**Instructions for running the R codes**

The codes consist of two files: Isotopes.R and RateConstantSimulation.R. Each of the files has several functions. Isotopes.R file contains the functions for calculations of isotope distributions of peptides given the amino acid sequence. The isotope distributions are computed using the fft (Fast Fourier Transform) function of R. Other functions in the file compute the number of exchangeable hydrogens and the mass of each peptide sequence. It should be the first file to “source” into R.

RateConstantSimulation.R should be “sourced” into the R environment after Isotopes.R. It contains functions for computing original (I1\_t and I2\_t) and transformed (I1\_t\_tilde and I2\_t\_tilde) RAs of M1 and M2. Both original and transformed RAs are computed from formulas presented in the manuscript, Eqs. (4), (5), (8), and (10). RateConstantSimulation.R uses isotope calculation function of Isotopes.R.

To generate the profile of the first four mass isotopomers and transformed RAs of the first and second mass isotopomers, for a peptide sequence (e.g., TVLMNPNIASVQTNEVGLK) the following function is called from inside the R:

Profile\_Peptide("TVLMNPNIASVQTNEVGLK", 0.35)

0.35 is the maximum value of the deuterium enrichment in this example. The sequence and deuterium enrichment can be changed. The function will generate **Figure 2** in the manuscript.

To generate **Figure 4** in the main text of the manuscript (**Figure 3** similar), type the following R function:

Rate\_Constant\_Simulation("EPLFGISTGNIITGLAAGAK", deg\_rate = 0.110, dates=c(0, 3, 5, 7, 14, 21), noise= c(0, exp(-8)), BWE = 0.03)

Deg\_rate is the true rate constant used in the simulation, dates – are the time points of labeling, noise is a two component vector, the first component is the location parameter, and the second component is the scale parameter of the Laplace distribution, BWE is the body water enrichment in deuterium.

The function returns the values of the rate constants in the Rates (six component variable) of the results list. The first component is the true rate constant (equal to 0.110 in the example above), the second component is the rate constant computed form I0(t), the third is computed from I1(t), the fourth from the transformed I1(t), the fifth from I2(t), and the sixth from the transformed I2(t).

To run the code using the peptides in the Peptides.csv file, first read the peptides into the R environment:

Peptides\_Rates = read.csv(“Peptides.csv”)

The command:

Rates\_Experim\_Noise = All\_Peptides(Peptides\_Rates,c(0, 3, 5, 7, 14, 21), c(-0.0035, 0.0159), pW = 0.03)

will compute the rate constants of all distinct peptides assuming time points of labeling: 0, 3, 5, 7, 14, 21 days, and the location and scale parameters: 0.0035, 0.0159, respectively. All results will be in Rates\_Experim\_Noise list variable.