Year of publication 2019


**Membrane reshaping by micrometric curvature sensitive septin filaments**

*Nature communications* : [DOI: 10.1038/s41467-019-08344-5]

**Summary**

Septins are cytoskeletal filaments that assemble at the inner face of the plasma membrane. They are localized at constriction sites and impact membrane remodeling. We report in vitro tools to examine how yeast septins behave on curved and deformable membranes. Septins reshape the membranes of Giant Unilamellar Vesicles with the formation of periodic spikes, while flattening smaller vesicles. We show that membrane deformations are associated to preferential arrangement of Septin filaments on specific curvatures. When binding to bilayers supported on custom-designed periodic wavy patterns displaying positive and negative micrometric radii of curvatures, septin filaments remain straight and perpendicular to the curvature of the convex parts, while bending negatively to follow concave geometries. Based on these results, we propose a theoretical model that describes the deformations and micrometric curvature sensitivity observed in vitro. The model captures the reorganizations of septin filaments throughout cytokinesis in vivo, providing mechanistic insights into cell division.

Year of publication 2016

Séverine Affeldt, Louis Verny, Hervé Isambert (2016 Jan 20)

**3off2: A network reconstruction algorithm based on 2-point and 3-point information statistics.**

*BMC bioinformatics* : [DOI: 10.1186/s12859-015-0856-x]

**Summary**

The reconstruction of reliable graphical models from observational data is important in bioinformatics and other computational fields applying network reconstruction methods to large, yet finite datasets. The main network reconstruction approaches are either based on Bayesian scores, which enable the ranking of alternative Bayesian networks, or rely on the identification of structural independencies, which correspond to missing edges in the underlying network. Bayesian inference methods typically require heuristic search strategies, such as hill-climbing algorithms, to sample the super-exponential space of possible networks. By contrast, constraint-based methods, such as the PC and IC algorithms, are expected to run in polynomial time on sparse underlying graphs, provided that a correct list of conditional independencies is available. Yet, in practice, conditional independencies need to be ascertained from the available observational data, based on adjustable statistical significance levels, and are not robust to sampling noise from finite datasets.
Year of publication 2015

Param Priya Singh, Jatin Arora, Hervé Isambert (2015 Jul 17)
Identification of Ohnolog Genes Originating from Whole Genome Duplication in Early Vertebrates, Based on Synteny Comparison across Multiple Genomes.
*PLoS computational biology* : e1004394 : [DOI : 10.1371/journal.pcbi.1004394]

**Summary**

Whole genome duplications (WGD) have now been firmly established in all major eukaryotic kingdoms. In particular, all vertebrates descend from two rounds of WGDs, that occurred in their jawless ancestor some 500 MY ago. Paralogs retained from WGD, also coined ‘ohnologs’ after Susumu Ohno, have been shown to be typically associated with development, signaling and gene regulation. Ohnologs, which amount to about 20 to 35% of genes in the human genome, have also been shown to be prone to dominant deleterious mutations and frequently implicated in cancer and genetic diseases. Hence, identifying ohnologs is central to better understand the evolution of vertebrates and their susceptibility to genetic diseases. Early computational analyses to identify vertebrate ohnologs relied on content-based synteny comparisons between the human genome and a single invertebrate outgroup genome or within the human genome itself. These approaches are thus limited by lineage specific rearrangements in individual genomes. We report, in this study, the identification of vertebrate ohnologs based on the quantitative assessment and integration of synteny conservation between six amniote vertebrates and six invertebrate outgroups. Such a synteny comparison across multiple genomes is shown to enhance the statistical power of ohnolog identification in vertebrates compared to earlier approaches, by overcoming lineage specific genome rearrangements. Ohnolog gene families can be browsed and downloaded for three statistical confidence levels or recompiled for specific, user-defined, significance criteria at http://ohnologs.curie.fr/. In the light of the importance of WGD on the genetic makeup of vertebrates, our analysis provides a useful resource for researchers interested in gaining further insights on vertebrate evolution and genetic diseases.

Affeldt S., Isambert H. (2015 Jan 1)
Robust reconstruction of causal graphical models based on conditional 2-point and 3-point information
*Proceedings of the Thirty-First Conference on Uncertainty in Artificial Intelligence, UAI 2015* : 42-51

**Summary**

We report a novel network reconstruction method, which combines constraint-based and Bayesian frameworks to reliably reconstruct graphical models despite inherent sampling noise in finite observational datasets. The approach is based on an information theory result tracing back the existence of colliders in graphical models to negative conditional 3-point information between observed variables. In turn, this provides a confident assessment of structural independencies in causal graphs, based on the ranking of their most likely
contributing nodes with (significantly) positive conditional 3-point information. Starting from a complete undirected graph, dispensible edges are progressively pruned by iteratively “taking off” the most likely positive conditional 3-point information from the 2-point (mutual) information between each pair of nodes. The resulting network skeleton is then partially directed by orienting and propagating edge directions, based on the sign and magnitude of the conditional 3-point information of unshielded triples. This “3off2” network reconstruction approach is shown to outperform constraint-based, search-and-score and earlier hybrid methods on a range of benchmark networks.

Year of publication 2014

Param Priya Singh, Séverine Affeldt, Giulia Malaguti, Hervé Isambert (2014 Jul 31)
**Human dominant disease genes are enriched in paralogs originating from whole genome duplication.**
*PLoS computational biology*: e1003754 : [DOI : 10.1371/journal.pcbi.1003754](https://doi.org/10.1371/journal.pcbi.1003754)

**Summary**

Giulia Malaguti, Param Priya Singh, Hervé Isambert (2014 Feb 18)
**On the retention of gene duplicates prone to dominant deleterious mutations.**
*Theoretical population biology*: 38-51 : [DOI : 10.1016/j.tpb.2014.01.004](https://doi.org/10.1016/j.tpb.2014.01.004)

**Summary**

Recent studies have shown that gene families from different functional categories have been preferentially expanded either by small scale duplication (SSD) or by whole-genome duplication (WGD). In particular, gene families prone to dominant deleterious mutations and implicated in cancers and other genetic diseases in human have been greatly expanded through two rounds of WGD dating back from early vertebrates. Here, we strengthen this intriguing observation, showing that human oncogenes involved in different primary tumors have retained many WGD duplicates compared to other human genes. In order to rationalize this evolutionary outcome, we propose a consistent population genetics model to analyze the retention of SSD and WGD duplicates taking into account their propensity to acquire dominant deleterious mutations. We solve a deterministic haploid model including initial duplicated loci, their retention through sub-functionalization or their neutral loss-of-function or deleterious gain-of-function at one locus. Extensions to diploid genotypes are presented and population size effects are analyzed using stochastic simulations. The only difference between the SSD and WGD scenarios is the initial number of individuals with duplicated loci. While SSD duplicates need to spread through the entire population from a single individual to reach fixation, WGD duplicates are de facto fixed in the small initial post-WGD population arising through the ploidy incompatibility between post-WGD individuals and the rest of the pre-WGD population. WGD duplicates prone to dominant deleterious mutations are then shown to be indirectly selected through purifying selection in post-WGD species, whereas SSD duplicates typically require positive selection. These results highlight the long-term evolution mechanisms behind the surprising accumulation of WGD duplicates prone to
dominant deleterious mutations and are shown to be consistent with cancer genome data on the prevalence of human oncogenes with WGD duplicates.

Summary

The emergence and evolutionary expansion of gene families implicated in cancers and other severe genetic diseases is an evolutionary oddity from a natural selection perspective. Here, we show that gene families prone to deleterious mutations in the human genome have been preferentially expanded by the retention of “ohnolog” genes from two rounds of whole-genome duplication (WGD) dating back from the onset of jawed vertebrates. We further demonstrate that the retention of many ohnologs suspected to be dosage balanced is in fact indirectly mediated by their susceptibility to deleterious mutations. This enhanced retention of “dangerous” ohnologs, defined as prone to autosomal-dominant deleterious mutations, is shown to be a consequence of WGD-induced speciation and the ensuing purifying selection in post-WGD species. These findings highlight the importance of WGD-induced nonadaptive selection for the emergence of vertebrate complexity, while rationalizing, from an evolutionary perspective, the expansion of gene families frequently implicated in genetic disorders and cancers.
Summary

We study the expansion of biomolecular networks from the viewpoint of first evolutionary principles based on the duplication and divergence of ancestral genes. The expansion of gene families and subnetworks is analyzed in terms of logistic map compositions, which capture the varying functional constraints of individual genes in the course of evolution. Using a mean-field approach, we then demonstrate the existence of spontaneous growth-rate variations between gene families and discuss the relevance of such heterogeneous expansions for the emergent properties of actual biomolecular networks.

Girish C Shukla, Farzin Haque, Yitzhak Tor, L Marcus Wilhelmsson, Jean-Jacques Toulmé, Hervé Isambert, Peixuan Guo, John J Rossi, Scott A Tenenbaum, Bruce A Shapiro (2011 May 24) 
A boost for the emerging field of RNA nanotechnology.
ACS nano : 3405-18 : DOI : 10.1021/nn200989r

Summary

This Nano Focus article highlights recent advances in RNA nanotechnology as presented at the First International Conference of RNA Nanotechnology and Therapeutics, which took place in Cleveland, OH, USA (October 23-25, 2010) (http://www.eng.uc.edu/nanomedicine/RNA2010/), chaired by Peixuan Guo and co-chaired by David Rueda and Scott Tenenbaum. The conference was the first of its kind to bring together more than 30 invited speakers in the frontier of RNA nanotechnology from France, Sweden, South Korea, China, and throughout the United States to discuss RNA nanotechnology and its applications. It provided a platform for researchers from academia, government, and the pharmaceutical industry to share existing knowledge, vision, technology, and challenges in the field and promoted collaborations among researchers interested in advancing this emerging scientific discipline. The meeting covered a range of topics, including biophysical and single-molecule approaches for characterization of RNA nanostructures; structure studies on RNA nanoparticles by chemical or biochemical approaches, computation, prediction, and modeling of RNA nanoparticle structures; methods for the assembly of RNA nanoparticles; chemistry for RNA synthesis, conjugation, and labeling; and application of RNA nanoparticles in therapeutics. A special invited talk on the well-established principles of DNA nanotechnology was arranged to provide models for RNA nanotechnology. An Administrator from National Institutes of Health (NIH) National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer discussed the current nanocancer research directions and future funding opportunities at NCI. As indicated by the feedback received from the invited speakers and the meeting participants, this meeting was extremely successful, exciting, and informative, covering many groundbreaking findings, pioneering ideas, and novel discoveries.

Year of publication 2009

Bastien Cayrol, Claude Nogues, Alexandre Dawid, Irit Sagi, Pascal Silberzan, Hervé Isambert
A nanostructure made of a bacterial noncoding RNA.

Journal of the American Chemical Society : 17270-6 : DOI : 10.1021/ja906076e

Summary

Natural RNAs, unlike many proteins, have never been reported to form extended nanostructures, despite their wide variety of cellular functions. This is all the more striking, as synthetic DNA and RNA forming large nanostructures have long been successfully designed. Here, we show that DsrA, a 87-nt noncoding RNA of Escherichia coli, self-assembles into a hierarchy of nanostructures through antisense interactions of three contiguous self-complementary regions. Yet, the extended nanostructures, observed using atomic force microscopy (AFM) and fluorescence microscopy, are easily disrupted into >100 nm long helical bundles of DsrA filaments, including hundreds of DsrA monomers, and are surprisingly resistant to heat and urea denaturation. Molecular modeling demonstrates that this structural switch of DsrA nanostructures into filament bundles results from the relaxation of stored torsional constraints and suggests possible implications for DsrA regulatory function.

Hervé Isambert, Richard R Stein (2009 Aug 26)

On the need for widespread horizontal gene transfers under genome size constraint.

Biology direct : 28 : DOI : 10.1186/1745-6150-4-28

Summary

While eukaryotes primarily evolve by duplication-divergence expansion (and reduction) of their own gene repertoire with only rare horizontal gene transfers, prokaryotes appear to evolve under both gene duplications and widespread horizontal gene transfers over long evolutionary time scales. But, the evolutionary origin of this striking difference in the importance of horizontal gene transfers remains by and large a mystery.

Alexandre Dawid, Bastien Cayrol, Hervé Isambert (2009 Jul 3)

RNA synthetic biology inspired from bacteria: construction of transcription attenuators under antisense regulation.

Physical biology : 025007 : DOI : 10.1088/1478-3975/6/2/025007

Summary

Among all biopolymers, ribonucleic acids or RNA have unique functional versatility, which led to the early suggestion that RNA alone (or a closely related biopolymer) might have once sustained a primitive form of life based on a single type of biopolymer. This has been supported by the demonstration of processive RNA-based replication and the discovery of ‘riboswitches’ or RNA switches, which directly sense their metabolic environment. In this
paper, we further explore the plausibility of this ‘RNA world’ scenario and show, through synthetic molecular design guided by advanced RNA simulations, that RNA can also perform elementary regulation tasks on its own. We demonstrate that RNA synthetic regulatory modules directly inspired from bacterial transcription attenuators can efficiently activate or repress the expression of other RNA by merely controlling their folding paths ‘on the fly’ during transcription through simple RNA-RNA antisense interaction. Factors, such as NTP concentration and RNA synthesis rate, affecting the efficiency of this kinetic regulation mechanism are also studied and discussed in the light of evolutionary constraints. Overall, this suggests that direct coupling among synthesis, folding and regulation of RNAs may have enabled the early emergence of autonomous RNA-based regulation networks in absence of both DNA and protein partners.

Hervé Isambert (2009 Jul 1)
The jerky and knotty dynamics of RNA.
Methods (San Diego, Calif.) : 189-96 : DOI : 10.1016/j.ymeth.2009.06.005

Summary

RNA is known to exhibit a jerky dynamics, as intramolecular thermal motion, on <0.1 micros time scales, is punctuated by infrequent structural rearrangements on much longer time scales, i.e. from >10 micros up to a few minutes or even hours. These rare stochastic events correspond to the formation or dissociation of entire stems through cooperative base pairing/unpairing transitions. Such a clear separation of time scales in RNA dynamics has made it possible to implement coarse grained RNA simulations, which predict RNA folding and unfolding pathways including kinetically trapped structures on biologically relevant time scales of seconds to minutes. RNA folding simulations also enable to predict the formation of pseudoknots, that is, helices interior to loops, which mechanically restrain the relative orientations of other non-nested helices. But beyond static structural constraints, pseudoknots can also strongly affect the folding and unfolding dynamics of RNA, as the order by which successive helices are formed and dissociated can lead to topologically blocked transition intermediates. The resulting knotty dynamics can enhance the stability of RNA switches, improve the efficacy of co-transcriptional folding pathways and lead to unusual self-assembly properties of RNA.

A L Sellerio, B Bassetti, H Isambert, M Cosentino Lagomarsino (2009 Jan 22)
A comparative evolutionary study of transcription networks. The global role of feedback and hierachical structures.

Summary

We present a comparative analysis of large-scale topological and evolutionary properties of transcription networks in three species: the two distant bacteria E. coli and B. subtilis, and the yeast S. cerevisiae. The study focuses on the global aspects of feedback and hierarchy in transcriptional regulatory pathways. While confirming that gene duplication has a significant
impact on the shaping of all the analyzed transcription networks, our results point to distinct trends between the bacteria, which display a hierarchical network structure with short transcription cascades, and yeast, which seems able to sustain a higher wiring complexity, including larger feedback, longer transcription cascades, and the combinatorial use of heterodimers made of duplicate transcription factors, absent in E. coli.