Optimus User Manual

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Contents

Introduction

Motivation

For a complex model, where the unknown parameters cannot be determined by conventional linear or non-linear fitting techniques, methods for optimisation, based on the biased random sampling of the parameter space, are the methods of choice (Cowles and Carlin 1996). In such cases, the quality of the solution found, following some optimisation protocol, depends on that protocol's ability to effectively explore the parameter space (Gilks, Richardson, and Spiegelhalter 1996) and be drawn to more favourable areas in that space. Many existing methods perform well for certain modelling scenarios, but fail in others due, in part, to an inefficient exploration of the parameter space and easy trapping into local minima with regard to the metrics for the quality of the found solutions. In this manual, we present Optimus, a universal Monte Carlo optimisation engine in R with acceptance ratio annealing, replica exchange and adaptive thermoregulation. It can universally interface with any modelling initiative through its interfacing functions, and optimise the model parameters by effectively exploring the parameter space. Depending on the desires of the user, Optimus can execute either an annealing or a replica exchange procedure, however, both driven by acceptance ratio adjustment, rather than pseudo-temperature, for the acceptance or rejection of moves.

This manual will begin with a basic overview of Monte Carlo optimisation and the common temperature-based simulated annealing framework. It will then proceed with a presentation of the acceptance ratio annealing procedure of Optimus, its adaptive thermoregulation feature, and its replica exchange procedure. After an explanation of how to download the Optimus R package from GitHub and install it locally, five stand-alone tutorials will be presented to illustrate how users should employ Optimus and to demonstrate its flexibility as an optimisation engine across a wide variety of optimisation scenarios. Finally, an "Advanced User Manual" section is included, in which all possible input parameters to Optimus are outlined and the output formats are detailed.

Briefly on Monte Carlo and Temperature-Driven Simulated Annealing Procedure

Let us assume that our model is a certain function $m()$ that performs operations on the inputted $\mathbf{K}$ coefficient set and returns the observable object $O = m(\mathbf{K})$. Our task is to optimise $\mathbf{K}$, the set of coefficients, so that the error metric $u(O)$ that measures the violations from the target O^{trg} set by the model-generated O is minimal. In a Monte Carlo optimisation procedure, we can define a pseudo-energy $e(u)$ of the system as a function of $u()$, where lower values of the pseudo-energy e correspond to better candidate solutions $\mathbf{K}$. In order to find a better set of $\mathbf{K}$, we need to alter it by a certain rule $r()$ that, if repeated many times, enables the sampling of the parameter space for $\mathbf{K}$. One can then evaluate the pseudo energies before and after the alterations:

$$E_1 = e \circ u \circ m(\mathbf{K})$$
$$E_2 = e \circ u \circ m \circ r(\mathbf{K})$$

We then accept or reject the move, meaning we accept the new set of $r(\mathbf{K})$ coefficients as the new $\mathbf{K}$ or revert back to the previous $\mathbf{K}$, guided by the following acceptance probability, as postulated in a Metropolis criterion (Chib and Greenberg 1995), (Chen and Roux 2015):

$$p_{accept} = min(1, e^{-\frac{\Delta E}{T}})$$
$$\Delta E = E_2 - E_1$$

where T is the pseudo temperature, that should be always greater than 0. For a given $\Delta E > 0$ energy difference, one would have different stringency for accepting the move, depending on the value of the pseudo

temperature T. Therefore, in case the Monte Carlo simulation was to drive the **K** set to a state where any further move would increase the pseudo energy great enough for the moves to be almost always rejected, then one could overcome that and further sample the other values in the parameter space by increasing the value of the pseudo temperature.

To this end, one way to overcome the barriers is by using the technique known as simulated annealing, where we anneal the temperature gradually from some higher value to a lower value during the course of the simulation (Kirkpatrick 1984). The parts of the simulation where the pseudo temperature is higher, allows relatively unconstrained exploration of the parameter search space, whereas those parts with a lower pseudo temperature limit the search to a more local area of the energy landscape and associated parameter space. Multiple cycles of this annealing procedure can thus be executed to increase the overall sampling.

Acceptance Ratio Annealing Procedure

A significant limitation of pseudo-temperature-based simulated annealing, while used only in an optimisation objectives, is that a given scheme of temperature annealing might be efficient for some models or pseudo-energy metrics, but not efficient for others (Ingber 1993). A temperature for a given system at a given point of the annealing cycle that is designated to be quite permissive in terms of accepting the moves, can actually not be permissive for some other models or systems simulated. This depends on the value and scale of the ΔE energy difference, as can be seen in the equation for p_{accept}, and can be affected by any of the $e()$, $u()$, $m()$ components and the system configuration **K**. This necessitates a pre-adjustment of the pseudo-temperature values from one modelling objective to another. Furthermore, even within a single model optimisation procedure on a defined system, the pseudo-energy metric can shift into a scale (due to a significant alteration/shift in the system as per the alteration rule $r()$) that does not match with the selected temperature scheme anymore, leading to a poor sampling of the parameter space when optimisation is at stake within restricted time and computational capacity. This can often be the case when the pseudo energy of the system does not exhibit a smooth dependency on **K**, loosely meaning that similar values of **K** do not necessarily produce similar pseudo-energy values.

To this end, in general cases where

A) we do not deal with energies and temperatures that display the smoothness or roughness emulating real physical systems, such as while simulating molecular systems through Monte Carlo simulations;
B) we are only interested in final optimised configuration of **K**, and do not need to characterise the statistical populance of the ensemble of reachable states/solutions,

we can anneal a metric for crossing different barriers that is more transferable to different systems and system configurations. As such a metric, Optimus, when in its default mode, uses the acceptance ratio, expressed as a fraction of accepted moves within certain number of past steps (STATWINDOW).

In a given annealing cycle, Optimus constructs a linear target acceptance ratio schedule for each step based on an initial target acceptance ratio, a final acceptance ratio and the number of iterations in each cycle for a given optimisation run (all of which can be specified as inputs). Once the optimisation process begins, Optimus calculates an observed acceptance ratio at the end of each STATWINDOW (a fixed number of steps which can be specified by the user) by calculating the fraction of the accepted moves from all the past trials in the current STATWINDOW. Thereafter, Optimus compares the observed acceptance ratio with the target acceptance ratio based on the annealing schedule and determines whether and how to alter the system pseudo-temperature (adaptive thermoregulation) to align the observed acceptance ratio with the target ratio at the end of the following STATWINDOW. Thus, by employing acceptance ratio annealing and adaptive thermoregulation, Optimus is able to methodically explore the parameter space for **K** even when no smooth relationship exists between **K** and the system pseudo-energy.

Adaptive Thermoregulation

All decisions governing the adaptive pseudo-temperature alterations on the system are made by a Temperature Control Unit (TCU) in Optimus. Note, that the TCU is completely encapsulated as a backend unit, such that modifications can be easily made by advanced users if needed. This section articulates the exact protocol followed by the default state of the TCU.

The initial system temperature is specified as an input argument. At the end of each STATWINDOW, if the observed acceptance ratio is within a fixed range T.DELTA (specified as an input argument) of the target acceptance ratio based on the annealing schedule, the TCU will make no change to the current system pseudo temperature. If the observed acceptance ratio is less than the ideal ratio and outside the range of T.DELTA, the TCU will increase the system pseudo temperature by a value T.ADJSTEP (the initial value of T.ADJSTEP is specified as an input argument). Similarly, if the observed acceptance ratio is greater than the ideal ratio and outside the range of T.DELTA, the TCU will reduce the temperature by a value T.ADJSTEP.

If the observed acceptance ratio keeps being below the ideal acceptance ratio for TSCLnum (an integer input argument) number of subsequent STATWINDOWs, T.ADJSTEP will be increased by a factor T.SCALING (an input argument). Similarly, T.ADJSTEP will also be decreased by a factor T.SCALING if the observed acceptance ratio is greater than the ideal acceptance ratio for TSCLnum subsequent STATWINDOWs. T.ADJSTEP is reset to its original input value whenever a series of subsequent observed acceptance ratios being greater than/less than ideal acceptance ratios is broken. If ever the TCU subtracts T.ADJSTEP from the current temperature and the result is a negative value, the system pseudo-temperature is set to T.MIN (an input argument). The final feature of the TCU is that although the initial system pseudo temperature is specified by the user, if multiple annealing cycles are employed, the initial pseudo-temperature for acceptance ratio annealing cycles after the first cycle is inferred from the decisions of the TCU on previous cycles.

This collection of decision rules that comprise the TCU result in pseudo-temperature alterations that cause the observed acceptance ratios during Optimus optimsation runs to follow the ideal acceptance ratios remarkably well. Moreover, as will be highlighted in the five tutorials below, large temperature alterations are often required to align the observed acceptance ratios with the ideal ratios, a task which Optimus excels at, whereas other protocols would have difficulty and result in poor parameter sampling.

Replica Exchange Procedure

Optimus additionally supports replica exchange as an optimisation mode which can be selected in place of acceptance ratio annealing, provided that the user has access to multiple processors (ideally at least 4, and preferably 8 or more). The inspiration for this additional mode was taken from the parallel tempering Monte Carlo techniques and Replica Exchange Molecular Dynamics (REMD) simulations (Sugita and Okamoto 1999). In particular, REMD simulation is a technique employed to obtain equilibrium sampling of a molecule (for instance, a protein) at a certain fixed (usually the lowest in a range) temperature. Let $T = \{T_1, T_2, ..., T_n\}$ be a set of n distinct temperatures for which $T_1 < T_2 < ... < T_n$. In REMD, n replicas of molecular dynamics simulations for a given system (molecule) are initialised at each $T_i \in T$. Note that each temperature T_i corresponds to a slightly different potential of the examined system to roam the energy landscape and cross the barriers. States possible to populate at a temperature T_i can become a bit more accessible at a temperature T_{i+1} and so on. If the state configurations in adjacent replicas are allowed to exchange, the simulation will be able to overcome energy barriers at various temperature replicas and thoroughly explore the parameter space. Moreover, for configuration x_n in replica T_i and configuration x_m in replica T_{i+1}, equilibirum sampling is achieved by selecting appropriate exchange probabilities (Sugita and Okamoto 1999), generally expressed as:

$$p_{re} = min(1, P(T_{i+1} - T_i; E(x_n) - E(x_m))$$

Thus, overall, replica exchange simulations can be executed by simulating n replicas of a simulation at distinct temperatures simultaneously and independently; and randomly selecting two configurations in adjacent replicas and exchanging them with probability p_{re}.

Optimus modifies the Monte Carlo analogue of the replica exchange approach to apply to any arbitrary optimisation problem with two primary modifications. Firstly, due to the aforementioned transferability of utilising acceptance ratio as a controlling metric rather than pseudo temperature in arbitrary systems, Optimus initialises n replicas with different fixed target acceptance ratios as opposed to fixed temperatures, and uses the previously described TCU for the adaptive thermoregulation to keep up with the fixed acceptance ratio values for varying $\mathbf{K}$ within a given replica. Secondly, since that Optimus is only concerned with finding an optimal solution and is not compliant with any equilibrium sampling of the parameter space (see the A and B criteria described above), after two candidate configurations are selected for exchange, they are necessarily exchanged (this can be viewed as setting $p_{re} = 1$ in the above procedure) (Ballard and Jarzynski 2009). The exchange regiment is controlled through the input, with default optimal value that works well in most cases. By relaxing the equilibrium sampling criterion, the parameter space can be more extensively explored for the sole reason of finding an optimal solution. This approach produced good results, as illustrated in the tutorials, and is a viable alternative to the acceptance ratio annealing mode in Optimus, when the user has access to better computing resources.

Installation Instructions

Installing Optimus locally for immediate use requires only R and a connection to the internet. After opening an R client, execute the commands below to install Optimus. Note that the latest version of Rtools is required for this installation to work. If it is not available locally and the installation is attempted from within RStudio, a prompt will appear to download and install Rtools. After following those instructions, restart the RStudio session before reattempting the Optimus installation.

```
install.packaes("devtools")            # install devtools
library(devtools)                      # load devtools
install_github("SahakyanLab/Optimus") # install Optimus
library(Optimus)                       # load Optimus
```

Execution Instructions

Optimus optimisation engine works seamlessly and requires little to no intervention from the user while applied to a wide variety of optimisation tasks. The part where the user must intervene is the specification of $\mathbf{K}$, and the R functions corresponding to $r()$, $m()$, and the combined $e \circ u()$. The port through which user's data or objects can be supplied to be used in Optimus is implemented through the `DATA` argument in the model function `m()`. All the interfacing functions and objects have a minimal and well defined internal compliance rules in Optimus, and otherwise can be as simple or as complicated as the user requires, to plug Optimus to a desired modelling task.

The five tutorials below showcase the usage of Optimus for five broadly different usage scenarios, with the particular focus on how to write the interfacing functions, and how the acceptance ratio annealing mode performs in comparison to the replica exchange one. The five examples below also cover the usage scenario where any external, more complicated programs can be linked with the R procedure. Moreover, we provide a built in function `OptimusExamples()`, which can

Tutorial 1: Finding Coefficients for a Polynomial Function

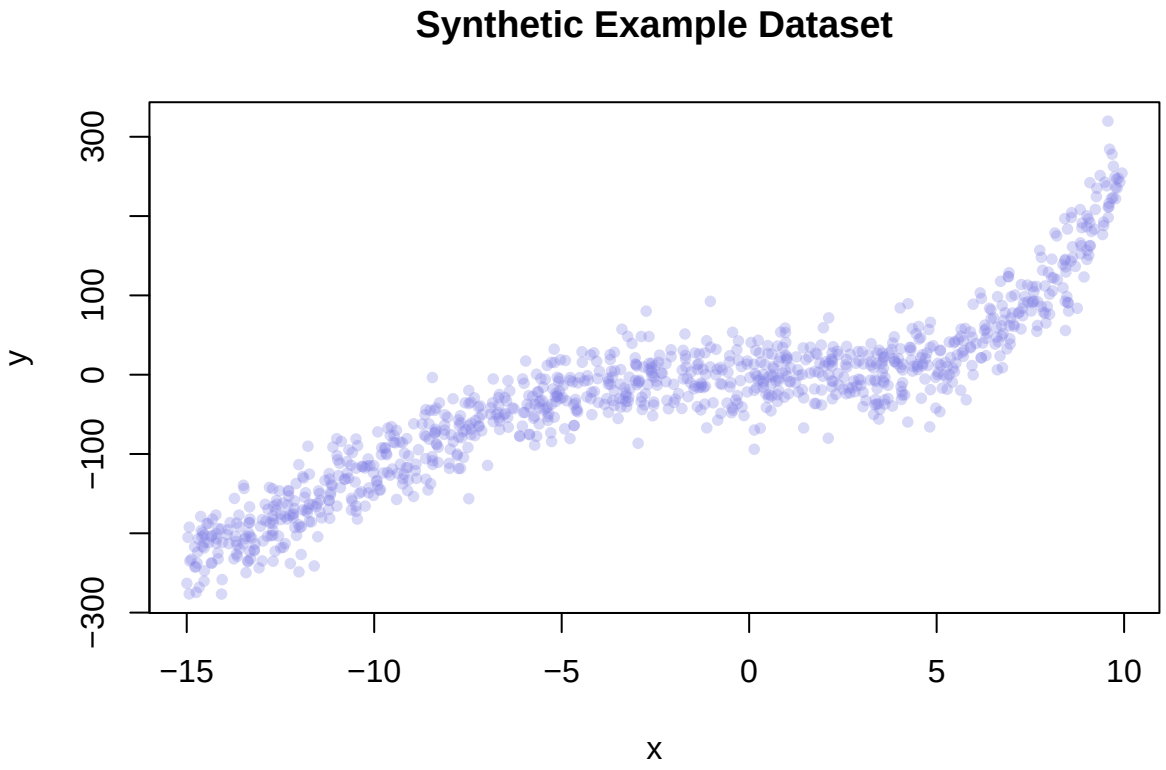
Problem Statement

In this example, we shall use Optimus to find the coefficients of the polynomial function that is known to represent the observations y the best. This, of course, is a simple task that can be addressed more robustly by least-squares linear model fitting. However, starting with this example will focus our attention on the organisation of the Optimus input, rather than the complexity of the task.

First of all, let us create some data for the example.

```
set.seed(845)
x <- runif(1000, min=-15, max=10)
y <- -1.0*x - 0.3*x^2 + 0.2*x^3 + 0.01*x^4 + rnorm(length(x),mean=0,sd=30)
```

The good side of this noisy data generation is that we know the original function that describes it: $y = -1.0x - 0.3x^2 + 0.2x^3 + 0.01x^4$. Hence, we can check how well Optimus performs at finding the correct coefficients. The synthetic "real world" noisy data that we generated looks like this:

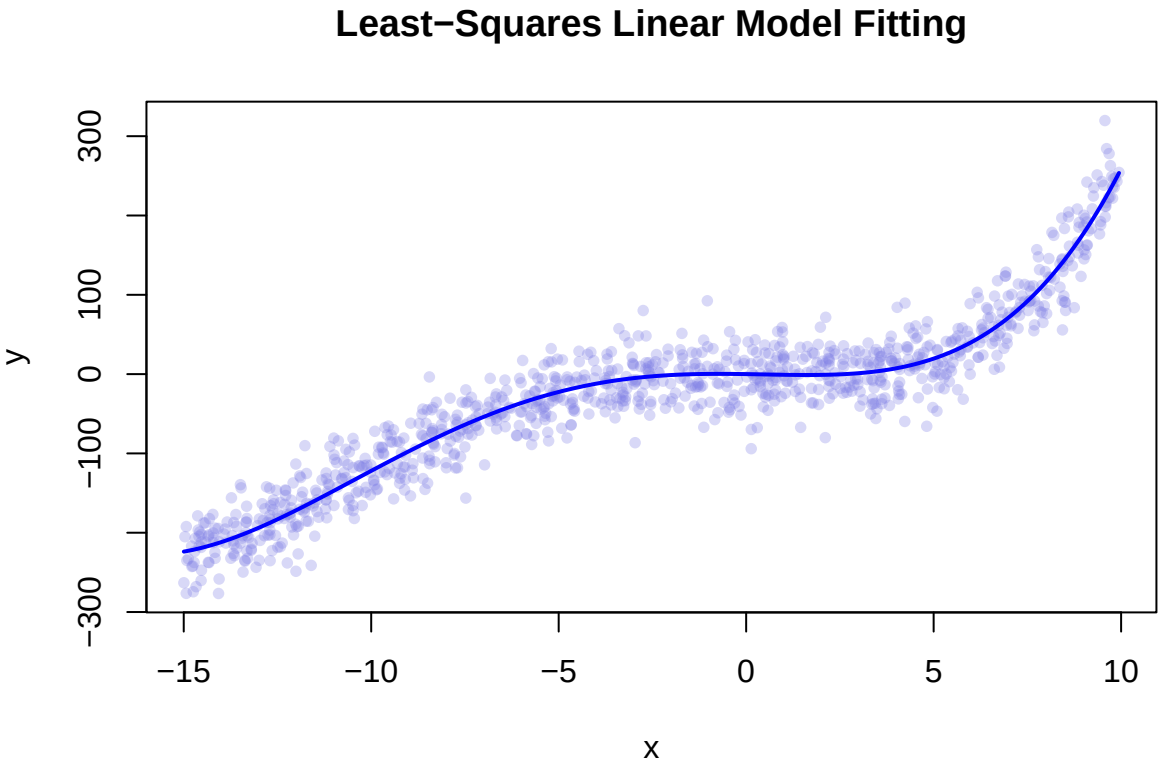


Before we turn to Optimus, let us see how the proper linear model fitting will perform using this data.

```
lm.model <- lm(y ~ x + I(x^2) + I(x^3) + I(x^4) + 0)
lm.model
```

```
##
## Call:
## lm(formula = y ~ x + I(x^2) + I(x^3) + I(x^4) + 0)
##
## Coefficients:
##         x    I(x^2)    I(x^3)    I(x^4)
## -0.74056  -0.30735   0.19777   0.00991
```

The least-squares linear model fitting for the coefficients to the known functional form is quite close to the original equation: $y = -0.741x - 0.307x^2 + 0.198x^3 + 0.010x^4$.



The RMSD between the observed data y and the linear model fitting outcome is:

```
y.pred <- predict(newdata=data.frame(x=x), object=lm.model)
sqrt(mean((y-y.pred)^2))
```

```
## [1] 28.82655
```

which is even slightly better in describing the noisy data, as compared to the maximum possible RMSD based on the de-noised data:

```
y.realdep <- -1.0*x - 0.3*x^2 + 0.2*x^3 + 0.01*x^4
sqrt(mean((y-y.realdep)^2))
```

```
## [1] 28.85858
```

Defining Optimus Inputs

Now we can set up the inputs for the Optimus run. We shall use the model $k_1x + k_2x^2 + k_3x^3 + k_4x^4$ to fit the y observables based on the values for x. The dependent functions that are needed for setting up an Optimus run, are given as inputs in the Optimus function call.

First, we need to create an object K, which stores the initial values for the parameter(s) to be optimised. K can be an object of any type. From a single numeric or character value to a vector of values or a data frame holding, say, Cartesian coordinates of a molecule to be optimised. The only requirement for K is that it should be something alterable (via a rule function $r()$, see below) and something that influences the outcome of another required model function - $m()$ (see below). In this example, we have 4 coefficients to optimise from some random initial state. We can thus make K be a numeric vector of size 4. Let us start from all the components being 1.0, which, as entries in K, can be both named and unnamed. Though not the case

here, the entry-named data for K can be essential for some models that specifically use coefficient names, for instance when a system of ODEs is used in the model function $m()$.

```
K <- c(k1=1.0, k2=1.0, k3=1.0, k4=1.0) # entries are named as k1, k2, k3 and k4
```

Second, we should create the function m for the model. The function m should be designed to operate on the whole set of parameter snapshot K and return the corresponding observable object O. Please note that the size of K and O are not necessarily to match, depending on the nature of the model used. Operating on K is the only hard condition on $m()$, which can optionally operate on other data as well. In our situation, the function $m()$ should operate on the provided instance of four coefficients (in the object K), and, additionally on the values x. It should then return a vector of observations O (to be compared with y target observations) of the same size as vector x. Any additional data required by the model, in our case an object with the set of 1000 x values, must be provided to the function in an input variable DATA, a list holding the additional data that must be accessed by $m()$ and $u()$ (see below). The variable DATA must be provided to Optimus in the function call, and $m()$ must take it as an input (in the case that neither $m()$ nor $u()$ require additional data, the two functions should still be created such that they take a variable DATA as an input, and the variable DATA passed to Optimus will be set to NULL).

```
DATA   <- NULL
DATA$x <- x
DATA$y <- y

m <- function(K,DATA){
  x <- DATA$x
  O <- K["k1"]*x + K["k2"]*x^2 + K["k3"]*x^3 + K["k4"]*x^4
  return(O)
}
```

At this point, calling $m(K = K, DATA = DATA)$ will return the predicted O set from the initial, non-optimal values for K, hence rather far from the target $O^{trg} = y$.

In this example, the optimisation goal is for the O model outcomes to come as close as possible to the target observations y, to be achieved by optimising the coefficients K. The object y holding the target values therefore also needs to be specified and given as an input to the $Optimus()$ function (as an entry in the DATA variable), just like x required, in this example, by the function $m()$.

Now, we need to define how the performance of a given snapshot of coefficients K is to be evaluated. For Optimus, this is done by specifying a function $u()$, which should necessarily take as inputs O (the output of $m()$) and the variable DATA. The output should have two components, Q holding a single number of the quality of the K coefficients, and E holding a (pseudo)energy for the given snapshot K. It is important that the returned (pseudo)energy value is lower for better performance/version of K, never vice-versa. The Q component of the $u()$ function output is only used for plotting the optimisation process, and, if desired, can just repeat the value of the E component.

For our example, the $u()$ function will assess the agreement between the snapshot of predictions O and the complete set of real observables (target) y. Here, we can use RMSD between O and y as a measure of K snapshot quality (Q). Since bettter agreement means better RMSD, it can be directly used as a pseudo-energy (E), without putting a negative sign or performing some other mathematical operation on Q.

```
u <- function(O,DATA){
  y <- DATA$y
  Q <- sqrt(mean((O-y)^2))
  E <- Q # For RMSD, <-> negative sign or other mathematical operation
         # is not needed.

  RESULT <- NULL
  RESULT$Q <- Q
```

```
  RESULT$E <- E
  return(RESULT)
}
```

And finally, we need to define the rule, by which the K coefficient vector is to be altered from one step to another. This is done by defining a rule function $r()$ that must take K, and return an object equivalent to K, but with some alteration(s). In this example, for each snapshot of K, we shall randomly select one of its four coefficients, then either increment or decrement (chosen randomly) it by 0.0005, returning the altered set of coefficients.

```
r <- function(K){
  K.new <- K
  # Randomly selecting a coefficient to alter:
  K.ind.toalter <- sample(size=1, x=1:length(K.new))
  # Creating a potentially new set of coefficients where one entry is altered
  # by either +move.step or -move.step, also randomly selected:
  move.step <- 0.0005
  K.new[K.ind.toalter] <- K.new[K.ind.toalter] + sample(size=1, x=c(-move.step,      move.step))

  ## Setting the negative coefficients to 0 (not necessary in this example,
  ## useful for optimising rate constants):
  #neg.ind <- which(K.new < 0)
  #if(length(neg.ind)>0){ K.new[neg.ind] <- 0 }

  return(K.new)
}
```

All the constructed objects (K) and functions (m, u, r), as well as the data required by $m()$ and $u()$ (stored in the variable DATA) should be defined in an R session and given to Optimus as inputs. The users are free to define some dependencies as additional files (for example initial protein geometry for a Monte-Carlo optimisation), which should be called from within the function definitions.

Acceptance Ratio Annealing Optimus Run

Having constructed K, DATA, $m()$, $u()$ and $r()$, we are now ready to call Optimus. Let us first investigate the Acceptance Ratio Annealing (SA) version of Optimus on 4 processors (the vast majority of personal computers currently have 4 processors), which can be executed as follows:

```
Optimus(NCPU = 4, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, OPT.TYPE = "SA", DATA = DATA, OPTNAME =
```

Note that the field $LONG = FALSE$ is included in the function call so that all data from the optimsation process is saved. Calling Optimus with $LONG = TRUE$ will result in a memory saving optimisation process (more details in the Advanced User Manual). Of the 4 optimisation replicas, the second and fourth processors found the best parameter configuration (lowest RMSD):

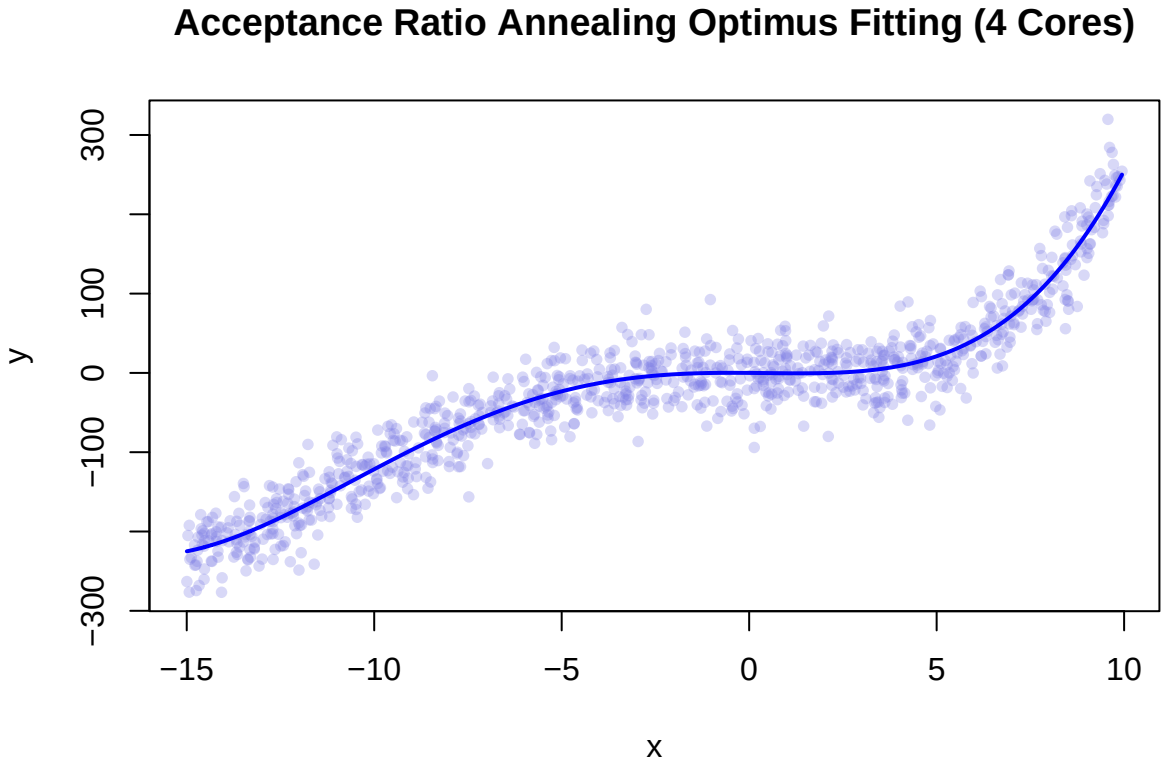


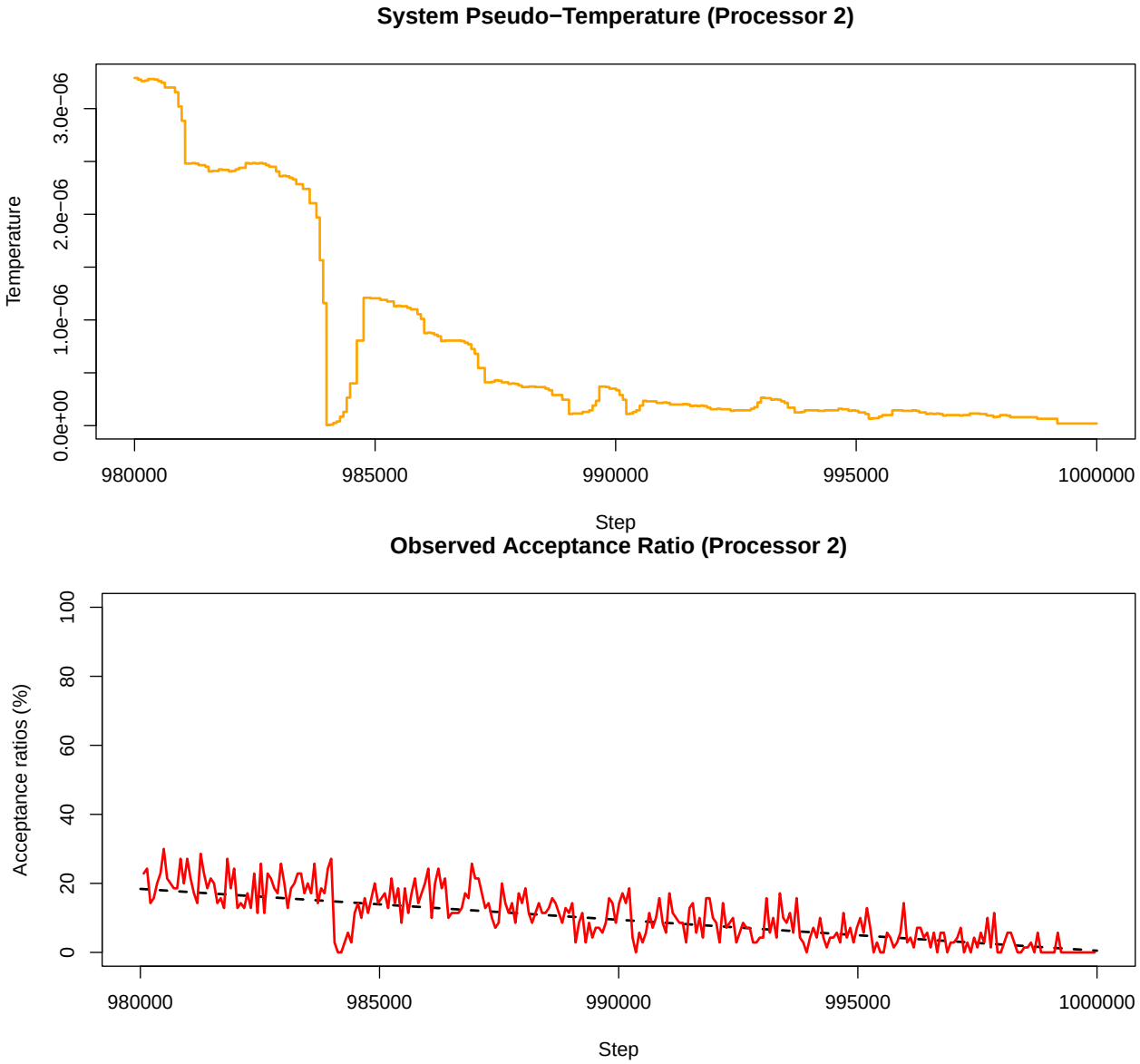
Table 1: 4 Core Acceptance Ratio Annealing Optimus Run Results

	E (RMSD)	K1	K2	K3	K4
Processor 1	28.857	-0.1560	-0.2850	0.1905	0.0095
Processor 2	28.841	-0.3760	-0.2825	0.1920	0.0095
Processor 3	28.864	-0.1045	-0.2820	0.1905	0.0095
Processor 4	28.841	-0.3760	-0.2825	0.1920	0.0095

The equation recovered by Processor 2 (and 4) is $y = -0.3760x - 0.2825x^2 + 0.192x^3 + 0.0095x^4$.

Notice that although the RMSD of this solution, 28.841, is greater than the RMSD of the least squares solution, 28.82655, it is less than the RMSD of the de-noised data found above, 28.85858.

The two graphs below illustrate the evolution of the system pseudo-temperature in response to alterations made by the Temperature Control Unit (TCU) as a function of the optimsation iteration and the observed acceptance ratio as a function of the optimisation iteration respectively. The graphs show data from the last 20 000 iterations of the optimisation executed by Processor 2.



In the graph titled "Observed Acceptance Ratio (Processor 2)," the solid red line tracks the observed acceptance ratios calculated by Optimus at the end of each STATWINDOW and the dashed black line tracks the target acceptance ratio based on the annealing schedule. From the above two graphs, notice that while the observed acceptance ratio tracks the target acceptance ratio closely, the system pseudo-temperature changes significantly and non-monotonically. This illustrates that the adaptive thermoregulation of the TCU allows Optimus to effectively anneal the system acceptance ratio.

Replica Exchange Optimus Run

Let us now consider the Replica Exchange version of Optimus on 12 processors. Let us reiterate that the purpose here is to illustrate how to run an optimisation using the Replica Exchange version of Optimus; this method is of course not the most robust method to solve this simple task and is likely overkill.

In addition to the arguments specified above, the Replica Exchange version of Optimus also requires an input variable ACCRATIO which is a vector that defines the acceptance ratio to be used for each of the Replicas initiated, 12 in this case (note that the length of ACCRATIO must always be equal to the argument NCPU).

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

Having defined the acceptance ratios for each level, the optimisation can be executed as follows:

```
Optimus(NCPU = 12, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, ACCRATIO = ACCRATIO, OPT.TYPE = "RE", D
```

Of the 12 optimisation replicas, replica 8 finds the best parameter configuration (lowest RMSD):

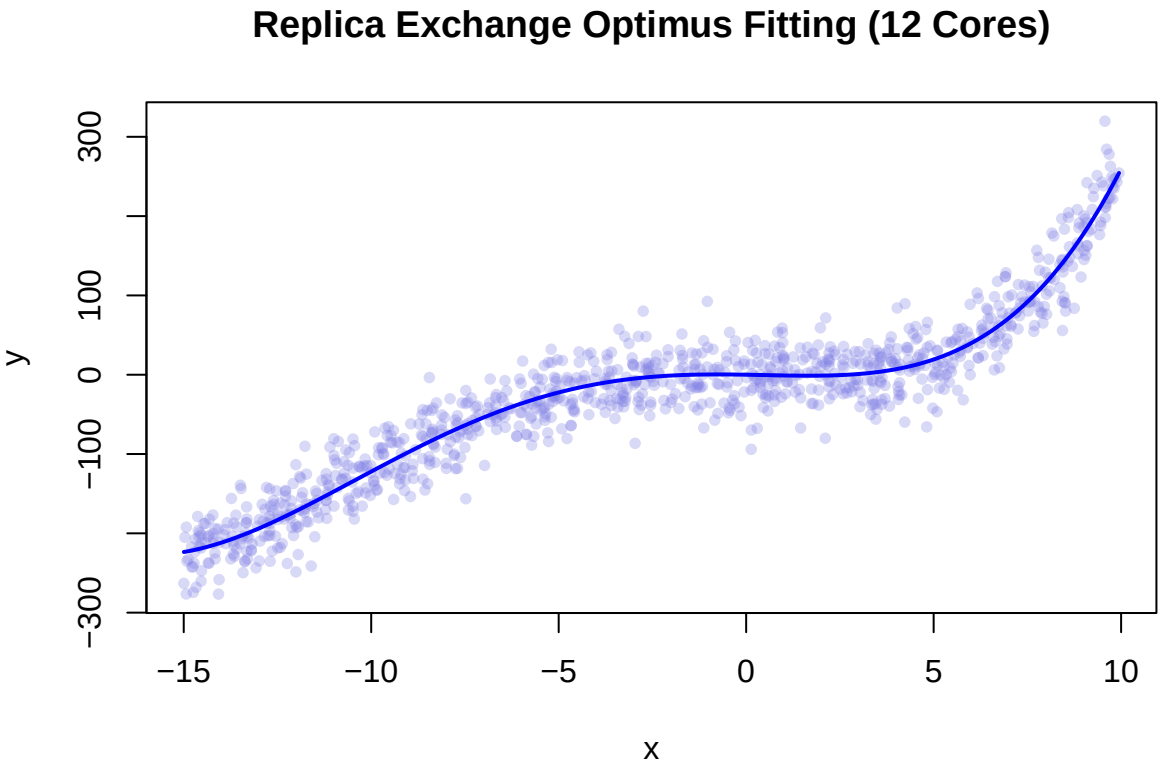


Table 2: 12 Core Replica Exchange Optimus Run Results

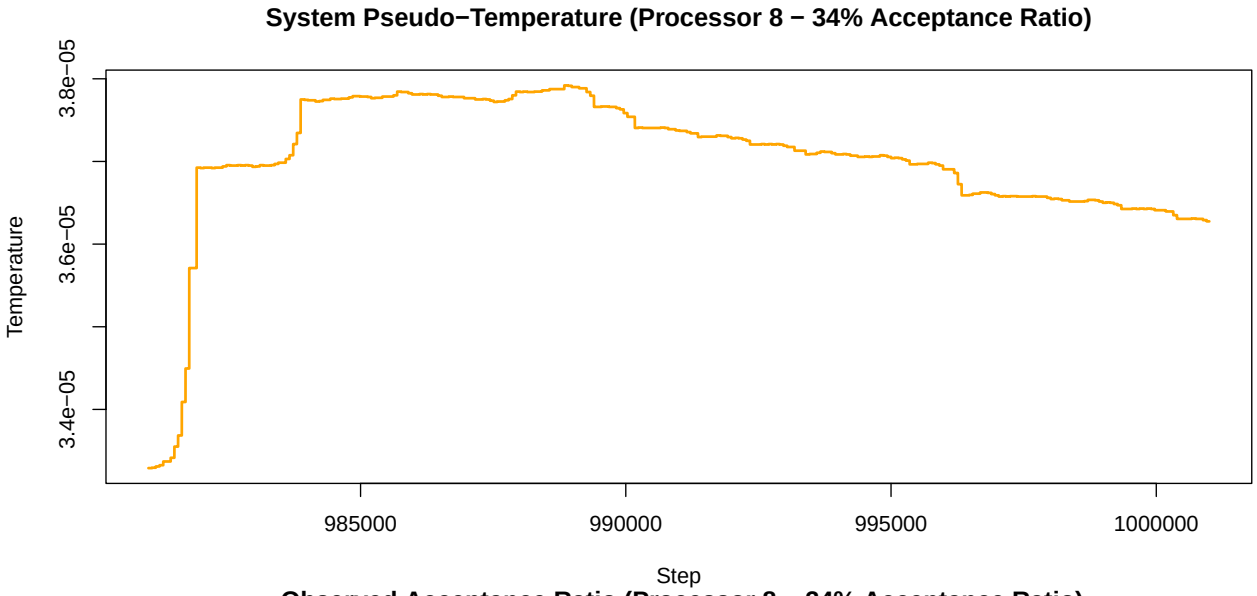
	Replica Acceptance Ratio	E (RMSD)	K1	K2	K3	K4
Processor 1	90	29.71934	-3.2760	-0.5760	0.2395	0.0135
Processor 2	82	29.51819	-3.4445	-0.3755	0.2300	0.0115
Processor 3	74	28.88707	-0.0340	-0.2375	0.1870	0.0090
Processor 4	66	30.10499	-3.8095	-0.6630	0.2435	0.0140
Processor 5	58	29.06293	-2.3575	-0.4180	0.2200	0.0115
Processor 6	50	29.70906	-3.7360	-0.3785	0.2320	0.0115
Processor 7	42	28.85095	-1.1370	-0.3515	0.2045	0.0105
Processor 8	34	28.82721	-0.8175	-0.3130	0.1990	0.0100
Processor 9	26	28.84057	-0.5760	-0.2740	0.1940	0.0095
Processor 10	18	29.48785	-2.7805	-0.5420	0.2325	0.0130
Processor 11	10	28.85095	-1.1370	-0.3515	0.2045	0.0105
Processor 12	2	29.41377	1.2255	-0.0895	0.1645	0.0070

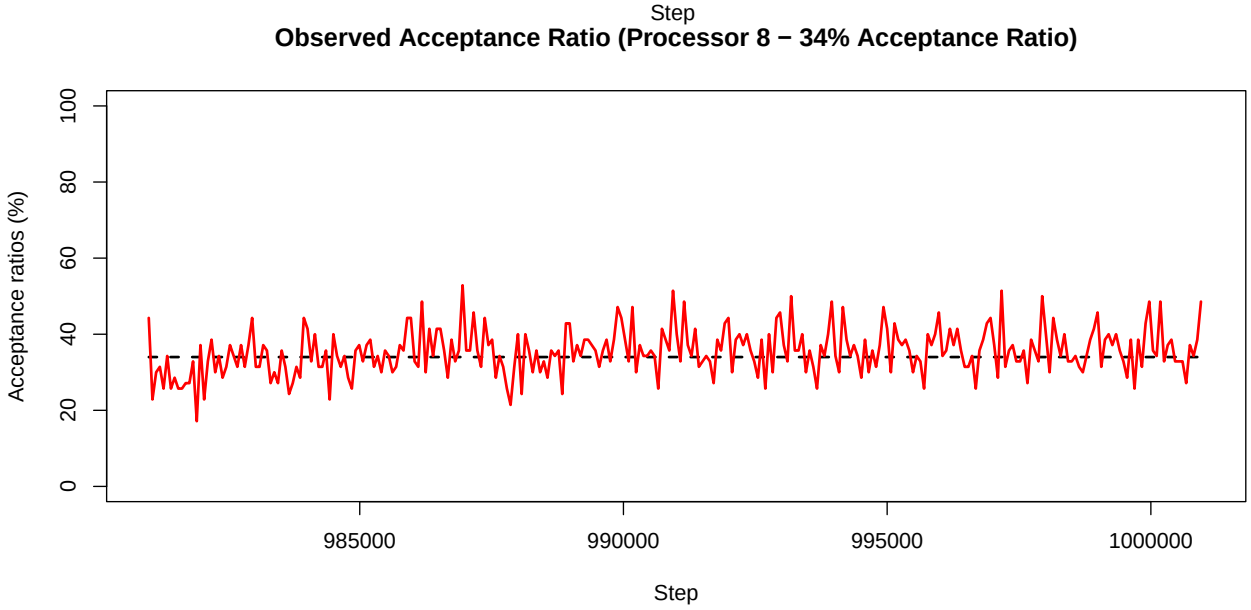
The equation recovered by Processor 8 is $y = -0.8175x - 0.313x^2 + 0.199x^3 + 0.01x^4$.

Notice that the RMSD of this solution, 28.82721, is less than the RMSD of the Acceptance Ratio Annealing solution, 28.841, and only slightly greater than the RMSD of the least squares solution, 28.82655.

Let us now briefly examine the evolution of the system pseudo-temperature in response to alterations made by

the Temperature Control Unit (TCU) as a function of the optimsation iteration and the observed acceptance ratio as a function of the optimisation iteration for the Replica Exchange version of Optimus. The following two graphs represent data from the last 20 000 iterations of the optimisation replica running on Processor 8 (34% target acceptance ratio).





Notice that in the observed acceptance ratio graph, the dashed line indicating the target acceptance ratio is constant (as opposed to linearly changing as in acceptance ratio annealing). This is because each processor in the replica exchnage mode has a single target acceptance ratio, as articulated in the previous section of this manual which addressed the theoretical underpinnings of Optimus. Here again, adaptive decisions made by the TCU result in non-monotonic, non uniform psuedo-temperature adjustments while the observed acceptance ratios fluctuates relatively closely around the target ratio.

Summary

We now understand the input requirements to interface with the Acceptance Ratio Annealing and Replica Exchange versions of Optimus. In this example, both the Acceptance Ratio Annealing and Replica Exchange

Optimus versions retrieved solutions having a lower RMSD than the de-noised data and only a slightly greater RMSD than the optimal Least Squares solution. Replica Exchange resulted in a better solution than Acceptance Ratio Annealing, at the cost of greater computing resources.

Table 3: Summary of Solutions

	E (RMSD)	K1	K2	K3	K4
De-noised Function	28.85858	-1.00000	-0.30000	0.20000	0.01000
Optimus (Acceptance Ratio Annealing)	28.84100	-0.37600	-0.28250	0.19200	0.00950
Optimus (Replica Exchange)	28.82721	-0.81750	-0.31300	0.19900	0.01000
Least Squares	28.82655	-0.74056	-0.30735	0.19777	0.00991

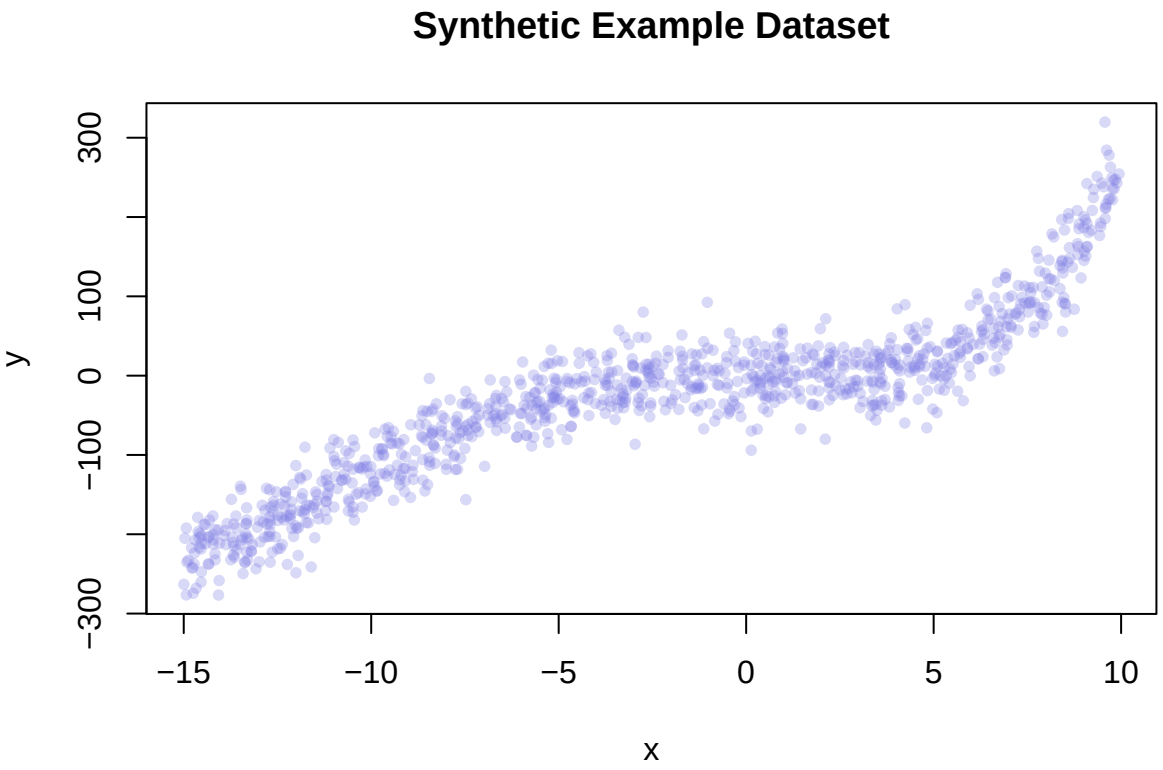
Tutorial 2: Selecting Terms for a Least Squares Representation of Data

Problem Statement

Consider again the synthetic data that was created in Tutorial 1. Suppose that we were only provided with the data and, unlike in Tutorial 1, had no knowledge of the best terms to be included in a functional representation of said data. In this example, we shall use Optimus to determine which terms should be used in a Least Squares representation of the data to achieve a representation with low RMSD while not overfitting the data.

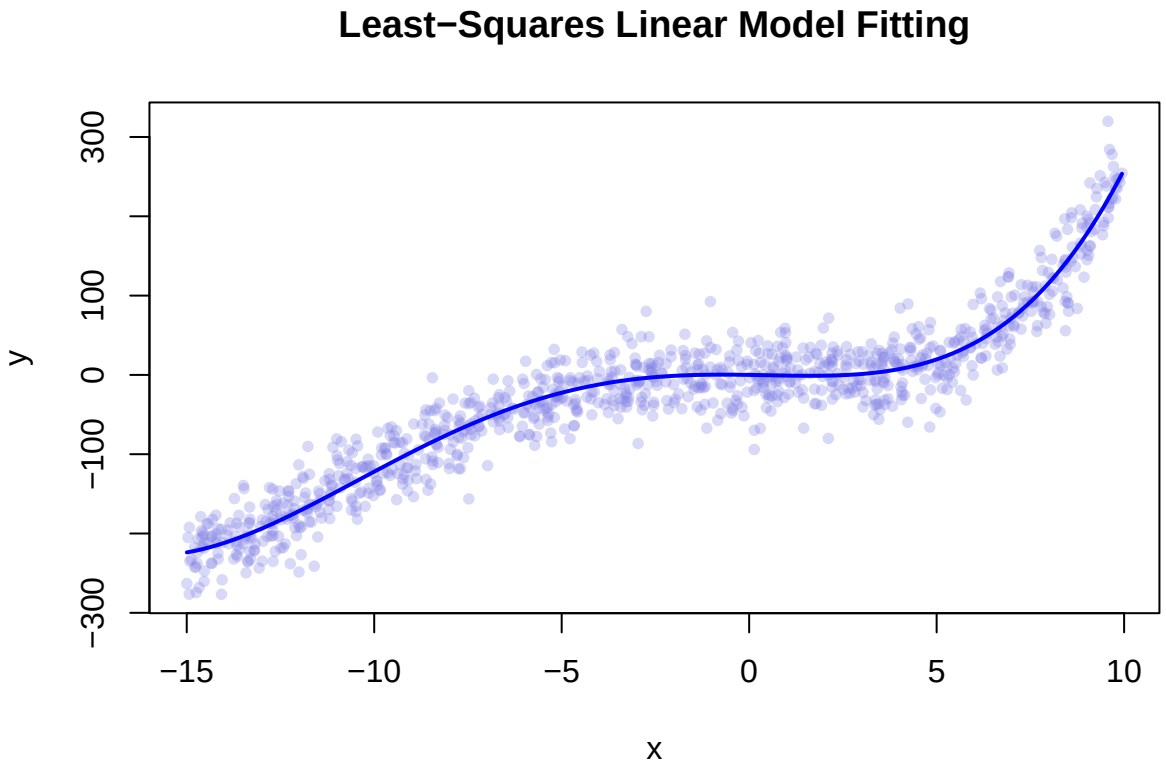
Let us start by generating the same data which was used in Tutorial 1:

```
set.seed(845)
x <- runif(1000, min=-15, max=10)
y <- -1.0*x - 0.3*x^2 + 0.2*x^3 + 0.01*x^4 + rnorm(length(x),mean=0,sd=30)
```



From Tutorial 1, we know that if presented with this data and under the assumption that the most appropriate model to describe the data is $k_1x + k_2x^2 + k_3x^3 + k_4x^4$, the Least Squares model fitting is $y = -0.741x - 0.307x^2 + 0.198x^3 + 0.010x^4$. We also know that the RMSD between the observed data y and the linear model fitting outcome is:

```
## [1] 28.82655
```



Defining Optimus Inputs

Let us first define an ordered set $terms$ that is a collection of candidate terms to include in the representation of the data:

$terms = \{x, x^2, x^3, x^4, x^5, x^6, x^7, x^8, x^9, x^{10}, e^x, |x|, sin(x), cos(x), tan(x), sin(x)cos(x), sin^2(x), cos^2(x), sin(x^2), sin(x^3), cos(x^2), cos(x^3), sin(x^3)cos(-x), cos(x^3)sin(-x), sin(x^5)cos(-x), cos(x^5)sin(-x), e^x sin(x), e^x cos(x), |x|sin(x), |x|cos(x)\}$

Let $terms_i$ denote the i^{th} term in the set $terms$ (for example, $terms_{14} = cos(x)$). We shall use the model:

$$y = b + \sum_{i=1}^{\mathbf{card}(terms)} k_i c_i terms_i$$

where each k_i is a binary variable (meaning a variable taking a value of either 0 or 1) indicating whether the i^{th} term is included in the representation, each c_i is a non-zero coefficient for the i^{th} term and b is a real number (the intercept). In our case, $\mathbf{card}(terms) = 30$ so explicitly, our model is:

$y = b + k_1c_1x + k_2c_2x^2 + k_3c_3x^3 + k_4c_4x^4 + k_5c_5x^5 + k_6c_6x^6 + k_7c_7x^7 + k_8c_8x^8 + k_9c_9x^9 + k_{10}c_{10}x^{10} + k_{11}c_{11}e^x + k_{12}c_{12}|x| + k_{13}c_{13}six(x) + k_{14}c_{14}cos(x) + k_{15}c_{15}tan(x) + k_{16}c_{16}sin(x)cos(x) + k_{17}c_{17}sin^2(x) + k_{18}c_{18}cos^2(x) + k_{19}c_{19}sin(x^2) + k_{20}c_{20}sin(x^3) + k_{21}c_{21}cos(x^2) + k_{22}c_{22}cos(x^3) + k_{23}c_{23}sin(x^3)cos(-x) + k_{24}c_{24}cos(x^3)sin(-x) + k_{25}c_{25}sin(x^5)cos(-x) + k_{26}c_{26}cos(x^5)sin(-x) + k_{27}c_{27}e^x sin(x) + k_{28}c_{28}e^x cos(x) + k_{29}c_{29}|x|sin(x) + k_{30}c_{30}|x|cos(x)$

Formally, K will be a numeric vector of length $\mathbf{card}(terms)$ whose i^{th} entry is k_i. K uniquely specifies a set $activeTerms = \{terms_i \, \forall \, i \, | k_i = 1\}$. Note that $activeTerms \subseteq terms$. Each binary variable k_i should be initialized randomly as below:

```
K <- c(term1=rbinom(n=1, size=1, prob=0.5),
       term2=rbinom(n=1, size=1, prob=0.5),
```

```
       term3=rbinom(n=1, size=1, prob=0.5),
       term4=rbinom(n=1, size=1, prob=0.5),
       term5=rbinom(n=1, size=1, prob=0.5),
       term6=rbinom(n=1, size=1, prob=0.5),
       term7=rbinom(n=1, size=1, prob=0.5),
       term8=rbinom(n=1, size=1, prob=0.5),
       term9=rbinom(n=1, size=1, prob=0.5),
       term10=rbinom(n=1, size=1, prob=0.5),
       term11=rbinom(n=1, size=1, prob=0.5),
       term12=rbinom(n=1, size=1, prob=0.5),
       term13=rbinom(n=1, size=1, prob=0.5),
       term14=rbinom(n=1, size=1, prob=0.5),
       term15=rbinom(n=1, size=1, prob=0.5),
       term16=rbinom(n=1, size=1, prob=0.5),
       term17=rbinom(n=1, size=1, prob=0.5),
       term18=rbinom(n=1, size=1, prob=0.5),
       term19=rbinom(n=1, size=1, prob=0.5),
       term20=rbinom(n=1, size=1, prob=0.5),
       term21=rbinom(n=1, size=1, prob=0.5),
       term22=rbinom(n=1, size=1, prob=0.5),
       term23=rbinom(n=1, size=1, prob=0.5),
       term24=rbinom(n=1, size=1, prob=0.5),
       term25=rbinom(n=1, size=1, prob=0.5),
       term26=rbinom(n=1, size=1, prob=0.5),
       term27=rbinom(n=1, size=1, prob=0.5),
       term28=rbinom(n=1, size=1, prob=0.5),
       term29=rbinom(n=1, size=1, prob=0.5),
       term30=rbinom(n=1, size=1, prob=0.5))
```

Next, we must define the model function m that will operate on the parameter snapshot K and return an observable object O. For a given set $activeTerms$ specified by K, $m()$ will fit a linear model to the data using the entries in $activeTerms$ and using the built in generalized linear model ($glm()$) function in R, thereby determining values for the variables c_i and b. Accordingly, $m()$ will require access to the variables x and y, which will be provided as entries in DATA, a variable of type list, as in Tutorial 1. The object O will be the corresponding output of the function $glm()$. In the case that the set $activeTerms$ is the empty set (meaning that all entries in K are 0), $m()$ will fit a model using the relationship y~x.

```
DATA   <- NULL
DATA$x <- x
DATA$y <- y

m <- function(K, DATA){
  y <- DATA$y
  x <- DATA$x

  terms <- c("+x",
             "+I(x^2)",
             "+I(x^3)",
             "+I(x^4)",
             "+I(x^5)",
             "+I(x^6)",
             "+I(x^7)",
             "+I(x^8)",
             "+I(x^9)",
```

```
              "+I(x^10)",
              "+I(exp(x))",
              "+I(abs(x))",
              "+I(sin(x))",
              "+I(cos(x))",
              "+I(tan(x))",
              "+I(sin(x)*cos(x))",
              "+I((sin(x))^2)",
              "+I((cos(x))^2)",
              "+I(sin(x^2))",
              "+I(sin(x^3))",
              "+I(cos(x^2))",
              "+I(cos(x^3))",
              "+I(sin(x^3)*cos(-x))",
              "+I(cos(x^3)*sin(-x))",
              "+I(sin(x^5)*cos(-x))",
              "+I(cos(x^5)*sin(-x))",
              "+I(exp(x)*sin(x))",
              "+I(exp(x)*cos(x))",
              "+I(abs(x)*sin(x))",
              "+I(abs(x)*cos(x))")

  ind.terms <- which(K == 1)
  if(length(ind.terms)!=0){
    equation <- paste(c("y~",terms[ind.terms]), collapse="")
  } else {
    equation <-"y~x" # In case there are no active terms, use a simple linear model.
  }

  O <- glm(equation, data = environment())

  return(O)
}
```

Having defined the function m, we can now proceed to define the function u, which will define how well a given configuration of parameters K is performing by operating on the observable object O outputted by $m()$ and on the variable DATA. Here, to quantify (and thus be able to compare) the desirability of a given model for the data, we will employ the Aikake Information Criterion (AIC) from Information Theory, defined as follows where p is the number of parameters in the fitted model M and L is the likelihood of the model given the data:

$$AIC(M) = 2p - 2ln(L)$$

The target representation will be the fitted model M (whose terms are elements of $terms$) that minimizes the AIC. It is important to note that the $2p$ term in the AIC penalizes overfitting by increasing AIC as function of the number of parameters while the $-2ln(L)$ term rewards models that better represent the data by decreasing AIC as a function of the likelihood of the model.

As articulated in Tutorial 1, the output of $u()$ should have a component E holding a pseudo-energy for the parameter snapshot K and a component Q that can be used for plotting the optimisation process. In this case, E will be equal to the value of AIC (implemented using the built in $AIC()$ function in R) and Q will be equal to the RMSD between the predicted values of y from the fitted model and the actual y values. Consequently, $u()$ will need access to the variable y. The definition of $u()$ is below:

```
u <- function(O, DATA){
  y <- DATA$y

  Q <- sqrt(mean((O$fitted.values-y)^2))
  E <- AIC(O)/1000 # Akaike's information criterion.

  result   <- NULL
  result$Q <- Q
  result$E <- E
  return(result)
}
```

Finally, we need to define the rule function r. We will adopt the following simply procedure: randomly select an entry in K and switch its value to the other binary value.

```
r <- function(K){
  K.new <- K
  # Randomly selecting a term:
  K.ind.toalter <- sample(size=1, x=1:length(K.new))
  # If the term is on (1), switching it off (0) or vice versa:
  if(K.new[K.ind.toalter]==1){
    K.new[K.ind.toalter] <- 0
  } else {
    K.new[K.ind.toalter] <- 1
  }
  return(K.new)
}
```

Having defined all the necessary inputs, we are now ready to call Optimus.

An important remark is that modelling this problem in this manner results in an objective function (AIC) that is not smooth because small changes in the parameter set K (as defined by $r()$) can produce significantly large changes in the objective value because an entirely different model is being used to fit the data. Despite this, we will see that Optimus arrives at good solutions largely as a consequence of its adaptive thermoregulation. Whereas other optimisation procedures don't work or do poorly in such situations (non smooth objective function), Optimus will get the job done.

Acceptance Ratio Annealing Optimus Run

In addition to the inputs defined above, Optimus can optionally take other inputs to dictate the optimisation process (see the Advanced User Manual), all of which have built in default values and some of which will be altered in this example due to the increased computational complexity of the model defined in this Tutorial compared to that of Tutorial 1. The variable NUMITER represents the number of iterations of the optimisation process (per core) and has a default value of 1 000 000. For this example, 200 000 iterations will be used to reduce the running time of Optimus given that each iteration is more computationally demanding than in Tutorial 1. The variable CYCLES (unique to Acceptance Ratio Annealing Optimus) denotes the number of acceptance ratio annealing cycles. Its default value is 10, however it will be set to 2 in this example so that each annealing cycle has 100 000 iterations just as in Tutorial 1 (the number of iterations per cycle is calculated as NUMITER/CYCLES). Lastly, the variable DUMP.FREQ, the frequency (in iterations) with which the best found model is outputted by the function, will be set to 100 000 (its default value is 10 000).

Let us again investigate the Simulated Annealing (SA) version of Optimus on 4 processors, which can be executed as follows:

```
Optimus(NCPU = 4, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, OPT.TYPE = "SA", DATA = DATA, OPTNAME =
```

Interestingly, each of the 4 processors arrive at the same solution in this instance.

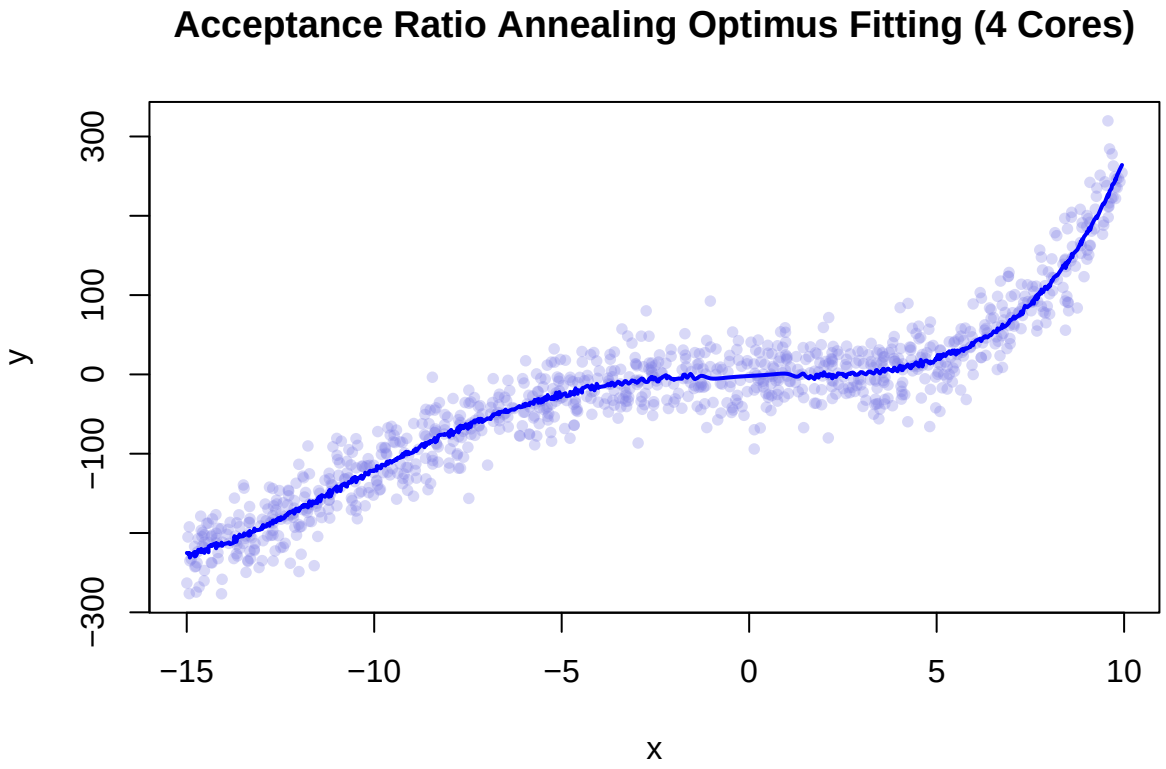


Table 4: 4 Core Acceptance Ratio Annealing Optimus Run Results

	Processor 1	Processor 2	Processor 3	Processor 4
E (AIC)	9.567	9.567	9.567	9.567
Q (RMSD)	28.693	28.693	28.693	28.693
Term 1	0.000	0.000	0.000	0.000
Term 2	1.000	1.000	1.000	1.000
Term 3	1.000	1.000	1.000	1.000
Term 4	1.000	1.000	1.000	1.000
Term 5	0.000	0.000	0.000	0.000
Term 6	0.000	0.000	0.000	0.000
Term 7	0.000	0.000	0.000	0.000
Term 8	0.000	0.000	0.000	0.000
Term 9	0.000	0.000	0.000	0.000
Term 10	0.000	0.000	0.000	0.000
Term 11	1.000	1.000	1.000	1.000
Term 12	0.000	0.000	0.000	0.000
Term 13	0.000	0.000	0.000	0.000
Term 14	0.000	0.000	0.000	0.000
Term 15	0.000	0.000	0.000	0.000
Term 16	0.000	0.000	0.000	0.000
Term 17	0.000	0.000	0.000	0.000
Term 18	0.000	0.000	0.000	0.000
Term 19	0.000	0.000	0.000	0.000
Term 20	1.000	1.000	1.000	1.000

	Processor 1	Processor 2	Processor 3	Processor 4
Term 21	0.000	0.000	0.000	0.000
Term 22	0.000	0.000	0.000	0.000
Term 23	0.000	0.000	0.000	0.000
Term 24	0.000	0.000	0.000	0.000
Term 25	0.000	0.000	0.000	0.000
Term 26	1.000	1.000	1.000	1.000
Term 27	0.000	0.000	0.000	0.000
Term 28	0.000	0.000	0.000	0.000
Term 29	0.000	0.000	0.000	0.000
Term 30	0.000	0.000	0.000	0.000

Thus, the optimal functional representation found by Optimus has the following form:

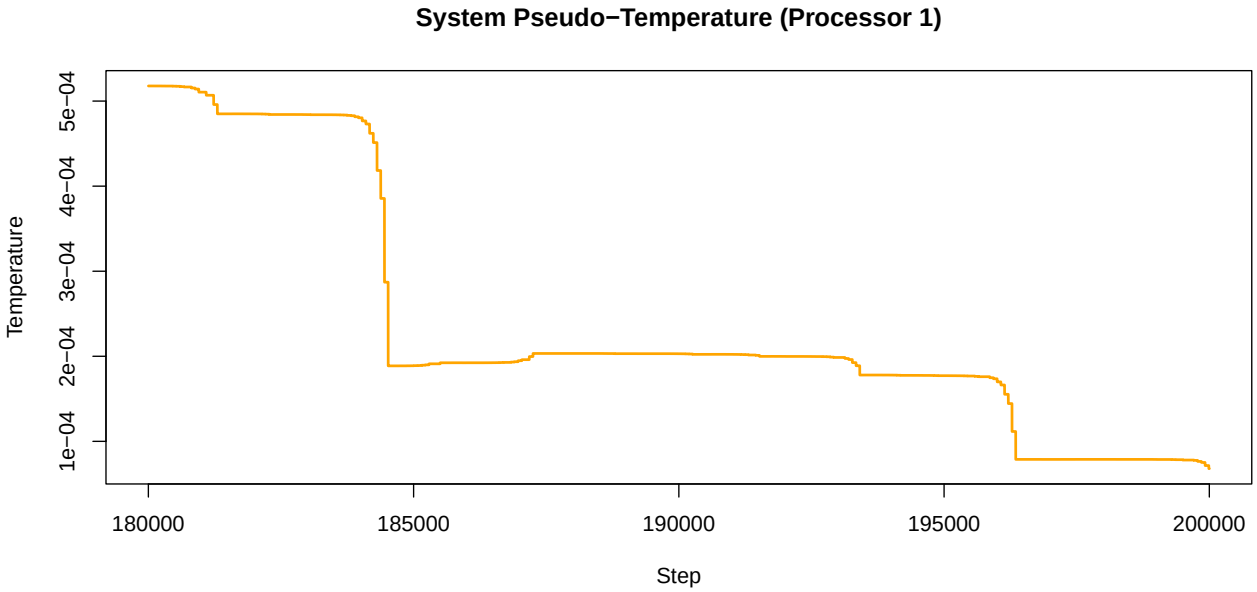
$$y = b + c_2x^2 + c_3x^3 + c_4x^4 + c_{11}e^x + c_{20}sin(x^3) + c_{26}cos(x^5)sin(-x)$$

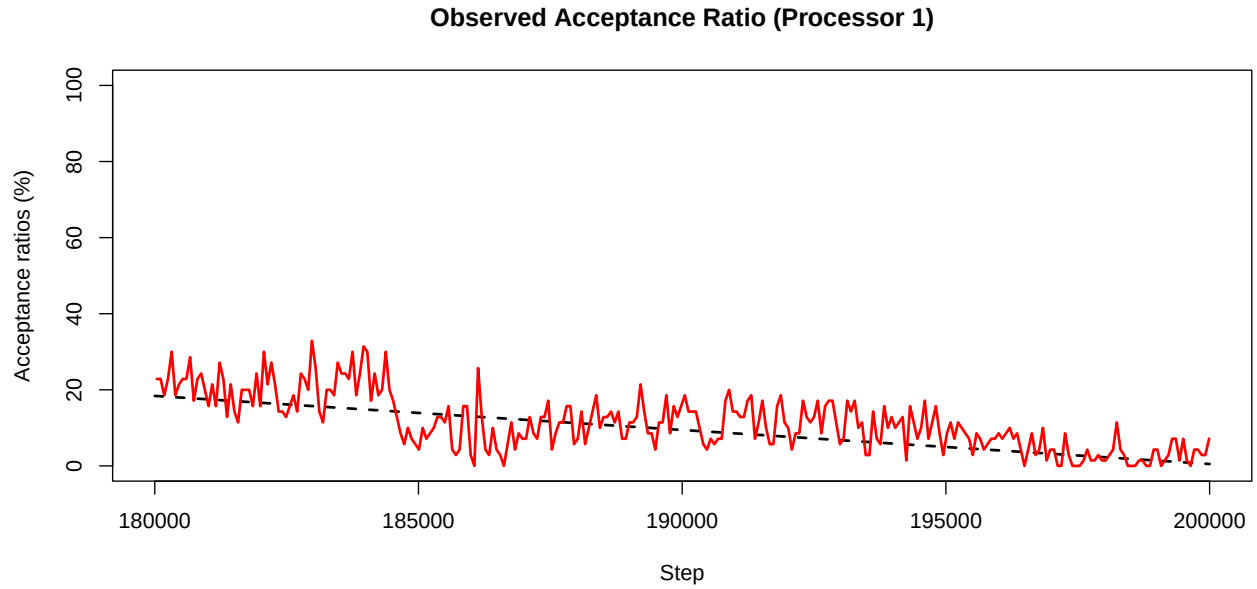
Below is the explicit representation after determing the coefficients c_i and b:

```
##
## Call:  glm(formula = equation, data = environment())
##
## Coefficients:
##           (Intercept)                I(x^2)                I(x^3)
##             -1.988699             -0.253437              0.178807
##                I(x^4)             I(exp(x))           I(sin(x^3))
##              0.008567              0.001569              1.878796
## I(cos(x^5) * sin(-x))
##             -2.770457
##
## Degrees of Freedom: 999 Total (i.e. Null);  993 Residual
## Null Deviance:       10850000
## Residual Deviance: 823300    AIC: 9567
```

Notice that the solution selected by Optimus results in an RMSD of 28.693 which is lower than the RMSD of the Least Squares Solution (28.82655) which assumes the appropriate model is $k_1x + k_2x^2 + k_3x^3 + k_4x^4$. Optimus selected a model which does not include all terms from the form used to generate the data. If a user were concerned by the fact that the model Optimus selected contains more terms (6) than are used in the representation of the de-noised data (4), the user could either increase the multiplicative factor associated with the term p in the AIC to more strongly penalize representations involving a greater number of parameters. Alternatively, the user could also modify the function r() to ensure that only a fixed number of terms are ever active.

Let us now take a look at how the Temeperature Control Unit performed given this highly non-smooth objective. The graphs below should now feel very familiar, they represent data taken from the last 20 000 iterations of the optimisation protocol executed by Processor 1.





Despite optimising a completely different model with a non-smooth objective function, the TCU succeeds in dynamically adjusting the system pseudo-temperature such that the observed acceptance ratio follows the annealing schedule rather well.

Replica Exchange Optimus Run

Let us now consider the Replica Exchange version of Optimus on 12 processors with the variable ACCRATIO defined as in Tutorial 1.

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

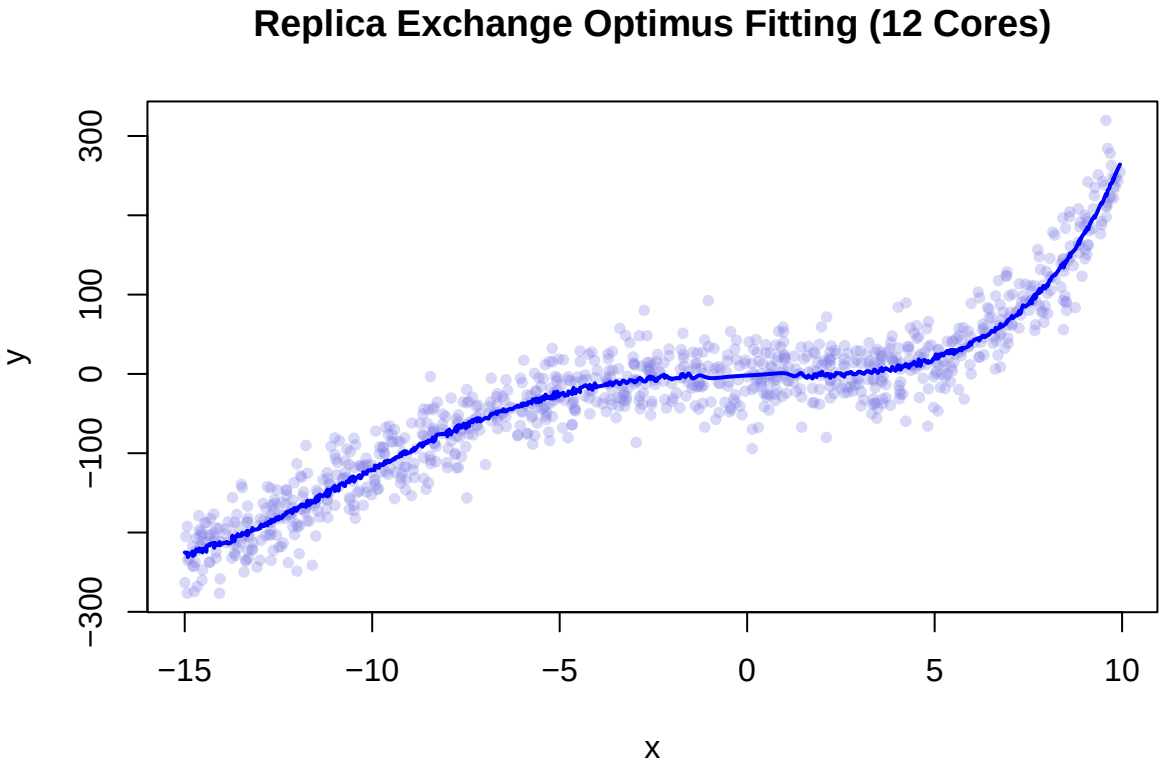
As in the Acceptance Ratio Annealing run above, we will again execute the optimisation procedure for 200 000 iterations. The Replica Exchange version of Optimus takes an input argument EXCHANGE.FREQ (default value 1000) which specifies the total number of exchanges that will occur during the optimisation process. Consequently, the number of optimisation iterations that occur between subsequent exchanges between replicas can be calculated as $NUMITER/EXCHANGE.FREQ$, which is 200 iterations in this

case.

Here we will set the input parameter STATWINDOW to have value 50 (its default value is 70). This signifies that the TCU will update the system pseudo-temperature once every 50 iterations on each optimisation replica. This guarantees that 4 temperature adjustments will be made if a given replica is involved in two subsequent exchanges (because the number of iterations between exchanges is 200, as explained in the preceding paragraph) as opposed to merely 2 adjustments which would be the case if STATWINDOW were left to take its default value and could result in poor agreement between the observed acceptance ratio of the replica in question and the target acceptance ratio. The following line executes Optimus with the above specified inputs:

```
Optimus(NCPU = 12, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, ACCRATIO = ACCRATIO, OPT.TYPE = "RE", DA
```

Nine of the optimisation replicas (Processors 1, 2, 3, 5, 6, 8, 9, 10 and 12) recovered the same solution that was found by the Acceptance Ratio Annealing Optimus run. Moreover, this solution is better (lower AIC) than those recovered by Processors 4, 7 and 11. Thus, in this example, the Acceptance Ratio Annealing and Replica Exchange versions produce the same solution.



Please note that for convenience, only those replicas which produced a unique solution are listed in the table below (replicas 1, 2, 3, 6, 8, 9, 10 and 12 produced the same solution as replica 5; replica 11 produced the same solution as replica 7).

Table 5: 12 Core Replica Exchange Optimus Run Results

	Processor 4	Processor 5	Processor 7
Replica Acceptance Ratio	66.00000	58.00000	42.00000
E (AIC)	9.56730	9.56720	9.56730
Q (RMSD)	28.66639	28.69324	28.69512
Term 1	0.00000	0.00000	0.00000
Term 2	1.00000	1.00000	1.00000
Term 3	1.00000	1.00000	1.00000
Term 4	1.00000	1.00000	1.00000

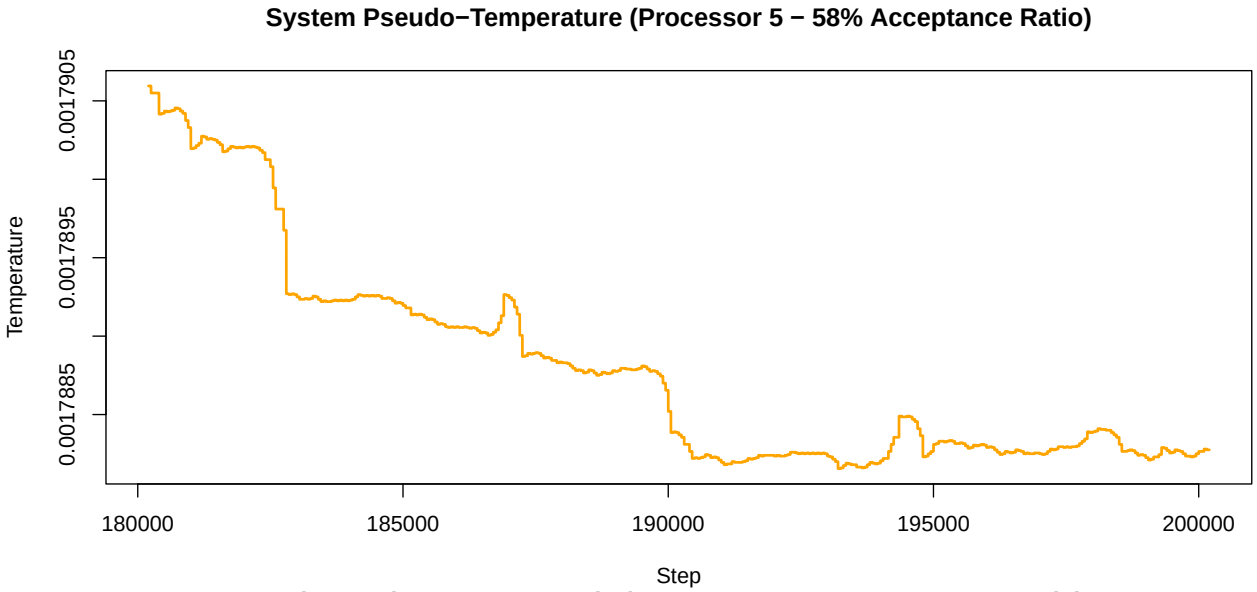
	Processor 4	Processor 5	Processor 7
Term 5	0.00000	0.00000	0.00000
Term 6	0.00000	0.00000	0.00000
Term 7	0.00000	0.00000	0.00000
Term 8	0.00000	0.00000	0.00000
Term 9	0.00000	0.00000	0.00000
Term 10	0.00000	0.00000	0.00000
Term 11	1.00000	1.00000	0.00000
Term 12	0.00000	0.00000	0.00000
Term 13	1.00000	0.00000	1.00000
Term 14	0.00000	0.00000	0.00000
Term 15	0.00000	0.00000	0.00000
Term 16	0.00000	0.00000	0.00000
Term 17	0.00000	0.00000	0.00000
Term 18	0.00000	0.00000	0.00000
Term 19	0.00000	0.00000	0.00000
Term 20	1.00000	1.00000	0.00000
Term 21	0.00000	0.00000	0.00000
Term 22	0.00000	0.00000	0.00000
Term 23	0.00000	0.00000	0.00000
Term 24	0.00000	0.00000	0.00000
Term 25	0.00000	0.00000	0.00000
Term 26	1.00000	1.00000	1.00000
Term 27	0.00000	0.00000	0.00000
Term 28	0.00000	0.00000	1.00000
Term 29	0.00000	0.00000	0.00000
Term 30	0.00000	0.00000	0.00000

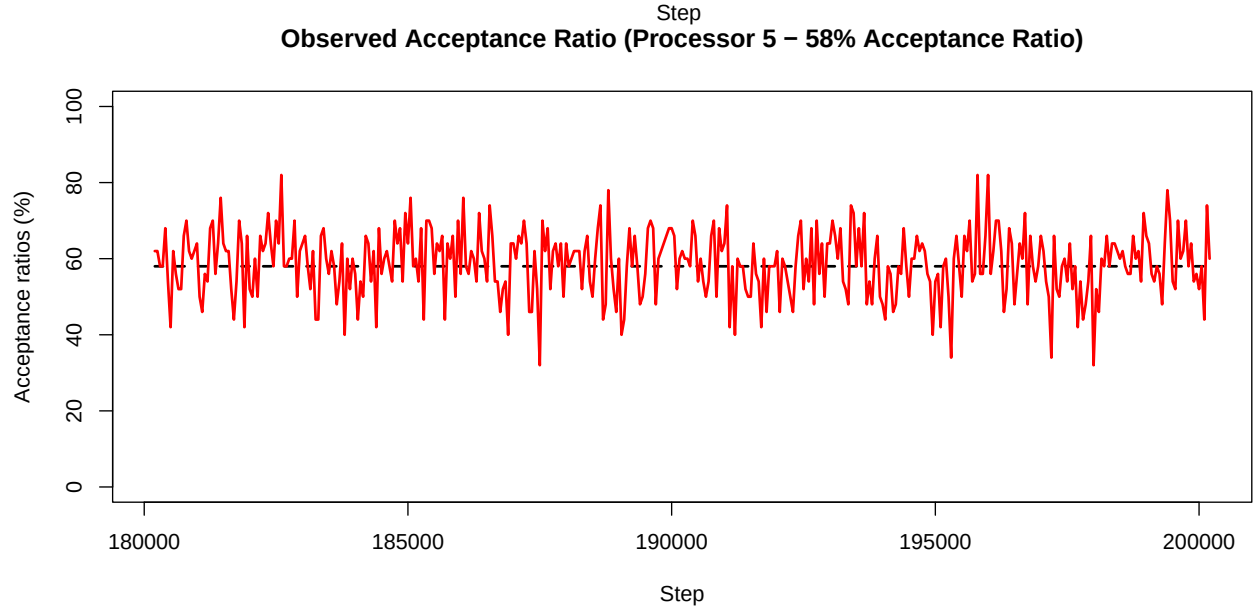
Note that the various replica outcomes illustrate the penalizing effects of the AIC on models using a greater number of parameters. Consider the solutions found by the 66% acceptance ratio replica and the 58% acceptance ratio replica (Processors 4 and 5 respectively). Let y_i denote the solution found by Processor i. Then, we have:

$$y_4 = b + c_2x^2 + c_3x^3 + c_4x^4 + c_{11}e^x + k_{13}c_{13}six(x) + c_{20}sin(x^3) + c_{26}cos(x^5)sin(-x)$$

$$y_5 = b + c_2x^2 + c_3x^3 + c_4x^4 + c_{11}e^x + c_{20}sin(x^3) + c_{26}cos(x^5)sin(-x)$$

Although the RMSD of y_4, 28.66639, is lower than the RMSD of y_5, 28.69324, y_5 has a lower value for AIC because it contains one less term than y_4. Since AIC was specified as the objective metric, Optimus (perhaps counterintuitively) selecyed y_5 as the more optimal solution to reduce overfitting.





The above graphs are produced using data from the last 20 000 iterations of the 58% acceptance ratio replica (Processor 5). It is clear that the observed acceptance ratio more strongly oscillated around the target acceptance ratio than was the case in the Acceptance Ratio Annealing run from the previous part of this tutorial. More generally, it should be expected that the observed acceptance ratio fluctuates more significantly around the target acceptance ratio in Replica Exchange than in Acceptance Ratio Annealing, especially when the objective function is non-smooth as is the case in this example. This is because an exchange between two replicas has the same effect as restarting a Monte Carlo optimisation from a random initial configuration with a temperature that very likely is not conducive to the target acceptance ratio for the given configuration. As such, each time an exchange occurs, significant deviations from the target acceptance ratio may occur and may require several STATWINDOWs for the TCU to correct. Despite this challenge, the TCU performs satisfactorily.

Summary

We now understand how to employ Optimus to solve a more general problem than was addressed in Tutorial 1 and one with a non-smooth objective function. Additionally, we have a better understanding of the

performance of the Temperature Control Unit. Using the Aikake Information Criterion (AIC) as a metric with which to evaluate the performance of a candidate model, taking into account the desire to represent the data while avoiding to overfit the data, both the Acceptance Ratio Annealing and Replica Exchange versions of Optimus recovered a better functional form to describe the data than the form which was assumed in Tutorial 1 (based on how the data had been generated).

Table 6: Summary of Solutions

	E (AIC)	Q (RMSD)
Least Squares (Tutorial 1)	9.570471	28.82655
Optimus (Acceptance Ratio Annealing)	9.567200	28.69324
Optimus (Replica Exchange)	9.567200	28.69324

Least Squares(Tutorial 1):

$$y = c_1 x + c_2 x^2 + c_3 x^3 + c_4 x^4$$

Optimus (Acceptance Ratio Annealing):

$$y = b + c_2 x^2 + c_3 x^3 + c_4 x^4 + c_{11} e^x + c_{20} sin(x^3) + c_{26} cos(x^5) sin(-x)$$

Optimus (Replica Exchange):

$$y = b + c_2 x^2 + c_3 x^3 + c_4 x^4 + c_{11} e^x + c_{20} sin(x^3) + c_{26} cos(x^5) sin(-x)$$

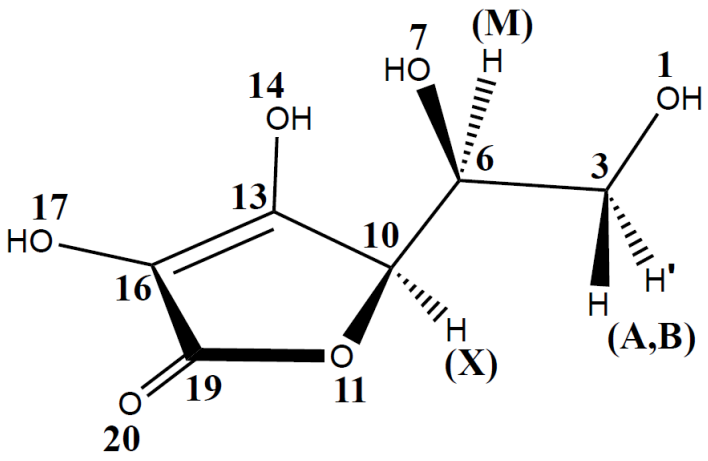
Tutorial 3: Vitamin C Molecular Geometry Optimisation

Problem Statement

The focus of this Tutorial is to depart from problem classes involving the search for functions to represent data and demonstrate how Optimus can be flexibly applied to arbitrary problem classes provided that they are formulated in accordance with Optimus specifications. Additionally, this Tutorial will illustrate that Optimus 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, Optimus will be used to solve a molecular geometry optimisation problem. Specifically, Optimus will be used to determine the 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 sigma bond and the potential for intramolecular hydroxy groups and lone pair donating oxygen atoms. Moreover, Vitamin C is not a particularly large molecule. Due to these circumstances, Vitamin C has a non trivial groud energy state (as opposed to a molecule like ethane for instance) but one that does not require several days or weeks of simulation to arrive at (the optimisation procedures below took roughly 14-18 hours to terminate).

This is the molecular structure of Vitamin C:

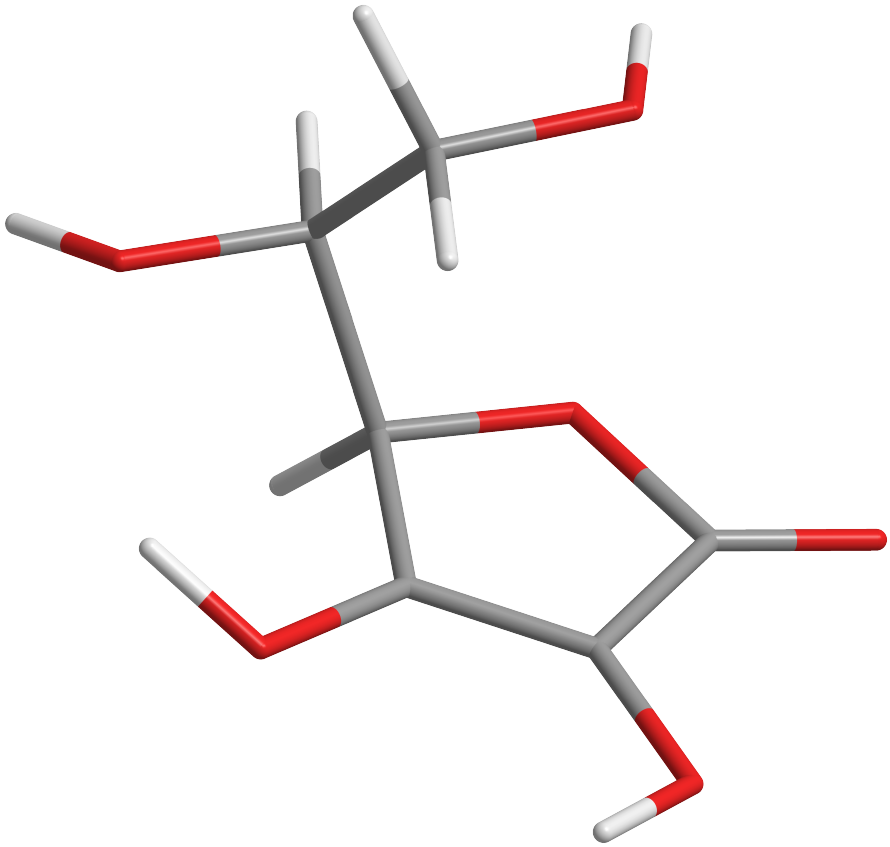


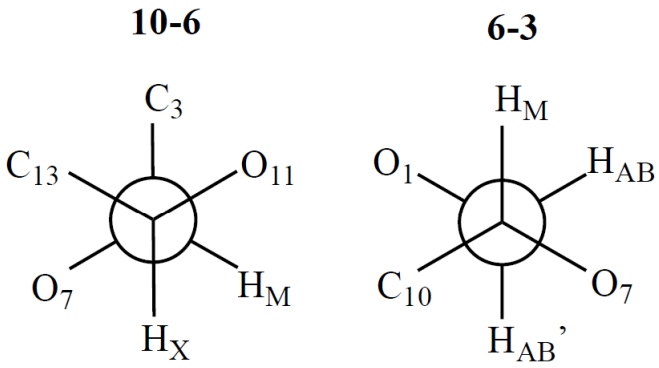
Free rotation is possible around two sigma bonds in this structure: the bond joining carbon 3 and 6, and the bond joining carbon 6 and 10. The ground state conformation of Vitamin C will be a conformation such that steric clash between the constituent members bonded to the freely rotating bonds is minimized while also allowing for close proximity between hydrogen bond donating and hydrogen bond accepting groups. In the following sections, we formalize this optimisation problem and use Optimus to arrive at the solution.

Defining Optimus Inputs

As in the previous Tutorials, we must first rigorously define the parameters which we are optimising. Let us begin by defining a dihedral angle as it applies to 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 sigma 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 6, 7, 10 and 11. Loosely, ψ can be thought of as the angle between oxygen atoms 1 and 7 while ϕ can be thought of as the angle between oxygen atoms 7 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 initialize 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 denoted Carbon, red denotes Oxygen and white denoted Hydrogen.

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

Now we will specify a model function $m()$ which 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 a completely external program: MOPAC (2016). MOPAC is a geometry optimiser that uses EigenFollowing to arrive at a local minimum (note that calling MOPAC for a single 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 relationships needed to define the molecule. $m()$ will then call MOPAC with the newly constrcuted Z matrix, specifiying that all relationships may be altered except the input dihedral angles K. Finally, $m()$ will return the energy calculated by MOPAC.

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. Also, note that although $m()$ requires no additonal data on top of K to operate, $m()$ must still be defined to take an input DATA in accordance with Optimus specifications. Lastly, note that a local installation of MOPAC (2016) is required to execute this optimisation procedure. Below is the definition of $m()$:

```
m <- function(K, DATA = NULL){

  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.
  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 physcial energy of the candidate Vitamin C conformation, $u()$ can simply set E to be the 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 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 = NULL){
  result   <- NULL
  result$Q <- -O
  result$E <- O
  return(result)
}
```

Finally, we define the 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 3 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 by off-loading a significant amount of computation to an external program is one of the many strengths of Optimus.

Defining a Benchmark Solution

Before calling Optimus, we must establish a benchmark solution which will be used to evaluate the efficacy of Optimus. In order to explore the energy landscape associated with the parameter space of ψ and ϕ, a PM6 optimization was performed on 10 conformers from an MM2 optimization run (the details of PM6 and MM2 are not important for the purposes of this tutorial) which resulted in the identification of 7 local energy minima, shown in the table below (listed in increasing order by energy):

Table 7: 7 Vitamin C Conformational Local Minima

	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 represent all conformational local minima in the parameter space of ψ and ϕ. Under this assumption, Conformation 1 should be considered the ground state conformation of Vitamin C. The accuracy of the results produced by Optimus can thus be judged by comparing them to the data listed in this table. It is important to recognize that the "resolution" of ψ and ϕ when being optimized by Optimus is 2 degrees due to the manner in which $r()$ was defined. As such, results produced by Optimus that are within plus or minus 2 degrees of a reference conformation should be tolerated.

Acceptance Ratio Annealing Optimus Run

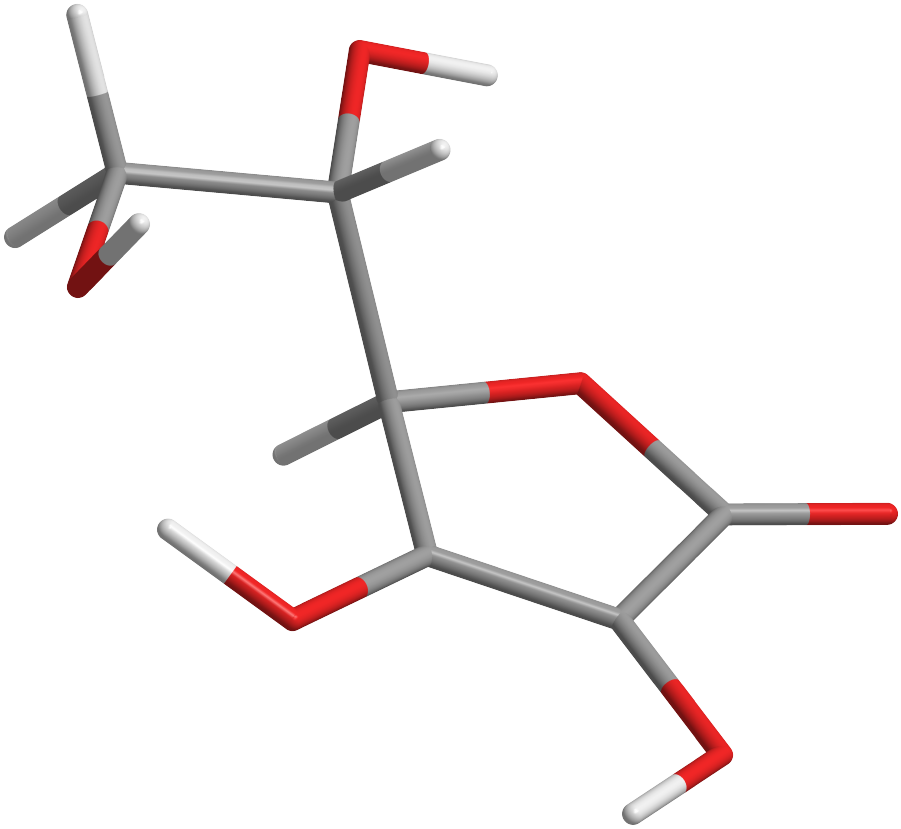
For the Acceptance Ratio Annealing run, we will set NUMITER = 100 000 because each optimsation step is more costly due to the relatively computationally expensive calls to MOPAC. Moreover, we will set CYCLES = 2. Although this shortens the length of an annealing cycle to 50 000 steps (whereas 100 000 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.

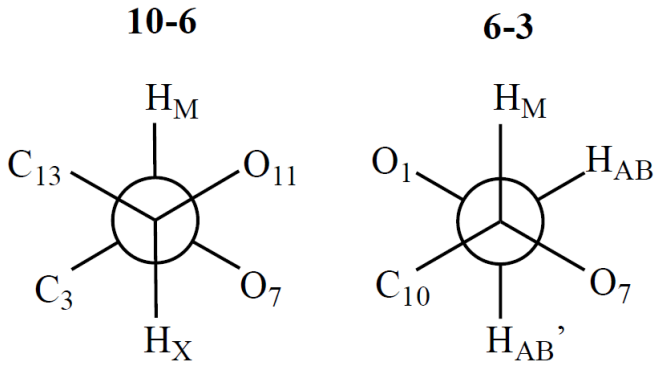
```
Optimus(NCPU = 4, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, OPT.TYPE = "SA", OPTNAME = "vitamin_4_SA
```

Table 8: 4 Core Acceptance Ratio Annealing Optimus Run Results

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

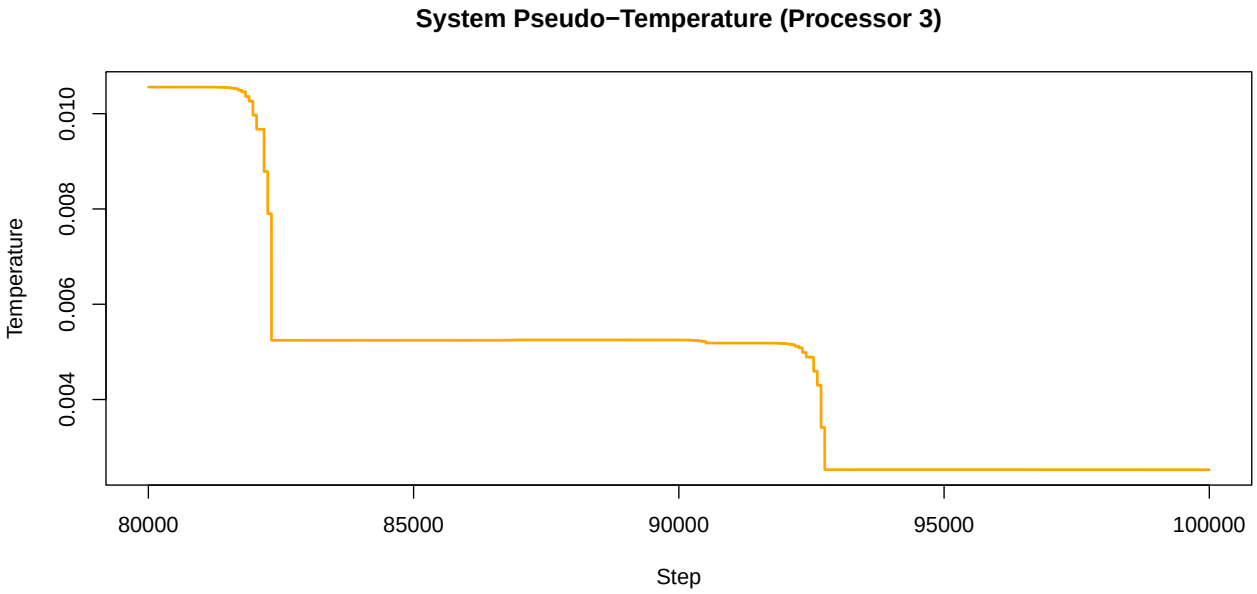
Processors 1, 3 and 4 all arrived at a conformation defined by $\{\phi = 50, \psi = -172\}$, with an energy of -232.874 kcal/mol. The below 3D structure and Newman Projections depict this solution:

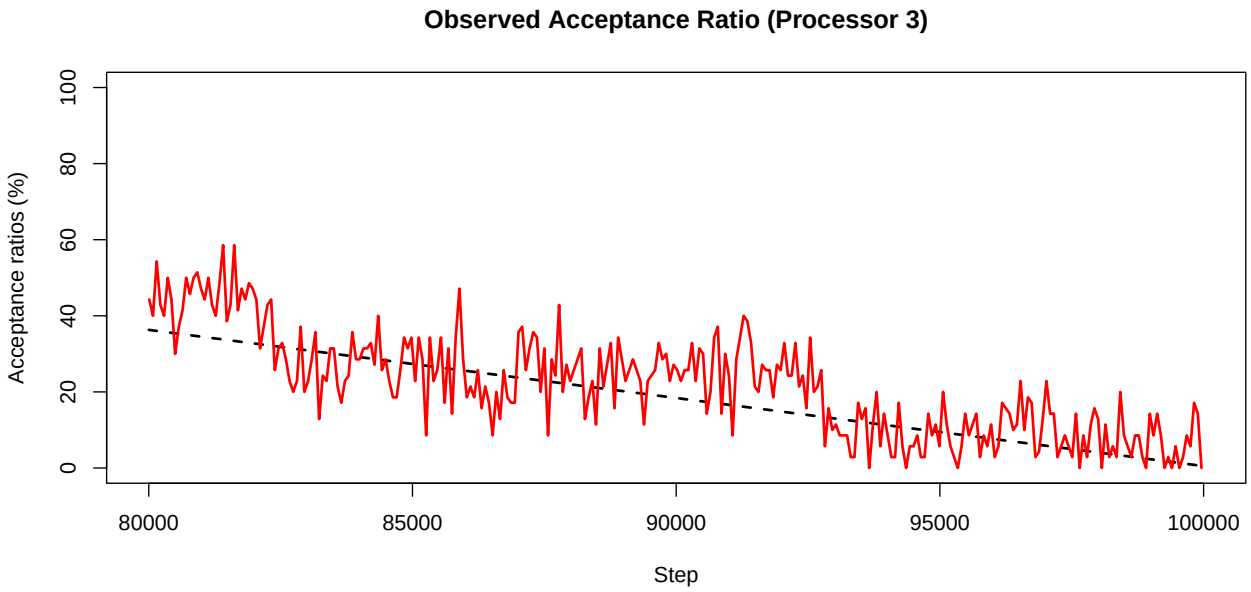




This conformation is equivalent to benchmark Conformation 2. Thus, in this example, Acceptance Ratio Annealing was able to find the Vitamin C conformation with the second lowest energy in the parameter space. This performance is strong, especially given that the energy difference between Conformation 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 Processor 3.





Replica Exchange Optimus Run

Let us now consider the Replica Exchange version of Optimus 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)
```

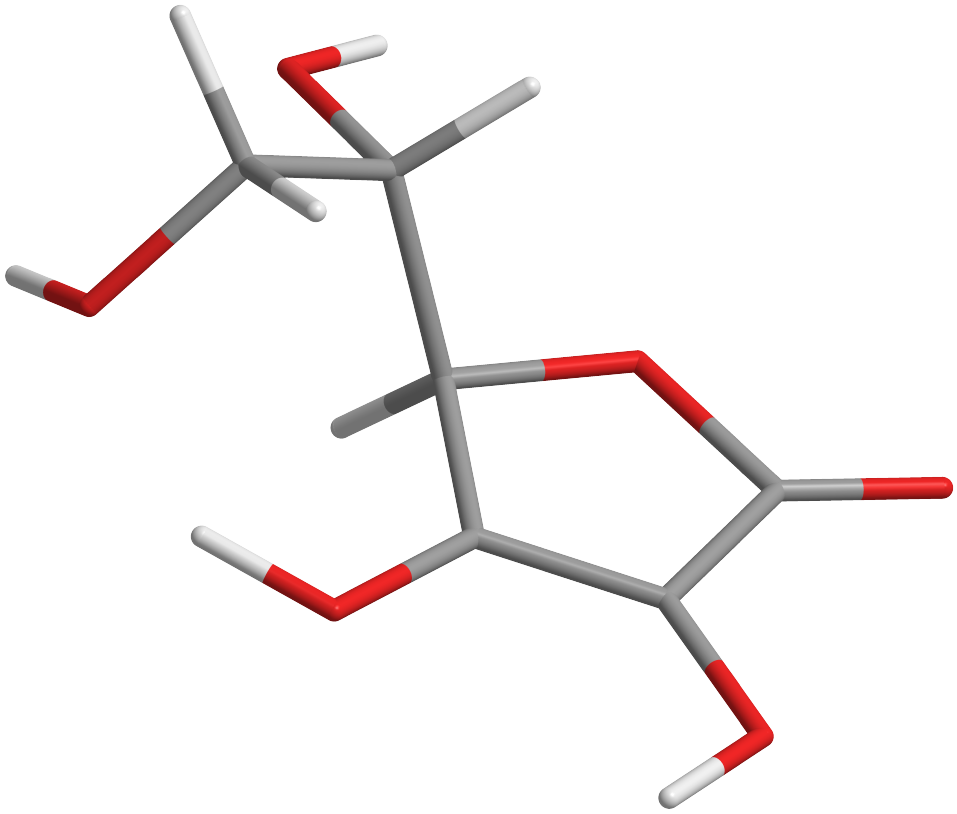
Just as in the Acceptance Ratio Annealing run, we will set NUMITER = 100 000. Moreover, we will set EXCHANGE.FREQ = 500 such that the number of iterations between subsequent exchanges between replicas is 200 as it was in Tutorial 2. For the same reasons as in Tutorial 2, we will set STATWINDOW = 50 for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

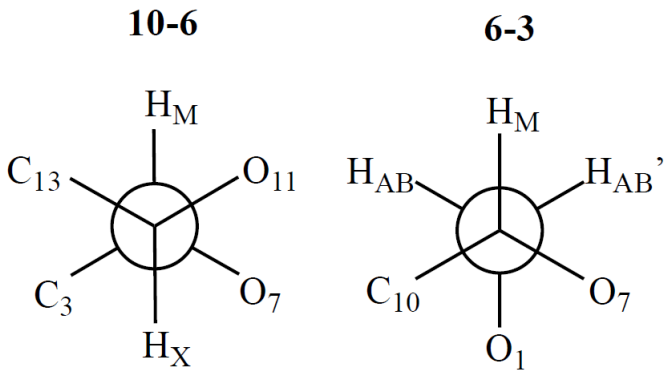
```
Optimus(NCPU = 12, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, ACCRATIO = ACCRATIO, OPT.TYPE = "RE", D
```

Table 9: 12 Core Replica Exchange Optimus Run Results

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

Of the 12 replicas, Processor 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:

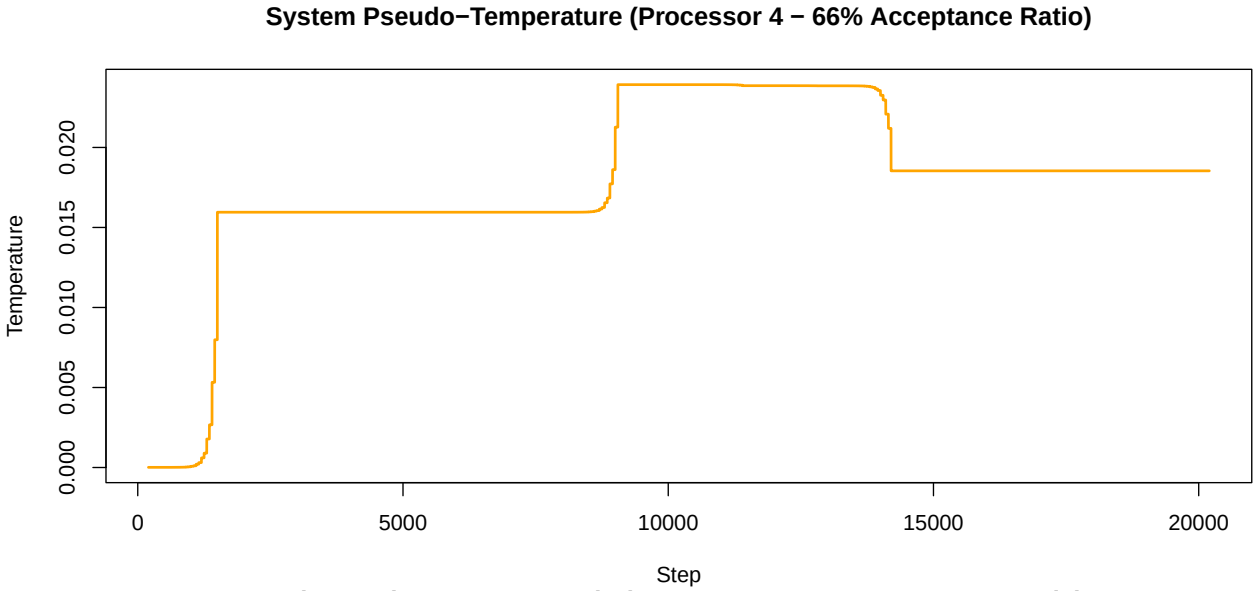


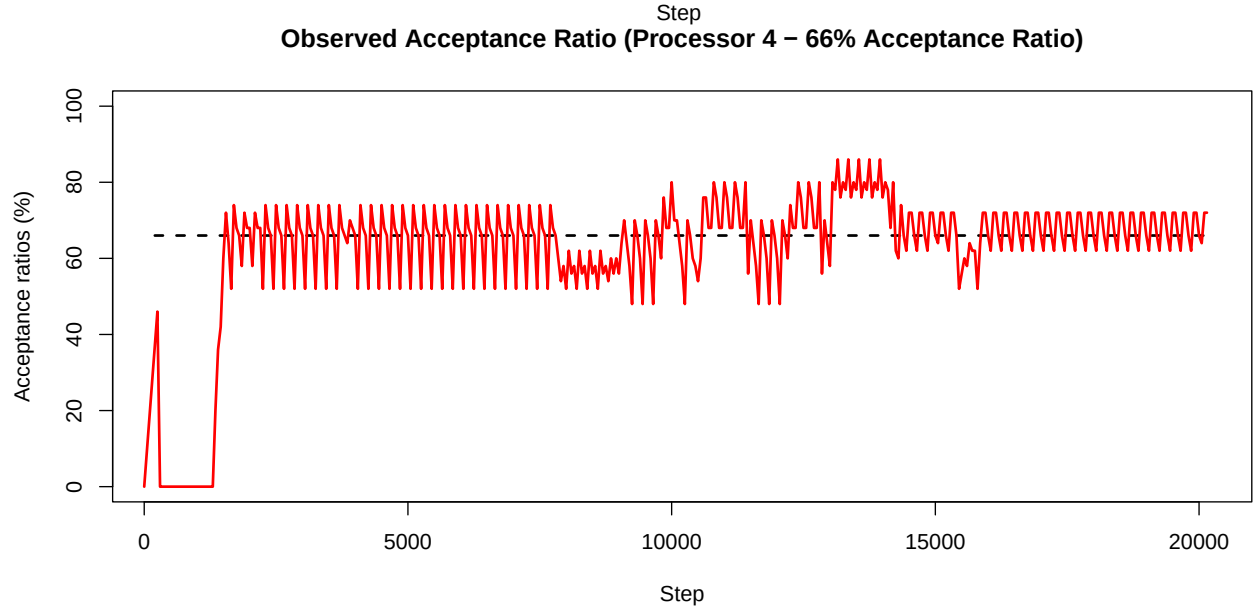


This solution corresponds to reference Conformation 1, the global minimum energy state for Vitamin C. Thus, for this optimisation problem, the Replica Exchange version of Optimus outperformed Acceptance Ratio Annealing by succeeding in finding the global minimum of the energy landscape while the latter version found only the second lowest local energy minimum.

If we compare the solution found by Processor 4 to benchmark Conformation 1, it is evident that the value for ϕ found by Optimus lies slightly outside of the plus or minus 2 degree window that was discussed earlier. Contrarily, Processor 7 finds a solution $\{\phi = 94, \psi = 74\}$ which does lie strictly within the resolution window. Despite this, the solution of Processor 4 has a slightly lower energy (-233.1979) than the solution of Processor 7 (-233.1947) and so represents a better solution. Given that the local energy landscape around Conformation 1 is unknown, it is not unreasonable that within this local area, a conformation "closer" to Conformation 1 does not necessarily result in a lower energy. Finally, notice that Replica 6 recovered the same conformation that was identified by Acceptance Ratio Annealing Optimus.

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





When the optimisation process is first initialized, it is very unlikely that the input initial temperature is conducive to the target acceptance ratio. As such, the Temperature Control Unit 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 catalyzes significant temperature adjustments executed by the TCU. 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 molecular geometry optimisation problem to be solved with Optimus as a kernel while interfacing with an entirely external program, MOPAC, to handle a significant amount of the necessary computation. Using 7 local minima identified by a PM6 optimization of 10 conformers from an MM2 run as validation, we saw that the Acceptance Ratio Annealing mode of Optimus was able to find the second lowest local minima while the Replica Exchange mode recovered the global energy minimum (outperforming Acceptance Ratio Annealing).

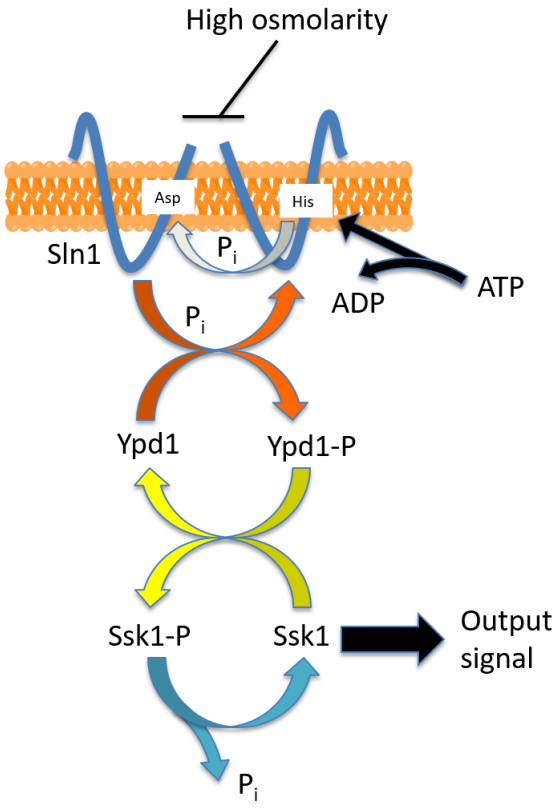
Table 10: Summary of Solutions

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

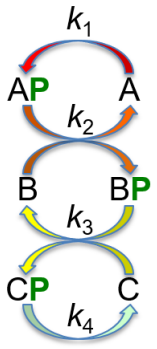
Tutorial 4: Determining Rate Constants for Coupled ODEs Modelling a Biological System

Problem Statement

This Tutorial will demonstrate the use of Optimus to address a problem from yet another problem class. We will employ Optimus to recover the rate constants for a system of coupled ordinary differential equations (ODEs) modelling a biological pathway. Specifically, we will study a phosphorelay system from the high osmolarity glycerol (HOG) pathway in Yeast. A phosphorelay system is a network involving multiple proteins in which after an initial phosphorylation event using ATP (or an alternate phosphate donor), the phosphorylation and dephosphorylation events of proteins in the network proceed without further consumption of ATP (Klipp et al. 2009). The below diagram illustrates the phosphorelay system that will be studied in detail (Klipp et al. 2009):



Under normal circumstances, the transmembrane protein Sln1, which is present as a dimer, autophosphorylates at a histidine residue (consuming ATP). The phosphate group is then transferred to an aspartate residue of Sln1. Thereafter, the phosphate is transferred to the protein Ypd1 and finally to the protein Ssk1. Ssk1 is continuously dephosphortylated to give an output signal. The signalling pathway is inhibitted by an increase is osmolarity outside of the cell (Klipp et al. 2009). If we let A represent Sln1, B represent Ypd1, C represent Ssk1 and XP represent the phophorylated form of protein X, then the above network can be represented by the below schematic (Klipp et al. 2009):



where each k_i represents the rate constant for the relevant phosphorylation/dephosphorylation reaction.

The above graphic allows us to arrive at the following equations to describe the temporal behavior of the phosphorelay system:

$$\frac{d}{dt}[A] = -k_1[A] + k_2[AP][B]$$
$$\frac{d}{dt}[B] = -k_2[AP][B] + k_3[BP][C]$$
$$\frac{d}{dt}[C] = -k_3[BP][C] + k_4[CP]$$

Moreover, under the generally accepted assumption that the degradation and production of proteins occurs on a time scale that far exceeds that of phosphorylation events, we have the following conservation relationships (Klipp et al. 2009):

$$[A]_{total} = [A] + [AP]$$
$$[B]_{total} = [B] + [BP]$$
$$[C]_{total} = [C] + [CP]$$

where $[A]_{total}$, $[B]_{total}$ and $[C]_{total}$ are constants. Differentiating, we have:

$$\frac{d}{dt}[AP] = -\frac{d}{dt}[A]$$
$$\frac{d}{dt}[BP] = -\frac{d}{dt}[B]$$
$$\frac{d}{dt}[CP] = -\frac{d}{dt}[C]$$

Given this model of the phosphorelay system, the question we desire to answer is as follows: given initial concentrations of the three proteins $\{[A]_i, [B]_i, [C]_i\}$ and target concentrations of the three proteins $\{[A]_t, [B]_t, [C]_t\}$, what are the values $\{k_1, k_2, k_3, k_4\}$ that result in the proteins having the target concentrations at steady state when the system is allowed to equilibrate from the initial concentrations? This formulation assumes that no information is known about the rate constants and that initial and target concentrations can be determined experimentally, which is often the case in practice (Raue et al. 2013). The problem formulation could be altered depending on the information that is known or that can be determined experimentally.

Defining Optimus Inputs

Having outlined how the behaviour of the phosphorelay system can be modelled using a system of differential equations, we can now proceed with defining input parameters for Optimus. We will create a variable state that will be a numeric vector holding the names and initial concentrations of all species in the network. For this Tutorial, we will choose $[A]_i = [B]_i = [C]_i = 100$ and $[AP]_i = [BP]_i = [CP]_i = 0$. Note that the units are arbitrary and that the total sum of units across this vector will remain constant throughout the simulation of the dynamics of the phosphorelay system.

```
state  <- c(cA=100, cB=100, cC=100, cAP=0, cBP=0, cCP=0)
```

Next, we will create a variable target which will be a numeric vector holding the names and target concentration of all species in the network. We will arbitrarily choose target values of $[A]_t = 90$, $[B]_t = 20$, $[C]_t = 70$, $[AP]_t = 10$, $[BP]_t = 80$ and $[CP]_t = 30$. Note that the chosen target values must be consistent with the above defined conservation equations, meaning we must have $[X]_i + [XP]_i = [X]_t + [XP]_t, \forall\, X \in \{A, B, C\}$.

```
target <- c(cA=90, cB=20, cC=70, cAP=10, cBP=80, cCP=30)
```

In order to determine the steady state behavior of the ODE system, we will employ the function *ode*() from the R package deSolve (this function interfaces with the Fortran library typically used to solve systems of differential equations). This function requires as input a function that describes the dynamics of the ODE system. We will call this function *model*(). At a high level, *model*() will simply define the equations derived in the previous section that describe the network. It should contain equations that use the objects with the names specified within state above, and should have equations that assign the outcomes to new objects that have the same order and names as specified in state, but with "d" at the beginning (a more detailed description of the requirements of *model*() can be found in the documentation of *ode*()).

```
model <- function(t, state, K){

  with( as.list(c(state, K)), {
    # rate of change
    dcA  <- -k1*cA+k2*cAP*cB
    dcB  <- -k2*cAP*cB+k3*cBP*cC
    dcC  <- -k3*cBP*cC+k4*cCP
    dcAP <- -dcA
    dcBP <- -dcB
    dcCP <- -dcC
    # return the rate of change
    list(c(dcA, dcB, dcC, dcAP, dcBP, dcCP))
  })
}
```

The variables *state* and *target*, and the function *model*() should be stored as entries in a list $DATA$ which will be given to the functions $m()$ and $u()$ as inputs.

```
DATA <- NULL
DATA$state  <- state
DATA$target <- target
DATA$model  <- model
```

We will make K be a numeric vector holding the set of rate constants $\{k_1, k_2, k_3, k_4\}$. We will (arbitrarily) initialize each rate constant to have value 1.0.

```
K <- c(k1=1.0, k2=1.0, k3=1.0, k4=1.0)
```

The function $m()$ will take as input the vector K of rate constants and the list $DATA$. It will return an object O that contains the concentrations of the six species in the network when the system is simulated from the initial state specified in $DATA$ using the K rate constants for 10 time steps. Note that it is not

necessarily guaranteed that the system will reach a steady state after 10 time steps; the number of time steps was chosen such that the optimisation procedure would terminate within 1-2 hours. $m()$ will call the function *ode*() from the package deSolve, so we must first ensure that deSolve is installed.

```
install.packages("deSolve")
```

```
library(deSolve)
m <- function(K, DATA){
  state <- DATA$state
  model <- DATA$model

  span = 10.0

  times <- c(0, span)
  O   <- ode(y=state, times=times, func=model, parms=K)[2,2:(length(state)+1)]
  return(O)
}
```

Recall that the function $u()$ must return an energy E and a quality Q of the candidate solution. Here, $u()$ will set both E and Q to be the RMSD between the steady state concentrations of the network correponding to the current set of rate constants K, as determined by $m()$, and the target concentrations.

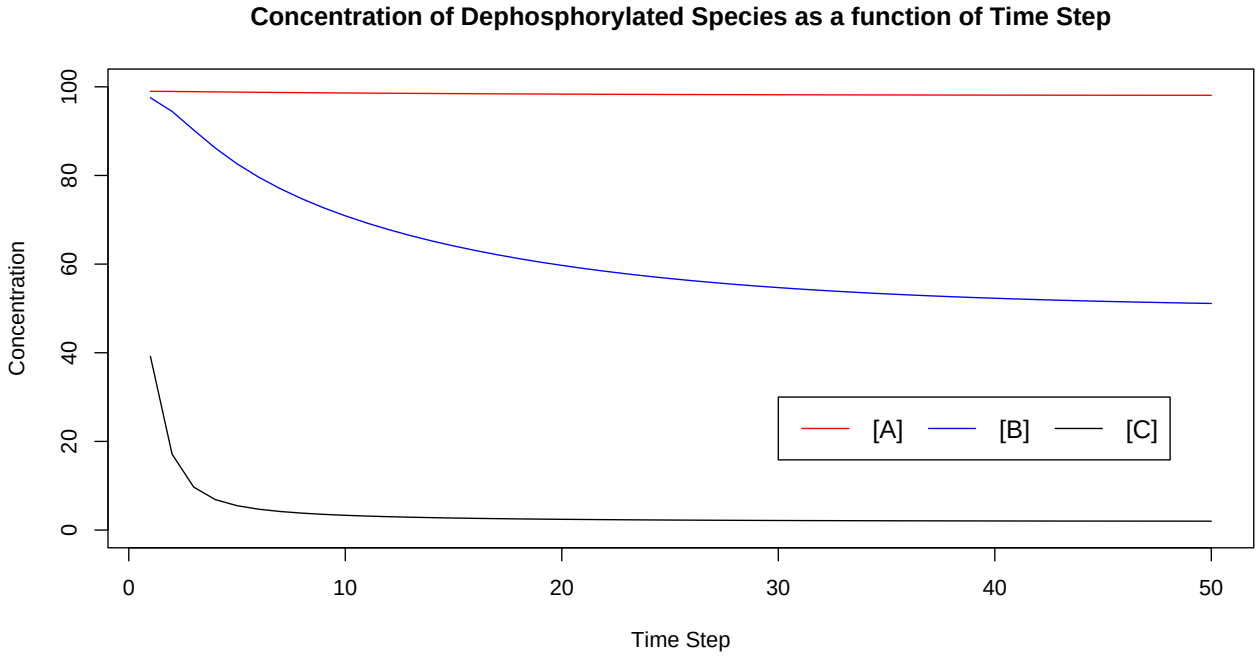
```
u <- function(O, DATA){
  target <- DATA$target
  RESULT <- NULL
  RESULT$Q <- sqrt(mean((O-target)^2)) # measure of the fit quality
  RESULT$E <- RESULT$Q # the pseudoenergy derived from the above measure

  return(RESULT)
}
```

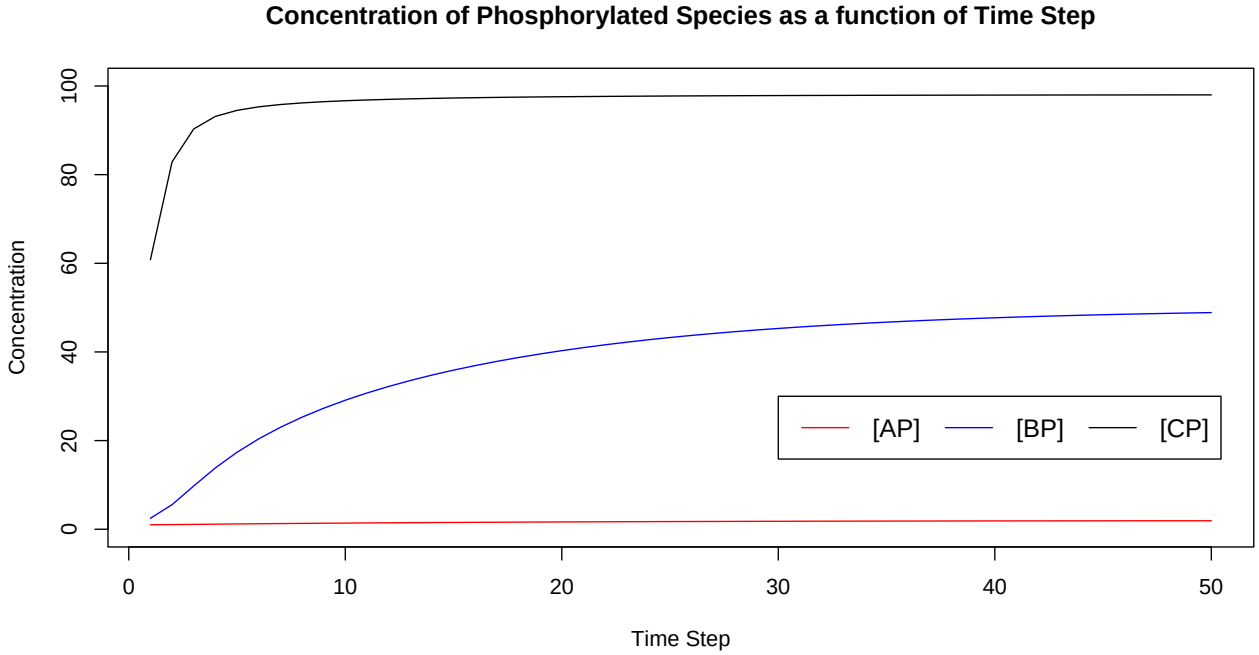
The final mandatory input to Optimus which must be defined is the alteration fucntion $r()$. Just as in Tutorial 1, for each snapshot of K, we shall randomly select one of its four coefficients, then either increment or decrement (chosen randomly) it by 0.0002, returning the altered set of coefficients. Since we are dealing with rate constants in this case, if ever $r()$ were to make an entry in K negative, that entry will automatically be set to 0.

```
r <- function(K){
  K.new <- K
  # Randomly selecting a coefficient to alter:
  K.ind.toalter <- sample(size=1, x=1:length(K.new))
  # Creating a potentially new set of coefficients where one entry is altered
  # by either +move.step or -move.step, also randomly selected:
  move.step <- 0.0002
  K.new[K.ind.toalter] <- K.new[K.ind.toalter] + sample(size=1, x=c(-move.step, move.step))

  ## Setting the negative coefficients to 0
  neg.ind <- which(K.new < 0)
  if(length(neg.ind)>0){ K.new[neg.ind] <- 0 }

  return(K.new)
}
```

Exploring the System Dynamics

Before calling Optimus to solve this problem, let us first simulate the system of ODEs from the chosen initial state using a few sets of arbitrary rate constants to become familiar with how the system evolves. The below graphs illustrate the evolution of the system for 50 time steps for the rate constants $\{k_1 = 1.0, k_2 = 1.0, k_3 = 1.0, k_4 = 1.0\}$:





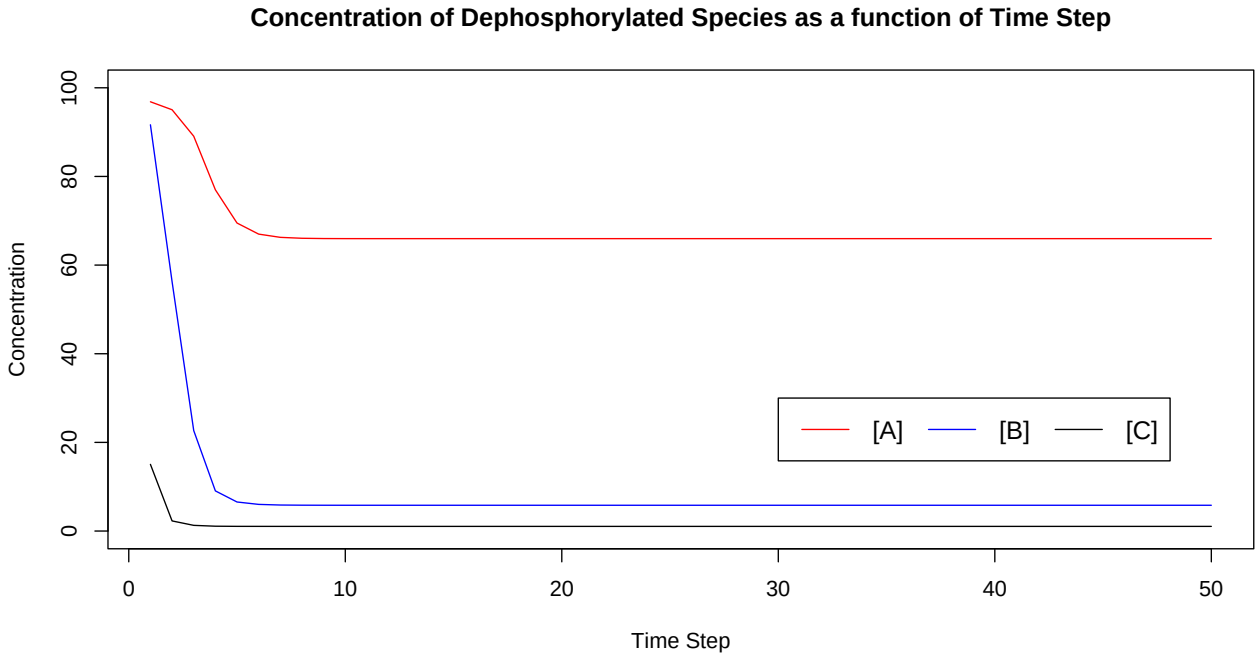
The table below summarizes the initial and final concentrations of the various species when the system is simulated for 50 time steps using the rate constants $\{k_1 = 1.0, k_2 = 1.0, k_3 = 1.0, k_4 = 1.0\}$:

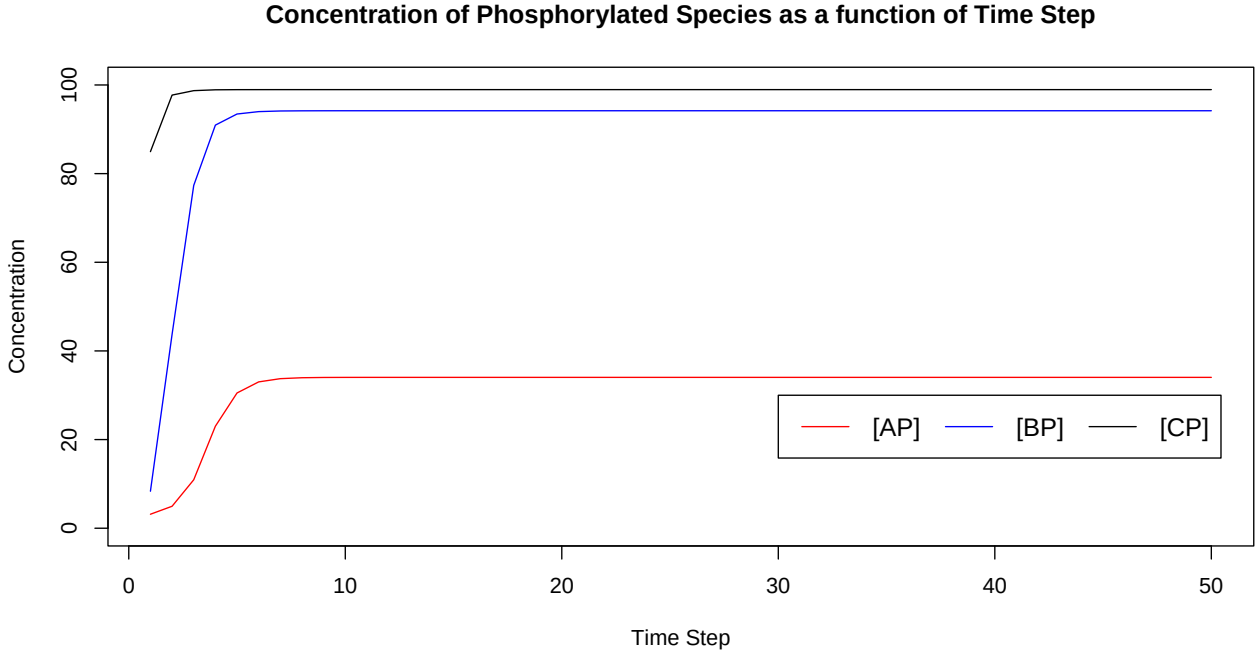
	[A]	[B]	[C]	[AP]	[BP]	[CP]

Table 11: System Summary for k1 = k2 = k3 = k4 = 1.0

	[A]	[B]	[C]	[AP]	[BP]	[CP]
Initial	100.00000	100.00000	100.000000	0.000000	0.00000	0.00000
Final (after 50 time steps)	98.08145	51.12118	2.004924	1.918549	48.87882	97.99508

If instead we use the set of rate constants $\{k_1 = 1.5, k_2 = 0.5, k_3 = 1.0, k_4 = 1.0\}$, the system evolves as follows:





The table below summarizes the initial and final concentrations of the various species when the system is

simulated for 50 time steps using the rate constants $\{k_1 = 1.5, k_2 = 0.5, k_3 = 1.0, k_4 = 1.0\}$:

Table 12: System Summary for k1 = 1.5, k2 = 0.5, k3 = k4 = 1.0

	[A]	[B]	[C]	[AP]	[BP]	[CP]
Initial	100.00000	100.000000	100.000000	0.00000	0.00000	0.00000
Final (after 50 time steps)	65.96628	5.814787	1.050583	34.03372	94.18521	98.94942

Acceptance Ratio Annealing Optimus Run

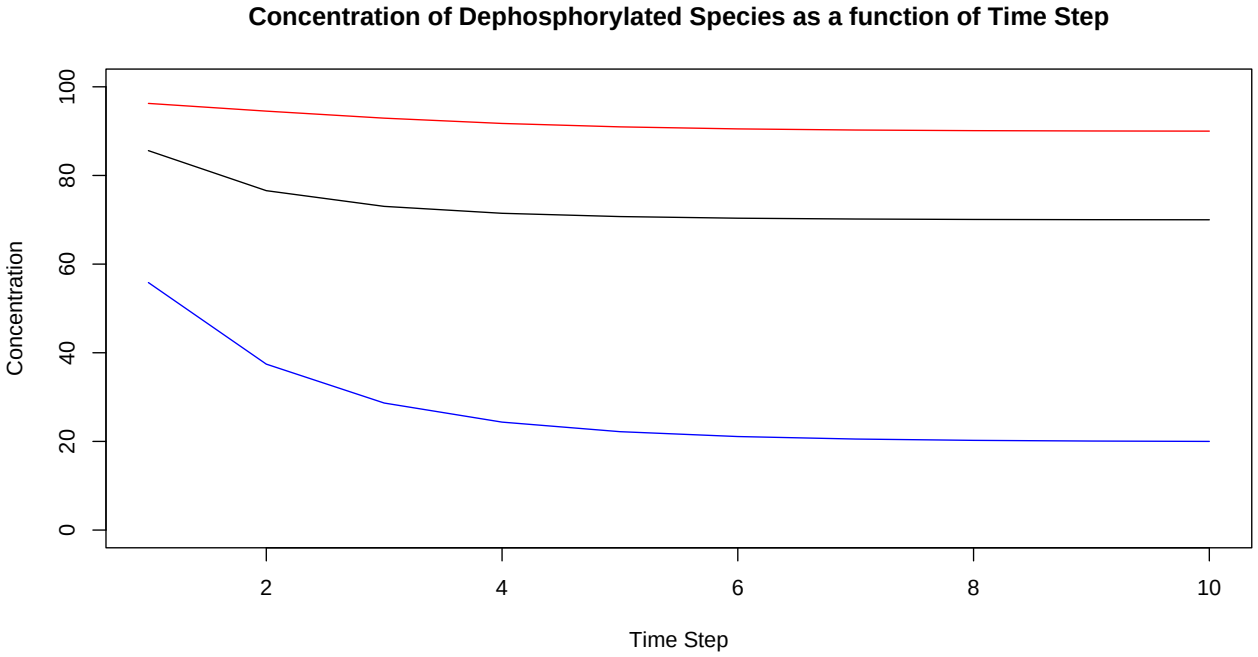
We will now call Acceptance Ratio Annealing Optimus to solve our problem. Similarly to Tutorial 2, we will execute 200 000 optimisation iterations and perform 2 annealing cycles. We will set DUMP.FREQ to have a value of 100 000.

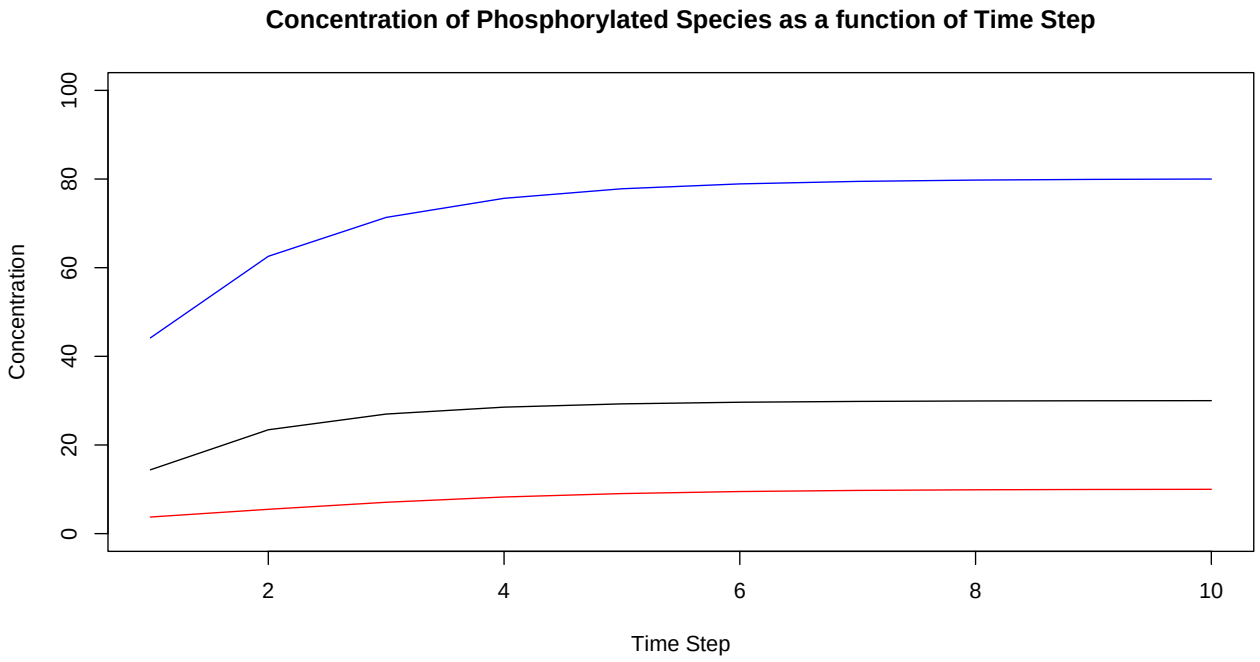
```
Optimus(NCPU = 4, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, OPT.TYPE = "SA", OPTNAME = "DE_4_SA", DA
```

Table 13: 4 Core Acceptance Ratio Annealing Optimus Run Results

	E (RMSD)	K1	K2	K3	K4
Processor 1	0.0012516	0.7974	0.3586	0.0128	2.3886
Processor 2	0.0017556	0.7850	0.3532	0.0126	2.3512
Processor 3	0.0013625	0.8098	0.3642	0.0130	2.4262
Processor 4	0.0012516	0.7974	0.3586	0.0128	2.3886

Of the 4 optimisation replicas, Processors 1 and 4 find the best set of rate constants, $\{k_1 = 0.7974, k_2 = 0.3586, k_3 = 0.0128, k_4 = 2.3886\}$. This set of rate constants results in an RMSD (after 10 iterations) of 0.0012516. Let us simulate how the system evolves according to these rate constants for 10 time steps:





The table below summarizes the initial and final concentrations of the various species when the system is simulated for 10 time steps using the rate constants $\{k_1 = 0.7974, k_2 = 0.3586, k_3 = 0.0128, k_4 = 2.3886\}$:

Table 14: System Summary for k1 = 0.7974, k2 = 0.3586, k3 = 0.0128, k4 = 2.3886

	[A]	[B]	[C]	[AP]	[BP]	[CP]
Initial	100.00000	100.00000	100.00000	0.00000	0.00000	0.00000
Final (after 10 time steps)	89.99814	20.00081	69.99924	10.00186	79.99919	30.00076

As can be seen in the above table, the concentration of the species in the system after 10 time steps are very close to the target values $[A]_t = 90$, $[B]_t = 20$, $[C]_t = 70$, $[AP]_t = 10$, $[BP]_t = 80$ and $[CP]_t = 30$. As alluded to earlier, it is possible that the system has not reached a steady state after 10 time steps, however the above graphs suggest that the concentrations after 10 steps are already extremely close to, if not equal to, steady state values. The optimisation process could be re-executed after increasing the value of the parameter *span* in the function $m()$ to simulate the system for a larger number of time steps.

Replica Exchange Optimus Run

Let us now examine how replica exchange Optimus using 12 cores performs on this task. We will use 200 000 optimisation iterations and set STATWINDOW to equal 50, similarly to Tutorials 2 and 3.

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

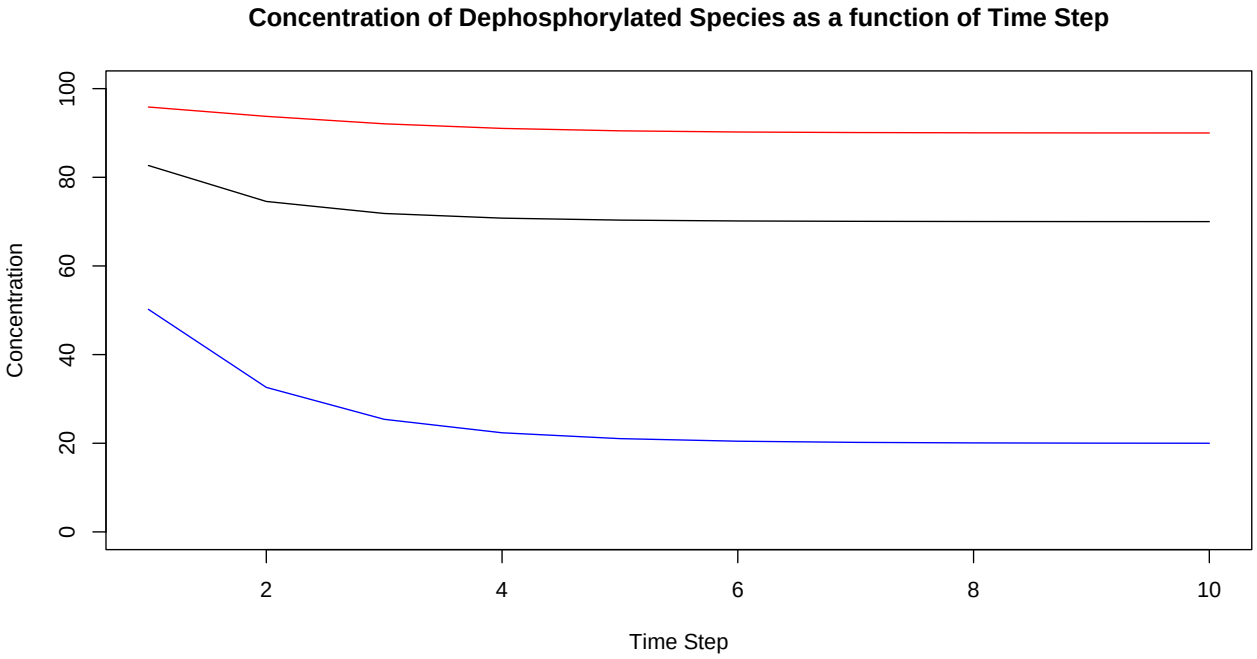
```
Optimus(NCPU = 12, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, ACCRATIO = ACCRATIO, OPT.TYPE = "RE", DA
```

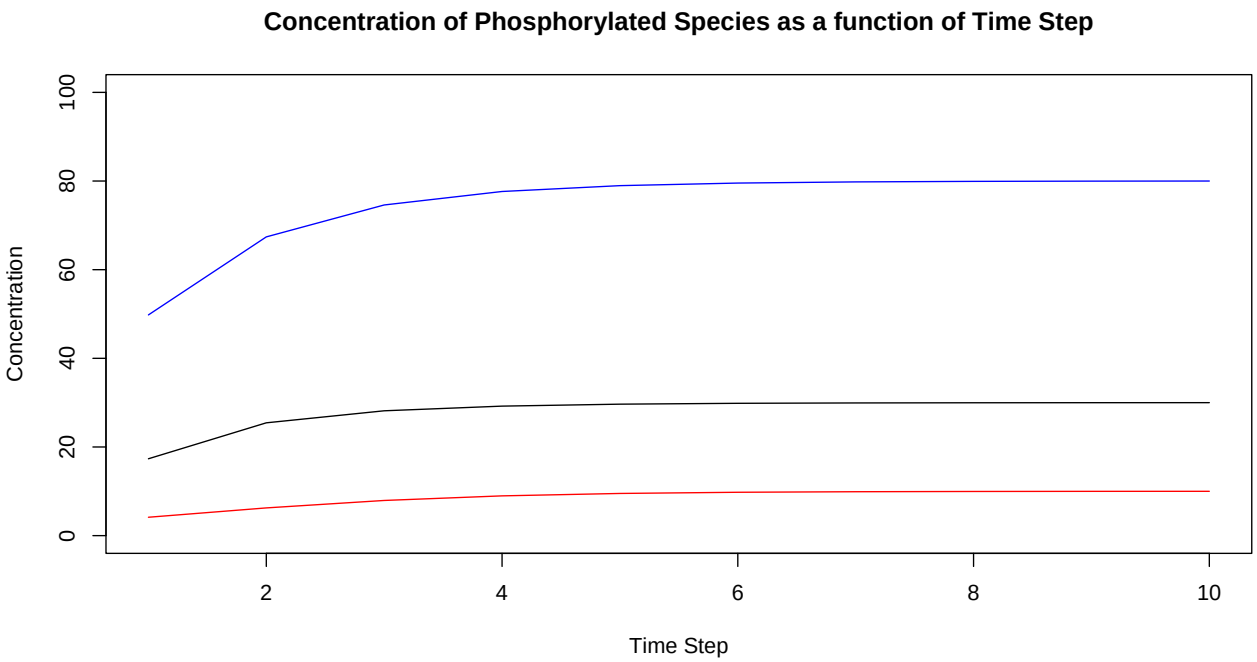
Table 15: 12 Core Replica Exchange Optimus Run Results

	Replica Acceptance Ratio	E (RMSD)	K1	K2	K3	K4
Processor 1	90	0.0026225	0.9088	0.4090	0.0146	2.7246
Processor 2	82	0.0026343	0.8346	0.3754	0.0134	2.5012

	Replica Acceptance Ratio	E (RMSD)	K1	K2	K3	K4
Processor 3	74	0.0019724	0.7234	0.3252	0.0116	2.1644
Processor 4	66	0.0020945	0.9586	0.4312	0.0154	2.8748
Processor 5	58	0.0029243	0.9338	0.4200	0.0150	2.8002
Processor 6	50	0.0025811	0.8964	0.4034	0.0144	2.6872
Processor 7	42	0.0028685	0.8592	0.3866	0.0138	2.5752
Processor 8	34	0.0025121	0.8840	0.3978	0.0142	2.6500
Processor 9	26	0.0011265	0.9834	0.4424	0.0158	2.9492
Processor 10	18	0.0025811	0.8964	0.4034	0.0144	2.6872
Processor 11	10	0.0012516	0.7974	0.3586	0.0128	2.3886
Processor 12	2	0.0017556	0.7850	0.3532	0.0126	2.3512

Of the 12 optimisation replicas, Processor 9 (26% acceptance ratio) finds the best set of rate constants, $\{k_1 = 0.9834, k_2 = 0.4424, k_3 = 0.0158, k_4 = 2.9492\}$. This set of rate constants results in an RMSD (after 10 iterations) of 0.0011265, which is lower than the RMSD of the solution found by acceptance ratio annealing Optimus (0.0012516). Let us simulate how the system evolves according to these rate constants for 10 time steps:





The table below summarizes the initial and final concentrations of the various species when the system is simulated for 10 time steps using the rate constants $\{k_1 = 0.9834, k_2 = 0.4424, k_3 = 0.0158, k_4 = 2.9492\}$:

Table 16: System Summary for k1 = 0.9834, k2 = 0.4424, k3 = 0.0158, k4 = 2.9492

	[A]	[B]	[C]	[AP]	[BP]	[CP]
Initial	100.00000	100.00000	100.00000	0.00000	0.00000	0.00000
Final (after 10 time steps)	89.99807	19.99983	70.00022	10.00193	80.00017	29.99978

Here again, we see that the species' concentrations after 10 time steps are remarkably close to the target values $[A]_t = 90$, $[B]_t = 20$, $[C]_t = 70$, $[AP]_t = 10$, $[BP]_t = 80$ and $[CP]_t = 30$ and the graphs suggests that these concetrations have either converged or are very close to converging to steady state.

Summary

We have seen how Optimus can be empoyed to recover rate constants for a system of coupled ODEs that describes a biological pathway. Given an initial state of the system and a target state, both Acceptance Ratio Annealing Optimus and Replica Exchange Optimus found a set of rate constants that resulted in the desired system behaviour upon simulation of the system. Replica Exchange Optimus retrieved a solution that resulted in a lower RMSD after 10 time steps (0.0011265) than the solution found by Acceptance Ratio Annealing Optimus (0.0012516).

Table 17: Summary of Species' Concentrations after 10 Time Steps

	[A]	[B]	[C]	[AP]	[BP]	[CP]
Target	90.00000	20.00000	70.00000	10.00000	80.00000	30.00000
Optimus (Acceptance Ratio Annealing)	89.99814	20.00081	69.99924	10.00186	79.99919	30.00076
Optimus (Replica Exchange)	89.99807	19.99983	70.00022	10.00193	80.00017	29.99978

Table 18: Summary of Recovered Rate Constants

	E (RMSD)	K1	K2	K3	K4
Optimus (Acceptance Ratio Annealing)	0.0012516	0.7974	0.3586	0.0128	2.3886
Optimus (Replica Exchange)	0.0011265	0.9834	0.4424	0.0158	2.9492

Tutorial 5: Shuffling a set of genomic contacts to form a new set

Problem Statement

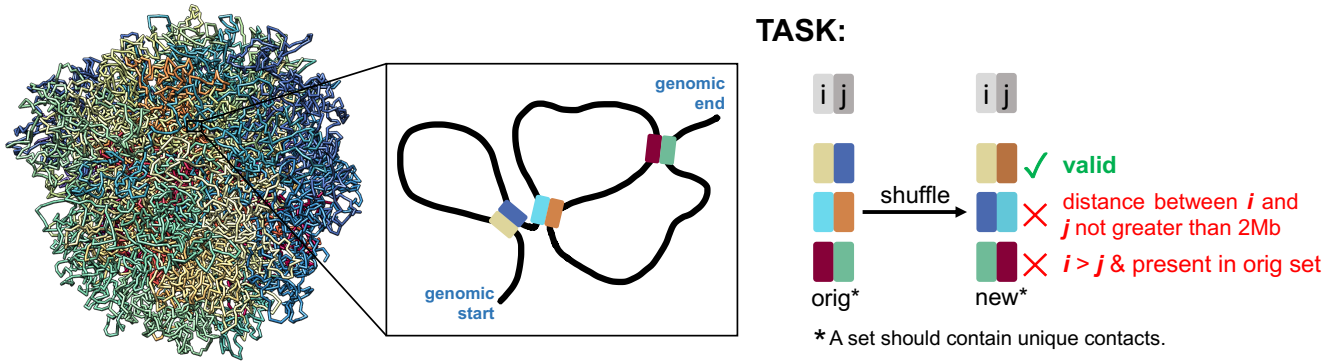
In this tutorial, an example is taken from the field of 3D genome biology to show how Optimus can solve a basic shuffling task given certain conditions.

Mammalian genomes are packaged into a complex three-dimensional (3D) structure inside the nucleus. They are efficiently folded bringing DNA regions near or far from each other into contact, facilitating the tight regulation of replication and gene expression.

We have taken a set of 734 pairs of i and j 40-kilobase DNA regions that are known to be in contact inside a cell. In our set, a 40-kb DNA region is represented as a single integer that is equal to its end position divided by the length of the region, which is 40 kb. For instance, a region, with start and end positions at the 1st and 40000th nucleotides, respectively, is denoted as **1** ($40000th/40000$ bases $= 1$). This simplifies the notation for a contact to a pair of positive integers as shown below

```
##        i   j
## [1,]  96 151
## [2,]  96 174
## [3,] 322 374
## [4,] 309 392
## [5,] 321 392
## [6,] 373 460
```

, where $i \in Z^+$ and $j \in Z^+$.



Take note that our set of contacts complies with the following criteria:

1. The set only contains **unique, long-range contacts**, with i and j regions always separated by greater than 2 megabases/Mb. In terms of integer, the threshold is 50 ($2Mb/40kb = 50$), such that $j - i > 50$.
2. i is set to be always less than j. This avoids duplicate contacts in the set, such as

```
##        i   j
## [1,] 181 273
## [2,] 273 181
```

3. A region can take part in more than one contact (as in region 96 in rows 1 and 2 in the table above), given that the contacts it forms comply with the two aforementioned criteria.

The task is to take the DNA regions from the original set (shown above) and to shuffle them to produce a new set of contacts. This is useful for specific research on genomic 3D contacts requiring good quality negative controls. The challenge here is to maximise the number of

new contacts that are valid, meaning that they (A) still satisfy the aforementioned criteria and (B) are not present in the original set.

Defining Optimus Inputs

Now, we solve the problem using Optimus by doing the following:

1. Keeping the original order of i's in the original set (referred hereinafter as IJ.ORIG), randomly shuffle once all j's without replacement. The output will be object K to be supplied to Optimus().

```
K <- IJ.ORIG
# Shuffle all j's once
K[,"j"] <- sample(x=K[,"j"], size=nrow(K), replace=FALSE)
```

2. Define the rest of Optimus inputs:

The $m()$ function should operate on the object K, which is the original set of contacts with all j's shuffled once (from Step 1). It can also accept a supplementary object $DATA$ that holds data necessary for its calculations or comparisons. Output of $m()$ is the observable object O that is the percentage of contacts not satisfying the aforementioned criteria or are already in the original set. To get O, $m()$ will require the following additional data: a. original set of contacts (IJ.ORIG), b. number of contacts, and c. gap threshold set between contacting regions in terms of positive integer (50). These are stored in the $DATA$ object that is supplied to $m()$.

```
DATA <- NULL
DATA$IJ.ORIG <- IJ.ORIG
DATA$gaplimit <- 50
DATA$numContacts <- 173

m <- function(K, DATA){
  # Total number of erroneous contacts in the new set
  errCont <- sum(
    # Contacts not satisfying the threshold value of the gap between their two regions
    ( (K[,"j"]-K[,"i"]) <= DATA$gaplimit )  |
    # Contacts also present in the original set
    ( K[,"j"]==DATA$IJ.ORIG[,"j"]        )  |
    # Duplicated contacts in the new set
    ( duplicated(K)                      )
  )
  # Percentage of erroneous contacts
  O <- (errCont/DATA$numContacts)*100
  return(O)
}
```

Dictated by the $u()$ function, the error percentage, O, will be directly used as the pseudo-energy, E, since we do want to minimise this value. Meanwhile, the K snapshot quality, Q, which we want to improve, can be the negative of O.

```
u <- function(O){
  RESULT <- NULL
  RESULT$Q <- -O
  RESULT$E <- O
  return(RESULT)
}
```

Finally, $r()$, which defines how object K will be altered at every iteration, takes two j's and then swaps them, without changing the order of their partner i's.

```
r <- function(K){
  K.new <- K
  # Indices of two randomly chosen j's to swap
  new.ind <- sample(x=1:length(K.new[,"j"]), size=2, replace=FALSE)
  # Swap the j's
  K.new[new.ind,"j"] <- K.new[rev(new.ind),"j"]
  return(K.new)
}
```

3. Perform acceptance ratio annealing and replica exchange Optimus runs.

Acceptance Ratio Annealing Optimus Run

We first use the Acceptance Ratio Annealing Optimus to solve the problem. As in Tutorials 2 and 4, Optimus is set to do 200 000 iterations, 2 annealing cycles and to produce 4 replicas of the same simulations.

```
Optimus(NCPU = 4, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, OPT.TYPE = "SA",
        OPTNAME = "IJ.NEW.OPTI.SA", DATA = DATA, NUMITER = 2e+05, CYCLES = 2,
        DUMP.FREQ = 1e+05, LONG = FALSE)
```

Note that if additional data is required by $m()$, that object should be assigned to $DATA$ argument of Optimus(), otherwise $DATA$ defaults to NULL.

The 4 new sets obtained have the following error percentages:

Table 19: OPTIMUS SA: % of Erroneous Contacts

Set	%
1	11.5804
2	11.4441
3	11.7166
4	11.7166

Replica Exchange Optimus Run

Now, we use replica exchange Optimus using 12 cores and the same number of iterations (200 000) as in the acceptance ratio annealing Optimus run. Similarly to Tutorials 2 to 4, STATWINDOW is set to 50 and the acceptance ratios are as follows:

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

Optimus(NCPU = 12, K.INITIAL = K, rDEF = r, mDEF = m, uDEF = u, ACCRATIO = ACCRATIO,
        OPT.TYPE = "RE", DATA = DATA, OPTNAME = "IJ.NEW.OPTI.RE", NUMITER = 2e+05,
        STATWINDOW = 50, DUMP.FREQ = 1e+05, LONG = FALSE)
```

Table 20: OPTIMUS RE: % of Erroneous Contacts

Set	Replica Acceptance Ratio	%
1	90	18.3924
2	82	21.5259
3	74	21.1172
4	66	20.2997
5	58	20.1635

Set	Replica Acceptance Ratio	%
6	50	17.9837
7	42	18.9373
8	34	24.1144
9	26	21.3896
10	18	21.7984
11	10	17.8474
12	2	19.7548

Notably, none of the 12 new sets of contacts from the replica exchange run are better than the sets produced by the acceptance ratio annealing Optimus.

Summary

We have added yet another one to the diverse applications of Optimus, this time by performing a basic shuffling of pairs of positive integers that, in this case, represent contacts between DNA regions, to form a new set of contacts. Additionally, Optimus showed to be a platform, where certain restrictions or conditions can easily be incorporated to a given task, which usually is required for specific research objectives. The table below shows the % of erroneous contacts of the best outputs from the acceptance ratio annealing and replica exchange Optimus runs, with the former producing the better set with 650 valid contacts out of the 734 total number of original contacts.

Table 21: Best Outputs: % of Erroneous Contacts

Method	%
Optimus (Acceptance Ratio Annealing)	11.4441
Optimus (Replica Exchange)	17.8474

Advanced User Manual

This section will document all possible input arguments to Optimus and will describe the output format of Optimus. The code snippet below is the first part of the definition of Optimus which lists all input arguments. We will refer to input arguments without default values as mandatory input arguments and those with default values as optional input arguments (with the exception of K.INITIAL, which will be considered a mandatory input argument).

```
Optimus <- function(NUMITER       = 1000000,
                    STATWINDOW    = 70,
                    T.INI         = 0.00001,
                    T.ADJSTEP     = 0.000000005,
                    TSCLnum       = 2,
                    T.SCALING     = 3,
                    T.MIN         = 0.000000005,
                    T.DELTA       = 2,
                    DUMP.FREQ     = 10000,
                    LIVEPLOT      = TRUE,
                    LIVEPLOT.FREQ = 100000,
                    PDFheight     = 29,
                    PDFwidth      = 20,
                    NCPU          = 4,
                    LONG          = TRUE,
                    SEED          = 840,
                    OPTNAME       = "",
                    DATA          = NULL,
                    K.INITIAL     = 0,
                    rDEF,
                    mDEF,
                    uDEF,
                    EXCHANGE.FREQ = 1000,
                    ACCRATIO      = c(90, 50, 5, 1),
                    CYCLES        = 10,
                    ACCRATIO.IN   = 90,
                    ACCRATIO.FIN  = 0.5,
                    OPT.TYPE = "SA"
                    ){...}
```

Mandatory Input Arguments

All mandatory input arguments have necessarily already been defined in the Tutorials. However, we will reiterate these definitions in this section.Optimus has four mandatory inputs, mDEF, uDEF, rDEF (refered to as $m()$, $u()$ and $r()$ respectively in the Tutorials) and K.INITIAL.

mDEF

mDEF must be of type closure. mDEF should be a function designed to operate on the whole set of parameter snapshot K and return the corresponding observable object O. Please note, that the size of K and O are not necessarily to match, depending on the nature of the model used. mDEF must necessarily take K and DATA as input variables, and it must necessarily operate on K to produce O (operating on DATA in optional, see Tutorial 3 for an illustration).

uDEF

uDEF must be of type closure. uDEF should be a function designed to evaluate the performance of a given snapshot of coefficients K. uDEF should necessarily take as inputs O (the output of mDEF) and the variable DATA. The output of uDEF should have two components, Q holding a single number of the quality of the K coefficients, and E holding a (pseudo)energy for the given snapshot K. It is important that the returned (pseudo)energy value is lower for better performance/version of K, never vice-versa. The Q component of the uDEF function output is only used for plotting the optimisation process, and, if desired, can just repeat the value of the E component.

rDEF

rDEF must be of type closure. rDEF should be a function that defines a rule by which the K coefficient vector is to be altered from one step to another. rDEF must accept K as an input and return an object equivalent to K, but with some alteration(s).

K.INITIAL

K.INITIAL is an object of any type which stores the initial values for the parameter(s) to be optimised. The only requirement for K is that it should be something alterable via rDEF and something that influences the outcome of mDEF.

Optional Input Arguments

NUMITER

NUMITER is a variable of type double that is the number of iterations (or steps) of the optimisation process per core. It has a default value of 1 000 000.

STATWINDOW

STATWINDOW is a variable of type double that is the number of iterations executed between subsequent temperature adjustments executed by the Temperature Control Unit (STATWINDOW is also the number of iterations used to calculate the observed aceptance ratio). It has a default value of 70.

T.INI

T.INI is a variable of type double that represents the initial system pseudo-temperature at the beginning of the optimisation procedure. It has a default value of 0.00001.

T.ADJSTEP

T.ADJSTEP is a variable of type double that represents the baseline temperature change step-size for temperature auto-adjustment. It has a default value of 0.000000005.

TSCLnum

TSCLnum is a variable of type double that indicates the maximum number of STATWINDOWS for which the observed acceptance ratio can sequentially be below or above the ideal acceptance ratio before T.ADJSTEP is scaled by T.SCALING. It has a default value of 2.

T.SCALING

T.SCALING is a variable of type double that represents the value by which T.ADJSTEP is scaled in accordance with the condition specified by TSCLnum. It has a default value of 3.

T.MIN

T.MIN is a variable of type double and is the value that the system pseudo-temperature is automatically set to if at any time, the Temperature Control Unit attempts to make the pseudo-temperature a negative value. It has a default value of 0.000000005.

T.DELTA

T.DELTA is a variable of type double. If after a STATWINDOW, the observed acceptance ratio is within T.DELTA of the ideal acceptance ratio, the Temperature Control Unit will make no change to the system pseudo-temperature. It has a default value of 2.

DUMP.FREQ

DUMP.FREQ is a variable of type double. It is the frequency in steps of printing the best found model to the working directory. It has a default value of 10 000.

LIVEPLOT

LIVEPLOT is a variable of type logical that indicates whether the optimisation process will be plotted in a pdf file in the working directory. It has a default value of TRUE.

LIVEPLOT.FREQ

LIVEPLOT.FREQ is a variable of type double that indicates the frequency in steps of printing the optimisation process in a pdf (this variable is only relevant if LIVEPLOT = TRUE). It has a default value of 100 000.

PDFheight

PDFheight is a variable of type double that indicates the height of the PDF that is produced (if LIVEPLOT = TRUE). It has a default value of 29.

PDFwidth

PDFwidth is a variable of type double that indicates the width of the PDF that is produced (if LIVEPLOT = TRUE). It has a default value of 20.

NCPU

NCPU is a variable of type double that indicates the number of Optimisation replicas to execute. If calling the Replica Exchange Version of Optimus, NCPU must be greater than 1. NCPU has a default value of 4.

LONG

LONG is a variable of type logical. If LONG = TRUE, a memory-friendly version of Optimus will be activated (in anticipation of a long simulation) and only data from the optimal explored parameter configuration and the last 10 000 optimisation iterations will be stored. LONG has a default value of TRUE.

SEED

SEED is a variable of type double which sets the seed for the random number generator. It has a default value of 840.

OPTNAME

OPTNAME is a variable of type character that can be thought of as the name of the optimisation process. OPTNAME is used when creating the file names of the Optimus output. OPTNAME = "" is the default value.

DATA

DATA is a variable of type list holding any additional data that must be accessed by mDEF and uDEF. The default value for DATA is NULL.

OPT.TYPE

OPT.TYPE is a variable of type character which specifies the mode of Optimus to execute and should always be equal to "SA" or "RE." If equal to "SA" (for Simulated Annealing), the Acceptance Ratio Annealing version of Optimus will be executed. If equal to "RE" (for Replica Exchange), the Replica Exchange version of Optimus will be executed. The default value of OPT.TYPE is "SA."

DIR

DIR is a variable of type character which specifies the directory to save the Optimus outputs. The default value for DIR is '.' which means the current directory while running Optimus.

starcore

starcore is a variable of type list holding some parameters for in-lab starcore use only. For example, starcore can be c('MAXCOEFORDER'=4) which will specify the maximum coefficient order. The default value for starcore is NULL which means the in-lab use of starcore is not activated.

Acceptance Ratio Annealing Specific Optional Inputs

The below optional input arguments only impact the Acceptance Ratio Annealing mode of Optimus.

CYCLES

CYCLES is a variable of type double that specifies the number of annealing cycles to execute per core during the optimisation process. It has a default value of 10.

ACCRATIO.IN

ACCRATIO.IN is a variable of type double that specifies the initial target acceptance ratio for the annealing schedule in each annealing cycle. It has a default value of 90.

ACCRATIO.FIN

ACCRATIO.FIN is a variable of type double that specifies the final target acceptance ratio for the annealing schedule in each annealing cycle. It has a default value of 0.5.

Replica Exchange Specific Optional Inputs

The below optional input arguments only impact the Replica Exchange mode of Optimus.

EXCHANGE.FREQ

EXCHANGE.FREQ is a variable of type double that specifies the number of optimisation iterations to execute between subsequent parameter configuration exchanges between adjacent replicas. It has a default value of 1000.

ACCRATIO

ACCRATIO is a vector of doubles that must have length equal to the value of NCPU. ACCRATIO specifies the target acceptance ratio for each optimisation replica. It has a default value of c(90, 50, 5, 1).

Optimus Output

Optimus creates multiple output files in a user's working directory during an optimisation run. Each core used will generate 4 or 5 output files (depending on the value of LIVEPLOT):

1) [OPTNAME][Core number]_model_ALL
2) [OPTNAME][Core number]_model_K
3) [OPTNAME][Core number]_model_O
4) [OPTNAME][Core number]_model_QE
5) [OPTNAME][Core number]

Note that the 5th file is only produced if LIVEPLOT = TRUE. As an illustration, for the Acceptance Ratio Annealing run from Tutorial 1, Optimus generates 20 output files with the following names: poly_4_SA1_model_ALL, poly_4_SA1_model_K, poly_4_SA1_model_O, poly_4_SA1_model_QE, poly_4_SA1, poly_4_SA2_model_ALL, poly_4_SA2_model_K, poly_4_SA2_model_O, poly_4_SA2_model_QE, poly_4_SA2, poly_4_SA3_model_ALL, poly_4_SA3_model_K, poly_4_SA3_model_O, poly_4_SA3_model_QE, poly_4_SA3,poly_4_SA4_model_ALL, poly_4_SA4_model_K, poly_4_SA4_model_O, poly_4_SA4_model_QE and poly_4_SA4.

[OPTNAME][Core number]_model_ALL

This is the most important output file in that essentially all contents from the other output files is contained in this file. The *_model_ALL file is an R workspace that contains a variable OUTPUT of type list. For Acceptance Ratio Annealing, OUTPUT has 12 fields (numbered 1-12 below) while for Replica Exchange, OUTPUT contains an additional 14 fields (numbered 13-26 below). Note that the additional fields of OUTPUT in Replica Exchange were included to facilitate the writing of the code; they can largely be ignored by the user.

1) K.stored
2) O.stored
3) STEP
4) PROB.VEC
5) T.DE.FACTO
6) IDEAL.ACC.VEC
7) ACC.VEC.DE.FACTO
8) STEP4ACC.VEC.DE.FACTO
9) ENERGY.DE.FACTO
10) Q.STRG
11) ACCEPTANCE
12) STEP.STORED
13) E.stored
14) E.old
15) Q.old
16) K
17) T
18) Step.stored
19) ENERGY.TRIAL.VEC
20) STEP.add
21) NumofAccRatSMIdeal
22) NumofAccRatGRIdeal
23) t.adjstep
24) AccR.category
25) new.T.INI
26) instanceOFswitch

K.stored holds the optimal parameter configuration found by the given processor. O.stored holds the object O generated by mDEF from the optimal parameter configuration K.stored. STEP is a double that holds the current optimisation iteration number. PROB.VEC is a vector that holds the acceptance probability for each optimisation step. T.DE.FACTO is a vector that holds the system pseudo-temperature during each optimisation iteration. IDEAL.ACC.VEC is a vector that holds the target acceptance ratio for each optimisation iteration in the case of Acceptance Ratio Annealing. In the case of Replica Exchange, IDEAL.ACC.VEC holds the same value as the input variable ACCRATIO. ACC.VEC.DE.FACTO is a vector that holds the observed acceptance ratio at the end of each STATWINDOW. STEP4ACC.VEC.DE.FACTO is a vector that holds the optimisation step numbers that correspond to the end of a STATWINDOW. ENERGY.DE.FACTO is a vector that holds the actual system energy E at each optimisation step. Q.STRG is a vector that holds the system quality Q at each optimisation step. ACCEPTANCE is a vector of binary variables whose i^{th} entry is 1 if the candidate parameter configuration was accepted on the i^{th} optimisation step and 0 otherwise. STEP.STORED is a vector storing the number of each optimisation step.

E.stored is a double that stores the energy E associated with the optimal parameter configuration K.stored. E.old is a double that stores the energy E associated with the most recently considered parameter configuration. Q.old is a double that stores the quality Q associated with the most recently considered parameter configuration. K hold the most recently considered parameter configuration. T is a double that holds the current system temperature. Step.stored is a double that holds the optimisation step number on which the optimal parameter

configuration K.stored was discovered. ENERGY.TRIAL.VEC is a vector that holds the energy E of the candidate parameter configuration at every optimisation step. STEP.add is a double that facilitates indexing into output vectors. NumofAccRatSMIdeal is a double that represents the number of times the observed acceptance ratio has sequentially been smaller than the target acceptance ratio. NumofAccRatGRIdeal is a double that represents the number of times the observed acceptance ratio has been sequentially greater than the target acceptance ratio. t.adjstep is a double holding the current value by which the system pseudo-temperature is increased or decreased each STATWINDOW by the Temperature Control Unit. AccR.category is a character that indicates whether the observed acceptance ratio was above or below the target acceptance ratio during the previous STATWINDOW. new.T.INI is a double that stores an estimate for the ideal initial system pseudo-temperature deduced by the Temperature Control Unit. Finally, instanceOFswitch is a double that tracks the number of times the observed acceptance ratio has transitioned from being less than the target ratio to greater than the target ratio or vice versa.

[OPTNAME][Core number]_model_K

The *_model_K file is an R workspace that contains a variable K.stored of the same type as K.INITIAL. It holds the optimal parameter configuration found by the given processor.

[OPTNAME][Core number]_model_O

The *_model_O file is an R workspace that contains a variable O.stored that holds the object O generated by mDEF from the optimal parameter configuration K.stored.

[OPTNAME][Core number]_model_QE

The *_model_QE file is a text file that stores the values of E and Q that are produced from the optimal parameter cofiguration K.stored and, in the case of the Replica Exchange Version of Optimus, stores the target acceptance ratio associated with the given replica.

[OPTNAME][Core number]

The * file is a pdf file that includes 5 plots:

1) Acceptance probability as a function of optimisation iteration.
2) System psuedo-temperature as a function of optimisation iteration.
3) Observed (red solid line) and target (black dashed line) acceptance ratio as a function of optimisation iteration.
4) Energy E as a function of optimisation iteration.
5) Quality Q as a function of optimisation iteration.

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