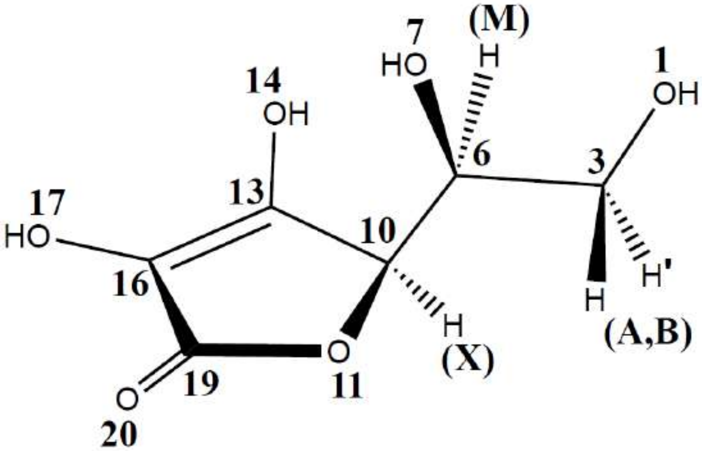
Tutorial 3: Geometry Optimisation of Vitamin C Molecule

Problem Statement

The focus of this tutorial is to depart from problem classes involving the search for functions to represent data, and demonstrate how ROptimus can be flexibly applied to arbitrary problem classes provided that they are formulated in accordance with ROptimus specifications. Additionally, this tutorial will illustrate that ROptimus can act as an optimisation kernel while calling external programs to execute a significant amount of the necessary computation for the optimisation process.

In this tutorial, ROptimus will be used, as an illustrative example, to 3D geometry optimise a molecular structure. Specifically, ROptimus will be used to determine the optimal values of two dihedral angles in the L-ascorbic acid (Vitamin C) molecule such that the molecule is in its ground state energy conformation. Vitamin C was selected to be the studied molecule because it has more than one freely rotating carbon-carbon bond and the potential for intramolecular hydrogen bonding due to the presence of multiple hydroxyl groups. Moreover, Vitamin C is not a particularly large molecule. Due to these circumstances, Vitamin C can serve as a non-trivial case (as opposed to simpler molecules like ethane for instance), but one that does not require several days or weeks of calculations to arrive to optimal solutions (the optimisation procedures below took roughly 14-18 hours to terminate).

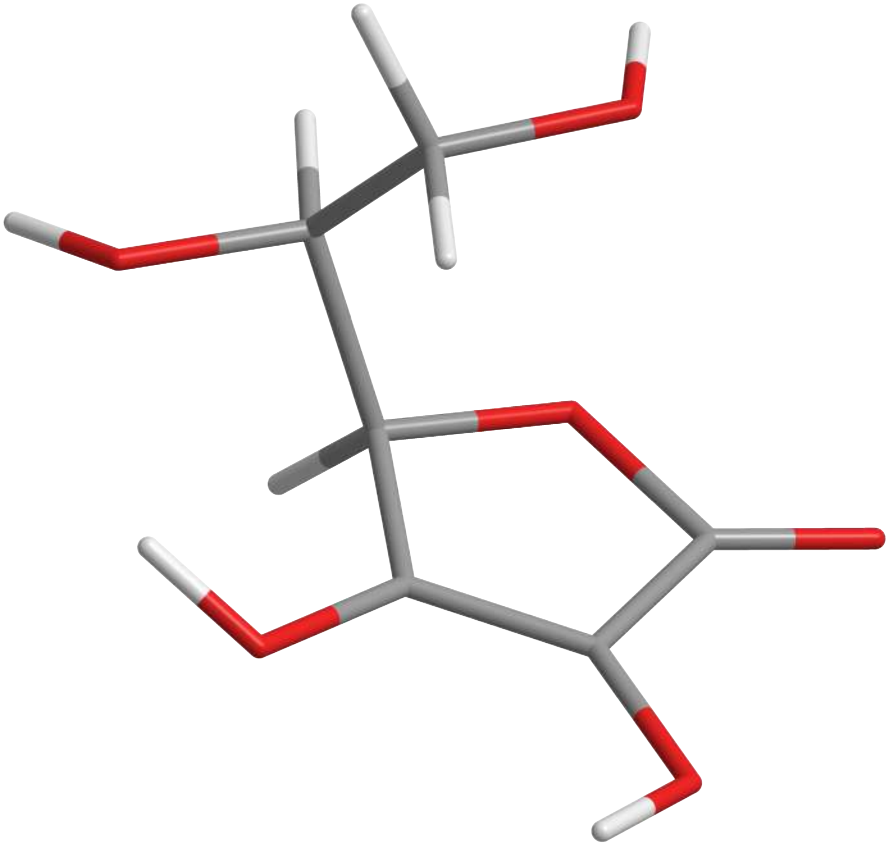
This is the molecular structure of Vitamin C, with the numbering of non-hydrogen atoms provided from the scheme used in geometry specification:

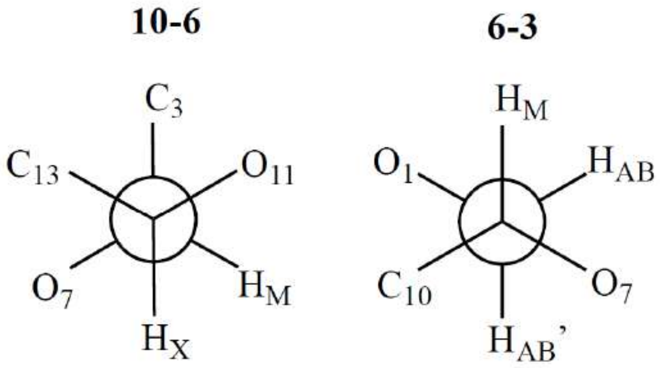


The major geometric features that drive the overall state of the molecule are the two C-C bonds in this structure: the bond joining carbon 3 and 6, and the bond joining carbon 6 and 10. The ground state conformation of Vitamin C will likely be a conformation such that steric clashes are minimised while also allowing for close proximity and right orientation between hydrogen bond donor and acceptor atoms. In the following sections, we formalise this optimisation problem and use ROptimus to arrive at the solution.

Defining ROptimus Inputs

As in the previous tutorials, we must first rigorously define the parameters that we are optimising. Let us begin by defining a dihedral angle as it will be used to our molecular geometry: a dihedral angle is the angle between two intersecting planes, where each plane is specified by 3 atoms of which 2 are common between both planes. Thus, a total of 4 atoms are needed to specify a dihedral angle. The conformation of Vitamin C with respect to its two freely rotating C-C bonds can be specified *via* two dihedral angles. Let ψ be the dihedral angle defined by the atoms numbered 1, 3, 6 and 7 and let ϕ be the dihedral angle defined by the atoms numbered 7, 6, 10 and 11. Having defined these two angles, we can now define the parameter set `K` as a numeric vector of length 2 whose entries are ψ and ϕ. We will arbitrarily initialise ψ and ϕ to have value 180. The corresponding Vitamin C conformation is illustrated below using a 3D structure and Newman projections along the two rotatable carbon-carbon bonds:





In the 3D structure, grey denotes carbon, red denotes oxygen and white denotes hydrogen atoms.

```r
K <- c(PHI=180, PSI=180)
```

Now we will specify a model function `m()` that will operate on `K`. Starting from an arbitrary molecular conformation, altering the value of `K` will likely cause certain clashes or non-optimal interactions between atoms in the molecule that are not used in the definition of the angles ψ and ϕ. As such, after receiving an input set of parameters `K`, `m()` will have to alter the 3D location of constituents atoms while holding `K` fixed to arrive at the most stable geometry for the input `K`. Here, unlike in previous tutorials, to accomplish this task m() will call an external program MOPAC. MOPAC is a program for semiempirical quantum mechanics (QM) calculations, and can perform constrained and unconstrained geometry optimisations to arrive at a stationary state (note that calling MOPAC for a single initial geometry instance does not guarantee a global minimum will be found). MOPAC takes as input the specification of an initial molecular geometry in addition to an indication of which molecules the program is able to displace (or angles it can alter) and outputs a nearby local minimum molecular conformation with its corresponding energy in kcal/mol. For this optimisation problem, the input to MOPAC will be structured as a Z matrix, a common form for describing a molecular conformation which consists of using lengths, angles and dihedral angles with respect to previously defined atoms to define new atoms in the conformation.

The function m() will construct a Z matrix for Vitamin C using the input dihedral angles K and default values for the remaining geometric relationships needed to define the molecule. m() will then call MOPAC with the newly constructed Z matrix, specifying that all relationships may be altered by QM optimisation, except the input dihedral angles K. Finally, m() will return the energy calculated by MOPAC *via* PM6 Hamiltonian.

Note that to avoid non-convergence issues when calling MOPAC, m() returns a default energy value of −100 kcal/mol if a call to MOPAC does not terminate within 10 seconds (over-simplifications just for the sake of this illustrative example). Also, note that although m() requires no additional data on top of K to operate, m() must still be defined to take an input DATA in accordance with ROptimus specifications. Lastly, note that a local installation of MOPAC (2016) is required to execute this optimisation procedure. Below is the definition of m():

```r
m <- function(K, DATA){

  notconvergedE = -100.00
  # this should be your local path to MOPAC
  mopac.cmd = "/home/group/prog/mopac2016/MOPAC2016.exe"
  clean = TRUE

  # MOPAC semiempirical QM input file preparation, with given PHI and PSI
  # dihedral angles.

  geo <- c(
    "RHF PM6 EF GEO-OK MMOK T=10 THREADS=1",
    "Vitamin C with two controllable dihedral angles psi(7,6,3,1) and phi(11,10,6,7)",
    "  ",
    "O     0.00000000  0    0.0000000  0    0.0000000  0     0     0     0",
    "H     0.98468620  1    0.0000000  0    0.0000000  0     1     0     0",
    "C     1.43651250  1  110.7230618  1    0.0000000  0     1     2     0",
    "H     1.10751723  1  103.6603154  1 -167.5282722  1     3     1     2",
    "H     1.10658657  1  110.2236860  1  -51.3620456  1     3     1     2",
    "C     1.53950336  1  112.8074046  1 -123.2791585  1     3     4     5",
    paste0("O     1.42824262  1  103.4315186  1 ",K["PSI"]," 0     6     3     1"),
    "H     0.99584949  1  109.9022382  1 -165.7055126  1     7     6     3",
    "H     1.11472171  1  108.4417082  1   75.1535637  1     6     7     8",
    "C     1.54244170  1  109.4042184  1 -120.8240216  1     6     7     9",
    paste0("O     1.46313669  1  105.7792445  1 ",K["PHI"]," 0    10     6     7"),
    "H     1.11252563  1  112.8336666  1 -114.5813834  1    10     6    11",
    "C     1.51686608  1  113.4849244  1 -112.8332453  1    10    12    11",
    "O     1.34410484  1  125.3617342  1  179.6090511  1    13    10    11",
    "H     1.03381724  1  110.9736522  1  -13.3419919  1    14    13    10",
    "C     1.36084908  1  124.8906459  1  167.6242325  1    13    14    15",
    "O     1.35614887  1  131.9374989  1   -0.0333000  1    16    13    14",
    "H     1.00338885  1  109.4220239  1    0.3798200  1    17    16    13",
    "C     1.49109250  1  118.0837177  1 -179.7749947  1    16    17    18",
    "O     1.18961787  1  136.9144035  1   -0.6060924  1    19    16    17",
    "  "
  )

  # Submitting the MOPAC optimisation job, where all the spatial parameters
  # are relaxed except the pre-set PHI and PSI angles. The job is run requesting
  # maximum 10 seconds of time limitation. Most (if not all) complete within
  # half a second. Cases with unrealistic clashes will likely take much longer,
  # hence the job will be interrupted and notconvergedE value will be returned
  # for the energy evaluation.
  random.id <- as.character(sample(size=1, x=1:10000000))
  write(geo, file=paste0(random.id,".mop"))
  system(paste0(mopac.cmd," ",random.id,".mop"))

  if( file.exists(paste0(random.id,".arc")) ){
    e.line <- grep("HEAT OF FORMATION",
                   readLines(paste0(random.id,".arc")),
                   value=TRUE)
    e.line <-  strsplit(e.line," ")[[1]]
    O <- as.numeric(e.line[e.line!=""][5])
  } else {
    O <- notconvergedE
  }

  if(clean){
    file.remove(grep(random.id, dir(), value=TRUE))
  }

  return(O) # heat of formation in kcal/mol
}
```

Next, we define the function `u()` which returns an energy `E` and a quality `Q` of the candidate solution. Since the `m()` will already output a value for the physical energy of the candidate Vitamin C conformation, `u()` can simply set `E` to be the same return value of `m()`. We will make `u()` set `Q` to be the negative of the return value of `m()` such that candidate conformations with lower energies produce higher values of quality `Q`. Again, although `u()` does not require any additional data to accomplish this functionality, it must nevertheless be written to optionally accept an input parameter `DATA`.

```
u <- function(O, DATA){
  result   <- NULL
  result$Q <- -O
  result$E <-  O
  return(result)
}
```

Finally, we define the alteration function `r()`. `r()` will randomly select either ψ or ϕ to alter. Thereafter, `r()` randomly increases or decreases the selected angle by 2 degrees. `r()` will also ensure that $\psi, \phi \in [-180.0, 180.0]$ throughout the optimisation process.

```
r <- function(K){
  K.new <- K
  # Setting the alteration angle to 2 degrees:
  alter.by <- 2
  # Randomly selecting a term:
  K.ind.toalter <- sample(size=1, x=1:length(K.new))
  # Altering that term by either +alter.by or -alter.by
  K.new[K.ind.toalter] <-
    K.new[K.ind.toalter] + sample(size=1, x=c(alter.by, -alter.by))

  # Setting the dihedral angles to be always within the -180 to 180 range.
  if( K.new[K.ind.toalter] > 180.0 ){
    K.new[K.ind.toalter] <- K.new[K.ind.toalter] - 360
  }

  if( K.new[K.ind.toalter] < -180.0 ){
    K.new[K.ind.toalter] <- K.new[K.ind.toalter] + 360
  }

  return(K.new)
}
```

The process of determining the energy of a conformation corresponding to a given set of angles ψ, ϕ is the most computationally intensive part of this optimisation formulation. Having defined the necessary inputs for `Optimus()`, it should be apparent that this calculation will entirely be handled by MOPAC. This ability to serve as an optimisation kernel and flexibly be knitted to an external program is one of the many strengths of ROptimus.

Defining a Benchmark Solution

Before calling `Optimus()`, we have established a benchmark solution to be used to independently evaluate the ability of ROptimus to arrive to correct ψ and ϕ combination. In order to explore the energy landscape associated with the parameter space of ψ and ϕ, a PM6 optimisation was performed on 10 conformers picked from the wells pf a more comprehensive potential energy surface scanning through MM2 molecular mechanics force field (the details of PM6 and MM2 are not important for the purposes of this tutorial). This resulted in the identification of 7 energy minima, shown in the table below (listed in increasing order by energy):

Table 7: Seven conformational minima calculated for Vitamin C with PM6.

	E (kcal/mol)	PHI	PSI
Conformation 1	-233.206	92.58	74.19
Conformation 2	-232.877	50.60	-172.79
Conformation 3	-231.800	-169.67	-41.23
Conformation 4	-230.822	47.43	-166.61
Conformation 5	-230.274	-172.20	-54.45
Conformation 6	-225.214	-75.69	-104.44
Conformation 7	-224.875	-73.31	155.02

We will assume that the above listed conformations comprehensively represent most, if not all, of the possible minima in the parameter space of ψ and ϕ. Under this assumption, Conformation 1 should be considered as the ground state conformation of Vitamin C. The accuracy of the results produced by ROptimus can thus be judged by comparing them to the data listed in the above table. It is important to recognize that the "resolution" of ψ and ϕ when being optimised by ROptimus is set to 2 degrees due to the manner in which `r()` was defined. As such, results produced by ROptimus that are within plus or minus 2 degrees of a reference conformation should be tolerated.

Acceptance Ratio Simulated Annealing ROptimus Run

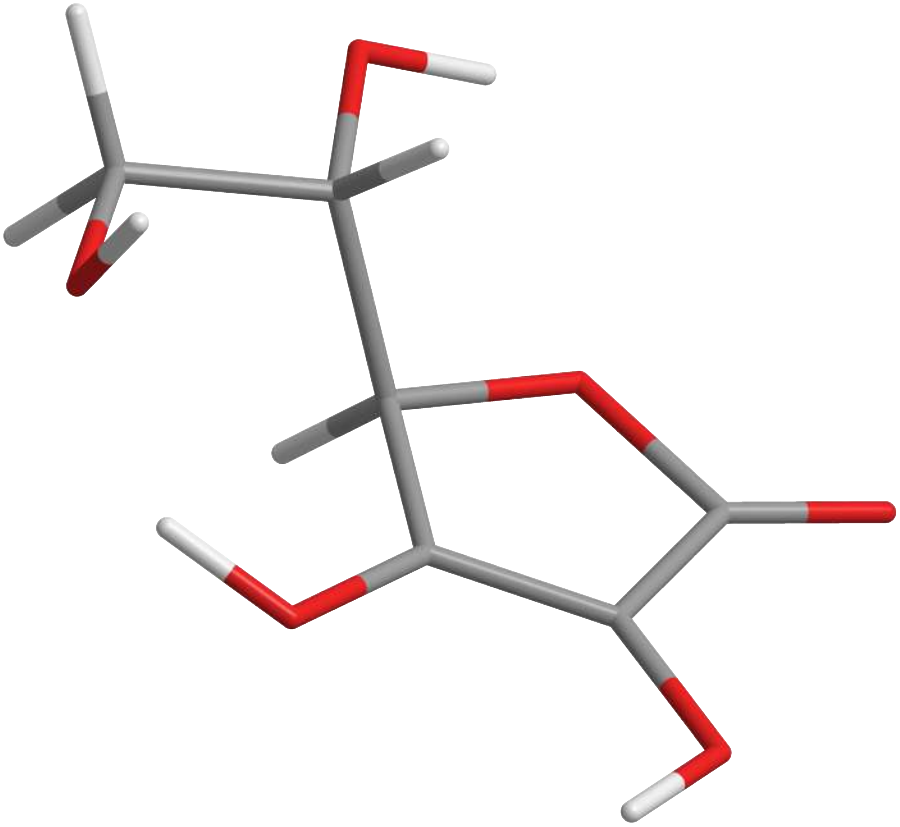
For the Acceptance Ratio Annealing run, we will set `NUMITER` to 100 000 because each optimsation step is more costly due to the relatively computationally expensive calls to MOPAC. Moreover, we will set `CYCLES` to 2. Although this shortens the length of an annealing cycle to 50 000 steps (whereas 100 000 steps per cycle has been kept constant over the previous tutorials), having more than 1 annealing cycle is likely more beneficial than insisting on a cycle lasting 100 000 steps as opposed to 50 000.

```
Optimus(NCPU=4, OPTNAME="vitamin_4_SA",
        NUMITER=100000, CYCLES=2, DUMP.FREQ=50000, LONG=FALSE,
        OPT.TYPE="SA",
        K.INITIAL=K, rDEF=r, mDEF=m, uDEF=u, DATA=NULL)
```

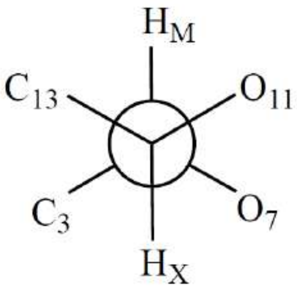
Table 8: 4-core Acceptance Ratio Simulated Annealing results from ROptimus runs.

	E (kcal/mol)	PHI	PSI
CPU 1	-232.874	50	-172
CPU 2	-232.353	-158	30
CPU 3	-232.874	50	-172
CPU 4	-232.874	50	-172

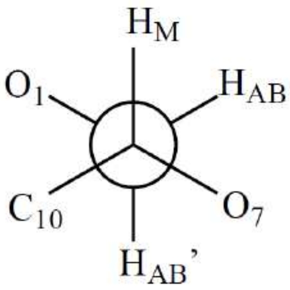
CPUs 1, 3 and 4 all arrived at a conformation defined by $\{\phi = 50, \psi = -172\}$, with an energy of -232.874 kcal/mol. The below 3D structure and Newman projections depict this solution:



10-6

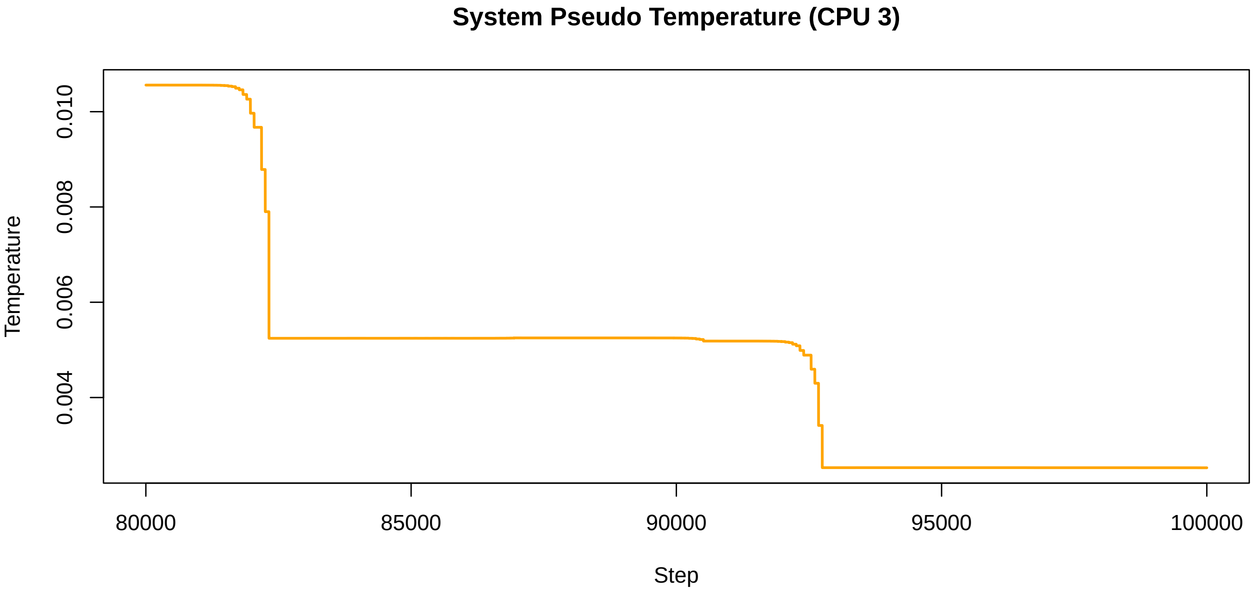


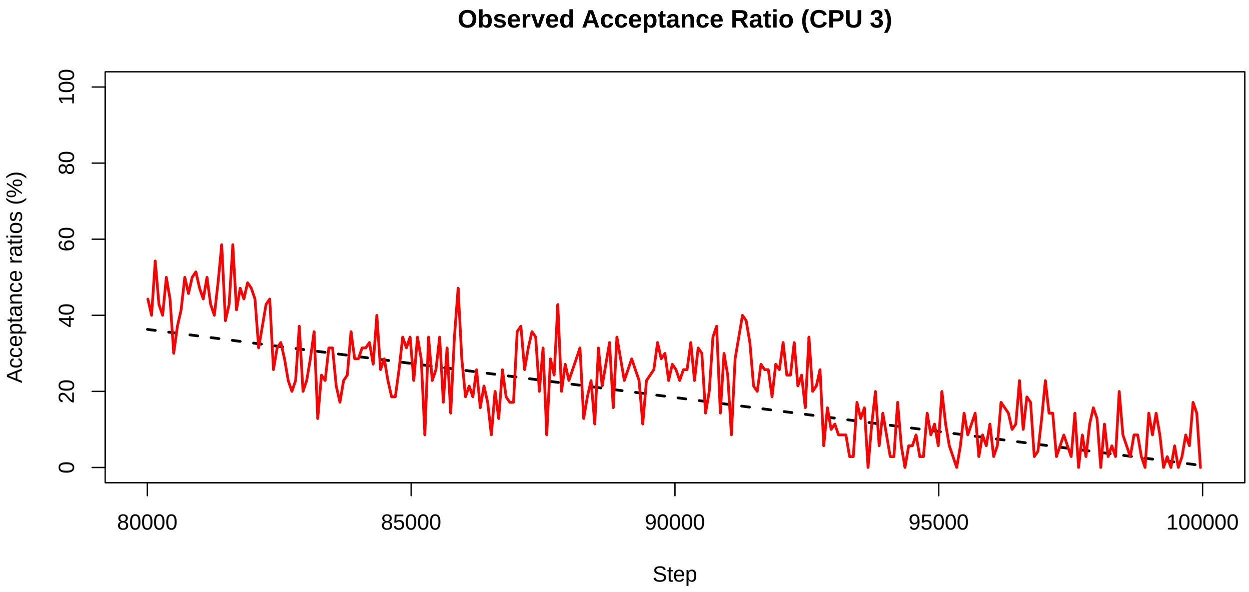
6-3



This conformation is equivalent to benchmark Conformation 2. Thus, in this example, Acceptance Ratio Simulated Annealing was able to find the Vitamin C conformation with the second lowest energy in the parameter space. This performance is strong, especially given that the limited steps and cycles executed, and that the energy difference between Conformation 1 and Conformation 2 is only −0.329 kcal/mol.

The graphs below illustrate the system psuedo temperature and observed acceptance ratio for the last 20 000 optimisation iterations executed by CPU 3.





Acceptance Ratio Replica Exchange ROptimus Run

Let us now consider the Replica Exchange version of ROptimus on 12 processors with the variable `ACCRATIO` defined as in the previous tutorials.

```
ACCRATIO <- c(90, 82, 74, 66, 58, 50, 42, 34, 26, 18, 10, 2)
```

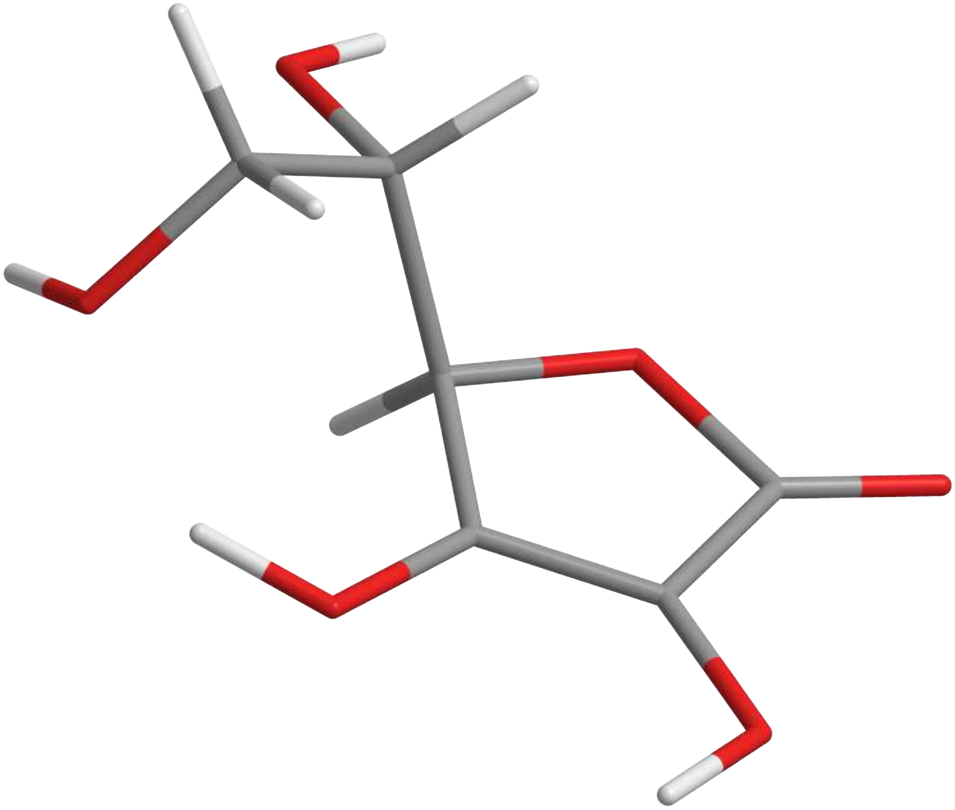
Just as in the Acceptance Ratio Simulated Annealing run, we will set `NUMITER` to 100 000. Furthermore, we will set `EXCHANGE.FREQ` to 500 such that the number of iterations between subsequent exchanges between replicas is 200 as it was in **Tutorial 2**. For the same reasons as in **Tutorial 2**, we will set `STATWINDOW` to 50 for the Replica Exchange run.

```
Optimus(NCPU=12, OPTNAME="vitamin_12_RE",
        NUMITER=100000, EXCHANGE.FREQ=500, STATWINDOW=50, DUMP.FREQ=50000, LONG=FALSE,
        OPT.TYPE="RE", ACCRATIO=ACCRATIO,
        K.INITIAL=K, rDEF=r, mDEF=m, uDEF=u, DATA=NULL)
```

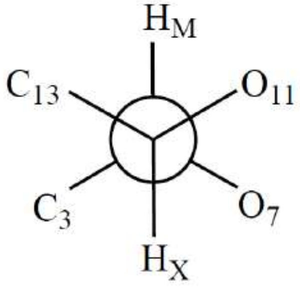
Table 9: 12-core Acceptance Ratio Replica Exchange results from ROptimus run.

	Replica Acceptance Ratio	E (kcal/mol)	PHI	PSI
CPU 1	90	-229.2359	-164	-178
CPU 2	82	-229.2359	-164	-178
CPU 3	74	-233.1453	82	84
CPU 4	66	-233.1979	90	76
CPU 5	58	-229.2359	-164	-178
CPU 6	50	-232.8742	50	-172
CPU 7	42	-233.1947	94	74
CPU 8	34	-229.2359	-164	-178
CPU 9	26	-229.2359	-164	-178
CPU 10	18	-227.6394	180	158
CPU 11	10	-229.2359	-164	-178
CPU 12	2	-229.2359	-164	-178

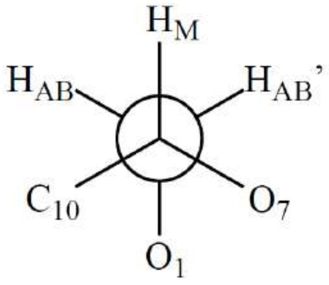
Of the 12 replicas, CPU 4 recovered the conformation with the lowest energy (−233.1979), defined by $\{\phi = 90, \psi = 76\}$. The below 3D structure and Newman projections depict this solution:



10-6



6-3

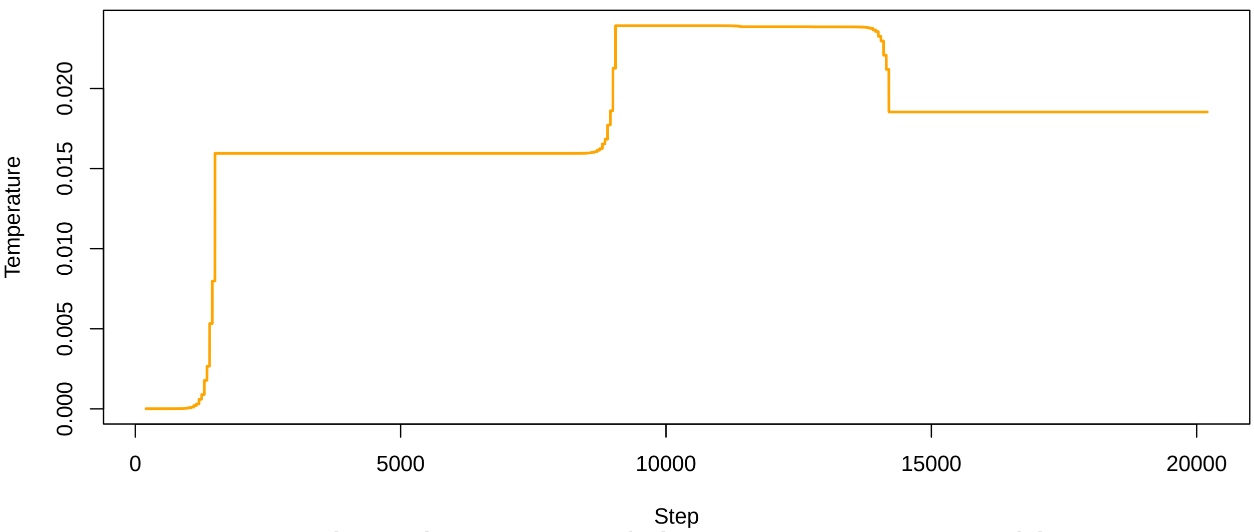


This solution corresponds to reference Conformation 1, the global minimum energy state for Vitamin C. Thus, for this optimisation problem, under the limits of the set number of steps and cycles, the Replica Exchange version of ROptimus outperformed Acceptance Ratio Annealing by succeeding in finding the global minimum of the energy landscape.

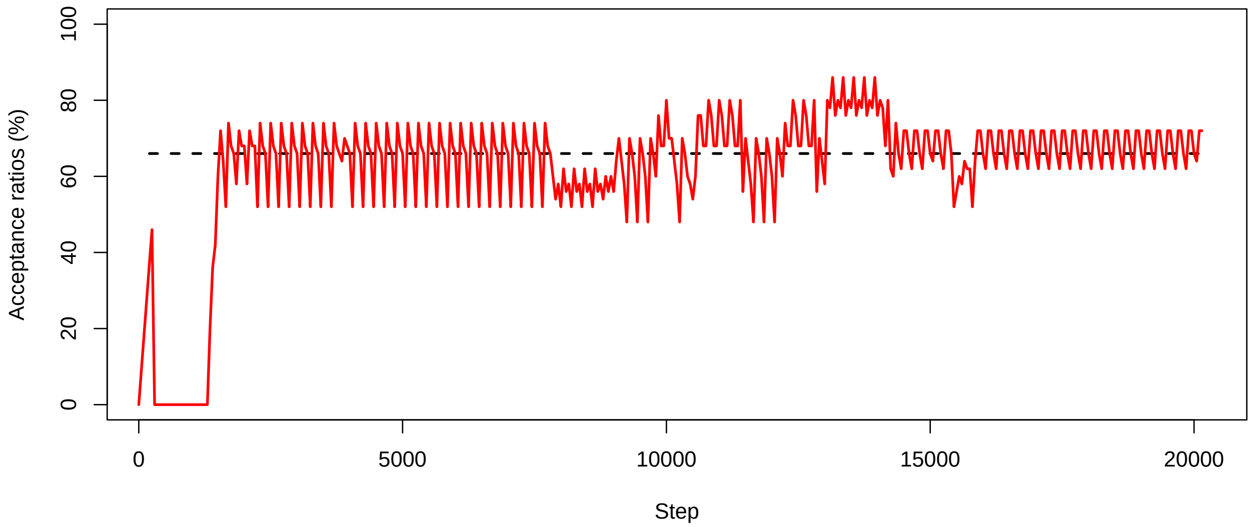
If we compare the solution found by CPU 4 to benchmark Conformation 1, it is evident that the value for ϕ found by ROptimus lies slightly outside of the plus or minus 2 degree window that was discussed earlier. Contrarily, CPU 7 finds a solution $\{\phi = 94, \psi = 74\}$ which does lie strictly within the resolution window. Despite this, the solution of CPU 4 has a slightly lower energy (−233.1979) than the solution of CPU 7 (−233.1947) and so represents a better solution. Finally, notice that Replica 6 recovered the same conformation that was identified by Acceptance Ratio Simulated Annealing ROptimus.

The below graphs illustrate the system pseudo temperature and observed acceptance ratio for the first 20 000 optimisation iterations executed by CPU 4 (66% acceptance ratio replica).

System Pseudo Temperature (CPU 4 – 66% Acceptance Ratio)



Observed Acceptance Ratio (CPU 4 – 66% Acceptance Ratio)



When the optimisation process is first initialised, it is very unlikely that the input initial temperature is conducive to the target acceptance ratio. As such, the adaptive thermoregulation alters the system pseudo-temperature considerably and rapidly to align the observed acceptance ratio with the target acceptance ratio, as can be seen in the above two graphs. Moreover, as stated in the previous tutorial, an exchange between two replicas often has a similar effect of introducing a parameter configuration that is not conducive to the current system pseudo temperature, which necessitates significant temperature adjustments. Accordingly, sharp increases or decreases in the system pseudo temperature and significant changes in the value around which the observed acceptance ratio oscillates in the graph above likely indicate steps at which an exchange involving replica 4 occurred.

Summary

We are now familiar with how to structure a more complex optimisation problem, involving an external program, to be solved with ROptimus as a kernel. On the particular example of geometry optimisation here, we saw that the Simulated Annealing mode of ROptimus was able to find the second lowest local minimum (under restricted number of annealing cycles), while the Replica Exchange mode recovered the global energy minimum.

Table 10: Summary of solutions.

	Energy (kcal/mol)	PHI	PSI
Ground State Reference	-233.2060	92.58	74.19
ROptimus (AR Simulated Annealing)	-232.8740	50.00	-172.00
ROptimus (AR Replica Exchange)	-233.1979	90.00	76.00