The Detailed
3D Multi-Loop Aggregate/Rosette Chromatin Architecture
and
Functional Dynamic Organization of the Human and Mouse Genomes

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Towards a Holistic Understanding of Genomes!

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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, embryogenesis, or cancer development is still unclear.
Chromatin Conformation and Higher-Order Topologies

It becomes increasingly clearer, that the chromatin conformation is a random organization of nucleosomes, which depending on external or modification conditions has different condensation degrees, with a prevalence for the 30 nm fiber with ~6 nucleosomes per 11 nm. This seems to make loops which further cluster to form aggregates more or less rosette-like which then constitute the chromosome.

A-C: Voeit & Voit; D: Reznik et al.

Courtesy P. Fransz, Amsterdam

Integral Models of Cell Nuclear Organization I

Already Rabl and Boveri were aware of the obvious fact that the organization of genomes has to be consistent from the sequence level to the morphology of the whole cell nucleus. Although they might be different in detail their common seem is recursive folding and clustering thereof with variation/modification and dynamics accounting for different nuclear states and function.
Integral Models of Cell Nuclear Organization

The biggest advantage of integral models is the again obvious and simple fact, that they allow the validation from the consistency of different levels of organization from the other levels. Thus, e.g. the so called Interchromosomal Domain Model can be ruled out by simple voluminous thought...

Random-Walk/Giant-Loop Multi-Loop-Subcompartment Model

RW/GL-Model
- Loop size: 3Mbp-5Mbp
- Loop length: 30 to 50 µm

MLS-Model
- Loop size: 126kbp
- Loop length: 1200nm

Linker between rosettes consists of DNA (126 kbp)
(in contrast to backbone)
Selective Chromosome Interaction Capture (T2C)

T2C is a novel selective high-resolution high-throughput chromosome interaction capture, in which the relation between region size, resolution, interaction frequency range, and sequencing depth can be designed towards the goal of the experiment. T2C reaches the limit of the “genomic” uncertainty principle and statistical mechanics.
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HS IGF locus ~2.1 Mbp
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We Reached the Level of the Genomic Uncertainty Principle!

The Conformation of Chromatin and the 3D Architecture can be Derived with Tremendous Resolution!
Stable Consensus Architecture of Genomes

Due to the high signal-to-noise ratio of T2C reaching 5-6 orders of magnitude interaction maps reveal definitely an extremely high degree of similarity between different species, cell types, or functional states, thus functional differences are variation of a stable theme persisting through the cell cycle.
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Fine Structure of Loop Aggregates/Rosettes

Depending on the resolution, the loops within a domain and their arrangement in loop aggregates/rosettes can be shown as well as the details of how the loops are organized at their base as well as their aggregated rosette core: parallel loop fibres exist at the loop base with ~6kbp and these form the core.

~ 800 kbp
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Simulation of Single Chromosomes

The 30 nm chromatin fiber is modeled as a polymer chain with stretching, bending, and excluded volume interactions. Monte Carlo and Brownian Dynamic methods lead to thermodynamical equilibrium configurations.

All models form chromosome territories with big voids and different chromatin morphologies. Experimental territory and subcompartment diameters agree best with an MLS model with 80 to 120 kbp loops and linkers.

Metaphase starting configuration with ideogram bands in red/green, linker in grey.

RW/GL model, loop size 5 Mbp, after ~80,000 MC and 1000 relaxing BD steps. Large loops intermingle freely and reach out of the chromosome territory, thus forming no distinct features like in MLS model.

MLS model, loop size 126kbp, linker size 126 kbp, after ~50,000 MC and 1000 relaxing BD steps. Here rosettes form subcompartments as separated organizational and dynamic entities.

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Simulation of Whole Nuclei with all 46 Chromosomes

Starting with some metaphase arrangement of cylindrical chromosomes, interphase nuclei with a 30 nm fiber resolution and at thermodynamical equilibrium are created in 4 steps using simulated annealing and Brownian Dynamics methods with stretching, bending, excluded volume and a spherical boundary interactions.

The chromosome territory position depends on their metaphase position and is reasonably stable.
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Simulated Interaction Maps

Simulated spatial distance maps as well as simulated interaction maps result in the representation of every parameter variation, and also exhibit the fine-structure describing the loop base as well as rosette core. Thus from the quasi-fibre to the entire chromosome the architecture can be understood in detail.
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Variation of a Consensus Architecture Scheme

The difference between different cell types, functional states or even species is minor despite depending on the region. From this, the chromatin fibre conformation, loop position, and their association into loop aggregates/rosettes can be derived, simulated by polymer models and finally visualized.
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3D Architecture of the Prader-Willi Region

Fluorescence *in situ* hybridization with various protocols of small probes within the Prader-Willi region combined with spectral precision distance confocal laser scanning microscopy and comparison with large-scale computer simulations shows a Multi-Loop Subcompartiment organization of the Prader-Willi region.
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3D Architecture & Function of the IgH Locus

Fluorescence in situ hybridization of the IgH locus combined with spectral precision distance epifluorescence microscopy, analytical trilateration and comparison with computer simulations shows again a Multi-Loop Subcompartment organization of the IgH locus with functional relevant distances.
“Synoptic” 3D Architecture of Various Loci

A history “synoptic” comparison of the spatial distance mapping from their original background and aim, FISH methodological protocols, via microscopic imaging and restoration analysis procedures, to their interpretation, reveals that with time Multi-Loop Subcompartment models are favoured.
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<table>
<thead>
<tr>
<th>Genomic Distance [Mbp]</th>
<th>Mean Position Independent Spatial Distance [µm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>2.0</td>
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DNA Sequence Organization

Determination of the concentration fluctuation function $C(l)$ and its local slope the correlation coefficient $\delta(l)$ are an indication for the i) degree of long-rang scaling behavior, ii) general multi-scaling, and iii) fine-structure features, which all are connected to all levels of genome organization and especially also the three-dimensional genome architecture.

\[
C(l) = \sqrt{\langle (c_l - \bar{c}_L)^2 \rangle_s}
\]

\[
C(l) = \frac{1}{L-l+1} \sum_{s=1}^{L-l} \left( \frac{1}{l} \sum_{k=1}^{l} n - \frac{1}{L} \sum_{k=1}^{L} N \right)^2
\]

\[
C(l) = \frac{1}{Ll} \sqrt{\frac{1}{L-l} \sum_{s=1}^{L-l} \left[ \left( \sum_{k=1}^{L} Ln \right) - \left( \sum_{k=1}^{L} lN \right) \right]^2}
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DNA Sequence Organization

Derived from the Sequence and Show the Holistics!
Scaling Analysis

Scaling analysis show again the entire bandwidth of architectural effects in an aggregated manner. Beyond, they show the scale bridging of the structures and the evolutionary holistic entanglement between the 3D architecture and the DNA sequence organization itself.
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Scaling of the Chromatin Fiber Topology

The spatial-distance and exact yard-stick dimension distinguish between the simulated models in detail. The MLS model shows a globular and fine-structured multi scaling behaviour due to the loops forming rosettes. This agrees with DNA fragmentation by Carbon ion irradiation and the appearance of fine-structured multi-scaling long-range correlations found in the sequential organization of genomes.
From Fiber Topology to Nuclear Morphology

Chromosome territories form in the RW/GL and the MLS model. However, only the MLS model leads distinct subcompartments and low chromosome and subcompartment overlap. Best agreement is reached for an MLS model with 80 to 120 kbp loops and linkers in nuclei with 8 to 10 µm diameter.

The simulated nuclear morphology reflects the chromosome fiber topology of different models in detail.

A: MLS in 6 µm nucleus
   I: 63 kbp loops, 63 kbp linkers
   II: 63 kbp loops, 252 kbp linkers
   III: 126 kbp loops, 252 kbp linkers

B: MLS in 8 µm nucleus
   I: 126 kbp loops, 126 kbp linkers
   II: 84 kbp loops, 126 kbp linkers

C: MLS in 10 µm nucleus
   126 kbp loops, 126 kbp linker, not totally relaxed

D: RW/GL in 12 µm nucleus
   5 Mbp loops
   not totally relaxed
Fine Morphology of Nuclei

High resolution rendering and simulated electron microscopy including territory painting reveal not only again the model details but also that any location in the nucleus is accessible to biological molecules <15 nm in diameter and that even the Extended Interchromosominal Domain hypothesis is oversimplified.

MLS models model with 126 kbp loops and linkers in a 10 µm nucleus.
In vivo Morphology & Chromatin Distribution

The stable expression of fusions between histones and autofluorescent proteins and the integration into nucleosomes allows the minimal invasive investigation of the structure and dynamics of chromatin.

The clustered morphology in detail favour an MLS like chromatin topology.
Scaling of the Chromatin Morphology & Distribution

The local (inverse-) mass dimension distribution distinguishes between the models in detail and show also a multi-scaling behaviour with globular feature for the MLS model like the scaling of the fiber topology. With the mass dimension as function of intensity separates very well between different nuclei in vivo.

Consequently, the chromatin morphology is causally and quantitatively connected to the fiber topology.
Quantified TSA induced Morpholoy Changes

Trichostatin A induced histone acetylation can be quantified by in vivo H2A-GFP confocal images and image correlation spectroscopy (iFCS), which is a scaling analysis, and reveals the opening of chromatin, and thus reorganization changes on scales from 0.2 to ~1µm, consistent with MLS models.
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Counting Nucleosomes *In Vivo*

Counting nucleosomes in living cells with a combination of fluorescence correlation spectroscopy (FCS) and confocal laser scanning microscopy (CLSM) reveals not only the free unbound histone component but also the concentration in absolute numbers of bound histones. Thus, the absolute concentration distribution of histones can be determined and reveals again the typical expected distribution of aggregated chromatin loops.
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Also The Dynamics Can Only Be Based On A Quasi-Fibre Forming Rosettes!
DNA Fragment Distribution after Ione-Irradiation

The length distribution of DNA fragments after irradiation with e.g. C or Ca with an inhomogeneous spatial double strand breakage probability depends on the detailed folding topology of the chromatin fiber and the RW/GL and MLS models differ largely.
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-6
-4
-2
0
2
4
6

x-Position [µm]

-6
-4
-2
0
2
4
6

y-Position [µm]

10
100
1000
10000
100000

Dose in Gy

mass [10^8 kbp]

mass [10^9 kbp]

mass m [10^8 kbp]

mass [10^9 kbp]

mass [10^7 kbp]

logarithmically compressed

The genome organization and evolution are also tightly entangled!

DNA Fragment Distribution after Ionen-Irradiation
Conclusion

The compacted chromatin quasi-fibre, folds into loop-aggregates connected by a linker!

Every structural level of nuclear organization including its dynamics is connected and represented in all the other levels in a holistic systems genomics manner.

- The 3D genomes architecture consists of chromatin quasi-fibres (5±1 nuc. / 11 nm, \( L_p \) of 80-120 nm), forming stable loop aggregates/rosettes (~40-100 kbp loops, ~60 kbp linkers).
- The dynamics of genomes follows the 3D genome architecture in detail and determines in an inseparable entanglement with the architecture genome function.
- From the single base pair to the entire cell nucleus, all genomic levels represent all other levels and by modification a code is present and used to store genetic information.
- Genomes have a consensus organization with only small variation from the basic theme on each compaction level of the genome and these small variations determine genome function.
- Genome organization and function cannot be determined or understood from a single organizational level but only in a holistic systems genomics manner integrating all parts of the system.
- The genome behaves on the basis of a genomic statistical mechanics with a genomic uncertainty principle attached!
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Knoch, T. A.

New York University, New York, New York, USA, 11th December, 2014.

Abstract
The dynamic three-dimensional chromatin architecture of genomes and the obvious co-evolutionary connection to its function – the storage and expression of genetic information – is still, after ~170 years, a central question of current research. With a systems genomics approach using a novel selective high-throughput chromosomal interaction capture (T2C) technique together with quantitative polymer simulations and scaling analysis of genomic structures and the DNA sequence, we determined the architecture of genomes with unprecedented molecular resolution and dynamic range from single base pair entire chromosomes: for several genetic loci of different species, cell type, and functional states we find a chromatin quasi-fibre exists with 5±1 nucleosome per 11 nm, which folds into 40-100 kbp loops forming aggregates/rosettes which are connected by a ~50 kbp chromatin linker. Polymer simulations using Monte Carlo and Brownian dynamics approaches confirm T2C results and allow to predict and to explain additional experimental findings. This agrees also with novel dynamics information from fluorescence correlation spectroscopy (FCS) analysis of chromatin relaxations in vivo. Beyond, we find a fine-structured multi-scaling behaviour of both the architecture and the DNA sequence, which shows for the first time the tight entanglement between architecture and sequence. Since, T2C allows reaching an optimal combination of resolution, interaction frequency range, multiplexing, and an unseen signal-to-noise ratio at molecular resolution this, hence, opens the door to architectural sequencing of genomes. Additionally, we have reached the level of genome mechanics, i.e. corresponding statistical mechanics and uncertainty principles appear and need to be considered. Hence, we determined the three-dimensional architecture and dynamics of genomes for the first time in a consistent system genomics manner from several angles which are all in agreement as well as additionally also with the heuristics of the research of the last 170 years. This will lead to a detailed understanding of genomes with fundamental new insights and huge novel perspectives for diagnosis and treatment.

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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 correlation spectroscopy, spatial precision distance microscopy, super-resolution microscopy, two dimensional 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 operationality, macro operationality, grid psychology micro riskmanagement, macro riskmanagement.

Literature References


