Обобщенный частотно-временной анализ динамических биомолекуляных систем

Generalized time-frequency analysis of dynamical biomolecular systems

Александр Ратушный

ИЦиГ СО РАН, 4 июля 2012

Outline

- Motivation and goal of the project

- Trade-off between responsiveness and noise suppression in biomolecular system responses to environmental cues

- Generalized time-frequency analysis (TFA) of dynamical properties of biomolecular networks

- TFA analysis of yeast metabolic responses to environmental change

- TFA analysis of LPS/TLR4-induced transcriptional network

- Conclusions

Motivation and goal

1. Living systems are highly responsive to the environment and at the same time sufficiently stable to reliably execute a physiological program. These competing requirements establish a fundamental trade-off in biological systems between their responsiveness and noise suppression.

Motivation and goal

1. Trade-off between responsiveness and noise suppression in biomolecular system responses to environmental cues.

2. Quantitative description of nonlinear biomolecular network responses to transient stimuli, in the context of varying topologies and kinetic properties of combinatorial and synergistic regulatory interactions, typified by biological networks, remains a significant challenge.

Motivation and goal

1. Trade-off between responsiveness and noise suppression in biomolecular system responses to environmental cues.

2. Quantitative description of nonlinear biomolecular network … remains a significant challenge.

3. To explore how different network topologies enable different system properties we need to develop a generalized system-level approach for investigating the dynamics of nonlinear biomolecular networks.

Motivation and goal

1. Trade-off between responsiveness and noise suppression in biomolecular system responses to environmental cues.

2. Quantitative description of nonlinear biomolecular network … remains a significant challenge.

3. … to develop a generalized system-level approach for investigating the dynamics of nonlinear biomolecular networks.

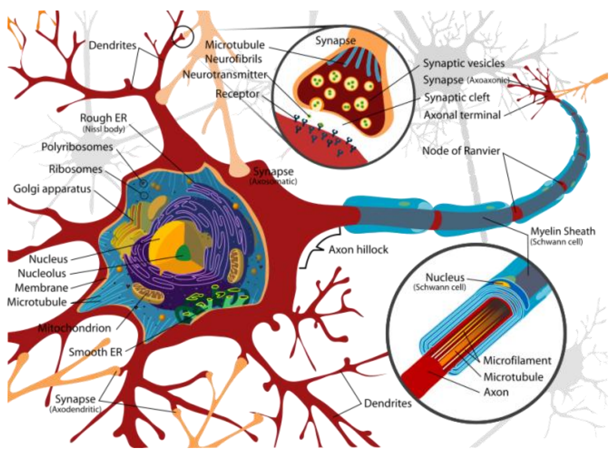
4. This approach should entail systematically comparing time-frequency characteristics of inputs (stimuli) and outputs (responses) while varying system parameters. This methodology should allow for the exploration and quantitative comparisons of system-level behaviors relative to these parameters.

Living cells and information processing systems

inputs

outputs

environmental stimuli



responses

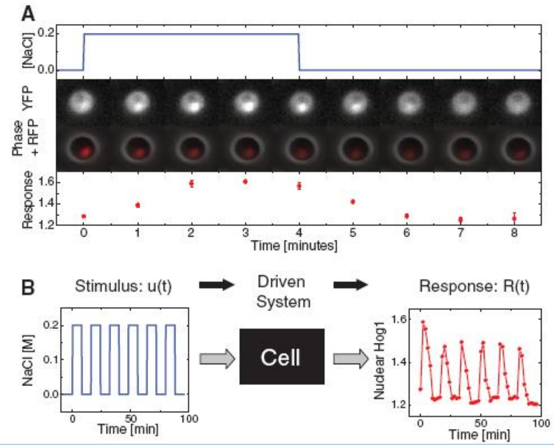
Living cells and information processing systems

REPORTS

The Frequency Dependence of Osmo-Adaptation in *Saccharomyces cerevisiae*

Jerome T. Mettetal,[1] Dale Muzzey,[1,2] Carlos Gómez-Uribe,[1,3] Alexander van Oudenaarden[1*]

482 25 JANUARY 2008 VOL 319 SCIENCE www.sciencemag.org

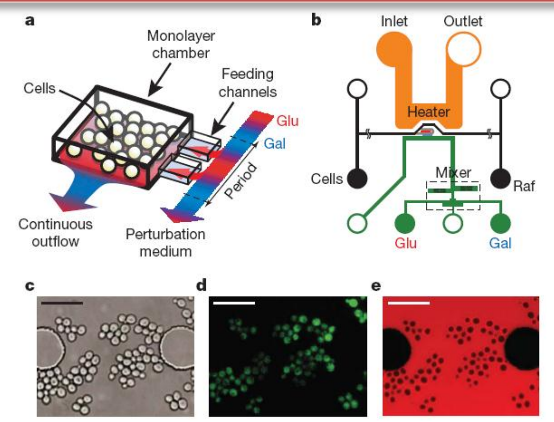


Vol 454 | 28 August 2008 | doi:10.1038/nature07211 nature

LETTERS

Metabolic gene regulation in a dynamically changing environment

Matthew R. Bennett[1,2*], Wyming Lee Pang[1*†], Natalie A. Ostroff[1], Bridget L. Baumgartner[1], Sujata Nayak[1], Lev S. Tsimring[2] & Jeff Hasty[1,2]



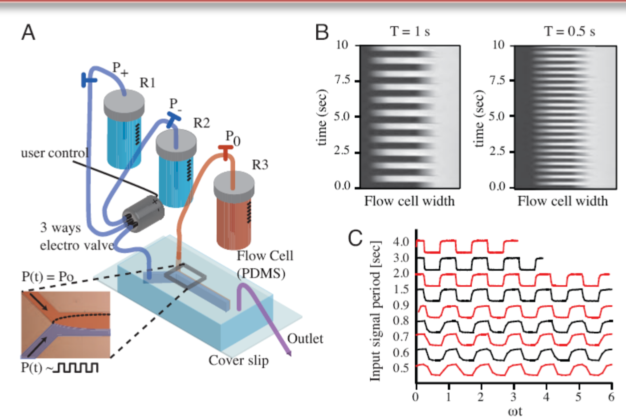
Signal processing by the HOG MAP kinase pathway

Pascal Hersen[†‡], Megan N. McClean[†§], L. Mahadevan[§], and Sharad Ramanathan[†¶||]

[†]FAS Center for Systems Biology and [§]School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138; [‡]Laboratoire Matière et Systèmes Complexes, Centre National de la Recherche Scientifique and Université Paris Diderot, 75205 Paris Cedex 13, France; and [¶]Bell Laboratories, Alcatel–Lucent, Murray Hill, NJ 07974

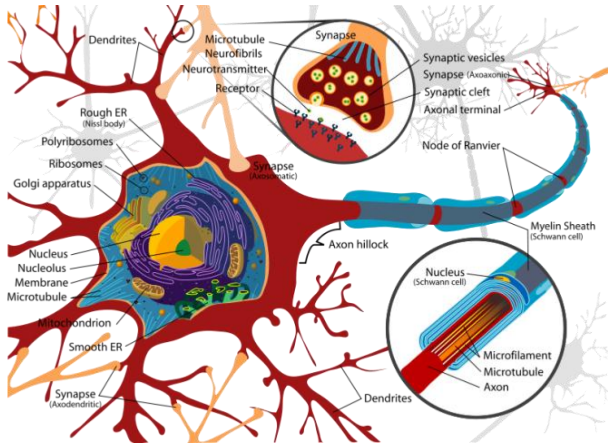
Edited by Charles F. Stevens, Salk Institute for Biological Studies, La Jolla, CA, and approved February 29, 2008 (received for review November 13, 2007)

www.pnas.org/cgi/doi/10.1073/pnas.0710770105 PNAS | May 20, 2008 | vol. 105 | no. 20 | 7165–7170



Respond or not respond

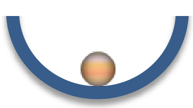
stimulus



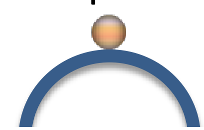
response to environmental changes

ignore insignificant signals (filter noise)

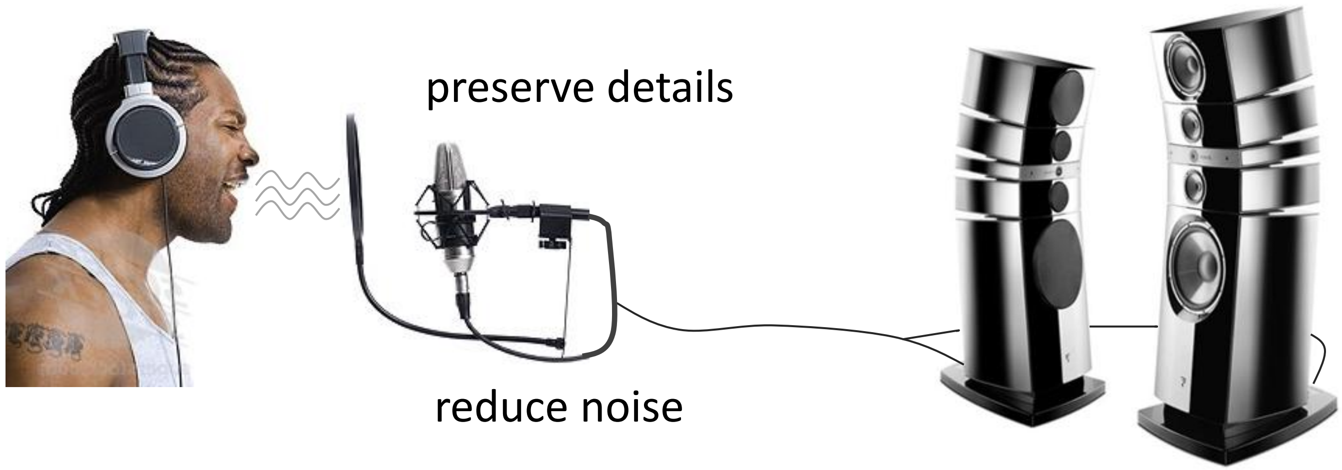
not respond



respond

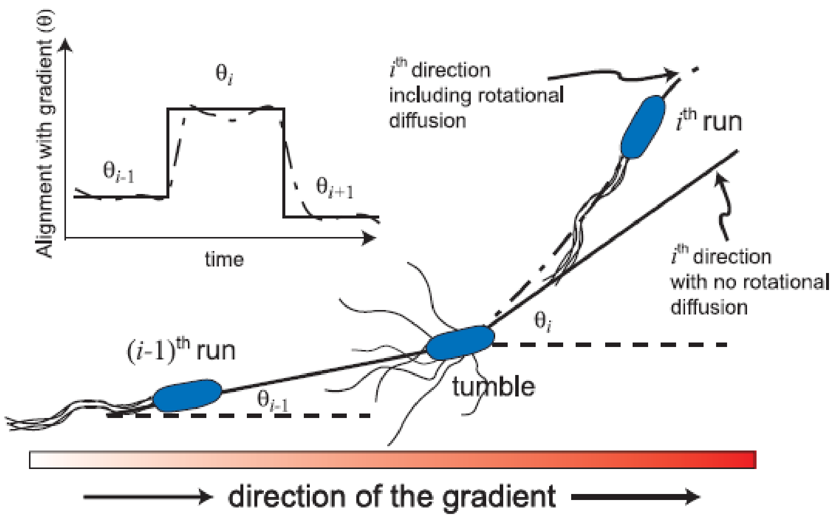


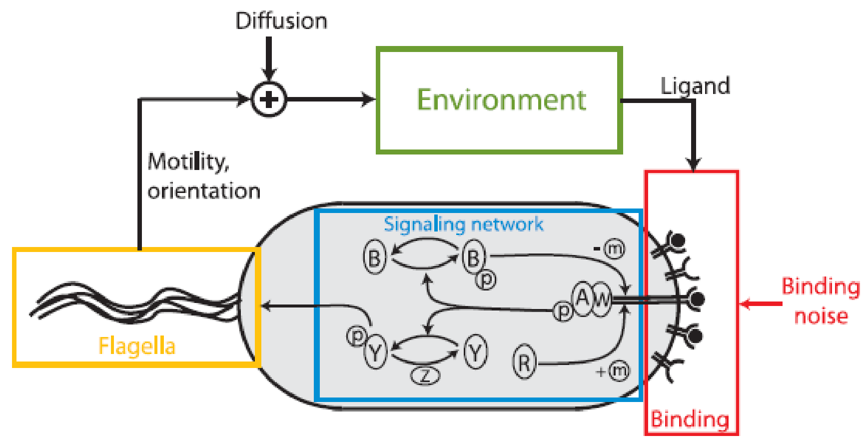
Optimal response in the presence of noise



An optimal system must extract the information from a signal in the presence of noise in order to make the most reliable estimate of some quantity of interest.

Optimal response in the presence of noise

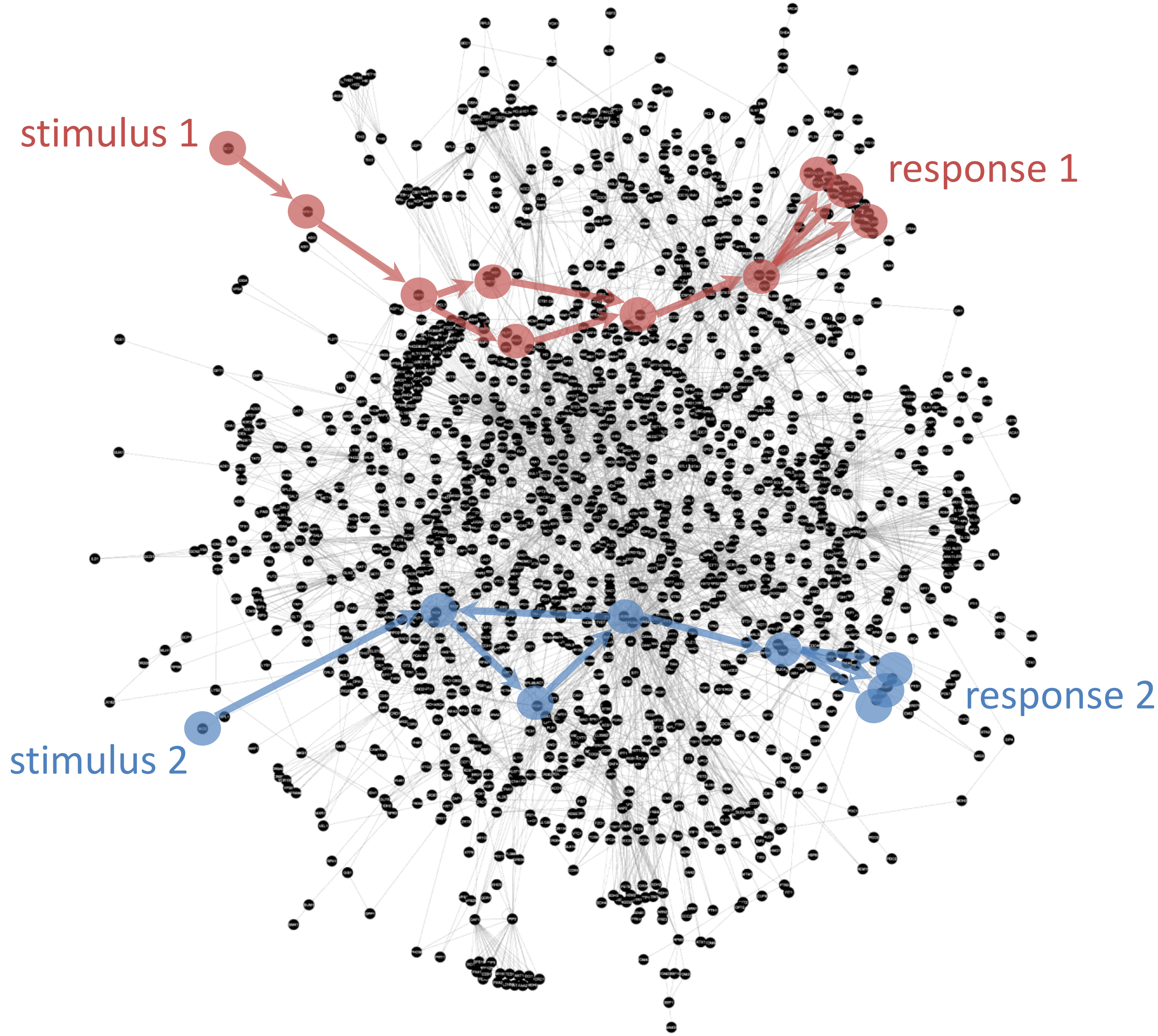




Andrews *et al.*, 2006

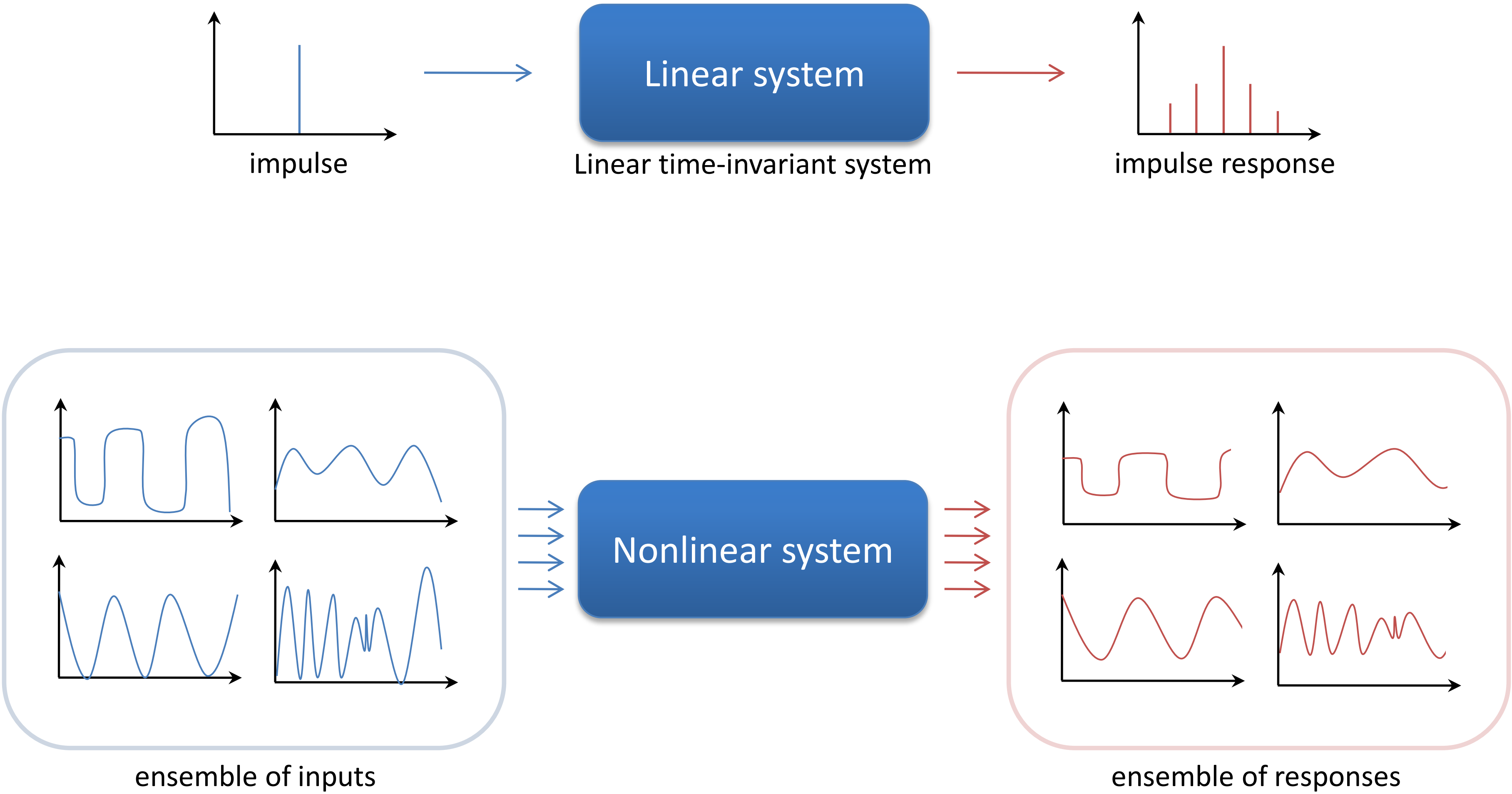
The cell must estimate the state of the extracellular environment from noisy input stimuli. *E. coli* estimate the time derivative of a signal along which they chemotax.

What are the principles of cellular decision making?

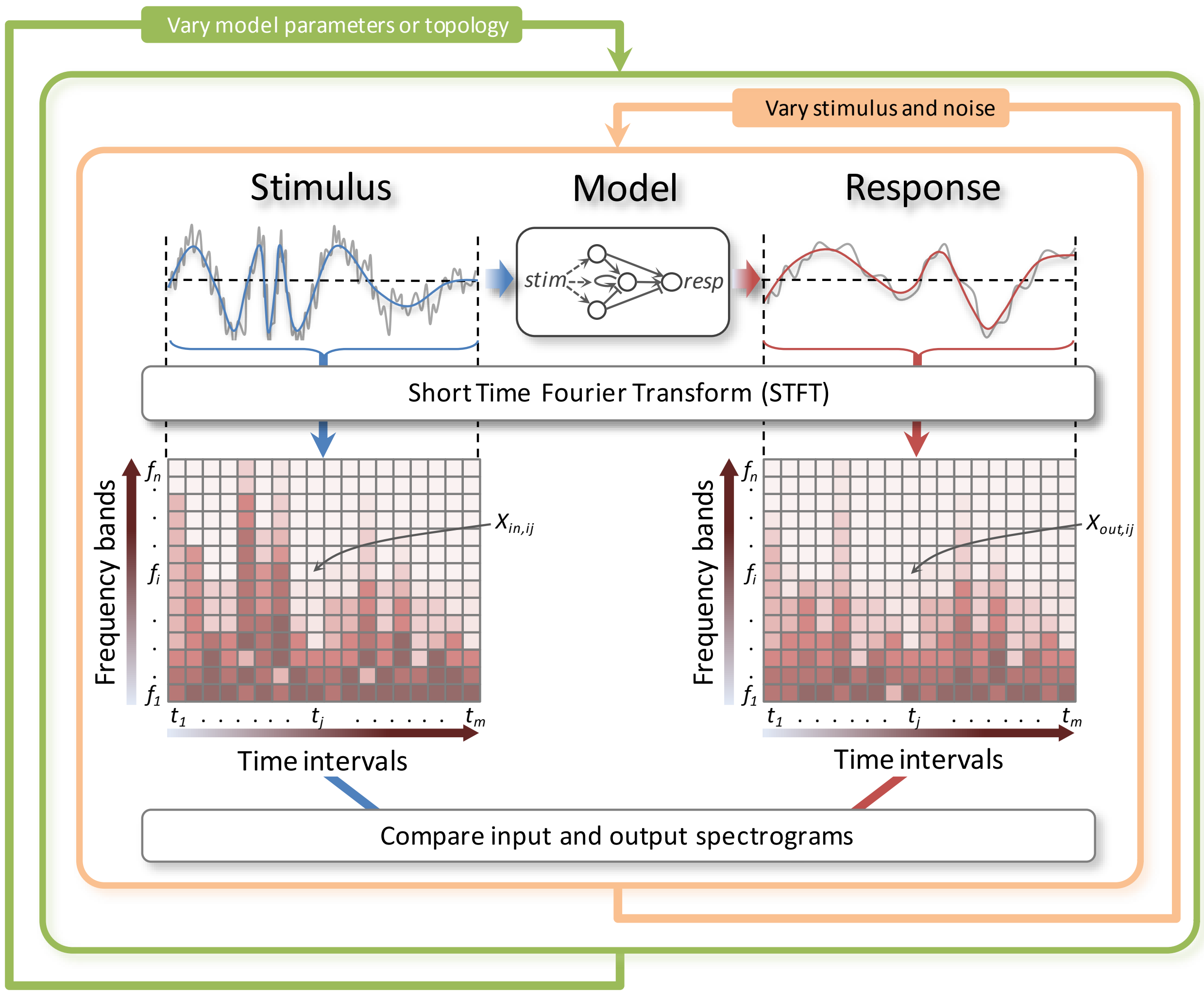


biological roles of subsystems, evolutionarily conserved network topology and kinetic parameters

Linear vs. nonlinear systems



Generalized time-frequency analysis of molecular system dynamics



Ratushny et al., 2011

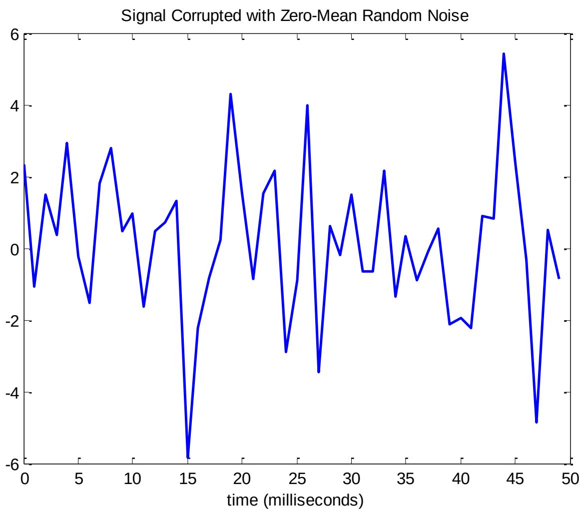
Time-frequency analysis: illustration

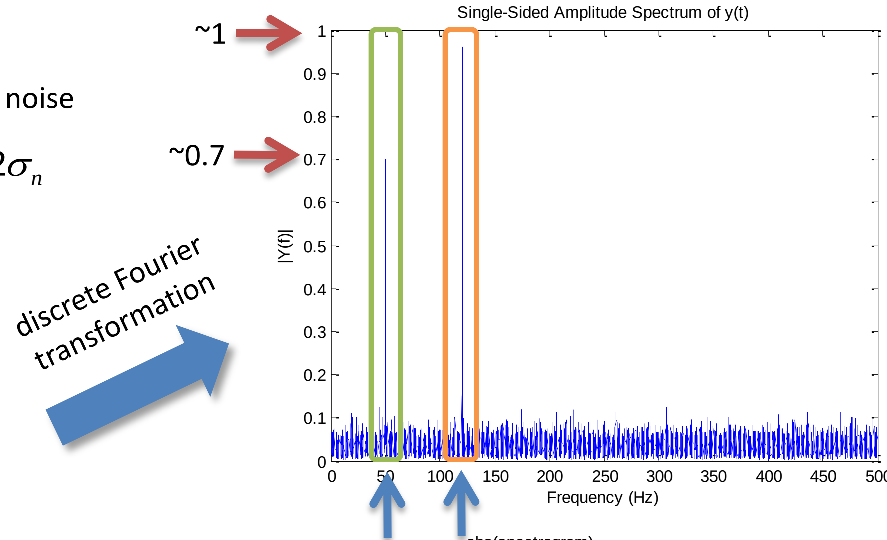
Signal function:

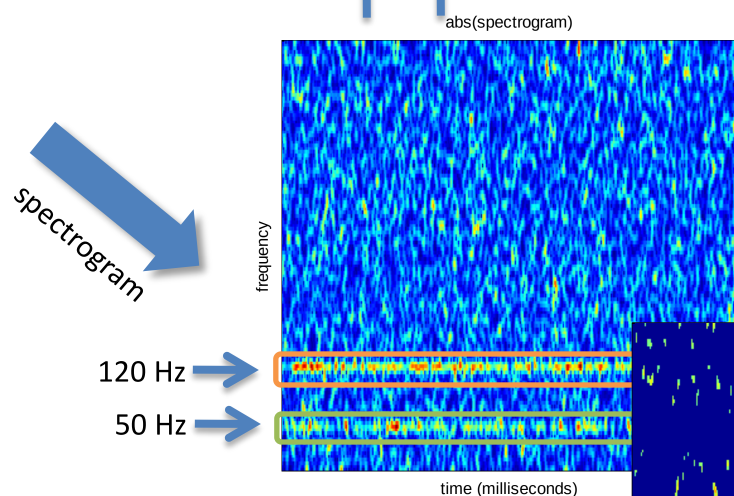
$$y(t) = \boxed{0.7\sin(50\cdot 2\pi t)} + \boxed{\sin(120\cdot 2\pi t)} + 2\sigma_n$$

random noise

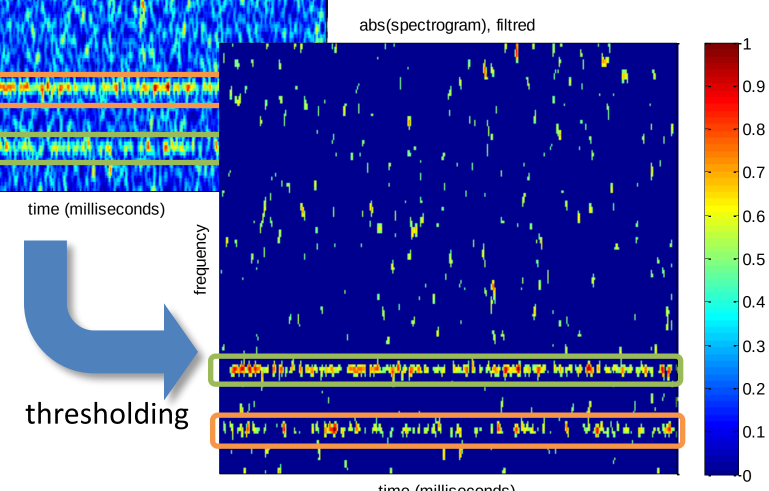
amplitude frequency







A spectrogram is an image that shows how spectral density of a signal varies with time.



A common use of Fourier transforms is to find the frequency components of a signal buried in a noisy time domain signal.

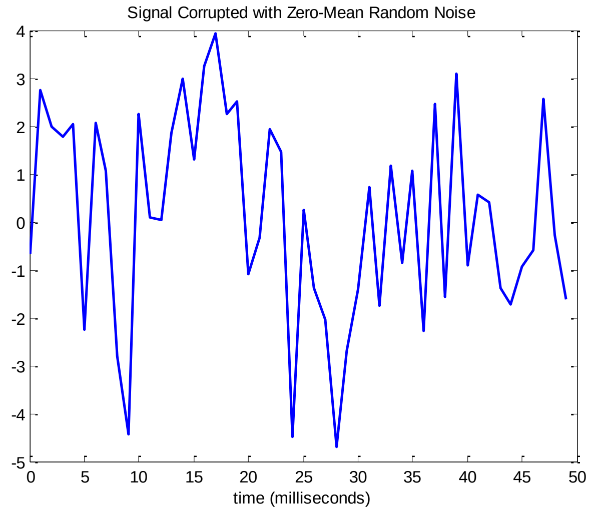
Time-frequency analysis: illustration

Signal function:

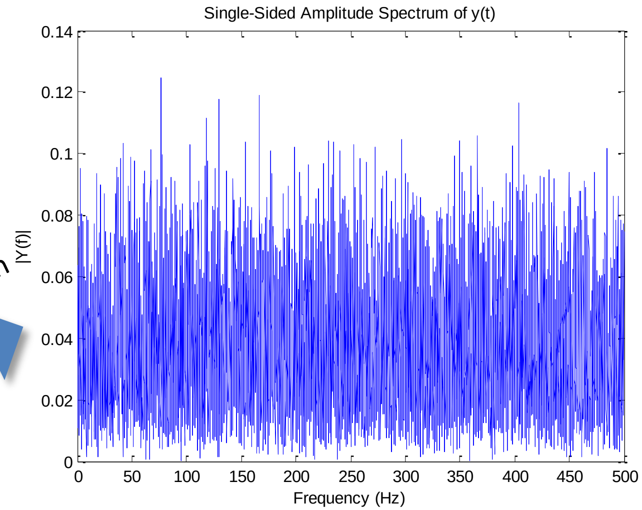
random noise

$$y(t) = \sin(2\pi t \cdot f(t)) + 2\sigma_n, \; where \; f(t) = 10 \cdot (1 + 2t)$$

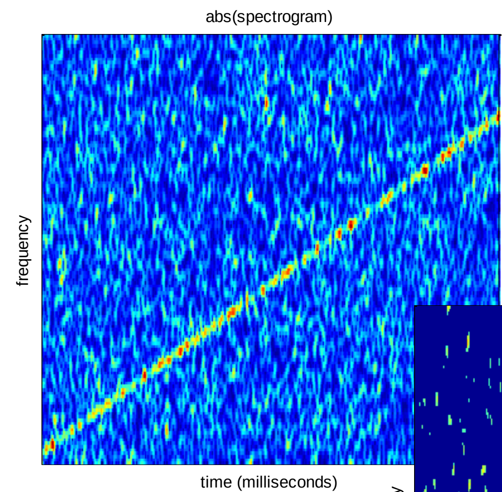
time dependent frequency term



discrete Fourier transformation

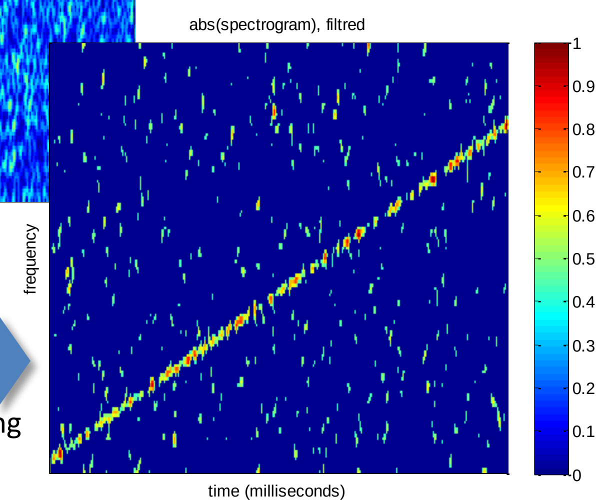


spectrogram



A spectrogram is an image that shows how spectral density of a signal varies with time.

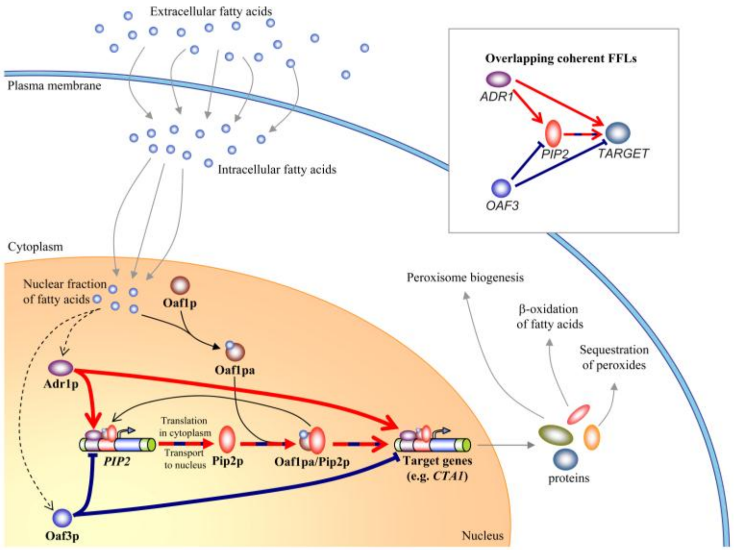
thresholding



A common use of Fourier transforms is to find the frequency components of a signal buried in a noisy time domain signal.

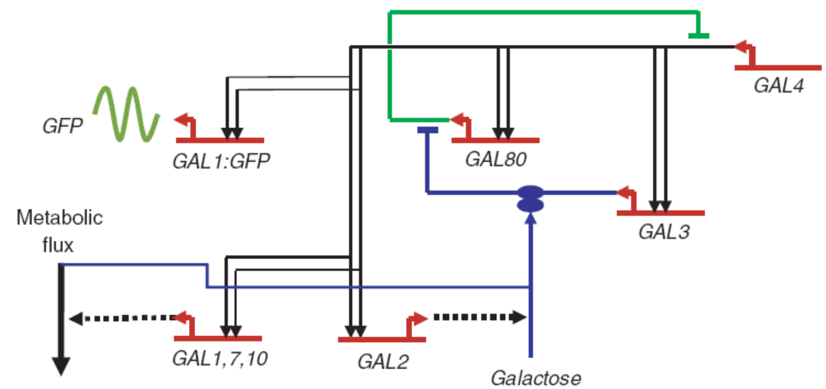
TFA analysis of yeast metabolic responses to environmental change

Oleate-responsive system

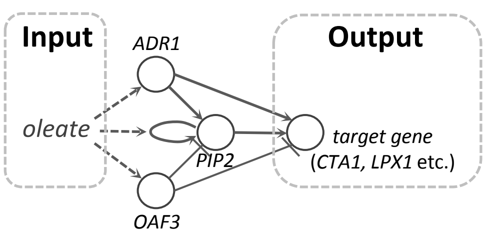


Ratushny *et al.*, 2008

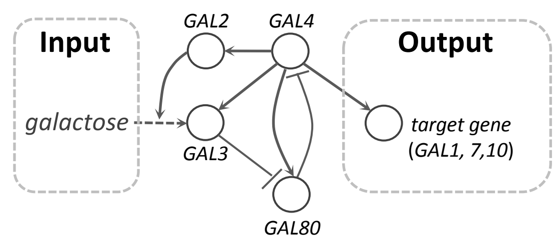
Galactose-responsive system



Ramsey *et al.*, 2006



Overlapping positive and negative FFLs

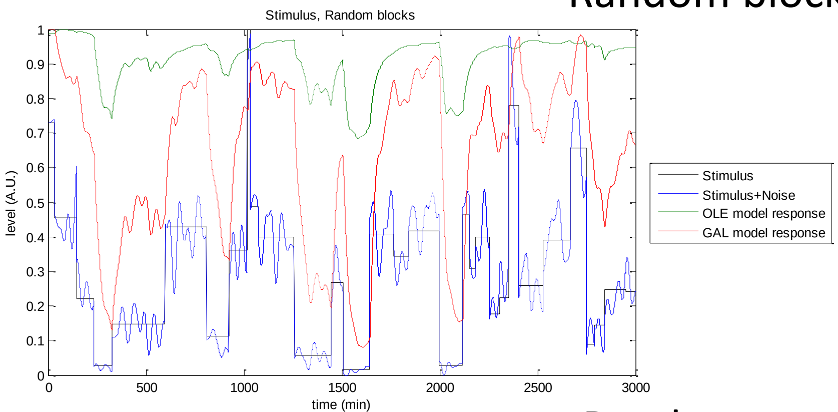


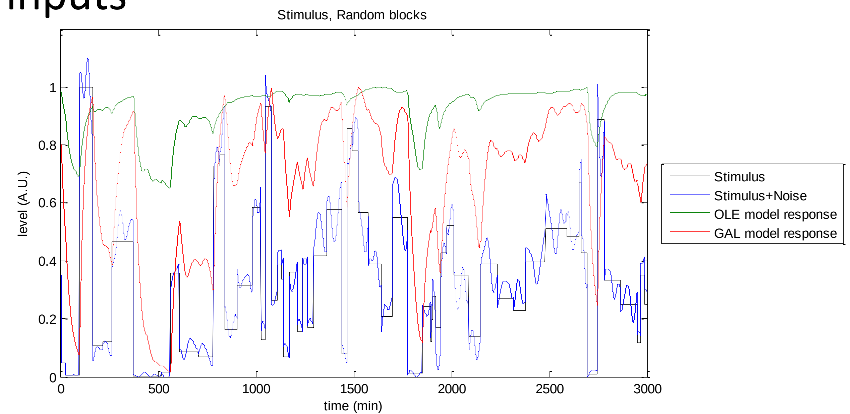
Interlinked positive and negative FBLs

Cells depend on each network to respond to carbon source shifts, yet each network is comprised of fundamentally different architectures.

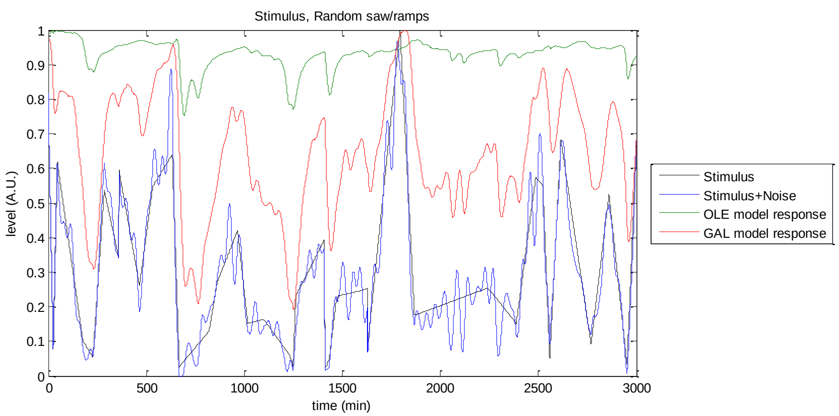
Examples of stimuli and network responses

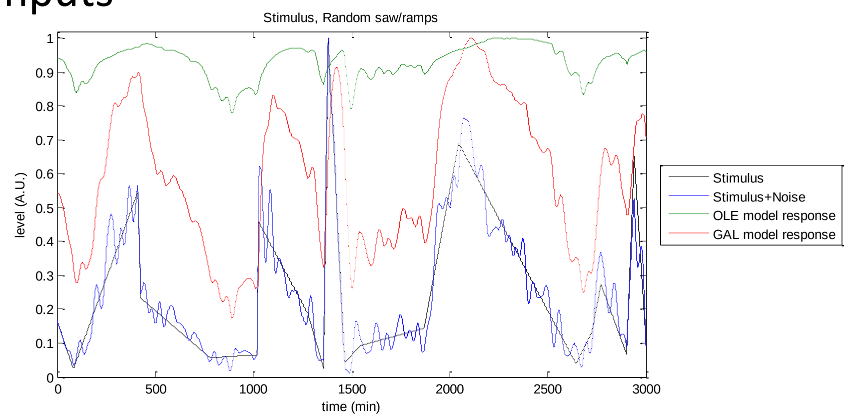
Random block inputs



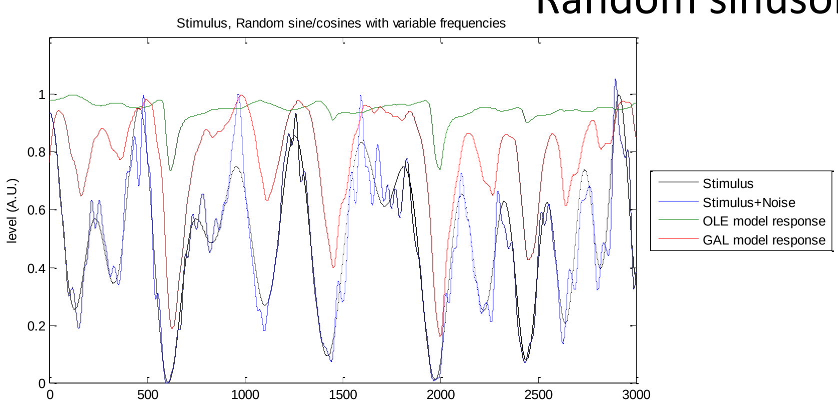


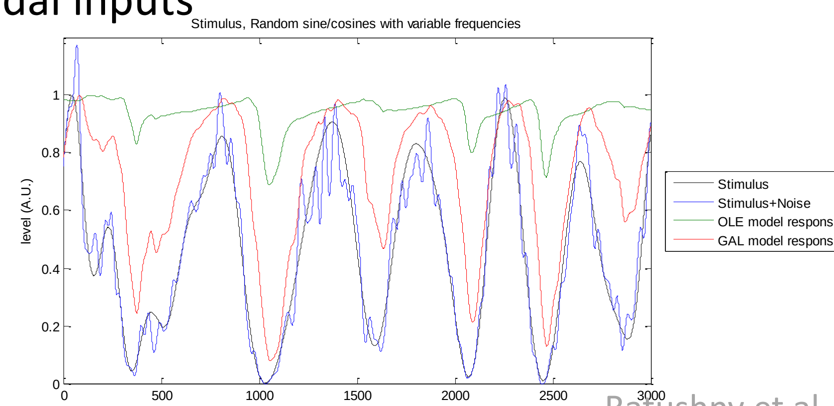
Random saw inputs





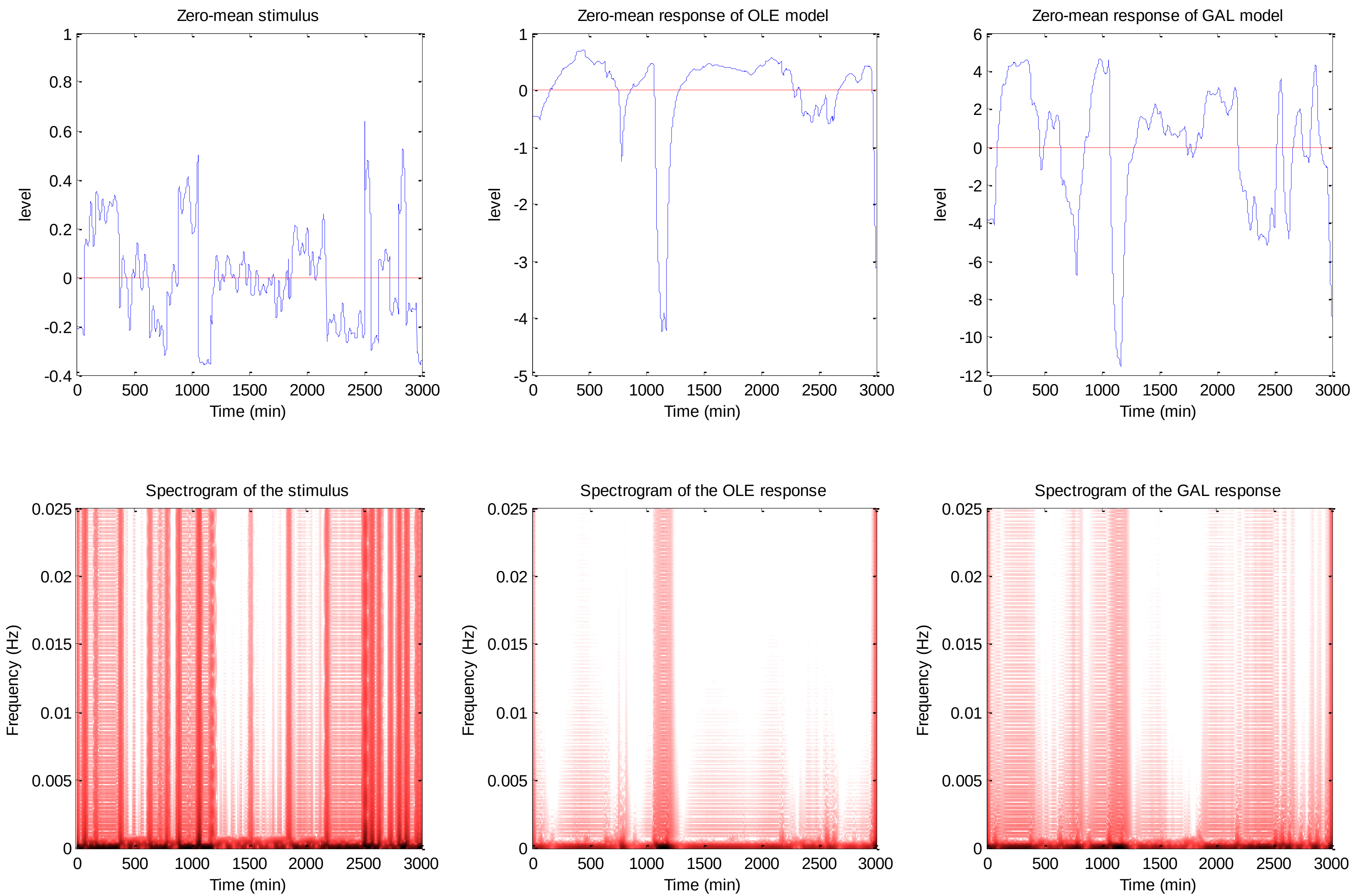
Random sinusoidal inputs





Ratushny et al., 2011

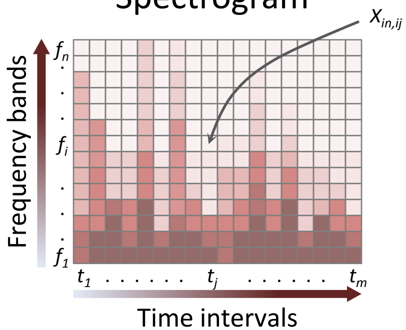
Time-frequency analysis of *OLE* and *GAL* model responses to a particular noisy stimulus



Ratushny et al., 2011

Time-frequency analysis of *OLE* and *GAL* model responses to a particular noisy stimulus: noise suppression

Spectrogram

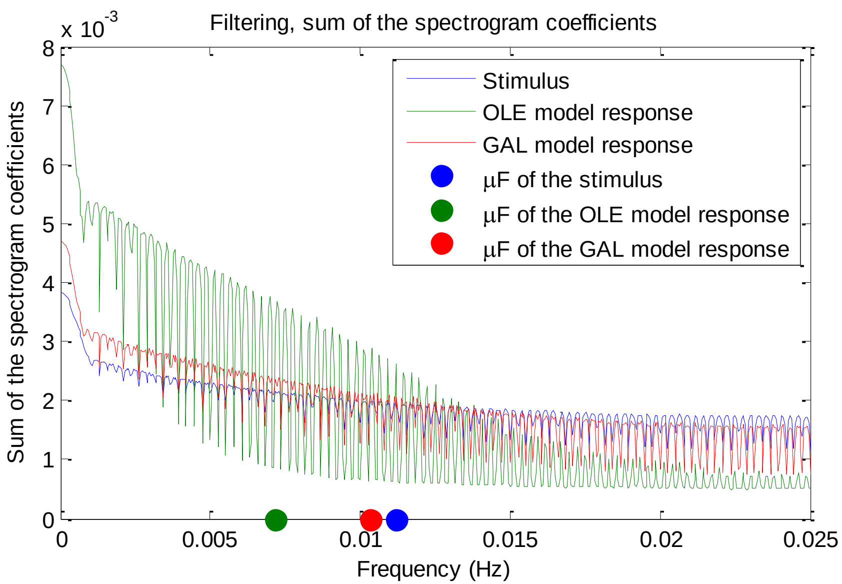


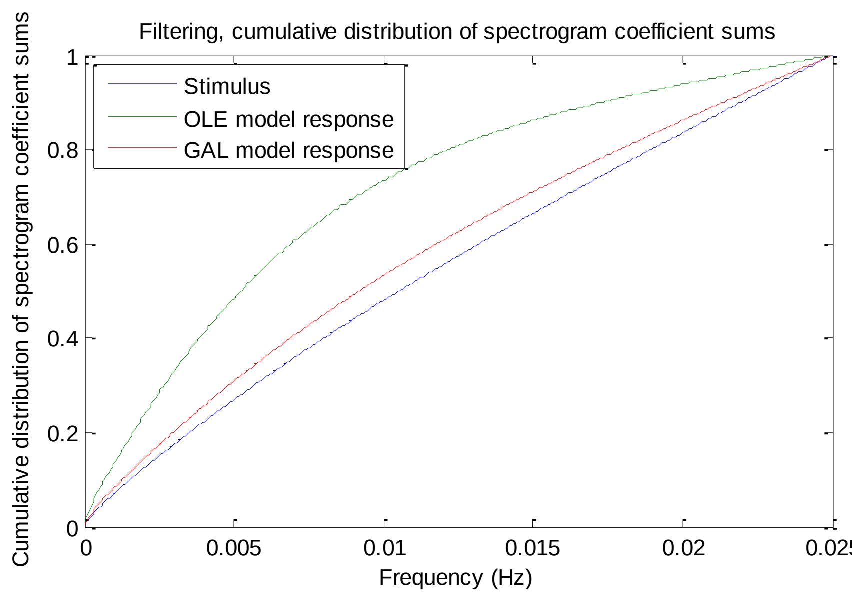
Mean frequency of the signal (μF)

$$\mu F = \sum_{i=1}^{N}\left(f_i \sum_{j=1}^{M} X_{i,j} \right)$$

Noise suppression (ξ) or ability to filter high frequency stimulus fluctuations

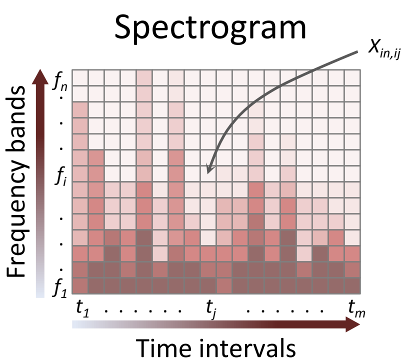
$$\xi = \frac{\mu F_{in}}{\mu F_{out}}$$





Ratushny et al., 2011

Time-frequency analysis of *OLE* and *GAL* model responses to a particular noisy stimulus: responsiveness



Total variation of spectrogram coefficients (TV_i) within f_i frequency band

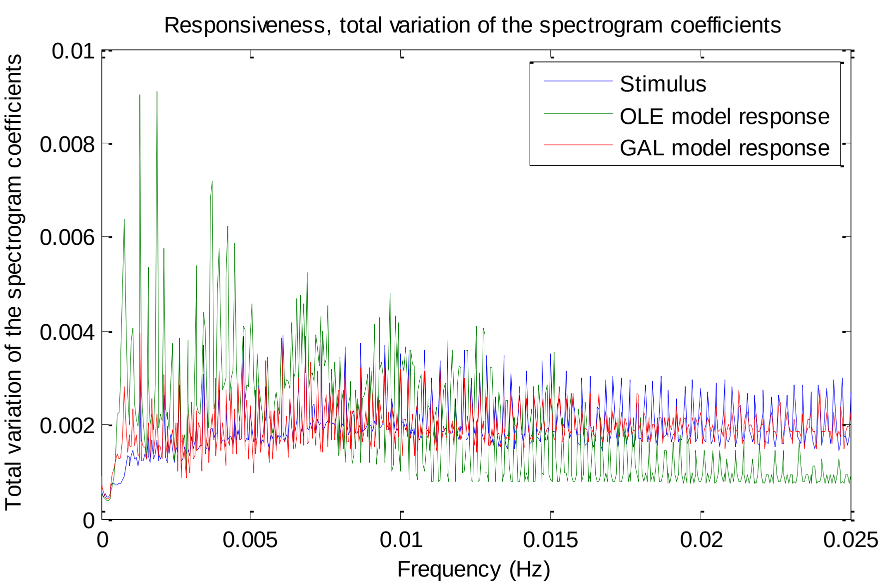
$$TV_i = \sum_{j=1}^{M-1} \left| X_{i,j+1} - X_{i,j} \right|$$

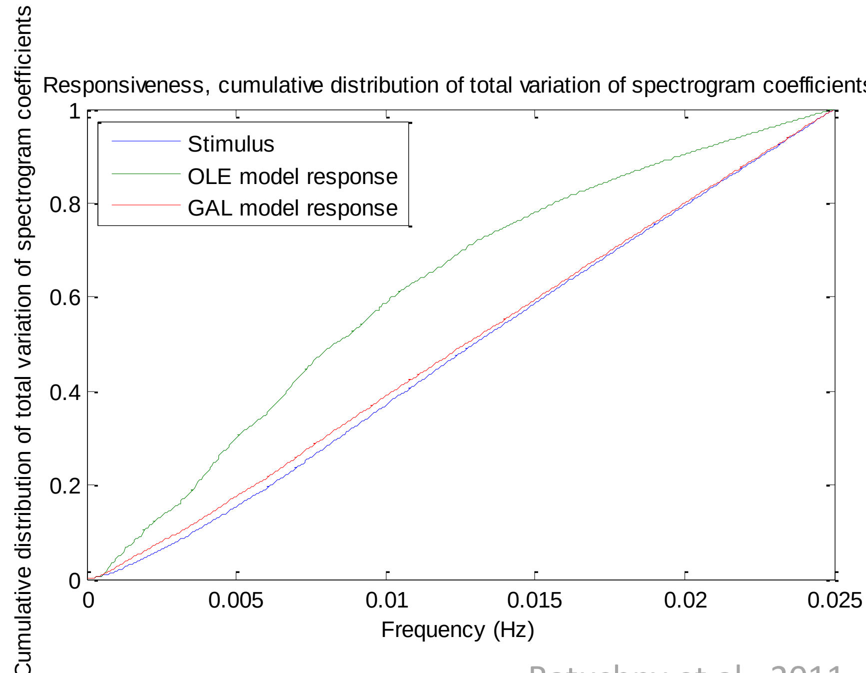
Symmetric Kullback-Leibler divergence ($sD_{KL,TV}$) between the TV distributions of the input (TV_{in}) and output (TV_{out}) spectrogram coefficients across all frequencies

$$sD_{KL,TV} = \frac{1}{2}\sum_{i=1}^{N} TV_{i,in} \log\left(\frac{TV_{i,in}}{TV_{i,out}}\right) + \frac{1}{2}\sum_{i=1}^{N} TV_{i,out} \log\left(\frac{TV_{i,out}}{TV_{i,in}}\right)$$

Responsiveness (ρ)

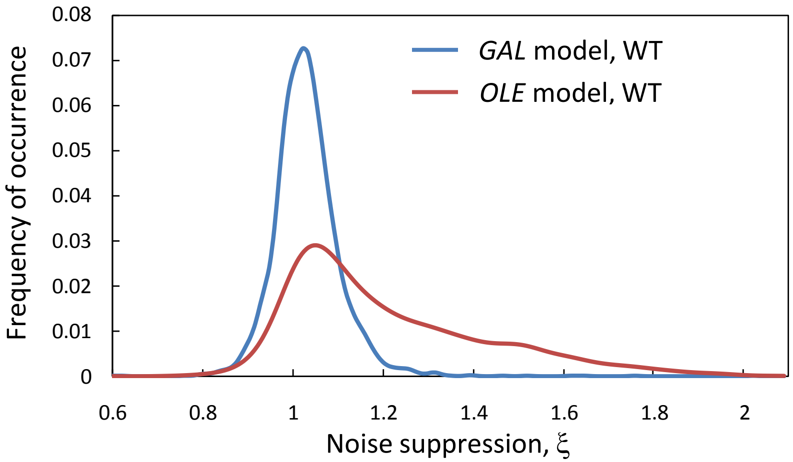
$$\rho = sD_{KL,TV}^{\;-1}$$

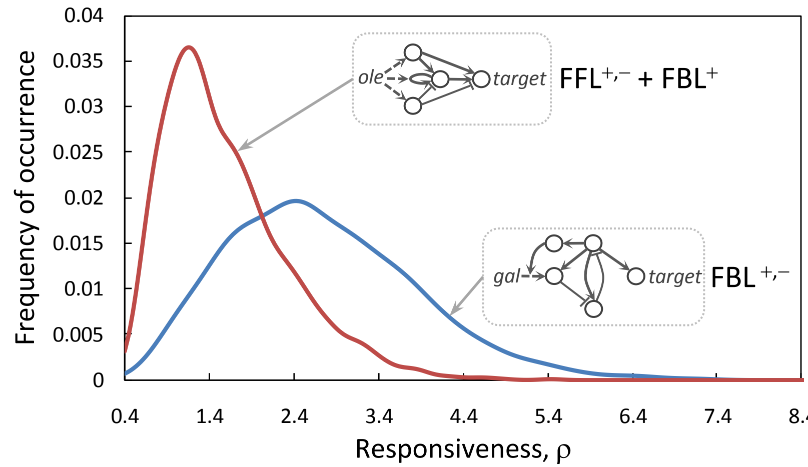


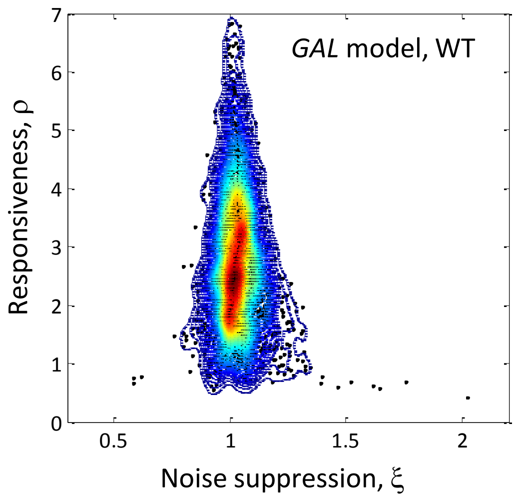


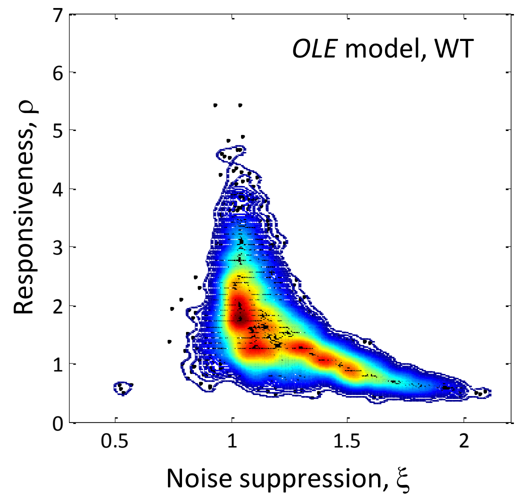
Ratushny et al., 2011

TFA characteristics of *GAL* vs. *OLE* networks, WT





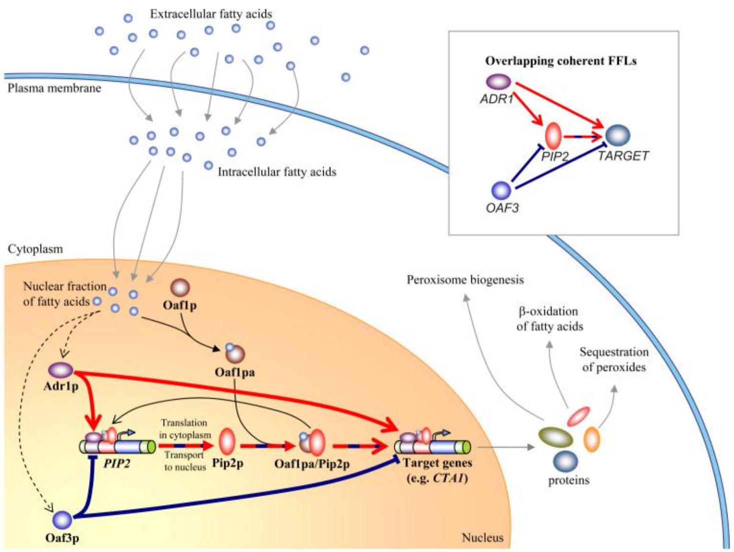




These results are based on the TFA of 3000 random noisy stimuli and corresponding network responses

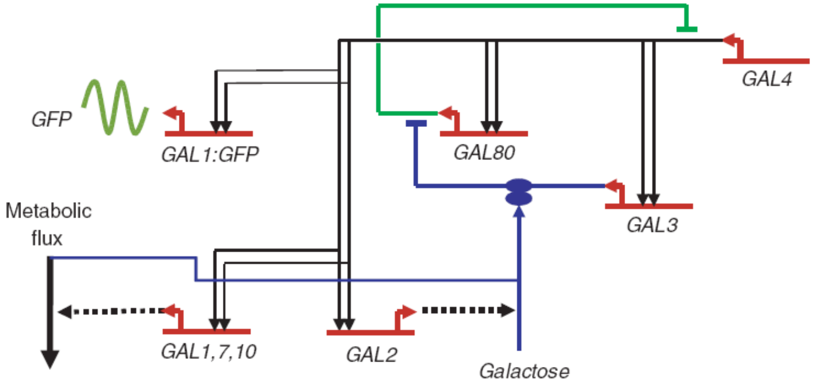
Ratushny et al., 2011

Biological roles of the networks



OLE system

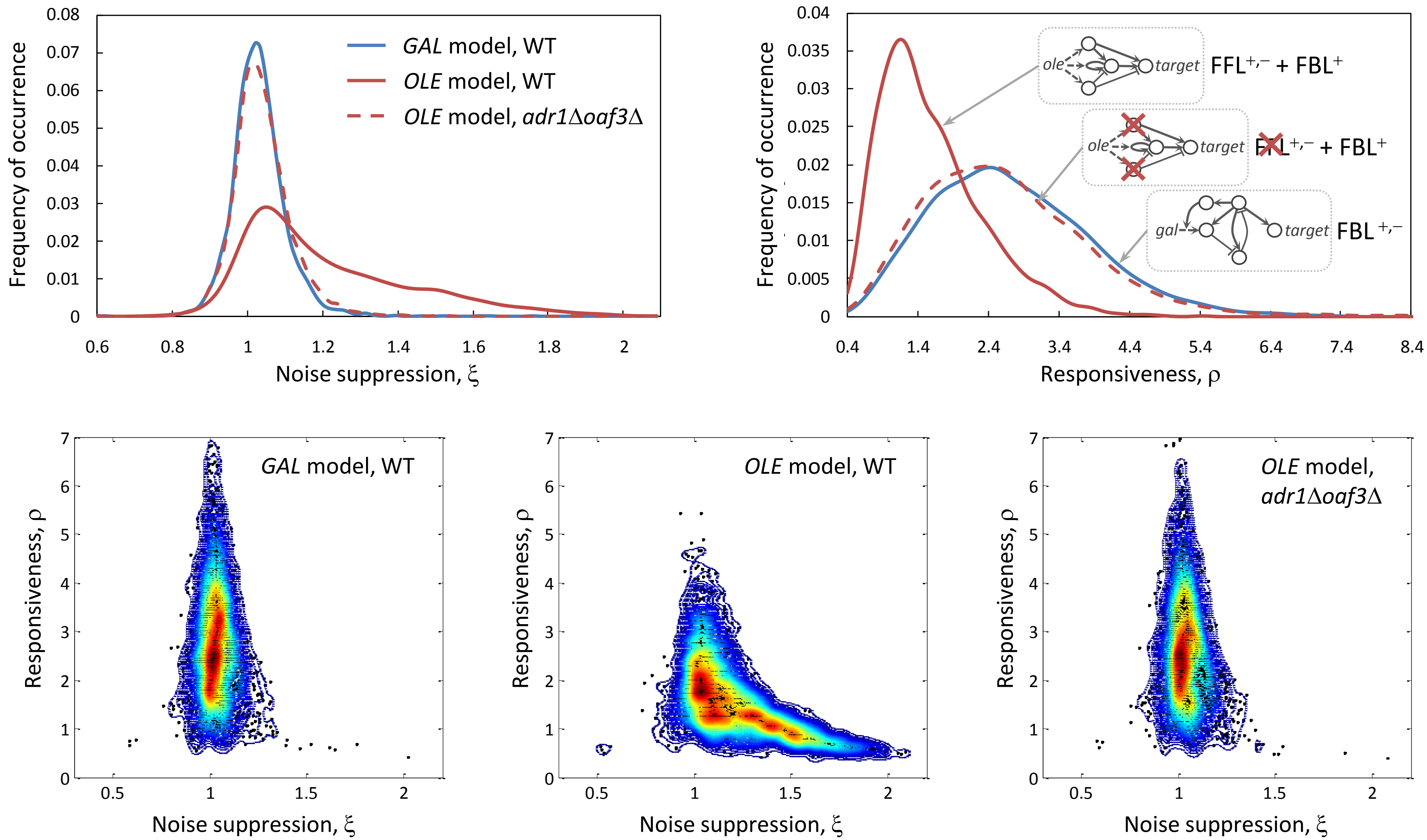
- shift from glucose to fatty-acid;
- build and maintain new organelles;
- switch from fermentative to non-fermentative metabolism;
- mitochondrial respiration;
- coordination of responses to the stress associated with exposure to fatty acids



GAL system

- switch from glucose to galactose;
- requires relatively few enzymes and transporters to convert galactose into glucose-1P for glycolysis

TFA characteristics of *GAL* vs. *OLE* networks, *adr1Δoaf3Δ*

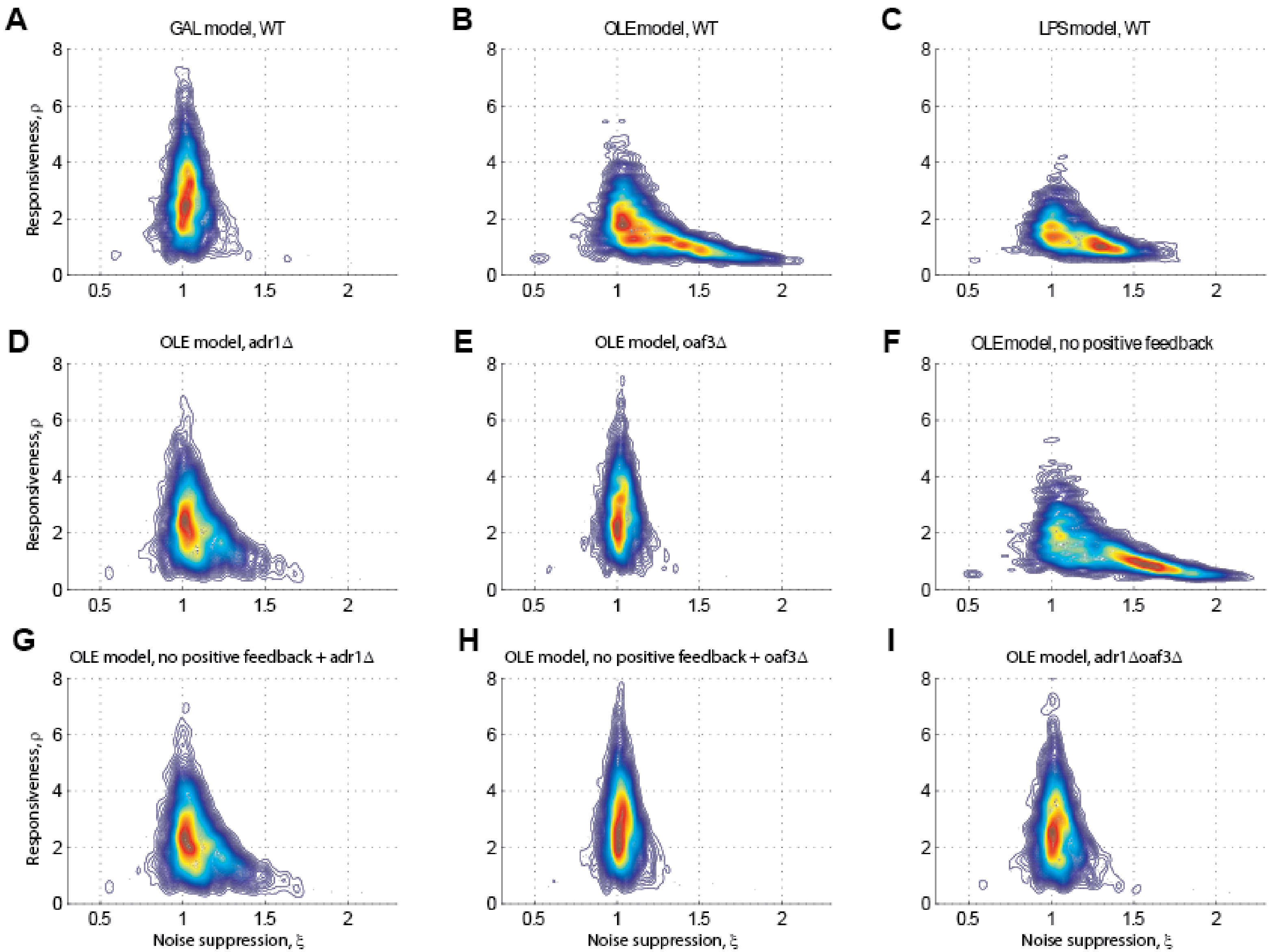


Feed-forward loops provide for the *OLE* system the better ability to filter high-frequency fluctuations of the stimulus whereas feedback loops of the *GAL* network allow the system to be more responsive to the environmental changes.

Ratushny et al., 2011

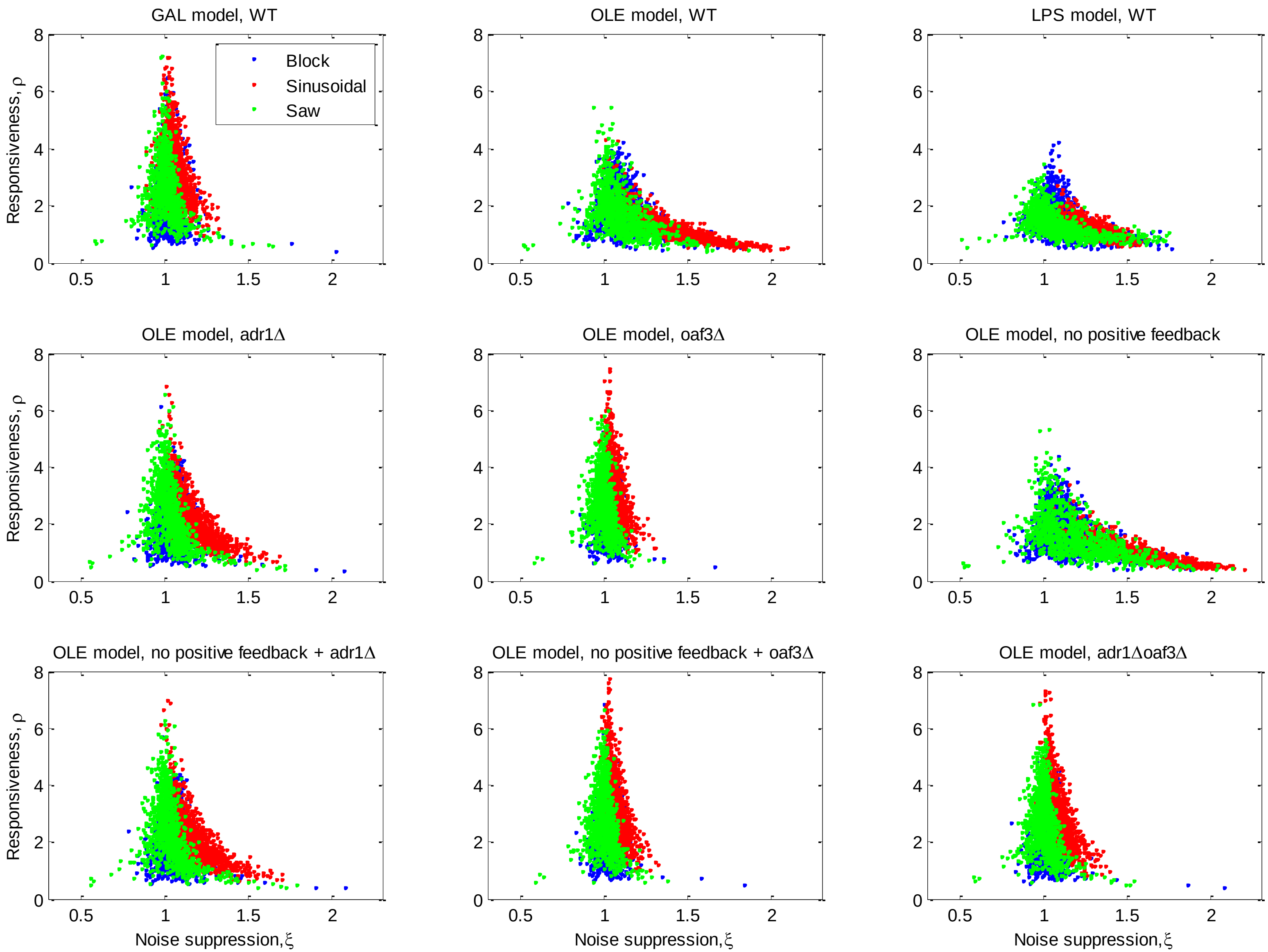
These results are based on the TFA of 3000 random noisy stimuli and corresponding network responses

TFA characteristics of *GAL* vs. *OLE* networks, WT and mutants



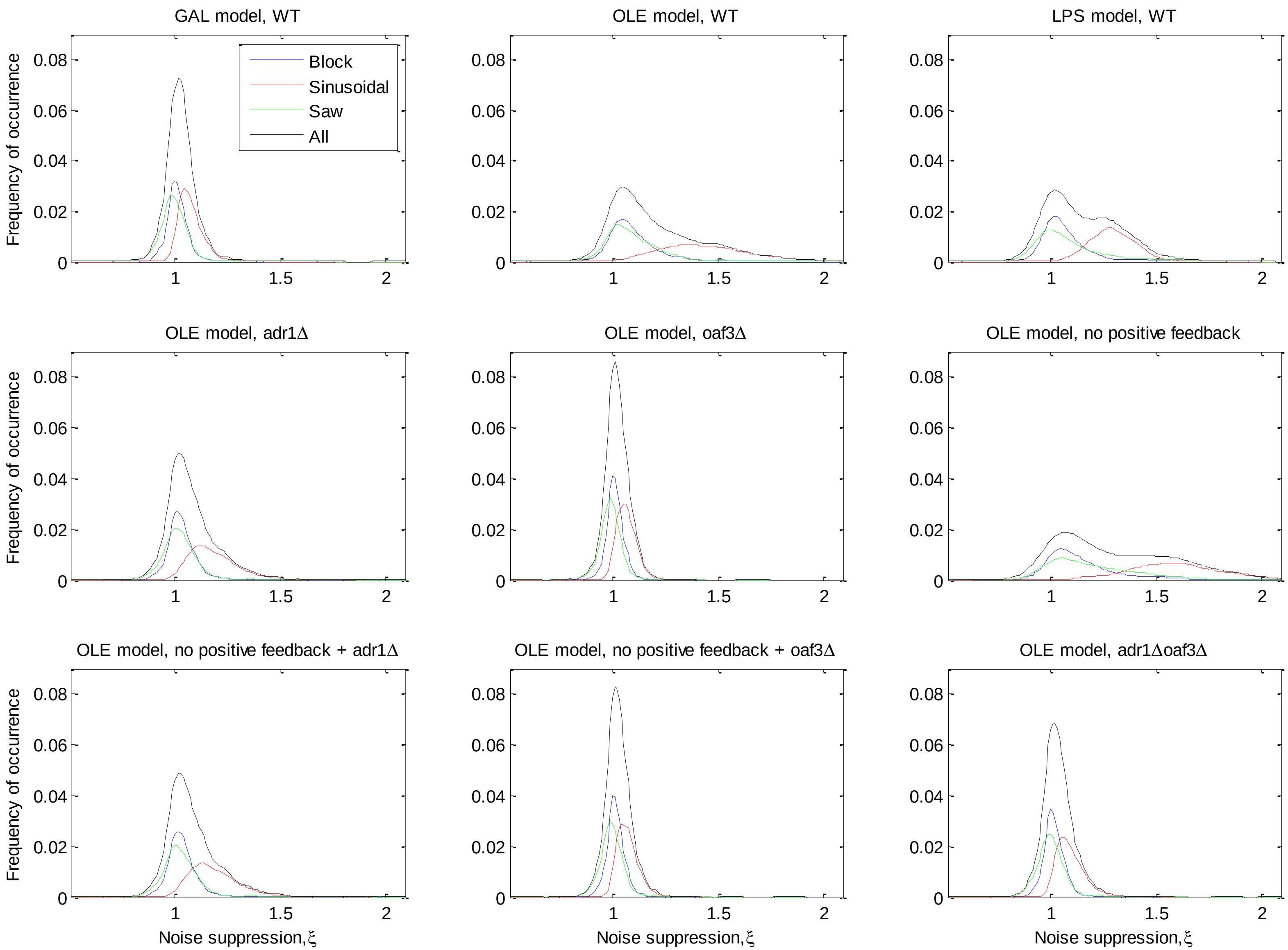
Ratushny et al., 2011

TFA characteristics of *GAL* vs. *OLE* networks, WT and mutants



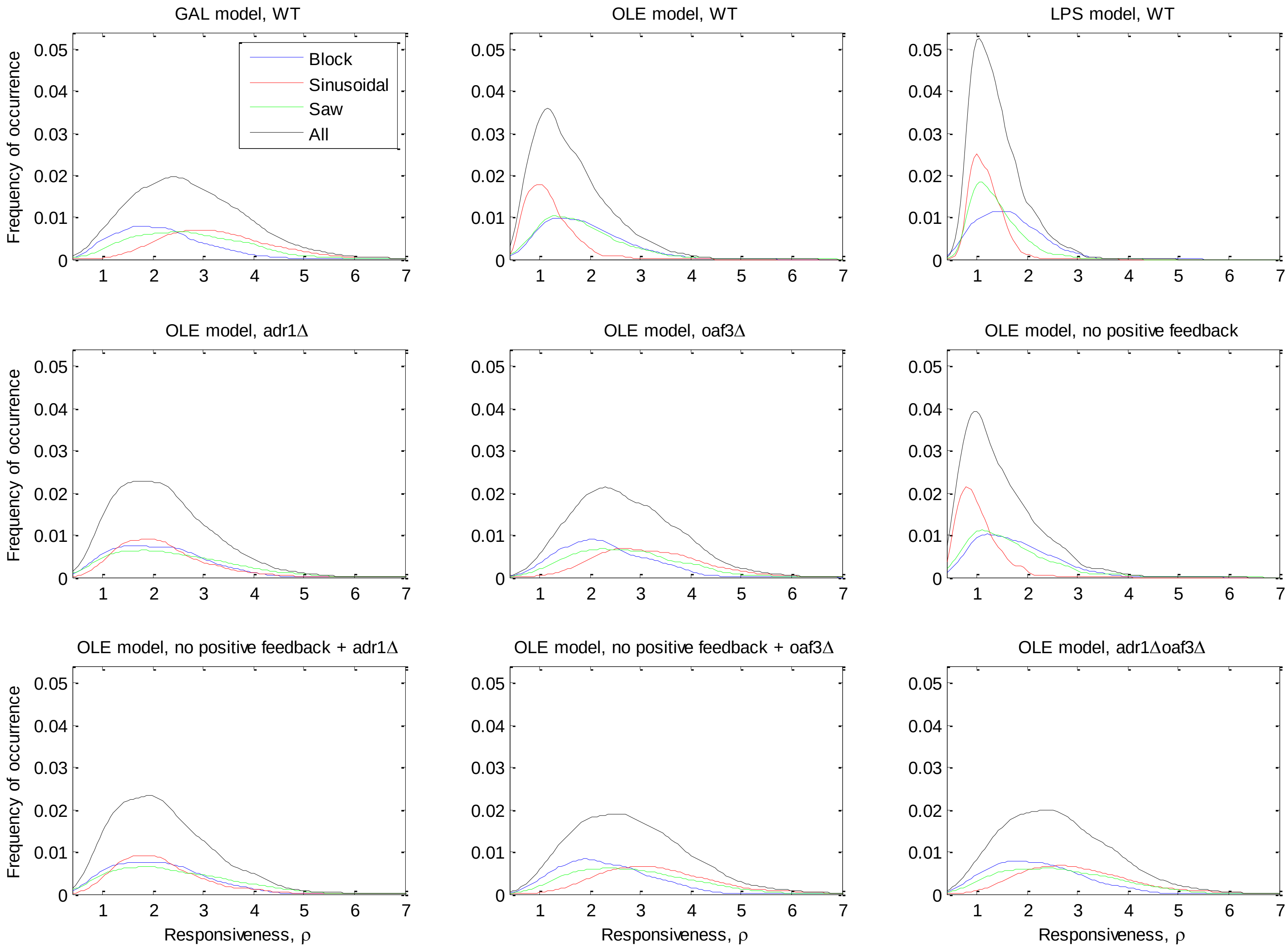
Ratushny et al., 2011

TFA characteristics of *GAL* vs. *OLE* networks, WT and mutants



Ratushny et al., 2011

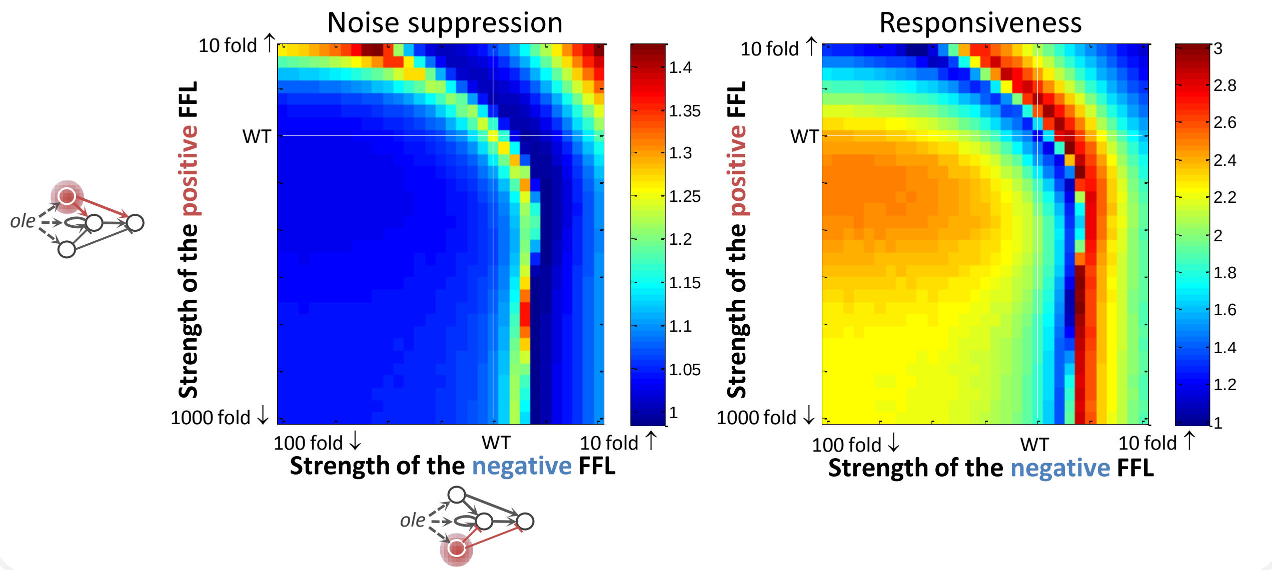
TFA characteristics of *GAL* vs. *OLE* networks, WT and mutants



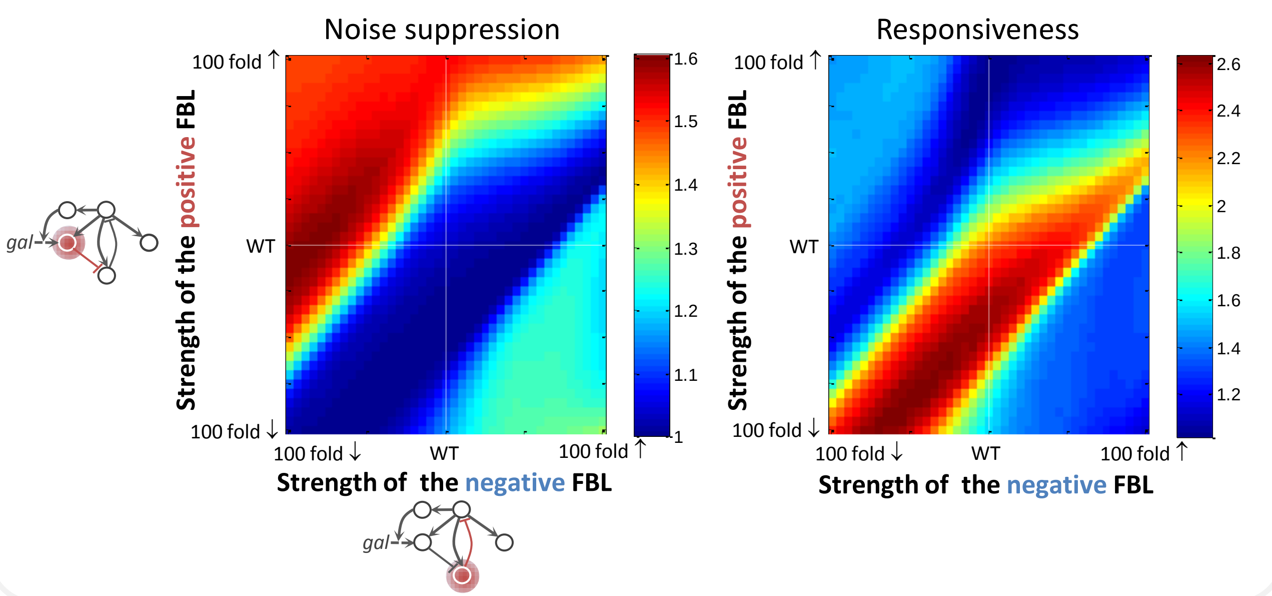
Ratushny et al., 2011

Noise suppression vs. responsiveness

Oleate-responsive network



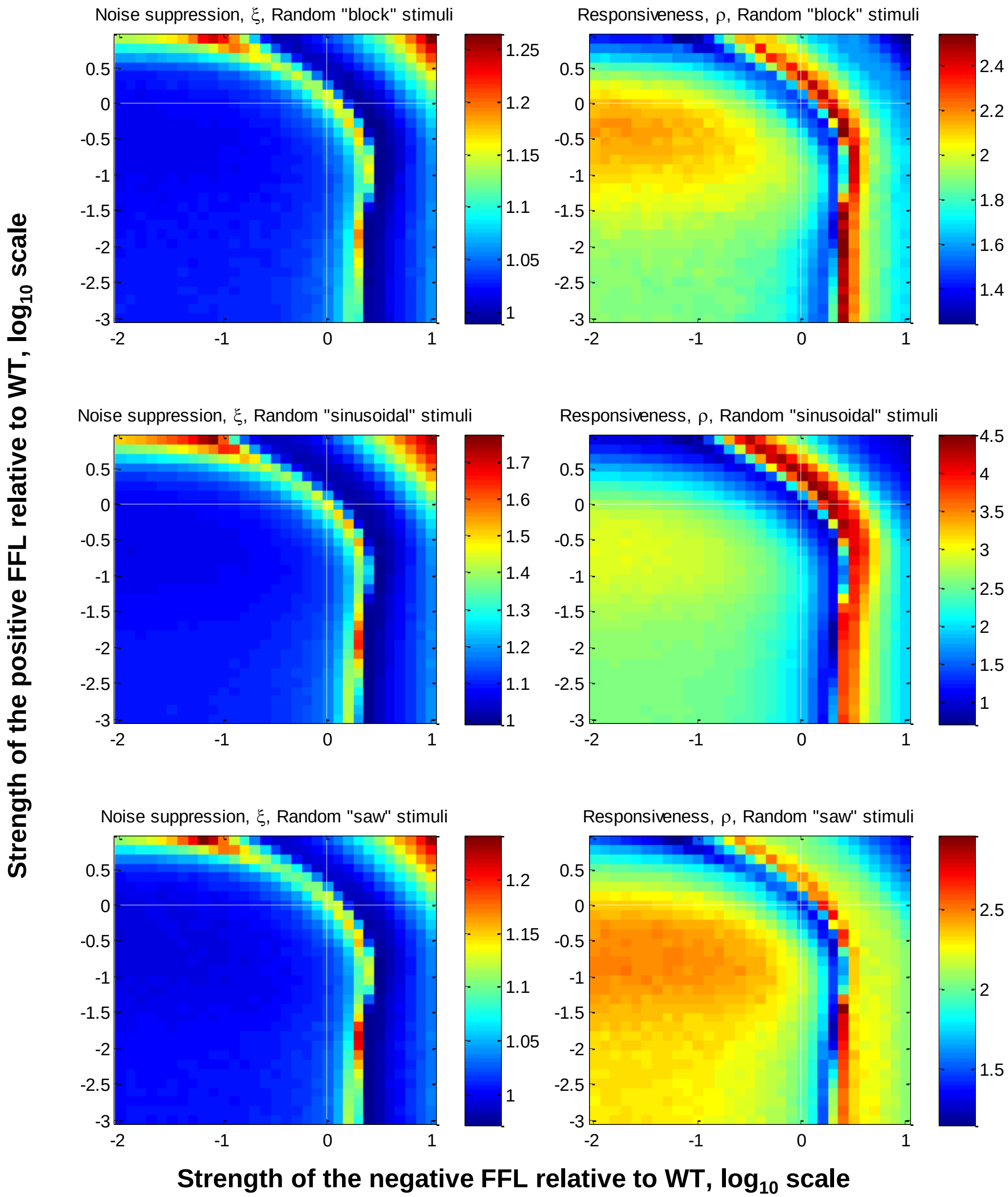
Galactose-responsive network



Totally ~2.65×10^5 model calculations are performed; ~2.65×10^3 sets of model parameters are explored; ~2000 cluster calculation hours.

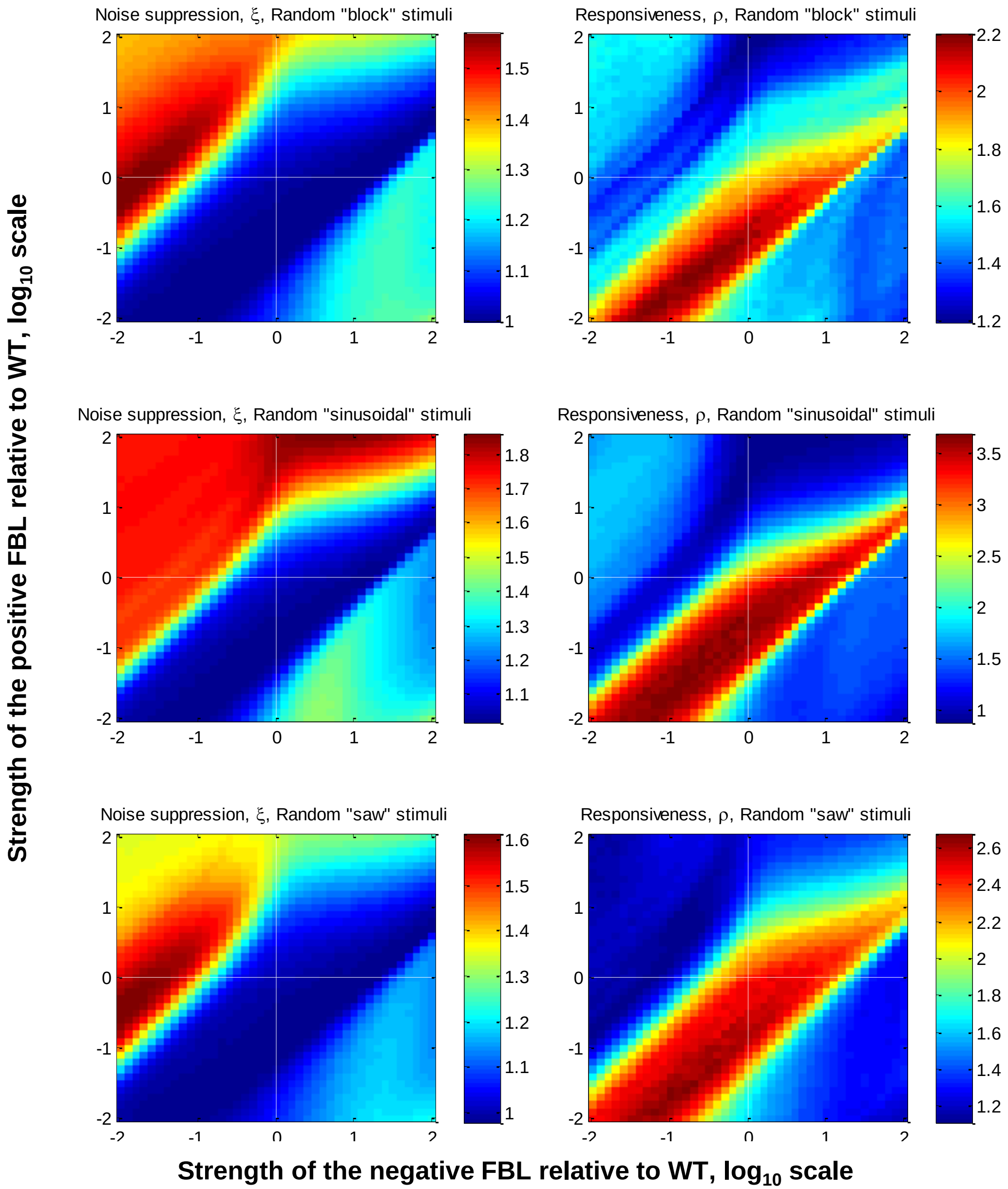
Ratushny et al., 2011

Noise suppression vs. responsiveness



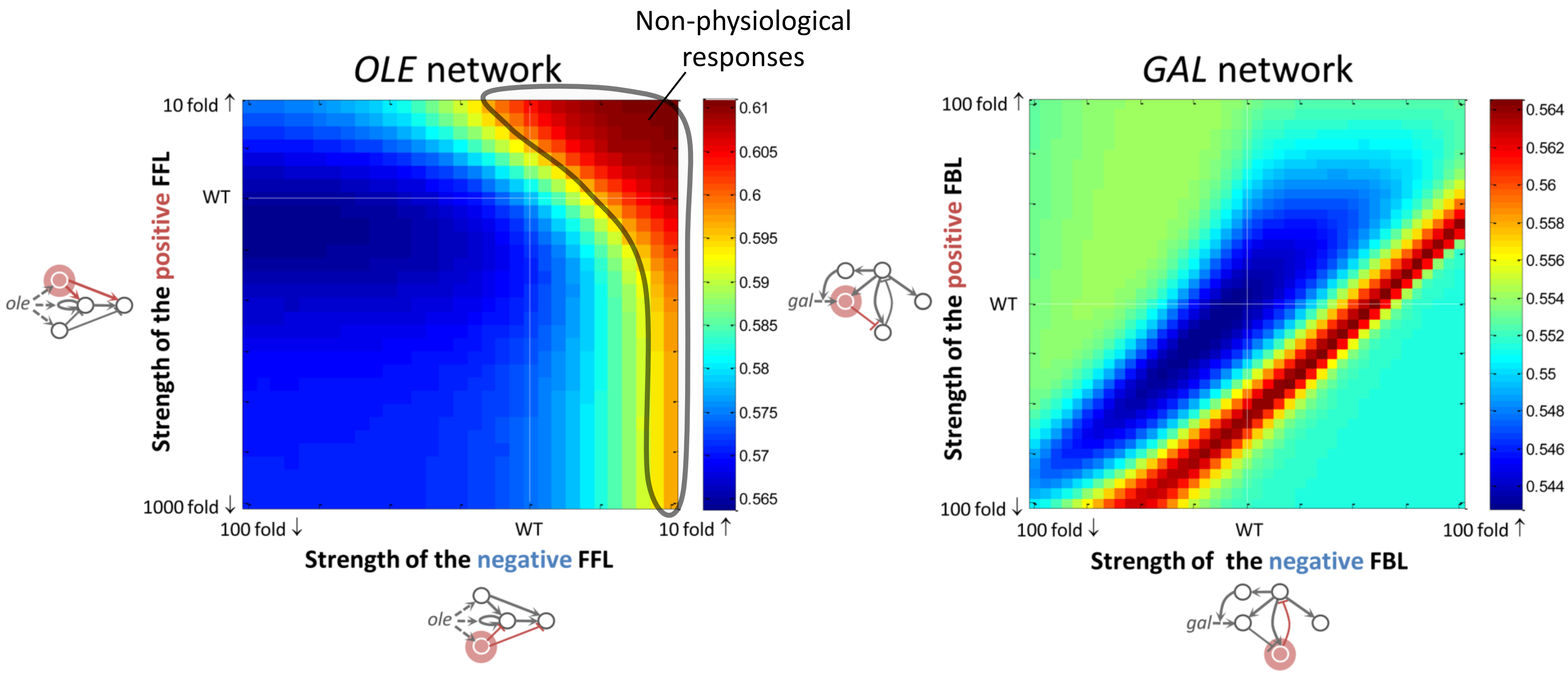
Ratushny et al., 2011

Noise suppression vs. responsiveness



Ratushny et al., 2011

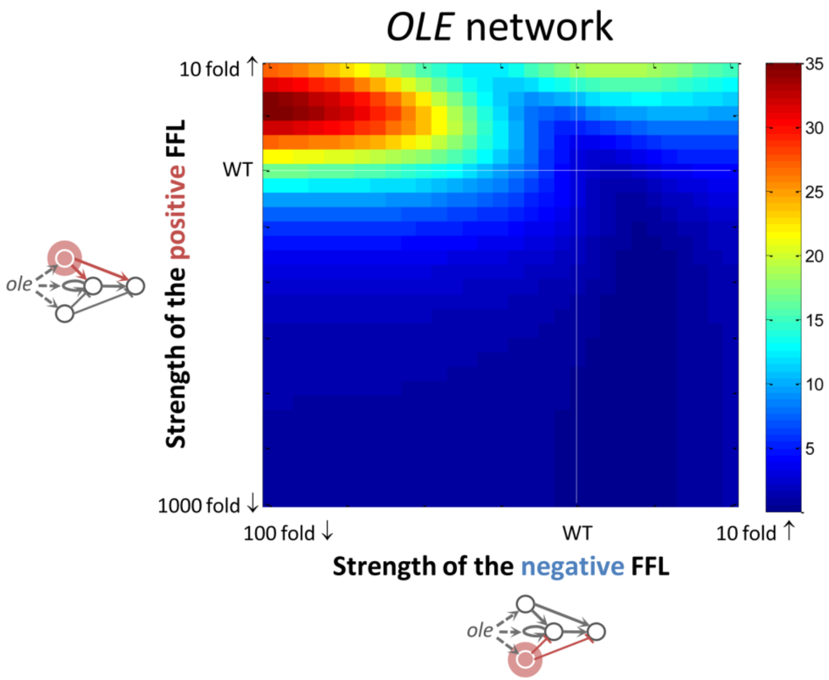
Physiological vs. non-physiological responses

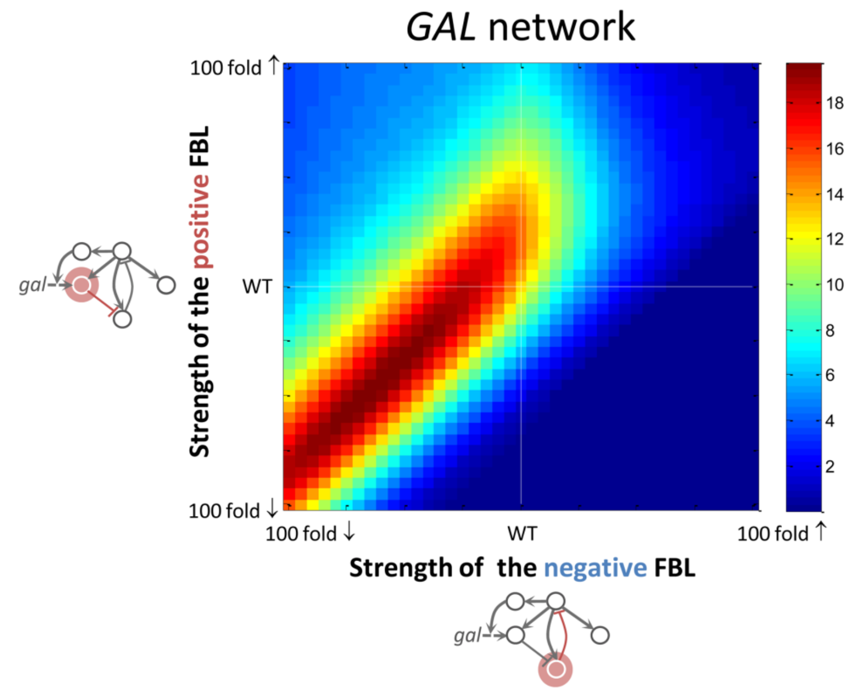


Euclidian distance between input and output derivatives of the *OLE* and *GAL* networks

Ratushny et al., 2011

Other trade-offs: the amplitude of network responses

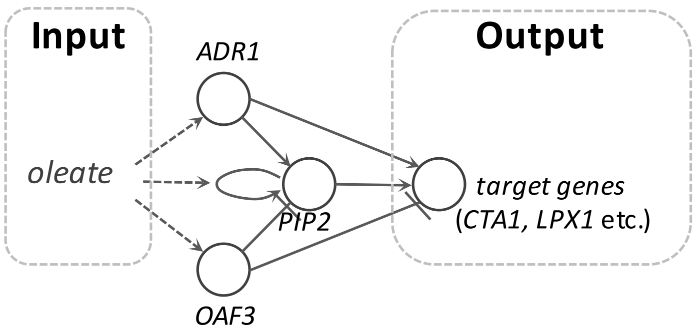




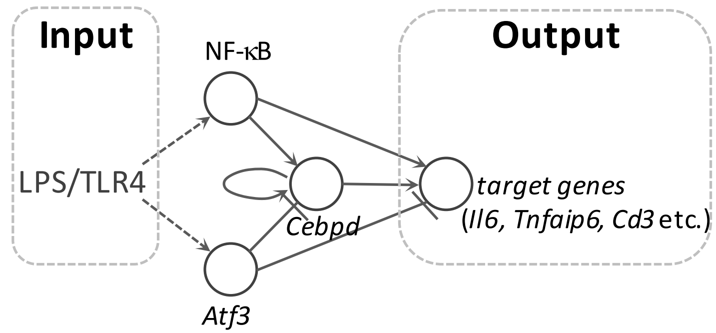
Ratushny et al., 2011

Network topology vs. kinetic parameters

Oleate-induced regulatory network



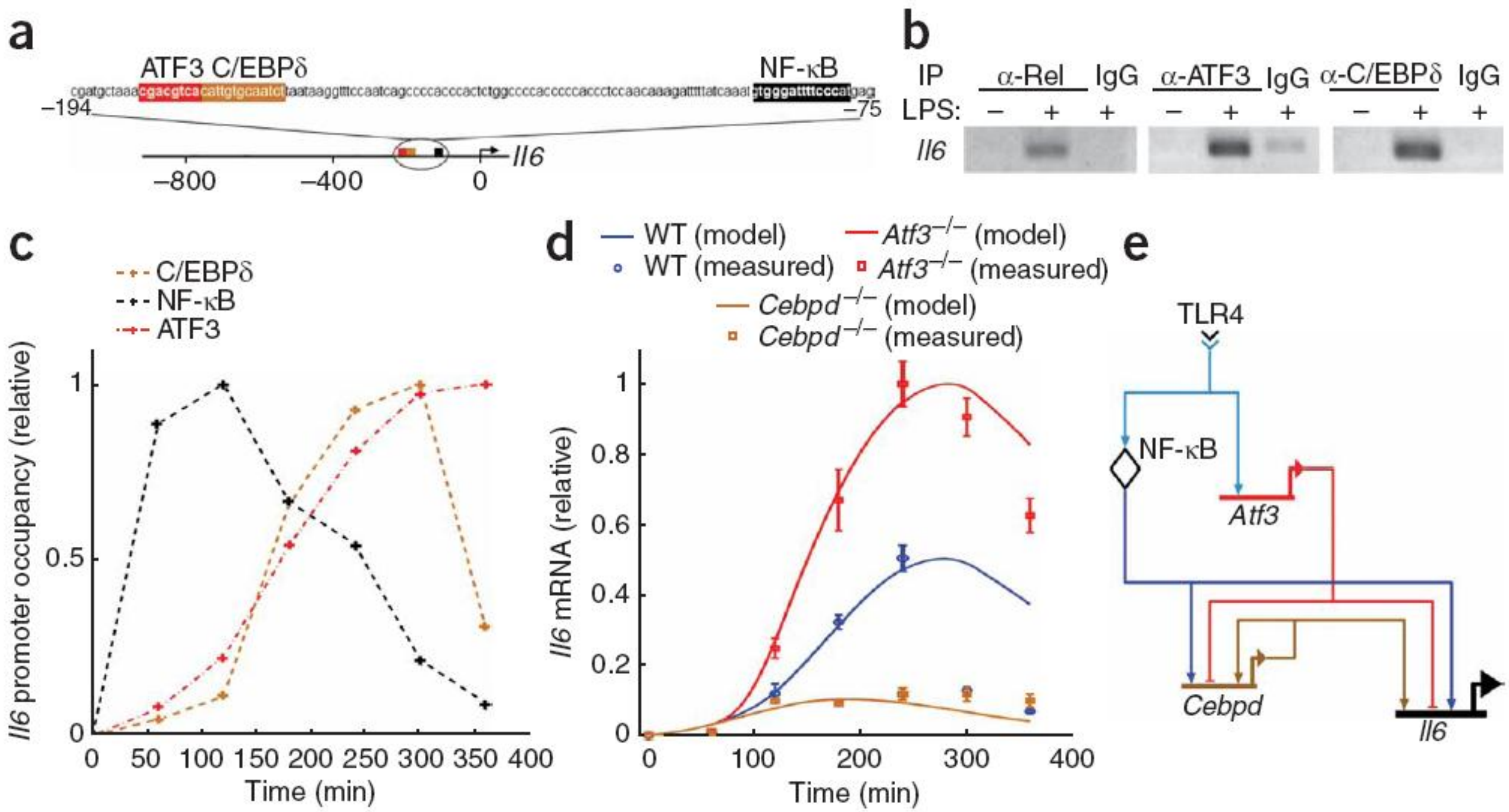
LPS/TLR4-induced regulatory network



What is the extent to which overall network architecture (versus kinetic parameters) defines the dynamical properties of a system?

Ratushny et al., 2011

LPS/TLR4-induced transcriptional network

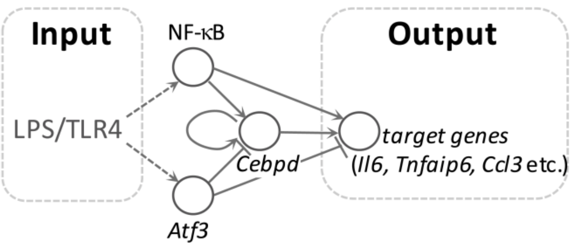


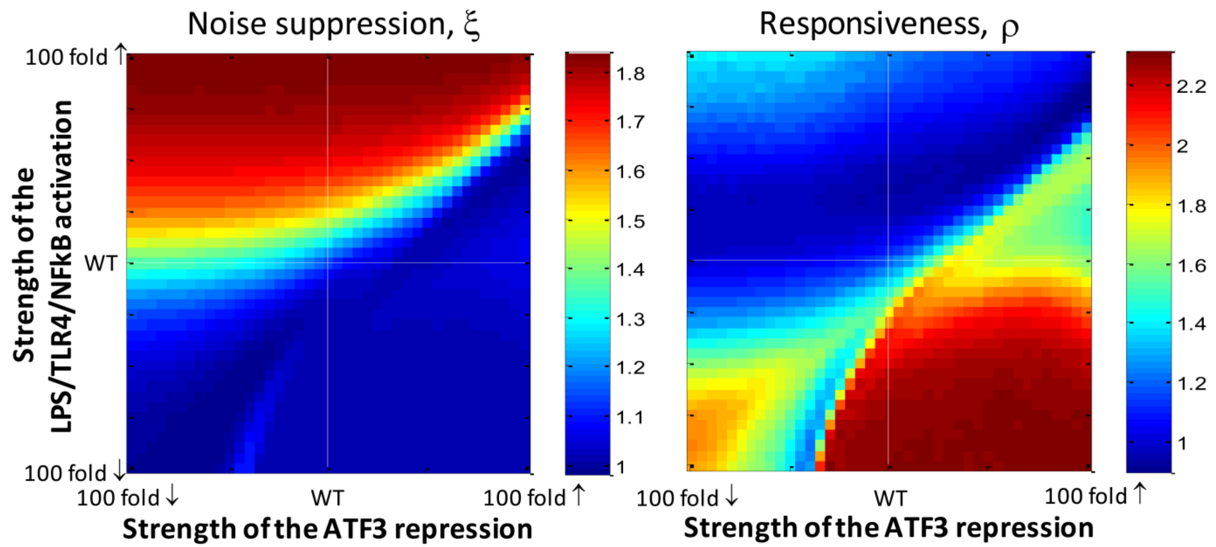
Litvak *et al.*, 2009

The network must be tightly regulated to respond vigorously to the presence of a pathogen, but at the same time must remain in check to avoid uncontrolled inflammatory responses.

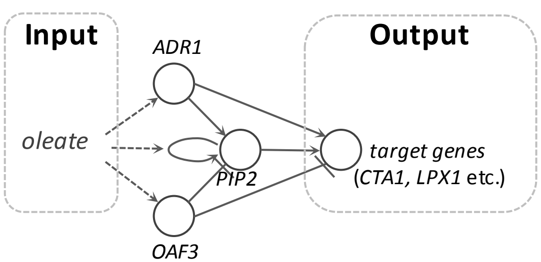
TFA analysis of the LPS/TLR4-induced transcriptional network

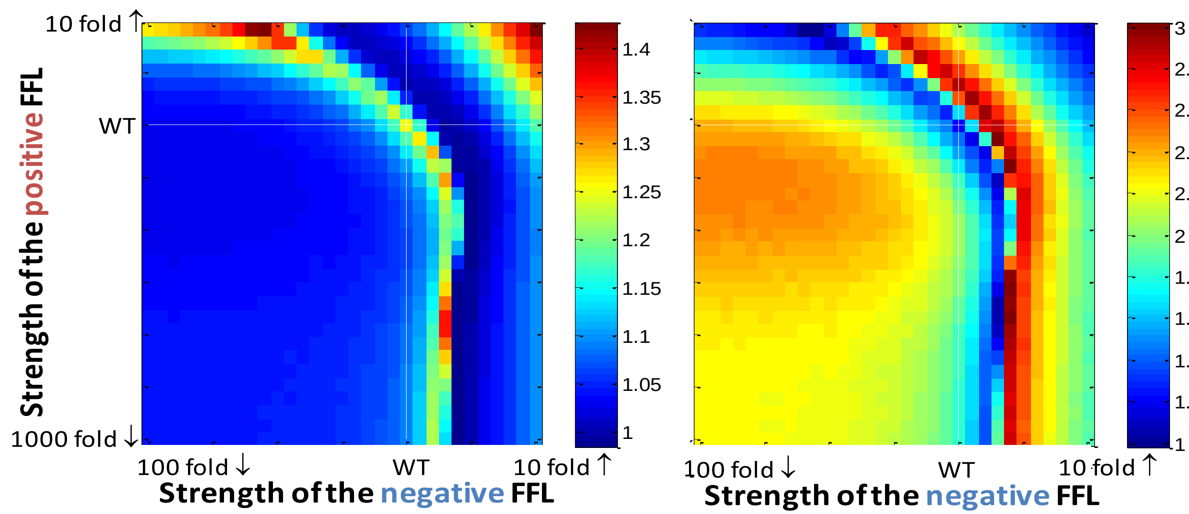
LPS-induced regulatory network





Oleate-induced regulatory network





Ratushny et al., 2011

Conclusions

While experimental tools of systems biology allow us to discern molecular network structures, it is evident that the parameters governing the interactions within the system are essential for understanding its dynamics.

One has only partial knowledge of the parameter values in the system, with many parameters being either entirely undetermined or known only imprecisely.

The generalized TFA framework is particularly useful in such scenarios as it can reveal various aspects of dynamical system behavior such as noise suppression, responsiveness, and their trade-offs, relative to the parameter space of the system.

Other dynamical properties of a network can be investigated in the same manner by extracting appropriate features from the time-frequency representations or other metrics for features such as noise suppression and responsiveness can readily be incorporated and compared in the TFA framework.

The generalized TFA framework is not constrained by the STFT; wavelets or other multiresolution or multiscale analysis approaches can also be used for time-frequency representations.

The noise suppression and responsiveness portraits of *OLE*, *GAL* and the LPS-induced networks reveal radically different behaviors and biological roles for these circuits.

Such portraits can also suggest new avenues for experimental research in synthetic biology aimed at modulating the biochemical properties of the interactions to affect systems-level trade-offs, while maintaining physiologically viable responses.

Acknowledgements

Stephen Ramsey
Jennifer Smith
Ramsey Saleem
Theo Knijnenburg
Vladimir Litvak
Kerry Deutsch
Pekka Ruusuvuori
Greg Carter
Alan Aderem
Leroy Hood
Aitchison lab

Ilya Shmulevich
John Aitchison

Supported by NIH/NIGMS (R01-GM075152, R01-GM072855 and P50-GM076547).