

Sampling RNA Secondary Structure Landscapes for Kinetics Simulations

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RNA Folding Kinetics

Secondary Structure Free Energy Landscapes

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

- X ... Set of secondary structures
- N ... Structures obtained by insertion / removal of 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

$$\frac{dp_i(t)}{dt} = \sum_{j \neq i} p_j(t)r_{ji} - p_i(t)r_{ij}$$

$$\frac{d}{dt}\vec{p}(t) = \mathbf{R}\vec{p}(t) \quad \text{with formal solution} \quad \vec{p}(t) = e^{t \cdot \mathbf{R}} \cdot \vec{p}(0)$$

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. `kifold`¹, `Kinefold`²
- Lump state space into macro states, e.g. `barriers` / `treekin`³

¹Flamm et al. 2001

²Isambert et al. 2001

³Wolfinger et al. 2004

RNA Folding Kinetics

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Still, vast numbers of trajectories or exhaustive enumeration of all states is required!

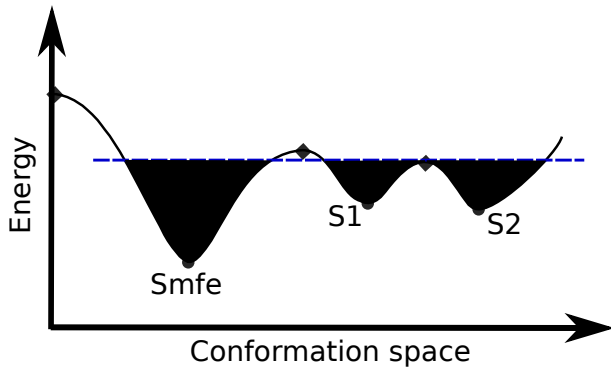
¹Flamm et al. 2001

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³Wolfinger et al. 2004

Sampling Strategies

1. Exhaustive Enumeration⁴

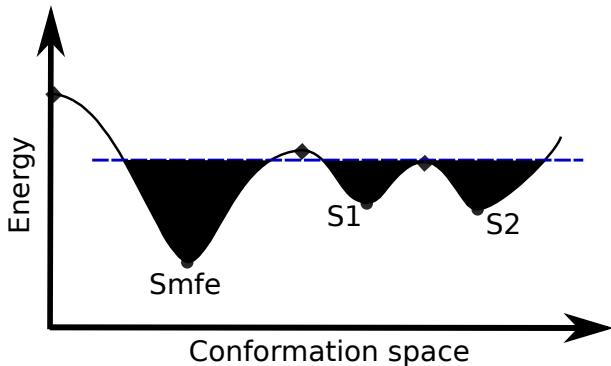


- up to certain threshold δ above MFE
- only applicable to short sequences

⁴Wuchty et al. 1999

Sampling Strategies

1. Exhaustive Enumeration⁴



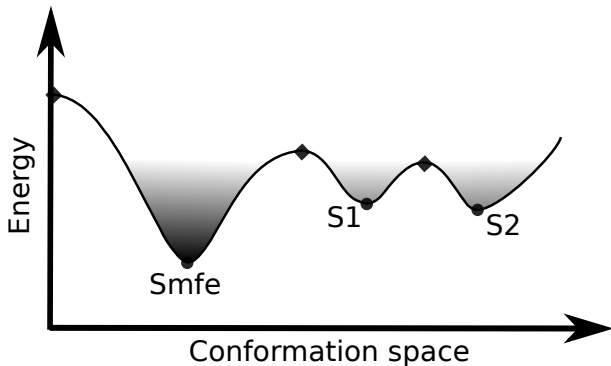
- up to certain threshold δ above MFE
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Draw representative structure samples instead...

⁴Wuchty et al. 1999

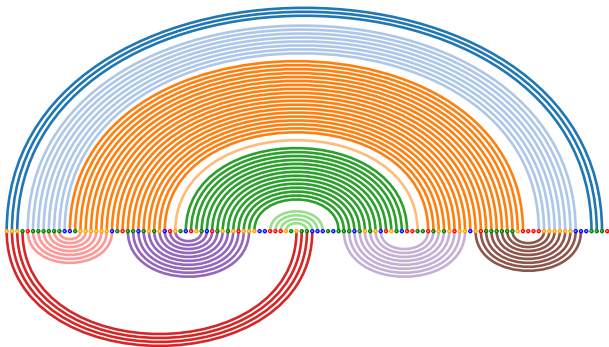
Sampling Strategies

2. Boltzmann Sampling⁵



- 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

Example: Q_{β} replicase template SV11⁶

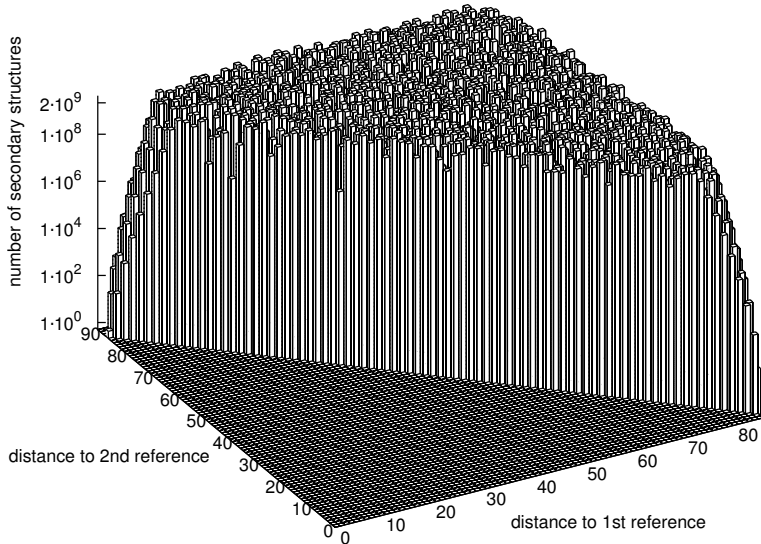


- artificial RNA sequence of 115 nt
- initially folds into metastable conformation
- metastable state is perfect template for Q_{β} replicase
- spontaneously refolds into very stable rod-like MFE structure
- metastable state $> 30kcal/mol$ above MFE

⁶Biebricher et al. 1992

Example: $Q\beta$ replicase template SV11

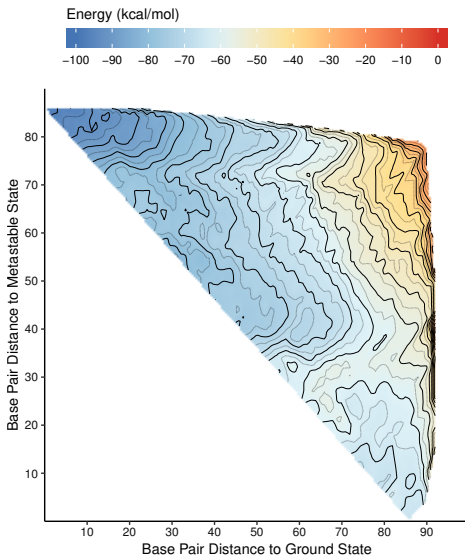
2D Projection of Secondary Structure Landscape⁷



⁷Lorenz et al. 2009

Example: Q_β replicase template SV11

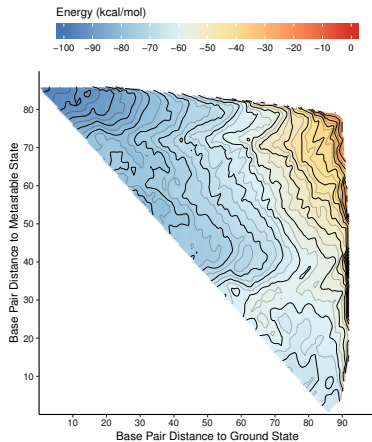
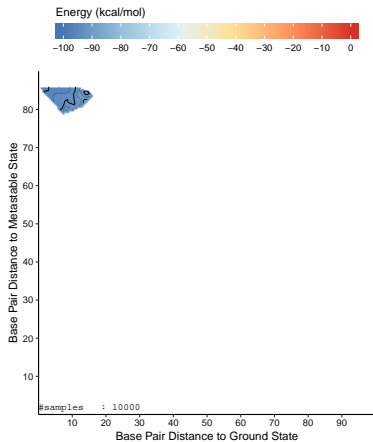
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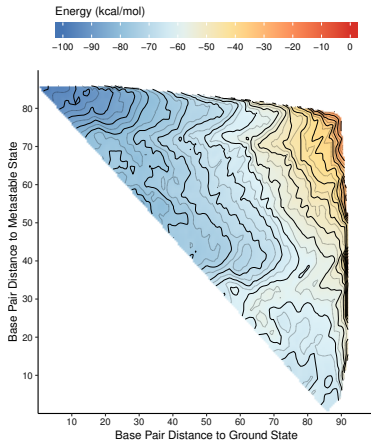
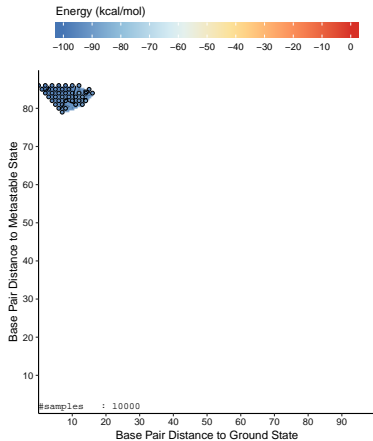
Regular Boltzmann sampling



samples: 10,000, # local minima: 35

Example: Q_β replicase template SV11

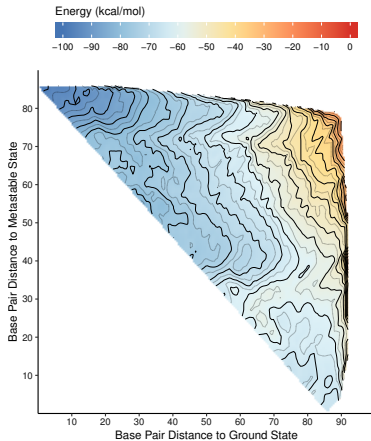
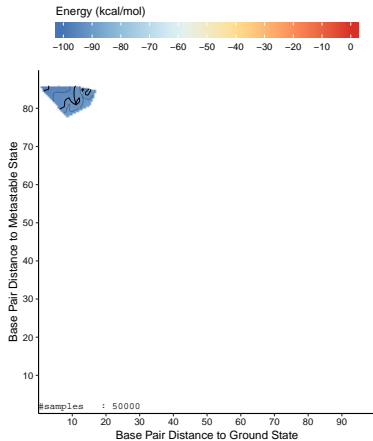
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Example: Q_β replicase template SV11

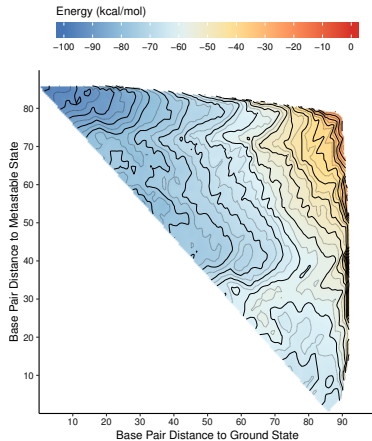
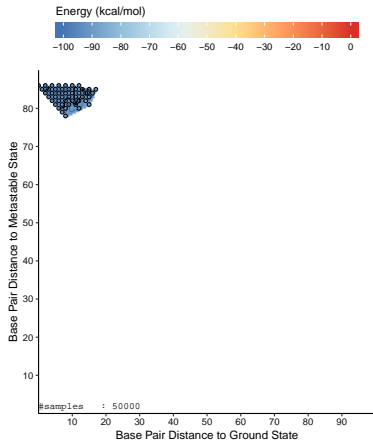
Regular Boltzmann sampling



samples: 50,000 / # local minima: 49

Example: Q_β replicase template SV11

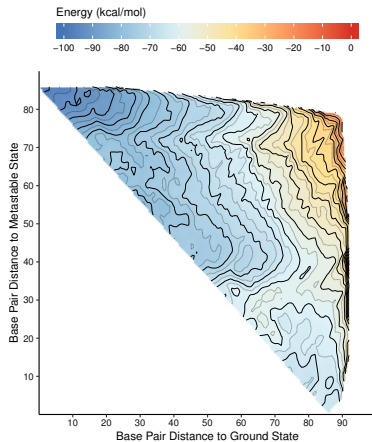
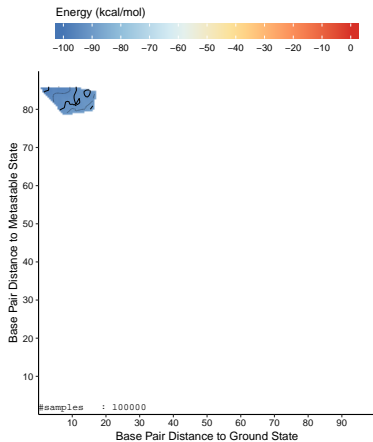
Regular Boltzmann sampling



samples: 50,000 / # local minima: 49

Example: $Q\beta$ replicase template SV11

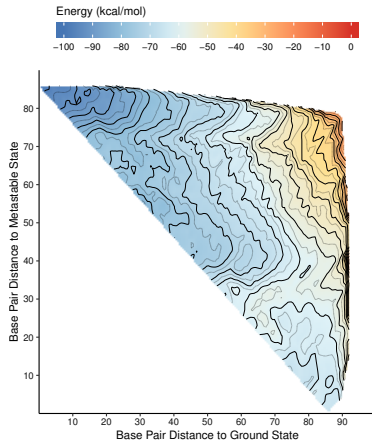
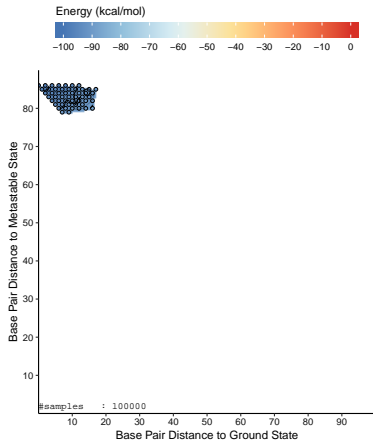
Regular Boltzmann sampling



samples: 100,000 / # local minima: 58

Example: $Q\beta$ replicase template SV11

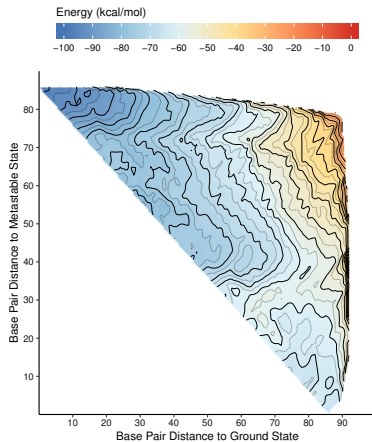
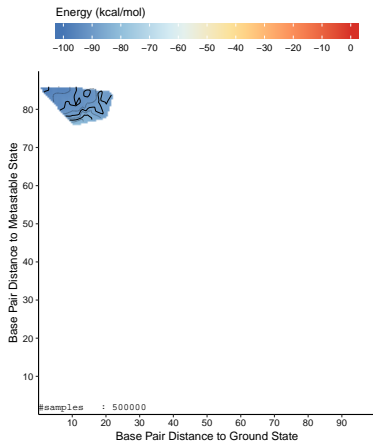
Regular Boltzmann sampling



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Example: $Q\beta$ replicase template SV11

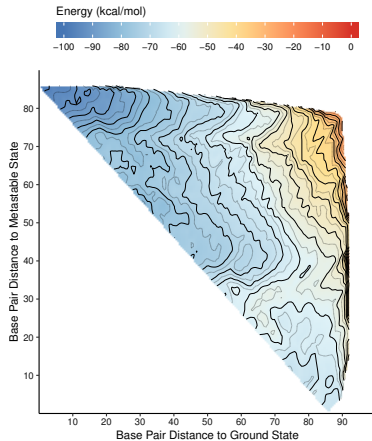
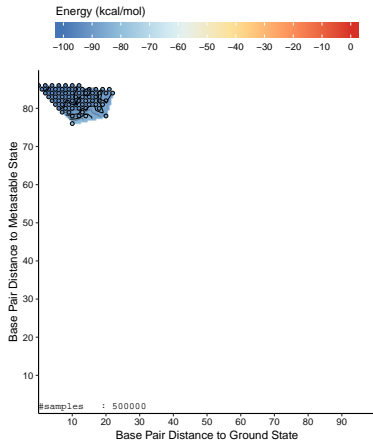
Regular Boltzmann sampling



samples: 500,000 / # local minima: 101

Example: $Q\beta$ replicase template SV11

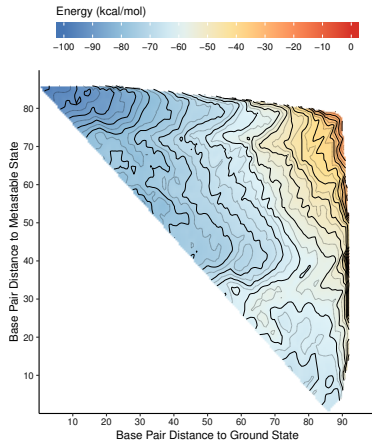
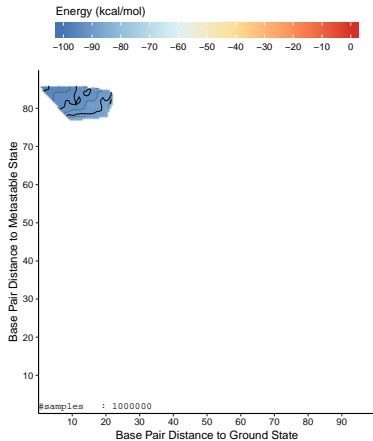
Regular Boltzmann sampling



samples: 500,000 / # local minima: 101

Example: Q_β replicase template SV11

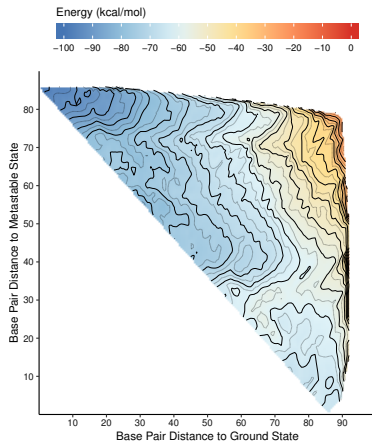
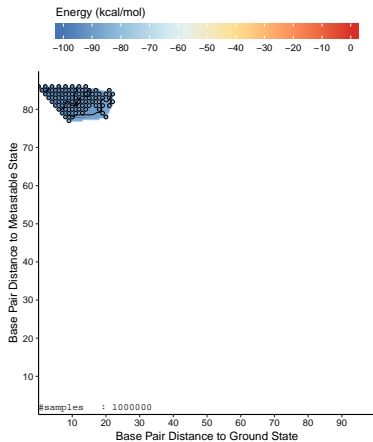
Regular Boltzmann sampling



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

Example: Q_β replicase template SV11

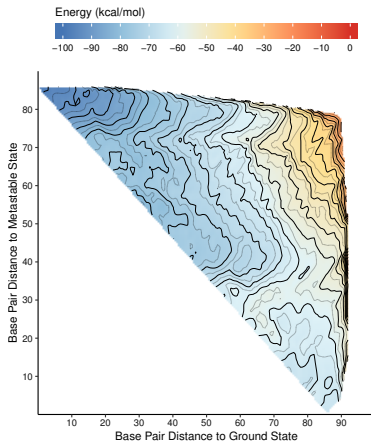
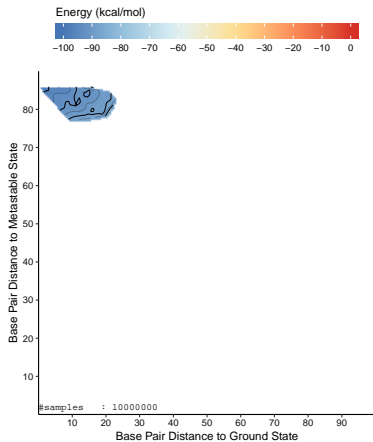
Regular Boltzmann sampling



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

Example: Q_β replicase template SV11

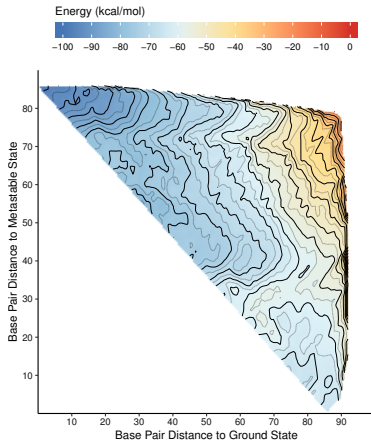
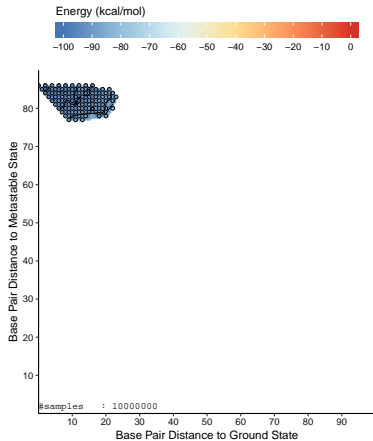
Regular Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

Regular Boltzmann sampling



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

Sampling Strategies

3. Restrict Conformation Space

- Local minima (RNA_{locopt}⁷)
- Flat structures (RNANR⁸)
- Local optimal stack configurations (RNASLOpt⁹)
- Shape abstraction (RNAShapes¹⁰)

drawbacks:

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

⁷Lorenz WA et al. 2011

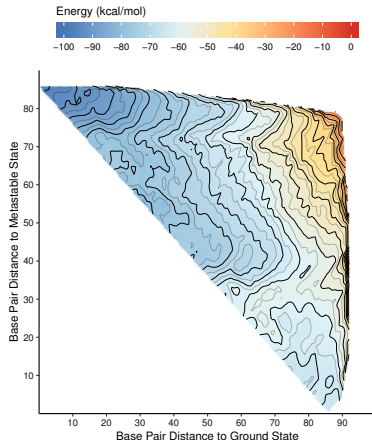
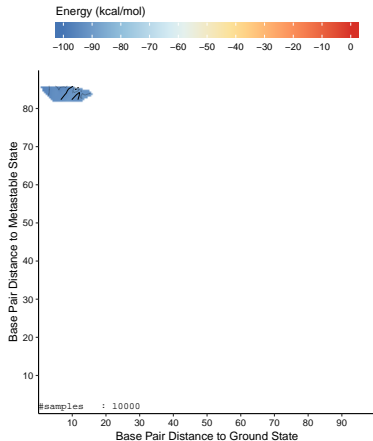
⁸Michalik et al. 2017

⁹Li et al. 2011

¹⁰Steffen et al. 2005

Example: Q_{β} replicase template SV11

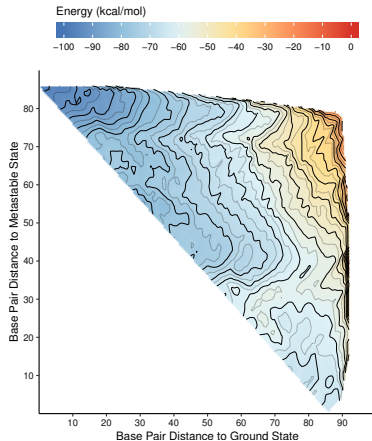
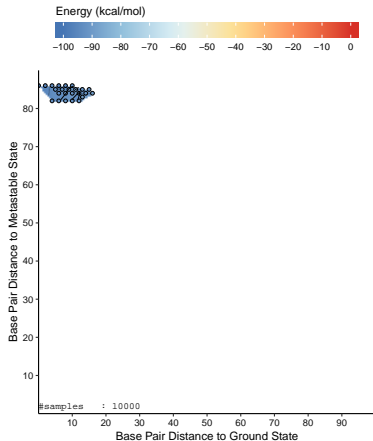
RNAloopt Boltzmann sampling



samples: 10,000, # local minima: 41

Example: Q_β replicase template SV11

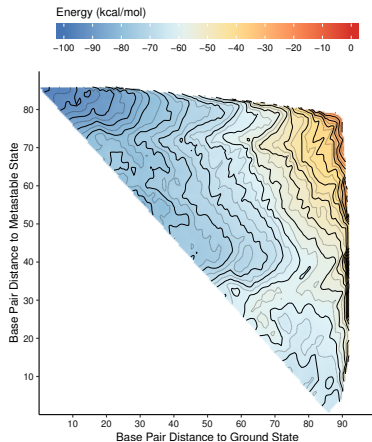
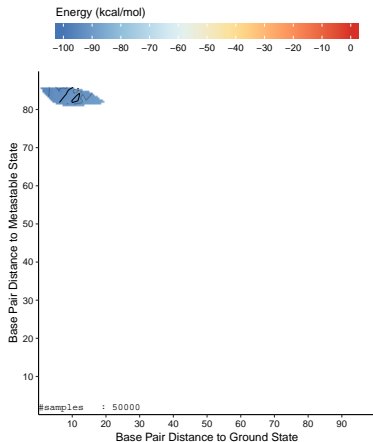
RNAlocopt Boltzmann sampling



samples: 10,000, # local minima: 41

Example: Q_{β} replicase template SV11

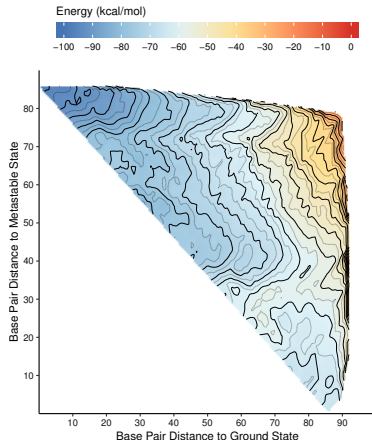
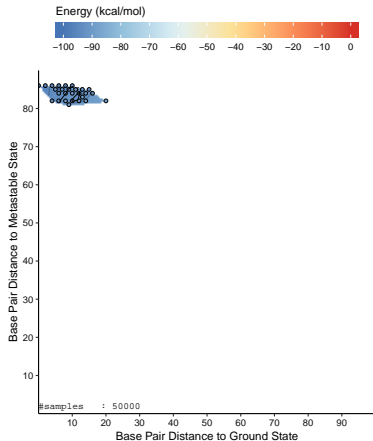
RNAlocopt Boltzmann sampling



samples: 50,000, # local minima: 61

Example: Q_β replicase template SV11

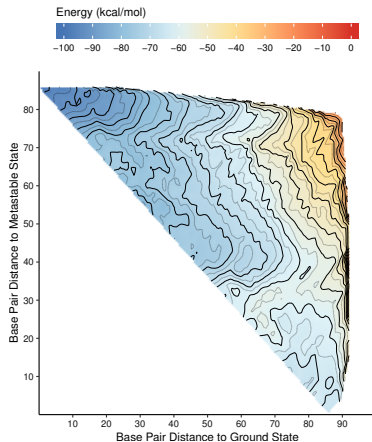
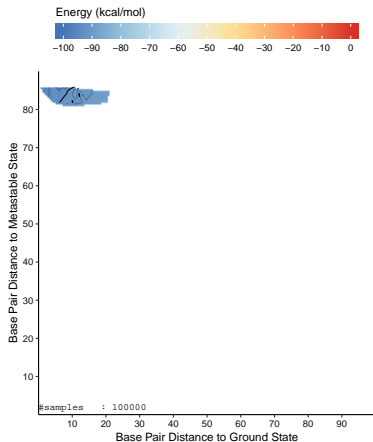
RNAloopt Boltzmann sampling



samples: 50,000, # local minima: 61

Example: Q_β replicase template SV11

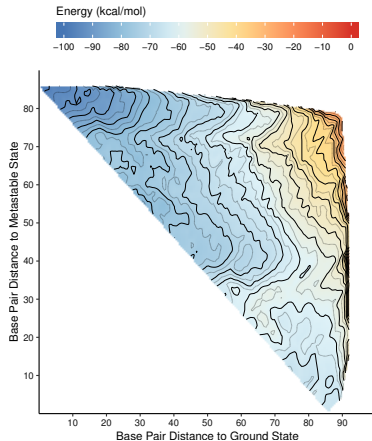
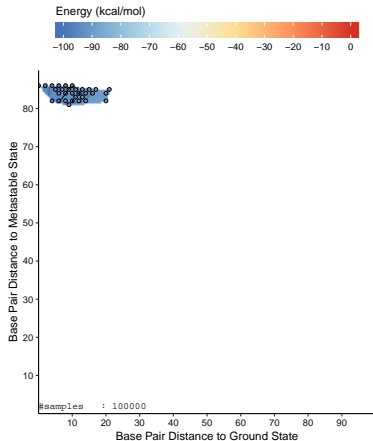
RNAlocopt Boltzmann sampling



samples: 100,000, # local minima: 72

Example: $Q\beta$ replicase template SV11

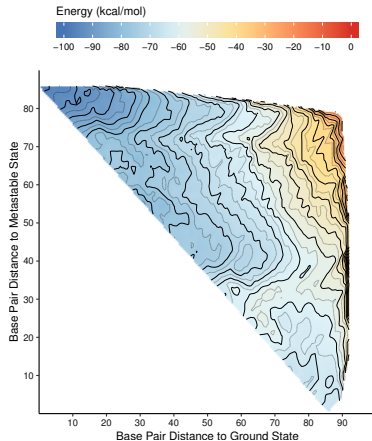
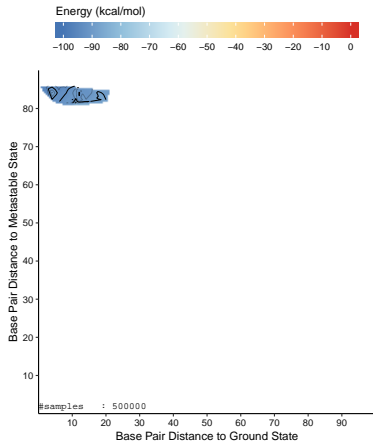
RNAlocopt Boltzmann sampling



samples: 100,000, # local minima: 72

Example: $Q\beta$ replicase template SV11

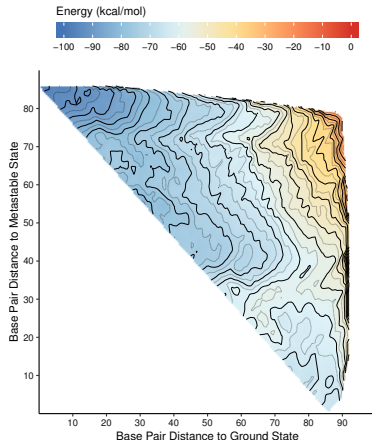
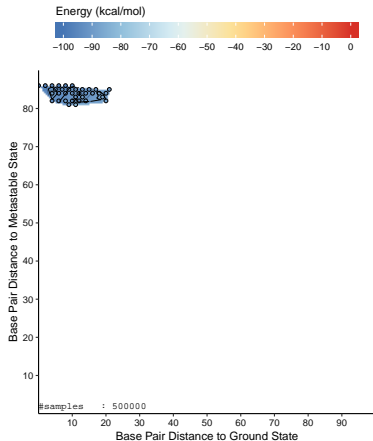
RNAlocopt Boltzmann sampling



samples: 500,000, # local minima: 107

Example: Q_β replicase template SV11

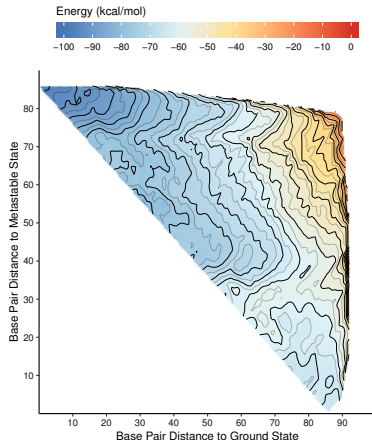
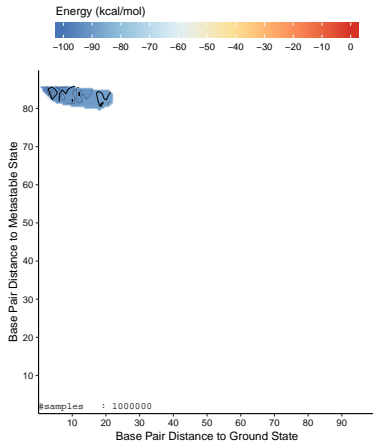
RNAlocopt Boltzmann sampling



samples: 500,000, # local minima: 107

Example: $Q\beta$ replicase template SV11

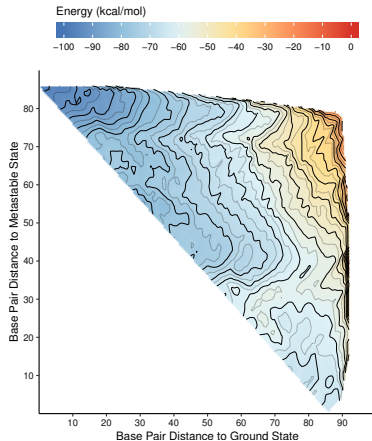
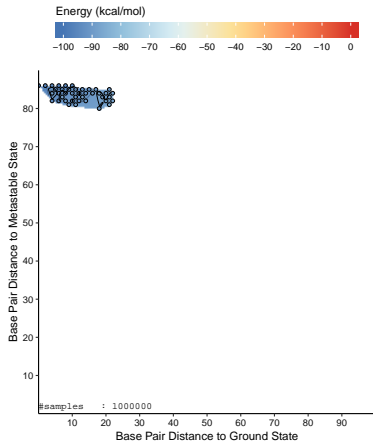
RNAloopt Boltzmann sampling



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

Example: Q_β replicase template SV11

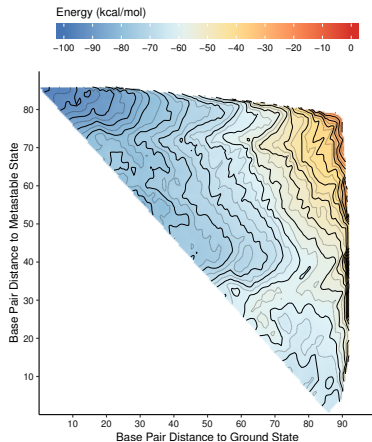
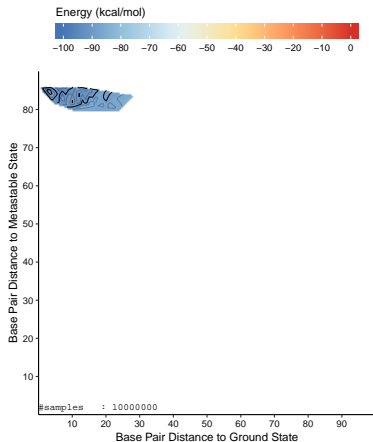
RNAloopt Boltzmann sampling



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

Example: Q_β replicase template SV11

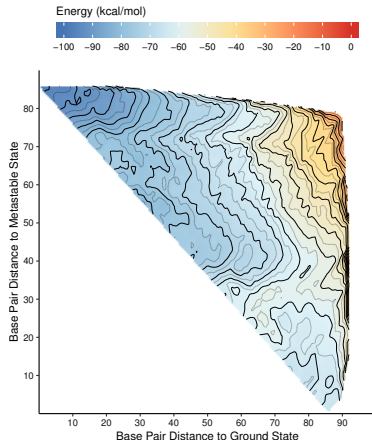
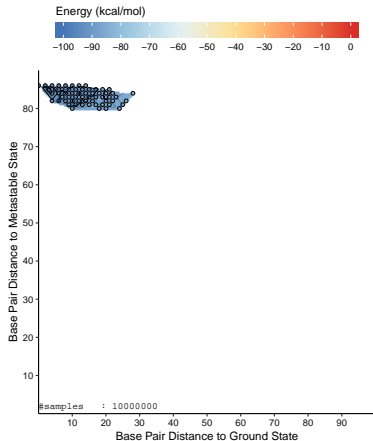
RNAloopt Boltzmann sampling



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

Example: Q_β replicase template SV11

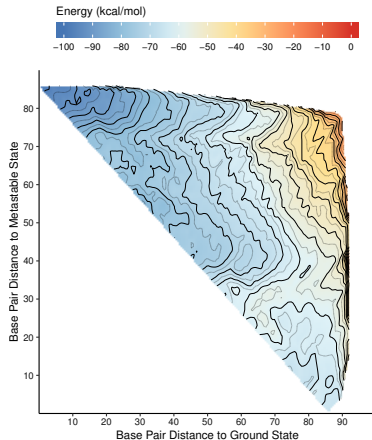
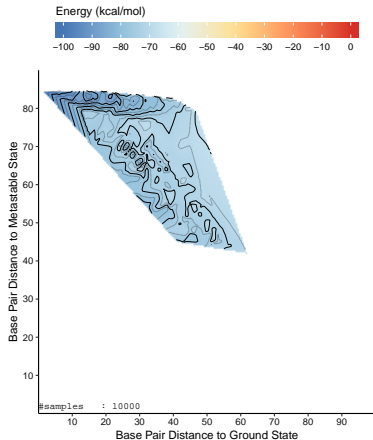
RNAloopt Boltzmann sampling



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

Example: Q_β replicase template SV11

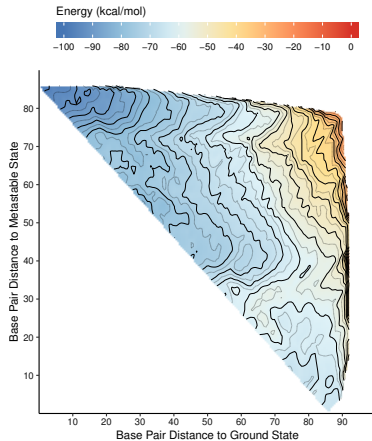
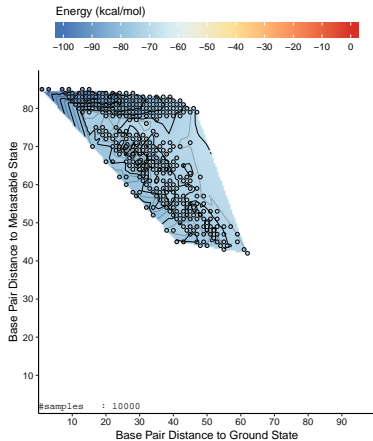
RNANR non-redundant Boltzmann sampling



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

Example: Q_β replicase template SV11

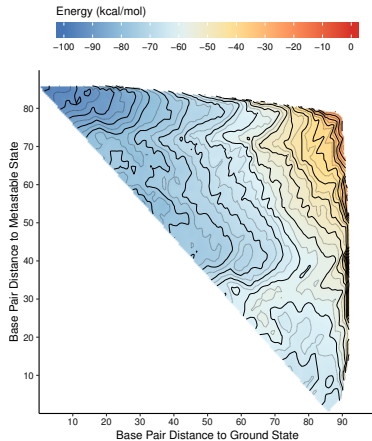
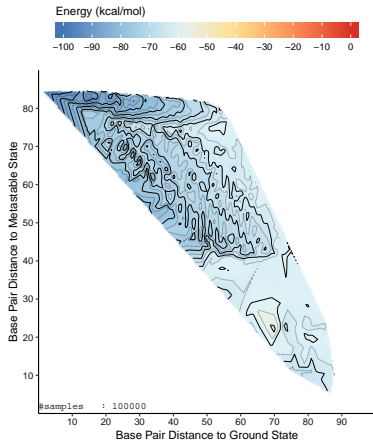
RNANR non-redundant Boltzmann sampling



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

Example: Q_β replicase template SV11

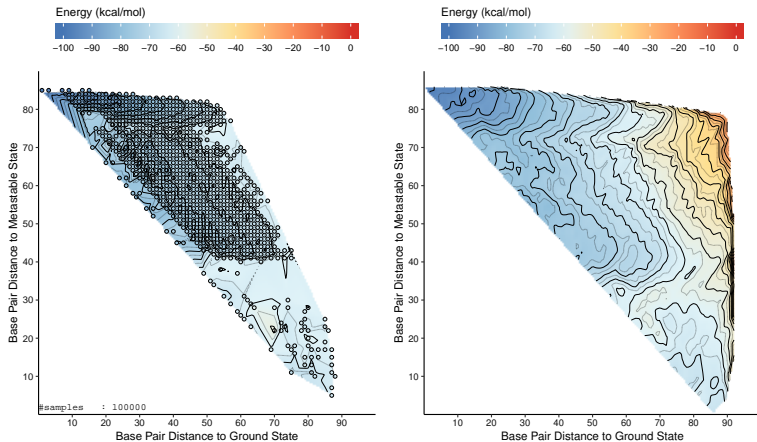
RNANR non-redundant Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

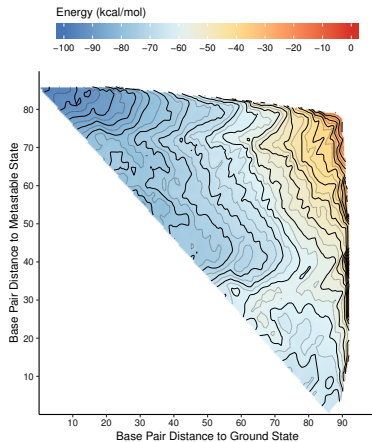
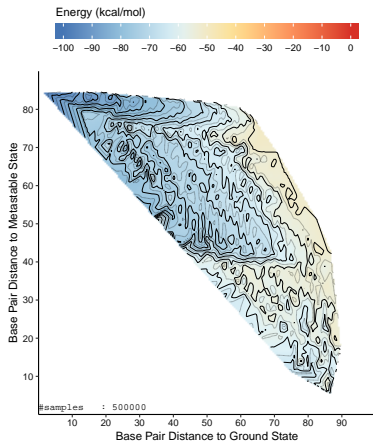
RNANR non-redundant Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

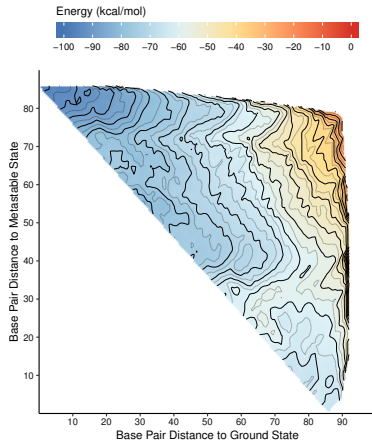
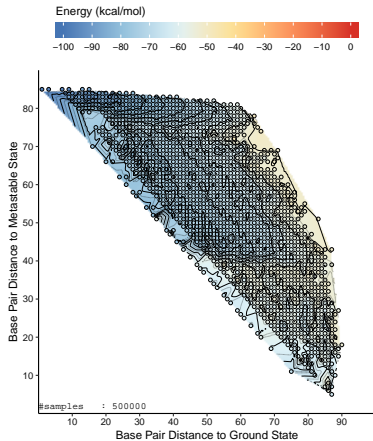
RNANR non-redundant Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

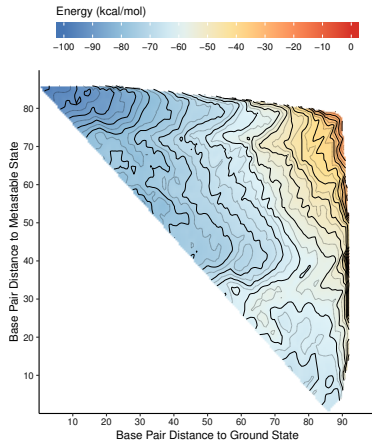
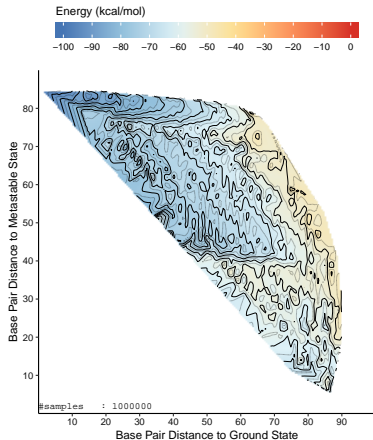
RNANR non-redundant Boltzmann sampling



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

Example: Q_β replicase template SV11

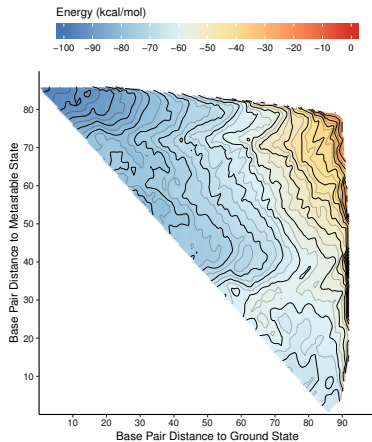
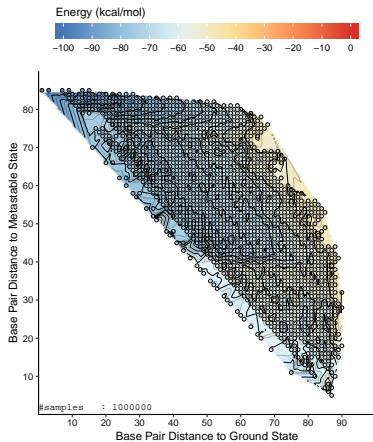
RNANR non-redundant Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

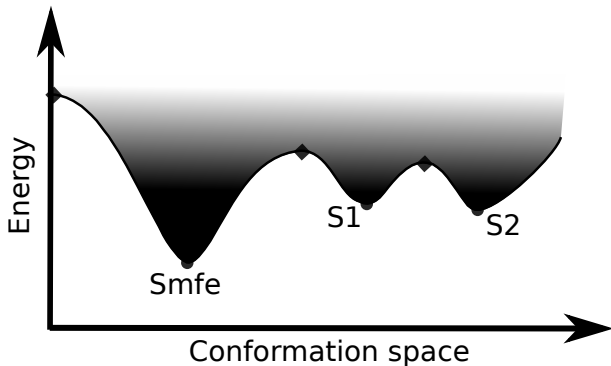
RNANR non-redundant Boltzmann sampling



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

Sampling Strategies

4. Elevated Temperature Boltzmann Sampling

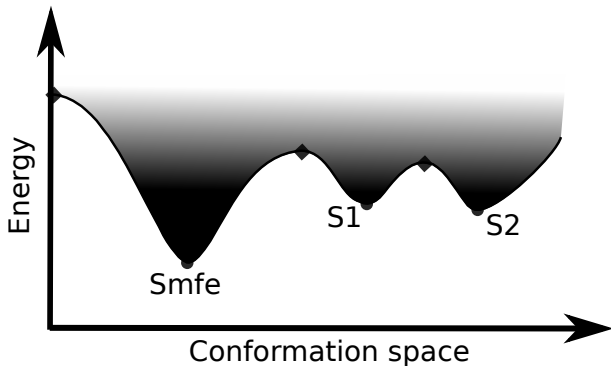


- iteratively draw samples at different $T = \xi \cdot T_0, \xi > 1$
- RNAlocmin¹¹

¹¹Kucharik et al. 2014

Sampling Strategies

4. Elevated Temperature Boltzmann Sampling



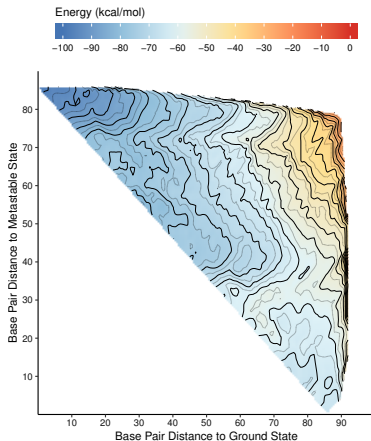
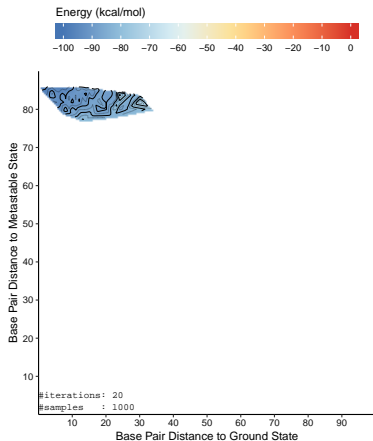
- iteratively draw samples at different $T = \xi \cdot T_0$, $\xi > 1$
- RNAlocmin¹¹

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

¹¹Kucharik et al. 2014

Example: Q_β replicase template SV11

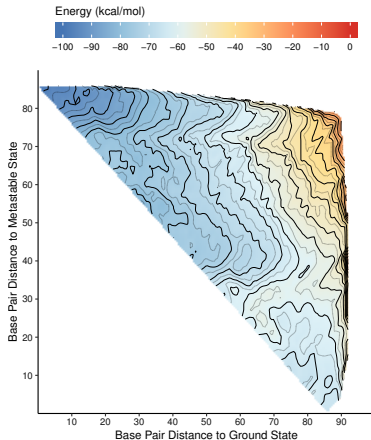
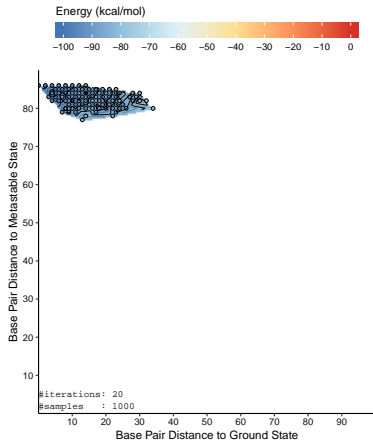
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

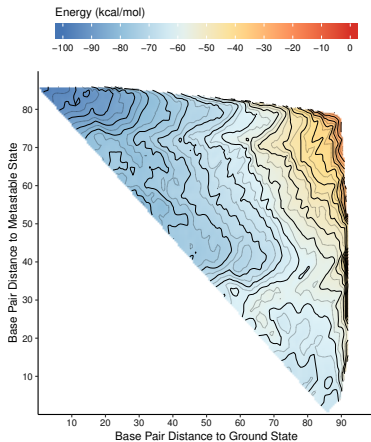
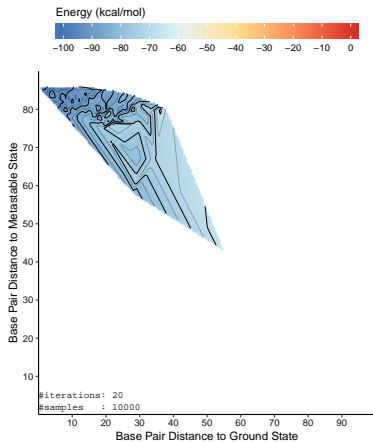
RNAlocmin temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

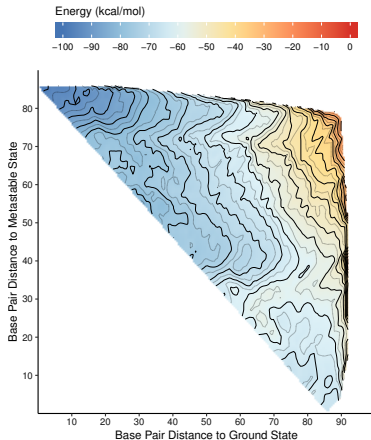
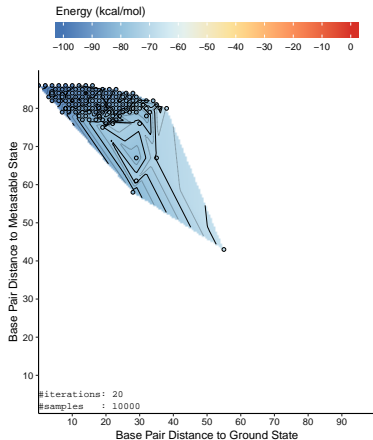
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

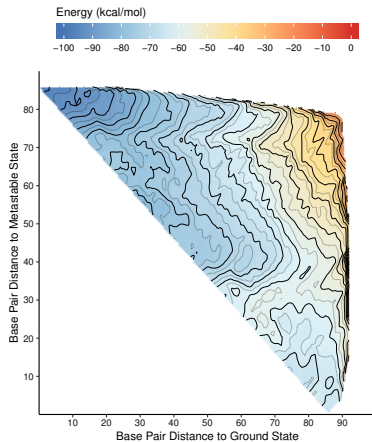
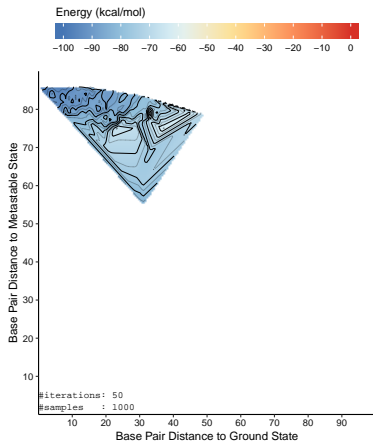
RNAlocmin temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

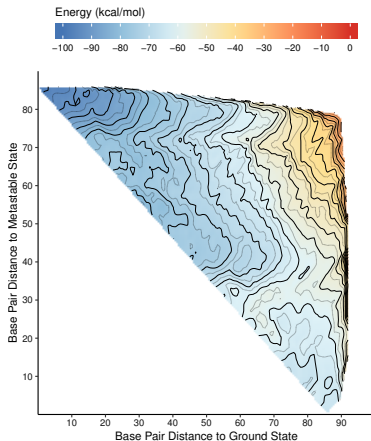
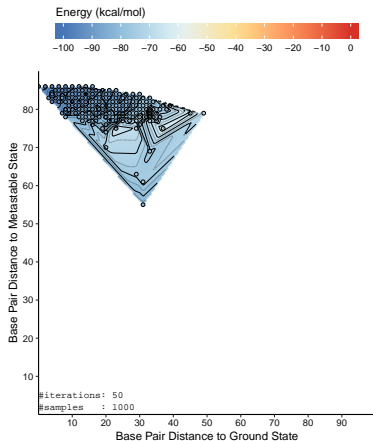
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

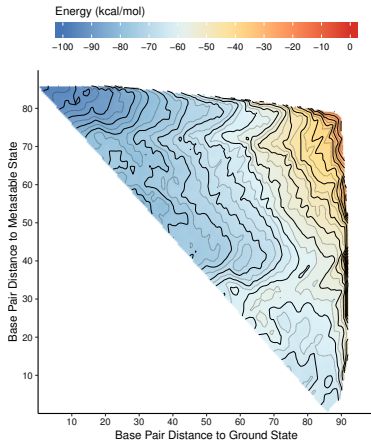
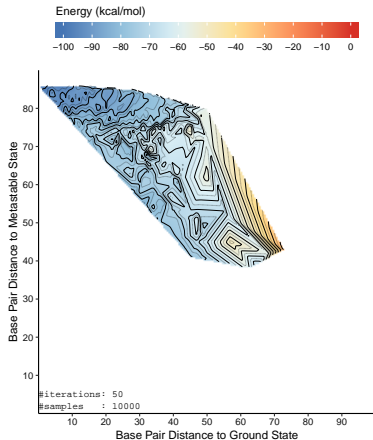
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

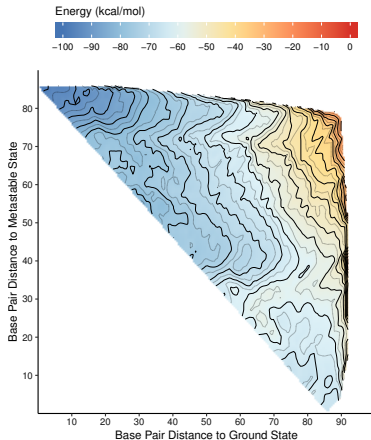
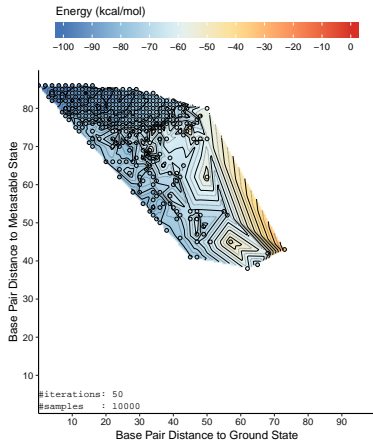
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

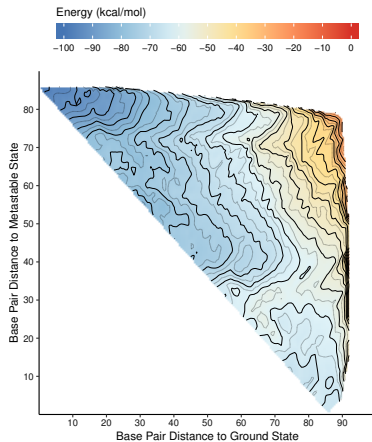
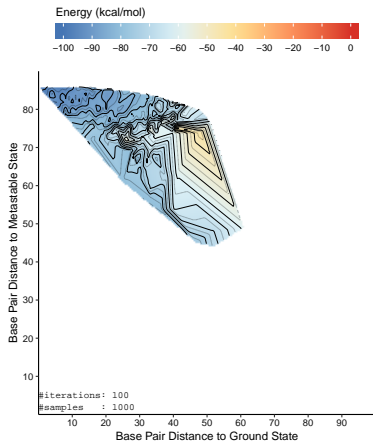
RNAlocmin temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

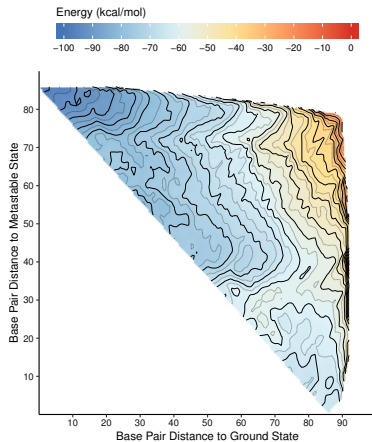
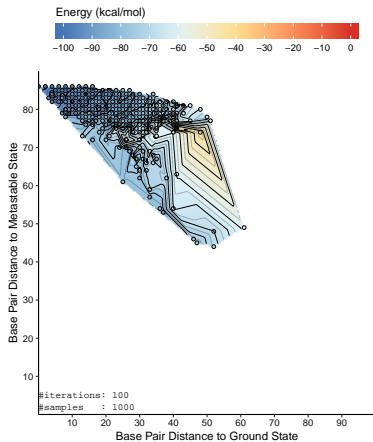
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

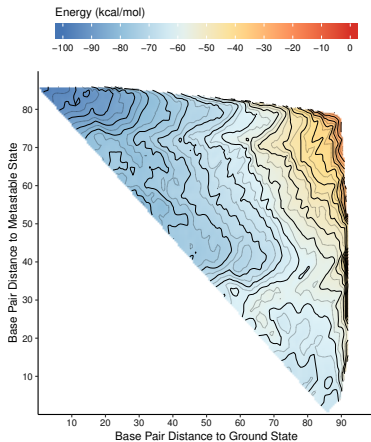
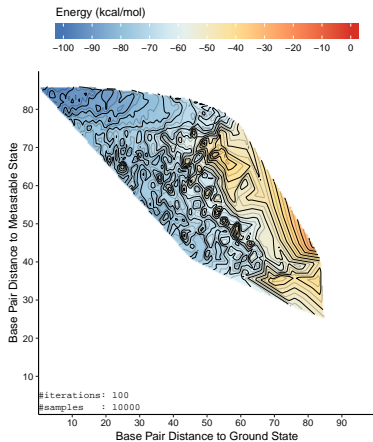
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

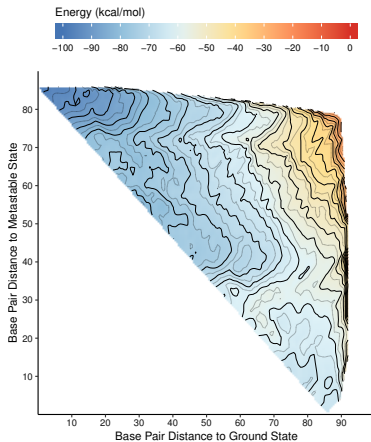
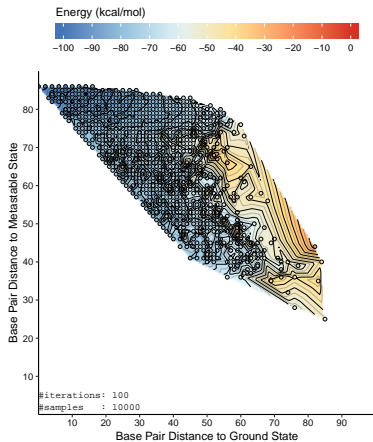
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

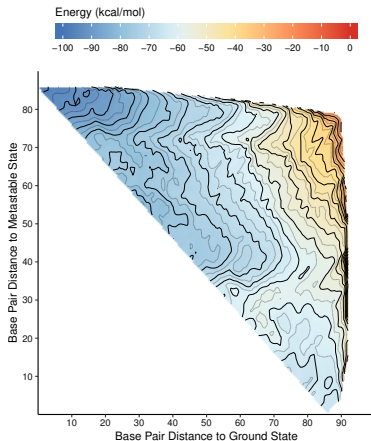
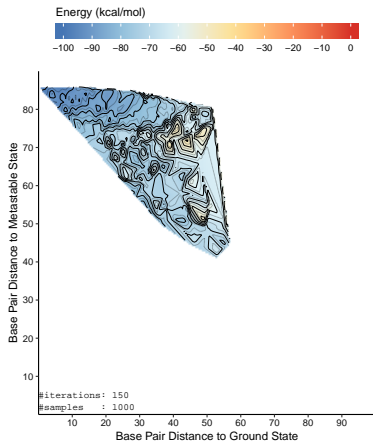
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

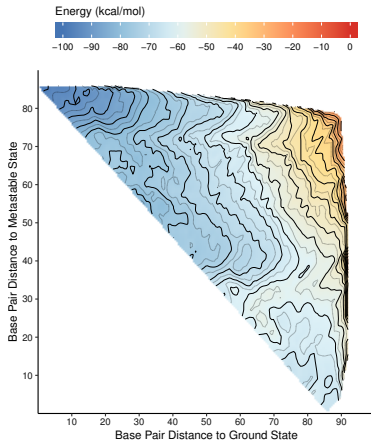
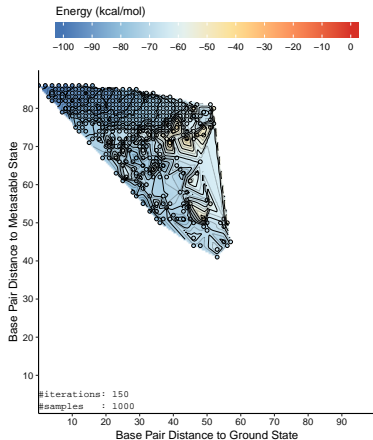
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

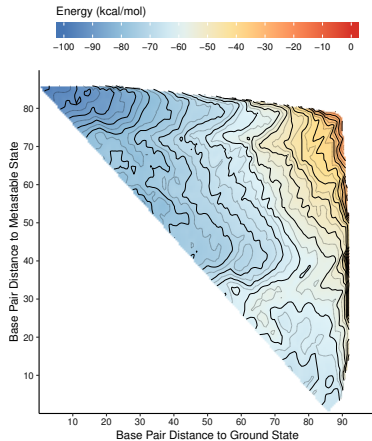
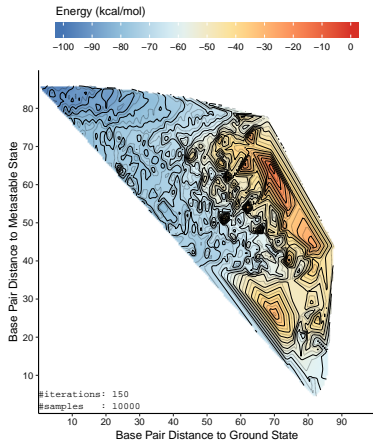
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

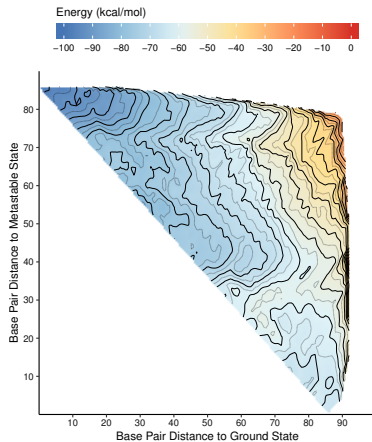
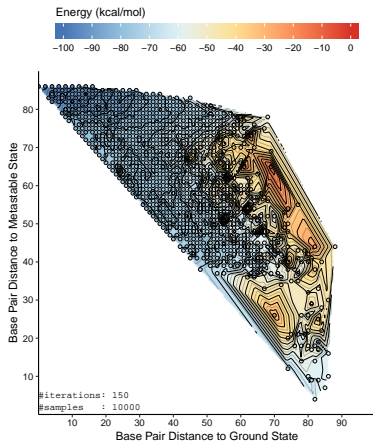
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

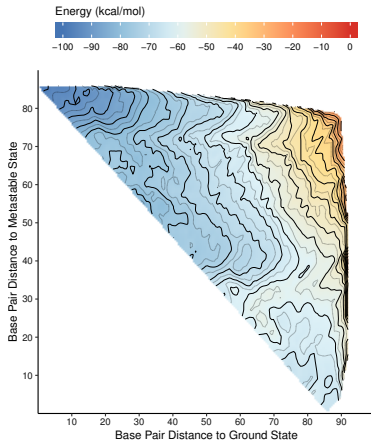
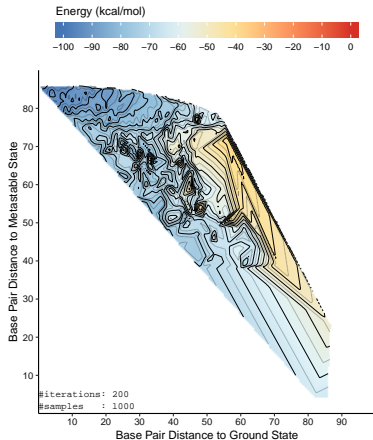
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

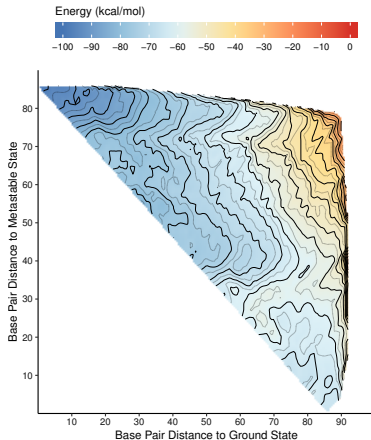
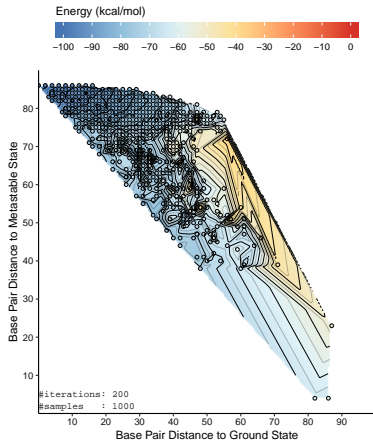
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

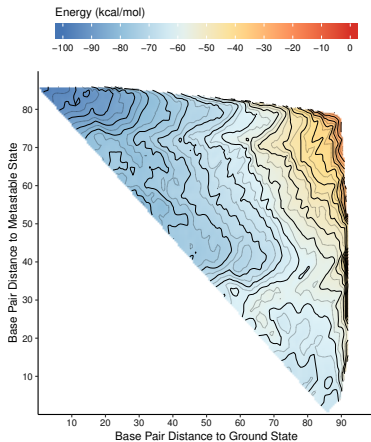
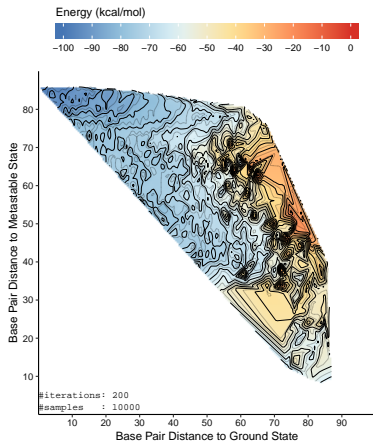
RNAlocmin temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

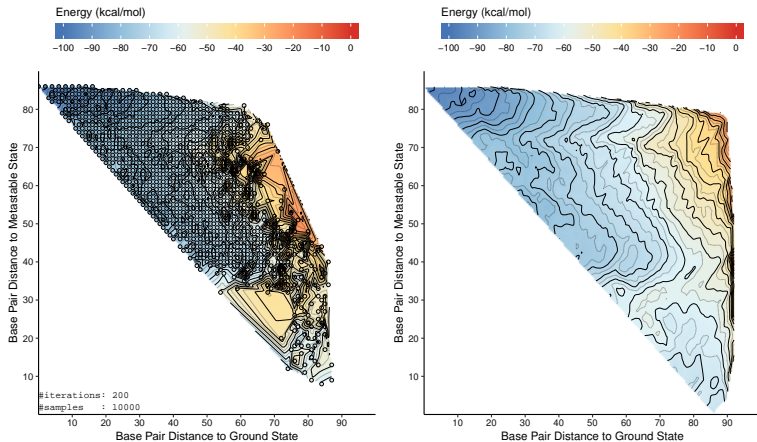
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

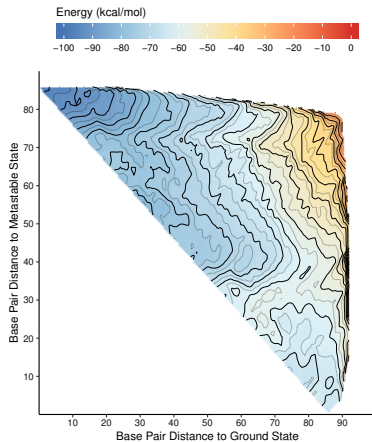
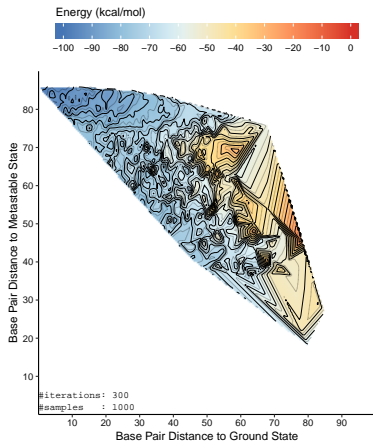
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

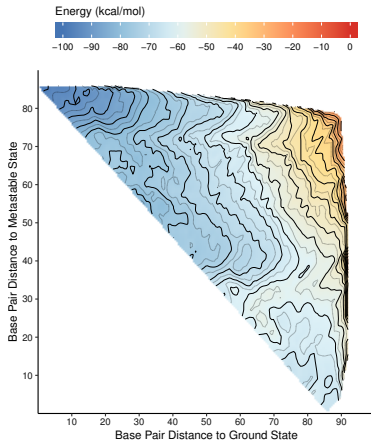
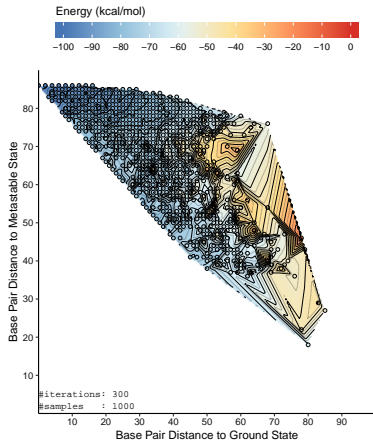
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

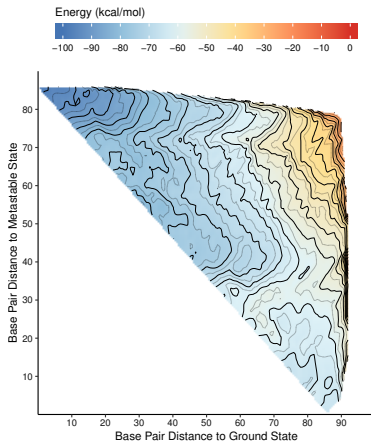
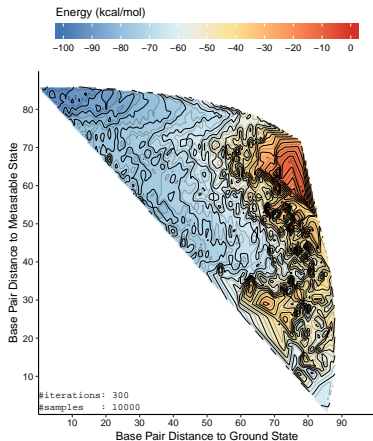
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

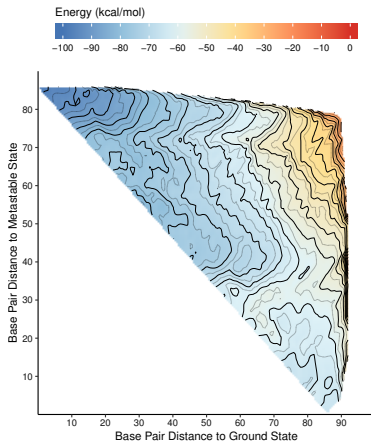
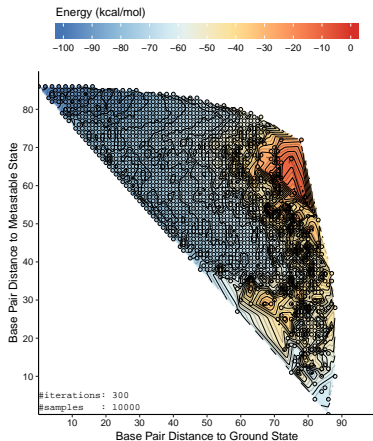
RNAlocmin temperature elevation scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

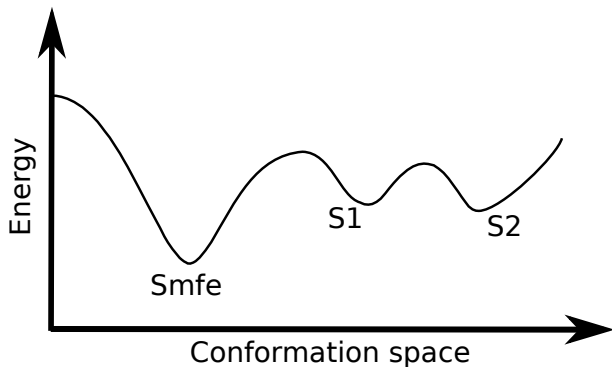
RNA_{locmin} temperature elevation scheme Boltzmann sampling



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

Sampling Strategies

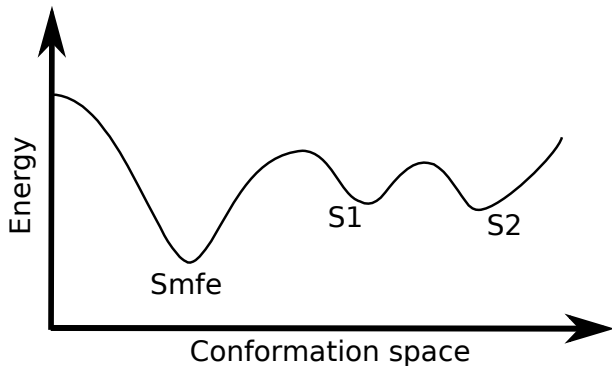
5. Sampling with Guiding Potentials (RNAexplorer)¹²



¹²Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (RNAexplorer)¹²

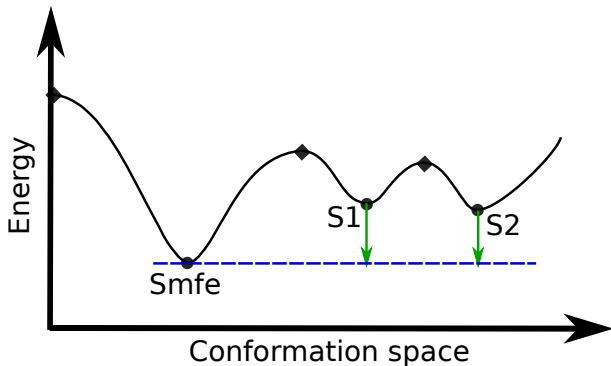


- $p(s) = \frac{\exp(-\beta E(s))}{Z}$

¹²Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (RNAexplorer)¹²

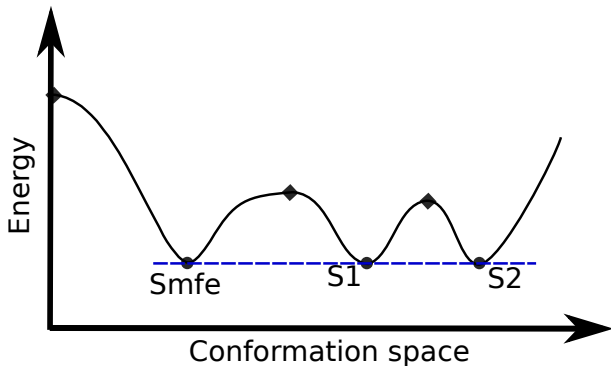


- $p(s) = \frac{\exp(-\beta E(s))}{Z}$
- $E(s_{mfe}) = [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)]$

¹²Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (RNAexplorer)¹²

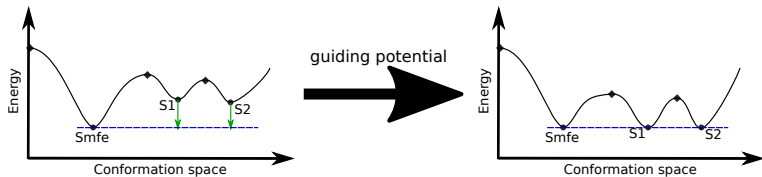


- $p(s) = \frac{\exp(-\beta E(s))}{Z}$
- $E(s_{mfe}) = [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)]$
- $p(s_{mfe}) = p(s_1) = p(s_2)$

¹²Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (RNAexplorer)¹²



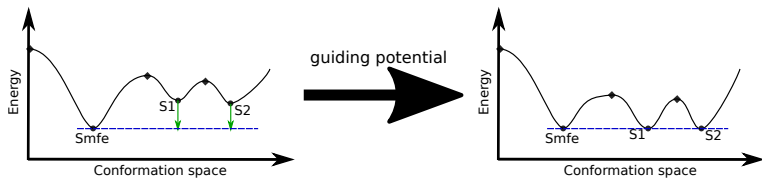
Guiding potential needs to allow for efficiently:

- computing partition function Q
- sampling from distorted energy ensemble

¹²Entzian et al. (manuscript in preparation)

Sampling Strategies

5. Sampling with Guiding Potentials (RNAexplorer)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 Package¹³

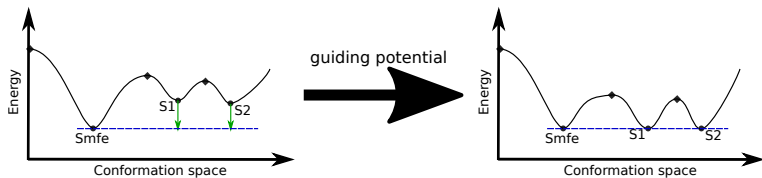
$$E(s_{mfe}) = [E(s_1) + \hat{E}(s_1)] = [E(s_2) + \hat{E}(s_2)]$$
$$\hat{E}(s) = d_{BP}(s, s_1) \cdot w_1 + d_{BP}(s, s_2) \cdot w_2$$

¹²Entzian et al. (manuscript in preparation)

¹³Lorenz et al. 2016

Sampling Strategies

5. Sampling with Guiding Potentials (RNAexplorer)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 Package¹³

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

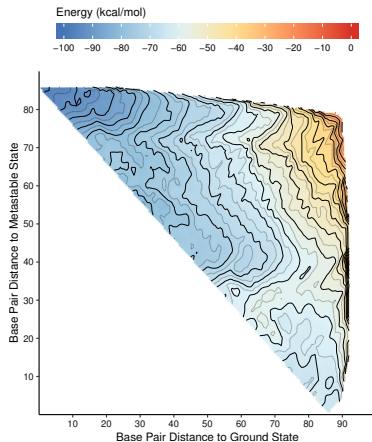
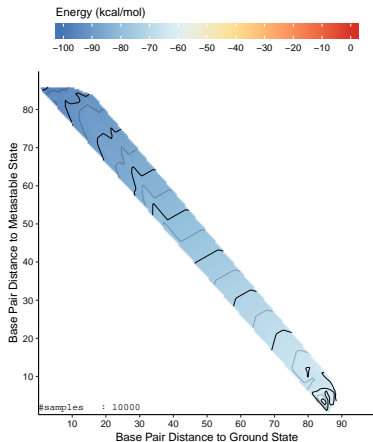
How to choose reference structures s_x ?

¹²Entzian et al. (manuscript in preparation)

¹³Lorenz et al. 2016

Example: $Q\beta$ replicase template SV11

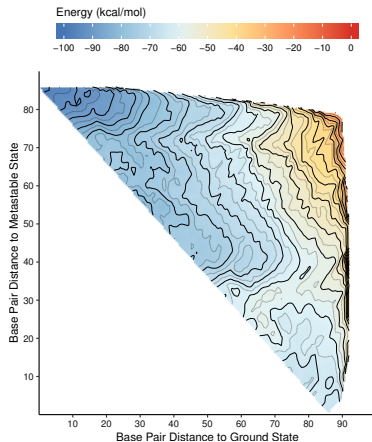
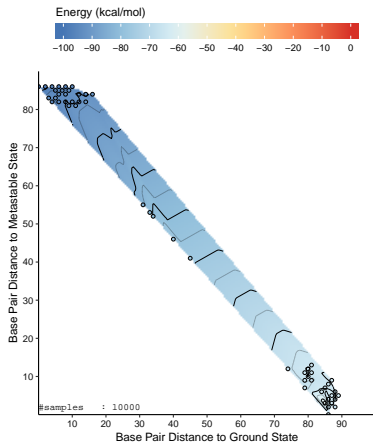
RNExplorer attraction scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

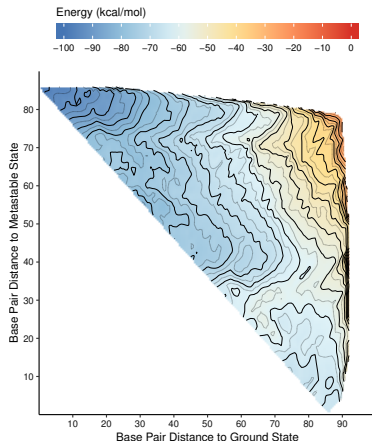
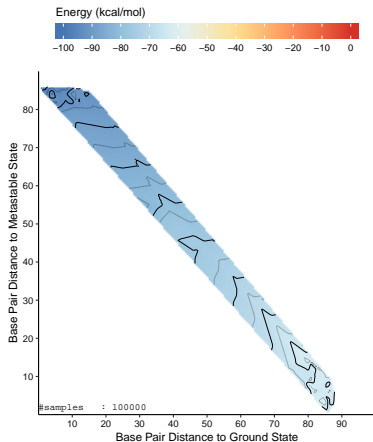
RNExplorer attraction scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

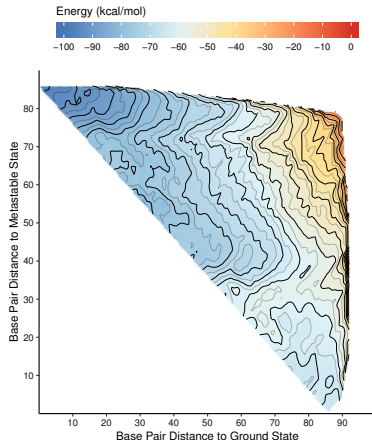
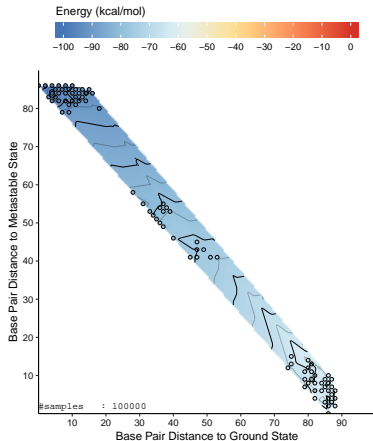
RNAexplorer attraction scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

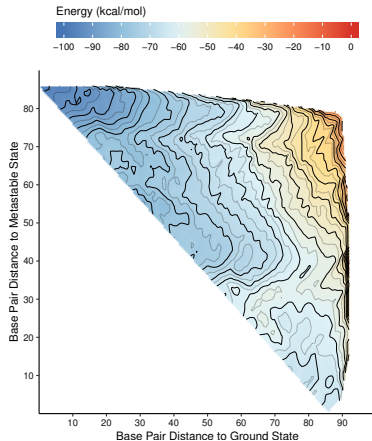
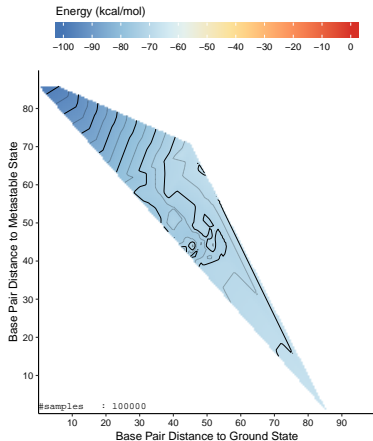
RNAexplorer attraction scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

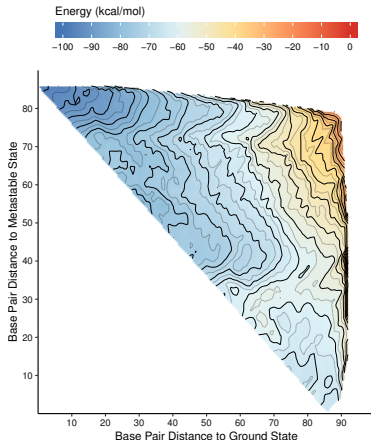
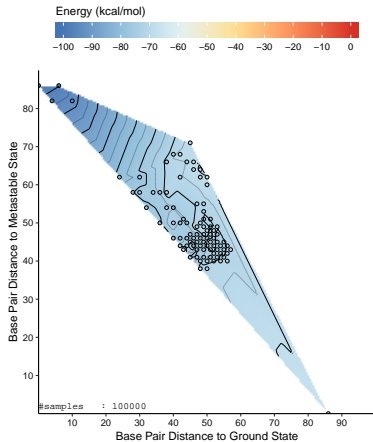
RNExplorer attraction scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

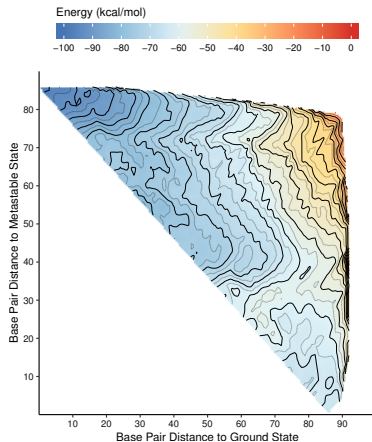
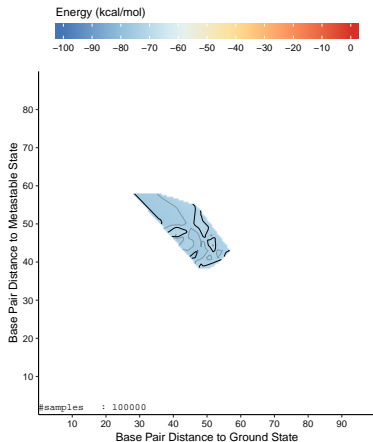
RNAexplorer attraction scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

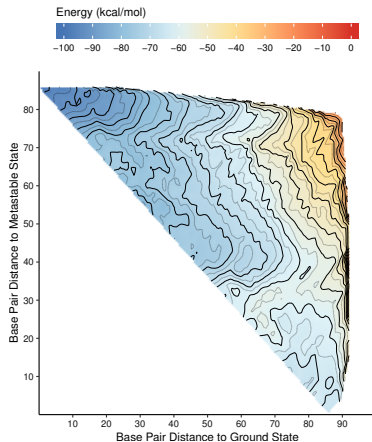
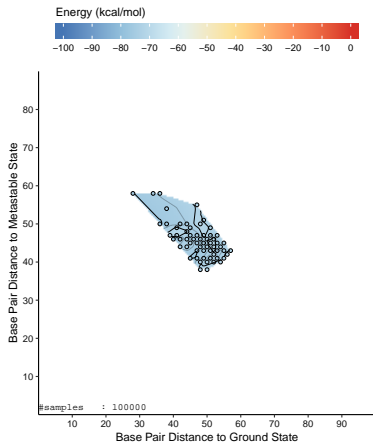
RNAexplorer attraction scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

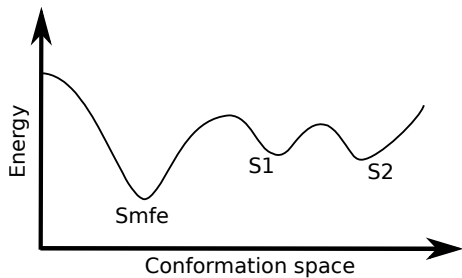
RNAexplorer attraction scheme Boltzmann sampling



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

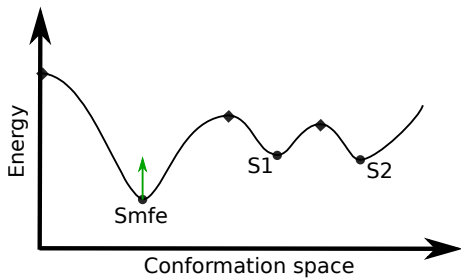
Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



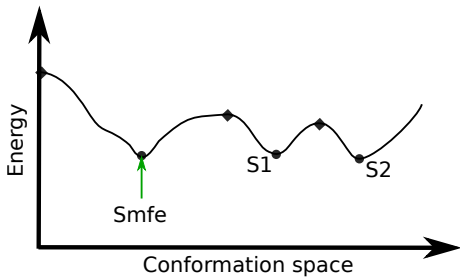
Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



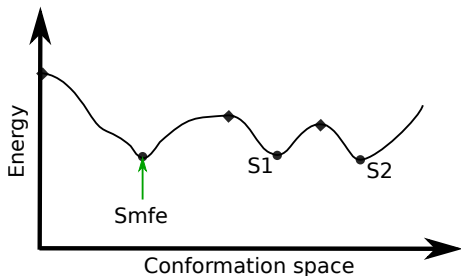
Sampling Strategies

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.

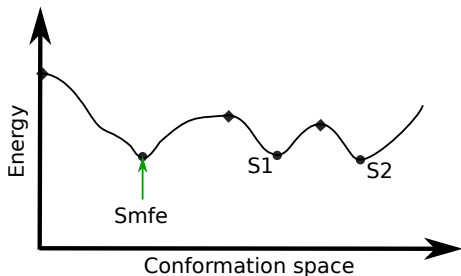
$$\hat{E}(s) = \sum_{s_m \in L} w(s_m) \cdot \frac{|s \cap s_m|}{|s_m|}$$

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

...

Sampling Strategies

5b. Sampling with (repellent) Guiding Potentials



- draw samples and determine corresponding local minima
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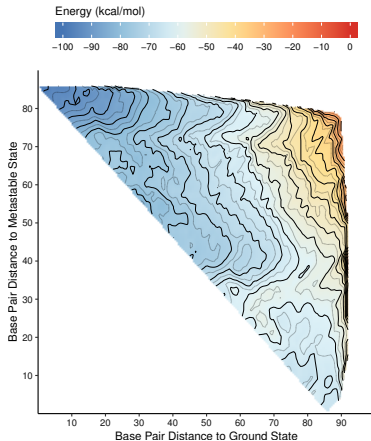
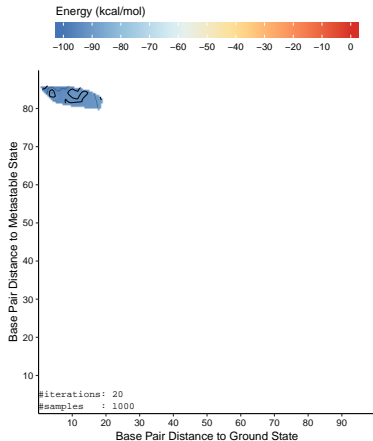
$$\hat{E}(s) = \sum_{s_m \in L} w(s_m) \cdot (d_{BP}^{max}(s_m) - d_{BP}(s, s_m))$$

...

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

Example: Q_β replicase template SV11

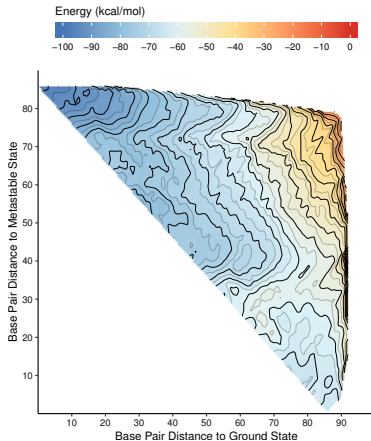
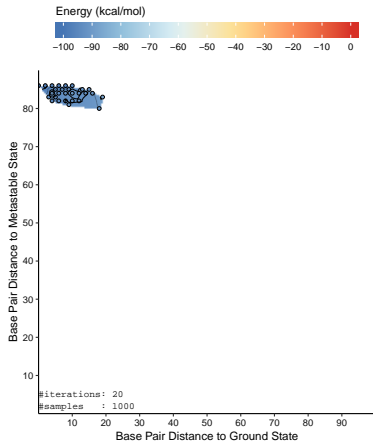
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

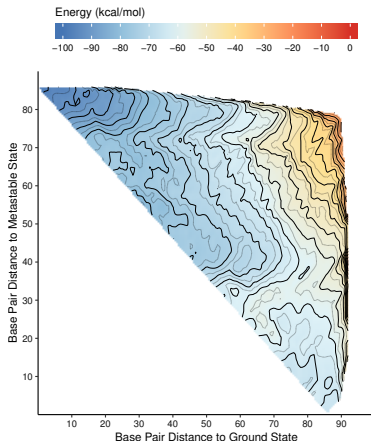
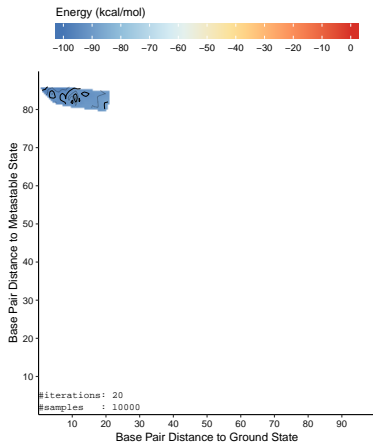
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

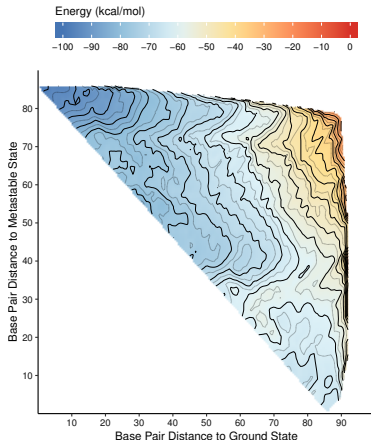
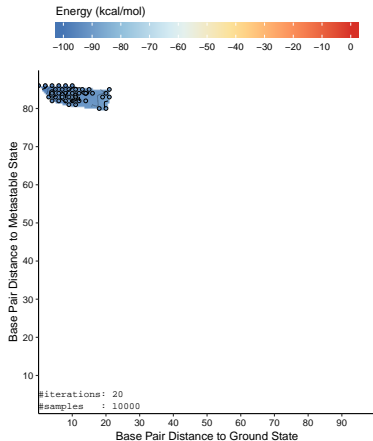
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

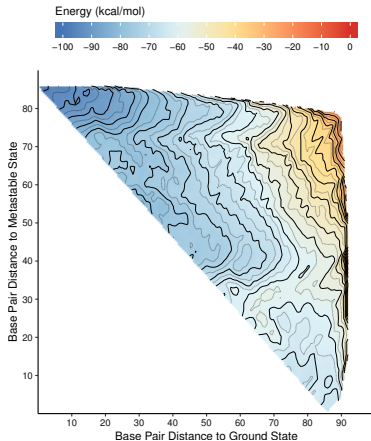
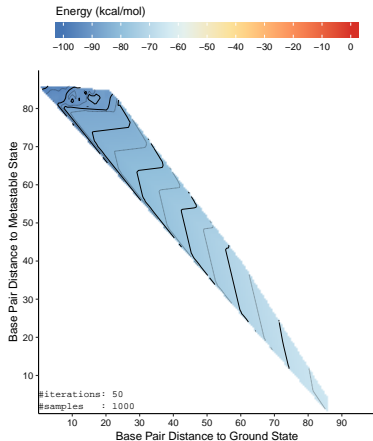
RNExplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

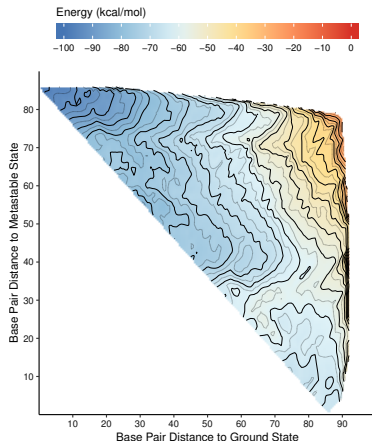
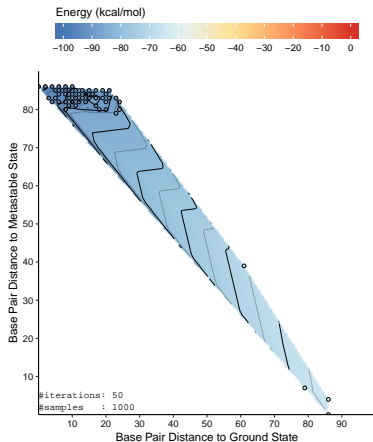
RNExplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

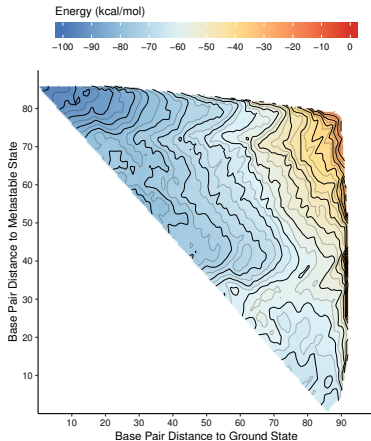
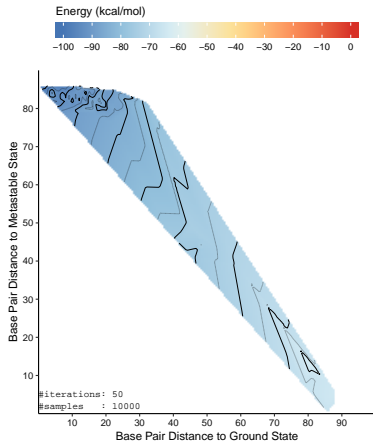
RNExplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

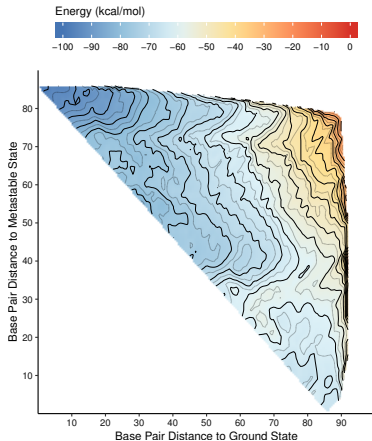
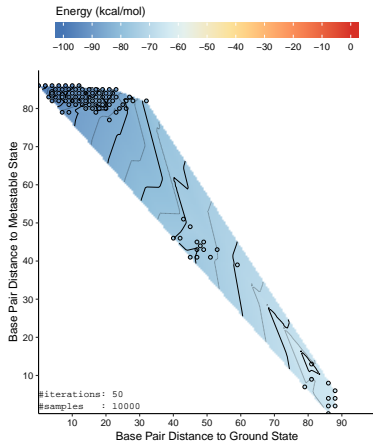
RNExplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

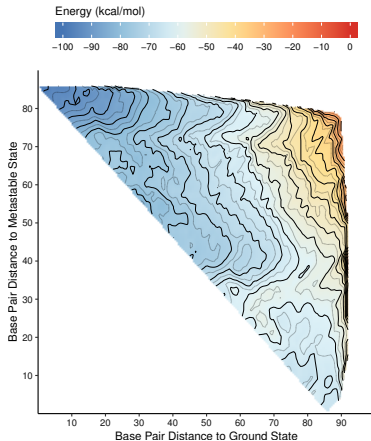
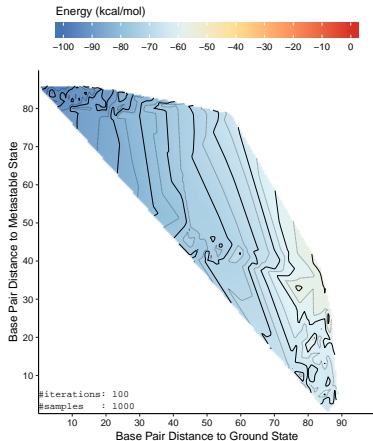
RNAexplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

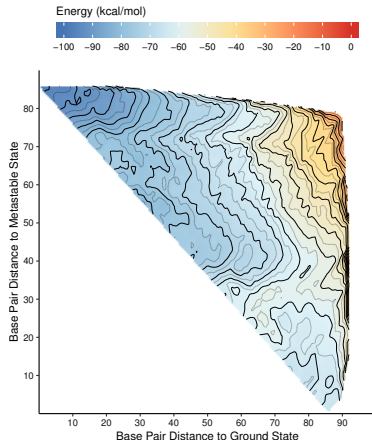
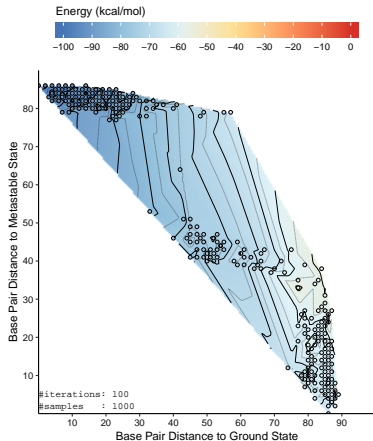
RNExplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

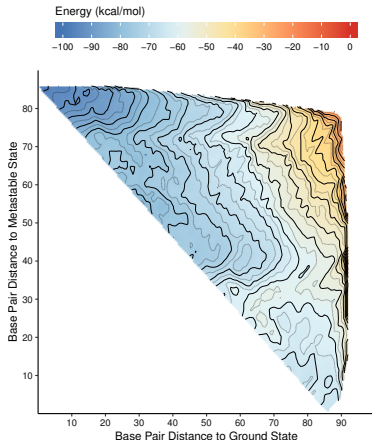
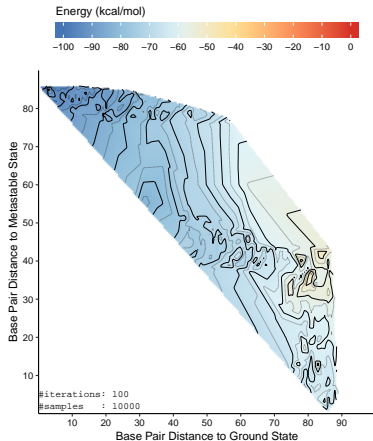
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

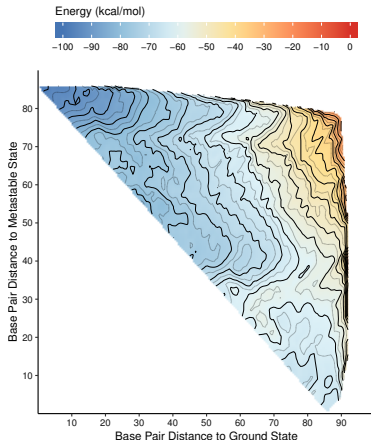
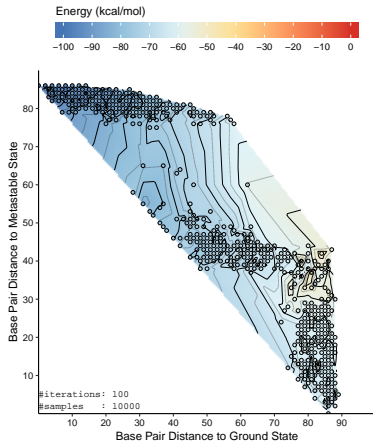
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

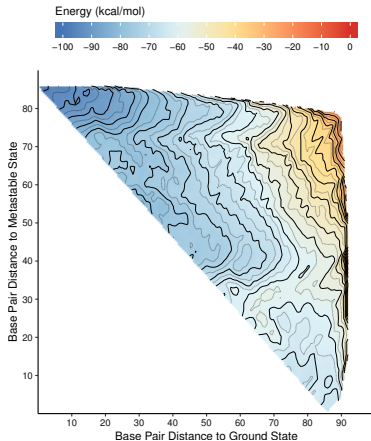
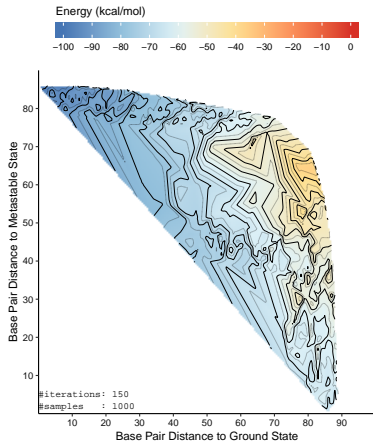
RNAexplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

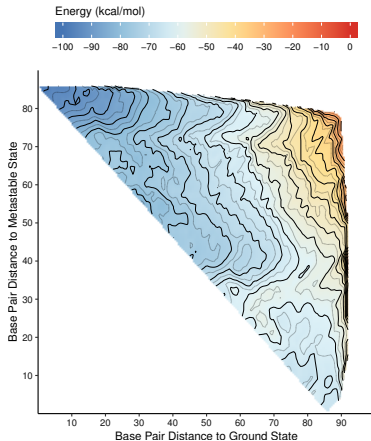
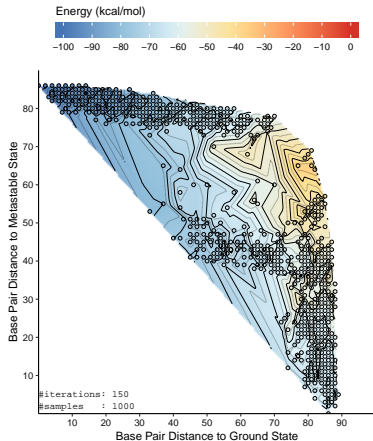
RNExplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

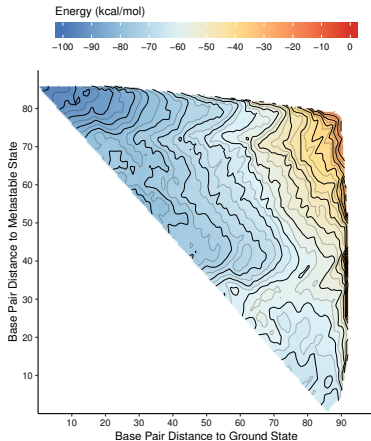
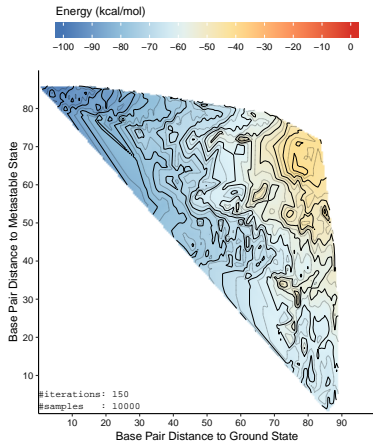
RNAexplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

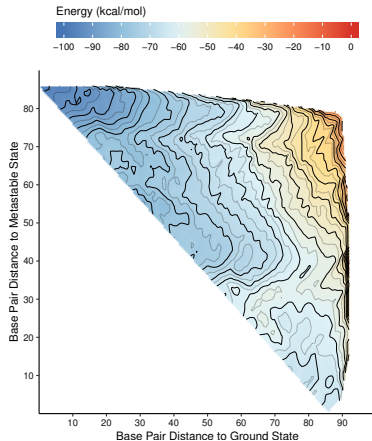
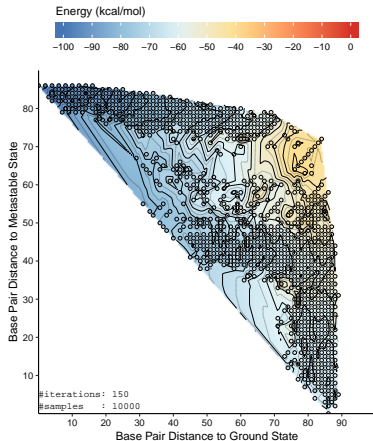
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

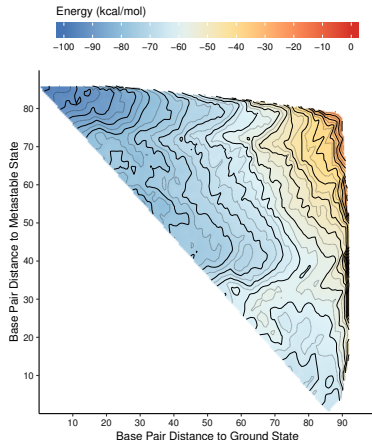
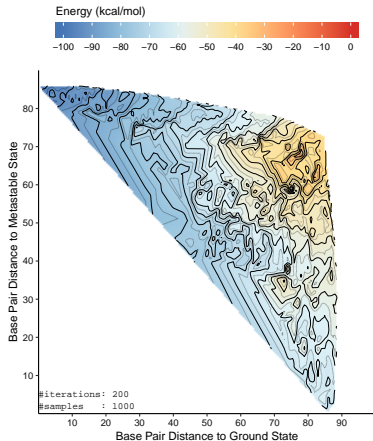
RNAexplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

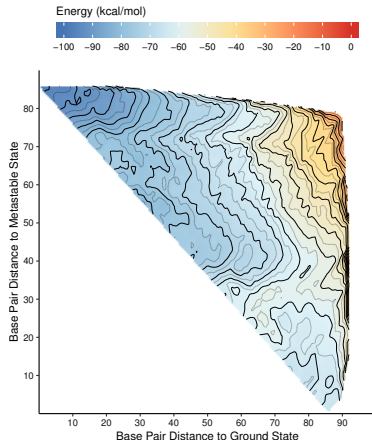
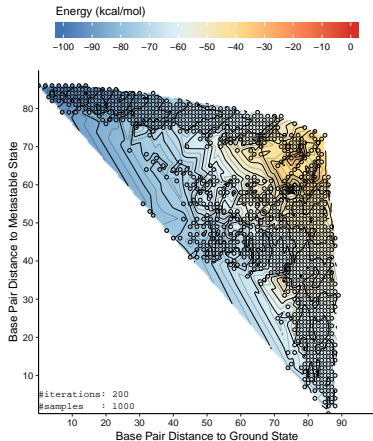
RNExplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

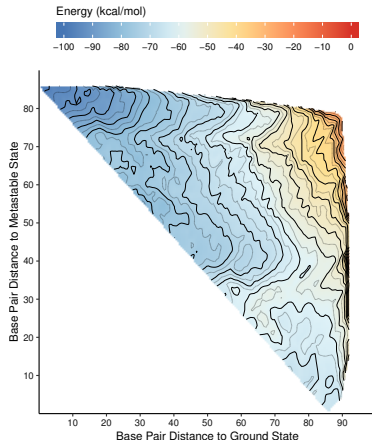
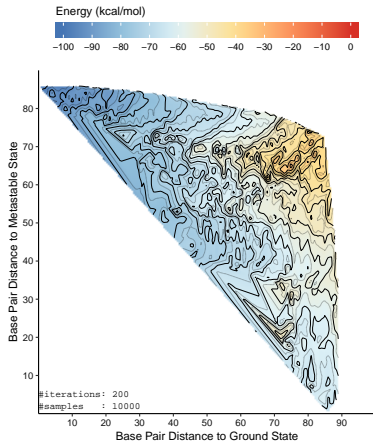
RNAexplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

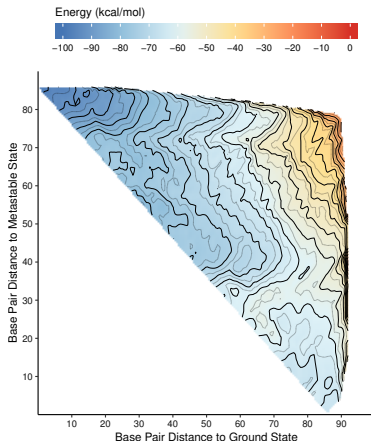
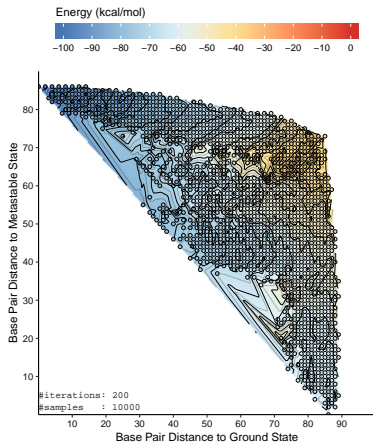
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

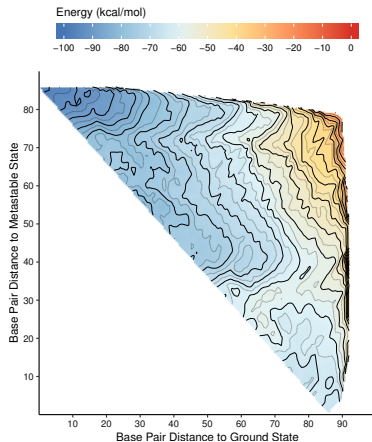
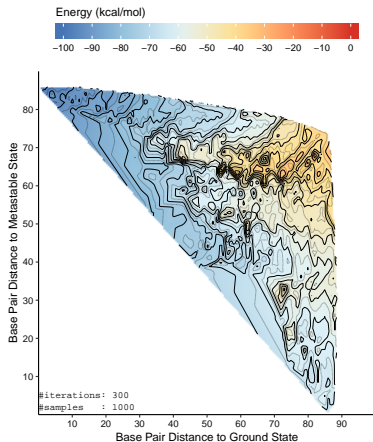
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

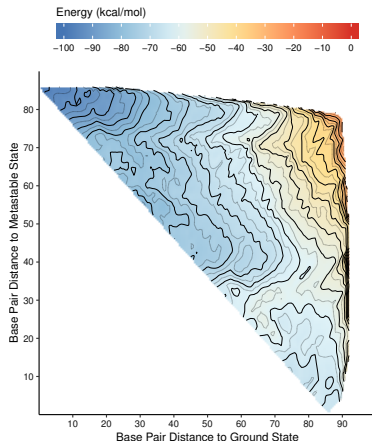
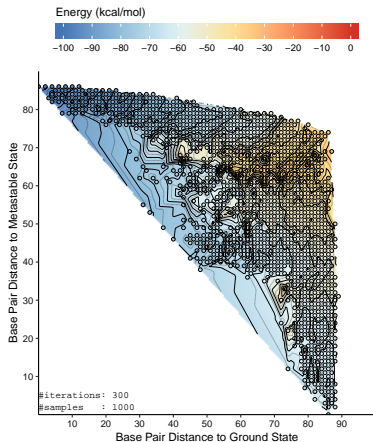
RNAexplorer repulsion scheme Boltzmann sampling



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

Example: $Q\beta$ replicase template SV11

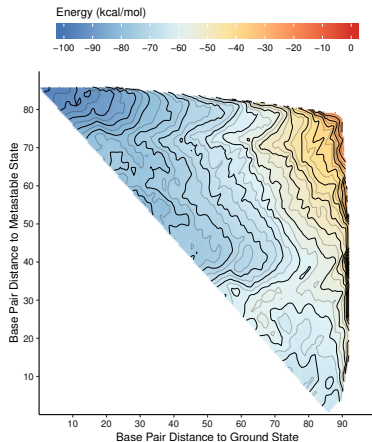
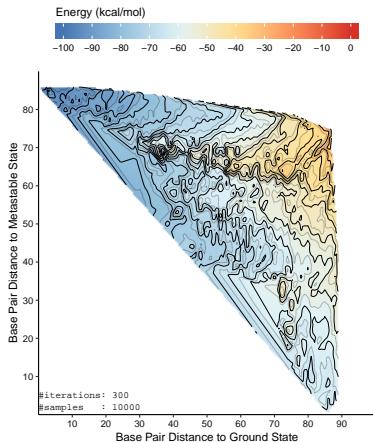
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

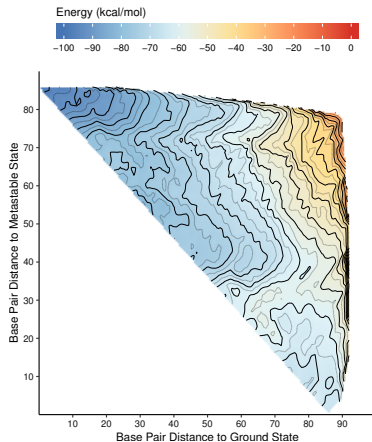
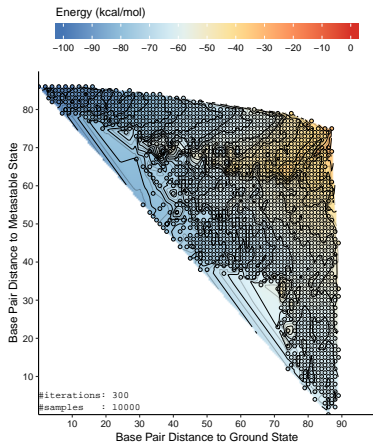
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

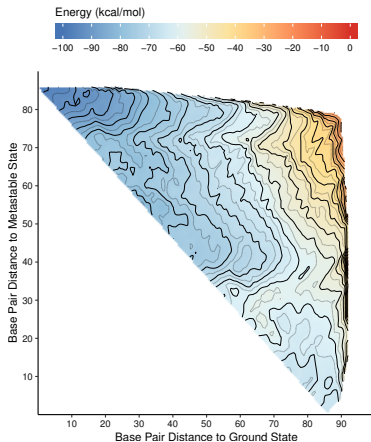
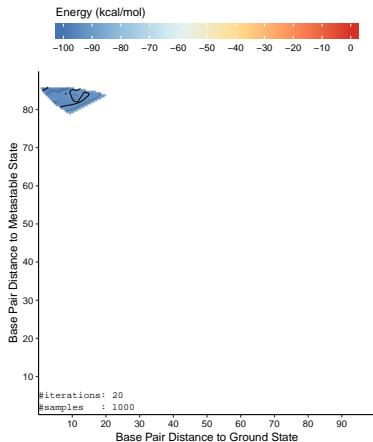
RNExplorer repulsion scheme Boltzmann sampling



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

Example: Q_β replicase template SV11

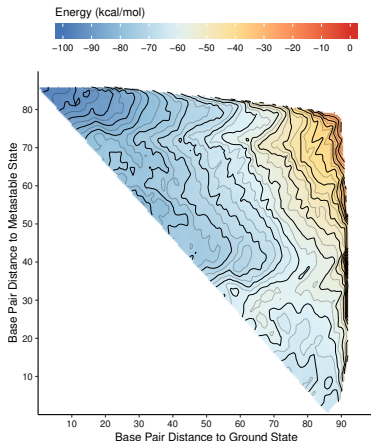
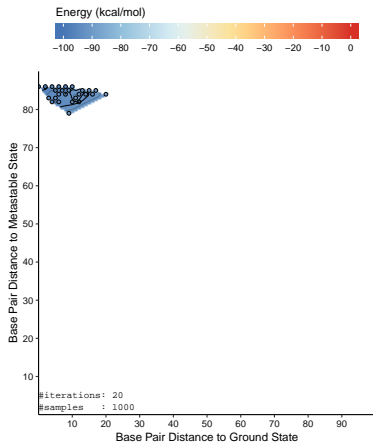
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

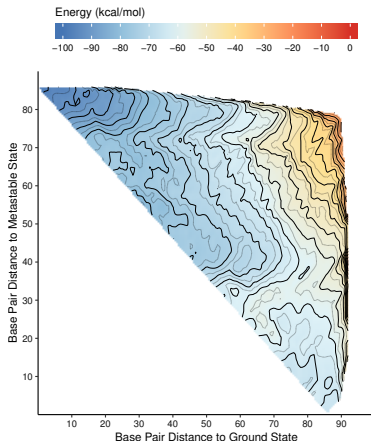
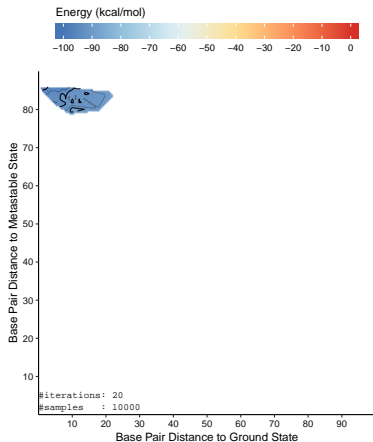
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

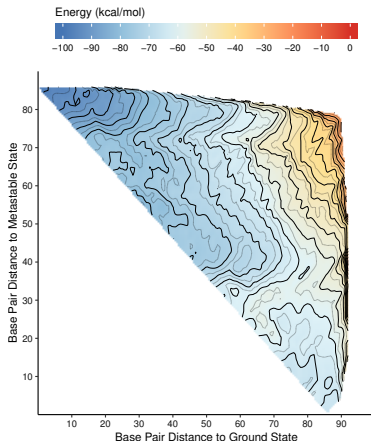
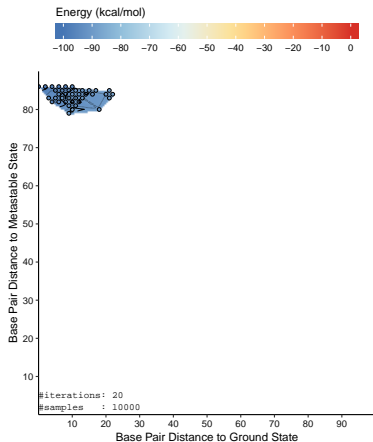
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

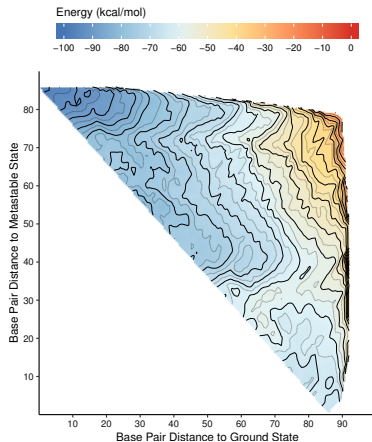
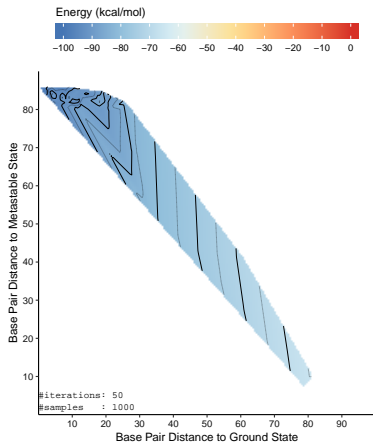
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

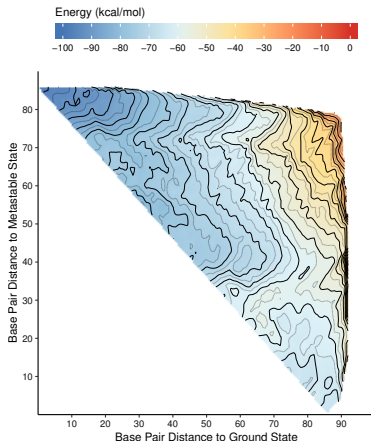
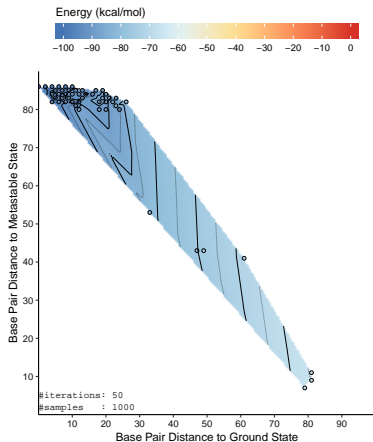
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

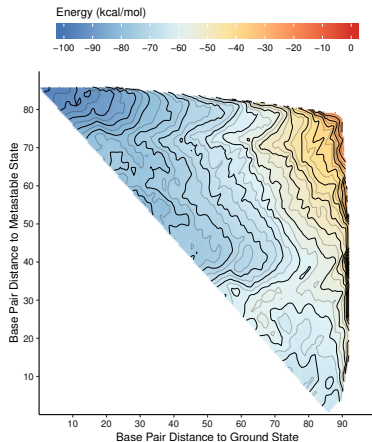
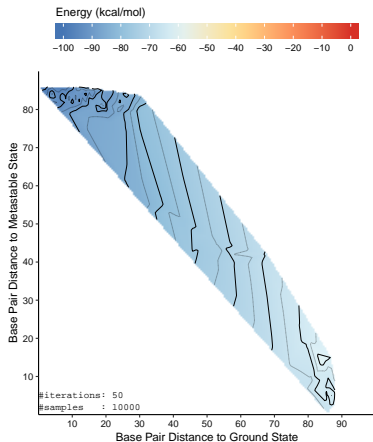
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

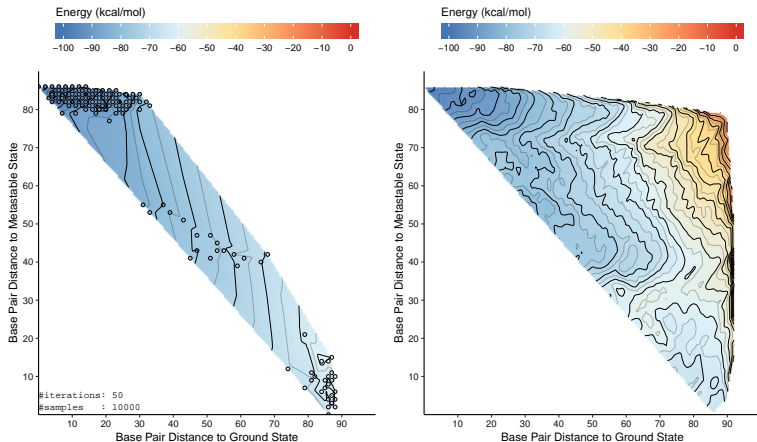
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

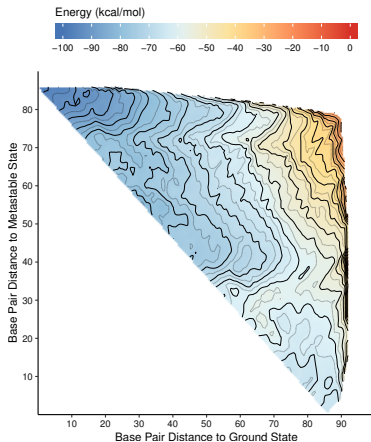
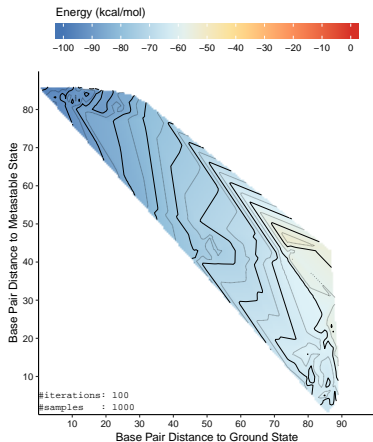
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

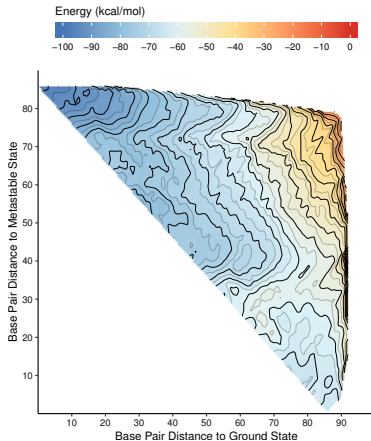
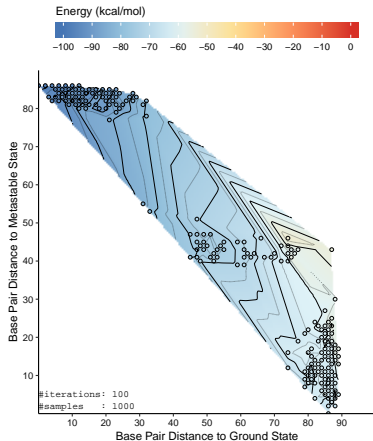
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

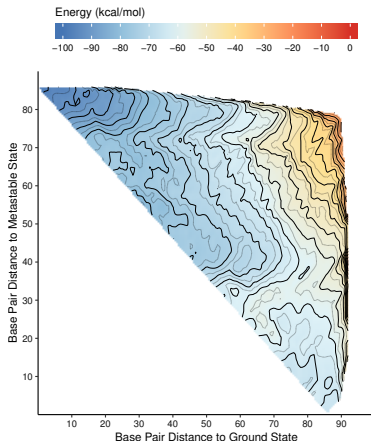
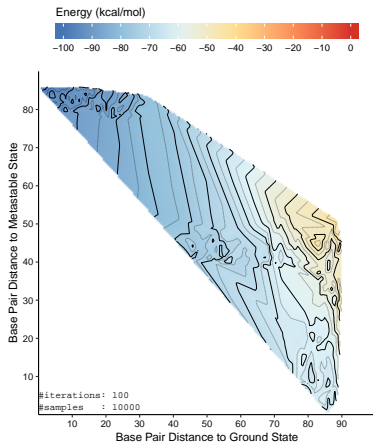
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

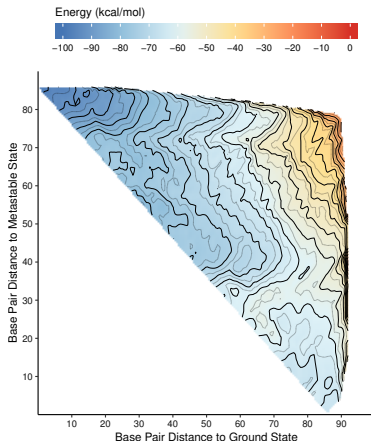
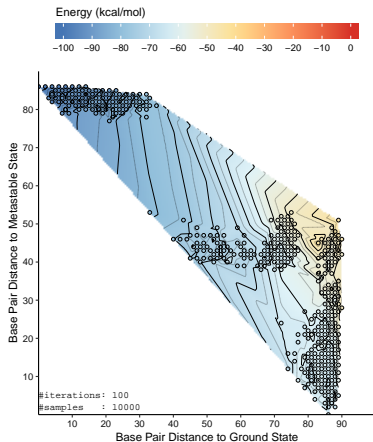
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

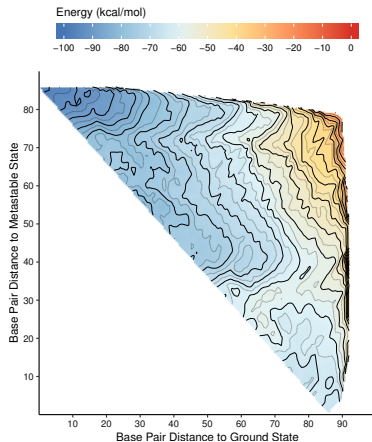
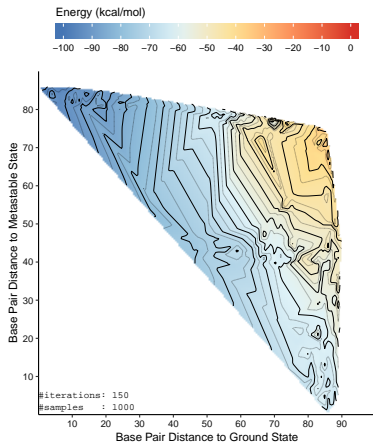
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

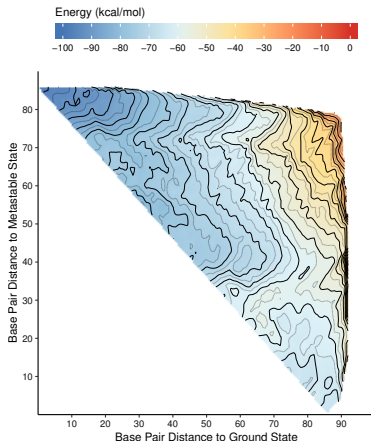
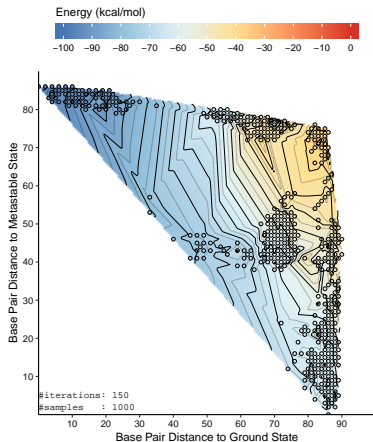
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

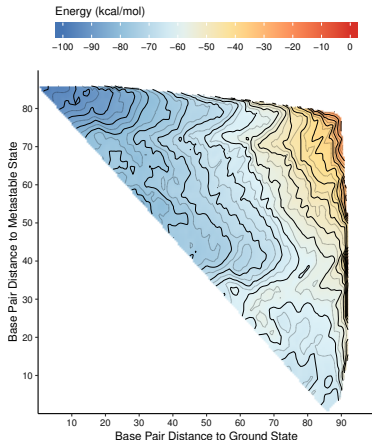
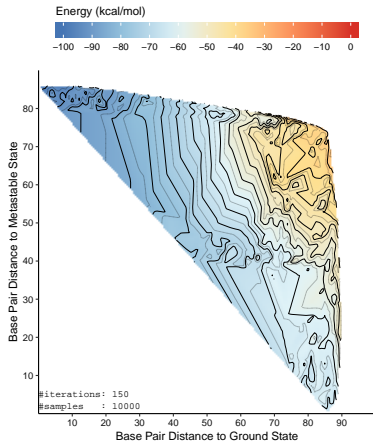
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

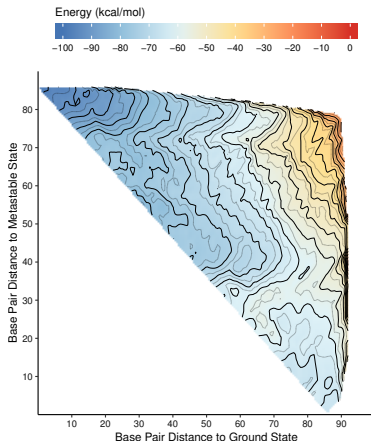
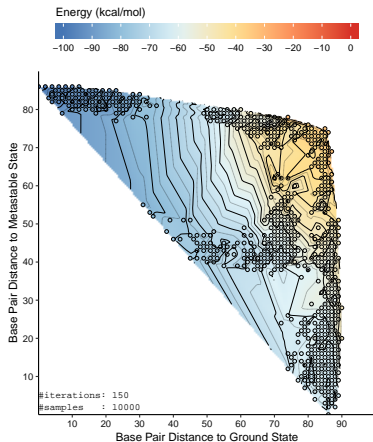
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

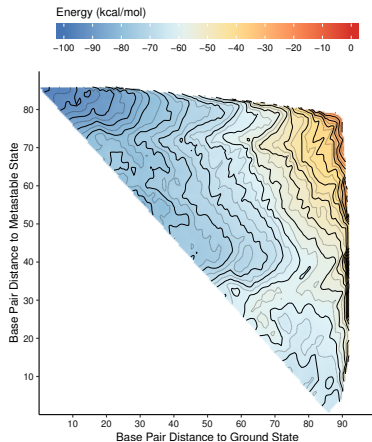
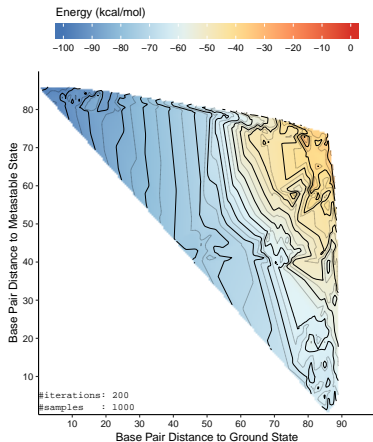
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

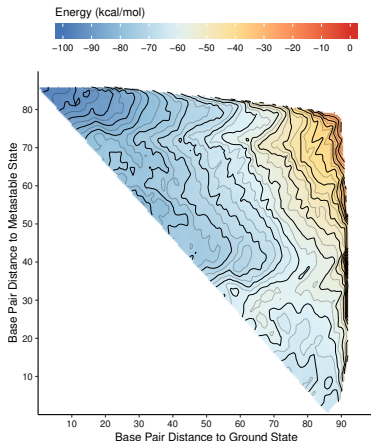
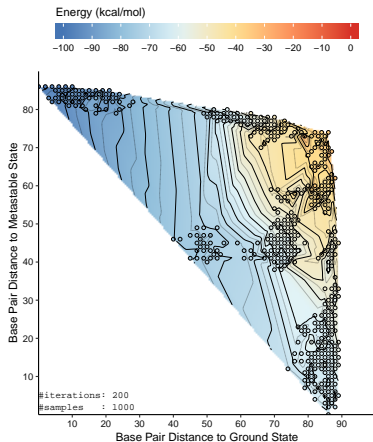
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

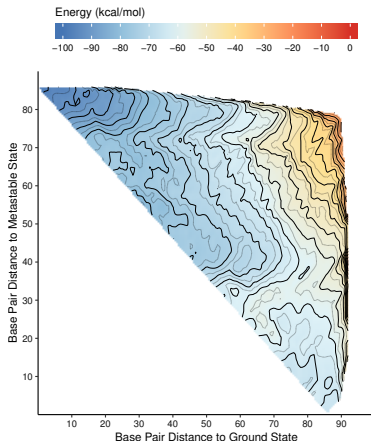
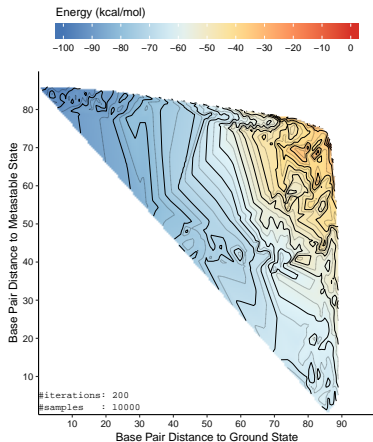
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: Q_β replicase template SV11

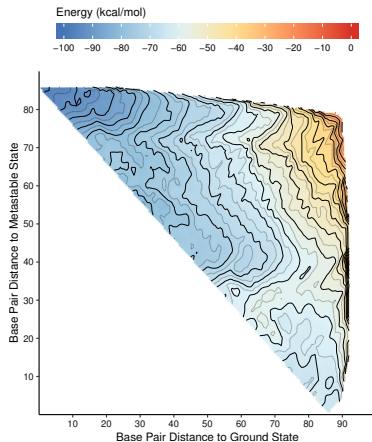
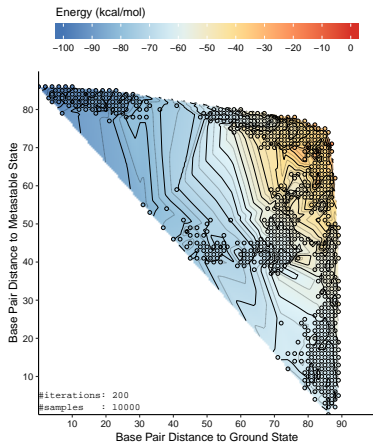
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

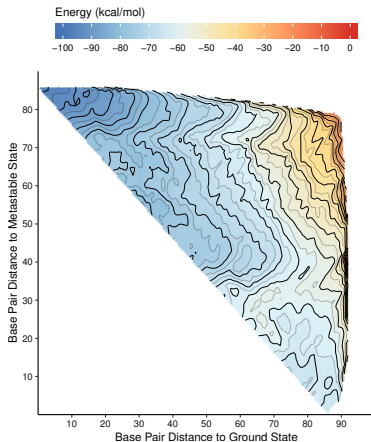
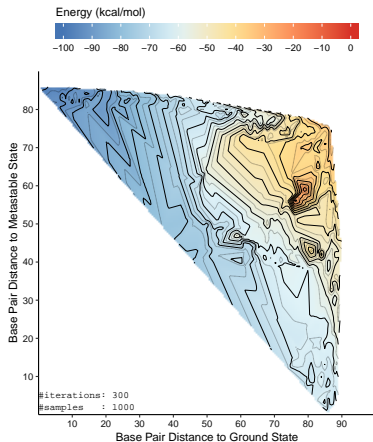
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

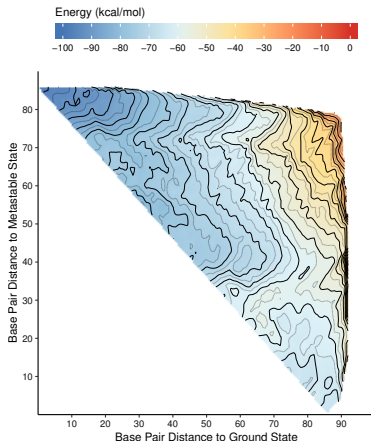
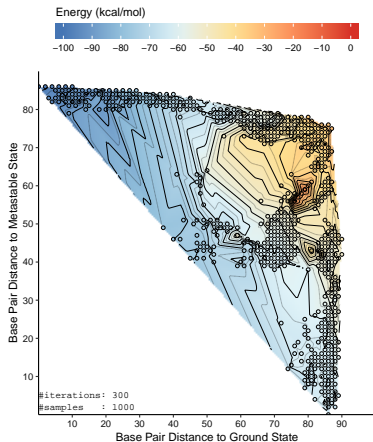
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

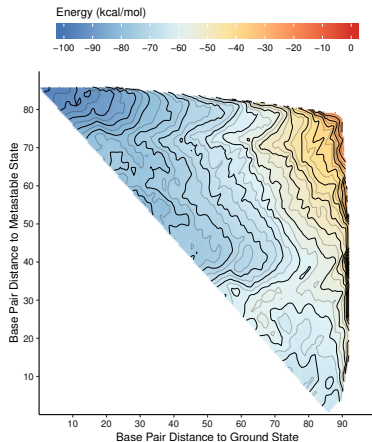
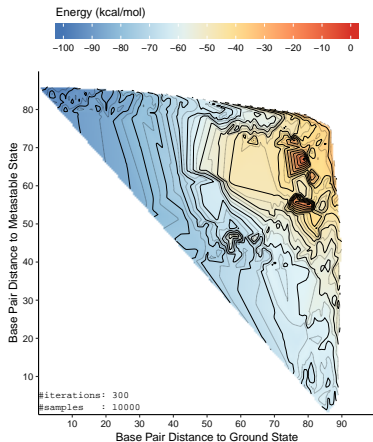
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

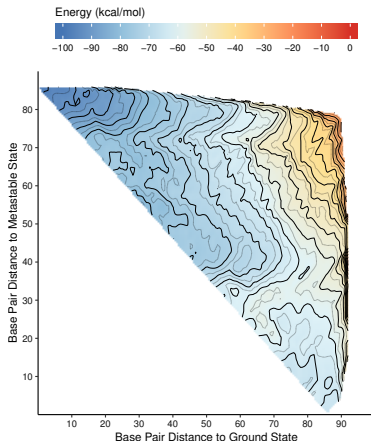
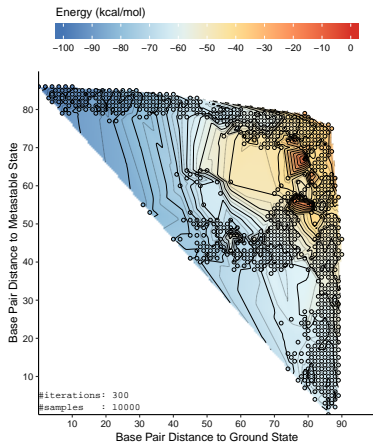
RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



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

Example: $Q\beta$ replicase template SV11

RNAexplorer 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 `RNAexplorer` 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



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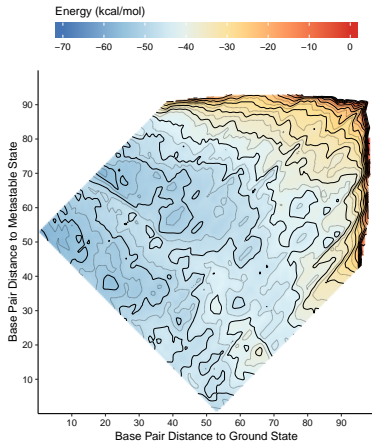
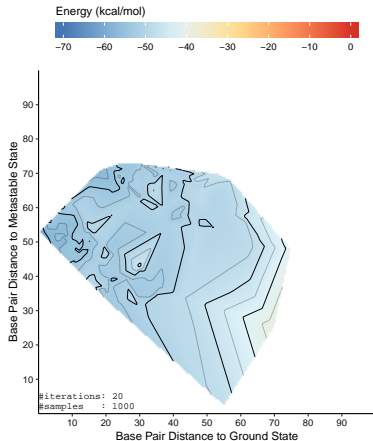
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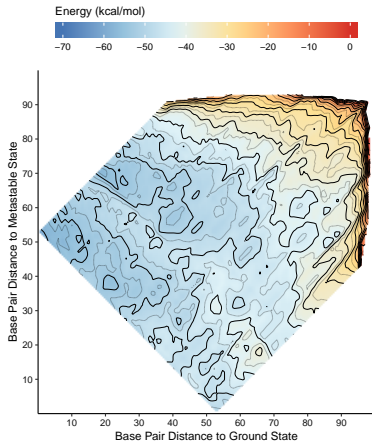
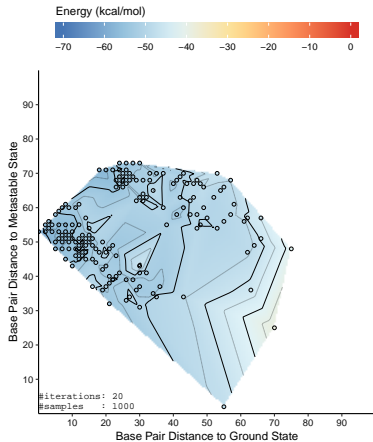
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



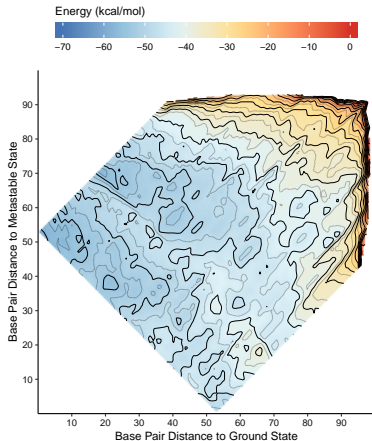
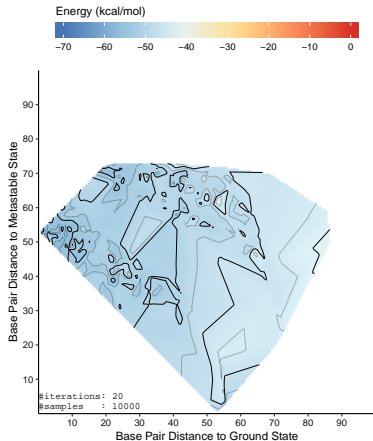
Example: 5UTR of MS2 coat protein mRNA

RNAsplorer repulsion scheme Boltzmann sampling



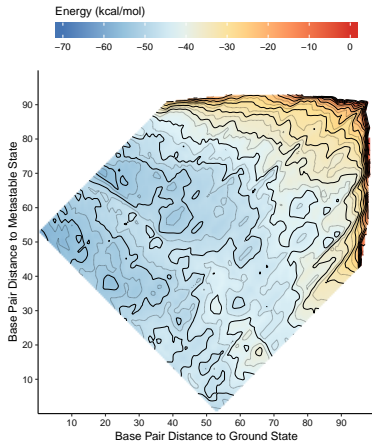
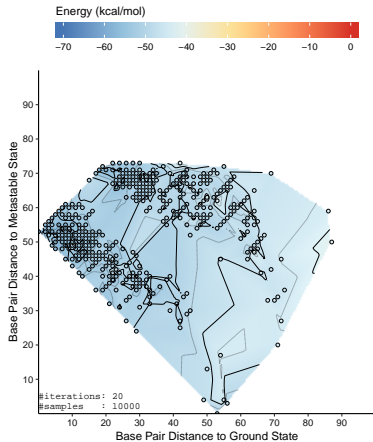
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



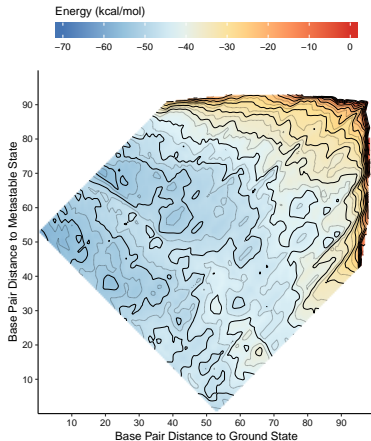
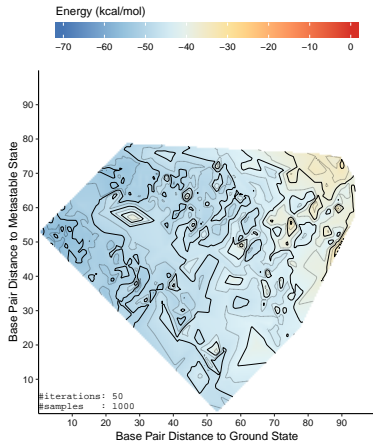
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



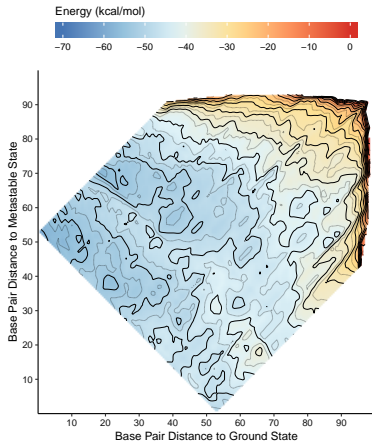
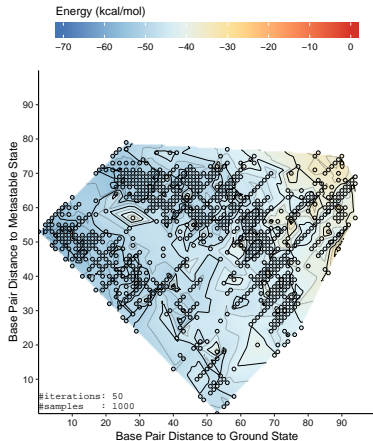
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



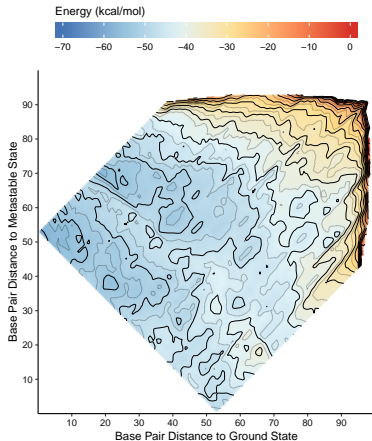
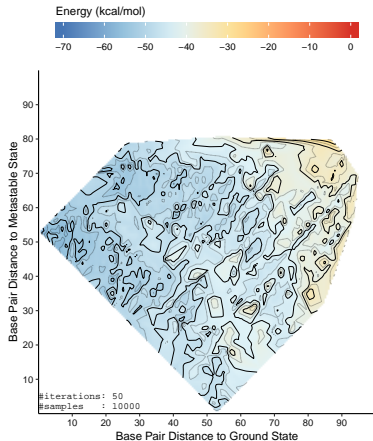
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



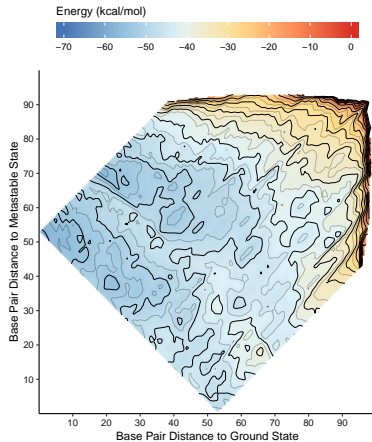
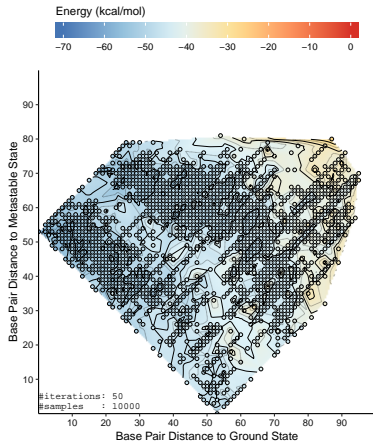
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



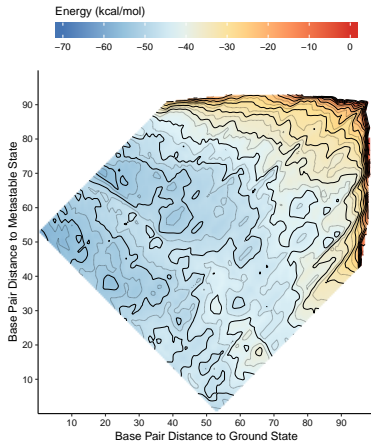
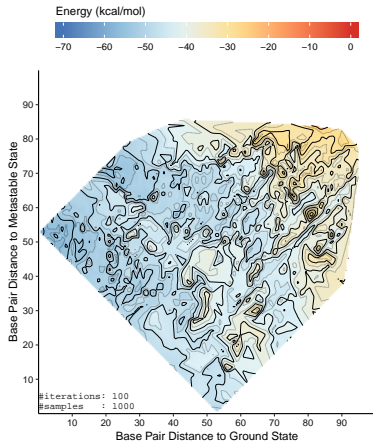
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



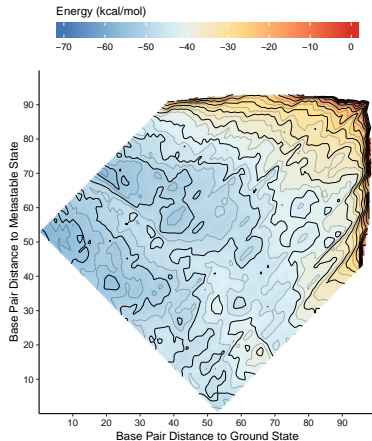
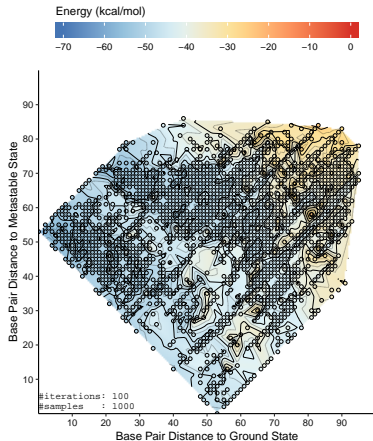
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



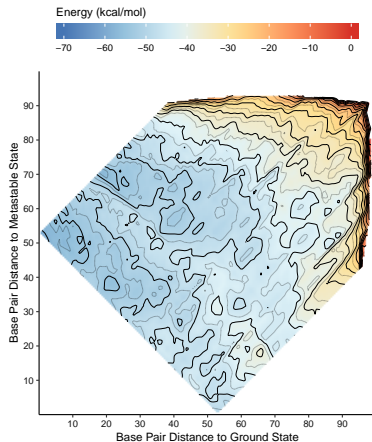
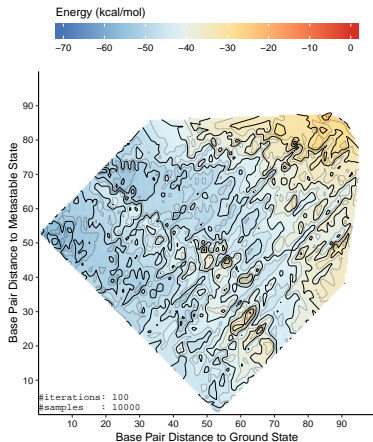
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



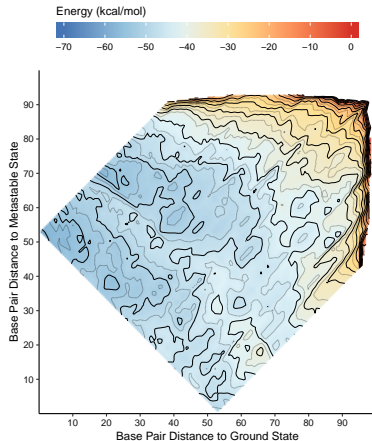
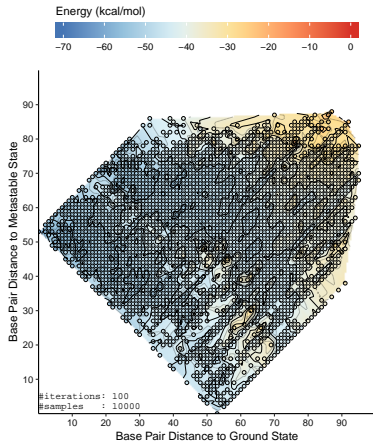
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RNAexplorer repulsion scheme Boltzmann sampling



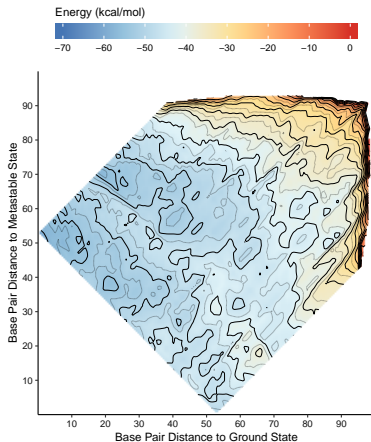
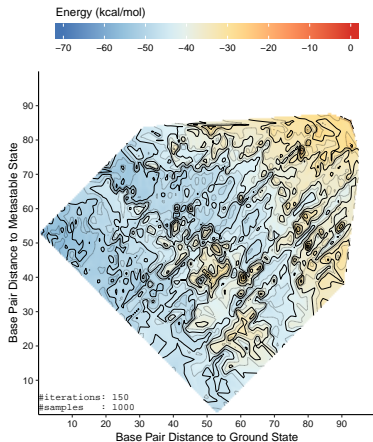
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



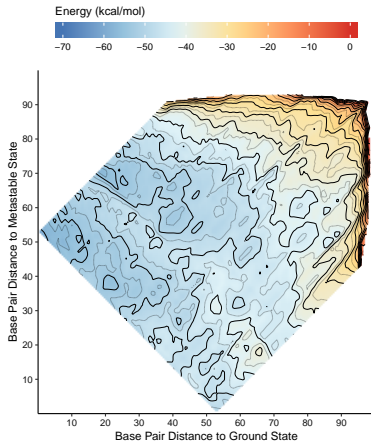
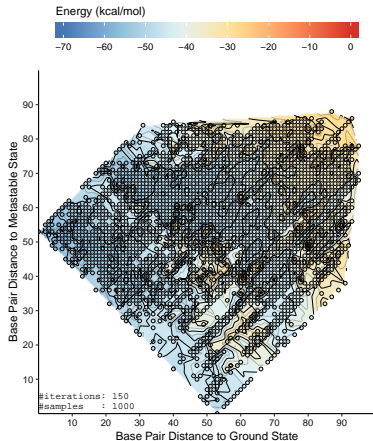
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



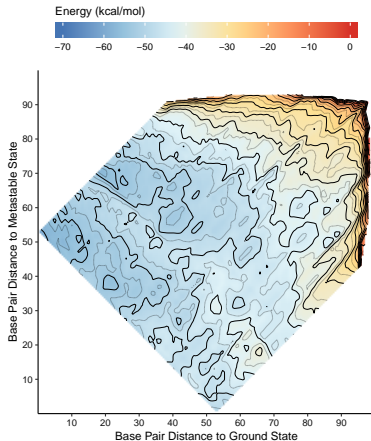
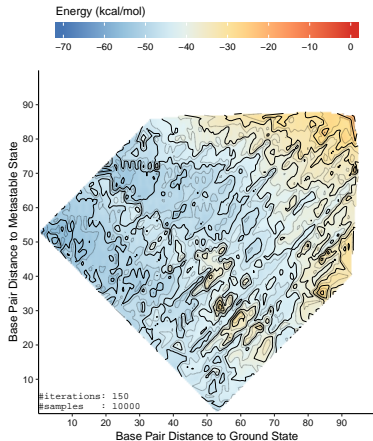
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



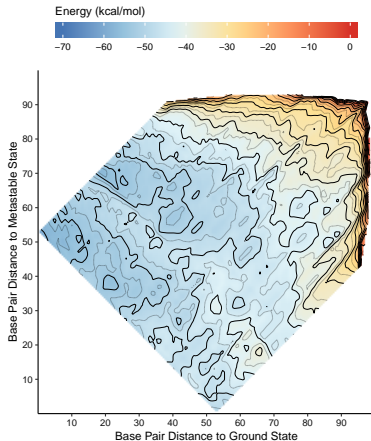
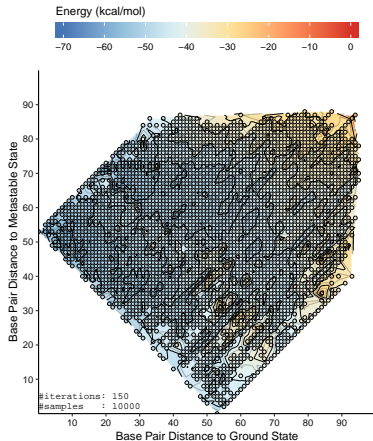
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



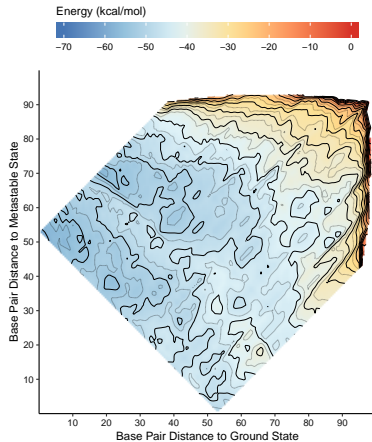
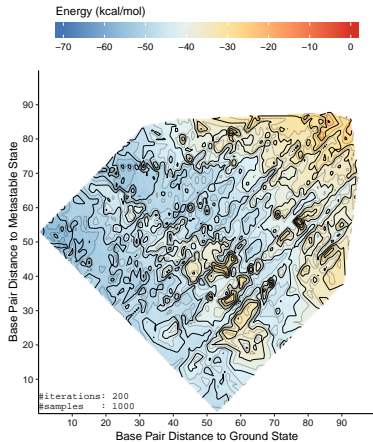
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



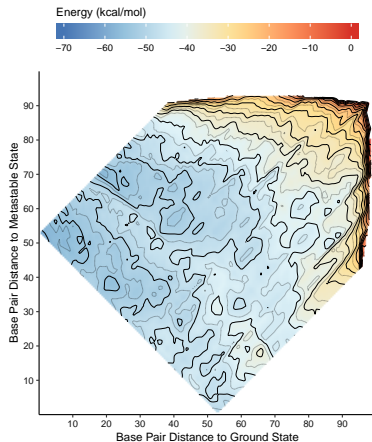
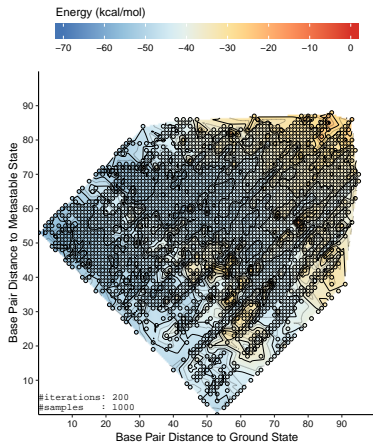
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



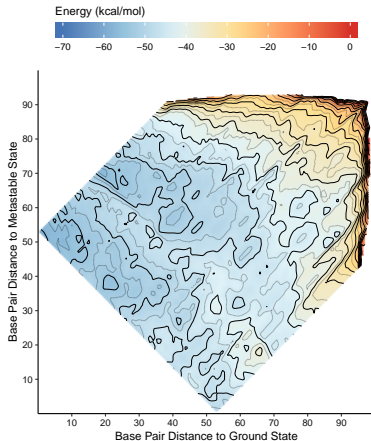
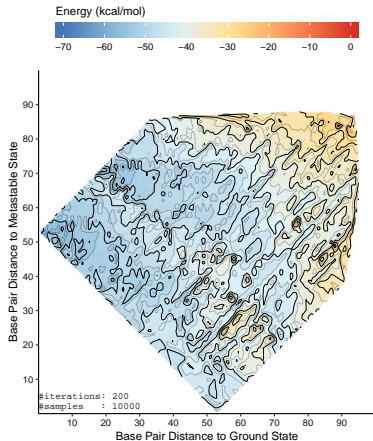
Example: 5UTR of MS2 coat protein mRNA

RNAsplorer repulsion scheme Boltzmann sampling



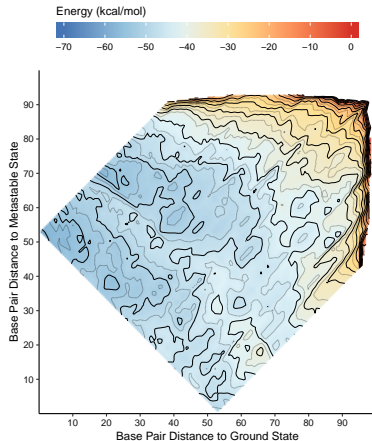
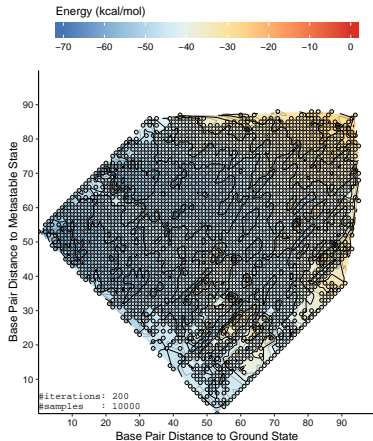
Example: 5UTR of MS2 coat protein mRNA

RNAsplorer repulsion scheme Boltzmann sampling



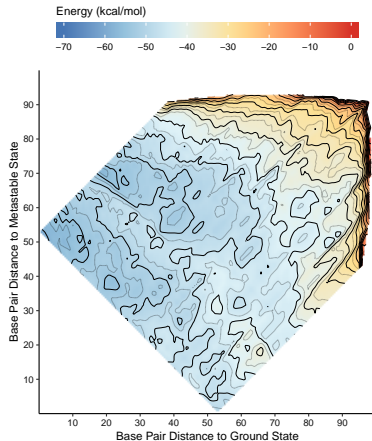
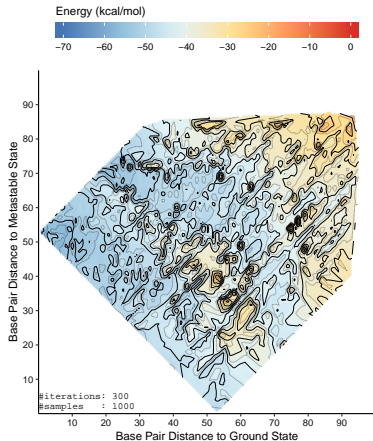
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



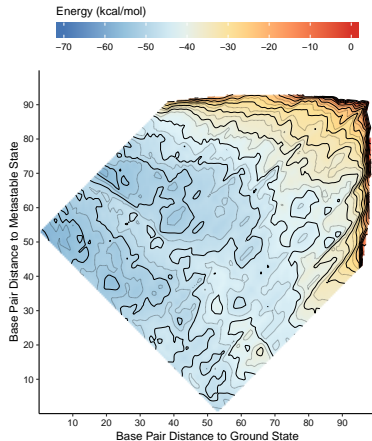
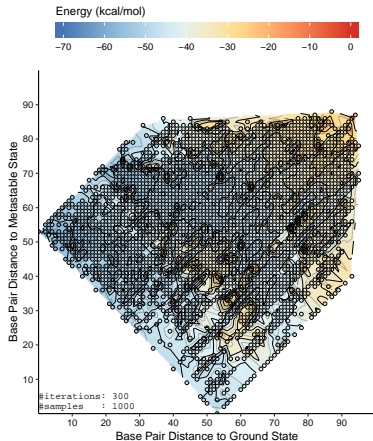
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RNAsplorer repulsion scheme Boltzmann sampling



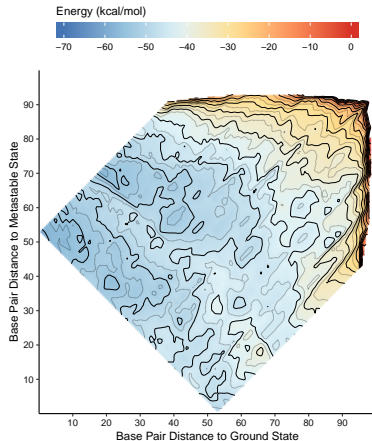
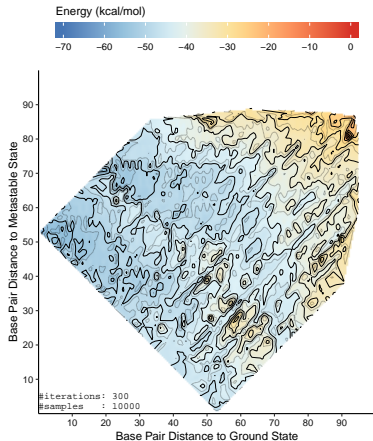
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



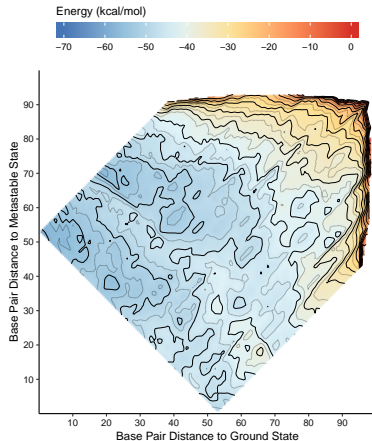
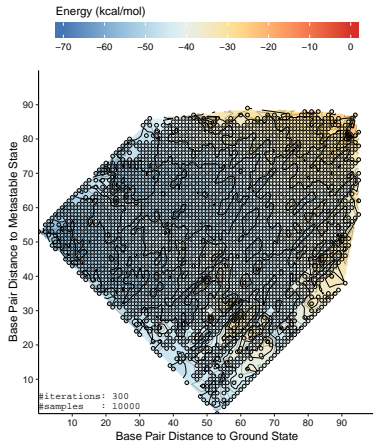
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



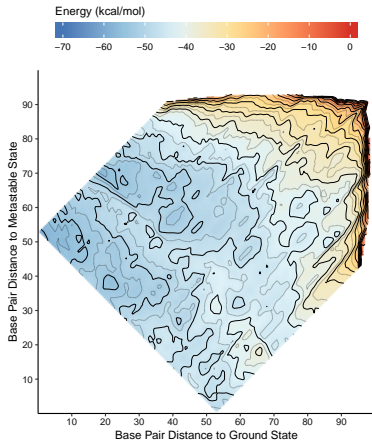
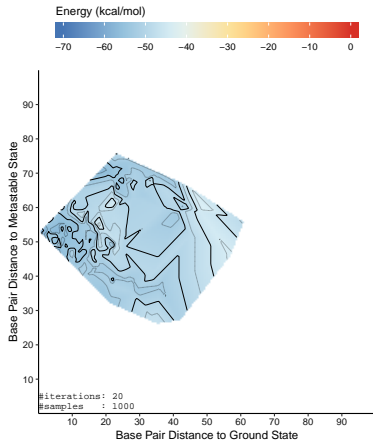
Example: 5UTR of MS2 coat protein mRNA

RNAexplorer repulsion scheme Boltzmann sampling



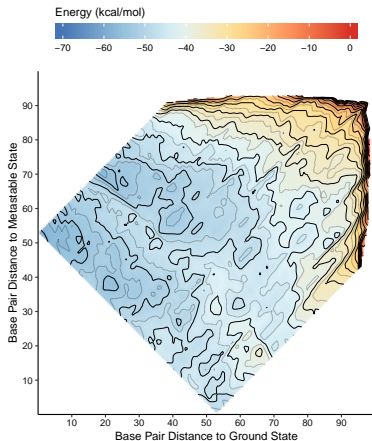
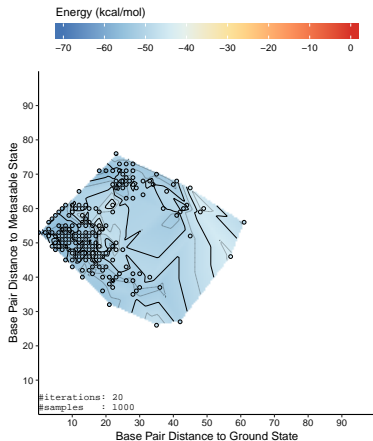
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



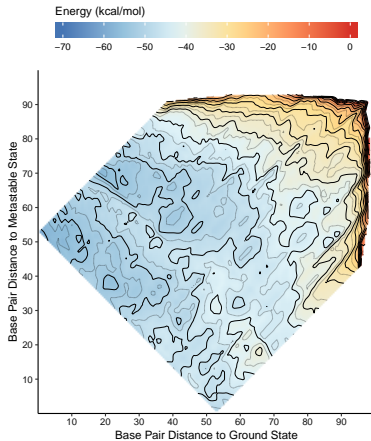
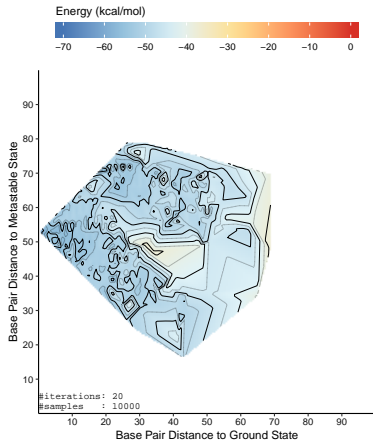
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



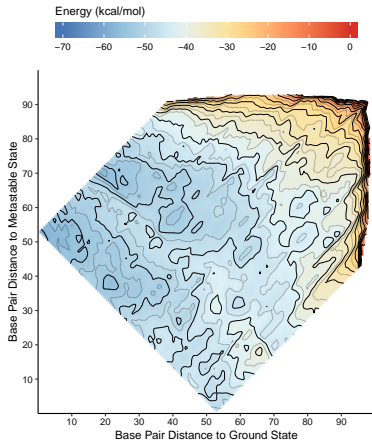
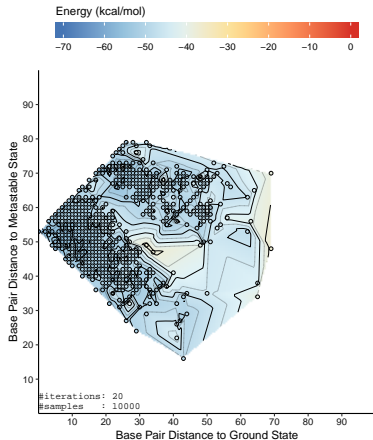
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



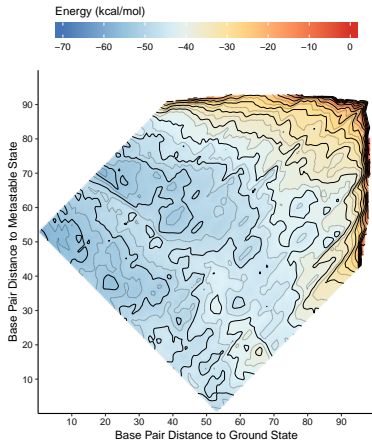
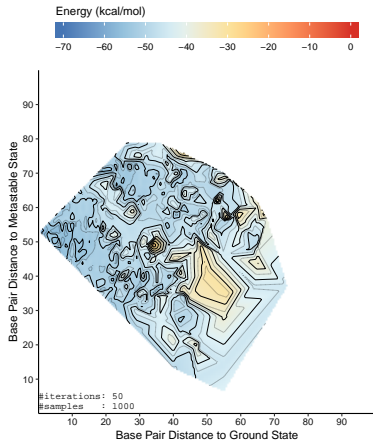
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



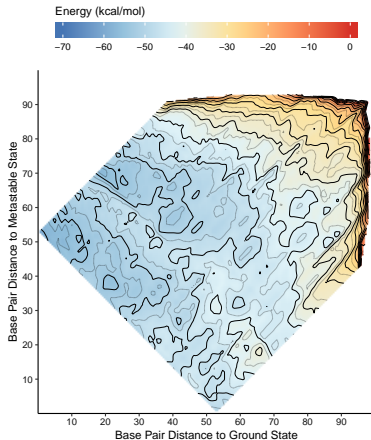
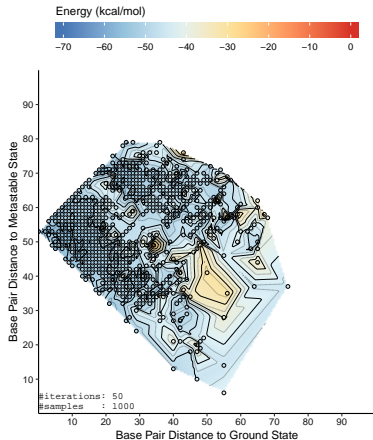
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



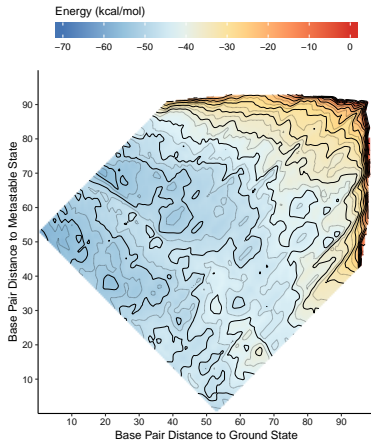
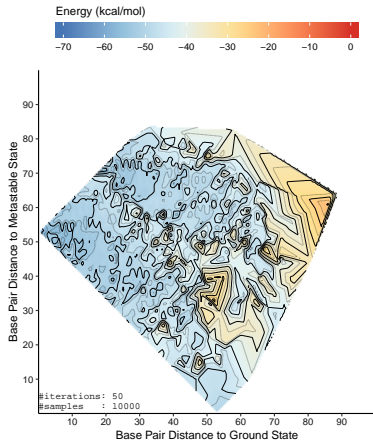
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



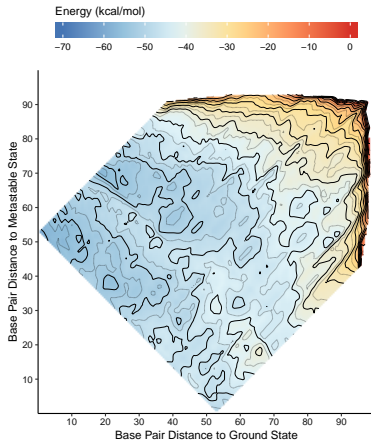
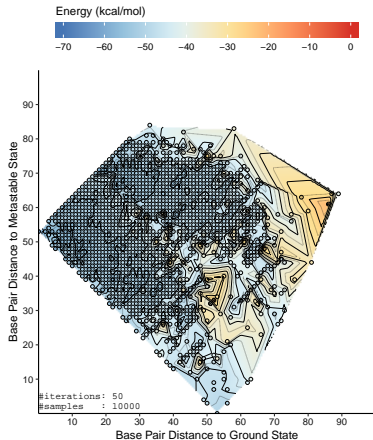
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



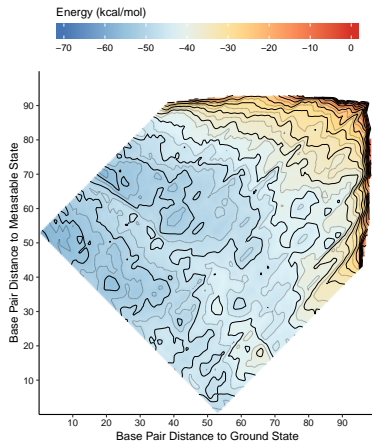
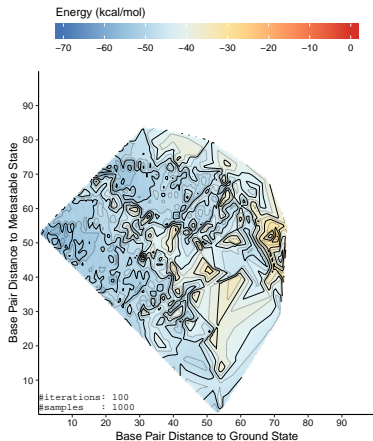
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RNAlocmin temperature elevation scheme Boltzmann sampling



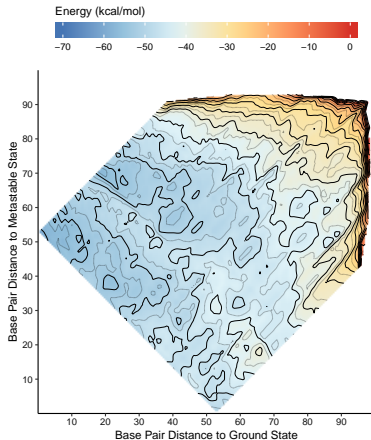
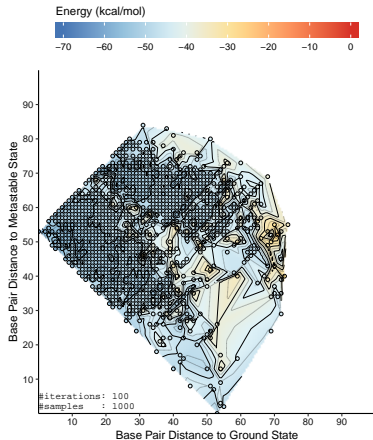
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RNAlocmin temperature elevation scheme Boltzmann sampling



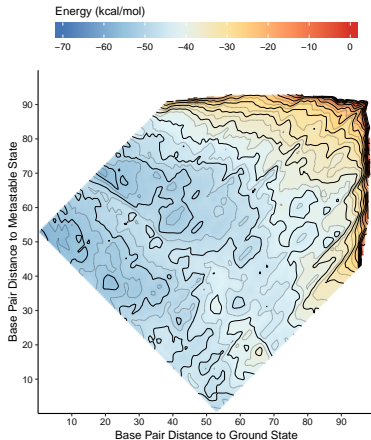
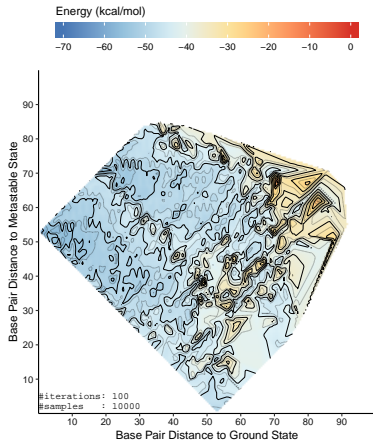
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



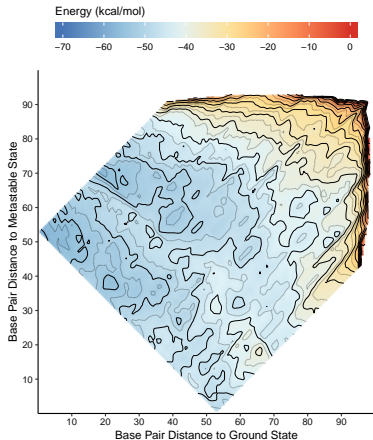
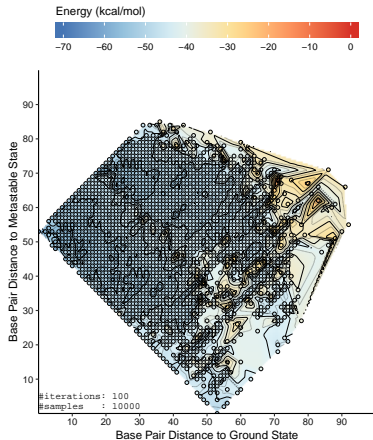
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



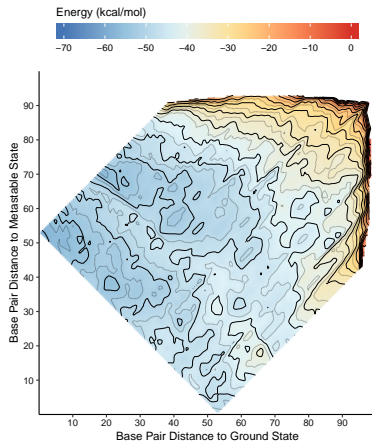
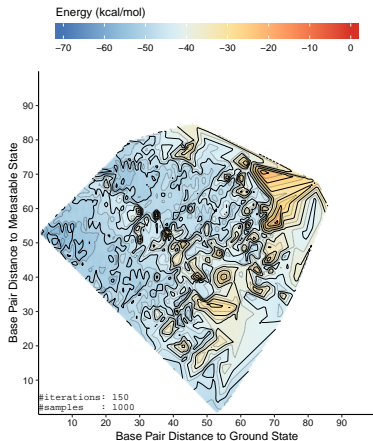
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RNAlocmin temperature elevation scheme Boltzmann sampling



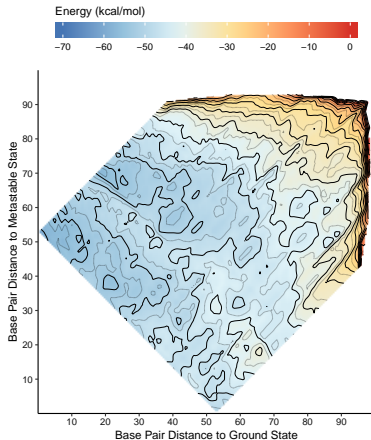
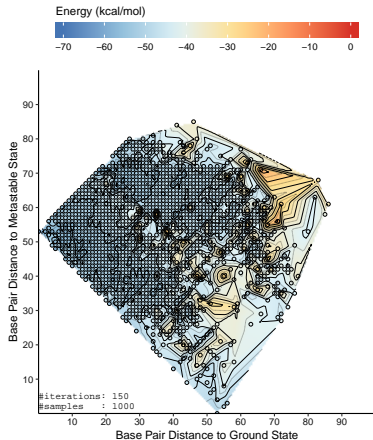
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RNAlocmin temperature elevation scheme Boltzmann sampling



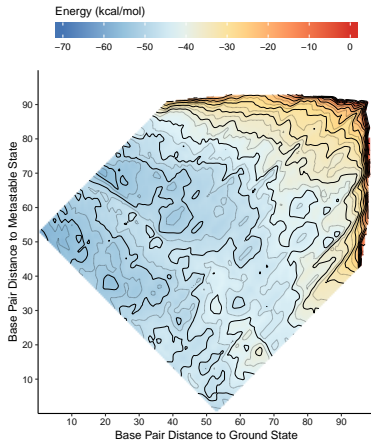
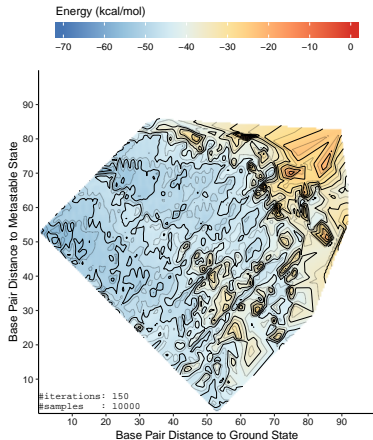
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



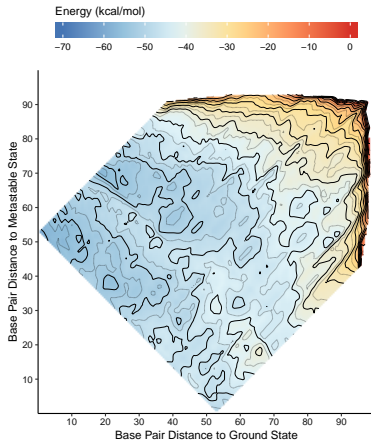
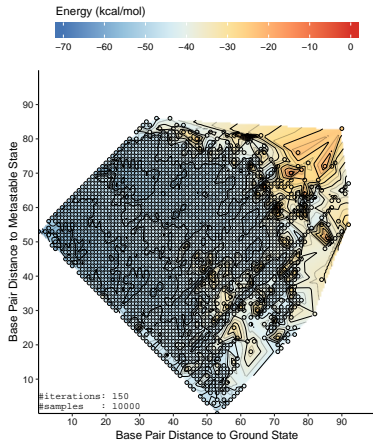
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



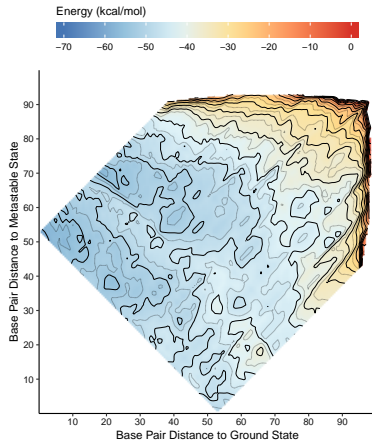
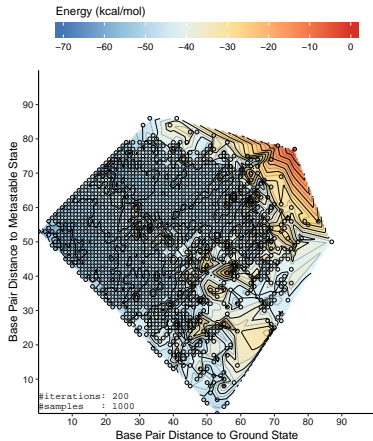
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



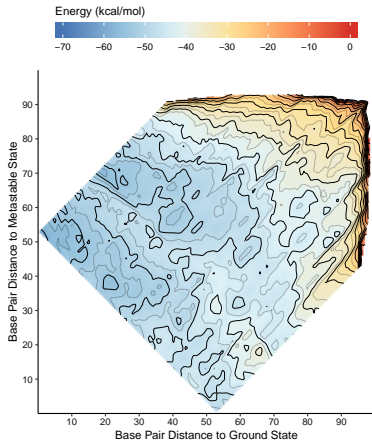
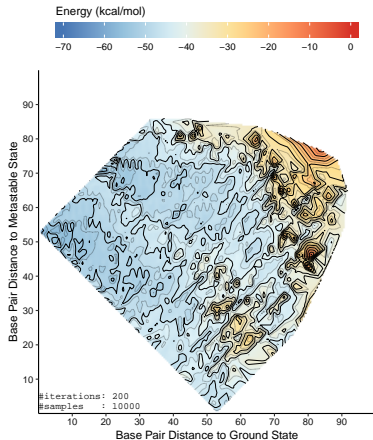
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



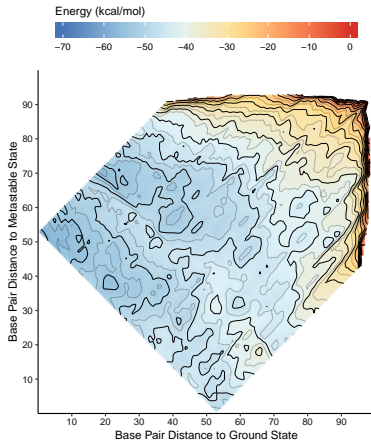
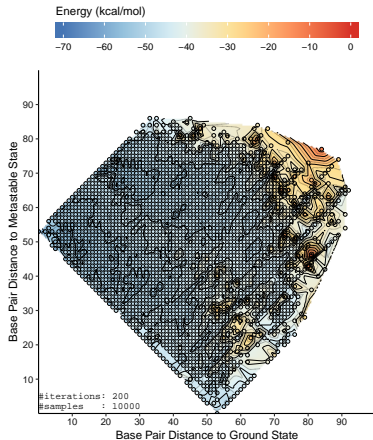
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



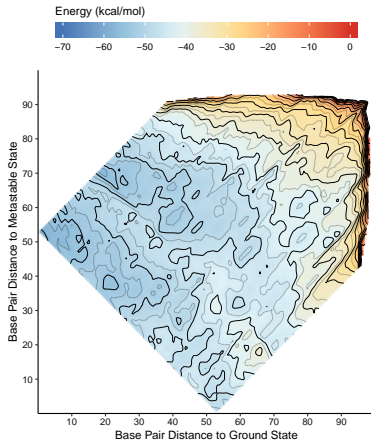
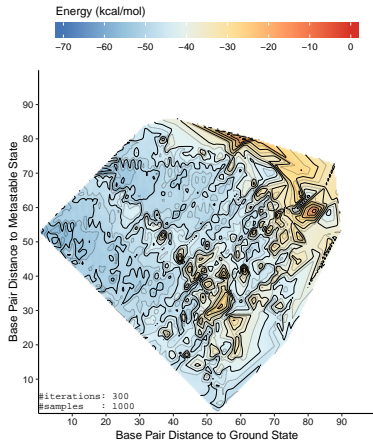
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



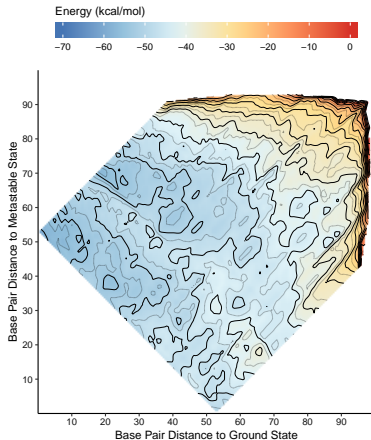
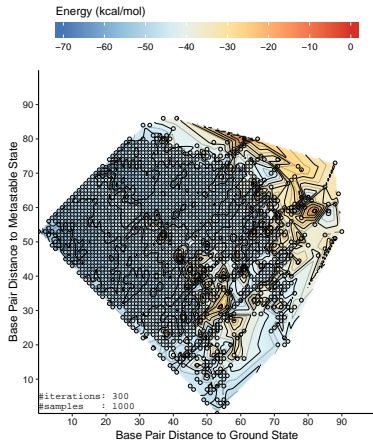
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



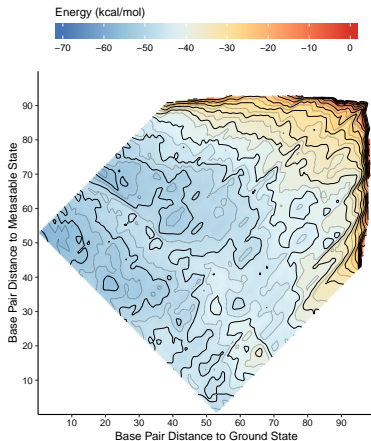
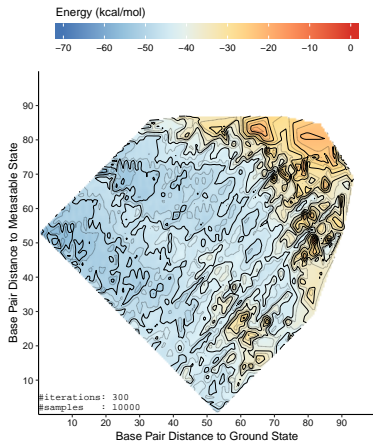
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



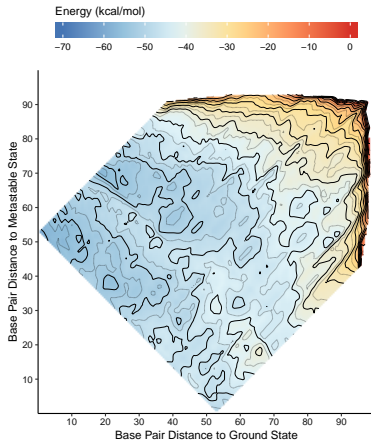
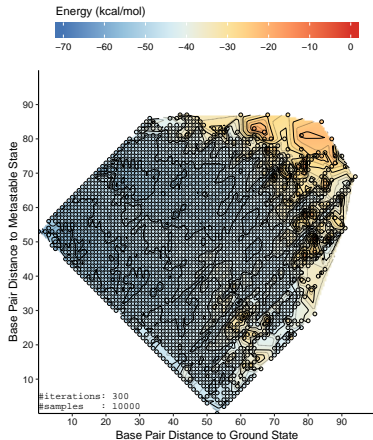
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



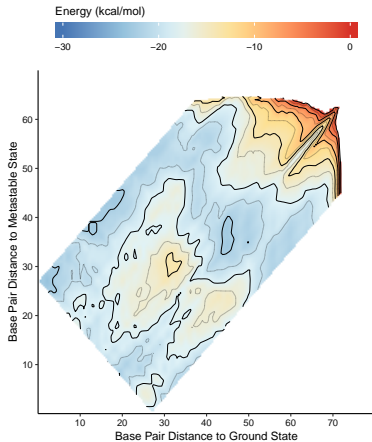
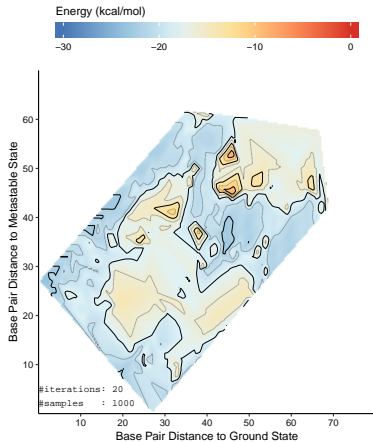
Example: 5UTR of MS2 coat protein mRNA

RNAlocmin temperature elevation scheme Boltzmann sampling



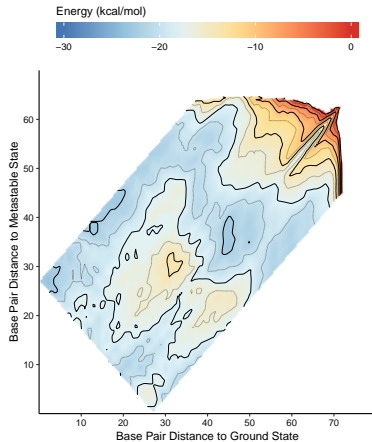
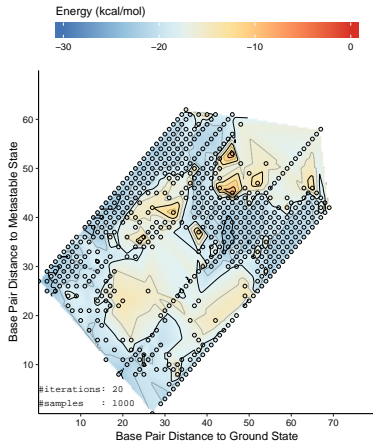
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



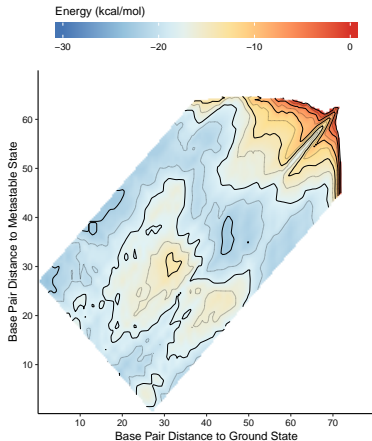
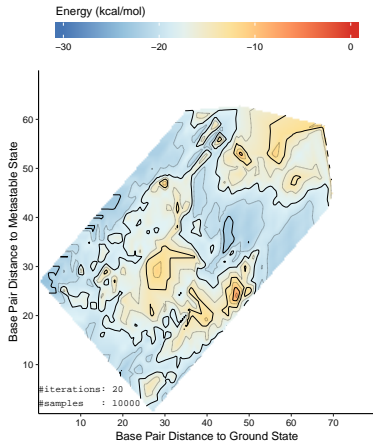
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RNExplorer repulsion scheme Boltzmann sampling



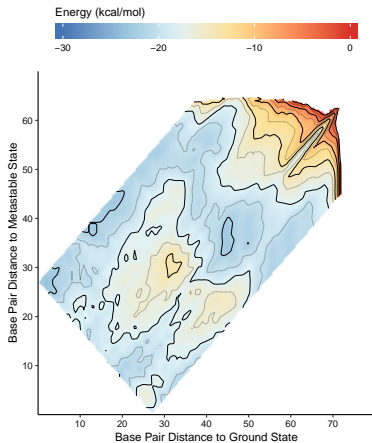
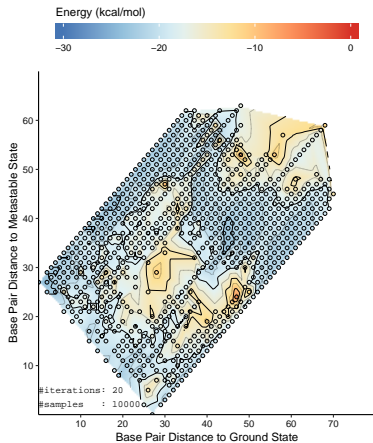
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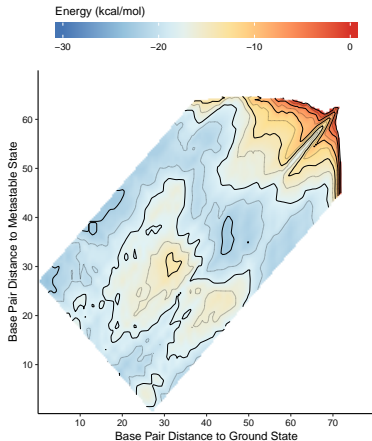
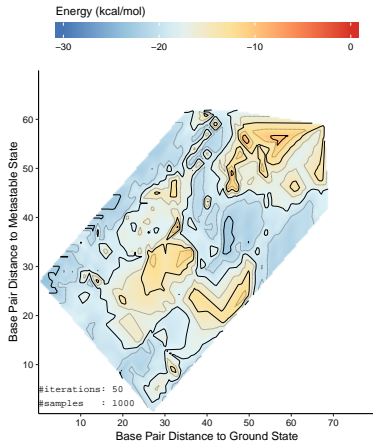
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RNExplorer repulsion scheme Boltzmann sampling



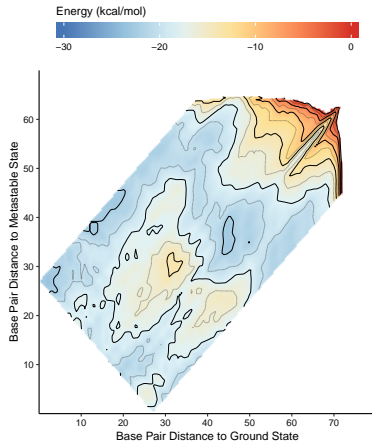
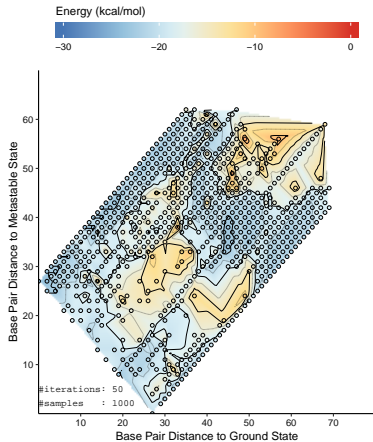
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RNExplorer repulsion scheme Boltzmann sampling



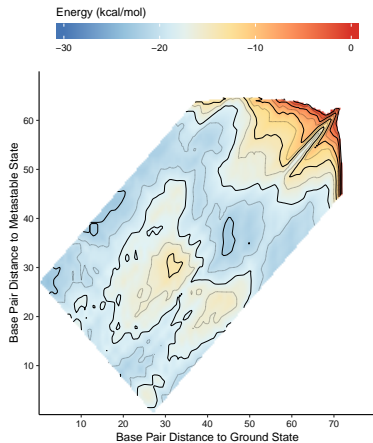
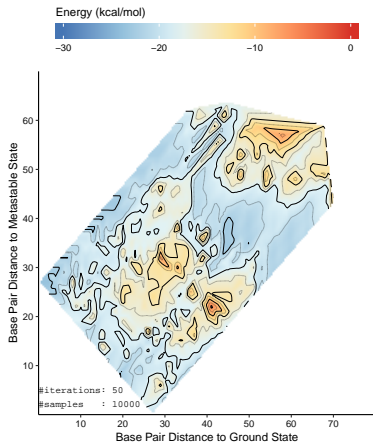
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RNExplorer repulsion scheme Boltzmann sampling



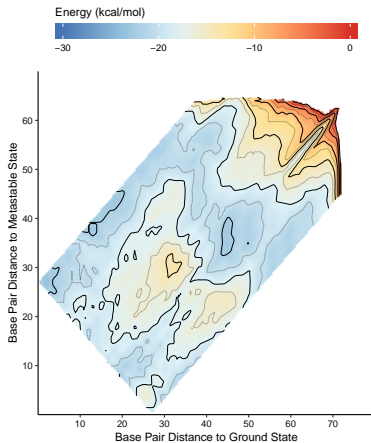
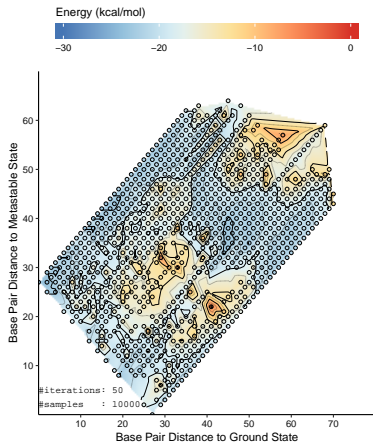
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RNExplorer repulsion scheme Boltzmann sampling



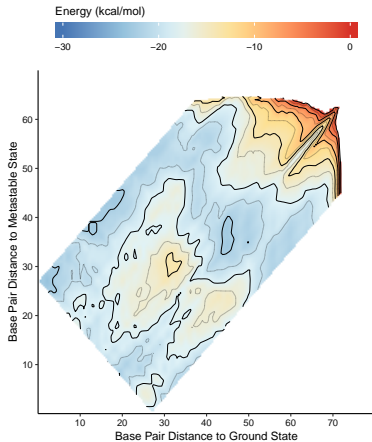
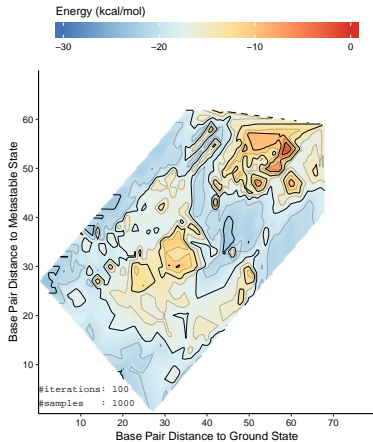
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



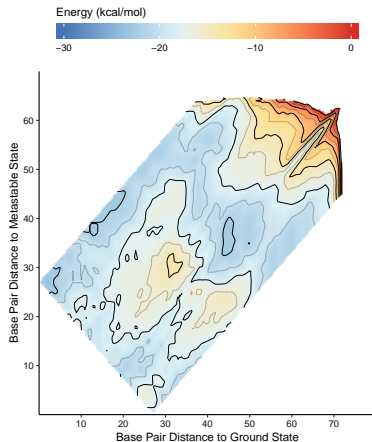
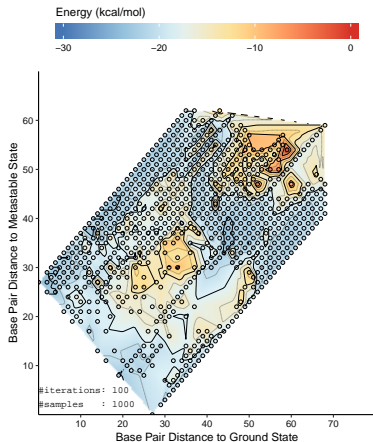
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



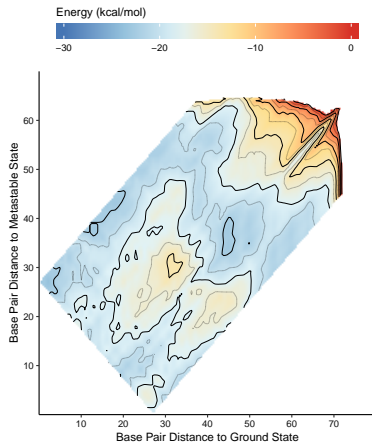
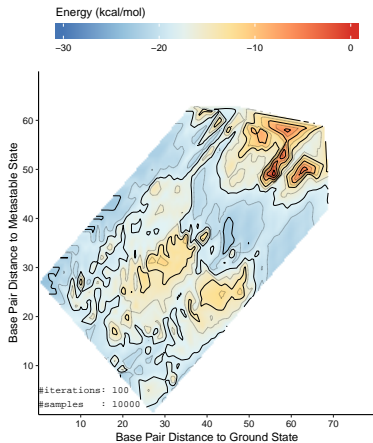
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RNExplorer repulsion scheme Boltzmann sampling



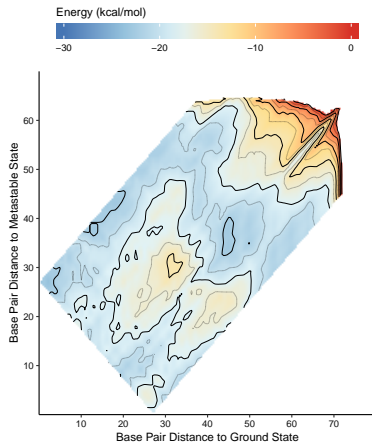
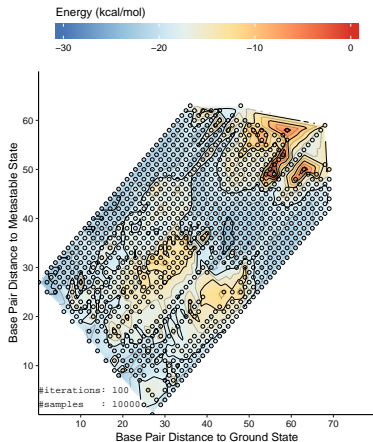
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RNExplorer repulsion scheme Boltzmann sampling



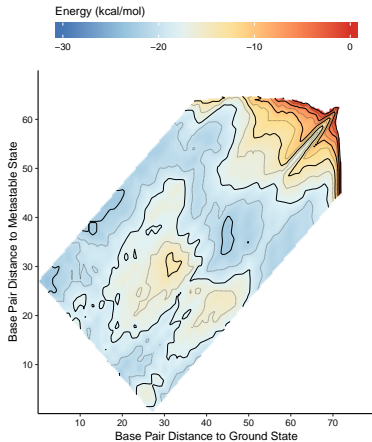
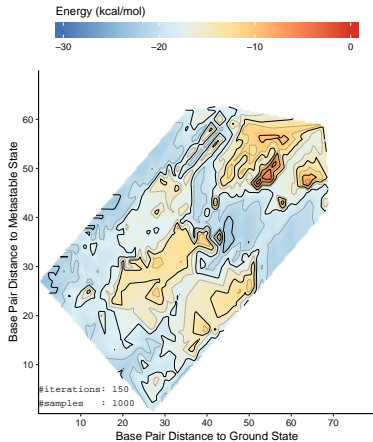
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RNExplorer repulsion scheme Boltzmann sampling



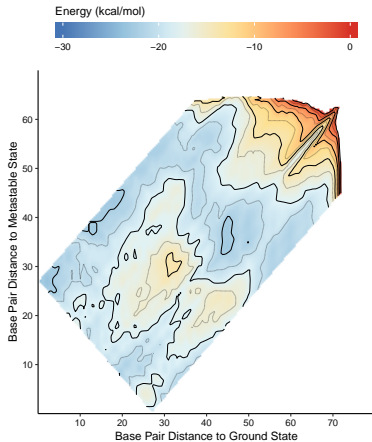
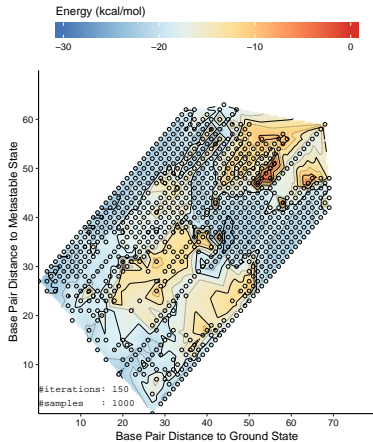
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RNExplorer repulsion scheme Boltzmann sampling



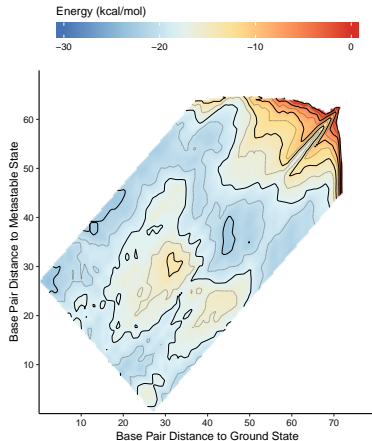
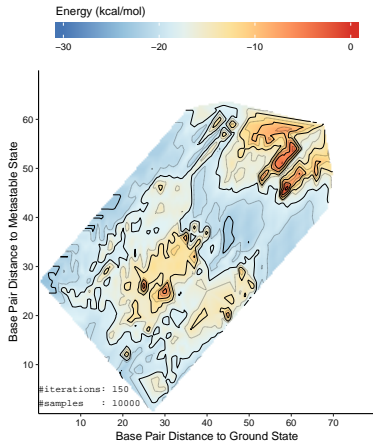
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RNExplorer repulsion scheme Boltzmann sampling



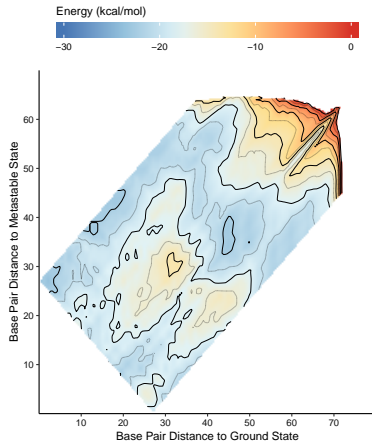
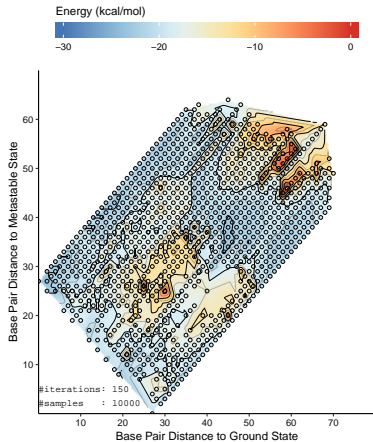
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RNExplorer repulsion scheme Boltzmann sampling



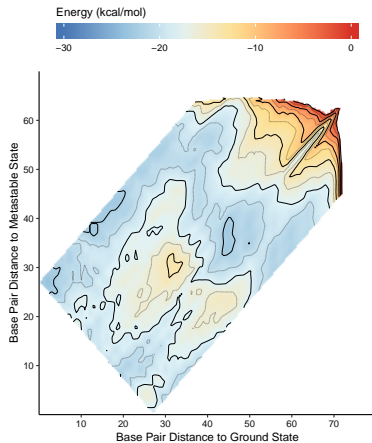
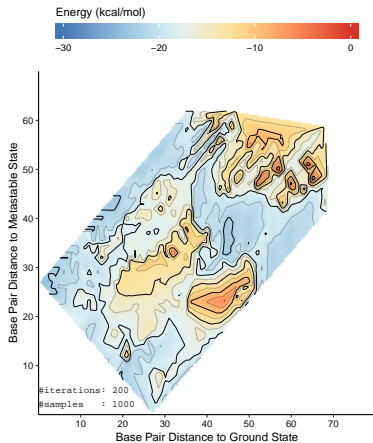
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



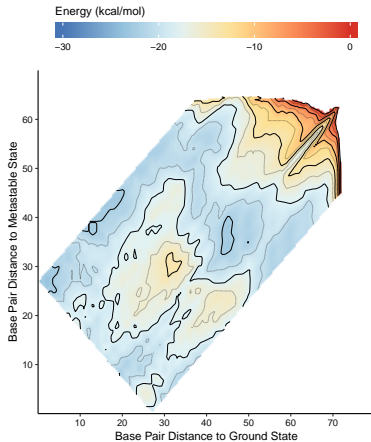
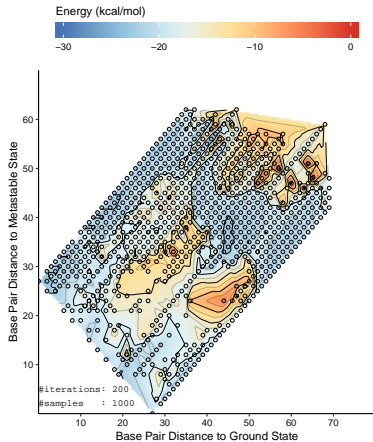
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RNExplorer repulsion scheme Boltzmann sampling



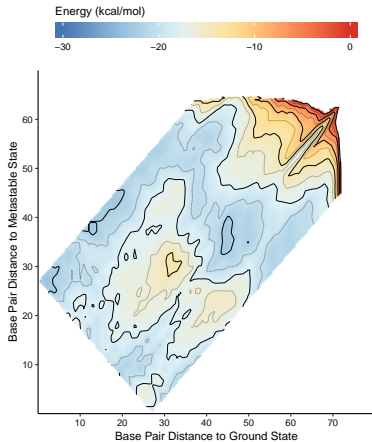
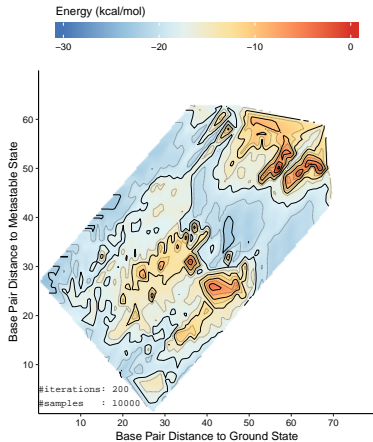
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RNExplorer repulsion scheme Boltzmann sampling



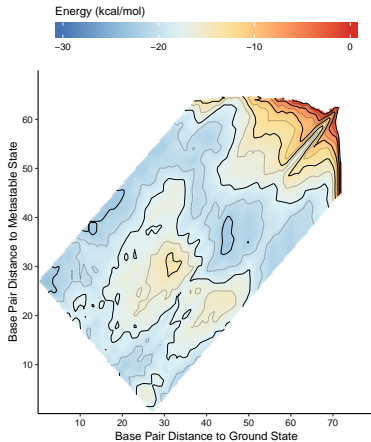
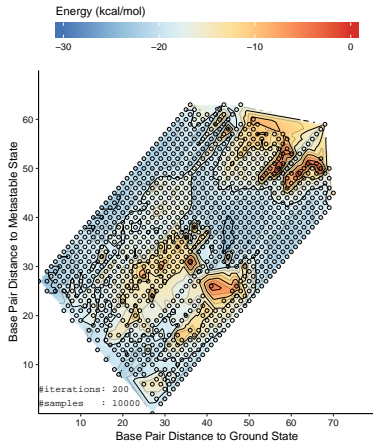
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RNExplorer repulsion scheme Boltzmann sampling



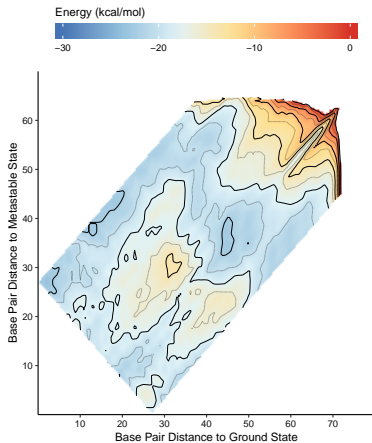
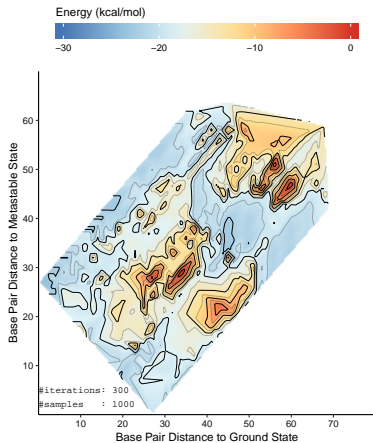
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



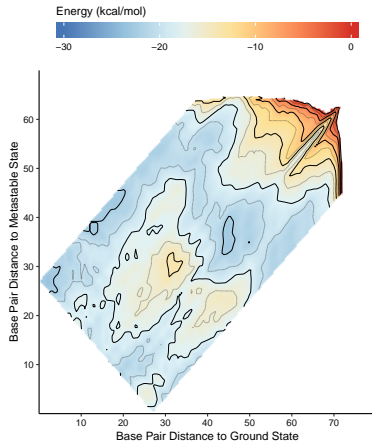
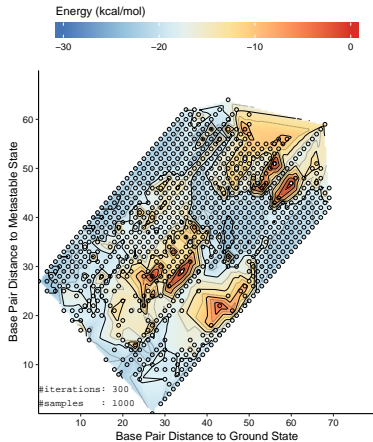
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



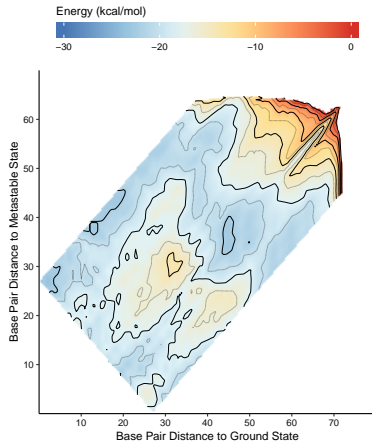
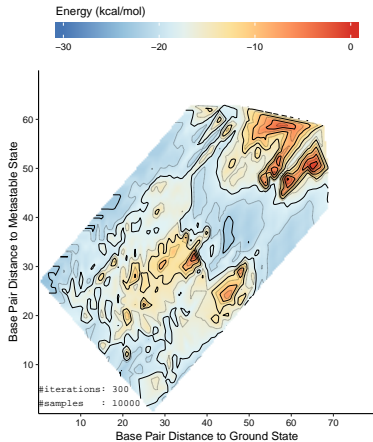
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



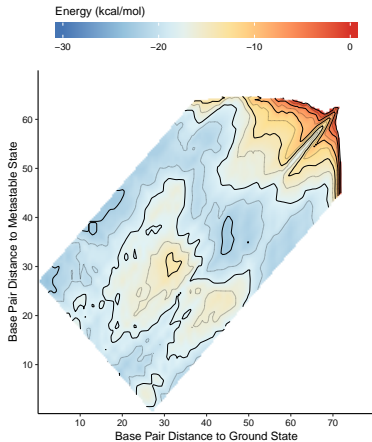
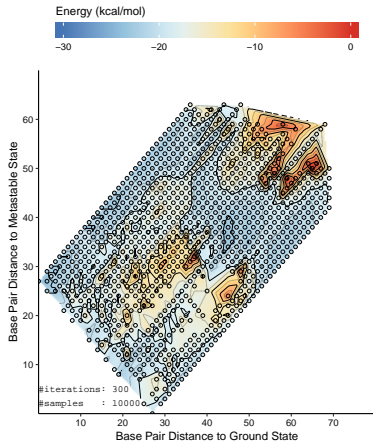
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



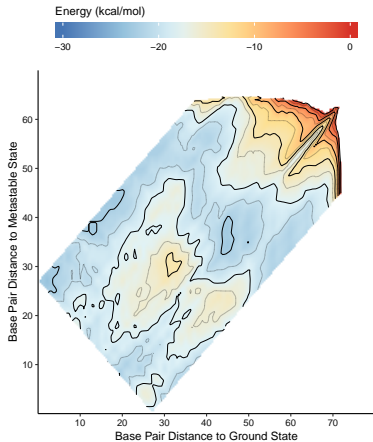
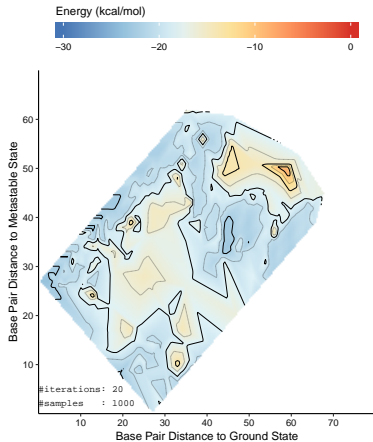
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling



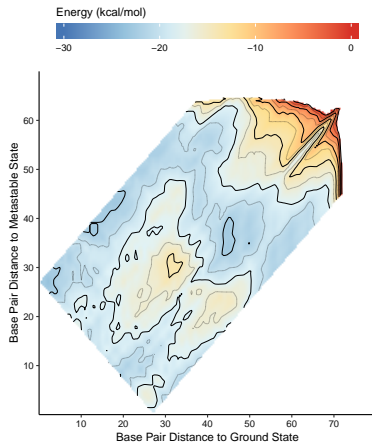
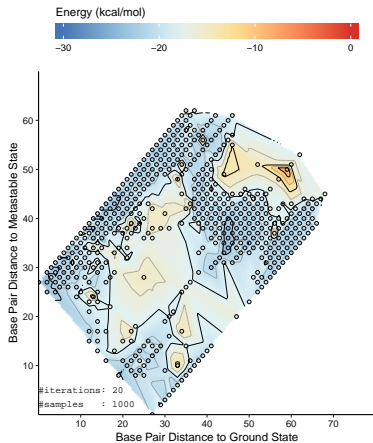
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



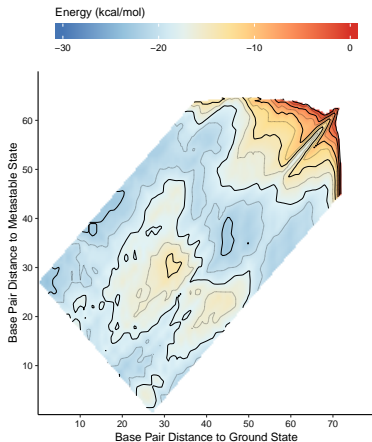
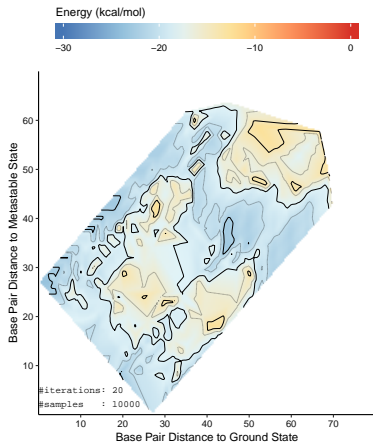
Example: add riboswitch V.culnificus

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



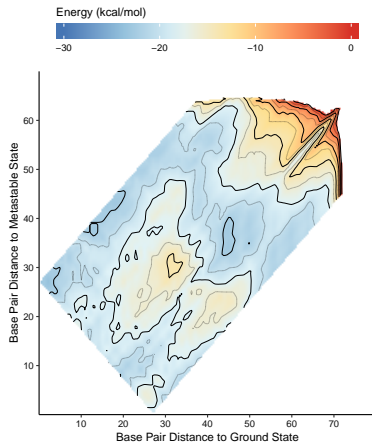
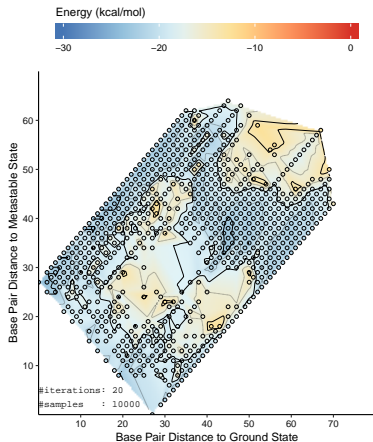
Example: add riboswitch V.culnificus

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



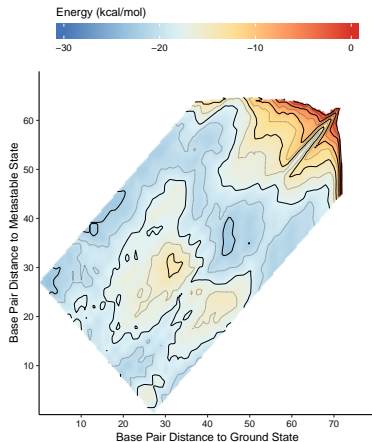
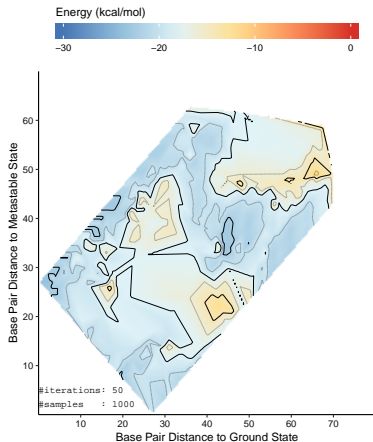
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



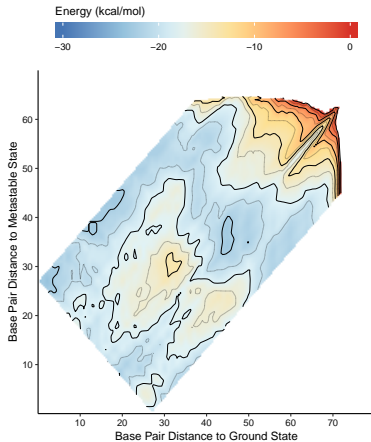
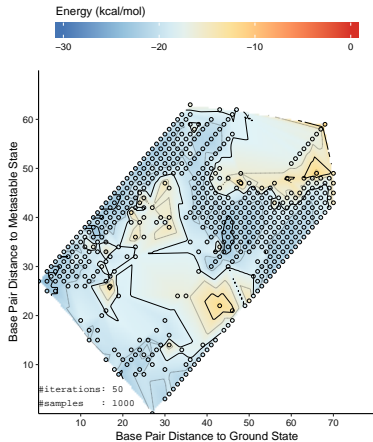
Example: add riboswitch V.culnificus

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



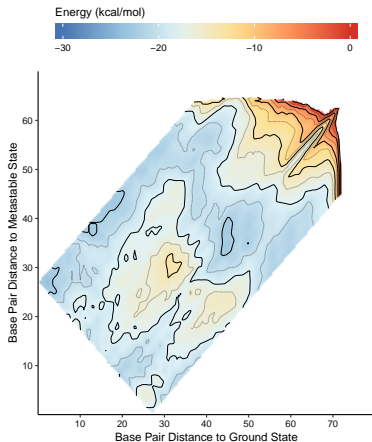
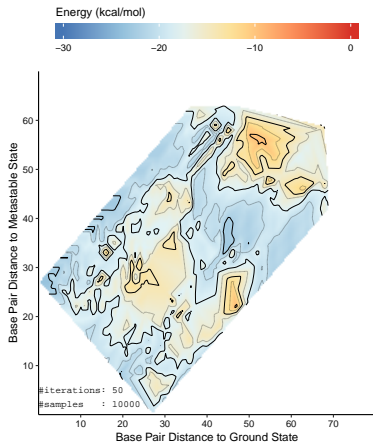
Example: add riboswitch V.culnificus

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



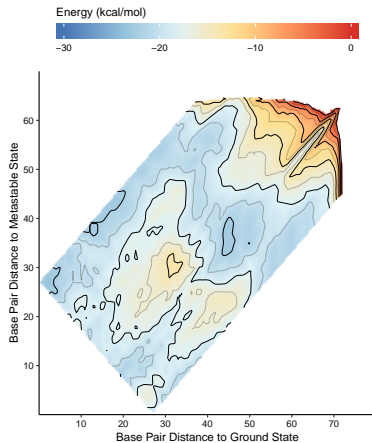
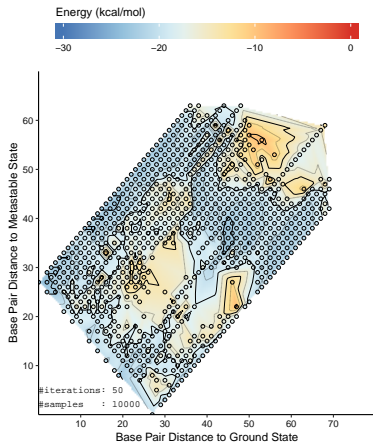
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



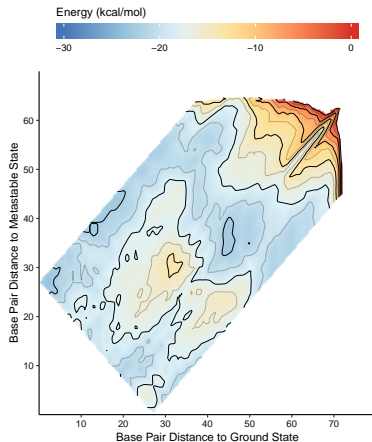
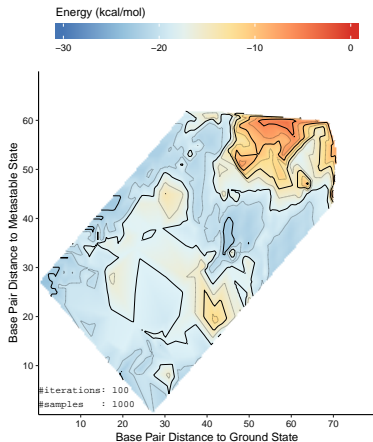
Example: add riboswitch V.culnificus

RNAsplorer repulsion scheme Boltzmann sampling (*distance*)



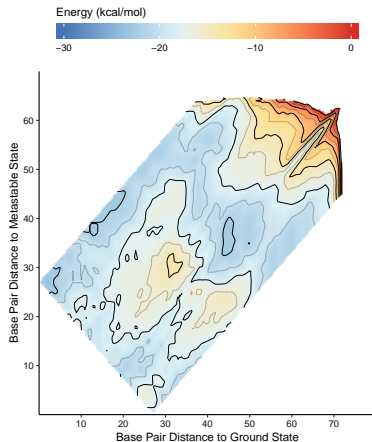
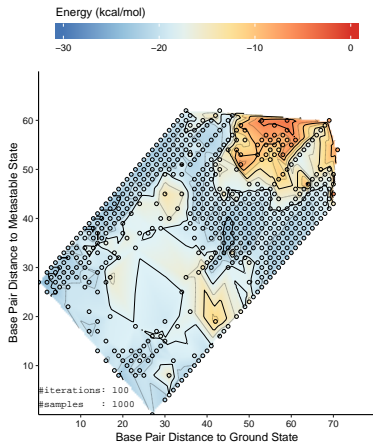
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



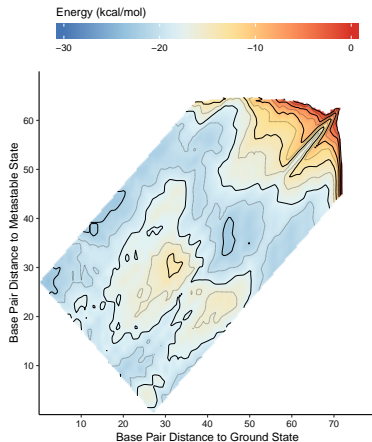
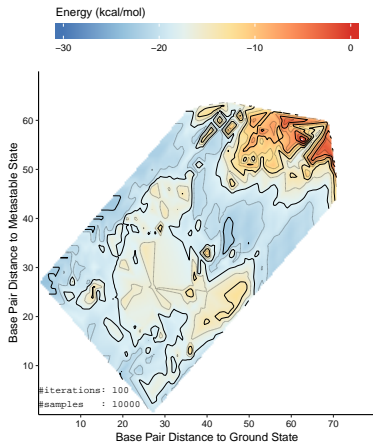
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



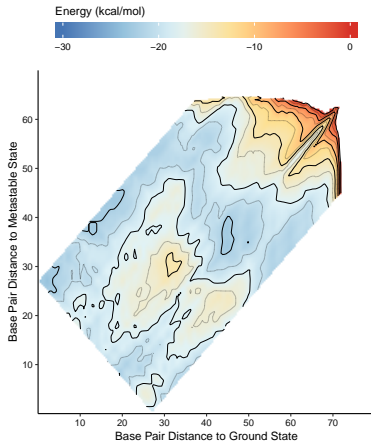
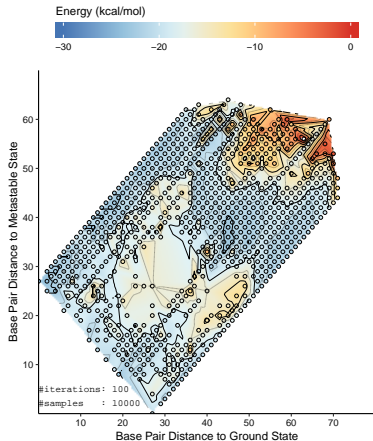
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



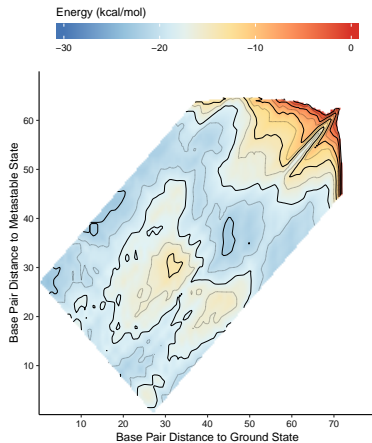
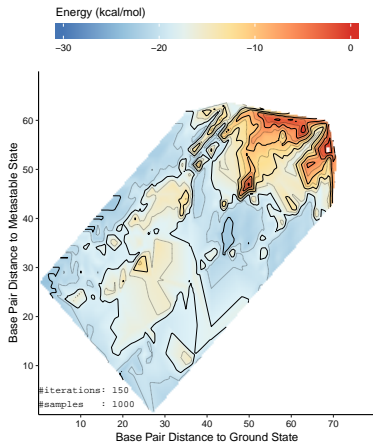
Example: add riboswitch V.culnificus

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



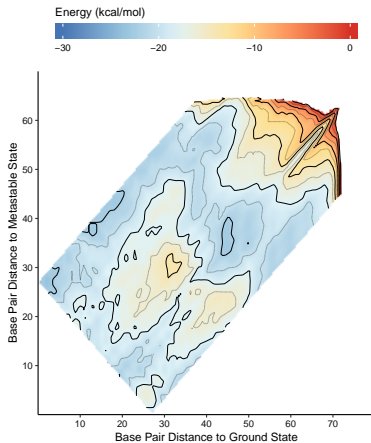
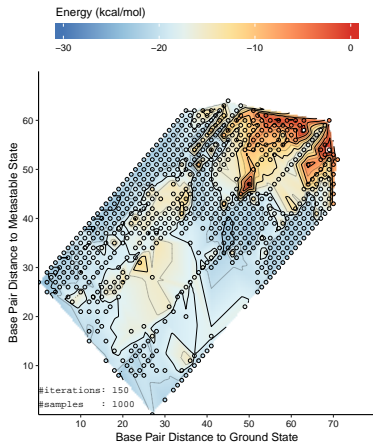
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



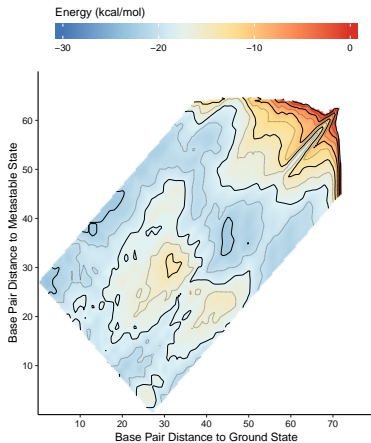
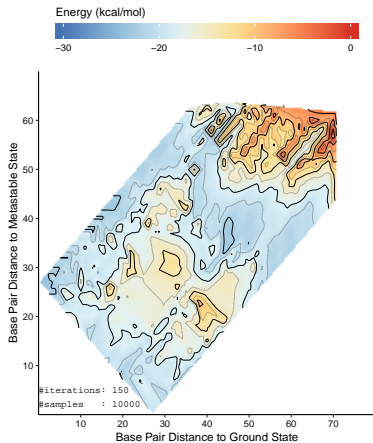
Example: add riboswitch *V.culnificus*

RNAsplorer repulsion scheme Boltzmann sampling (*distance*)



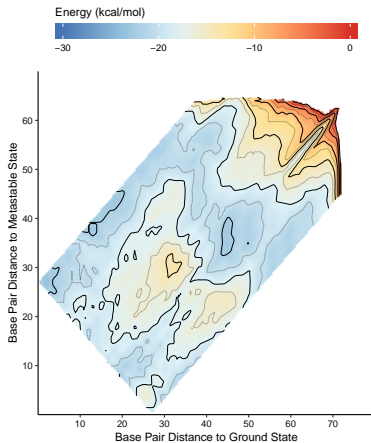
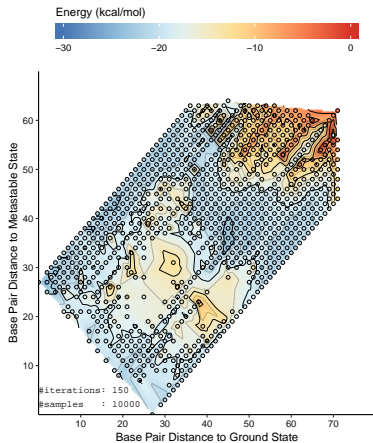
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



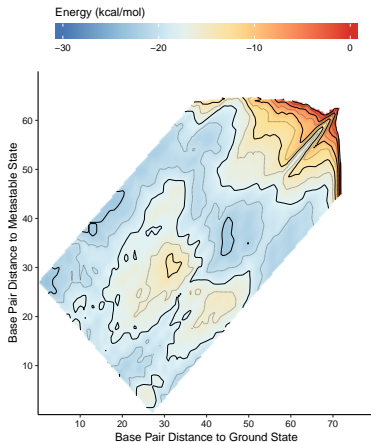
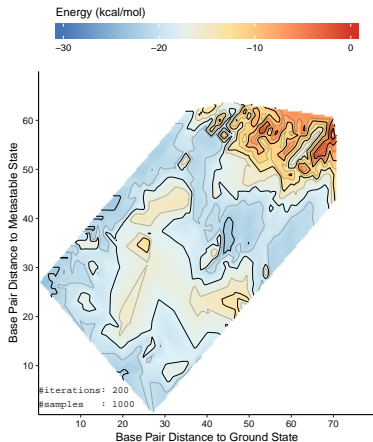
Example: add riboswitch V.culnificus

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



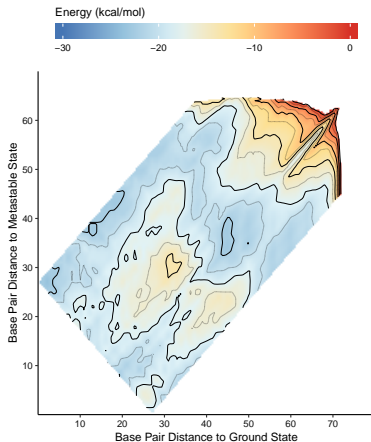
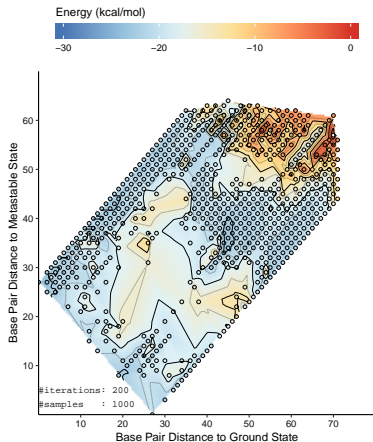
Example: add riboswitch V.culnificus

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



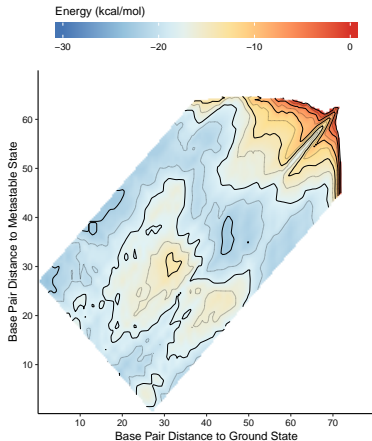
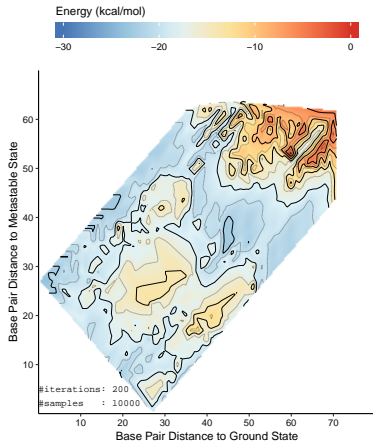
Example: add riboswitch V.culnificus

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



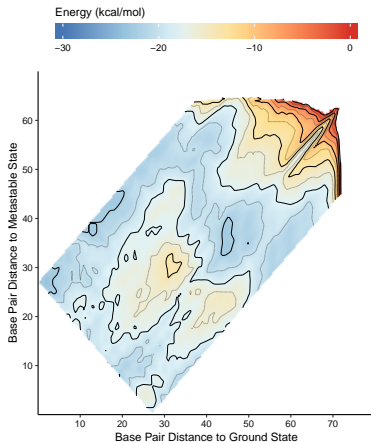
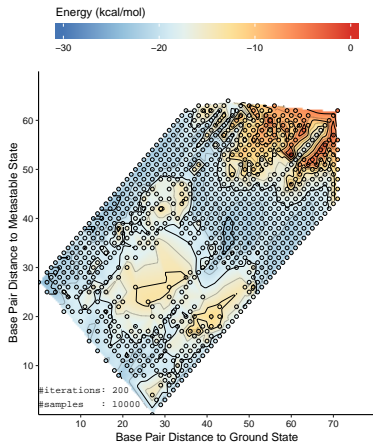
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



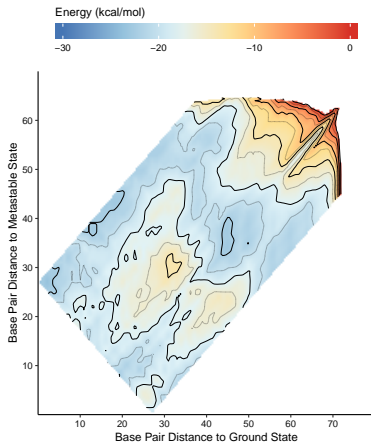
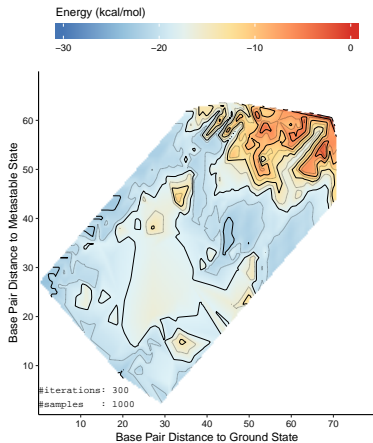
Example: add riboswitch V.culnificus

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



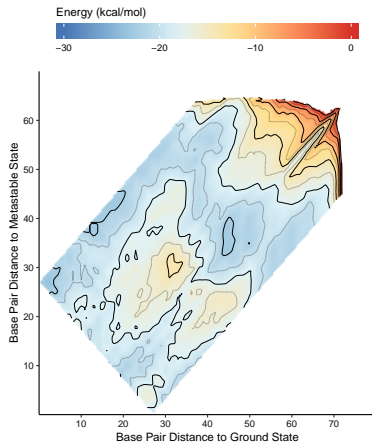
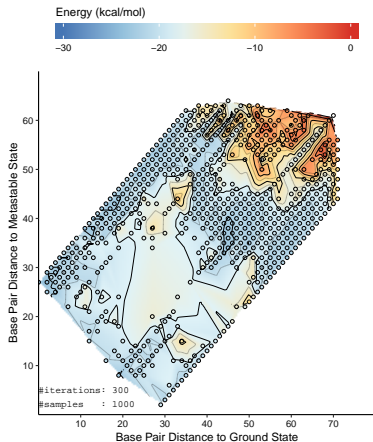
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



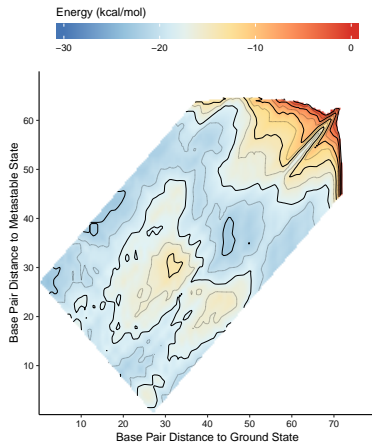
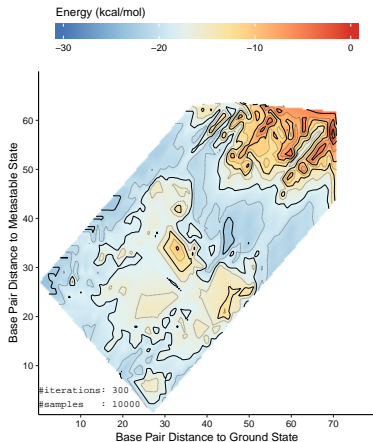
Example: add riboswitch V.culnificus

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



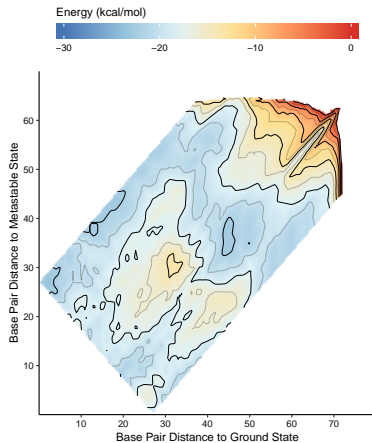
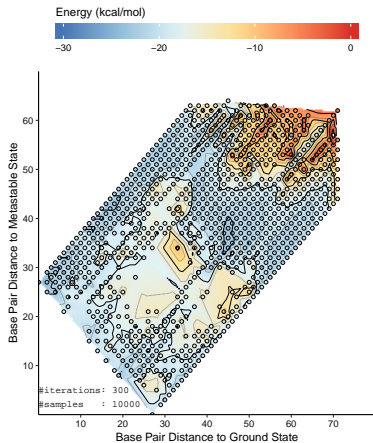
Example: add riboswitch *V.culnificus*

RNAexplorer repulsion scheme Boltzmann sampling (*distance*)



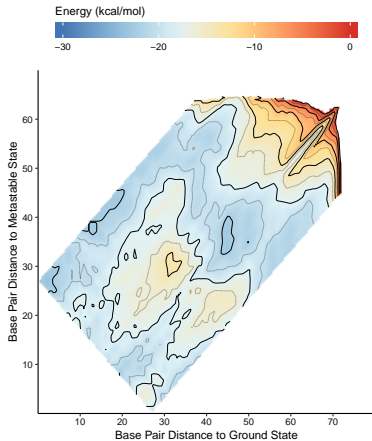
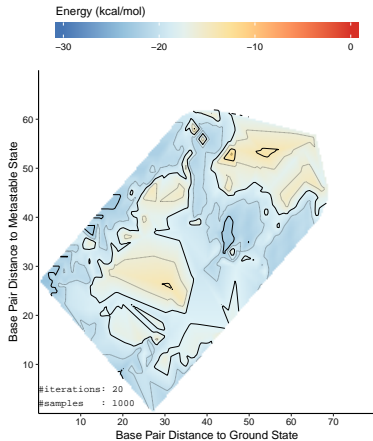
Example: add riboswitch *V.culnificus*

RNExplorer repulsion scheme Boltzmann sampling (*distance*)



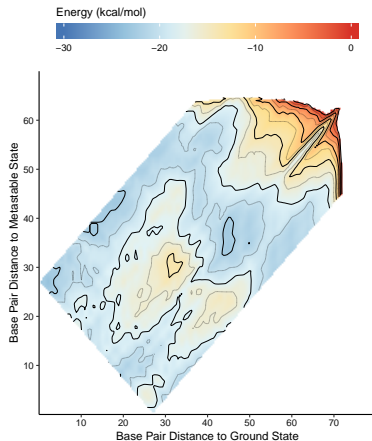
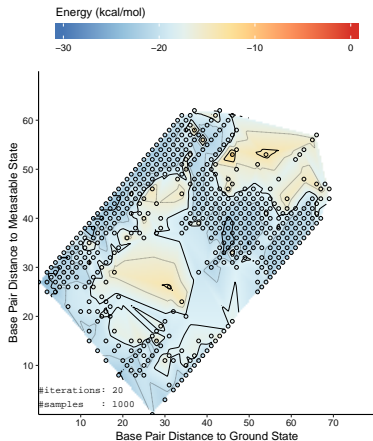
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



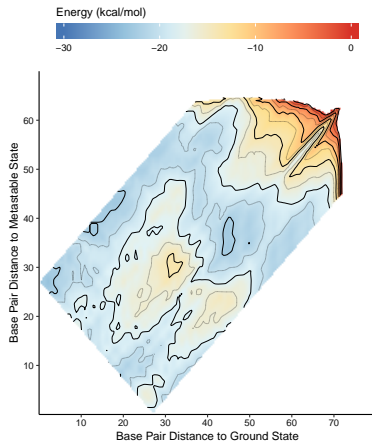
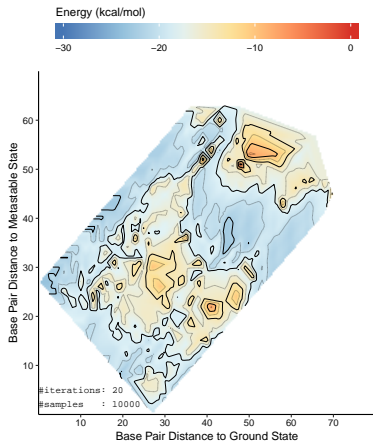
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



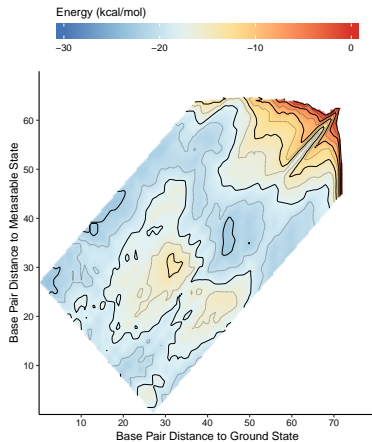
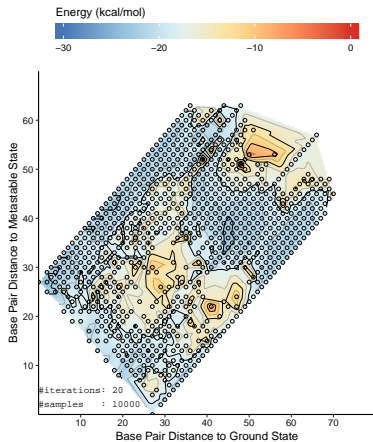
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



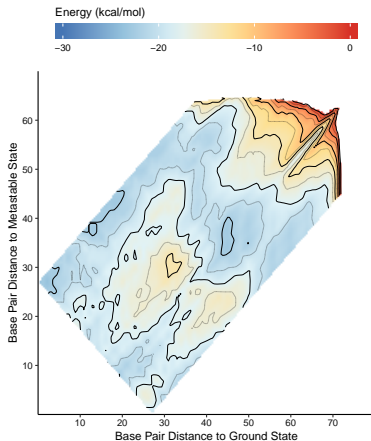
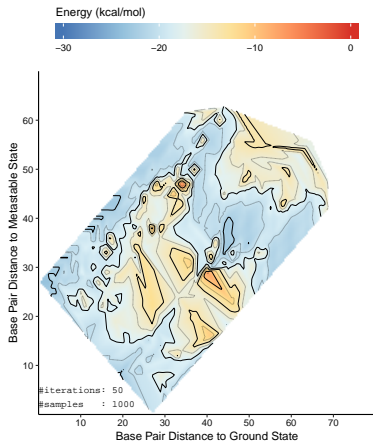
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RNAlocmin temperature elevation scheme Boltzmann sampling



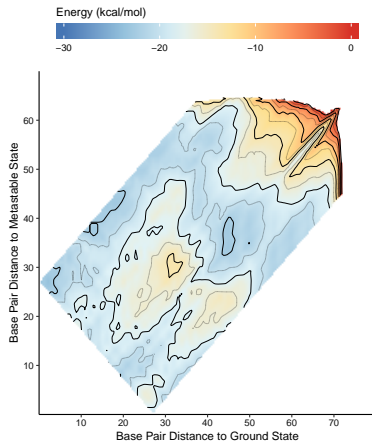
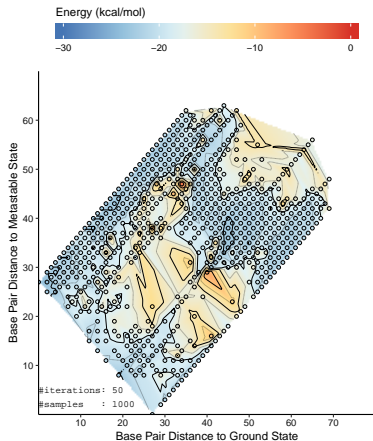
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RNAlocmin temperature elevation scheme Boltzmann sampling



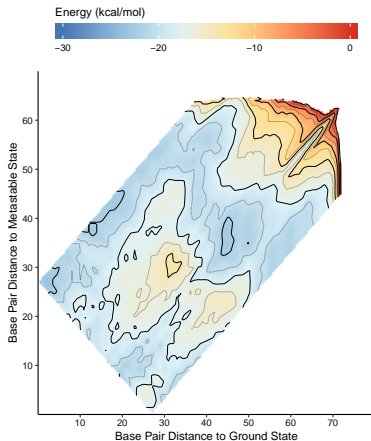
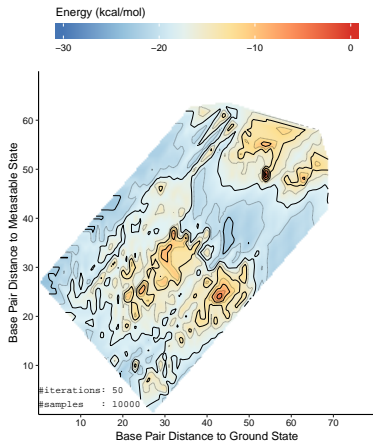
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RNAlocmin temperature elevation scheme Boltzmann sampling



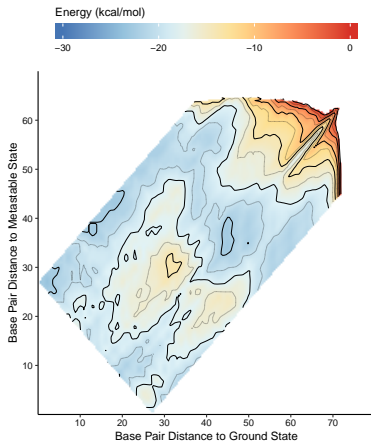
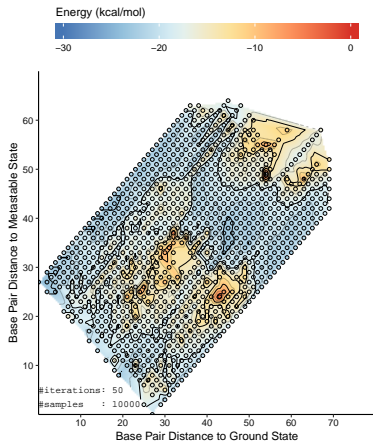
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



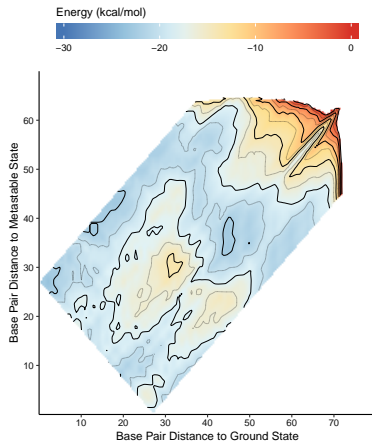
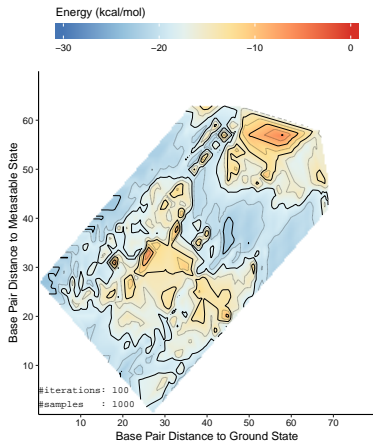
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



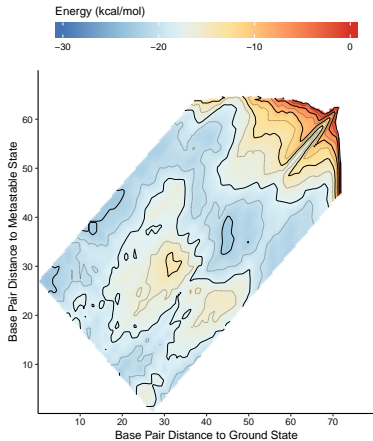
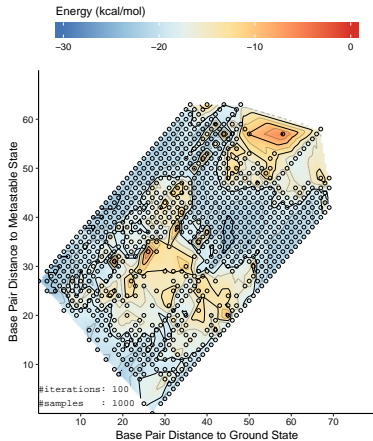
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



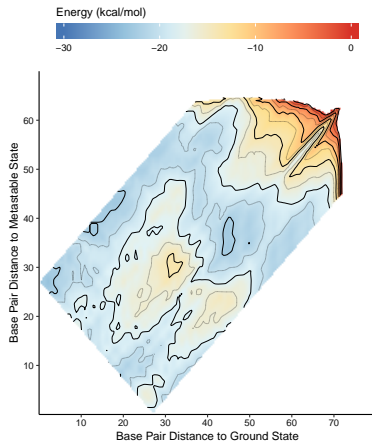
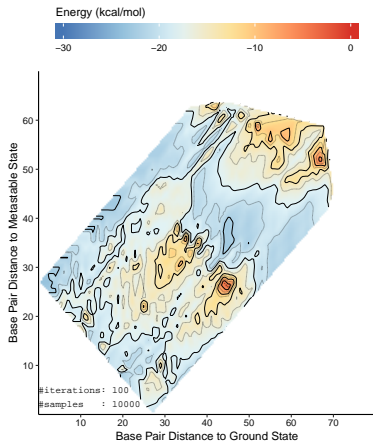
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



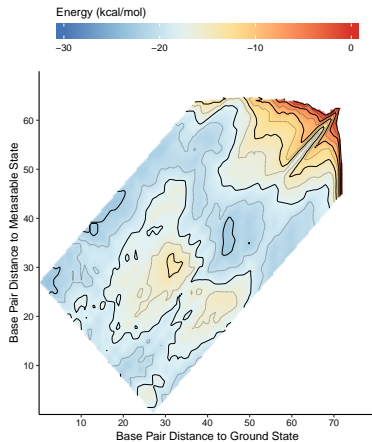
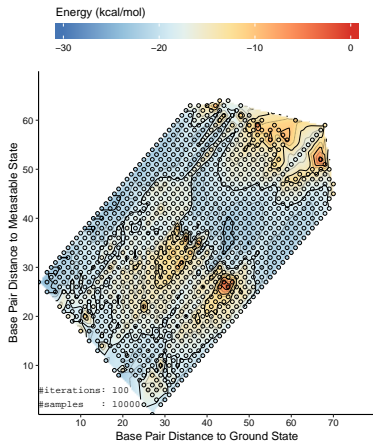
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RNAlocmin temperature elevation scheme Boltzmann sampling



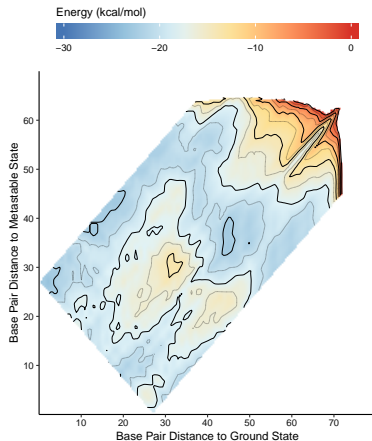
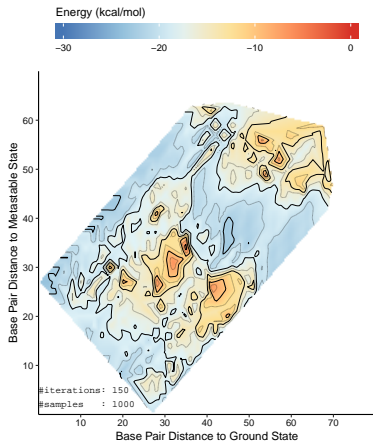
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RNAlocmin temperature elevation scheme Boltzmann sampling



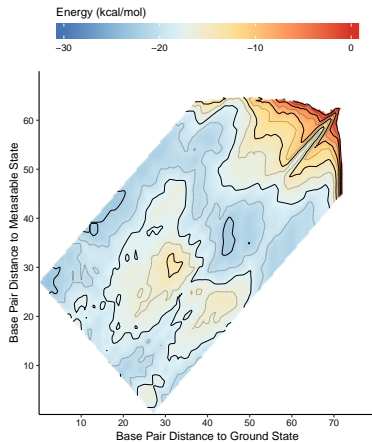
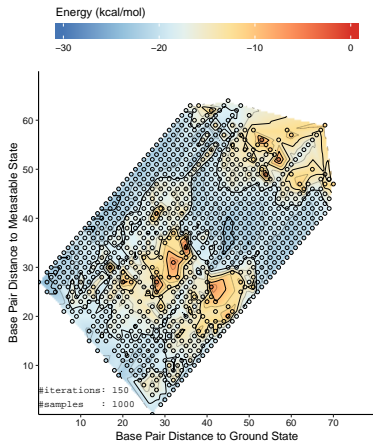
Example: add riboswitch *V.culnificus*

RNAlocmin temperature elevation scheme Boltzmann sampling



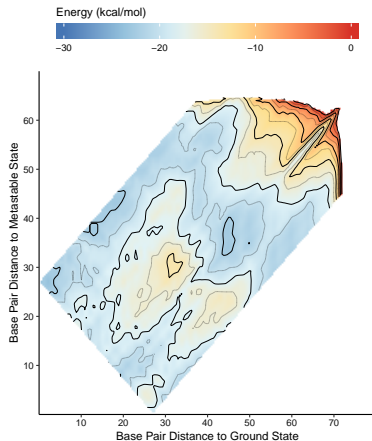
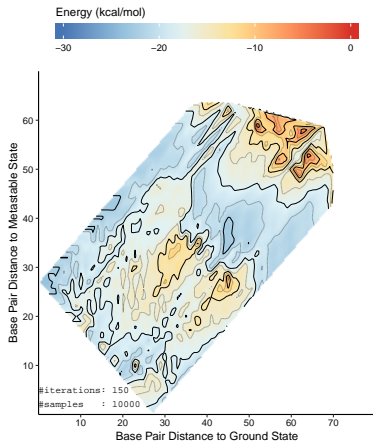
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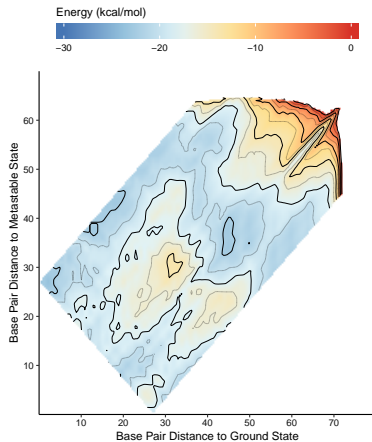
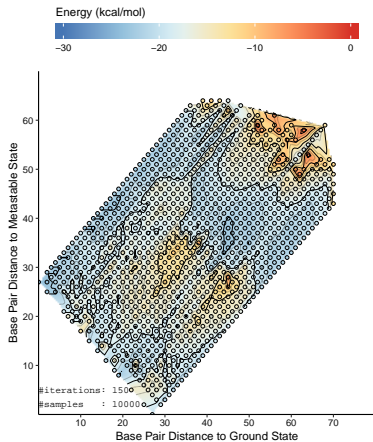
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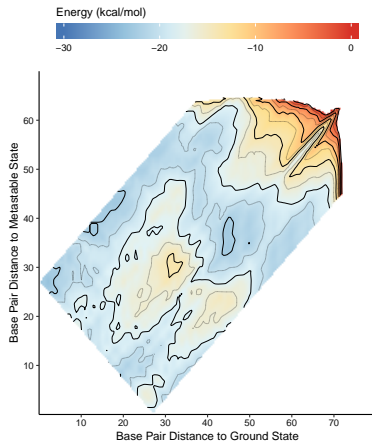
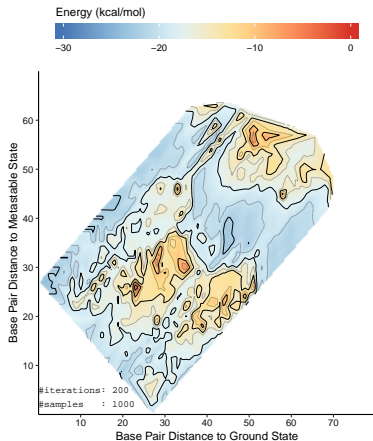
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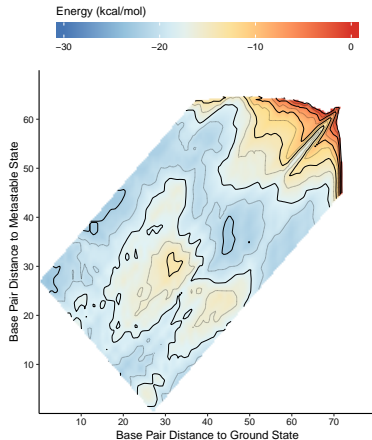
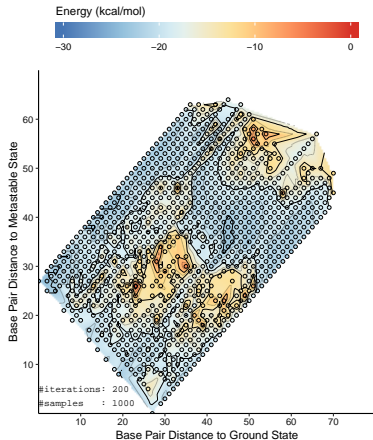
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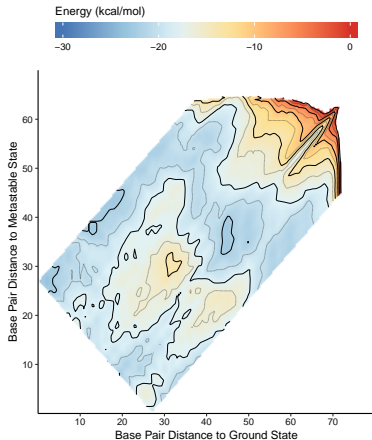
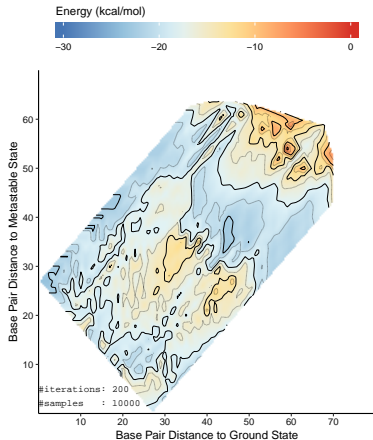
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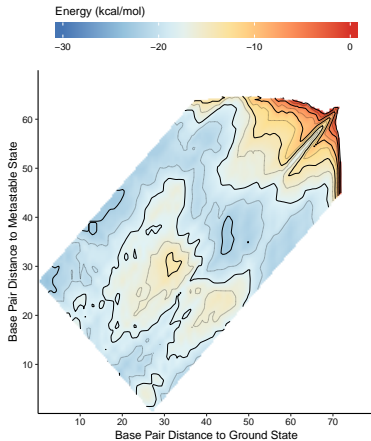
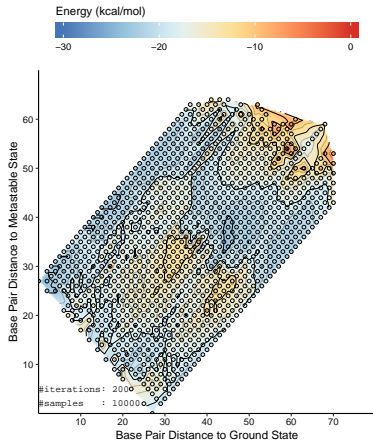
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RNAlocmin temperature elevation scheme Boltzmann sampling



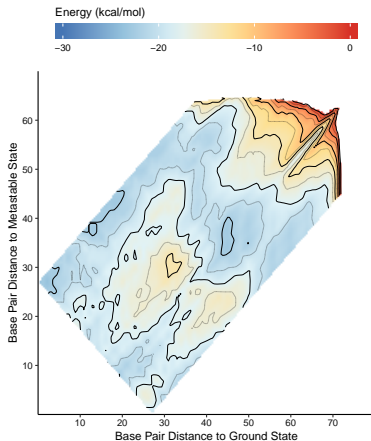
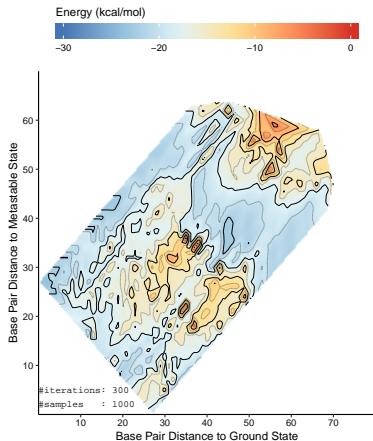
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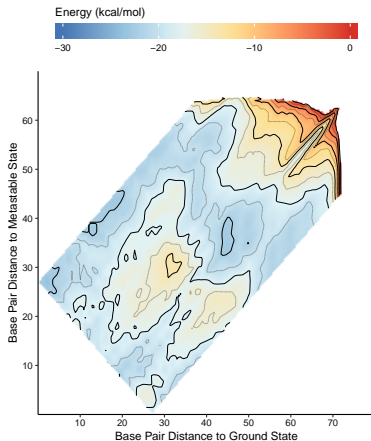
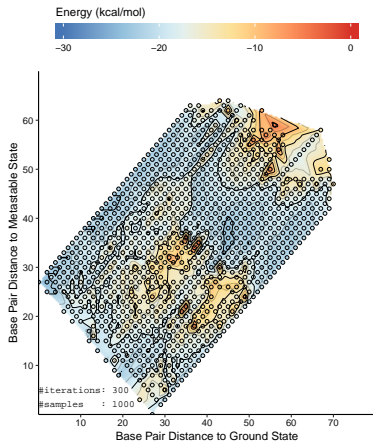
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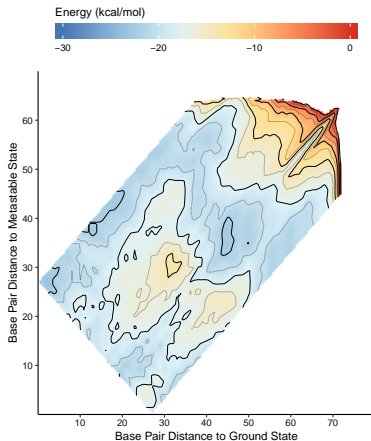
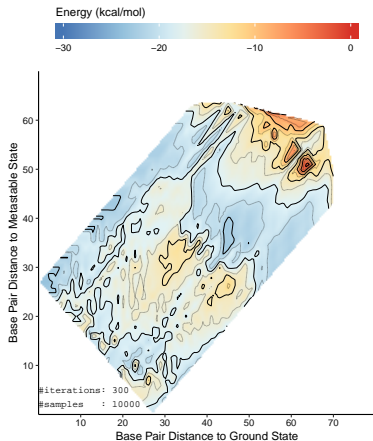
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