Simulated annealing for solving protein structures using restraints and molecular fitting

Overview

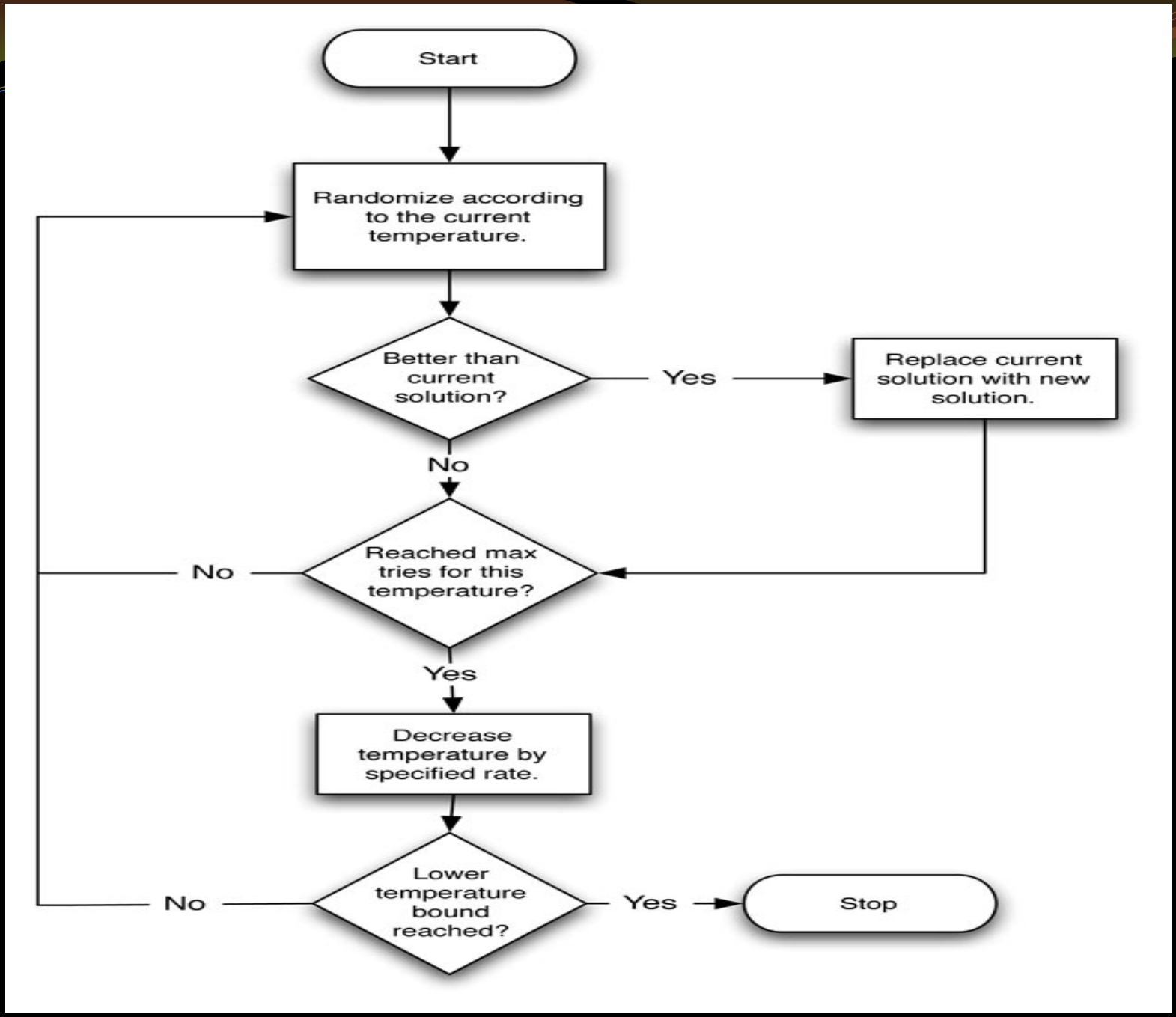
- Simulated Annealing
- Solving protein structures Using restrained molecular Dynamics
- X-ray Crstallographic Refinement
- Molecular Dynamics Refinement of NMR Data
- Molecular Fitting

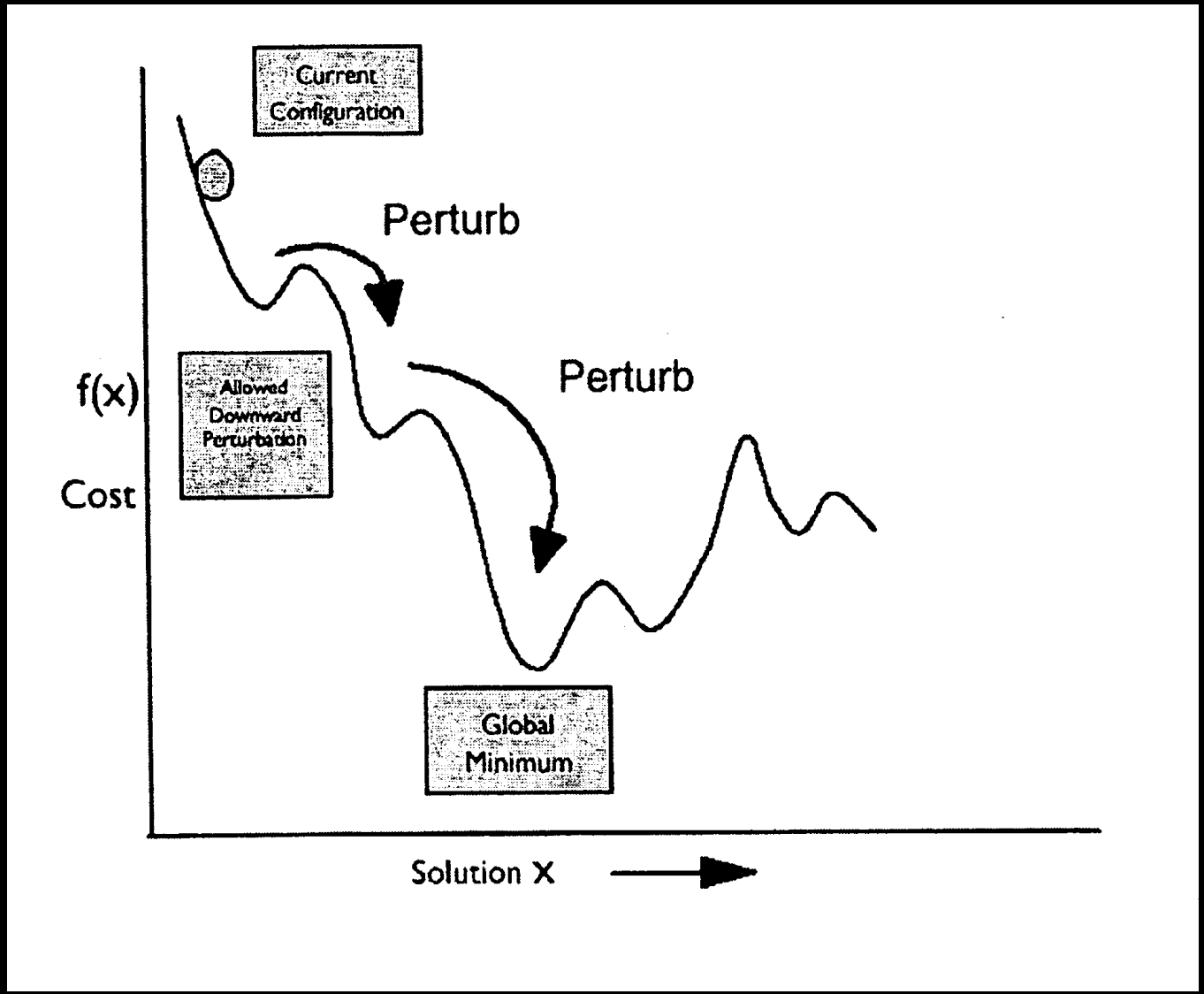
Simulated Annealing

- Annealing is the process in which the temperature of a molten substance is slowly reduced until the material crystallises to give a large scale crystal.

- The perfect crystal that is obtained corresponds to the global minimum of the free energy.

- Simulated annealing is a computational method that mimics the process in order to find the optimal or best solutions to problems which have a large number of possible solutions.

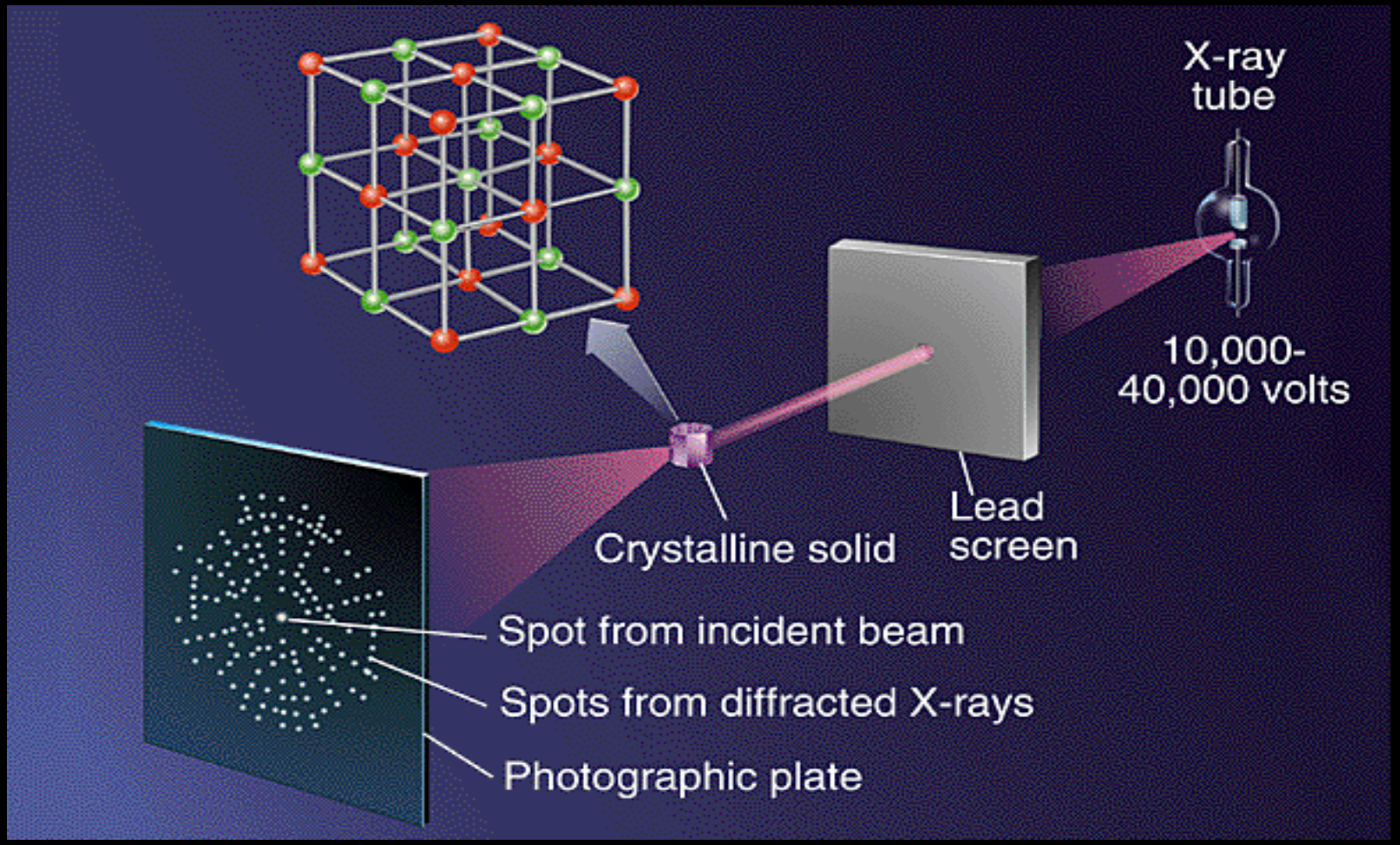

Start
Randomize according to the current temperature.
Better than current solution?
Yes
Replace current solution with new solution.
No
Reached max tries for this temperature?
No
Yes
Decrease temperature by specified rate.
Lower temperature bound reached?
No
Yes
Stop


Current Configuration
Perturb
Perturb
Allowed Downward Perturbation
f(x)
Cost
Global Minimum
Solution X

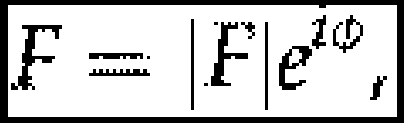
Solving protein structures with restrained Molecular Dynamics and Simulated Annealing

- A particularly important application of molecular dynamics, in conjugation with simulated annealing is in the refinement of X-ray and NMR data to determine three dimensional structures.

X-ray Crystallographic refinement



- The total signal reaching the detector is obtained by integrating the electron density over the whole crystal and is expressed as the structure factor, F.



Phase Problem:

- To obtain the electron density distribution it is necessary to guess, calculate or indirectly estimate the phases.

- For proteins the most common stratergy is multiple isomorphous replacement.

- The objective of the refinement is to obtain a structure that gives the best possible agreement with the experimental data.

$$R = \frac{\sum \left| |F_{obs}| - |F_{calc}| \right|}{\sum |F_{obs}|}$$

- X-ray refinement is time consuming ,requires substantial human involvement and is a skill which usually takes several years to acquire.

- Jack and Levitt introduced molecular modelling techniques into the refinement in the form of an energy minimization step that was performed alternately with the least squares refinement.

- This approach was shown to give convergence to better structures.

- These methods have a dramatic impact on the refinement of X-ray and NMR structure of proteins.

- In the restrained MD approach the total potential energy is written as the sum of the usual potential energy and the penalty term, as usual:

$$E_{\text{tot}} = \mathcal{V}(\mathbf{r}^N) + E_{\text{sf}}$$

- The additional penalty function that is added to the empirical potential energy function in restrained dynamics X-ray refinement has the form:

$$E_{\text{sf}} = S \sum [|F_{\text{obs}}| - |F_{\text{calc}}|]^2$$

Molecular dynamics refinement of NMR Data

- In the simplest molecular dynamics approach harmonic restrain terms of the form $k(d - d_0)^2$ is incorporated.
- d is the distance between the atoms in the current conformation
- d0 is the desired distance dynamics approach derived from the NMR spectrum.
- k is a force constant

$$v(d) = k(d - d_0)^2 \qquad d > d_0$$

$$v(d) = 0 \qquad d \leq d_0$$

$$v(d) = k_l(d - d_l)^2 \qquad d < d_l$$

$$v(d) = 0 \qquad d_l \leq d \leq d_u$$

$$v(d) = k_u(d - d_u)^2 \qquad d_u < d$$

Molecular Fitting

- Fitting is the procedure whereby two or more conformations of the same or different molecules are oriented in space so that particular atoms or functional groups are optimally superimposed upon each other.
- The molecular fitting algorithm requires a numerical measure of the difference between two structures when they are positioned in space.
- The objective of the fitting procedure is to find the relative orientations of the molecules in which this function is minimized

- The most common measure of the fit between two structures is the RMSD.

$$\mathrm{RMSD} = \sqrt{\frac{\sum_{i=1}^{N_{\mathrm{atoms}}} d_i^2}{N_{\mathrm{atoms}}}}$$

Reference:

- http://bioinfopakistan.ucoz.com/news/simulated_annealing/2011-08-23-191
- Leach A.R., Molecular modelling Principles and Applications., 2nd edition,2001,9,483-491

THANK YOU