

# The evolution of the bifurcation phenotype: phylogenetic and dynamical analysis of fungal GATA networks

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## Abstract

GATA-type transcription factors are involved in auto-regulatory feedback and feedforward networks of competitively binding activators and inhibitors [1, 2]. Such transcriptional feedback networks have long been studied theoretically as a possible basis for complex expression dynamics like switches and oscillators, and hypothesized to underlie phenotypical effects like cell differentiation, rhythmic behavior and morphogenetic patterning. Little is however known about emergence and evolution of their complex dynamical properties. How does gene duplication of an auto-regulatory transcription factor influence expression dynamics? To address this kind of questions we tested a potentially fruitful approach combining diverse methodologies of bioinformatics and systems biology.

First, we study the extent of gene duplication of auto-regulatory GATA networks in 15 fully sequenced fungal genomes by sequence conservation analysis and motif searches, see e.g. [3, 4]. All *Ascomycota* and *Hemiascomycota* share one or more nitrogen-sensitive activators and strongly auto-regulatory, competitive repressors, while only two clades (*Aspergilli* and close relatives of *budding yeast*) also carry auto-regulatory motifs in their nitrogen-sensitive activator genes. (See figure 1 for reconstructed networks.) These conserved network properties as well as network growth by gene duplication are then analyzed by ODE-based models of gene expression [2]. In the case of the yeast *nitrogen catabolite repression* system, we show that both - bistable and oscillatory potential - can provide useful cross-talk mechanisms between cell growth requirements in G1 phase and external nutrient availability. Such dynamics could help to synchronize nitrogen metabolism (and in some cases iron requirements) with fundamental cellular processes, such as the cell cycle as well as (cell-cycle gating) respiratory rhythms.

We analyze the potential consequences of gene duplication and subsequent mutation paths by exploring the parameter space within physiologically realistic orders of magnitude by *forward and inverse bifurcation analysis* [5, 6, 7, 8]. Our models predict strong gene dosage effects for transcriptional feedback cycles with multistable expression dynamics. *Hypersensitivity* to the incoming signals could strongly impair proper transcriptional responses to metabolic state (see Figure 2a). We propose that such adverse effects on the *bifurcation phenotype* constitute an important driving force in the evolution of transcriptional feedback networks, and can path the way towards new network architectures such as cascades or feedforward loops, allowing for diversification of target gene cohorts. An additional loss of the transactivating domain in one of two duplicated auto-activators can easily create a competitively binding inhibitor and thus introduce negative feedback. The generation of oscillatory expression dynamics

from an initially bistable auto-activator seems fairly easy (see Figure 2b). Notably, such a mechanism would fundamentally differ from the so far discussed *evolution-by-redundancy* scenarios of gene and genome duplication events [9]. On the other hand, the strong gene dosage effects could also be highly relevant for several clinical syndromes known to be based on GATA factor haploinsufficiencies [10].

## References

- [1] T. G. Cooper. Transmitting the signal of excess nitrogen in *Saccharomyces cerevisiae* from the Tor proteins to the GATA factors: connecting the dots. *FEMS Microbiol Rev*, 26(3):223–38, August 2002.
- [2] T. Hofer, H. Nathansen, M. Lohning, A. Radbruch, and R. Heinrich. GATA-3 transcriptional imprinting in Th2 lymphocytes: a mathematical model. *Proc Natl Acad Sci U S A*, 99(14):9364–8, Jul 9 2002.
- [3] B. Morgenstern. DIALIGN 2: improvement of the segment-to-segment approach to multiple sequence alignment. *Bioinformatics*, 15(3):211–8, March 1999.
- [4] C. T. Su, C. Y. Chen, and Y. Y. Ou. Protein disorder prediction by condensed PSSM considering propensity for order or disorder. *BMC Bioinformatics*, 7:319, 2006.
- [5] S. Müller, J. Hofbauer, L. Endler, C. Flamm, S. Widder, and P. Schuster. A generalized model of the repressilator. *J Math Biol*, 53(6):905–37, December 2006.
- [6] S. Widder, J. Schicho, and P. Schuster. Dynamic patterns of gene regulation I: simple two-gene systems. *J Theor Biol*, 246(3):395–419, Jun 7 2007.
- [7] J. Lu, H. W. Engl, and P. Schuster. Inverse bifurcation analysis: application to simple gene systems. *Algorithms Mol Biol*, 1:11, 2006.
- [8] J. Lu, H. W. Engl, R. Machné, and P. K. Schuster. Inverse bifurcation analysis of a model for the mammalian G1/S regulatory module. In *Bioinformatics Research and Development BIRD 2007, Berlin*, volume 4414 of *Lecture Notes in Bioinformatics*. Springer, 2007.
- [9] Susumu Ohno. *Evolution by gene duplication*. Springer-Verlag, 1970.
- [10] H. Van Esch, P. Groenen, M. A. Nesbit, S. Schuffenhauer, P. Lichtner, G. Vanderlinden, B. Harding, R. Beetz, R. W. Bilous, I. Holdaway, N. J. Shaw, J. P. Fryns, W. Van de Ven, R. V. Thakker, and K. Devriendt. GATA3 haplo-insufficiency causes human HDR syndrome. *Nature*, 406(6794):419–22, Jul 27 2000.

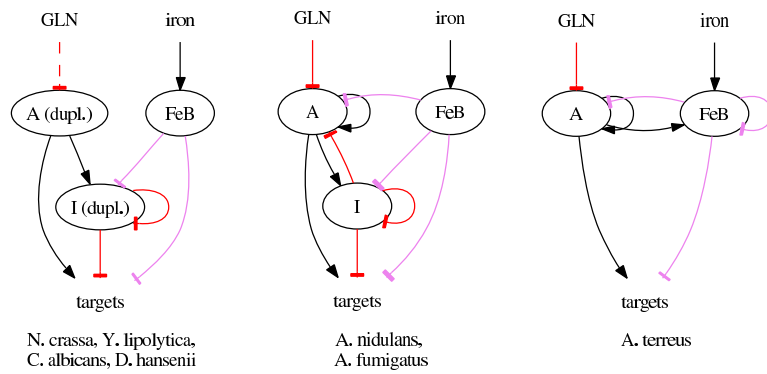


Figure 1: Auto-regulation of fungal GATA systems: reconstructed networks. (GLN: glutamine, FeB: iron-sensitive repressor, A: activator, I: repressor, targets: target gene cohorts)

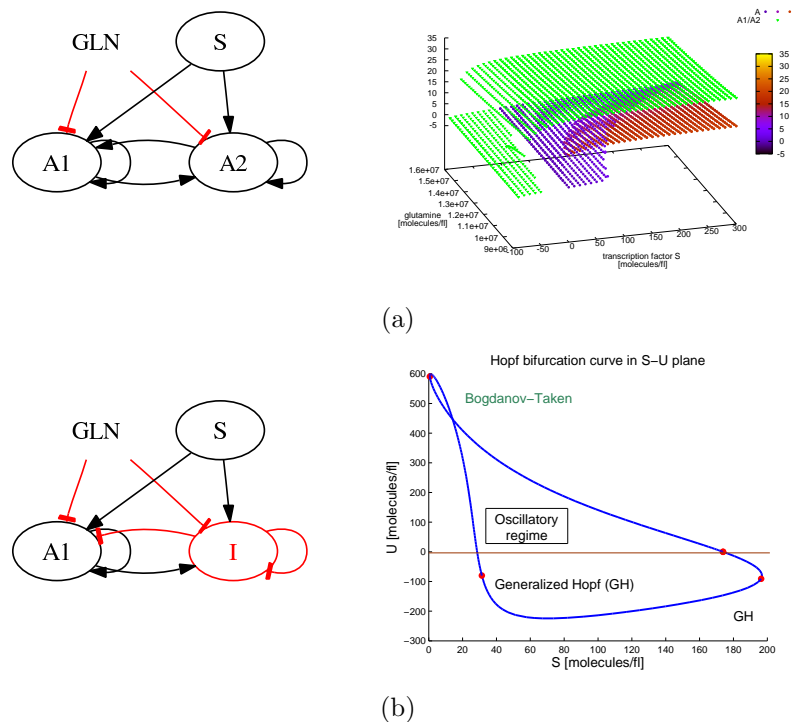


Figure 2: Gene duplication in fungal GATA systems: gene dosage effects and subsequent mutations. (a) Hypersensitivity to signal after gene duplication. Left: network diagram. Right: steady state concentrations of auto-activator as a function of signal concentrations before and after duplication (red and green dots). (b) Signal-dependent oscillations in gene expression after loss of the transactivation domain in one of the duplicates and only few additional mutations. Left: network diagram. Right: bifurcation diagram in the plane of signal concentrations. (Continuation of Hopf bifurcations, existence of Generalized Hopf-bif. and Bogdanov-Takens-bif.)