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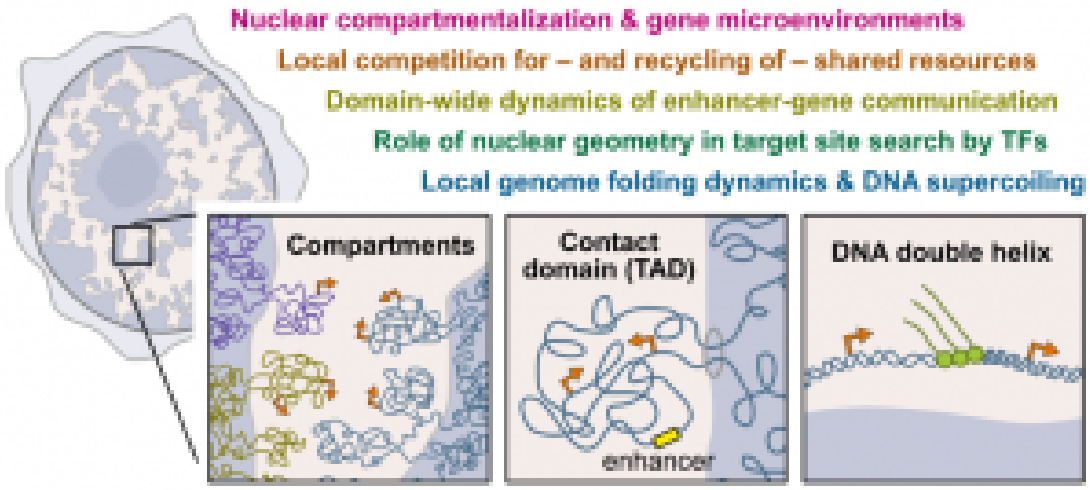
Our group is affiliated with UMR3664 and UMR168.

We currently have openings. More info on our website: www.coulonlab.org

Our goal is to understand the two-way relationship between the spatio-temporal organization and dynamics of the genome and the coordinated regulation of its expression – through an approach at the interface between physics, computer science and biology.

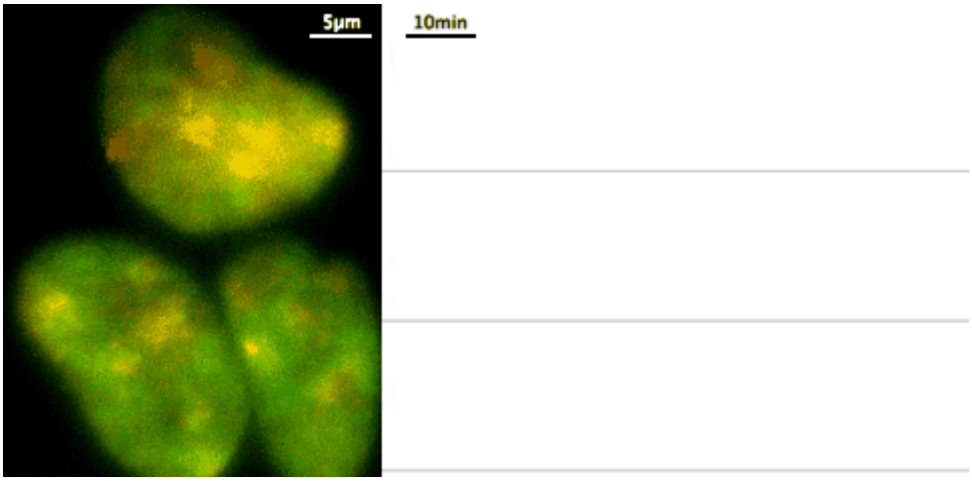


The eukaryotic genome is highly organized in both space and sequence. Preferred positions in the nucleus are observed from whole chromosomes to single genes. This arrangement is cell-type dependent, altered in response to external signals, and perturbed in cancer. Gene position is tightly linked to expression: co-regulated genes (e.g. controlled by the same TFs) tend to show

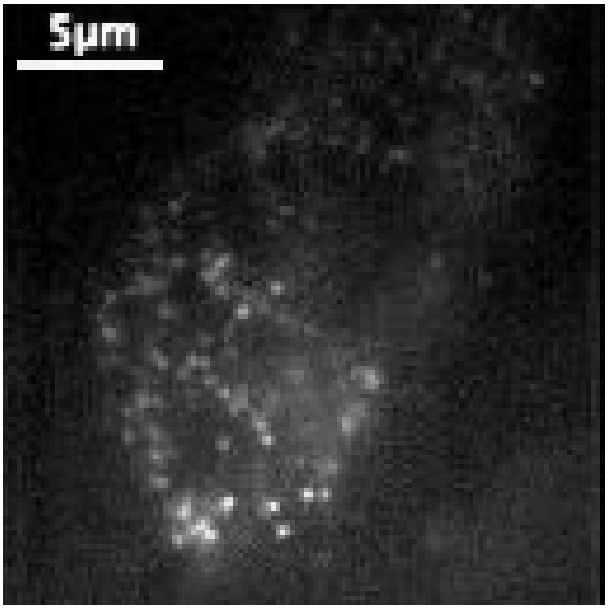
physical proximity even if distant in sequence and transcriptional noise patterns suggest domain-wide regulatory mechanisms. Hence, current data indicate a complex spatio-temporal relationship between co-regulated genes.

However, most existing experimental techniques give an incomplete picture. Fixed-cell microscopy approaches, such as FISH, give a static snapshot of gene position and/or expression. Live-cell approaches often reveal motion of loci without transcriptional readout. Population-level assays (Hi-C, RNA-seq…) miss the stochastic and single-cell aspects of the problem. A true understanding of the mechanisms underlying coordination of genes in 4D is missing, giving a rather correlative picture where causes and consequences remain unclear. How co-regulated genes physically behave and coordinate over time in a single nucleus remains unknown. As an example, when certain co-regulated genes are shown by FISH to co-localize in space more frequently than by random chance, one cannot distinguish a stable co-localization in 10% of the cells -vs- a dynamic co-localization in every cell 10% of the time. Reality is likely in-between these extreme situations, might be gene-dependent, and has broad implications for understanding transcriptional coordination, cell-to-cell variability, the (meta-)stability of cell states, and the occurrence of rare events such as those possibly leading to disease. And so do a number of similar questions at other levels in the multi-scales organization of the genome.

Our lab combines cutting-edge single-molecule microscopy, signal-theory data analysis and physical modeling to study how genes coordinate in space and time in a single nucleus. We are interested in questions spanning a broad range of scales (see illustration) – from nuclear organization to the topology of the DNA double helix. Our hypothesis at each level is that, by acting on their microenvironment, genes shape their co-expression with other genes.



***Real-time imaging of gene transcription in two colors**. With MS2 and PP7 RNA-labeling, we follow the transcriptional activity of genes by monitoring the amount of nascent RNAs being transcribed over time at individual loci of interest.*



***Single-particle tracking microscopy**. By labeling proteins with fluorescent dyes using the HaloTag technologies, we can follow the dynamics of individual proteins in the nuclear space.*

Our approach relies on the combination of the three areas of expertise of the group:

- **Live-cell single-molecule microscopy to observe RNA and protein dynamics in real time**. We use MS2 and PP7 RNA labeling to visualize the transcripts from individual genes with single-RNA resolution. This technique allows **imaging transcription "in 4D"** by monitoring the amount of nascent RNA on genes of interest and their position/motion in the nuclear space. We used these techniques in the past to study single-RNA synthesis and splicing kinetics, non-coding transcription, and gene bursting (eLife 2014, Mol. Cell 2015). We also use single-particle tracking (SPT) to observe trajectories of individual proteins in the nuclear space.
- **Signal-theory approaches for analyzing spatio-temporal data.** We develop analytical tools to extract information from complex trajectories and transcriptional time series – such as the *fluctuation analysis* technique for interpreting transcription dynamics (Meth. Enzymol. 2016, eLife 2014). From these approaches, we obtain spatio-temporal signatures that reveal mechanistic information on the underlying processes involved in gene regulation and genome dynamics.
- **Mathematical/physical modeling to understand spatio-temporal nuclear processes.** To further interpret experimental data and propose validation experiments, we use a variety of modeling and simulation approaches – including models of resource sharing, transcriptional dynamics, diffusion in constrained geometries and polymer dynamics.

Deciphering nuclear complexity in 4D will be key in the coming years to advance our structure-dynamics-function understanding of genomes. Taking upon this timely challenge, we expect to

uncover how the functional organization of the linear genome relates to its physical properties and dynamics in 4D.

Key publications

Year of publication 2016

A Coulon, D R Larson (2016 Jun 1)
Fluctuation Analysis: Dissecting Transcriptional Kinetics with Signal Theory.
Methods in enzymology : 159-91 : DOI : 10.1016/bs.mie.2016.03.017

Year of publication 2015

Tineke L Lenstra, Antoine Coulon, Carson C Chow, Daniel R Larson (2015 Nov 10)
Single-Molecule Imaging Reveals a Switch between Spurious and Functional ncRNA Transcription.
Molecular cell : 597-610 : DOI : 10.1016/j.molcel.2015.09.028

Diana A Stavreva, Antoine Coulon, Songjoon Baek, Myong-Hee Sung, Sam John, Lenka Stixova, Martina Tesikova, Ofir Hakim, Tina Miranda, Mary Hawkins, John A Stamatoyannopoulos, Carson C Chow, Gordon L Hager (2015 Feb 14)
Dynamics of chromatin accessibility and long-range interactions in response to glucocorticoid pulsing.
Genome research : 845-57 : DOI : 10.1101/gr.184168.114

Year of publication 2014

Antoine Coulon, Matthew L Ferguson, Valeria de Turris, Murali Palangat, Carson C Chow, Daniel R Larson (2014 Oct 2)
Kinetic competition during the transcription cycle results in stochastic RNA processing.
eLife : DOI : 10.7554/eLife.03939

Year of publication 2013

Antoine Coulon, Carson C Chow, Robert H Singer, Daniel R Larson (2013 Jul 10)
Eukaryotic transcriptional dynamics: from single molecules to cell populations.
Nature reviews. Genetics : 572-84 : DOI : 10.1038/nrg3484