

The GLOBE 3D Genome Platform

A New Paper Tool for Systems Biological/Medical Data Integration

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Introduction

The systems biological/medical combination of genome sequence and structure, its annotation and experimental data in an accessible and comprehensible way is a major challenge. Increasingly there is a large number of extremely divergent data sets: the sequence itself, genes, regulatory regions, various forms of reoccurring sequence features and clone sets etc. Currently, one possibility to represent this information in a visual form - and thus to reveal its scientific meaning - is to use genome browsers such as "Ensembl" or the "UCSC Genome Browser". These browsers have been beneficial in the understanding of the complex organization of genomes. However, there are also limitations concerning their focus on linear presentation, standardized input and data bank accessibility. Also customizability by a remote user with special requirements is difficult. Here we show successfully with the GLOBE 3D Genome Platform ways to visualize multi-dimensional data sets from various sources in an easily accessible way. This allows the integration of these data sets into a single holistic virtual display system giving a systems biological/medical oriented view of genomes advancing basic research, diagnostics and new treatments.

Multi-Mapping

The platform allows the mapping of classical and experimental data tracks projected onto metaphase chromosomes simultaneously (Fig. 1). The general track and every single track element layout is customizable e.g. in position, shape and colour. The viewer allows to visualize in principle an unlimited number of elements.

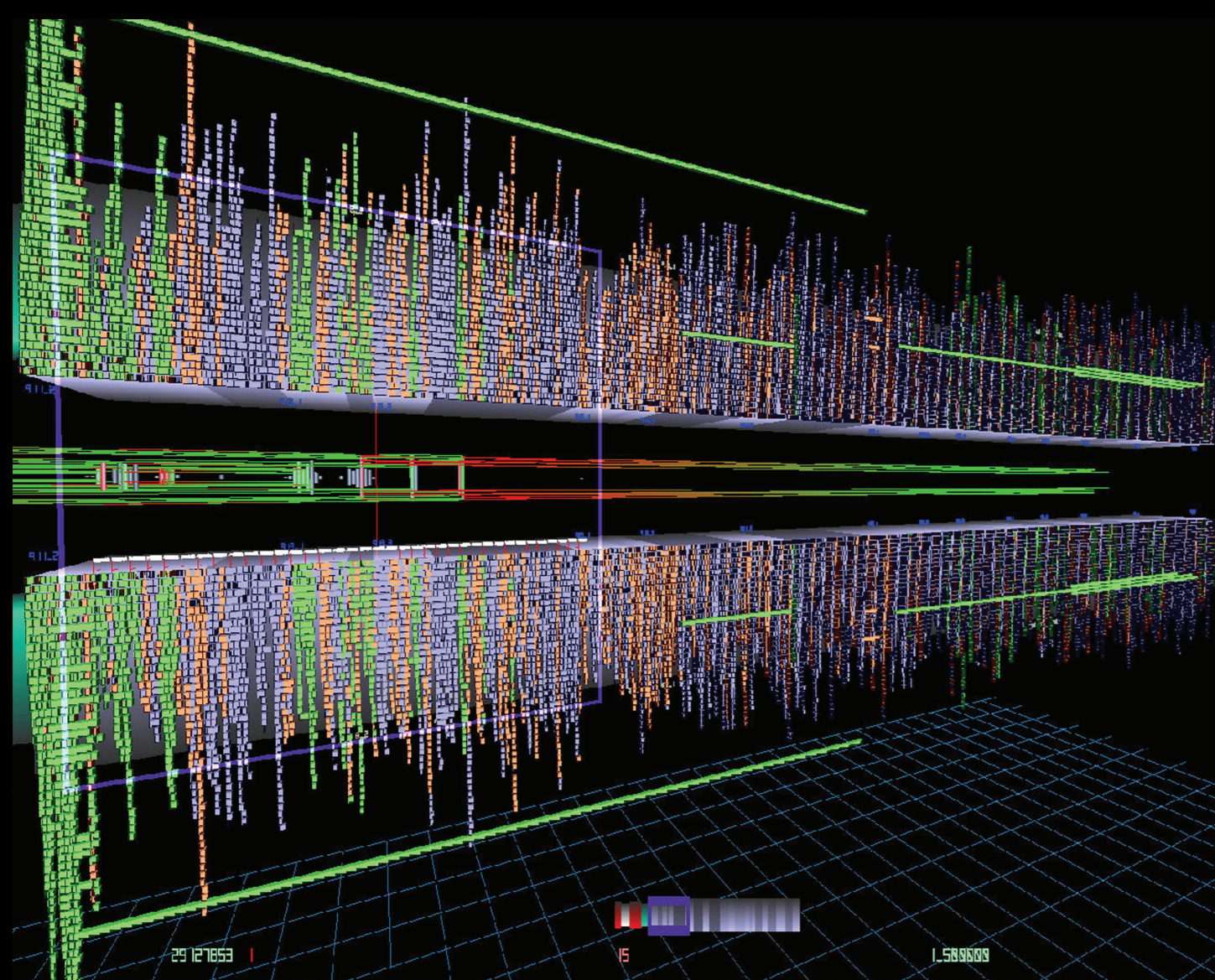


Fig. 1: Complete merged clone set (UCSC, NCBI, Ensembl) of chr. 15; colours represent association with duplication regions.

Inter-Relations

In addition to the simultaneous mapping on one chromosome, the platform allows the analysis of inter-chromosomal relationships based either on an external input (Fig. 2) or internal correlation analysis (Fig. 1-8). Every genome dependent item is relatable e.g. syndromes to duplicons or gene families to breakpoints.

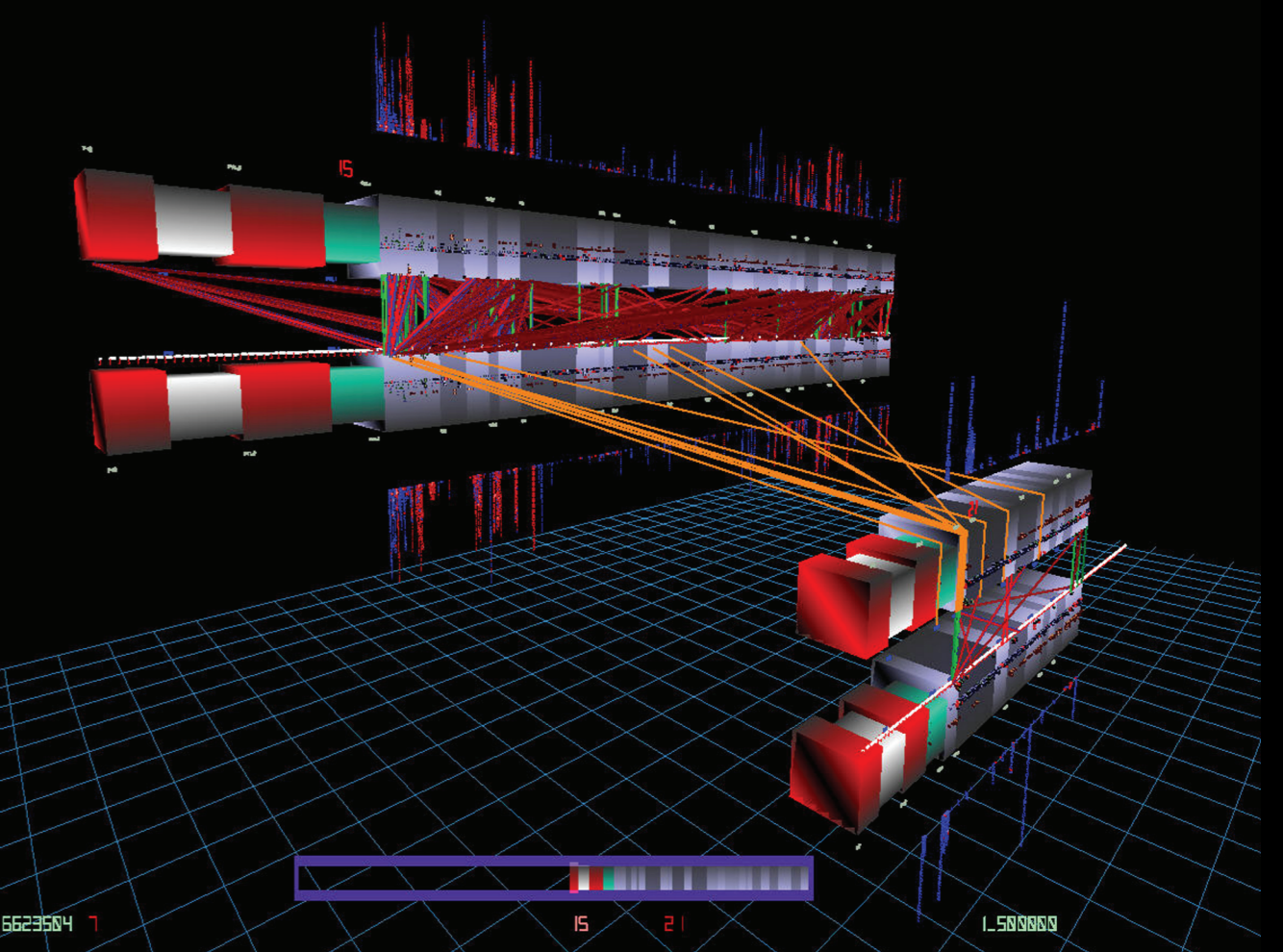


Fig. 2: Multi-chromosomal relation view between duplication regions between chr. 15 & 21. Colours: duplication spreading degree.

Features

Flexible
Customizable
Intuitive Navigation

Real-Time Interaction & Analysis
Dynamical Resolution & Arrangement
Extremely Large & Multi-Dimensional Data

Bridge ALL Scales from Sequence to Morphology

Conclusion

The GLOBE 3D Genome Platform presented here enables researchers to visualize and analyse the multi-dimensional aspects of genomes in a new intuitive way. In combination with a data-warehouse and a computing grid also being set-up in parallel, an environment with entire new inspiring possibilities has been created. This opens new perspectives for future research leading to a better understanding of the holistic systems biological/medical properties of genomes, which is necessary for advanced diagnostic services and perhaps ultimate treatments.

Data Tracks

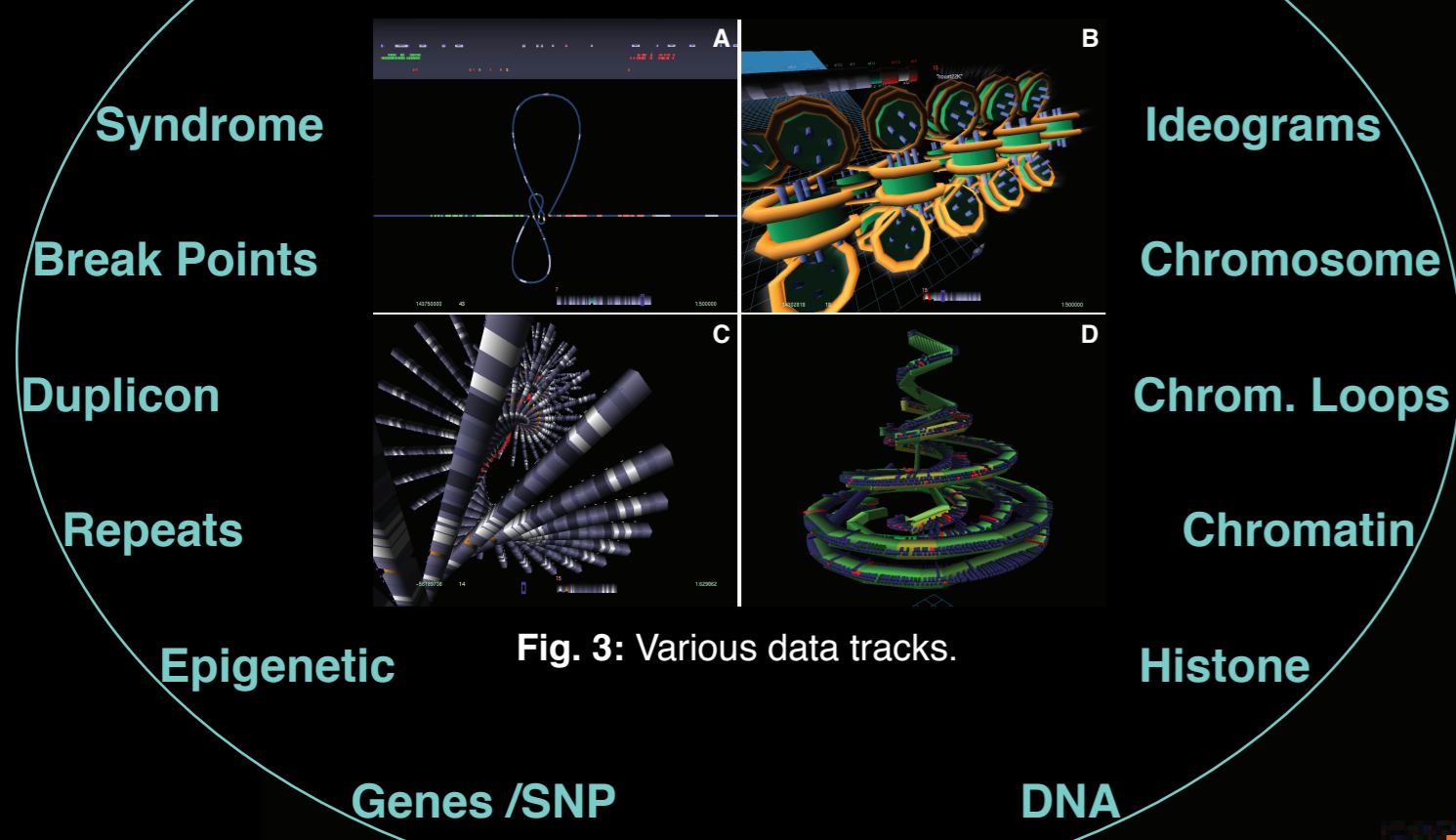


Fig. 3: Various data tracks.

Data Tracks

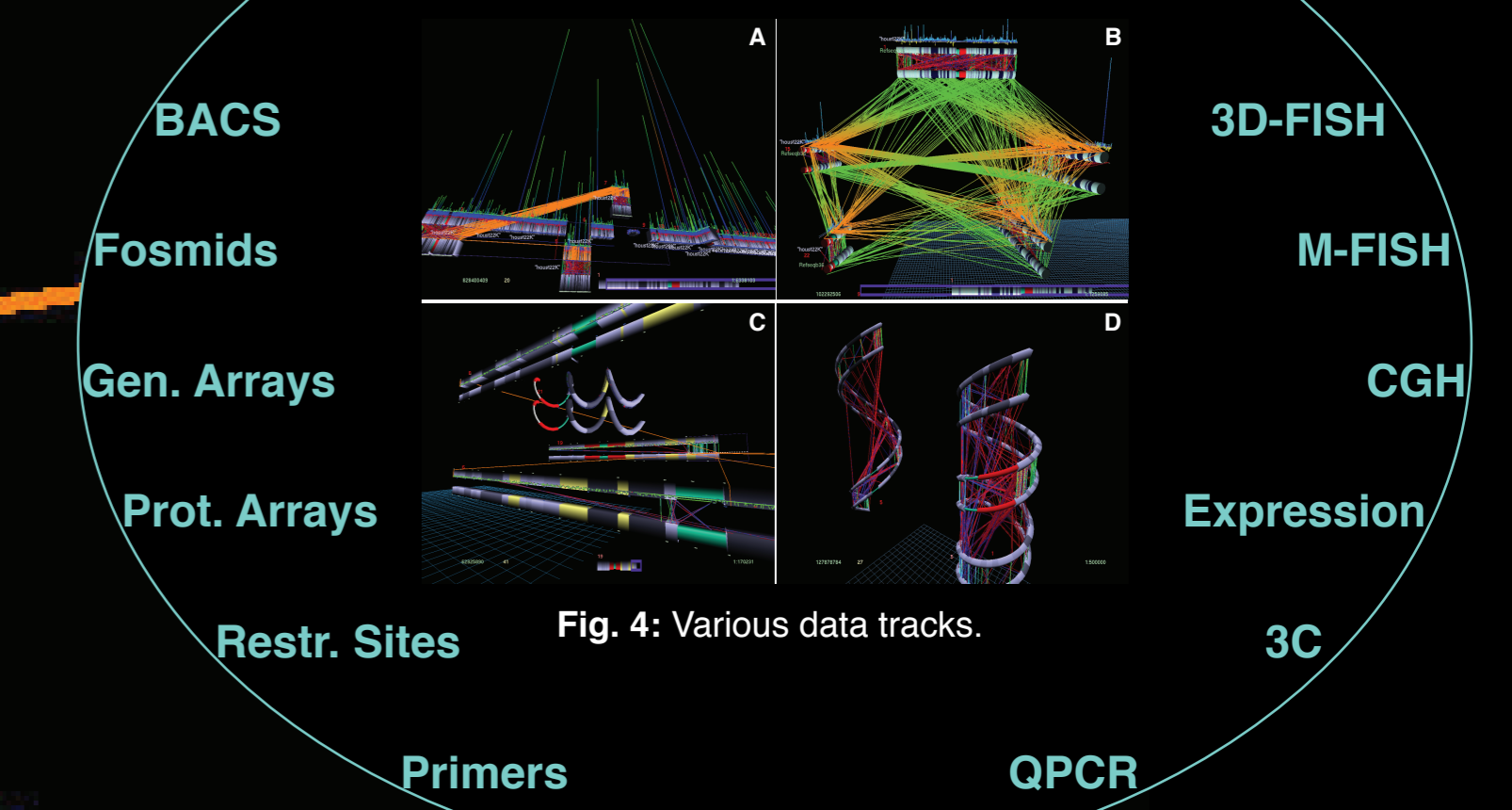


Fig. 4: Various data tracks.

Intra-Relations

Using the dynamic scaling range of the intra-chromosomal relationships can be studied in detail in relation to the track mapping (Fig. 1, 2, 4) concerning basic research, diagnostics and treatments. Assays can be projected, related, reviewed and redefined thus leading on various genome levels to scale-free insights.

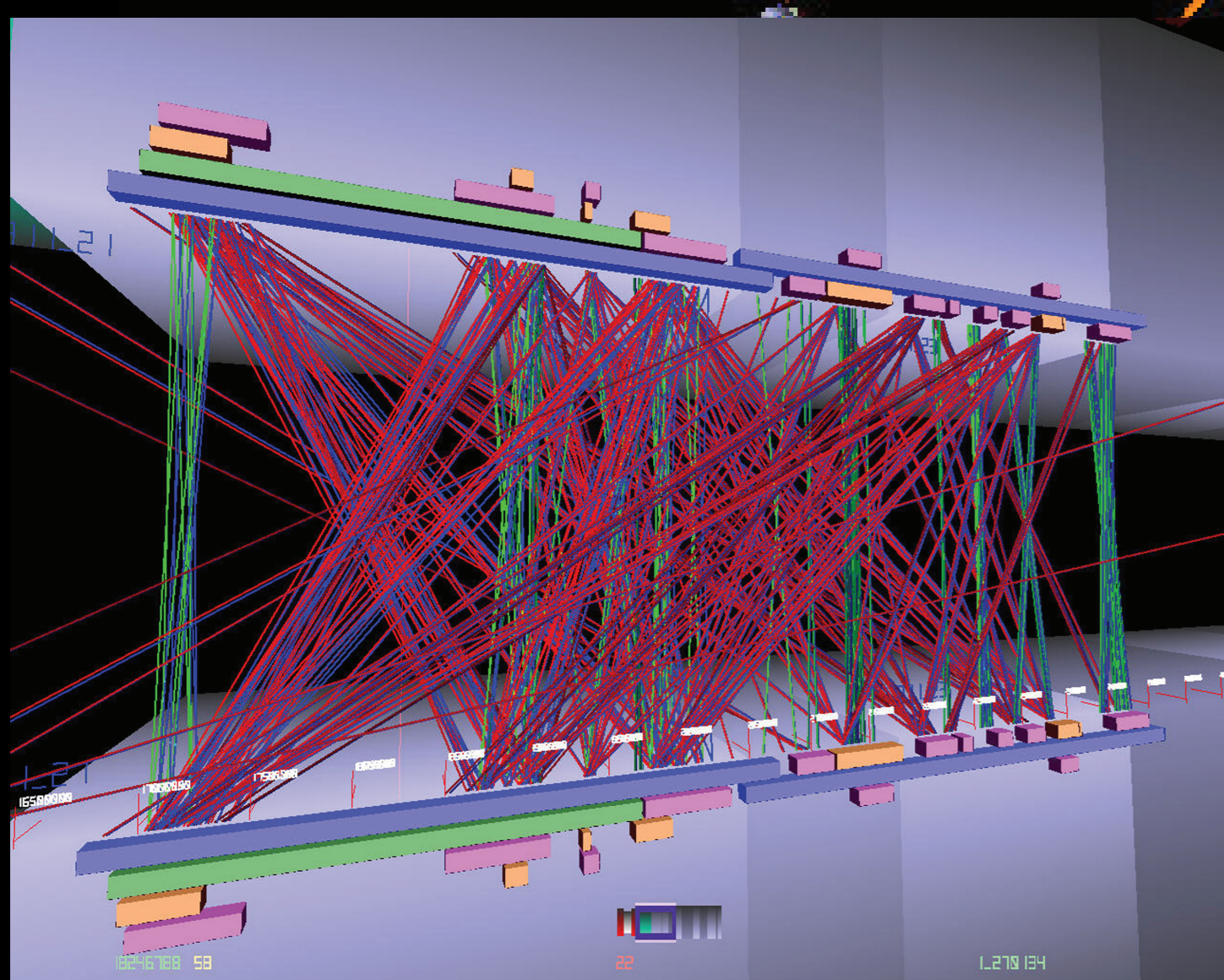


Fig. 5: Intra-chromosomal duplicons (Eichler et al.) compared to syndromes (blue/green), literature hot-spots (orange), and our defined hot-spots (pink) of the chr. 22q.11 region.

Structure

There are several physical levels of genetic information storage, e.g. DNA, chromatin and chromosomes. The interaction between information and the structural carrier is of critical importance for genome function. The platform visualizes 3D genomic structures and to project and link these to a classical linear representation (Fig. 6).

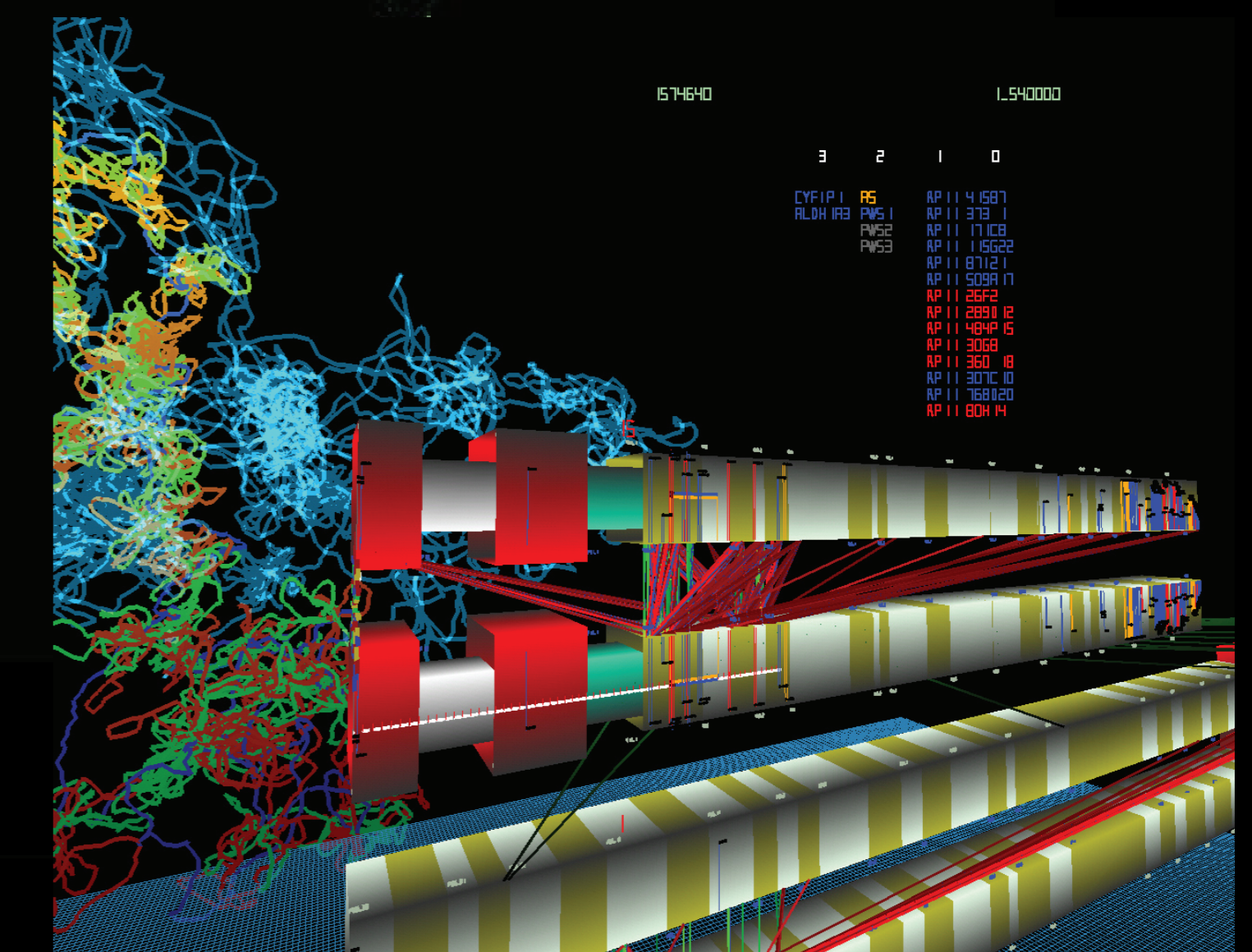


Fig. 8: Correlation of a simulated 3D chromatin/chromosome topology combined with the - in principle - linear information content in the DNA sequence and multi-dimensional mapping of chr. 15.

Resolution Scale

The platform has a large dynamic range in the size and resolution of the features it can display: from whole genomes (Fig. 7) or chromosomes (Fig. 8) to individual bases (Fig. 6). This new environment creates entire new possibilities for understanding genome organization.

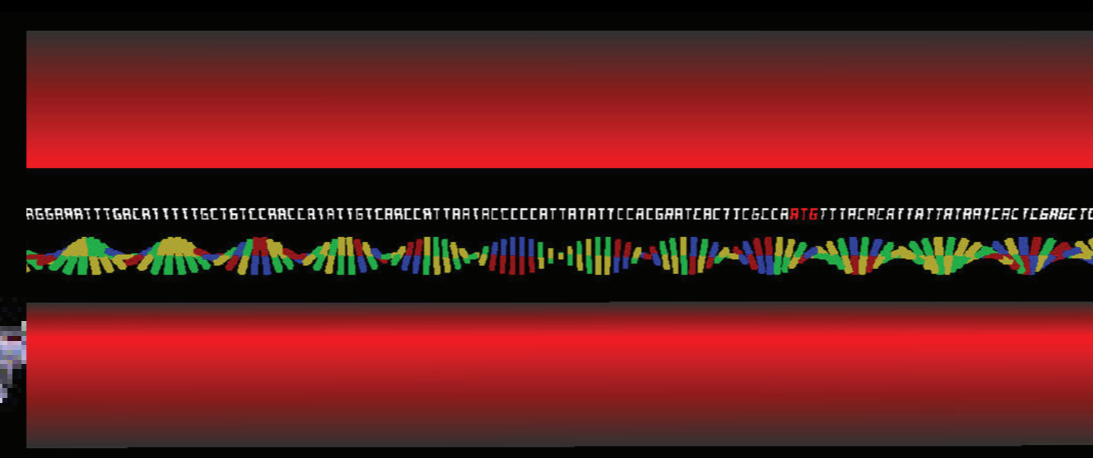


Fig. 6: Dynamic zoom into the level of the DNA.

Fig. 7: Background image: Multi-chromosomal relation between the breakpoints of chr. 15 to all other chromosomes. Colours: as in Fig. 2.

The GLOBE 3D Genome Platform – A New Virtual Paper Tool for Systems Biological/Medical Data Integration

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Abstract

Genomes are tremendous co-evolutionary holistic systems for molecular storage, processing and fabrication of information. Their system-biological complexity remains, however, still largely mysterious, despite the huge advances in the understanding of the general sequential, three-dimensional and regulatory organization. With the development of the *GLOBE 3D Genome Platform* we have created a completely novel grid based virtual “paper” tool and in fact the first systems biological/medical genome browser integrating the holistic complexity of genomes in a single easy comprehensible way, which is used in WP1-5. Based on a detailed study of biophysical and IT requirements, every architectural level from sequence to morphology of one or several genomes can be approached in a real (WP1-3) and in a simulated symbolic representation (WP4) simultaneously and navigated by continuous scale-free zooming within a three-dimensional OpenGL and grid driven environment. In principle several multi-dimensional data sets can be visualized, customized in terms of arrangement, shape, colour, and texture etc. as well as accessed and annotated individually or in groups using internal or external data bases/facilities. Hence, the GLOBE 3D Genome Platform is an example of a grid based approach towards a virtual holistic desktop for system biological/medical genomic work combining the three fundamental distributed resources: i) visual data representation, ii) data access and management, and iii) data analysis and creation.

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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.

Literature References

- Knoch, T. A.** Dreidimensionale Organisation von Chromosomen-Domänen in Simulation und Experiment. (Three-dimensional organization of chromosome domains in simulation and experiment.) *Diploma Thesis*, Faculty for Physics and Astronomy, Ruperto-Carola University, Heidelberg, Germany, 1998, and TAK Press, Tobias A. Knoch, Mannheim, Germany, ISBN 3-00-010685-5 and ISBN 978-3-00-010685-9 (soft cover, 2nd ed.), ISBN 3-00-035857-9 and ISBN 978-3-00-0358857-0 (hard cover, 2nd ed.), ISBN 3-00-035858-7, and ISBN 978-3-00-035858-6 (DVD, 2nd ed.), 1998.
- Knoch, T. A., Münkkel, C. & Langowski, J.** Three-dimensional organization of chromosome territories and the human cell nucleus - about the structure of a self replicating nano fabrication site. *Foresight Institute - Article Archive*, Foresight Institute, Palo Alto, CA, USA, <http://www.foresight.org>, 1- 6, 1998.
- Knoch, T. A., Münkkel, C. & Langowski, J.** Three-Dimensional Organization of Chromosome Territories and the Human Interphase Nucleus. *High Performance Scientific Supercomputing*, editor Wilfried Juling, Scientific Supercomputing Center (SSC) Karlsruhe, University of Karlsruhe (TH), 27- 29, 1999.
- Knoch, T. A., Münkkel, C. & Langowski, J.** Three-dimensional organization of chromosome territories in the human interphase nucleus. *High Performance Computing in Science and Engineering 1999*, editors Krause, E. & Jäger, W., High-Performance Computing Center (HLRS) Stuttgart, University of Stuttgart, Springer Berlin-Heidelberg-New York, ISBN 3-540-66504-8, 229-238, 2000.
- Bestvater, F., **Knoch, T. A.**, Langowski, J. & Spiess, E. GFP-Walking: Artificial construct conversions caused by simultaneous cotransfection. *BioTechniques* 32(4), 844-854, 2002.
- Gil-Parado, S., Fernández-Montalván, A., Assfalg-Machleidt, I., Popp, O., Bestvater, F., Holloschi, A., **Knoch, T. A.**, Auerswald, E. A., Welsh, K., Reed, J. C., Fritz, H., Fuentes-Prior, P., Spiess, E., Salvesen, G. & Machleidt, W. Ionomycin-activated calpain triggers apoptosis: A probable role for Bcl-2 family members. *J. Biol. Chem.* 277(30), 27217-27226, 2002.
- Knoch, T. A. (editor)**, Backes, M., Baumgärtner, V., Eysel, G., Fehrenbach, H., Göker, M., Hampl, J., Hampl, U., Hartmann, D., Hitzelberger, H., Nambena, J., Rehberg, U., Schmidt, S., Weber, A., & Weidemann, T. Humanökologische Perspektiven Wechsel - Festschrift zu Ehren des 70. Geburtstags von Prof. Dr. Kurt Egger. Human Ecology Working Group, Ruperto-Carola University of Heidelberg, Heidelberg, Germany, 2002.
- Knoch, T. A.** Approaching the three-dimensional organization of the human genome: structural-, scaling- and dynamic properties in the simulation of interphase chromosomes and cell nuclei, long- range correlations in complete genomes, *in vivo* quantification of the chromatin distribution, construct conversions in simultaneous co-transfections. *Dissertation*, Ruperto-Carola University, Heidelberg, Germany, and TAK†Press, Tobias A. Knoch, Mannheim, Germany, ISBN 3-00-009959-X and ISBN 978-3-00-009959-5 (soft cover, 3rd ed.), ISBN 3-00-009960-3 and ISBN 978-3-00-009960-1 (hard cover, 3rd ed.), ISBN 3-00-035856-9 and ISBN 978-3-00-010685-9 (DVD, 3rd ed.) 2002.
- Westphal, G., van den Berg-Stein, S., Braun, K., **Knoch, T. A.**, Dümmerling, M., Langowski, J., Debus, J. & Friedrich, E. Detection of the NGF receptors TrkaA and p75NTR and effect of NGF on the growth characteristics of human tumor cell lines. *J. Exp. Clin. Canc. Res.* 21(2), 255-267, 2002.
- Westphal, G., Niederberger, E., Blum, C., Wollman, Y., **Knoch, T. A.**, Dümmerling, M., Rebel, W., Debus, J. & Friedrich, E. Erythropoietin Receptor in Human Tumor Cells: Expression and Aspects Regarding Functionality. *Tumori* 88(2), 150-159, 2002.
- Gil-Parado, S., Popp, O., **Knoch, T. A.**, Zahler, S., Bestvater, F., Felgenträger, M., Holoshi, A., Fernández-Montalván, A., Auerswald, E. A., Fritz, H., Fuentes-Prior, P., Machleidt, W. & Spiess, E. Subcellular localization and subunit interactions of over-expressed human μ -calpain. *J. Biol. Chem.* 278(18), 16336-15346, 2003.
- Knoch, T. A.** Towards a holistic understanding of the human genome by determination and integration of its sequential and three-dimensional organization. *High Performance Computing in Science and Engineering 2003*, editors Krause, E., Jäger, W. & Resch, M., High-Performance Computing Center (HLRS) Stuttgart, University of Stuttgart, Springer Berlin-Heidelberg-New York, ISBN 3- 540-40850-9, 421-440, 2003.
- Wachsmuth, M., Weidemann, T., Müller, G., Urs W. Hoffmann-Rohrer, **Knoch, T. A.**, Waldeck, W. & Langowski, J. Analyzing intracellular binding and diffusion with continuous fluorescence photobleaching. *Biophys. J.* 84(5), 3353-3363, 2003.

- Weidemann, T., Wachsmuth, M., **Knoch, T. A.**, Müller, G., Waldeck, W. & Langowski, J. Counting nucleosomes in living cells with a combination of fluorescence correlation spectroscopy and confocal imaging. *J. Mol. Biol.* 334(2), 229-240, 2003.
- Fejes Tóth, K., **Knoch, T. A.**, Wachsmuth, M., Frank-Stöhr, M., Stöhr, M., Bacher, C. P., Müller, G. & Rippe, K. Trichostatin A induced histone acetylation causes decondensation of interphase chromatin. *J. Cell Science* 177, 4277-4287, 2004.
- Ermler, S., Kronic, D., **Knoch, T. A.**, Moshir, S., Mai, S., Greulich-Bode, K. M. & Boukamp, P. Cell cycle-dependent 3D distribution of telomeres and telomere repeat-binding factor 2 (TRF2) in HaCaT and HaCaT-myc cells. *Europ. J. Cell Biol.* 83(11-12), 681-690, 2004.
- Kost, C., Gama de Oliveira, E., **Knoch, T. A.** & Wirth, R. Spatio-temporal permanence and plasticity of foraging trails in young and mature leaf-cutting ant colonies (*Atta spp.*). *J. Trop. Ecol.* 21(6), 677- 688, 2005.
- Winnefeld, M., Grewenig, A., Schnölzer, M., Spring, H., **Knoch, T. A.**, Gan, E. C., Rommelaere, J. & Cziepluch, C. Human SGT interacts with BAG-6/Bat-3/Scythe and cells with reduced levels of either protein display persistence of few misaligned chromosomes and mitotic arrest. *Exp. Cell Res.* 312, 2500-2514, 2006.
- Sax, U., Weisbecker, A., Falkner, J., Viezens, F., Yassene, M., Hartung, M., Bart, J., Krefting, D., **Knoch, T. A.** & Semler, S. Grid-basierte Services für die elektronische Patientenakte der Zukunft. *E- HEALTH-COM - Magazin für Gesundheitstelematik und Telemedizin*, 4(2), 61-63, 2007.
- de Zeeuw, L. V., **Knoch, T. A.**, van den Berg, J. & Grosveld, F. G. Erasmus Computing Grid - Het bouwen van een 20 TeraFLOP virtuele supercomputer. *NIOC proceedings 2007 - het perspectief van lange termijn.* editor Frederik, H. NIOC, Amsterdam, The Netherlands, 52-59, 2007.
- Rauch, J., **Knoch, T. A.**, Solovei, I., Teller, K. Stein, S., Buiting, K., Horsthemke, B., Langowski, J., Cremer, T., Hausmann, M. & Cremer, C. Lightoptical precision measurements of the Prader- Willi/Angelman Syndrome imprinting locus in human cell nuclei indicate maximum condensation changes in the few hundred nanometer range. *Differentiation* 76(1), 66-82, 2008.
- Sax, U., Weisbecker, A., Falkner, J., Viezens, F., Mohammed, Y., Hartung, M., Bart, J., Krefting, D., **Knoch, T. A.** & Semler, S. C. Auf dem Weg zur individualisierten Medizin - Grid-basierte Services für die EPA der Zukunft. *Telemedizinführer Deutschland 2008*, editor Jäckel, A. Deutsches Medizinforum, Minerva KG, Darmstadt, ISBN 3-937948-06-6, ISBN-13 9783937948065, 47-51, 2008.
- Drägestein, K. A., van Capellen, W. A., van Haren, J. Tsibidis, G. D., Akhmanova, A., **Knoch, T. A.**, Grosveld, F. G. & Galjart, N. Dynamic behavior of GFP-CLIP-170 reveals fast protein turnover on microtubule plus ends. *J. Cell Biol.* 180(4), 729-737, 2008.
- Jhunjhunwala, S., van Zelm, M. C., Peak, M. M., Cutchin, S., Riblet, R., van Dongen, J. J. M., Grosveld, F. G., **Knoch, T. A.**⁺ & Murre, C.⁺ The 3D-structure of the Immunoglobulin Heavy Chain Locus: implications for long-range genomic interactions. *Cell* 133(2), 265-279, 2008.
- Krefting, D., Bart, J., Beronov, K., Dzhimova, O., Falkner, J., Hartung, M., Hoheisel, A., **Knoch, T. A.**, Lingner, T., Mohammed, Y., Peter, K., Rahm, E., Sax, U., Sommerfeld, D., Steinke, T., Tolxdorff, T., Vossberg, M., Viezens, F. & Weisbecker, A. MediGRID - Towards a user friendly secured grid infrastructure. *Future Generation Computer Systems* 25(3), 326-336, 2008.
- Knoch, T. A.**, Lesnussa, M., Kepper, F. N., Eussen, H. B., & Grosveld, F. G. The GLOBE 3D Genome Platform - Towards a novel system-biological paper tool to integrate the huge complexity of genome organization and function. *Stud. Health. Technol. Inform.* 147, 105-116, 2009.
- Knoch, T. A.**, Baumgärtner, V., de Zeeuw, L. V., Grosveld, F. G., & Egger, K. e-Human Grid Ecology: Understanding and approaching the Inverse Tragedy of the Commons in the e-Grid Society. *Stud. Health. Technol. Inform.* 147, 269-276, 2009.
- Dickmann, F., Kaspar, M., Löhnardt, B., **Knoch, T. A.**, & Sax, U. Perspectives of MediGRID. *Stud. Health. Technol. Inform.* 147, 173-182, 2009.
- Knoch, T. A.**, Göcker, M., Lohner, R., Abuseiris, A. & Grosveld, F. G. Fine-structured multi-scaling long-range correlations in completely sequenced genomes - features, origin and classification. *Eur. Biophys. J.* 38(6), 757-779, 2009.
- Dickmann, F., Kaspar, M., Löhnardt, B., Kepper, N., Viezens, F., Hertel, F., Lesnussa, M., Mohammed, Y., Thiel, A., Steinke, T., Bernarding, J., Krefting, D., **Knoch, T. A.** & Sax, U. Visualization in health-grid environments: a novel service and business approach. *LNCS 5745*, 150-159, 2009.

- Dickmann, F., Kaspar, M., Löhnhardt, B., Kepper, N., Viezens, F., Hertel, F., Lesnussa, M., Mohammed, Y., Thiel, A., Steinke, T., Bernarding, J., Krefling, D., **Knoch, T. A.** & Sax, U. Visualization in health-grid environments: a novel service and business approach. *Grid economics and business models - GECON 2009 Proceedings, 6th international workshop, Delft, The Netherlands*. editors Altmann, J., Buyya, R. & Rana, O. F., GECON 2009, LNCS 5745, Springer-Verlag Berlin Heidelberg, ISBN 978-3-642-03863-1, 150-159, 2009.
- Estrada, K.^{*}, Abuseiris, A.^{*}, Grosveld, F. G., Uitterlinden, A. G., **Knoch, T. A.**⁺ & Rivadeneira, F.⁺ GRIMP: A web- and grid-based tool for high-speed analysis of large-scale genome-wide association using imputed data. *Bioinformatics* 25(20), 2750-2752, 2009.
- de Wit, T., Dekker, S., Maas, A., Breedveld, G., **Knoch, T. A.**, Langeveld, A., Szumska, D., Craig, R., Bhattacharya, S., Grosveld, F. G.⁺ & Drabek, D. Tagged mutagenesis of efficient minos based germ line transposition. *Mol. Cell Biol* 30(1), 66-77, 2010.
- 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 Technol. Inform.* 159, 171-180, 2010.
- 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 Technol. Inform.* 159, 264-271, 2010.
- 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 Technol. Inform.* 159, 277-282, 2010.
- Knoch, T. A.**, Baumgärtner, V., Grosveld, F. G. & Egger, K. Approaching the internalization challenge of grid technologies into e-Society by e-Human “Grid” Ecology. *Economics of Grids, Clouds, Systems, and Services – GECON 2010 Proceedings, 7th International Workshop, Ischia, Italy*, editors Altman, J., & Rana, O. F., Lecture Notes in Computer Science (LNCS) 6296, Springer Berlin Heidelberg New York, ISSN 0302-9743, ISBN-10 3-642-15680-0, ISBN-13 978-3-642-15680-9, 116-128, 2010.
- Dickmann, F., Brodhun, M., Falkner, J., **Knoch, T. A.** & Sax, U. Technology transfer of dynamic IT outsourcing requires security measures in SLAs. *Economics of Grids, Clouds, Systems, and Services – GECON 2010 Proceedings, 7th International Workshop, Ischia, Italy*, editors Altman, J., & Rana, O. F., Lecture Notes in Computer Science (LNCS) 6296, Springer Berlin Heidelberg New York, ISSN 0302-9743, ISBN-10 3-642-15680-0, ISBN-13 978-3-642-15680-9, 1-115, 2010.
- Knoch, T. A.** Sustained Renewability: approached by systems theory and human ecology. *Renewable Energy* 2, editors M. Nayeripour & M. Keshti, Intech, ISBN 978-953-307-573-0, 21-48, 2011.
- Kolovos, P., **Knoch, T. A.**, F. G. Grosveld, P. R. Cook, & Papanonis, A. Enhancers and silencers: an integrated and simple model for their function. *Epigenetics and Chromatin* 5(1), 1-8, 2012.
- Dickmann, F., Falkner, J., Gunia, W., Hampe, J., Hausmann, M., Herrmann, A., Kepper, N., **Knoch, T. A.**, Lauterbach, S., Lippert, J., Peter, K., Schmitt, E., Schwardmann, U., Solodenko, J., Sommerfeld, D., Steinke, T., Weisbecker, A. & Sax, U. Solutions for Biomedical Grid Computing - Case Studies from the D-Grid Project Services@MediGRID. *JOCS* 3(5), 280-297, 2012.
- Estrada, K., Abuseiris, A., Grosveld, F. G., Uitterlinden, A. G., **Knoch, T. A.** & Rivadeneira, F. GRIMP: A web- and grid-based tool for high-speed analysis of large-scale genome-wide association using imputed data. *Dissection of the complex genetic architecture of human stature and osteoporosis*. cumulative dissertation, editor Estrada K., Erasmus Medical Center, Erasmus University Rotterdam, Rotterdam, The Netherlands, ISBN 978-94-6169-246-7, 25-30, 1st June 2012.
- van de Corput, M. P. C., de Boer, E., **Knoch, T. A.**, van Cappellen, W. A., Quintanilla, A., Ferrand, L., & Grosveld, F. G. Super-resolution imaging reveals 3D folding dynamics of the β -globin locus upon gene activation. *J. Cell Sci.* 125 (Pt 19), 4630-4639, 2012.
- da Silva, P. S. D., Delgado Bieber, A. G., Leal, I. R., **Knoch, T. A.**, Tabarelli, M., Leal, I. R., & Wirth, R. Foraging in highly dynamic environments: leaf-cutting ants adjust foraging trail networks to pioneer plant availability. *Entomologia Experimentalis et Applicata* 147, 110-119, 2013.
- Zuin, J., Dixon, J. R., van der Reijden, M. I. J. A., Ye, Z., Kolovos, P., Brouwer, R. W. W., van de Corput, M. P. C., van de Werken, H. J. G., **Knoch, T. A.**, van IJcken, W. F. J., Grosveld, F. G., Ren, B. & Wendt, K. S. Cohesin and CTCF differentially affect chromatin architecture and gene expression in human cells. *PNAS* 111(3), 9906-1001, 2014.
- Kolovos, P., Kepper, N., van den Werken, H. J. G., Lesnussa, M., Zuin, J., Brouwer, R. W. W., Kockx, C. E. M., van IJcken, W. F. J., Grosveld, F. G. & **Knoch, T. A.** Targeted Chromatin Capture (T2C): A novel high

resolution high throughput method to detect genomic interactions and regulatory elements. *Epigenetics & Chromatin* 7:10, 1-17, 2014.

Diermeier, S., Kolovos, P., Heizinger, L., Schwartz, U., Georgomanolis, T., Zirkel, A., Wedemann, G., Grosveld, F. G., **Knoch, T. A.**, Merkl, R., Cook, P. R., Längst, G. & Papantonis, A. TNF α signalling primes chromatin for NF- κ B binding and induces rapid and widespread nucleosome repositioning. *Genome Biology* 15(12), 536-548, 2014.

Knoch, T. A., Wachsmuth, M., Kepper, N., Lesnussa, M., Abuseiris, A., A. M. Ali Imam, Kolovos, P., Zuin, J., Kockx, C. E. M., Brouwer, R. W. W., van de Werken, H. J. G., van IJcken, W. F. J., Wendt, K. S. & Grosveld, F. G. The detailed 3D multi-loop aggregate/rosette chromatin architecture and functional dynamic organization of the human and mouse genomes. *bioRxiv preprint*, 16.07.2016.

Kolovos, P., Georgomanolis, T., Koferle, A., Larkin, J. D., Brant, J., Nikolić, M., Gusmao, E. G., Zirkel, A., **Knoch, T. A.**, van IJcken, W. F. J., Cook, P. R., Costa, I. G., Grosveld, F. G. & Papantonis, A. Binding of nuclear kappa-B to non-canonical consensus sites reveals its multimodal role during the early inflammatory response. *Genome Research* 26(11), 1478-1489, 2016.

Wachsmuth, M., **Knoch, T. A.** & Rippe, K. Dynamic properties of independent chromatin domains measured by correlation spectroscopy in living cells. *Epigenetics & Chromatin* 9:57, 1-20, 2016.

Knoch, T. A., Wachsmuth, M., Kepper, N., Lesnussa, M., Abuseiris, A., A. M. Ali Imam, Kolovos, P., Zuin, J., Kockx, C. E. M., Brouwer, R. W. W., van de Werken, H. J. G., van IJcken, W. F. J., Wendt, K. S. & Grosveld, F. G. The detailed 3D multi-loop aggregate/rosette chromatin architecture and functional dynamic organization of the human and mouse genomes. *Epigenetics & Chromatin* 9:58, 1-22, 2016.