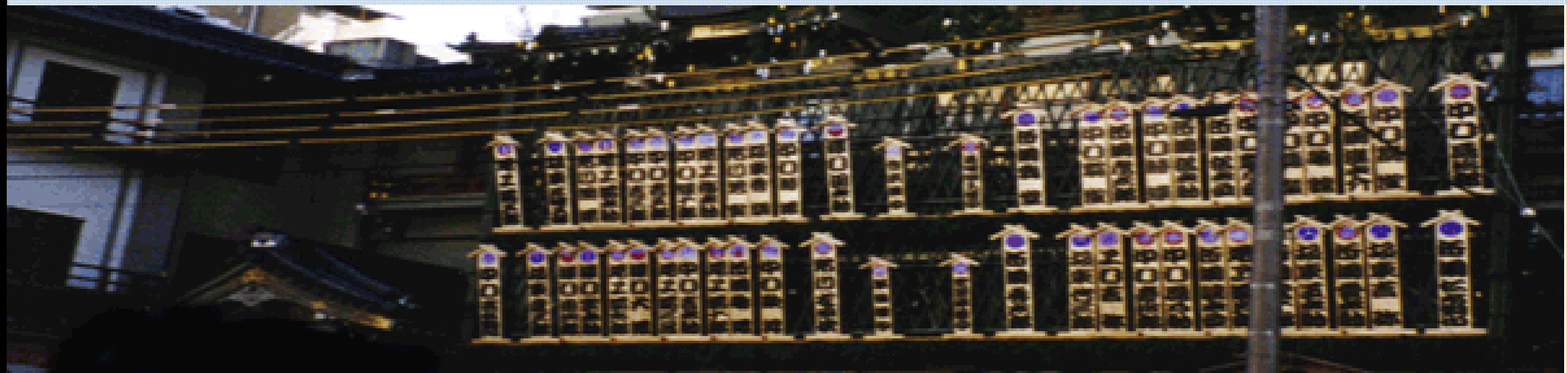
redundancy, control and collective computation



in network dynamics

luis m. rocha

school of informatics & computing

indiana university, bloomington, usa

and

instituto gulbenkian de ciência

oeiras, portugal

rocha@indiana.edu
http://informatics.indiana.edu/rocha

casci CNetS Cognitive Science Program FUNDAÇÃO CALOUSTE GULBENKIAN Instituto Gulbenkian de Ciência

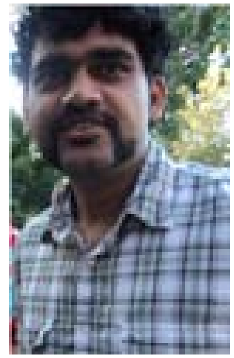
INDIANA UNIVERSITY

acknowledgements

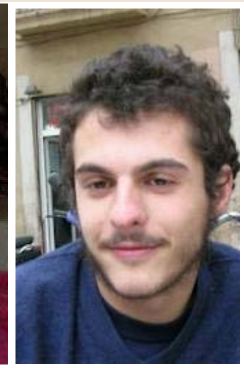
CASCI group


Manuel Marques-Pita


Tiago Simas


Santosh Manicka


Alexander Gates


Artemy Kolchinsky


Ian Wood


Jason Yoder


Rion Brattig Correia


Yizhi Jing


Thomas Parmer

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF ENERGY · UNITED STATES OF AMERICA

PERSISTENT

NSF

IARPA BE THE FUTURE

FUNDAÇÃO LUSO-AMERICANA

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

careerbuilder®

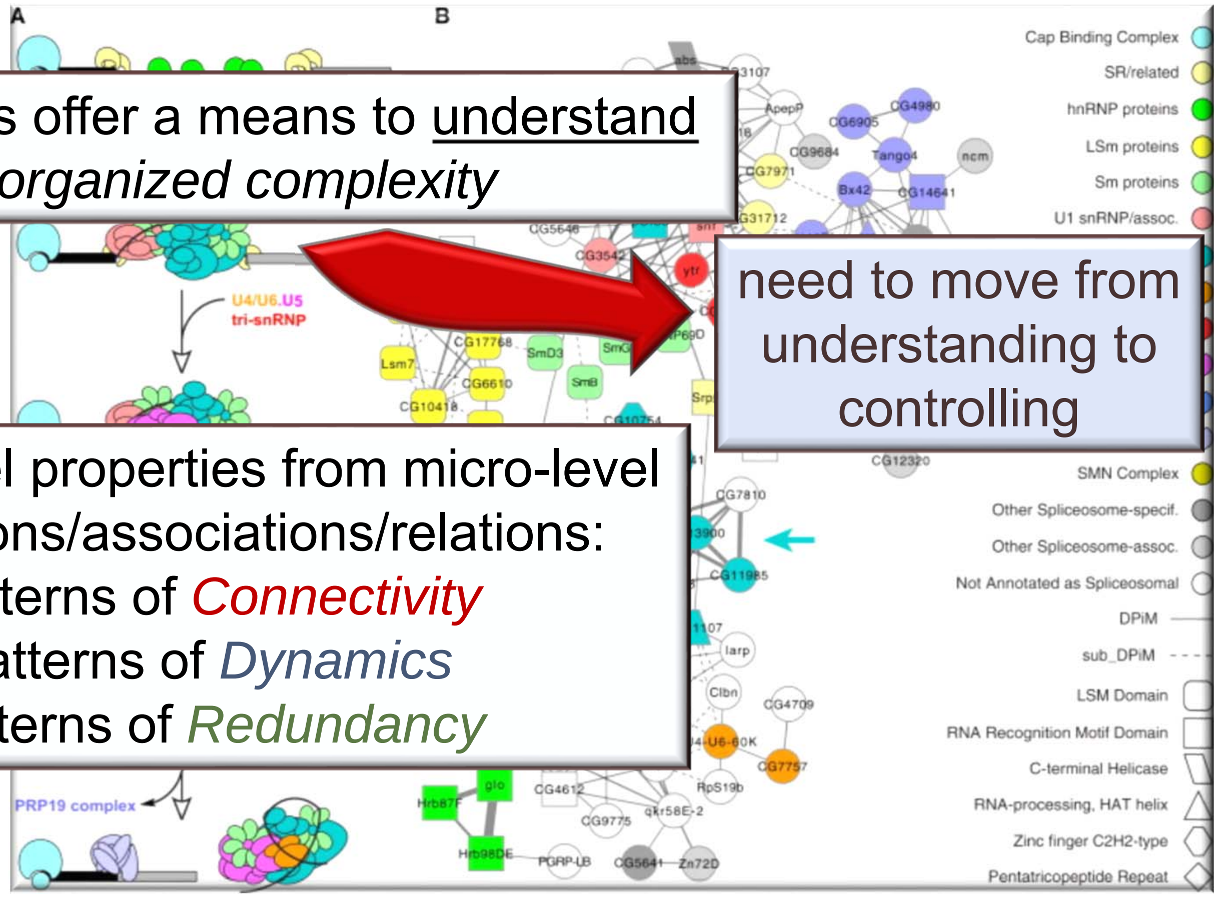
Indiana University Collaborative Research Grants

rocha@indiana.edu
http://informatics.indiana.edu/rocha

large-scale *drosophila protein interaction Map* (DPiM)

Informatics
luis rocha 2014

Guruharsha et al [2011]. "A Protein Complex Network of Drosophila melanogaster." *Cell*.**147**(3):690-703.



Networks offer a means to <u>understand</u> *organized complexity*

need to move from understanding to controlling

Macro-level properties from micro-level interactions/associations/relations:
Patterns of *Connectivity*
Patterns of *Dynamics*
Patterns of *Redundancy*

Modularity of the spliceosome subnetwork: 12 well-connected clusters representing interaction of snRNPs with pre-mRNA and other proteins in the process of splicing introns.

INDIANA UNIVERSITY

rocha@indiana.edu
http://informatics.indiana.edu/rocha

PATTERNS OF REDUNDANCY IN DYNAMICS

rocha@indiana.edu
http://informatics.indiana.edu/rocha

an automata network model built from qualitative data

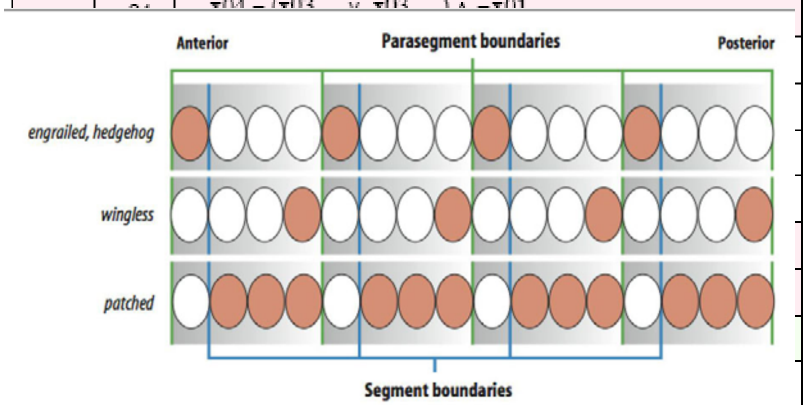
Based on the ODE model of von Dassow et al. (2000), consists of 4-cell parasegments, each cell with 15 interacting genes and proteins.

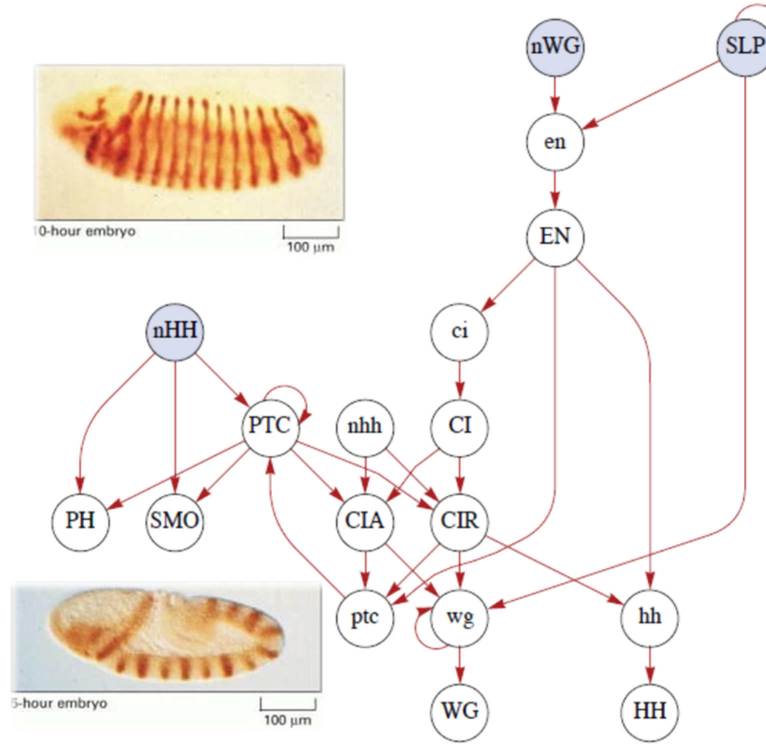
2^{60} network configurations

Reproduces wild-type and mutant gene expression patterns in development of fruit fly

- 2 intercellular inputs: **nhh** (*hedgehog*), **nWG** (*wingless*)
- 1 intracellular input: **SLP** (*sloppy paired*)

SLP	x01	x01
wg	x02	x02 = (x14 ∧ x01 ∧ ¬x15) ∨ (x02 ∧ (x14 ∨ x01) ∧ ¬x15)
WG	x03	x03 = x02
CI	x13	x13 = x12
CIA	x14	$x14 = x13 \wedge (x01 \vee x06_{i-1} \vee x06_{i+1})$
CIR	x15	$x15 = x13 \wedge \neg x11 \wedge \neg x06_{i-1} \wedge \neg x06_{i+1}$





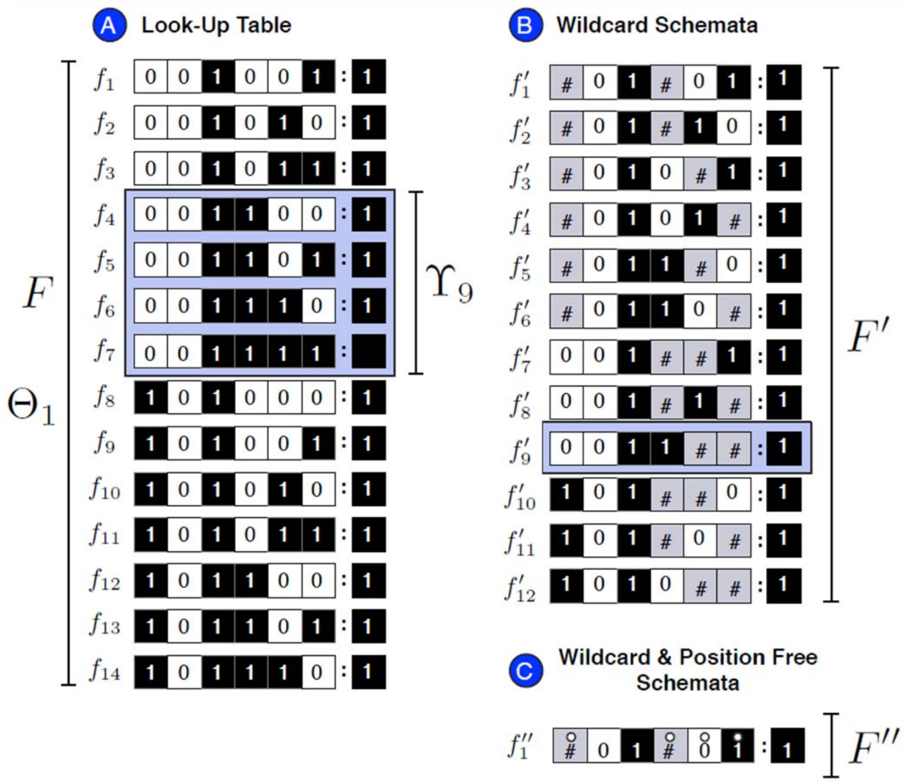
Albert & Othmer [2003]. *J. Theor. Bio.* **223**: 1-18.

INDIANA UNIVERSITY
rocha@indiana.edu
http://informatics.indiana.edu/rocha

Informatics
luis rocha 2014

quantifying micro-level canalization

input redundancy, effective connectivity and input symmetry



$$k(x) = 6$$

$$k_r(x) = \frac{\sum_{f_\alpha \in F} \max_{\theta | f_\alpha \in \Theta_\theta} \left(n_\theta^{\#}\right)}{2^k}$$

$$k_e(x) = k(x) - k_r(x)$$

$$k_s(x) = \frac{\sum_{f_\alpha \in F} \min_{\theta | f_\alpha \in \Theta_\theta} \left|n_\theta^{o}\right|}{2^k}$$

- Measuring two forms of *canalization*
  - $K_r = 2$
  - $K_e = 6 - 2 = 4$
  - $K_s = 4$

Prime Implicants (Quine-McCluskey) plus **group invariance**

Marques-Pita & Rocha, [2013]. *PLoS ONE*, **8**(3): e55946.

INDIANA UNIVERSITY

rocha@indiana.edu
http://informatics.indiana.edu/rocha

Informatics
luis rocha 2014

In biological Boolean network models

- extracting micro-level canalization
  - drosophila segment polarity genes network

node	inhibition	expression	k	k_e	k_r	k_s	k_r^*	k_s^*
wg	SLP, wg, CIA, CIR : wg; $f''_{2:1}$; $f''_{2:2}$	SLP, wg, CIA, CIR : wg; $f''_{2:3}$	4	1.75	2.25	2.25	0.56	0.56
PTC	ptc, PTC, HH_{i-1}, HH_{i+1} : PTC; $f''_{9:1}$; $f''_{9:2}$	ptc, PTC, HH_{i-1}, HH_{i+1} : PTC; $f''_{9:3}$; $f''_{9:4}$	4	1.56	2.44	0.75	0.61	0.19
PH	PTC, HH_{i-1}, HH_{i+1} : PH; $f''_{10:1}$; $f''_{10:2}$	PTC, HH_{i-1}, HH_{i+1} : PH; $f''_{10:3}$	3	1.5	1.5	0.75	0.5	0.25
SMO	PTC, HH_{i-1}, HH_{i+1} : SMO; $f''_{11:1}$	PTC, HH_{i-1}, HH_{i+1} : SMO; $f''_{11:2}$; $f''_{11:3}$	3	1.25	1.75	1.5	0.58	0.5
ci	EN : ci; $f''_{12:1}$	EN : ci; $f''_{12:2}$	1	1	0	0	0	0
CI	ci : CI; $f''_{13:1}$	ci : CI; $f''_{13:2}$	1	1	0	0	0	0
CIA	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIA; $f''_{14:1}$; $f''_{14:2}$	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIA; $f''_{14:3}$; $f''_{14:4}$	6	1.55	4.45	1.875	0.74	0.32
CIR	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIR; $f''_{15:1}$; $f''_{15:2}$	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIR; $f''_{15:3}$	6	1.08	4.92	5.25	0.82	0.88

INDIANA UNIVERSITY

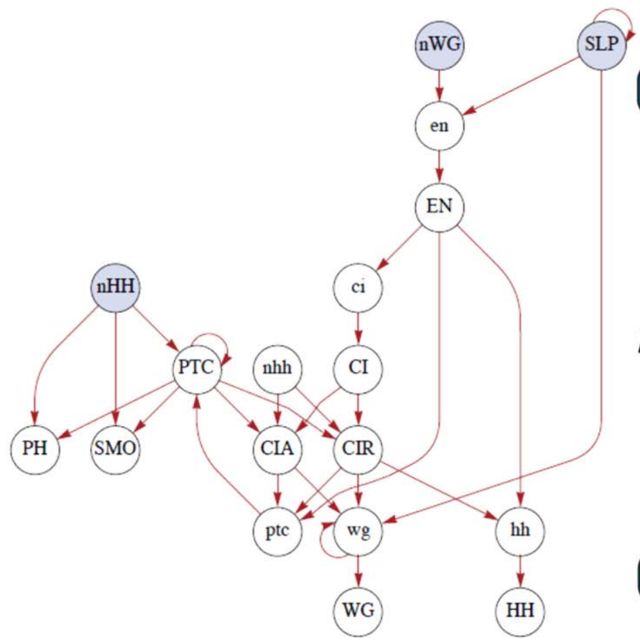
Informatics
luis rocha 2014

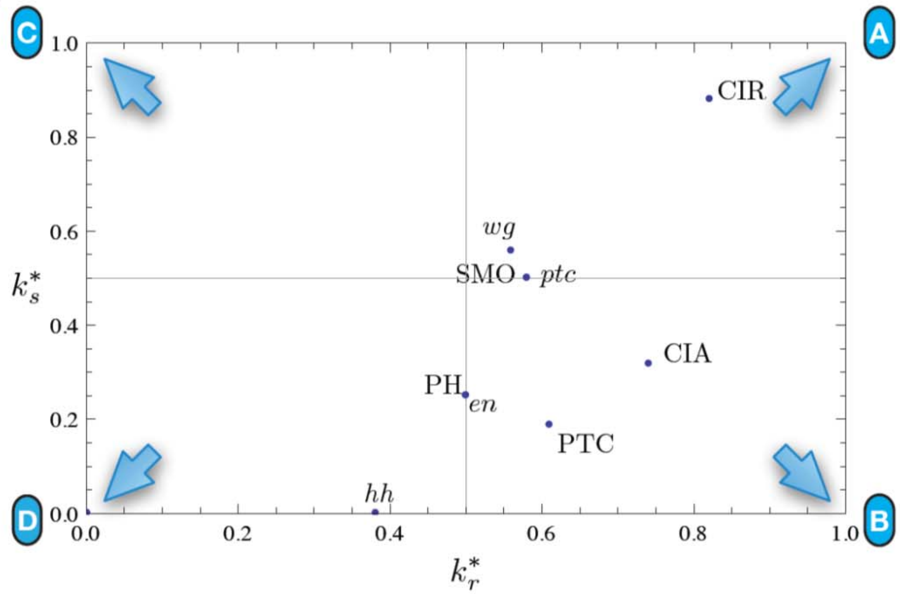
INDIANA UNIVERSITY

per-node schema redescription

In biological Boolean network models

- extracting micro-level canalization
  - drosophila segment polarity genes network





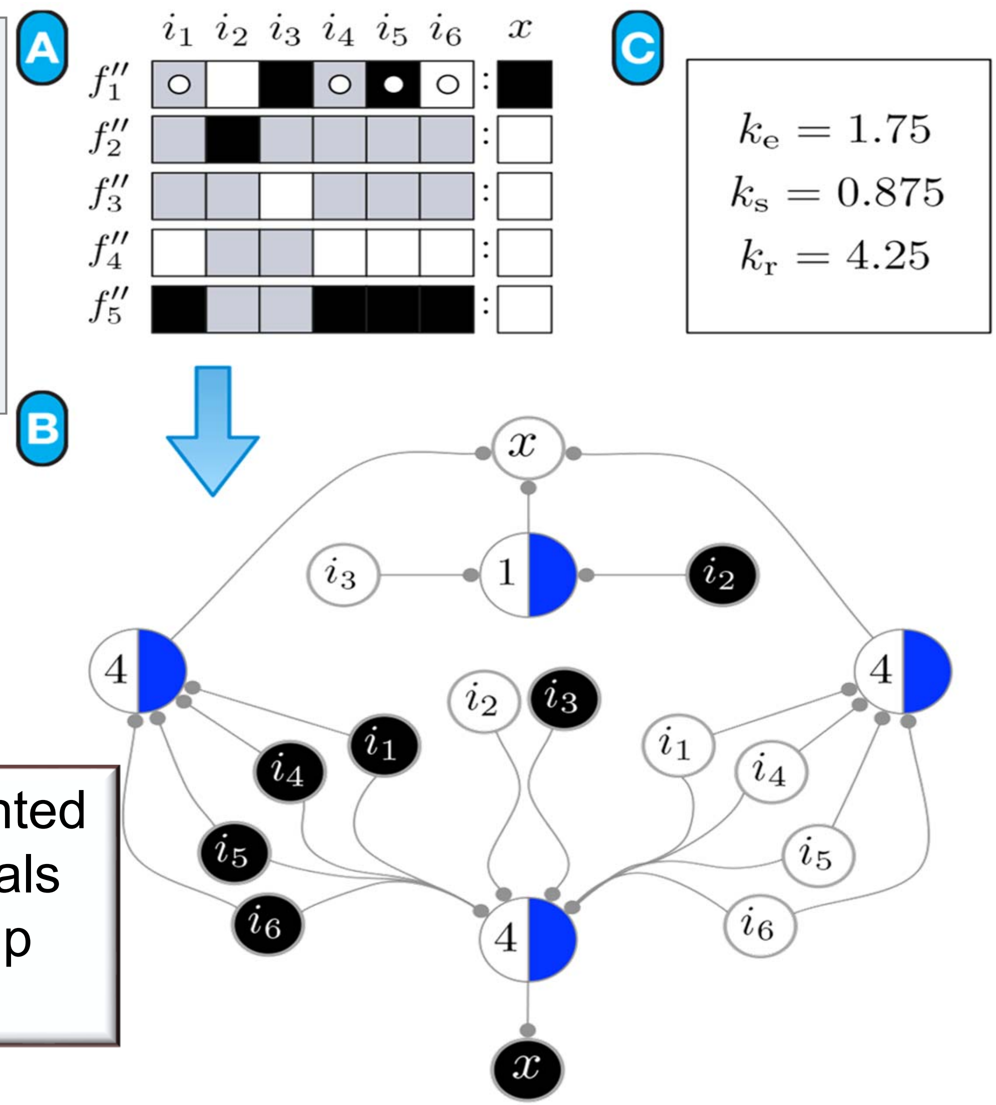
node	inhibition	expression	k	k_e	k_r	k_s	k_r^*	k_s^*
CIA	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIA $f''_{14:1}$ $f''_{14:2}$	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIA $f''_{14:3}$ $f''_{14:4}$	6	1.55	4.45	1.875	0.74	0.32
CIR	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIR $f''_{15:1}$ $f''_{15:2}$	PTC, CI, hh_{i-1}, hh_{i+1}, HH_{i-1}, HH_{i+1} : CIR $f''_{15:3}$	6	1.08	4.92	5.25	0.82	0.88

Informatics
luis rocha 2014

canalization map as minimal control

two-symbol schemata as threshold networks

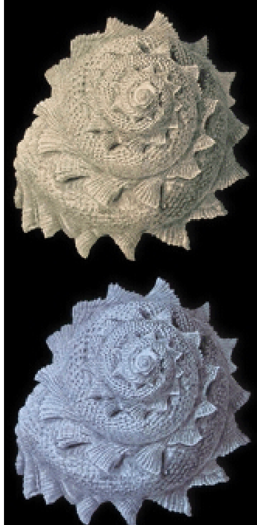
- understanding natural "computation"
  - minimal wiring (control) of **micro-level**



Each schema represented by conjunction of literals and symmetric group constraints

INDIANA UNIVERSITY

rocha@indiana.edu
http://informatics.indiana.edu/rocha

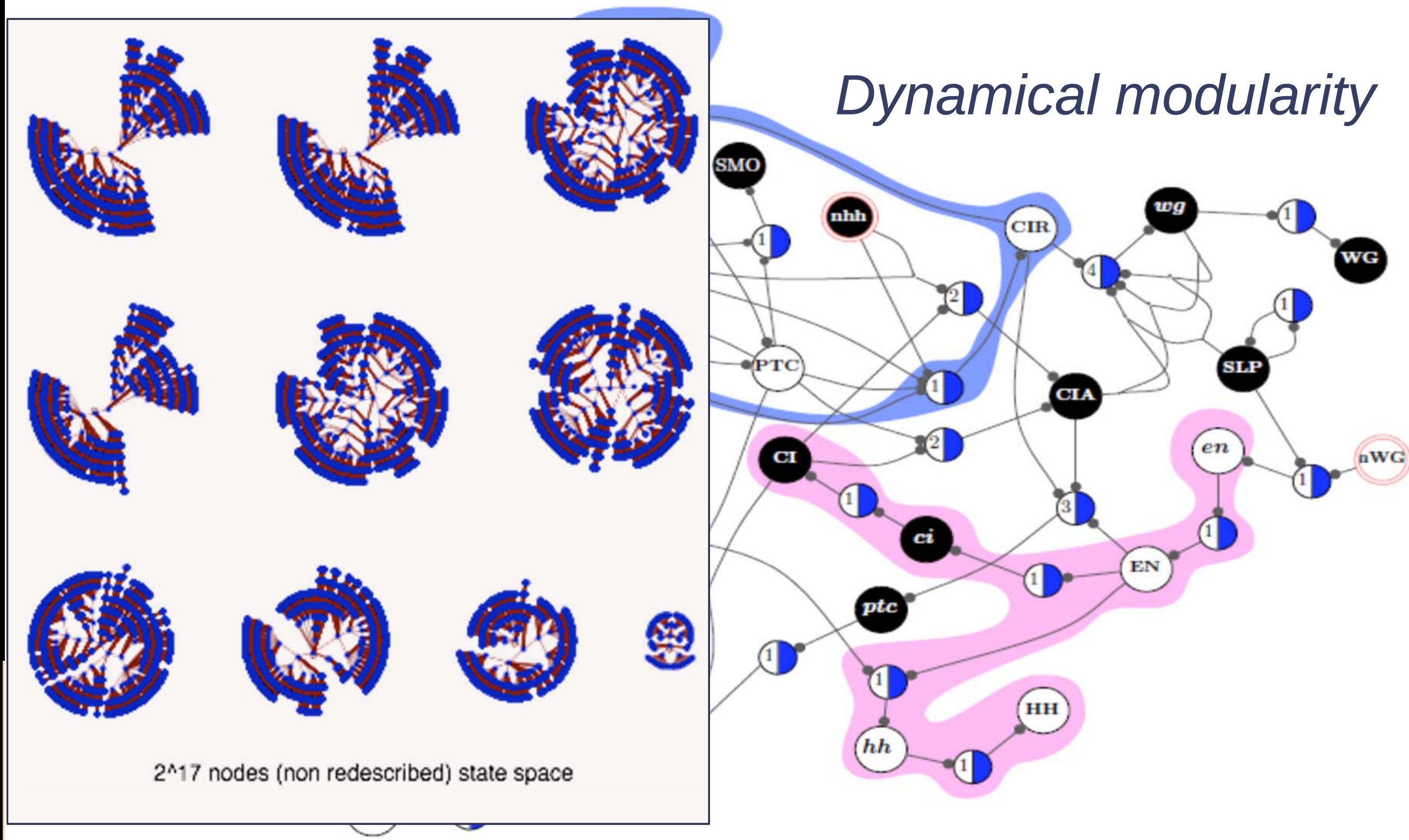


INDIANA
UNIVERSITY

(macro-level) dynamics canalization map

from per-node schemata redescription

- Full dynamics (of single-cell model) captured by threshold network of 2*N+M nodes



Marques-Pita & Rocha, [2013]. *PLoS ONE*, **8**(3): e55946.

rocha@indiana.edu
http://informatics.indiana.edu/rocha

CONTROL FROM PATTERNS OF REDUNDANCY IN DYNAMICS

rocha@indiana.edu
http://informatics.indiana.edu/rocha

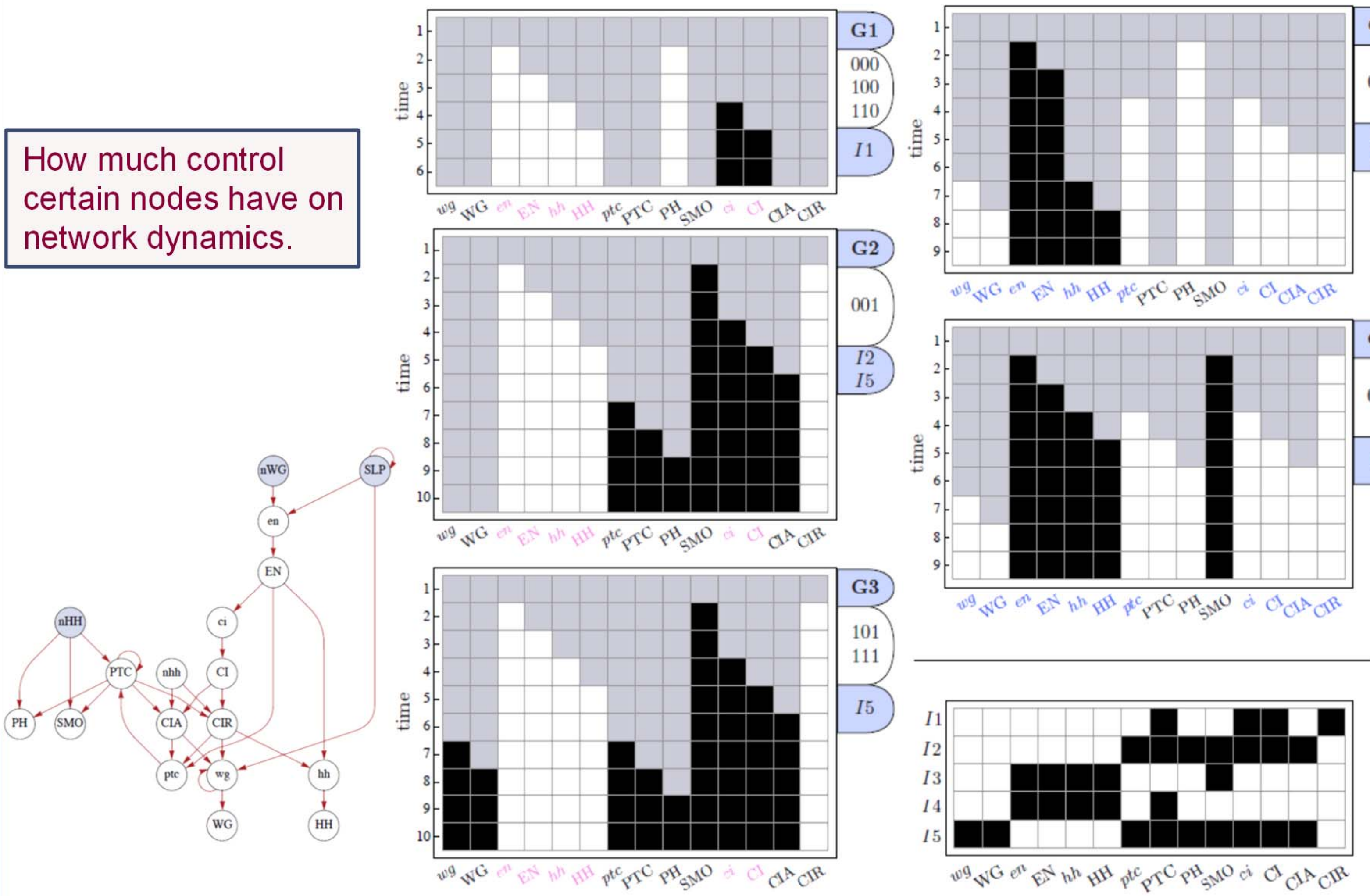
Informatics
luis rocha 2014

(macro-level) control

Dynamical unfolding from partial information

- inputs in drosophila segment polarity net: SLP, nWG, nhh

How much control certain nodes have on network dynamics.



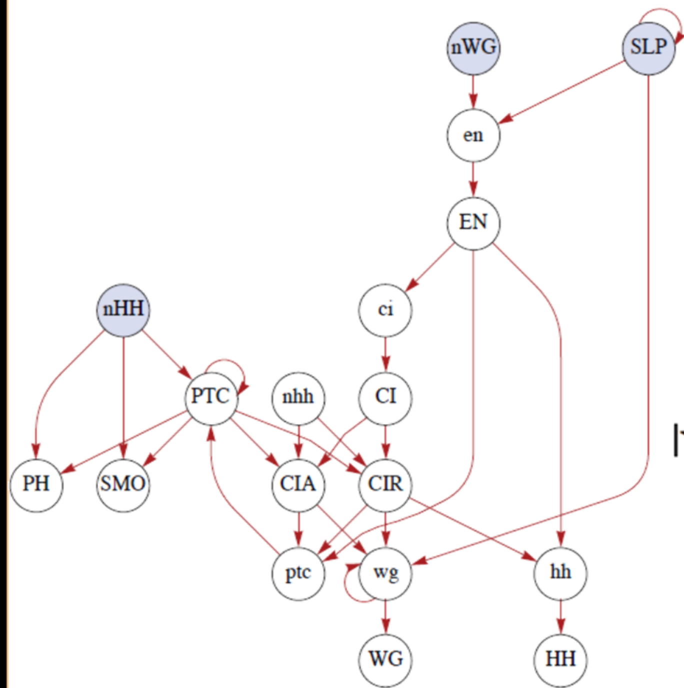
Marques-Pita & Rocha, [2013]. *PLoS ONE*, **8**(3): e55946.

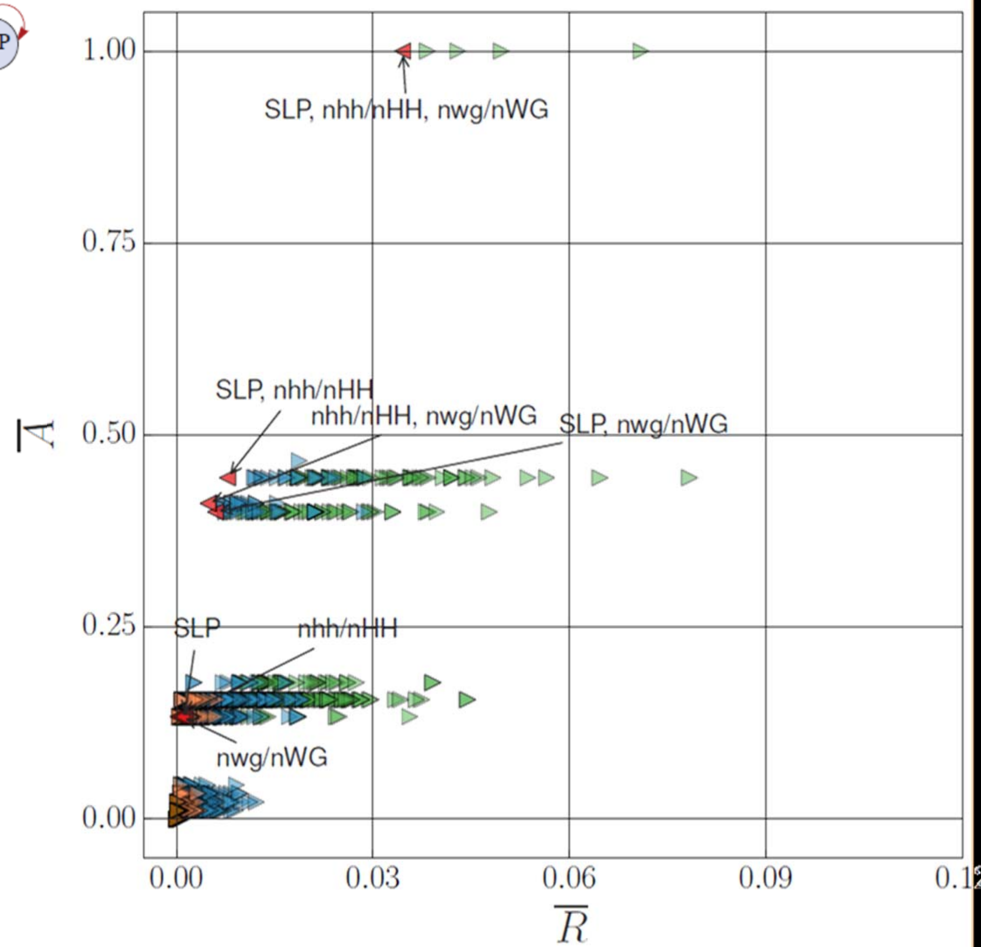
INDIANA UNIVERSITY

rocha@indiana.edu
http://informatics.indiana.edu/rocha

Can structural controlability uncover control?

Drosophila model (Albert et al)





4 nodes predicted by structural control:

$\{SLP, nWG, nhh/nHH, PH\}$,
$\{SLP, nWG, nhh/nHH, SMO\}$,
$\{SLP, nWG, nhh/nHH, CIR\}$,
$\{SLP, nWG, nhh/nHH, CIA\}$

Gates & Rocha [2014]. *ALIFE 2014*: 429-430.
Gates & Rocha [2014]. *Submitted.*

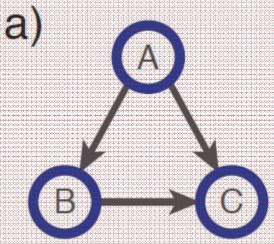
rocha@indiana.edu
http://informatics.indiana.edu/rocha

Informatics
luis rocha 2014

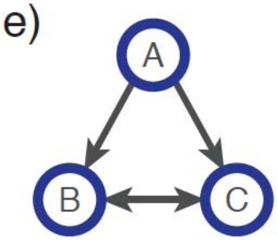
In presence of dynamics

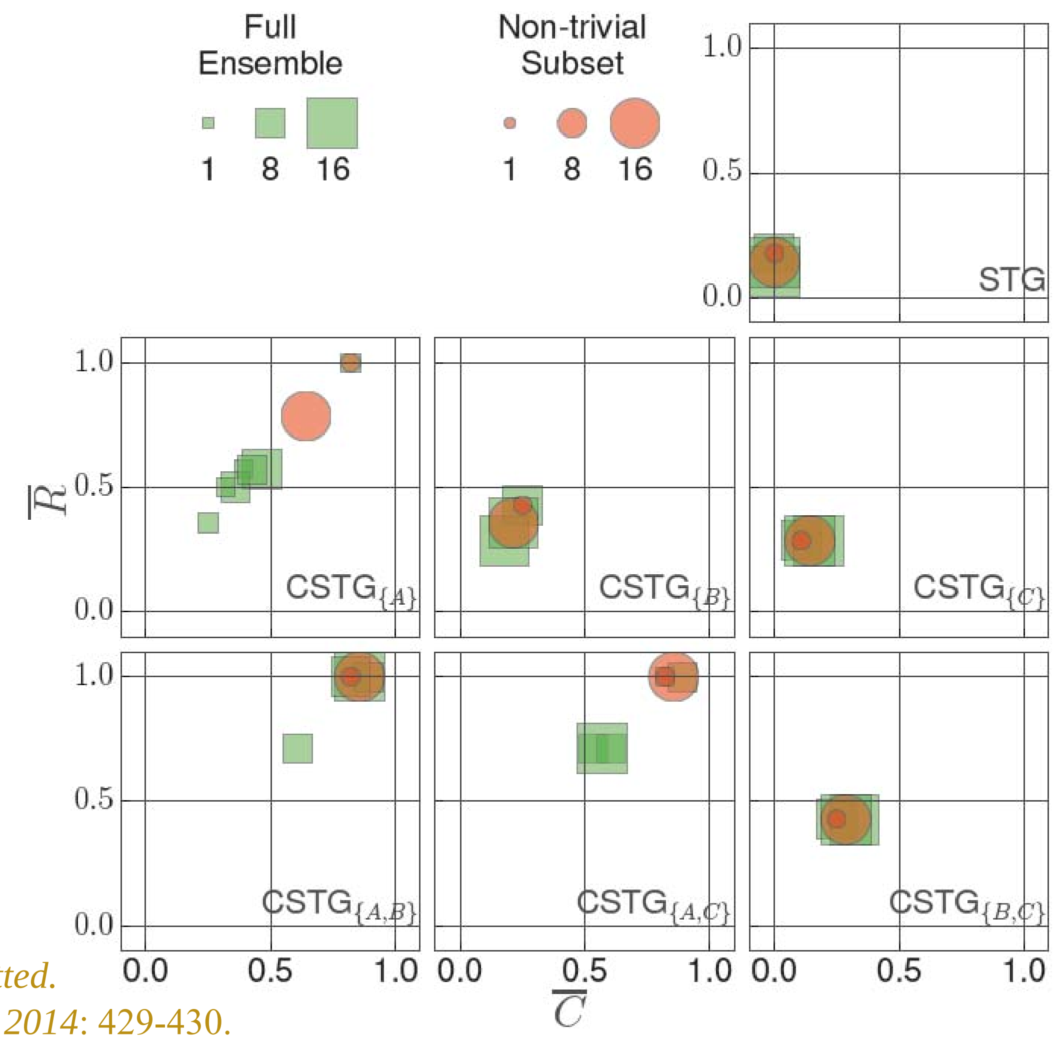
Consider small network motifs:

a)



e)





The larger the ***canalization***, the less predictable is structural control

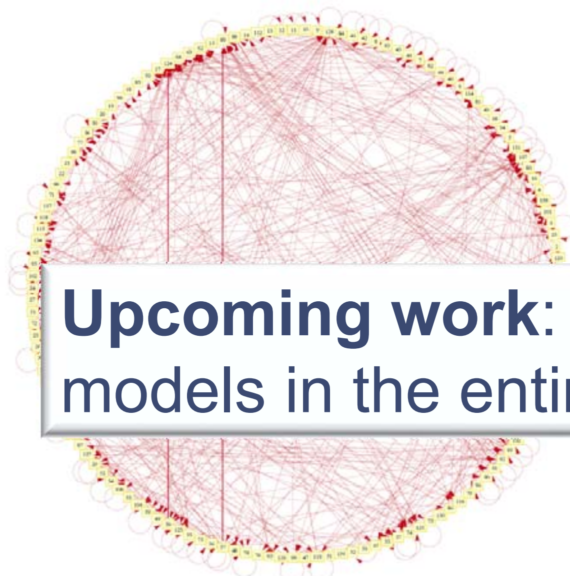
Gates & Rocha [2014]. *Submitted.*
Gates & Rocha [2014]. *ALIFE 2014*: 429-430.

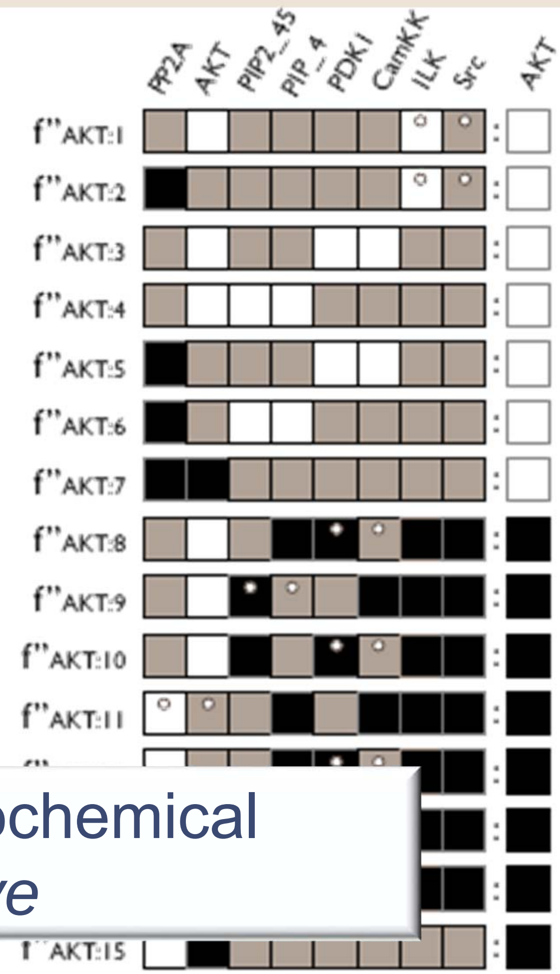
INDIANA UNIVERSITY

redundancy in intracellular signaling networks

canalization

- Activation of AKT in generic fibroblasts (130 node BN)
  - LUT of 2^8=256 entries redescribed by only 15 schemata
    - Large amount of **canalization**
  - Very few actual inputs need to be known to determine state-transition





Upcoming work: analysis of biochemical models in the entire *cell collective*

Helikar et al [2008]. PNAS **105**: 1913-8

rocha@indiana.edu
http://informatics.indiana.edu/rocha

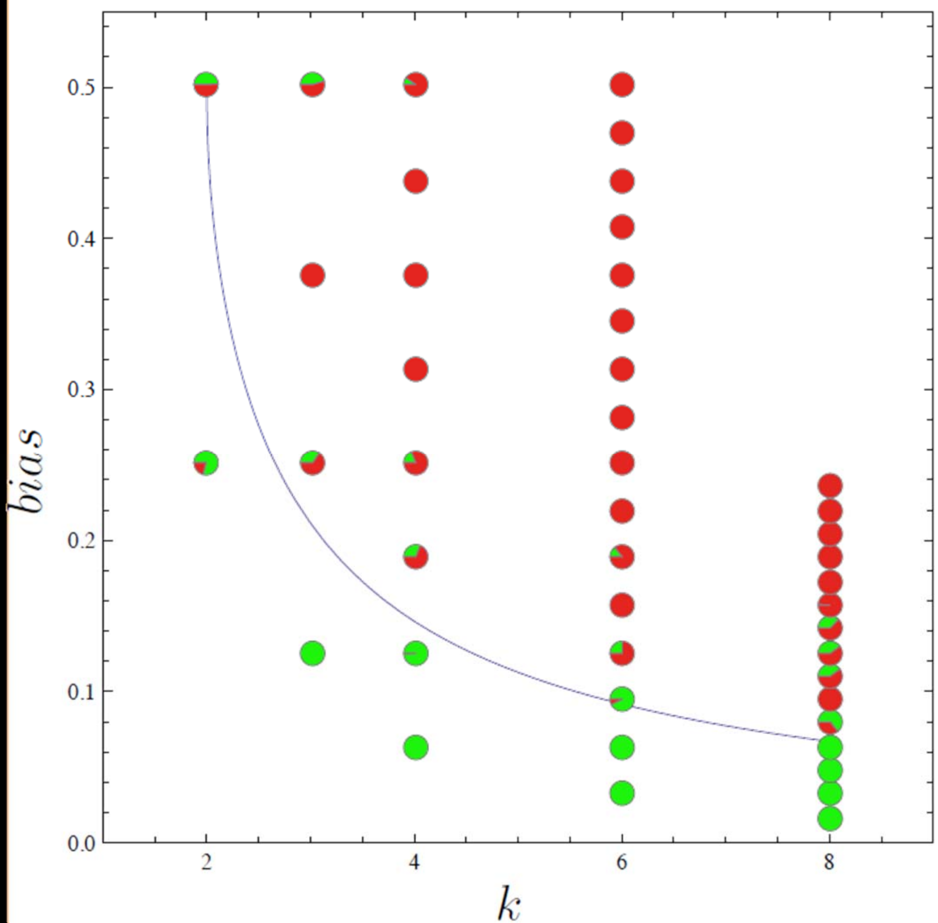
Informatics
luis rocha 2014

PATTERNS OF DYNAMICS

rocha@indiana.edu
http://informatics.indiana.edu/rocha

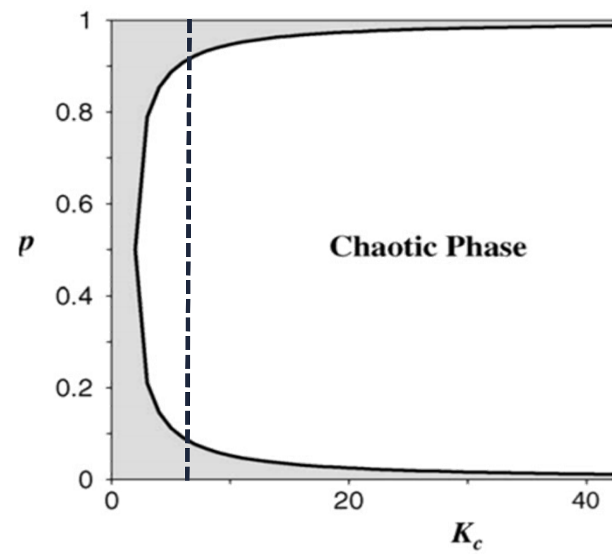
INDIANA
UNIVERSITY

Current theory



$$p = \frac{1}{2}\left(1 - \sqrt{1 - \frac{2}{k}}\right)$$

Aldana, M. [2003]. *Physica D*. **185**: 45–66



Marques-Pita, Manicka, Teuscher & Rocha, [2014]. Submitted

INDIANA UNIVERSITY
rocha@indiana.edu
http://informatics.indiana.edu/rocha

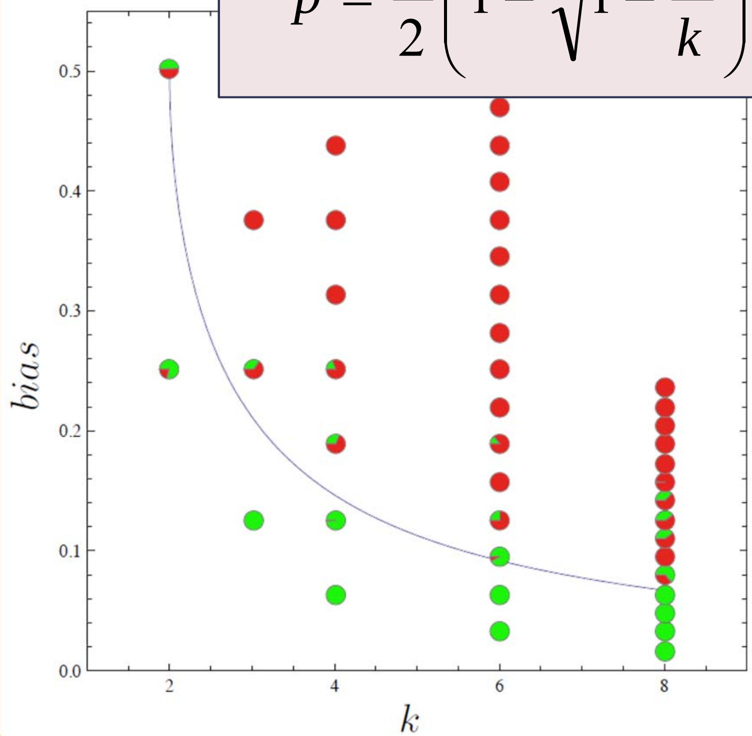
Informatics
luis rocha 2014

input redundancy, effective connectivity

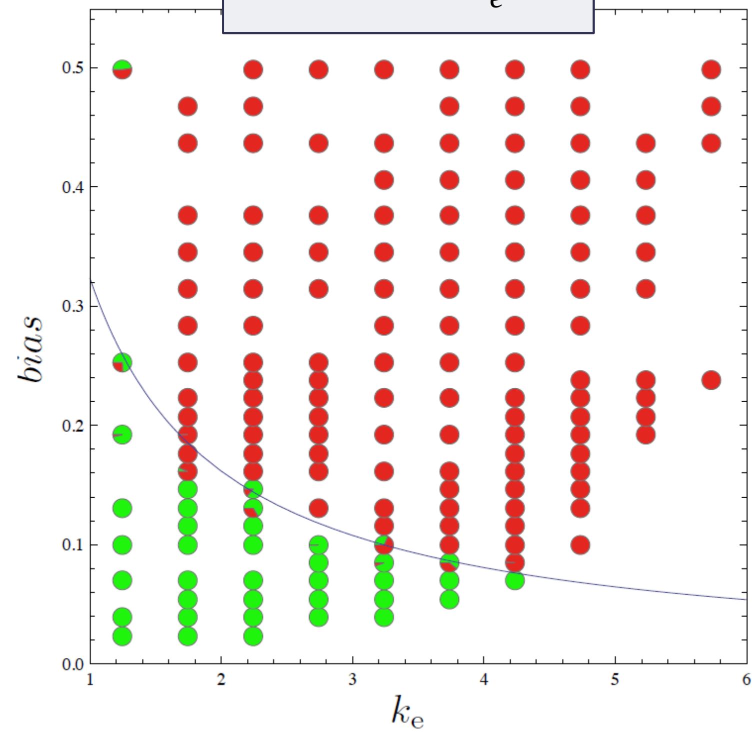
$$k_r(x) = \frac{\sum_{f_\alpha \in F} \max_{\theta | f_\alpha \in \Theta_\theta} \left(n_\theta^\#\right)}{2^k}$$

$$k_e(x) = k(x) - k_r(x)$$

$$p = \frac{1}{2}\left(1 - \sqrt{1 - \frac{2}{k}}\right)$$



$$p_{crit} = \frac{0.32}{k_e}$$



Marques-Pita, Manicka, Teuscher & Rocha, [2014]. Submitted

INDIANA UNIVERSITY

rocha@indiana.edu
http://informatics.indiana.edu/rocha

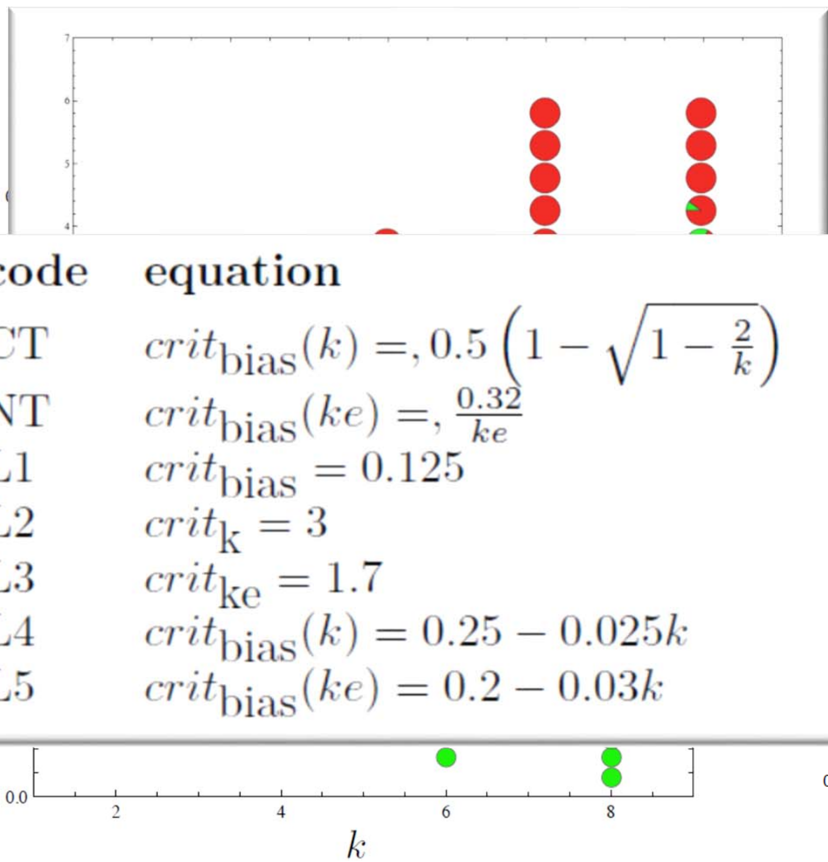
Informatics
luis rocha 2014

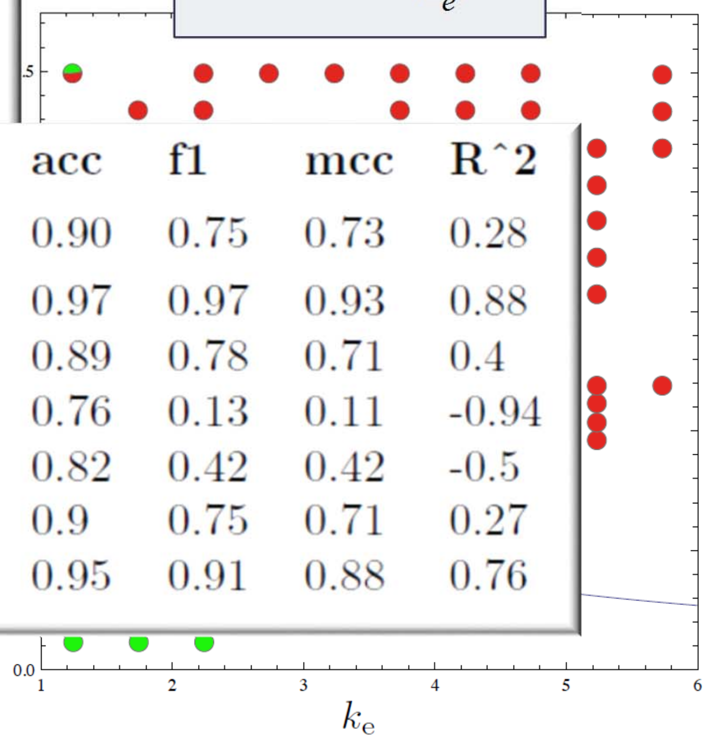
input redundancy, effective connectivity

$$k_r(x) = \frac{\sum_{f_\alpha \in F} \max_{\theta | f_\alpha \in \Theta_\theta} \left(n_\theta^{\#}\right)}{2^k}$$

$$k_e(x) = k(x) - k_r(x)$$

$$p_{crit} = \frac{0.32}{k_e}$$





code	equation	acc	f1	mcc	R^2
CT	$crit_{\mathrm{bias}}(k) =, 0.5\left(1-\sqrt{1-\frac{2}{k}}\right)$	0.90	0.75	0.73	0.28
NT	$crit_{\mathrm{bias}}(ke) =, \frac{0.32}{ke}$	0.97	0.97	0.93	0.88
L1	$crit_{\mathrm{bias}} = 0.125$	0.89	0.78	0.71	0.4
L2	$crit_{\mathrm{k}} = 3$	0.76	0.13	0.11	-0.94
L3	$crit_{\mathrm{ke}} = 1.7$	0.82	0.42	0.42	-0.5
L4	$crit_{\mathrm{bias}}(k) = 0.25 - 0.025k$	0.9	0.75	0.71	0.27
L5	$crit_{\mathrm{bias}}(ke) = 0.2 - 0.03k$	0.95	0.91	0.88	0.76

Marques-Pita, Manicka, Teuscher & Rocha, [2014]. Submitted

INDIANA UNIVERSITY
rocha@indiana.edu
http://informatics.indiana.edu/rocha