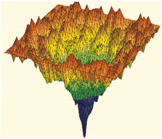
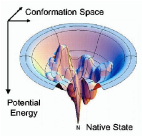
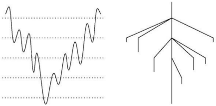
Exploration and characterization of energy landscapes: selected tools from the Structural Bioinformatics Library

`http://sbl.inria.fr`







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Introduction

Software: the SBL

Energy Landscapes analysis

Energy landscapes comparison

Comparing two clusterings

Exploration and characterization of energy landscapes: tools from the SBL

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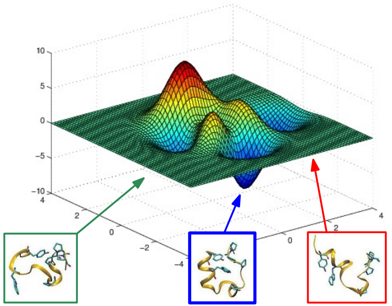
Emergence of macromolecular function(s) from Structure – Thermodynamics – Dynamics

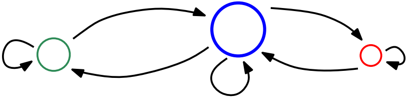


Potential Energy Landscape

- large number of local minima
- enthalpic barriers
- entropic barriers

Structure: stable conformations i.e. local minima of the PEL

Thermodynamics: meta-stable conformations i.e. ensemble of conformations easily inter-convertible into one - another.



Dynamics: transitions between meta-stable conformations e.g. Markov state model

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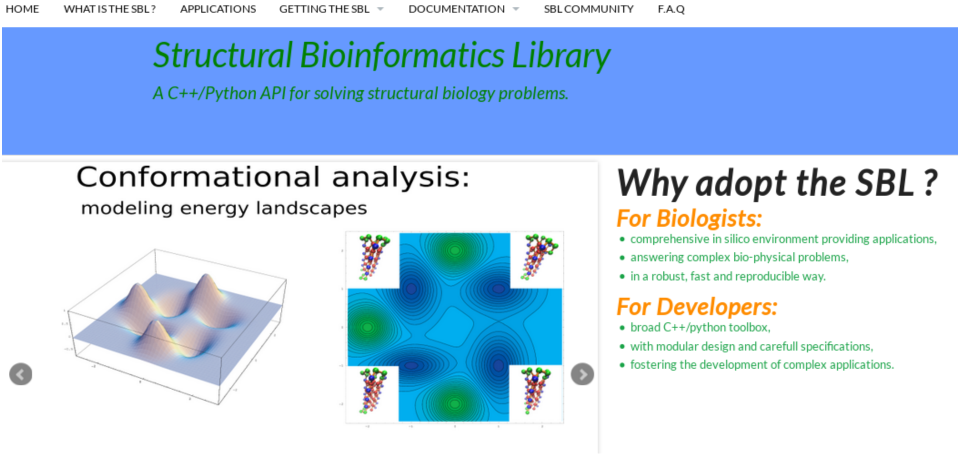
The Structural Bioinformatics Library

- Rationale for starting yet another library:
  - Many excellent environment / libraries, but low level algorithms and end-user applications entangled
  - Often hard / impossible to play legos with software components
  - Often hard / impossible to hybridize biophysical models (atomic, CG) and low level algorithms/applications

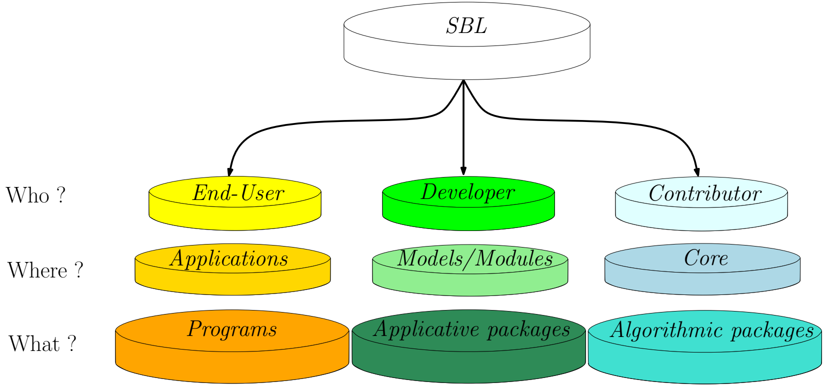
The Structural Bioinformatics Library

http://sbl.inria.fr



▷Ref: Cazals and Dreyfus; Bioinformatics, 2017

The Structural Bioinformatics Library: Architecture



Tour of the web site

- Web site: `http://sbl.inria.fr`
  - Applications
  - Online documentation

Using the SBL: the easy way

- Install with conda from the conda https://anaconda.org/sbl/
  - Delivers: executables (sbl-*.exe), documentation, demo / data sets
  - Currently: only linux package provided; MacOS . . . soon.
- Run demos provided in the Jupyter notebooks
  - Voronoi interfaces: https://sbl.inria.fr/doc/Space_filling_model_interface-user-manual.html
  - Lanscape explorers: https://sbl.inria.fr/doc/Landscape_explorer-user-manual.html

Advanced software design: C++ templates

- Template: parameter class used to instantiate a generic class/algorithm
- Traits class: template parameter with specific requirements

```
template <class Traits> class Explorer{
 public:

  typedef typename Traits::Conformation         Conformation;
  typedef typename Traits::Move_set_class       Extender;
  typedef typename Traits::Metropolis_criterion Accept_criterion;
};
```

- Template classes yields an un-challenged flexibility:
  - SBL-CORE: templated algorithmic classes coming with requirements
  - SBL-MODELS: models (geometric, biophysical) used to assemble traits classes
  - SBL-APPLICATIONS: *glued* models and core algorithms

Advanced software design C++: illustrations

▷ Example 1: force fields: three packages yield all force fields (CHARMM, AMBER, MARTINI,. . .)

– Rationale: a force field generically requires iterating and typing pairs / triples / quadruples of (pseudo-)atoms

– Base classes:
http://sbl.inria.fr/doc/group__Molecular__covalent__structure-package.html
http://sbl.inria.fr/doc/group__Molecular__coordinates-package.html
http://sbl.inria.fr/doc/group__Molecular__potential__energy-package.html

– Configuration files:
individual force fields in ffXML format

– Applications:
http://sbl.inria.fr/doc/group__Landscape__explorer-package.html
http://sbl.inria.fr/doc/group__Energy__landscape__analysis-package.html
http://sbl.inria.fr/doc/group__Energy__landscape__comparison-package.html

▷ Example 2: interfaces of macro-molecular complexes

– Rationale: an interface in a space filling model (atomic or CG) generically requires *facing* atoms

– Base classes:
http://sbl.inria.fr/doc/group__Molecular__structure__classifier-package.html
http://sbl.inria.fr/doc/group__Pointwise__interactions-package.html
http://sbl.inria.fr/doc/group__Molecular__interfaces-package.html

– Applications:
http://sbl.inria.fr/doc/group__Space__filling__model__interface-package.html
http://sbl.inria.fr/doc/group__Space__filling__model__interface__finder-package.html

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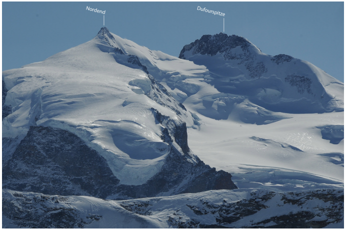
Landscapes: Significant Features versus Noise

When is a Local Maximum/minimum a Significant Peak/Lake?

- Key features in a landscape: lakes , peaks, passes
  - local minima, maxima, and *saddles* of the elevation function
- Defining a peak . . . a matter of scales
  - prominence: closest distance to the nearest local maximum with higher elevation
  - **culminance**: elevation drop to the saddle leading to a higher local maximum
- Some well known peaks have tame statistics: the Norden peak
  - fourth highest peak of the Mont Rose massif, 4609 meters
  - prominence: 575 meters; culminance: 94 meters



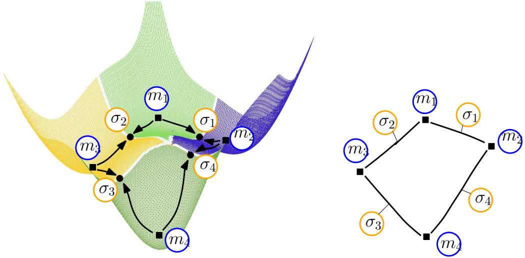
▷Ref:

http://www.zermatt.ch/en/page.cfm/zermatt_matterhorn/4000er/nordend

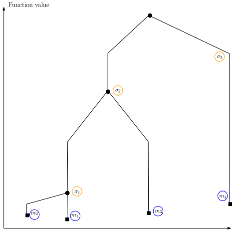
Height Functions and their Critical points: Key Concepts from Morse Theory

▷ Example: the Himmelblau function:

$$f(x, y) = (x^2 + y - 11)^2 + (x + y^2 - 7)^2.$$



Transition graphs



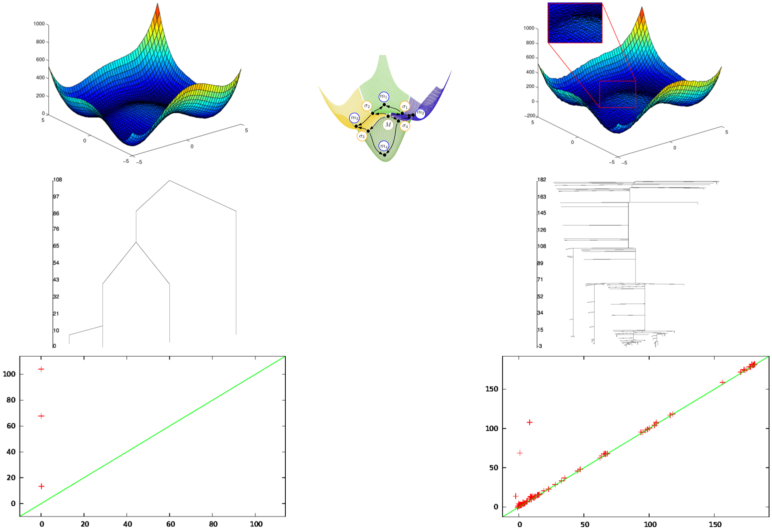
Disconnectivity graph

▷ NB: critical points and their connexions define the Morse-Smale-Witten (MSW) complex

```
▷Ref:  Milnor, Morse Theory, 1963
▷Ref:  Banyaga and Hurtubise, Morse homology, 2004
```

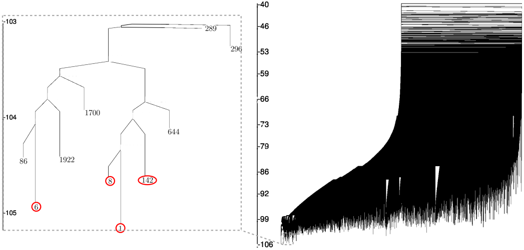
Landscape Analysis at a Glimpse: topological persistence

The Himmelblau function: $f(x, y) = (x^2 + y - 11)^2 + (x + y^2 - 7)^2$

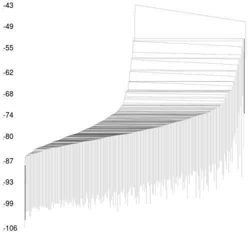


BLN69: Persistence reveals Frustration

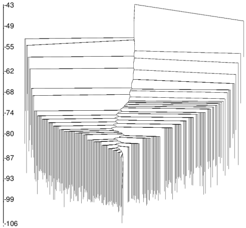
▷ Whole disconnectivity graph for the 458,082 local minima



▷ Persistence reveals frustration: persistence threshold 15 ϵ



▷ Persistence + clubbing saddles in energy slices of 0.5ϵ

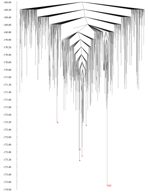


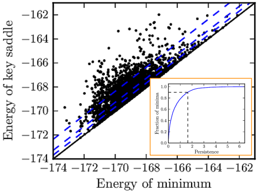
▷Ref: Cazals et al, J. Comp. Chem., 2015

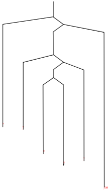
Analysis of sampled energy landscapes

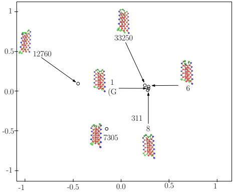
- ▷ Contributions: novel concepts and algorithms to

– Analyze conformational ensembles
– Analyze sampled energy landscapes: coarse graining with topological persistence









- ▷ Assessment:

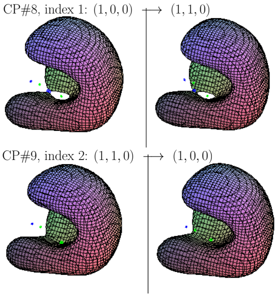
– State-of-the-art algorithms analysis/coarse-graining methods
– Most of the analysis geared towards potential energy landscapes
work ahead on free energy landscapes

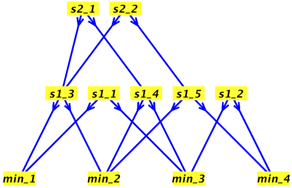
▷Ref: Cazals, Dreyfus, Mazauric, Roth, Robert; J. Comp. Chem., 2015
▷Ref: Carr, Mazauric, Cazals, Wales; J. Chem. Phys.; 2016

Morse Homology: Illustration

▷ Example: evolving homology of a 3D landscape defined by a polynomial

$$P = \left(x^2 + y^2 + z - 1\right)^2 + \left(z^2 + y^2 + x - 3\right)^2 + \left(x^2 + z^2 + y - 2\right)^2$$





NB: max at infinity not represented.

▷ Key construction: the **Morse-Smale-Witten chain complex** i.e. the connections between critical points whose indices differ by one is sufficient to compute the Betti numbers

▷Ref: R. Tom, Sur une partition en cellules...; CRAS; 1449
▷Ref: S. Smale; Differentiable dynamical systems; Bull. AMS; 1967
▷Ref: R. Boot, Morse theory indomitable, Pub. IHES, 1988

Intermezzo: higher order homology

- Stability of basins: order 0 homology
- Stability of loops: order 1 homology
  - Loops in RNA?
- ...

SBL packages

- Transition_graph_of_energy_landscape_builders
  - http://sbl.inria.fr/doc/Transition_graph_of_energy_landscape_builders-user-manual.html
- Energy_landscape_analysis
  - http://sbl.inria.fr/doc/Energy_landscape_analysis-user-manual.html

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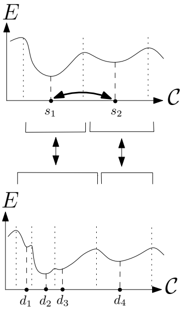
Comparing (Sampled) Energy Landscapes: Motivation

- Comparing (sampled) landscapes:
  - Assessing the coherence of two force2 fields for a given system (atomic, CG)
  - Comparing two related systems: e.g. wild type/mutated proteins
  - Comparing two simulations: different initial conditions and/or algorithms



- Idea: find a mapping between basins considering
  - the similarity between the *native states* (one per basin)
  - the coherence between the *volumes* of the basins (their probabilities)
  - the connectivity between basins

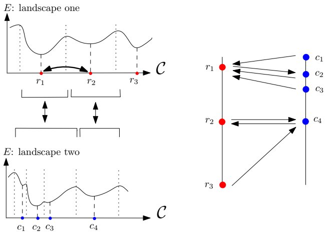
- Terminology: sampled (potential) energy landscape:
  - portion revealed by a simulation
  - given: minima, transitions between them, volumes of basins

Comparing Sets of Local Minima using a Minimum Oriented Spanning Forest (MSF): method

- ▷ Given two sets of local minima and a distance metric to compare them:

  each local minimum chooses its nearest neighbor (e.g. in the lRMSD sense)

- ▷ Example: comparing local minima of two landscapes



NB: local minima

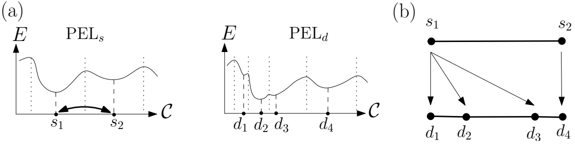
- all those discovered during exploration
- persistent ones only (remove ruggedness)

- ▷ Statistics:
  - ave. weight of edges from the first landscape to the second one: $\overline{w}^{MSF}_{1\rightarrow 2}$
  - ave. weight of edges from the second landscape to the first one: $\overline{w}^{MSF}_{2\rightarrow 1}$
- ▷ Remarks:
  - can be combined with topological persistence
  - algorithm, cf MST: Borůvka/ distributed Kruskal

Comparisons without Connectivity Constraints:

the Earth Mover Distance yields a Linear Program

- ▷ Consider two landscapes: PEL_s with n_s basins, PEL_d with n_d basins



- ▷ Problem Earth-Mover-Distance (EMD):
  find the transport plan of minimum cost, i.e. solution of the following linear program

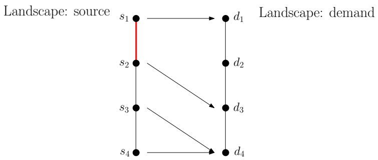
$$LP \begin{cases} \text{Cost: Min} \sum_{i=1,\ldots,n_s, j=1,\ldots,n_d} f_{ij} \times d_{\mathcal{C}}(s_i, d_j) & \\ \sum_{i=1,\ldots,n_s} f_{ij} = w_j^{(d)} & \forall j \in 1,\ldots,n_d, \\ \sum_{j=1,\ldots,n_d} f_{ij} \leq w_i^{(s)} & \forall i \in 1,\ldots,n_s, \\ f_{ij} \geq 0 & \forall i \in 1,\ldots,n_s, \forall j \in 1,\ldots,n_d \end{cases}$$

- ▷ Property: in OPT, the number of edges carrying flow is $O(n_s + n_d - 1)$
- ▷ Pros and cons:
  - Information used: location of minima, weight of basins
  - Linear program: solved in polynomial time
  - Connectivity information not used

▷Ref: Chvátal, Linear programming, 1983; Rubner, Tomasi, Guibas, IJCV,

Comparisons with Connectivity Constraints

▷ Earth Mover Distance: may violate the connectivity constraints



▷ Def: Transport plan with connectivity constraints: every connected subgraph of PEL_s exports towards a connected subgraph of PEL_d
There may exist an exponential number of connected subgraphs

▷ Problem EMD-CCC: maximum flow under constraints of {maximum cost, connectivity constraints (and transport plan size M)}

▷ Complexity results

- Decision versions of EMD-CC and EMD-CCC: NP-complete
- Optimization version of EMD-CC is not in APX
  If $\mathbf{P} \neq \mathbf{NP}$: no polynomial algorithm with constant approx factor

▷ Algorithm `Alg-EMD-CCC-G`

- Greedy polynomial algorithm producing solutions i.e. respecting the connectivity constraints and the max cost. Complexity: $O(n^3 m^2)$, with n and m the num. vertices of the graphs

SBL packages

- Energy_landscape_comparison
  - http://sbl.inria.fr/doc/Energy_landscape_comparison-user-manual.html

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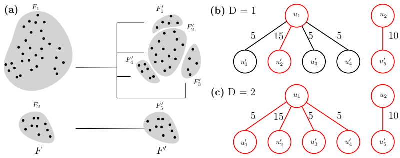
Comparing two clusterings using matchings between clusters of clusters

F. Cazals, D. Mazauric, R. Tetley, and R. Watrigant

Preprint 2017

https://sbl.inria.fr/doc/D_family_matching-user-manual.html



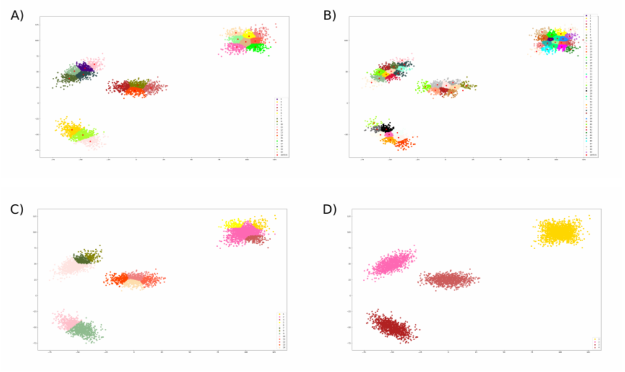
Comparing clusterings: at which *scale* do clusters merge?

What is the *right* number of clusters?

▷ Example:

- Using `k-means++` to cluster 5000 samples from five Gaussian blobs
- Using D-family matching to infer the *right/natural* # of clusters

(A) k-means++, $k = 20$ (B) k-means++, $k = 50$

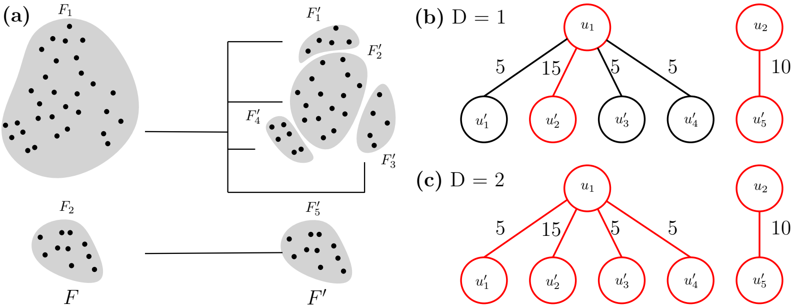


(C) $D = 3$, 17 meta clusters, $\Phi_D(G) = 4068$ (D) $D = 4$, 4 meta clusters, $\Phi_D(G) = 5000$

On the stability of clusterings

- Clustering methods:
  Come in many guises
  Have (a plethora of) parameters

- Key questions: are clusterings stables / what is the right clustering?



- Comparing clusterings via clusters of clusters
  - Find a matching between clusters of clusters
  - Meta-cluster: induced connected component of the *intersection graph*
  - Matching complexity governed by the *diameter* of the metaclusters

Comparing clusterings using matchings between clusters of clusters

▷ Contributions:

– Formalization of the D-family matching problem

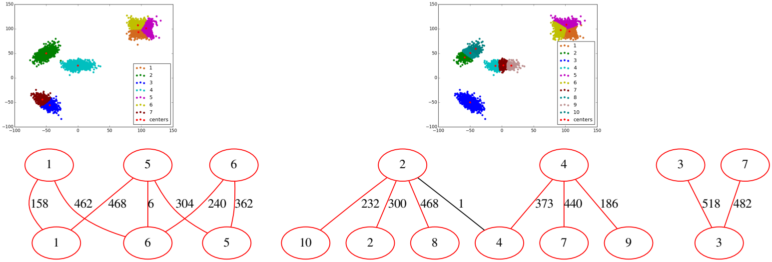
– NP-completeness results and unbounded approximation ratio for simple strategies
  Open: is the problem APX hard?

– Exact polynomial time algos. for selected intersection graphs (trees)

– Heuristics for general graphs

– Extensive experiments (vs. the variation of information)

▷ Stability of kmeans++:



▷Ref: Cazals, Mazauric, Tetley, Watrigant; submitted

SBL packages

- D_family_matching:
  - http://sbl.inria.fr/doc/D_family_matching-user-manual.html

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Enjoy. . .

- ▷ The science

Enjoy. . .

- ▷ The scenery

Enjoy. . .

▷ The SBL

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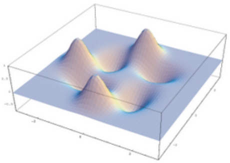
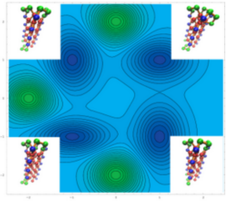
Structural Bioinformatics Library

A C++/Python API for solving structural biology problems.

Conformational analysis:

modeling energy landscapes





Why adopt the SBL ?

For Biologists:

- comprehensive in silico environment providing applications,
- answering complex bio-physical problems,
- in a robust, fast and reproducible way.

For Developers:

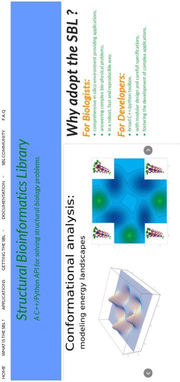
- broad C++/python toolbox,
- with modular design and carefull specifications,
- fostering the development of complex applications.

Enjoy. . .

- Find the right mixture. . .

The Science

The Scenery



The SBL