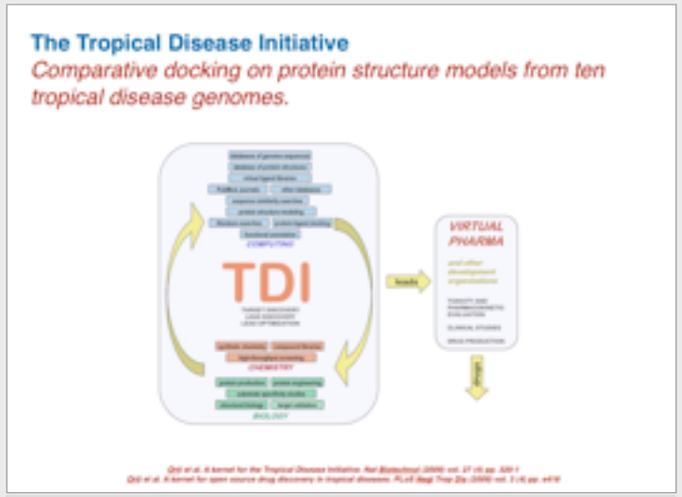
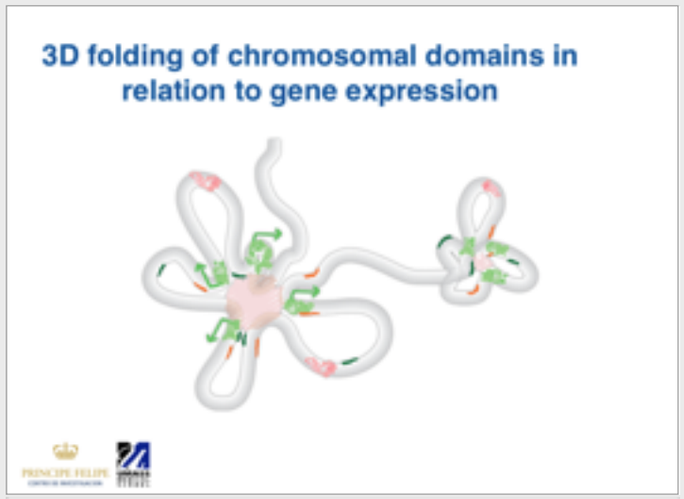
Towards a third dimension in cell regulation:
ligands, (RNA) and genomes





Stefania Bosi

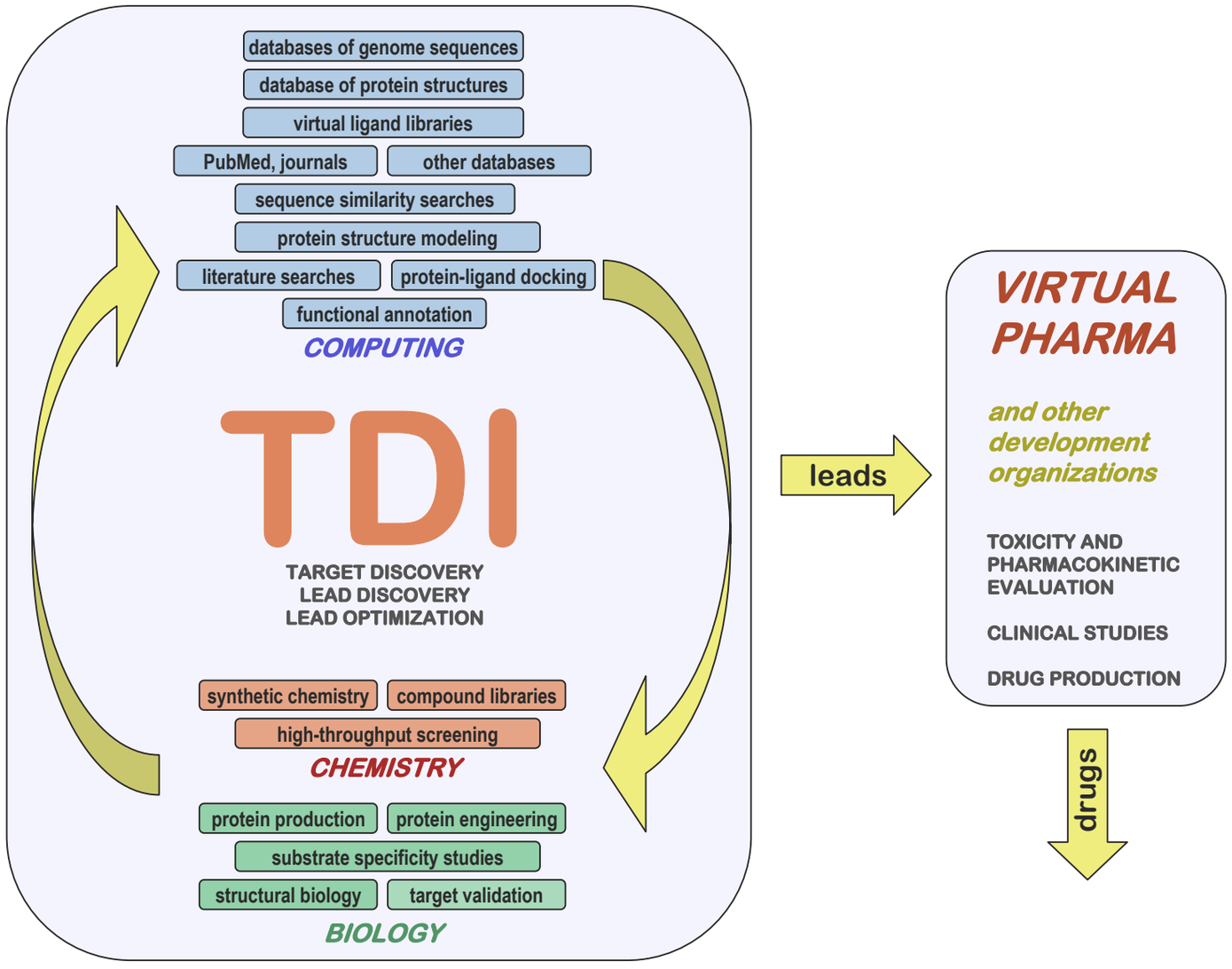
Dr. Davide Baù

Marc A. Marti-Renom
http://sgu.bioinfo.cipf.es

Structural Genomics Unit
Bioinformatics & Genomics Department
Prince Felipe Research Center (CIPF), Valencia, Spain

The Tropical Disease Initiative

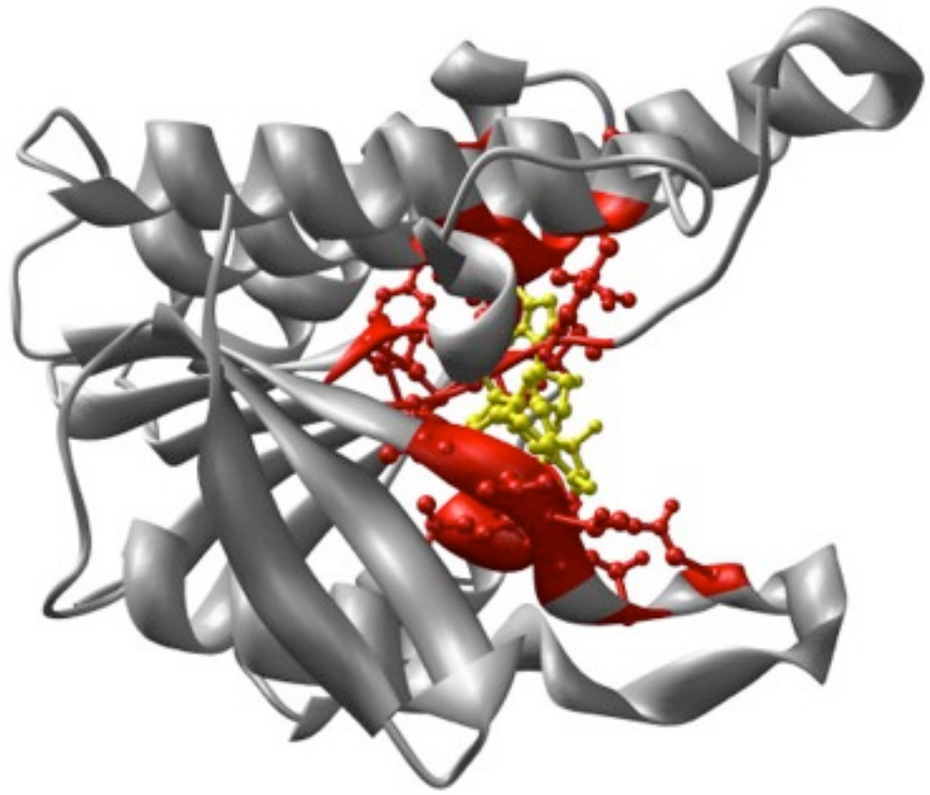
Comparative docking on protein structure models from ten tropical disease genomes.



Ortí et al. A kernel for the Tropical Disease Initiative. Nat Biotechnol (2009) vol. 27 (4) pp. 320-1
Ortí et al. A kernel for open source drug discovery in tropical diseases. PLoS Negl Trop Dis (2009) vol. 3 (4) pp. e418

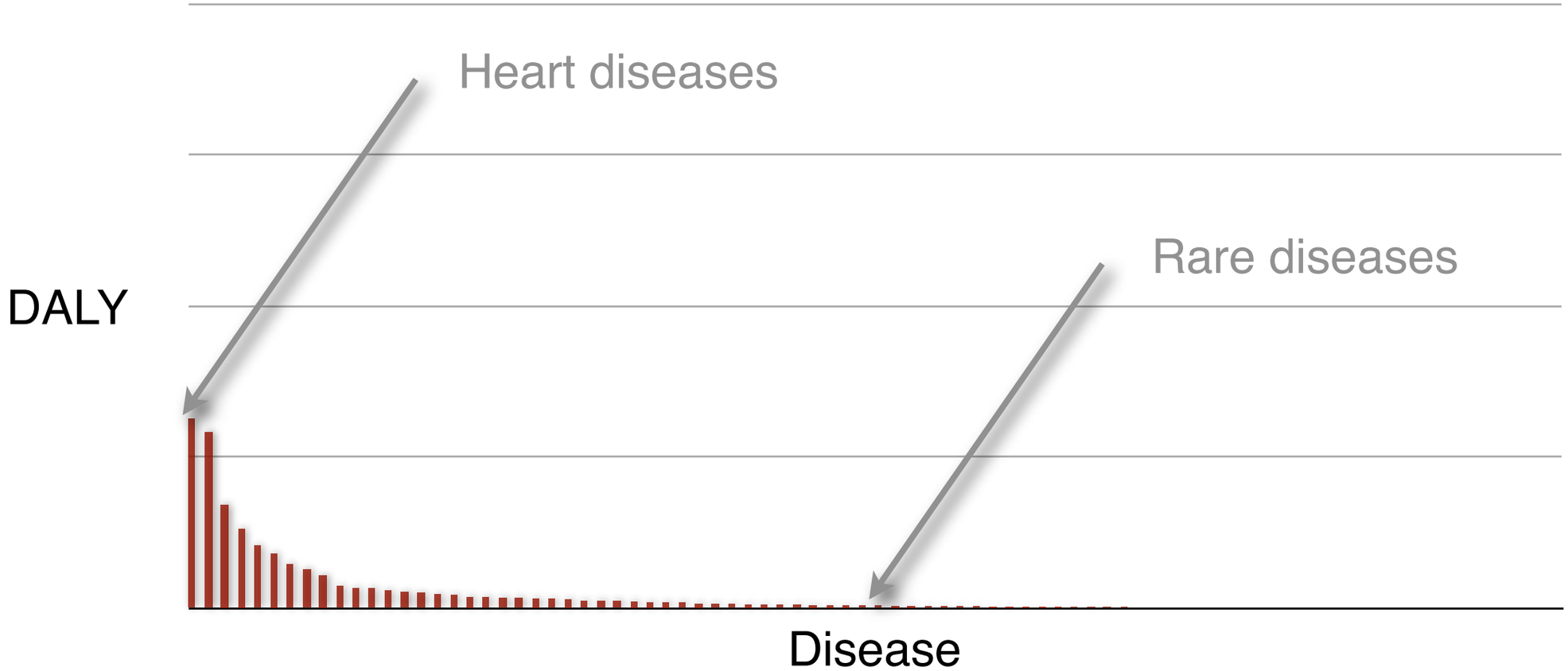
Aim

Identify target-drug pairs for open source drug discovery in tropical diseases.



Need is High in the Tail

- DALY Burden Per Disease in Developed Countries
- DALY Burden Per Disease in Developing Countries



Disease data taken from WHO, *World Health Report 2004*

DALY - Disability adjusted life years

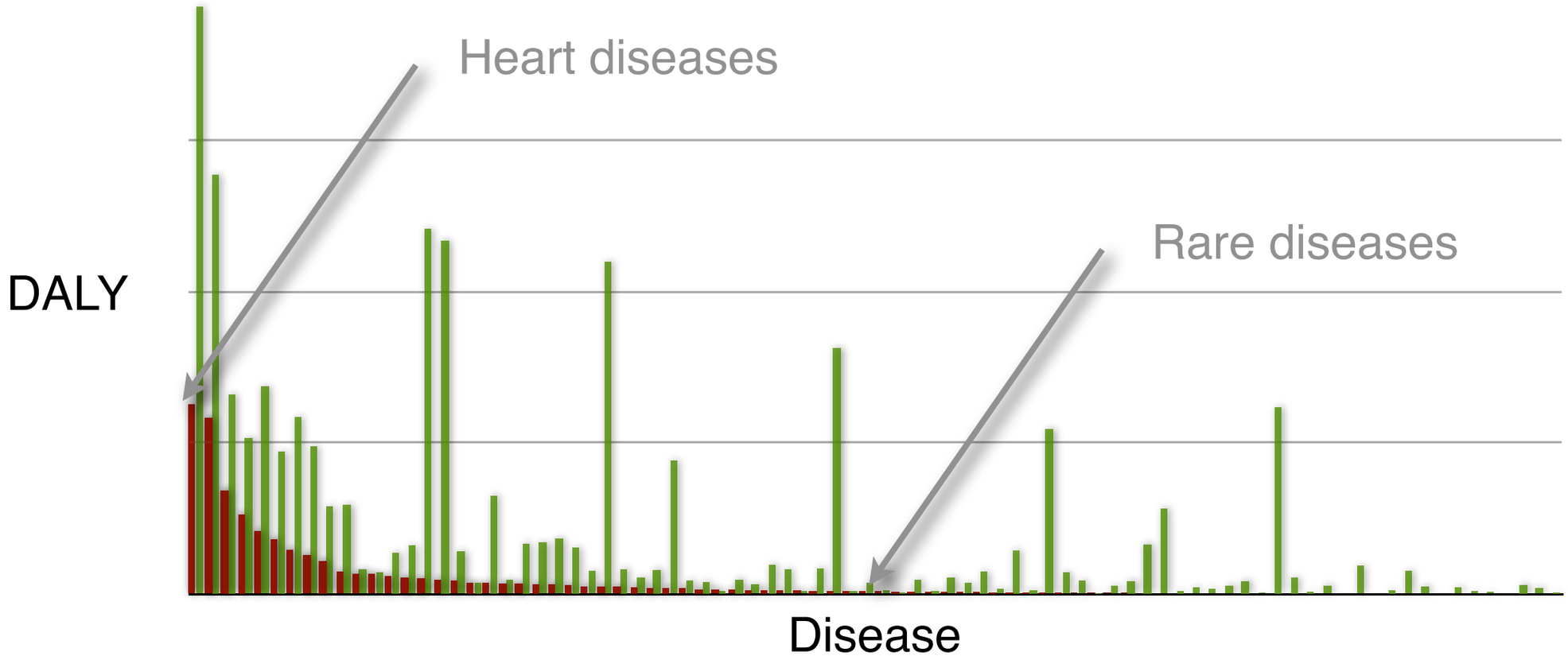
DALY is not a perfect measure of market size, but is certainly a good measure for importance.

DALYs for a disease are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition. The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of 'healthy' life lost in states of less than full health, broadly termed disability. One DALY represents the loss of one year of equivalent full health.

Need is High in the Tail

DALY Burden Per Disease in Developed Countries

DALY Burden Per Disease in Developing Countries



Disease data taken from WHO, *World Health Report 2004*

DALY - Disability adjusted life years

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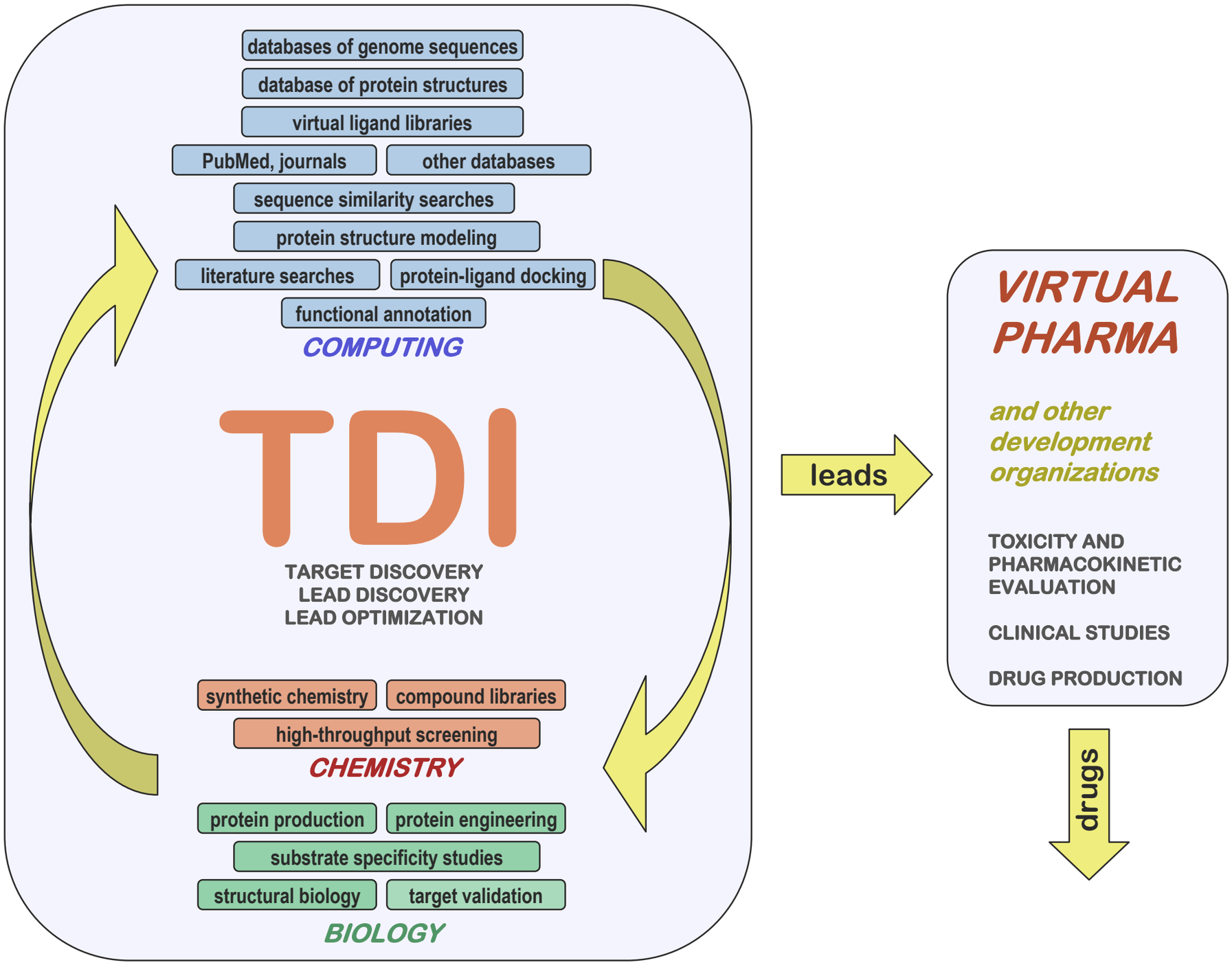
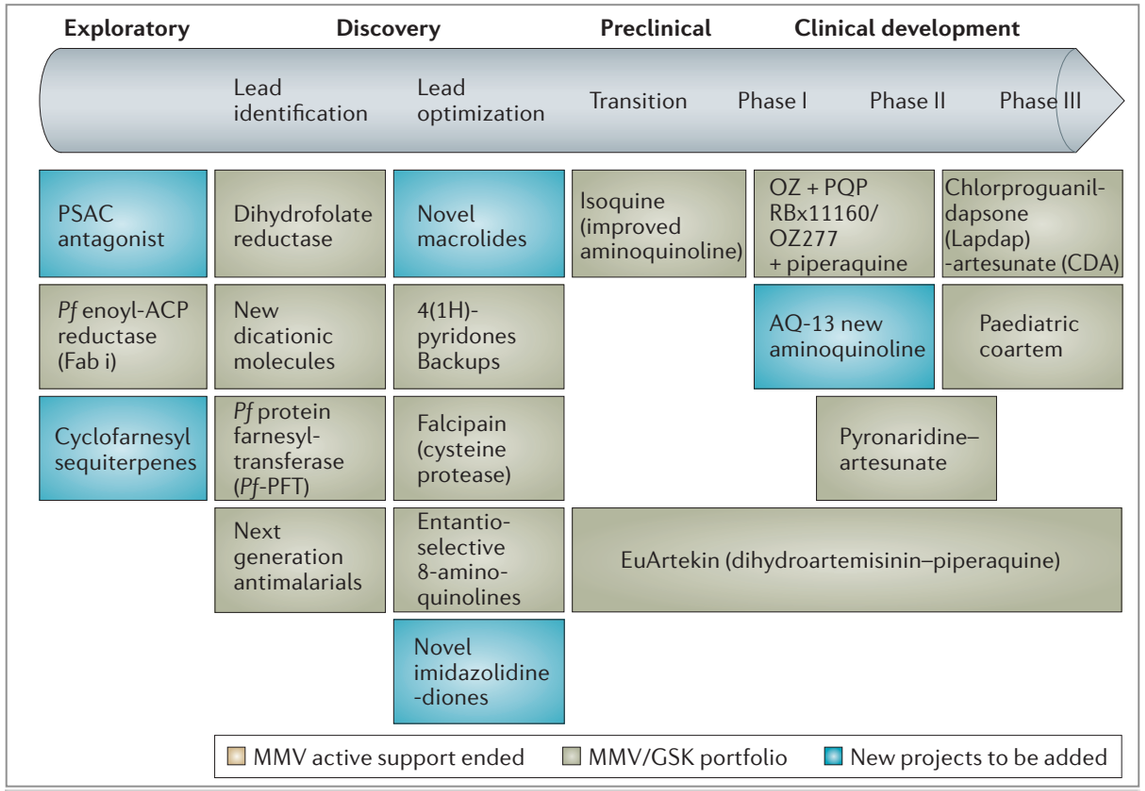
DALYs for a disease are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition. The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of 'healthy' life lost in states of less than full health, broadly termed disability. One DALY represents the loss of one year of equivalent full health.

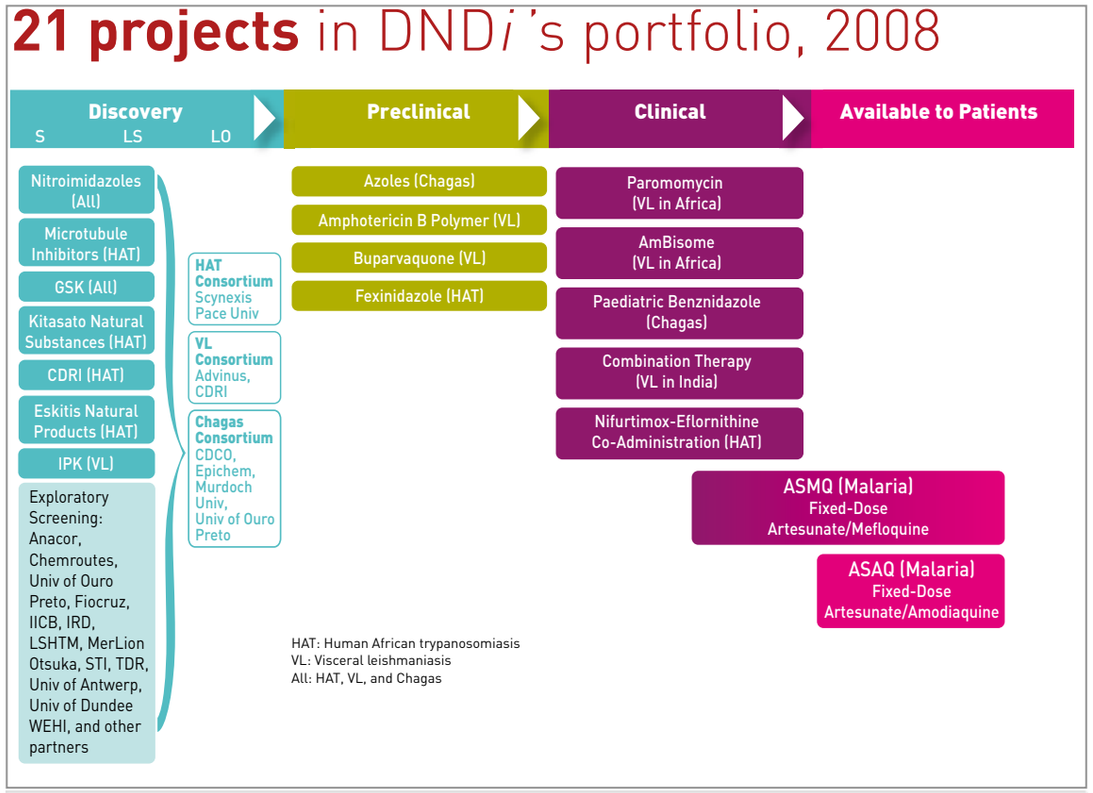
TDI flowchart



Non-Profit organizations

Open-Source + Out-Source = low cost business model





Munos (2006) Nature Reviews. Drug Discovery.

“Unprofitable” Diseases and Global DALY (in 1000’s)

Malaria*	**46,486**
Tetanus	7,074
Lymphatic filariasis*	**5,777**
Syphilis	4,200
Trachoma	2,329
Leishmaniasis*	**2,090**
Ascariasis	1,817
Schistosomiasis*	**1,702**
Trypanosomiasis*	**1,525**

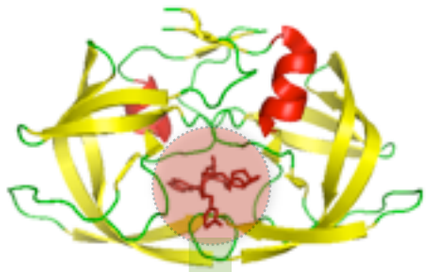
Trichuriasis	1,006
Japanese encephalitis	709
Chagas Disease*	**667**
Dengue*	**616**
Onchocerciasis*	**484**
Leprosy*	**199**
Diphtheria	185
Poliomyelitise	151
Hookworm disease	59

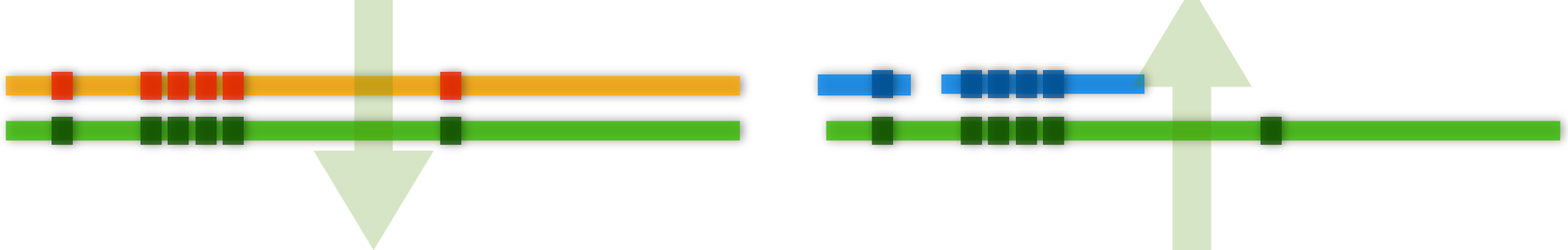
Disease data taken from WHO, *World Health Report 2004*
DALY - Disability adjusted life year in 1000’s.
* Officially listed in the WHO Tropical Disease Research disease portfolio.

Comparative docking

Expansion

co-crystalized protein/ligand

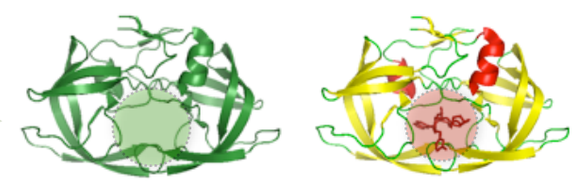




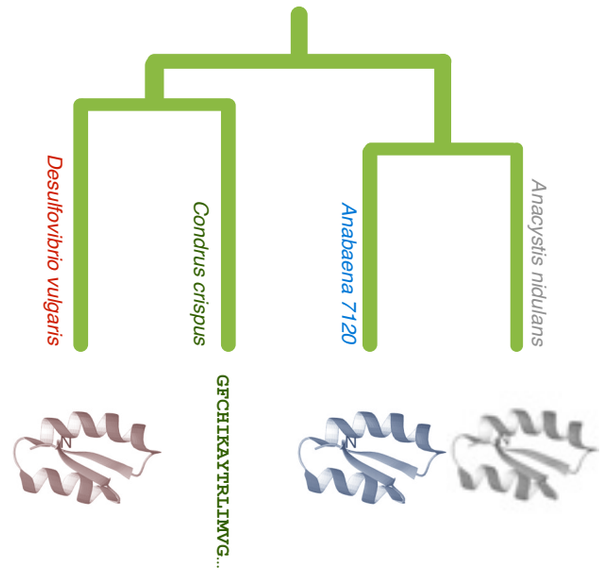
crystalized protein

2. Inheritance

model



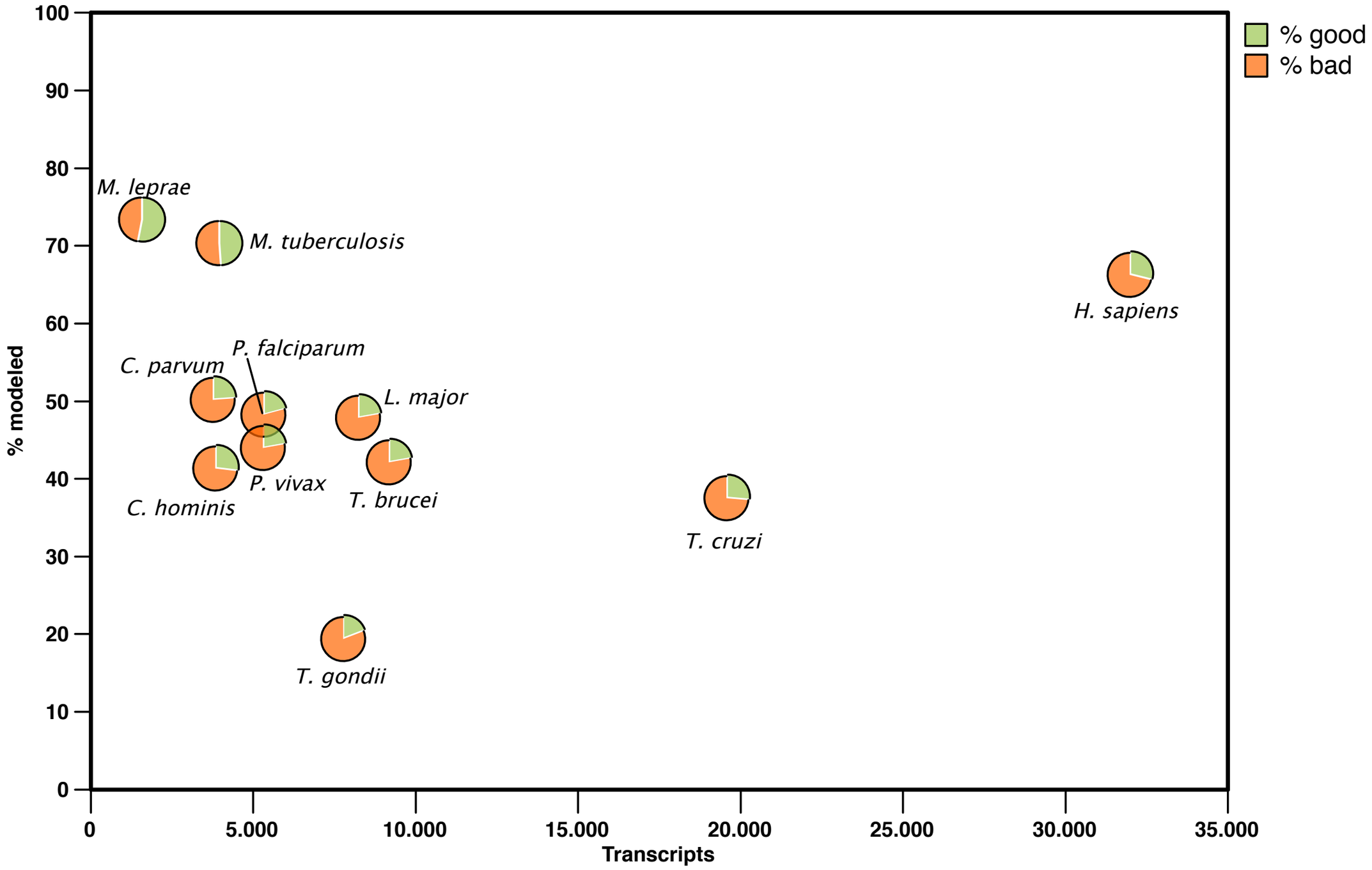
template



1. Modeling

Modeling Genomes

data from models generated by ModPipe (Eswar, Pieper & Sali)



A good model has MPQS of 1.0 or higher

Summary table

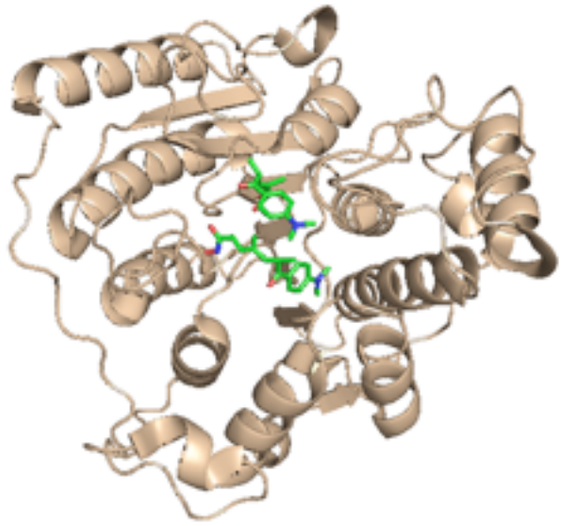
models with inherited ligands

29,271 targets with good models, 297 inherited a ligand/substance similar to a known drug in DrugBank

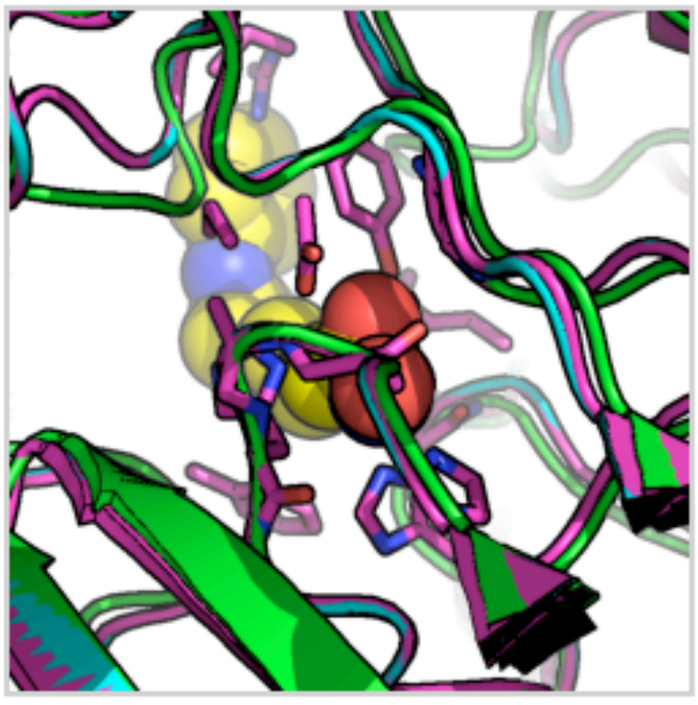
	Transcripts	Modeled targets	Selected models	Inherited ligands	Similar to a drug	Drugs
C. hominis	3,886	1,614	666	197	20	13
C. parvum	3,806	1,918	742	232	24	13
L. major	8,274	3,975	1,409	478	43	20
M. leprae	1,605	1,178	893	310	25	6
M. tuberculosis	3,991	2,808	1,608	365	30	10
P. falciparum	5,363	2,599	818	284	28	13
P. vivax	5,342	2,359	822	268	24	13
T. brucei	7,793	1,530	300	138	13	6
T. cruzi	19,607	7,390	3,070	769	51	28
T. gondii	9,210	3,900	1,386	458	39	21
TOTAL	**68,877**	**29,271**	**11,714**	**3,499**	**297**	**143**

L. major Histone deacetylase 2 + Vorinostat

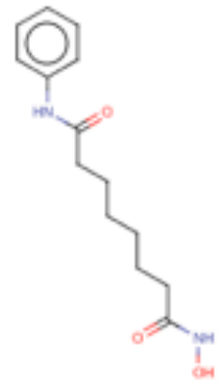
Template 1t64A a human HDAC8 protein.



PDB		Template		Model		Ligand	Exact	SupStr	SubStr	Similar
1c3sA	83.33/80.00	1t64A	36.00/1.47	LmjF21.0680.1.pdb	90.91/100.00	SHH	DB02546	DB02546	DB02546	DB02546



DB02546 Vorinostat



Small Molecule; Approved; Investigational

Drug categories:

Anti-Inflammatory Agents, Non-Steroidal
Anticarcinogenic Agents
Antineoplastic Agents
Enzyme Inhibitors

Drug indication:

For the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

L. major Histone deacetylase 2 + Vorinostat

Literature

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 13143–13147, November 1996
Medical Sciences

Apicidin: A novel antiprotozoal agent that inhibits parasite histone deacetylase

(cyclic tetrapeptide/Apicomplexa/antiparasitic/malaria/coccidiosis)

SANDRA J. DARKIN-RATTRAY*†, ANNE M. GURNETT*, ROBERT W. MYERS*, PAULA M. DULSKI*, TAMI M. CRUMLEY*, JOHN J. ALLOCCO*, CHRISTINE CANNOVA*, PETER T. MEINKE‡, STEVEN L. COLLETTI‡, MARIA A. BEDNAREK‡, SHEO B. SINGH§, MICHAEL A. GOETZ§, ANNE W. DOMBROWSKI§, JON D. POLISHOOK§, AND DENNIS M. SCHMATZ*

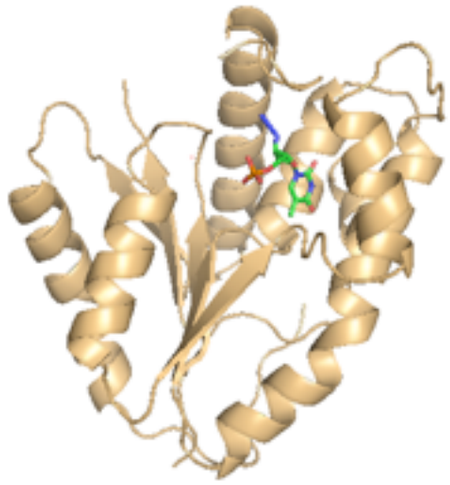
Departments of *Parasite Biochemistry and Cell Biology, ‡Medicinal Chemistry, and §Natural Products Drug Discovery, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2004, p. 1435–1436 Vol. 48, No. 4
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.4.1435–1436.2004

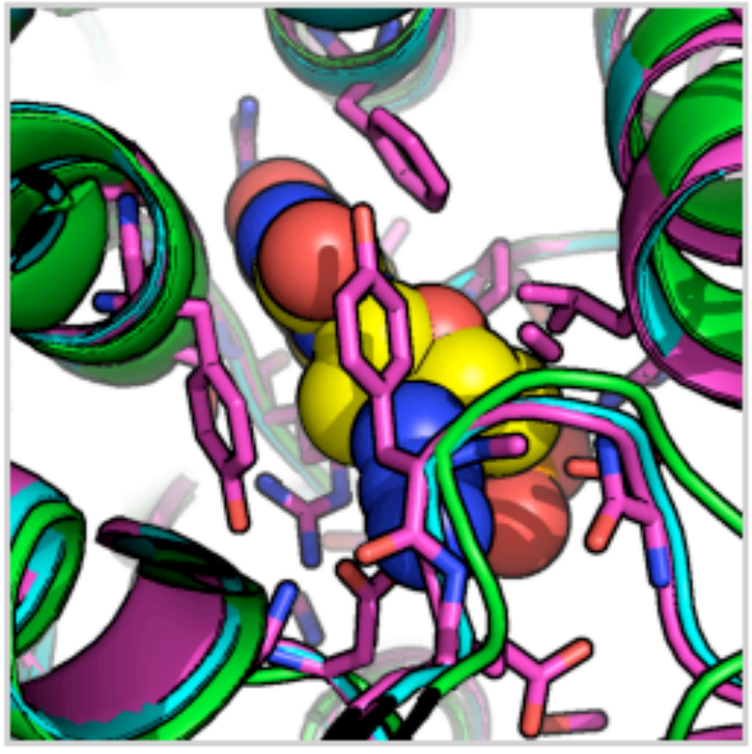
Antimalarial and Antileishmanial Activities of Aroyl-Pyrrolyl-Hydroxyamides, a New Class of Histone Deacetylase Inhibitors

P. falciparum tymidylate kinase + zidovudine

Template 3tmkA a yeast tymidylate kinase.



PDB		Template		Model		Ligand	Exact	SupStr	SubStr	Similar
2tmkB	100.00/100.00	3tmkA	41.00/1.49	PFL2465c.2.pdb	82.61/100.00	ATM		DB00495		DB00495

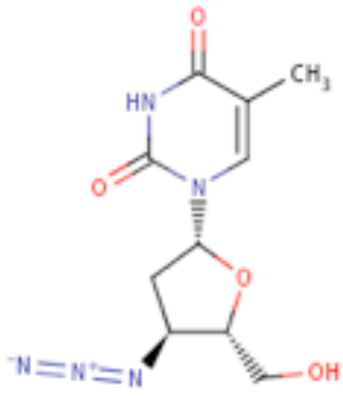


DB00495 Zidovudine

Small Molecule; Approved

Drug categories:

Anti-HIV Agents
Antimetabolites
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

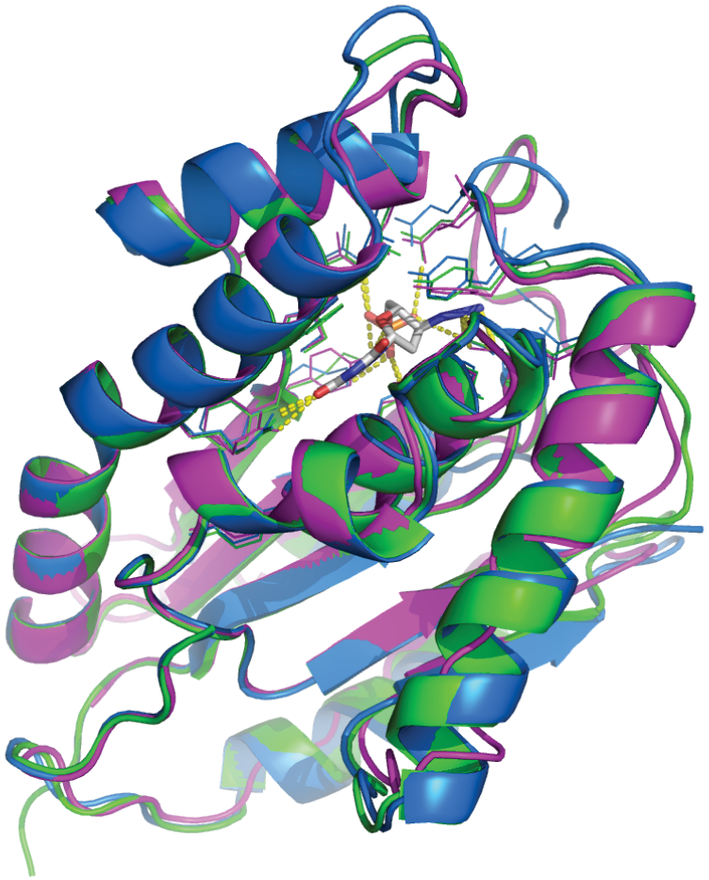


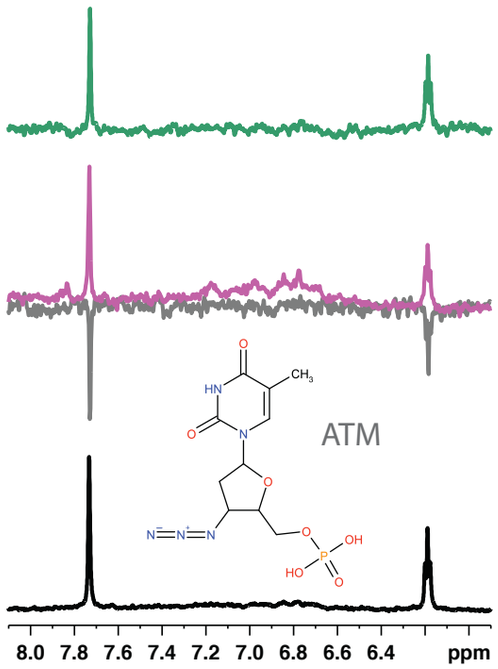
Drug indication:

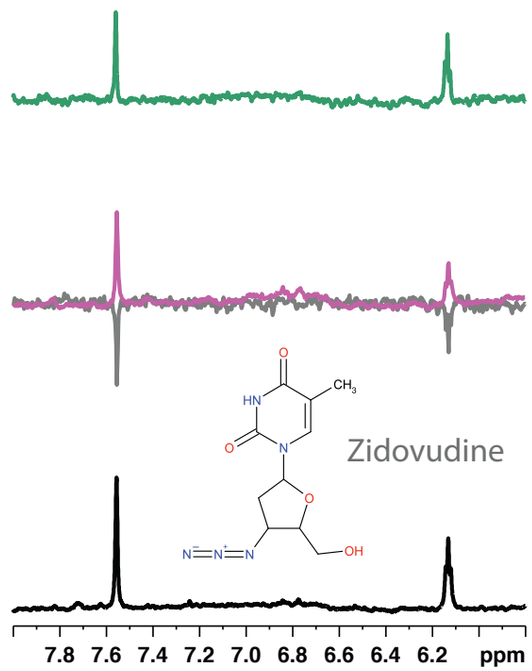
For the treatment of human immunovirus (HIV) infections.

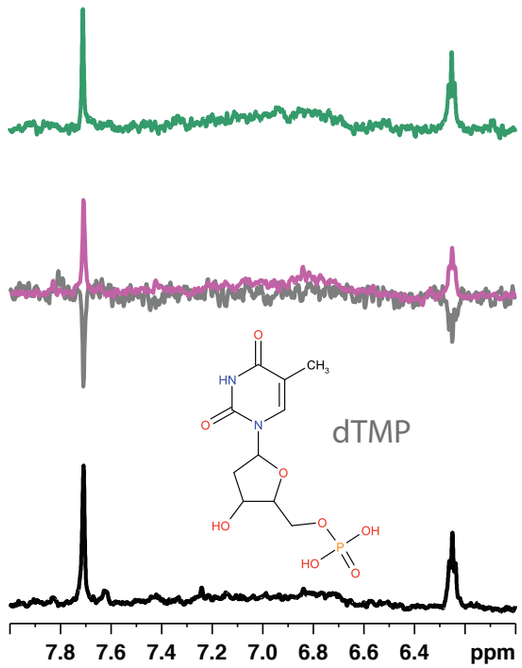
P. falciparum thymidylate kinase + zidovudine

NMR Water-LOGSY and STD experiments





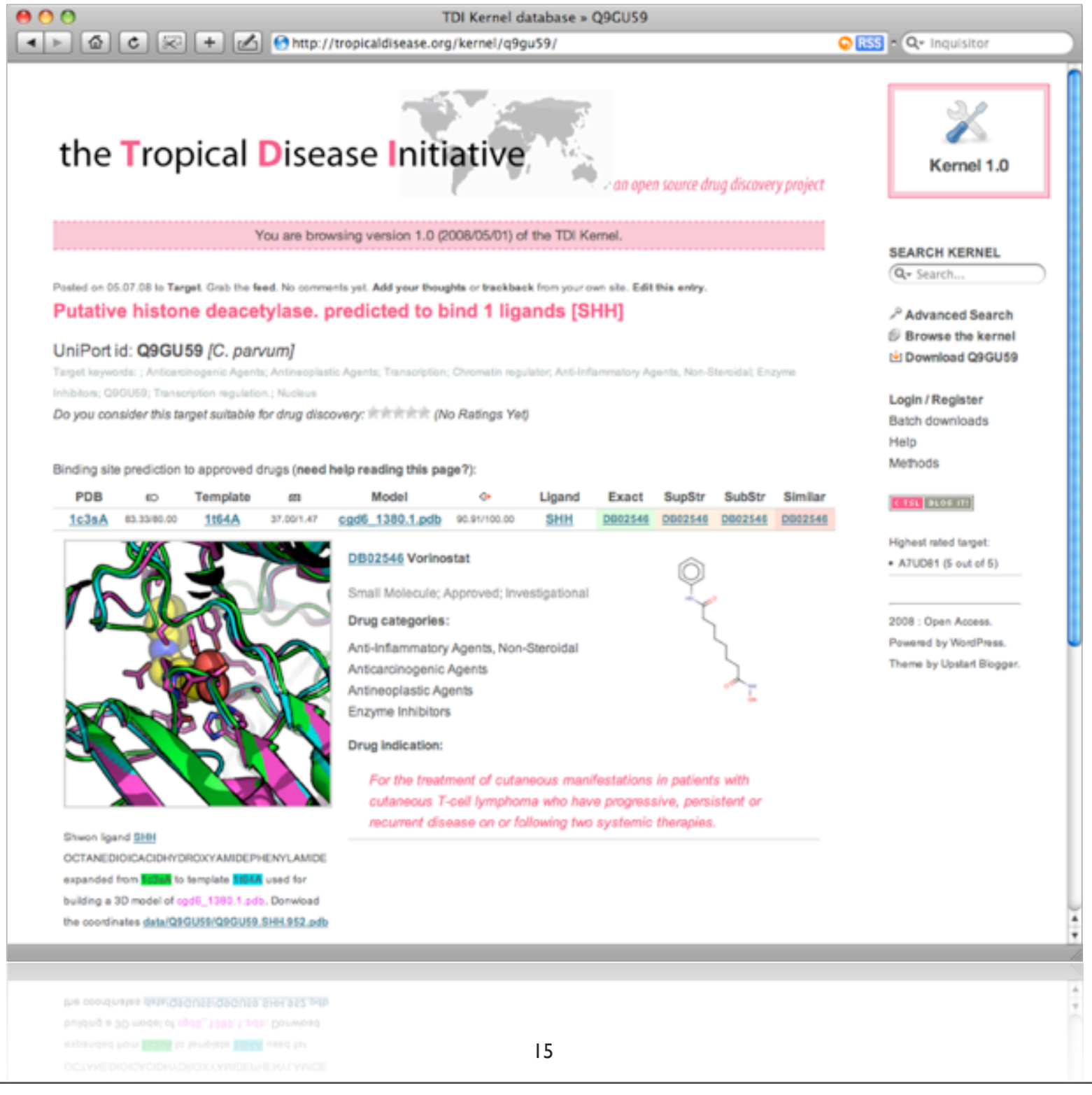




Leticia Ortí, Rodrigo J. Carbajo, and Antonio Pineda-Lucena

TDI's kernel

http://tropicaldisease.org/kernel



TDI's kernel

http://tropicaldisease.org/kernel

L. Orti *et al.*, *Nat Biotechnol* **27**, 320 (2009).

L. Orti *et al.*, *PLoS Negl Trop Dis* **3**, e418 (2009).

CORRESPONDENCE

A kernel for the Tropical Disease Initiative

To the Editor:

Identifying proteins that are good drug targets and finding drug leads that bind to them is generally a challenging problem. It is particularly difficult for neglected tropical diseases, such as malaria and tuberculosis, where research resources are relatively scarce[1]. Fortunately, several developments improve our ability to deal with drug discovery for neglected diseases: first, the sequencing of many complete genomes of organisms that cause tropical diseases; second, the determination of a large number of protein structures; third, the creation of compound libraries, including already-approved drugs; and fourth, the availability of improved bioinformatics analysis, including methods for comparative protein structure modeling, binding site identification, virtual ligand screening and drug design. Therefore, we are now in a position to increase the odds of identifying high-quality drug targets and drug leads for neglected tropical diseases. Here we encourage a collaboration among scientists to engage in drug discovery for tropical diseases by providing a 'kernel' for the Tropical Disease Initiative (TDI, http://www.tropicaldisease.org/)[2]. As the Linux kernel did for open source code development, we suggest that the TDI kernel may help overcome a major stumbling block, in this case, for open source drug discovery: the absence of a critical mass of preexisting work that volunteers can build on incrementally. This kernel complements several other initiatives on neglected tropical diseases[3–5], including collaborative web portals (e.g., http://www.thesynapticleap.org/), public-private partnerships (e.g., http://www.mmv.org/) and private foundations (e.g., http://www.gatesfoundation.org/); for an updated list of initiatives, see the TDI website above.

The TDI kernel was derived with our software pipeline[6,7] for predicting structures of protein sequences by comparative modeling, localizing small-molecule binding sites on the surfaces of the models and predicting ligands that bind to them. Specifically, the pipeline linked 297 proteins from ten pathogen genomes with already approved drugs that were developed for treating other diseases (**Table 1**). Such links, if proven experimentally, may significantly increase the efficiency of target identification, target validation, lead discovery, lead optimization and clinical trials. Two of the kernel targets were tested for their binding to a known drug by NMR spectroscopy, validating one of our predictions (**Fig. 1** and **Supplementary Data** online). It is difficult to assess the accuracy of our computational predictions based on this limited experimental testing. Thus, we encourage other investigators to donate their expertise and facilities to test additional predictions. We hope the testing will occur within the open source context, where results are made available with limited or no restrictions.

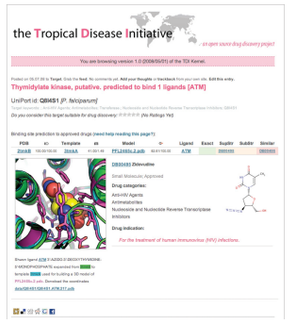


Figure 1 TDI kernel snapshot of the web page for the *Plasmodium falciparum* thymidylate kinase target (http://tropicaldisease.org/kernel/q8i4s1/). Our computational pipeline predicted that thymidylate kinase from *P. falciparum* binds ATM (3′-azido-3′-deoxythymidine-5′-monophosphate), a supra-structure of the zidovudine drug approved for the treatment of HIV infection. The binding of this ligand to a site on the kinase was experimentally validated by one-dimensional Water-LOGSY[9] and saturation transfer difference[10] NMR experiments.

A freely downloadable version of the TDI kernel is available in accordance with the Science Commons protocol for implementing open access data (http://sciencecommons.org/projects/publishing/open-access-data-protocol/), which prescribes standard academic attribution and facilitates tracking of work but imposes no other restrictions. We do not seek intellectual property rights in the actual discoveries based on the TDI kernel, in the hope of reinvigorating drug discovery for neglected tropical diseases[8]. By minimizing restrictions on the data, including viral terms that would be inherited by all derivative works, we hope to attract as many eyeballs as we possibly can to use and improve the kernel. Although many of the drugs in the kernel are proprietary under diverse types of rights, we believe that the existence of public domain pairs of targets and compounds will reduce the royalties that patent owners can charge and sponsors must pay. This should decrease the large sums of money governments and

Table 1 TDI kernel genomes

Organism[a]	Transcripts[b]	Modeled targets[c]	Similar[d]	Exact[e]
Cryptosporidium hominis	3,886	666	20	13
Cryptosporidium parvum	3,806	742	24	13
Leishmania major	8,274	1,409	43	20
Mycobacterium leprae	1,605	893	25	6
Mycobacterium tuberculosis	3,991	1,608	30	10
Plasmodium falciparum	5,363	818	28	13
Plasmodium vivax	5,342	822	24	13
Toxoplasma gondii	7,793	300	13	6
Trypanosoma cruzi	19,607	3,070	51	28
Trypanosoma brucei	9,210	1,386	39	21
Total	68,877	11,714	297	143

[a]Organisms in bold are included in the World Health Organization (Geneva) Tropical Disease portfolio. [b]Number of transcripts in each genome. [c]Number of targets with at least one domain accurately modeled (that is, MODPIPE quality score of at least 1.0). [d]Number of modeled targets with at least one predicted binding site for a molecule with a Tanimoto score[11] of at least 0.9 to a drug in DrugBank[12]. [e]Number of modeled targets with at least one predicted binding site for a molecule in DrugBank.

OPEN ACCESS Freely available online PLoS NEGLECTED TROPICAL DISEASES

A Kernel for Open Source Drug Discovery in Tropical Diseases

Leticia Ortí[1,2], Rodrigo J. Carbajo[2], Ursula Pieper[3], Narayanan Eswar[3¤], Stephen M. Maurer[4], Arti K. Rai[5], Ginger Taylor[6], Matthew H. Todd[7], Antonio Pineda-Lucena[2], Andrej Sali[3]*, Marc A. Marti-Renom[1]*

1 Structural Genomics Unit, Bioinformatics and Genomics Department, Centro de Investigación Príncipe Felipe, Valencia, Spain, **2** Structural Biology Laboratory, Medicinal Chemistry Department, Centro de Investigación Príncipe Felipe, Valencia, Spain, **3** Department of Bioengineering and Therapeutic Sciences, Department of Pharmaceutical Chemistry, and California Institute for Quantitative Biosciences, University of California San Francisco, San Francisco, California, United States of America, **4** Gould School of Law, University of Southern California, Los Angeles, California, United States of America, **5** School of Law, Duke University, Durham, North Carolina, United States of America, **6** The Synaptic Leap, San Ramon, California, United States of America, **7** School of Chemistry, University of Sydney, Sydney, New South Wales, Australia

Abstract

Background: Conventional patent-based drug development incentives work badly for the developing world, where commercial markets are usually small to non-existent. For this reason, the past decade has seen extensive experimentation with alternative R&D institutions ranging from private–public partnerships to development prizes. Despite extensive discussion, however, one of the most promising avenues—open source drug discovery—has remained elusive. We argue that the stumbling block has been the absence of a critical mass of preexisting work that volunteers can improve through a series of granular contributions. Historically, open source software collaborations have almost never succeeded without such "kernels".

Methodology/Principal Findings: Here, we use a computational pipeline for: (i) comparative structure modeling of target proteins, (ii) predicting the localization of ligand binding sites on their surfaces, and (iii) assessing the similarity of the predicted ligands to known drugs. Our kernel currently contains 143 and 297 protein targets from ten pathogen genomes that are predicted to bind a known drug or a molecule similar to a known drug, respectively. The kernel provides a source of potential drug targets and drug candidates around which an online open source community can nucleate. Using NMR spectroscopy, we have experimentally tested our predictions for two of these targets, confirming one and invalidating the other.

Conclusions/Significance: The TDI kernel, which is being offered under the Creative Commons attribution share-alike license for free and unrestricted use, can be accessed on the World Wide Web at http://www.tropicaldisease.org. We hope that the kernel will facilitate collaborative efforts towards the discovery of new drugs against parasites that cause tropical diseases.

Citation: Ortí L, Carbajo RJ, Pieper U, Eswar N, Maurer SM, et al. (2009) A Kernel for Open Source Drug Discovery in Tropical Diseases. PLoS Negl Trop Dis 3(4): e418. doi:10.1371/journal.pntd.0000418

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Competing Interests: The authors have declared that no competing interests exist.

* E-mail: sali@salilab.org (AS); mmarti@cipf.es (MAM-R)

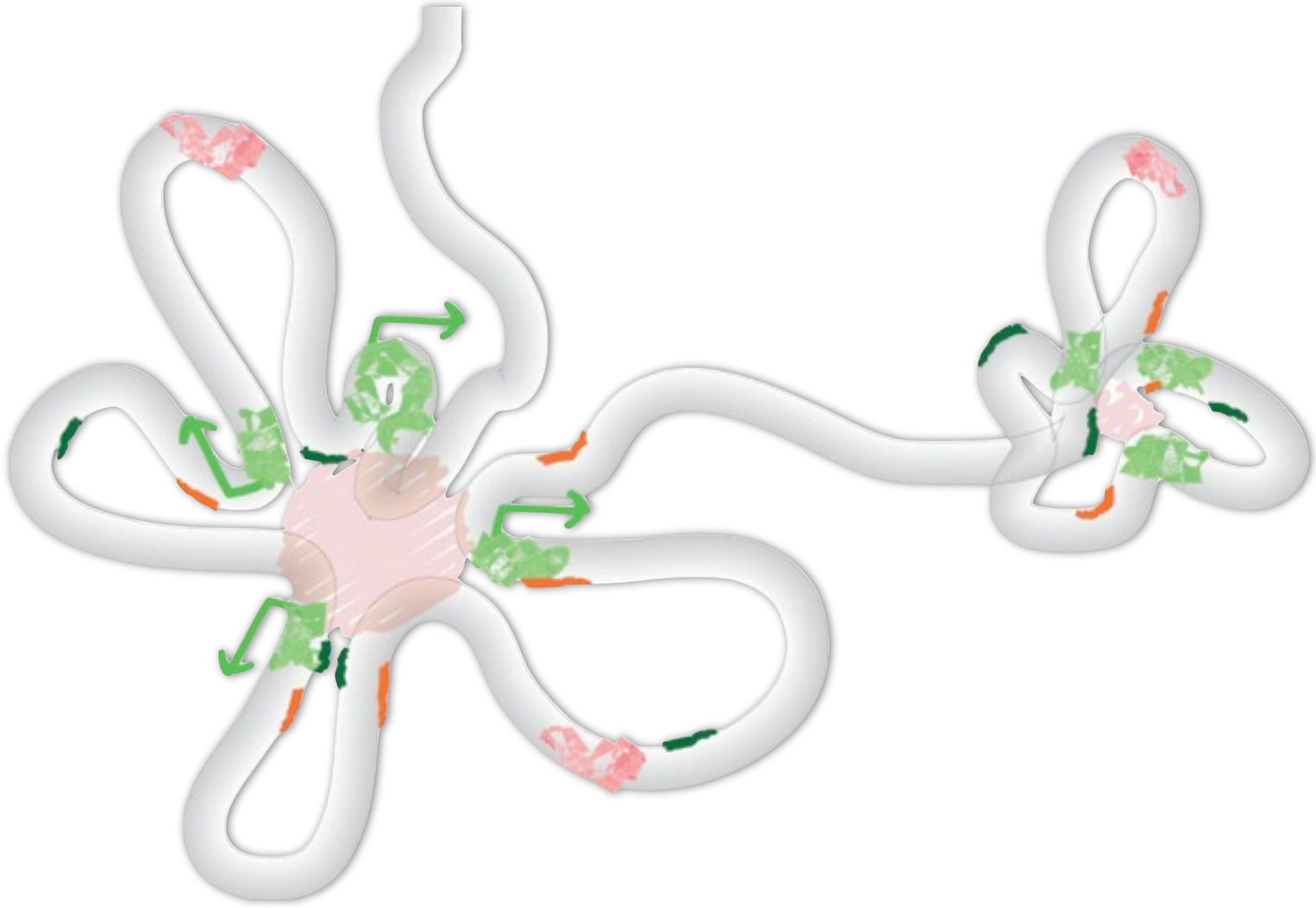
¤ Current address: DuPont Knowledge Center, Hyderabad, India

Introduction

There is a lack of high-quality protein drug targets and drug leads for neglected diseases [1,2]. Fortunately, many genomes of organisms that cause tropical diseases have already been sequenced and published. Therefore, we are now in a position to leverage this information by identifying potential protein targets for drug discovery. Atomic-resolution structures can facilitate this task. In the absence of an experimentally determined structure, comparative modeling can provide useful models for sequences that are detectably related to known protein structures [3,4]. Approximately half of known protein sequences contain domains that can be currently predicted by comparative modeling [5,6]. This coverage will increase as the number of experimentally determined structures grows and modeling software improves. A protein model can facilitate at least four important tasks in the early stages of drug discovery [7]: prioritizing protein targets for drug discovery [8], identifying binding sites for small molecules [9,10], suggesting drug leads [11,12], and optimizing these leads [13–15].

Here, we address the first three tasks by assembling our computer programs into a software pipeline that automatically and on large-scale predicts protein structures, their ligand binding sites, and known drugs that interact with them. As a proof of principle, we applied the pipeline to the genomes of ten organisms that cause tropical diseases ("target genomes"). We also experimentally tested two predicted drug-target interactions using Nuclear Magnetic

3D folding of chromosomal domains in relation to gene expression



PRINCIPE FELIPE
CENTRO DE INVESTIGACION





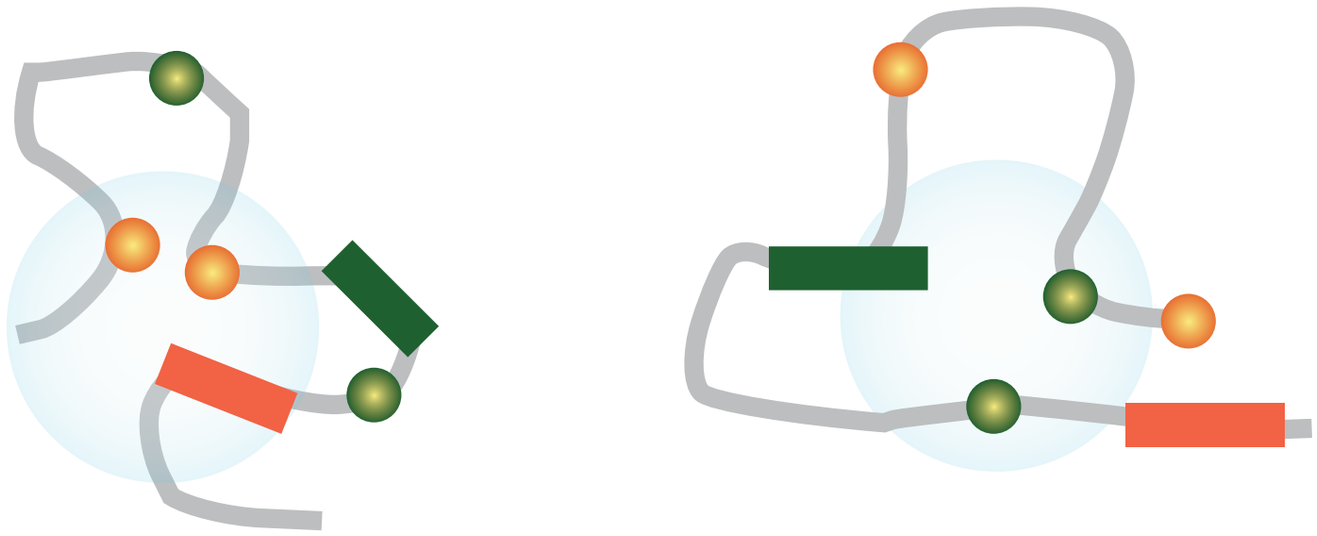

UMASS MEDICAL SCHOOL

Aim

Can we relate structure and expression?

Simple genomes

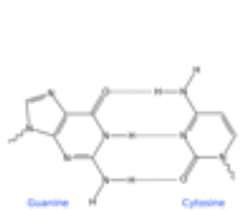
Complex genomes

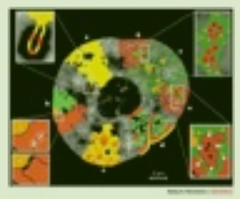


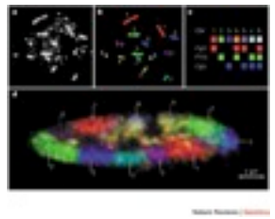
Resolution

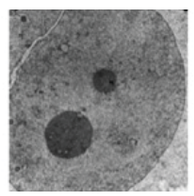
Limited knowledge...

Knowledge









DNA length

10^0 10^3 10^6 10^9 nt

Volume

10^{-9} 10^{-6} 10^{-3} 10^0 10^3 μm^3

Time

10^{-10} 10^{-8} 10^{-6} 10^{-4} 10^{-2} 10^0 10^2 10^3 s

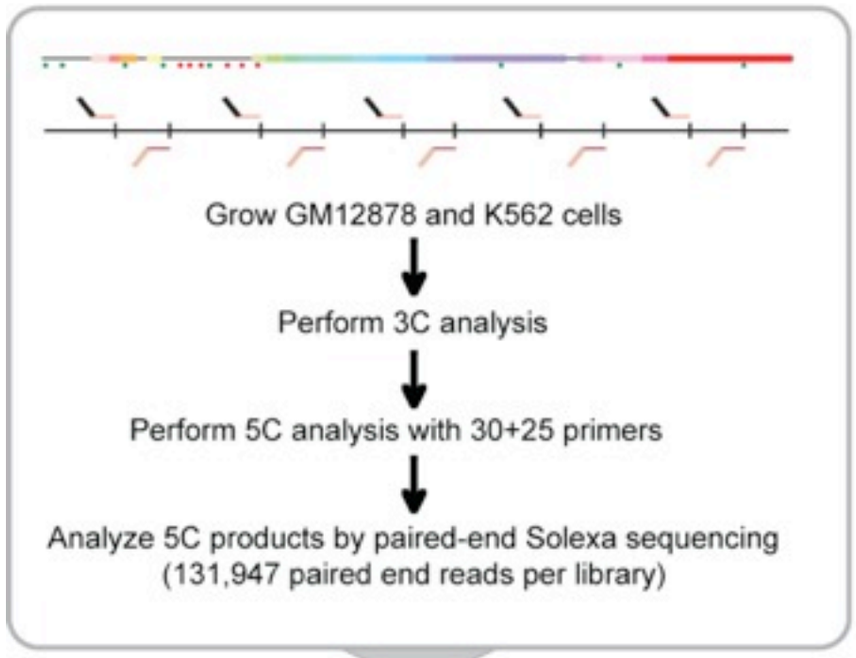
Resolution

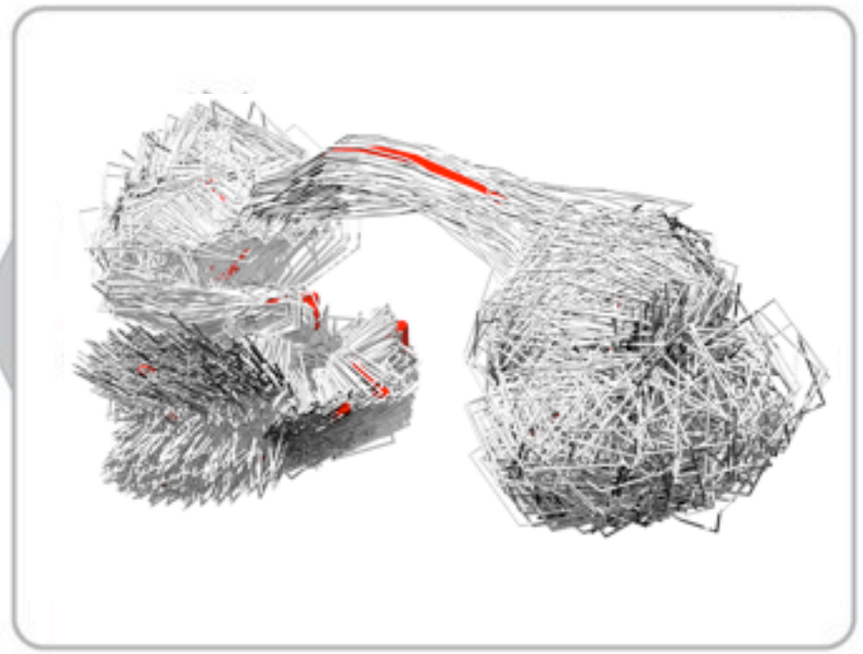
10^{-3} 10^{-2} 10^{-1} µ

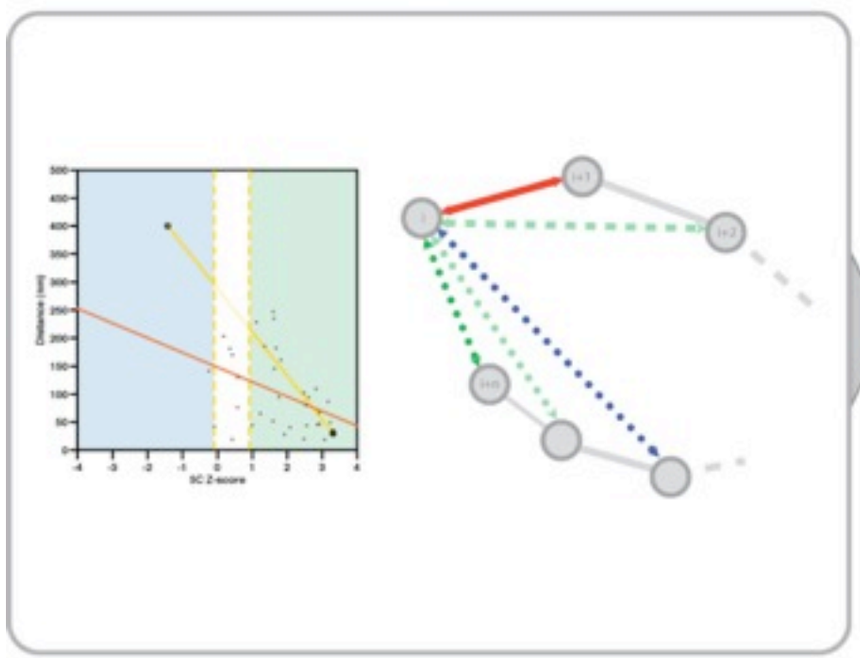
Adapted from:
Langowski and Heermann. Semin Cell Dev Biol (2007) vol. 18 (5) pp. 659-67

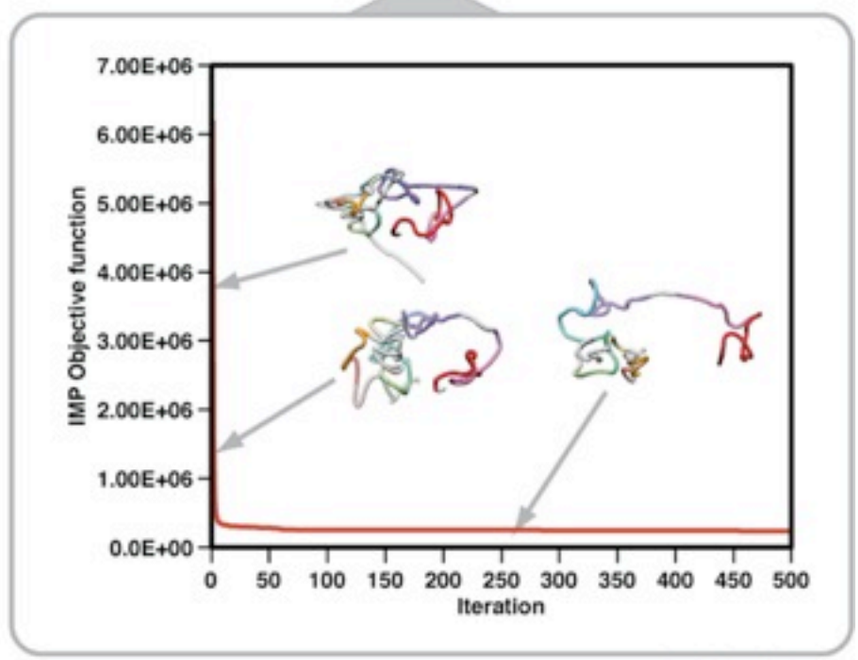
Integrative and iterative approach

Experiments









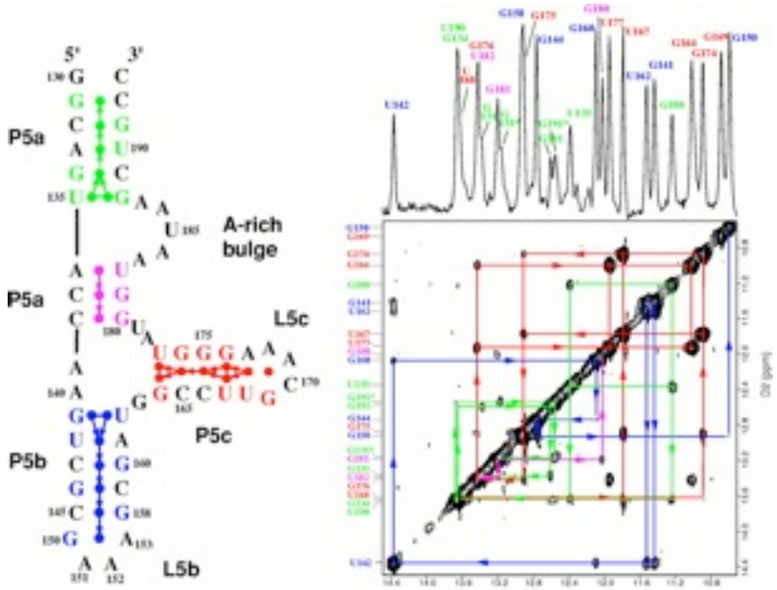
Computation

Structure determination

Integrative Modeling Platform

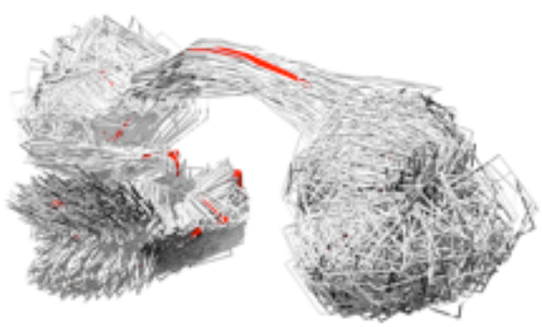
http://www.integrativemodeling.org

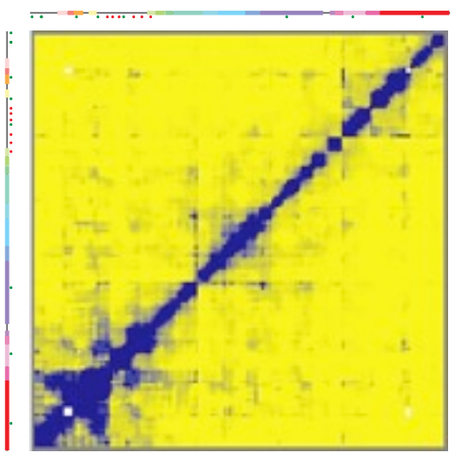
Alber et al. Nature (2007) vol. 450 (7170) pp. 683-94



Biomolecular structure determination

2D-NOESY data





Chromosome structure determination

5C data

Human α-globin domain

ENm008 genomic structure and environment

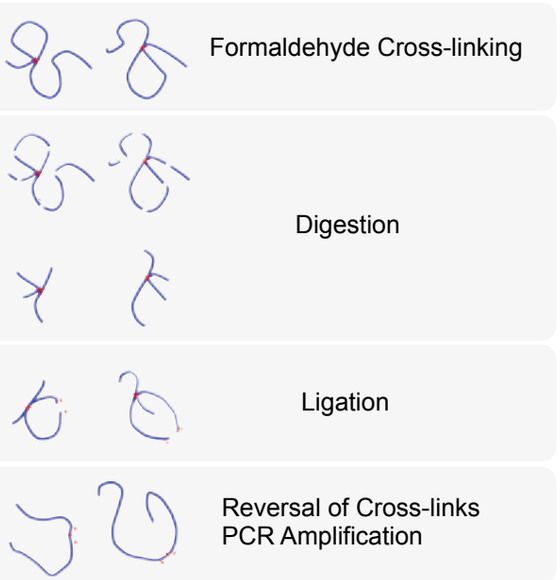
ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816

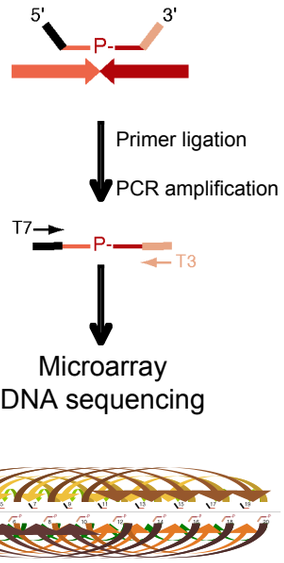
The ENCODE data for ENm008 region was obtained from the UCSC Genome Browser tracks for: RefSeq annotated genes, Affymetrix/CSHL expression data (Gingeras Group at Cold Spring Harbor), Duke/NHGRI DNaseI Hypersensitivity data (Crawford Group at Duke University), and Histone Modifications by Broad Institute ChIP-seq (Bernstein Group at Broad Institute of Harvard and MIT).

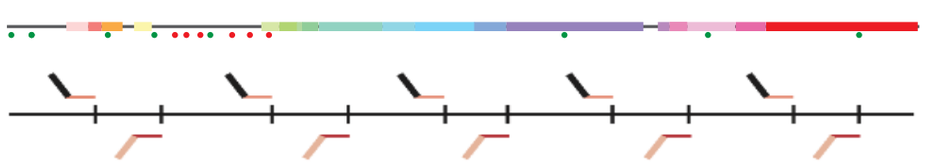
5C experiments

http://my5C.umassmed.edu

B. R. Lajoie, N. L. van Berkum, A. Sanyal et al., Nat Methods 6 (10), 690 (2009).







Grow GM12878 and K562 cells

↓

Perform 3C analysis

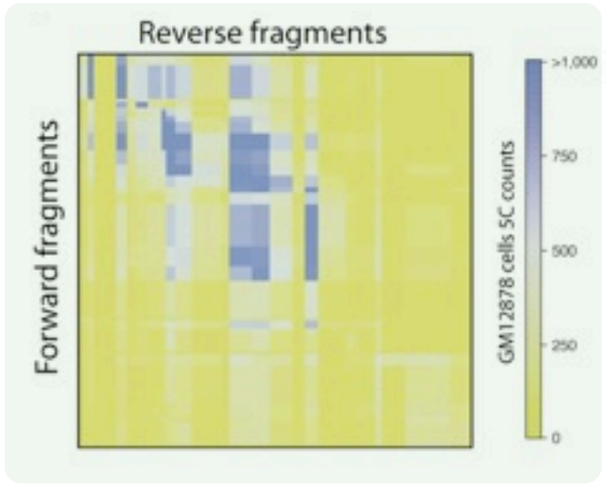
↓

Perform 5C analysis with 30+25 primers

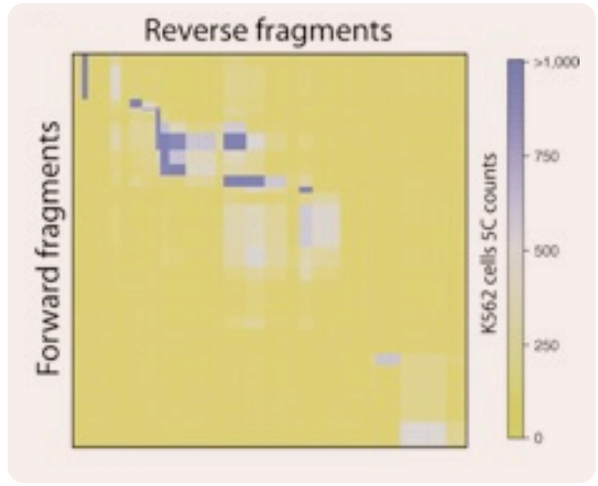
↓

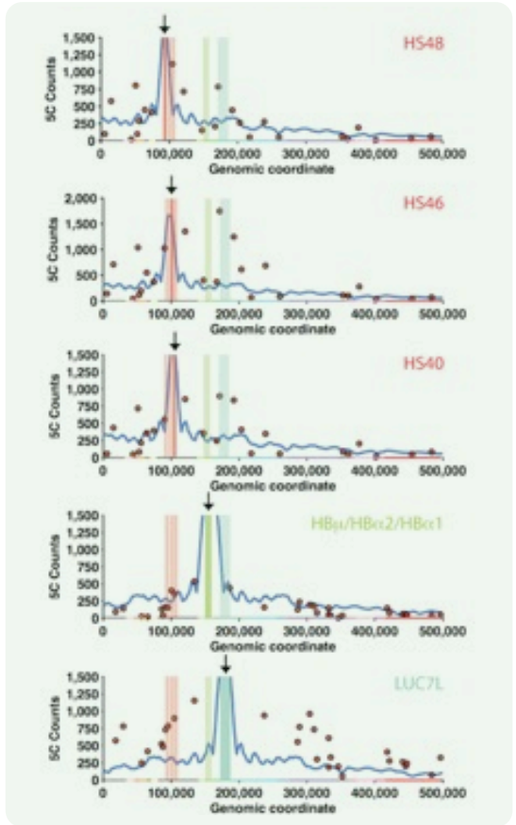
Analyze 5C products by paired-end Solexa sequencing
(131,947 paired end reads per library)

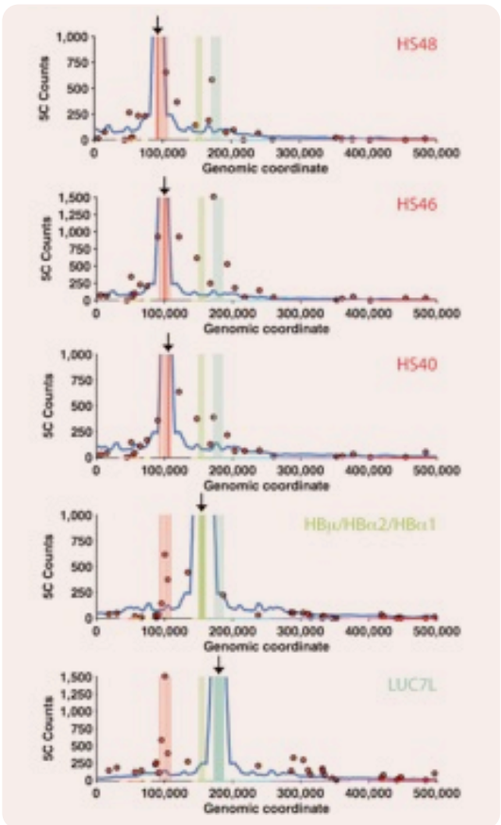
GM12878



K562

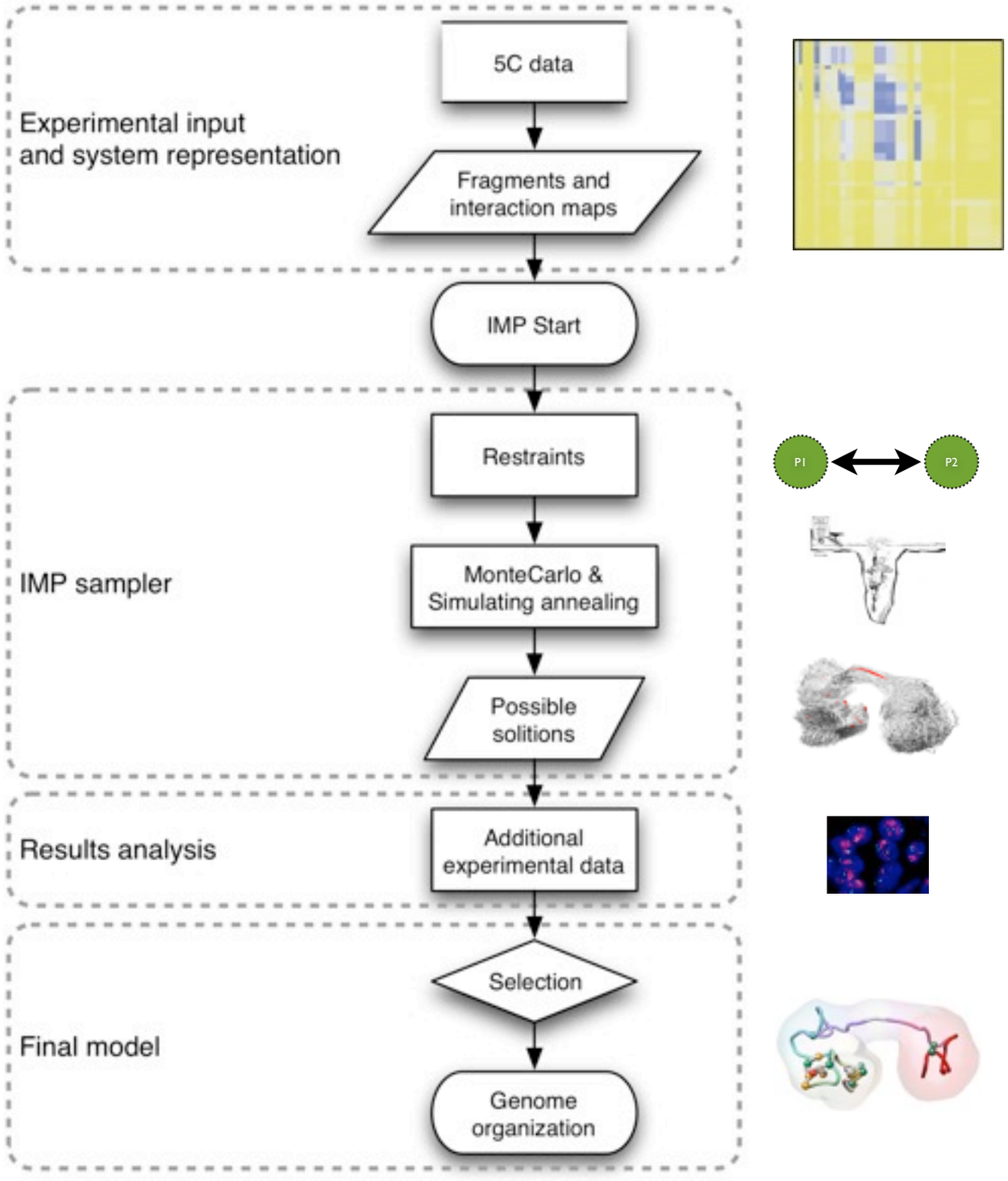






Integrative Modeling

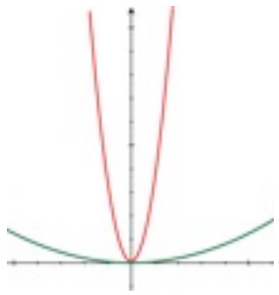
http://www.integrativemodeling.org



Representation

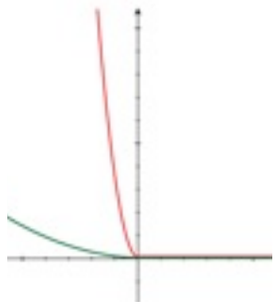
Harmonic

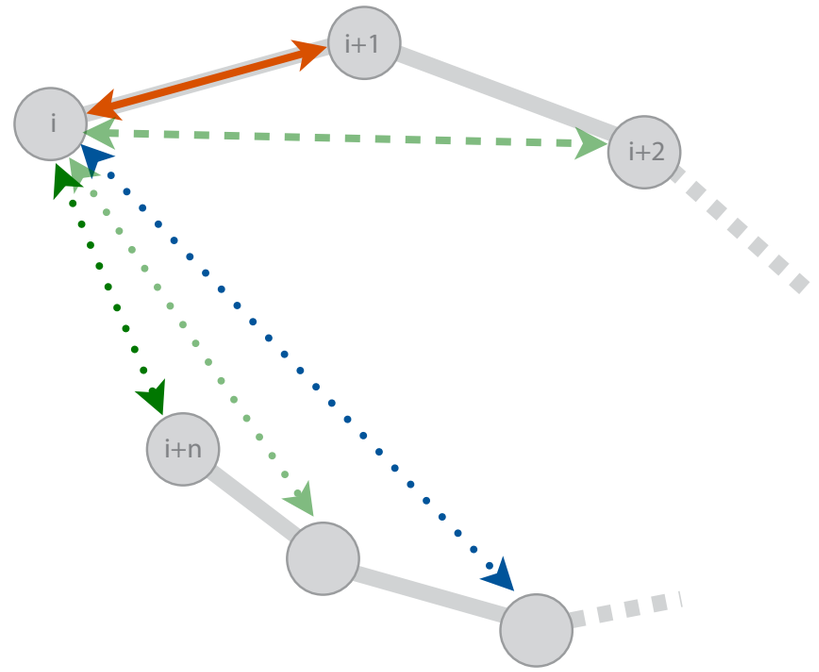
$$H_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2$$



Harmonic Lower Bound

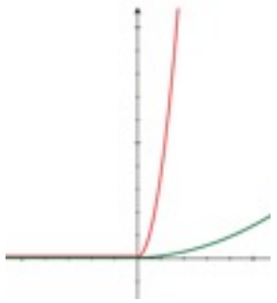
$$\begin{cases} if \;\; d_{i,j} \le d^0_{i,j}; & lbH_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2 \\ if \;\; d_{i,j} > d^0_{i,j}; & lbH_{i,j} = 0 \end{cases}$$





Harmonic Upper Bound

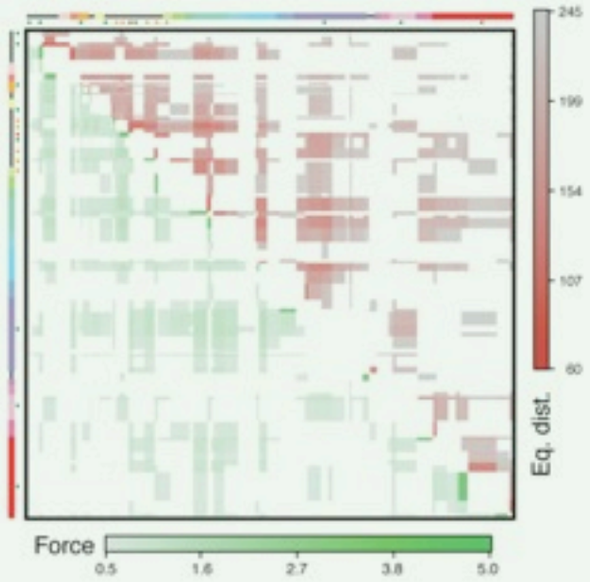
$$\begin{cases} if \;\; d_{i,j} \ge d^0_{i,j}; & ubH_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2 \\ if \;\; d_{i,j} < d^0_{i,j}; & ubH_{i,j} = 0 \end{cases}$$

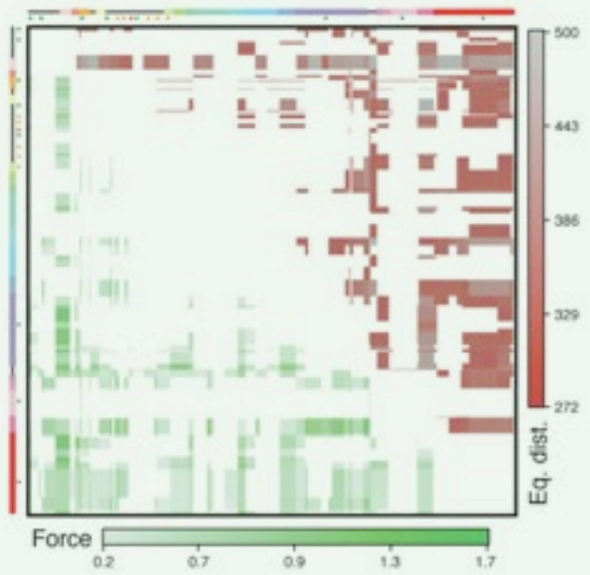


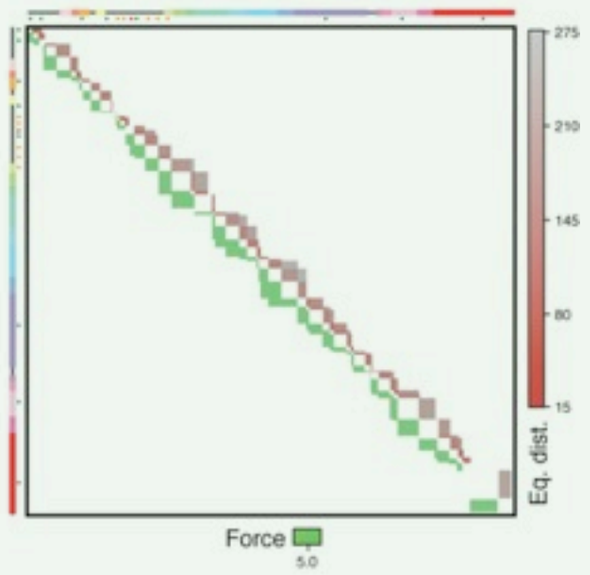
Scoring

GM12878

70 fragments
1,520 restraints



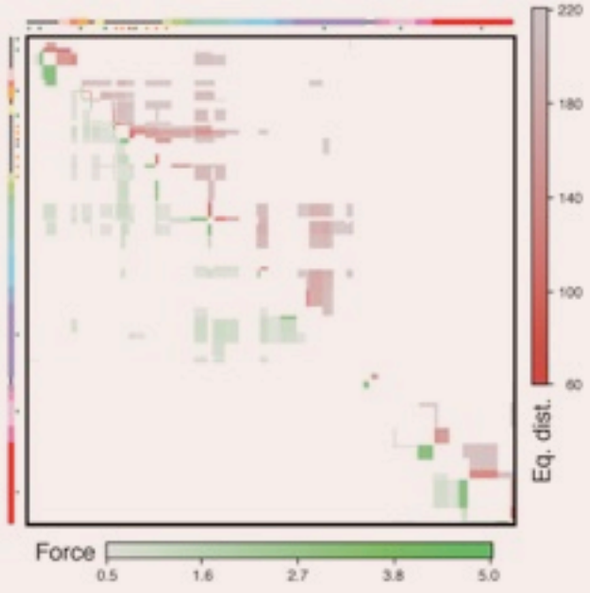


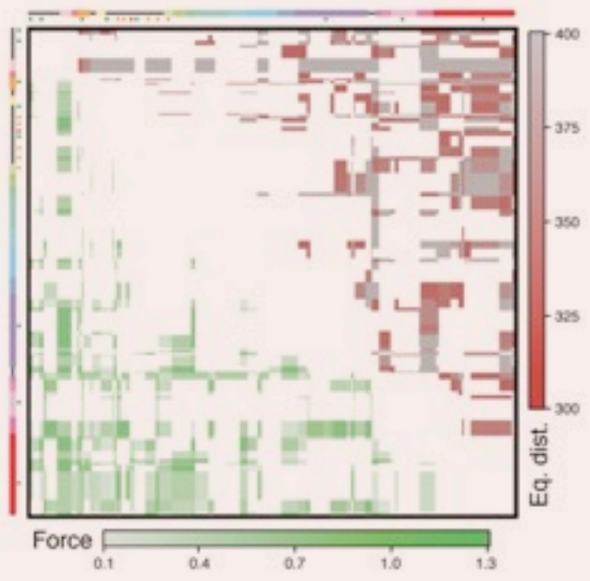


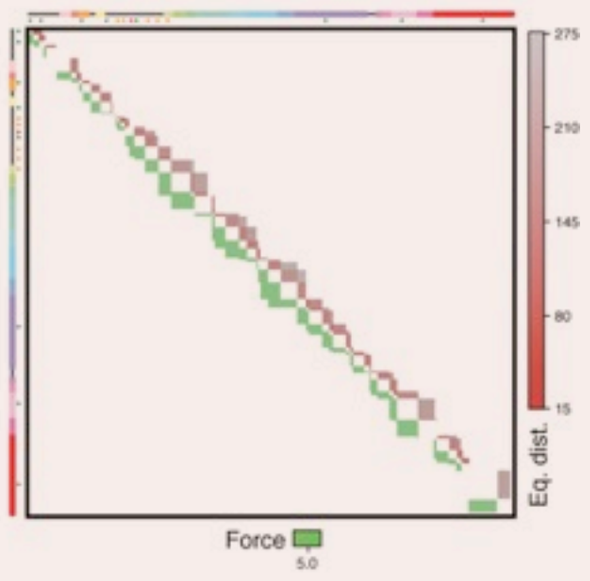
Harmonic | Harmonic Lower Bound | Harmonic Upper Bound

K562

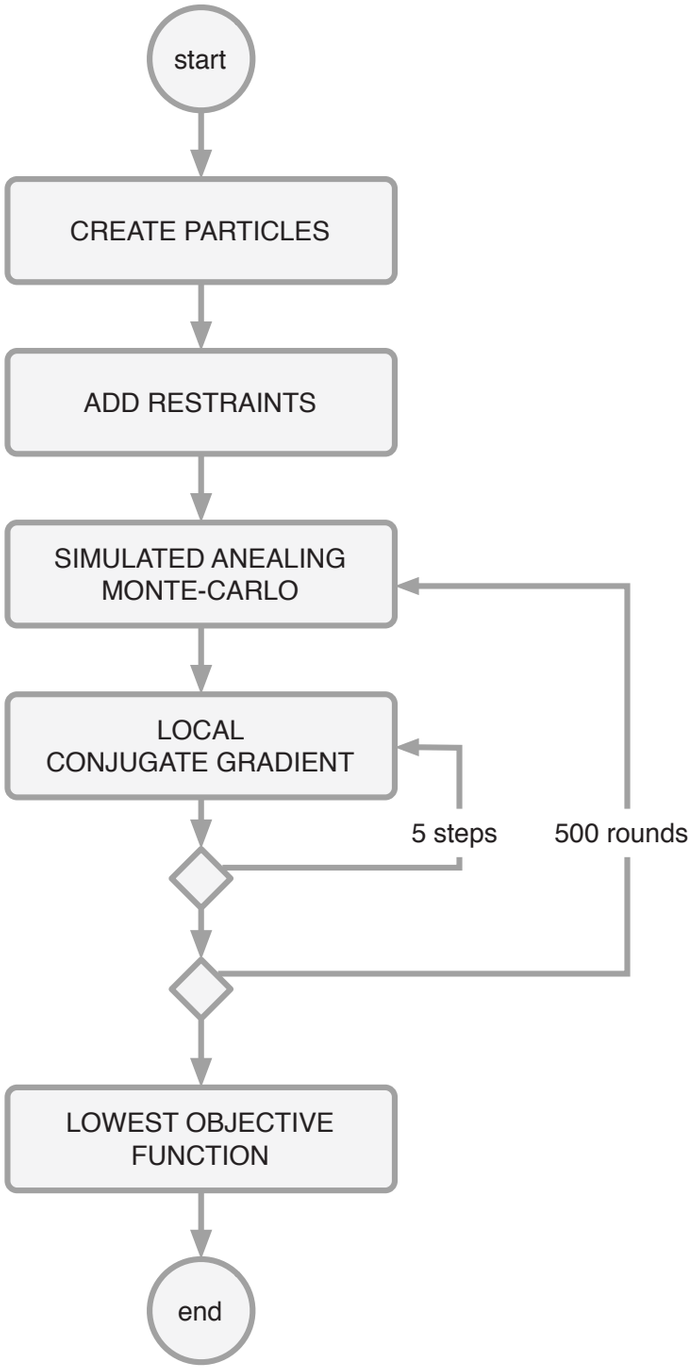
70 fragments
1,049 restraints

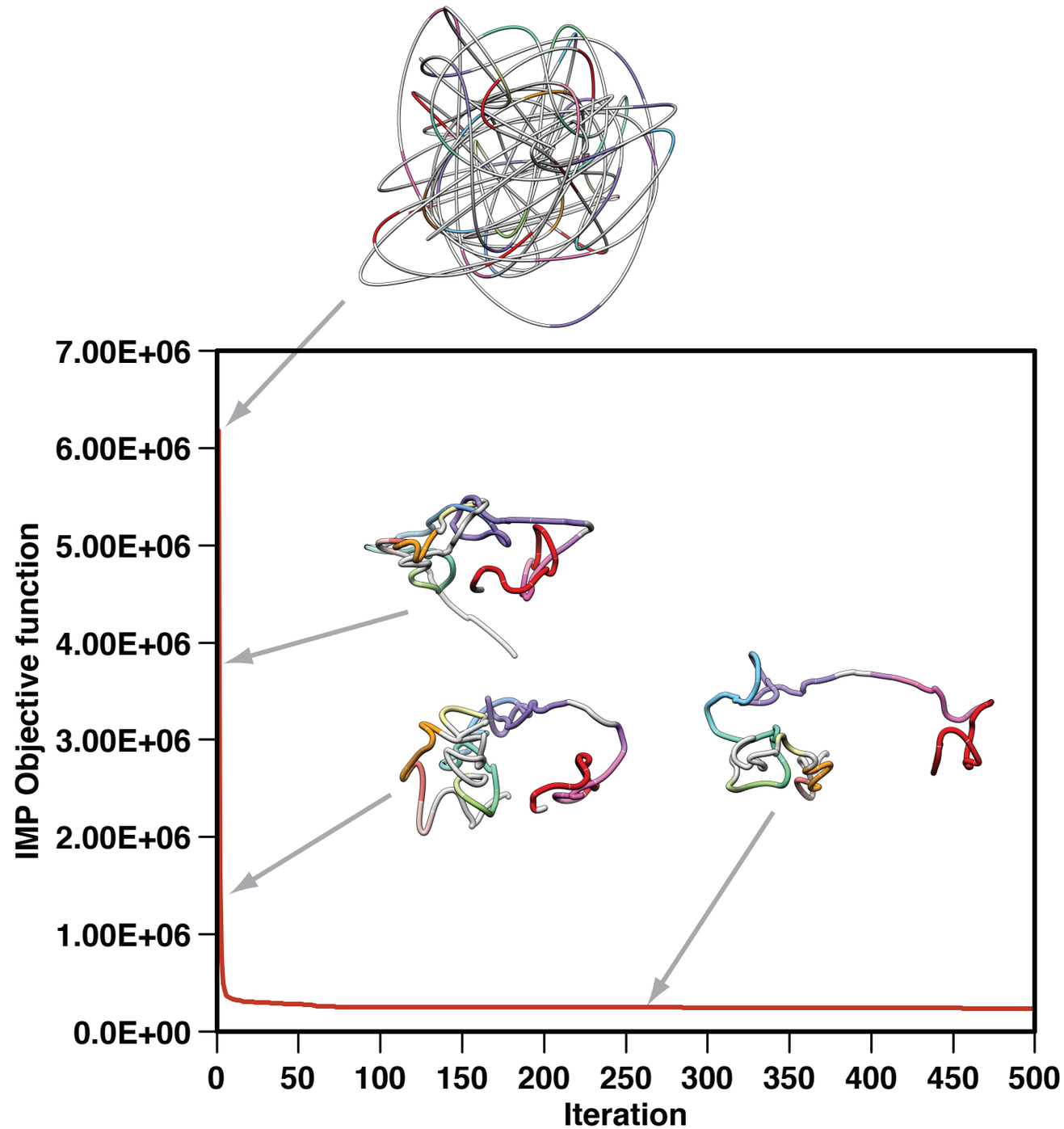






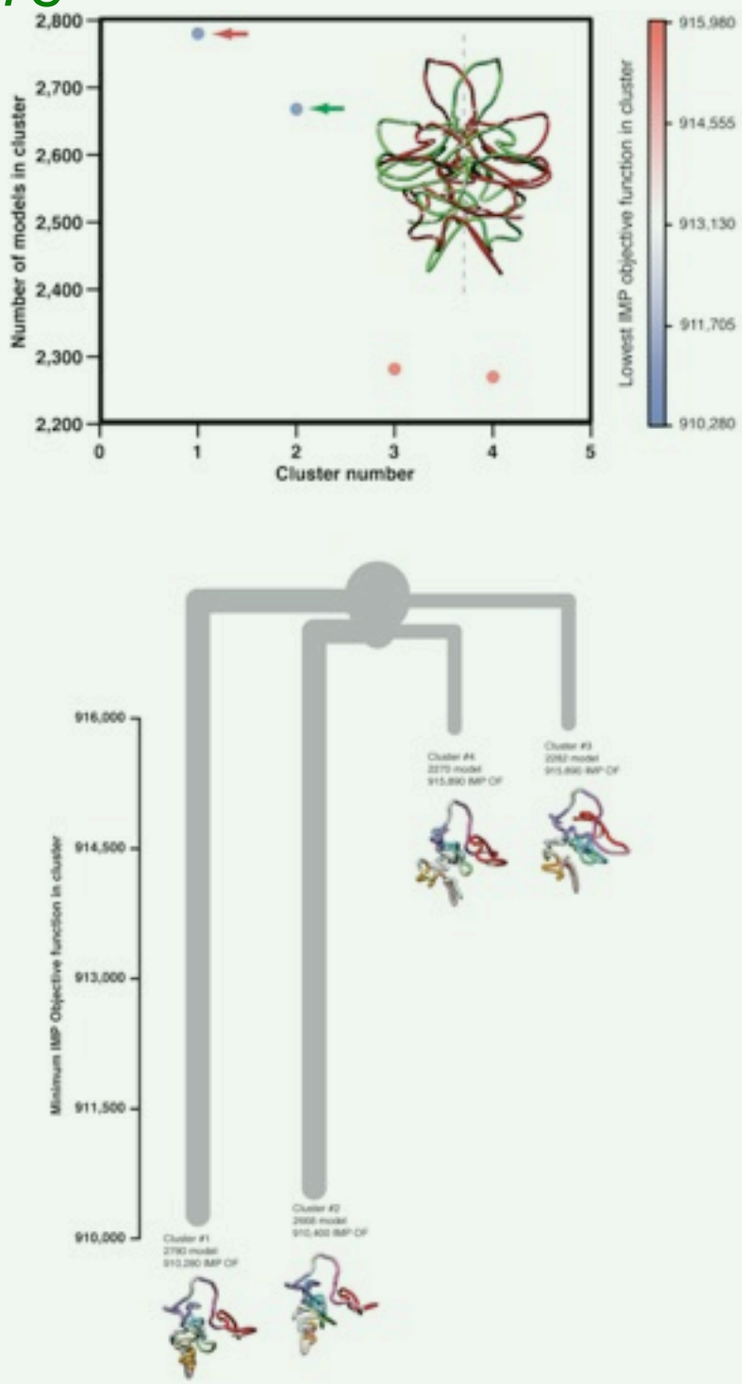
Optimization



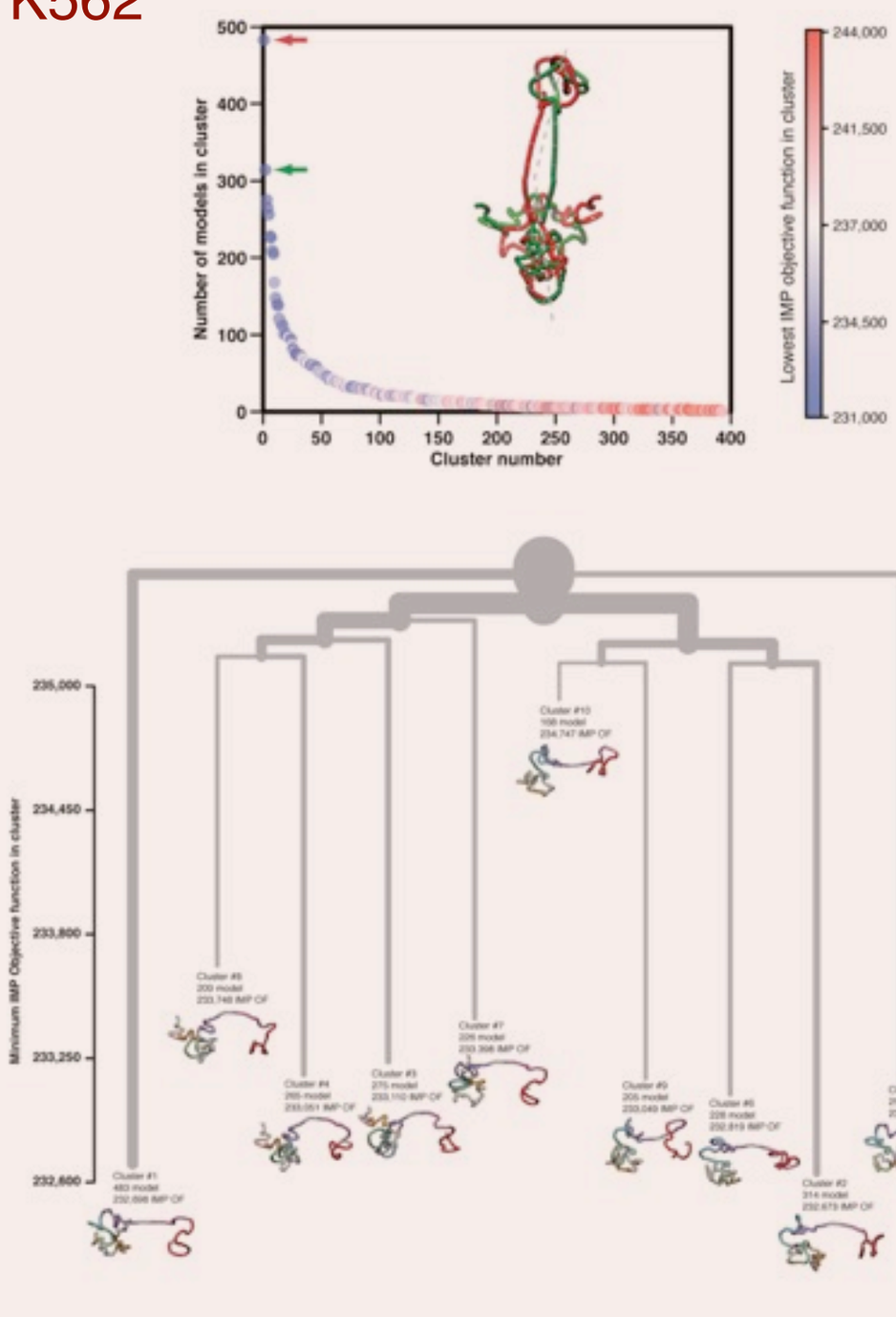


Not just *one* solution

GM12878

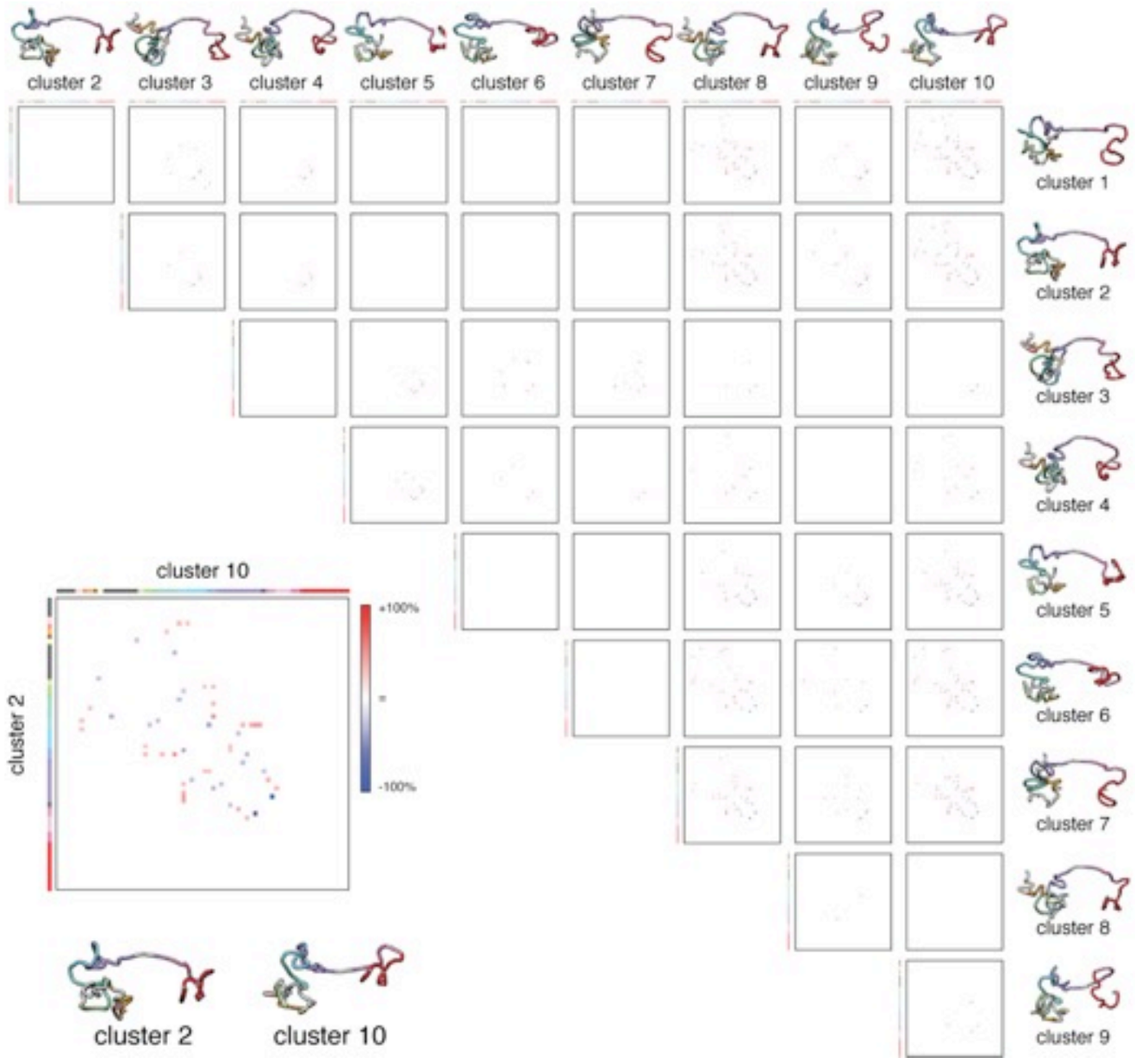


K562



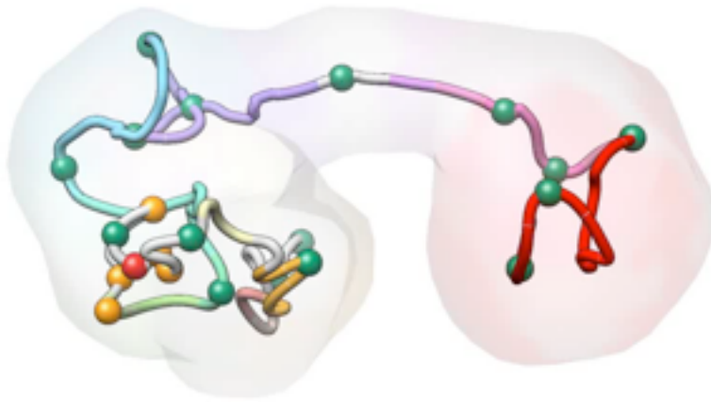
Not just *one* solution

and we can de-convolute them!

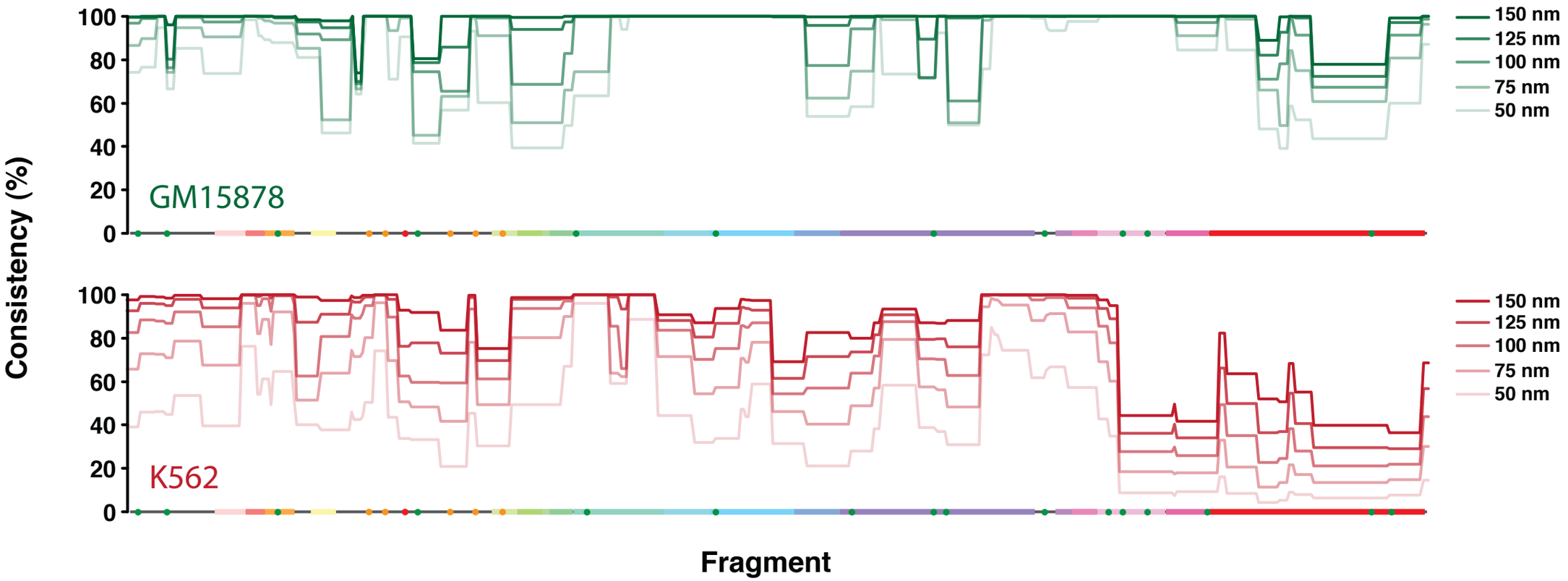


Consistency

GM12878
Cluster #1
2780 model



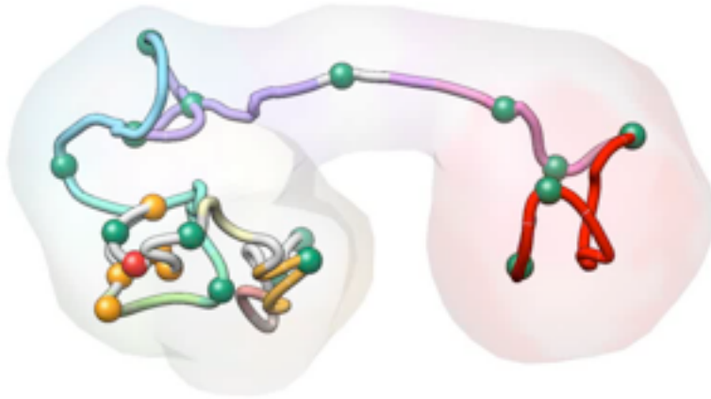
K562
Cluster #2
314 model



Regulatory elements

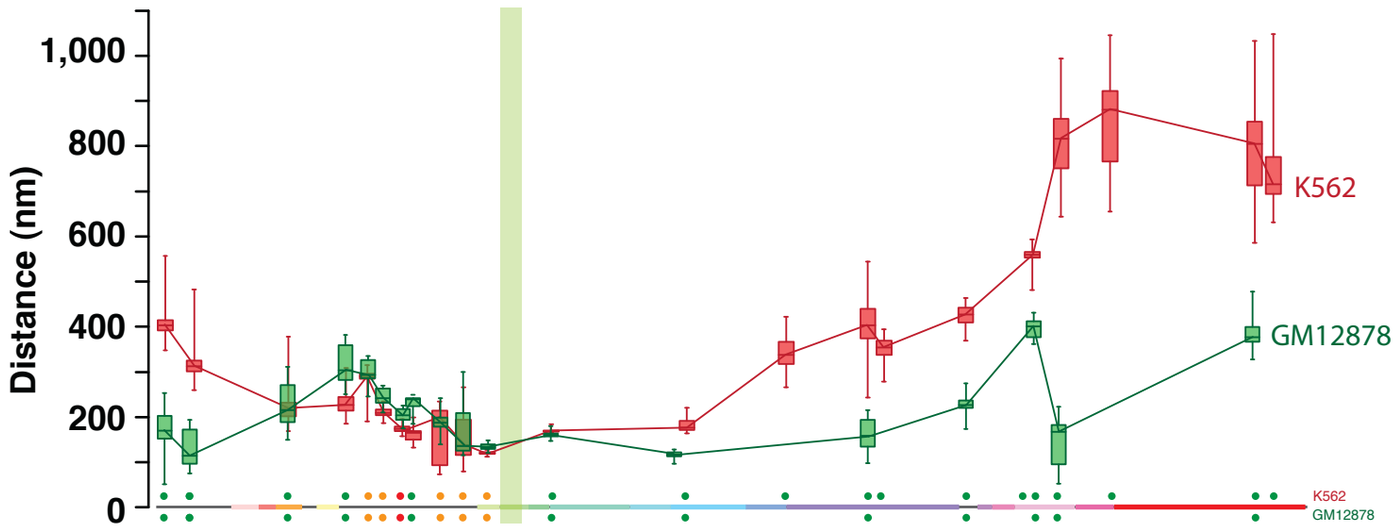
GM12878

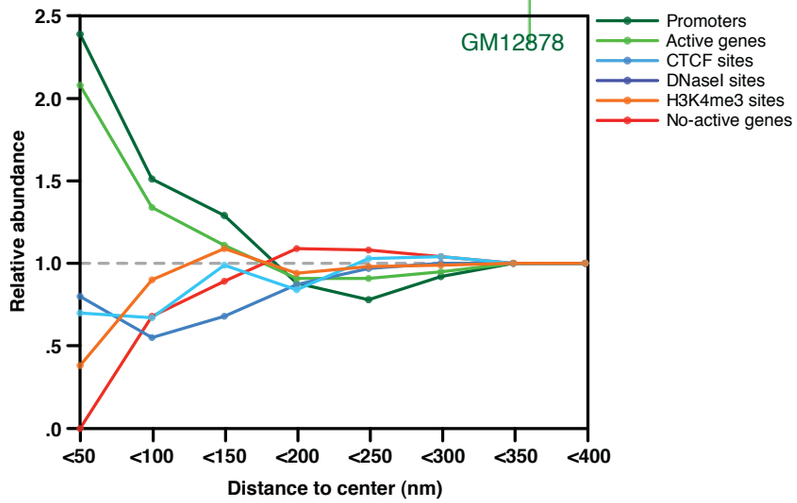
Cluster #1
2780 model

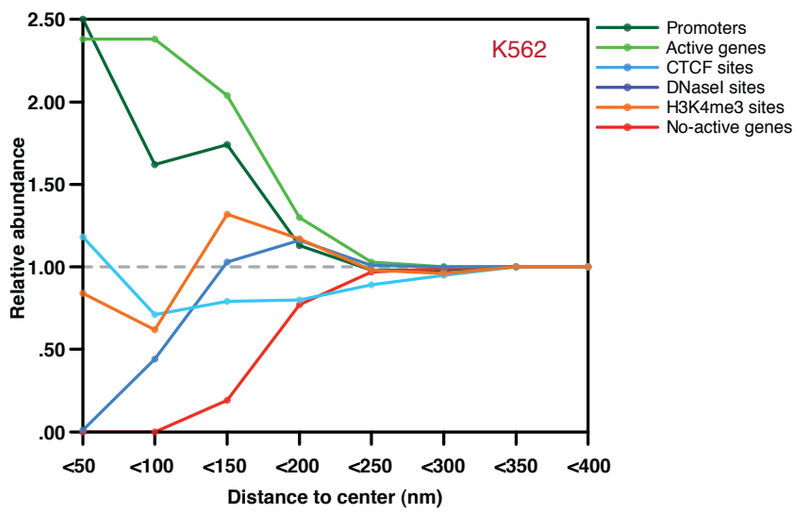


K562

Cluster #2
314 model

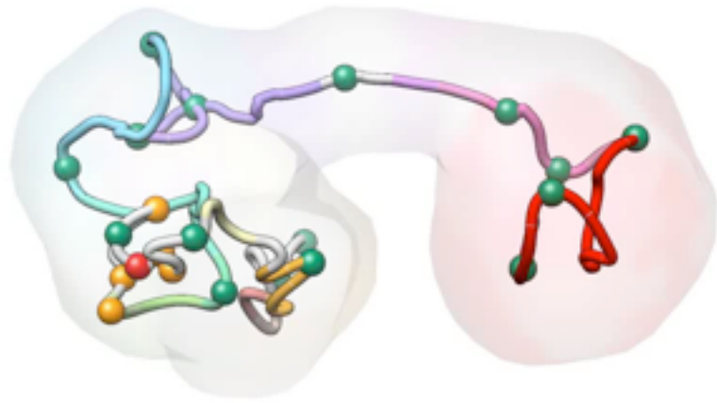




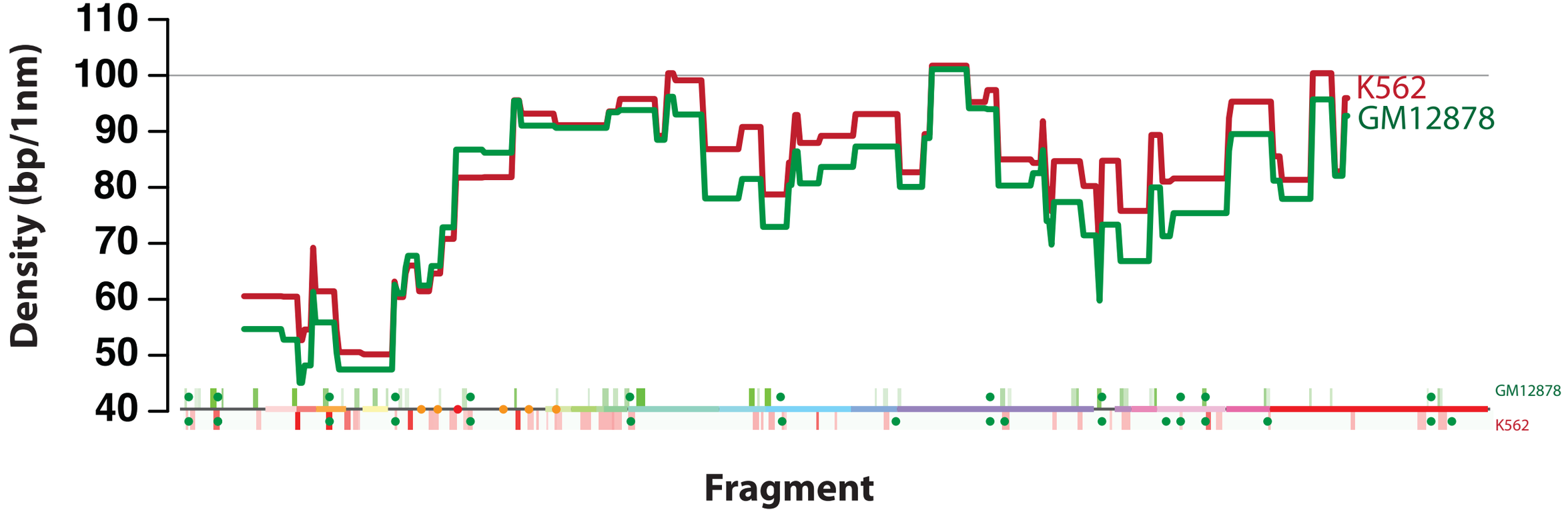


Compactness

GM12878
Cluster #1
2780 model



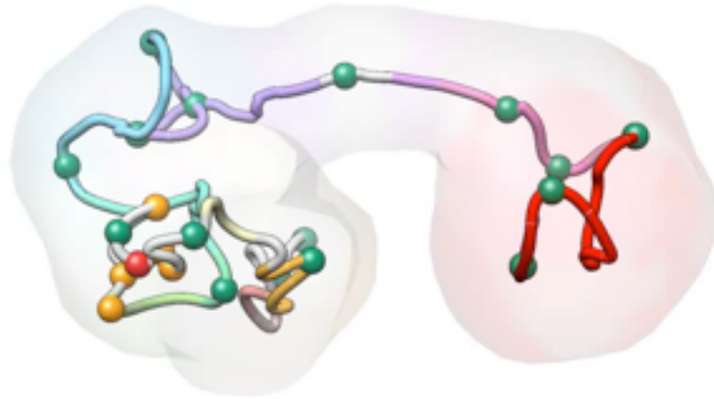
K562
Cluster #2
314 model



Multi-loops

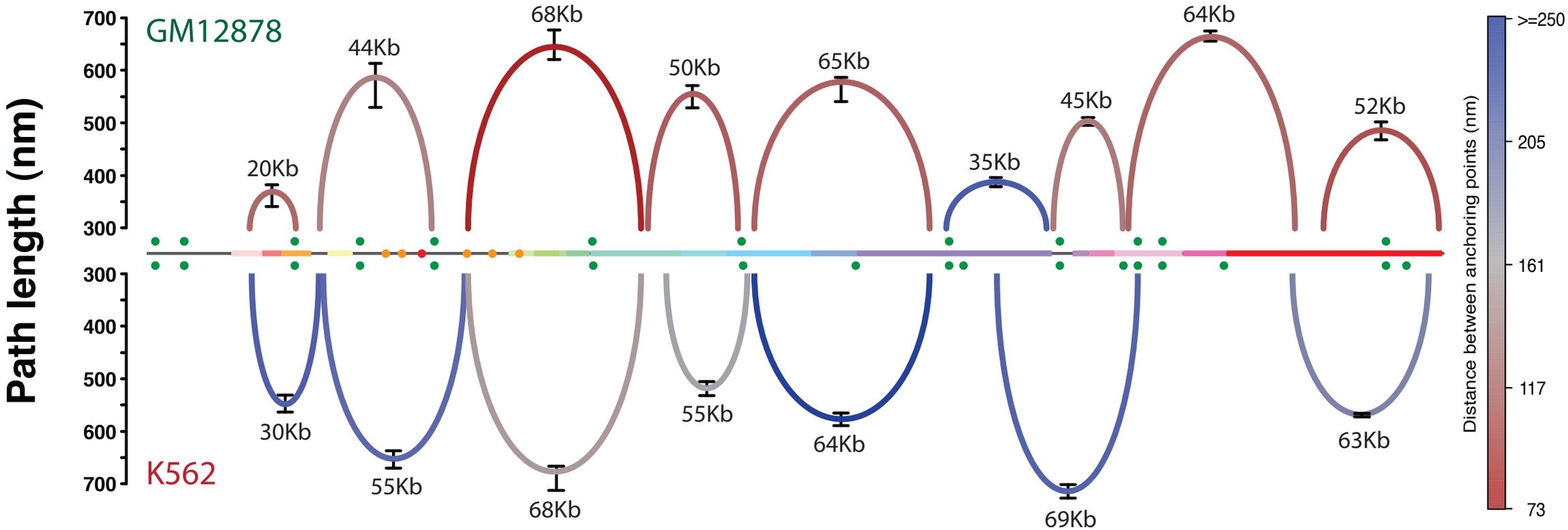
GM12878

Cluster #1
2780 model



K562

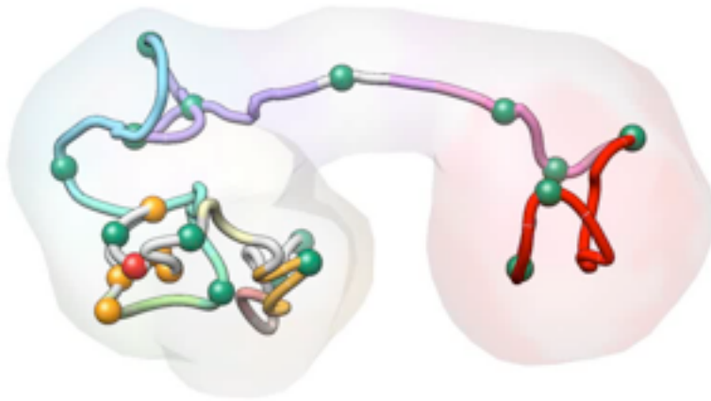
Cluster #2
314 model



Expression

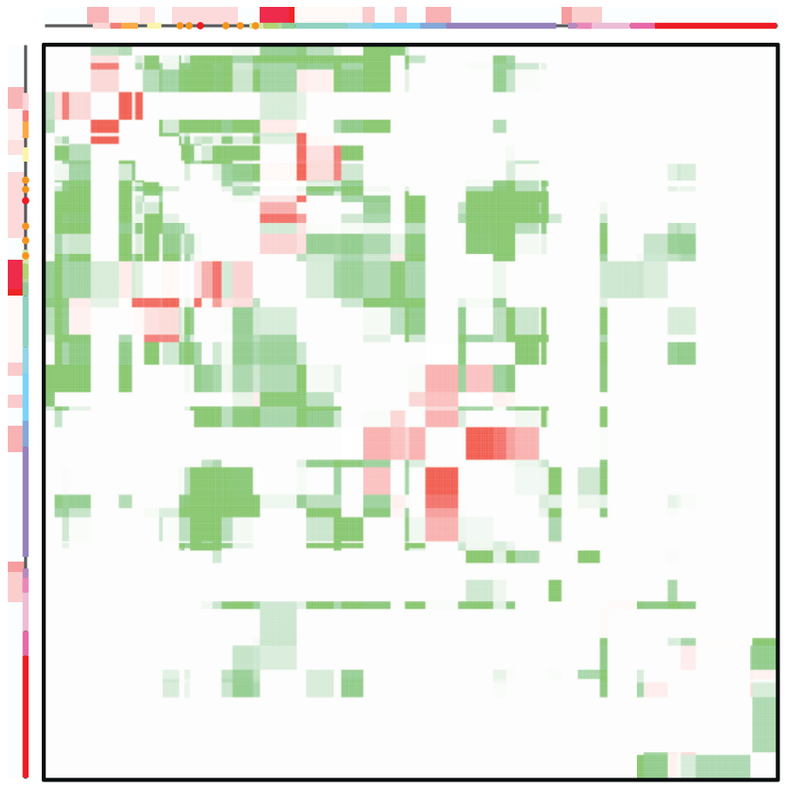
GM12878

Cluster #1
2780 model



K562

Cluster #2
314 model



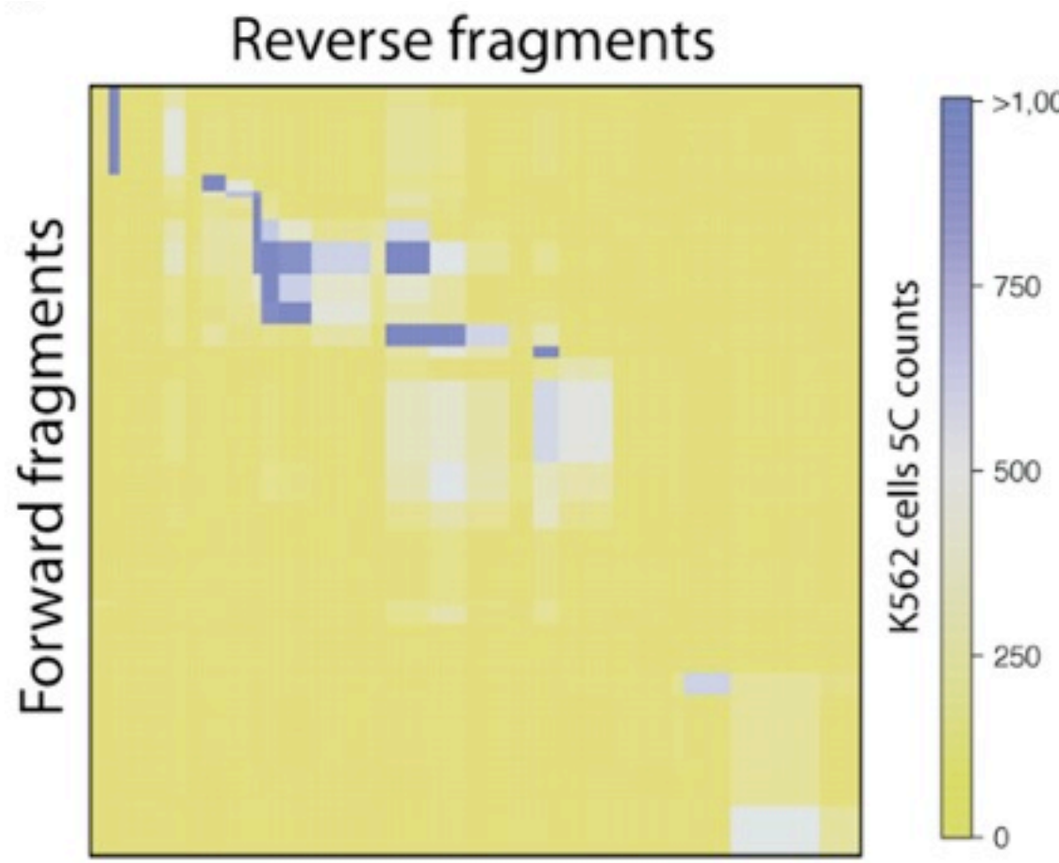
Increased in GM12878

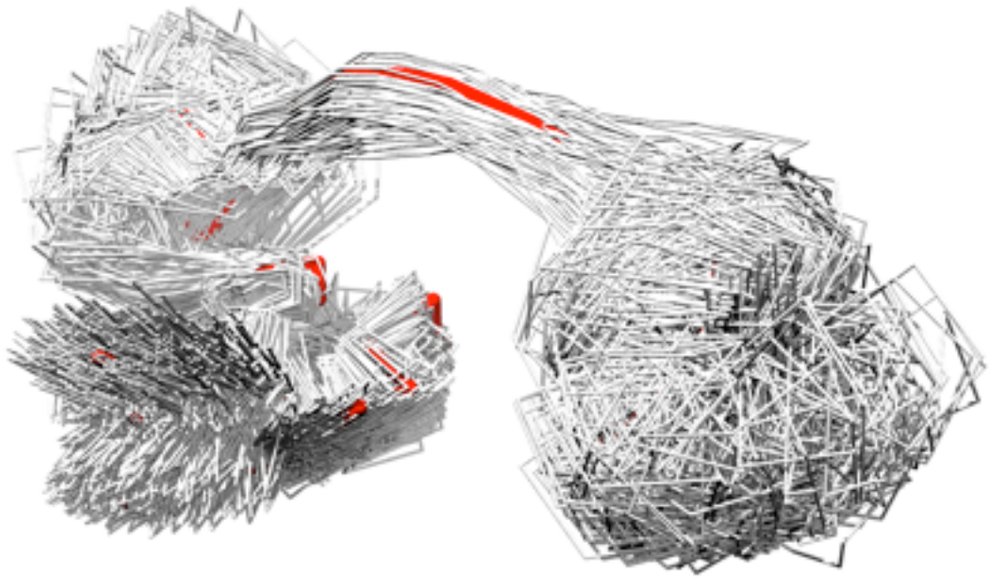
=

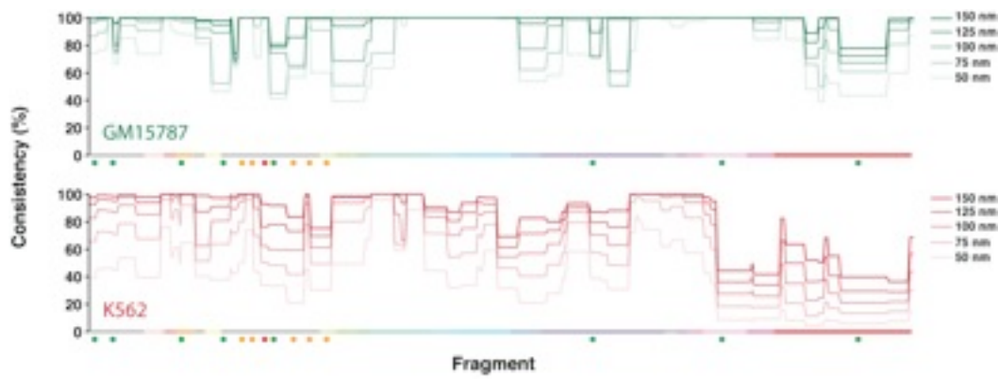
Increased in K562

Summary

5C data results in comprehensive interaction matrices to build a consistent 3D model







Summary

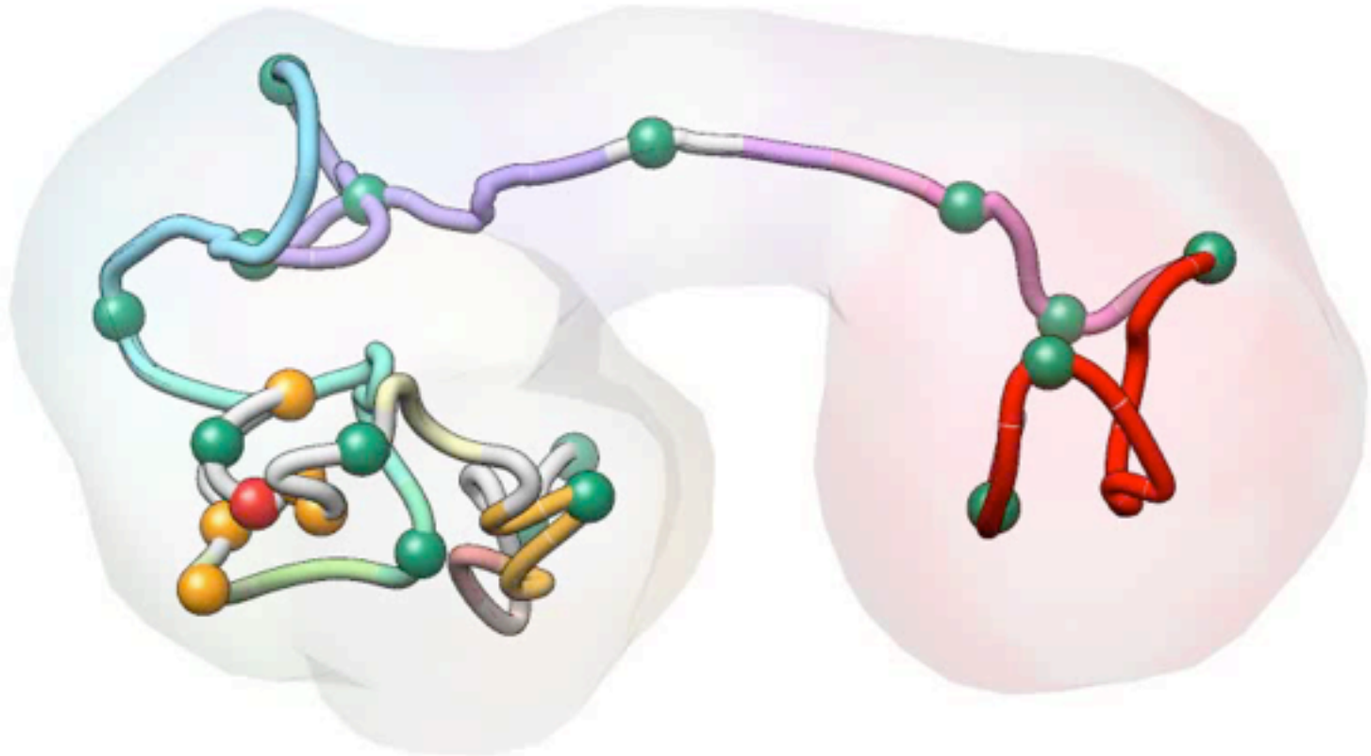
Models allow for 5C data de-convolution

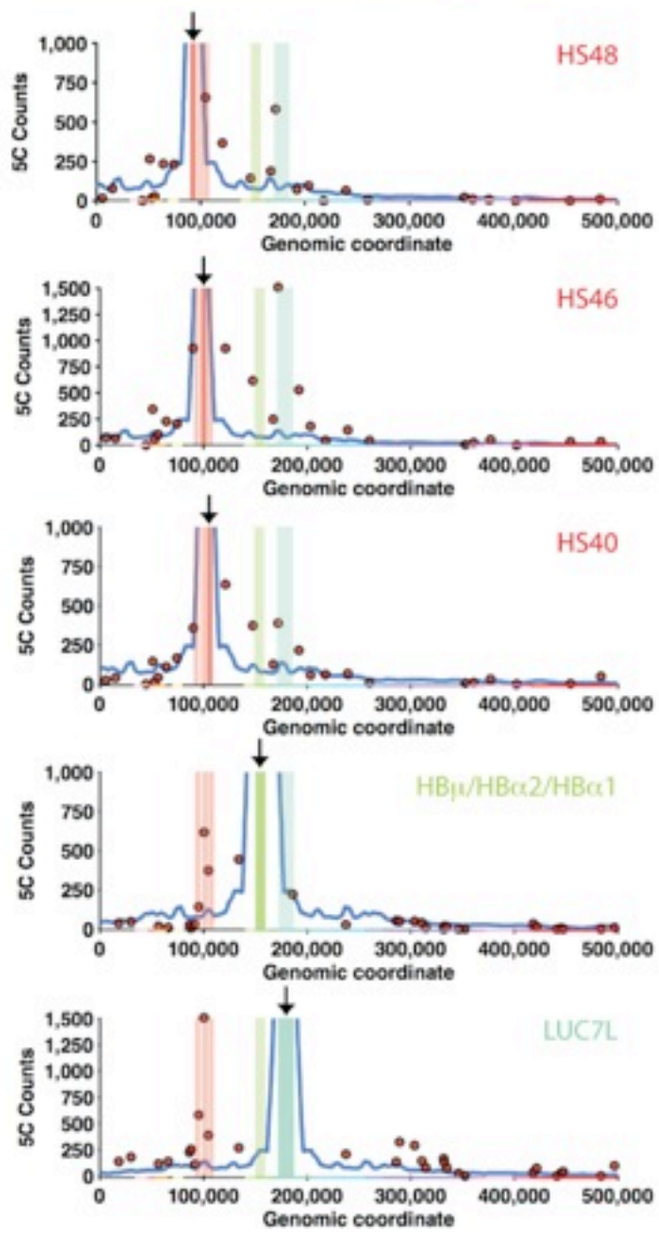
Summary

Models allow for 5C data de-convolution

Summary

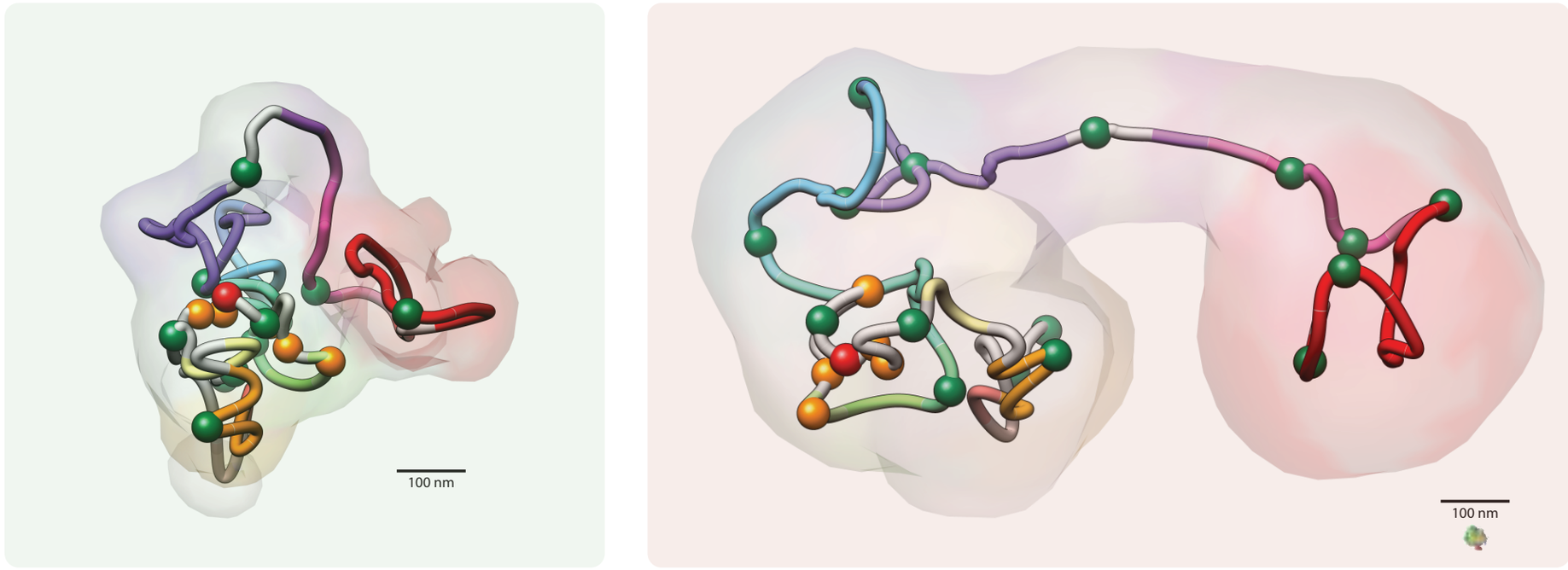
Selected models reproduce known (**and new**) interactions

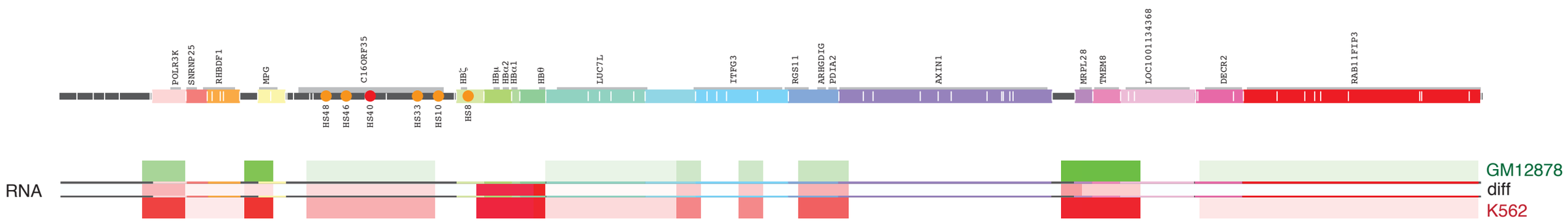




Summary

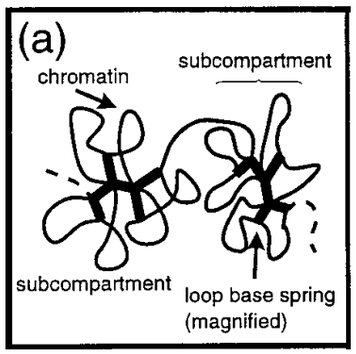
Large-scale changes in conformation correlate with gene expression of resident genes



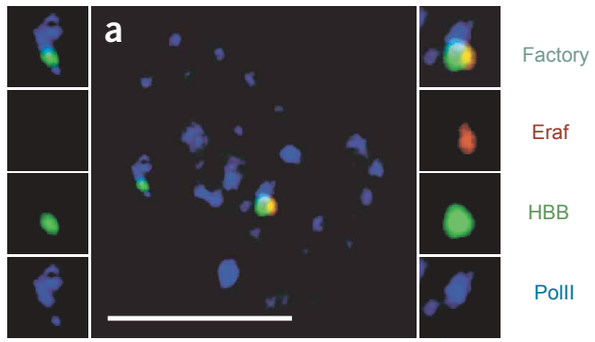


Summary

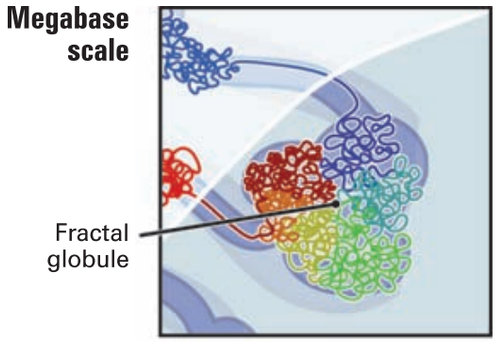
"Chromatin Globule" model



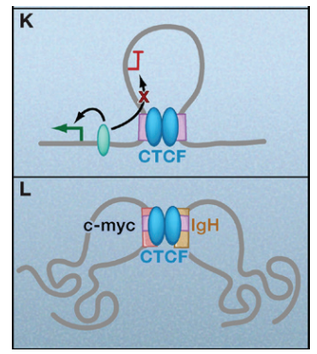
Münkel et al. JMB (1999)



Osborne et al. Nat Genet (2004)



Lieberman-Aiden et al. Science (2009)



Phillips and Corces. Cell (2009)

Acknowledgments

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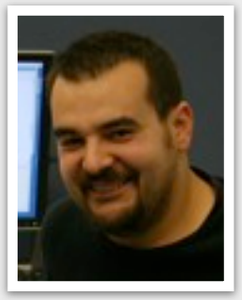
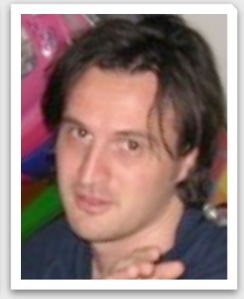

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