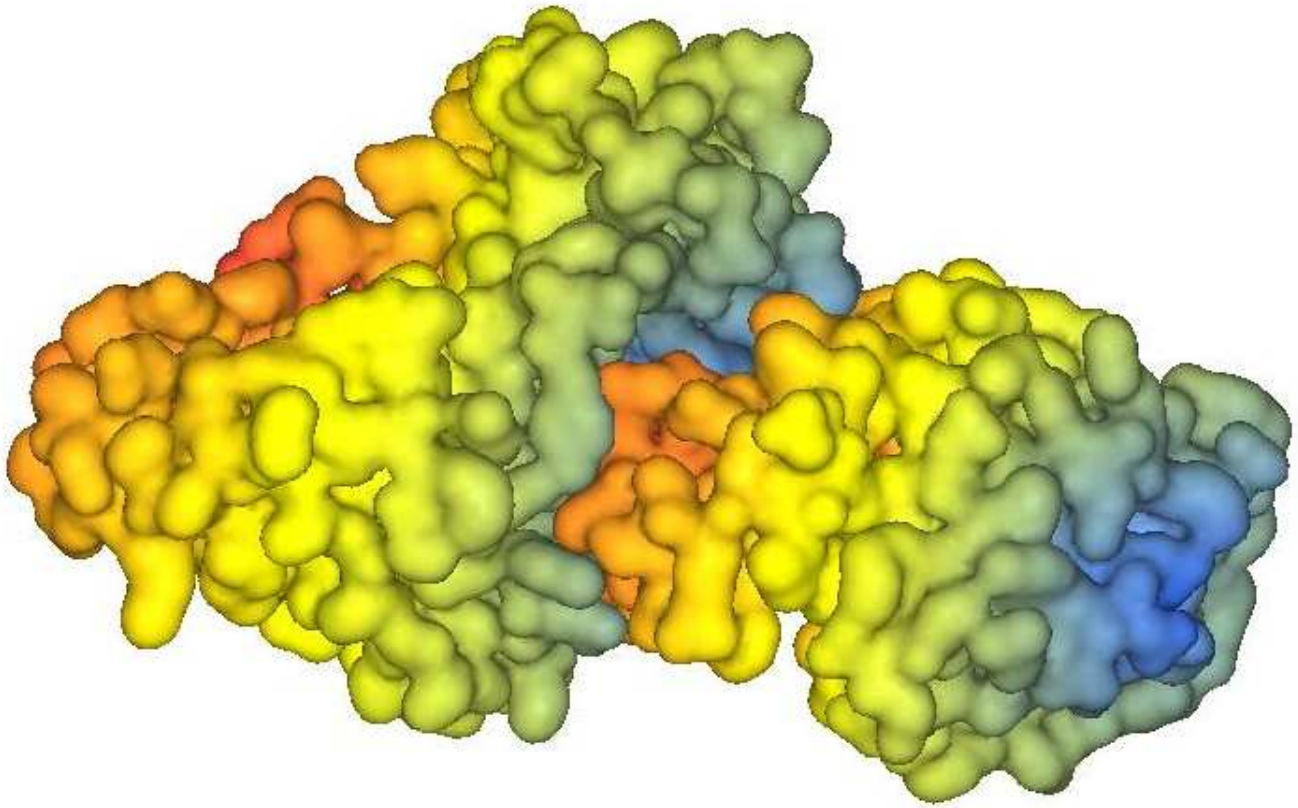
Using Graphics Processors to Accelerate Protein Docking Calculations



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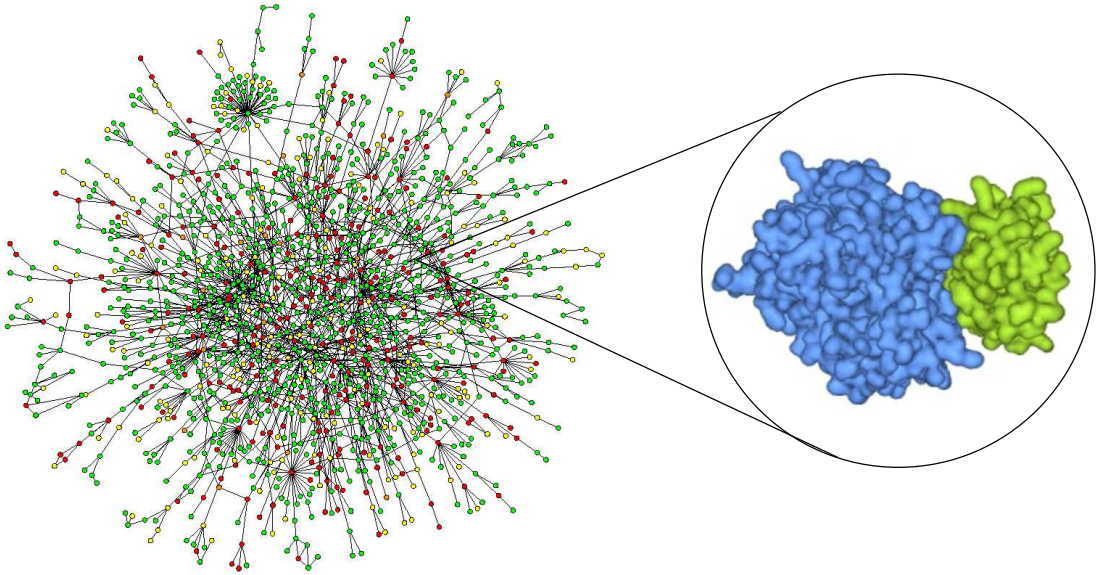
Protein-Protein Interactions – Why Are They Important ?

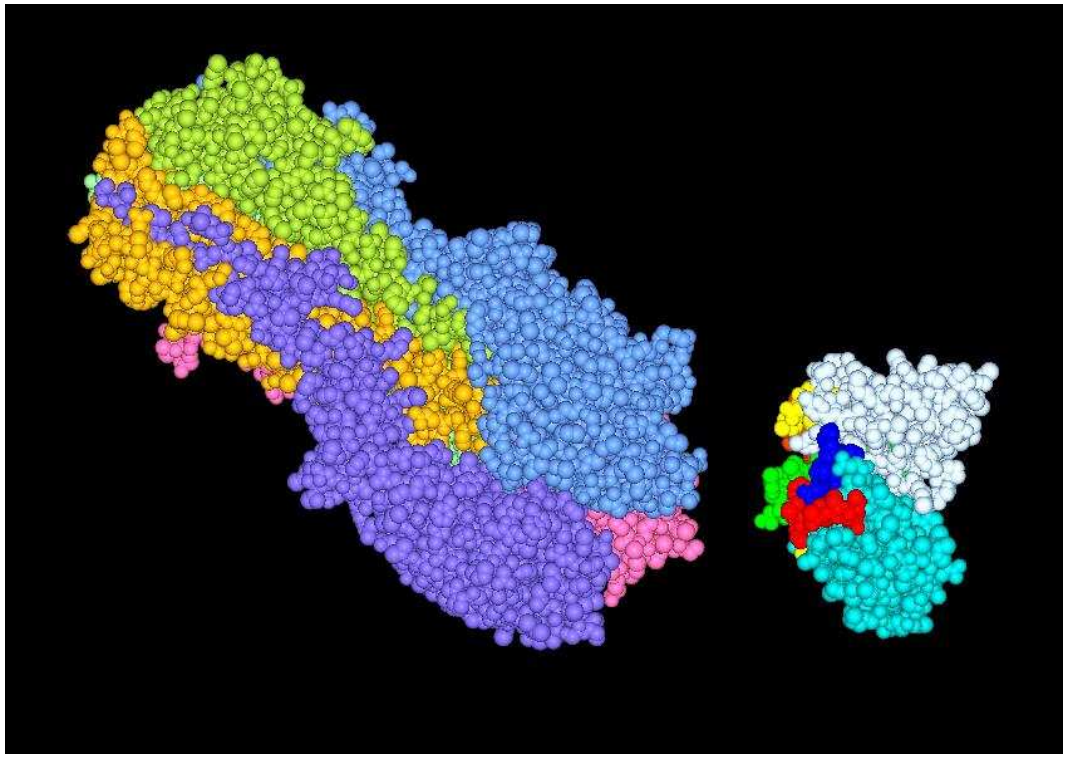
- Protein-protein interactions (PPIs) define the "machinery" of life
- Humans have about 30,000 proteins, each having about 5 PPIs



- Understanding PPIs could lead to immense scientific advances
- Controlling PPIs could have huge therapeutic benefits (new drug molecules)

What is Protein Docking ?

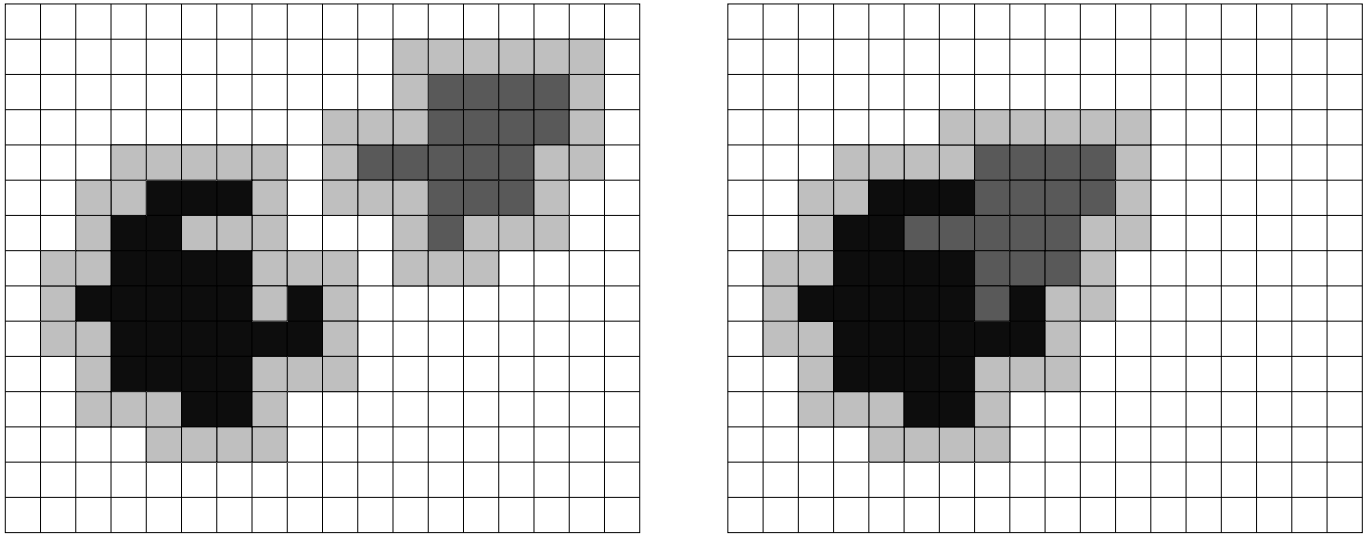
- Protein docking = predicting protein interactions at the molecular level



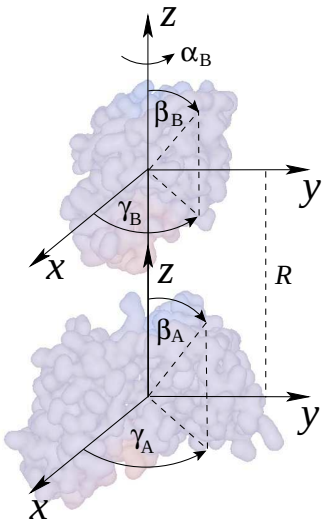
- If proteins are rigid => six-dimensional search space
- But proteins are flexible => multi-dimensional space!
- Modeling protein-protein interactions accurately is difficult!

Protein Docking Using Fast Fourier Transforms

- **Conventional approaches digitise proteins into 3D Cartesian grids...**



Surface: +1 Interior: −15 Interior: +1



- **...and use FFTs to calculated TRANSLATIONAL correlations:**

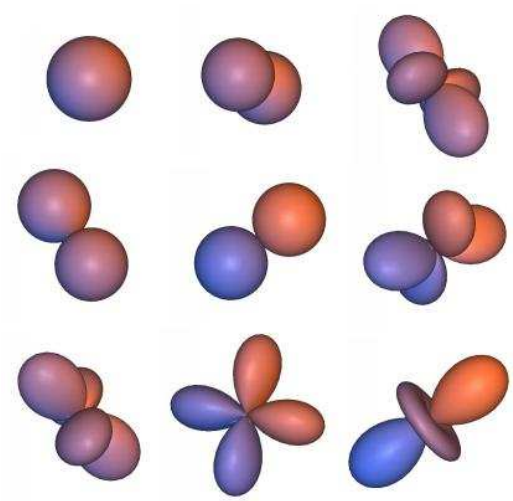
$$C[\Delta x, \Delta y, \Delta z] = \sum_{x,y,z} A[x, y, z] \times B[x + \Delta x, y + \Delta y, z + \Delta z]$$

- **BUT have to rotate one protein and REPEAT, which becomes EXPENSIVE!**

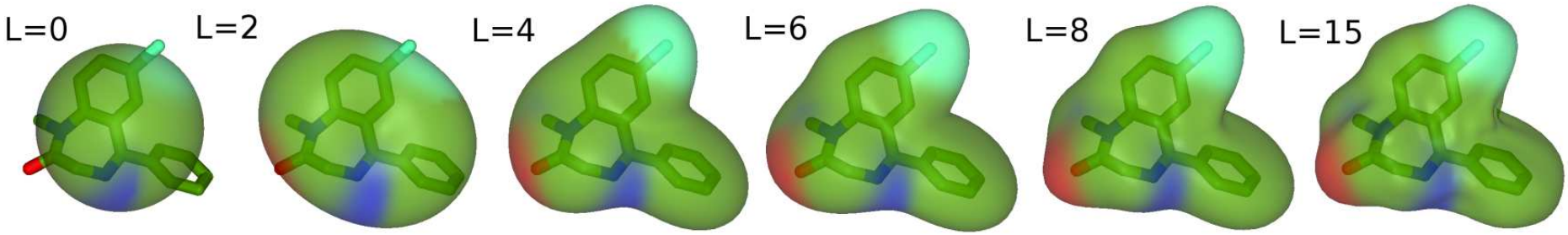
- **POLAR coordinates allow ROTATIONAL nature of the problem to be exploited**

Some Theory – 2D Spherical Harmonic Surfaces

- Use spherical harmonics (SHs) as orthogonal shape "building blocks"



- Reals SHs $y_{lm}(\theta, \phi)$, and coeffcients a_{lm}
- Encode distance from origin as SH series to order L:
- $r(\theta, \phi) = \sum_{l=0}^{L} \sum_{m=-l}^{l} a_{lm} y_{lm}(\theta, \phi)$
- Calculate coefficients by numerical integration
- ROTATIONS: $a'_{lm} = \sum_{m'=-l}^{l} R^{(l)}_{mm'}(\alpha, \beta, \gamma) a_{lm'}$

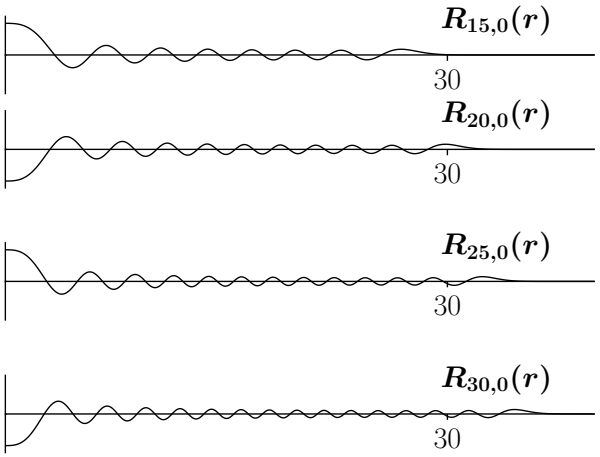


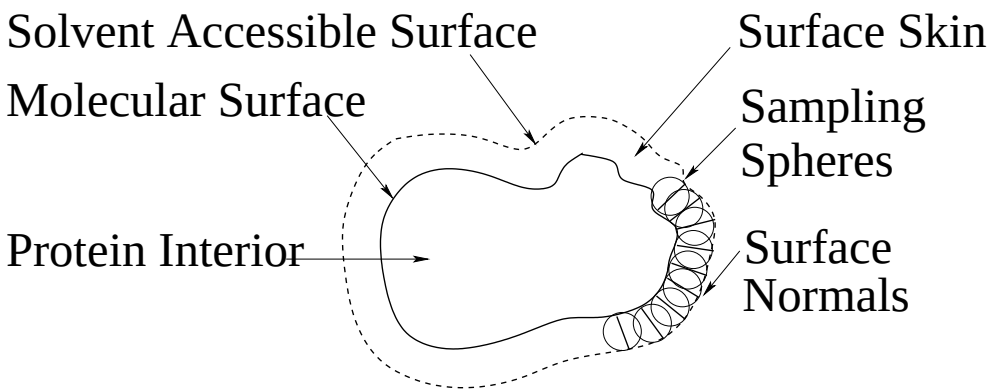
- Good for shape-matching, not so good for docking...

Ritchie and Kemp (1999) J. Comp. Chem. 20 383–395

Docking Needs a 3D "Spherical Polar Fourier" Representation

- **Need to introduce special orthonormal Laguerre-Gaussian radial functions, $R_{nl}(r)$**
- $\boldsymbol{R_{nl}(r) = N_{nl}^{(q)} e^{-\rho/2} \rho^{l/2} L_{n-l-1}^{(l+1/2)}(\rho); \qquad \rho = r^2/q, \quad q = 20.}$





- **Surface Skin:** $\sigma(\underline{r}) = \begin{cases} 1; & \underline{r} \in \text{surface skin} \\ 0; & \text{otherwise} \end{cases}$ **Interior:** $\tau(\underline{r}) = \begin{cases} 1; & \underline{r} \in \text{protein atom} \\ 0; & \text{otherwise} \end{cases}$
- **Parametrise as:** $\sigma(\underline{r}) = \sum_{nlm}^{N} a_{nlm}^{\tau} R_{nl}(r) y_{lm}(\theta, \phi)$, **etc.**
- **TRANSLATIONS:** $a_{nlm}^{\sigma\prime\prime} = \sum_{n'l'}^{N} T_{nl,n'l'}^{(|m|)}(R) a_{n'l'm}^{\sigma}$

SPF Protein Shape-Density Reconstruction

Interior density: $$\tau(\underline{r}) = \sum_{n=1}^{N} \sum_{l=0}^{n-1} \sum_{m=-l}^{l} a^{\sigma}_{nlm} R_{nl}(r)\, y_{lm}(\theta, \phi)$$

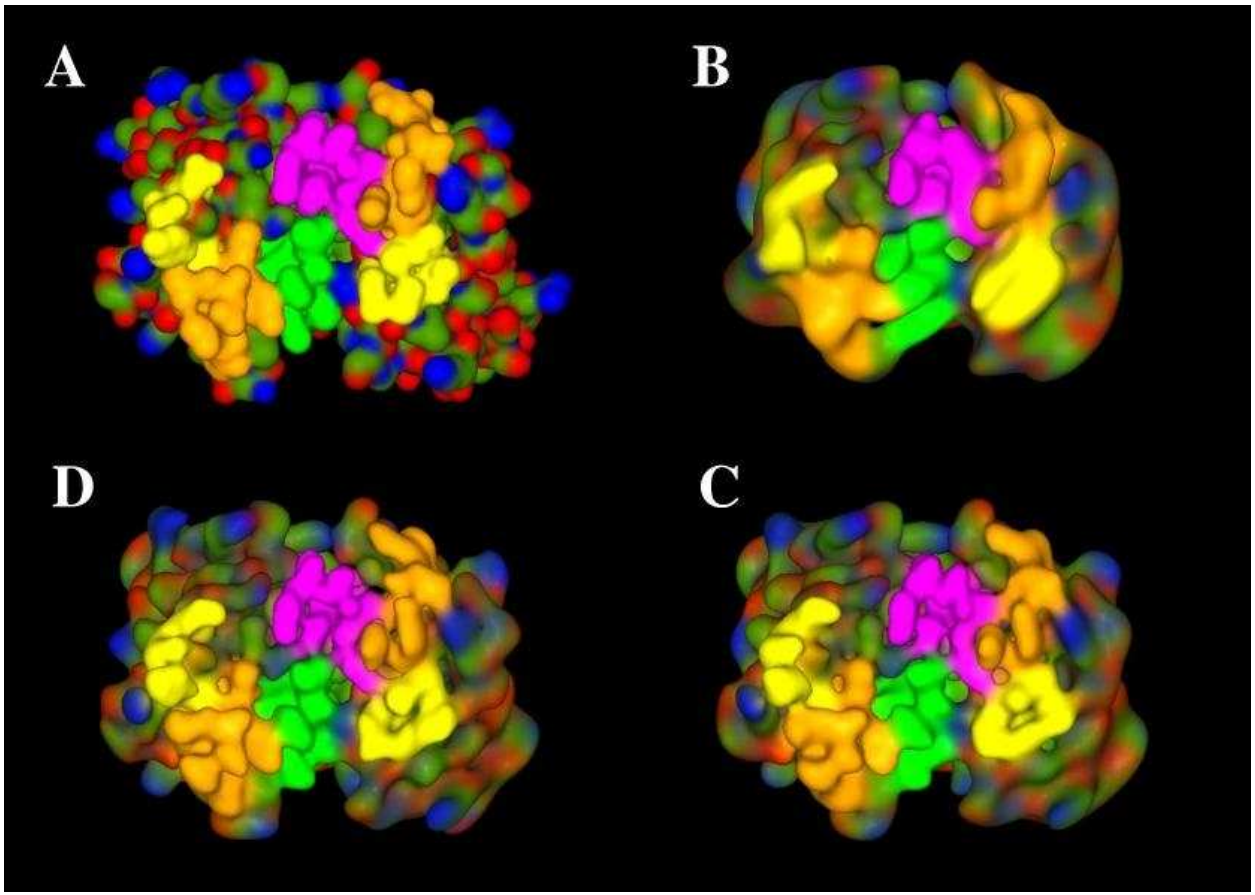
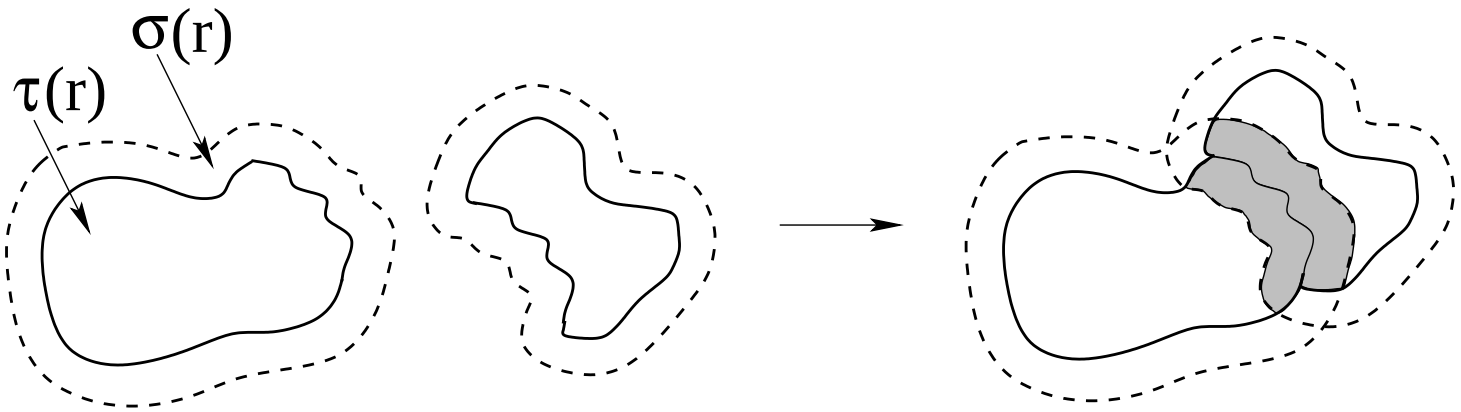


Image	Order	Coefficients
A	Gaussians	-
B	N = 16	1,496
C	N = 25	5,525
D	N = 30	9,455

DW Ritchie (2003) Proteins Struct. Funct. Bionf. 52 98–106

Protein Docking Using SPF Density Functions



Favourable: $\int (\sigma_A(\underline{r}_A)\tau_B(\underline{r}_B) + \tau_A(\underline{r}_A)\sigma_B(\underline{r}_B))\mathrm{d}V$

Unfavourable: $\int \tau_A(\underline{r}_A)\tau_B(\underline{r}_B)\mathrm{d}V$

Score: $S_{AB} = \int (\sigma_A\tau_B + \tau_A\sigma_B - Q\tau_A\tau_B)\mathrm{d}V$ **Penalty Factor:** $Q = 11$

Orthogonality: $S_{AB} = \sum_{nlm} \left(a^{\sigma}_{nlm}b^{\tau}_{nlm} + a^{\tau}_{nlm}(b^{\sigma}_{nlm} - Qb^{\tau}_{nlm})\right)$

Search: **6D space = 1 distance + 5 Euler rotations:** $(R, \beta_A, \gamma_A, \alpha_B, \beta_B, \gamma_B)$

D.W. Ritchie and G.J.L. Kemp (2000) Proteins Struct. Funct. Bionf. 39 178–194

Nvidia Graphics Processors

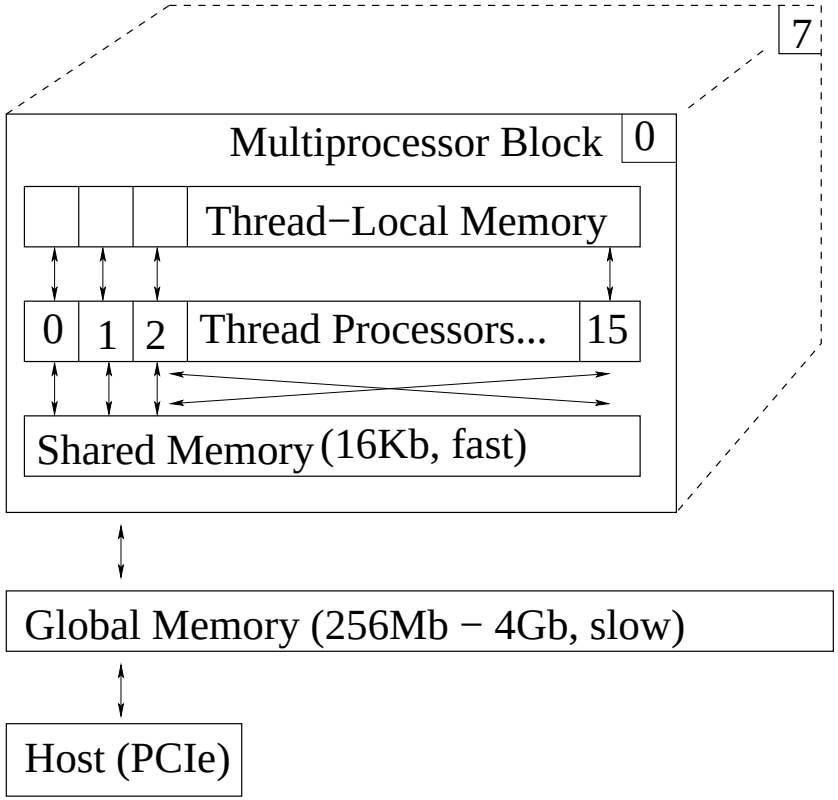
- Modern GPUs have very high compute performance
- SIMT architecture = simultaneous instructions, multiple threads

- NVIDIA GPUs:
- Up to 4Gb memory
- Up to 240 arithmetic "cores"
- Up to Tera-flop performance
- Easy API with C++ syntax
- Grid of threads SIMT model

- BUT – for best results, need to understand the hardware...

The CUDA Device Architecture

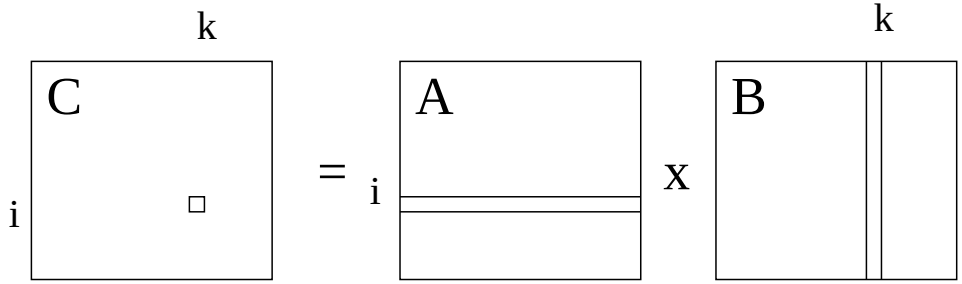
- **Typically 8–16 multi-processor blocks, each with 16 thread units**



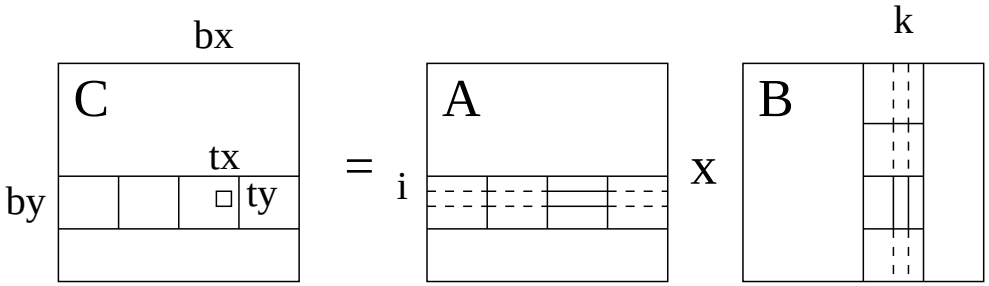
- **NB. only a very small amount of fast shared memory is available**
- **NB. global memory is $\sim$ 80x slower than shared memory**
- **Strategy: aim for "high arithmetic intensity" in shared memory**

CUDA Programming Example - Matrix Multiplication

- **Matrix multiplication C = A * B**
- **Each thread is responsible for calculating one element: C[i,k]**



- **Conventional algorithm: rows and columns**
- **C[i,k] = A[i] * B[k]**



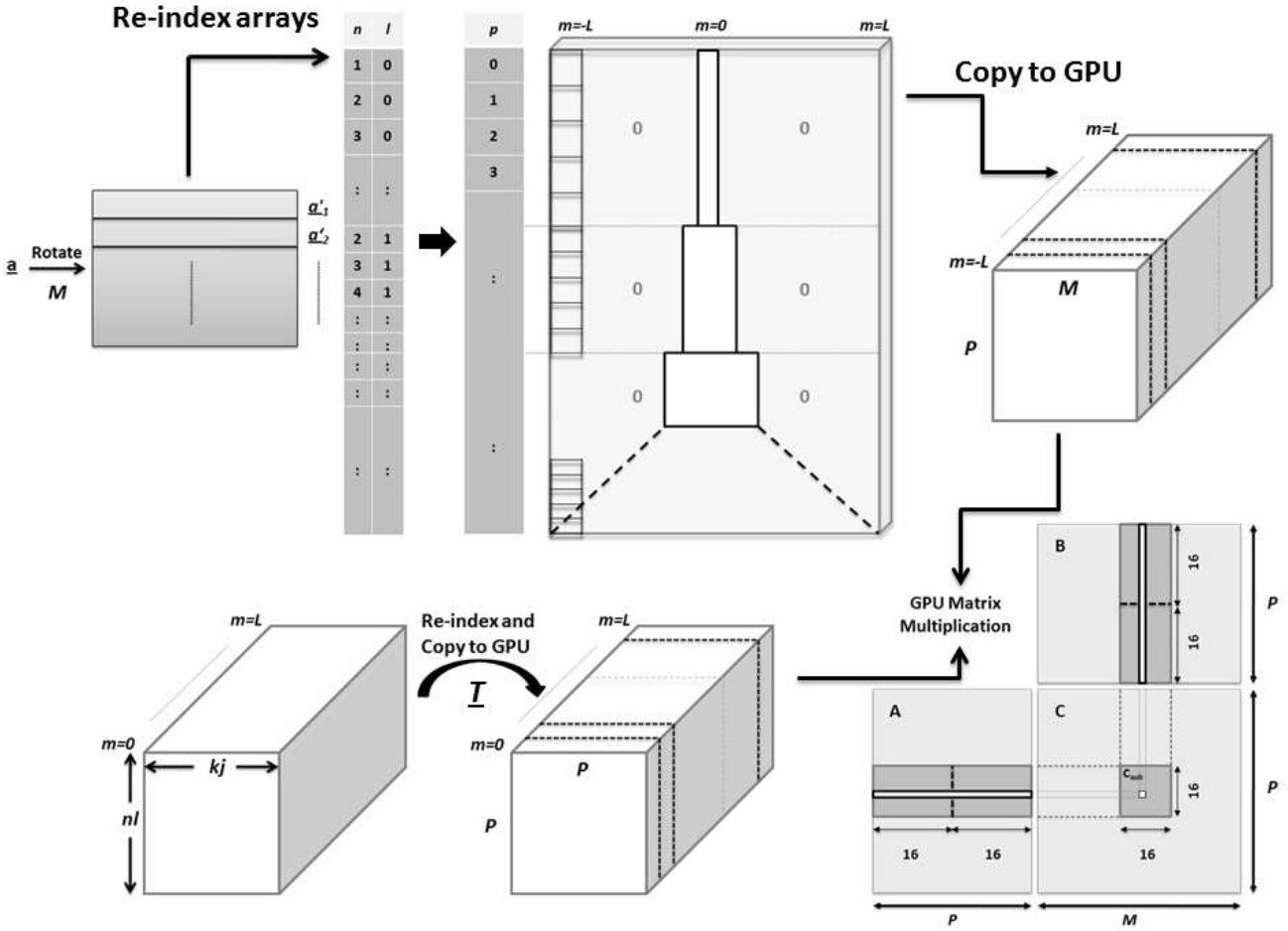
- **Thread-block algorithm working on tiles**
- **Threads co-operate by reading & sharing tiles of A & B**
- **Multi-processor launches multiple blocks to compute all of C**
- **Executing thread-blocks concurrently hides global memory latency**

CUDA Programming Example – Matrix Multiplication Kernel

```
__global__ void matmul(int wA, int wB, float *A, float *B, float *C)
{
   float Cik = 0.0;                                  // thread-local result variable
   int bx = blockIdx.x, tx = threadIdx.x;            // thread subscripts
   int by = blockIdx.y, ty = threadIdx.y;            // ("this" thread is one of a 2-D grid)

   __shared__ float a_sub[16][16], b_sub[16][16]; // declare shared memory

   for (int j=0; j<wA; j+=16) {                      // thread-local loop over tiles of A and B

      int ij = (16*by+ty)*wA + (j+tx);               // thread-local array subscripts
      int jk = (j+ty)*wB + (16*bx+tx);

      a_sub[ty][tx] = A[ij];                         // copy global data to shared memory ("I/O")
      b_sub[ty][tx] = B[jk];

      __syncthreads();                               // wait until all memory I/O has finished

      for (int jj=0; jj<16; jj++) {

         Cik += a_sub[ty][jj] * b_sub[jj][tx];       // multiply row*column in current tiles
      }

      __syncthreads();                               // synchronise threads before starting more I/O
   }

   C[(16*by+ty)*wB + (16*bx+tx)] = Cik;              // copy local result -> global memory
}
```

GPU Implementation Part 1 – Rotate and Translate Protein A

1. On CPU, calculate multiple (β_A, γ_A) rotations of protein A
2. On CPU, re-index translation matrices and rotated coefficients into regular sparse arrays
3. On GPU, translate multiple protein A coeffcients using tiled matrix multiplication

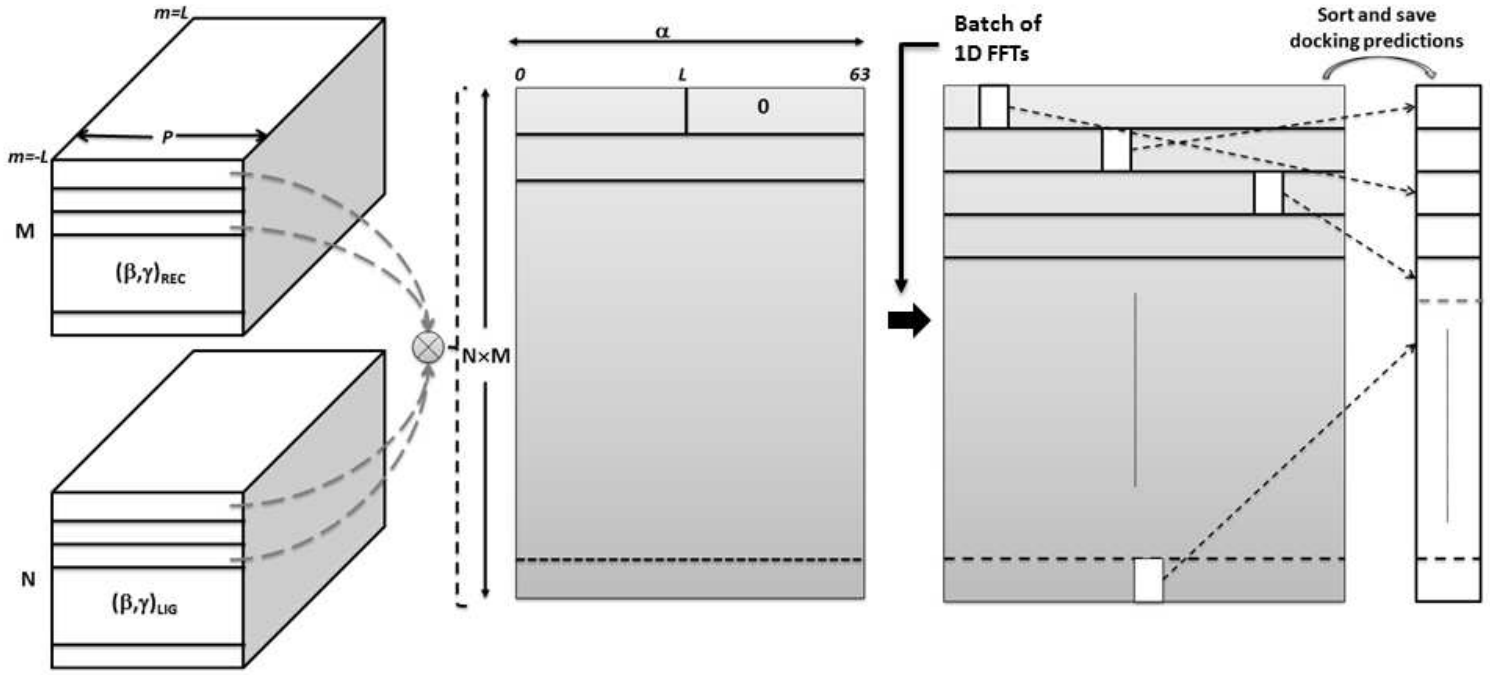


GPU Implementation Part 2 – Perform Multiple FFTs

- **The overall aim is to calculate multiple 1D FFTs of the form:**

$$C(\alpha_B) = \sum_m e^{-im\alpha_B} \sum_{nl} A^{\sigma}_{nlm}(R, \beta_A, \gamma_A) \times B^{\tau}_{nlm}(\beta_B, \gamma_B)$$

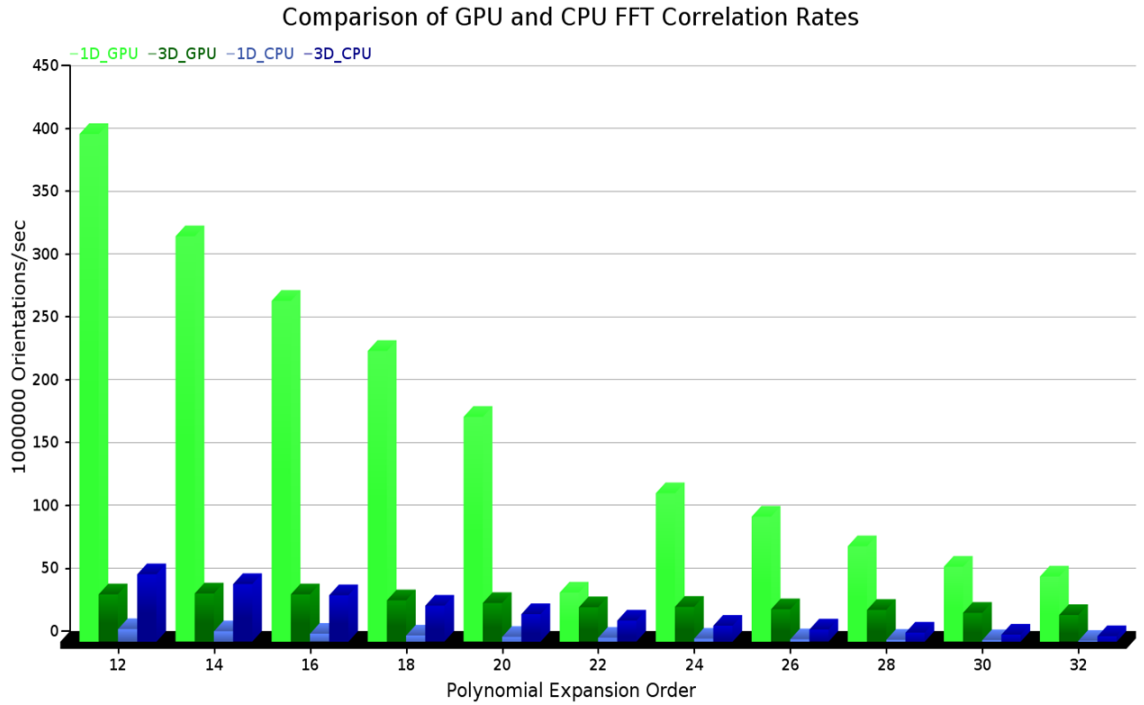
4. **On GPU, cross-multiply transformed A with rotated B coefficients (as above)**
5. **On GPU, perform batch of 1D FFTs using cuFFT and save best orientations**



- **3D FFTs in $(\alpha_B, \beta_B, \gamma_B)$ can be calculated in a similar way...**

Results – GPU v's CPU Docking Performance

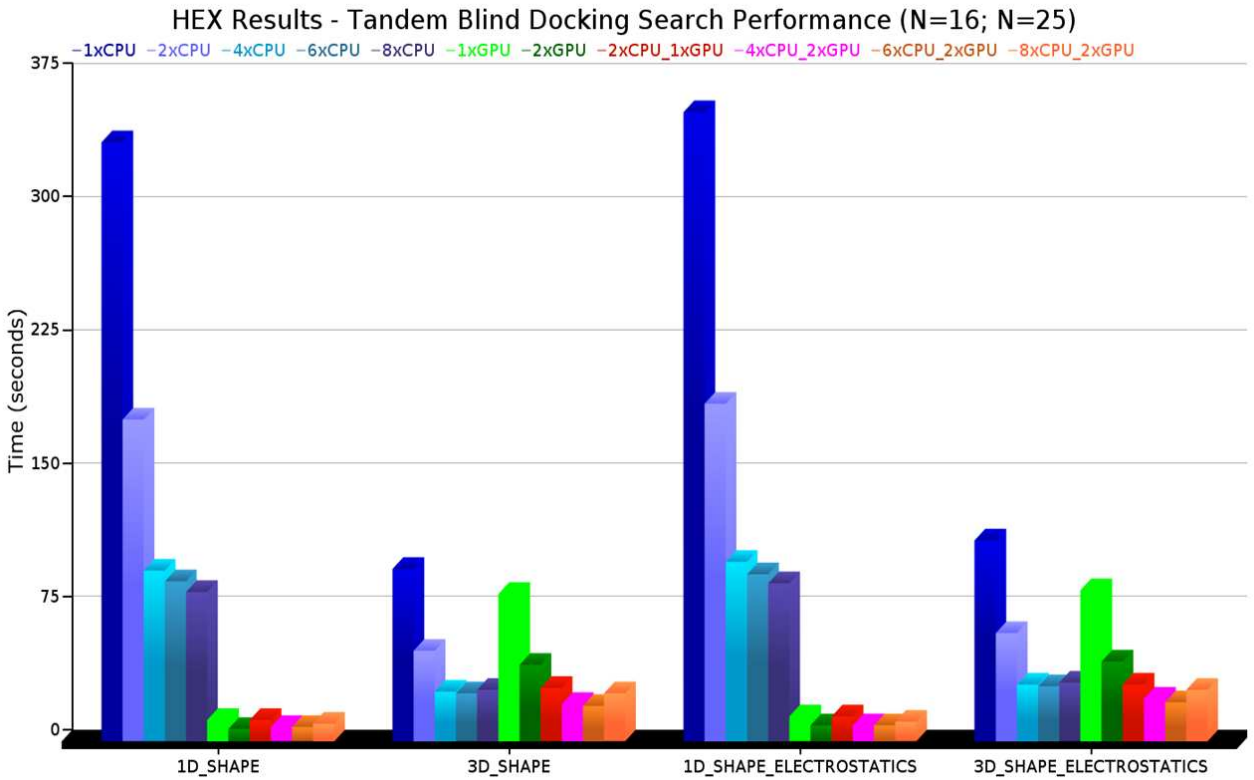
- Key Hex functions implemented using only 5 or 6 CUDA kernels
- 1D and 3D FFTs are calculated using Nvidia's cuFFT library
- Here, GPU = Nvidia FX-5800, CPU = Intel i7-965



- Hex 1D correlations are up to 100x faster on FX-5800 than on iCore7
- Overall, including set-up, Hex 1D FFT is about 45x faster on FX-5800 than on iCore7

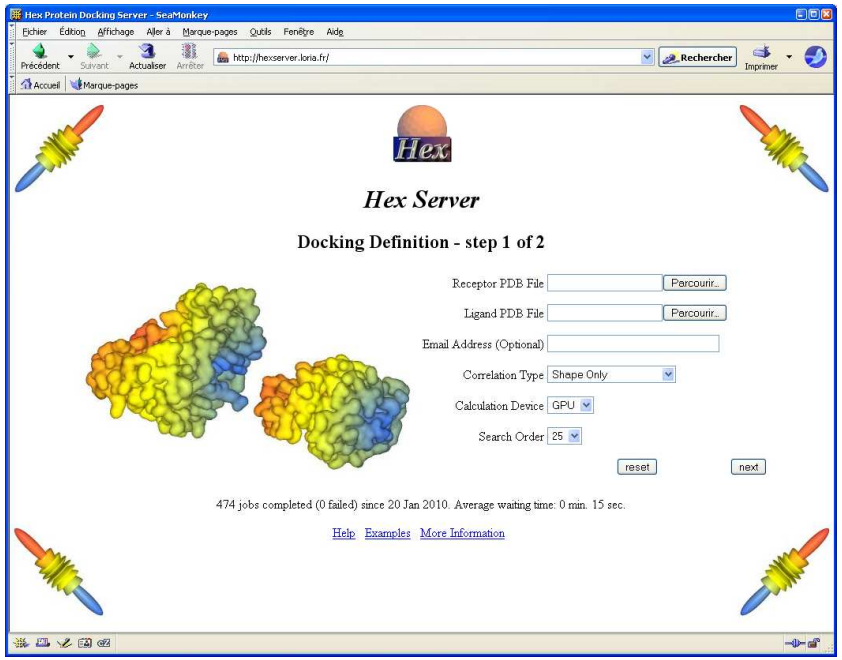
Results – Multiple GPUs and CPUs

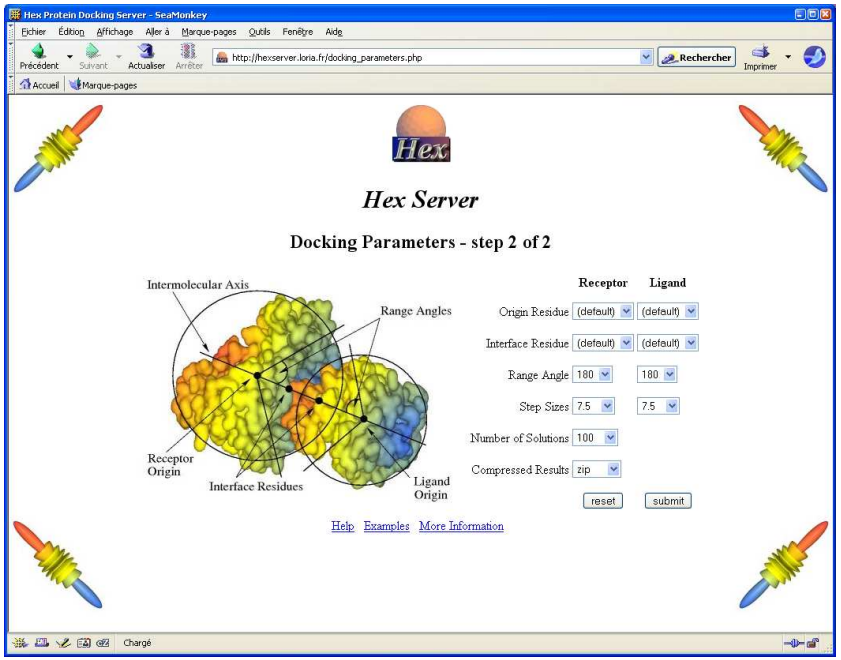
- **With Multi-threading, we can use as many GPUs and CPUs as are available**

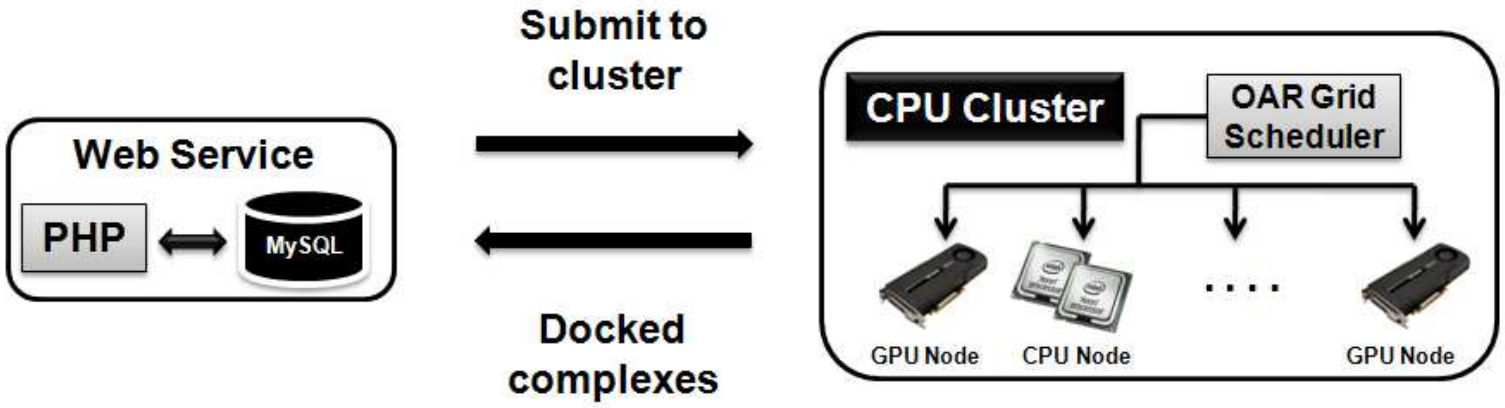


- **For best performance: use 2 GPUs alone, or 6 CPUs plus 2 GPUs**
- **With 2 GPUs, docking takes only about 15 seconds – very important for large-scale!**

“Hex” and “HexServer” – Publicly Available Docking Tools



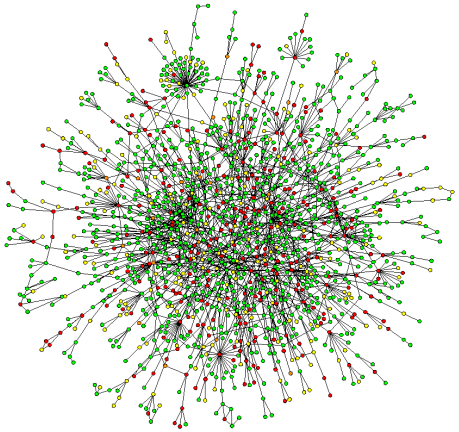


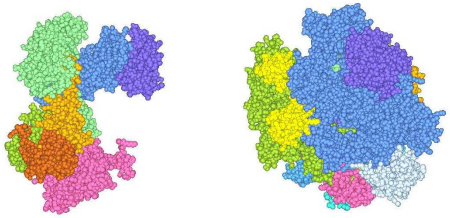


Macindoe et al. (2010), Nucleic acids Research (featured article)

Conclusions and Future Prospects

- Protein-protein docking on a GPU now takes only a few seconds:
  - This was implemented using only 5 or 6 GPU kernels
  - But a lot of low-level CPU code had to be re-written
- High-throughput multi-shape comparison is now be feasible:
  - Probing PPI networks...
  - Assembling multi-component machines...
  - Electron-microscopy density fitting...
  - Full 3D small-molecule virtual screening...
  - Protein shape matching and classification...





Acknowledgments

BBSRC 1996–2000
EPSRC 2000–2006

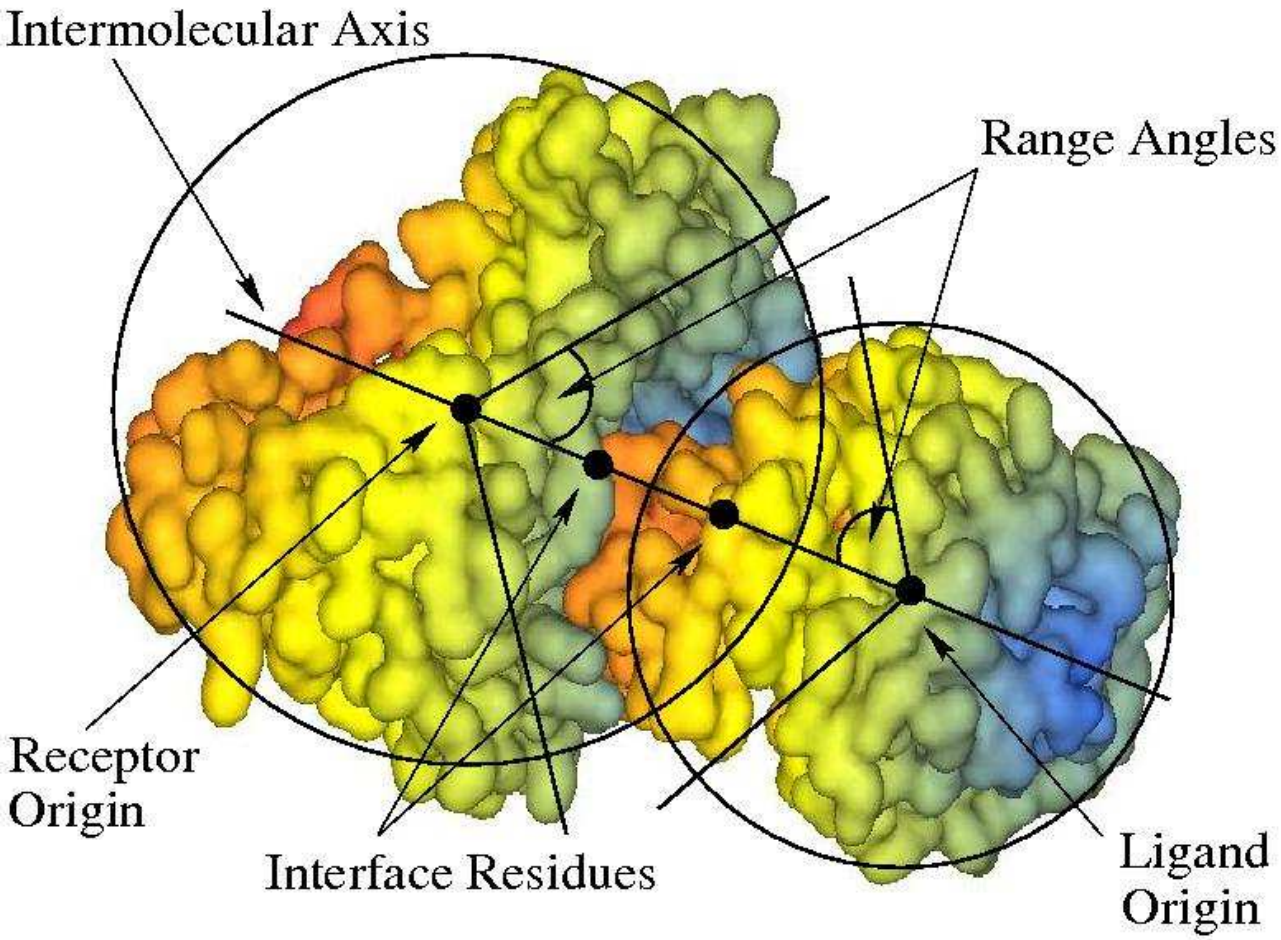
ANR 2009–2010

Software & Papers: http://hex.loria.fr/

HexServer: http://hexserver.loria.fr/

Extra Slides

Exploiting Prior Knowledge in SPF Docking



- **Knowledge of even only one key residue can reduce search space enormously...**
- **This accelerates the calculation and helps to reduce false-positive predictions**

5D FFT Correlations from Complex Overlap Expressions

(Ritchie, Kozakov, Vajda, (2008) Bioinformatics, 24, 1865–1873)

Complex SHs, Y_{lm}: $$y_{lm}(\theta,\phi) = \sum_t U^{(l)}_{mt} Y_{lt}(\theta,\phi)$$

Complex coefficients: $$A_{nlm} = \sum_t a_{nlt} U^{(l)}_{tm}$$

Complex overlap: $$S = \sum_{kjsmnlv} D^{(j)*}_{ms}(0,\beta_A,\gamma_A) A^*_{kjs} T^{(|m|)}_{kj,nl}(R) D^{(l)}_{mv}(\alpha_B,\beta_B,\gamma_B) B_{nlv}$$

Collect coefficients: $$S^{(|m|)}_{js,lv}(R) = \sum_{kn} A^*_{kjs} T^{(|m|)}_{kj,nl}(R) B_{nlv}, \qquad k > j; n > l$$

To give: $$S = \sum_{jsmlv} D^{(j)*}_{ms}(0,\beta_A,\gamma_A) S^{(|m|)}_{js,lv}(R) D^{(l)}_{mv}(\alpha_B,\beta_B,\gamma_B)$$

Expand as exponentials: $$D^{(l)}_{mv}(\alpha,\beta,\gamma) = \sum_t \Gamma^{tm}_{lv} e^{-im\alpha} e^{-it\beta} e^{-iv\gamma}$$

Hence: $$S = \sum_{jsmlvrt} \Gamma^{rm}_{js} S^{(|m|)}_{js,lv}(R) \Gamma^{tm}_{lv} e^{-i(r\beta_A - s\gamma_A + m\alpha_B + t\beta_B + v\gamma_B)}$$

Translation Matrices From Fourier-Bessel Transform Theory

Using spherical Bessel transforms:

$$\tilde{R}_{nl}(\beta) = \sqrt{\frac{2}{\pi}} \int_0^\infty R_{nl}(r) j_l(\beta r) r^2 \mathrm{d}r; \qquad R_{nl}(r) = \sqrt{\frac{2}{\pi}} \int_0^\infty \tilde{R}_{nl}(\beta) j_l(\beta r) \beta^2 \mathrm{d}\beta$$

it can be shown that

$$T^{(|m|)}_{n'l',nl}(R) = \sum_{k=|l-l'|}^{l+l'} A_k^{(ll'|m|)} \int_0^\infty \tilde{R}_{nl}(\beta) \tilde{R}_{n'l'}(\beta) j_k(\beta R) \beta^2 \mathrm{d}\beta$$

where

$$A_k^{(ll'|m|)} = (-1)^{\frac{k+l'-l}{2}+m} (2k+1) \left[(2l+1)(2l'+1)\right]^{1/2} \begin{pmatrix} l & l' & k \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} l & l' & k \\ m & \overline{m} & 0 \end{pmatrix}$$

- **Can derive analytic formulae for both GTO and ETO radial functions**
- **Requires high precision math library (GMP)...**
- **Calculate once for $R = 1, 2, 3, ...50\mathring{A}$ and store on disk ($\sim$ 200Mb)**

Inside Hex – High Order FFTs and GPUs

- **The SPF gives an analytic way to calculate TRANSLATIONAL + ROTATIONAL correlations:**

In particular:

$$S_{AB} = \sum_{jsmlvrt} \Lambda_{js}^{rm} T_{js,lv}^{(|m|)}(R) \Lambda_{lv}^{tm} e^{-i(r\beta_A - s\gamma_A + m\alpha_B + t\beta_B + v\gamma_B)}$$

- **This allows high order FFTs to be used – 1D, 3D, and 5D**
- **It also allows calculations to be easily ported to modern GPUs**

- **Up to 240 arithmetic "cores"**
- **Grid of threads SIMT model**
- **Correlation speed-up $\geq$ 100x**
- **Overall speed-up = 45x**

- **GPU docking takes 15 seconds (475x faster than ZDOCK) – very important for large-scale!**

D.W. Ritchie, D. Kozakov, S. Vajda (2008) Bioinformatics 24 1865–1873

D.W. Ritchie, et al. HealthGrid (2010), To Appear

D.W. Ritchie, V. Venkatraman (2010), In review