Table I: Initial State

Component	Mod	Loc	Component	Mod	Loc	Component	Mod	Loc	Component	Mod	Loc
4Fe4S	none	CLc	EgfR	none	CLm	Muc1	none	CLm	Rgl2	none	CLc
1433x1	none	CLc	Eif2	none	CLc	Myl9	none	CLc	Rgl3	none	CLc
1433x2	none	CLc	Eif3	none	CLc	Mylk	none	CLc	Rheb	GTP	CLi
1433x3	none	CLc	Eif4a1	none	CLc	Nck1	none	CLc	Rhoa	GDP	CLi
Abi1	none	CLc	Eif4e	none	CLc	Nckap1	none	CLc	Rhoq	GDP	CLc
Abi2	none	CLc	Eif4ebp1	none	CLc	Nfatc2	none	CLc	Rhpn1	none	CLi
Abl1	none	CLc	Eif4g1	none	CLc	Nfatc4	none	CLc	Rictor	none	CLc
Abl2	none	CLc	Elmo1	none	CLc	Nras	GDP	CLi	Rin1	none	CLc
ACC	none	CLc	Eps8	none	CLc	P38	none	CLc	Rock1	none	CLc
Aco1	none	CLc	Eps15	none	CLc	PA	none	CLm	Rps6	none	CLc
Actin	mono	CLc	ErbB2	none	CLm	Pag1	none	CLm	Rps6kb1	none	CLc
Adam17	none	CLo	Erk1	none	CLc	Pak1	none	CLc	Rras	GDP	CLi
Akt1	none	CLc	Erk2	none	CLc	PC	none	CLm	Rsk1	none	CLc
Ampk	none	CLc	Fer	none	CLi	Pdpk1	none	CLc	Rtkn	none	CLi
Ap2	none	CLc	Fnbp1l	none	CLc	Pfn1	none	CLc	Sh2d3c	none	CLc
Apc	none	CLc	Frap1	none	CLc	Pi3k	none	CLc	Sh3bgrl3	none	CLc
Araf	none	CLc	Gab1	none	CLc	PI4P	none	CLm	Sh3kbp1	none	CLc
Arfip2	none	CLi	Grb2	none	CLc	Pik3c2b	none	CLc	Shc1p46	none	CLc
ArhGef7	none	CLi	Gsk3	none	CLc	PIP2	none	CLm	Shc1p52	none	CLc
Arp23	none	CLc	Gsn	none	CLc	Pip5k1c	none	CLc	Shc1p66	none	CLc
Axin1	none	CLc	Hgs	none	CLi	Plcb	none	CLc	Shoc2	none	CLc
Bad	none	CLc	Hpk1	none	CLc	Plcd1	none	CLc	Smad2	none	CLc
Baiap2	none	CLi	Hras	GDP	CLi	Plce1	none	CLc	Smad3	none	CLc
Bcar1	none	CLc	Hspc300	none	CLc	Plcg1	none	CLc	Snca	none	CLc
Bmx	none	CLc	Inppl1	none	CLc	Pld1	none	CLc	Sos1	none	CLc
Braf	none	CLc	Integrins	none	CLm	Plscr1	none	CLm	Src	none	CLi
Brap	none	CLc	IqGap1	none	CLc	PP1	none	CLi	Ssh	none	CLc
Calm	none	CLc	Jak1	none	CLi	PP2a	none	CLc	Stat1	none	CLc
Camk2	none	CLc	Jak2	none	CLi	Ppp1ca	none	CLc	Stat3	none	CLc
Cbl	none	CLc	Jip1	none	CLc	Prkca	none	CLc	Stat5	none	CLc
Cblb	none	CLc	Jnk	none	CLc	Prkcd	none	CLc	Stk4	none	CLc
Cd2ap	none	CLc	Jun	none	NUc	Prkce	none	CLc	Stk11	none	CLc
Cdc42	GDP	CLi	Kras	GDP	CLi	Prkcl1	none	CLi	SynGap1	none	CLc
Cdc42ep1	none	CLc	Ksr1	phos	CLc	Prkcz	none	CLc	Tab1	none	CLc
Cdc42ep4	none	CLc	Ktn1	none	CLi	Pten	none	CLi	Tbk1	none	CLc
Choline	none	CLm	L1cam	none	CLm	Ptk2	none	CLi	Tiam1	none	CLc
Cit	none	CLi	Limk1	none	CLi	Ptk2b	none	CLi	Tln	none	CLc
Citrate	none	CLc	Lipe	none	CLi	Ptk6	none	CLc	Tmsb4x	none	CLc
Cofilin	none	CLc	Lst8	none	CLc	Ptpn6	none	CLc	Tnk2	none	CLc
Creb1	none	NUc	Map2k3	none	CLc	Ptpn11	none	CLc	Tns3	none	CLc
Crk	none	CLc	Map2k4	none	CLc	Pxn	none	CLc	Traf2	none	CLc
Crkl	none	CLc	Map2k6	none	CLc	Rac1	GDP	CLi	Trip10	none	CLi
Csk	none	CLc	Map2k7	none	CLc	Raf1	none	CLc	Tsc1	none	CLi
Csnk1	none	CLc	Map3k1	none	CLc	Rala	GDP	CLi	Tsc2	none	CLc
Ctnnb1	none	CLc	Map3k5	none	CLc	Ralbp1	none	CLi	Txn	red	CLc
Ctnnd1	none	CLc	Map4k4	none	CLc	RalGds	none	CLc	Ube2l3	ubiq	CLi
Cttn	none	CLc	Mapkap1	none	CLc	Rap1a	GDP	CLi	Usp6nl	none	CLc
Cyfip1	none	CLi	Mapkapk2	none	CLc	Rap2b	GDP	CLi	Vav2	none	CLc
Cyfip2	none	CLc	Marcks	none	CLi	RapGef1	none	CLc	Was	none	CLc
Dgk	none	CLi	Matk	none	CLc	RapGef6	none	CLc	Wasf1	none	CLc
Diaph1	none	CLc	Mcf2	none	CLc	Raptor	none	CLc	Wasf2	none	CLc
Dock1	none	CLc	Mek1	none	CLc	Rasa1	none	CLc	Wasl	none	CLc
Dok1	none	CLc	Mek2	none	CLc	RasGrf1	none	CLc	Waspip	none	CLc
Dok2	none	CLc	Mknk1	none	CLc	RasGrp3	none	CLc	Ywhab	none	CLc
Eef2	none	CLc	Mlk3	none	CLc	Rassf1	none	CLc	Ywhaq	none	CLc
Eef2k	none	CLc	Mras	GDP	CLi	Rassf5	none	CLc	Ywhaz	none	CLc
Egf	none	out	Msk1	none	CLc	Rgl1	none	CLc	Zap70	none	CLc

Table II: Protein States Resulting from Short Term Stimulus with Egf

Component	Modification	Location	Component	Modification	Location
Abl1	act	CLi	Muc1	Yphos	CLm
Akt1	act	CLi	Nck1	reloc	CLi
Ap2	reloc	CLi	Nras	GTP	CLi
Bmx	Yphos	CLi	P38	act	CLc
Braf	act	CLi	Pag1	Yphos	CLm
Cbl	Yphos	CLi	Pak1	act	CLi
Cblb	Yphos	CLi	Pi3k	act	CLi
Cdc42	GTP	CLi	Pik3c2b	reloc	CLi
Cofilin	phos	CLc	Plcg1	act	CLi
Creb1	act	NUc	Plscr1	act	CLm
Crk	Yphos	CLi	Ptk2b	act	CLi
Crkl	reloc	CLi	Ptk6	act	CLi
Csk	reloc	CLi	Ptpn6	act	CLi
Ctnnb1	reloc	CLi	Ptpn11	Yphos	CLi
Ctnnd1	Yphos	CLi	Pxn	Yphos	CLi
Dok1	Yphos	CLi	Rac1	GTP	CLi
Dok2	Yphos	CLi	Raf1	act	CLi
Eps15	Yphos	CLi	Rala	GTP	CLi
ErbB2	act	CLm	RalGds	reloc	CLi
Erk1	act	CLi	Rap1a	GTP	CLi
Erk2	act	CLi	Rap2b	GTP	CLi
Fer	Yphos	CLi	RapGef1	act	CLi
Gab1	Yphos	CLi	Rasa1	reloc	CLi
Grb2	reloc	CLi	RasGrf1	act	CLi
Gsk3	Sphos	CLc	RasGrp3	act	CLi
Hgs	Yphos	CLi	Rsk1	act	CLi
Hpk1	act	CLi	Sh2d3c	Yphos	CLi
Hras	GTP	CLi	Sh3bgrl3	reloc	CLi
Inppl1	Yphos	CLi	Sh3kbp1	ubiq	CLi
Jak1	act	CLi	Shc1	Yphos	CLi
Jak2	act	CLi	Shc1p66	Yphos	CLi
Jnk	act	CLc	Shoc2	reloc	CLi
Jun	act	NUc	Src	act	CLi
Kras	GTP	CLi	Stat1	act	CLi
Map3k1	act	CLi	Stat3	act	CLi
Mapkapk2	act	CLc	Stat5	act	CLi
Mcf2	Yphos	CLi	Stk11	act	CLi
Mek1	act	CLi	Tnk2	act	CLi
Mknk1	act	CLc	Tns3	Yphos	CLi
Mlk3	act	CLi	Usp6nl	Yphos	CLi
Mras	GTP	CLi	Vav2	act	CLi
Msk1	act	CLc	Ywhaz	reloc	CLi

Table III: Proteins Required for Erk activation by EGF (less than 20 min)

Protein	Requires	Inhibition Method	Activation Assay*	Reference
Braf	no	Knock-out	phos(TEY)	15199148
Braf	yes	siRNA	phos(TEY)	15258589
Braf	yes	Dominant-Negative	phos(TEY)	16093354
cPKCs	no	Go6976	phos(TEY)	11358964
EgfR	yes	AG1478	phos(TEY)	11907028
Eps8	no	Knock-out	IPKA(MBP)	11099046
Gab1	yes	Dominant-Negative	IPKA(MBP)	10788507
Gab1	yes	Dominant-Negative	IPKA(MBP)	11323411
Gab1	partial	Knock-out	phos(TEY)	12667697
Hras	yes	Dominant-Negative	IPKA(MBP)	11524436
Hras	yes	Dominant-Negative	phos(TEY)	12169697
Hras	no	siRNA	phos(TEY)	16980617
IqGap1	yes	siRNA	phos(TEY)	14970219
Map3k1	?	Dominant-Negative	IPKA(EgfR)	9305638
Map3k1	no	Knock-out	phos(TEY)	12048245
Map3k2	no	Dominant-Negative	IPKA(EgfR)	9305638
Map3k3	no	Dominant-Negative	IPKA(EgfR)	9305638
Map3k4	no	Dominant-Negative	IPKA(EgfR)	9305638
Mapkap1	no	Knock-out	phos(TEY)	16962653
Meks	yes	PD184352	phos(TEY)	11909979
Mlk3	yes	siRNA	phos(TEY)	15258589
Mlk3	yes	siRNA	phos(TEY)	16537381
Mras	no	Knockout	phos(TEY)	16980617
Mras/Hras	no	Knock-out/siRNA	phos(TEY)	16980617
Msk1	no	Knock-out	phos(TEY)	11909979
Msk1/Msk2	no	Double Knock-out	phos(TEY)	11909979
Msk2	no	Knock-out	phos(TEY)	11909979
nPKCs	no	GF109203X	phos(TEY)	10671553
nPKCs	no	GF109203X	phos(TEY)	11358964
P38	no	SB203580	phos(TEY)	11909979
Pak1	no	Knock-out	phos(TEY)	16129686
Pak1/Pak2	no	Double Knock-out	phos(TEY)	16129686
Pi3k	no	Wortmannin	phos(TEY)	10671553
Pi3k	partial	Wortmannin	phos(TEY)	16687399
Ppp2r1a	no	siRNA	phos(TEY)	16129692
Ptk2b	partial	Dominant-Negative	phos(TEY)	14963068
Raf1	no	Knock-in	IPKA(MBP)	11296227
Raf1	no	Knock-in	phos(TEY)	11296227
Raf1	no	Knock-out	phos(TEY)	11296227
Raf1	no	Knock-out	IPKA(MBP)	11296227
Raf1	no	Knock-out	phos(TEY)	11296228
Raf1	no	Knock-out	phos(TEY)	12048245
Raf1	yes	siRNA	phos(TEY)	15258589
Raf1	yes	Dominant-Negative	phos(TEY)	16093354
Rala	?	Dominant-Negative	phos(TEY)	10675331
Shoc2	?	siRNA	phos(TEY)	16630891
Sos1	no	Knock-out	IPKA(MBP)	10675333
Src	partial	Dominant-Negative	phos(TEY)	14963068

*Assay Abbreviations:
phos(TEY): Western Blot with Antibody to phospho-Erk1-T201/Y203 and phospho-Erk2-T184/Y186
IPKA(MBP): Erk1/2 immunoprecipitation kinase assay using MBP as substrate
IPKA(EefR): Erk1/2 immunoprecipitation kinase assay using an EgfR peptide as substrate

Glossary

- **Chemical**: a small molecule
- **Common Rules**: Maude Rules that are are based on state changes caused by expressed proteins.
- **Component**: a protein, protein family, protein composite, chemical, nucleic acid, or a stimulus
- **Braf:** a Pathway Logic Protein name
  - Synonyms: B-Raf proto-oncogene serine/threonine-protein kinase, p94, Oncogene BRAF, v-Raf murine sarcoma viral oncogene homolog B1, BRAF1, RAFB1, Rmil
  - Swiss Protein Assession Number: P15056
  - Hugo Gene Symbol: BRAF
- **Egf**: a Pathway Logic protein name
  - Synonyms: Epidermal growth factor, Urogastrone, Pro-epidermal growth factor precursor
  - Swiss Protein Assession Number: P01133
  - Hugo Gene Symbol: EGF
- **EgfR**: a Pathway Logic protein name
  - Synonyms: Epidermal growth factor receptor precursor, ERBB1, Receptor tyrosine-protein kinase ErbB-1
  - Swiss Protein Assession Number: P00533
  - Hugo Gene Symbol: EGFR
- **Egf Rules**: Maude Rules that are based on state changes caused by short term Egf treatment.
- **Erk1**: a Pathway Logic protein name
  - Synonyms: Mitogen-activated protein kinase 3, Erk1, Extracellular signal-regulated kinase 1, Insulin-stimulated MAP2 kinase, MAP kinase 1, MAPK 1, p44-ERK1, ERT2, p44-MAPK, Microtubule-associated protein-2 kinase, ERK1, PRKM3
  - Swiss Protein Assession Number: P27361
  - Hugo Gene Symbol: MAPK3
- **Erk2**: a Pathway Logic protein name
  - Synonyms: Mitogen-activated protein kinase 1, 42 kDa mitogen-activated protein kinase, Erk2, Extracellular signal-regulated kinase 2, Mitogen-activated protein kinase, MAP kinase 2, MAPK 2, p42-MAPK, ERT1, ERK2, PRKM1, PRKM2, Mapk2, Mapk1, ERK-2
  - Swiss Protein Assession Number: P28482
  - Hugo Gene Symbol: MAPK1
- **Evidence Item**: a shorthand summary of a published experiment used as evidence for a Rule
- **Fire**: the execution of a rule
- **Gab1**: a Pathway Logic protein name
  - Synonyms: GRB2-associated binding protein 1; GRB2-associated binder-1
  - Swiss Protein Assession Number: Q13480
  - Hugo Gene Symbol: GAB1
- **Goal**: an occurrence to be reached.
- **Grb2**: a Pathway Logic protein name
  - Synonyms: for Growth factor receptor-bound protein 2, GRB2 adapter protein, SH2/SH3 adapter GRB2, Abundant Src homology protein, Ash protein, Ash
  - Swiss Protein Assession Number: P62993
  - Hugo Gene Symbol: GRB2
- **Jnk1**: a Pathway Logic protein name
  - Synonyms: Mitogen-activated protein kinase 8; Stress-activated protein kinase, SAPK1c; c-Jun N-terminal kinase 1, JNK-46, JNK1, PRKM8
  - Swiss Protein Assession Number: P45983
  - Hugo Gene Symbol: MAPK8
- **Jnk2**: a Pathway Logic protein name
  - Synonyms: Mitogen-activated protein kinase 9; Stress-activated protein kinase, SAPK1a; Jnk2, c-Jun N-terminal kinase 2, JNK-55, JNK2, PRKM9
  - Swiss Protein Assession Number: P45984
  - Hugo Gene Symbol: MAPK9• **Jnk3**: a Pathway Logic protein name
  - Synonyms: Mitogen-activated protein kinase 10; Jnk3, Stress-activated protein kinase JNK3; c-Jun N-terminal kinase 3; MAP kinase p49, 3F12, JNK3, JNK3A, PRKM10
  - Swiss Protein Assession Number: P53779
  - Hugo Gene Symbol: MAPK10

Glossary (continued)

- **Jnk**: a Pathway Logic protein-family name
  - Members: Jnk1, Jnk2, Jnk3
- **Location**: specific cellular compartment
  - Locations are abbreviated using upper case letters to represent the compartment and the lower case letters o, m, i, and c to represent the outer surface, the membrane, the inside surface, and the interior of the compartment, respectively.
  - Examples of cellular compartments are the following:
    CL - Cell, NU - Nucleus, MO - Mitochondria Outer Compartment, MI - Mitochondria Inner Compartment,
    ER - Endoplasmic Reticulum, GA - Golgi Apparatus, LE - Late Endosome, EE - Early Endosome,
    LY - Lysosome, CP - Clathrin Coated Pit
- **LoLa**: (a Low Level Petri Net Analyzer) a non commercial tool developed by Karsten Schmidt at Humboldt-Universität zu Berlin.
- **Mek1**: a Pathway Logic protein name
  - Synonyms: Dual specificity mitogen-activated protein kinase kinase 1, MAPKK 1; MAP kinase kinase 1; ERK activator kinase 1; MAPK/ERK kinase 1; MKK1; PRKMK1
  - Swiss Protein Assession Number: Q02750
  - Hugo Gene Symbol: MAP2K1
- **Mek2**: a Pathway Logic protein name
  - Synonyms: Dual specificity mitogen-activated protein kinase kinase 2; MAP kinase kinase 2; MAPKK 2; ERK activator kinase 2; MAPK/ERK kinase 2; MEK2; MKK2; PRKMK2A
  - Swiss Protein Assession Number: P36507
  - Hugo Gene Symbol: MAP2K2
- **Mlk3**: a Pathway Logic protein name
  - Synonyms: Mitogen-activated protein kinase kinase kinase 11; Mlk3, Mixed lineage kinase 3; SPRK, Src-homology 3 domain-containing proline-rich kinase; PTK1
  - Swiss Protein Assession Number: Q16584
  - Hugo Gene Symbol: MAP3K11
- **Modification**: any change to the state of a component that is consistent both with the biology described by a particular model and its level of abstraction
  - examples: act (for activation), on (for induced gene expression), reloc (for proteins relocated to another location)
- **Occurrence**: component, it's modifications, and it's location.
  - An occurrence is represented by an oval or "place" in Petri net notation.
- **Path**: also called a LoLa Path; sequence of transitions reaching some state• **Petri net**: a directed bipartite graph with nodes representing either "places" (represented by circles) or "transitions" (represented by rectangles).
- **Place:** an oval node in a Petri net
- **PMID**: PubMed ID, A unique identifier for an article in the PubMed database
- **Prkcz**: a Pathway Logic protein name
  - Synonyms: Protein kinase C, zeta; nPKC-zeta; PKC2
  - Swiss Protein Assession Number: Q05513
  - Hugo Gene Symbol: PRKCZ• **Protein**: a gene product made up of amino acids.
- **Protein Composites**: complexes of different proteins that are treated by source data as a functional unit.
  - Example: "Ampk" consists of a catalytic alpha-subunit (Prkaa1 or Prkaa2), a regulatory beta-subunit (Prkab1 or Prkab2), and a regulatory gamma- subunit (Prkag1, Prkag2, or Prkag3).
- **Protein Family**: groups of stucturally and functionally related proteins that are treated by the soure data as indistinquishable.
  - Example: the "Erk" family includes Erk1 and Erk2, which are considered functionally equivalent.
- **Ptpn11**: a Pathway Logic protein name
  - Synonyms: Protein-tyrosine phosphatase, non-receptor type 11; Protein-tyrosine phosphatase 2C, PTP-2C; PTP-1D: SH-PTP3; SH-PTP2; SHP-2; PTP2C; SHPTP2; SH2 containing protein tyrosine phosphatase 2; Tyrosine phosphatase SHP2; Syp; SHPTP3; SHPTP2
  - Swiss Protein Assession Number: Q06124
  - Hugo Gene Symbol: PTPN11
- **Raf1**: a Pathway Logic protein name
  - Synonyms: RAF proto-oncogene serine/threonine-protein kinase; Transforming replication defective murine retrovirus 3611-MSV; Raf-1; C-RAF; cRaf; RAF; Oncogene MIL
  - Swiss Protein Assession Number: P04049
  - Hugo Gene Symbol: RAF1

Glossary (continued)

- **Rala:** a Pathway Logic name
  - Synonyms: Ras-related protein Ral-A, Ras like protein A, V-Ral simian leukemia viral oncogene homolog A, RAL
  - Swiss Protein Assession Number: P11233
  - Hugo Gene Symbol: RALA
- **RasGef**: a Ras guanyl-nucleotide exchange factor
  - a protein that stimulates the exchange of guanyl nucleotides by a GTPase of the Ras superfamily
- **RasGrf1**: a Pathway Logic protein name
  - Synonyms: Guanine nucleotide releasing protein GNRP, Ras-specific nucleotide exchange factor CDC25
  - Swiss Protein Assession Number: Q13972
  - Hugo Gene Symbol: RASGRF1
- **RasGrf2**: a Pathway Logic protein name
  - Synonyms: Ras protein-specific guanine nucleotide-releasing factor 2; GRF2; Ras-GRF2
  - Swiss Protein Assession Number: O14827
  - Hugo Gene Symbol: RASGRF2
- **RasGrp1**: a Pathway Logic protein name
  - Synonyms: RAS guanyl releasing protein 1 (calcium and DAG-regulated); Calcium and DAG-regulated guanine nucleotide exchange factor II; CALDAG-GEFII; RASGRP
  - Swiss Protein Assession Number: O95267
  - Hugo Gene Symbol: RASGRP1
- **RasGrp3**: a Pathway Logic protein name
  - Synonyms: RAS guanyl releasing protein 3 (calcium and DAG-regulated); Calcium and DAG-regulated guanine nucleotide exchange factor III; Guanine nucleotide exchange factor for Rap1; KIAA0846; GRP3
  - Swiss Protein Assession Number: Q8IV61
  - Hugo Gene Symbol: RASGRP3
- **RasGrp4**: a Pathway Logic protein name
  - Synonyms: RAS guanyl releasing protein 4; Guanyl nucleotide releasing protein 4
  - Swiss Protein Assession Number: Q8TDF6
  - Hugo Gene Symbol: RASGRP4
- **Requirement**: a protein which is required to be present in order for another protein to go through a state change in response to a stimulus.
- **Rule**: a reaction, represented by a rectangle or "transition" in Petri net notation.
- **Sos1**: a Pathway Logic protein name
  - Synonyms: Son of sevenless protein homolog 1; SOS-1; SOS1 guanine nucleotide exchange factor; Son of sevenless, drosophila homolog 1
  - Swiss Protein Assession Number: Q07889
  - Hugo Gene Symbol: SOS1
- **Src**: a Pathway Logic protein name
  - Synonyms: Proto-oncogene tyrosine-protein kinase Src; Avian sarcoma virus protein, ASV; Tyrosine kinase pp60c-src; Tyrosine protein kinase SRC-1; Protooncogene SRC, Rous sarcoma; v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog; p60-Src; c-Src; SRC1
  - Swiss Protein Assession Number: P12931
  - Hugo Gene Symbol: SRC
- **State change**: a change in a component's modification and/or a location.
- **State**: the modification and location of a component
- **Subnet**: a portion of a Petri net
  - If a goal is declared then everything not involved in reaching the goal is removed. If avoids are declared, a new Petri net is made from an initial state with the avoided components removed.
- **Transition:** a rectangular node in a Petri net
- **Ywhaz**: a Pathway Logic protein name
  - Synonyms: 1433z; 14-3-3 protein zeta/delta; KCIP-1; Protein kinase C inhibitor protein 1; Tyrosine 3 monooxygenase/tryptophan 5 monooxygenase activation protein, zeta isoform; Brain protein 14-3-3, zeta isoform; FAS; Factor activating exoenzyme S; Phospholipase A2
  - Swiss Protein Assession Number: P63104
  - Hugo Gene Symbol: YWHAZ