Sampling RNA Secondary Structure Landscapes for Kinetics Simulations

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RNA Folding Kinetics

Secondary Structure Free Energy Landscapes

$$\mathcal{L} = (X, N : X \to \mathcal{P}(X), f : X \to \mathbb{R})$$

- X . . . Set of secondary structures
- N . . . Structures obtained by formation / opening of a base pair
- f . . . Free energy $E(s)$ of structure s

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Describe dynamic process of state transition as Markov process with master equation

$$\begin{aligned} \frac{dp_i(t)}{dt} &= \sum_{j \neq i} p_j(t) r_{ji} - p_i(t) r_{ij} \\ \frac{d}{dt}\vec{p}(t) &= \mathbf{R}\vec{p}(t) \quad \text{with formal solution} \quad \vec{p}(t) = e^{t \cdot \mathbf{R}} \cdot \vec{p}(0) \end{aligned}$$

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State Space grows exponentially with Sequence Length!

RNA Folding Kinetics

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- Focus on individual RNAs and perform Monte Carlo simulation, e.g. `kinfold`[1], `Kinefold`[2]
- Lump state space into macro states, e.g. `barriers / treekin`[3]

[1] Flamm et al. 2001
[2] Isambert et al. 2001
[3] Wolfinger et al. 2004

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- Focus on individual RNAs and perform Monte Carlo simulation, e.g. `kinfold`[1], `Kinefold`[2]
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Still, vast numbers of trajectories or exhaustive enumeration of all states is required!

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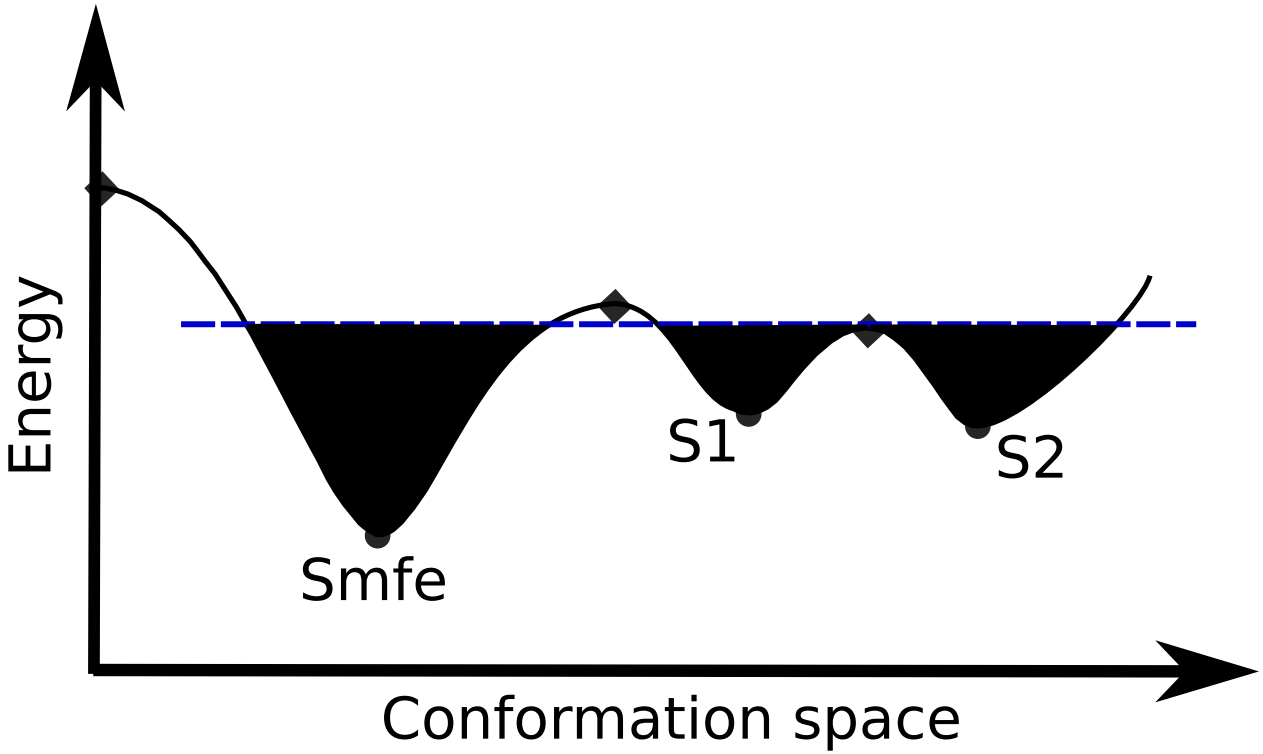
[1] Flamm et al. 2001
[2] Isambert et al. 2001
[3] Wolfinger et al. 2004

Sampling Strategies

1. Exhaustive Enumeration[4]



- up to certain threshold δ above MFE
- only applicable to short sequences

[4] Wuchty et al. 1999

Sampling Strategies

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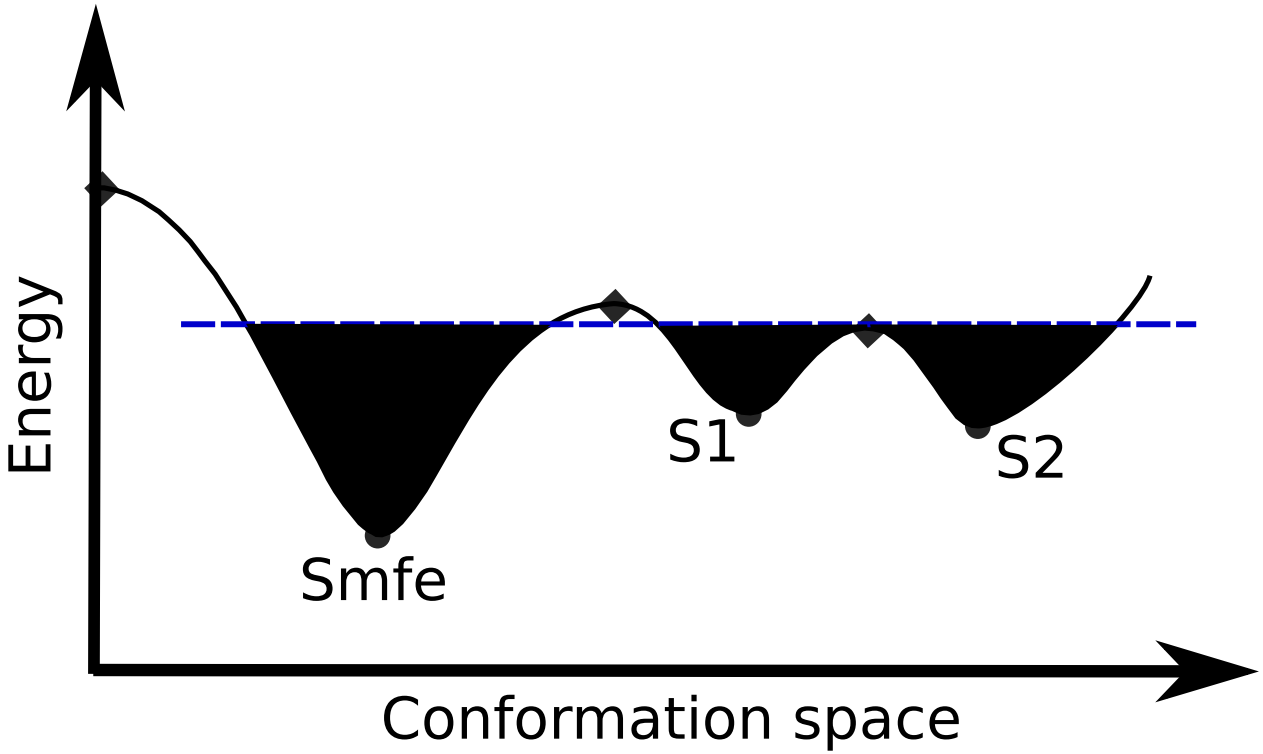


- up to certain threshold δ above MFE
- only applicable to short sequences

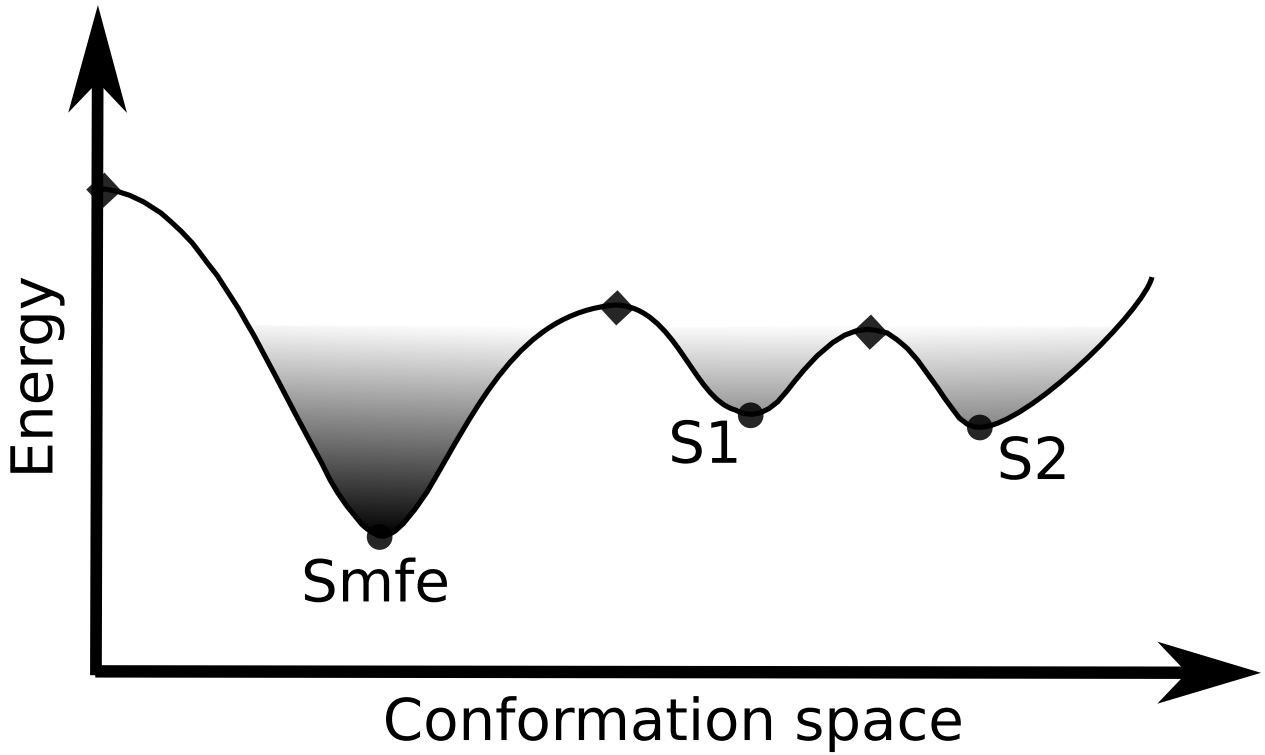
Draw representative structure samples instead...

---

[4] Wuchty et al. 1999

Sampling Strategies

2. Boltzmann Sampling[5]



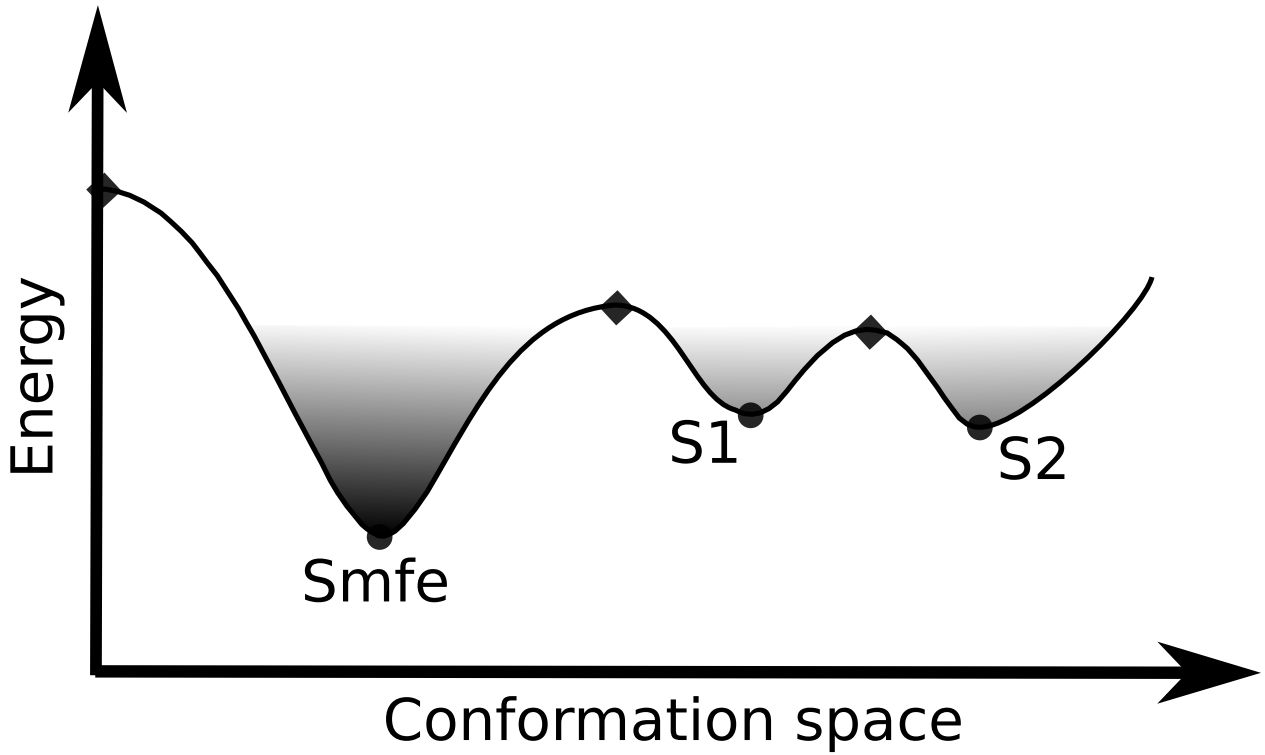
Boltzmann distribution:

- $p(s) \propto e^{-E(s)/RT}$

[5] Ding et al. 2003

Sampling Strategies

2. Boltzmann Sampling[5]



Boltzmann distribution:

- $p(s) = e^{-E(s)/RT}/Q$ with $Q = \sum_{x \in \Omega} e^{-E(x)/RT}$

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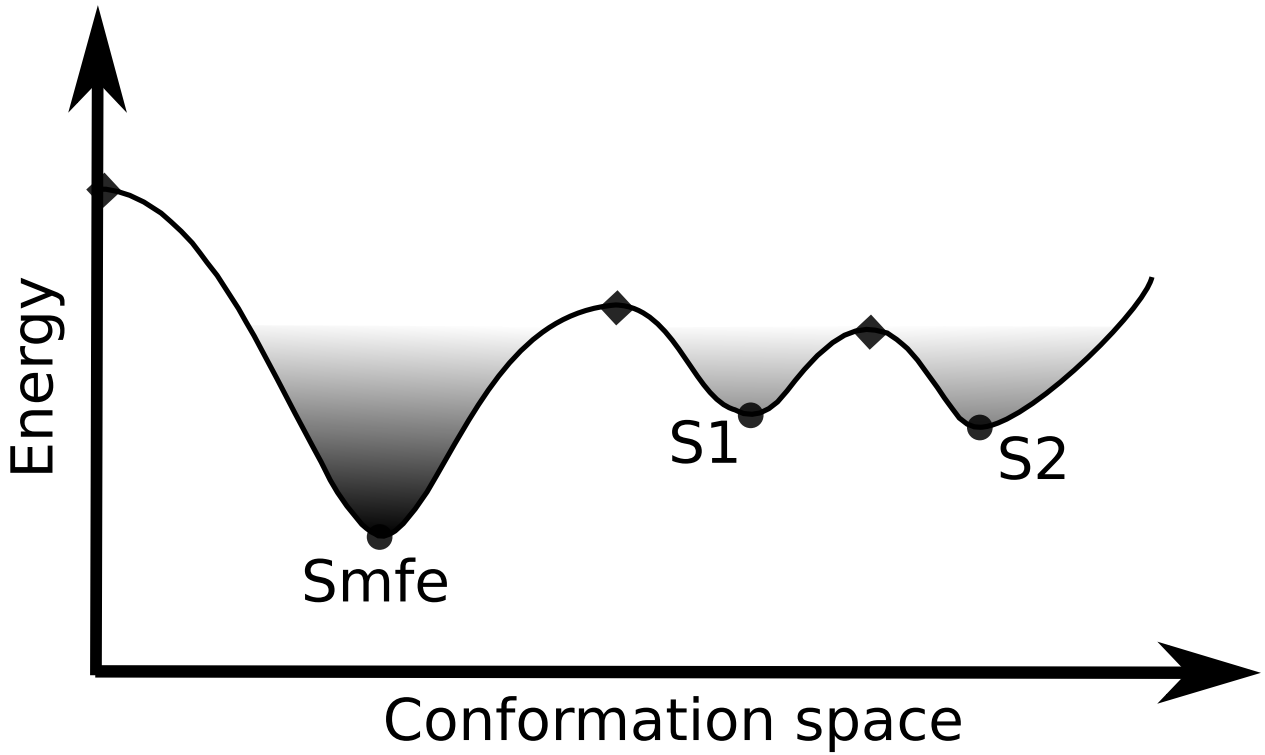
Sampling Strategies

2. Boltzmann Sampling[5]



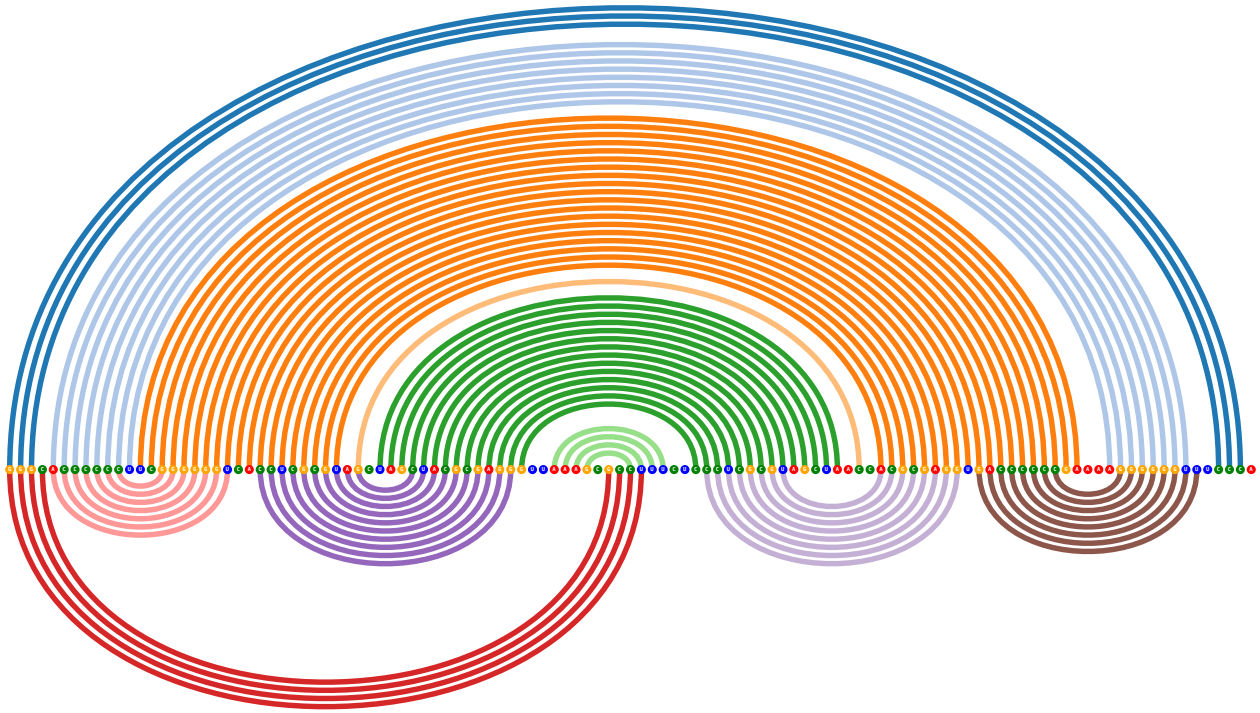
Boltzmann distribution:

- $p(s) = e^{-E(s)/RT}/Q$ with $Q = \sum_{x \in \Omega} e^{-E(x)/RT}$

Sample highly redundant and dominated by low energy states!

[5] Ding et al. 2003

Example: Qβ replicase template SV11[6]

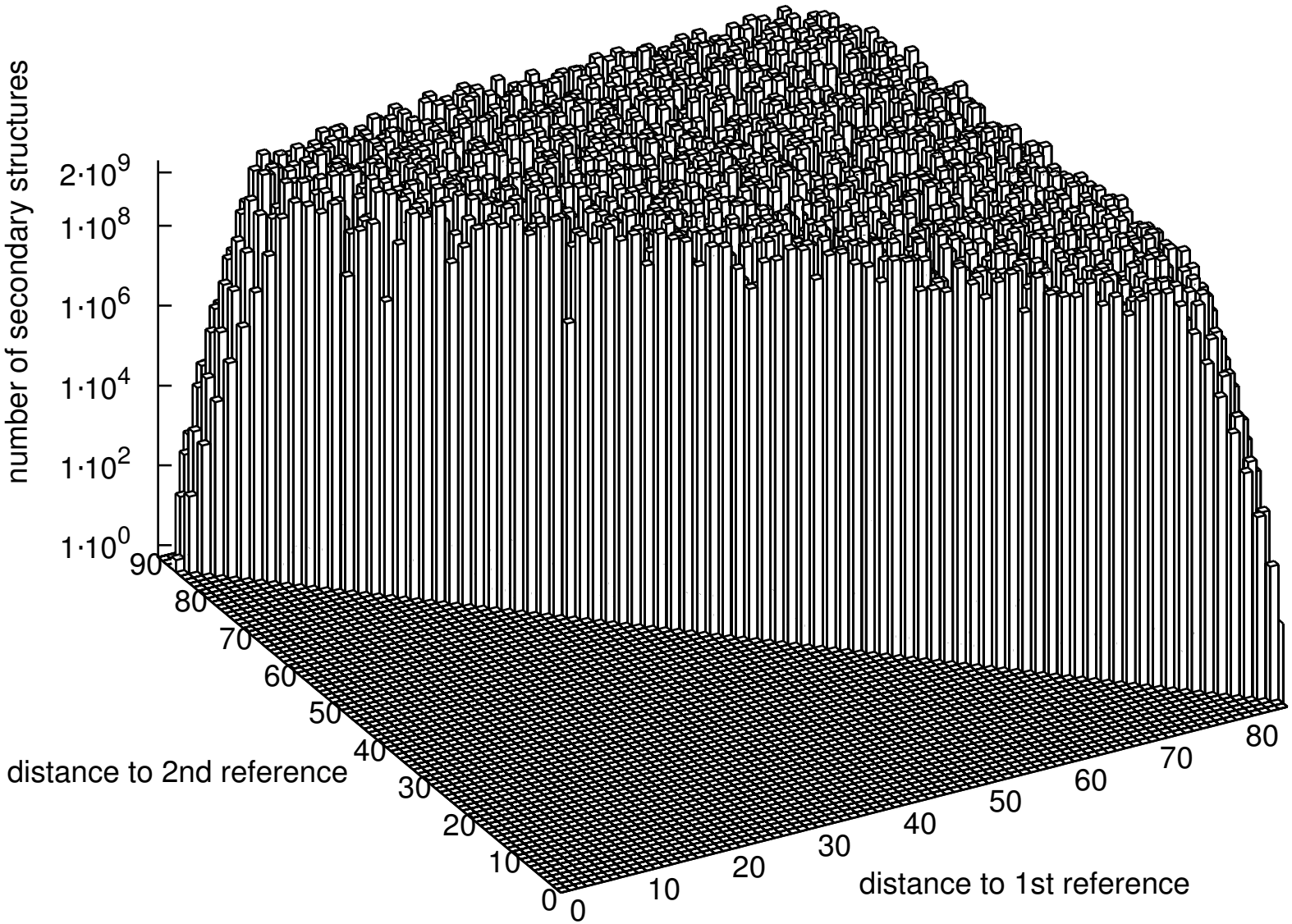


- artificial RNA sequence of 115 nt, $\approx 7 \cdot 10^{27}$ structures
- initially folds into metastable conformation
- metastable state is perfect template for Qβ replicase
- spontaneously refolds into very stable rod-like MFE structure
- metastable state $> 30 kcal/mol$ above MFE

[6] Biebricher et al. 1992

Example: Qβ replicase template SV11

2D Projection of Secondary Structure Landscape[7]



[7] Lorenz et al. 2009

Example: Qβ replicase template SV11

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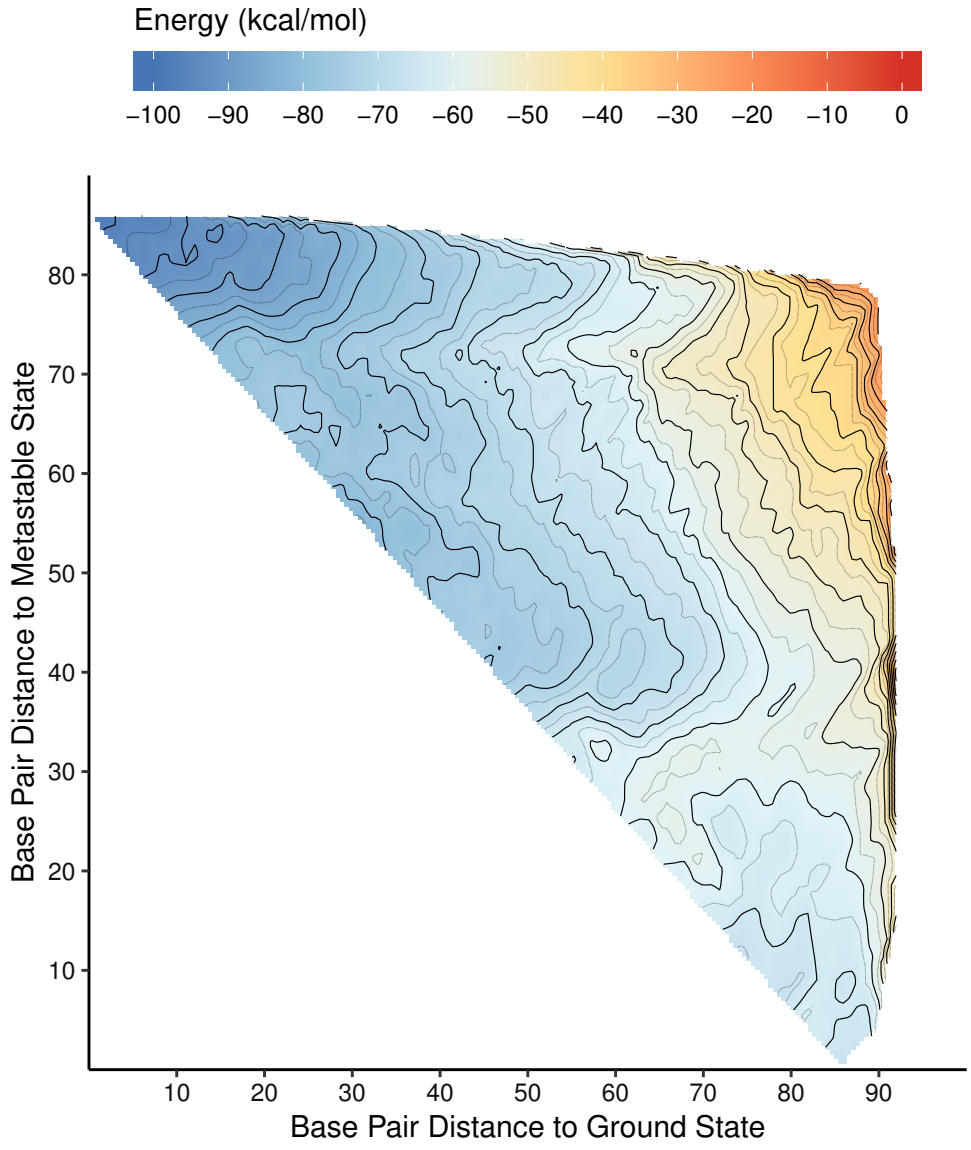

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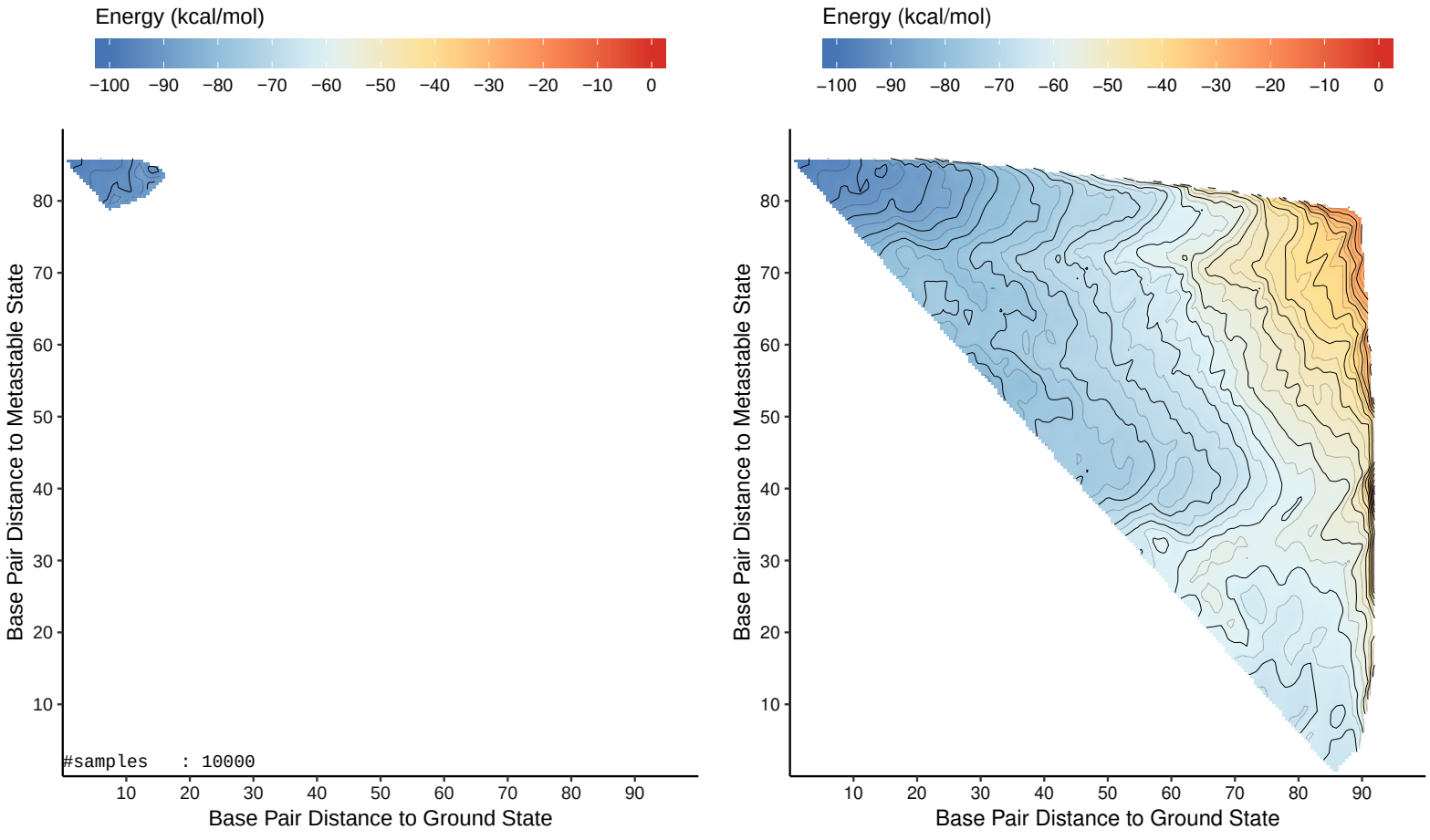
Example: Qβ replicase template SV11

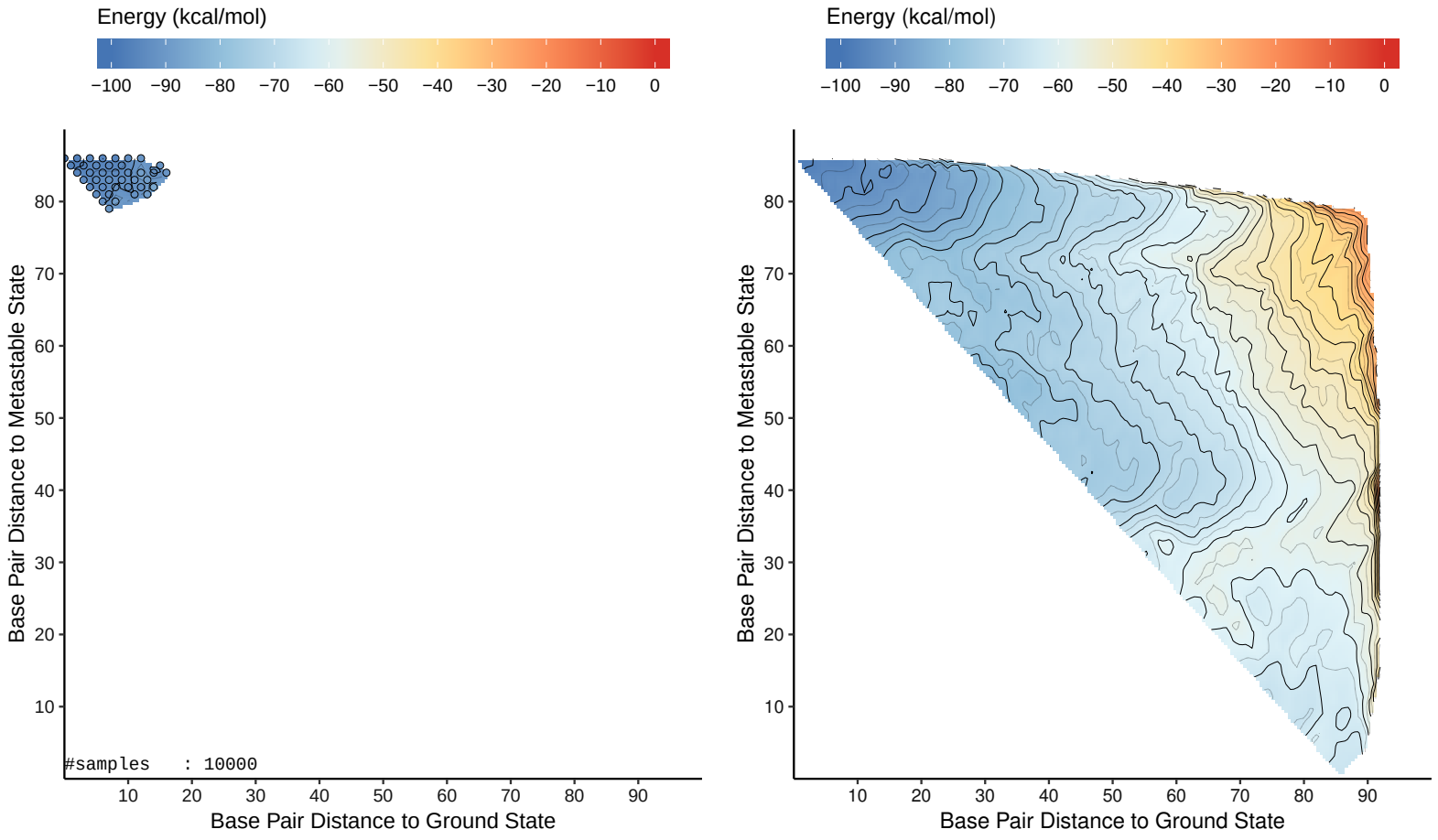
Regular Boltzmann sampling



samples: 10,000, # local minima: 35

Example: Qβ replicase template SV11

Regular Boltzmann sampling



samples: 10,000, # local minima: 35

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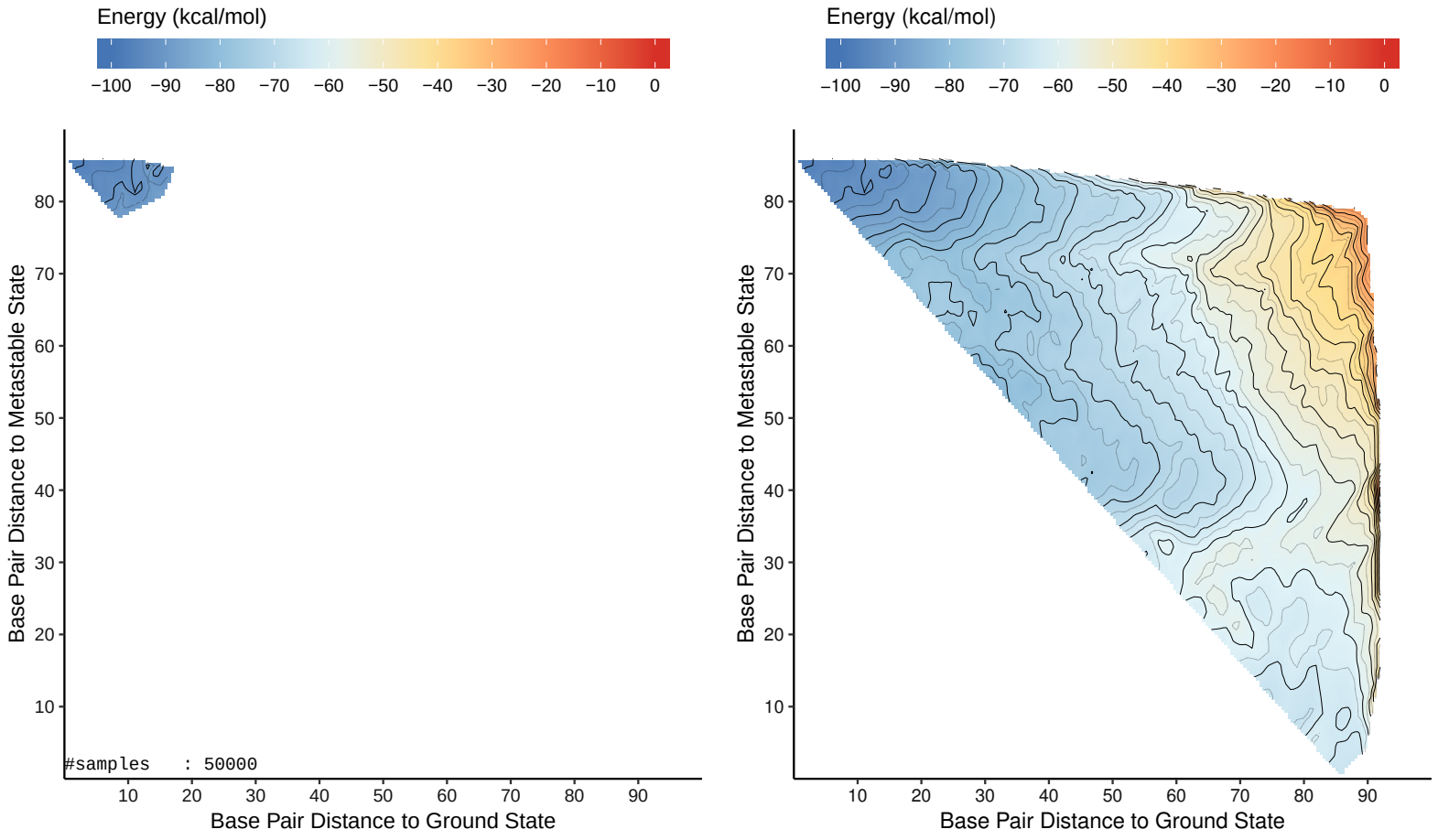
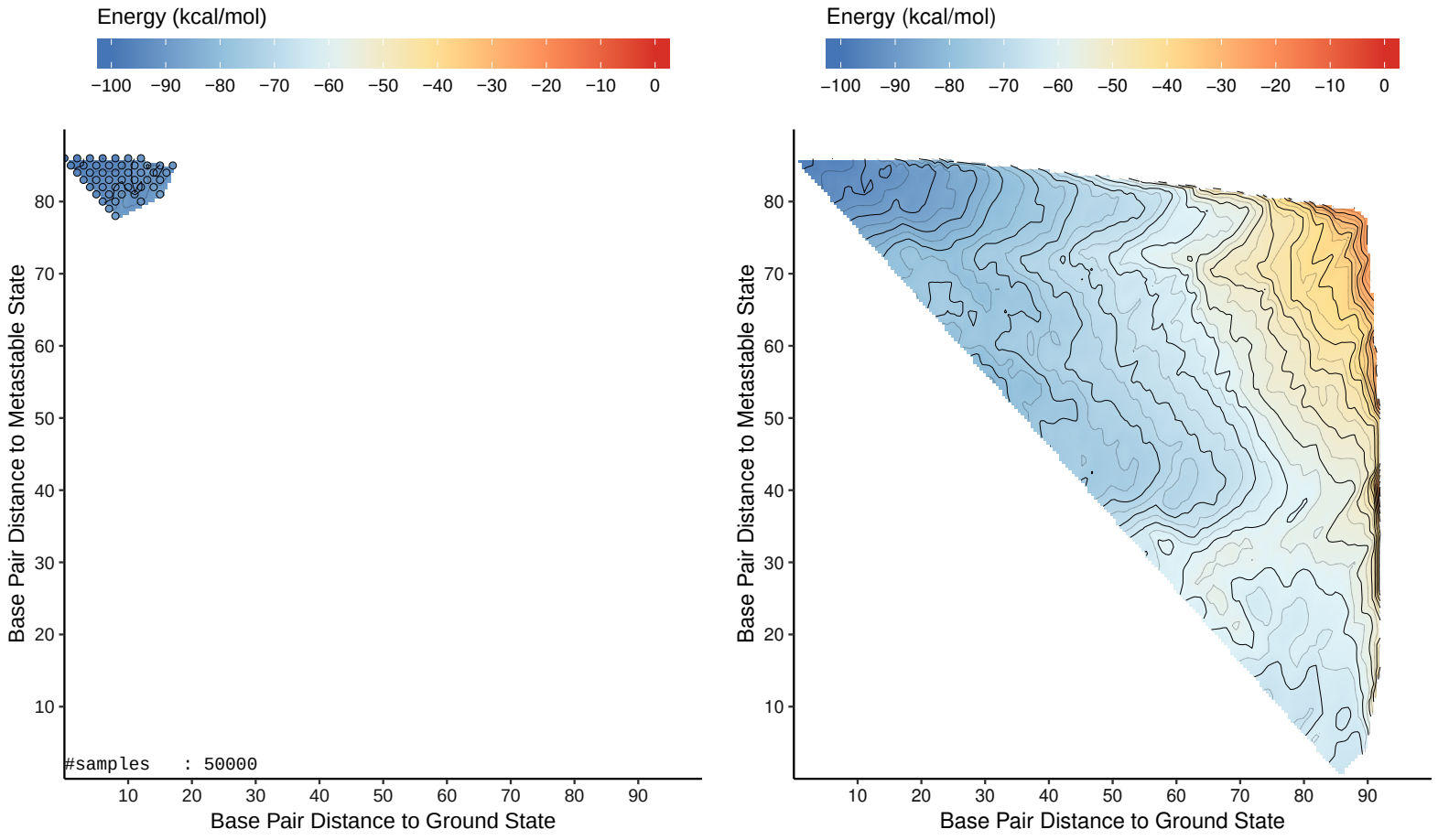


samples: 50, 000 / # local minima: 49

Example: Qβ replicase template SV11

Regular Boltzmann sampling



samples: 50, 000 / # local minima: 49

Example: Qβ replicase template SV11

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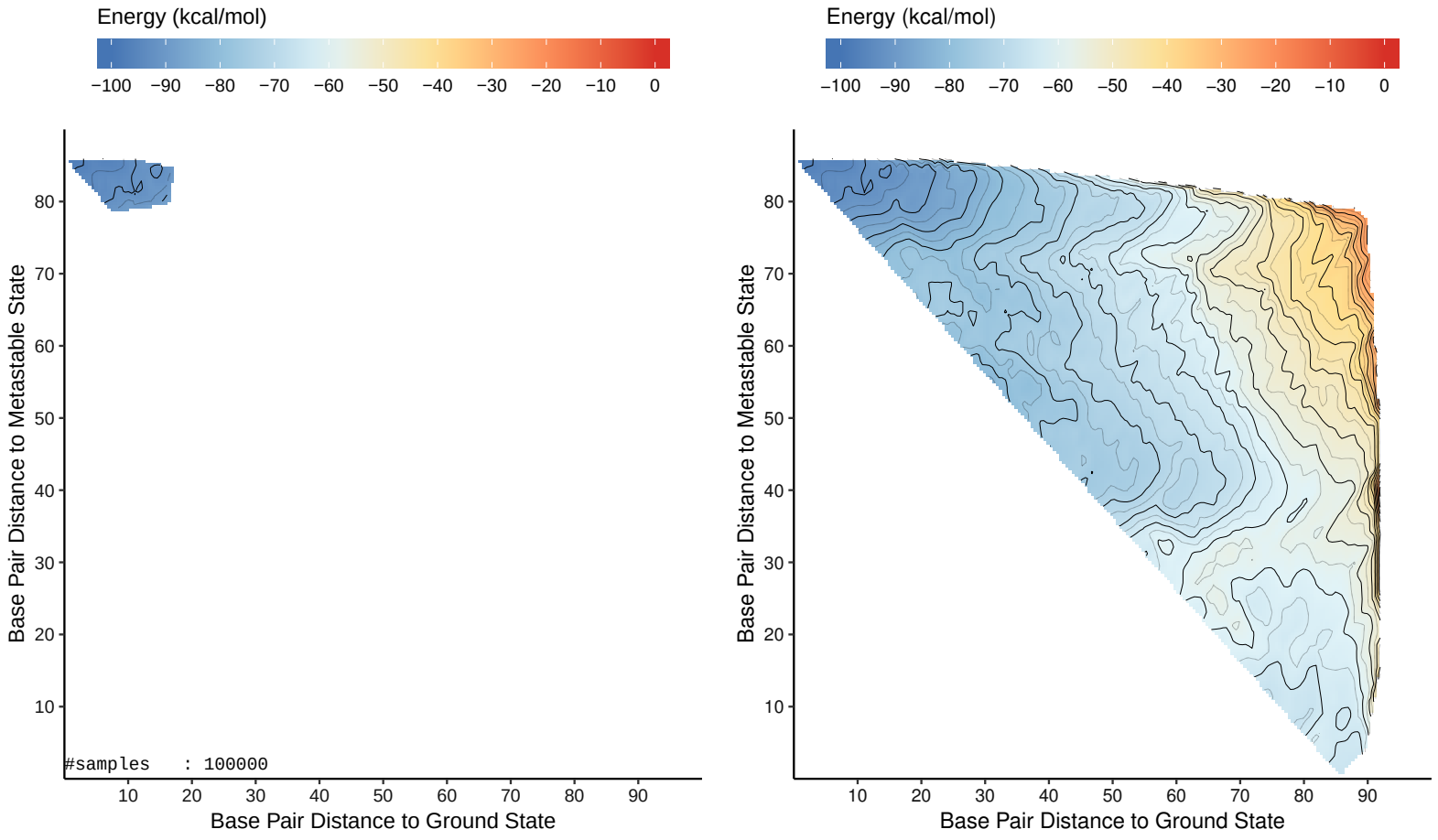
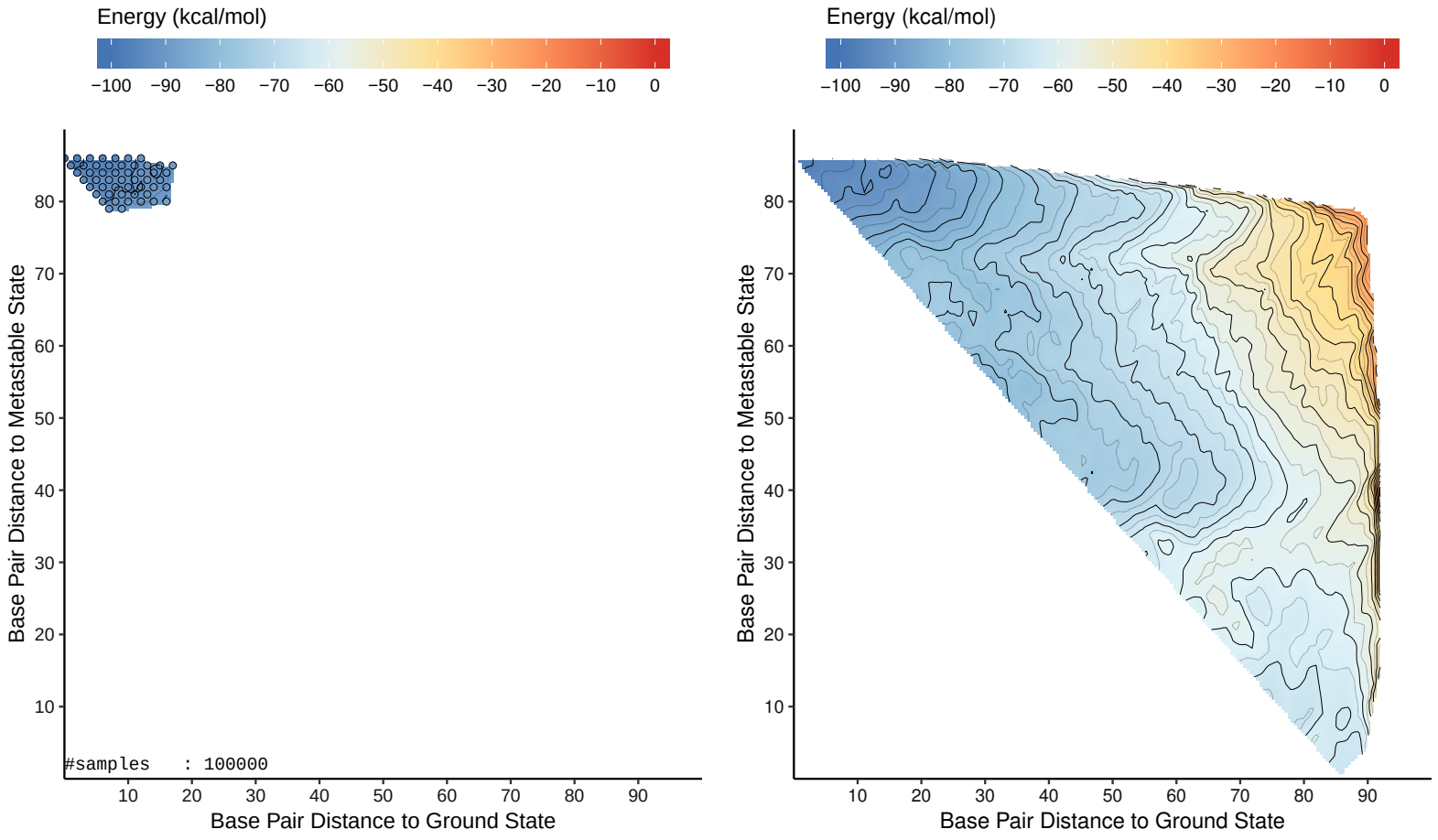


samples: 100, 000 / # local minima: 58

Example: Qβ replicase template SV11

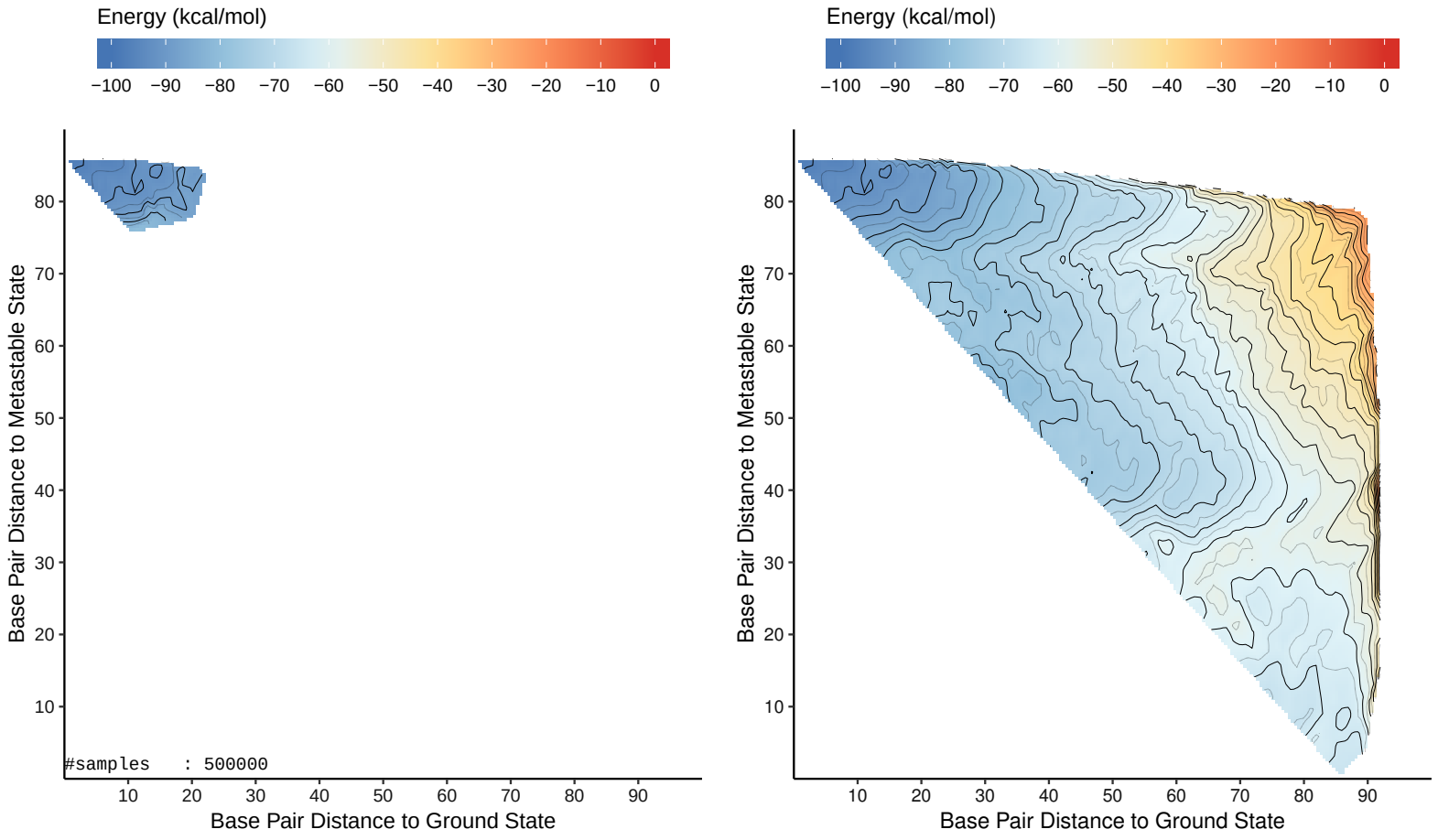
Regular Boltzmann sampling



samples: 100, 000 / # local minima: 58

Example: Qβ replicase template SV11

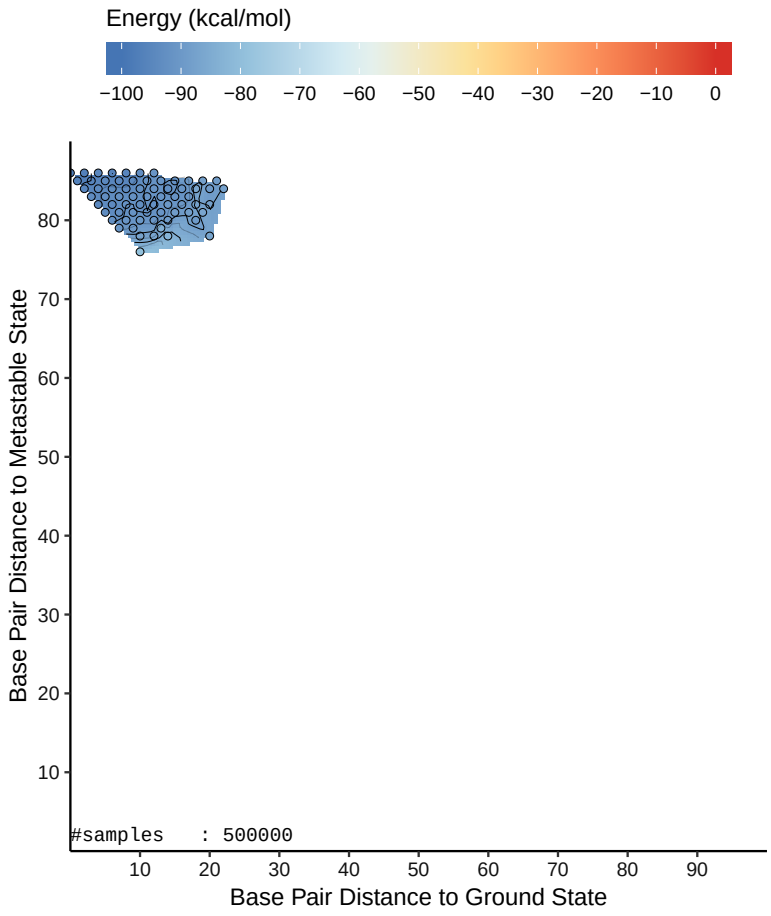
Regular Boltzmann sampling

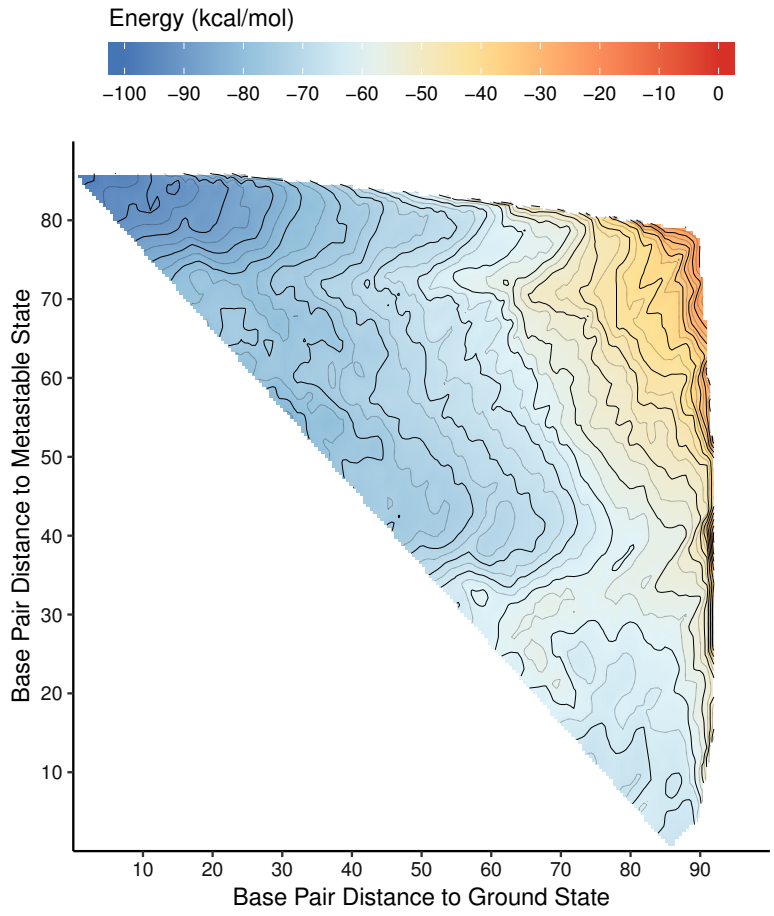


samples: 500, 000 / # local minima: 101

Example: Qβ replicase template SV11

Regular Boltzmann sampling





samples: 500, 000 / # local minima: 101

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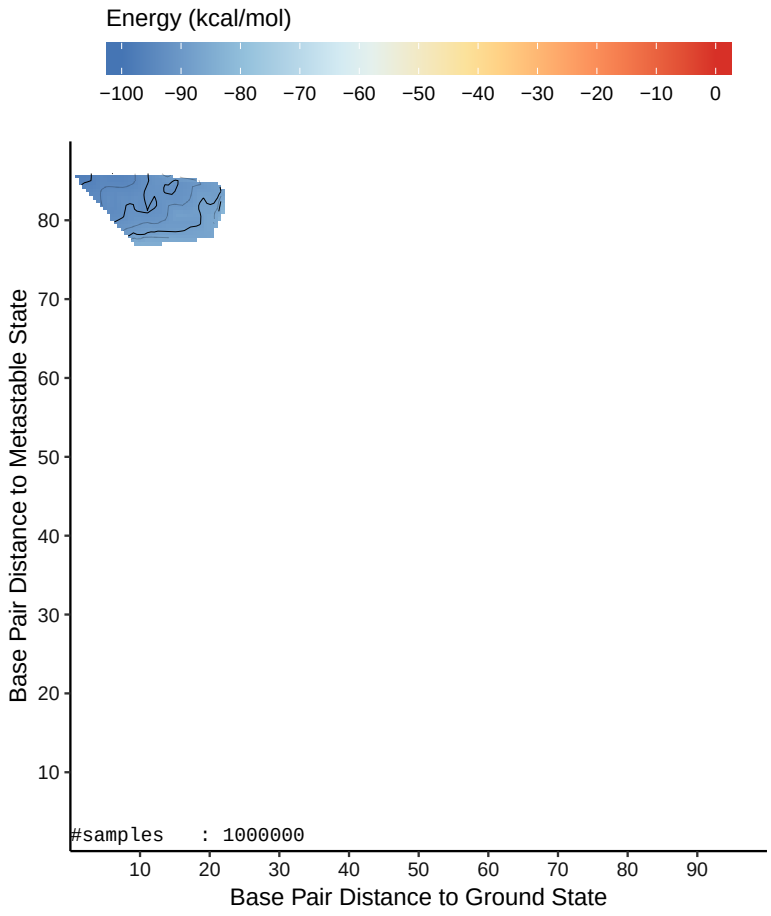
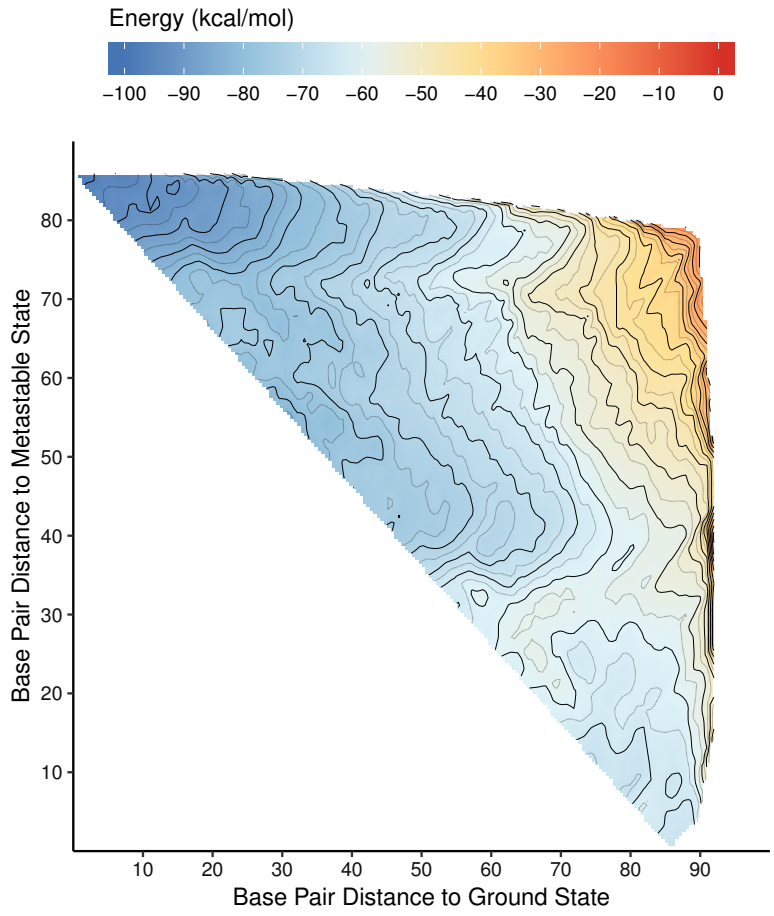
Regular Boltzmann sampling





samples: $1,000,000$ / # local minima: 132

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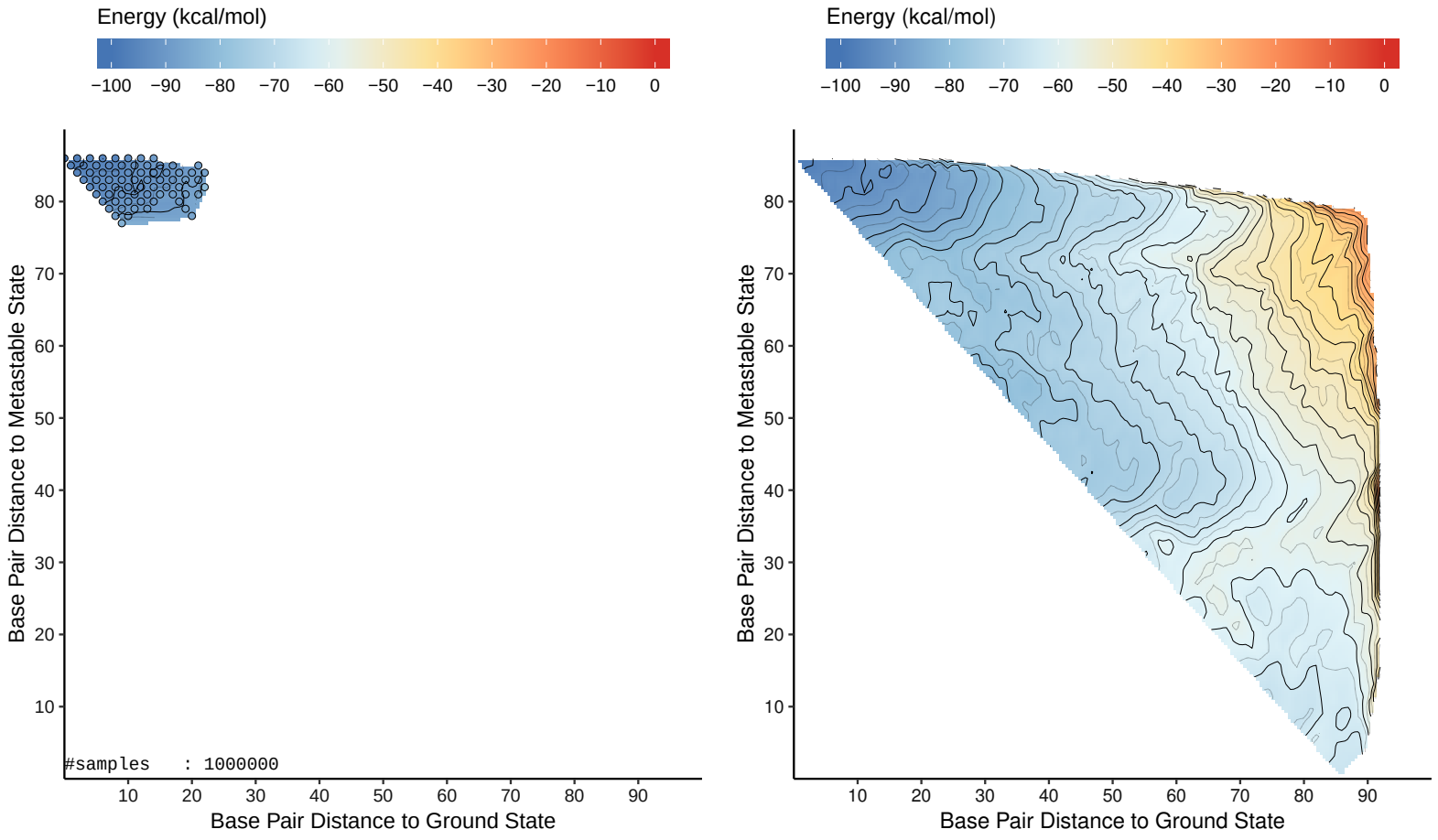

samples: $1,000,000$ / # local minima: 132

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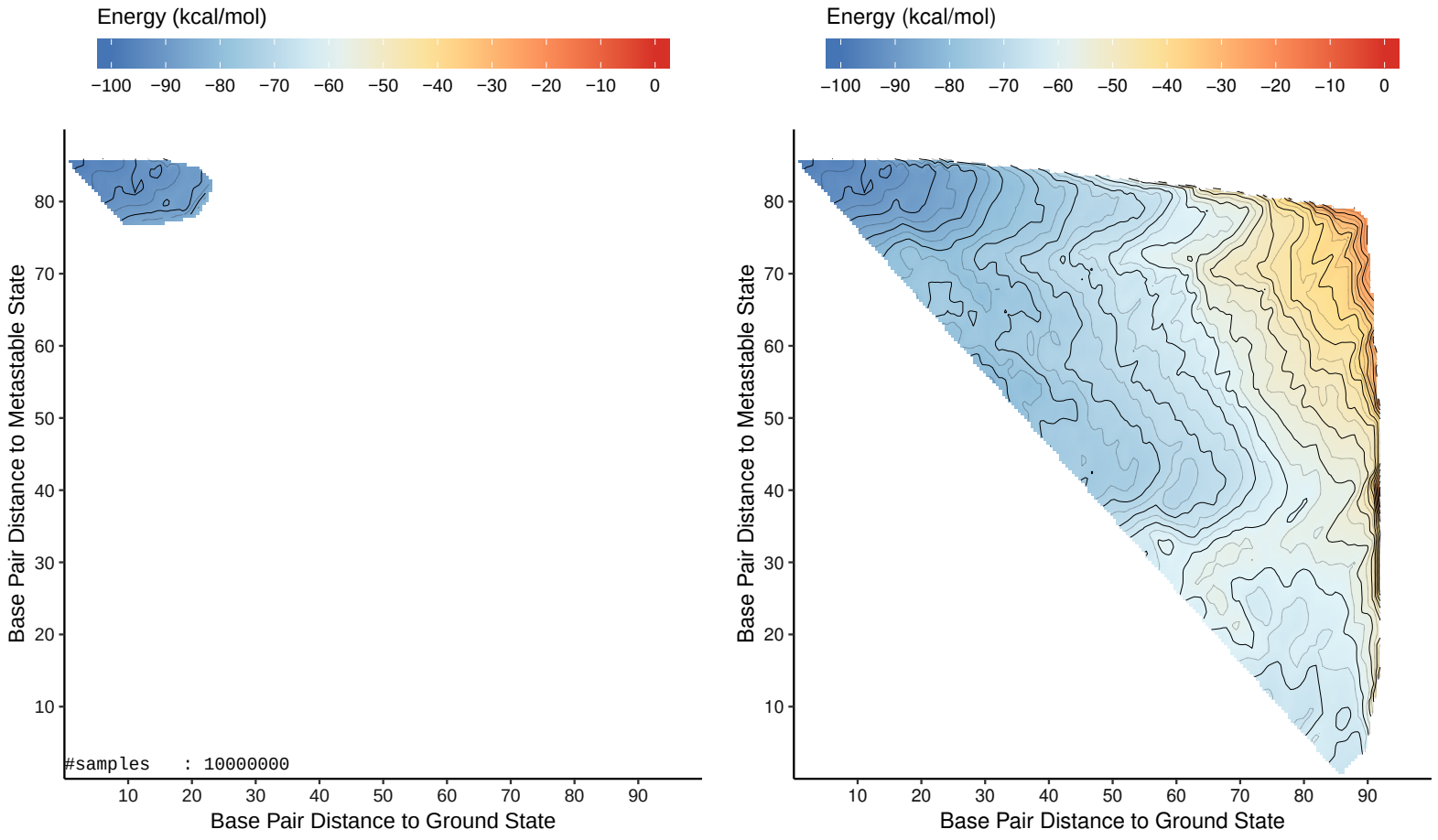
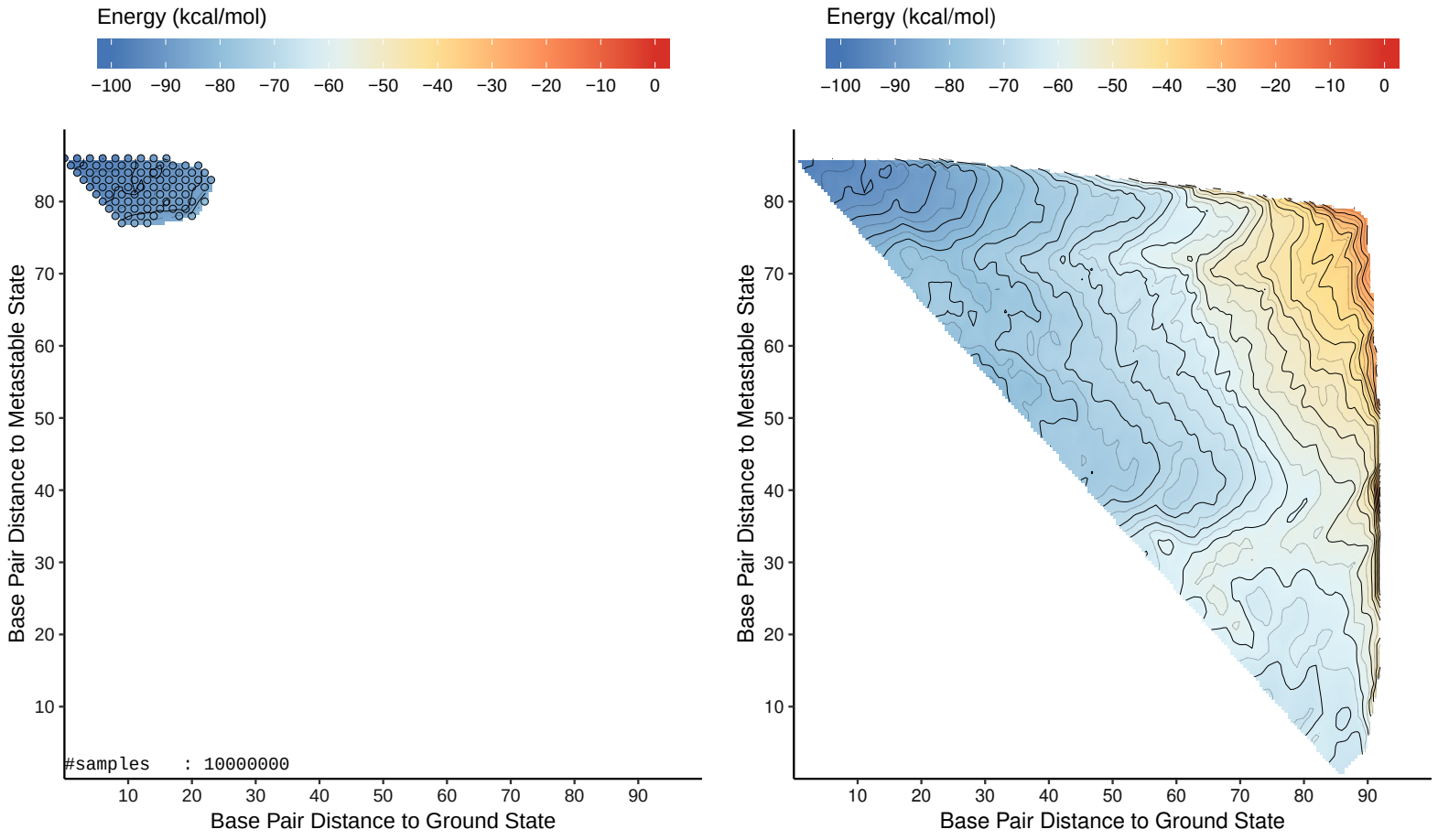


samples: $10,000,000$ / # local minima: 259

Example: Qβ replicase template SV11

Regular Boltzmann sampling



samples: $10,000,000$ / # local minima: 259

Sampling Strategies

3. Restrict Conformation Space

- Local minima (`RNAlocopt`[7])
- Flat structures (`RNANR`[8])
- Local optimal stack configurations (`RNASLOpt`[9])
- Shape abstraction (`RNAShapes`[10])

Unfortunately...

- # of local optimal structures still grow exponentially
- most approaches show rather high asymptotic time/memory complexities

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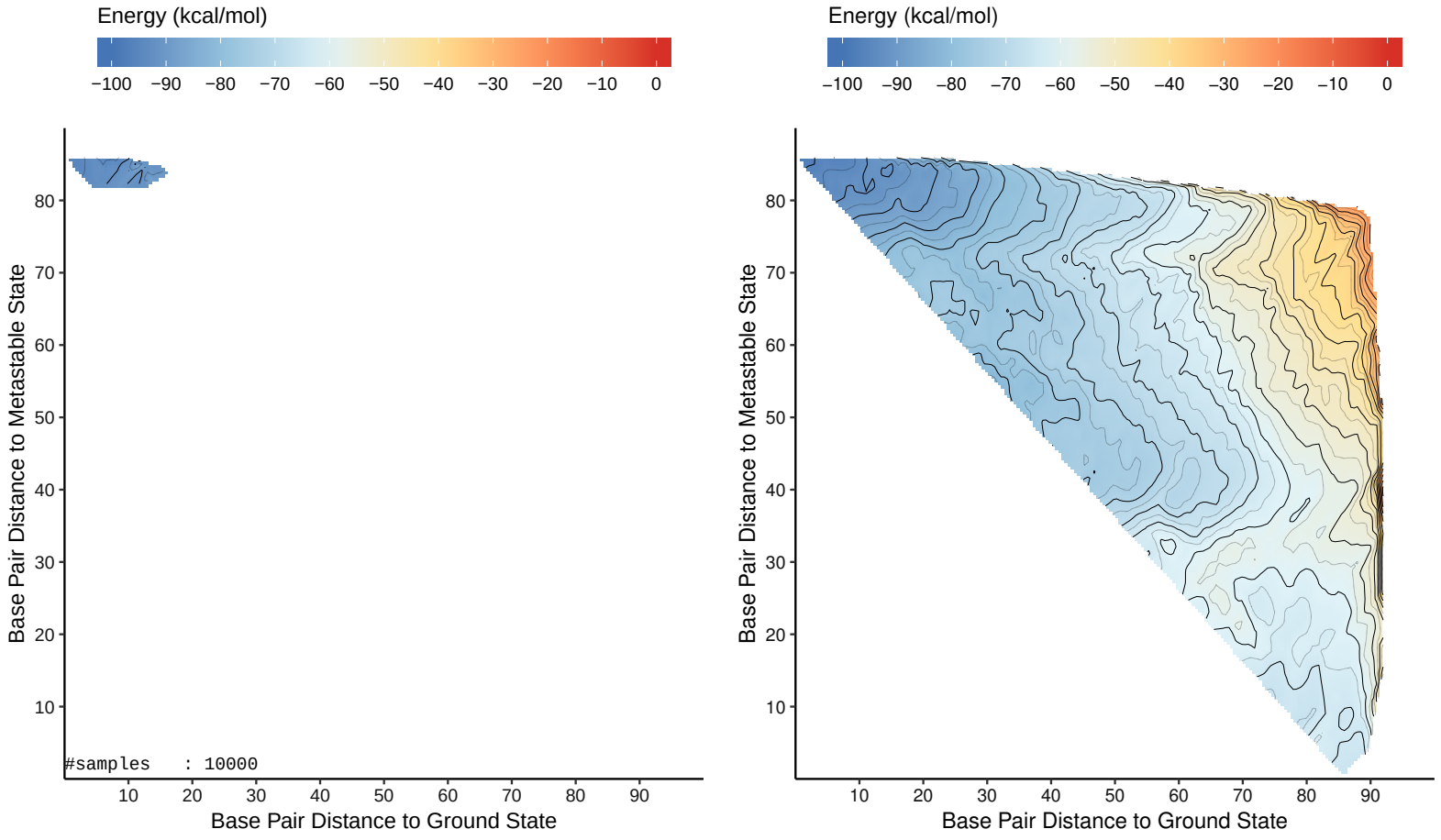
[7] Lorenz WA et al. 2011
[8] Michalik et al. 2017
[9] Li et al. 2011
[10] Steffen et al. 2005

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



samples: 10,000, # local minima: 41

Example: Qβ replicase template SV11

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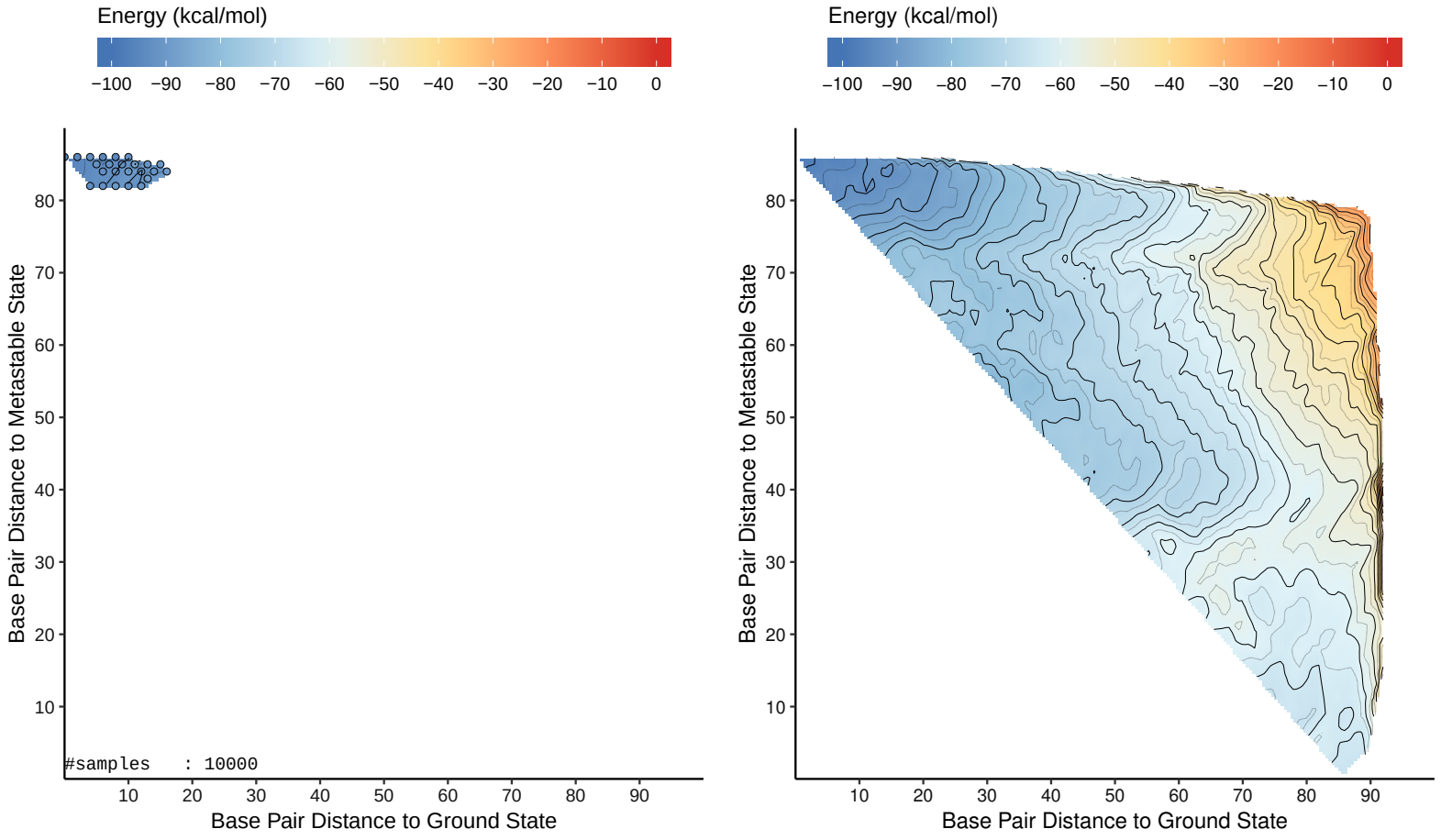

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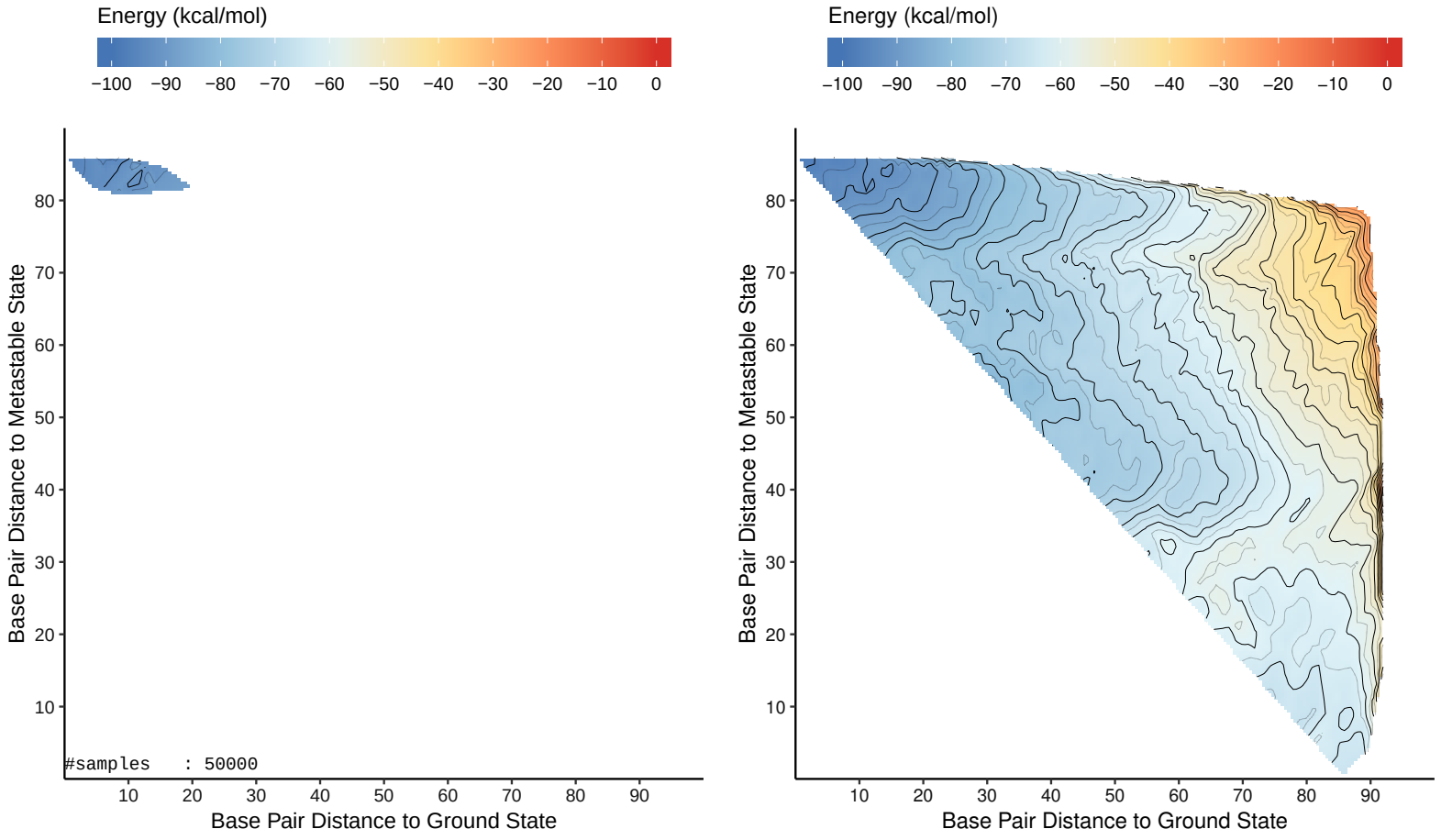

samples: 50, 000, # local minima: 61

Example: Qβ replicase template SV11

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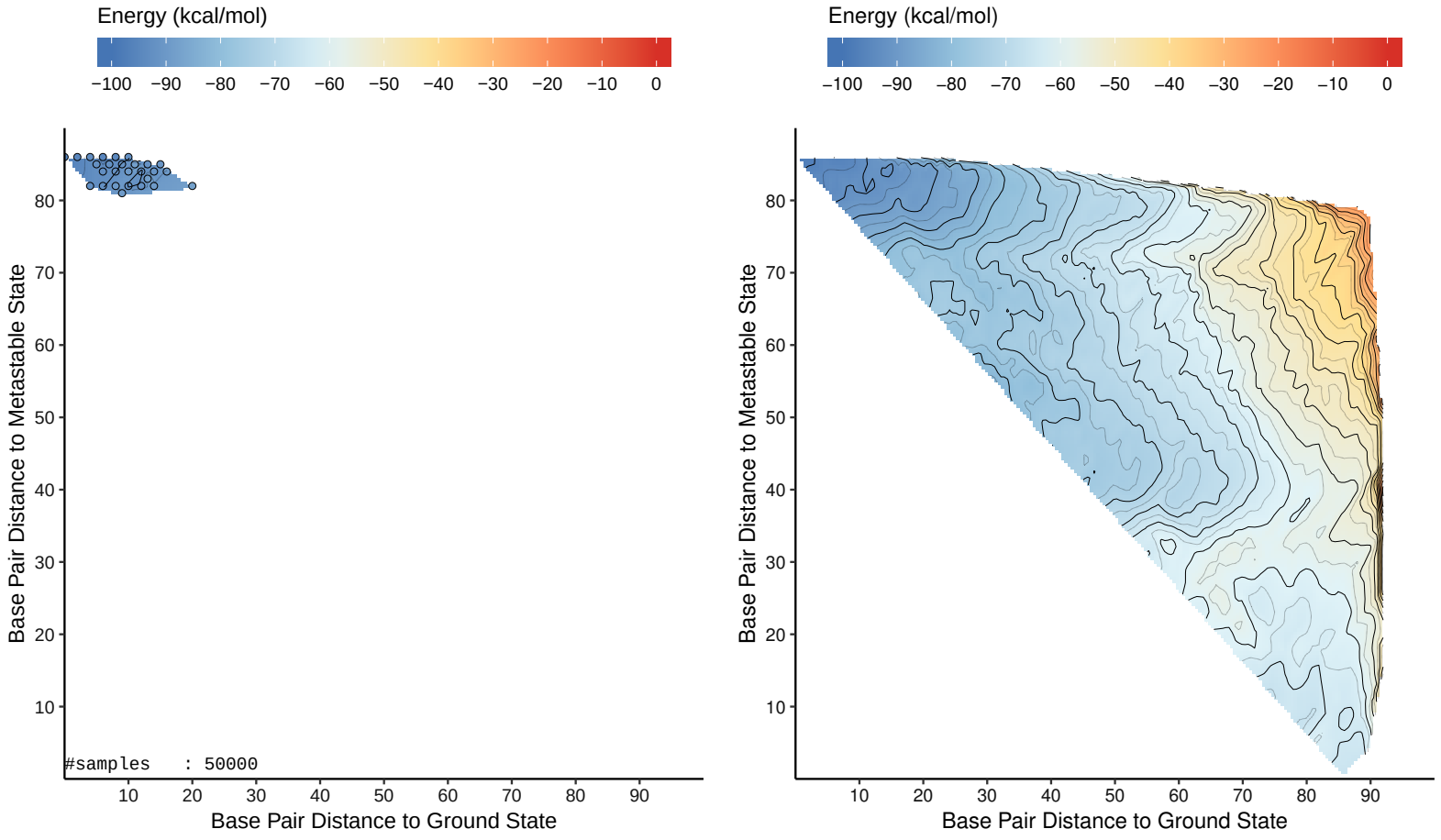

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Example: Qβ replicase template SV11

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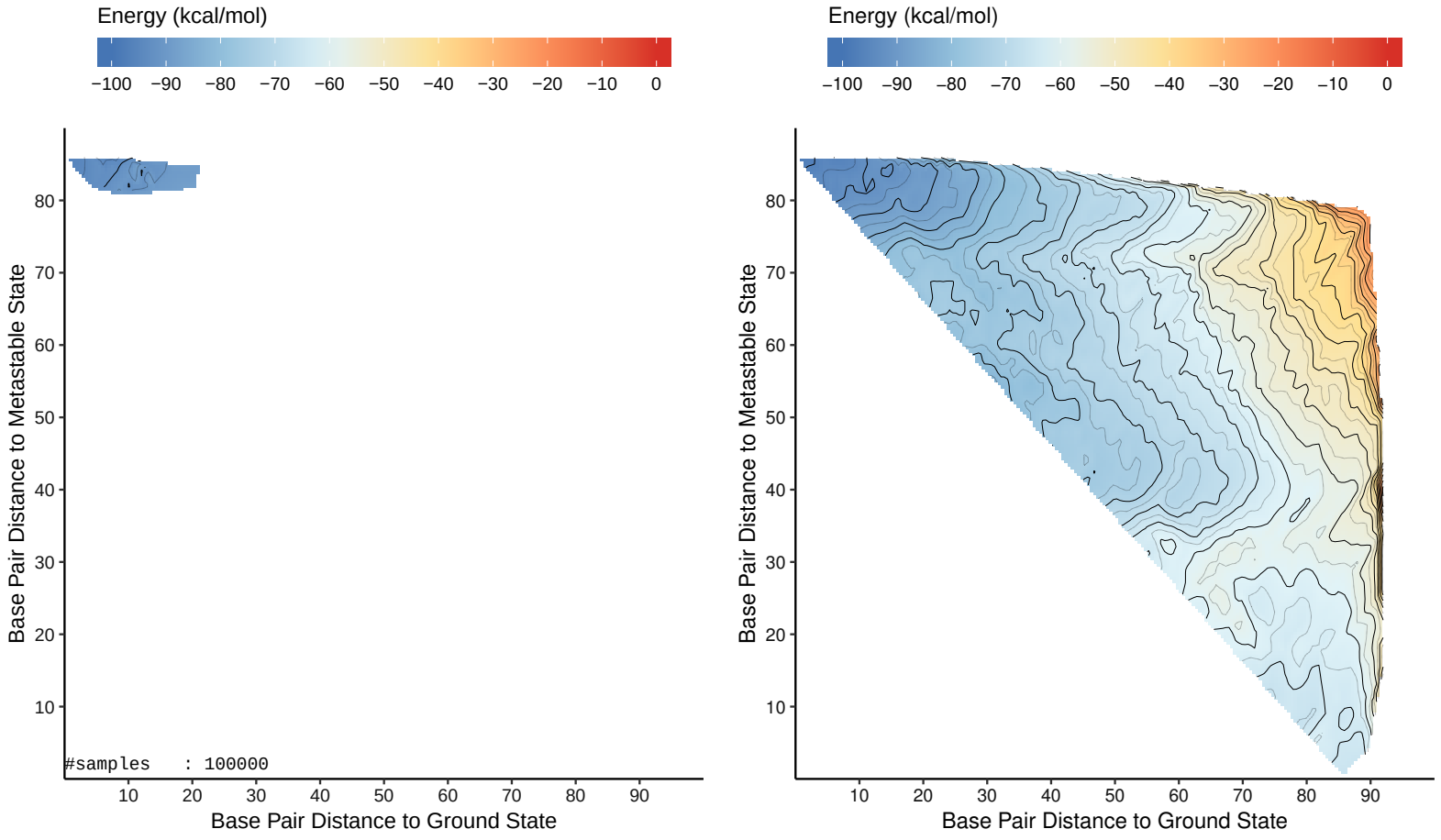
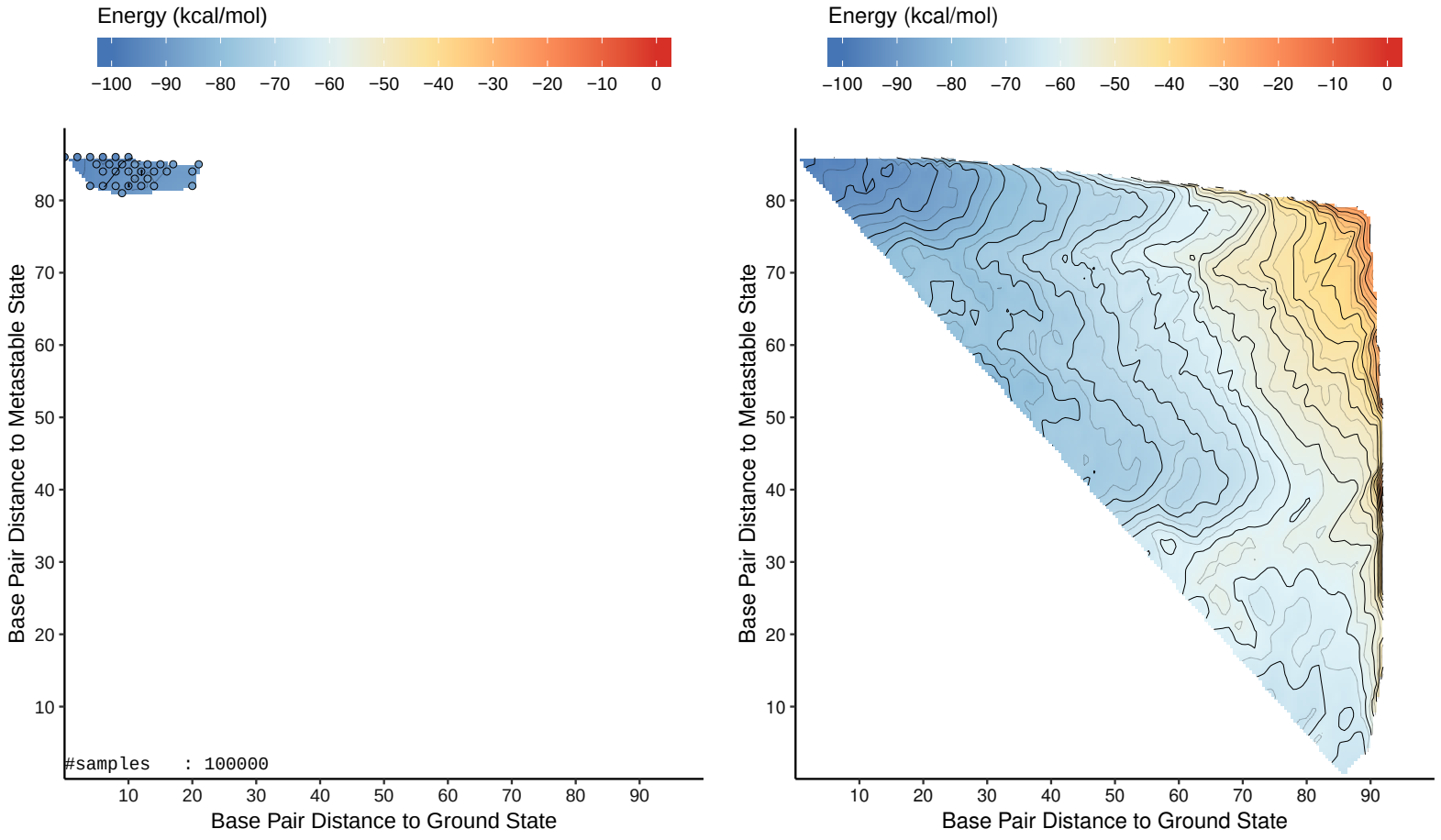


samples: 100, 000, # local minima: 72

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



samples: 100, 000, # local minima: 72

Example: Qβ replicase template SV11

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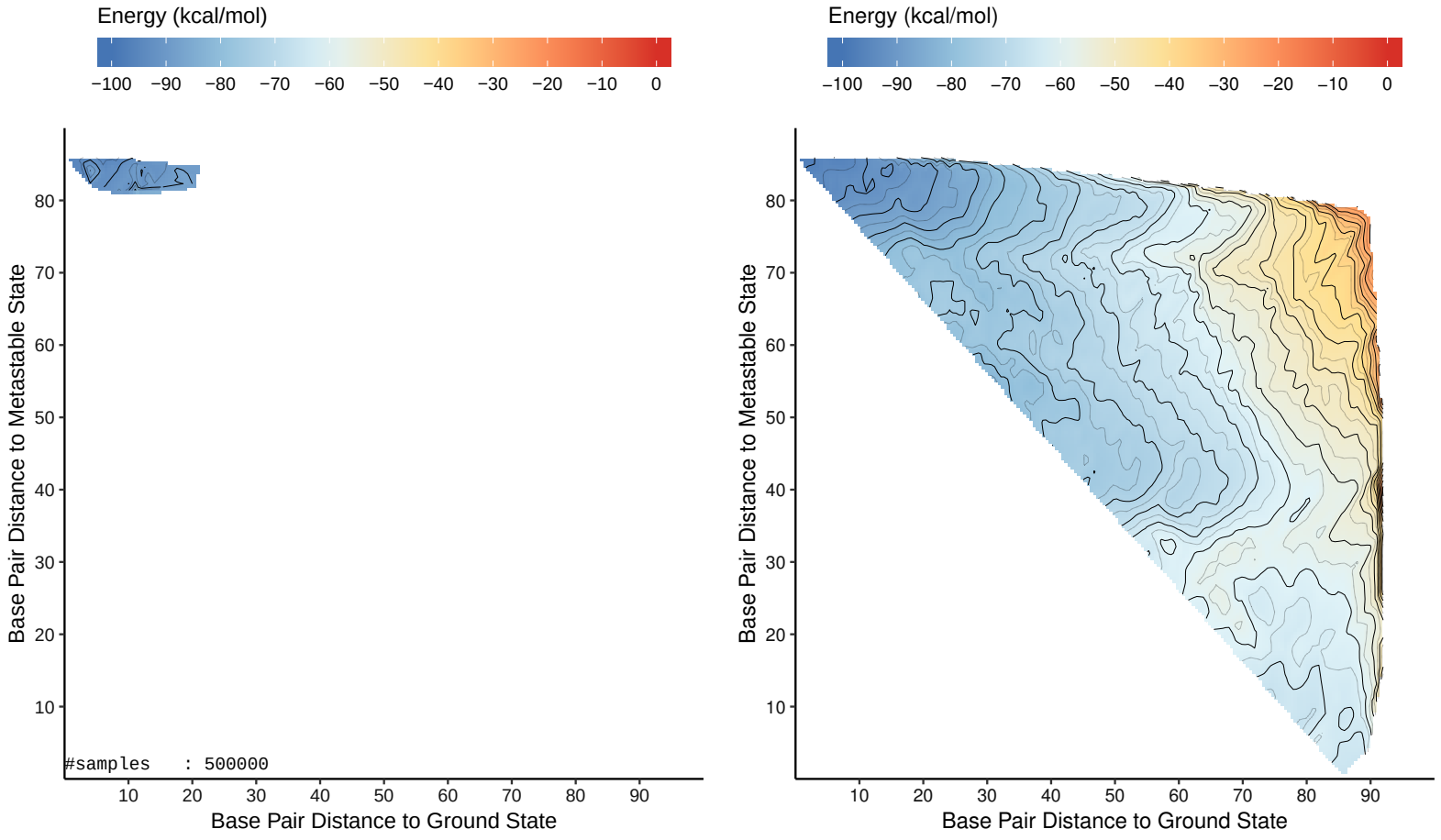
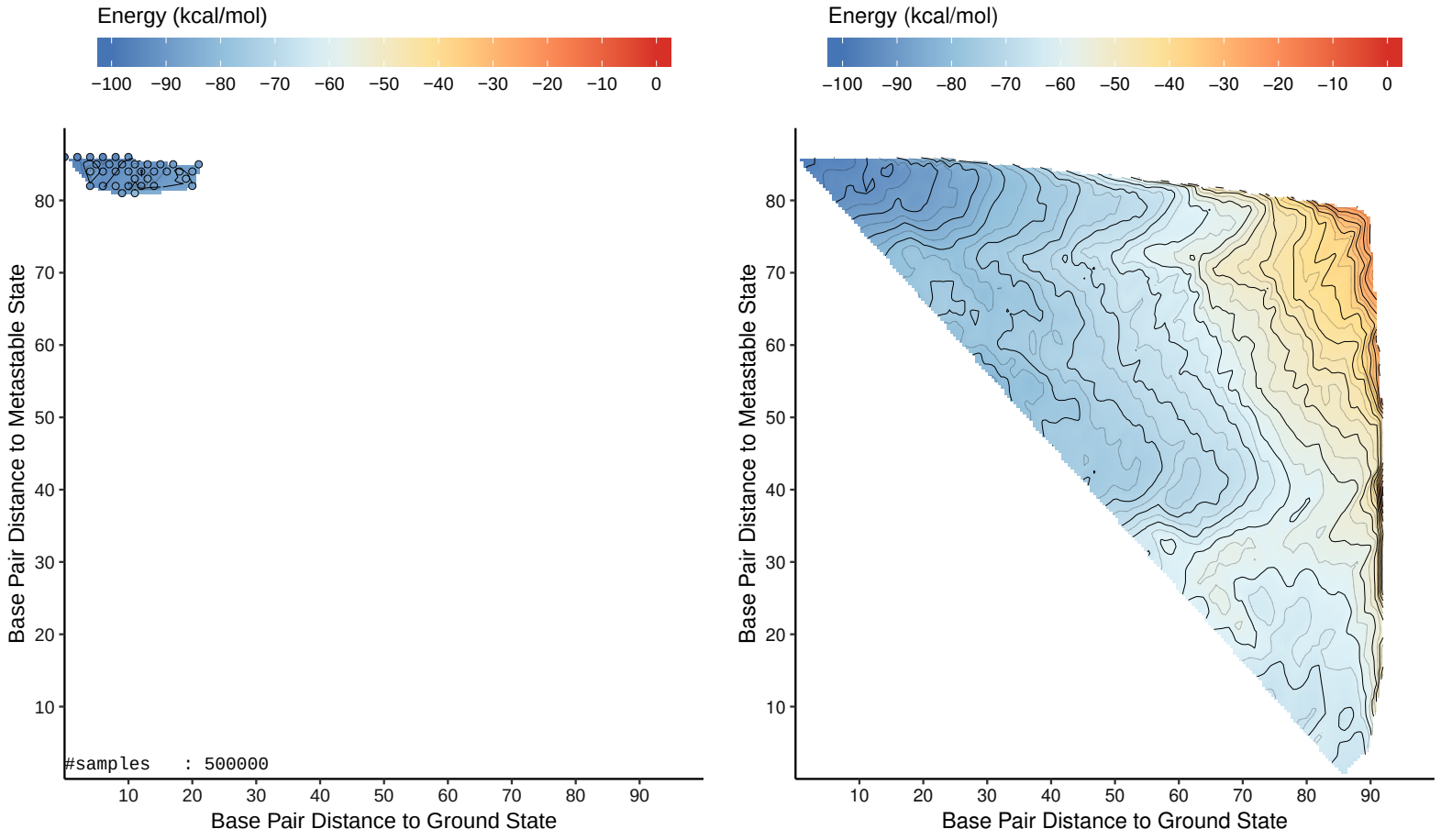


samples: 500, 000, # local minima: 107

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



samples: 500, 000, # local minima: 107

Example: Qβ replicase template SV11

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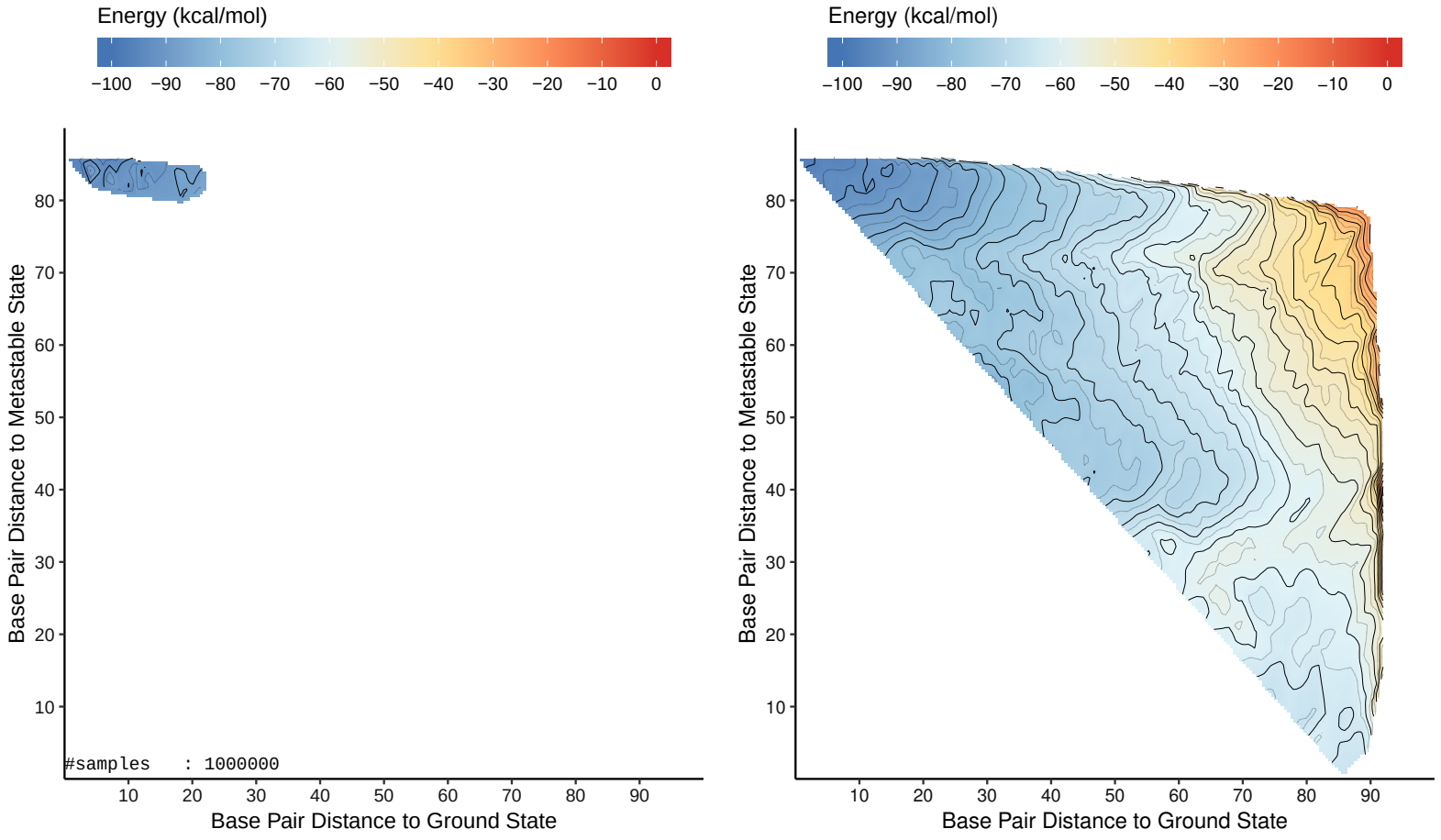
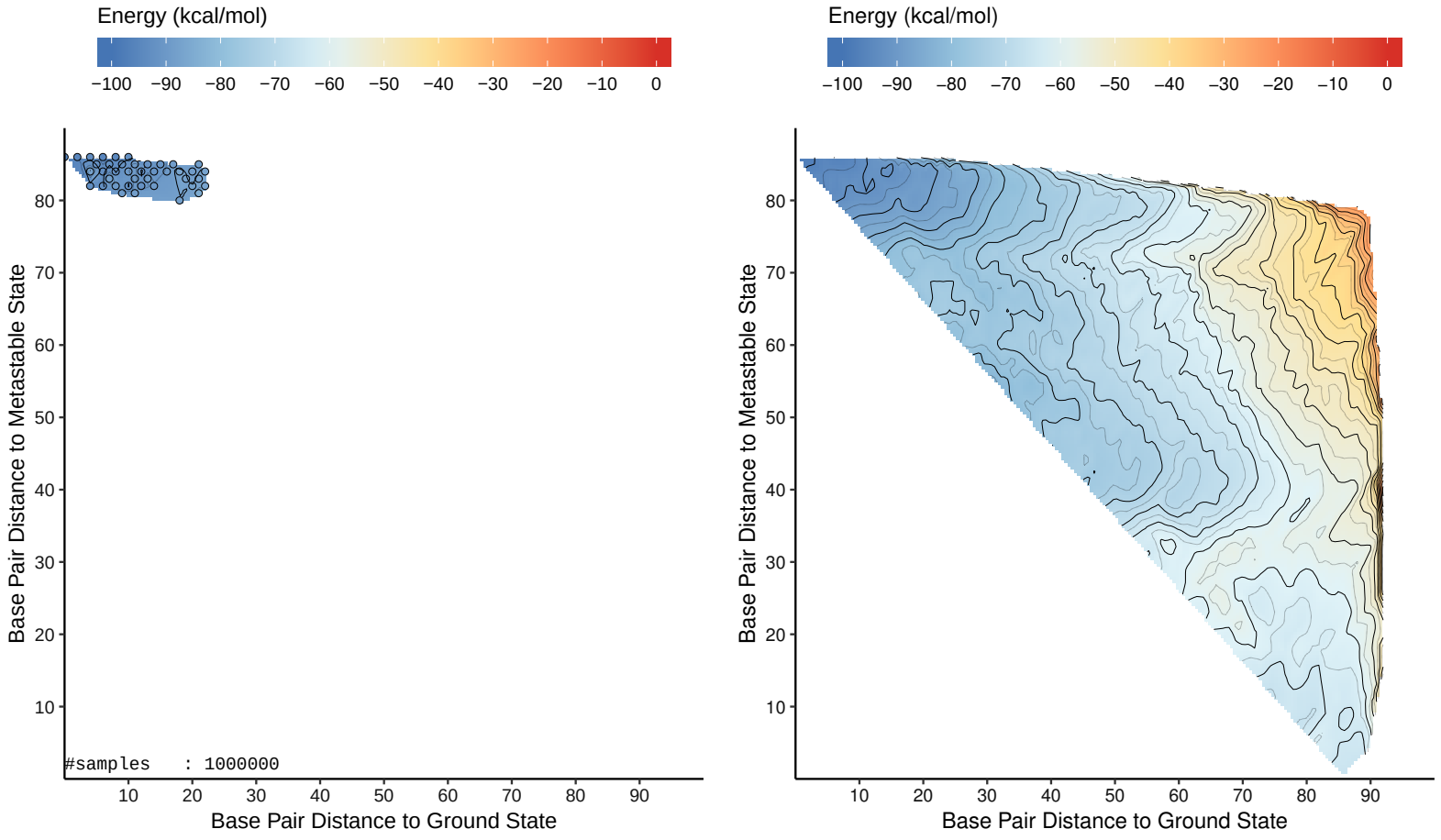


samples: $1,000,000$, # local minima: 130

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



samples: $1,000,000$, # local minima: 130

Example: Qβ replicase template SV11

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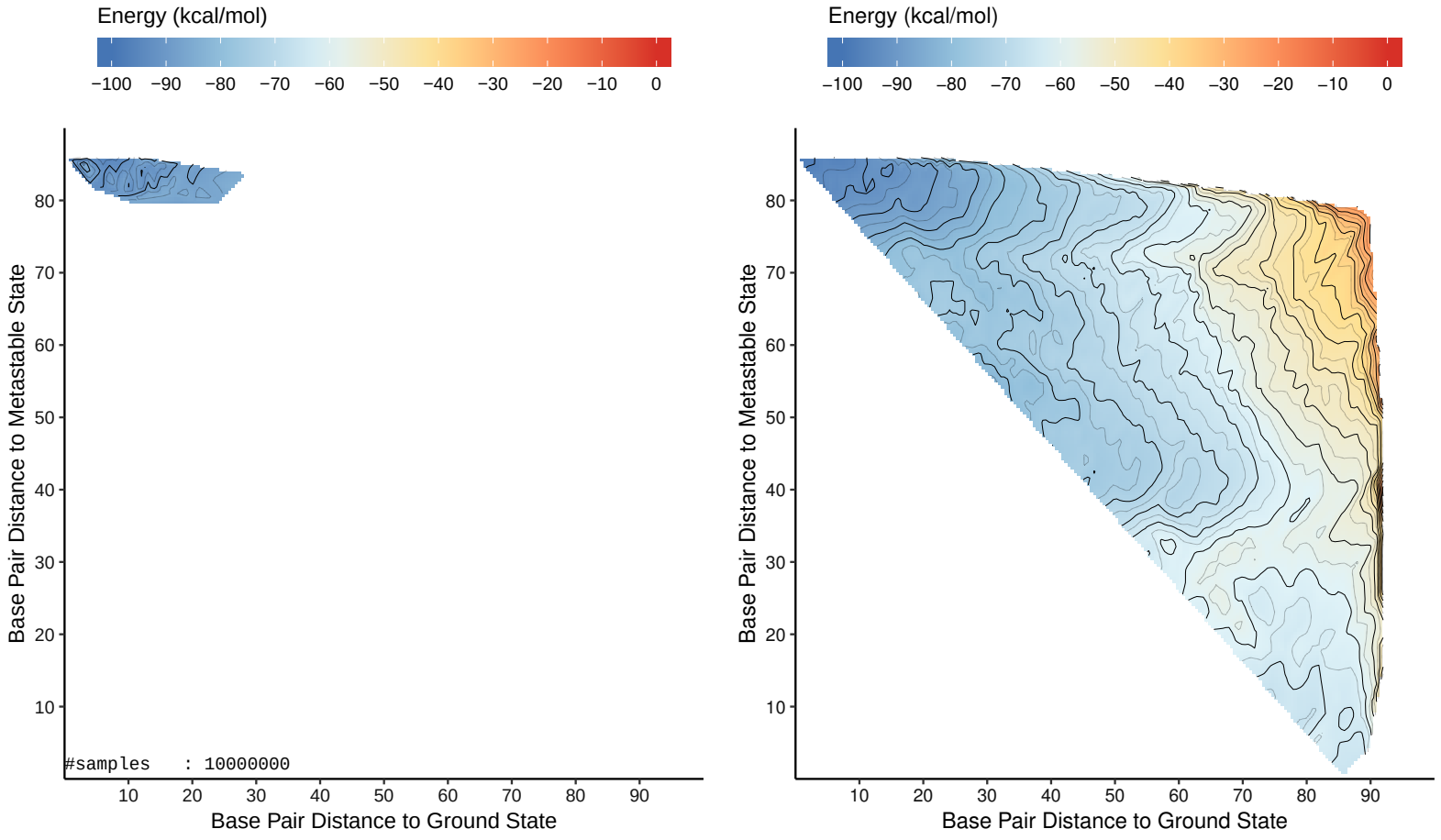

samples: $10,000,000$, # local minima: 272

Example: Qβ replicase template SV11

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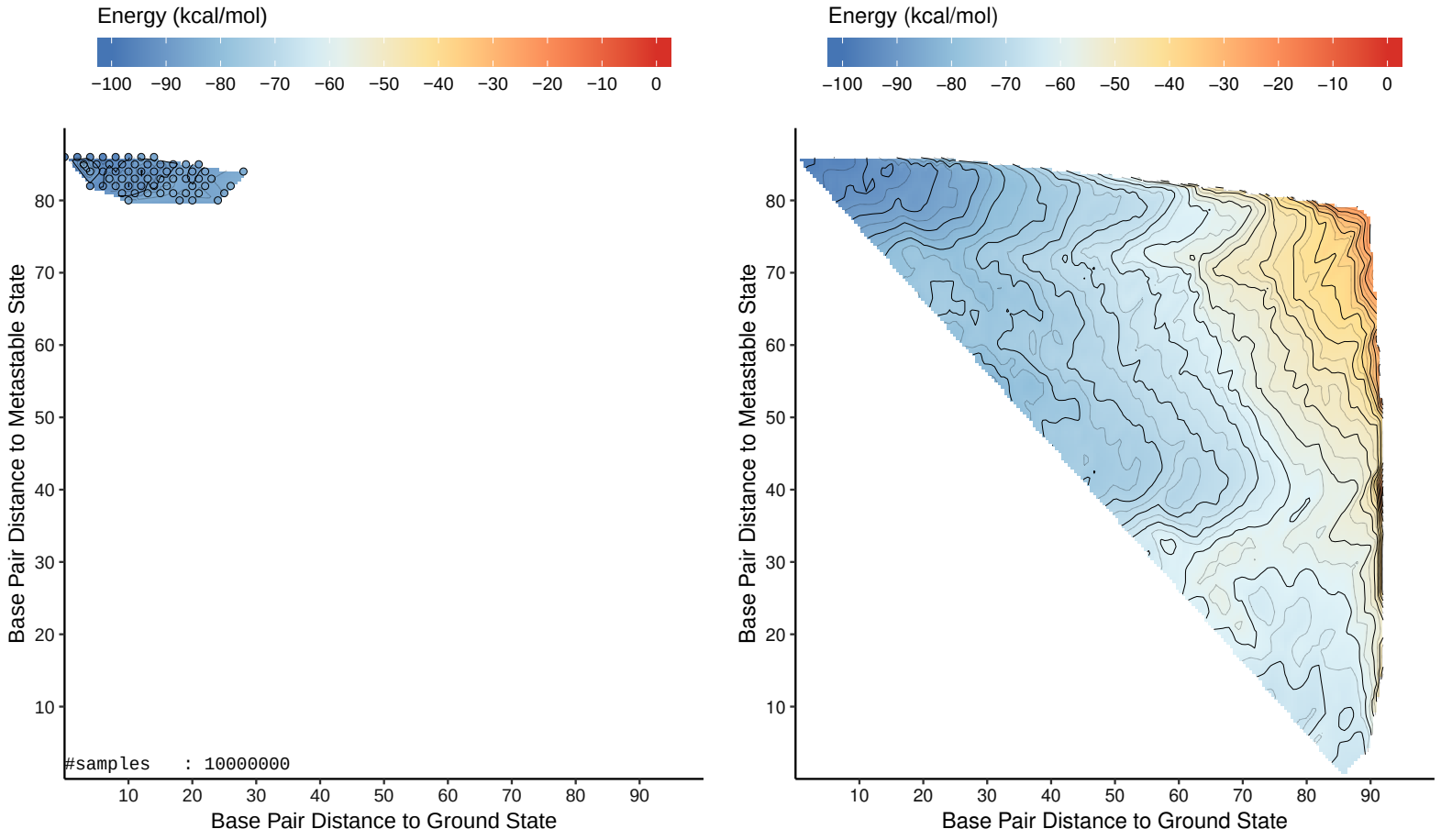
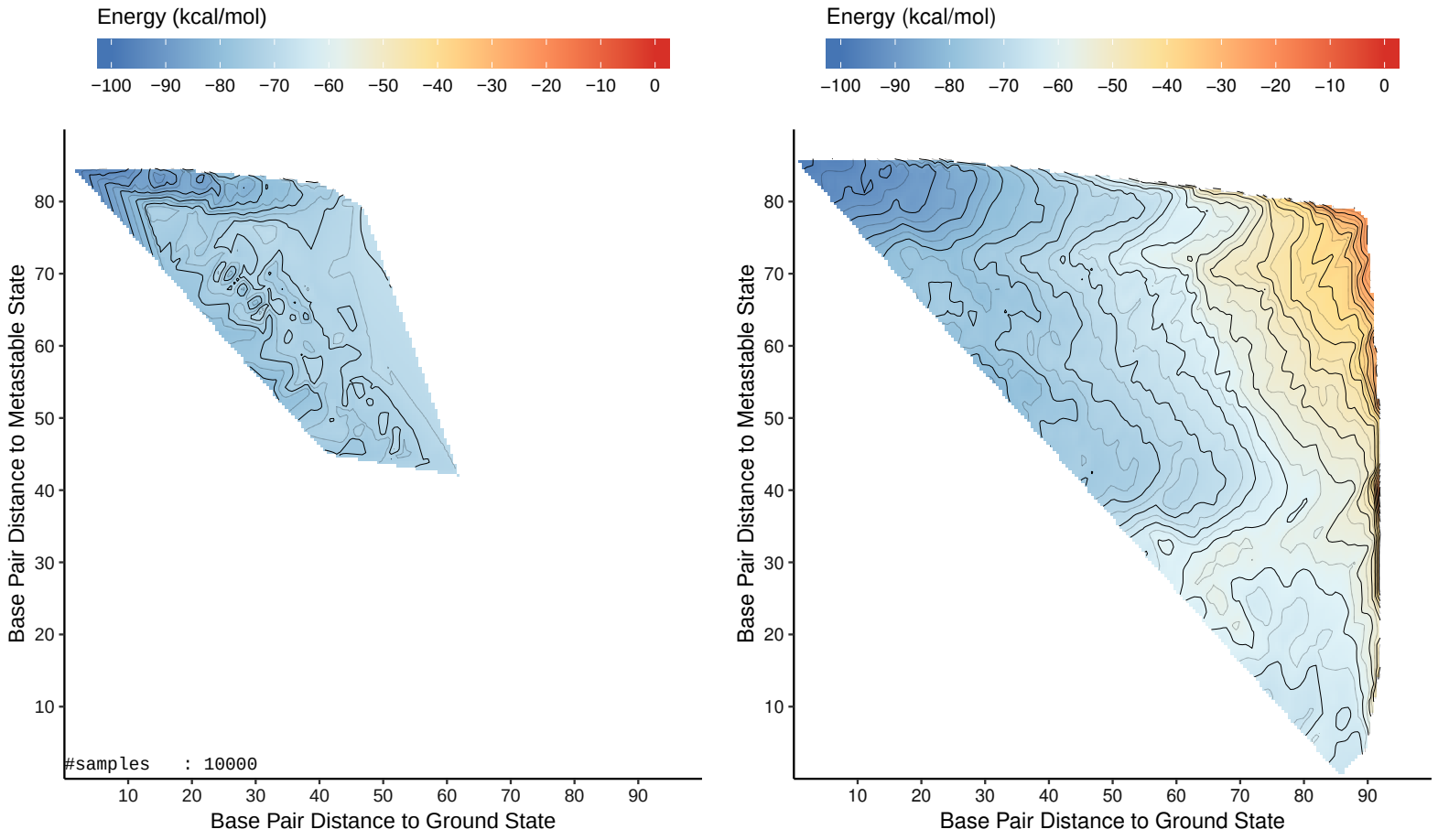


samples: $10,000,000$, # local minima: 272

Example: Qβ replicase template SV11

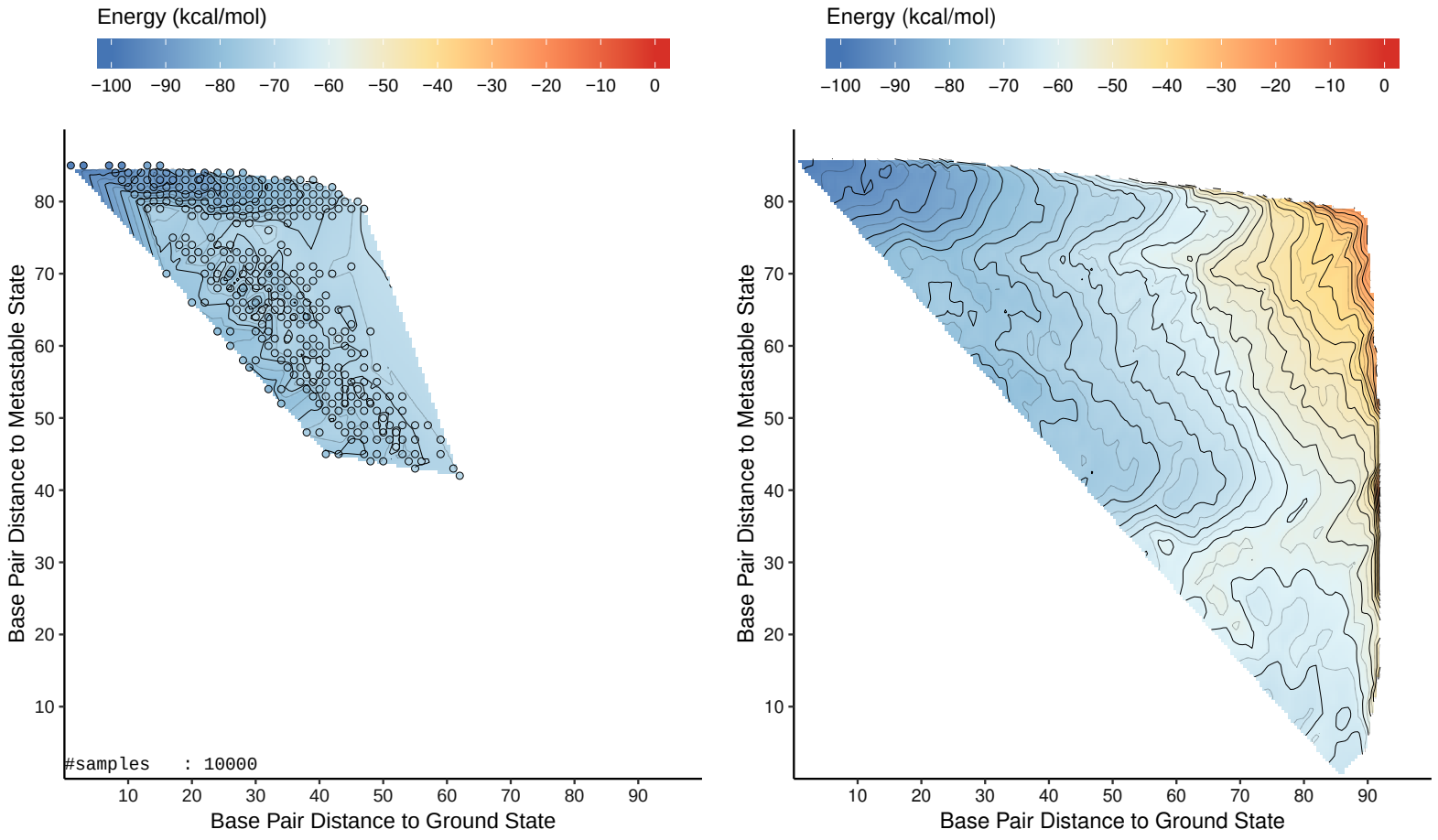
RNANR non-redundant Boltzmann sampling



samples: 10, 000, # local minima: 10, 000

Example: Qβ replicase template SV11

RNANR non-redundant Boltzmann sampling



samples: 10, 000, # local minima: 10, 000

Example: Qβ replicase template SV11

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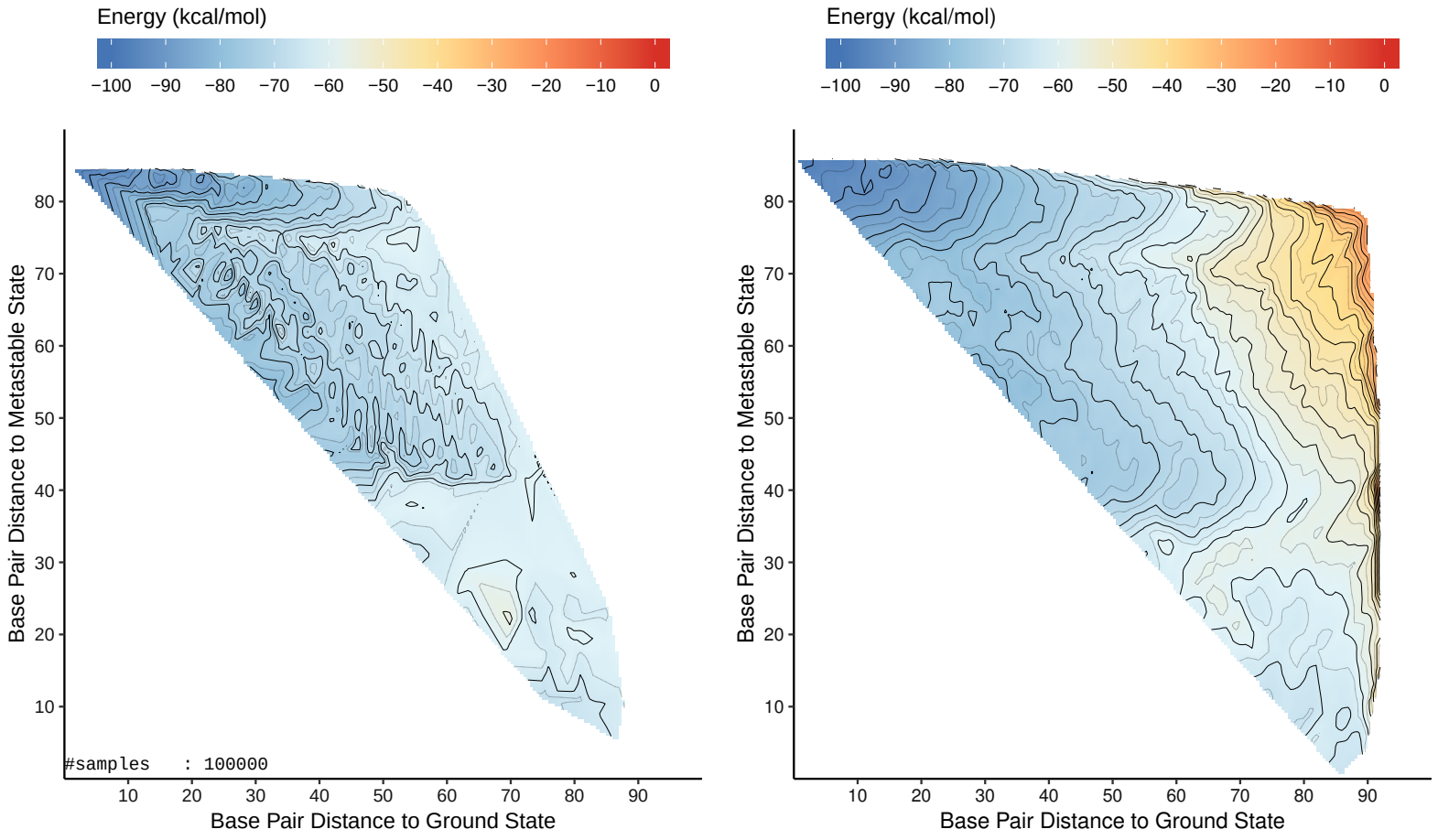

samples: 100, 000, # local minima: 100, 000

Example: Qβ replicase template SV11

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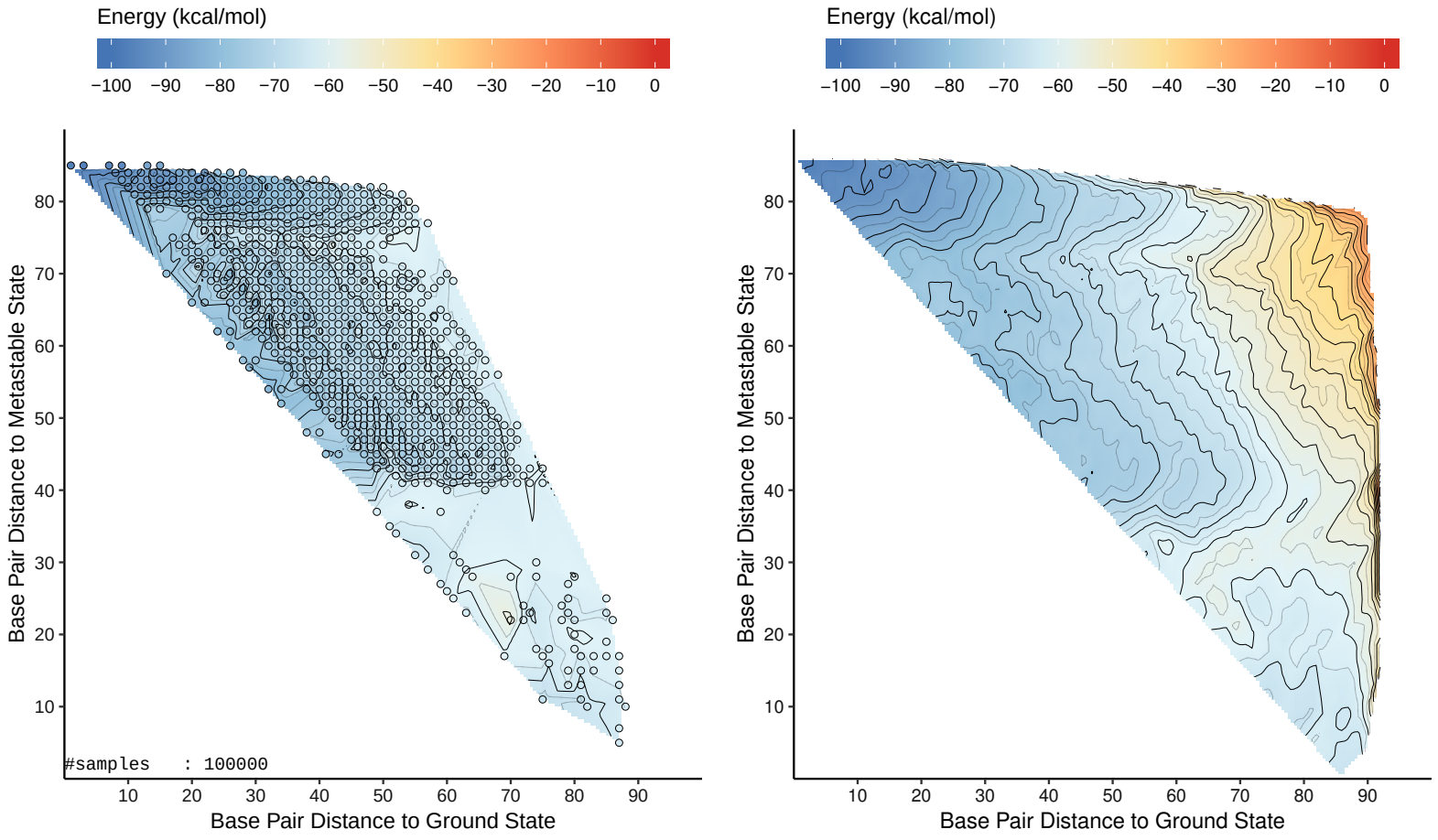
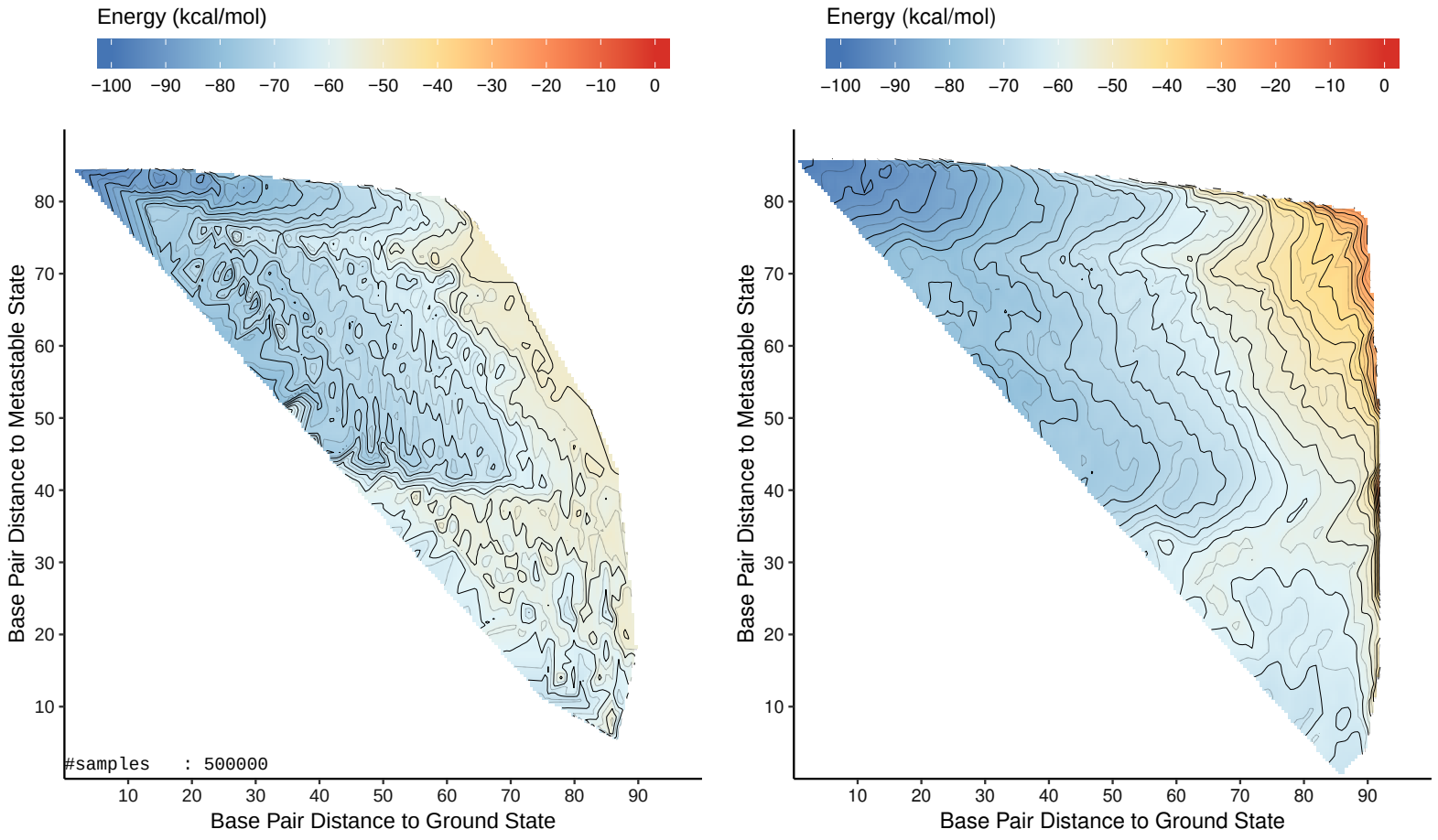


samples: 100, 000, # local minima: 100, 000

Example: Qβ replicase template SV11

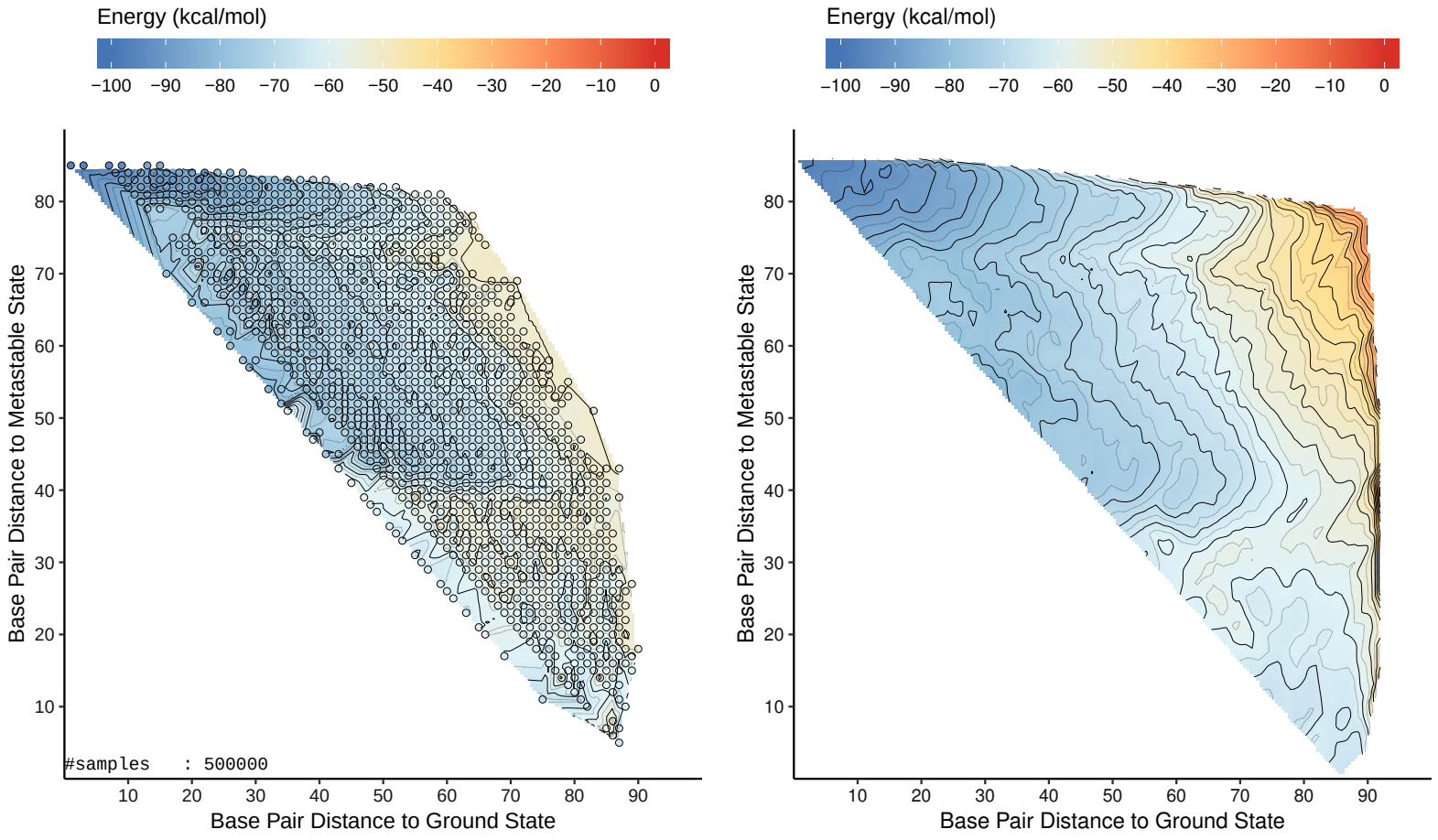
RNANR non-redundant Boltzmann sampling



samples: 500, 000, # local minima: 500, 000

Example: Qβ replicase template SV11

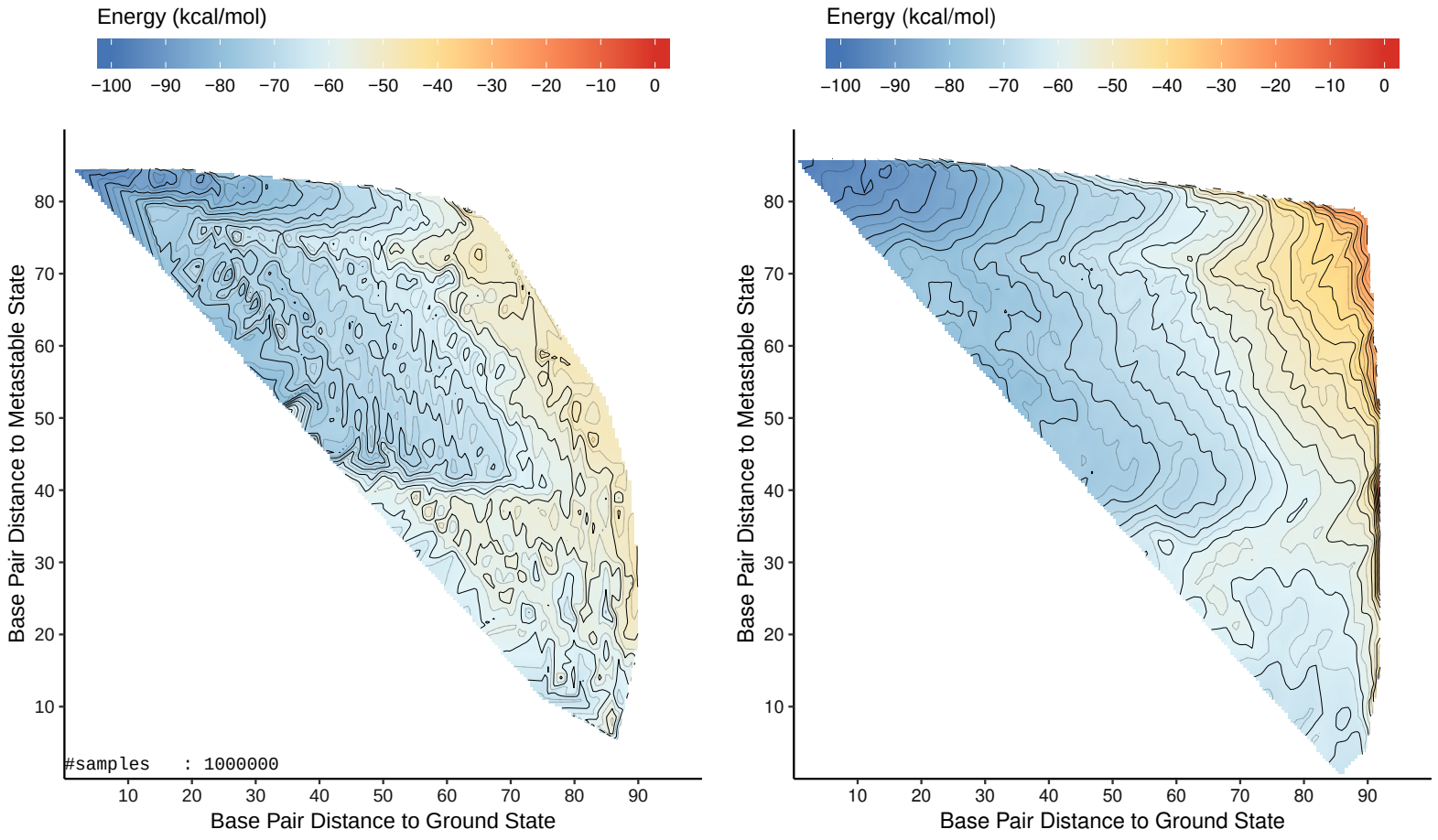
RNANR non-redundant Boltzmann sampling



samples: 500, 000, # local minima: 500, 000

Example: Qβ replicase template SV11

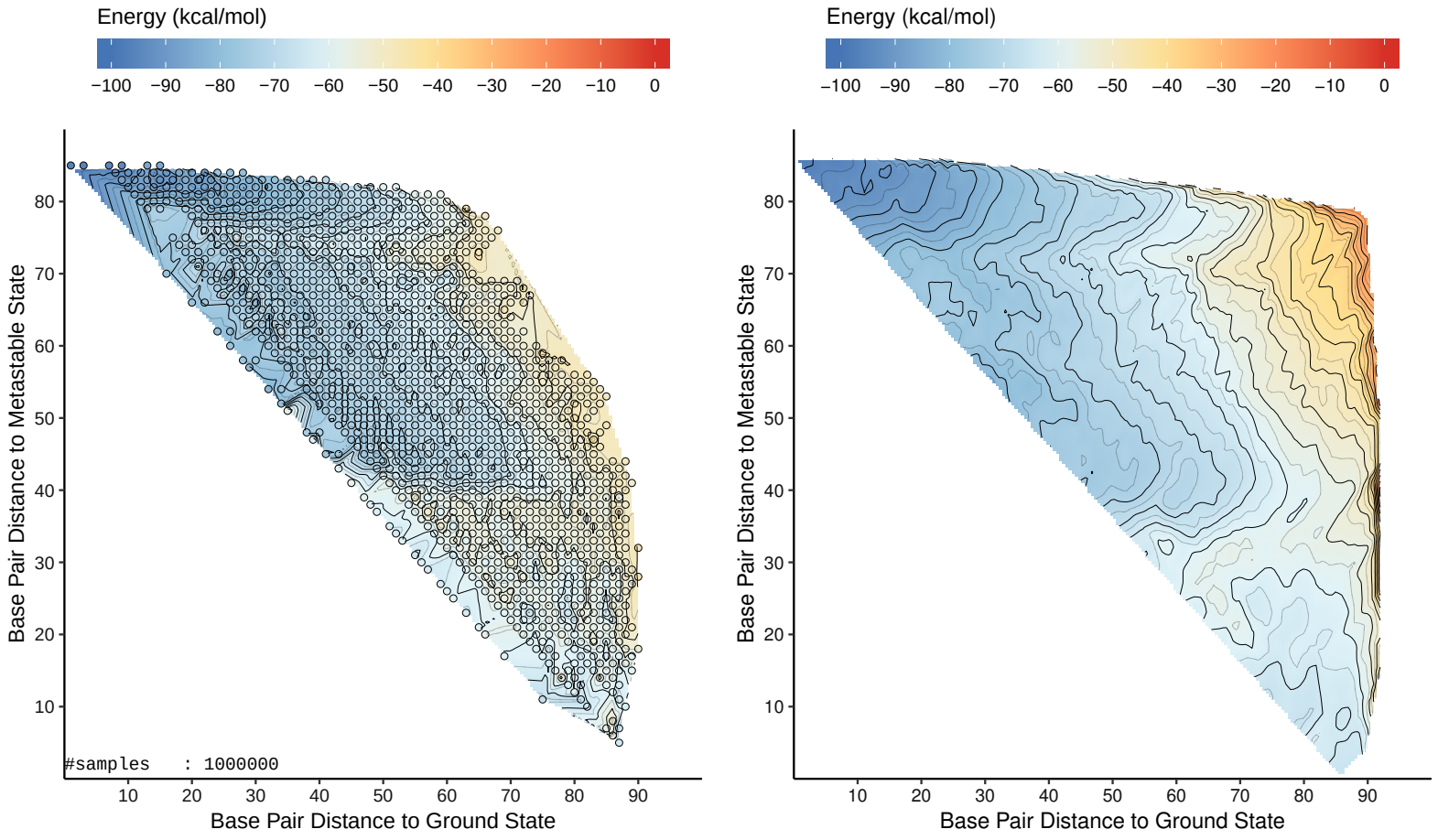
RNANR non-redundant Boltzmann sampling



samples: 1, 000, 000, # local minima: 1, 000, 000

Example: Qβ replicase template SV11

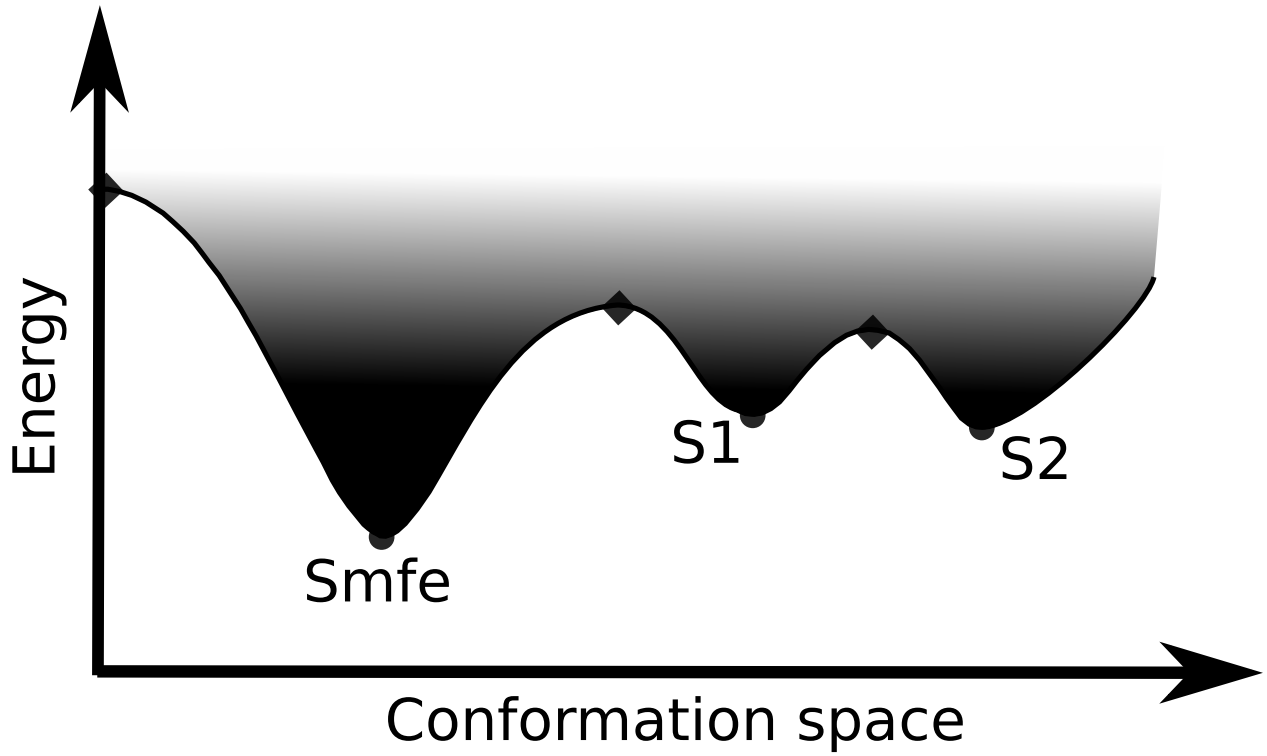
RNANR non-redundant Boltzmann sampling



samples: 1, 000, 000, # local minima: 1, 000, 000

Sampling Strategies

4. Elevated Temperature Boltzmann Sampling



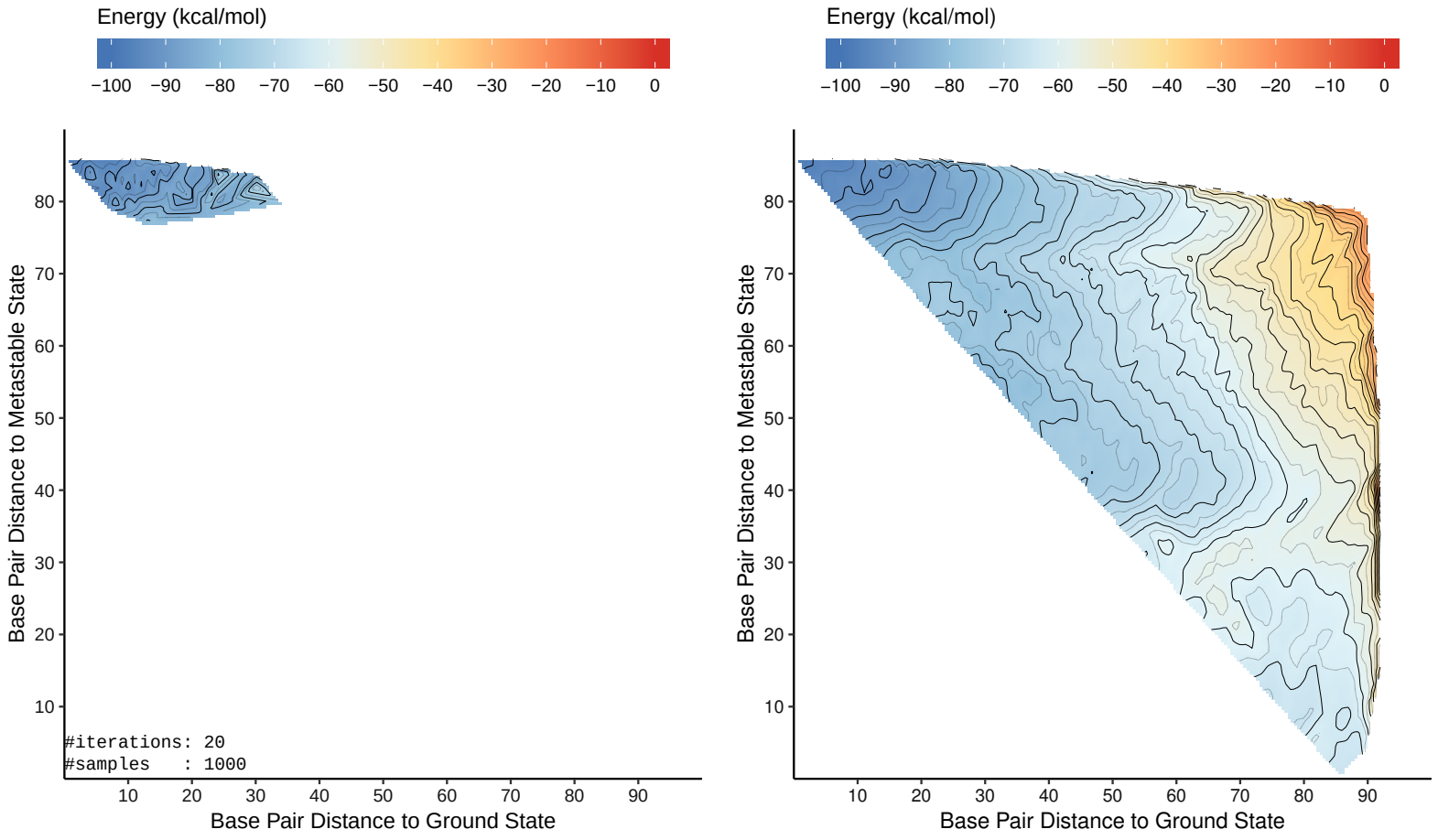
`RNAlocmin`[11]:

- reminder: $p(s) = e^{-E(s)/RT} / \sum_{x \in \Omega} e^{-E(x)/RT}$
- iteratively draw samples at different $T = \xi \cdot T_0, \xi > 1$
- $T \to \infty$: uniform distribution

[11] Kucharik et al. 2014

Example: Qβ replicase template SV11

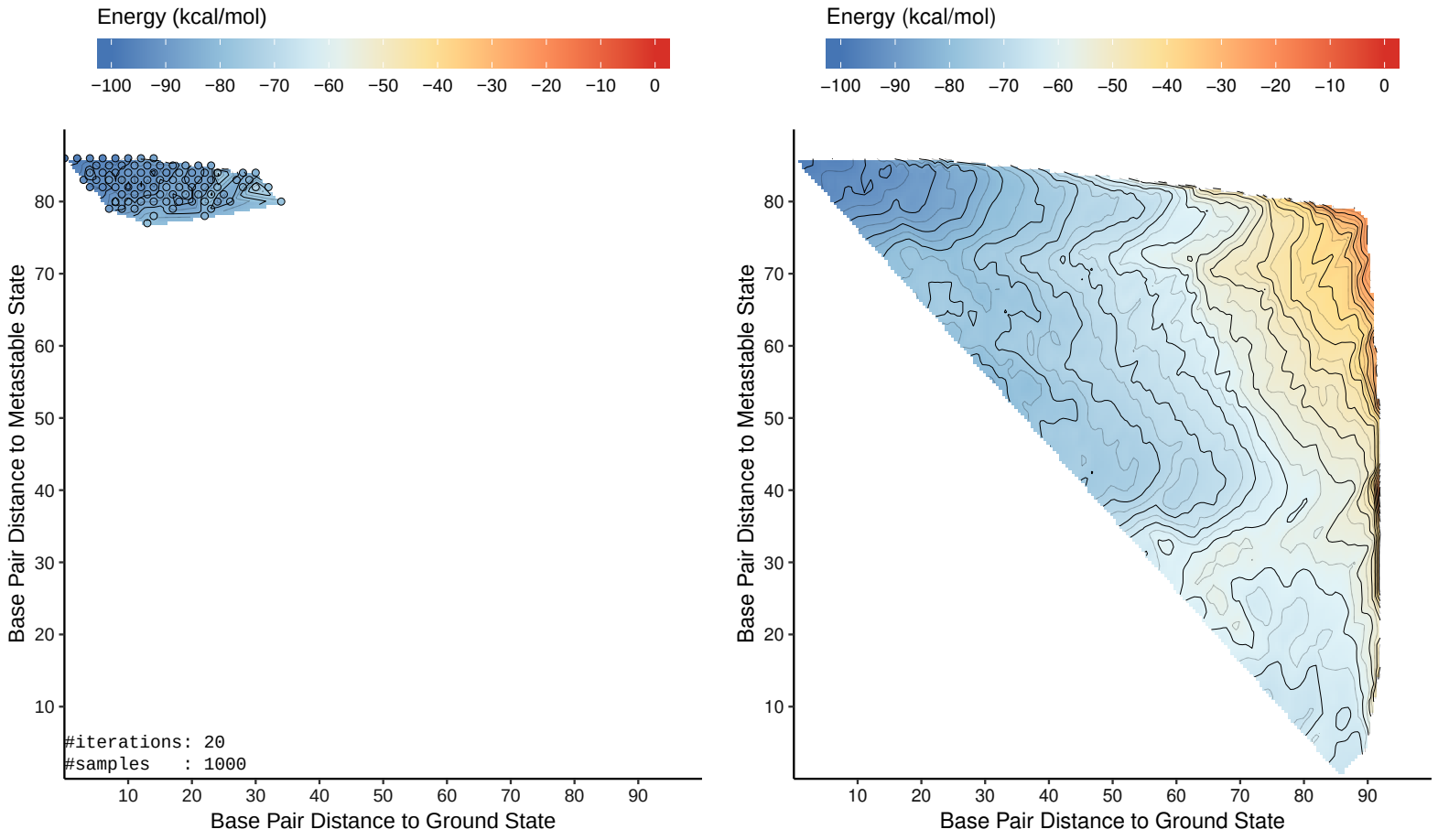
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 20, # samples: 1,000, # local minima: 528

Example: Qβ replicase template SV11

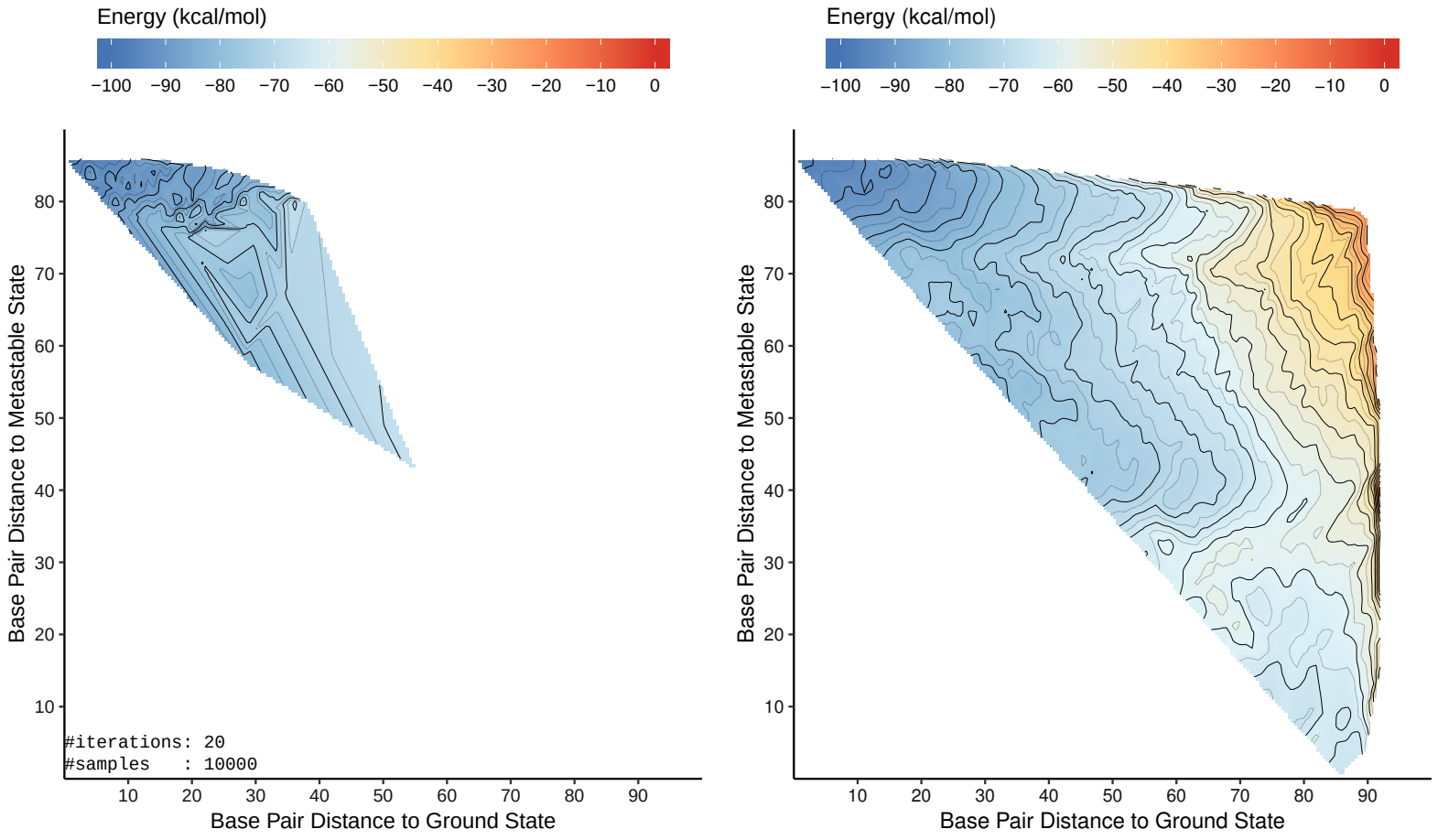
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 20, # samples: 1,000, # local minima: 528

Example: Qβ replicase template SV11

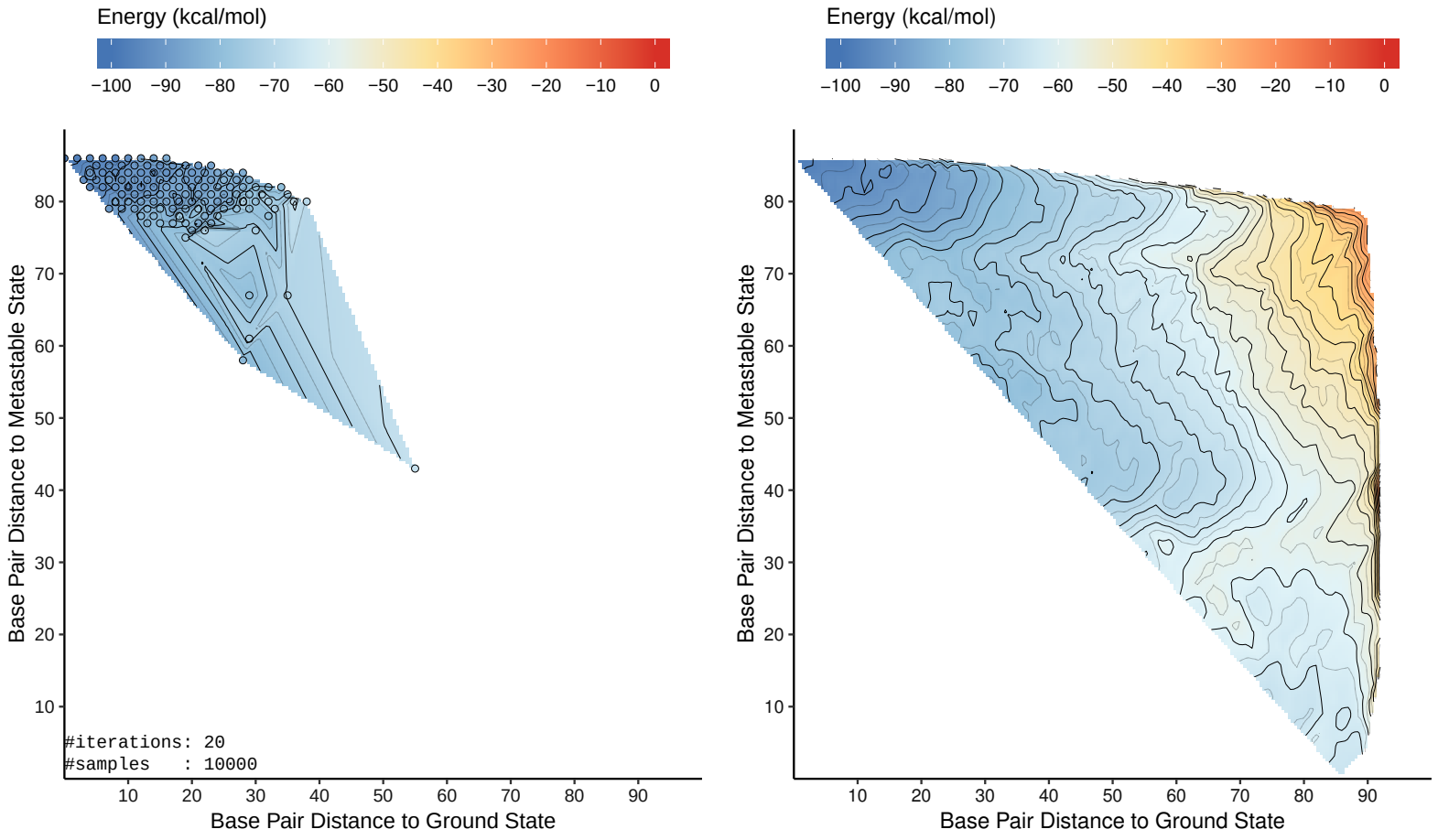
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 20, # samples: 10,000, # local minima: 2,283

Example: Qβ replicase template SV11

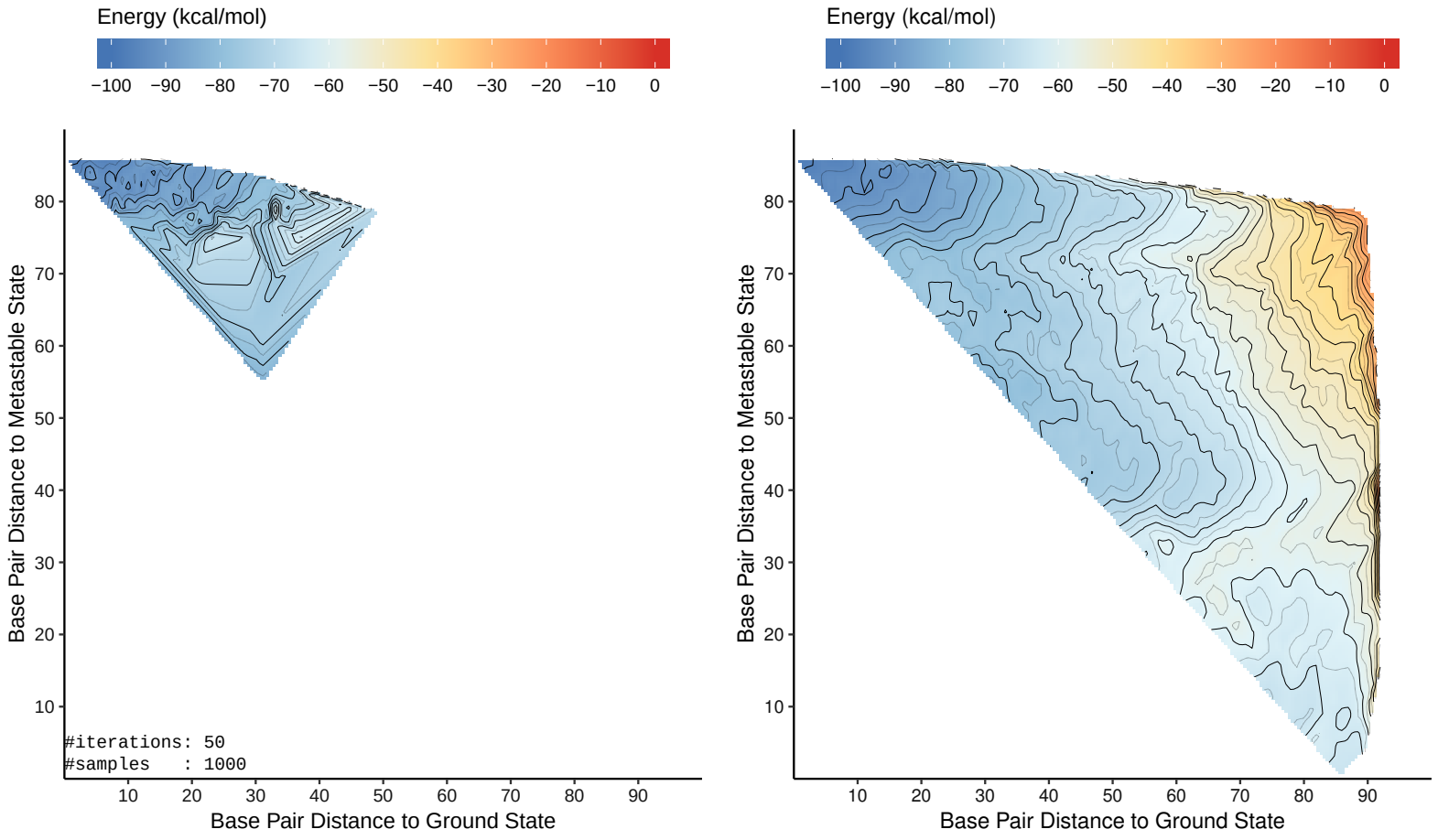
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 20, # samples: 10,000, # local minima: 2,283

Example: Qβ replicase template SV11

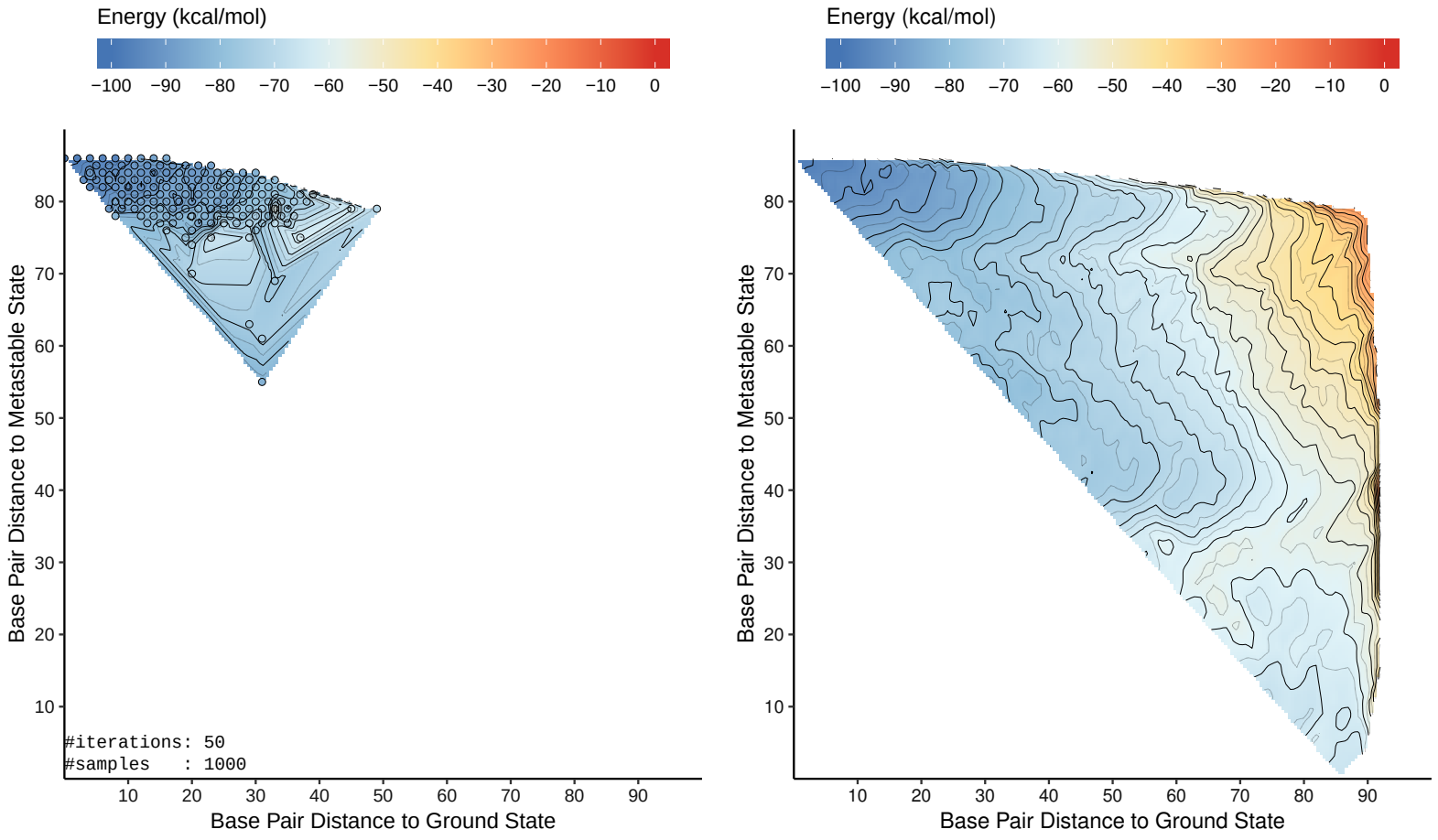
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 50, # samples: 1,000, # local minima: 2,669

Example: Qβ replicase template SV11

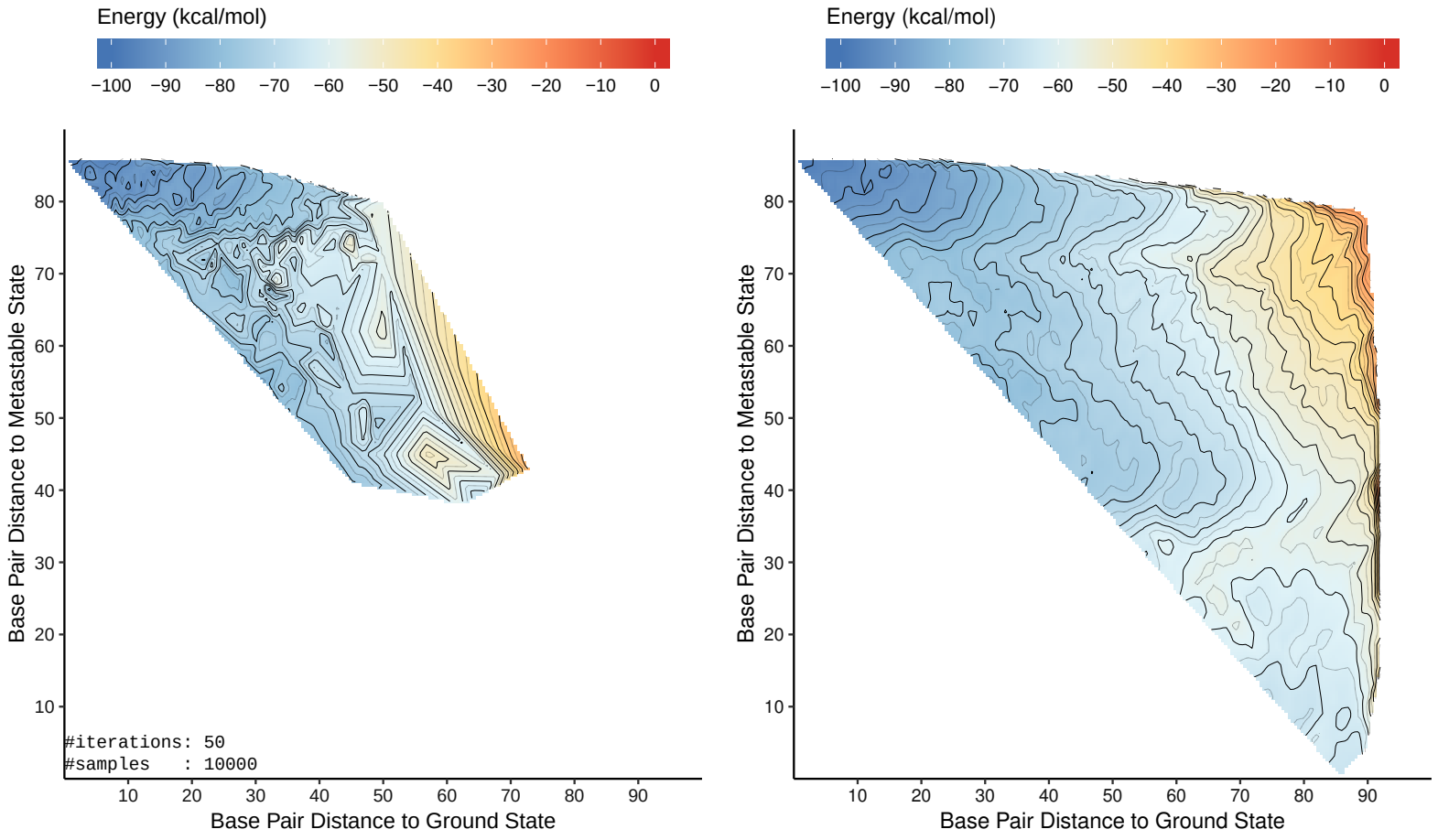
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 50, # samples: 1,000, # local minima: 2,669

Example: Qβ replicase template SV11

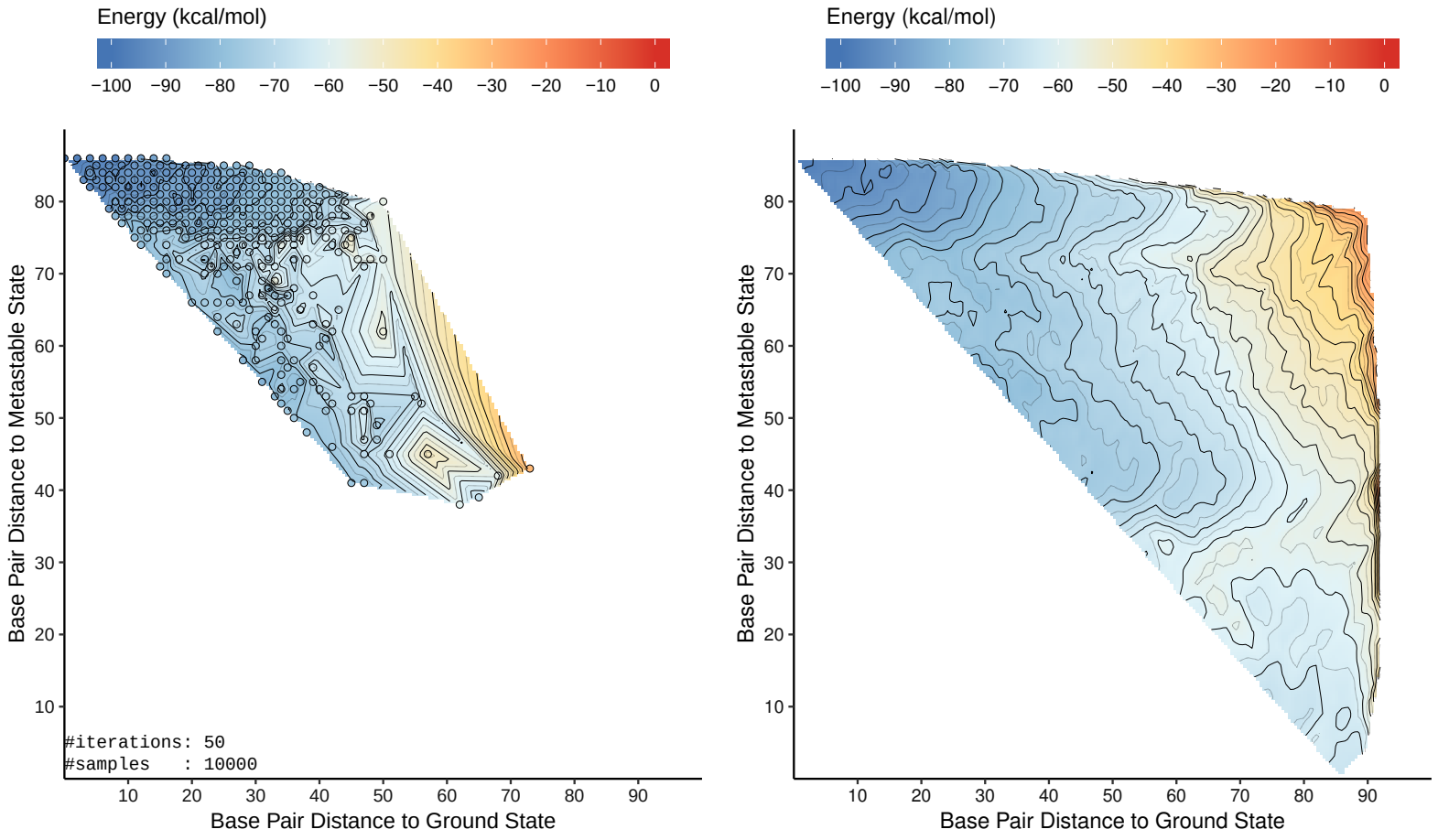
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 50, # samples: 10,000, # local minima: 14,092

Example: Qβ replicase template SV11

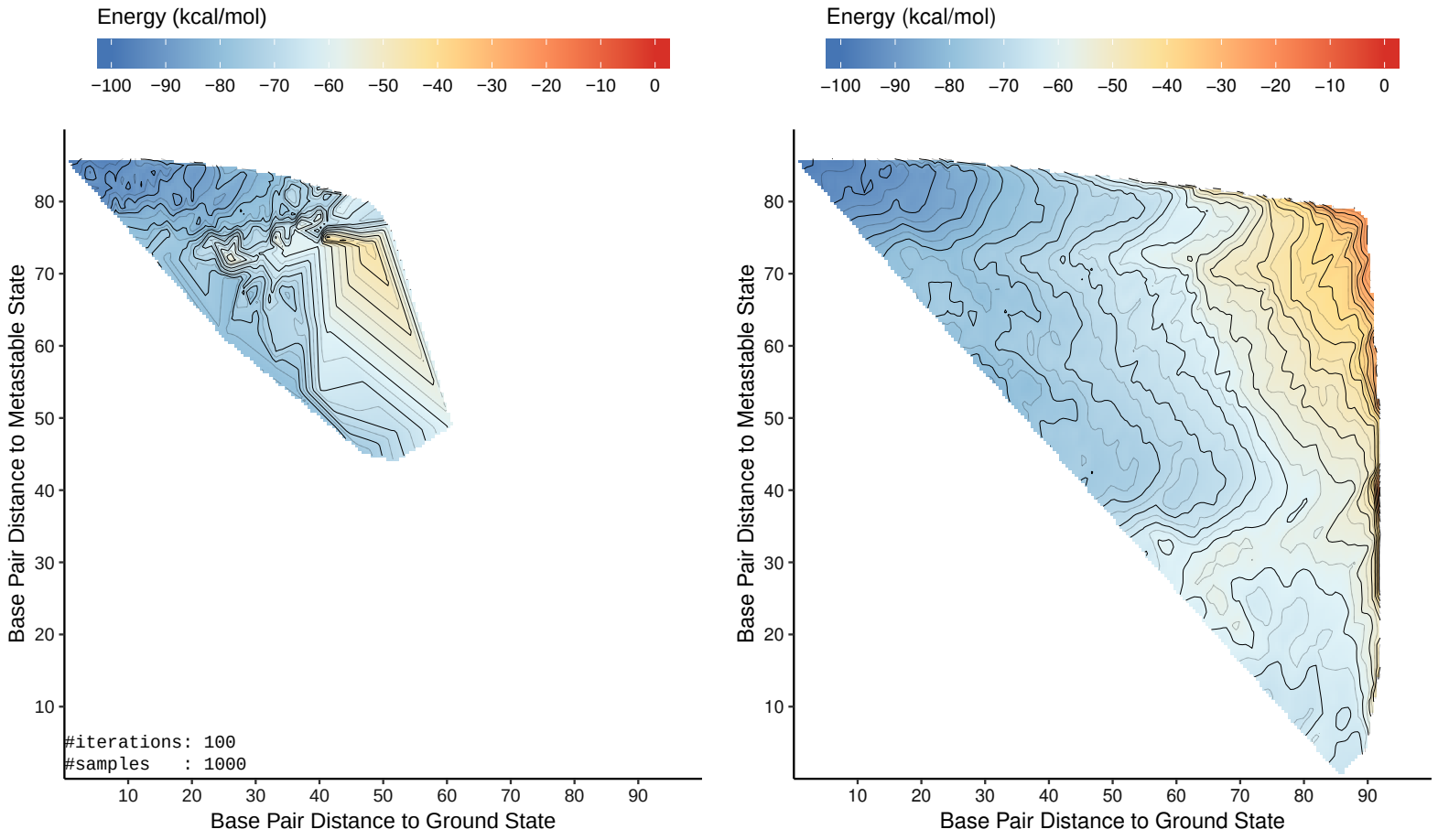
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 50, # samples: 10,000, # local minima: 14,092

Example: Qβ replicase template SV11

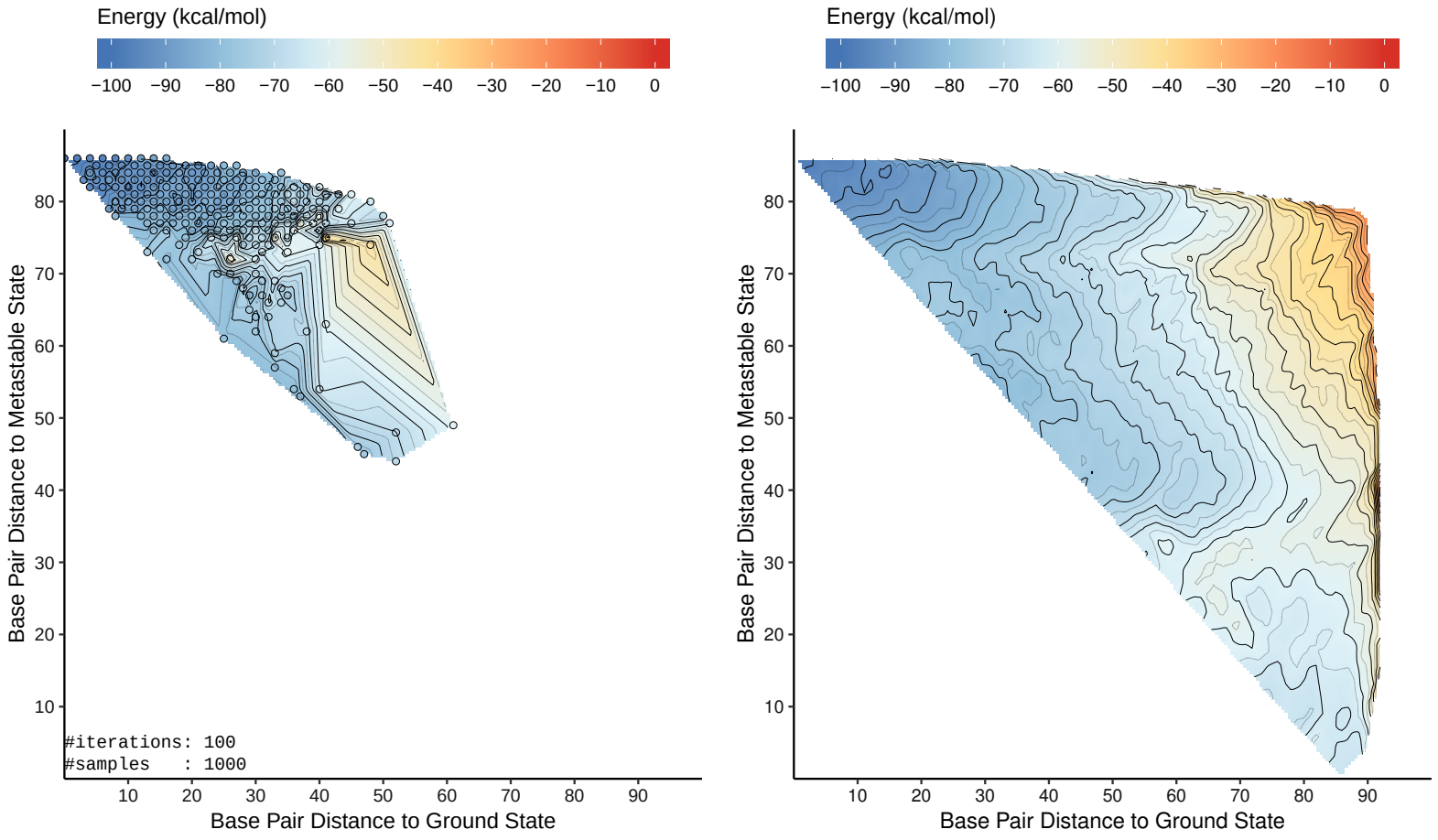
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 100, # samples: 1,000, # local minima: 6,422

Example: Qβ replicase template SV11

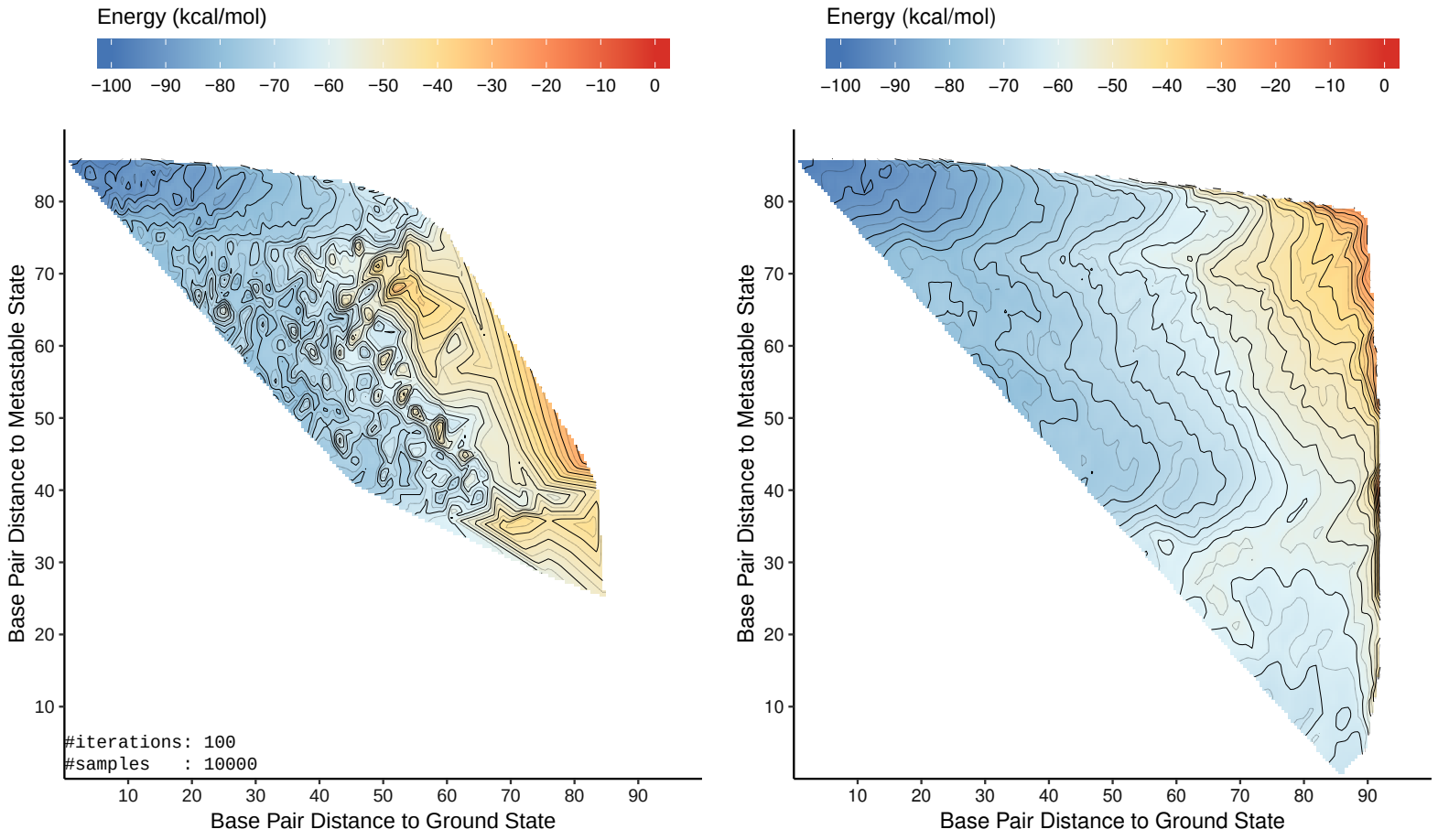
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 100, # samples: 1,000, # local minima: 6,422

Example: Qβ replicase template SV11

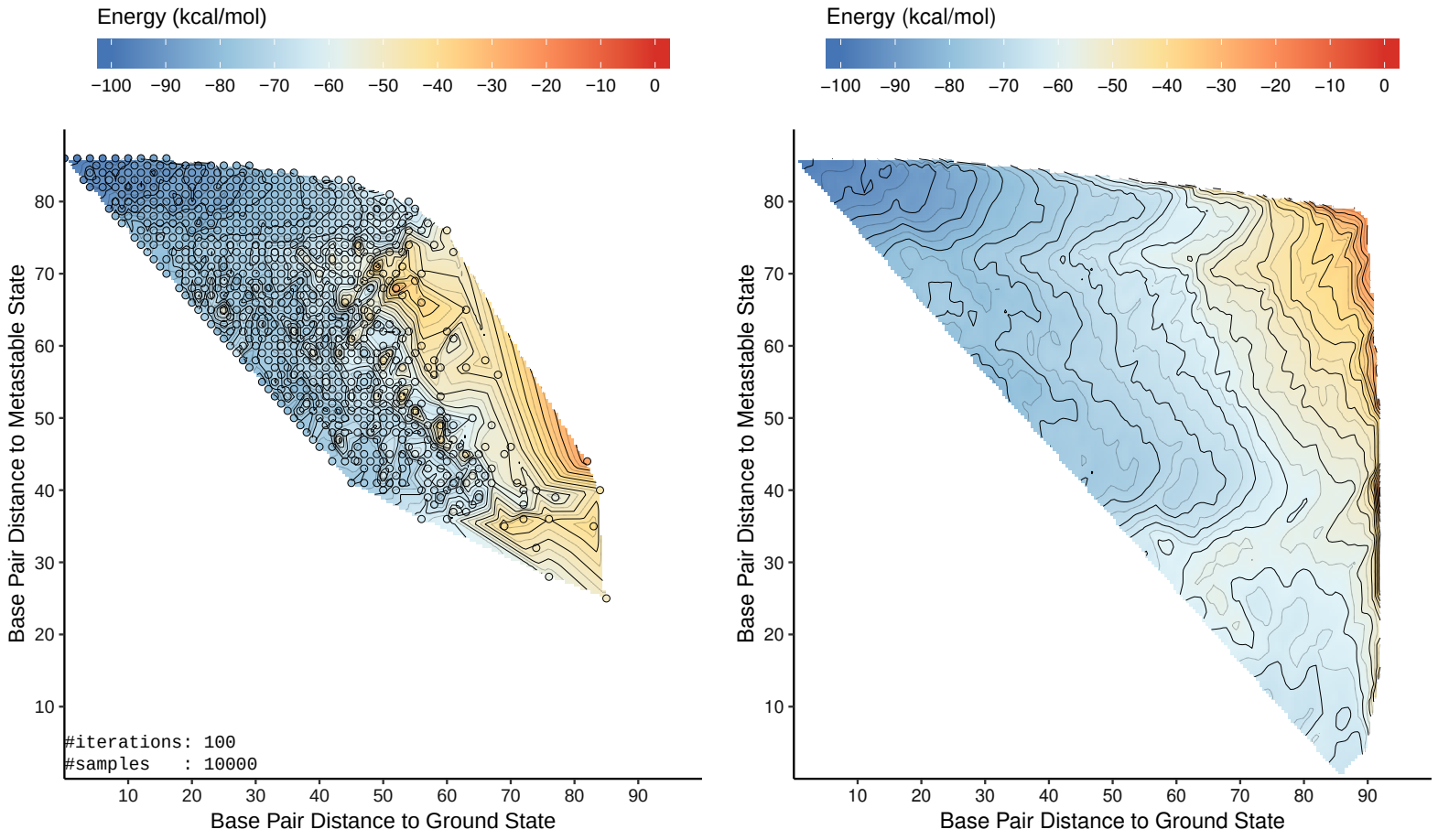
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 100, # samples: 10,000, # local minima: 51,470

Example: Qβ replicase template SV11

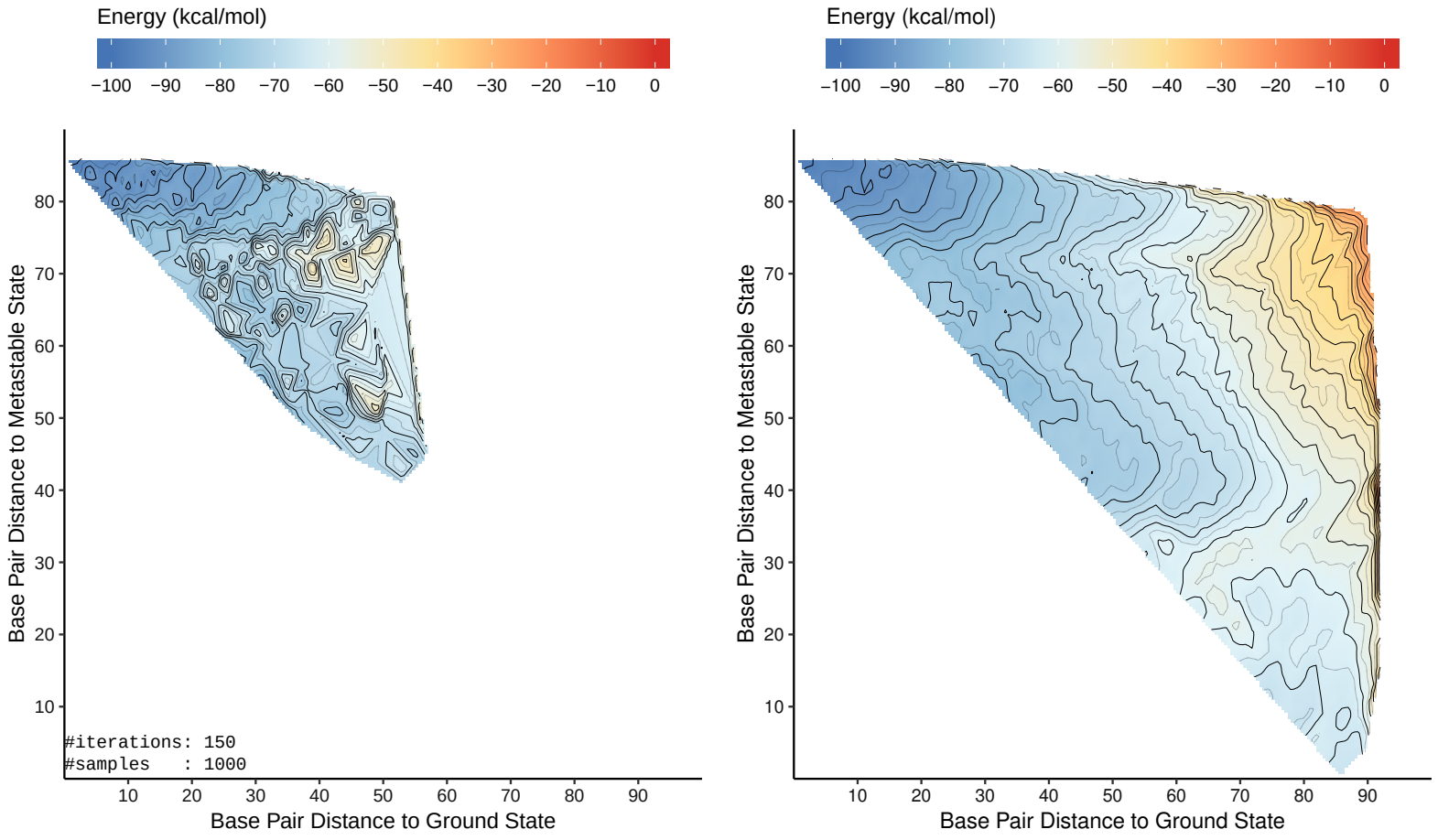
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 100, # samples: 10,000, # local minima: 51,470

Example: Qβ replicase template SV11

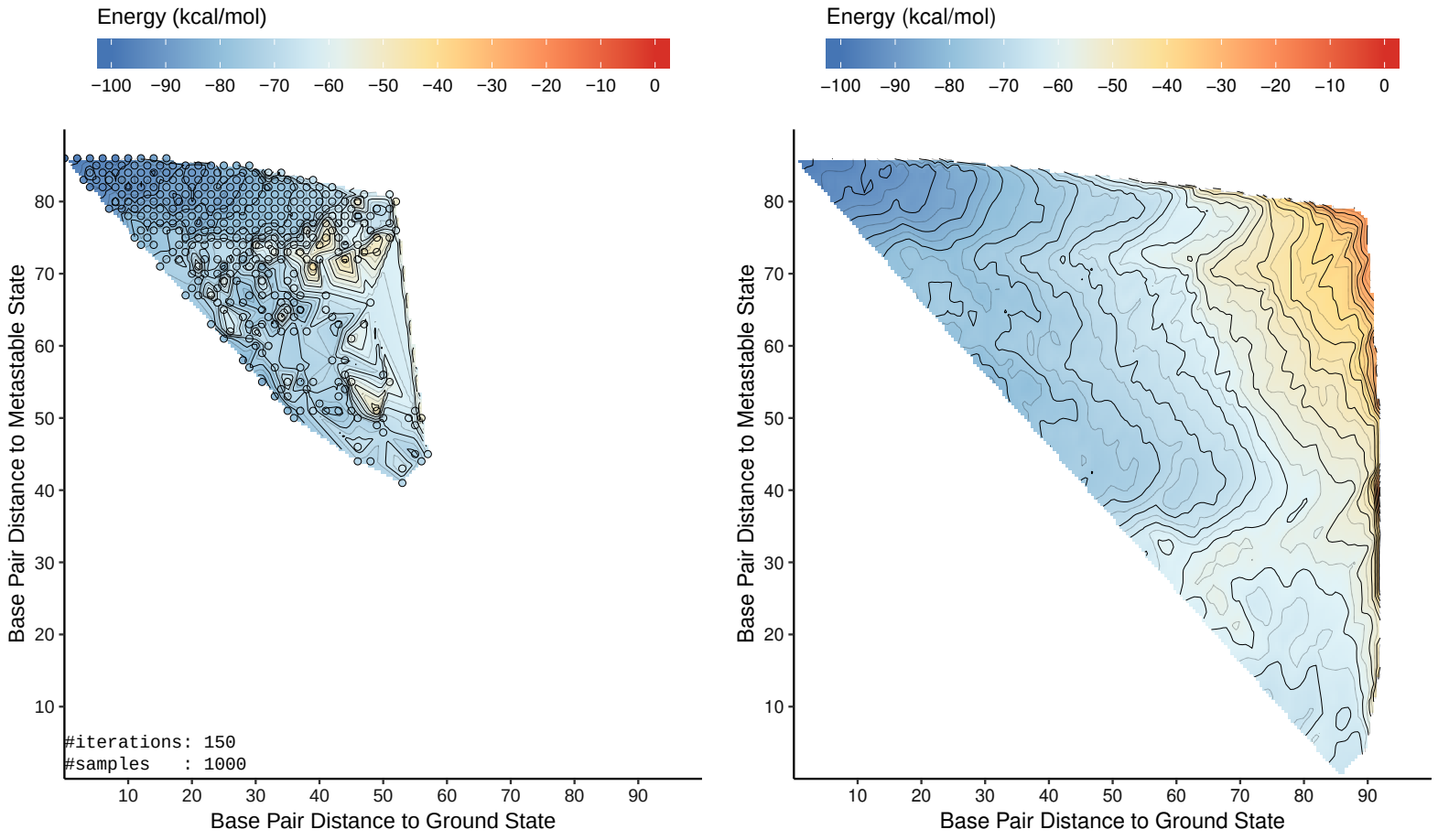
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 150, # samples: 1,000, # local minima: 12,741

Example: Qβ replicase template SV11

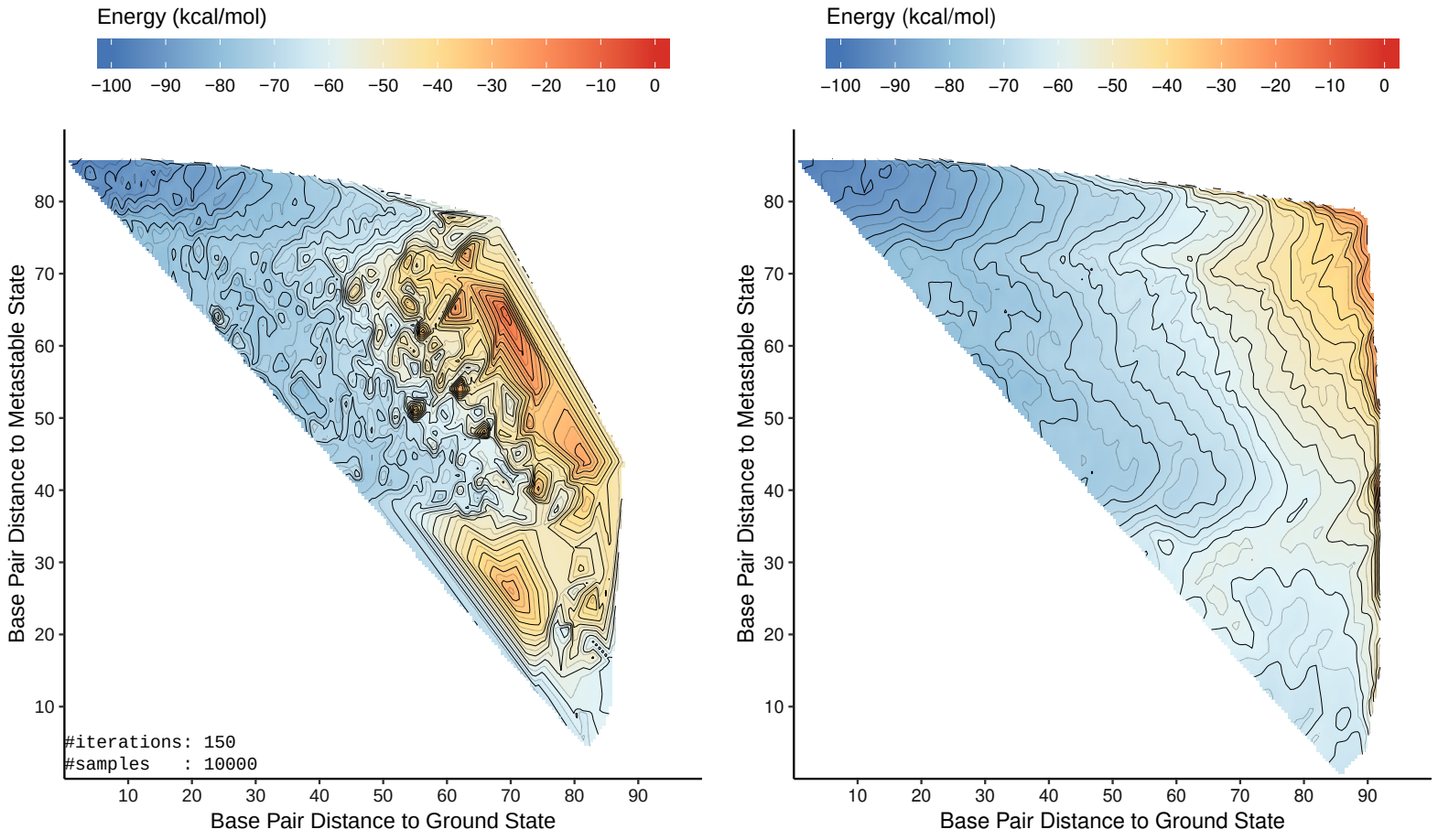
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 150, # samples: 1,000, # local minima: 12,741

Example: Qβ replicase template SV11

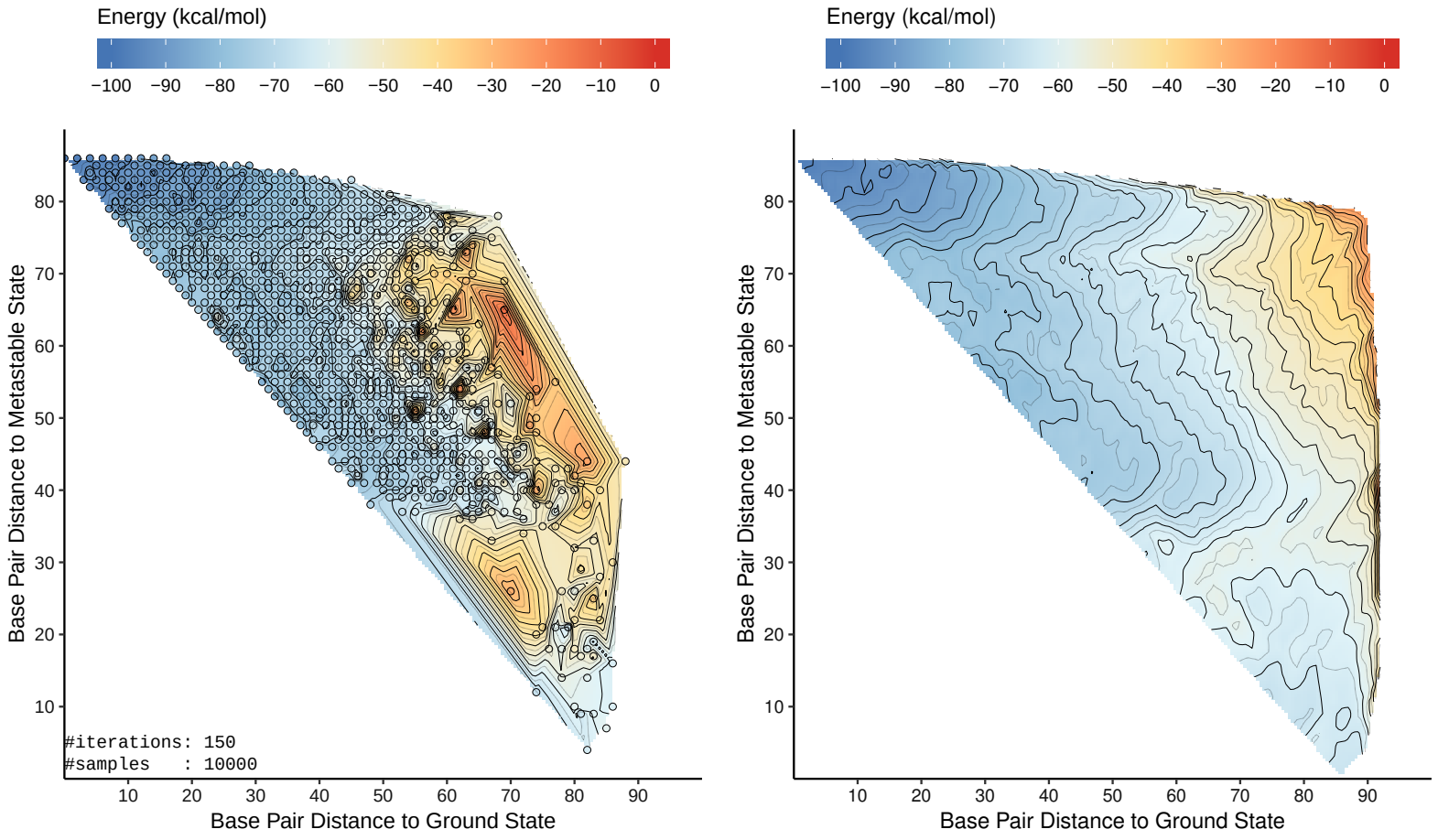
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 150, # samples: 10,000, # local minima: 97,756

Example: Qβ replicase template SV11

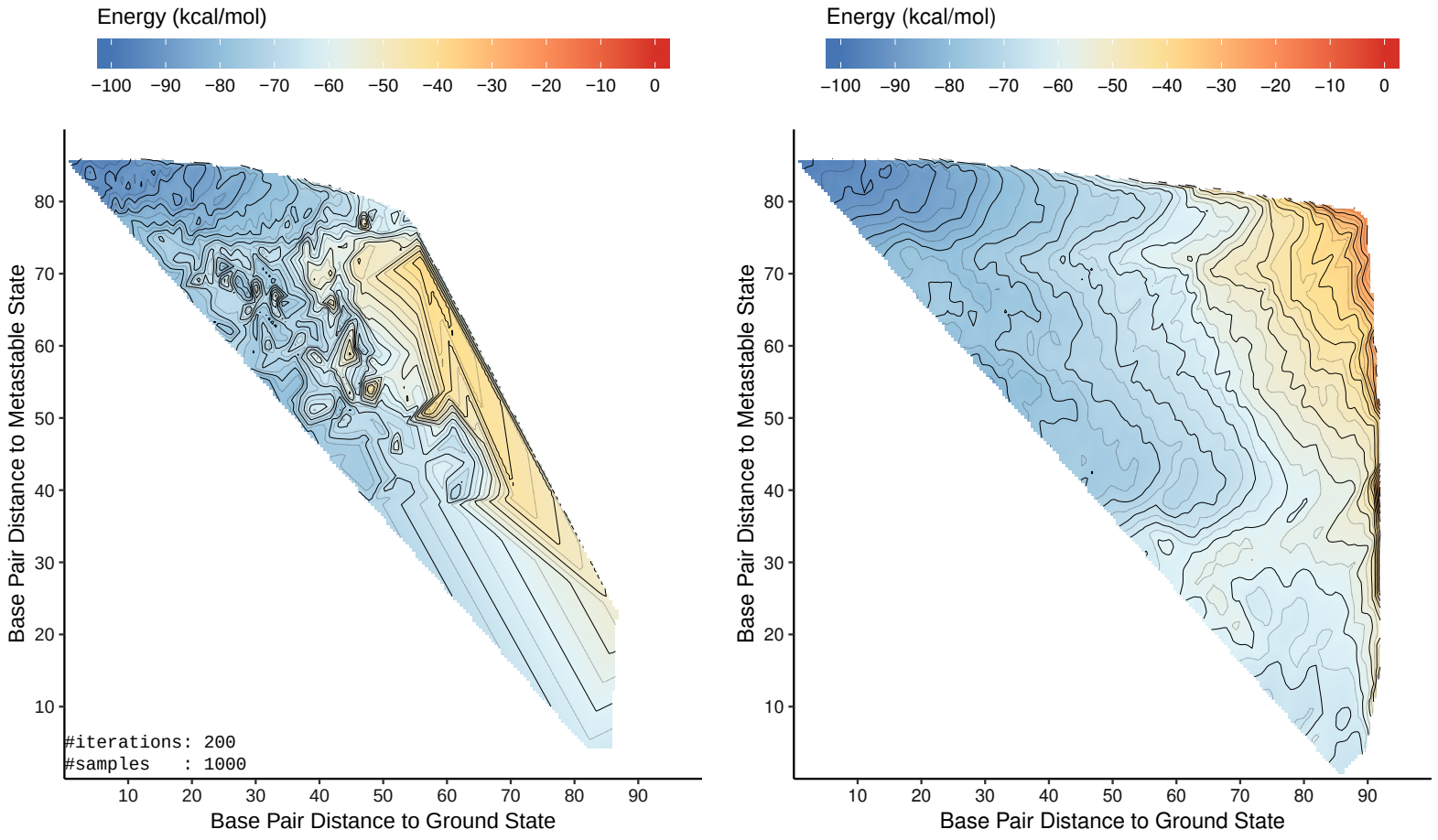
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 150, # samples: 10, 000, # local minima: 97, 756

Example: Qβ replicase template SV11

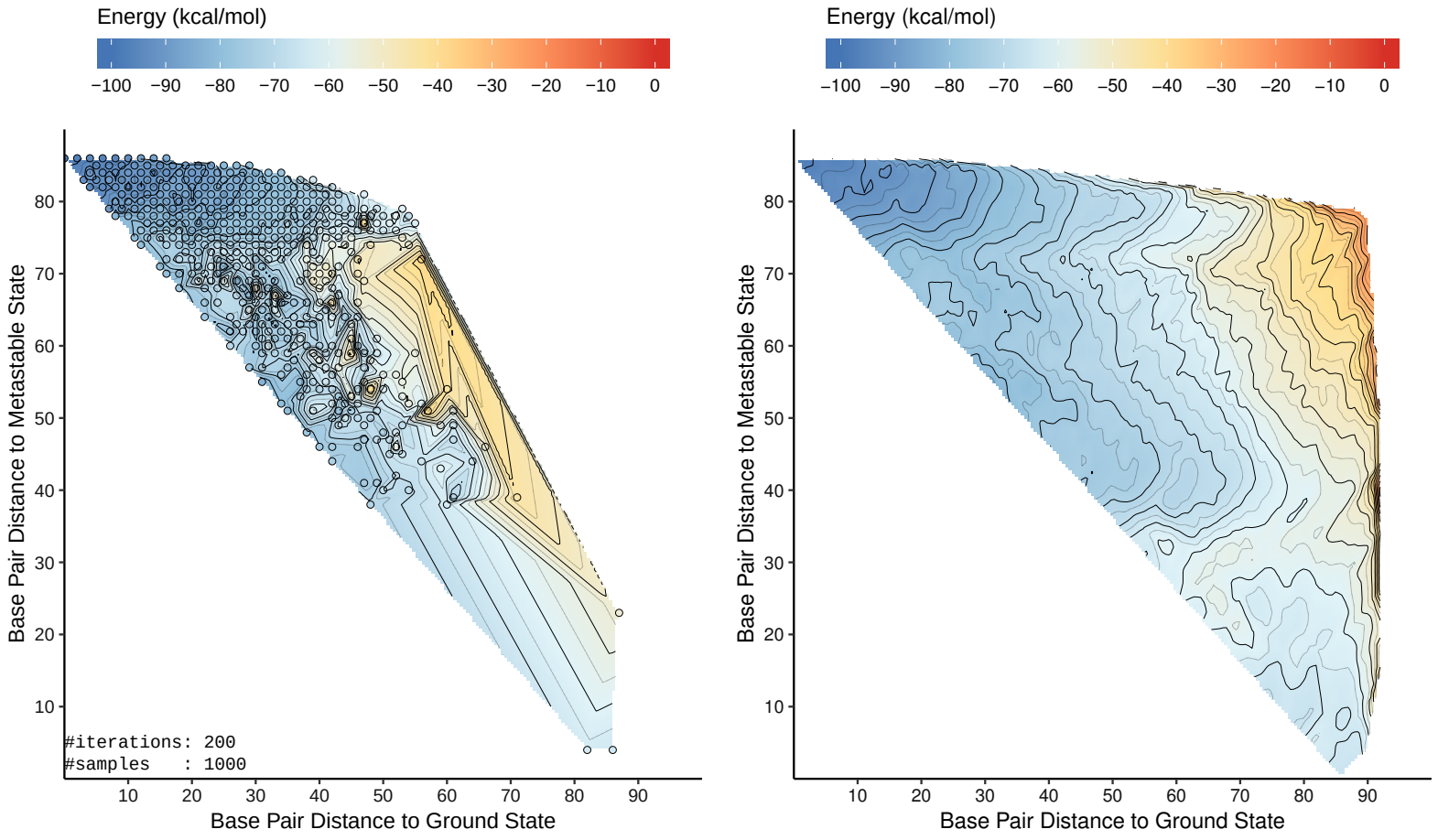
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 200, # samples: 1,000, # local minima: 18,221

Example: Qβ replicase template SV11

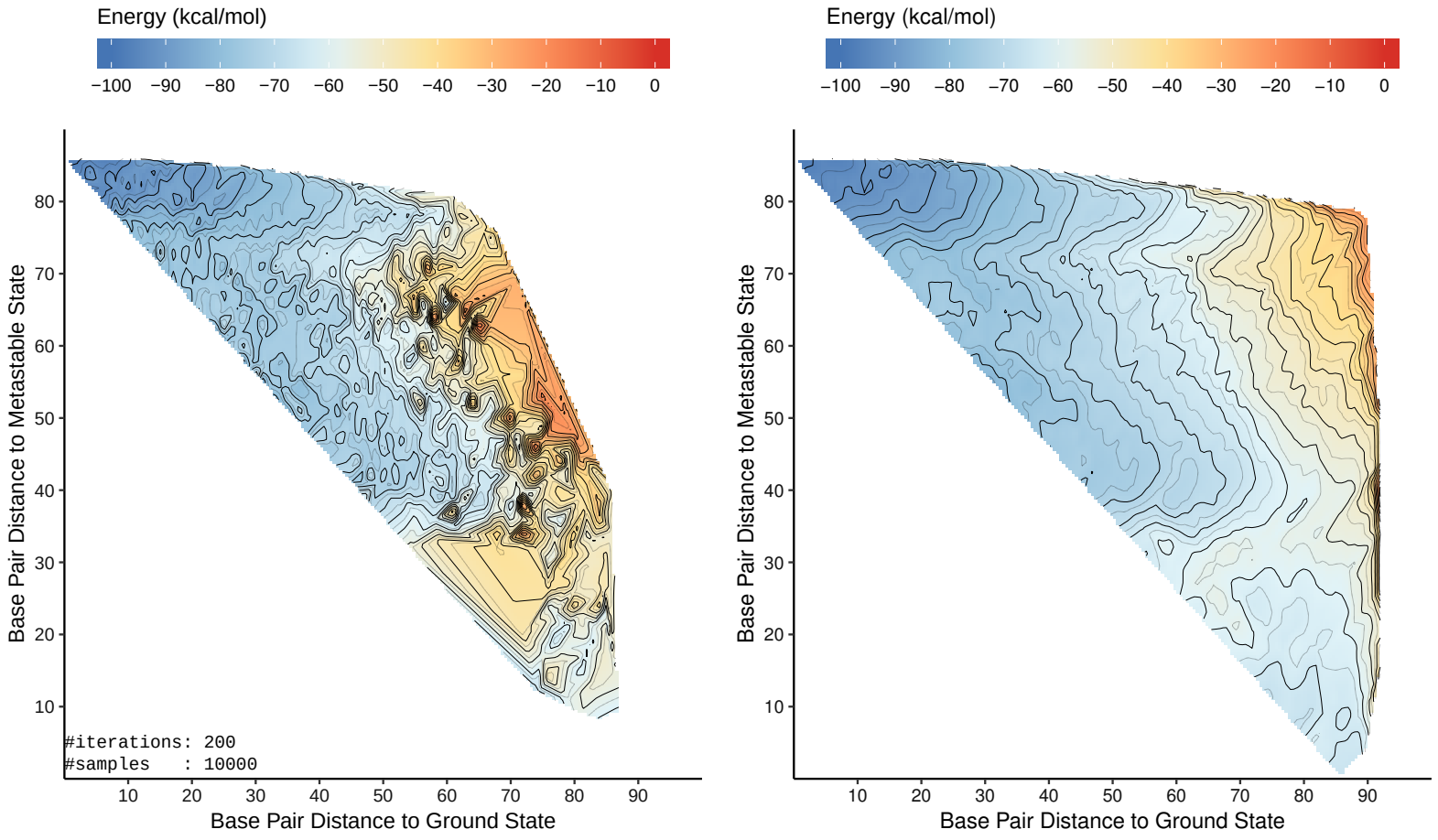
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 200, # samples: 1,000, # local minima: 18,221

Example: Qβ replicase template SV11

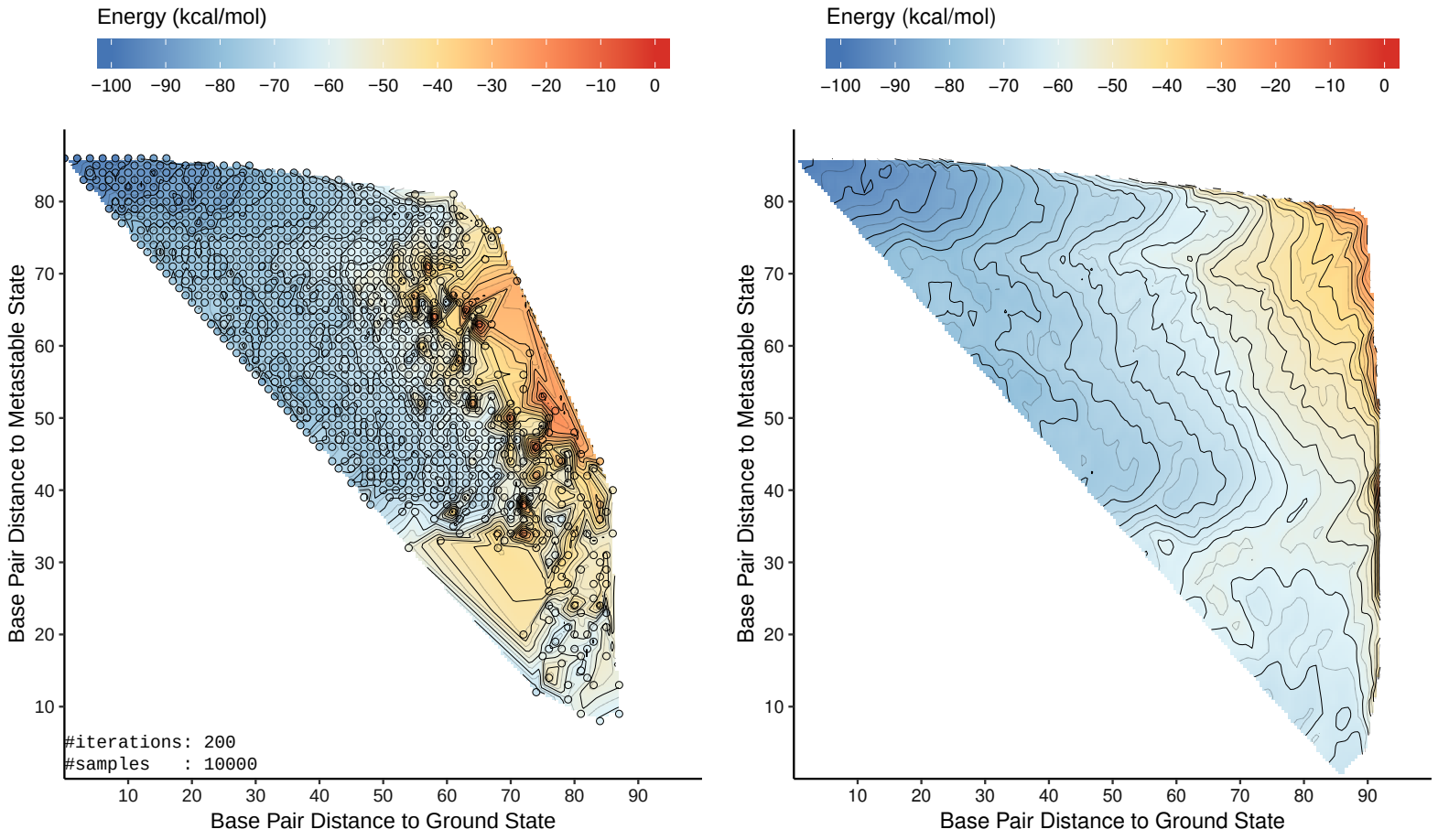
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 200, # samples: 10, 000, # local minima: 145, 391

Example: Qβ replicase template SV11

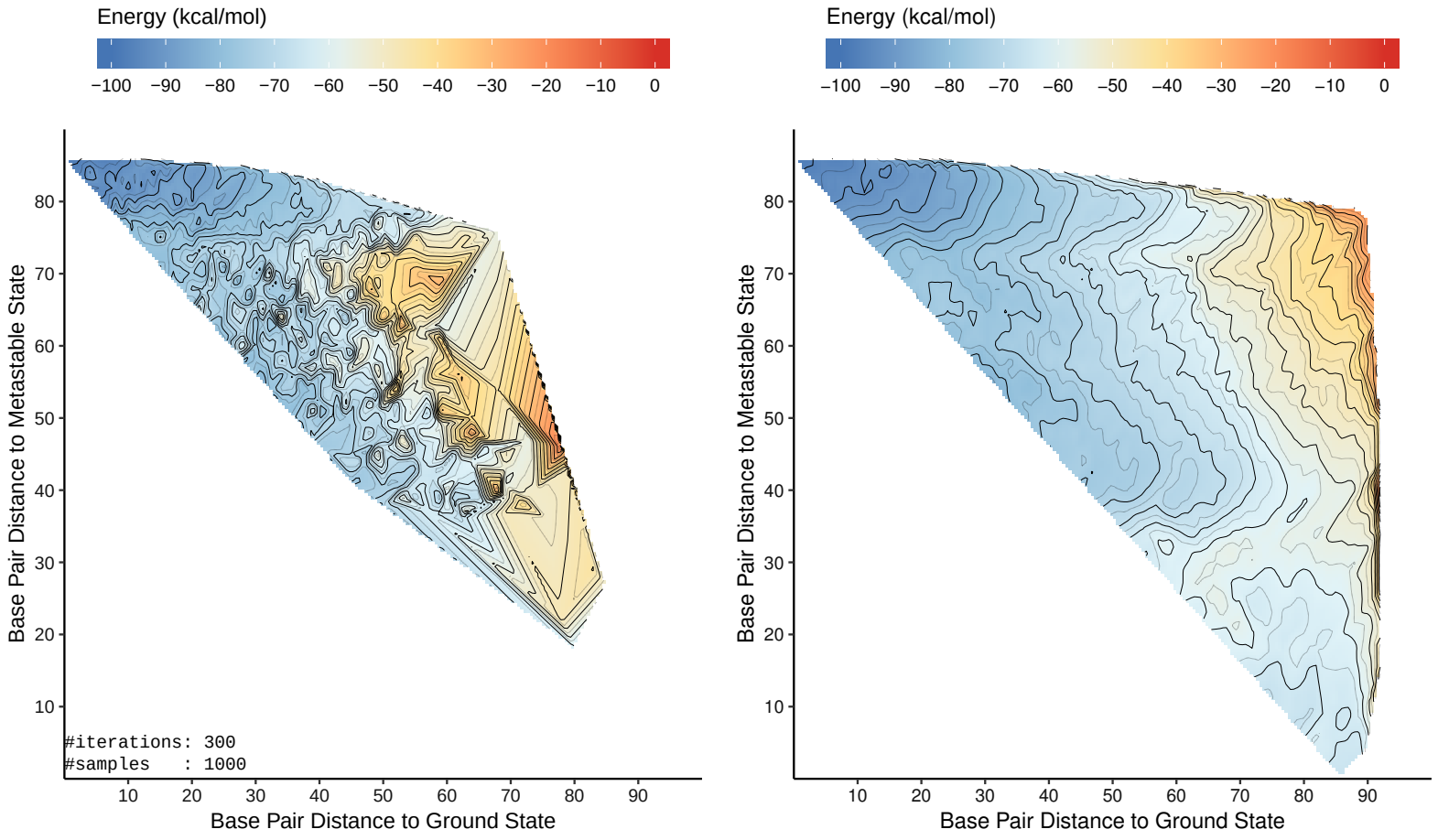
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 200, # samples: 10, 000, # local minima: 145, 391

Example: Qβ replicase template SV11

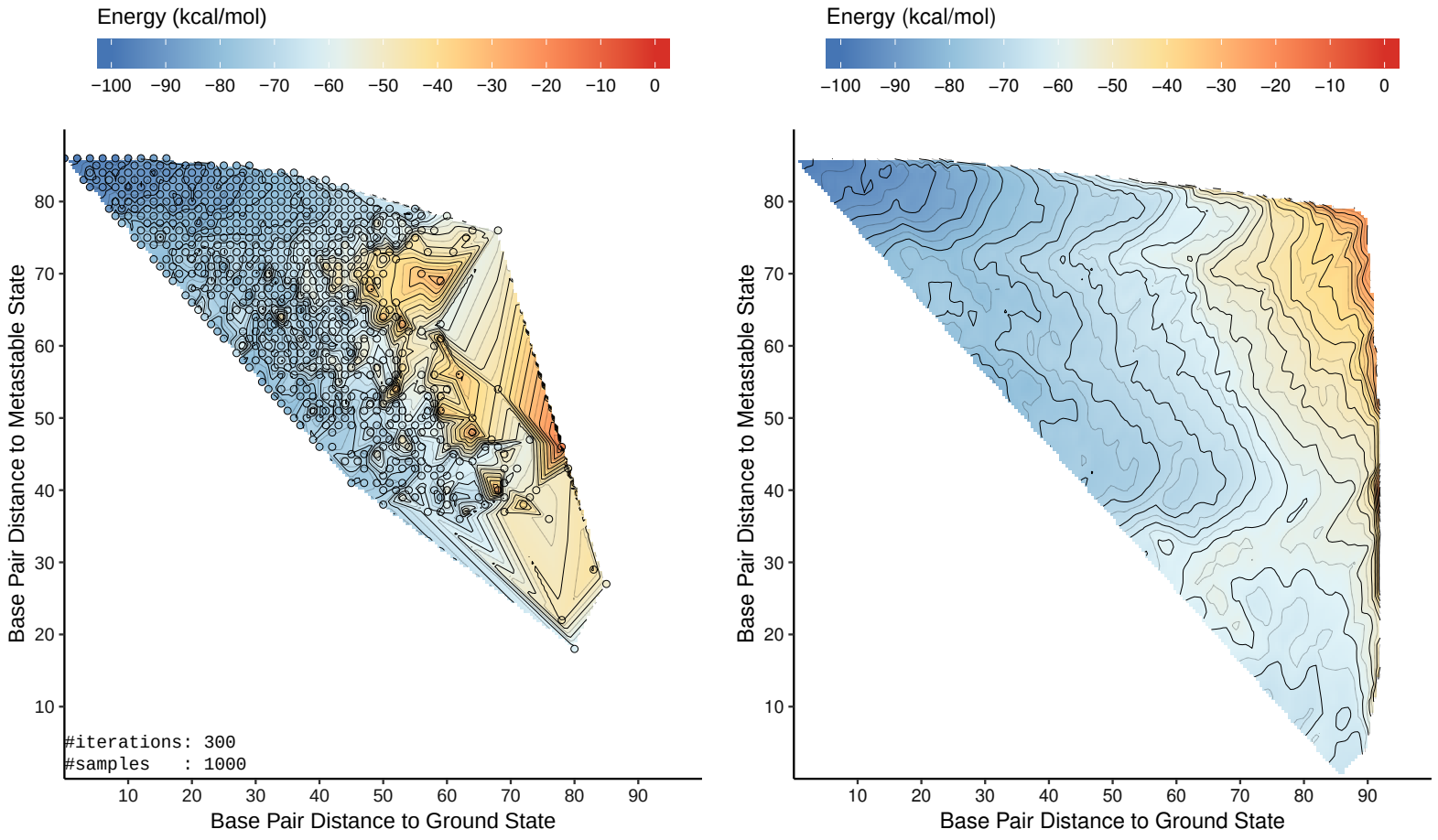
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 300, # samples: 1,000, # local minima: 32,569

Example: Qβ replicase template SV11

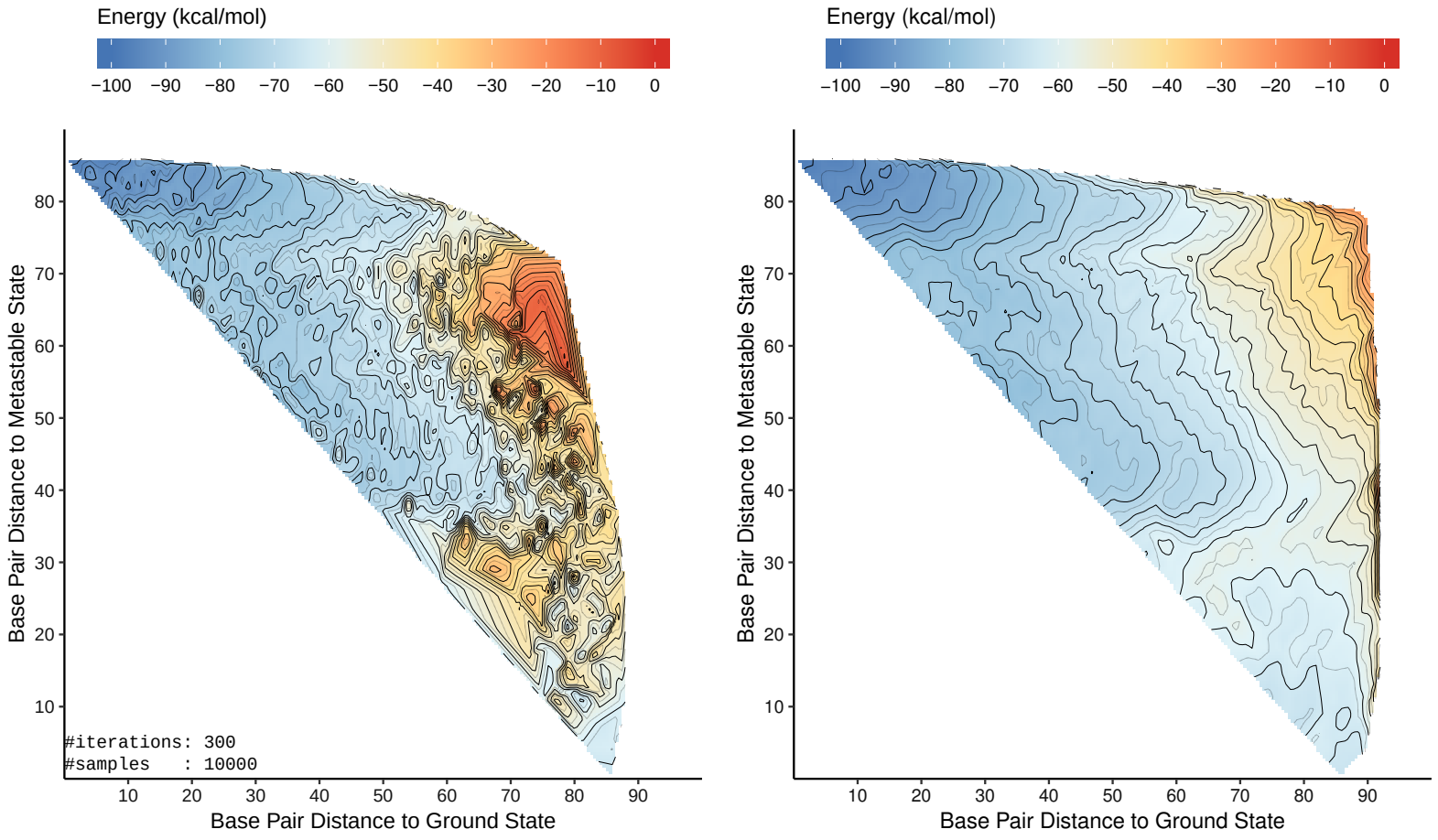
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 300, # samples: 1,000, # local minima: 32,569

Example: Qβ replicase template SV11

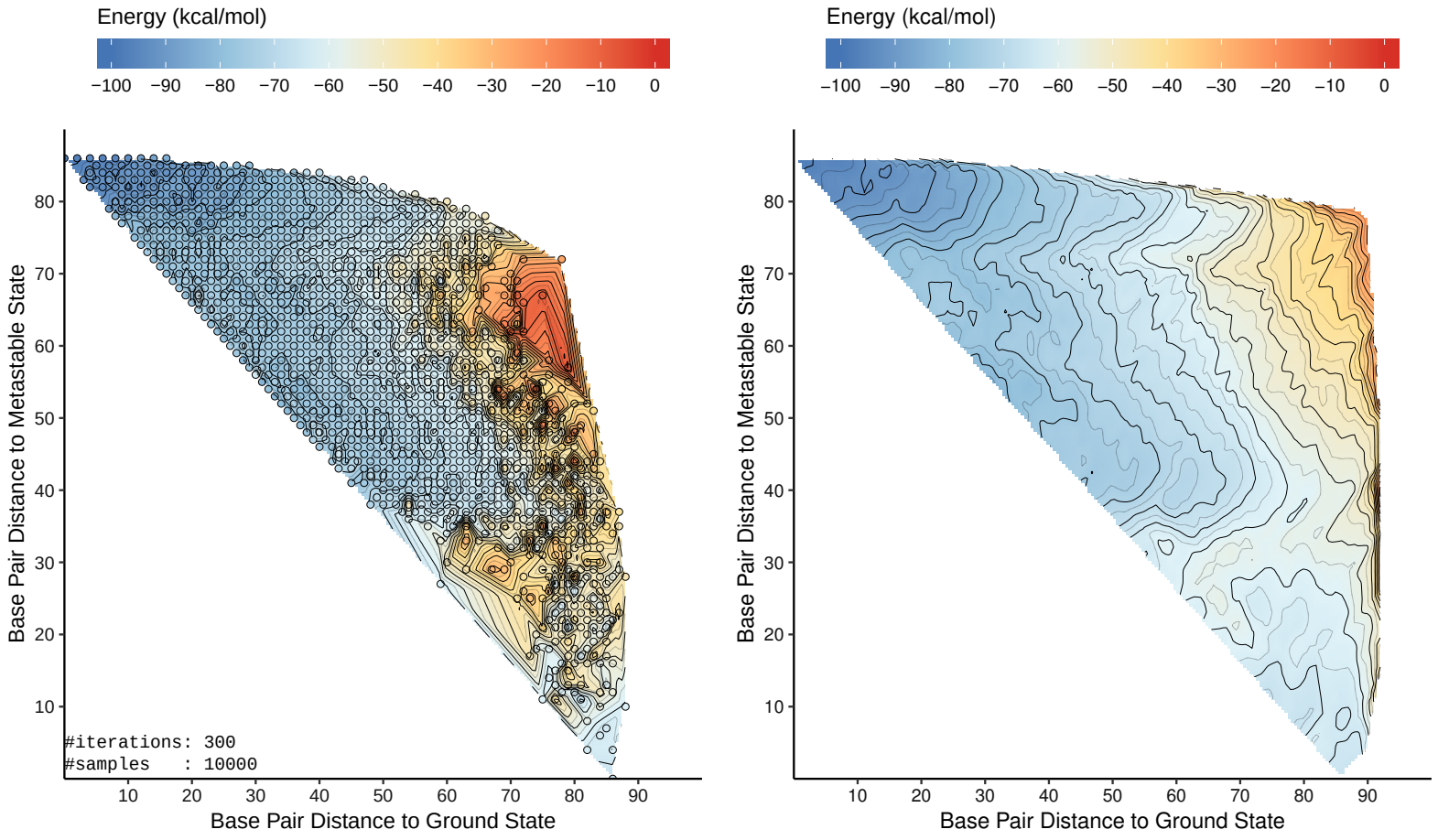
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 300, # samples: 10,000, # local minima: 260,994

Example: Qβ replicase template SV11

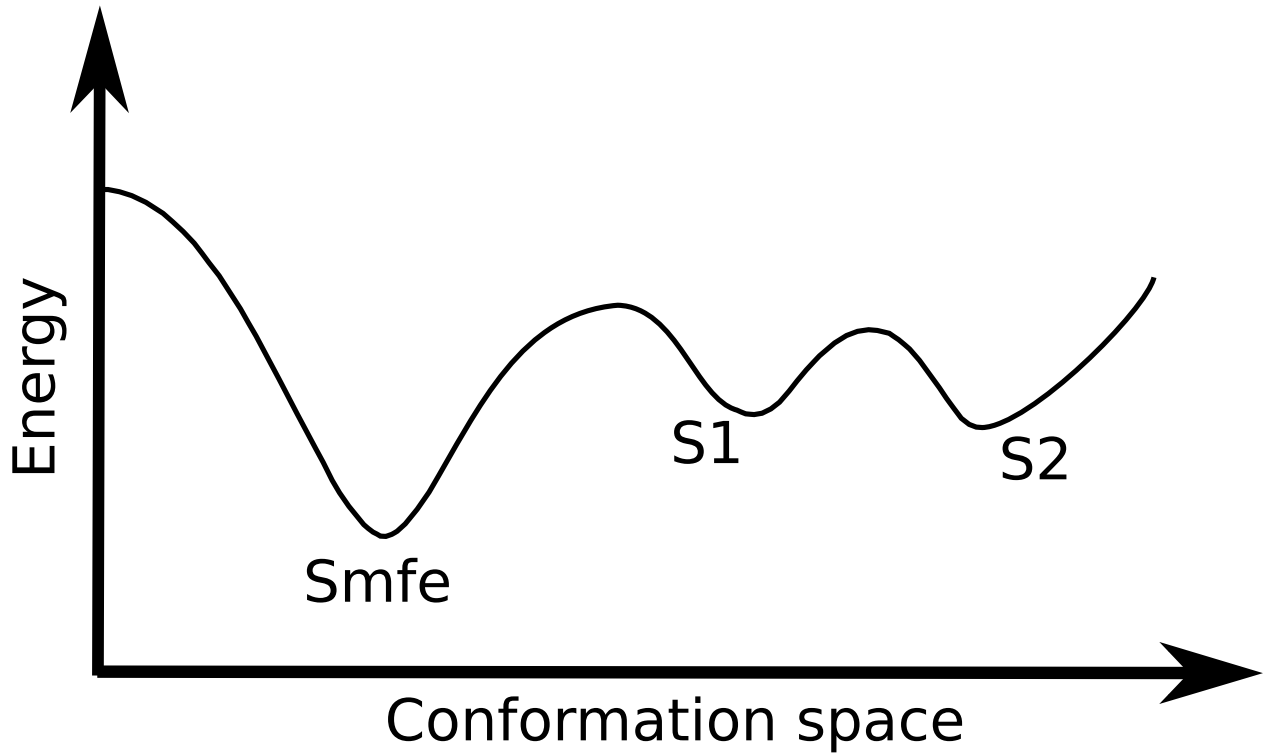
`RNAlocmin` temperature elevation scheme Boltzmann sampling



iterations: 300, # samples: 10, 000, # local minima: 260, 994

Sampling Strategies

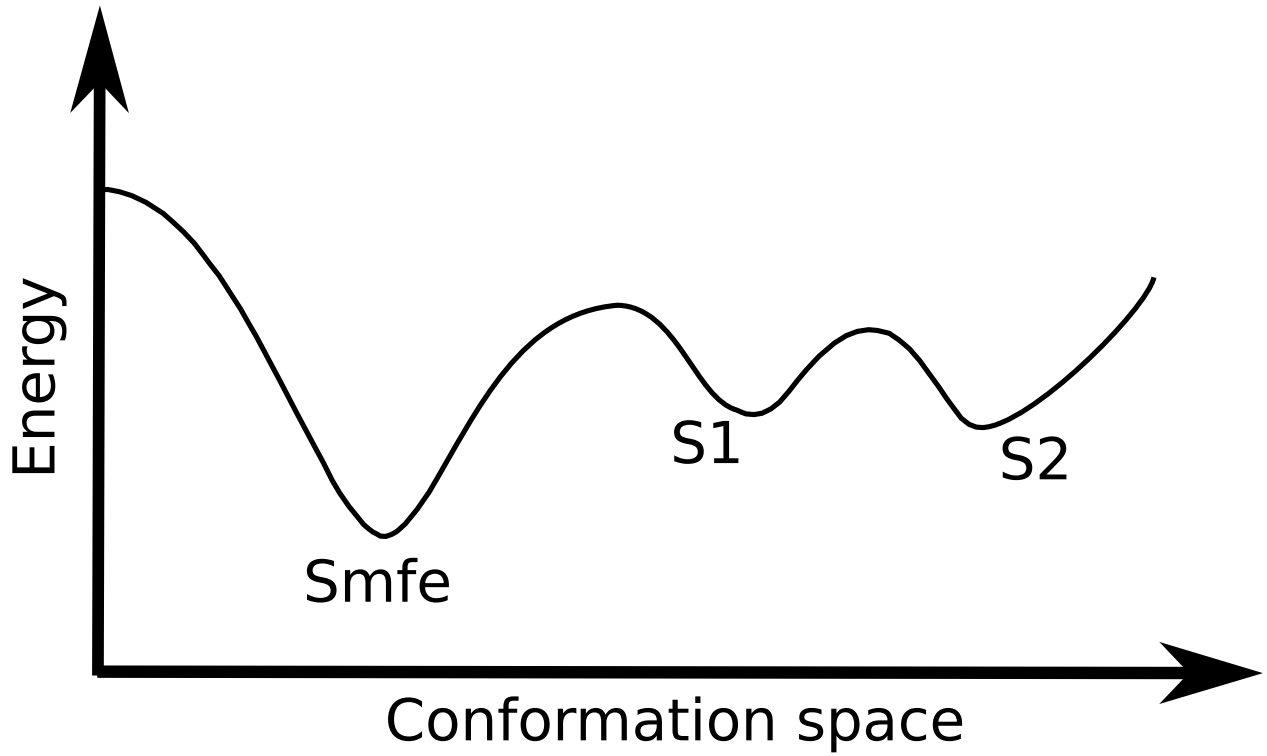
5. Sampling with Guiding Potentials (`RNAxplorer`)[12]



[12] Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (`RNAxplorer`)[12]

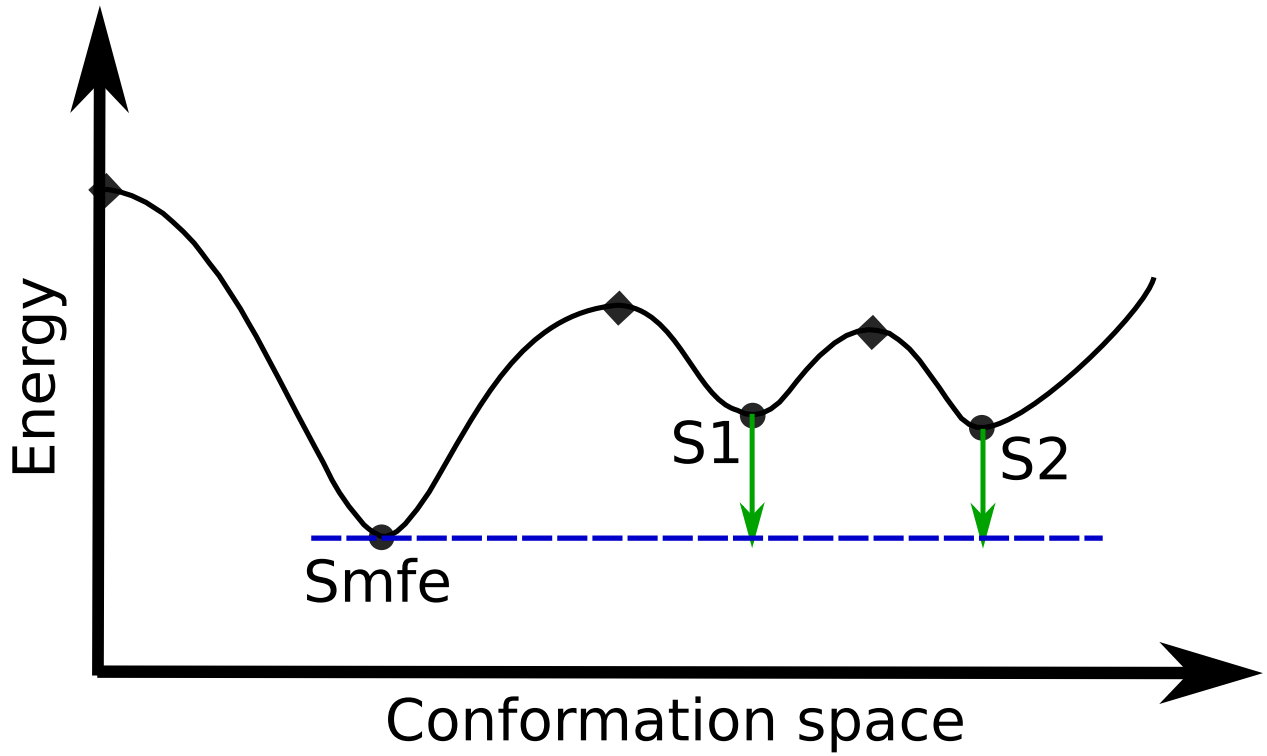


- $p(s) = e^{-E(s)/RT} / \sum_{x \in \Omega} e^{-E(x)/RT}$

[12] Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (`RNAxplorer`)[12]

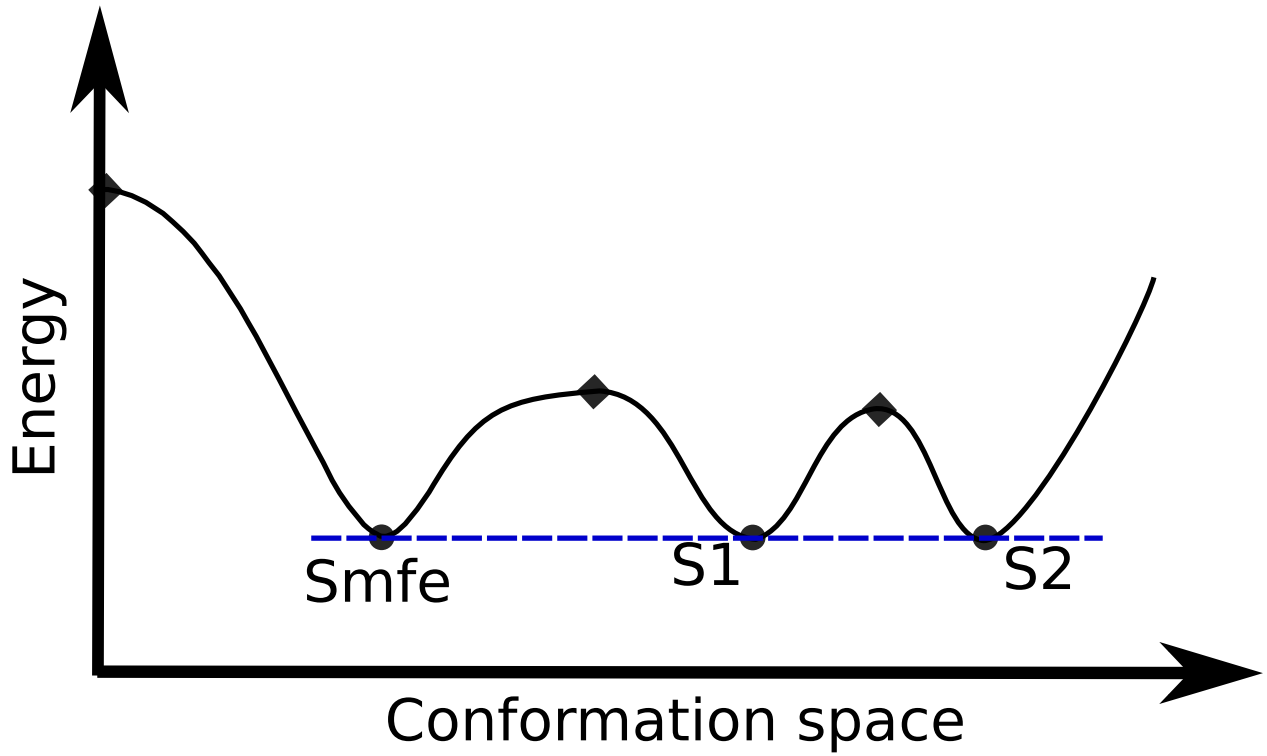


- $p(s) = e^{-E(s)/RT} / \sum_{x \in \Omega} e^{-E(x)/RT}$
- $E(s_{mfe}) = [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)]$

[12] Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (`RNAxplorer`)[12]



- $p(s) = e^{-E(s)/RT} / \sum_{x \in \Omega} e^{-E(x)/RT}$
- $E(s_{mfe}) = [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)]$
- $p(s_{mfe}) = p(s_1) = p(s_2)$

[12] Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (`RNAxplorer`)[12]

Guiding potential needs to allow for efficiently:

- computing partition function Q
- sampling from distorted energy ensemble

[12] Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (`RNAxplorer`)[12]

Guiding potential needs to allow for efficiently:

- computing partition function Q
- sampling from distorted energy ensemble

Make use of soft constraints feature of `ViennaRNA Package`[13]

$$
\begin{aligned}
E(s_{mfe}) &= [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)] \\
\hat{E}(s) &= d_{BP}(s, s_1) \cdot w_1 + d_{BP}(s, s_2) \cdot w_2
\end{aligned}
$$

[12] Entzian et al. (manuscript in preparation)
[13] Lorenz et al. 2016

Sampling Strategies

5. Sampling with Guiding Potentials (`RNAxplorer`)[12]

Guiding potential needs to allow for efficiently:

- computing partition function Q
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Make use of soft constraints feature of `ViennaRNA Package`[13]

$$\begin{aligned} E(s_{mfe}) &= [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)] \\ \hat{E}(s) &= d_{BP}(s, s_1) \cdot w_1 + d_{BP}(s, s_2) \cdot w_2 \end{aligned}$$

How to choose reference structures s_x?

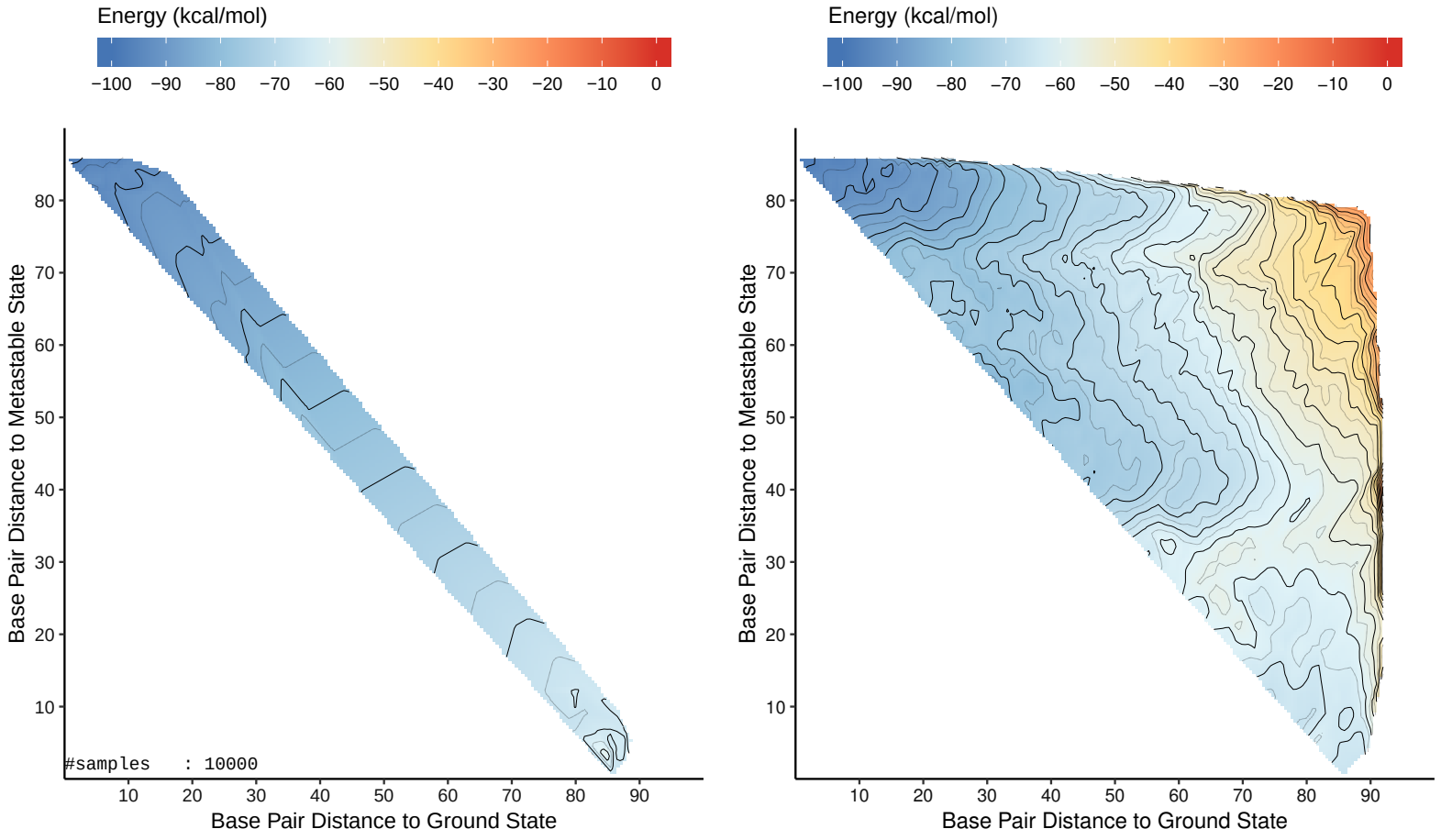
---

[12] Entzian et al. (manuscript in preparation)

[13] Lorenz et al. 2016

Example: Qβ replicase template SV11

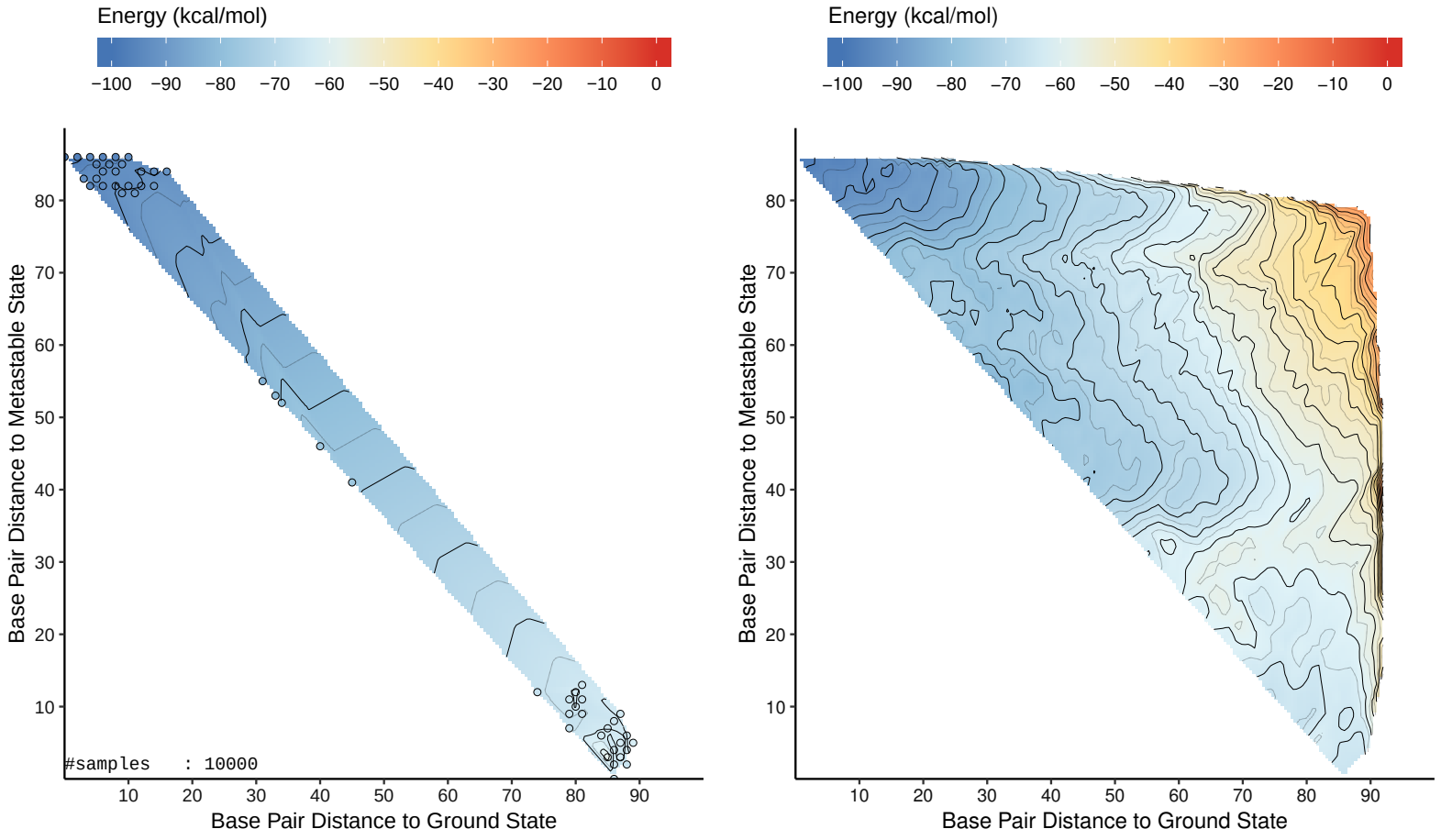
`RNAxplorer` attraction scheme Boltzmann sampling



references: 2, # samples: 10, 000, # local minima: 86

Example: Qβ replicase template SV11

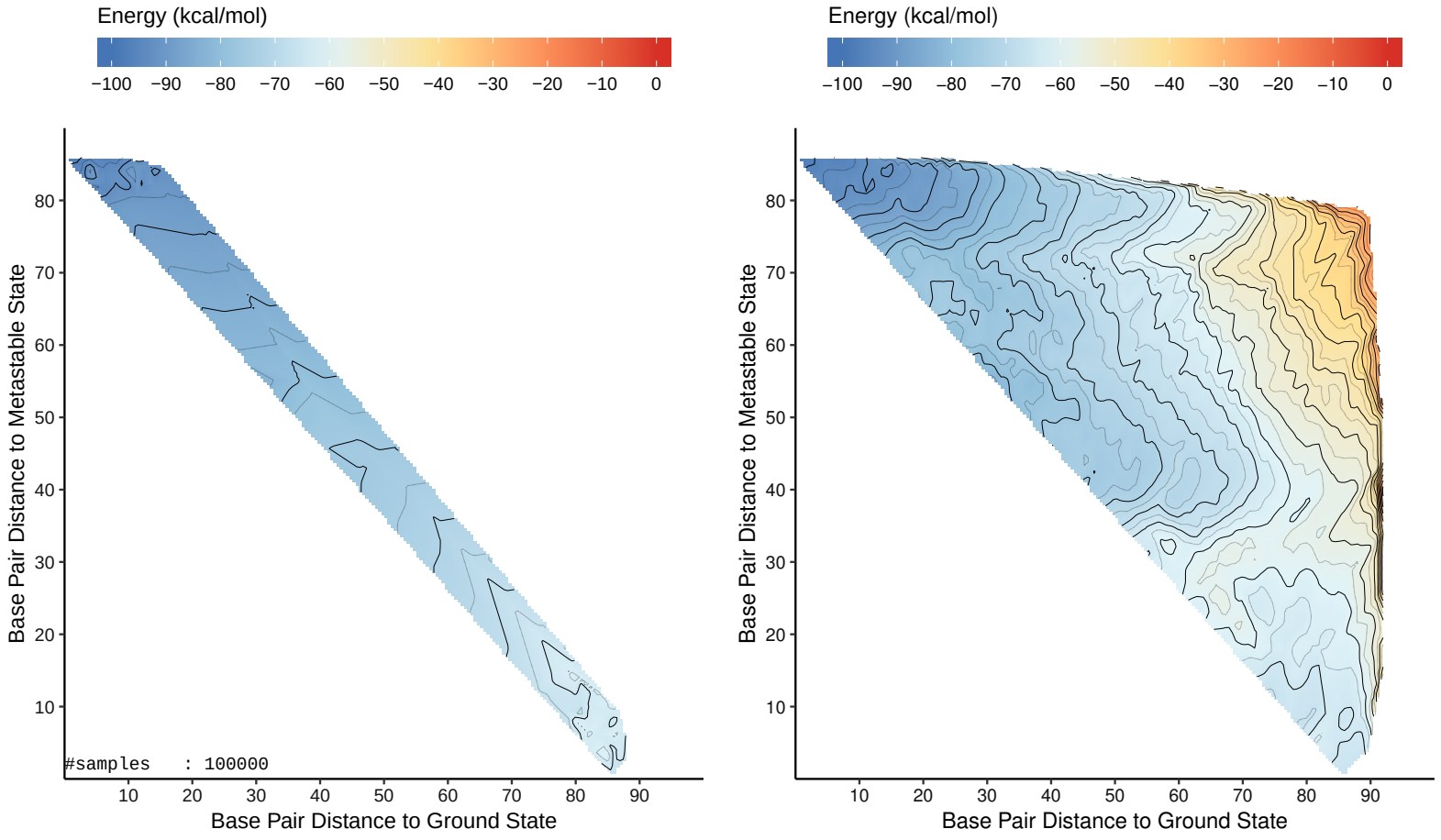
`RNAxplorer` attraction scheme Boltzmann sampling



references: 2, # samples: 10, 000, # local minima: 86

Example: Qβ replicase template SV11

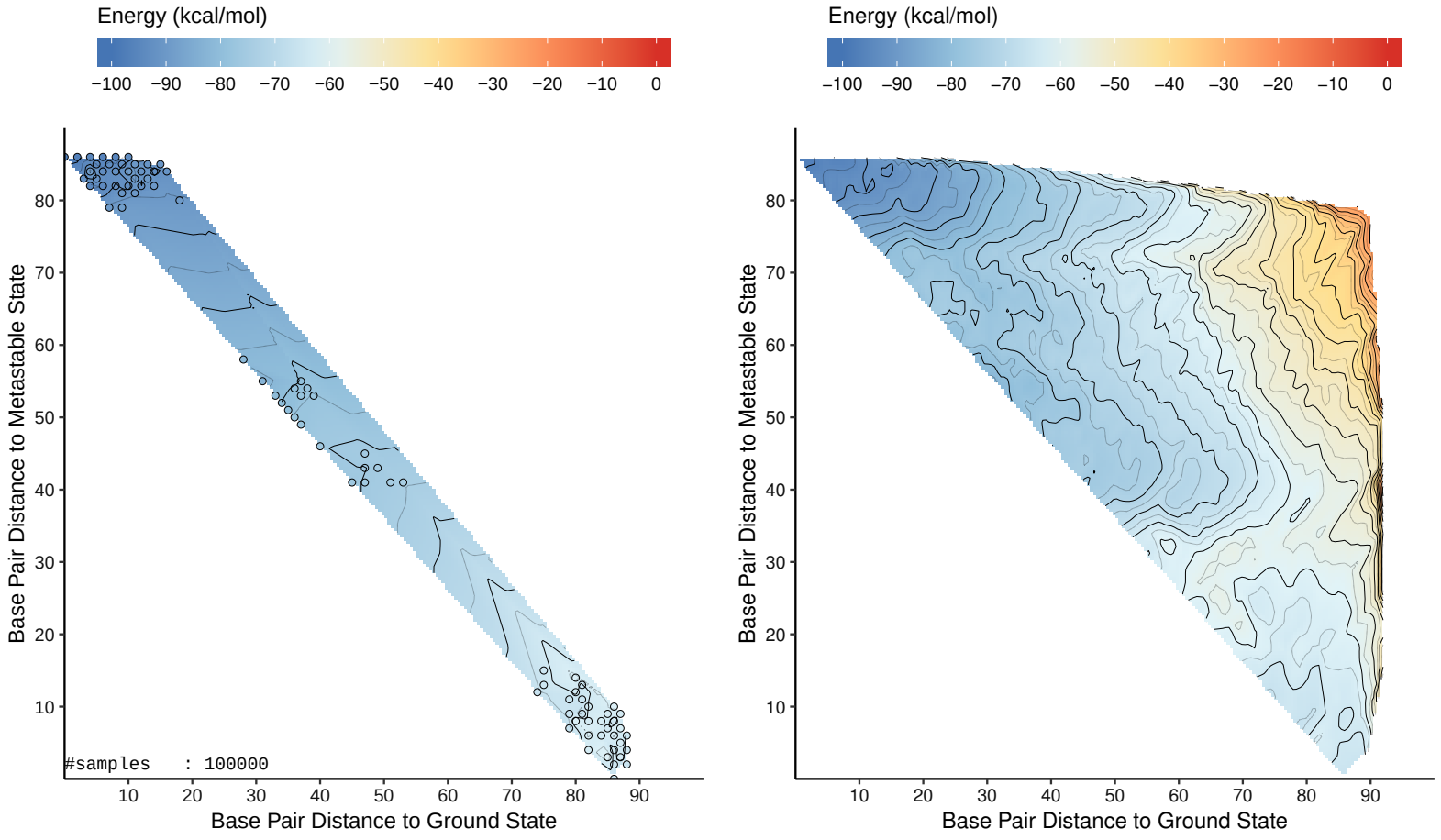
`RNAxplorer` attraction scheme Boltzmann sampling



references: 2, # samples: 100, 000, # local minima: 167

Example: Qβ replicase template SV11

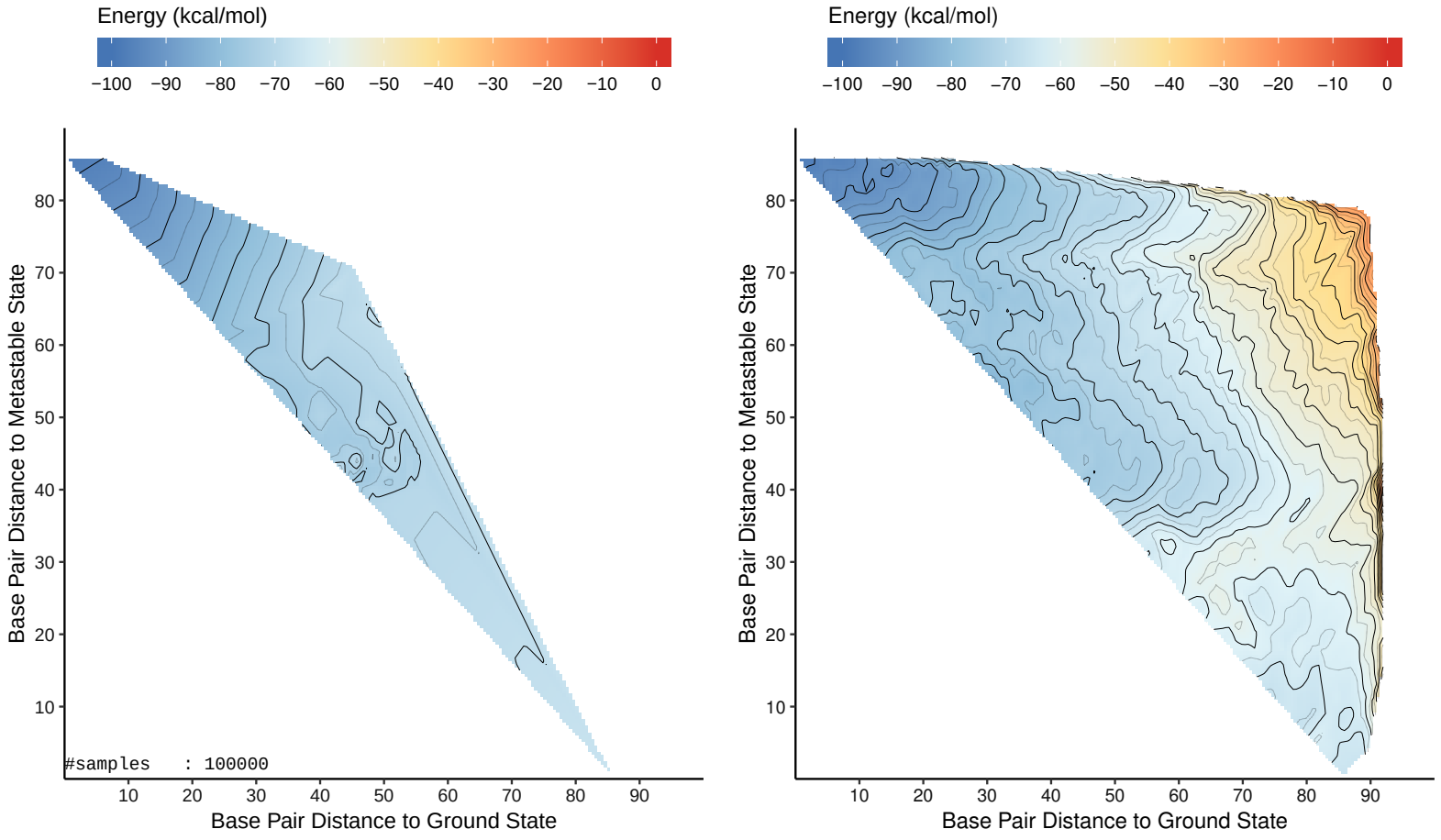
`RNAxplorer` attraction scheme Boltzmann sampling



references: 2, # samples: 100, 000, # local minima: 167

Example: Qβ replicase template SV11

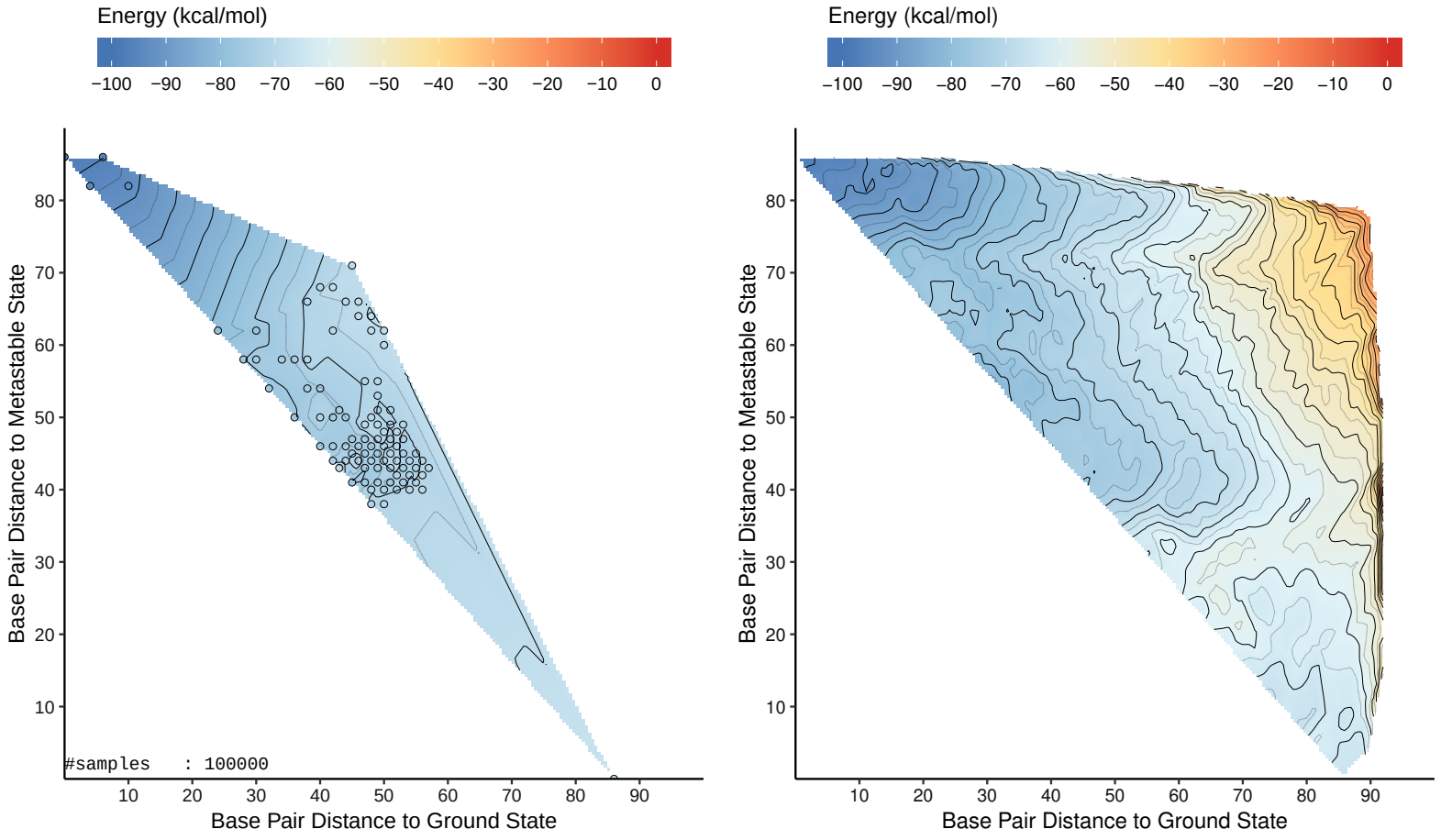
`RNAxplorer` attraction scheme Boltzmann sampling



references: 3, # samples: 100, 000, # local minima: 182

Example: Qβ replicase template SV11

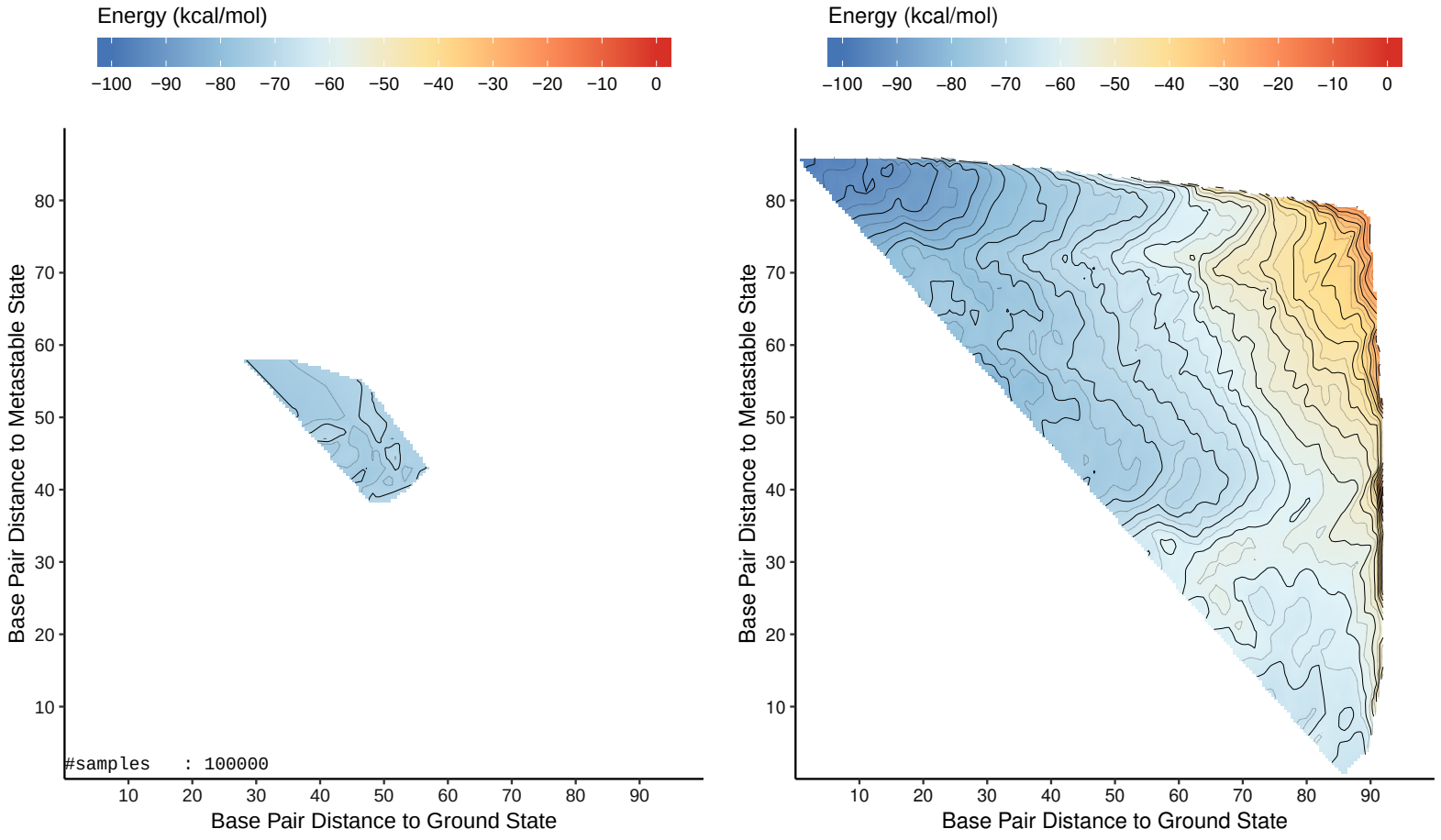
`RNAxplorer` attraction scheme Boltzmann sampling



references: 3, # samples: 100, 000, # local minima: 182

Example: Qβ replicase template SV11

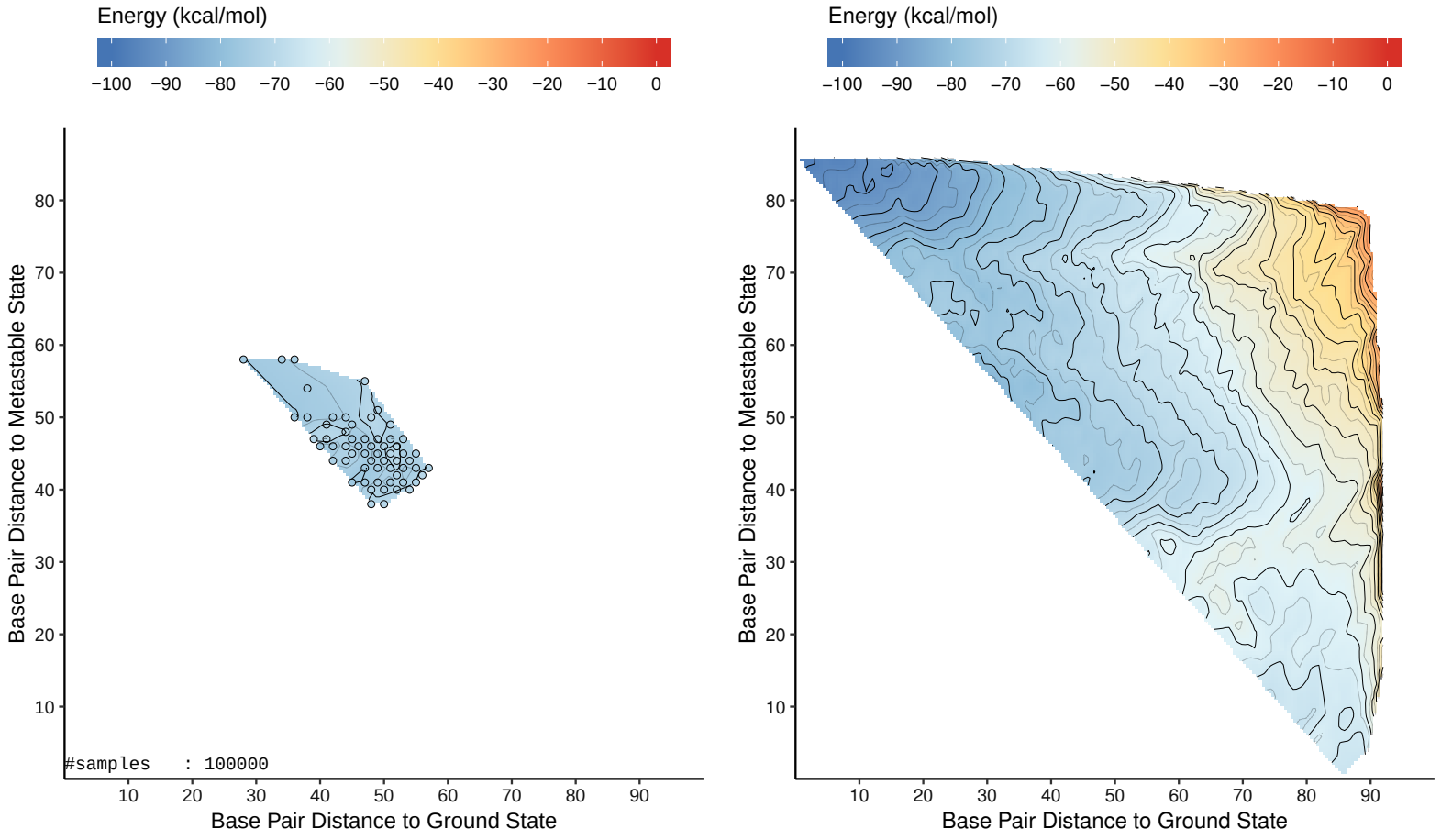
`RNAxplorer` attraction scheme Boltzmann sampling



references: 4, # samples: 100, 000, # local minima: 143

Example: Qβ replicase template SV11

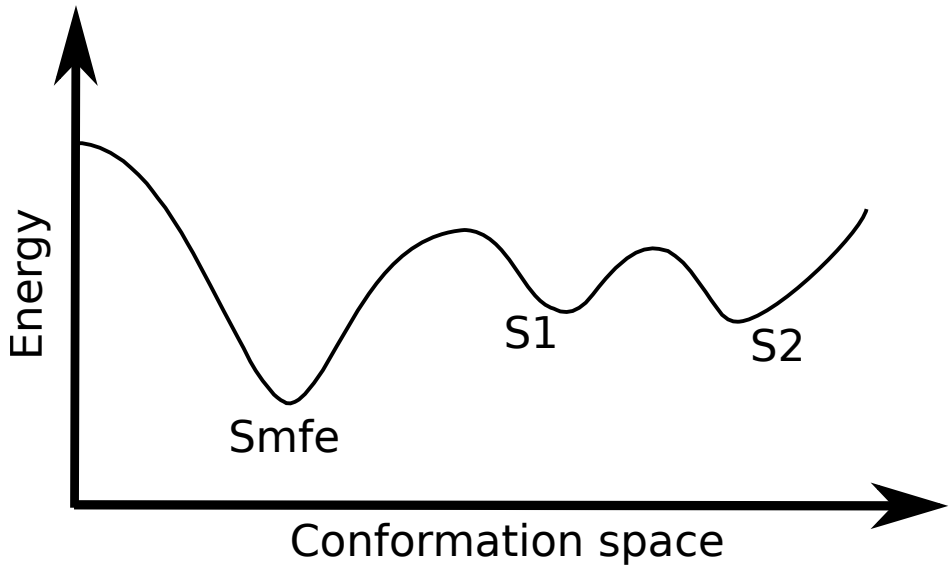
`RNAxplorer` attraction scheme Boltzmann sampling



references: 4, # samples: 100, 000, # local minima: 143

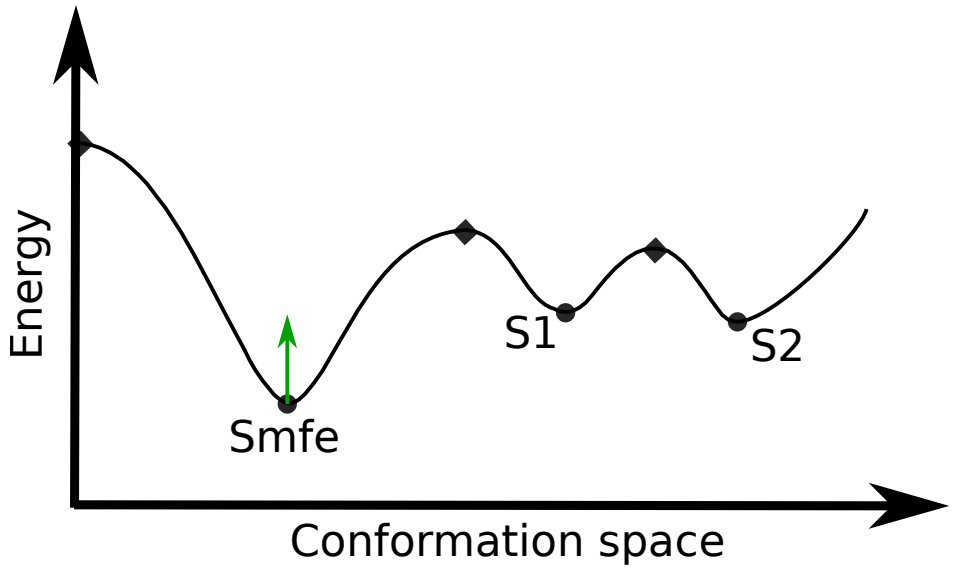
Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



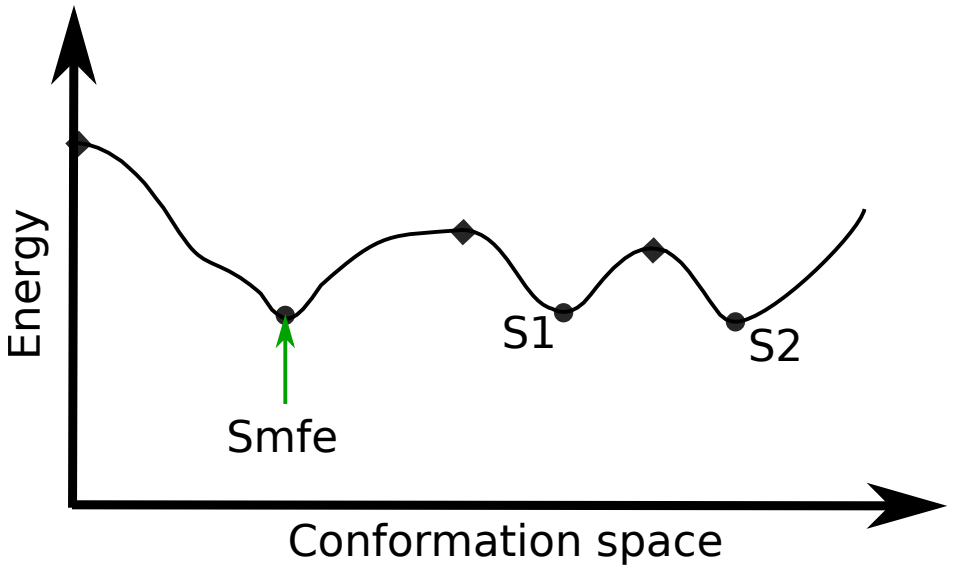
Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



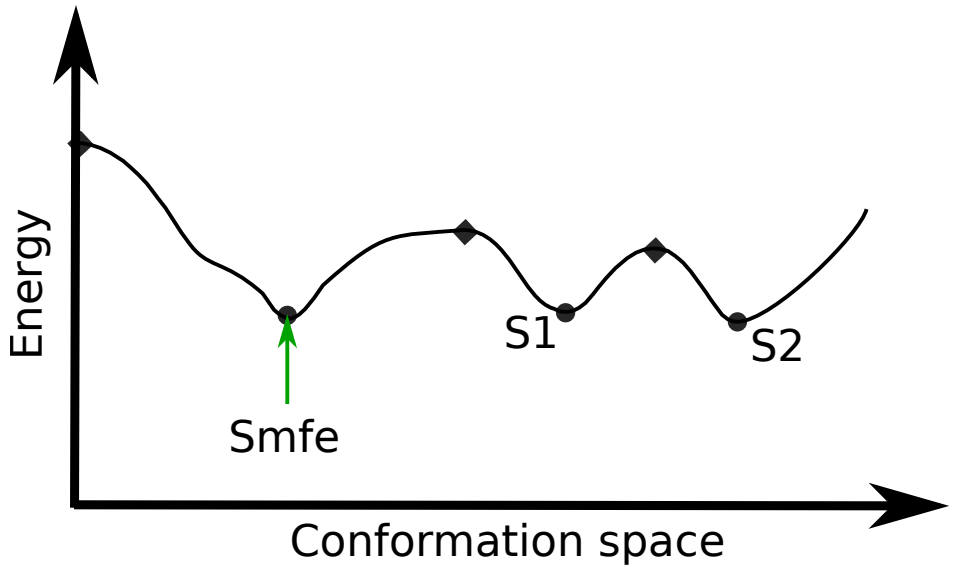
Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



- draw samples and determine corresponding local minima
- add most over-represented local minimum s_m to list L
- assign $\hat{E}(s)$ according to structures in L, e.g.

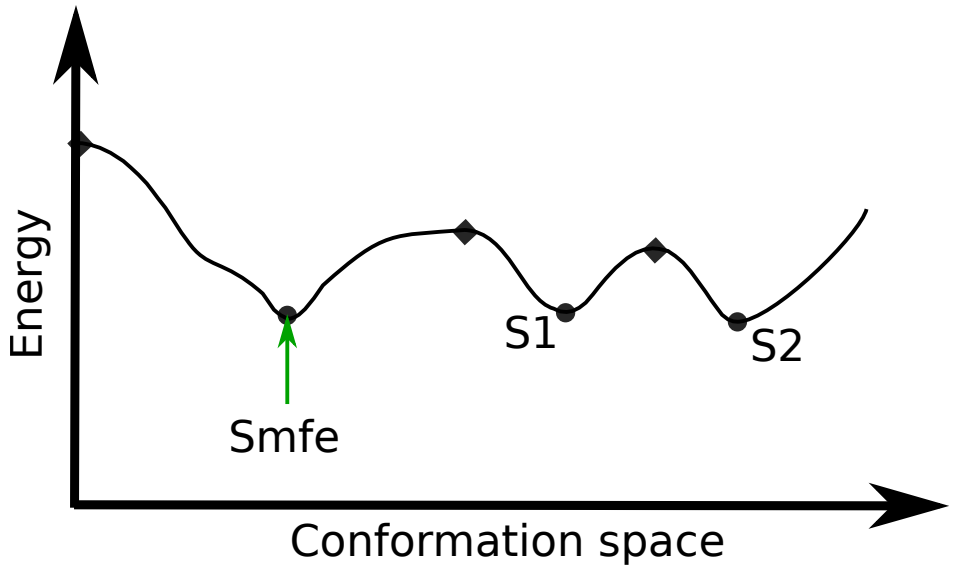
$$\hat{E}(s) = \sum_{s_m \in L} w(s_m) \cdot \frac{|s \cap s_m|}{|s_m|}$$

$$\hat{E}(s) = \sum_{s_m \in L} w(s_m) \cdot (d_{BP}^{max}(s_m) - d_{BP}(s, s_m))$$

$$\ldots$$

Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



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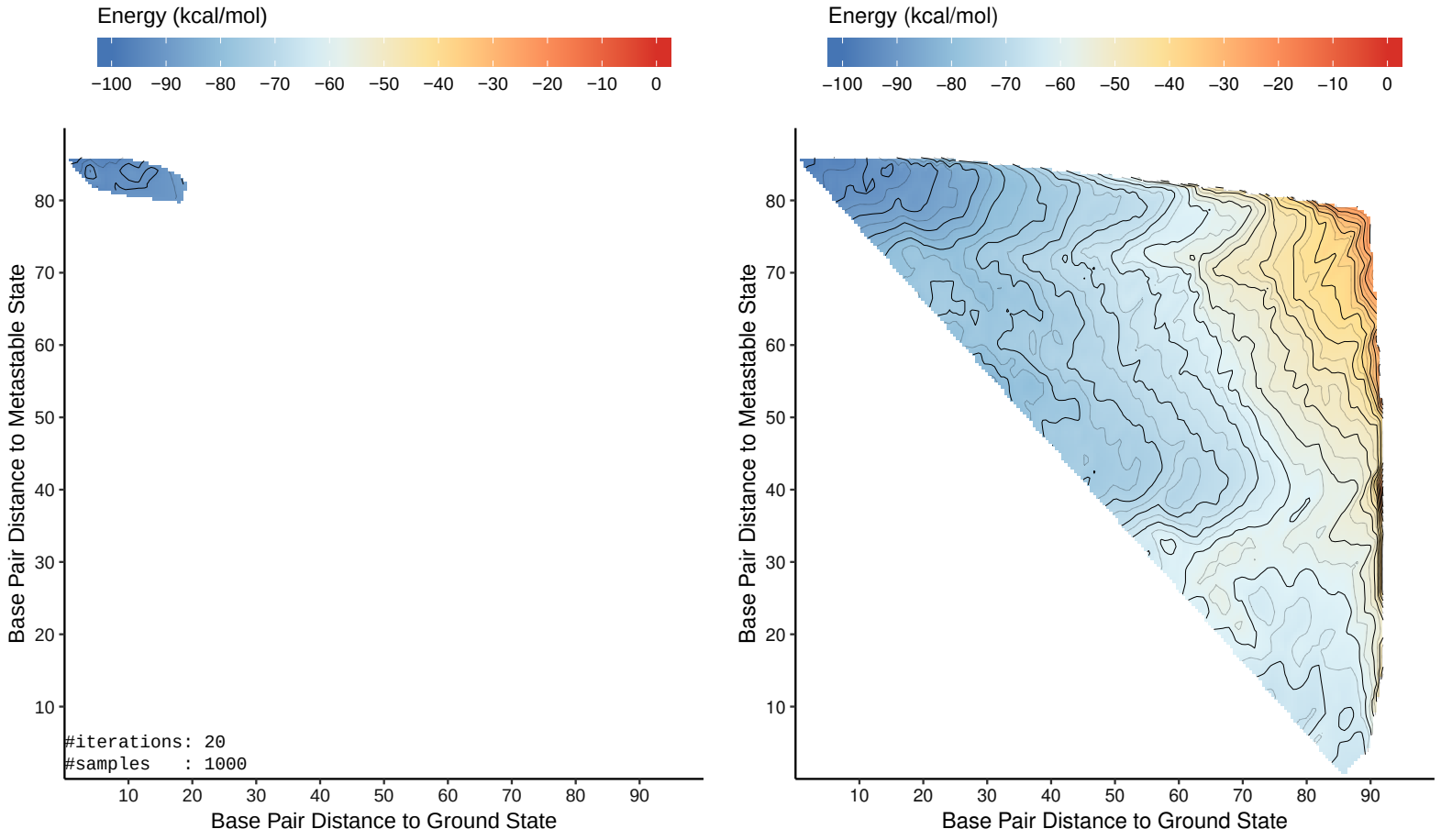
$$\hat{E}(s) = \sum_{s_m \in L} w(s_m) \cdot (d_{BP}^{max}(s_m) - d_{BP}(s, s_m))$$

$$\ldots$$

Choose moderate weighting factors, e.g. $w(s_m) = \gamma RT$

Example: Qβ replicase template SV11

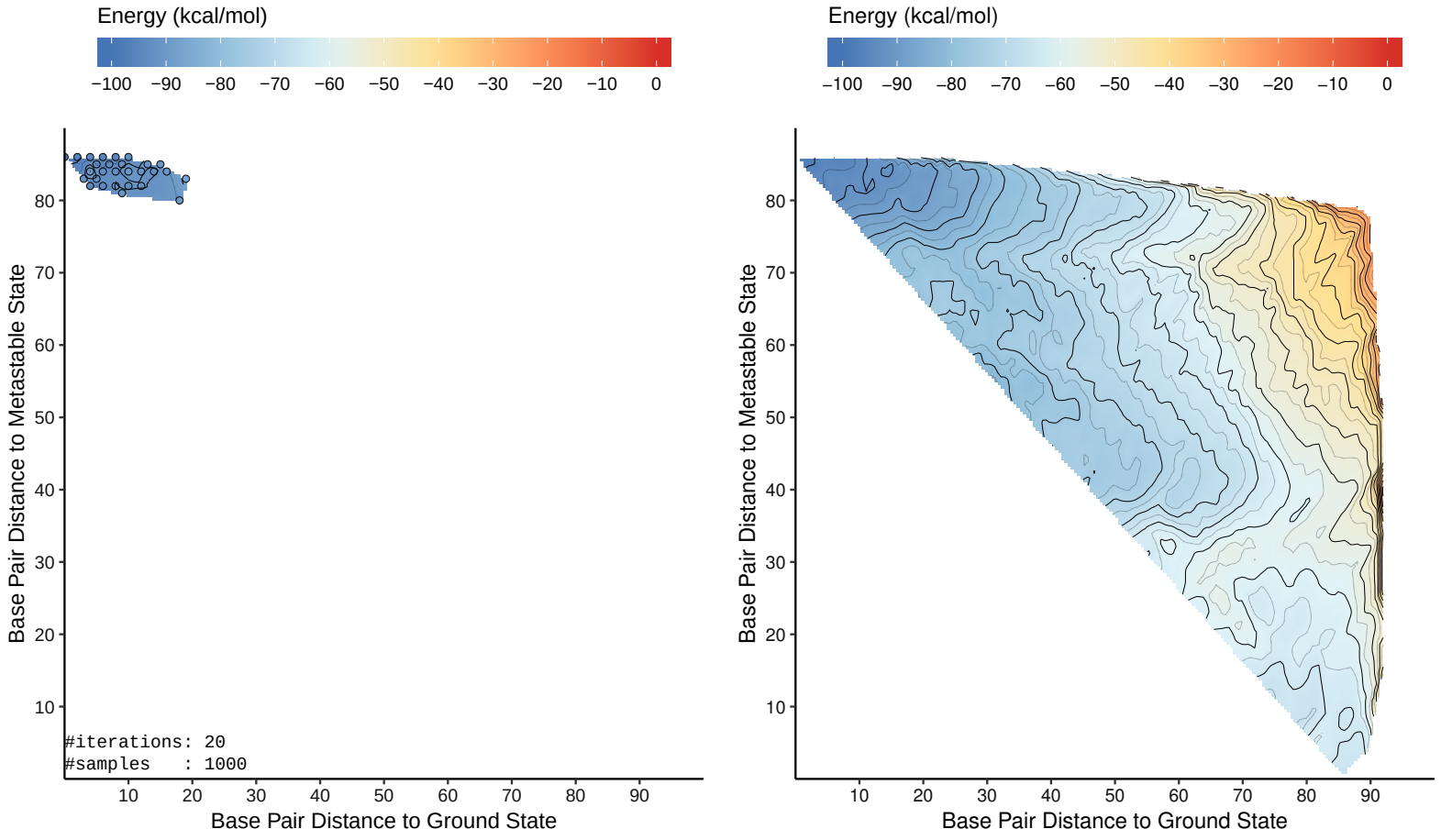
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 20, # samples: 1,000, # local minima: 52

Example: Qβ replicase template SV11

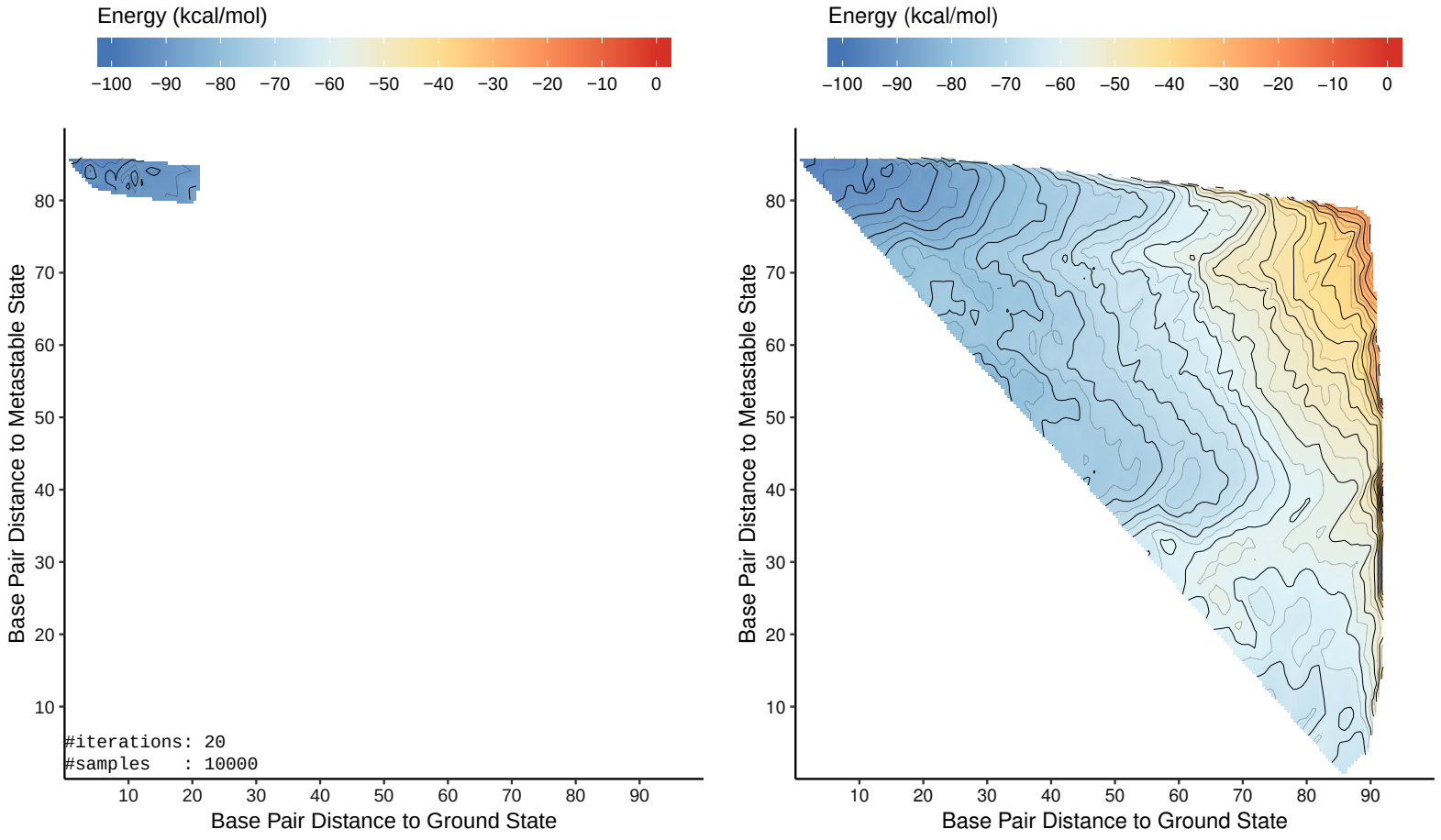
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 20, # samples: 1,000, # local minima: 52

Example: Qβ replicase template SV11

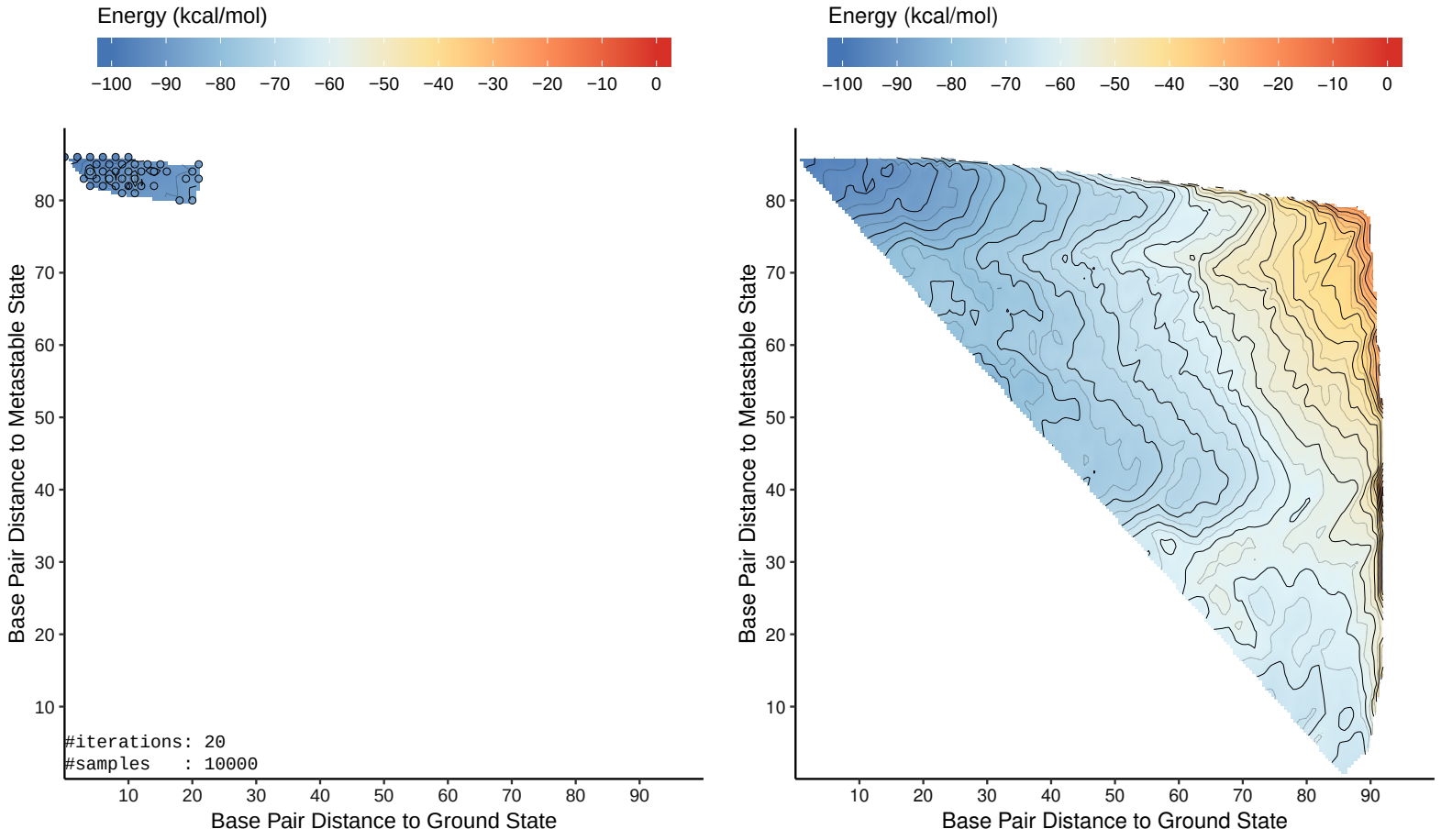
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 20, # samples: 10, 000, # local minima: 97

Example: Qβ replicase template SV11

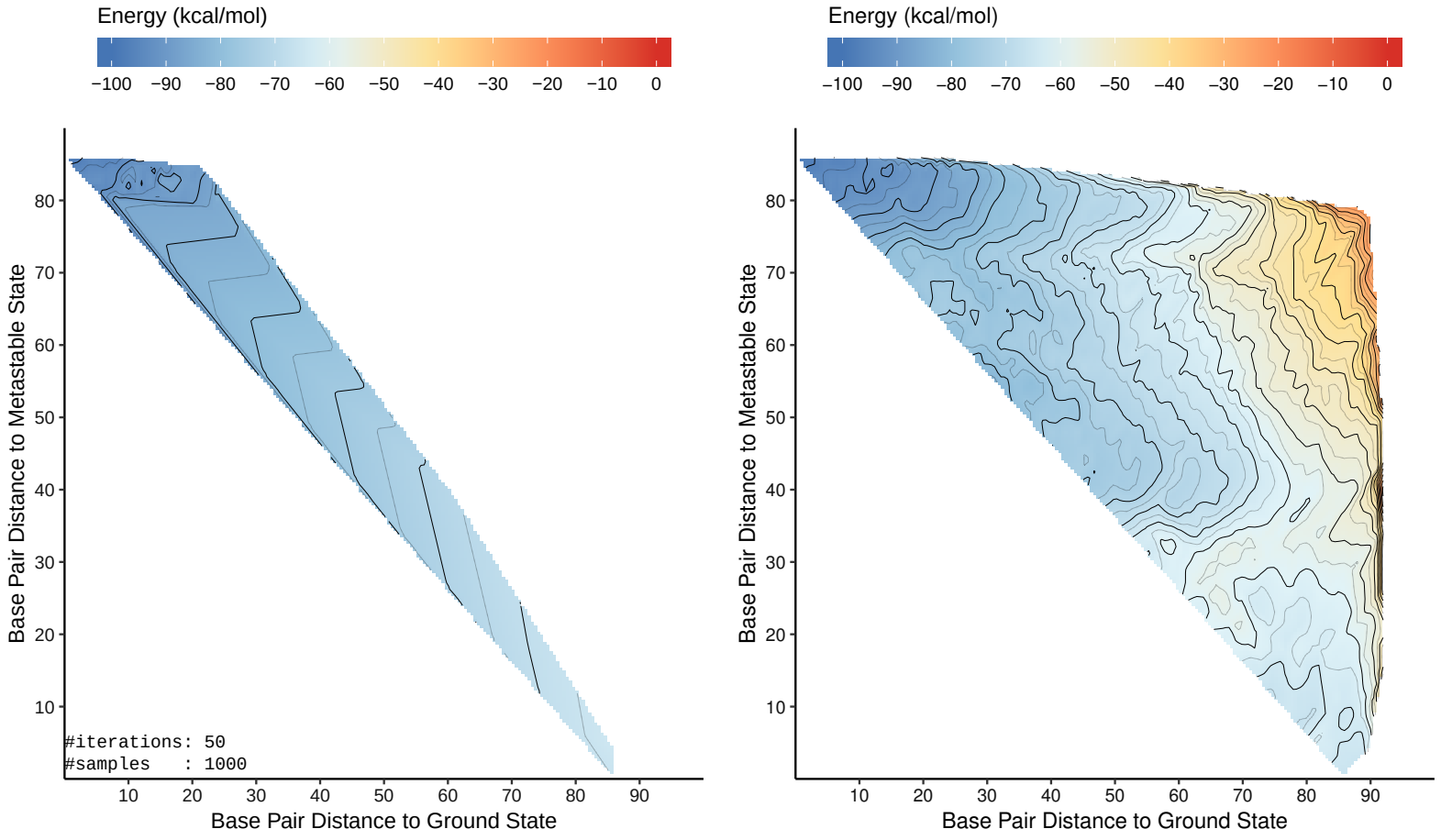
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 20, # samples: 10, 000, # local minima: 97

Example: Qβ replicase template SV11

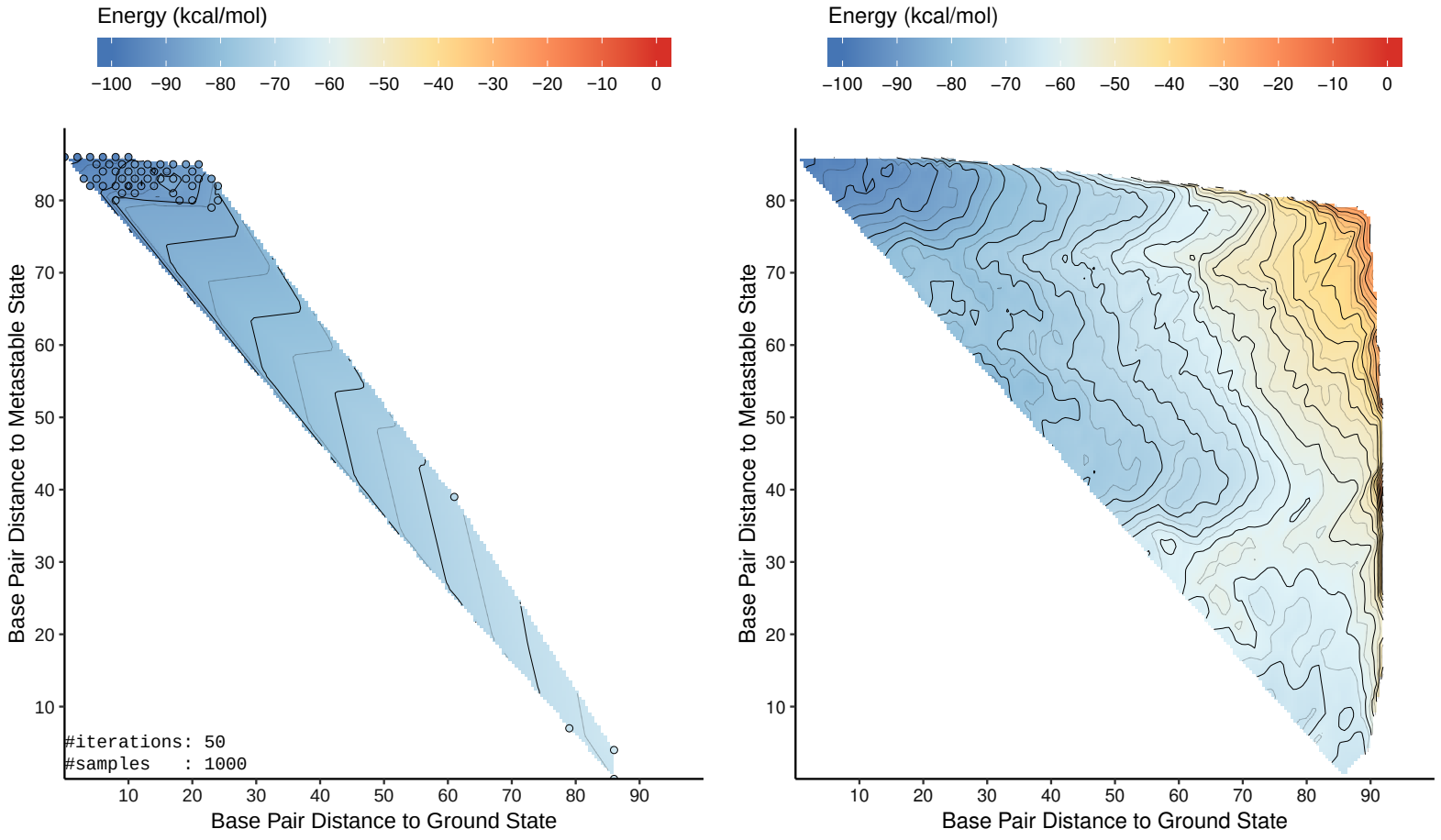
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 50, # samples: 1,000, # local minima: 133

Example: Qβ replicase template SV11

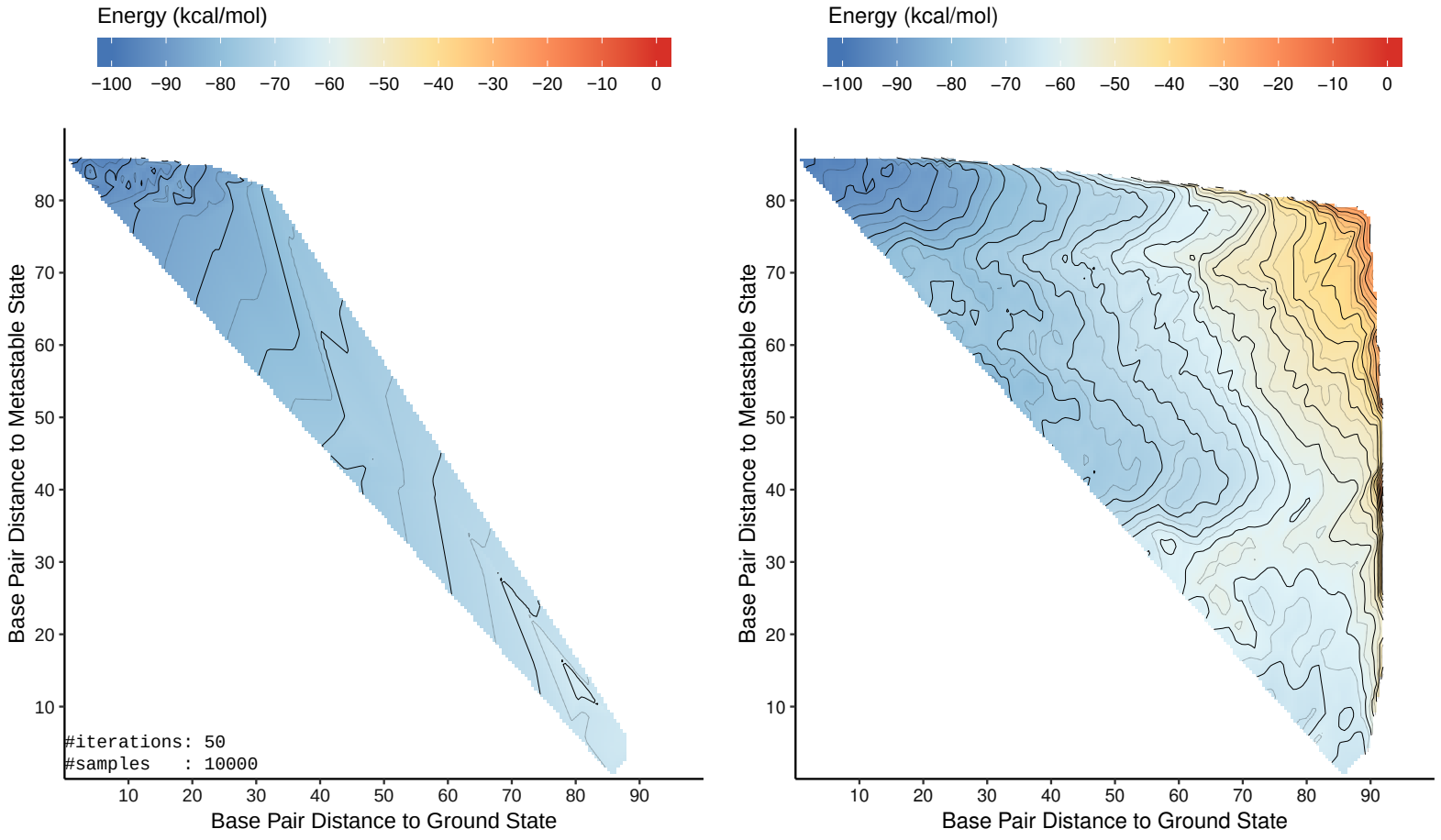
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 50, # samples: 1,000, # local minima: 133

Example: Qβ replicase template SV11

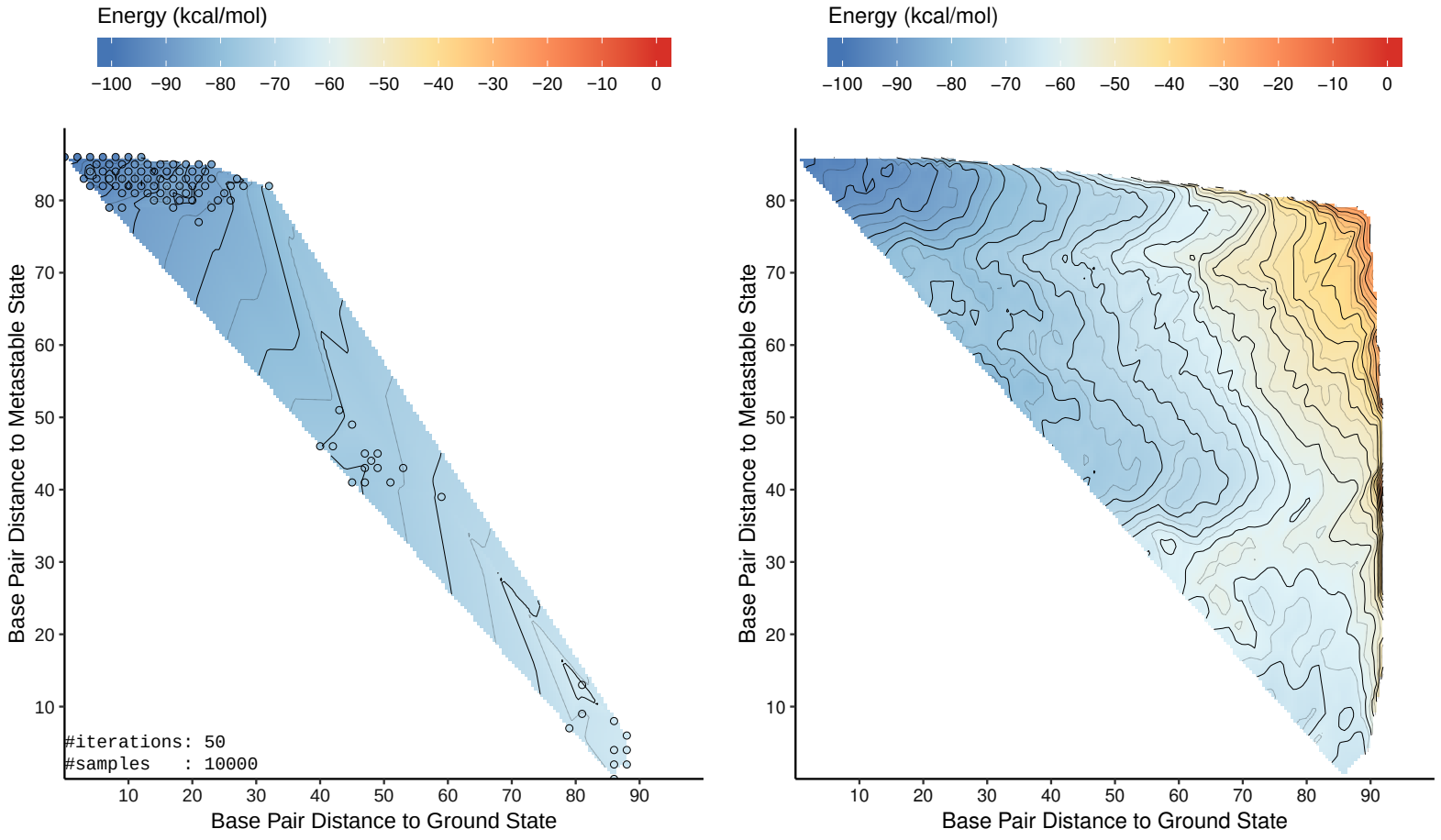
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 50, # samples: 10, 000, # local minima: 320

Example: Qβ replicase template SV11

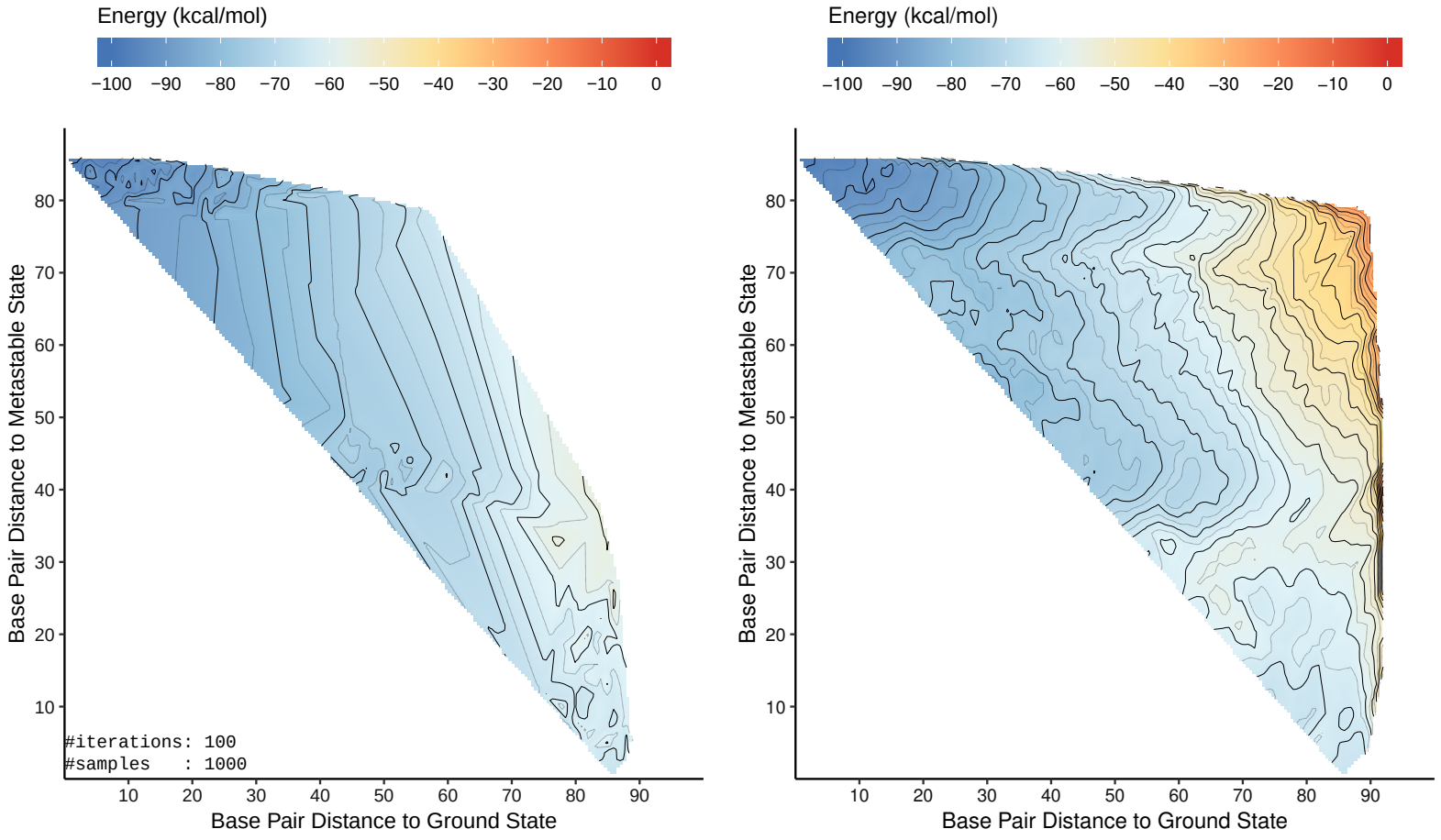
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 50, # samples: 10, 000, # local minima: 320

Example: Qβ replicase template SV11

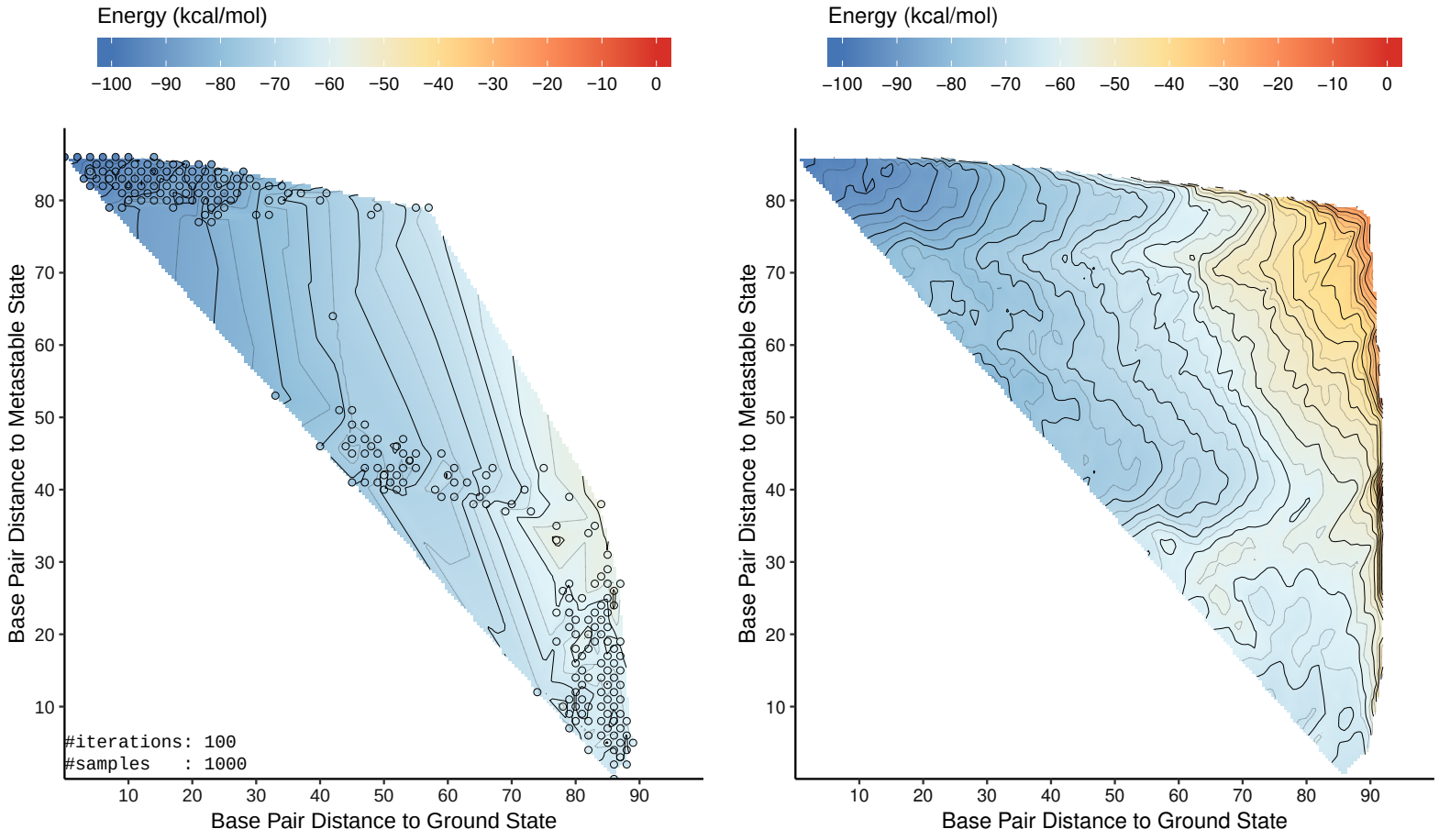
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 100, # samples: 1, 000, # local minima: 765

Example: Qβ replicase template SV11

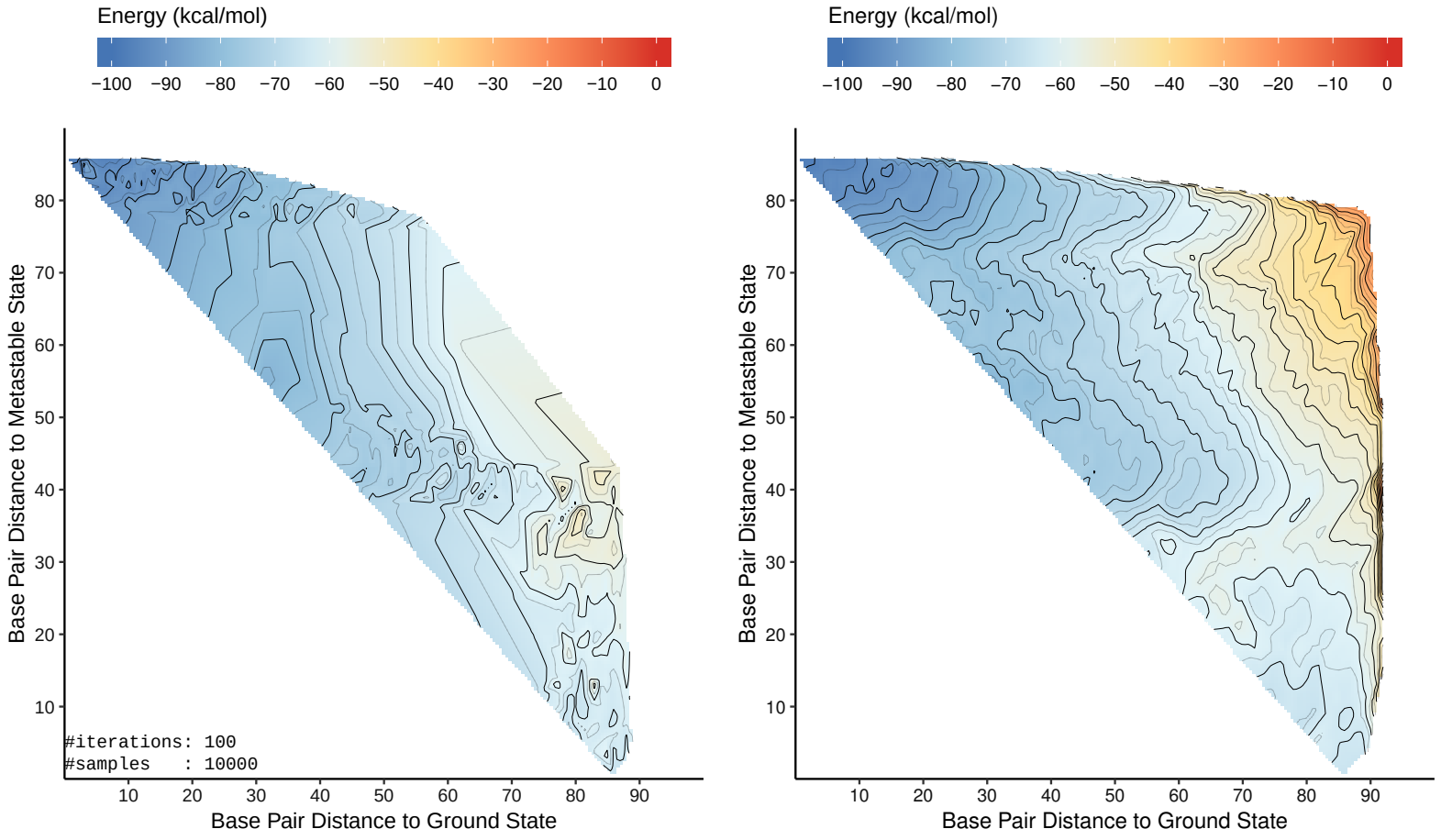
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 100, # samples: 1, 000, # local minima: 765

Example: Qβ replicase template SV11

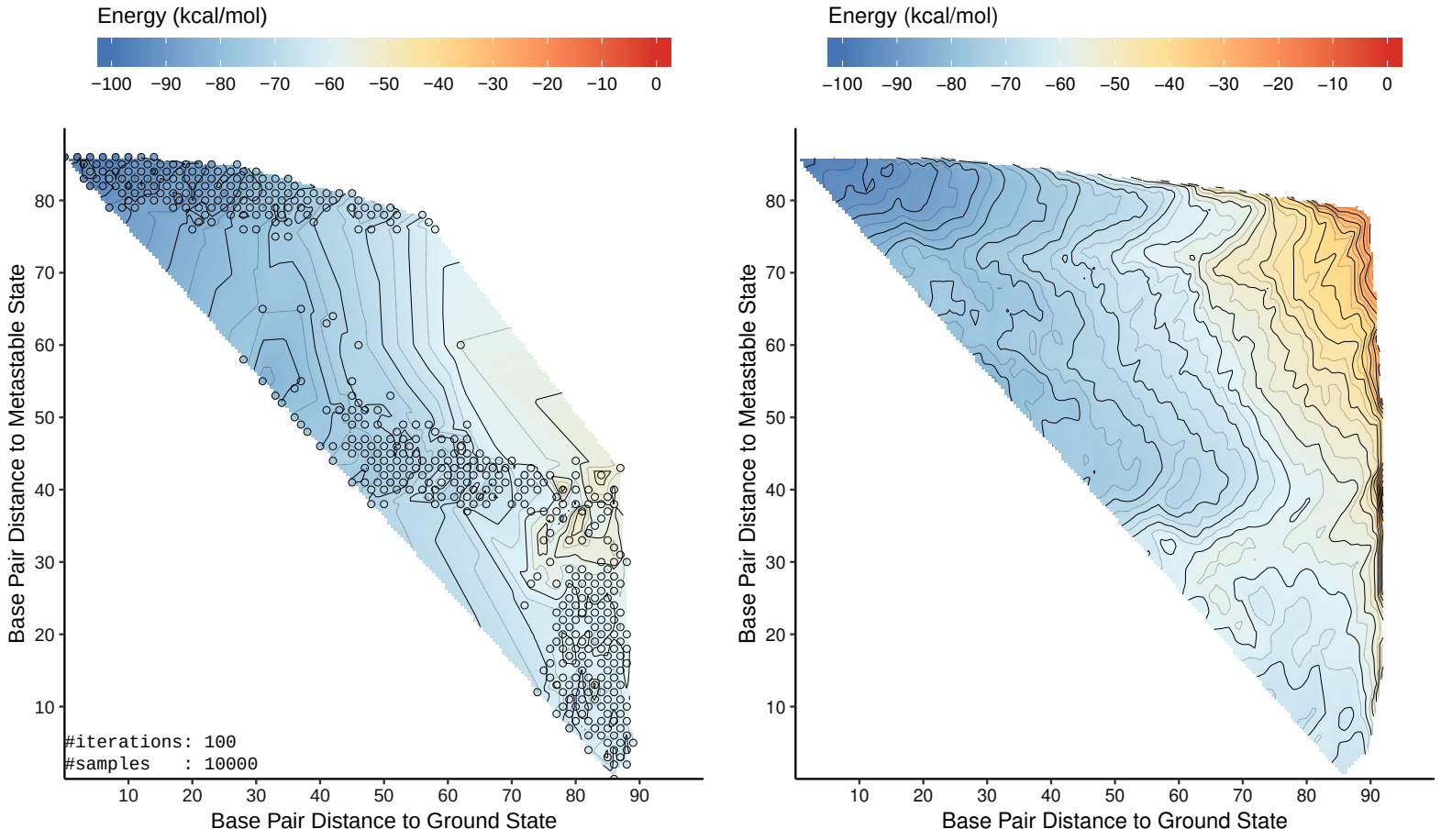
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 100, # samples: 10, 000, # local minima: 2, 549

Example: Qβ replicase template SV11

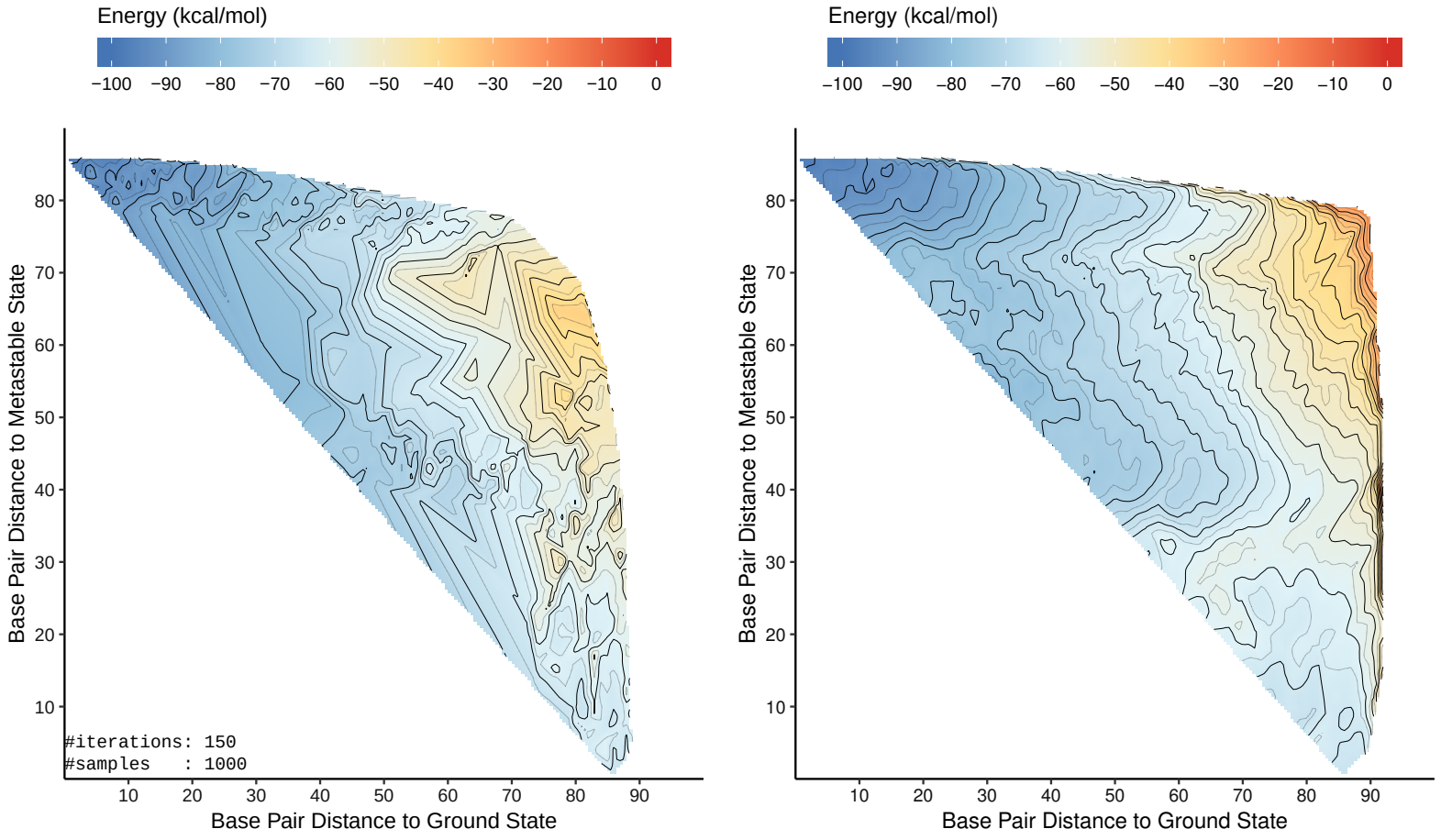
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 100, # samples: 10, 000, # local minima: 2, 549

Example: Qβ replicase template SV11

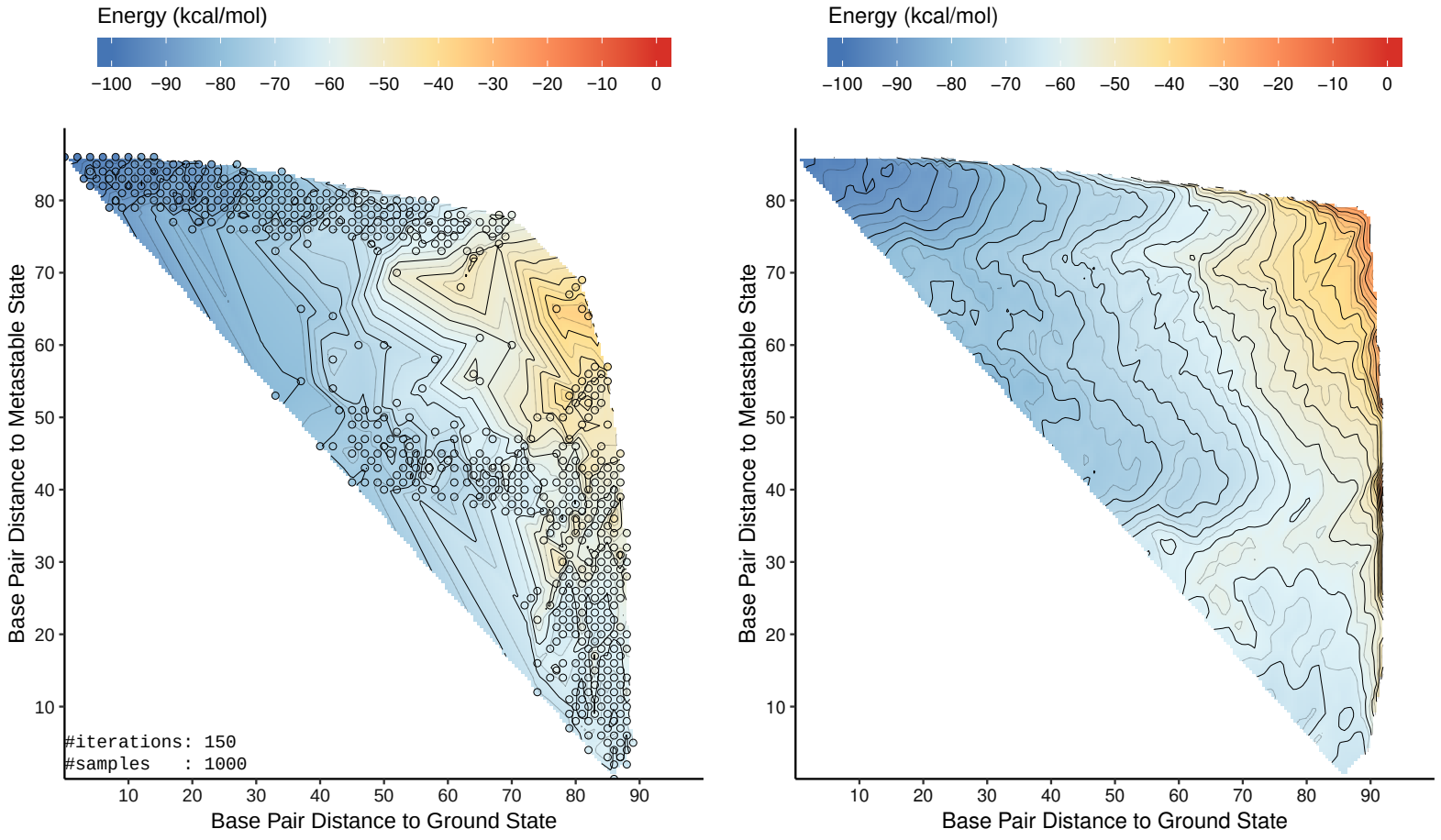
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 150, # samples: 1,000, # local minima: 3,781

Example: Qβ replicase template SV11

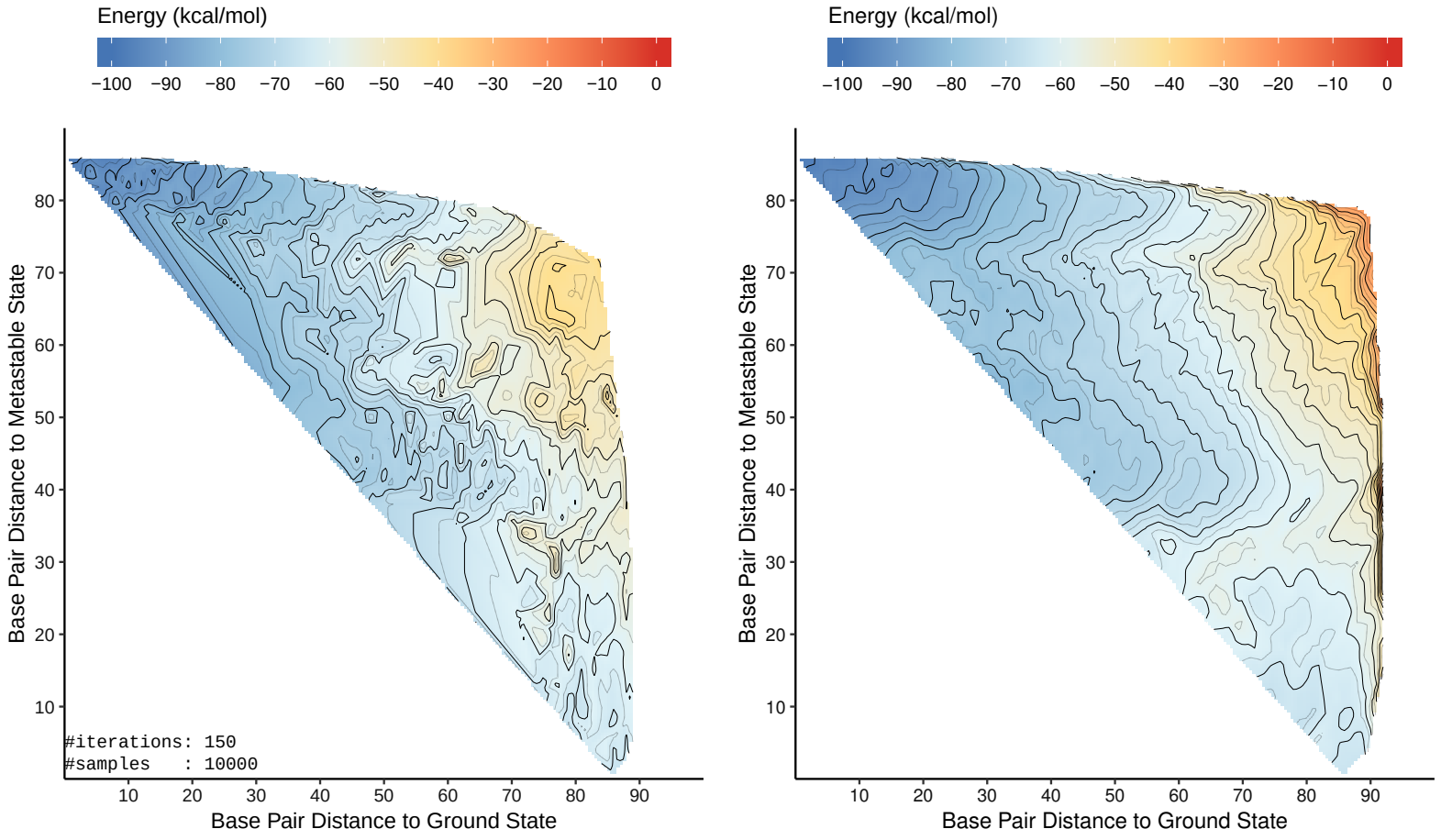
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 150, # samples: 1,000, # local minima: 3,781

Example: Qβ replicase template SV11

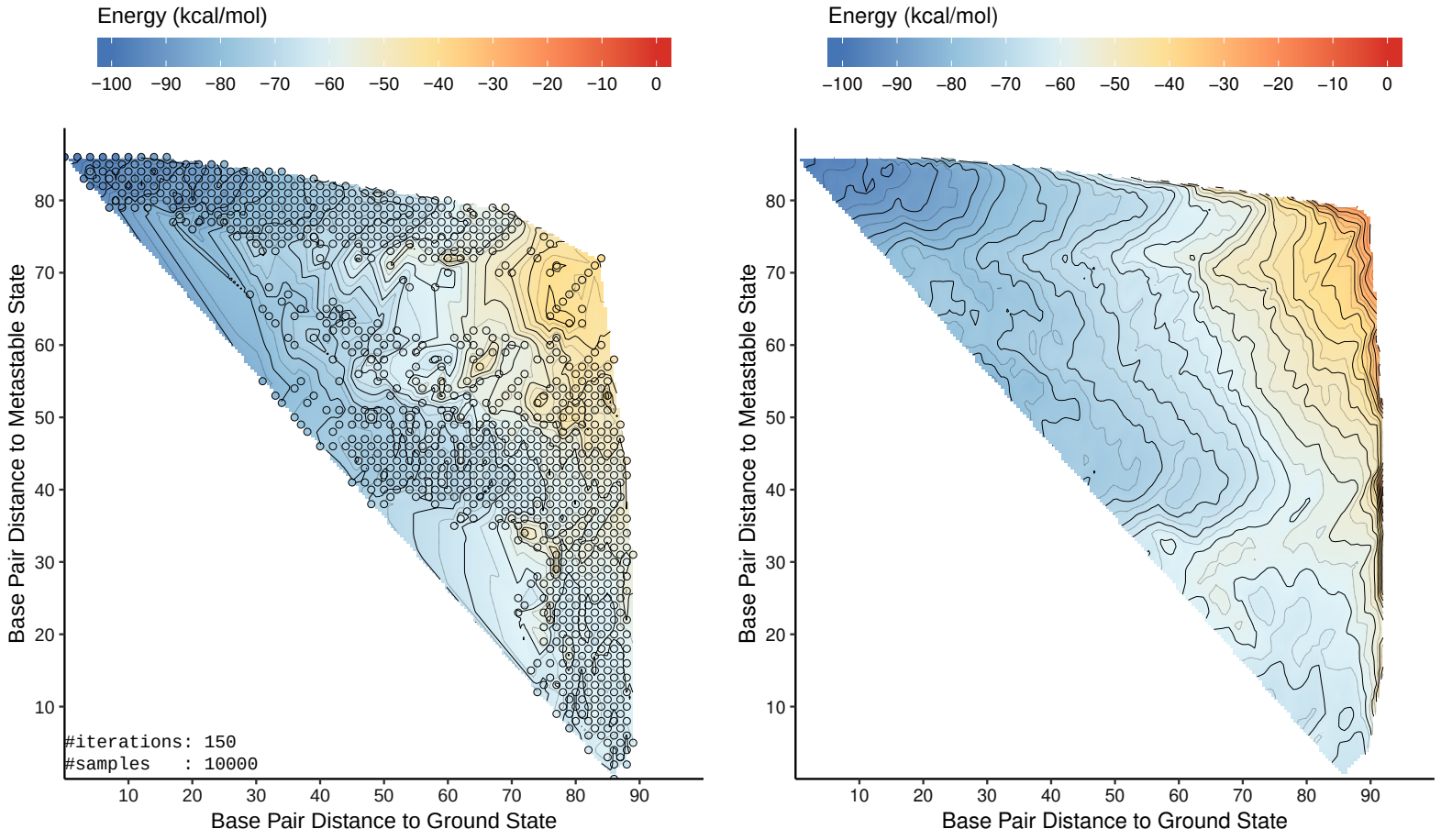
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 150, # samples: 10, 000, # local minima: 15, 041

Example: Qβ replicase template SV11

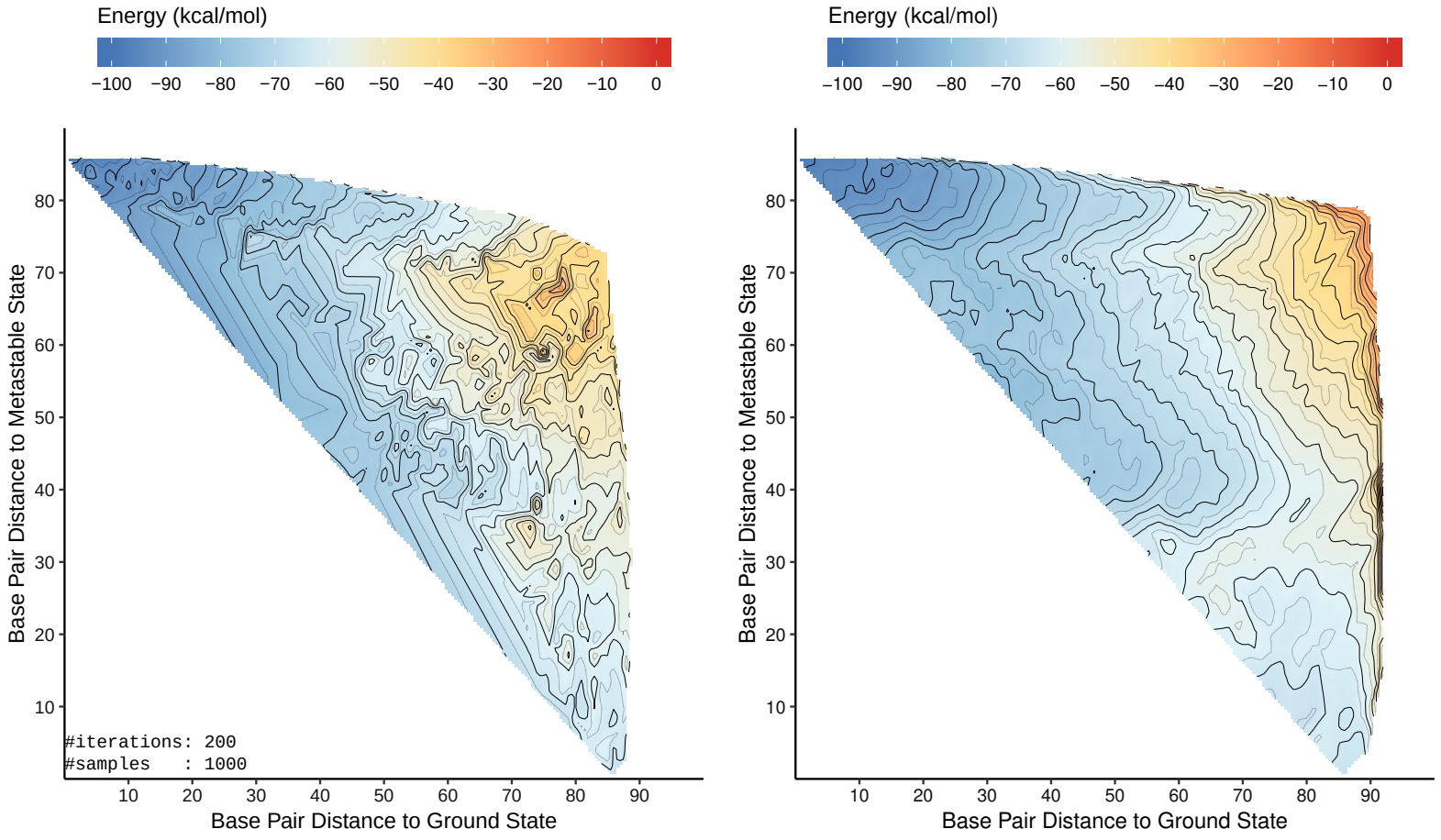
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 150, # samples: 10, 000, # local minima: 15, 041

Example: Qβ replicase template SV11

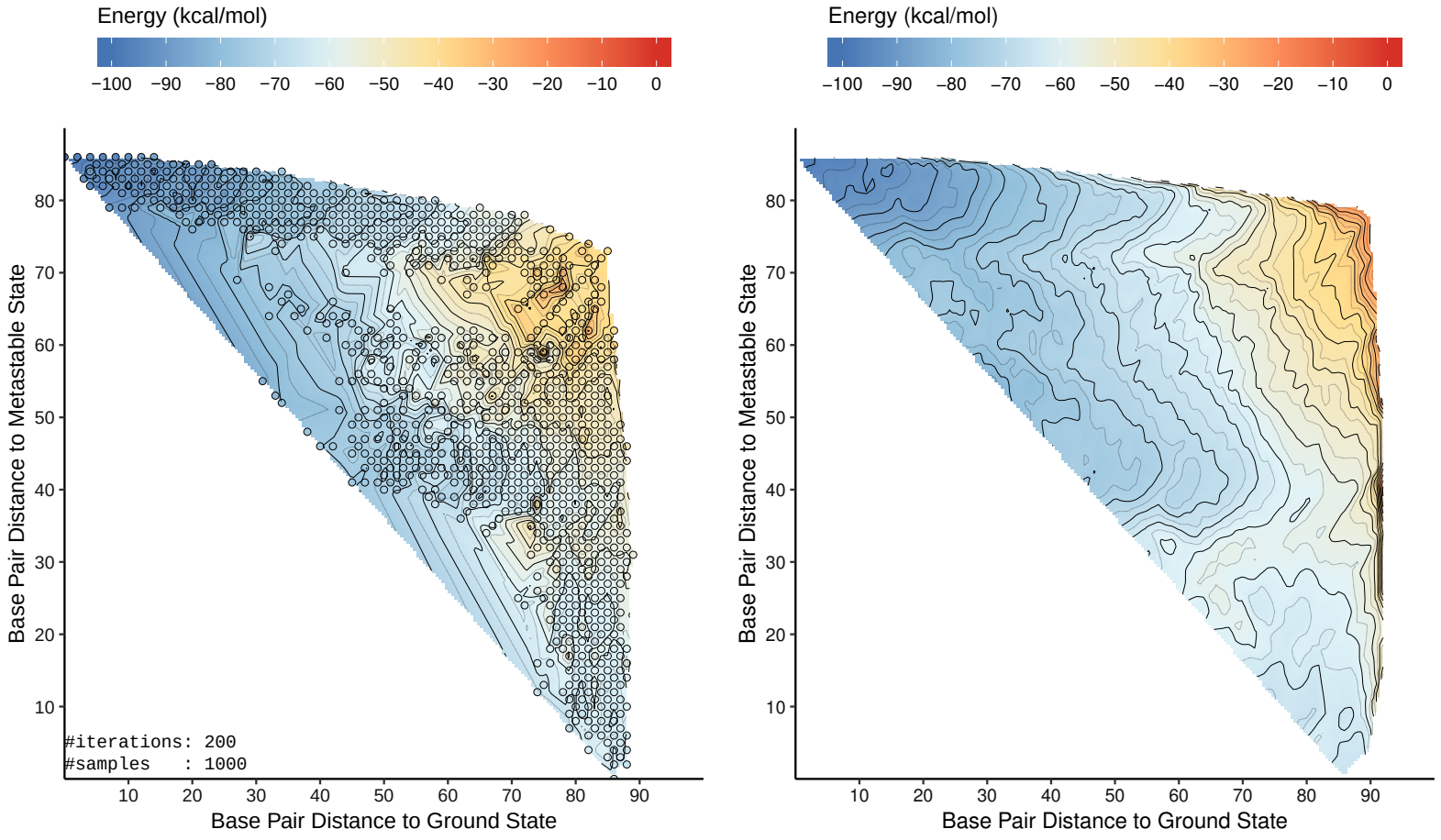
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 200, # samples: 1,000, # local minima: 13,066

Example: Qβ replicase template SV11

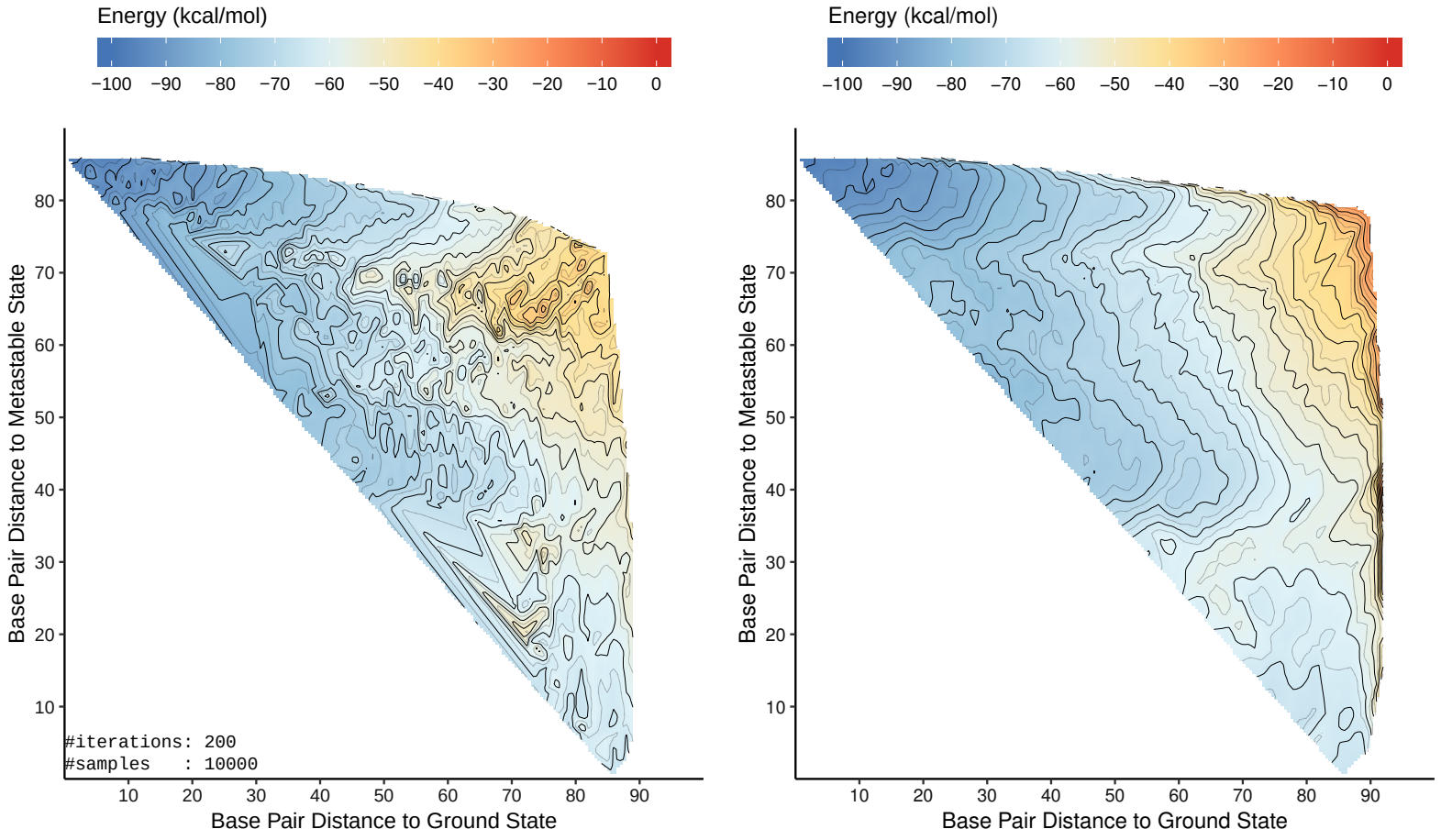
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 200, # samples: 1, 000, # local minima: 13, 066

Example: Qβ replicase template SV11

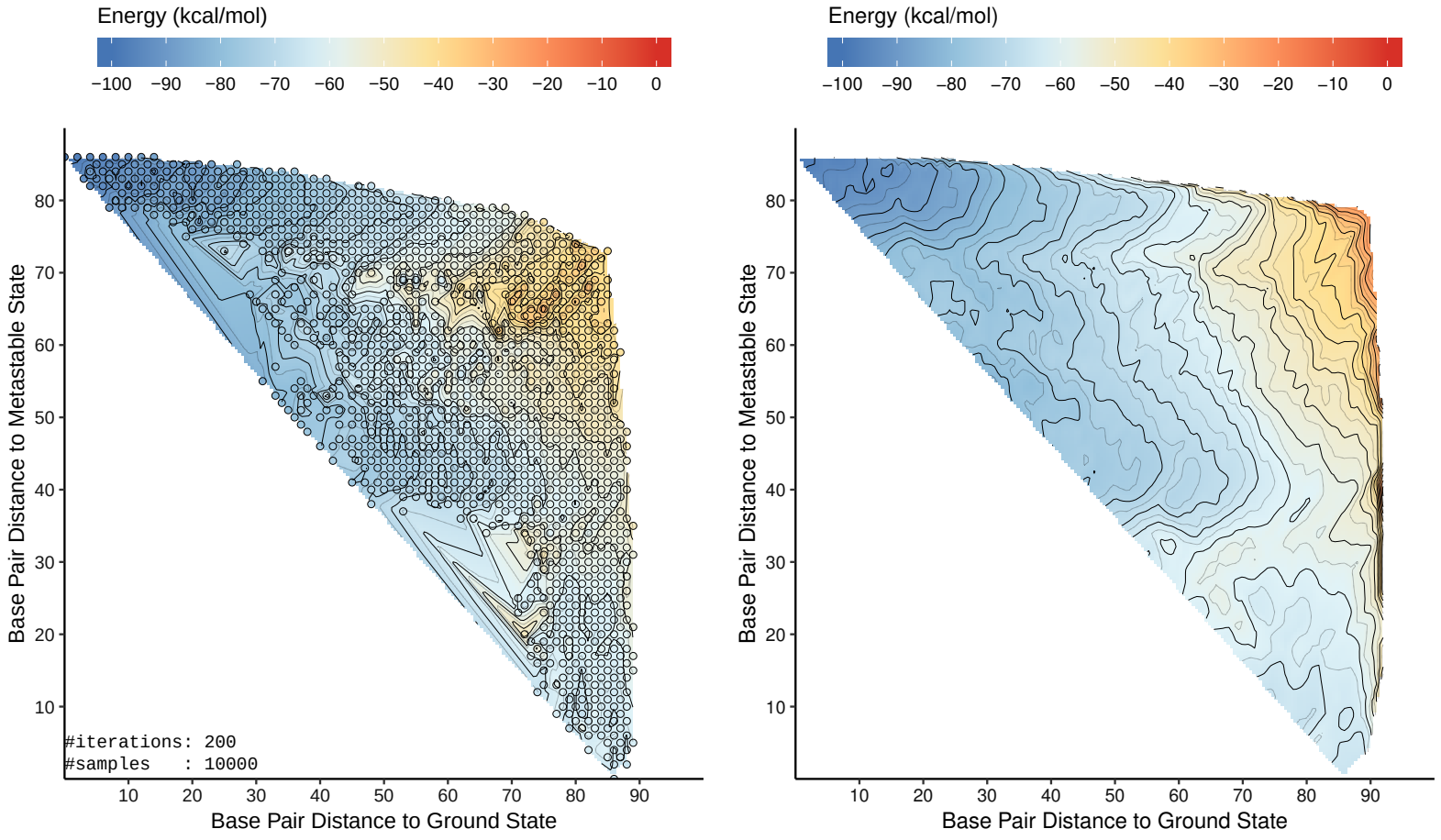
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 200, # samples: 10, 000, # local minima: 57, 296

Example: Qβ replicase template SV11

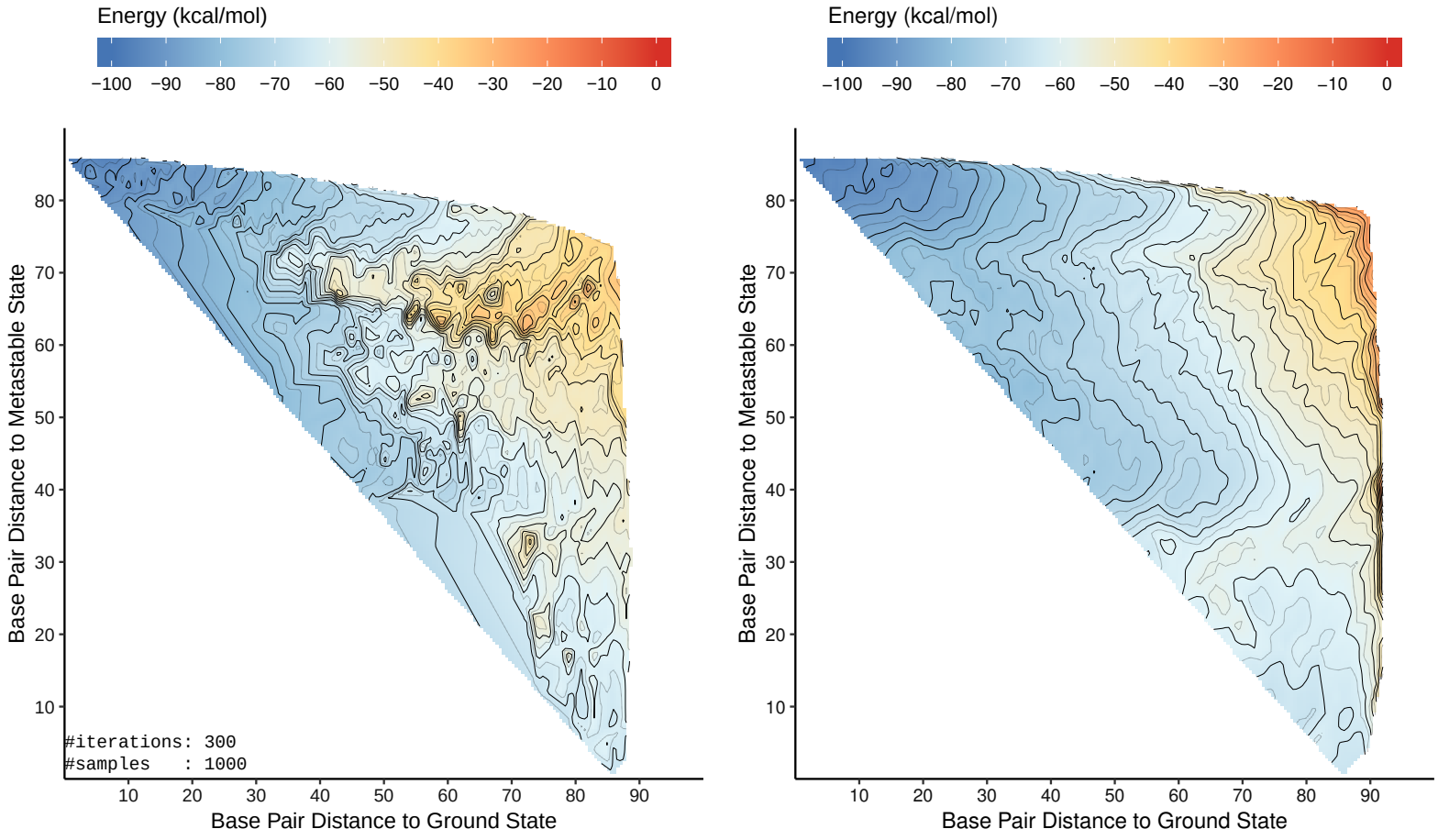
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 200, # samples: 10, 000, # local minima: 57, 296

Example: Qβ replicase template SV11

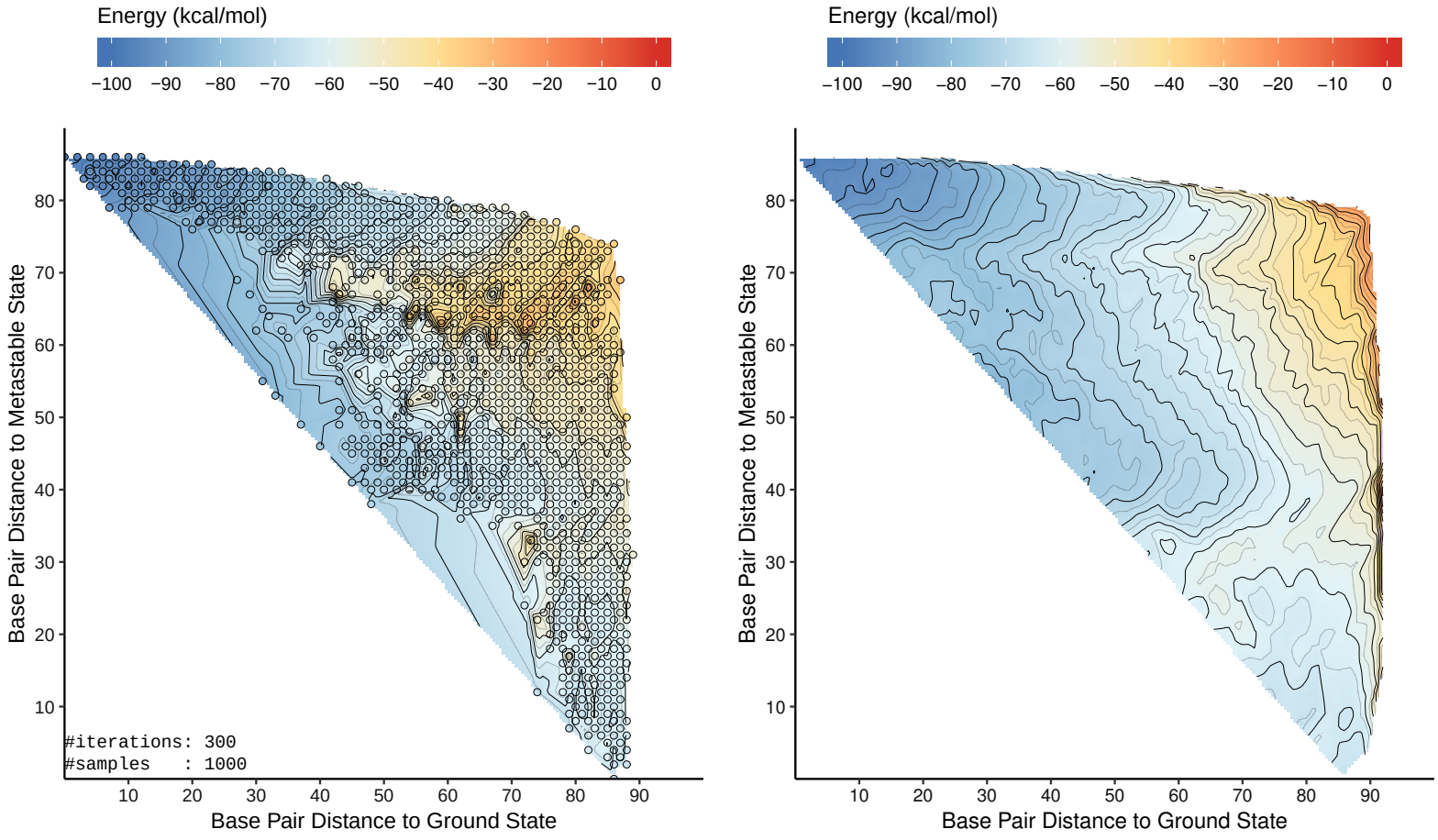
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 300, # samples: 1,000, # local minima: 61,952

Example: Qβ replicase template SV11

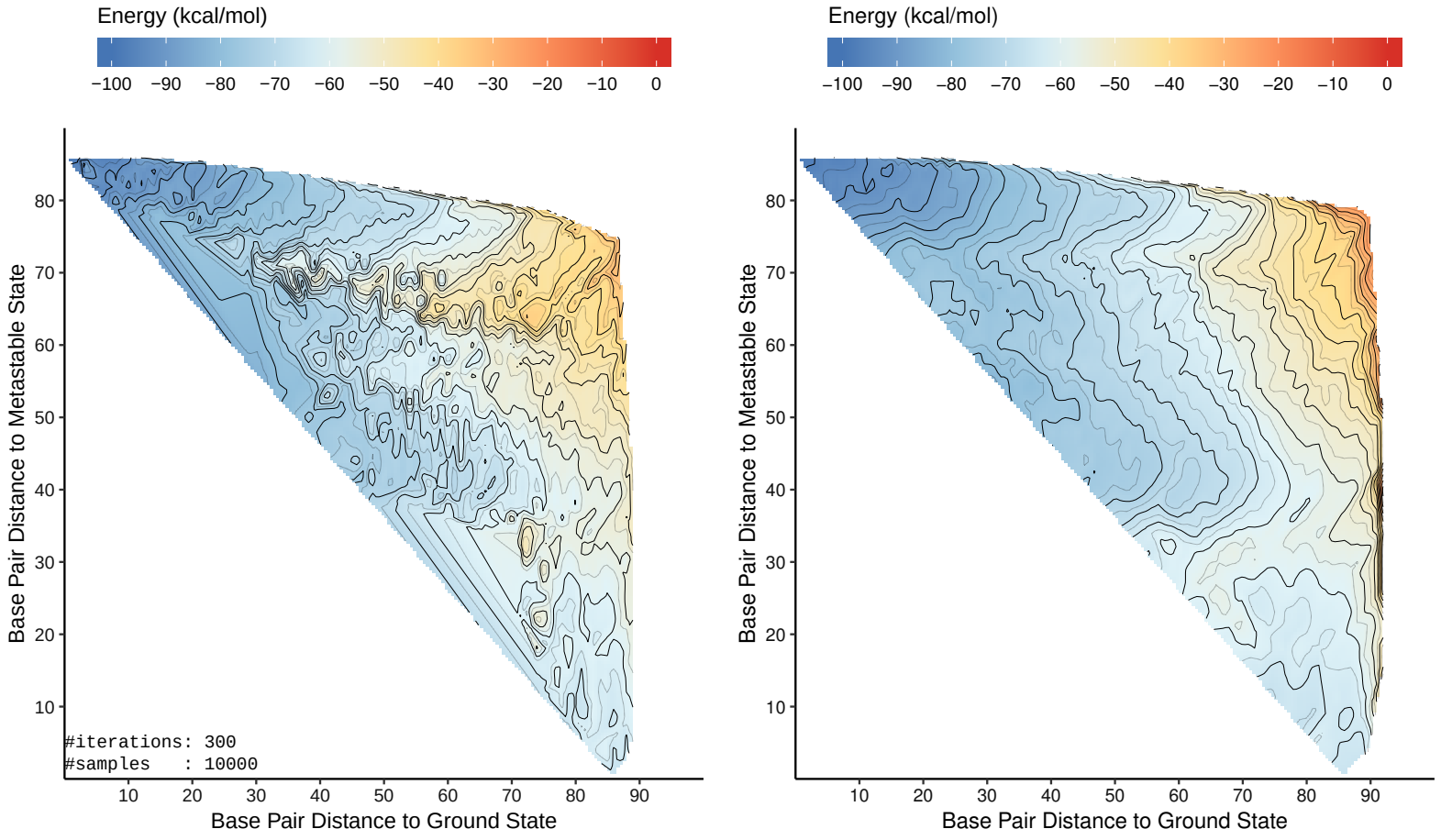
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 300, # samples: 1,000, # local minima: 61,952

Example: Qβ replicase template SV11

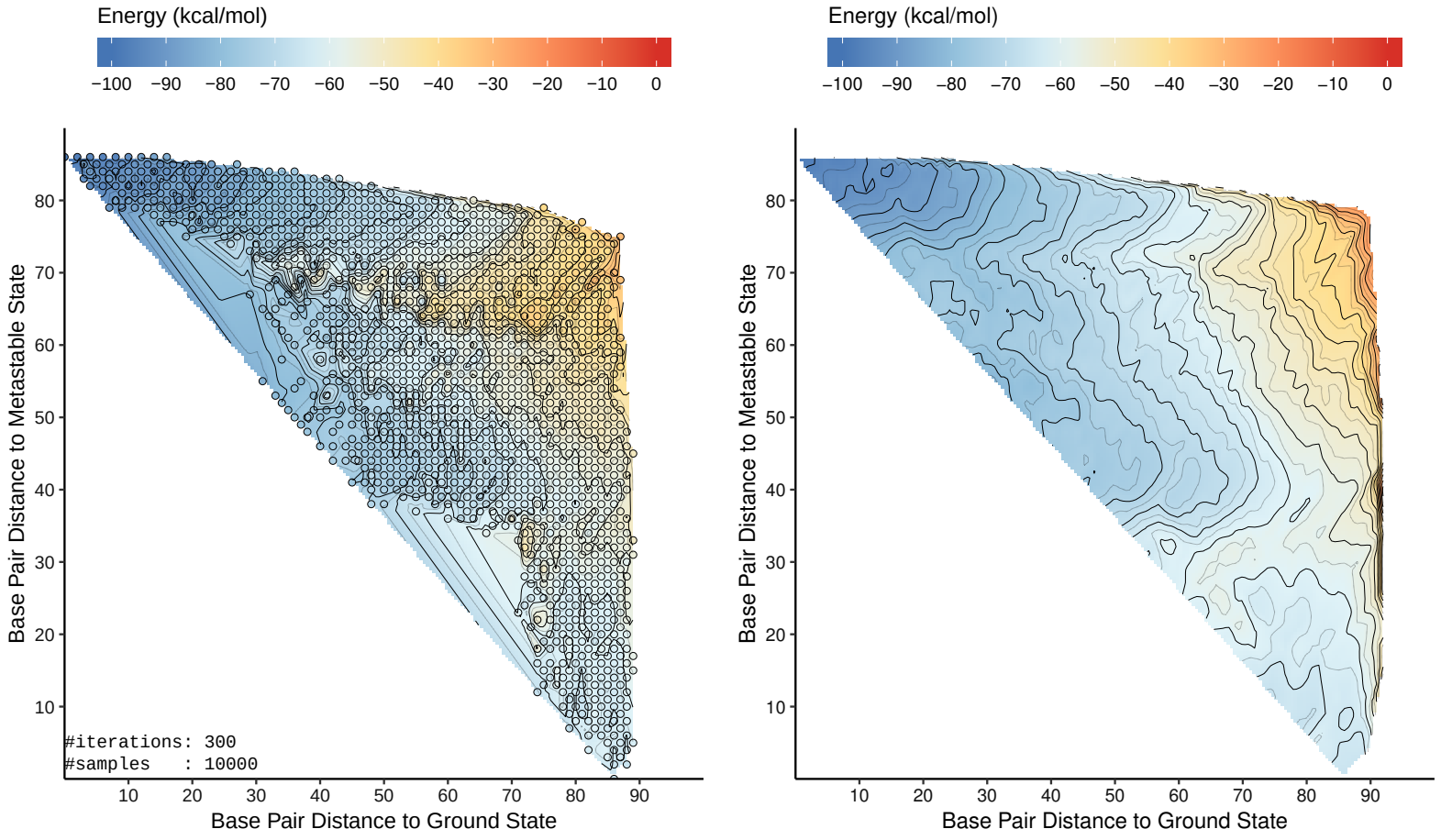
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 300, # samples: 10, 000, # local minima: 309, 669

Example: Qβ replicase template SV11

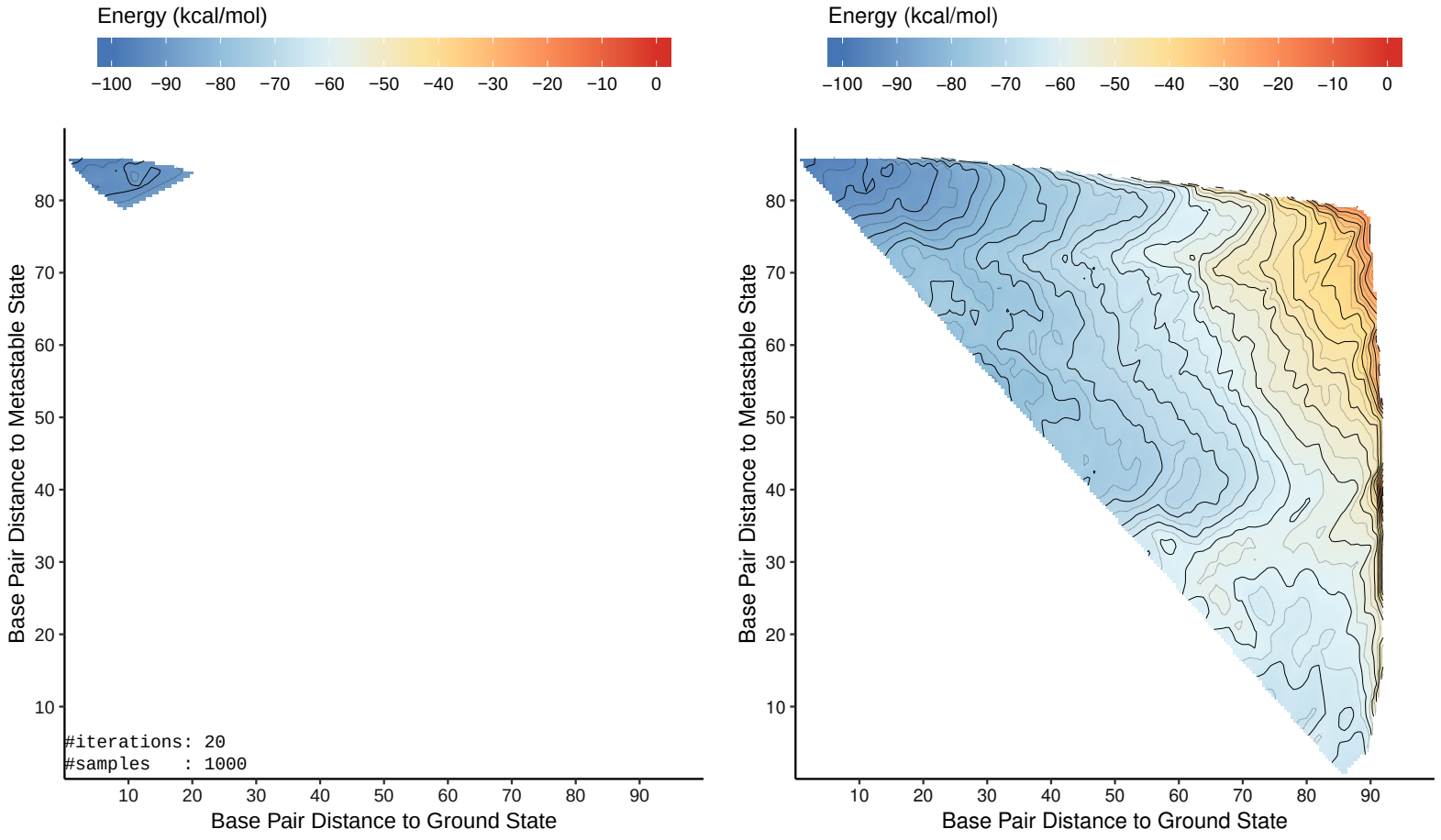
`RNAxplorer` repulsion scheme Boltzmann sampling



iterations: 300, # samples: 10, 000, # local minima: 309, 669

Example: Qβ replicase template SV11

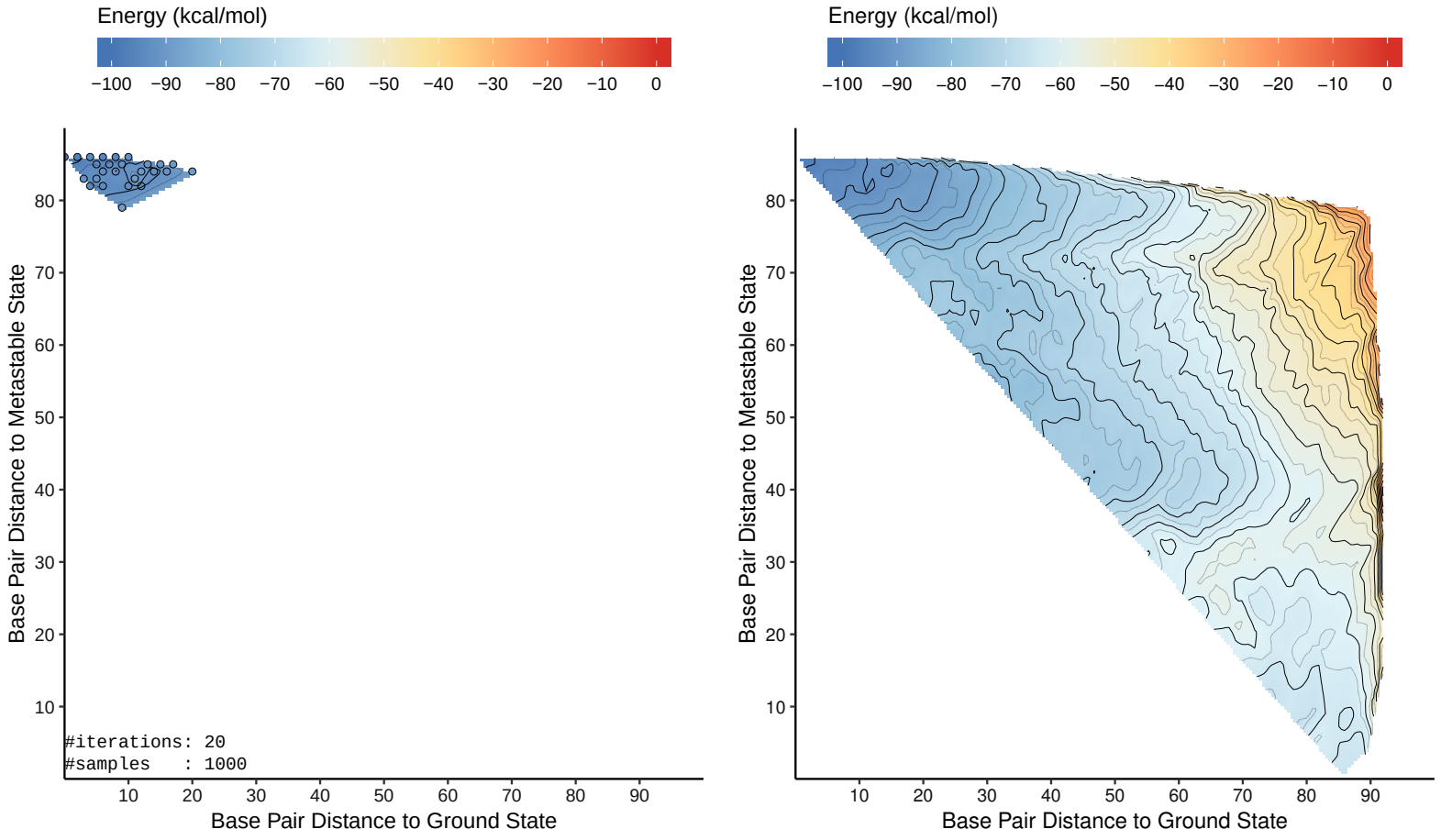
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 20, # samples: 1,000, # local minima: 47

Example: Qβ replicase template SV11

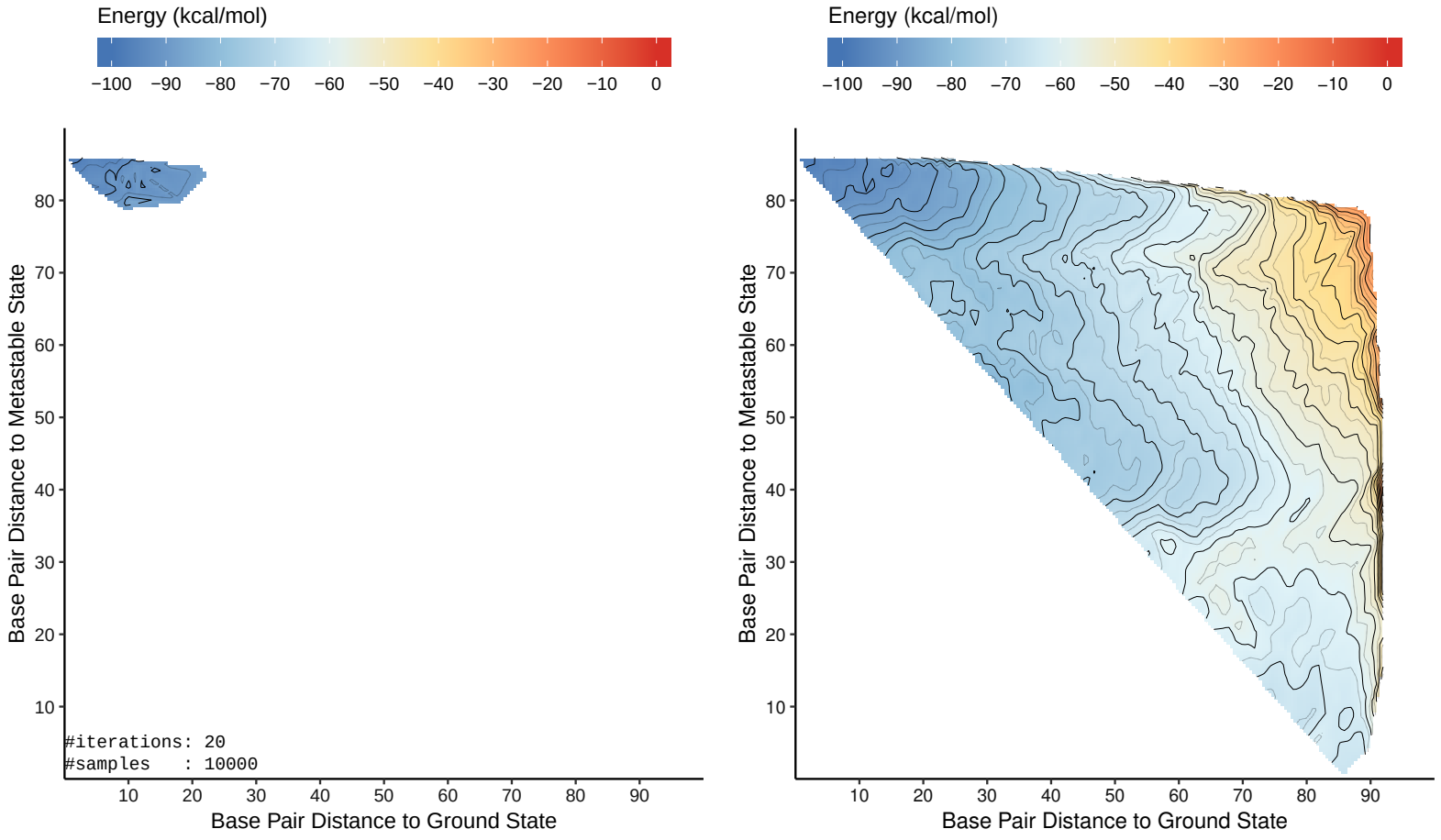
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 20, # samples: 1,000, # local minima: 47

Example: Qβ replicase template SV11

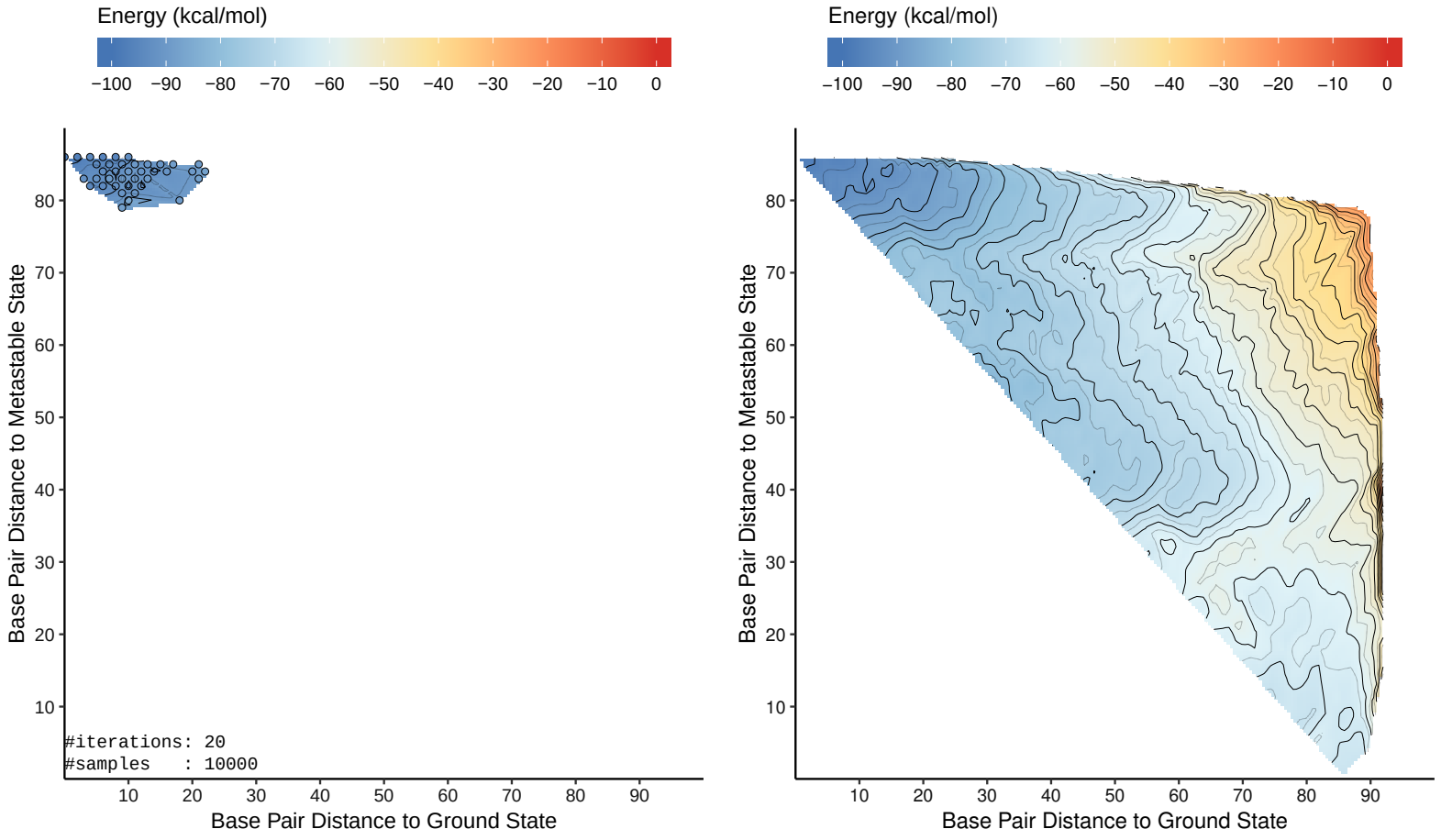
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 20, # samples: 10, 000, # local minima: 92

Example: Qβ replicase template SV11

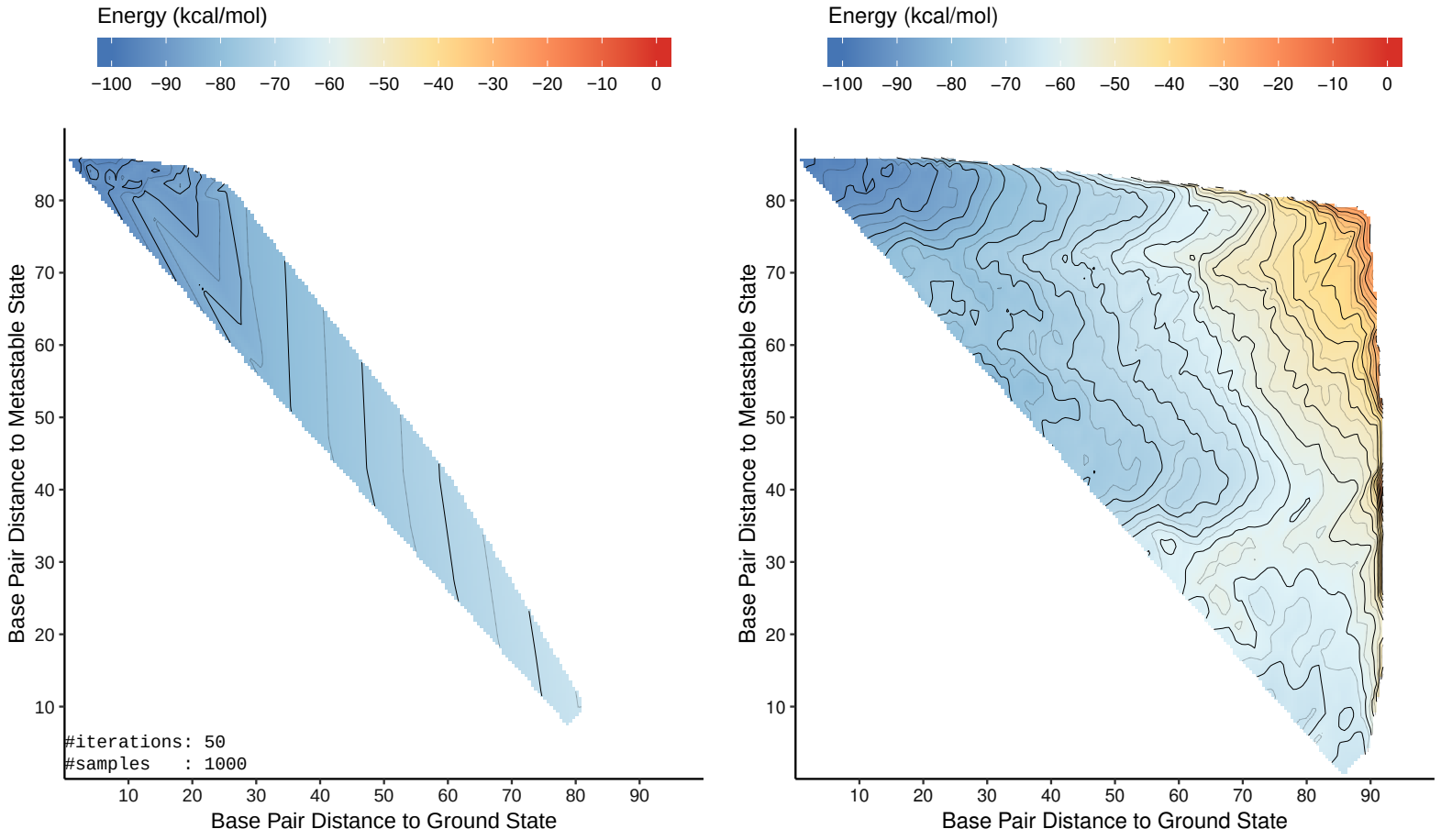
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 20, # samples: 10, 000, # local minima: 92

Example: Qβ replicase template SV11

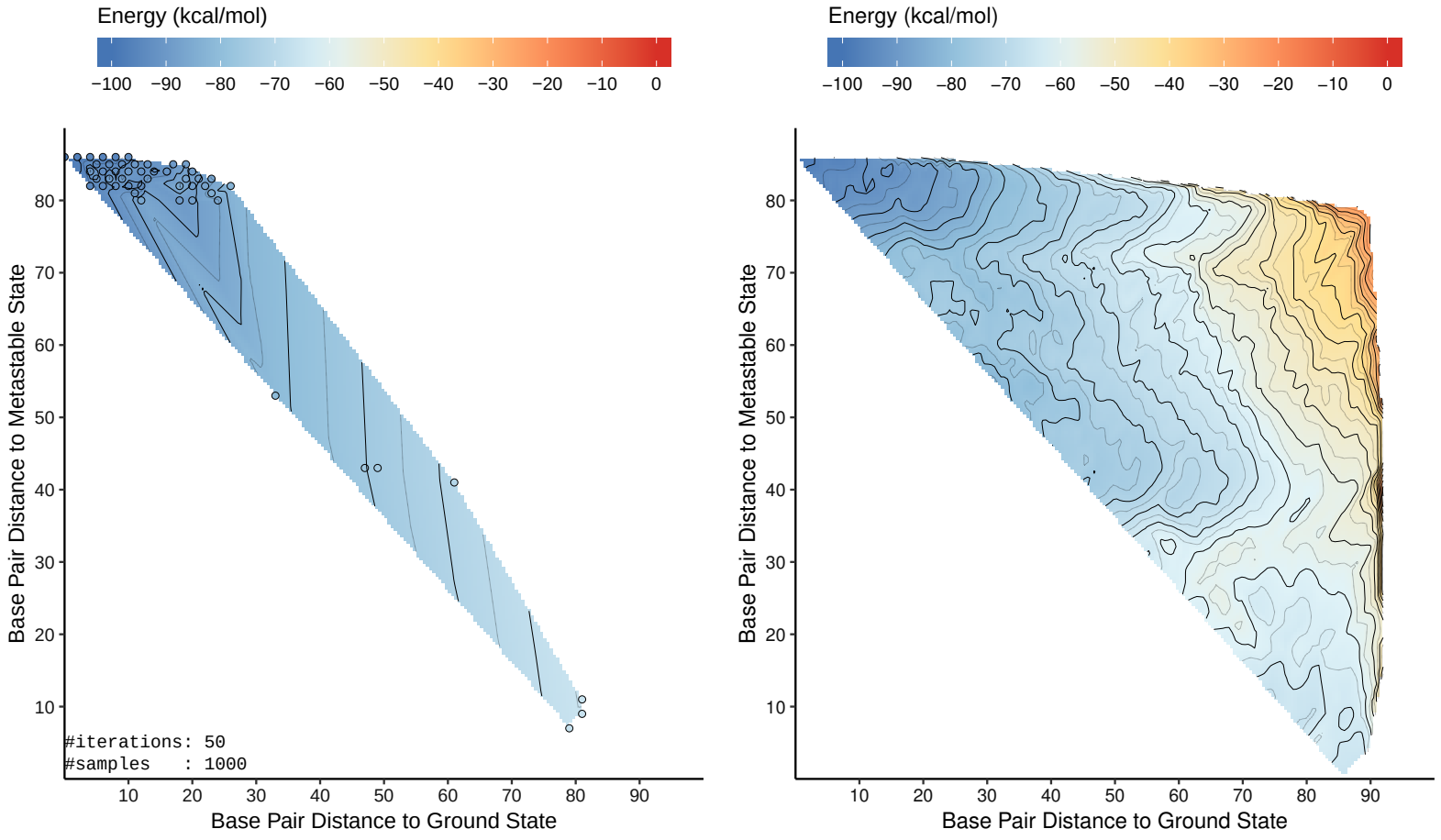
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 50, # samples: 1,000, # local minima: 119

Example: Qβ replicase template SV11

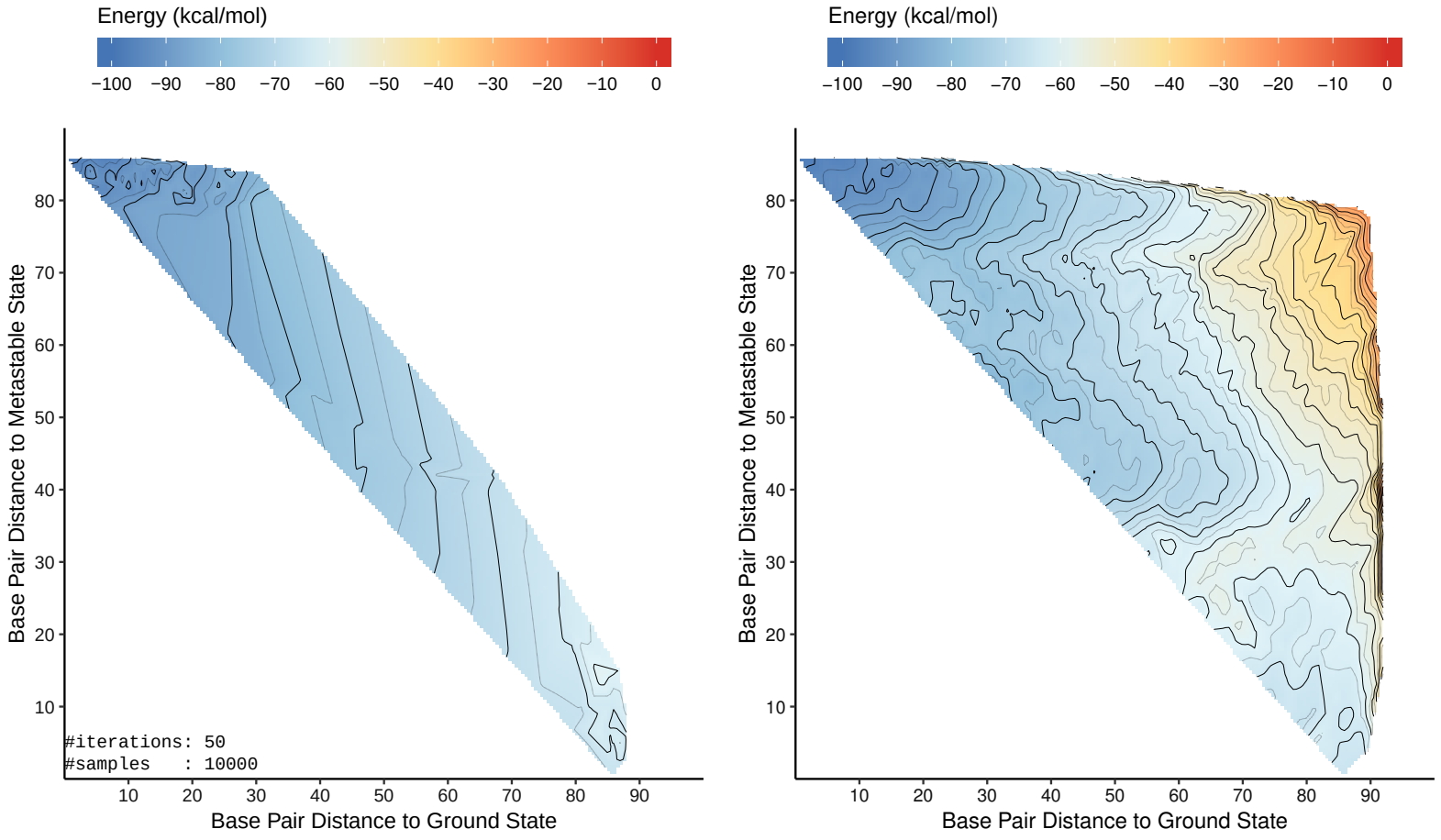
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 50, # samples: 1,000, # local minima: 119

Example: Qβ replicase template SV11

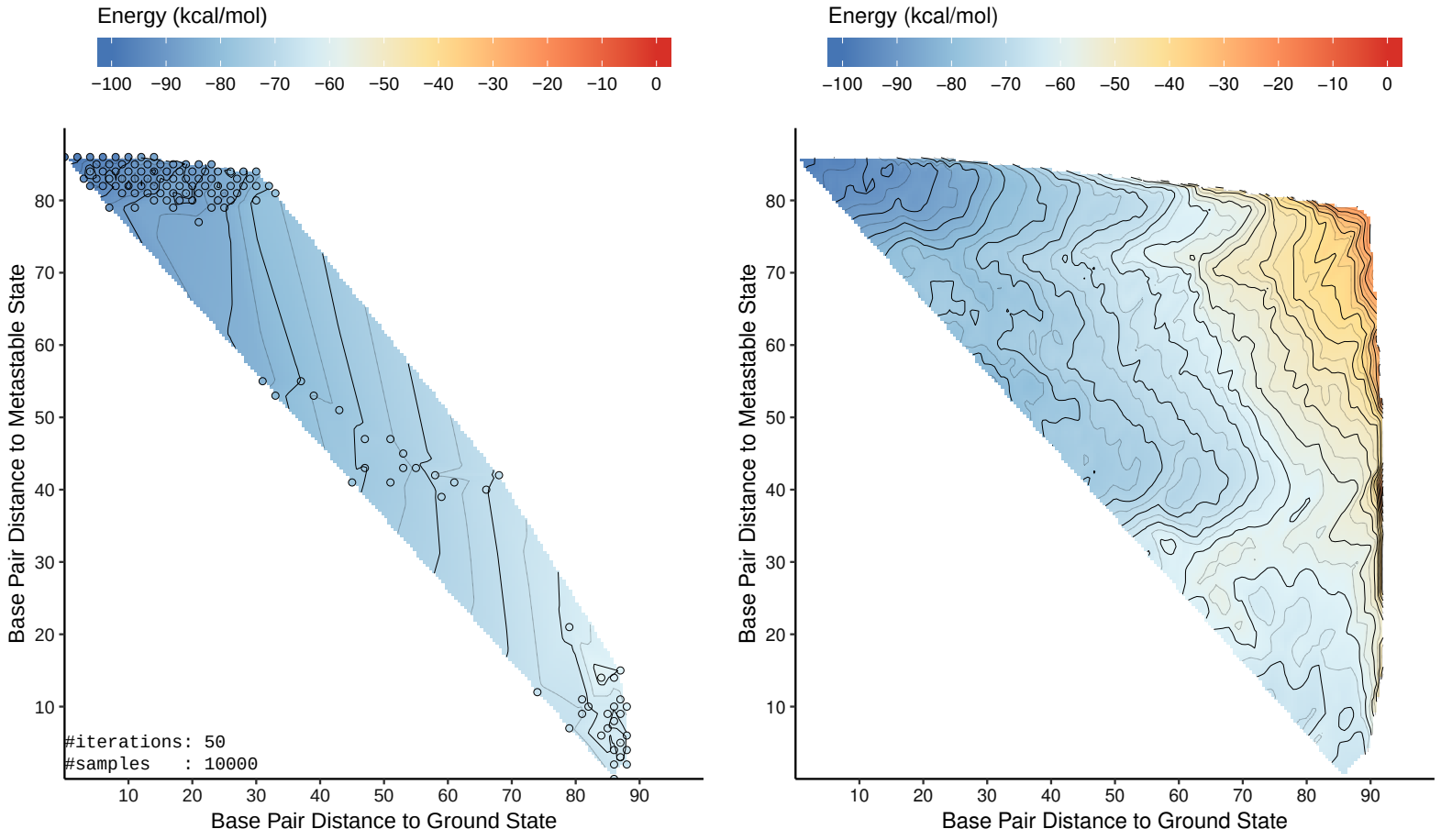
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 50, # samples: 10, 000, # local minima: 484

Example: Qβ replicase template SV11

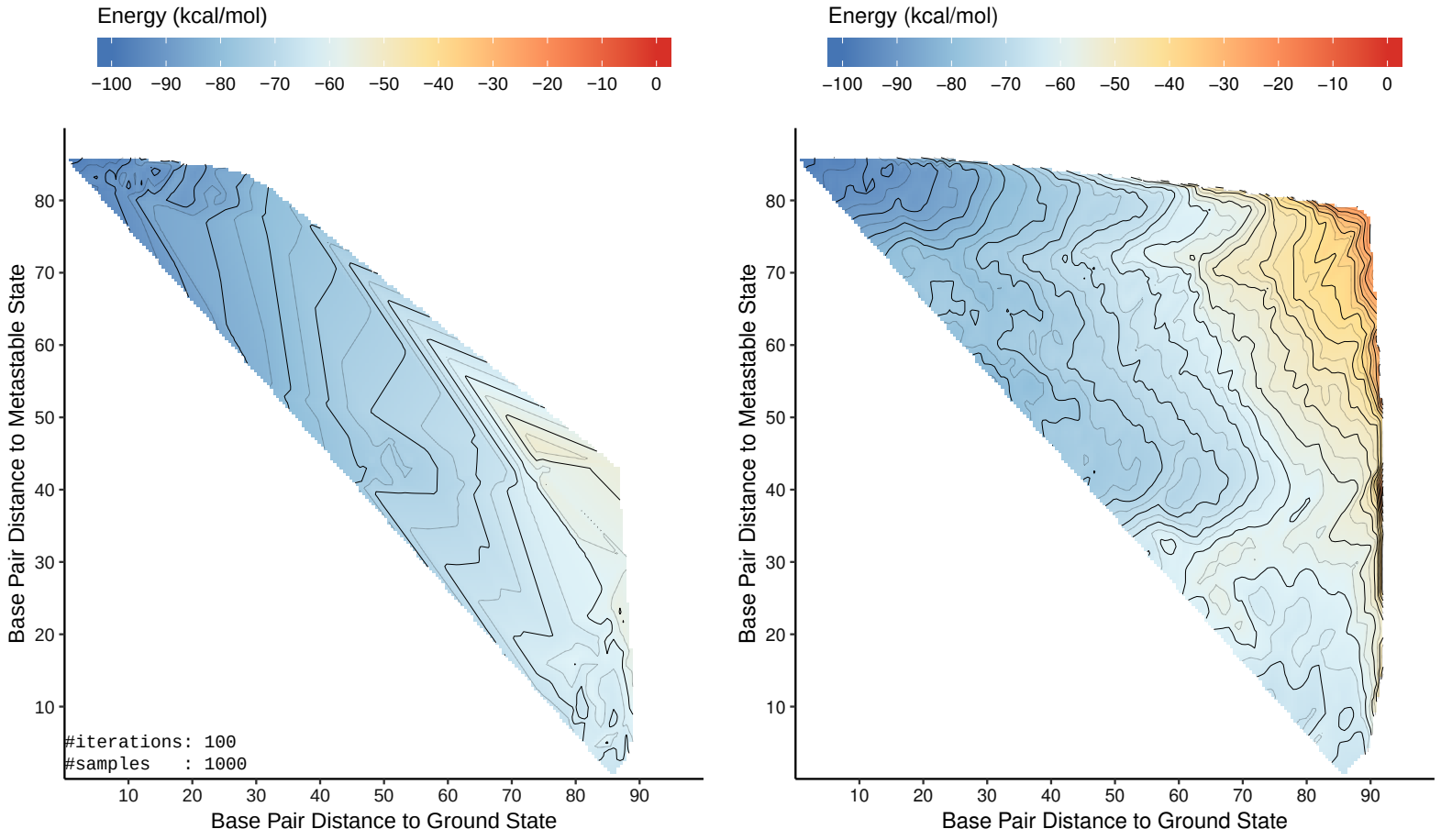
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 50, # samples: 10, 000, # local minima: 484

Example: Qβ replicase template SV11

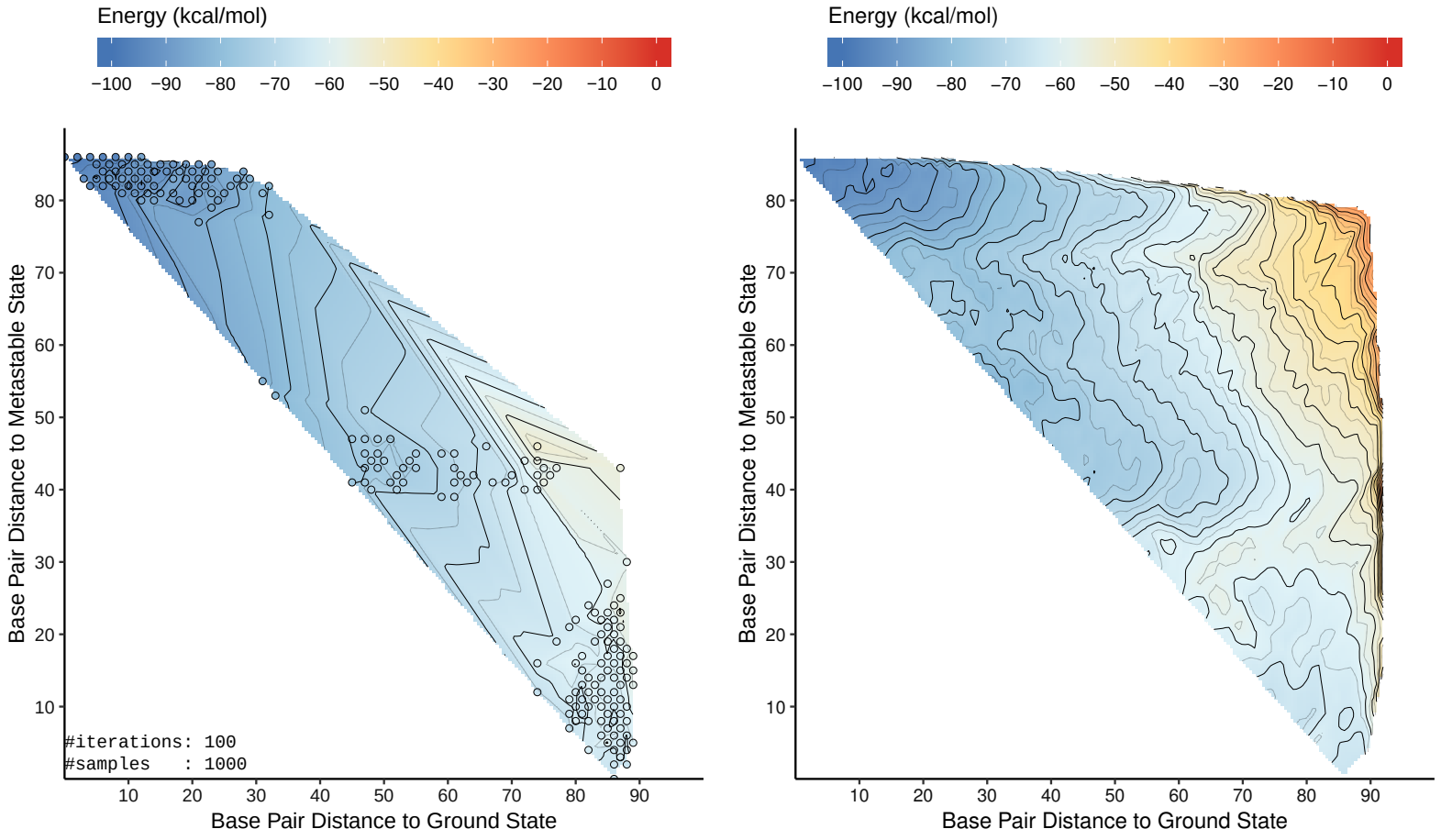
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 100, # samples: 1,000, # local minima: 608

Example: Qβ replicase template SV11

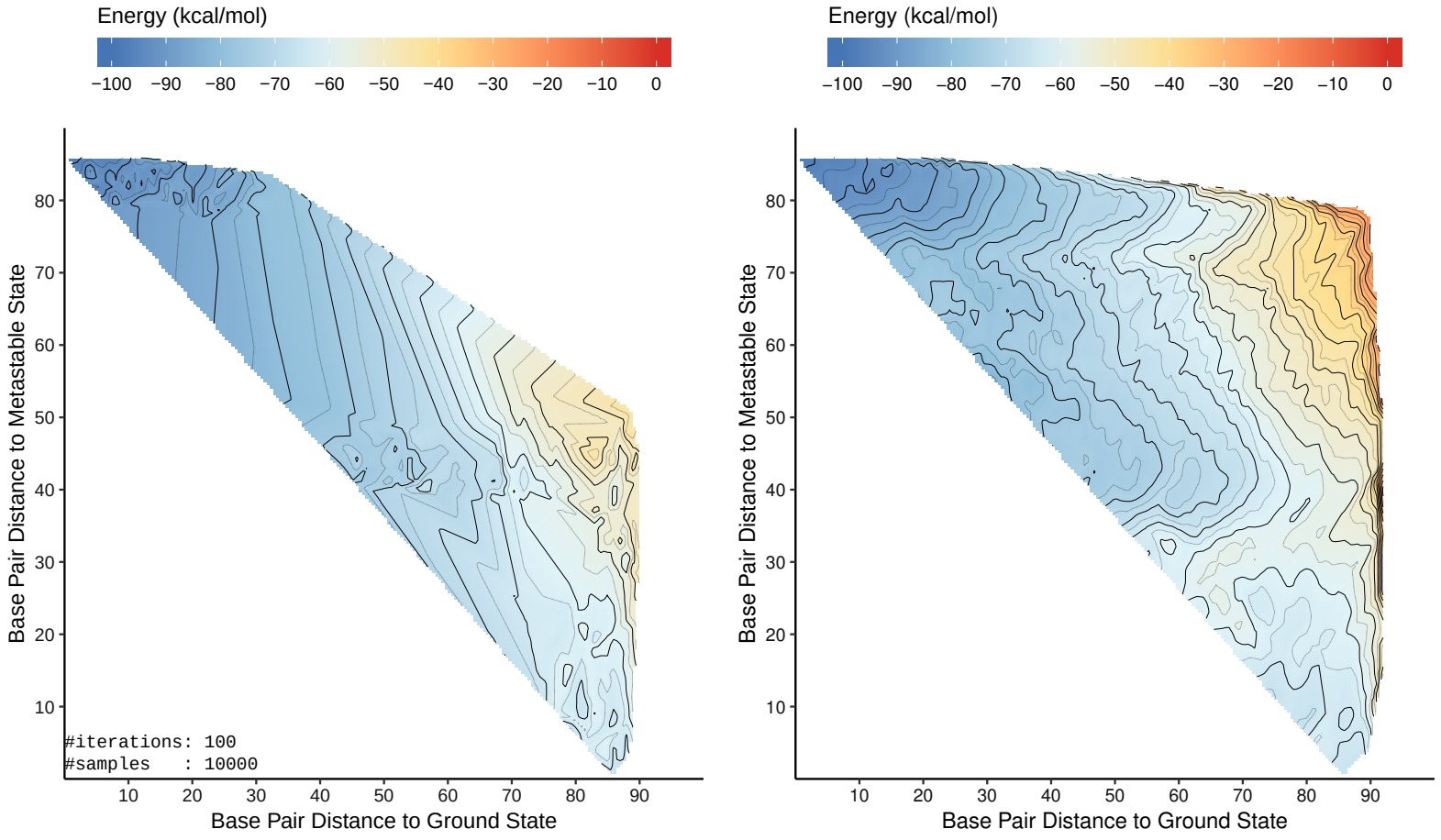
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 100, # samples: 1,000, # local minima: 608

Example: Qβ replicase template SV11

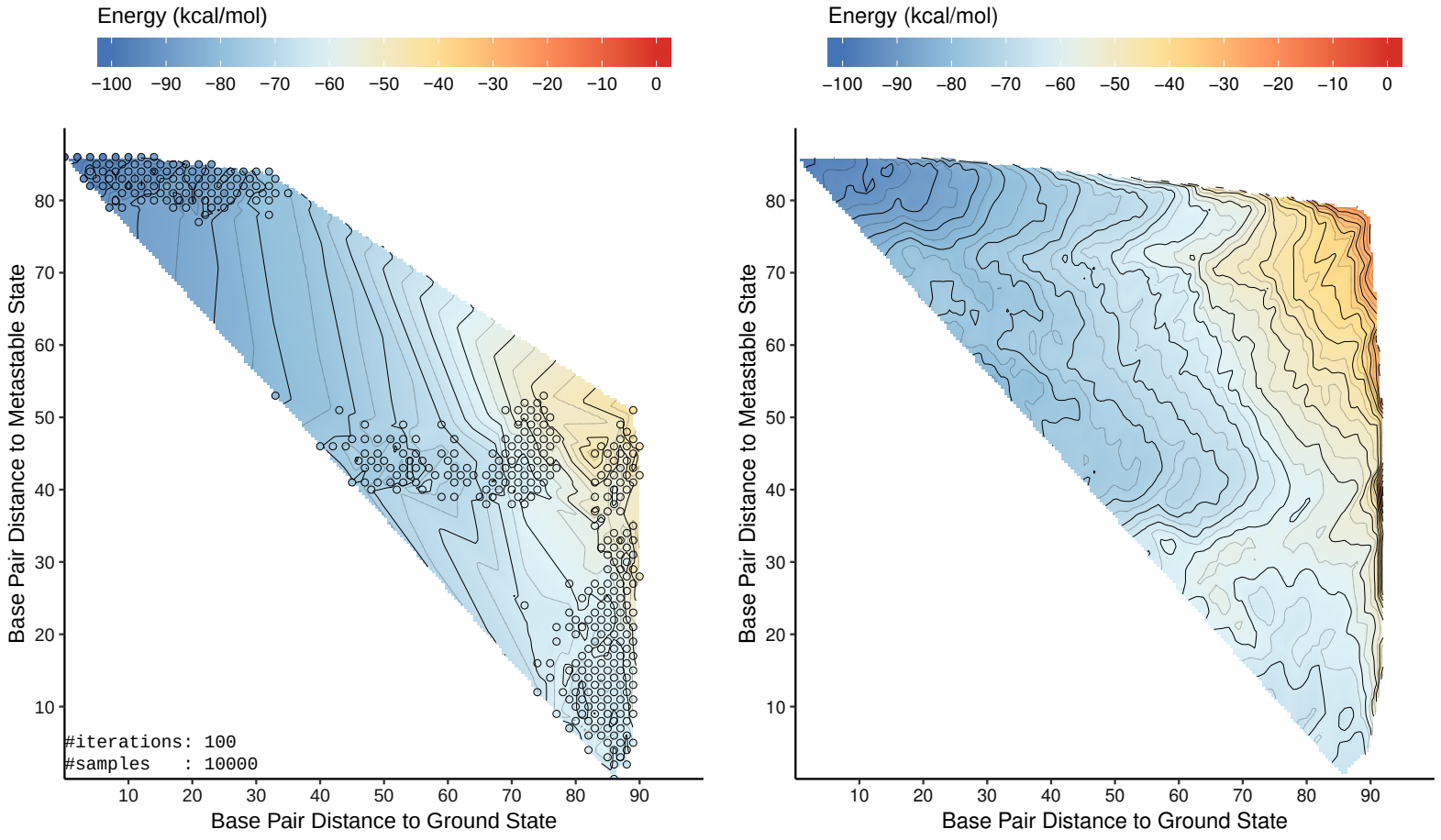
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 100, # samples: 10, 000, # local minima: 2, 853

Example: Qβ replicase template SV11

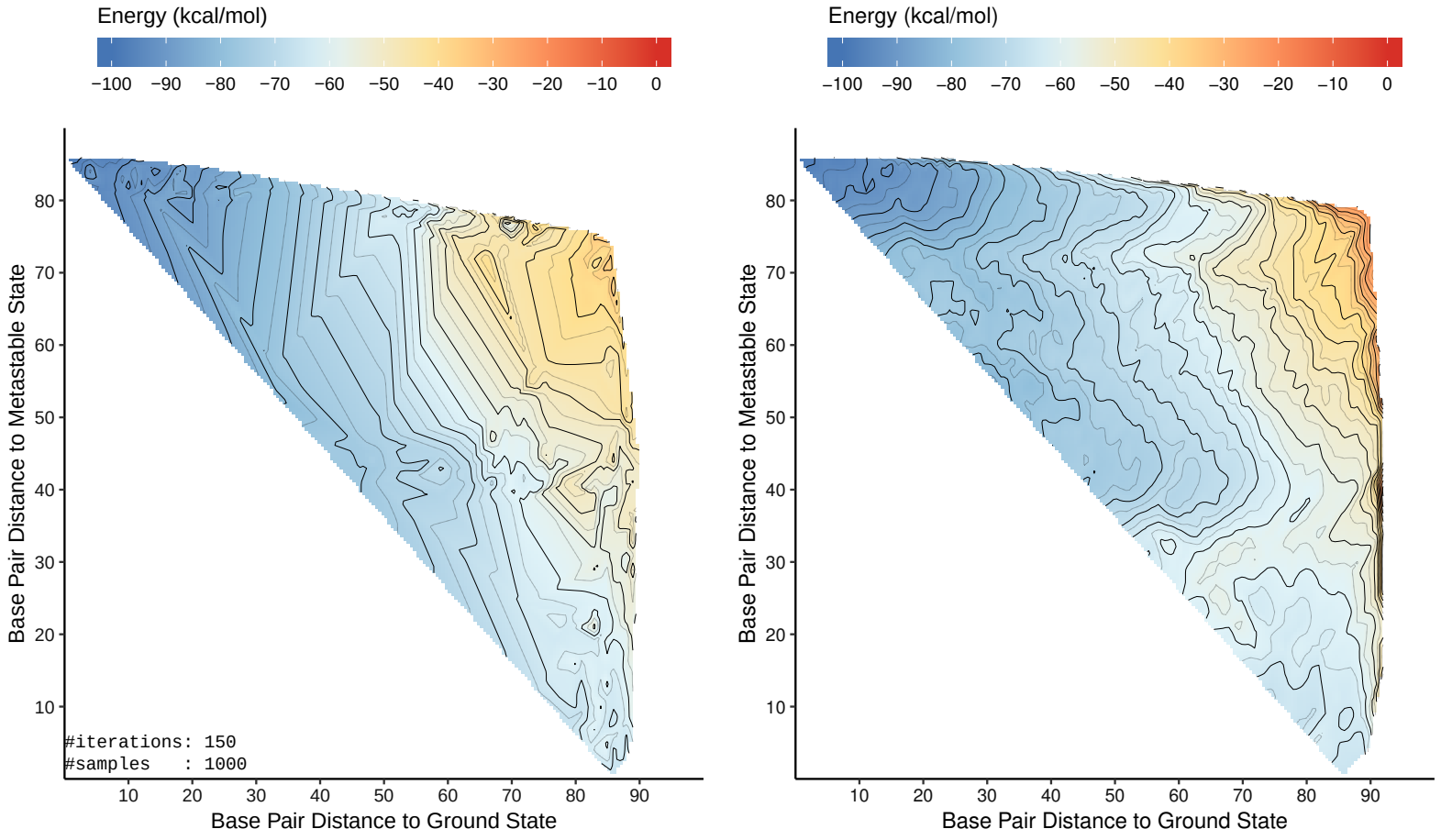
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 100, # samples: 10, 000, # local minima: 2, 853

Example: Qβ replicase template SV11

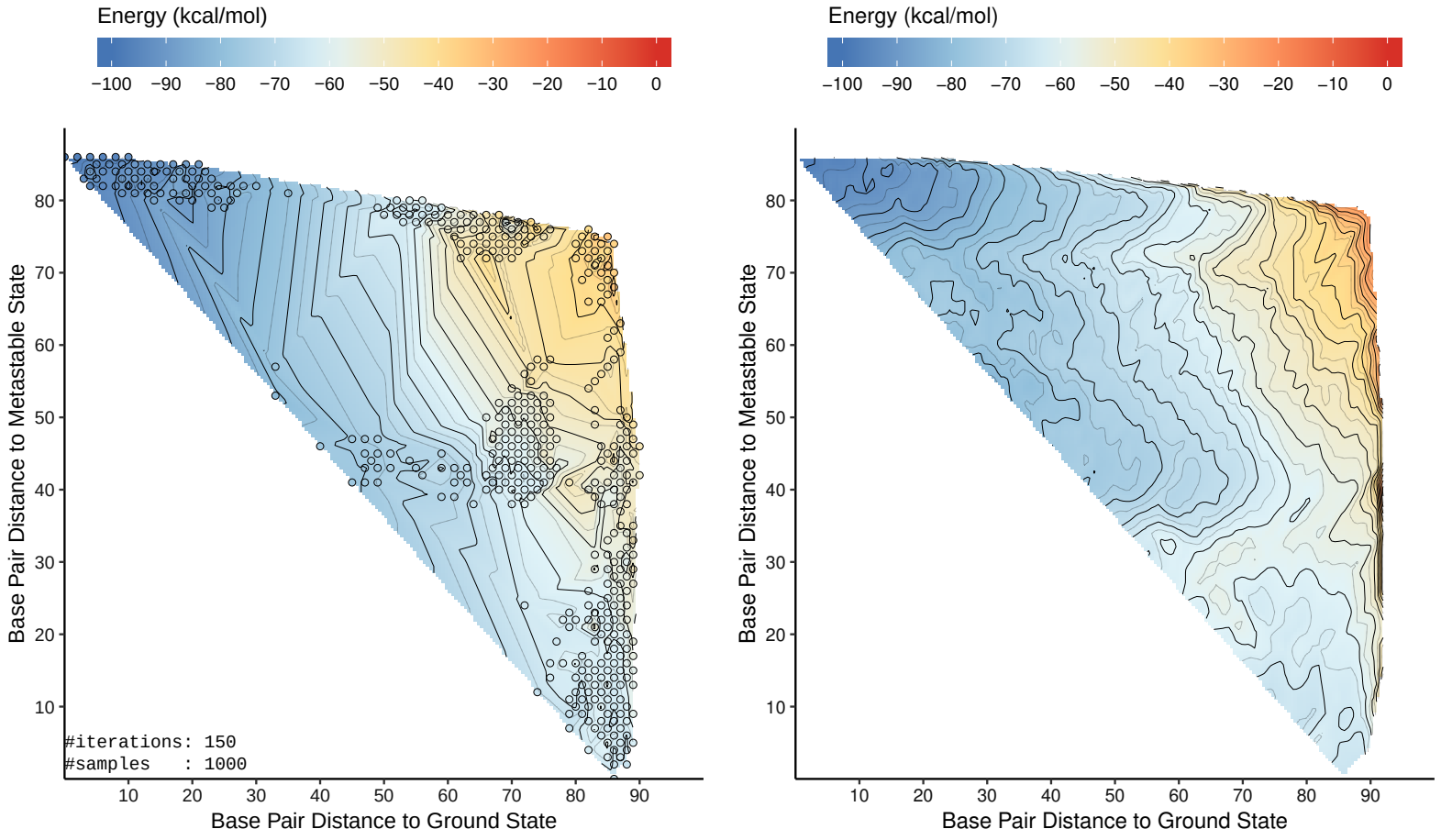
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 150, # samples: 1,000, # local minima: 2,818

Example: Qβ replicase template SV11

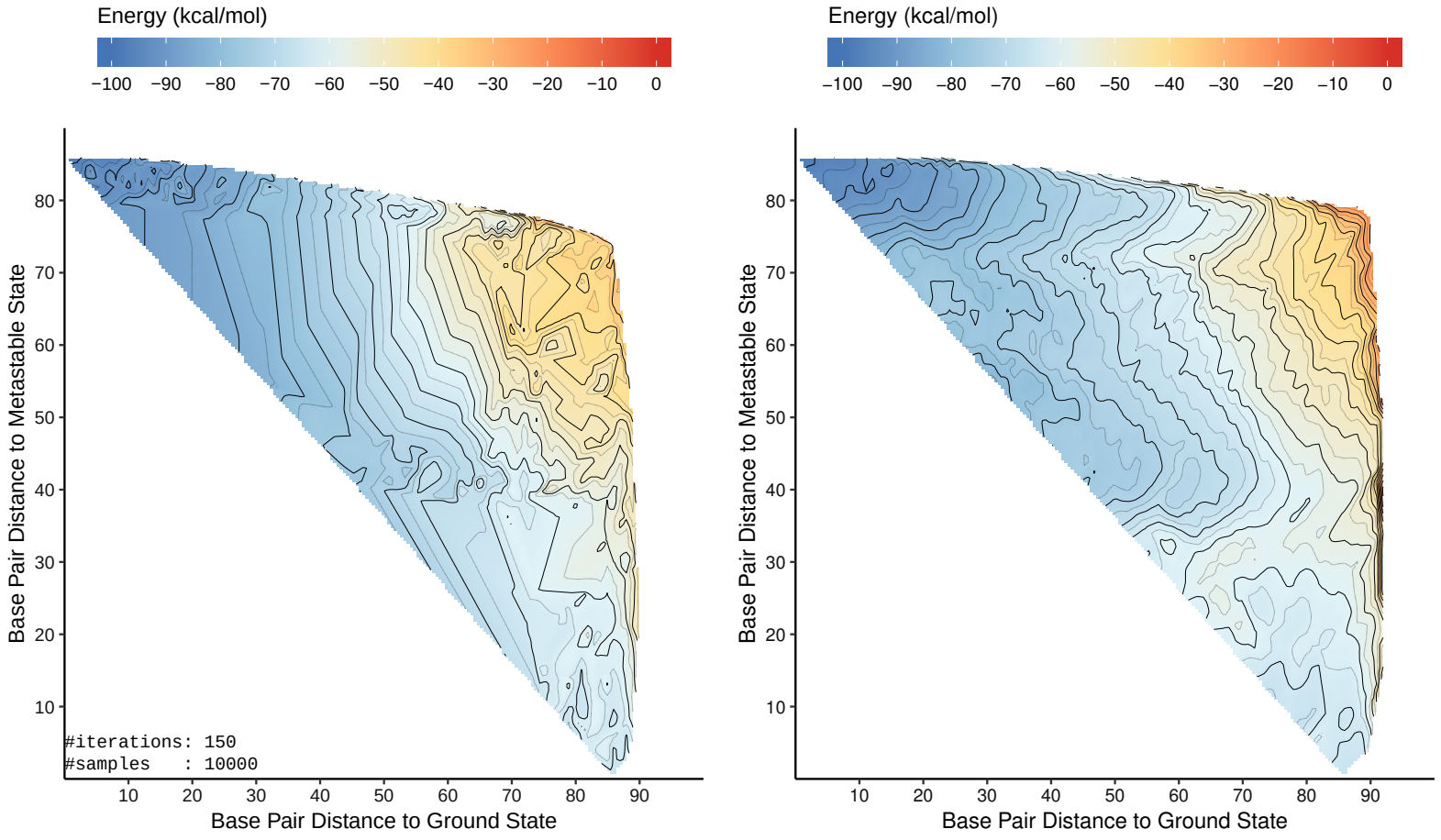
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 150, # samples: 1,000, # local minima: 2,818

Example: Qβ replicase template SV11

`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 150, # samples: 10, 000, # local minima: 7, 111

Example: Qβ replicase template SV11

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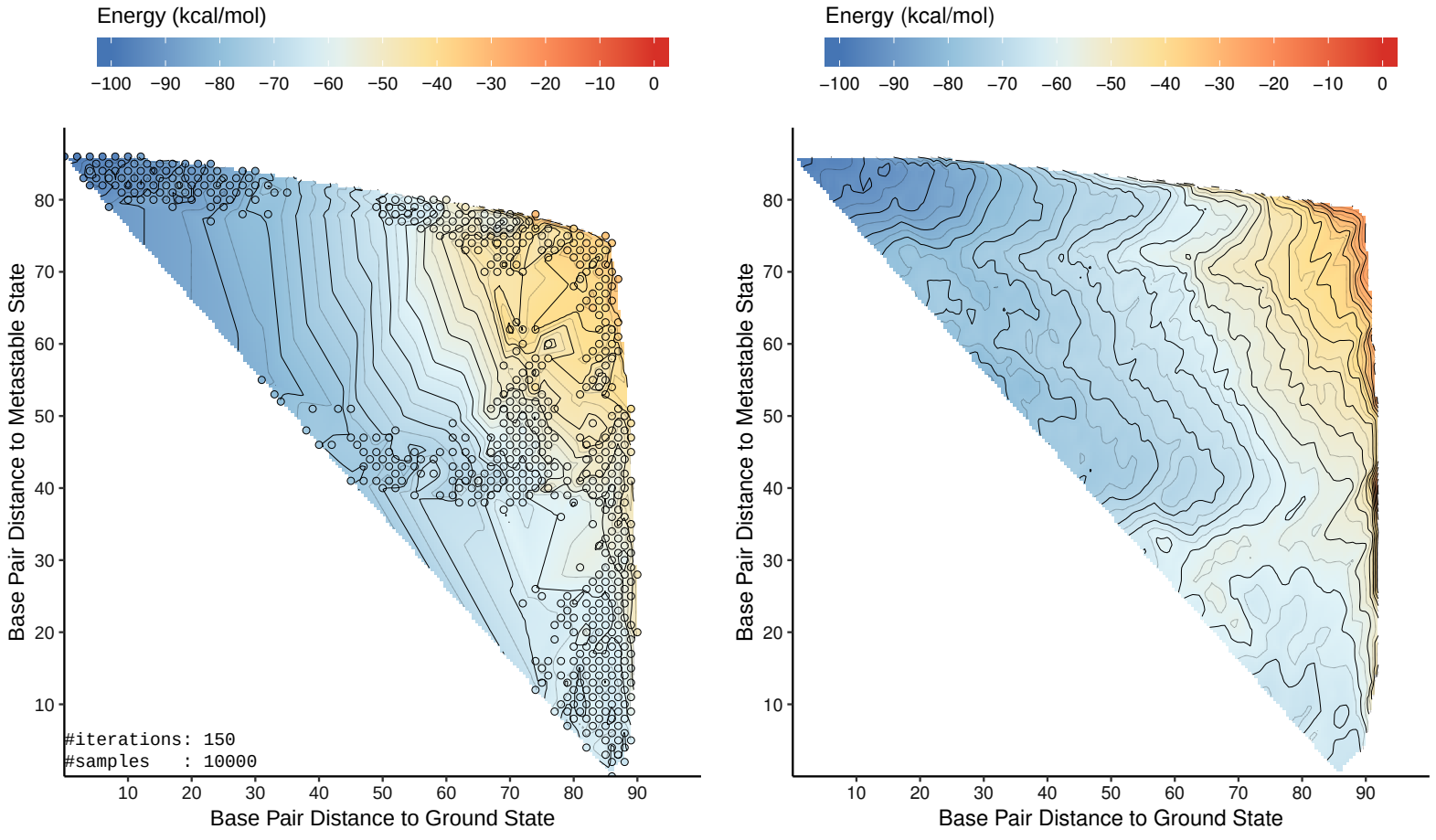

iterations: 150, # samples: 10, 000, # local minima: 7, 111

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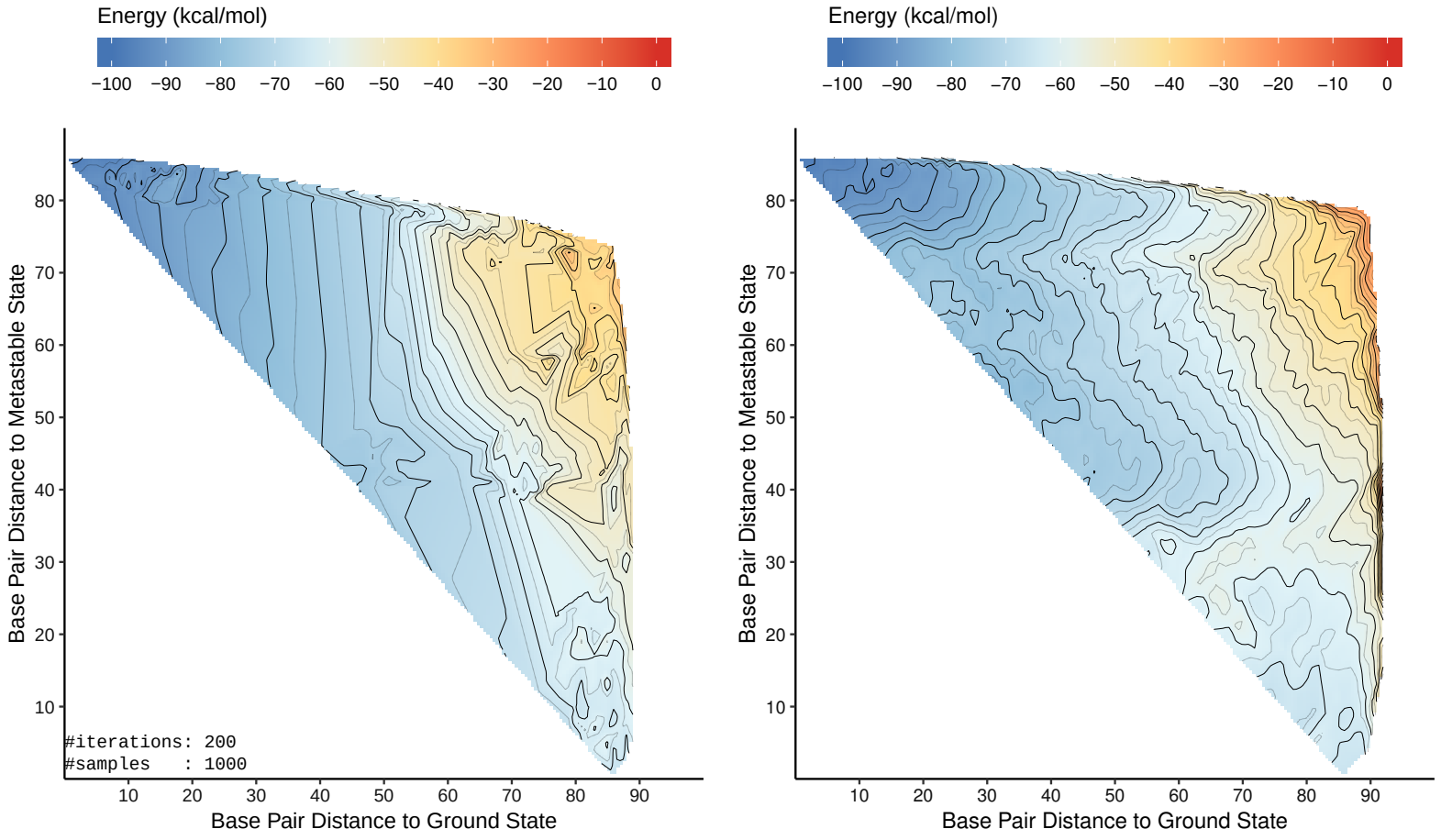
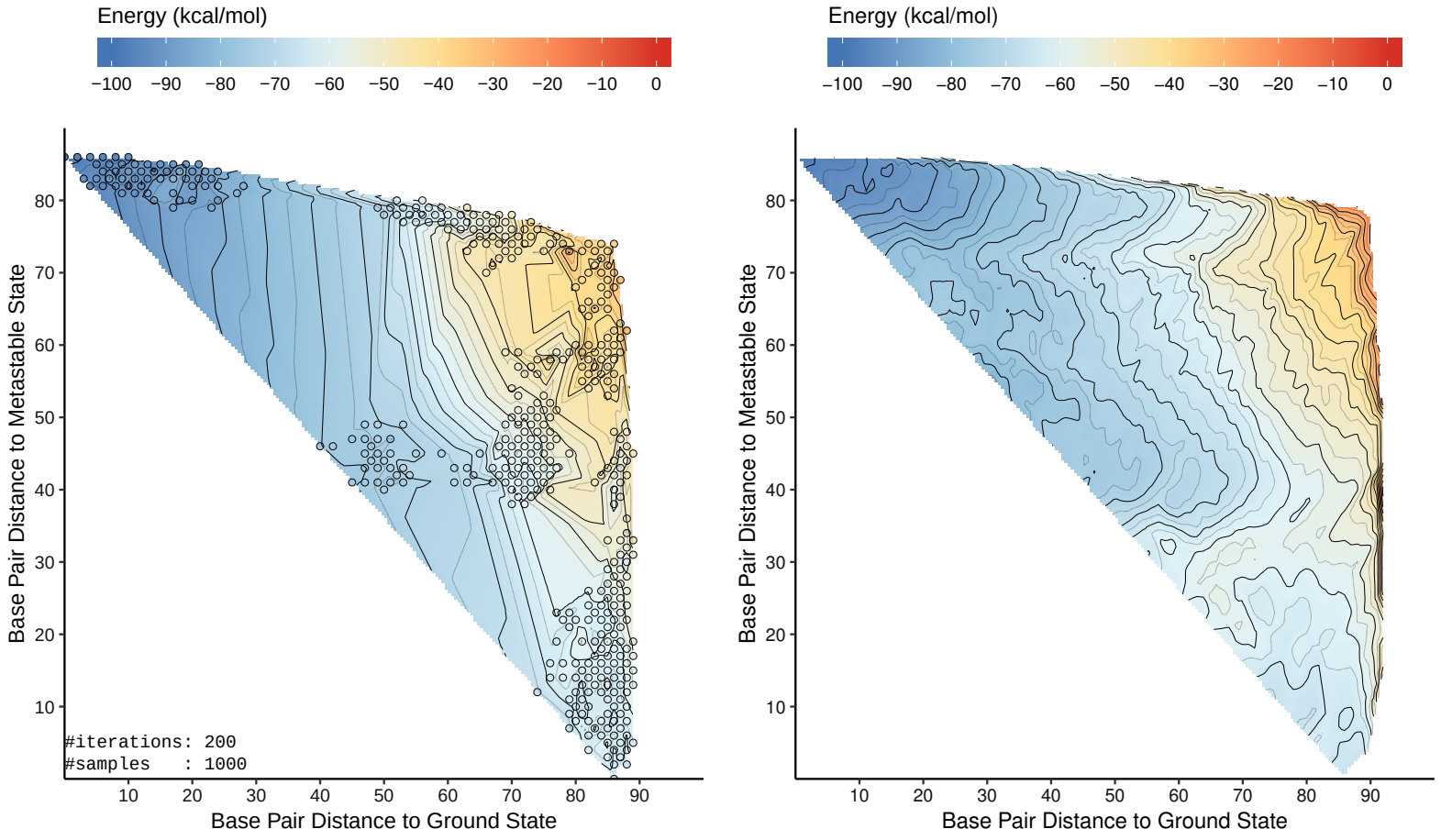


iterations: 200, # samples: 1,000, # local minima: 3,147

Example: Qβ replicase template SV11

`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 200, # samples: 1,000, # local minima: 3,147

Example: Qβ replicase template SV11

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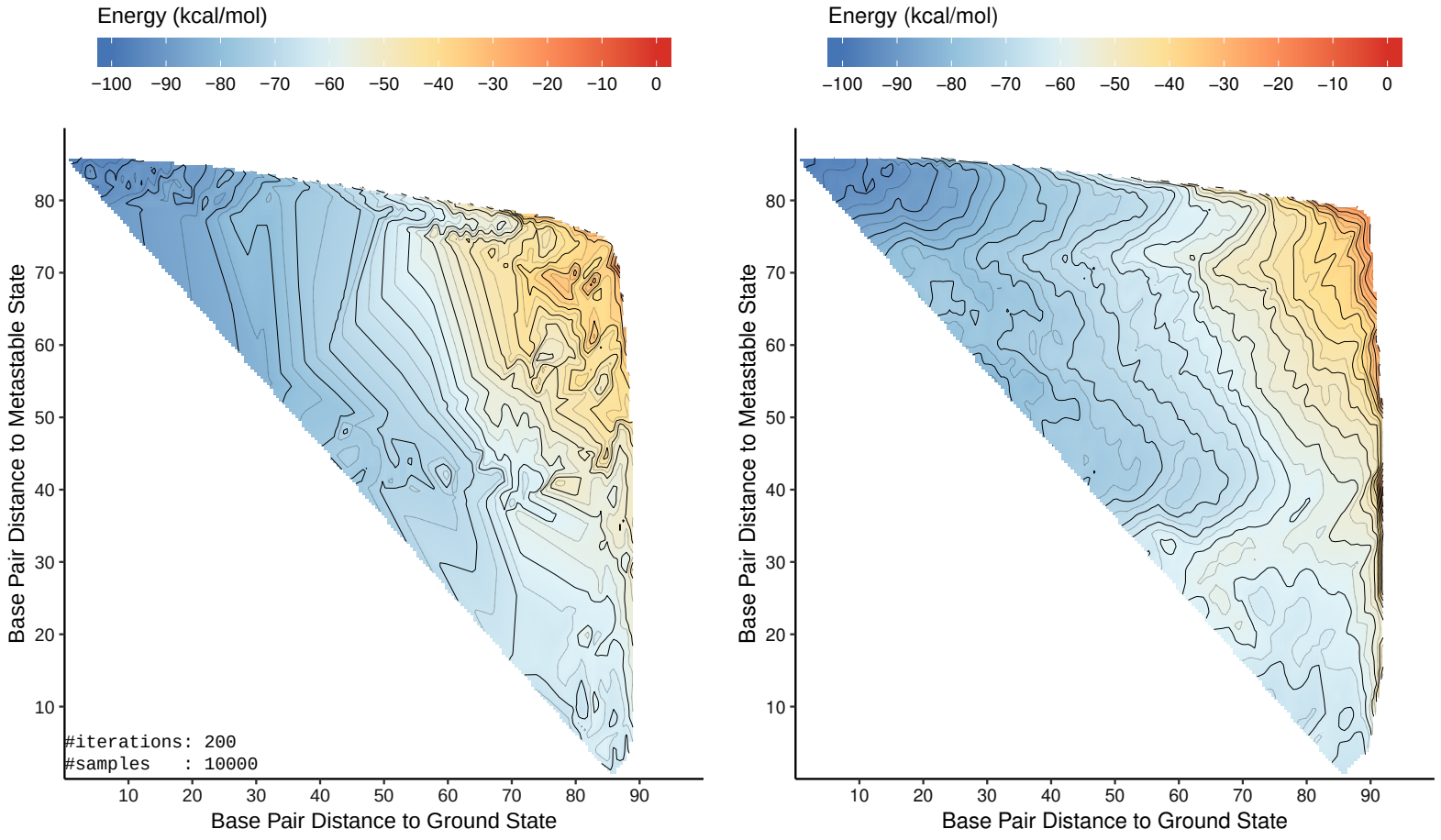
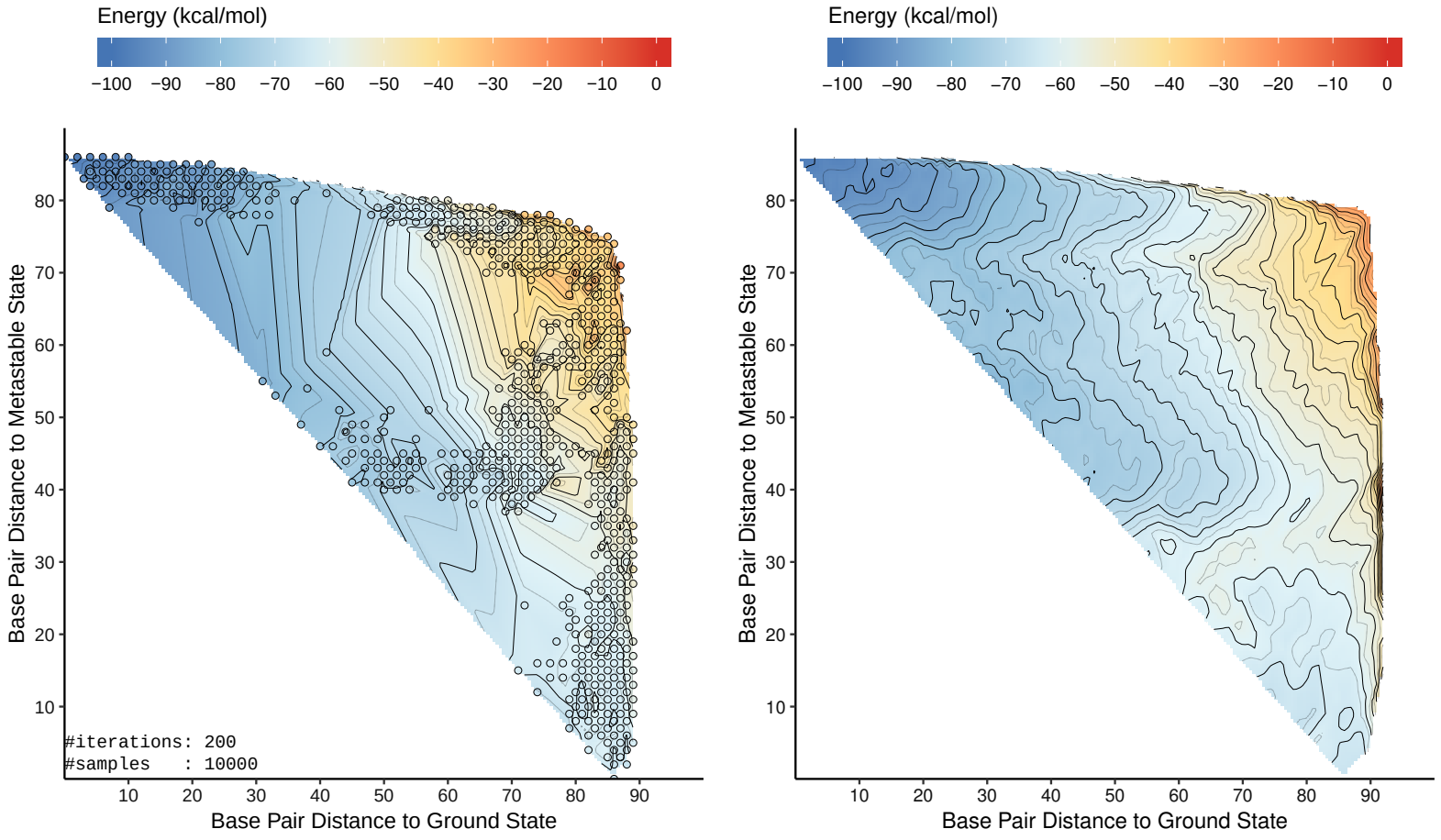


iterations: 200, # samples: 10, 000, # local minima: 10, 342

Example: Qβ replicase template SV11

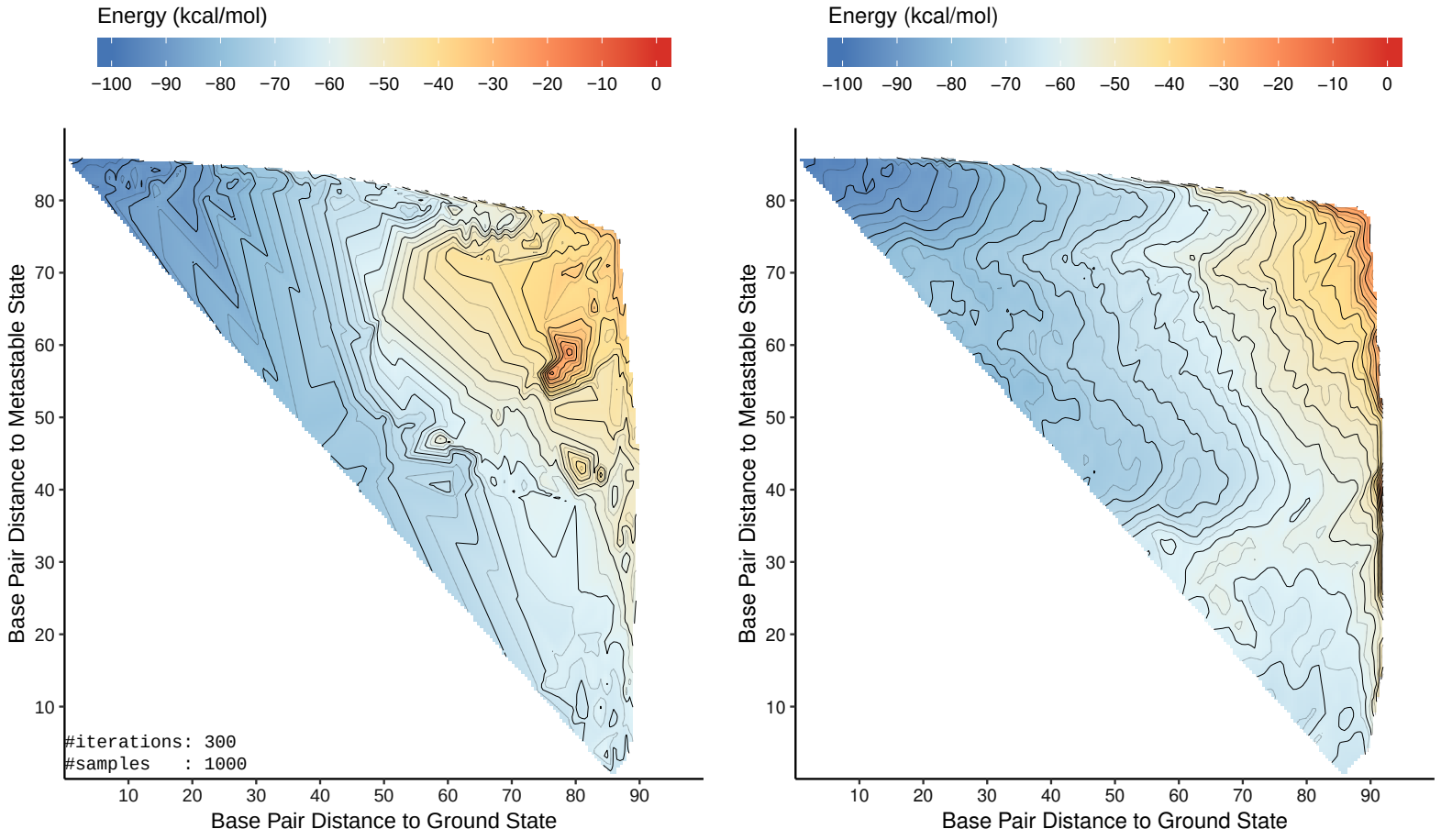
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 200, # samples: 10, 000, # local minima: 10, 342

Example: Qβ replicase template SV11

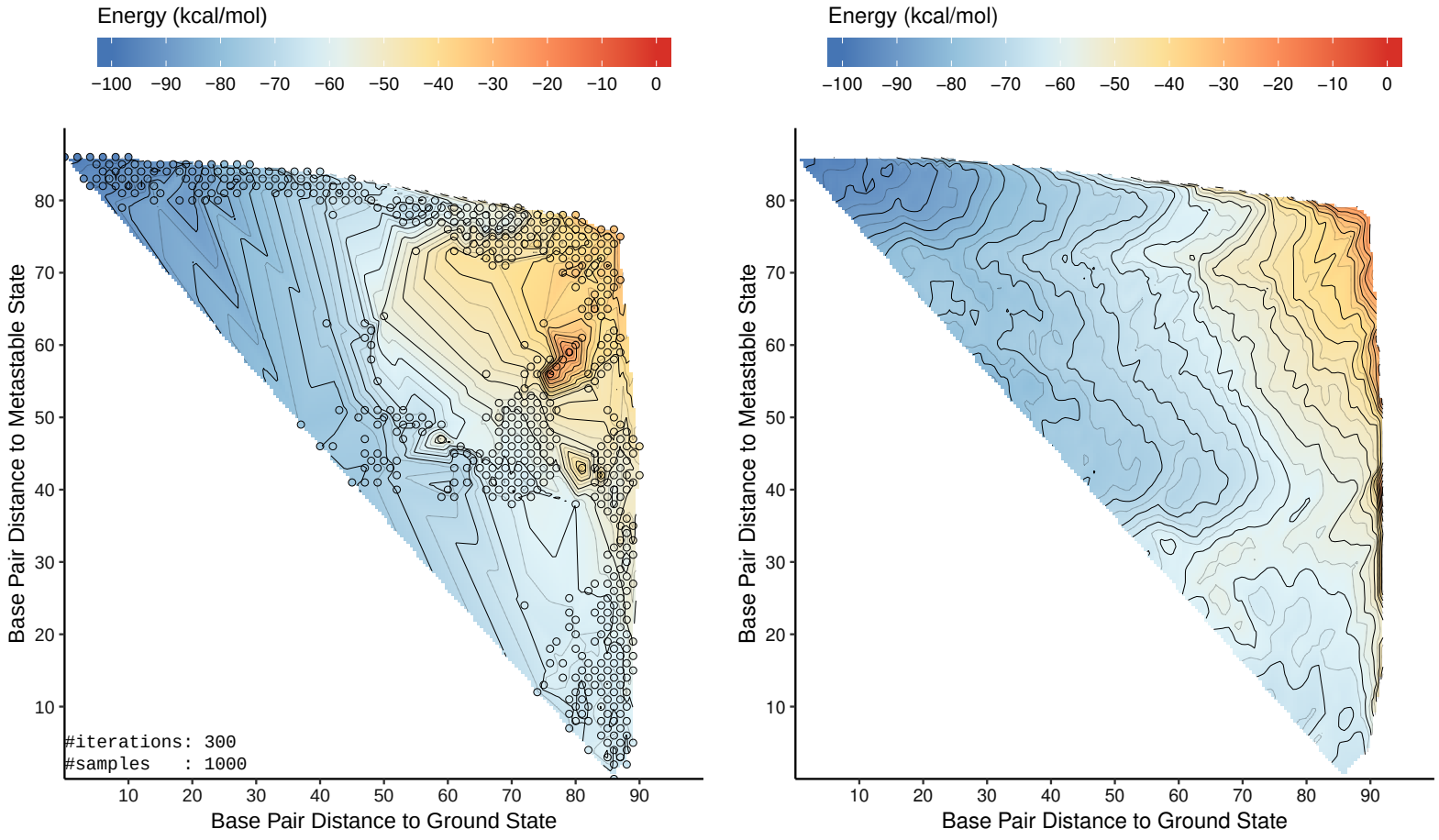
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



iterations: 300, # samples: 1, 000, # local minima: 4, 820

Example: Qβ replicase template SV11

`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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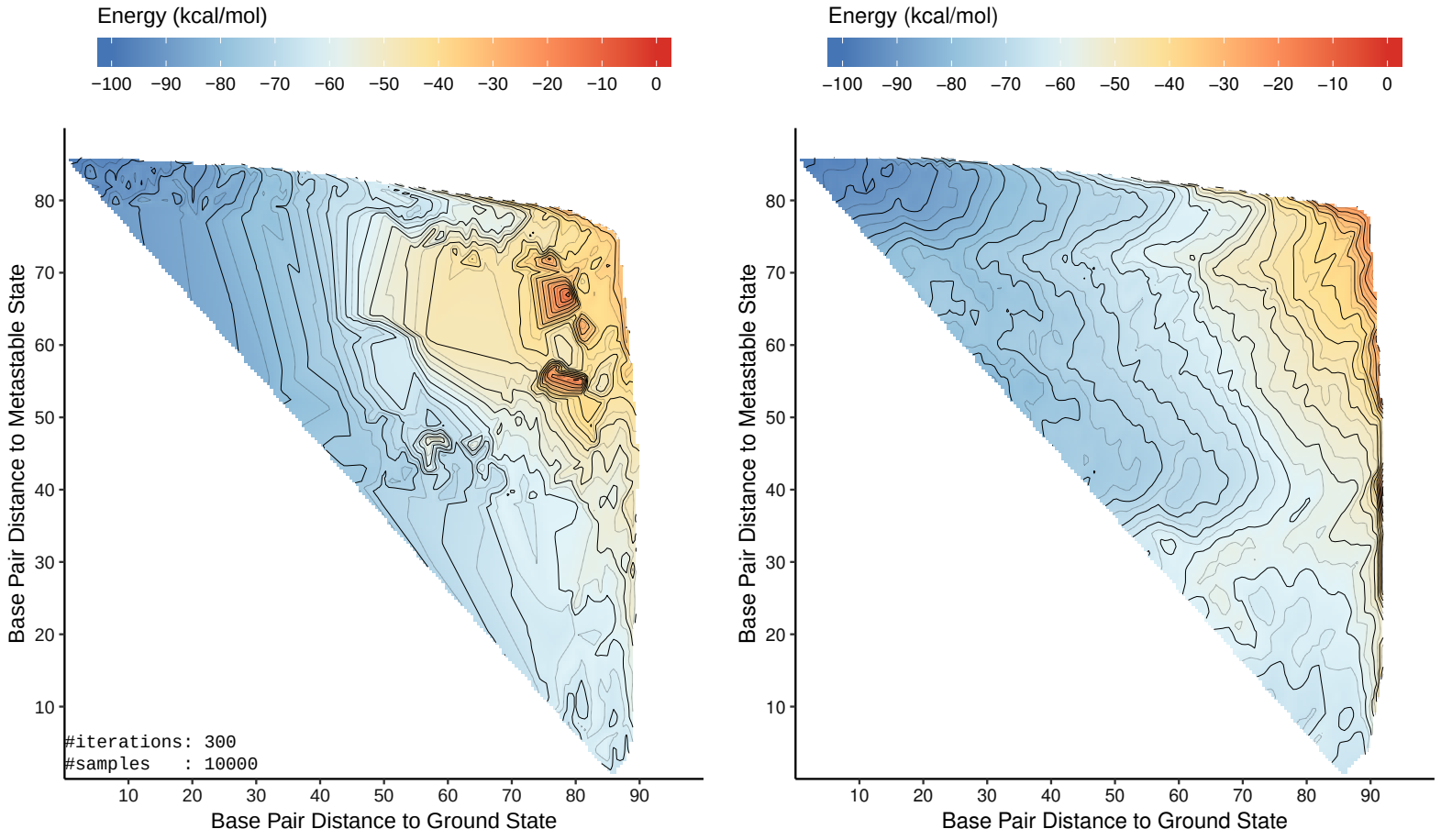

iterations: 300, # samples: 10, 000, # local minima: 12, 486

Example: Qβ replicase template SV11

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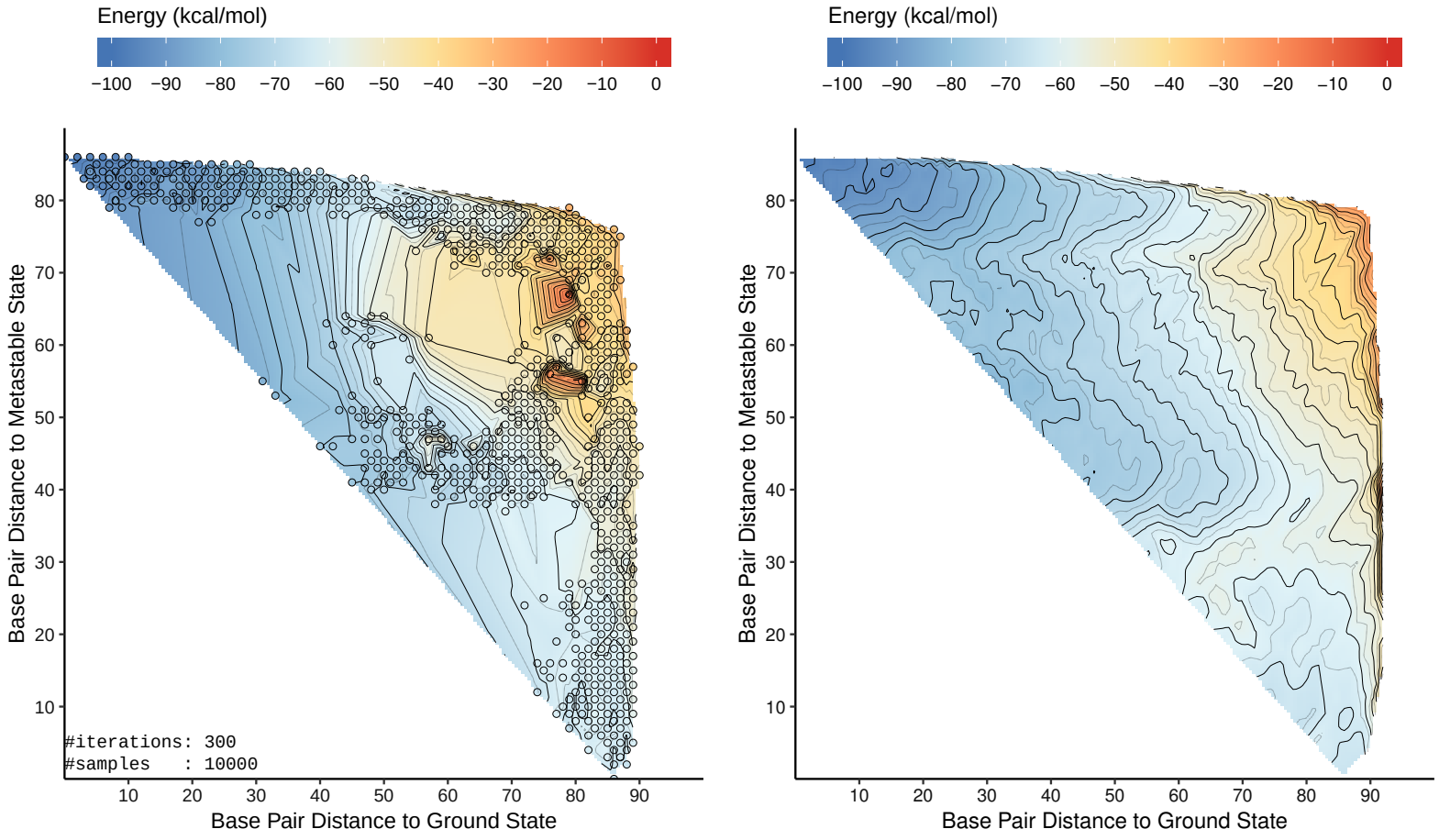


iterations: 300, # samples: 10, 000, # local minima: 12, 486

Sampling Quality

Goal:

- (reliatively) low number of representative structures
- capture a diverse, yet important set of states

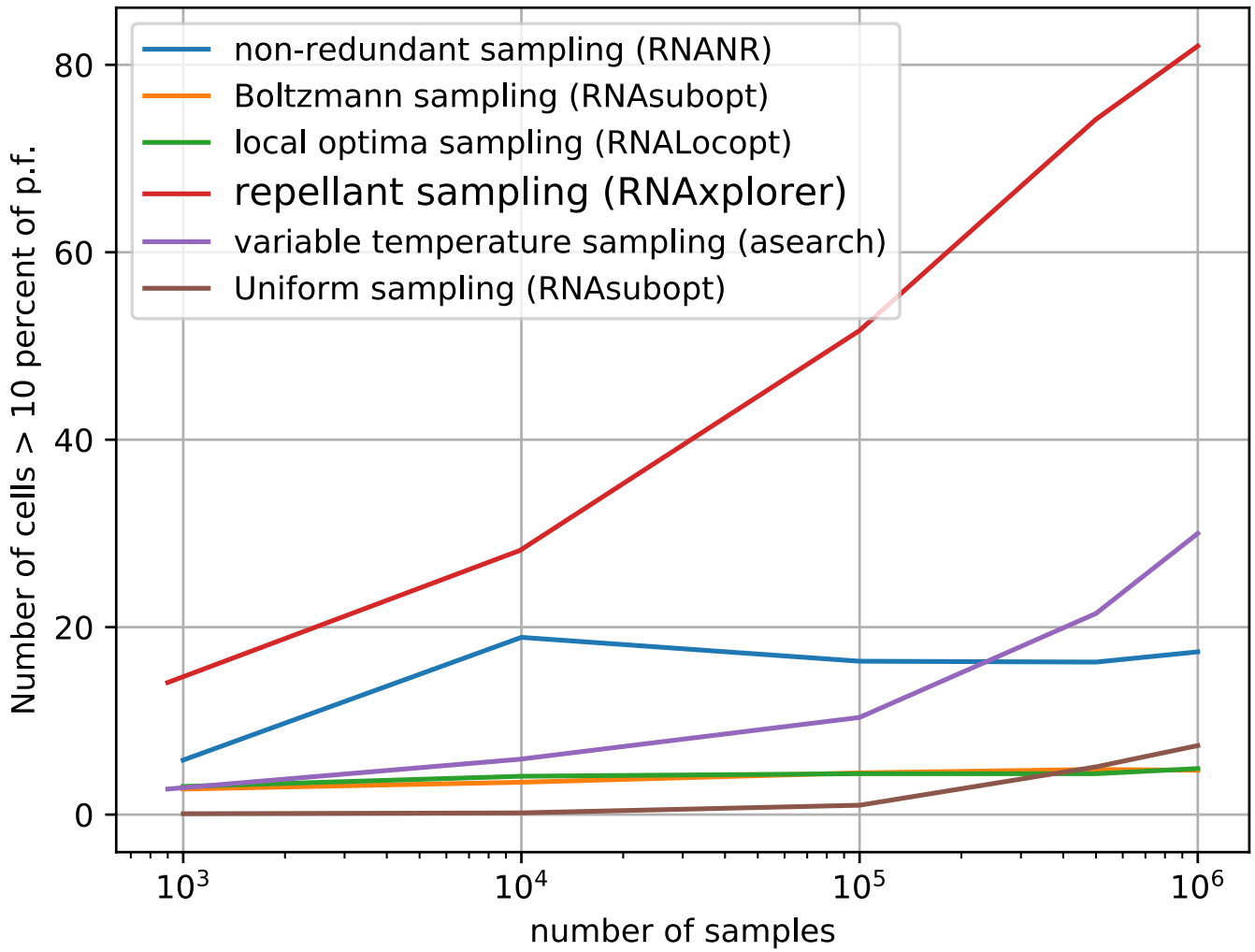
Use 2D projections and compare samples against `RNA2Dfold`[14]

- count number of samples per disance-class
- compute deviation of distance-class MFEs or Q, e.g. L1-norm
- distance-class coverage, e.g. $|\mathcal{C}(\delta)|$ with $\mathcal{C}(\delta) = \{\mathcal{C} | Q_{\mathcal{C}}^{\text{sampled}} \geq \delta \cdot Q_{\mathcal{C}}^{\text{real}}\}$

[14] Lorenz et al. 2009, computes MFE and Q in $\mathcal{O}(n^7)$

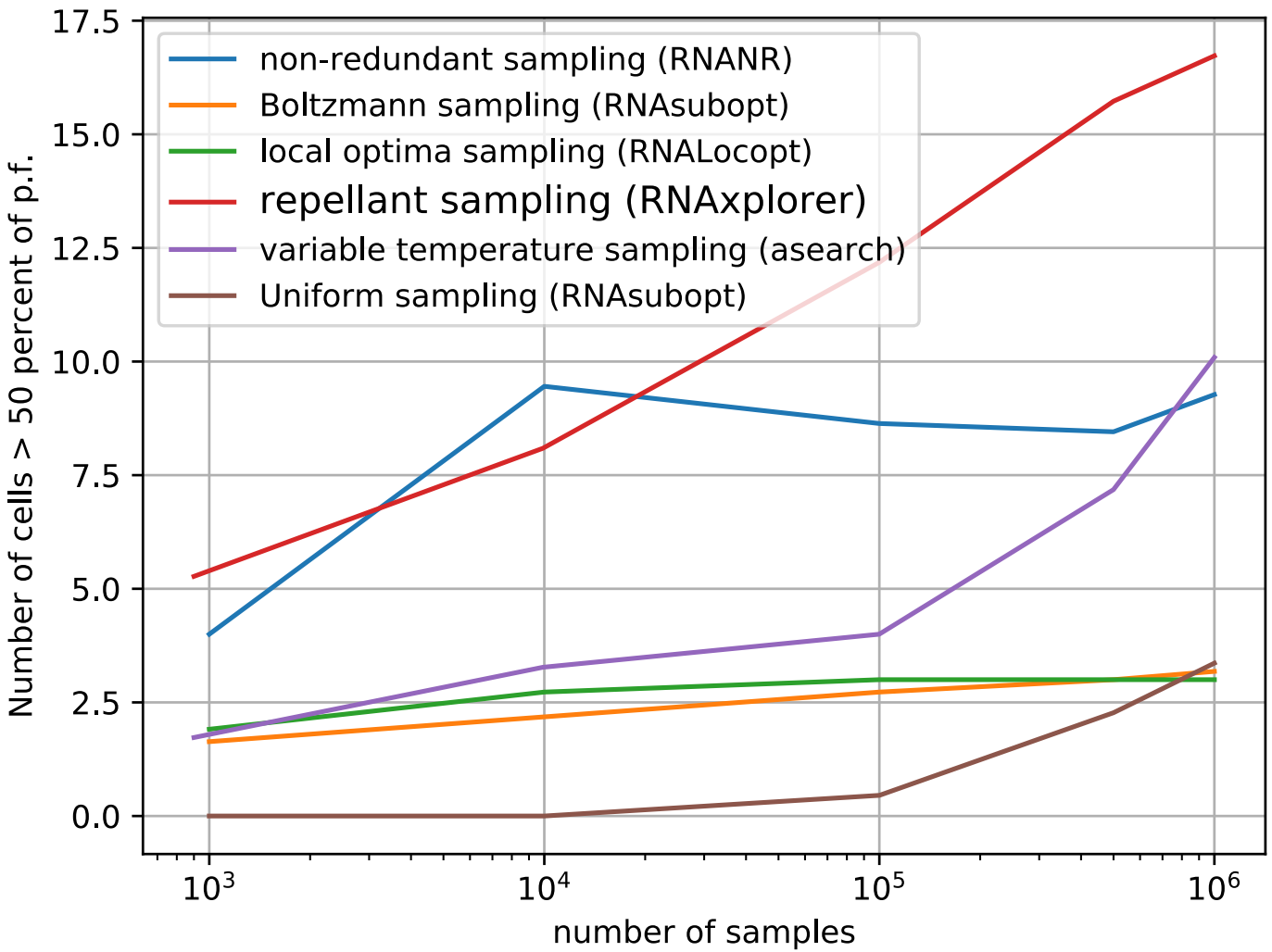
Sampling Quality - Partition Function Coverage

- SV11 example
- $\delta = 0.1$



Sampling Quality - Partition Function Coverage

- SV11 example
- $\delta = 0.5$



Conclusion

What's been done:

- Unsupervised directed repellent scheme
- Efficient Boltzmann sampling from distorted energy landscape $O(n^3) + O(k \cdot n \log n)$ for k samples per iteration
- Good approximation for even extreme cases

Next steps:

- Removal of too similar and shallow local minima
- Restrict guiding potential to structure domains
- Computation of effective transition rates
- Comparison of kinetics prediction against other programs
- Make `RNAxplorer` accessible
- Release non-redundant sampling for `RNAsubopt`

Thanks to

- **Gregor Entzian**
- **Andrea Tanzer**
- **Yann Ponty**
- **Juraj Michalik**
- Ivo L Hofacker
- TBI team

Thank You for your attention!

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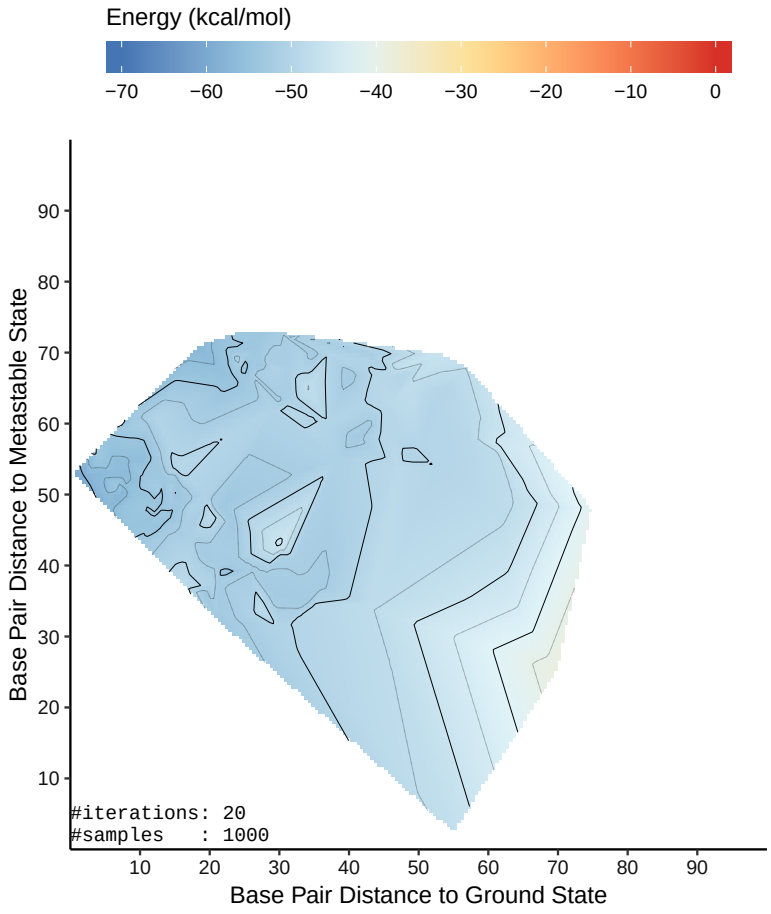
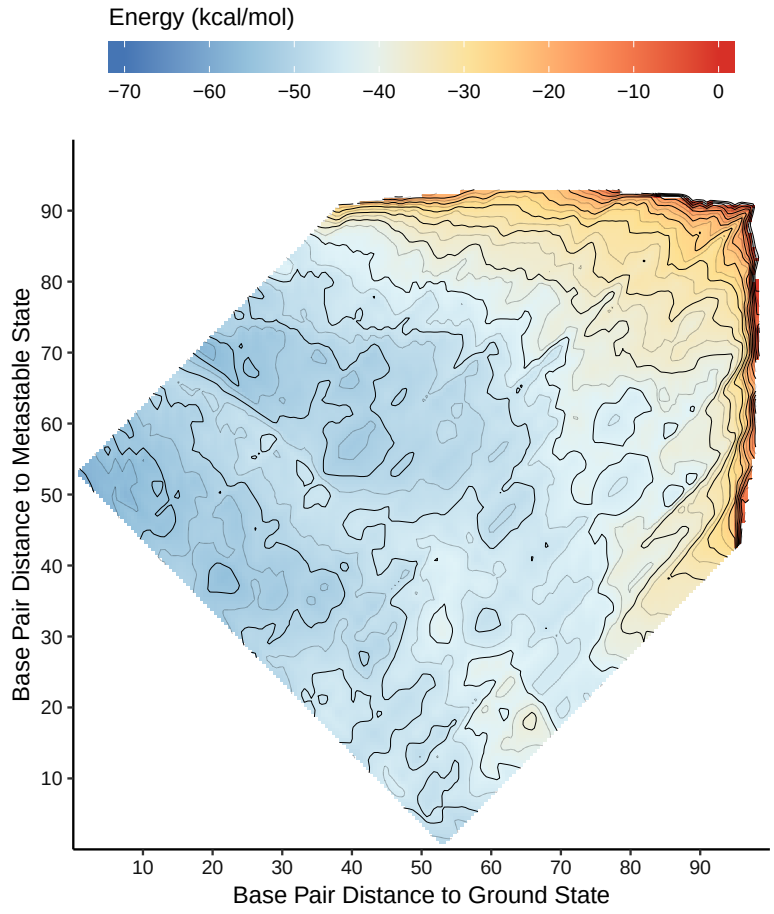
Example: 5UTR of MS2 coat protein mRNA

`RNAxplorer` repulsion scheme Boltzmann sampling





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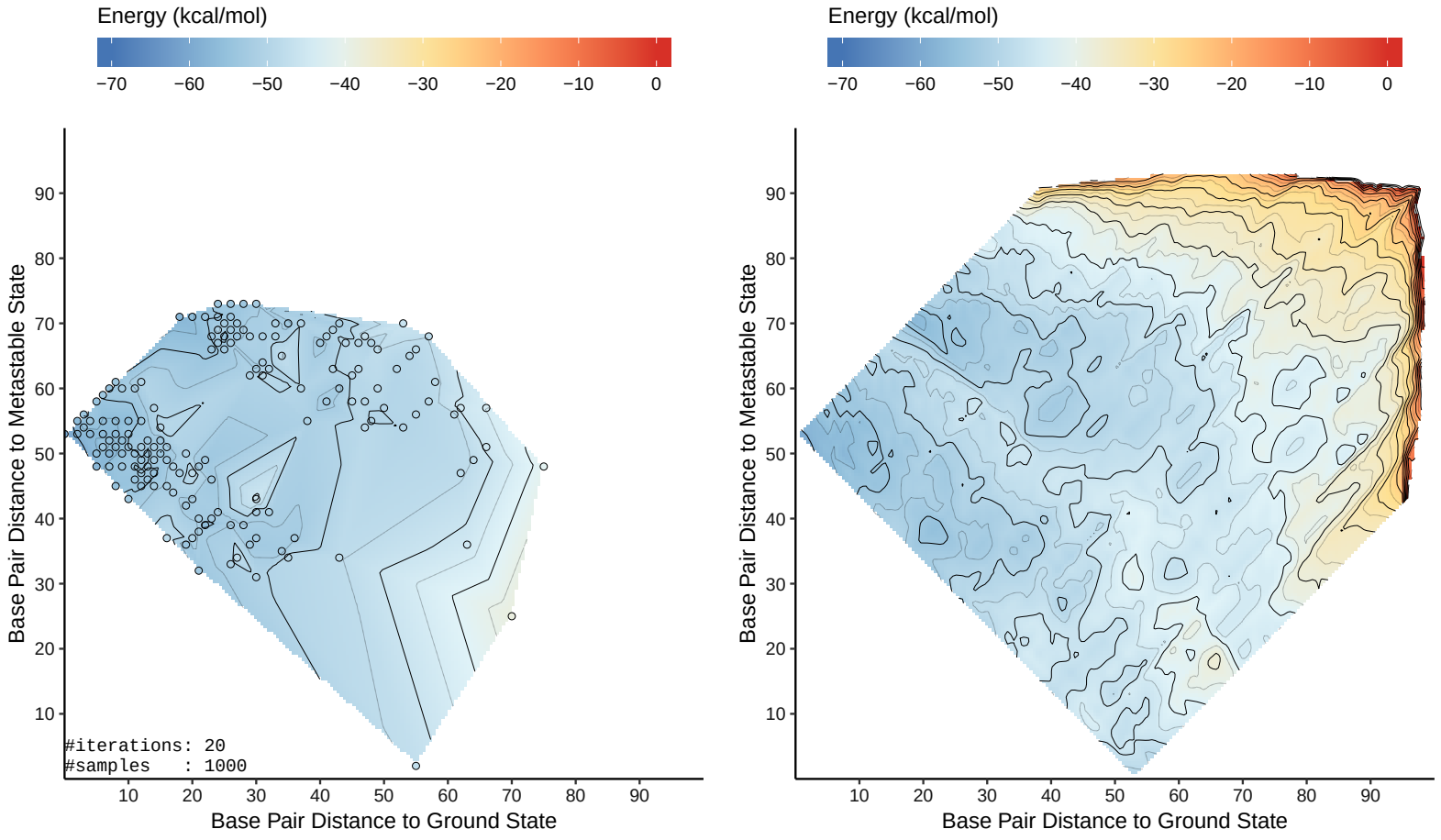

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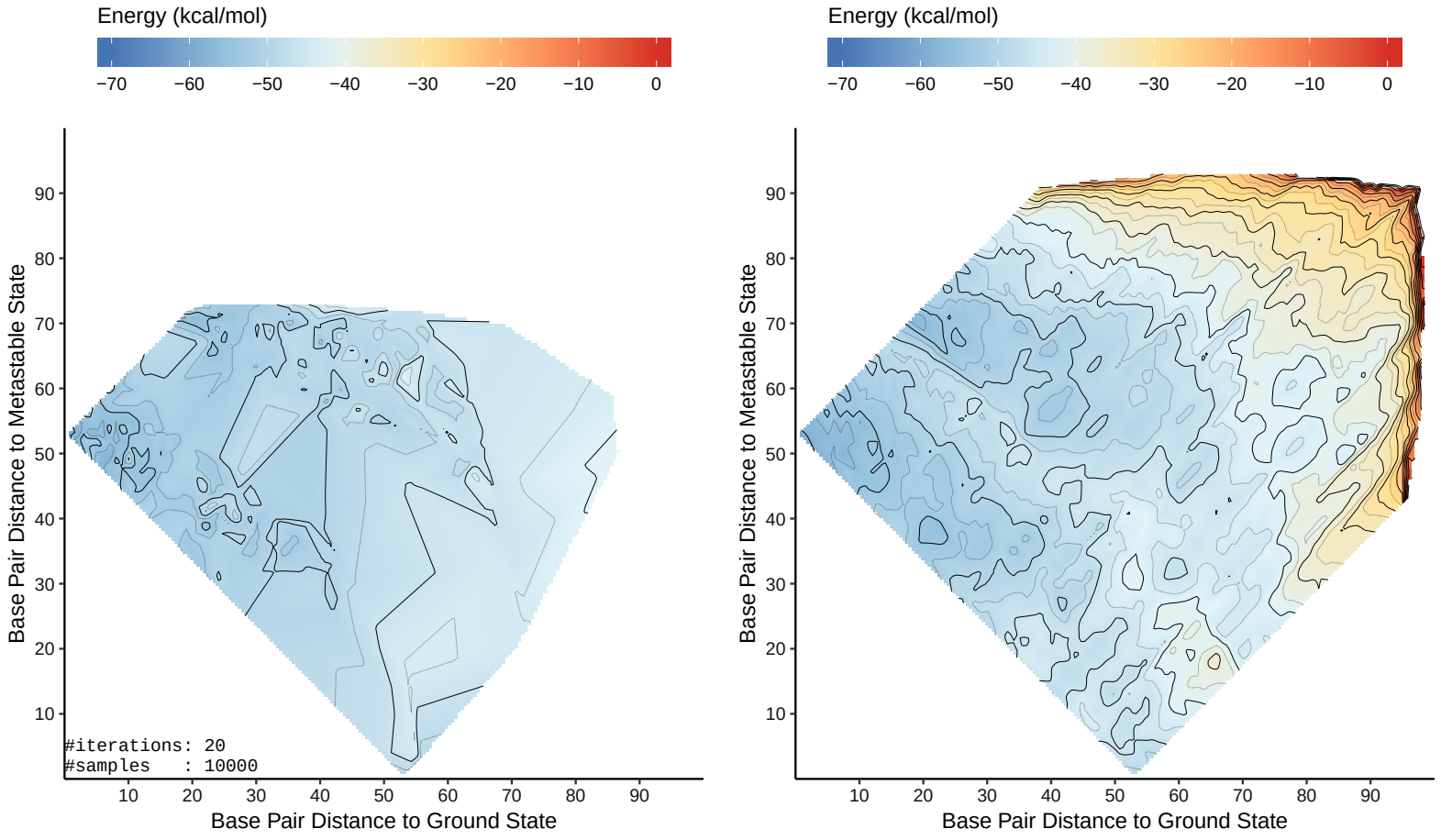

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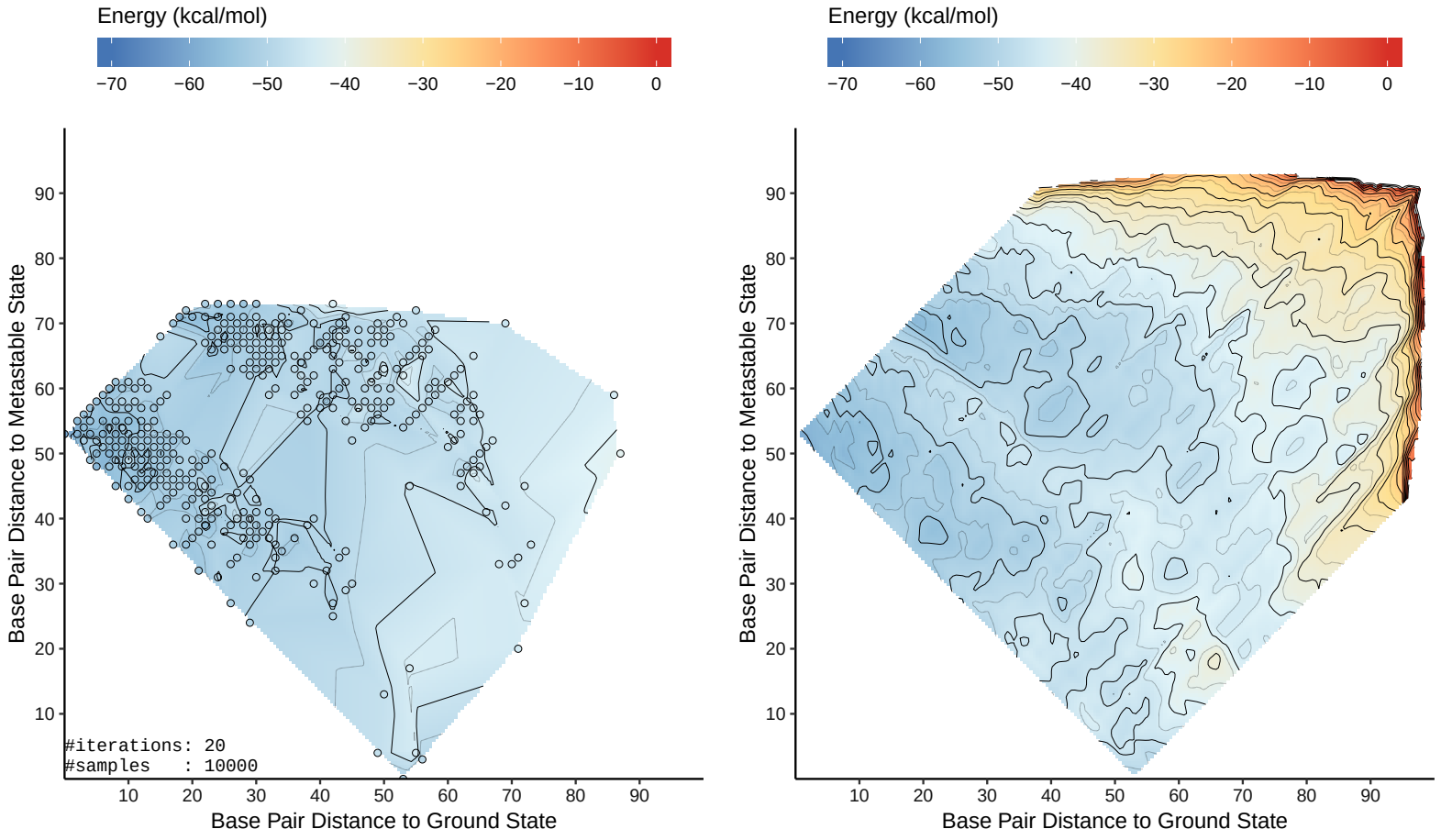

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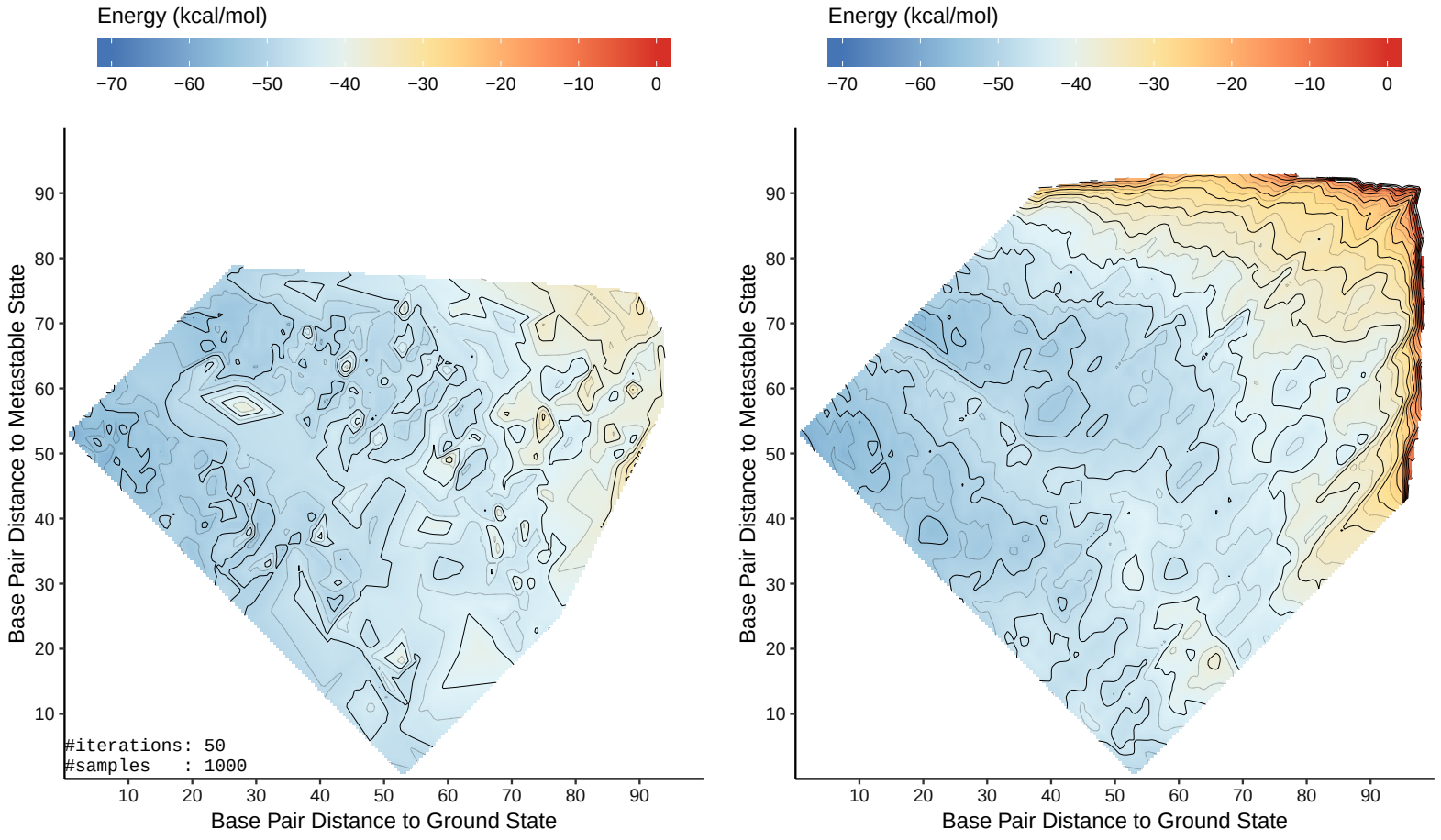

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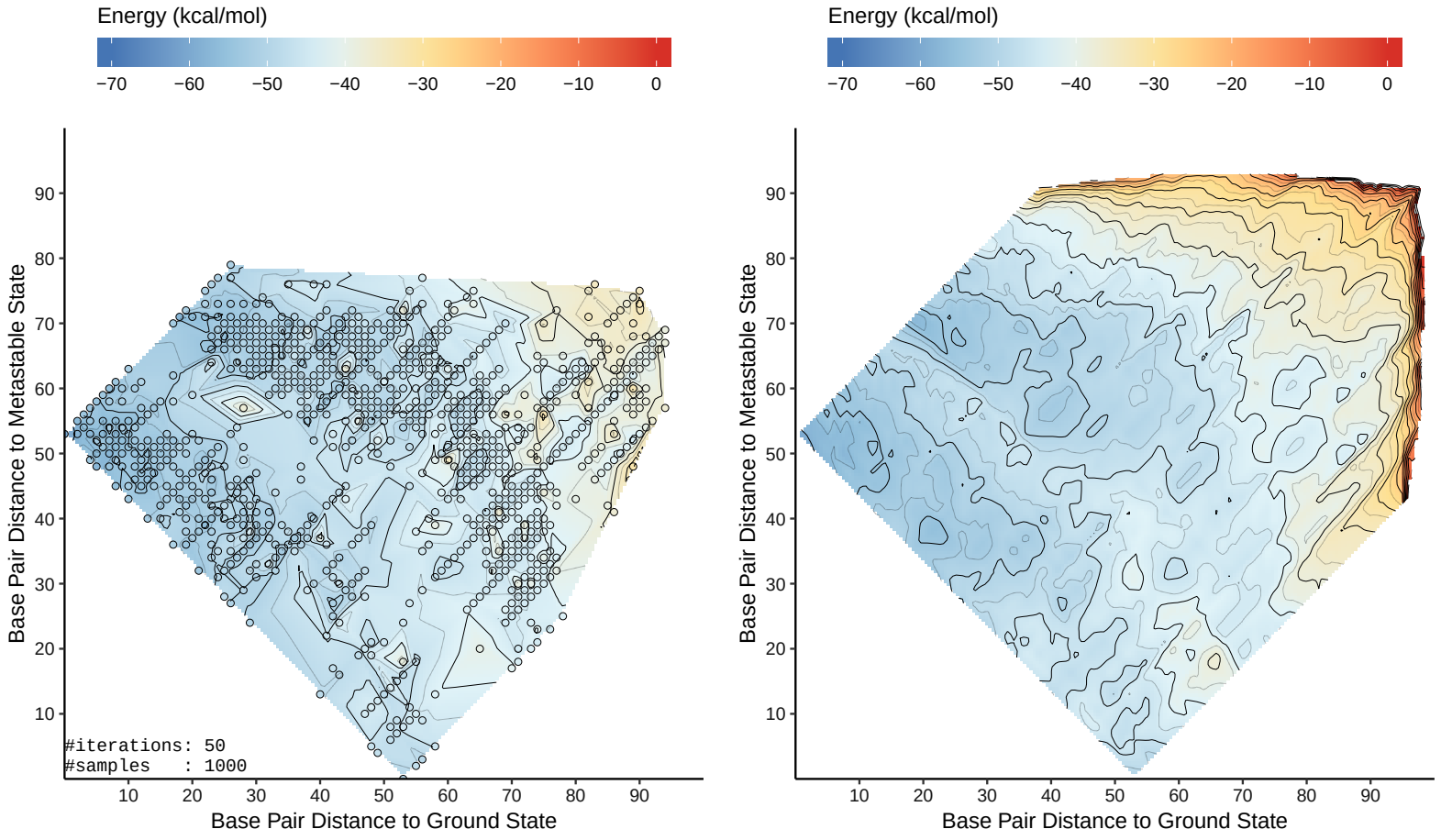

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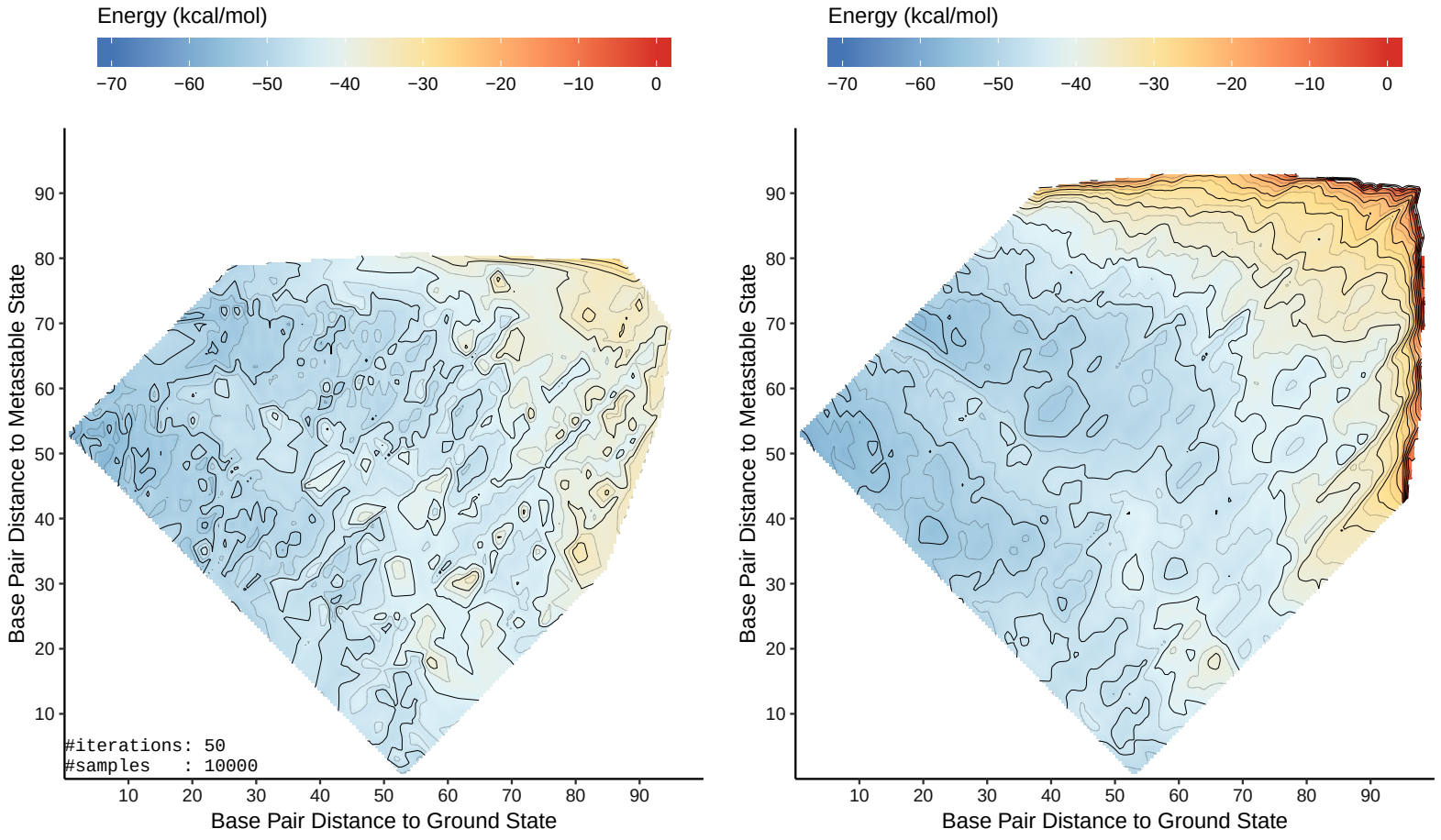

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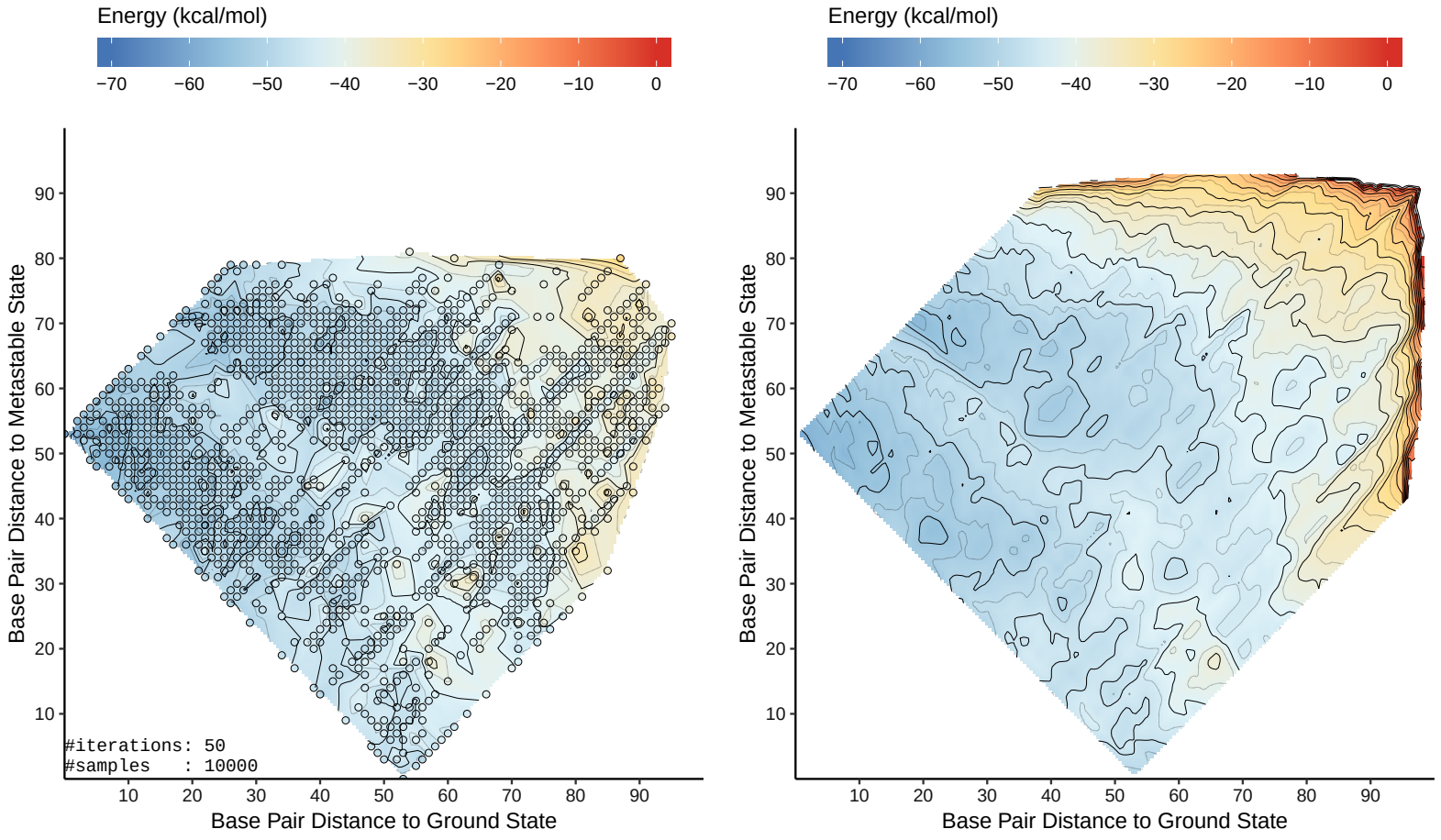

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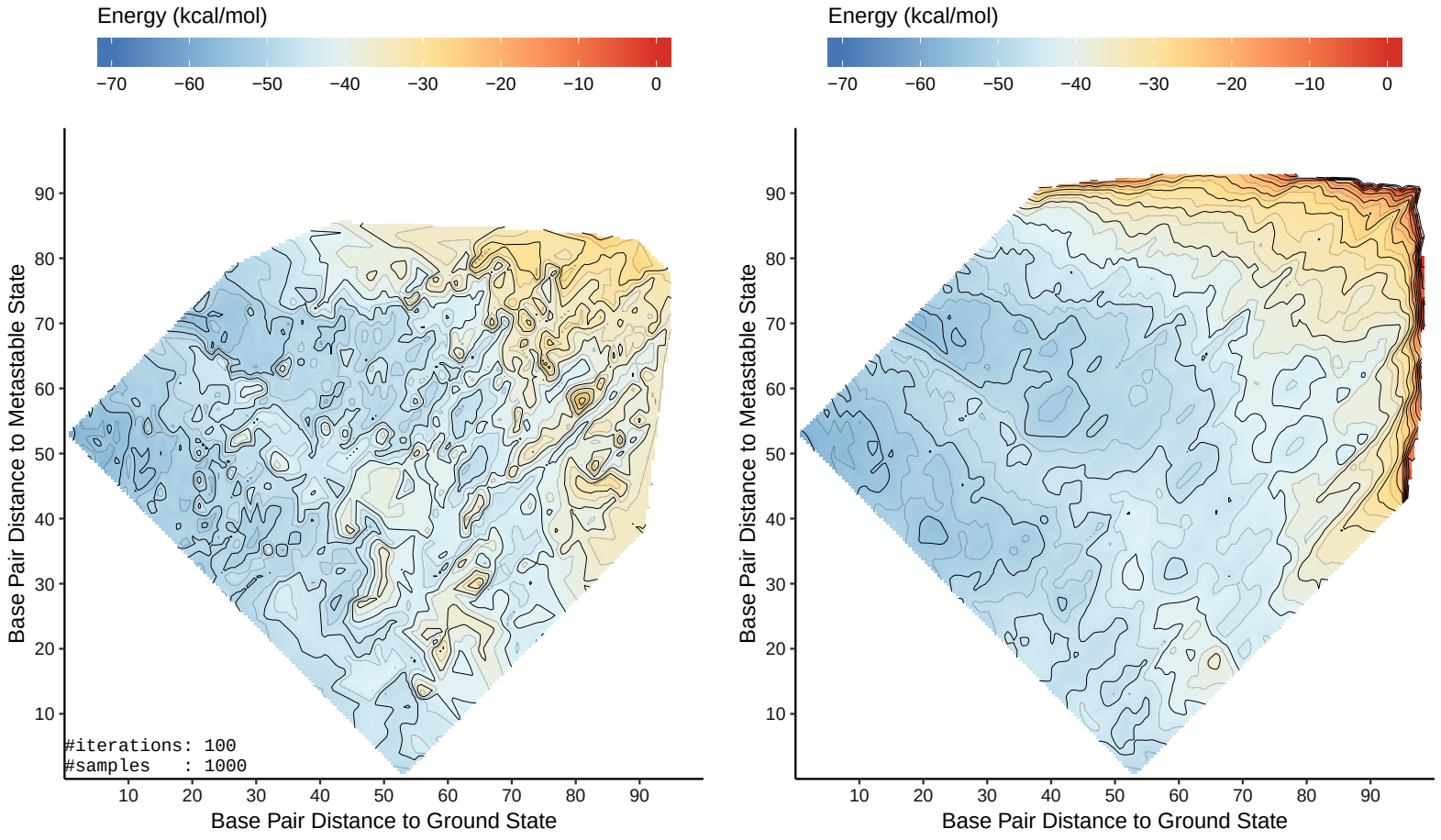

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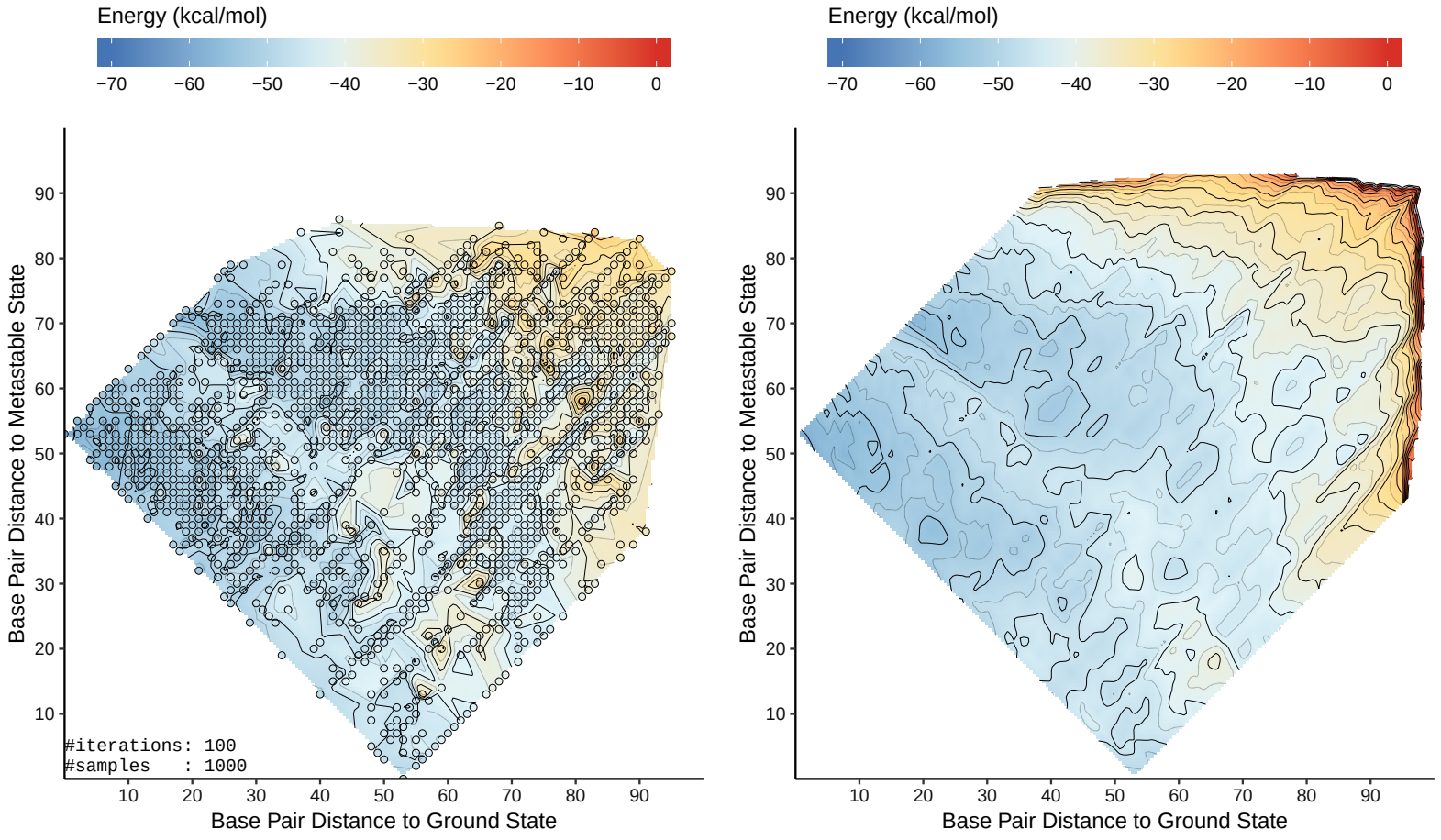

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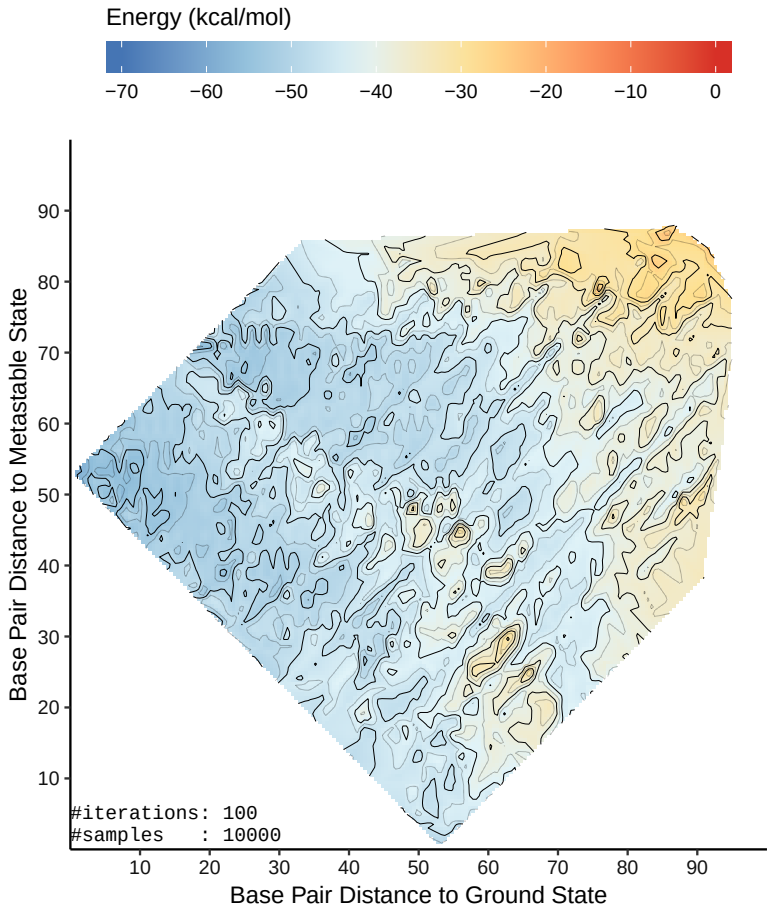

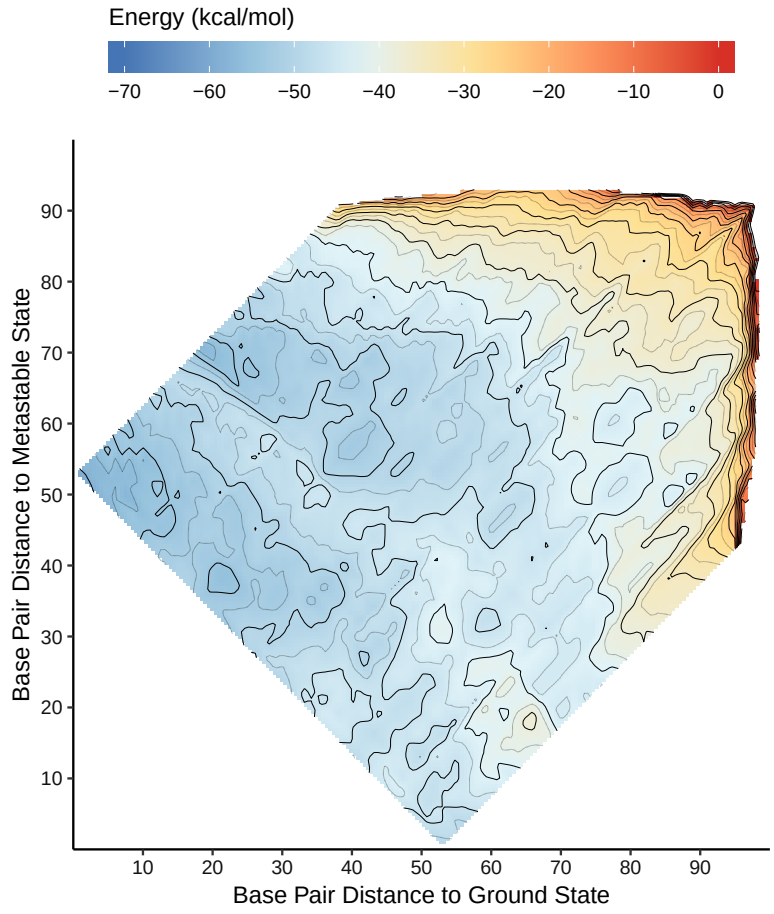

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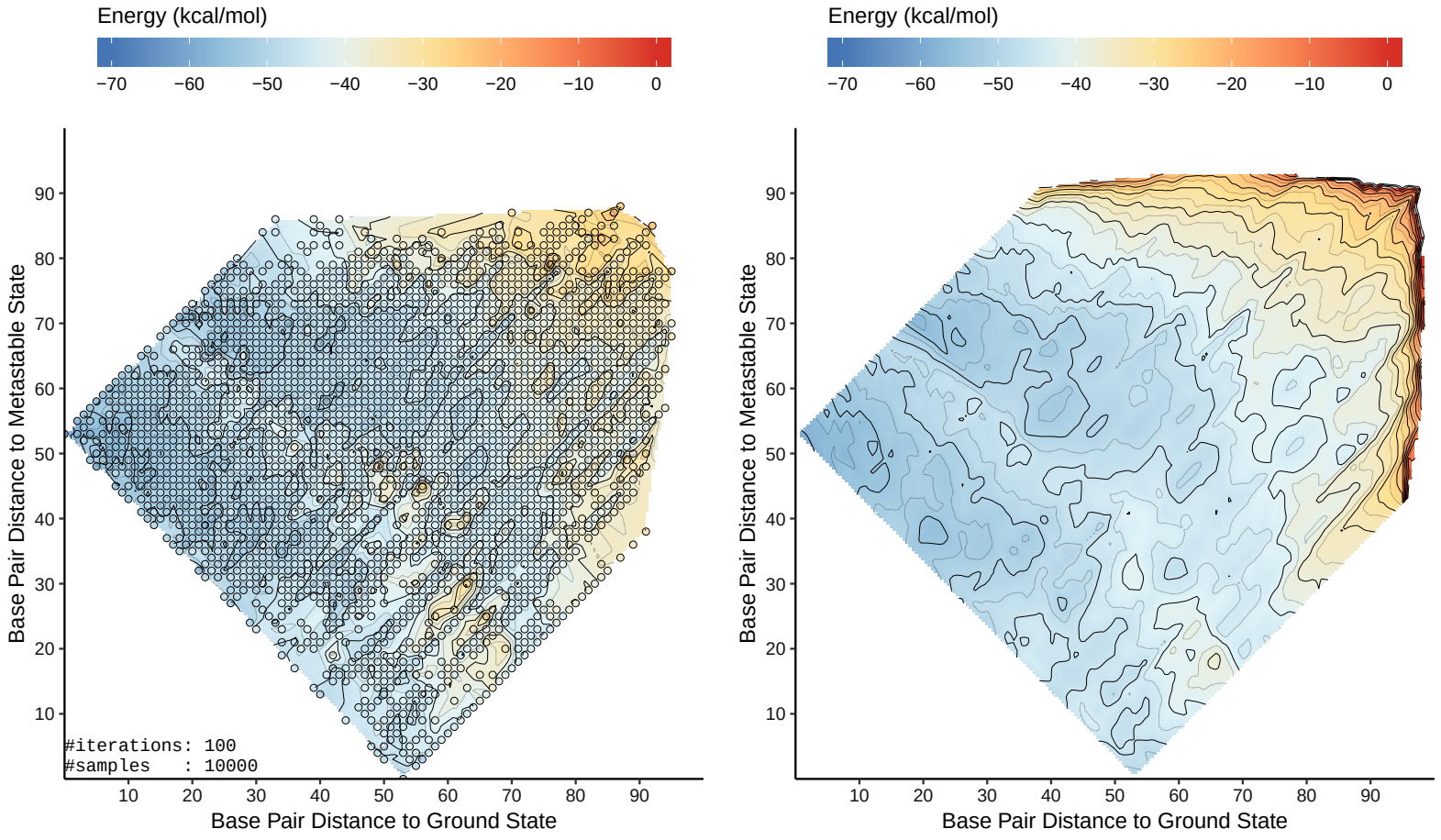

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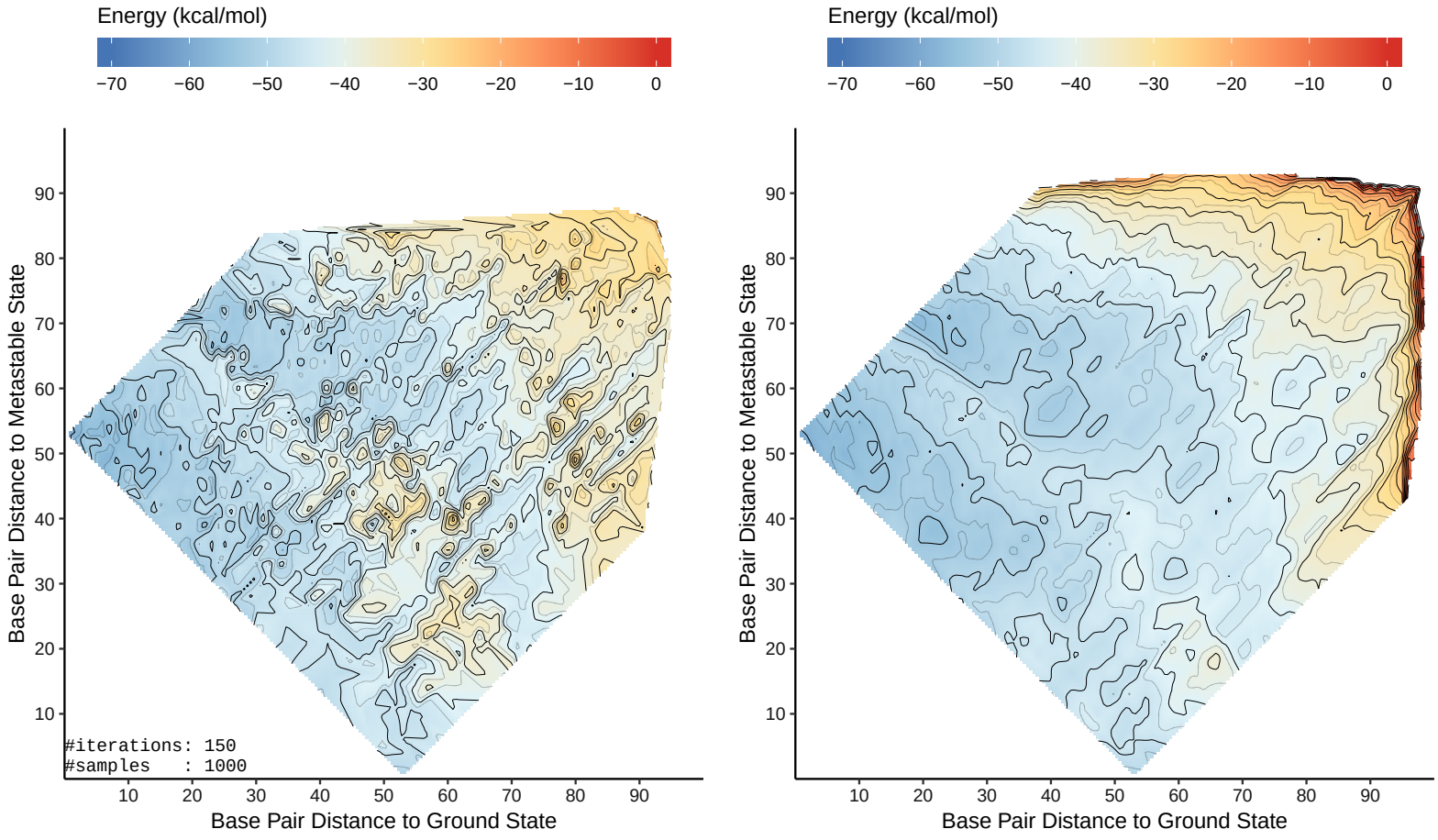

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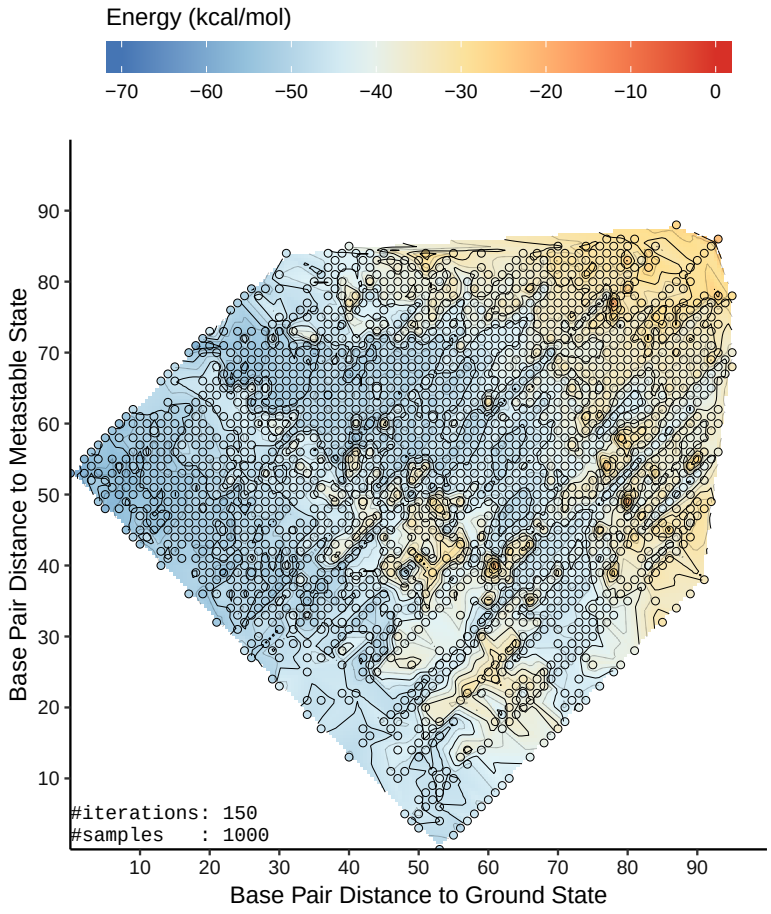

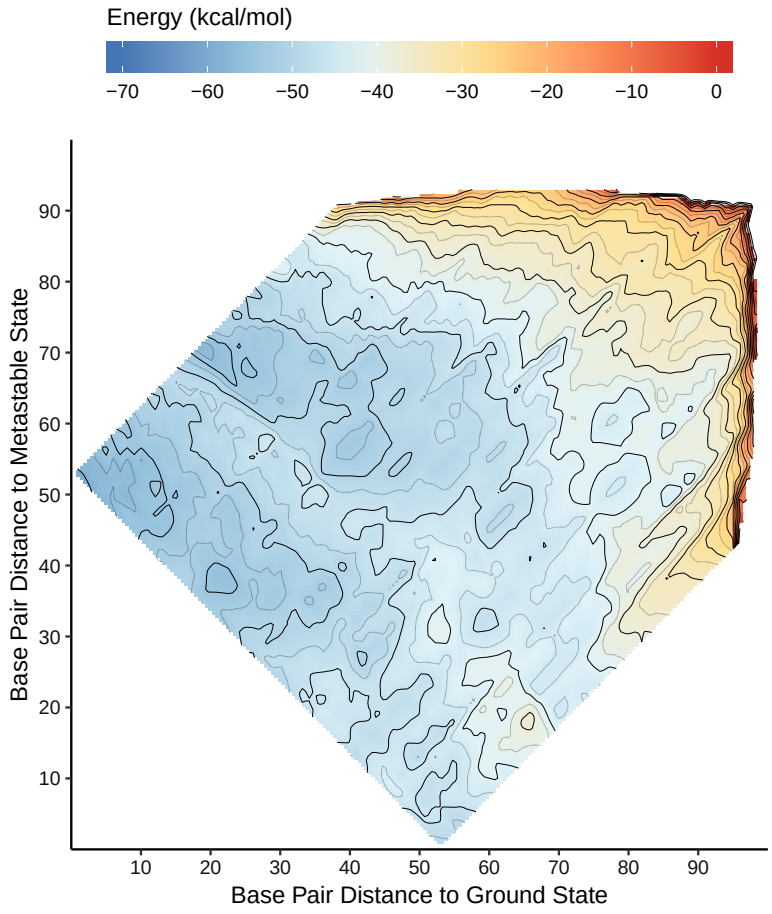

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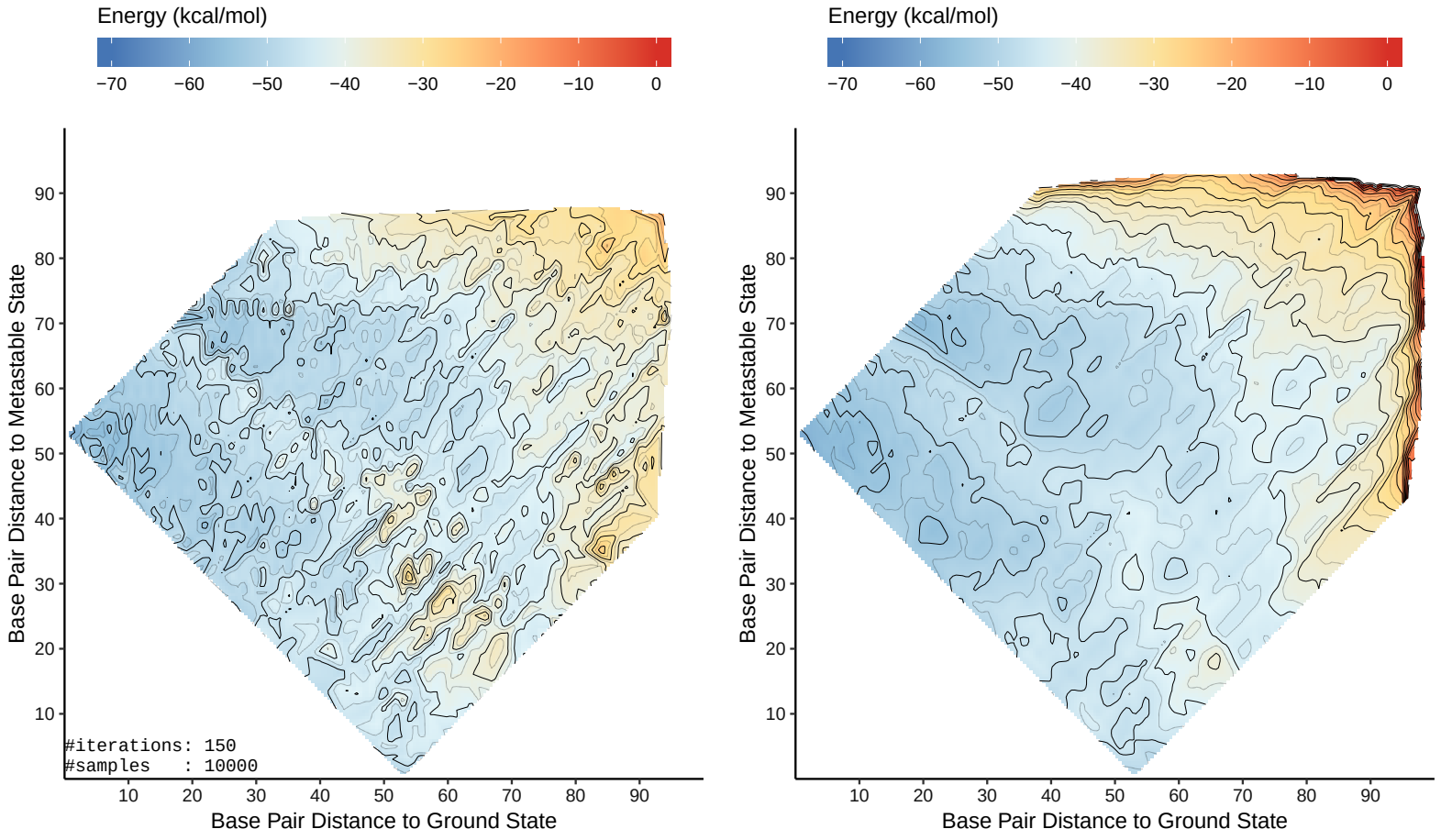

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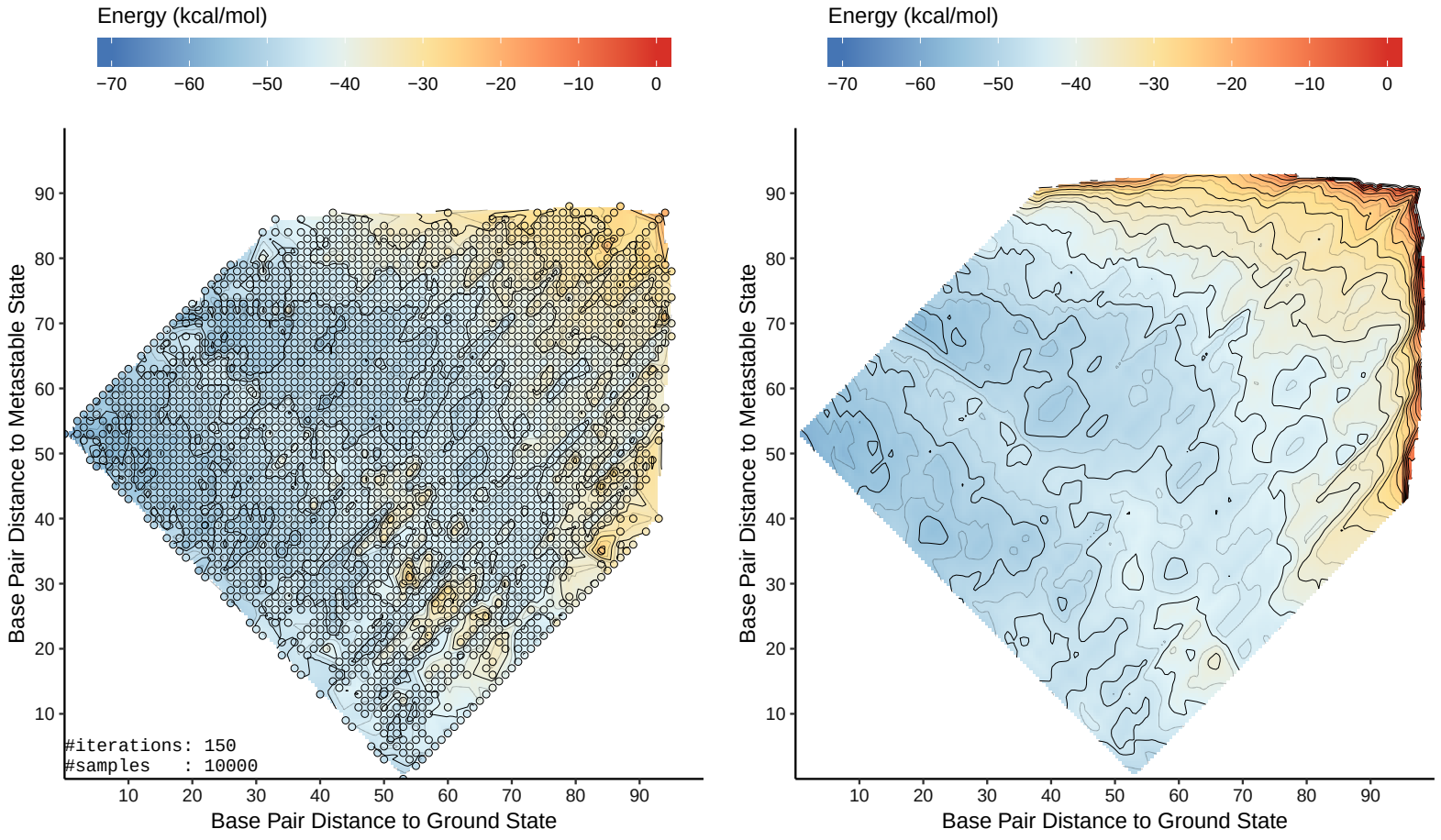

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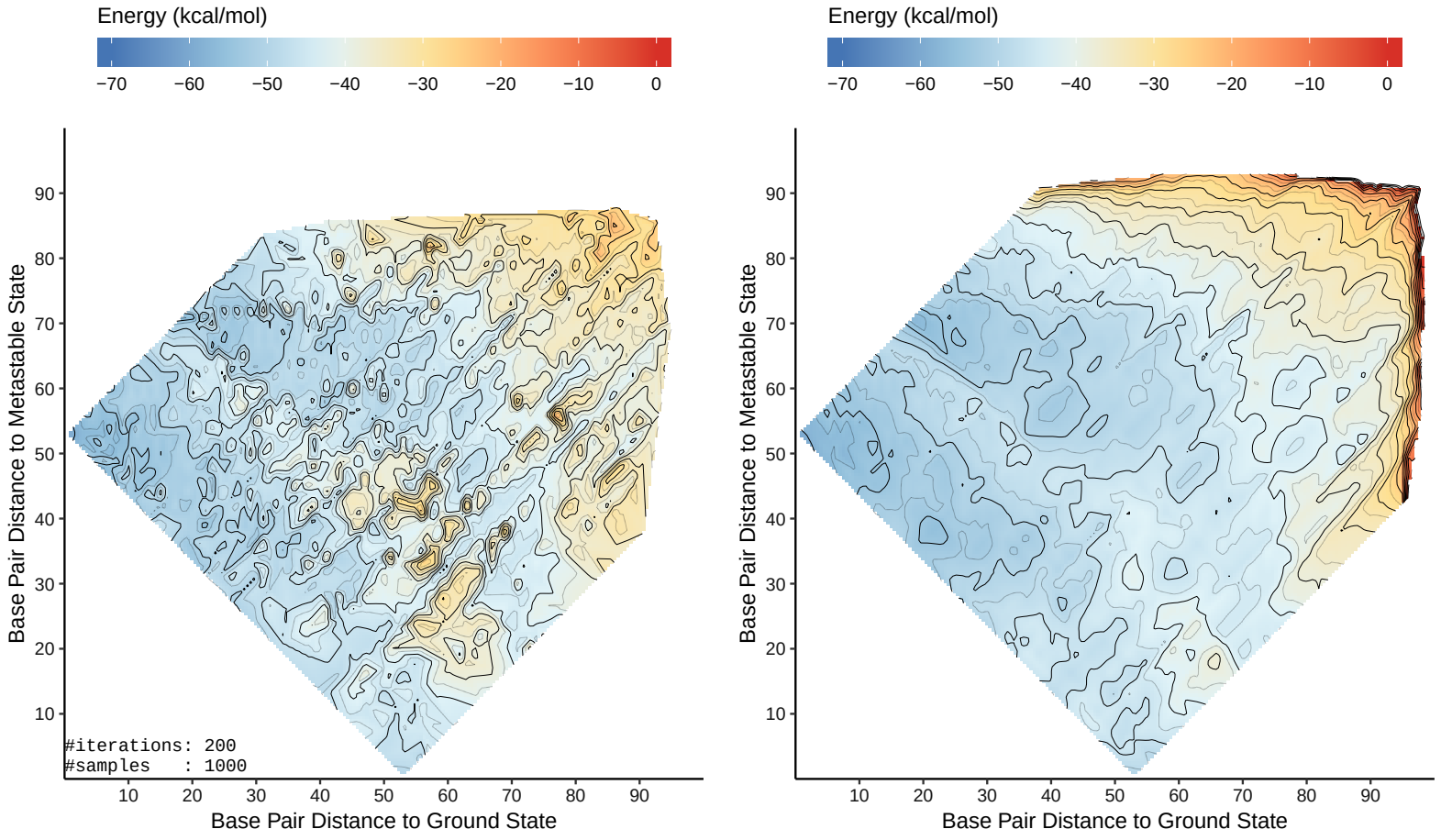

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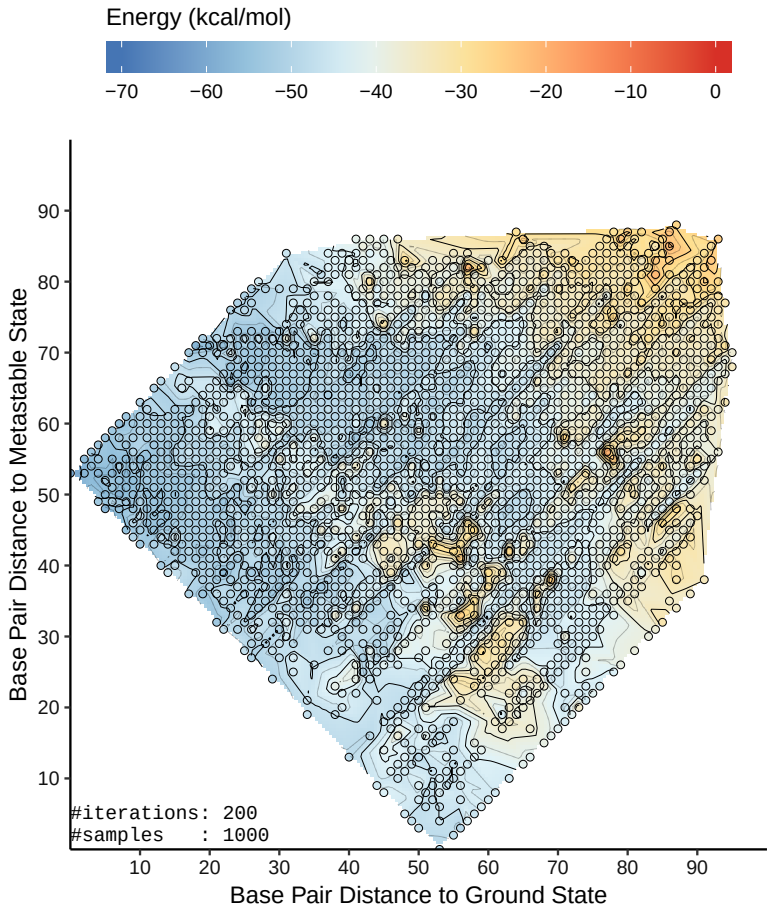

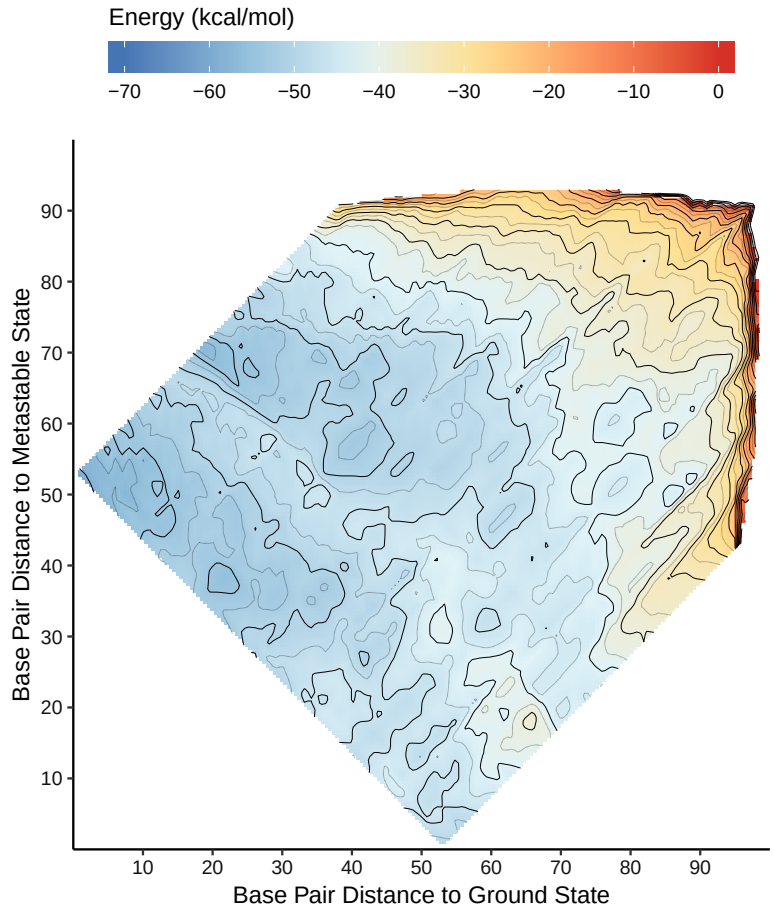

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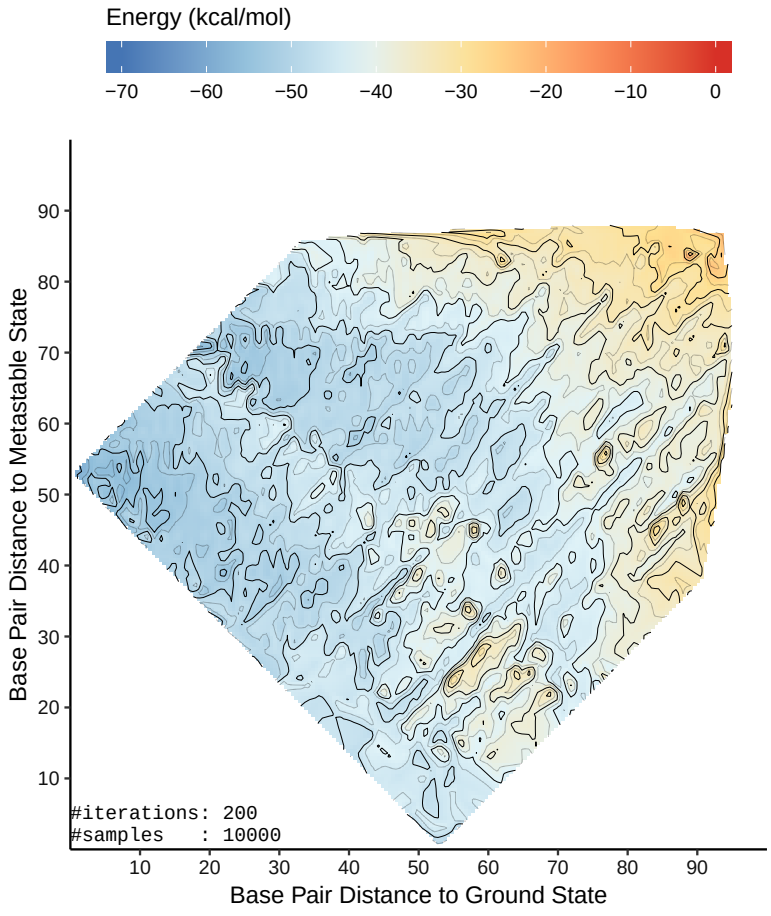

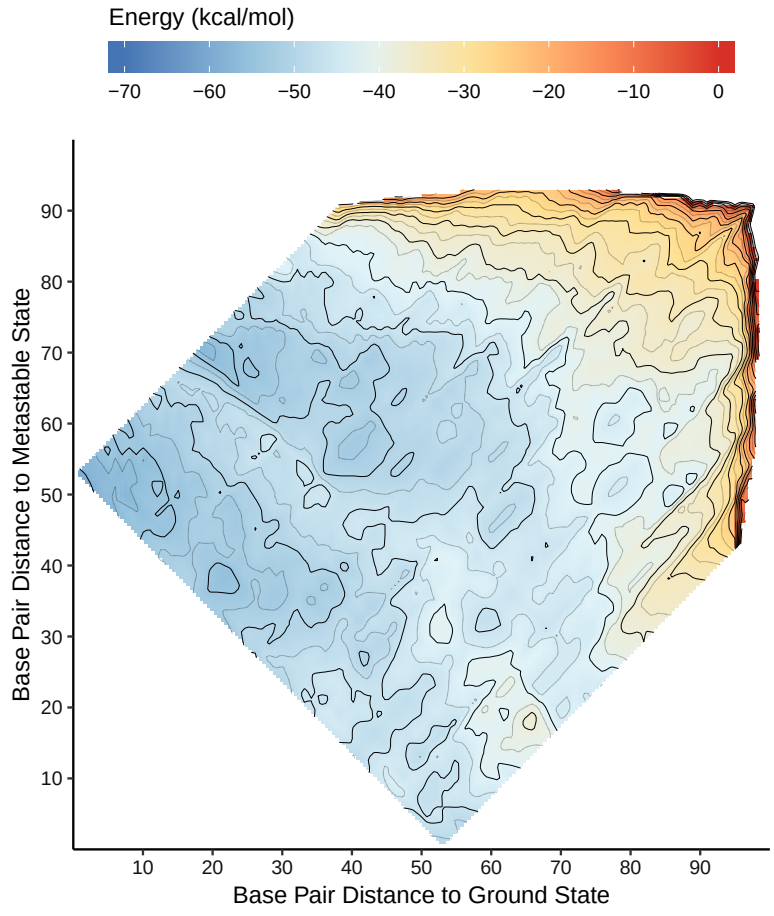

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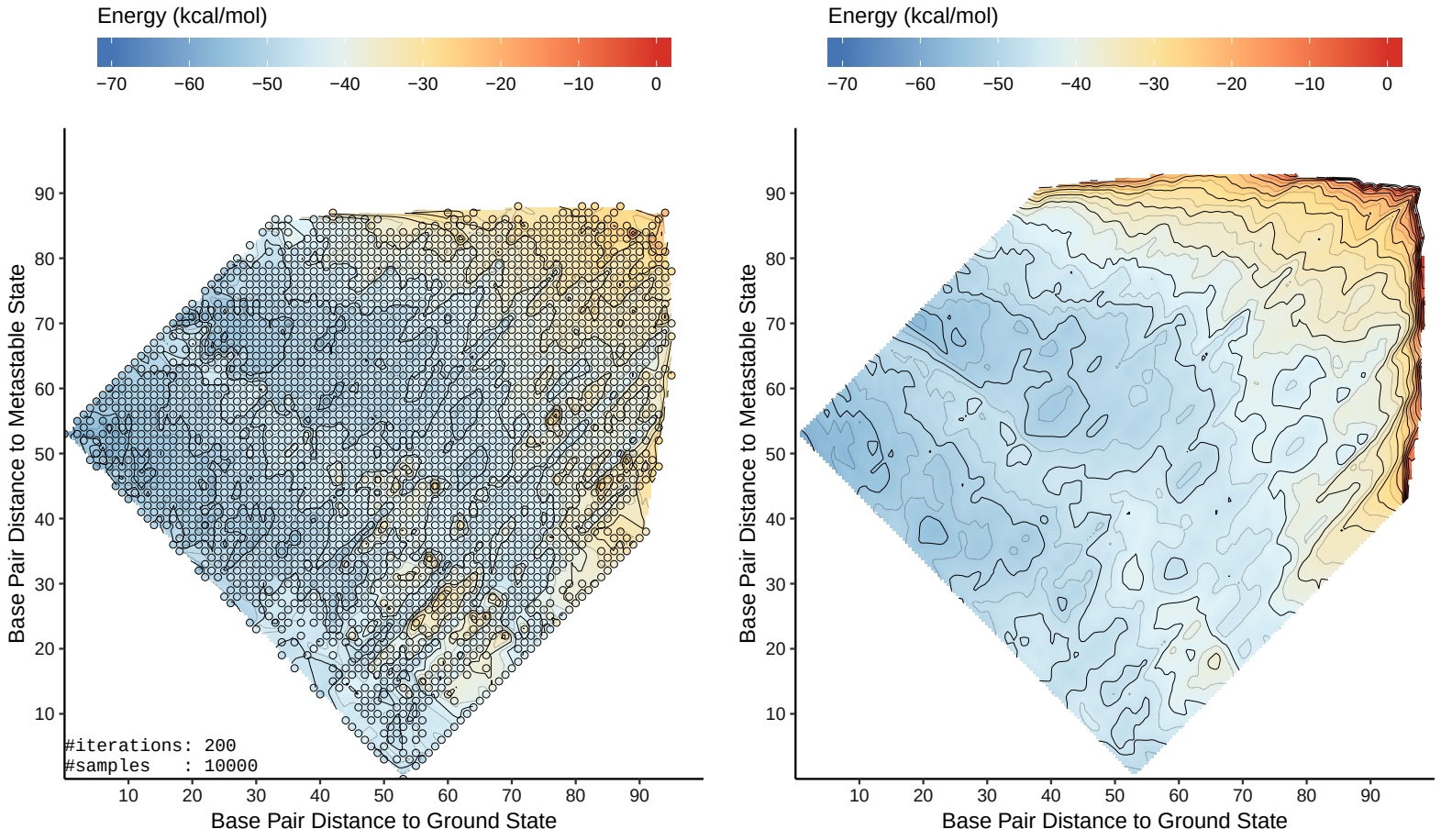

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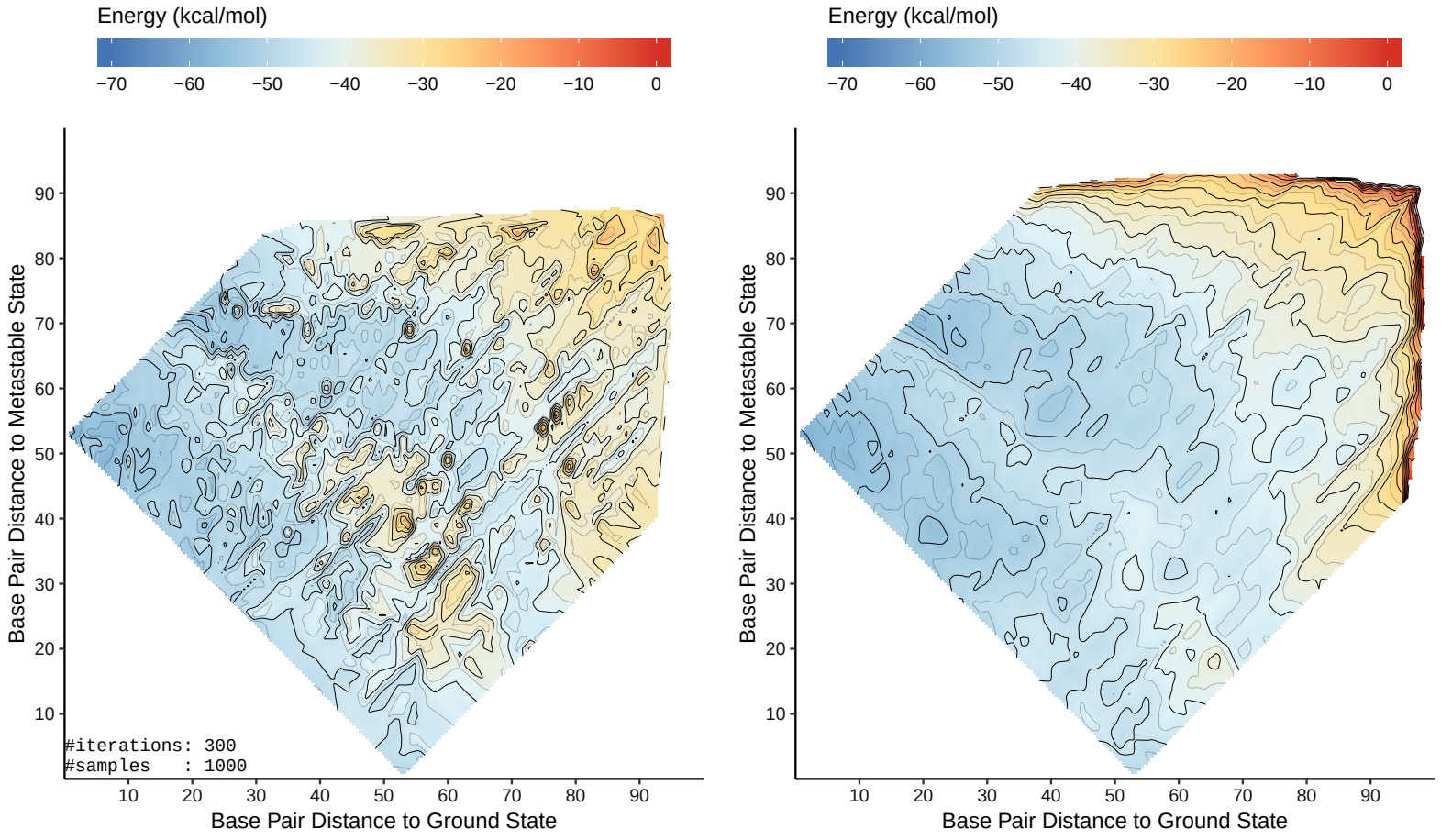

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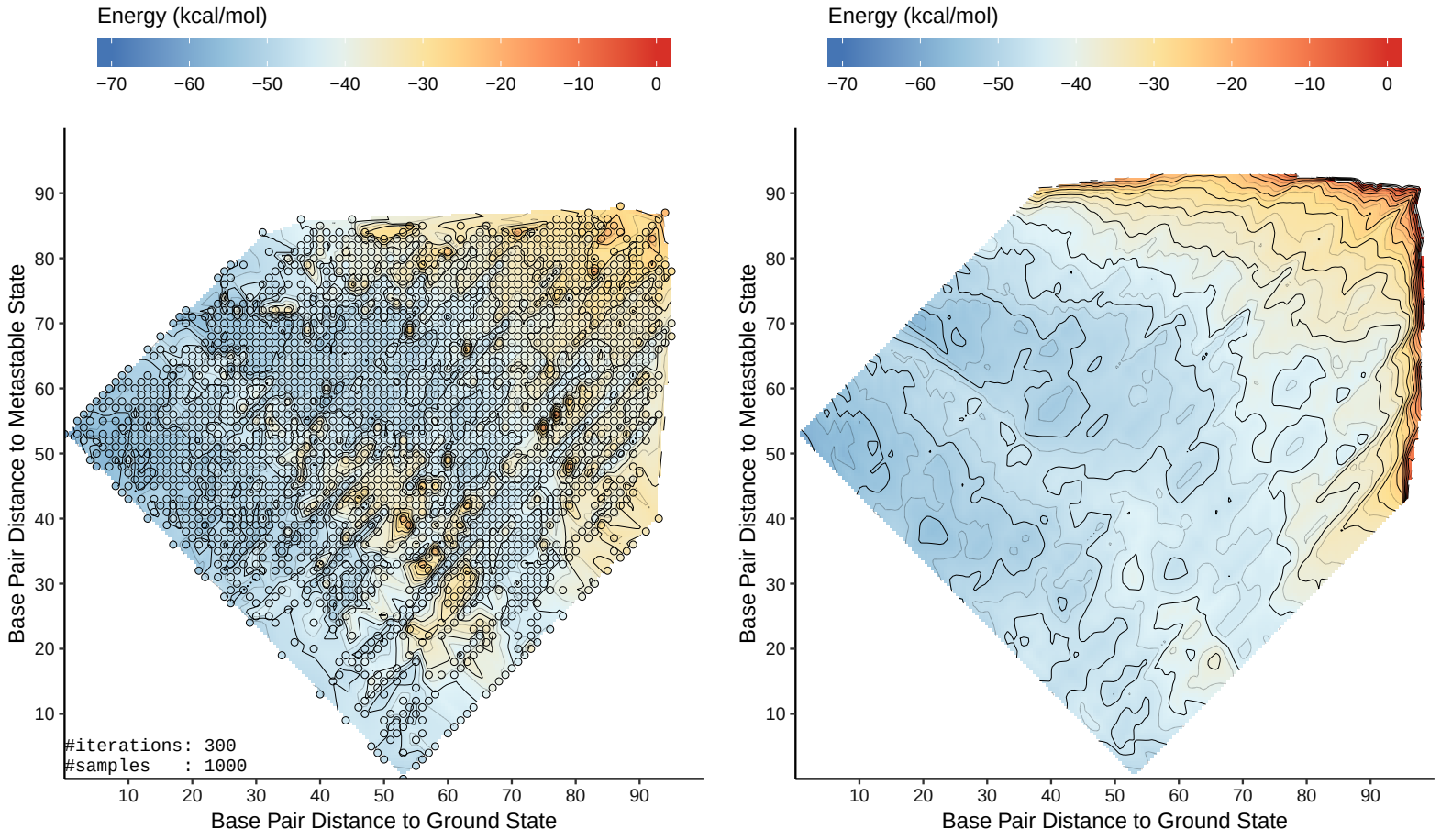

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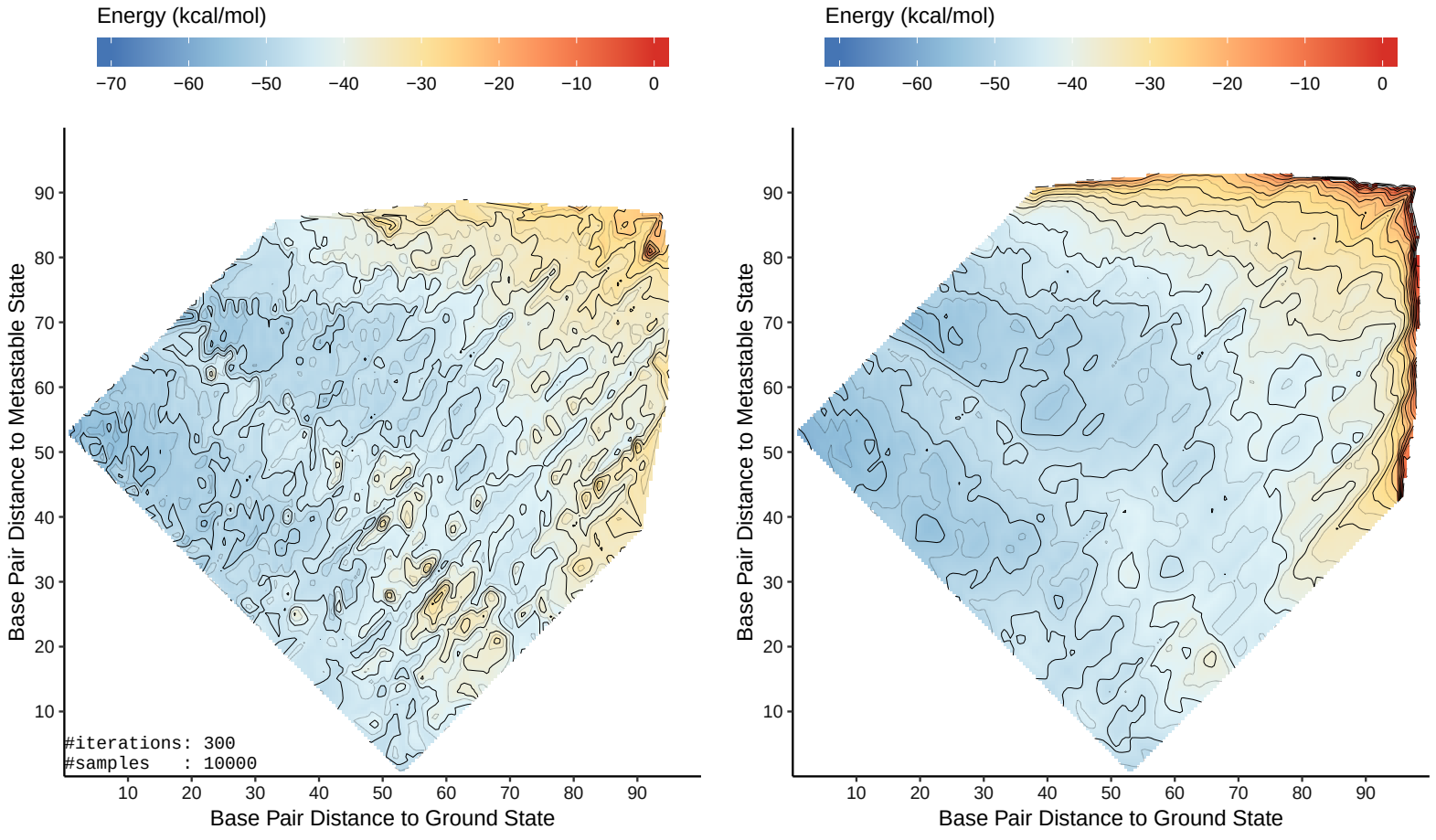

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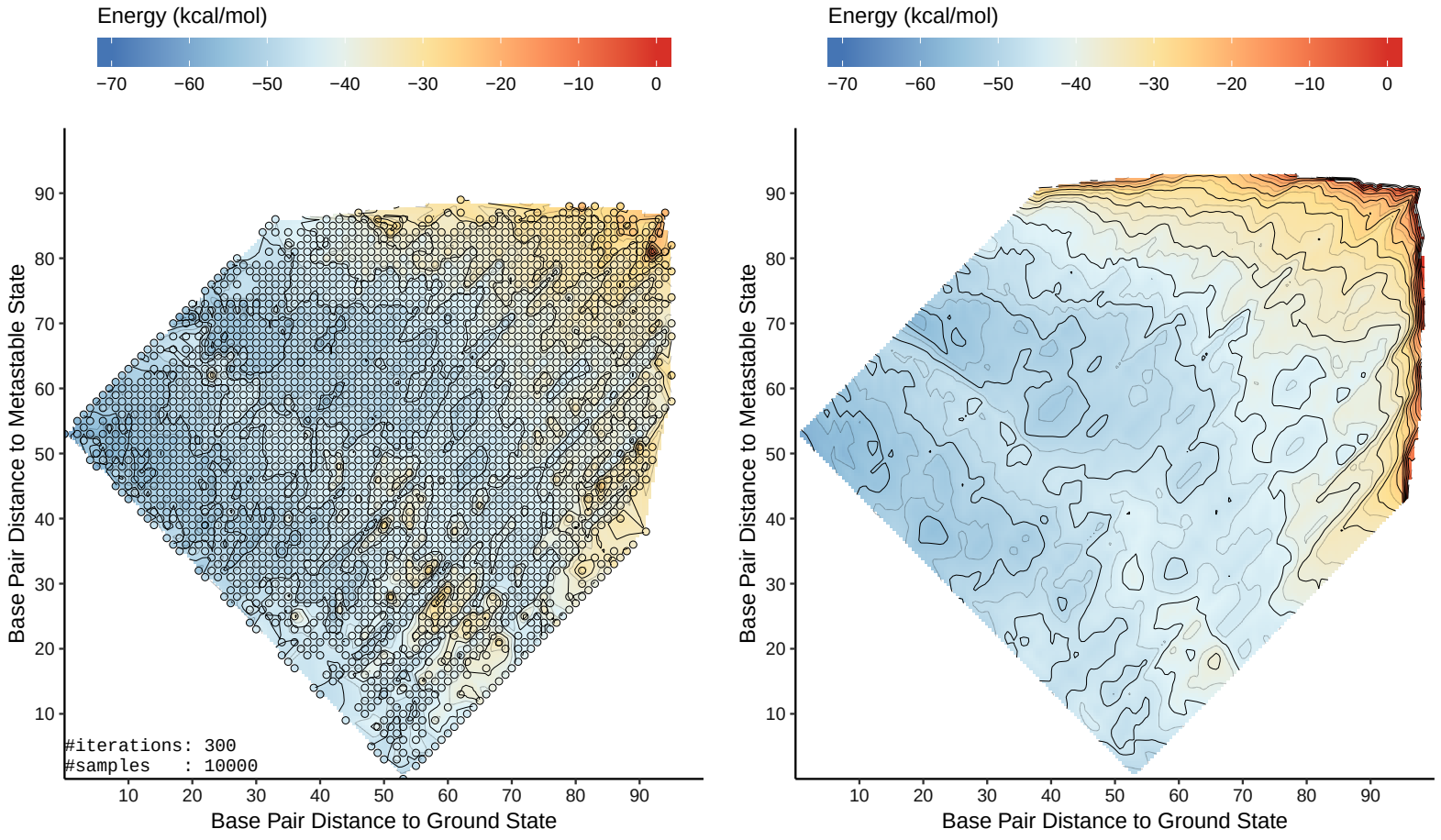
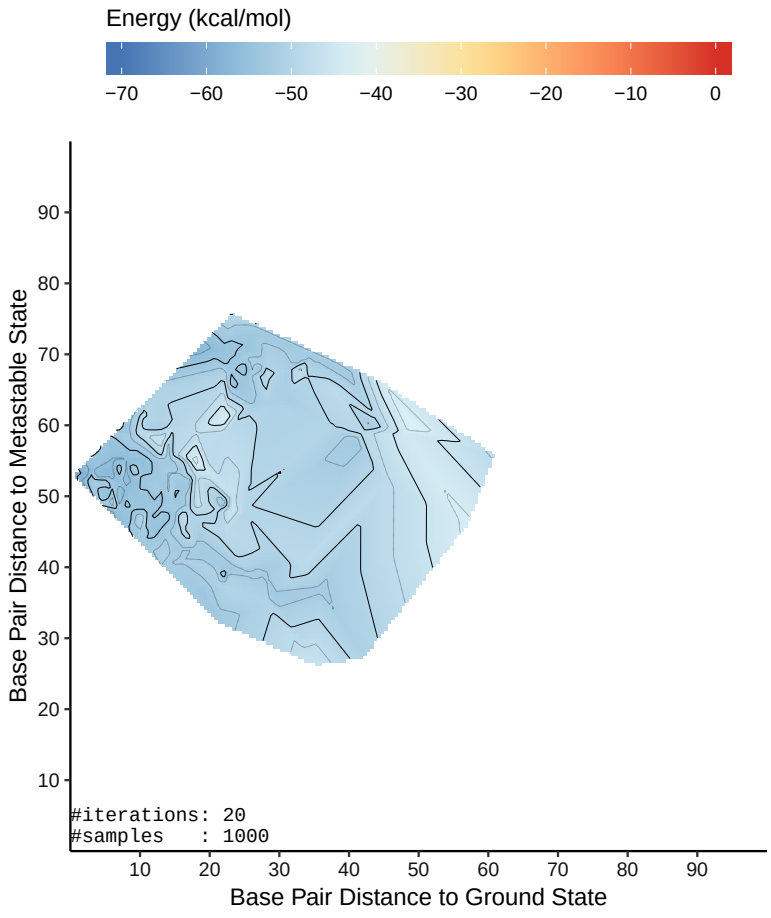
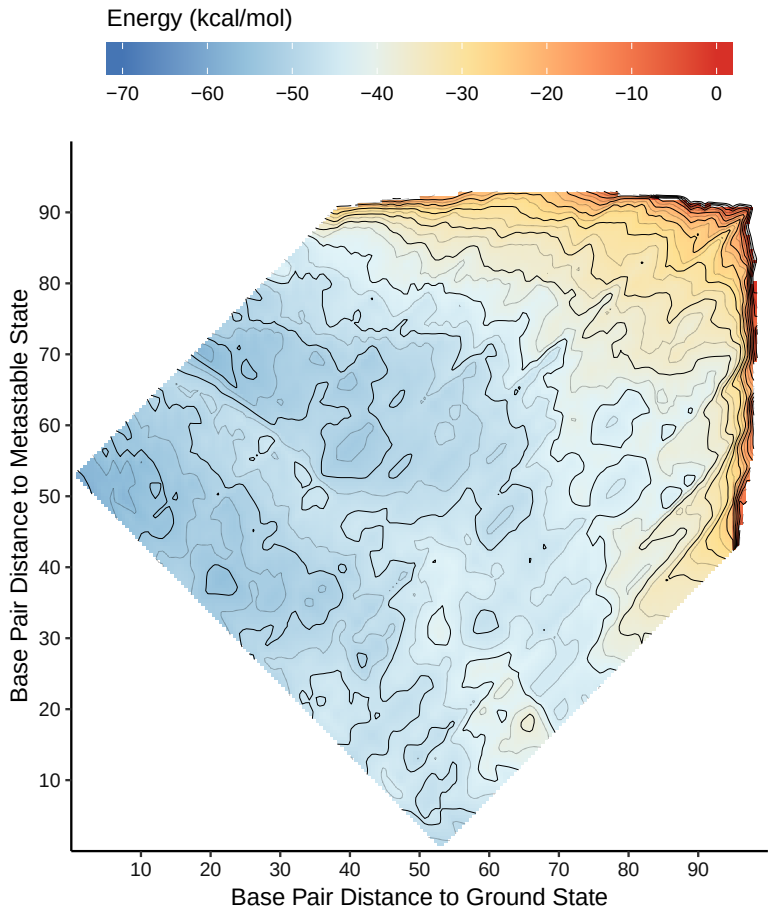


Example: 5UTR of MS2 coat protein mRNA

`RNAlocmin` temperature elevation scheme Boltzmann sampling





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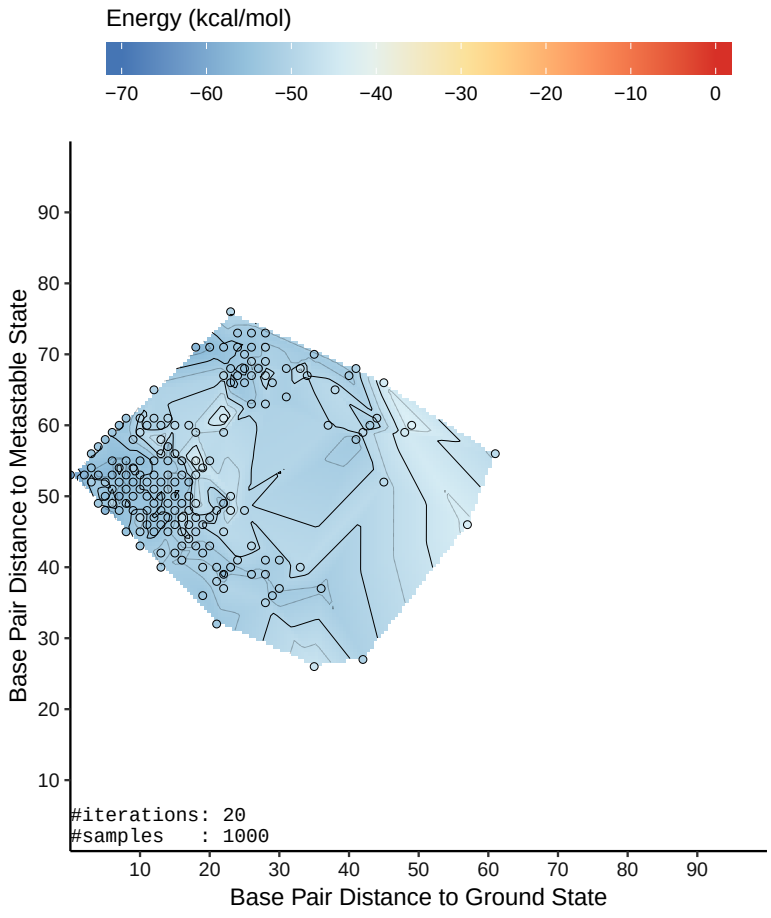

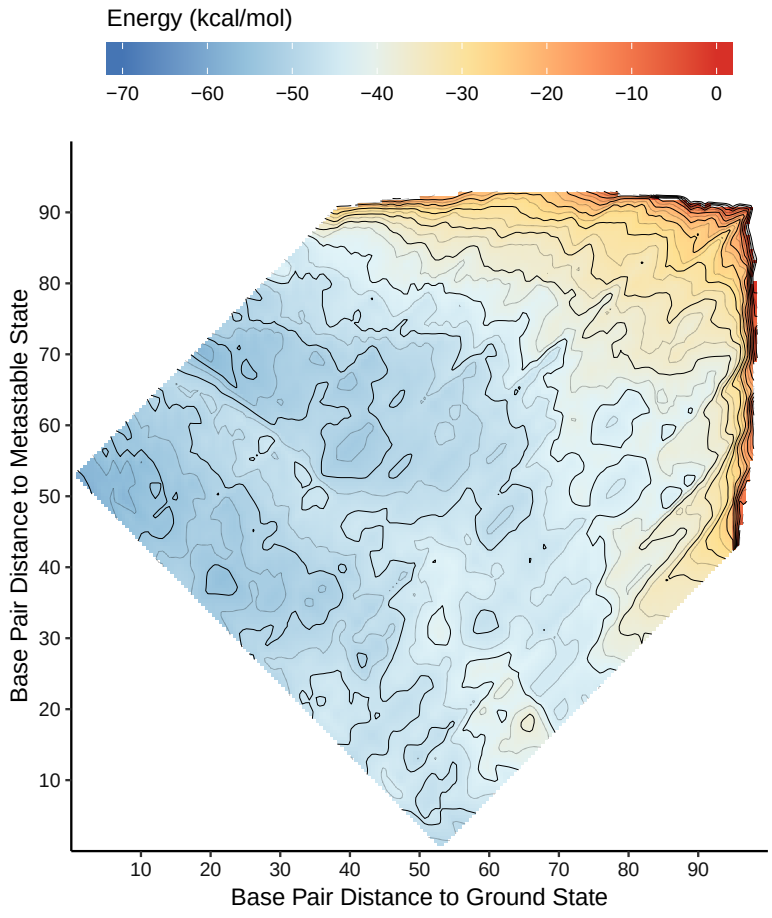

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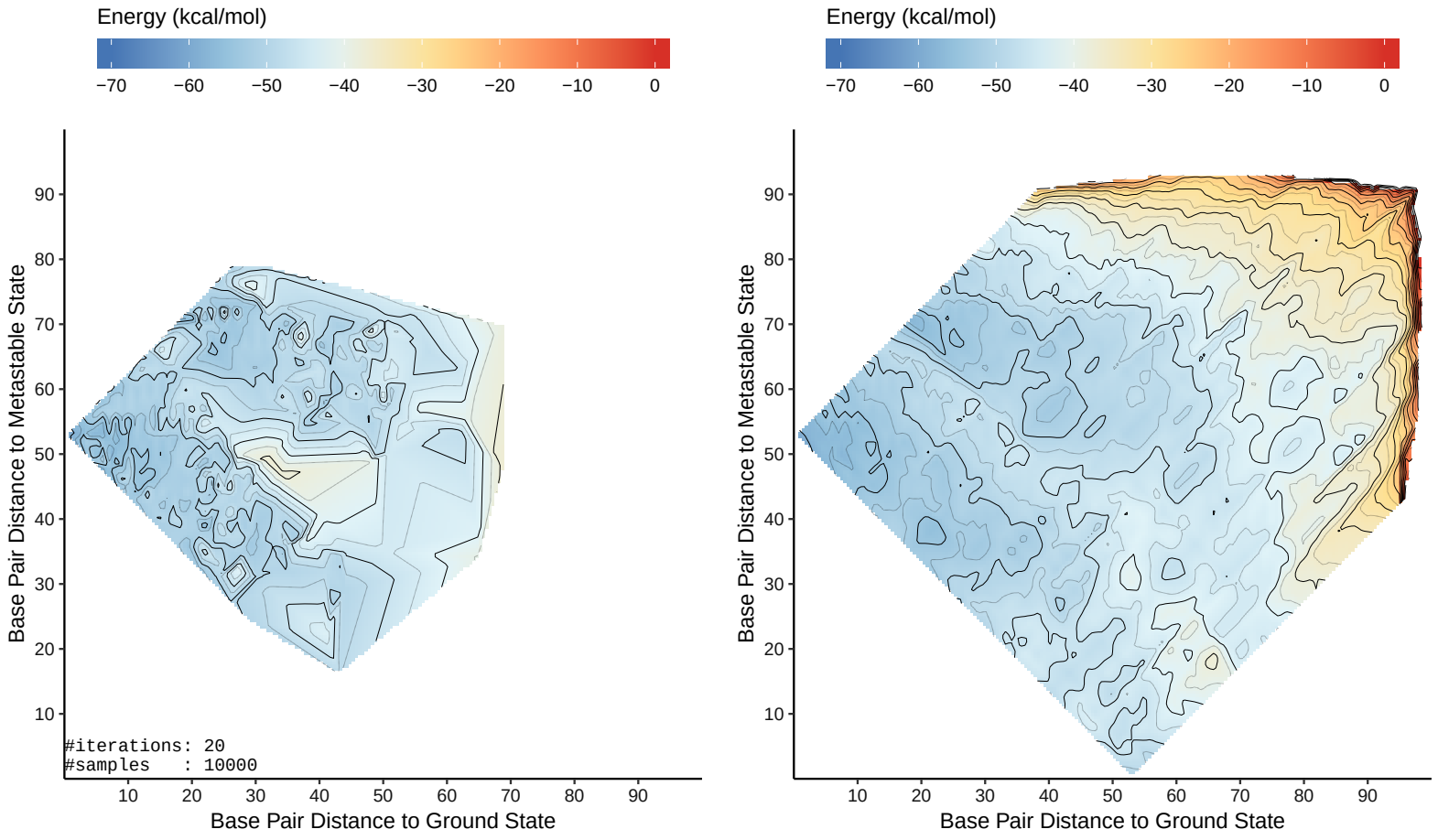
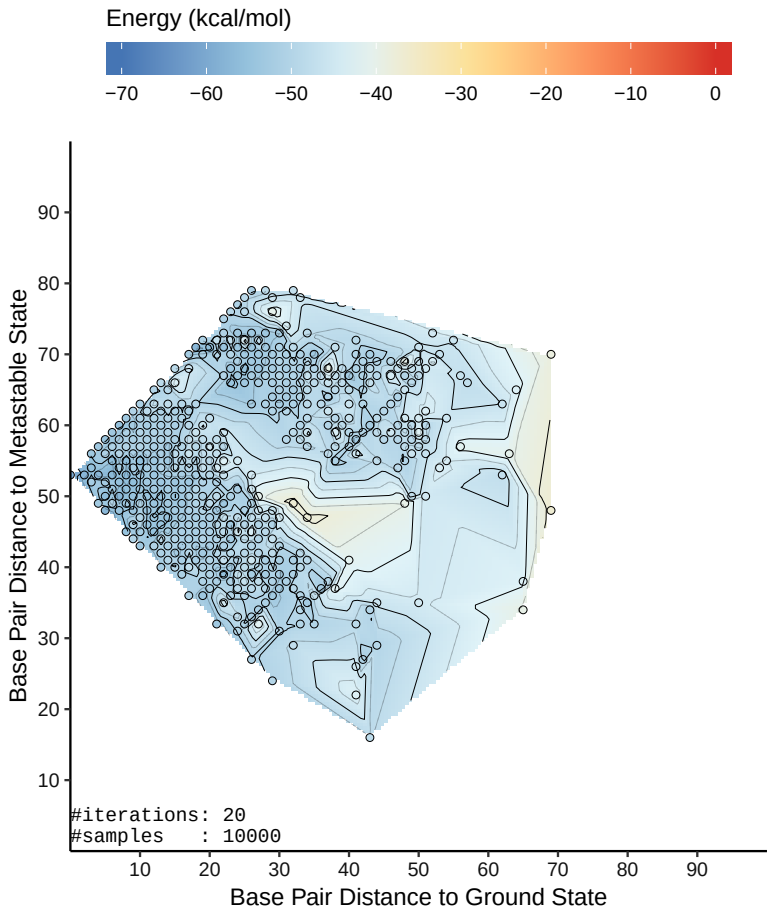
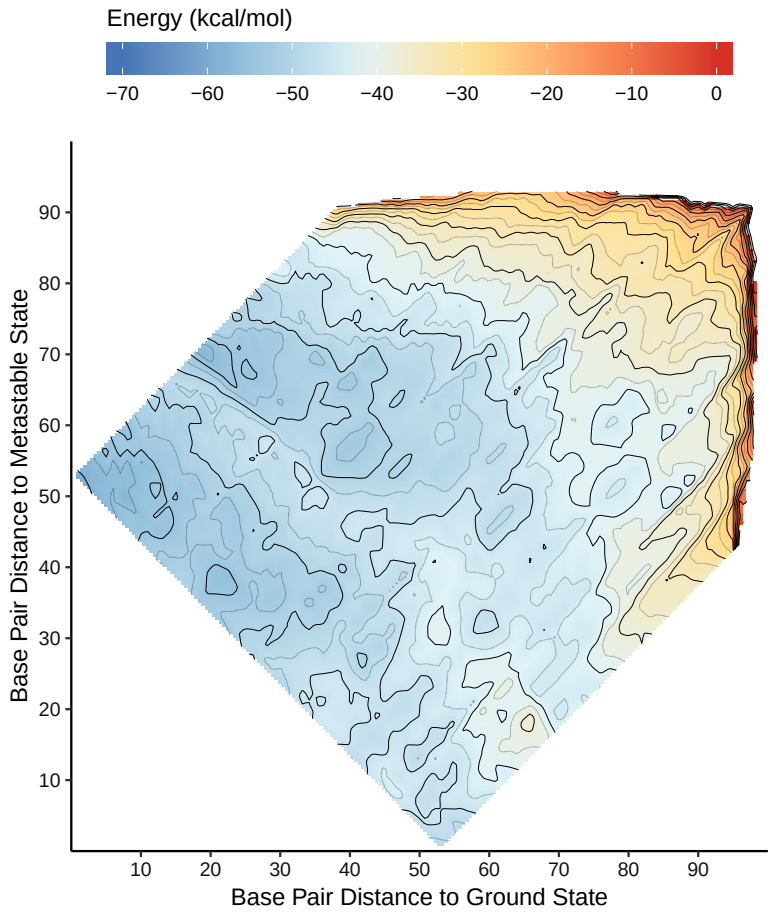


Example: 5UTR of MS2 coat protein mRNA

`RNAlocmin` temperature elevation scheme Boltzmann sampling





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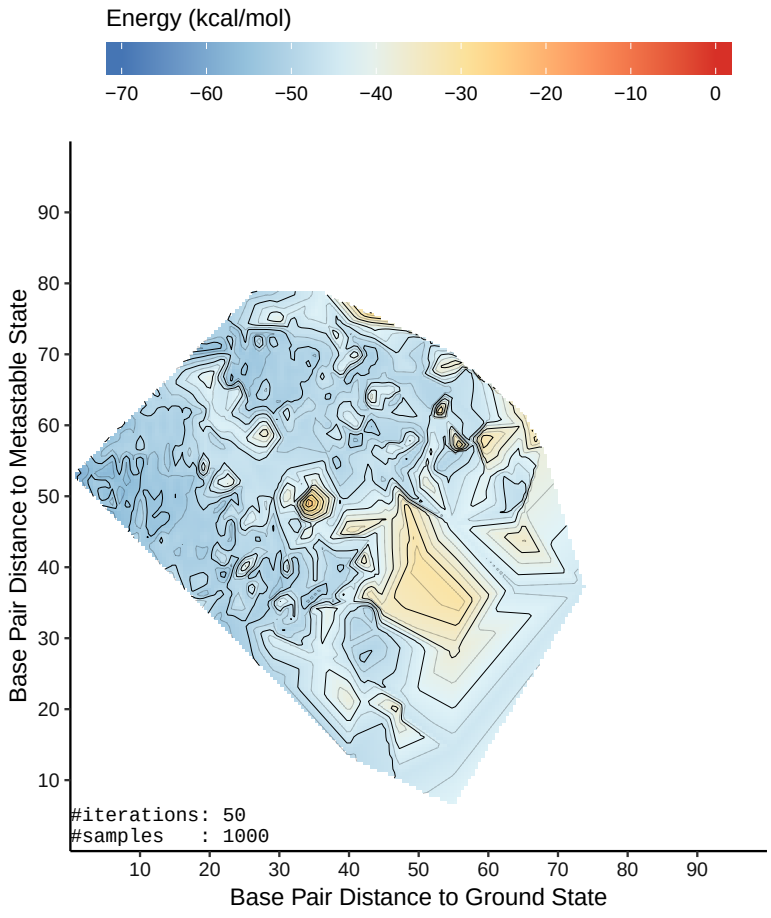

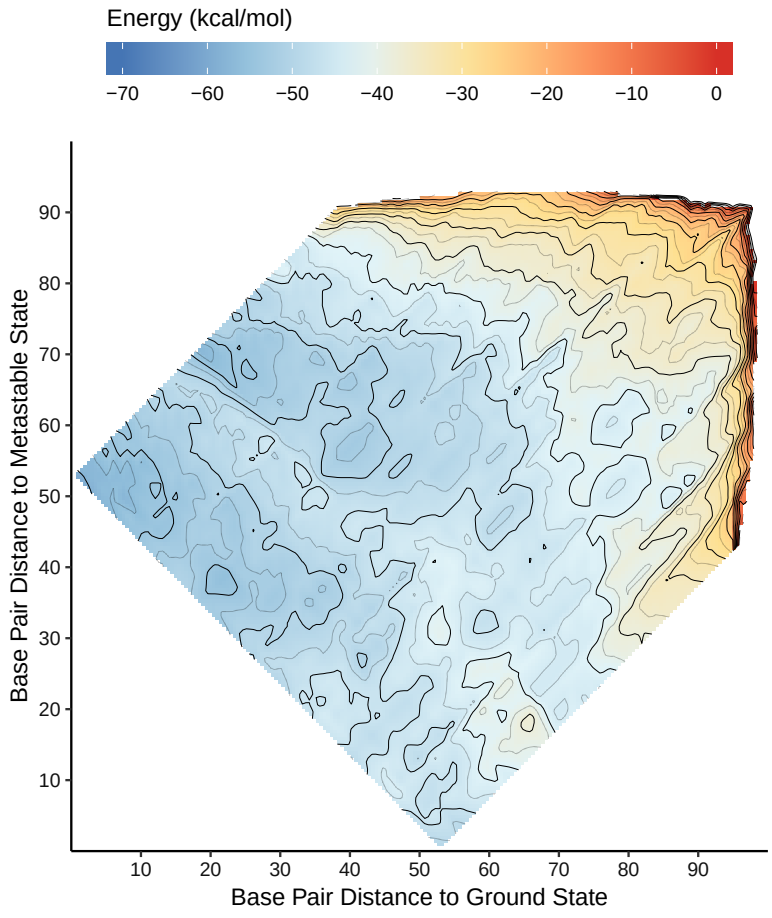

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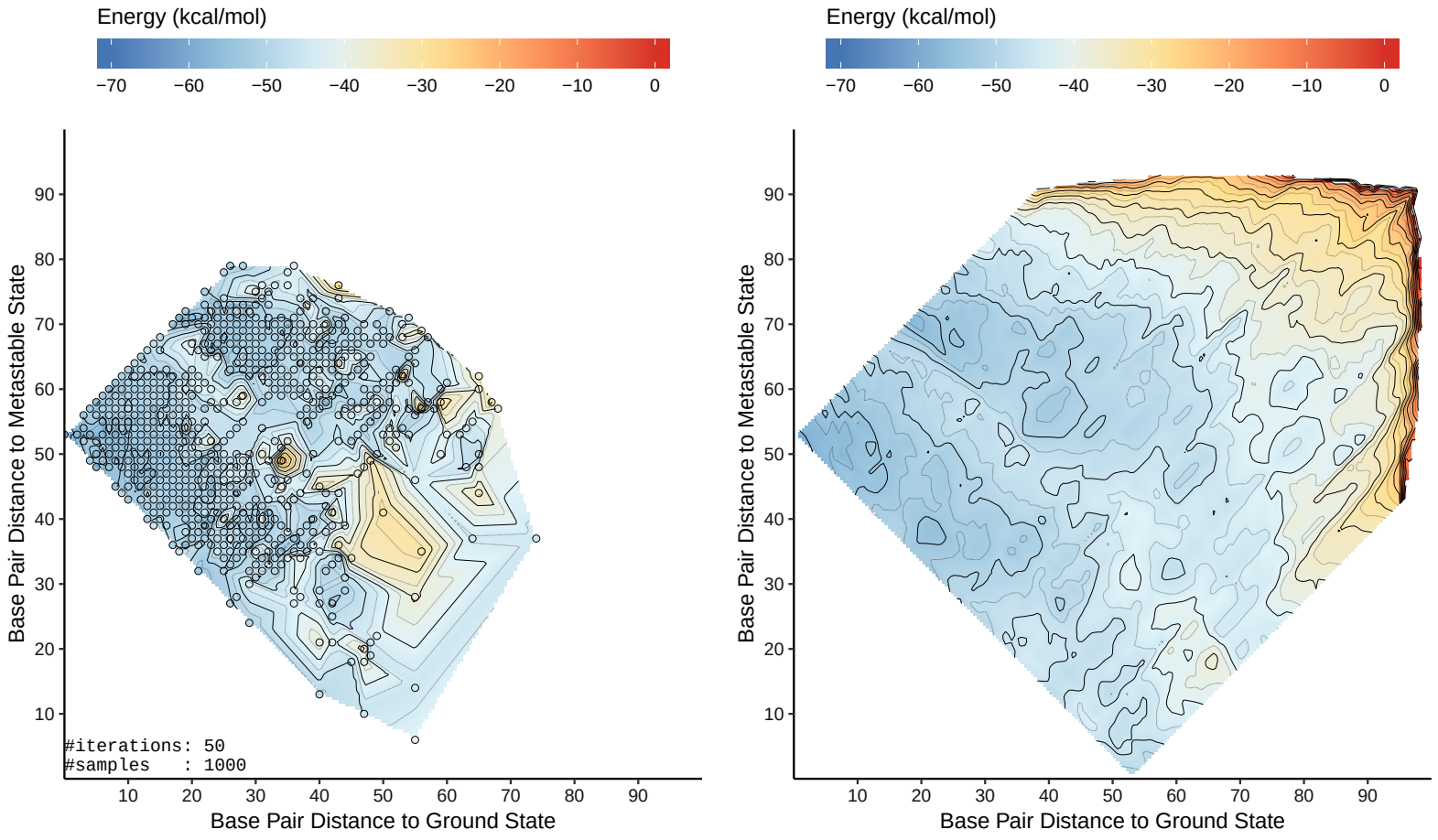

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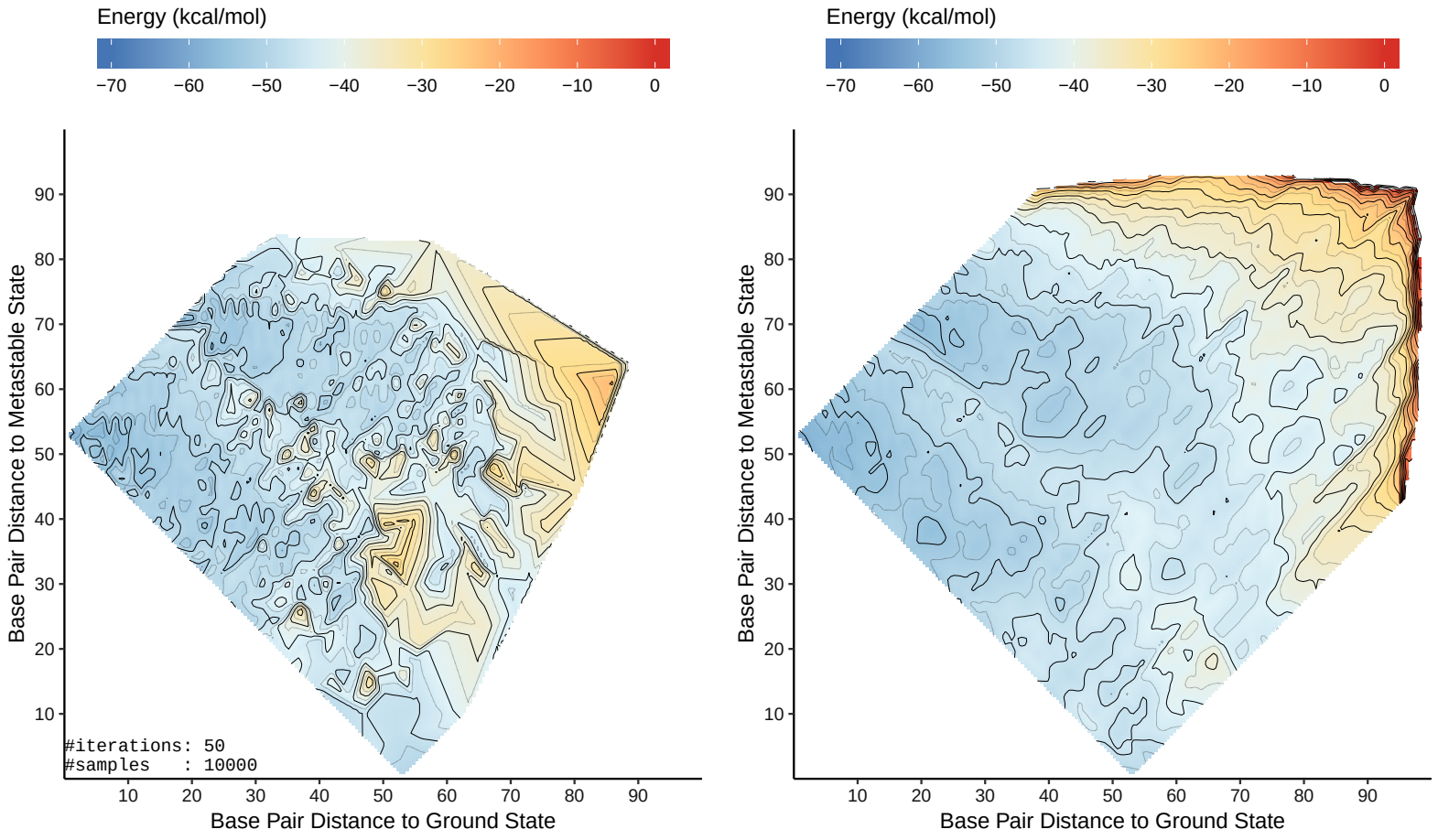

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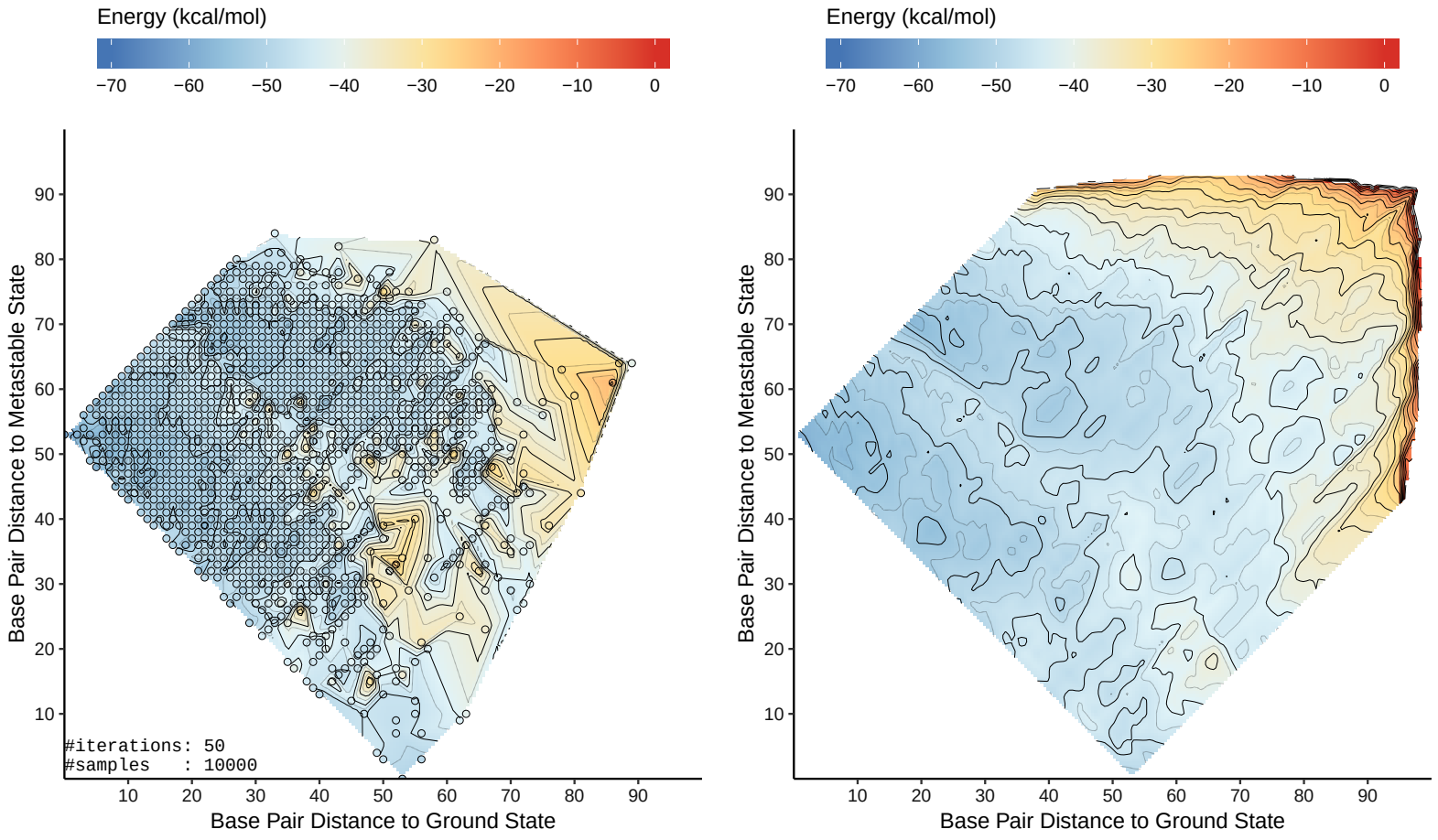

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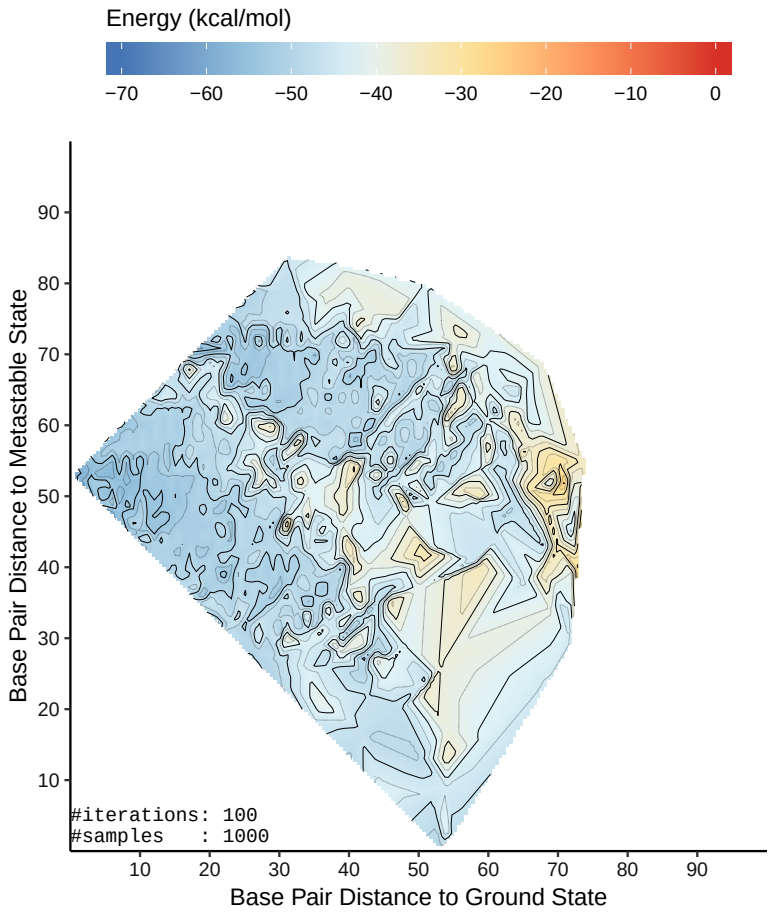

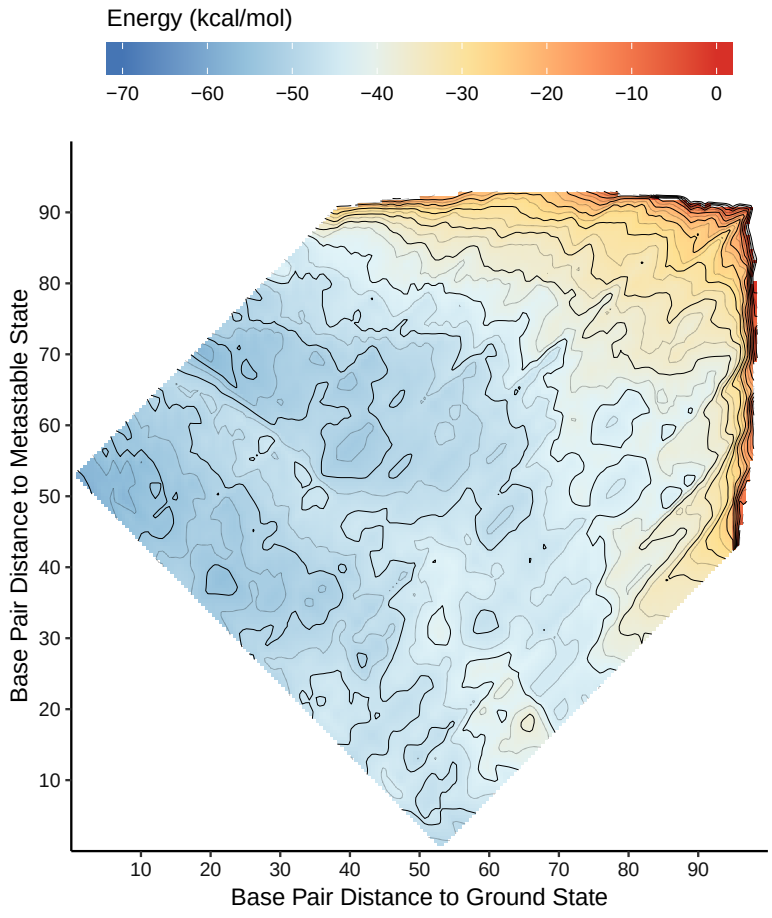

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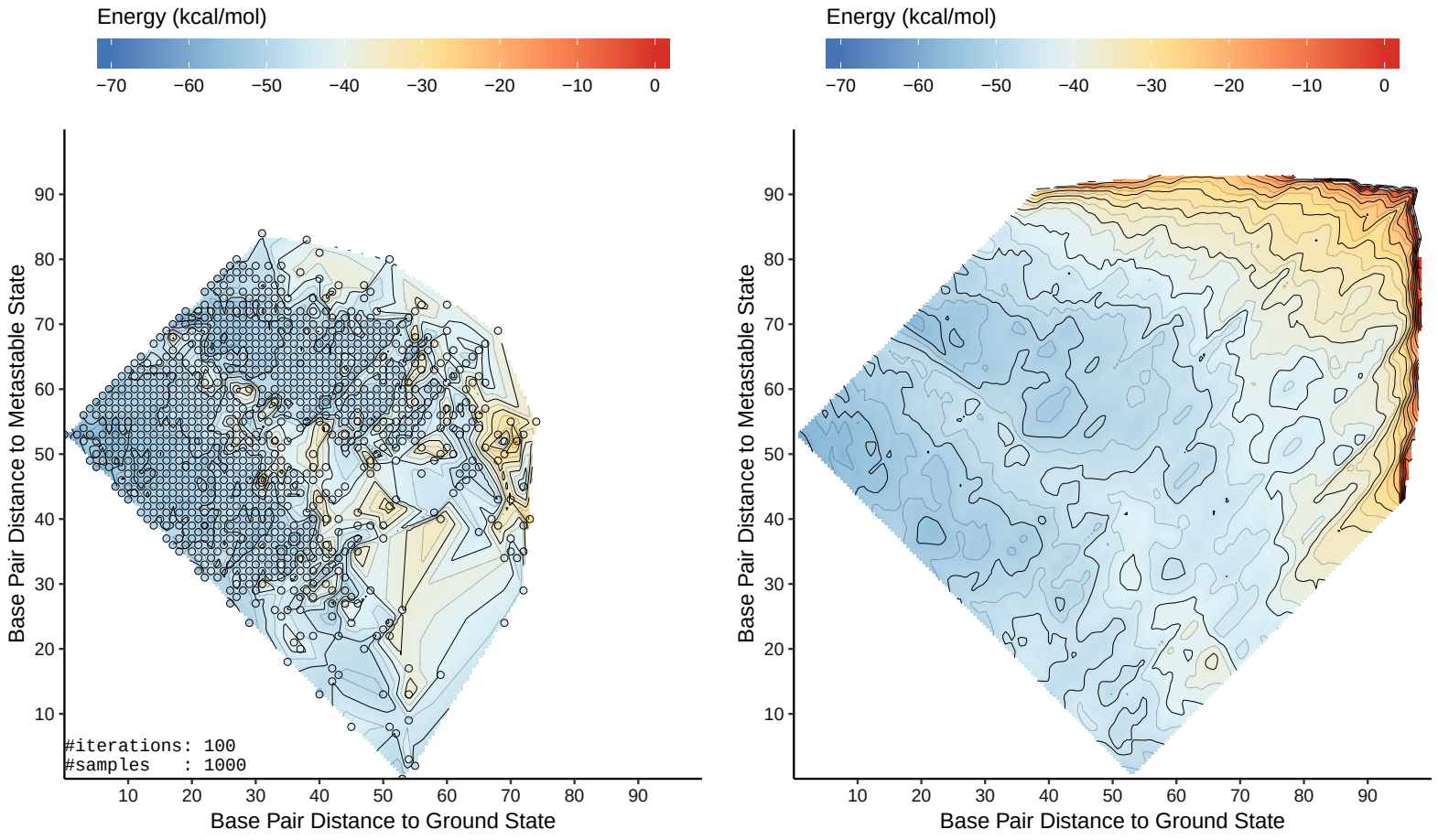

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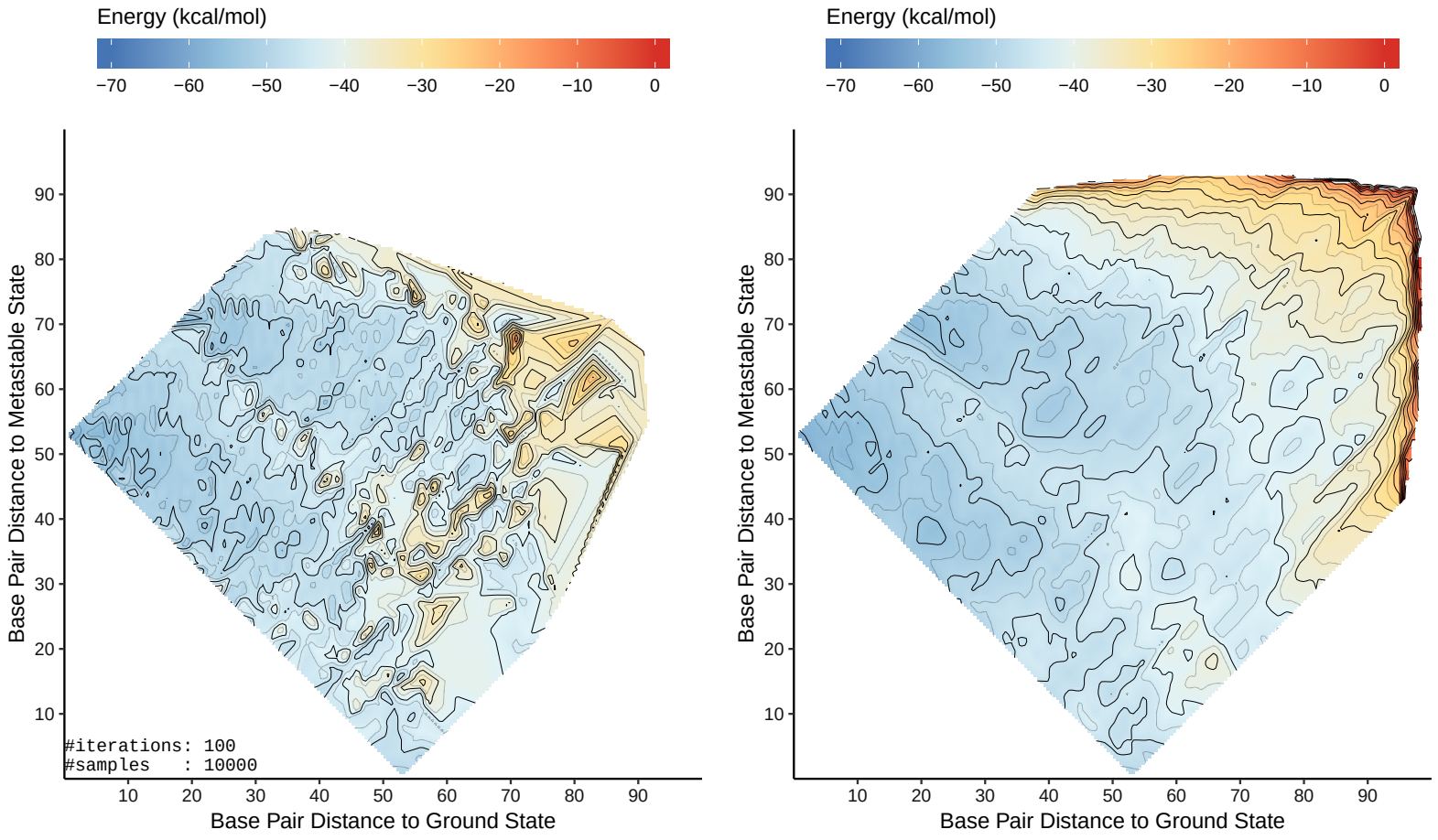

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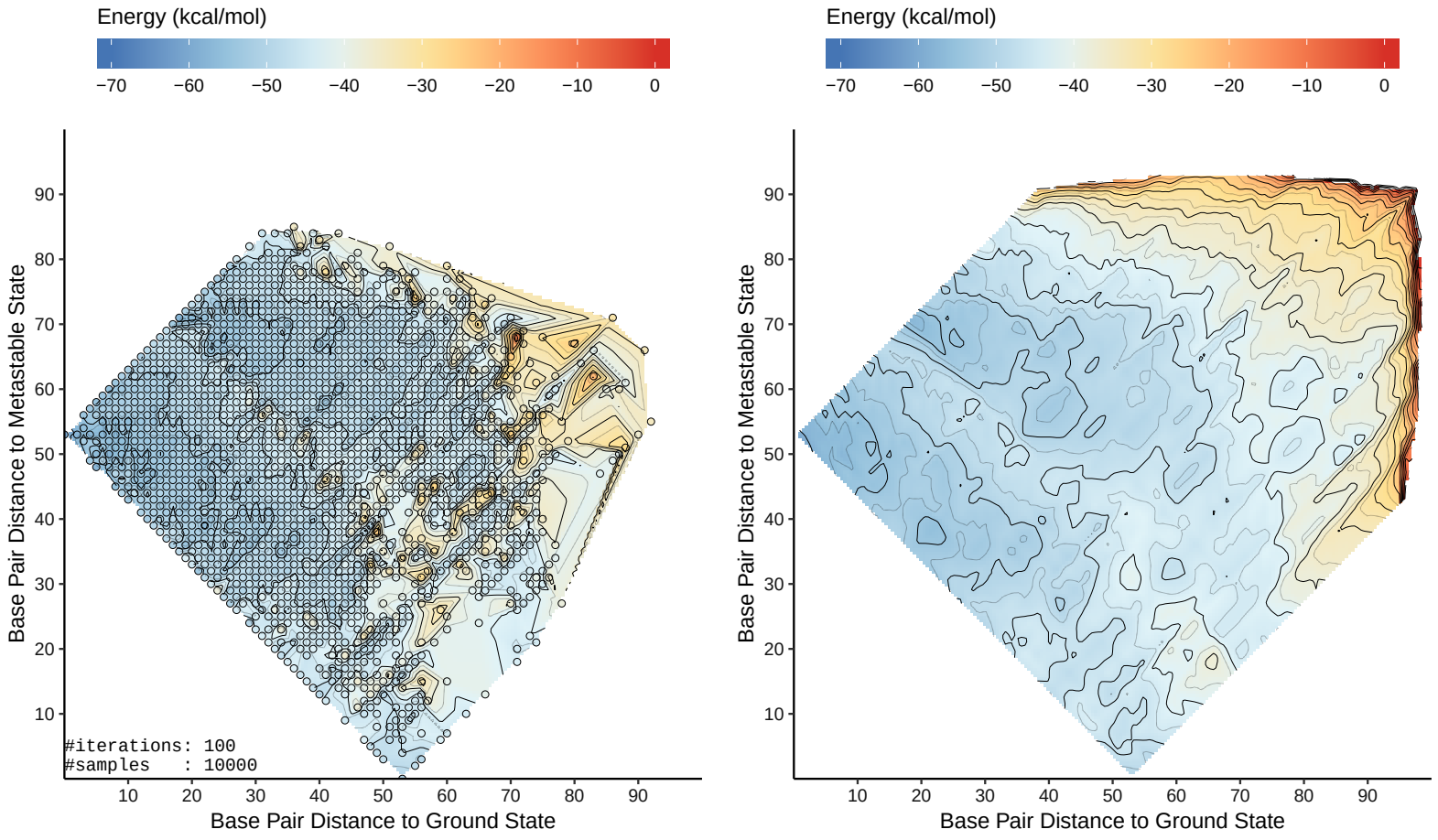

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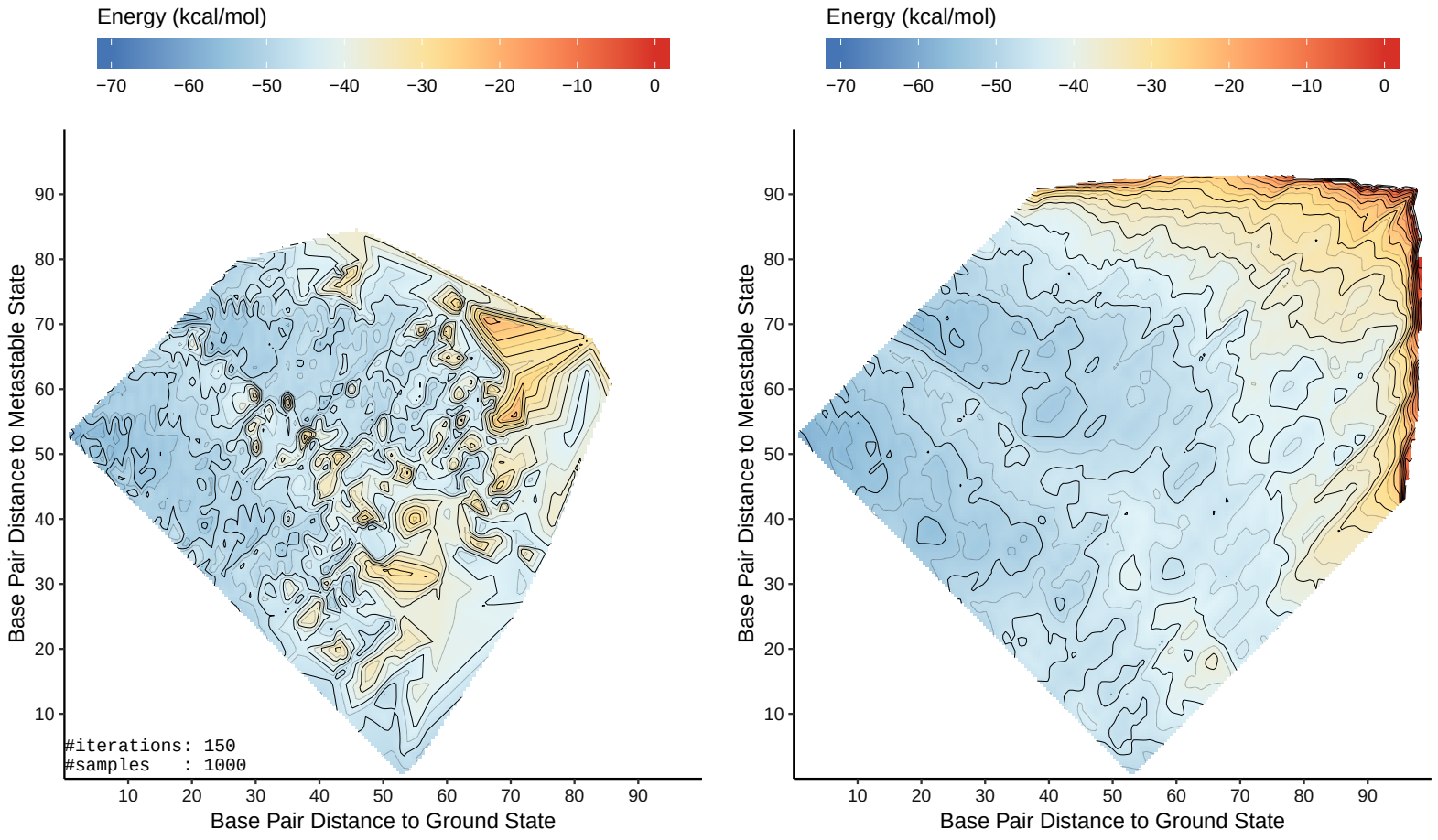

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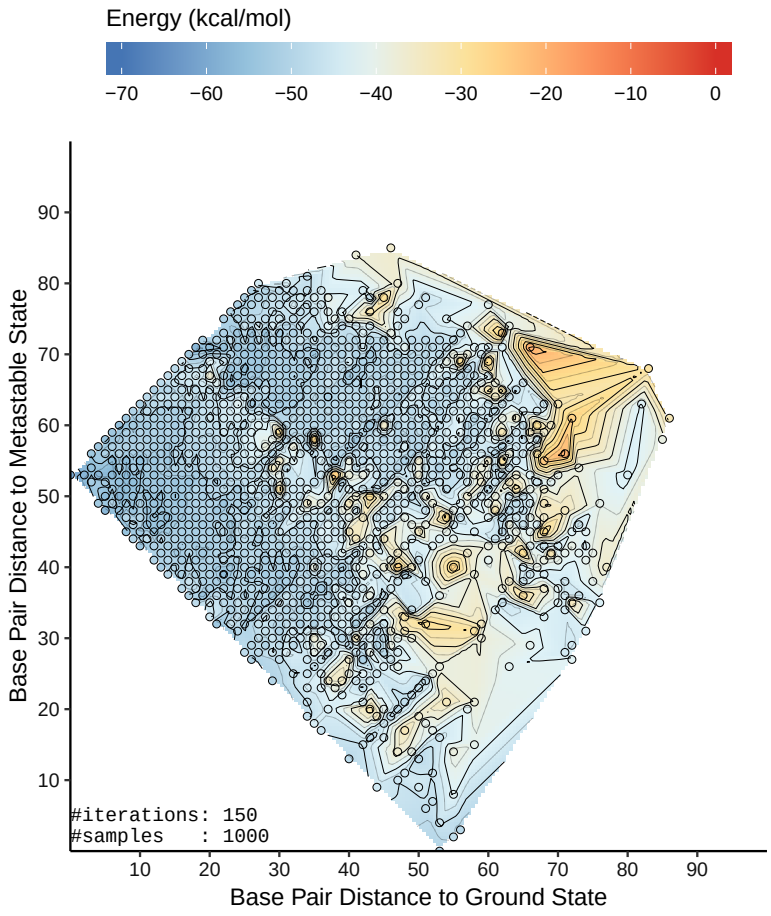

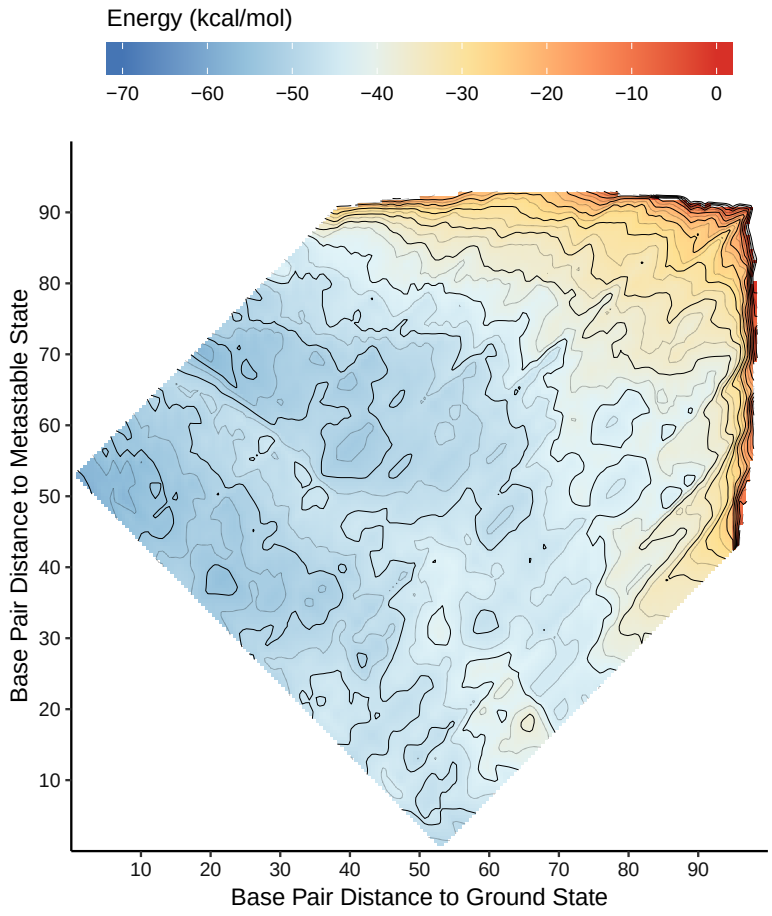

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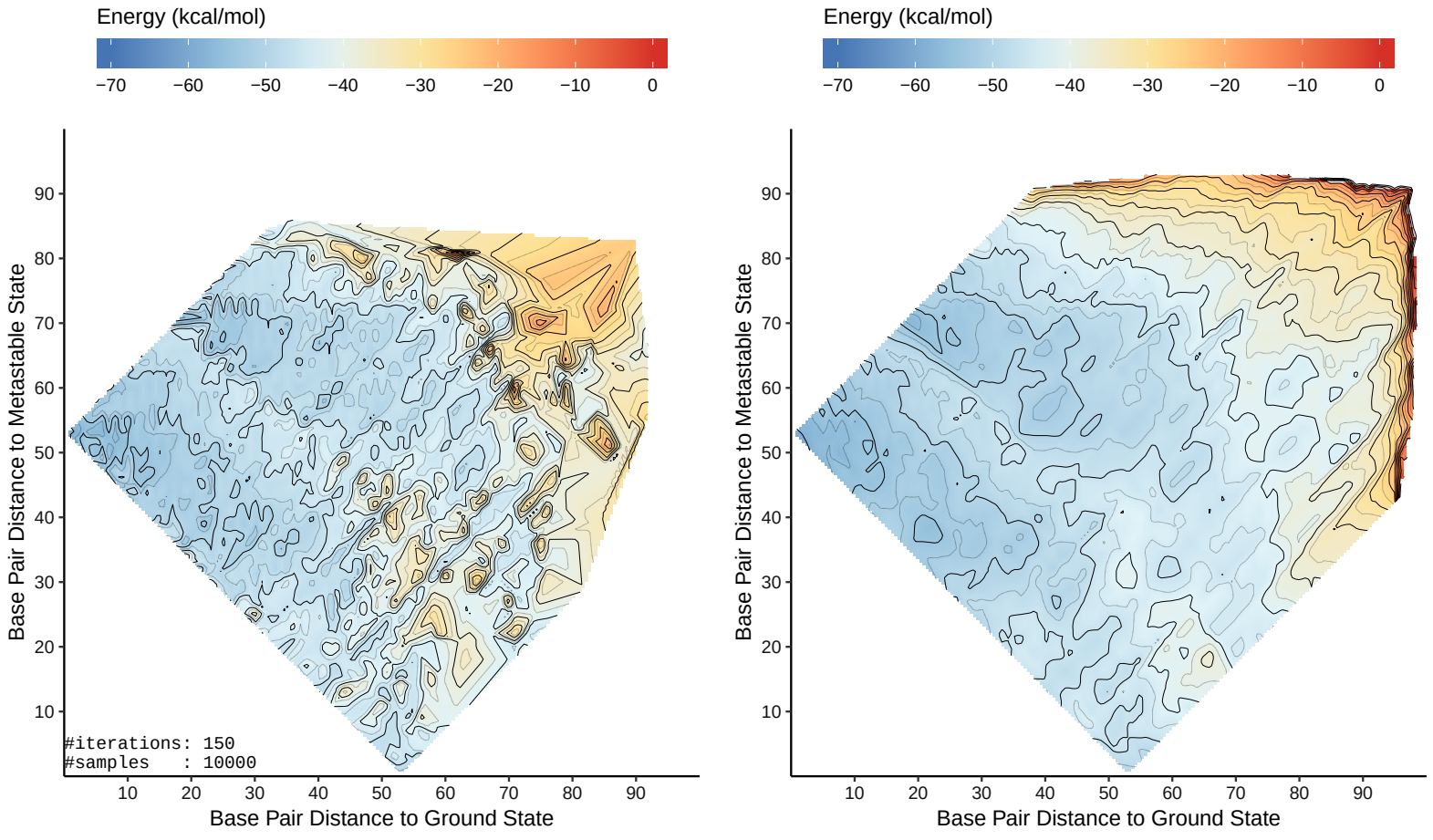

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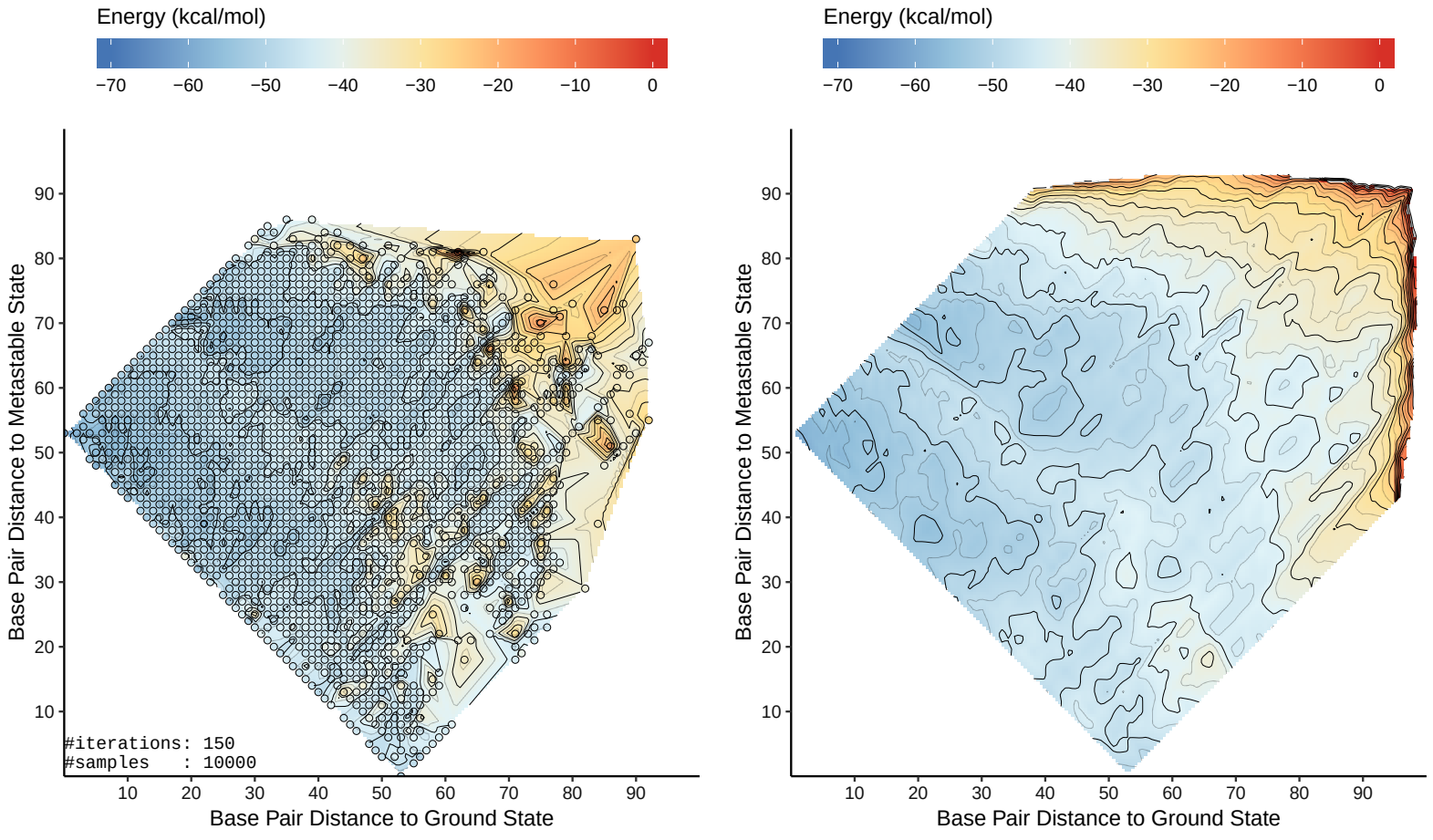

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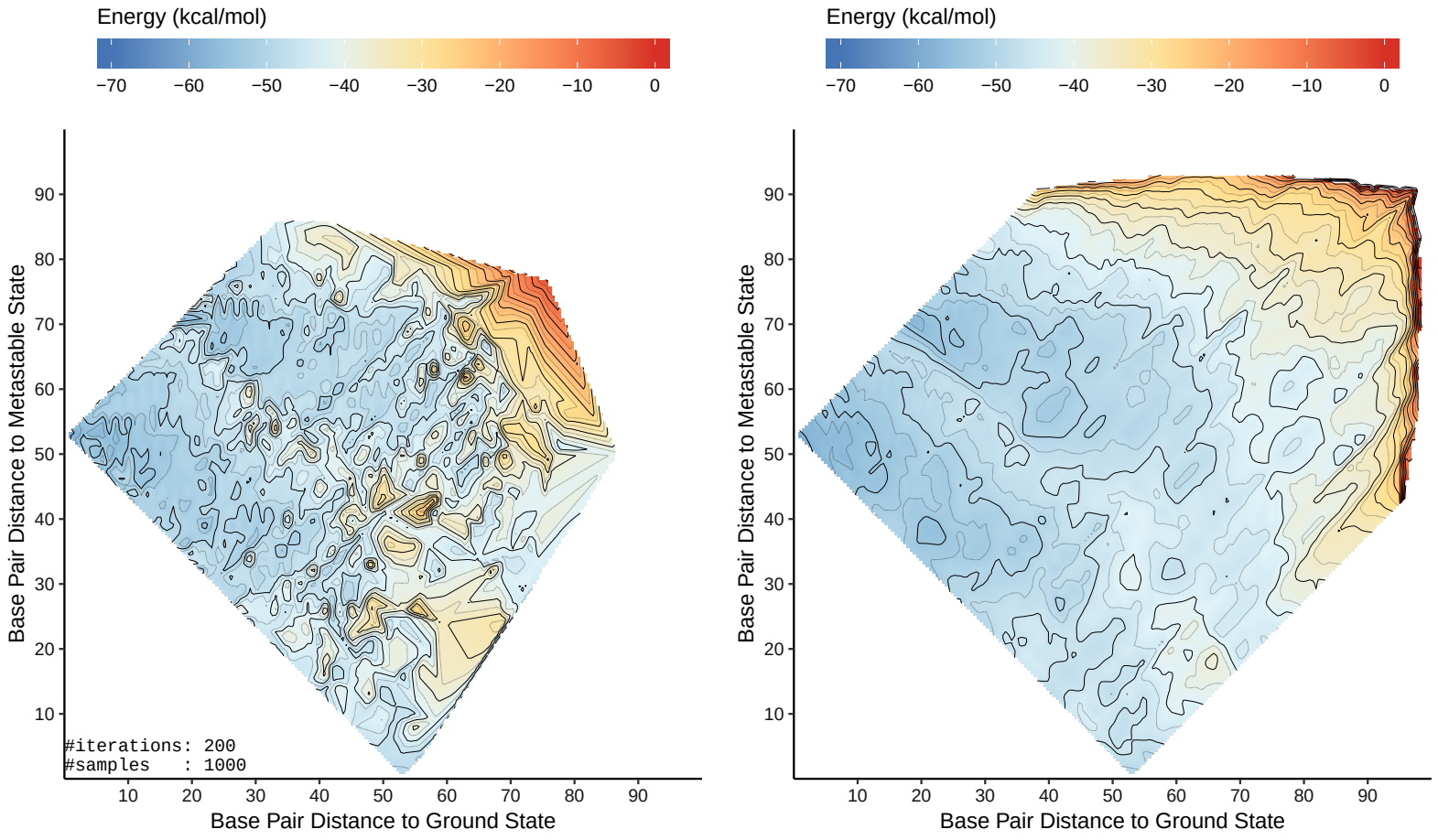

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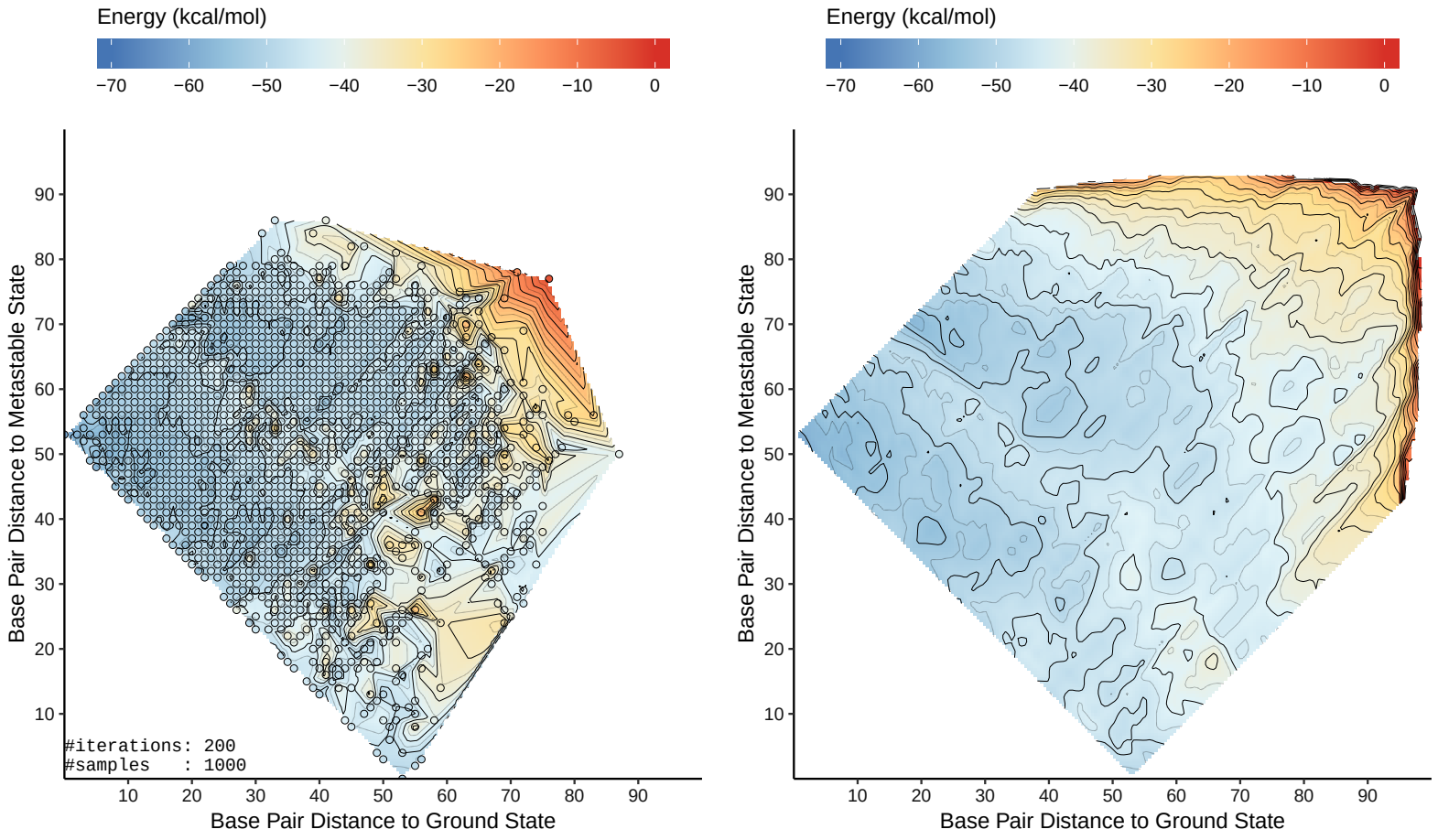

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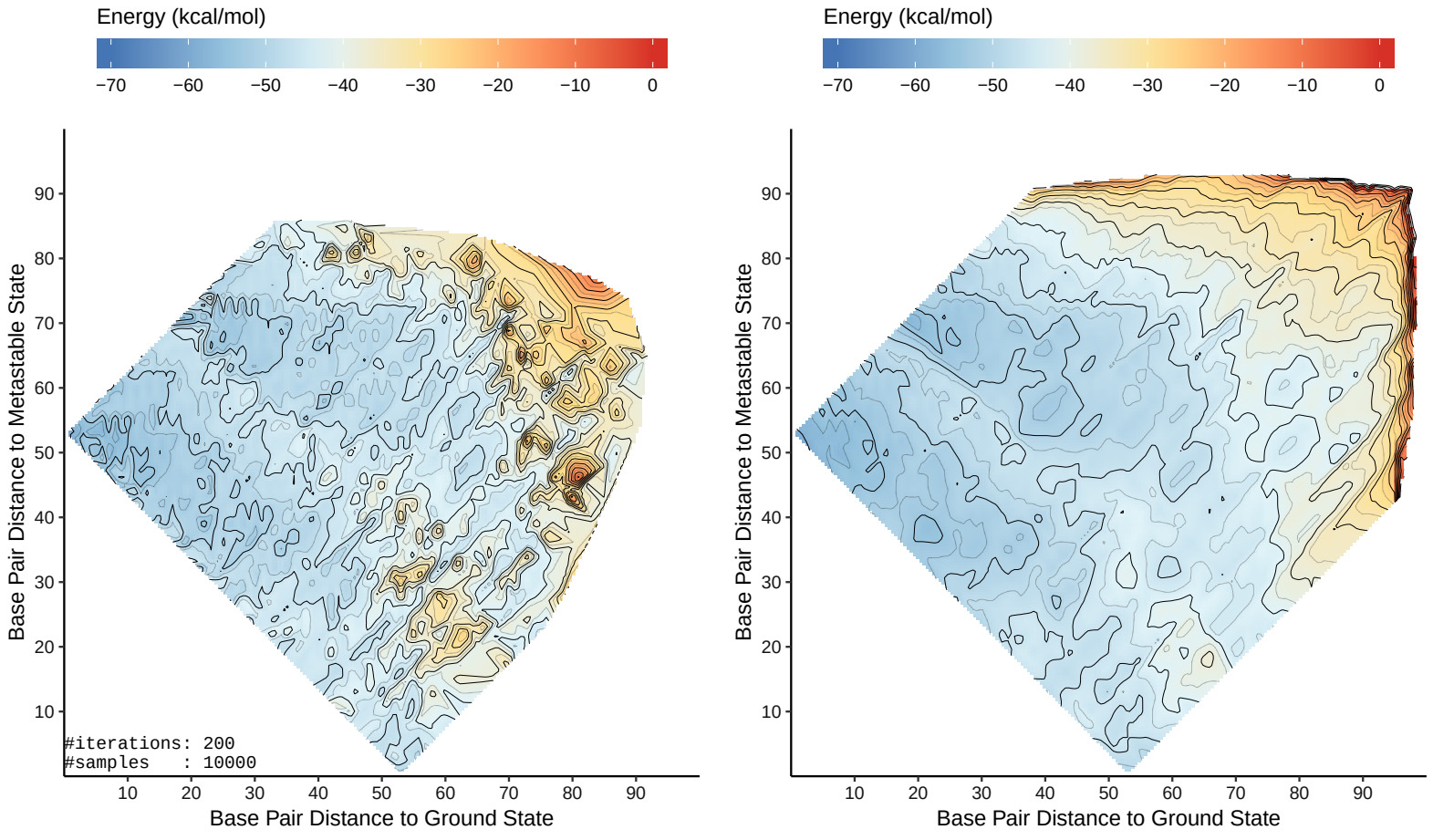

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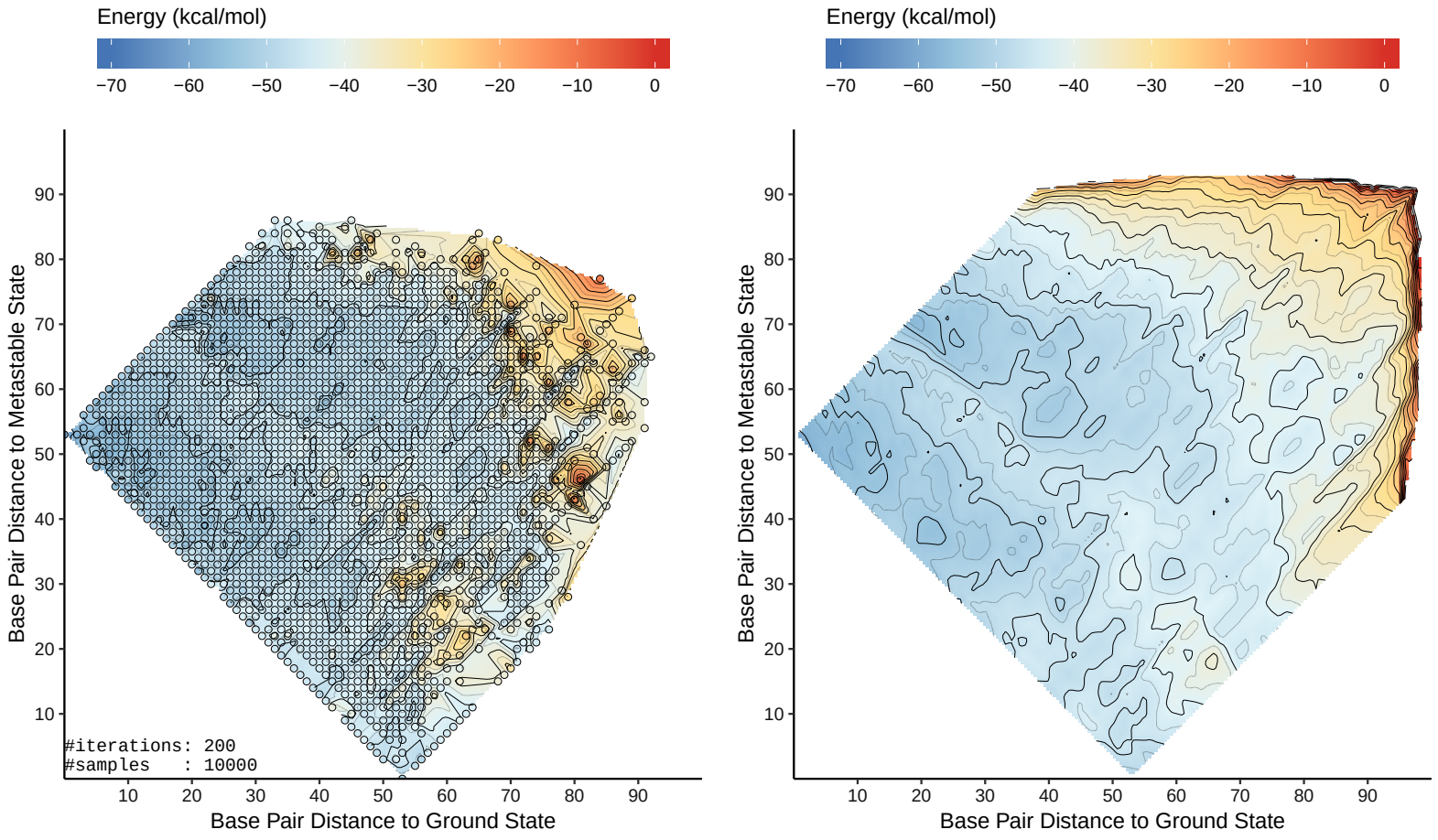

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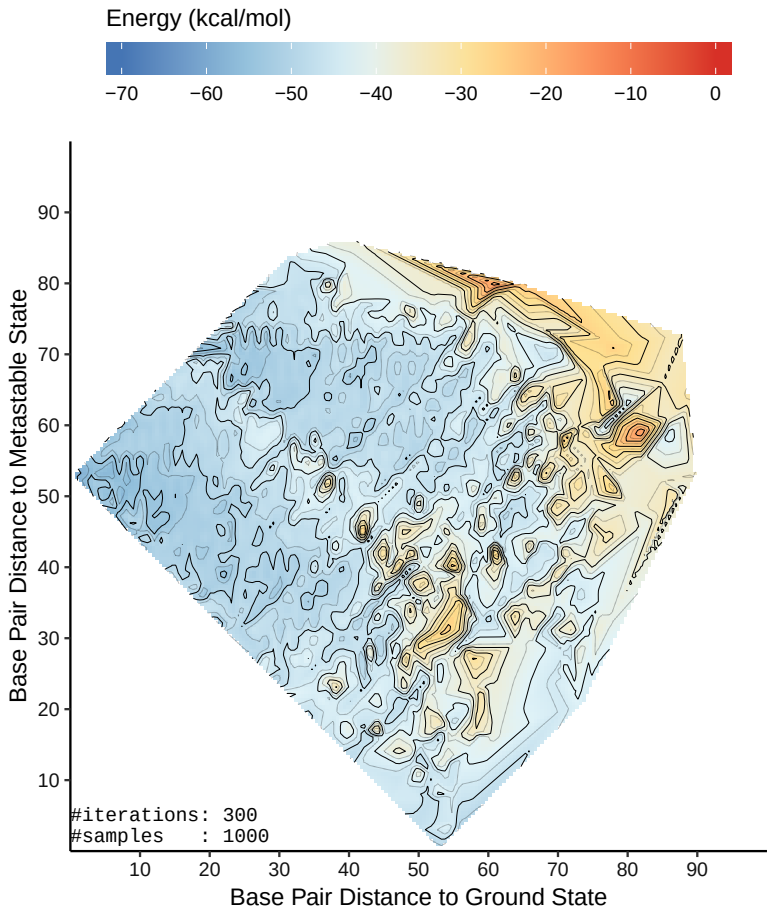

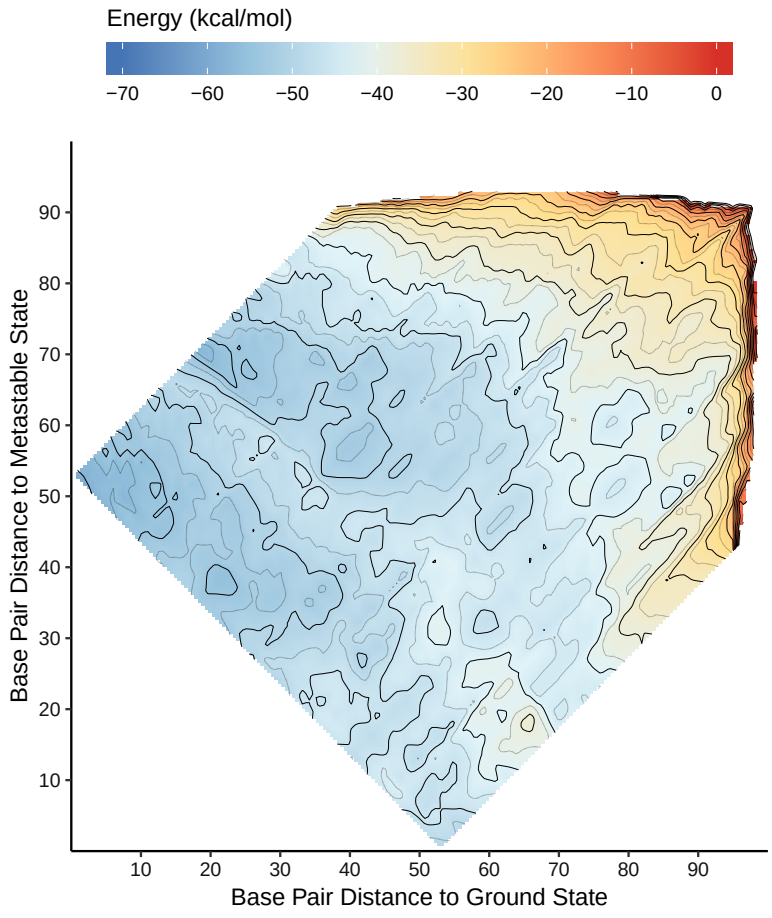

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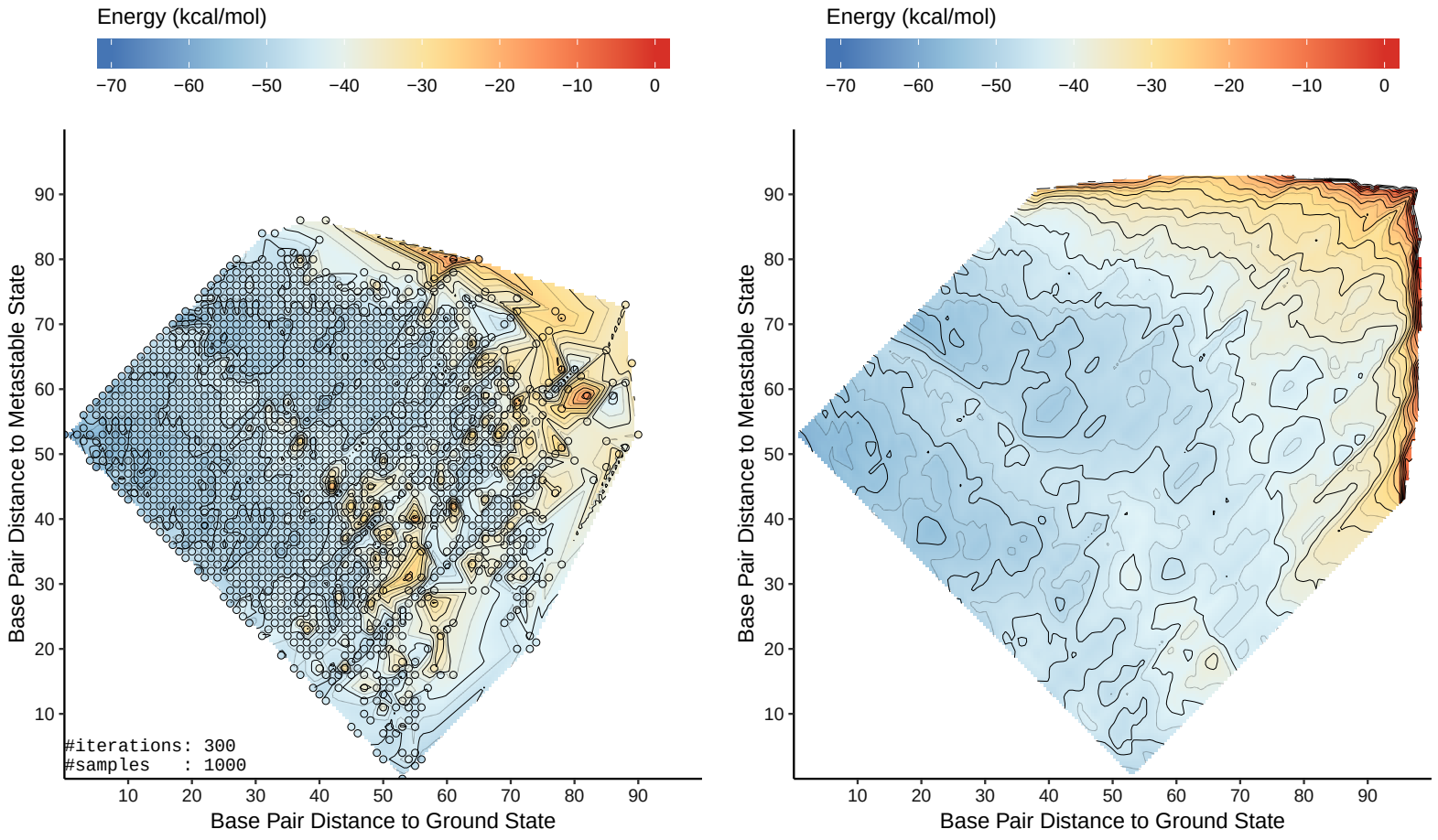

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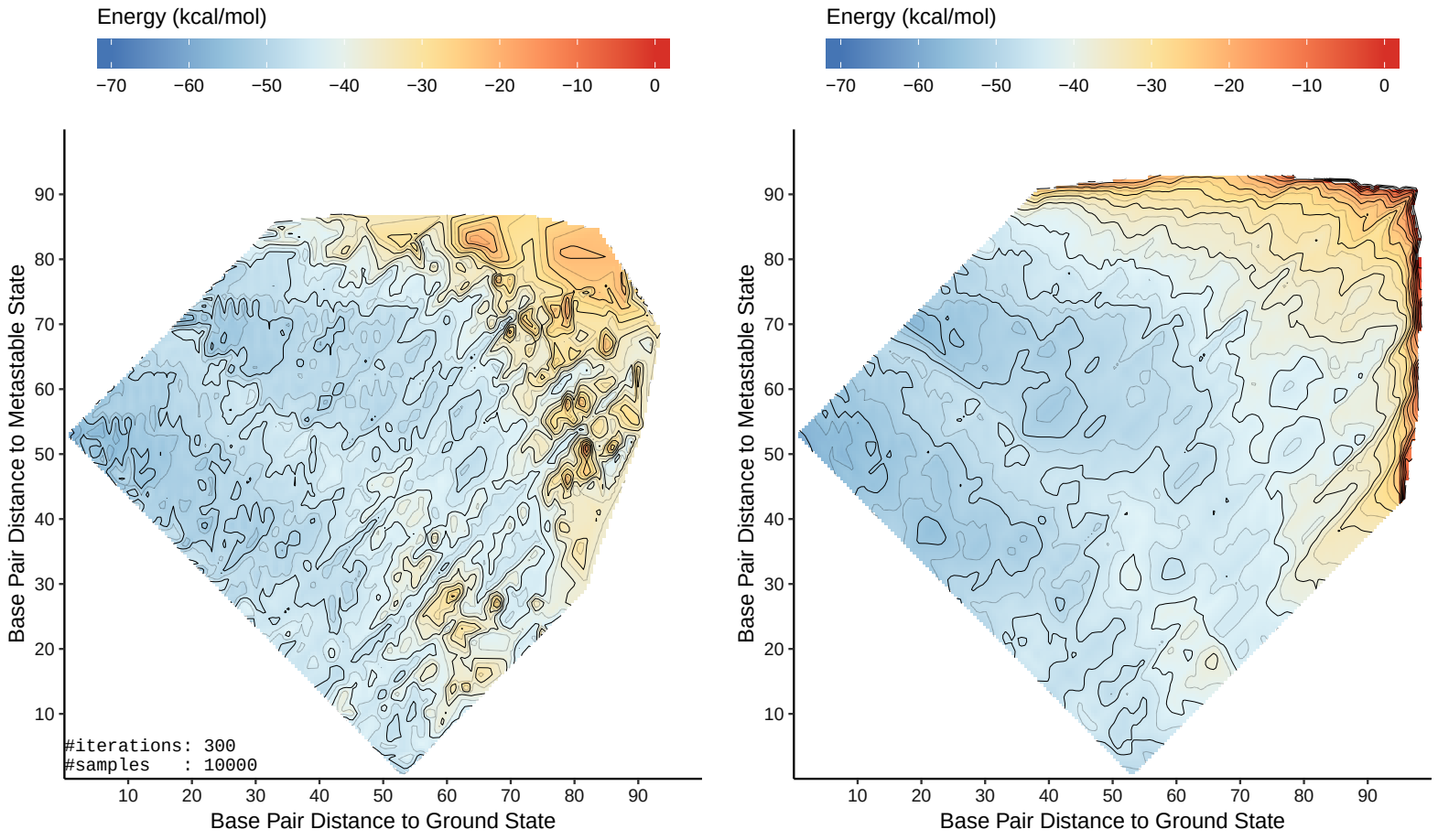

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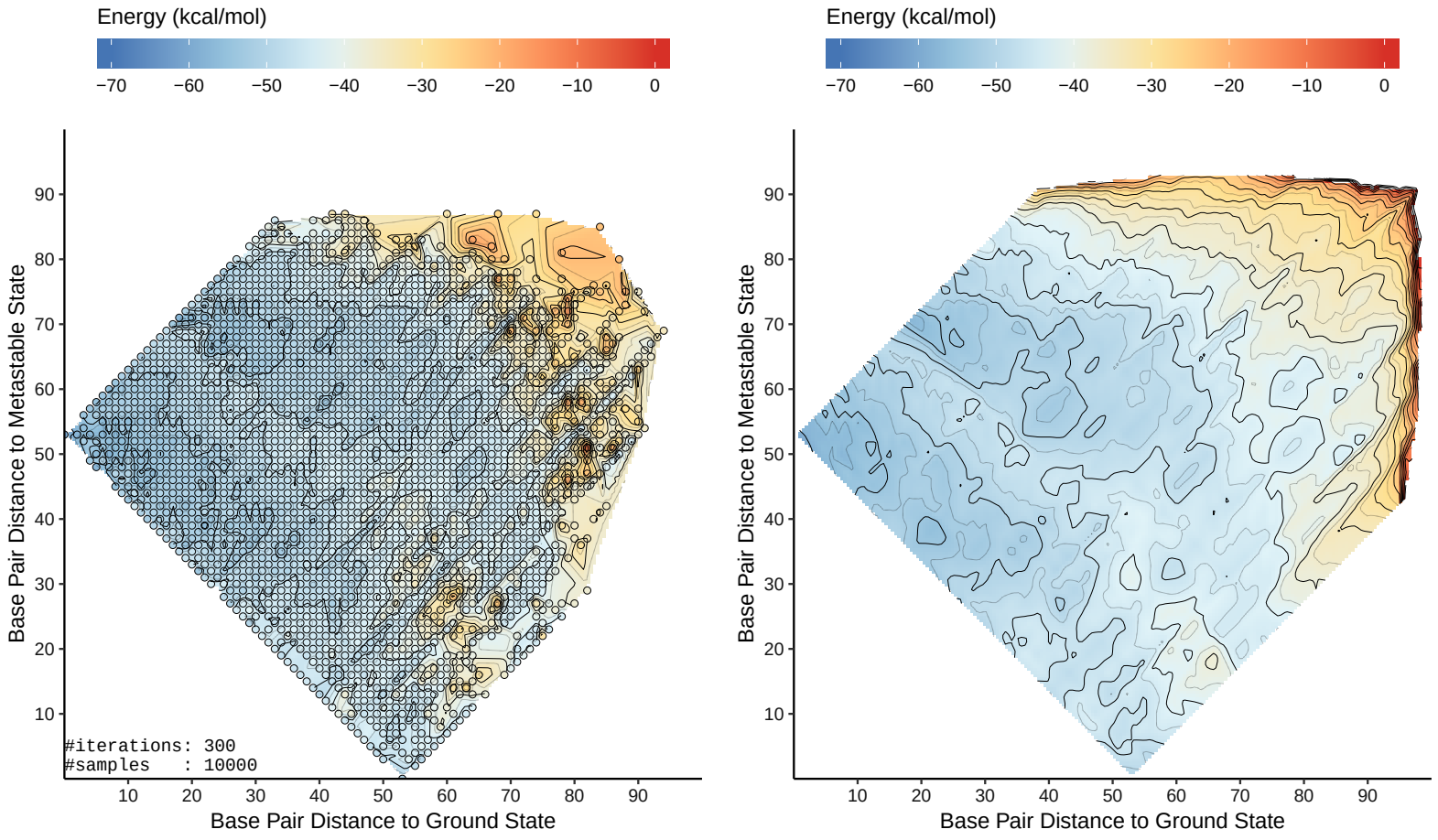
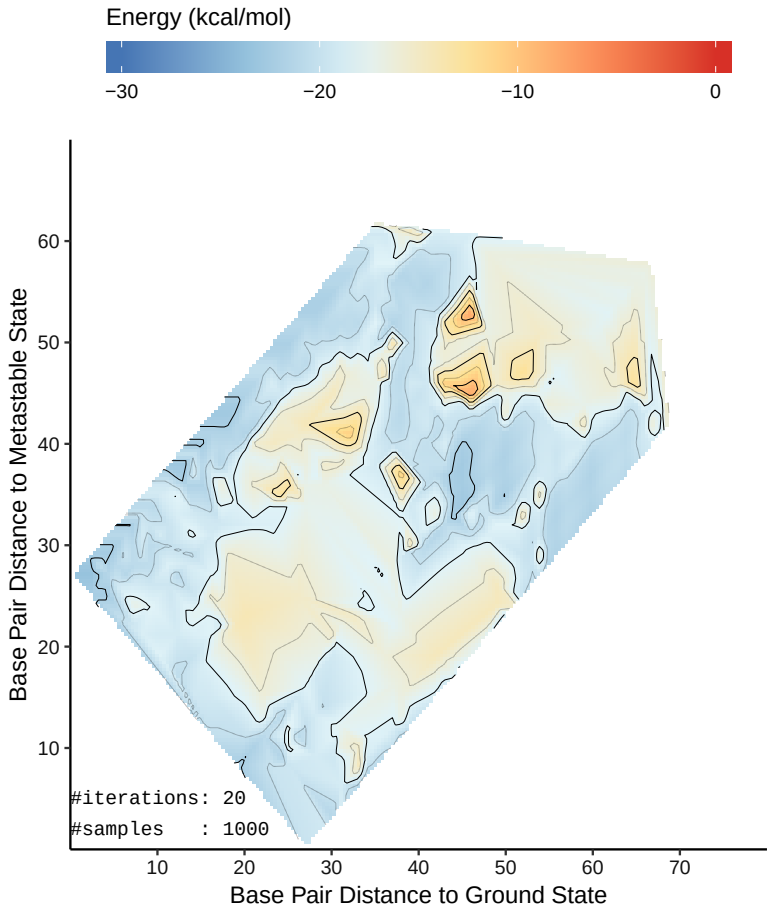
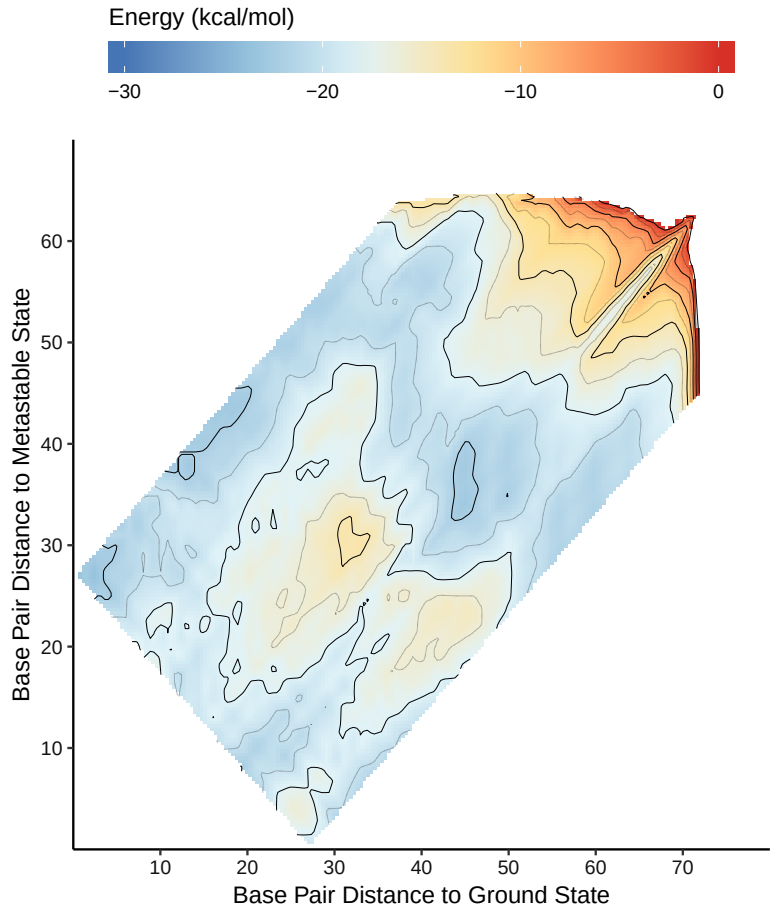


Example: add riboswitch V.culnificus

`RNAxplorer` repulsion scheme Boltzmann sampling





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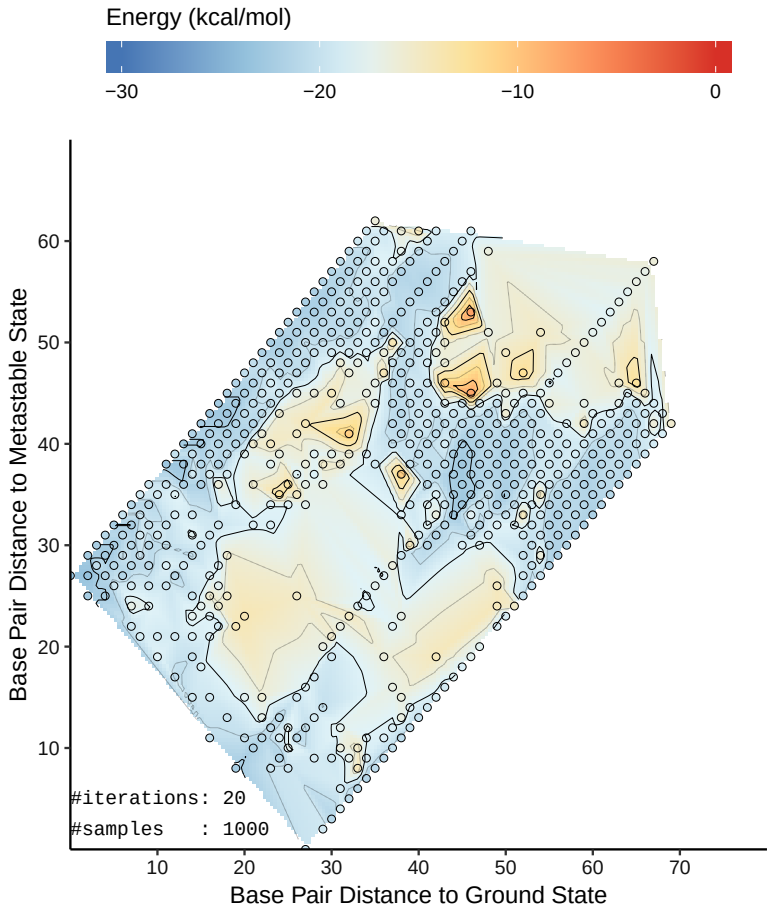

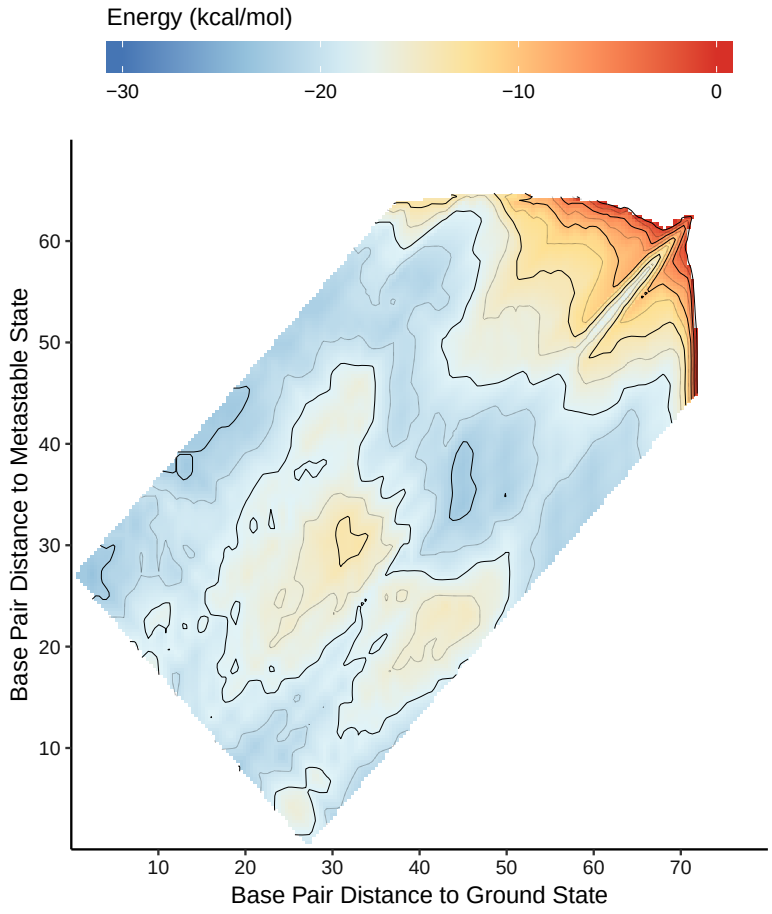

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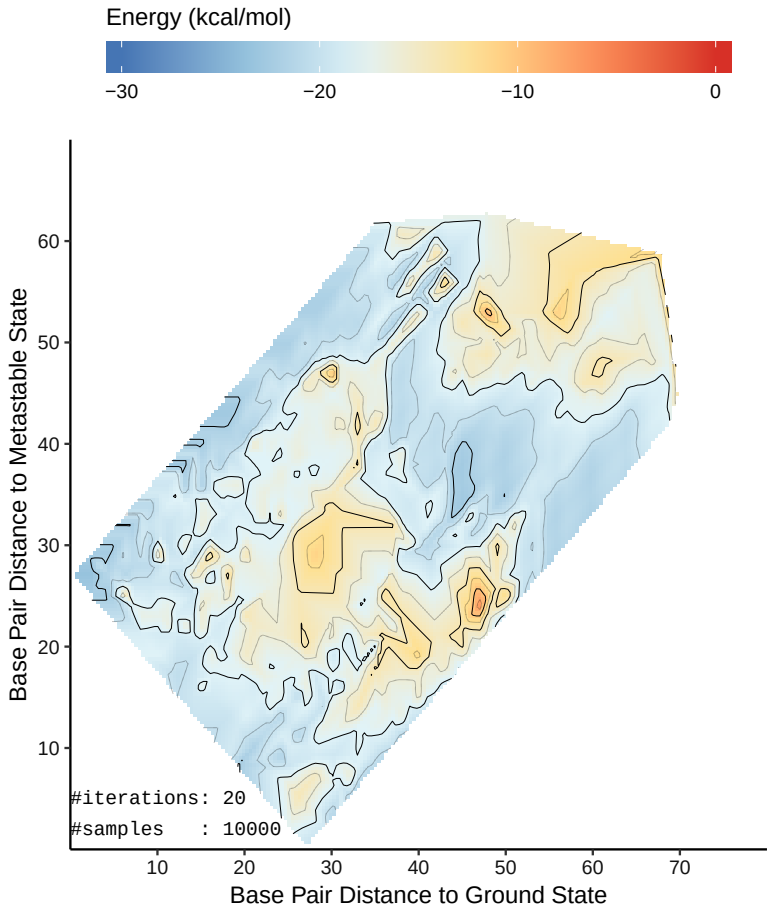

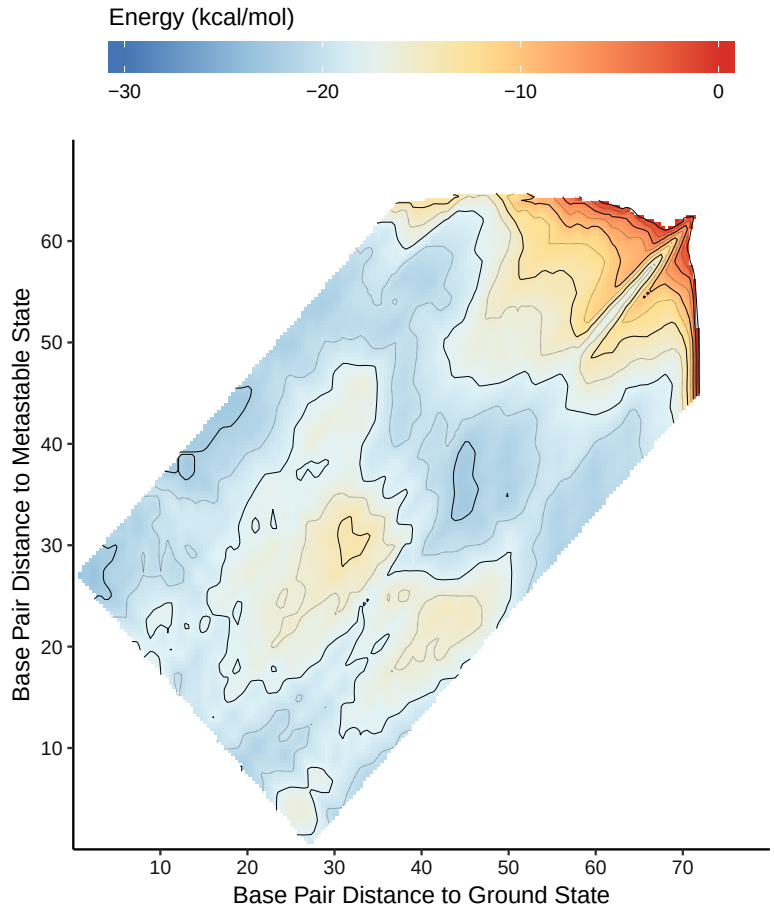

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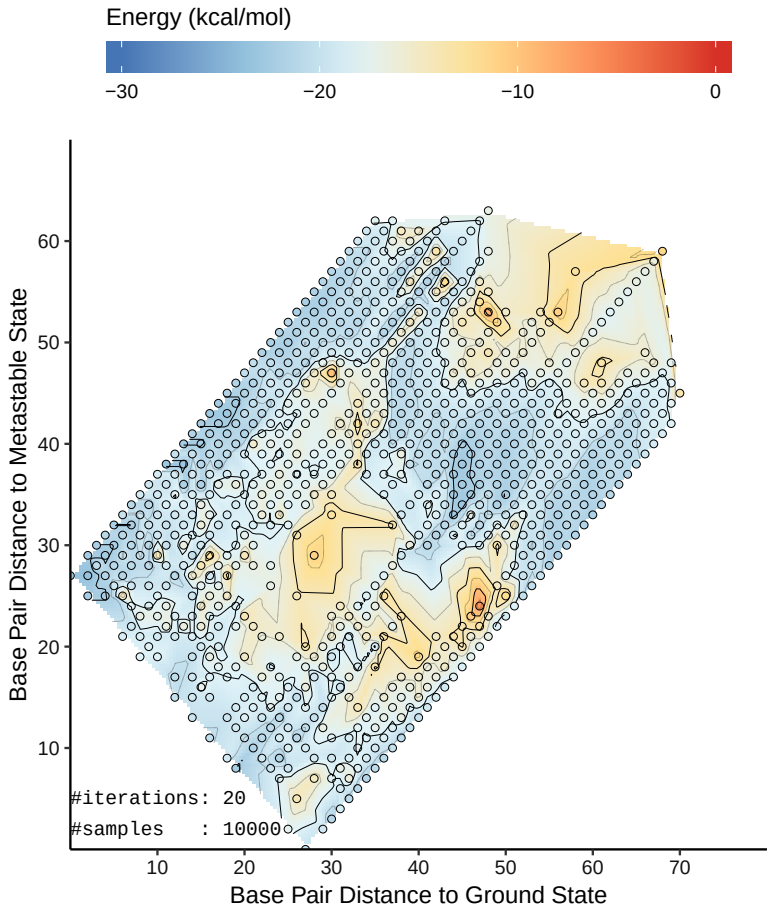

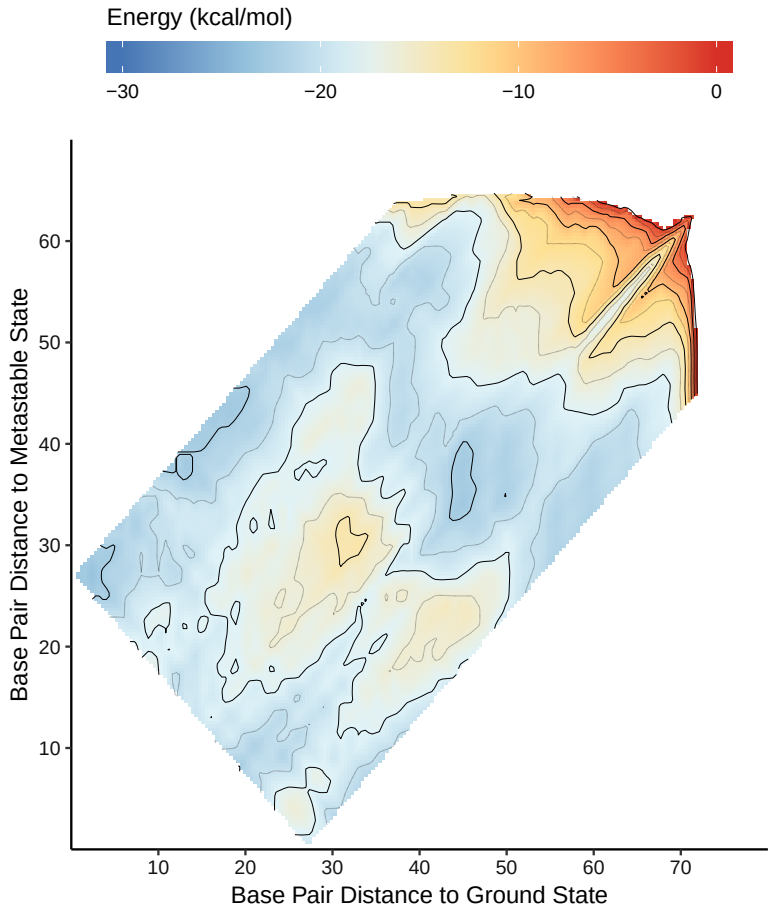

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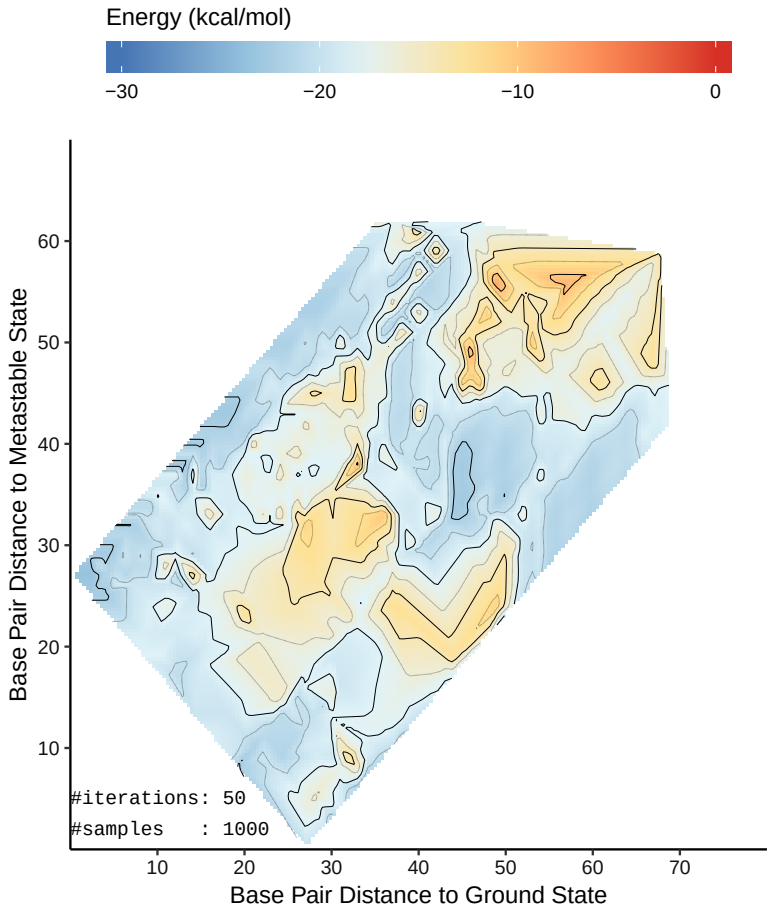

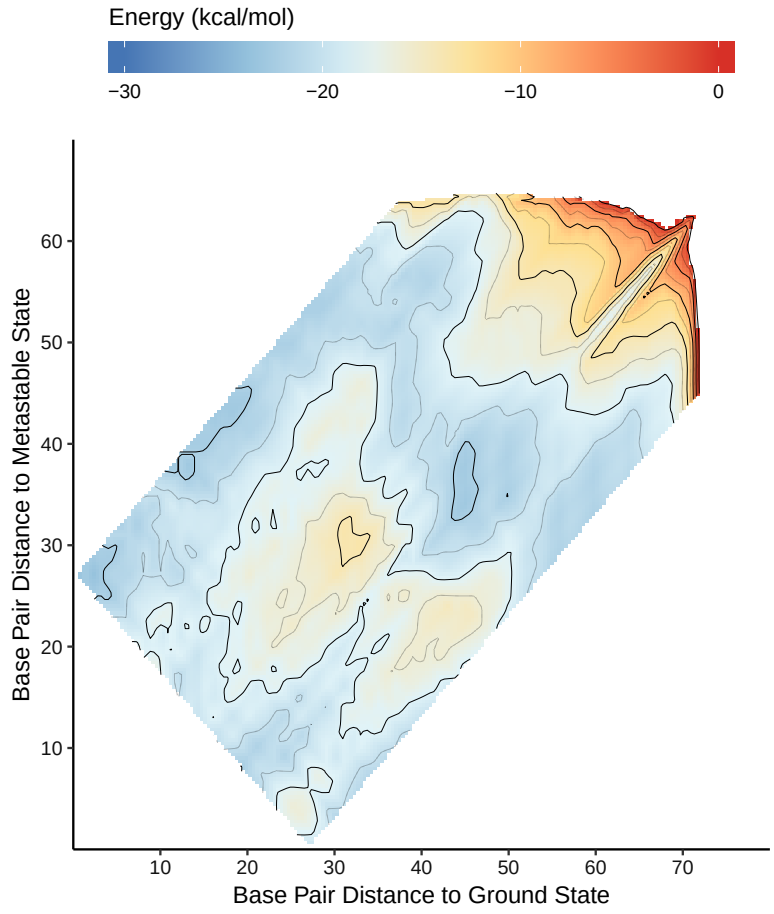

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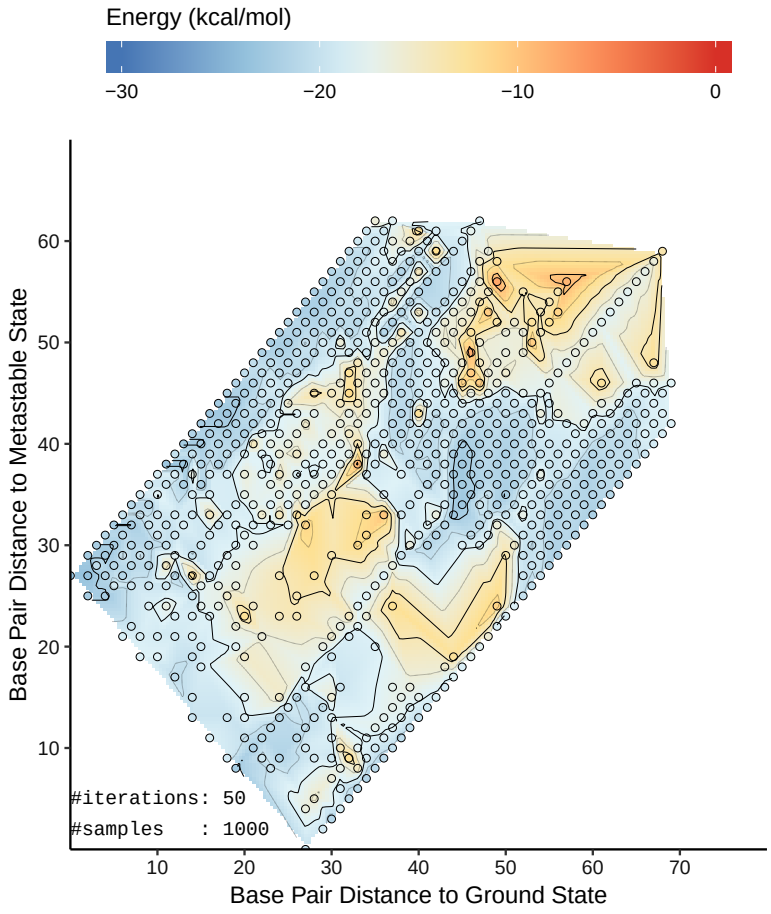

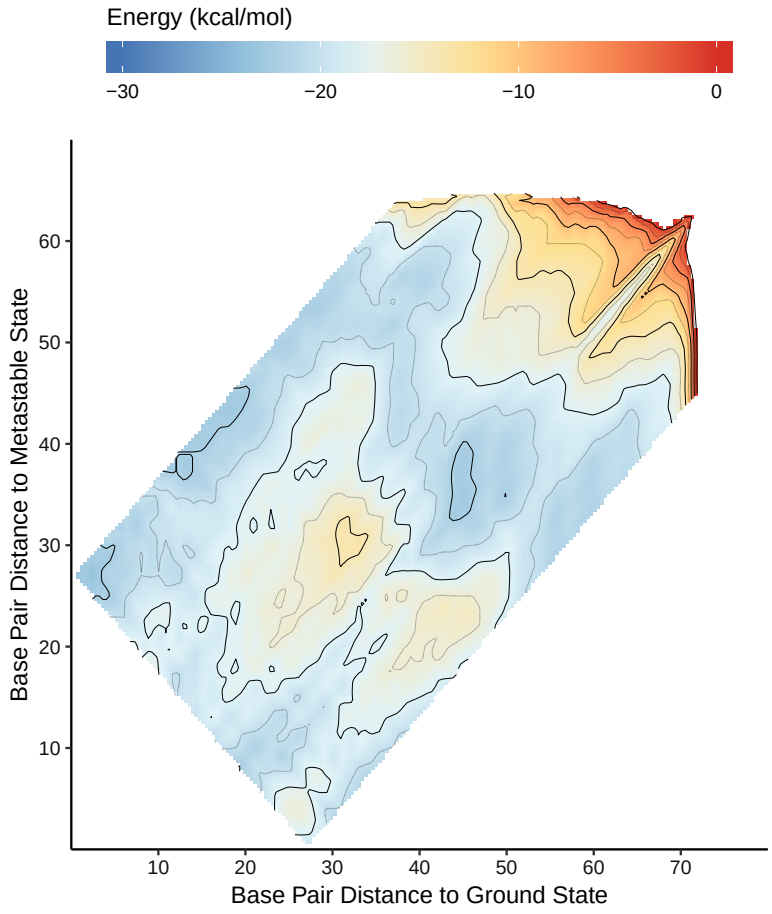

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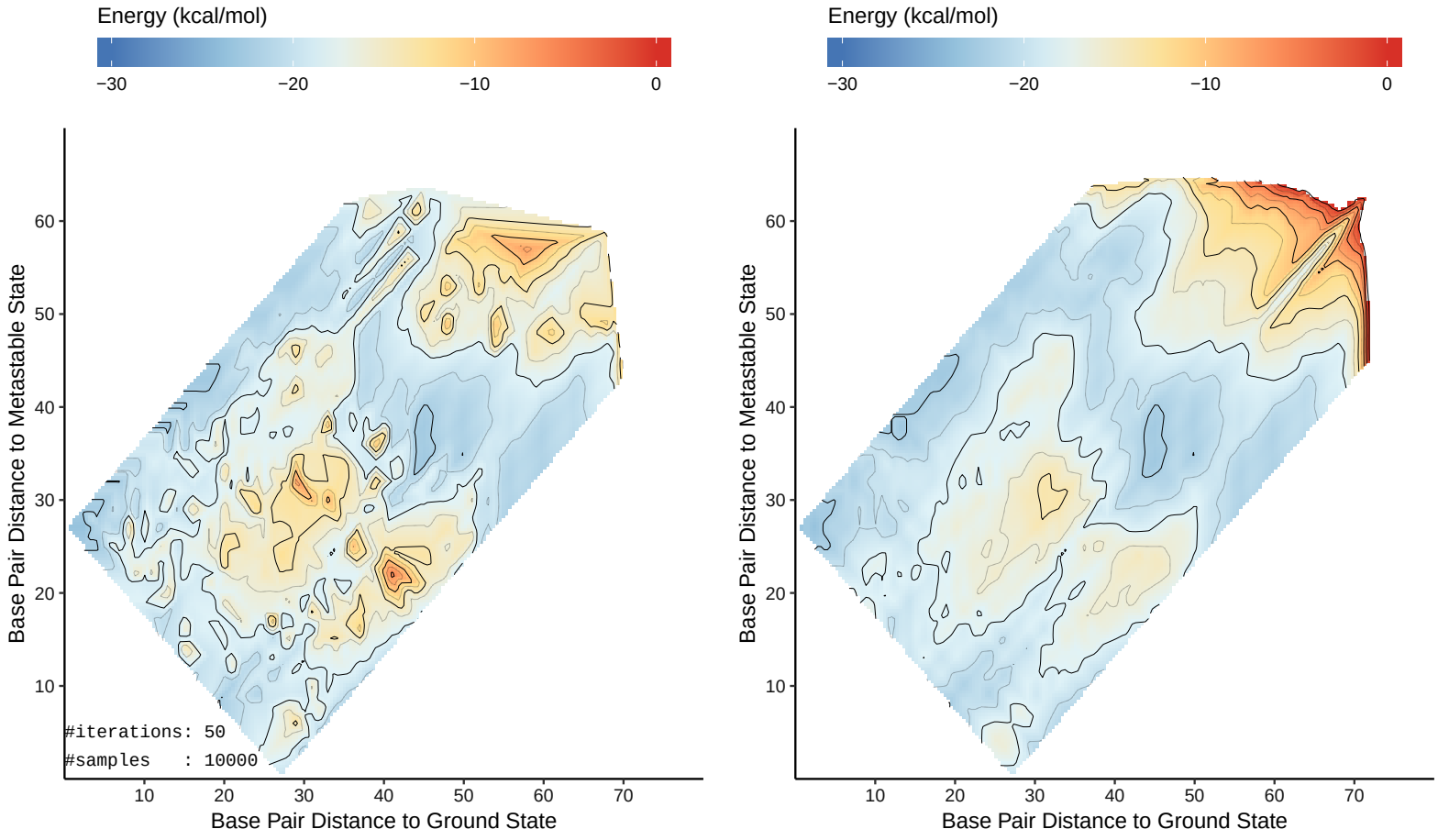

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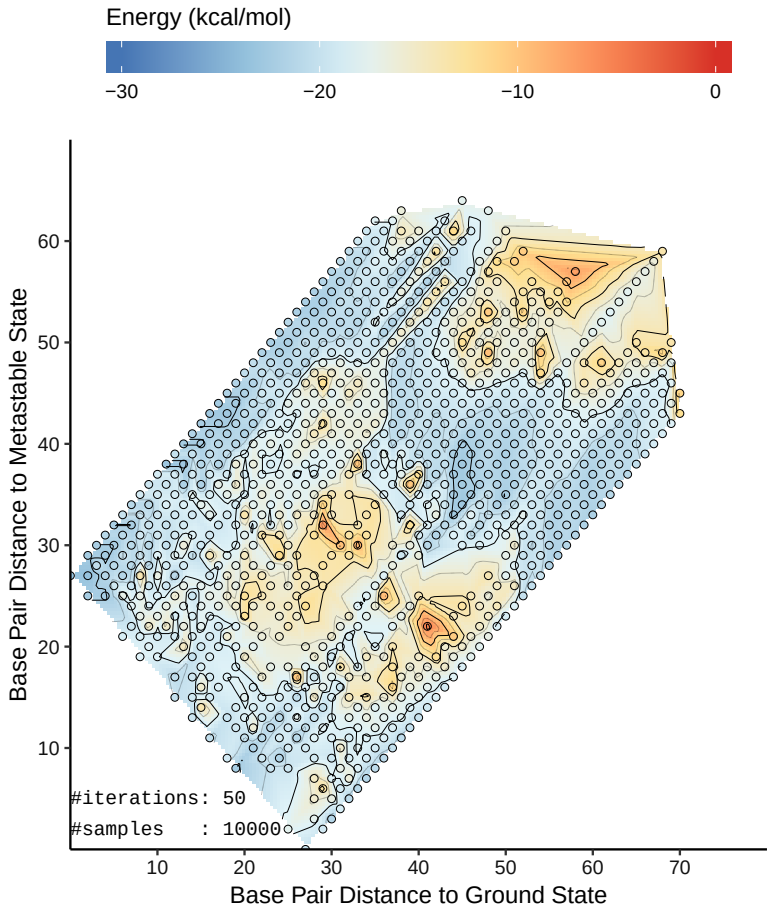

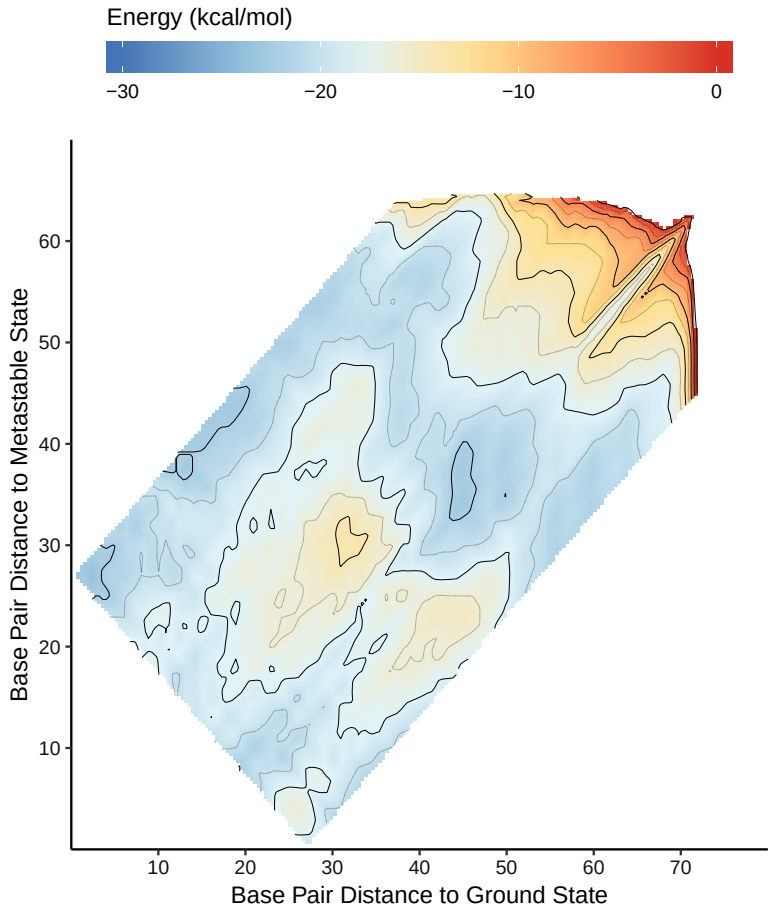

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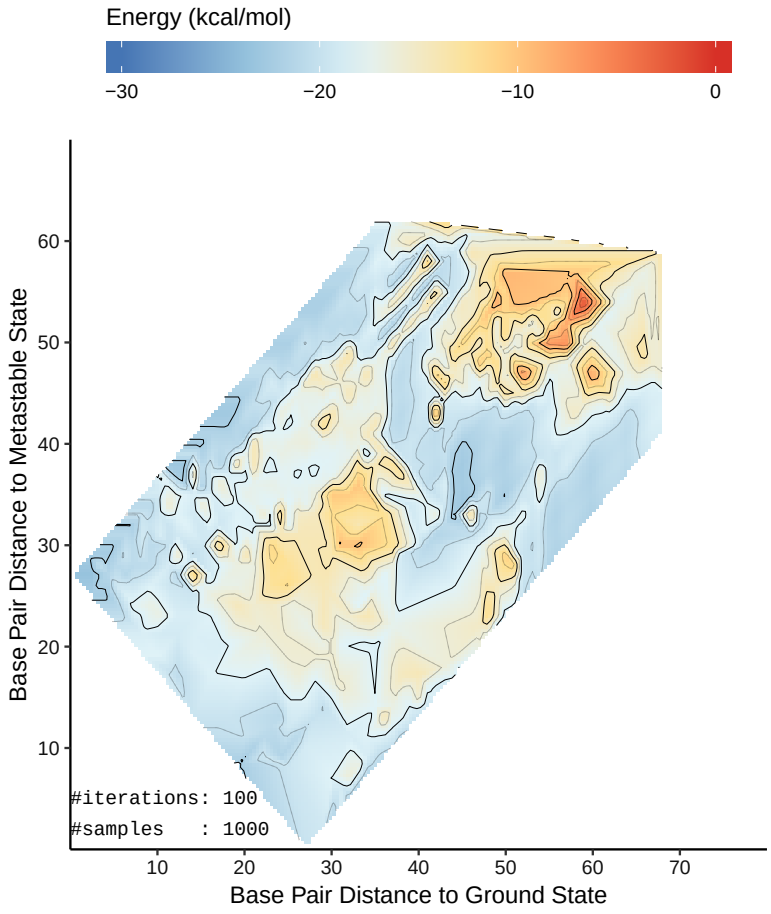

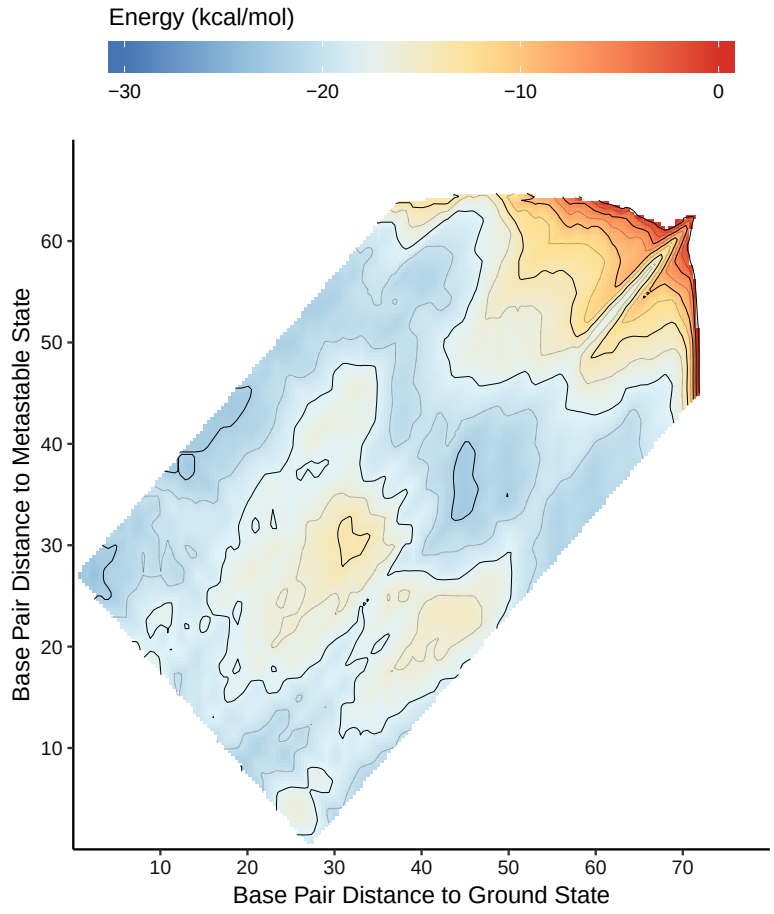

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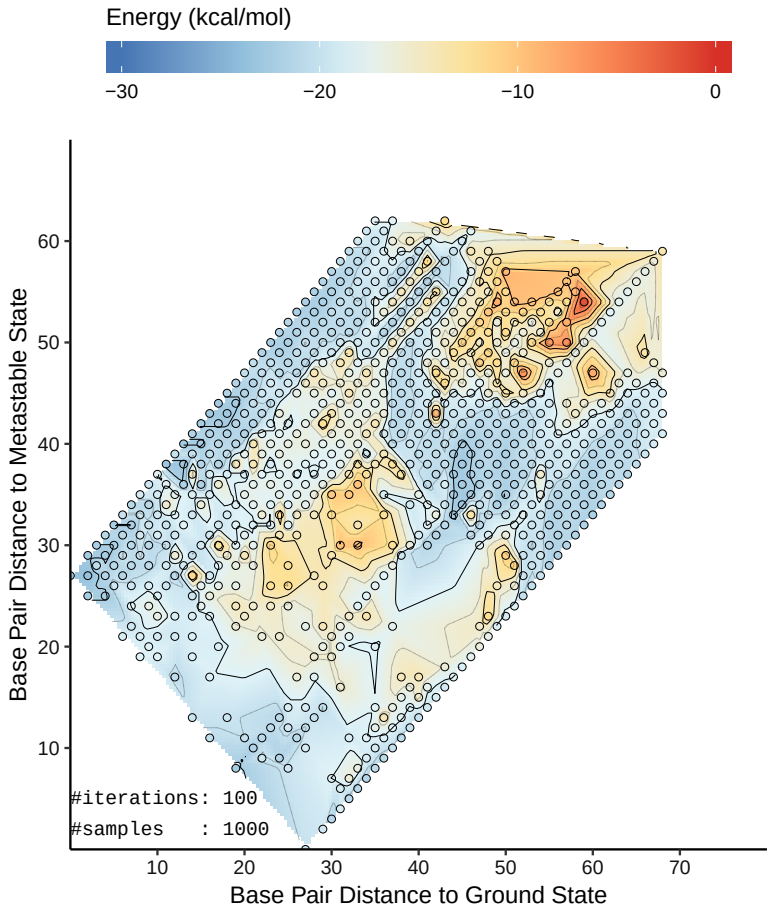

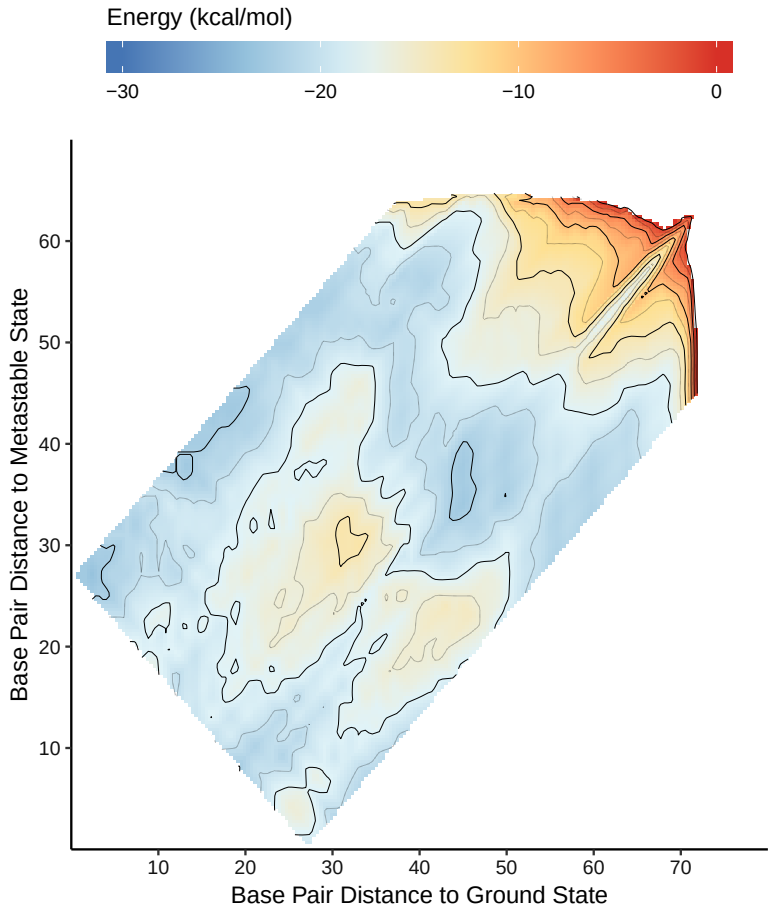

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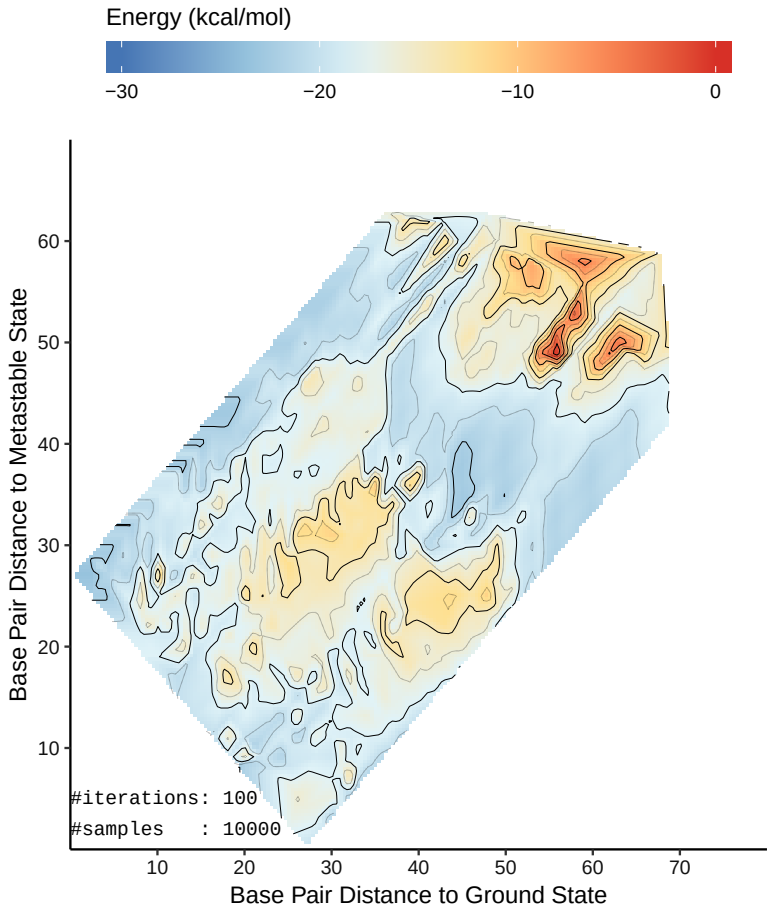

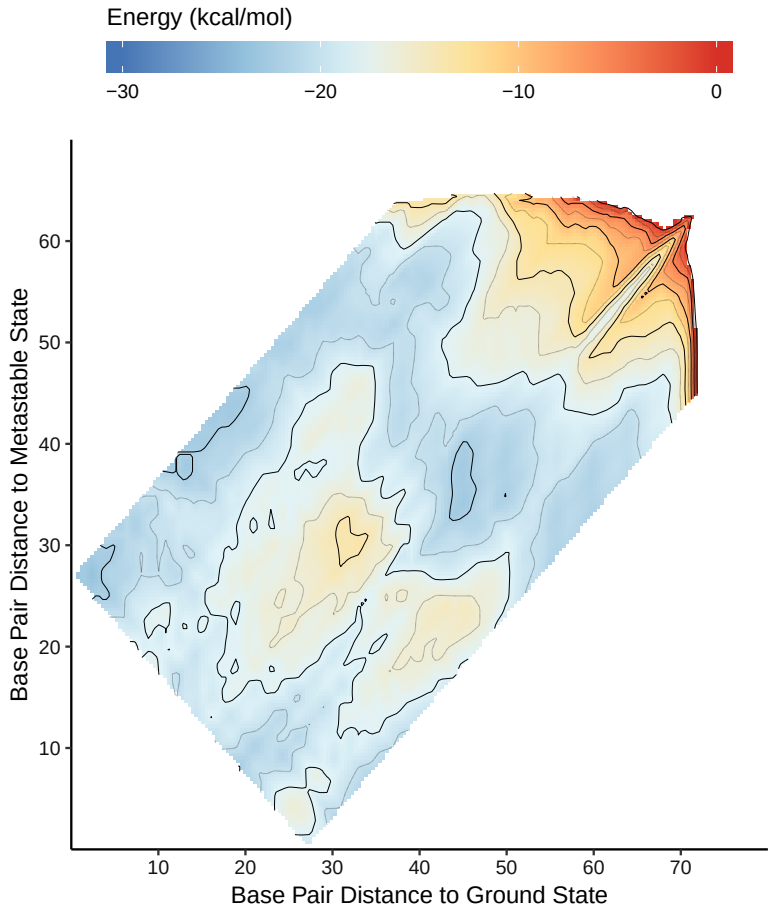

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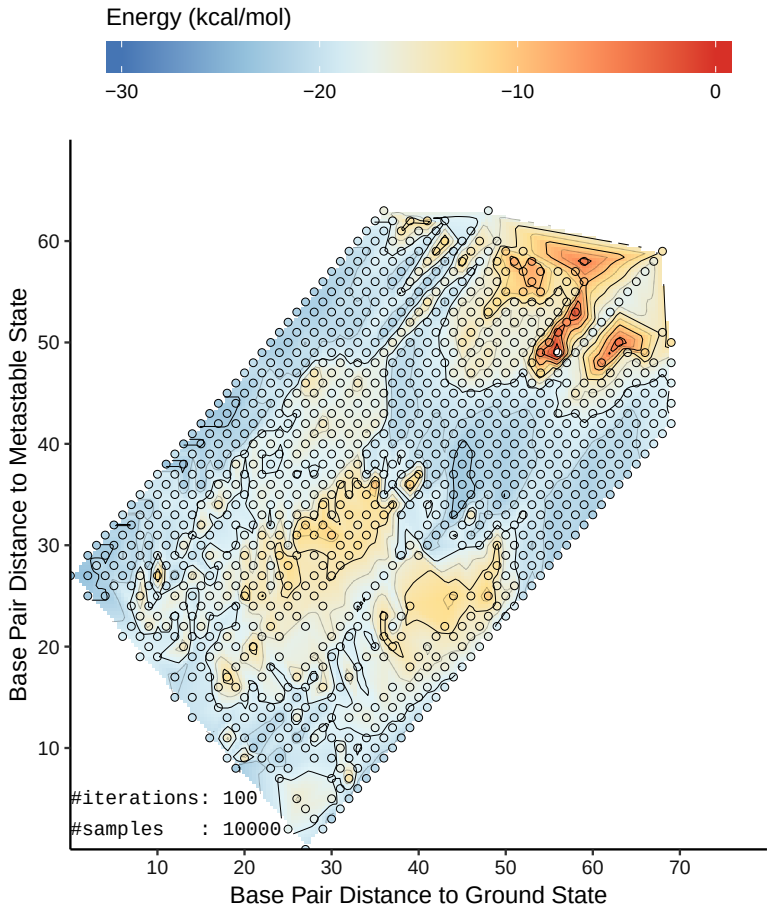

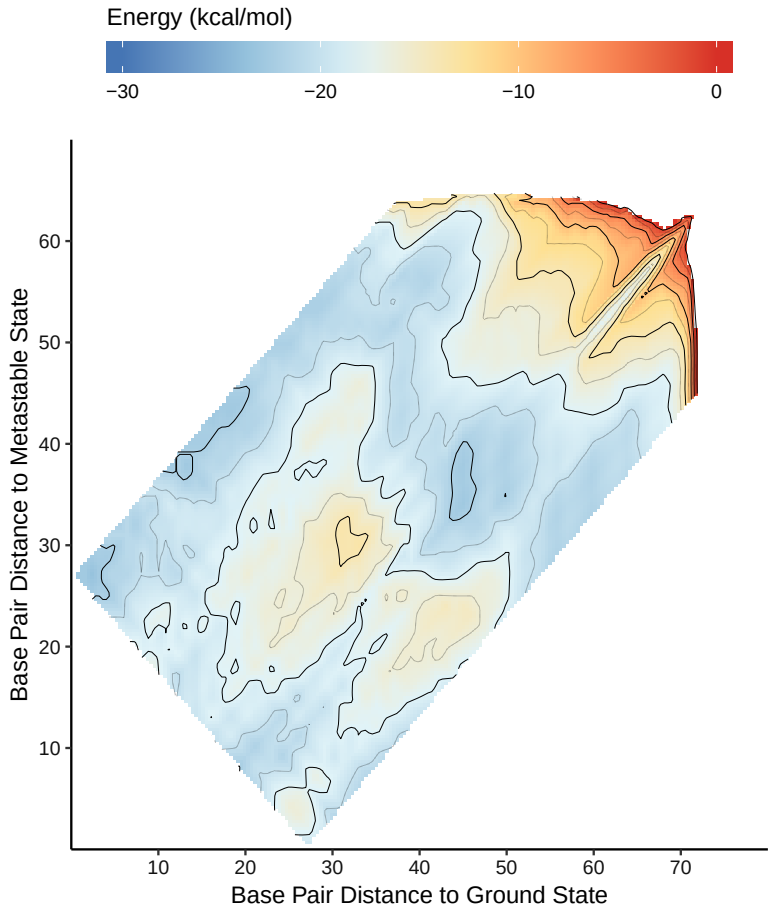

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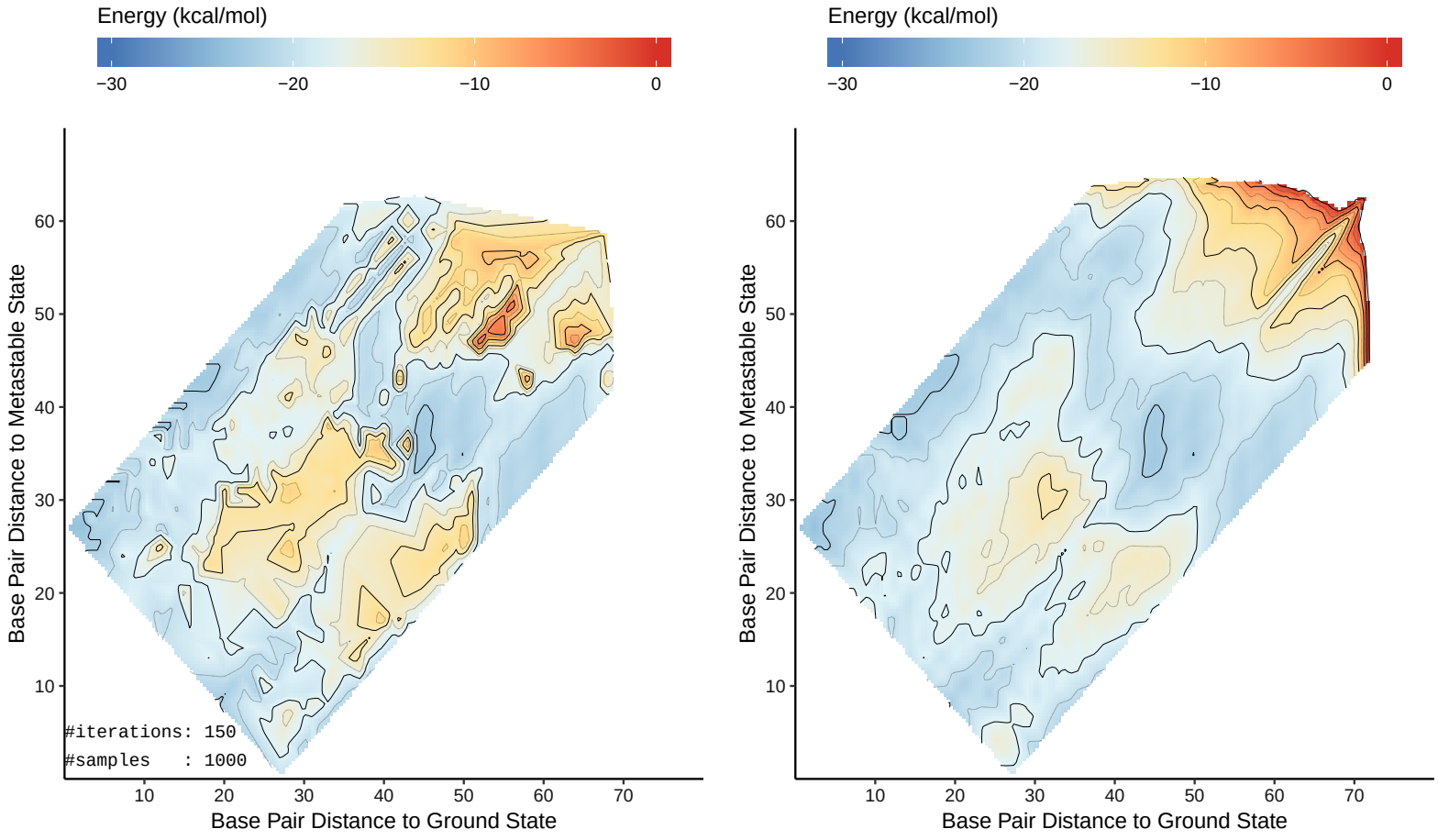

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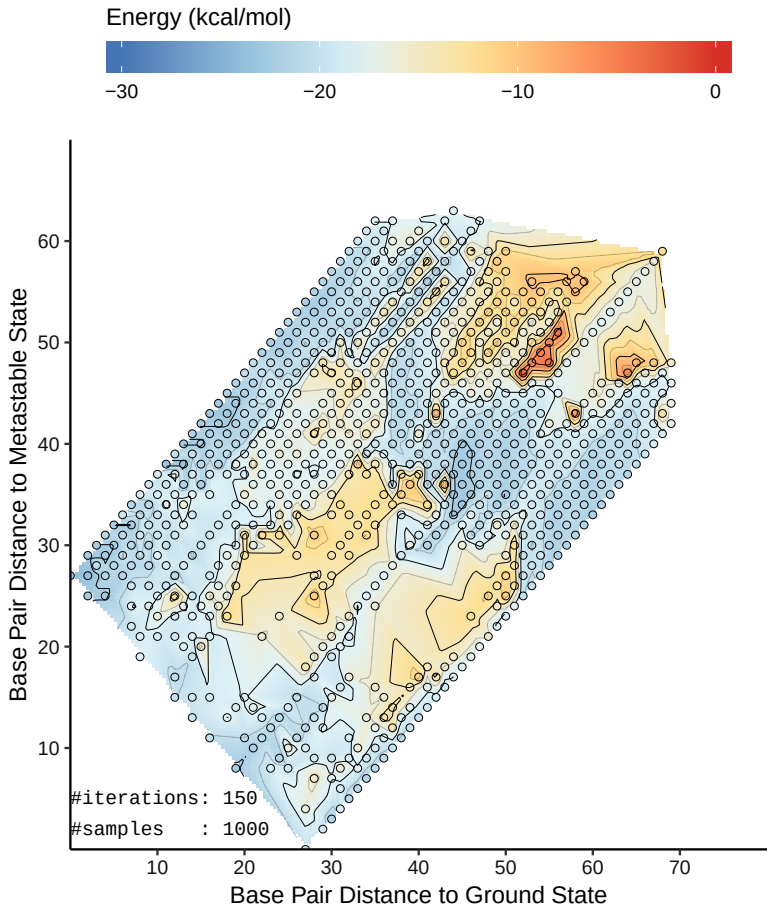

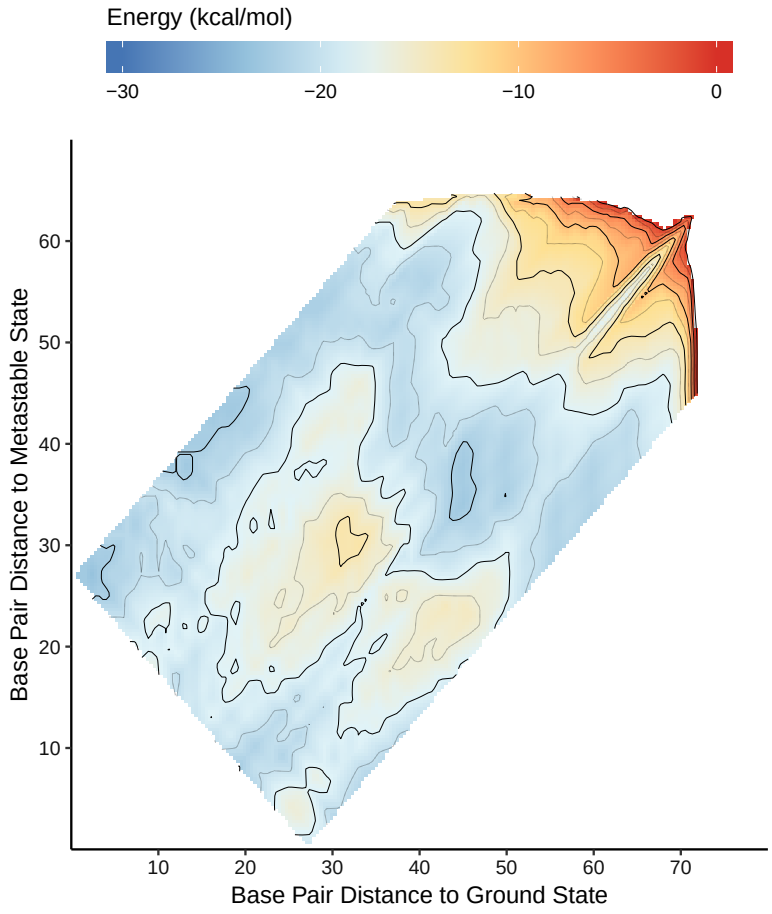

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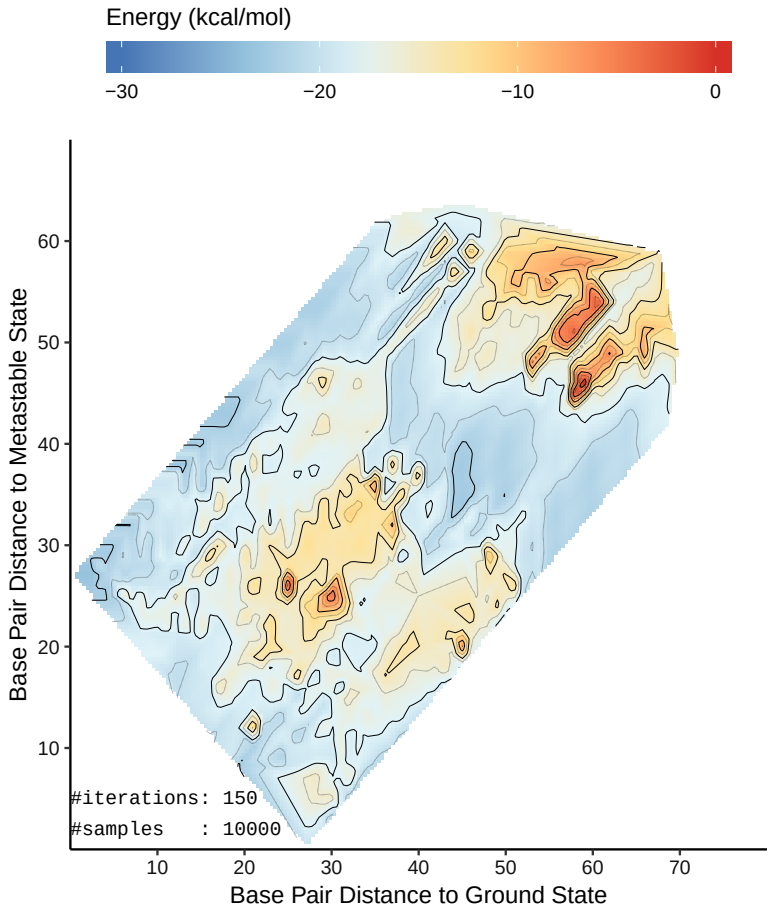

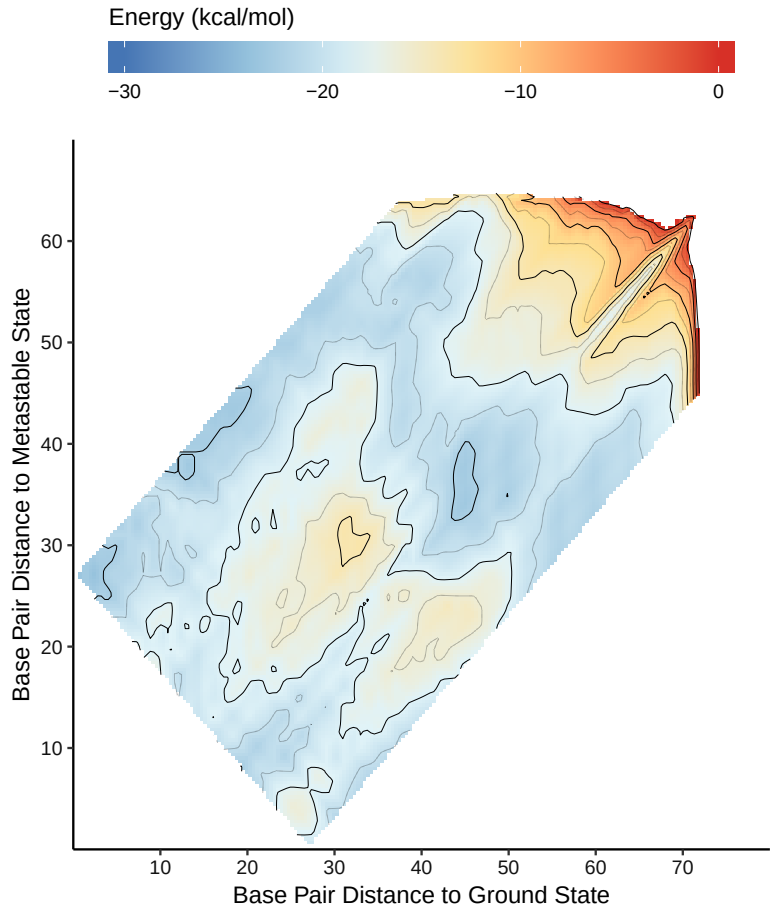

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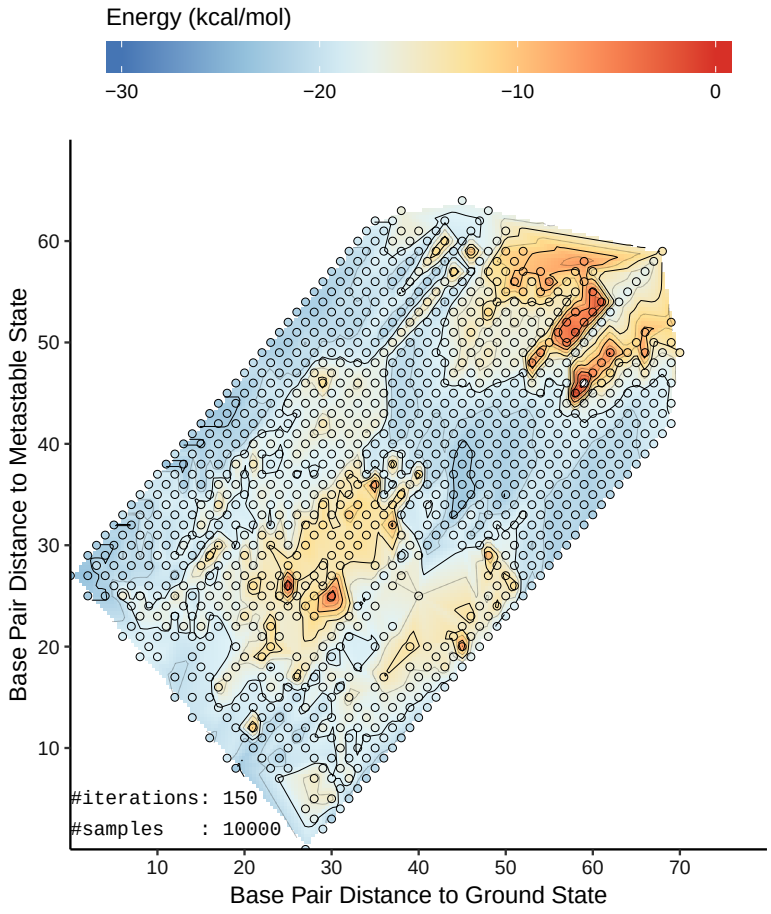

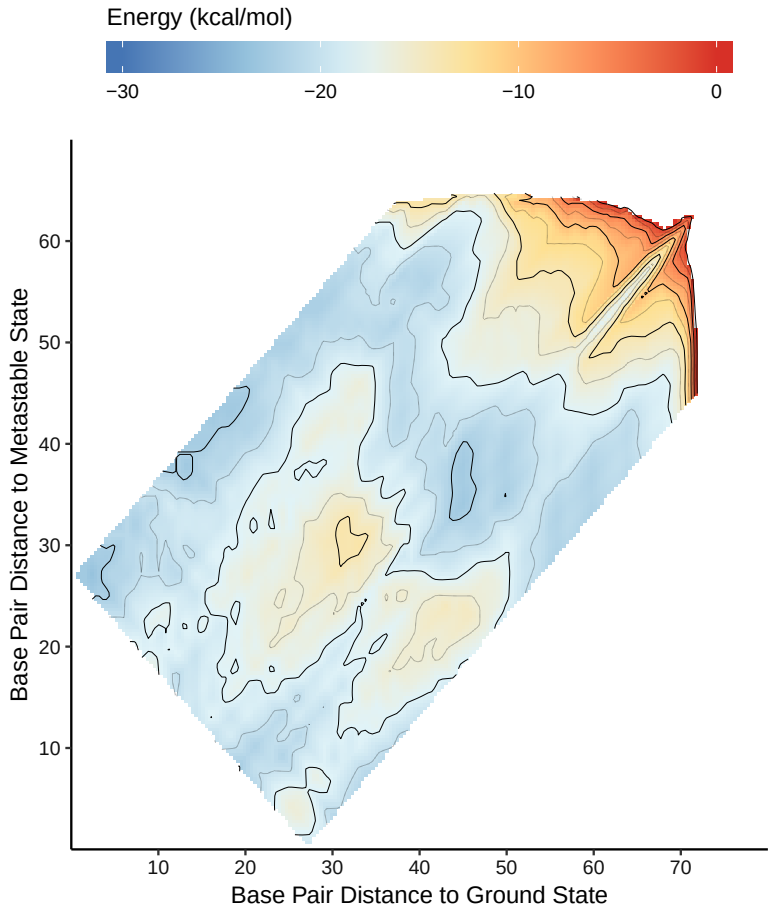

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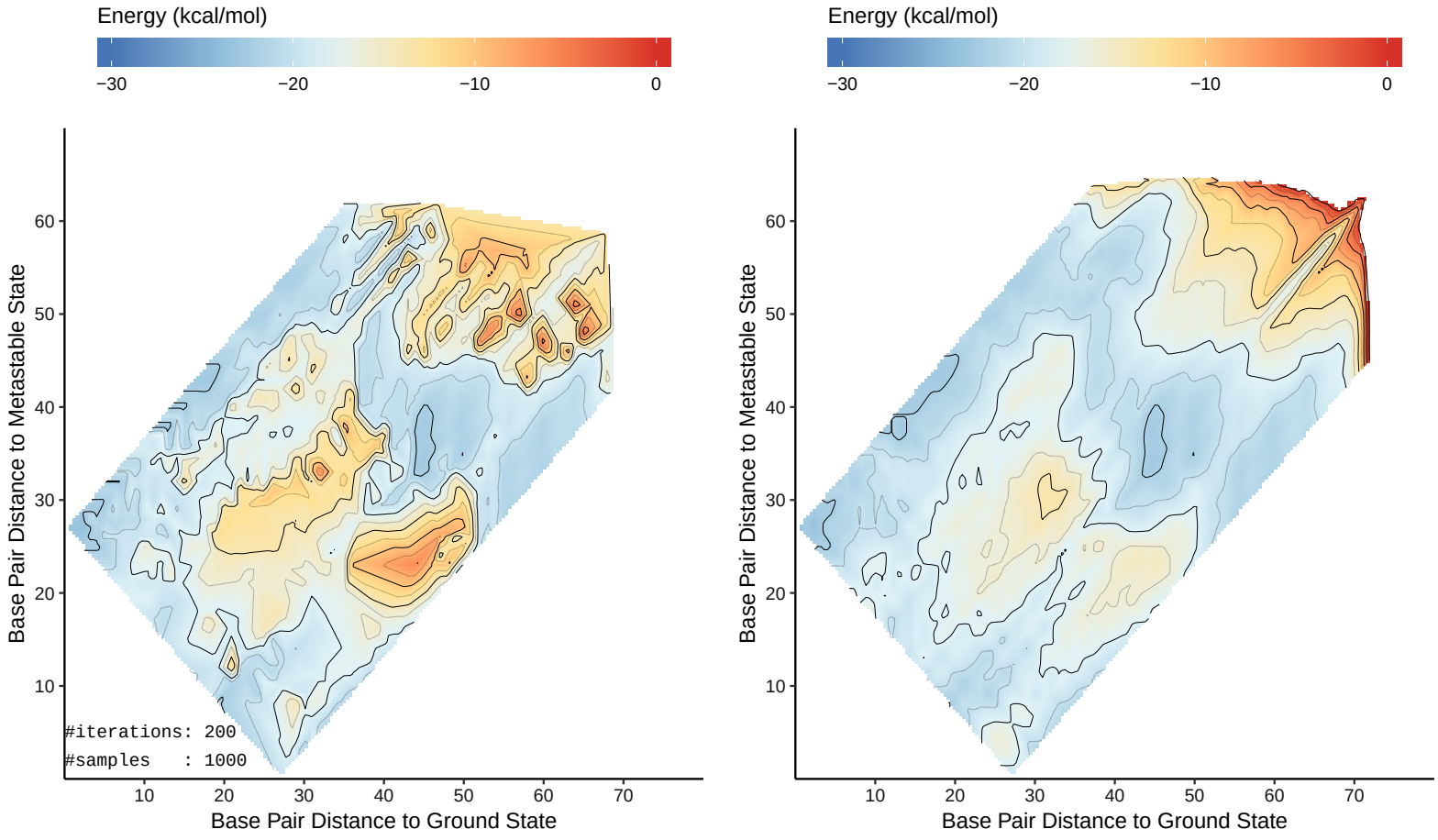

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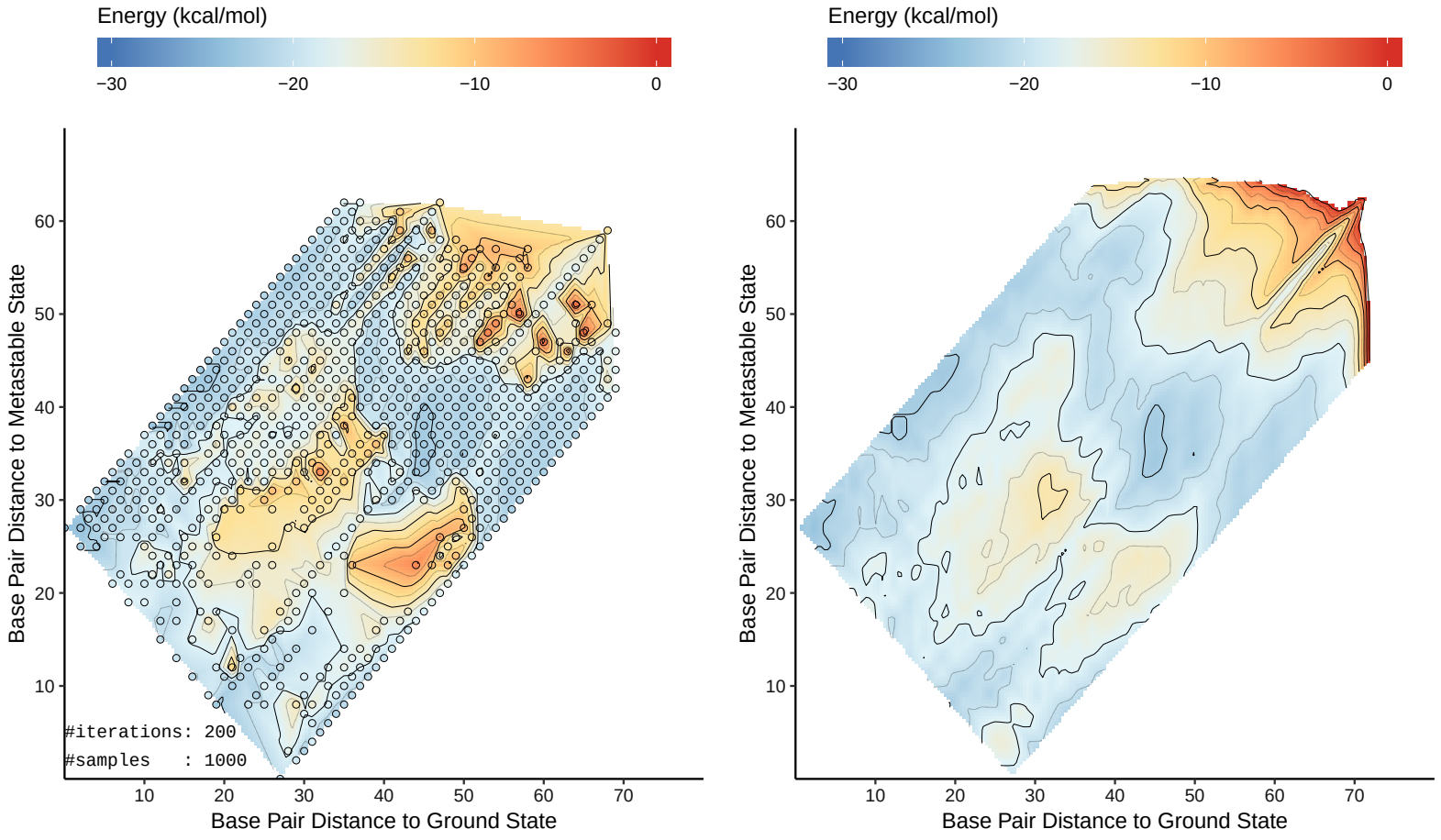

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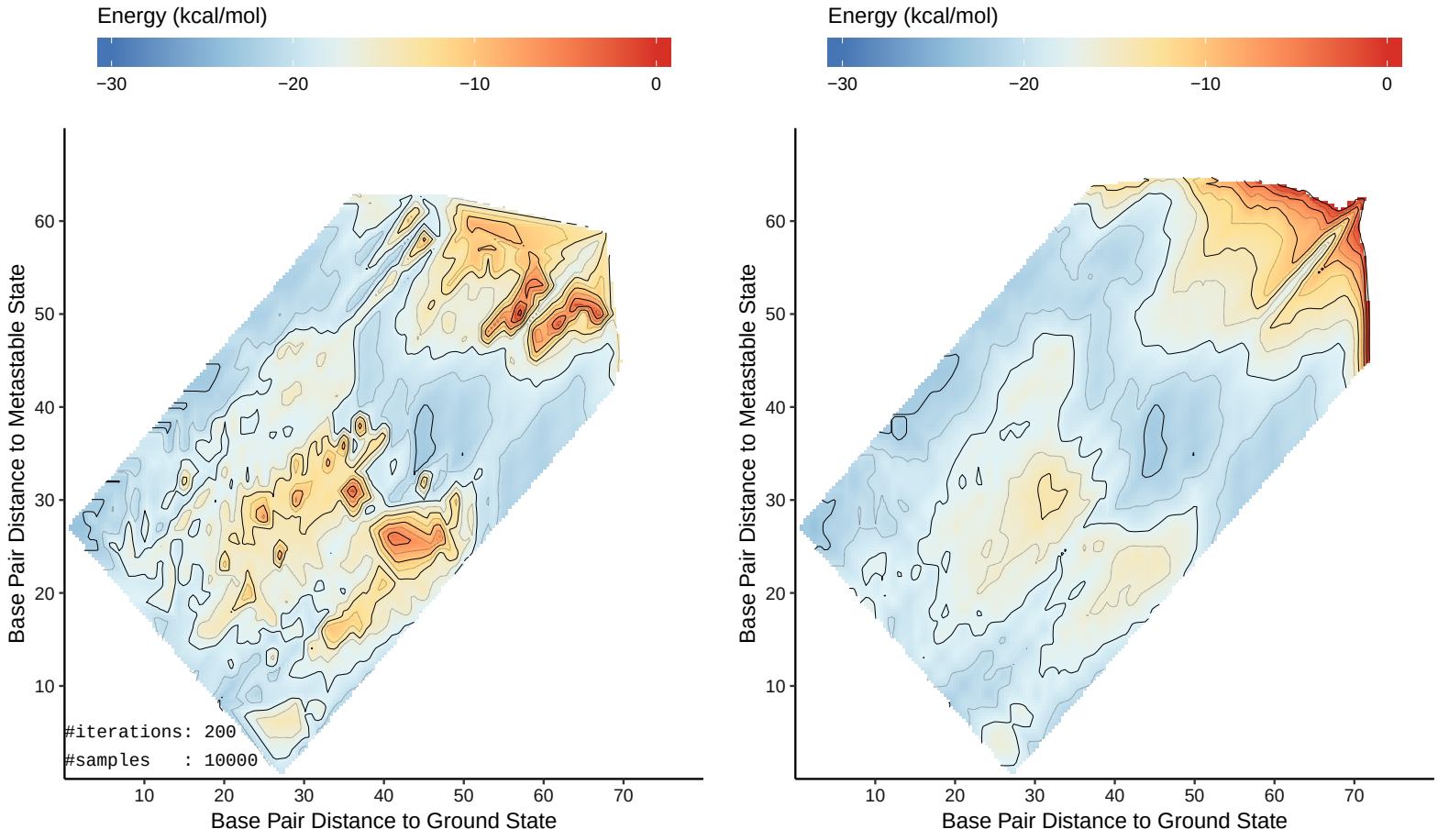

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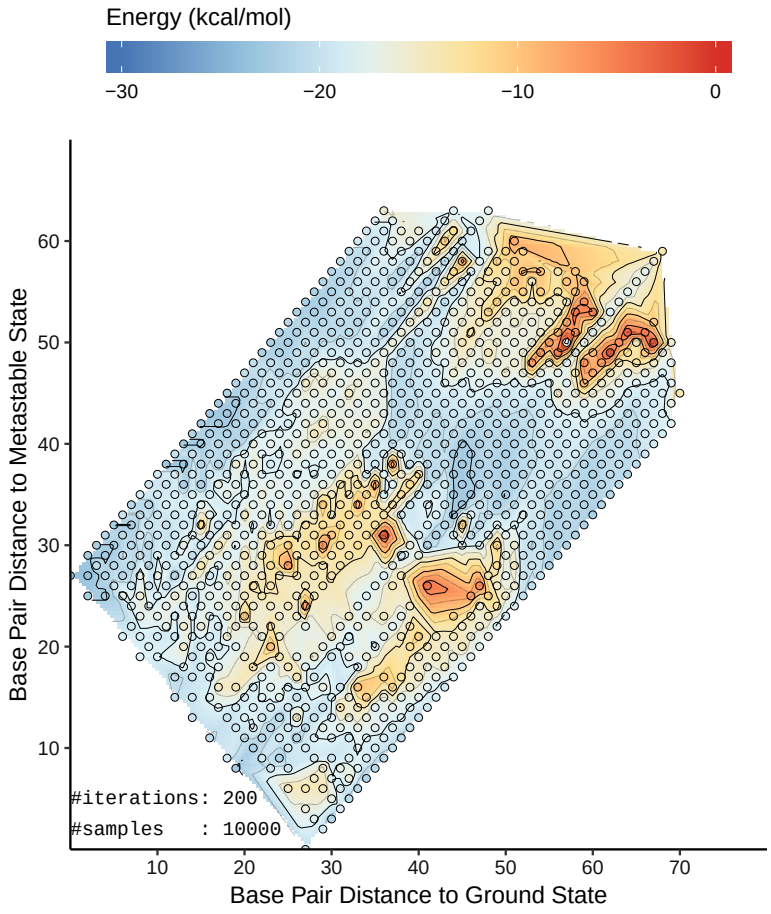

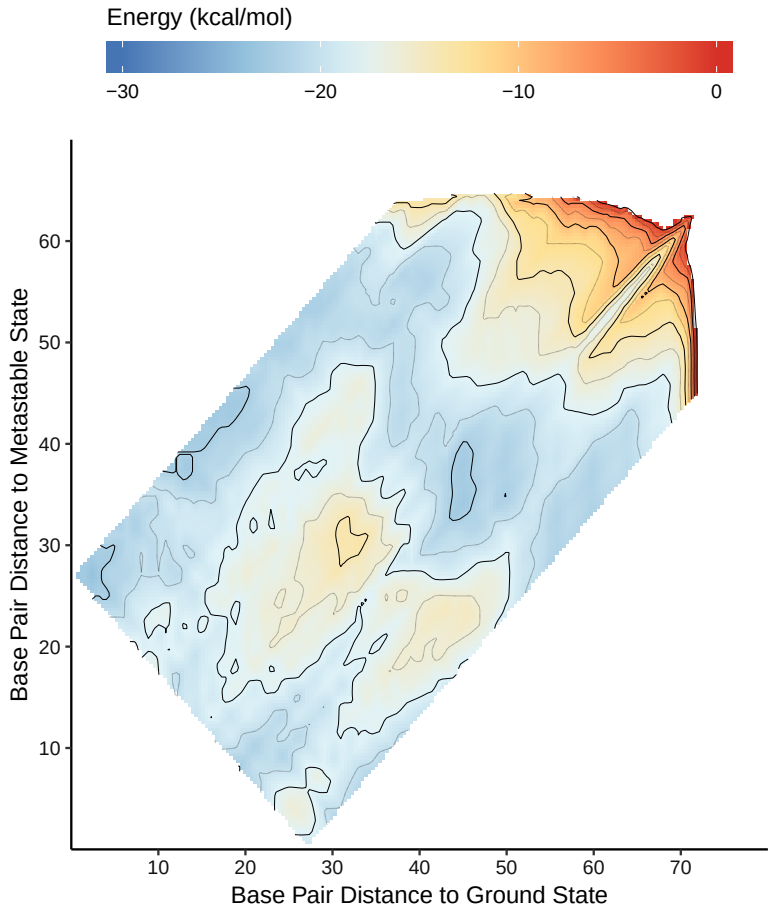

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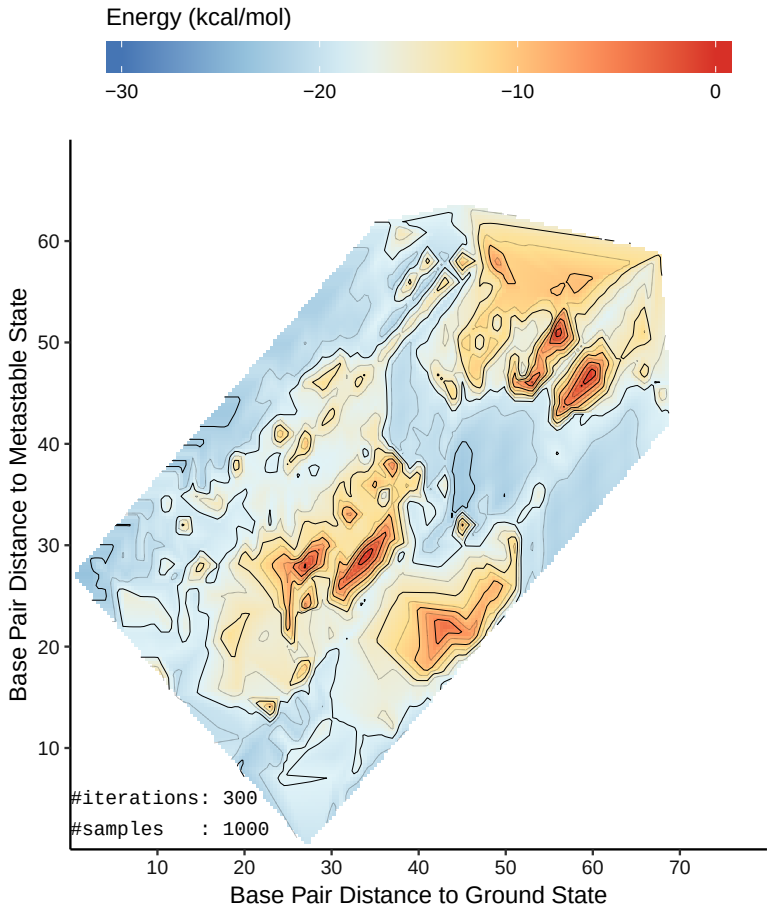

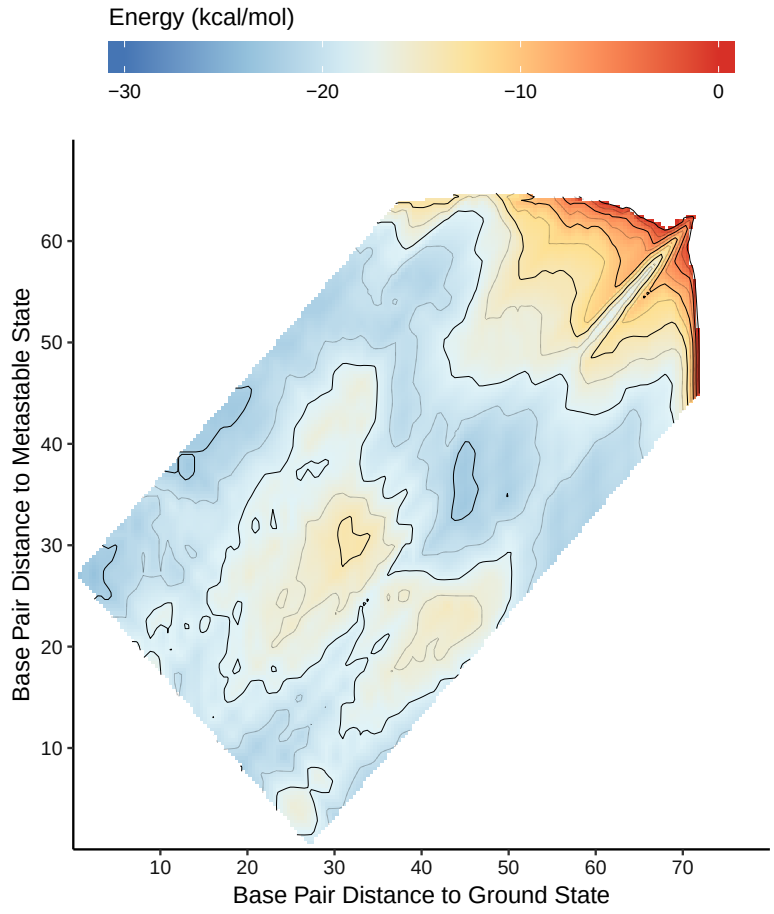

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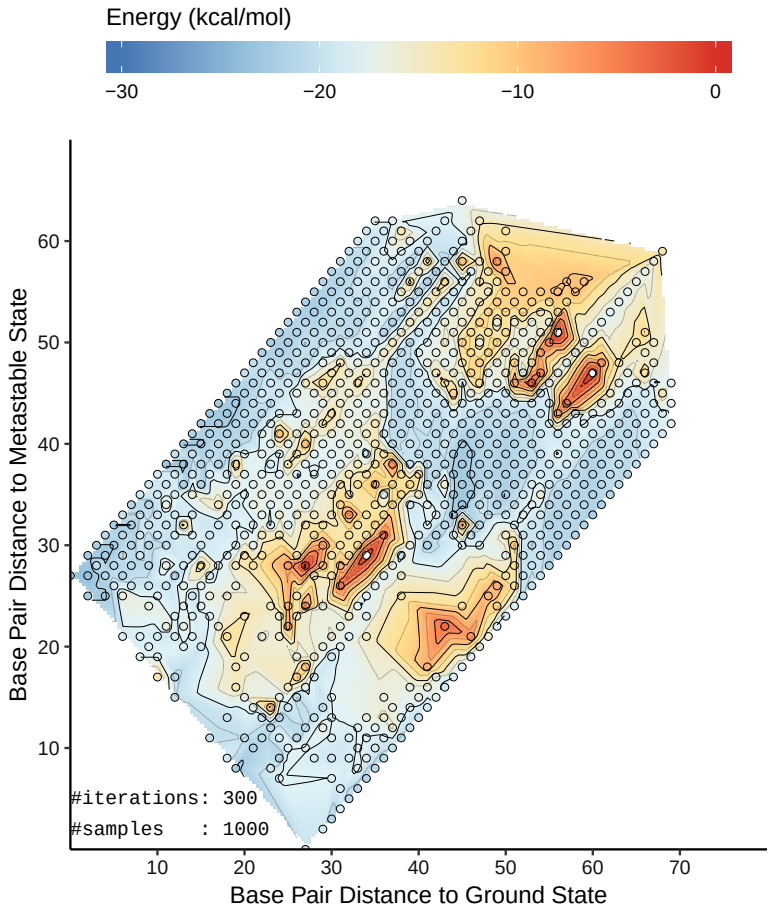

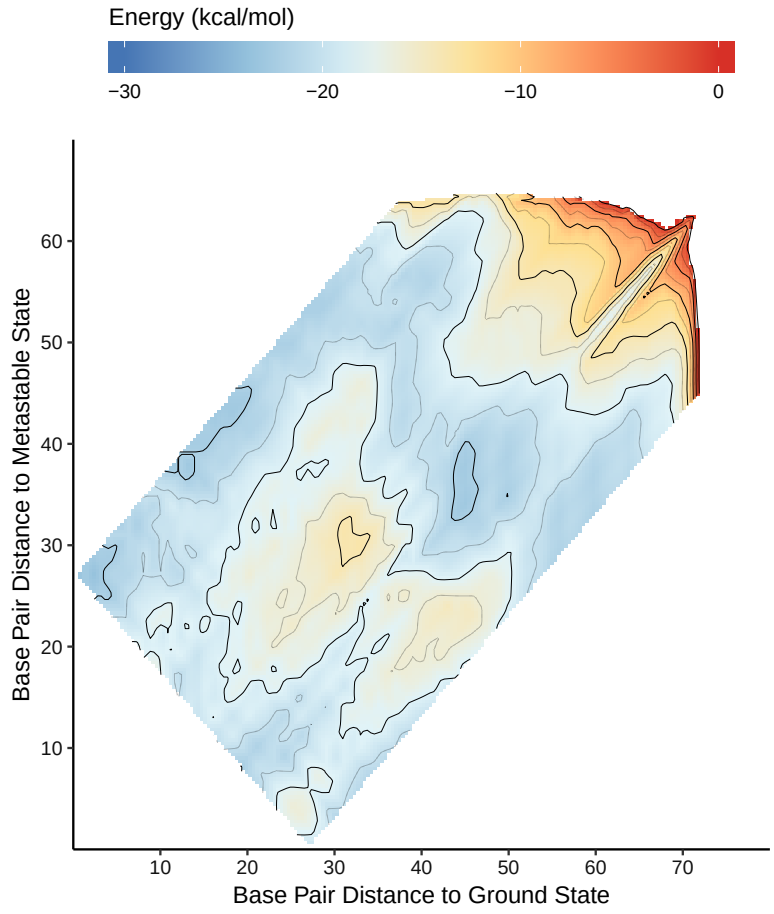

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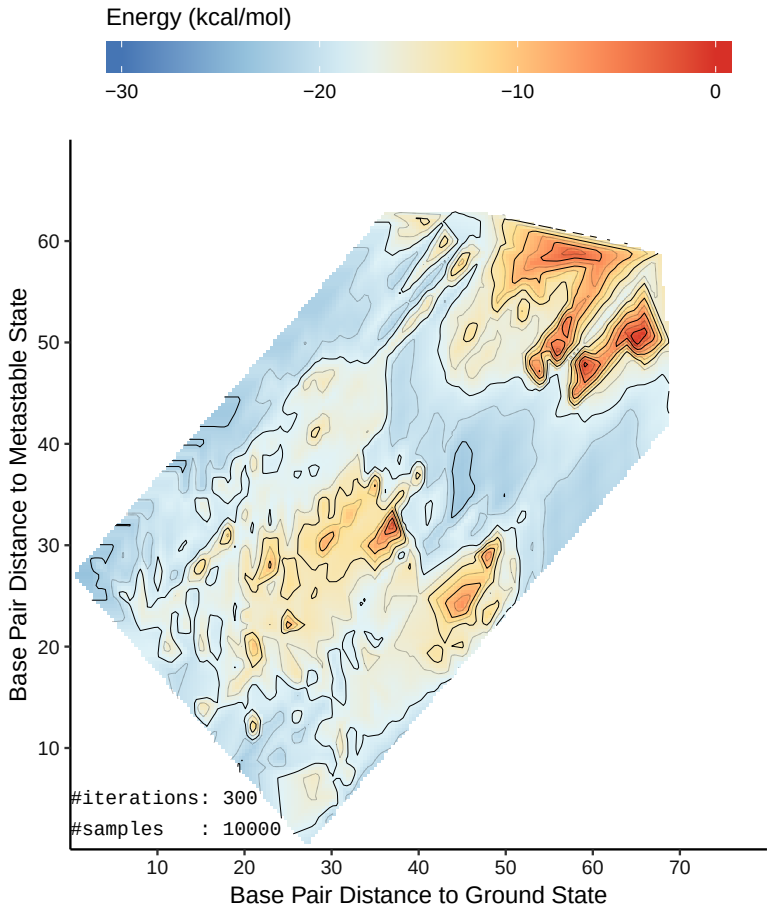

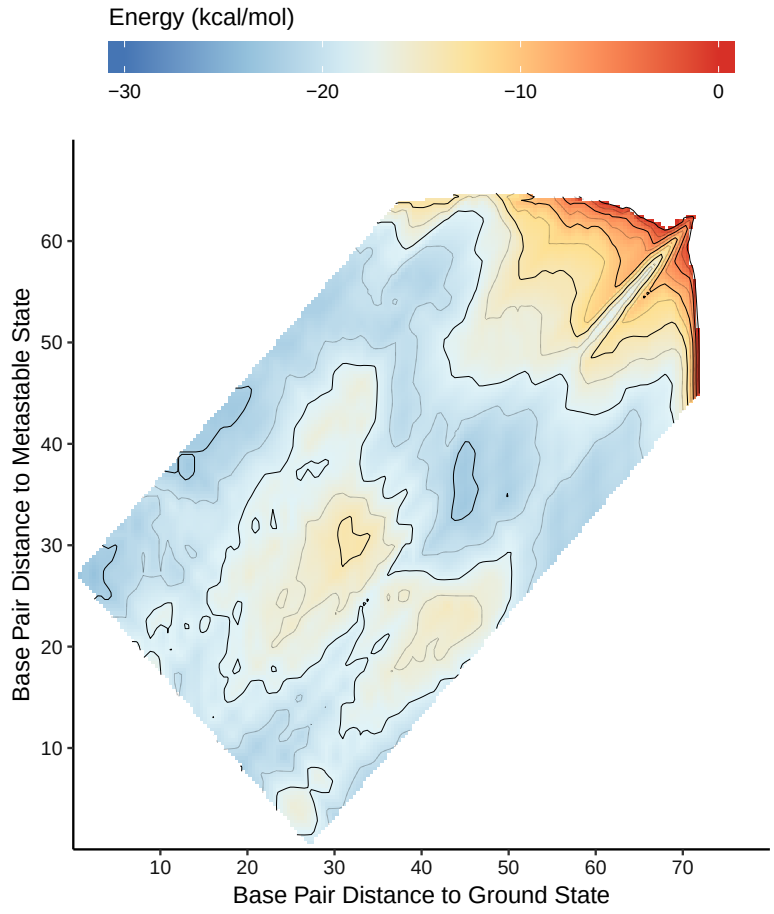

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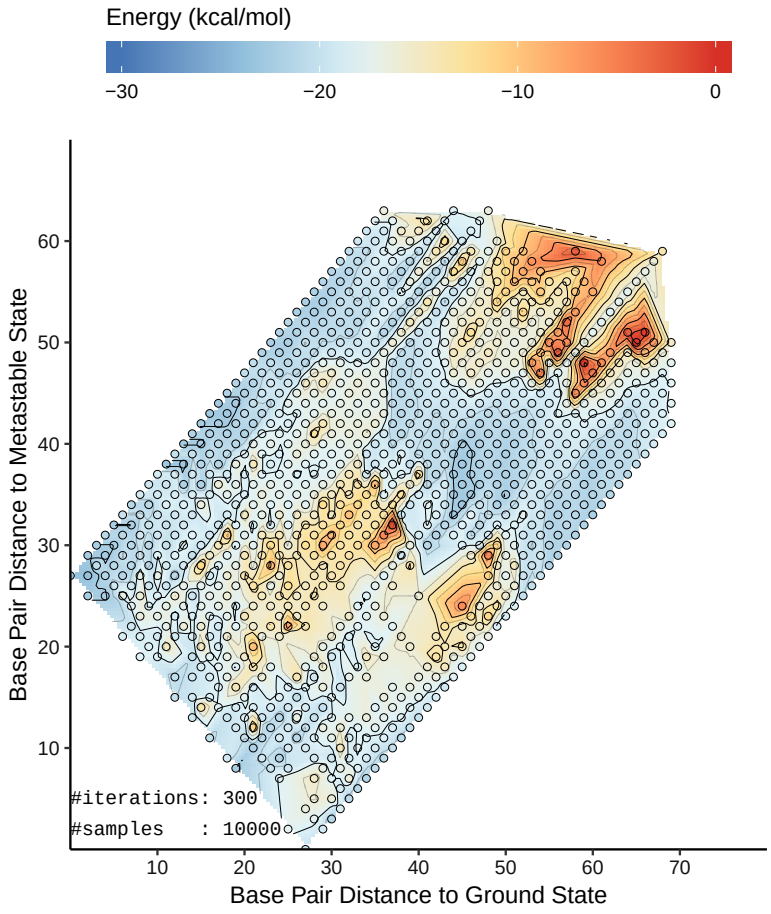

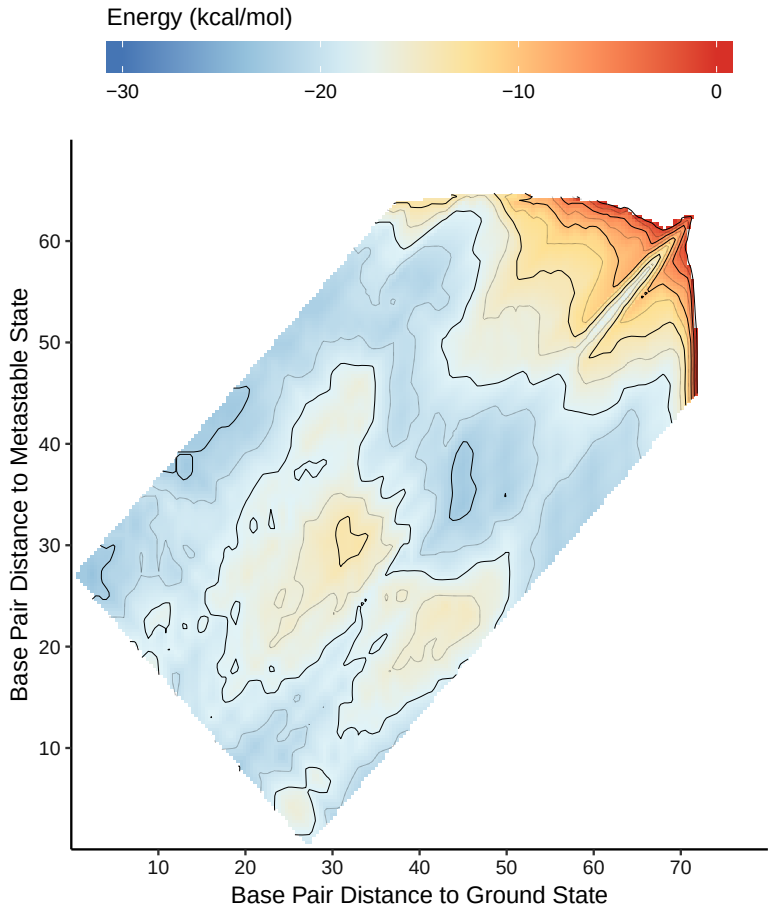

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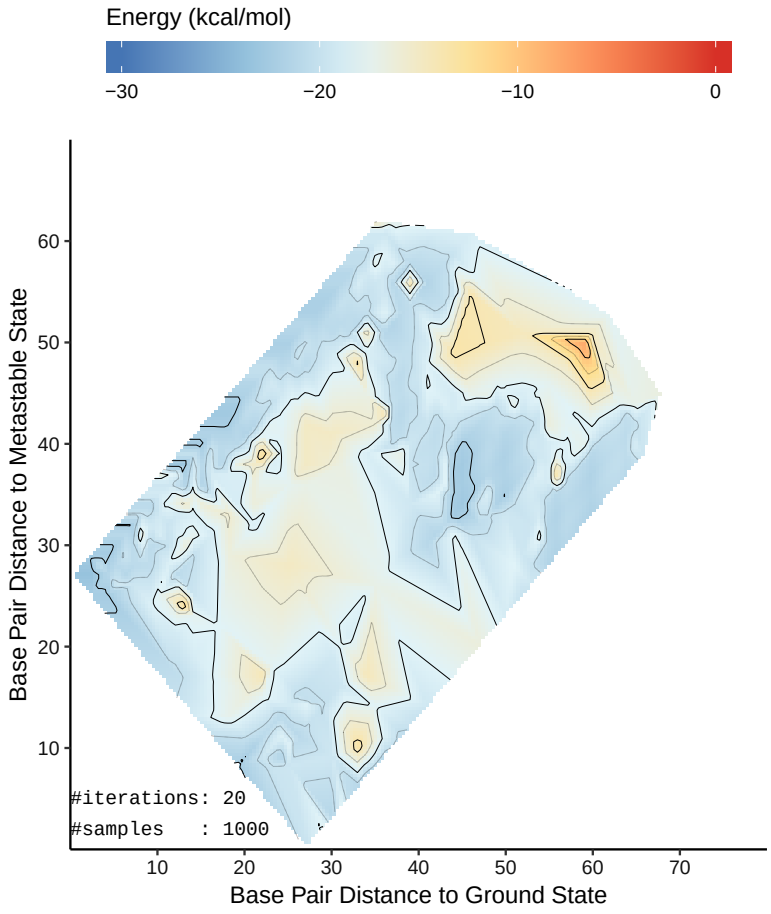

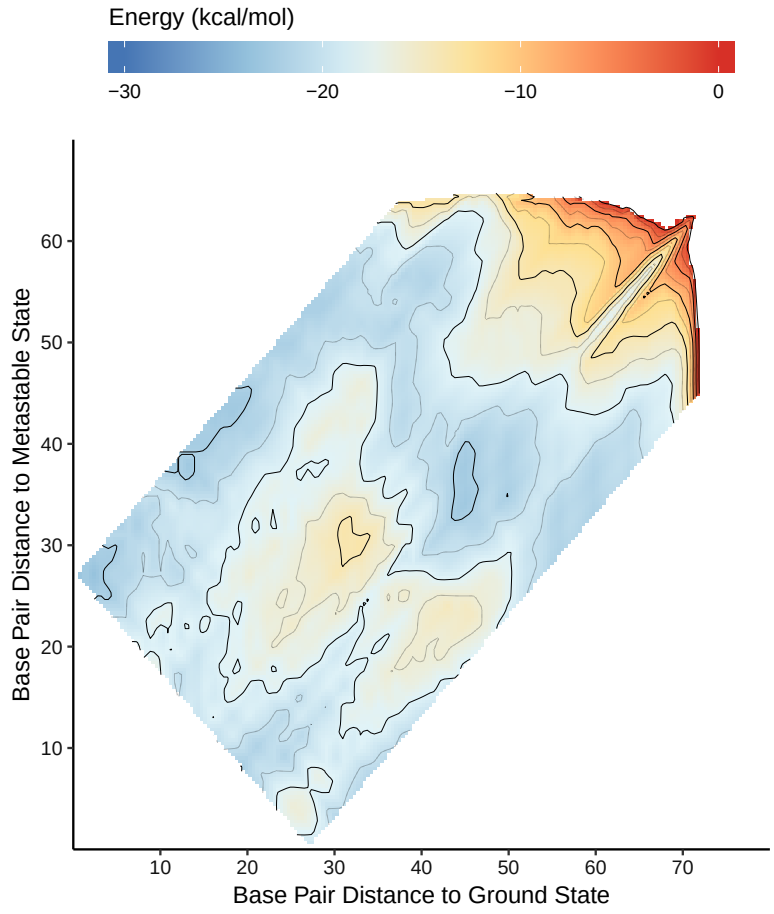

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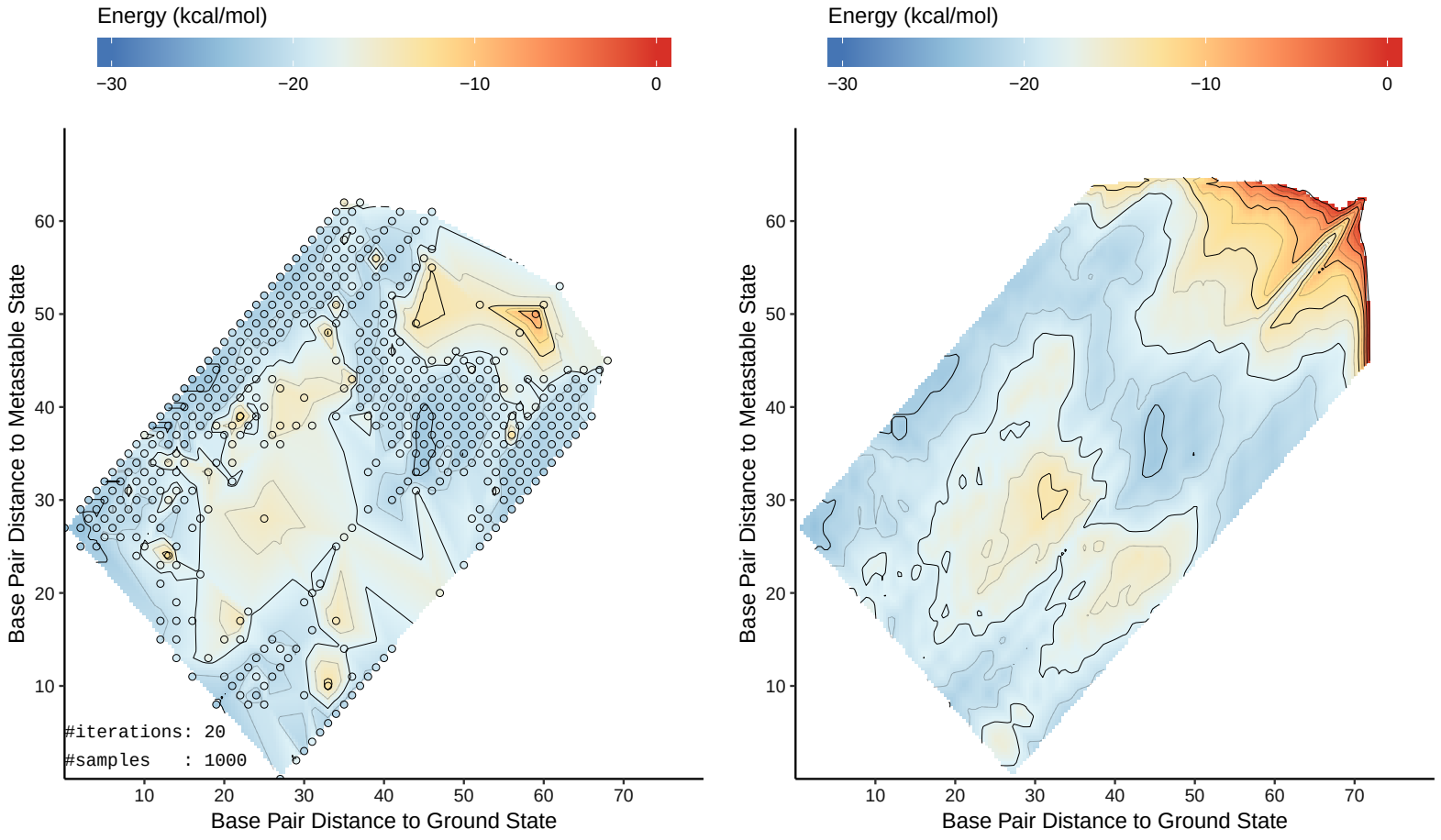

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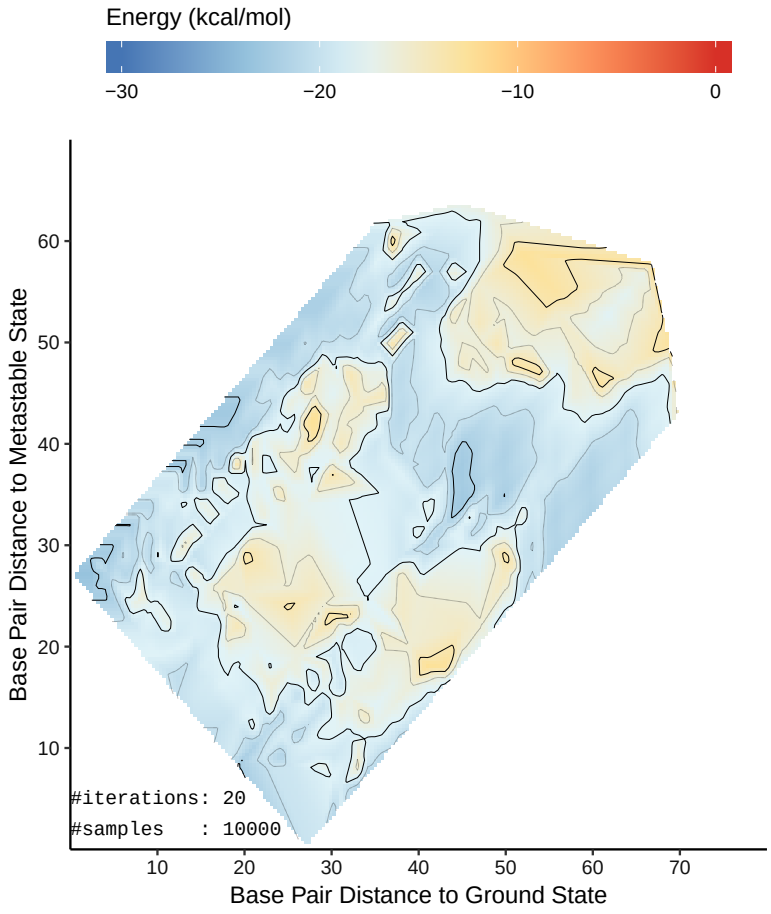

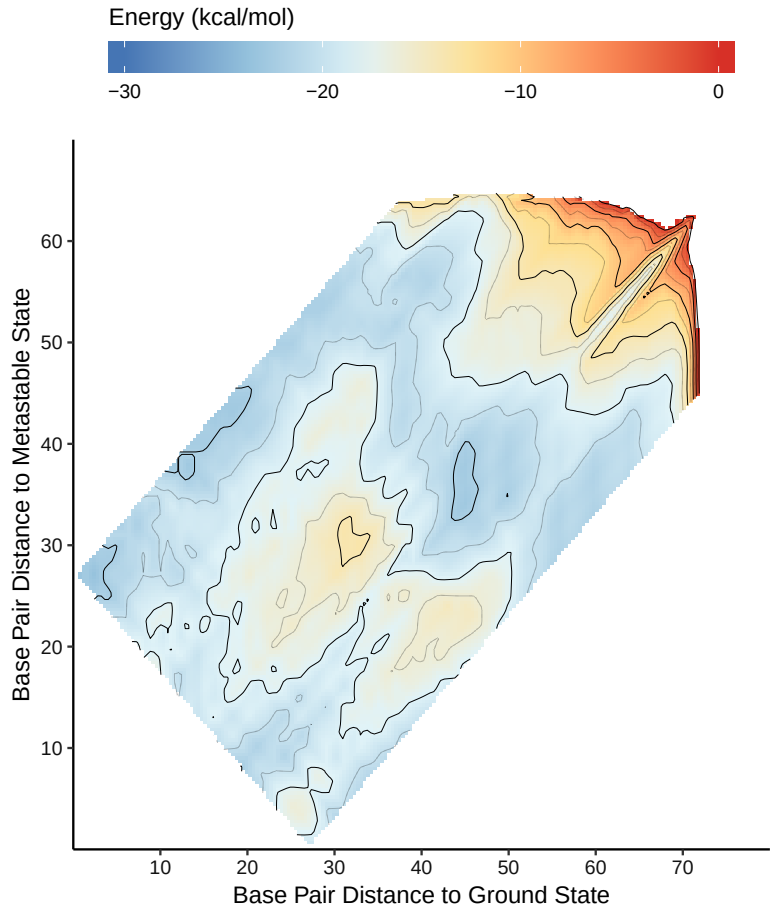

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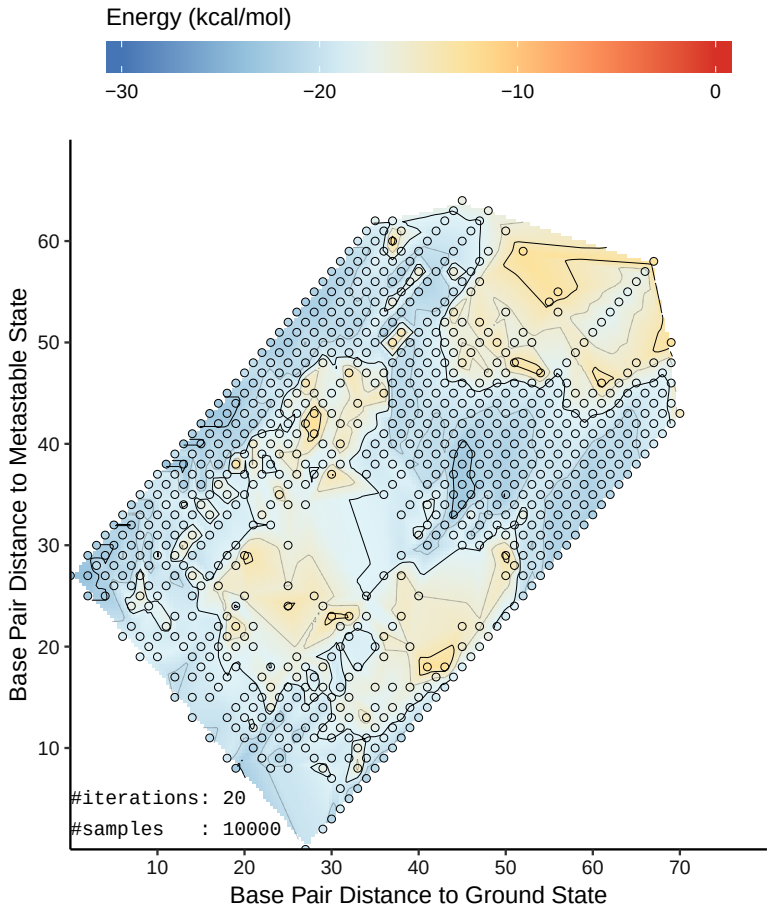

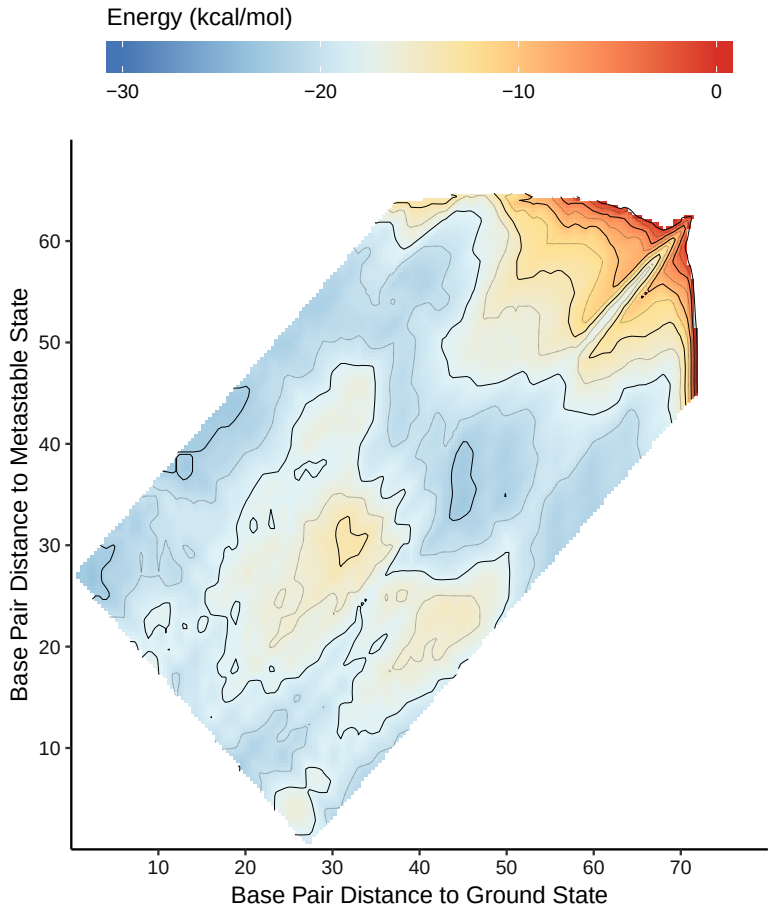

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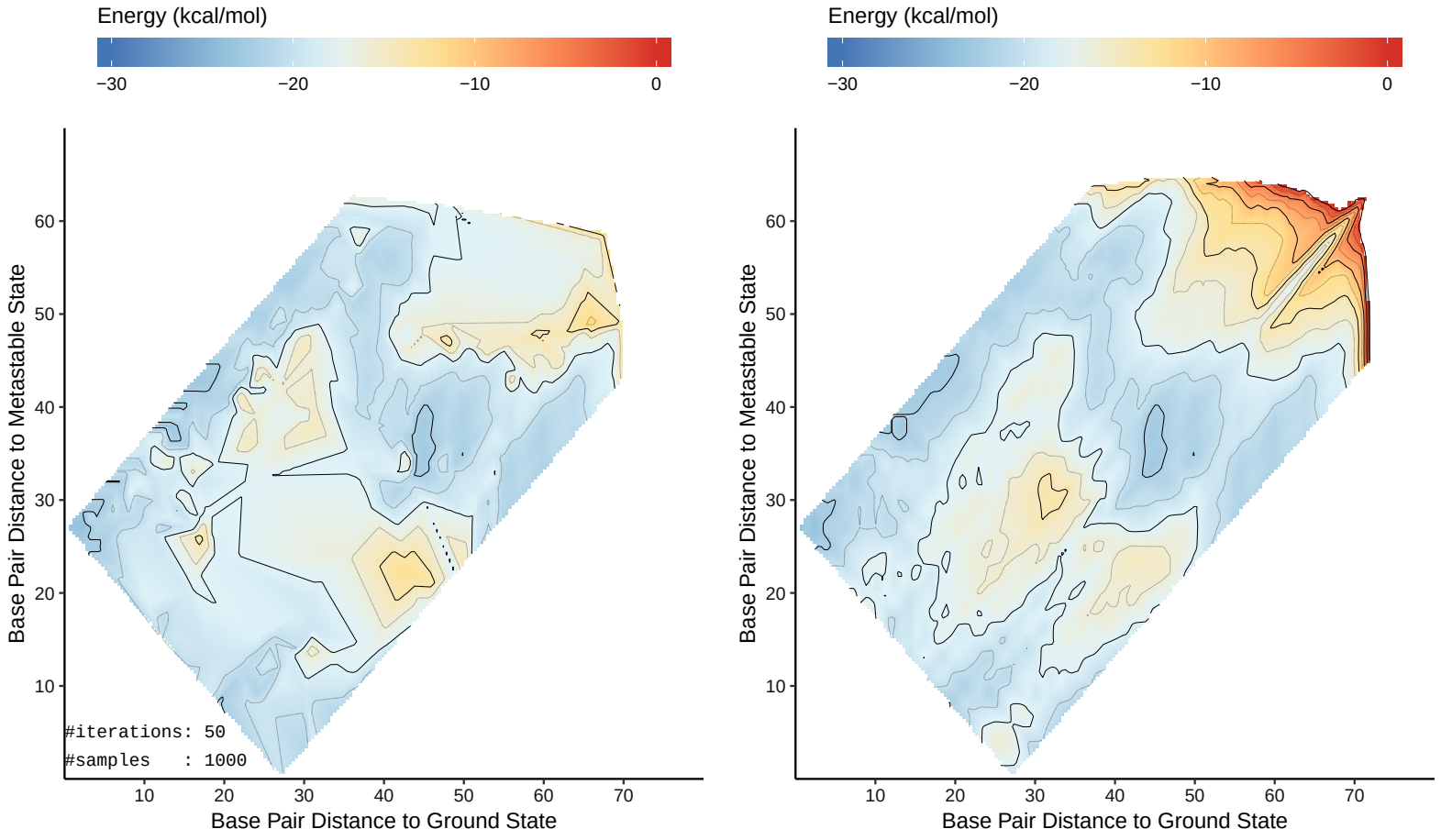

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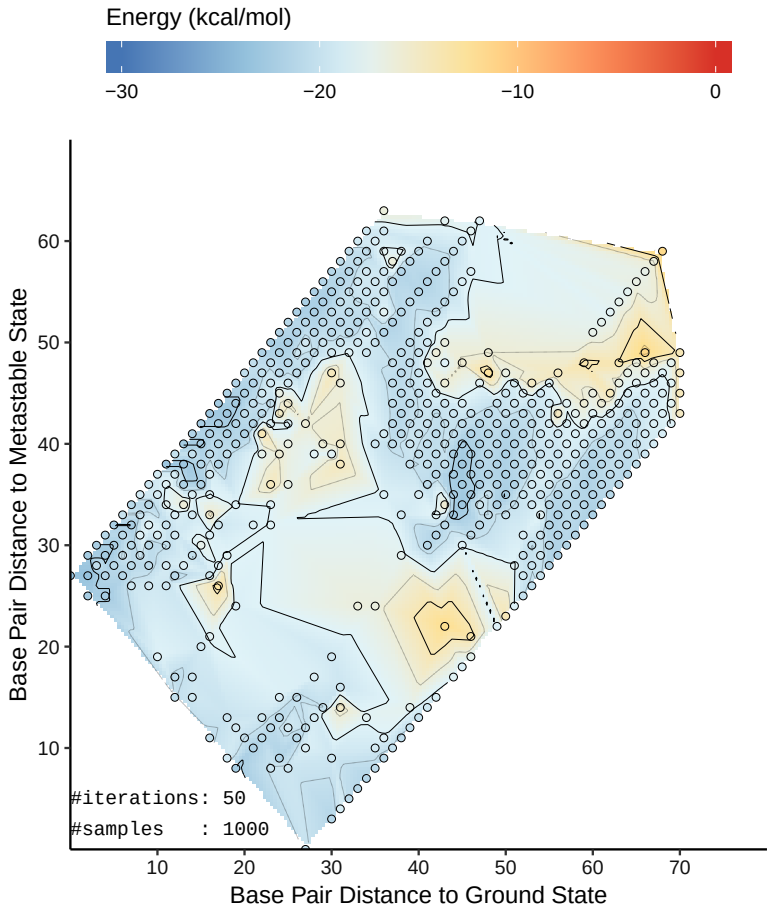

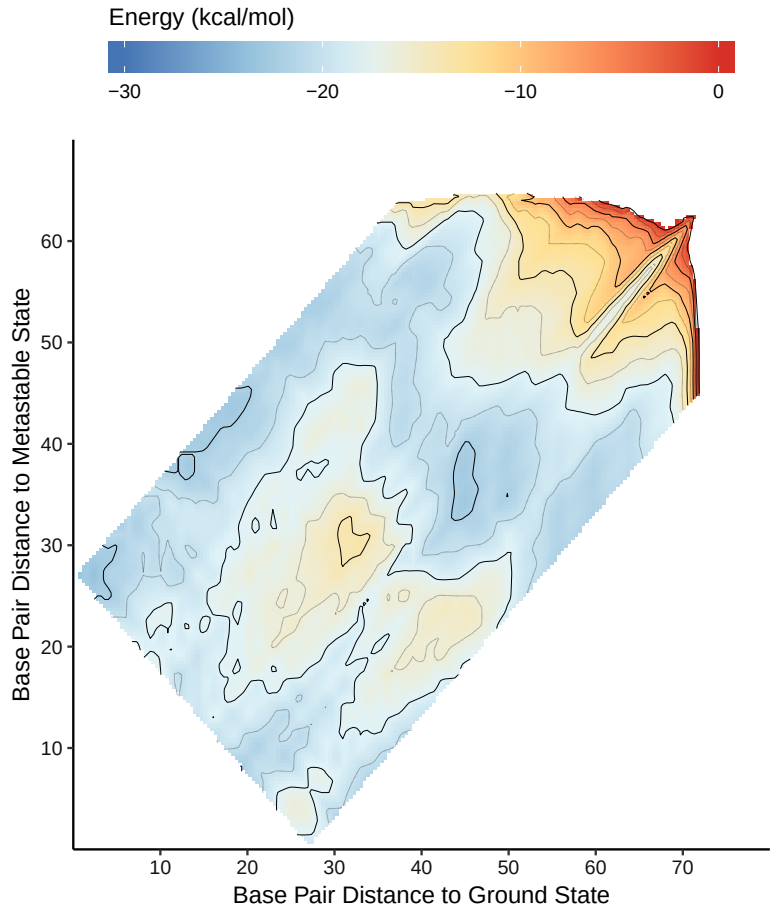

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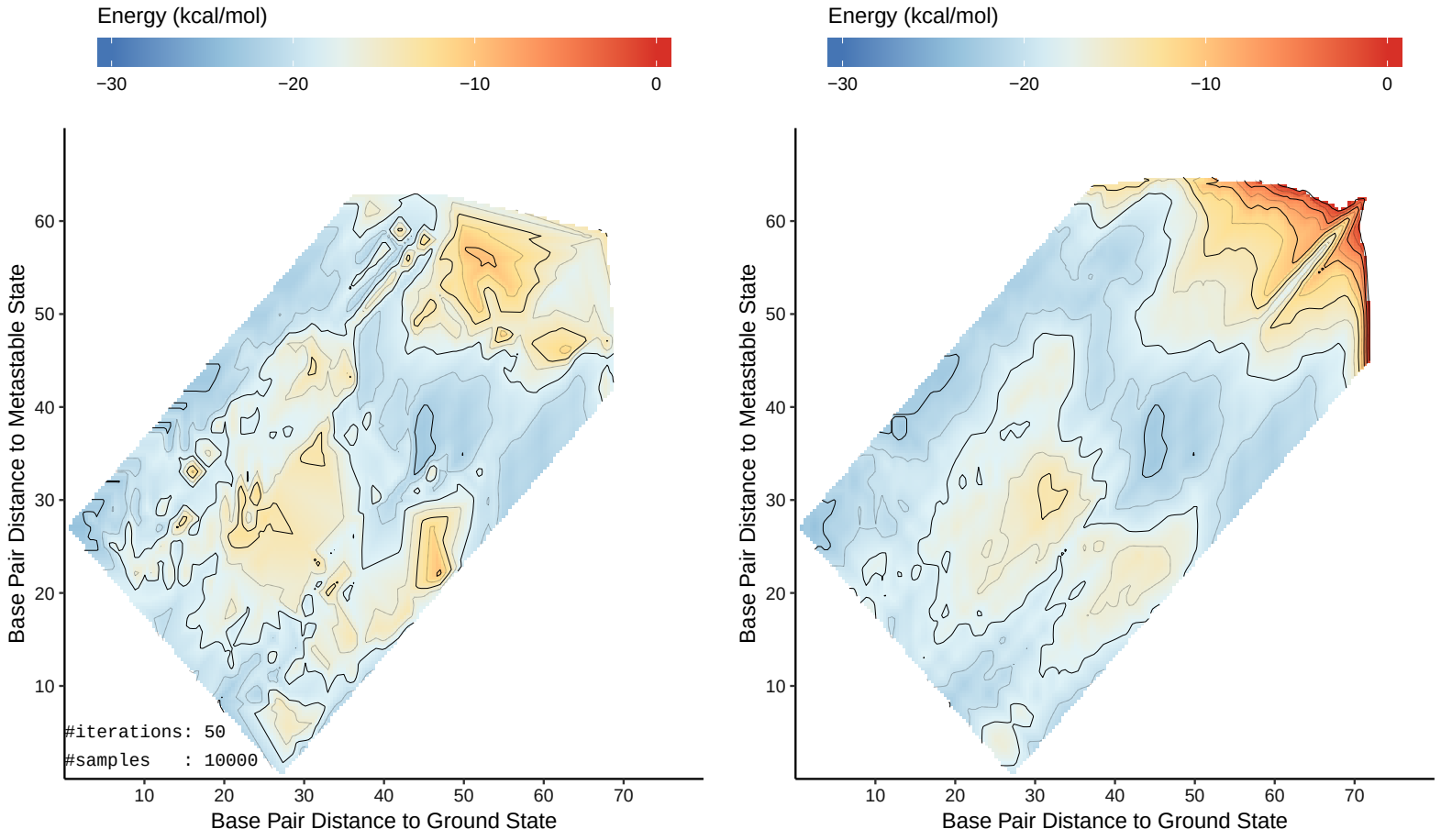

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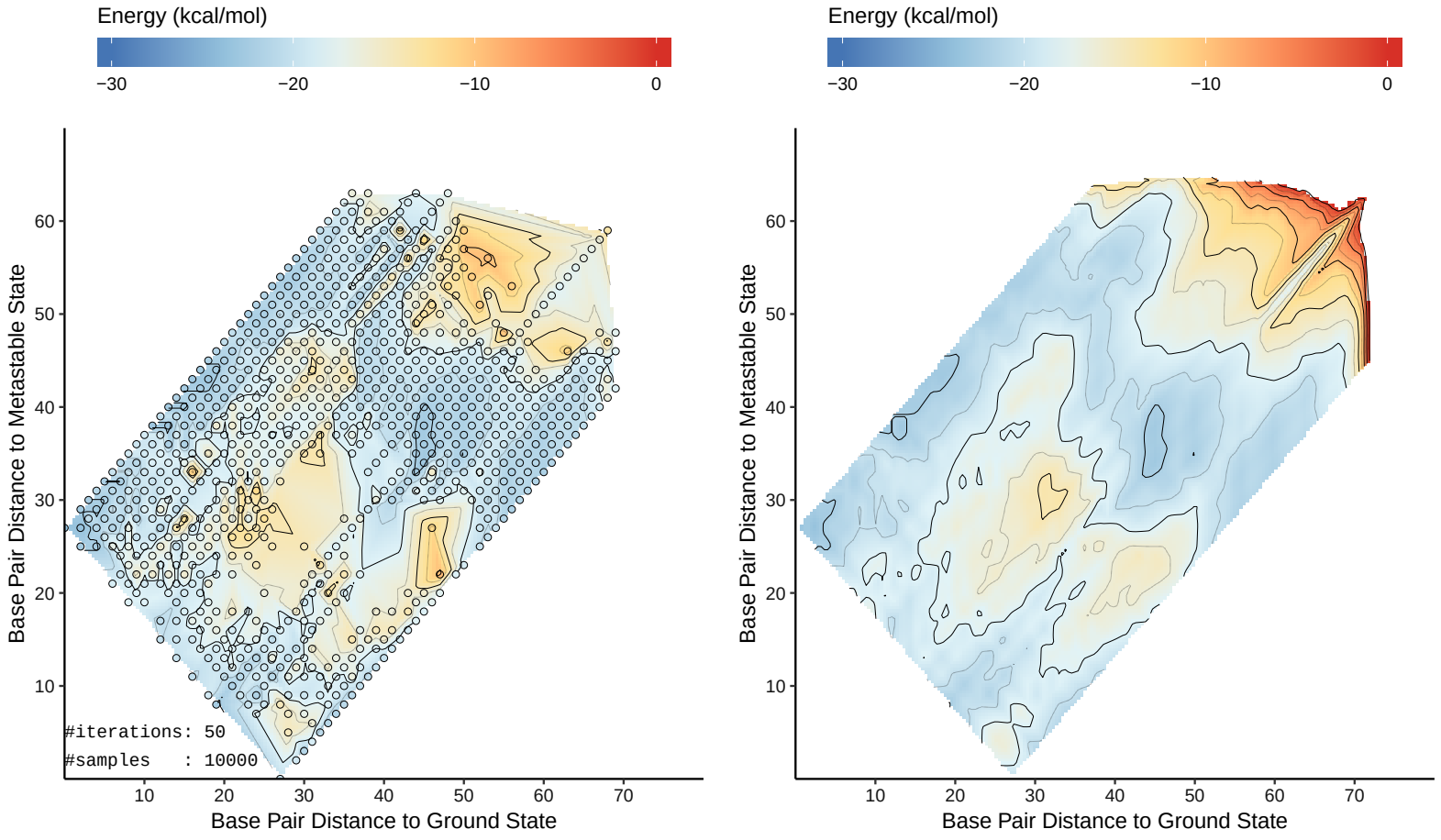

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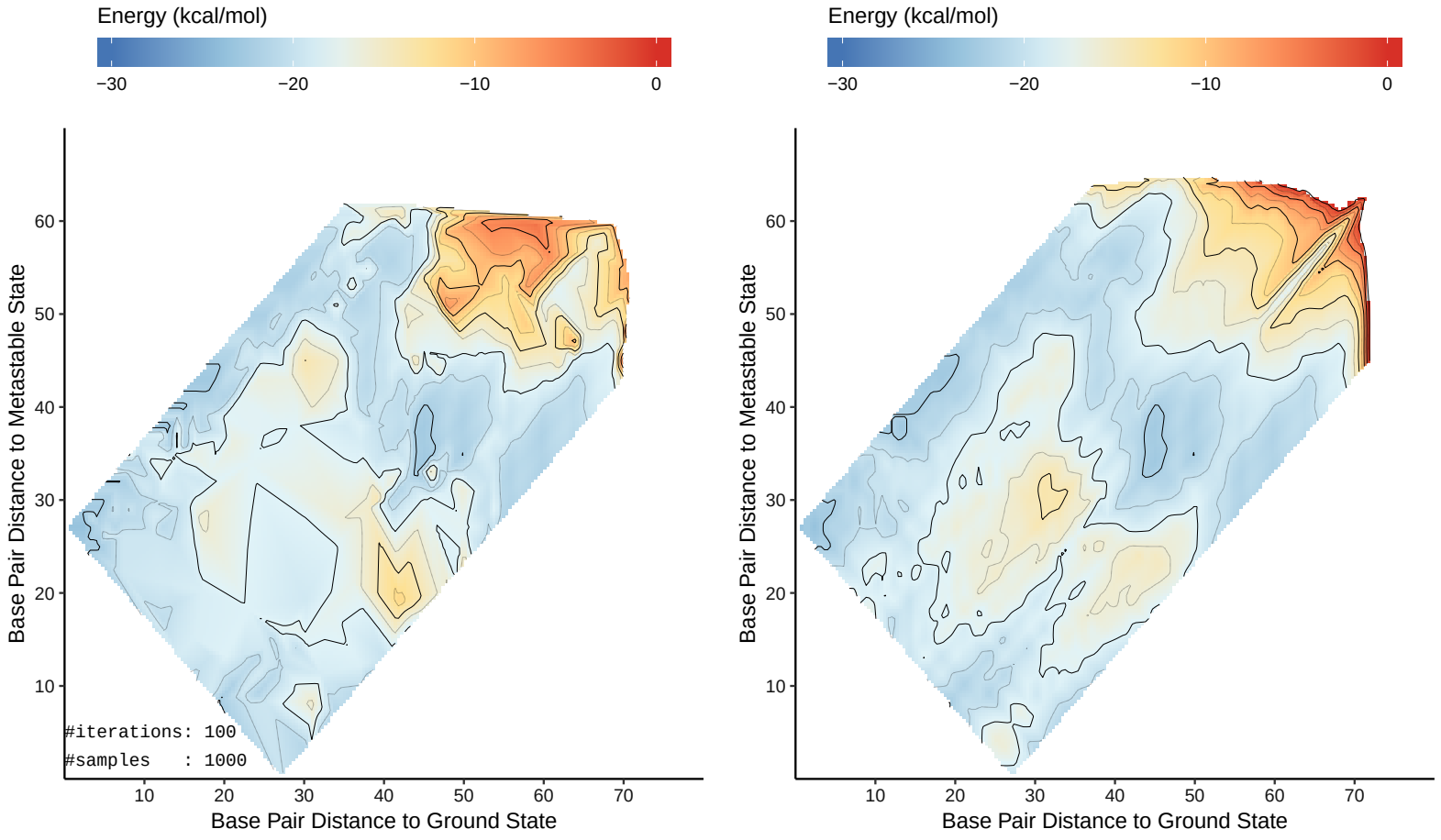

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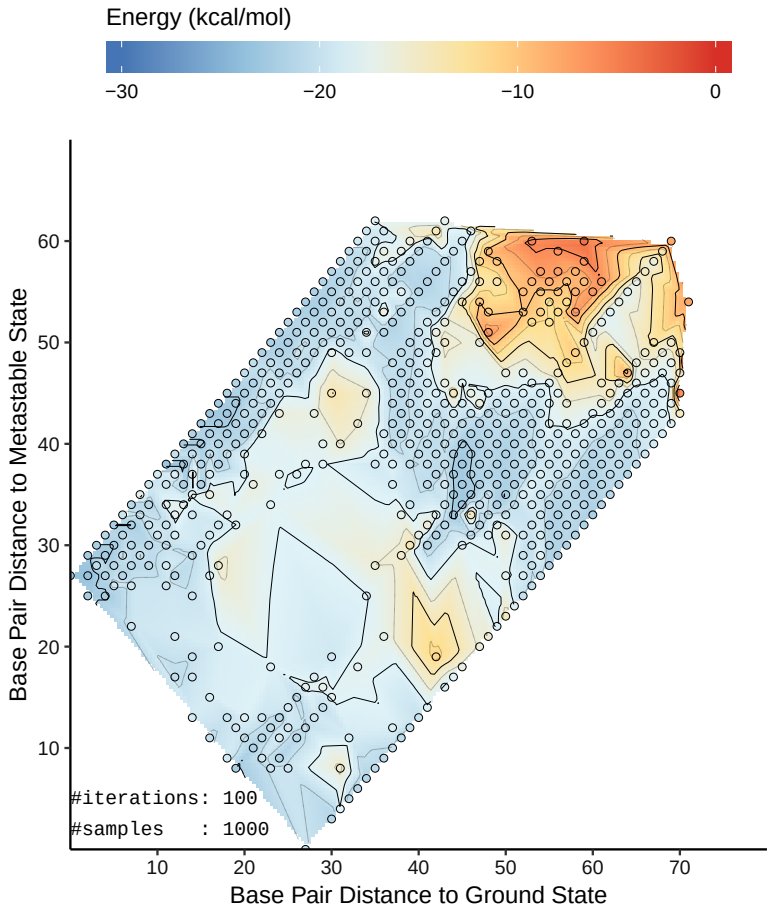

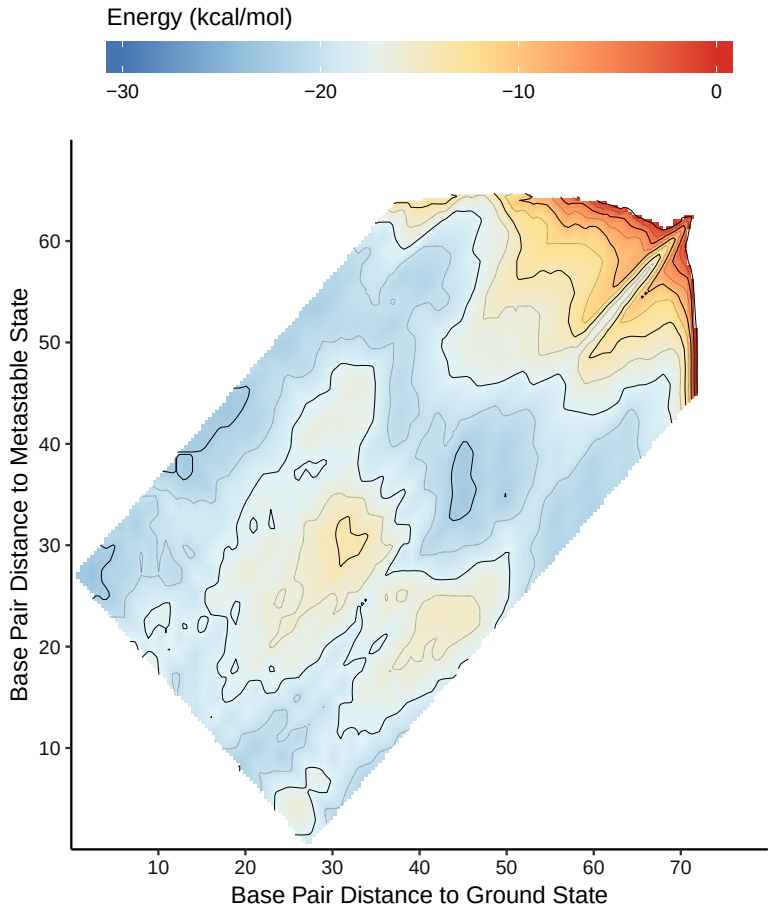

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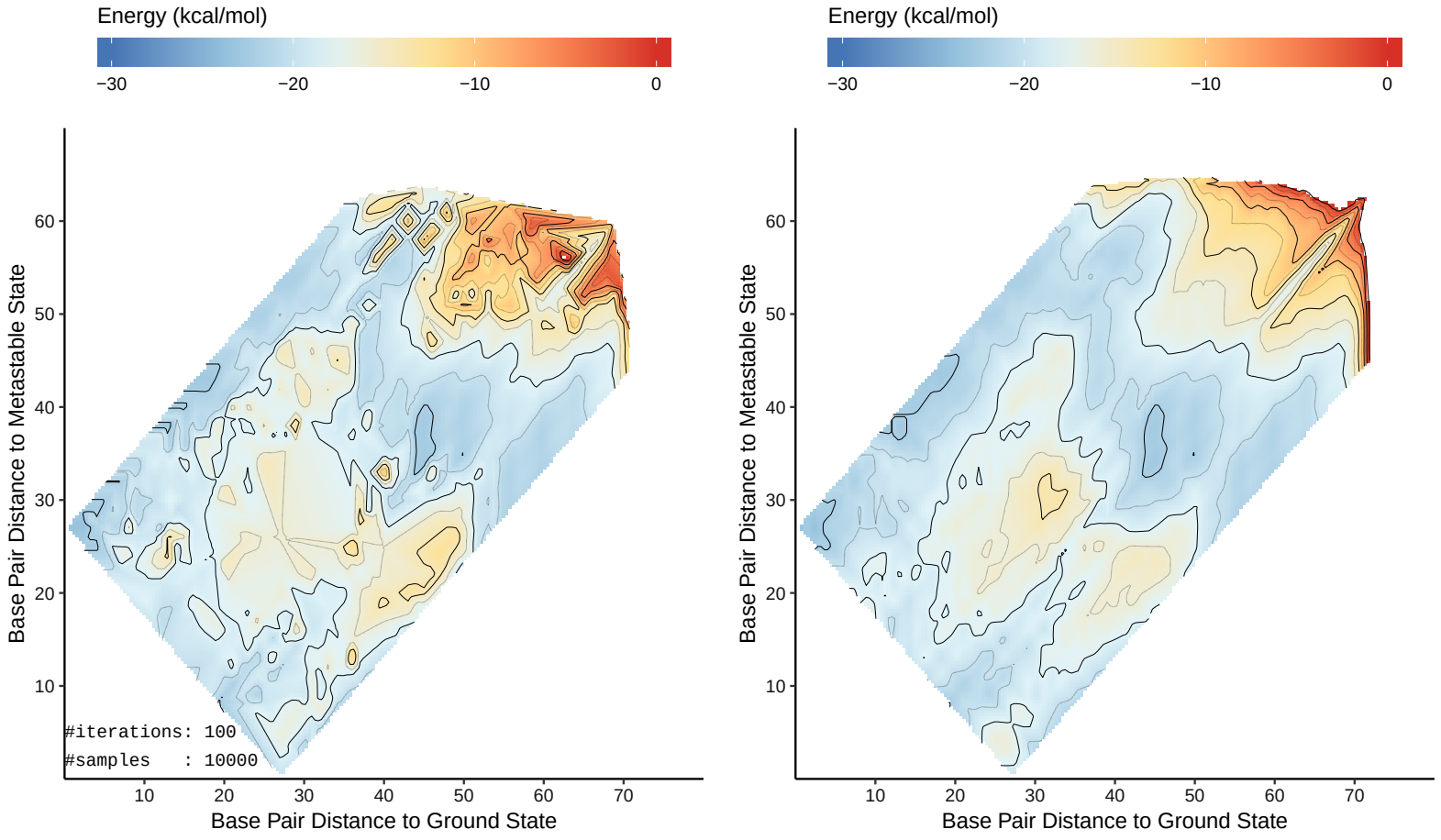

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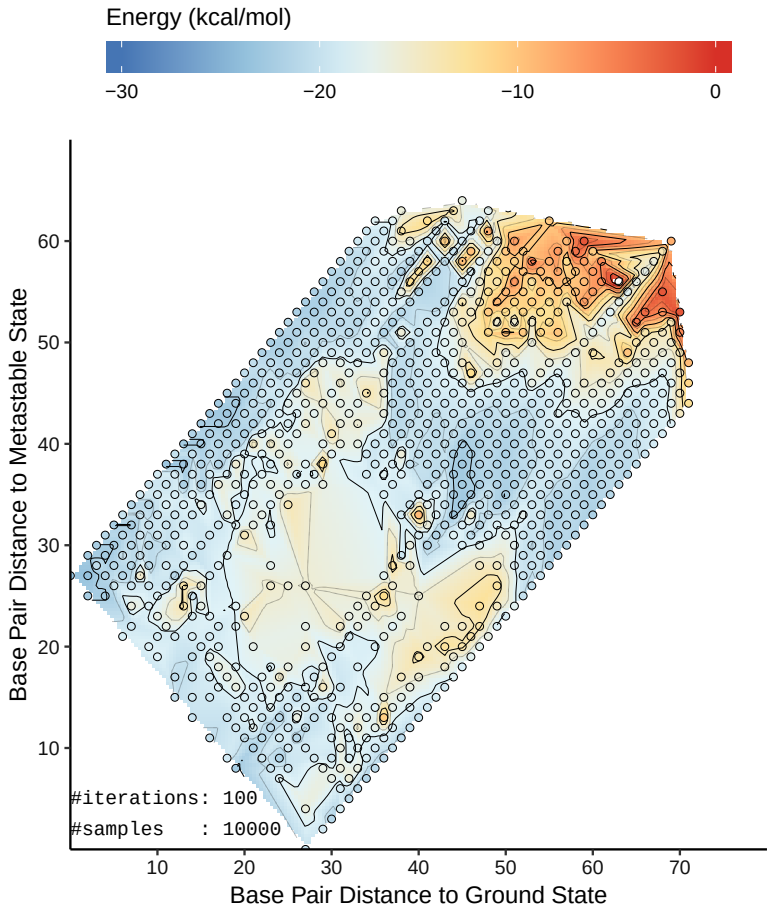

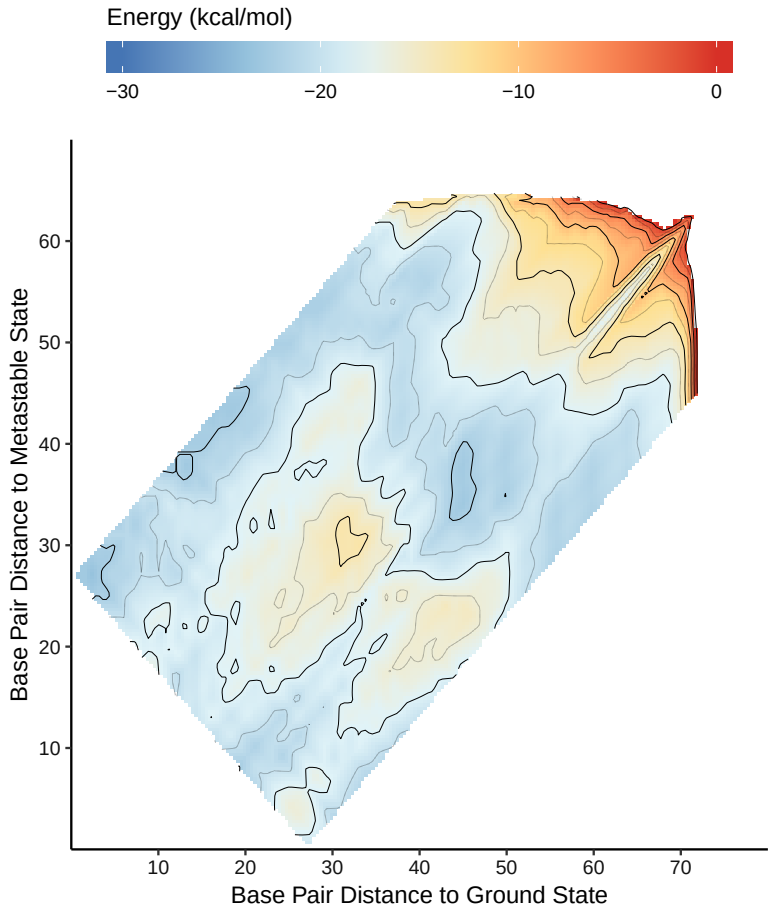

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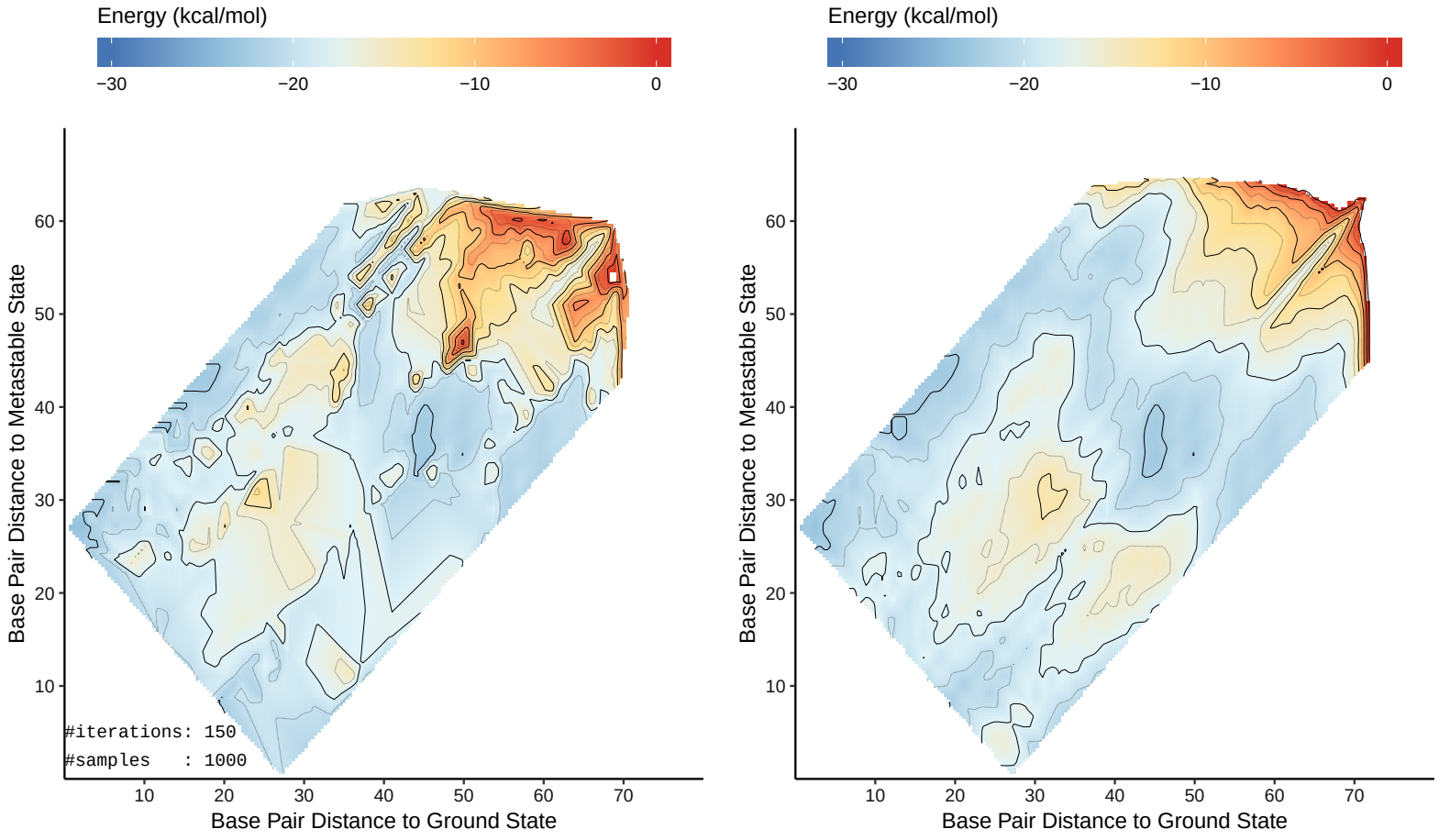

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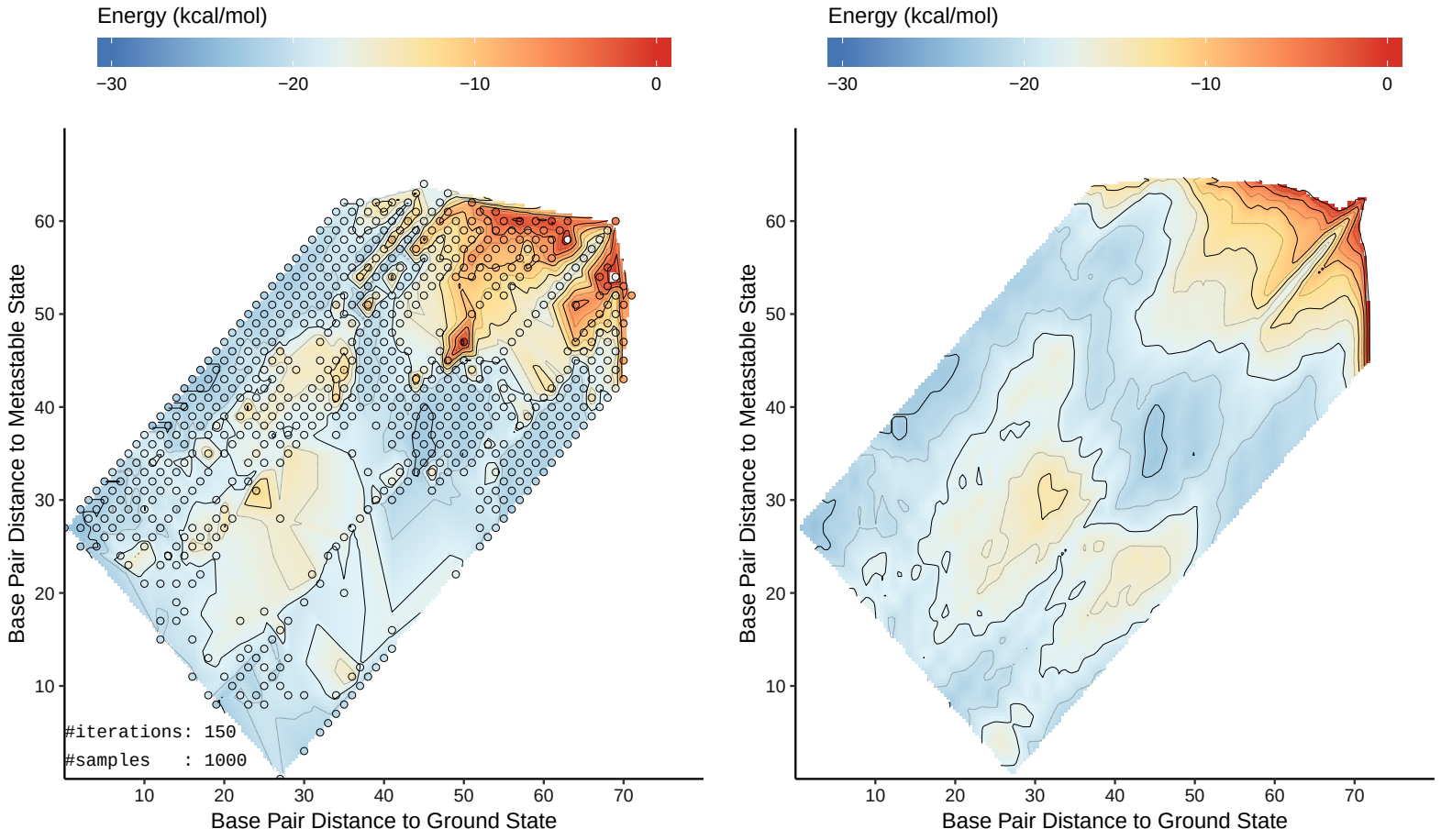

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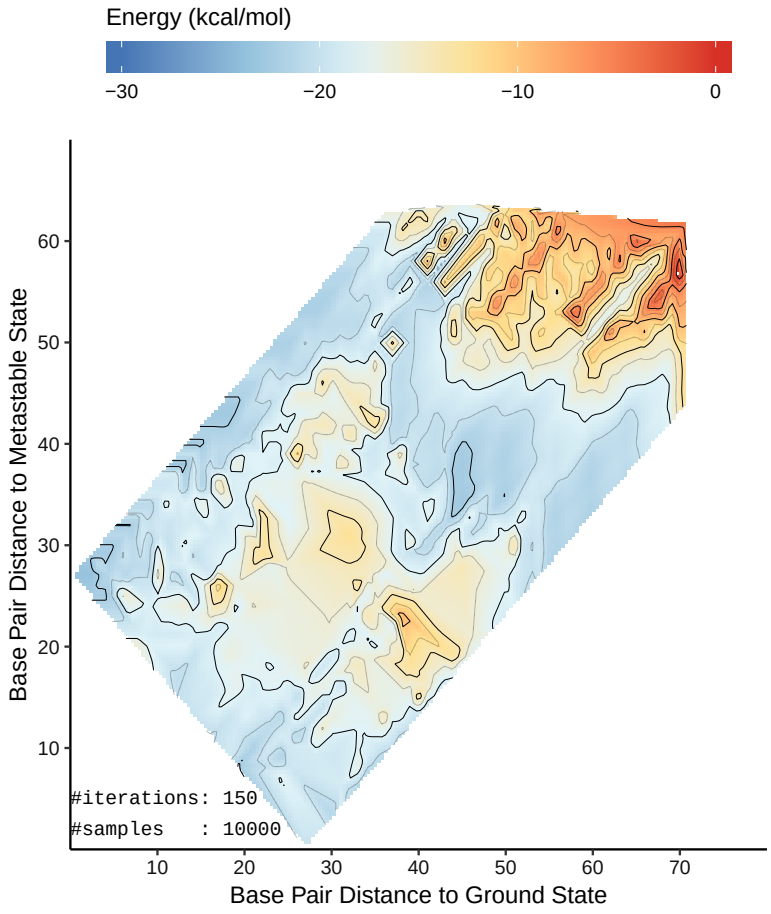

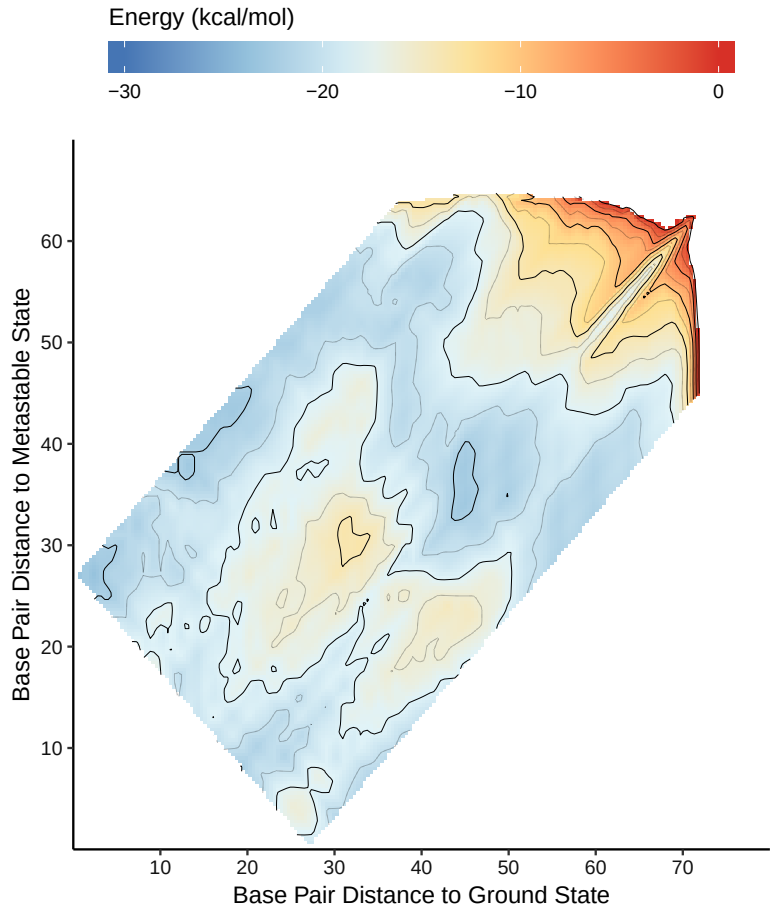

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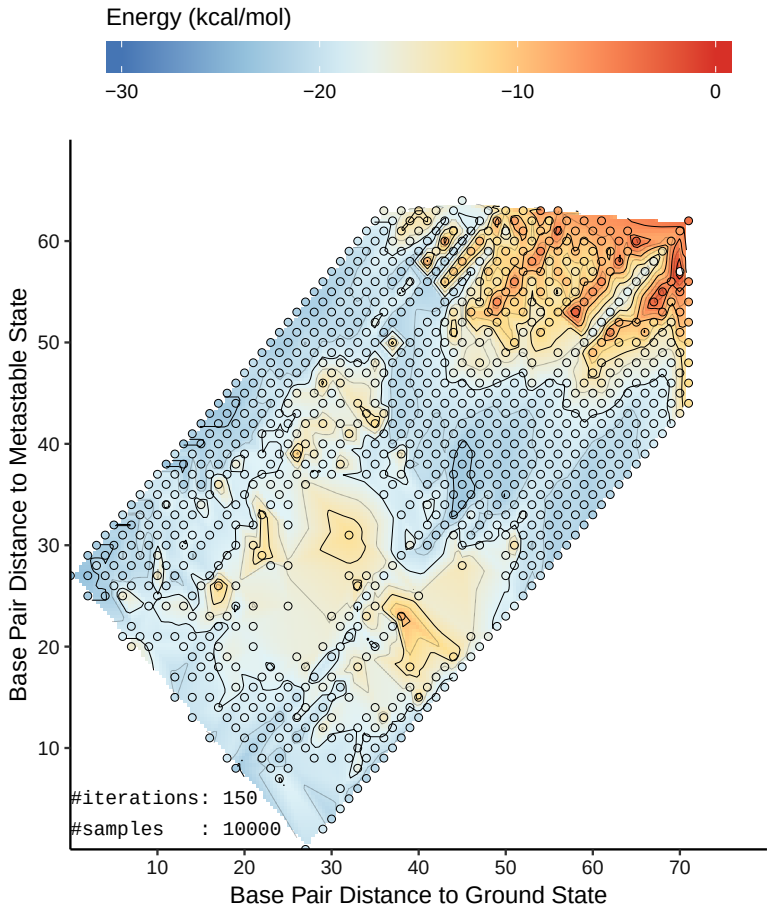

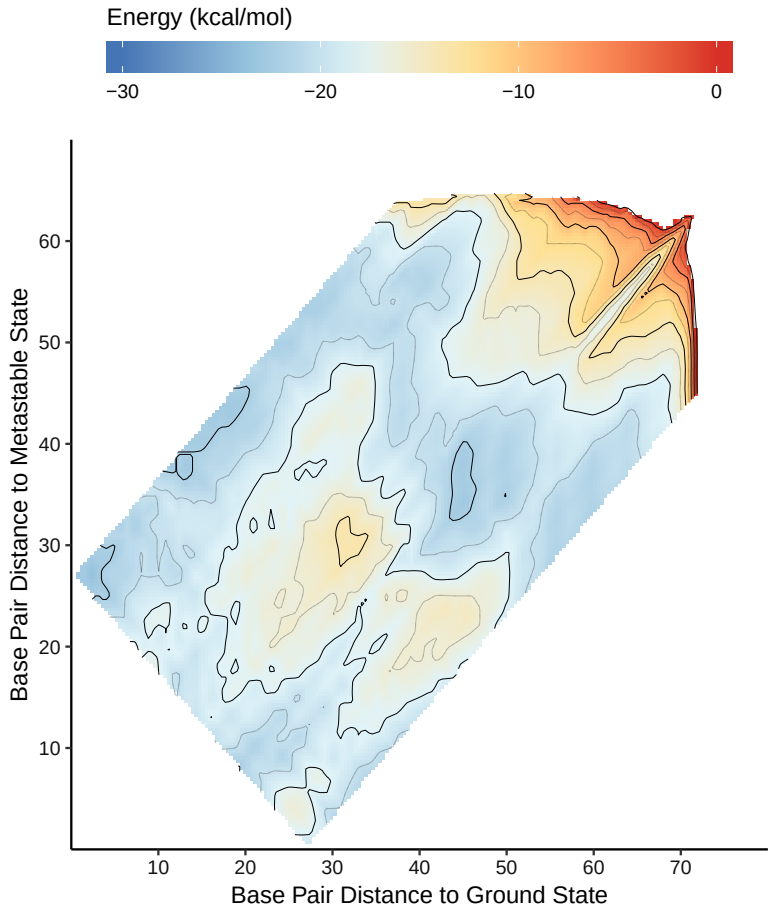

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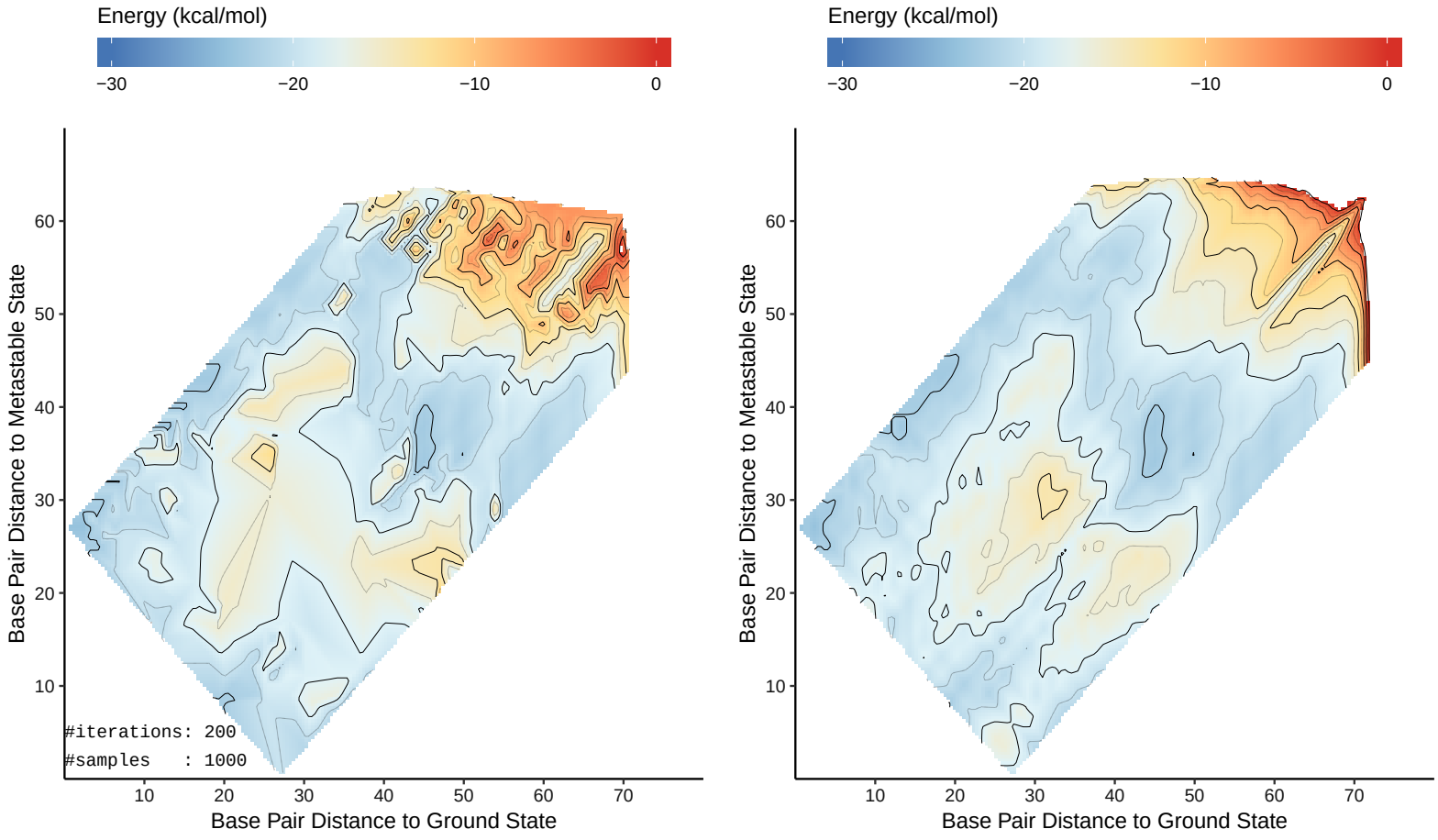

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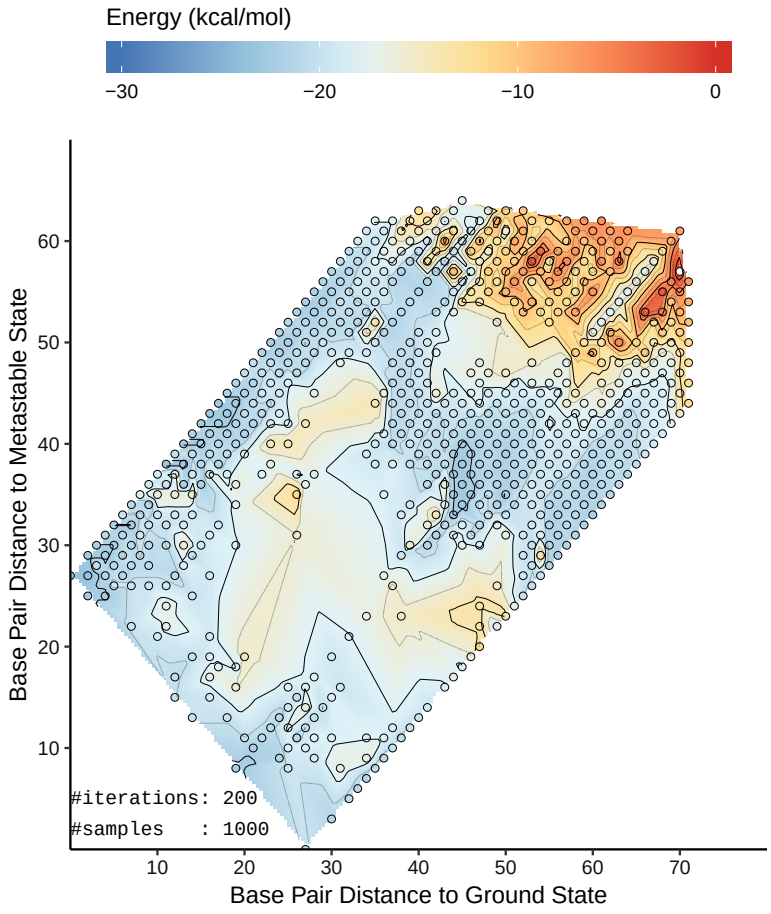

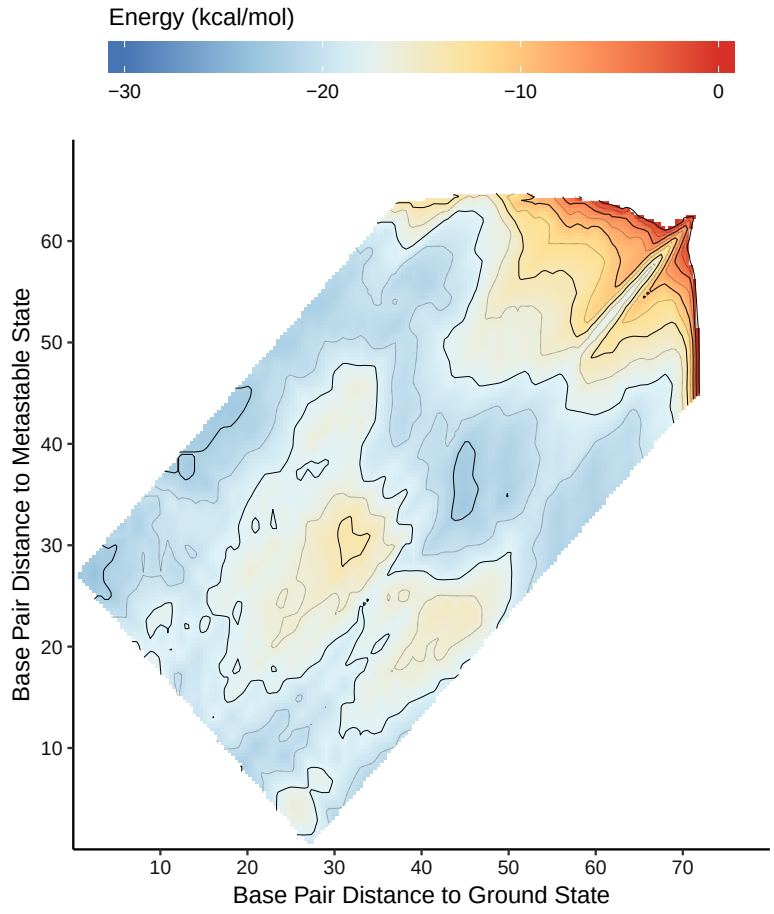

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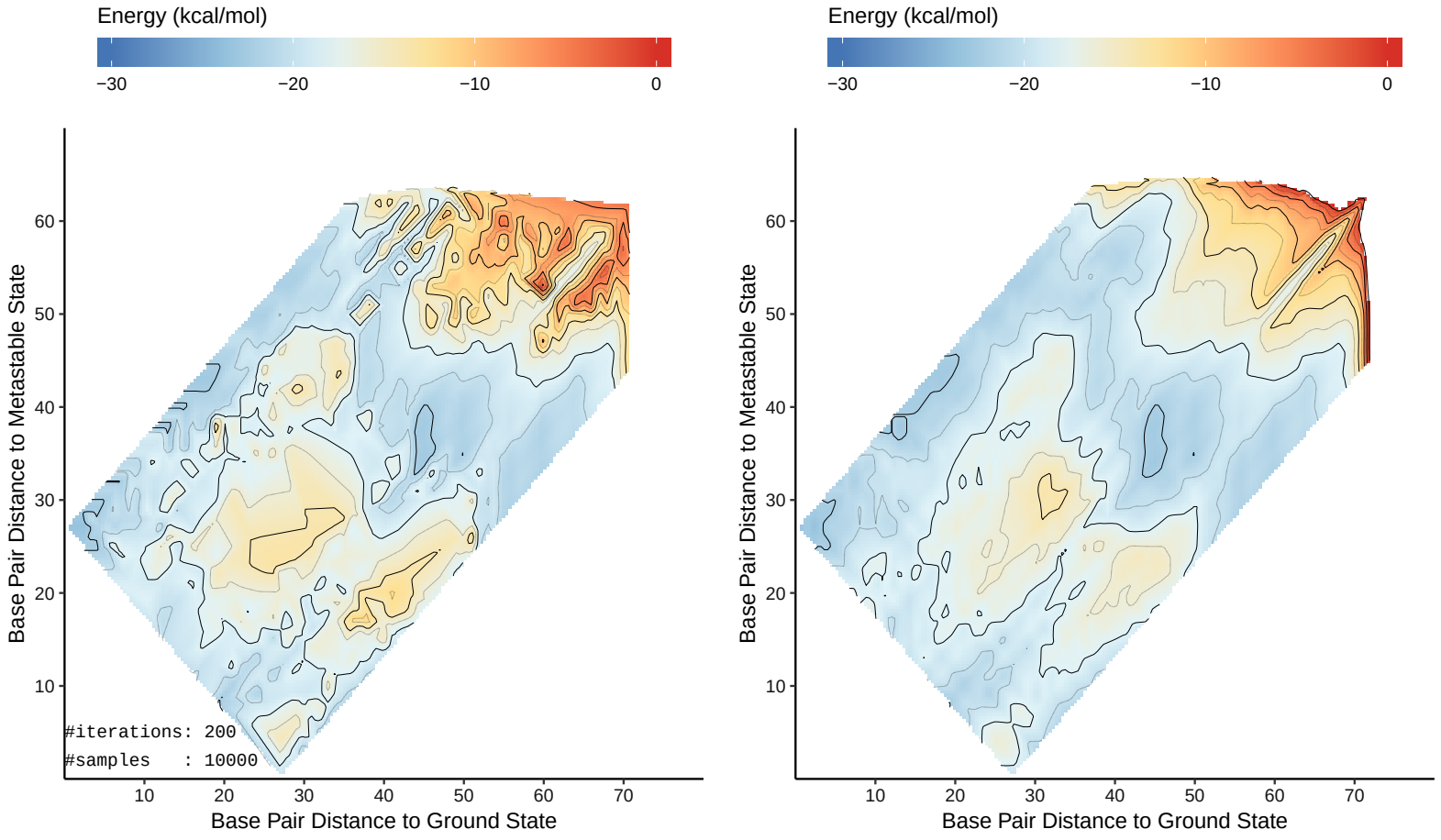

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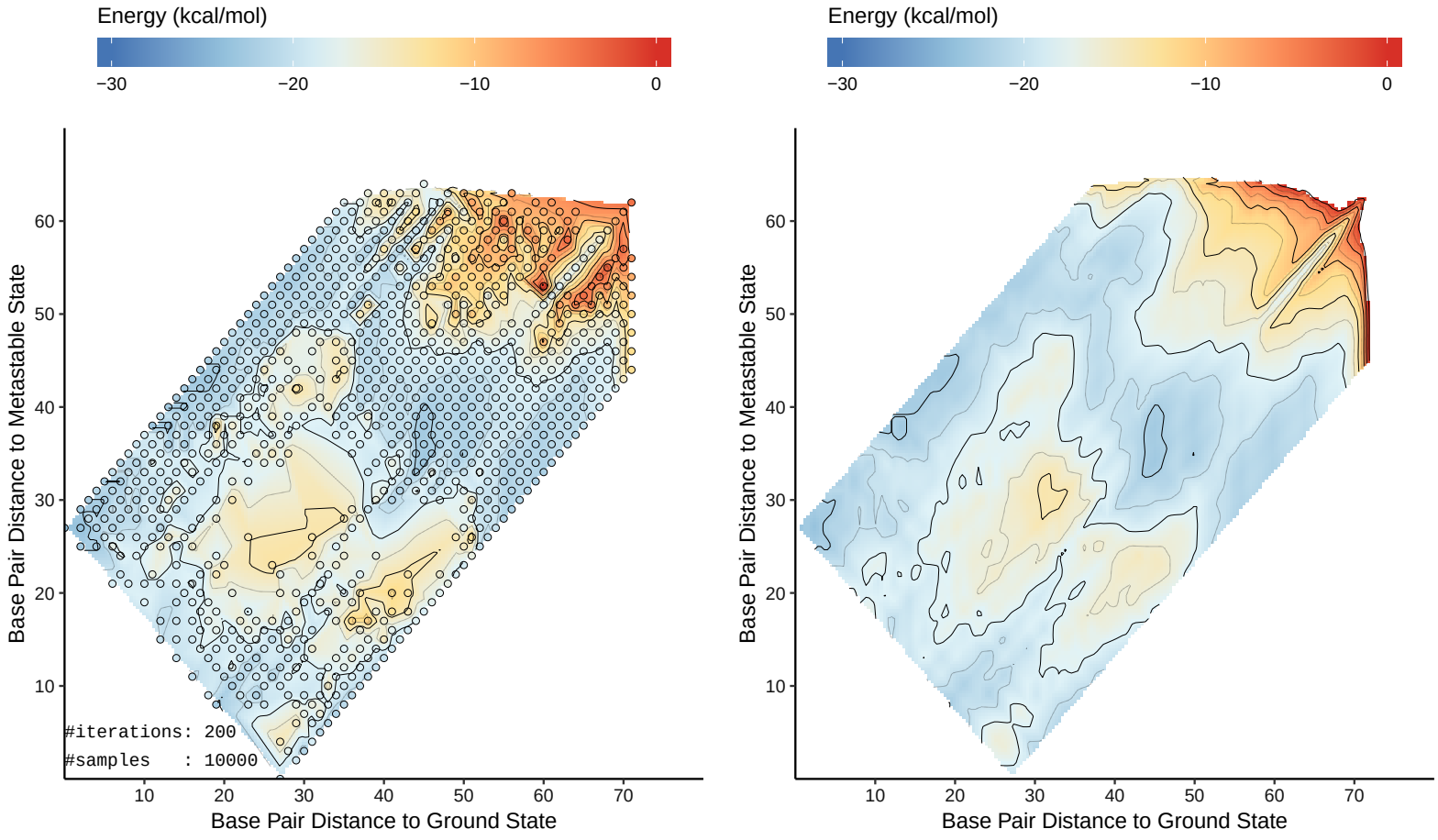

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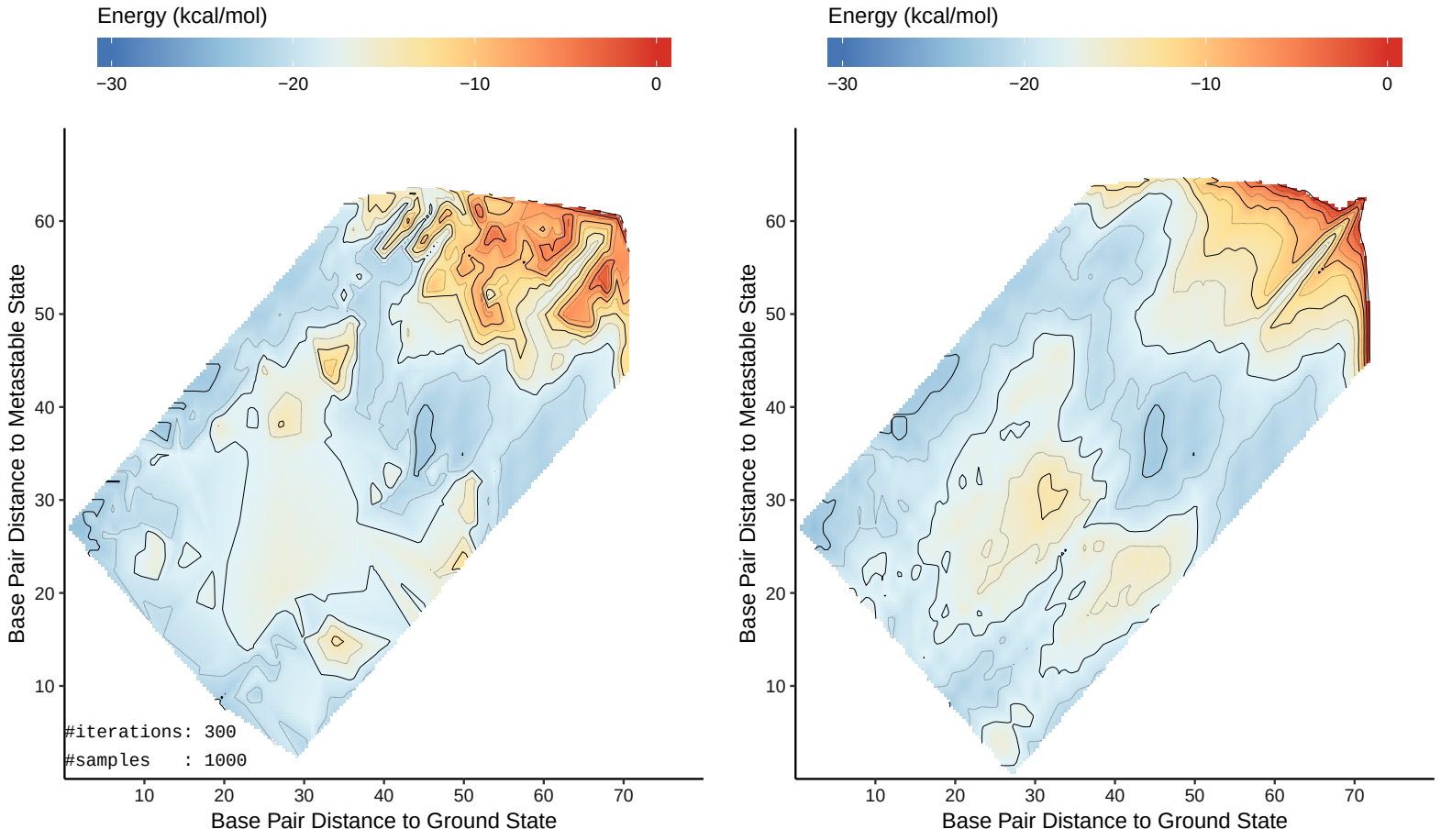

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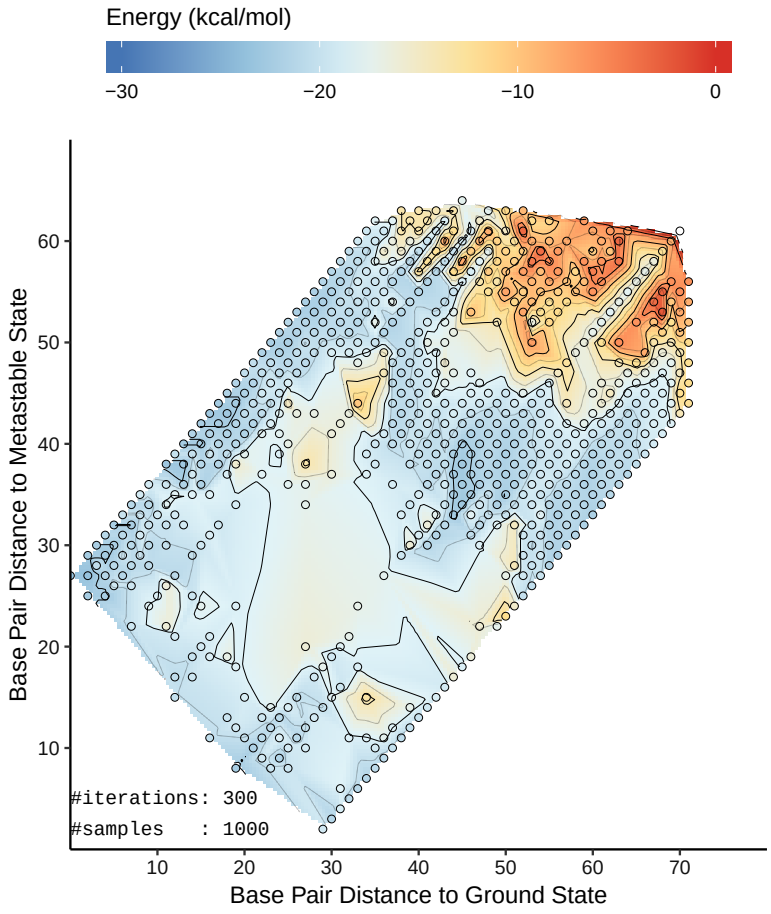

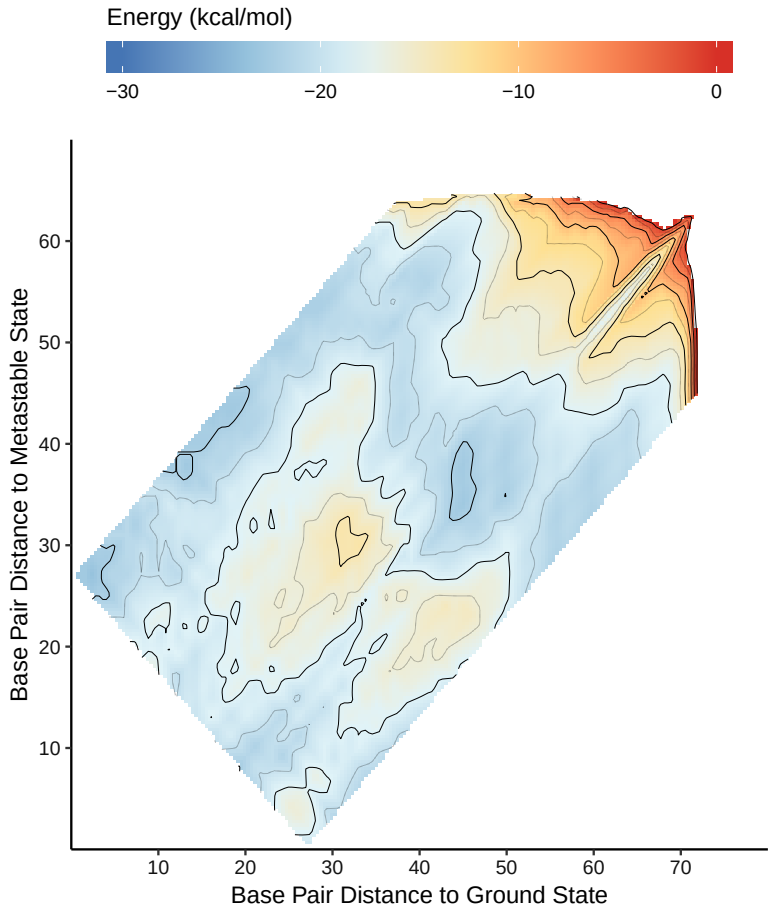

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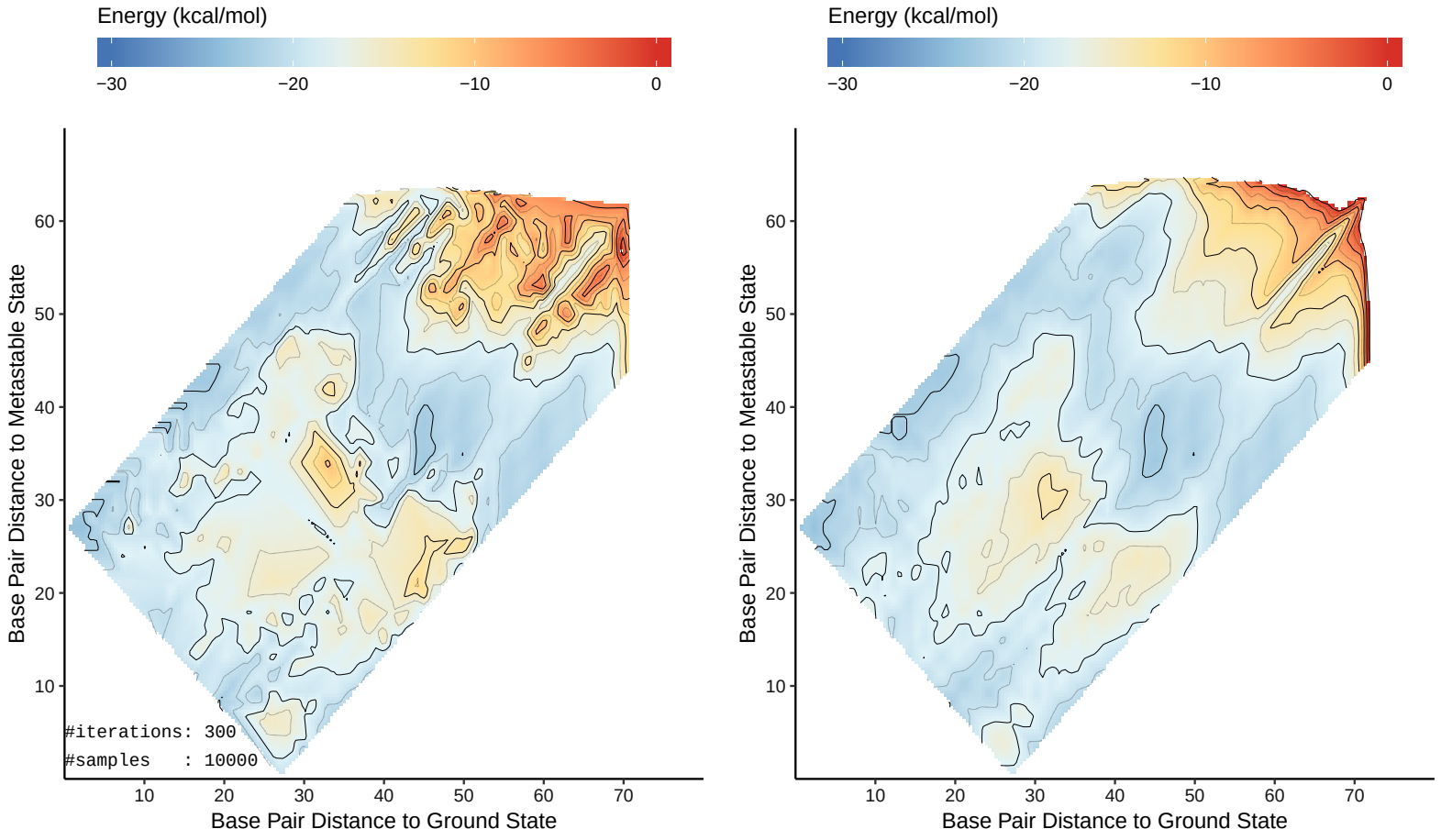
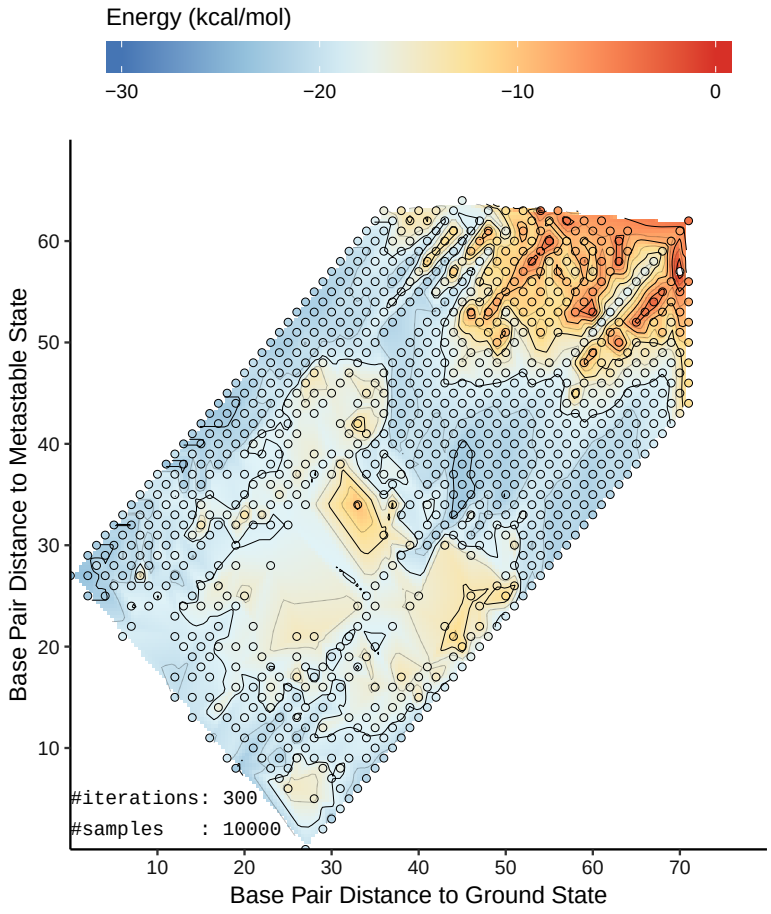
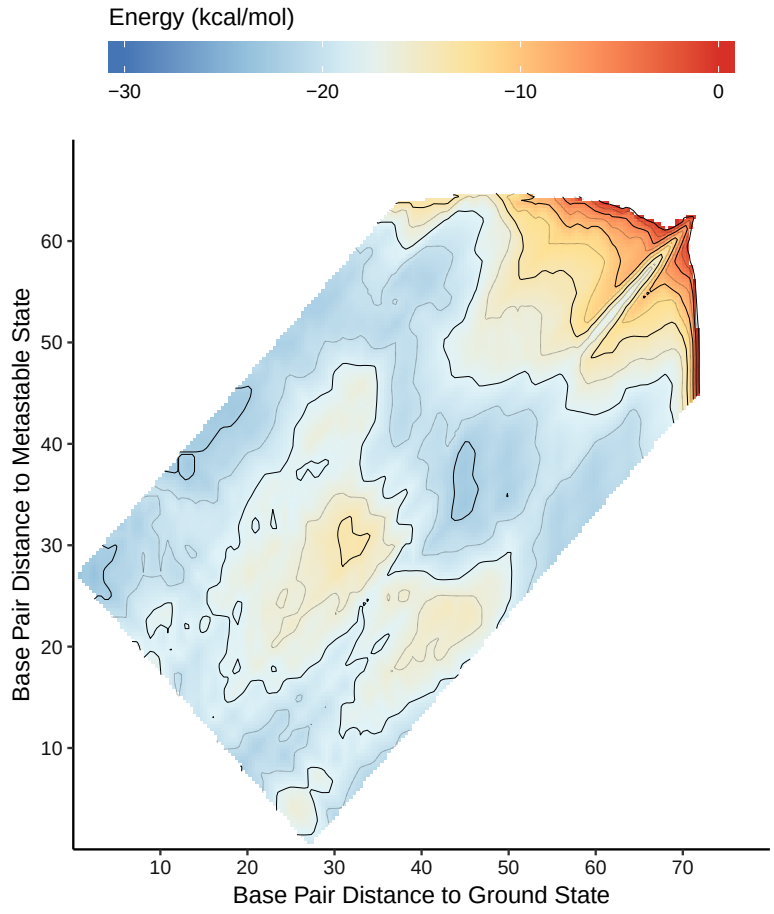
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



Example: add riboswitch V.culnificus

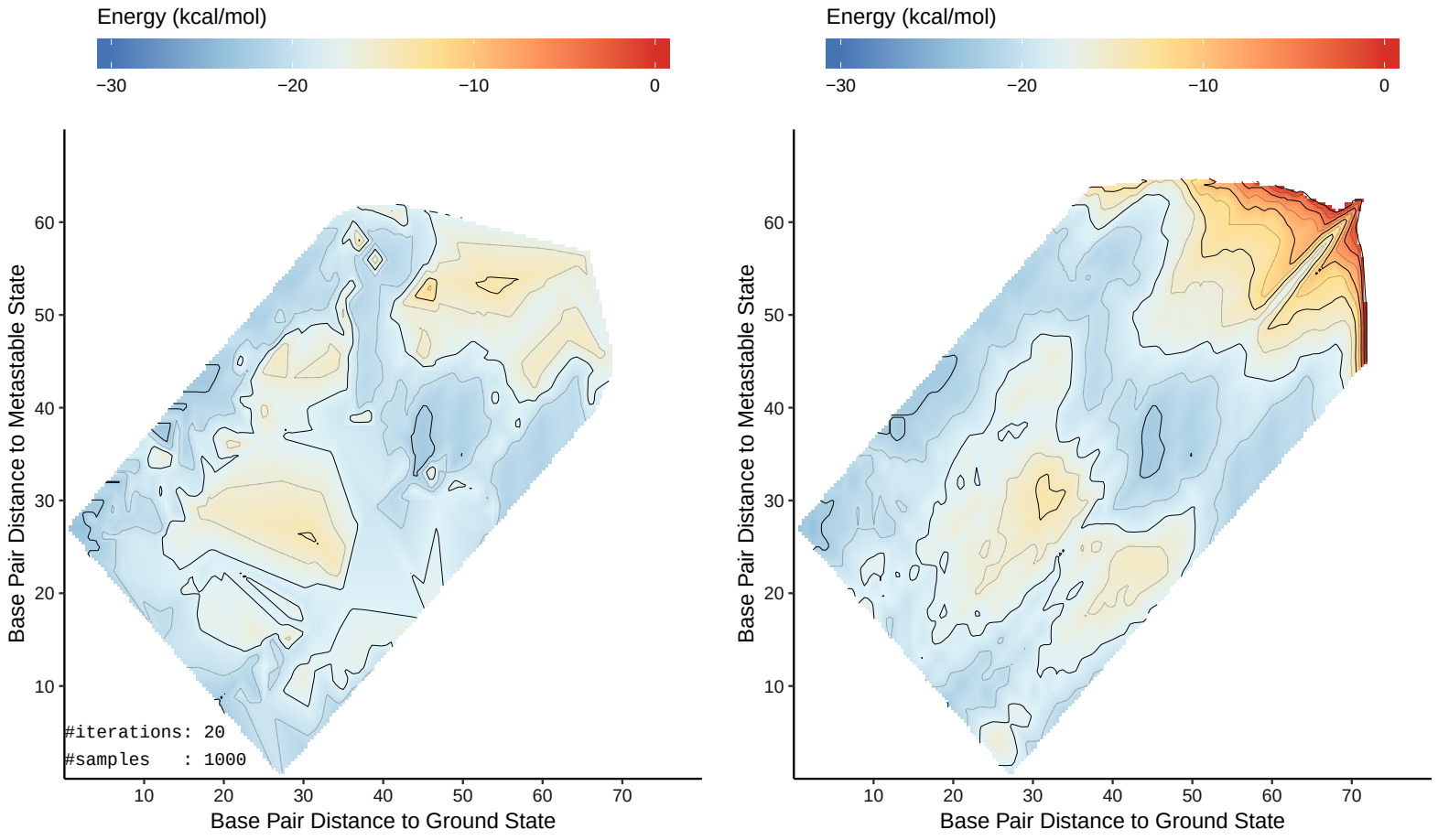
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*





Example: add riboswitch V.culnificus

`RNAlocmin` temperature elevation scheme Boltzmann sampling



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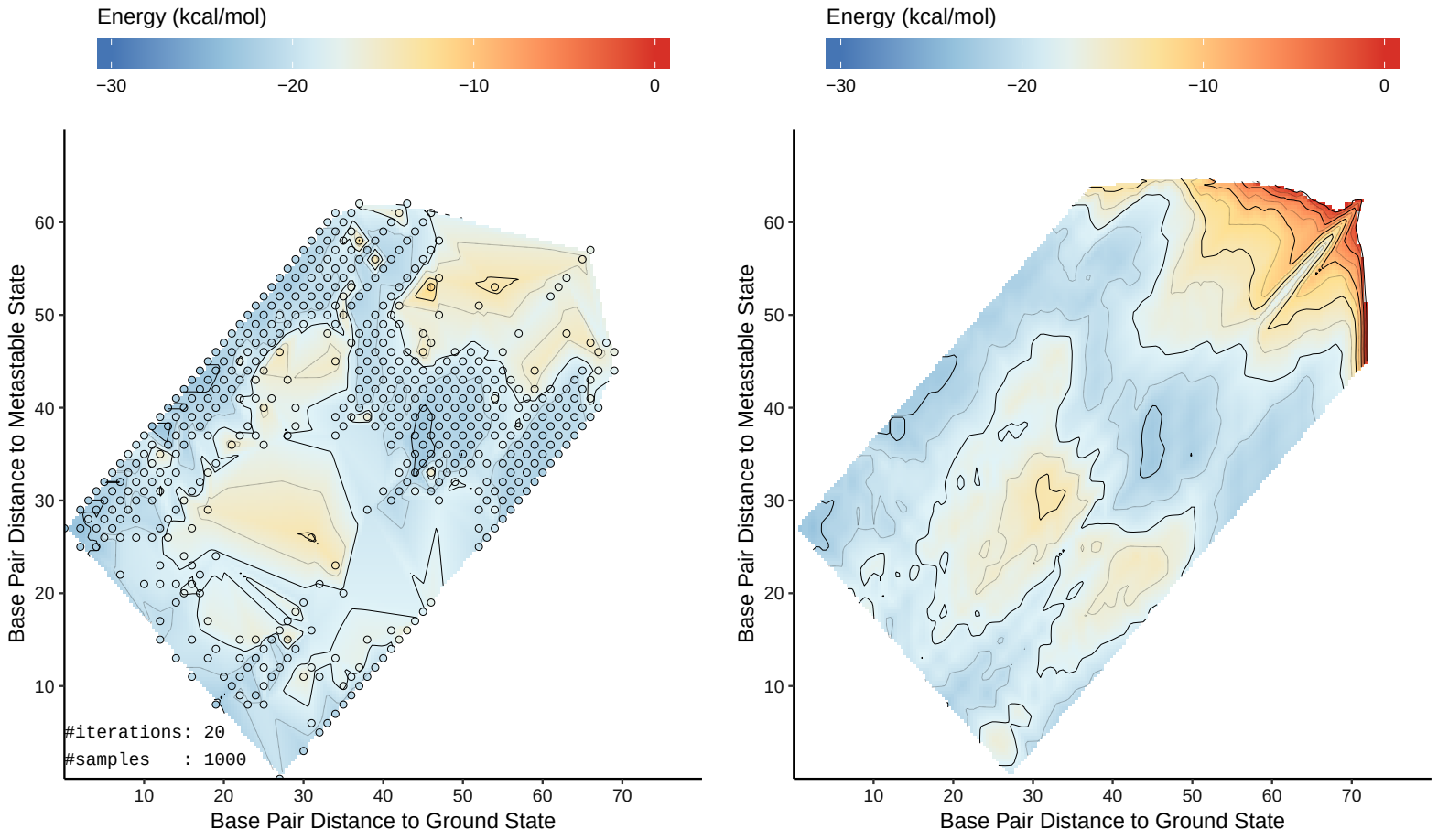
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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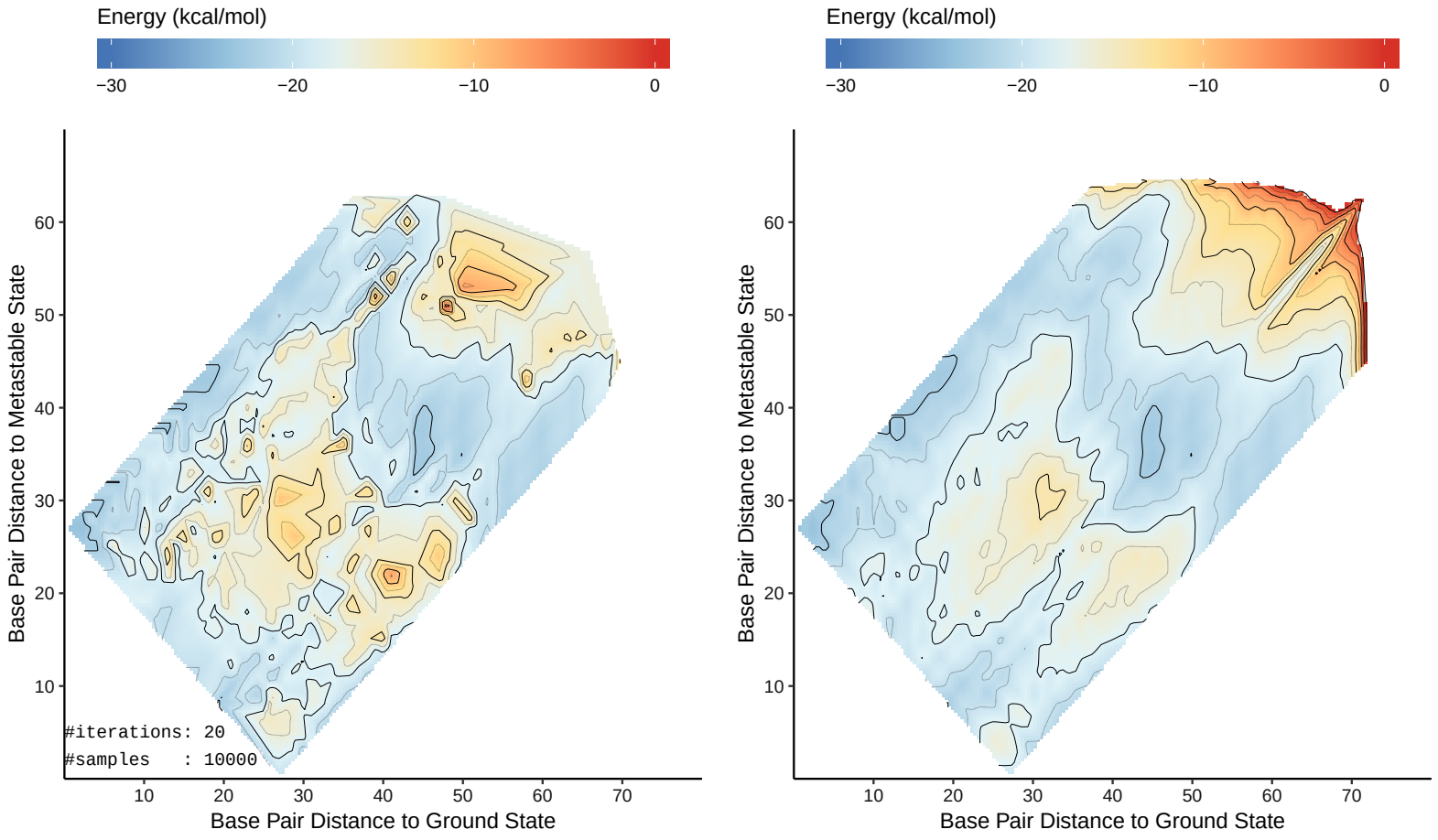
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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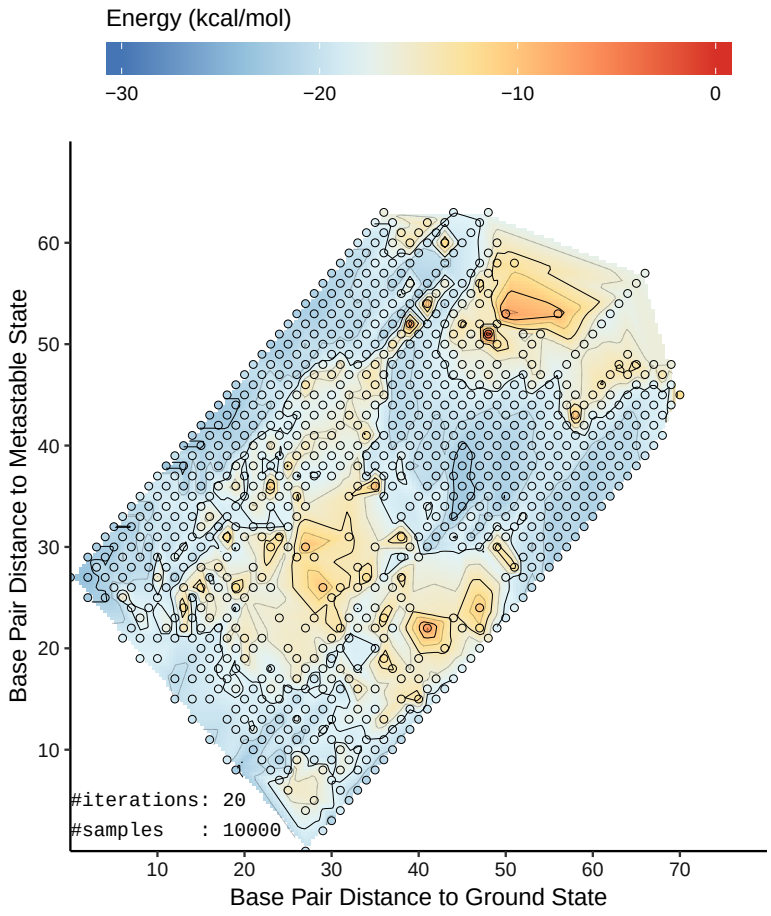
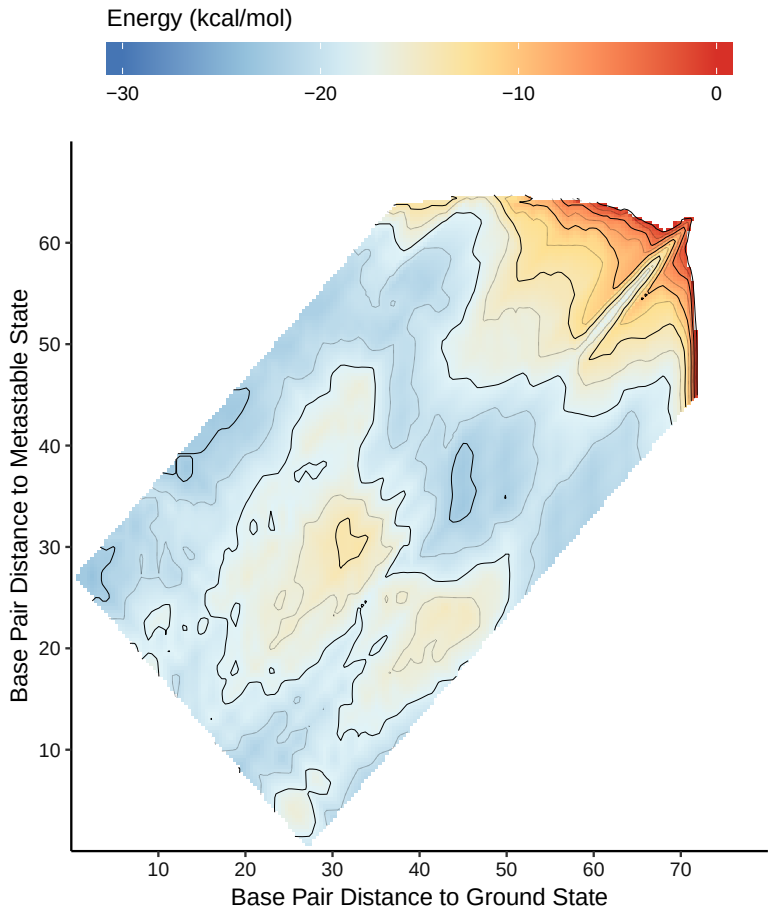
`RNAlocmin` temperature elevation scheme Boltzmann sampling





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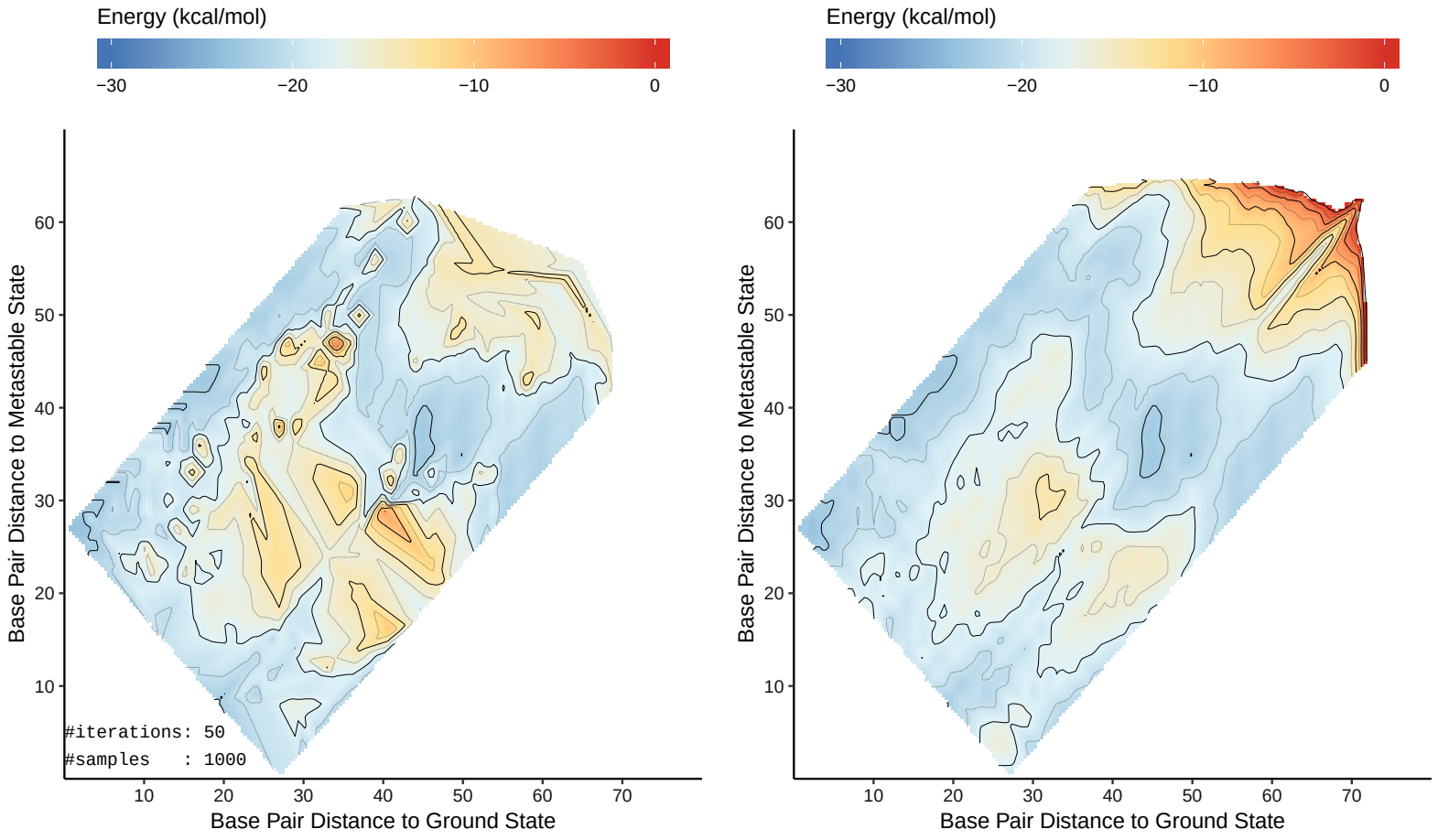
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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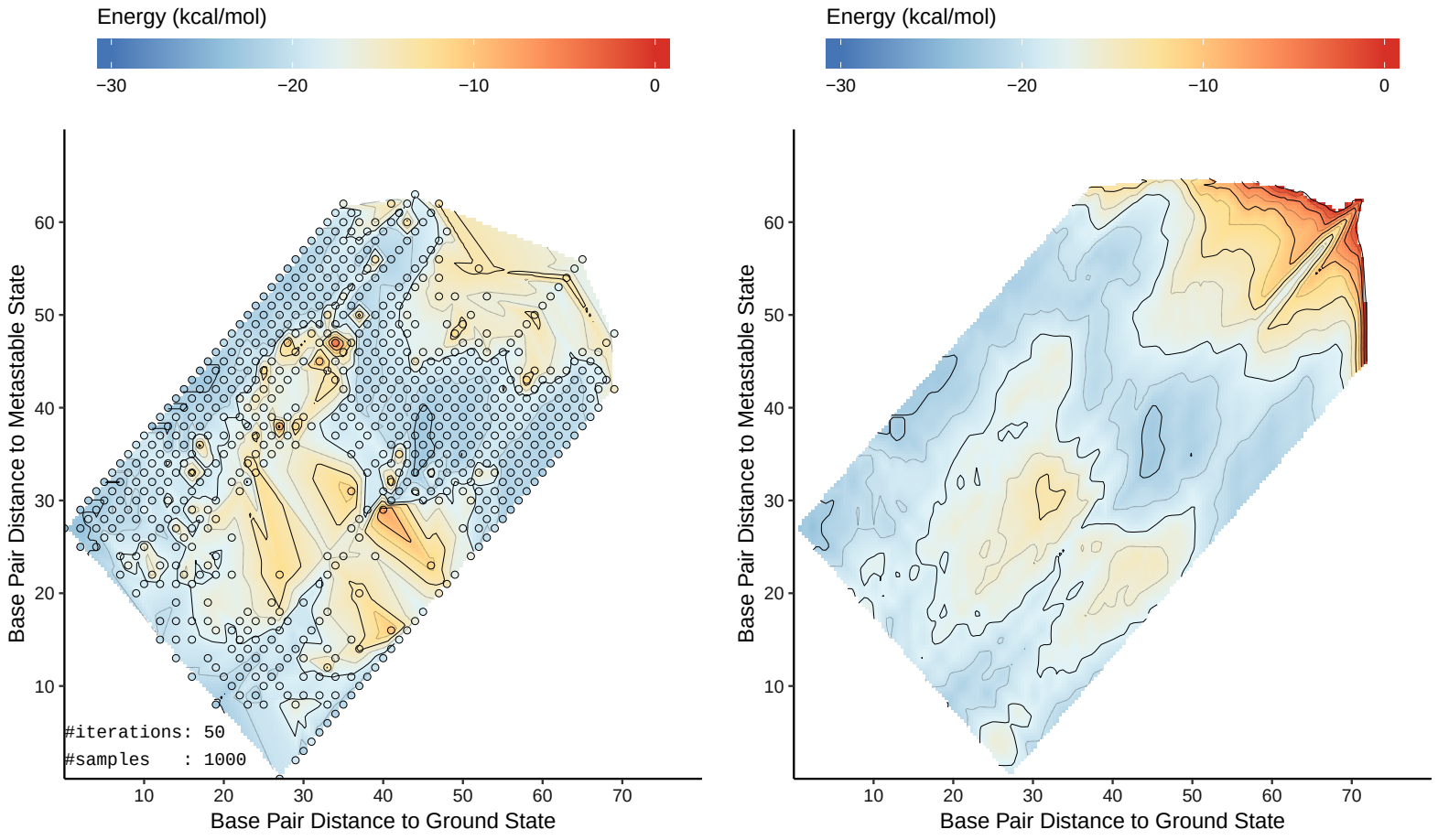
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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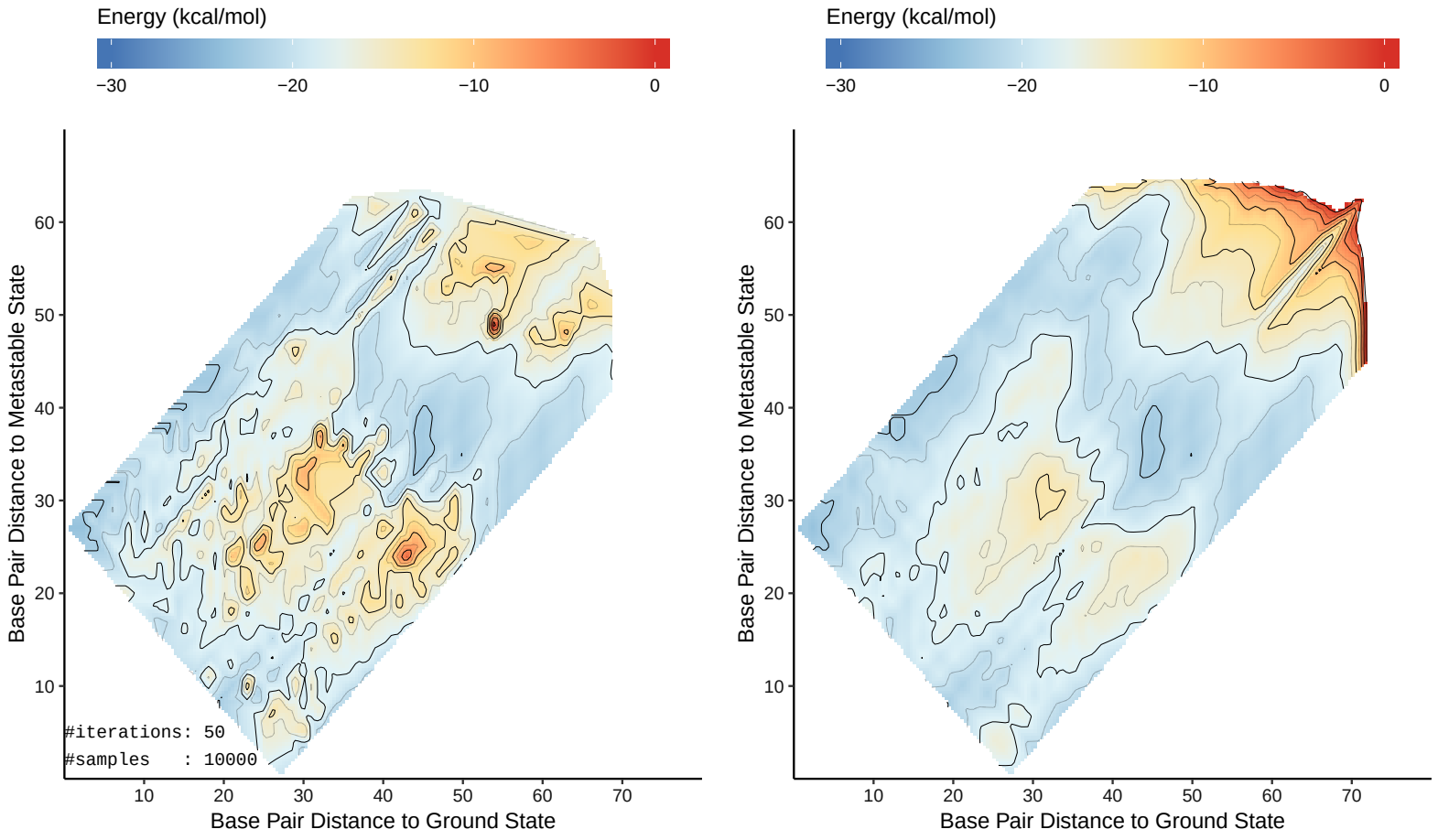

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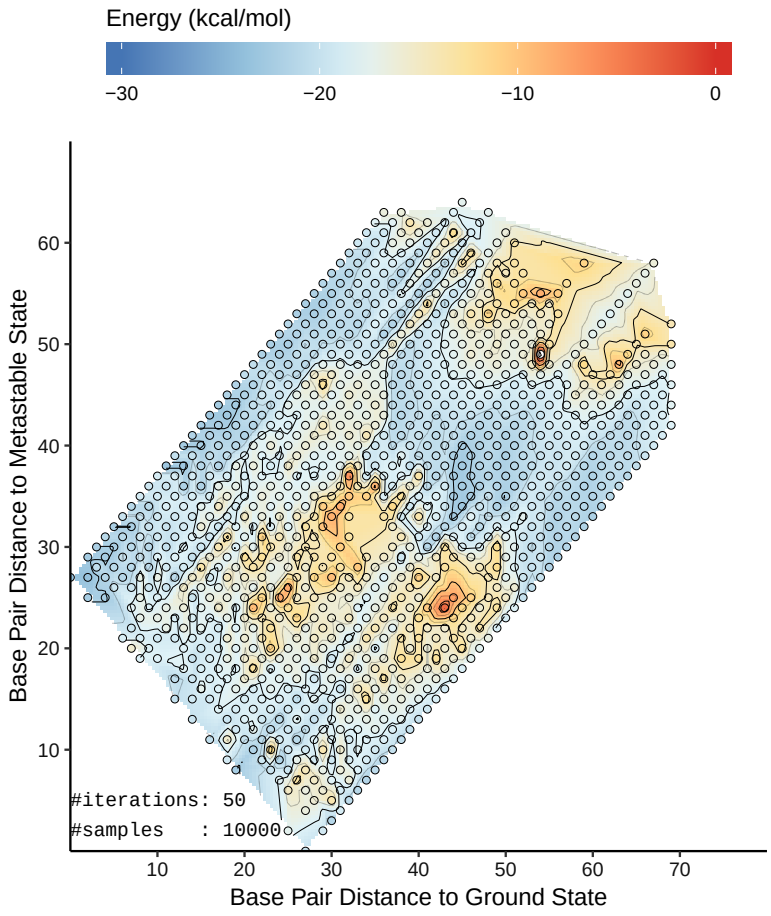
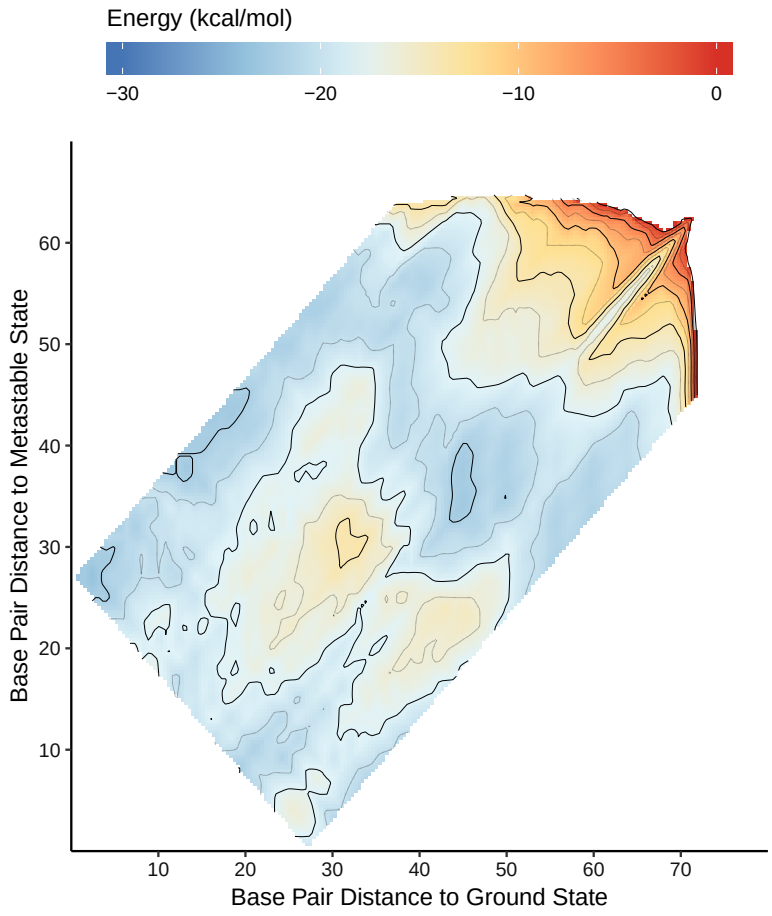
`RNAlocmin` temperature elevation scheme Boltzmann sampling





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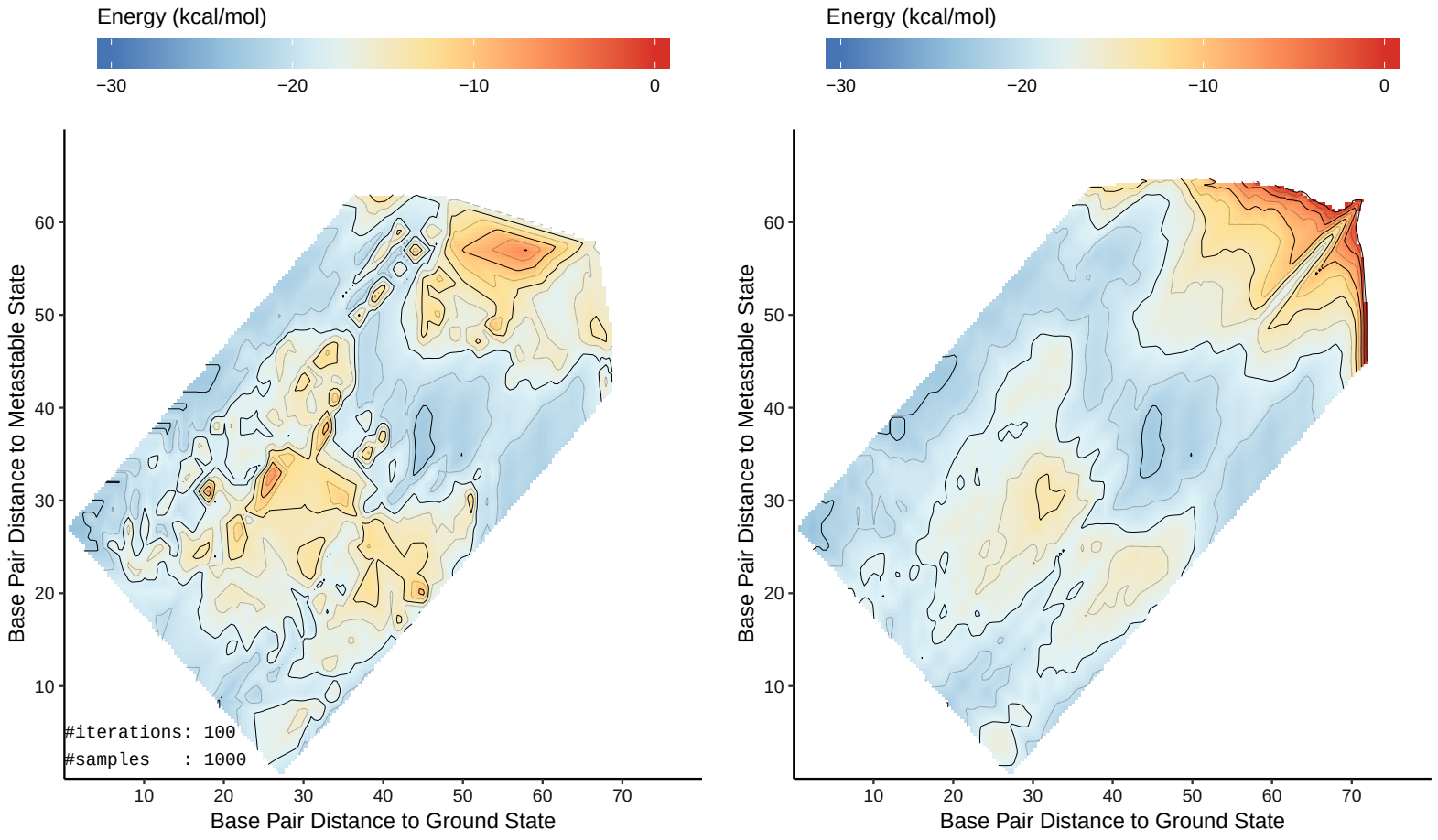

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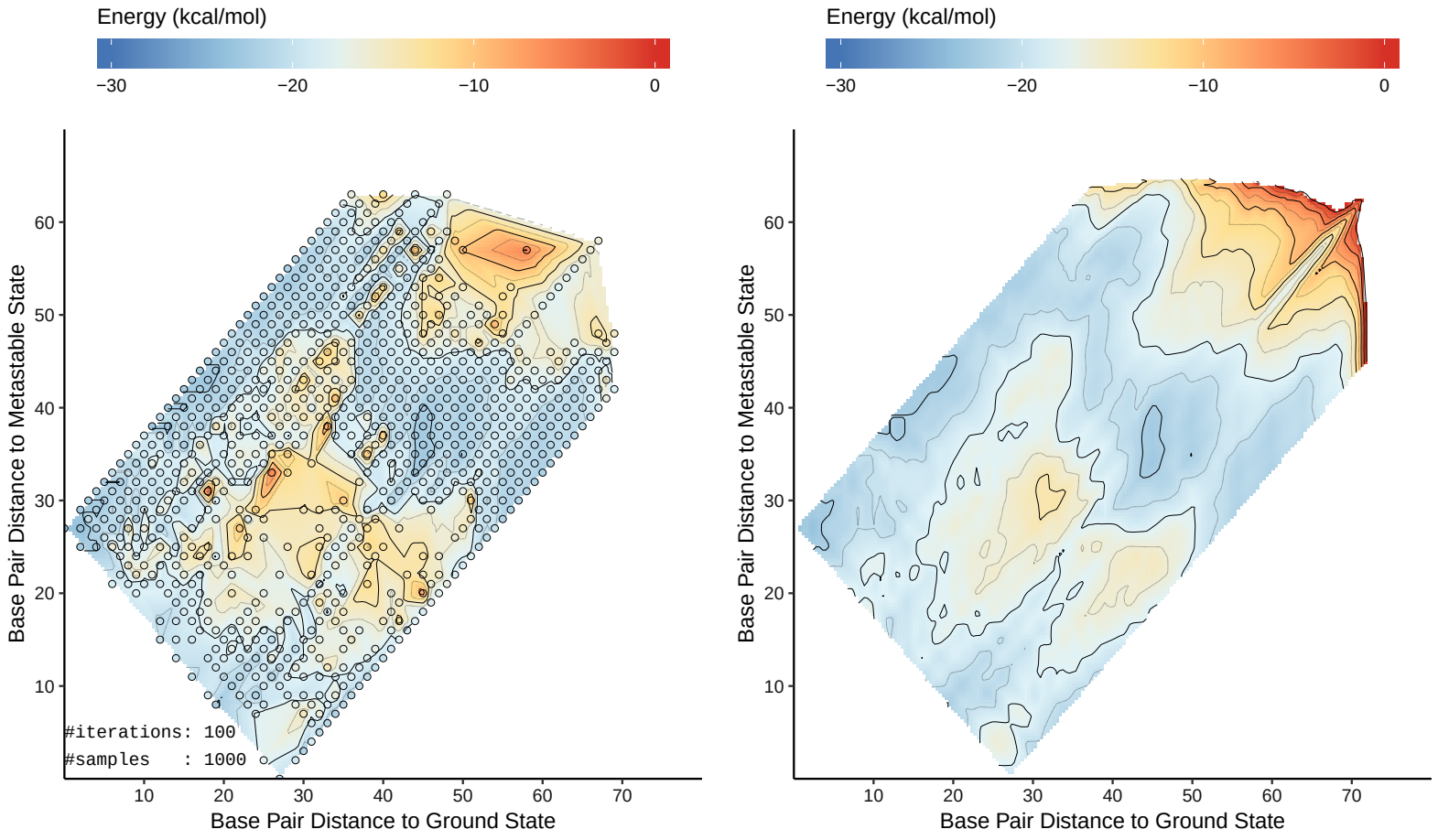
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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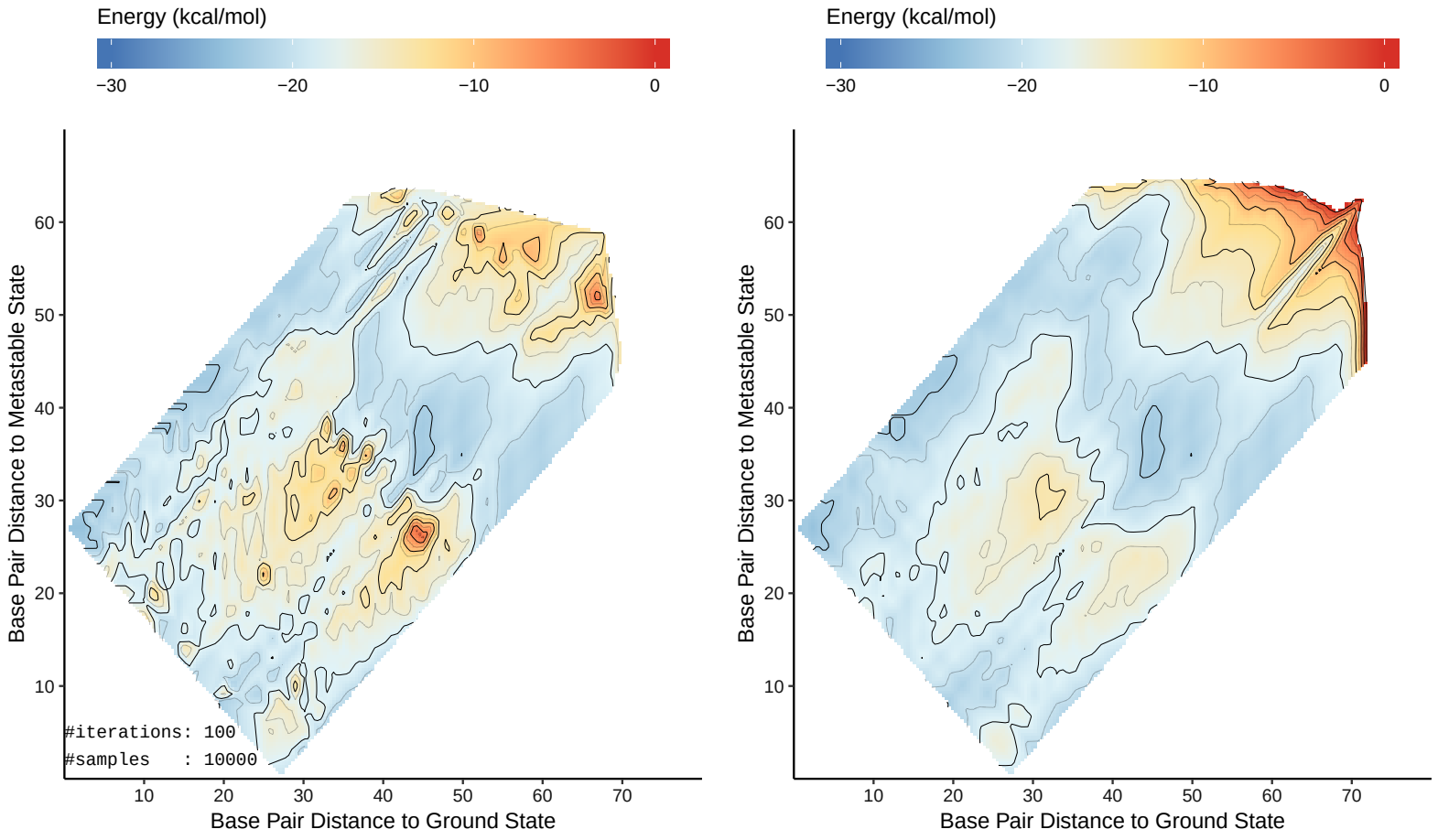

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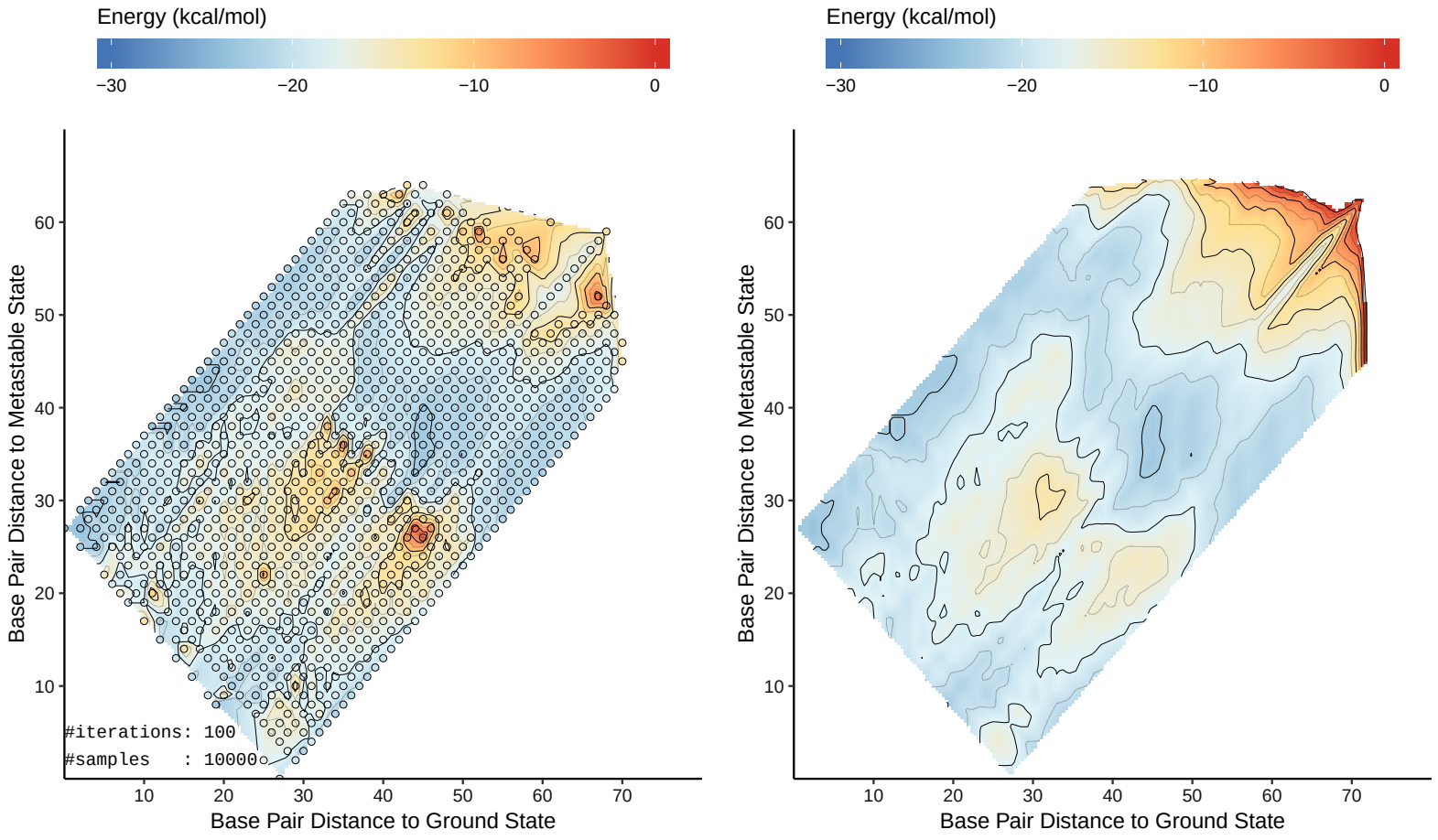

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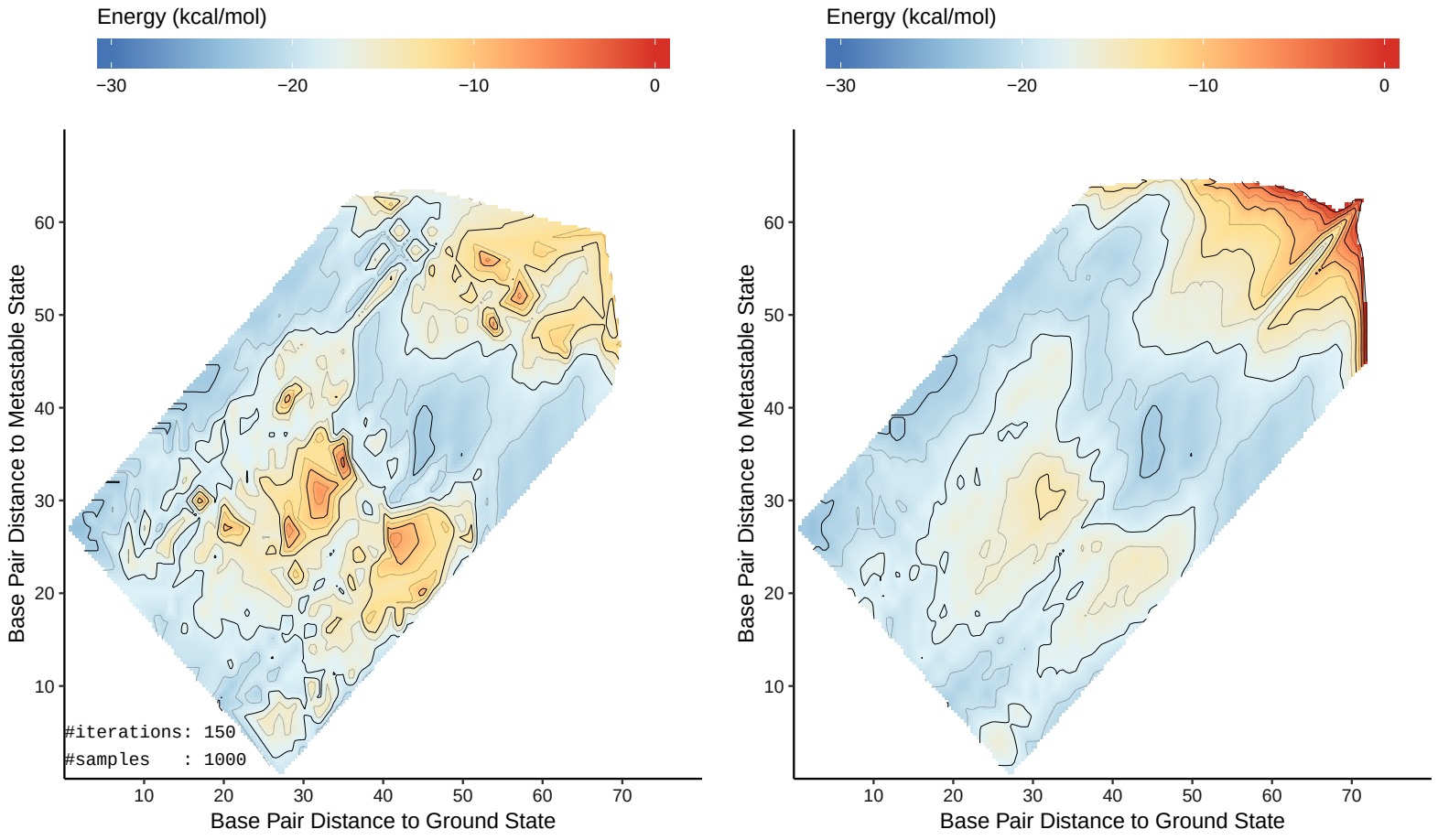

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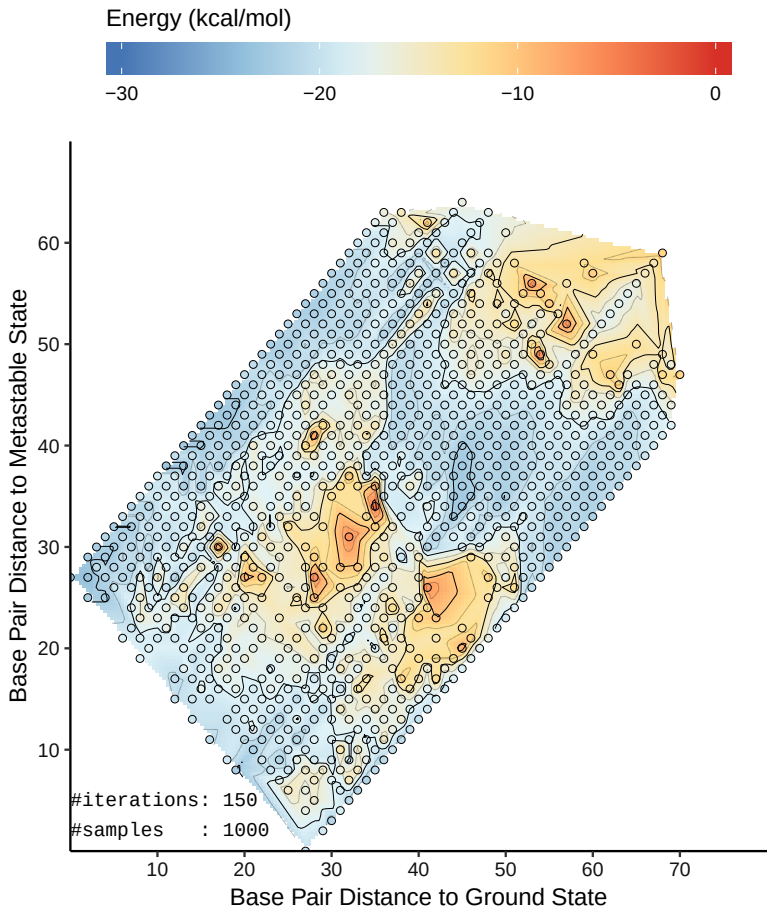

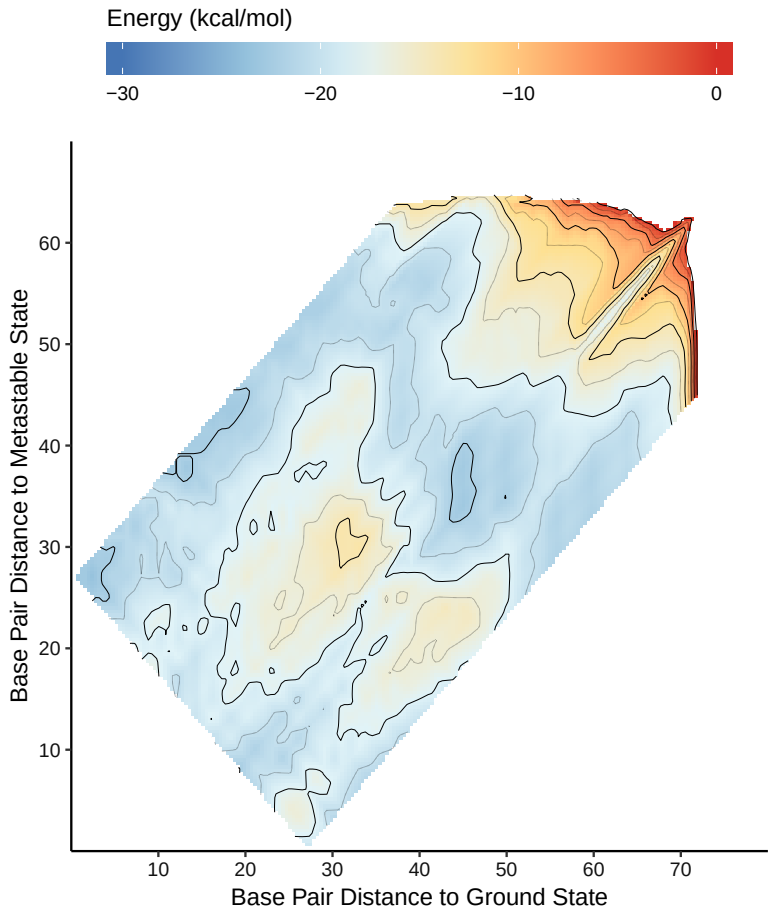

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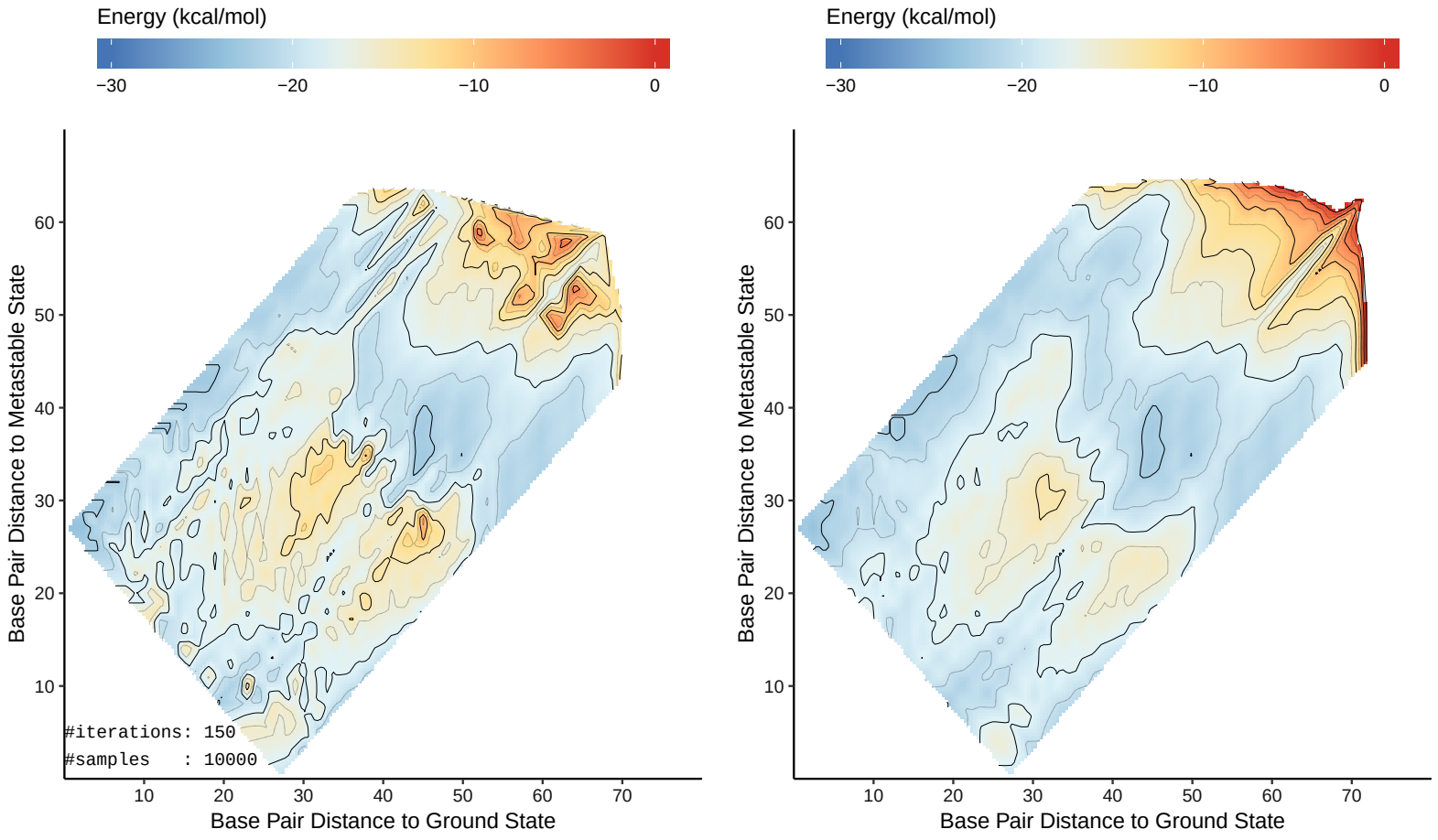

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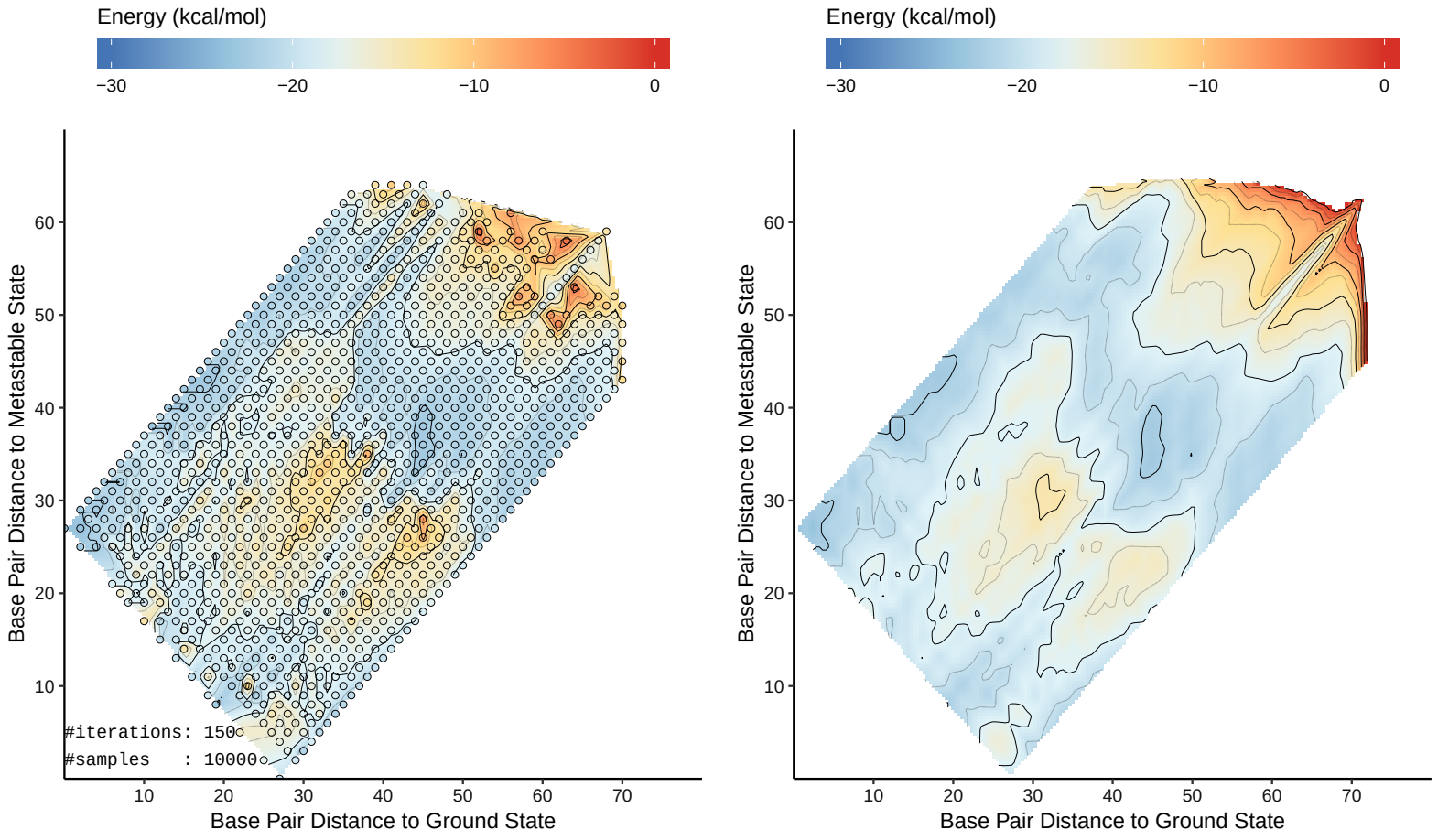

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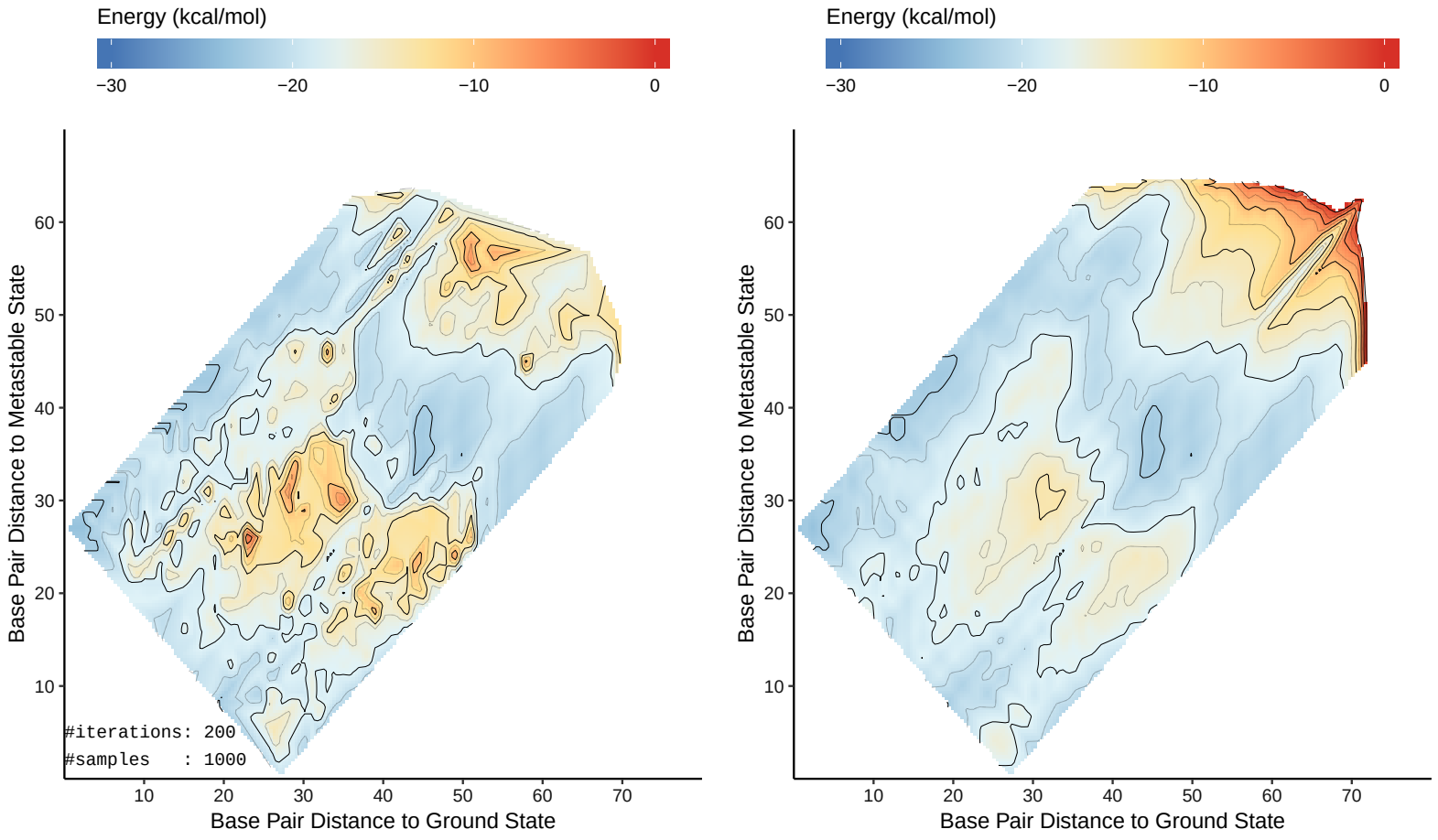

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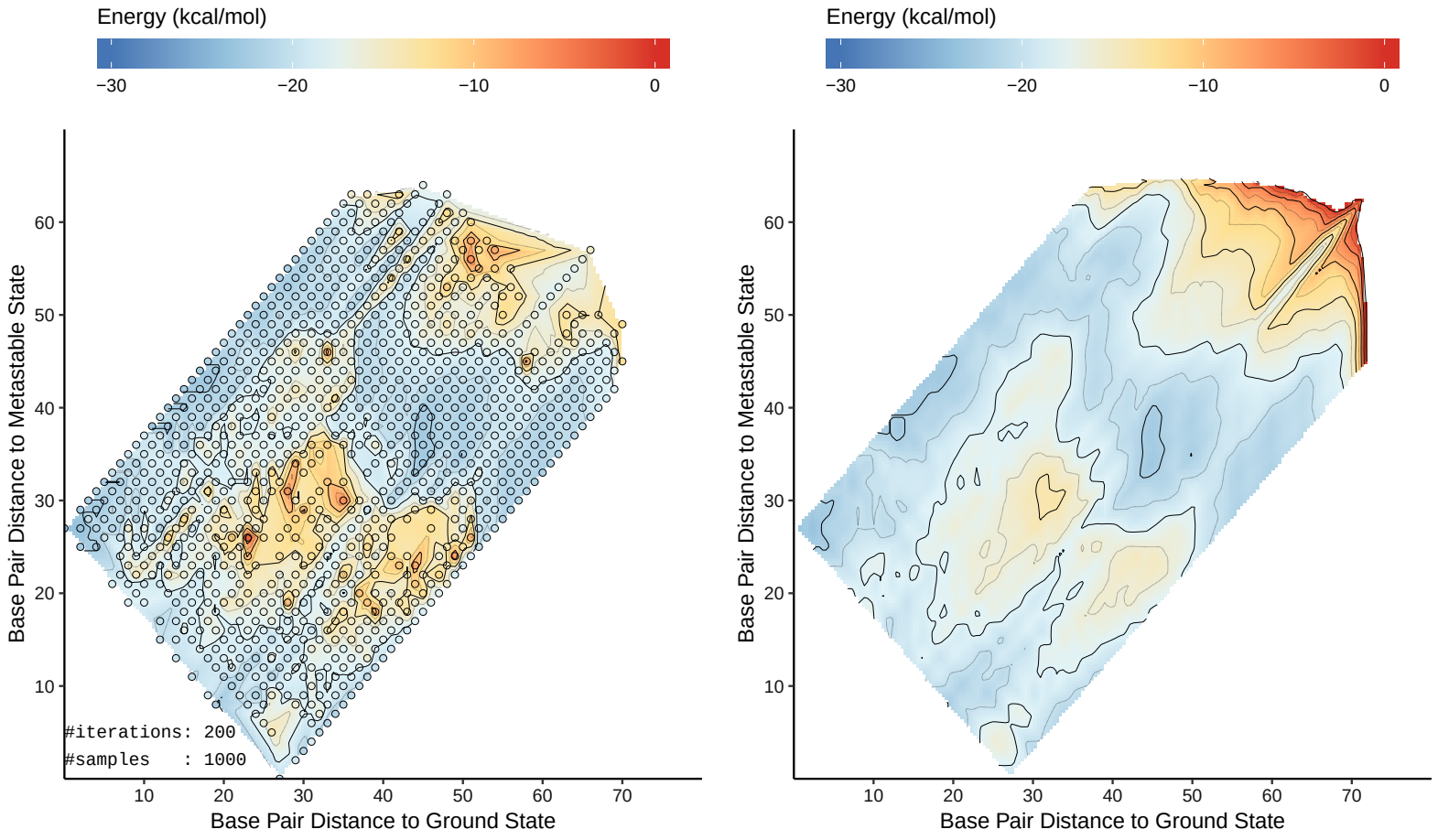

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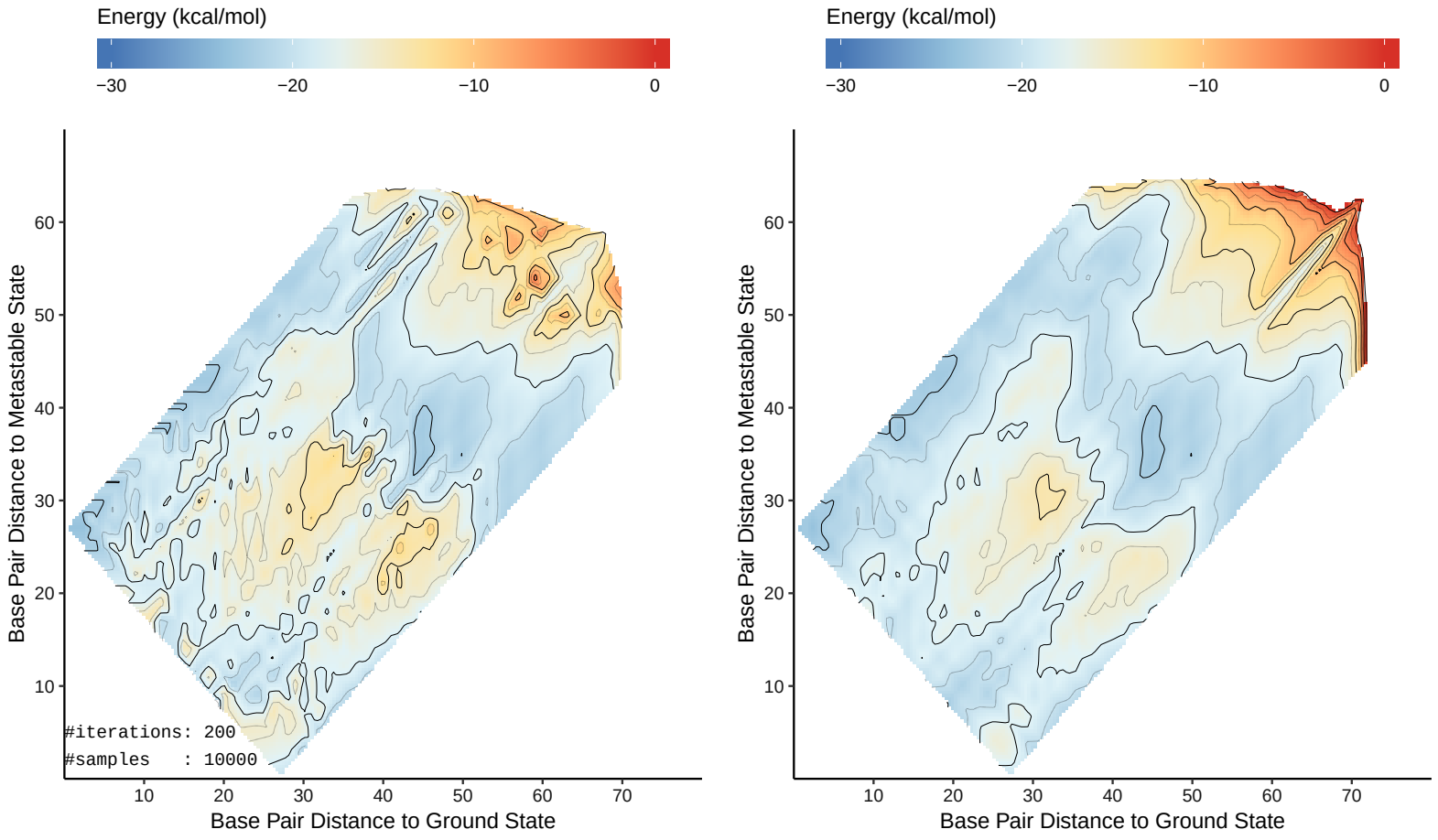

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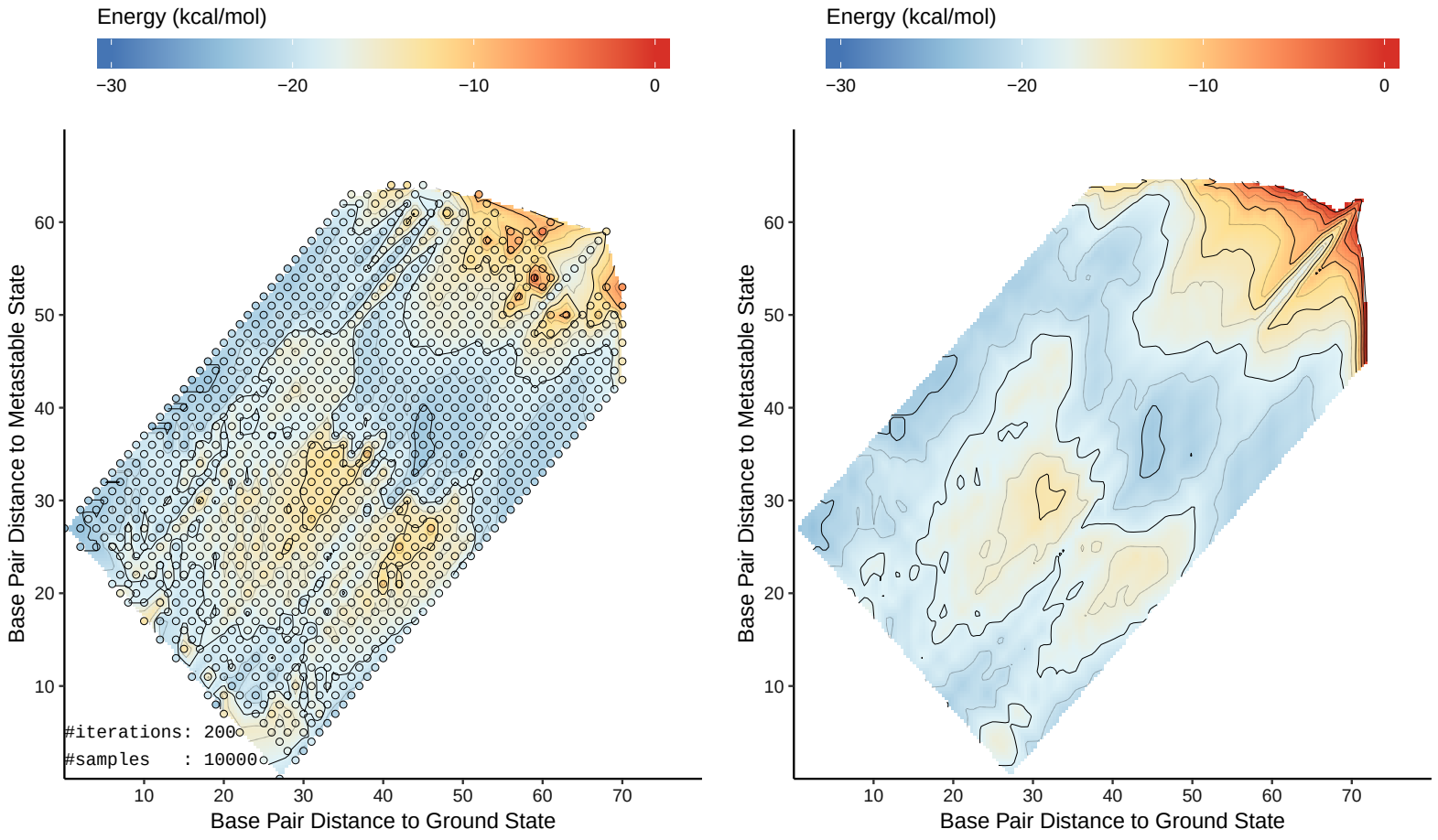

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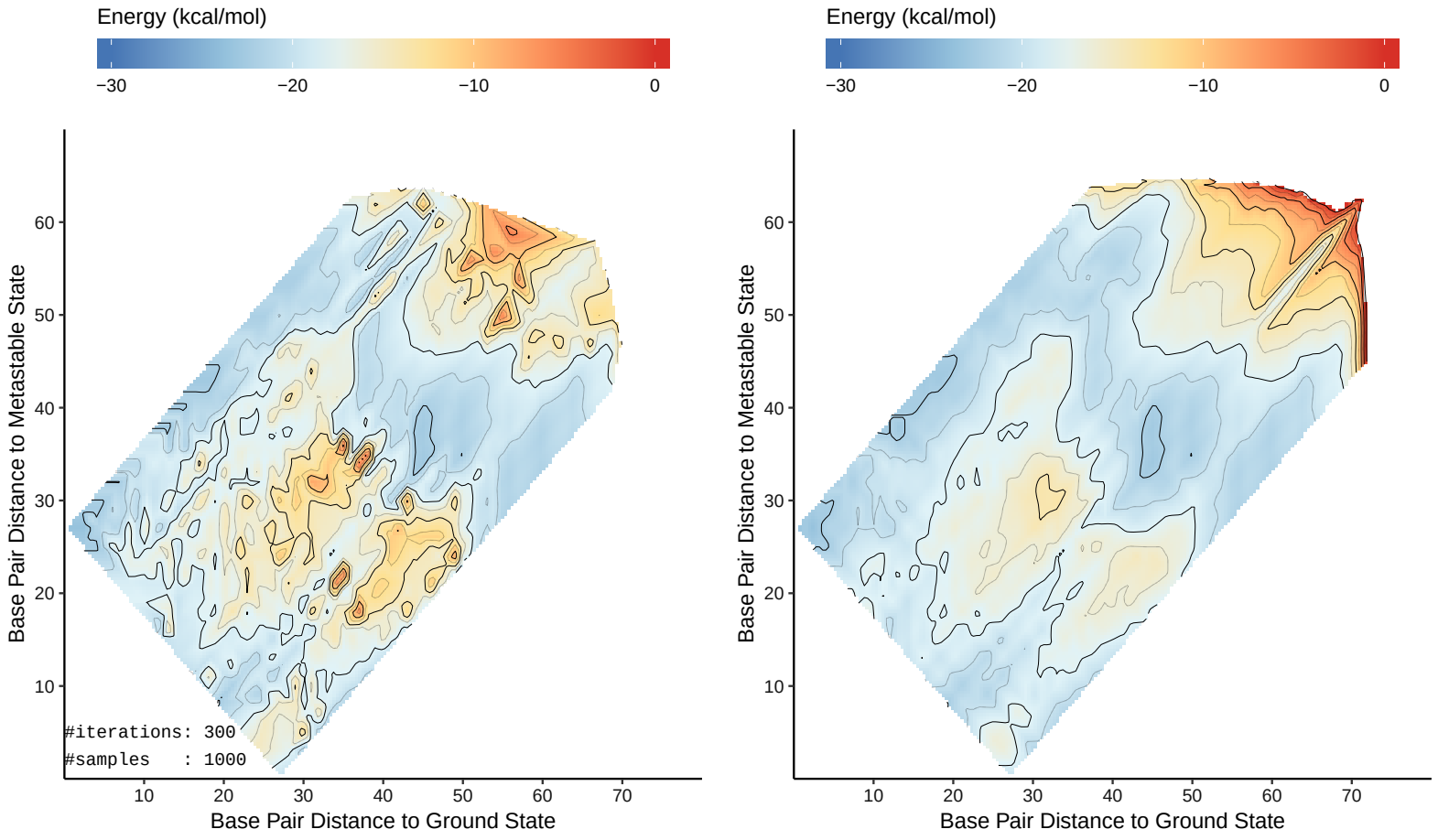

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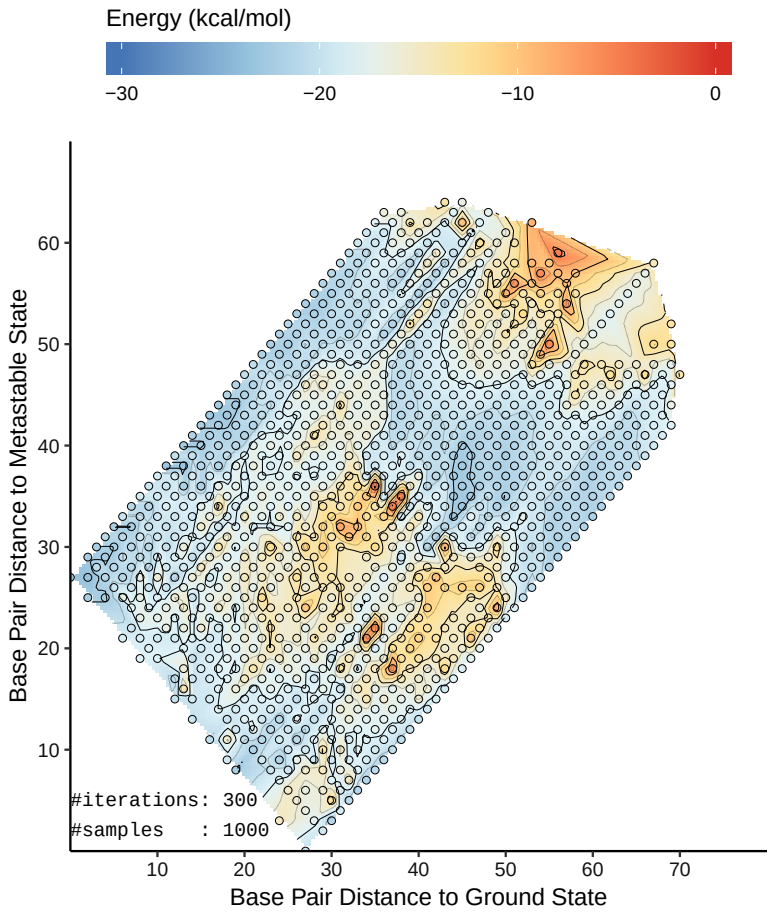

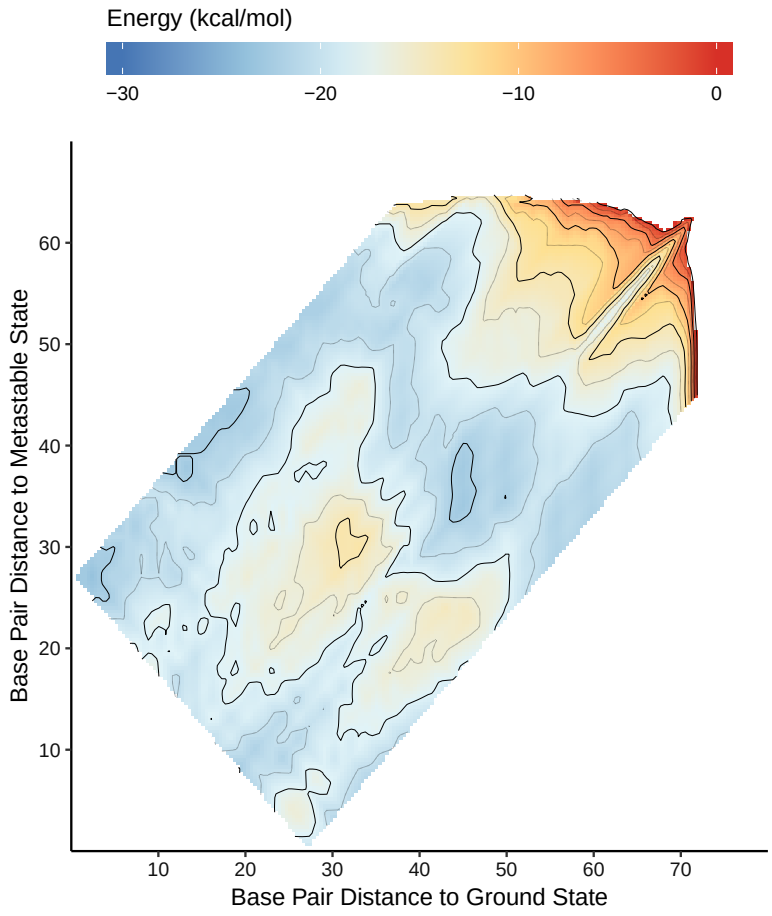

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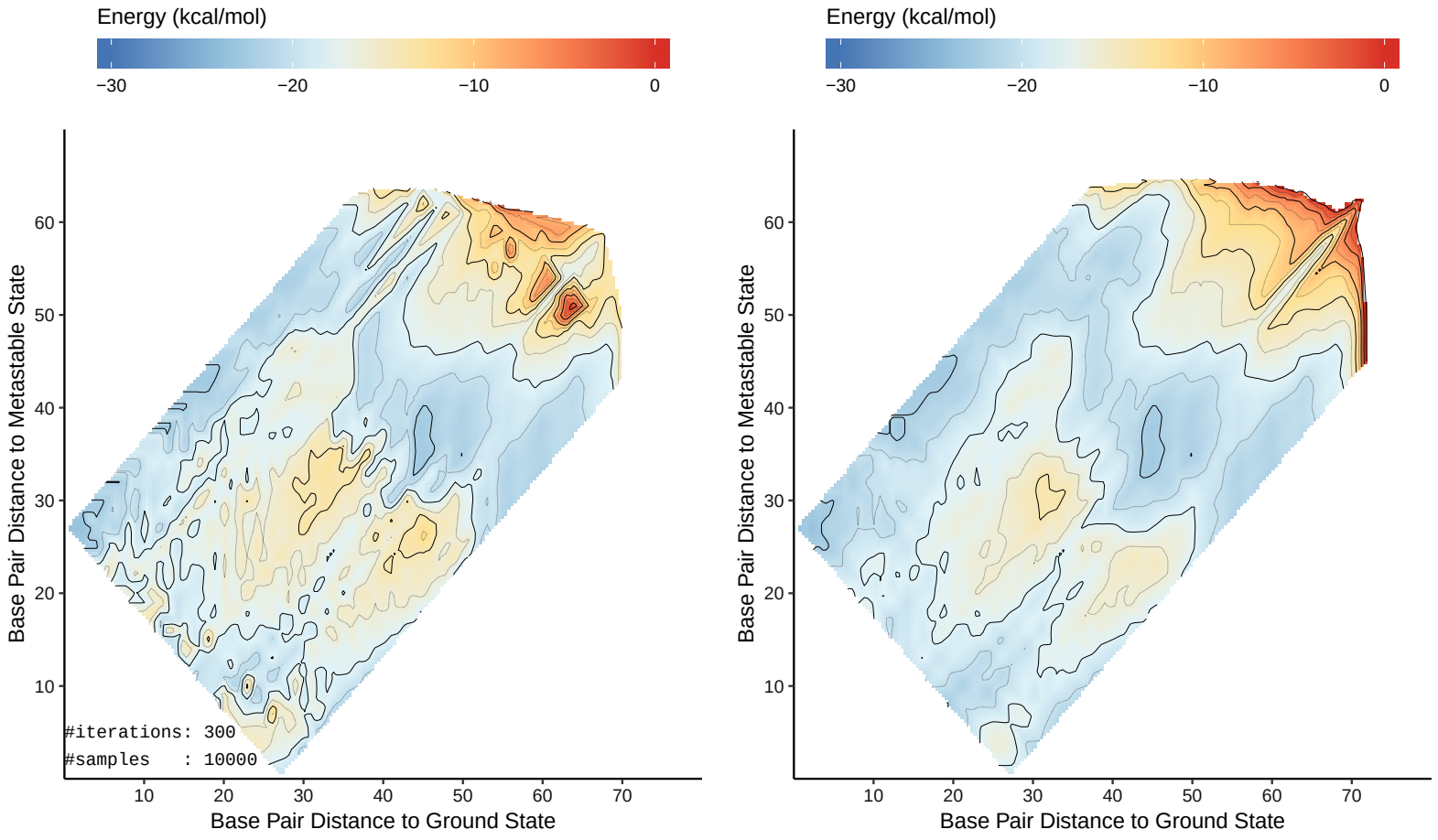

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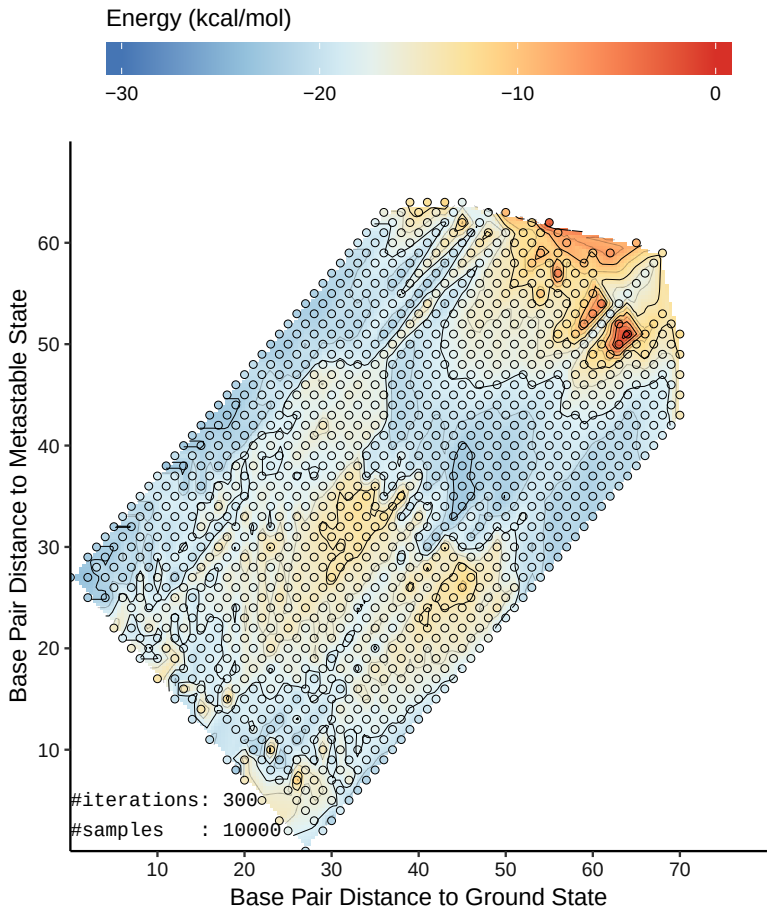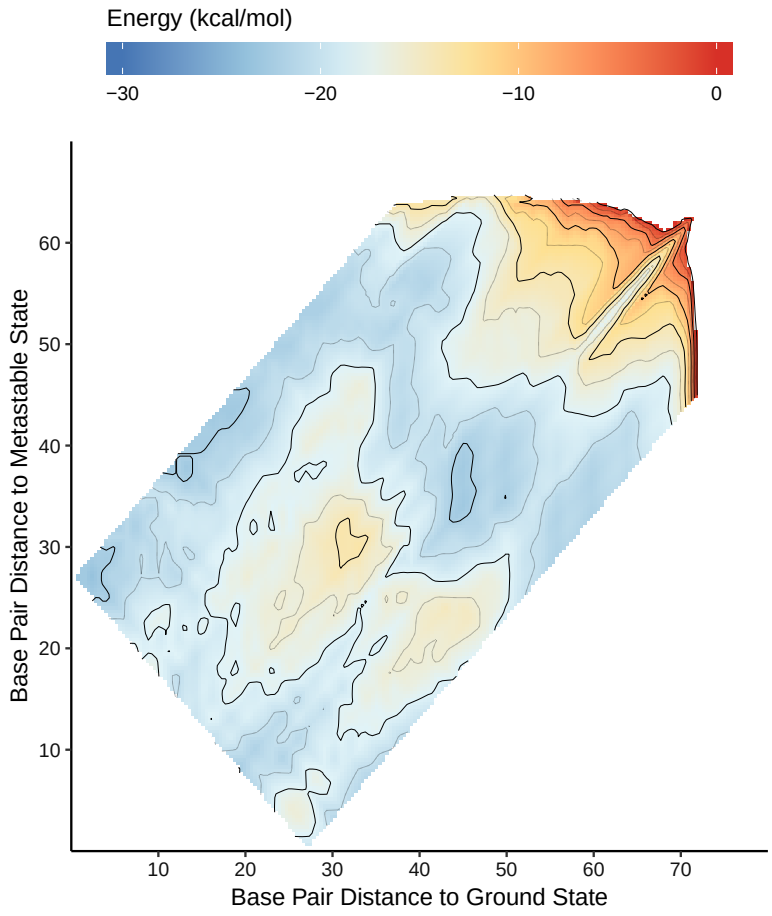
`RNAlocmin` temperature elevation scheme Boltzmann sampling