

# Infrequent Metadynamics

Shubhandra Tripathi

# Infrequent Metadynamics

$$t = t_{\text{MTD}} \alpha$$

Where,  $t$  is the rescaled time,  
 $t_{\text{MTD}}$  is the time measured in metadynamics, and  
 $\alpha$  is the acceleration factor.

$$\alpha = \langle e^{\beta V(s, t_{\text{MTD}})} \rangle_V$$

Where,  $\beta$  is the inverse of  $k_B T$ ,  
 $s$  is the value of CVs at the time of  $t_{\text{MTD}}$ .

In practice rescaled time is calculated by summing the time steps taken so far rescaled at each step

$$t = \sum_i^{n_{\text{MTD}}} dt e^{\beta V(s(t_{i\text{MTD}}), t_{i\text{MTD}})}$$

Where,  $n_{\text{MTD}}$  is the total number of steps in the metadynamics simulation and  $t_{i\text{MTD}} = i dt$  is the metadynamics time at the  $i^{\text{th}}$  step.

# Infrequent Metadynamics: Statistical Analysis

The process of counting number of transitions from state A to state B can be interpreted as stochastic process, in which Probability of observing  $n$  events in the time interval  $(0,t)$  follows a Poisson distribution with a characteristic transition time  $\tau$ ,

$$P_n = \frac{1}{n!} \left(\frac{t}{\tau}\right)^n \exp\left(-\frac{t}{\tau}\right)$$

If we are observing only one transition then the waiting time  $T_1$ , to observe the single transition follows the exponential distribution

$$f_{T1}(t) = \tau^{-1} \exp(-t/\tau)$$

Where,  $f_{T1}(t)$  represent the probability density function (PDF), and  $\tau$  corresponds to the average transition time  $\mu = (1/M) \sum_i^M t_i$ .

The distribution of waiting times has the following properties

1. Its mean ( $\mu$ ) and standard deviation ( $\sigma$ ) are equal ( $\mu/\sigma = 1$ )
2. Its median  $t_m$  and mean ( $\mu$ ) are related through the expression ( $t_m = \mu \ln 2$ )

Monitoring the average, standard deviation and median of the set of  $M$  transitions obtained from simulations, provides a qualitative estimate of goodness of Poisson model. However, both ( $\mu/\sigma = 1$ ) and ( $t_m = \mu \ln 2$ ) are extremely sensitive to insufficient sampling

The alternative approach is the construction of **empirical cumulative distribution frequency (ECDF)** from characteristic time associated with set of A to B transitions obtained from rare event simulation.

For a Poisson process cumulative distribution frequency (CDF) can be derived as probability to observe at least one transition by time  $t$  as

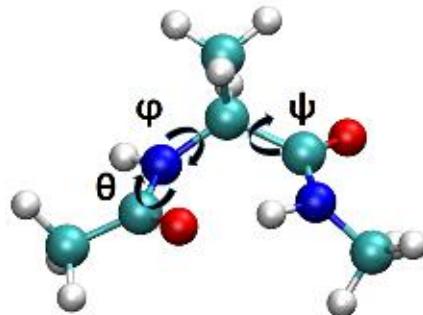
$$P_{n \geq 1} = 1 - P_0 = 1 - \exp\left(-\frac{t}{\tau}\right)$$

Using above eq<sup>n</sup> to fit the ECDF provides an estimate of the theoretical average rates associated with A to B transitions.

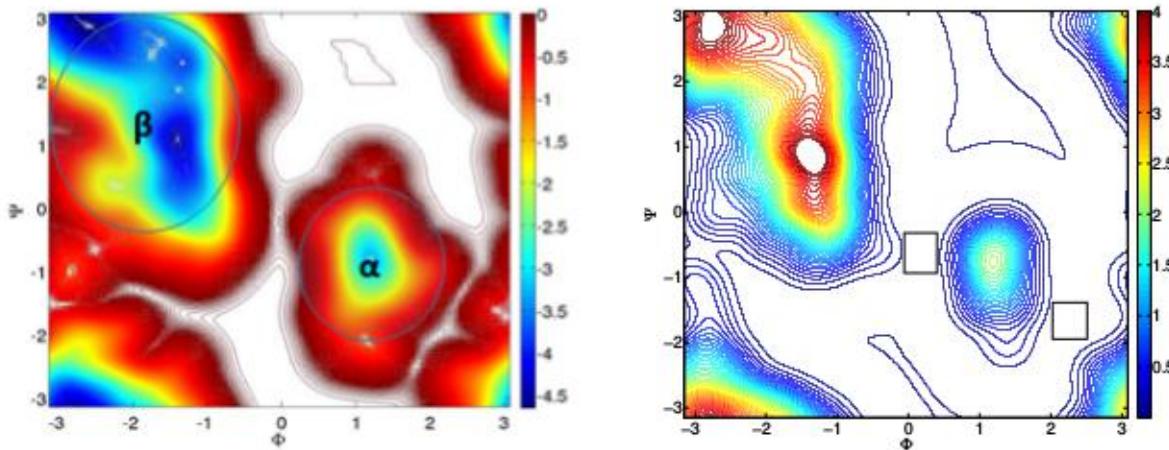
Two sample **Kolmogorov-Smirnov (KS) test**, is used to compare quantitatively the theoretical and empirical transition time distribution.

# Example: Alanine dipeptide in AMBER03 ff vacuum

1. Molecular dynamics simulation
2. Well tempered MD simulation (phi, psi)
3. Well tempered MD simulation (psi)



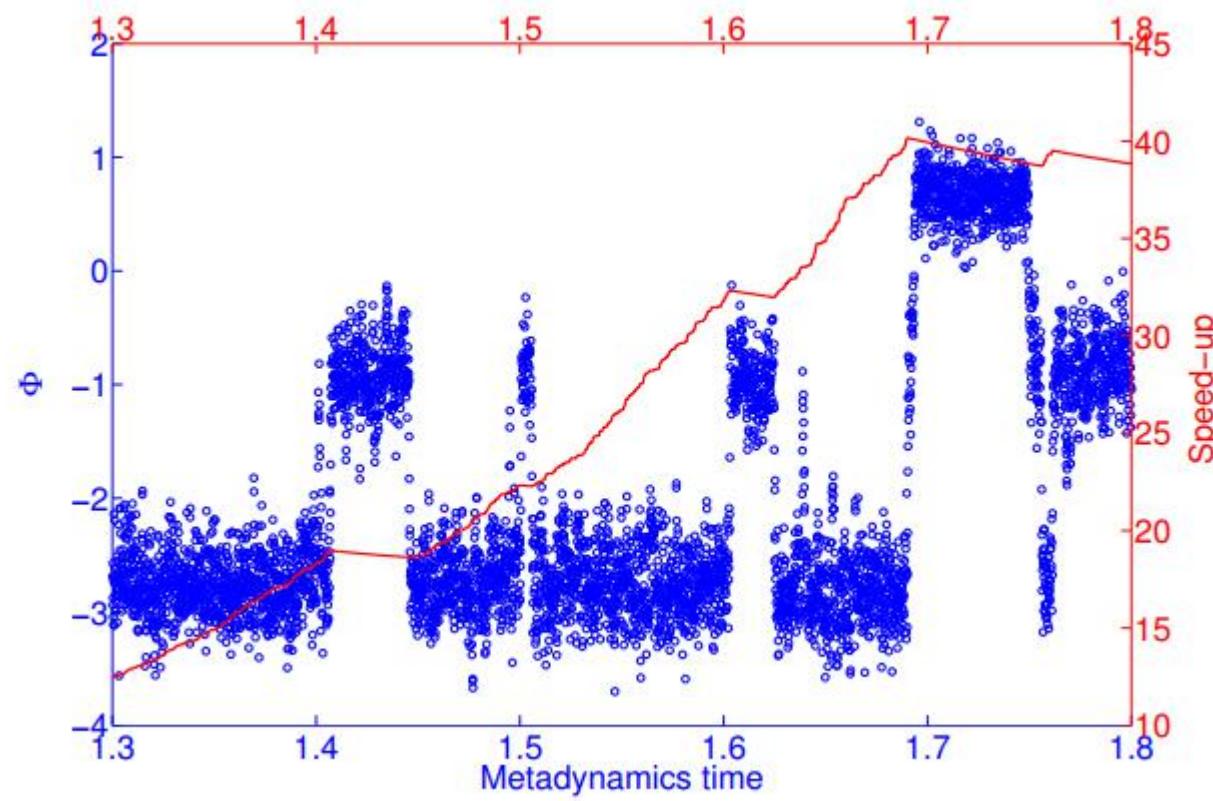
(a)



P. Tiwary and M. Parrinello, *Phys. Rev. Lett.* 2013, 111, 230602

M. Salvalaglio, P. Tiwary, and M. Parrinello *J. Chem. Theo. Comput.* 2014 10, 1420-1425

# Example: Alanine dipeptide in AMBER03 ff vacuum



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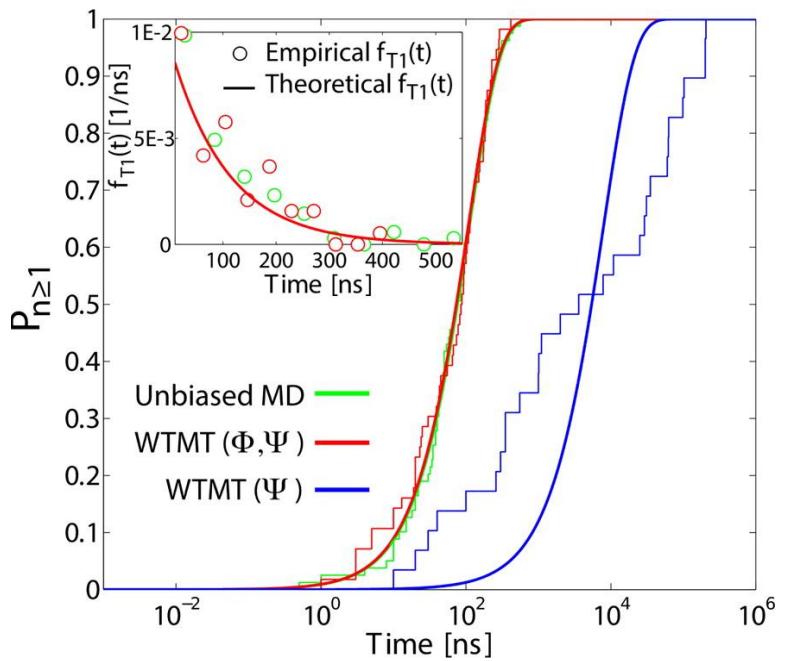
M. Salvalaglio, P. Tiwary, and M. Parrinello *J. Chem. Theo. Comput.* 2014 10, 1420-1425

# Example: Alanine dipeptide in AMBER03 ff vacuum

Table 1. Simulations of the  $\beta \rightarrow \alpha$  Conformational Transitions of the Alanine Dipeptide Molecule<sup>(16)</sup> in Vacuum

	MD	WTMT( $\Phi, \Psi$ )	WTMT( $\Psi$ )
$\mu$ [ns]	$108 \pm 12$	$102 \pm 12$	$3.9 \times 10^4 \pm 1.2 \times 10^4$
$\sigma$ [ns]	106	90	$6.3 \times 10^4$
$t_m$ [ns]	75	86.5	$3.6 \times 10^3$
$\mu/\sigma$	1.02	1.13	0.6
$(\mu \ln 2)/t_m$	1.00	0.82	7.6
$\tau$ [ns]	110.2	106.3	$1.73 \times 10^4$
$p$ -value	0.98	0.89	$2.17 \times 10^{-4}$

<sup>a</sup>Mean transition time  $\mu$ , standard deviation  $\sigma$ , and Poisson process characteristic time  $\tau$  are reported together with the  $\mu/\sigma$  and  $(\mu \ln 2)/t_m$  ratios. The  $p$ -value associated with the KS statistic is also reported.



## Example 1: Alanine dipeptide in AMBER03 ff vaccum (Infreq MTD)

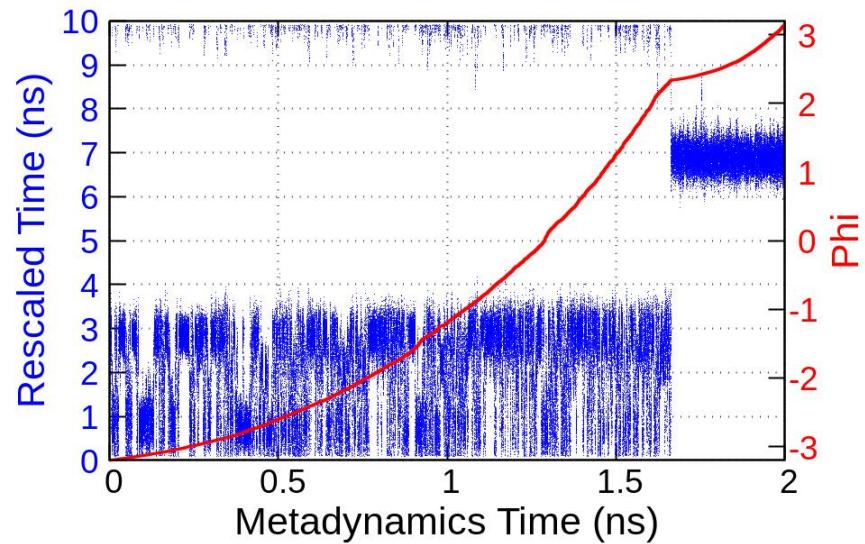
```
#PLUMED.dat Infrequent Metadynamics
phi: TORSION ATOMS=5,7,9,15
psi: TORSION ATOMS=7,9,15,17
# Activate metadynamics in phi and psi
# depositing a Gaussian every 500 time steps,
# with height equal to 1.2 kJoule/mol,
# and width 0.35 rad for both CVs.
metad: METAD ARG=phi,psi PACE=20000 HEIGHT=1.254 SIGMA=0.25,0.25
FILE=HILLS BIASFACTOR=5.0
# Monitor the two variables and the metadynamics bias potential
PRINT STRIDE=10 ARG=phi,psi,metad.bias FILE=COLVAR
```

### Rescaled Time from Metadynamics

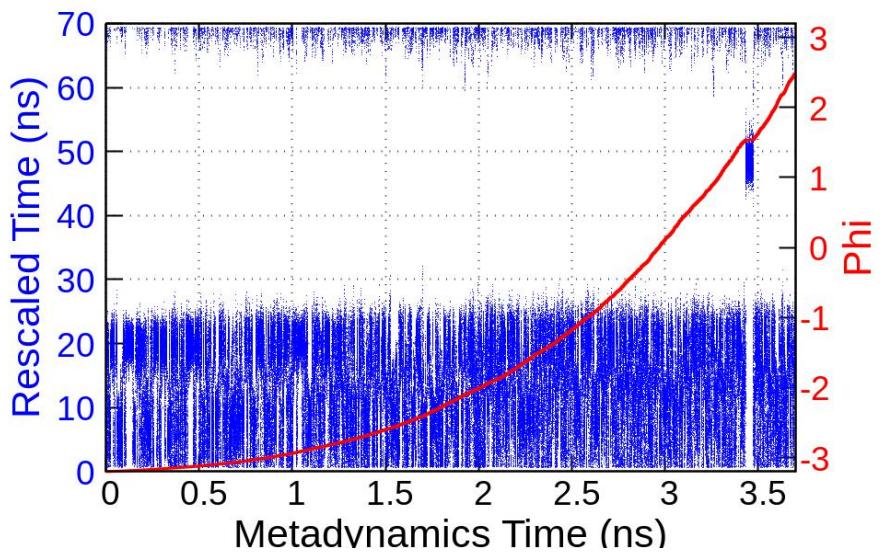
( $\$4$  is the Metadynamics bias column and  $\$1$  is the time period column in the COLVAR file)

# Example 1: Alanine dipeptide in AMBER03 ff vacuum (Infreq MTD)

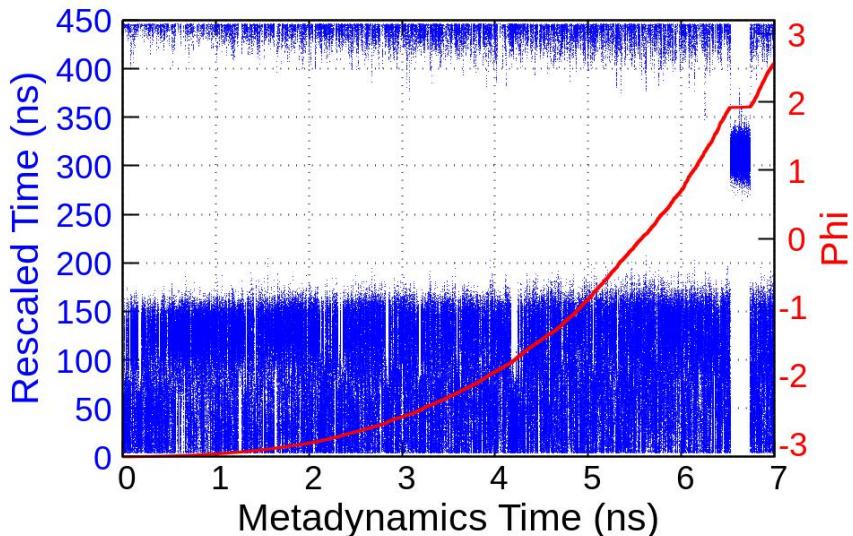
Run 01



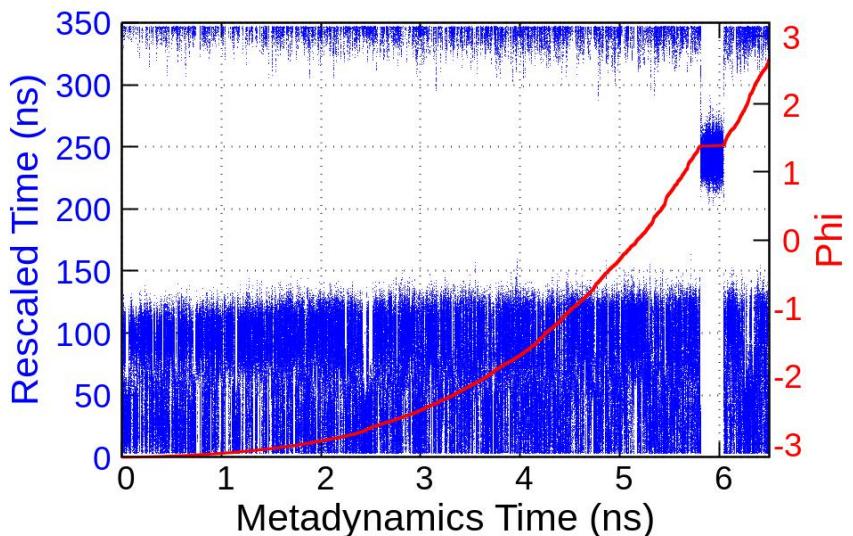
Run 02



Run 03

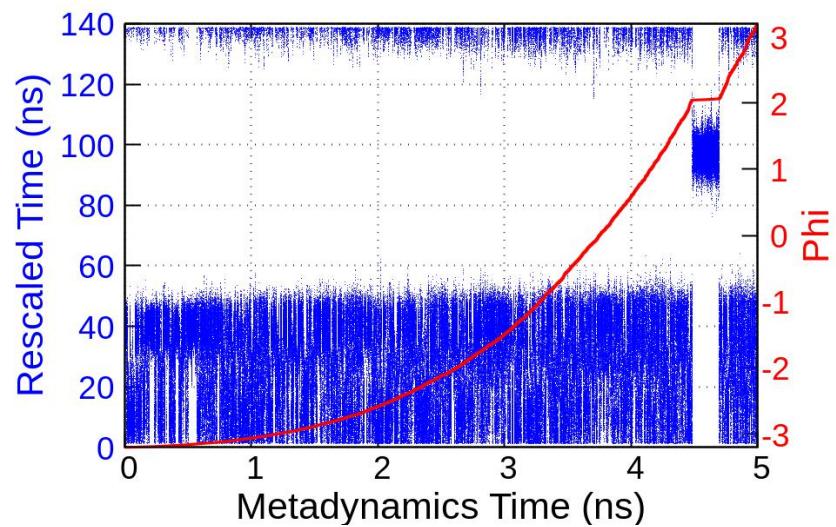


Run 04

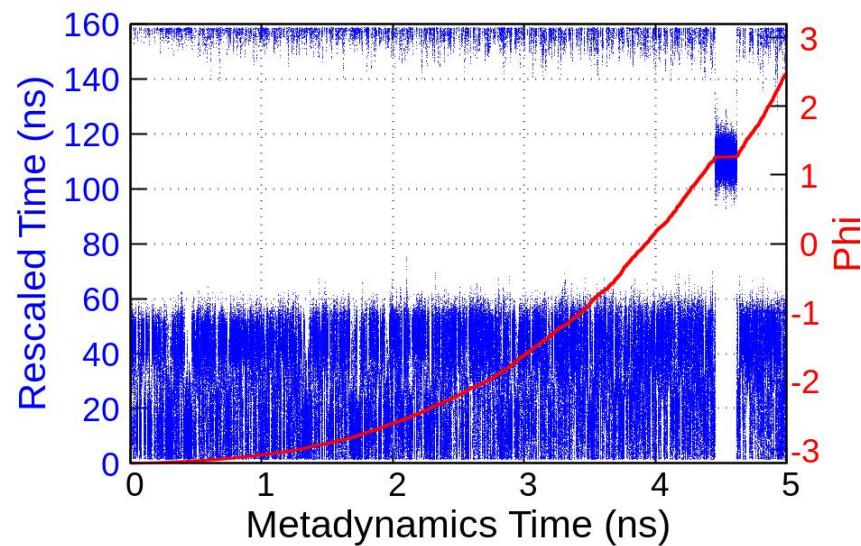


# Example 1: Alanine dipeptide in AMBER03 ff vacuum (Infrea MTD)

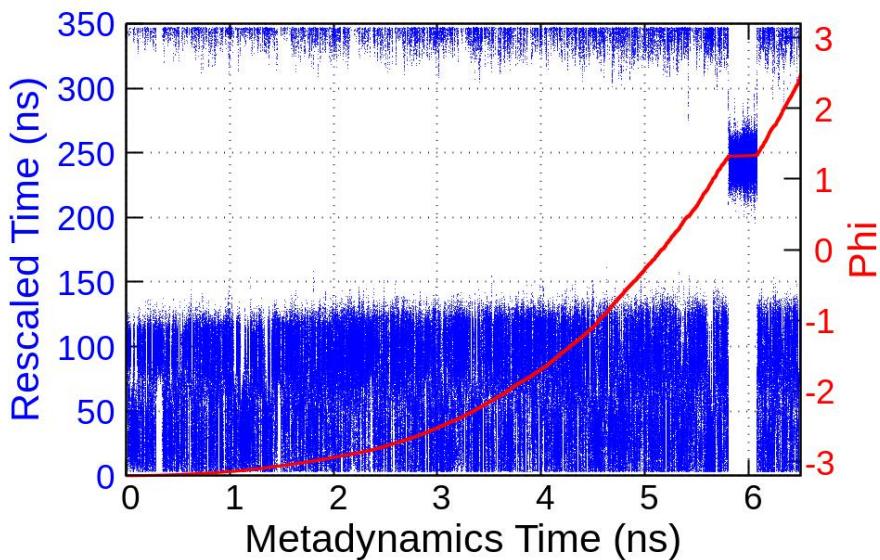
Run 05



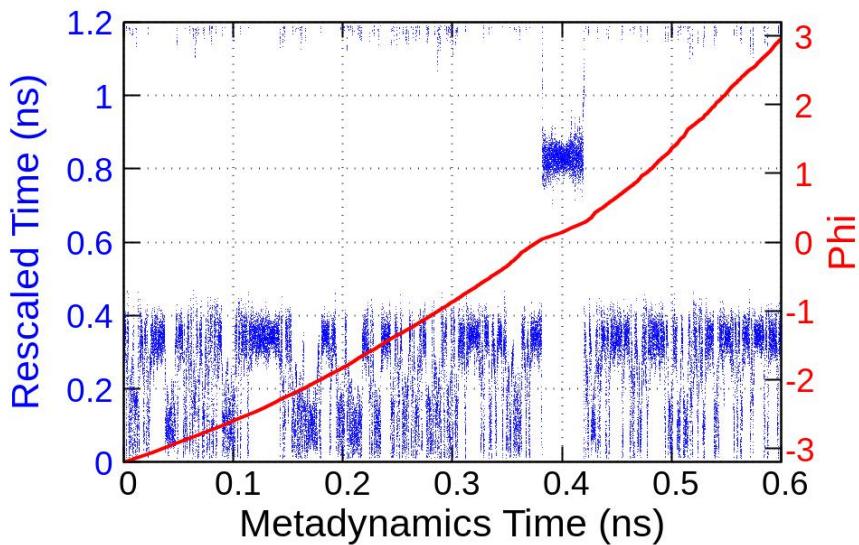
Run 06



Run 07

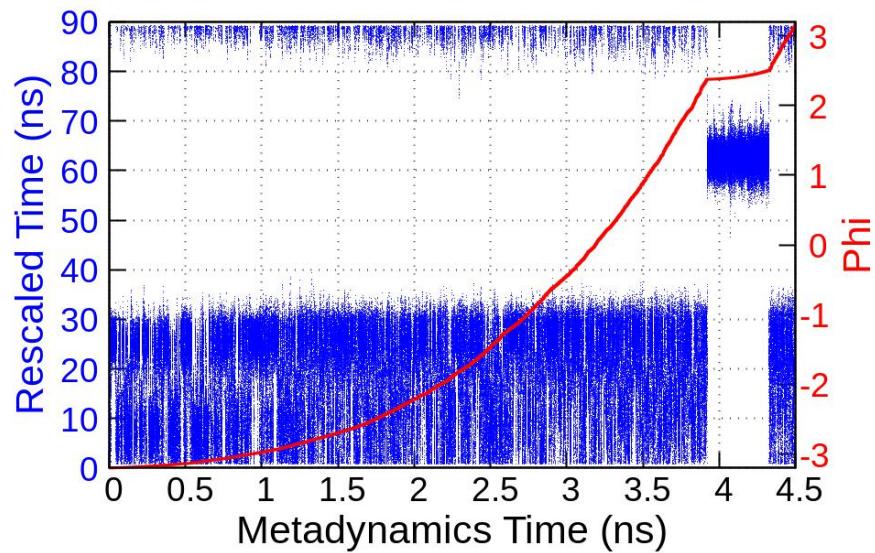


Run 08

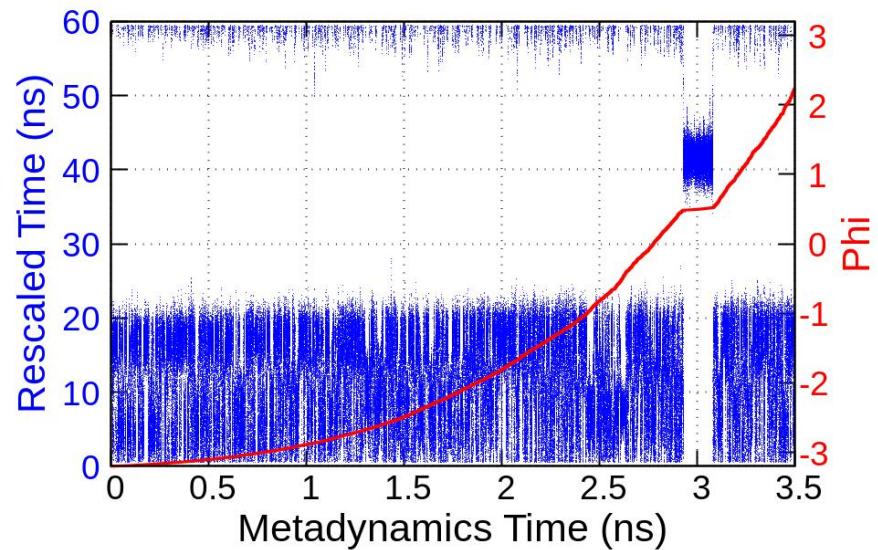


# Example 1: Alanine dipeptide in AMBER03 ff vacuum (Infrea MTD)

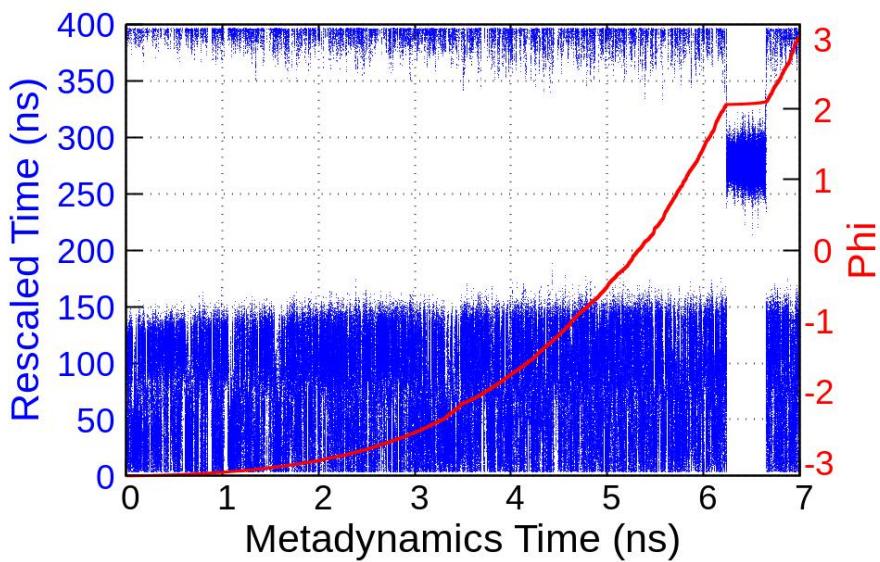
Run 09



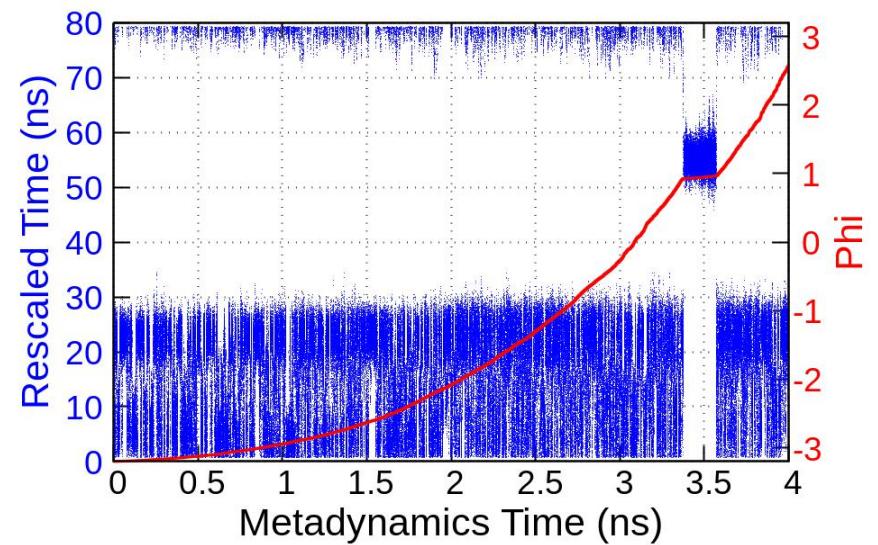
Run 10



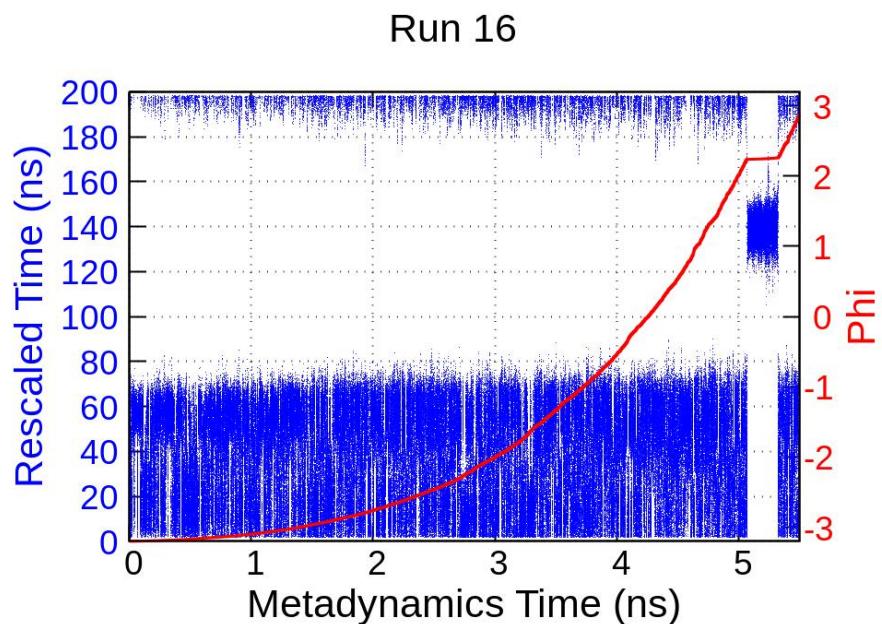
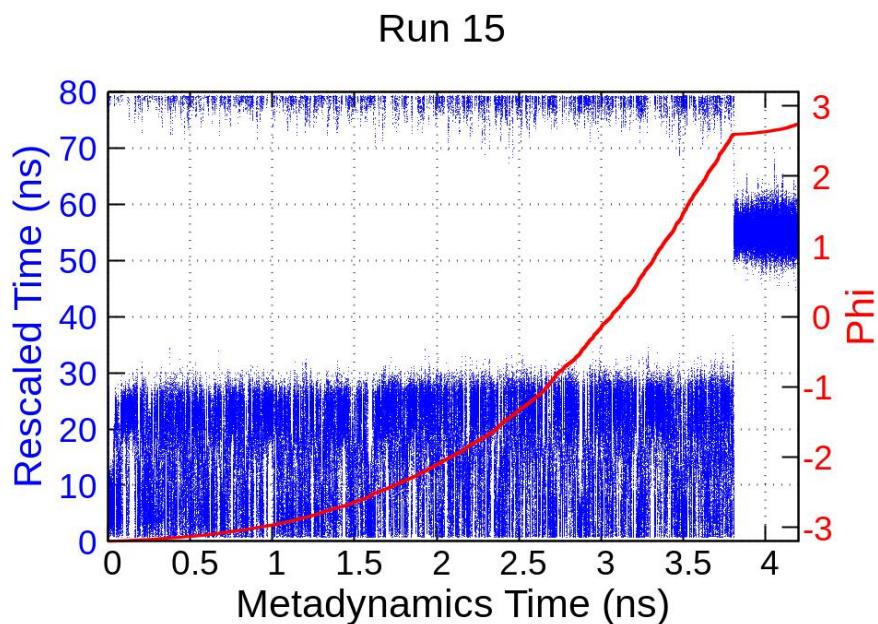
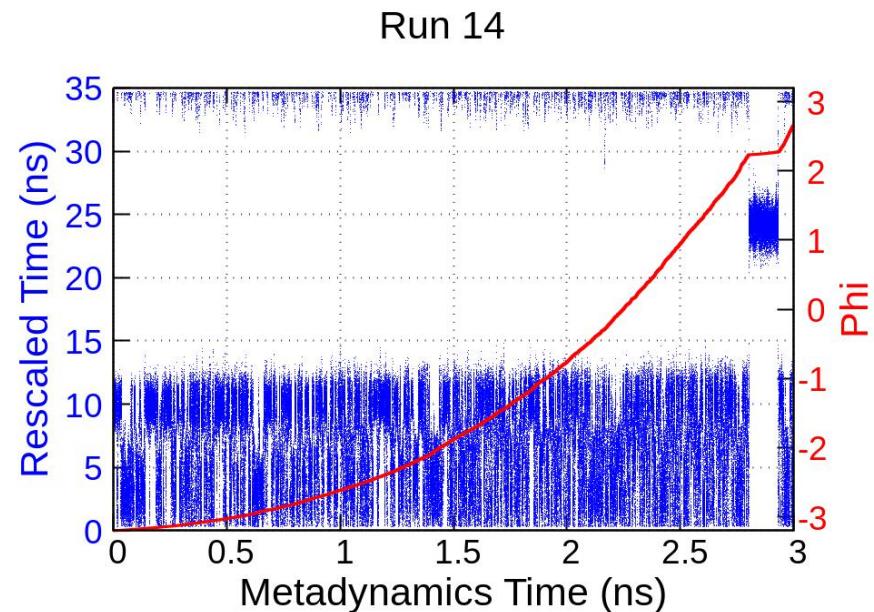
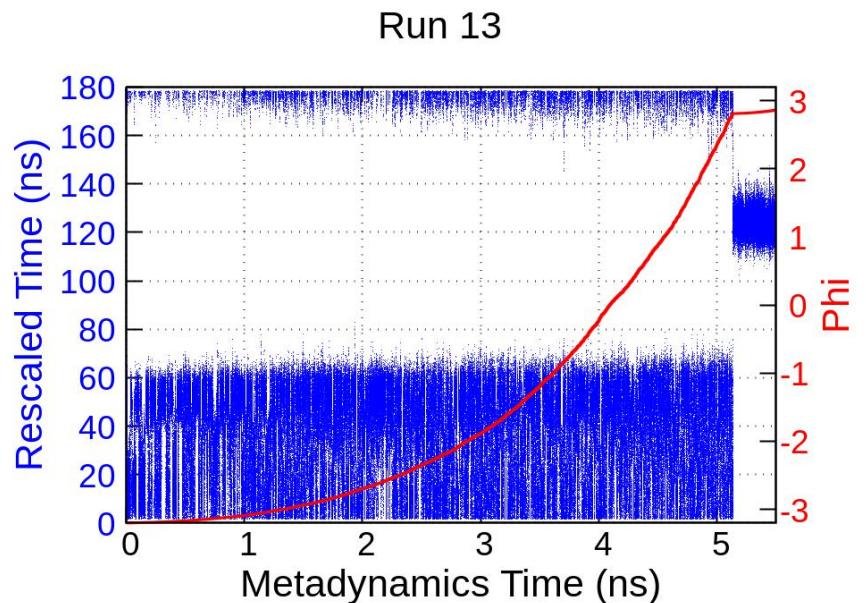
Run 11



Run 12

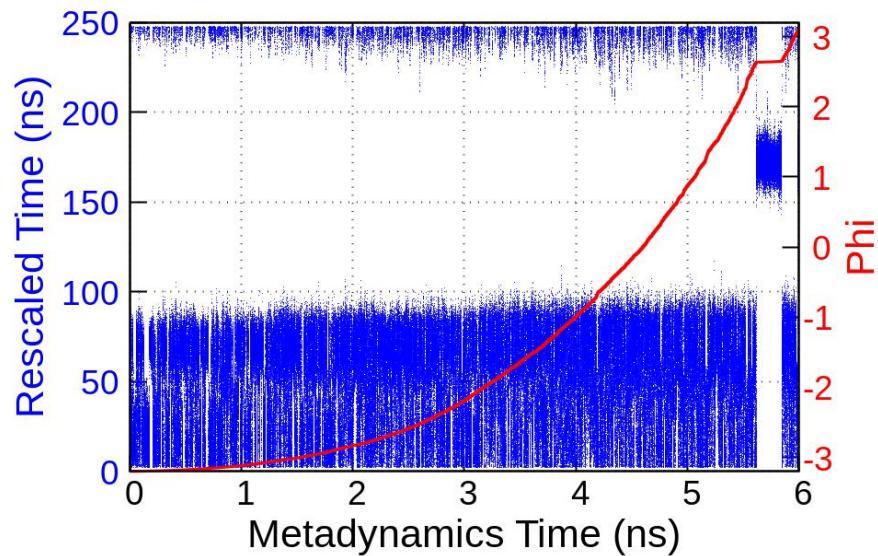


# Example 1: Alanine dipeptide in AMBER03 ff vaccum (Infreq MTD)

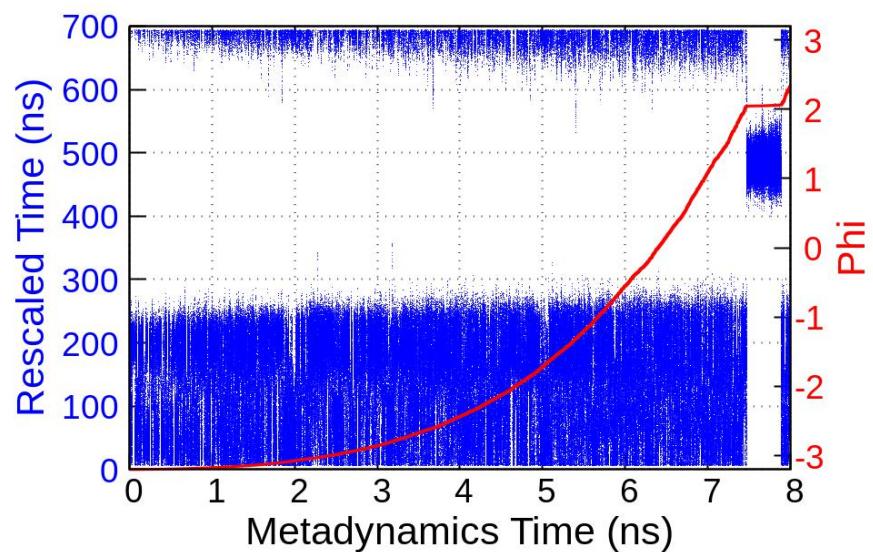


# Example 1: Alanine dipeptide in AMBER03 ff vaccum (Infreq MTD)

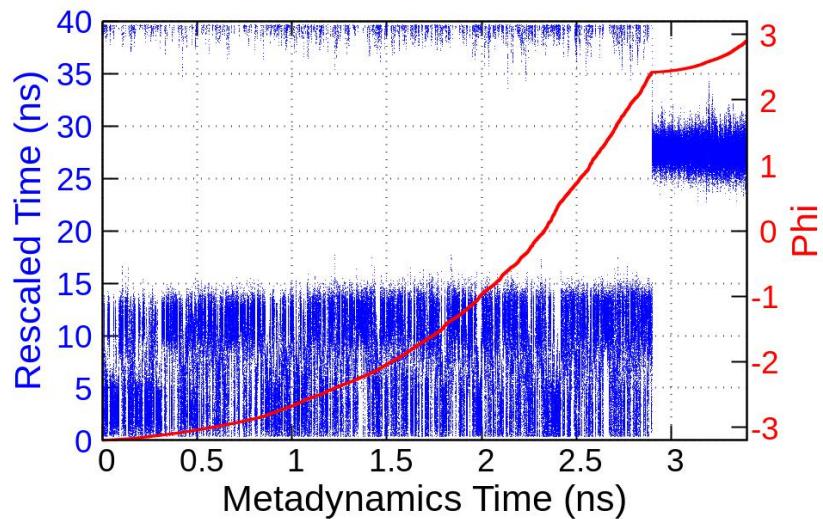
Run 17



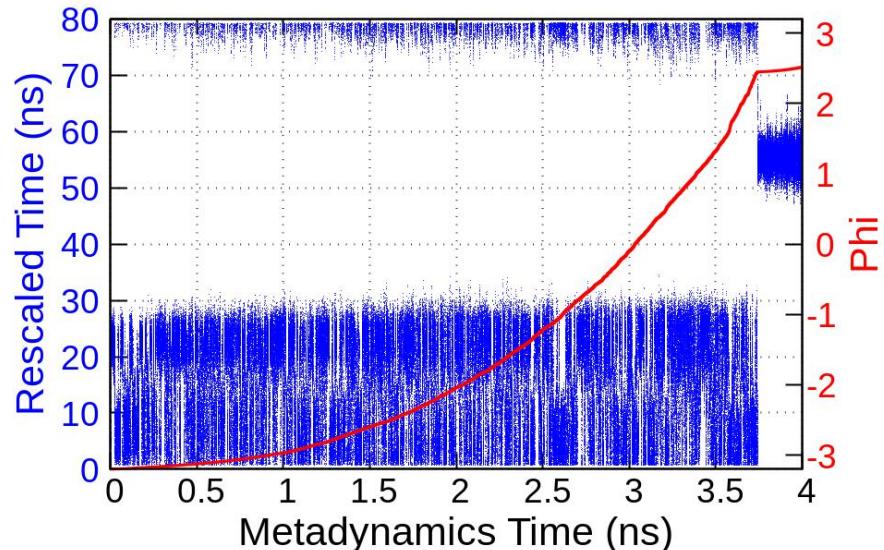
Run 18



Run 19

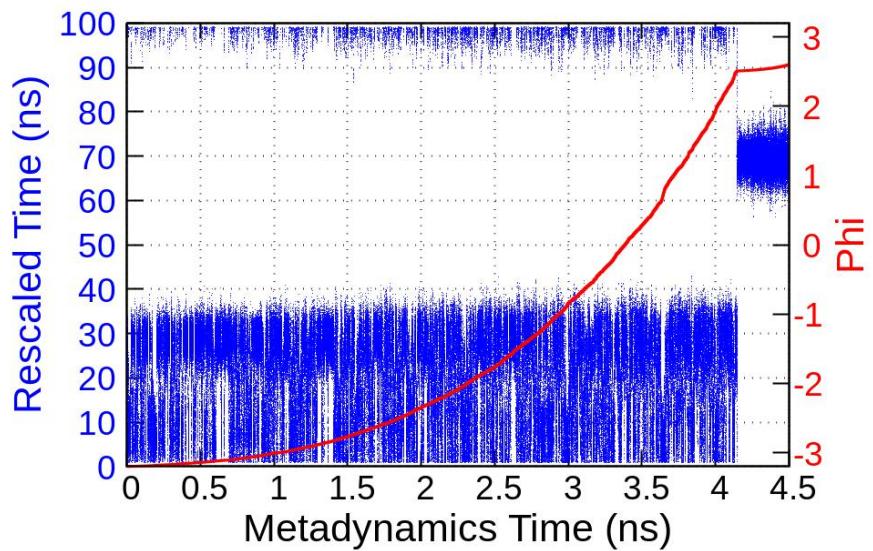


Run 20

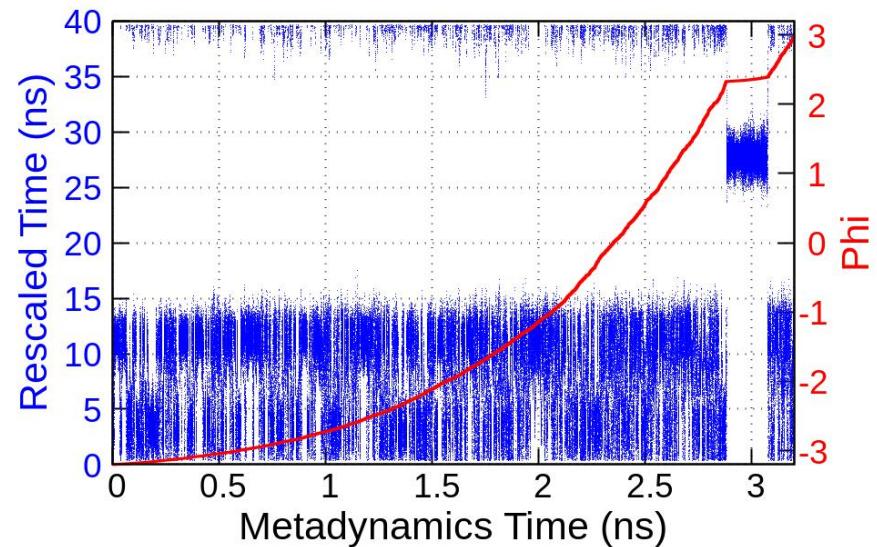


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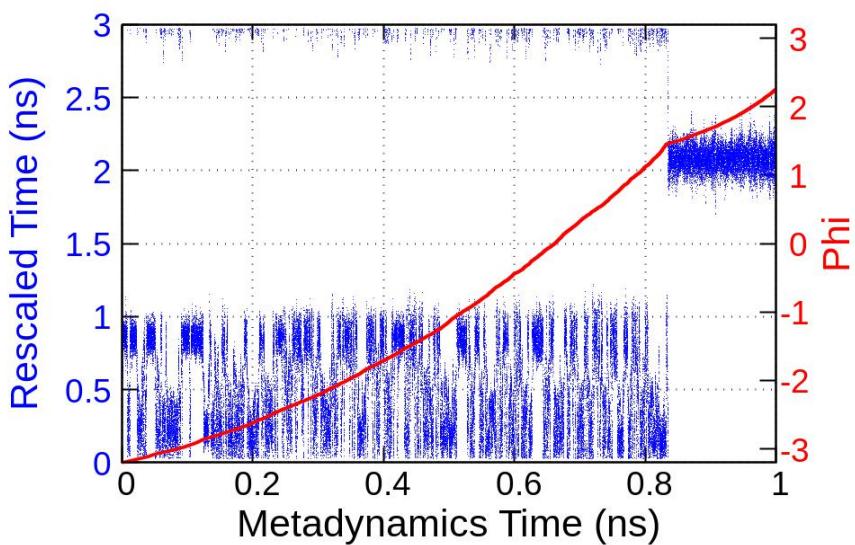
Run 21



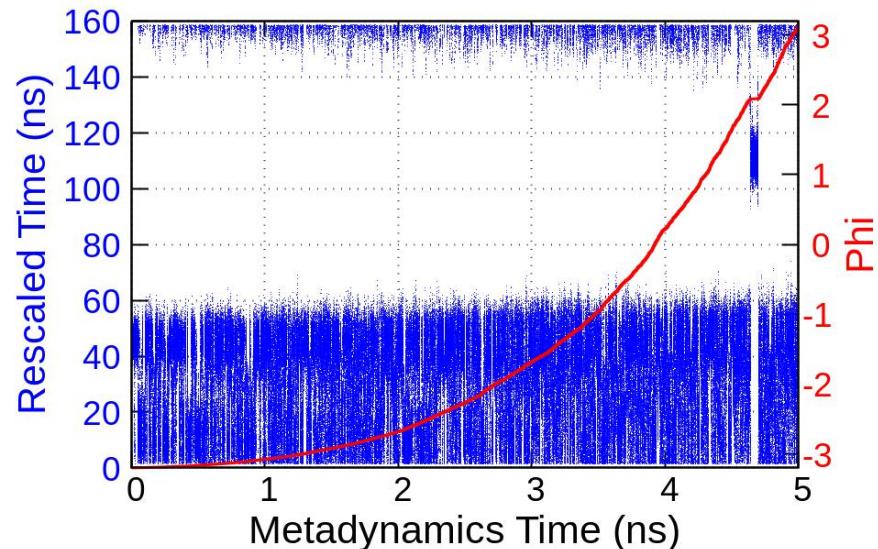
Run 22



Run 23

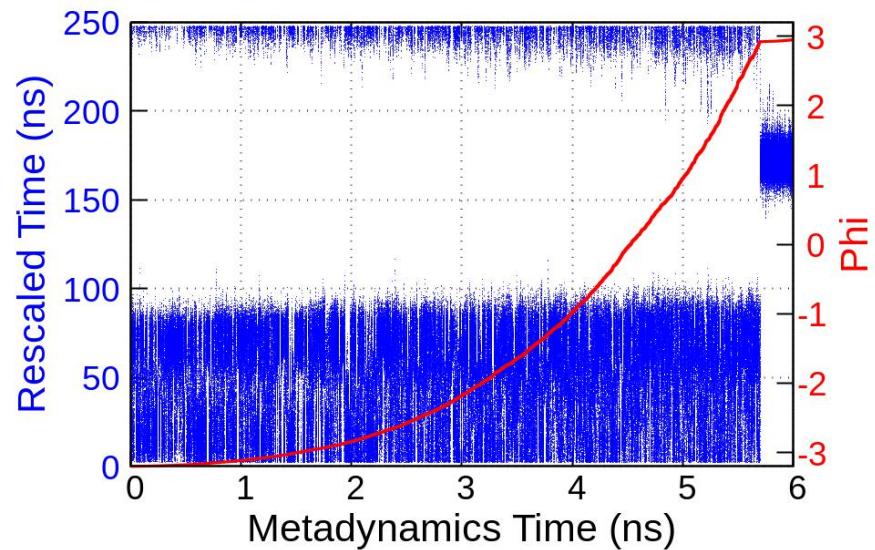


Run 24

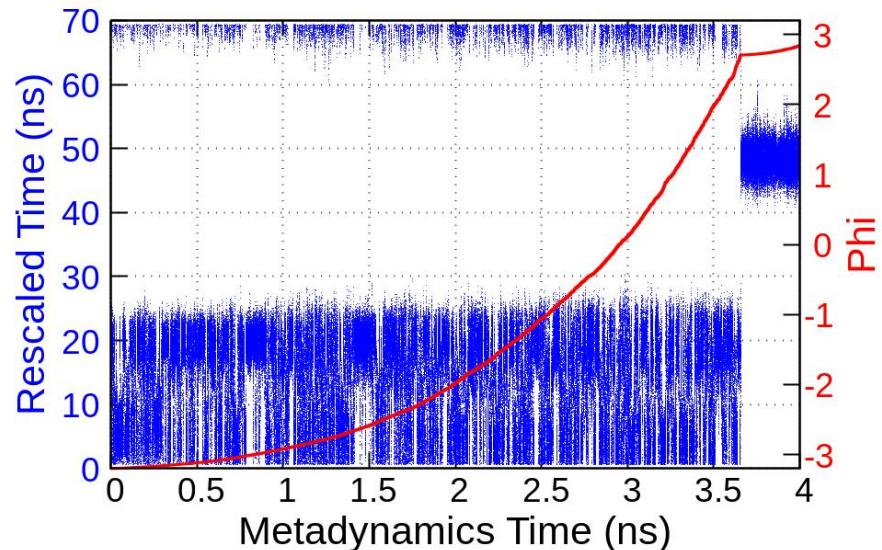


# Example 1: Alanine dipeptide in AMBER03 ff vaccum (Infreq MTD)

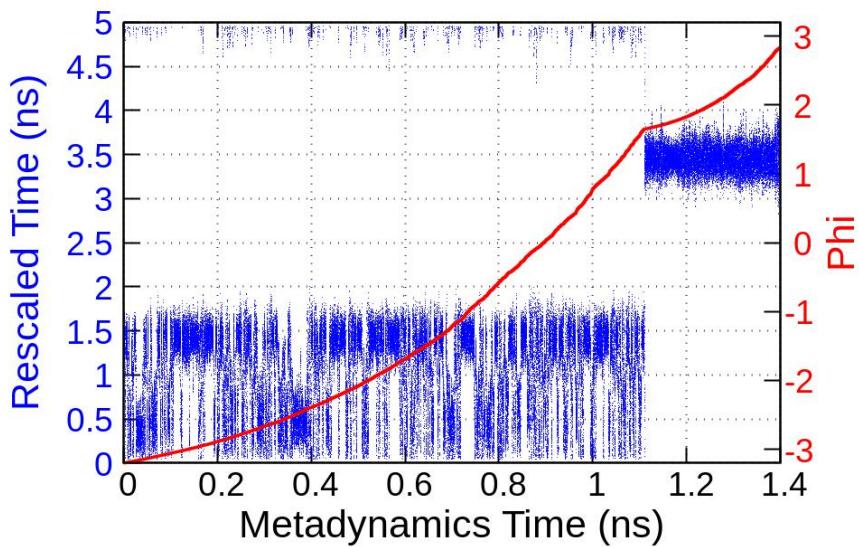
Run 25



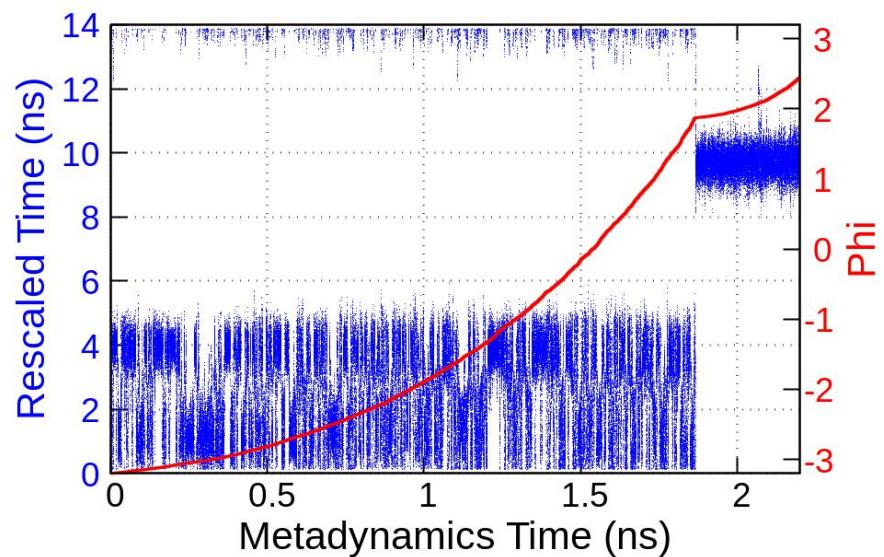
Run 26



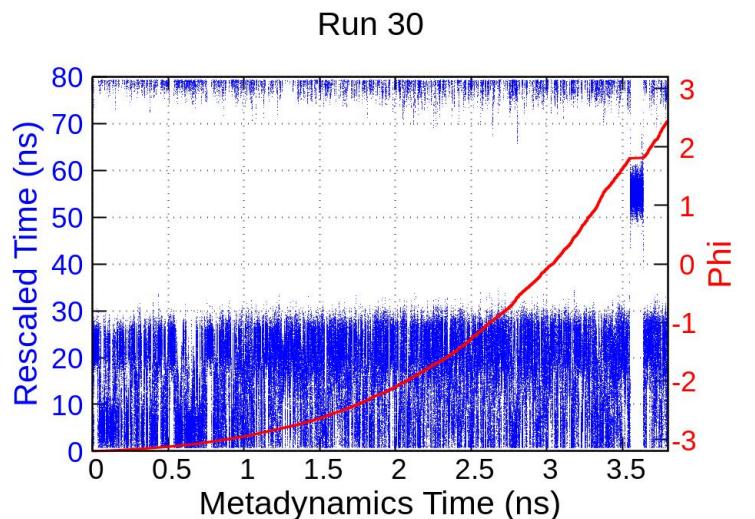
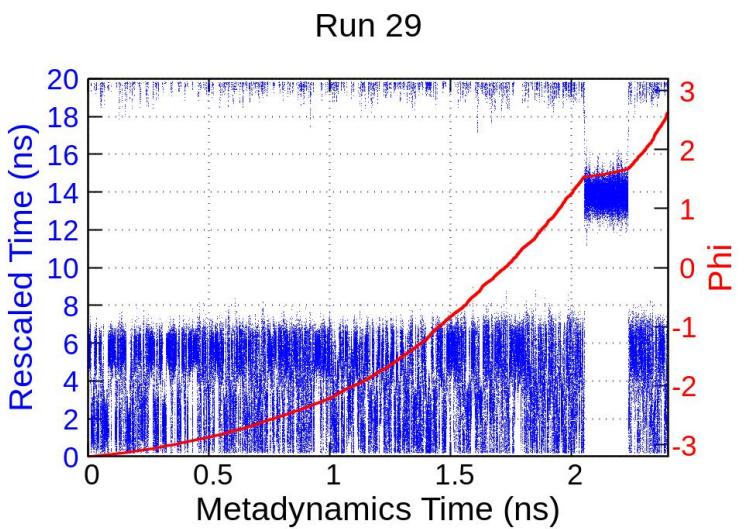
Run 27



Run 28



# Example 1: Alanine dipeptide in AMBER03 ff vacuum (Infreq MTD)

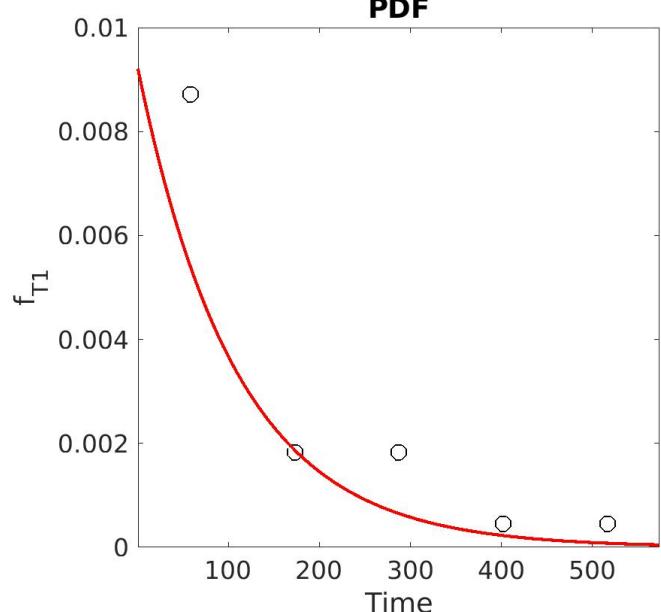
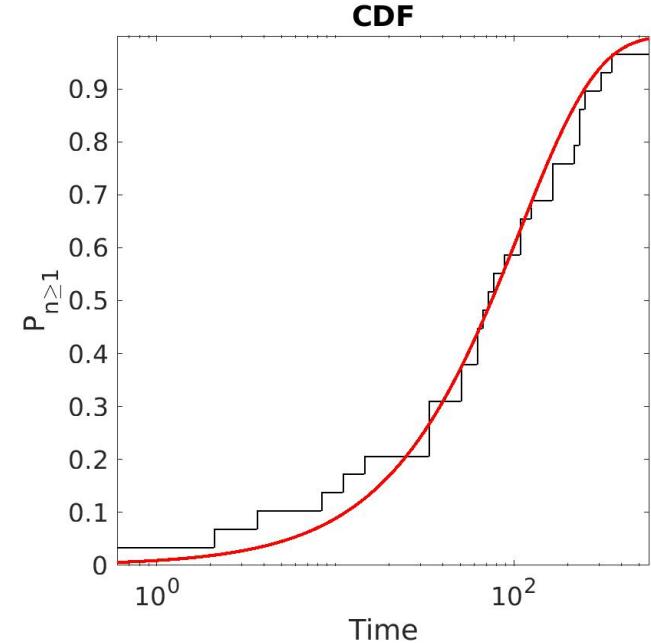


Total Simulation Run ~120 ns

Run	Real Time (ps)	Rescaled Time (ps)	Rescaled Time (ns)
1	1663	8645	8
2	3432	51776	51
3	6526	360080	360
4	5814	250549	250
5	4487	114732	114
6	4457	111428	111
7	5806	247400	247
8	380	608	0.6
9	3922	78404	78
10	2930	34546	34
11	6242	329047	329
12	3377	51599	51
13	5137	169030	169
14	2804	29717	29
15	3808	72433	72
16	5072	169962	169
17	5620	227947	227
18	7471	573699	573
19	2900	35128	35
20	3743	70603	70
21	4147	89235	89
22	2881	34537	34
23	835	2185	1
24	4643	132107	132
25	5701	239079	239
26	3657	64576	64
27	1110	3786	3
28	1866	11083	11
29	2053	14814	14

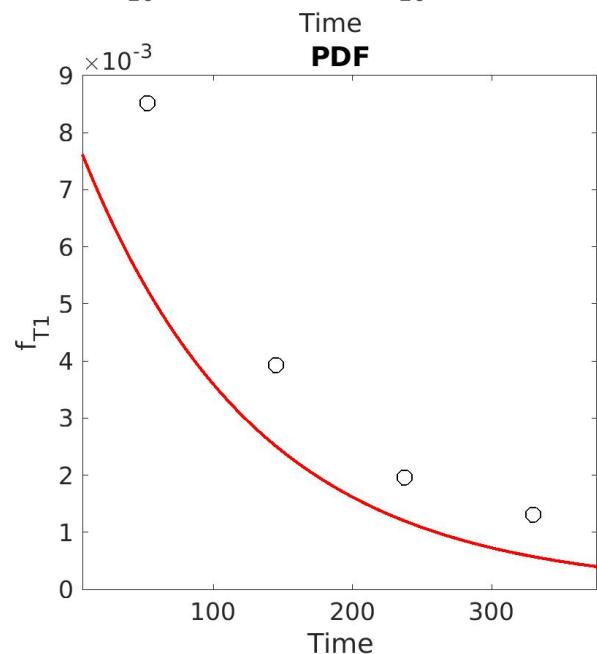
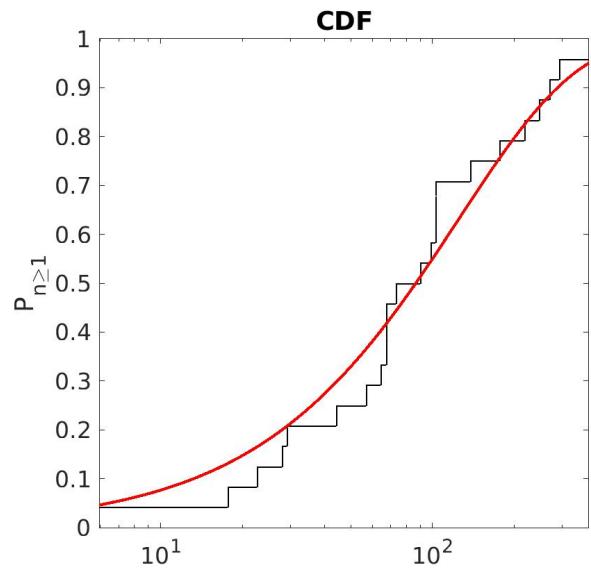
# Example 1: Alanine dipeptide in AMBER03 ff vaccum (Infreq MTD)

$\mu$ (Average Transition Time in ns)	<b>124.53</b>
$\mu$ Standar mean error	<b>24.63</b>
$\sigma$ (Standard Deviation in ns)	<b>132.65</b>
$t_m$ ( median in ns)	<b>72.43</b>
$\tau$ (Estimated Transition Time in ns)	<b>108.01</b>
$\mu / \sigma$ ratio	<b>0.93</b>
$(\mu \ln 2) / t_m$ ratio	<b>1.19</b>
$\tau / \mu$ ratio	<b>0.86</b>
p-value	<b>0.77</b>
Reject	<b>0</b>



# Example 1: Alanine dipeptide in AMBER03 ff vaccum (Unbiased Run)

Run	Real Time (ns)
1	23.25
2	376.01
3	106.87
4	90.48
5	65.20
6	178.32
7	98.81
8	250.50
9	69.95
10	17.65
11	29.90
12	28.69
13	105.80
14	45.60
15	59.40
16	5.93
17	69.15
18	294.70
19	75.30
20	224.78
21	69.05
22	138.60
23	271.90
24	104.70



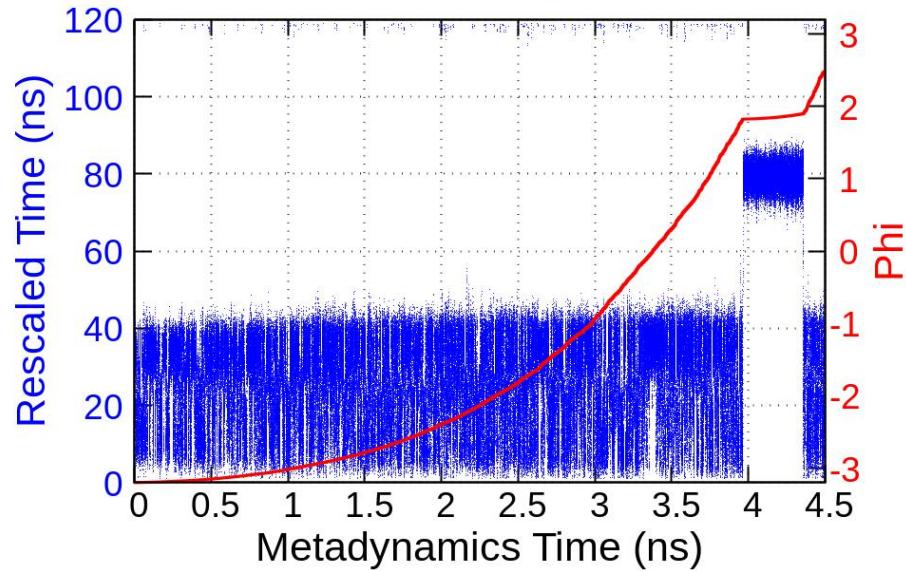
Total Simulation run ~2800 ns

# Example 1: Alanine dipeptide in AMBER03 ff vacuum (Unbiased Run)

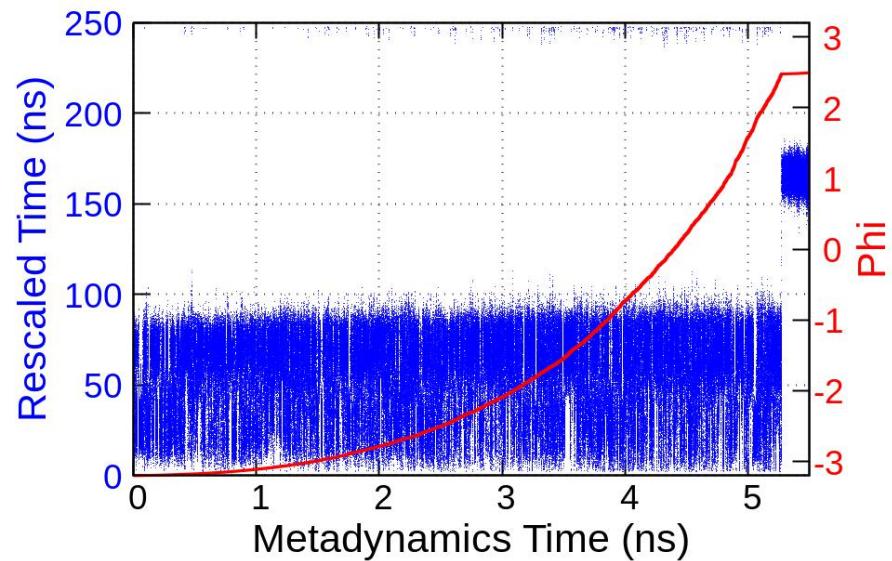
	Unbiased Run <sup>1</sup>	Infreq. MTD <sup>1</sup>	Unbiased (24 runs = ~2800 ns)	Infreq. MTD (30 runs = ~120 ns)
$\mu$ (Average Transition Time in ns)	<b>108 ± 12</b>	<b>102 ± 12</b>	116 ± 20	<b>124 ± 24</b>
$\sigma$ (Standard Deviation in ns)	<b>106</b>	<b>90</b>	98	<b>132</b>
$t_m$ ( median in ns)	<b>75</b>	<b>86.5</b>	82	<b>72</b>
$\tau$ (Estimated Transition Time in ns)	<b>110.2</b>	<b>106.3</b>	125	<b>108</b>
$\mu / \sigma$ ratio	<b>1.02</b>	<b>1.13</b>	1.18	<b>0.93</b>
$(\mu \ln 2) / t_m$ ratio	<b>1.00</b>	<b>0.82</b>	0.97	<b>1.19</b>
$\tau / \mu$ ratio	—	-	1.07	<b>0.86</b>
p-value	<b>0.98</b>	<b>0.89</b>	0.75	<b>0.77</b>
Reject	<b>0</b>	<b>0</b>	0	<b>0</b>

# Example 2: Alanine dipeptide AMBER99SB ff (Vaccum)

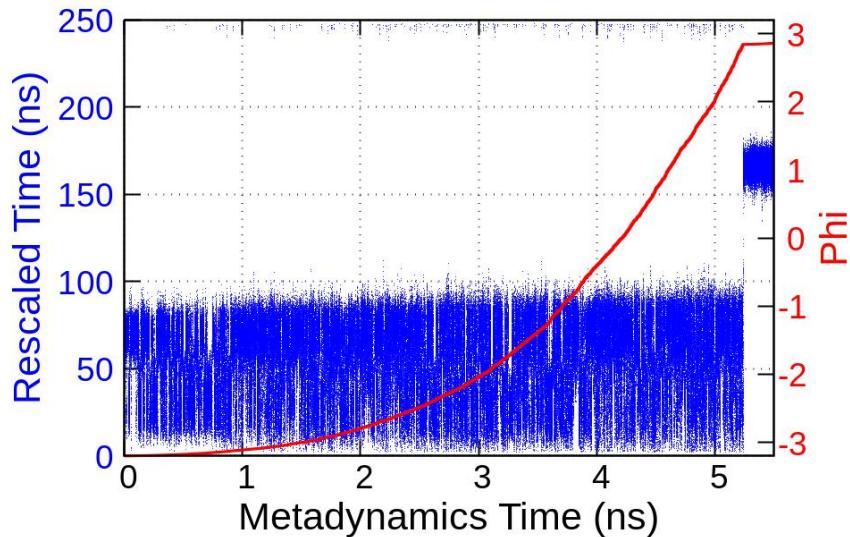
Run 01



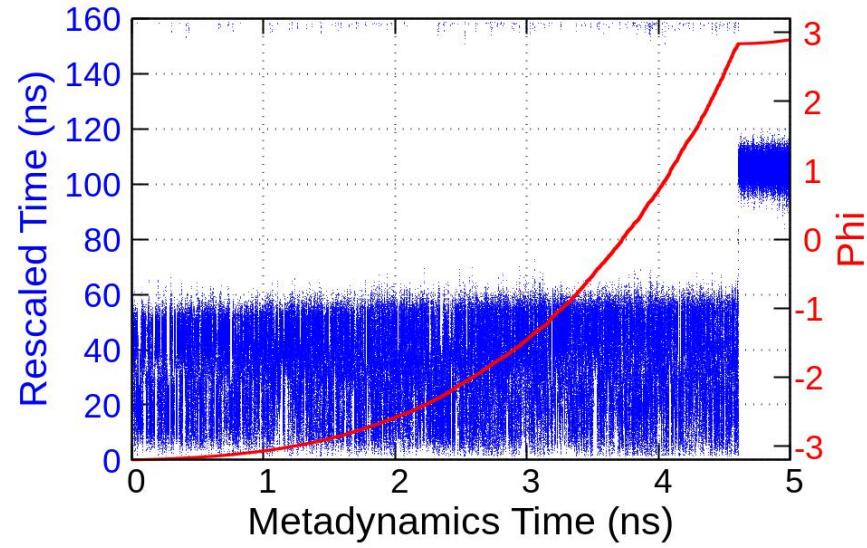
Run 02



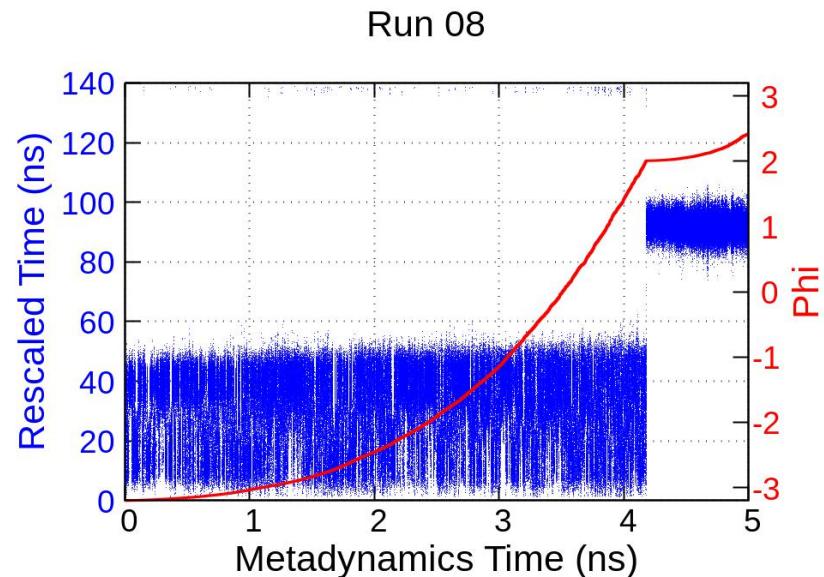
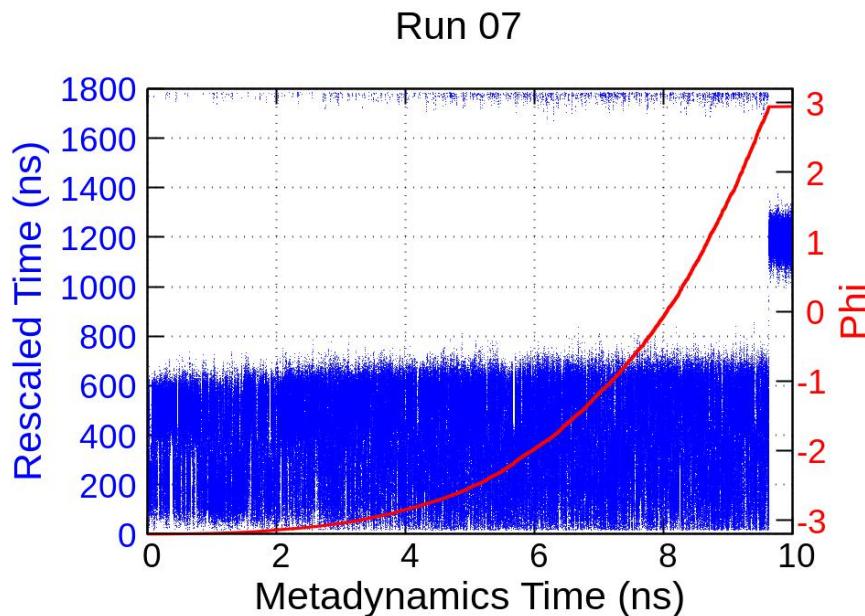
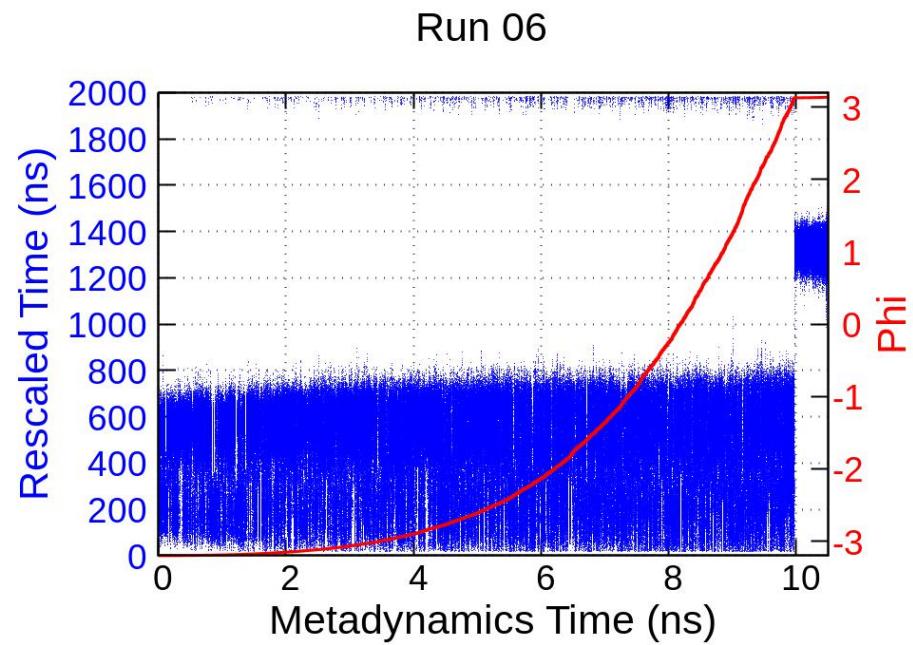
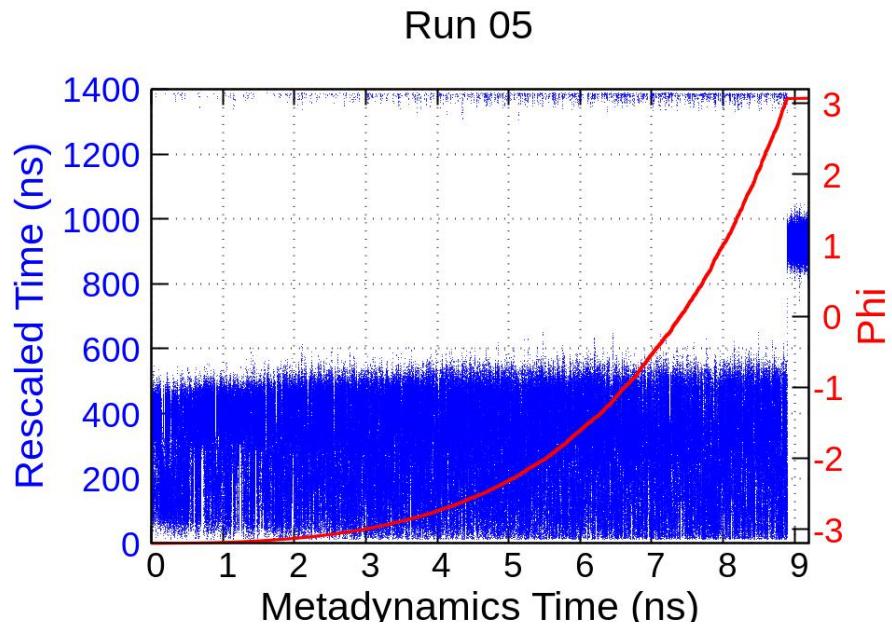
Run 03



Run 04

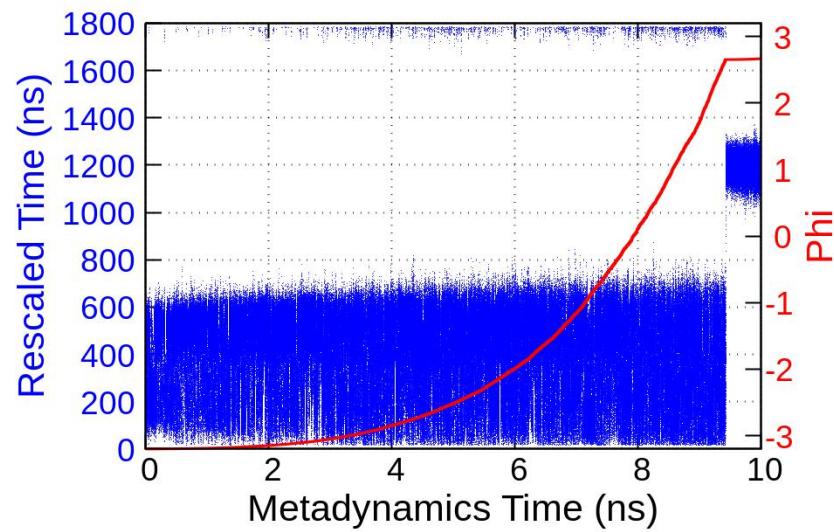


# Example 2: Alanine dipeptide AMBER99SB ff (Vaccum)

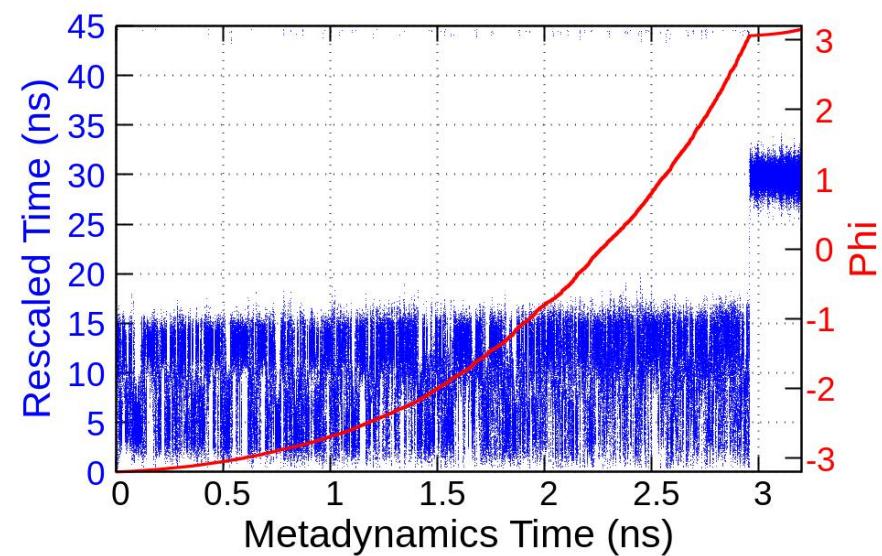


# Example 2: Alanine dipeptide AMBER99SB ff (Vaccum)

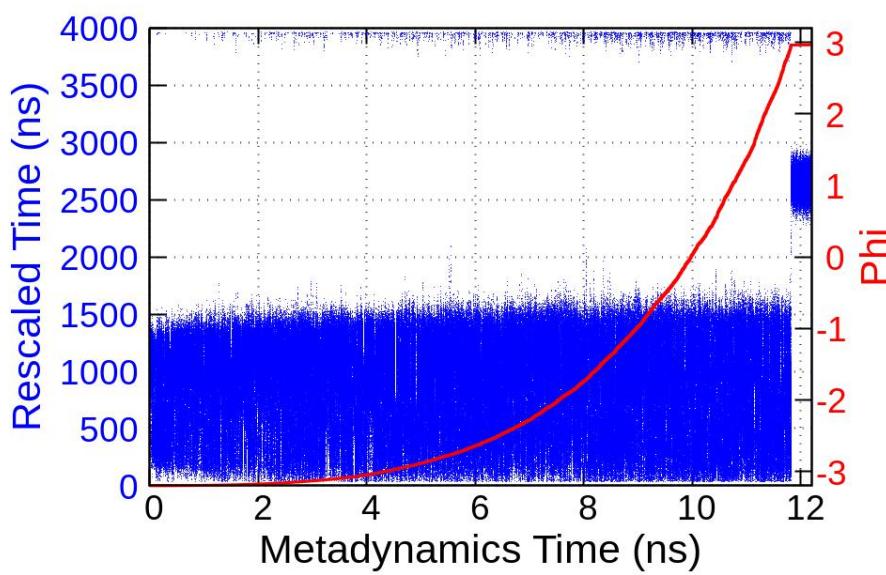
Run 09



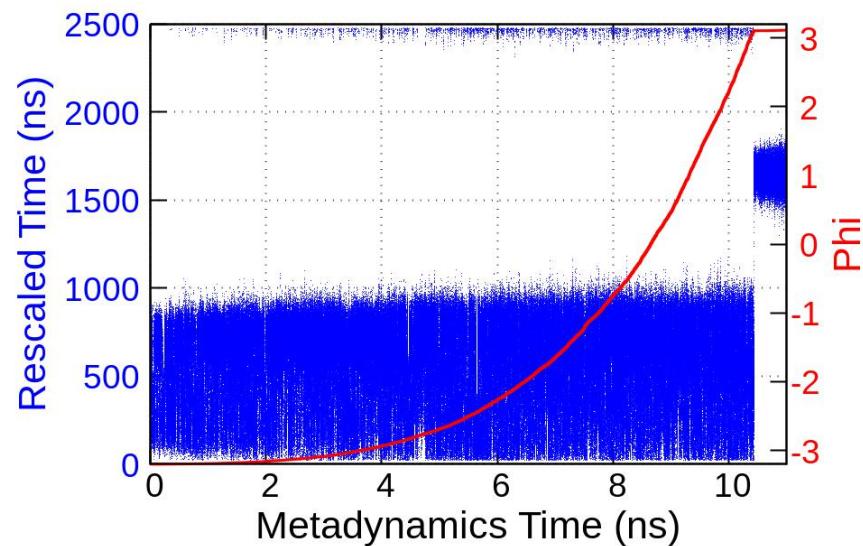
Run 10



Run 11

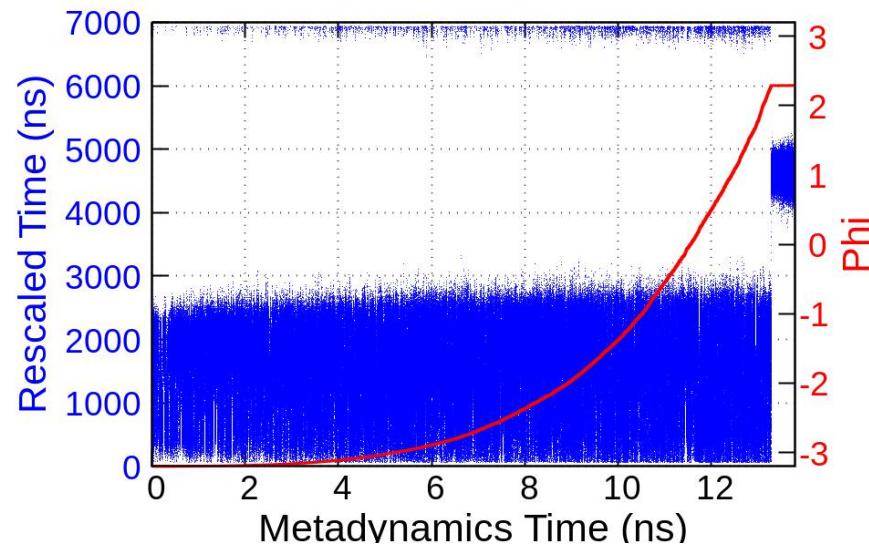


Run 12

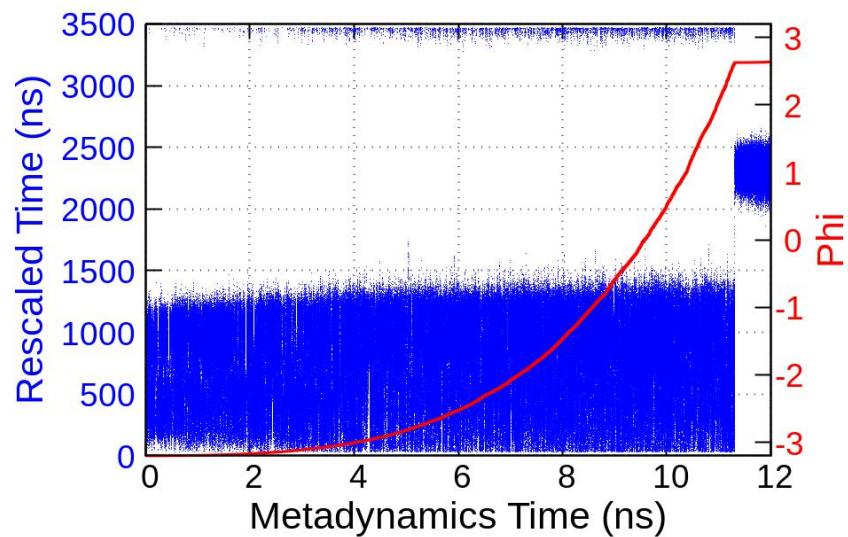


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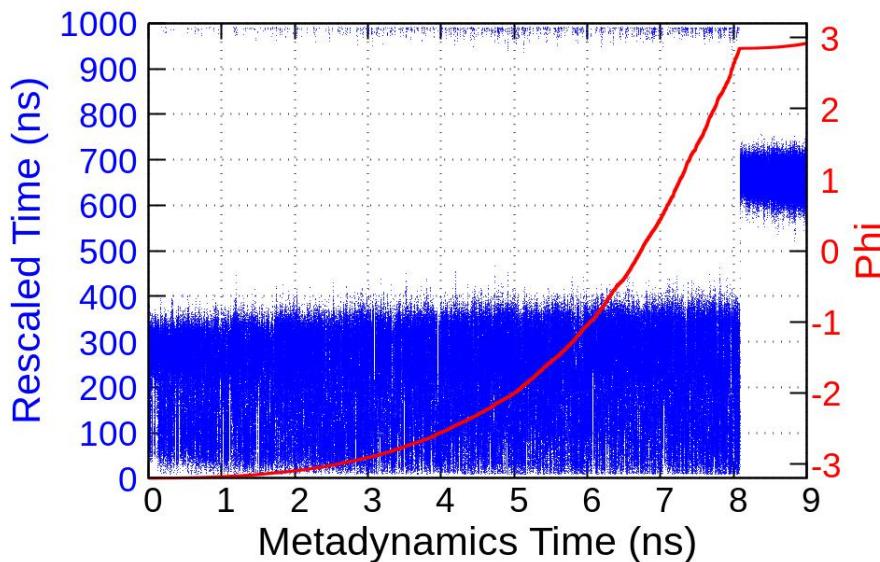
Run 13



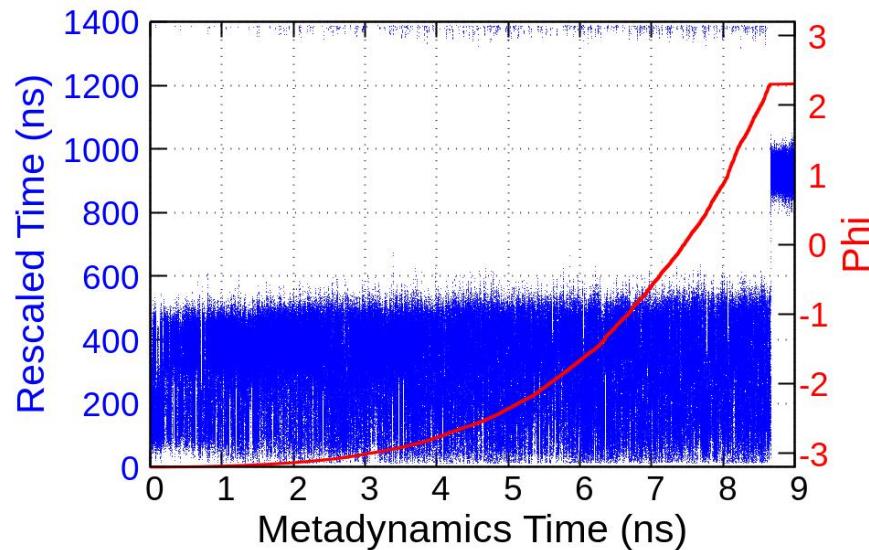
Run 14



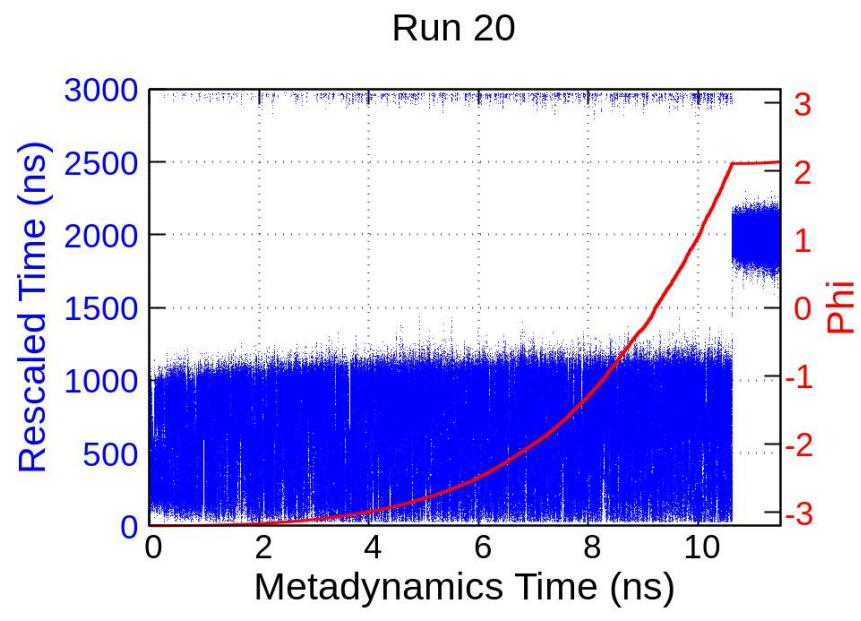
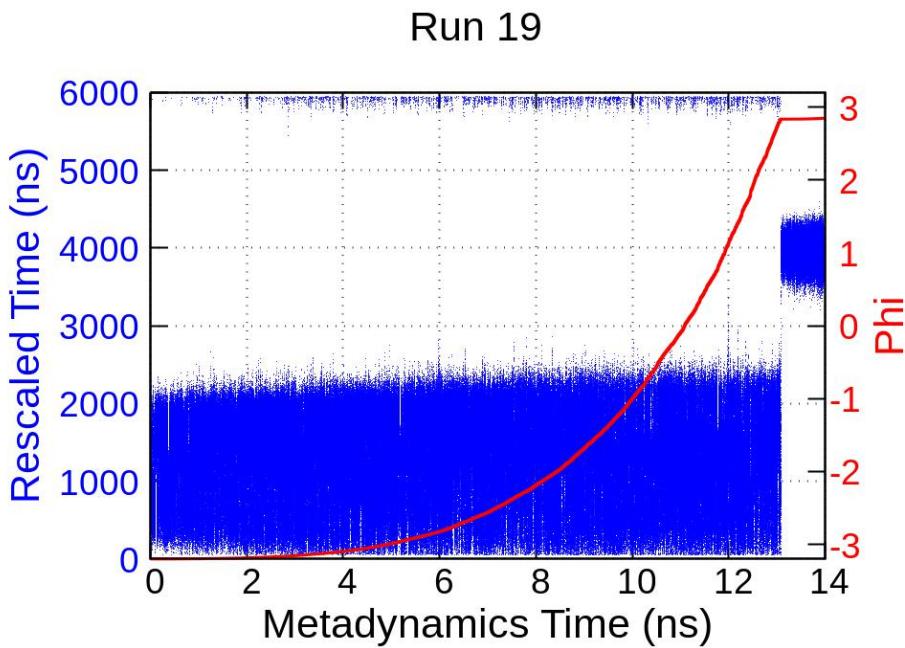
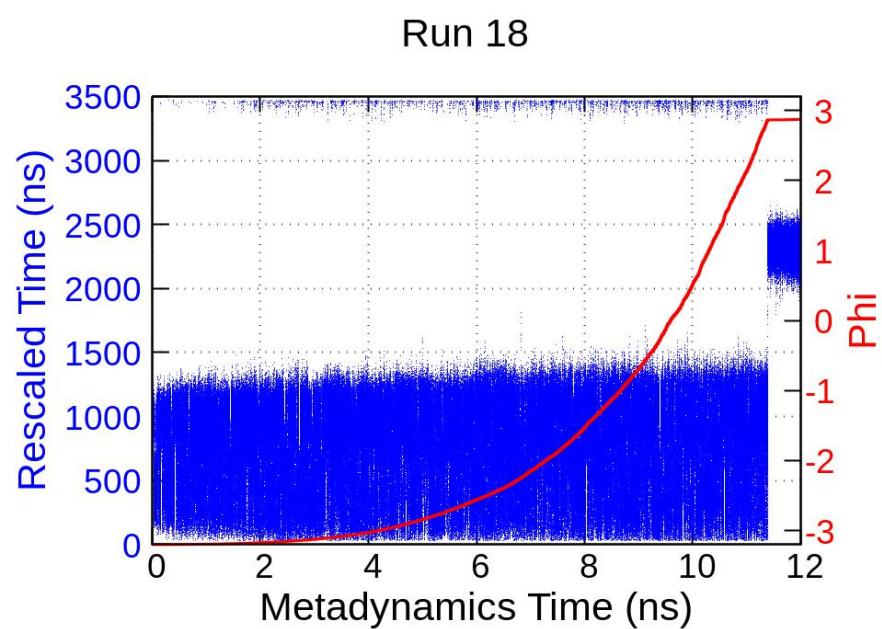
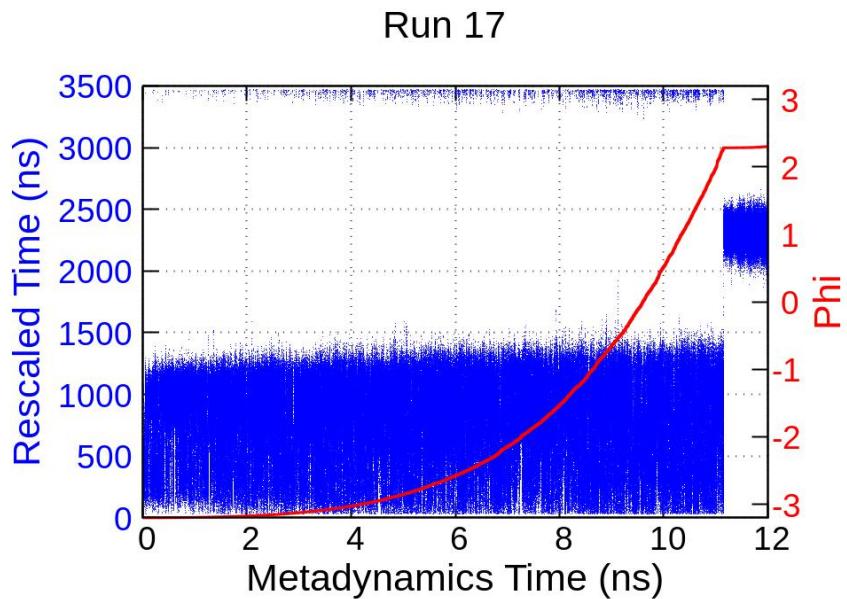
Run 15



Run 16

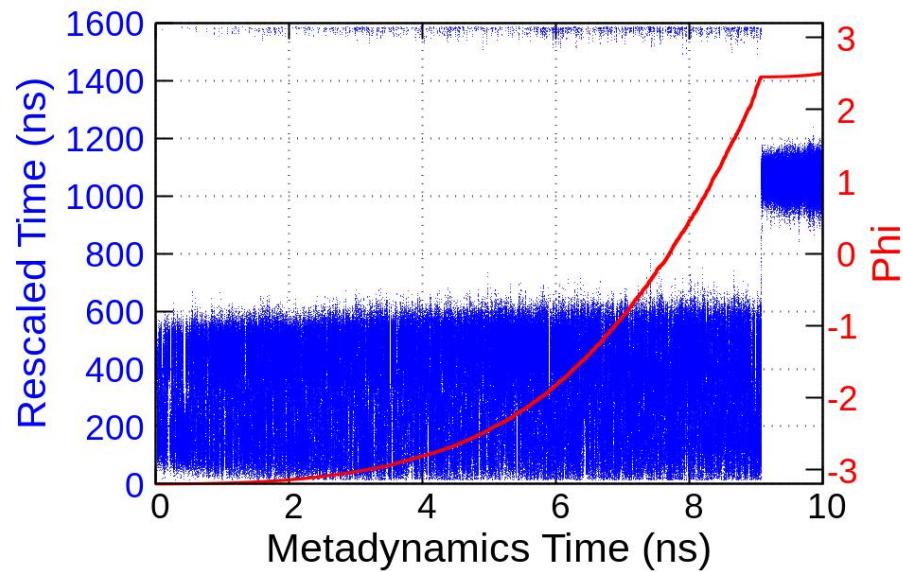


# Example 2: Alanine dipeptide AMBER99SB ff (Vaccum)

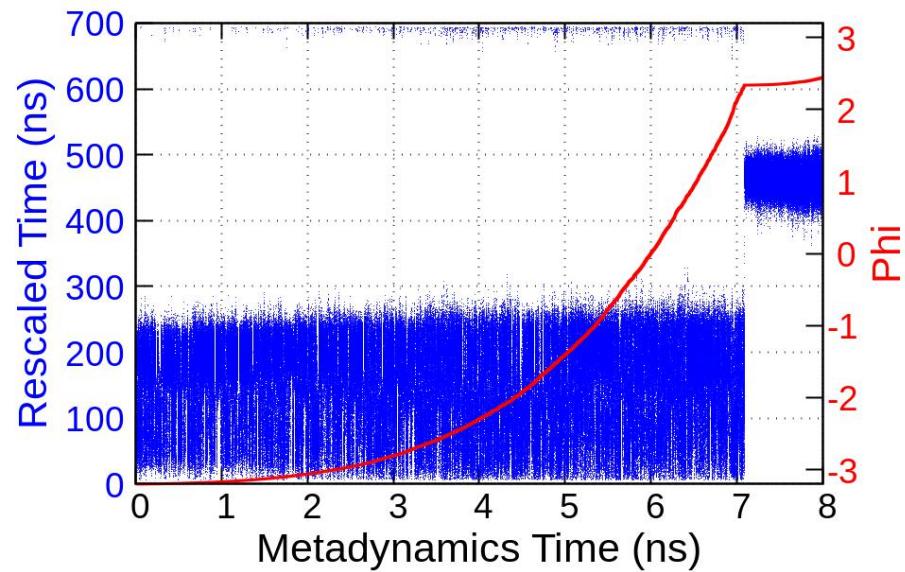


# Example 2: Alanine dipeptide AMBER99SB ff (Vaccum)

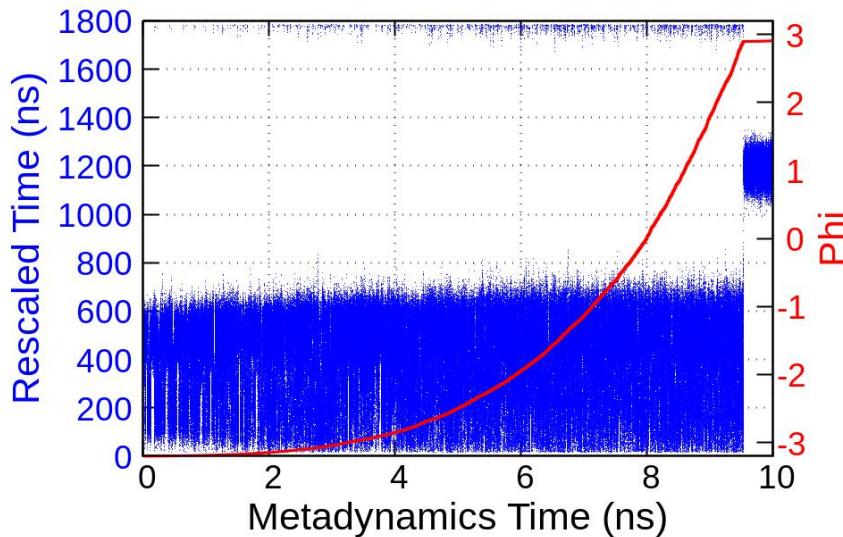
Run 21



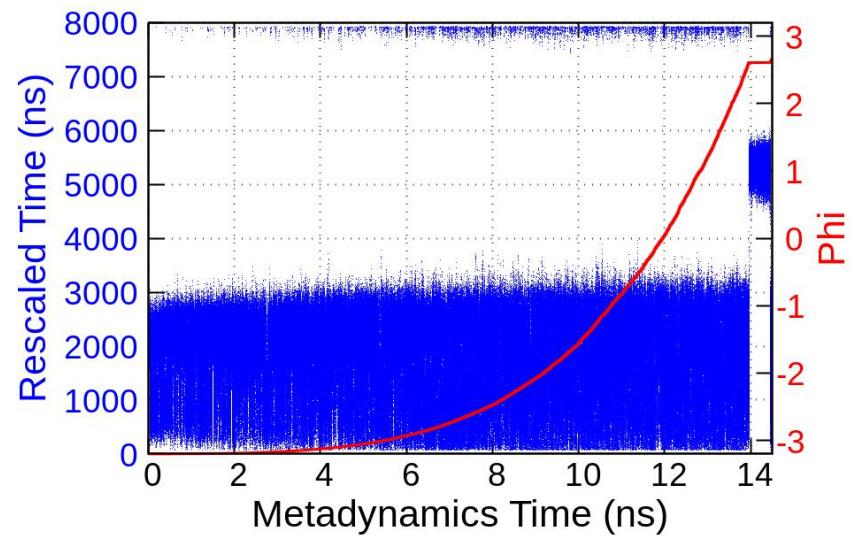
Run 22



Run 23



Run 24



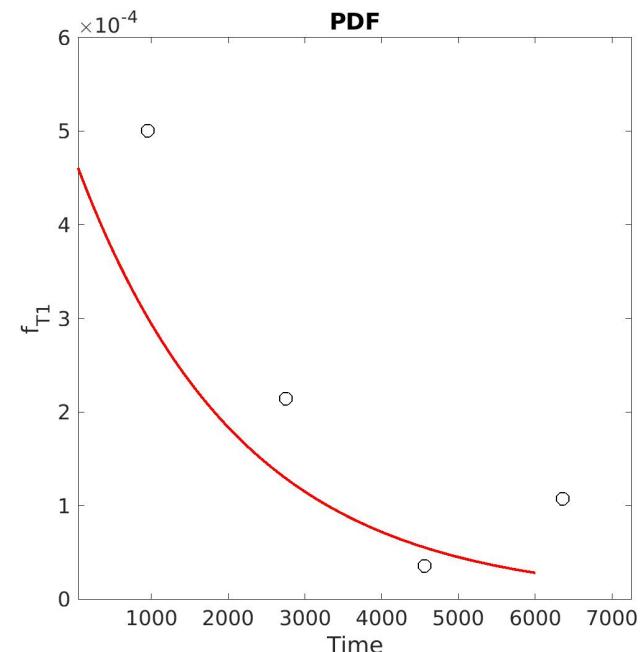
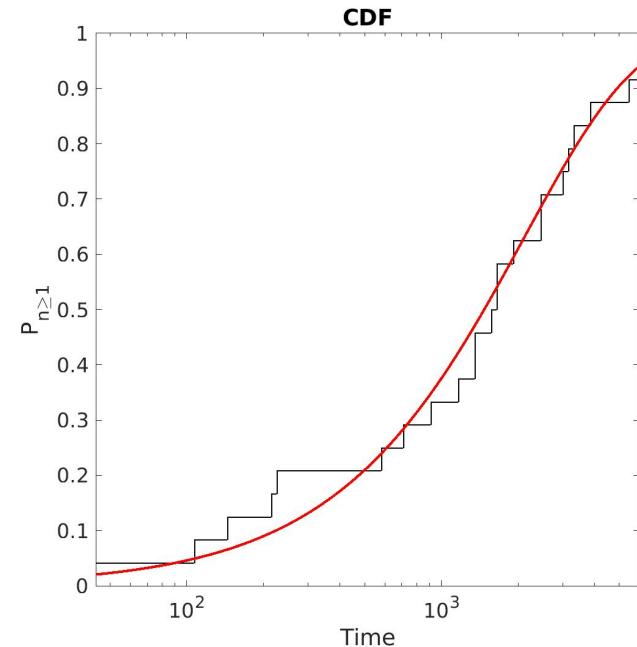
# Example 2: Alanine dipeptide AMBER99SB ff

Total Simulation Run ~220 ns

Run	Real Time (ps)	Rescaled Time (ps)	Rescaled Time (ns)
1	8004	742528	742
2	5276	221737	221
3	5241	235993	235
4	4608	150838	150
5	8896	1370920	1370
6	9973	1977320	1977
7	9636	1726610	1726
8	4183	113894	113
9	9427	1645960	1645
10	2958	44001	44
11	11826	3851880	3851
12	10441	2462600	2462
13	13291	6001880	6001
14	11309	3186350	3186
15	8087	944887	944
16	8664	1203370	1203
17	11155	2997880	2997
18	11390	3316800	3316
19	13080	5657080	5657
20	10616	2488980	2488
21	9082	1412850	1412
22	7089	605658	605
23	9537	1714750	1714
24	13965	7259080	7259

# Example 2: Alanine dipeptide AMBER99SB ff

$\mu$ (Average Transition Time in ns)	2138
$\mu$ Standar mean error	399
$\sigma$ (Standard Deviation in ns)	1955
$t_m$ ( median in ns)	1679
$\tau$ (Estimated Transition Time in ns)	2126
$\mu / \sigma$ ratio	1.09
$(\mu \ln 2) / t_m$ ratio	0.88
$\tau / \mu$ ratio	0.99
p-value	0.94
Reject	0



## Application:

- Protein-drug binding rates and drug residence time calculations
  - 1. Benzamidine trypsin unbinding rates, pathways
  - 2. p38 MAP Kinase Inhibitor unbinding kinetics

Thank you