

EpiGenSys

Systems Biological Determination

of the



Epigenomic Structure Function Relation

Nucleosomal Association Changes

Intra/Inter Chromosomal Architecture

Transcriptional Structure Relationship

Simulations of Nucleosomal / Chromatin Fiber / Chromosome Architecture & Dyna

System Biological/Medical Result Integration via the GLOBE 3D Genome P

Tobias A. Knoch

Biophysical Genomics & Erasmus Computing Grid

Peter R. Cook, Karsten Rippe, Gernot Längst, Gero Wedemann, & Frank G. Grosveld

Sir William Dunn School of Pathology, Genome Organization & Function, NWFIII/Biochemistry, System Engeneering and Information Management, Cell Biology & Genetics - Clinical Genetics & Virology

University of Oxford, BioQuant Centre / German Cancer Research Centre, University of Regensburg, University of Applied Sciences Stralsund, Erasmus Medical Centre

EpiGenSys

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Towards a Holistic understanding of Genore Towards a Holistic under the second of the ppe, Gernot Längst, Gero Wedemann, & Frank G. Grosveld ology, Genome Organization & Function, NWFIII/Biochemistry, System Management, Cell Biology & Genetics - Clinical Genetics & Virology

of Oxford, BioQuant Centre / German Cancer Research Centre, y of Regensburg, University of Applied Sciences Stralsund, Erasmus Medical Centre

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Dynamic and Hierarchical Genome Organization

The different organization levels of genomes bridge several orders of magnitude concerning space and time. How all of these organization levels connect to processes like gene regulation, replication, embryogeneses, or cancer development is still unclear?



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Complexity of e.g. Cytogenetic Diagnostics & Treatment

The process of cytogenetic analysis requires proper patient and sample analysis

as well as a comprehensive evaluation of the results.







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Systems Biological/Medical Determination of the Epigenomic Structure-Function Relation in: i) the Beta-Globin locus, ii) the Immuno Globin loci, iii) the SAMD4 region, and iv) the Prader-Willi / Angelmann Syndrom region, in mouse and human active and inactive cell states and their global context.



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Work Together and Communication in EpiGenSys

The work packages are implemented in such a way that they utilize the established expertise of individual partners (each with their own established network of contacts) while providing maximum benefit to the groups. Maximum output is guarantied by our virtual laboratory communication management.

WP1:	Nucleosomal association changes (Längst, Rippe, Wedemann, Knoch/Grosveld; T1-T5)
WP2	Intra/inter chromosomal architecture (Grosveld/Knoch, Cook, Rippe, Längst; T1-T3)
WP3	Transcription structure relationship (Cook, Grosveld/Knoch, Längst; T1-T4)
WP4	Simulations of nucleosomal, chromatin fiber and chromosome architecture
	and their dynamics (Wedemann, Knoch/Grosveld, Rippe; T1-T3)
WP5	System biological result integration via the GLOBE 3D Genome Platform

(Knoch/Grosveld, Cook, Rippe, Längst, Wedemann; **T1-T5**):

- 1. Two major meetings per year where all participants meet:
 - * The first meeting took place in Den Haag from 7th to 8th July 2010.
 - ***** The second meeting wass held in Regensburg from 6th to 8th April 2011.
- 2. A monthly online conference of lab heads according to theme.
- 3. Weekly conferences of the work force related to the specific tasks
- 4. Regular work meetings in participant labs with several exchanges.
- 5. Use of a web-based communication platforms with project database and forum (see WP5),



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- **WP1:**
- **WP2**
- **WP3**
- **WP4**
- **WP5**

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M&D Timeplan in EpiGenSys

The time plane according to the work packages is currently on track.



WP1

Milestone	es and deliverat	oles:
WP1-1	months 6	Isolation of nucleosomal DNA by <i>in situ</i> MNase digestions; differential MNase digestion.
WP1-2	months 12	Sequencing analysis of nucleosomal positions and epigenetic modifications; annotation of DNA sequences obtained.
WP1-3	months 24	Effects of 'knocked-down/in' remodellers on nucleosomal position
WP1-4 WP1-5	months 27 months 30	Determination of nuclear localization of nucleosomal DNAs by FISH. Bioinformatic analysis of nucleosomal sequences and epigenetic modifications.

WP2

Milestones and deliverables	:
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NP2_1	monthe 9	Availability of interaction mans obtained by deen sequencing
VVI <u>Z</u> -1	monuna a	Availability of interaction maps obtained by deep sequencing.
N/P2_2	months 18	Microscopic investigation of chromosome architecture
VVI Z-Z	monuns ro	where sugaron of chromosome architecture.
MD2 2	months 24	Theoretical determination of 2D obromosome prohitecture
VVPZ-J	monuns 24	medical determination of 5D chromosome architecture.
	months 26	Defined eveterne biological model of obvergence to alogy
VVPZ-4	monuns 36	Refined systems biological model of chromosome topology.

WP3

Milestone	es and deliverat	oles:
WP3-1	months 6	Use of 3C established; 4C and expression arrays designed.
WP3-3	months 18	Final 4C and expression results obtained.
WP3-4	months 24	Final results obtained for all egions; confirm selected 4C contacts using DNA FISH.
WP3-5	months 30	Confirm transcriptional activity of selected contacts by qRT PCR and RNA FISH.

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Milestone	s and deliverab	les:
WP4-1	months 6	Implement a nucleosome chain model for variation of local nucleosome geometry, the nucleosomal interactions potential, the linker DNA length.
WP4-2	months 12	Simulations of fibers with ~500-1000 nucleosomes.
WP4-3	months 18	Implementation of the chromatin bead model for 20 Mb genomic regions.
WP4-4 WP4-5	months 30 months 36	Whole chromosome and nuclei simulation models. Comparative analysis interaction maps by nucleosome and nuclei models.

WP5

Milestone	es and deliverat	oles:
WP5-1	months 6	Central data base and the GLOBE 3D Genome Platform available to the consortium.
WP5-2	months 12	Integrating nucleosome positioning (experimental, sequence prediction, remodeller activity).
WP5-3	months 18	Predicting local fiber compaction from nucleosome positions and other signals (e. g. epigenetics).
WP5-4	months 24	Full integration of interaction maps, DNA FISH and RNA FISH data higher order simulation data.
WP5-5	months 36	Full system biological model of EpiGenSys.





M&D Timeplan in EpiGenSys

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WP1-1	months 6	Isolation of nucleosomal DNA by <i>in situ</i> MNase digestions; differential MNase digestion.	
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WP3-1 WP3-2	months 6 months 12	Use of 3C established; 4C and expre Use of 4C and expression arrays
WP3-3 WP3-4	months 18 months 24	Final 4C and expression result
WP3-5	months 30	DNA FISH. Confirm transcripti





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Nucleosomal association in relation to the DNA sequence, epigenetic modifications and the activity of ATPdriven chromatin remodelling complexes using high-throughput sequencing is evaluated. The results are directly put into simulations and related to DNA sequence predictions.







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Isolation of cellular mono-, di- and trinucleosomes



Nucleosome positions determine the localization of methylated CpGs in vivo

Dnmt

- nucleosome positions are rather static in vivo

- nucleosomal DNA methylation is reduced compared to the linker DNA methylation



Dnmt3b2 free DNA nucleosomes 11 13 15 17 19 21 23 25 27 positioned nucleosome

In vitro DNA methylation assay

DNA methylation is enriched in the DNA linker region







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Nucleosomal Positioning Prediction WP1

The DNA sequence is analyzed by the most simplest scaling analysis to find unprejudiced patters as e.g. nucleosome positions as well as chromatin loops and rosettes. The analysis is done using our grid infrastructures and here especially our volunteer grid.



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Intra/inter chromosomal contacts are determined using a combination of chromosome conformation capture technology and highest-throughput deep sequencing. From the interaction maps 3D chromatin conformations and its higher-order structure is derived, i.e. its folding into loops and loop clusters.





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Intra/inter chromosomal contacts is determined using a novel combination of chromosome conformation capture technology and highest-throughput deep sequencing. Computer models of different 3D architectures reveal clearly distinct modell depending pattern, and in combination with the experiment its folding into loops and loop clusters.

Small Chromatin Loops 126 kbp

Large Chromatin Loops 3 Mbp

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The Combination of Modelling and Experiment The Combination Chromosomal Architecture The Reveals the Chromosoma and the Chromosomal Architecture



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Transcription rates are determined by qRT-PCR, RNA and DNA FISH using intronic probes and high-resolution laser scanning and single molecule imaging. Transcription-dependent changes of active and inactive loci compared result in the transcription structure-function relationship.





TNFα induces SAMD4A/EXT1 to Associate with other Responsive Genes





Transcription rates are determined by qRT-PCR, RNA and DNA FISH using intronic probes and high-resolution laser scanning and single molecule imaging. Transcription-dependent changes of active and inactive loci compared result in the transcription structure-function relationship.

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Transcription rates will be determined by qRT-PCR, RNA and DNA FISH using intronic probes and highresolution laser scanning and single molecule imaging. Transcription-dependent changes of active and inactive loci compared result in the transcription structure-function relationship.

Nascent Transcripts Colocalize with Responsive Genes





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Range of Responsiveness & RNA Polymerase II and NFzB

a Correlating responsiveness with nascent RNA levels



b RNA polll and p65 binding



C Correlating 3C contacts with p65 binding sites







Transcription rates will be determined by qRT-PCR, RNA and DNA FISH using intronic probes and highresolution laser scanning and single molecule imaging. Transcription-dependent changes of active and inactive loci compared result in the transcription structure-function relationship.

Contacts Evolve over Time



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By parallel super-computer simulations using novel algorithms allow to simulate nucleosome and chromatin fibers up to 1000 nucleosomes, with variations of the nucleosomal position and linker length inbetween. The unprecedented scale and variation leads to new before unseen chromatin states.



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Simulation of Nucleosomes, Chromatin, & Nuclei WP4

By parallel super-computer simulations using novel Monte Carlo and Brownian Dynamics approaches simulate chromosomes and whole nuclei with unprecedented resolution, resulting in novel predictions for the detailed folding of the chromatin fiber with corresponding impact on the experimental evaluation.

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Simulation of Nucleosomes, Chromatin, & Nuclei WP4

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Simulations with Better Statistics and Innormatical

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Systems Biological Result Communcation via Internal and External Communication Windows WP5

Three classic internal and external communication windows were opened: i) the EpiGenSys website communicates with the public, ii) the EpiGenSys Wiki functions is used for exchange, and iii) the EpiGenSys SysMO DB archives in a virtual labnote the data. All allow access to the systems and are the basis for the GLOBE 3D Genome Platform.

EpiGenSys Public Website

System Biological Determination of the Epigenomic Structure - Function Relation - EpiGenSvs -

E Plus The Project

Despite our knowledge of the sequence of the huma genome, the relation of its dynamic three-dimensional architecture with its function - the storage and expression of genetic information - remains one of the central unresolved issues in biology, However, it became very clear meanwhile, that this chromatin architecture (and changes thereof) are central factors for the epigenetic regulation of gene expression and other important genomic processes on multiple scales, comprising: i) the nucleosome, in which 147 DNA base pairs are wrapped around a histone octamer protei core, ii) folding of the nucleosome chain into the



chromatin fiber, iii) its higher-order organization into loops and iv) loop aggregates, as well as v) the chromasome. Despite recent advancements showing these levels to control holistically the function of genomes under normal and disease conditions we still remain unable to predict how active e.g. a gene might be when inserted into any one genomic location, i.e. another global context

Therefore, EpiGenSys will in a unique interdisciplinary systems biology virtual laboratory combine experiment with theory to analyze the (epi-)genomic structure-function relationships within the dynamic organization of several important genetic loci and the genome in general. We will investigate: i) the nucleosome and chromatin fiber organization, ii) 3D architecture of the genome, and iii) the transcription structure-function relationship. Therefore, we will use advanced high-throughput methods and highest-resolution microscopy. With extreme parallel super-computer simulations of the biological structures/architectures based on the experiments we will be able to evaluate and predict their outcome. Altogether the experimental and theoretic framework will be combined into a systems biology model using our GLOBE 3D EpiGenSys Platform – a completely novel virtual 'paper tool' for the analysis, manipulation and understanding of complex genome-wide data sets. Consequently, the relation between DNA sequence, epigenetic modifications and spatial chromatin organization will be integrated with functional cell states in a truly systems biology approach - an essential requirement to fullfil the dreams for better diagnostics and treatment e.g. by gene therapy in the 21st century.









Epi-genomic structure-function

Despite our knowledge of the sequence of the human genome, the relation of its dynamic three-dimensional architecture with its function - the storage and expression of genetic information - remains one of the central unresolved issues in biology

The EpiGenSys consortium will combine experiment with theory to analyze the epigenomic structure-function relationships. We will investigate: i) the nucleosome and chromatin fiber organization, ii) 3D architecture of the genome, and iii) the transcription structure-function relationship.

Groupleader: T.A. Knoch, F. Grosveld, P. Cook, K. Rippe, G. Wedemann, G. Längsl

- Project Overview - EpiGenSys Meetings - Login for Members - Funding agencies - Publications - NEWS - Contact -

Work Packages

WP1 Nucleosomal association changes WP2 Intra/inter chromosomal architecture WP3 Transcriptional structure relationship WP4 Simulations of nucleosomal, chromatin fiber and chromosome architecture and dynamics WP5 System biological result integration via the GLOBE 3D Genome Platform



EpiGenSys SysMO DB



Publications

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Systems Biological Result Communcation via Internal and External Communication Windows WP5

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Publications



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The GLOBE 3D Genome Platform consists of individual components: i) the Sequence Archiving System stores complete genome sequences, ii) the Galaxy platform allows the analysis of genomes, and iii) for data analysis a gateway allows access to super-computer and grid access as our own established volunteer grid with a high public impact.



EpiGenSys Sequence Archiving Systems of Completely Sequenced Genomes

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Click here to browse the EMBL entries. Click here to browse the raw sequences.

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Database statistics

Totals



Introduction

An entry is a file containing DNA or RNA sequences and annotation of that sequence. Entries are uniquely identified by an accession number with a version.

This page allows you to query/search for EMBL entries, which will be returned in a list on another page. Each entry matches specified conditions, which can be set in the fields below. Only entries for which all conditions are vali true, will be returned in the list. (e.g. searching for a human accession number with "bacteria" as domain, will result in an empty list, since there are no humans accession numbers in the bacteria domain.)

The domain conditions allows you to specify in which domains the entry must be queried

Leaving a text field (e.g. Versice) empty means that the condition will match ANY value.**** Leaving all checkboxes of the domains empty means that all domains will be queried. This will be changed in the future.****

EpiGenSys Galaxy Analysis

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Metagenomic analyses	BILLIERGLIDAY C PODISBAAAN RD1 RD2-1-1-5-557/2 16 BILLIERGLIDAY C PODISBAAAN RD1 RD2-1-1-5-1548/2	chr4 145049008 288 34 0 chr11 109401947 25	5 301 ⁰	AAPCTTCLASSCTTGLASAAPCTGTTPCTTASTTT STATSCACCTCGAAACGTCAACGEDEAAT	888.6', e1888c+e99ACC8+2+1094824'8888 XA:5:0 MD:2:34 Md:1:0 AATAANAA 9=88CC8C8+2+108/888888c1+18;7=c3 XA:1:1 MD:2:14A21	bexplot on data
Genome Diversity	BILLIPHOLIDAY C PCDLWAAAX RD1 RD2:1:1:5:414/2 0	shald \$1244799 255 24	8 5 0	0 TASSCTITESTEATAATAAASTACKITATTOST	CATCOL 01 FOR DESCRIPTION OF DESC	1n_250U_FORWARD
EMBOSS	BILLIENCLIDAY & PCDILSRAAMS RDI RD2:1:1:5:15/2 16 RTLLIENCLIDAY & PCDILGRAAMS RDI RD2:1:1:5:16/2 16	cha5 53100545 255 54 cha5 1208756846 255 54		0 TOPPCTAATTATASATOPPCTAATTOPCTITIPOPTT 0 ATTATAGATTOALATATATATATATATATAT	77806889*748888,80C848A*,8C84,78C888 XA.110 MD.2.146 Md.110 R.10088071430884,638088844,4C28988888 XA.110 MD.2.20715 Md.110	15: Compute quality db R
NOT TOO BOX BETA	BILLIBROLIDAY & PCOLSBAAXX BD1 BD2-1-1-5-1056/2 BULLIBROLIDAY & PCOLSBAAXX BD1 BD2-1-1-5-1056/2	0 she1 229169714 23 cha1 158548105 255 55	5 364	0 0 BE0000CTCCCAAAECOCEBAGACTOCH	SOCATCAG 9-45458C581+227288CC,8588889+488884 XA+4-0 M2+2:24 50:41 MARKANANA MARKA1014ANAL02148.12-18 VL	statistics on data
	BILLIENCLIDAY C PCPOLSHAAAX RD1 RD2:1:1:5:154872 BILLIENCLIDAY C PCPOLSHAAAX RD1 RD2:1:1:5:1121/2	14 shall 35531419 21 0 shall 100584459 21	5 100 -	0 0 CCASSAAATCASACTCTTSTACACACS 0 0 AAASSEASTSSSACTSSCCCCTACSSTSS	479CCATT 7,4788888878888878888394888828888888888888888884**7; XA:1:0 MD:2:34 M	1n 250U FORWARD
NGS: OC and manipulation	BILLIENCLICAT (PC00L08AAAX B01 B02+1+1+1+148/2 14 BILLIENCLICAT (PC00L98AAAX B01 B02+1+1+5+148/2 14	sha13 23948307 288 54 0 sha17 21147014 25	5 300	0 AATEAAGAAAACAATAACACTOCTATCATOTTCT 0 0 BCTGCTCT0COTTTTTGBC0TGBCCA66	BBBBAAL97;788+BBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBBB	
NGS: SAM Tools	BILLIENGLIDAY & PCDOLWAAX BD1 BD2:1:1:5:1054/2 BILLIENGLIDAY (CPCDOLWAAX RD1 BD2:1:1:5:95/2 0	0 shalo 134274124 25 chr22_random 165609 255 04	N 2454 0	 BECEBSCCASCOTOSOGACCACCCASTOC ANNACARIACCACONNECTIVATACCCACTUTE 	20000000 ,CEREMENT CONTRACTOR CONTRACTOR SALES (2012) 20 2012 2 20 2012 2 20 2012 2 20 2012 2 20 2012 2 20 2012 2 20 2012 2 20 2012 2 2	hernist on data
NGS: Indel Analysis	BILLINGLIGAY 4 PC0158AAAX BD1 BD2-1-1-8-918/2 0 BILLINGLIGAY 4 PC0158AAAX BD1 BD2-1-1-8-1528/2 0	chall 120292394 288 34 14 sha7 81504678 28	5 101	 AddocdddaddcToCATOCATTCCCCCCAdCTELCC CCAAdaTC079CCACTOCACTCCAdCCTE 	*8,0005405 888-9,000 988 8878788887478 XA:5:0 MD:2:34 Md:5:0 A0075405 888-9,000 988 8878788887488008880088 XA:1:0 MD:2:34 Md:1:	1n.250U_REVERSE
NGS: Peak Calling	BILLIEHOLDAY C POIDLARAAN RD1 RD2:1:1:5:1078/2	16 cha16 0052014 255 04		0 TTCASTITCTTCKPSTAIAAATTAGAGATGAAAATA	*1*655	
NGS: RNA Analysis	BILLIENCLIDAY & PCDOLWAAAX RD1 RD2 1:1:5:1250/2	0 shal7 2000044 21	3 364	0 0 BEA000EAAA0000BAAACEAA00BA00B	AATGAAAA #4980C88*C888-8*88188 >*,8*885'88 XA:4:1 NO:2:24A9	13: Compute quality @ 0 2
NGS: Picard (beta)	BILLIENCLIDAY & PCDOLSRAAMS RD1 RD2:1:1:5:1176/2 RTLLIENCLIDAY & PCDOLGRAAMS RD1 RD2:1:1:5:1277/2	14 shal4 43143119 25 14 shal1 199229759 27	5 100	0 0 TROUTSCANCECANTATRICANTTERAAN	AACOUCTT , MECTICAN, TERCENSERSER, LINECOCCESSERS XA.1.0 MD.2.186 MC.1. ACOUCTT '22008888888888 B-8881+188888-8785085 XA.1.0 MD.2.16 MC.1.	1n 2SOU REVERSE
RGENETICS	BILLINGCIDAY @ PCDOLGAAAX BD1 BD2-1-1-8-81/2 16 BILLINGCIDAY @ PCDOLGAAAX BD1 BD2-1-1-8-1017/2	ohe2 \$1743146 233 34 0 she8 67744431 23	8 364 9	0 ATTPOORTETTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	.'', ('90'048,8*7-8*8388*08/888887 XA.L.O MC.2.0737370723 MA.L. AAAD7777 8800008888888880072788883,99.6')0388 XA.L.O MC.2.14 MA.L.	
SNP/WGA: Data: Filters	BILLIBHOLIDAY CTCDOLMAAAX RD1 BD2:1:1:5:4401/2 0 BILLIBHOLIDAY CTCDOLMAAAX RD1 BD2:1:1:5:544/2 16	oba2 182499124 255 24 chz2 125559990 255 94	M - 0	 ASASOCTOCCATARTATOCTATTOTASAGAATATT CASSAAATTOSAAATRAASCCATCTSASACTASA 	8*8,C88888-8418888C8,88774,.)4888*88 XA:L10 MD:2:34 38:L10 ,4888881-2278C24458895488;50885;888 XA:L10 MD:2:34 38:L10	12: Quality format @ 0 3
SNP/WGA: OC: LD: Plots	BILLIBROLIDAY & PCODLERAAX BOI BO2-1-1-8-684/2 0 BILLIBROLIDAY (PCODLERAAX BOI BO2-1-1-8-1918/2	14 chr9 124540216 25	8 in 1	0 0 CTTCCCTTAAAACTAATACTAACTAA	**************************************	Converter on Gata 19
SNP/WGA: Statistical Models	BILLIENCLIDAY (PCDOLSRAAMS RD1 RD2:1:1:5:506/2 0	cha5 119763414 255 34	N O	0 AAA95A6A7CACTTT9CH5ATTEAA99TTTAAT6AC	18809.8;8688888880-4887,29,1888982;< XA:1:0 MD:2:04 MM:1:0	11: Quality format @ 0
Workflows	BILLIERGLIDAY C PCPULSHAAAN RDS RDS 111575572 0	cha15 49997254 155 9	8 2 3	Contraction of the second seco	.8086C88; 8-886C8888888888************************	converter on data 9
	BILLIBROLDAY C PCDLSRAAAX RD1 RD2:1:1:5:1439/2 RTLLBROLDAY C PCDLSRAAAX RD1 RD2:1:1:5:1439/2 14	14 sha1 226407429 21 chaf \$5195141 245 25	5 364	0 0 INTEGRACIANDERSON OF TRACESSOR	82000203 -1/.80588.800888888-80-/.4084805188 XA110 80.2134 88.11 (XA.8.81078-46888888989888898888988888888888888888	10: EASTO colittee on th R
	BILLIENGLIDAY C PC00L9AAAAX BOI BO2:1:1:8:1997/2 BILLIENGLIDAY C PC00L9AAAAX BOI BO2:1:1:8:1441/2	0 chr15 42145714 21 14 chr17 14325814 27	5 10/ 5 10/ -	0 0 AAGGARTTAAAAGCAGGTOFTCAAATACT 0 0 AATCTOCCAGCACCTTCATCTTOGACTTT	2TACKEAT 0188,0000000000000000000000000000000000	data in 2500 2 REVERSE
	BILLIBROLIDAG CPCDOLMAAAXCBD2111151112/2 0 BILLIBROLIDAG CPCPOLMAAAXCBD2B0231115112/2 0	oba1 114334254 255 24 14 obx14 94559948, 85	5 HOI -	 ACGACTITITIAAAATTITATTIATTIATTITATTIAT 9 9588990568890000000000000000000000000000	48>+88888>4<79888888888888888888888888888888888888	
	BILLINGLIGAT C PCDILWAAAA RDI HDI:11151265/2 BILLINGLIDAT C PCDILWAAAA RDI HDI:11151265/2	16 char 144159476 25 0 char 149565519 25	5 366	0 0 DEGENTIONALITASCANFTCCALTOGRAFIA	CCTX20A *-CBB4*220008-CT*80*20CB8000C5, D*80 XA110 K0:2124 M0:11 XTGGGCGA *88888888; 888; 2888; 80018*888888818 XA110 K0:2124 M0:11	9: FASTO splitter on @ 0 2
	BILLIENGLIDAY CPCPOLSRAANCRO1 R02:1:1:5:647/2 0	sha5 7272652 255 26K		TASCATCCTCCAACCOTTACCASTTCCTATTAAASA 68000	50406804*1*006800**C008*8080*61> XX:1:1 M0:2:14421 M6:1:1 0000004*1*006800**C008*8080*61> XX:1:1 M0:2:14421 M6:1:1	SECONDER STREET
	BILLINGLIDAY C PCDOLSRAAAN RD1 B02-1-1-5-1155/2 BILLINGLIDAY C PCDOLSRAAAN BD1 B02-1-1-5-655/2	14 char2 \$9744971 25 char18 20139248 288 24	5 3404	0 0 CCATGEAGCDGGCCCCCTTTTTGATGCCG 0 ATCHIATTCCATCTACAGTTATTAGTAGTTTCC	69275027 043881128,8+9+4.68/9+2288,4998,7717 XA111 MD13111A24 828788822888228488483288.489998888 XA110 MD12128 M0110	B: Draw quality score @ 0
	BILLIENGLIDAY CPCDOLMAAAC BD1 BD2:1:1:5:1096/2 BILLIENGLIDAY CPCDOLMAAAC BD1 BD2:1:1:5:1096/2	14 sha7 10425995 25 14 sha13 33547827 25	5 100 1	0 0 0CACASAGATTCOTCOTTOSTOSTAATS 0 0 INTTINOOCCCCTACTCTTTCTAADCATC	ACATICIT D=0000001010000000000000000000000000000	boxplot on data in 2500_2
	BILLIENGLIDAY C PC00LSBAARD R01 R02:1:1:5:604/2 0 BILLIENGLIDAY C PC00LSBAARD R01 R02:1:1:5:604/2 0	cha2 47925599 255 24 cha2 110807747 288 24	M : 0	0 ASTRCCCASTSTTTSCCAAAATAAASASTSSTTTCT 0 ATGTSTGTTTTSCCTTTIASGTTGATCCCACIATGS	800868086878688880+<888885*6242808888 XA:1:0 MD:2:264 Ne:1:0 847768;88876+962888878*6442*67747* XA:1:0 MD:2:26A7 MD:1:	7: Compute quality @ 0 ?
	BILLIDHOLIDAY 6 PCDOLHAAAX RD1 BD2 1 1 1 5 1782/2 BILLIDHOLIDAY 6 PCDOLHAAAX RD1 BD2 1 1 6 1286/2	14 shab 67771378 21 14 shab 176580312 23	3 366	0 0 TOCAATTITCTOAACTCTTATOCTCTOC 0 0 TOCAATGACCTTTTAATAAATTITCTTTC	TTOCCTT *788864844888888-8, 80C8,8.88,8C80,* XA:1-3 NO:2:34 NO:1: CTTACATA >>8888888881988888888888888888888888888	statistics on data In 250U 2
	BILLINSCIDAY & PCDULSBAAM ROI BO211114490/24	ches 2205142 255 266		AAAGGAAPGTCCTAGAATGCCAGTCTGGAGCTGT 88888	889-1010, 8888888888888888888888888888888888	Caracia Commence and
	BILLIERCLIDAY & PCDDLEBAAX RD 802 111 6 711/2 16 BILLIERCLIDAY & PCDDLEBAAX RD 802 111 6 1031/2	che8 140810320 288 54	N - 0	5 TACCTITICIAMITUTACTOMAAAACCCCTTREAMT 0 0 XADACIACTAA000MAAA00CCTTREAMT	451**A595888-88.28/5888CC87 888888883 XA.1.0 MD-2.54 MM-1.0 97977007 88888888.44988-8278008888888888888888888888888888888	- data in 2500 2





The GLOBE 3D Genome Platform consists of individual components: i) the Sequence Archiving System stores complete genome sequences, ii) the Galaxy platform allows the analysis of genomes, and iii) for data analysis a gateway allows access to super-computer and grid access as our own established volunteer grid with a high public impact.



Project

Correlizer

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Revealing the Mysteries of Genome Organization

Genomes are fantastic keepers of genetic information and are the outcome of evolutionary replication, mutation and selection. Genomes organize functions from the cellular level, via the organismic level, up to the complex basis of mind. In human cells the genetic information controlling most processes from the cellular level, over embryogenesis to cognitive ability, manifests in a diploid set of 23 DNA molecules (chromosomes), combined they consist of ~3x10^9 base pairs (bp) stored in ~2.80 GB of data. This whole genome, whose added molecular length totals ~2m, is kept in comparably small cell nuclei with typical diameters of ~10 μ m or volumes of 500 μ m^3. The sequential organization of genomes, i.e. the relations between distant base pairs and regions within sequences, and its connection to the three-dimensional architectural organization of genomes is still a largely unresolved problem.



Correlizer has been set up to unravel these mysteries, and we found long-range power-law correlations on almost the entire observable scale of 132 completely sequenced chromosomes of 0.5×10^{6} to 3.0×10^{7} bp. Varying from Archaea, Bacteria, Arabidopsis thaliana, Saccharomyces cerevisiae, Schizosaccharomyces pombe, Drosophila melanogaster, and Homo sapiens. The local correlation coefficients show a species-specific multi-scaling behavior: close to random correlations on the scale of a few base pairs, a first maximum from 40 to 3,400 bp (for Arabidopsis thaliana and Drosophila melanogaster divided in two submaxima), and often a region of one or more second maxima from 10^{5} to 3×10^{5} bp. Within this multi-scaling behavior, an additional fine-structure is present and attributable to codon usage in all except the human sequences, where it is related to nucleosomal binding.

Computer-generated random sequences assuming a block organization of genomes, the codon usage, and nucleosomal binding explain these results. Mutation by sequence reshuffling destroyed all correlations. Thus, the stability of correlations seems to be evolutionarily tightly controlled and concepted to the certical conception conceptible.

User of the Day



Jeff17

I work in information technology. My primary interest is in the mathematical projects, but I have recently picked up an interest in some of the biology projects as well.



News

... more

News is available as an RSS feed RSS



The GLOBE 3D Genome Platform consists of individual components: i) the Sequence Archiving System stores complete genome sequences, ii) the Galaxy platform allows the analysis of genomes, and iii) for data analysis a gateway allows access to super-computer and grid access as our own established volunteer grid with a high public impact.



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Comunity Teams

Profiles User search

Project status

Server software version: 23903M / 7 Sep 2011 | 12:34:36 UTC

Server status

Project	Program	Host	Status
Correlizer	data-driven web pages	svahesrv2	Running
Background	upload/download server	svahesrv2	Running
Publications	scheduler	svahesrv2	Running
Contact	feeder	svahesrv2	Running
loining	transitioner	svahesrv2	Running
Johning	file_deleter	svahesrv2	Running
Acknowledgements	db_purge	svahesrv2	Running
Participante	ego_validator	svahesrv2	Running
	ego_assimilator	svahesrv2	Running
Your Account	ego_beta_validator	svahesrv2	Running
Server Status	ego_beta_assimilator	svahesrv2	Running
Applications	Running:	Program is operatir	ng normally
Certificate	Not Running:	Program failed or down	the project is
	Disabled:	Program is disabled	i

Computing status

Work	#	Users	#
Tasks ready to send	28,078	with recent credit	435
Tasks in progress	50,451	with credit	472
Workunits waiting for validation	1	registered in past 24 hours	4
Workunits waiting for assimilation	1	Computers	#
Workunits waiting for file deletion	3	with recent credit	1,158
Tasks waiting for file deletion	2	with credit	1,262
Transitioner backlog (hours)	0	registered in past 24 hours	16
		current GigaELOPs	1.422

Tasks by application						
application		unsent	in progress	avg runtime of last 100 results in h (min-max)	users in last 24h	
BioMedical Correlations	Genome	26,860	45,034	0.48 (0.29 - 1.07)	165	
Correlizer Applications	Beta	834	5,779	0.46 (0.15 - 1.07)	30	

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P.	Message	boards
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EpiGenSys Systems Biological Result Integration via the GLOBE 3D Genome Platform WP5

All results will be integrated using our GLOBE 3D Genome Platform, established for analysis, manipulation and understanding of multi-dimensional complex genome wide data. Thus in reiterative cycles between experiments and simulations a systems biological/medical genome model will be achieved.



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EpiGenSys Systems Biological Result Integration via the GLOBE 3D Genome Platform WP5

All results will be integrated using our GLOBE 3D Genome Platform, established for analysis, manipulative



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Publications of EpiGenSys

The EpiGenSys consortium approach will be exploited and disseminated in interdisciplinary research publications. Until know 12 research articles and reviews are published or in press. Currently, several are under way and will be published soon.

Research Articles:

- 1. Melnik, S., Deng, B., Papantonis, A., Babbo, S., Carr, I.M. & Cook, P.R. The proteomes of transcription factories containing polymerases I, II, or III. *Nat. Methods*, in press.
- 2. Ettig, R., Kepper, N., Stehr, R., Wedemann, G. & Rippe, K. Dissecting DNA-histone interactions by molecular dynamics simulations of unwrapping DNA from the nucleosome, *Biophys. J.*, in press.
- 3. Felle, M., Hofmeister, H., Rothammer, J., Fuchs, A., Exler, J., & Längst, G. Nucleosomes protect DNA from DNA methylation in vivo and in vitro. Nucleic Acids Res. DOI: 10.1093/nar/gkr263, 2011.
- 4. Teif, V. & Rippe, K. Nucleosome mediated cross-talk between transcription factors, Phys. Biol. 8, 044001, DOI: 10.1088/1478-3975/8/4/044001, 2011.
- 5. Kepper, N., Ettig, R., Stehr, R., Wedemann, G., & Rippe, K. Force spectroscopy of chromatin fibers: extracting energetics and structural information from Monte Carlo simulations. Biopolymers 95, 435-447, 2011.
- 6. Skrowny, D., Dickmann, F., Löhnhardt, B., Knoch, T. A., & Sax, U. Development of an information platform for new grid users in the biomedical field. Stud. Health Techno. Inform. 159, 277-282, 2010.
- 7. Kepper, N., Ettig, R., Dickmann, F., Stehr, R., Grosveld, F. G., Wedemann, G., & Knoch, T. A. Parallel high-performance grid computing: capabilities and opportunities of a novel demanding service and business class allowing highest resource efficiency. Stud. Health Techno. Inform. 159, 264-271, 2010.
- 8. Kepper, N., Schmitt, E., Lesnussa, M., Weiland, Y., Eussen, H. B., Grosveld, F. G., Hausmann, M., & Knoch, T. A. Visualization, analysis, and design of COMBO-FISH probes in the grid-based GLOBE 3D genome platform. Stud. Health Techno. Inform. 159, 159-171, 2010.

Reviews:

- 1. Papantonis, A. & Cook, P.R. Fixing the model for transcription: the DNA moves, not the polymerase. Transcription, 2, 41-44
- 2. Teif, V. & Rippe, K. Calculating transcription factor binding to nucleosomal DNA for large genomic regions, Briefings Biomf. 12, DOIL 10.1093/bib/bbr037, 2011.
- 3. Längst, G., Teif, V. B., & Rippe, K. Chromatin remodeling and nucleosome positioning. In *Genome organization and function in the cell of the general sector*, Rippe, K., ed., pp. 111-139, Wiley-VCH, Weinheim, 2011.
- A. Rippe, K., Stehr, R., Wedemann, G. Monte Carlo simulations of nucleosome chains to identify factors that control DNA compaction and a compaction and a compaction and a compact of a compact of the second s

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Research Articles:

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- 2. Ettig, R., Kepper, N., Stehr, R., Wedemann, G. & Rippe, K. Dissecting DNA unwrapping DNA from the nucleosome, *Biophys. J.*, in press.
- 3. Felle, M., Hofmeister, H., Rothammer, J., Fuchs, A., Exler, J., & Längst vitro. Nucleic Acids Res. DOI: 10.1093/nar/gkr263, 2011.
- 4. Teif, V. & Rippe, K. Nucleosome mediated cross 10.1088/1478-3975/8/4/044001, 2011.
- 5. Kepper, N., Ettig, R., Stehr, R., Wedemann, G., & J information from Monte Carlo simulations. Bior
- 6. Skrowny, D., Dickmann, F., Löhnhardt, B biomedical field. Stud. Health Techno.J
 - 7. Kepper, N., Ettig, R., Dickmann, capabilities and opportunities Inform. 159, 264-271, 2010
 - 8. Kepper, N., Schmitt, and design of CS

Reviews:

ag transcription factor binding to nucleosomal DNA for large genomic regions, Briefings Biomf. 12, DCI

& Rippe, K. Chromatin remodeling and nucleosome positioning. In Genome organization and function in the cell ., ed., pp. 111-139, Wiley-VCH, Weinheim, 2011.

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Presentations of EpiGenSys (before Holidays)

A major aim of the EpiGenSys consortium is to considerable contribute to systems biology in the genomic sector and increase the awareness and understanding of genomic complexity within society. Scientifically that means presenting our work at conferences. The list shown has increased over the holiday period tremendously.

- 1. Papantonis A., & Cook P. R. Active RNA polymerases are immobile molecular machines tethering dynamic intra- and inter-genic loops. 9th EMBL Conference "Chromatin and Transcription", EMBL, Heidelberg, Germany, 28th to 31th August 2010.
- 2. Cook, P.R. Active RNA polymerases are immobile molecular machines. The 69th Harden Conference ("RNAP2010 -Structure, function and evolution of RNA polymerases. A joint Biochemical Society / Wellcome Trust conference"), The Wellcome Trust, Hinxton, Cambridge, UK, 22th to 25th September 2010.
- 3. Cook, P. R. A model for all genomes: the role of RNA polymerases fixed in factories. GENOFIELD2011 ("International Symposium on the Physicochemical Field for Genetic Activities"), Awaji Island, Japan from 24th to 26th January 2011.
- 4. Cook, P. R. Active RNA polymerases are immobilized molecular machines. at 'The 46th WINTERSEMINAR ("Biophysical Chemistry, Molecular Biology and Cybernetics of Cell Functions"), Klosters, Switzerland, 15th to 29th January 2011.
- 5. Kepper, N., & Knoch, T. A. Parallel high-performance grid computing: capabilities and opportunities of a novel demanding service and business class allowing highest resource efficiency. HealthGrid 2010 ("Healthgrid Applications and core Technolgies"), University XI, Orsay, France, 28th to 30th June 2010.
- 6. Kepper, N., & Knoch, T. A. Visualization, analysis, and design of COMBO-FISH probes in the grid-based GLOBE 3D genome platform. HealthGrid 2010 ("Healthgrid Applications and core Technolgies"), University XI, Orsay, France, 28th to 30th June 2010.
- Müller, O., Stehr, R., Schöpflin, R., Ettig, R., Kepper, N., Rippe, K., & Wedemann, G.: Computer simulation of chromatin: Modeling the influence of nucleosome repositioning. DPG conference, Verhandl. DPG(VI) 46, 1/2011, p. 231, Dresden., 14th March 2011.
- 8. Rippe, K. Dissecting epigenetic networks. Workshop: Spatio-temporal dynamics challenges from fluorescence data. Symposium series Complexity and Systems Biology. Warwick University, UK, July 13-16th 2010.
- 9. Rippe, K. Chromatin remodelers from in vitro measurements to studies in living cells. Chromatin Days Workshop, Interdisciplinary Research Institute USR 3078 CNRS, Lille, France, October 7-8th 2010.



10. Schubert, T., Pusch, M., Diermeier, S., Gröbner-Ferreira, R., Imhof, A. and Längst, G. Chromatin interacting RNA maintains accessible higher order structures of chromatin, EMBL Transcription Meeting, Heidelberg 2010.



Presentations of EpiGenSys (before Holidays)

A major aim of the EpiGenSys consortium is to considerable contribute to systems biology in the genomic sector and increase the awareness and understanding of genomic complexity within society. Scientifically that means presenting our work at conferences. The list shown has increased over the holiday period tremendously

- Gensys and ErasysBiot is ver 1. Papantonis A., & Cook P. R. Active RNA polymerases are immobile molecular. inter-genic loops. 9th EMBL Conference "Chromatin and Transcription", F August 2010.
- 2. Cook, P.R. Active RNA polymerases are immobile molecular mack Structure, function and evolution of RNA polymerases. A joint Wellcome Trust, Hinxton, Cambridge, UK, 22th to 25th Sept
- 3. Cook, P. R. A model for all genomes: the role of RNA Symposium on the Physicochemical Field for Genet
- 4. Cook, P. R. Active RNA polymerases are immore Chemistry, Molecular Biology and Cyberp
- 5. Kepper, N., & Knoch, T. A. Paral demanding service and business. core Technolgies"), Universit
- 6. Kepper, N., & Knoch, 7 genome platform. to 30th June 2010

7. Müller, O

Model

- ("RNAP2010 · ust conference"), The
- **IELD2011 ("International** rom 24th to 26th January 2011. 46th WINTERSEMINAR ("Biophysical switzerland, 15th to 29th January 2011.
- ting: capabilities and opportunities of a novel ency. HealthGrid 2010 ("Healthgrid Applications and
- esign of COMBO-FISH probes in the grid-based GLOBE 3D cations and core Technolgies"), University XI, Orsay, France, 28th
- Apper, N., Rippe, K., & Wedemann, G.: Computer simulation of chromatin: ositioning. DPG conference, Verhandl. DPG(VI) 46, 1/2011, p. 231, Dresden., 14th

networks. Workshop: Spatio-temporal dynamics challenges from fluorescence data. y and Systems Biology. Warwick University, UK, July 13-16th 2010.

emodelers - from in vitro measurements to studies in living cells. Chromatin Days Workshop, search Institute USR 3078 CNRS, Lille, France, October 7-8th 2010.

Pusch, M., Diermeier, S., Gröbner-Ferreira, R., Imhof, A. and Längst, G. Chromatin interacting RN accessible higher order structures of chromatin, EMBL Transcription Meeting, Heidelberg 2010.

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Patents and Additional Funding

Each of the technologies used (and their future developments), plus the synergies that might arise from their combined use, have potential for commercialization due to their uniqueness, novelty, and frontier position, e.g. concerning academic, diagnostic and commercial aspects. These successes also generates new funding opportunities.

Patens:

- 1. Patent 1 by the Knoch/Grosveld group. WP 2.
- 2. Patent 2 by the Knoch/Grosveld group. WP 2.

Funding due to EpiGenSys:

- 1. 1,000,000 Euros on funding the Erasmus Computing Grid over 5 years in end 2009 due to the EpiGenSys expected granting. WP 1 to WP 5.
- 2. Computer time at the supercomputer center in Hannover twice: i) 24,500 Euros for computation time 2008/2009, and ii) 42,000 Euros for computation time in 2009/2010. WP 1 and WP 2.







Patents and Additional Funding

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EpiGenSys

Systems Biological Determination of the Epigenomic Structure Function Relation: Nucleosomal Association Changes, Intra/Inter Chromosomal Architecture, Transcriptional Structure Relationship, Simulations of Nucleosomal/Chromatin Fiber/Chromosome Architecture and Dynamics, and Systems Biological/Medical Result Integration via the GLOBE 3D Genome Platform.

Knoch, T. A.

EpiGenSys Midterm Meeting and Evaluation Conference, Hotel Kaiserwasser, Vienna, 15th September, 2011.

Abstract

Although the sequence of the human genome is known, the relation of its three-dimensional dynamic architecture with its function – the storage and expression of genetic information – remains one of the central unresolved issues of our time. Here we show how simulations of the structural-, scaling- and dynamic properties of interphase chromosomes and cell nuclei with Monte Carlo and Brownian Dynamics methods (WP4) can be combined with experimental structure preserving 3D FISH combined with high-resolution fluorescence microscopy that allows determination of the centre of mass of target fluorophors at a resolution of ~30 nm – beyond the classical resolution limit (WP2), *in vivo* chromatin labelling (WP2) as well as our newly developed combination of chromosome conformation capture technology and high-throughput deep sequencing (WP2). Best agreement is reached both for the Prader-Willi/Angelmann region and the Immunoglobin heavy-chain (Igh) locus for a Multi-Loop-Subcompartment (MLS) model of chromosome organization predicting 60-150 kbp loop aggregates separated by a similar linker. Beyond, DNA sequence correlation analysis of completely sequenced genomes reveals fine structured multi-scaling long-range correlations. The fine structure in the human case is attributable to nucleosome positioning (WP1) and transcription (WP3). In summary, genomes show a complex sequential and three-dimensional organization related closely to each other in a system biological/medical co-evolutionarily developed entity.

Corresponding author email contact: TA.Knoch@taknoch.org

Keywords:

Genome, genomics, genome organization, genome architecture, structural sequencing, architectural sequencing, systems genomics, coevolution, holistic genetics, genome mechanics, genome statistical mechanics, genomic uncertainty principle, multilism genotype-phenotype, genome function, genetics, gene regulation, replication, transcription, repair, homologous recombination, simultaneous co-transfection, cell division, mitosis, metaphase, interphase, cell nucleus, nuclear structure, nuclear organization, chromatin density distribution, nuclear

morphology, chromosome territories, subchromosomal domains, chromatin loop aggregates, chromatin rosettes, chromatin loops, chromatin quasi fibre, chromatin density, persistence length, spatial distance measurement, histones, H1.0, H2A, H2B, H3, H4, mH2A1.2, DNA sequence, complete sequenced genomes, molecular transport, obstructed diffusion, anomalous diffusion, percolation, long-range correlations, fractal analysis, scaling analysis, exact yard-stick dimension, box-counting dimension, lacunarity dimension, local nuclear dimension, nuclear diffuseness, parallel super computing, grid computing, volunteer computing, polymer model, analytic mathematical model, Brownian Dynamics, Monte Carlo, fluorescence *in situ* hybridization (FISH), targeted chromatin capture (T2C) confocal laser scanning microscopy, fluorescence correlations spectroscopy (2D-FCS) auto-fluorescent proteins, CFP, GFP, YFP, DsRed, fusion protein, *in vivo* labelling, information browser, visual data base access, holistic viewing system, integrative data management, extreme visualization, three-dimensional virtual environment, virtual paper tool, human ecology, e-human grid ecology, society, social systems, e-social challenge, inverse tragedy of the commons, grid phenomenon, micro-sociality, macro-sociality, autopoietic tragedy of social sub-systems, micro subsystems, macro subsystems, micro

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