Comparative Modeling / Docking for the *Tropical Disease Initiative*

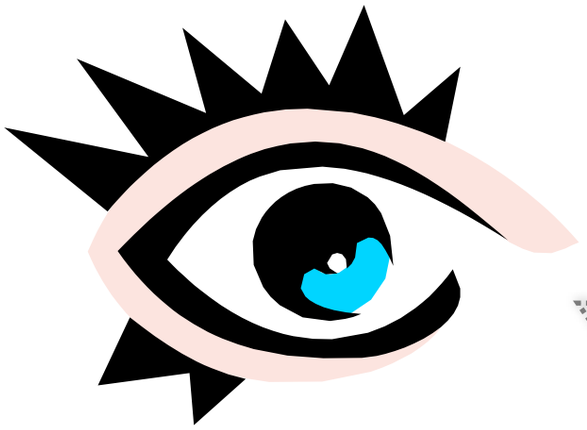
&

3D Caulobacter Genome

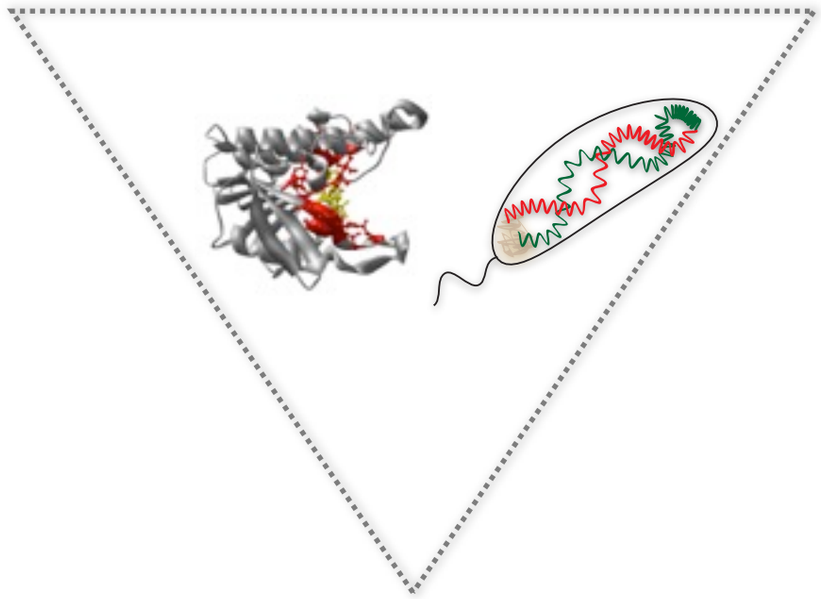
Marc A. Marti-Renom
Genome Biology Group (CNAG)
Structural Genomics Group (CRG)

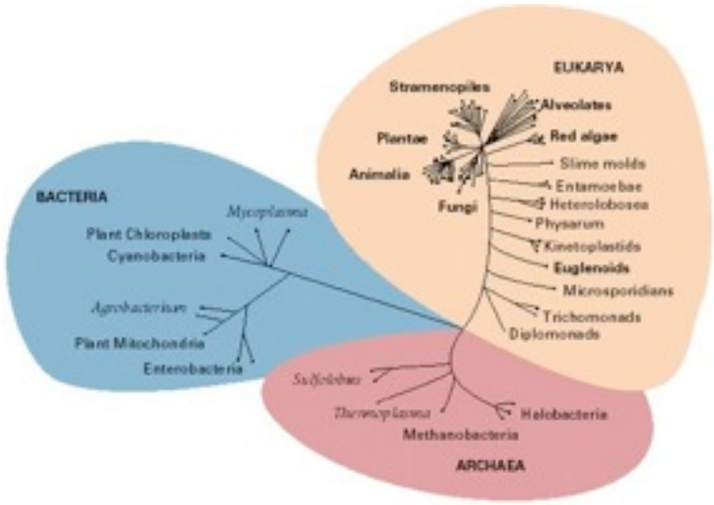
Integrative Modeling Platform

http://www.integrativemodeling.org

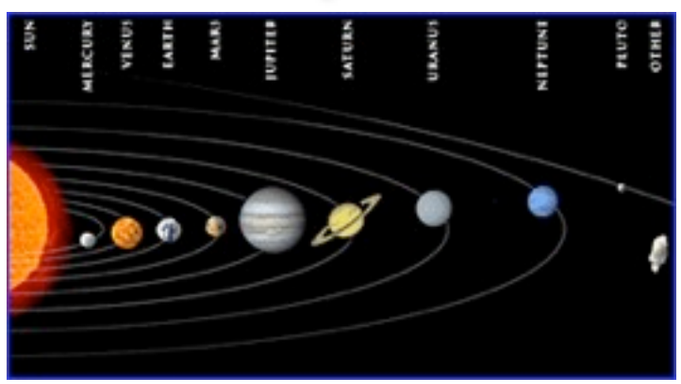


Experimental observations





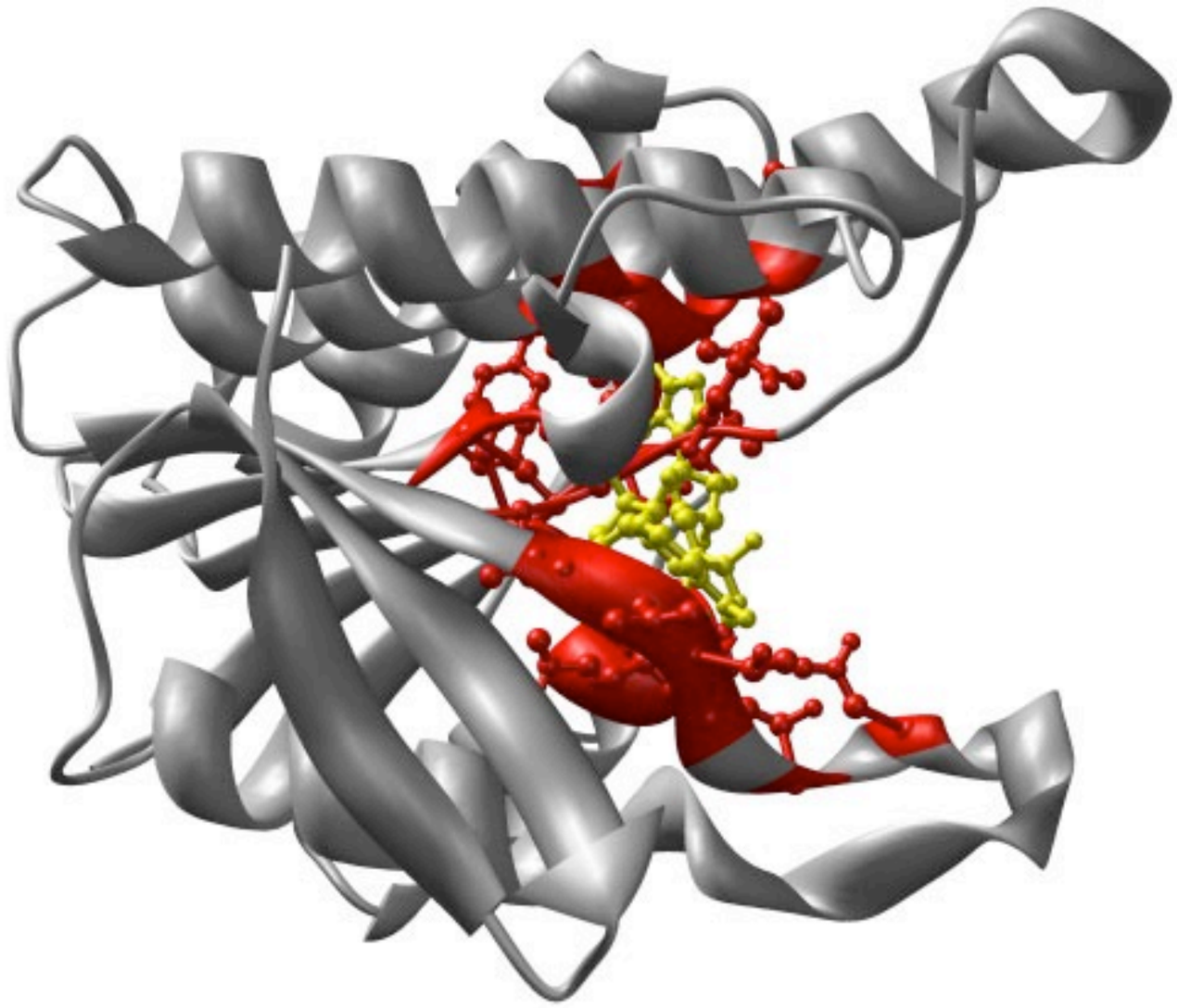
Statistical rules



Laws of physics

cnag CRG

the TROPICAL DISEASE INITIATIVE



TDI *a story*

2004

.Steve Maurer (Berkeley) and Arti Rai (Duke)
.PLoS Medicine, Dec. 2004. Vol 1(3):e56

2005

.TDI web site `http://TropicalDisease.org`
.Ginger Taylor and The Synaptic Leap

2006

.Maurer and Sali 41th in “50 Who Matter”
.TSL web site `http://TheSynapticLeap.org`

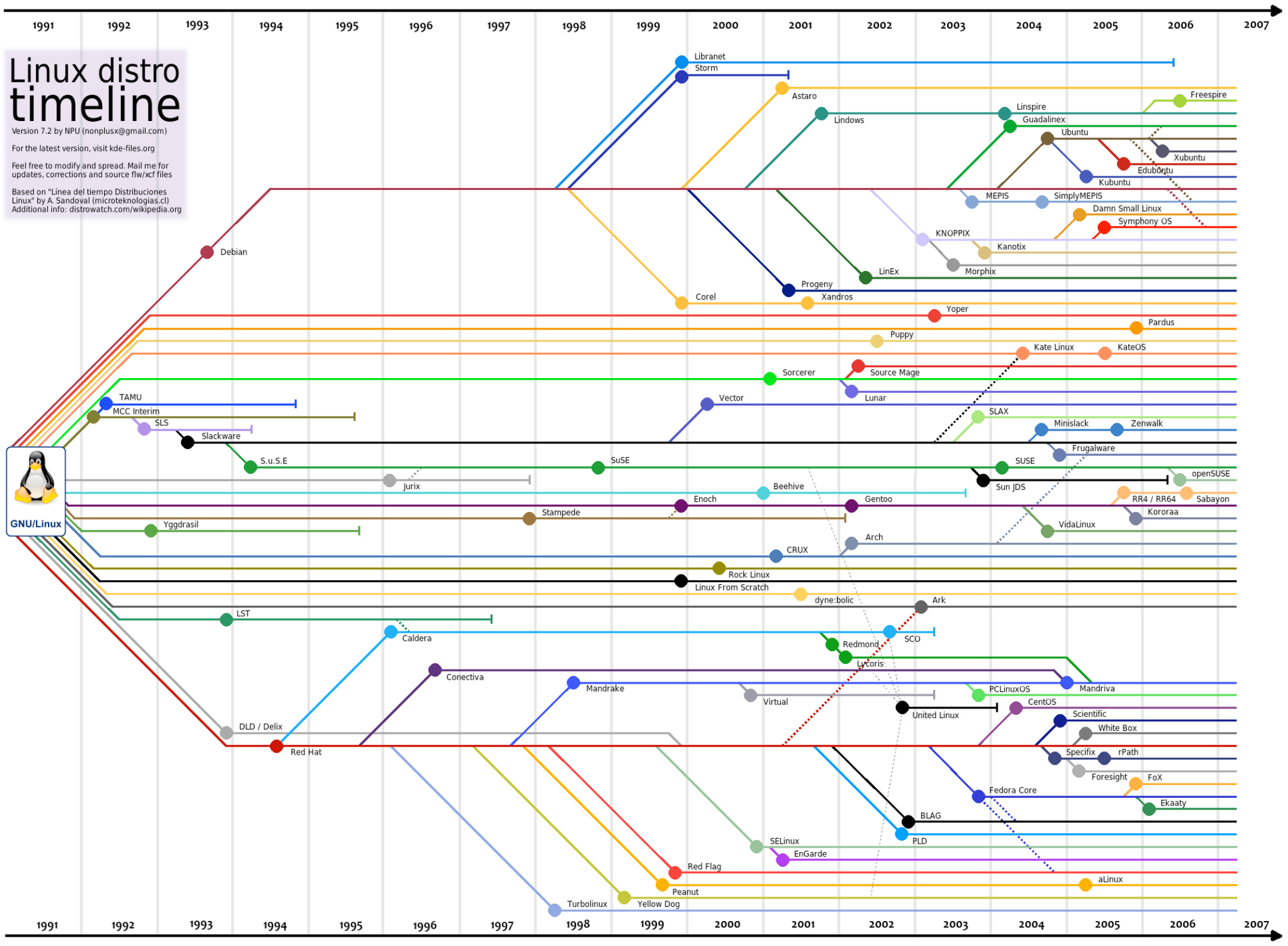
2009

.TDI kernel `http://TropicalDisease.org/kernel`

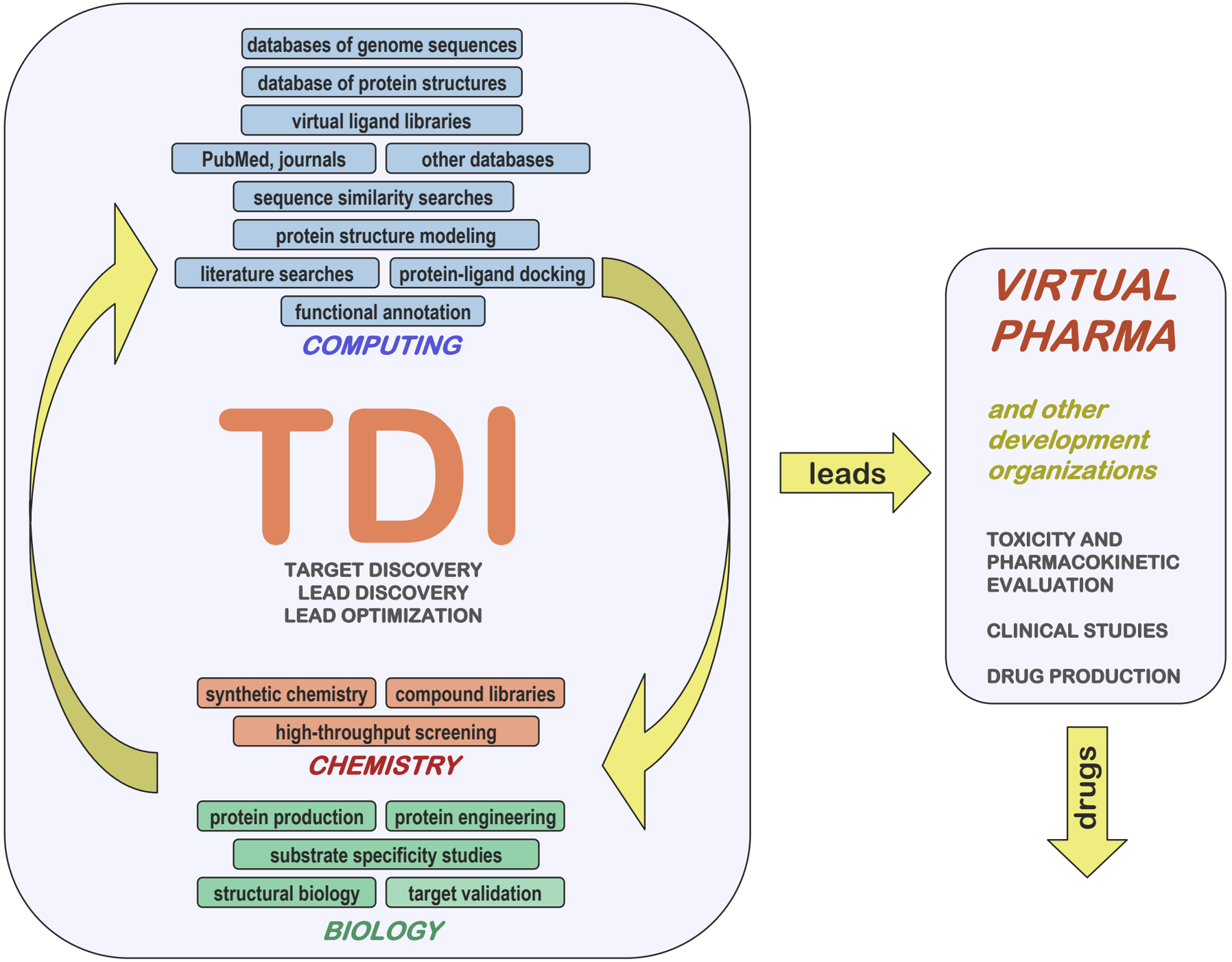
2010...

. (OUR) Applications of the Kernel

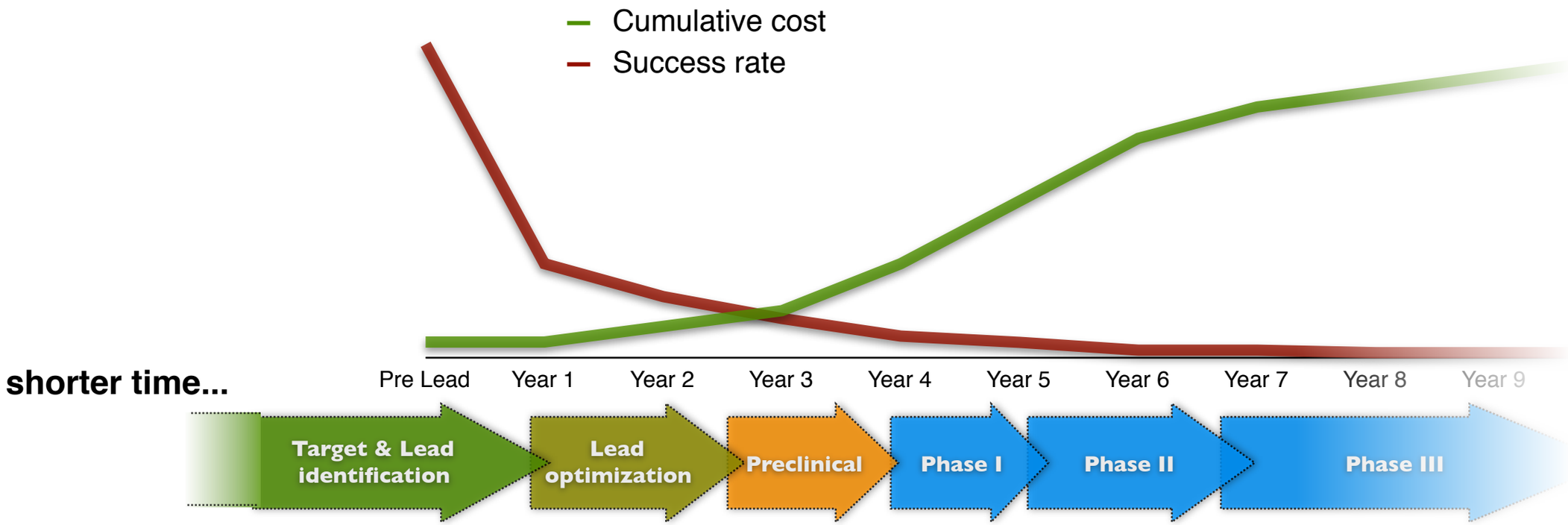
Open Source without a Kernel?



TDI flowchart



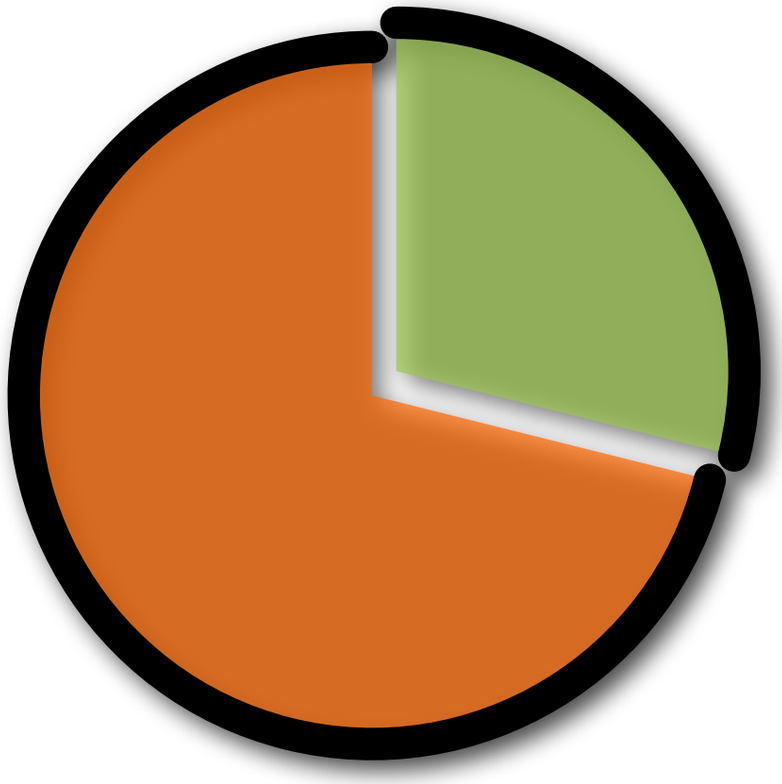
Drug Discovery pipeline

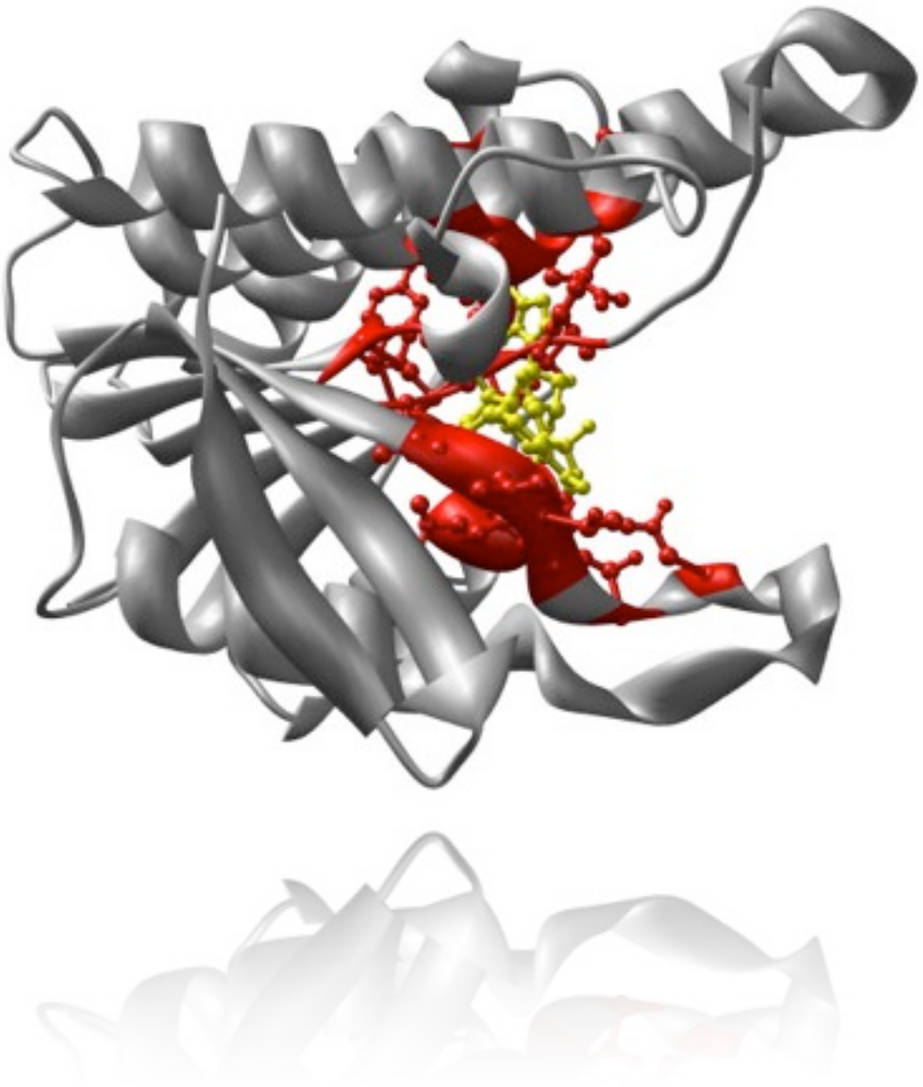


TDI

+ Completeness of genome projects (*eg*, Malaria)
+ New and more complete biological databases
+ New software and computers (cheaper and faster)
+ Internet == more people == less cost

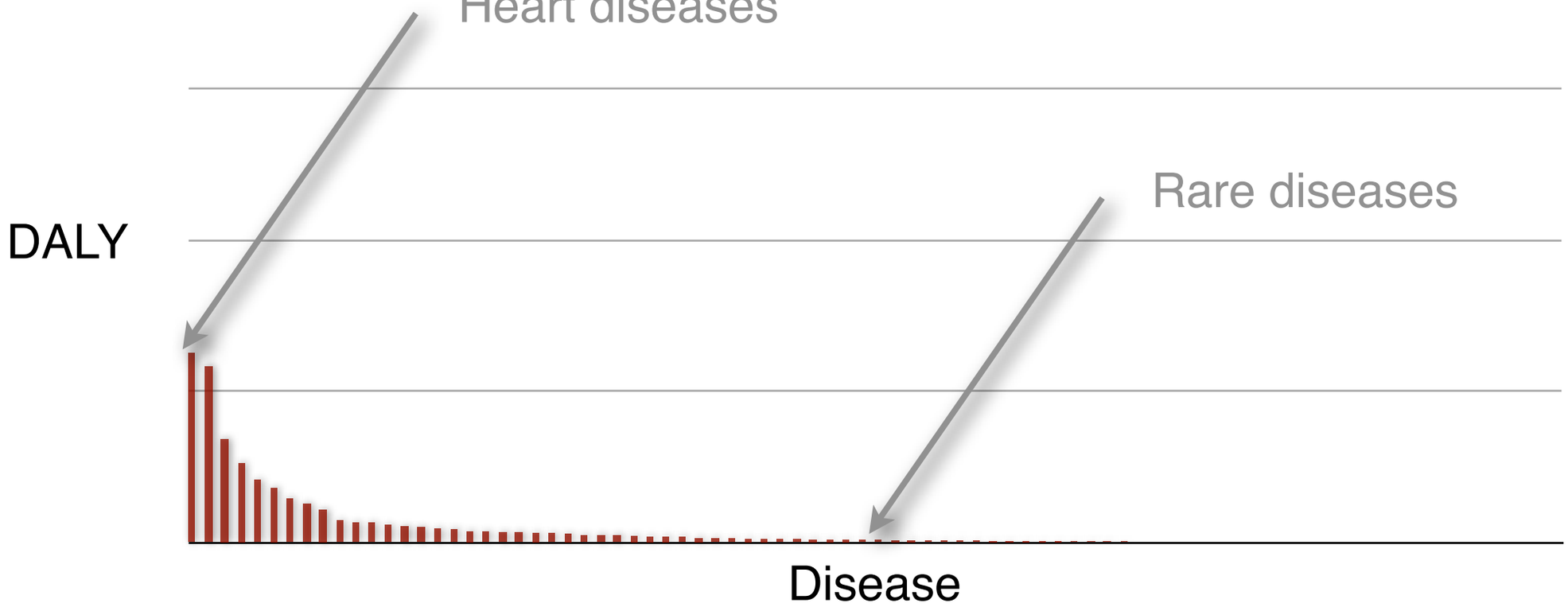
Predicting binding sites in protein structure models of Tropical Diseases





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.

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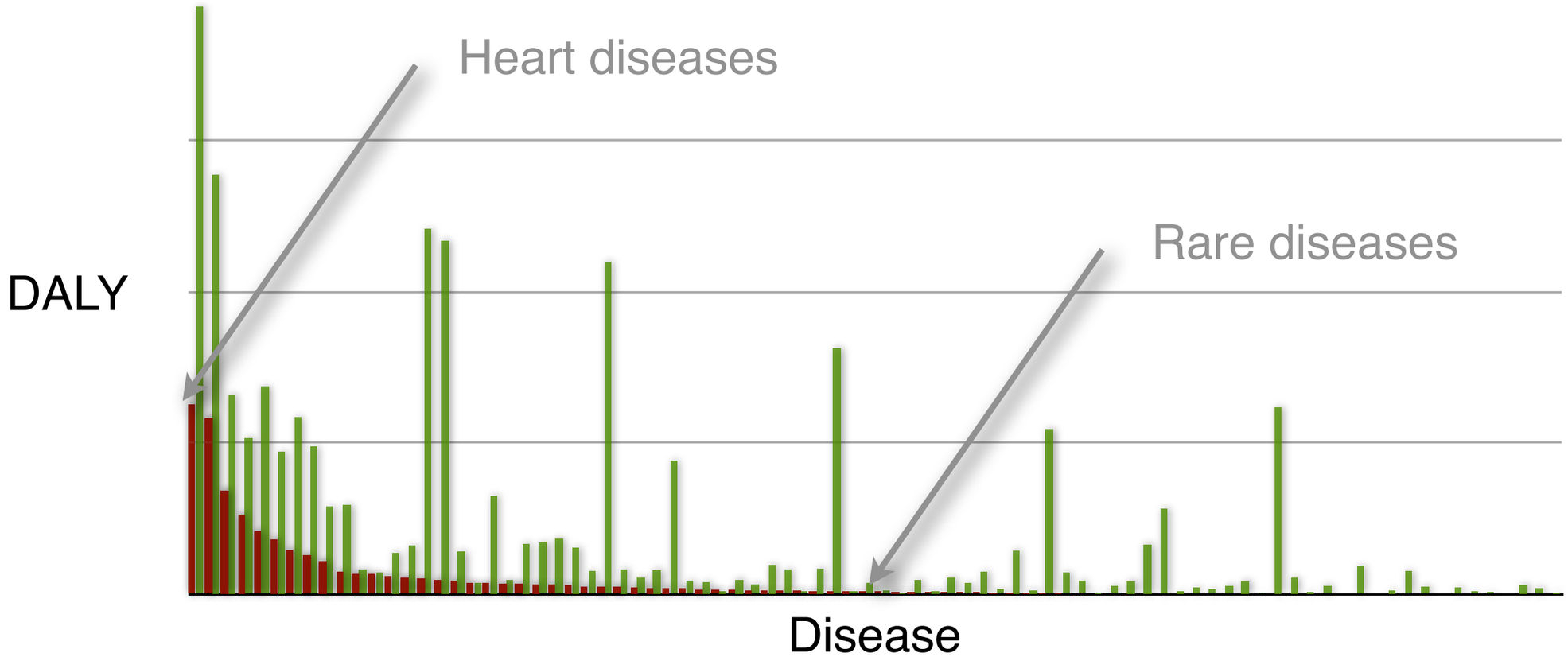
Need is High in the Tail

DALY Burden Per Disease in Developed Countries

DALY Burden Per Disease in Developing Countries



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"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.

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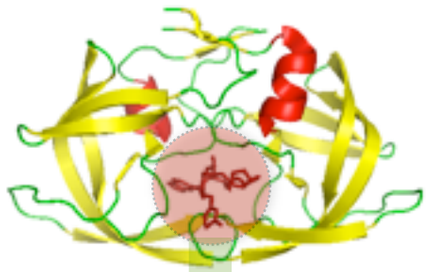
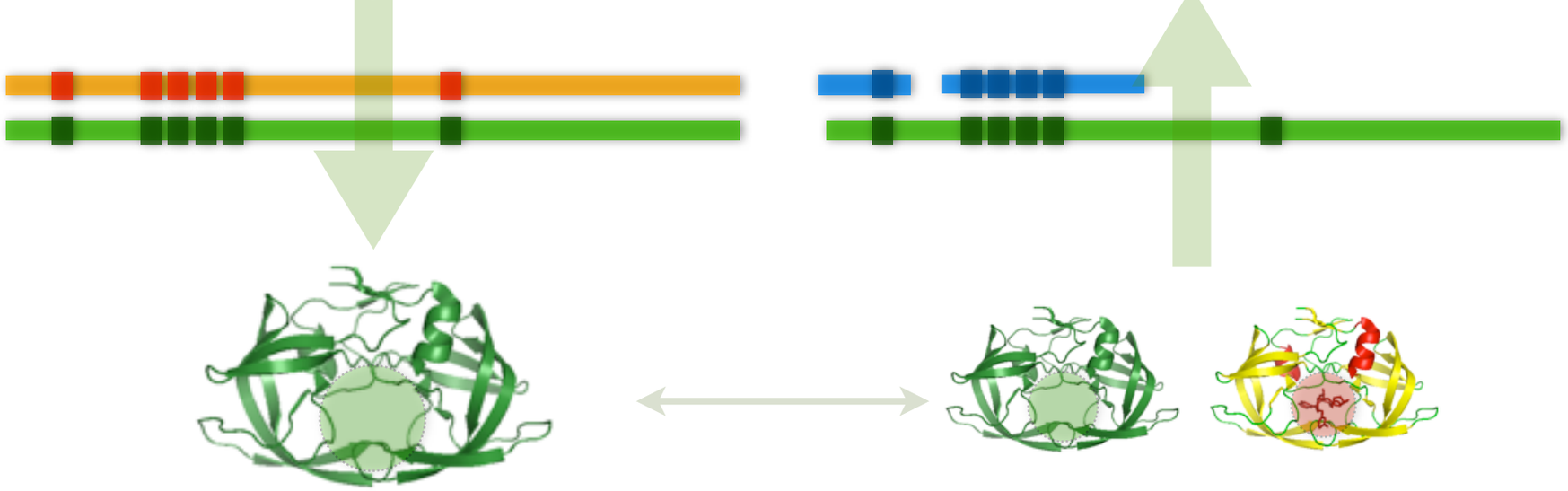
Comparative docking

Expansion

co-crystalized protein/ligand



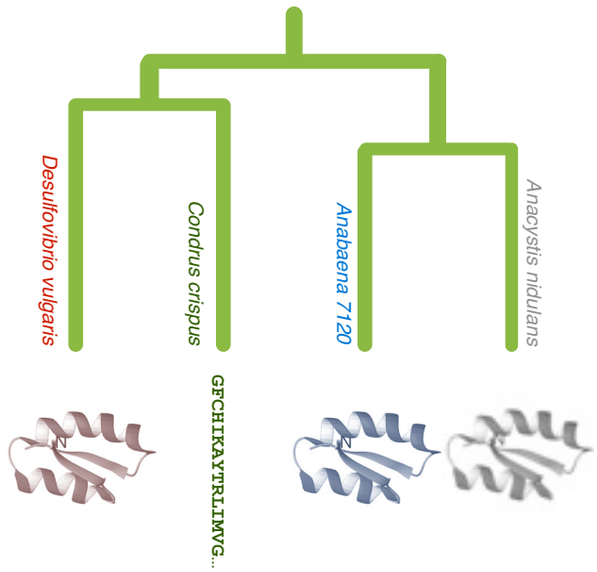


crystalized protein

2. Inheritance

model

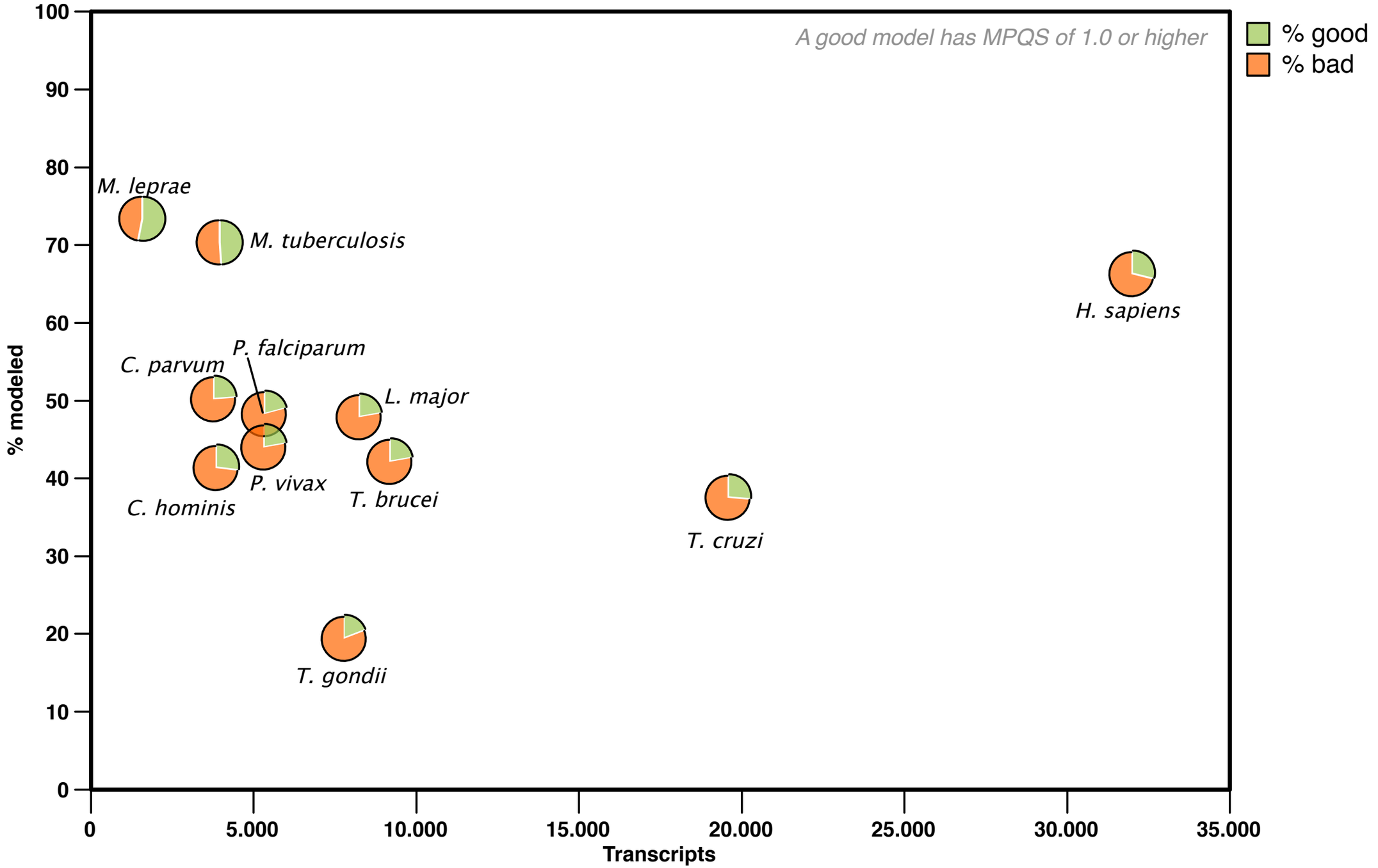
template



1. Modeling

Modeling Genomes

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



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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**

http://tropicaldisease.org

Creative Commons (no viral!)

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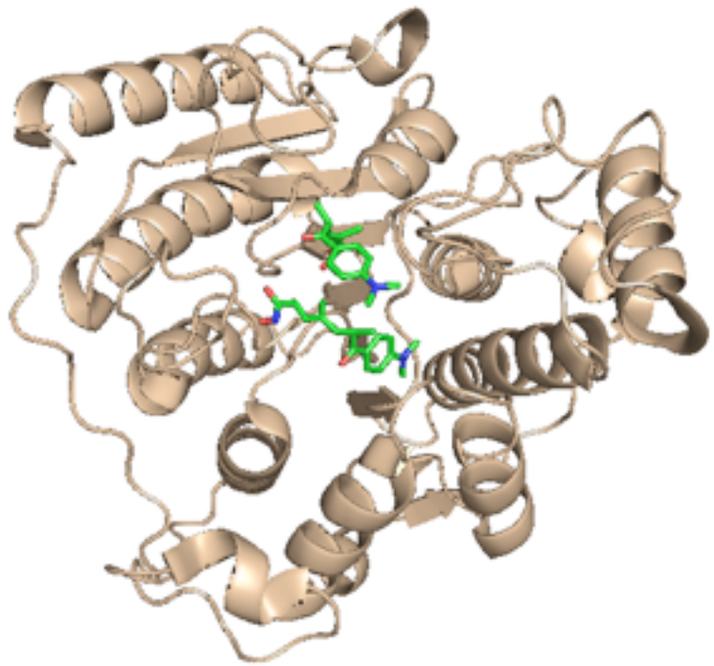
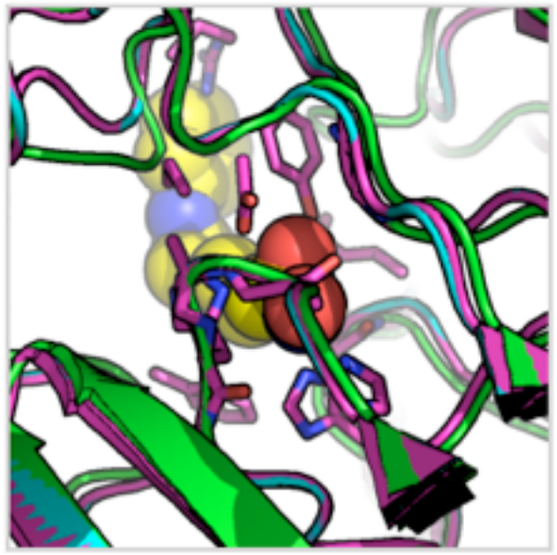
L. major Histone deacetylase 2 + Vorinostat

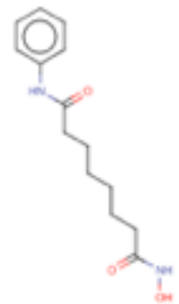
Template 1t64A a human HDAC8 protein.



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.

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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*

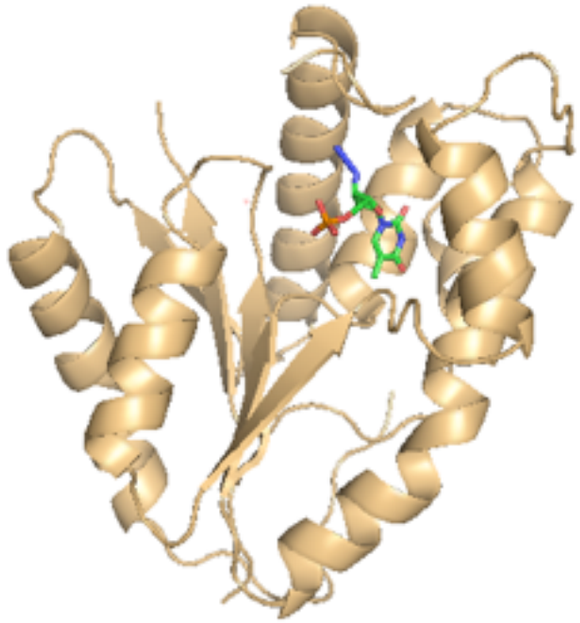
Departments of *Parasite Biochemistry and Cell Biology, ‡Medicinal Chemistry, and §Natural Products Drug Discovery, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

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

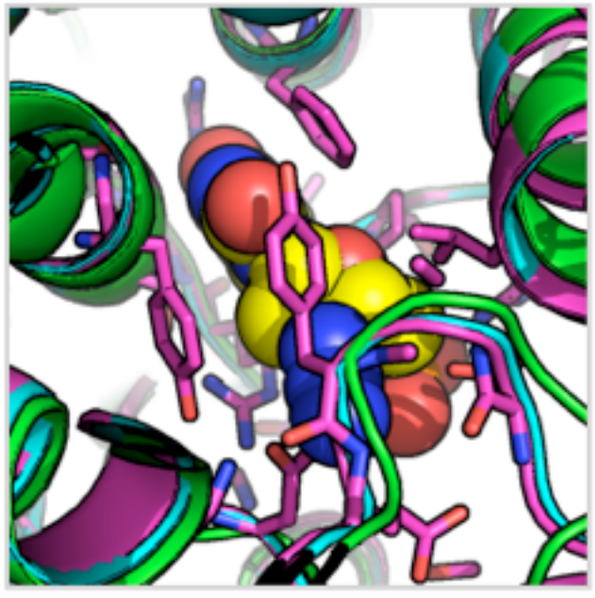
Antimalarial and Antileishmanial Activities of Aroyl-Pyrrolyl-Hydroxyamides, a New Class of Histone Deacetylase Inhibitors

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

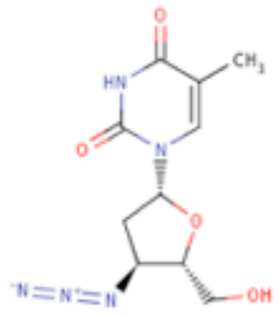


DB00495 Zidovudine

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.

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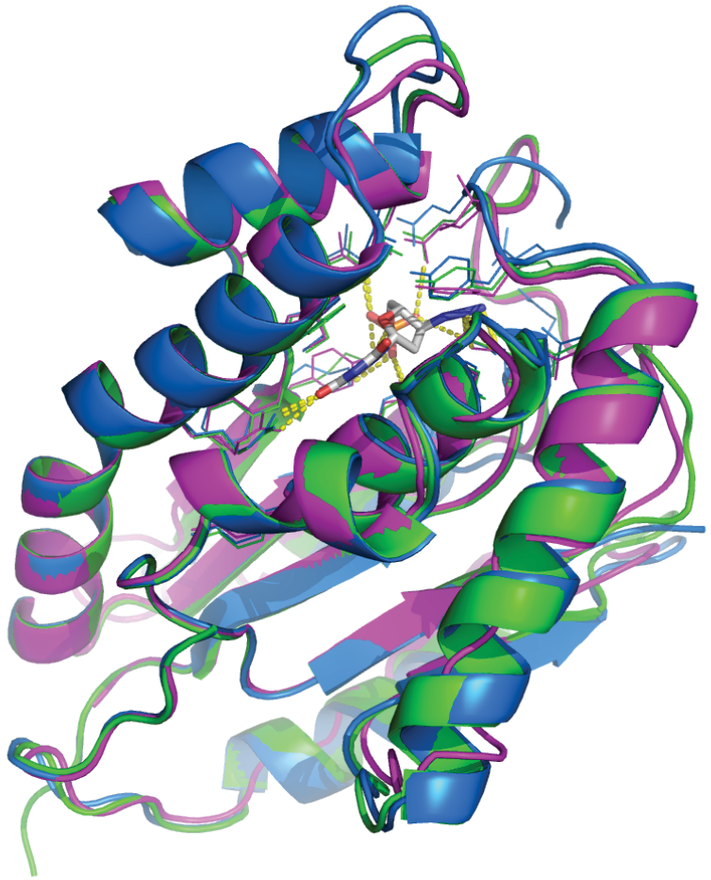
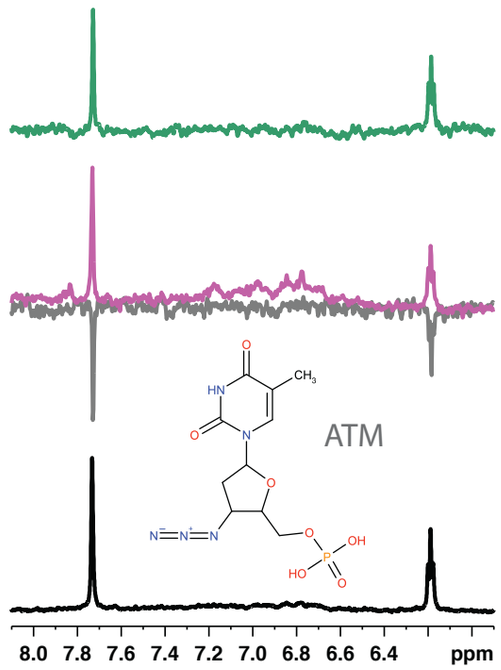
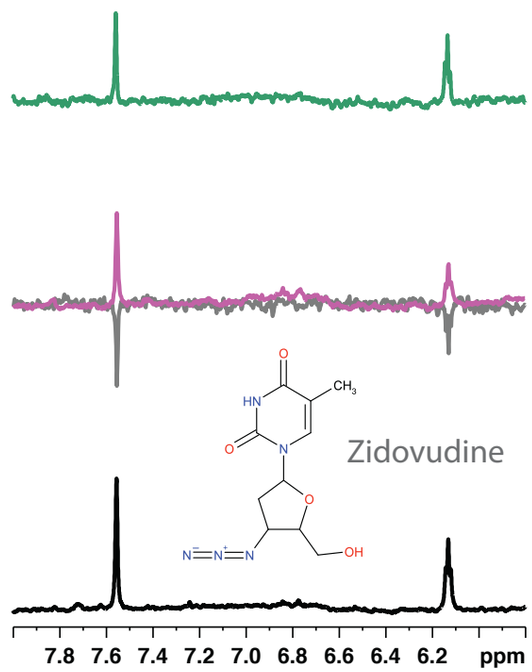
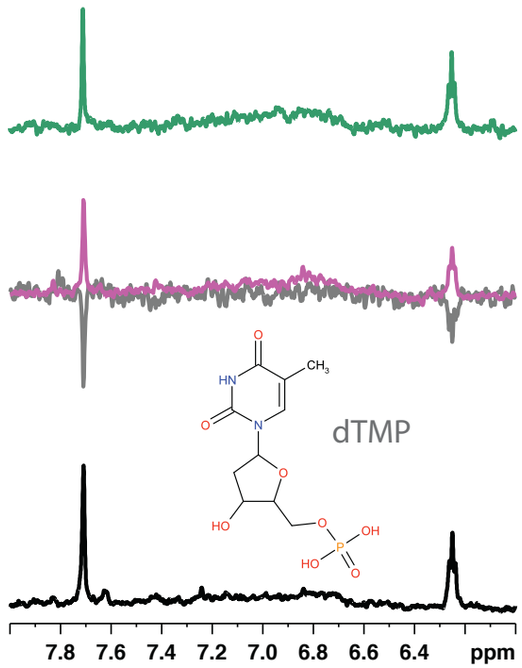
P. falciparum thymidylate kinase + zidovudine

NMR Water-LOGSY and STD experiments









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

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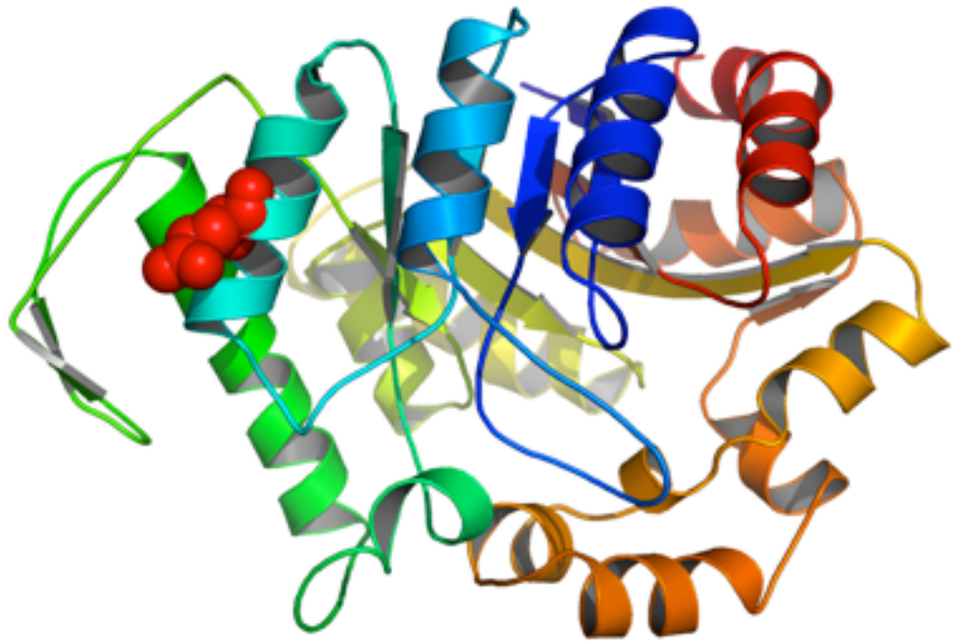
Impact of *fgd1* and *ddn* Diversity in *Mycobacterium tuberculosis* Complex on In Vitro Susceptibility to PA-824

Feuerriegel, S. et al. (2011). Antimicrobial Agents and Chemotherapy, 55(12), 5718–5722



Mutation	Buriedness	Residue rigidity	Neighborhood rigidity	Volume change	Charge change	Polarity change	Mutation likelihood	Phylogenetic entropy	Helix/turn breaker	Binding site proximity
Gln88Glu	25.7	−1.6	−1.2	+5.4	0 → −	2 → 2	+2 (No)	−0.14	NA	Yes
Gly145Ala	31.9	−0.4	−0.5	+28.5	0 → 0	1 → 1	0 (No)	−0.28	NA	No
Met208Ile	5.1	+2.1	+0.9	+3.8	0 → 0	0 → 0	+1 (Yes)	−0.36	NA	No
Lys270Met	55.3	+1.5	+1.2	−5.6	+ → 0	2 → 0	−1 (No)	−0.21	NA	No
Lys296Glu	28.0	+1.0	+0.9	−30.2	+ → −	2 → 2	+1 (No)	−0.14	NA	No

[a] Unfavorable structural properties of the mutations in question are doubly underlined, intermediate properties are underlined, and the remaining properties were favorable. NA, not applicable.

65 clinical strains and the PA-824-resistant control H37Rv-T3

TDI's kernel

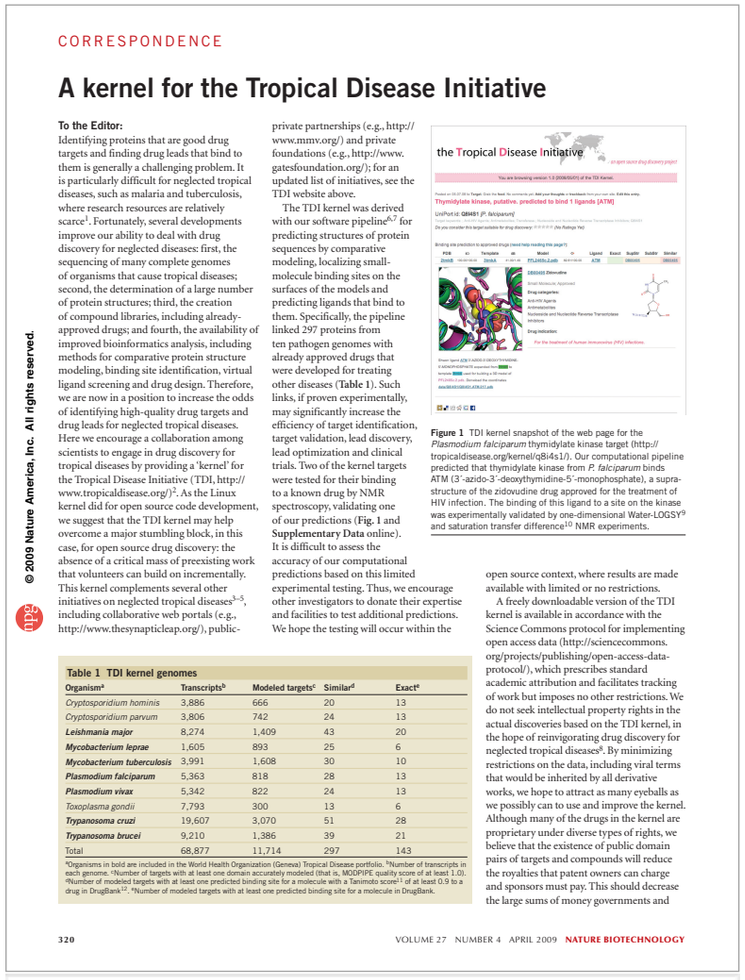
http://tropicaldisease.org/kernel

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/q8h4s1/). 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 Orti[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*]

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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: Orti 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

Editor: Timothy G. Geary, McGill University, Canada

Received December 29, 2008; **Accepted** March 23, 2009; **Published** April 21, 2009

Funding: MAM-R acknowledges the support from a Spanish Ministerio de Educación y Ciencia grant (BIO2007/66670). AS acknowledges the support from the Sandler Family Supporting Foundation and the National Institutes of Health (R01 GM54762, U54 GM074945, P01 AI035707, and P01 GM71790). AP-L acknowledges the support from a Spanish Ministerio de Ciencia e Innovación grant (SAF2008-01845). RJC acknowledges the support from the Ramon y Cajal Program of the Spanish Ministerio de Educación y Ciencia. We are also grateful for computer hardware gifts to AS from Ron Conway, Mike Homer, Intel, IBM, Hewlett-Packard, and NetApp. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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

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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

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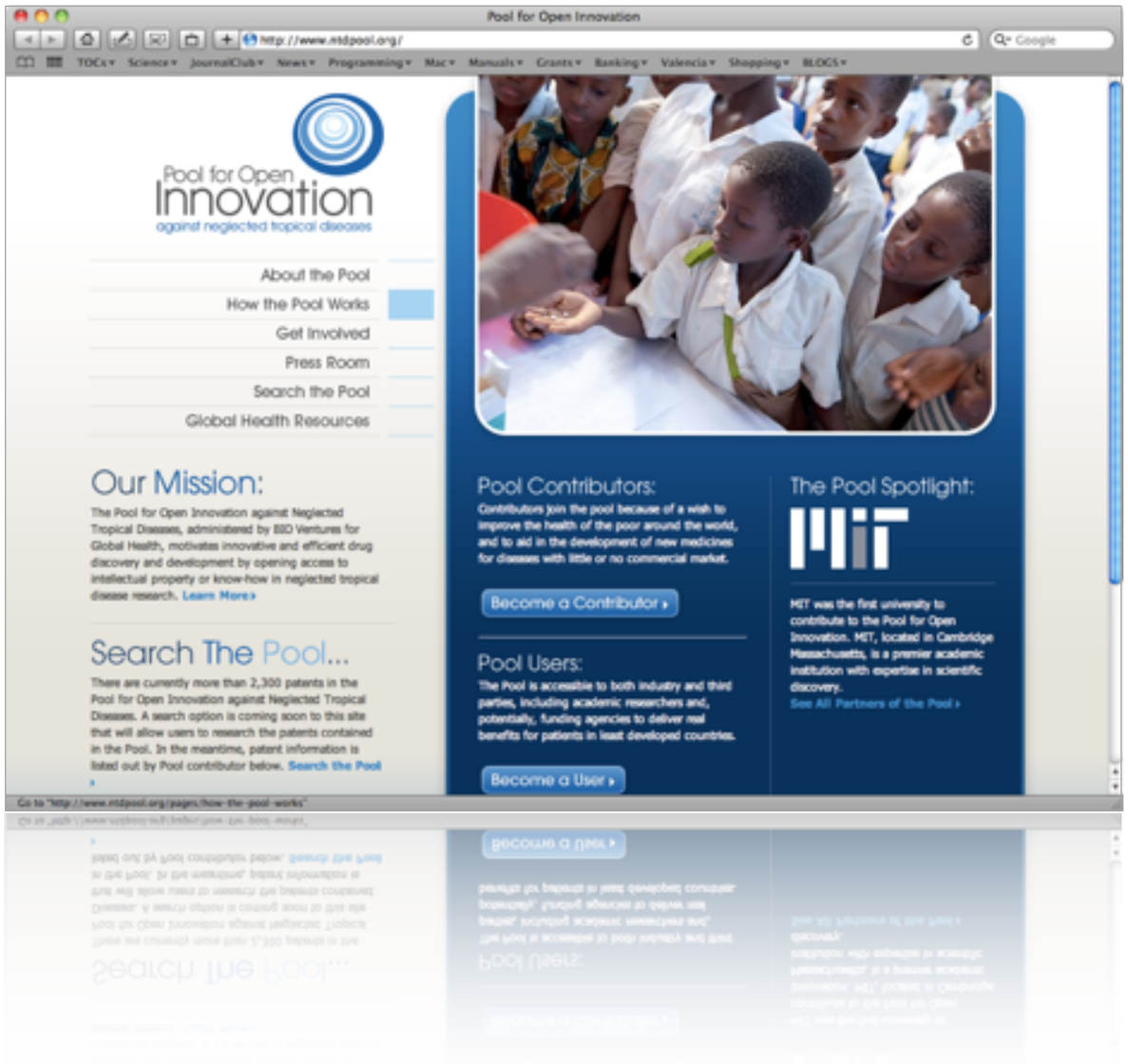
OpenPool/Lab GSK

http://ntdpool.org

Gamo *et al.* Nature (2010) vol. 465 (7296) pp. 305-10



Vol 465|20 May 2010|doi:10.1038/nature09107 nature

ARTICLES

Thousands of chemical starting points for antimalarial lead identification

Francisco-Javier Gamo[1], Laura M. Sanz[1], Jaume Vidal[1], Cristina de Cozar[1], Emilio Alvarez[1], Jose-Luis Lavandera[1], Dana E. Vanderwall[2], Darren V. S. Green[3], Vinod Kumar[4], Samiul Hasan[4], James R. Brown[4], Catherine E. Peishoff[5], Lon R. Cardon[6] & Jose F. Garcia-Bustos[1]

Malaria is a devastating infection caused by protozoa of the genus *Plasmodium*. Drug resistance is widespread, no new chemical class of antimalarials has been introduced into clinical practice since 1996 and there is a recent rise of parasite strains with reduced sensitivity to the newest drugs. We screened nearly 2 million compounds in GlaxoSmithKline's chemical library for inhibitors of *P. falciparum*, of which 13,533 were confirmed to inhibit parasite growth by at least 80% at 2 μM concentration. More than 8,000 also showed potent activity against the multidrug resistant strain Dd2. Most (82%) compounds originate from internal company projects and are new to the malaria community. Analyses using historic assay data suggest several novel mechanisms of antimalarial action, such as inhibition of protein kinases and host–pathogen interaction related targets. Chemical structures and associated data are hereby made public to encourage additional drug lead identification efforts and further research into this disease.

With approximately 243 million cases and 863,000 attributed deaths reported globally in 2009 (ref. 1), malaria is one of the most severe infectious diseases, primarily affecting the world's most disadvantaged populations. Of the four typically recognized *Plasmodium* species causing disease in humans, *Plasmodium falciparum* causes most mortality, mainly in children below the age of 5, and *Plasmodium vivax* most morbidity, additionally representing a reservoir of latent infection that hampers current control and future elimination efforts[2]. No new class of antimalarials has been introduced into clinical practice since 1996 (ref. 3), owing to the intrinsic difficulties in discovering and developing new antimicrobials, as well as a relative lack of public and private resource commitment towards antimalarial research. Today, the last class of widely efficacious drugs, the artemisinins, is being compromised by the rise of *P. falciparum* strains with reduced clinical response to artemisinin-containing drug combinations[4–6]. The genomics revolution has not yet led to new antimalarial medicines and target-based lead discovery has produced disappointing results, generally for lack of whole-cell activity as documented for antibacterials[7]. To secure that property in all chemical starting points for new antimalarial leads, we have tested the approximately 2 million-compound library used for high throughput screening at GlaxoSmithKline (GSK) for inhibitors of *P. falciparum*'s intraerythrocytic cycle, the *Plasmodium* species causing the highest mortality and the parasite growth phase responsible for disease symptoms as well as being amenable to *in vitro* culture. Here we describe 13,533 compounds confirmed to inhibit parasite growth by more than 80% at 2 μM concentration. Only 15% displayed some cytotoxicity in that they inhibited proliferation of the HepG2 human hepatoma cell line by more than 50% at 10 μM. All of these proven plasmodial inhibitors, of which 82% were previously proprietary and thus unknown to the general research community, are hereby made public to accelerate the pace of drug development for malaria.

Tres Cantos antimalarial compound set (TCAMS)

The 1,986,056 compounds present in GSK's screening collection in January 2009 were tested for inhibition of *P. falciparum* 3D7 at 2 μM under *in vitro* conditions described in Methods. 19,451 primary hits inhibiting parasite growth by more than 80% were obtained. Fresh samples of these primary hits were tested in two independent experiments and compounds displaying 80% or higher inhibition of parasite growth in at least two of the three assay runs were considered confirmed hits. 13,533 compounds were identified using this protocol (confirmation rate > 70%). We did not detect any compounds in this set as non-specific inhibitors of the biochemical readout system by testing directly for inhibition of lactate dehydrogenase (LDH) in *P. falciparum* extracts (Methods). Evidence of cytotoxicity against human hepatoma HepG2 cells (a widely used *in vitro* marker for liver toxicity[8]), or interference with the luciferase reporter system used in the cytotoxicity assay (Methods), was observed in just 1,982 of the compounds when tested at 10 μM. This relative lack of non-specific cell toxicity is probably due in part to the low (2 μM) primary screening concentration used[9]. Estimation of the concentrations producing 50% inhibition of *P. falciparum* growth (XC_{50}, see Methods) indicated that most compounds are sub-micromolar inhibitors. The full compound set (TCAMS) and data table (Supplementary Table 1 and available at http://www.ebi.ac.uk/chemblntd) contains 13,533 compound entries. We have detected 139 of these as variations in salt form or stereochemistry of 68 parent structures, which make good internal controls for the biological assay data. They appear as different compounds with the same structure. When the stereochemistry is resolved it shows in the SMILES structural code in Supplementary Table 1 and in the Chembl-NTD database (http://www.ebi.ac.uk/chemblntd).

Representatives from all but one class of clinically used antimalarials have been recovered in the screen, providing additional validation

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GeMoA

http://gemoa-era.net

TARGET-LIGAND

WP1

GSK
High-Throughput Screening
MedChem
Synthetic chemistry

CIPF
Protein-ligand binding prediction

WP4

EMBL
Functional assays
Heterologous expression
Protein purification
Protein crystallization

GSK
MedChem
Synthetic chemistry
Enzymatic assays

GENOME-WIDE

WP2

CIPF
Comparative structure prediction
Protein-protein network analysis
Protein-ligand network analysis
Genome-wide functional annotation

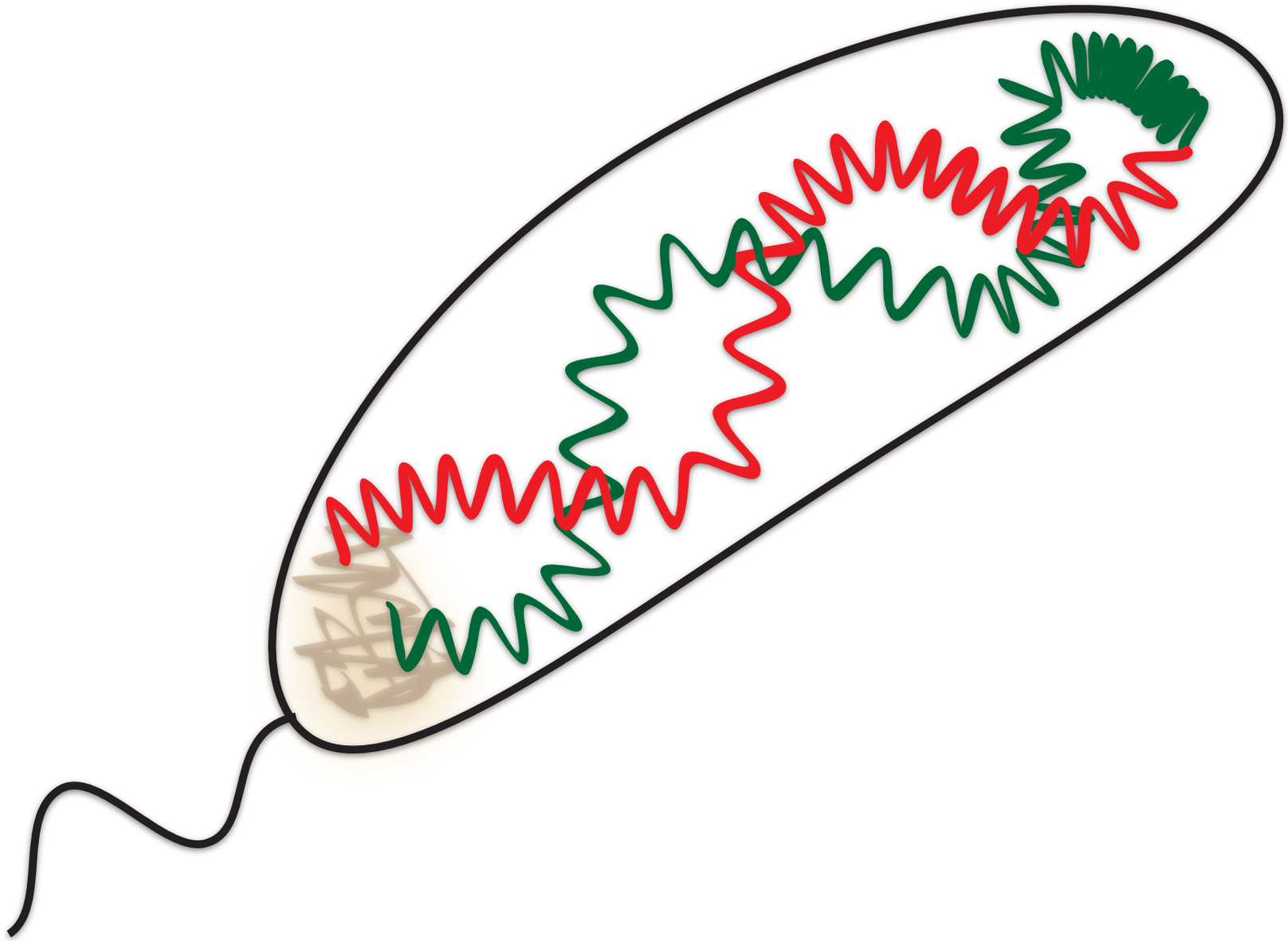
IPBS
Transcriptomics
Genotyping

WP3

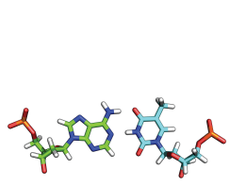
IPBS
Transcriptomics
Genotyping
Imaging

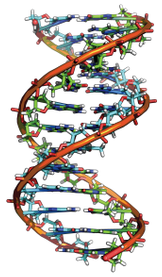
IP
Genomics
Mutant libraries
Genome sequencing
Imaging

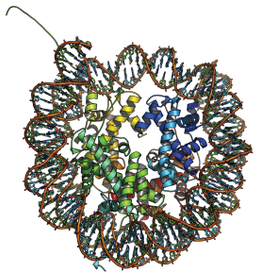
Caulobacter crescentus genome

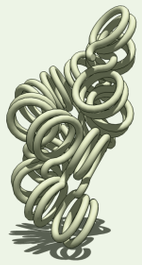


Knowledge



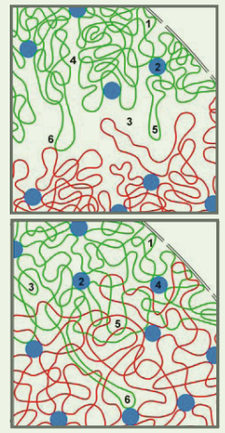


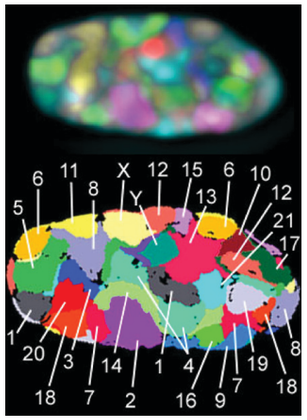




IDM

INM





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

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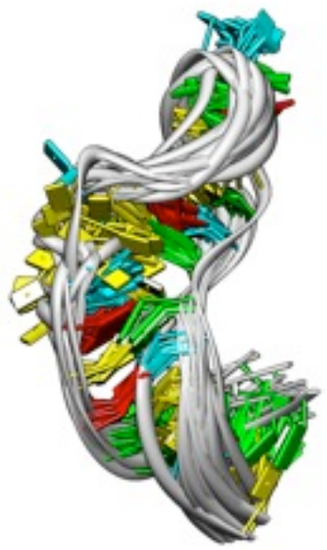
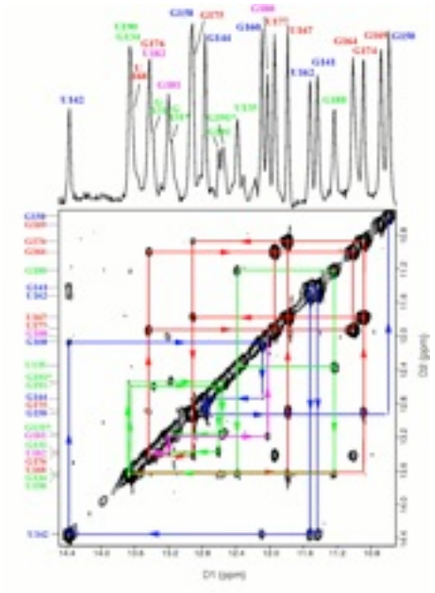
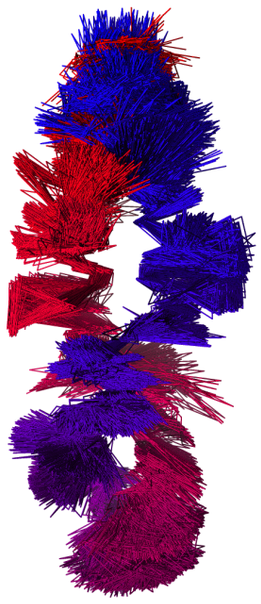
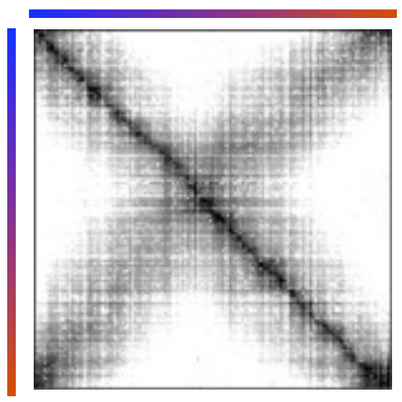




Biomolecular structure determination

2D-NOESY data





Chromosome structure determination

5C data

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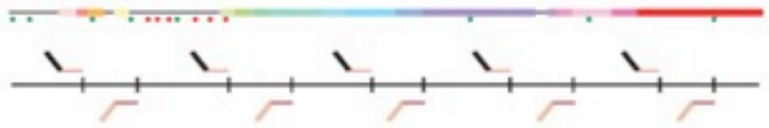
Experiments



Grow GM12878 and K562 cells

↓

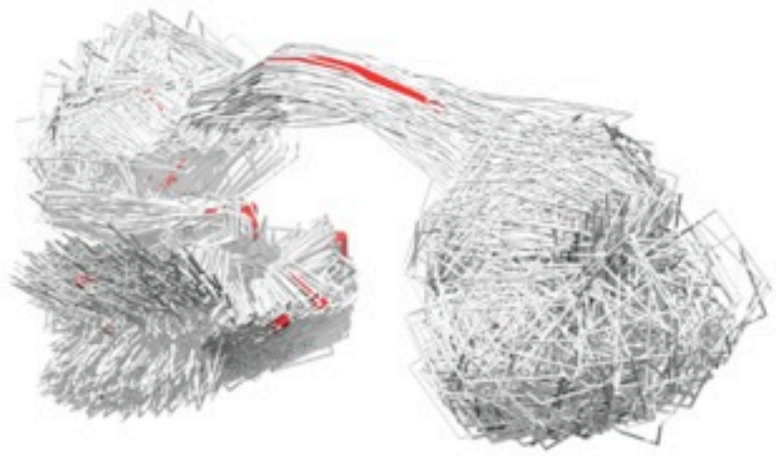
Perform 3C analysis

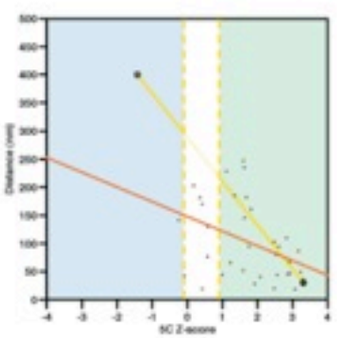
↓

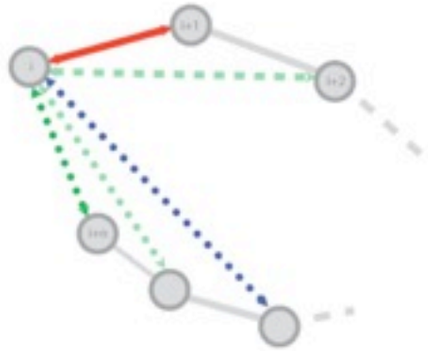
Perform 5C analysis with 30+25 primers

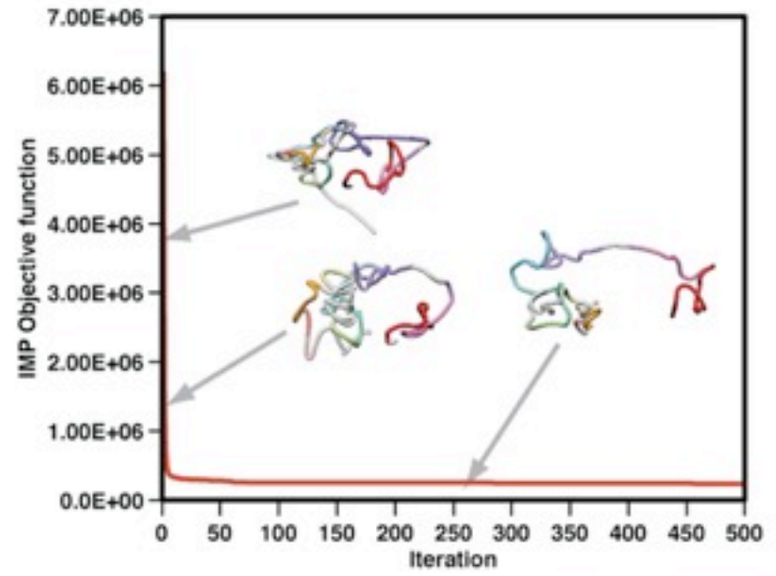
↓

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





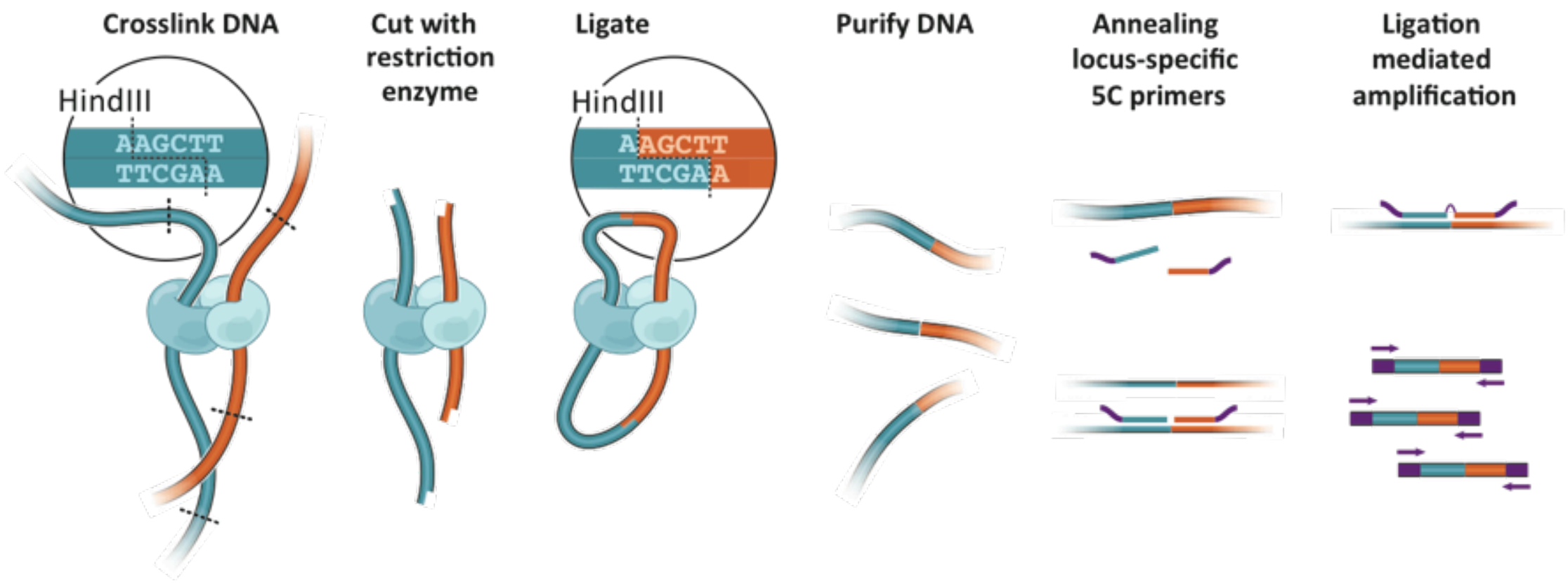




Computation

5C technology

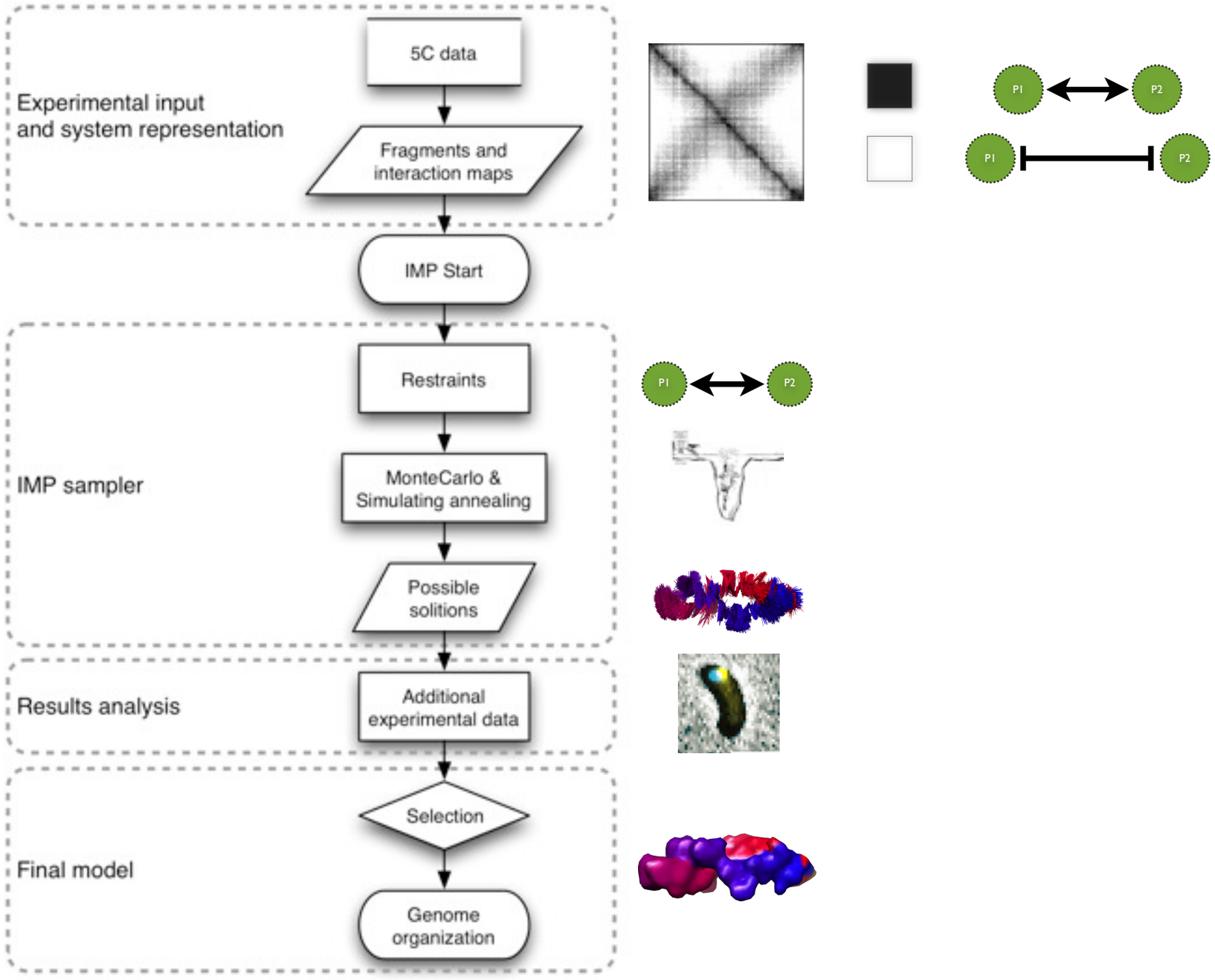
http://my5C.umassmed.edu



Dostie et al. Genome Res (2006) vol. 16 (10) pp. 1299-309

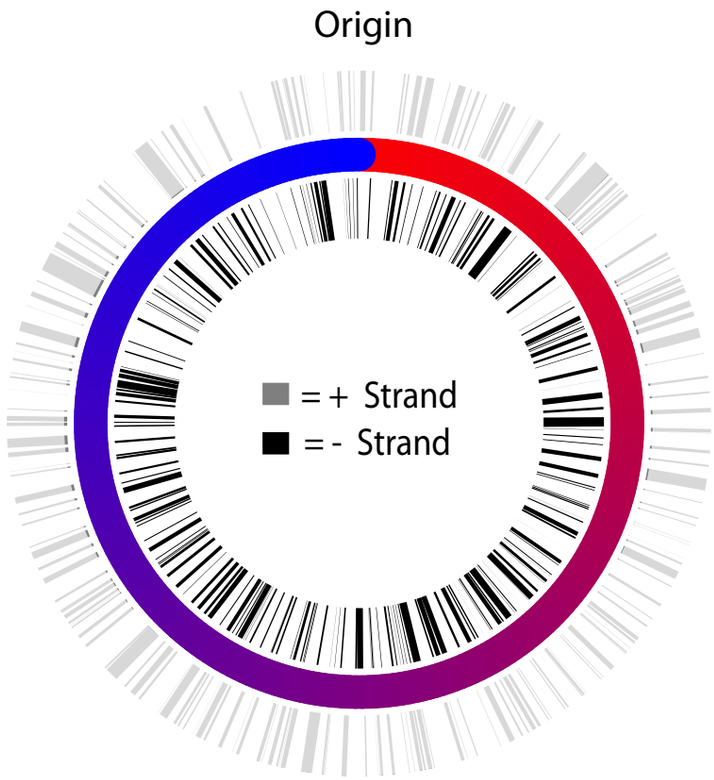
Integrative Modeling

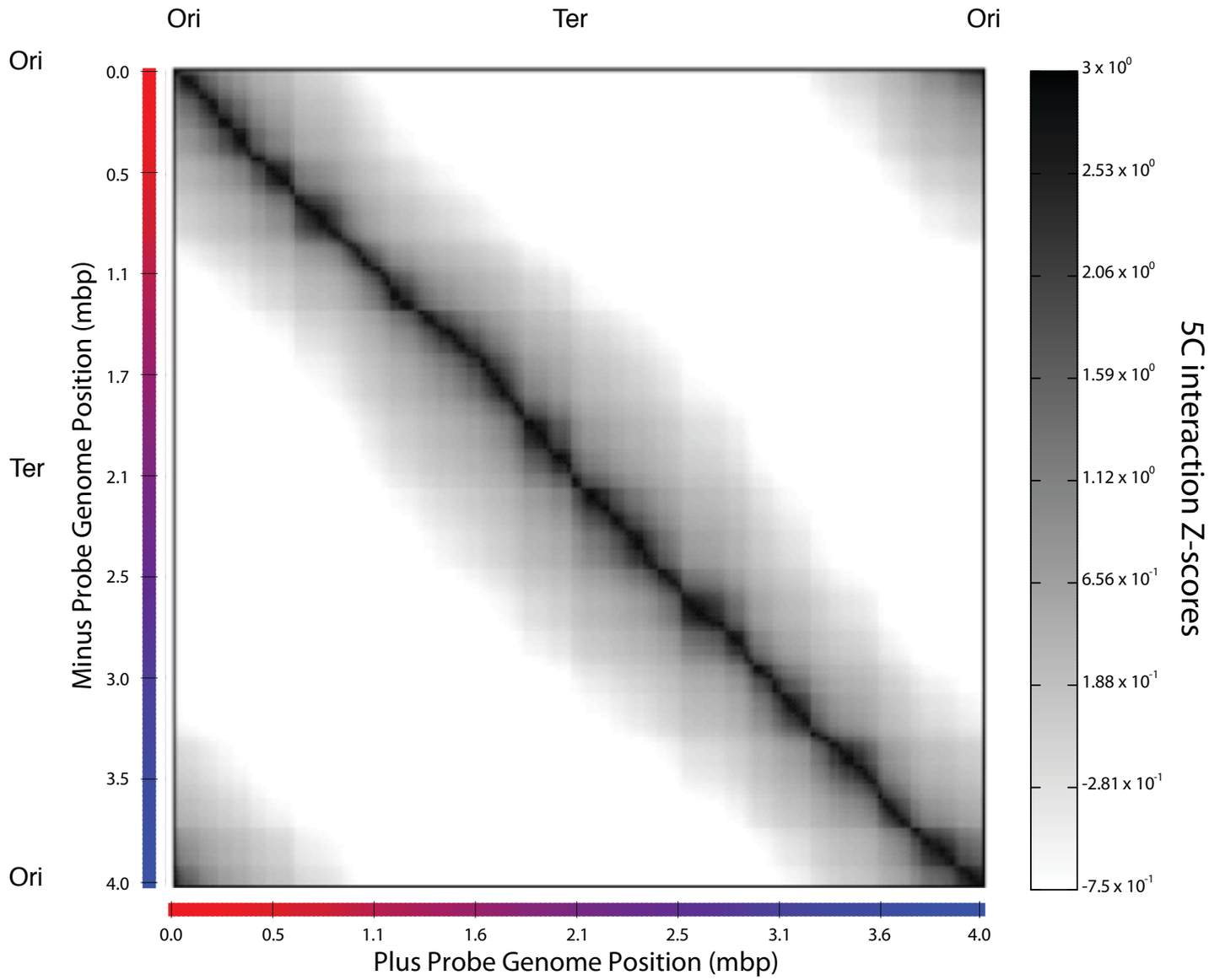
http://www.integrativemodeling.org



The 3D architecture of Caulobacter Crescentus

4,016,942 bp & 3,767 genes





169 5C primers on + strand

170 5C primers on – strand

28,730 chromatin interactions

~13Kb

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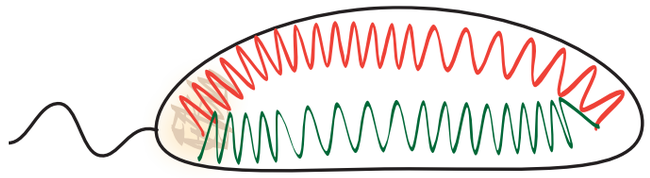
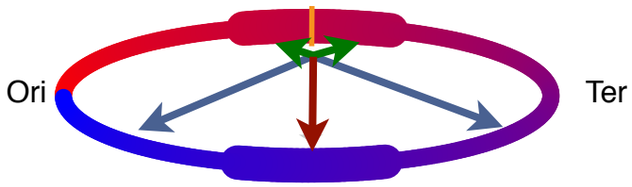
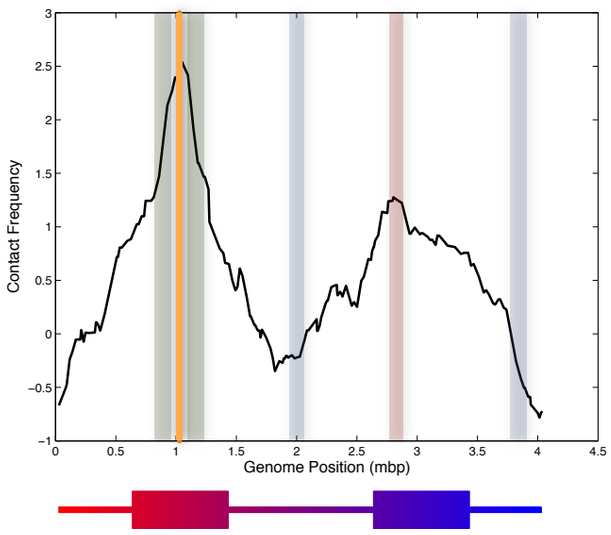
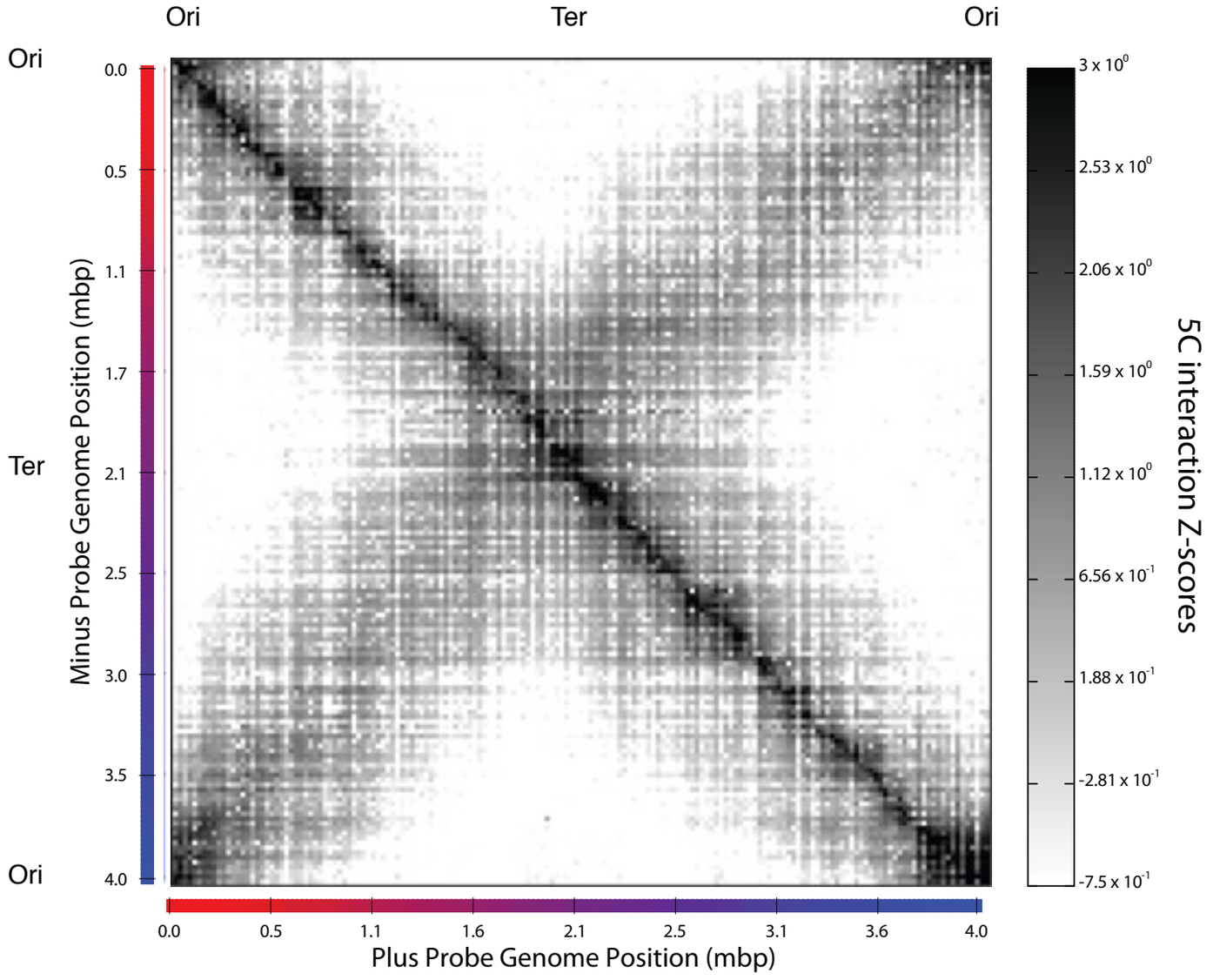
5C interaction matrix

ELLIPSOID for Caulobacter cresentus

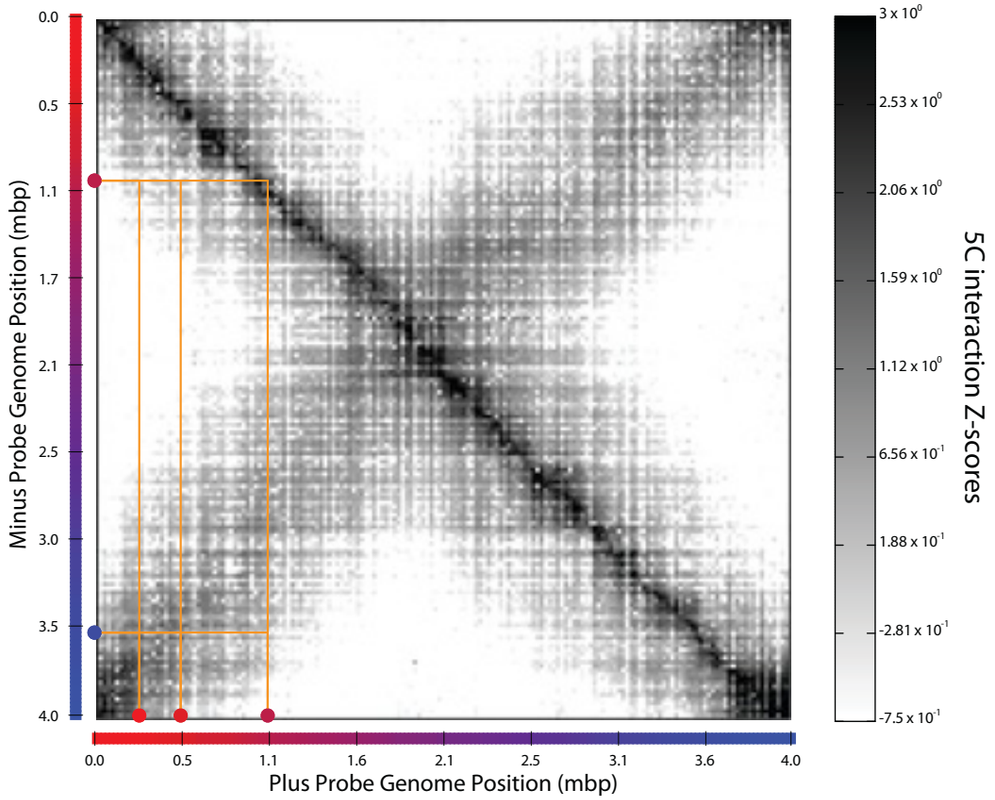




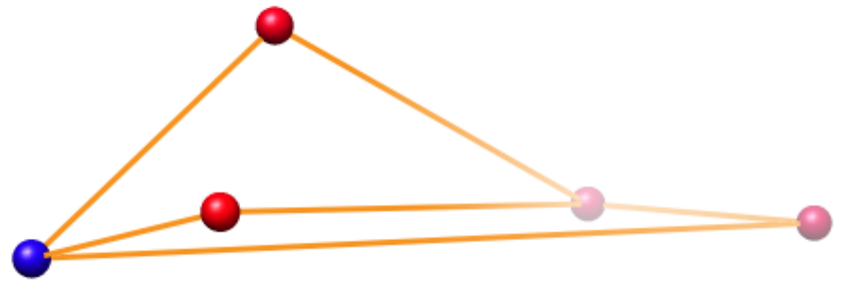


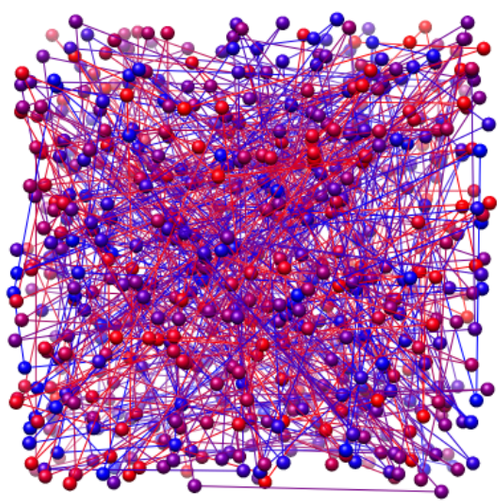


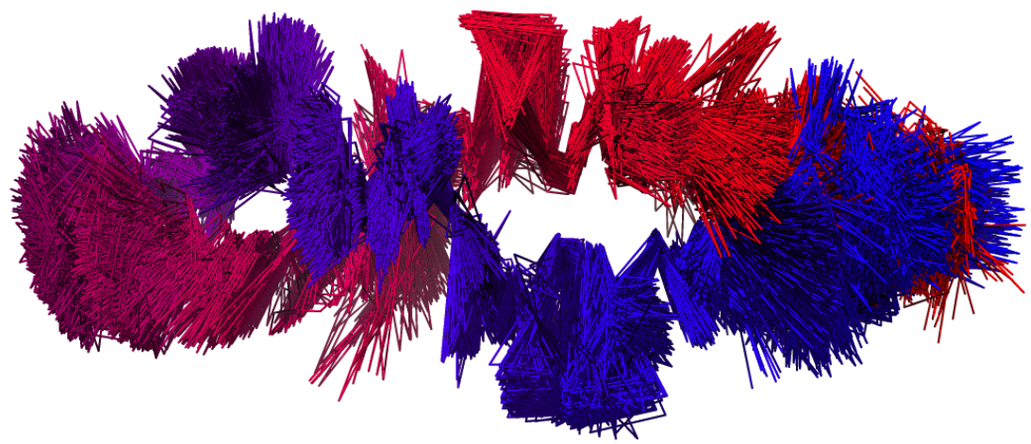
3D model building with the 5C + IMP approach



339 mers







Genome organization in Caulobacter crescentus

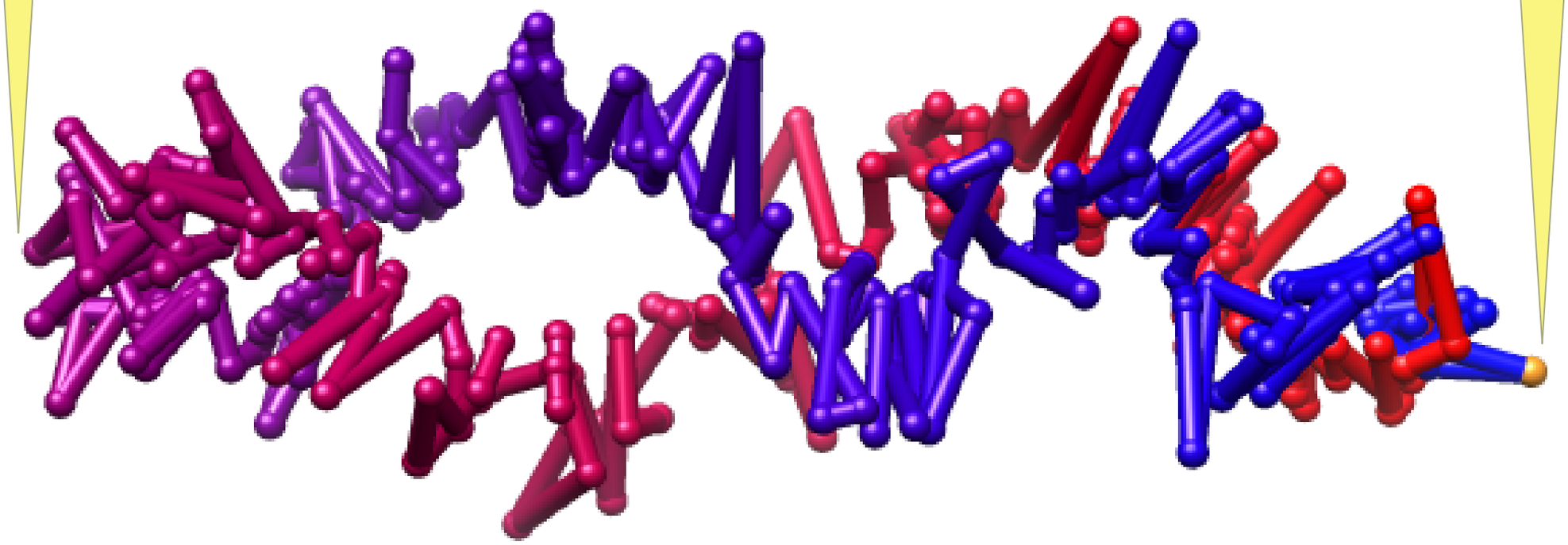
Arms are helical

dif site 47±17Kb from Ter

parS sites 25±17Kb from Ori

Resolution

Centromer-like



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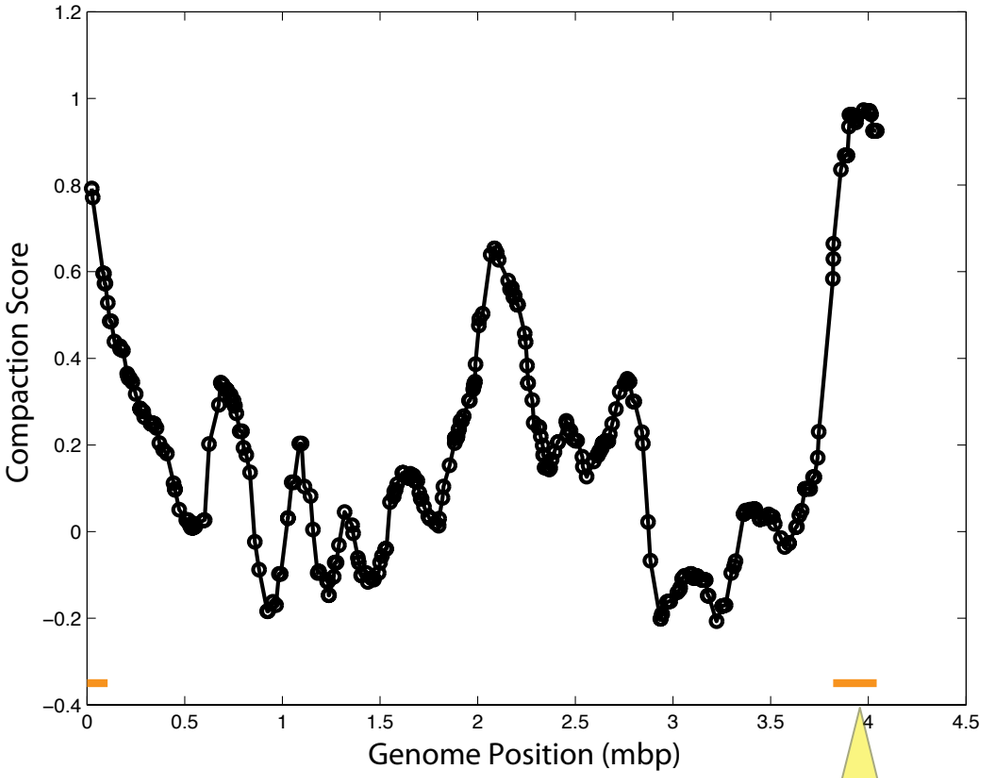
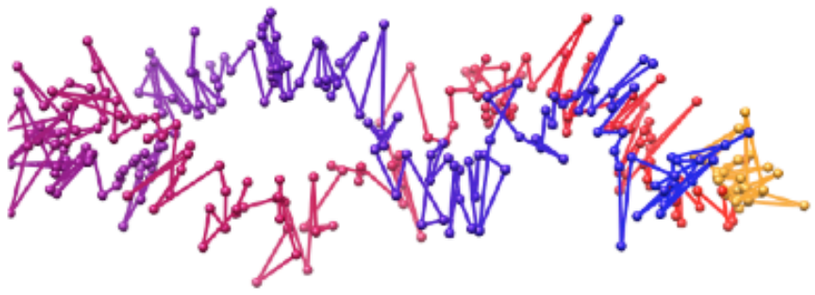
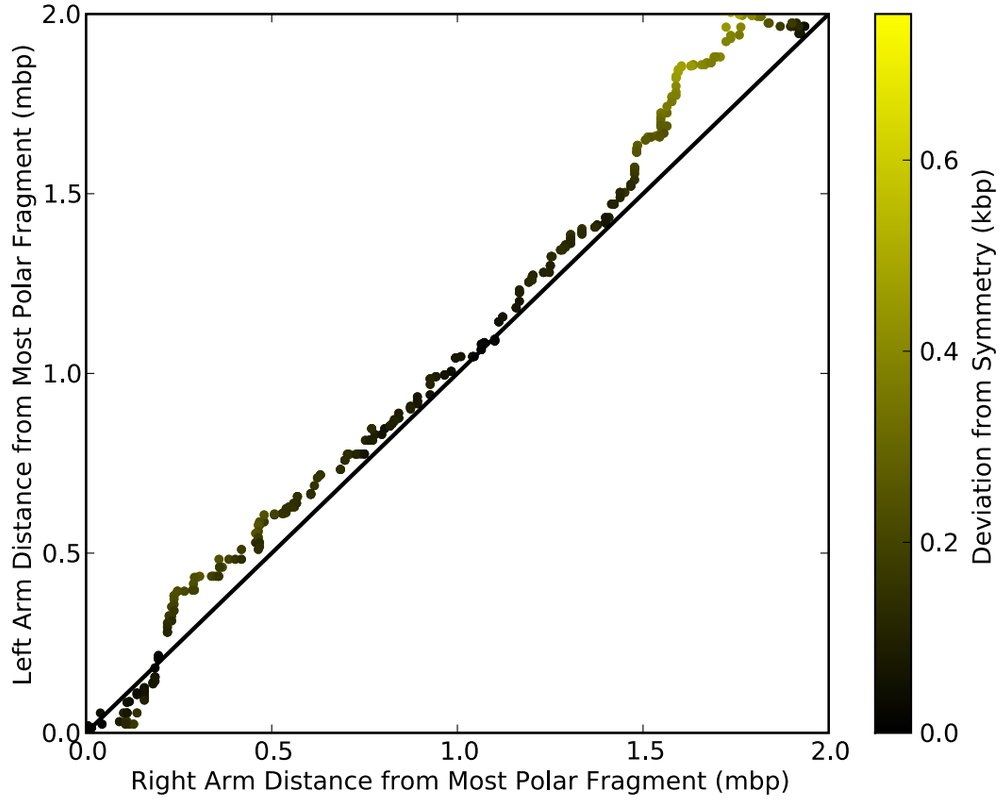
parS sites initiate compact chromatin domain

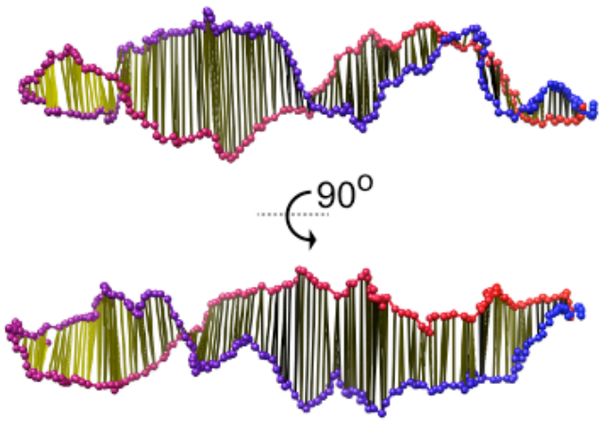


100-200Kb

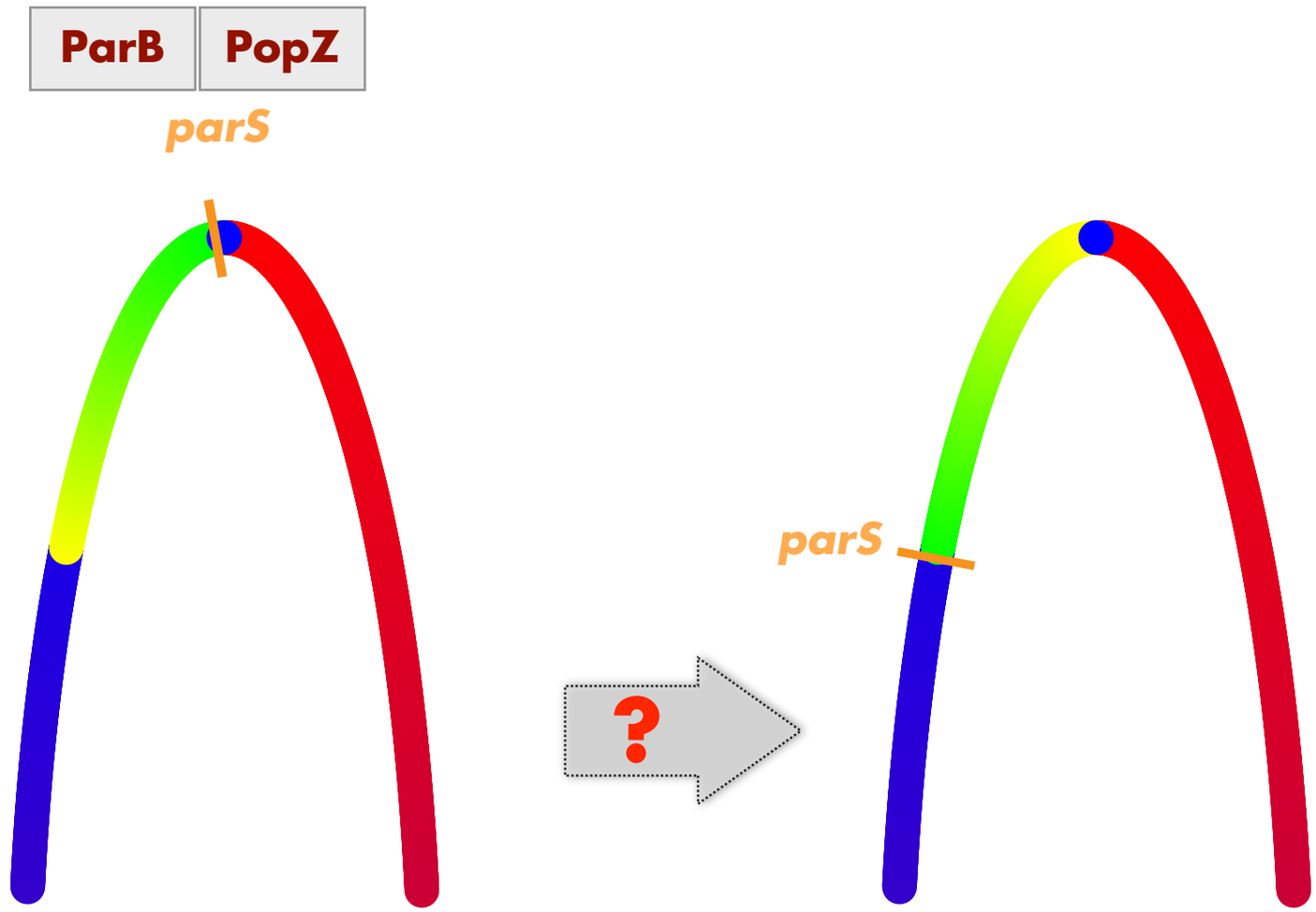


Chromosome arms are equidistant to the cell center





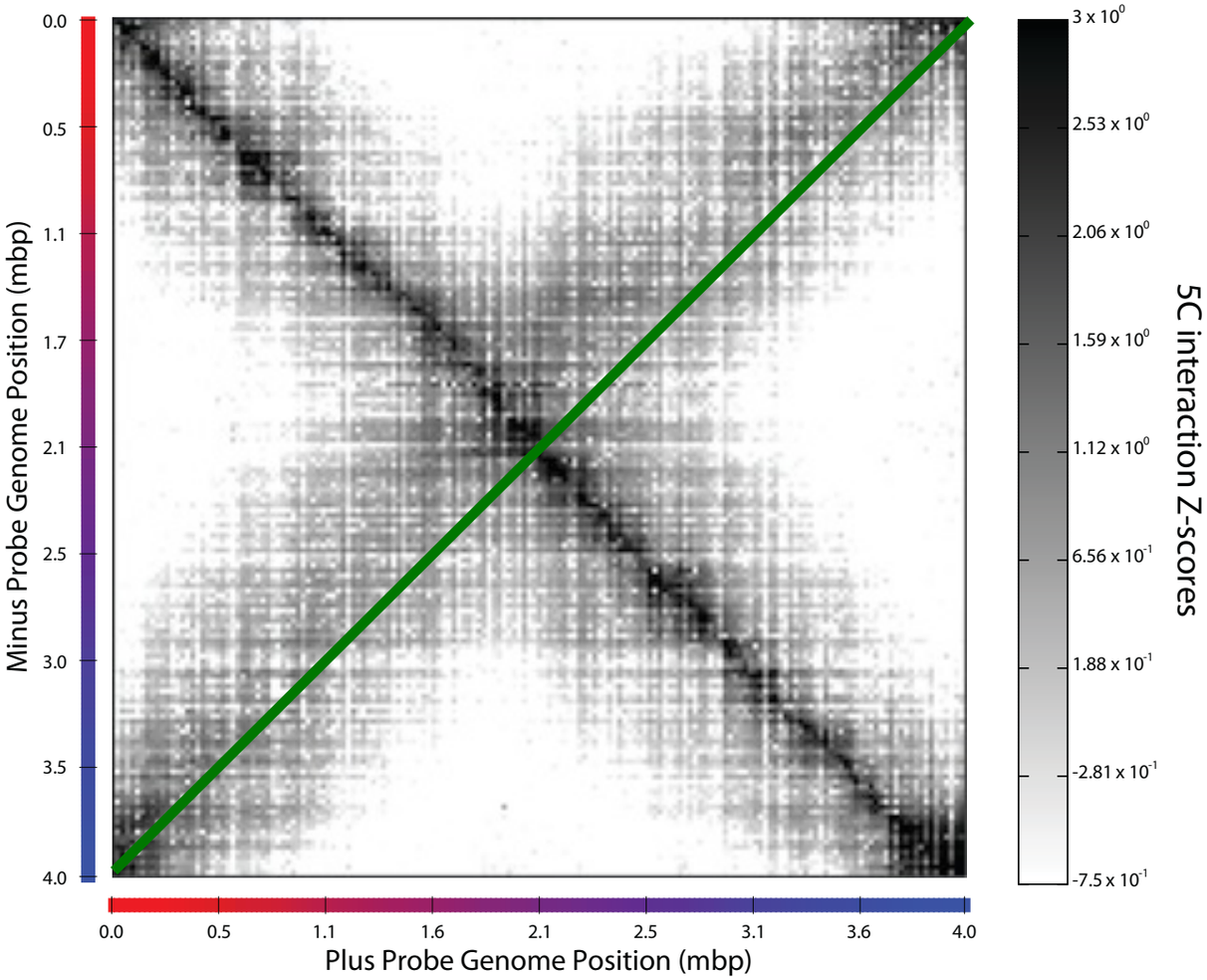
Moving the parS sites 400 Kb away from Ori

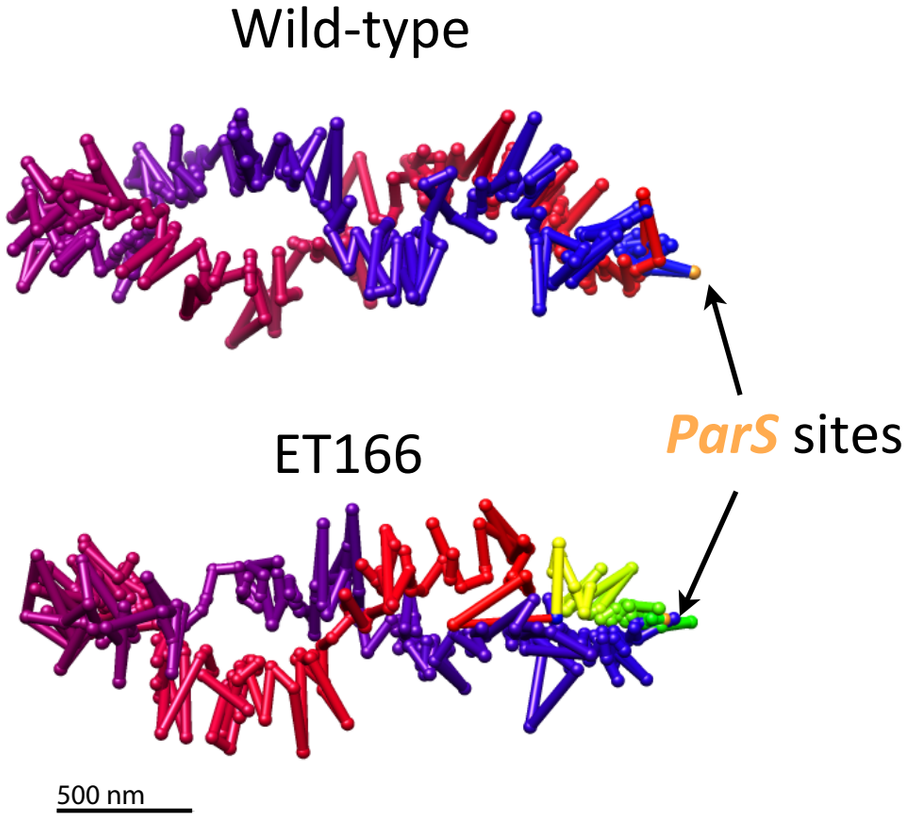


Wild-type

ET166

Moving the parS sites results in whole genome rotation!

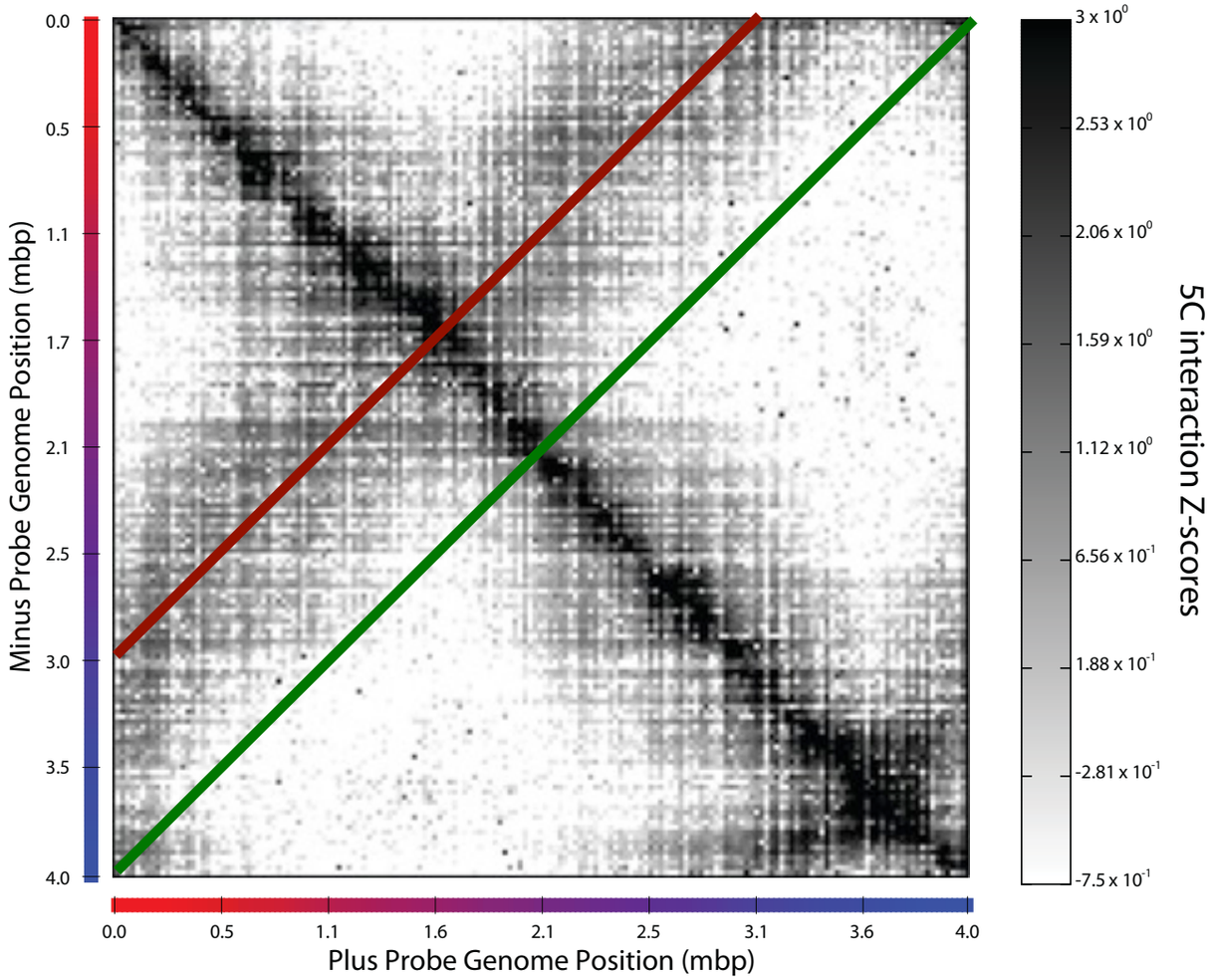


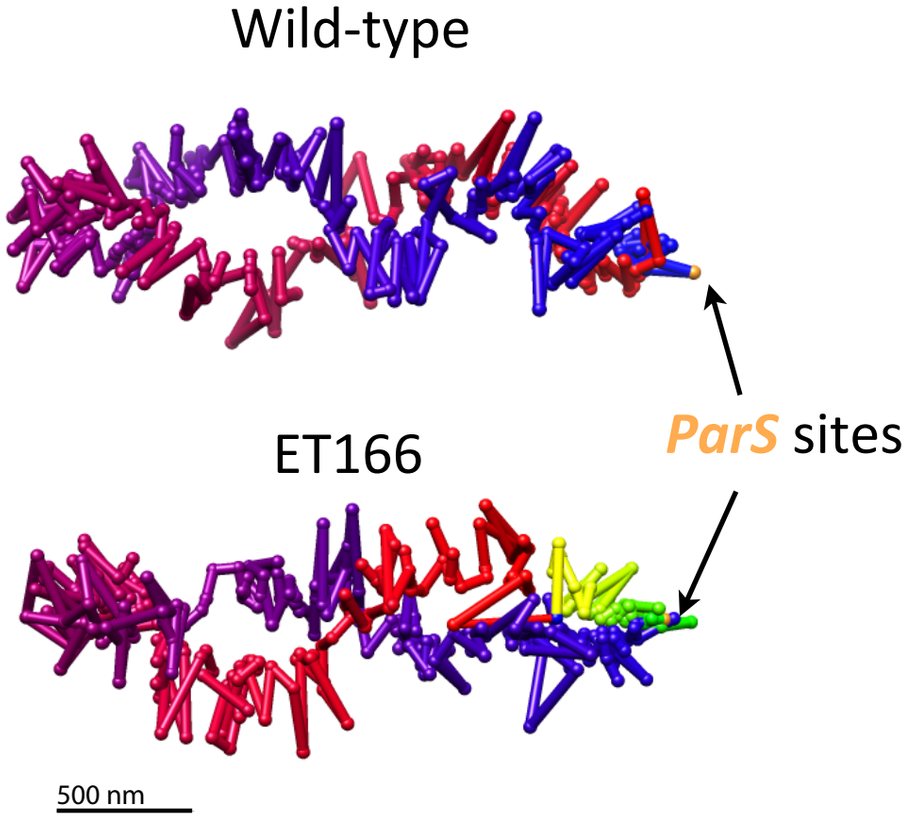


Arms are **STILL** helical

Structure & function PRESERVED!!!

Moving the parS sites results in whole genome rotation!



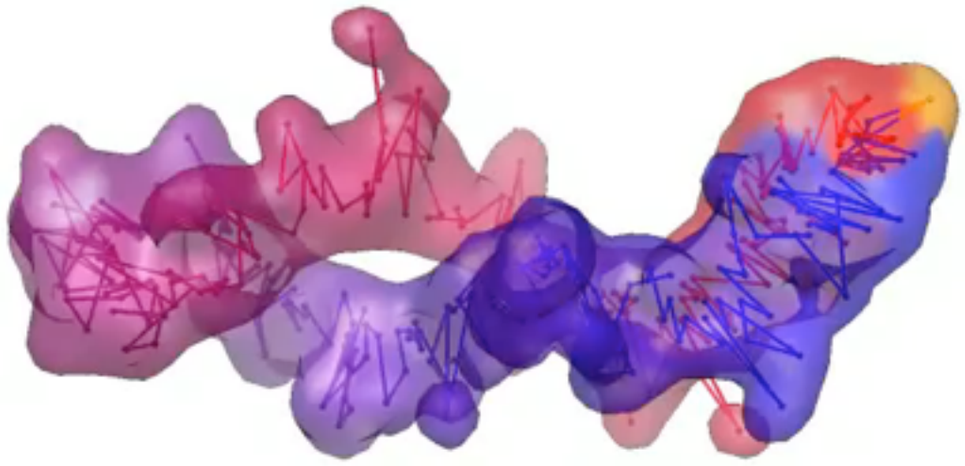


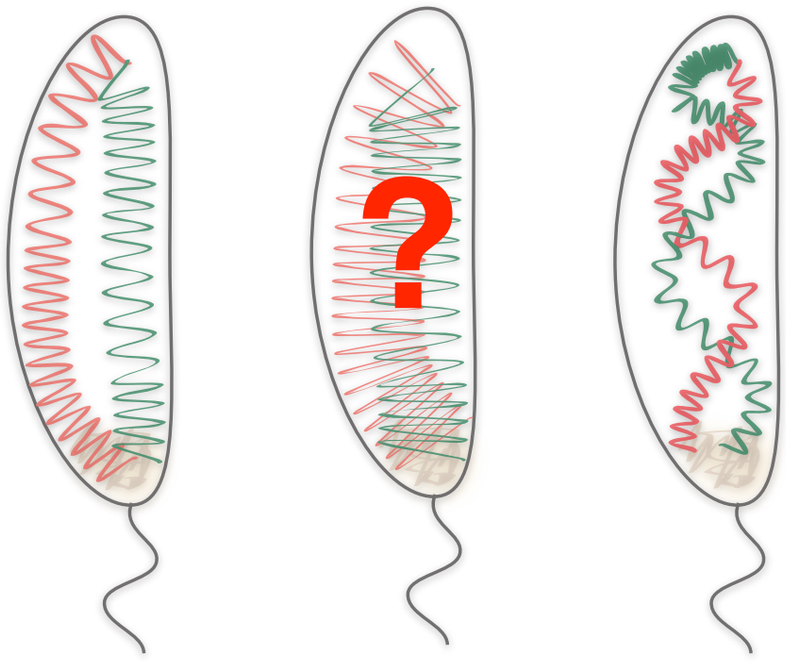
Arms are **STILL** helical

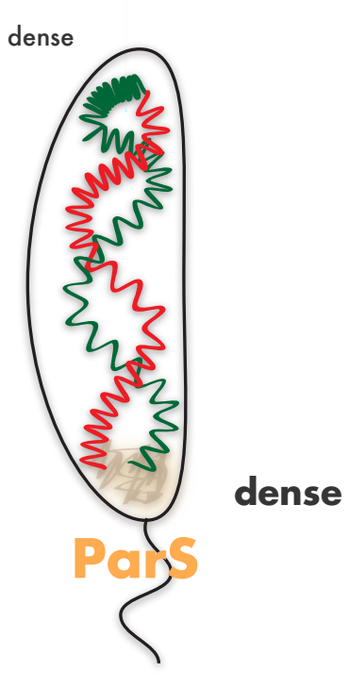
Structure & function PRESERVED!!!

Genome architecture in Caulobacter

M.A. Umbarger, et al. Molecular Cell (2011) 44:252–264







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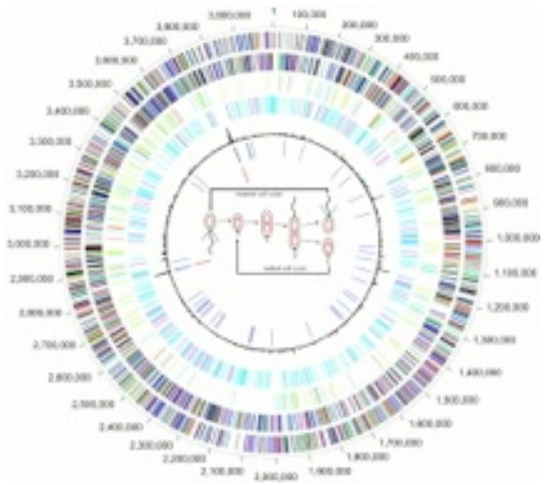
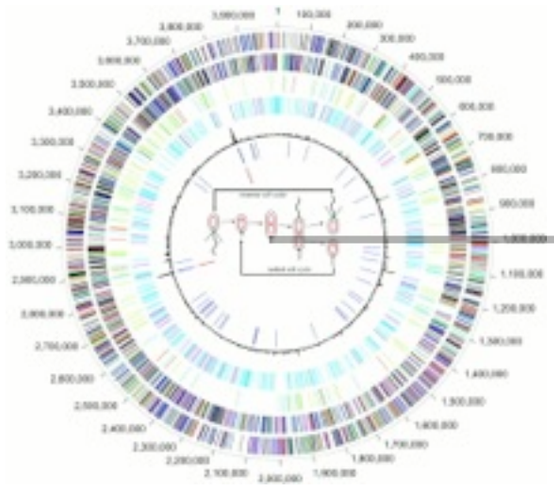
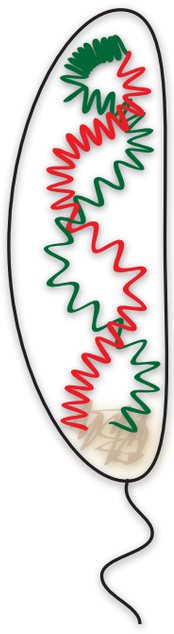
From Sequence to Function

D. Baù and M.A. Marti-Renom Chromosome Res (2011) 19:25-35.



Function!





Function!

Acknowledgments

COMPARATIVE MODELING
Andrej Sali (UCSF)
Narayanan Eswar (DuPont)
Ursula Pieper (UCSF)

NMR
Antonio Pineda-Lucena (CIPF)
Leticia Ortí
Rodrigo J. Carbajo

SNP Analysis
Stefan Niemann (RCB)
Claudio Koser (Cambridge)

Tropical Disease Initiative
Marc A. Marti-Renom (CNAG)
Stephen Maurer (UC Berkeley)
Arti Rai (Duke U)
Andrej Sali (UCSF)
Ginger Taylor (TSL)
Matthew Todd (U Sydney)

GeMoA
Marc A. Marti-Renom (CNAG)
Lluís Ballell (GSK)
Olivier Neyrolles (IPBS)
Matthias Wilmanns (EMBL)
Brigitte Cicquel (IP)

3D GENOMICS
George Church (Harvard)
Marc Umbarger (Harvard)
Lucy Shapiro (Stanford)
Job Dekker (UMASS)
Davide Baù (CNAG)

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