Density of Regulatory Interactions and the Dynamic Stability of Genetic Networks: a System's Biology Approach

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Abstract: Dynamic regulatory networks of any kind evolve through time until they reach two kinds of steady-state behaviours: a) a frozen state where all components of the network adopt a final constant value or b) a "fluid" state where many or all components adopt a final dynamic (cyclic or chaotic) steady state. Gene regulatory networks in all organisms are known to adopt stable patterns of dynamic expression regardless of external conditions matching corresponding biochemical and molecular cycles in stable cells and tissues. As gene expression is controlled by complex networks of regulatory interactions involving transcription factors and target genes, the extent to which the average density of transcriptional regulators per gene determines the dynamic fluidity of the transcriptome is not known. Here we use an in silico (computer simulated) model of gene regulatory networks to determine how density of regulatory inputs per gene influences the dynamic behaviour of the whole genome. We find that increasing regulatory density per gene (number of regulators per gene between 0 and 1, where density of 1 has all genes in the network acting as regulators) increases the likelihood of a gene regulatory network to become frozen and that maximum fluidity is attained by a narrow range of low regulatory density values. This result suggests that natural selection could favour a relatively low number of regulators per gene in order to ensure dynamic stability in natural transcriptomes.

Methods

We implemented a computer simulation of a gene regulatory network as follows:
Each network consist of a set of nodes and edges or arrows linking pairs of nodes. Each node represents a gene and each arrow between two nodes represents a regulatory interaction.

Effect of a single regulator on the individual or cumulative expression of its targets:
The rate of expression of each gene under the influence of a single regulator (Gi) is assumed to be to a sigmoid function of the level of expression of that single regulator:

$$f_i = A\left(\frac{1}{1+e^{B-cG_i}}\right)+1$$

Where G_i is the level of expression of the regulator; A, B and C are parameters controlling the maximum value, the inflexion point (threshold=B/C) and slope at that point for this function. Note that the f_i is defined in the interval [1, A+1]. This means that the minimum influence exerted by G_i is 1 and the maximum is A+1.

Effect of several regulators on a single target
This model assumes that the target expression level (under the influence of a single regulator) is itself the rate f with which that regulator will contribute to the expression of the target, and that when several regulators act on a gene, they interact cooperatively. IF f_i is the rate of expression induced by the regulator i , the overall expression of the target (Ex) under the influence of k regulators will be given by:

$$Ex = f_1 * f_2 * f_3 * \ldots f_k$$

Implementation of the study:
We simulated networks of 20, 50 100, 200 and 500 genes varying the regulatory density of each network and measuring the fluidity of each network after 300 dynamic iterations (or time points).
Regulatory density is defined as the total number of regulatory interactions divided by the maximum theoretical number of regulatory interactions in a network .
As maximum number of regulatory interactions equals N2.
Density is defined as D= Mean number of Regulators per gene / total number of genes.
Fluidity was measure as the proportion of nodes that did not adopt a frozen (constant) state after 300 time iterations.
For each measurement 50 independent networks were generated and each network was simulated starting from 20 independent initial states.

Figure 1 and 2 – An exampl small regulatory network w just ten nodes. Each node represents a gene and each arrow represents a directec regulatory interaction. Wh dynamically simulated start from a random initial expre fro all 10 genes the networ converges into a frozen sta

Fig1

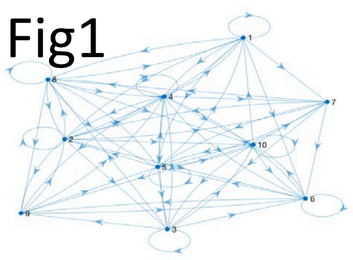

Fig 2

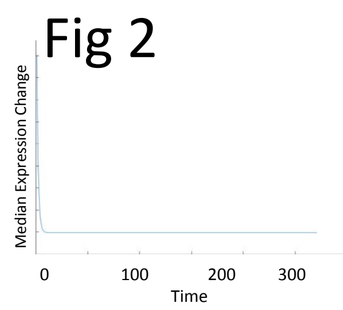

Figure 2 - Median expression change of all 10 genes, across successive time points in the simulation (for a total of 300 time points) , showing how the dynamics of the network converges into a "frozen" state where all genes adopt a constant expression (no fluidity in the steady state).

Fig 3

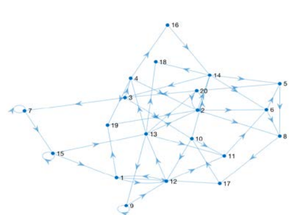

Figure 3. Another example of a gene regulatory network with a larger number of genes but a lower number of regulatory interactions per gene.

Fig 4

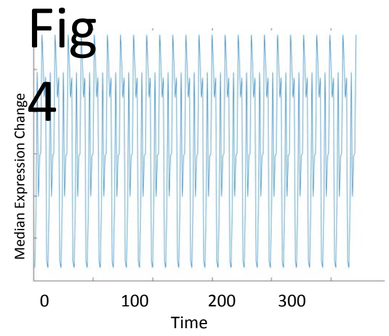

Figure 4 - Median expression change of all genes for this network across successive time points in the simulation (total of 300 time points) , showing how the dynamics of the network converges into a "fluid" and always changing state where all genes adopt a dynamic and periodic time course of expression.

Results:

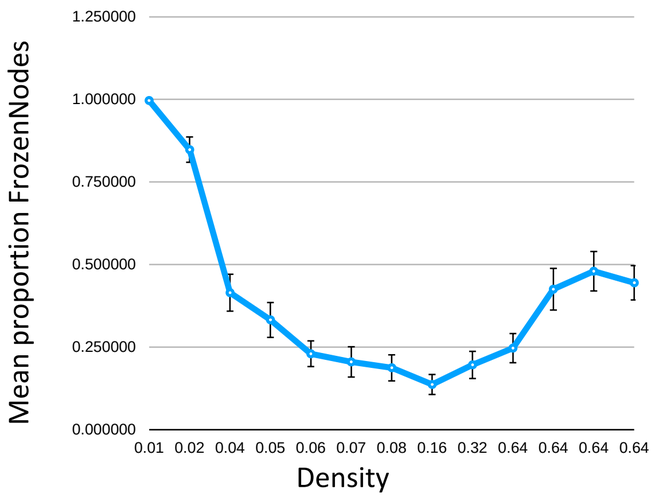

Figure 5 – Dynamic fluidity of N=100 networks, using 20 randomly generated initial states showing mean proportion of Frozen Nodes (± Standard Error) against density. Data point represents the mean of 50 independently generated networks ± standard error

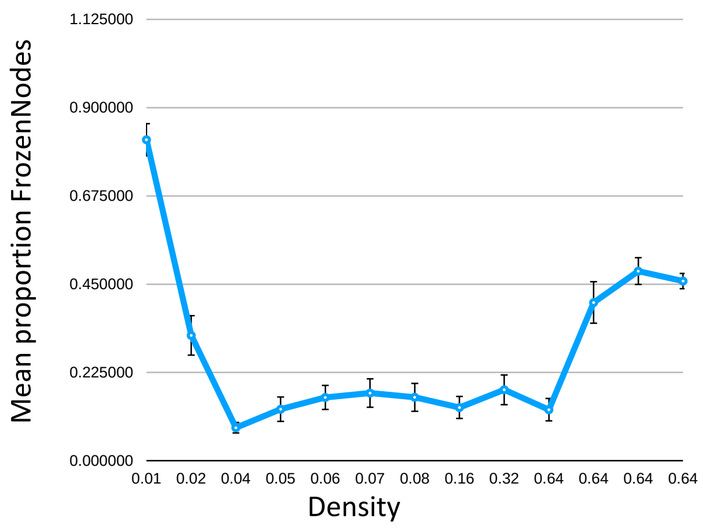

Figure 6 – Dynamic fluidity of N=200 networks, using 20 randomly generated initial states showing mean proportion of Frozen Nodes (± Standard Error) against density. Data point represents the mean of 50 independently generated networks ± standard error

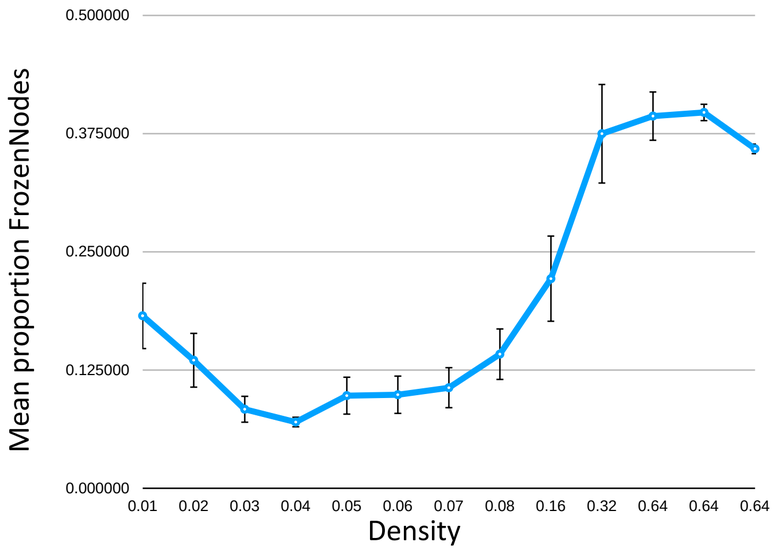

Figure 7 – Dynamic fluidity of N=400 networks, using 20 randomly generated initial states showing mean proportion of Frozen Nodes (± Standard Error) against density. Data point represents the mean of 50 independently generated networks ± standard error

Conclusion:

Results show that there is an optimal density (average number of transcriptional regulators per gene) at which the gene regulatory network attains maximum fluidity. While the window of optimal densities appears constant, it slightly shifts towards lower values as network size increases.
We propose that natural selection might have favoured an optimal average number of transcriptional regulators per gene, to optimise the dynamic stability of the gene regulatory network.

This model should, in principle, allow us to predict the average number of transcriptional regulators per gene in natural genomes.

While further studies are needed to ascertain the optimal density of transcriptional regulators in large genomes, such as those of humans, taking, the largest networks tested (N=400) as a basis in this study, with an optimal density is 0.04, we would predict an average of 800 regulators per gene (for a network size that is the same as that of humans; N=20 000 to 23 000 genes). Current experimental data estimate an inter-quartile range of 29 to 515 transcription factor binding sites per gene (Hurst, et al., 2014. Genome biology, 15(7), p.413.)

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