

Targeted Chromatin Capture (T2C): A Novel High Resolution High Throughput Method to Detect Genomic Interactions and Regulatory Elements.

Petros Kolovos^{1,4}, Harmen J. G. van de Werken¹, Nick Kepper^{2,4}, Michael Lesnussa^{2,4}, Jessica Zuin¹, Rutger W.W. Brouwer³, Christel E.M. Kockx³, Kerstin S. Wendt¹, Wilfred F.J. van IJcken³, Frank G. Grosveld¹ & Tobias A. Knoch^{1,2,4}

¹Cell Biology, Dept. Cell Biology & Genetics, Erasmus MC, Wytemaweg 80, 3015 CN Rotterdam, the Netherlands

²Deutsches Krebsforschungszentrum (DKFZ) & BioQuant, Im Neuenheimer Feld 280, Heidelberg 69120, Germany

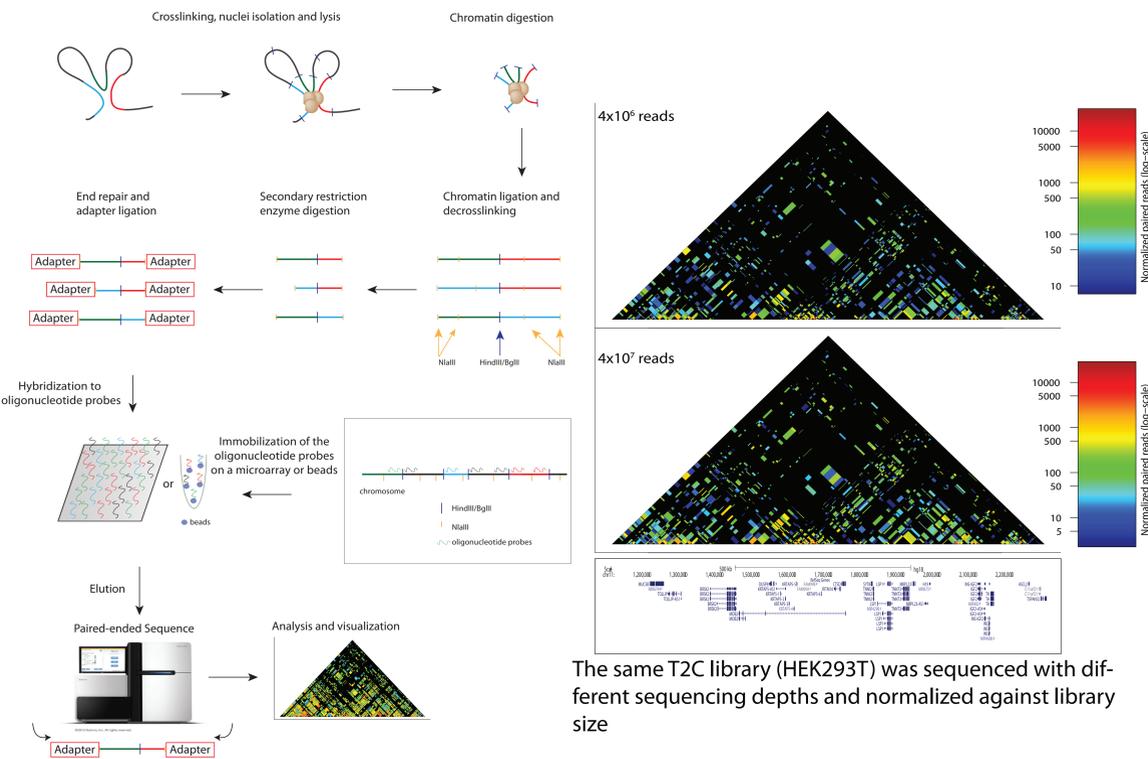
³Center for Biomics, Erasmus MC, Wytemaweg 80, 3015 CN Rotterdam, the Netherlands

⁴Biophysical Genomics, Dept. Cell Biology & Genetics, Erasmus MC, Wytemaweg 80, 3015 CN Rotterdam, the Netherlands

Introduction

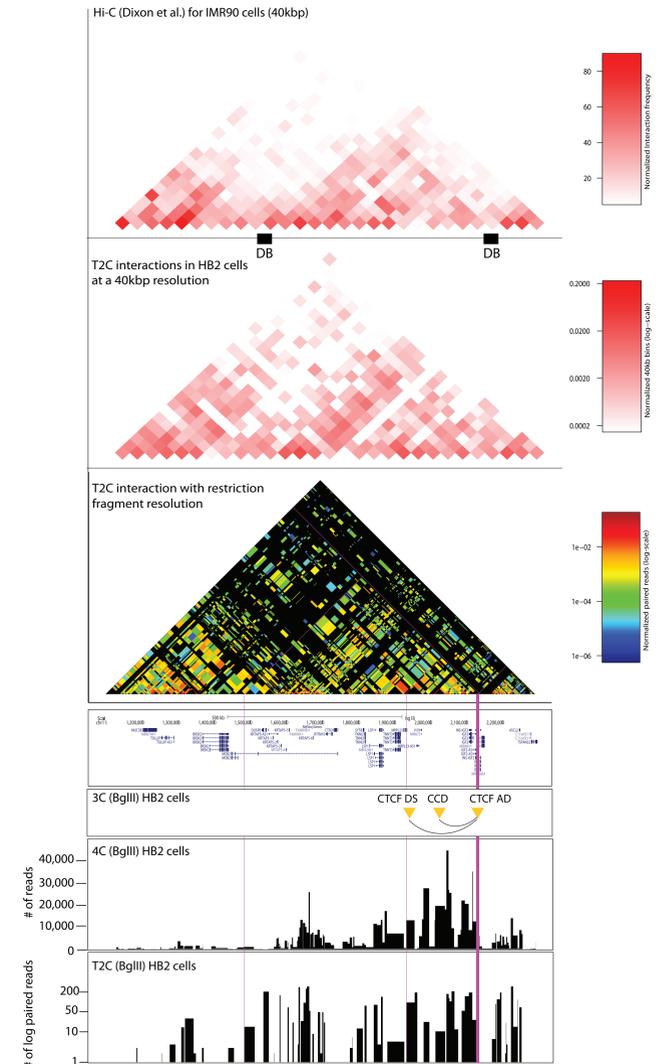
Chromosome conformation capture (3C) technology and its derivatives are important tools to unravel the organization and the interaction networks in the genome. However, many of these have limitations, such as being limited to one viewpoint, expensive with moderate to low resolution, and/or requiring a large sequencing effort with considerable costs.

- T2C:
- Investigates the local chromatin interactome and the compartmentalization of the genome
 - Offers significantly improved resolution (restriction fragment resolution, 2kbp) with lower sequencing effort relevant to Hi-C
 - Every restriction fragment can be used as in individual viewpoint to reveal its interactions.



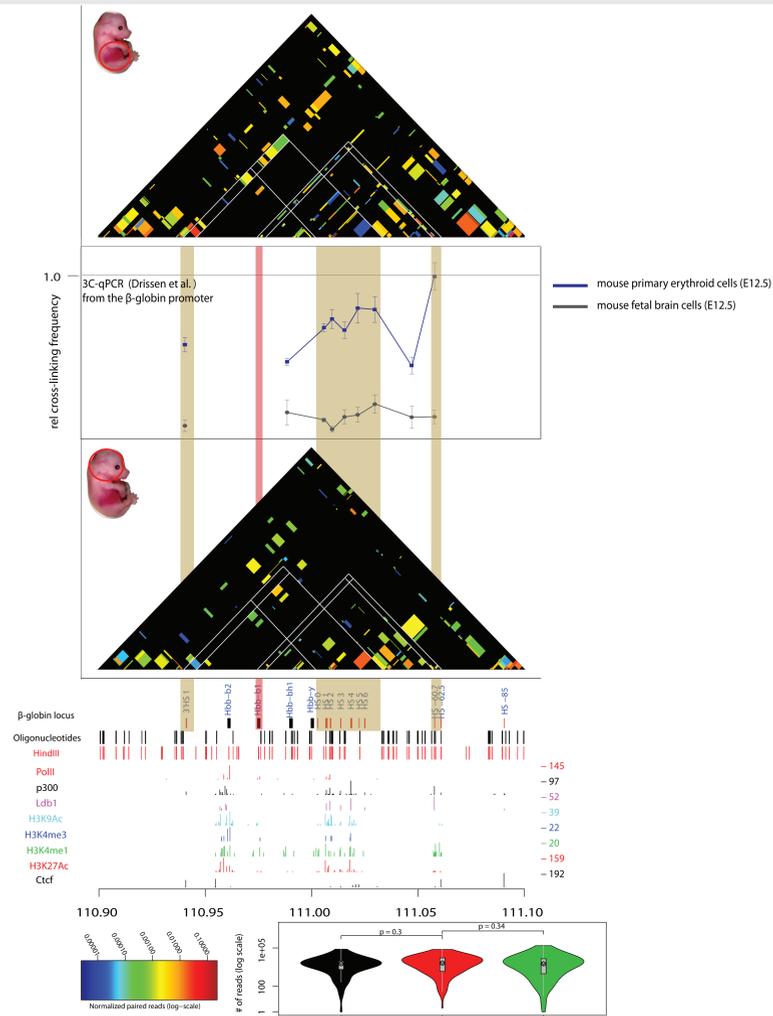
→ Different sequencing depth results in a similar output

T2C reveals the same interactions and topological domains relevant to other methods



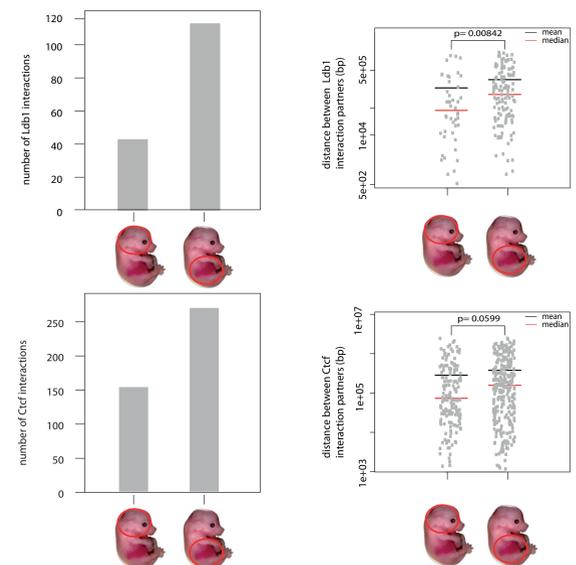
- T2C identifies the same topological domain boundaries as Hi-C
- T2C identifies known long range interactions with high resolution

T2C identifies the known interactions in the β -globin locus



- T2C identifies the known interactions between β -globin promoter and its LCR and LCR with 3' HS1 in mouse primary erythroid cells
- Those interactions are gone in the mouse fetal brain (β -globin is not active)
- T2C is normalized using the capture efficiency of each fragment
- Even fragments without oligonucleotide probe, are sufficiently covered

The number of Ldb1 and Ctf interactions and distance is different in the mouse primary erythroid cells compared to mouse fetal liver cells



Ldb1 is important for primitive mouse hematopoiesis and depletion is lethal for mouse embryos (E9.5)

Ldb1 and Ctf are involved in chromatin conformation

- In mouse primary erythroid cells (β -globin is active) we observe higher number of interacting fragments at larger linear distances

Conclusions

- Straightforward to design a set of oligonucleotides for a number of loci
- Restriction fragment resolution down to 2kbp
- Flexible method (multiplex samples with different barcodes to decrease costs)
- Explore the local spatial organization and chromatin interactions.

Targeted Chromatin Capture (T2C): A novel high resolution high throughput method to detect genomic interactions and regulatory elements.

Kolovos, P., van den Werken, H. J. G., Kepper, N., Lesnussa, M., Zuin, J., Brouwer, R. W. W., Kockx, C. E. M., Wendt, K. S, van IJcken, W. F. J., Grosveld, F. G. & **Knoch, T. A.**

Chromatin and Epigenetics: From Omics to Single Cells 2014, Institut de Genetique et de Biologie Moleculaire et Cellulaire (IGBMC), Strasbourg, France, 14th - 15th October, 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 of concentrated research, one of the central issues of our time. With a systems genomics combination of T2C and FCS together with analytical and simulated polymer models as well as scaling analysis of the architecture and the DNA sequence itself, we determined the architecture and dynamics with with molecular resolution from the single base to the mega base pair level!

T2C is a novel superior selective high-throughput high-resolution chromosomal interaction capture of all physical genomic interactions (T2C) which has great advantages since it allows to reach an optimal combination of resolution, interaction frequency range, and multi-plexability, at unprecedented signal-to-noise ratio of multiple orders of magnitude. Actually, with T2C the ultimate limits at the level of the “genomic uncertainty principle” and “genomic statistical mechanics”, is reached. In parallel, with a novel FCS approach it is possible to determine the relaxation of local concentration fluctuations of the chromatin fibre and derive based on an analytical polymer model the relation between average persistence length, mass density and chromatin architecture. Whereas T2C measures architectural parameters, the FCS approach allows to measure *in vivo* the dynamics of the architecture. As common ground polymer simulations using Monte Carlo and Brownian Dynamics approaches as well as scaling analysis of the architecture as well as the DNA sequence organization itself round-off the experimental techniques in detail. In combination all four approaches reach agreement concerning the 3D architecture and dynamics of genomes in detail.

With this we investigated several loci in detail of different species, cell type, and functional states from *some to the mega-base pair level and thus spanning 6 orders of magnitude (!)*, and finally determined the three-dimensional organization and dynamics for the first time in a consistent system genomics manner from the four mentioned angles. Beyond, the results are also in agreement with the heuristics of the research of the last 170 years.

Consequently, we have not only finally determined the architecture and dynamics of the mouse and human genome with base pair/molecular resolution, but this also opens now the detailed architectural and dynamic sequencing of genomes in a systems genomic manner which is of fundamental importance from fundamental genome understanding to diagnosis and treatment.

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 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, 2rd ed.), ISBN 3-00-035857-9 and ISBN 978-3-00-0358857-0 (hard cover, 2rd ed.), ISBN 3-00-035858-7, and ISBN 978-3-00-035858-6 (DVD, 2rd 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* 117, 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 perspective of 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., Löhnhardt, 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., Löhnhardt, 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., Krefting, 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, & Papantonis, 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., Schwarzmuth, 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-kB 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., Koeflerle, 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.