

Stochastic Modeling of Gene Transcription in a Single Cell

SEA 2012

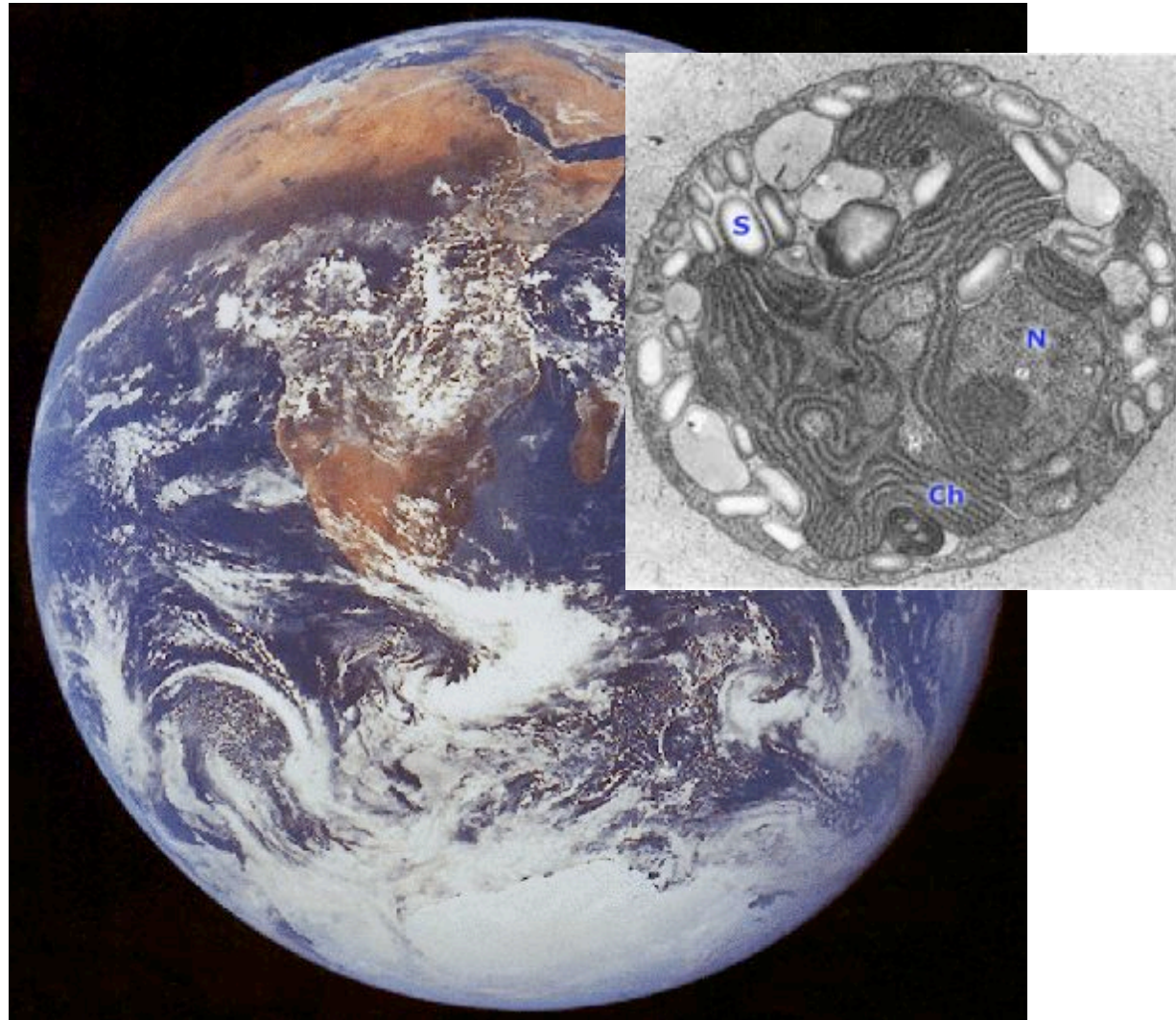
David Knox

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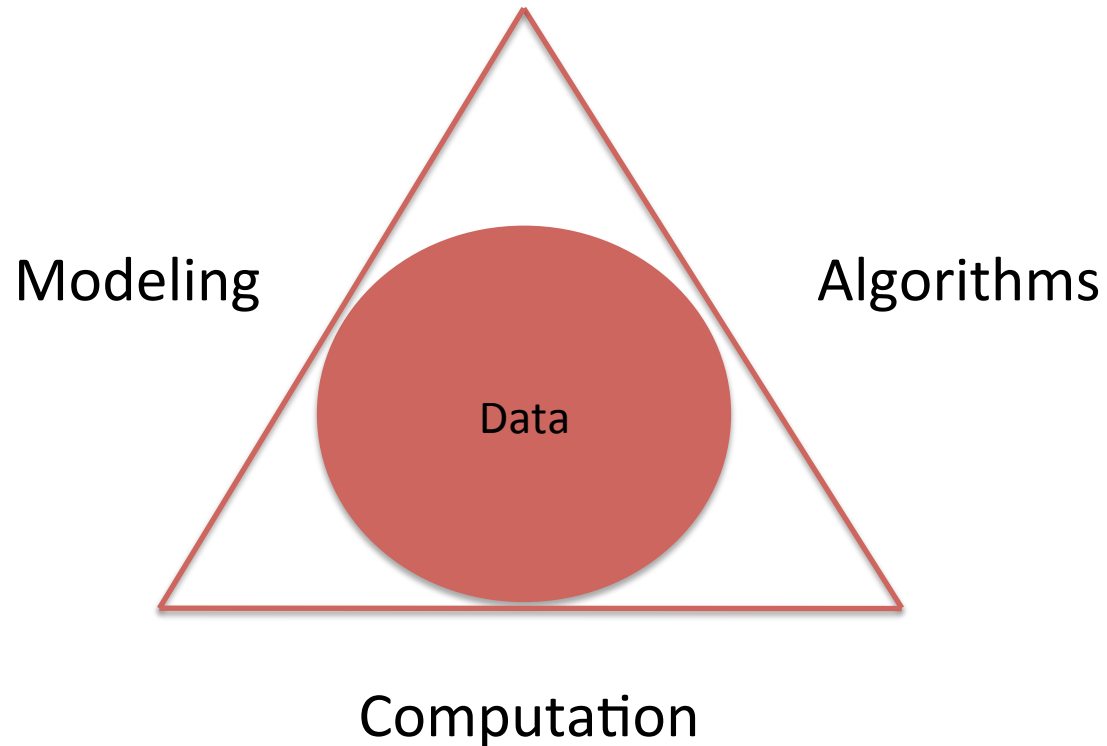
Your World



My World

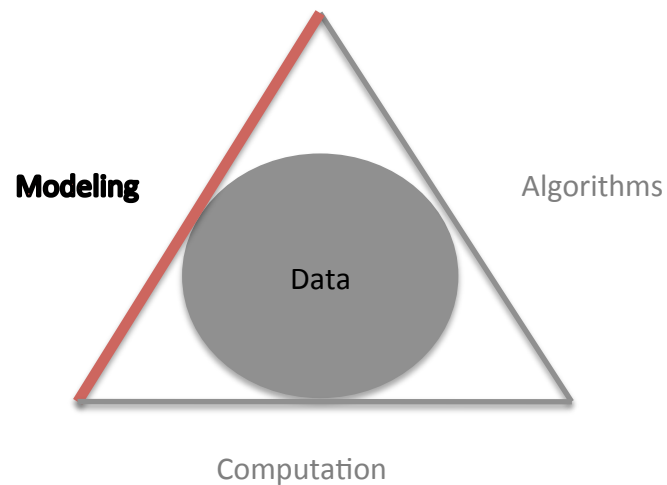


Computational Biology



Adapted from Dr. Alan Qi
Dept of Computer Science and Department of Statistics
Purdue University
SEA Conference February 2011

Modeling takes everything we know



Population Studies

Whole Cell Simulations

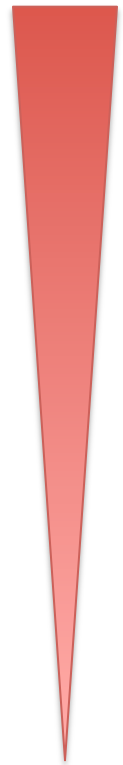
Heart/Kidney Simulations

Signaling Pathways

Protein Folding

Transcriptional Regulation

Molecular Dynamics



Stochastic Modeling of Gene Transcription in a Single Cell

- What is Transcription Regulation
- Modeling Paradigm
- Stochastic Rule Builder (SRB)
- Visualization of Simulation Results

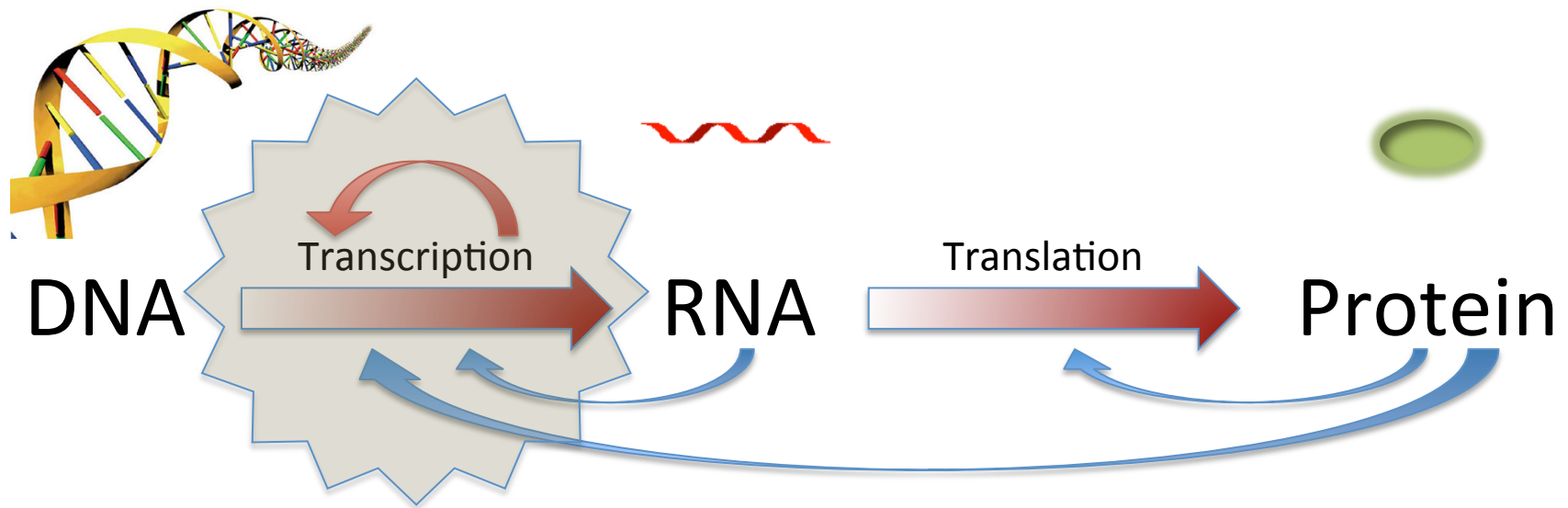
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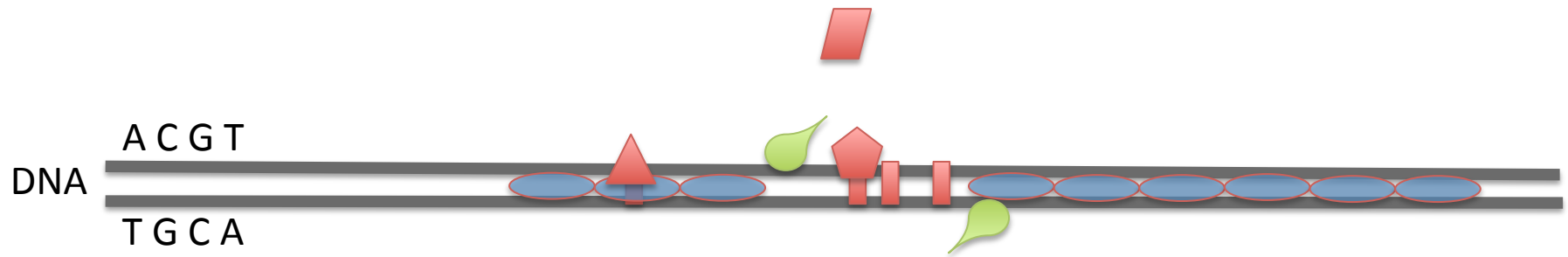
Transcriptional Regulation




Transcriptional Diversity and Regulation

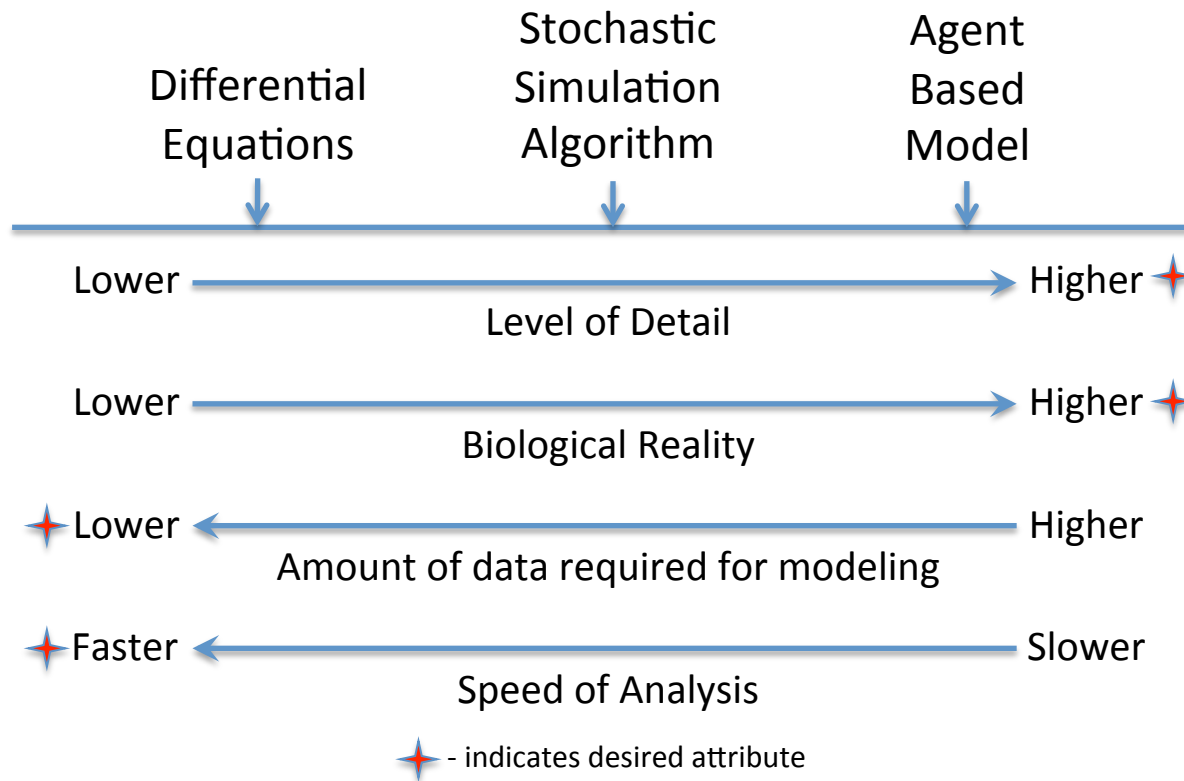


Modeling Transcriptional Regulation: The Players



Symbol	Component
	RNA Polymerase II , Transcription Machinery (TM)

Modeling Methods



Requirements and benefits of modeling methods. Adapted from “Modelling and analysis of gene regulatory networks”
Guy Karlebach and Ron Shamir, 2008.

All models are wrong; some are useful.
-- George Box

Modeling with the Stochastic Simulation Algorithm

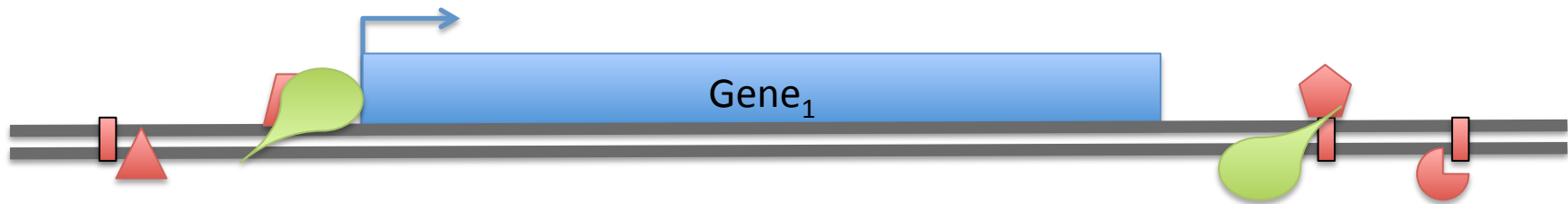
- The SSA is a Monte Carlo simulation of the master chemical equation
- Every interaction between components must be explicitly defined



Reactant + Reactant ... \rightarrow Resultant + ... @ RATE in STEPS

SSA Modeling of Transcription Factors

Activating / Repressing Transcription



$TF_a + DNA[7] \rightarrow TF_a_DNA[7] @ on_rate_a$ in S_a steps

$TF_a_DNA[7] \rightarrow TF_a + DNA[7] @ off_rate_a$

$TF_a_DNA[7] + TM \rightarrow TM_DNA[7] + TF_a @ on_rate_c$ in S_c steps

$TM + DNA[90] \rightarrow TM_DNA[90] @ rate$ in S steps

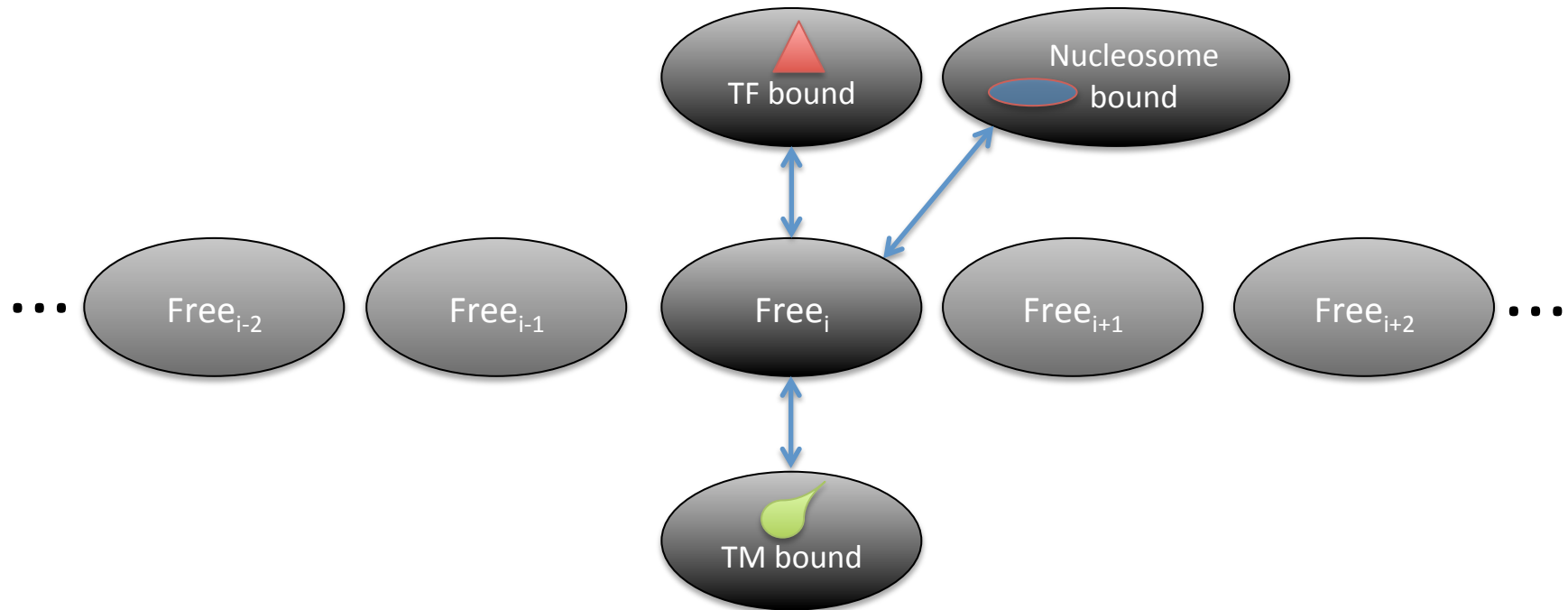
$TM_DNA[90] + DNA[91] \rightarrow TM_DNA[91] + DNA[90] @ rate$ in S steps

$TM_DNA[90] + DNA[89] \rightarrow TM_DNA[89] + DNA[90] @ rate$ in S steps

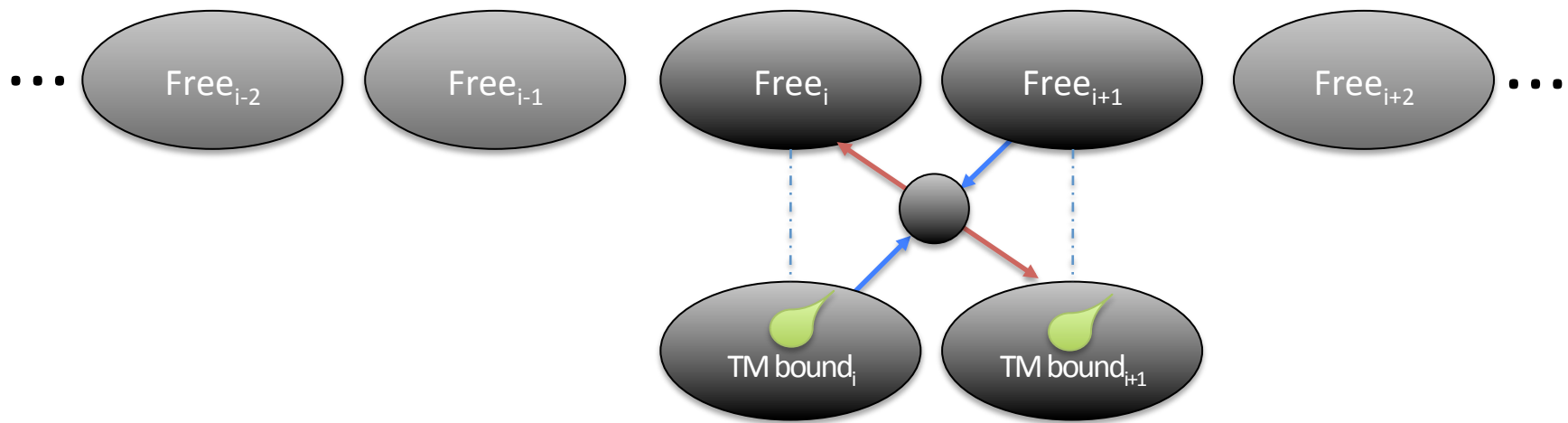
Stochastic Modeling of Gene Transcription in a Single Cell

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- **Modeling Paradigm**
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State Diagram for one DNA Position



State Diagram for TM Advancing one DNA Position

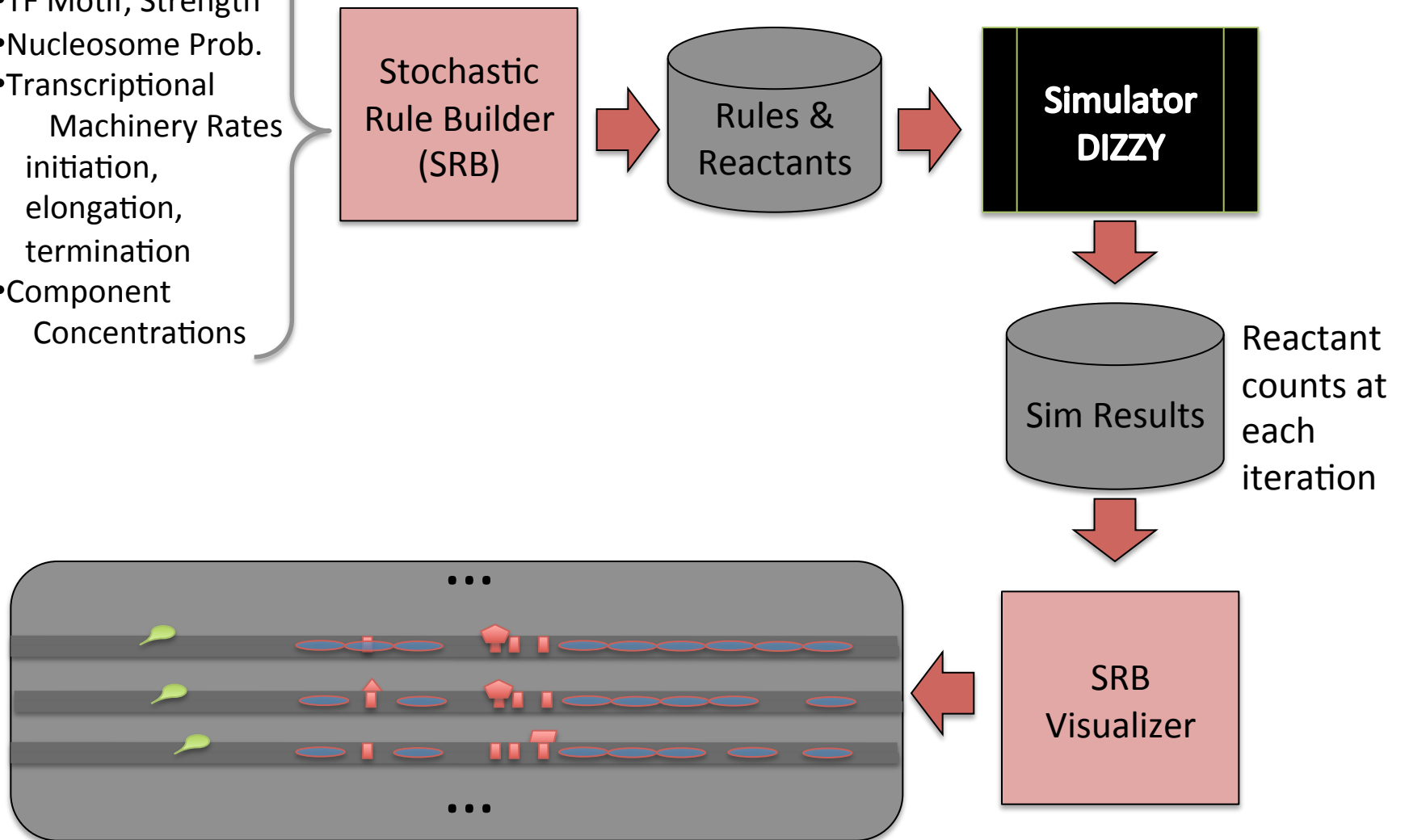


Stochastic Modeling of Gene Transcription in a Single Cell

- What is Transcription Regulation
- Modeling Paradigm
- **Stochastic Rule Builder (SRB)**
- Visualization of Simulation Results

Model System Overview

- State Diagrams
- DNA sequence
- TF Motif, Strength
- Nucleosome Prob.
- Transcriptional Machinery Rates initiation, elongation, termination
- Component Concentrations



Biological Detail vs Computer Resources

Sizes of SRB Generated Models

IME4 (2700 nt)

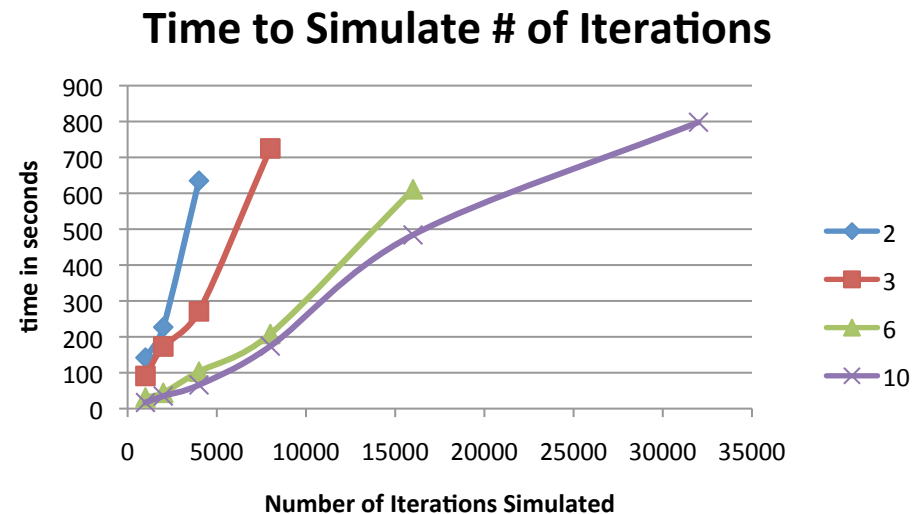
Nucleotides per group	# Reactants	# Rules
1	54366	405326
2	27361	127106
3	18361	68205
6	9361	26206
10	5758	14127

Using 30 nucleotides per group

- My manual creation, ~2000 rules, ~1000 reactants
- SRB produces ~4700 rules, ~2150 reactants

Time to Simulate Models using DIZZY

Time (in seconds) to Simulate Model of IME4 (2700nt)					
	Group Size				
# iterations	1	2	3	6	10
1000	---	142	91	31	17
2000	---	227	173	44	35
4000	---	635	271	103	66
8000	---	---	725	208	174
16000	---	---	---	611	484
32000	---	---	---	---	798



Dizzy Stochastic Simulator

Ramsey et al. "Dizzy: Stochastic simulation of large-scale genetic regulatory networks," J. Bioinformatics Comp. Biol. 2005

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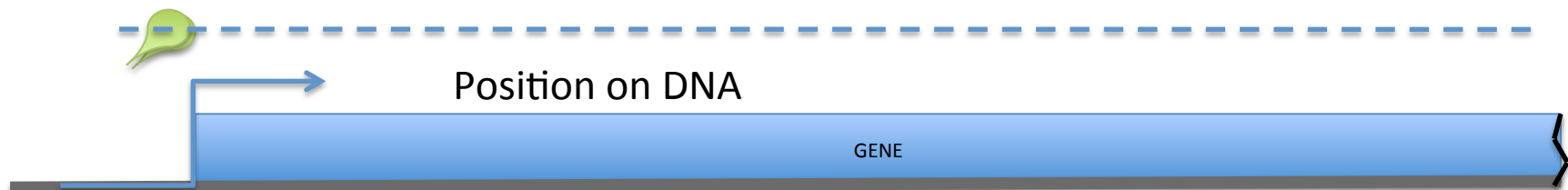
Visualizing the Process

```

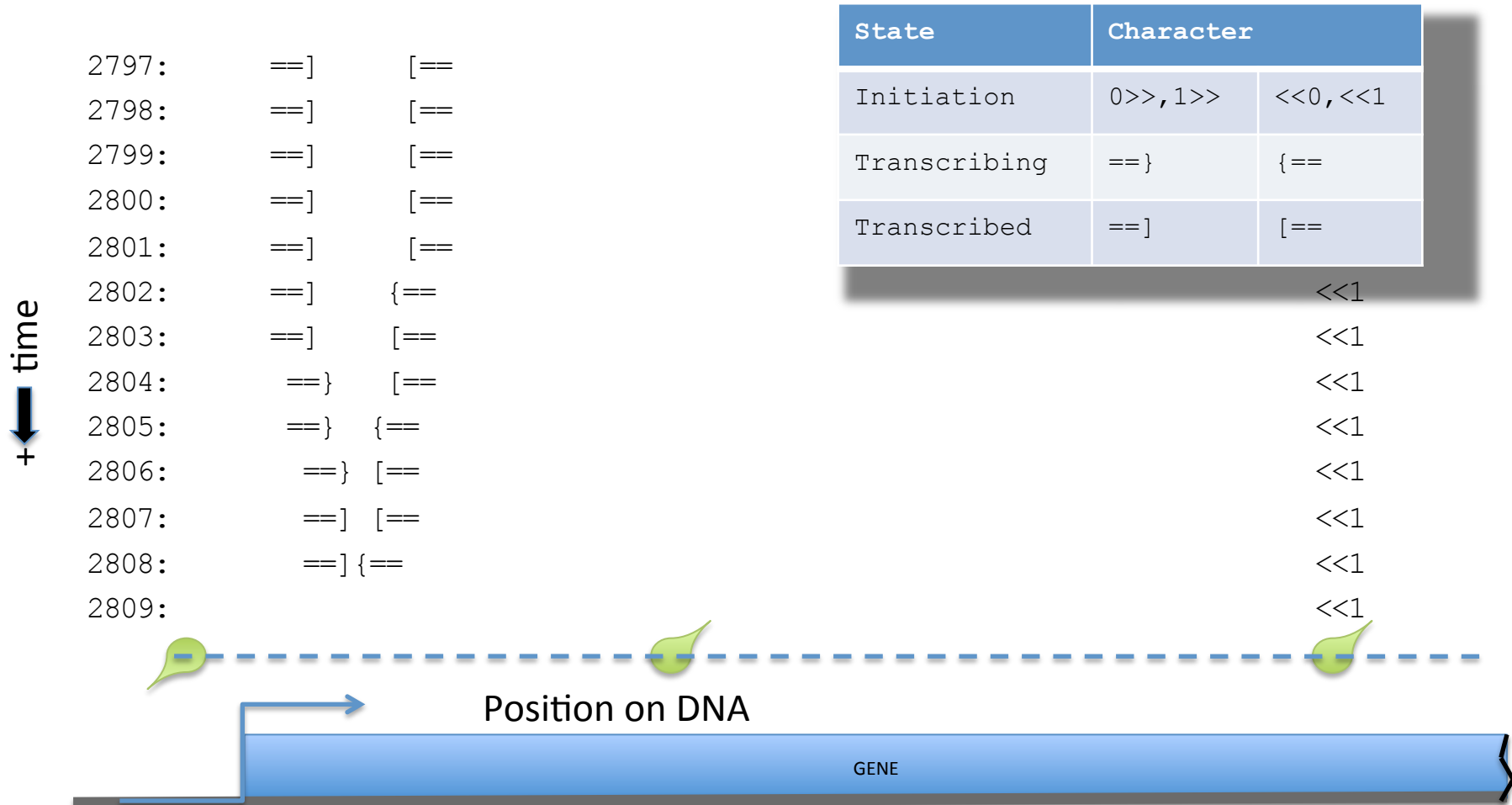
1602: 0>>
1603: 0>>
1604: 1>>
1605: ==]
1606: ==]
1607: ==]
1608: ==}
1609: ==]
1610: ==]
1611: ==]
1612: ==}
1613: ==}
1614: 0>> ==]
1615: 0>> ==]
    
```

+ time
↓

State	Character
Initiation	0>>, 1>>
Transcribing	==}
Transcribed	==]



Visualizing Transcriptional Interference



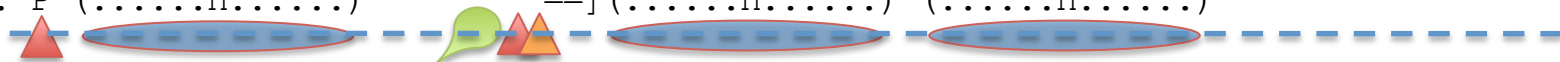
Visualizing Nucleosomes and Transcription Factors

```

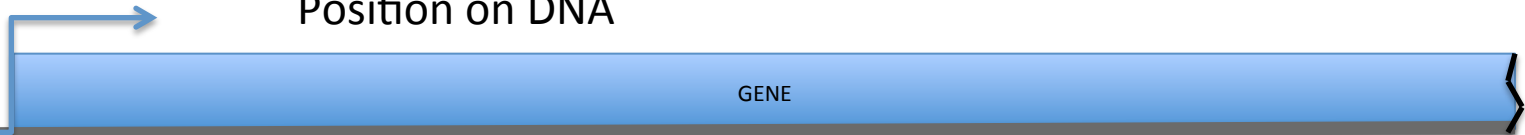
1139:                               .==].  (.....n.....)
1140: P (.....n.....)t'         .==]  (-----b-----)
1141: H (.....n.....)t'         . ==}  (-----b-----)
1142: O (-----b-----)t'       . ==]  (-----b-----)
1143: 2 (-----b-----)t'       . ==]  (-----b-----)
1144: (.....n.....)t'           . ==}  (.....n.....)
1145: (____u____)t'              . .==]  (.....n.....)
1146: P      (-----b-----) . ==]  (.....n.....)
1147:      O' (.....n.....)      ==}  (-----b-----)
1148: O      T' (.....n.....) . P ==}  (-----b-----)
1149: 2      (.....n.....)      . ==]  (.....n.....)
1150:      (-----b-----)      . ==]  (-----b-----)
1151: (-----b-----)          ..==]  (.....n.....)
1152: (.....n.....)            HP==]  (.....n.....)
1153: H (.....n.....)          . A ==]  (.....n.....)
1154: O (.....n.....)t'        ==]  (.....n.....)
1155: (____u____)t'            ==]  (____u____)  (.....n.....)
1156: (-----b-----)t'      .==]  (-----b-----)  (.....n.....)
1157: . (-----b-----)      ==]  (.....n.....)  (.....n.....)
1158: P (.....n.....)        ==]  (.....n.....)  (.....n.....)
  
```

State	Character	
Initiation	0>>,1>>	<<0,<<1
Transcribing	==}	{==
Transcribed	==]	[==
Stable Nucleosome	(...n...)	
Binding Nucleosome	(---b---	
Unbinding Nucleosome	(____u____)	

+ time
↓



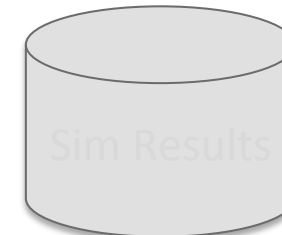
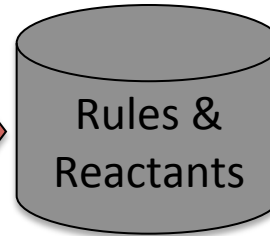
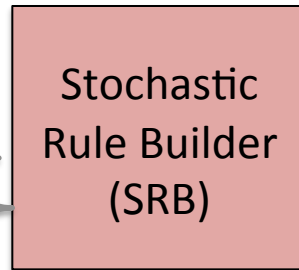
Position on DNA



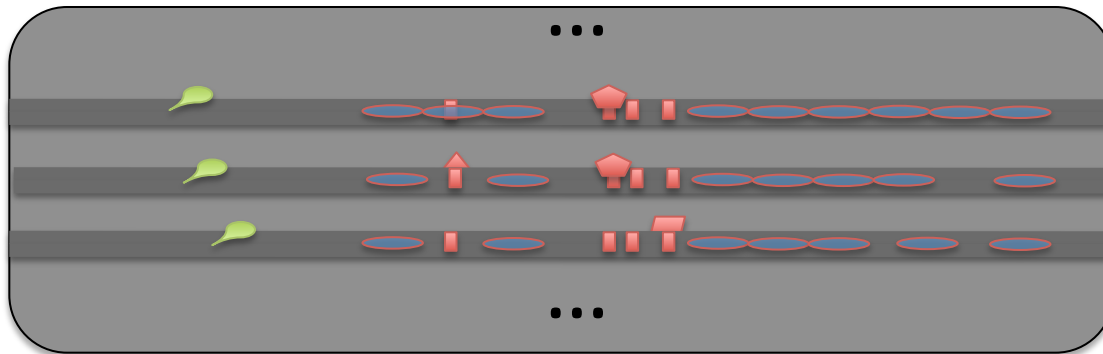
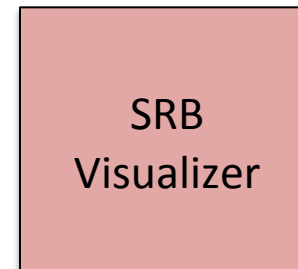
Summary

- State Diagrams
- DNA sequence
- TF Motif, Strength
- Nucleosome Prob.
- Transcriptional Machinery Rates initiation, elongation, termination
- Component Concentrations

- New Data
- Updated Data

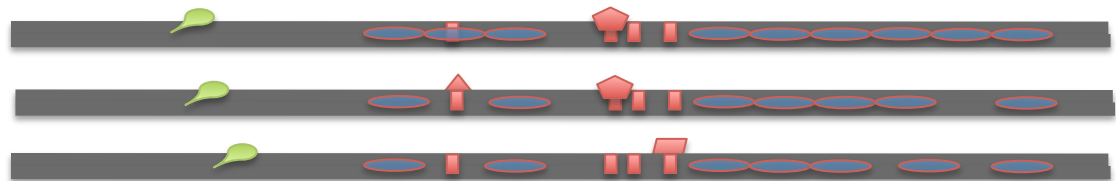


Reactant counts at each iteration

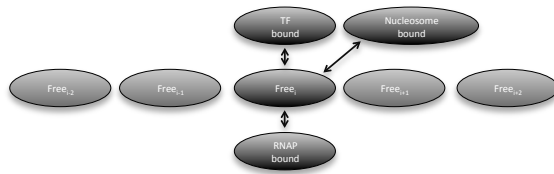


Future Work

- Parameter Search
- More Detailed Components and Complex Interactions
- Parallelize / Distributed
- Visualization via Animation



Acknowledgements



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