Sampling RNA Secondary Structure Landscapes for Kinetics Simulations

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Benasque, Spain, July 30, 2018

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

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

RNA Folding Kinetics

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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

RNA Folding Kinetics

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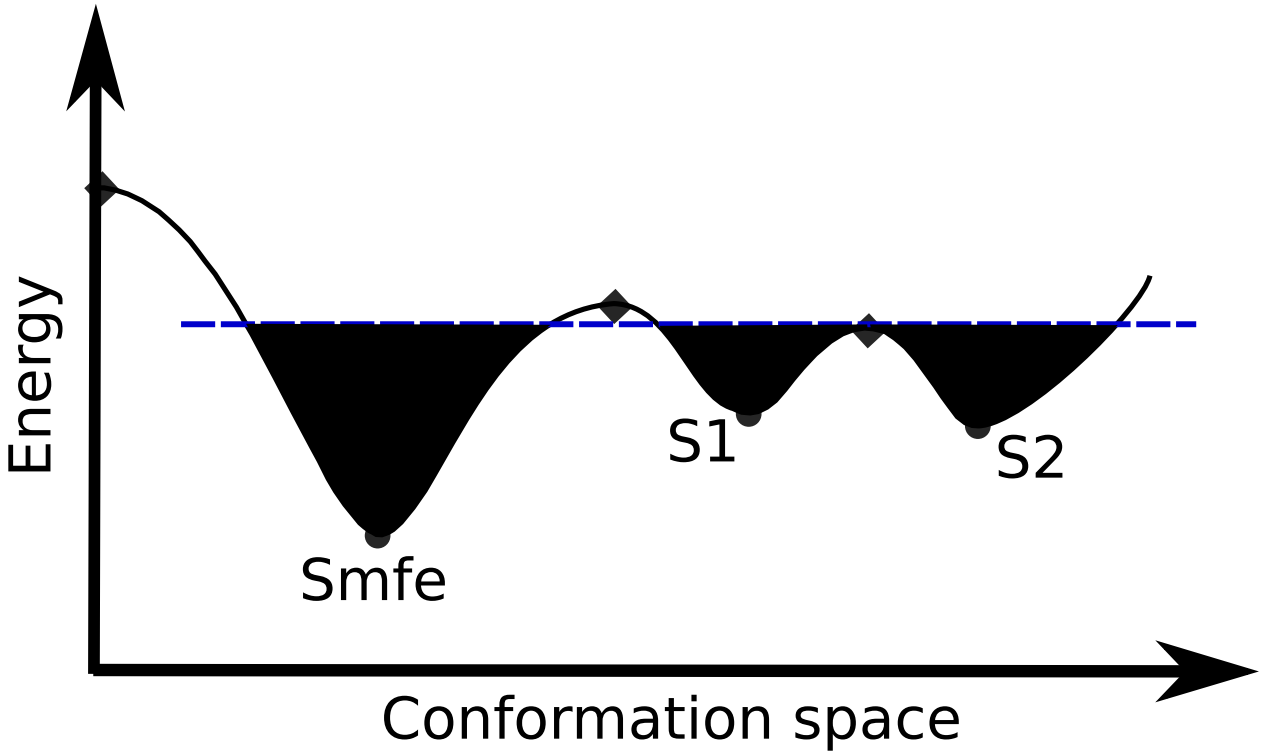
[1] Flamm et al. 2001
[2] Isambert et al. 2001
[3] Wolfinger et al. 2004

Sampling Strategies

1. Exhaustive Enumeration[4]

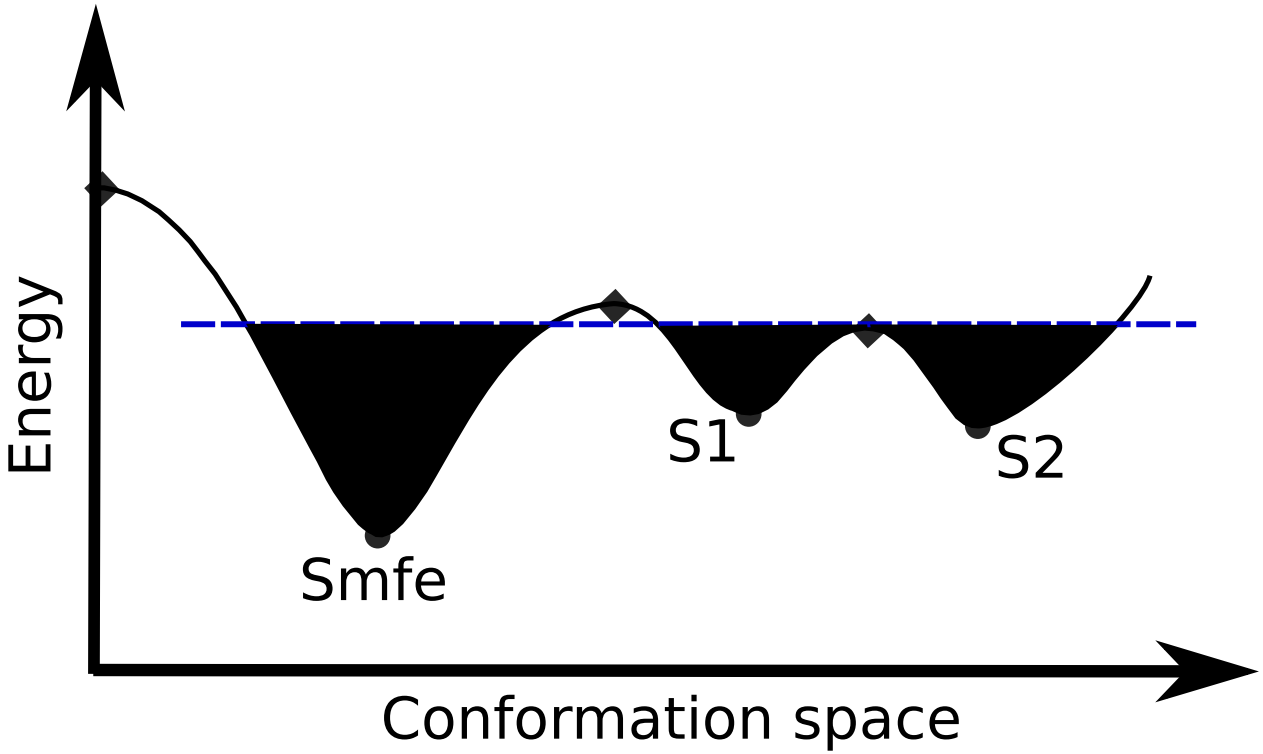


- up to certain threshold δ above MFE
- only applicable to short sequences

[4] Wuchty et al. 1999

Sampling Strategies

1. Exhaustive Enumeration[4]



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

Draw representative structure samples instead...

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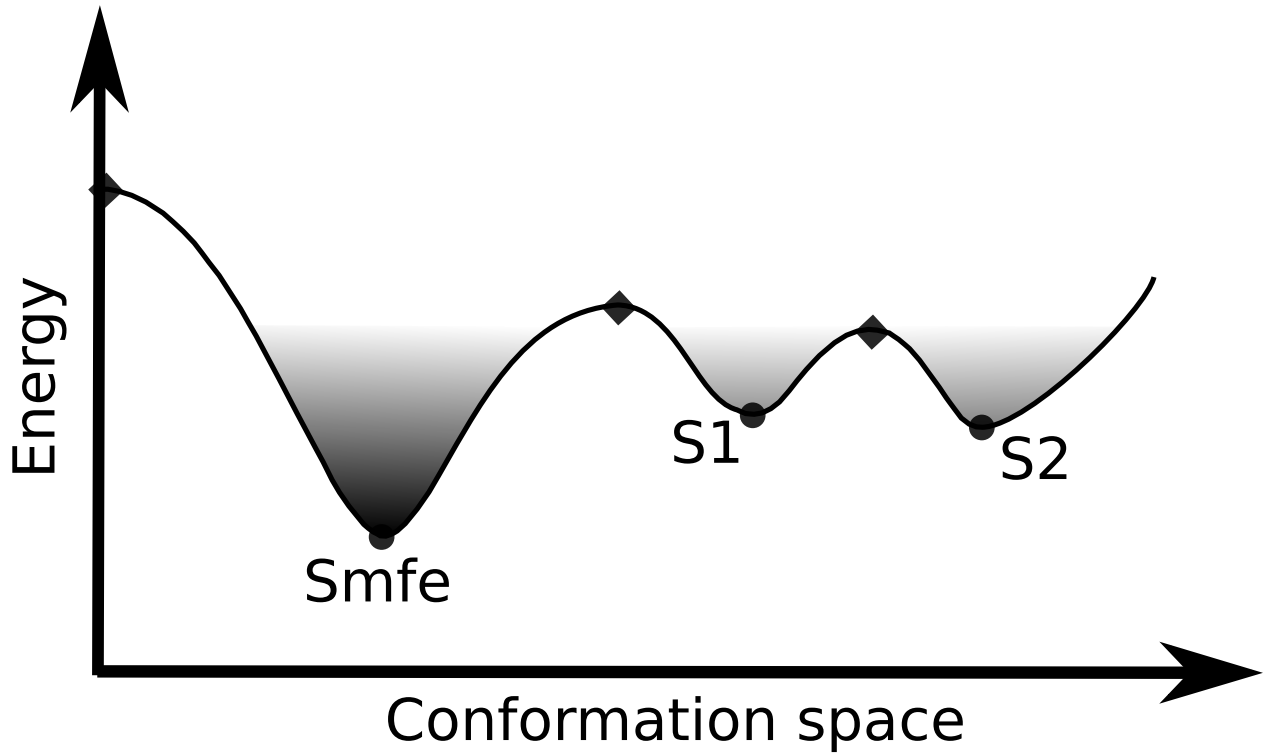
[4] Wuchty et al. 1999

Sampling Strategies

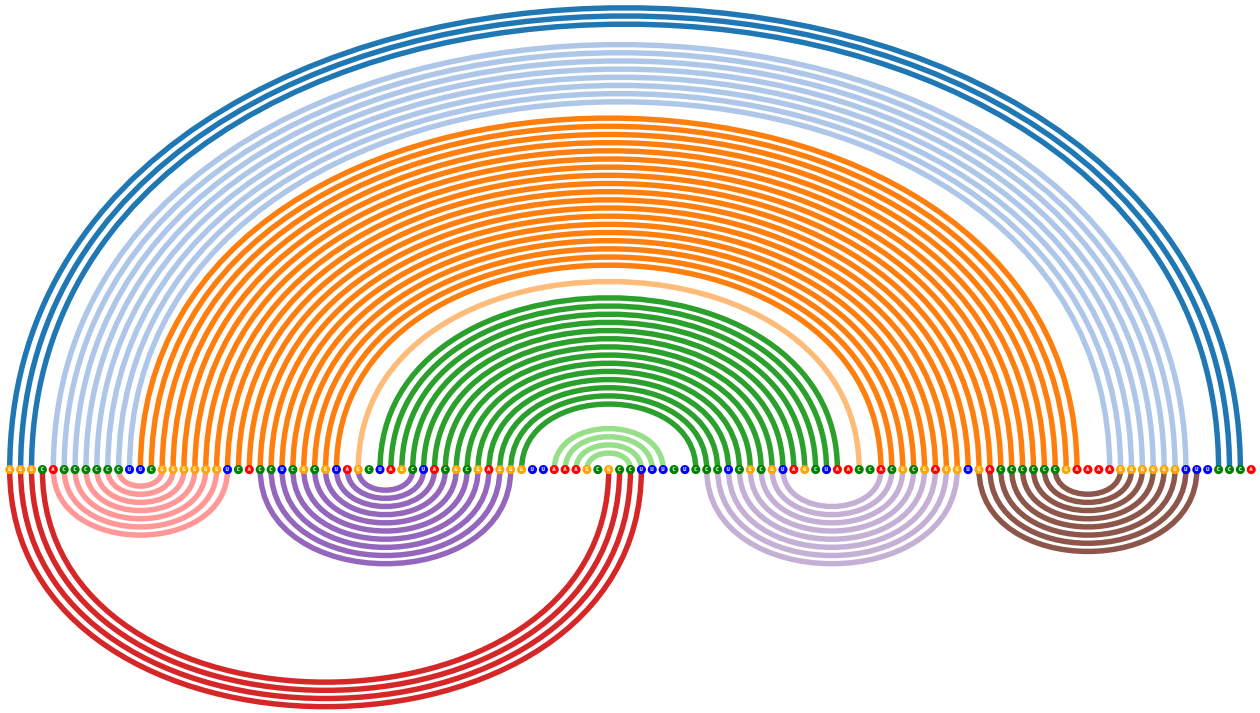
2. Boltzmann Sampling[5]



- obtain samples s with $p(s) = \frac{e^{-\frac{E(s)}{RT}}}{Q}$ and $Q = \sum_S e^{-\frac{E(s)}{RT}}$
- dominated by low energy structures and highly redundant

[5] Ding et al. 2003

Example: Qβ replicase template SV11[6]

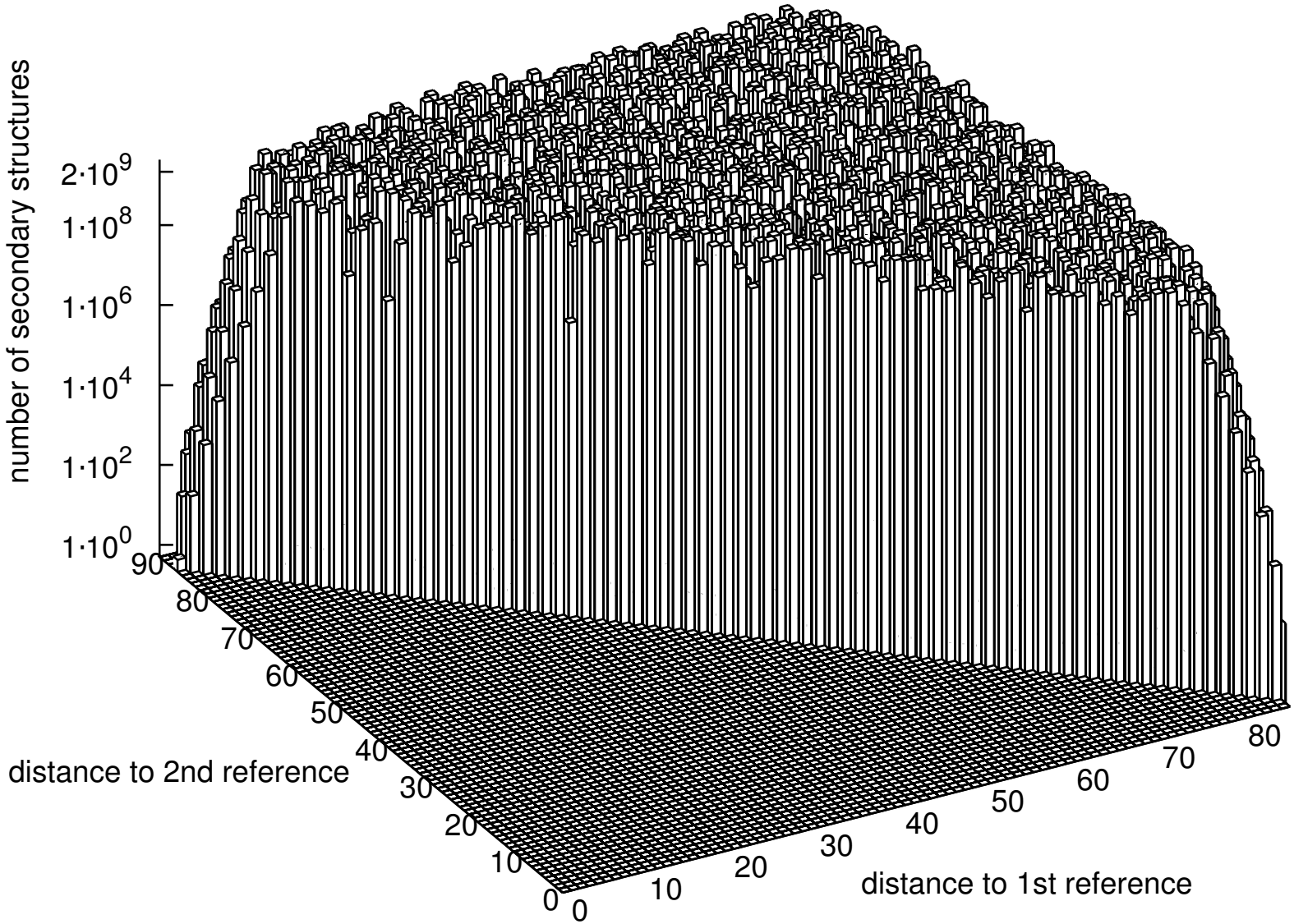


- artificial RNA sequence of 115 nt
- initially folds into metastable conformation
- metastable state is perfect template for Qβ replicase
- spontaneously refolds into very stable rod-like MFE structure
- metastable state $> 30 kcal/mol$ above MFE

[6] Biebricher et al. 1992

Example: Qβ replicase template SV11

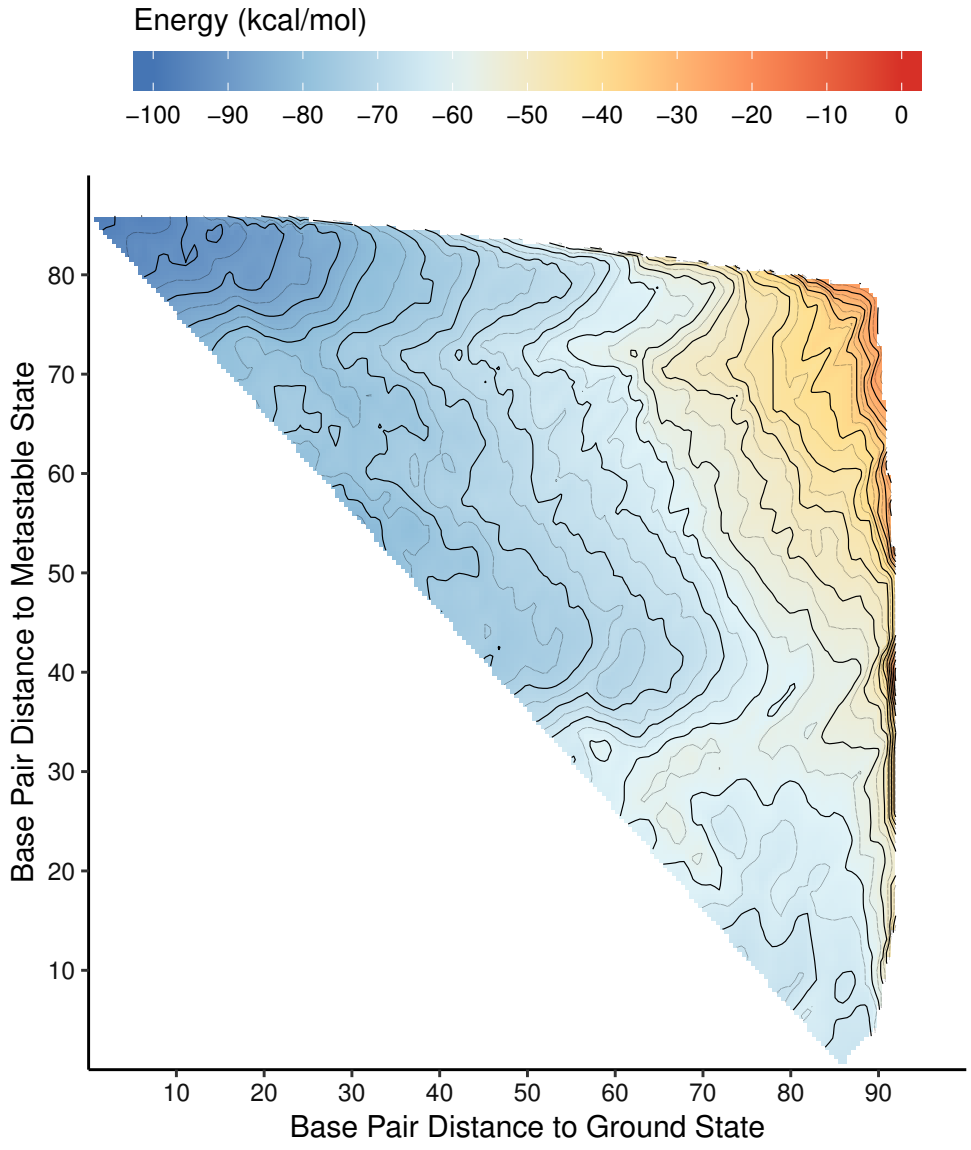
2D Projection of Secondary Structure Landscape[7]



[7] Lorenz et al. 2009

Example: Qβ replicase template SV11

2D Projection of Secondary Structure Landscape[7]



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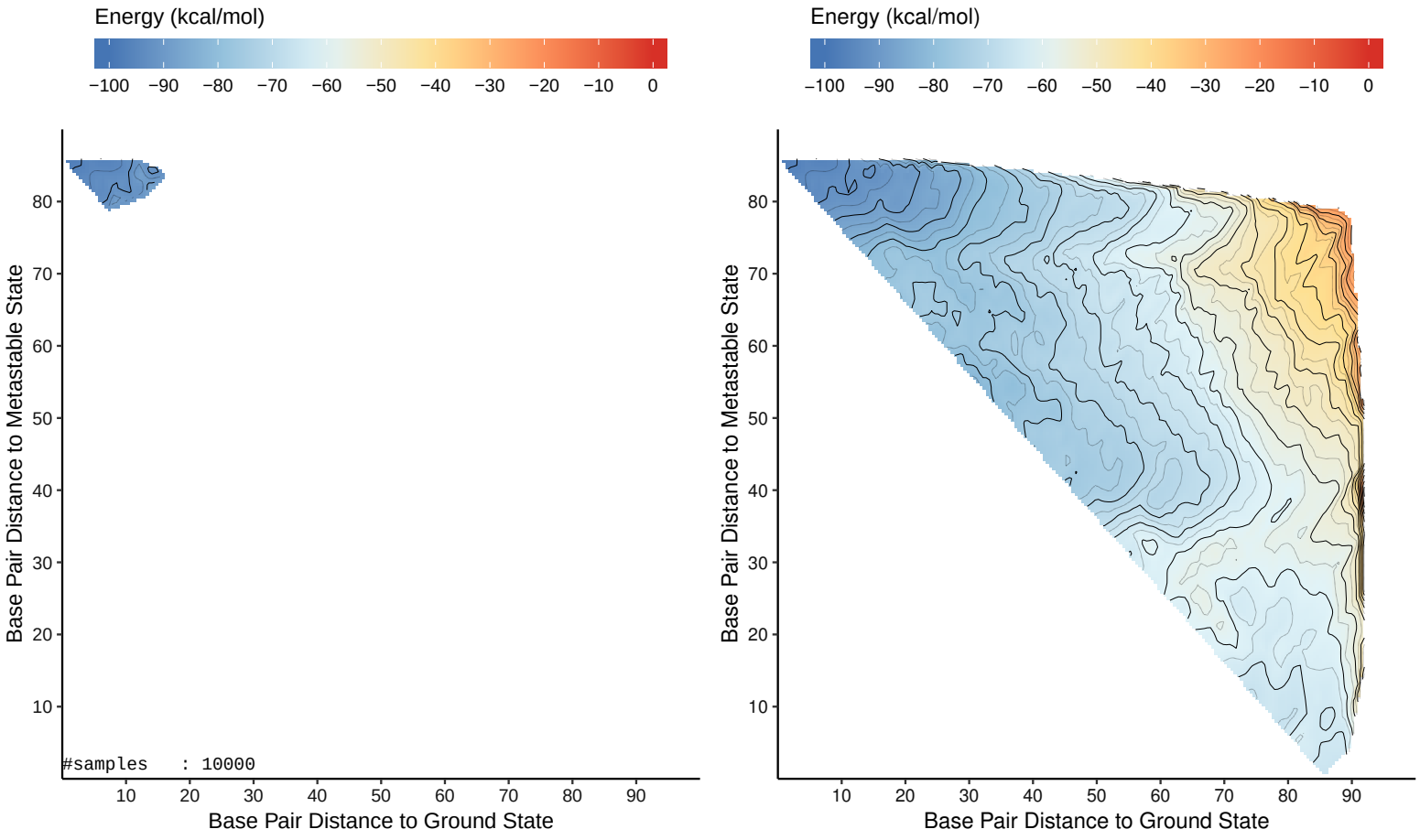
Example: Qβ replicase template SV11

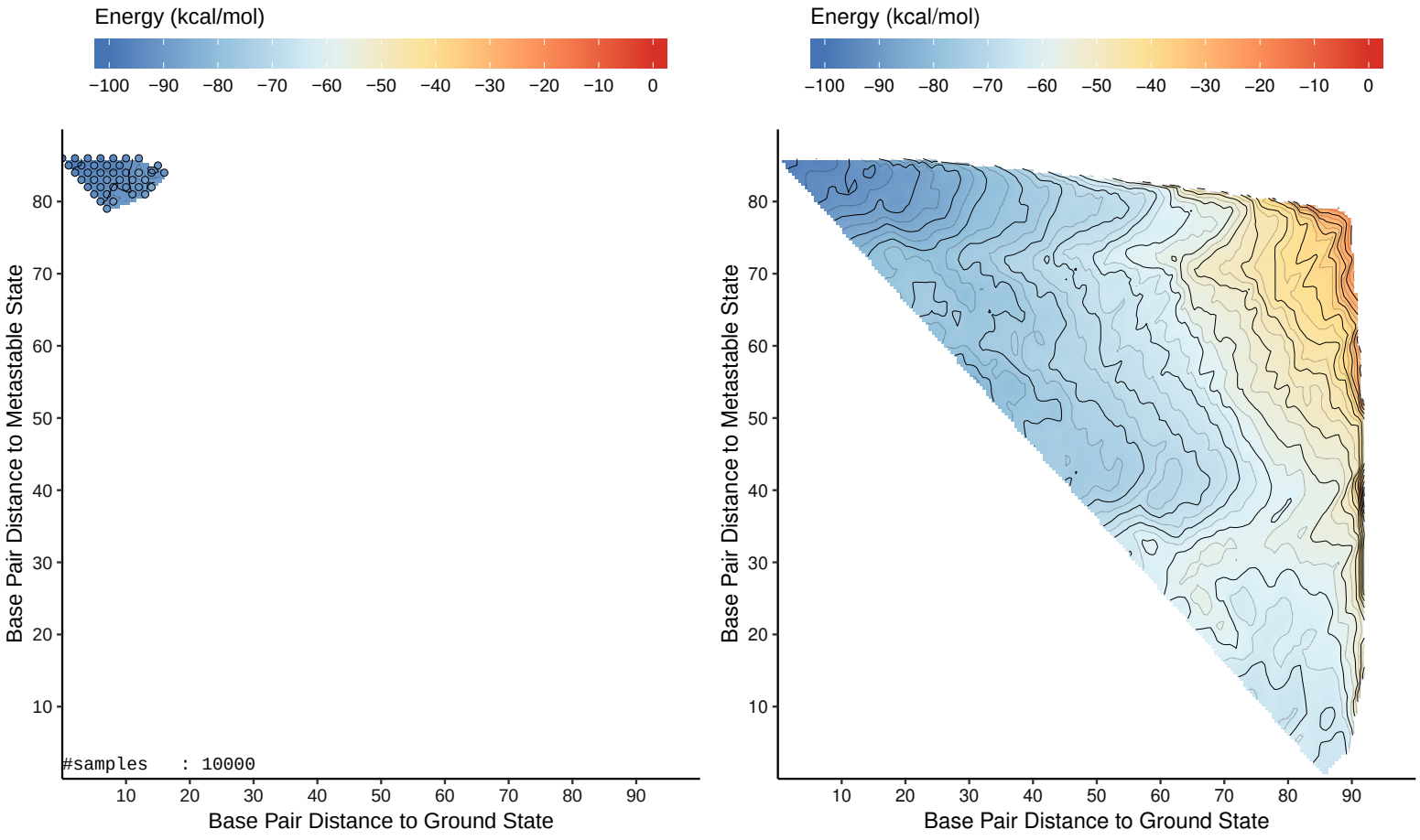
Regular Boltzmann sampling



samples: 10,000, # local minima: 35

Example: Qβ replicase template SV11

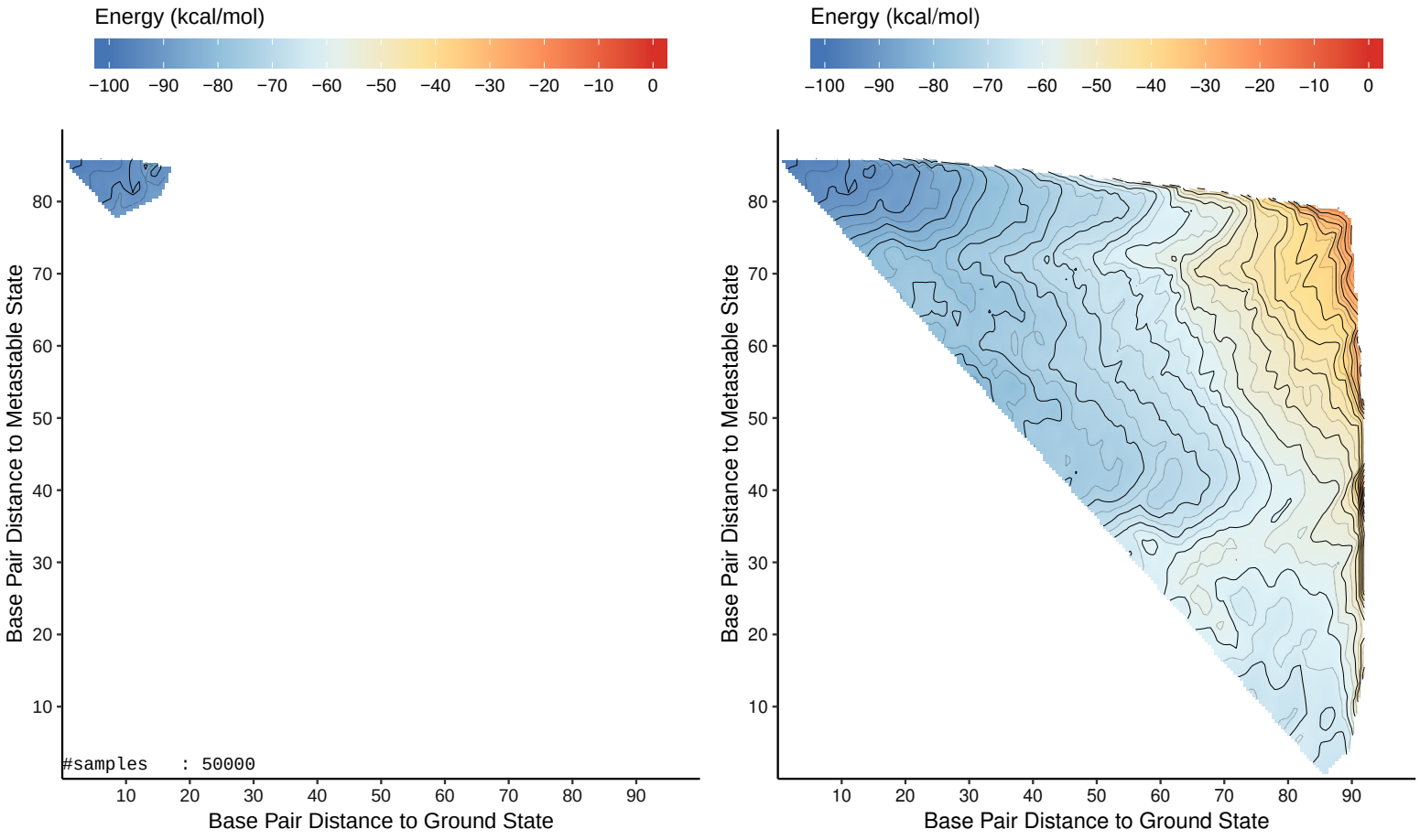
Regular Boltzmann sampling



samples: 10,000, # local minima: 35

Example: Qβ replicase template SV11

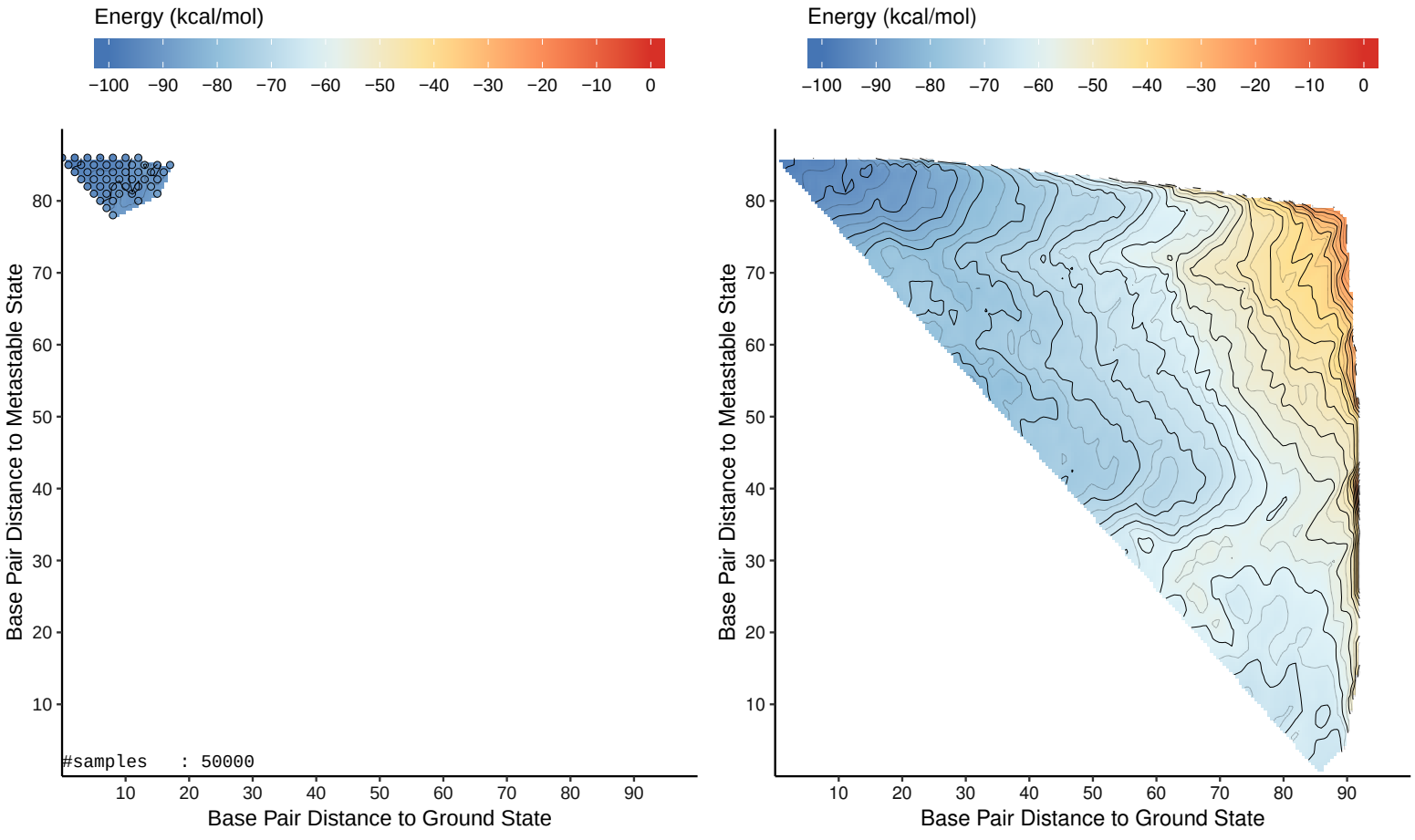
Regular Boltzmann sampling



samples: 50,000 / # local minima: 49

Example: Qβ replicase template SV11

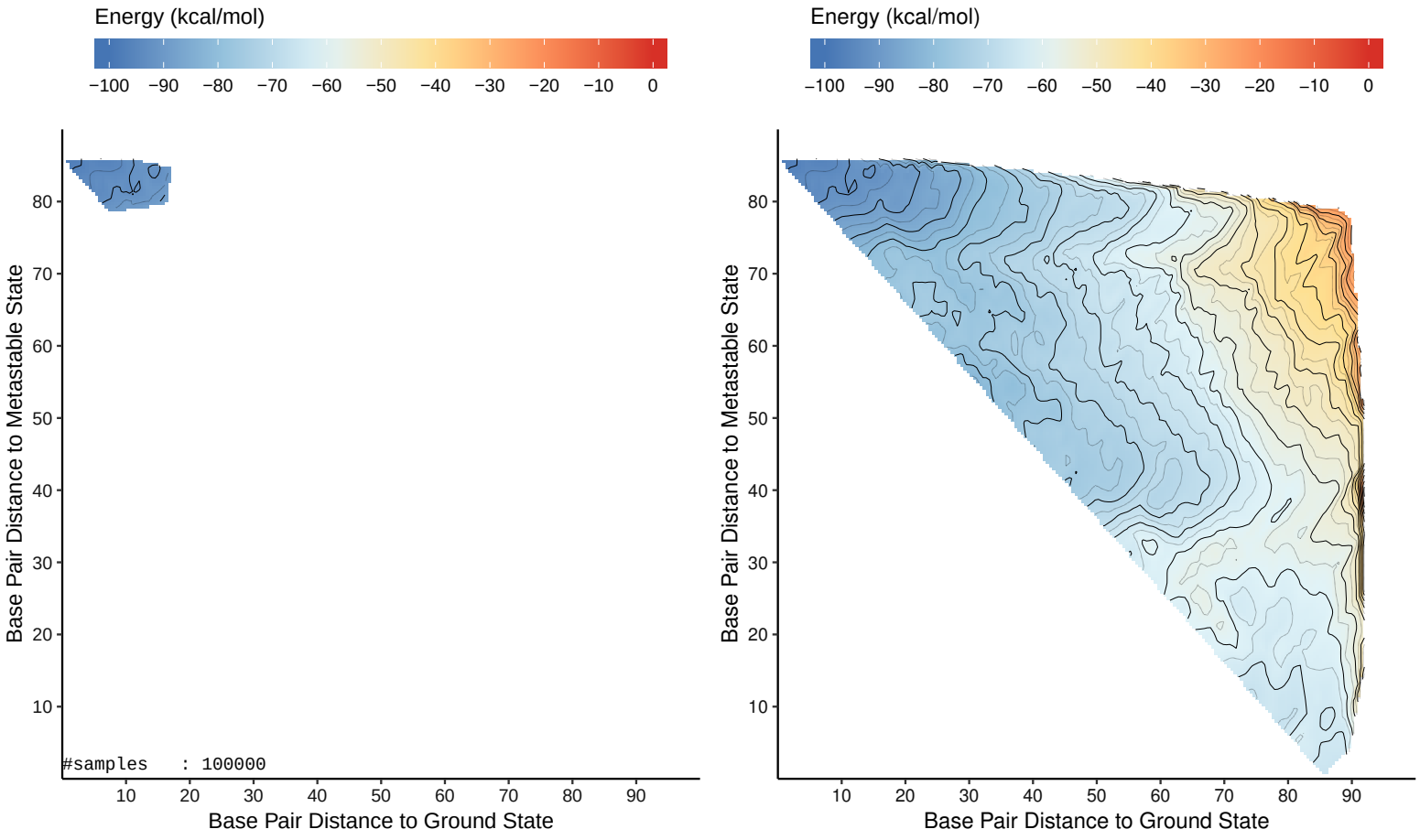
Regular Boltzmann sampling



samples: 50, 000 / # local minima: 49

Example: Qβ replicase template SV11

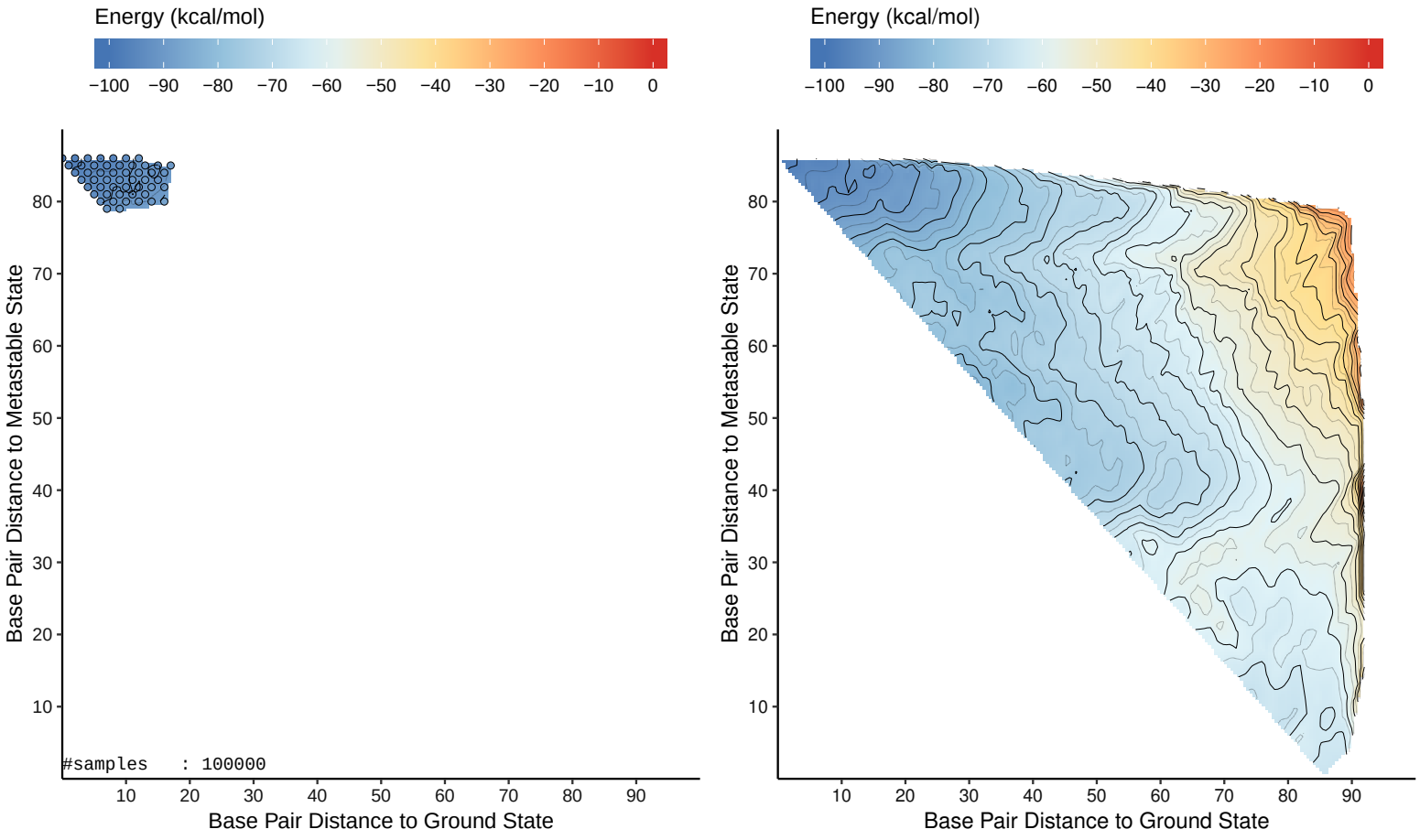
Regular Boltzmann sampling



samples: 100, 000 / # local minima: 58

Example: Qβ replicase template SV11

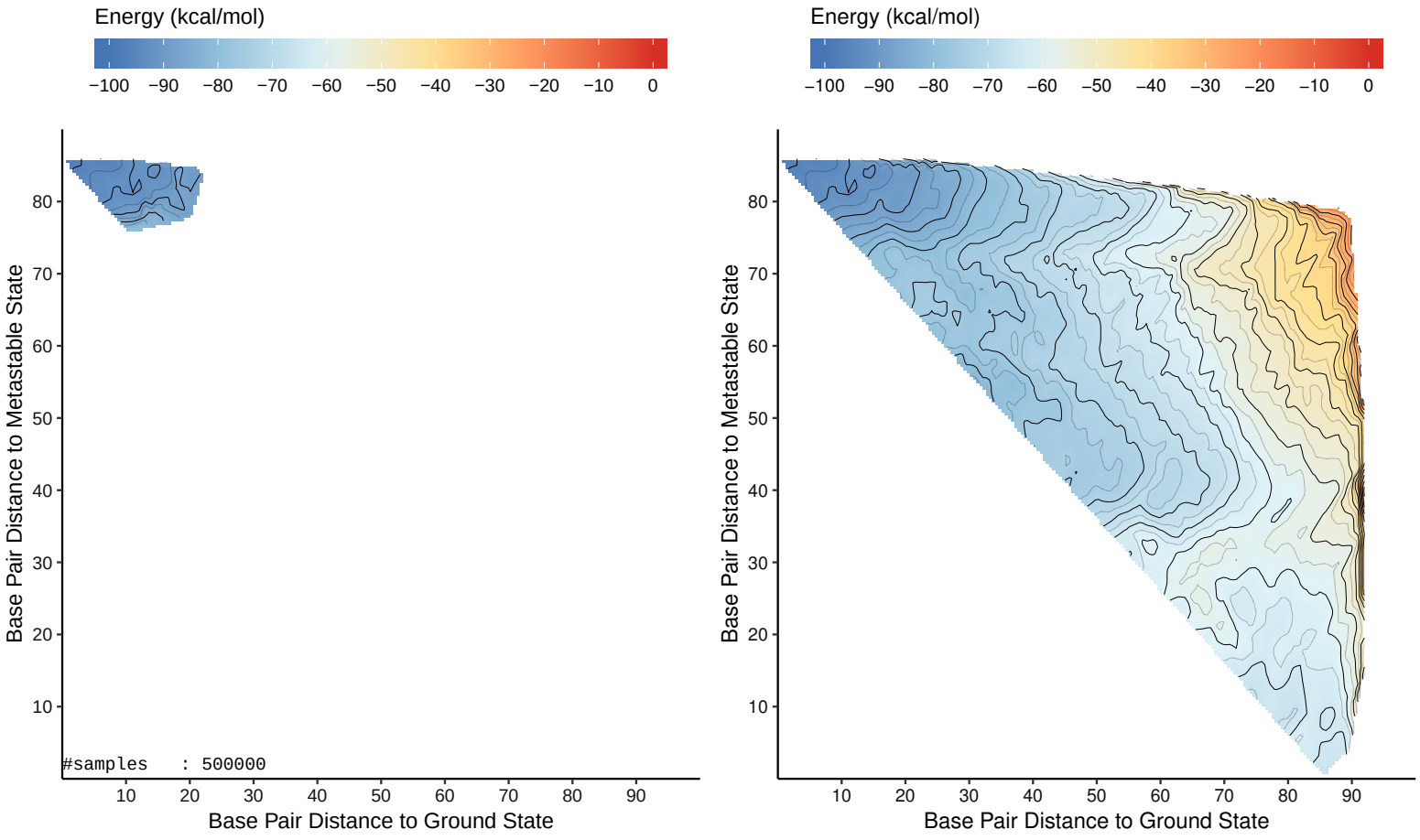
Regular Boltzmann sampling



samples: 100, 000 / # local minima: 58

Example: Qβ replicase template SV11

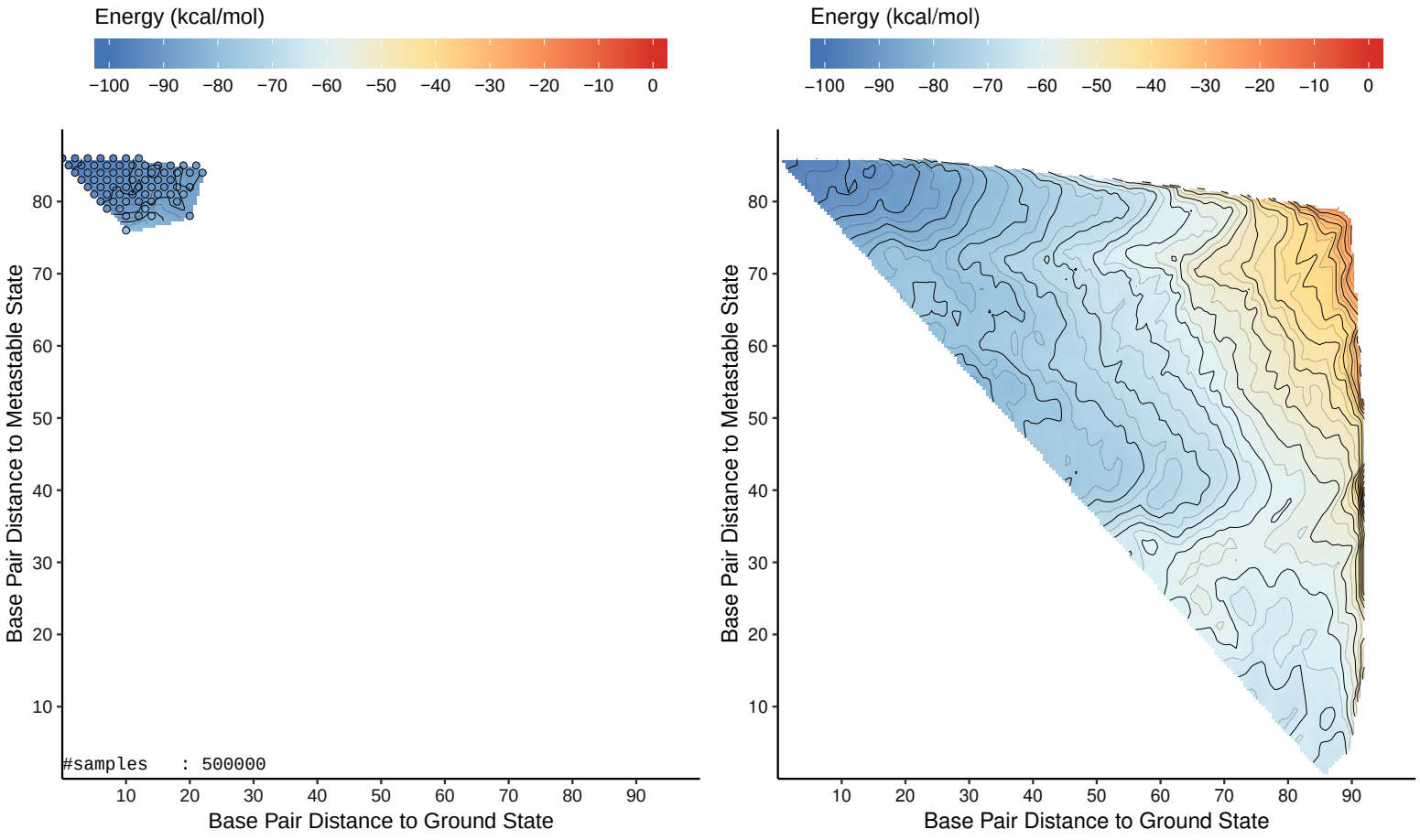
Regular Boltzmann sampling



samples: 500, 000 / # local minima: 101

Example: Qβ replicase template SV11

Regular Boltzmann sampling



samples: 500, 000 / # local minima: 101

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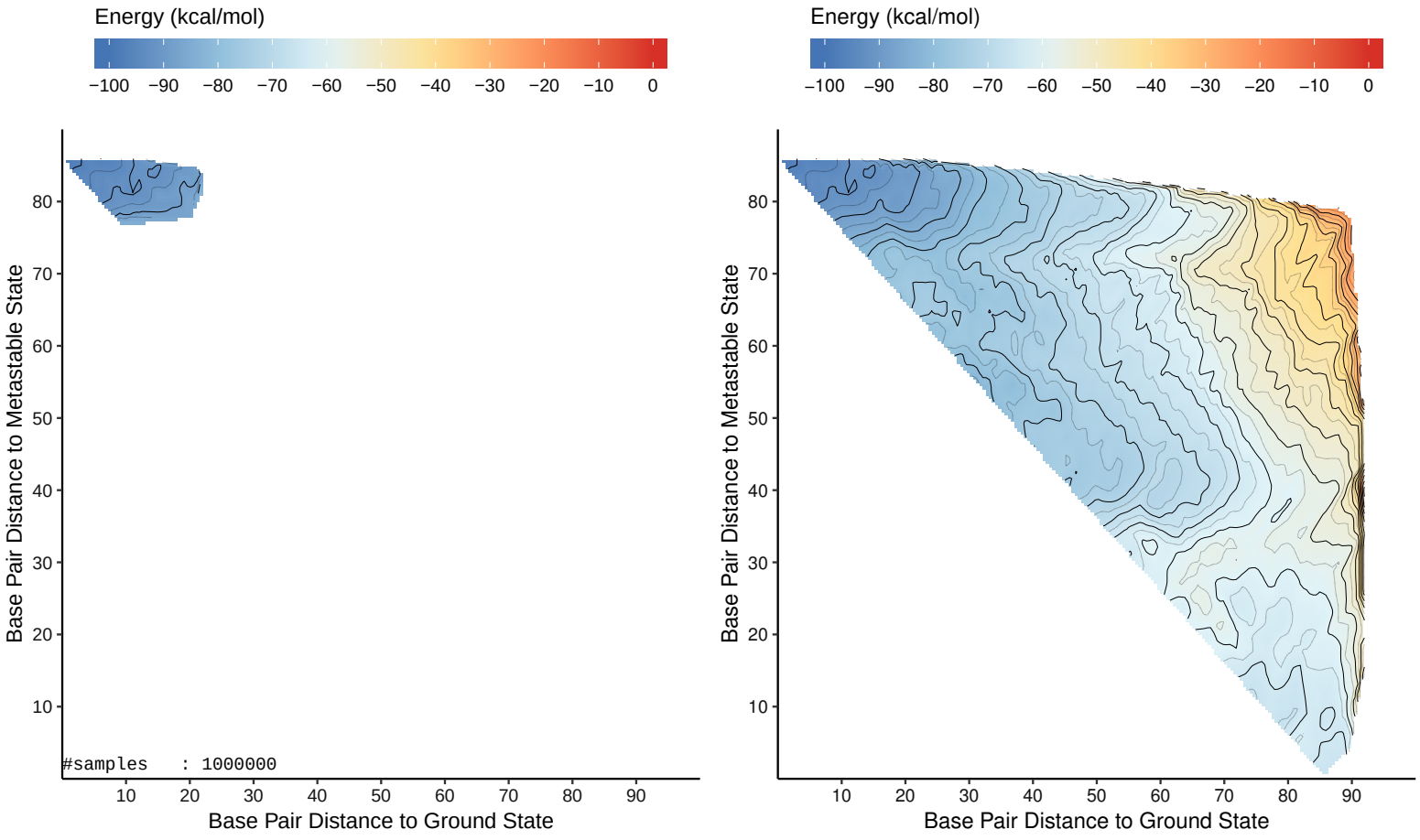
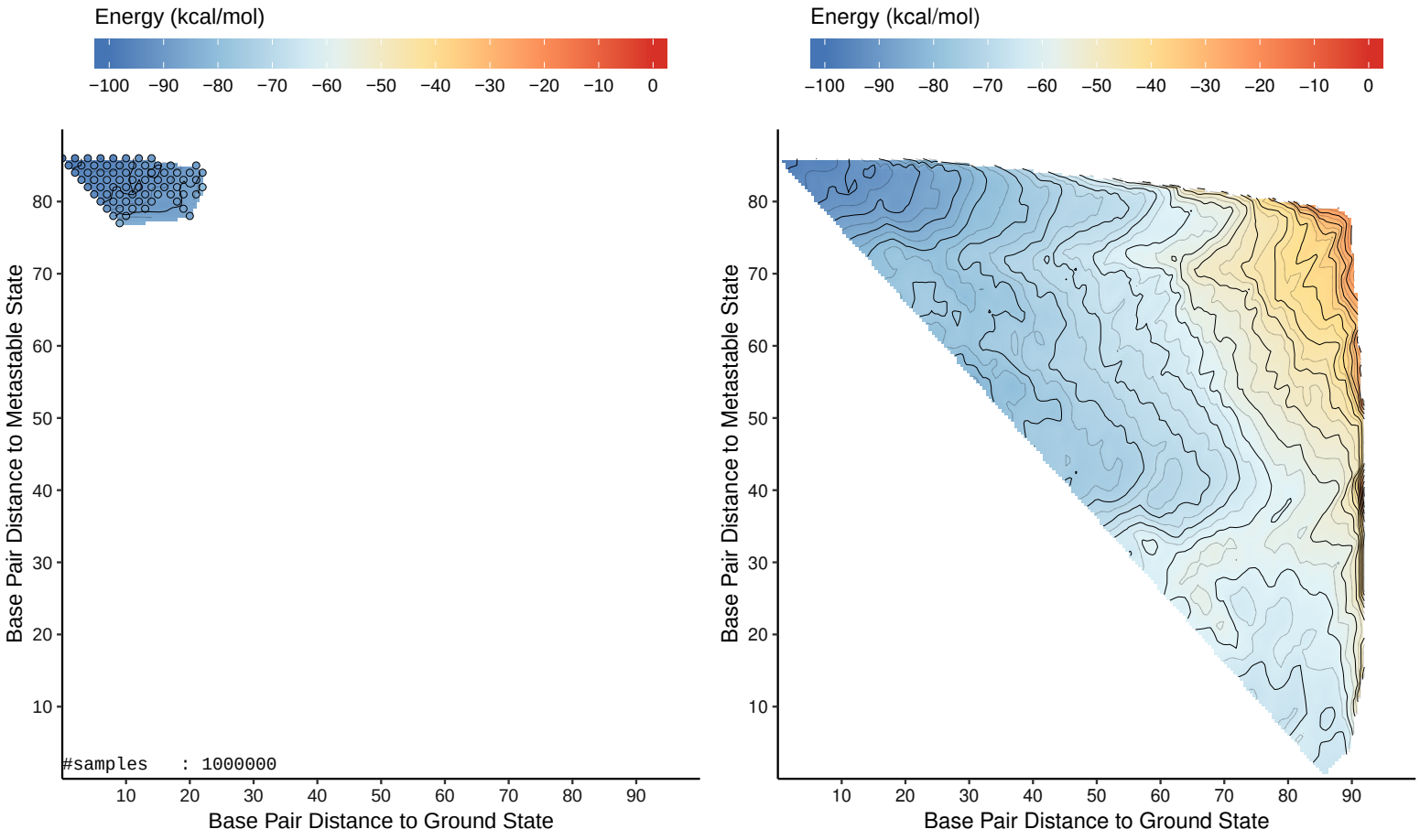


samples: $1,000,000$ / # local minima: 132

Example: Qβ replicase template SV11

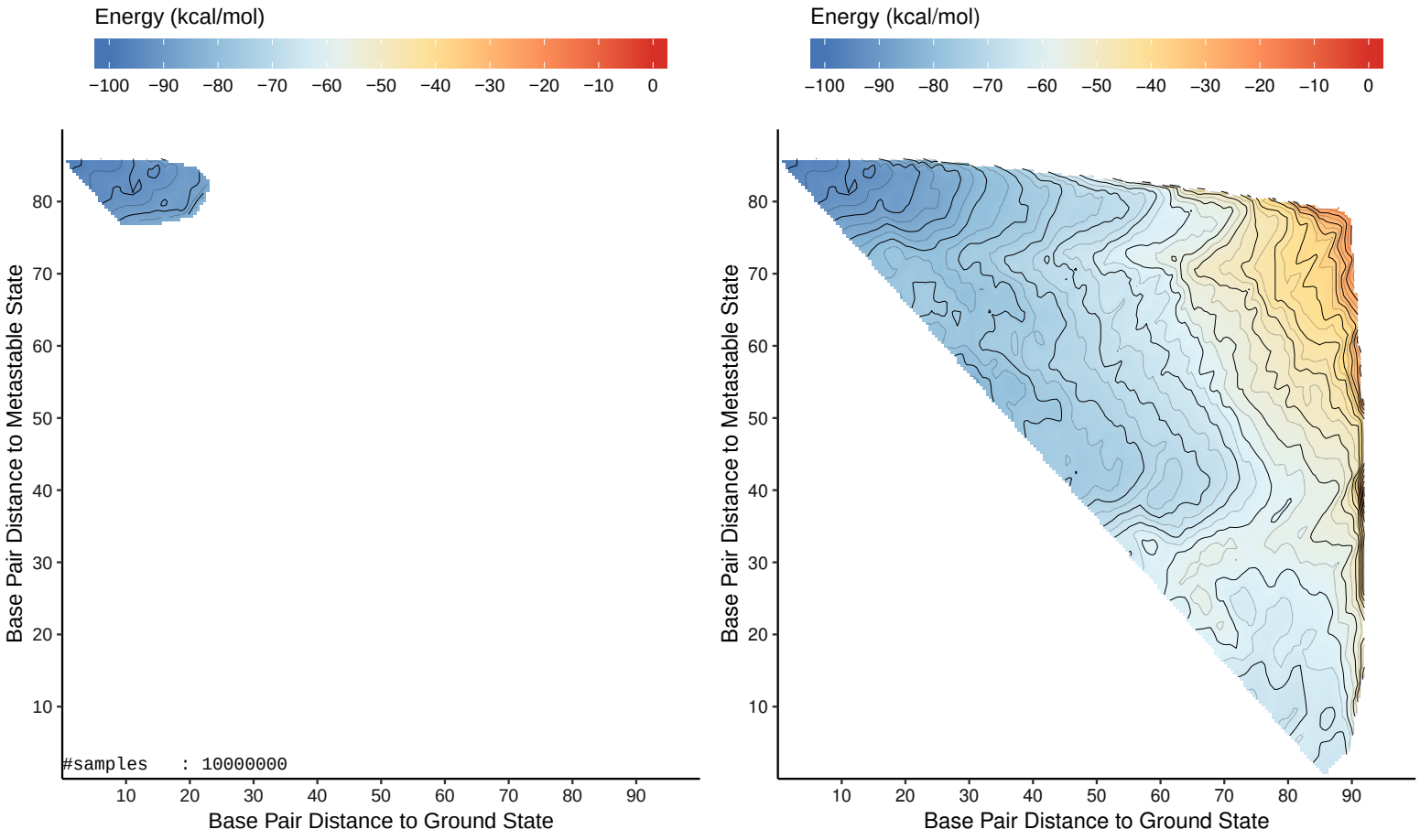
Regular Boltzmann sampling



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

Example: Qβ replicase template SV11

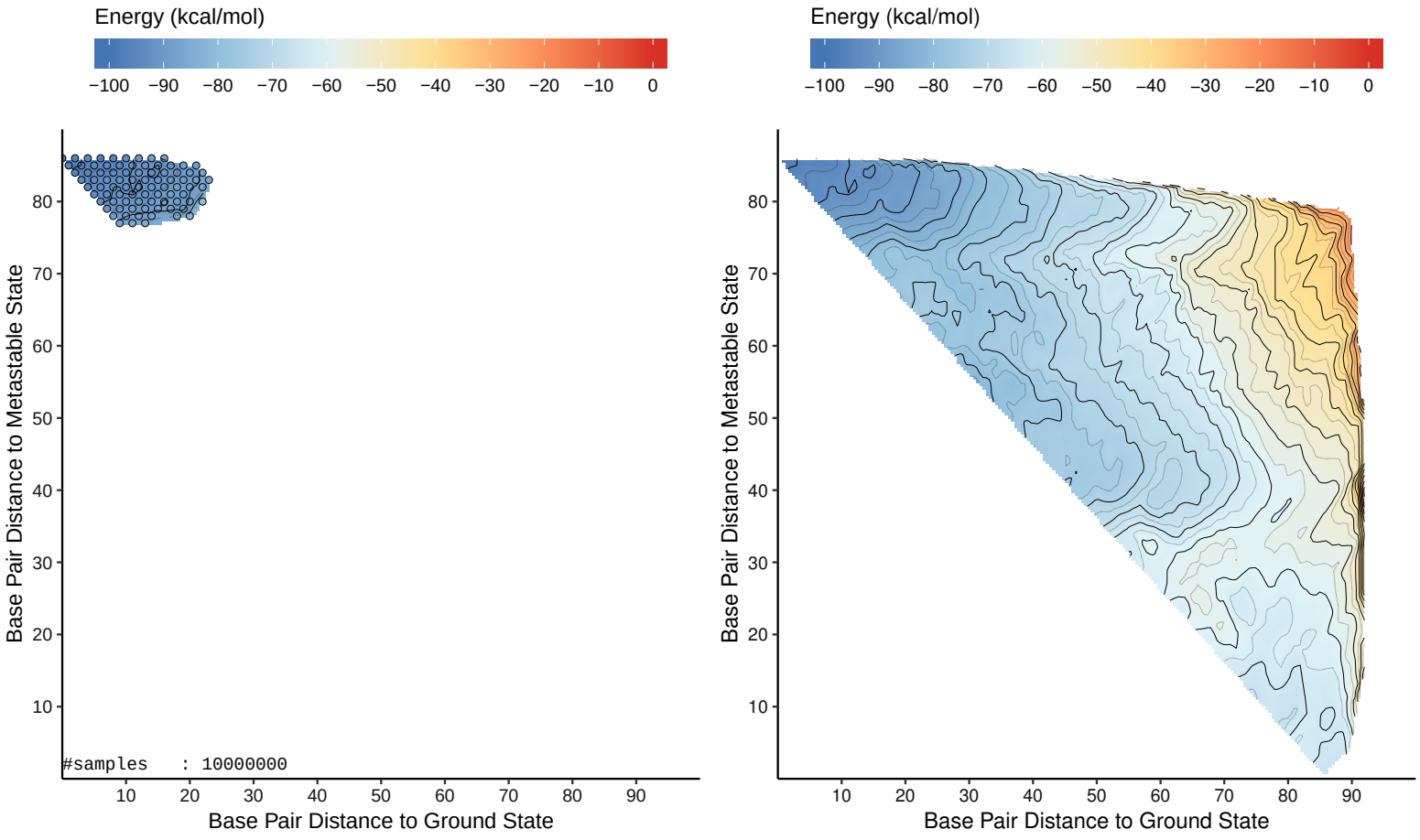
Regular Boltzmann sampling



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])

drawbacks:

- local optimal structures still grow exponentially
- rather high asymptotic time/memory complexities

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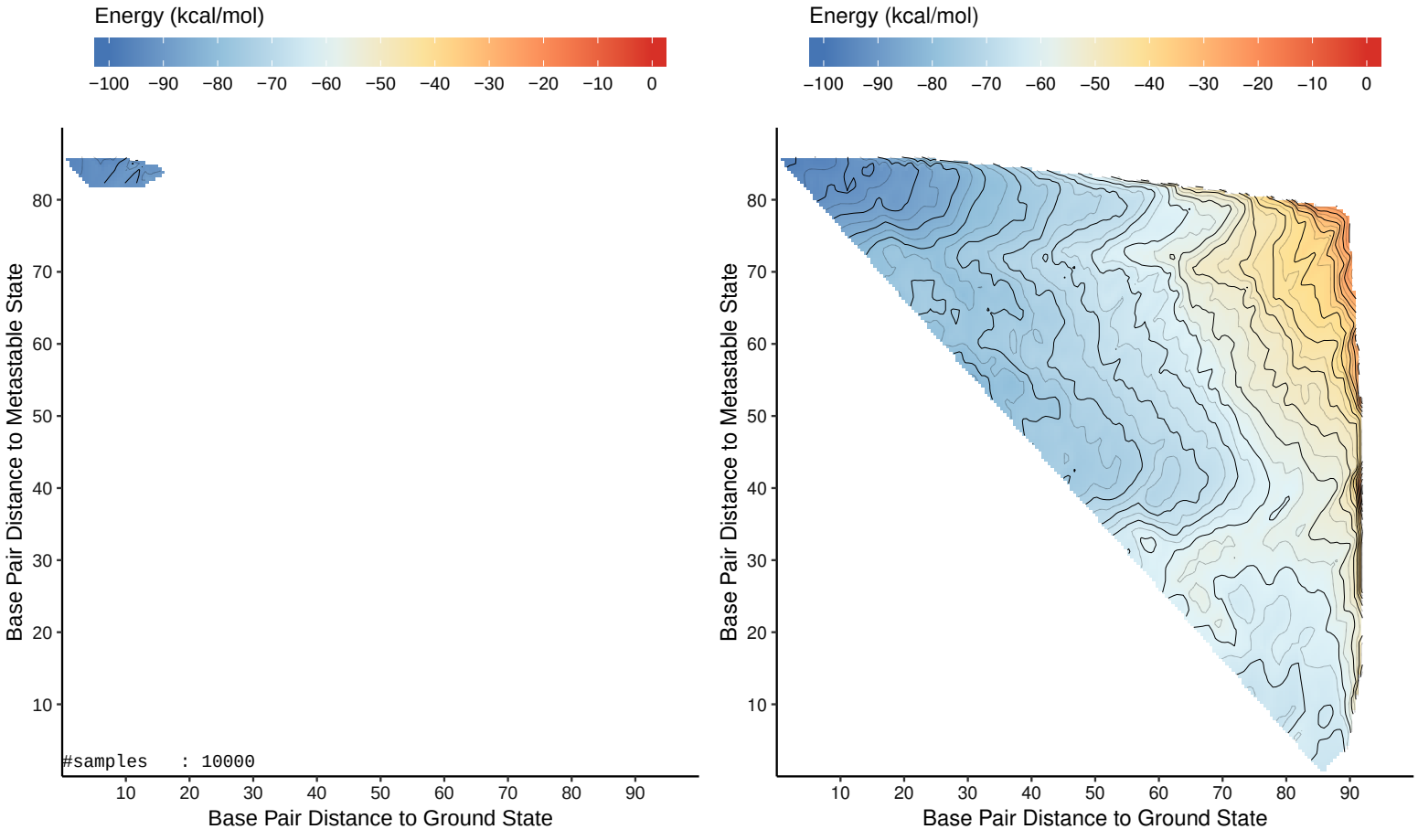
[7] Lorenz WA et al. 2011
[8] Michalik et al. 2017
[9] Li et al. 2011
[10] Steffen et al. 2005

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



samples: 10,000, # local minima: 41

Example: Qβ replicase template SV11

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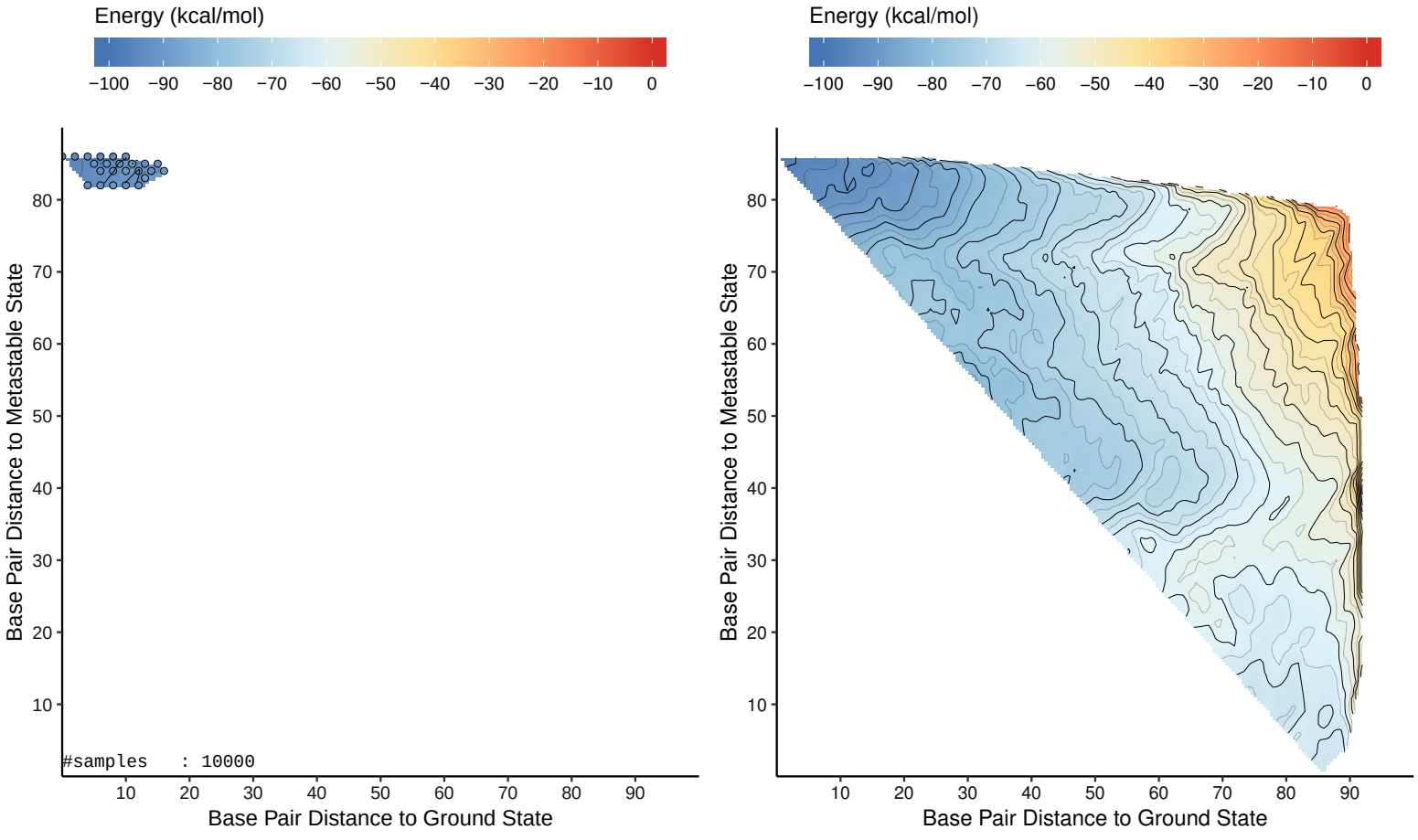

samples: 10,000, # local minima: 41

Example: Qβ replicase template SV11

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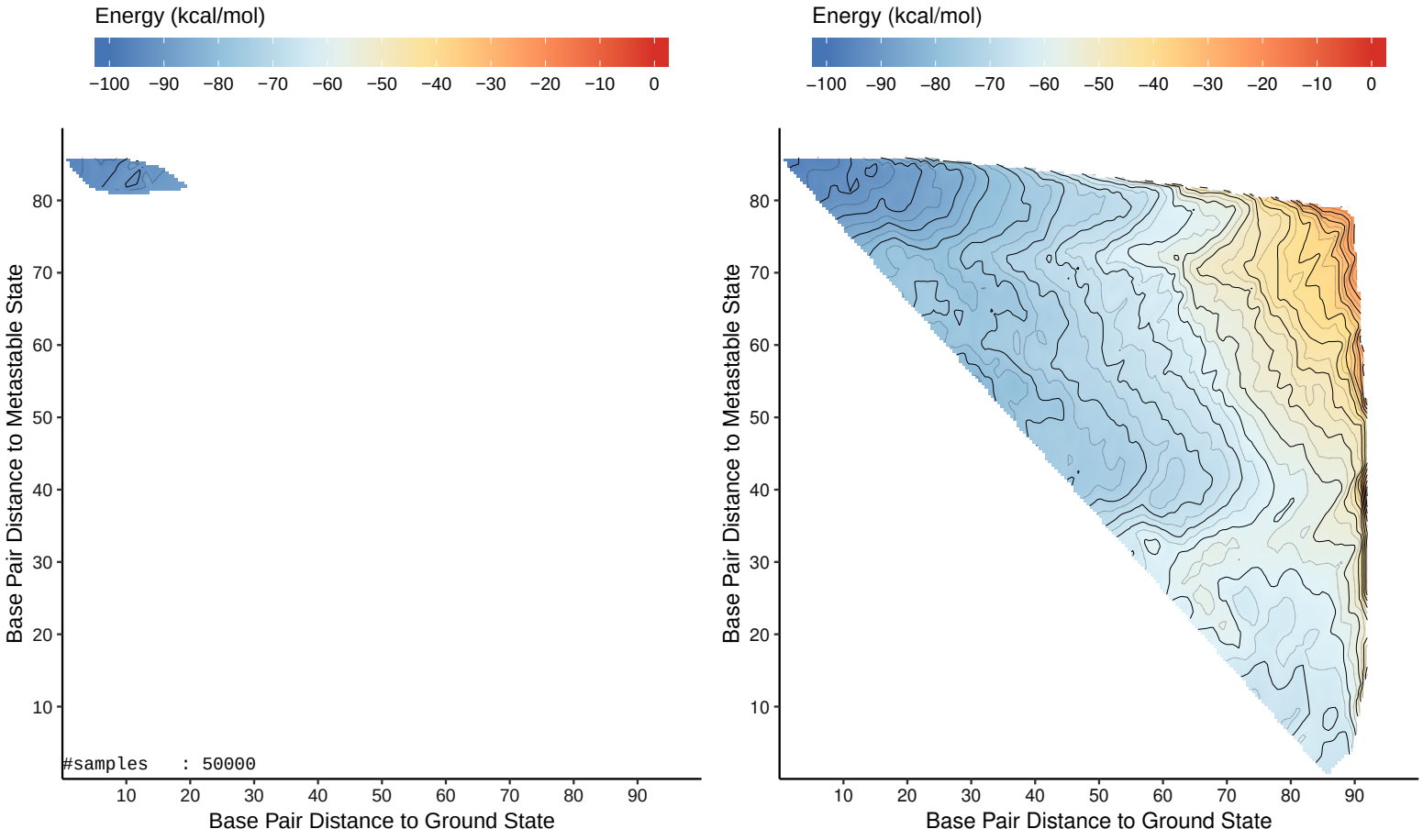

samples: 50, 000, # local minima: 61

Example: Qβ replicase template SV11

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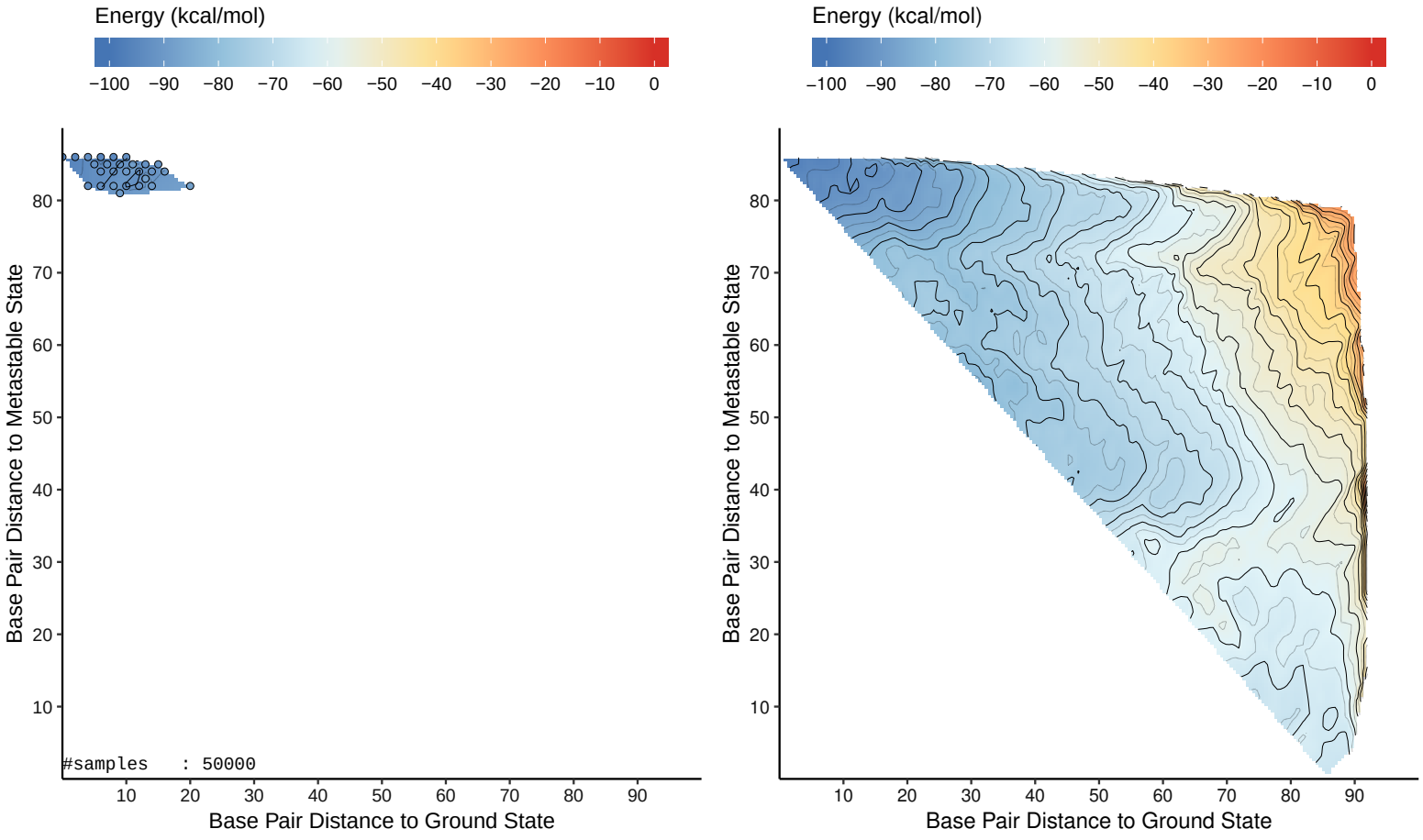

samples: 50, 000, # local minima: 61

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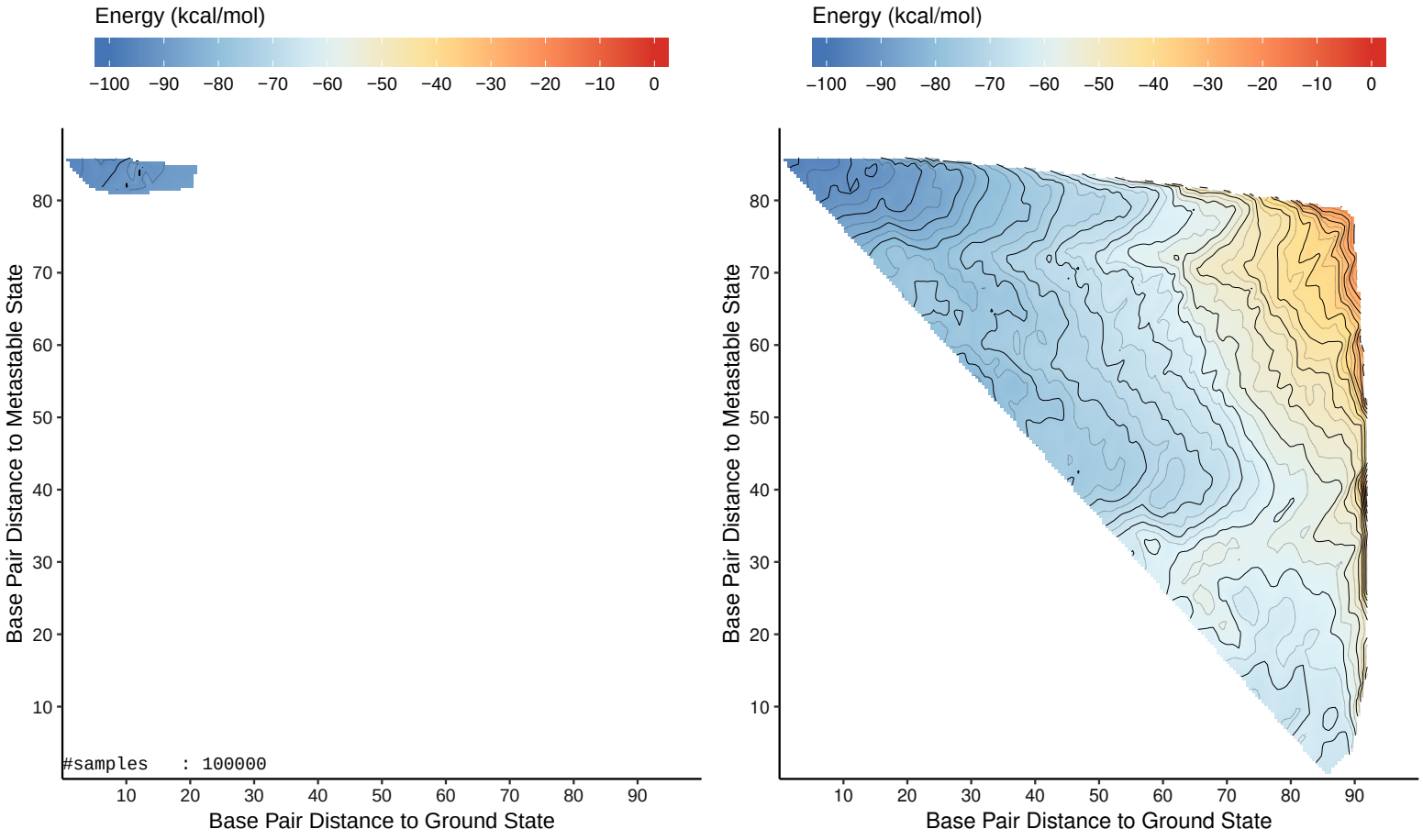
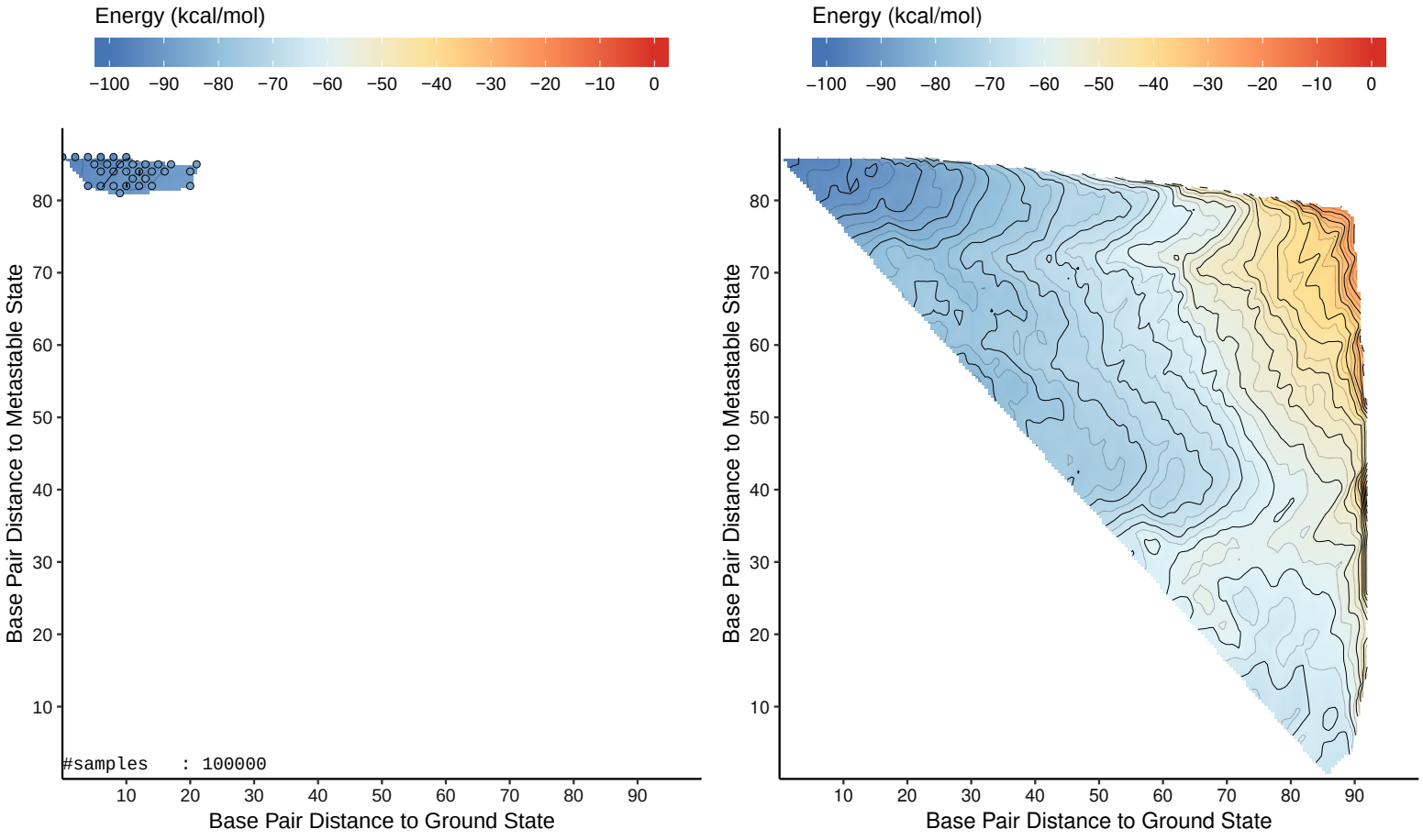


samples: 100, 000, # local minima: 72

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



samples: 100, 000, # local minima: 72

Example: Qβ replicase template SV11

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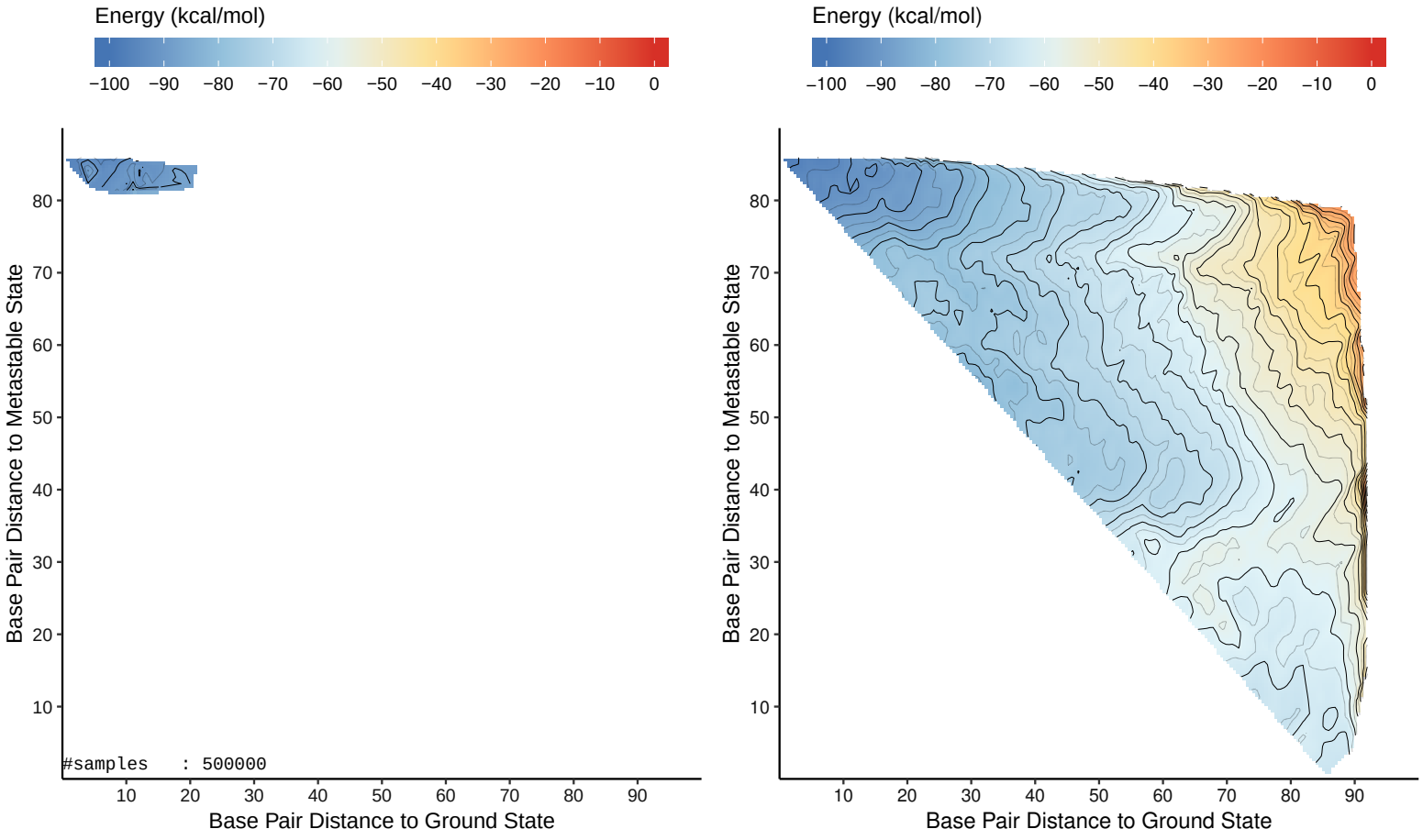
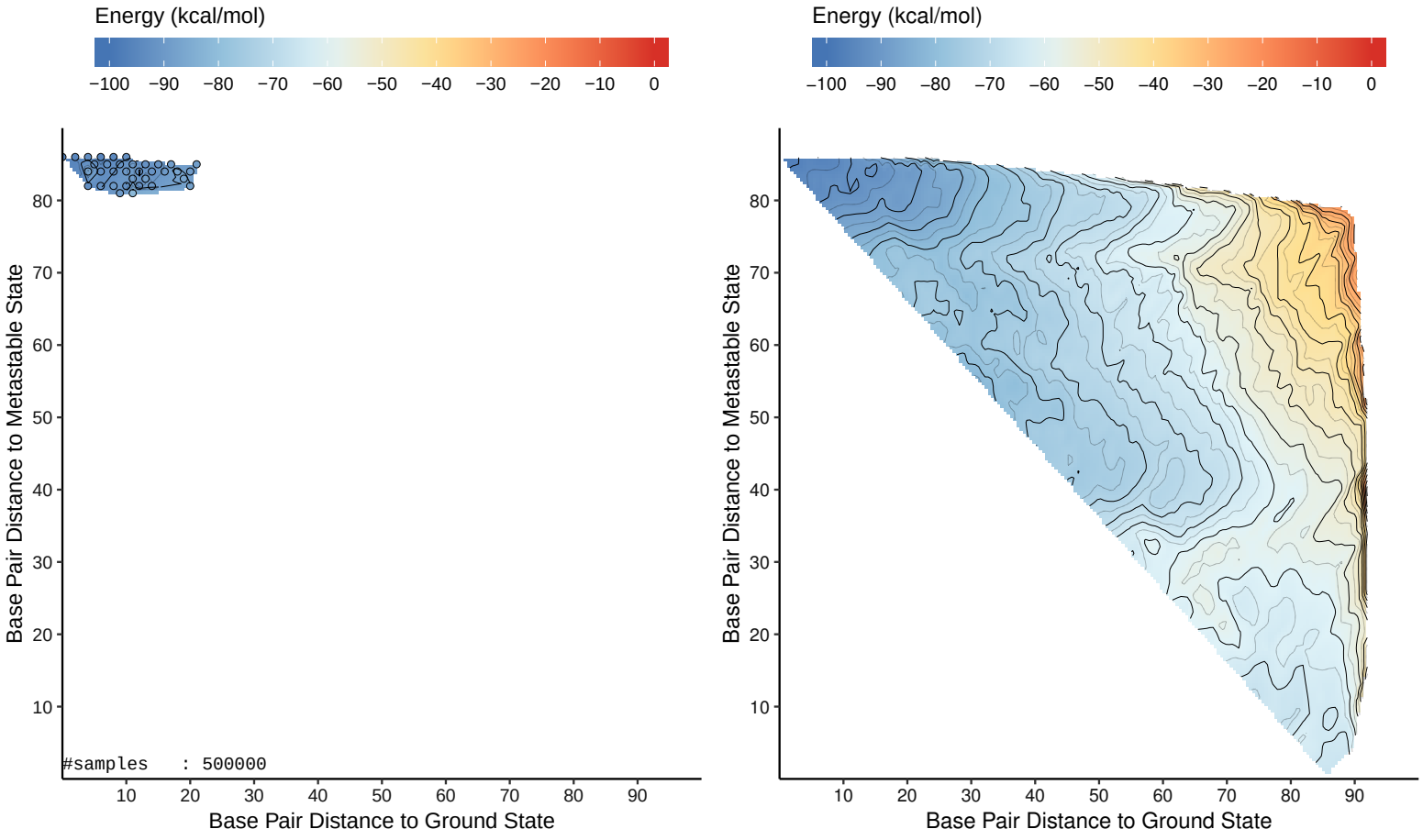


samples: 500, 000, # local minima: 107

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



samples: 500, 000, # local minima: 107

Example: Qβ replicase template SV11

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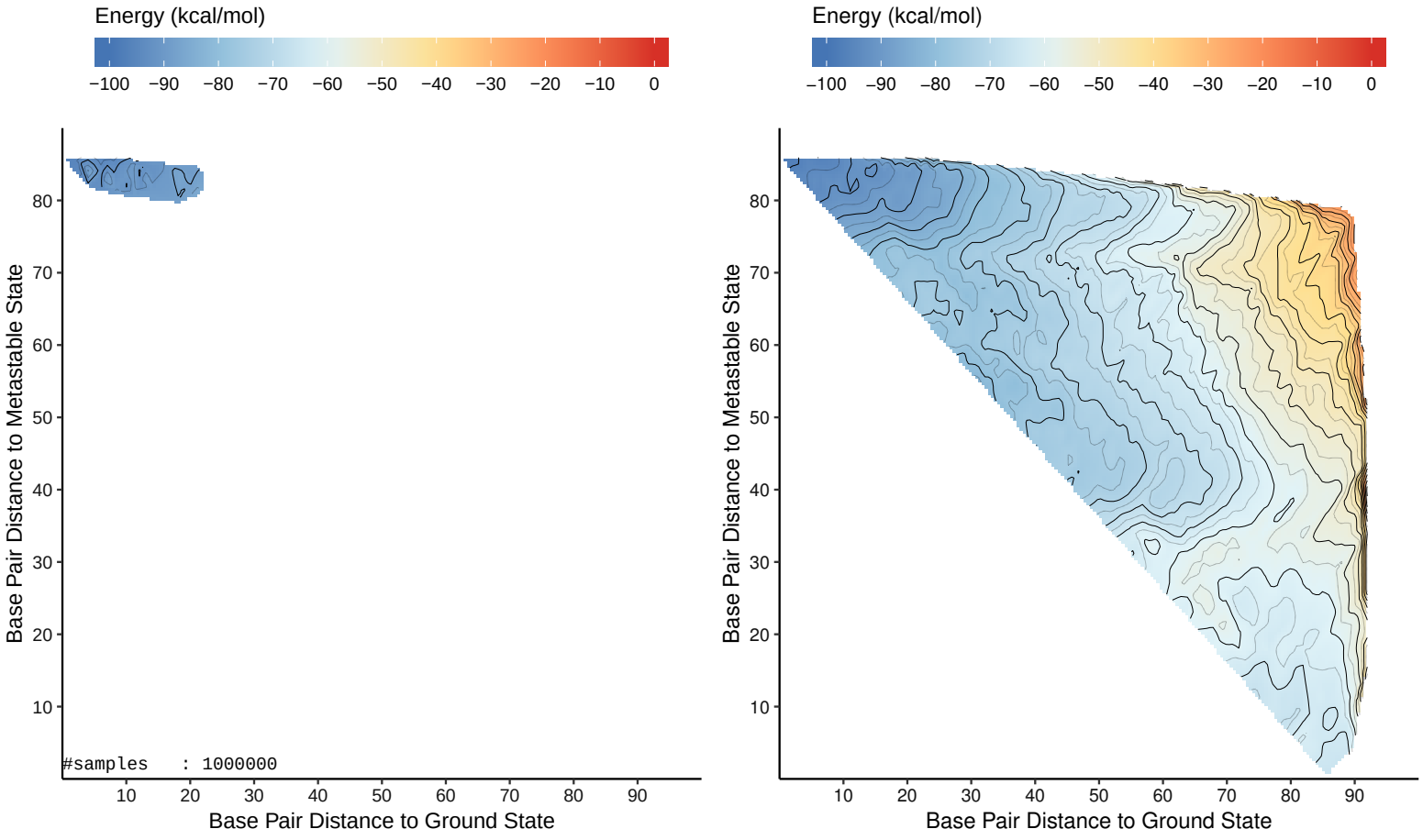
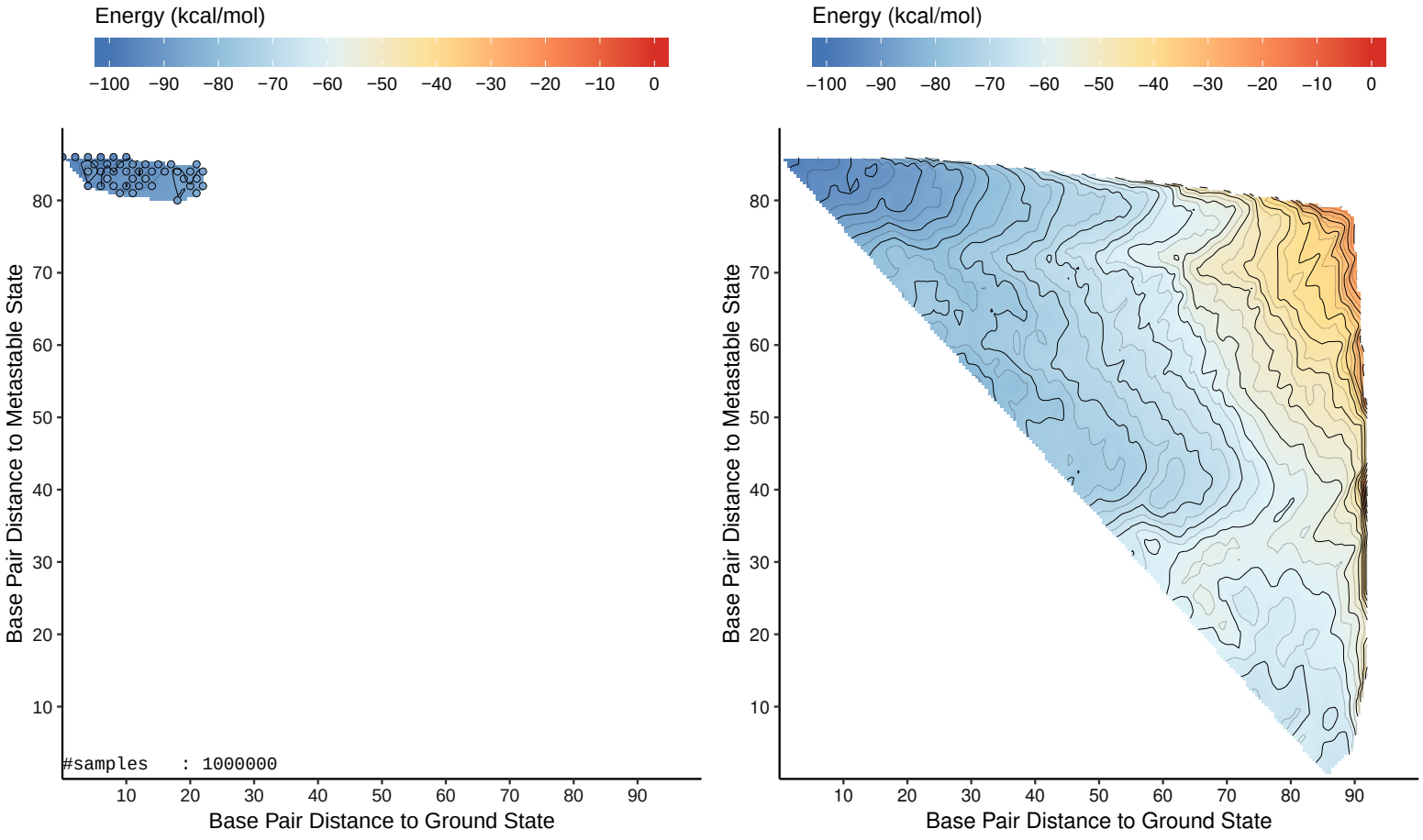


samples: $1,000,000$, # local minima: 130

Example: Qβ replicase template SV11

`RNAlocopt` Boltzmann sampling



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

Example: Qβ replicase template SV11

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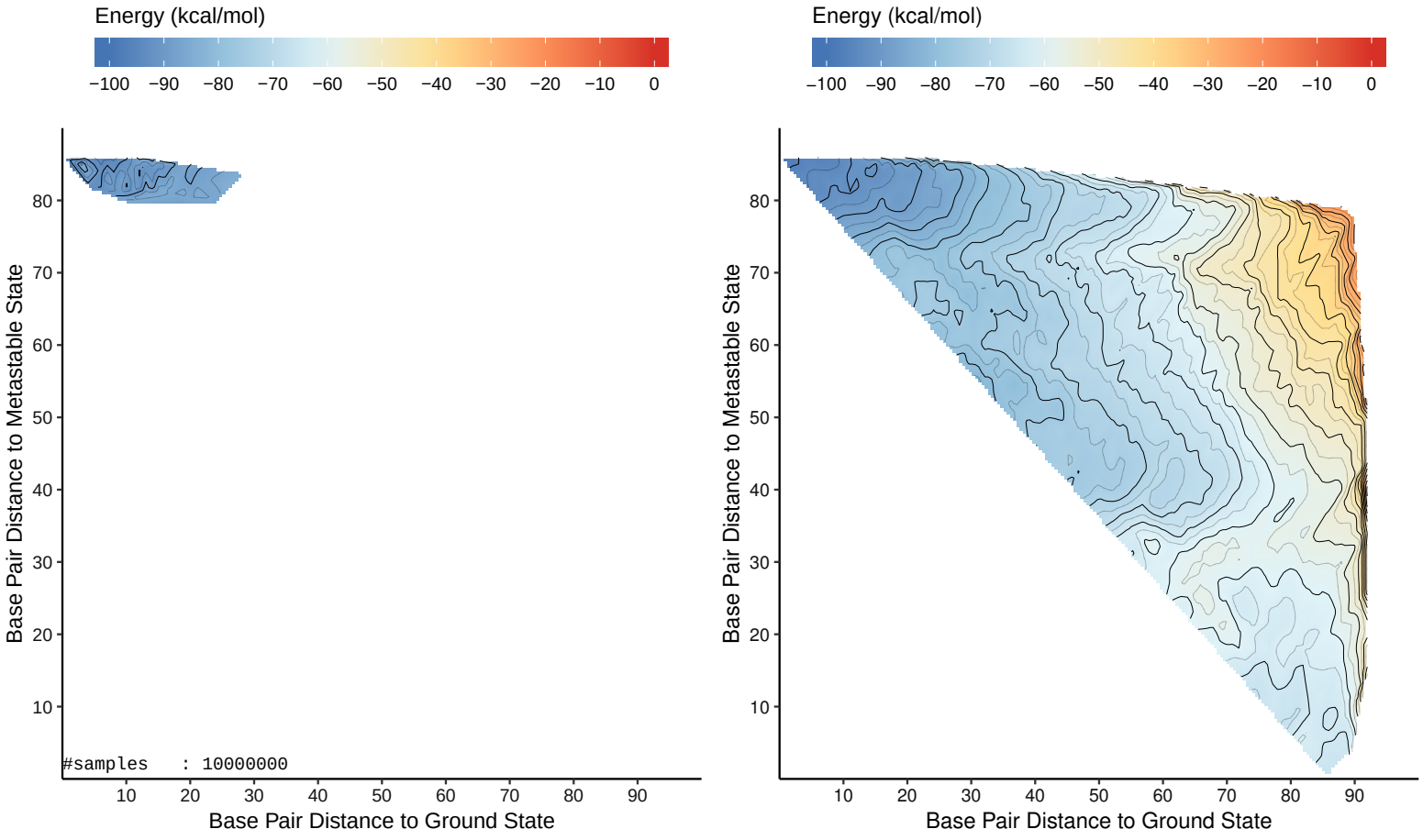
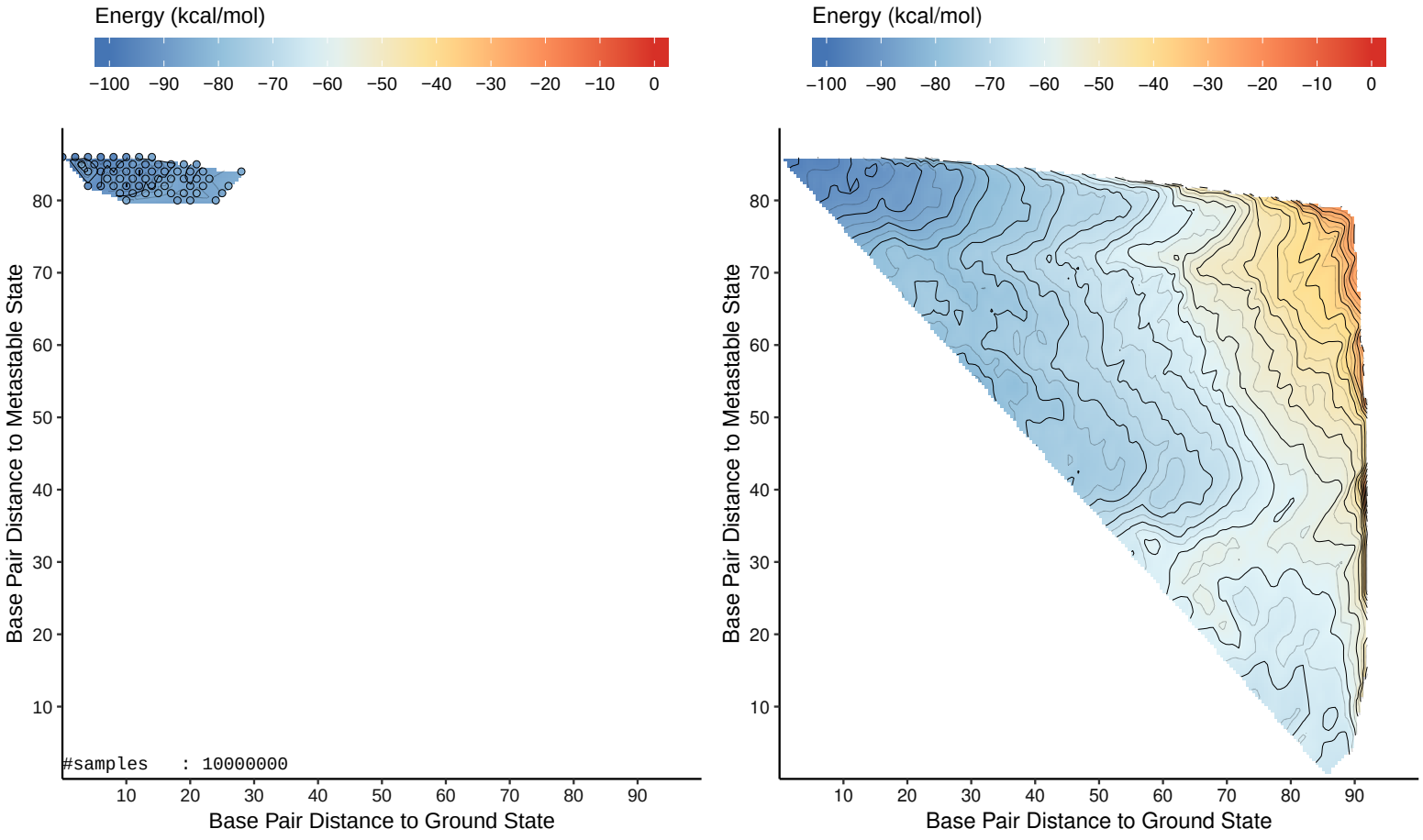


samples: $10,000,000$, # local minima: 272

Example: Qβ replicase template SV11

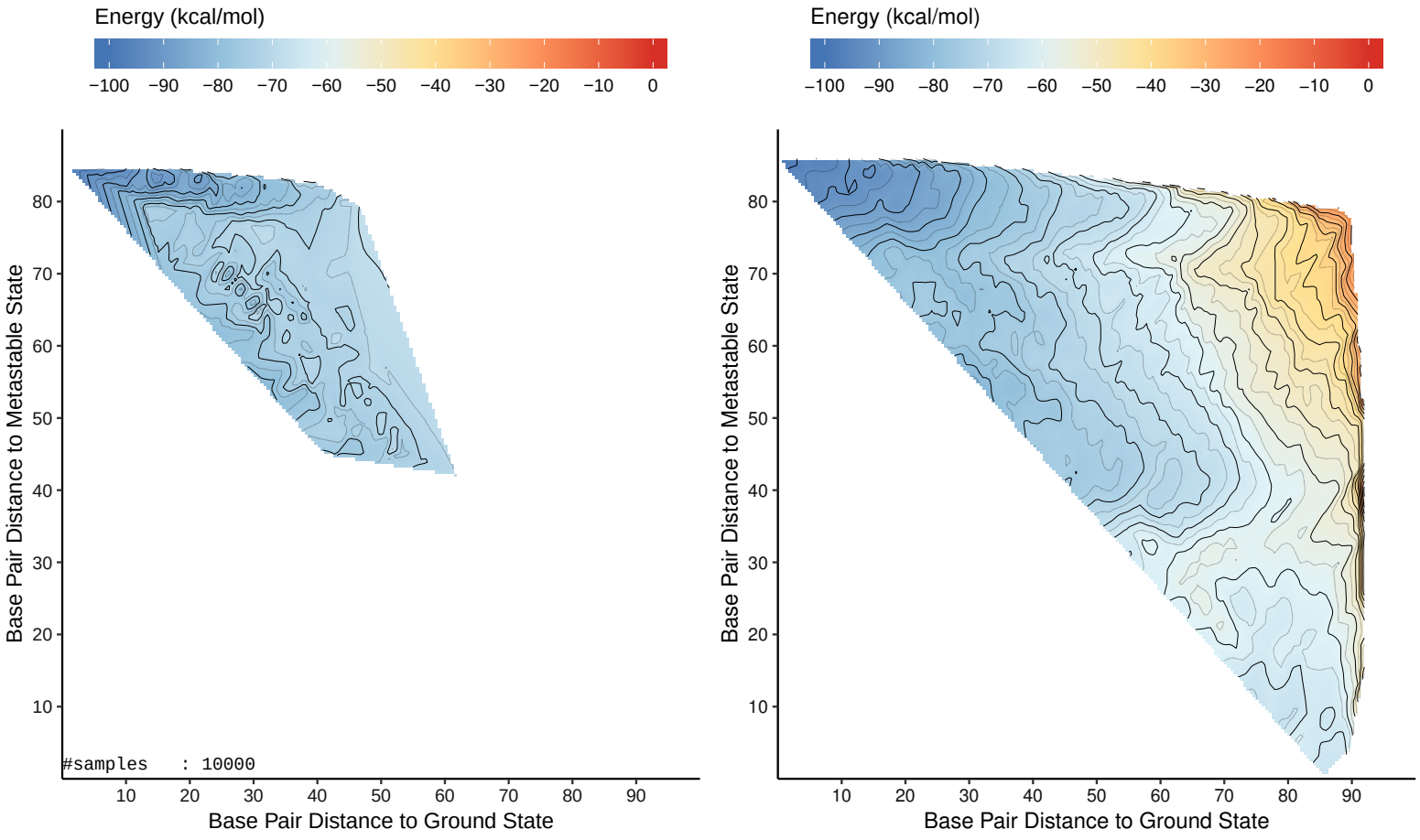
`RNAlocopt` Boltzmann sampling



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

Example: Qβ replicase template SV11

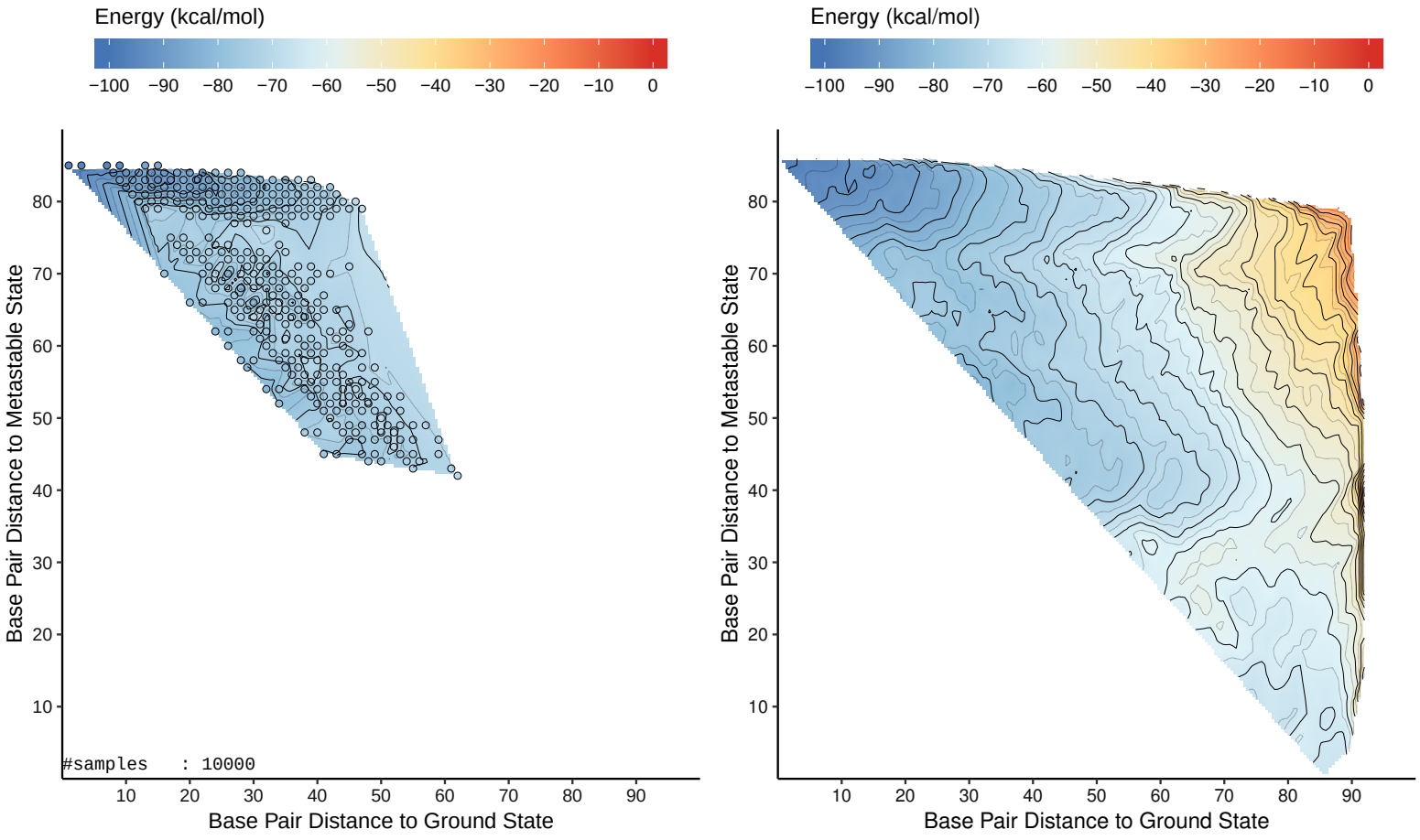
RNANR non-redundant Boltzmann sampling



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

Example: Qβ replicase template SV11

RNANR non-redundant Boltzmann sampling



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

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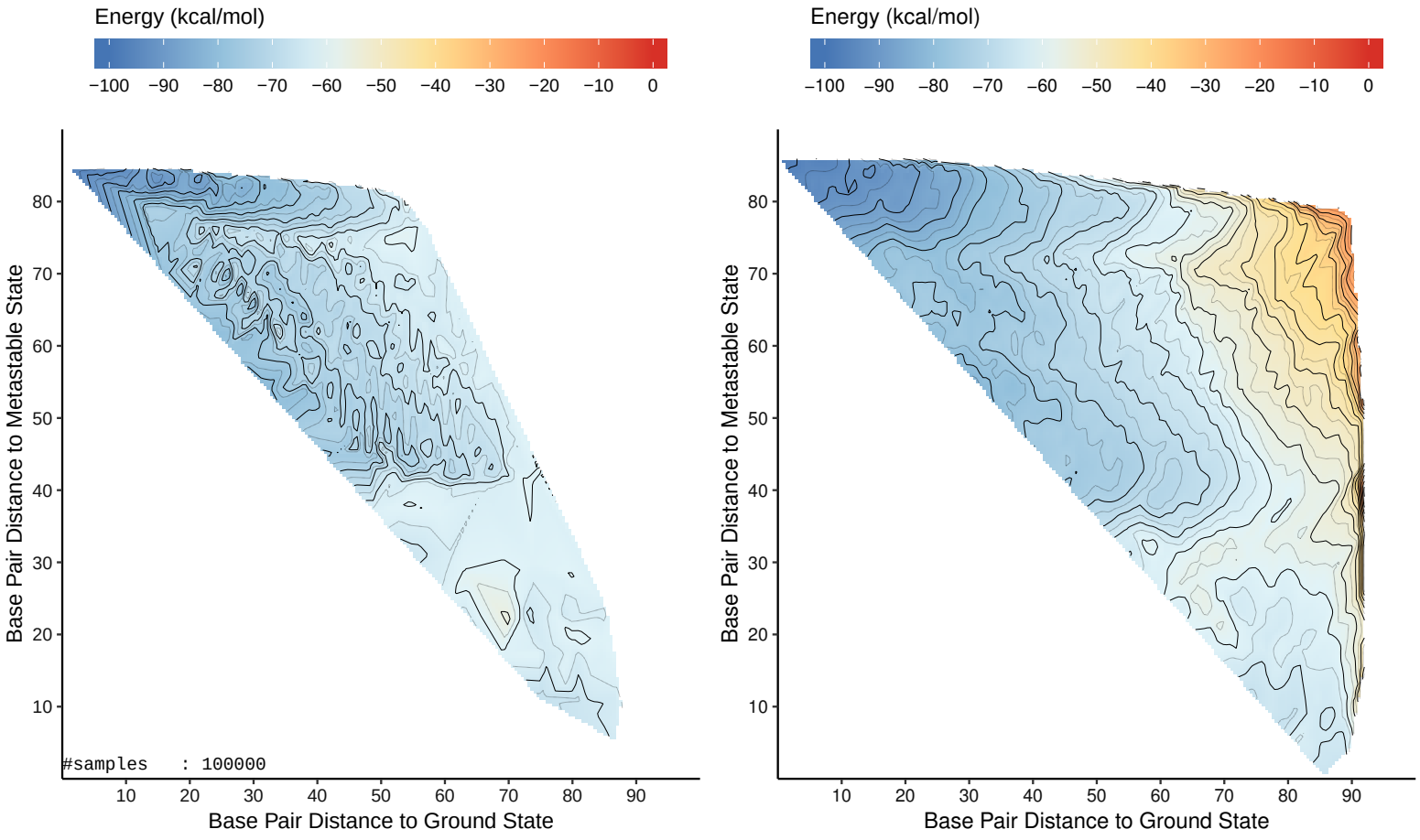
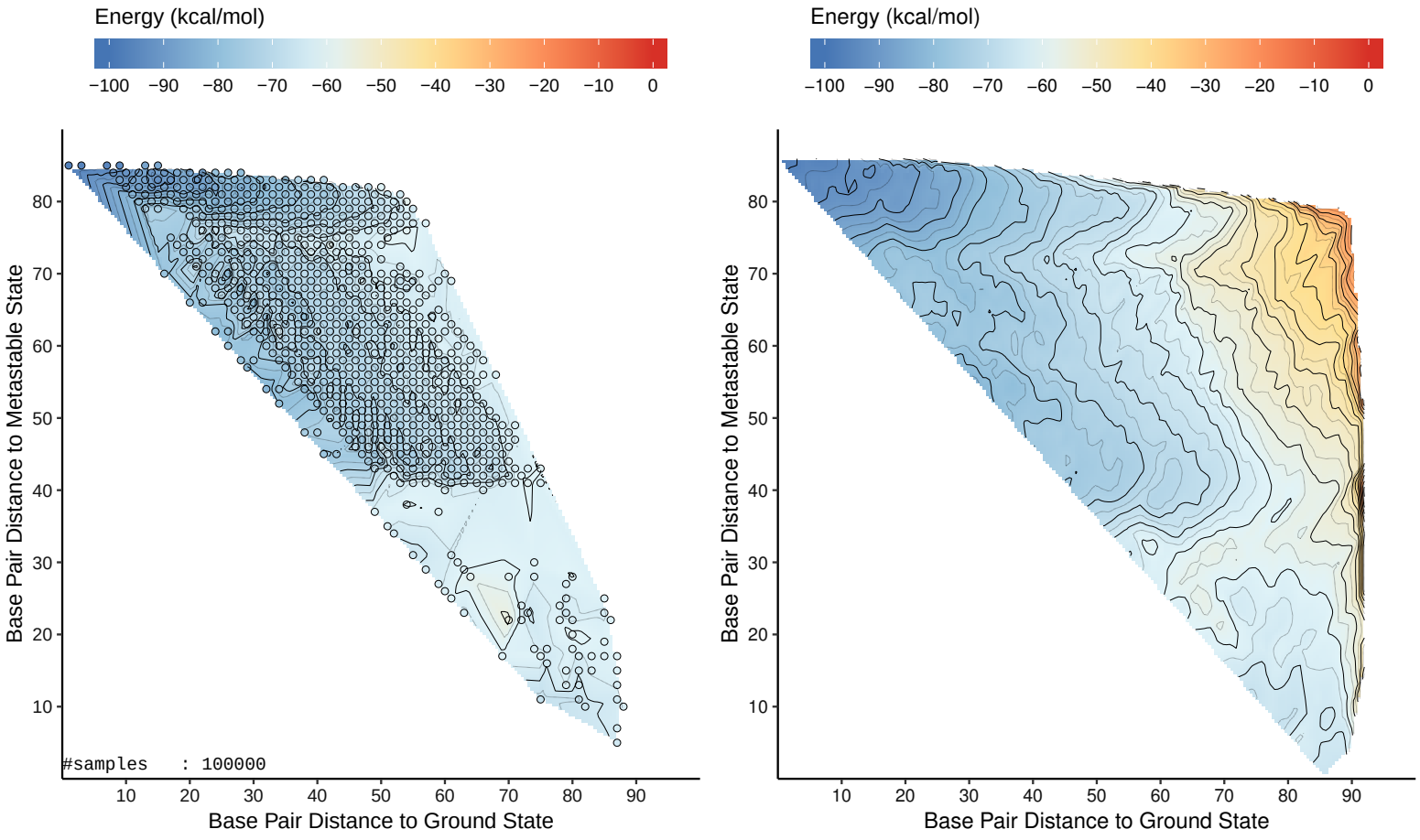


samples: 100, 000, # local minima: 100, 000

Example: Qβ replicase template SV11

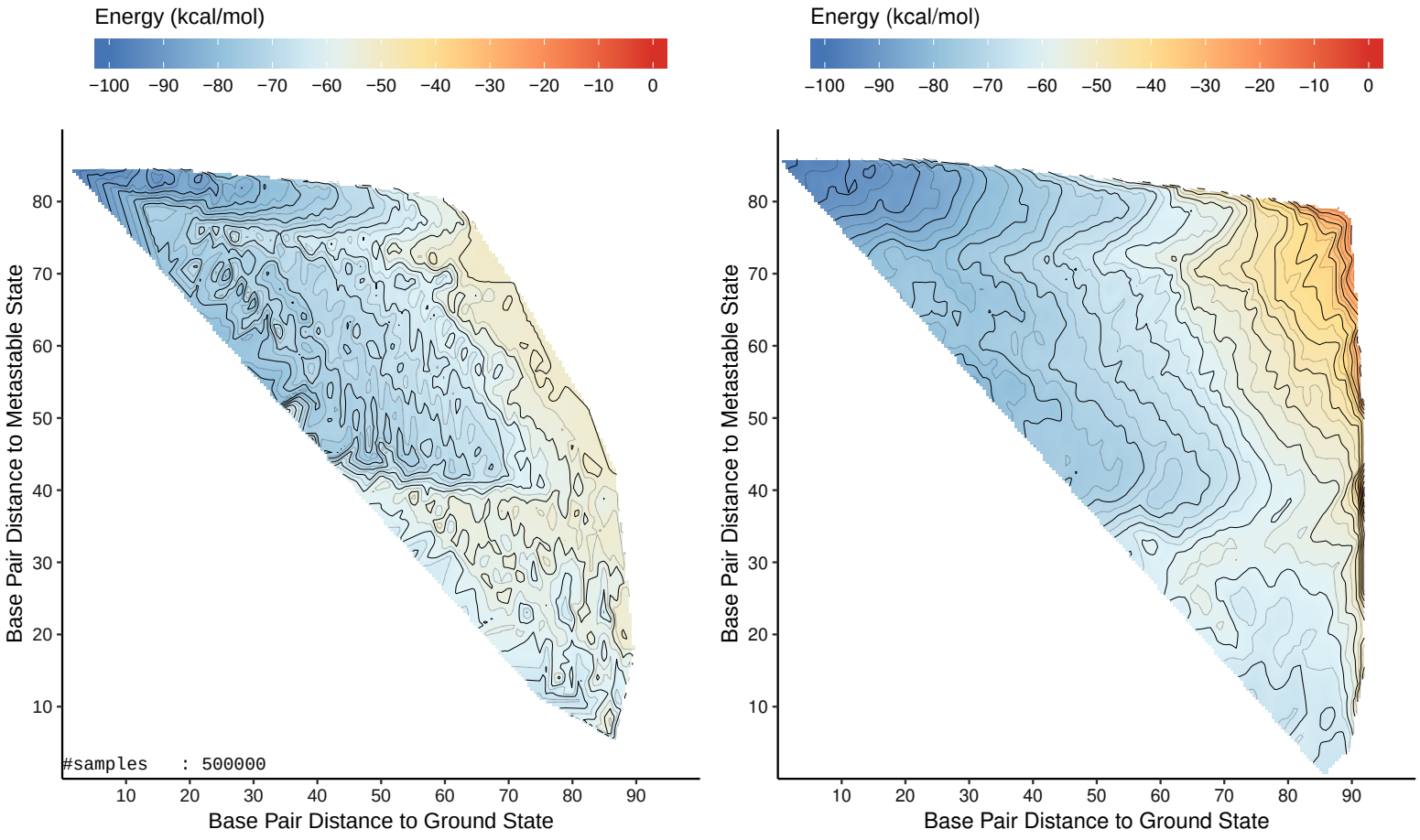
RNANR non-redundant Boltzmann sampling



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

Example: Qβ replicase template SV11

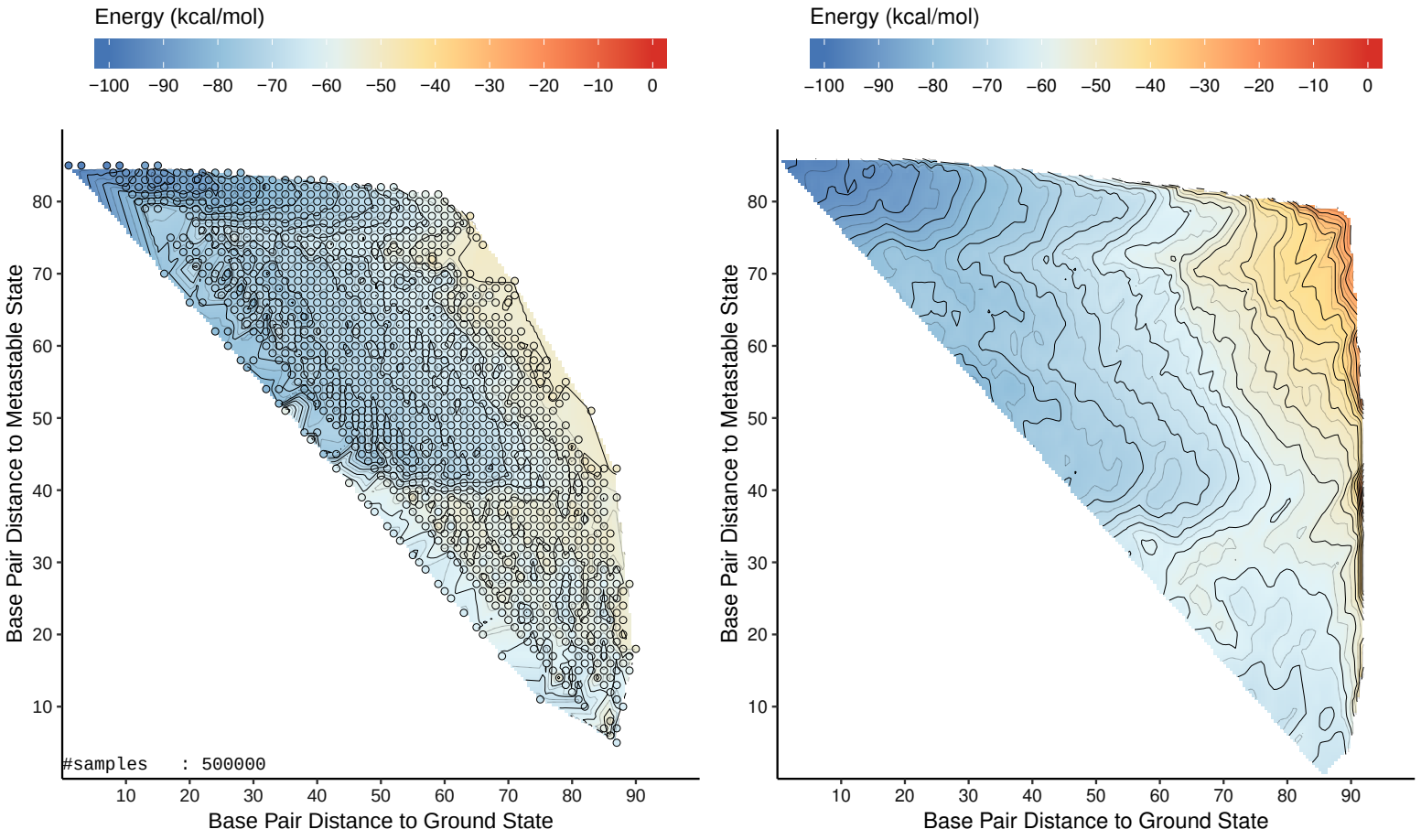
RNANR non-redundant Boltzmann sampling



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

Example: Qβ replicase template SV11

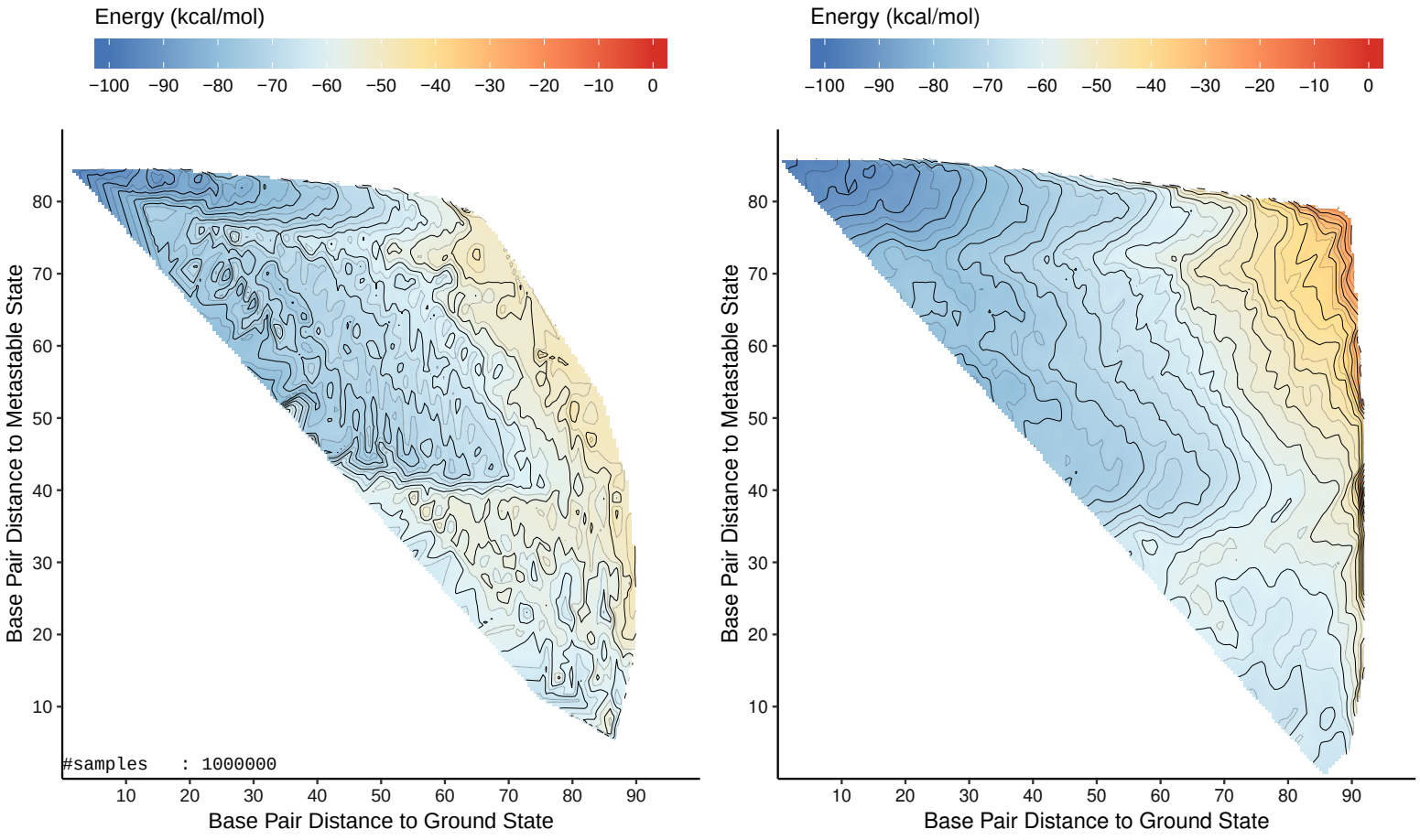
RNANR non-redundant Boltzmann sampling



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

Example: Qβ replicase template SV11

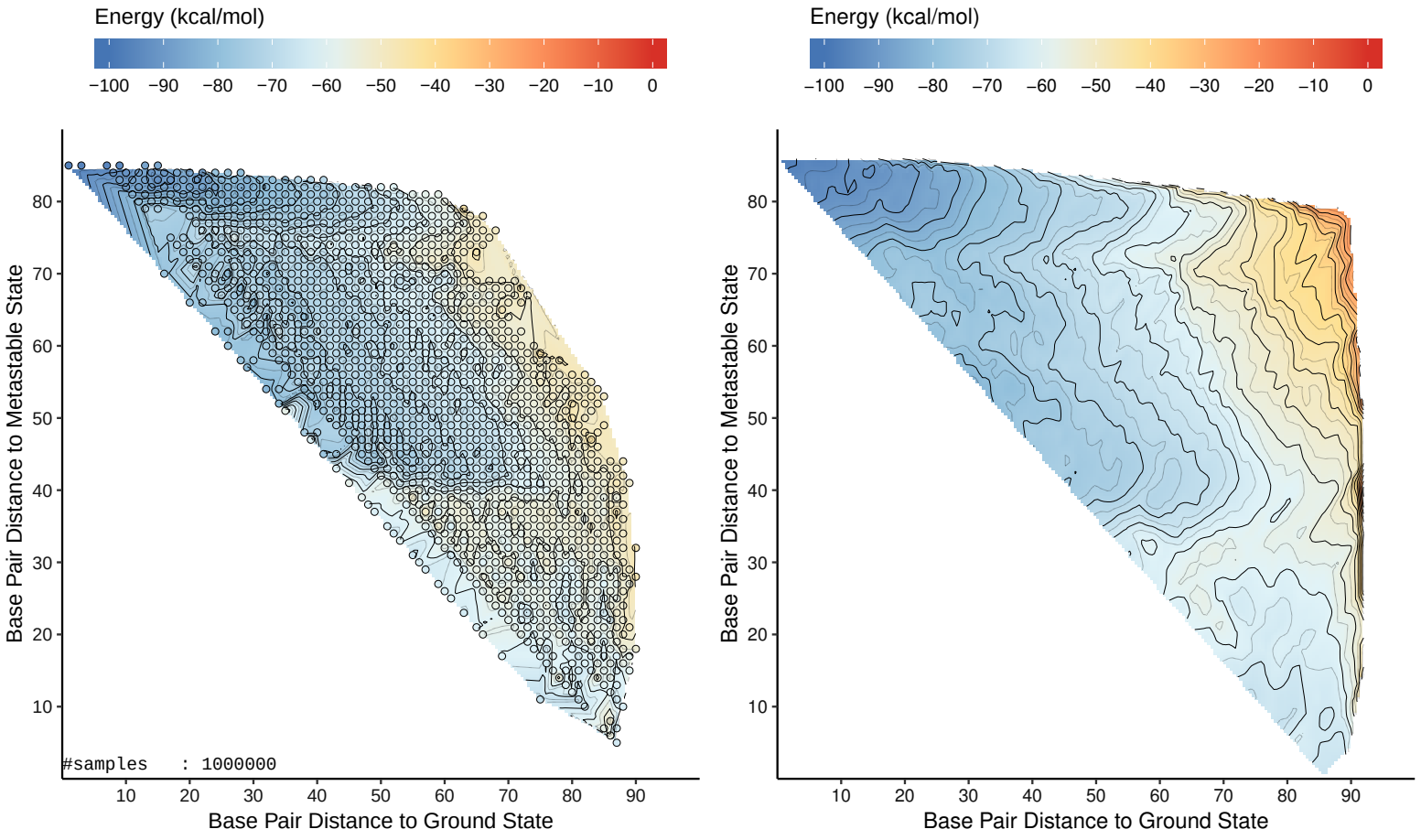
RNANR non-redundant Boltzmann sampling



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

Example: Qβ replicase template SV11

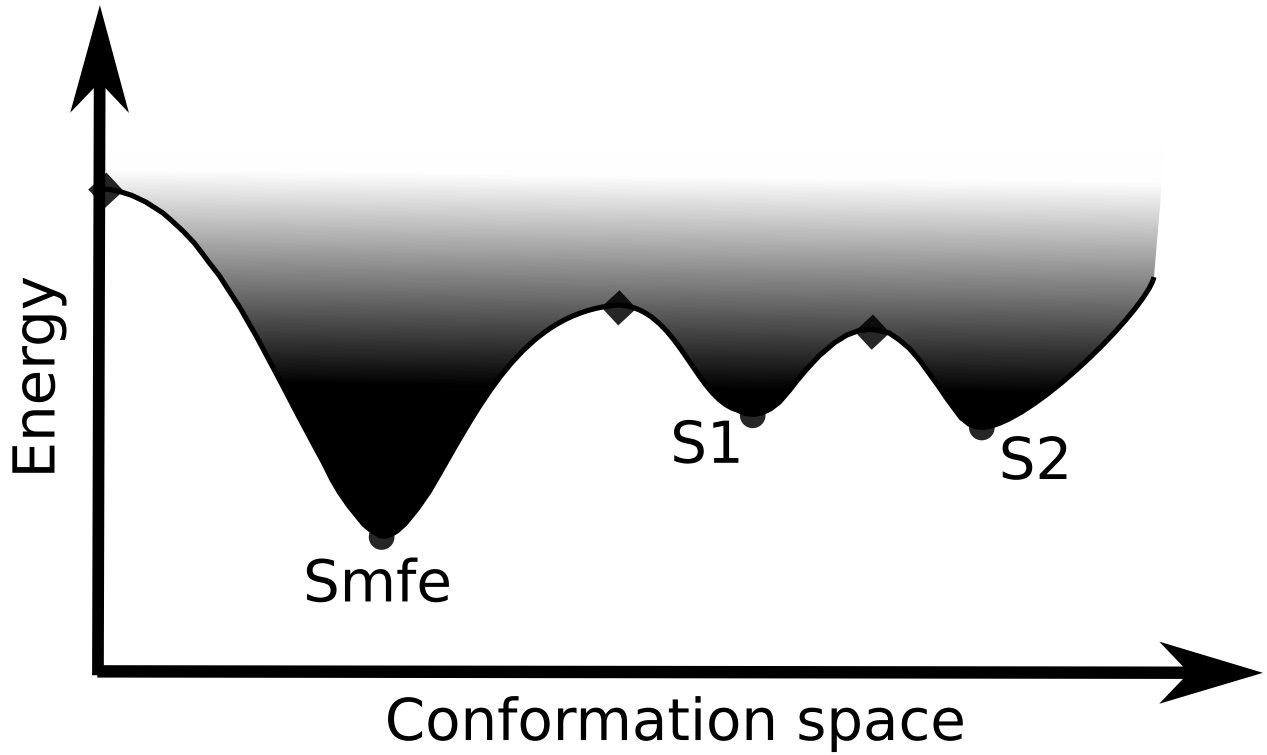
RNANR non-redundant Boltzmann sampling



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

Sampling Strategies

4. Elevated Temperature Boltzmann Sampling

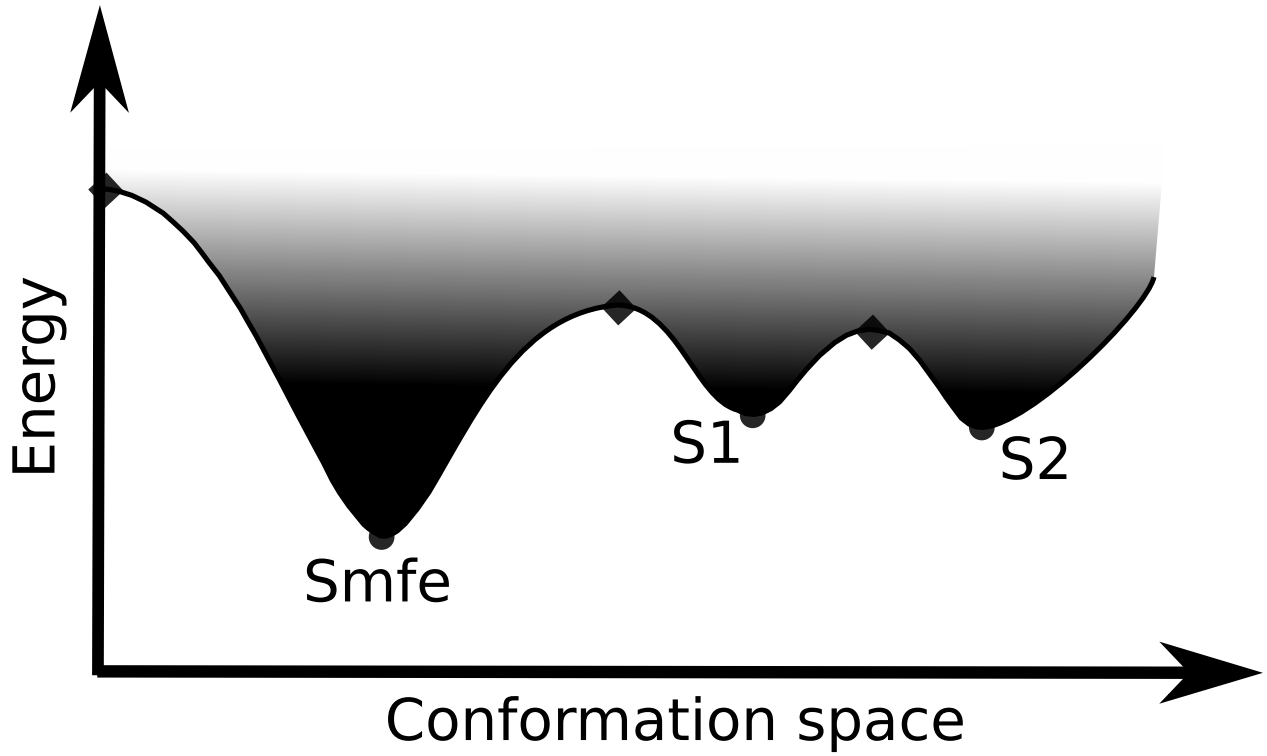


- iteratively draw samples at different $T = \xi \cdot T_0, \xi > 1$
- `RNAlocmin`[11]

[11] Kucharik et al. 2014

Sampling Strategies

4. Elevated Temperature Boltzmann Sampling



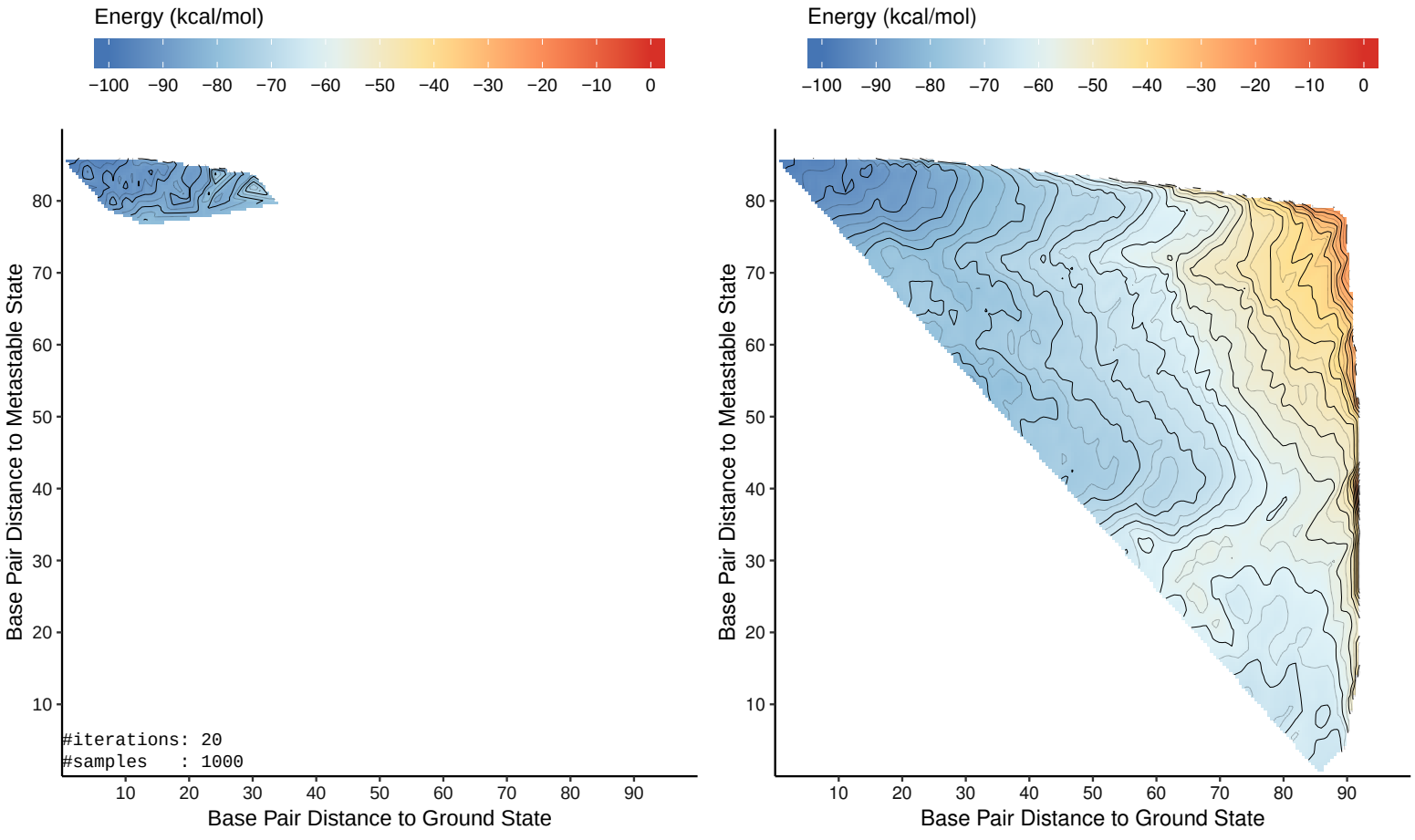
- iteratively draw samples at different $T = \xi \cdot T_0, \xi > 1$
- `RNAlocmin`[11]

Samples are drawn from uniform distribution for $T \to \infty$

[11] Kucharik et al. 2014

Example: Qβ replicase template SV11

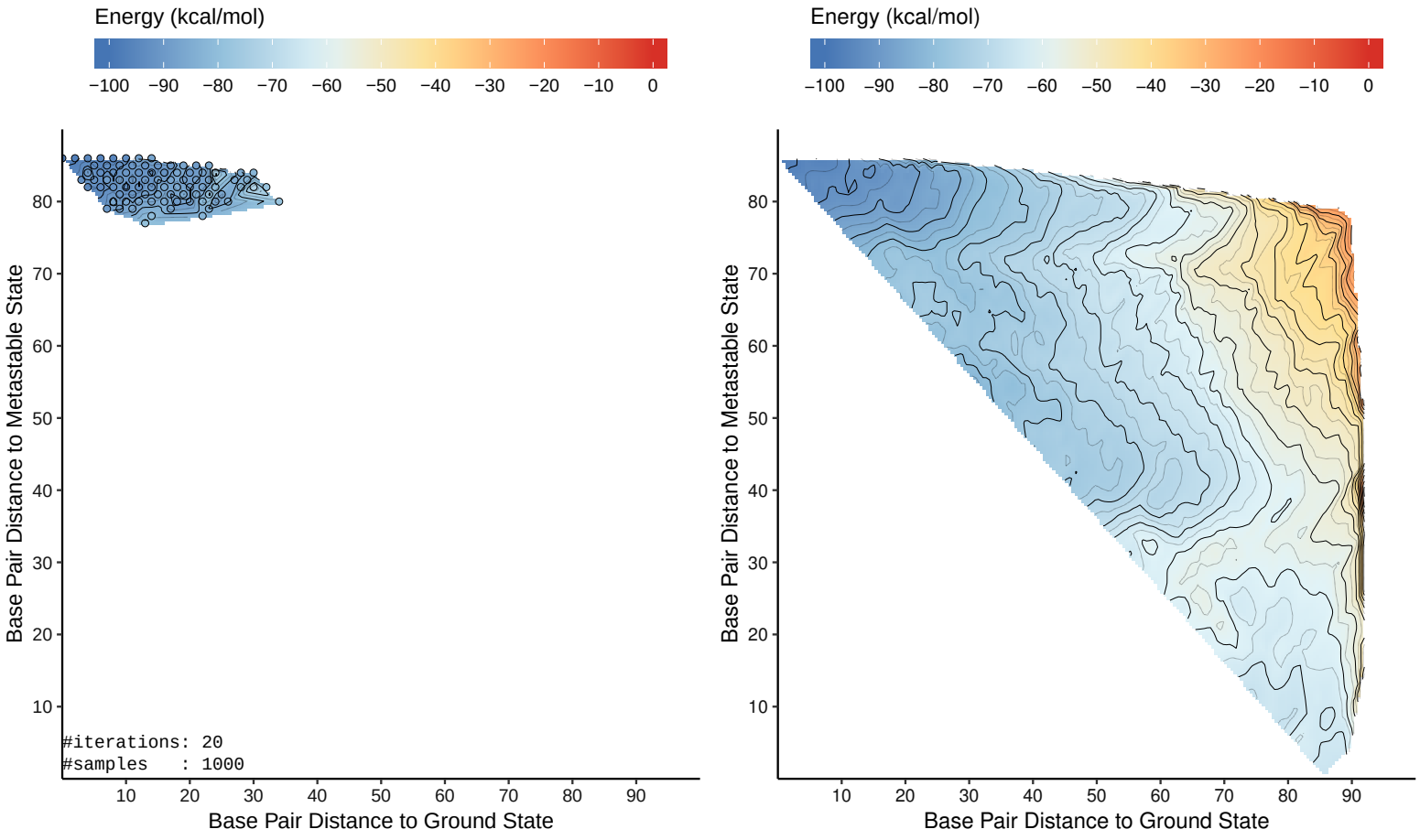
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

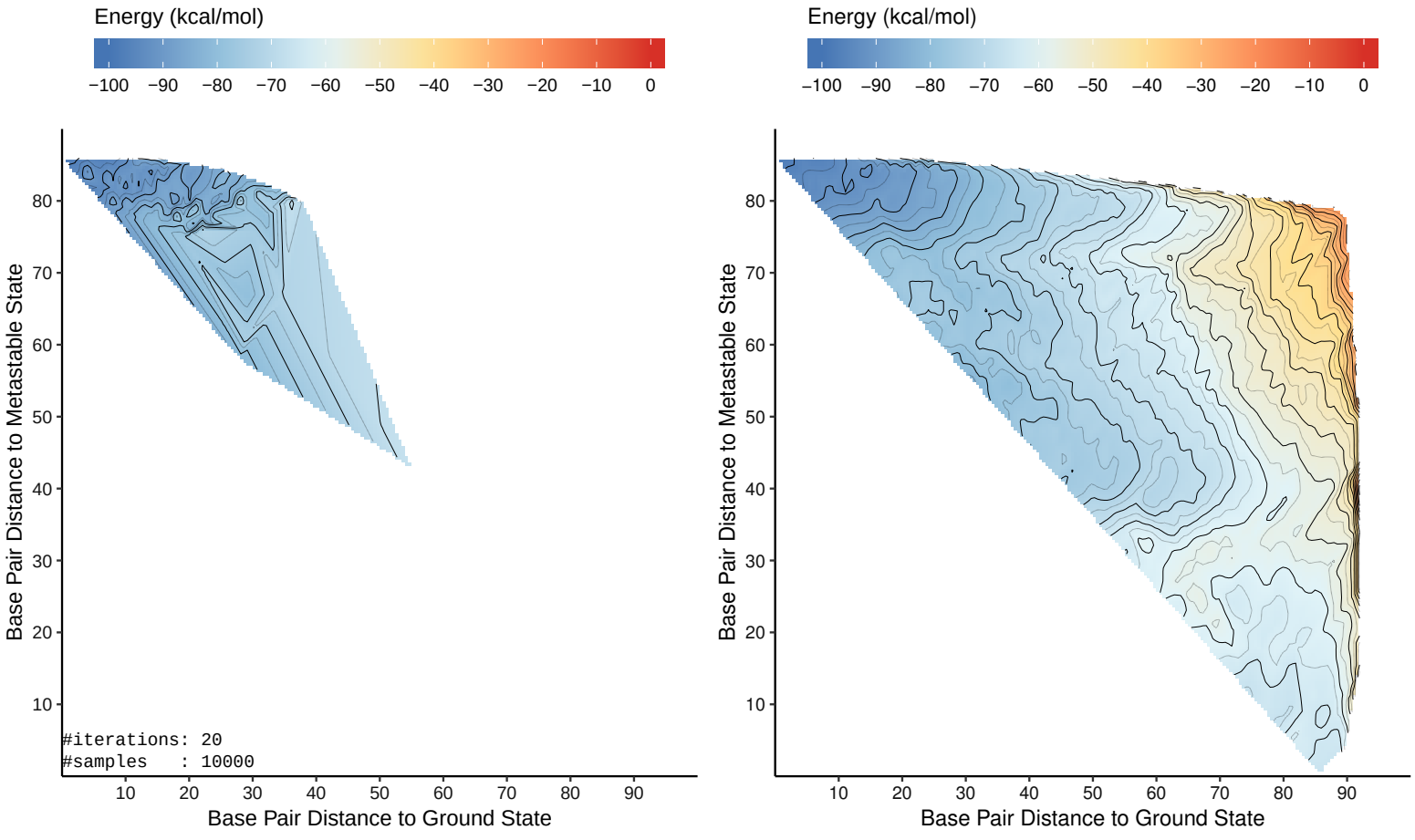
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

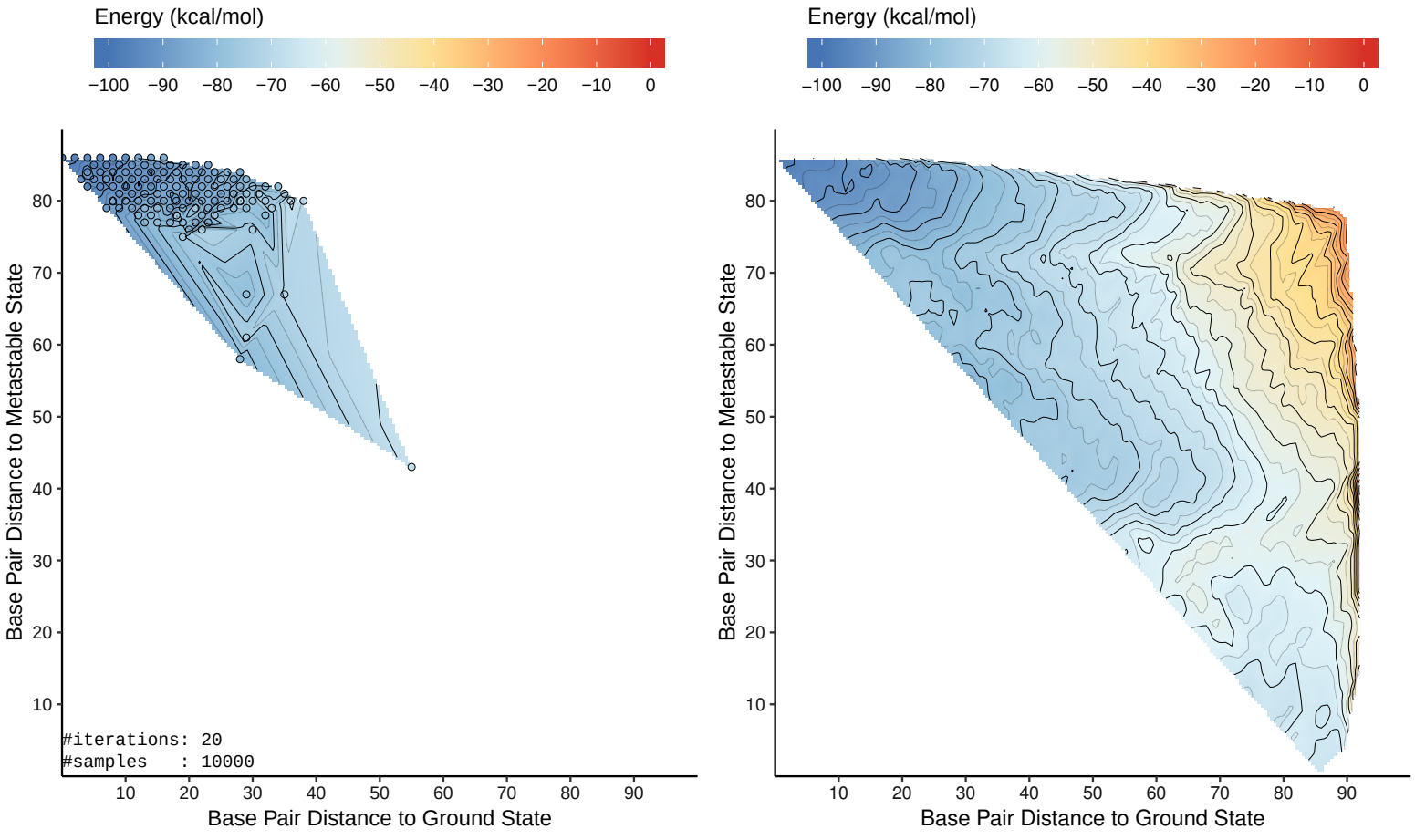
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

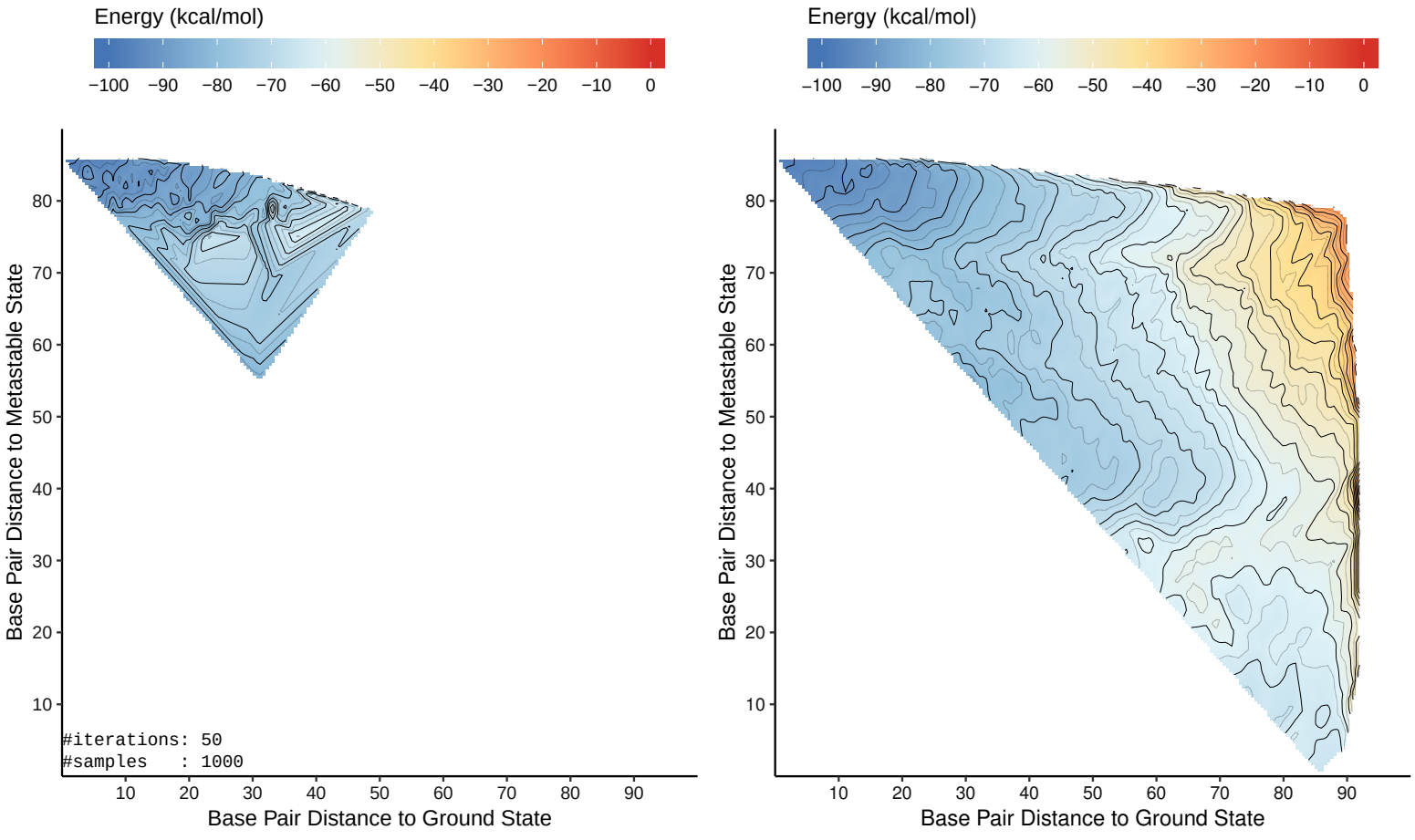
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

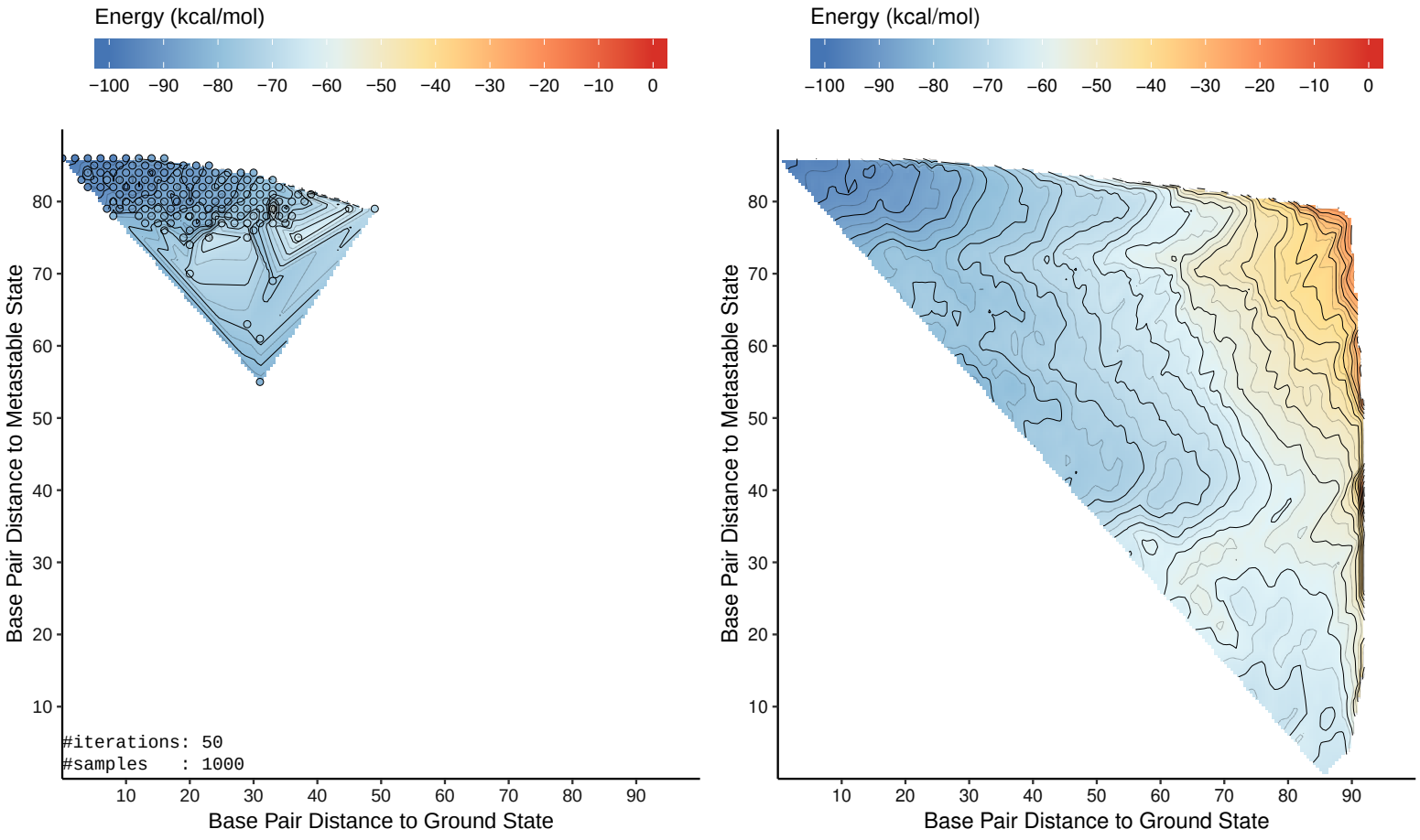
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

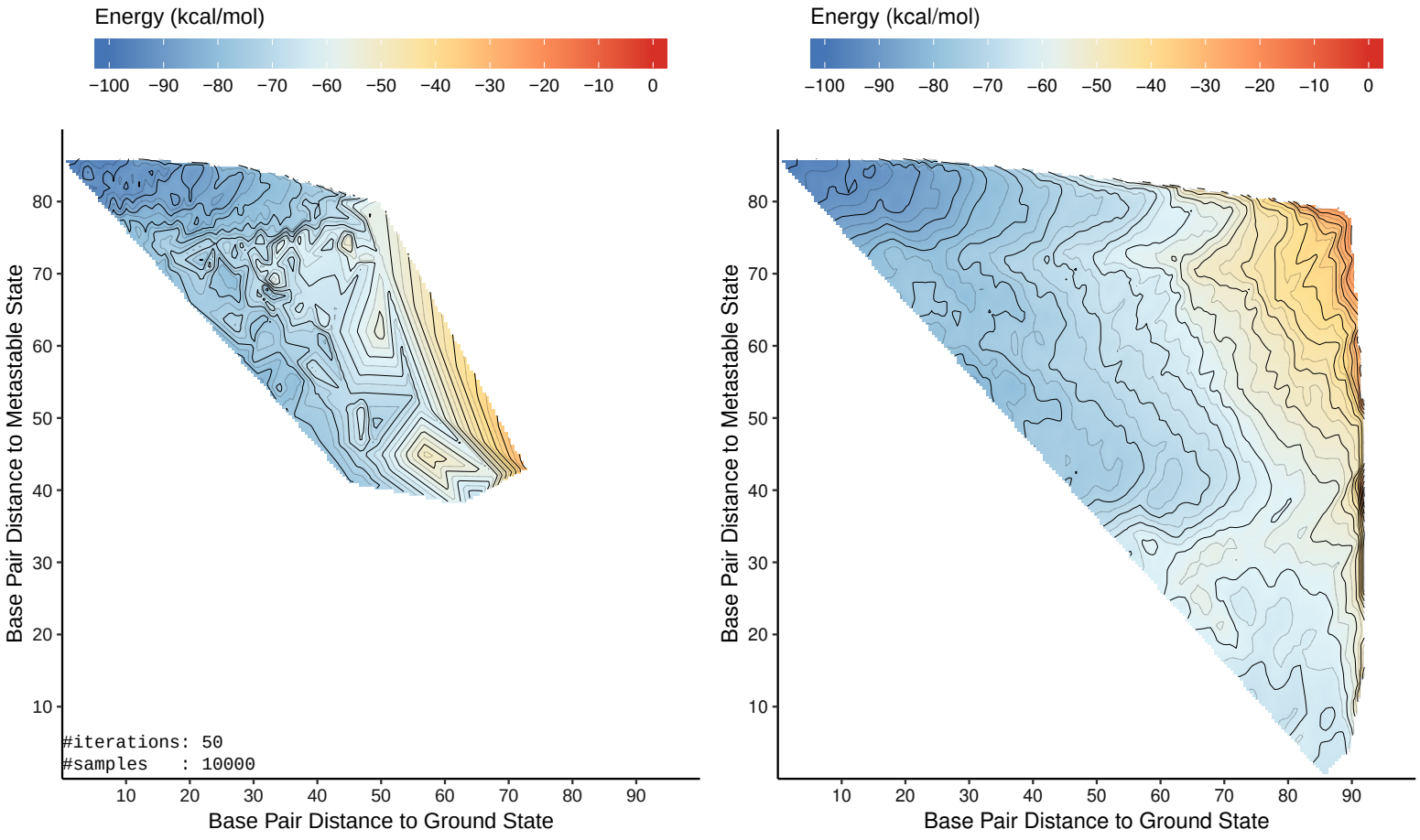
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

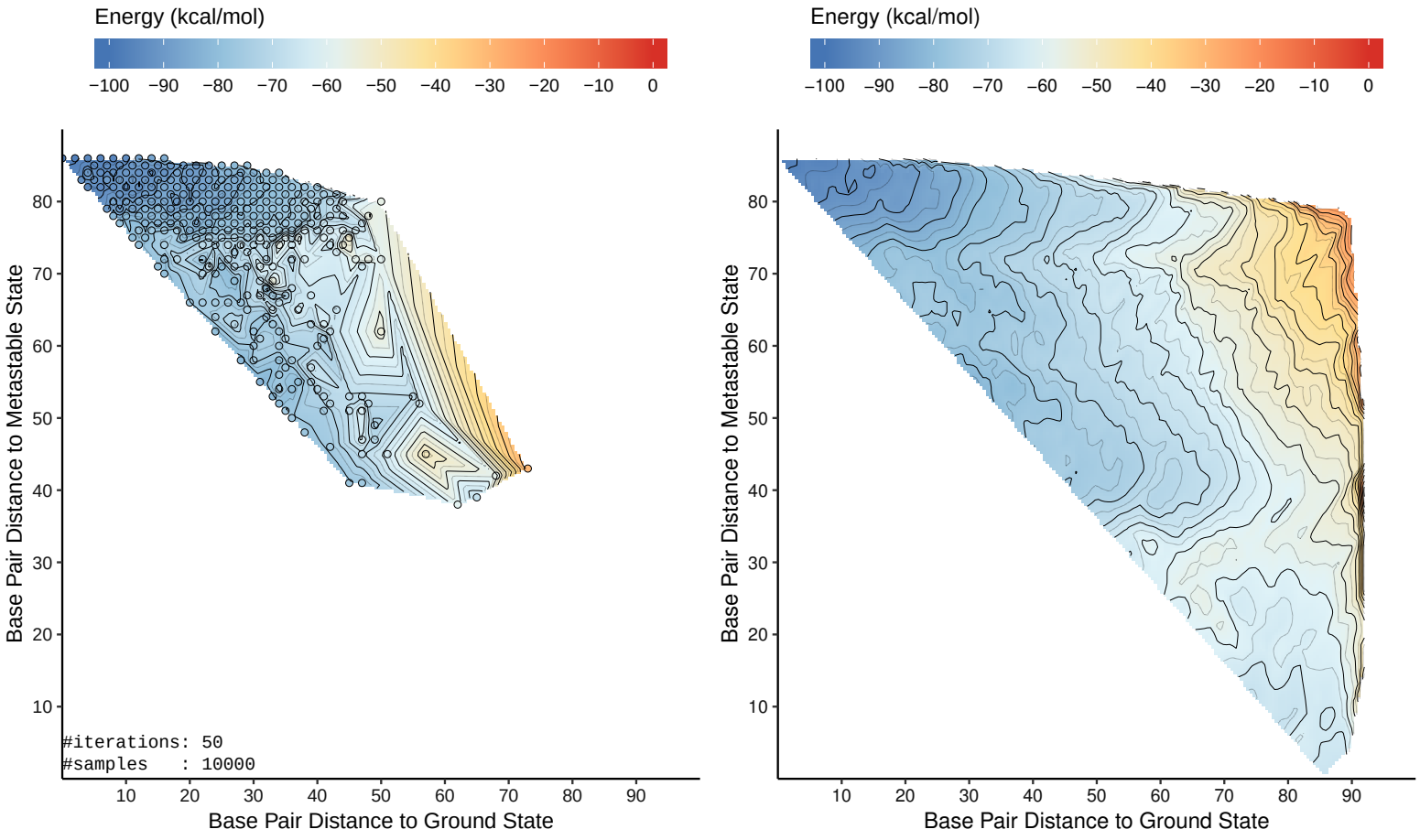
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

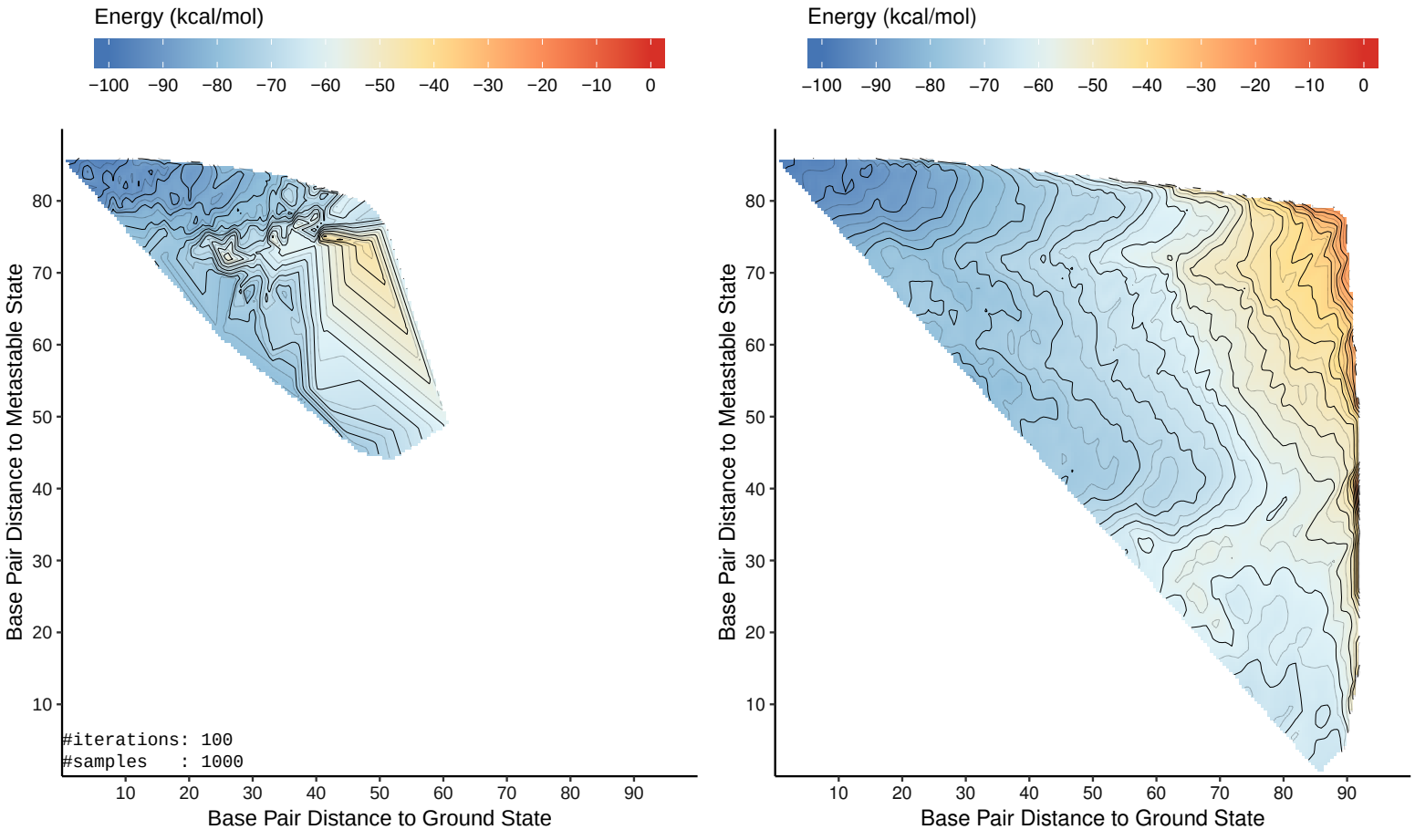
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

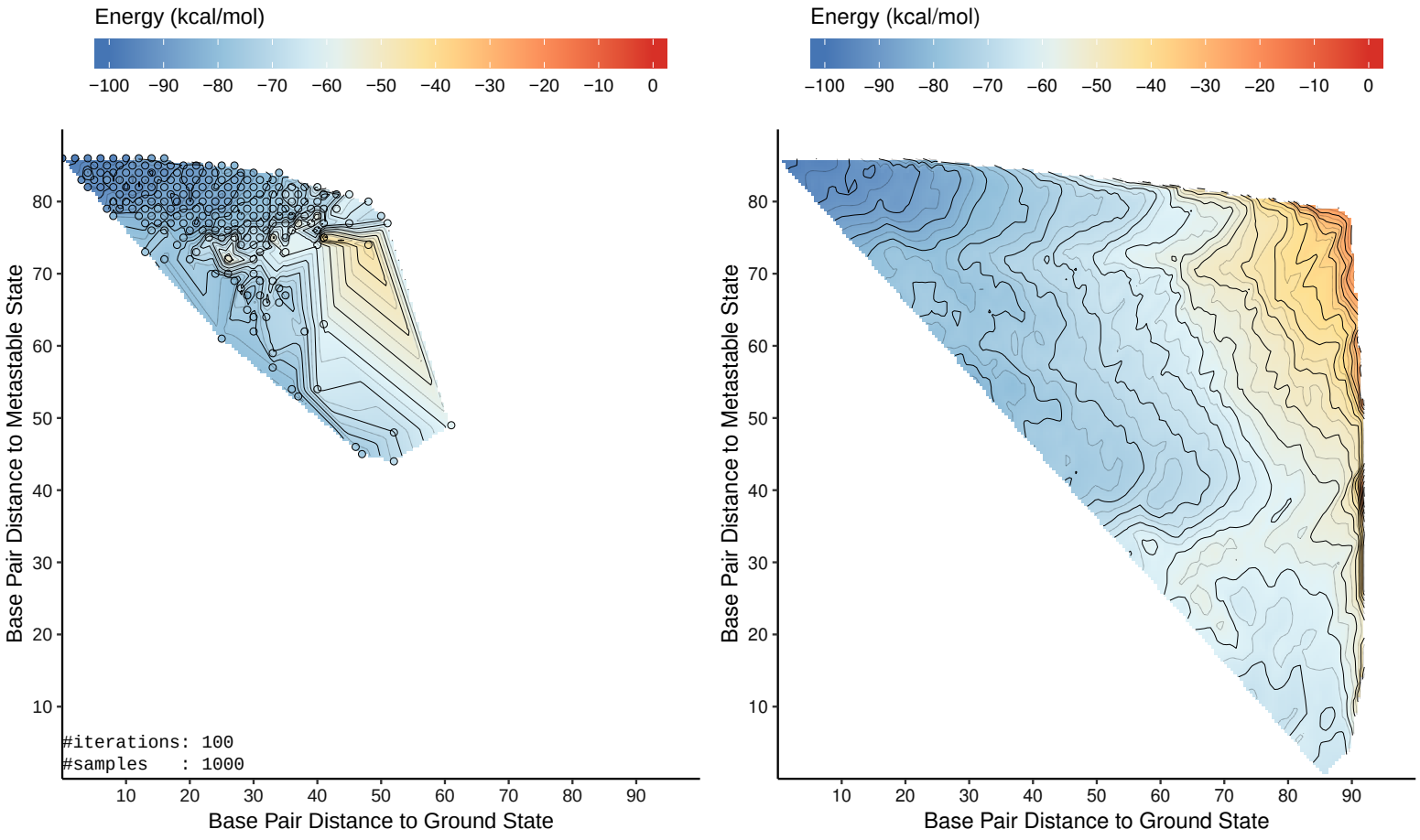
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

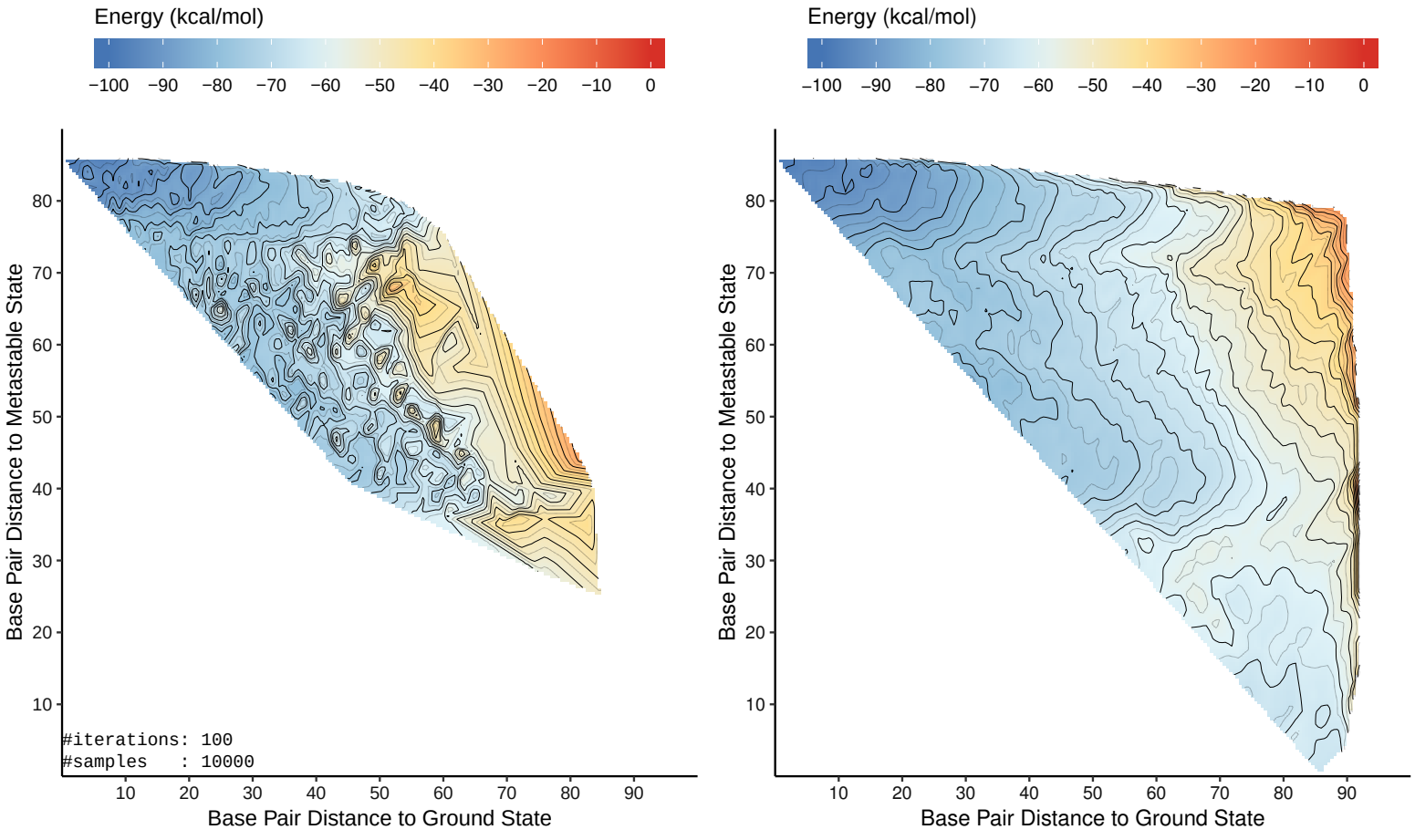
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

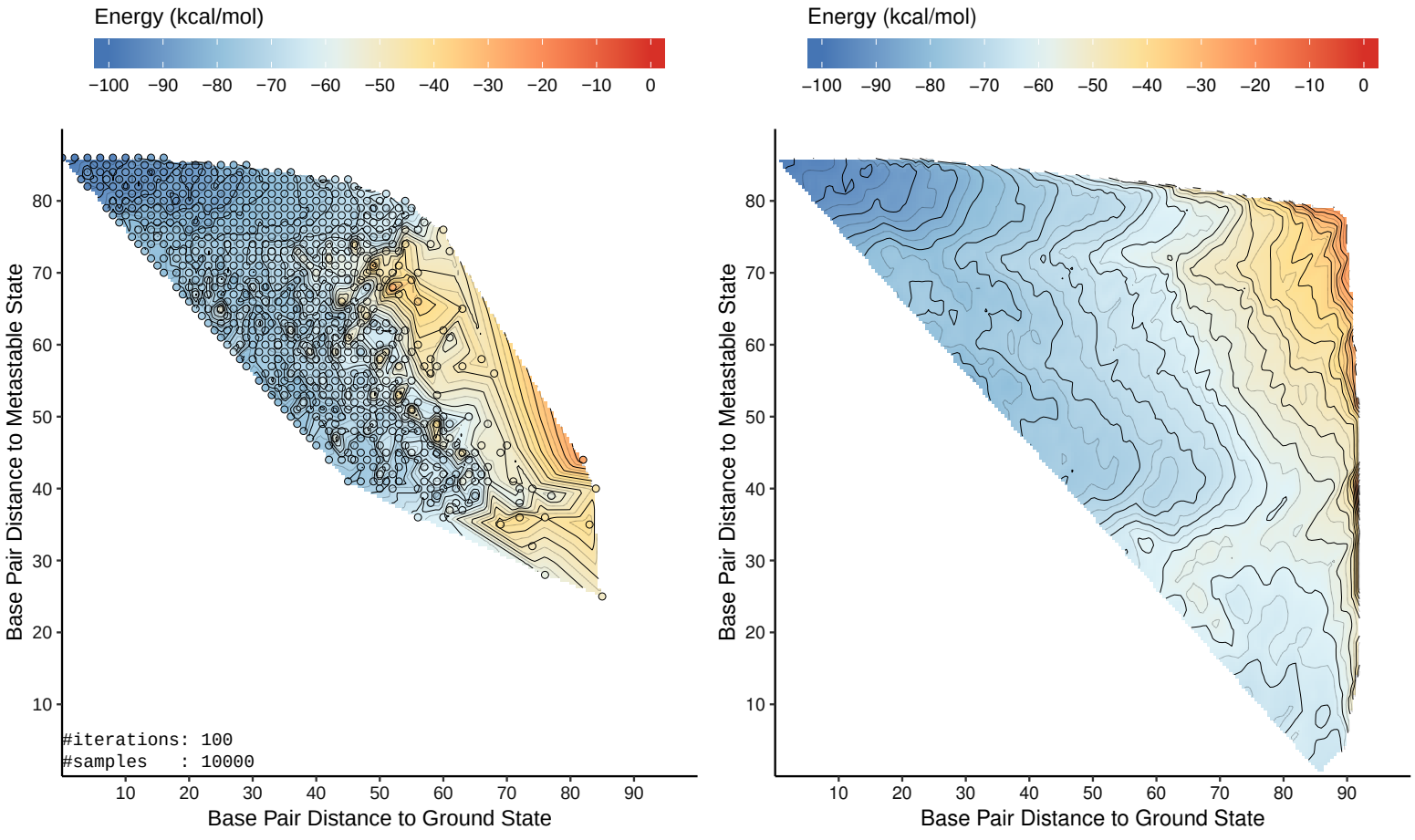
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

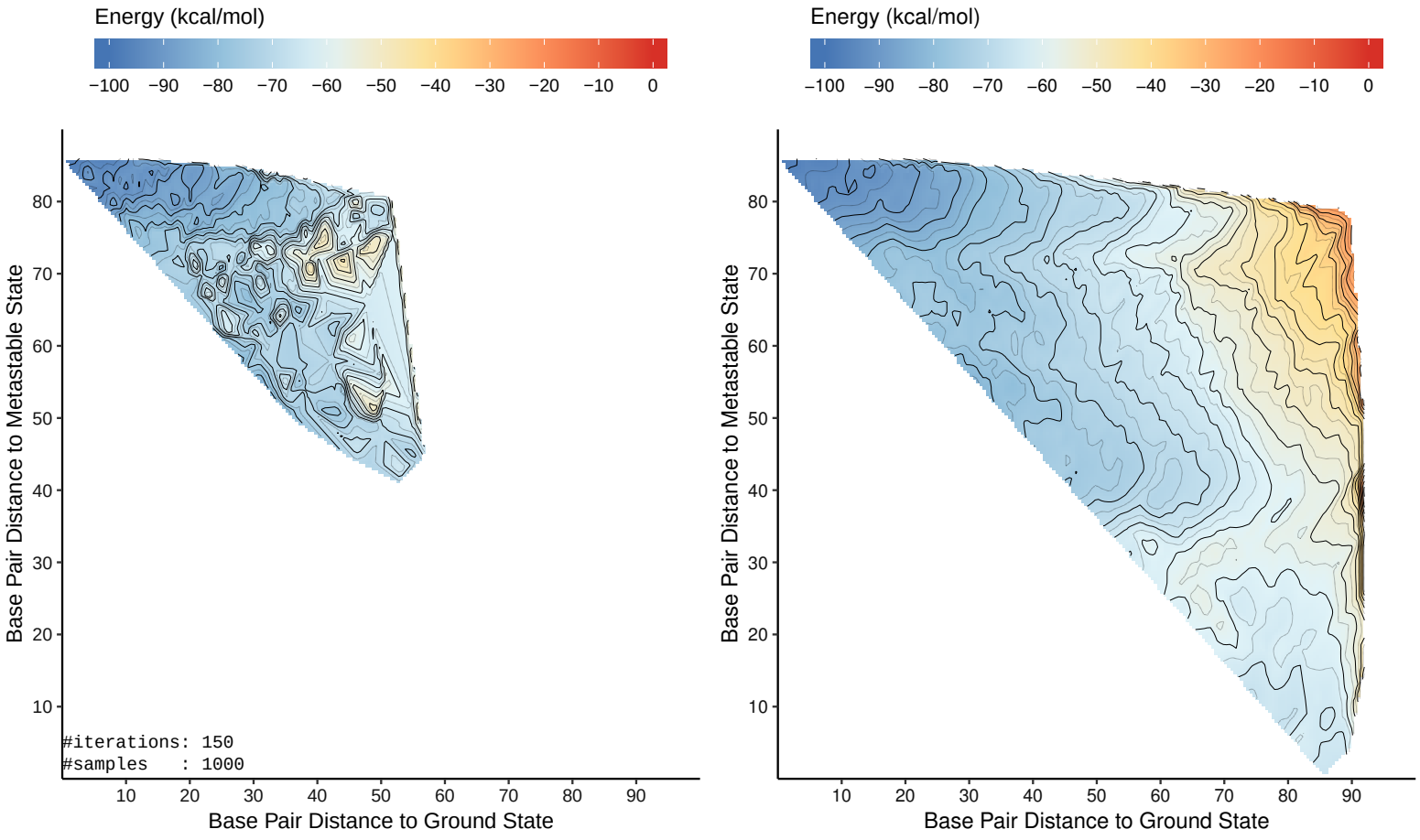
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

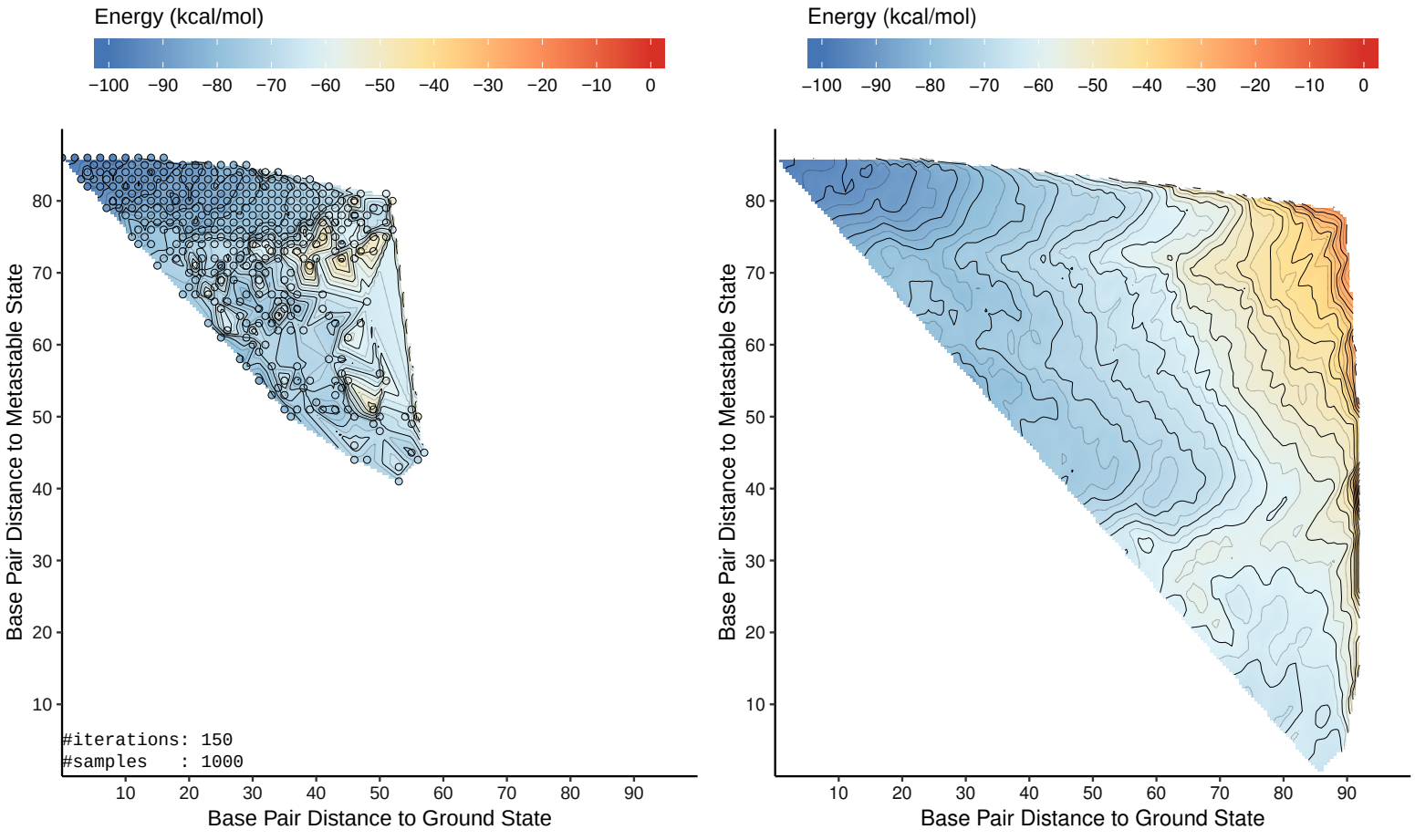
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

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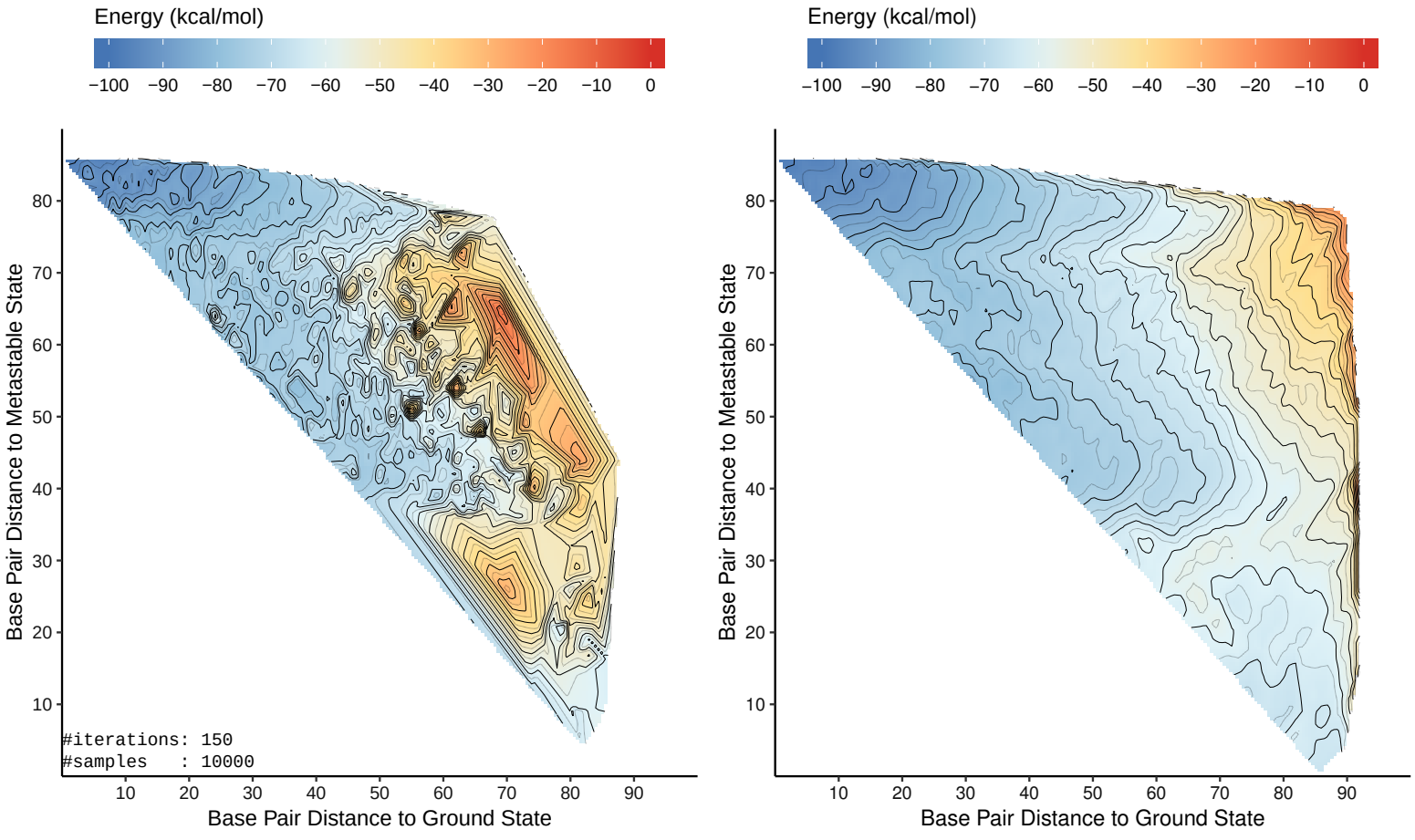
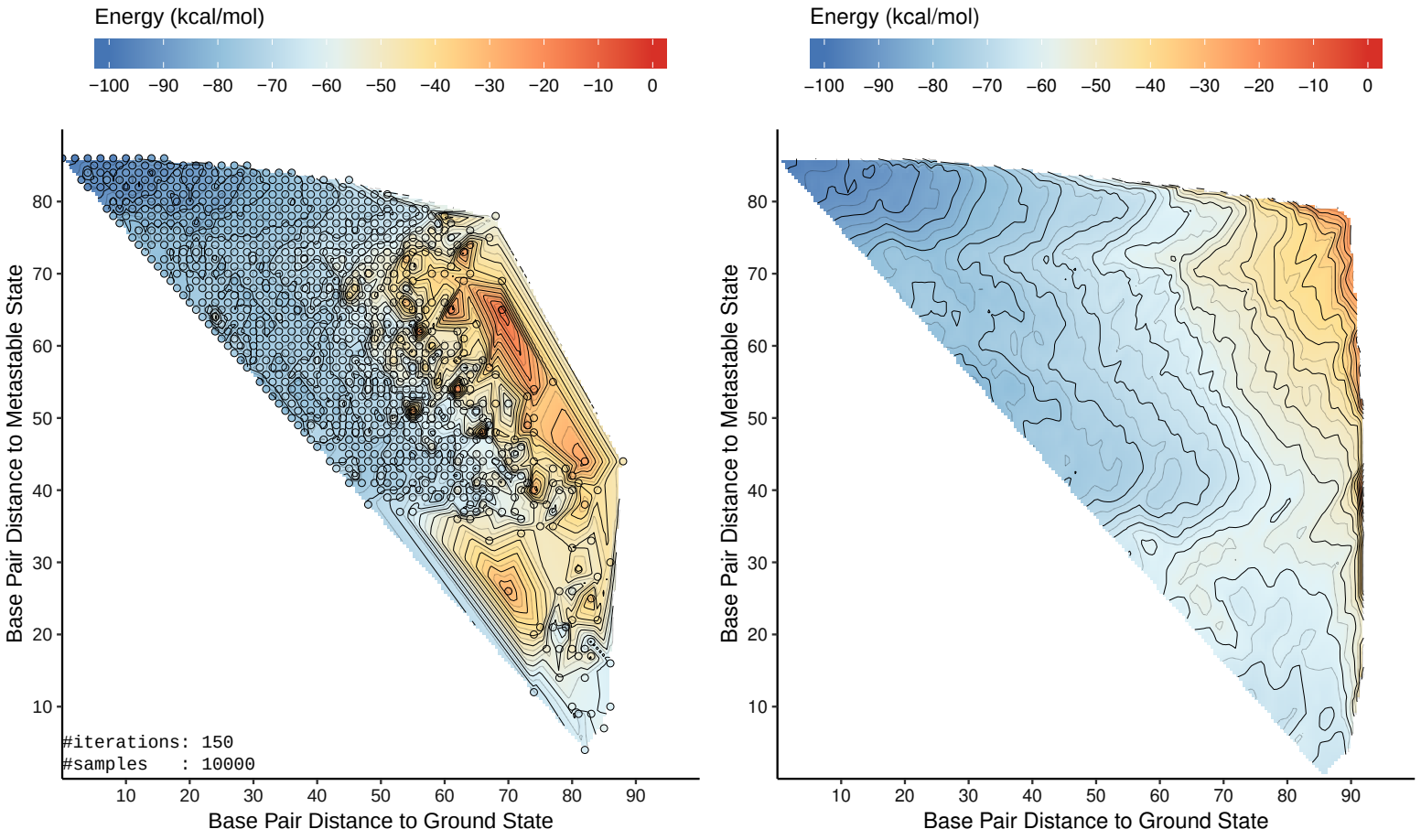


iterations: 150, # samples: 10,000, # local minima: 97,756

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

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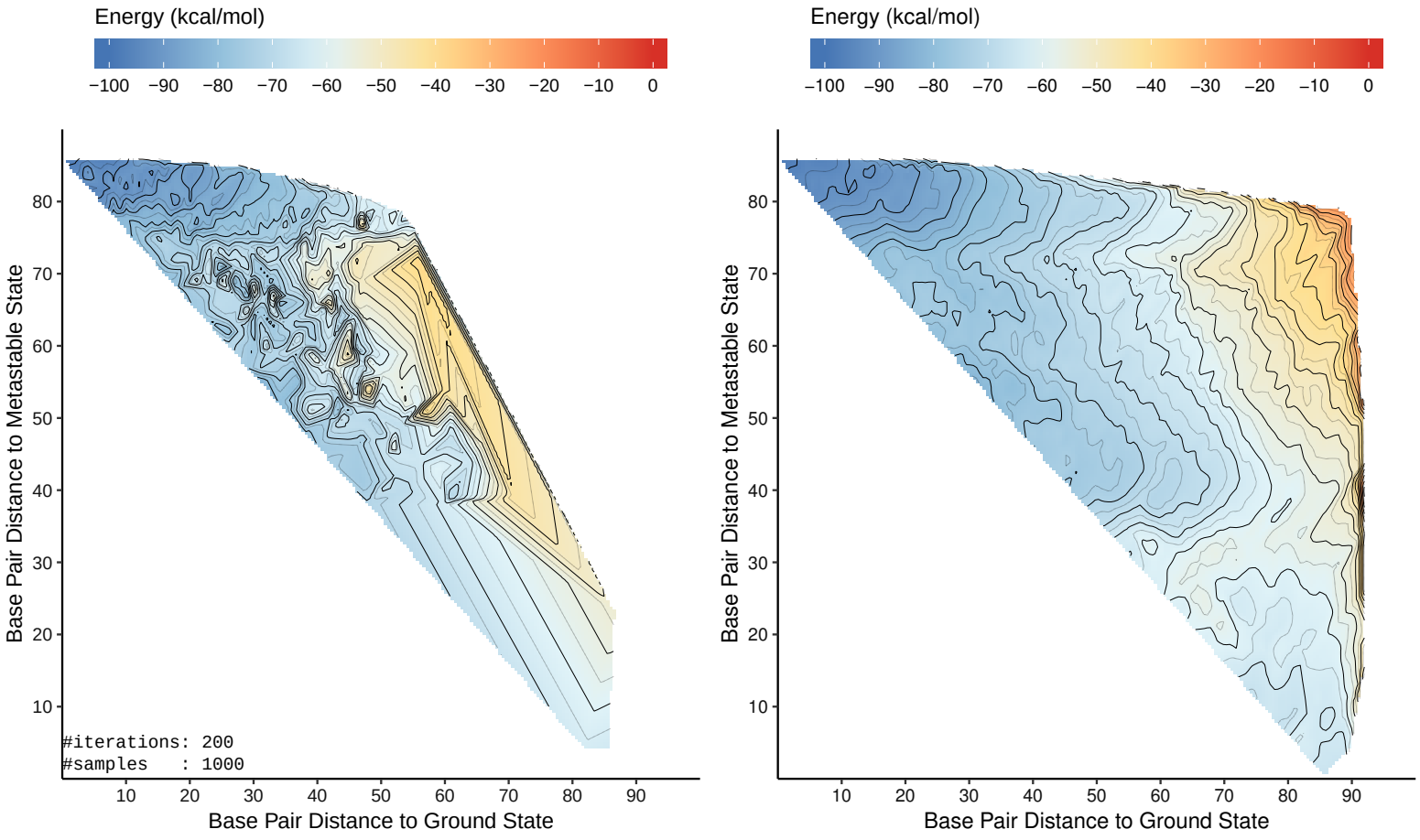
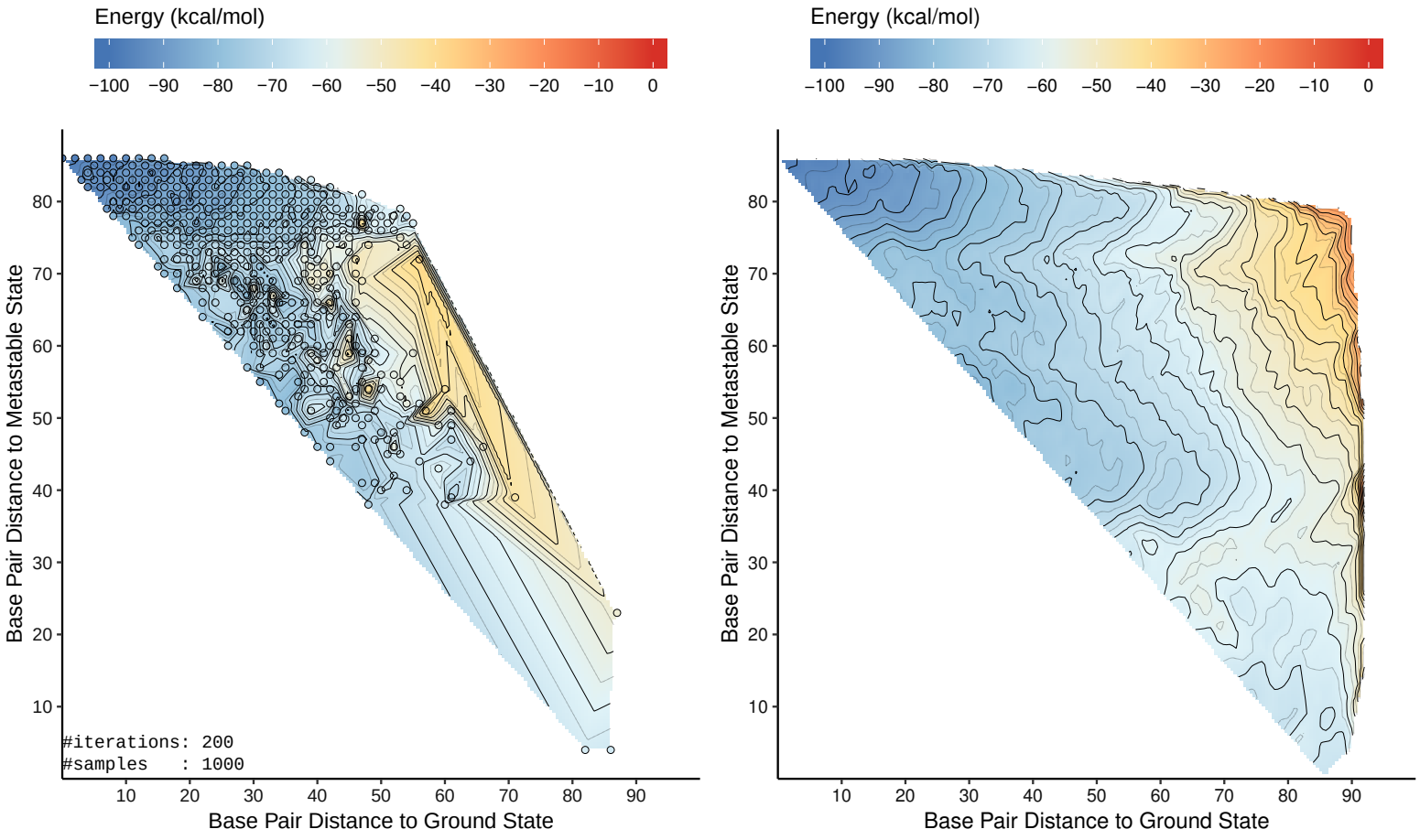


iterations: 200, # samples: 1, 000, # local minima: 18, 221

Example: Qβ replicase template SV11

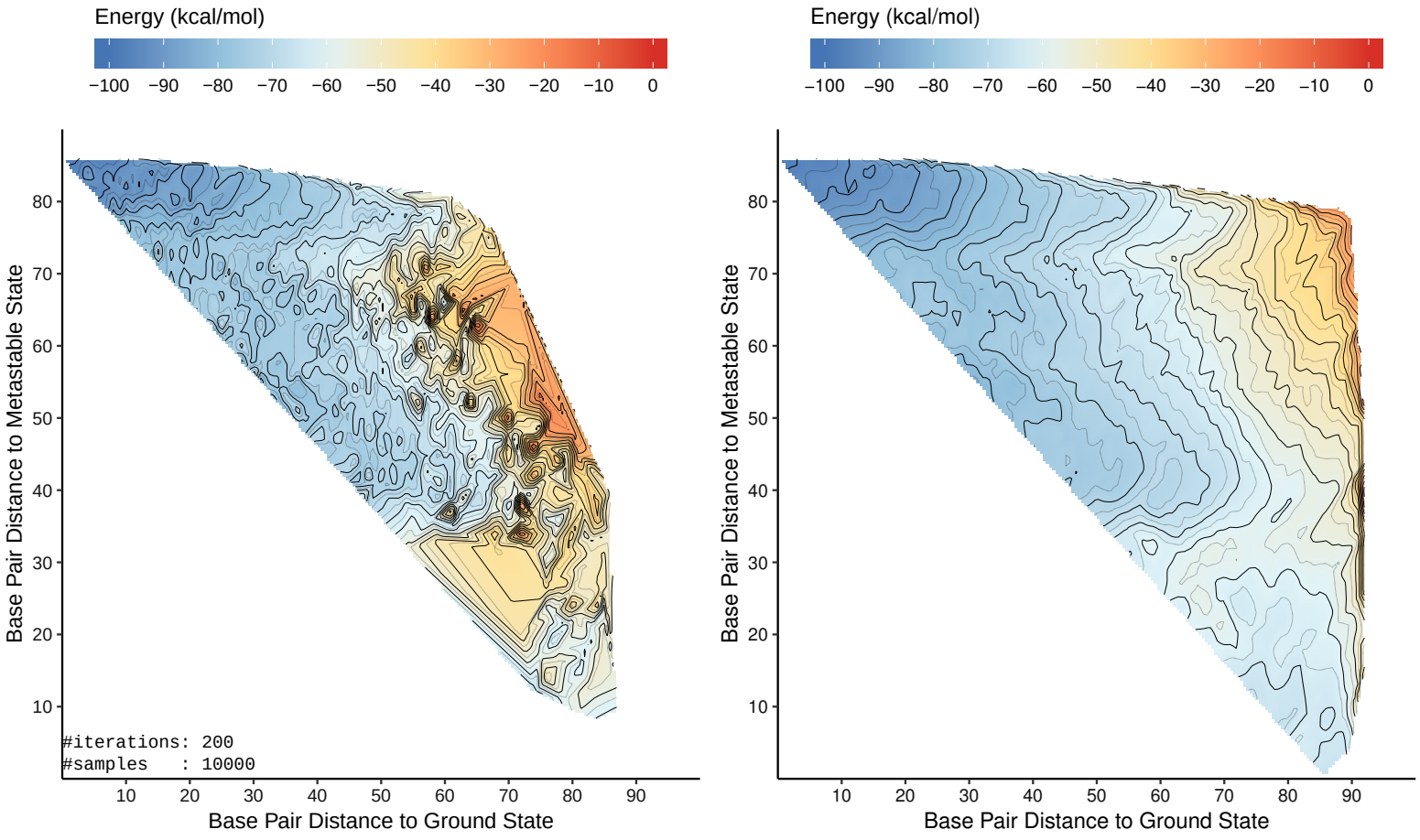
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

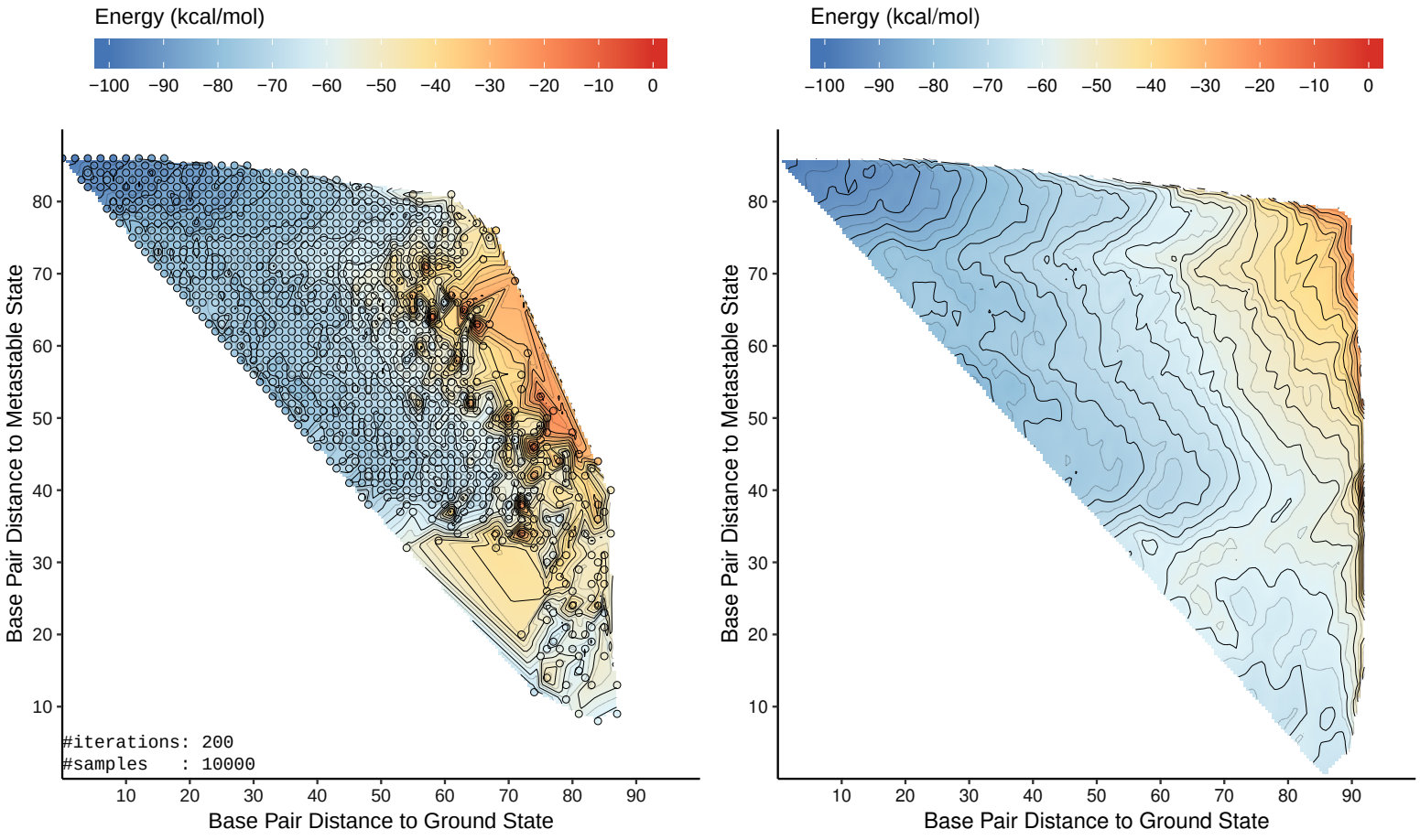
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

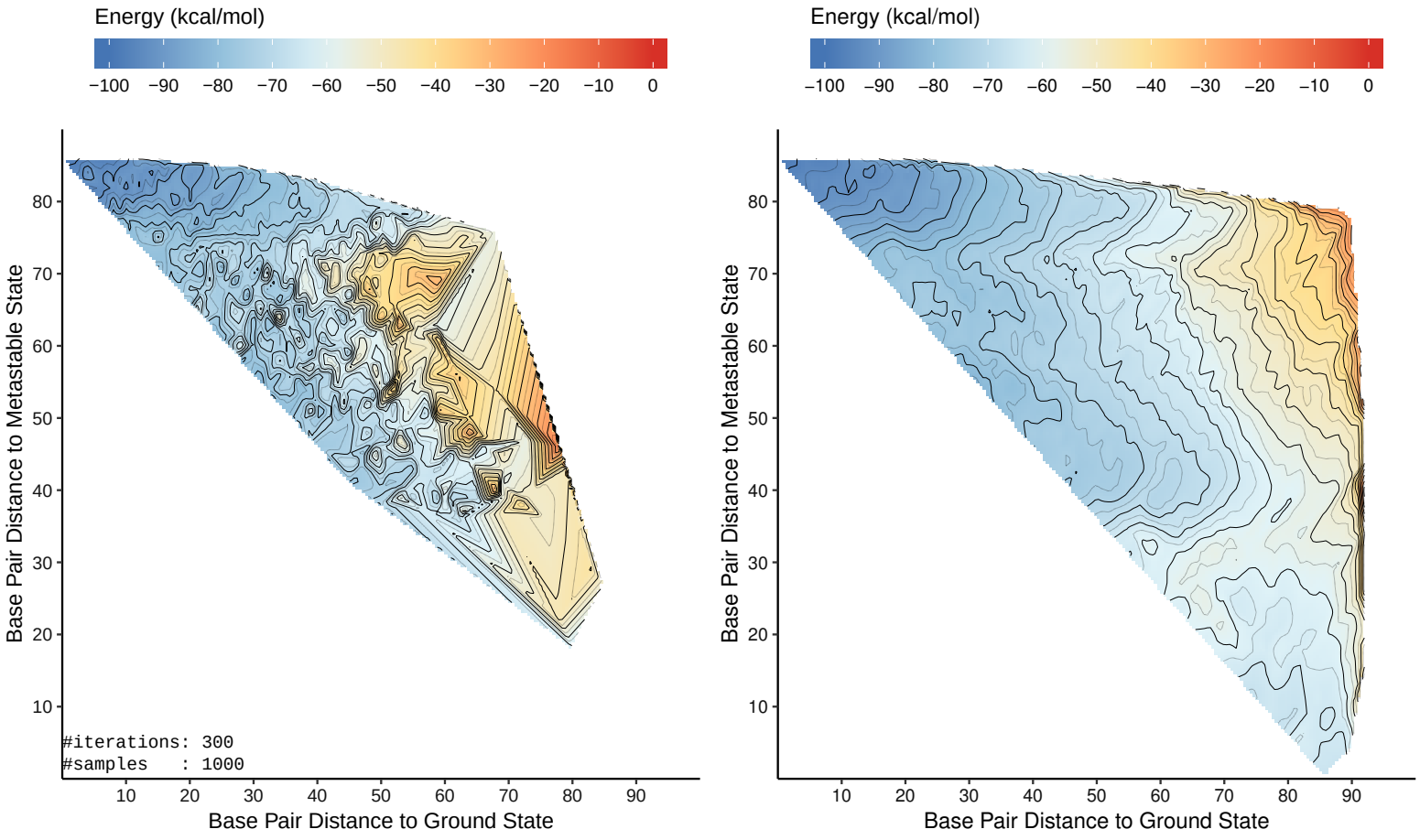
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

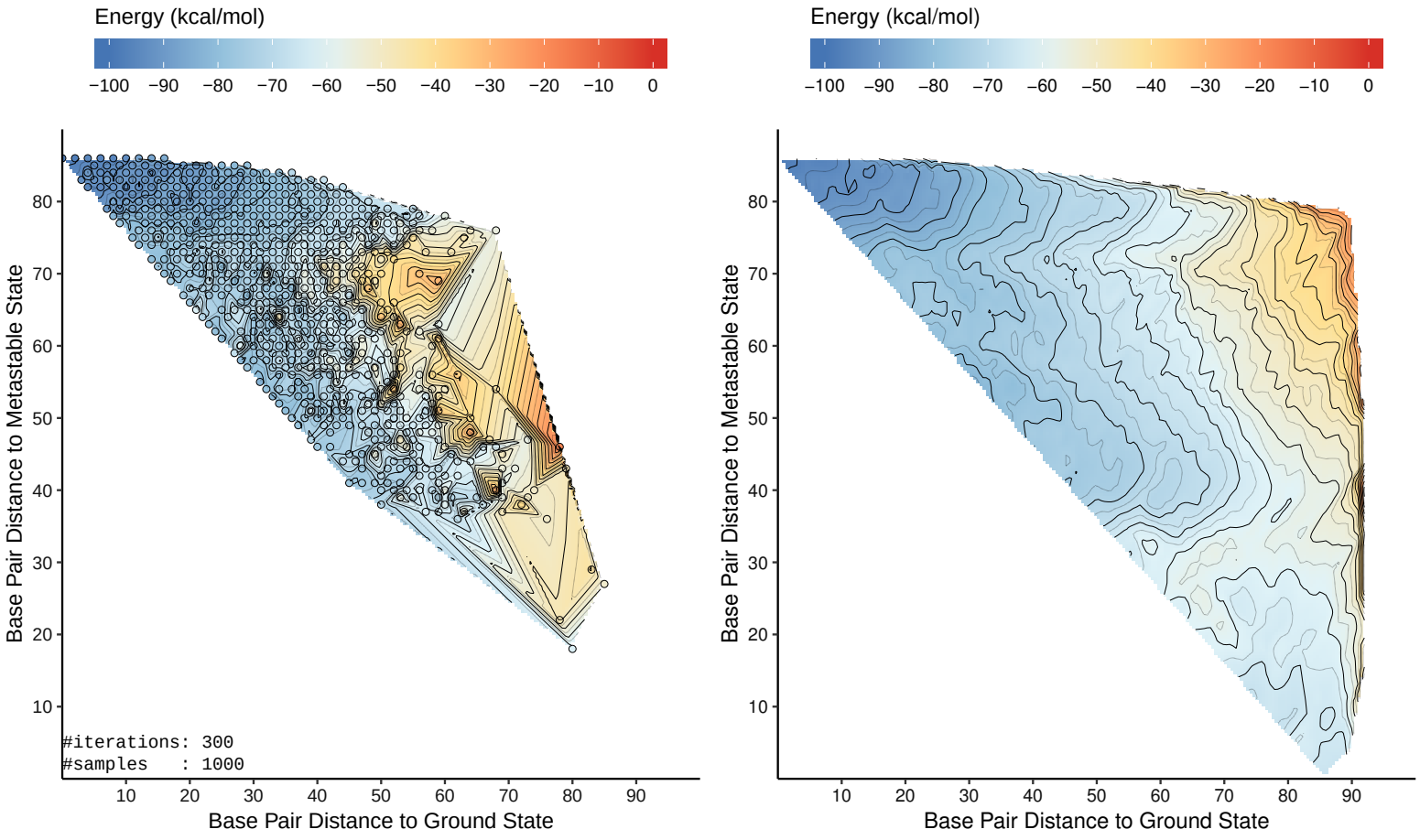
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

`RNAlocmin` temperature elevation scheme Boltzmann sampling



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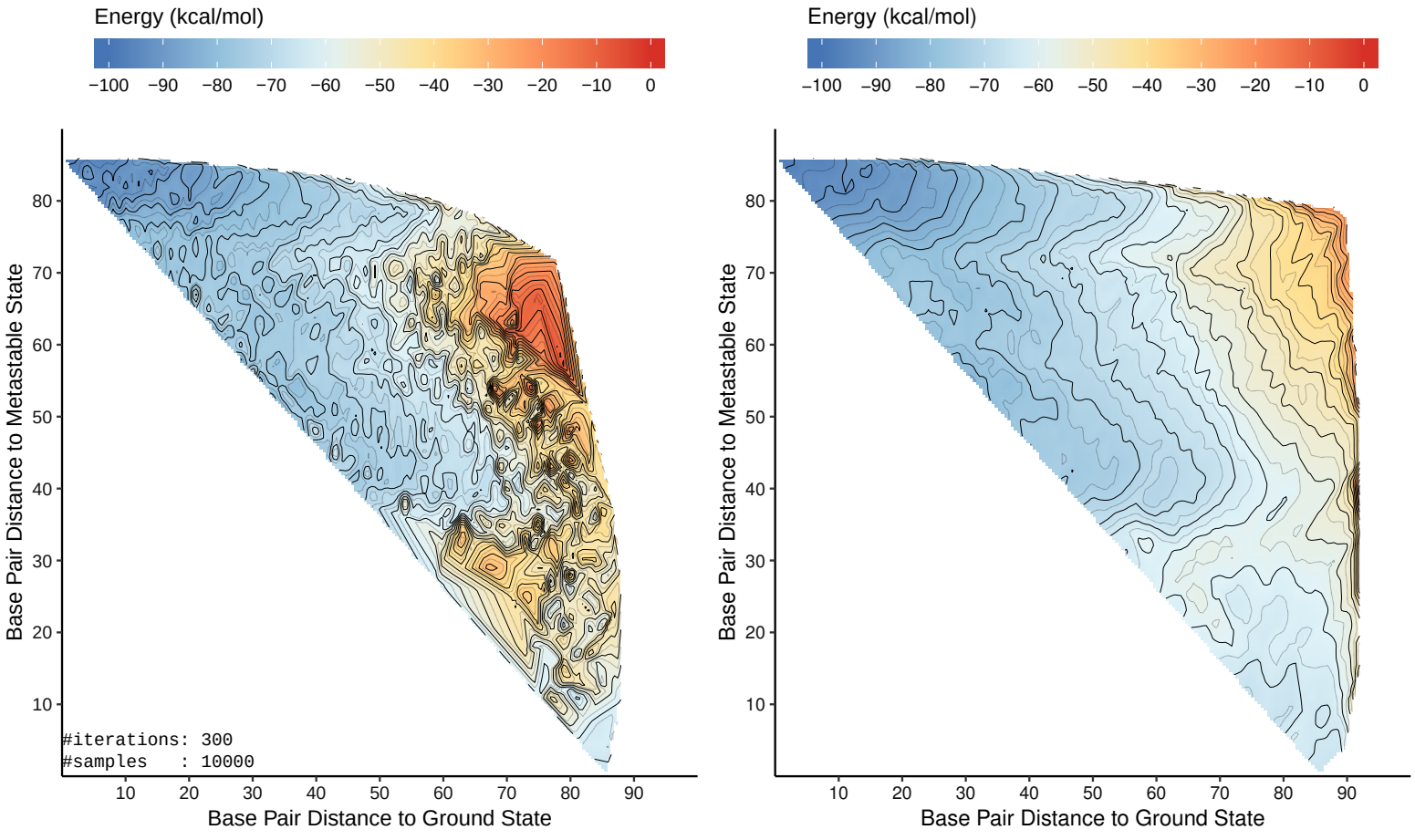
Example: Qβ replicase template SV11

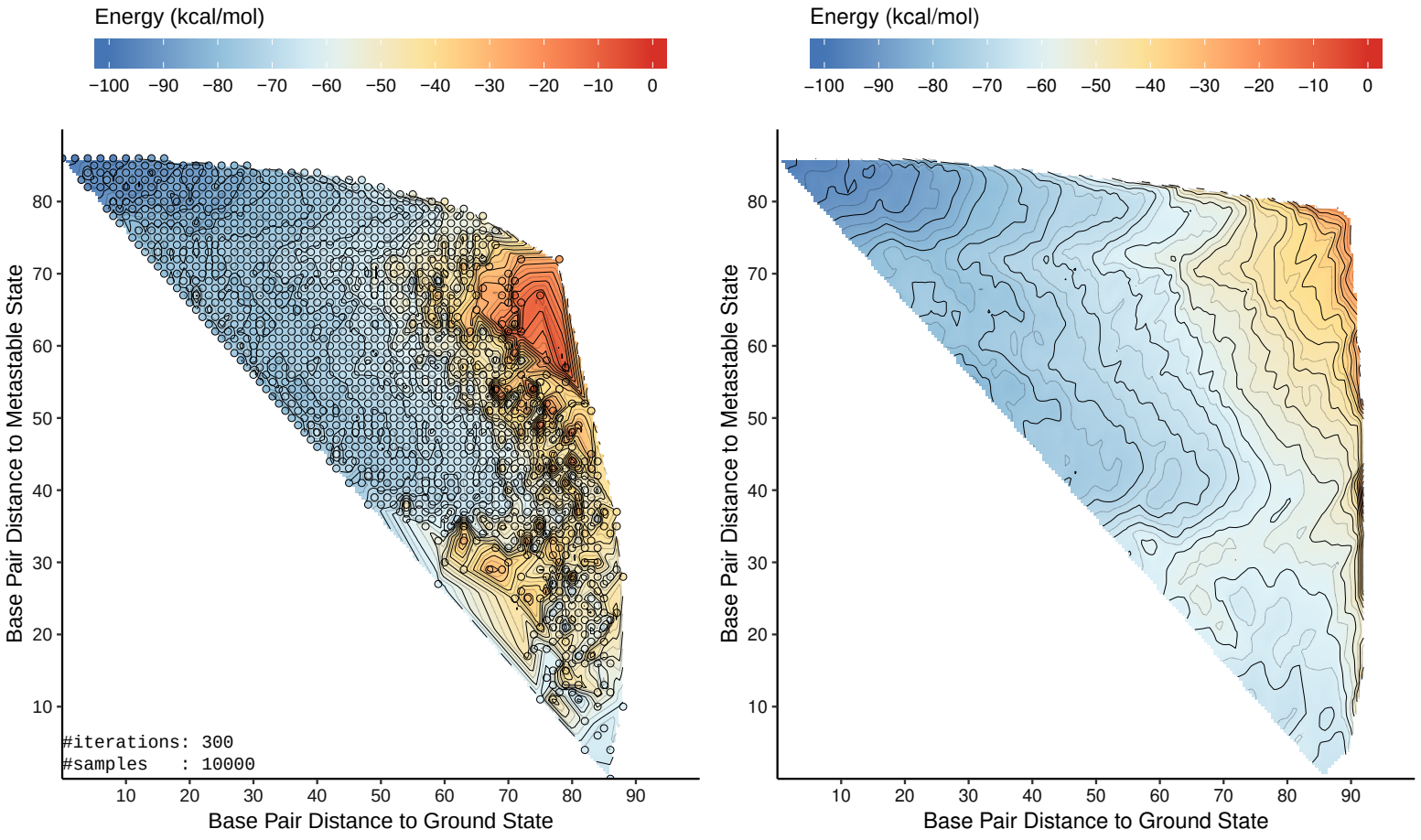
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

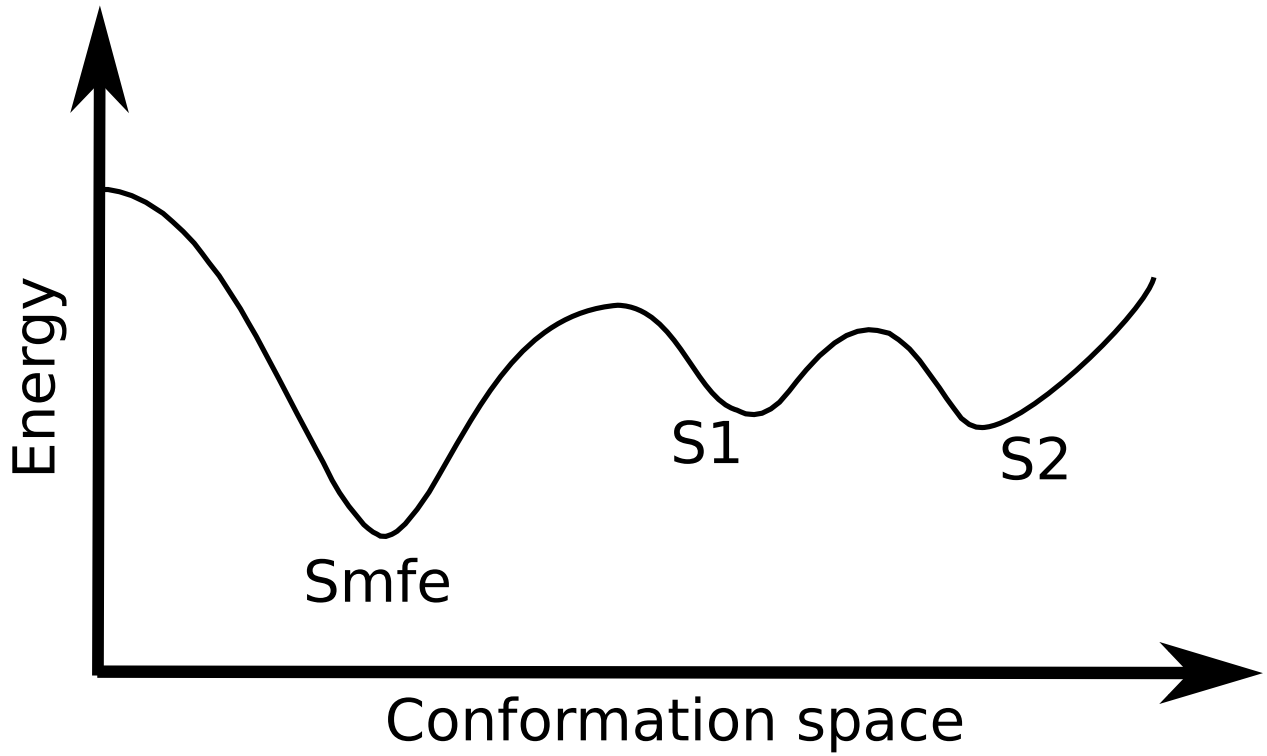
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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

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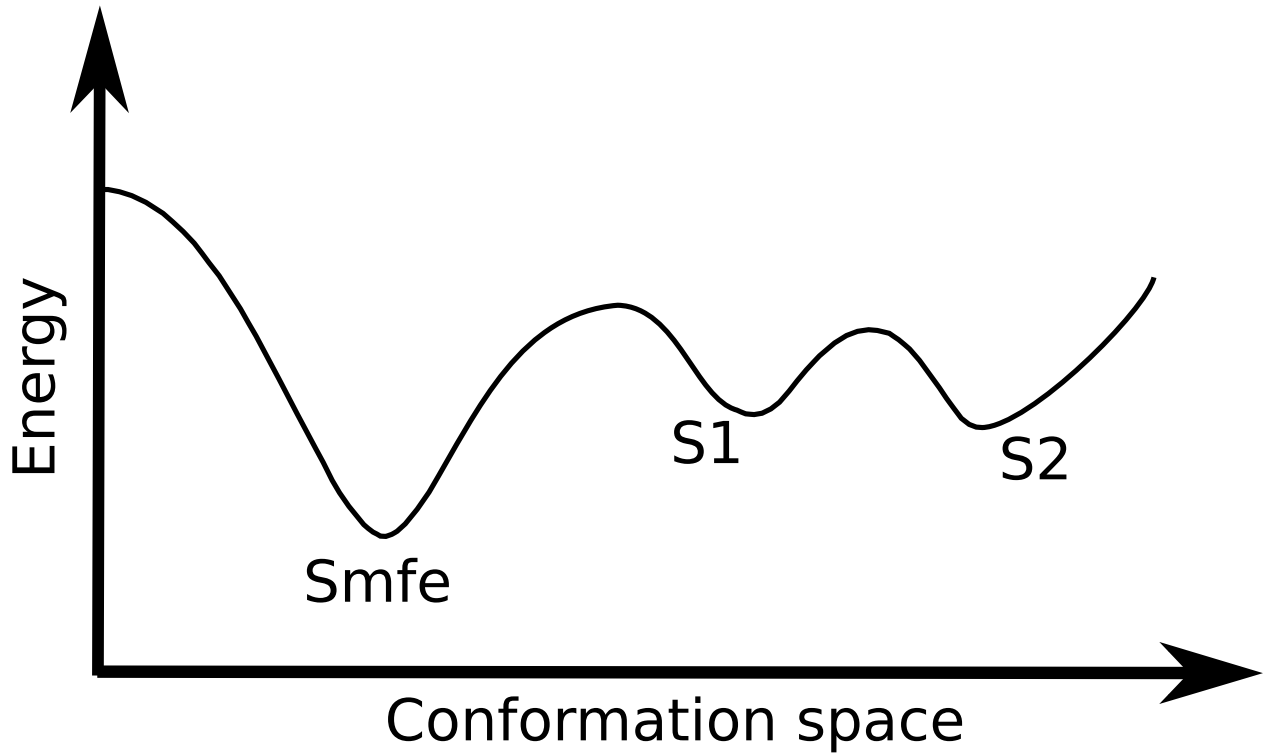

- $p(s) = \frac{exp(-\beta E(s))}{Z}$

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Sampling Strategies

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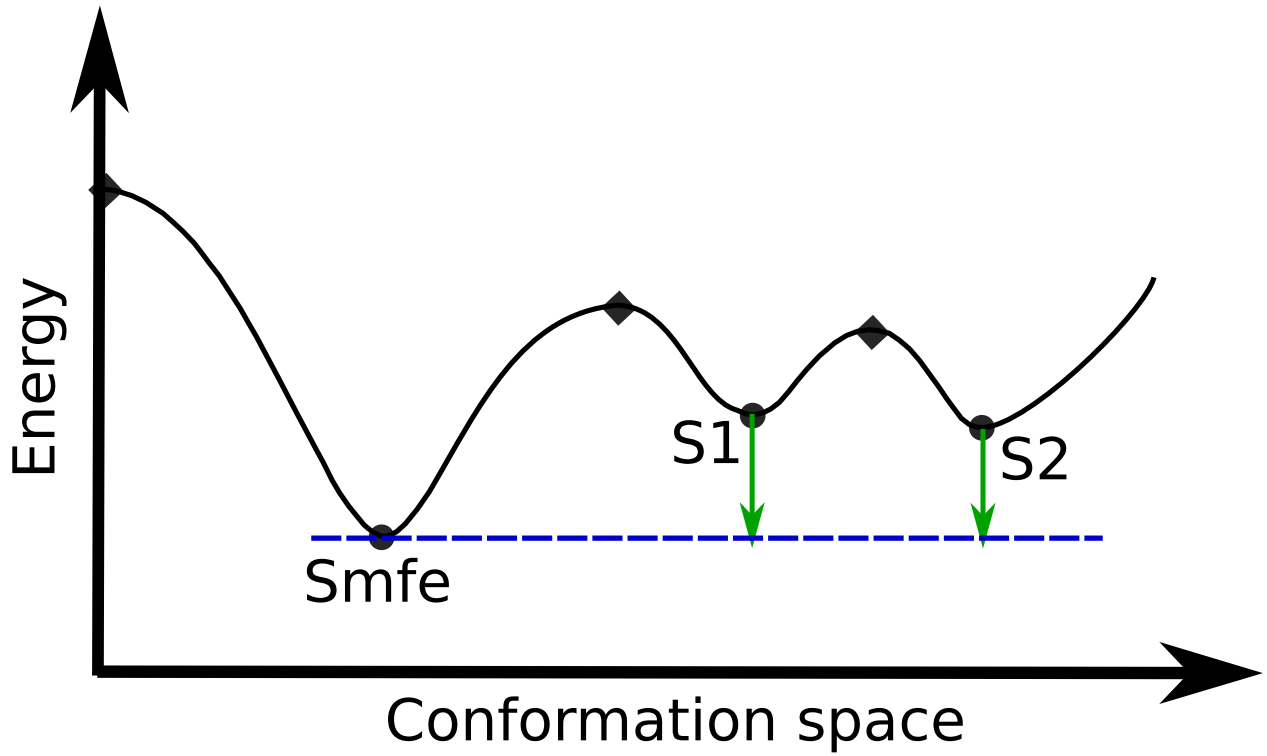

- $p(s) = \frac{exp(-\beta E(s))}{Z}$
- $E(s_{mfe}) = [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)]$

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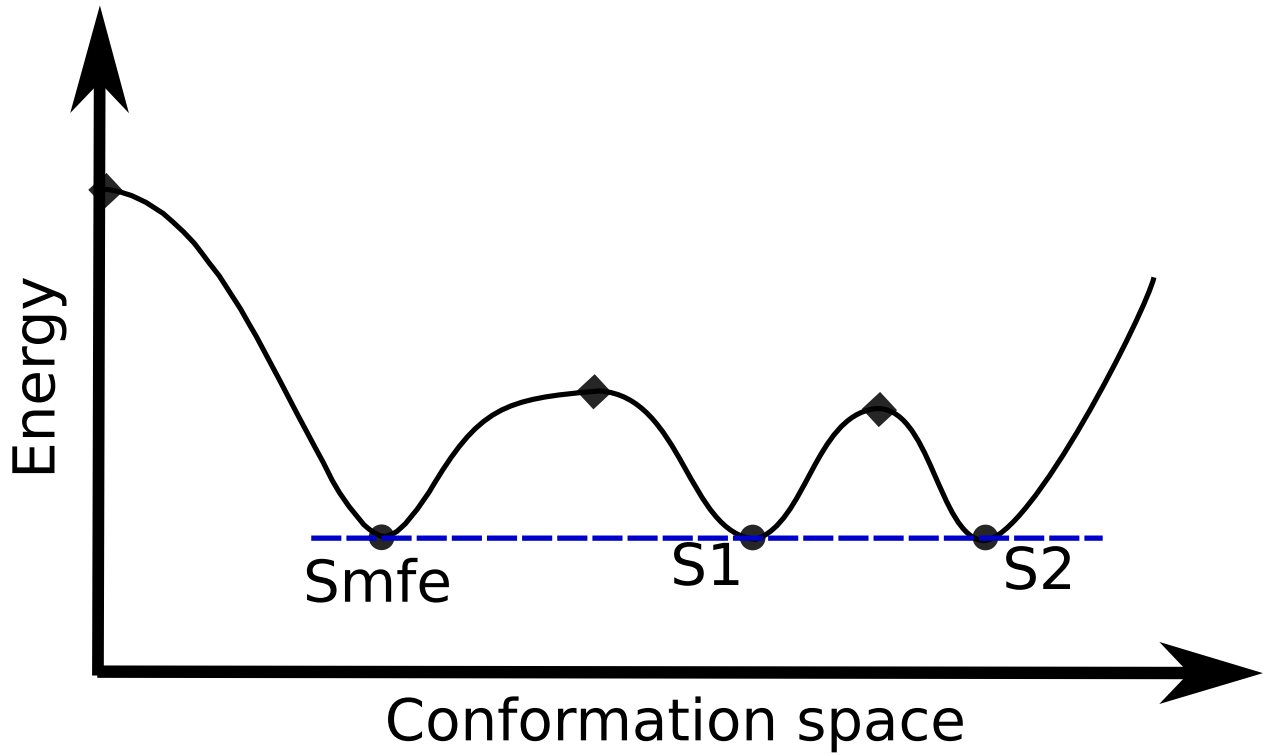

- $p(s) = \frac{exp(-\beta E(s))}{Z}$
- $E(s_{mfe}) = [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)]$
- $p(s_{mfe}) = p(s_1) = p(s_2)$

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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

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- 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

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How to choose reference structures s_x?

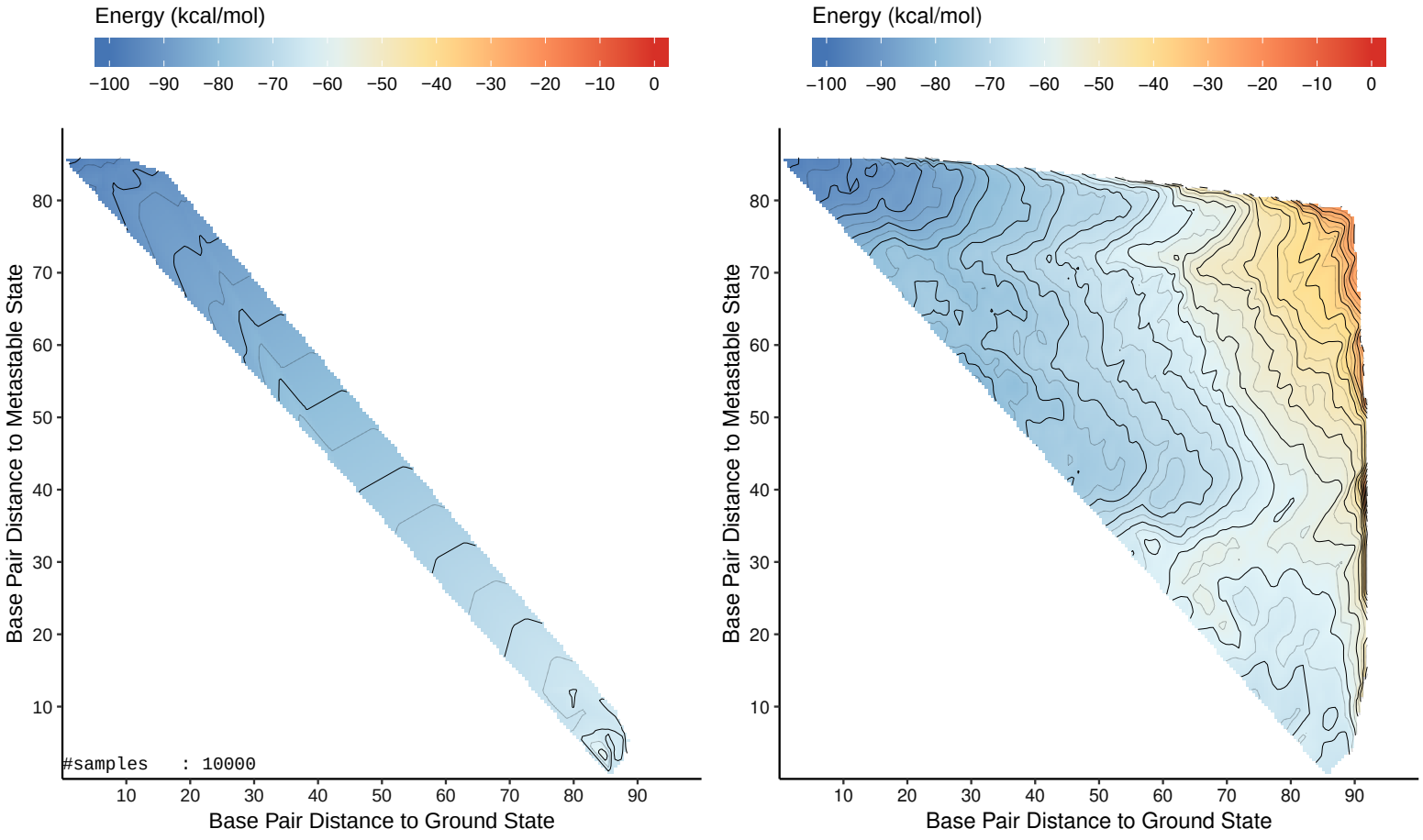
---

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

[13] Lorenz et al. 2016

Example: Qβ replicase template SV11

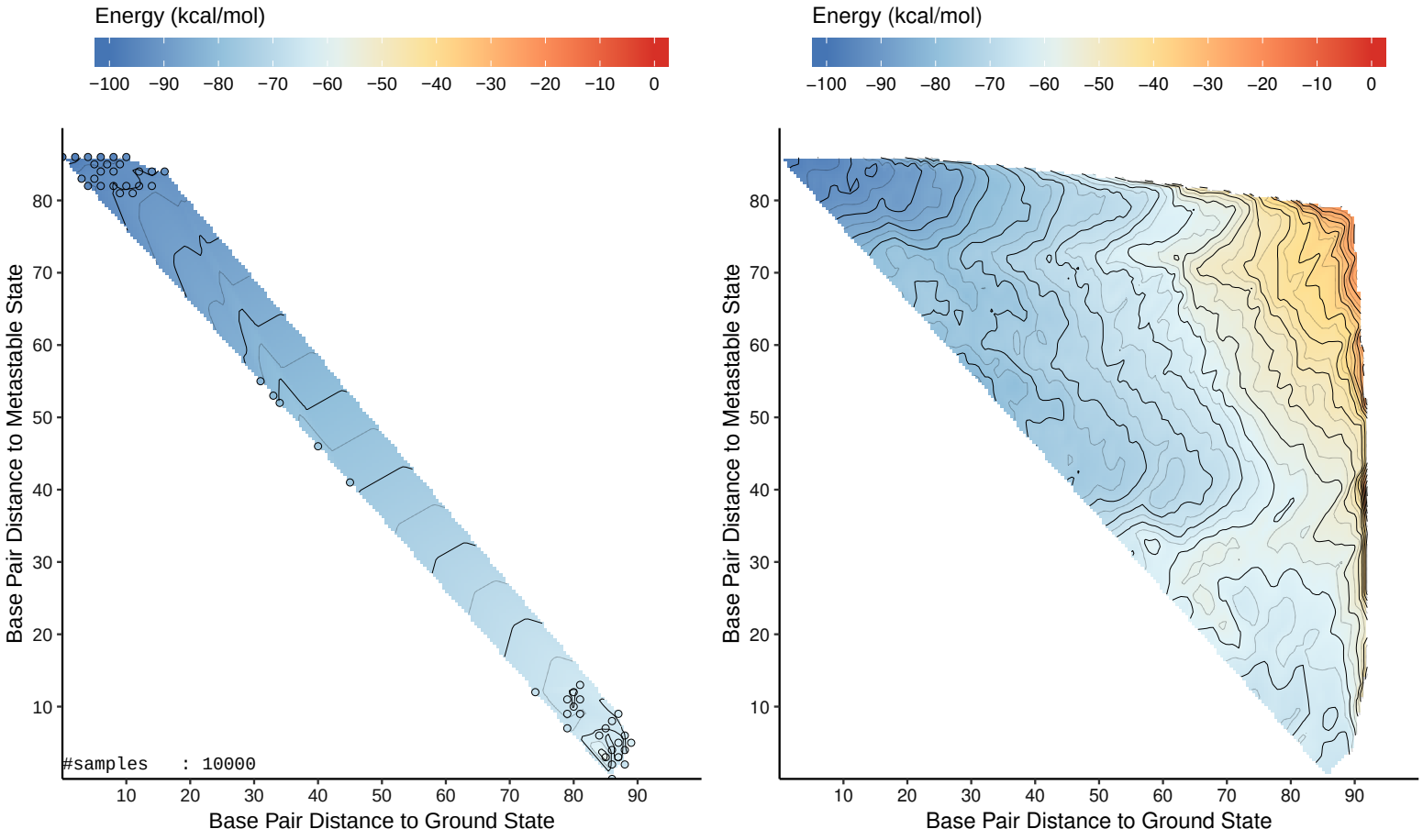
`RNAxplorer` attraction scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

`RNAxplorer` attraction scheme Boltzmann sampling



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Example: Qβ replicase template SV11

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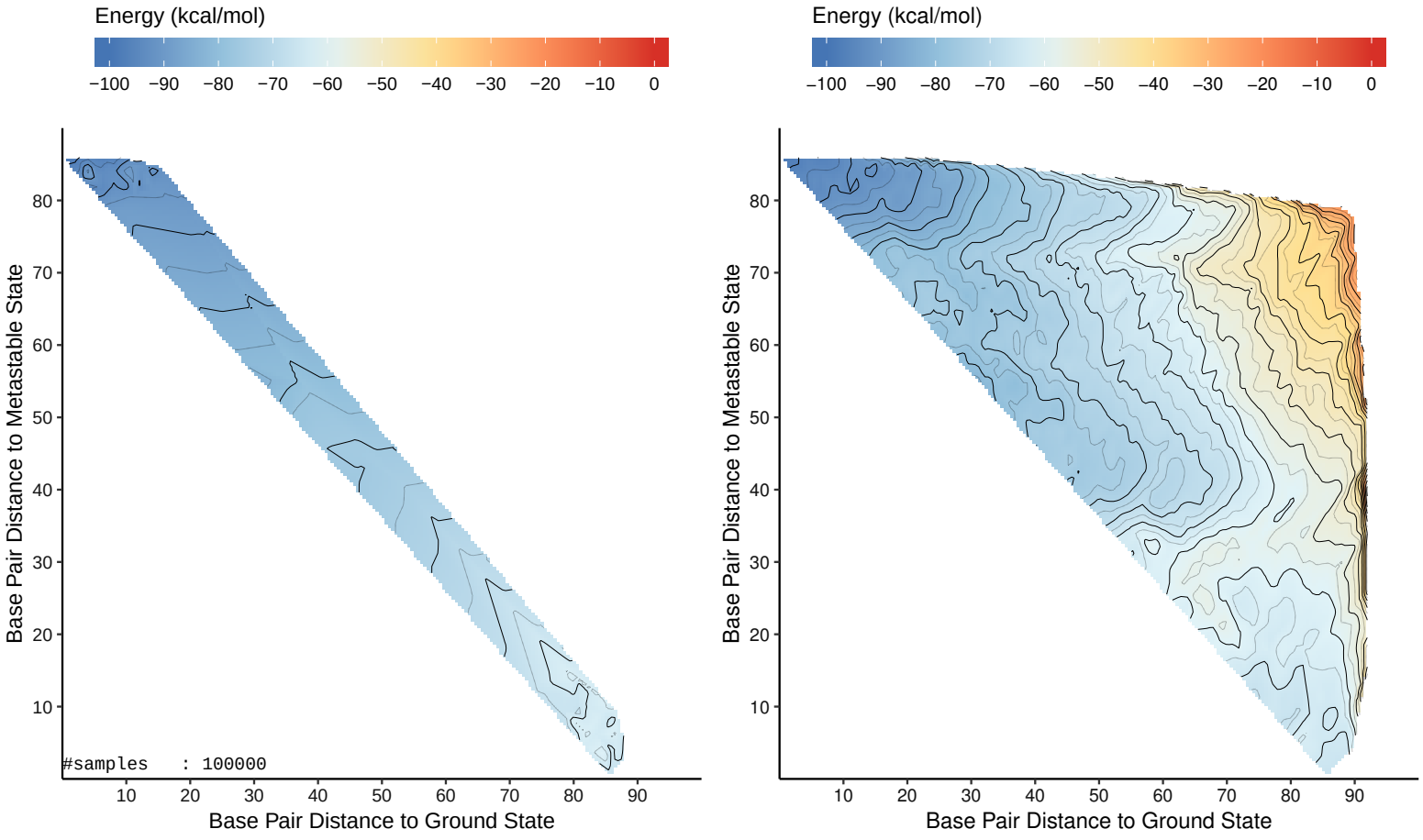

references: 2, # samples: 100, 000, # local minima: 167

Example: Qβ replicase template SV11

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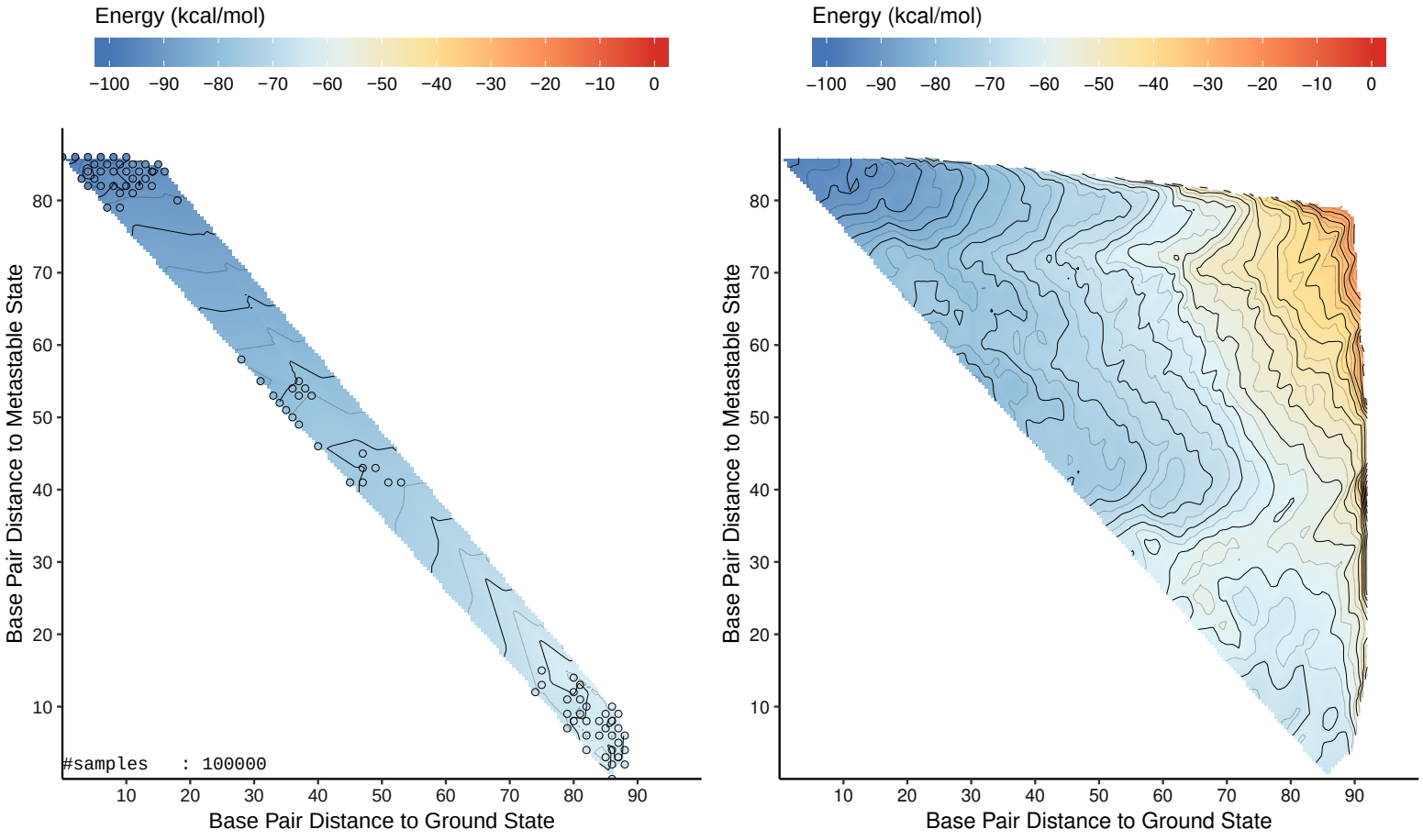

references: 2, # samples: 100, 000, # local minima: 167

Example: Qβ replicase template SV11

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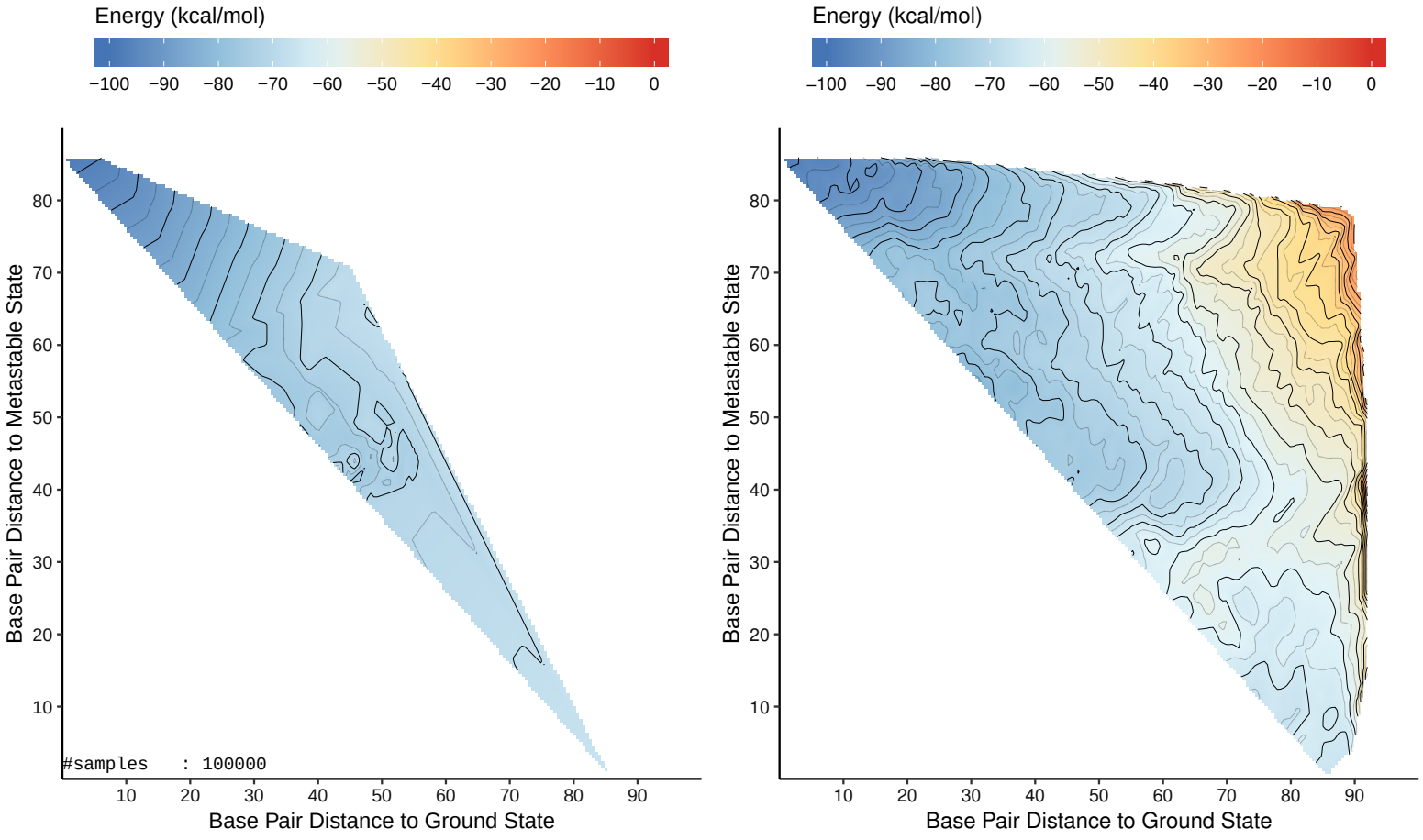
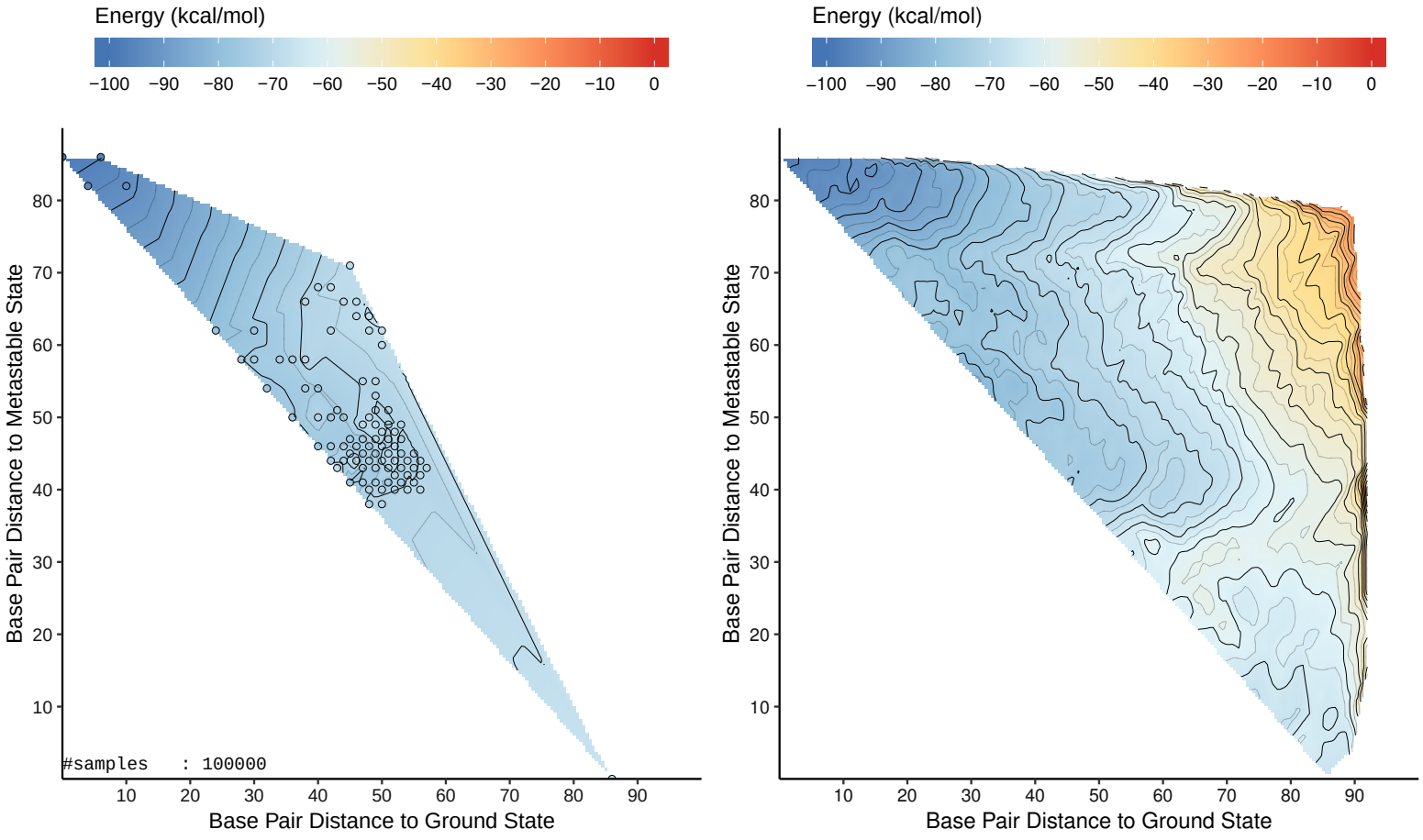


references: 3, # samples: 100, 000, # local minima: 182

Example: Qβ replicase template SV11

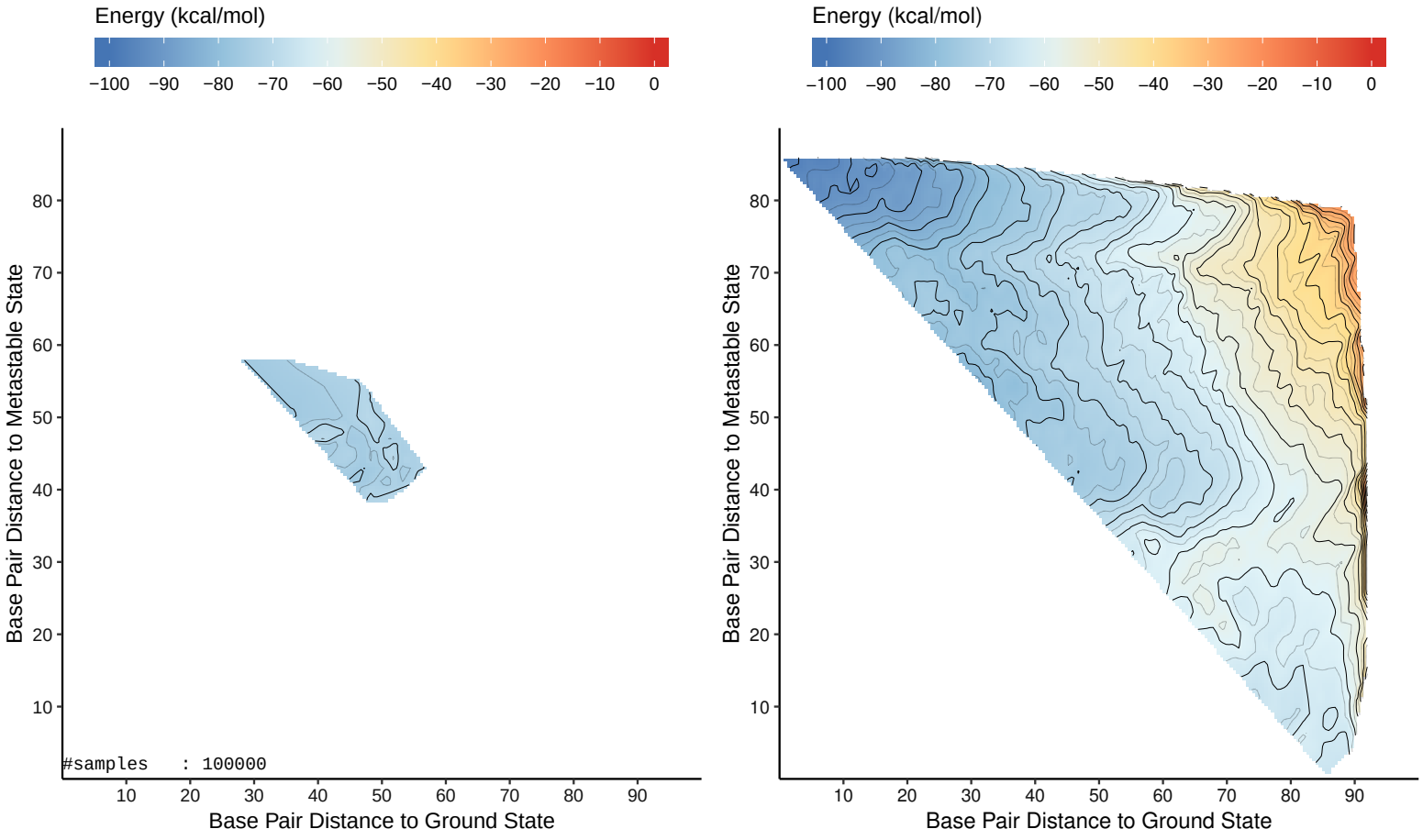
`RNAxplorer` attraction scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

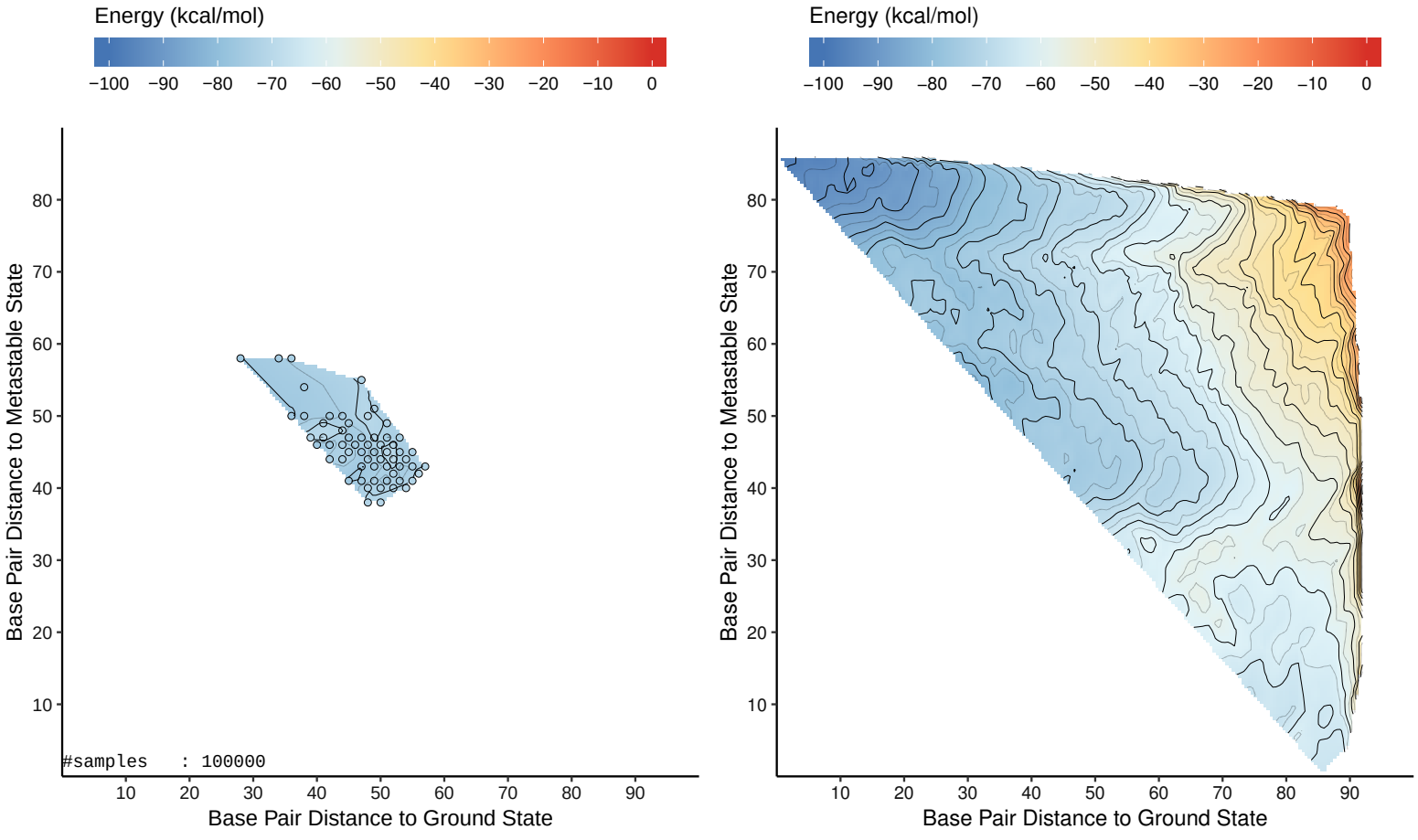
`RNAxplorer` attraction scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

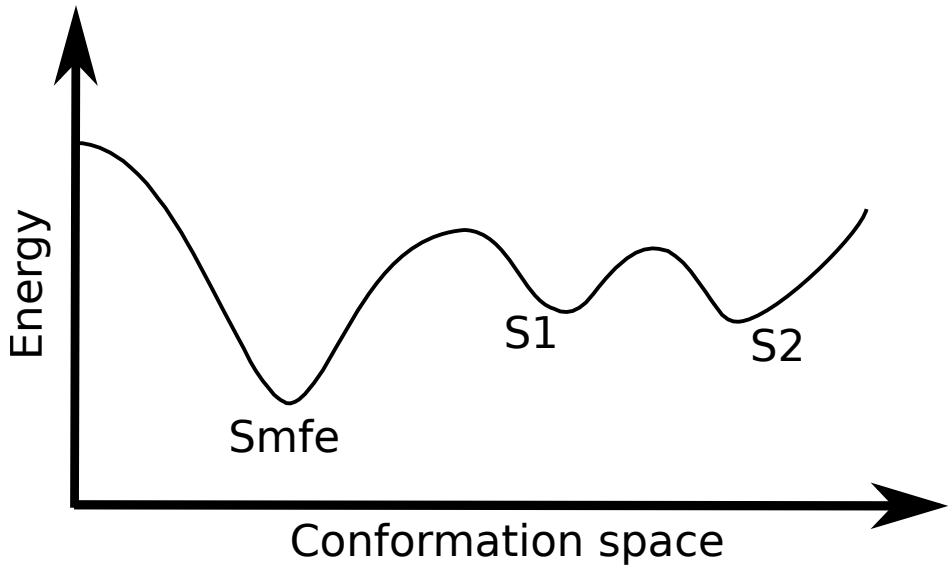
`RNAxplorer` attraction scheme Boltzmann sampling



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

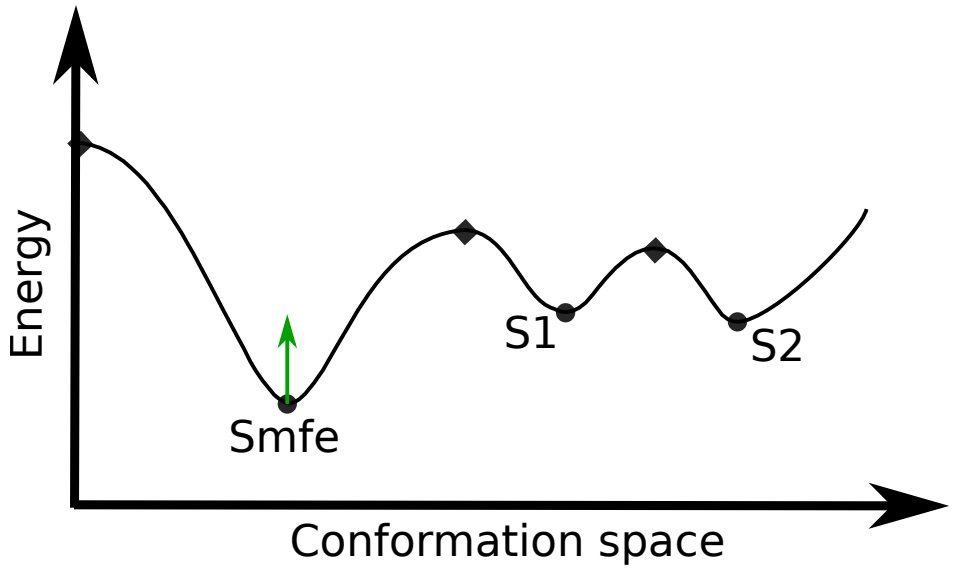
Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



Sampling Strategies

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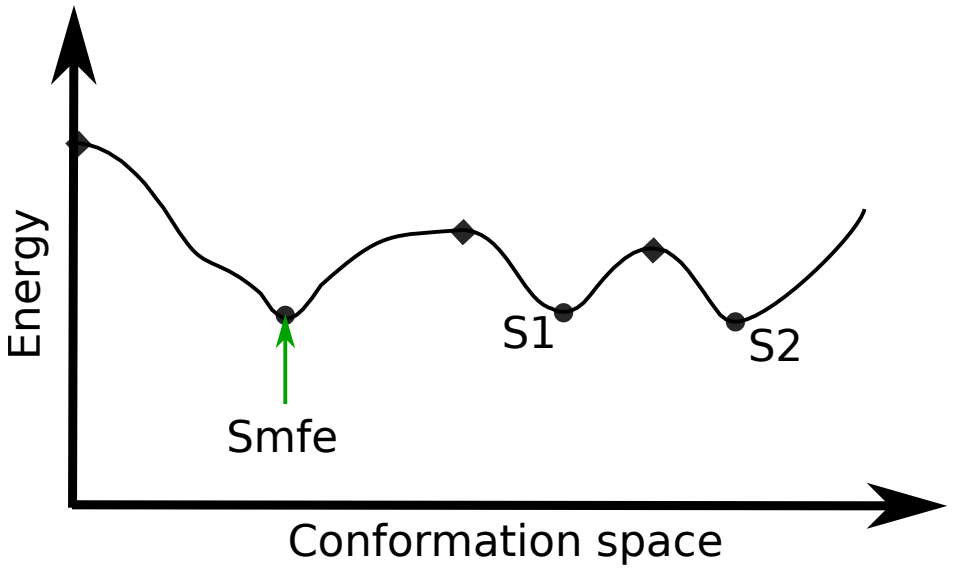

Sampling Strategies

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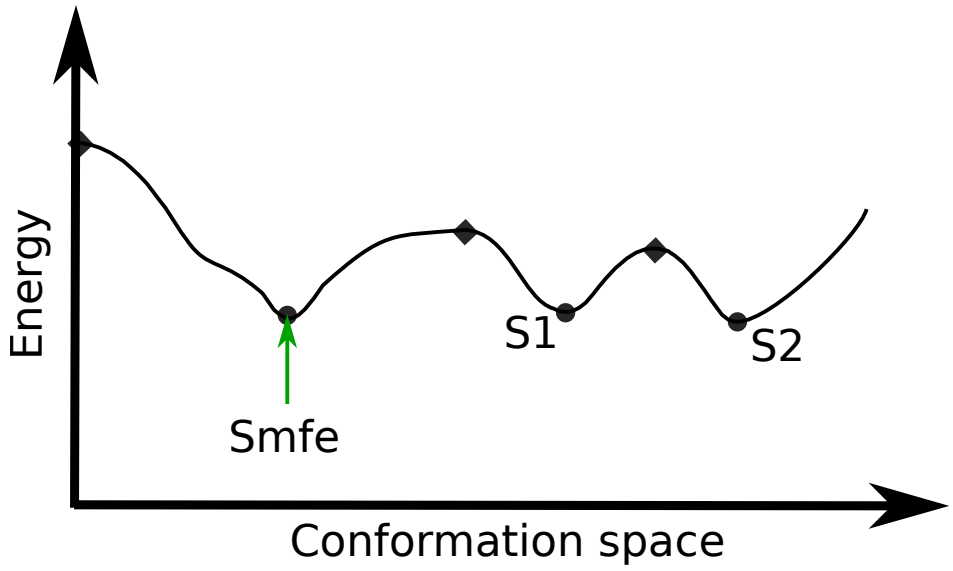

- draw samples and determine corresponding local minima
- add most over-represented local minimum s_m to list L
- assign $\hat{E}(s)$ according to structures in L, e.g.

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

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

$$\ldots$$

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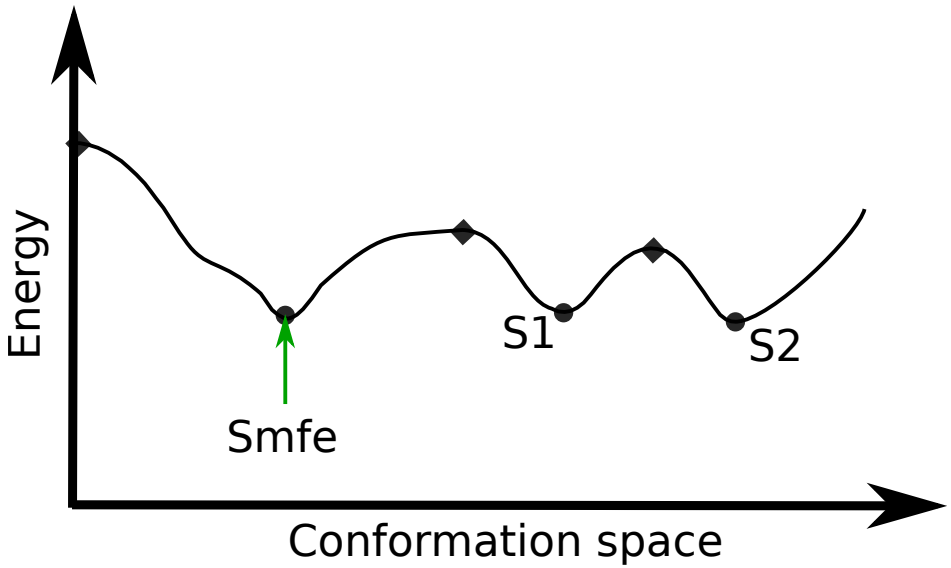

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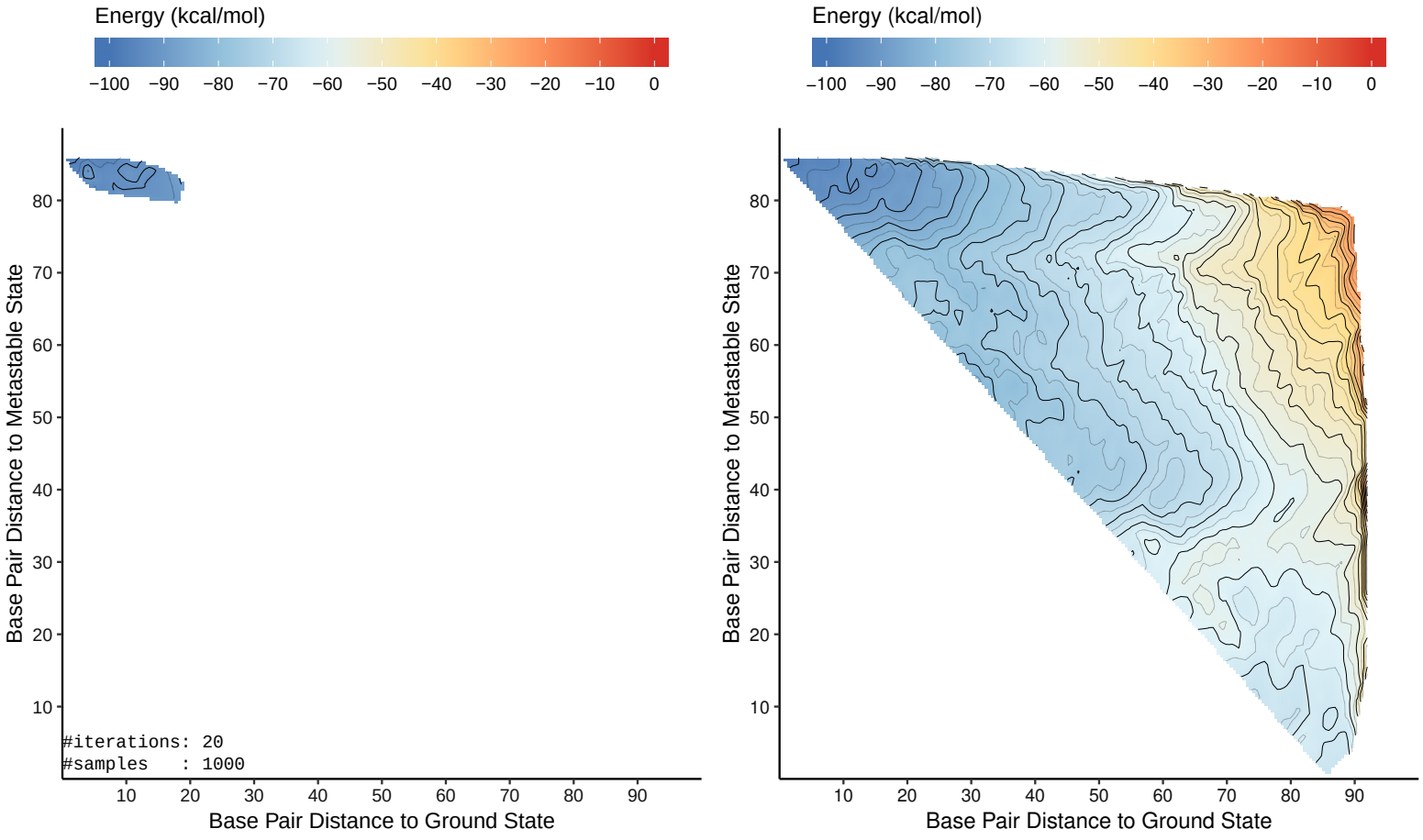
$$\ldots$$

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

Example: Qβ replicase template SV11

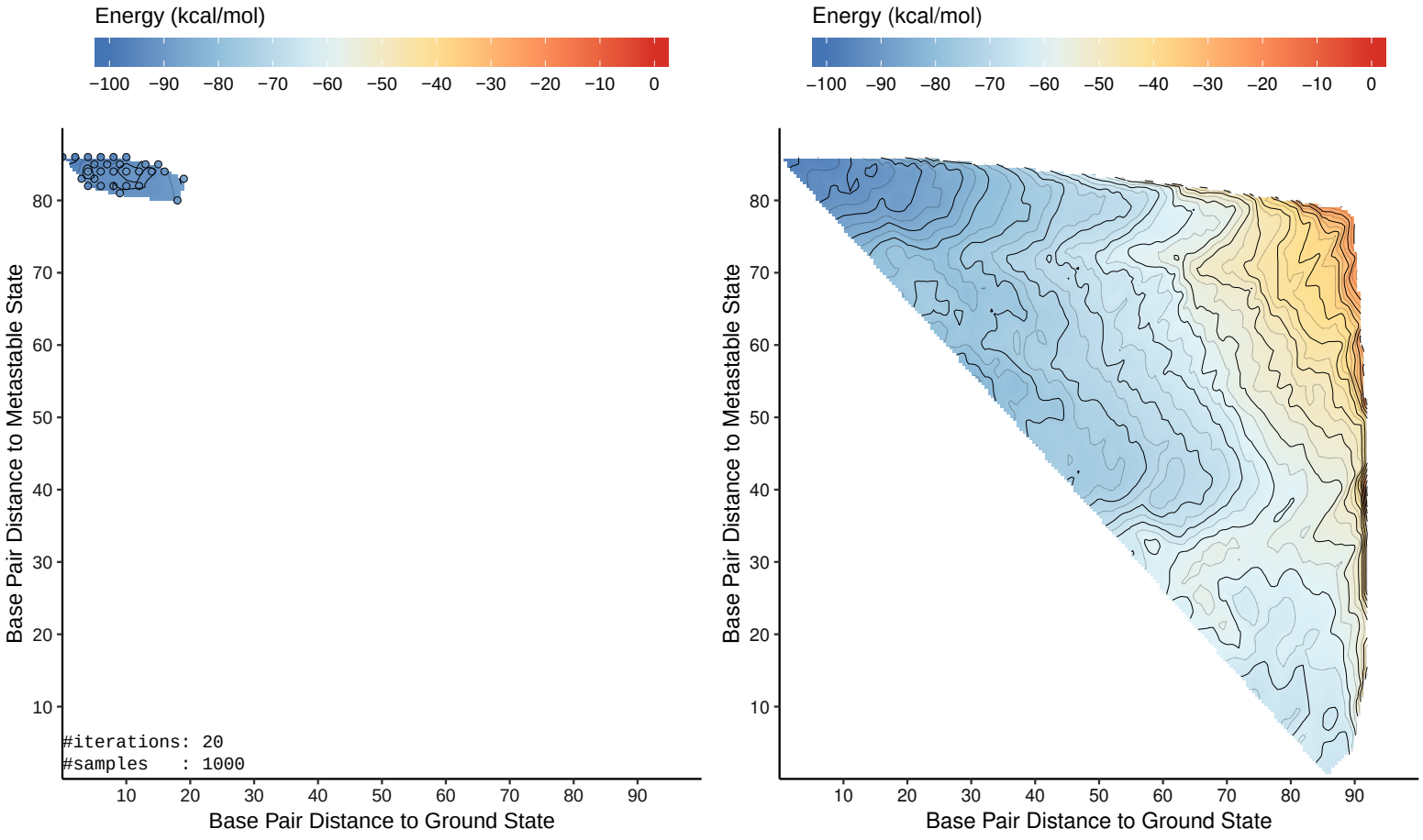
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

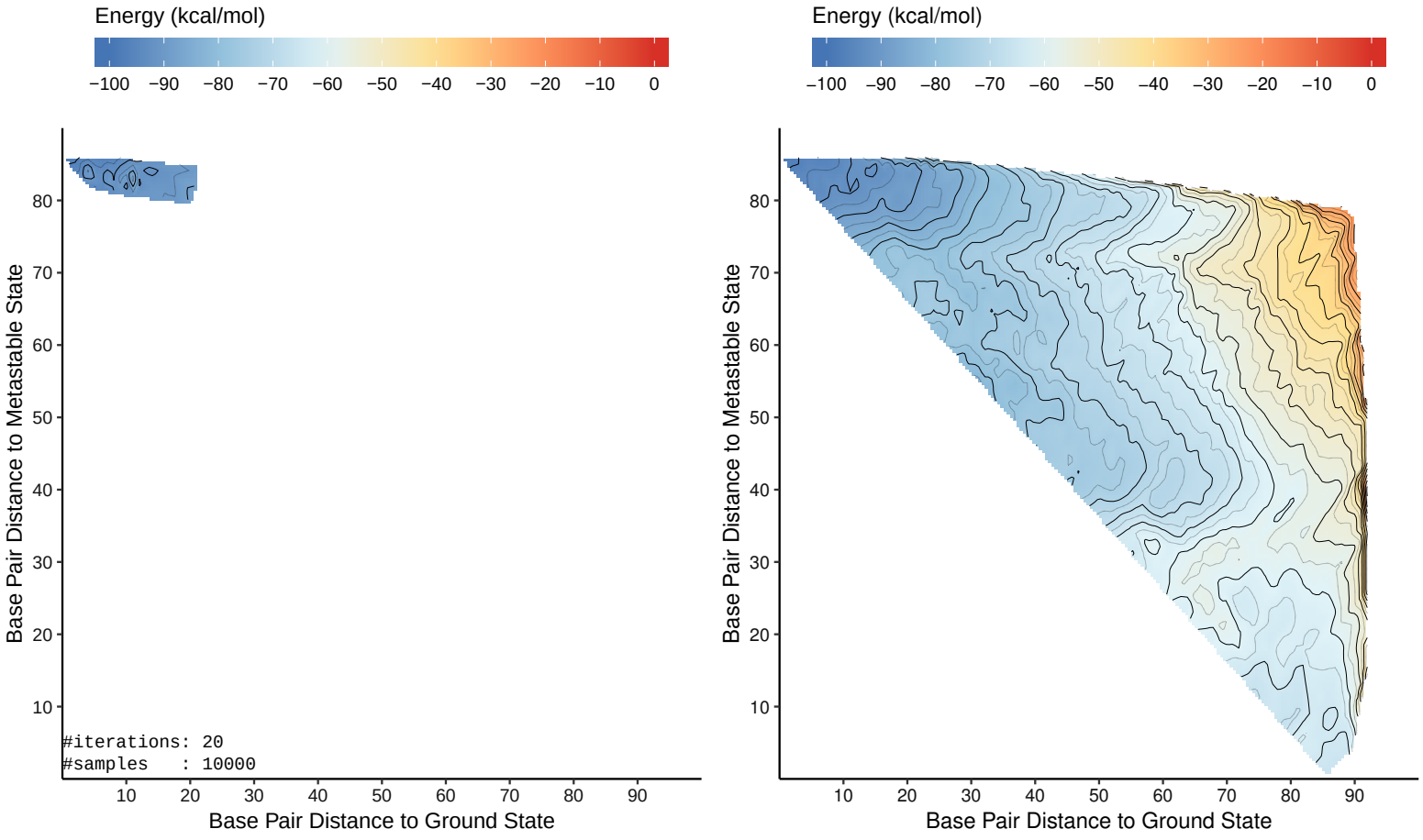
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

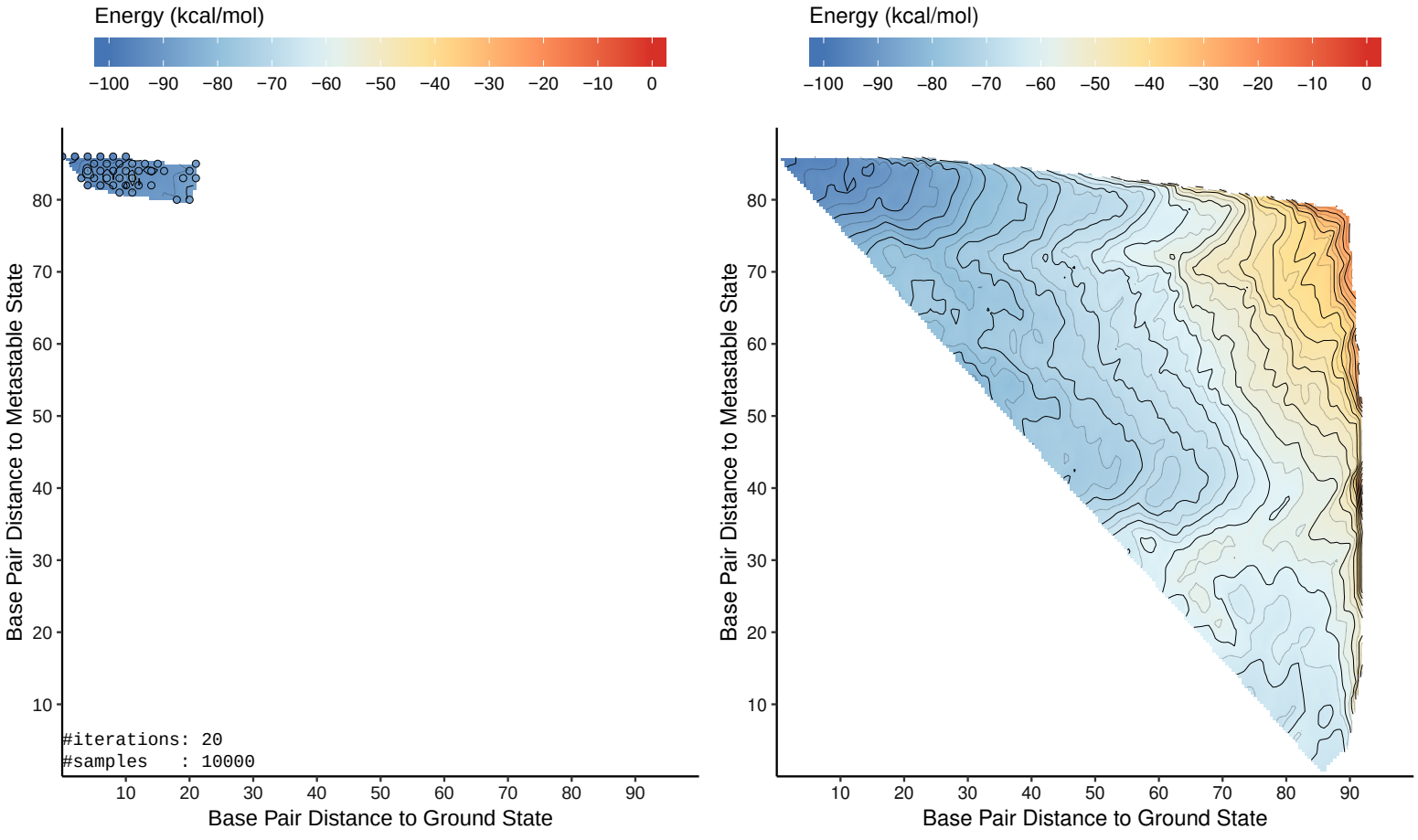
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

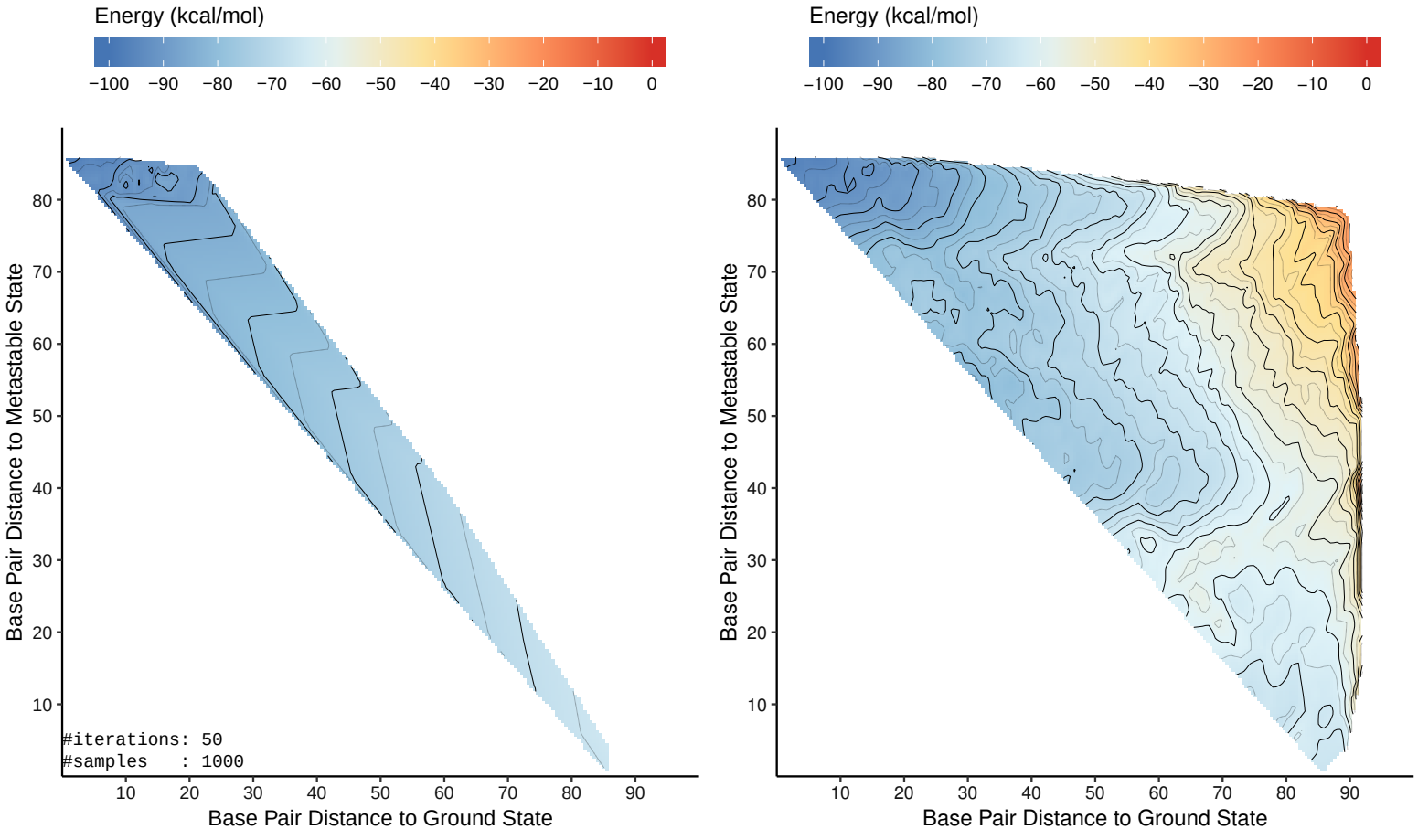
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

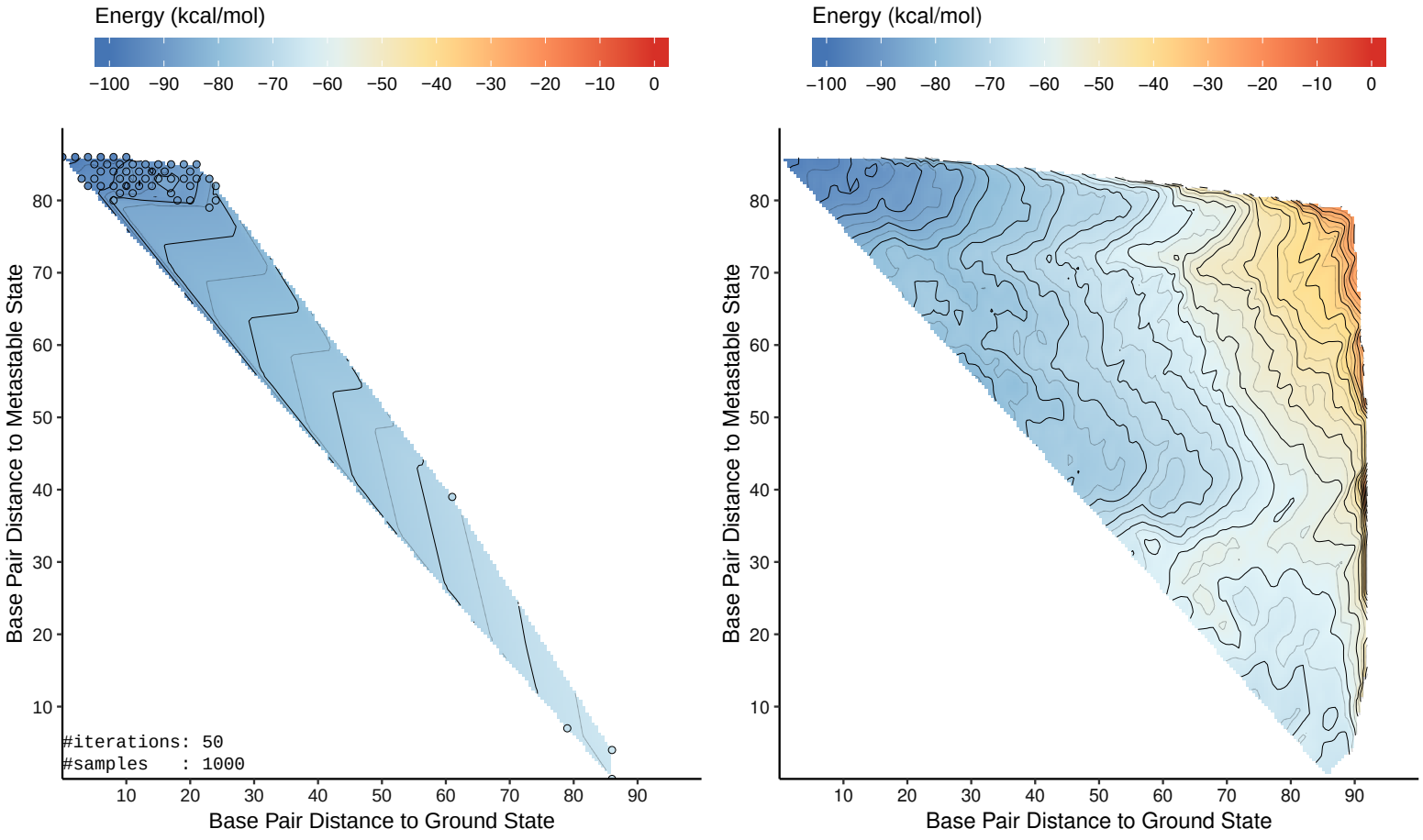
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

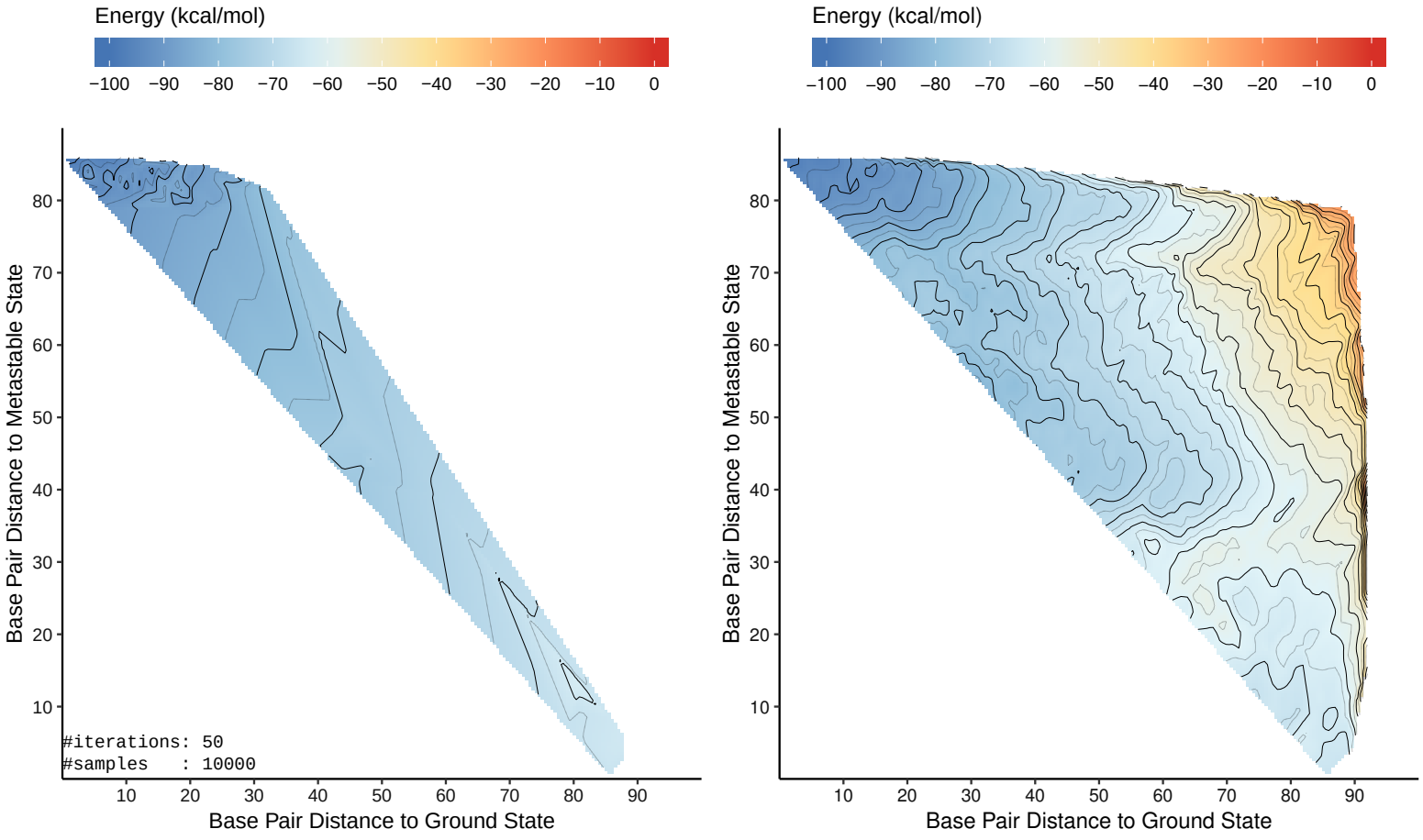
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

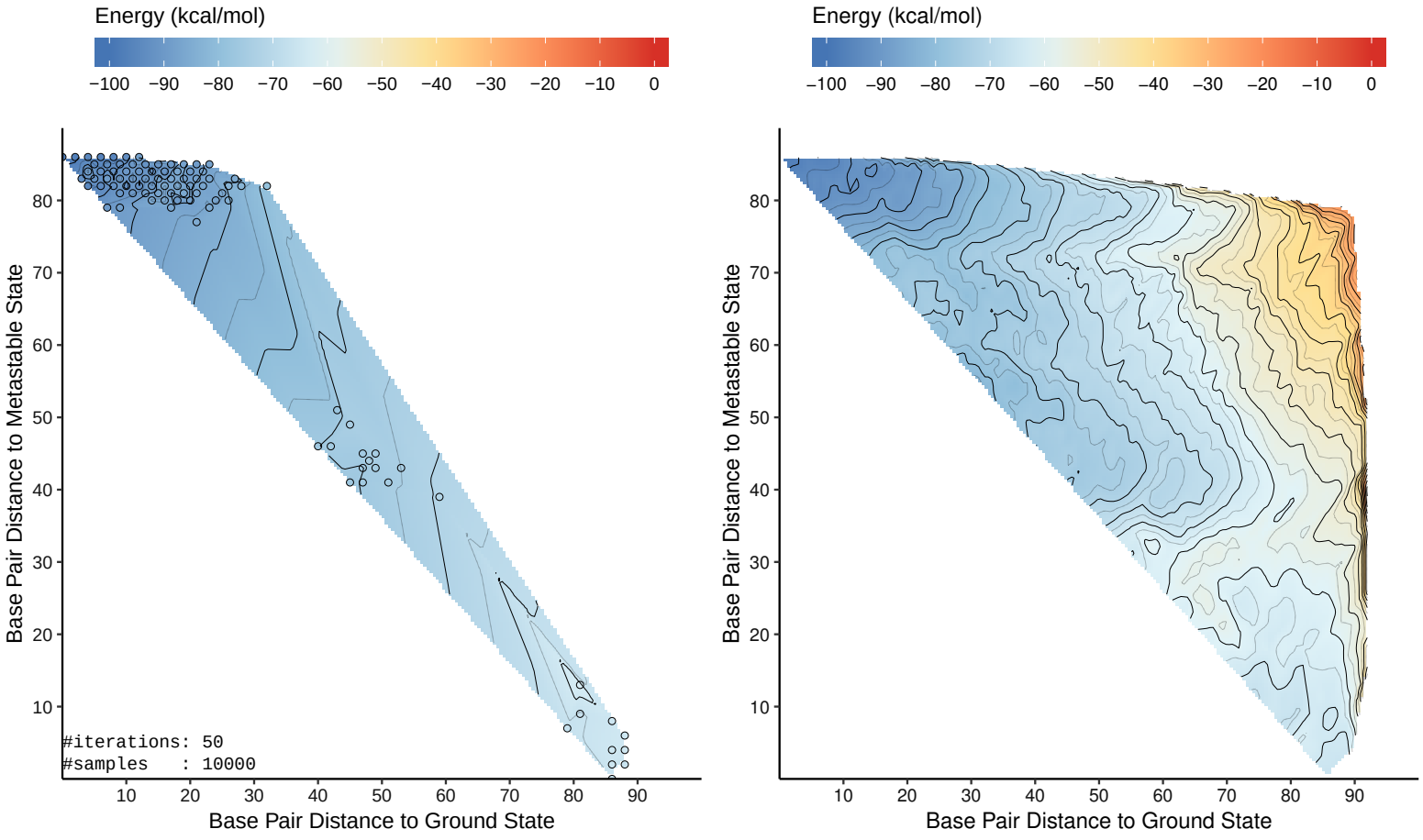
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

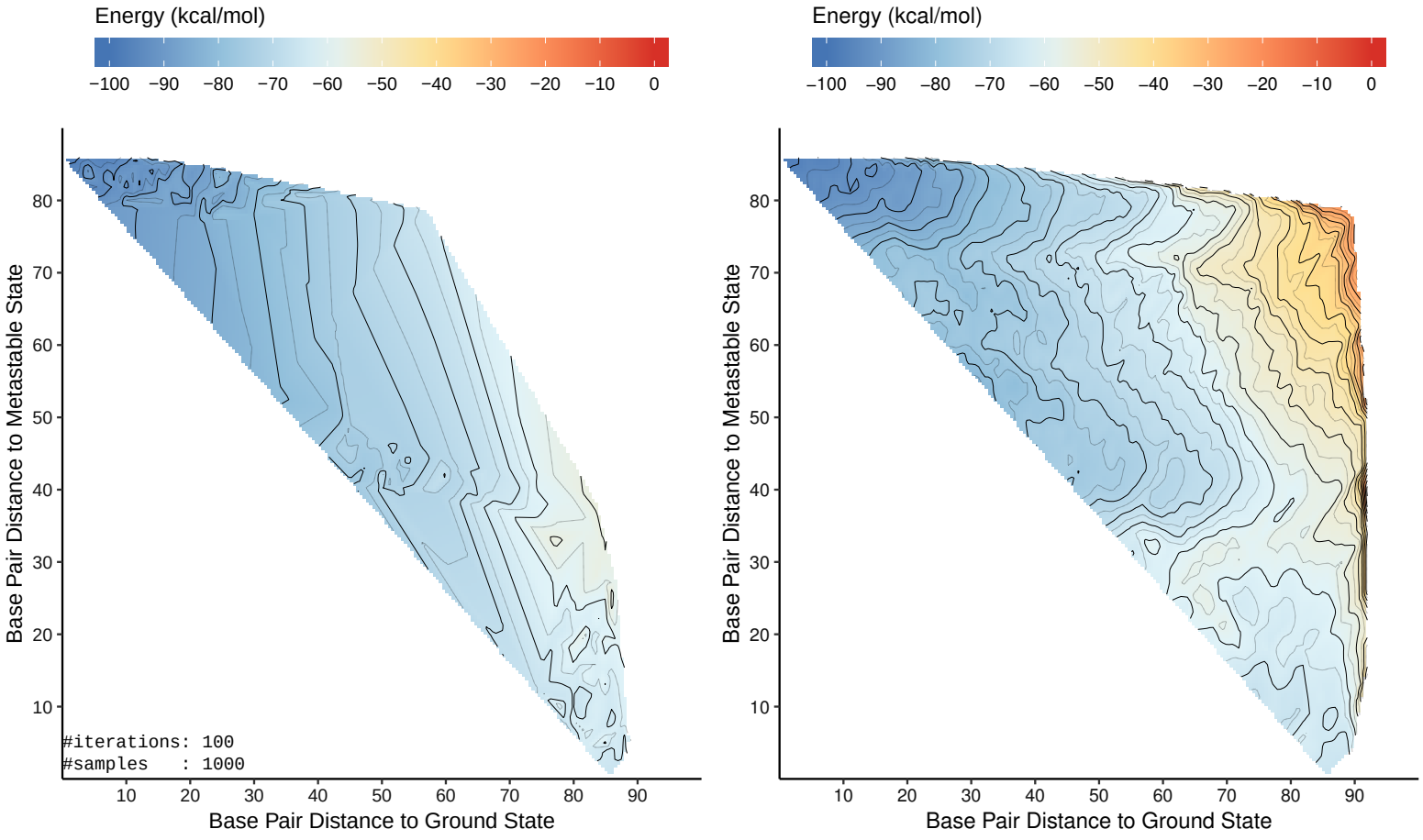
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

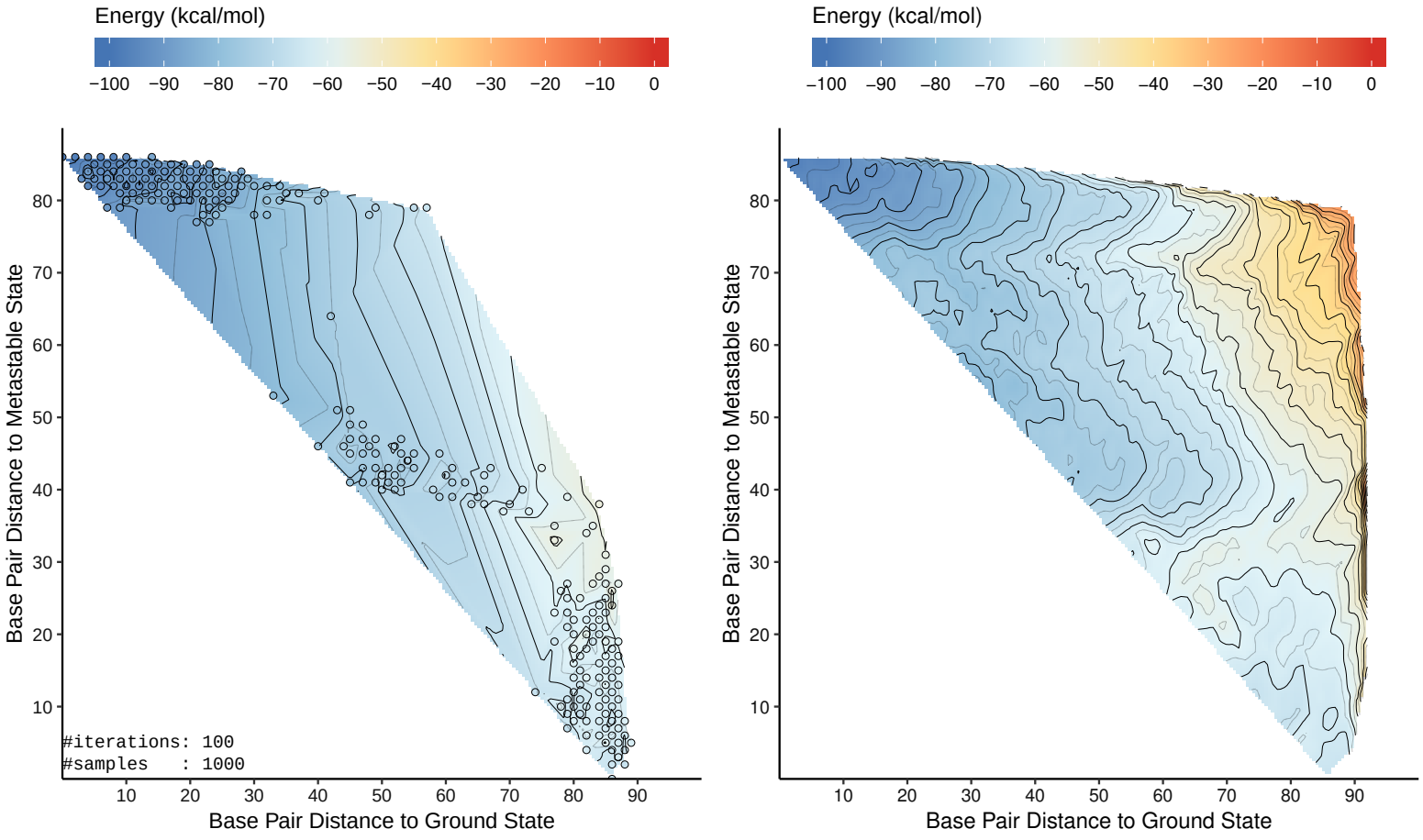
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

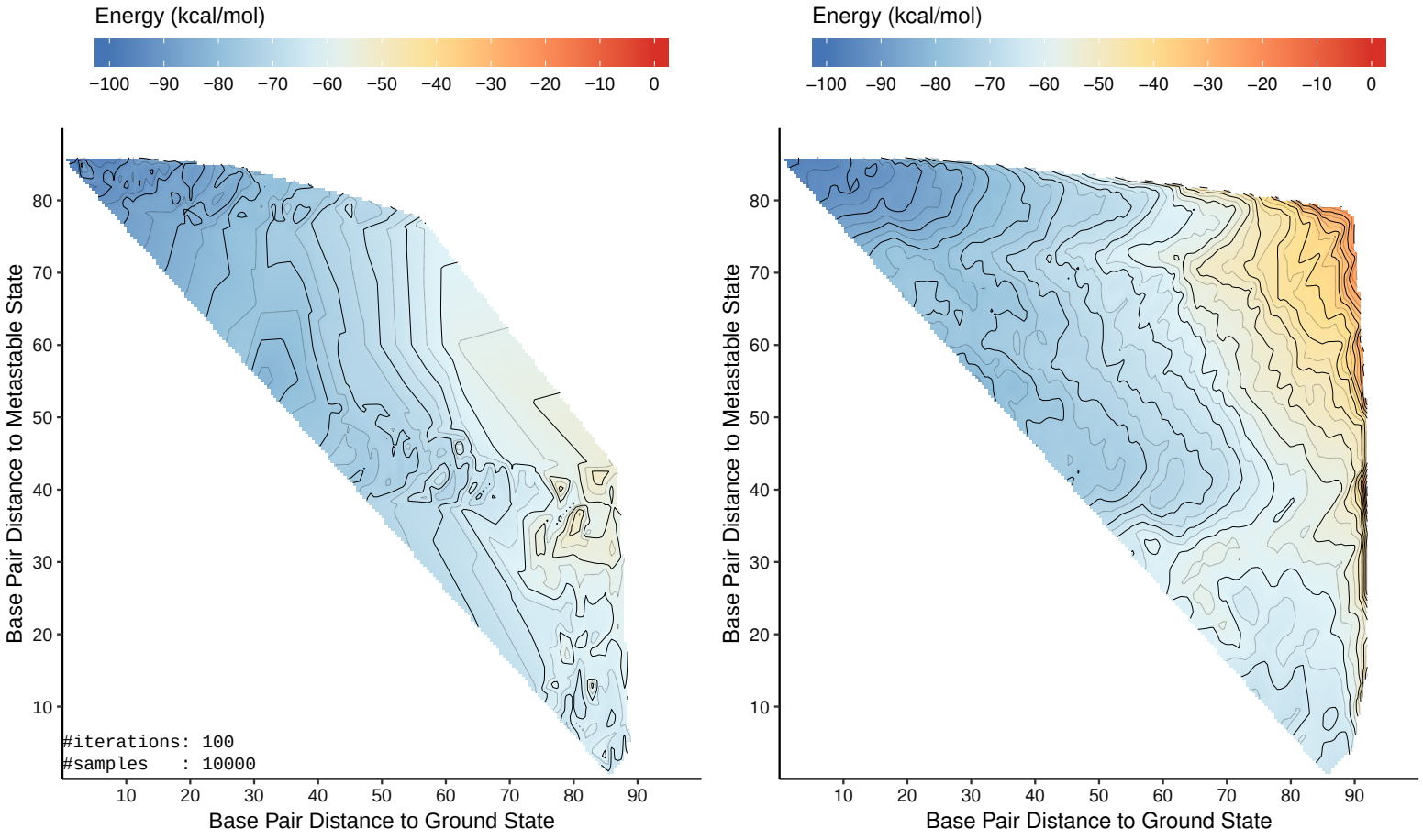
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

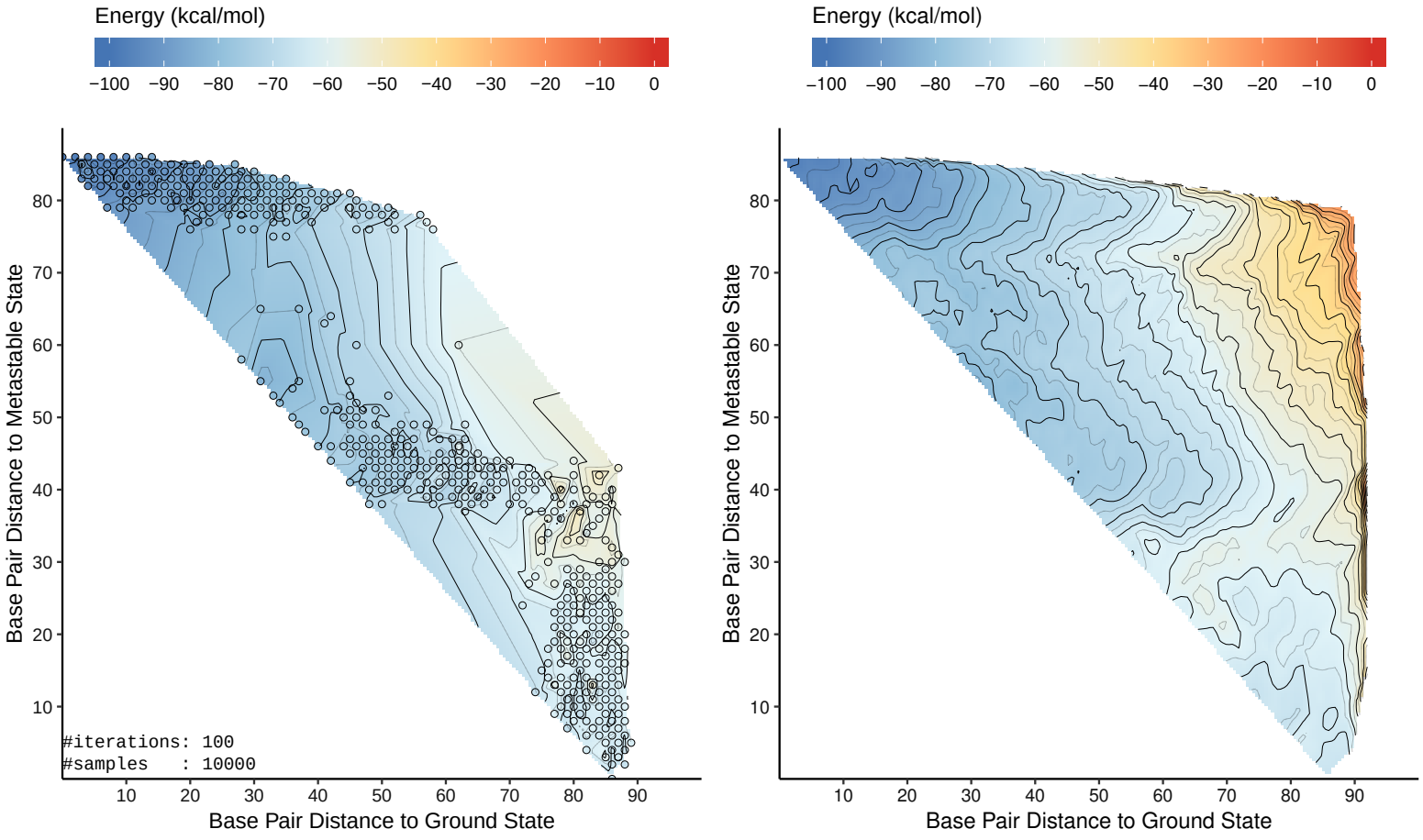
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

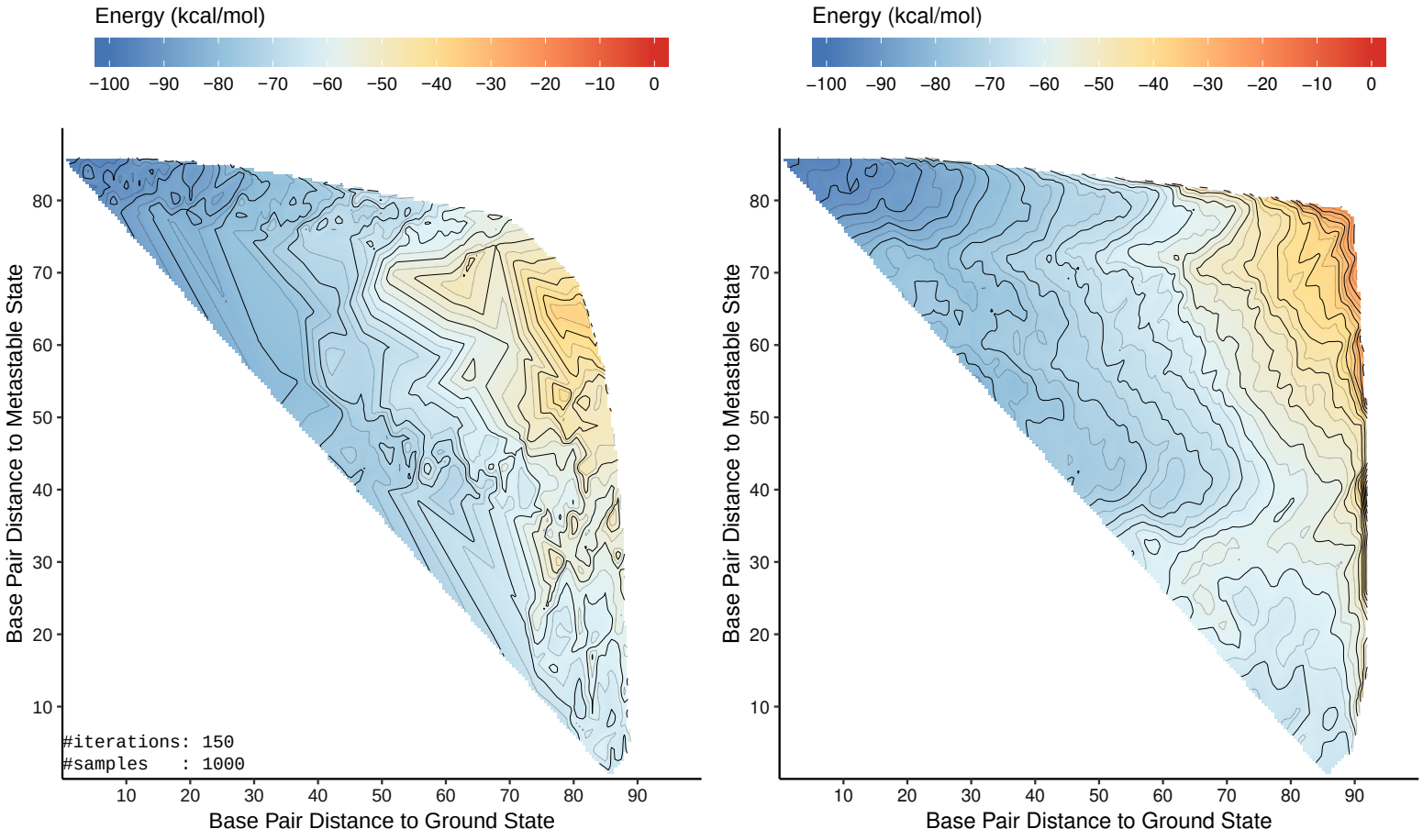
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

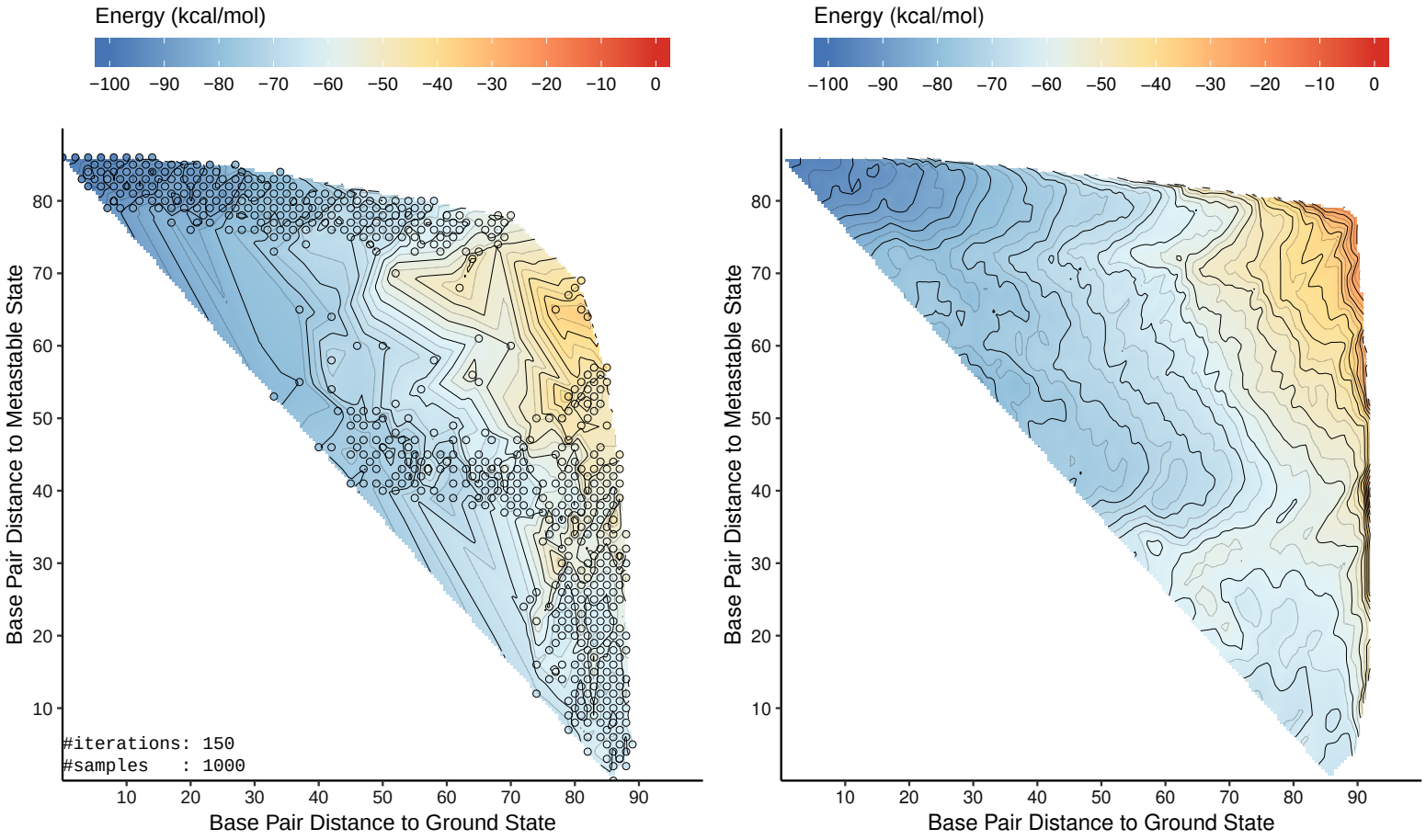
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

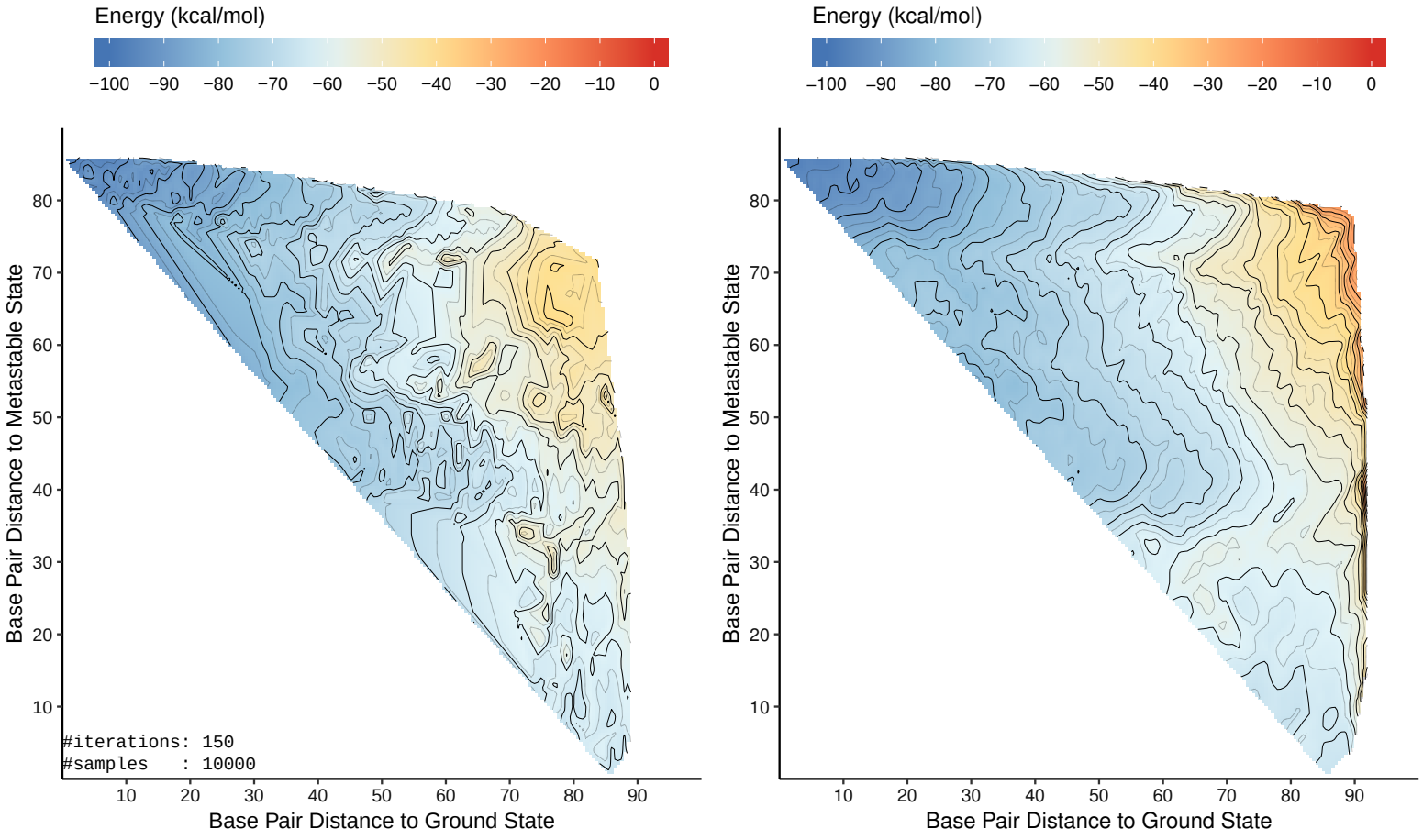
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

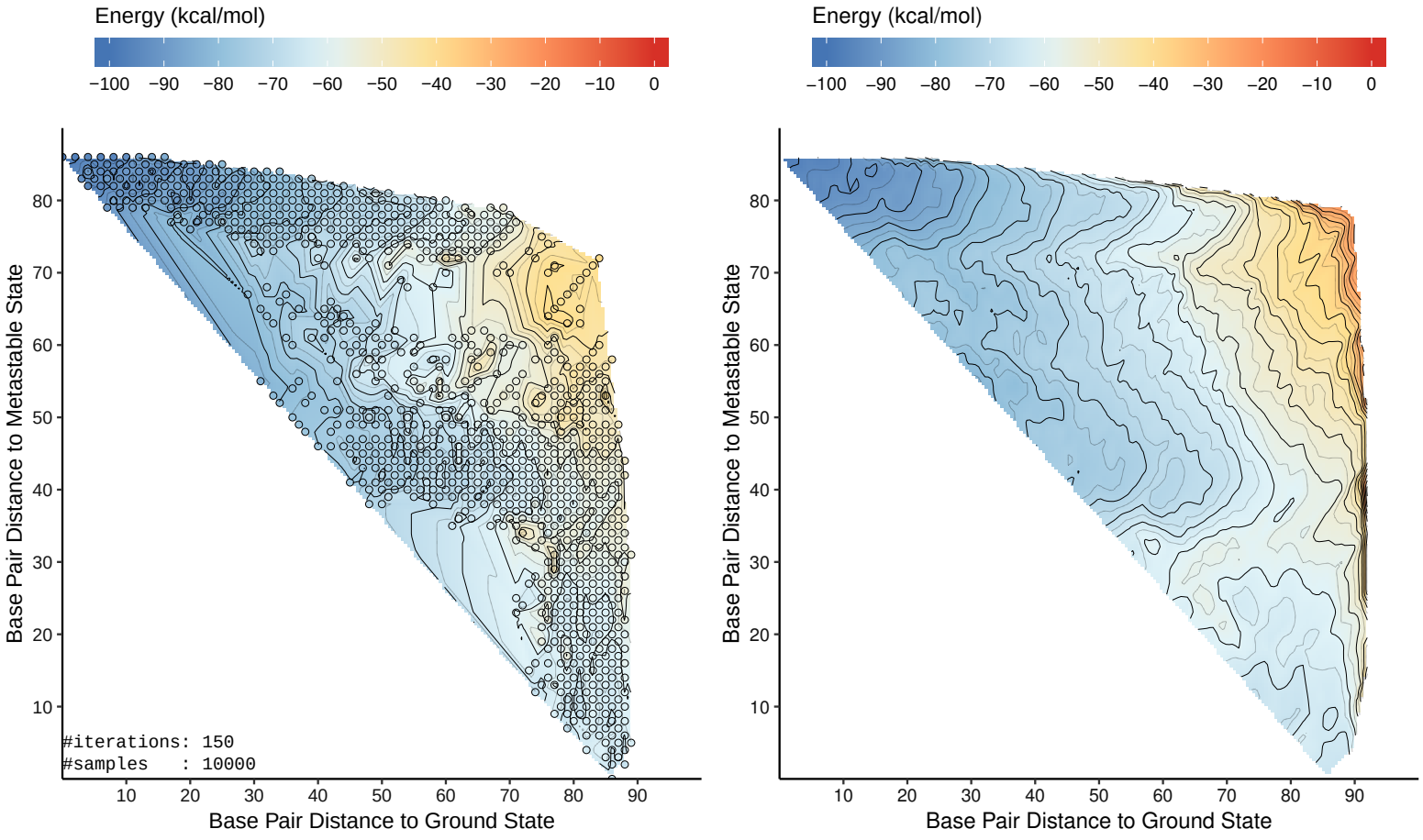
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

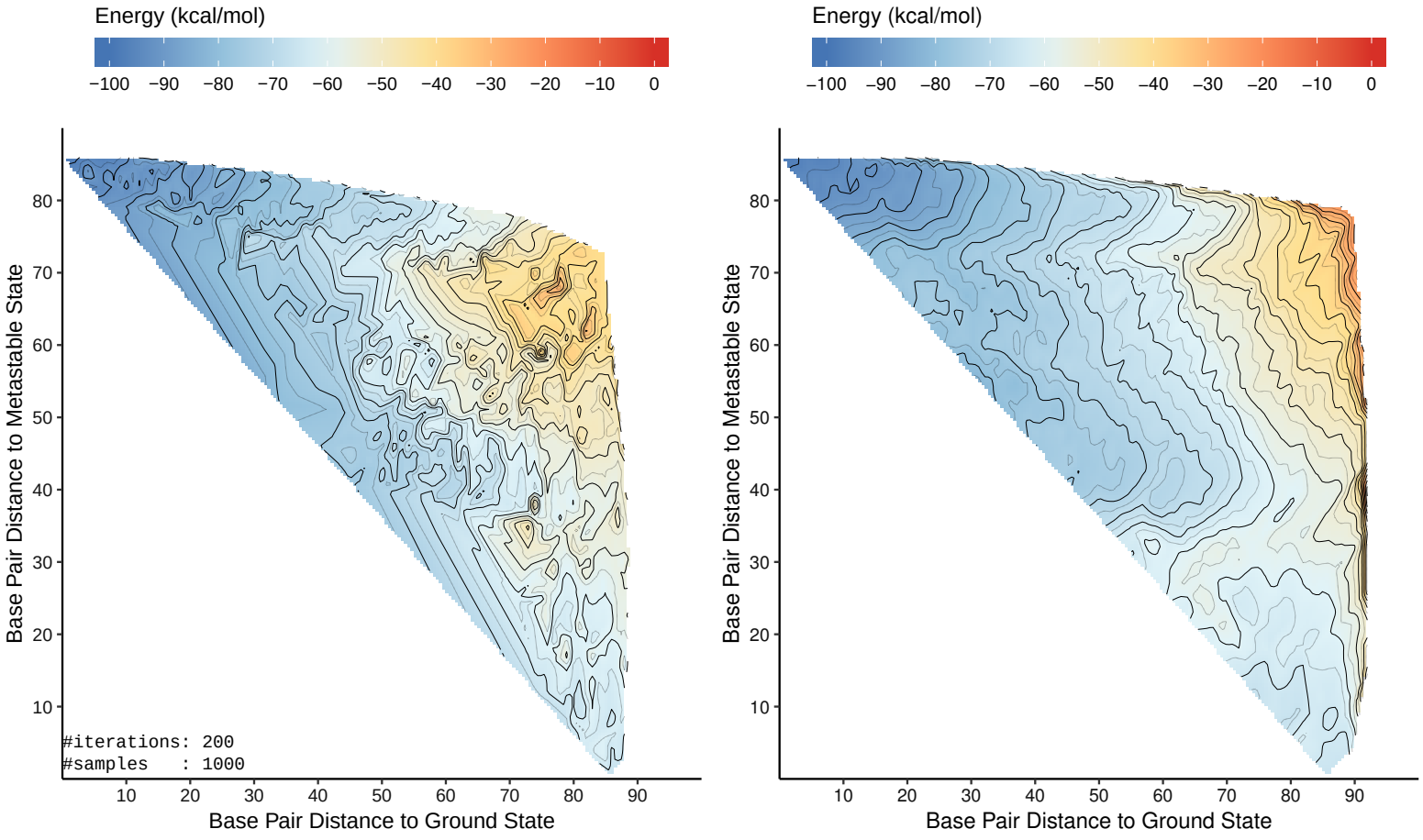
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

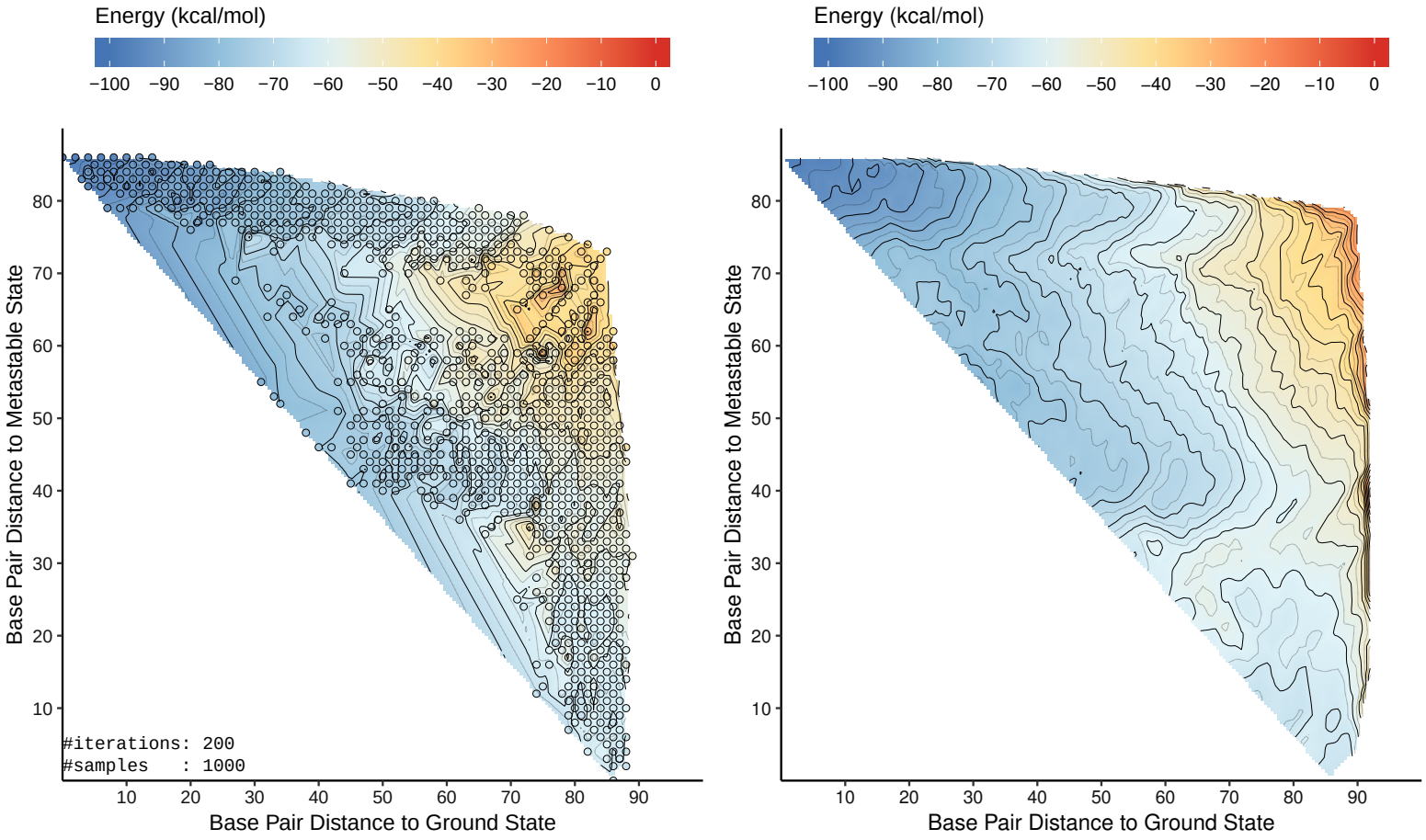
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

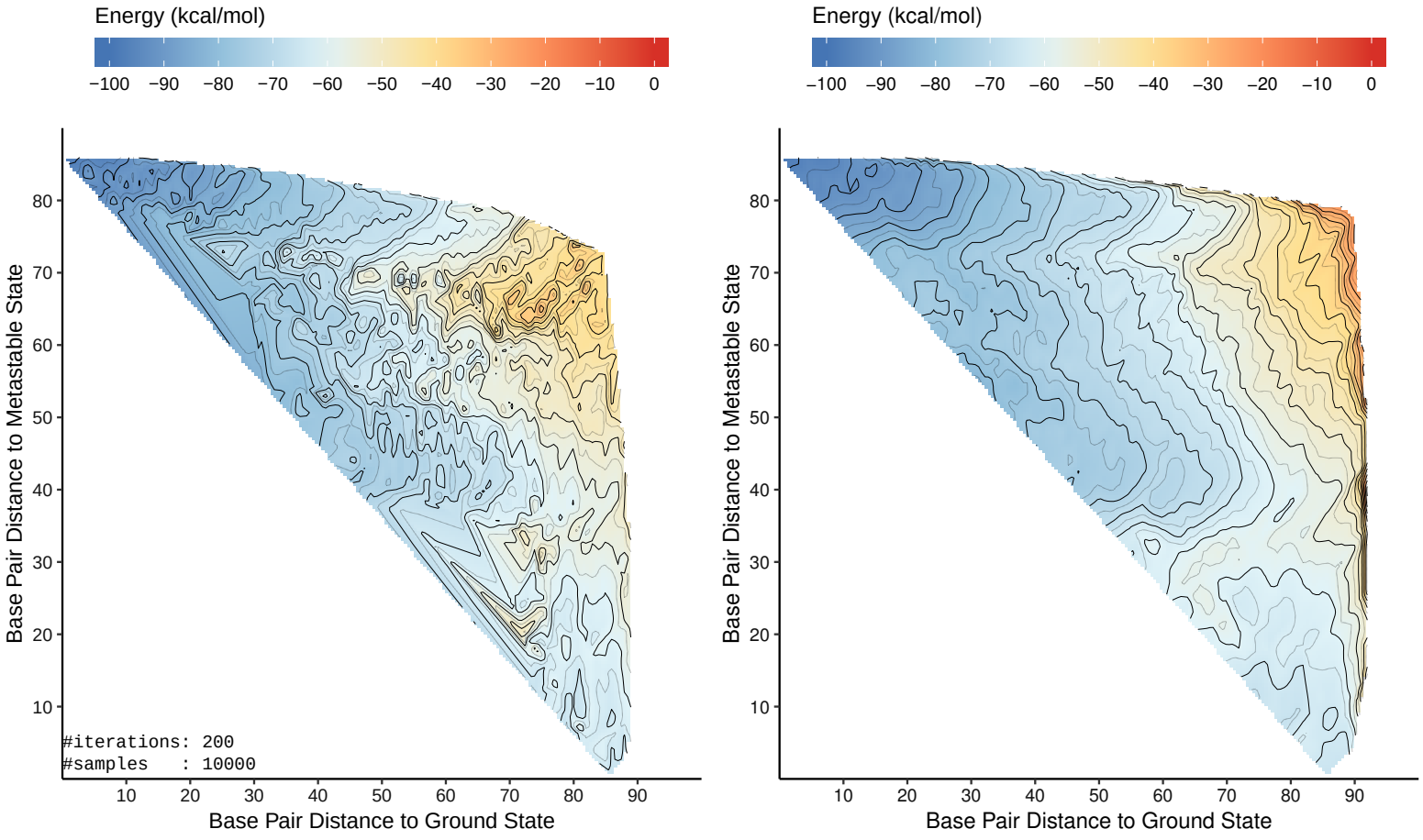
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

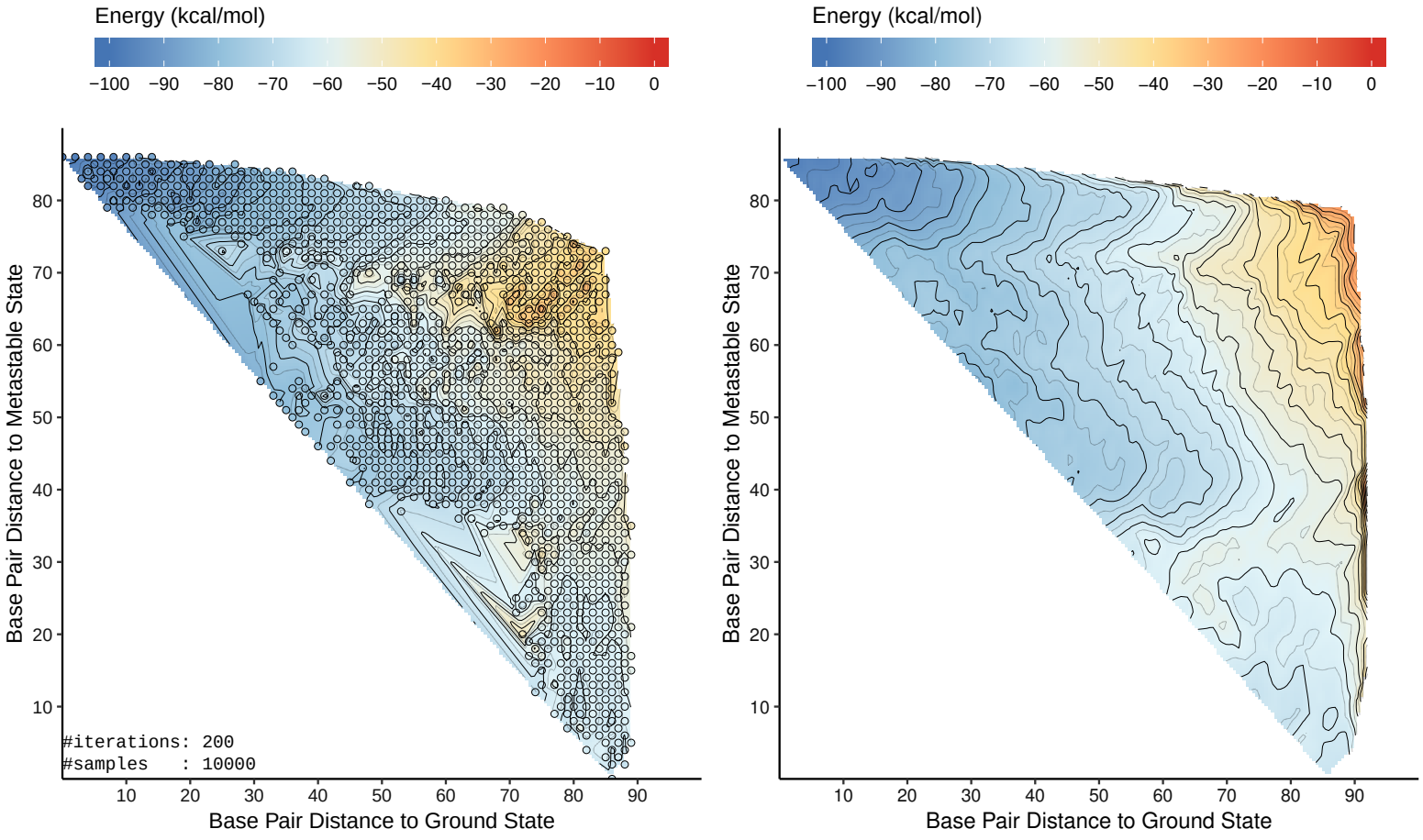
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

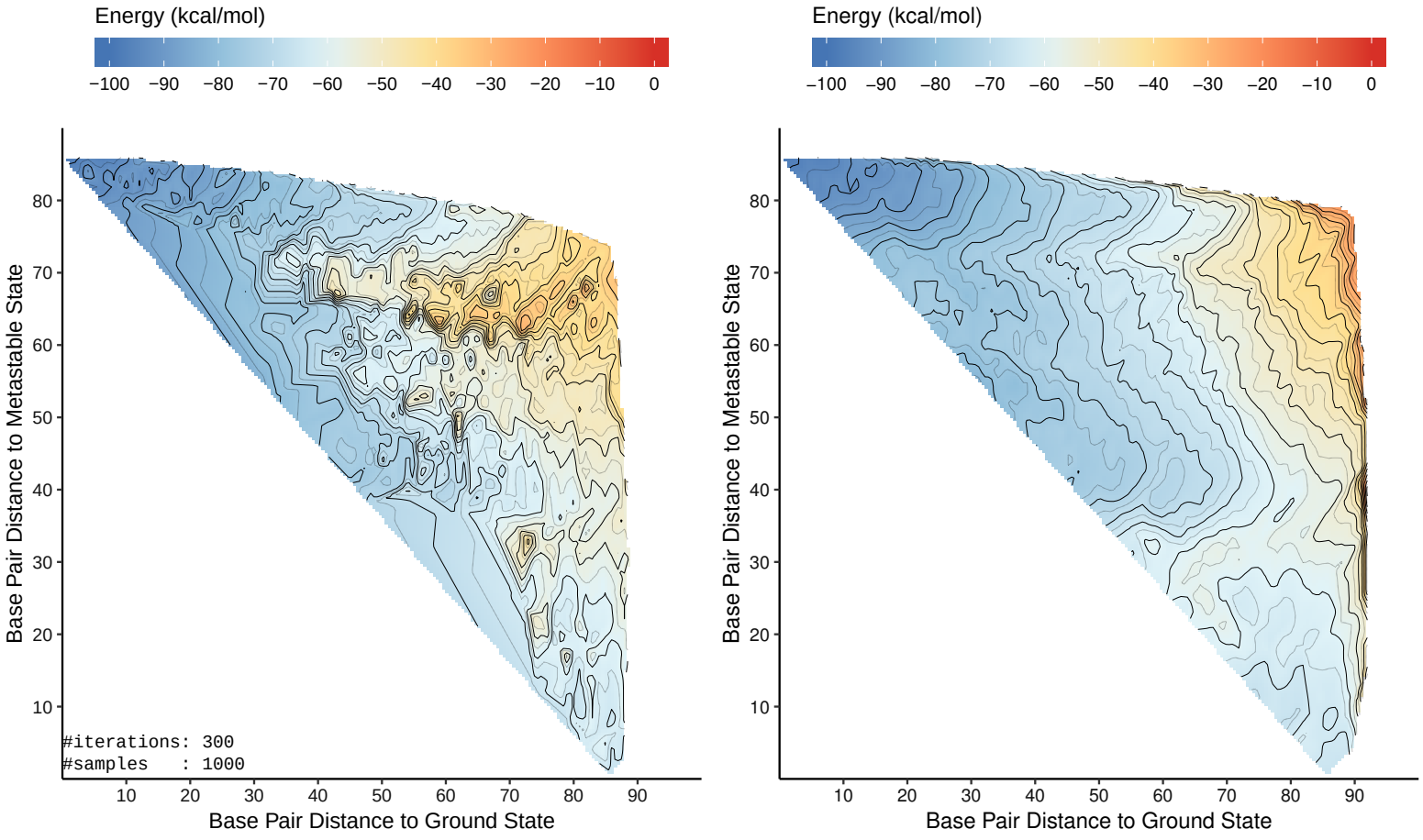
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

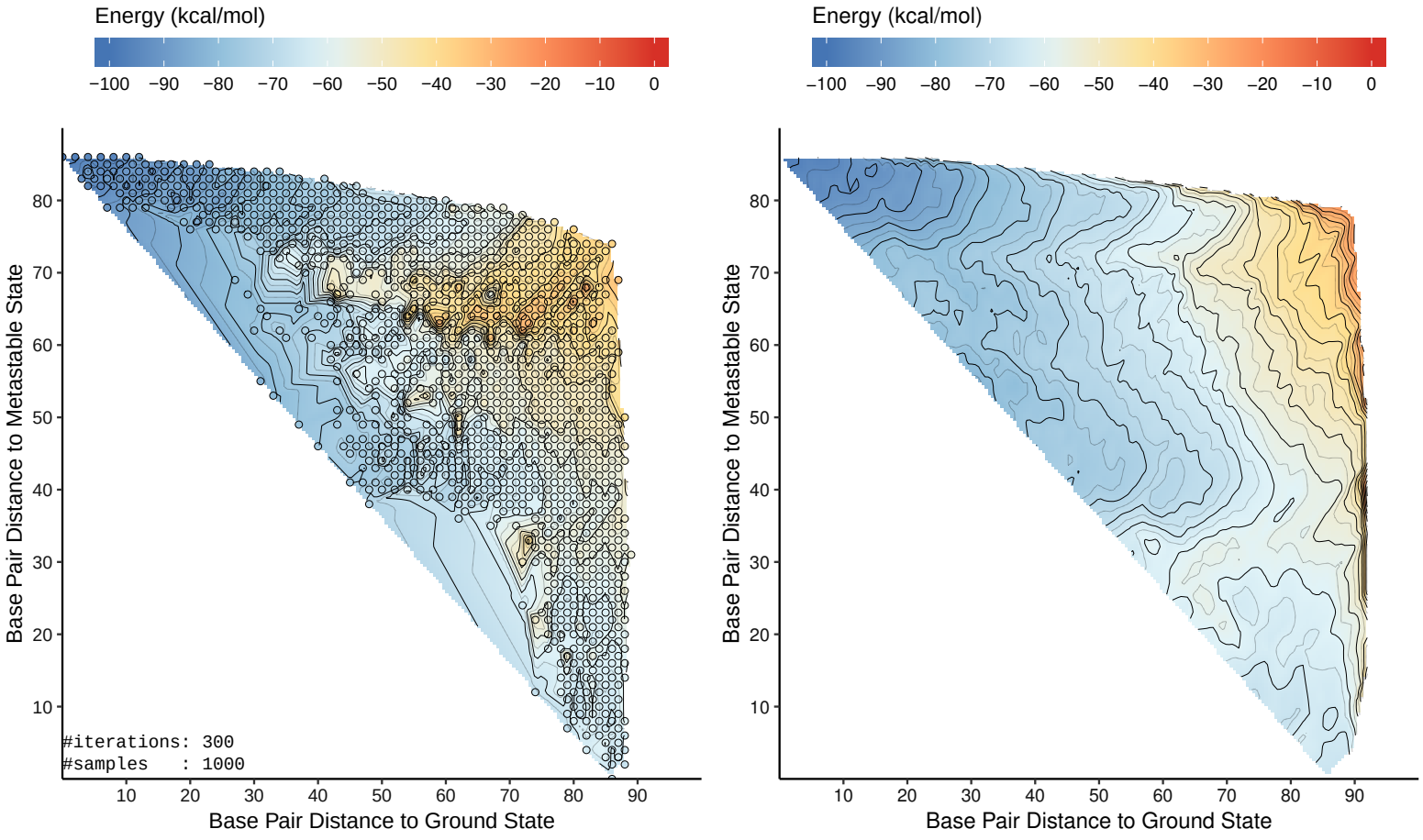
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

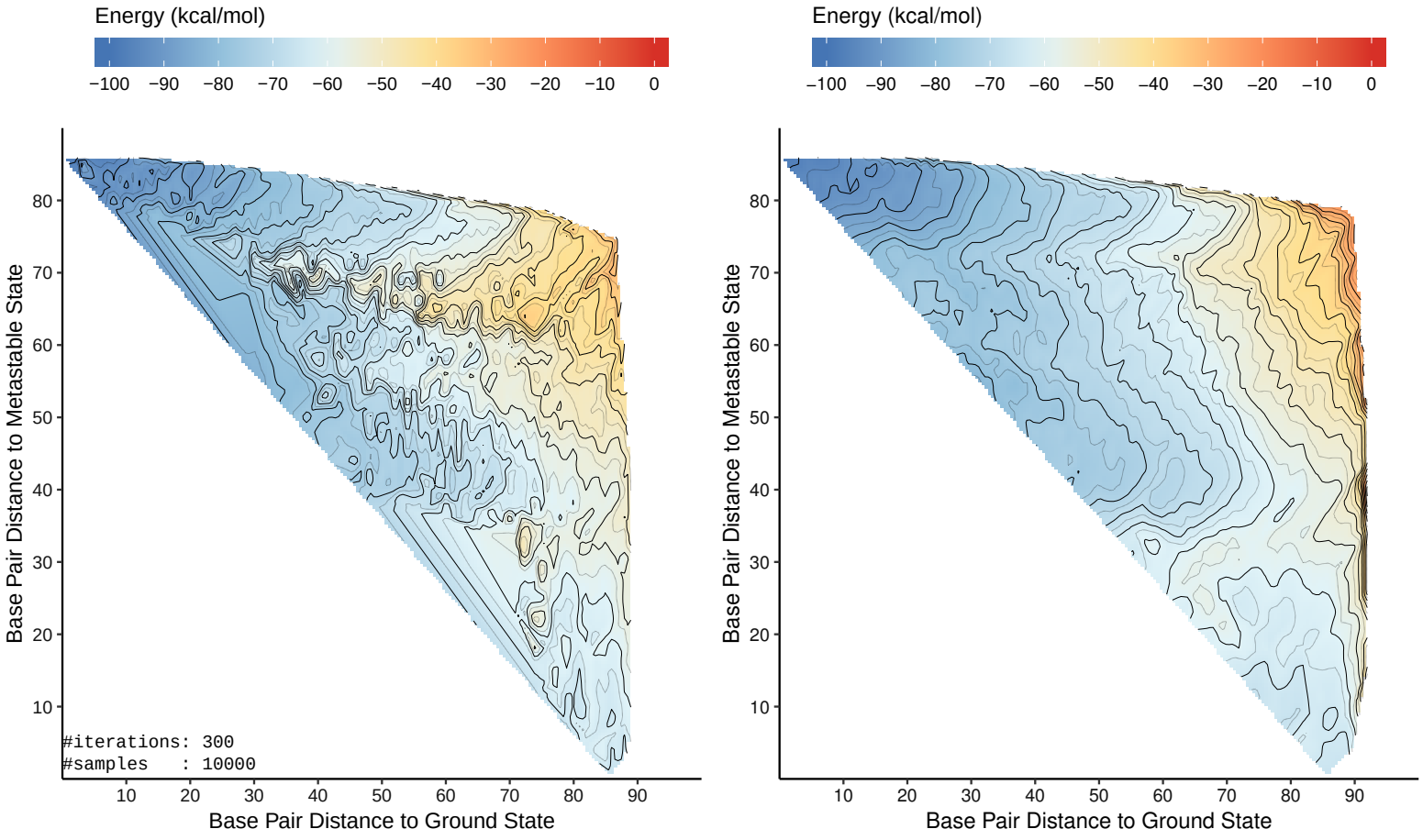
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

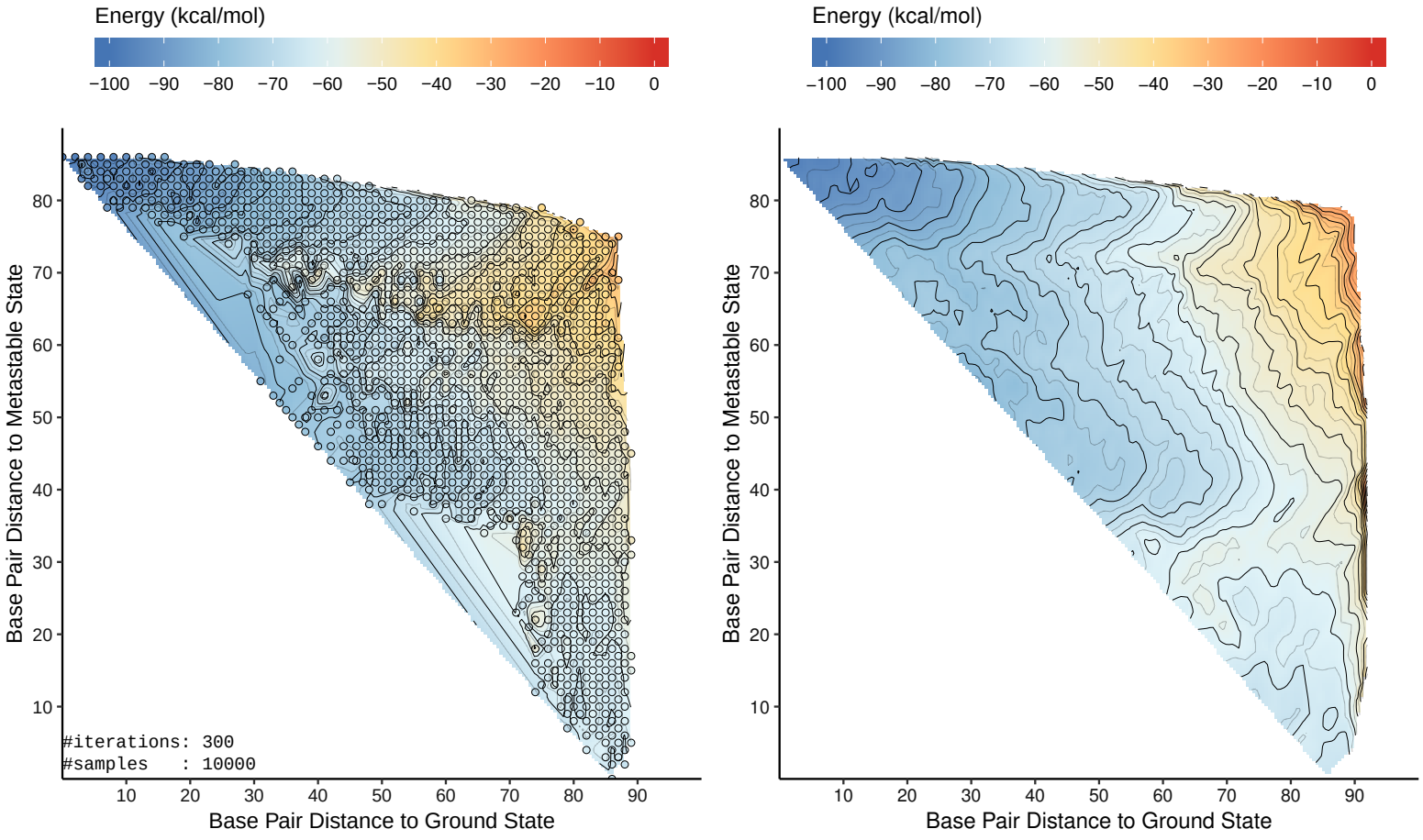
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

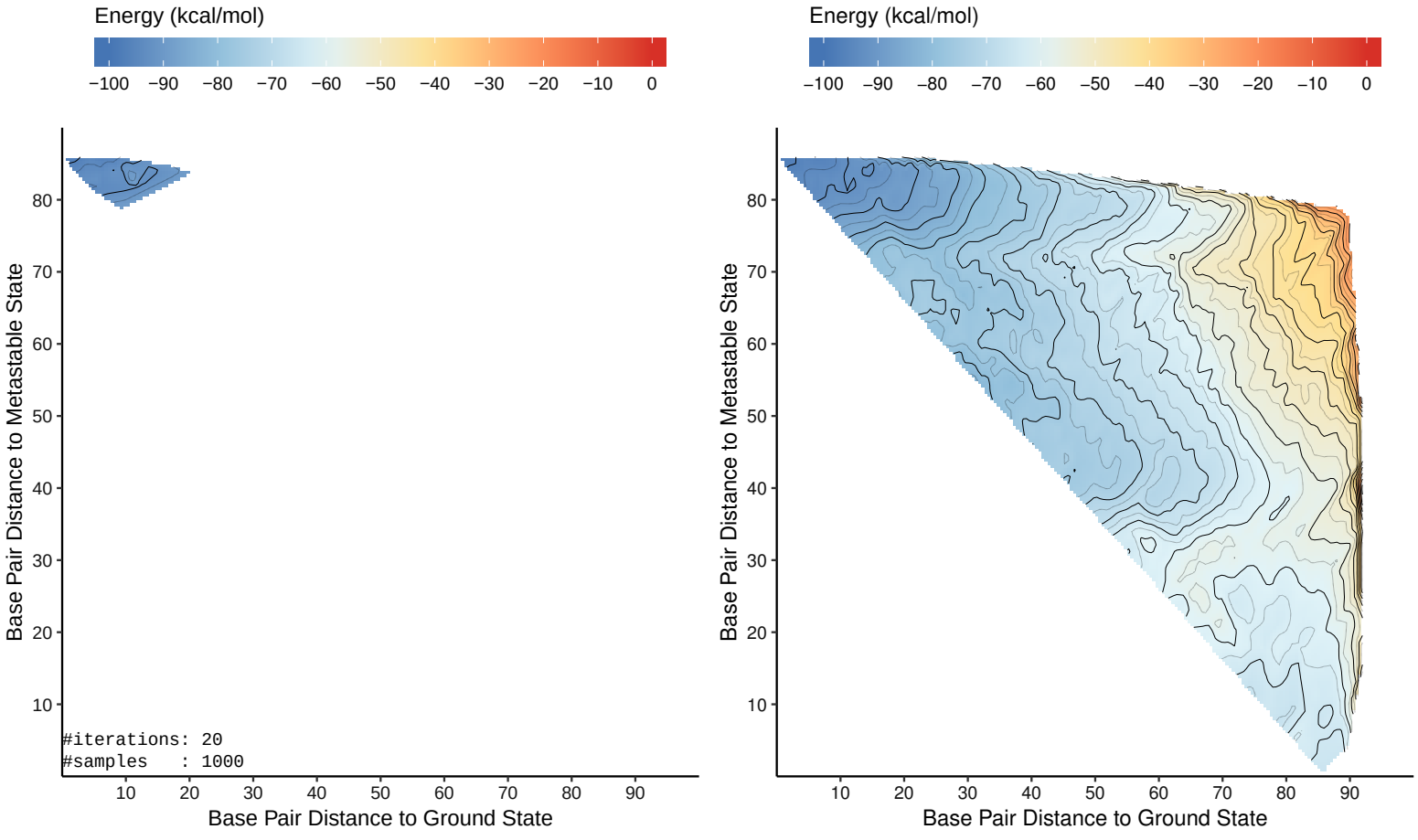
`RNAxplorer` repulsion scheme Boltzmann sampling



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

Example: Qβ replicase template SV11

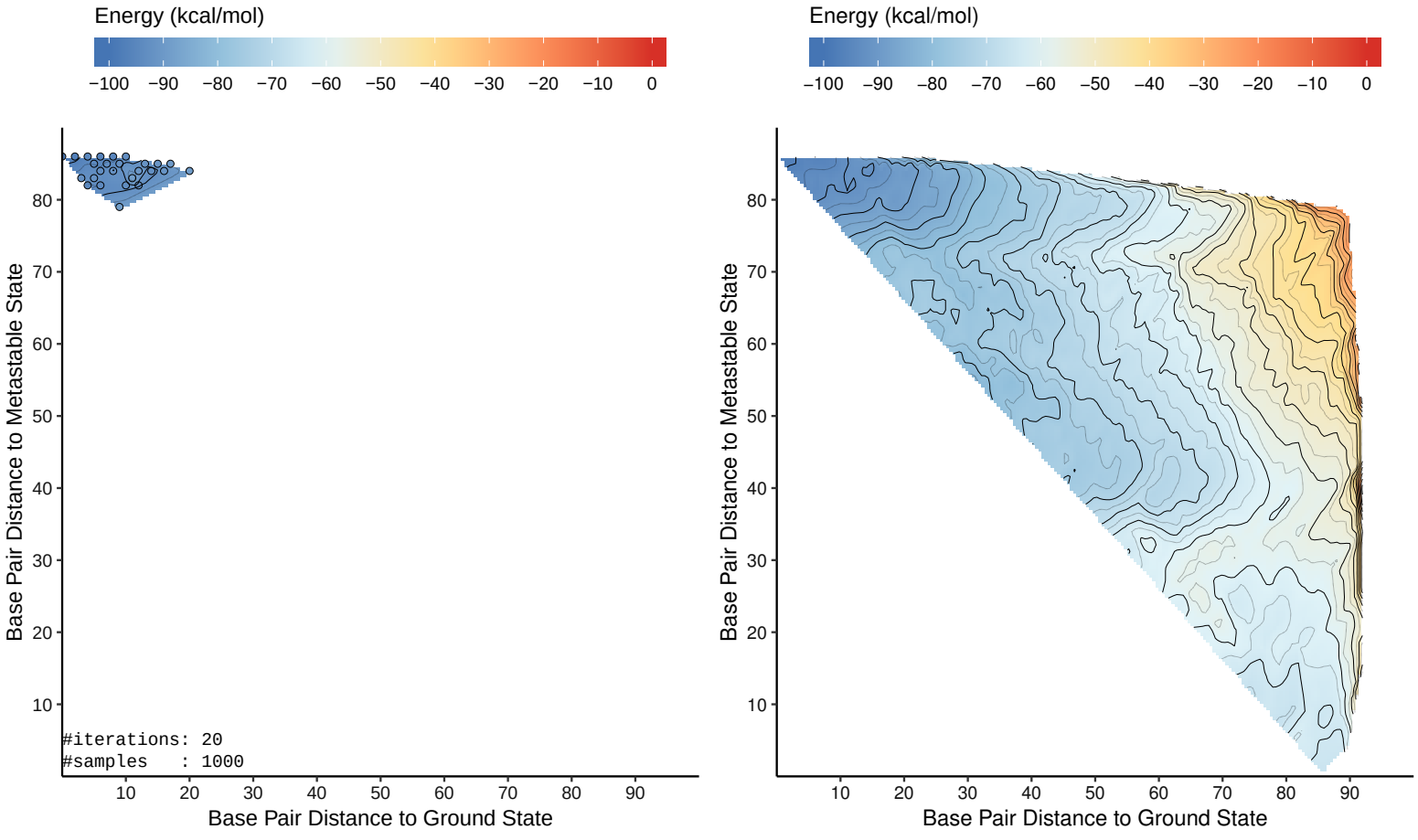
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

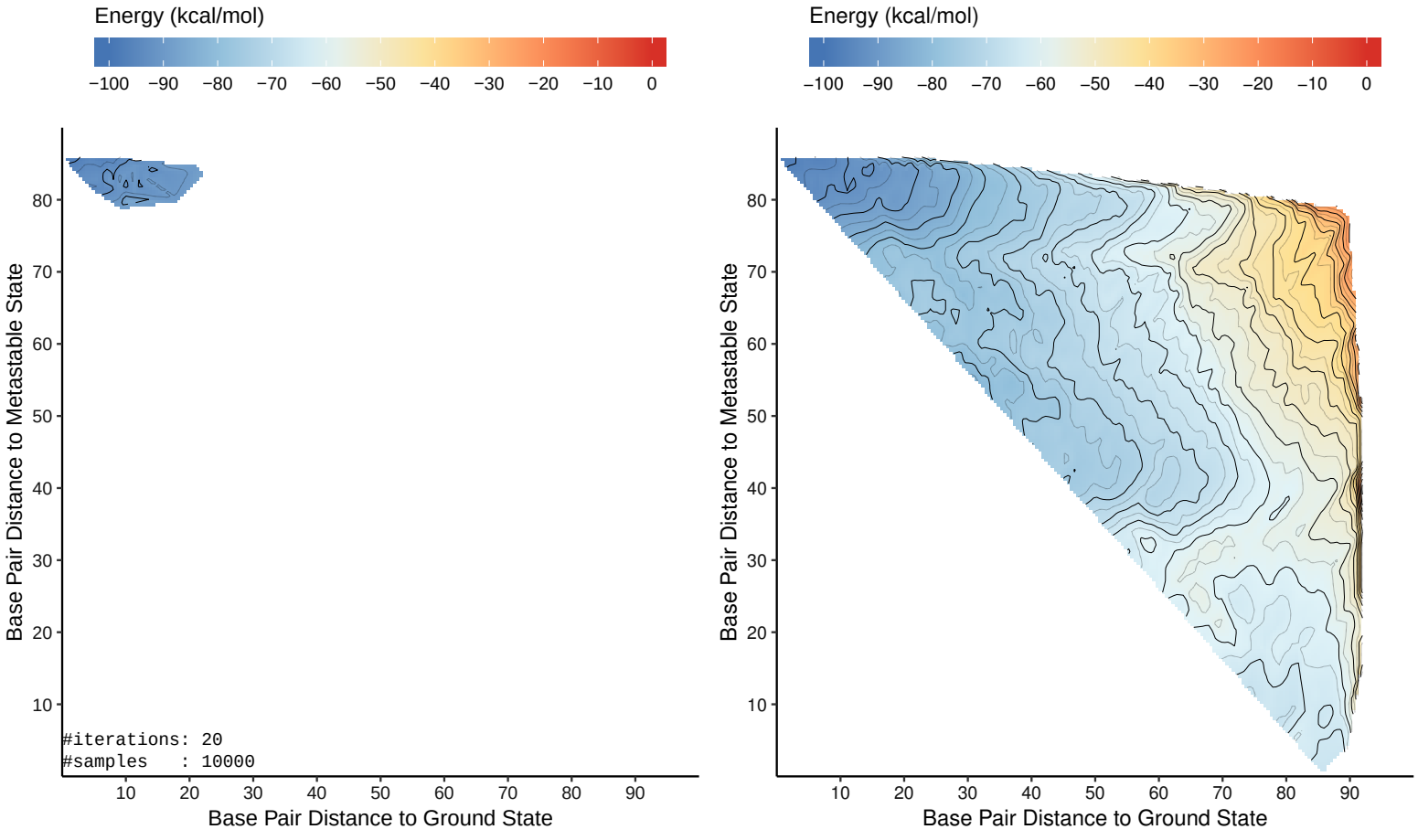
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

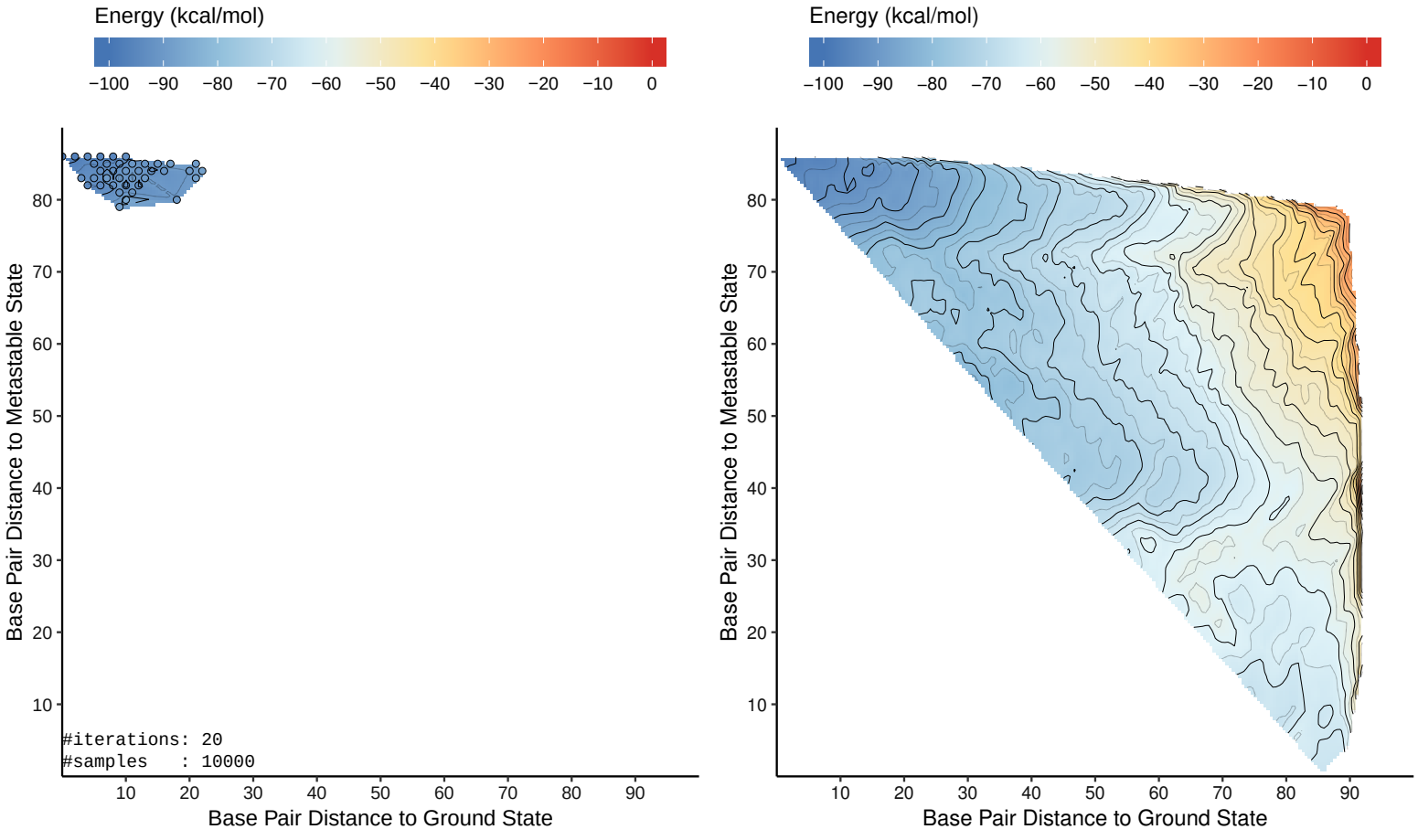
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

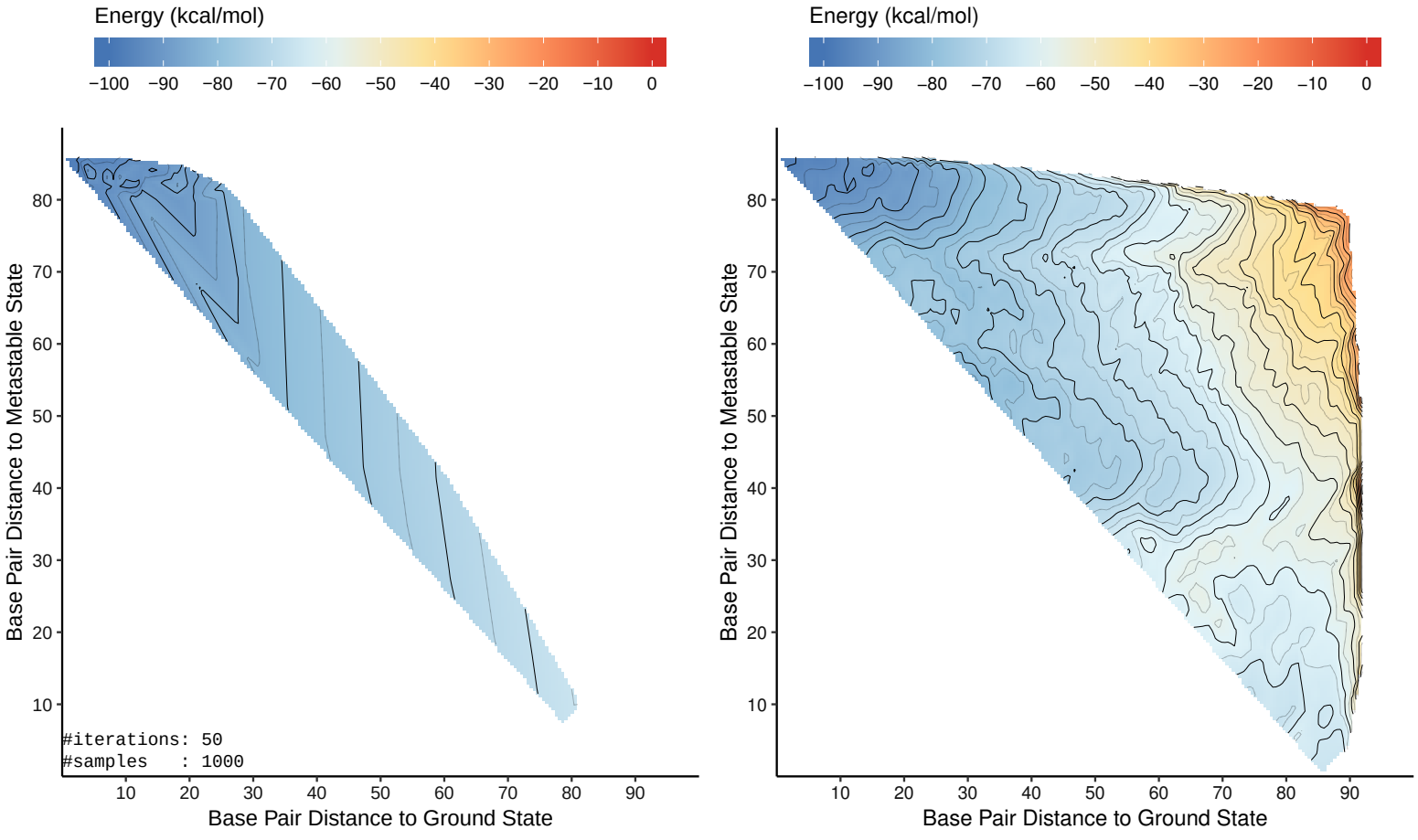
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

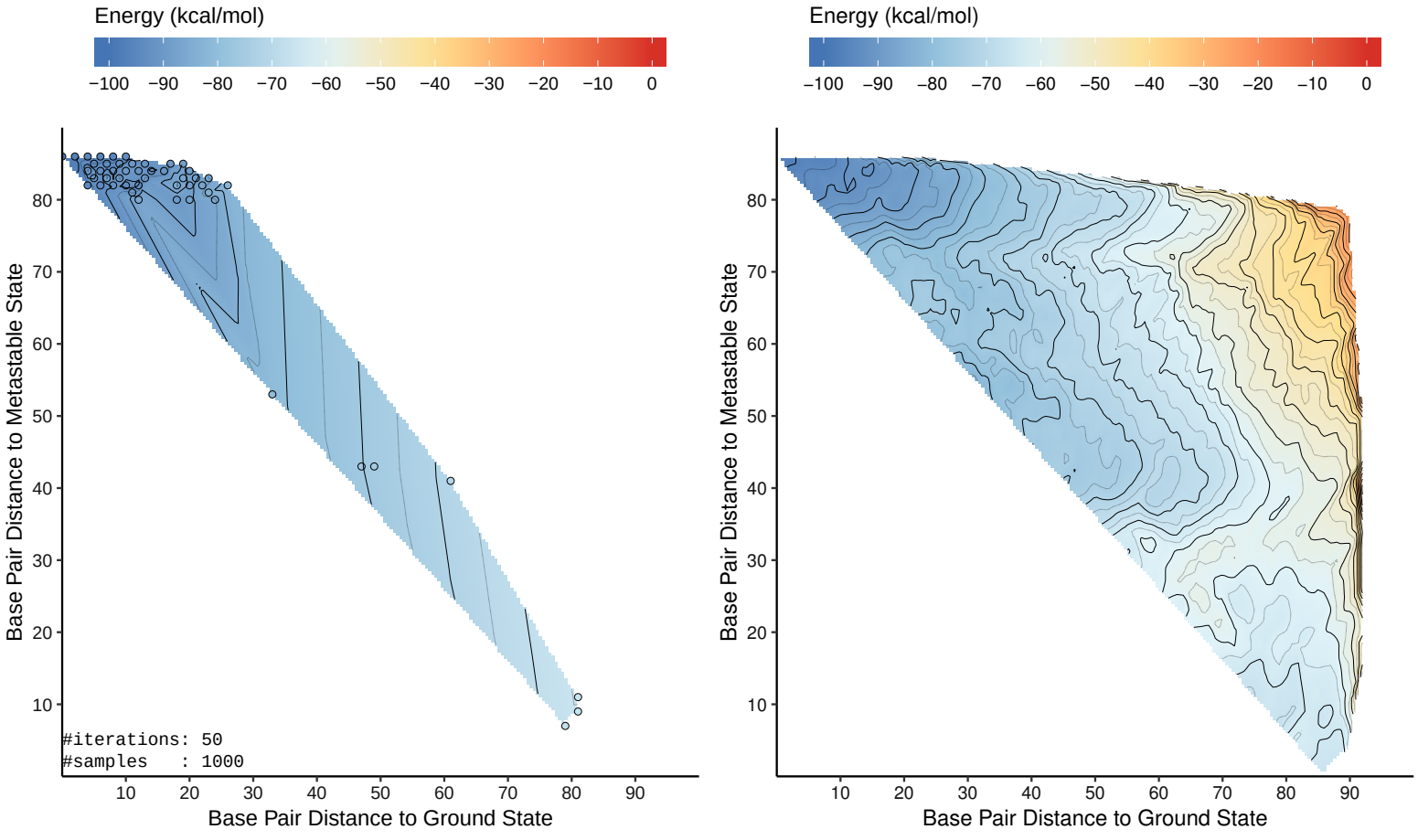
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

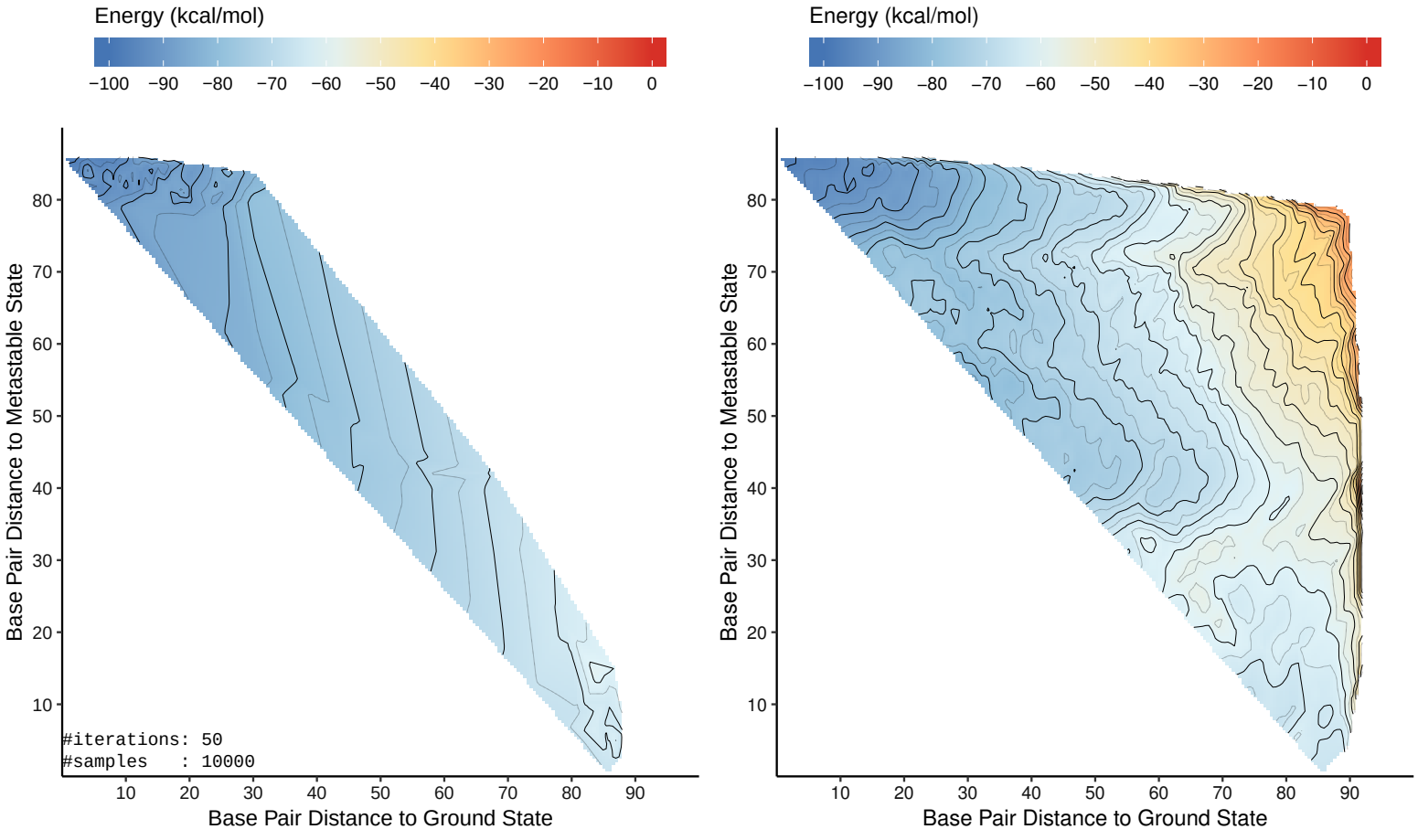
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

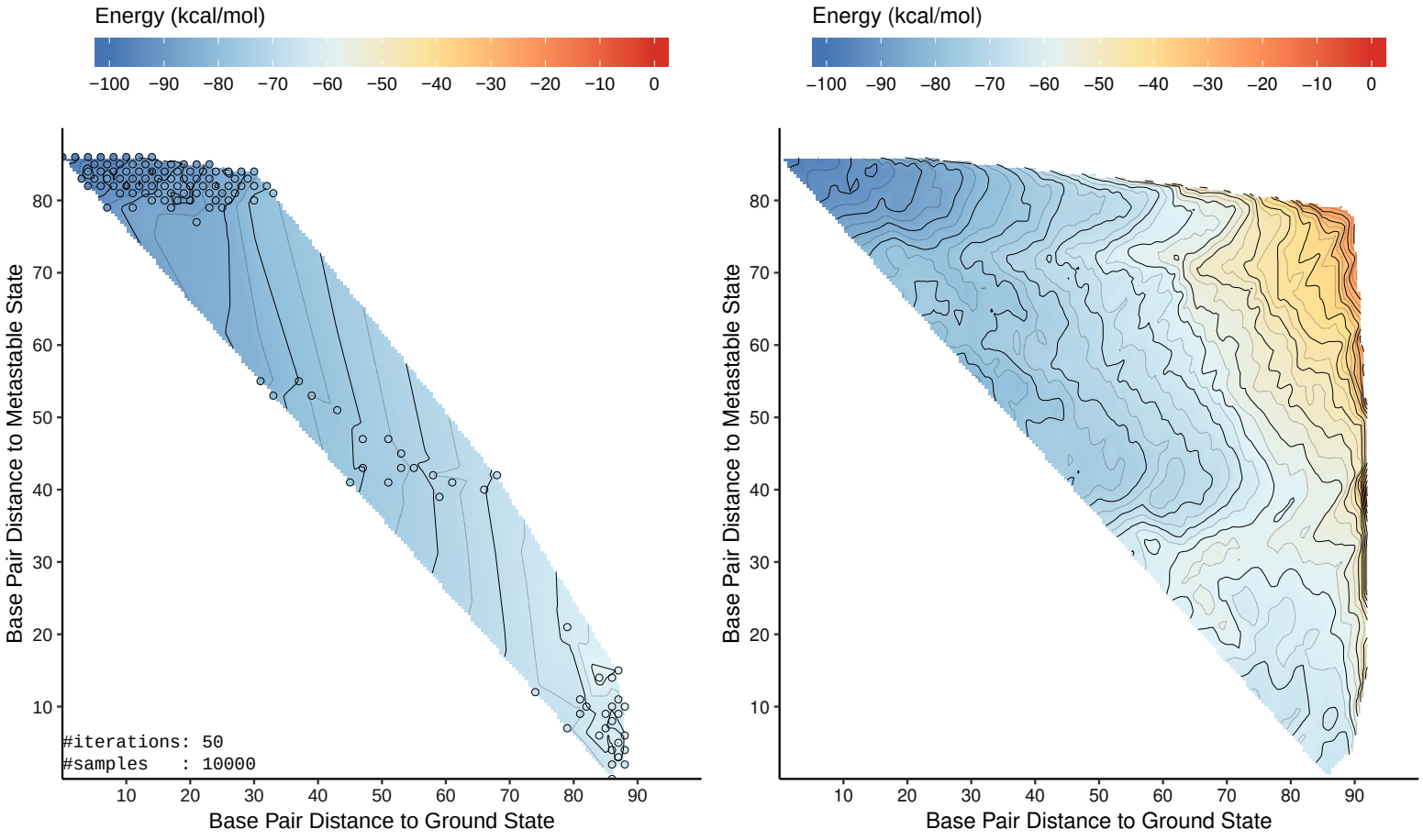
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

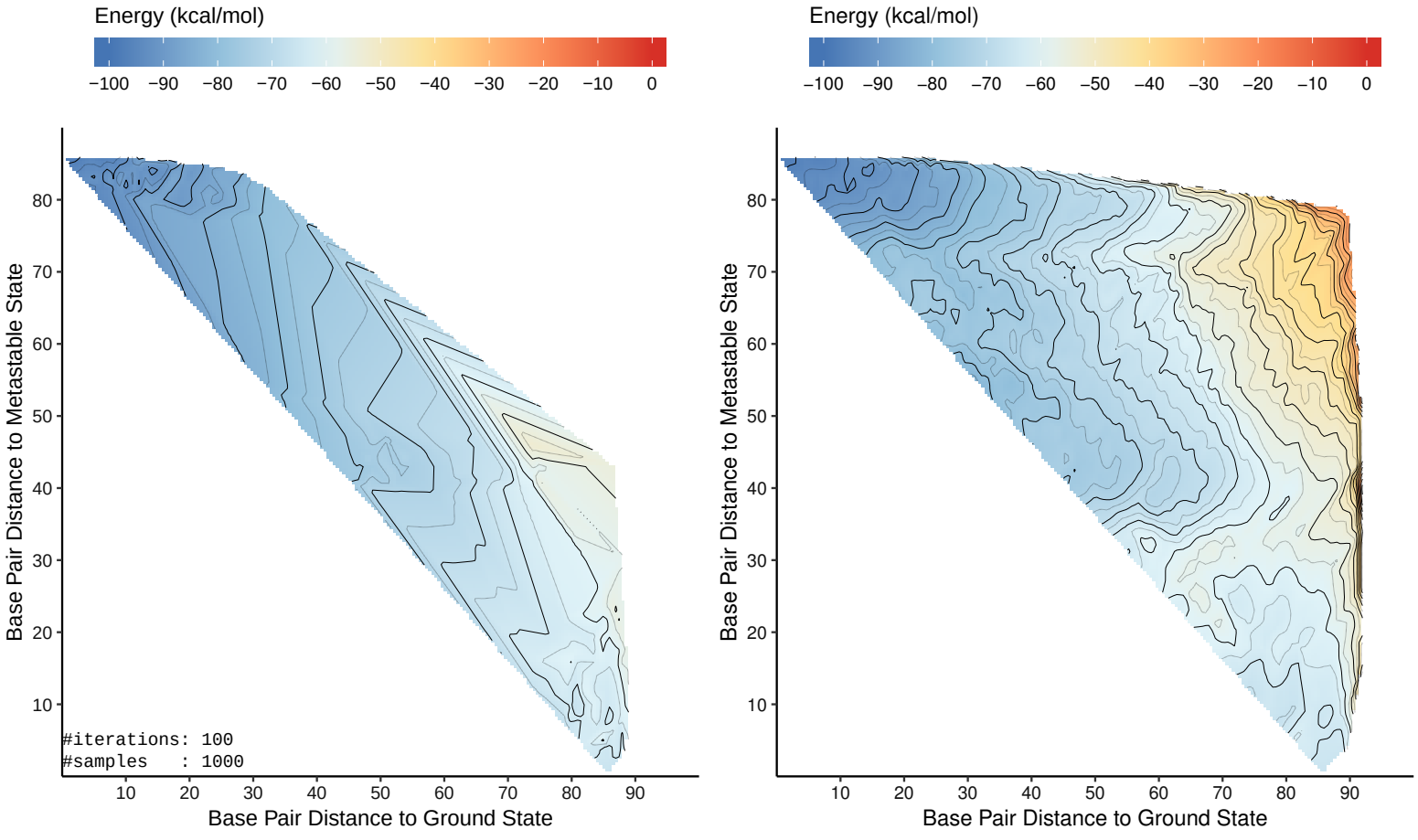
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

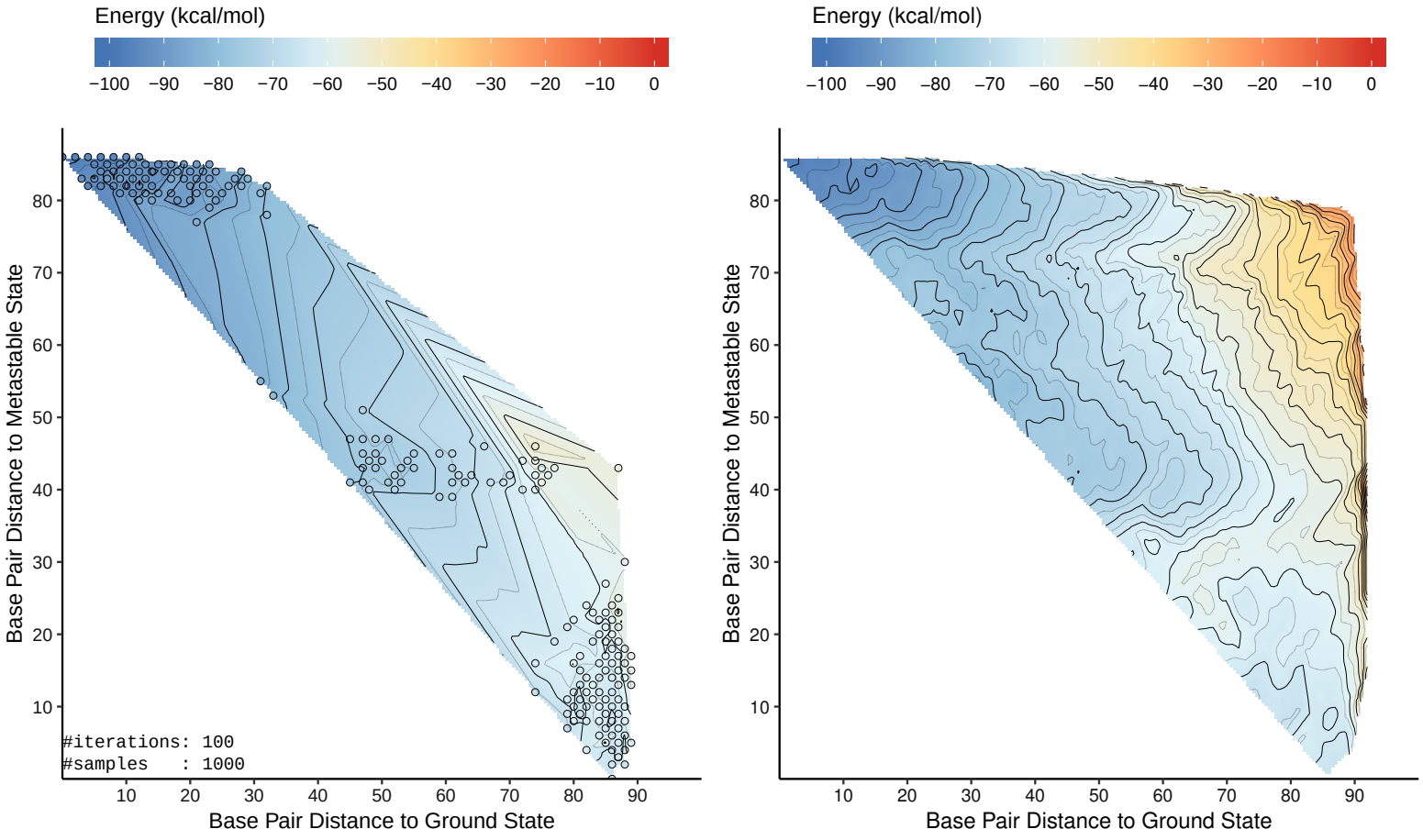
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

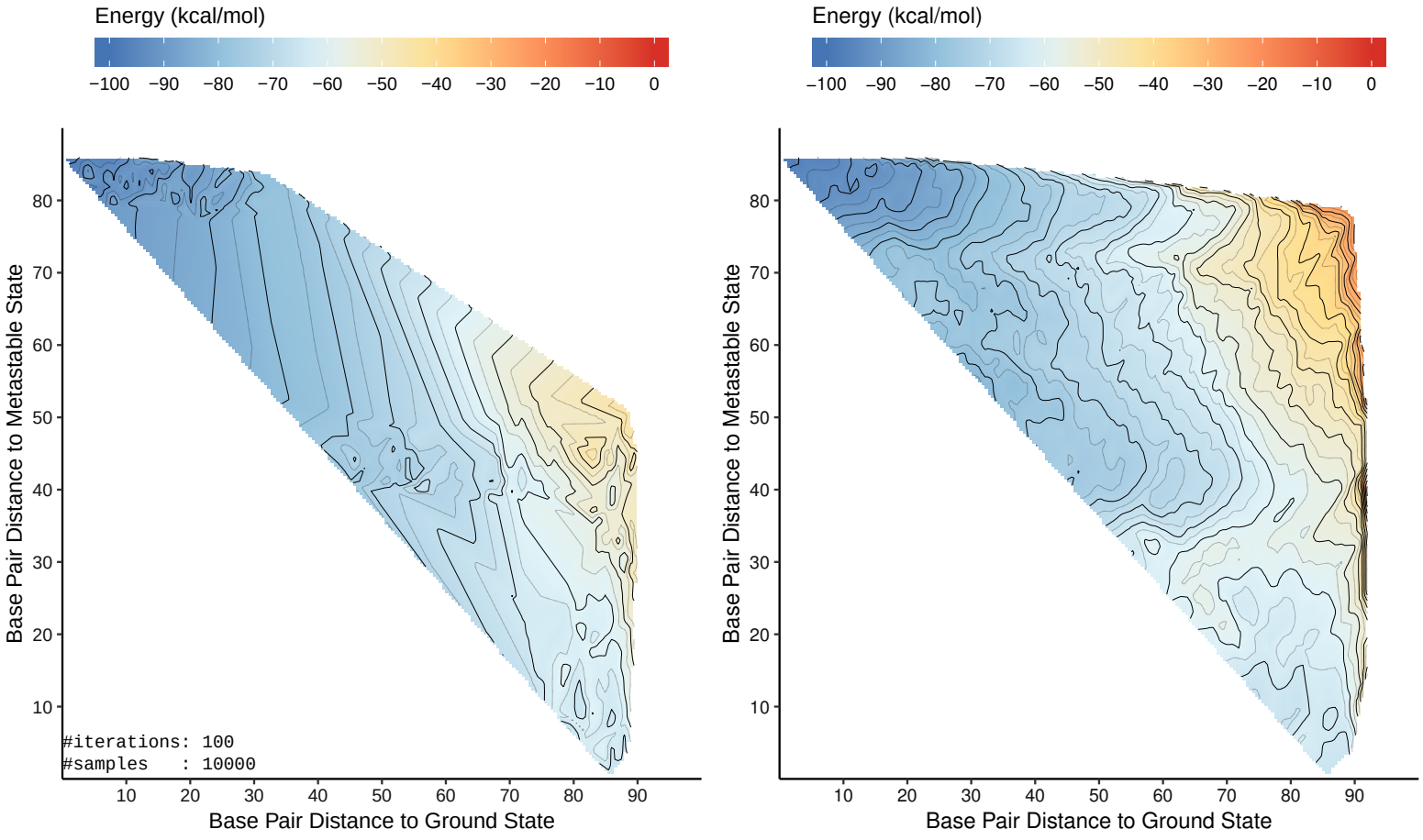
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

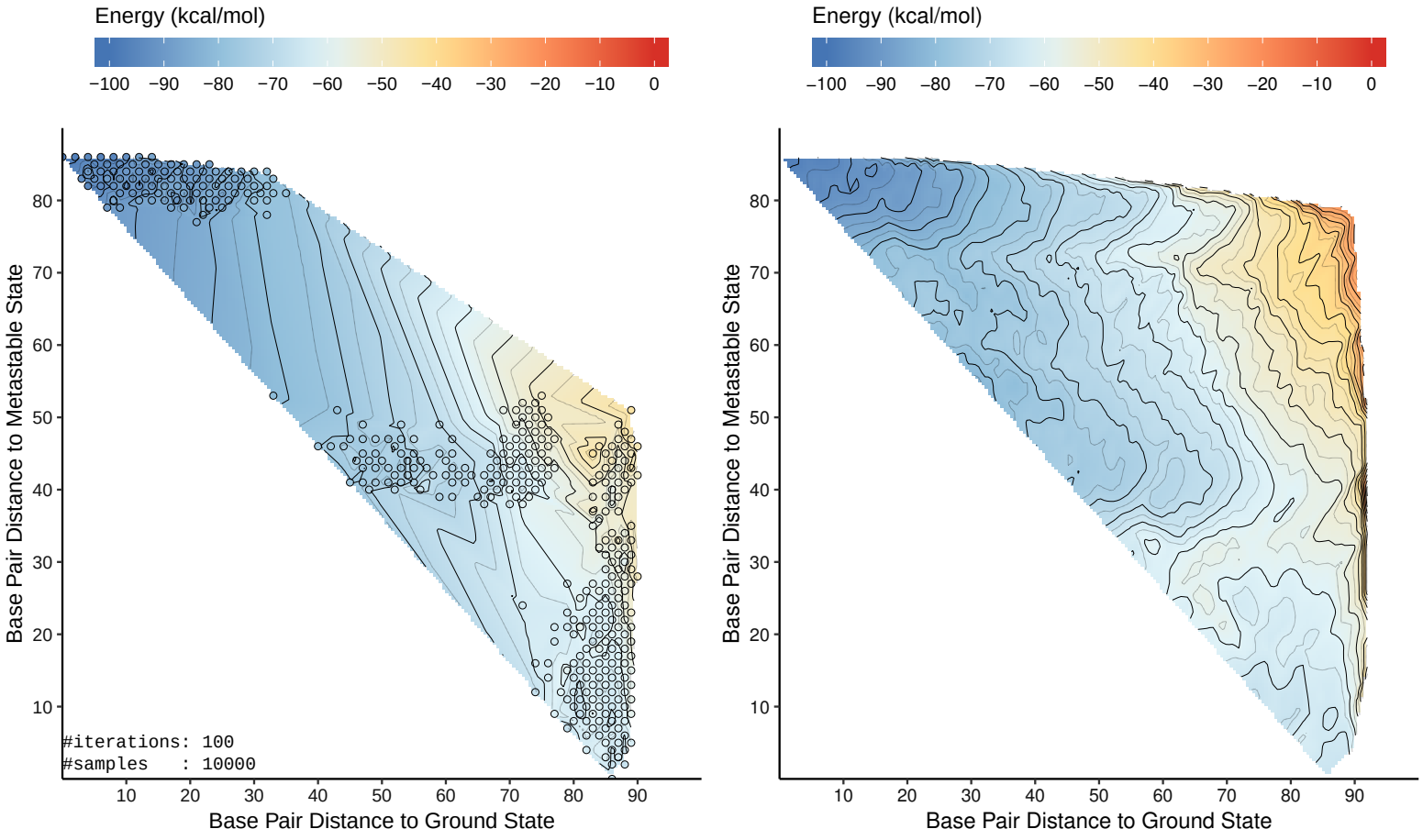
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

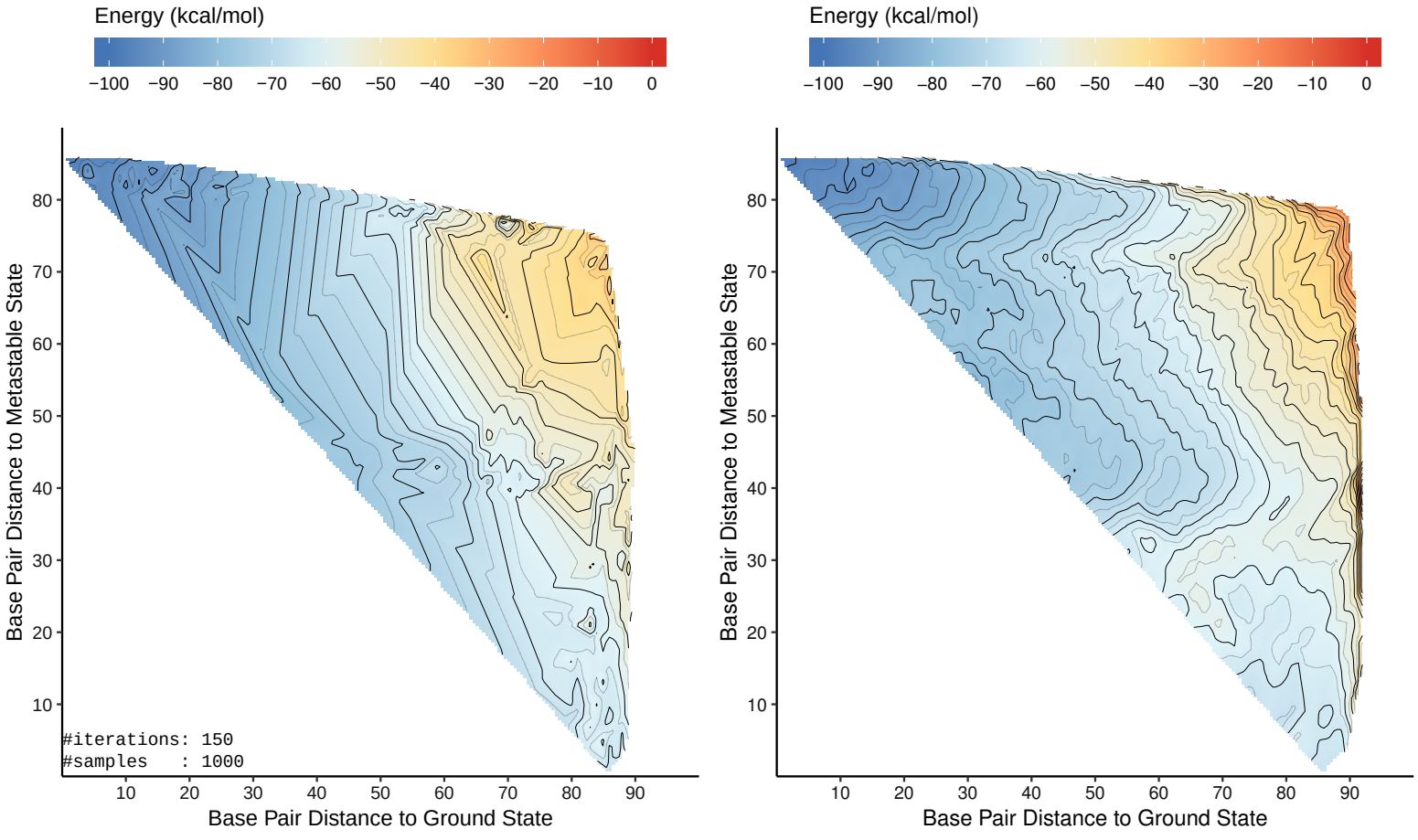
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

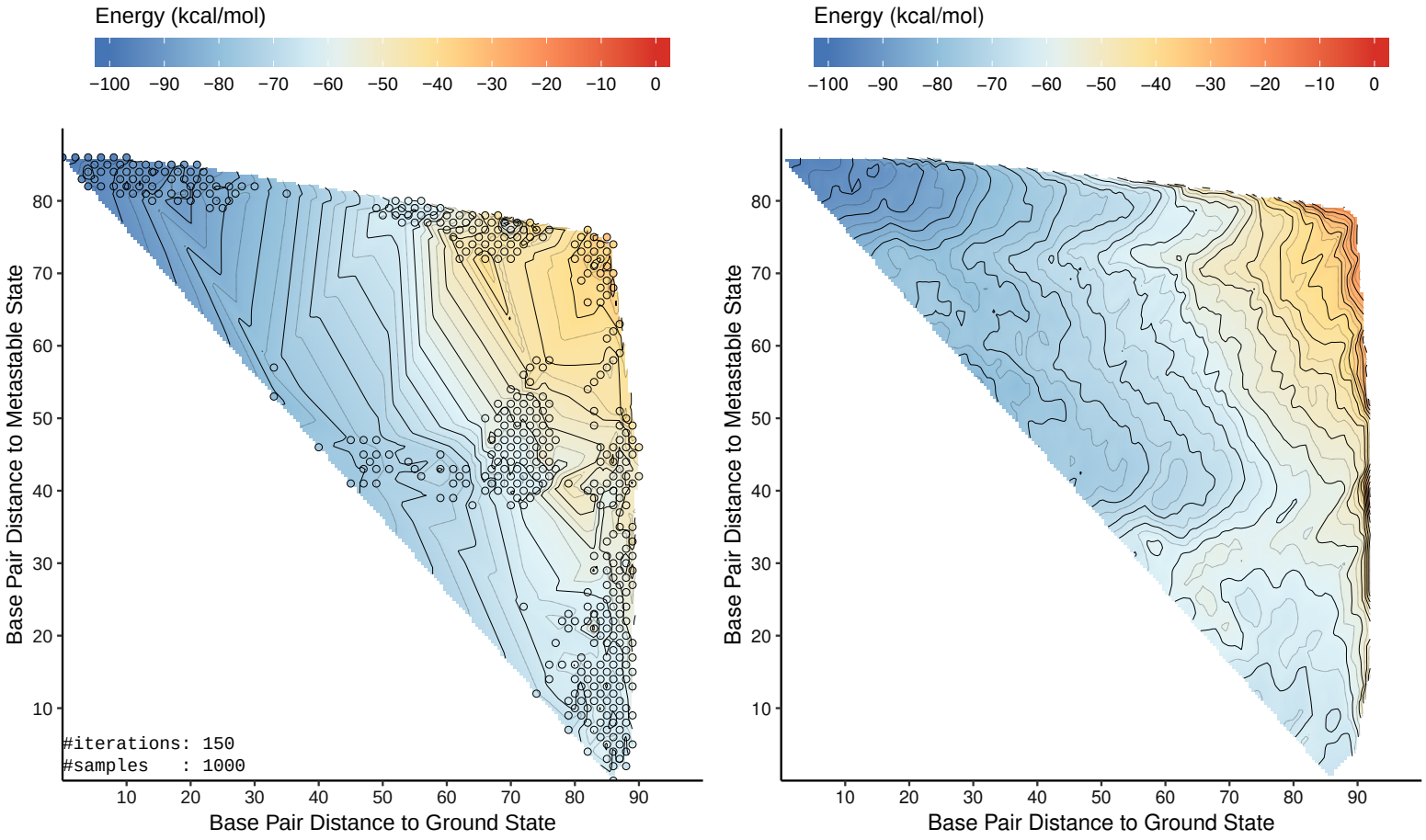
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

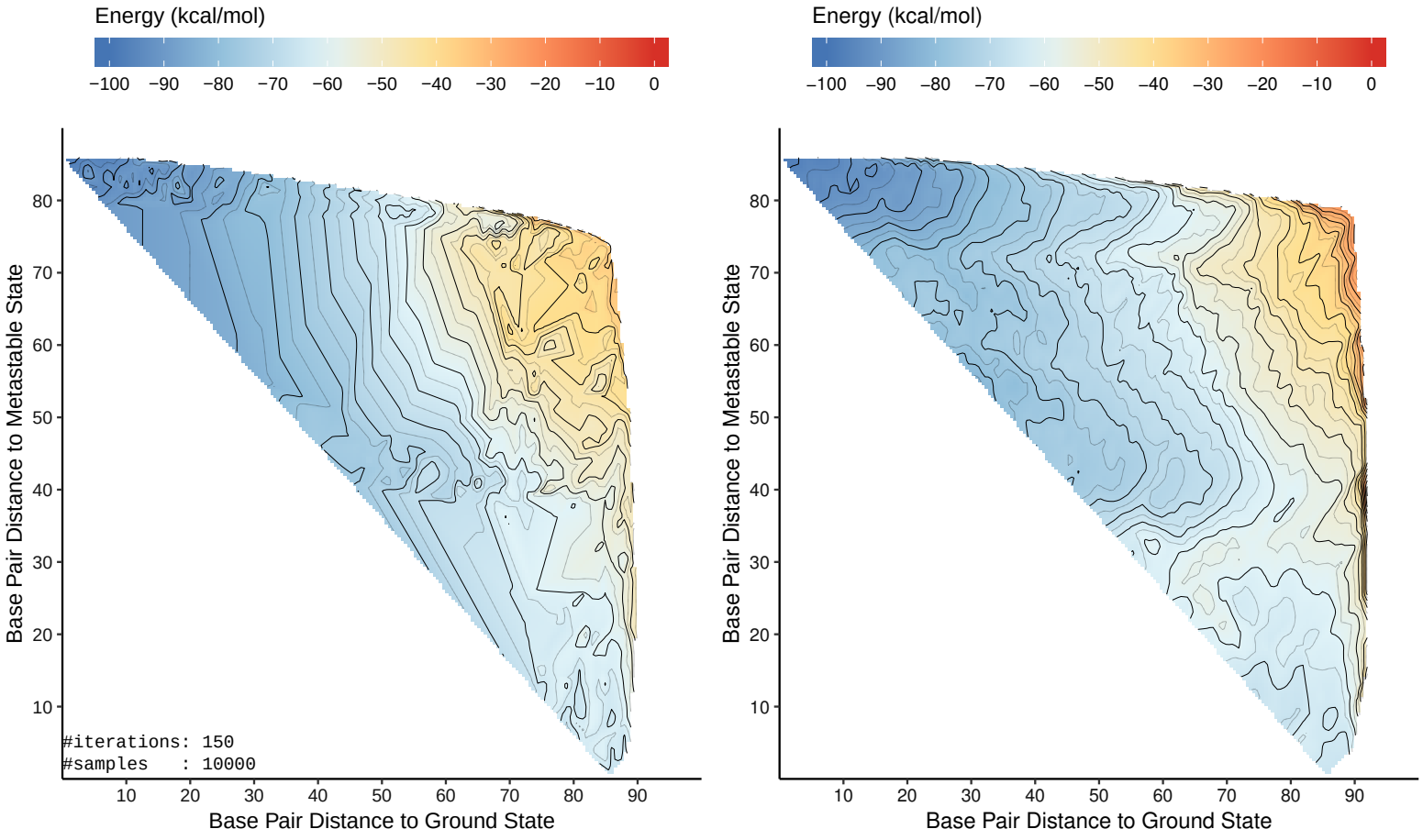
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

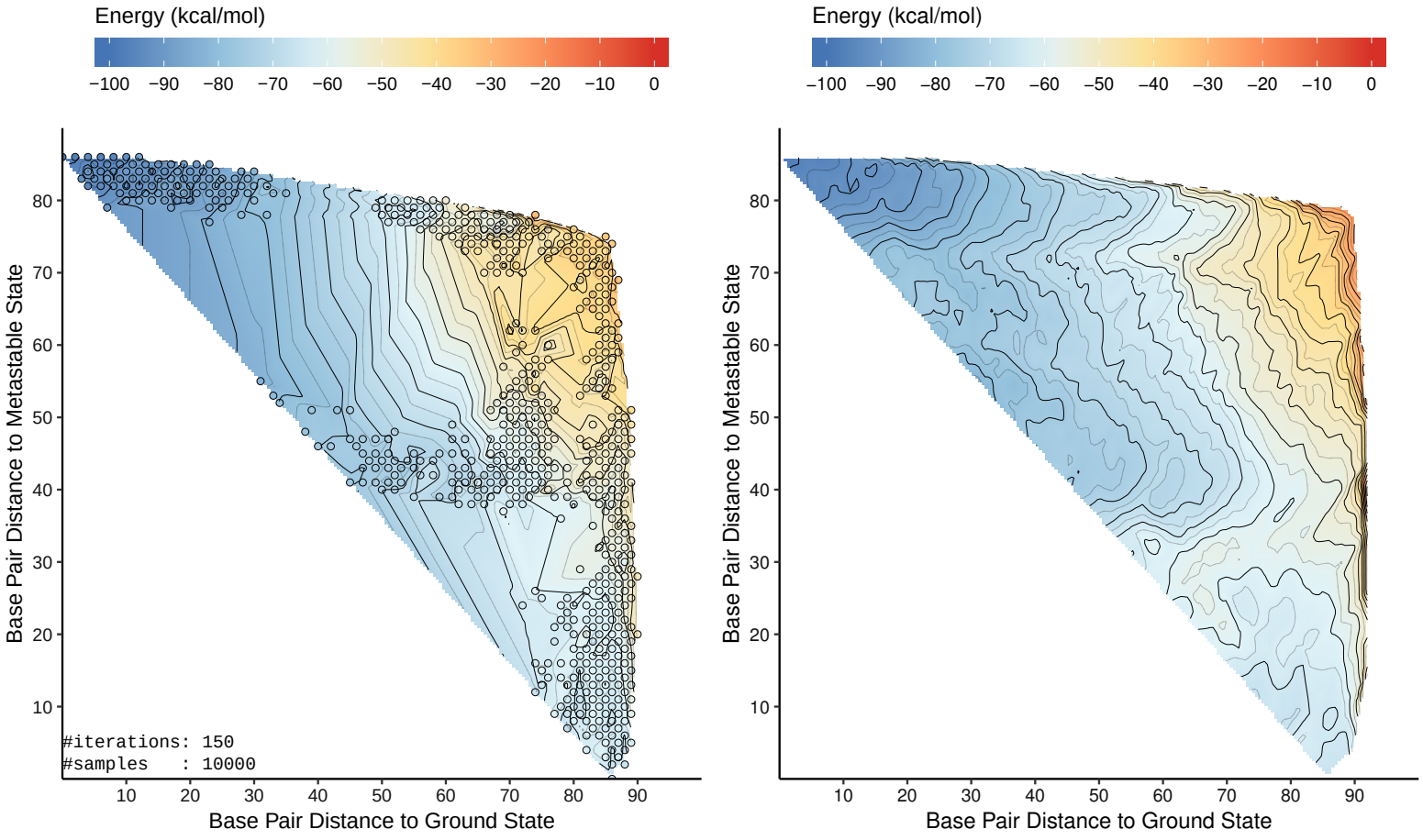
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

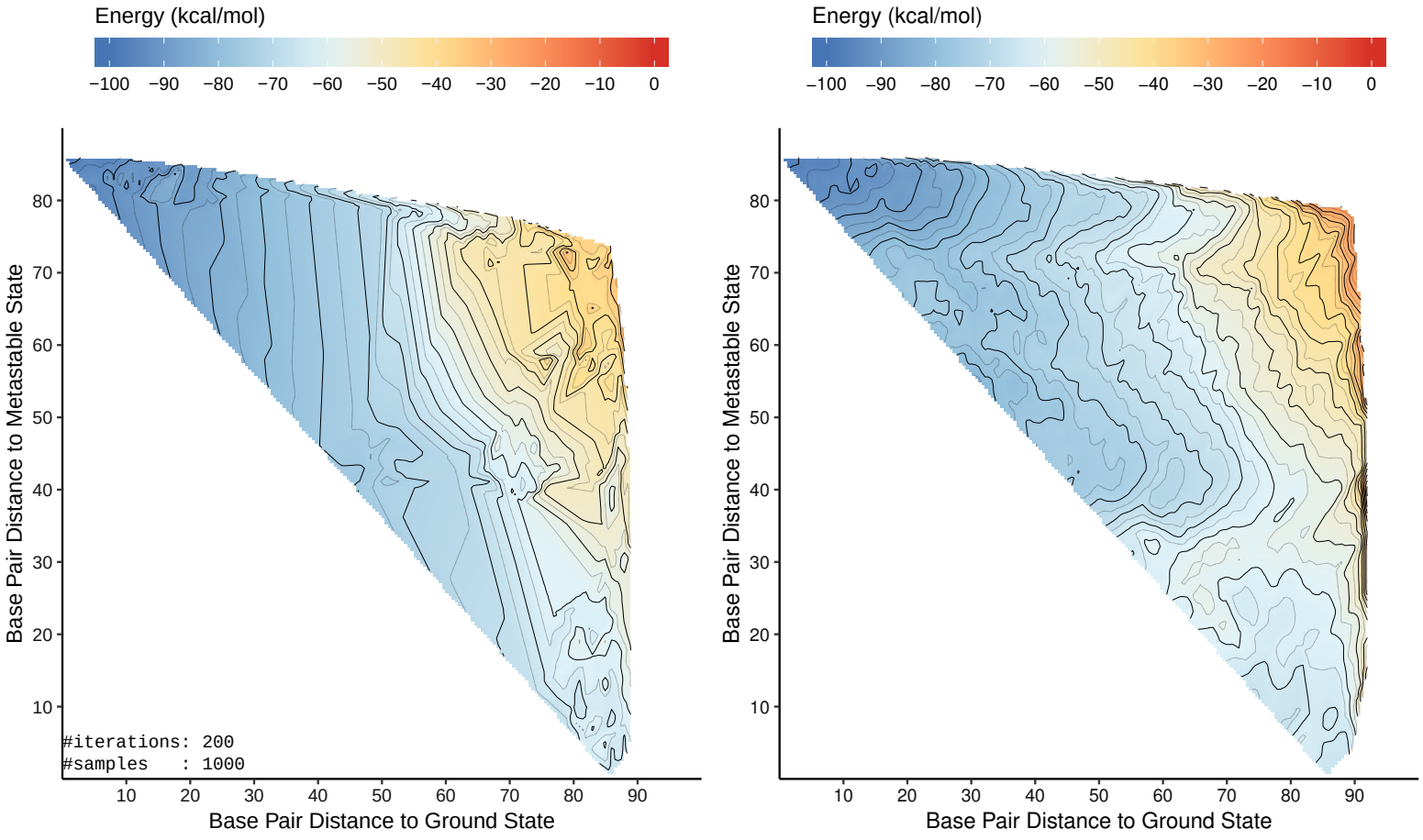
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

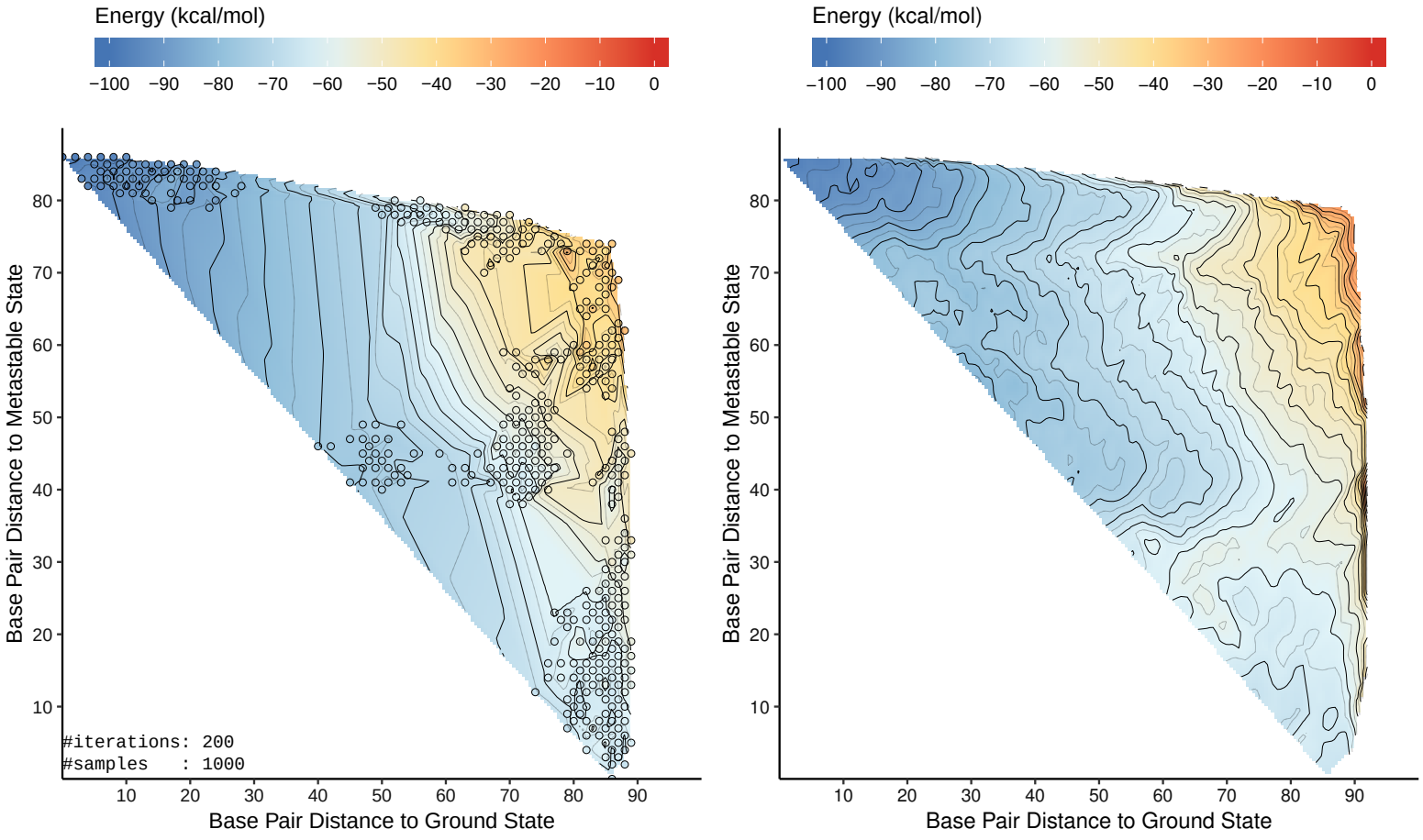
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

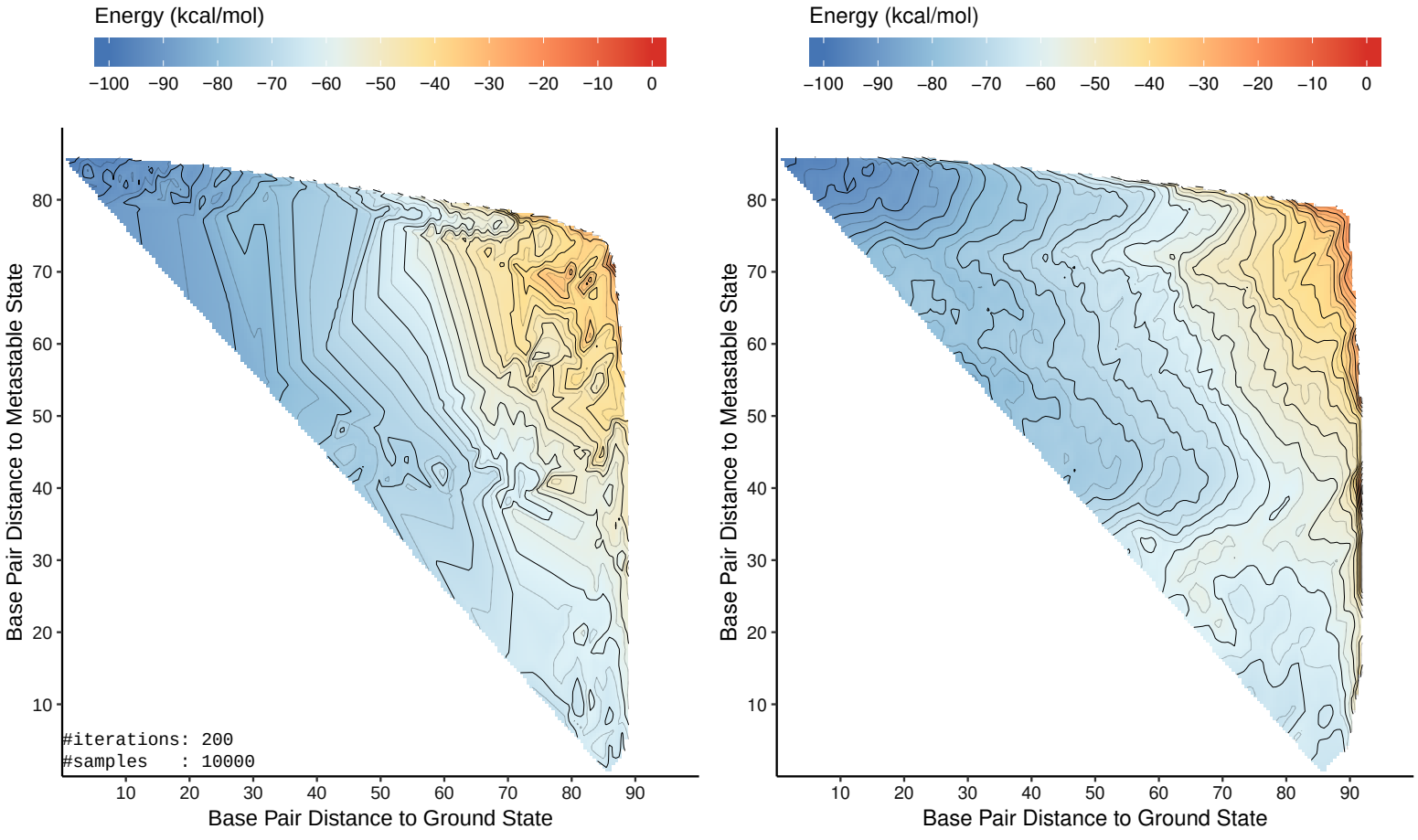
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

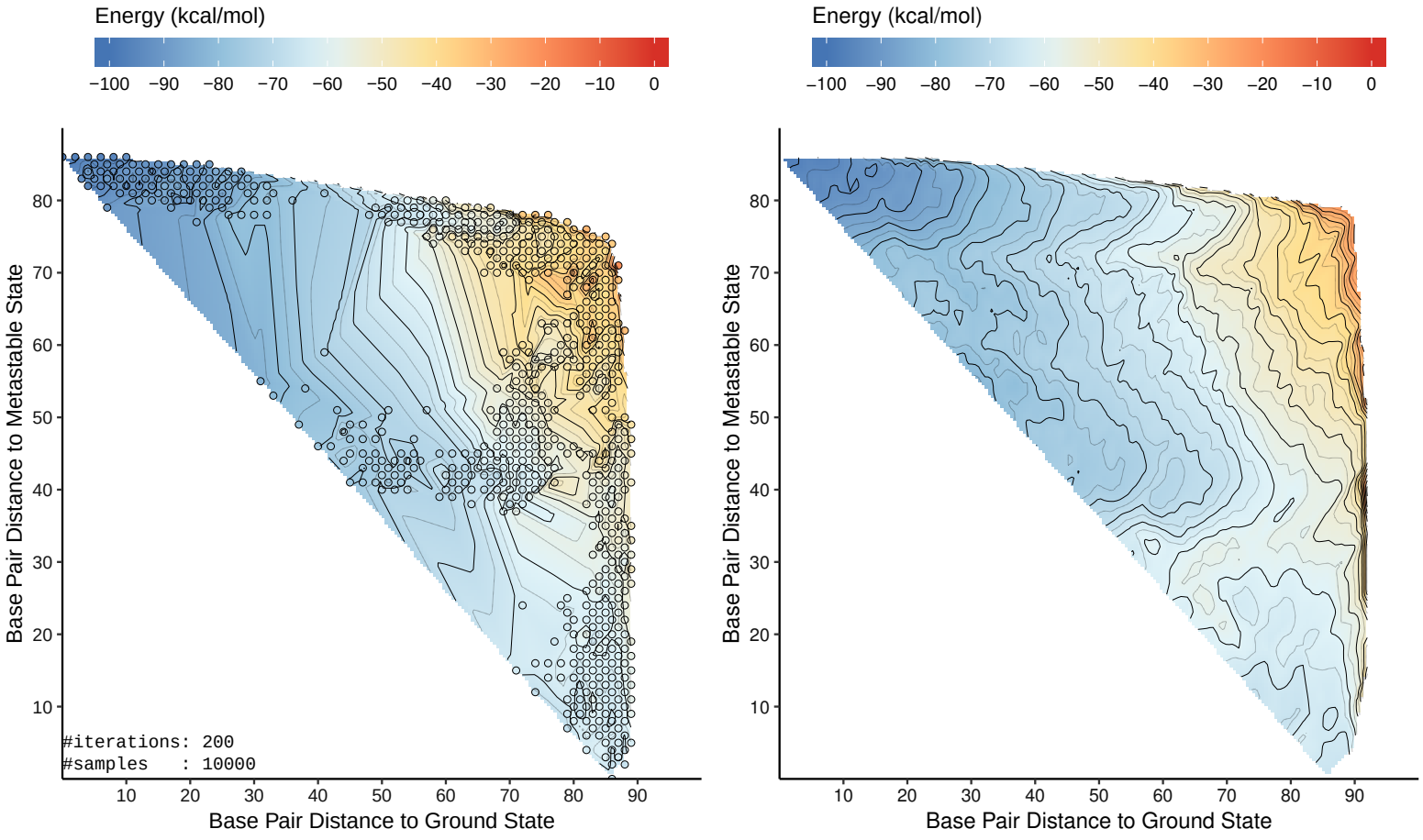
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

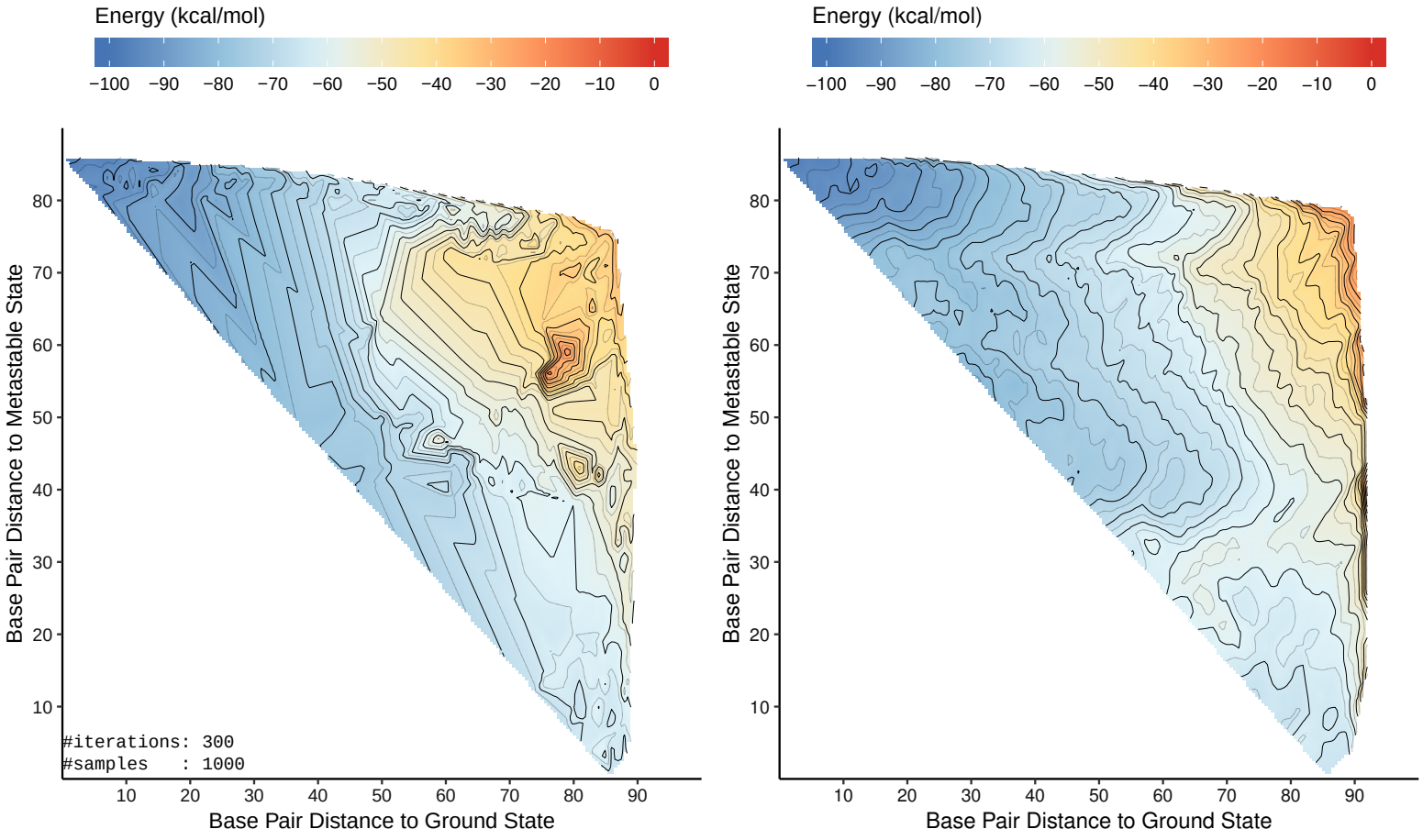
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

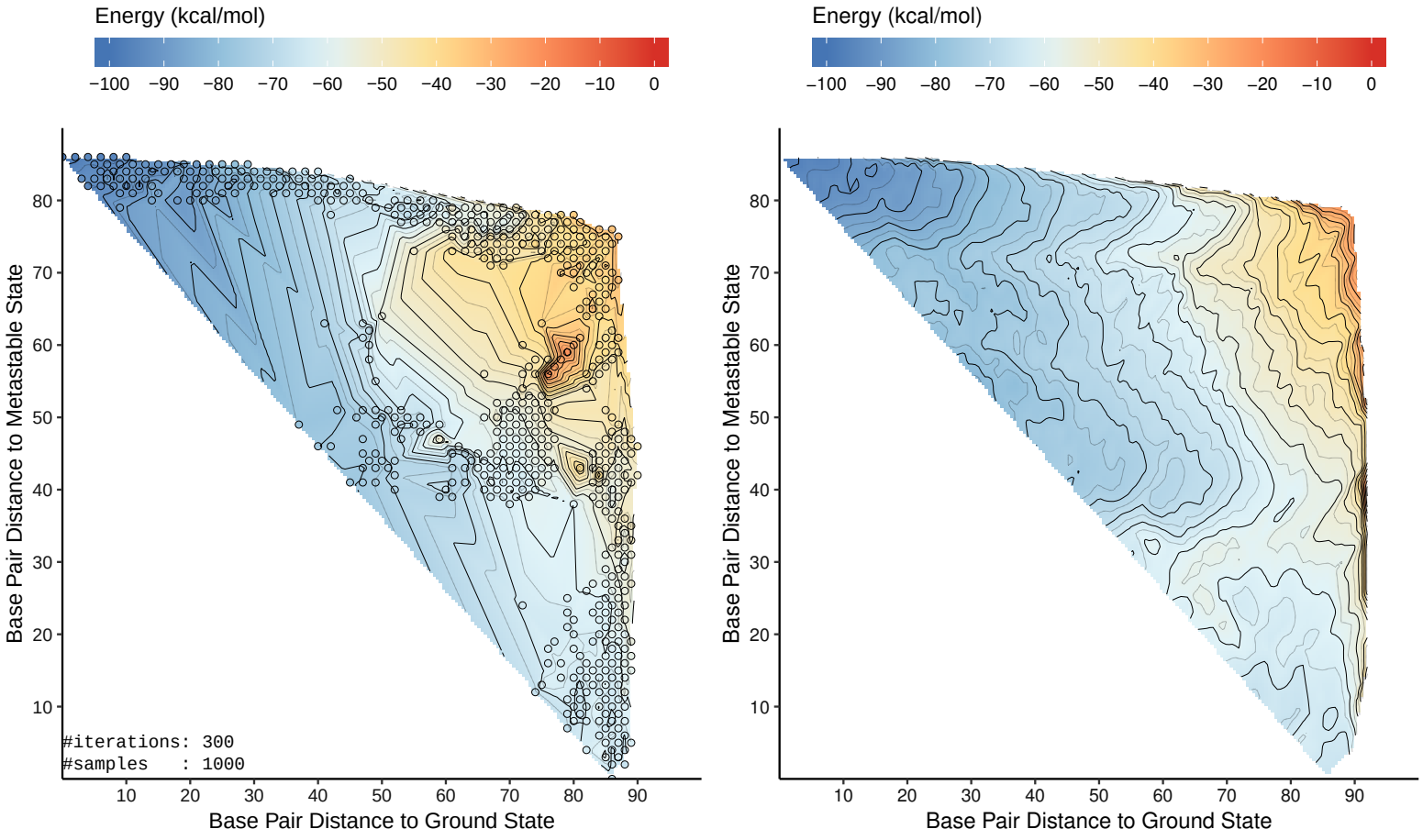
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

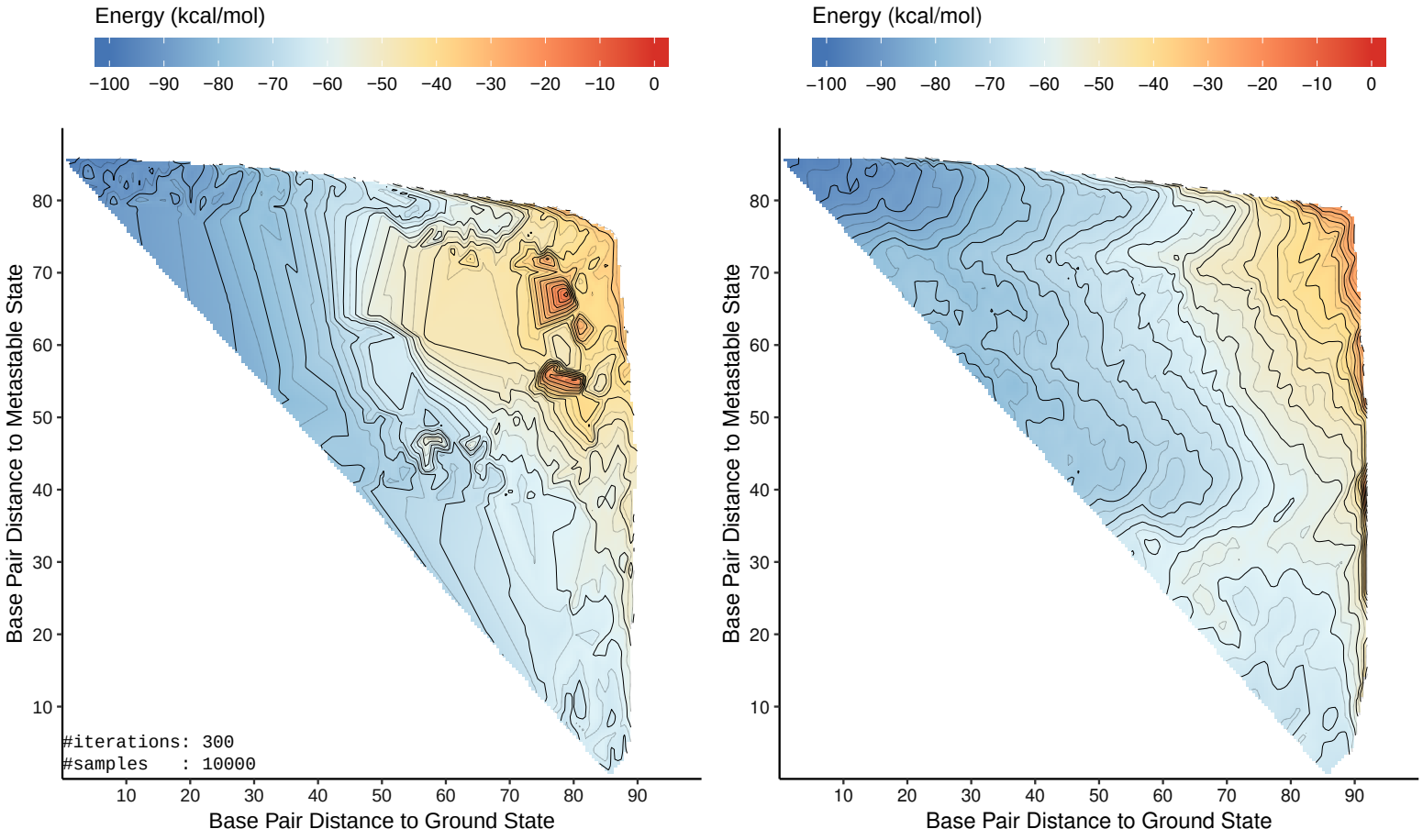
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

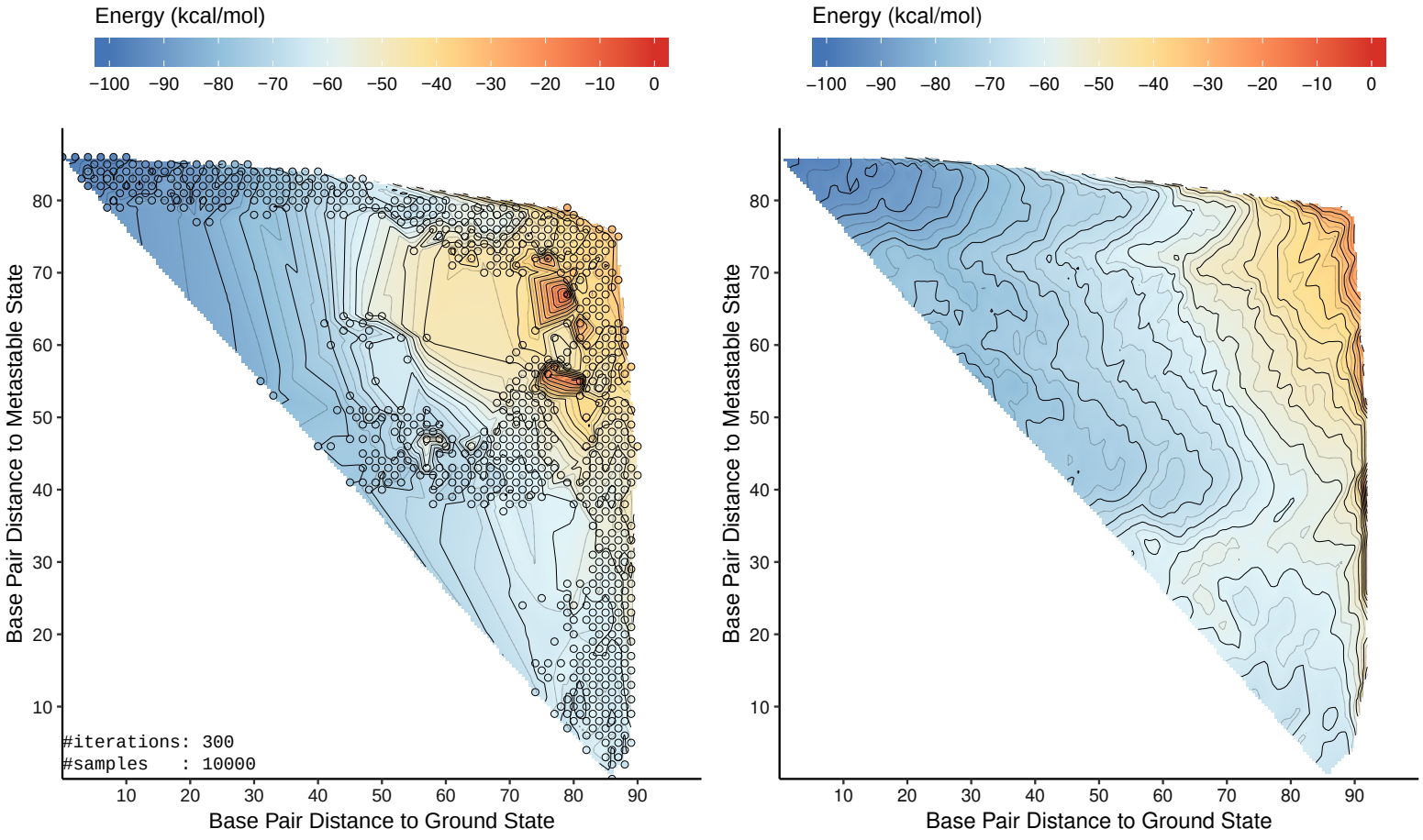
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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

Example: Qβ replicase template SV11

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



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

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!

This work was funded in parts by the Austrian/French project ‘RNAlands‘, FWF-I-1804-N28 and ANR-14-CE34-0011

Thanks to

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

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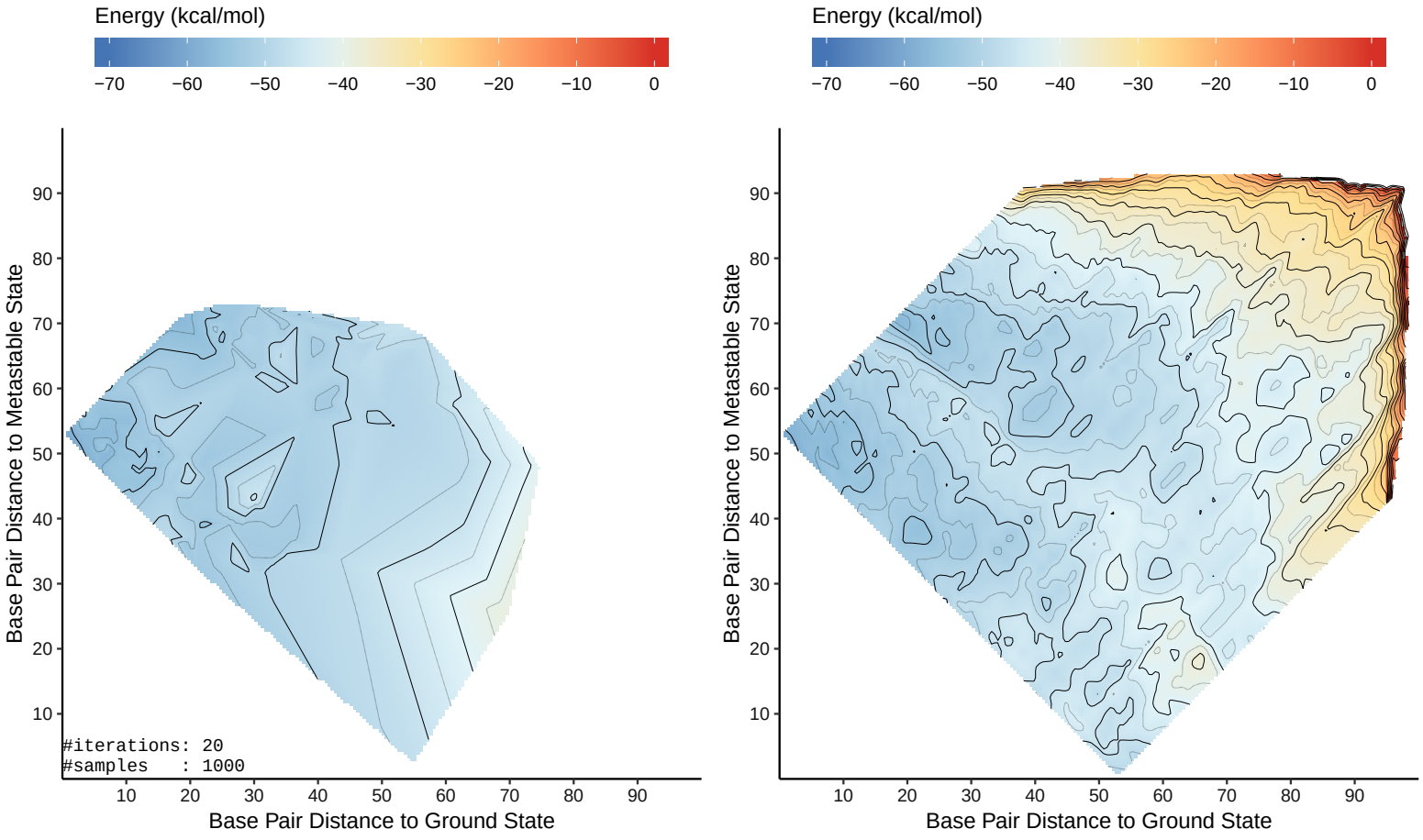
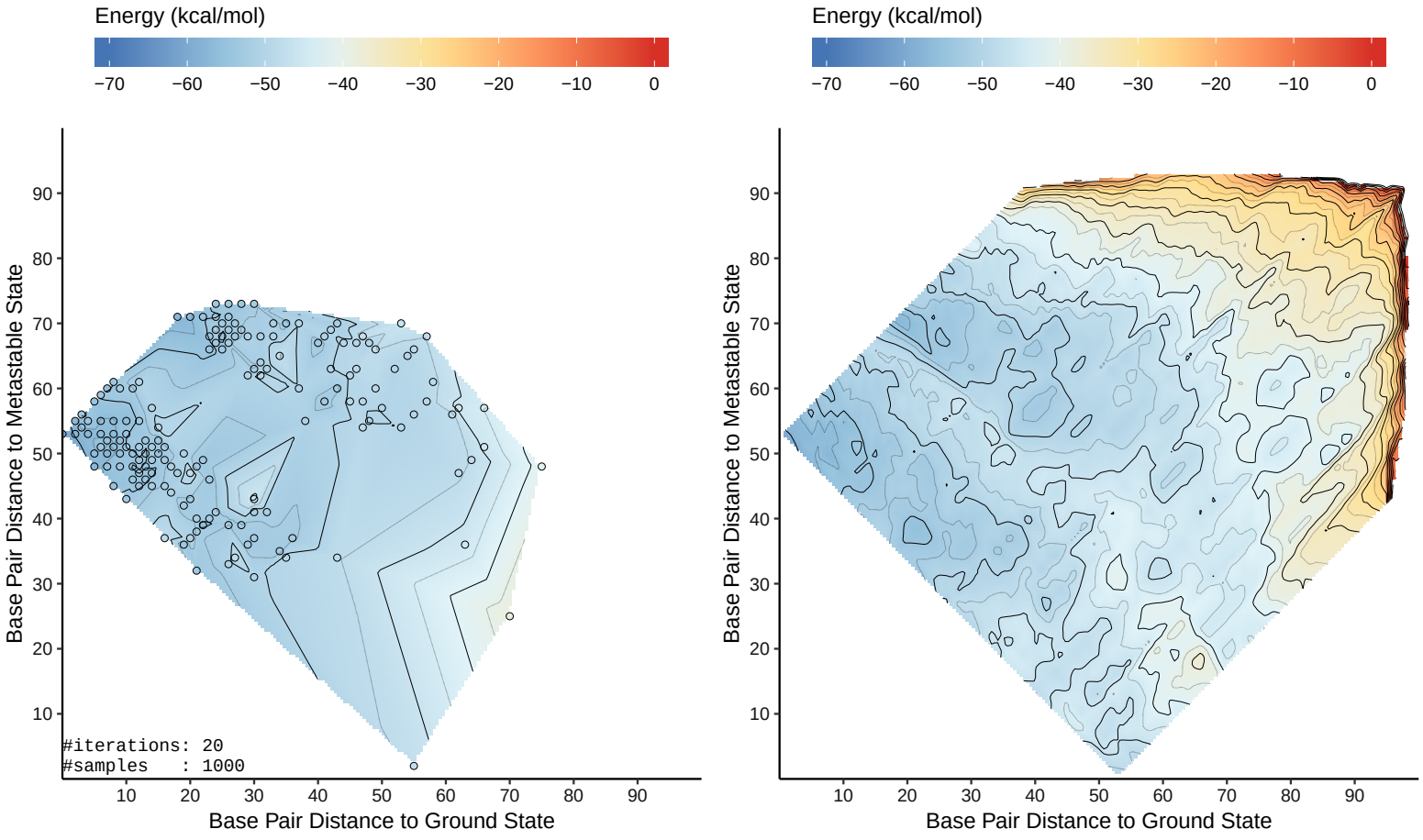
Example: 5UTR of MS2 coat protein mRNA

`RNAxplorer` repulsion scheme Boltzmann sampling



Example: 5UTR of MS2 coat protein mRNA

`RNAxplorer` repulsion scheme Boltzmann sampling



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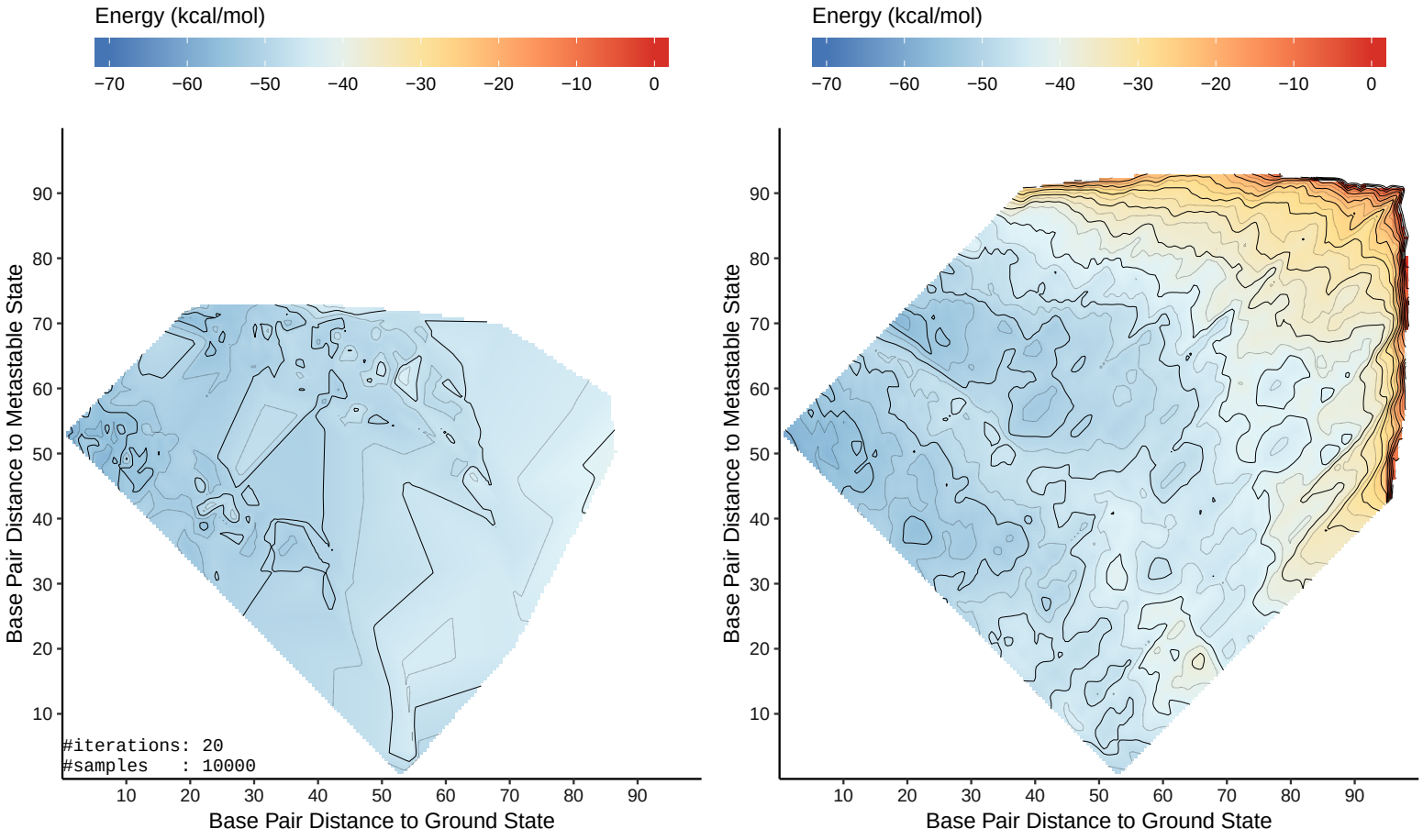

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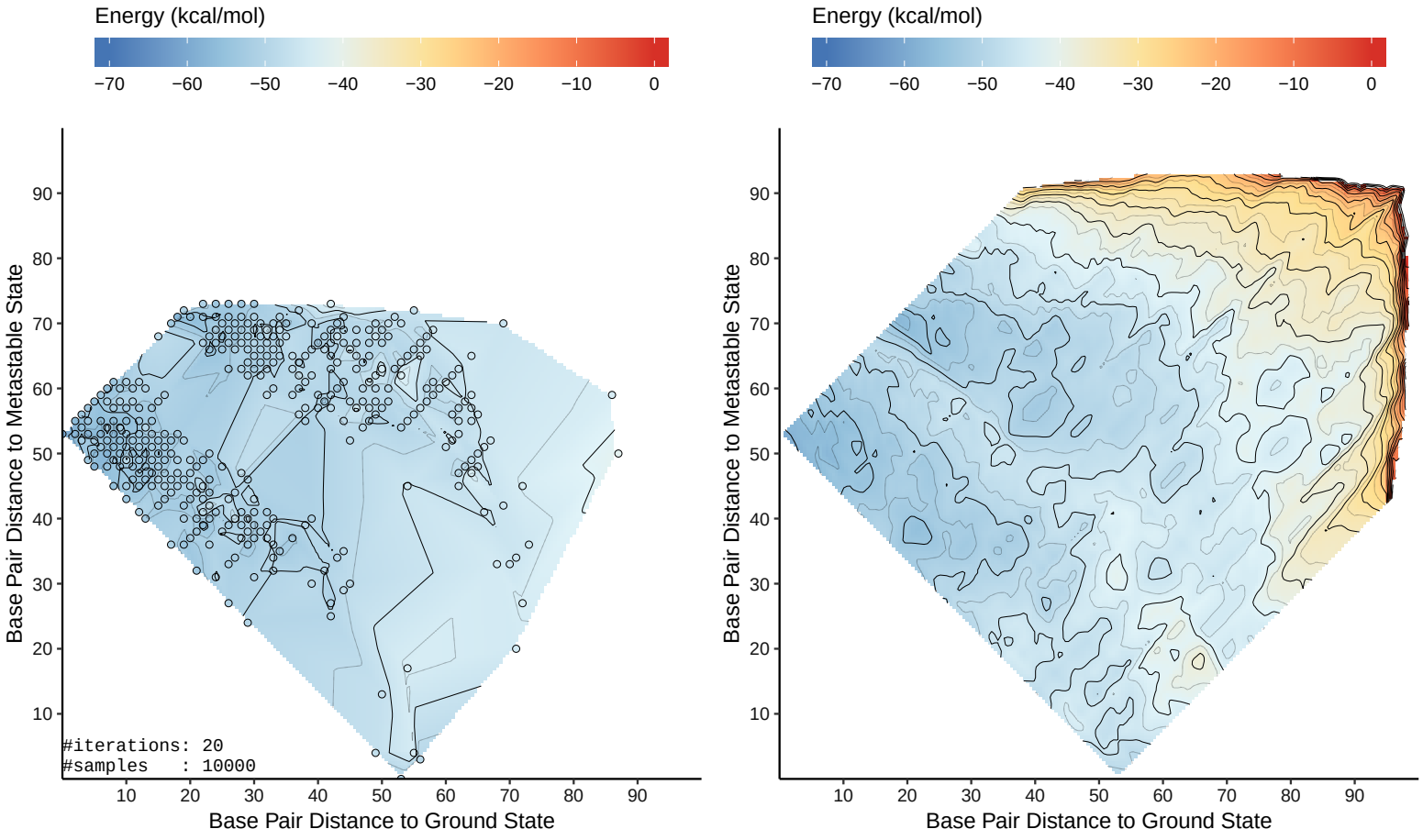

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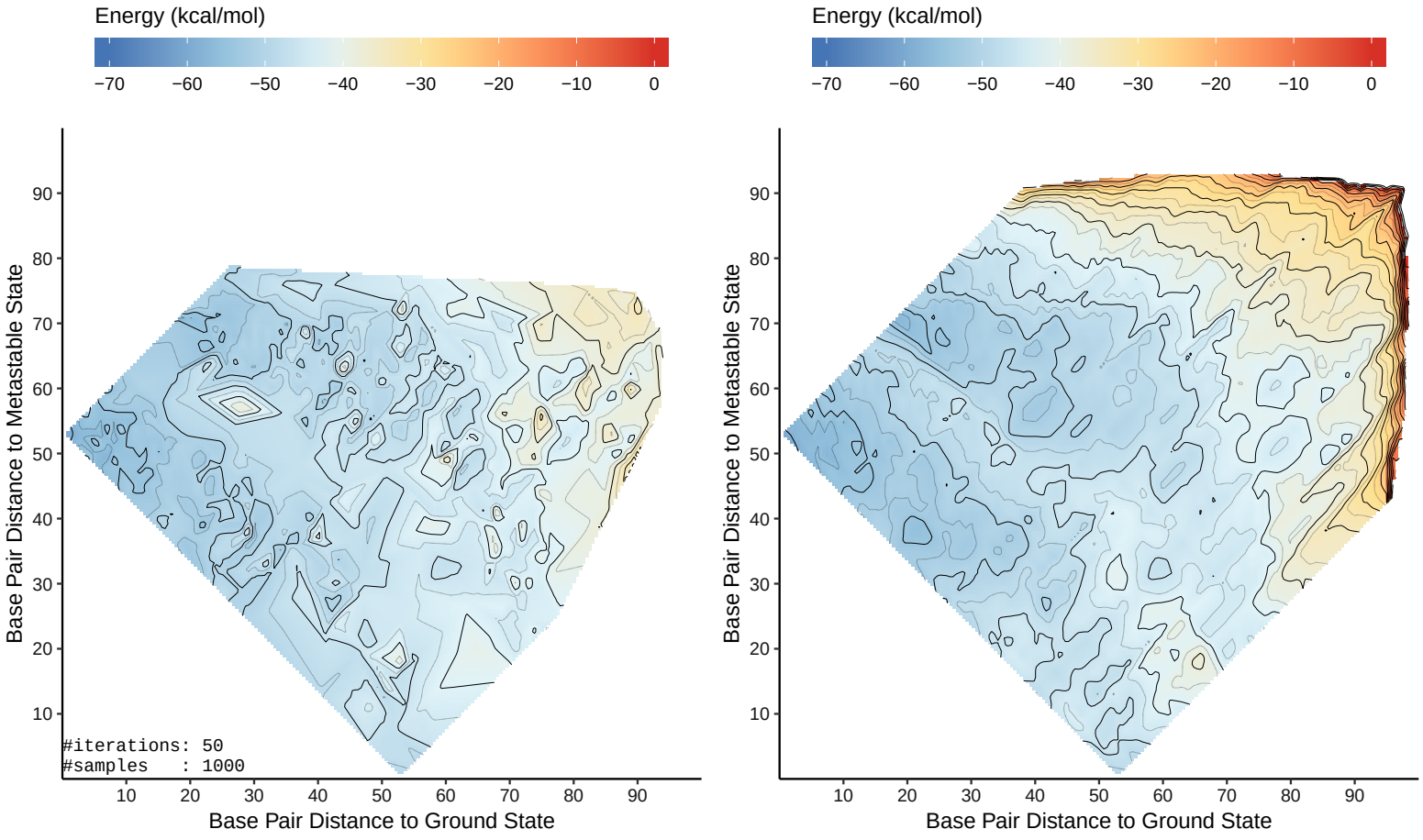

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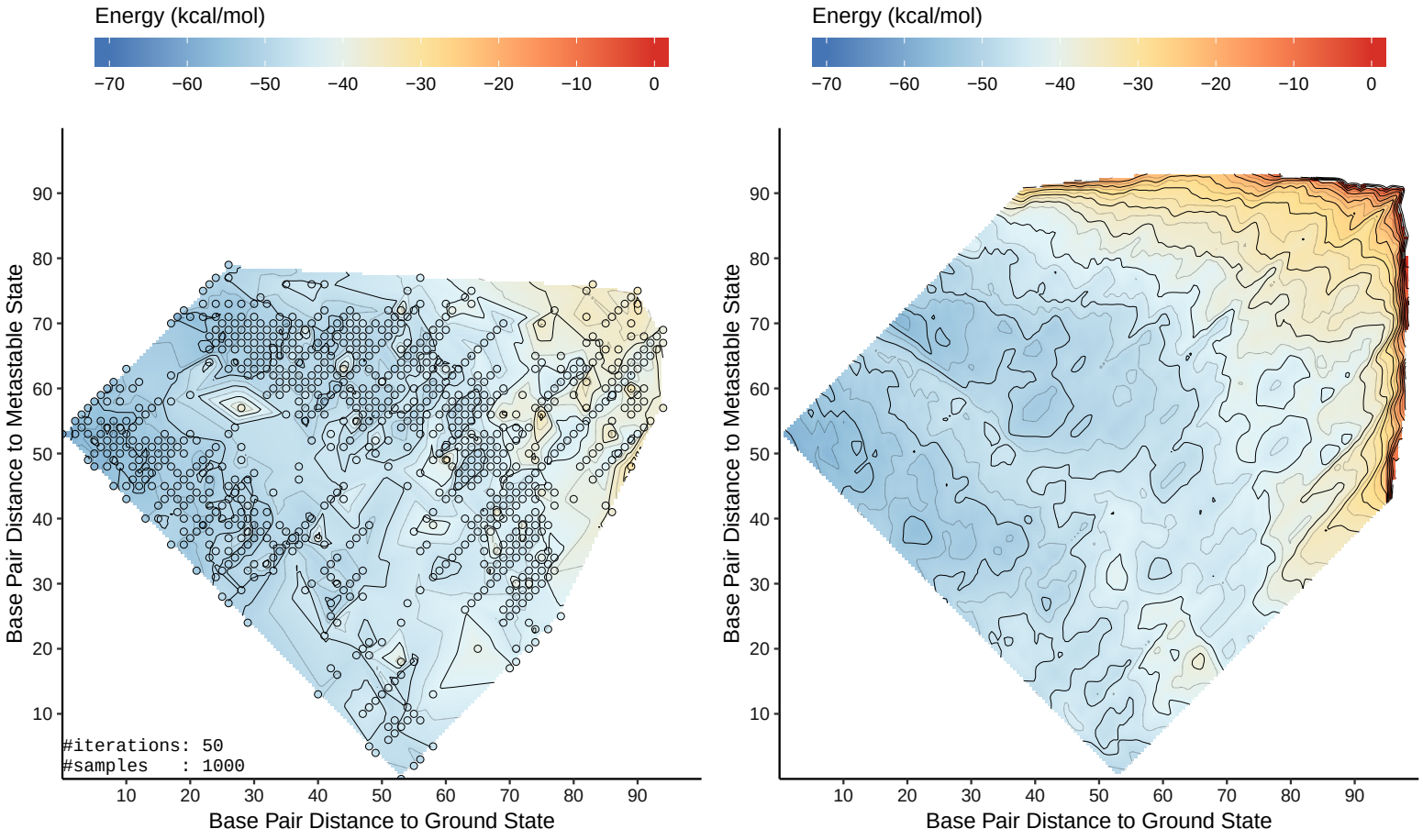

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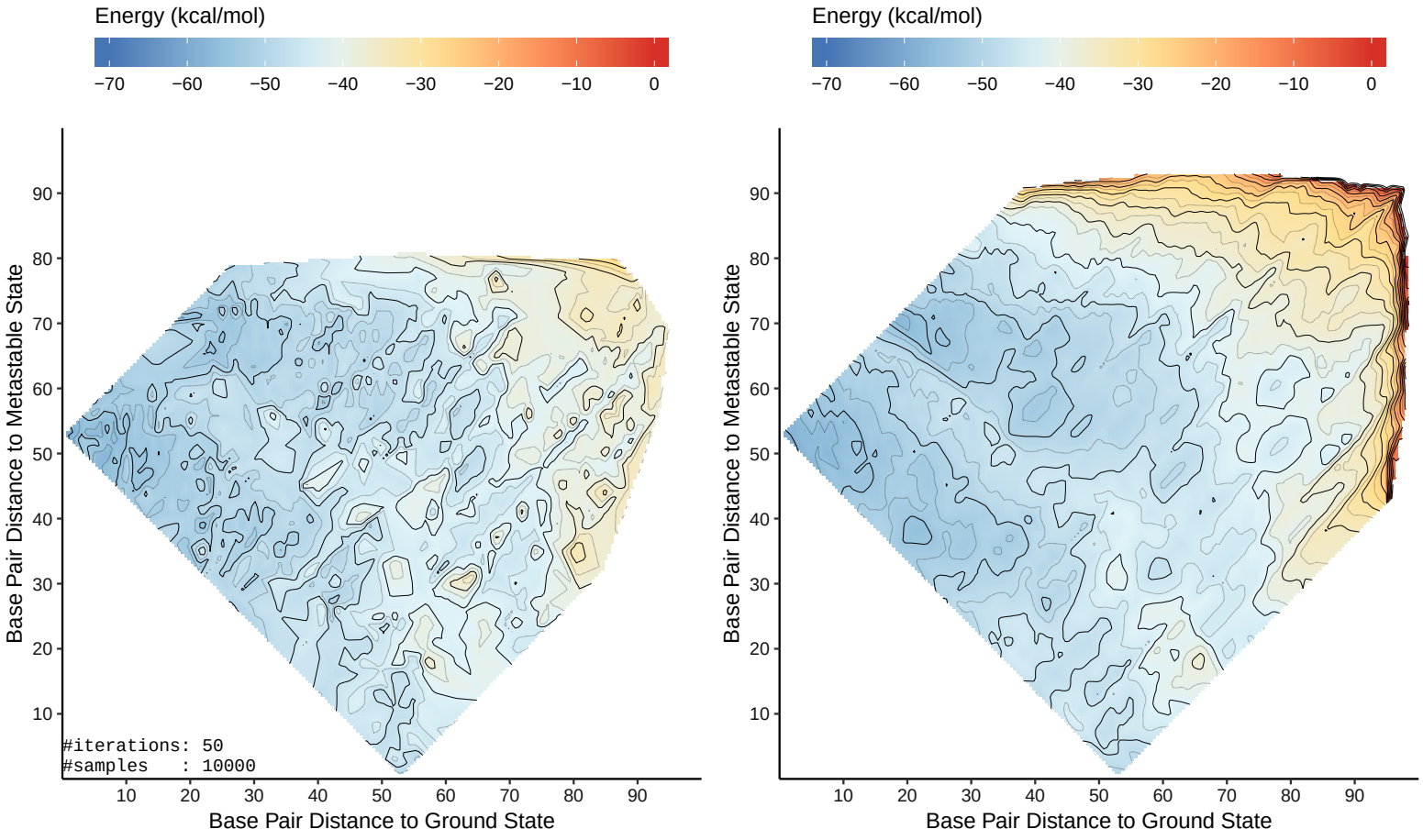

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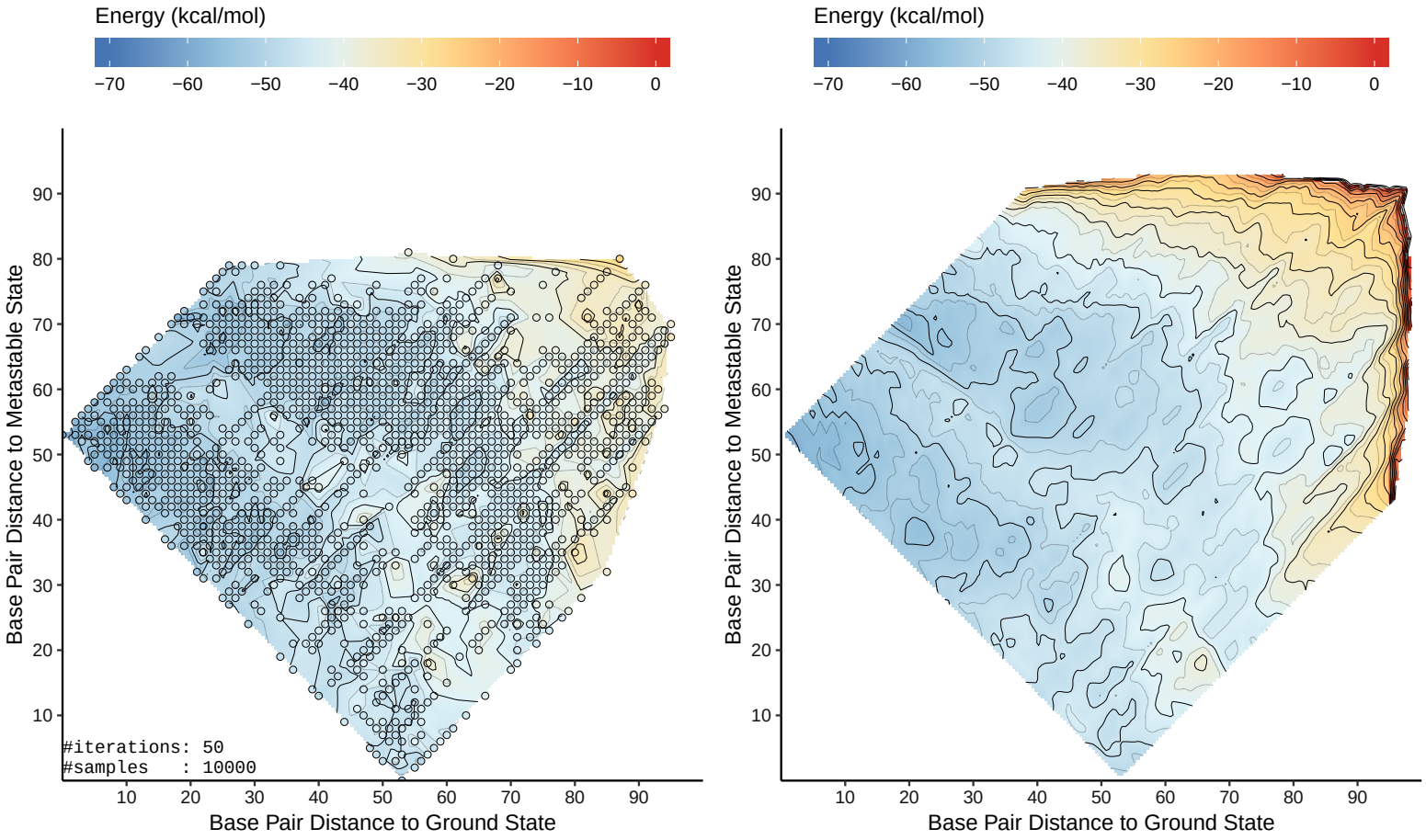

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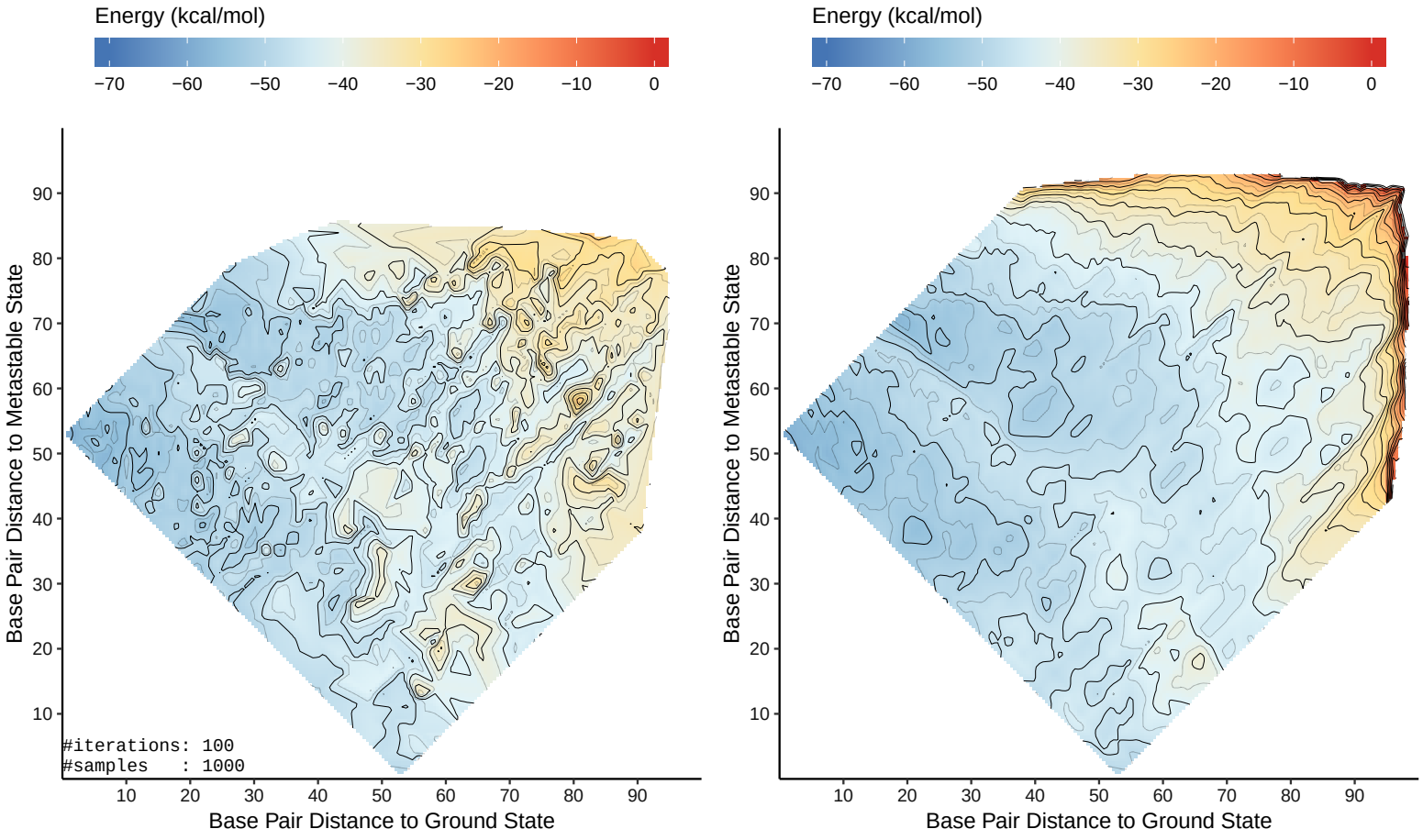

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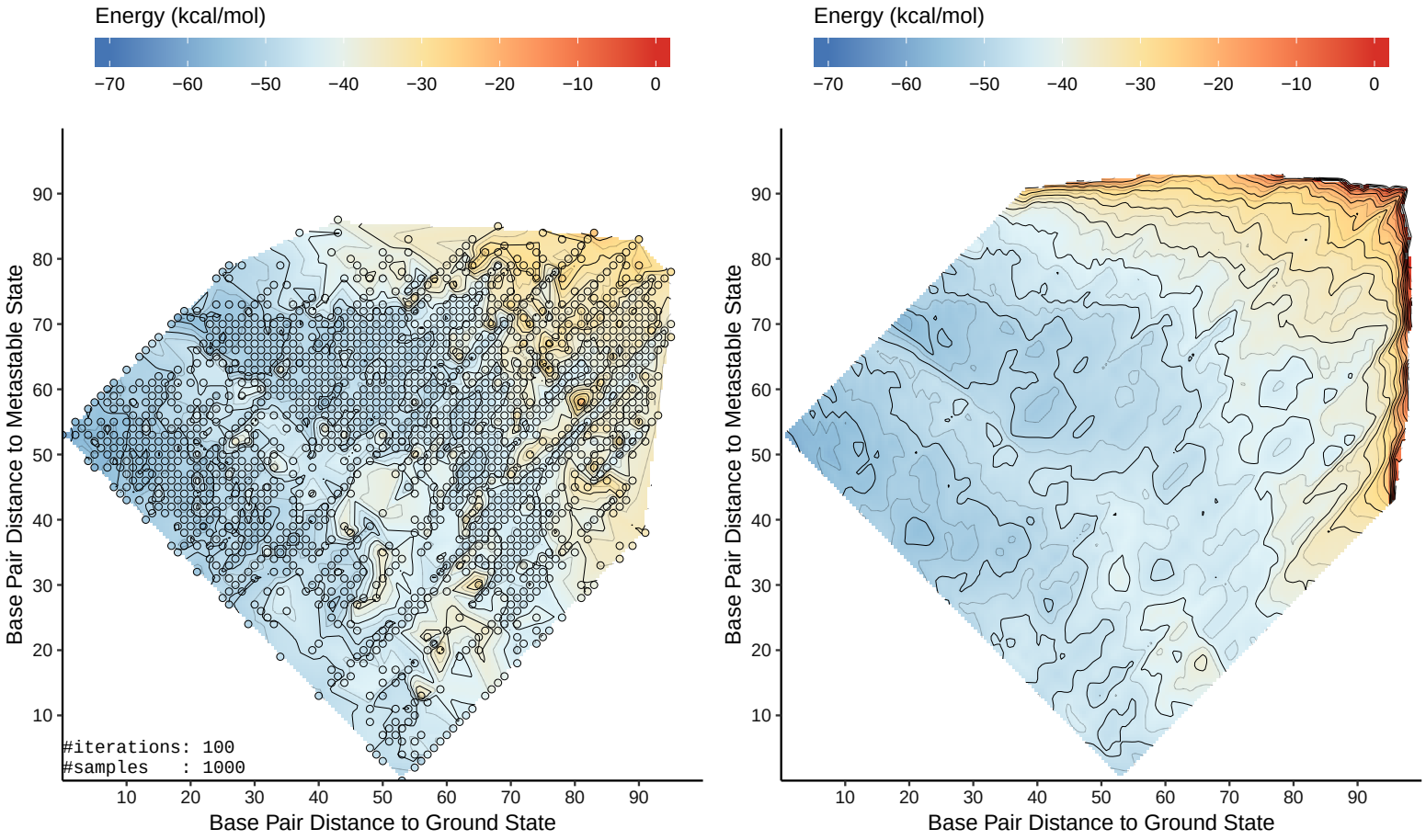

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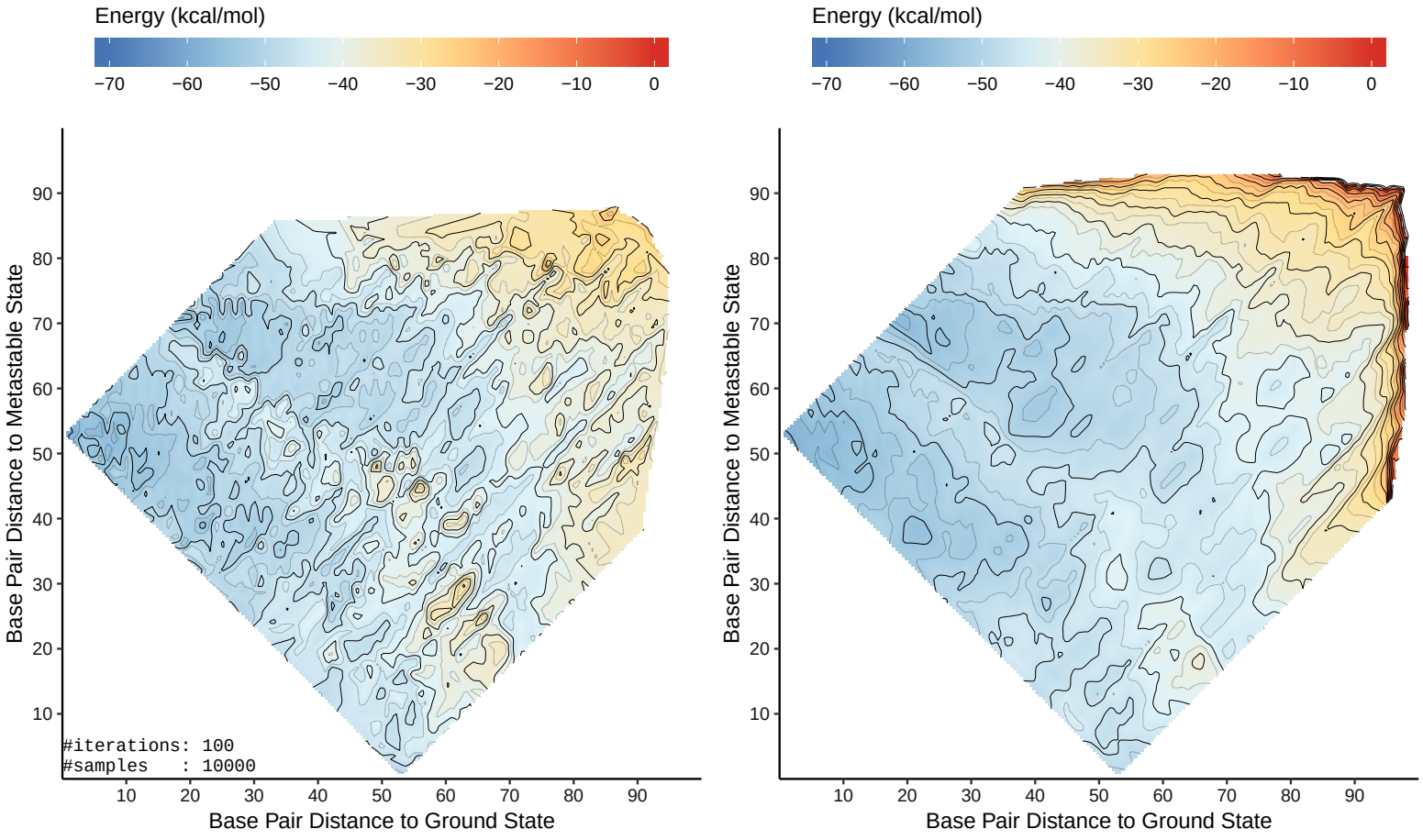

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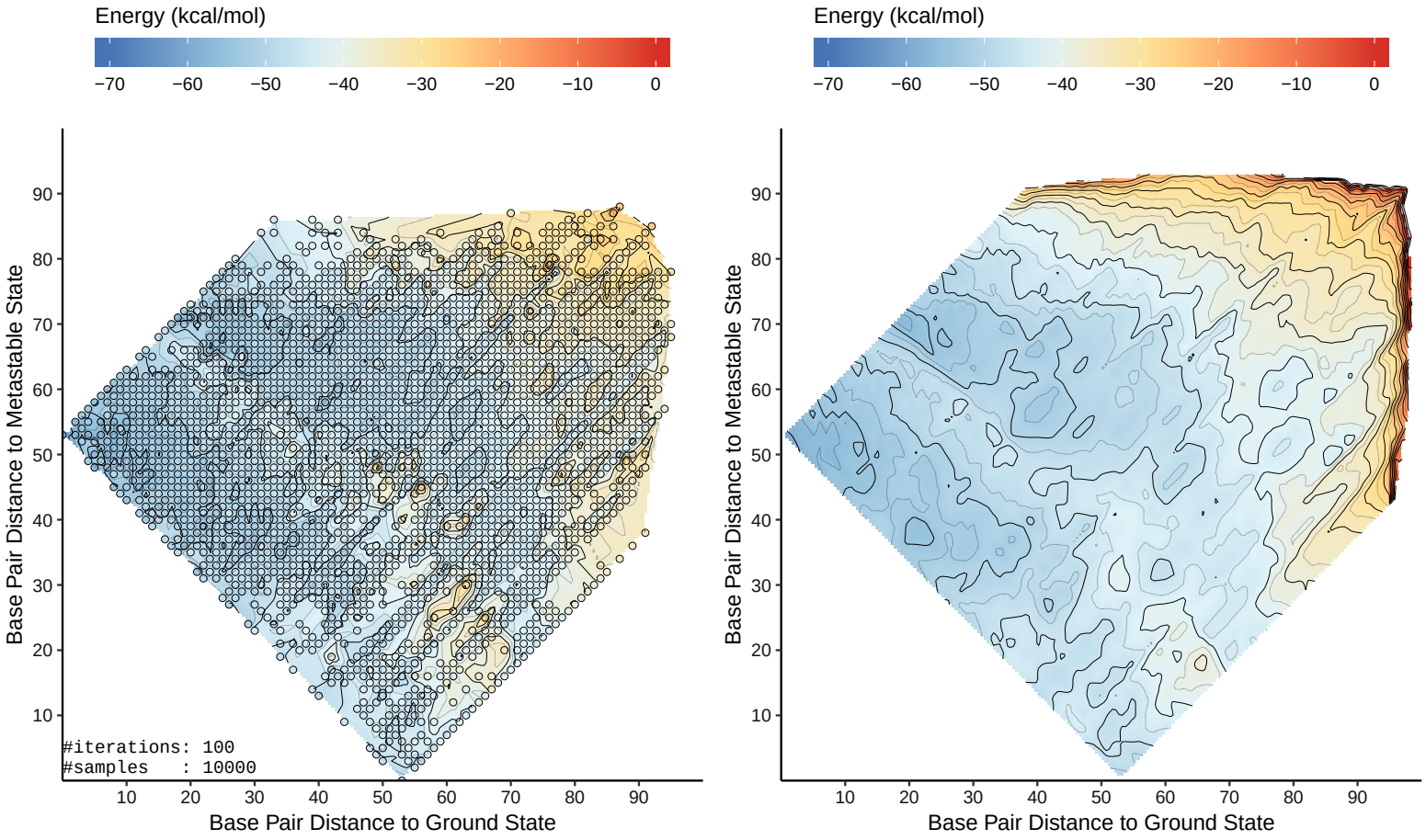

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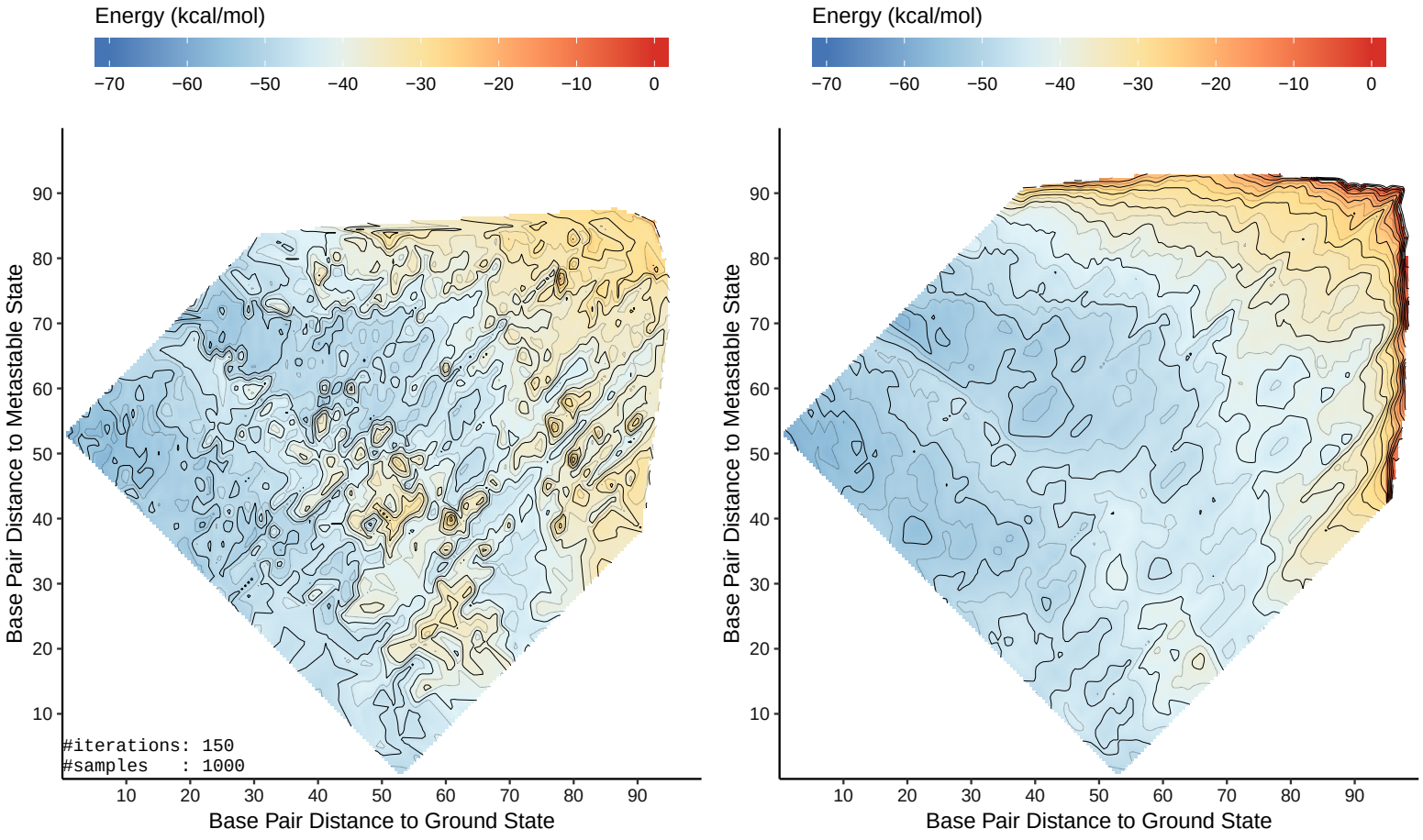

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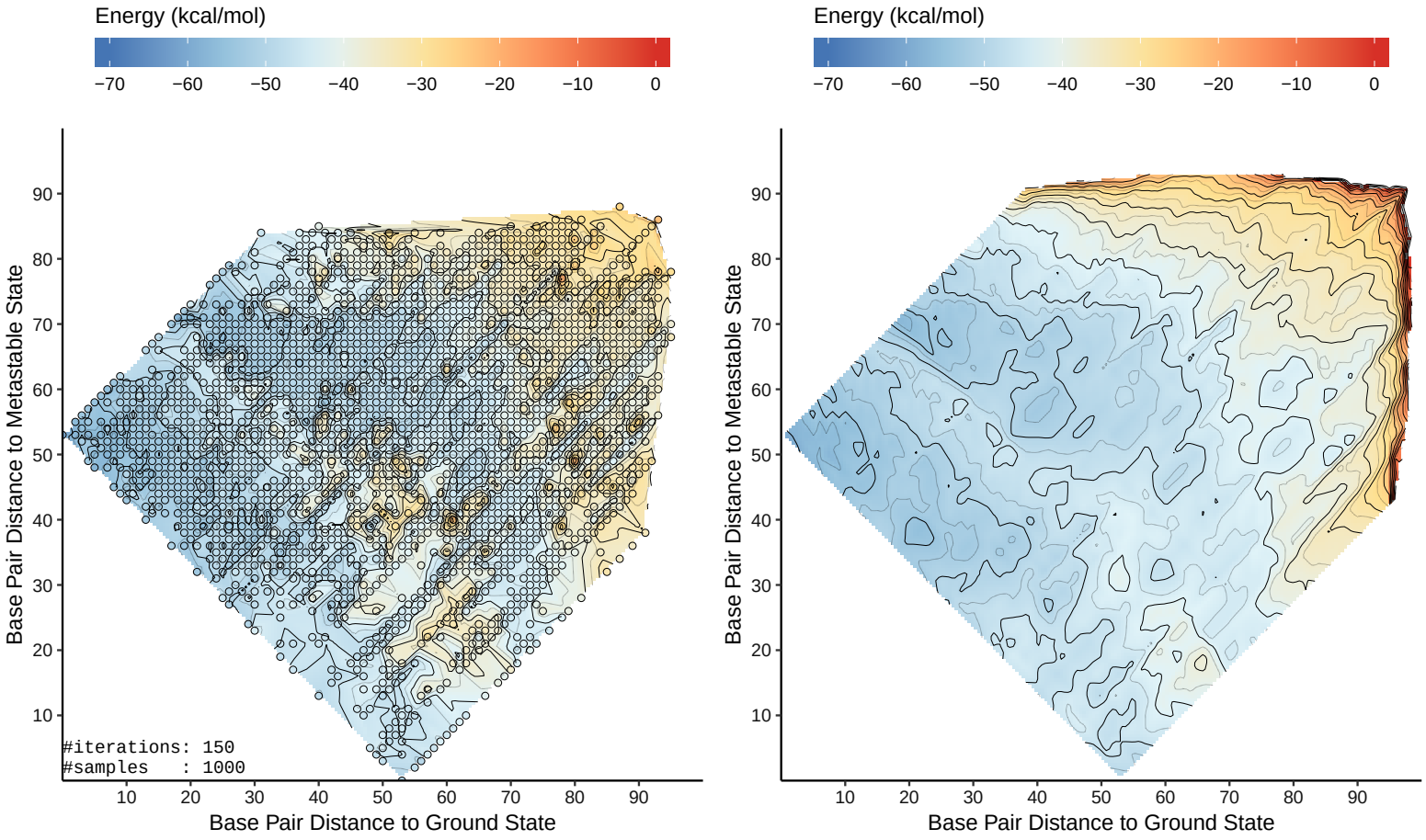

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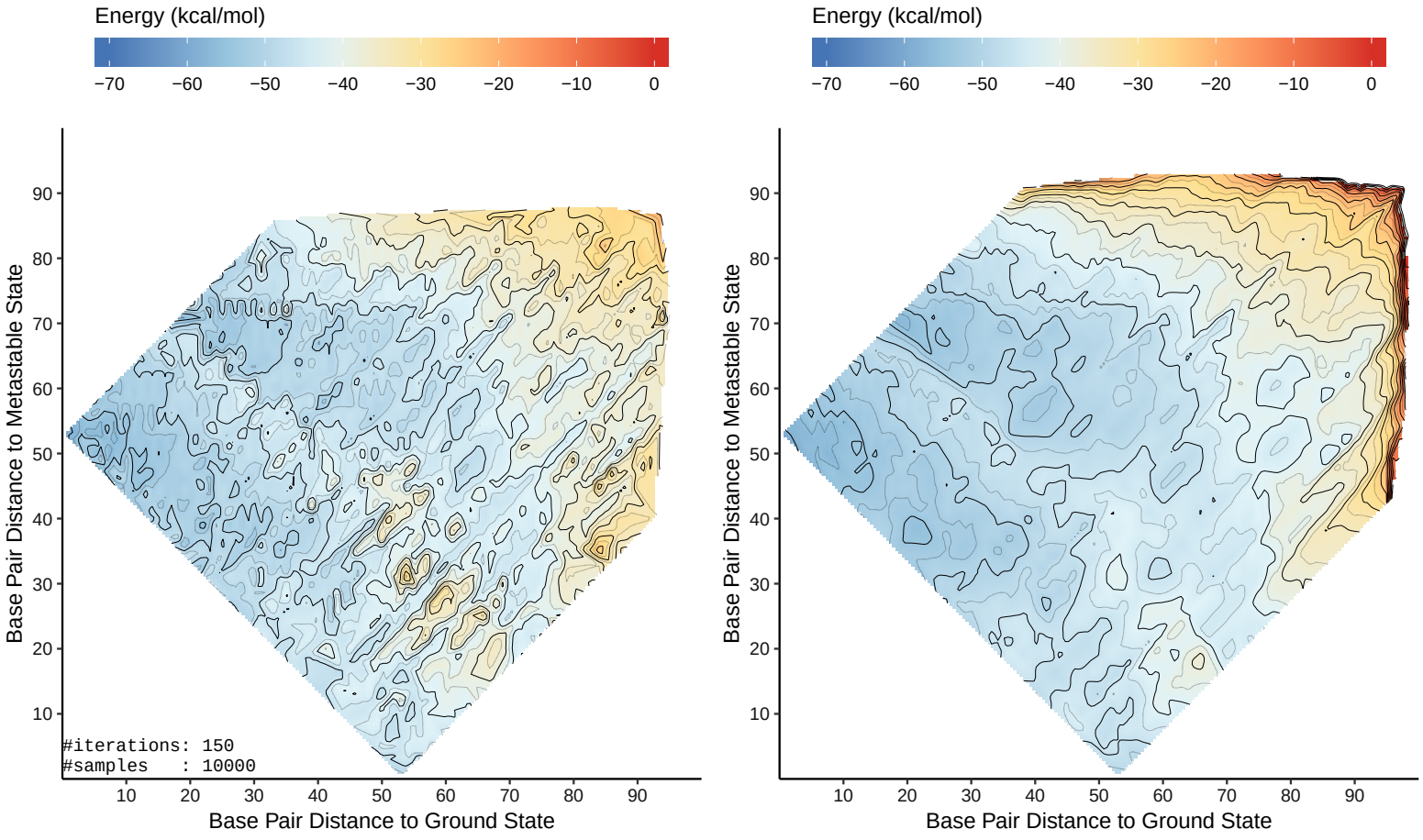

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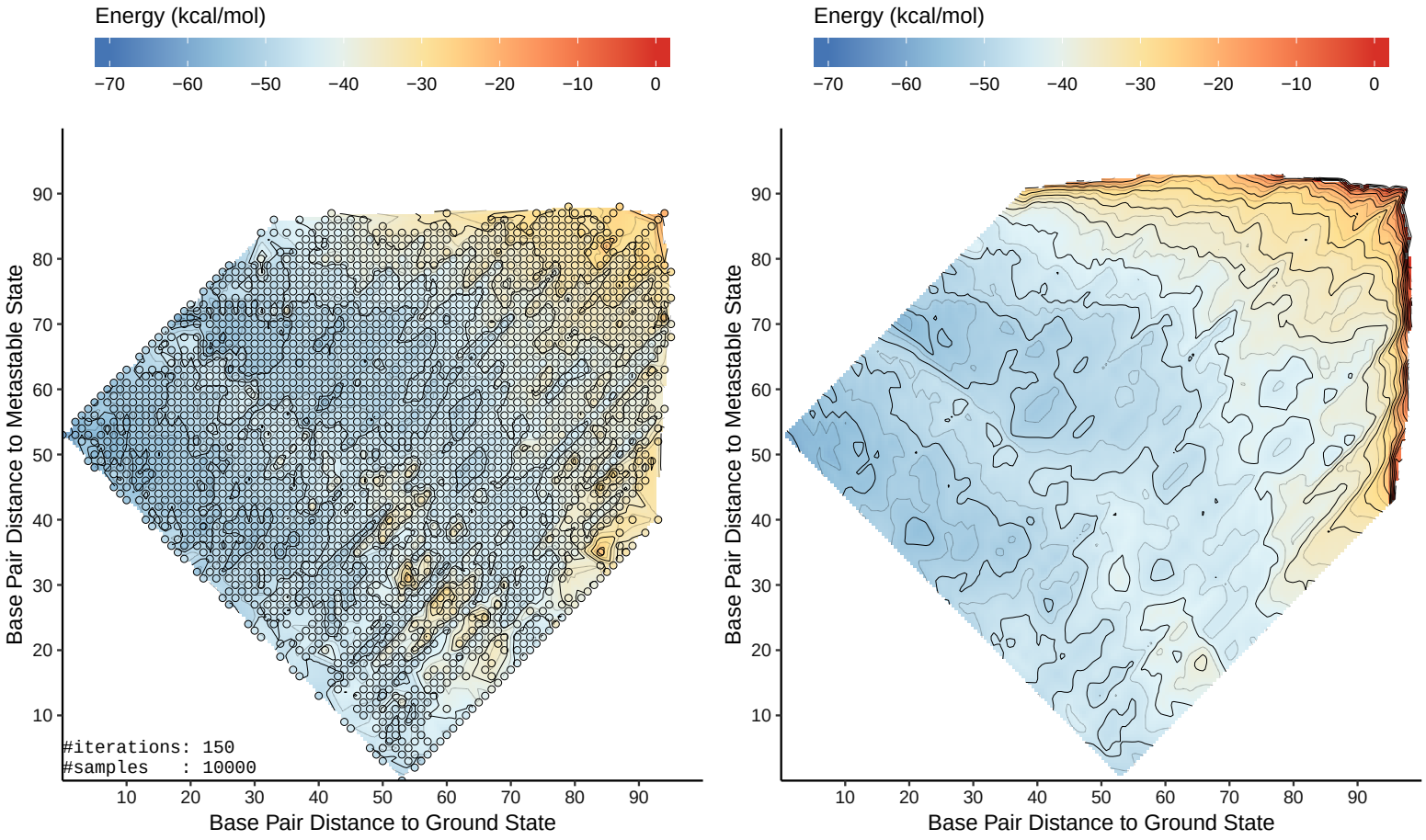

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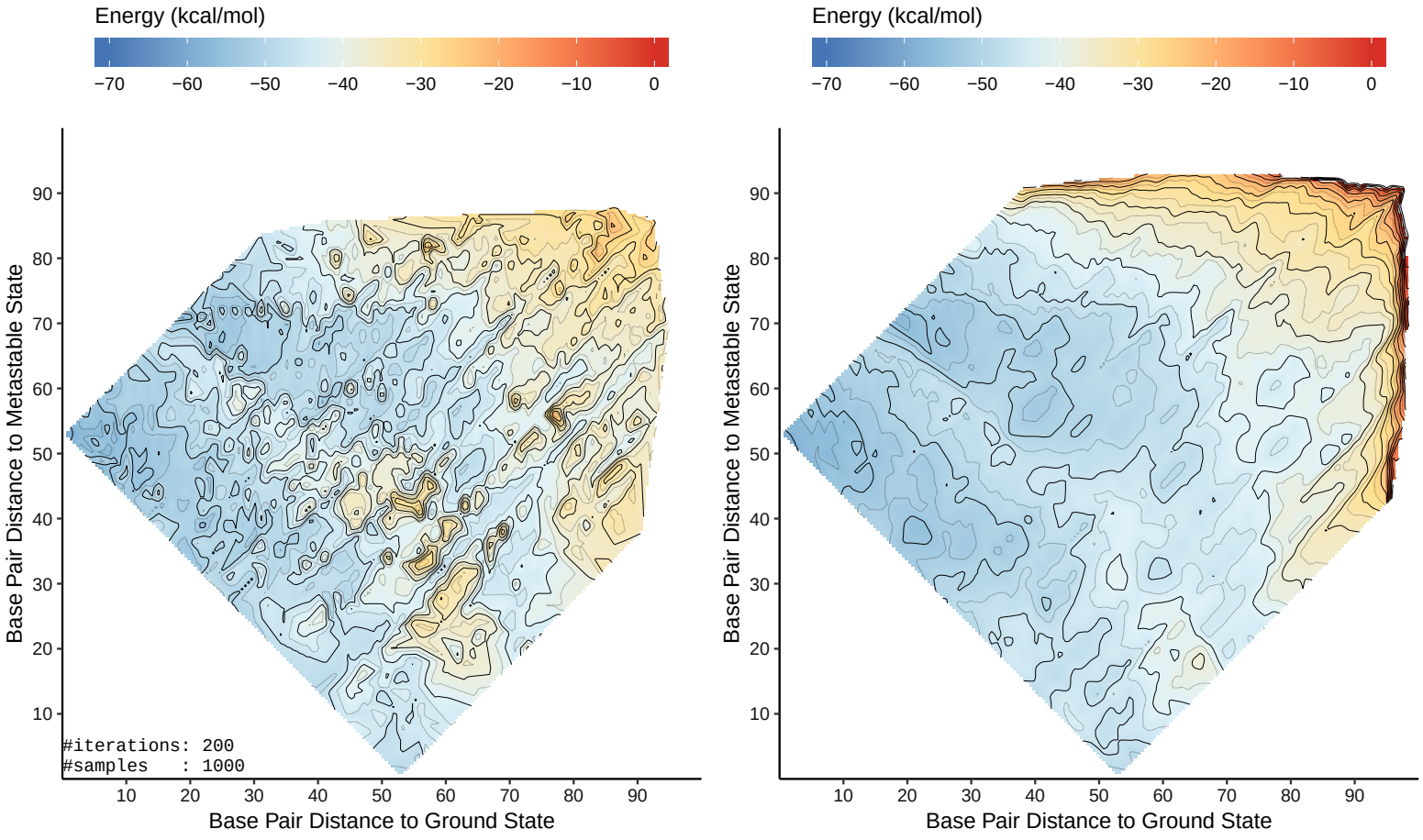

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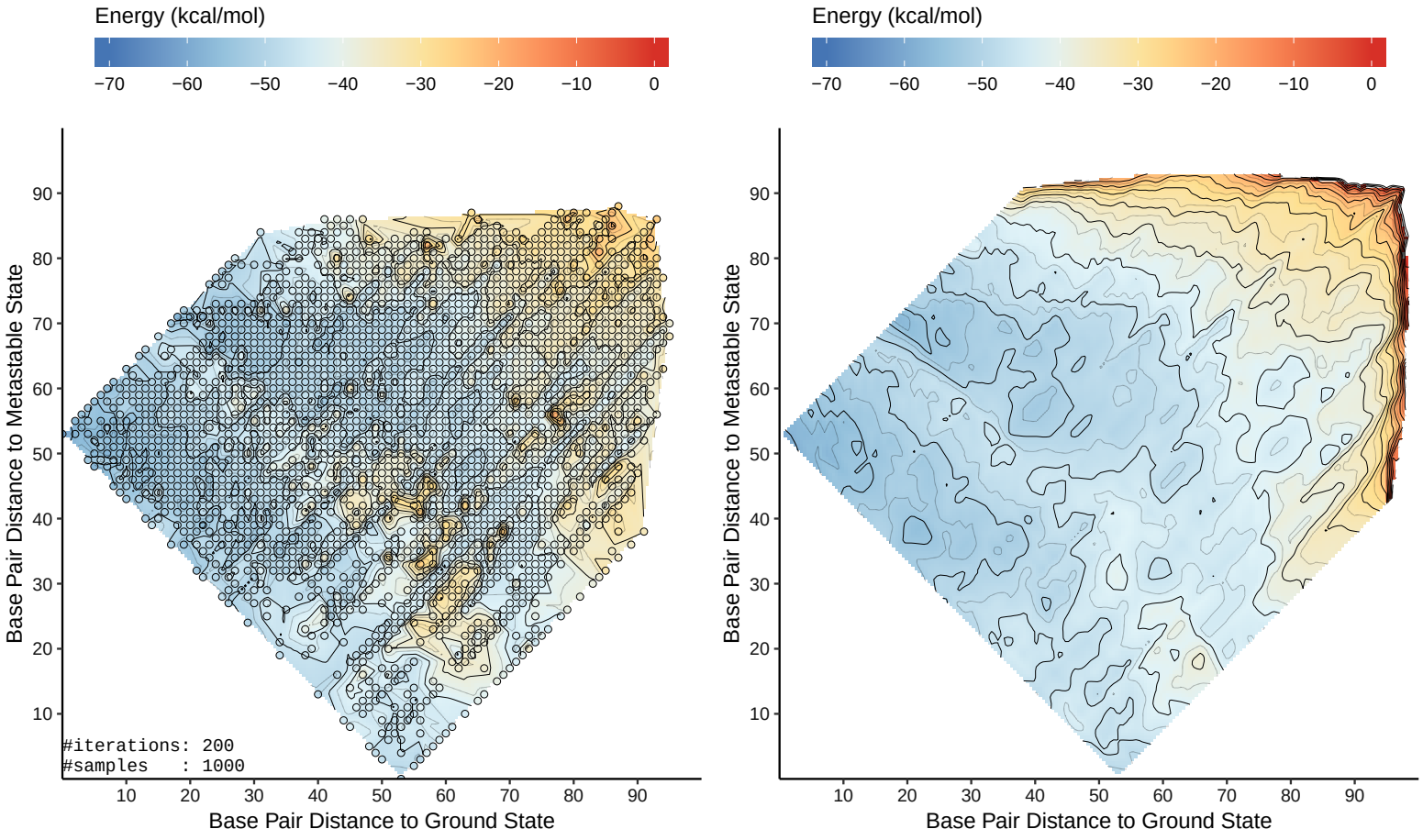

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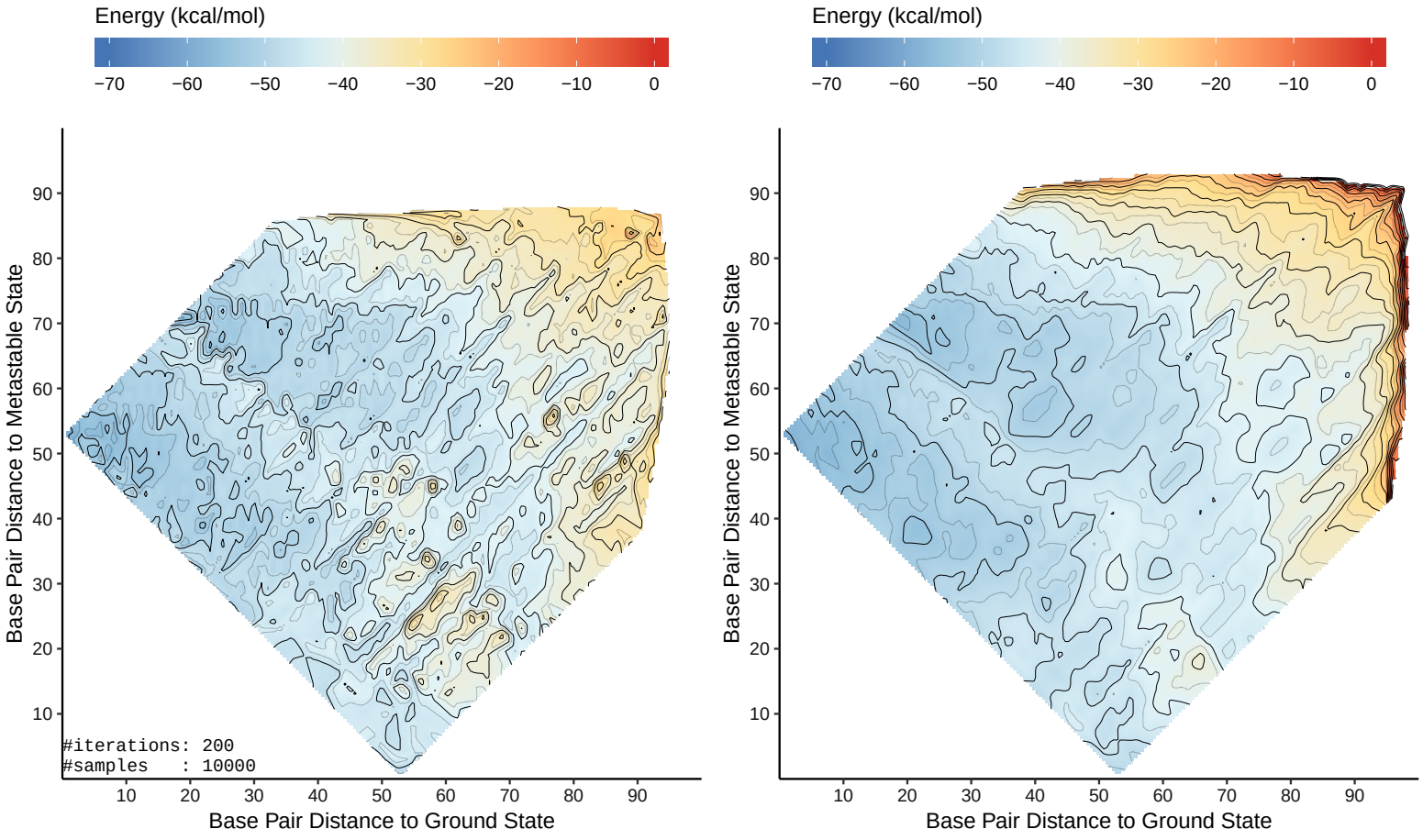

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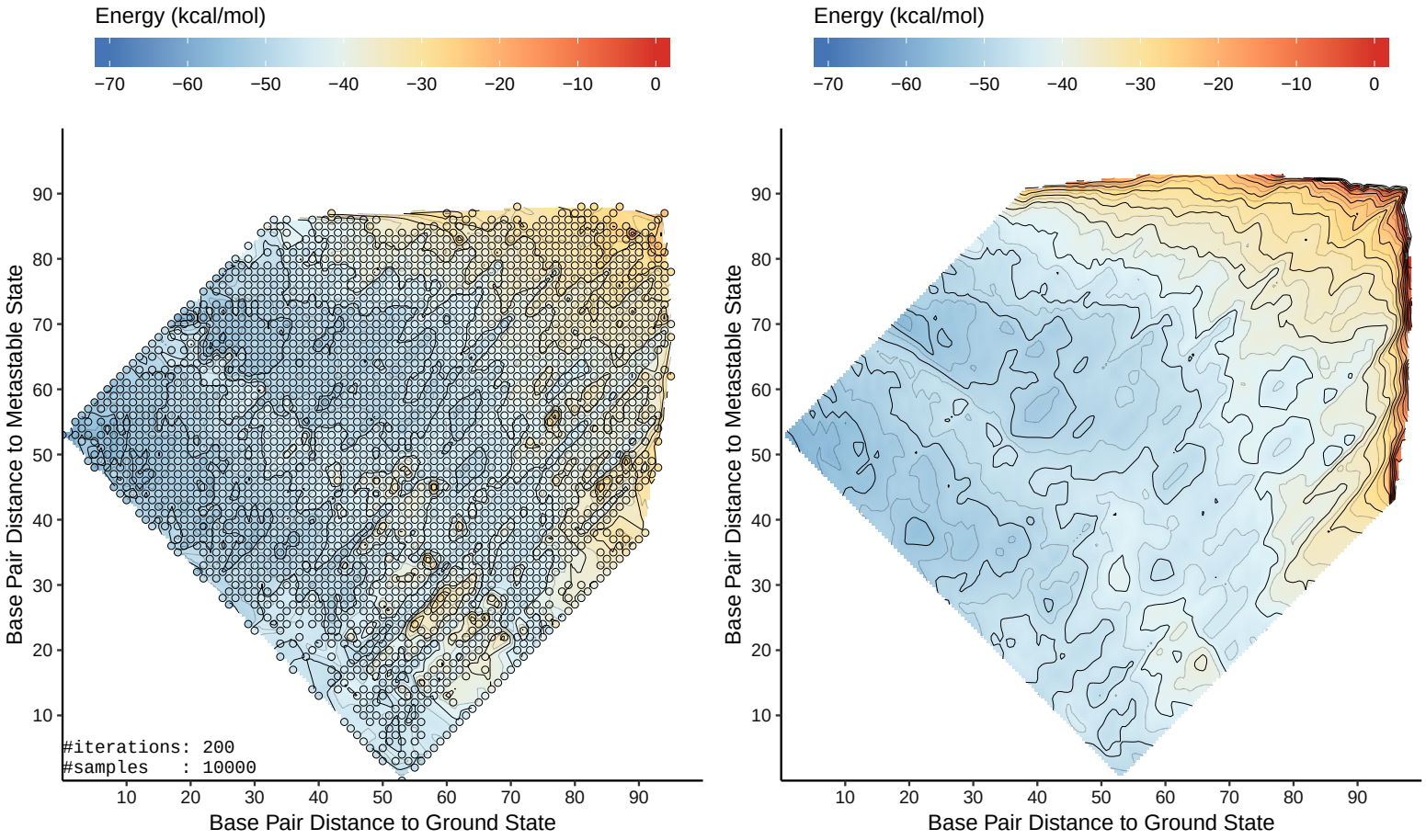

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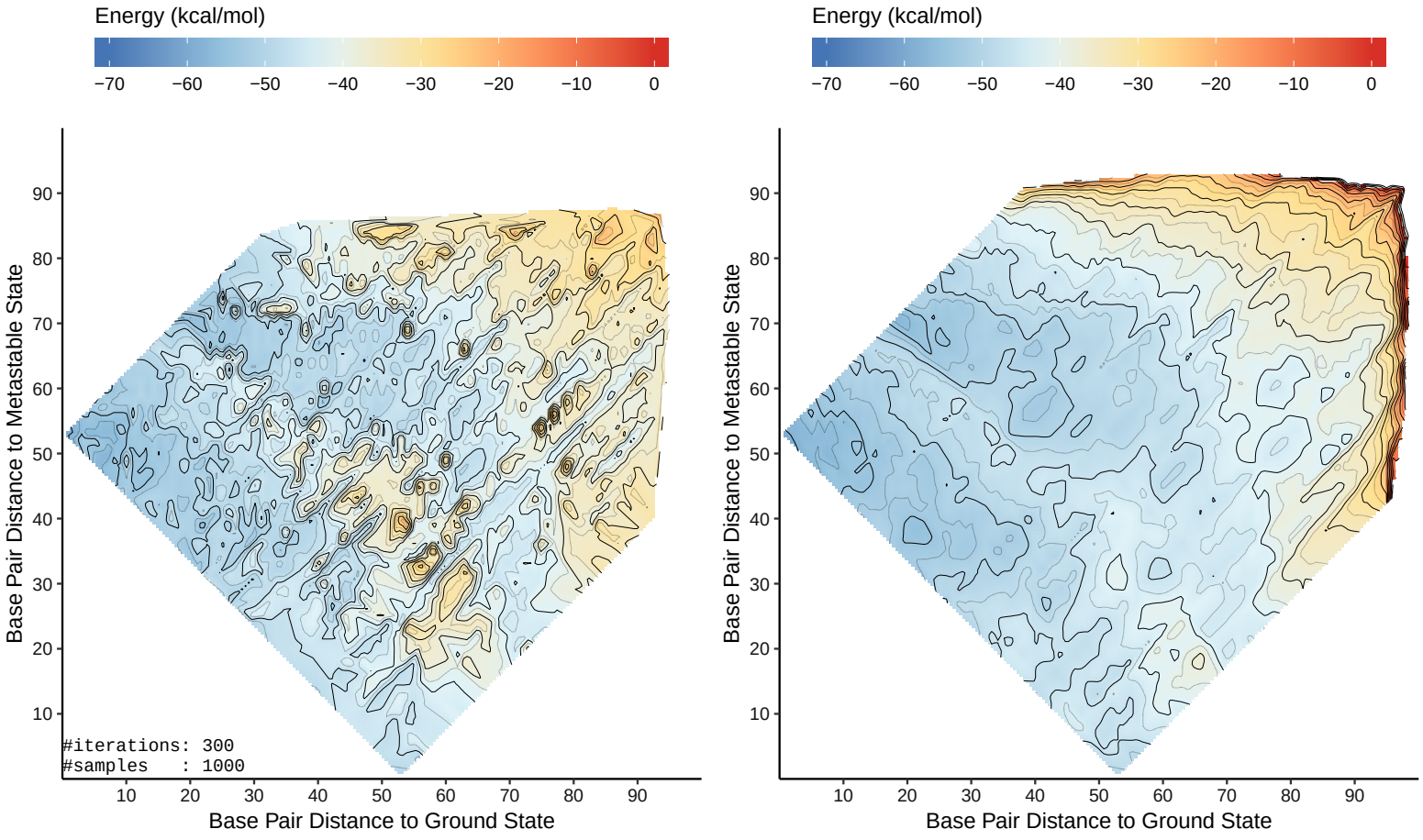

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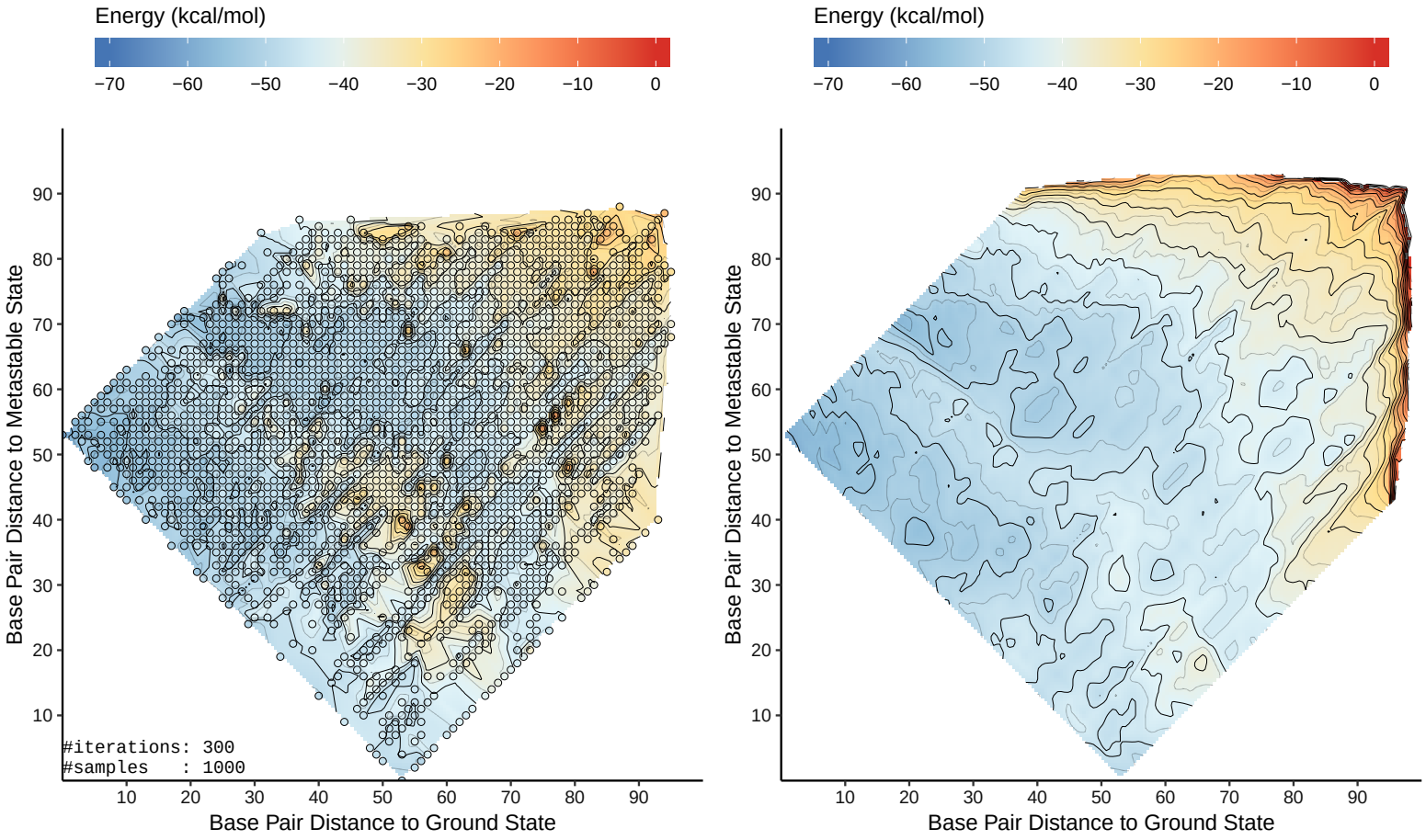

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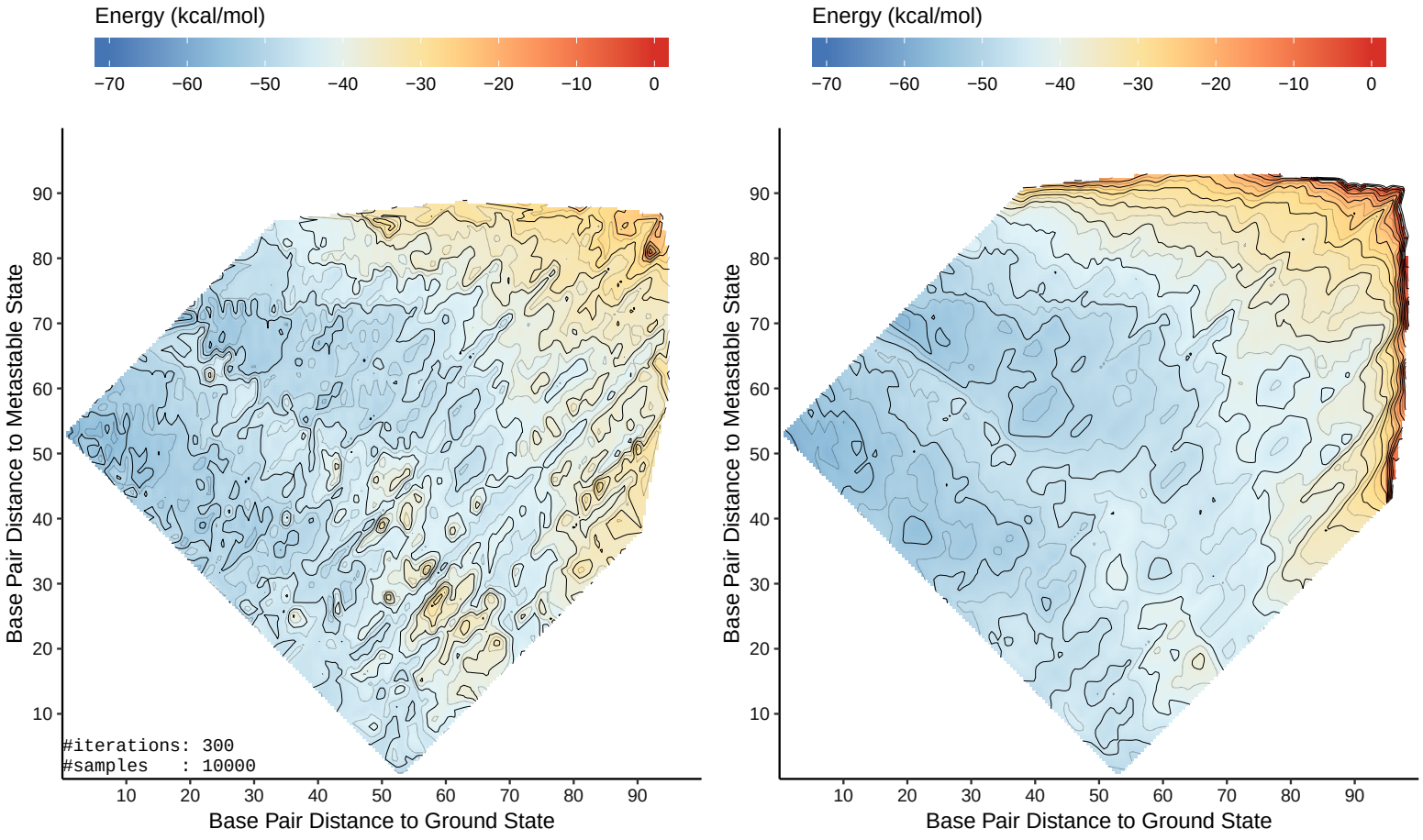

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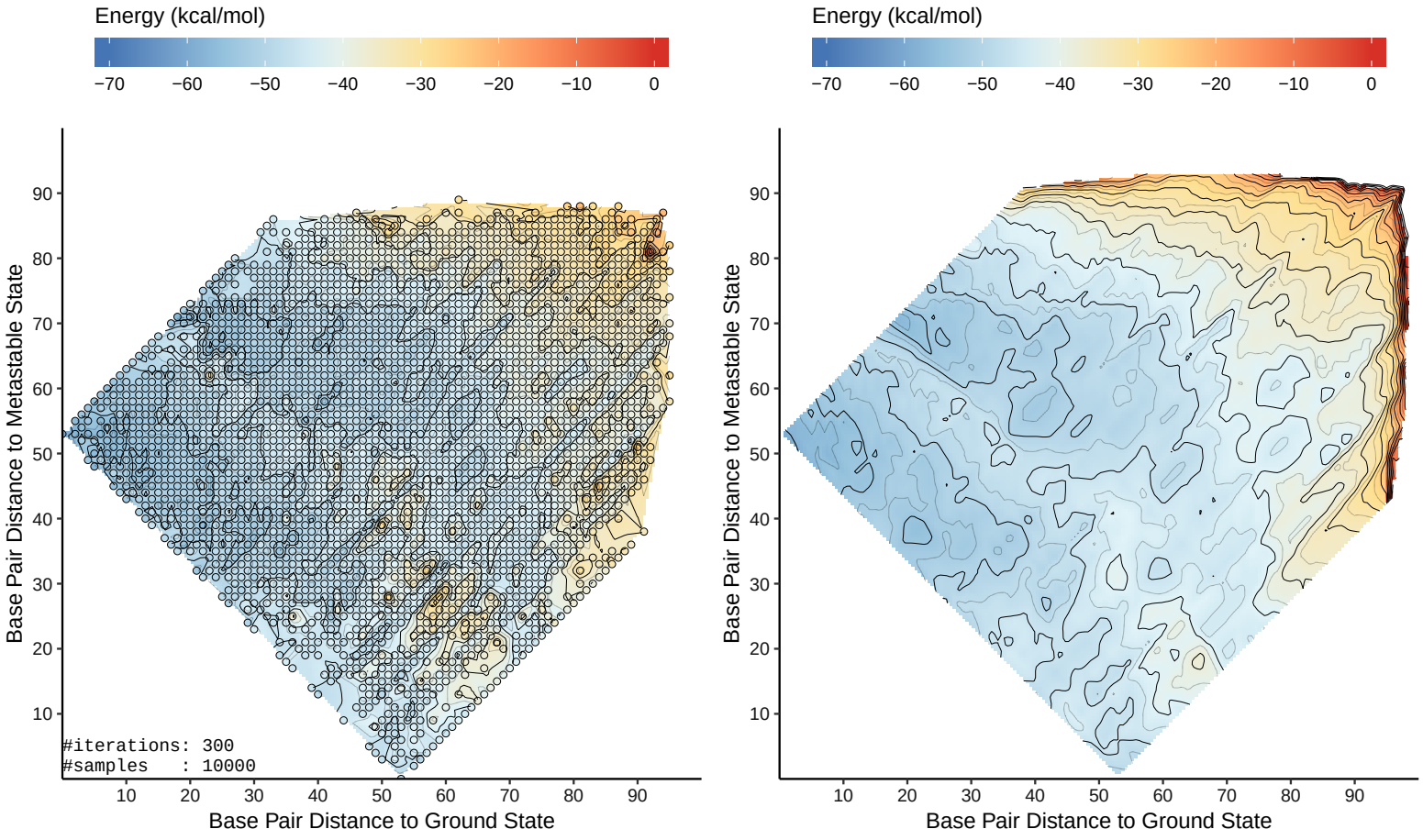
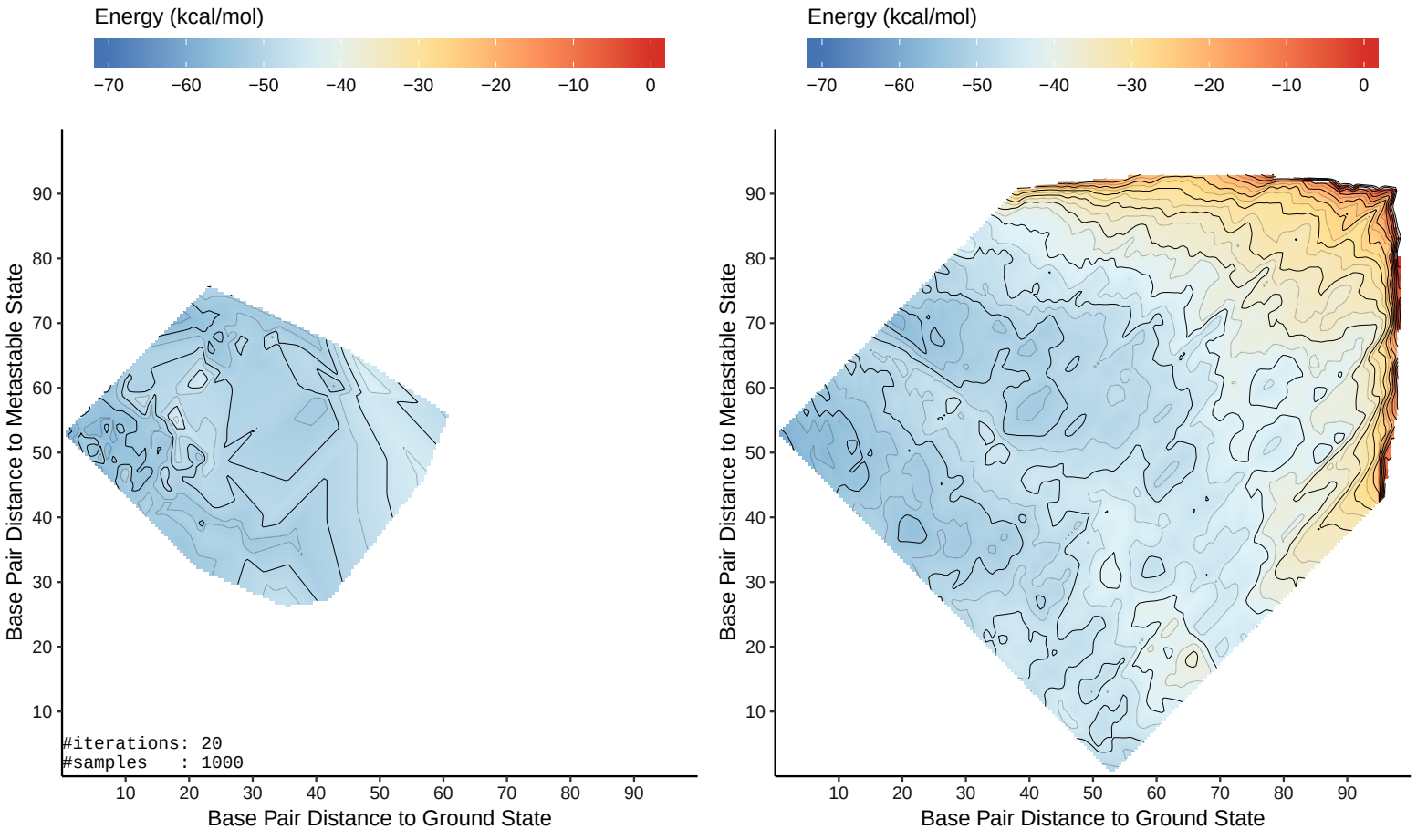


Example: 5UTR of MS2 coat protein mRNA

`RNAlocmin` temperature elevation scheme Boltzmann sampling



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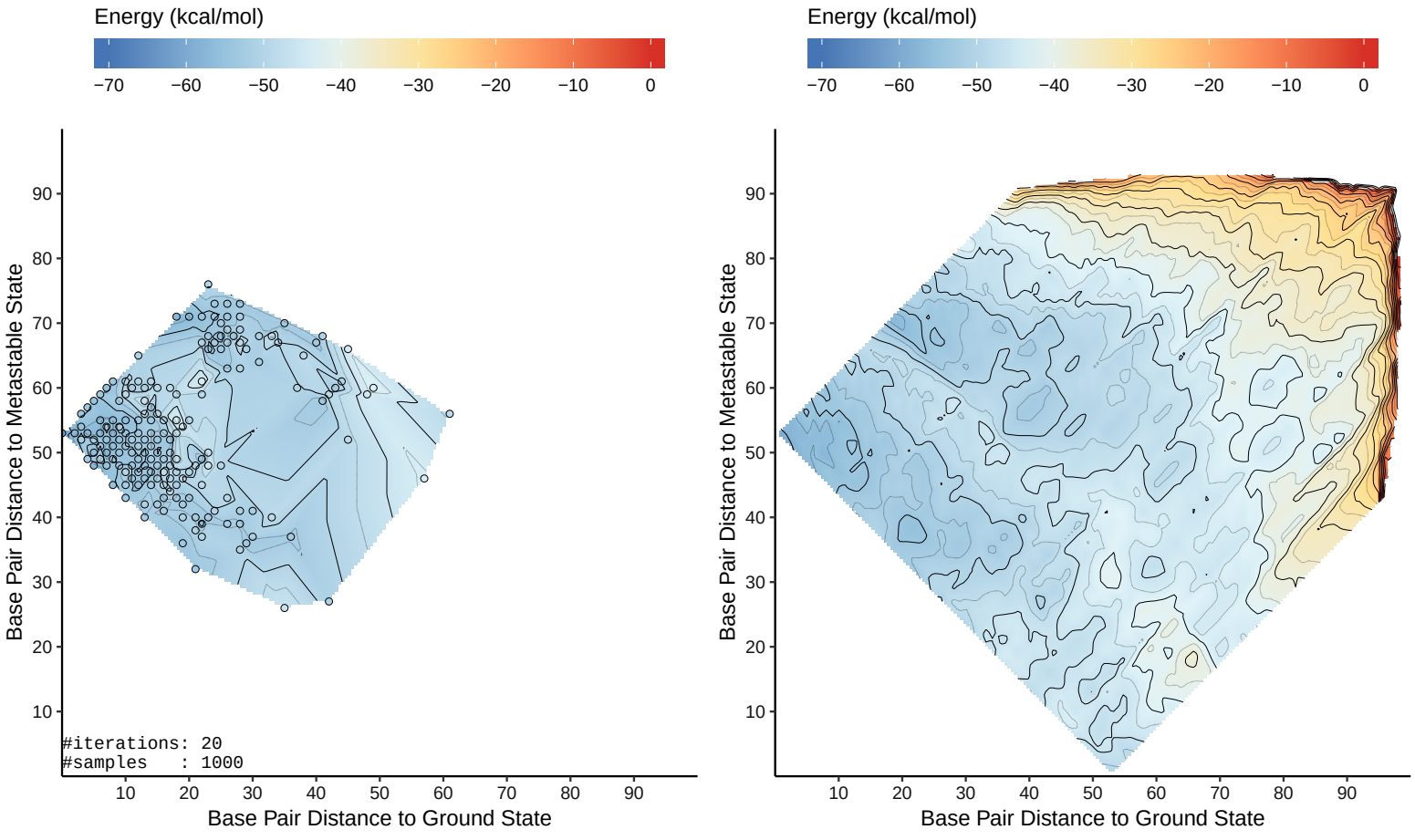

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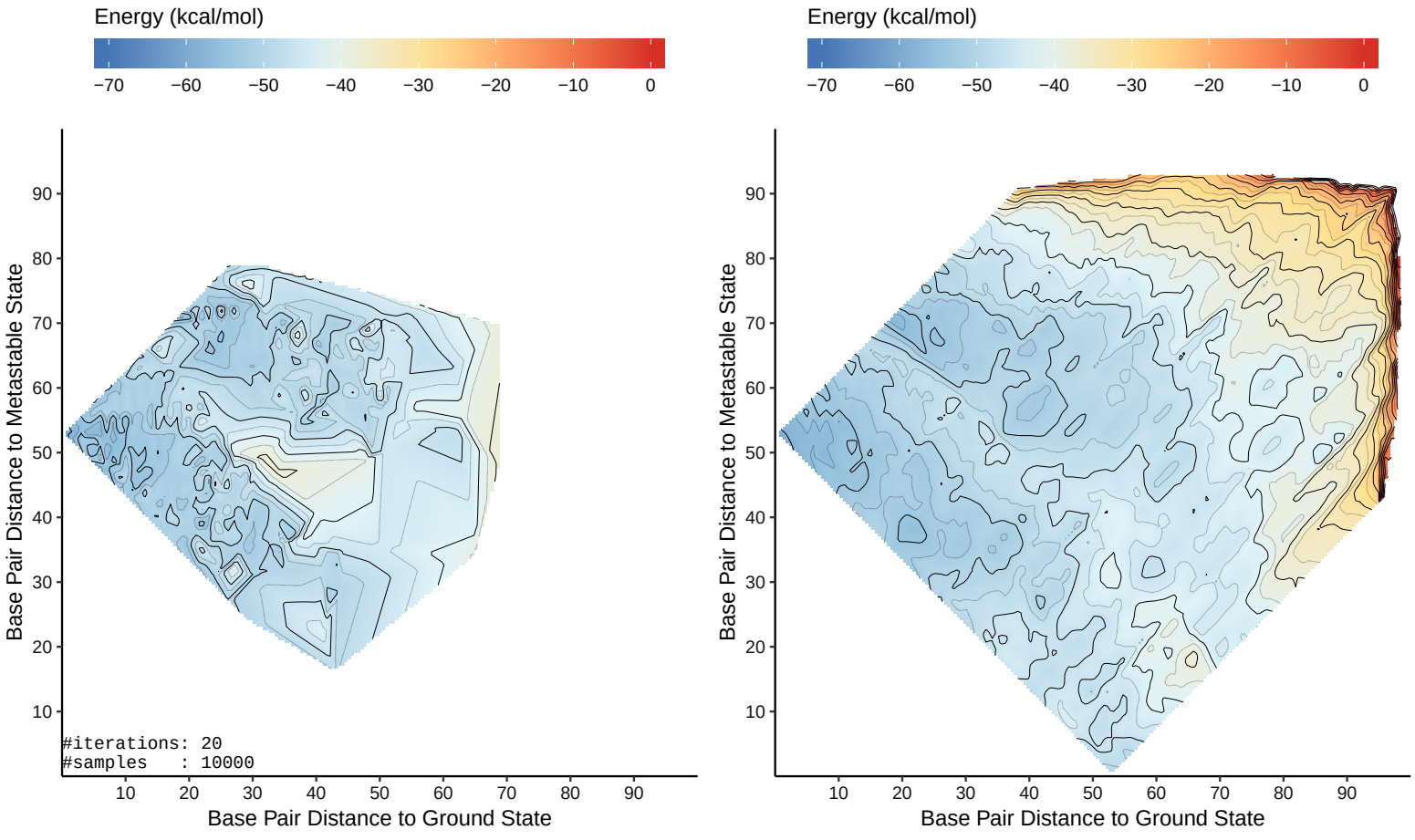

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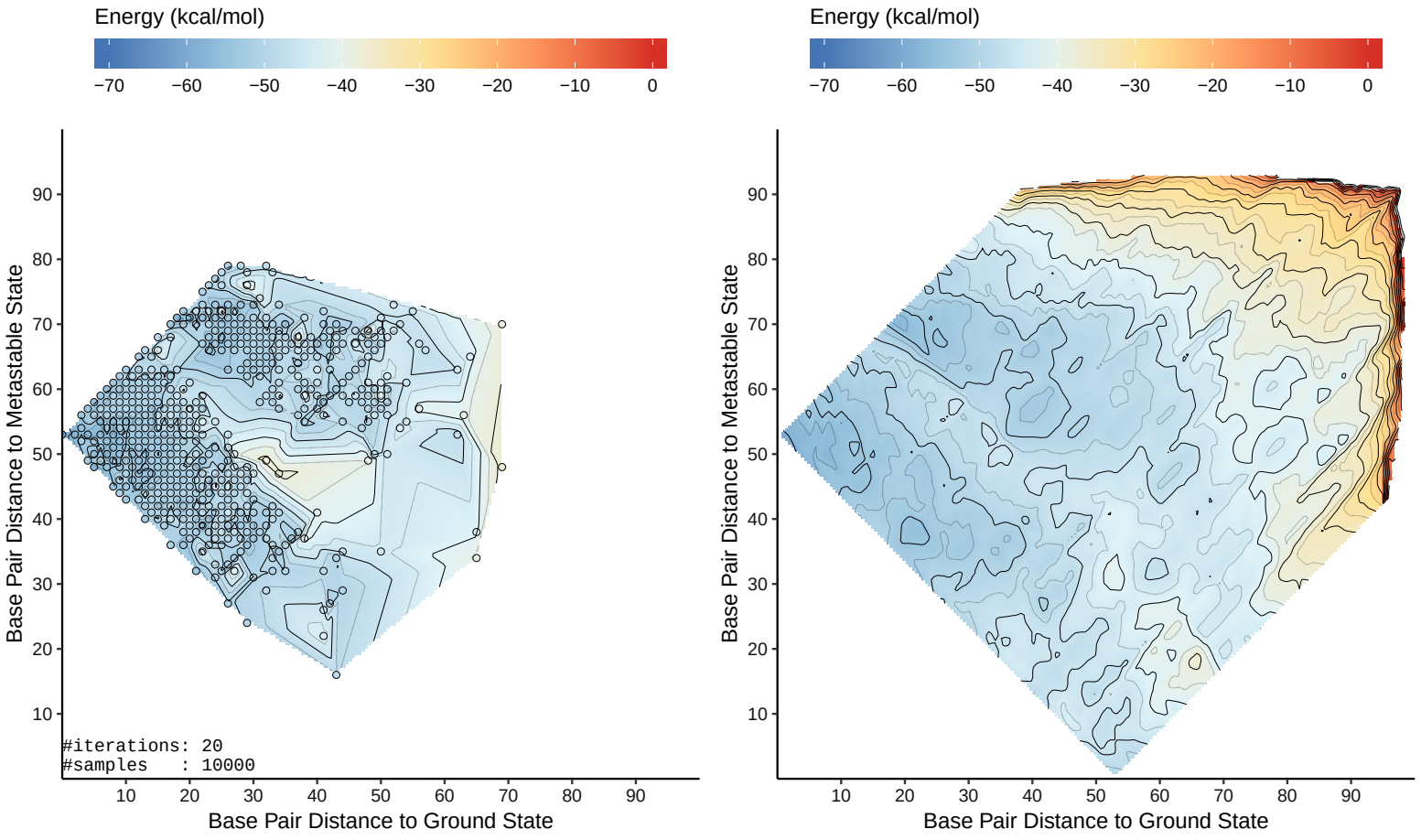

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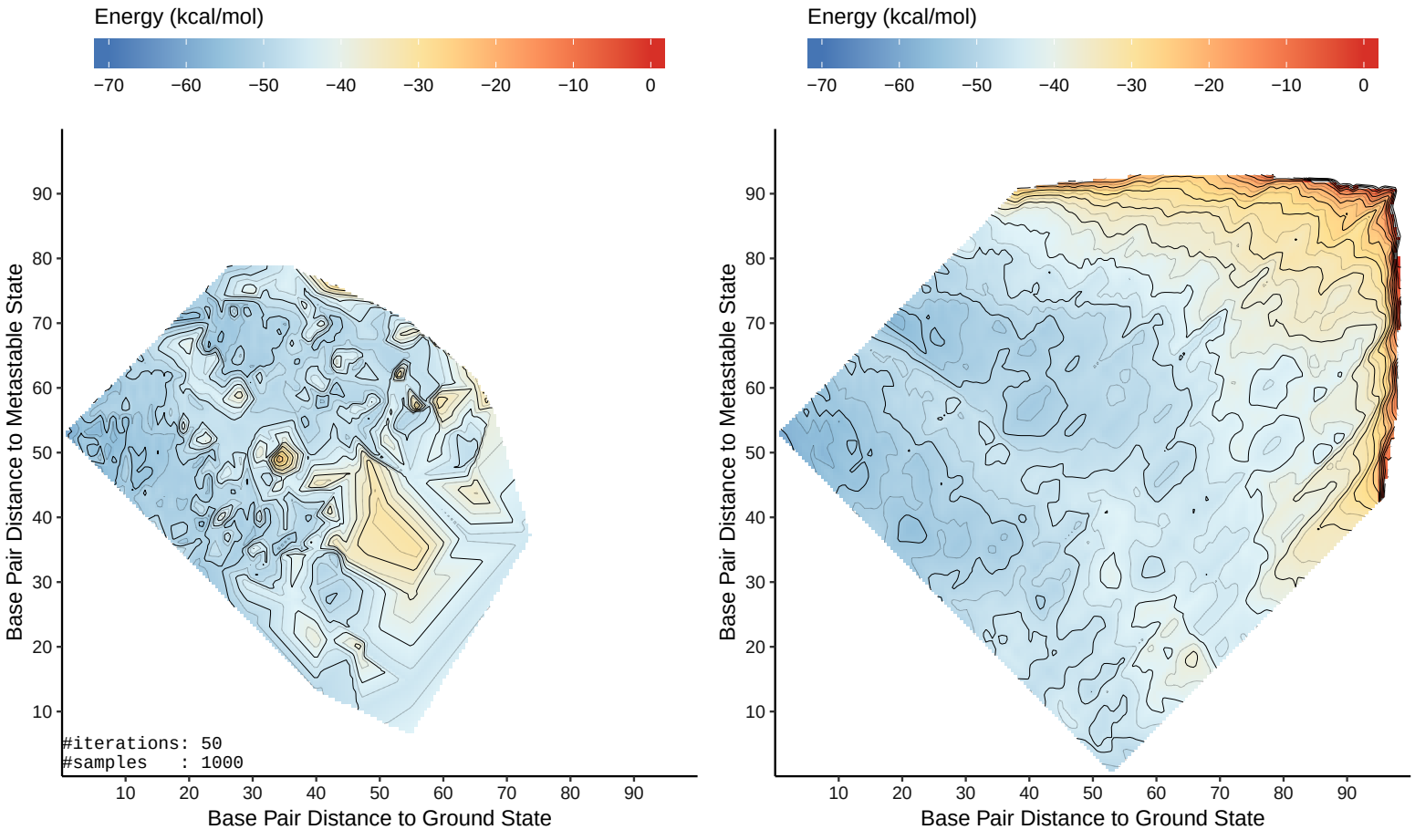

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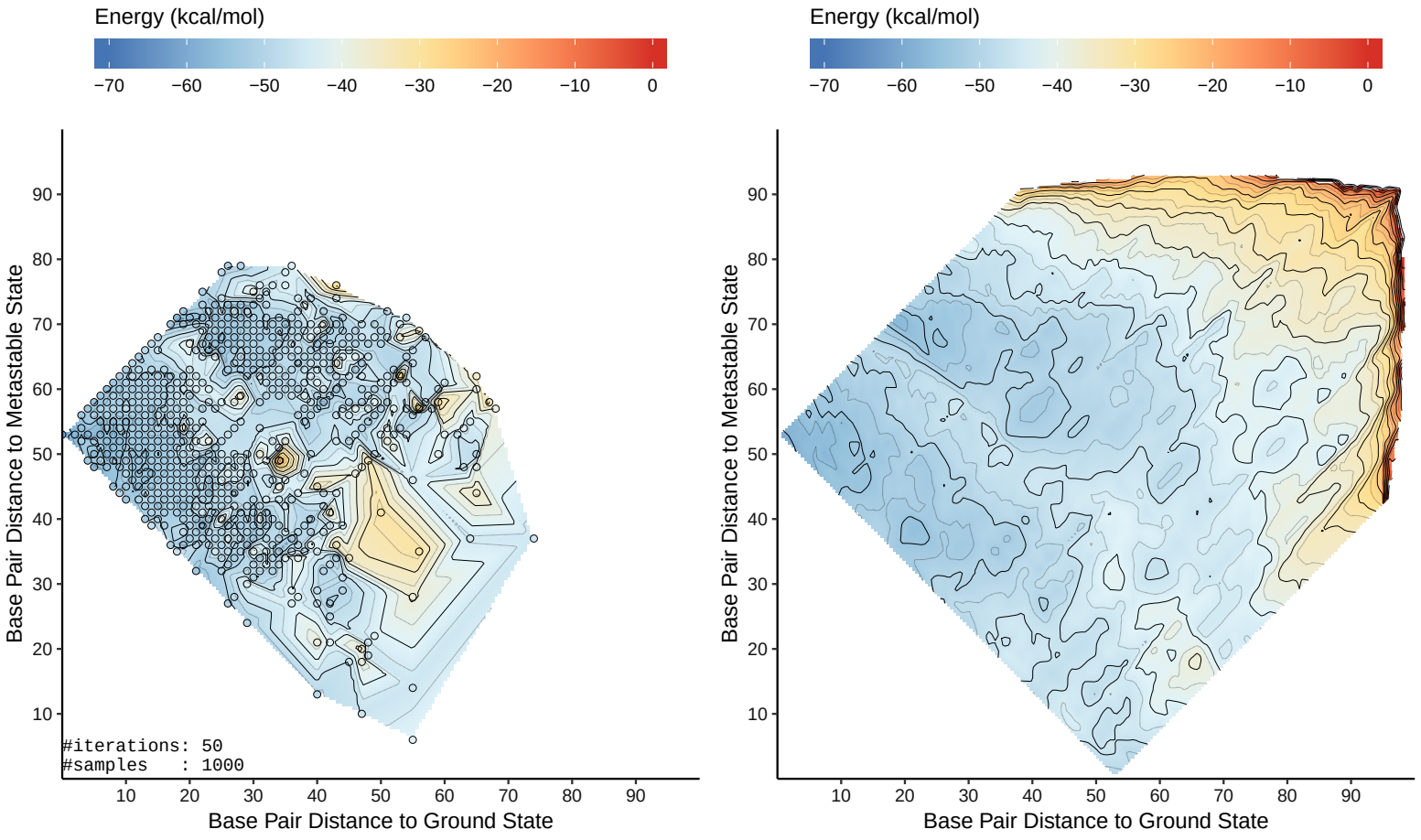

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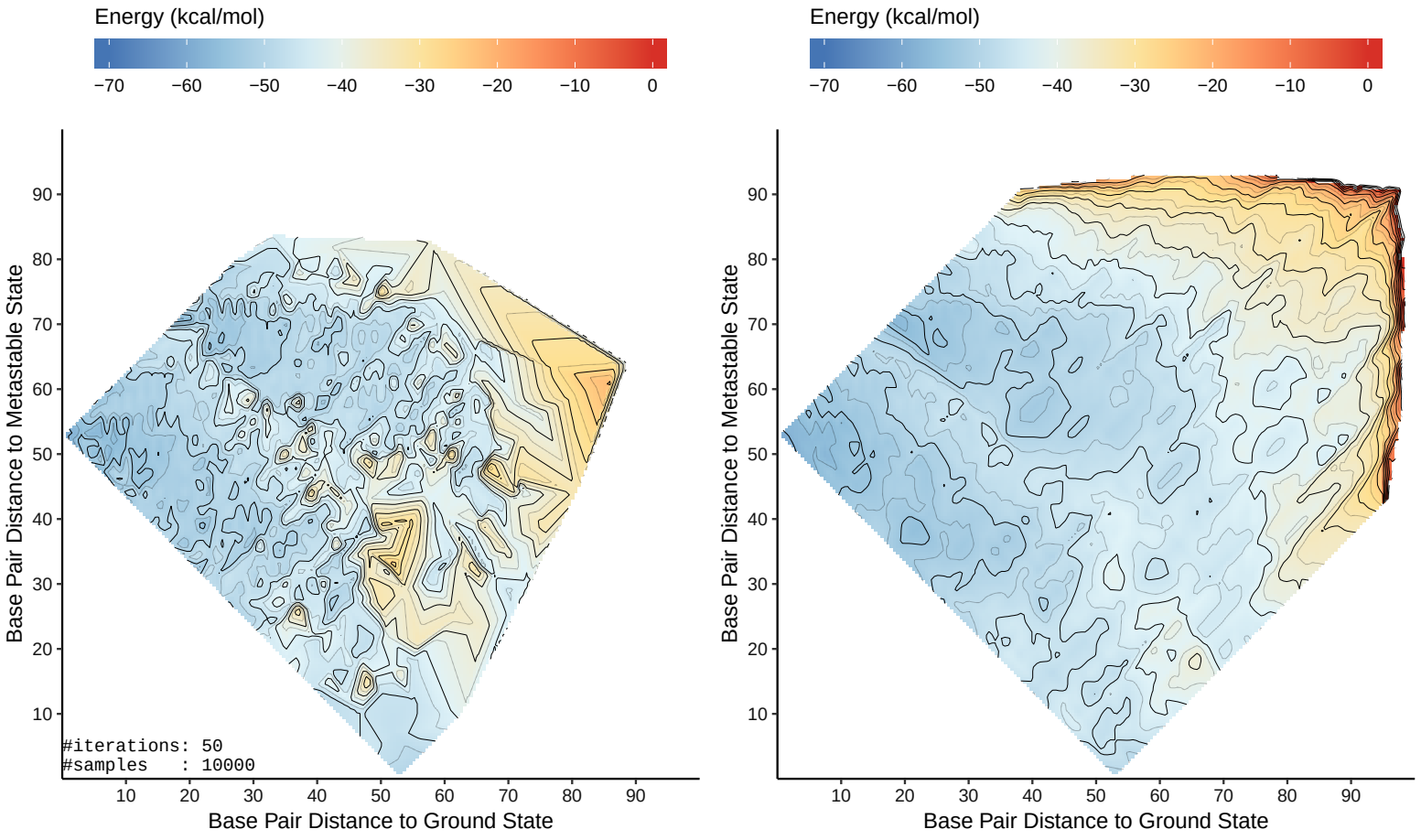

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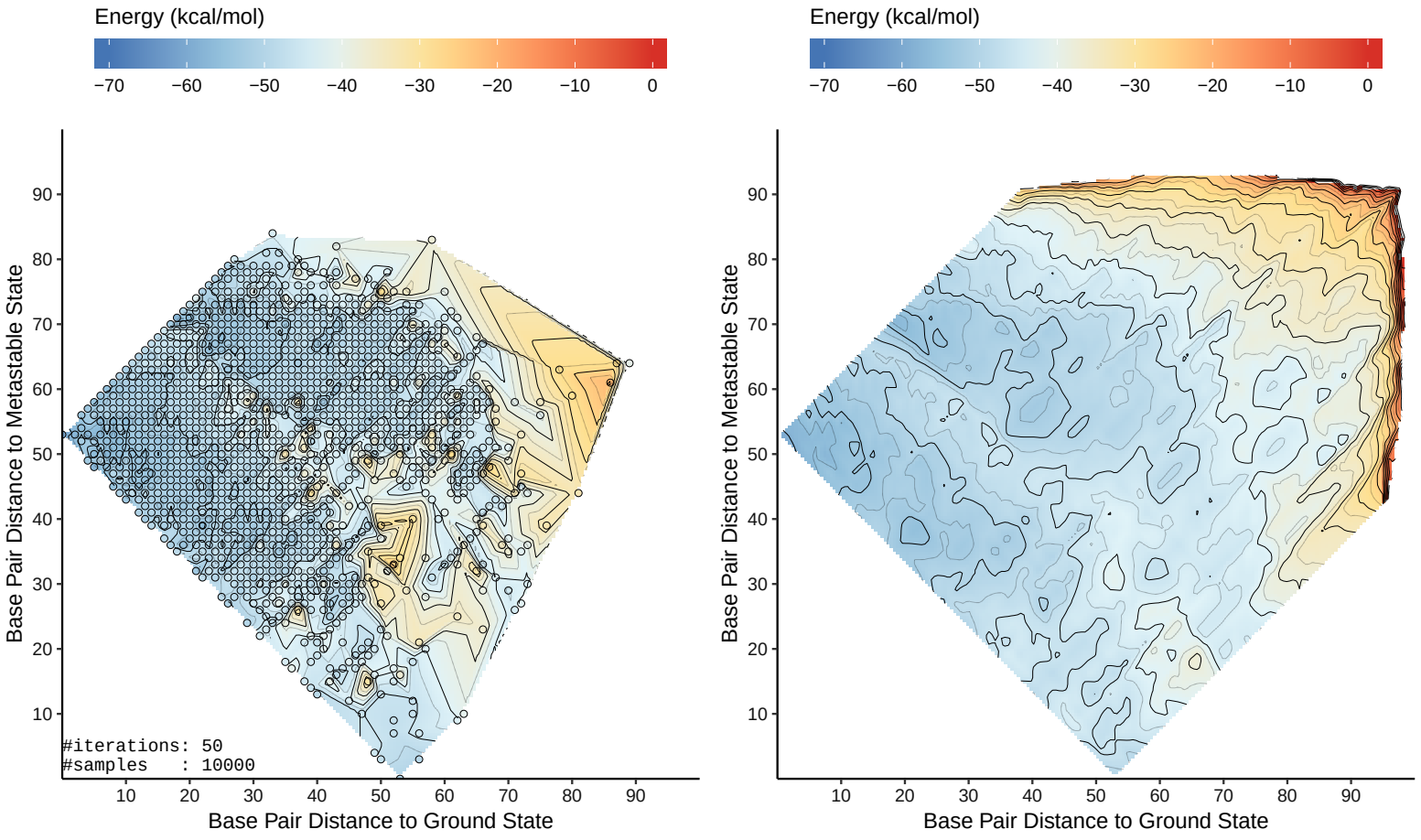

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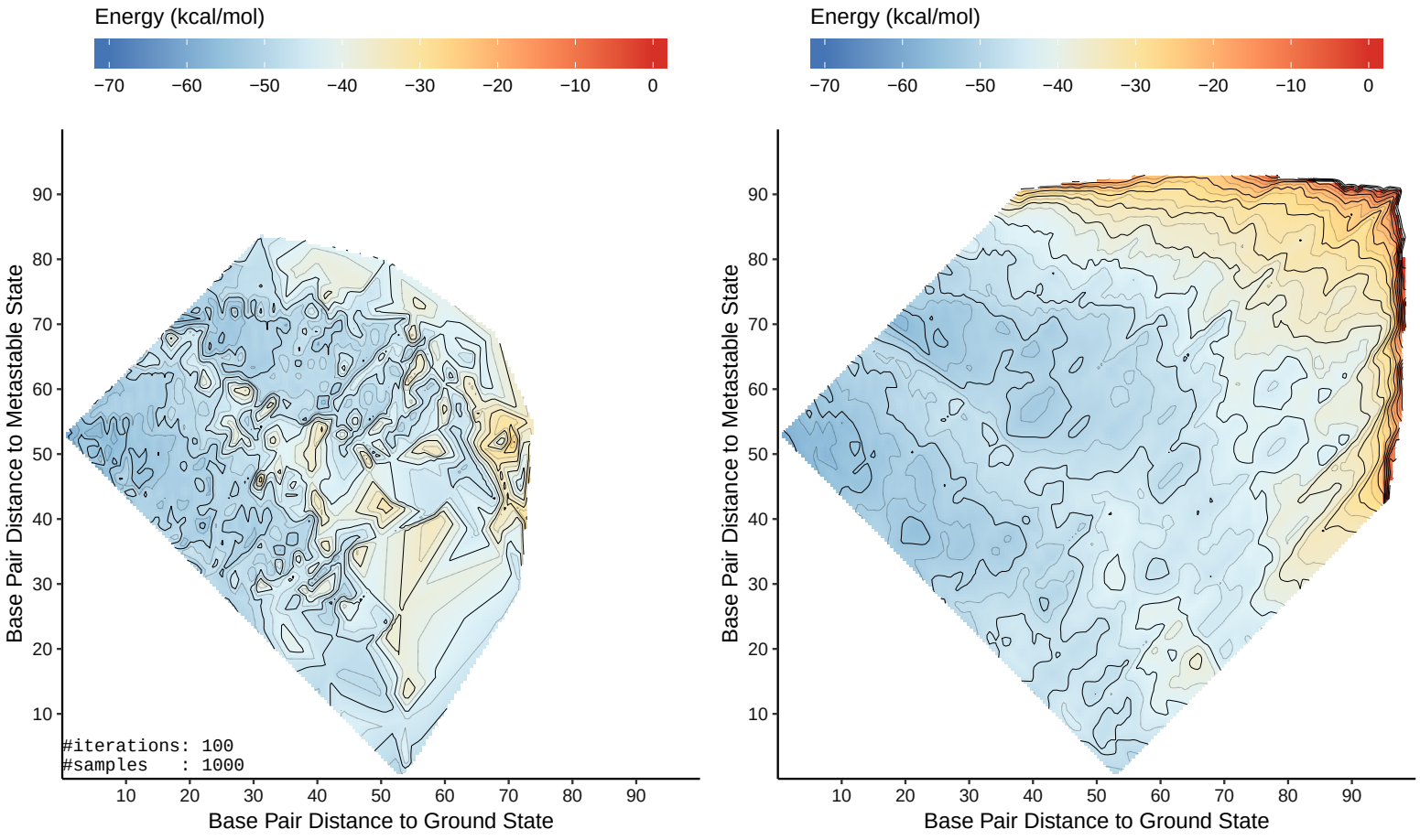

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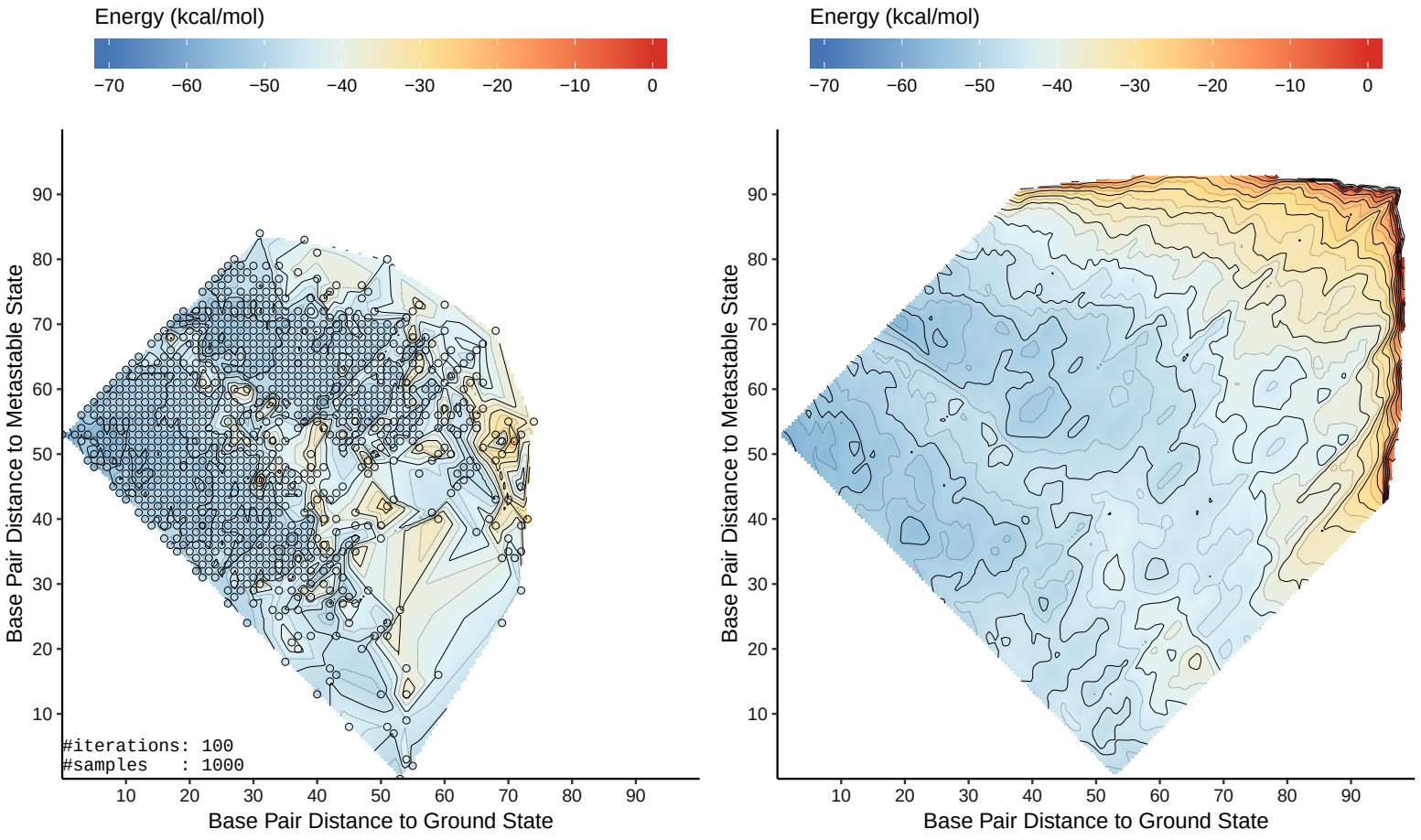

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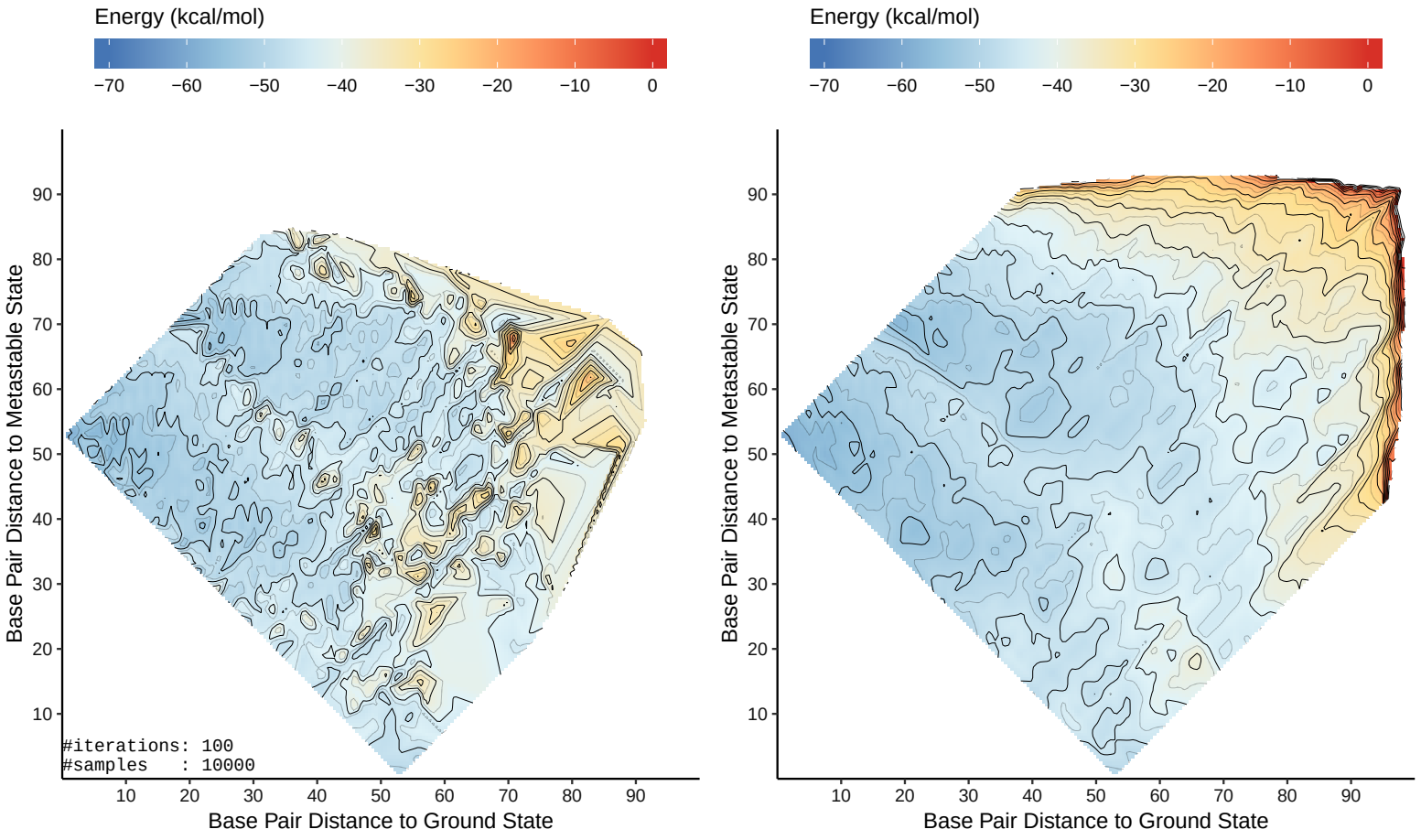

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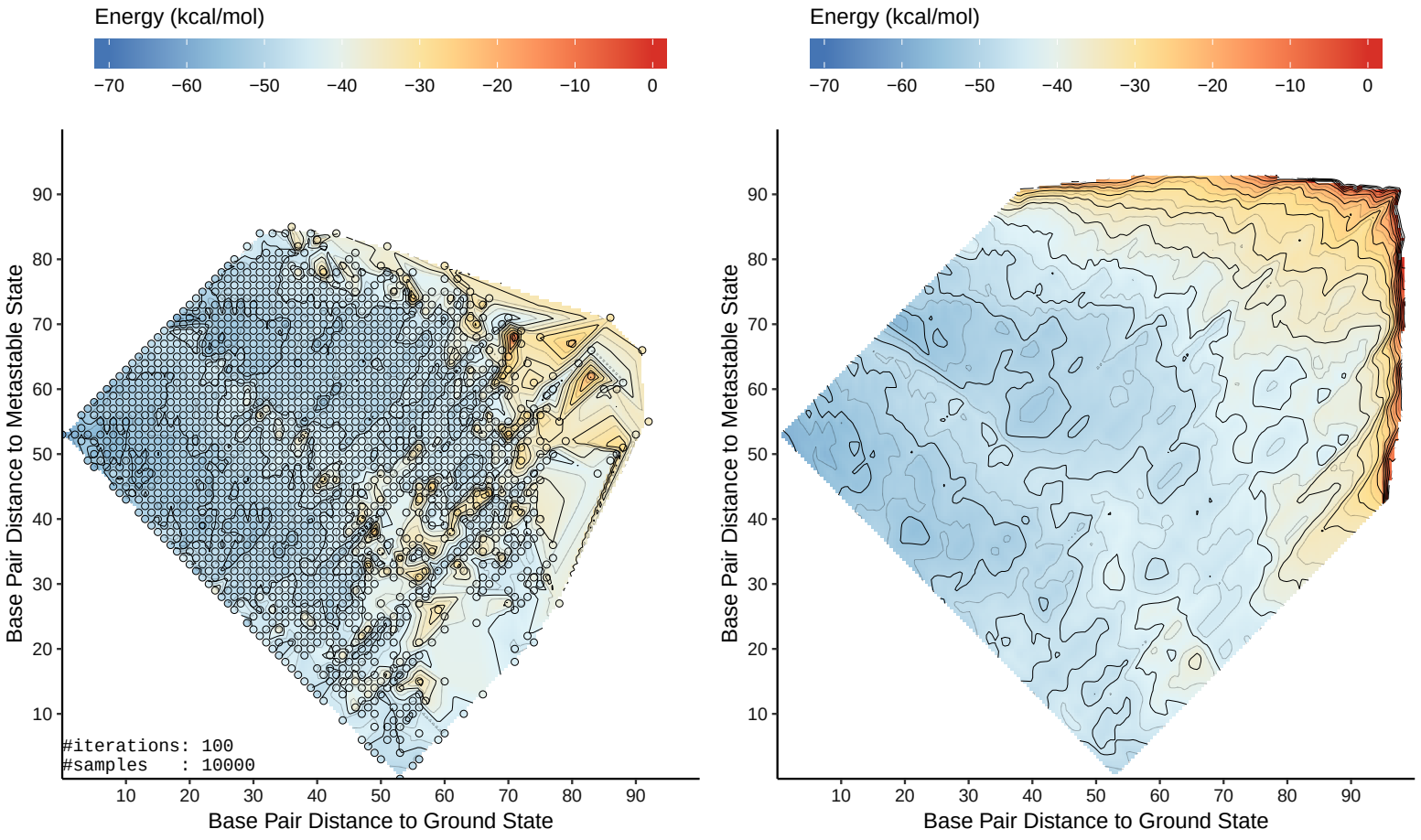

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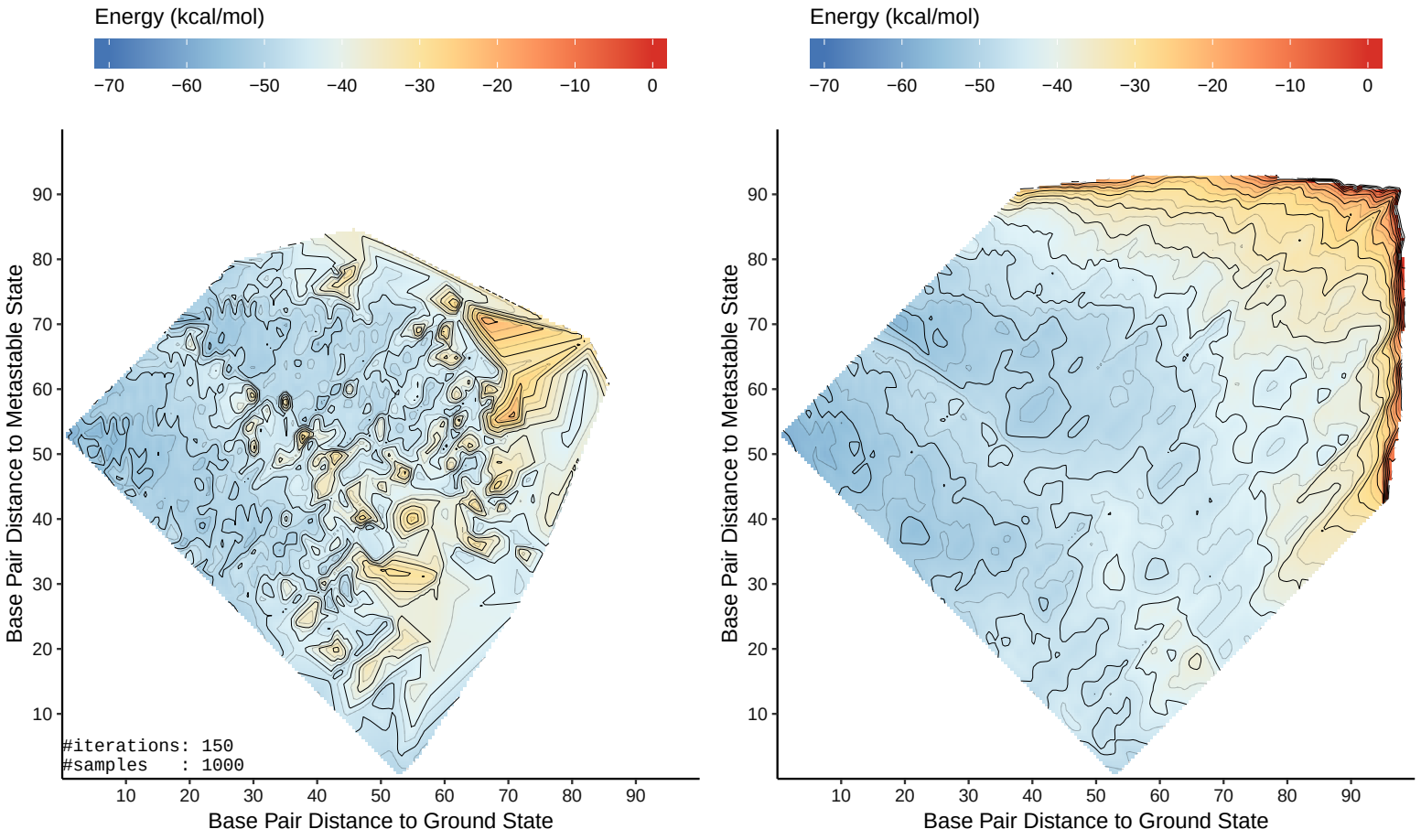

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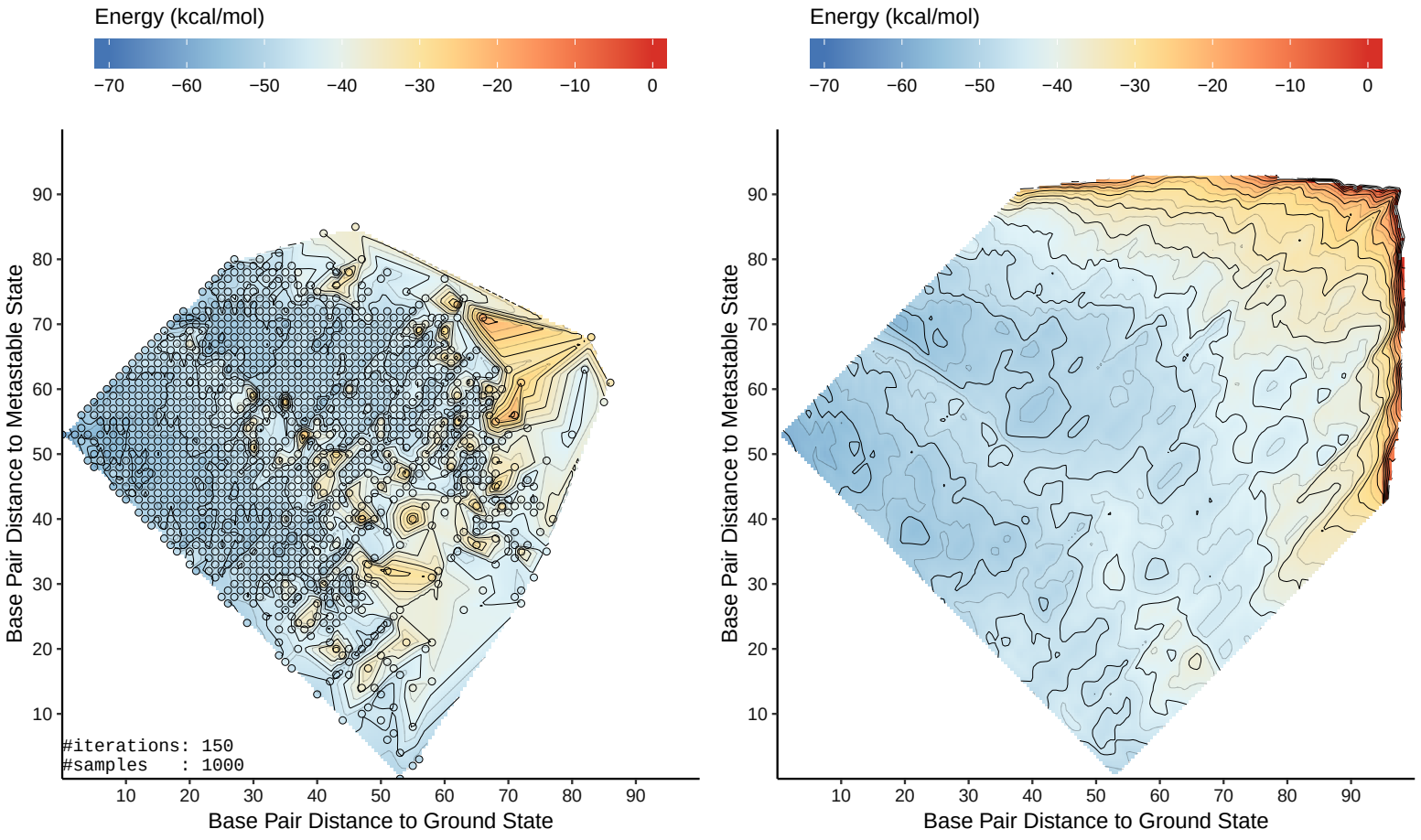

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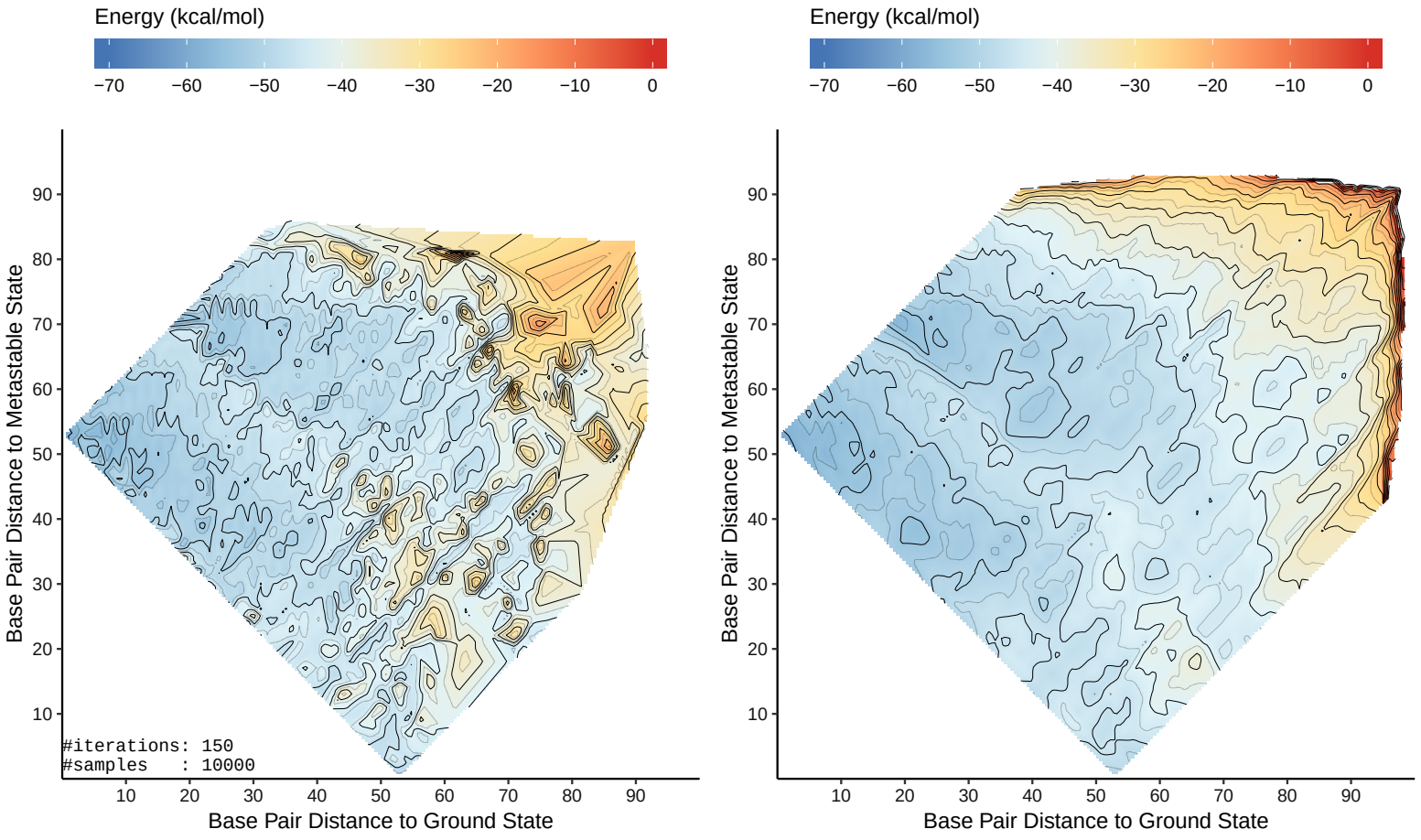

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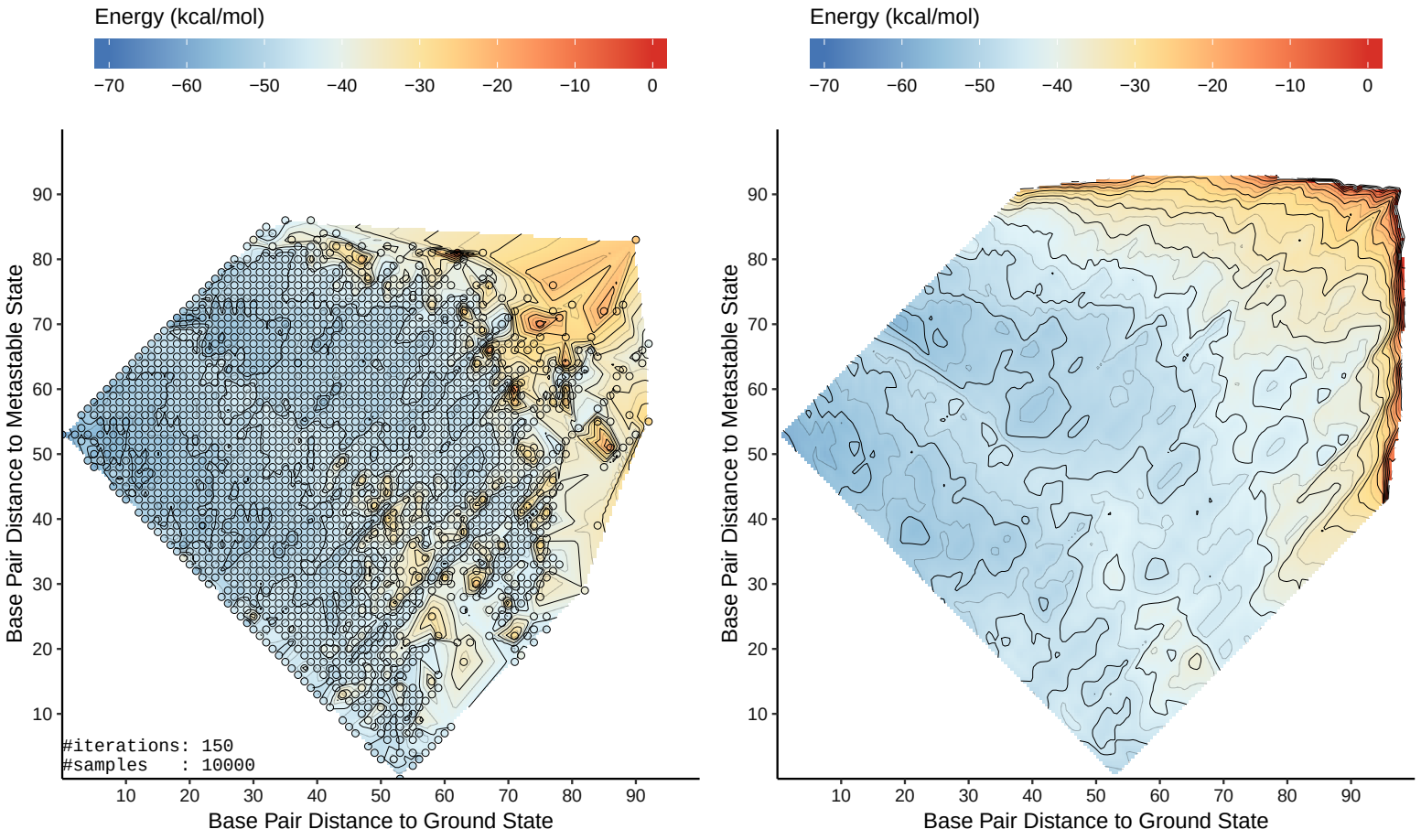

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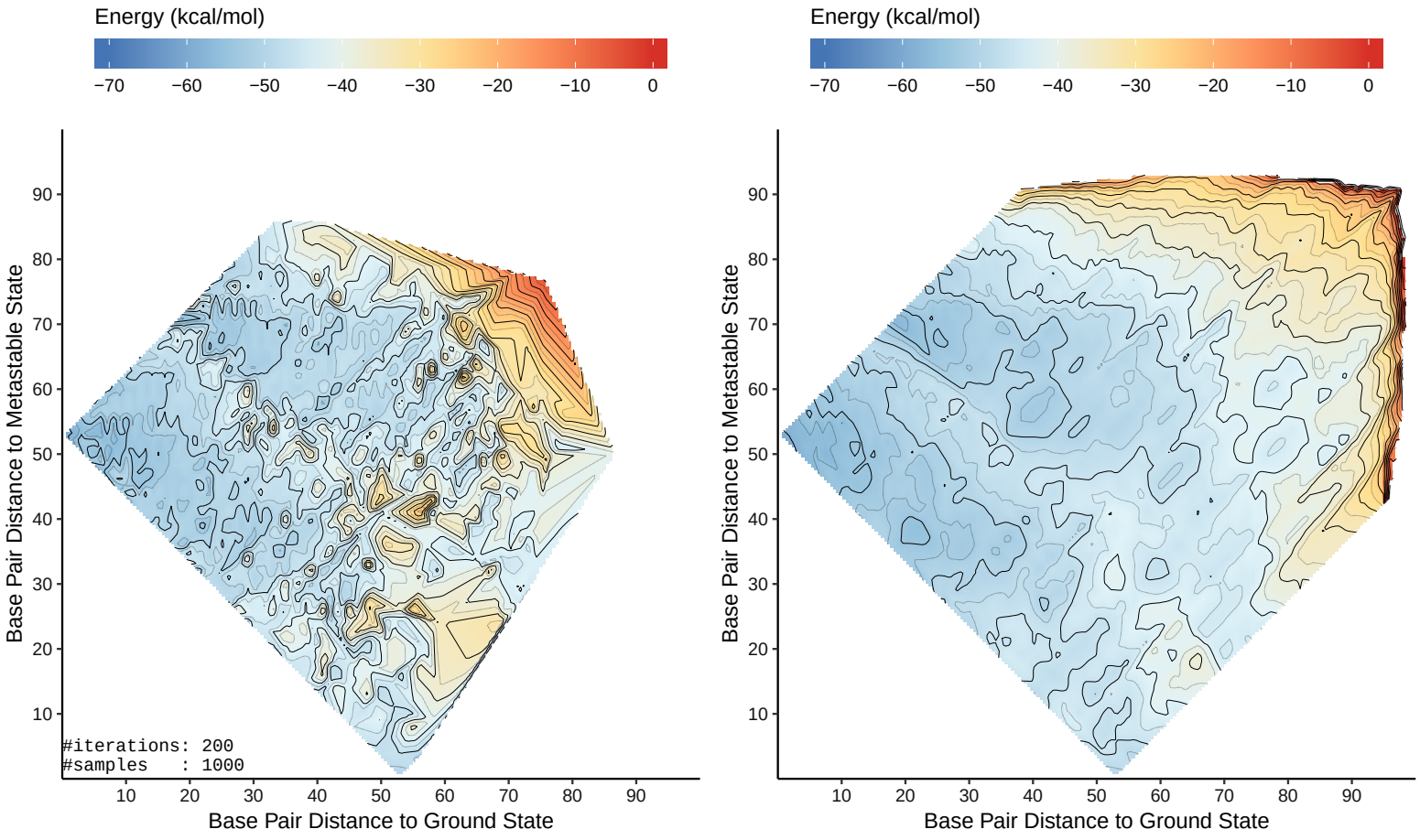

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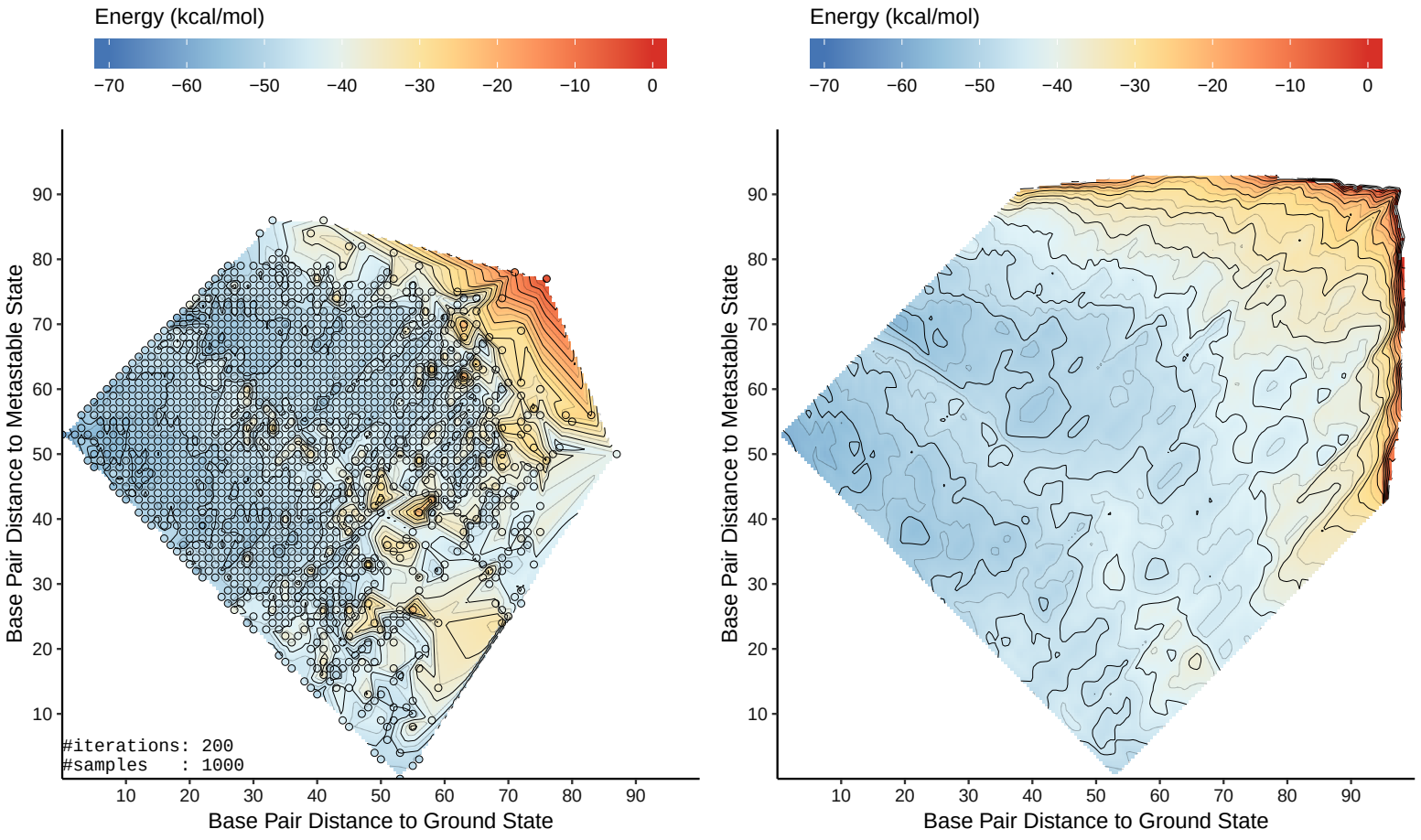

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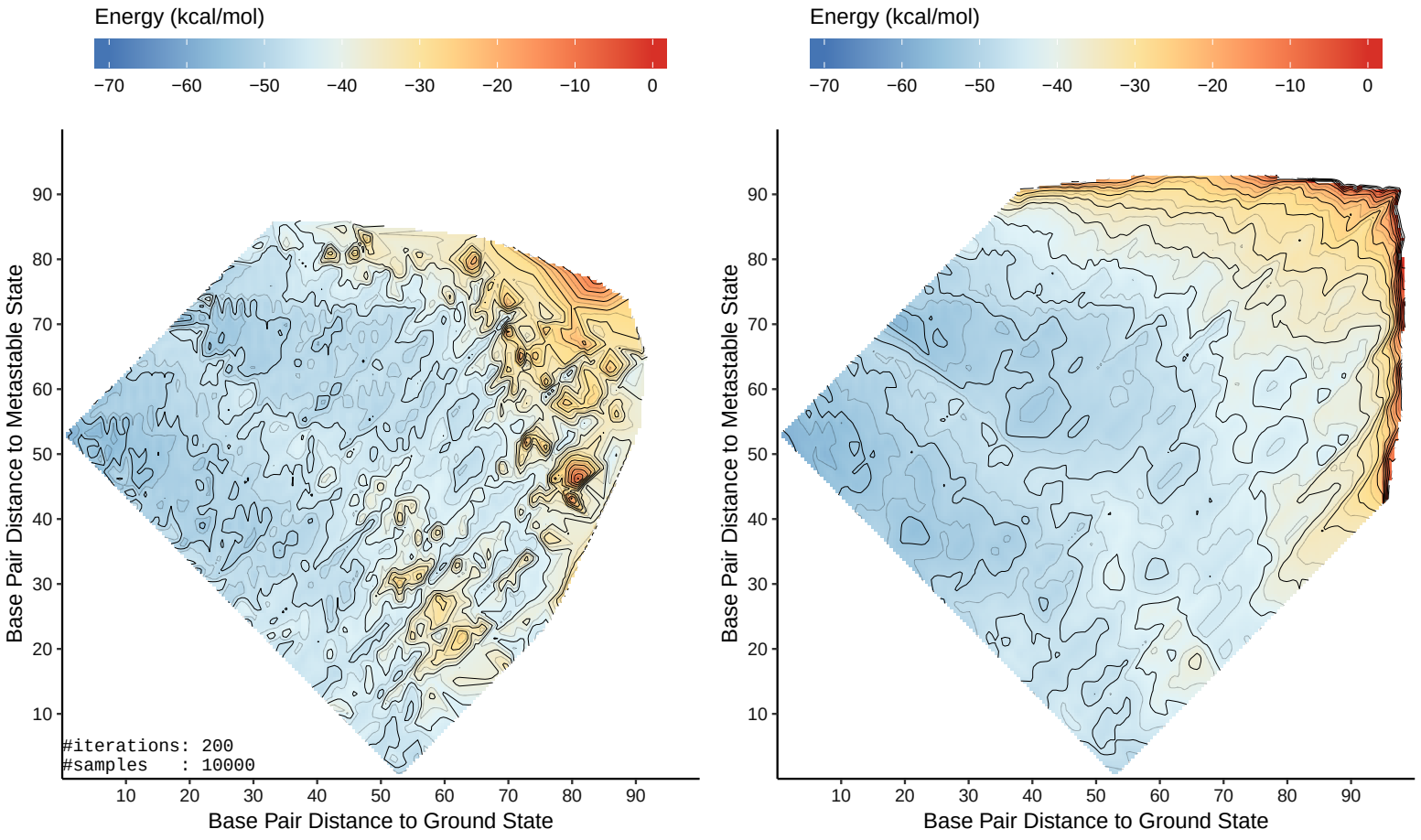

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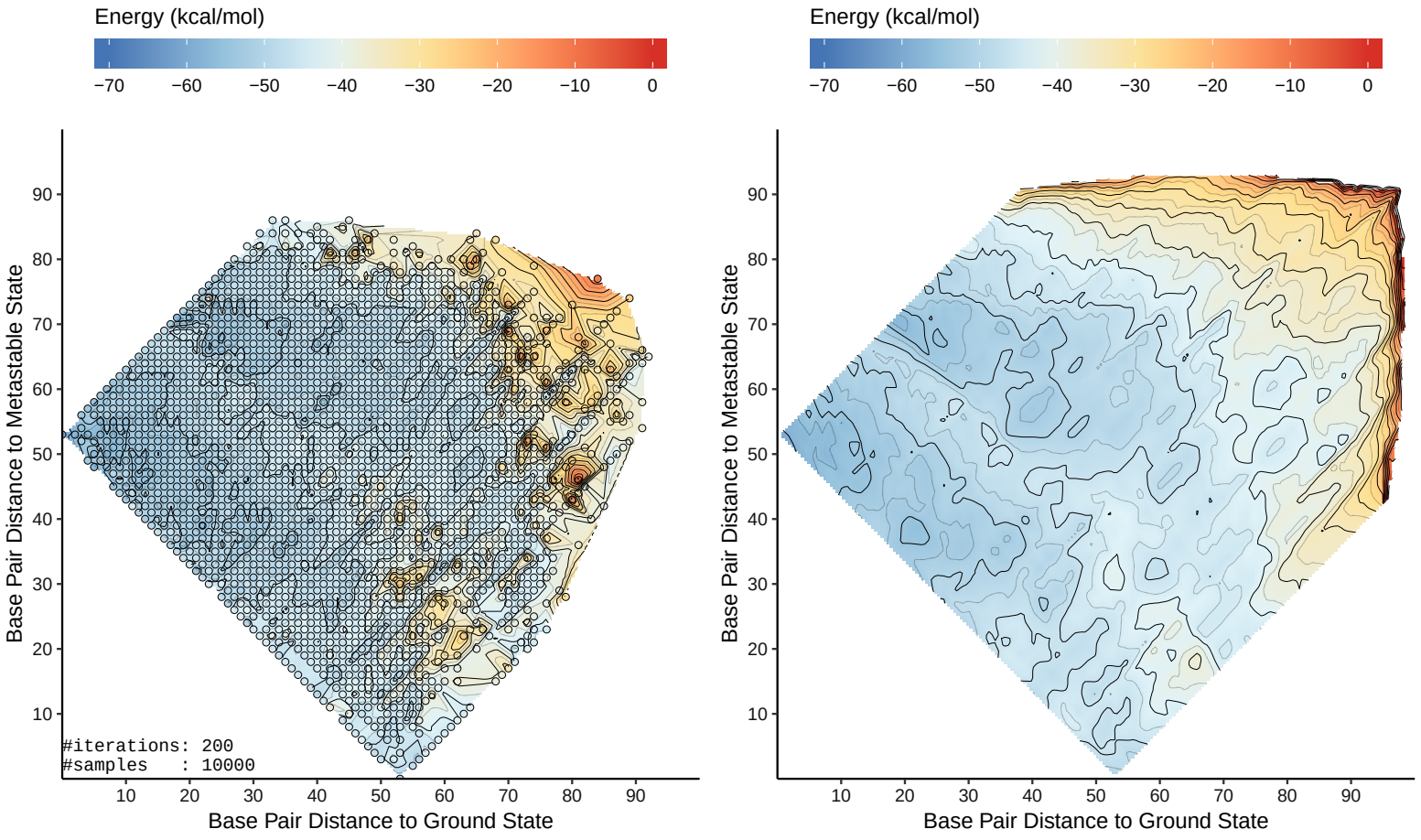

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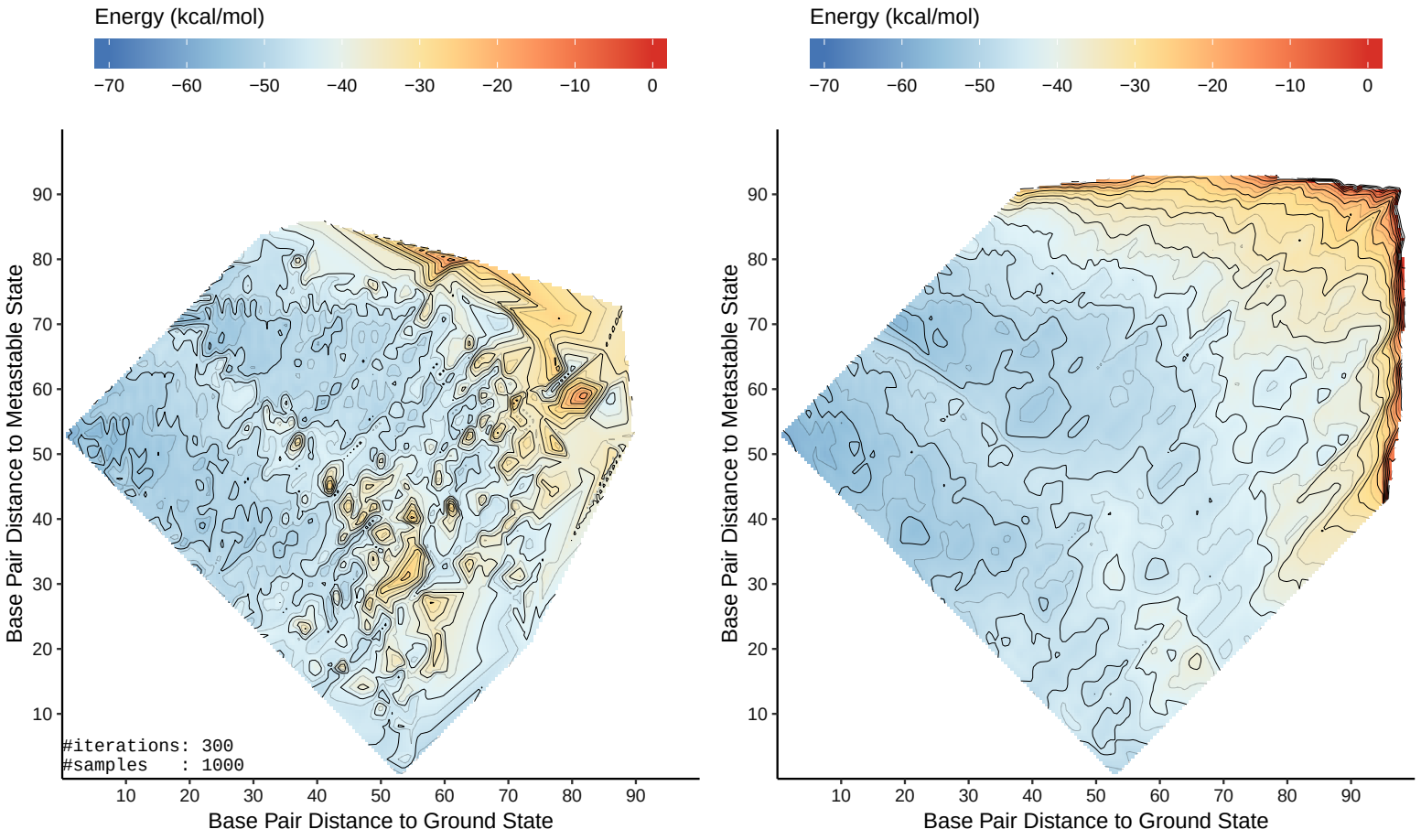

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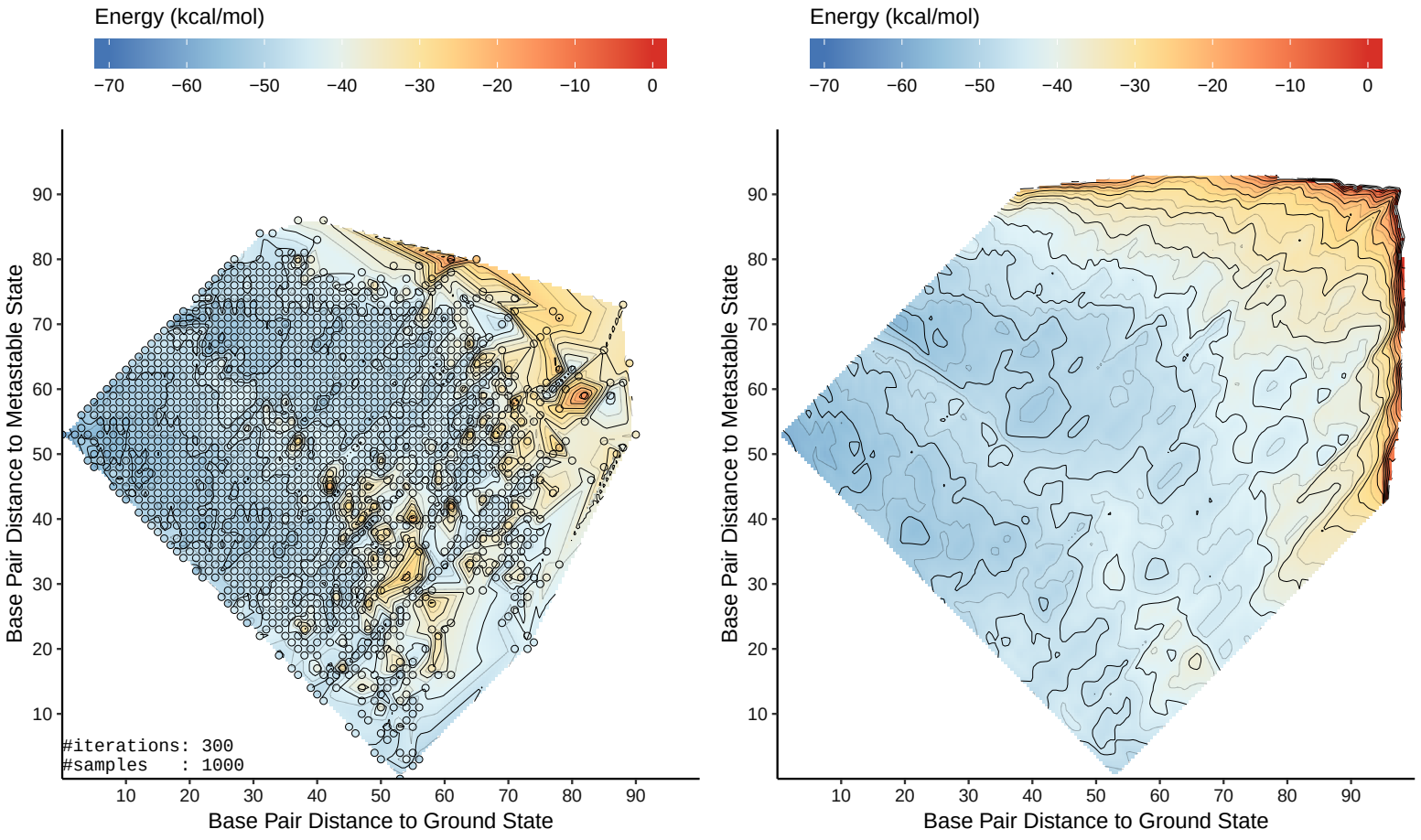

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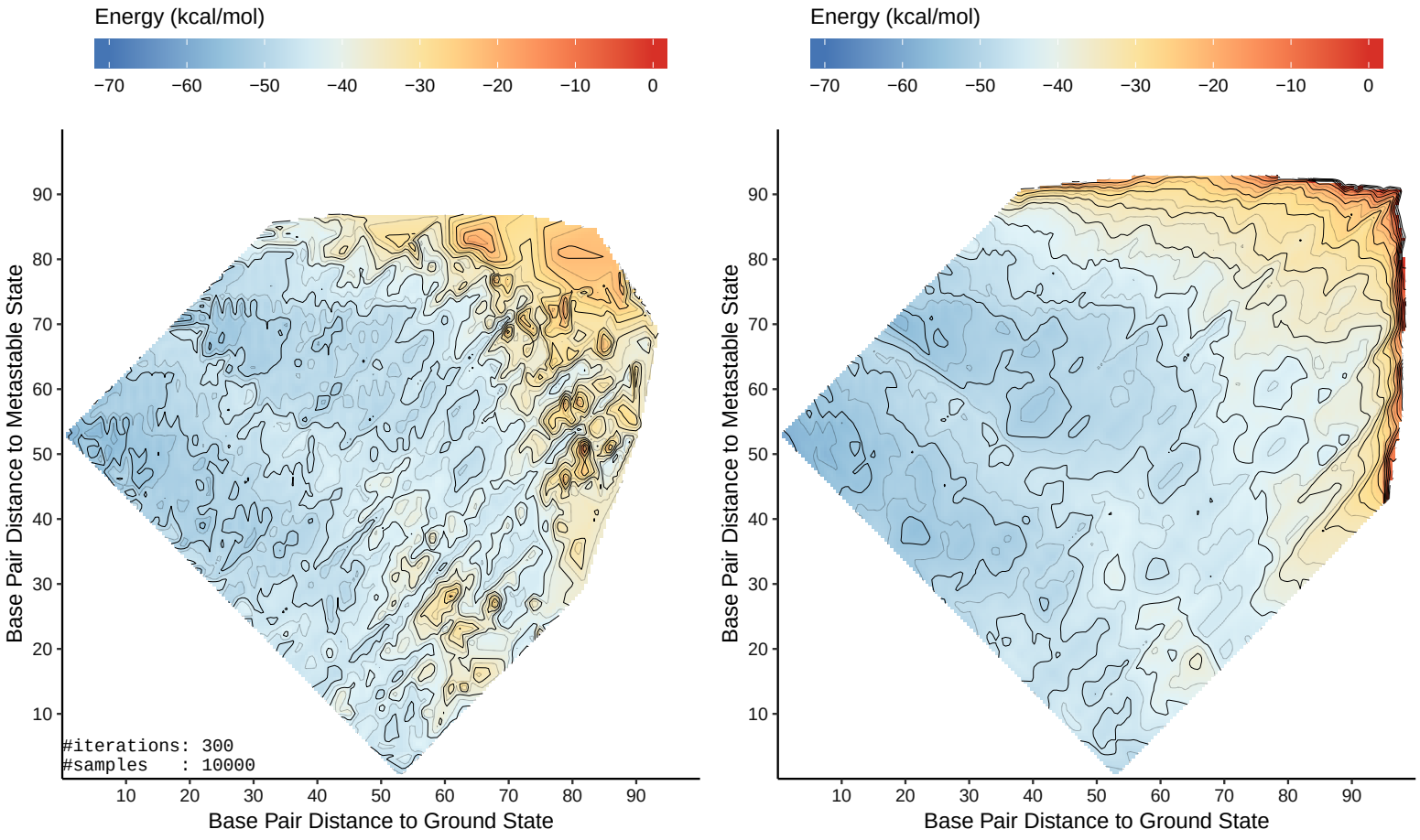

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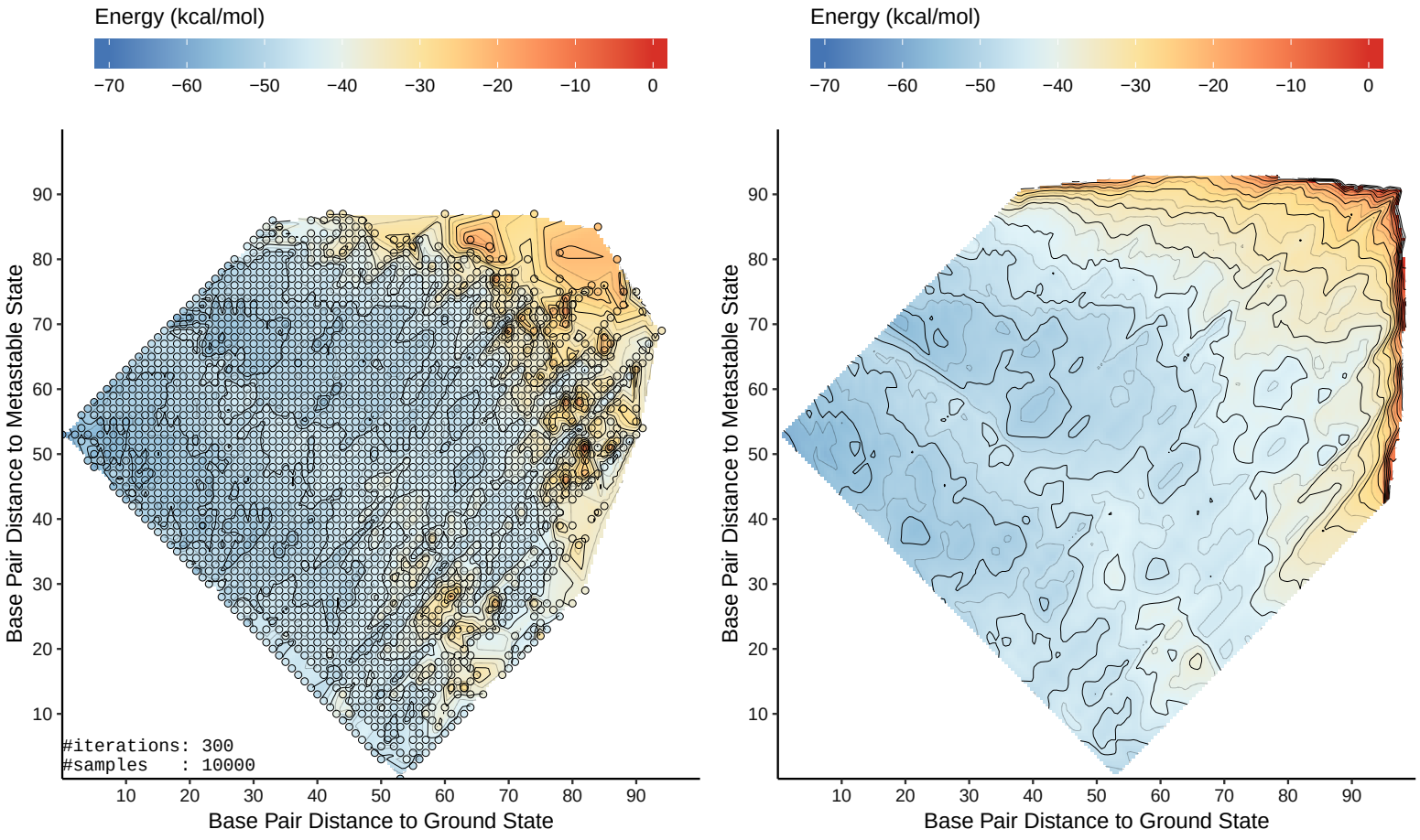
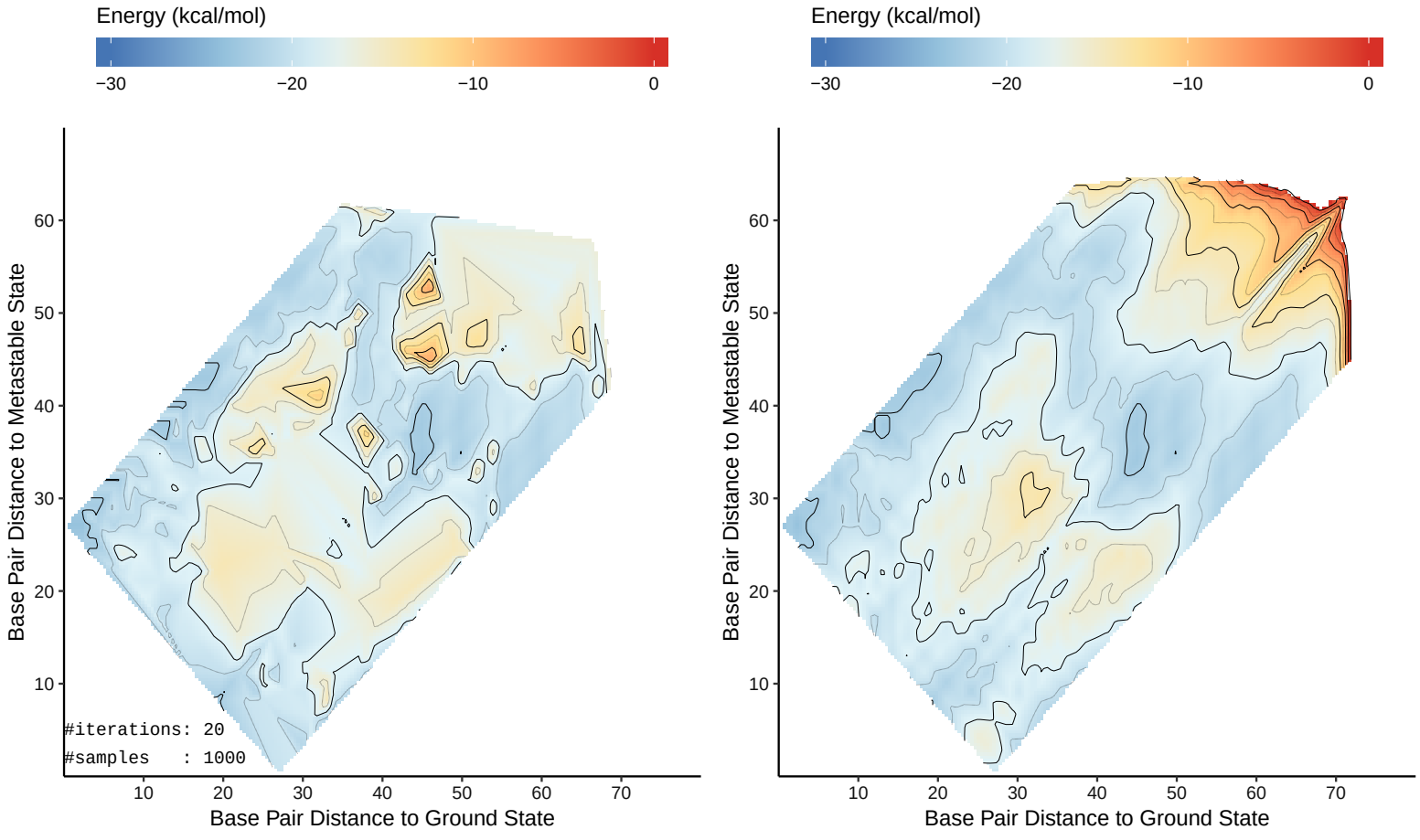


Example: add riboswitch V.culnificus

`RNAxplorer` repulsion scheme Boltzmann sampling



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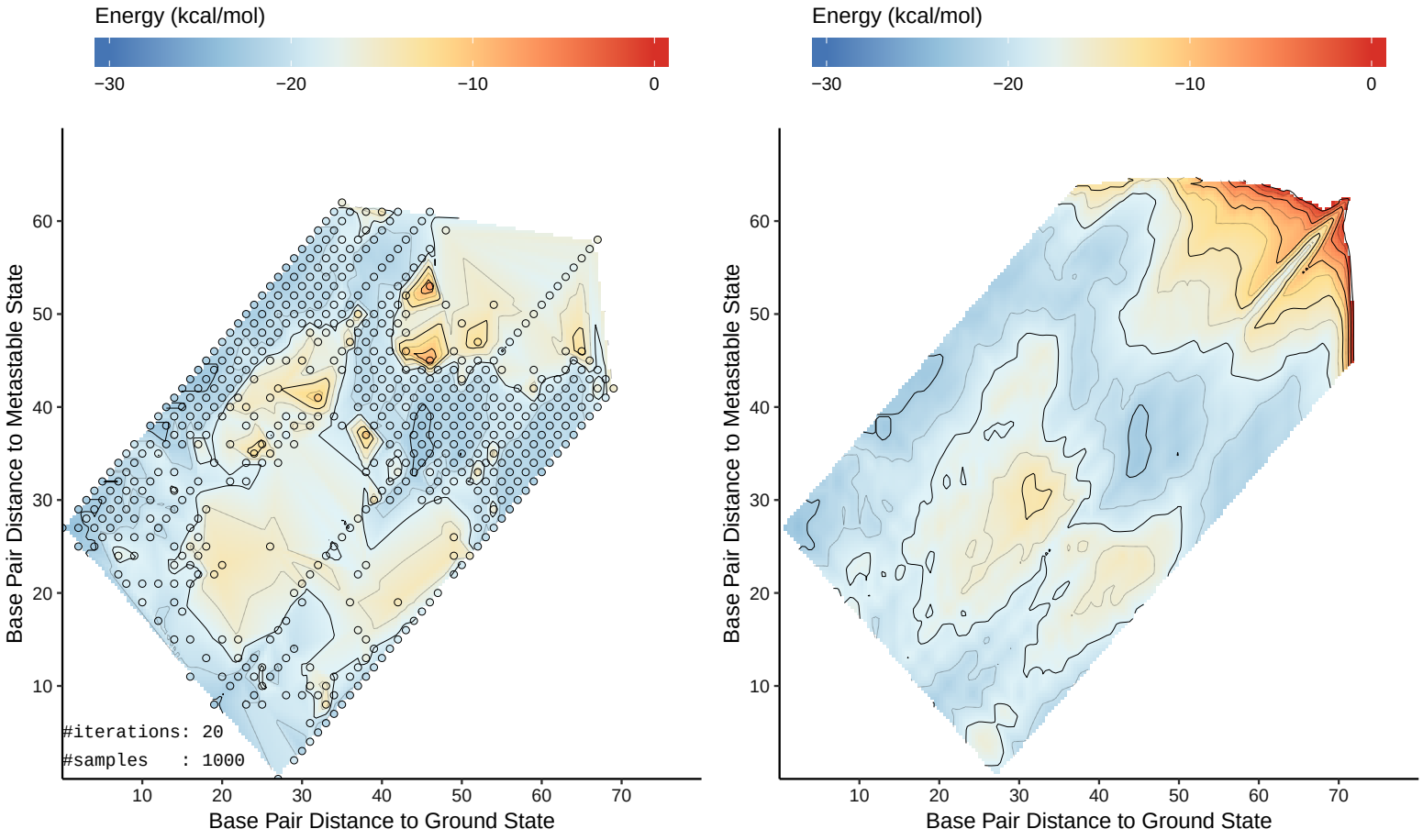

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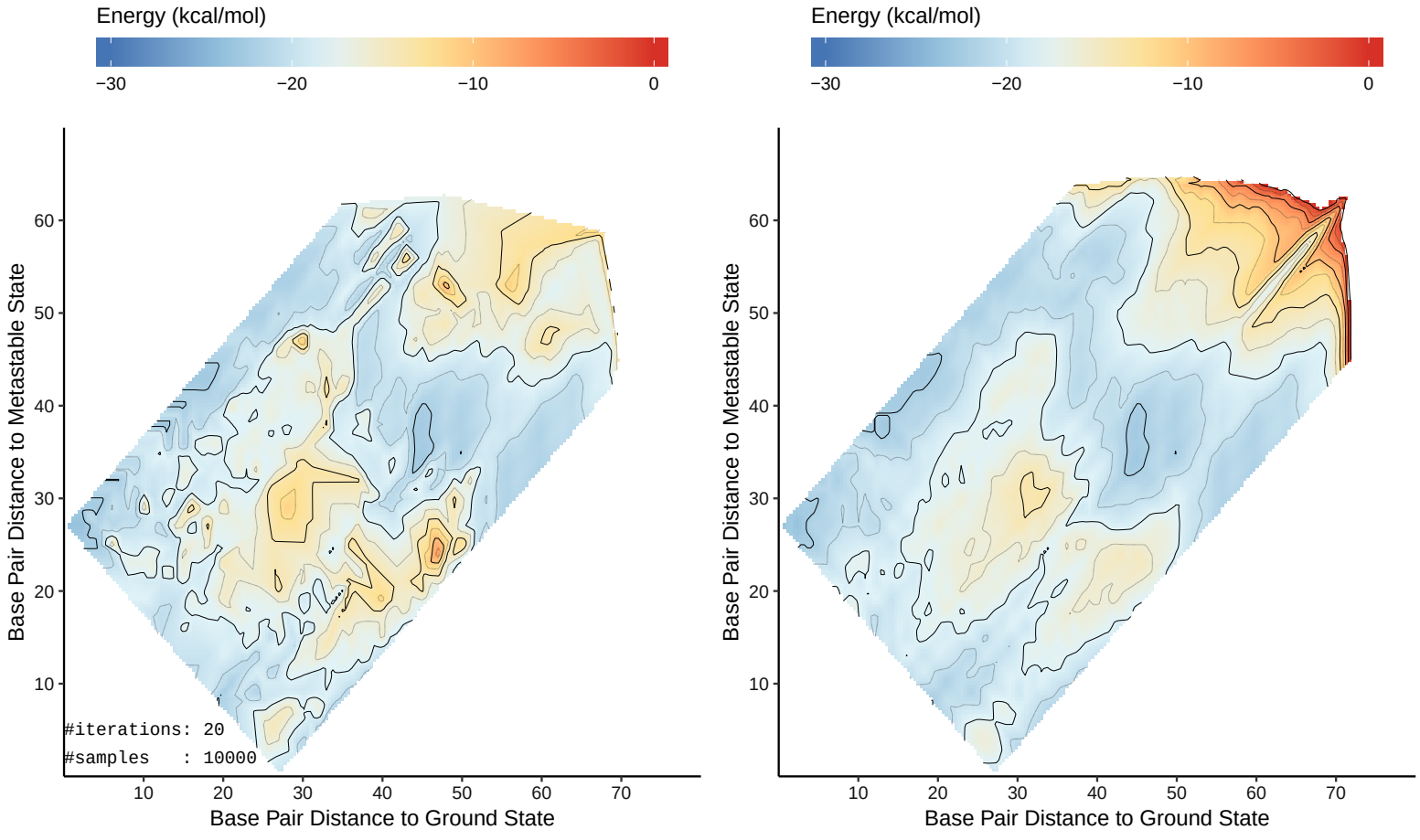

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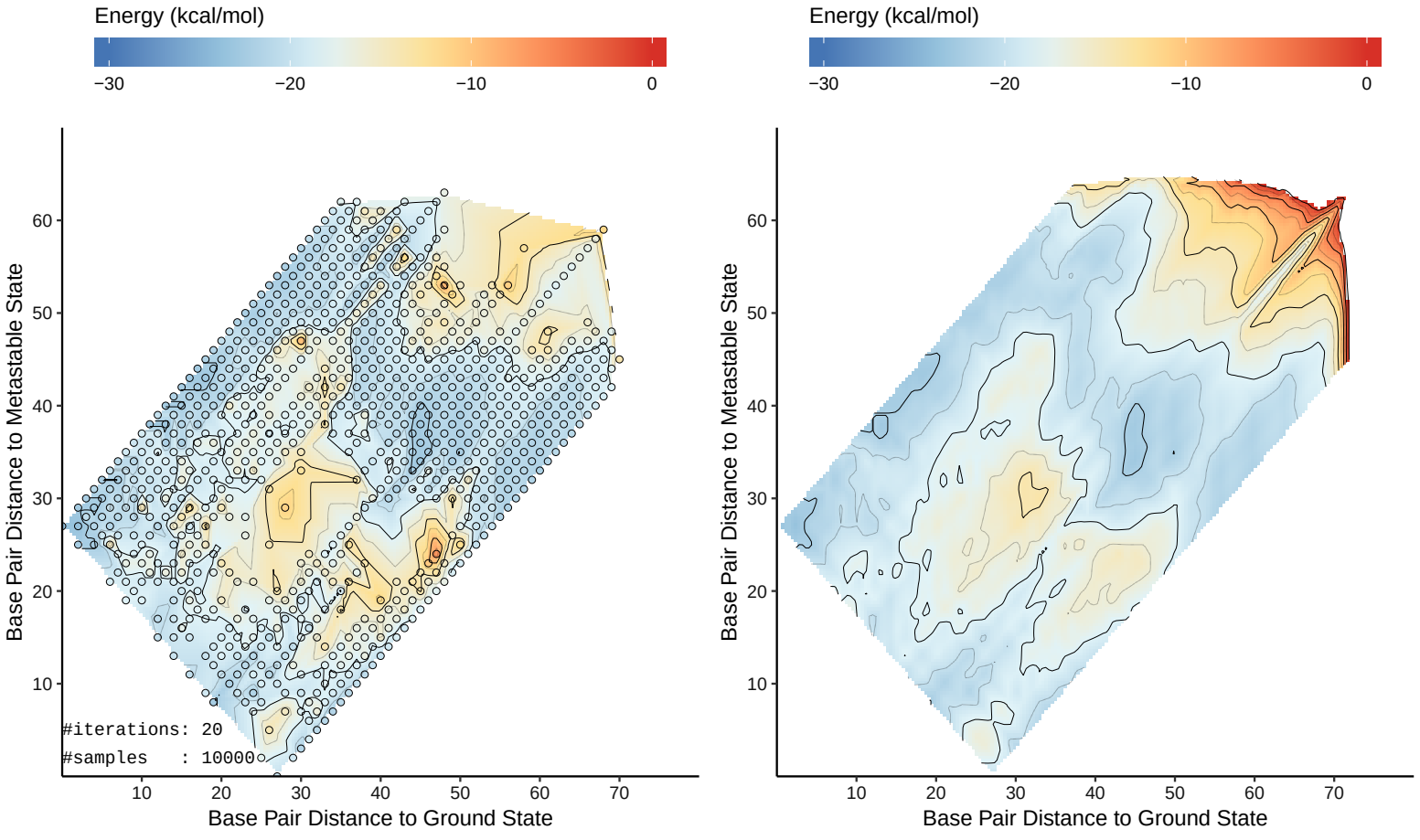

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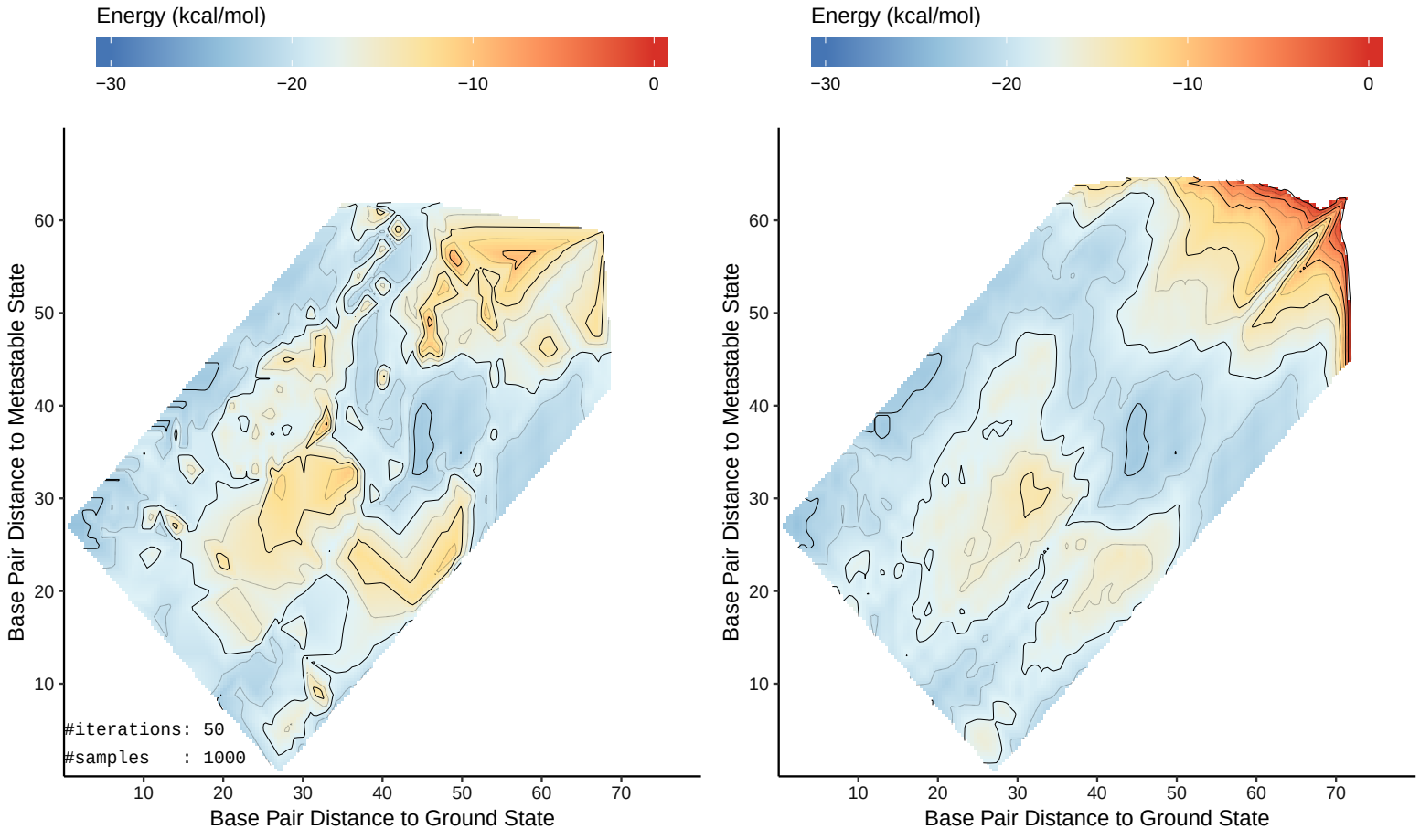

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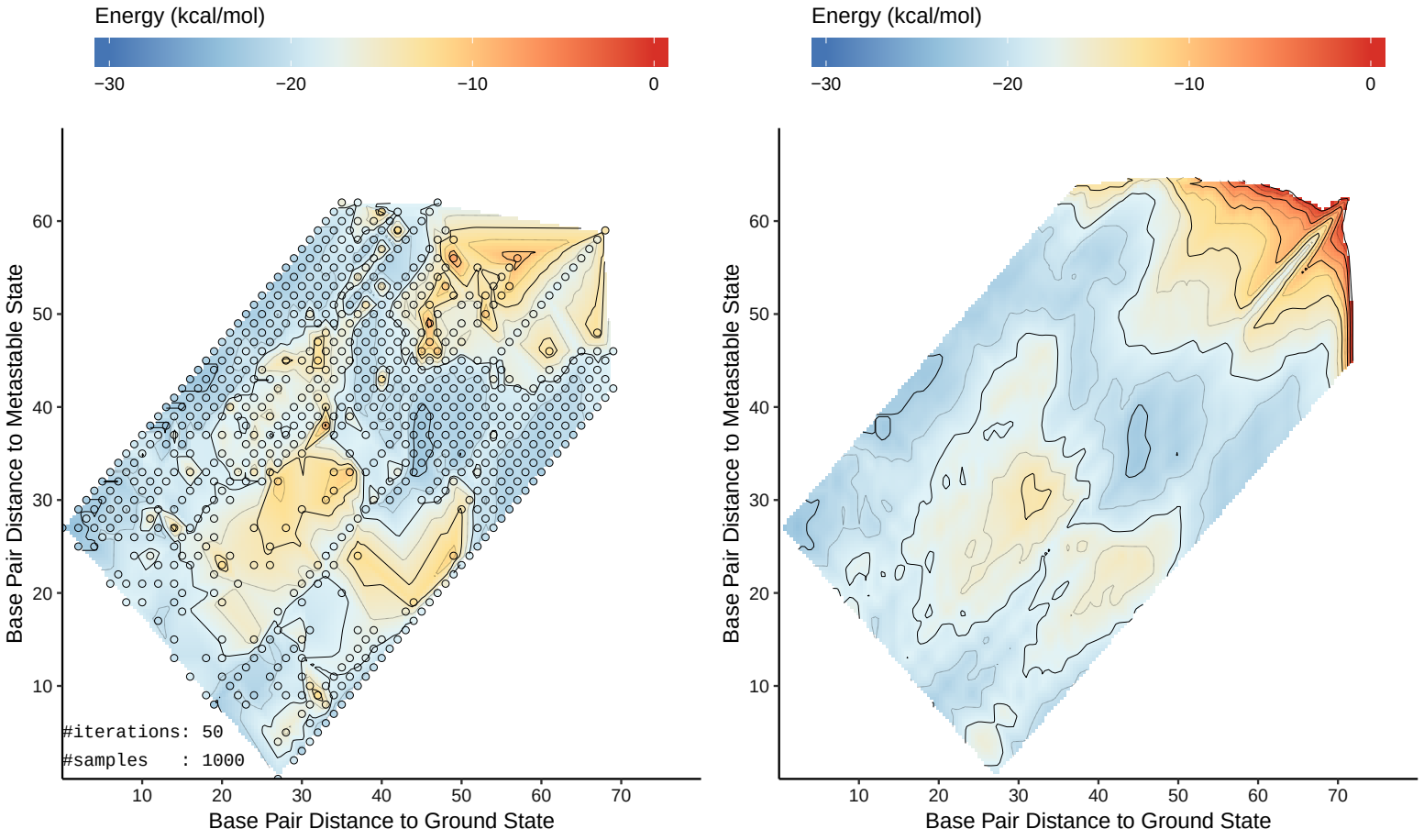

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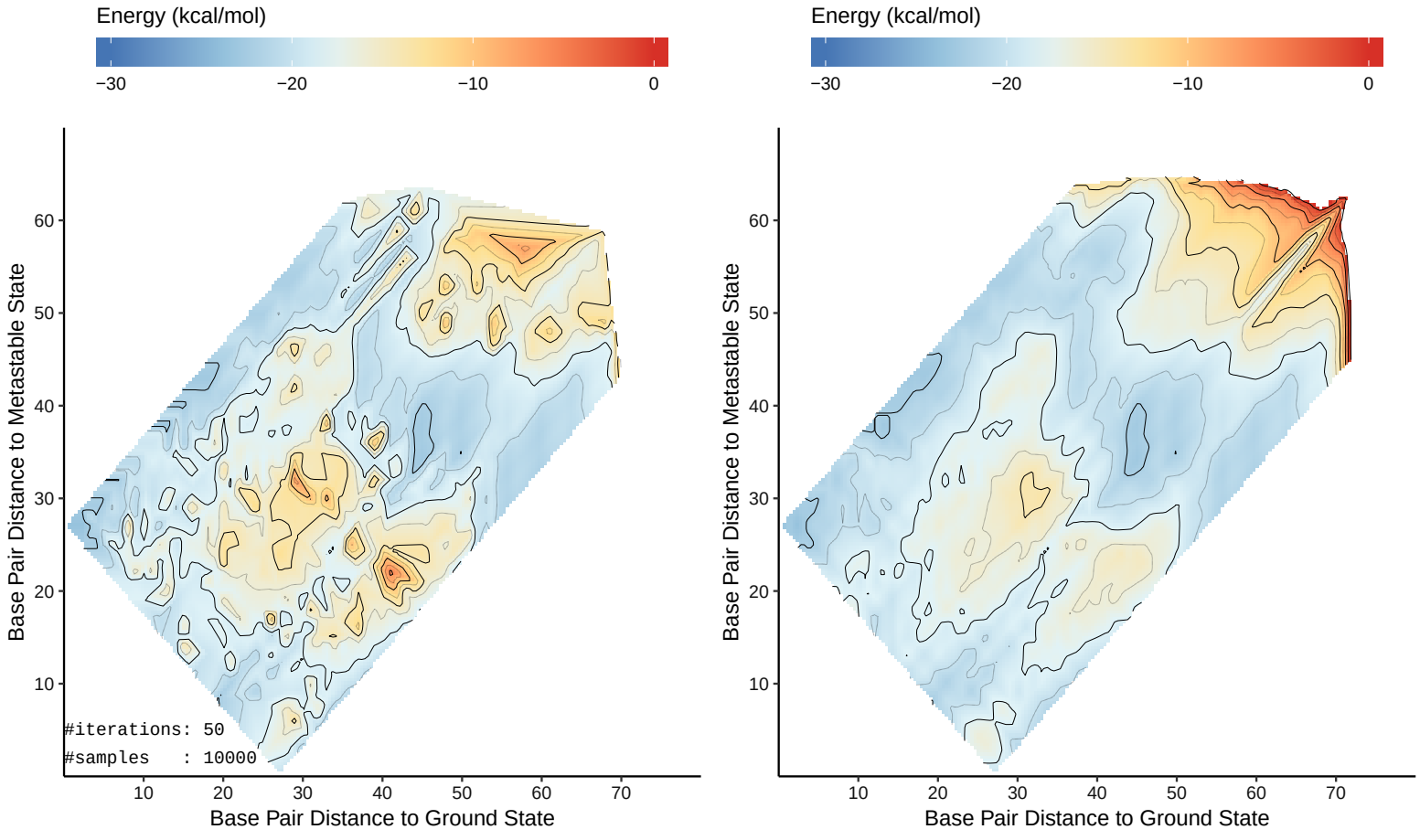
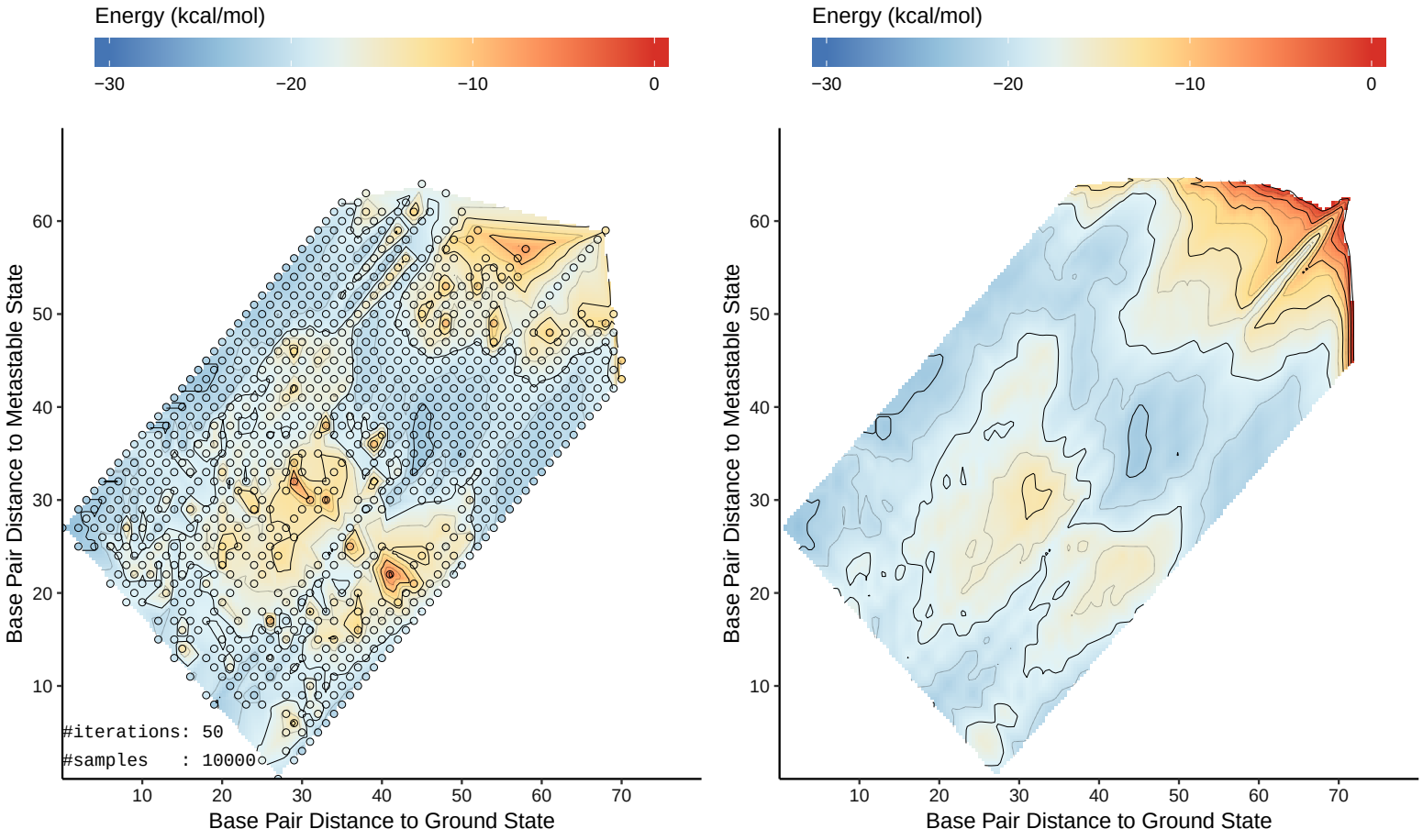


Example: add riboswitch V.culnificus

`RNAxplorer` repulsion scheme Boltzmann sampling



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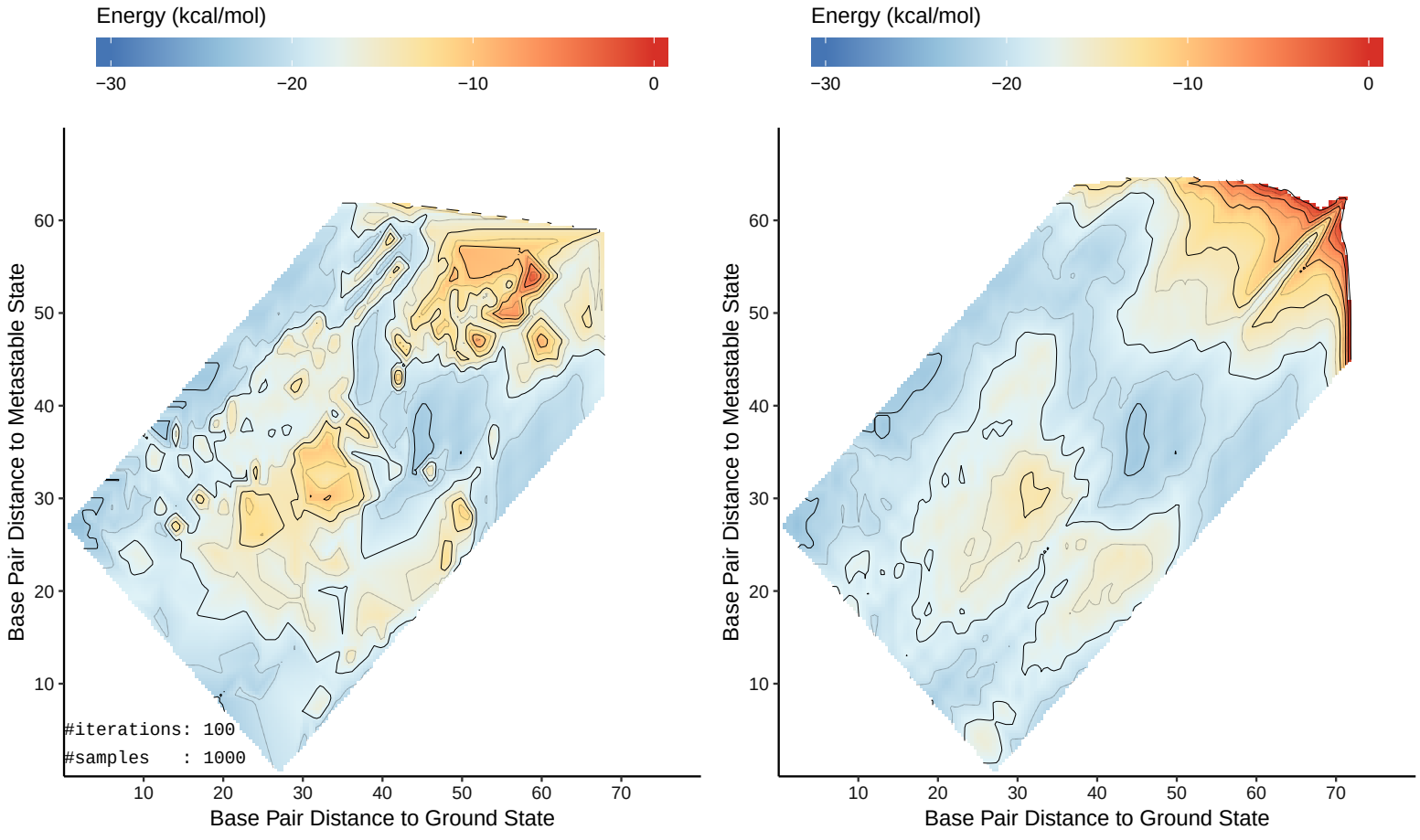
`RNAxplorer` repulsion scheme Boltzmann sampling



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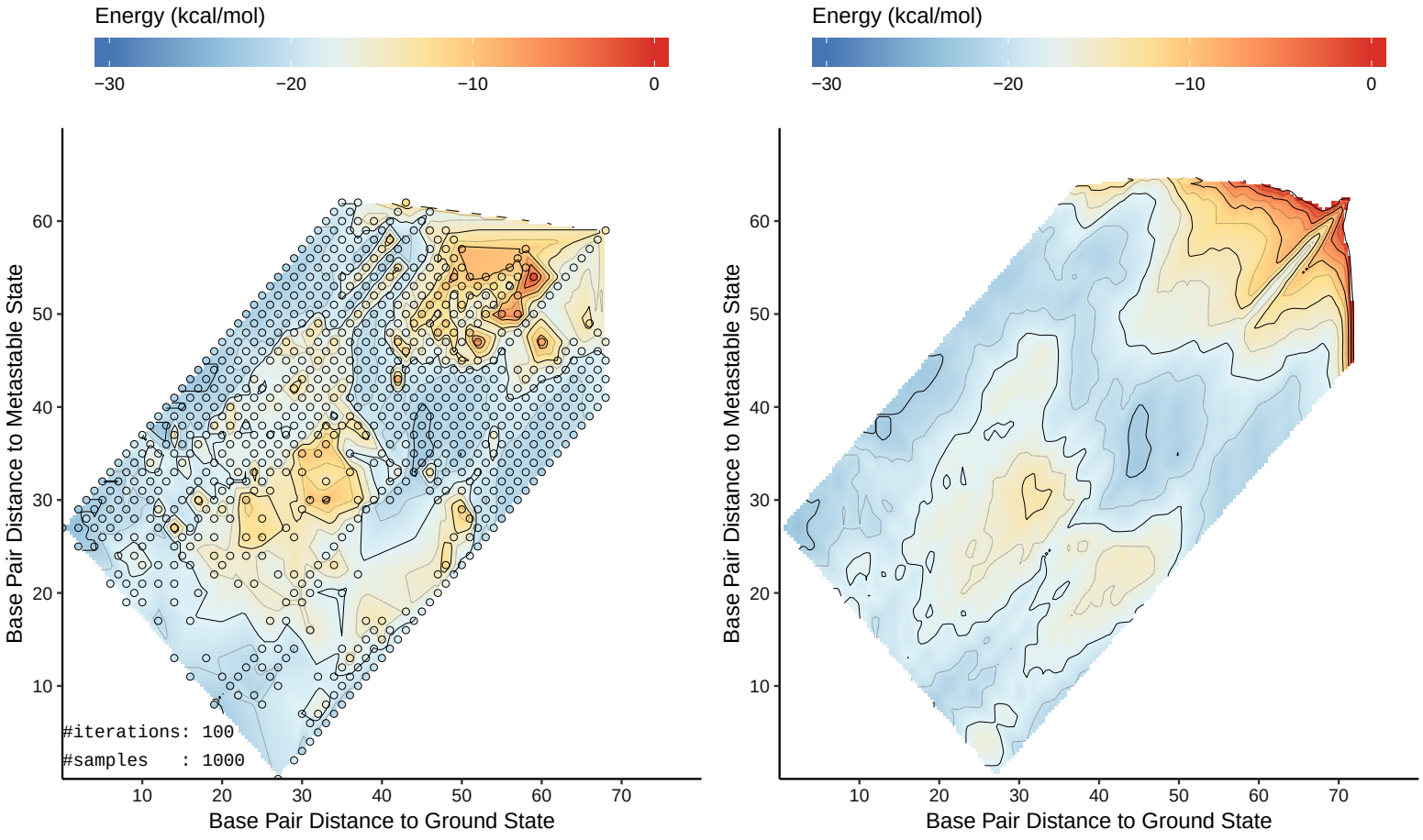

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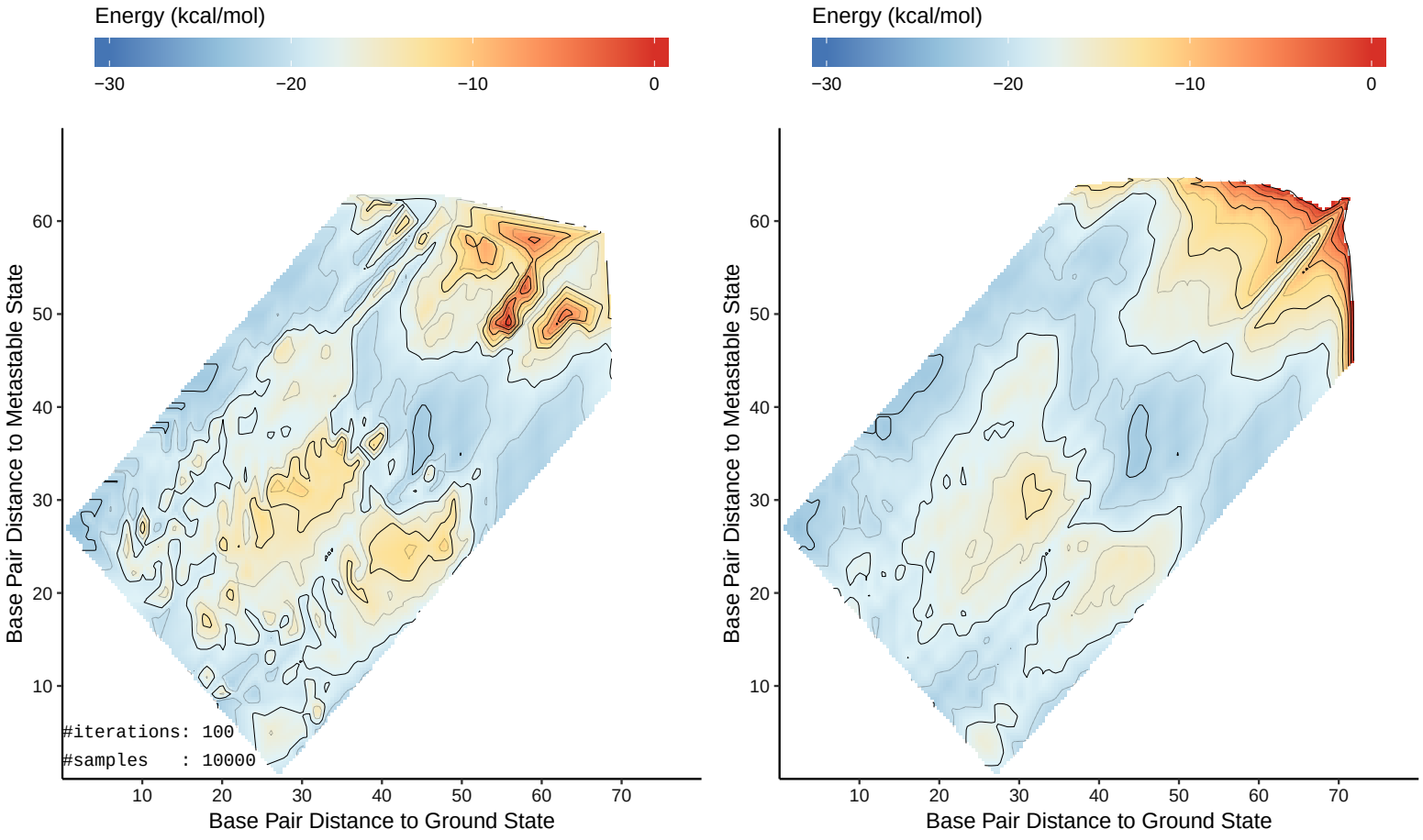

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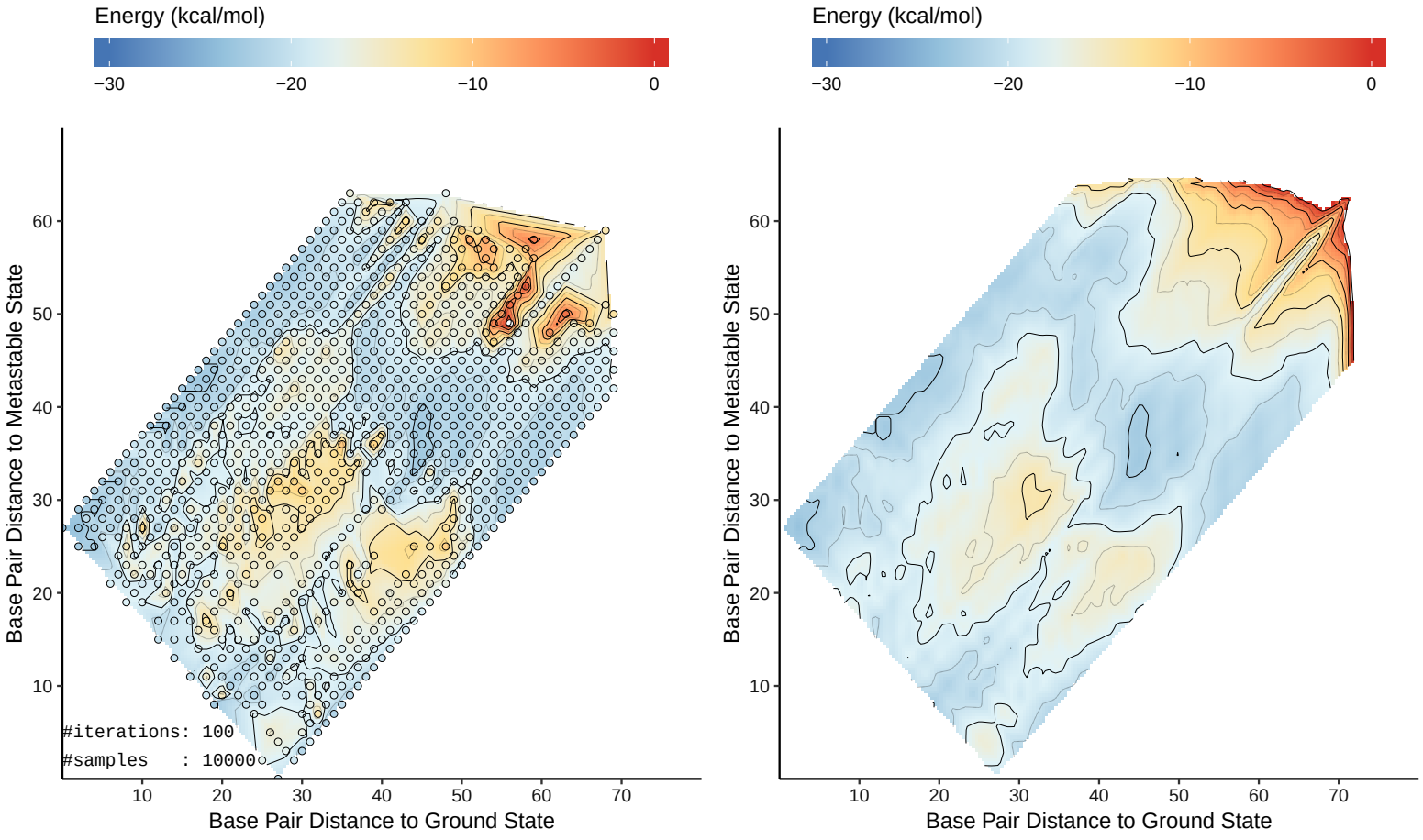

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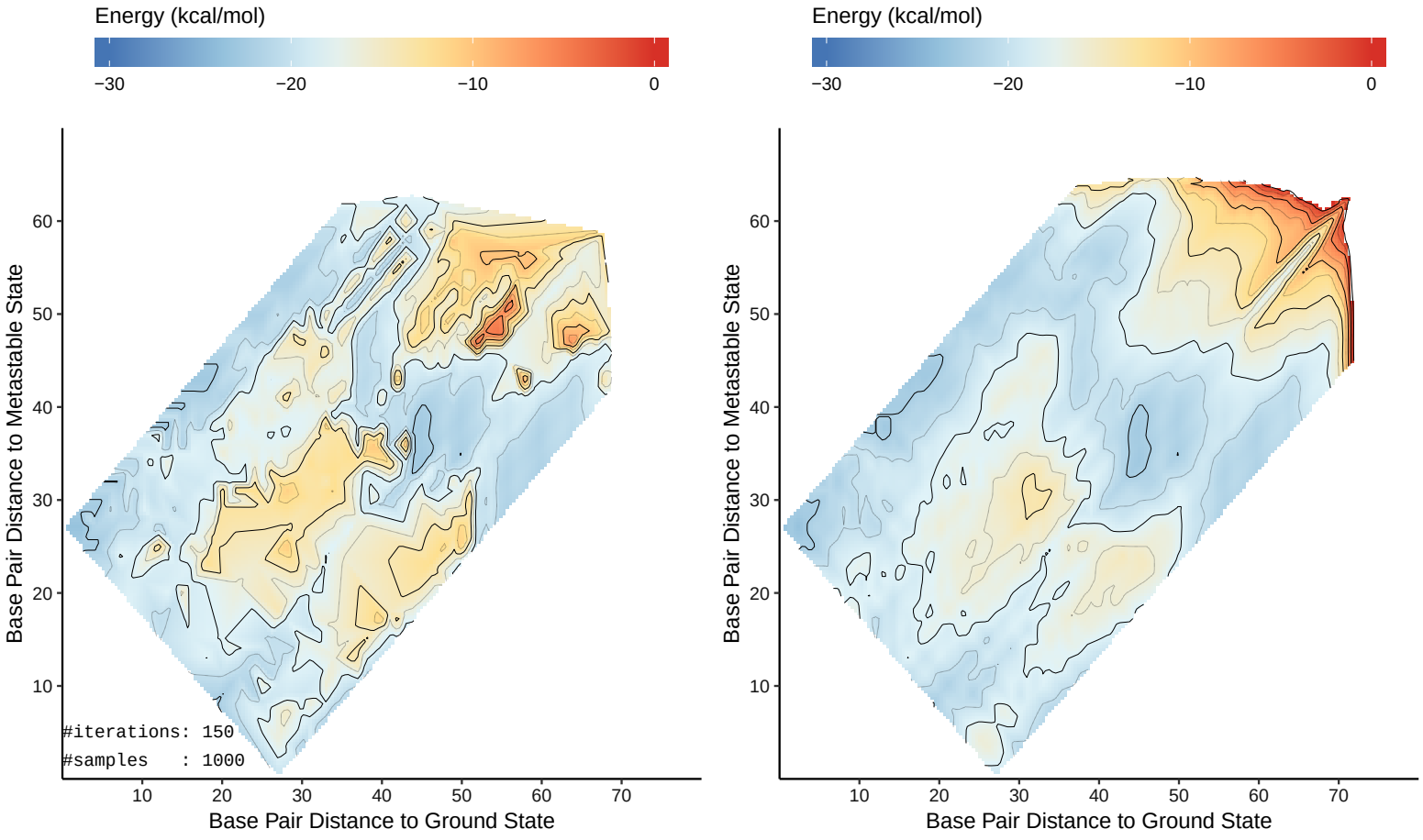

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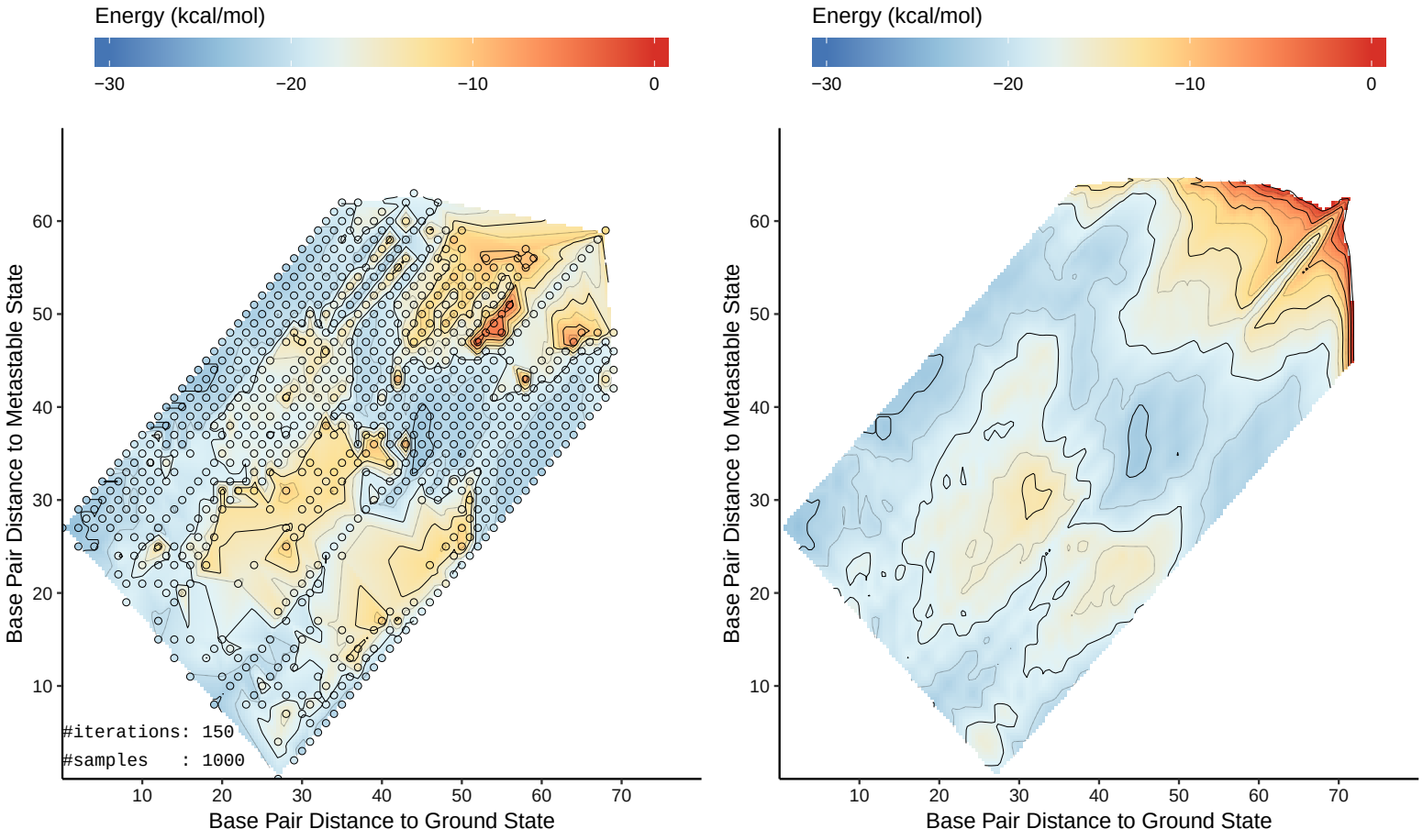

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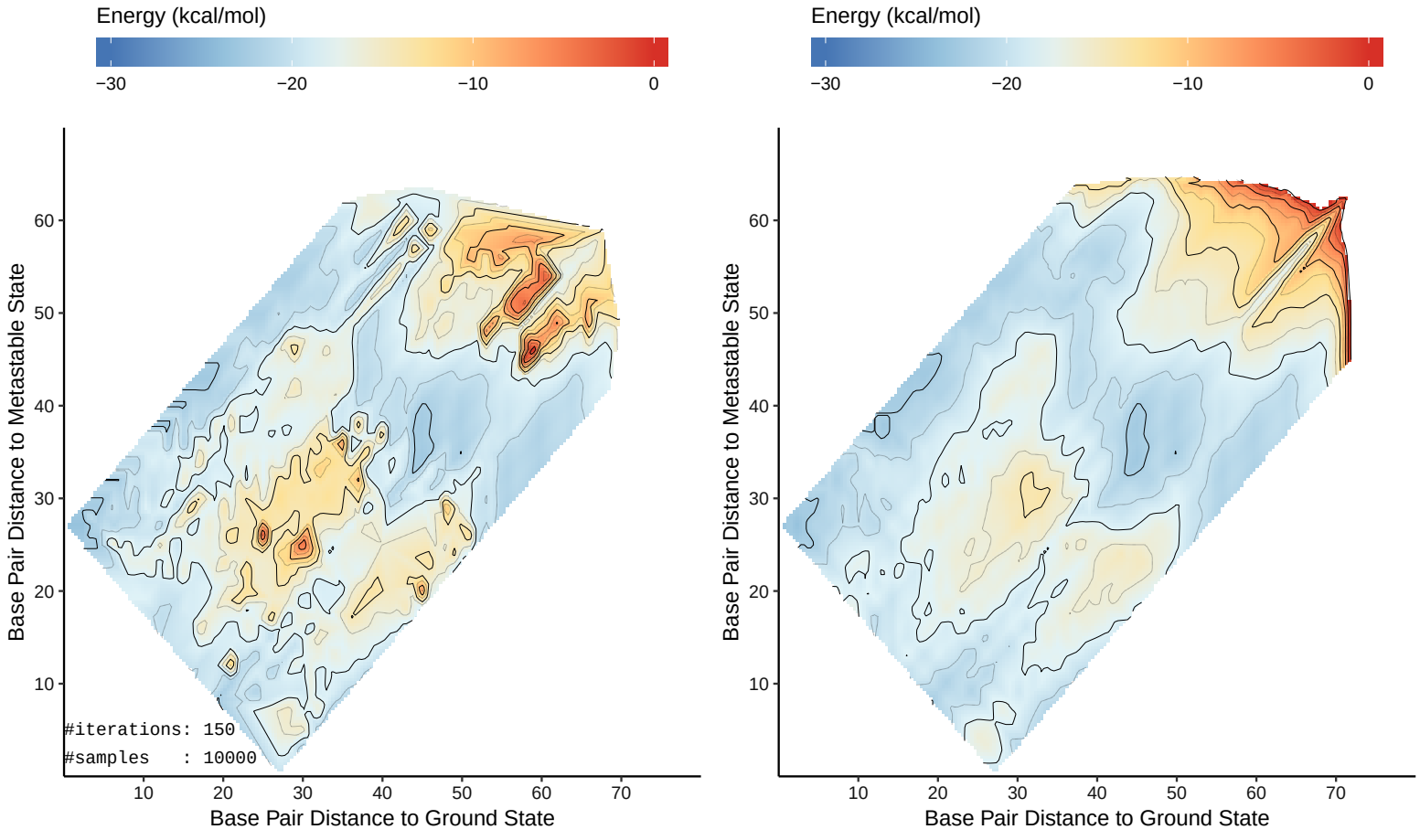

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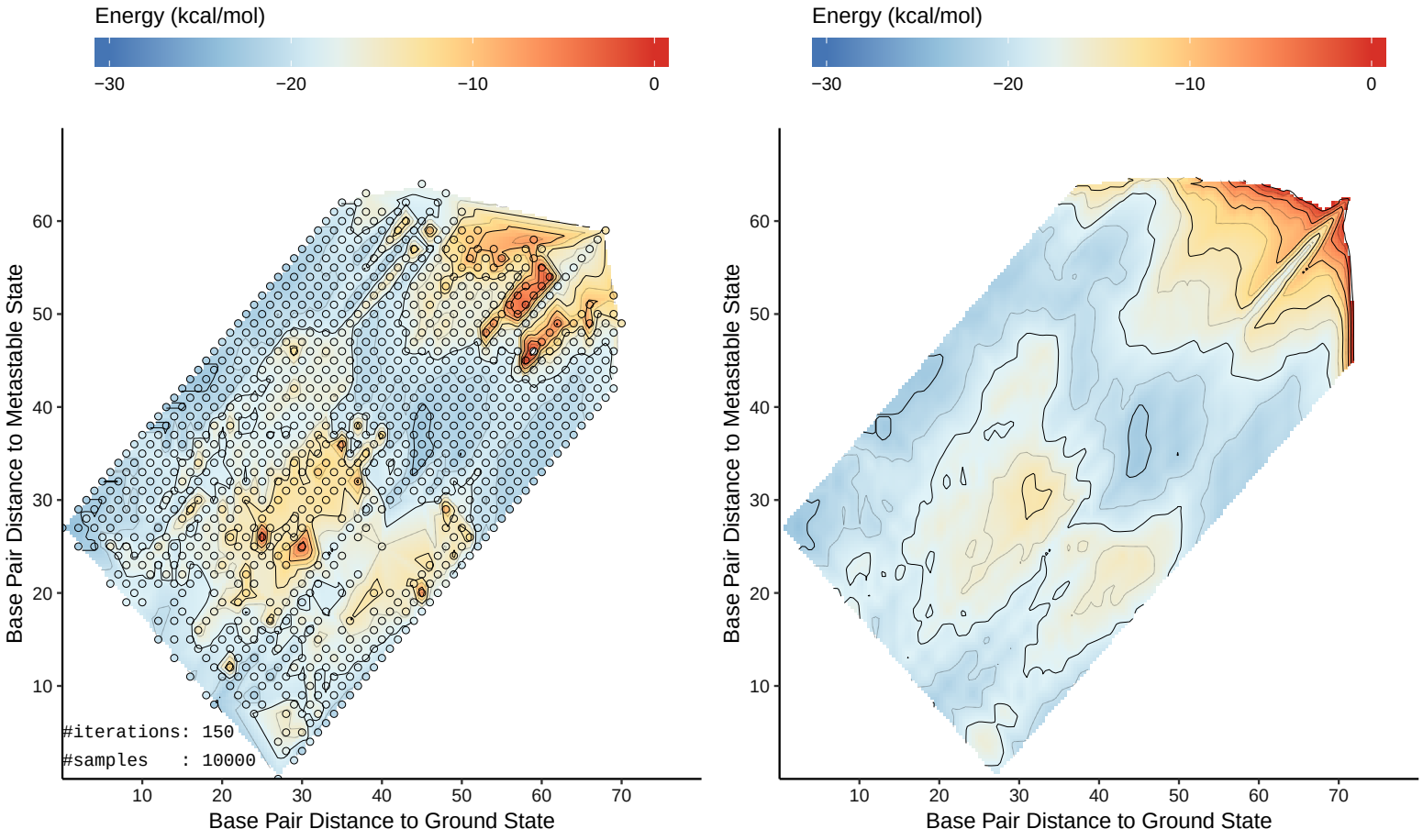

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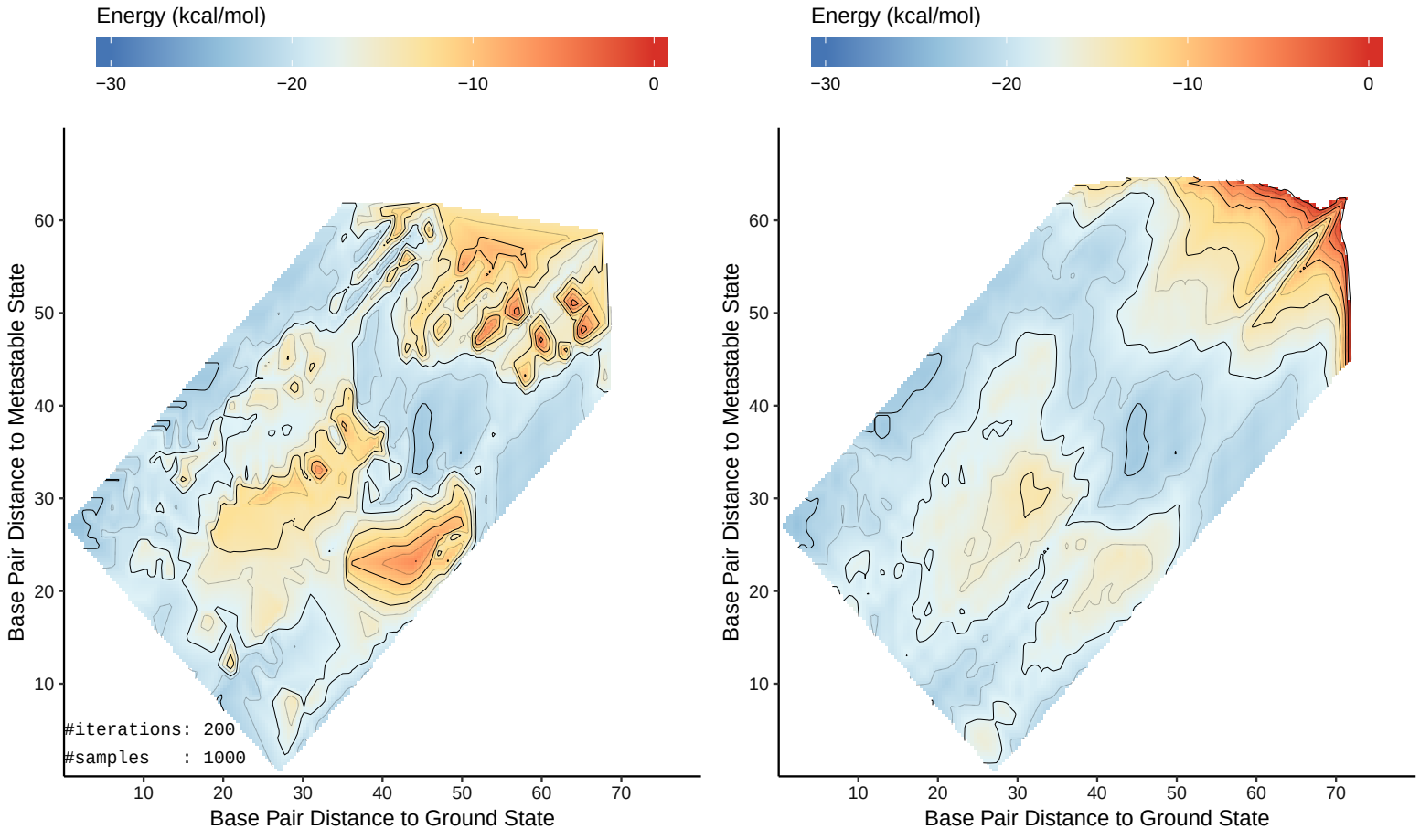
`RNAxplorer` repulsion scheme Boltzmann sampling



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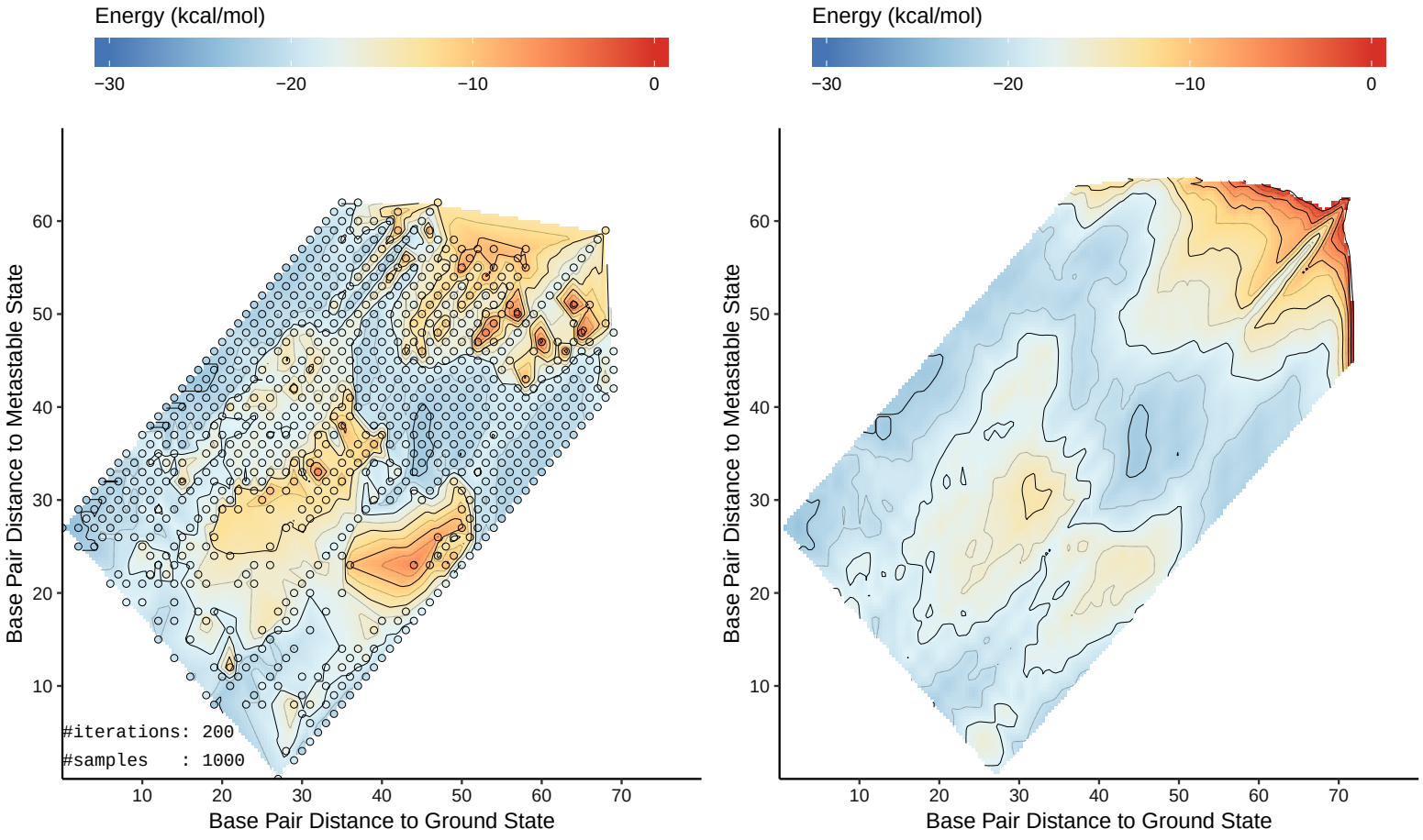

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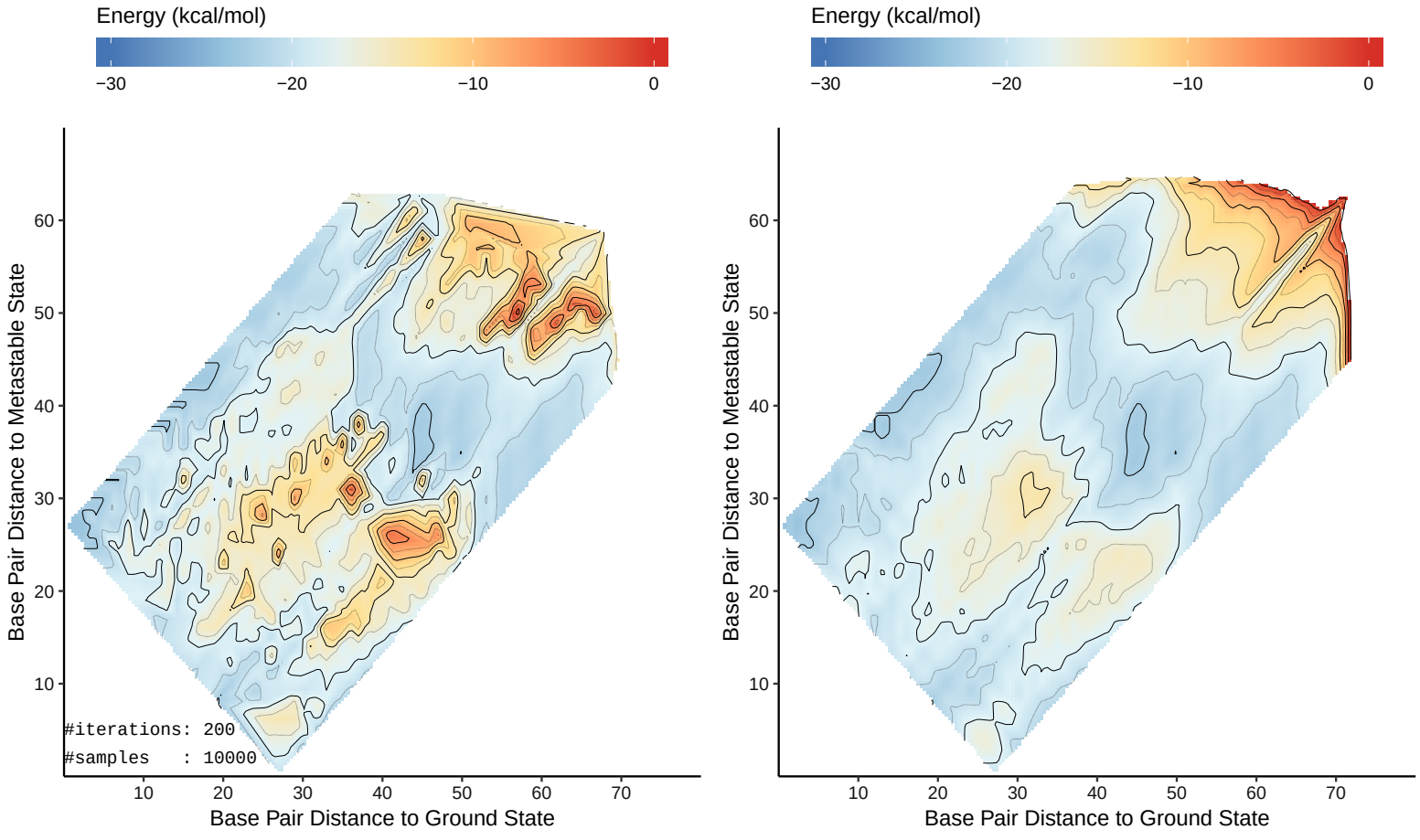

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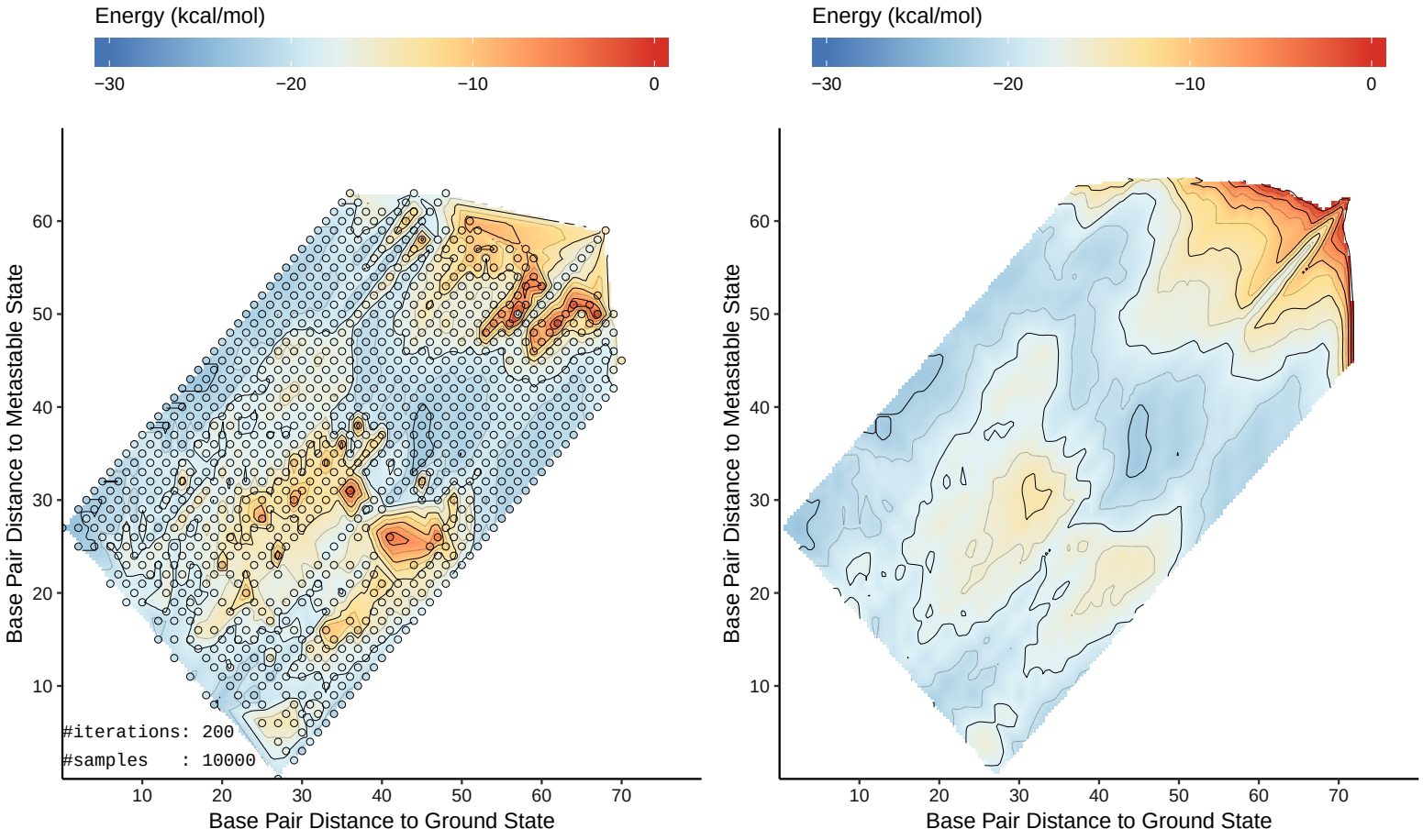

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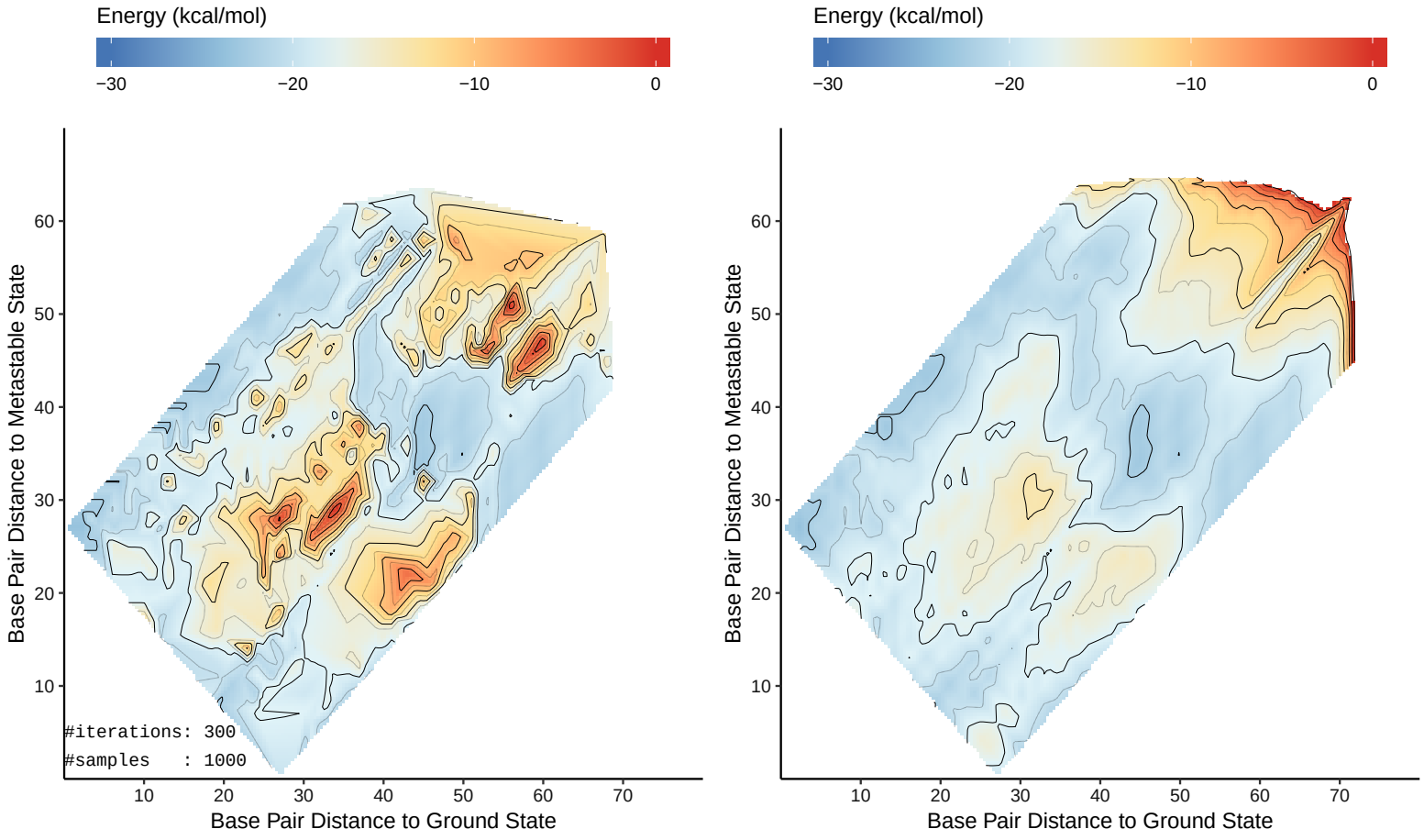

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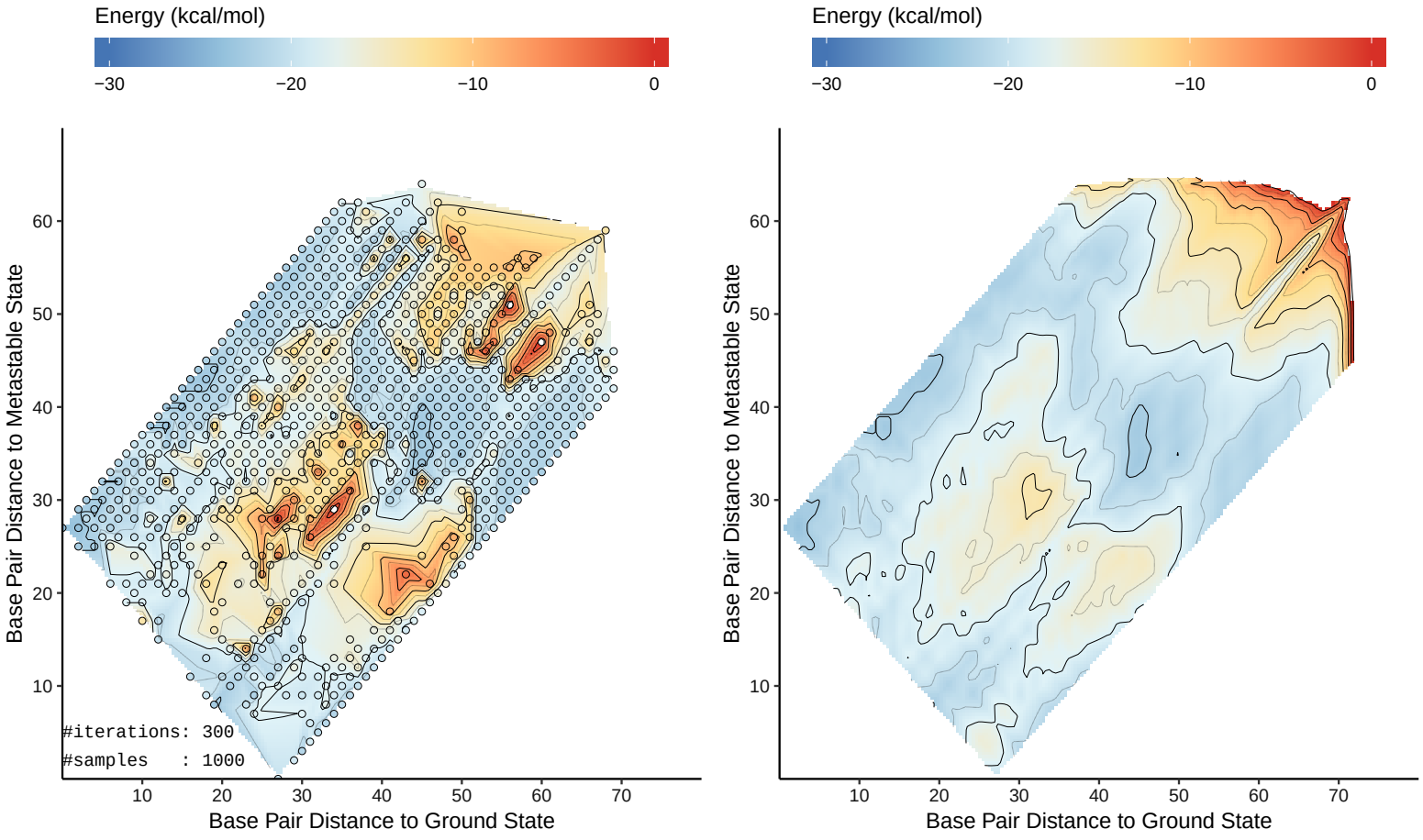

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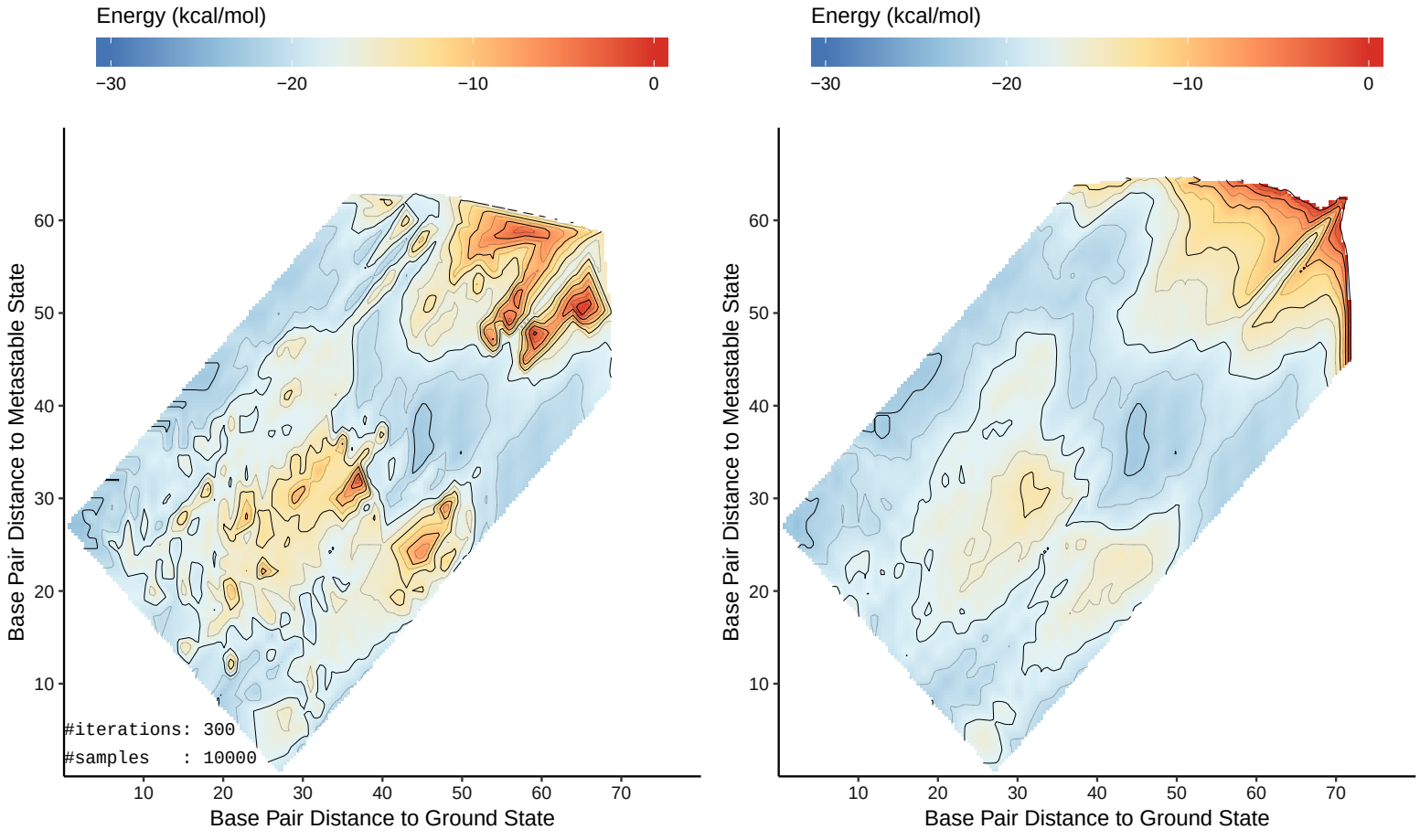

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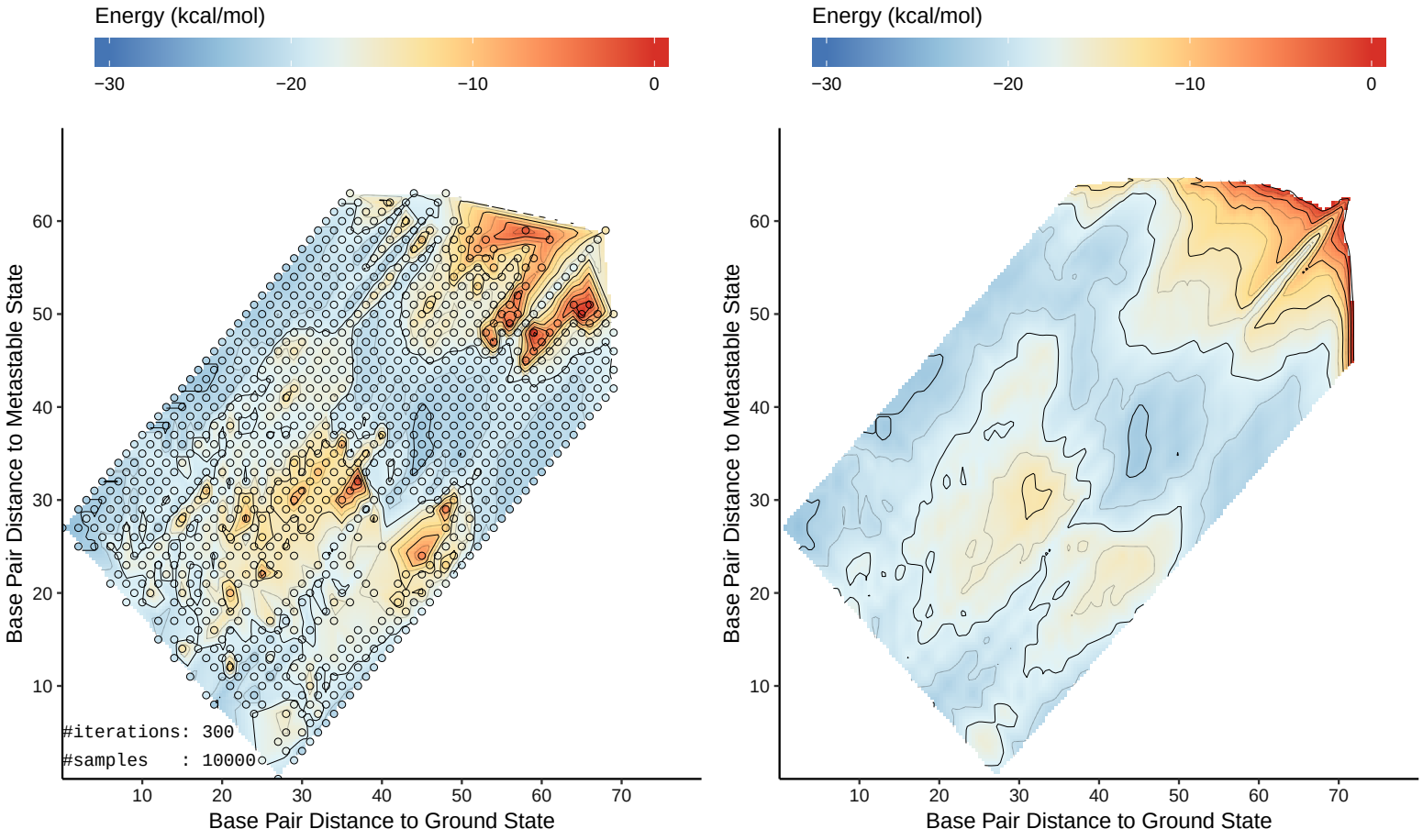
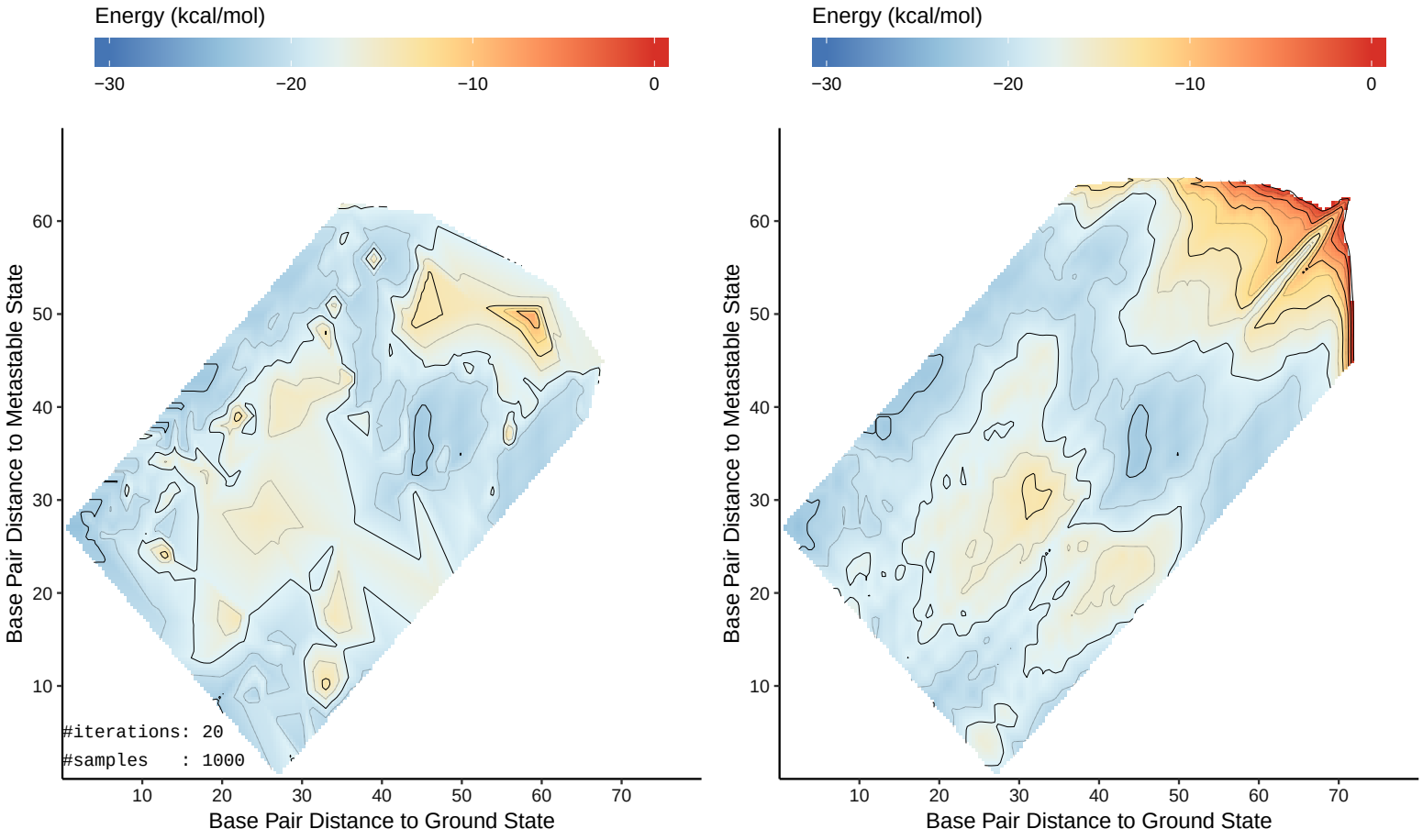


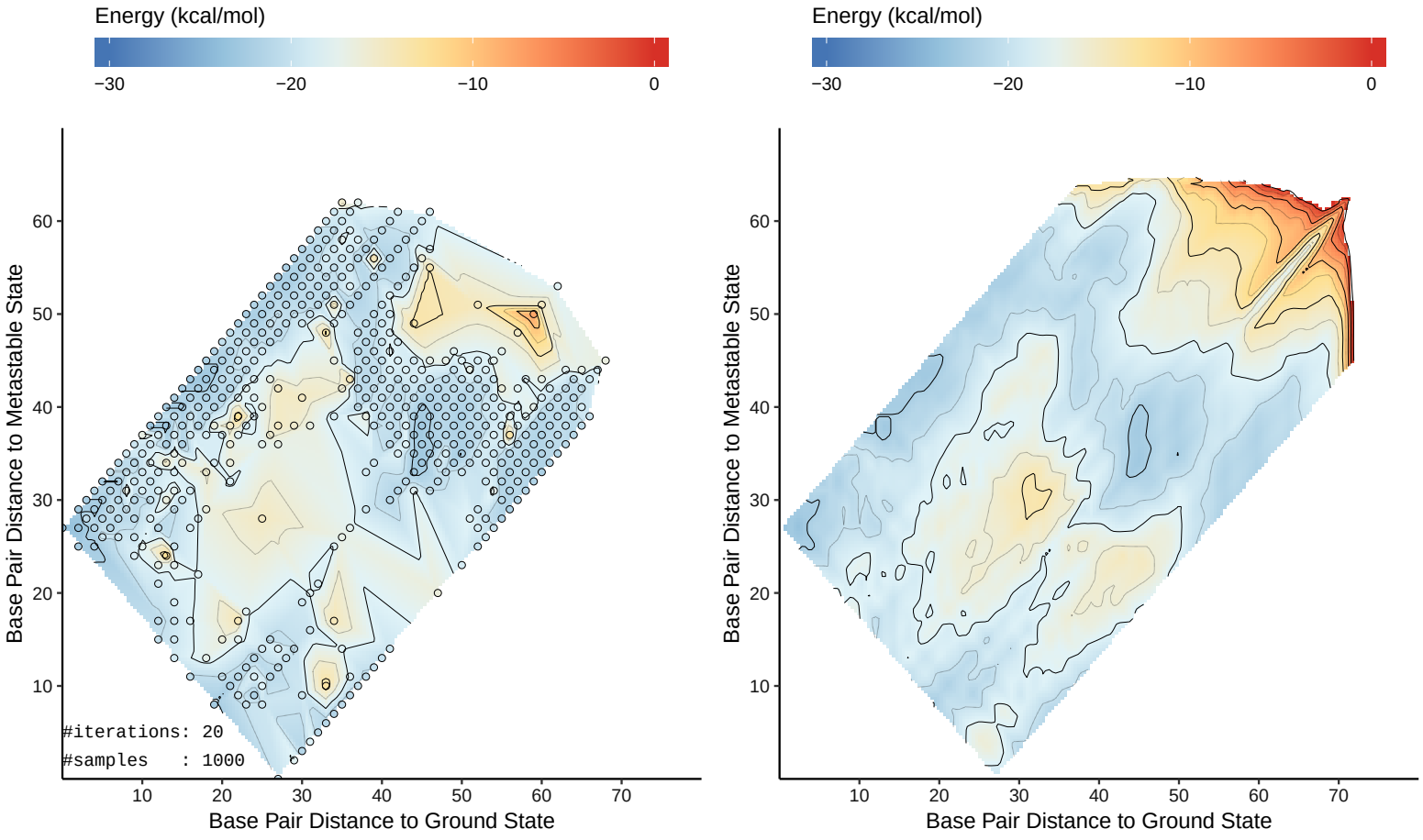
Example: add riboswitch V.culnificus

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



Example: add riboswitch V.culnificus

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



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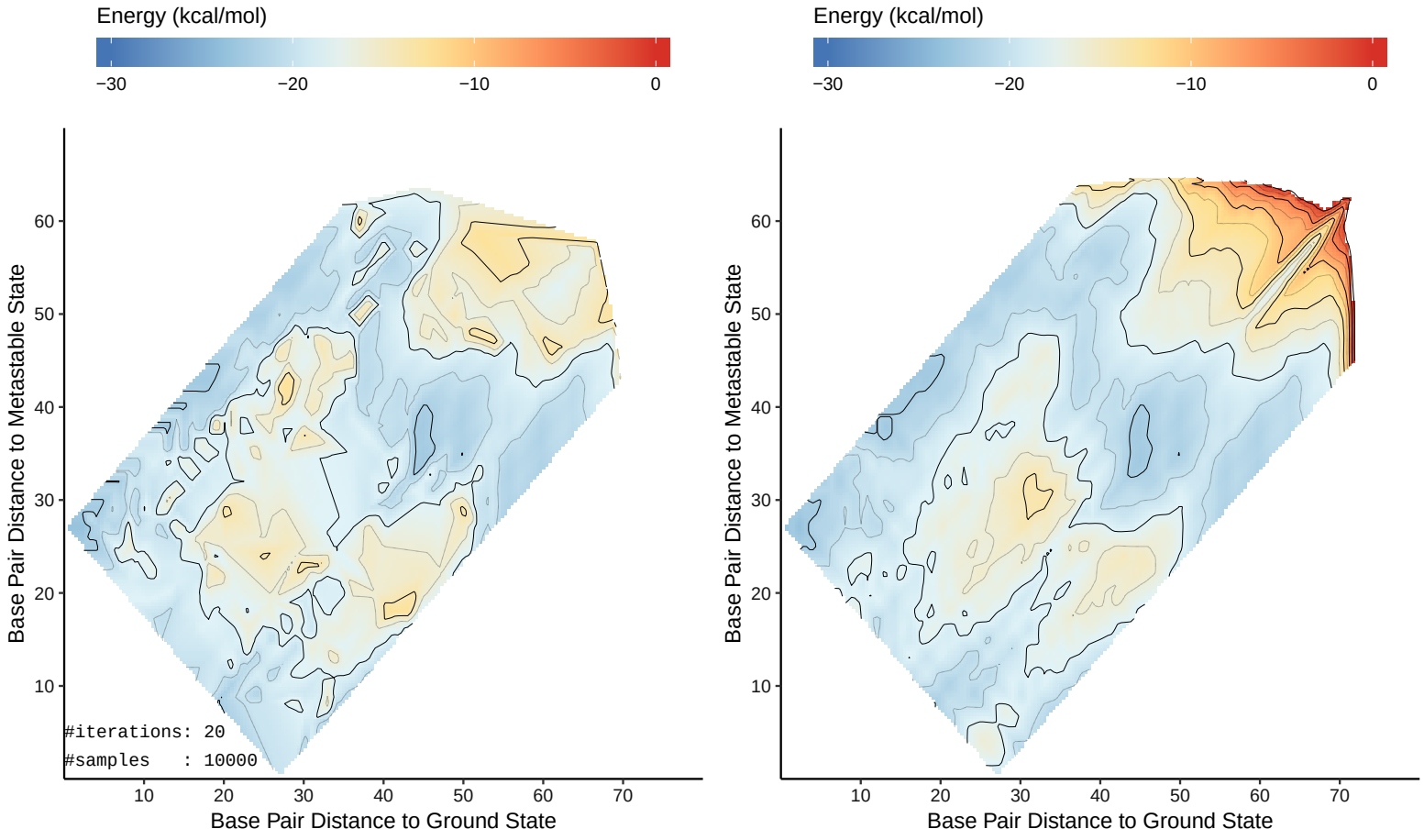
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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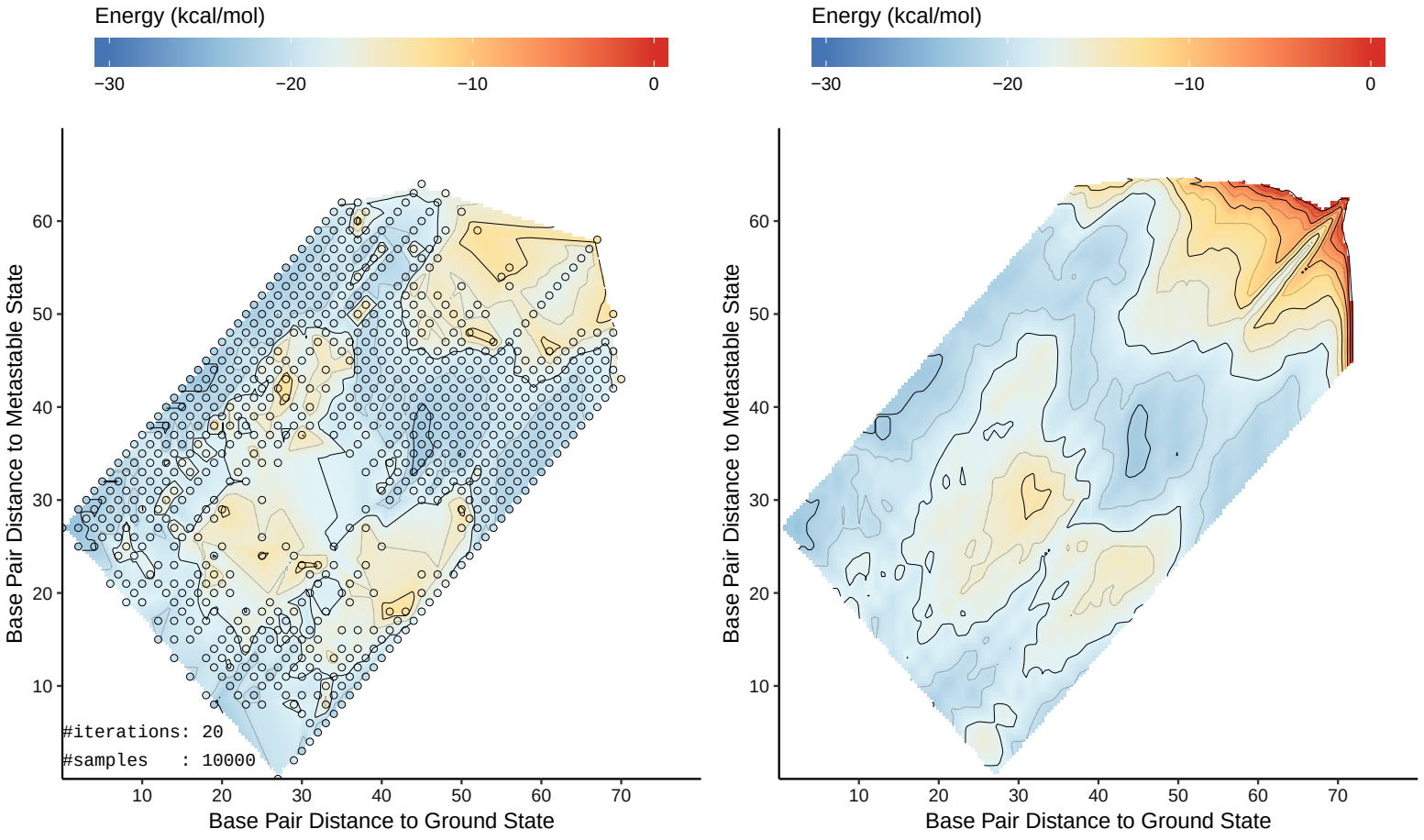
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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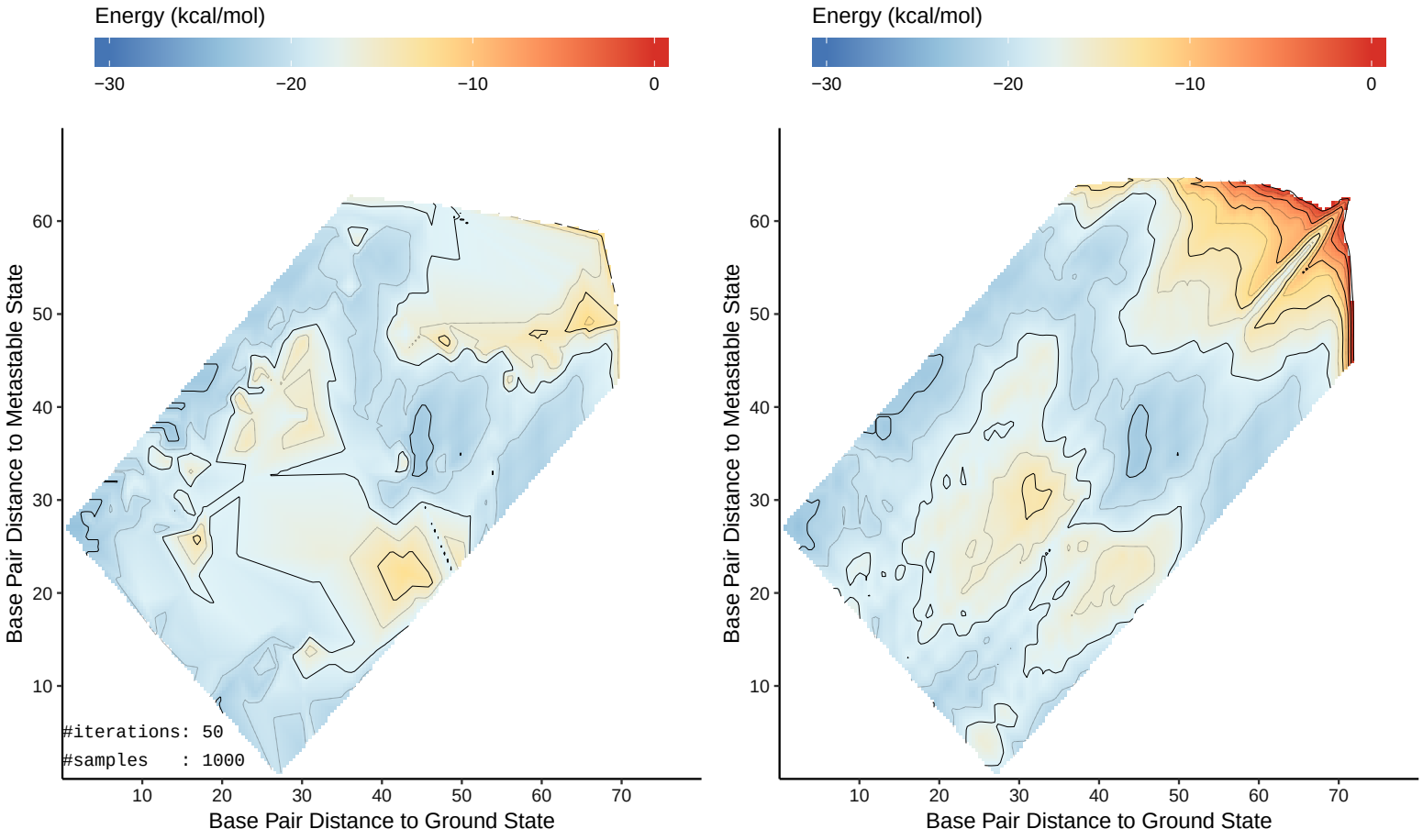
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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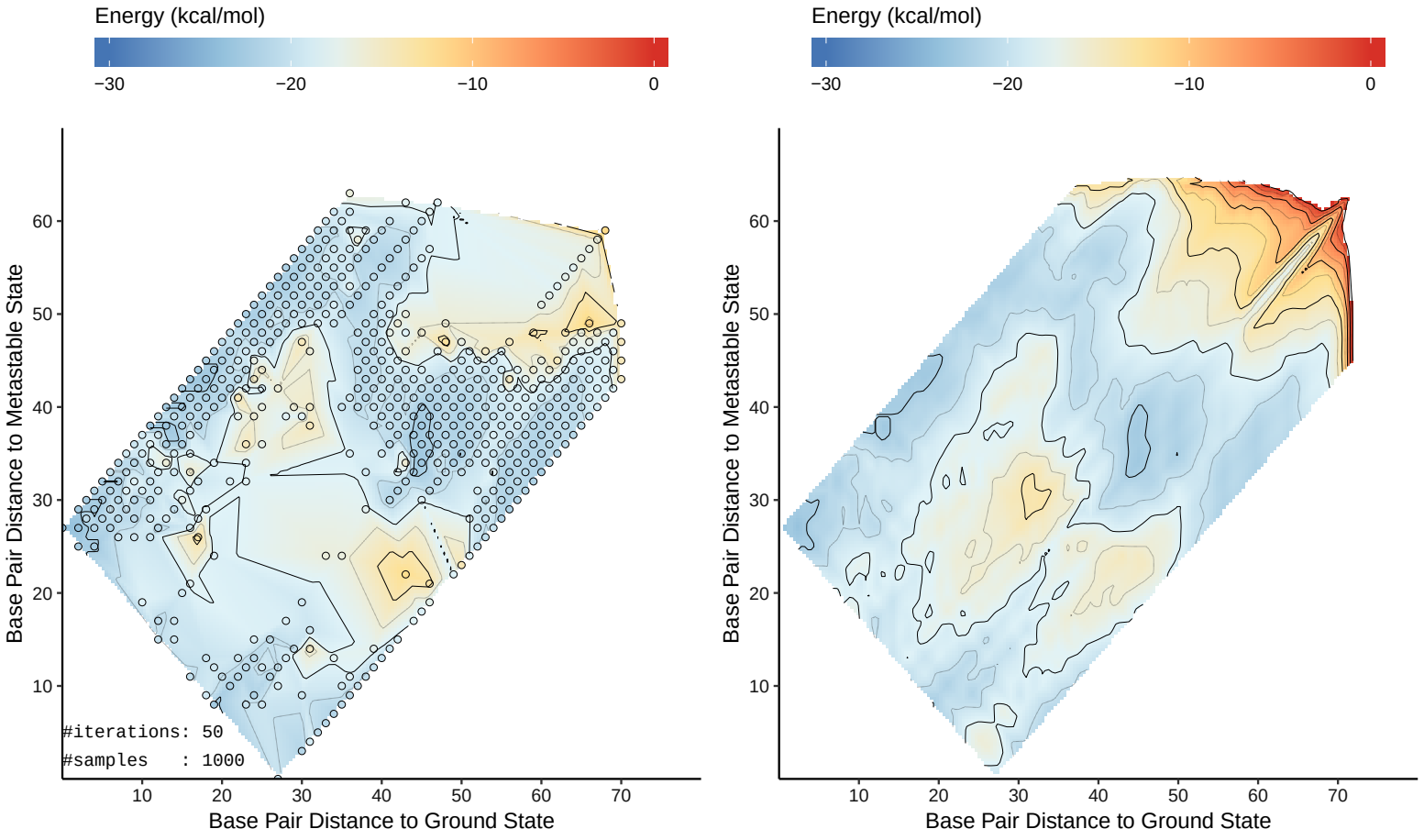

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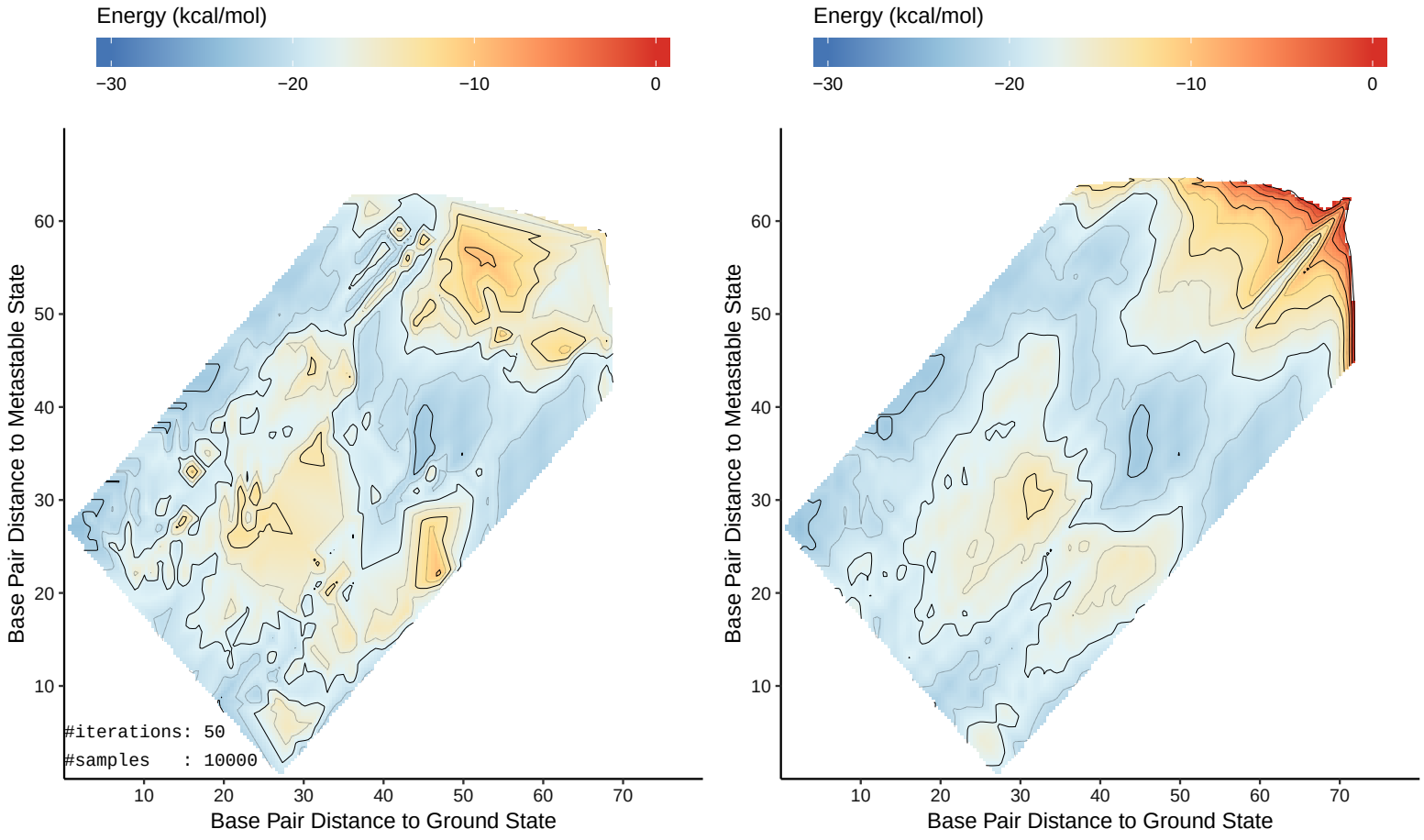

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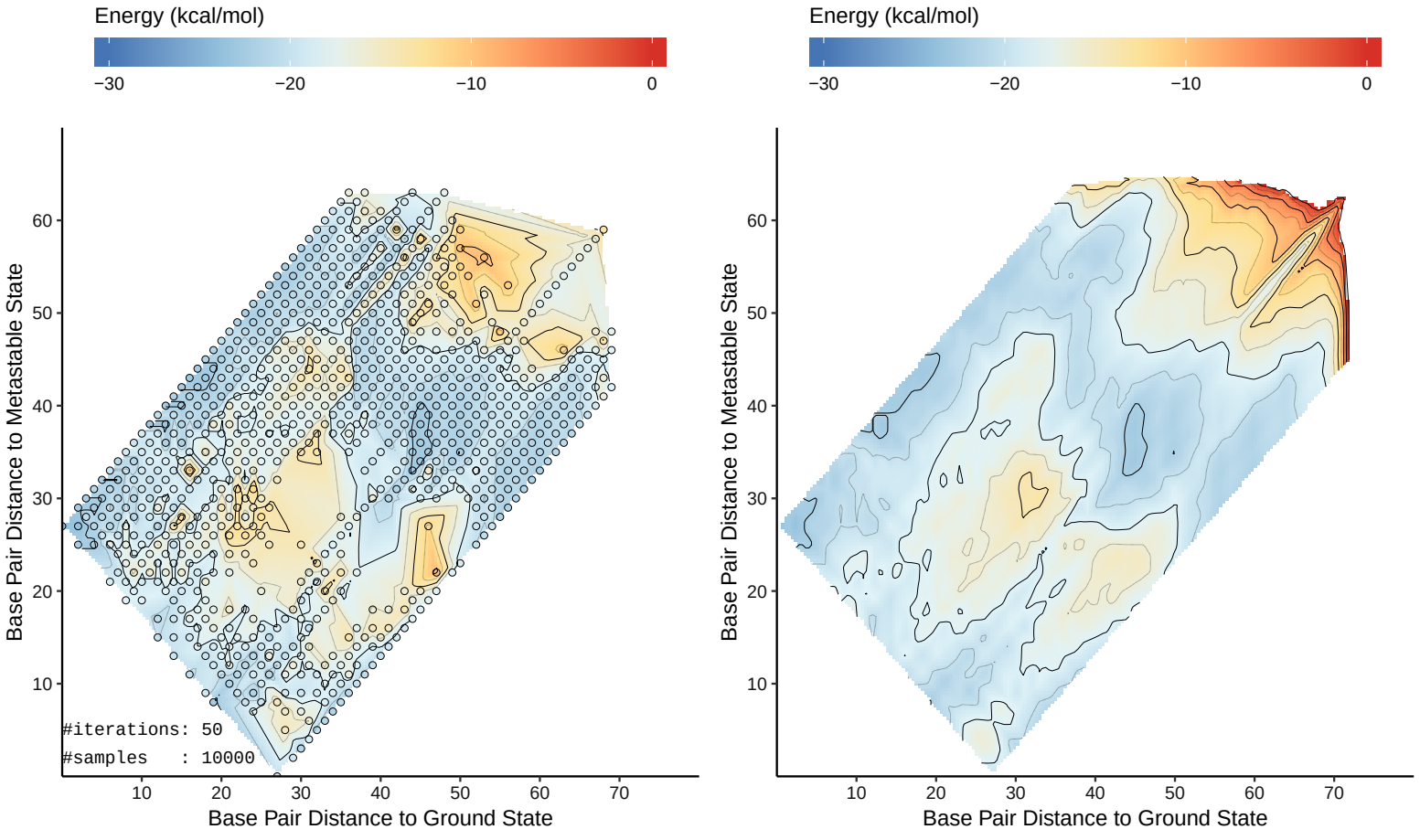
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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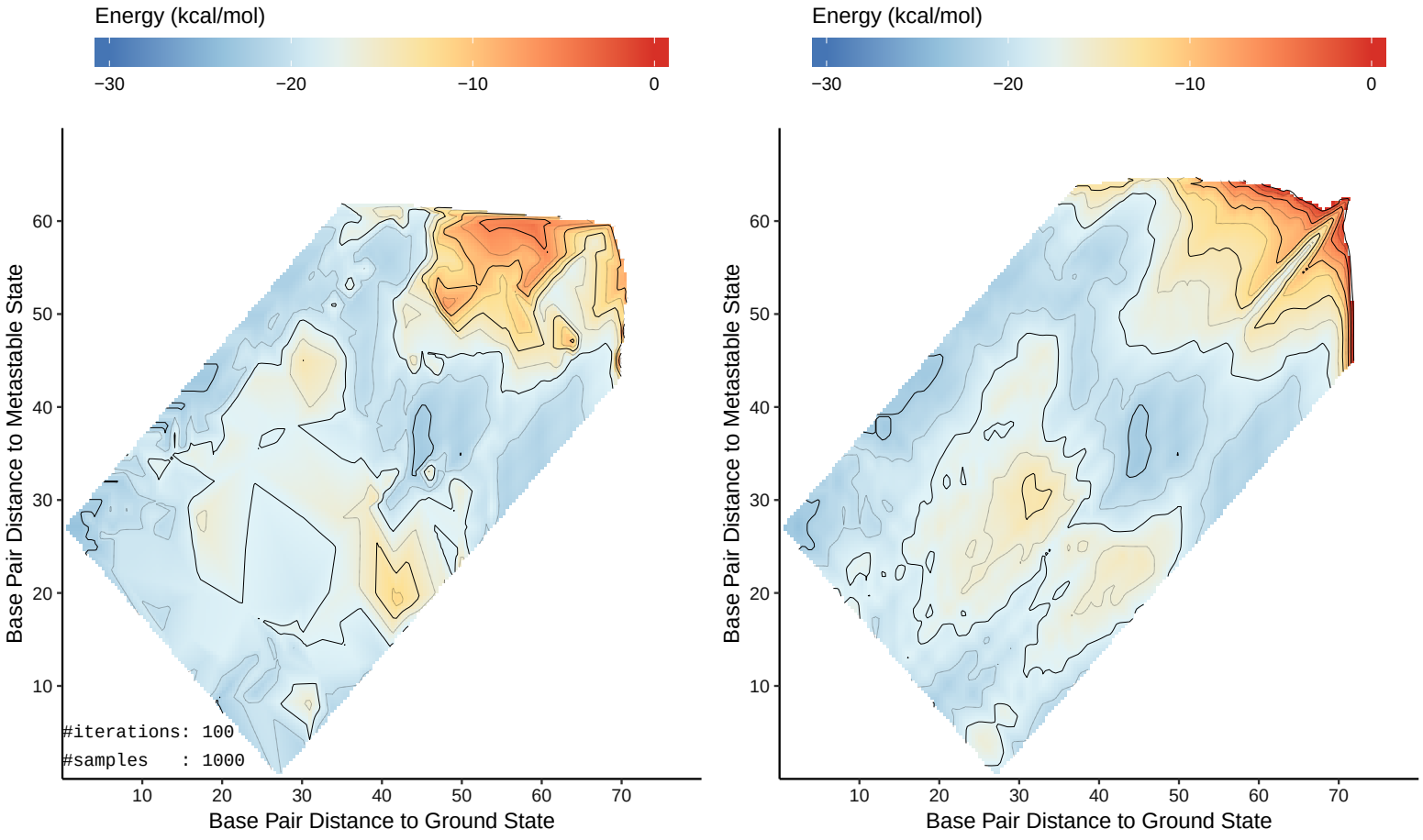

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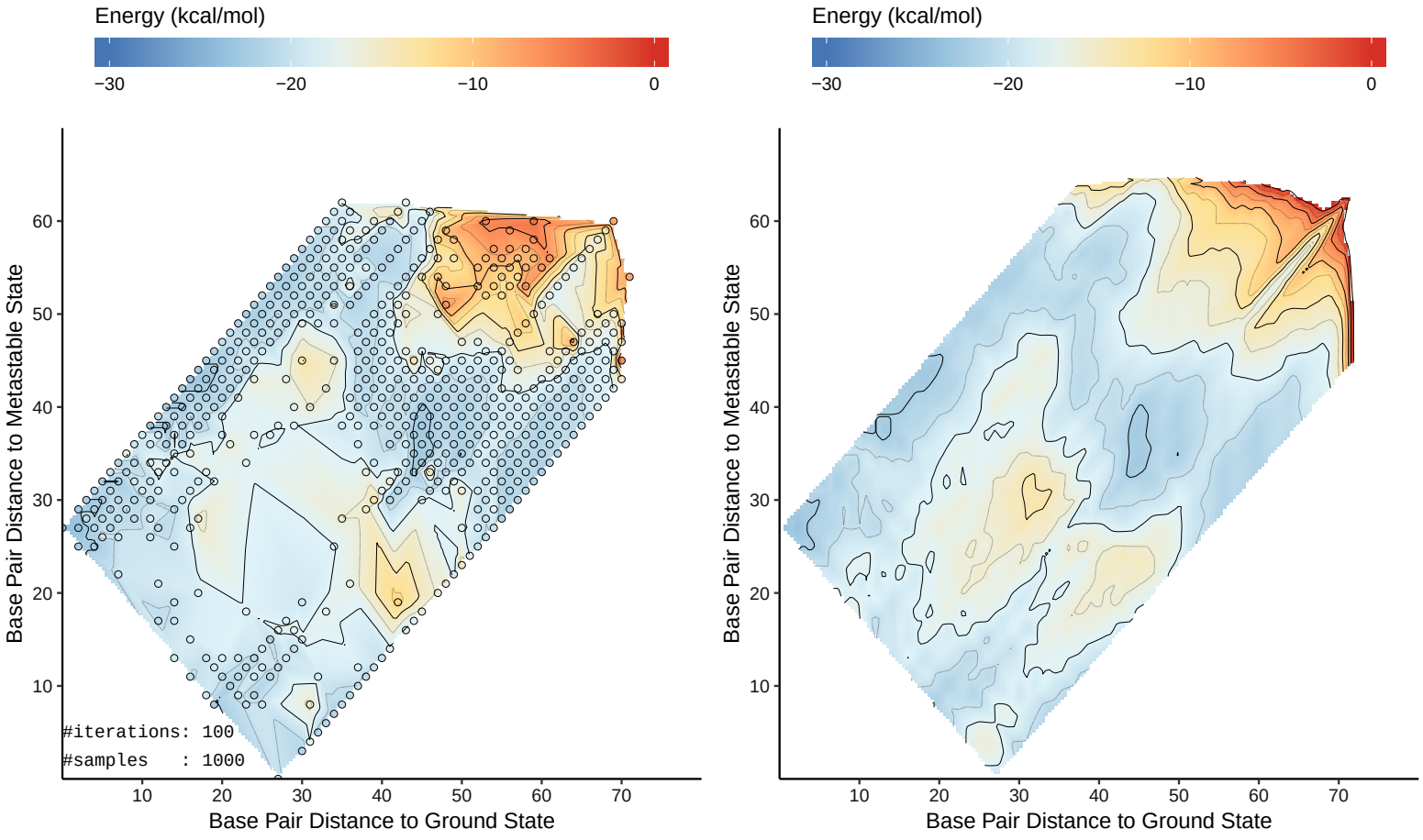

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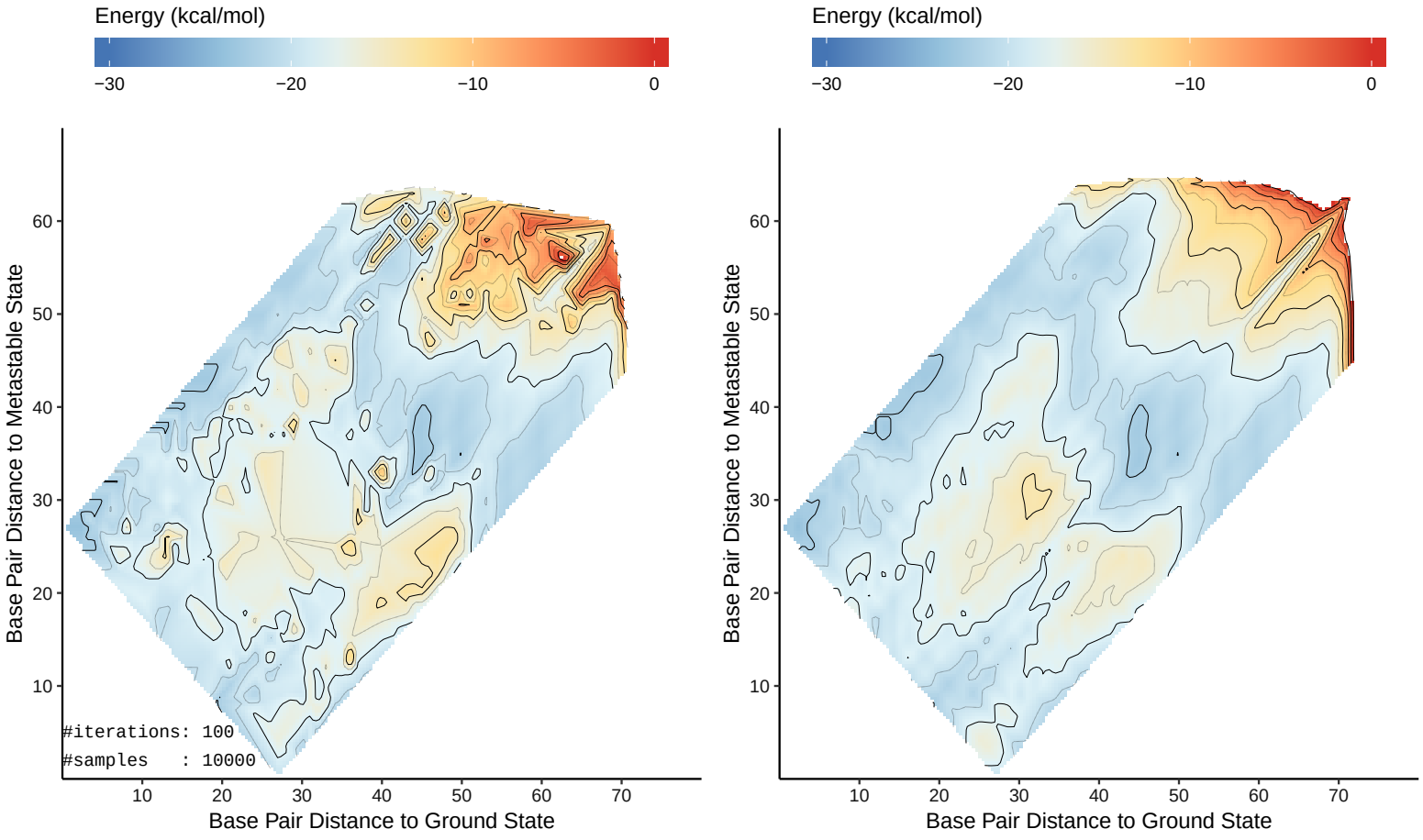
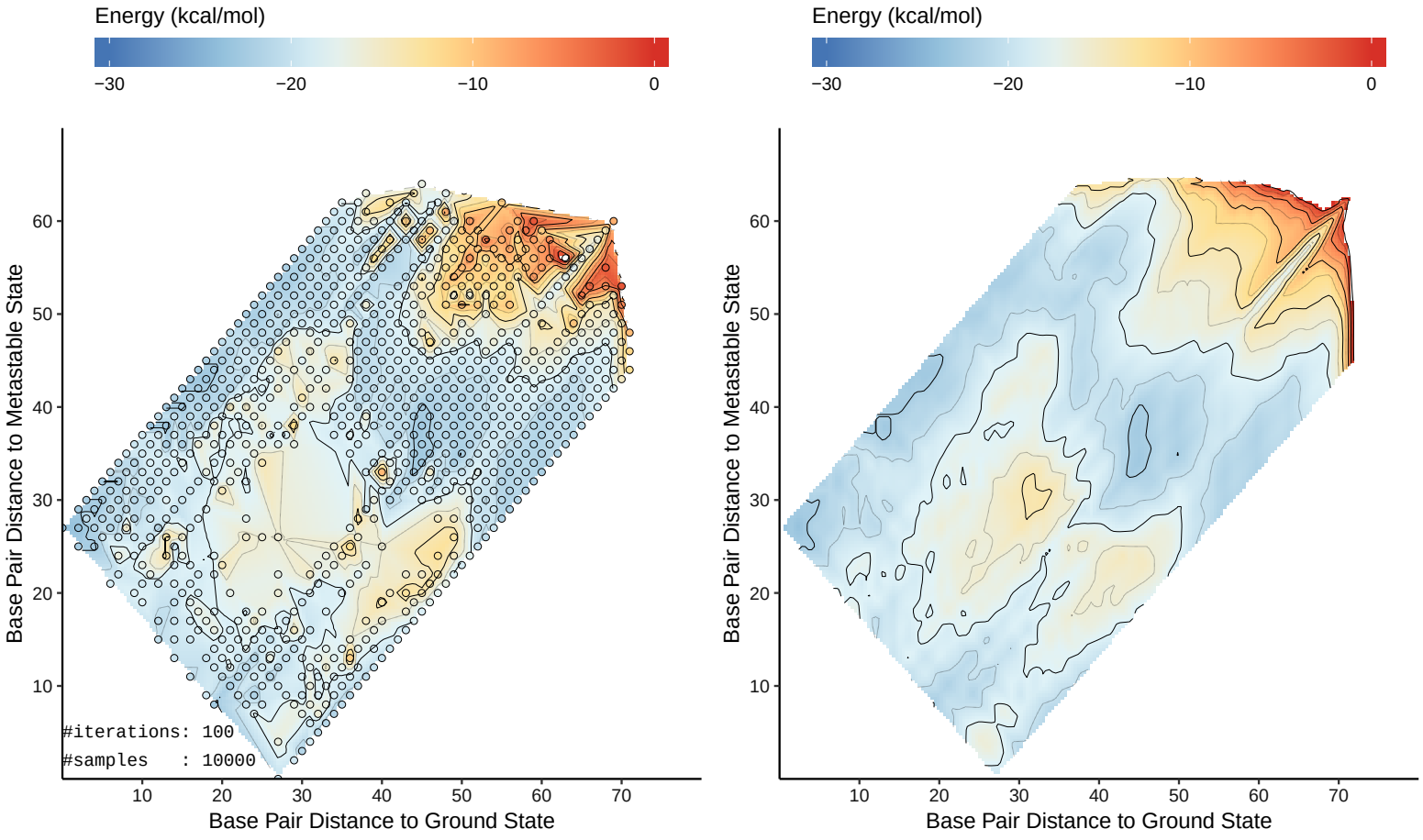


Example: add riboswitch V.culnificus

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



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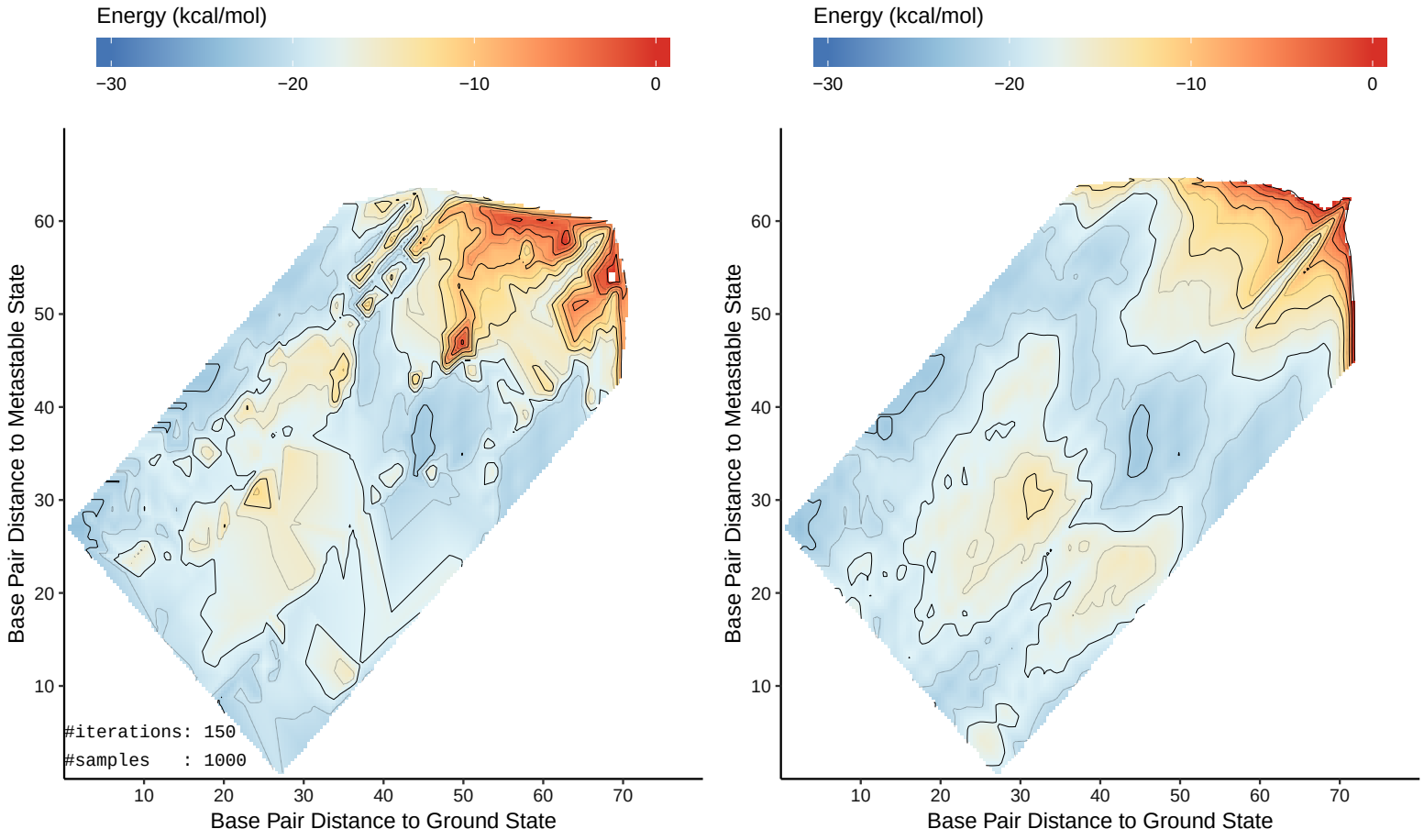
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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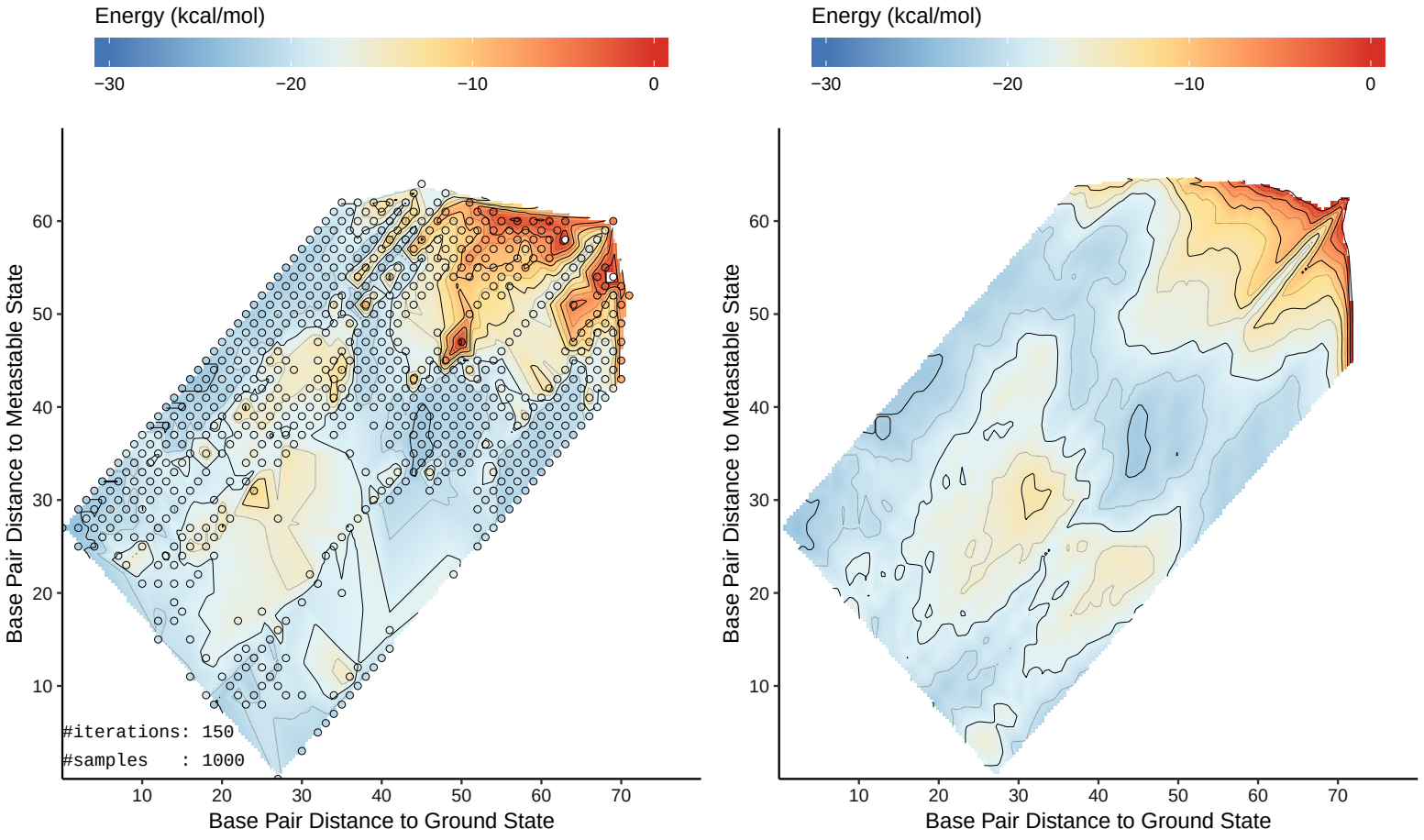
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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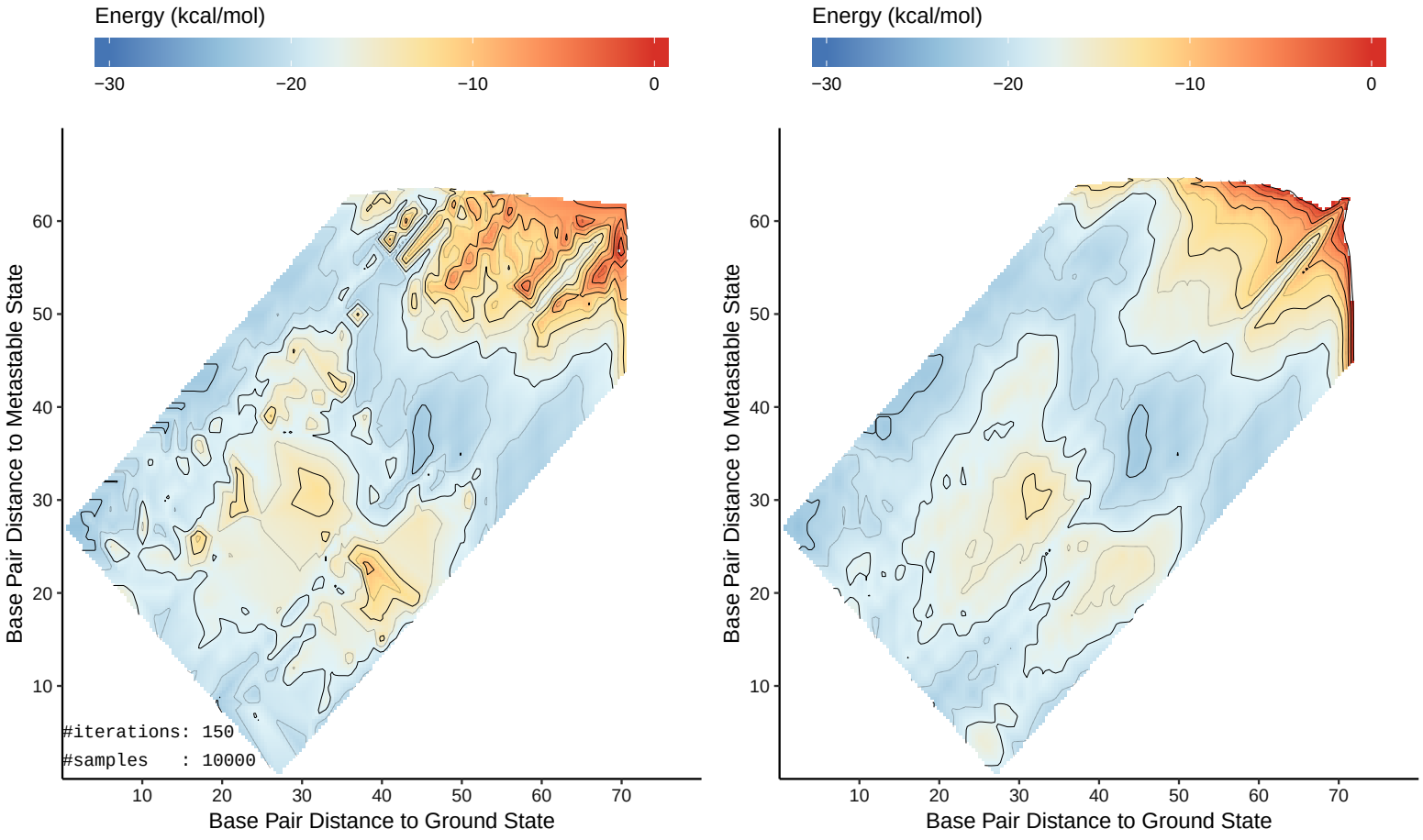
`RNAxplorer` repulsion scheme Boltzmann sampling *(distance)*



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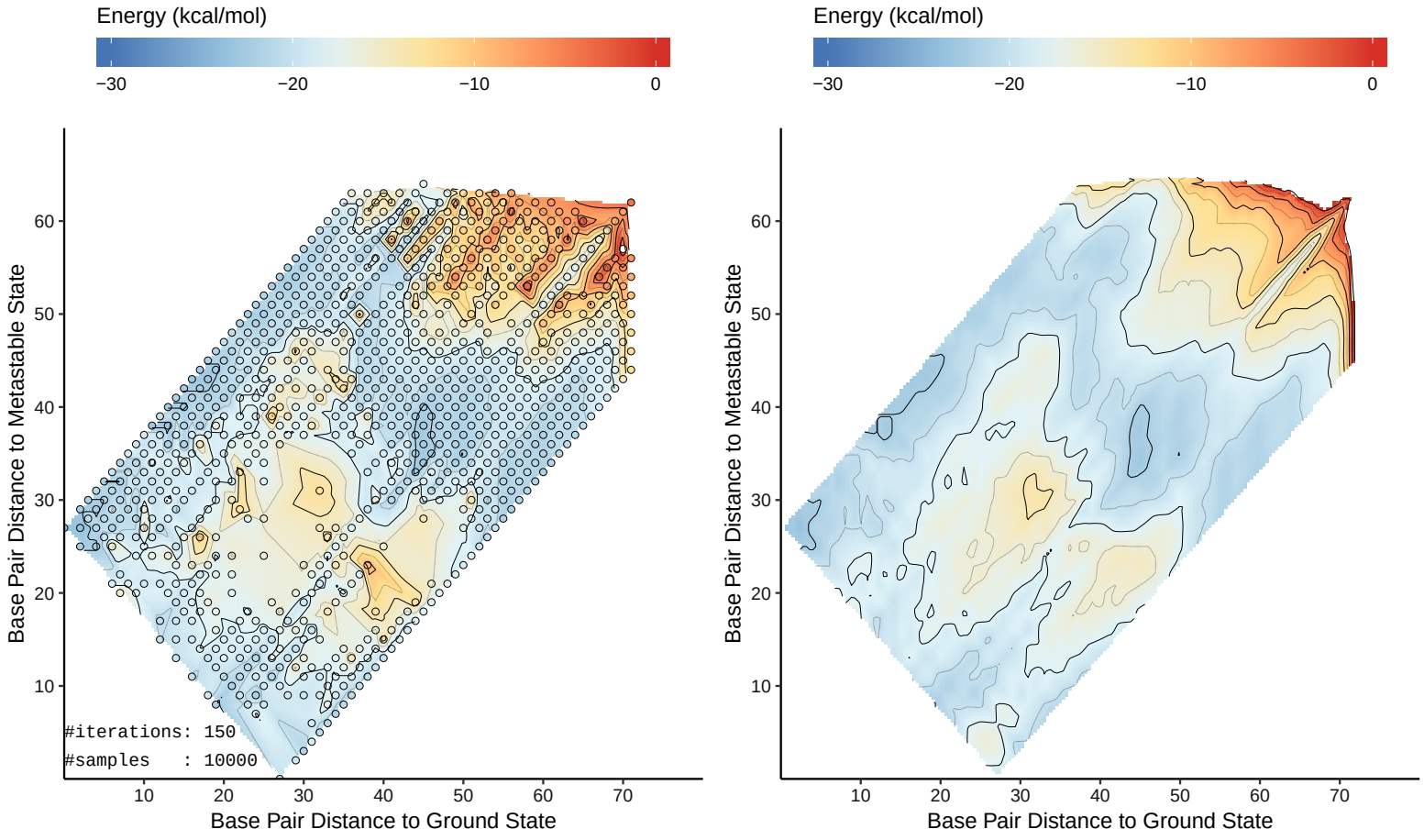

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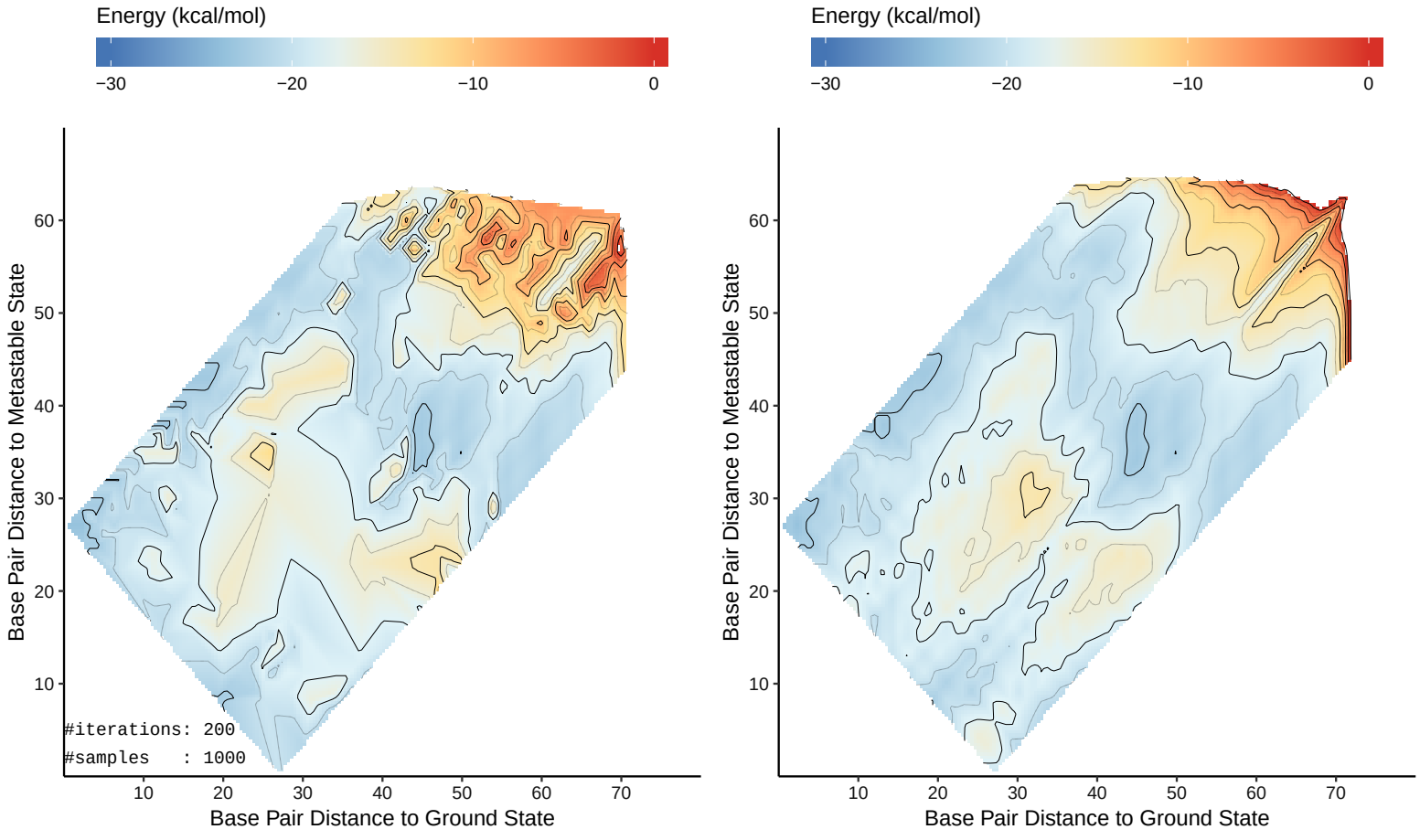

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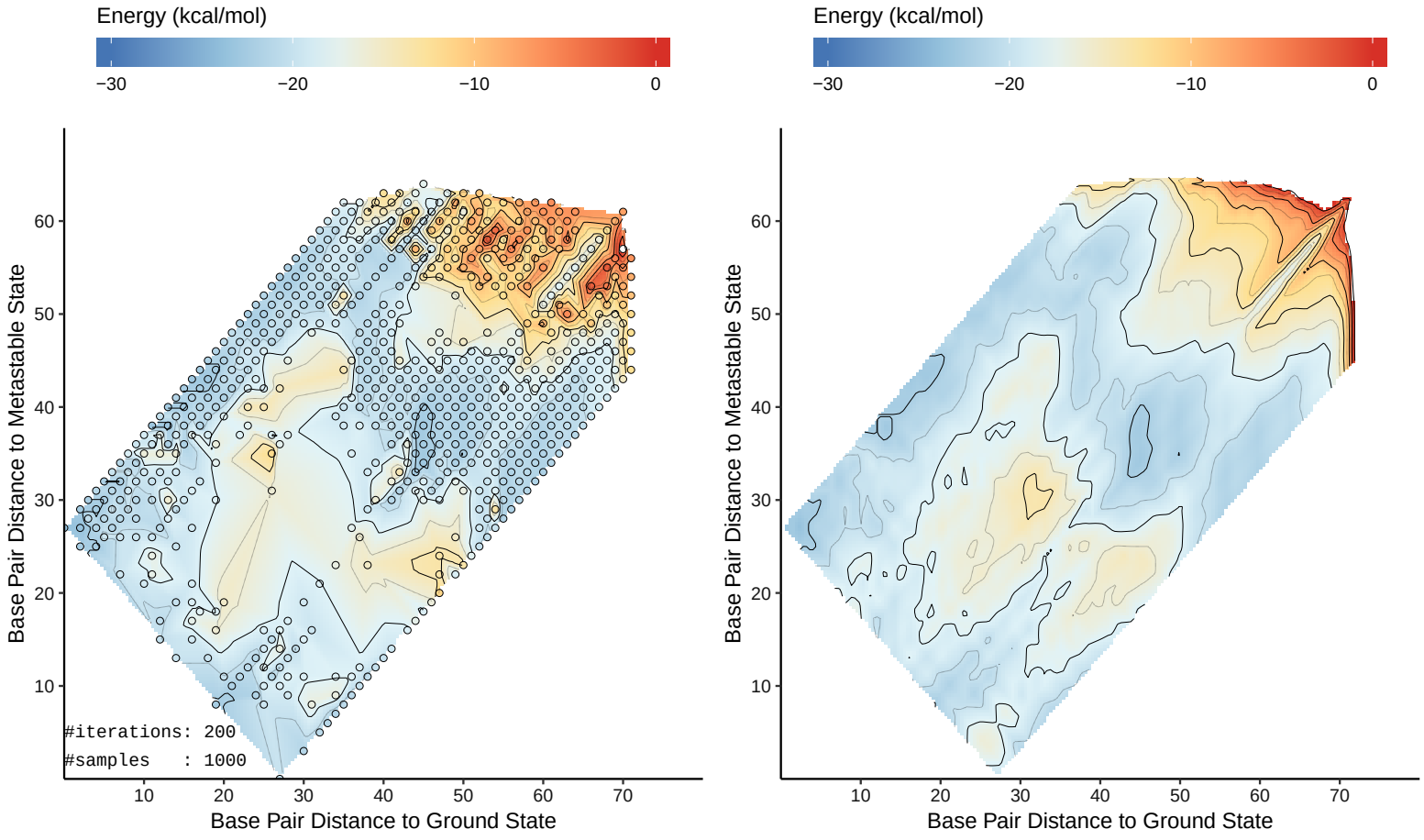

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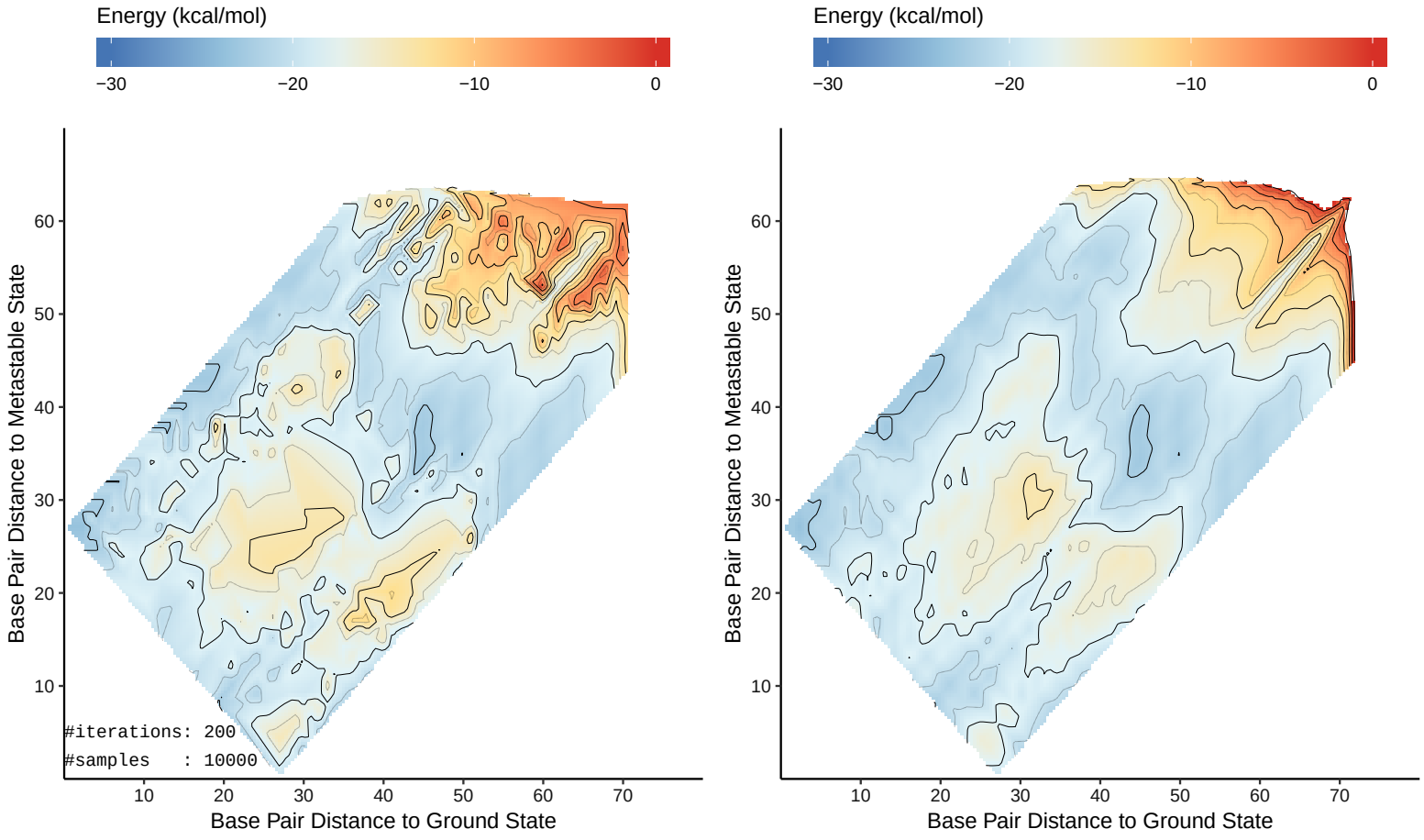

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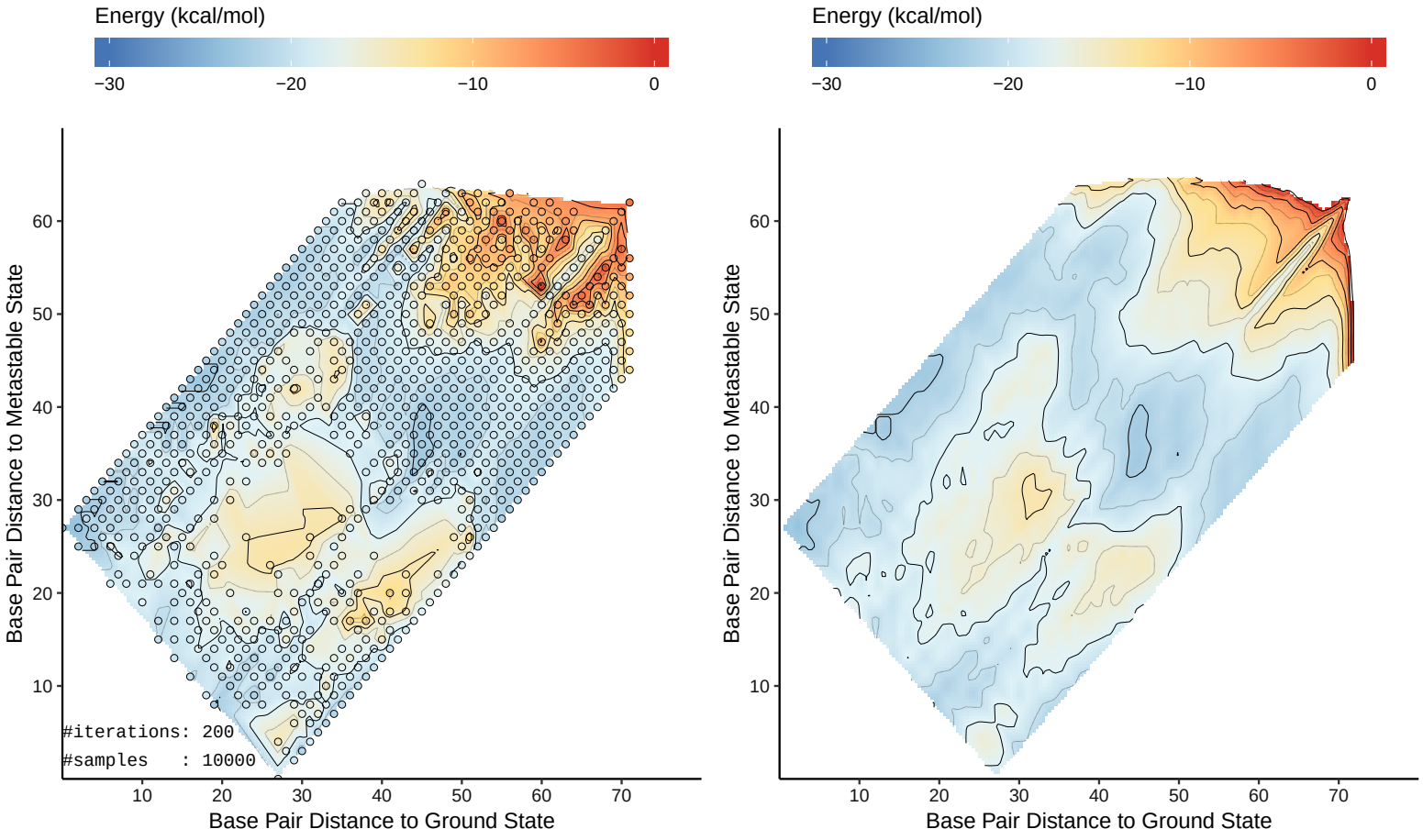

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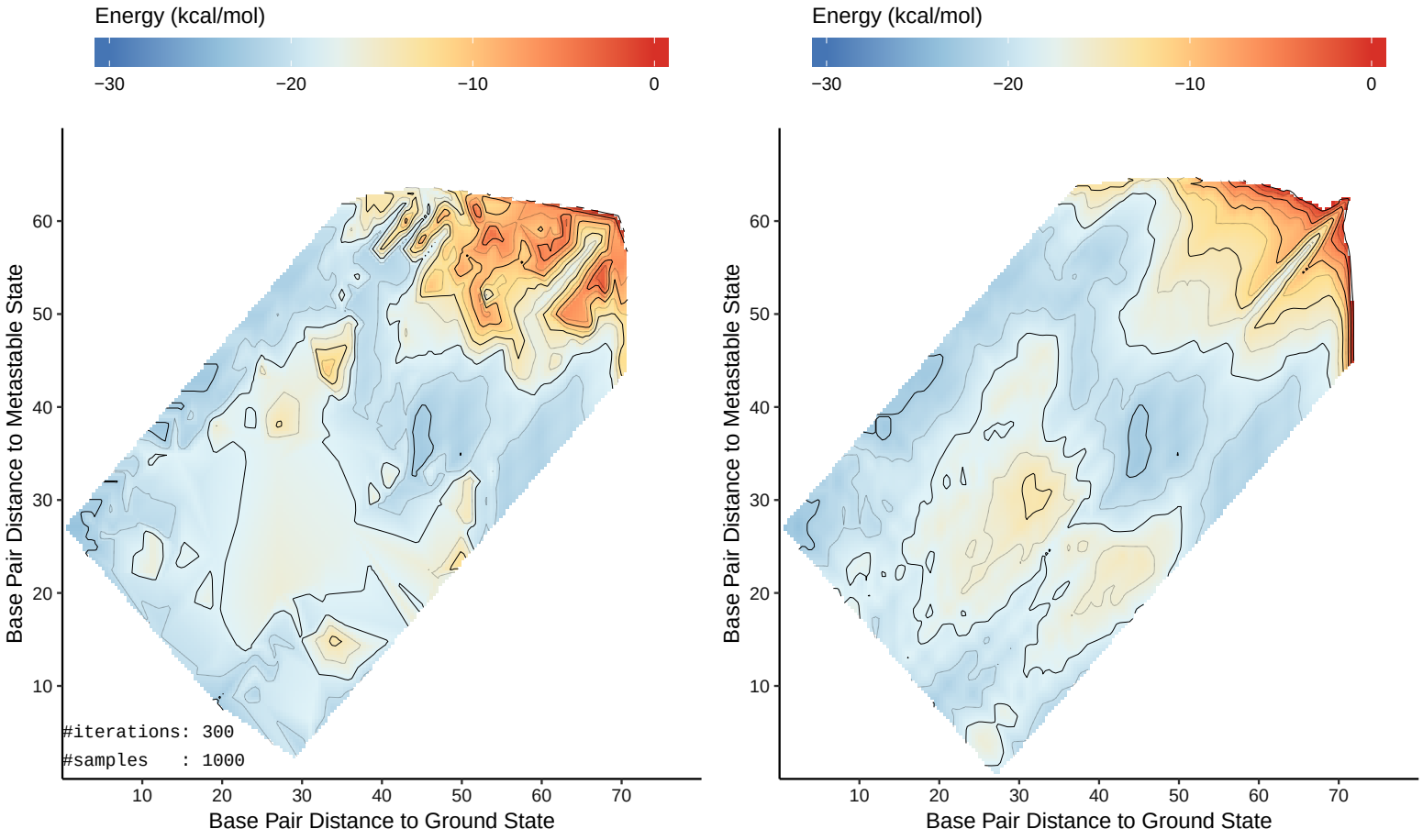

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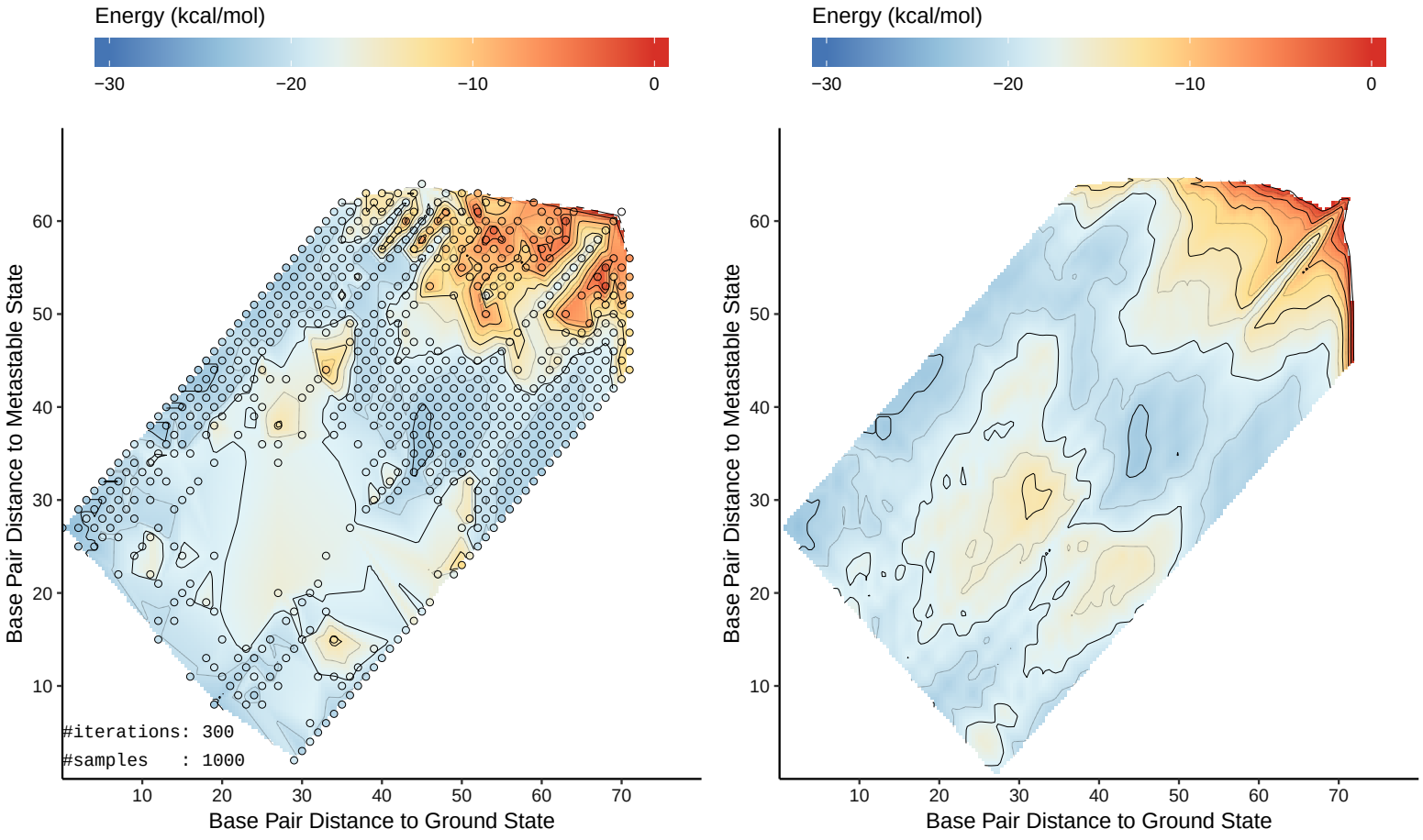

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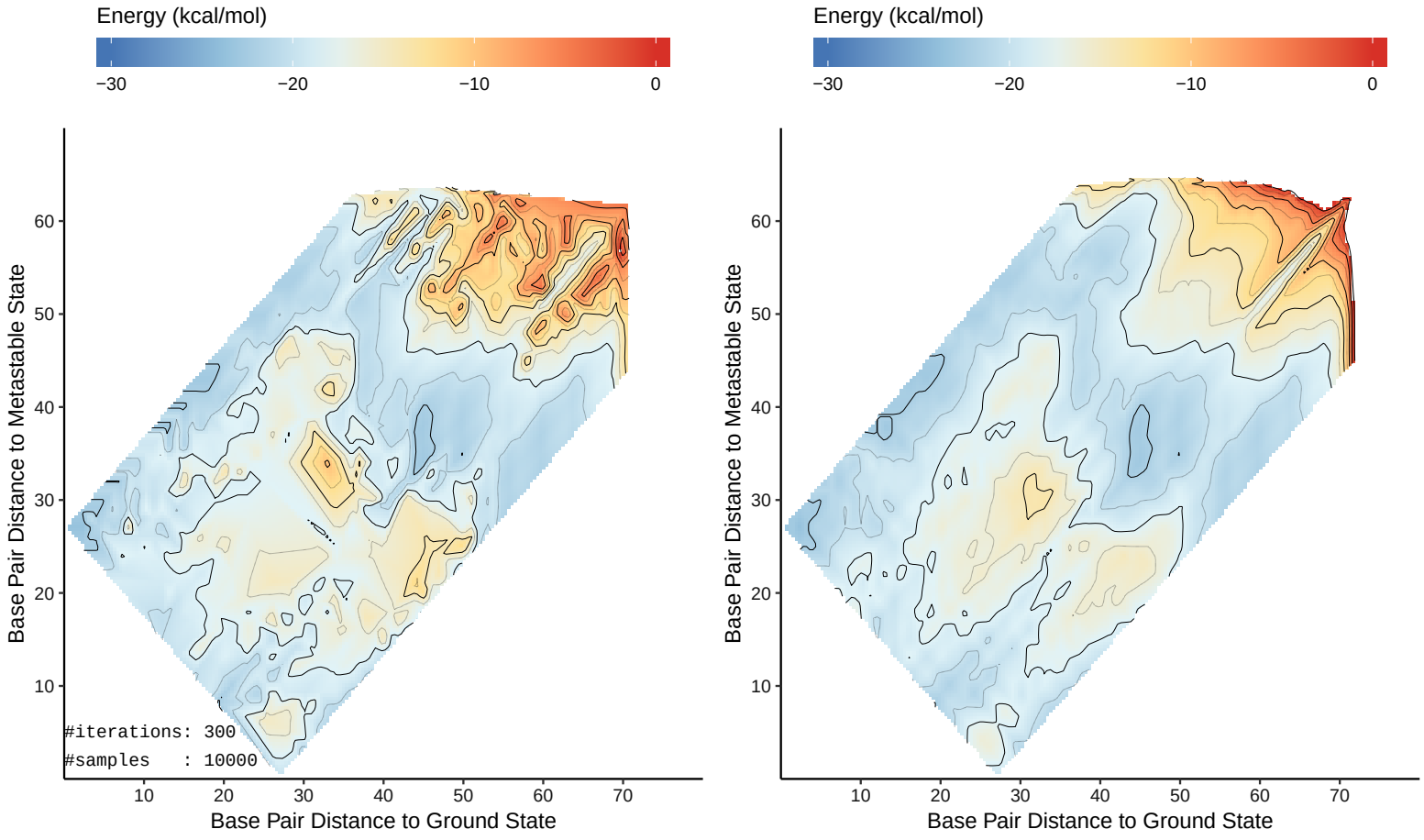

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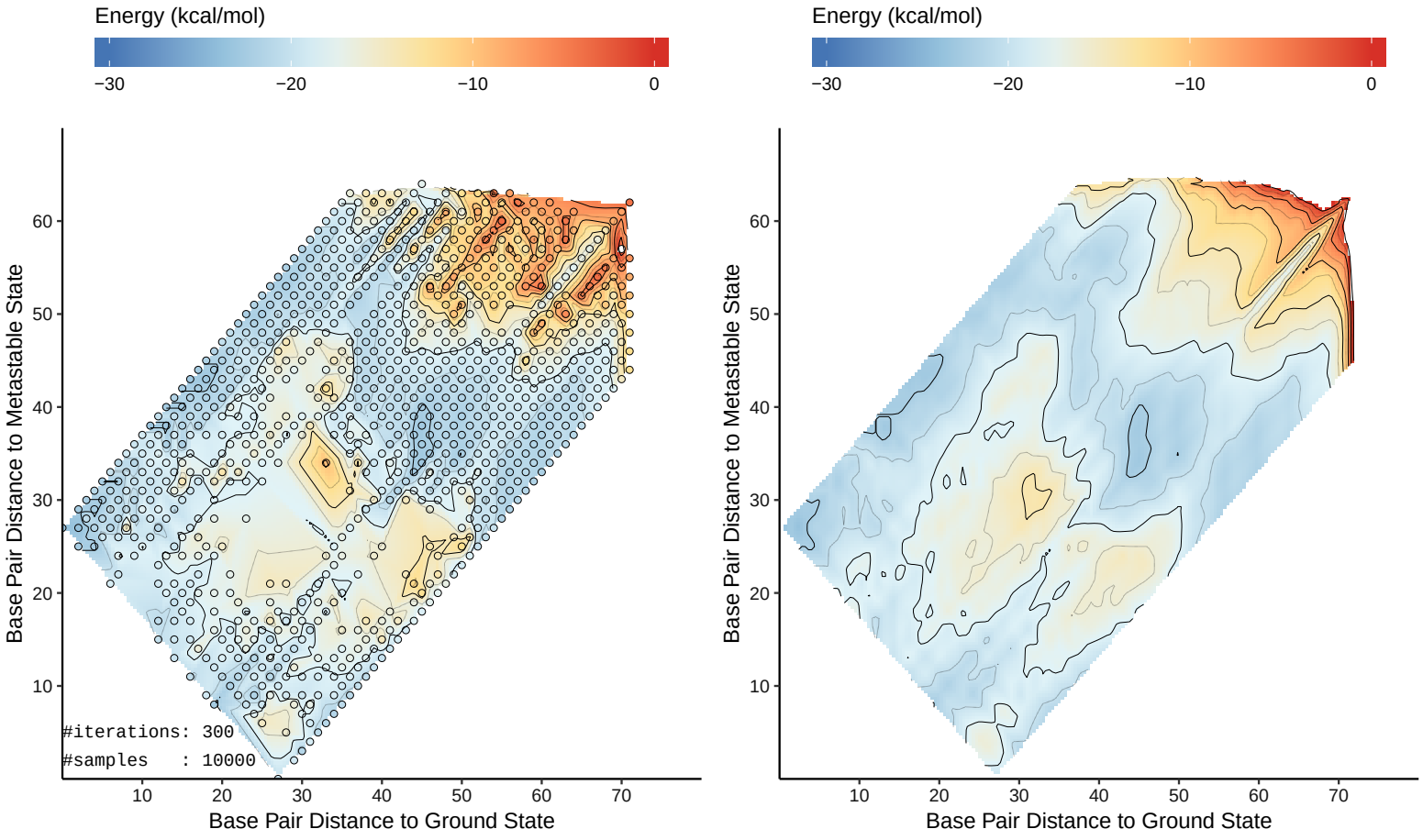
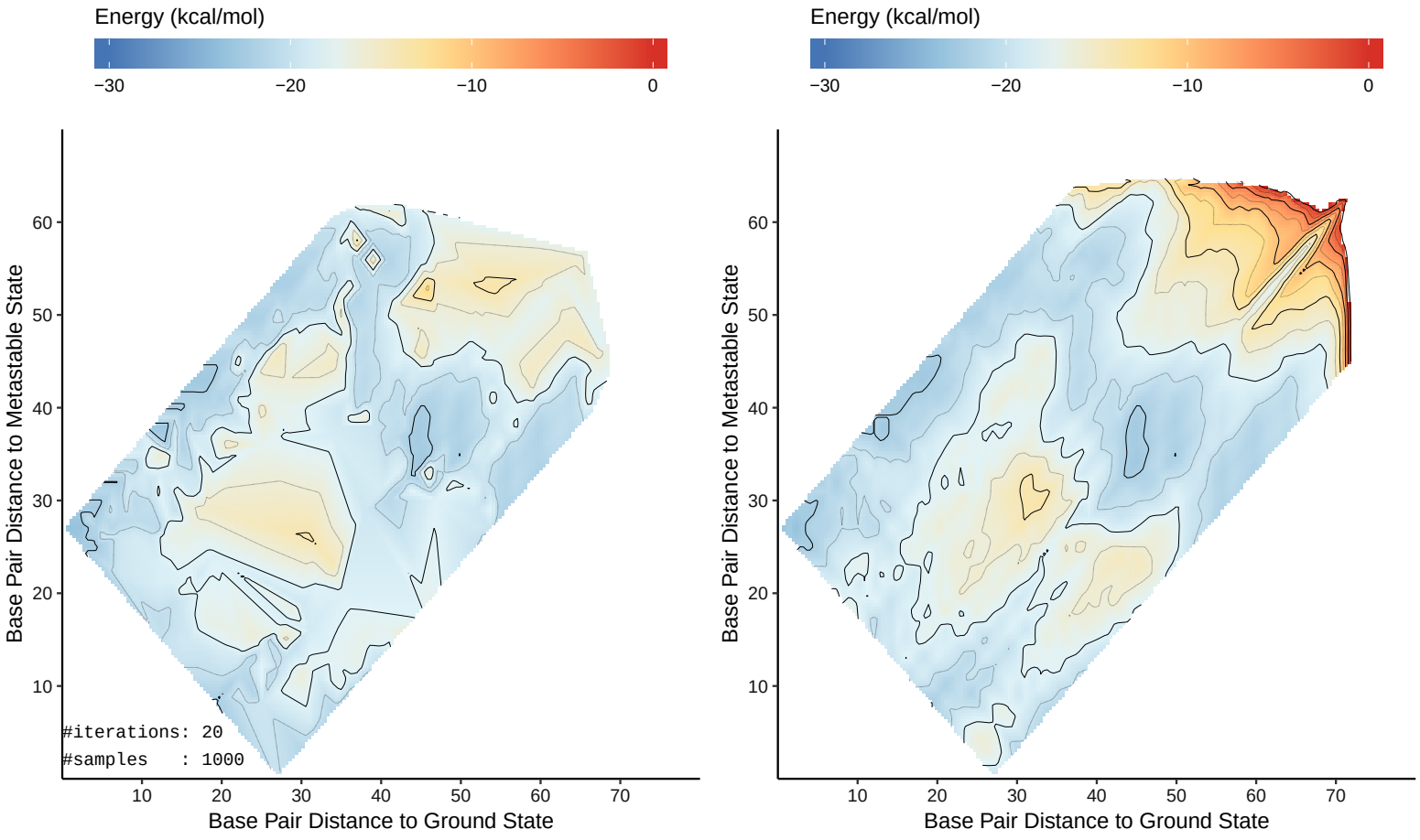


Example: add riboswitch V.culnificus

`RNAlocmin` temperature elevation scheme Boltzmann sampling



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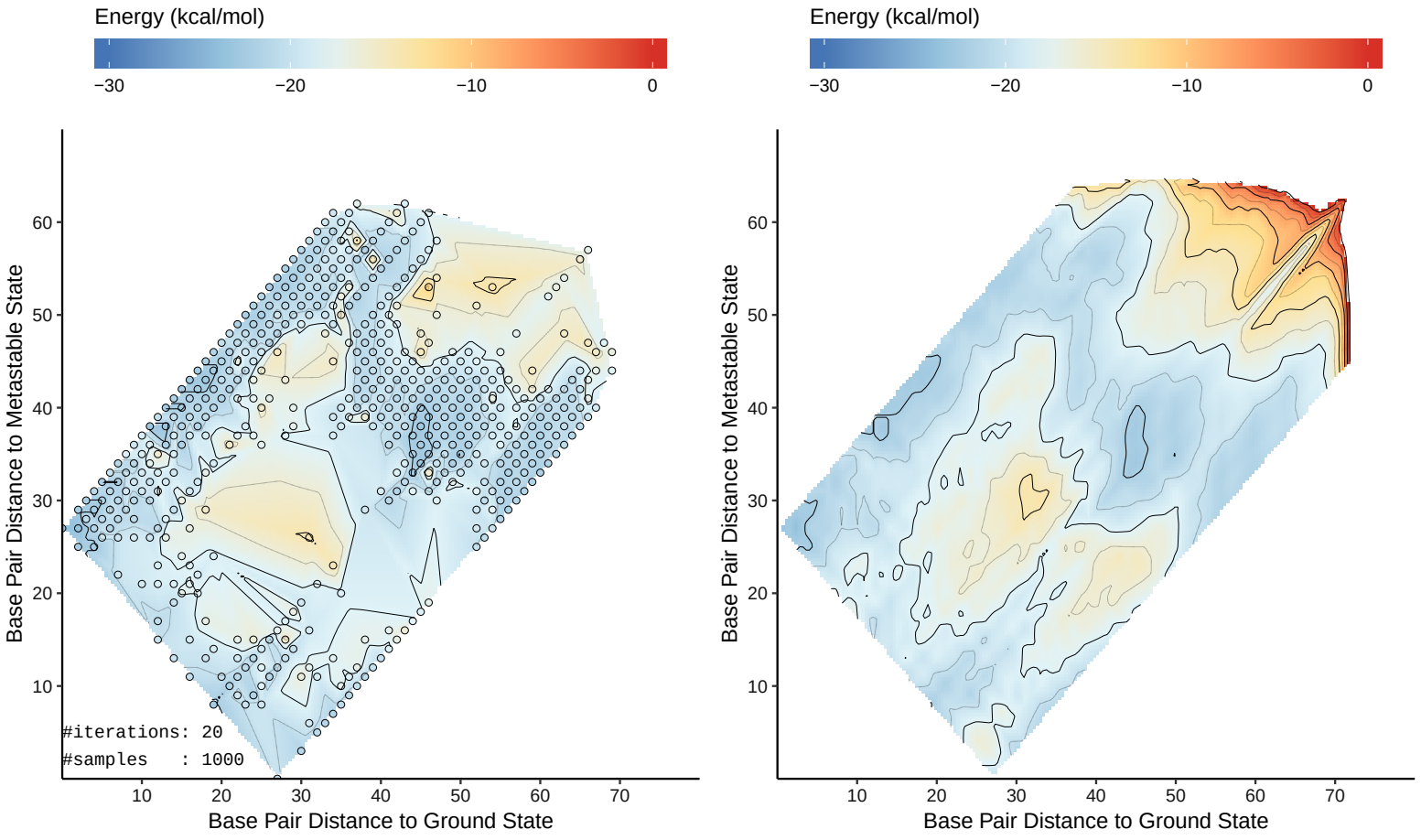
`RNAlocmin` temperature elevation scheme Boltzmann sampling



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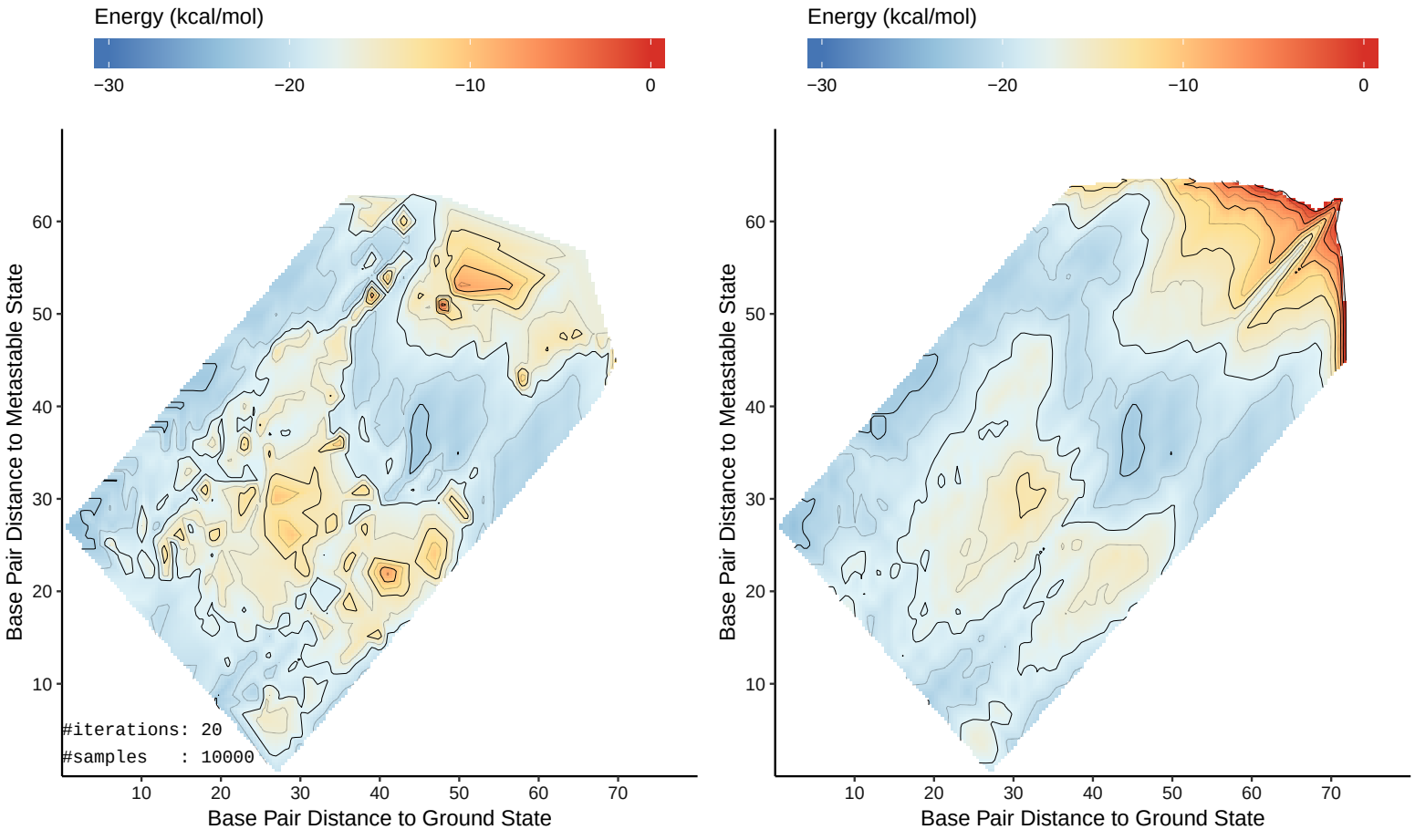

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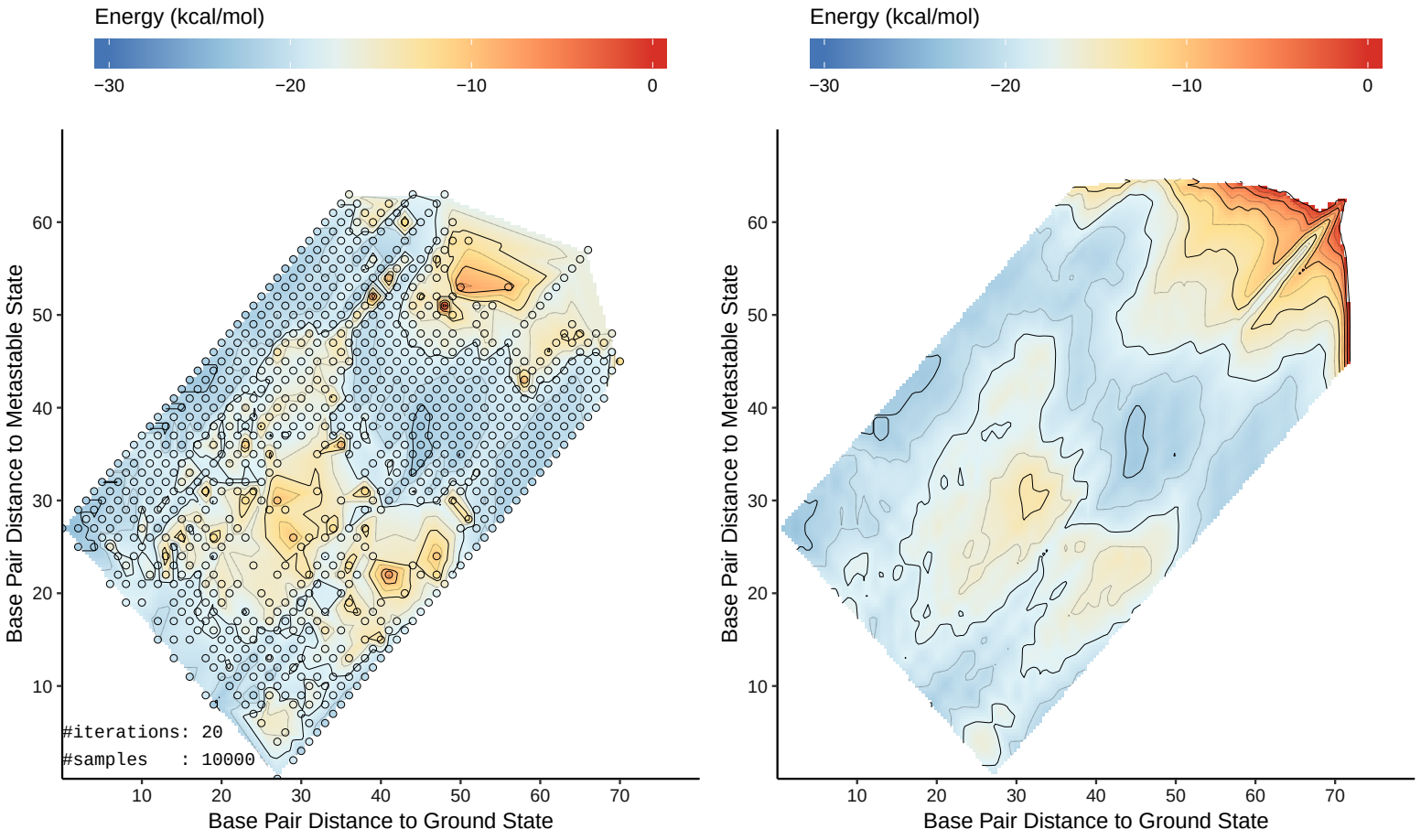

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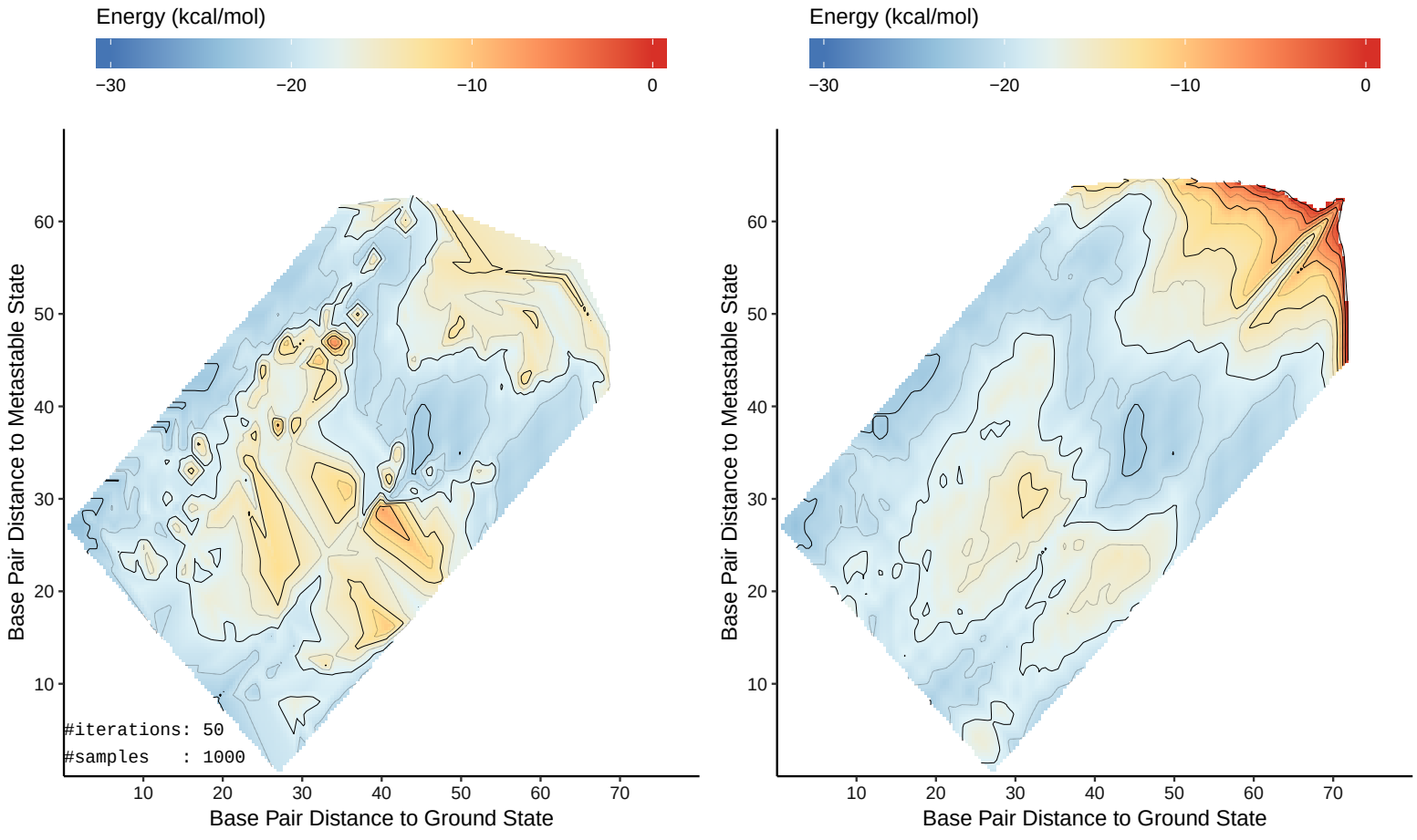

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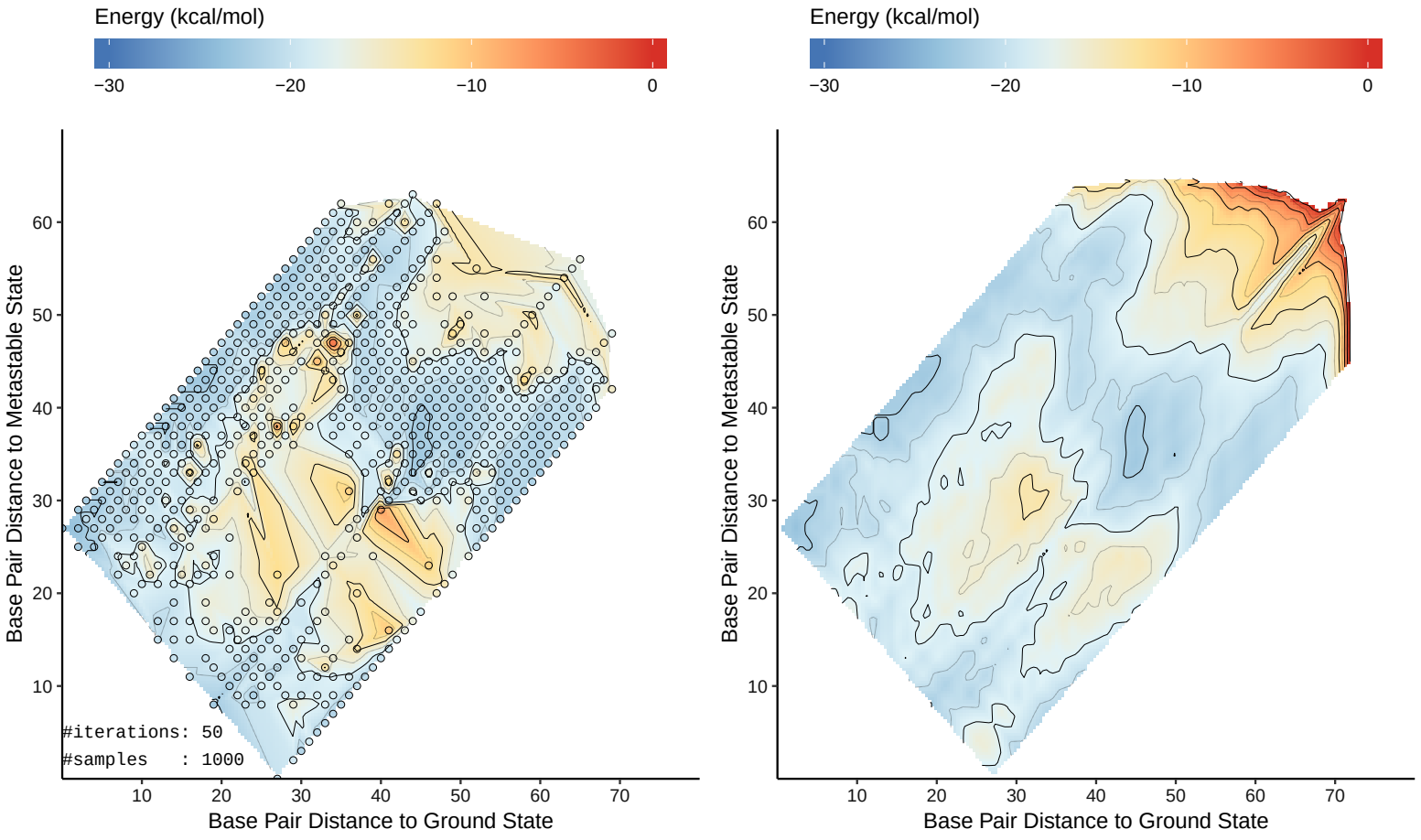

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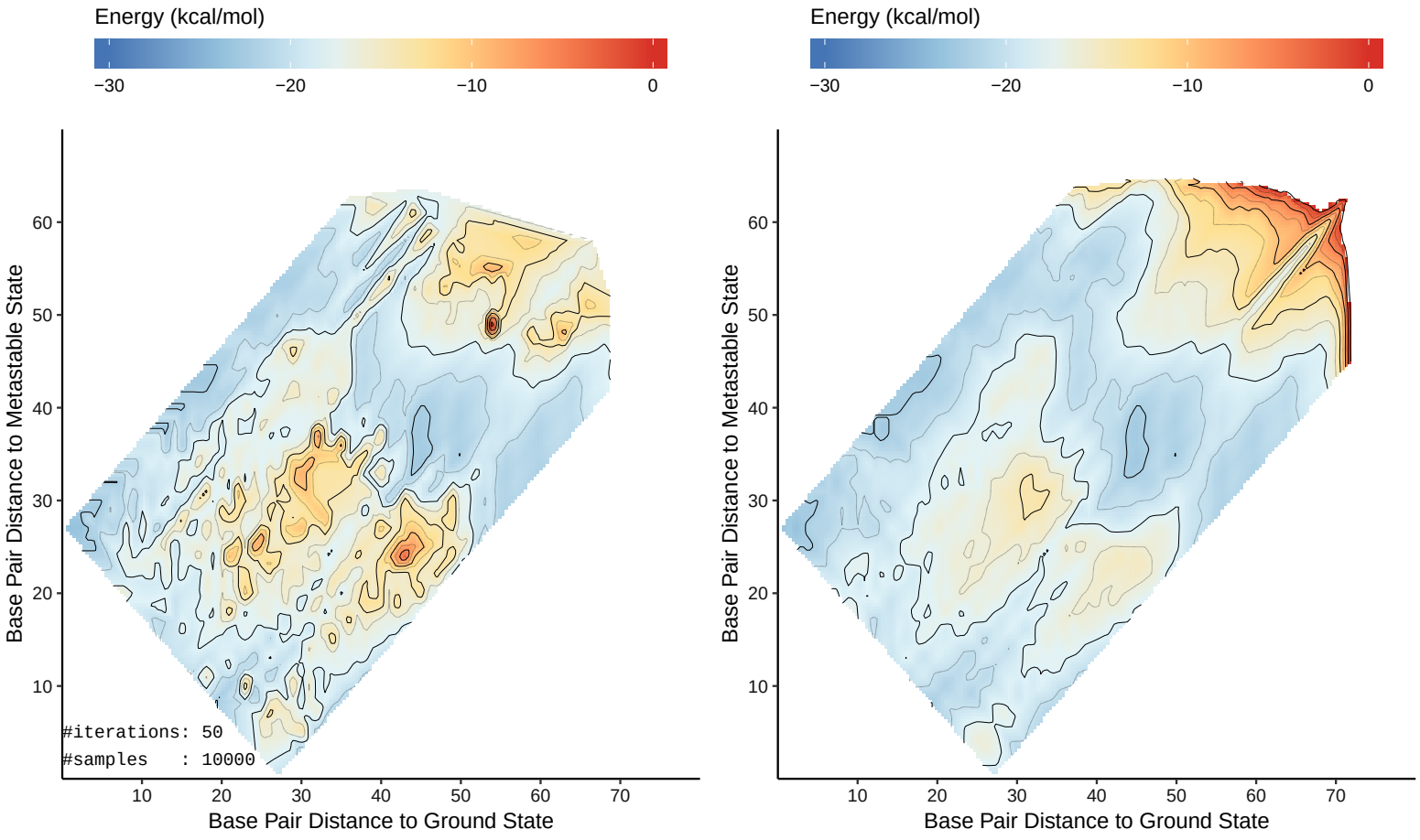

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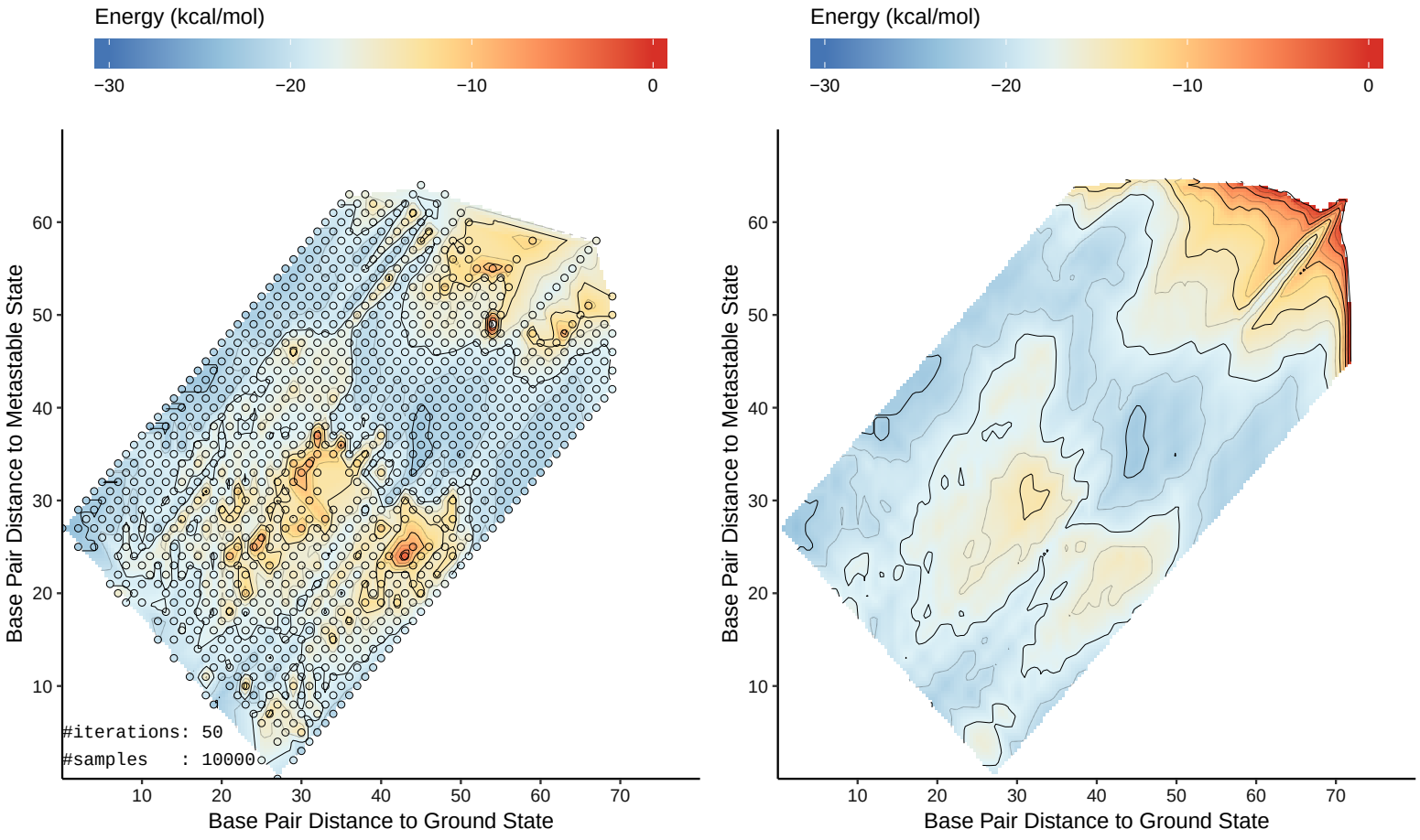

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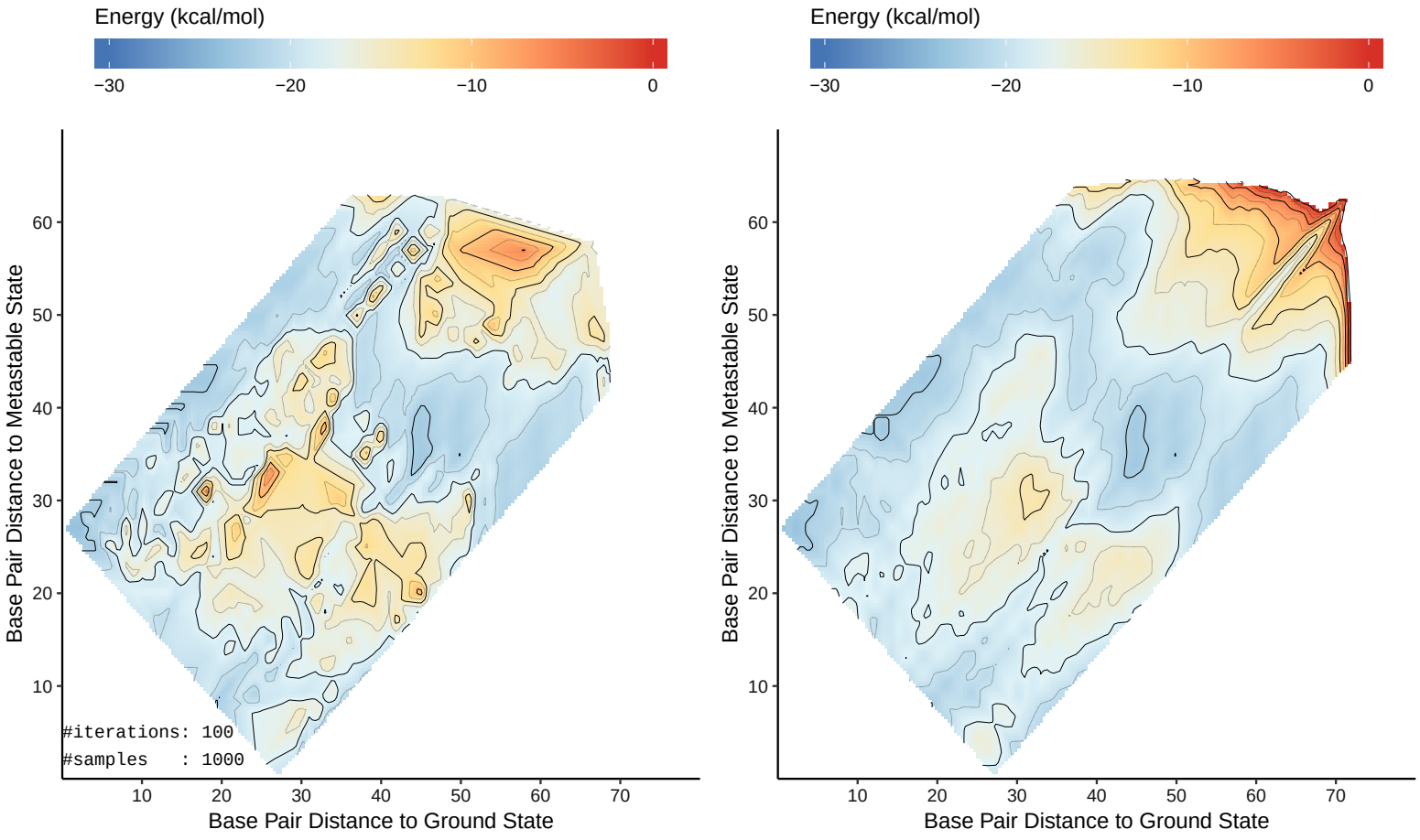

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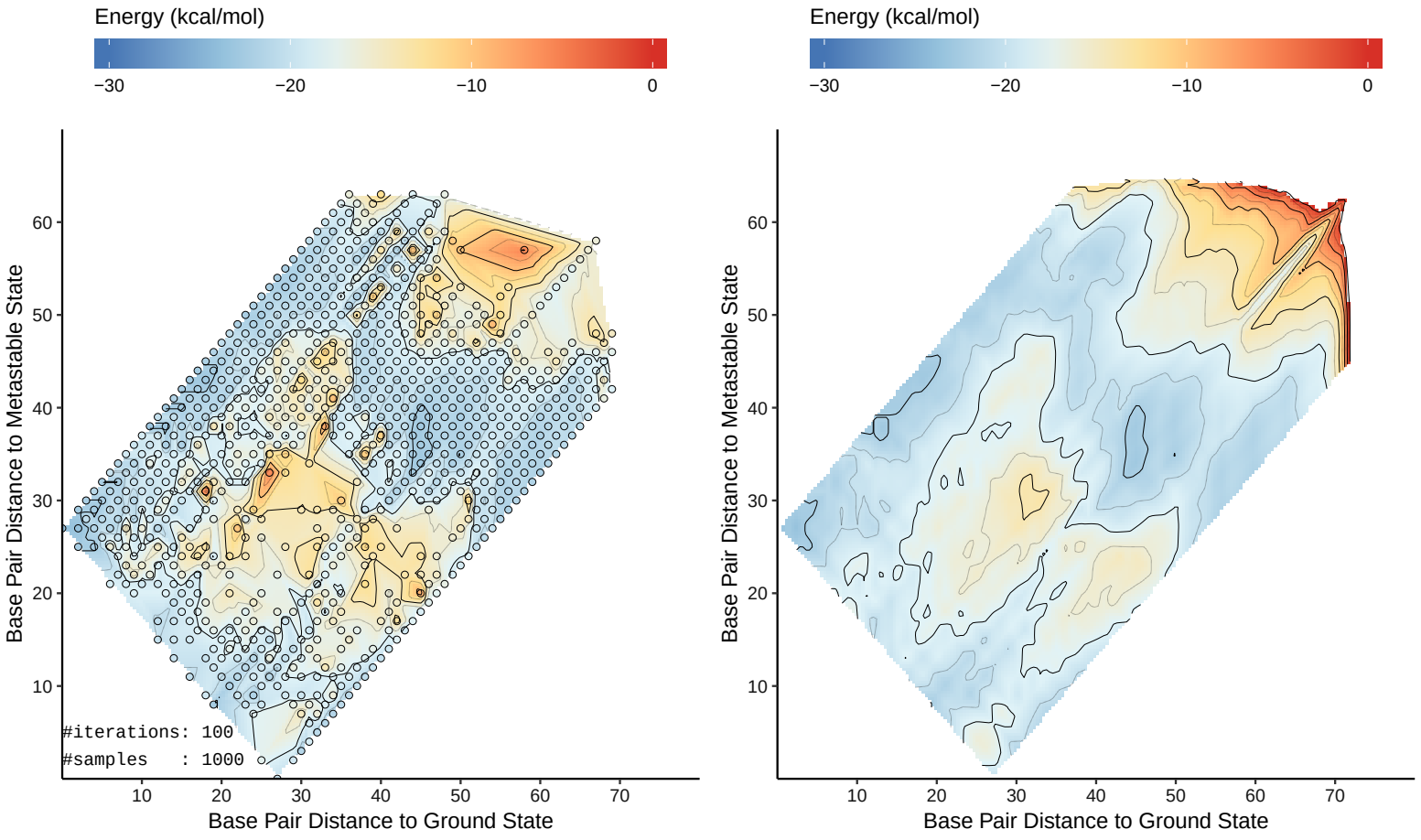
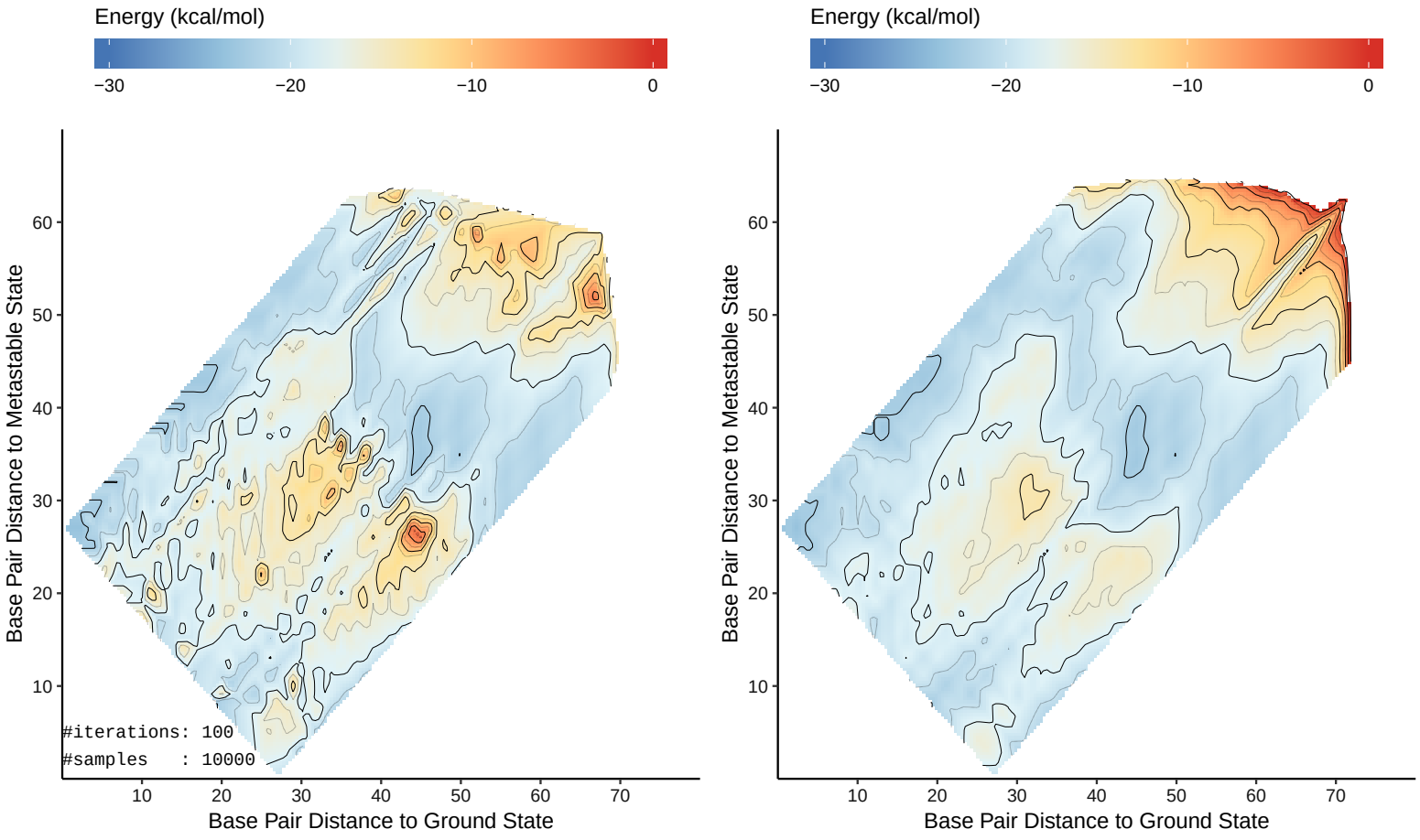


Example: add riboswitch V.culnificus

`RNAlocmin` temperature elevation scheme Boltzmann sampling



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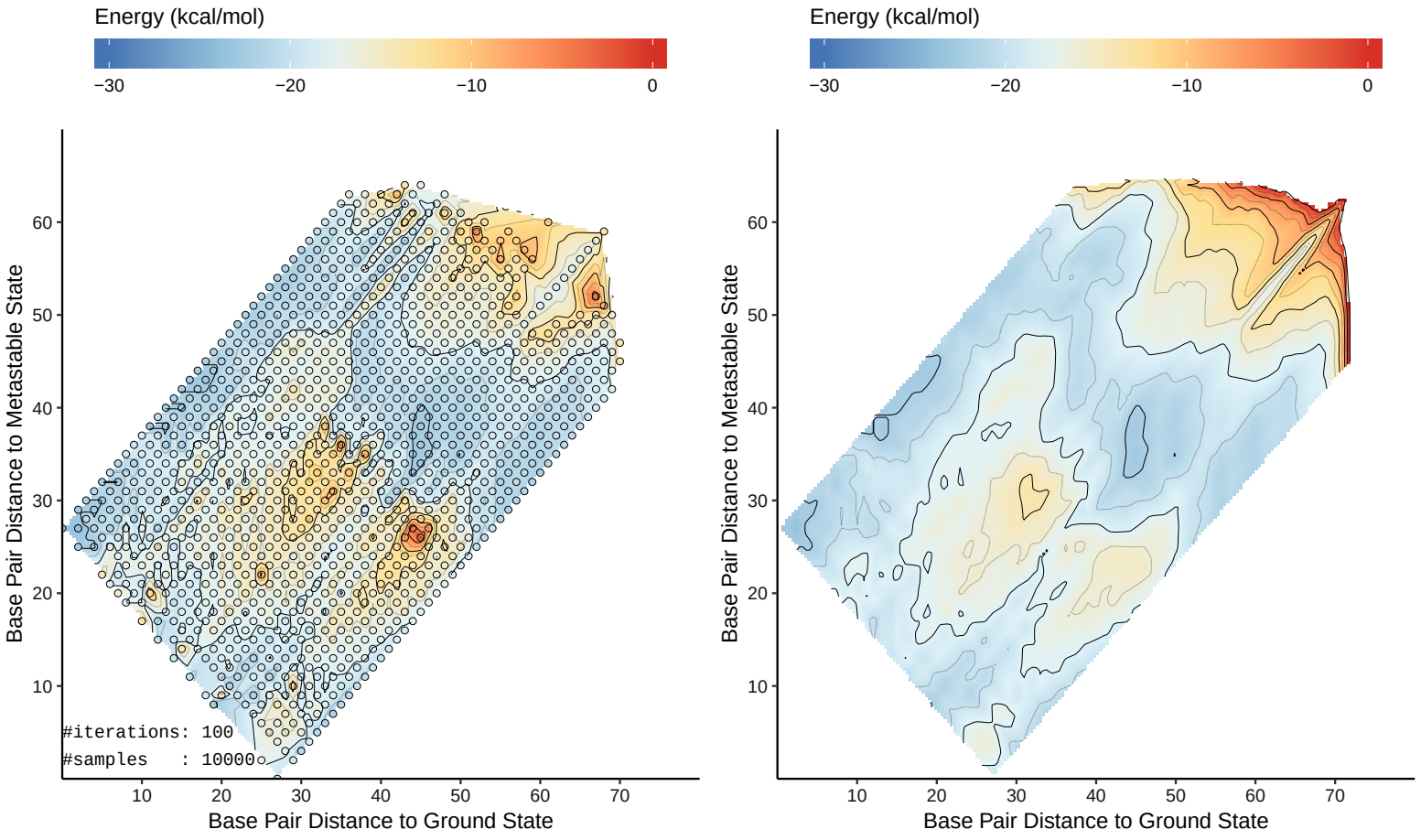

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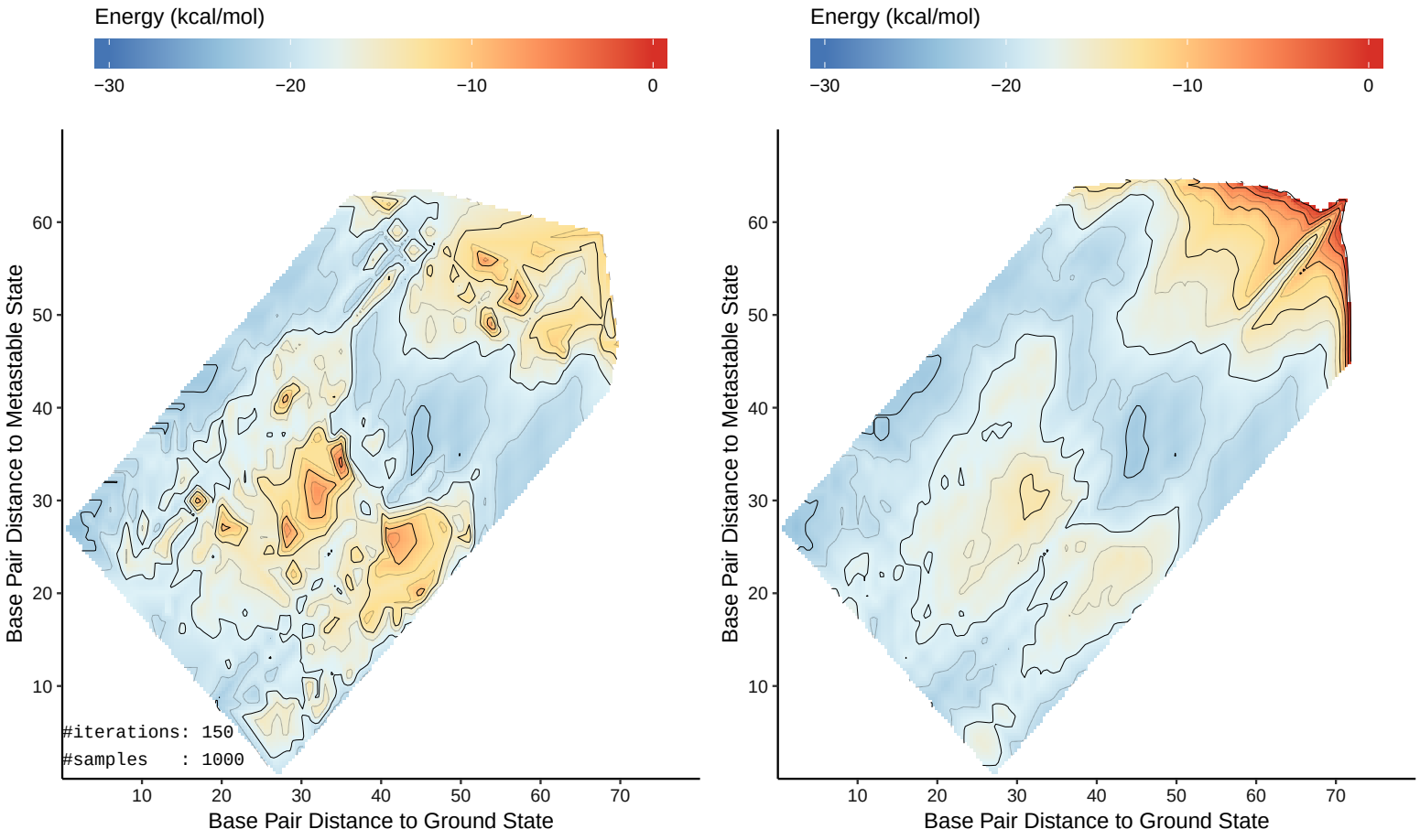

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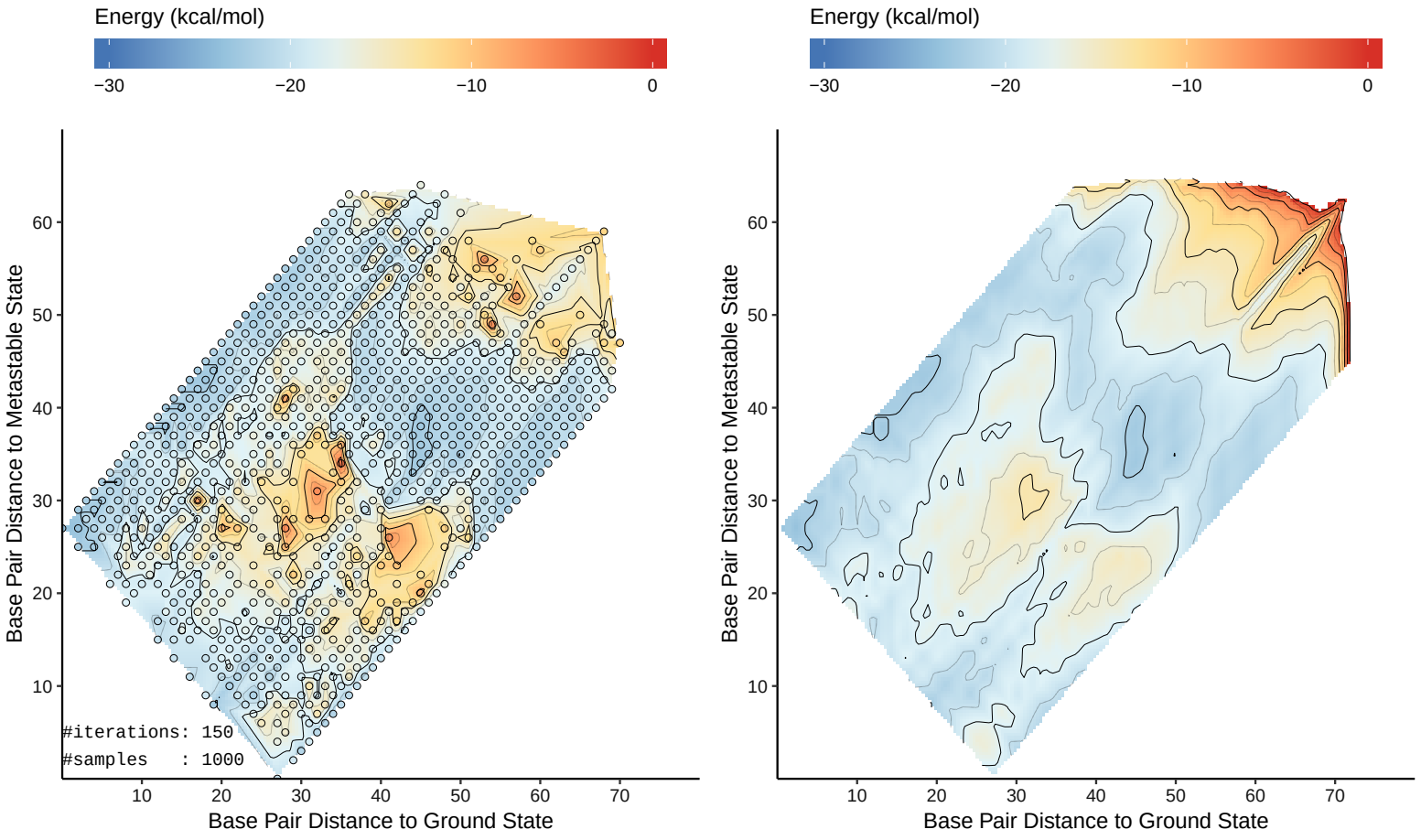

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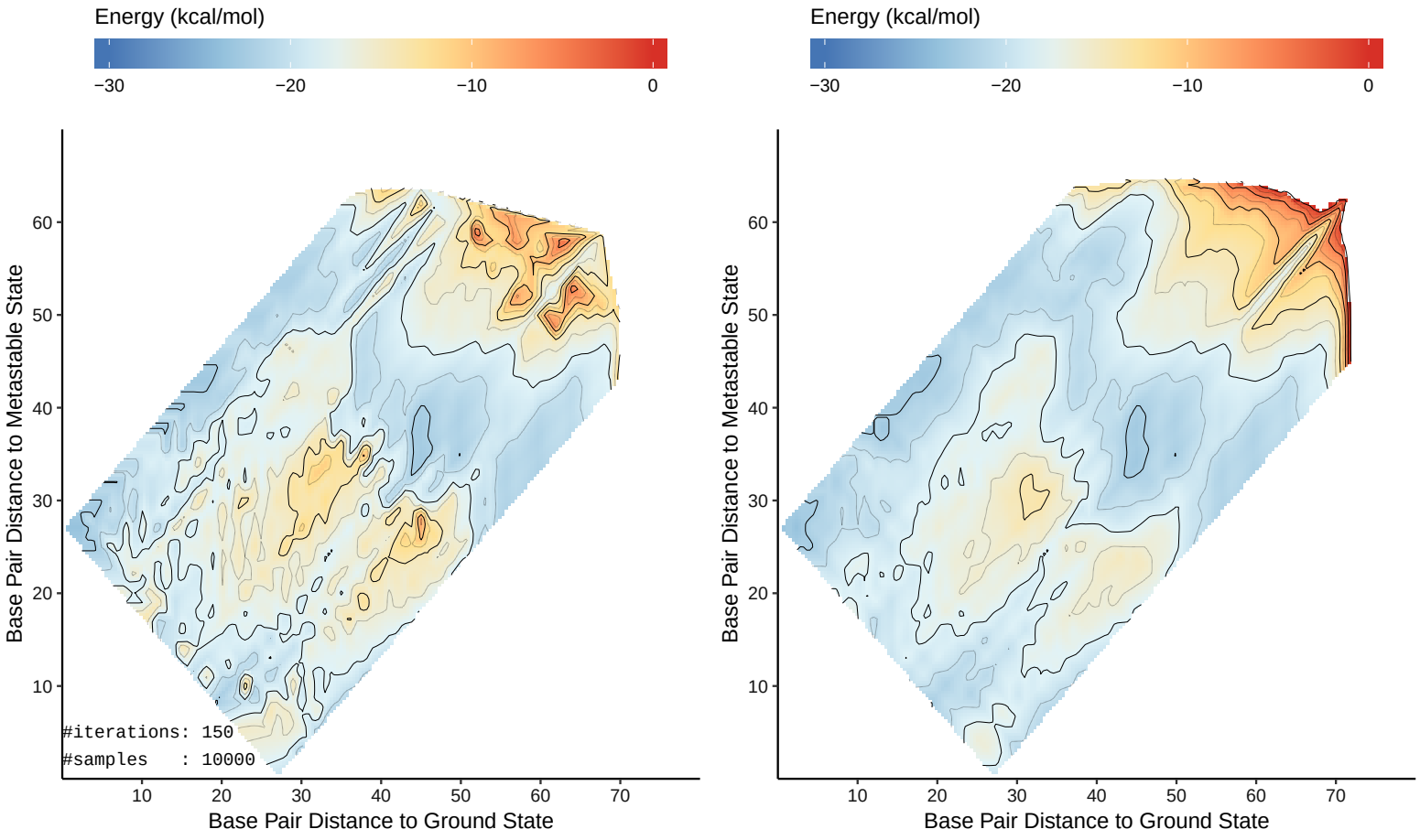

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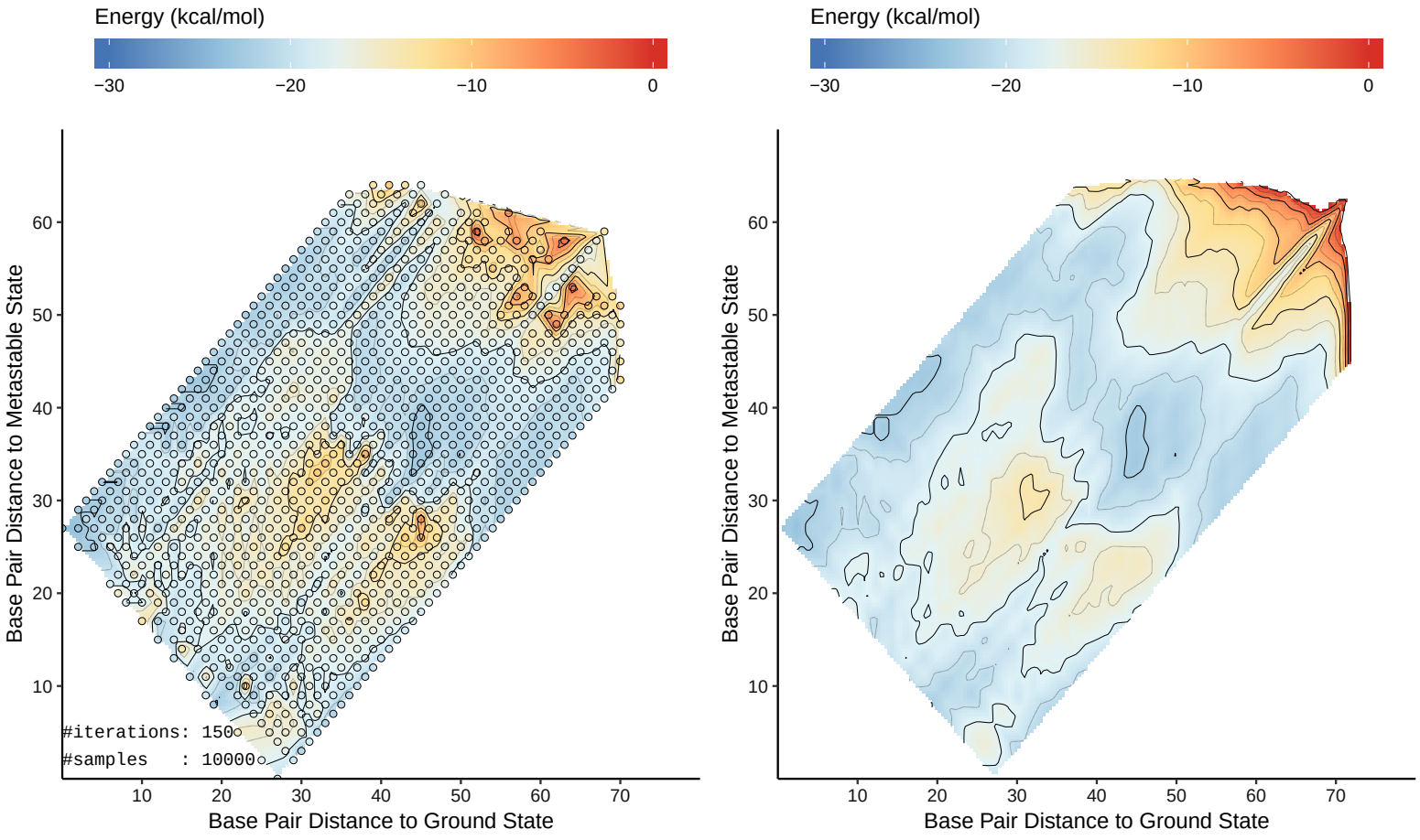

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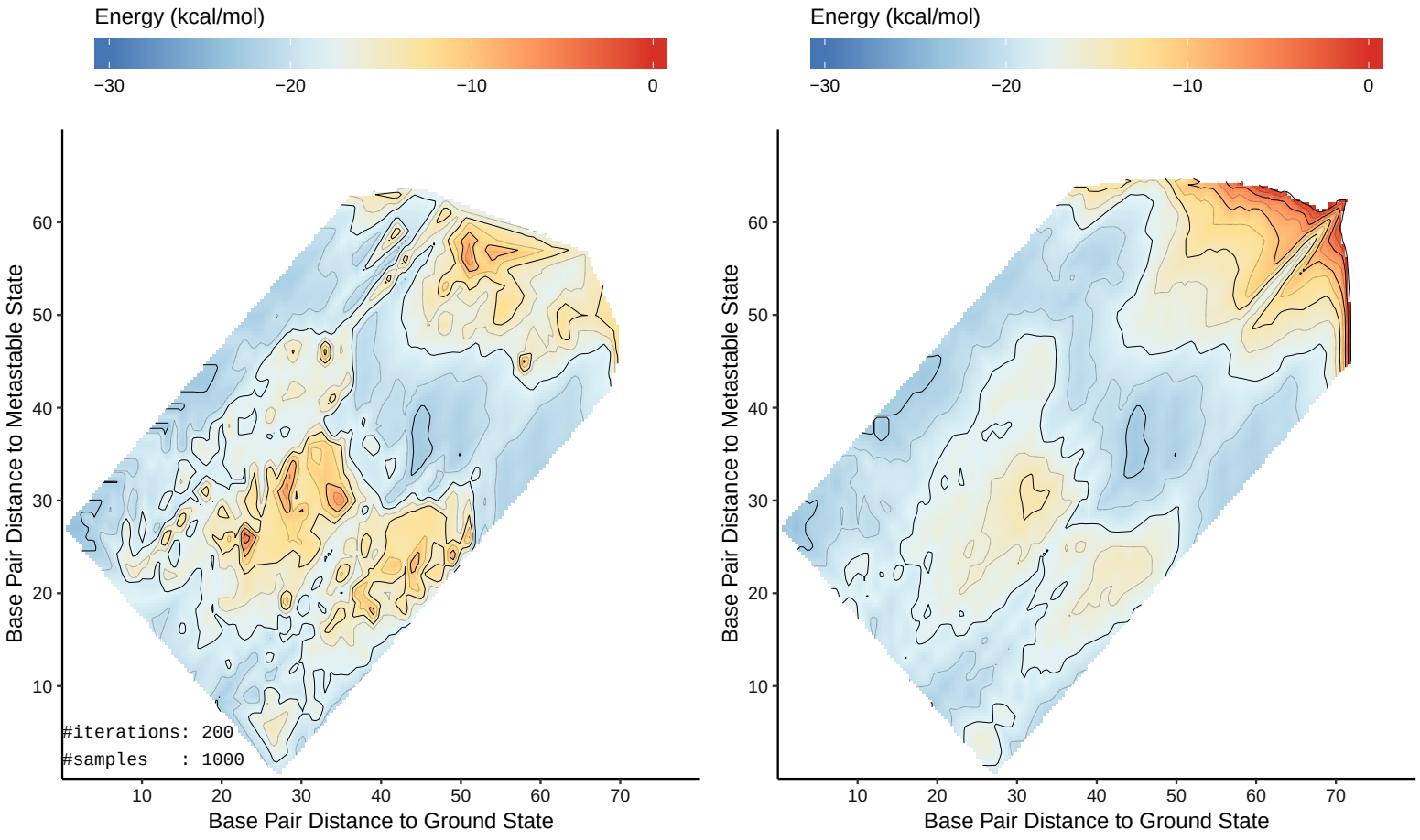

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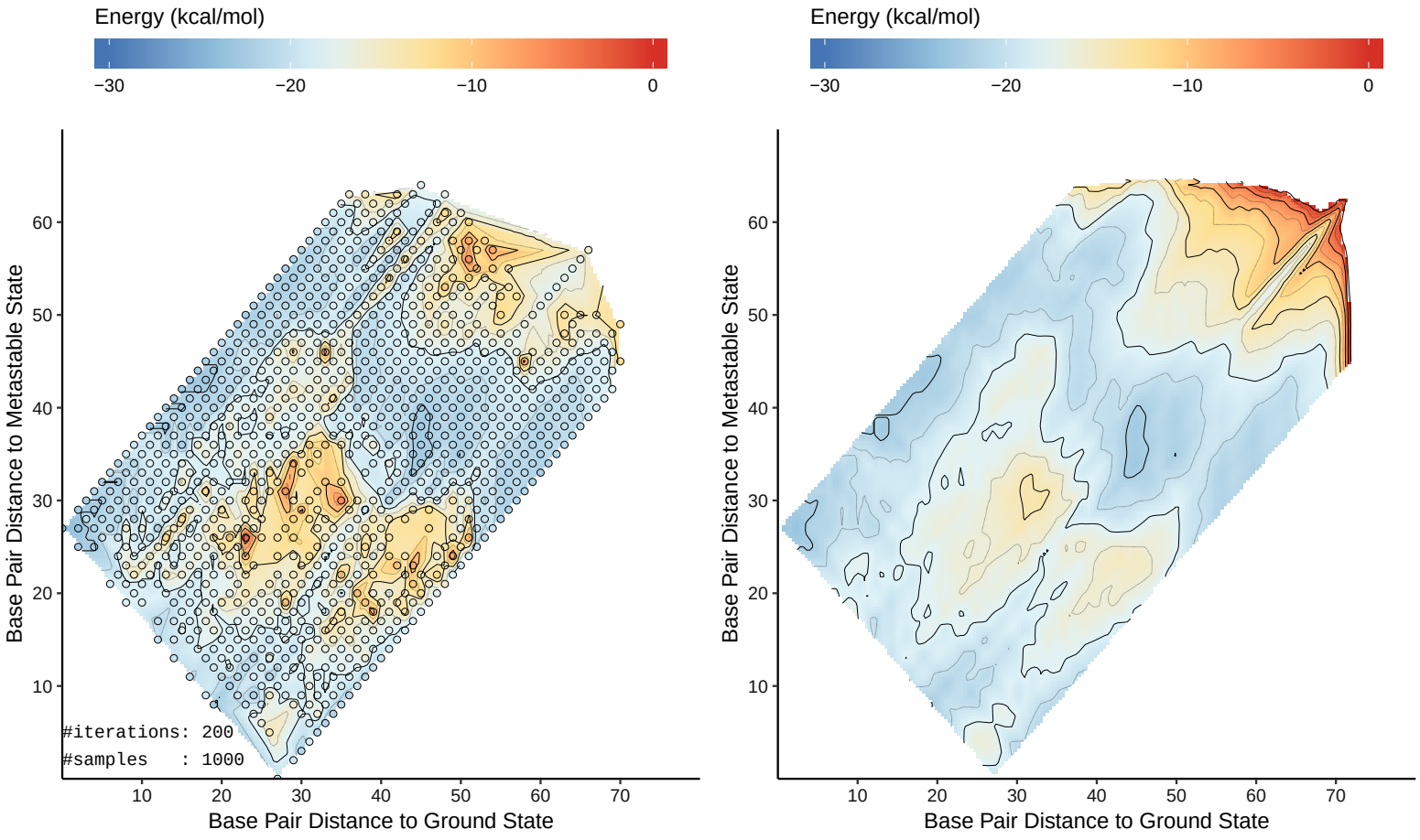

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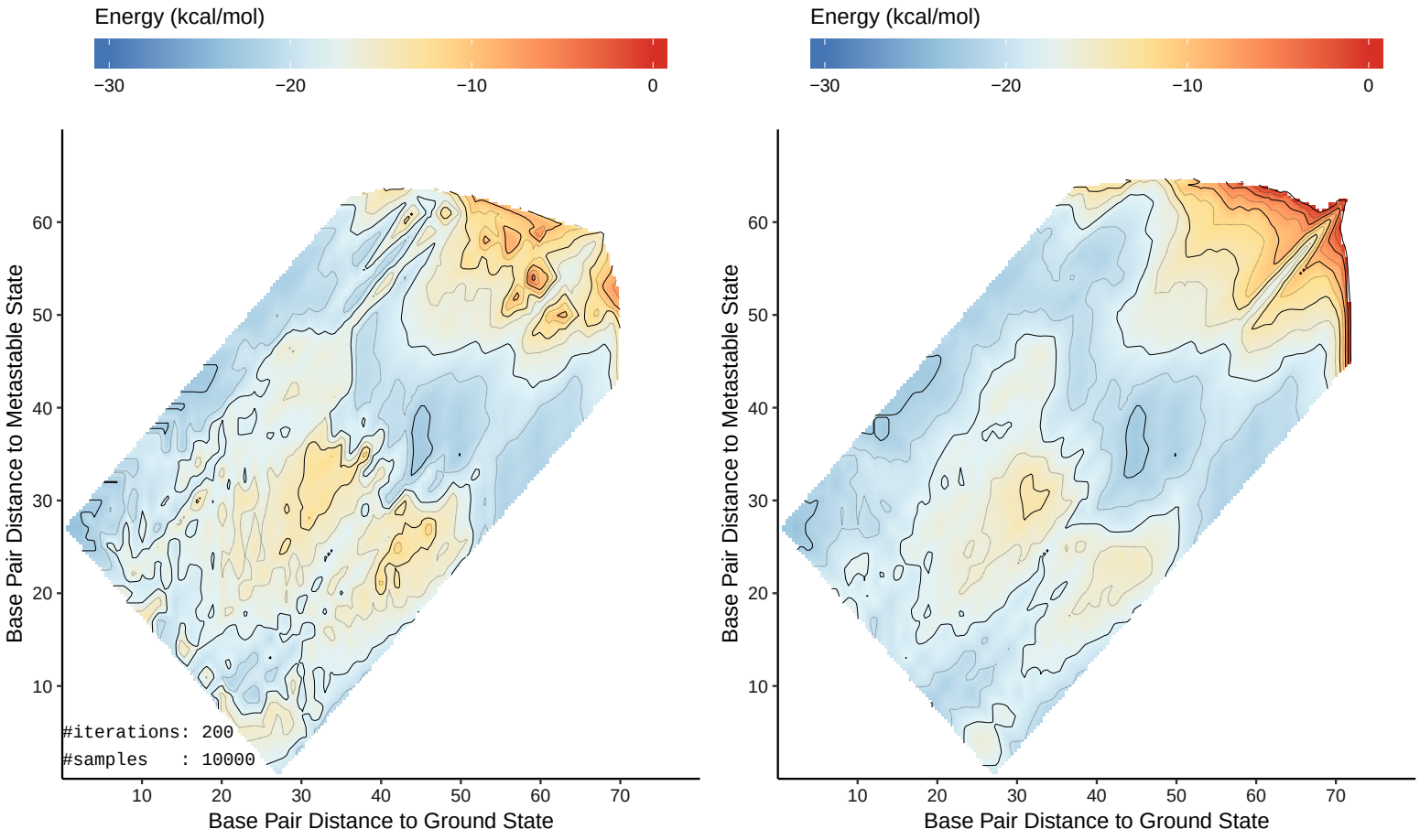

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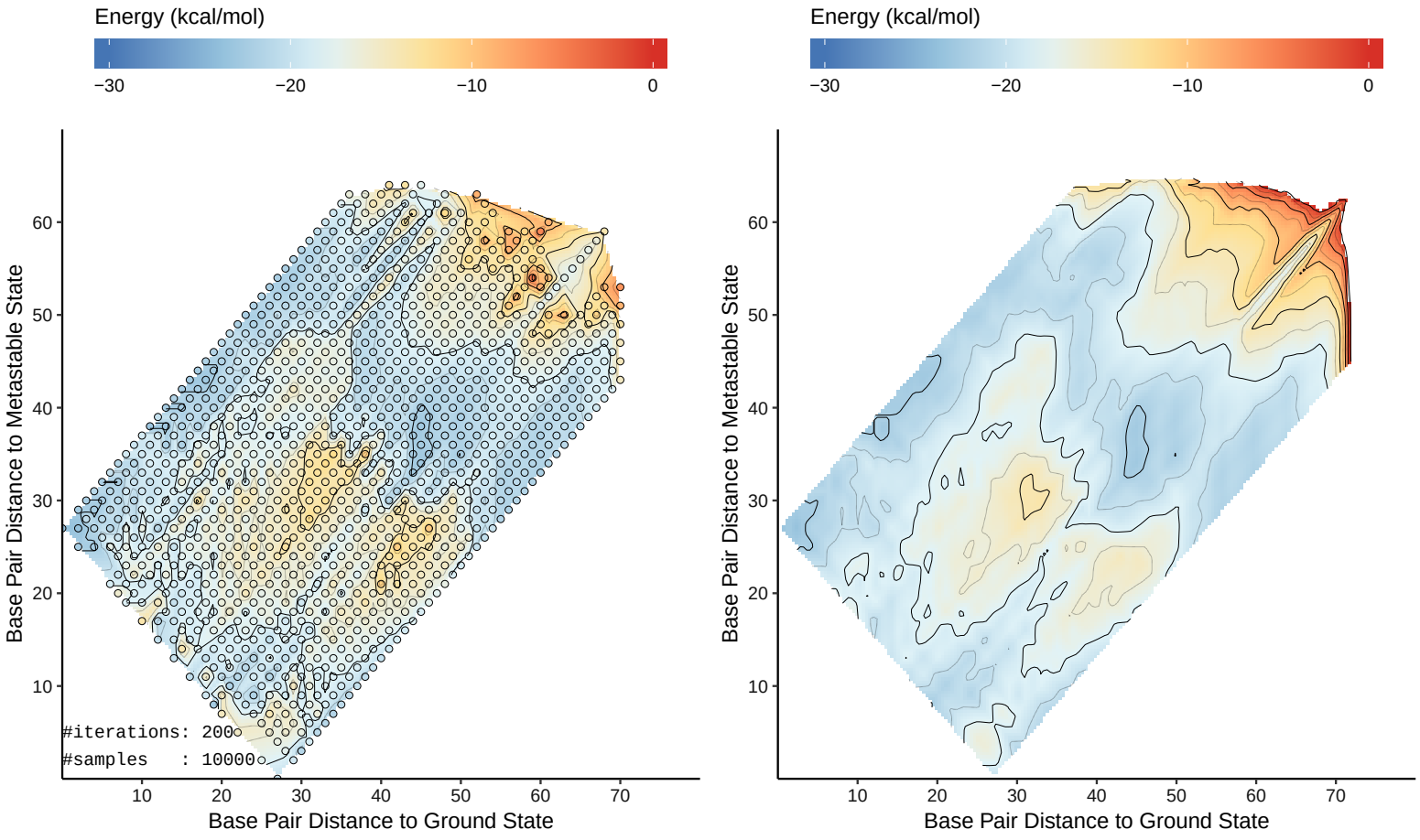

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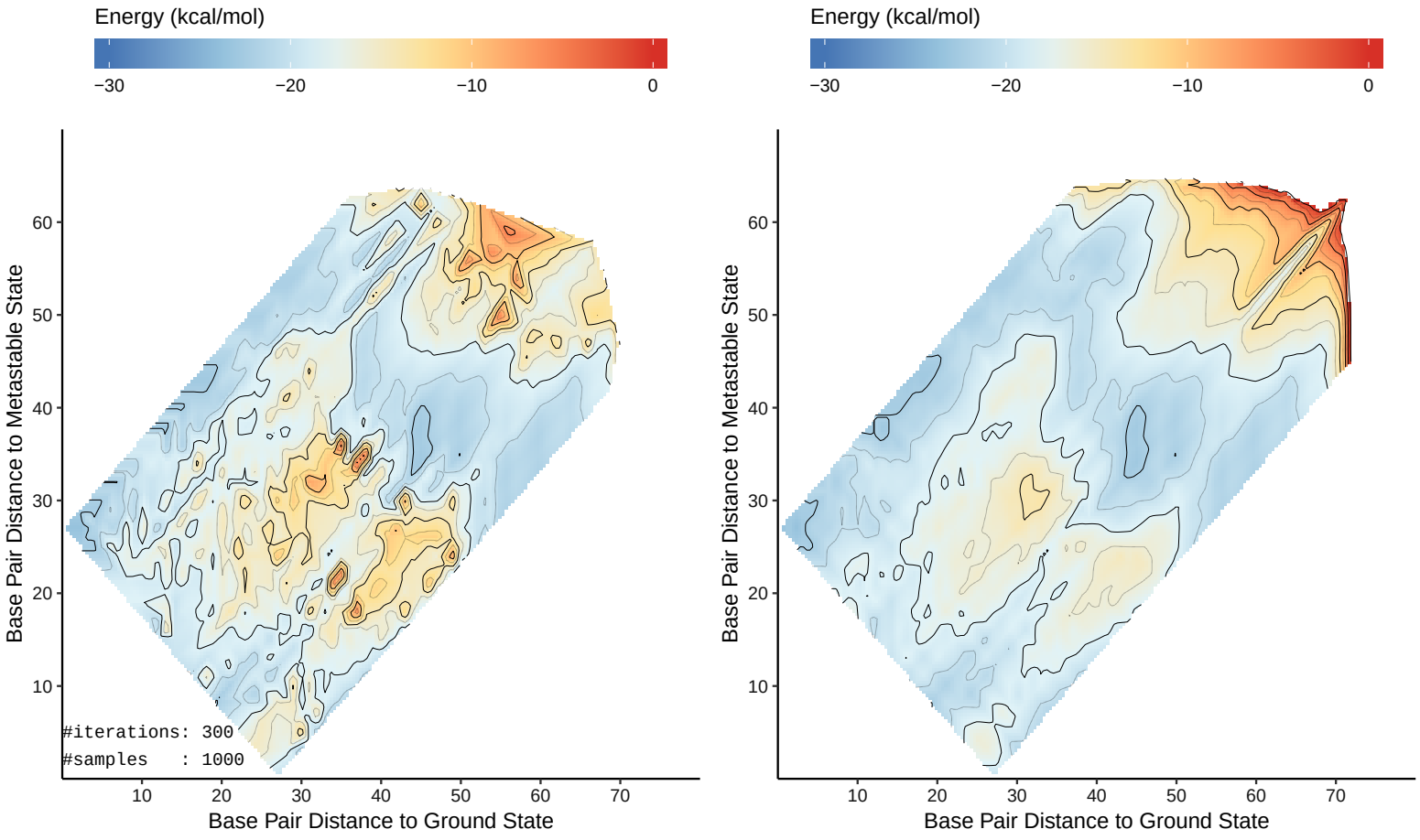

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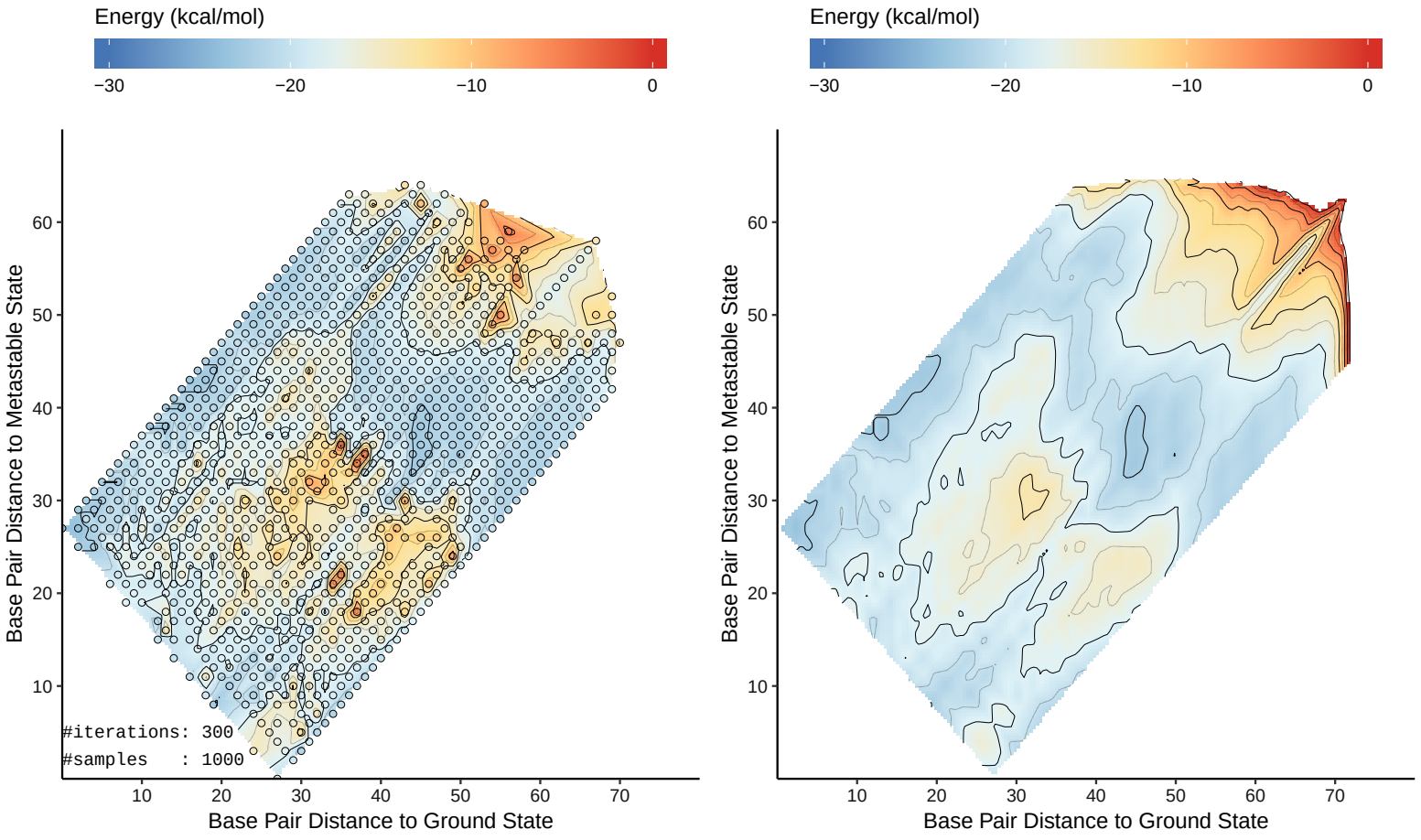

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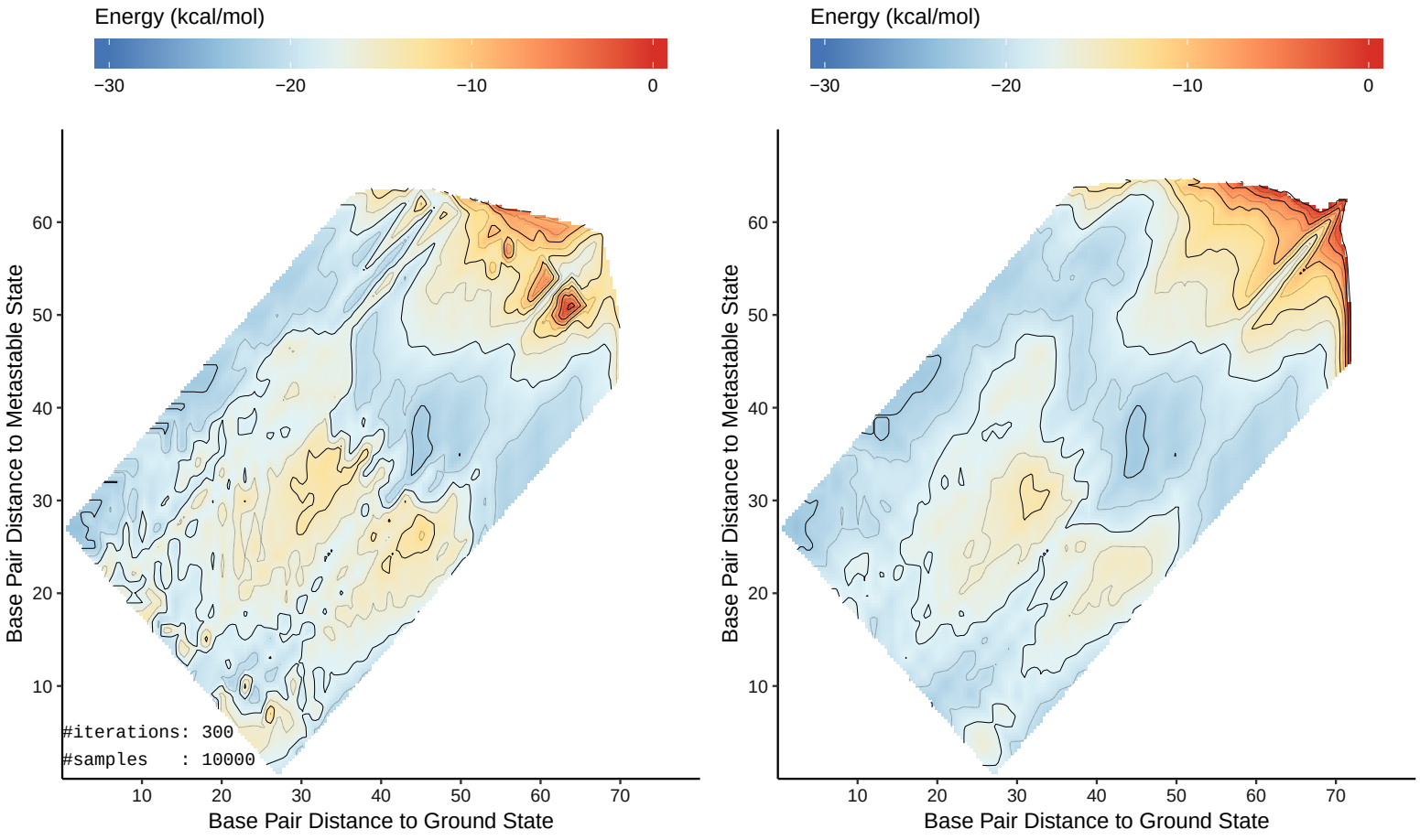

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