The potential impact of inter-individual genomic variations on disease susceptibility and treatment response

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Workshop on Mathematical Oncology III

The Fields Institute Centre for Mathematical Medicine

University of Toronto

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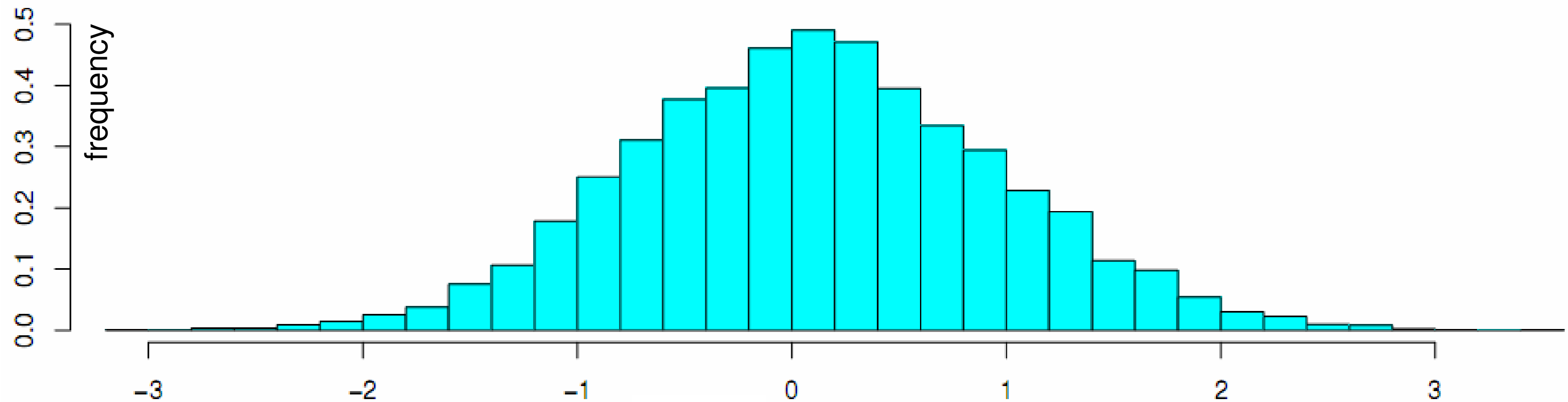
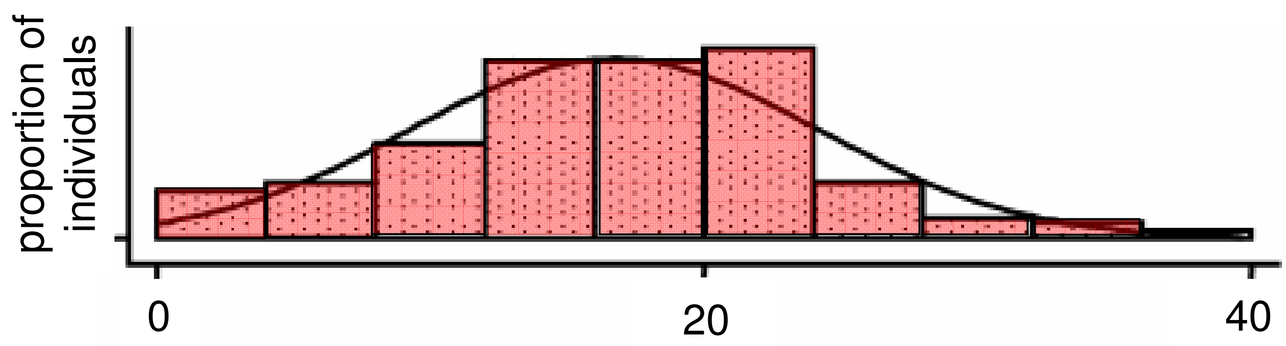


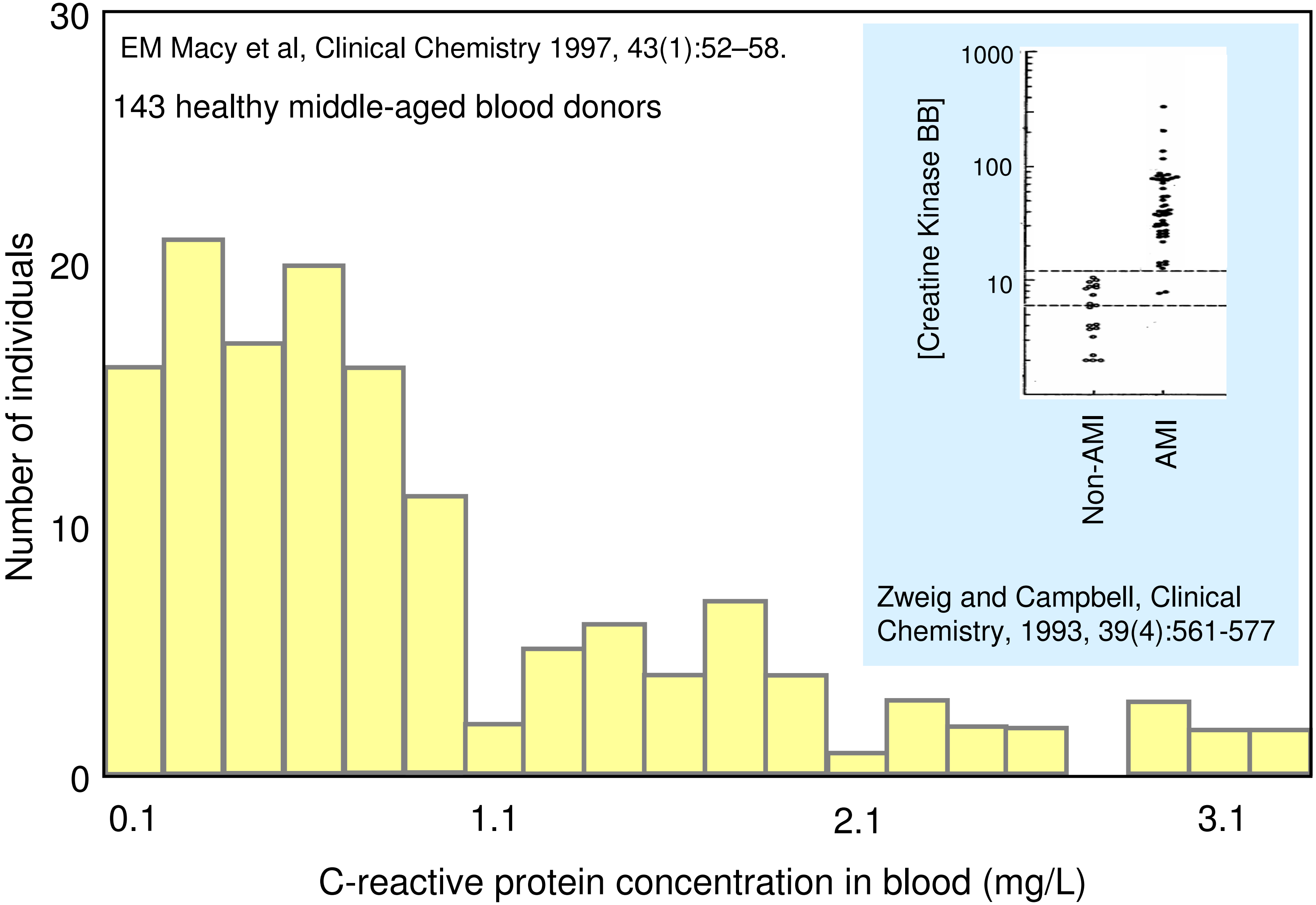
eosinophil counts ($\left(\frac{X-\mu}{\sigma}\right)$ per unit volume) in 9,392 people

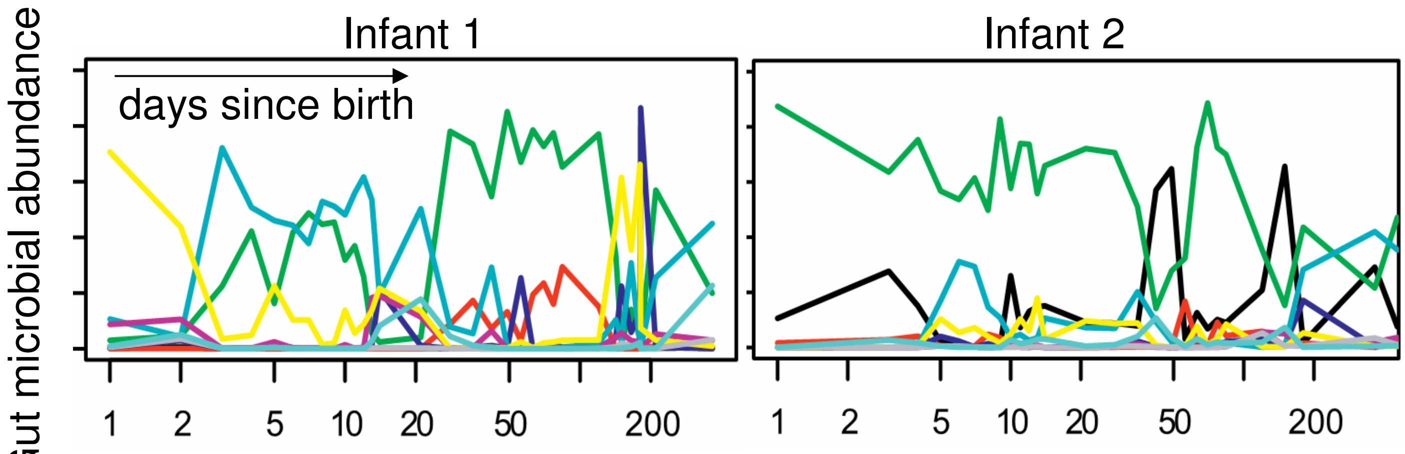
Gudbjartsson et al, Nature Genetics, 2009, 41(3):3423–47.



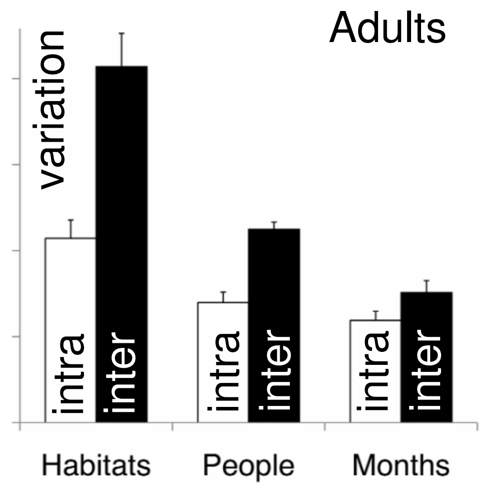
% TH1 (INF-γ expressing) cells among CD4+ cells in blood

Duramad et al, Cancer Epidemiology, Biomarkers and Prevention, 2004,13(9):1452–8

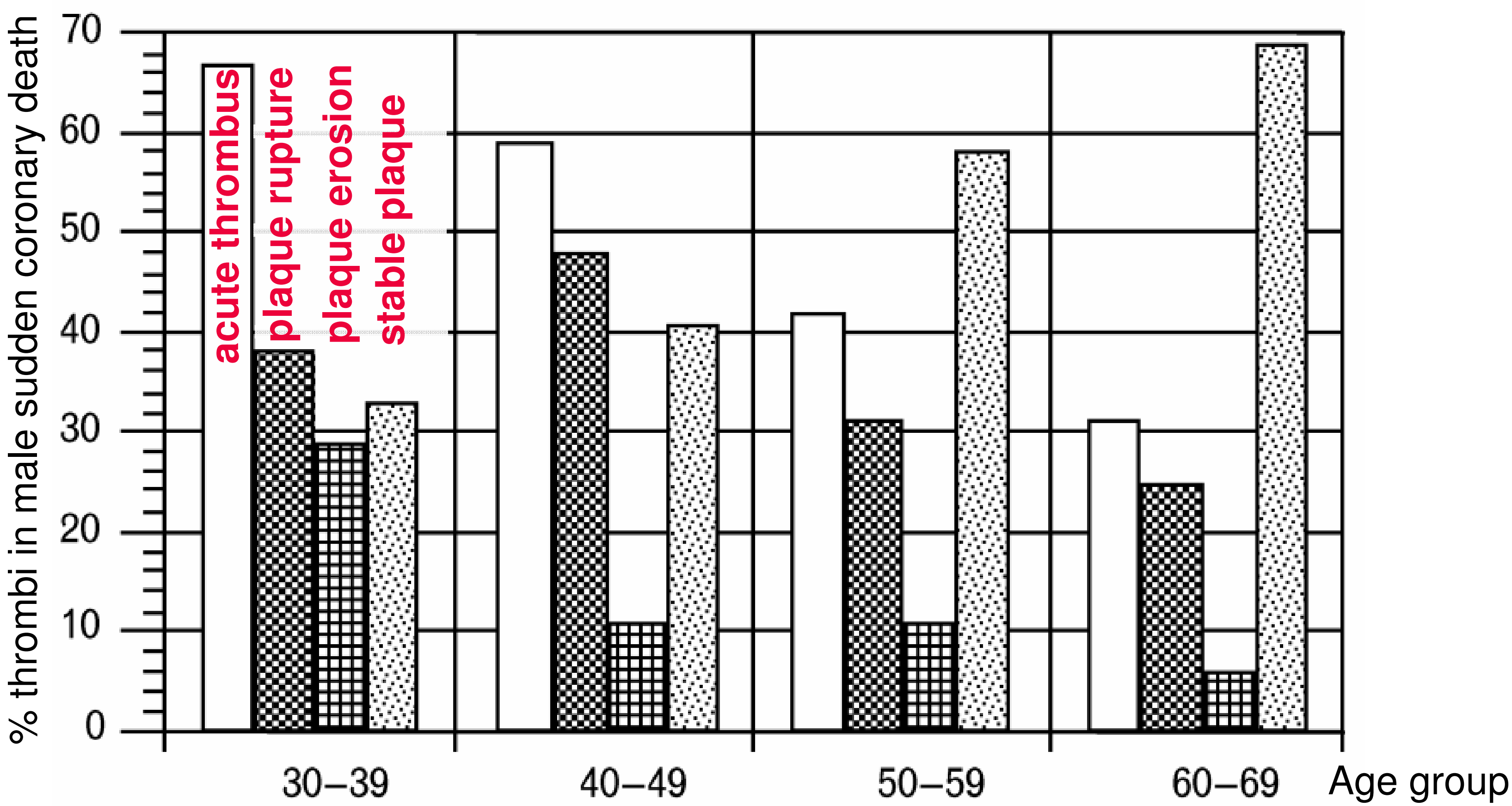

EM Macy et al, Clinical Chemistry 1997, 43(1):52–58.
143 healthy middle-aged blood donors
30
20
10
0
Number of individuals
0.1
1.1
2.1
3.1
C-reactive protein concentration in blood (mg/L)
[Creatine Kinase BB]
1000
100
10
Non-AMI
AMI
Zweig and Campbell, Clinical Chemistry, 1993, 39(4):561-577



Palmer et al, PLoS Biology, 2007, 5(7):e177.

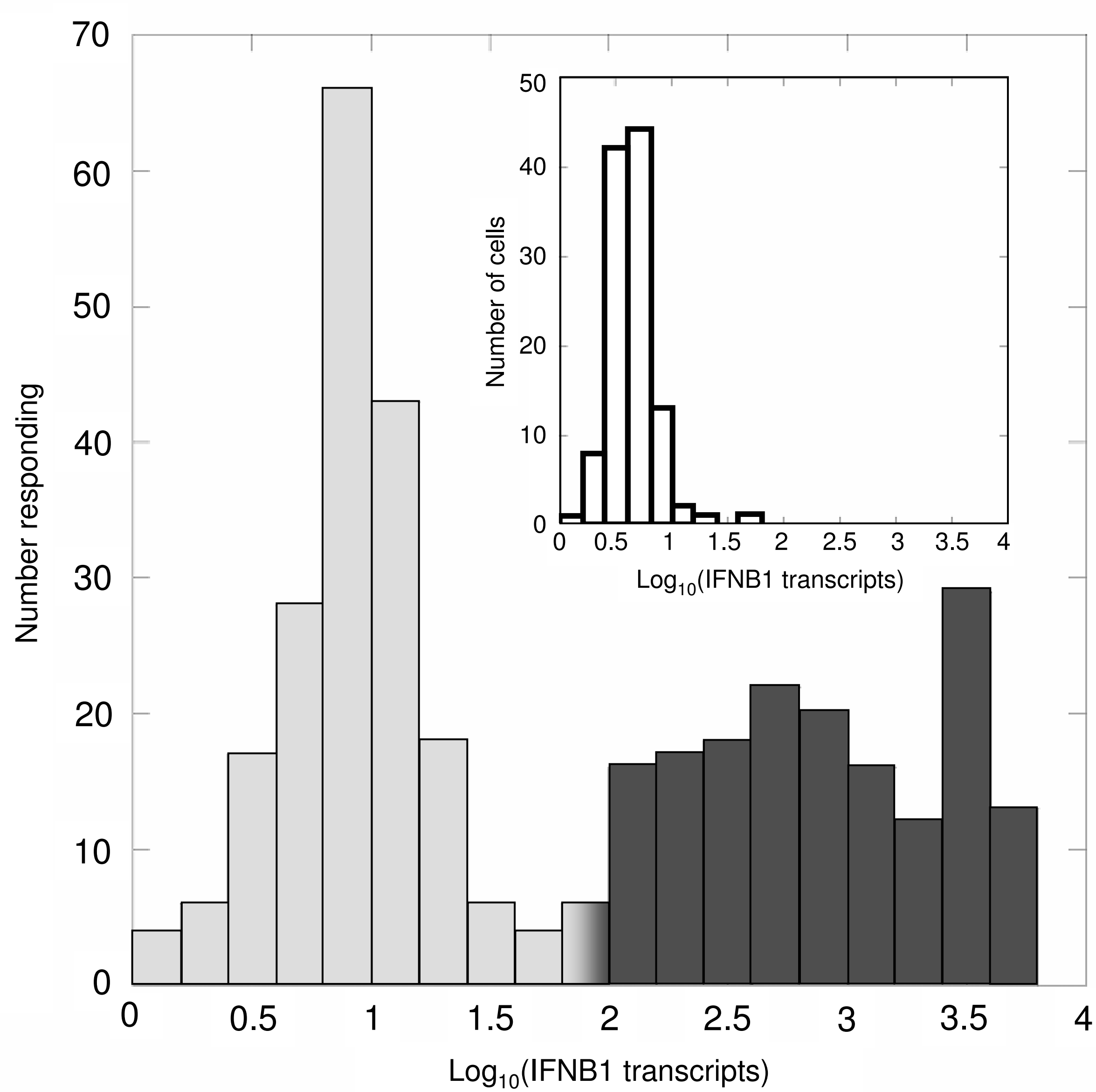


Costello et al, Science 2009, 326(5960):1694 - 1697



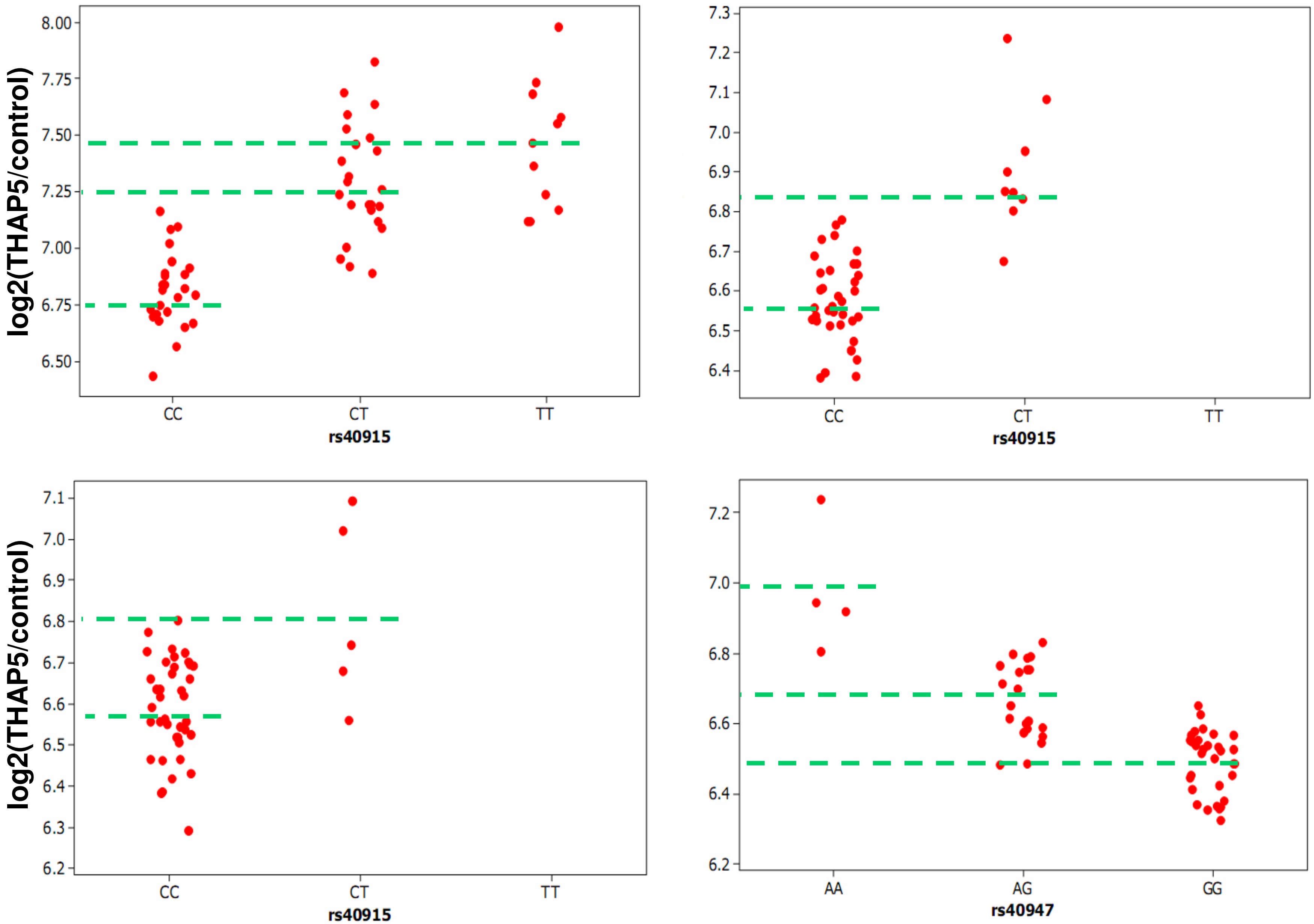
Tracy & Russell, Current Opinion in Lipidology 2008, 19:151–157

Primary DCs from 1 individual responding to in-vitro viral infection

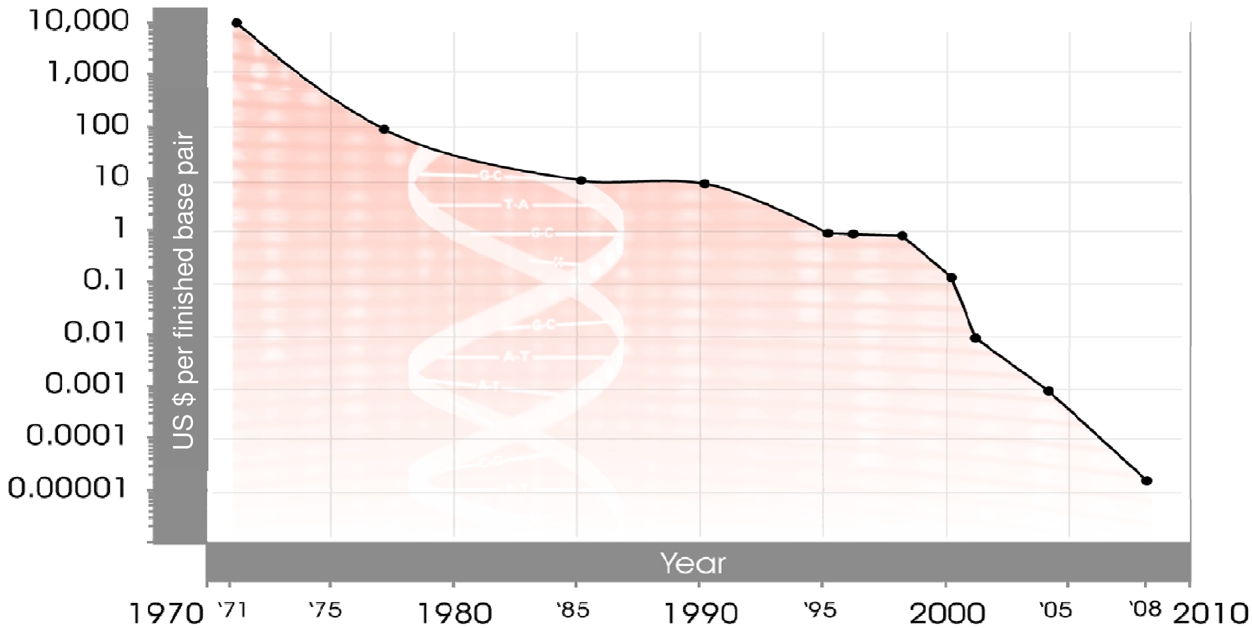


J Hu t al, Nucleic Acids Research, 2007, 35(15):5232–5241

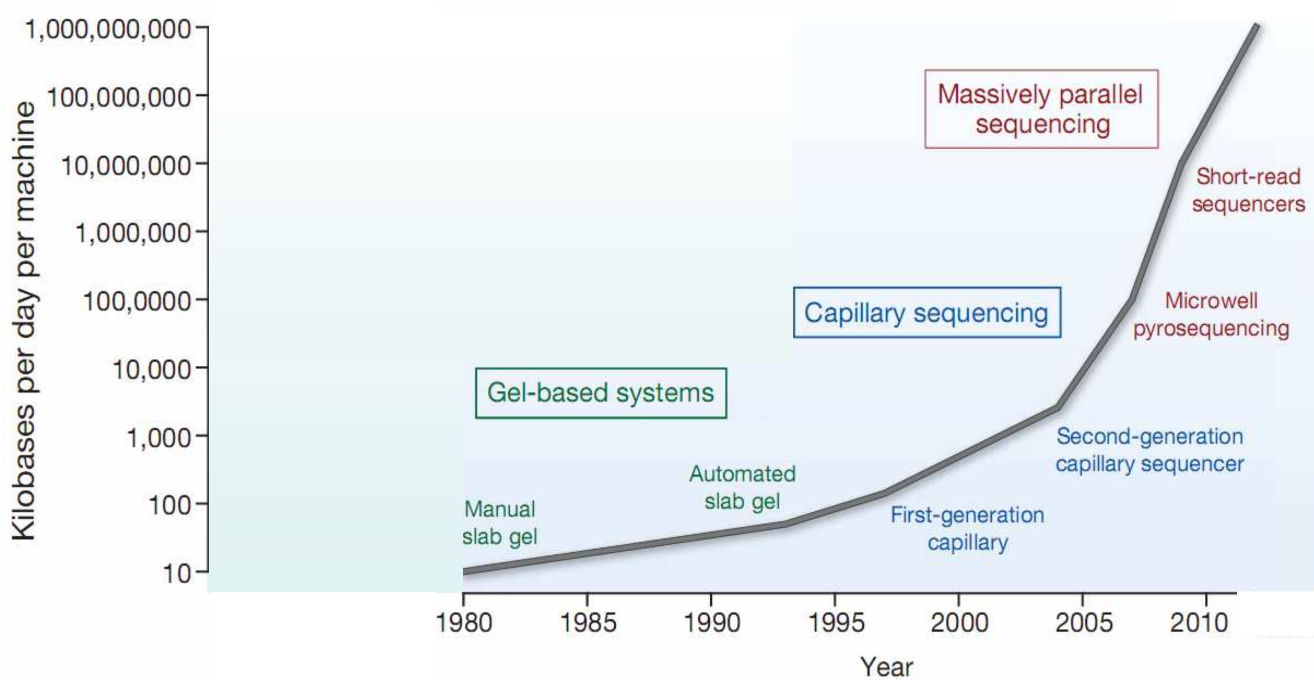
The effect of allelic variations on gene expression within & across Hu groups



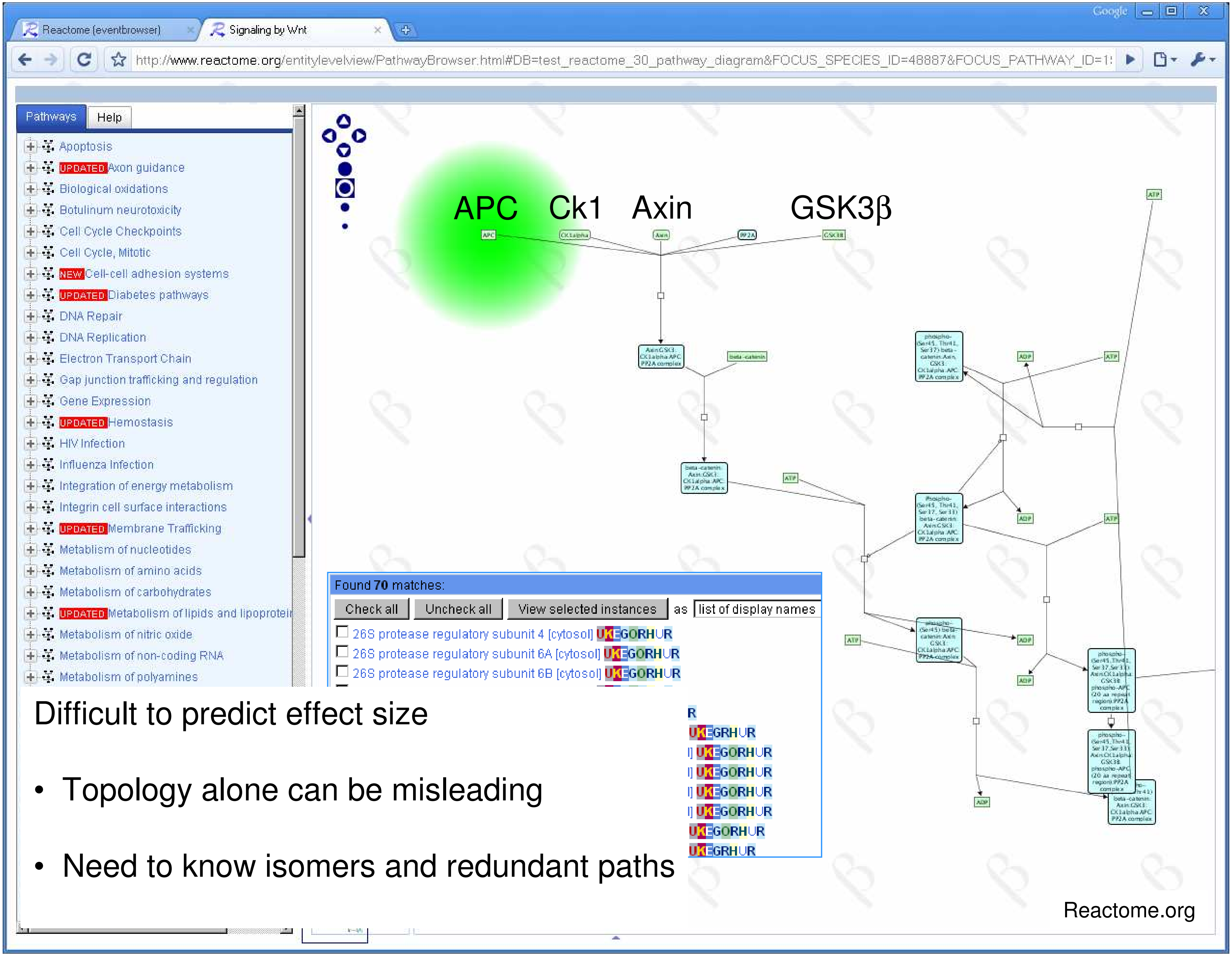
Adapted from Stranger et al, Science 2007 (315):848-853



Courtesy of Ray Kurzweil



Stratton et al, Nature, 2009, 458:719—724

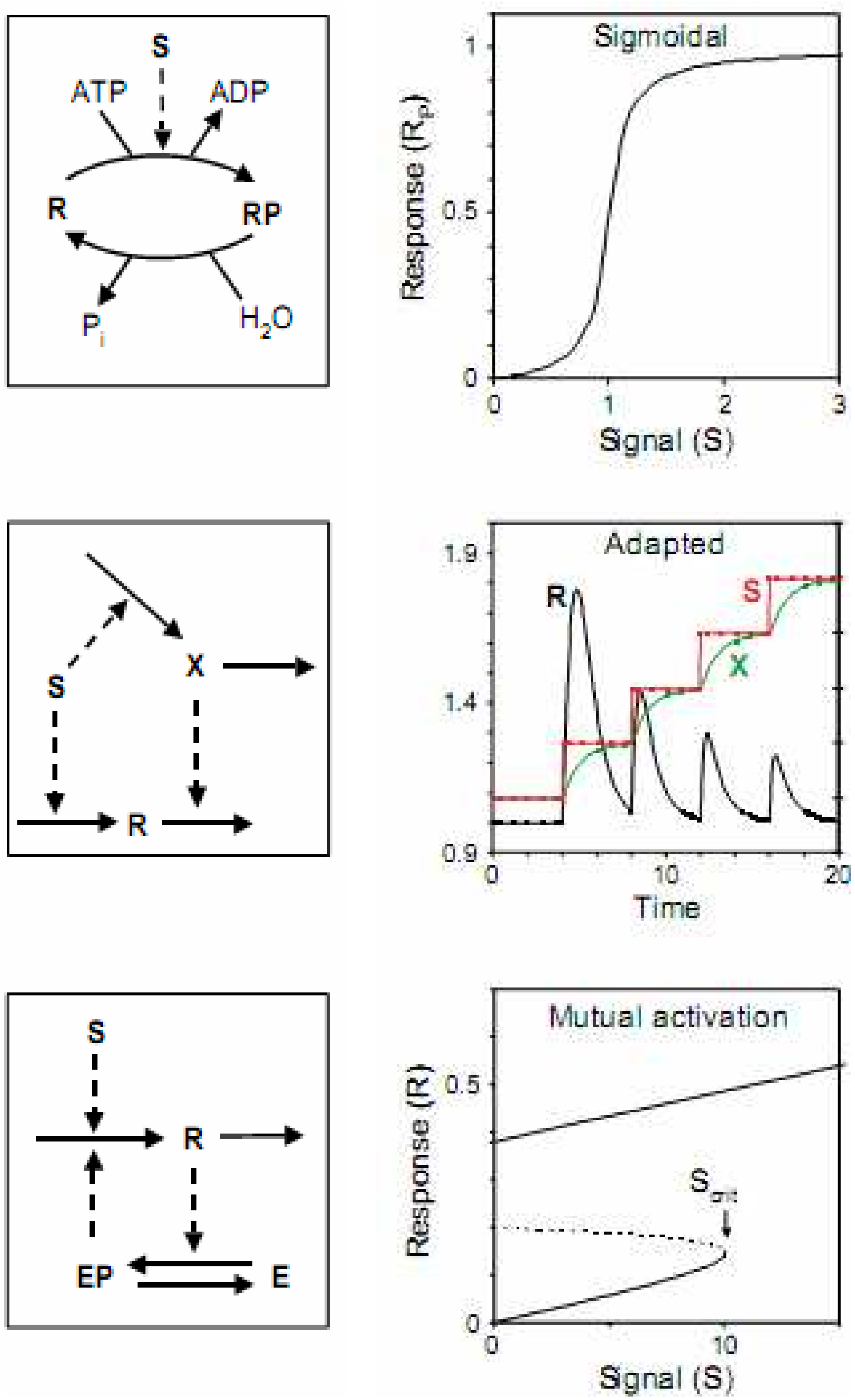


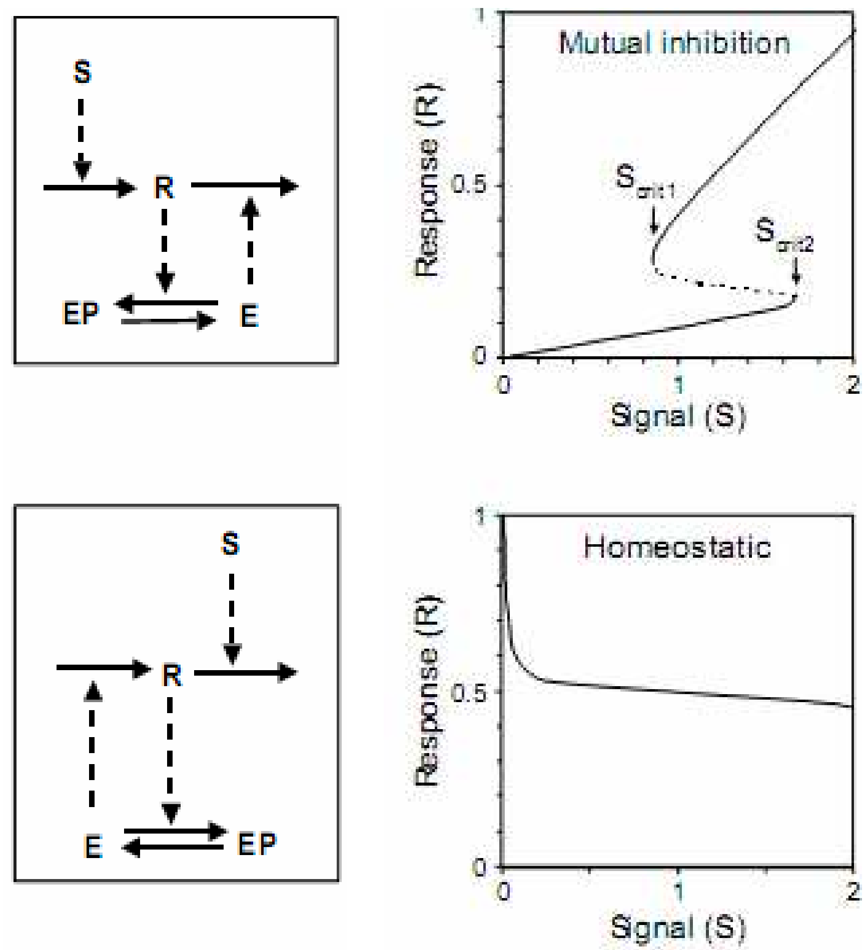
Difficult to predict effect size

- Topology alone can be misleading
- Need to know isomers and redundant paths

Reactome.org

Pathway building blocks

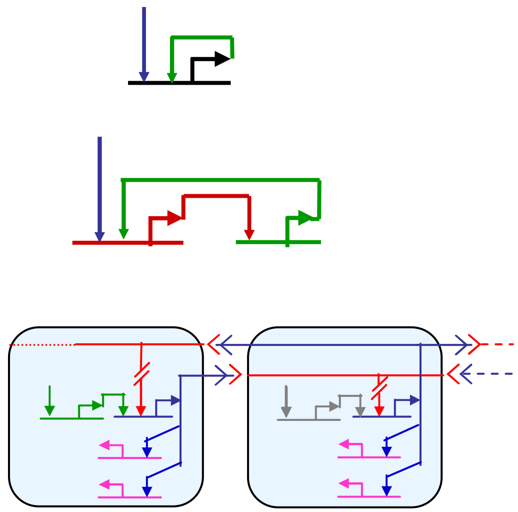




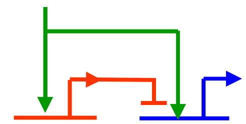
Tyson et al, Current Opinion in Cell Biology, 2003

Gene regulatory building blocks

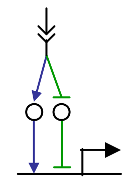
Latch



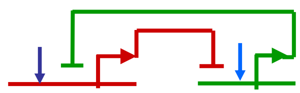
Perfect
adaptation

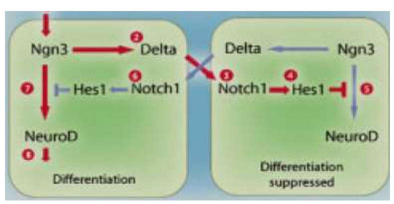


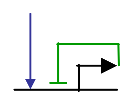
Toggle
Switch



Mutual
Exclusion







- Single-pulse
- Rapid response
- Fixed expression
- Oscillator

Bolouri & Davidson, BioEssays, 2002
Longabaugh & Bolouri, Current Genomics, 2006

DNA sequence variations affecting cellular signaling genes in two individuals

(W=Watson, V=Venter)

	frameshiftW	frameshiftV	nonsynonymousW	nonsynonymousV	UTR_W	UTR_V	splice_siteW	splice_siteV	No. genes
BCR	0	0	55	52	120	117	2	2	75
Ca	3	3	99	96	327	325	1	1	178
ErbB	3	3	29	24	161	187	0	1	87
Hh	0	0	24	32	74	83	1	3	56
JakStat	0	0	77	47	228	228	0	2	155
MAPK	1	0	128	127	436	451	9	3	269
mTOR	0	0	20	18	94	110	0	4	52
Notch	0	0	20	19	56	61	1	1	47
PI	0	0	55	61	159	175	0	0	76
TCR	0	0	49	42	153	163	1	0	108
TGFβ	0	0	27	28	85	139	0	1	87
TLR	0	0	43	39	126	139	12	8	101
VEGF	0	0	50	47	114	117	1	0	76
Wnt	0	2	55	51	279	246	1	2	163

Abbreviations:

BCR=B-cell receptor, Ca=Calcium, ErbB=the v-erb-b2 erythroblastic leukemia viral oncogene family (Receptor Tyrosine Kinases), Hh=Hedgehog, PI=Phosphatidylinositol, TCR=T-cell receptor, TLR=Toll-like receptor.

DNA sequence variations affecting cellular signaling genes in two individuals

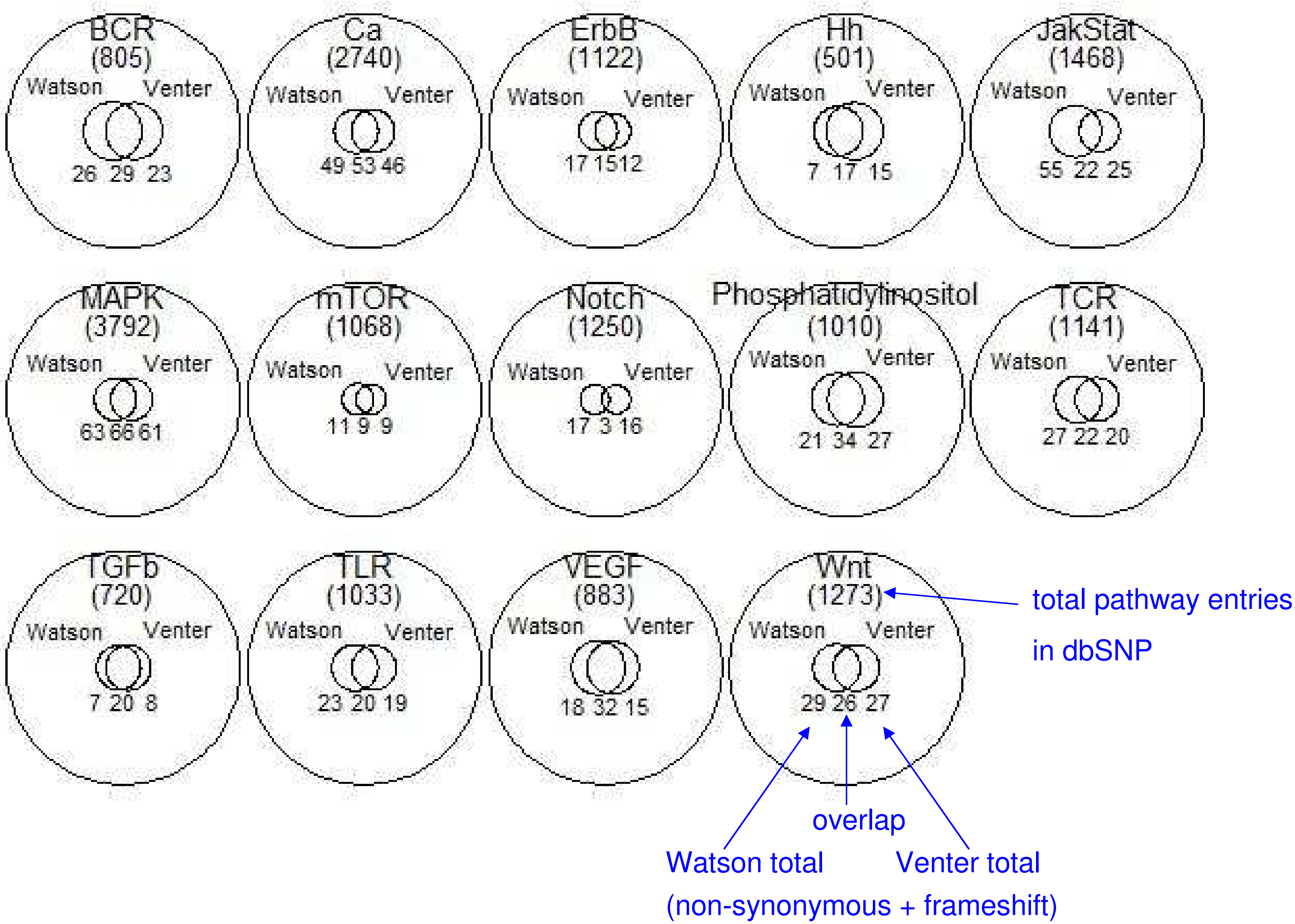


Table 1. Human Diseases Associated with Mutations of the Wnt Signaling Components

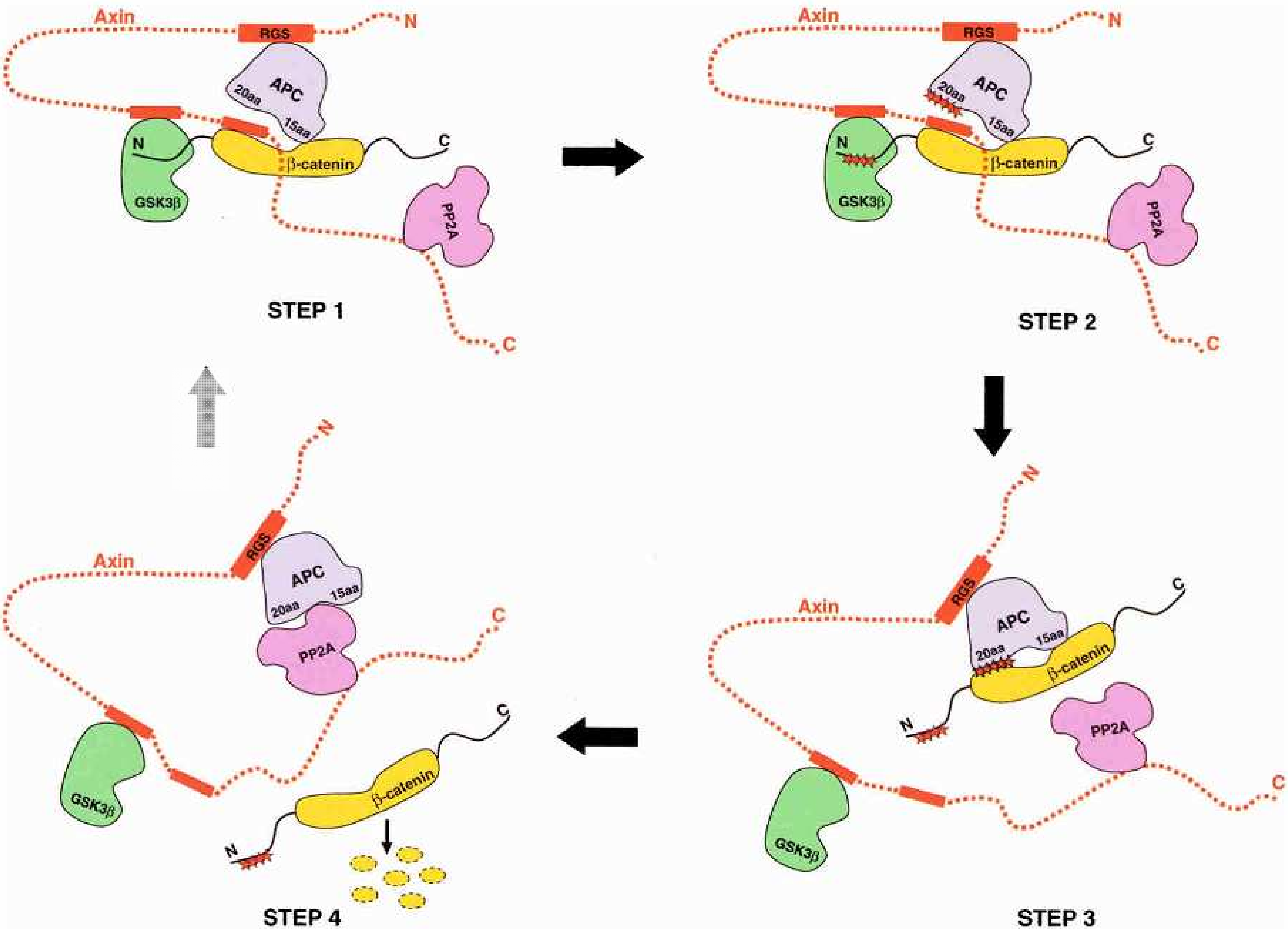
Gene	Function	Human Disease	References
▼ PORCN	+ Wnt lipid modification/processing	LOF X-linked Focal dermal hypoplasia	Grzeschik et al., 2007; Wang et al., 2007
▼ WNT3	+ Ligand for Wnt/β-catenin signaling	LOF tetra-amelia	Niemann et al., 2004
▼ WNT4	+ Ligand for Wnt/β-catenin signaling	LOF Mullerian-duct regression and viriliation	Biason-Lauber et al., 2004
WNT5B	+ Ligand for Wnt/β-catenin signaling	(?) type II diabetes	Kanazawa et al., 2004
▼ WNT7A	+ Ligand for Wnt/β-catenin signaling	LOF Fuhrmann syndrome	Woods et al., 2006
▼ WNT10A	+ Ligand for Wnt/β-catenin signaling	LOF odonto-onchyo-dermal hypoplasia	Adaimy et al., 2007
▼ WNT10B	+ Ligand for Wnt/β-catenin signaling	LOF obesity	Christodoulides et al., 2006
▼ RSPO1	+ Wnt agonist	LOF XX sex reversal with palmoplantar hyperkaratosis	Parma et al., 2006
▼ RSPO4	+ Wnt agonist	LOF autosomal recessive anonychia and hyponychia congenita	Bergmann et al., 2006; Blaydon et al., 2006
▲ SOST	- LRP5/6 antagonist predominantly expressed in osteocytes	LOF high bone mass, sclerosteosis, Van Buchem disease	Balemans et al., 2001; Balemans et al., 2002; Brunkow et al., 2001
▼ Norrin (NDP)	+ Specific ligand for FZD4 and LRP5 during eye development	LOF familial exudative vitreoretinopathy	Xu et al., 2004
▲ ▲ ▼ ▼ LRP5	+ Wnt coreceptor	GOF hyperparathyroid tumors (alt. splicing), GOF high bone mass, LOF osteoporosis-pseudoglioma, LOF FEVR eye vascular defects	Bjorklund et al., 2007; Boyden et al., 2002; Gong et al., 2001; Little et al., 2002; Toomes et al., 2004
▼ LRP6	+ Wnt coreceptor	LOF early coronary disease and osteoporosis	Mani et al., 2007
▼ FZD4	+ Wnt receptor	LOF familial exudative vitreoretinopathy	Robitaille et al., 2002
▲ Axin1	− facilitates β-catenin degradation; acts as a tumor suppressor	LOF caudal duplication, cancer	Oates et al., 2006; Satoh et al., 2000
▲ Axin2	− facilitates β-catenin degradation; acts as a tumor suppressor	LOF tooth agenesis, cancer	Lammi et al., 2004; Liu et al., 2000
▲ APC	− facilitates β-catenin degradation; acts as a tumor suppressor	LOF familial adenomatous polyposis, cancer	Kinzler et al., 1991; Nishisho et al., 1991
▲ WTX	− facilitates β-catenin degradation; acts as a tumor suppressor	LOF Wilms tumor	Major et al., 2007; Rivera et al., 2007
▲ β-catenin (CTNNB1)	+ primary Wnt effector; acts as anoncogene	GOF cancer	Korinek et al., 1997; Morin et al., 1997
TCF4 (TCF7L2)	+ β-catenin transcriptional partner	(?) type II diabetes	Florez et al., 2006; Grant et al., 2006

▼ signal lost

▲ signal gained

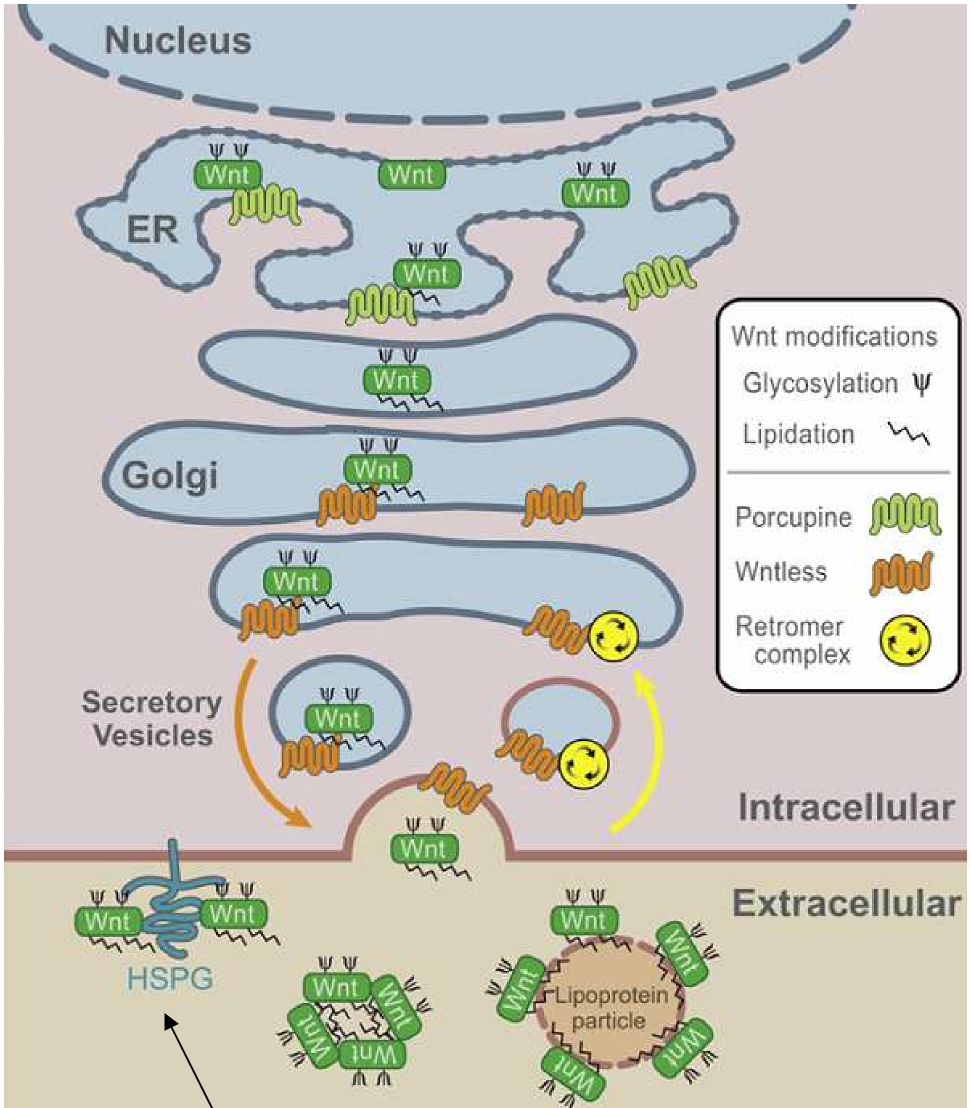
Bryan T. MacDonald,[1] Keiko Tamai,[2] and Xi He
Developmental Cell 17, July 21, 2009

In the absence of Wnt, β-catenin is degraded auto-catalytically

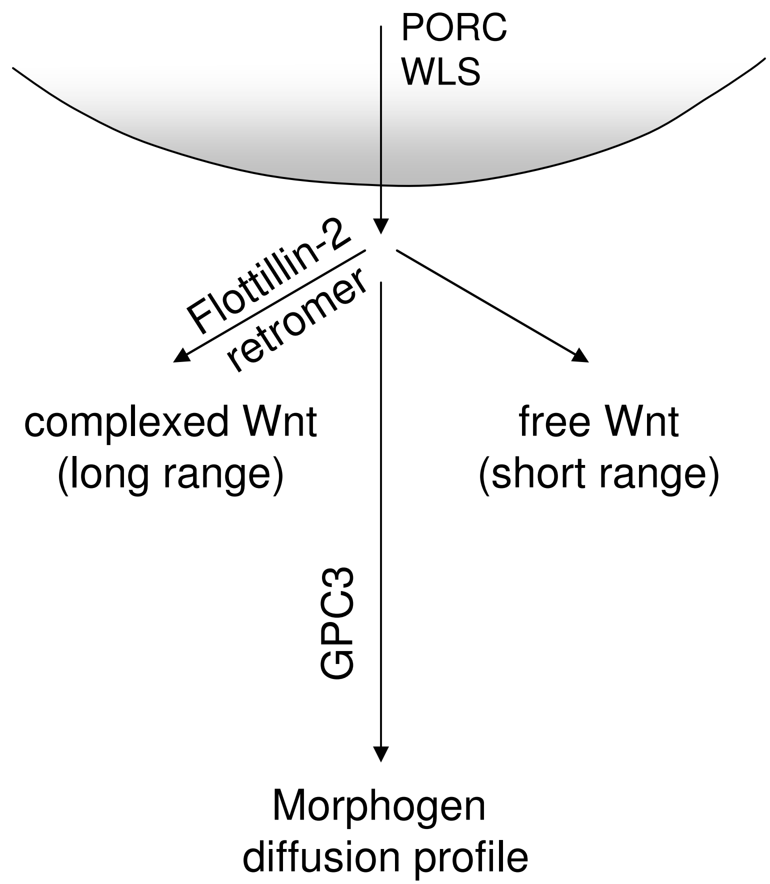


Xing et al, Genes & Dev. 2003 17: 2753-2764

Wnt ligand processing and secretion

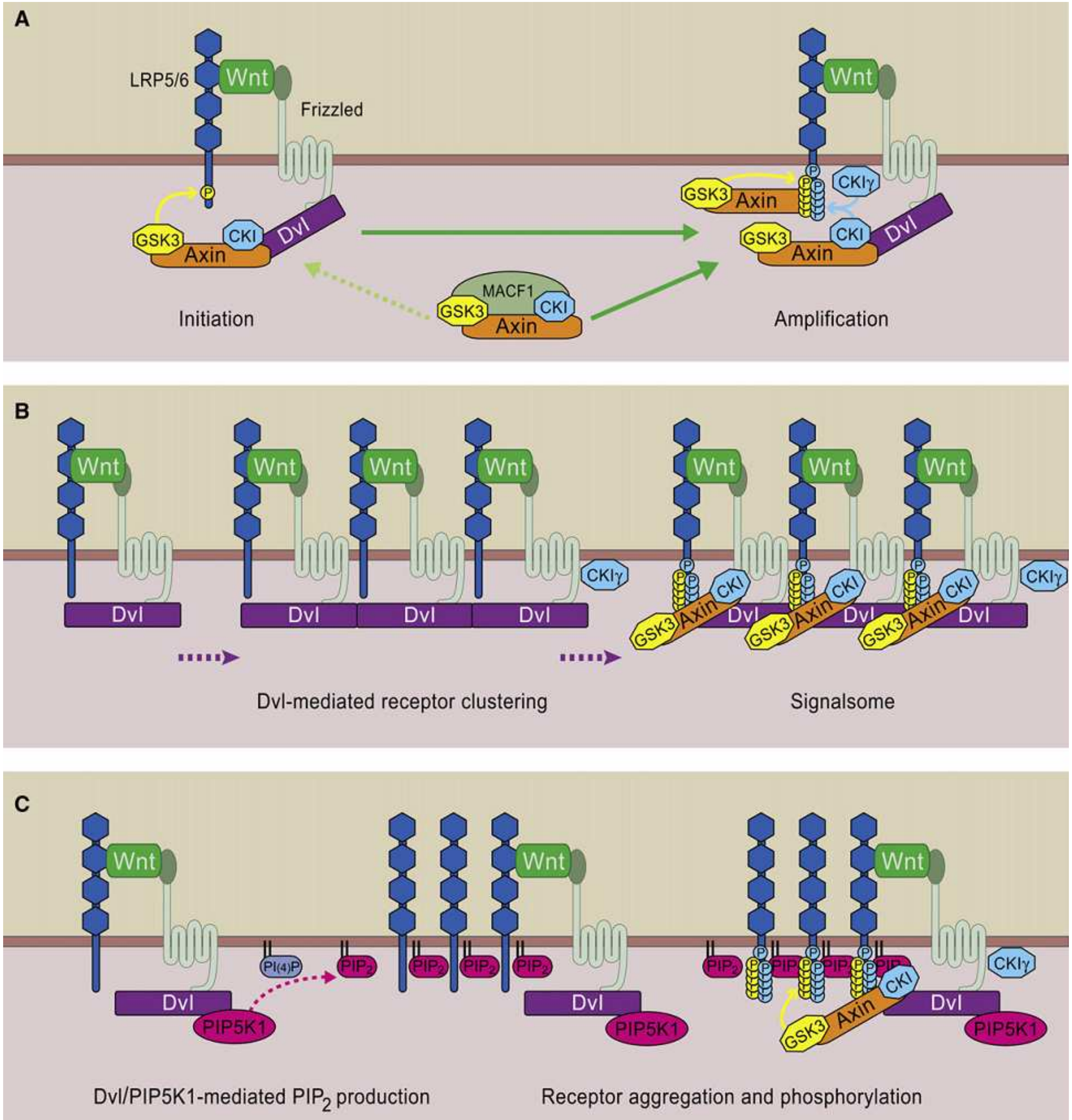


heparan sulfate proteoglycans:
GPC3



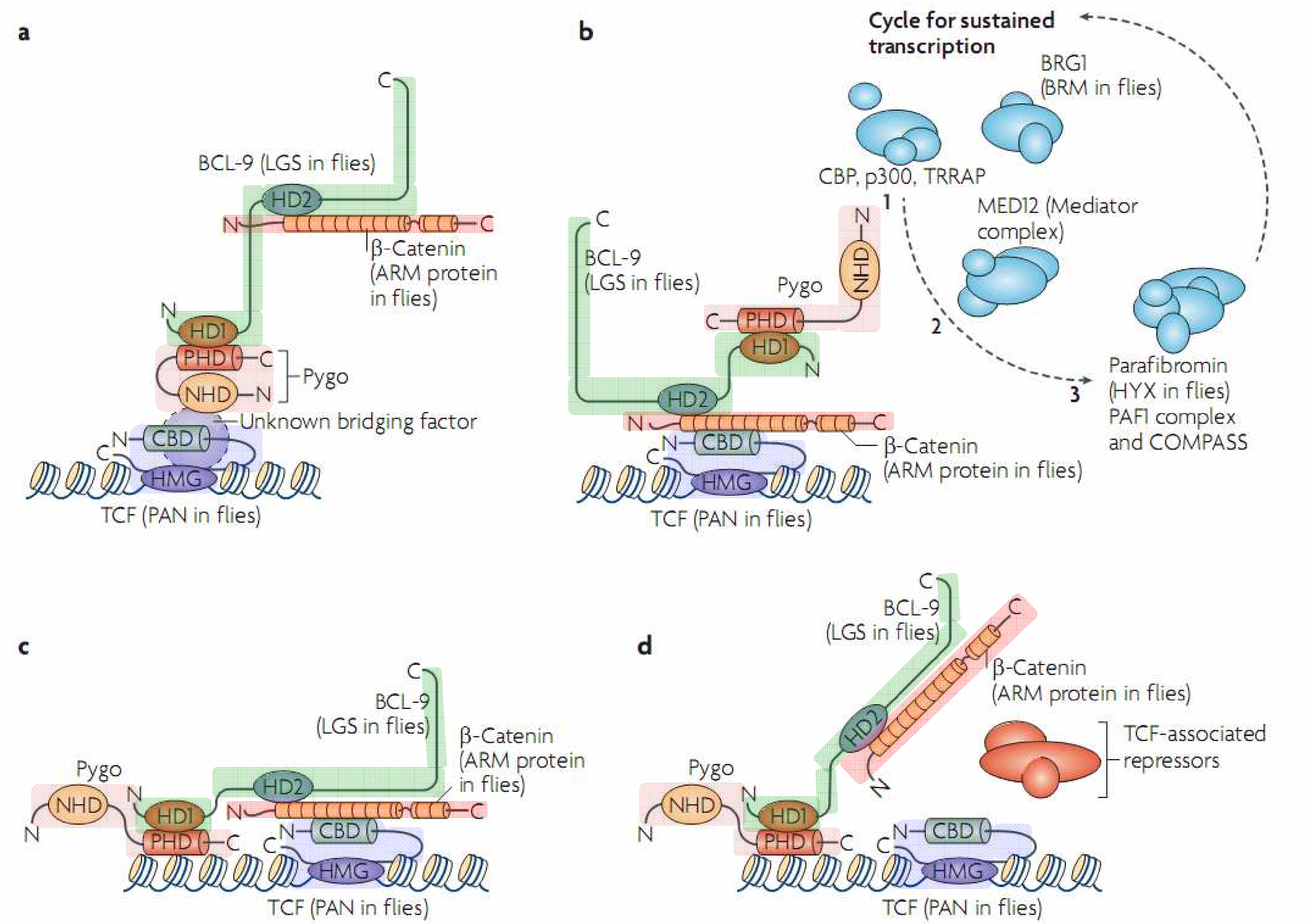
Shahana Baig-Lewis, Wynne Peterson-Nedry, Marcel Wehrli
Developmental Biology 306 (2007) 94–111

Josipa Bilić,[1] Ya-Lin Huang,[1] Gary Davidson,[1] Timo Zimmermann,[2] Cristina-Maria Cruciat,[1] Mariann Bienz,[3] Christof Niehrs[1]*
SCIENCE VOL 316 15 JUNE 2007



Bryan T. MacDonald,[1] Keiko Tamai,[2] and Xi He
Developmental Cell 17, July 21, 2009

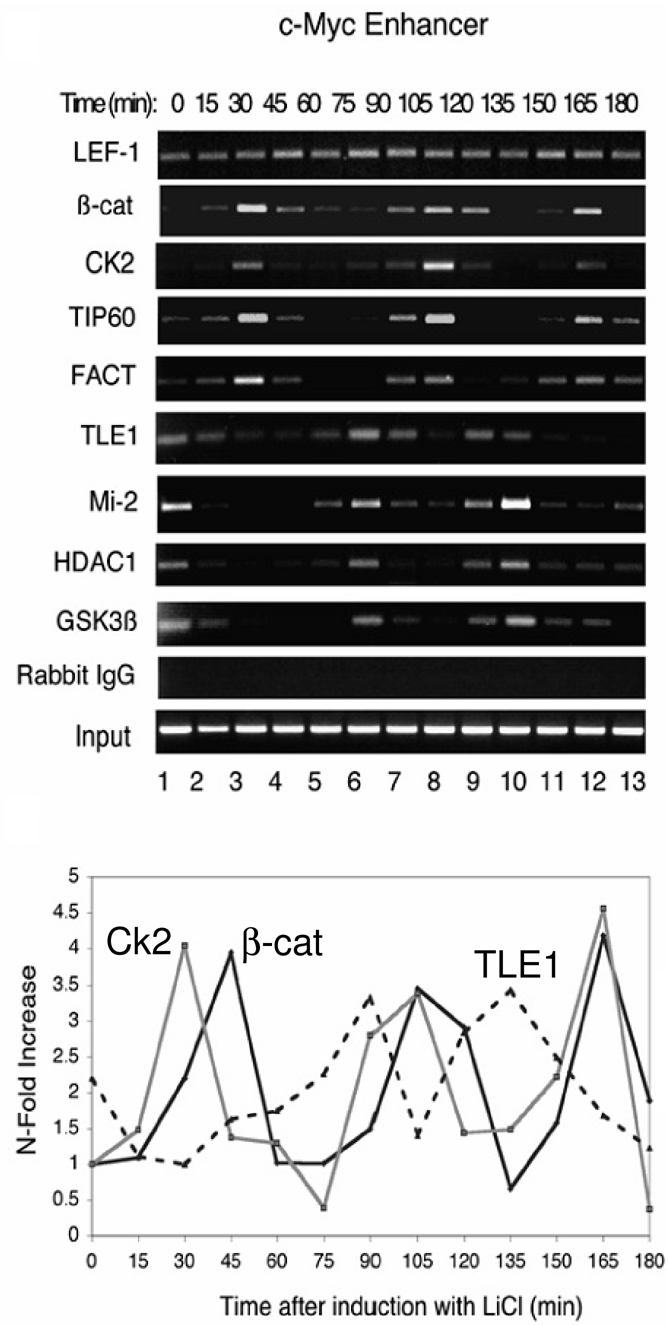
In the nucleus



Christian Mosimann‡, George Hausmann* and Konrad Basler*
NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 10 | APRIL 2009

+ phosphorylation of Tcf and Tle by Ck1 and Ck2

Oscillations in C2C12 mouse myoblast nuclei



S Wang & KA Jones

Current Biology 16, 2239–2244

SNPs and potential environmental factors impacting Craig Venter's genome

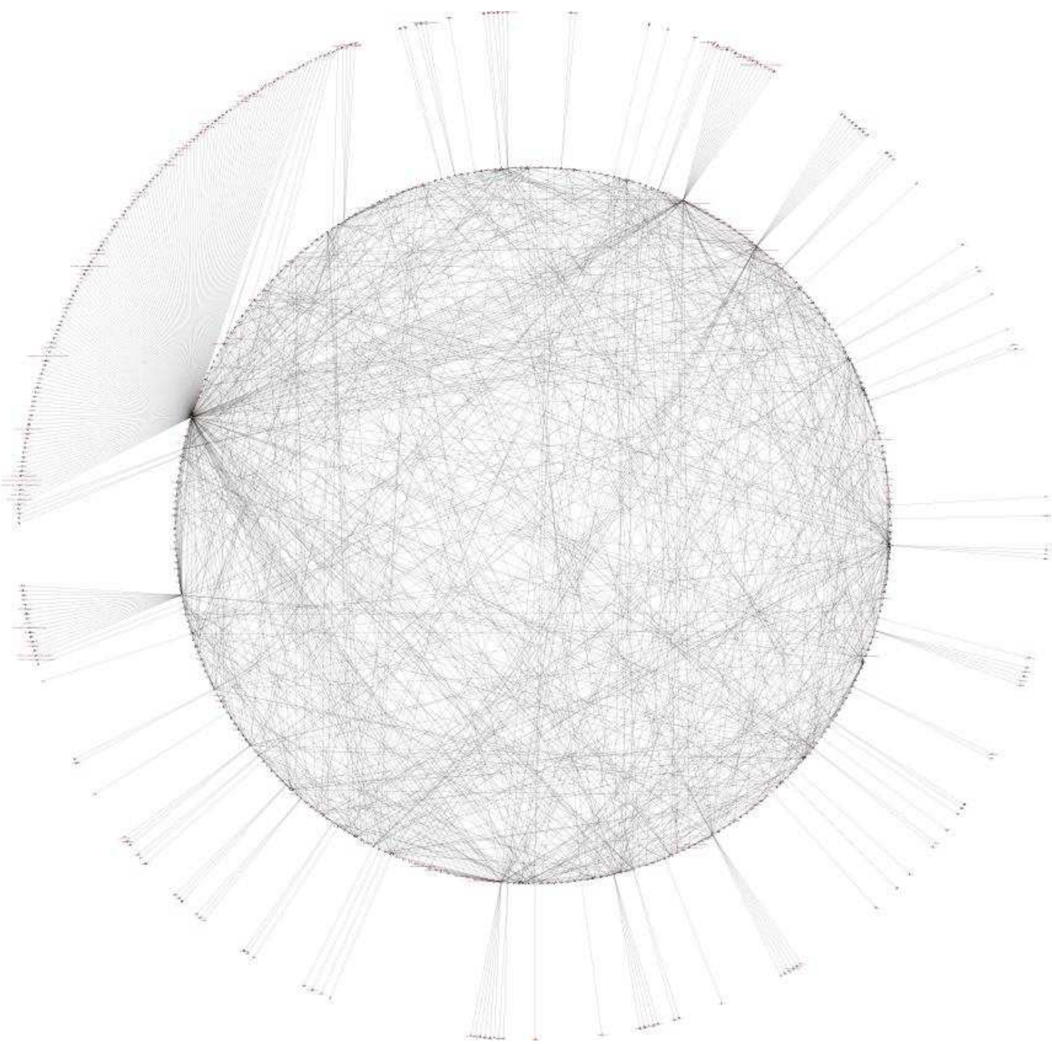
ns	non synonymous protein coding SNP
p	SNP in PreMod predicted cis-regulatory module (http://genomequebec.mcgill.ca/PReMod/)
sp	splice site SNP
fs	frame shift indel

TCD lists 2896 interactions affecting 151 out of 165 of Wnt-pathway genes

(395 substances affect Akt1 expression. The graph below excludes Akt1 and the substances that affect it & other genes.)

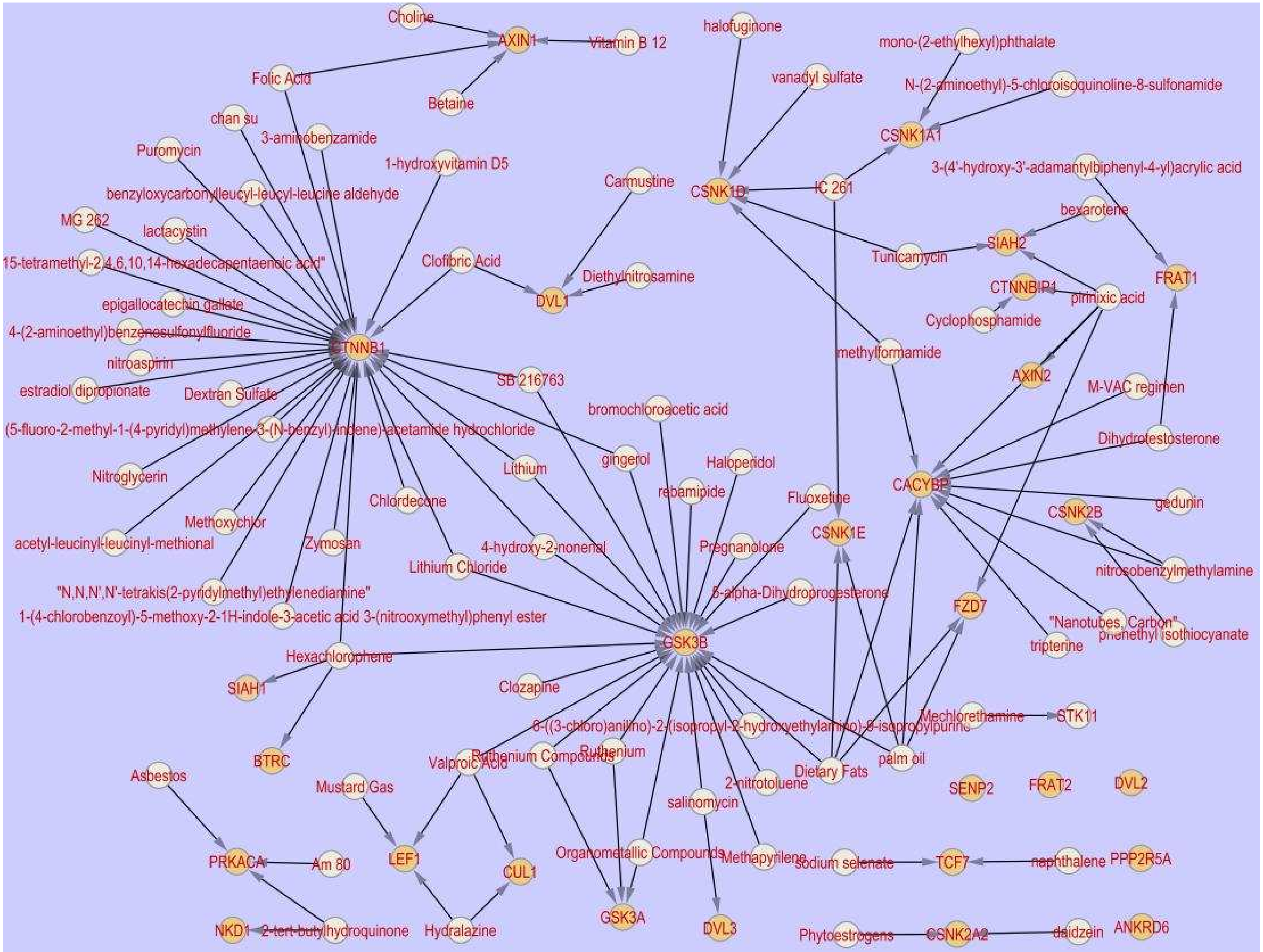
Of 165 Wnt-pathway associated genes, only 14 have no associations in TCD:

porc
shisa2
shisa3
shisa6
shisa7
shisa8
shisa9
skp1
trappc5
trappc6b
wls
wnt8a
wnt8b
wnt9b



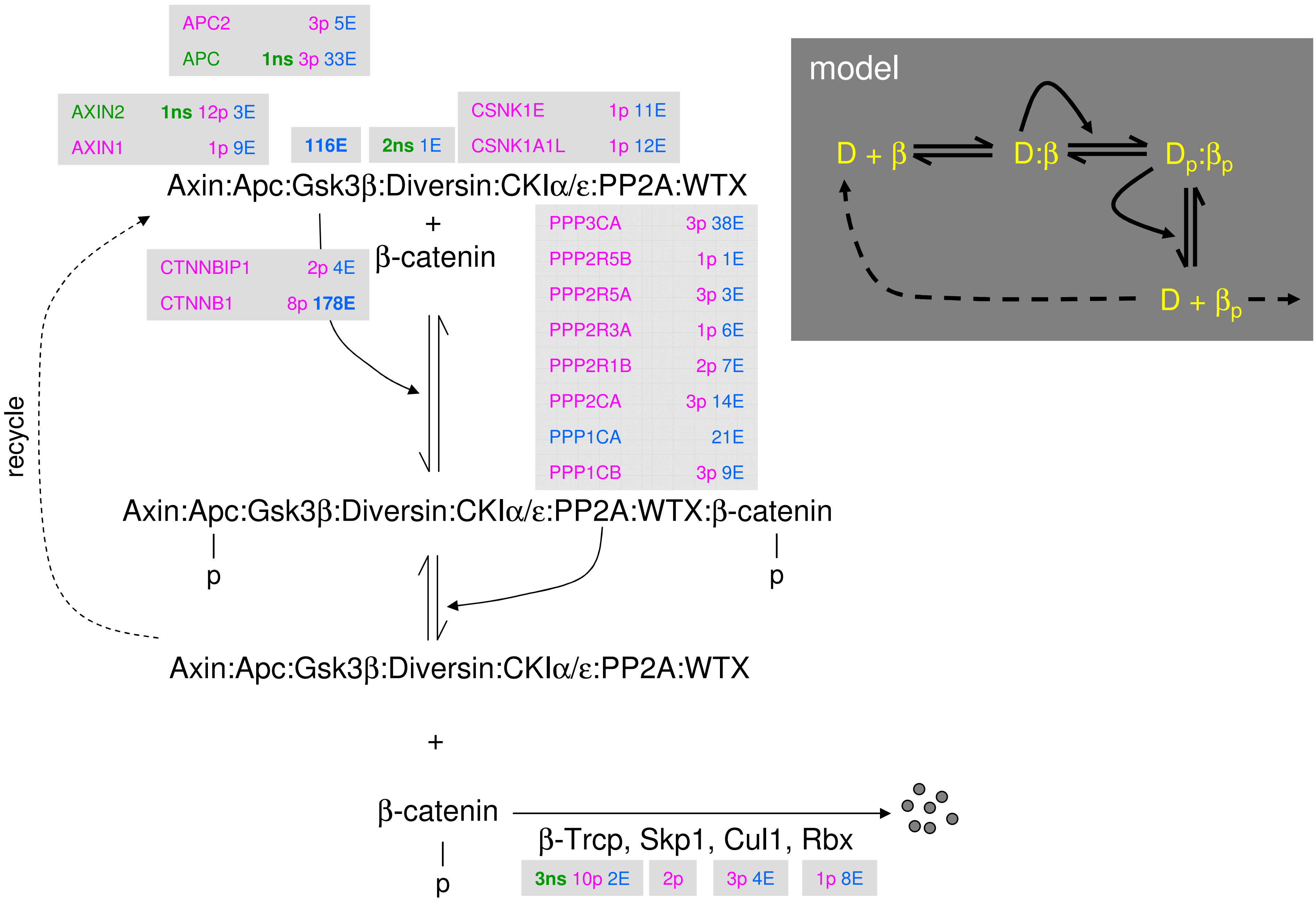
Comparative Toxicogenomics Database http://ctd.mdibl.org/

Wnt pathway targets of environmental exposures (CTD Wnt genes ≡ KEGG+Reactome)



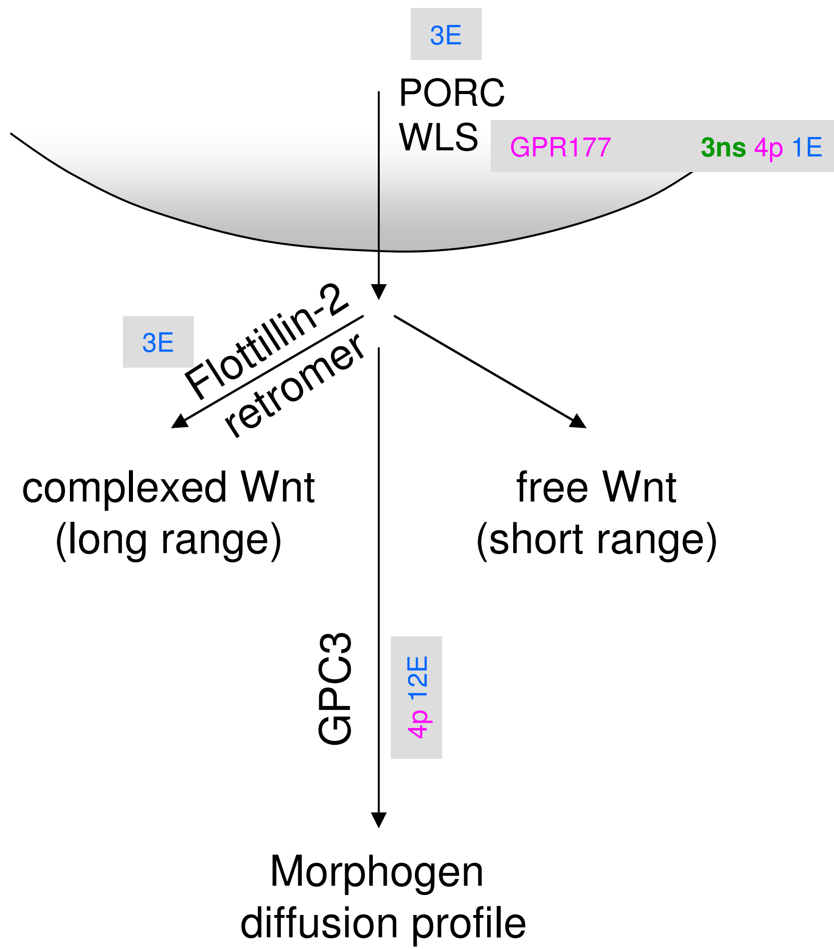
Comparative Toxicogenomics Database http://ctd.mdibl.org/

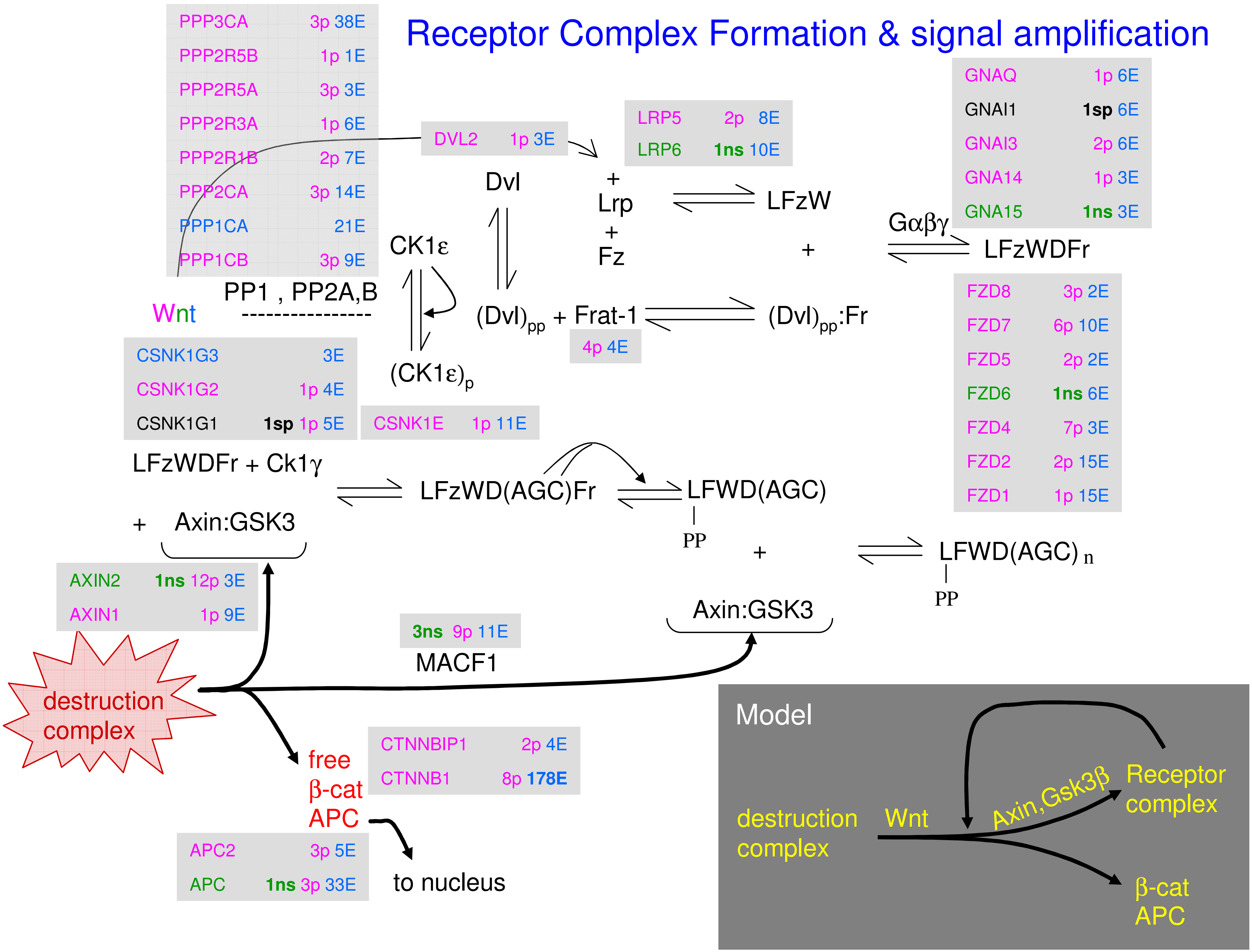
No Wnt signaling: β-catenin degradation



Wnt ligand processing and secretion

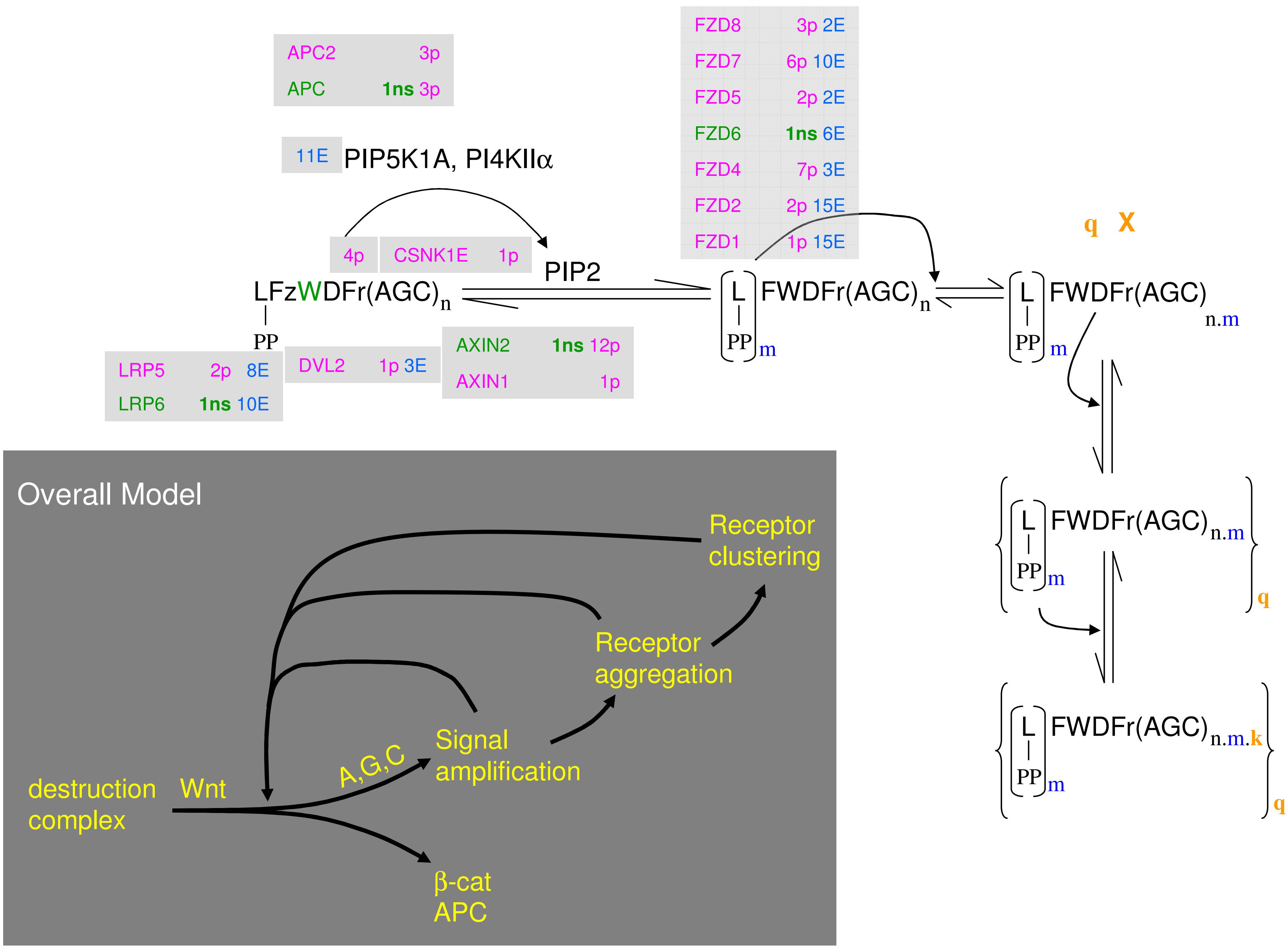
WNT9A	3p 2E
WNT9B	**1ns**
WNT8B	1p
~~WNT7A~~	~~20E~~
~~WNT7B~~	~~8E~~
~~WNT6~~	~~1E~~
~~WNT5B~~	~~**1sp** 4E~~
~~WNT5A~~	~~10p 26E~~
~~WNT4~~	~~**1sp** **1ns** 1p 15E~~
WNT3	1p 1E
WNT3A	6E
WNT2	9p 12E
WNT2B	1p 2E
WNT1	15E
~~WNT16~~	~~**3ns** 2E~~
~~WNT11~~	~~7p 5E~~
WNT10A	3E
WNT10B	**2ns** 1p 6E

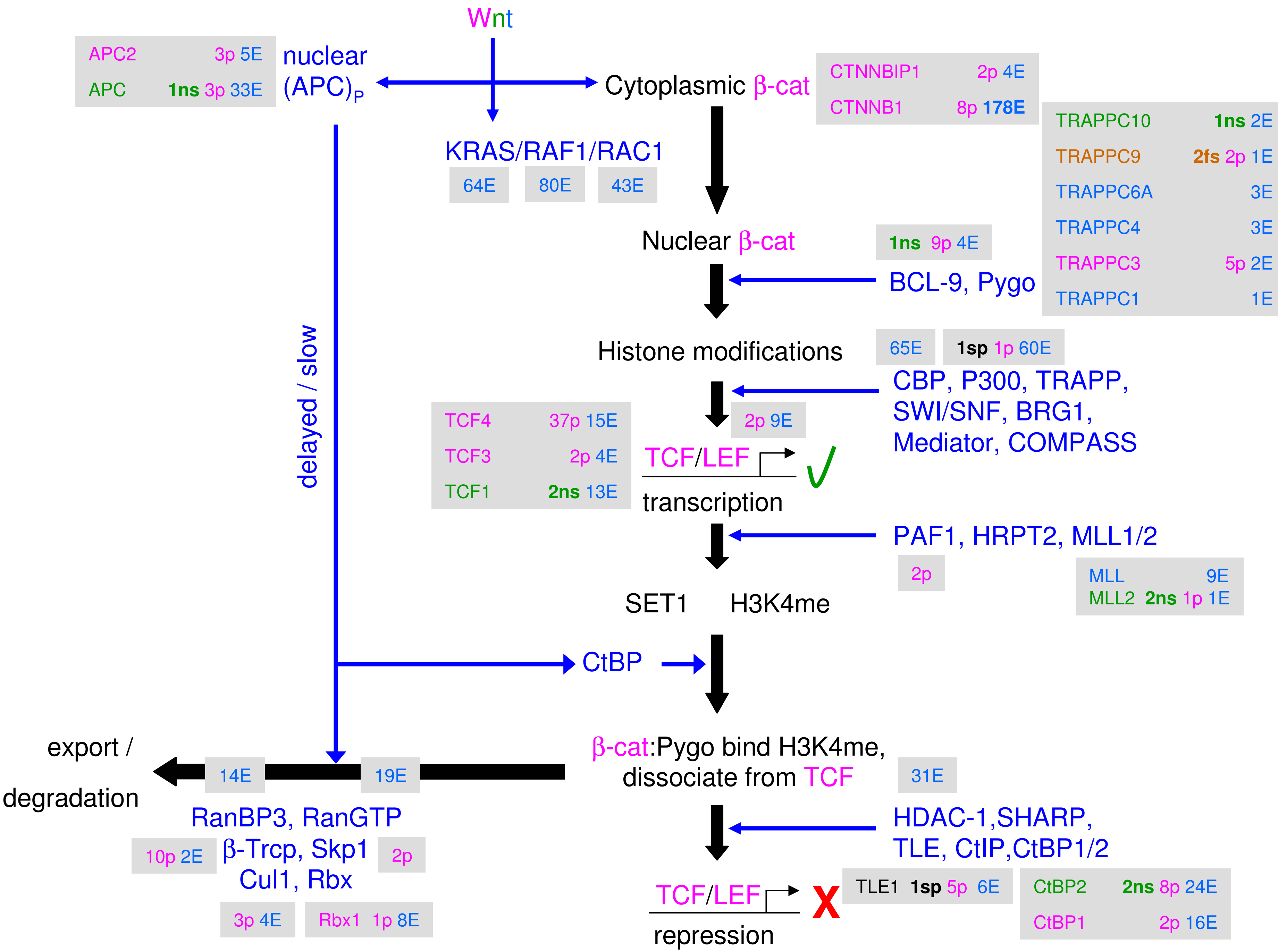




Receptor Complex Formation & signal amplification
PPP3CA 3p 38E
PPP2R5B 1p 1E
PPP2R5A 3p 3E
PPP2R3A 1p 6E
PPP2R1B 2p 7E
PPP2CA 3p 14E
PPP1CA 21E
PPP1CB 3p 9E
PP1 , PP2A,B
Wnt
DVL2 1p 3E
Dvl
LRP5 2p 8E
LRP6 1ns 10E
+ Lrp + Fz
LFzW
GNAQ 1p 6E
GNAI1 1sp 6E
GNAI3 2p 6E
GNA14 1p 3E
GNA15 1ns 3E
Gαβγ
+
LFzWDFr
CK1ε
(Dvl)pp + Frat-1
4p 4E
(Dvl)pp:Fr
(CK1ε)p
CSNK1G3 3E
CSNK1G2 1p 4E
CSNK1G1 1sp 1p 5E
CSNK1E 1p 11E
FZD8 3p 2E
FZD7 6p 10E
FZD5 2p 2E
FZD6 1ns 6E
FZD4 7p 3E
FZD2 2p 15E
FZD1 1p 15E
LFzWDFr + Ck1γ
+ Axin:GSK3
LFzWD(AGC)Fr
LFWD(AGC)
PP
+
LFWD(AGC) n
PP
AXIN2 1ns 12p 3E
AXIN1 1p 9E
3ns 9p 11E
MACF1
Axin:GSK3
destruction complex
free β-cat APC
CTNNBIP1 2p 4E
CTNNB1 8p 178E
APC2 3p 5E
APC 1ns 3p 33E
to nucleus
Model
destruction complex
Wnt
Axin,Gsk3β
Receptor complex
β-cat APC

Wnt signaling – (2) Receptor Aggregation & Clustering

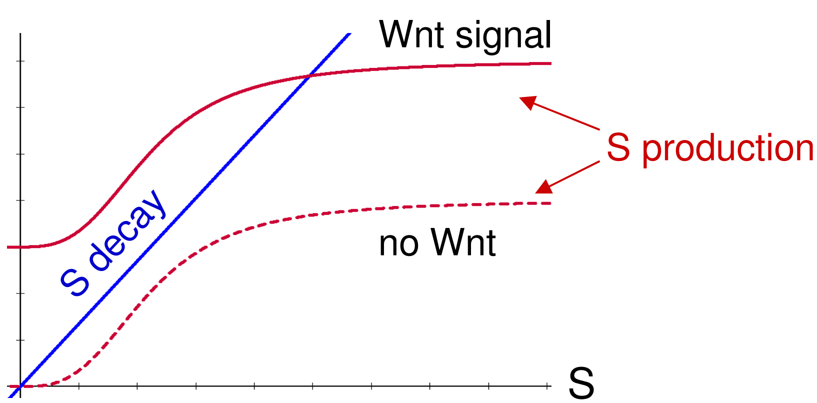


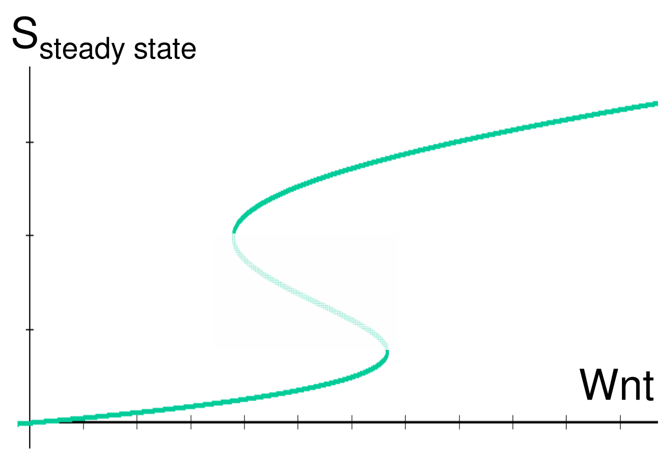


Wnt
APC2 3p 5E
APC 1ns 3p 33E
nuclear (APC)P
Cytoplasmic β-cat
CTNNBIP1 2p 4E
CTNNB1 8p 178E
KRAS/RAF1/RAC1
64E
80E
43E
TRAPPC10 1ns 2E
TRAPPC9 2fs 2p 1E
TRAPPC6A 3E
TRAPPC4 3E
TRAPPC3 5p 2E
TRAPPC1 1E
Nuclear β-cat
1ns 9p 4E
BCL-9, Pygo
Histone modifications
65E
1sp 1p 60E
CBP, P300, TRAPP, SWI/SNF, BRG1, Mediator, COMPASS
delayed / slow
TCF4 37p 15E
TCF3 2p 4E
TCF1 2ns 13E
2p 9E
TCF/LEF
transcription
PAF1, HRPT2, MLL1/2
2p
MLL 9E
MLL2 2ns 1p 1E
SET1 H3K4me
CtBP
export / degradation
14E
19E
β-cat:Pygo bind H3K4me, dissociate from TCF
31E
RanBP3, RanGTP
10p 2E
β-Trcp, Skp1
2p
Cul1, Rbx
3p 4E
Rbx1 1p 8E
HDAC-1,SHARP, TLE, CtIP,CtBP1/2
TCF/LEF
repression
X
TLE1 1sp 5p 6E
CtBP2 2ns 8p 24E
CtBP1 2p 16E

S = total signalosome activity

$$S' = \left(k_1 \,.\, Wnt + \frac{k_s . S^H}{K_{MS} + S^H} \right) - k_{ds} \,.\, S$$





Let A = membrane-bound Axin

A_T = total Axin

$A_{\text{destruction complex}} = A_T - A$

B = free β-catenin

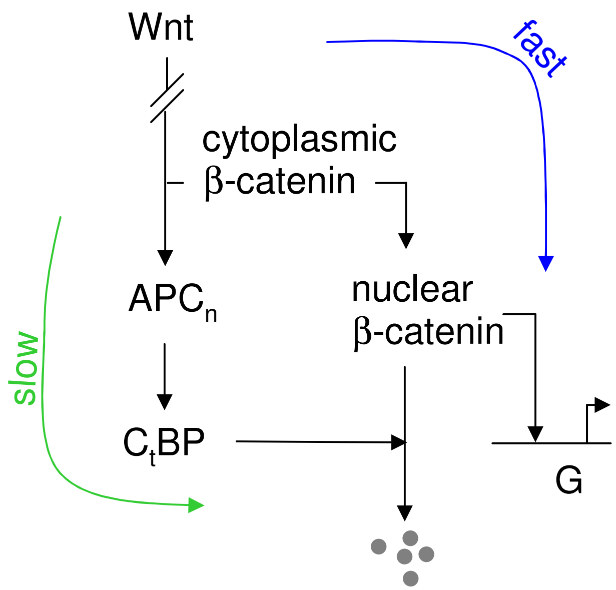
$$\begin{cases} A' = \left(k_W \cdot \dfrac{Wnt}{1+Wnt} + \dfrac{k_A . A^H}{K_{MA} + A^H} \right) - k_{dA} . A \\[2em] B' = k_{B1} - k_{B2}.(A_T - A).B - k_{B3}.B \end{cases}$$

At steady state:

$$\begin{cases} \dfrac{Wnt}{1+Wnt} = \dfrac{k_{dA}}{k_W}.A - \dfrac{\left(\dfrac{k_A}{k_W}\right).A^H}{K_{MA} + A^H} & A = f\ (Wnt) \\[2em] B = \dfrac{k_{B1}}{k_{B2}.(A_T - A) + k_{B3}} & B = f\ (A) = f\ (Wnt) \end{cases}$$

$(A \leq AT)$

Model for nuclear events following Wnt signaling

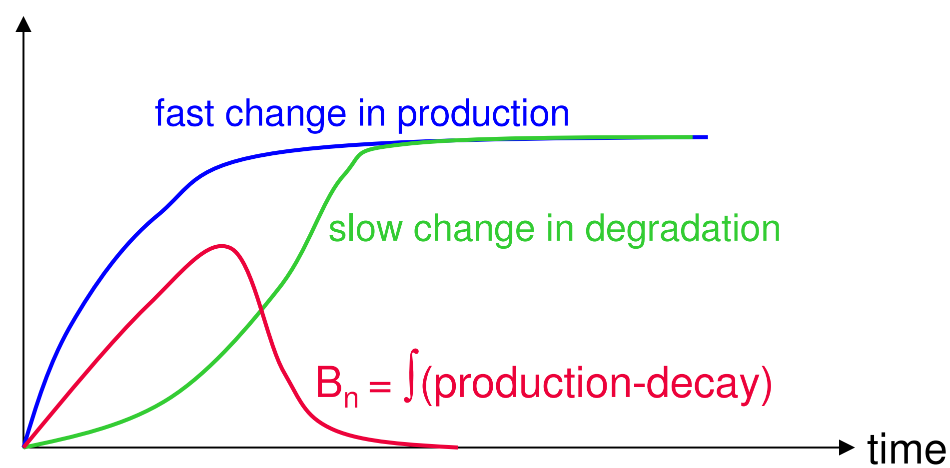


$$B_n' = k_{n1}.B - k_{n2}.(k_{nc}.C_t + 1).B_n$$

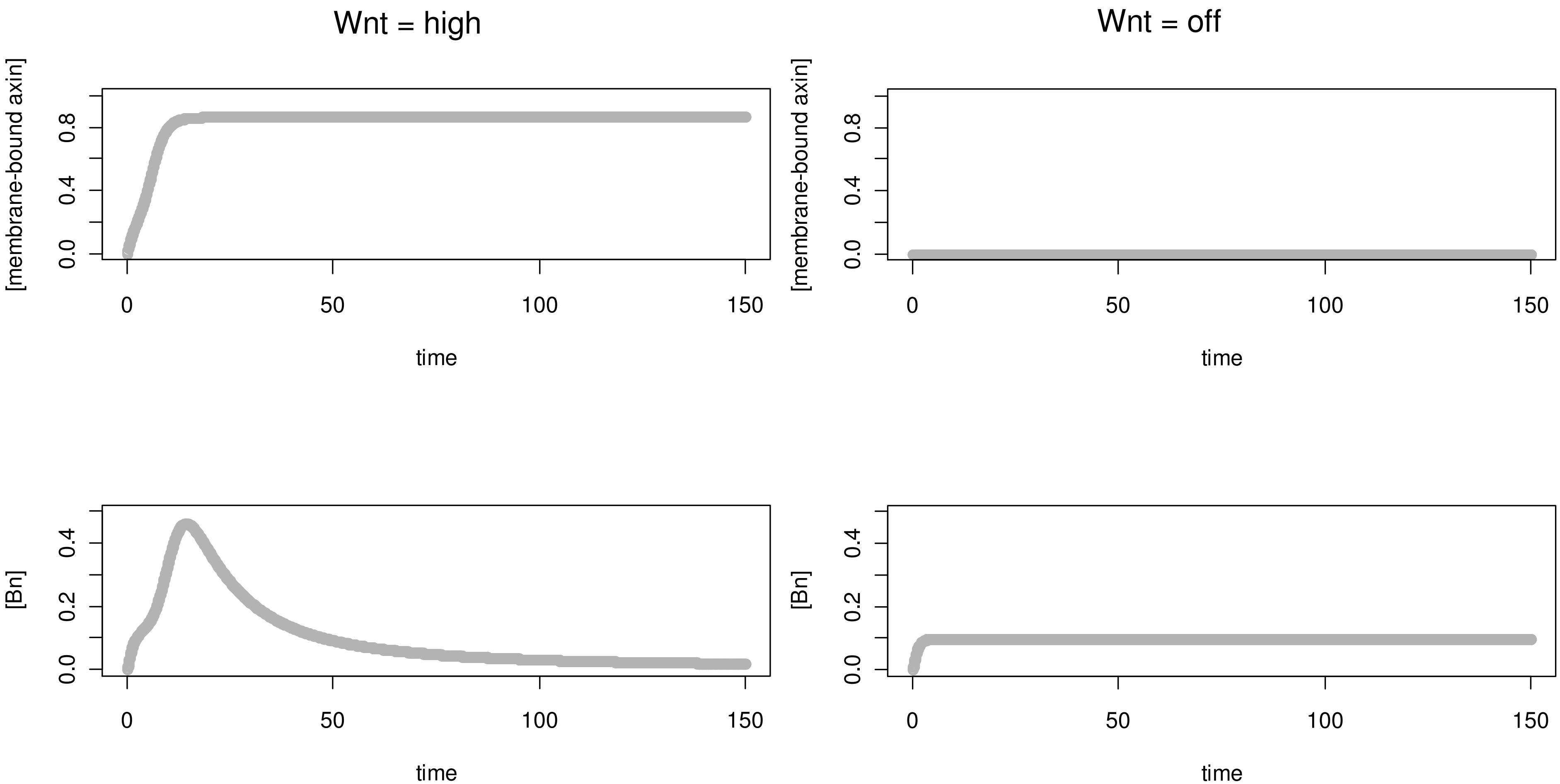
$$A_p' = k_{p1}.A - k_{p2}.A_p$$

$$C_t' = k_{p1}.A_p - k_{p2}.C_t$$

$$k_{p1}, k_{p2} < k_{n1}, k_{n2}.k_{nc}$$

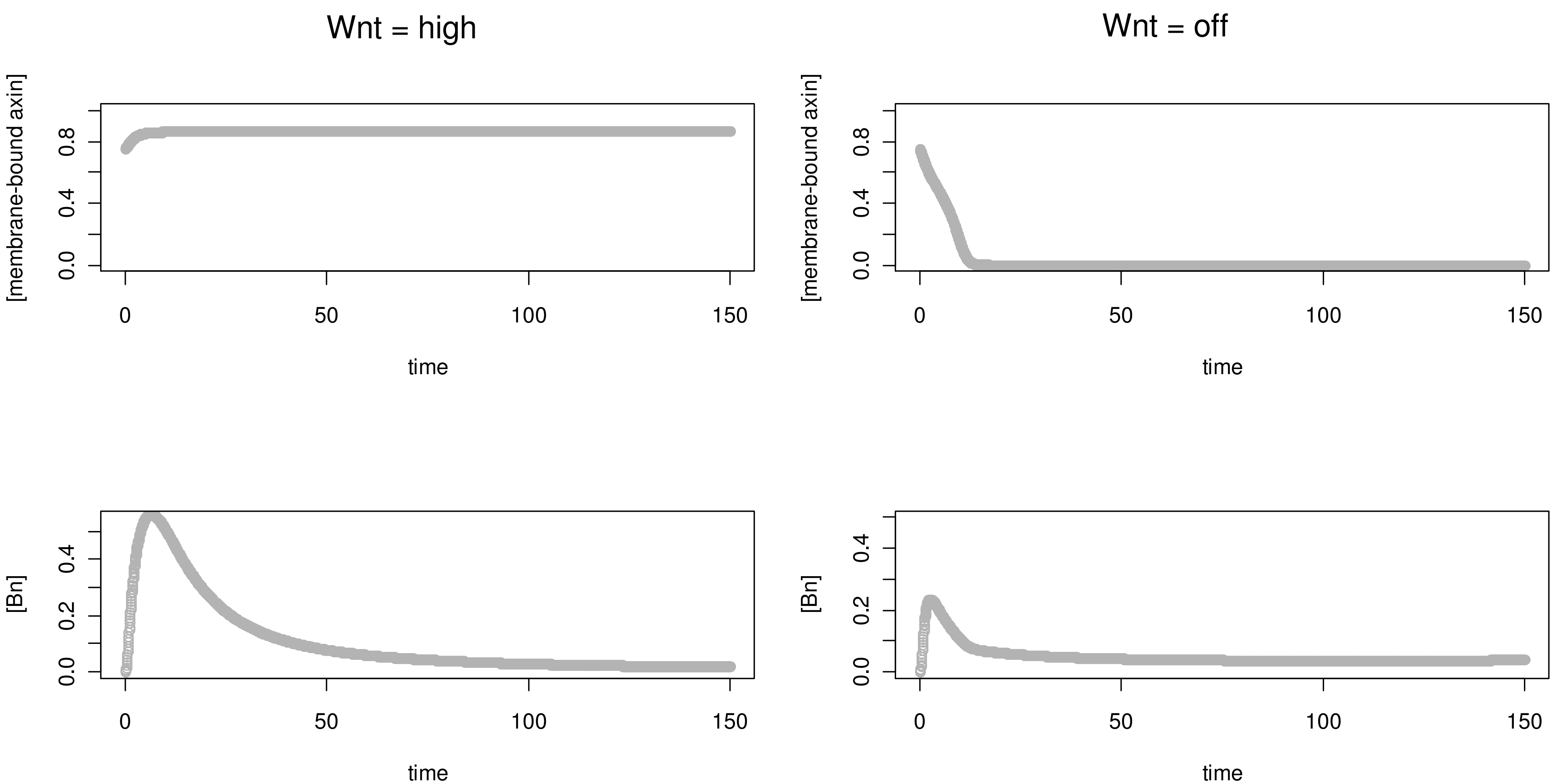


Time-course behavior of the model with nominal parameter values

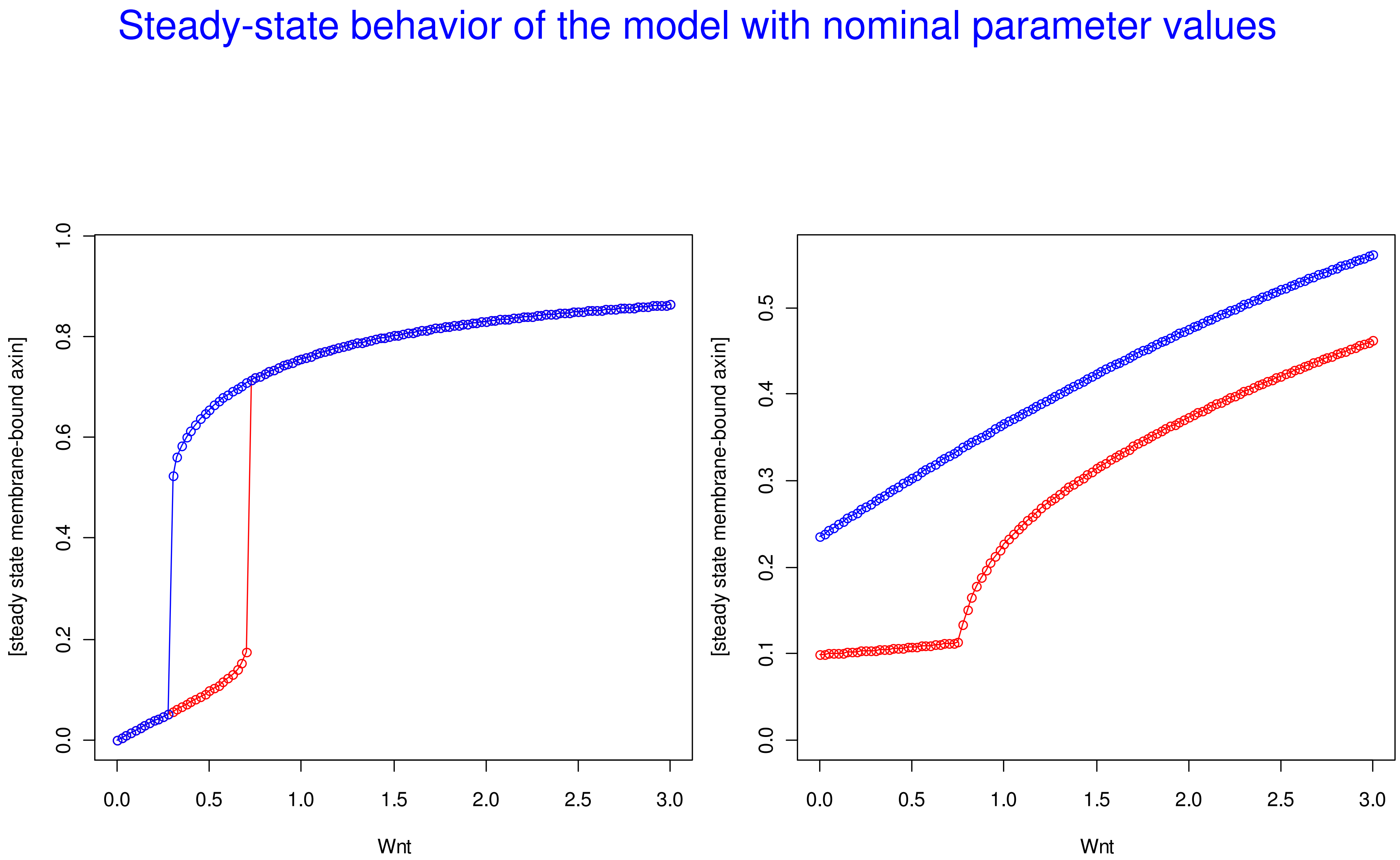


Initial conditions: "Ax"=0, "Bc"=0, "Bn"=0, "Ap"=0, "Ct"=0

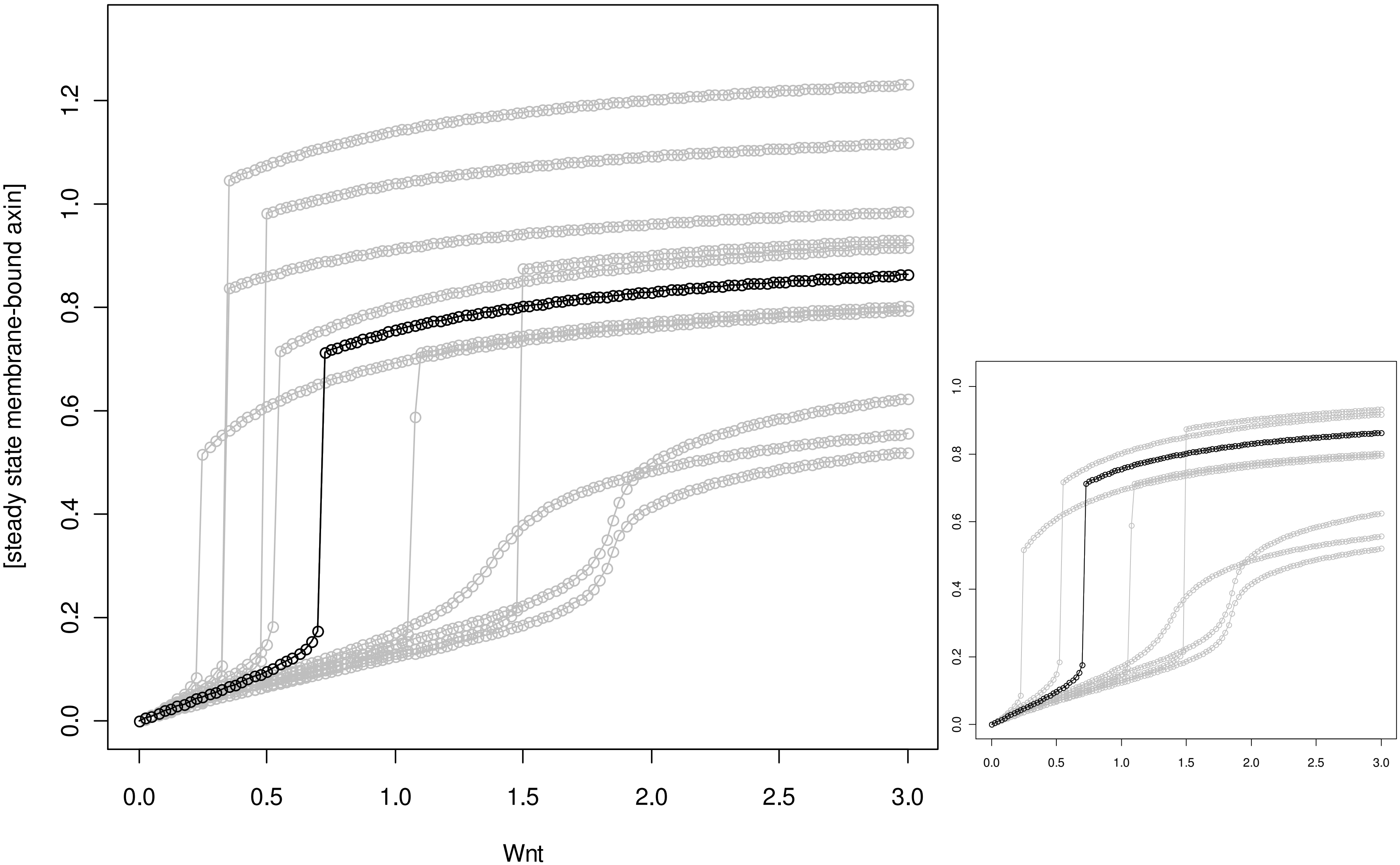
Time-course behavior of the model with nominal parameter values



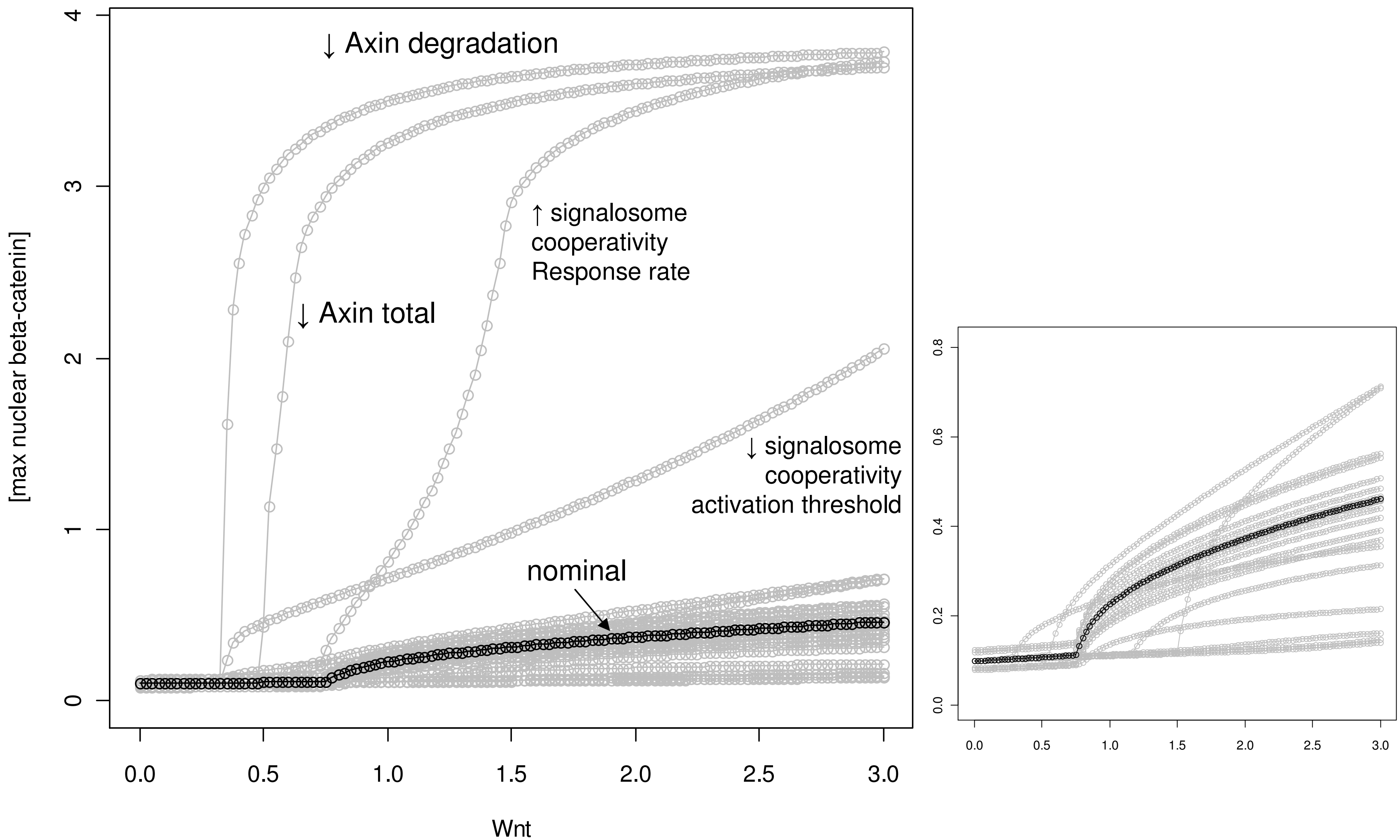
Initial conditions: "Ax"=0.75, "Bc"=0, "Bn"=0, "Ap"=0, "Ct"=0


Steady-state behavior of the model with nominal parameter values
[steady state membrane-bound axin]
Wnt
0.0
0.2
0.4
0.6
0.8
1.0
0.5
1.0
1.5
2.0
2.5
3.0
[steady state membrane-bound axin]
Wnt
0.0
0.1
0.2
0.3
0.4
0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0

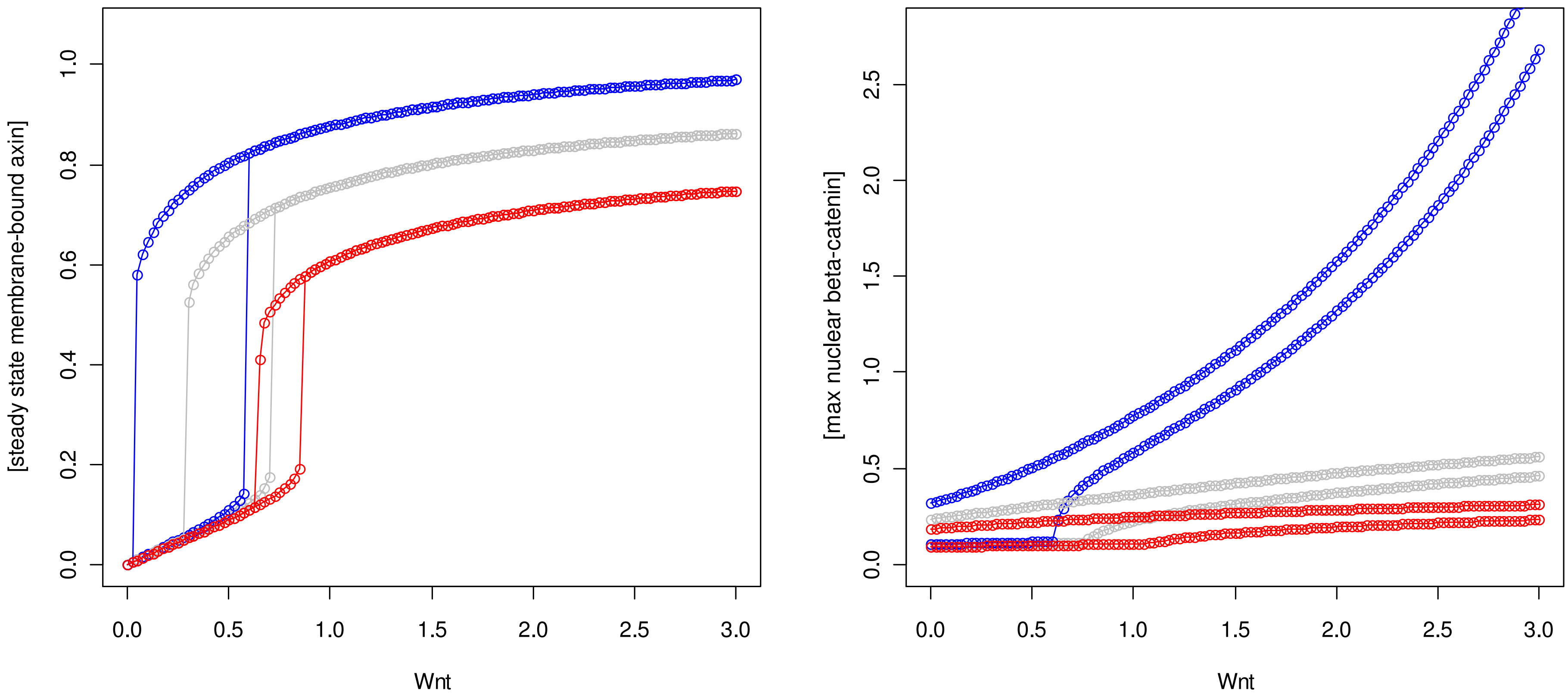
Varying 1 parameter at a time by ±20%



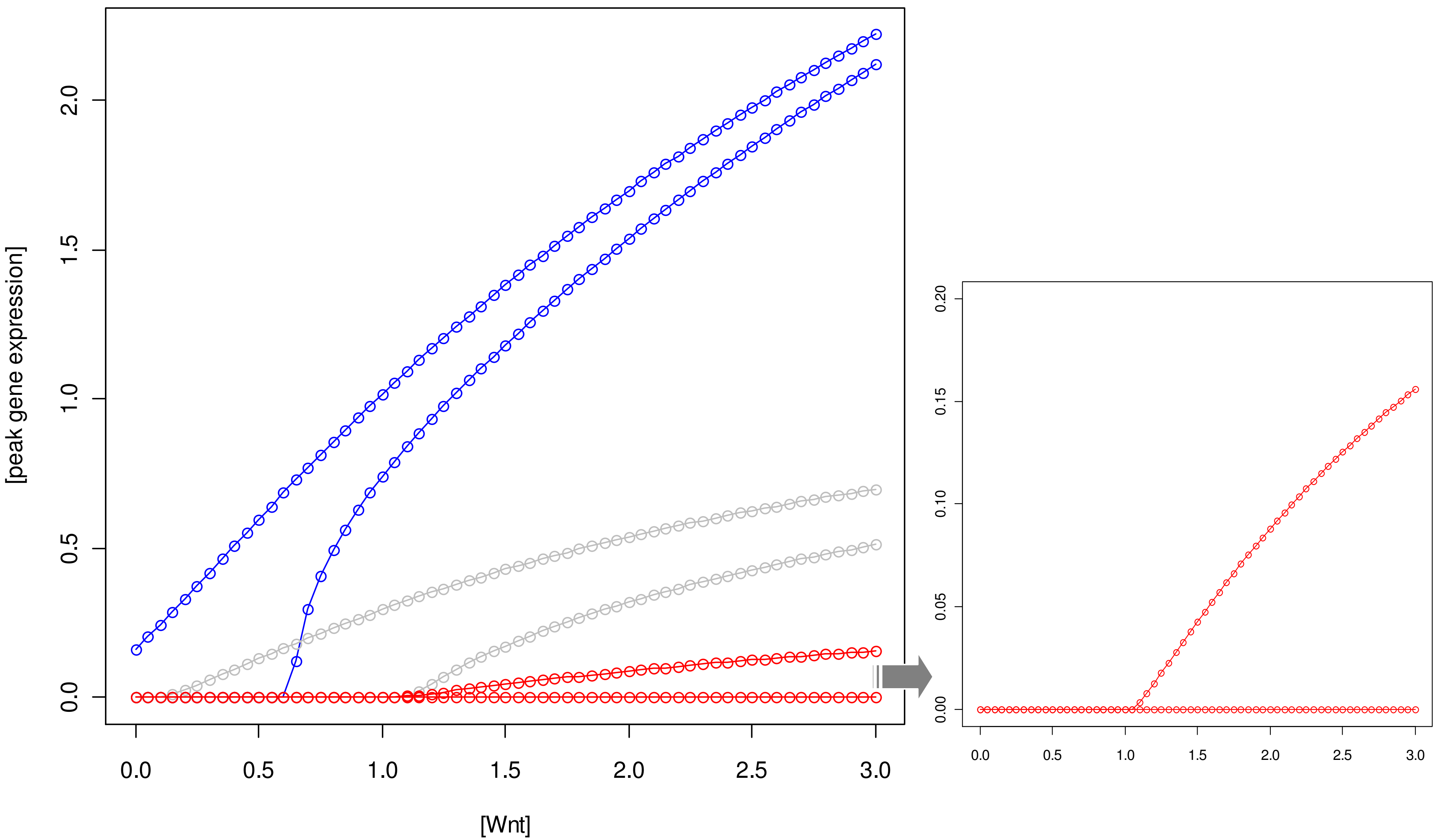
Varying 1 parameter at a time by ±20%



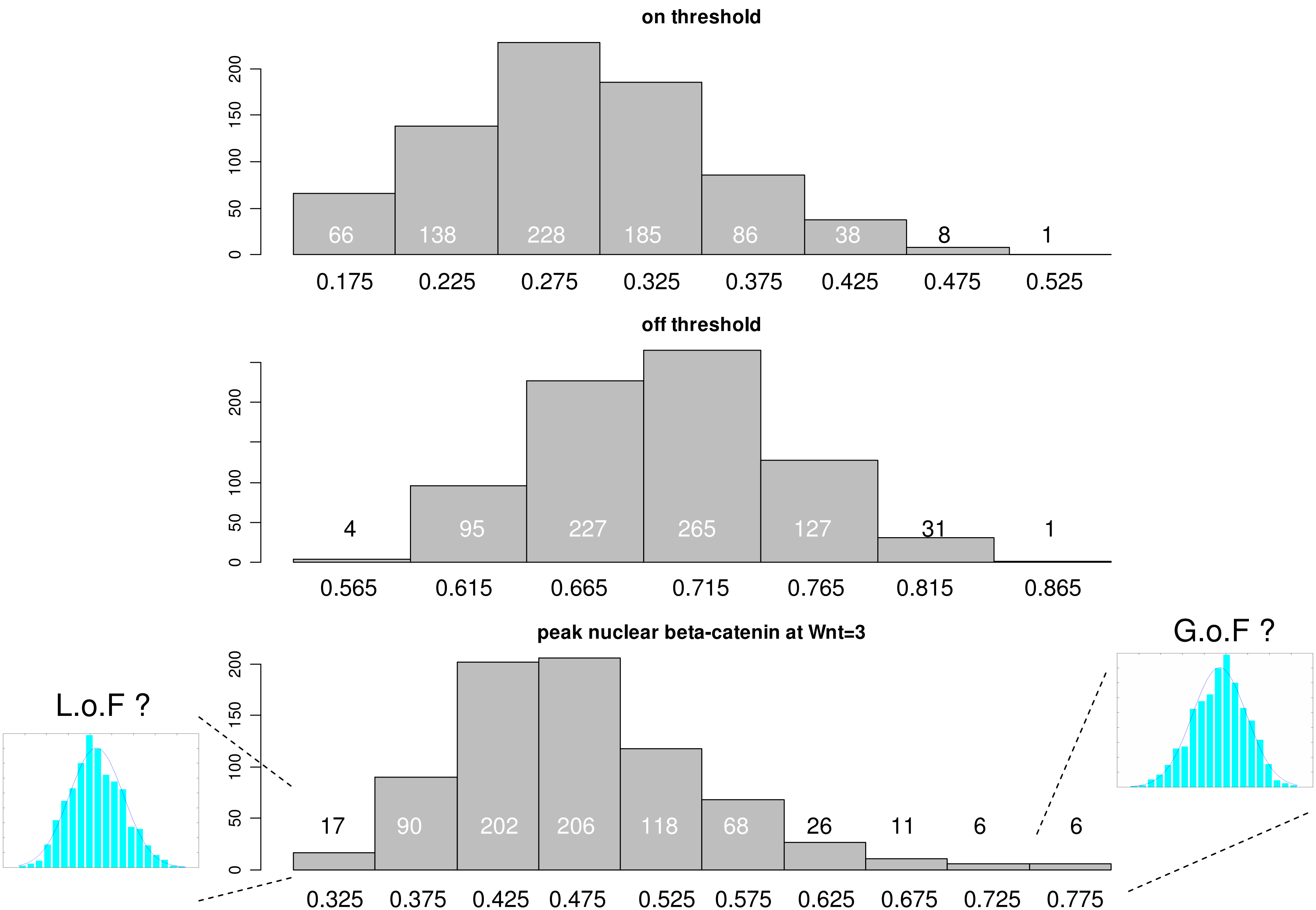
Co-varying all parameters by ±2.5%



Co-varying all parameters by ±2.5% : effect on target gene expression

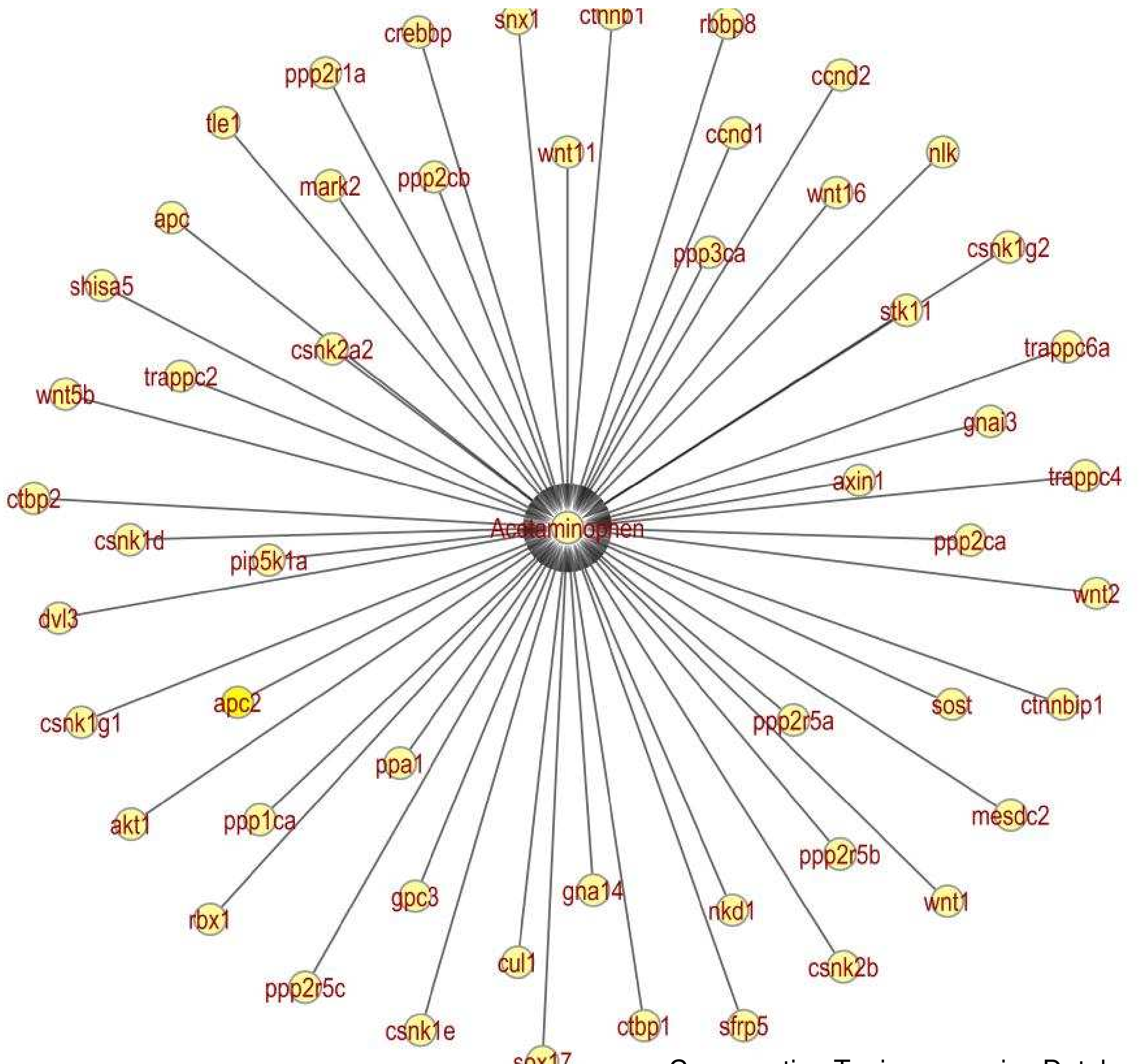


750 runs; all parameters Normally distributed with σ= 1% of μ

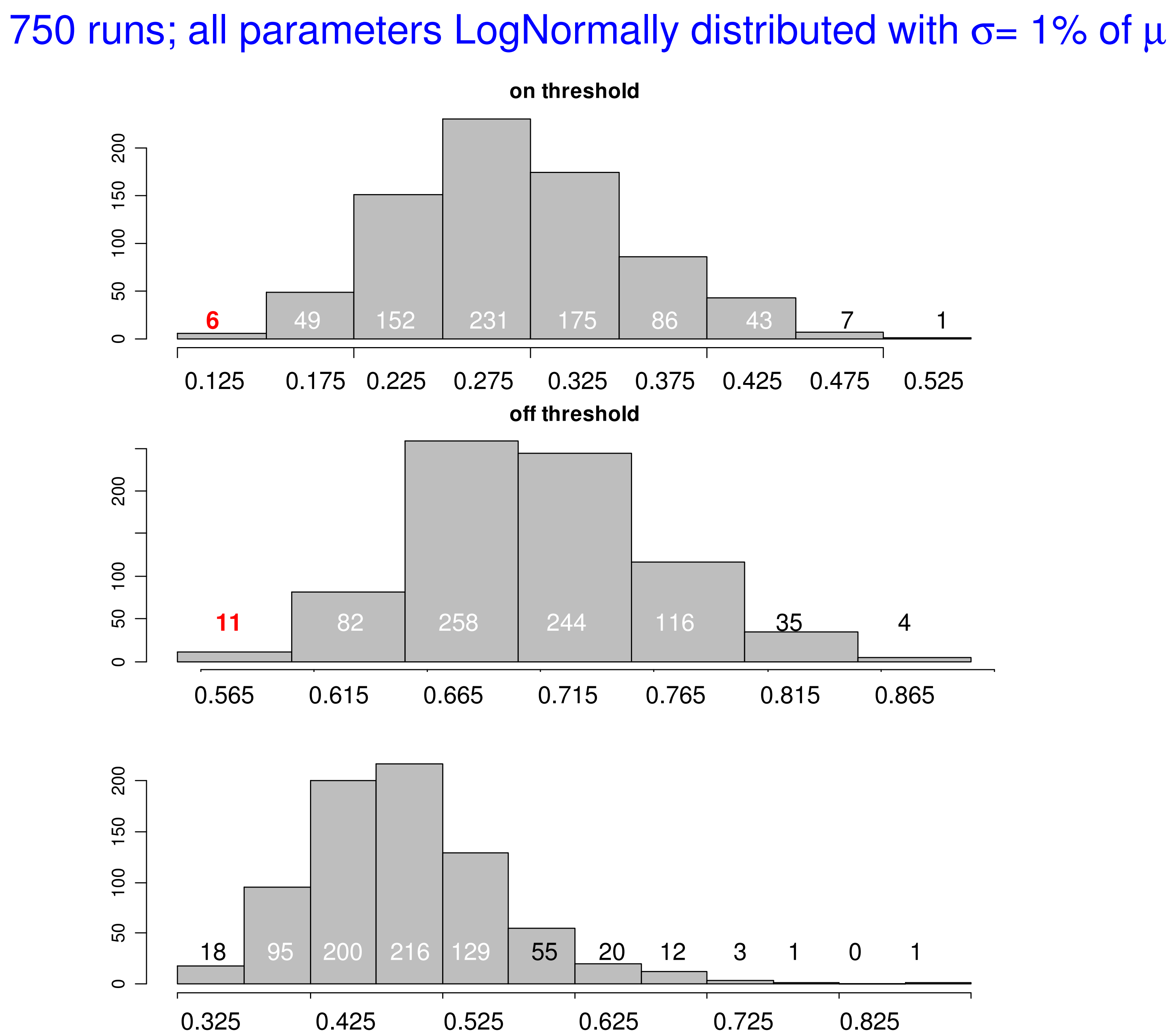


Acetaminophen (@ ~30X Tylenol) affects 53 (i.e. ~ 1/3) Wnt-pathway genes

(Measured in mouse livers. All Acetaminophen interactions = 6341. 3735 genes respond within 6 hours.)



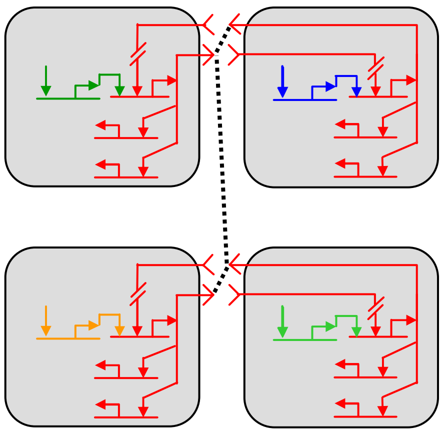
Comparative Toxicogenomics Database http://ctd.mdibl.org/

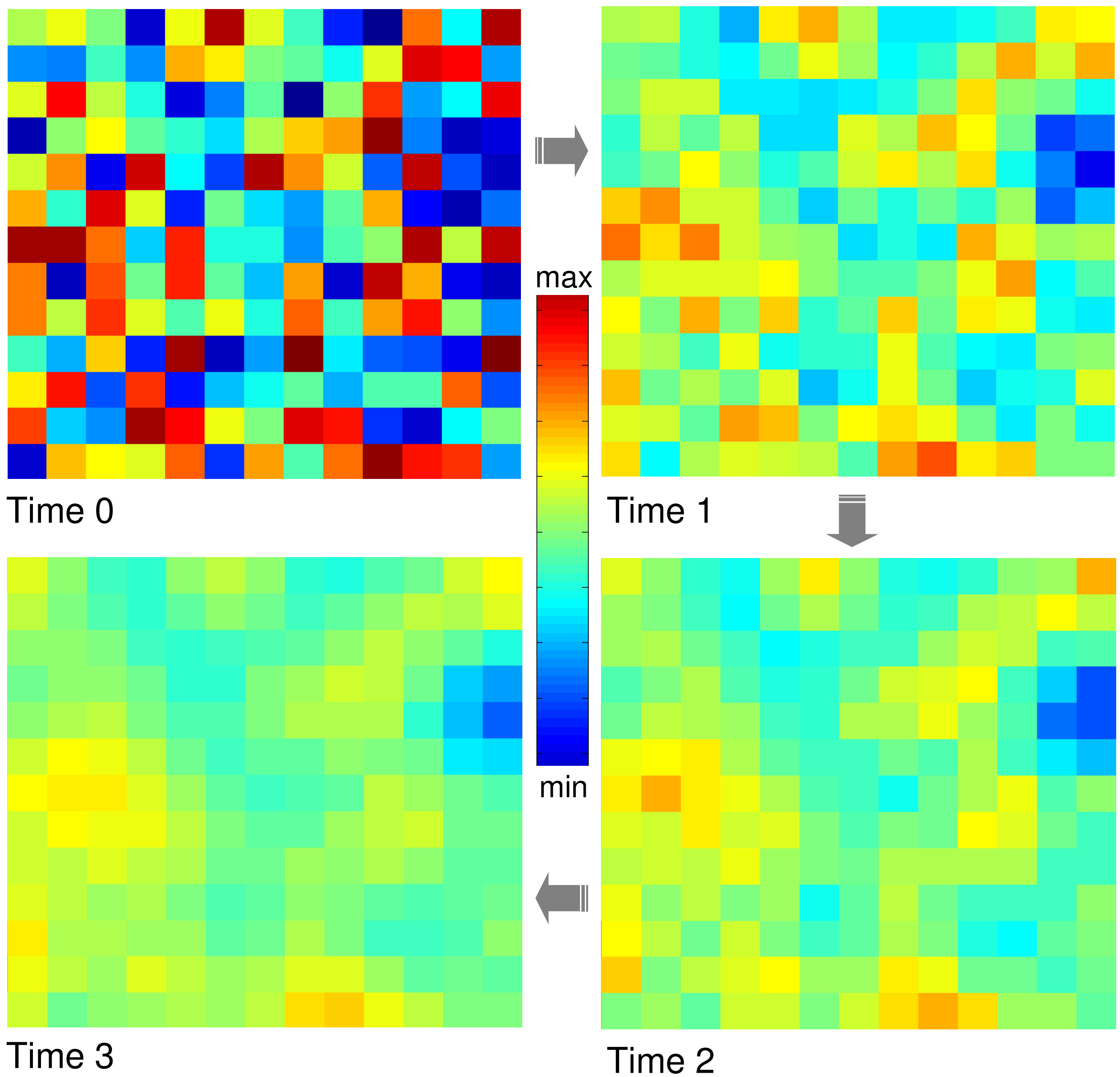


750 runs; all parameters LogNormally distributed with σ= 1% of μ
on threshold
6
49
152
231
175
86
43
7
1
0.125
0.175
0.225
0.275
0.325
0.375
0.425
0.475
0.525
off threshold
11
82
258
244
116
35
4
0.565
0.615
0.665
0.715
0.765
0.815
0.865
18
95
200
216
129
55
20
12
3
1
0
1
0.325
0.425
0.525
0.625
0.725
0.825

The Community Effect: robust Wnt signaling in early sea urchin development

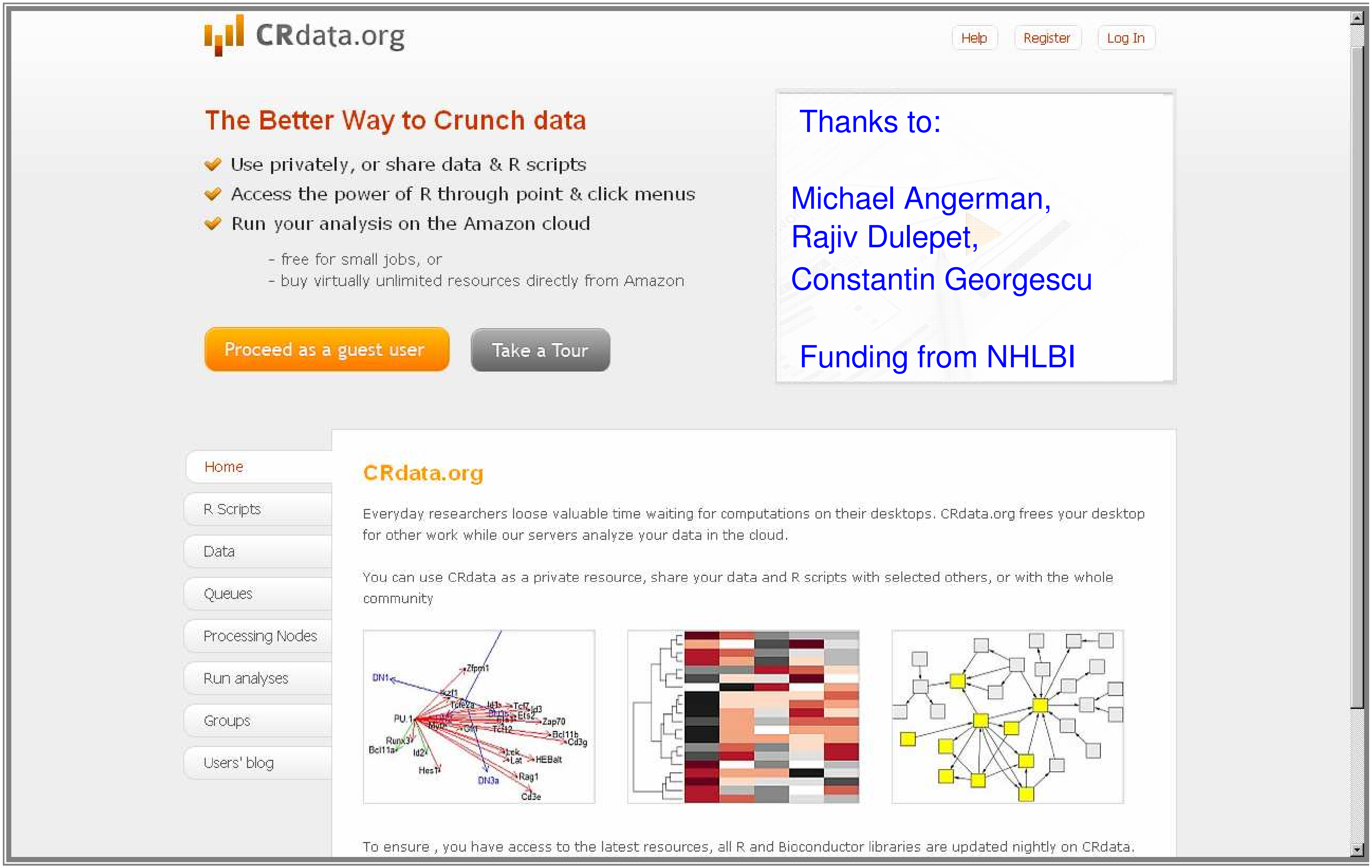
Ligand sharing – each cell receives ¼ of its ligands auto-catalytically, ¾ from its neighbors



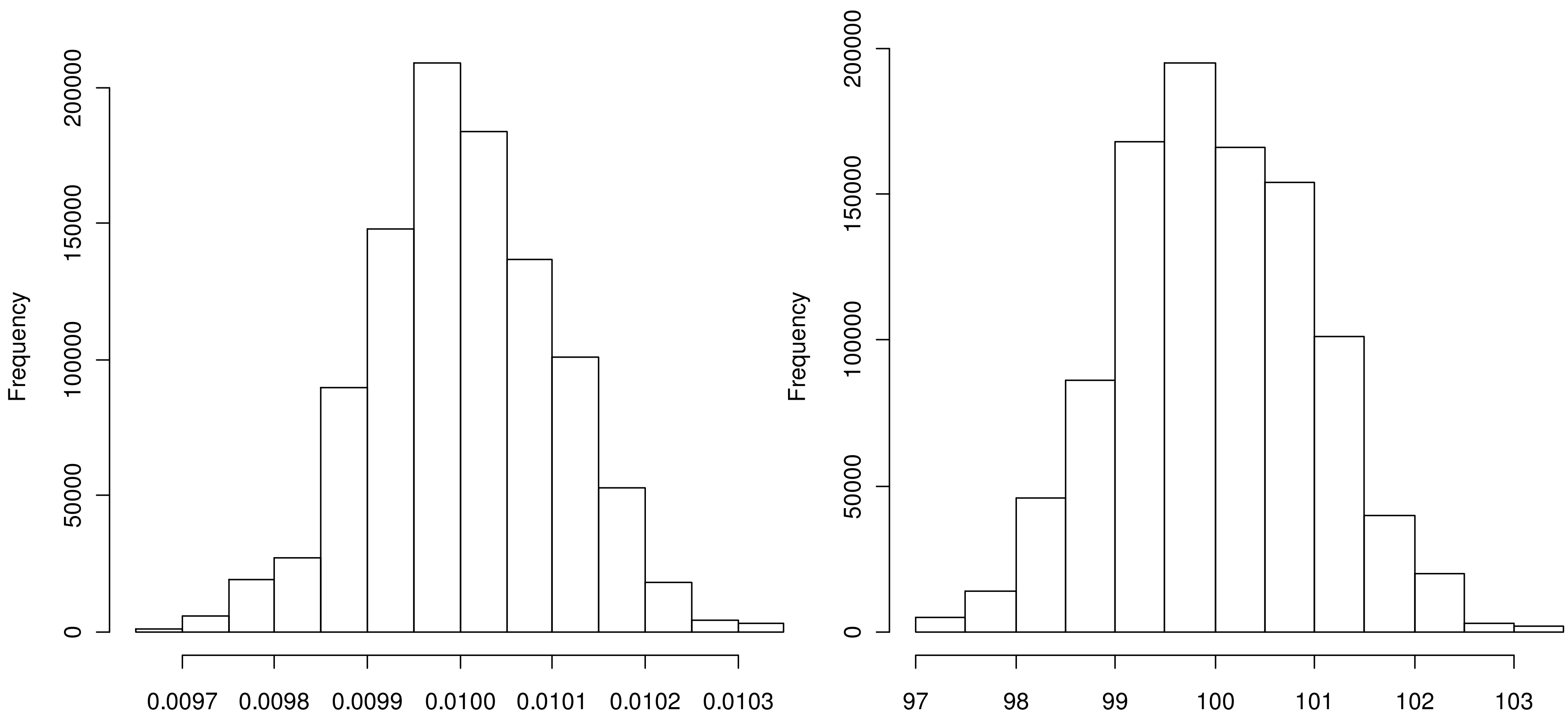


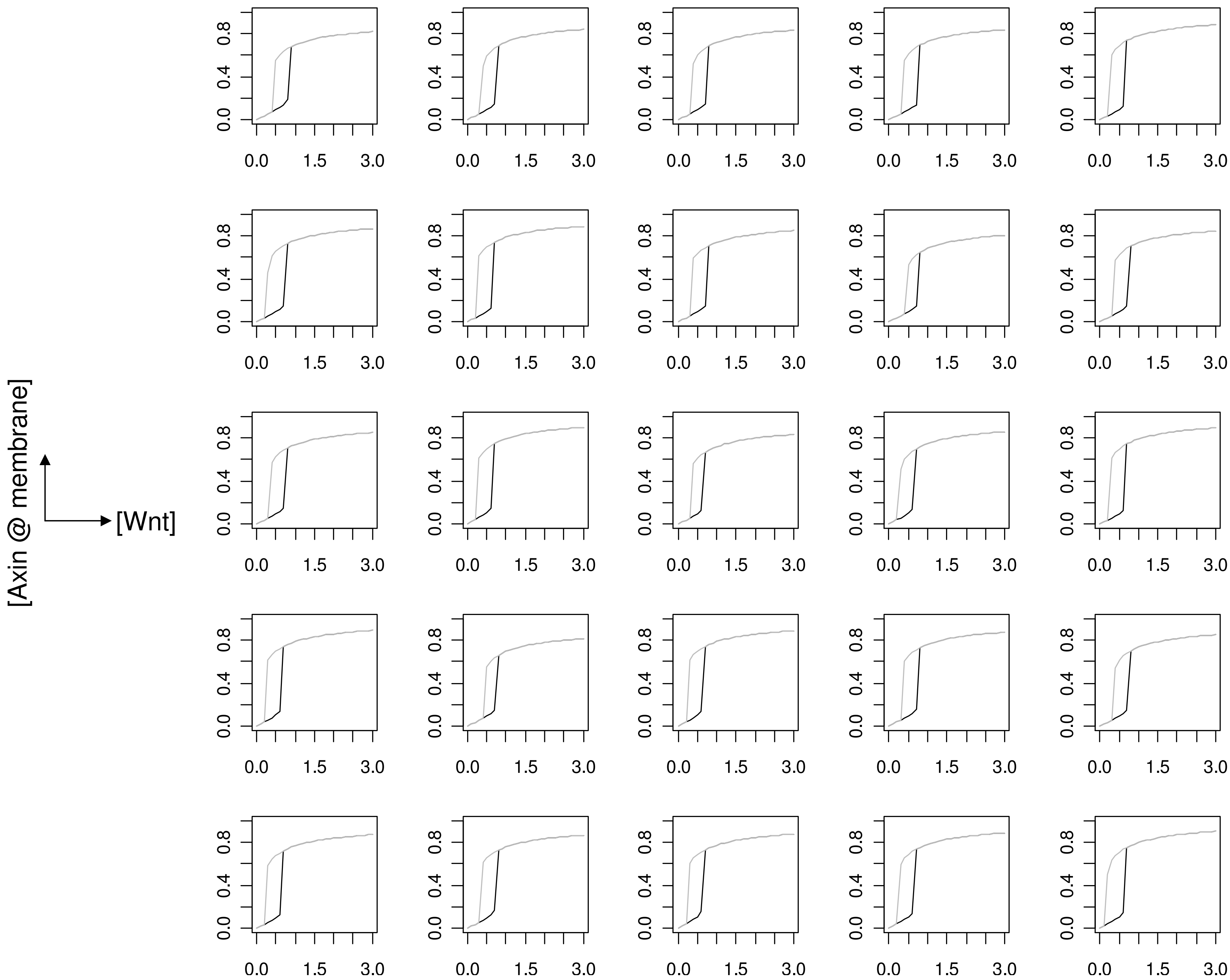
Bolouri & Davidson, BioEssays, 2002
&
Developmental Biology, In Press.

Reproducible & open-source research

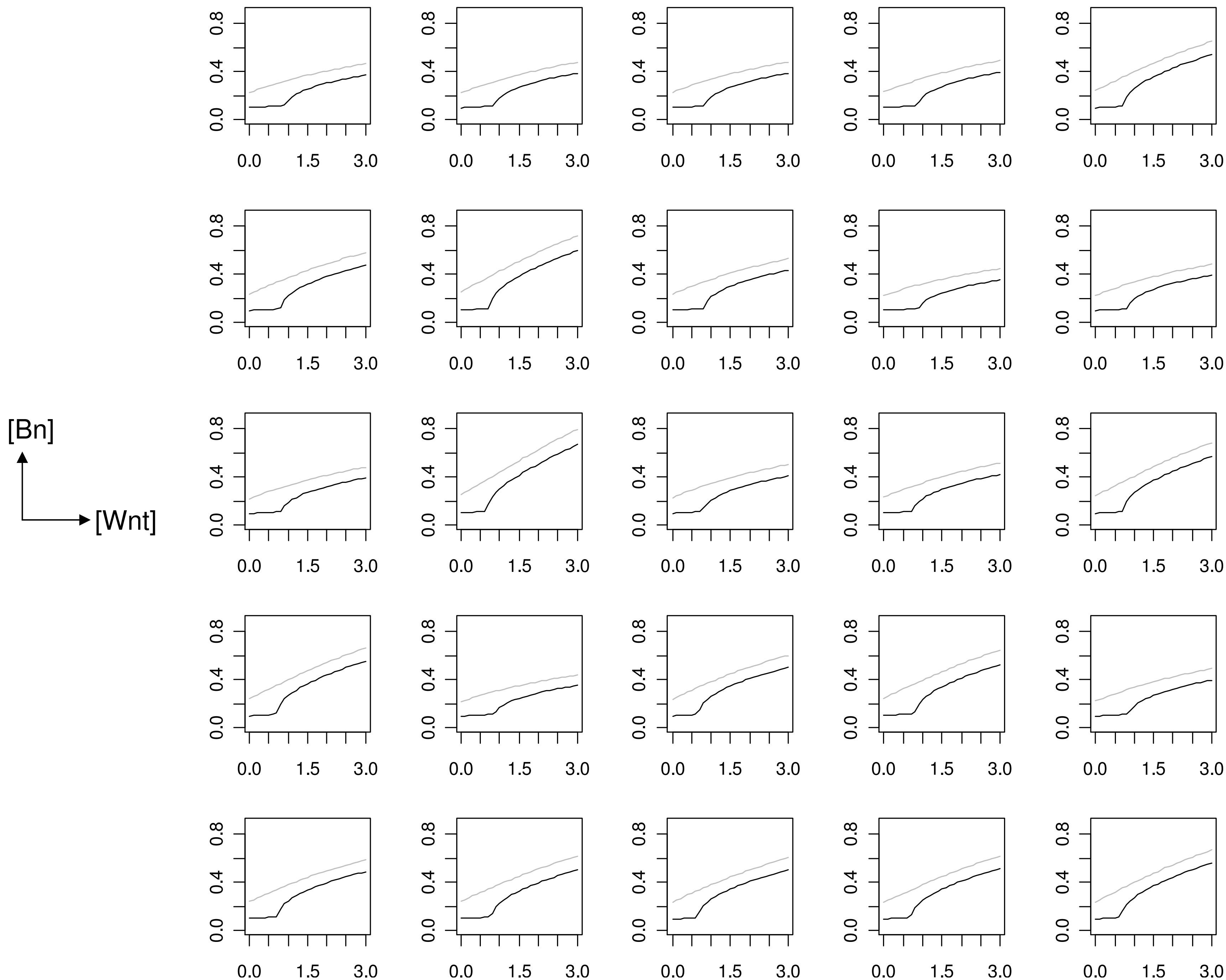


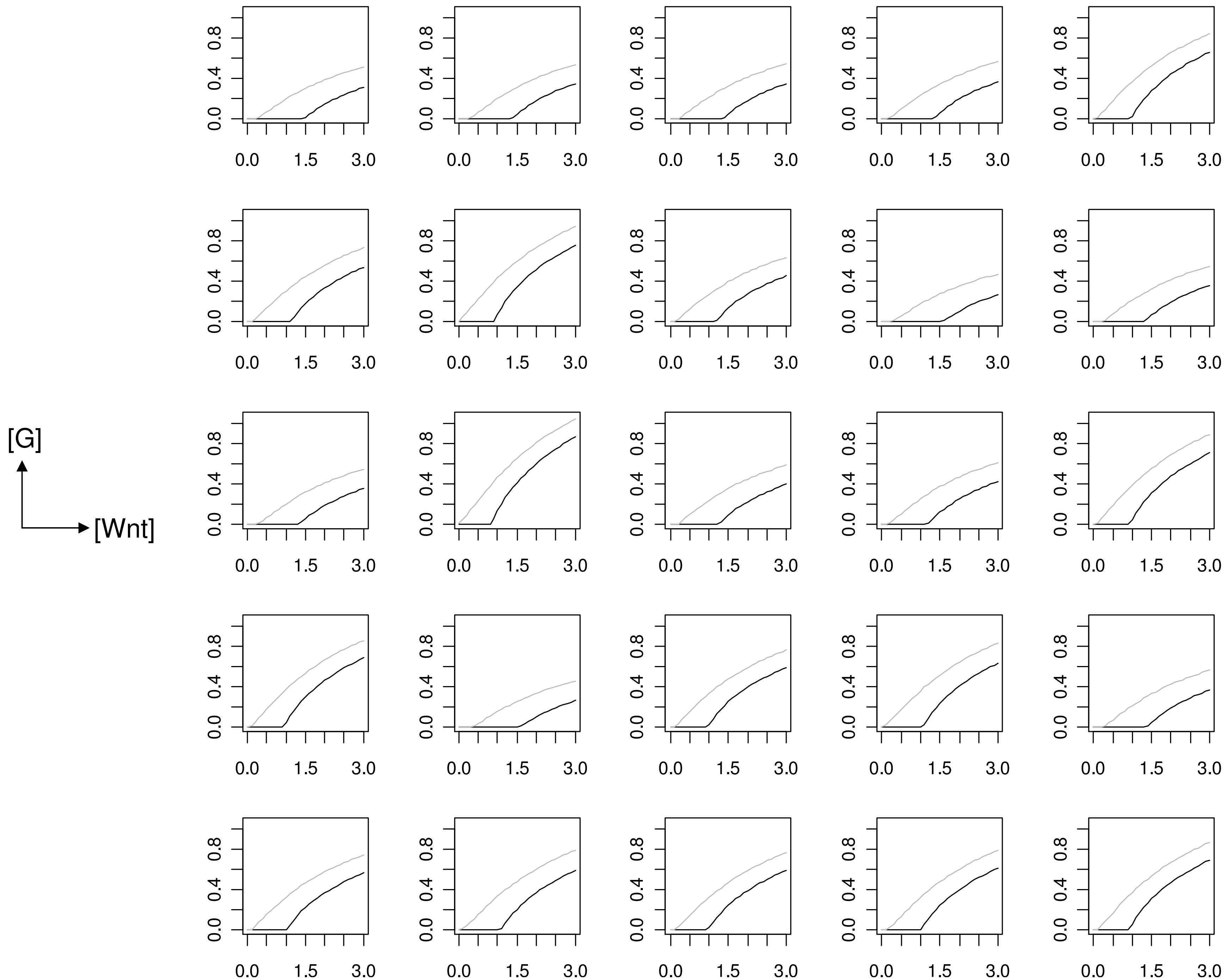
Example logNormal parameter distributions generated for MC simulations



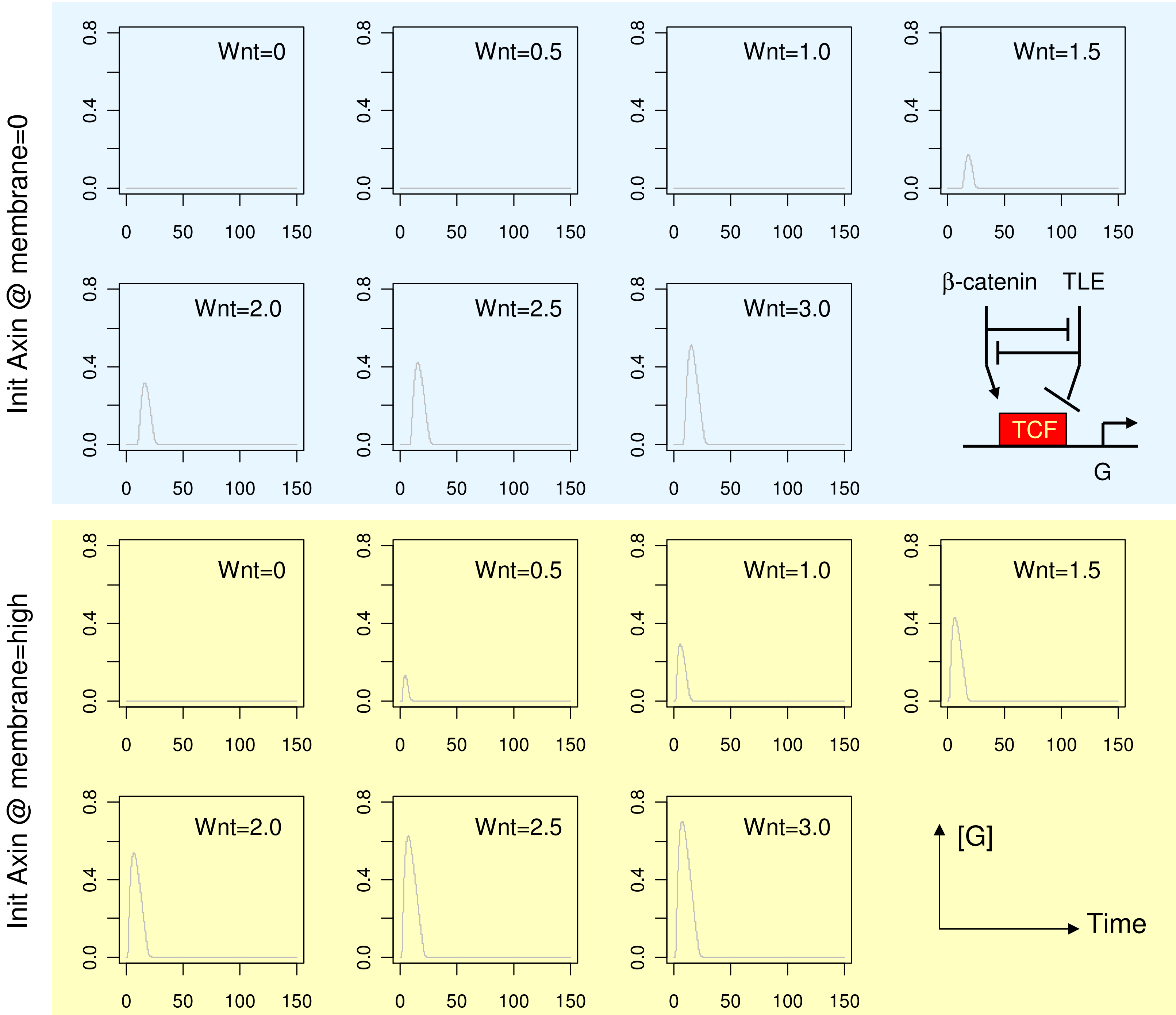


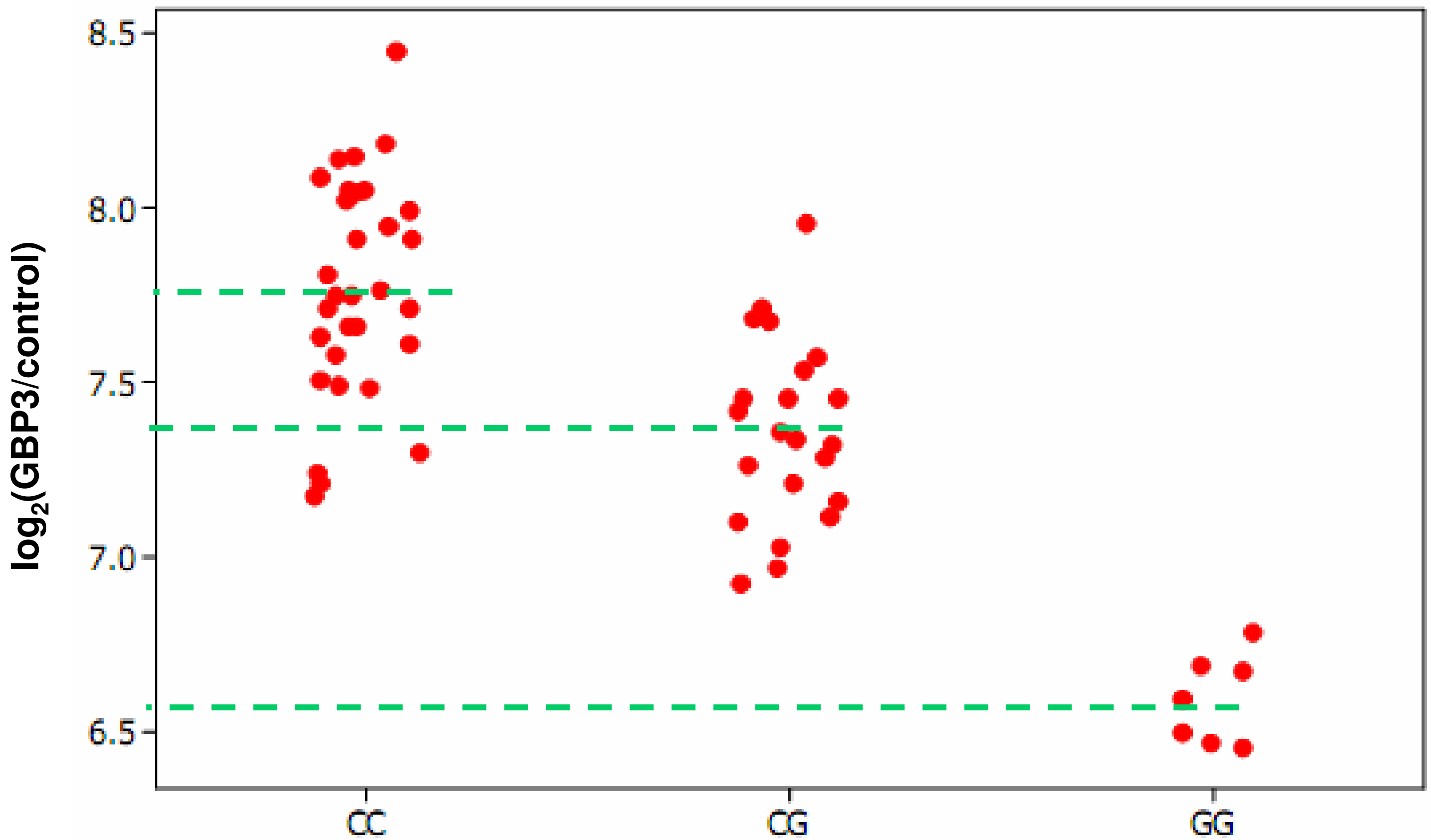
[Axin @ membrane]
[Wnt]


[Bn]
[Wnt]
0.0
0.4
0.8
0.0
1.5
3.0



[G]
[Wnt]
0.0
0.4
0.8
0.0
1.5
3.0


Init Axin @ membrane=0
Wnt=0
Wnt=0.5
Wnt=1.0
Wnt=1.5
Wnt=2.0
Wnt=2.5
Wnt=3.0
β-catenin
TLE
TCF
G
Init Axin @ membrane=high
Wnt=0
Wnt=0.5
Wnt=1.0
Wnt=1.5
Wnt=2.0
Wnt=2.5
Wnt=3.0
[G]
Time



Variation in *GBP3* gene expression for 3 haplotypes in 60 Europeans

Adapted from Stranger et al, Science 2007 (315):848-853