Hex – Modeling Protein Docking Using Polar Fourier Correlations

Dave Ritchie

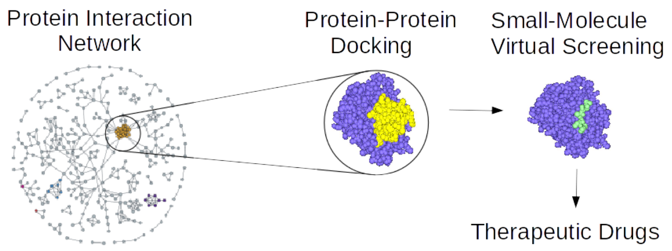
Team Orpailleur
Inria Nancy – Grand Est

Outline

Biological Importance of Protein-Protein Interactions

Protein interactions (PPIs) are central to many biological systems

- Humans have about 30,000 proteins, each having about 5 PPIs
- Understanding PPIs could lead to immense scientific advances

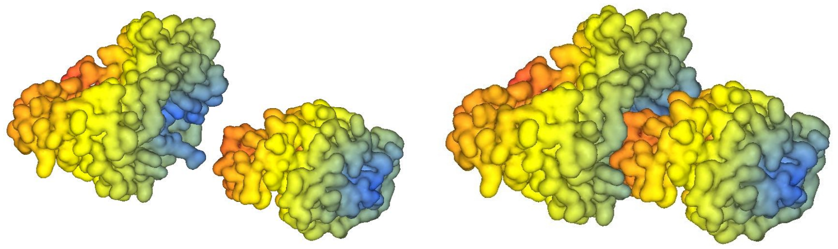


Protein-protein interactions as therapeutic drug targets

- Small “drug” molecules often inhibit or interfere with PPIs

Protein Docking – A Molecular Recognition Problem

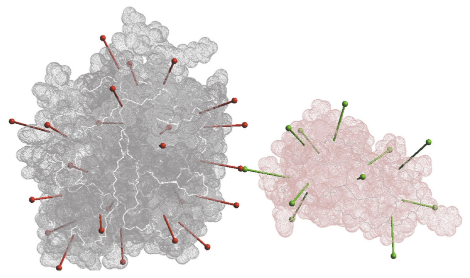
- A six-dimensional puzzle – do these proteins fit together?



- Yes, they fit!
- It is mostly a rotational problem: ONE translation plus FIVE rotations...
- But proteins are flexible => multi-dimensional space!
- So, how to calculate whether two proteins recognise each other?

ICM Docking – Multi-Start Pseudo-Brownian Search

- Stick pins in protein surfaces at 15Å intervals
- For each pair of pins, find minimum energy (6 rotations for each):
  - $E = E_{HVW} + E_{CVW} + 2.16E_{el} + 2.53E_{hb} + 4.35E_{hp} + 0.20E_{solv}$

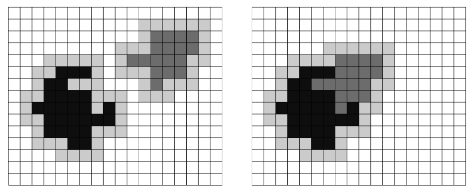


- Often gives good results, but is computationally expensive

Fernández-Recio, Abagyan (2004), J Mol Biol, 335, 843–865

Protein Docking Using Fast Fourier Transforms

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



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

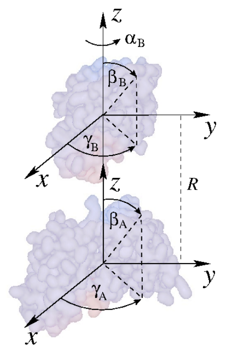
$$C[\Delta x, \Delta y, \Delta z] = \sum_{x,y,z} A[x,y,z] \times B[x+\Delta x, y+\Delta y, z+\Delta z]$$

- BUT for docking, have to repeat for many rotations – expensive!
- Conventional grid-based FFT docking = SEVERAL CPU-HOURS

Katchalski-Katzir *et al.* (1992) PNAS, 89 2195–2199

Protein Docking Using Polar Fourier Correlations

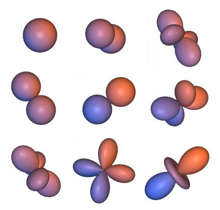
- Rigid docking can be considered as a largely ROTATIONAL problem
- This means we should use ANGULAR coordinate systems

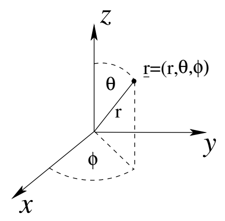


- With FIVE rotations, we should get a good speed-up?

Some Theory – 2D Spherical Harmonic Surfaces

- Spherical harmonics (SHs) are classical "special functions"

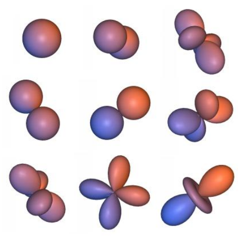




- SHs are products of Legendre polynomials and circular functions:
  - Real SHs: $y_{lm}(\theta,\phi) = P_{lm}(\theta)\cos m\phi + P_{lm}(\theta)\sin m\phi$
  - Complex SHs: $Y_{lm}(\theta,\phi) = P_{lm}(\theta)e^{im\phi}$
  - Orthogonal: $\int y_{lm} y_{kj} \mathrm{d}\Omega = \int Y_{lm} Y_{kj} \mathrm{d}\Omega = \delta_{lk}\delta_{mj}$
  - Rotation: $y_{lm}(\theta',\phi') = \sum_j R^{(l)}_{jm}(\alpha,\beta,\gamma) y_{lj}(\theta,\phi)$

Spherical Harmonic Molecular Surfaces

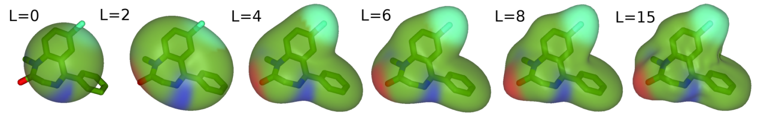
- Use spherical harmonics (SHs) as orthogonal shape "building blocks"



- Reals SHs $y_{lm}(\theta, \phi)$, and coeffcients a_{lm}
- Encode distance from origin as SH series:

$$r(\theta, \phi) = \sum_{l=0}^{L} \sum_{m=-l}^{l} a_{lm} y_{lm}(\theta, \phi)$$

- Calculate coefficients by numerical integration



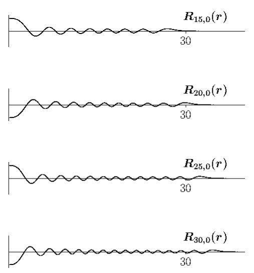
- Good for shape-matching, not so good for docking...

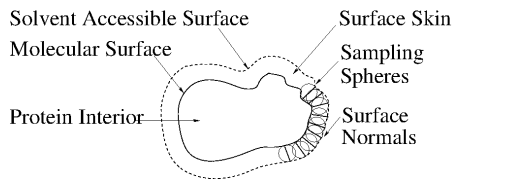
Ritchie and Kemp (1999), J. Comp. Chem. 20, 383–395

Docking Needs 3D Polar Fourier Representation

- Special orthonormal Laguerre-Gaussian radial functions, $R_{nl}(r)$

$$R_{nl}(r) = N_{nl}^{(q)} e^{-\rho/2} \rho^{l/2} L_{n-l-1}^{(l+1/2)}(\rho); \qquad \rho = r^2/q, \quad q = 20.$$





$$\sigma(\underline{r}) = \begin{cases} 1; & \underline{r} \in \text{surface skin} \\ 0; & \text{otherwise} \end{cases} \qquad \tau(\underline{r}) = \begin{cases} 1; & \underline{r} \in \text{protein atom} \\ 0; & \text{otherwise} \end{cases}$$

Polar Fourier polynomial: $\sigma(\underline{r}) = \sum_{n=1}^{N} \sum_{l=0}^{n-1} \sum_{m=-l}^{l} a_{nlm}^{\sigma} R_{nl}(r)\, y_{lm}(\theta, \phi)$

Analytic translations: $$a_{nlm}^{\sigma\prime} = \sum_{n'l'}^{N} T_{nl,n'l'}^{(|m|)}(R)\, a_{n'l'm}^{\sigma} \qquad (1)$$

SPF Protein Shape-Density Reconstruction

Interior density: $\tau(\underline{r}) = \sum_{nlm}^{N} a_{nlm}^{\tau} R_{nl}(r) y_{lm}(\theta, \phi)$

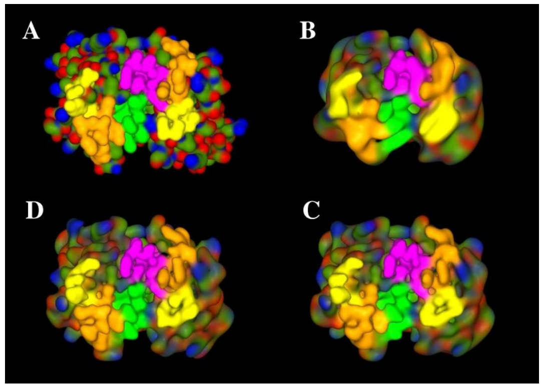
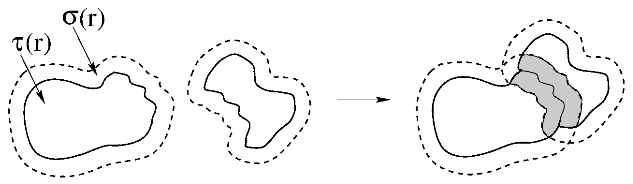


Image	Order	Coeffs
A	Gaussians	-
B	N = 16	1,496
C	N = 25	5,525
D	N = 30	9,455

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: $S_{AB} = \sum_{nlm} \left(a_{nlm}^{\sigma} b_{nlm}^{\tau} + a_{nlm}^{\tau}\left(b_{nlm}^{\sigma} - Q b_{nlm}^{\tau}\right)\right)$

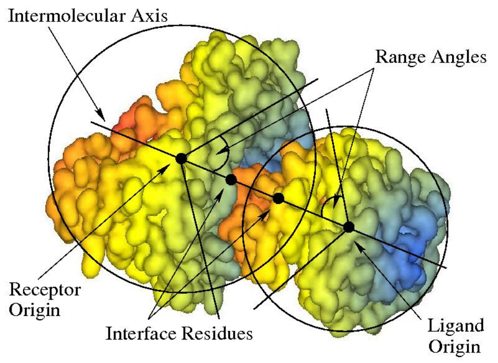
Search: 6D space = 1 distance + 5 Euler rotations: $(R, \beta_A, \gamma_A, \alpha_B, \beta_B, \gamma_B)$

Ritchie and Kemp (2000), Proteins Struct. Funct. Bionf. 39, 178–194

Hex SPF Correlation Example – 3D Rotational FFTs

- Set up 3D rotational FFT as a series of matrix multiplications:
- Rotate: $a'_{nlm} = \sum_{t=-l}^{l} R_{mt}^{(l)}(0, \beta_A, \gamma_A) a_{lt}$
- Translate: $a''_{nlm} = \sum_{kj}^{N} T_{nl,kj}^{(|m|)}(R) a'_{kjm}$
- Real to complex: $A_{nlm} = \sum_t a''_{nlt} U_{tm}^{(l)}, \quad B_{nlm} = \sum_t b_{nlt} U_{tm}^{(l)}$
- Multiply: $C_{muv} = \sum_{nl} A^*_{nlm} B_{nlv} \Lambda_{lv}^{um}$
- 3D FFT: $S(\alpha_B, \beta_B, \gamma_B) = \sum_{muv} C_{muv} e^{-i(m\alpha_B + 2u\beta_B + v\gamma_B)}$
- On one CPU, docking takes from 15 to 30 minute...

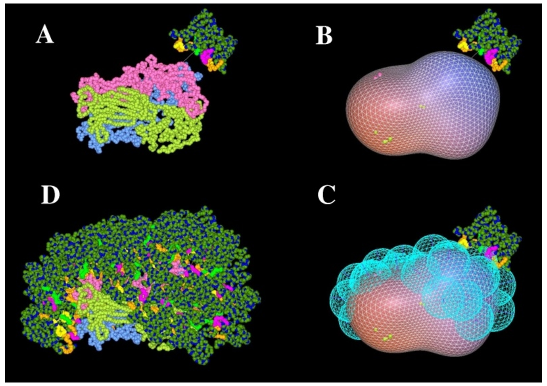
Exploiting Proir Knowledge in SPF Docking



- Knowing just one key residue can reduce search space enormously...
- This accelerates calculation and helps to reduce false-positives...

Docking Very Large Molecules Using Multi-Sampling

- Example: docking an antibody to the VP2 viral surface protein



The CAPRI Experiment

- CAPRI = "Critical Assessment of PRedicted Interactions"

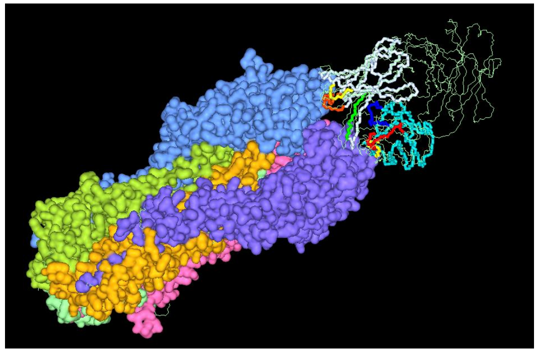
Predictor	Software	Algorithm	T1	T2	T3	T4	T5	T6	T7
Abagyan	ICM	FF			**			***	**
Camacho	CHARMM	FF	*					***	***
Eisenstein	MolFit	FFT	*	*					***
Sternberg	FTDOCK	FFT		*				**	*
Ten Eyck	DOT	FFT	*	*				**	
Gray		MC						**	***
Ritchie	Hex	SPF			**			***	
Weng	ZDOCK	FFT		**					**
Wolfson	BUDDA/PPD	GH	*						***
Bates	Guided Docking	FF	-	-	-				***
Palma	BIGGER	GF	-		-			**	*
Gardiner	GAPDOCK	GA	*	*	-	-	-	-	-
Olson	Surfdock	SH	*			-	-	-	-
Valencia		ANN	*	-	-	-	-	-	-
Vakser	GRAMM	FFT		*		-	-	-	-

$*$ low, $**$ medium, $***$ high accuracy prediction; $-$ no prediction

Mendez *et al.* (2003) Proteins Struct. Funct. Bionf. 52, 51–67

Hex Protein Docking Example – CAPRI Target 3

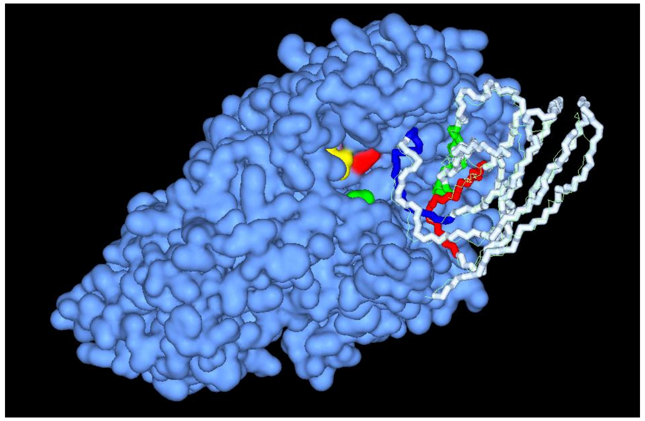
- Example: best prediction for CAPRI Target 3 – Hemagglutinin/HC63



Ritchie and Kemp (2000), Proteins Struct. Funct. Bionf. 39, 178–194

Ritchie (2003), Proteins Struct. Funct. Genet. 52, 98–106

Best Hex Orientation for Target 6 – Amylase/AMD9



- CAPRI "high accuracy" (Ligand RMSD $\leq$ 1Å)

Subsequent CAPRI Targets 8 – 19

Target	Description	Comments
T8	Nidogen-γ 3 - Laminin	U/U
T9	LiCT homodimer	build from monomer – 12Å RMS deviation
T10	TBEV trimer	build from monomer – 11Å RMS deviation
T11	Cohesin - dockerin	U/U; model-build dockerin
T12	Cohesin - dockerin	U/B
T13	SAG1 - antibody Fab	SAG1 conformational change: 10Å RMS
T14	MYPT1 - PP1δ	U/U; model-build PP1$\alpha \rightarrow$ PP1δ
T18	TAXI - xylanase	U/B
T19	Ovine prion - antibody Fab	model-build prion

- T15-T17 cancelled: solutions were on-line & found by Google !!
- T11, T14, T19 involved homology model-building step...

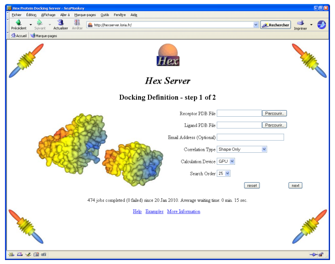
CAPRI Results: Targets 8–19 (2003 – 2005)

Software	T8	T9	T10	T11	T12	T13	T14	T18	T19
ICM	**		*	**	***	*	***	**	**
PatchDock	**	*	*	*	*	-	**	**	*
ZDOCK/RDOCK	**			*	***	***	***	**	**
FTDOCK	*		*	**	*		**	**	*
RosettaDock	-			**	***	**	***		***
SmoothDock	**				***	***	**	**	*
RosettaDock	***	-	-	**	***				**
Haddock	-	-	**	**		***	***		
ClusPro	**				***	*			*
3D-DOCK	**			*	*		**		*
MolFit	***			*	***		**		
Hex				**	***	*	*		
Zhou	-	-		-	***	**	*	*	
DOT					***	***	**		
ATTRACT	**		-	-	-	-	***		**
Valencia	*			*	*	-			-
GRAMM	-	-		-	-	-	**	**	
Umeyama				**	*				
Kaznessis	-	-			***				
Fano	-	-		*					

Mendez *et al.* (2005) Proteins Struct. Funct. Bionf. 60, 150-169

"Hex" and "HexServer"

- Hex: interactive docking ($\sim$ 33,000 downloads) – http://hex.loria.fr/
- Hexserver ($\sim$ 1,000 docking jobs/month) – http://hexserver.loria.fr/

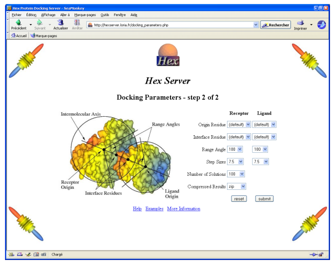

Hex Protein Docking Server - SeaMonkey
http://hexserver.loria.fr/

Hex Server

Docking Definition - step 1 of 2

Receptor PDB File	
Ligand PDB File	
Email Address (Optional)	
Correlation Type	Shape Only
Calculation Device	GPU
Search Order	25

474 jobs completed (0 failed) since 20 Jan 2010. Average waiting time: 0 min. 15 sec.
Fichier Édition Affichage Aller à Marque-pages Outils Fenêtre Aide
Précédent Suivant Actualiser Arrêter Rechercher Imprimer
Accueil Marque-pages
Hex
Parcourir..
reset
next
Help Examples More Information


Hex Protein Docking Server - SeaMonkey
http://hexserver.loria.fr/docking_parameters.php

Hex Server

Docking Parameters - step 2 of 2

	Receptor	Ligand
Origin Residue	(default)	(default)
Interface Residue	(default)	(default)
Range Angle	180	180
Step Sizes	7.5	7.5
Number of Solutions	100	
Compressed Results	zip	
Fichier Édition Affichage Aller à Marque-pages Outils Fenêtre Aide
Précédent Suivant Actualiser Arrêter Rechercher Imprimer
Accueil Marque-pages
Hex
Intermolecular Axis
Range Angles
Receptor Origin
Interface Residues
Ligand Origin
reset
submit
Help Examples More Information
Chargé

Ritchie and Kemp (2000), Proteins **39 178–194**

...

Macindoe et al. (2010), Nucleic acids Research, 38, W445–W449

Inside Hex – High Order FFTs, Multi-threading on GPUs

- SPF approach => analytic 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 2048 arithmetic "cores"
- Up to 8 Gb memory
- Easy API with C++ syntax
- Grid of threads model ("SIMT")

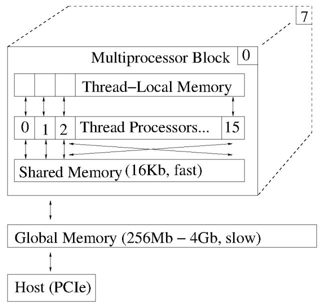
- BUT – for best results, need to understand the hardware...

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

Ritchie and Venkatraman (2010), Bioinformatics, 26, 2398–2405

CUDA Device Architecture

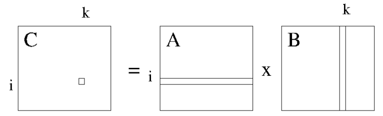
- Typically 8–16 multiprocessor blocks, each with 16 thread units


7
Multiprocessor Block 0
Thread–Local Memory
0 1 2 Thread Processors... 15
Shared Memory (16Kb, fast)
Global Memory (256Mb – 4Gb, slow)
Host (PCIe)

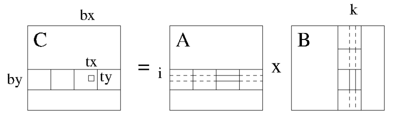
- NB. only a very small amount of fast shared memory is available
- NB. global memory is $\sim$ 80x slower than shared memory
- Strategy: aim for "high arithmetic intensity" in shared memory

CUDA Programming Example – Matrix Multiplication

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



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



- Thread-block algo uses TILES
- Tiles of 16x16 is just right!

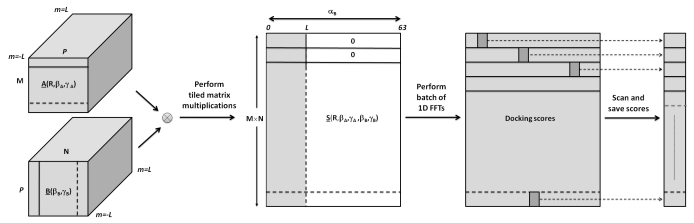
- Threads co-operate by reading & sharing tiles of A & B
- Multi-processor launches multiple blocks to compute all of C
- Executing thread-blocks concurrently hides global memory latency

GPU Implementation – Perform Multiple FFTs

- Calculate multiple 1D FFTs of the form:

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

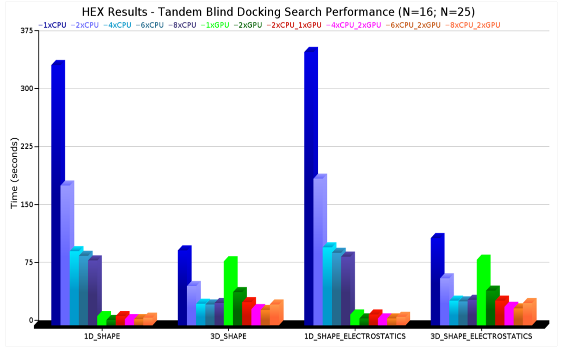
- Cross-multiply transformed A with rotated B coefficients
- Perform batch of 1D FFTs using cuFFT and save best orientations



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

Results – Multiple GPUs and CPUs

- With Multi-threading, we can use all available GPUs and CPUs



- Best performance: use 2 GPUs alone, or 6 CPUs plus 2 GPUs
- 2 GPUs => 6D docking in about 15 sec – important for large-scale!

Speed Comparison with ZDOCK and PIPER

- Hex: 52000 x 812 rotations, 50 translations (0.8Å steps)
- ZDOCK: 54000 x 6 deg rotations, 92Å 3D grid (1.2Å cells)
- PIPER: 54000 x 6 deg rotations, 128Å 3D grid (1.0Å cells)
- Hardware: GTX 285 (240 cores, 1.48 GHz)

	Kallikrein A / BPTI (233 / 58 residues)#					
	ZDOCK	PIPER[†]	PIPER[†]	*Hex*	*Hex*	*Hex*[‡]
FFT	1xCPU	1xCPU	1xGPU	1xCPU	4xCPU	1xGPU
3D	7,172	468,625	26,372	224	60	84
(3D)*	(1,195)	(42,602)	(2,398)	224	60	84
1D	–	–	–	676	243	15

- What's next ?
  - Better energy functions?
  - Modeling flexibility?
  - Multi-component complexes?
  - Cross-docking?

Conclusions

- (+) Rigid-body docking on a GPU now takes only a few seconds:
  - This was implemented using only 5 or 6 GPU kernels
- (–) Modeling protein flexibility during docking is still difficult
- SPF approach => high-throughput shape comparison now feasible:
  - All-vs-all docking ?
  - Electron-microscopy density fitting ?
  - Assembling multi-component machines ?
- (?) The next challenge – modeling "the structural interactome"

Thank You!

Acknowledgments

Vishwesh Venkatraman
Lazaros Mavridis

Anisah Ghoorah

Program and papers:

http://hex.loria.fr/

Hex Demo – Basic Operations

- Hex web site: http://hex.loria.fr/dist800/
- Loading structures into Hex
- Basic concepts: "receptor", "ligand", "complex" (reference)
- Graphical viewing modes
- Editing the scene (moving structures around)
- Setting docking parameters
- Launching a docking calculation
- Viewing the results
- Saving structures
- ...
- Ask me!
- Disclaimer: please remember, Hex is not "commercial" software!

Practical: CAPRI Target 40 – API-A/Trypsin

R Bao *at al.* (2009), J Biol Chem, 284, 26676–26684

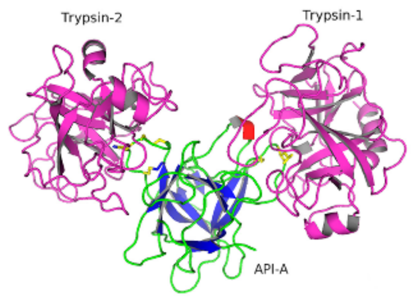
"The Ternary Structure of the Double-headed Arrowhead Protease Inhibitor API-A Complexed with Two Trypsins Reveals a Novel Reactive Site Conformation"

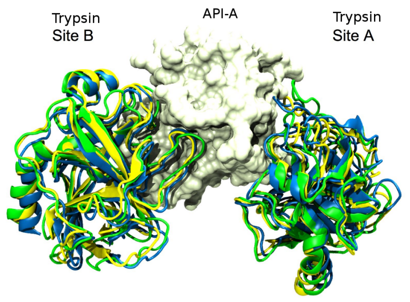
The double-headed arrowhead protease inhibitors API-A and -B from the tubers of *Sagittaria sagittifolia* (Linn) feature two distinct reactive sites, unlike other members of their family. Although the two inhibitors have been extensively characterized, the identities of the two P1 residues in both API-A and -B remain controversial. The crystal structure of a ternary complex at 2.84 Å resolution revealed that **the two trypsins bind on opposite sides of API-A and are 34 Å apart.** The overall fold of API-A site sides of API-A belongs to the β-trefoil fold and resembles that of the soybean Kunitz-type trypsin inhibitors. The two P1 residues [on API-A] were unambiguously assigned as **Leu87** and **Lys145**, and their identities were further confirmed by site-directed mutagenesis...

- The CAPRI challenge: **blind prediction of the two binding modes...**

CAPRI T40 Results

X-ray solution **Our predictions**





- Using Hex + MD refinement gave NINE "acceptable" solutions

Practical Activities

- Download the structures from: http://hex.loria.fr/emmsb/t40.tgz
    - t40_a.pdb (Trypsin 1)
    - t40_b.pdb (Trypsin 2)
    - t40_c.pdb (API-A)
    - t40_abc.pdb (solution)
    - t40.col (Hex colour file)
- Load the structures C+A or C+B as “receptor” and ”ligand”
- Experiment with different graphical viewing options
- Use the “edit mode” to try docking by hand
- Load the solution structure as “complex” and try again by hand
- Load the color file to highlight the key residues
- Does this help?
- Finally, place the API-A key residue near the trypsin site
- Set up and run a focused docking calculation (45 deg on each)
- View and analyse by eye the solutions generated