Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
GENERAL INTRODUCTION				
Representation	Process diagram representation. Process diagram is a state transition diagram. It represents a sequence of interactions as a state transition diagram.	Entity-relationship representation. First to produce canonical representation for molecular interactions. Heuristic Molecular Interaction Maps (MIM) are not restricted to a particular cell type or cell state and do not indicate a particular sequence of events. They show interactions that can occur if the relevant molecules are present.	Process diagram representation. PATIKA supports graph based representation at two levels. Bioentity level: o genetic, chemical and physical entities o interactions Mechanistic level: o Bioentities have states o Every state is associated with one or more transitions o A state is a substrate, a product or an effecter of a particular transition.	Emphasise logical interactions, sub cellular localisation and the state of species. o Provides an overview of a pathway o provides a mechanism to organise a pathway diagram hierarchically o Separating the logical representation from biochemical representation o Computationally rigorous notations
Aims of the Notations	**Requirements of a successful diagram scheme** o Allow representation of diverse biological objects and interactions o Be semantically and visually unambiguous o Be able to incorporate notations o Allow software tools to convert a graphically represented model into mathematical formulas for analysis and simulation o Have software support to draw the diagrams o Ensure that the community can freely use the notation scheme	**Aspects of MIM** o Show all of the known interactions o Allow the unknown contingencies to be left unspecified until they become available o Consistent and unambiguous representation of interactions	**Motivation** o To be able to store, integrate, access and analyze data about cellular processes at molecular level	**Aims of the Notations** o Provide a compact view of a signalling pathway o Provide a logical view of the interactions in the pathway o Show the sub cellular localisation of the interactions in the pathway o Allow for incomplete knowledge o Enable quantitative analysis of the pathway o Map to an unambiguous computational representation o Be understandable by biologist
Software Tool Support	CellDesinger, graphical editing software that has been developed to support visual editing of process diagrams.	There is no software tool to create MIM efficiently.	Pathway analysis tool for integration and knowledge acquisition (PATIKA) providing an integrated, multi-user environment for visualizing and manipulating network of cellular events.	Jak/Stat
Temporal order of reactions and states of molecules and complexes	Explicitly represents the temporal order of reactions and states of molecules and complexes at the cost of an increased number of nodes and lines in the diagram.	The interactions depicted in MIM are not limited to a linear sequence of events.	Explicitly represents the temporal order of reactions and states of molecules and complexes at the cost of an increased number of nodes and lines in the diagram.	Explicitly represents the temporal order of reactions and states of molecules and complexes without increased number of nodes.

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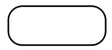
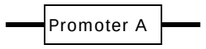
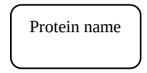
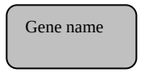
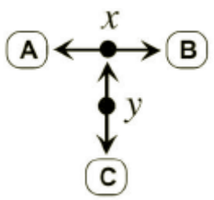
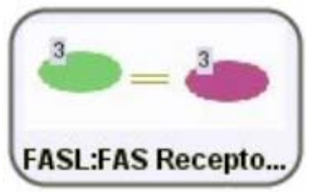
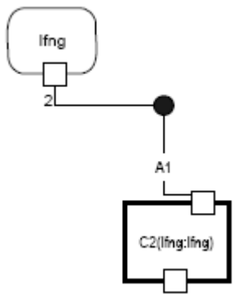
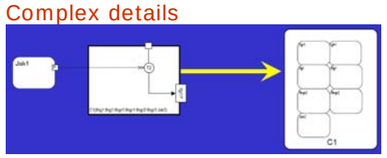
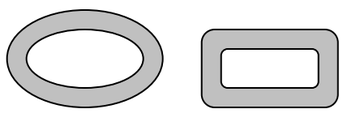
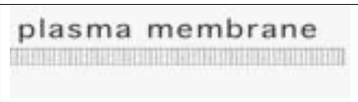
BIOLOGICAL ENTITIES				
Entity	**States** There are several types of state nodes. o Protein o Receptor o Ion channel (closed) o Ion channel (open) o Truncated protein o Gene o RNA o Anti-sense RNA o Ion o Simple Molecule o Unknown o Phenotype o Homodimer Each of these has a different shape.	**Named species** Elementary species are associated with a rectangle with round corners and are named.  DNA elements such as promoters, are represented by a box. 	**Bioentity** Biological or chemical groupings as bioentities and 'minor' changes in their information context are represented as states. Eg: a p53 protein may be in native, phosphorylated, and MDM2-bound forms. Several types of graphical notations bioentity view and mechanistic view o Protein, DNA, RNA, physical factor, small molecule Mechanistic view elements have filled icons oppose to non filled bioentity view elements.	**Species** Two species are described o Protein: a gene product that will be a monomeric protein. Multimers may be represented, but will be treated as an atomic unit. Must have at least one state.  o Gene: Must have at least one state. 
Complexes	A state node that have an N-tree data structure Members of a molecular complex may independently participate in different transitions.	Complex species are combinations or modifications of elementary species.  Node x is complex (A:B). Node y represents complex (A:B):C.	 A molecular complex with two states. Each member of a molecular complex is treated as a new state of its biological entity. The binding relations among complex members are denoted by double edges. Members of a molecular complex may independently participate in different transitions as well as the complex itself. Molecular complexes cannot be nested. Complexes have no bioentity associated with it.	A complex is an amalgam of protein subunits. It must have at least one state.  Complex details 
Compartments	Compartments are represented using a round edged rectangle or an oval. 	 Compartments can be of any shape.	Uses notion of compartments. Compartments are represented by resizable simple rectangles maintaining actual neighbourhood relations of real sub cellular locations. This is used to support easy editing and effective automated layout of pathways.	Uses notion of compartments. Compartments are divided using lines.

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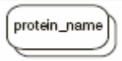
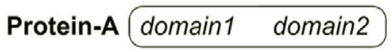
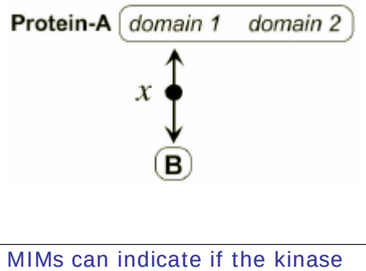
Homomer	 N-mer is represented by N stacked symbols	Homomers cannot be represented using Kohn's representation.	 The number written on the figure represents the value of N in N-mer.	
Protein domains	Protein symbol does not allow users to specify protein domains.	Can specify protein domains  Interactions details of individual domains can be expressed using this notation. 	Protein domains cannot be represented.	
Types of kinase activities	Do not make a distinction between types of kinase activities.	MIMs can indicate if the kinase activity is Ser/Thr/Tyr. However it does not use a different icon to represent kinase activity.	Do not make a distinction between types of kinase activities.	Do not make a distinction between types of kinases activities.
Species representation when it is used in multiple reactions	One state only appears once on the map. Multiple entities are used when a molecule is involved in lot of reactions for example ATP in metabolic pathways.	Named species appear in only one place on the map by convention. Molecular species that participate in multiple complexes or interactions are depicted as nodes on the interaction lines that describe each complex or interaction. Multiple entities are used when a molecule is involved in lot of reactions for example ATP in metabolic pathways.	PATIKA states are not duplicated. However, mechanistic entities are duplicated when the related biological entity is ubiquitous, such as ATP or water.	One species per localisation compartment and describes processes as state transitions.

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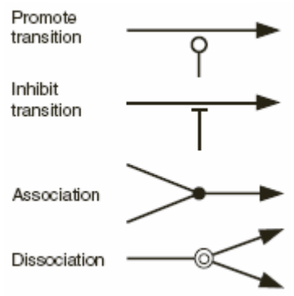
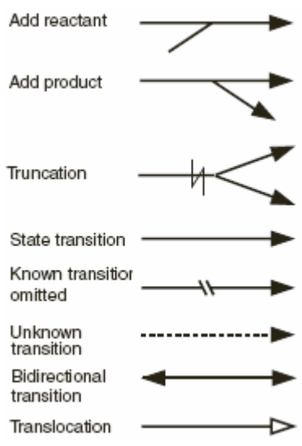
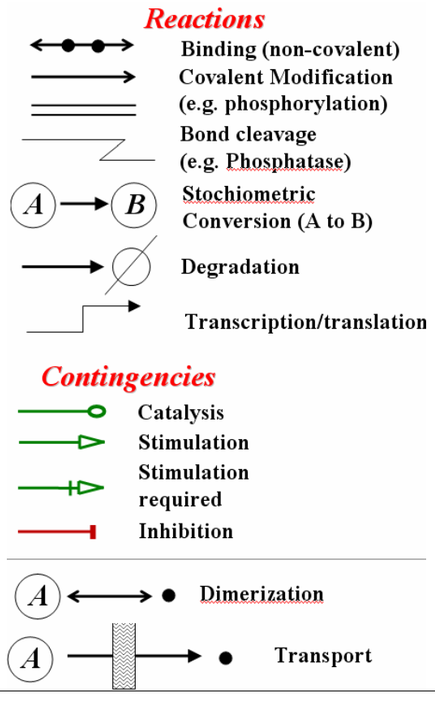
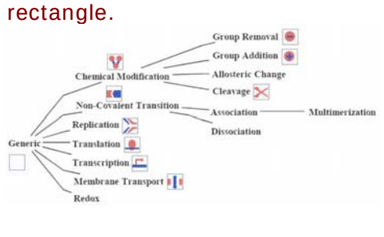
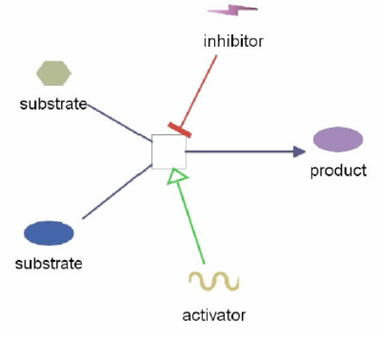
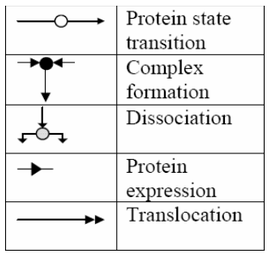
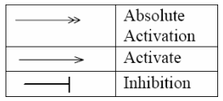
REACTIONS				
Interactions	Different connecting lines are used to represent different interactions to draw unambiguous diagrams. **Transition nodes**  **Edges**  	Different connecting lines are used to represent different interactions to draw unambiguous diagrams. Interaction lines can change direction but not by more than 90 degrees at a corner to prevent ambiguities at branch points. Two types of interactions: o reactions – operate on molecular species o contingencies – operate on reactions or on other contingencies ***Reactions***  ***Contingencies*** 	A transition occurs only when all of its substrates are present and activation conditions are satisfied. o Exhaustive transition When equilibrium constant of a transition is relatively much higher than the others. o Cooperative transition Transitions having the same order of equilibrium constant. Transitions are associated with a rectangle.  Connections between states and transitions.  	**Transitions and processes**  **Activation and dependences** 

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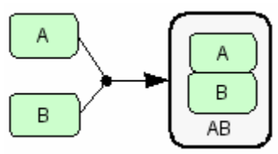
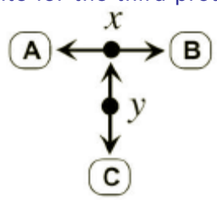
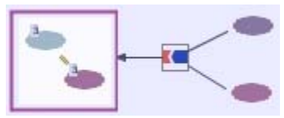
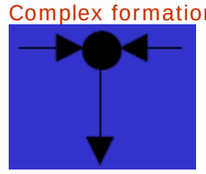
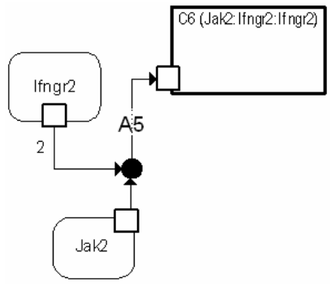
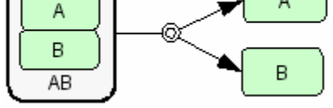
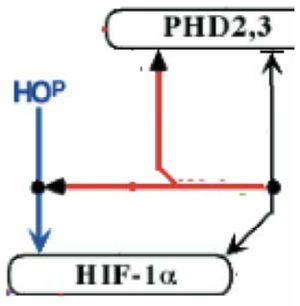
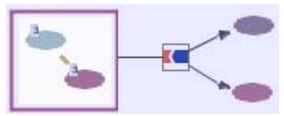
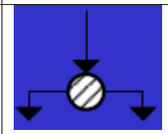
Association	**Association** Protein A and B binds to form complex C. However it does not show which protein has a binding site. 	Product of an interaction is indicated by placing a small filled circle on the line. This reduces crowding in a diagram. This diagram does not show which of the two proteins in the dimer contains binding site for the third protein.  Here A has two binding sites, one site for B and a different site for C. 	However it does not show which protein has a binding site. 	**Complex formation** Complex formation  Complex formation of a homodimer 
Dissociation	Complex C is separated into protein A and protein B. 	Reversible binding arrows can be used to represent dissociation. Unidirectional reactions, such as irreversible dissociations, are depicted as stoichiometric conversion (complex converted into its components). This convention is used in explicit MIMs to guide biological simulations.  The complex of PHD2,3 and HIF-1 alpha dissociates into PHD2,3 and the modified HIF-1 alpha.		

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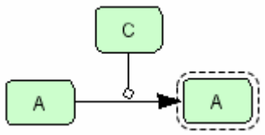
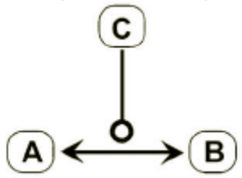
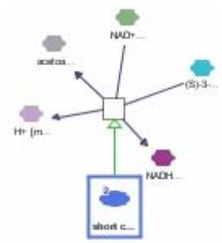
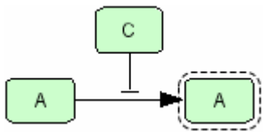
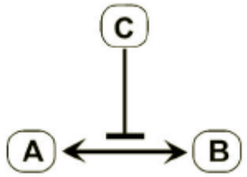
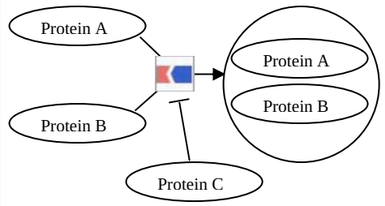
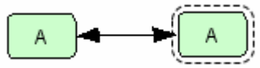
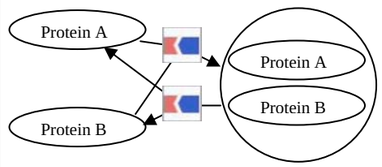
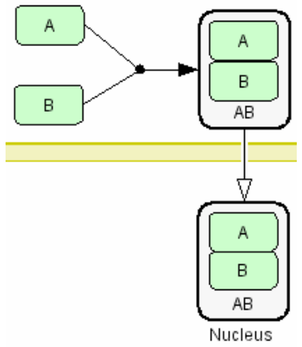
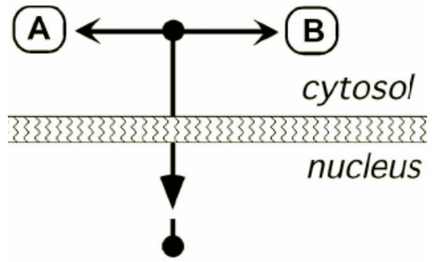
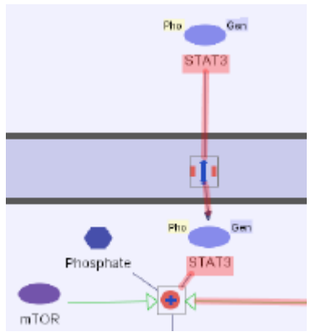
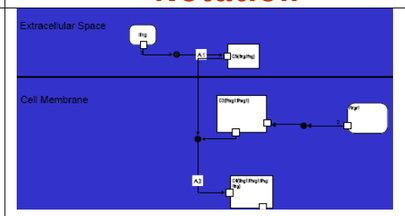
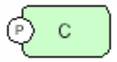
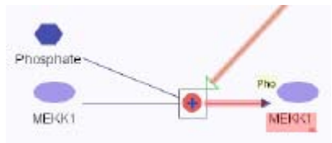
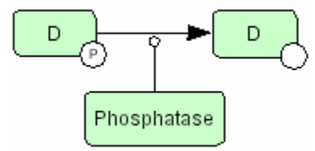
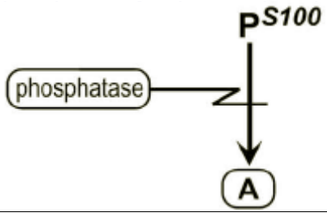
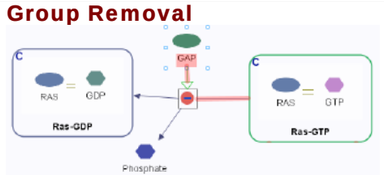
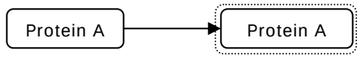
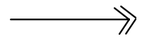
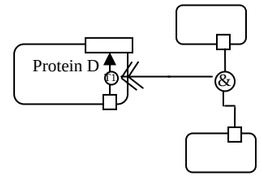
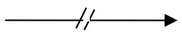
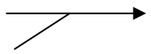
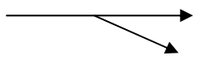
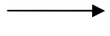
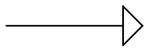
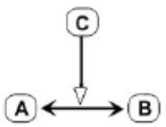
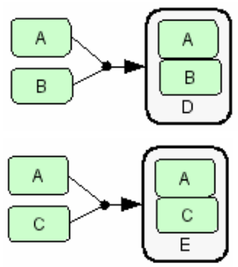
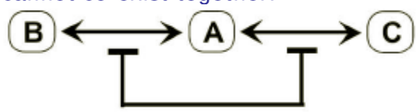
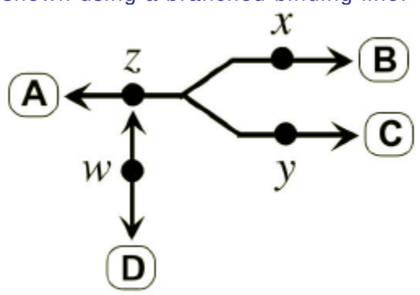
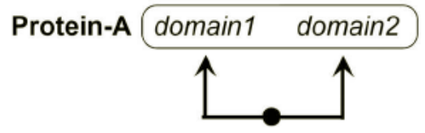
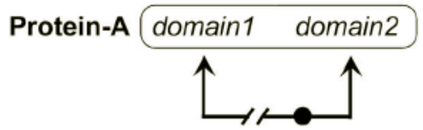
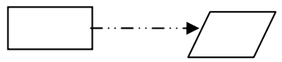
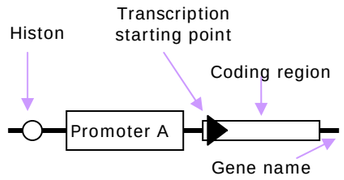
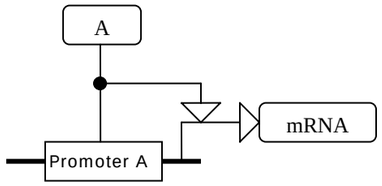
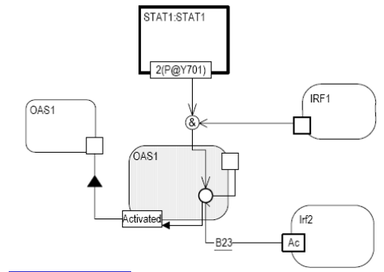
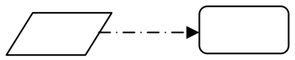
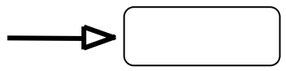
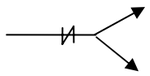
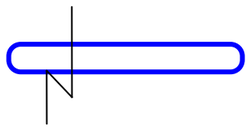
Promote	**Promote transition** Promotes state transitions. 	**Catalyzed binding or dissociation** 	**Activator** 	Initiates of a state transition. Only a protein or complex state can activate.  Only one activation arrow can link to a state transition. If more are required a logic gate must be used
Inhibited binding	Causes state transition not to occur. 			Causes a state transition not to occur. 
Bidirectional transition	**Bidirectional transition** 	**Non-covalent (reversible) binding** 	There is no explicit symbol to represent reversible bindings however this type of reactions can be expressed using combination of association and disassociation reactions. 	

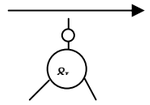
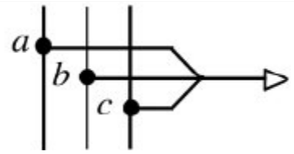
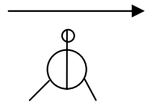
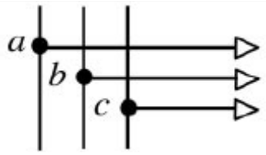
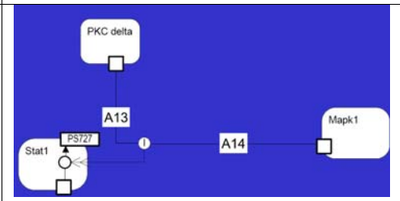
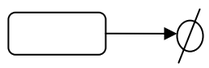
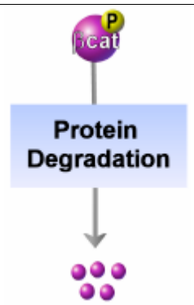
Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
Translocation	Translocation is shown using an arrow with unfilled arrow head. 	A:B dimer translocated into nucleus is shown using an isolated node convention.  MIM treats translocation of a molecule as a stoichiometric reaction where the molecule disappear from one place and an equal number of the same molecule appear at another place.	membrane transport  	 
Chemical addition	**Residue states** Represented by circles on the round-corner-box associated with the type and location of the residue.  Currently supported residues; empty, don't care, unknown, phosphorylated, acetylated, ubiquitinated, methylated, hydroxylated.	**Covalent modification** Node x is phosphorylated A  Covalent modification: phosphrylation, acetylation, myristoylation, ubiquitination.	**Group addition**  	State transition diagram is used to draw a high level view of phosphorylation and Kitano's notations are used to show the hidden details.
Cleavage of a covalent bond	**Dephosphorylation** Kitano uses state transitions to show dephosphorylation. 	**Cleavage of a covalent bond** Dephosphorylation – removal of a phosphate by a protein phosphatise. 	**Group Removal** 	State transition diagram is used to draw a high level view of dephosphorylation and Kitano's notations are used to show the hidden details.

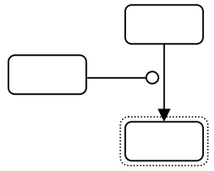
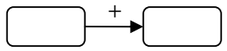
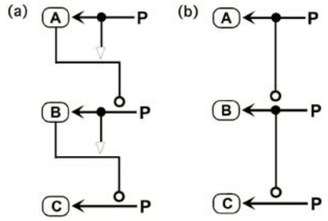
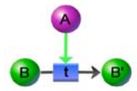
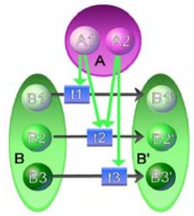
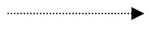
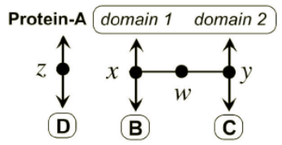
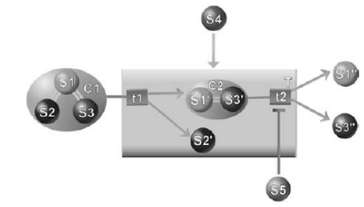
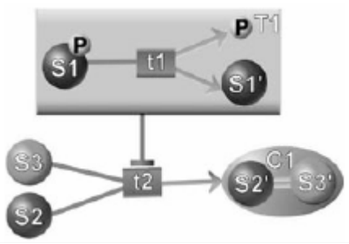
Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
Activation	Activation is represented by the state of the node.  Activation states are represented by different nodes reflecting the different states of the molecule 	Activation of a reaction by another reaction is depicted as a contingency on an interaction. Activation of a molecular species is implicit in its participation in molecular interactions.		**Absolute activation** Absolute activation: Initiation is a Boolean.  Always triggers a state transition. 
Covalent bond		This is a chemical level interaction 		
Other Interactions	Known transition omitted  Add reactant Difference between association and add reactant is not clear. It could be a different level of abstraction. This interaction type is best suited at chemical level.  Add product Difference between dissociation and add product is not clear. It could be a different level of abstraction. This interaction type is best suited at chemical level. 	Stoichiometric conversion  Products appear without loss of reactants & Simulation  This notation used as a reaction symbol when pointing to a species. This notation used as a contingency symbol when pointing to a line.  Requirement Binding  This symbol shows that the simulating agent is a requirement. It is difficult to see the difference between simulation and requirement binding.	Multimerization Redox Replication  Allosteric Change	

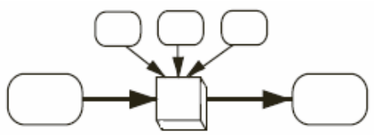
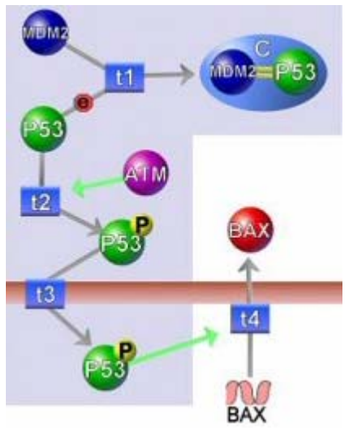
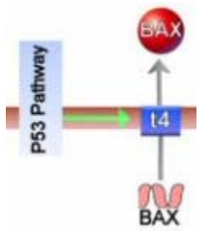
Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
BINDING TYPES				
Mutually exclusive binding	Can be represented by two different association reactions. 	This diagram means the bindings cannot co-exist together. 	Representation will be similar to Kitano's representation.	
Competitive binding		Competition for the same site is shown using a branched binding line.  This notation provides a compact representation of alternative bindings that have the same function eg. two dimers ABD and ACD		
Intramolecular binding		Binding between the domains within the same molecule 		

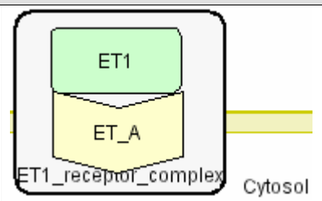
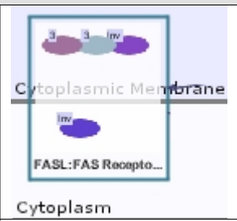
Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
Intermolecular binding		Binding between different molecules of the same type. The diagram indicates intermolecular binding between domain-1 of one molecule of A and domain-2 of another molecule of A. 		
Associations and combinatorial bindings of molecular species	Can not compactly describe the combinatorial bindings. All combinations may have to be enumerated where necessary. This problem is reduced by using modules. o Every different state has significance – every node is represented o Only initial and final state are important and a set of intermediate reactions can occur in random order but all intermediate reactions have to take place – represented by enumerating all intermediate states or by using AND logic symbol o Only the initial and final states are important and only one of the interactions is necessary for transition – represented by using parallel state transitions or OR symbol o Number of combinatorial states and associated state transitions are too large – represented using modules	Can be compactly described by an entity-relationship diagram.	Cannot compactly describe the combinatorial bindings.	

Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
GENE EXPRESSION				
Transcription	Introduced in reduced notations as Kitano only provides a high level description of transcriptional activities.  Described as a state transition of nucleotides into RNA. 			**Gene expression**  
Translation	Translation of amino acids into proteins.  Introduced as a reduced notation as Kitano's notations does not support detailed translation activities.	Translation is depicted as the appearance of a product without loss of reactants. 		
Truncation	**Truncation** 		**Cleavage** 	

Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
ABSTRACTION				
And				
Or				 
XOR				
NOT				
Degradation	o Category 1 Simplification of the visualisation and model representation of intermediate processes such as transcription, translation and degradation processes – can be used within detailed process diagrams. 			

Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
Reduced notation	**Reduced notation** o Category 2 Represents molecular interactions that lead to activation, inhibition and state change of the protein – only for visualization of specific pathways where temporal orders of events are not critical. Diagram showing A activates B in standard notation.  Reduced notation of the above. 	**Compact notation**  a) standard notation b) compact notation	**Homology abstractions Cleavage of a covalent bond**   	Edinburgh pathway notations aims to describe the change in the states of the proteins within the pathway without describing the detailed chemical processes that causes these state changes.
Incomplete Abstraction	**Unknown transition** 	 D bound to A at unknown location.	**Incomplete Abstraction** Two types of abstractions to represent information of incomplete nature. o Transition abstraction  o State abstraction  	

Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
Module Abstraction	**Module** 		**Abstraction** Abstractions are necessary to make effective analysis of cellular processes and dealing with complexity better.  Reduced notation  	Notations hides much of the detail in a pathway and uses sub diagrams to describe states and state transitions in details.
DATA MODEL				
Ontology			PATIKA describes an ontology to model networks of cellular processes through integration of information on individual pathways. The ontology is suitable for modelling incomplete information and abstractions of varying levels for complexity management.	

Criteria	Kitano	Kohn	PATIKA	Edinburgh Pathway Notation
OTHER FEATURES				
Complexes spanning multiple compartments				
Multiple Views			PATIKA supports two views mechanistic view and bioentity view.	
Colour	Symbol definitions are not affected by colour.	Symbol definitions are not affected by colour.	By default states are coloured with respect to their biological entities and may be changed through a colouring schema.	Symbol definitions are not affected by colour.
Automated Layout	Not supported	Not supported	Provides automated layout support.	
REFERENCE				
Reference	Kitano, H., et al., *Using process diagrams for the graphical representation of biological networks.* Nature Biotechnology, 2005. **23**.	Kohn, K.W., et al., *Molecular Interaction Maps of Bioregulatory Networks: A General Rubric for Systems Biology*. 2005.	E. Demir, O.B., U. Dogrusoz, A. Gursoy, G. Nisanci, R. Cetin-Atalay, M. Ozturk, *Patika: an integrated visual environment for collaborative construction and analysis of cellular pathways.* Bioinformatics, 2002. **18**: p. 996-1003.	Moodie, S., et al., *Edinburgh Pathway Notation.* 2006.