(Carl Adam Petri, Petri nets, Concurrency) and Systems Biology:

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Background

Petri nets

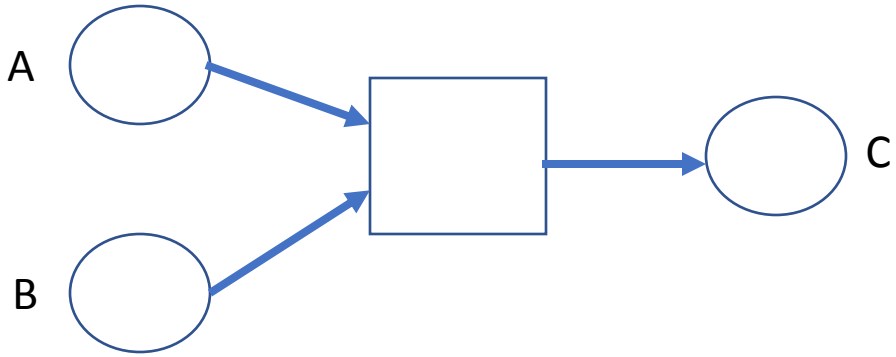
Carl Adam Petri

Concurrency theory

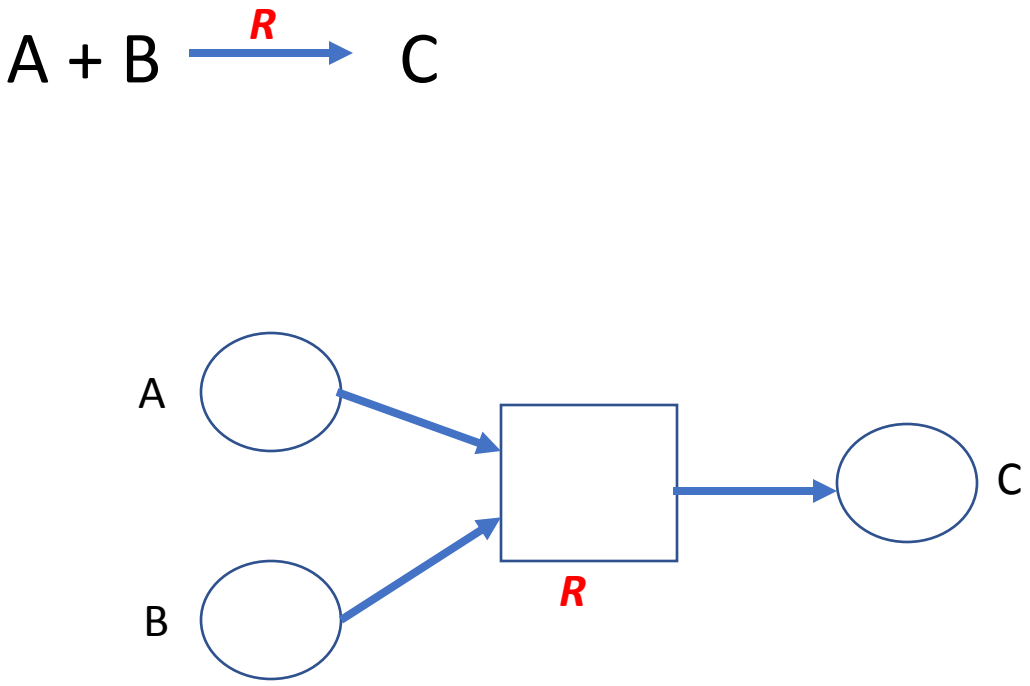
Computational systems biology

Carl Adam Petri , chemical reactions

- “Started” with chemistry
- places: reactants, products
- transitions: reactions
- A + B ⟶ C

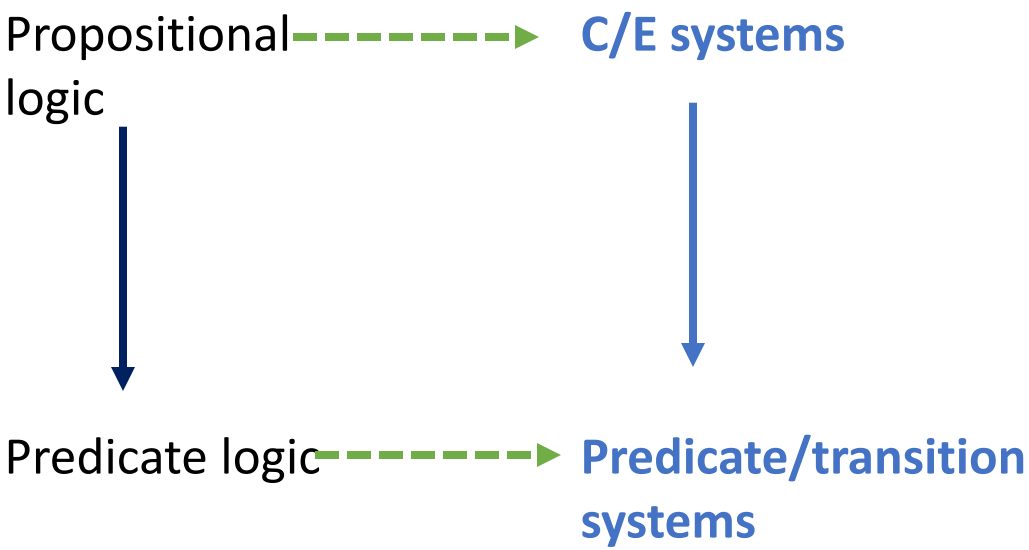


Carl Adam Petri : chemical reactions



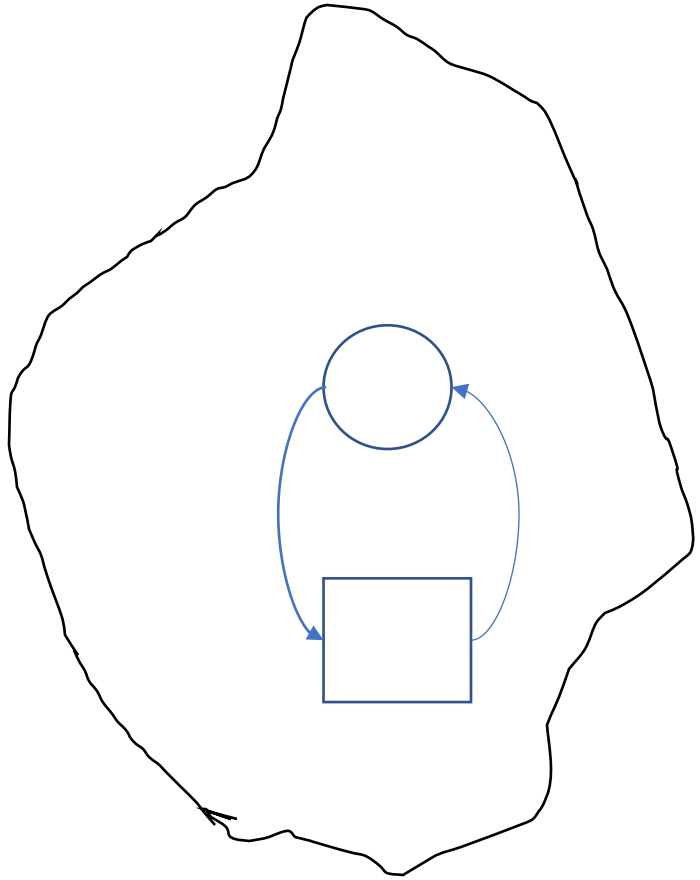
Extensions of C/E systems

- Carl Adam Petri “endorsed” two extensions:
  - Predicate/transition nets



Extensions of C/E systems

- Carl Adam Petri “endorsed” two extensions:
  - (1-safe Petri) nets with ***self-loops***
    - ***in C/E systems, events involved in self-loops are dead***



Enzymatic reactions

$$E + S \underset{k'}{\overset{k}{\rightleftharpoons}} ES \xrightarrow{k''} E + P$$

- *Enzymes speed up reactions*
  - *by dramatically lowering the activation energy needed to start the reactions.*
- *S ---- > P*
  - *will take too long without the enzyme*

Enzymatic reactions

$$E + S \underset{k'}{\overset{k}{\rightleftharpoons}} ES \xrightarrow{k''} E + P$$

$$\frac{dS}{dt} = -k \cdot S \cdot E + k' \cdot ES$$

$$\frac{dE}{dt} = -k \cdot S \cdot E + (k' + k'') \cdot ES$$

$$\frac{dES}{dt} = k \cdot S \cdot E - (k' + k'') \cdot ES$$

$$\frac{dP}{dt} = k'' \cdot ES$$

Under mass law

Enzymatic reactions

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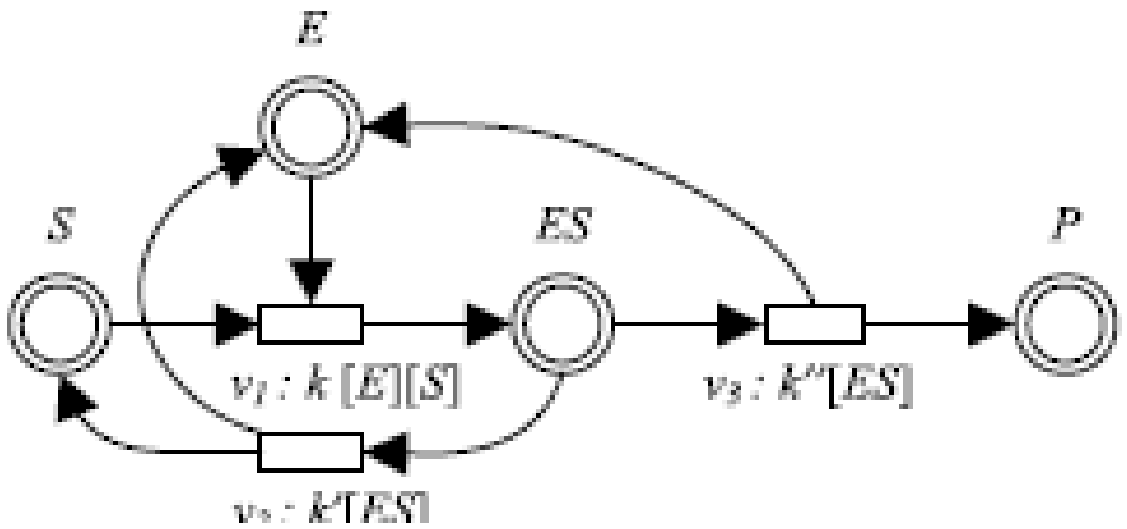

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The Michaelis-Menten model

$$E + S \underset{k'}{\overset{k}{\rightleftharpoons}} ES \xrightarrow{k''} E + P$$

(A1) ES reaches steady state much faster than the rate of product (P) formation.

(A2) [S] >> [E]; all of the enzyme is substrate bound

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Briggs, G. E., and Haldane, J. B. (1925) A Note on the Kinetics of Enzyme Action, Biochem J 19, 338-339

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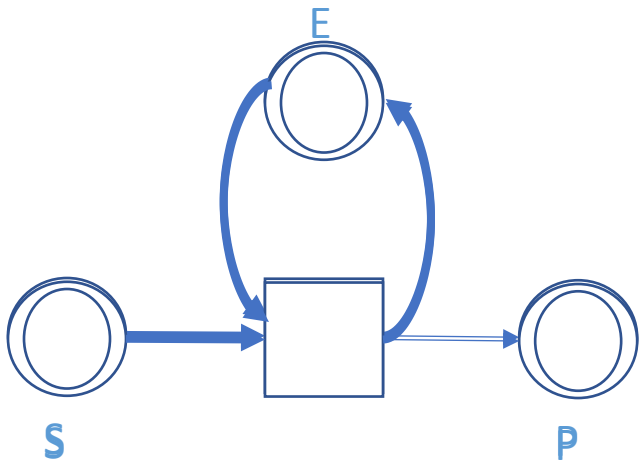
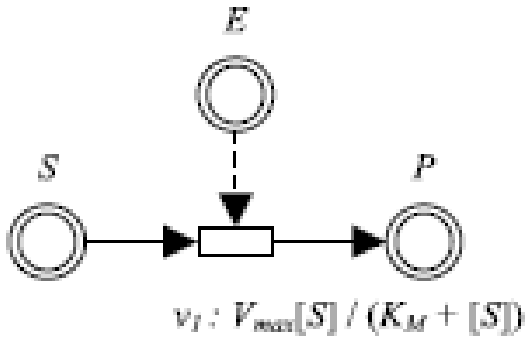


Self-loop!

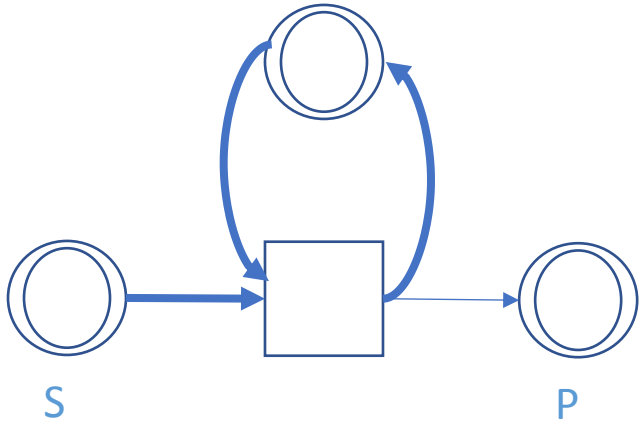
Self-loops or read -only arcs?

$$E + S \underset{k'}{\overset{k}{\rightleftharpoons}} ES \xrightarrow{k''} E + P$$



Read-only arc

$$dP/dt = \quad V_{max}\,[S]/K_M + [S]$$



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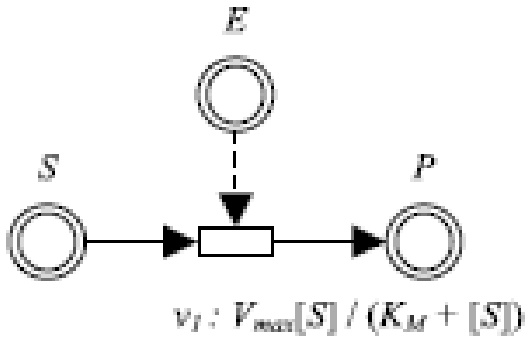

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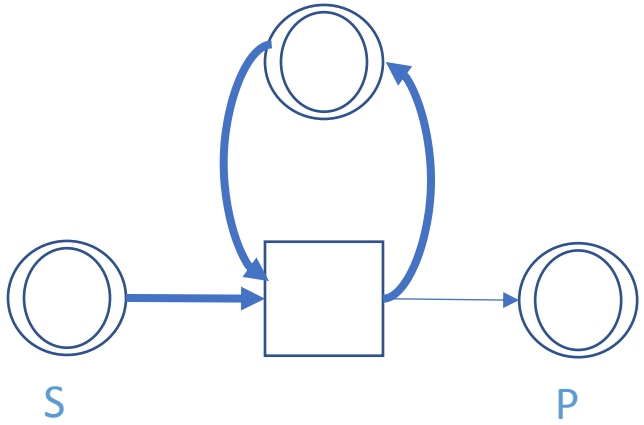


Self-loop!

*The **strongly connected components** of the underlying (bipartite) directed graphs will be different.*

Parameter estimation

- The values of rate constants is often not known
  - k, k', k''
- The initial concentrations also may not be known
  - $[S_0]$, $[E_0]$, $[ES_0]$, $[P_0]$
- Must be estimated
  - Using limited experimental data
  - via non-linear optimization techniques
    - evolutionary search procedures

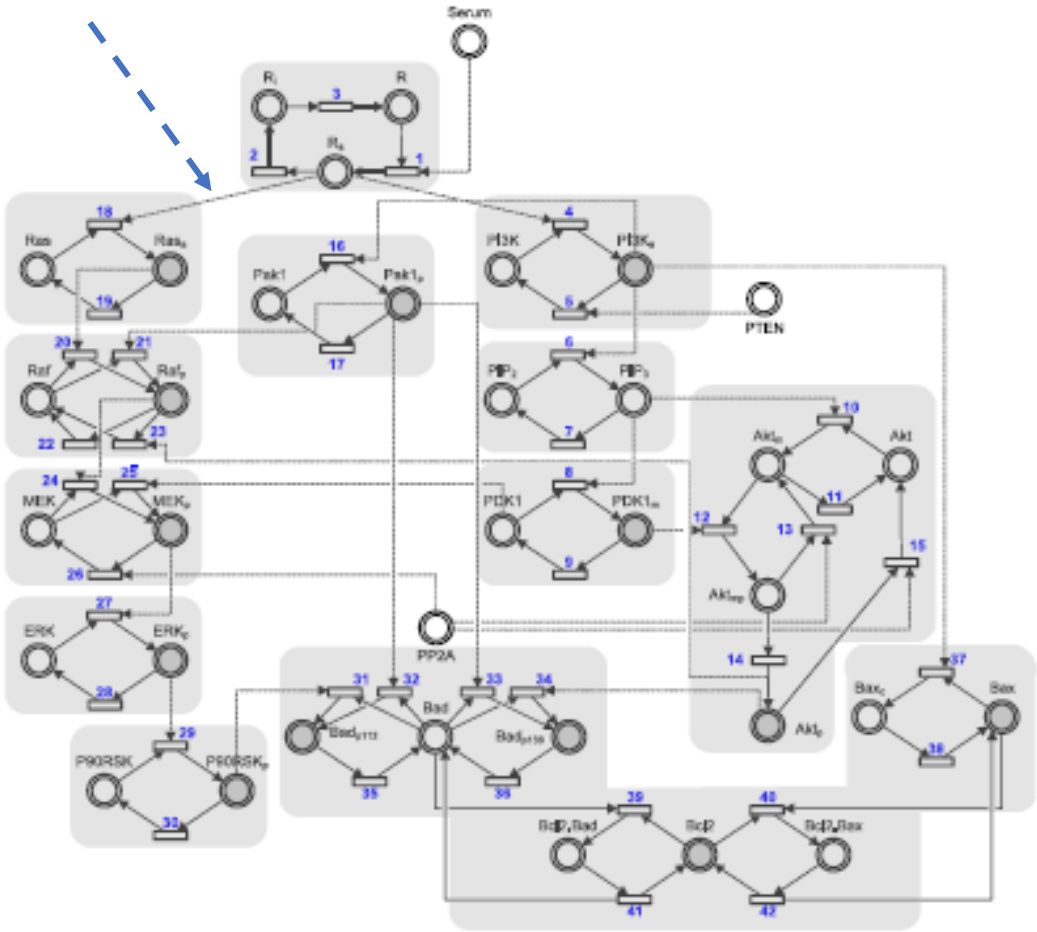
$$\frac{dS}{dt} = -k \cdot S \cdot E + k' \cdot ES$$
$$\frac{dE}{dt} = -k \cdot S \cdot E + (k' + k'') \cdot ES$$
$$\frac{dES}{dt} = k \cdot S \cdot E - (k' + k'') \cdot ES$$
$$\frac{dP}{dt} = k'' \cdot ES$$

Decompositions based parameter estimation

- Derive the net diagram from the ODEs system
- Decompose the net (bipartite digraph) into its maximal strongly connected components.
  - Use *read-only arcs* to model enzymatic reactions.
- Exploit the structure of the DAG of the maximal strongly connected components:
  - break down the parameter estimation problem into smaller ones.

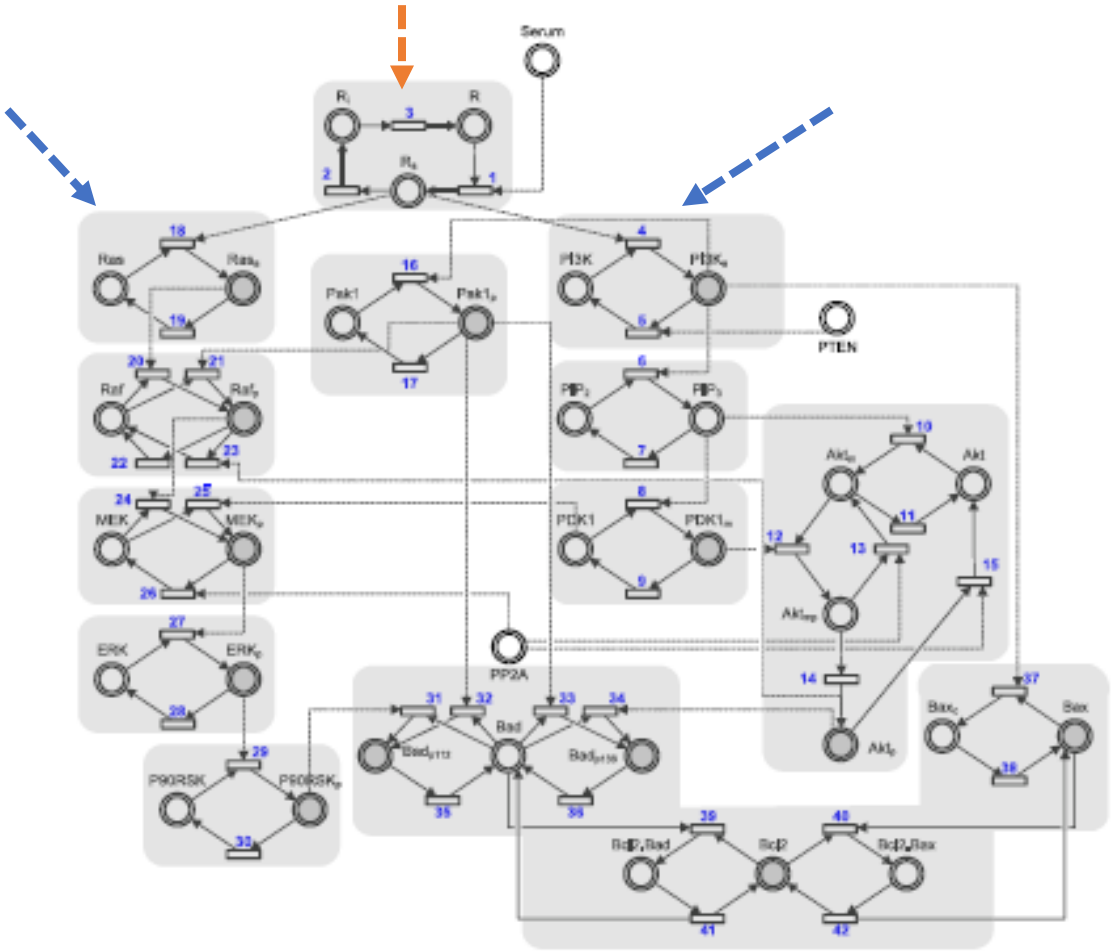
G. Koh et al. / Theoretical Computer Science 412 (2011) 2840–2853

Decompositions based parameter estimation



The decomposed AKT-MAPK signaling pathway

Decompositions based parameter estimation

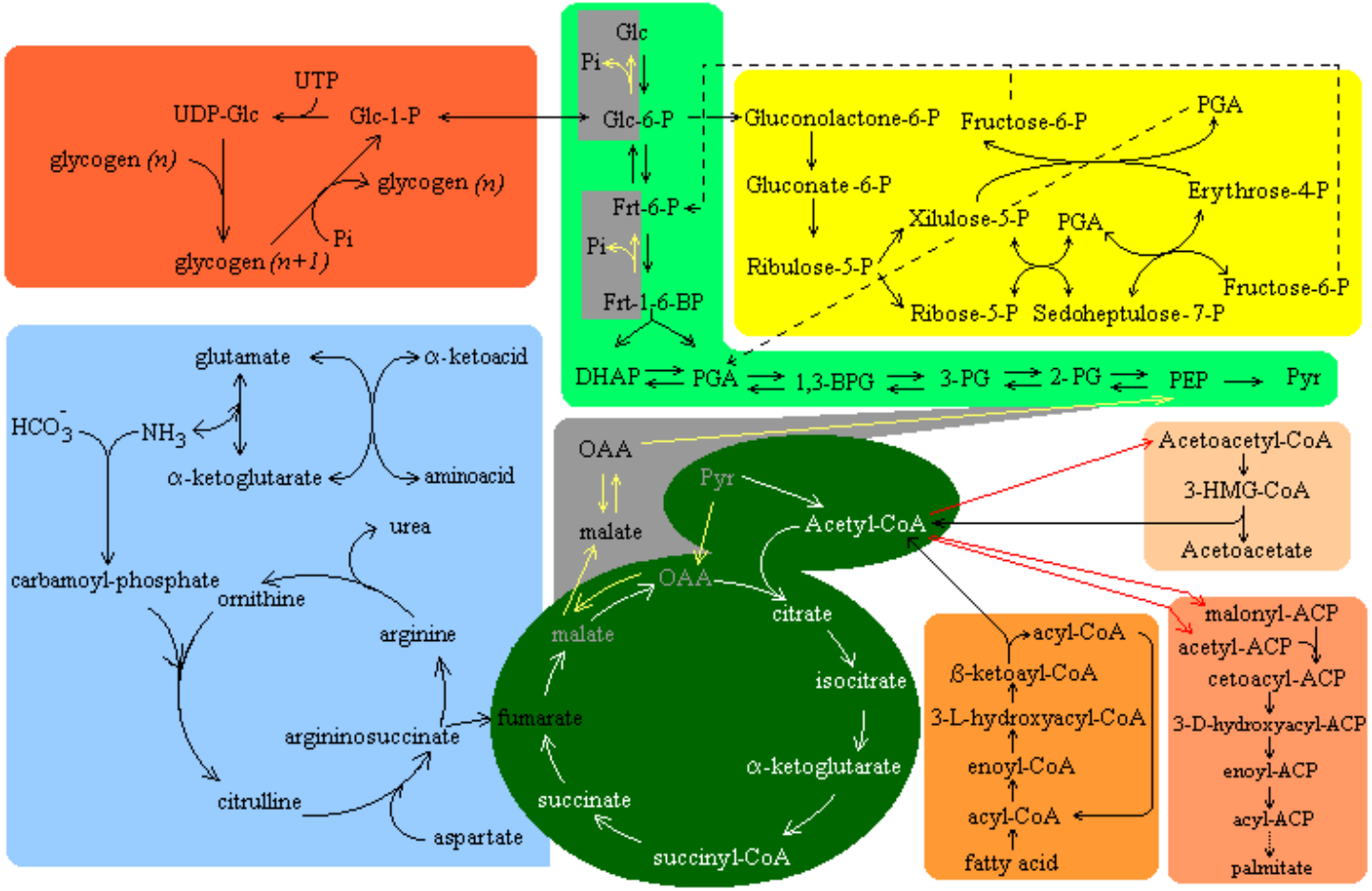


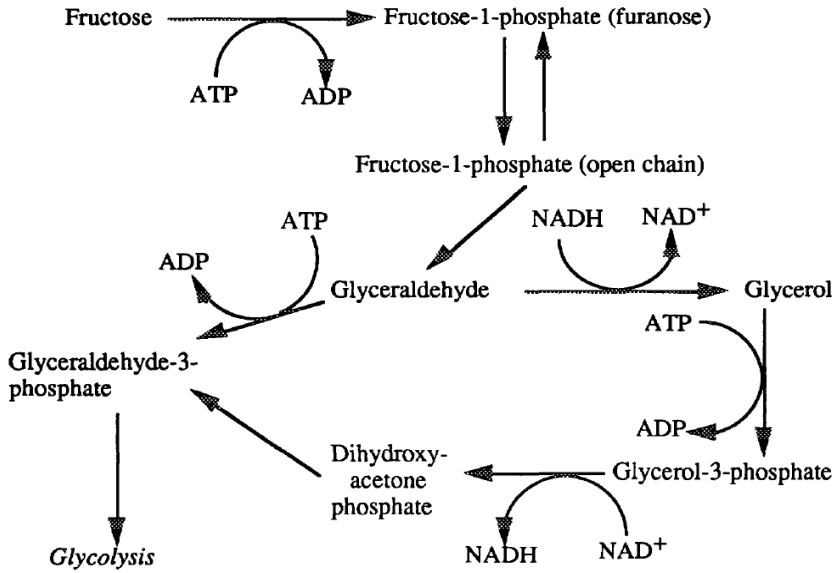
The decomposed AKT-MAPK signaling pathway

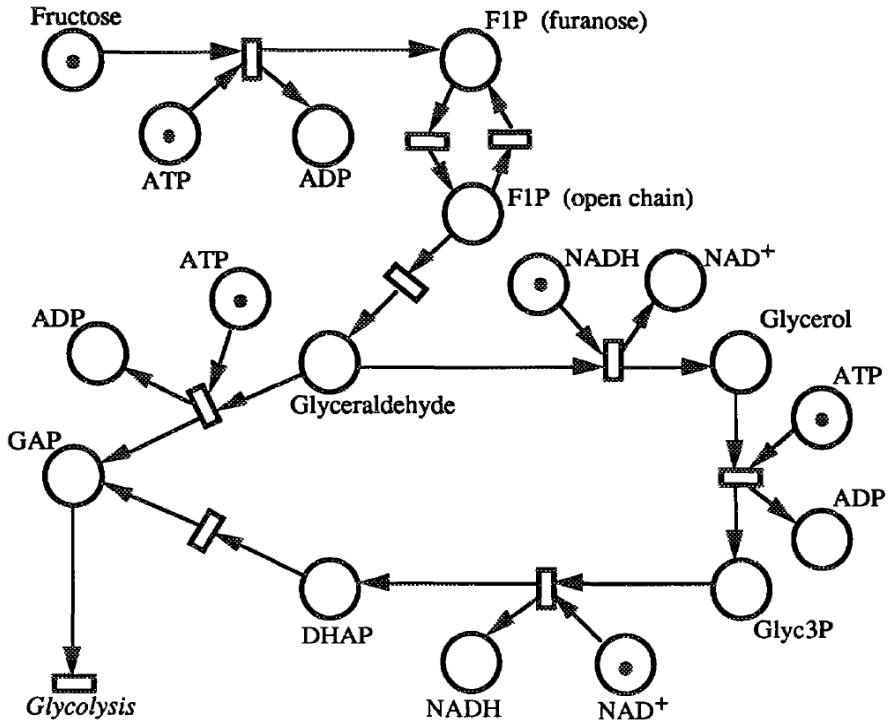
- Estimate the parameters of the upstream components first
- Complications:
  - Distribution of experimental data
  - Computing consistent global estimates from local ones.
    - *Belief propagation*

(~~Carl Adam Petri~~, Petri nets, ~~Concurrency~~) and systems biology

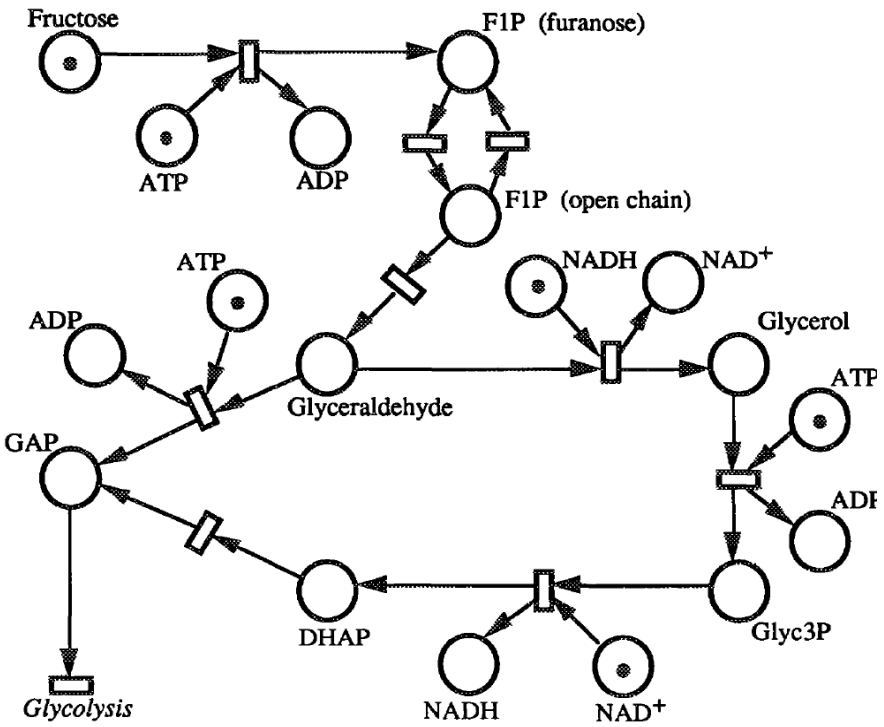
- ***Metabolic pathways***:
  - Complex biochemical networks that :
    - consume nutrients to obtain –and store- energy (*catabolism*)
    - Produce new cell components by consuming -stored- energy (*anabolism*)
  - Vital for living, growing, replenishing







$$\mathbf{N} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 1 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & -1 & -1 \\ 0 & 0 & 0 & 0 & -1 & -1 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$



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- *T-invariants*
  - *Flux analysis*
- *S-invariants*
  - *Dead cycles*

(~~Carl Adam Petri~~, Petri nets, ~~Concurrency~~) and systems biology

- Steady state analysis of metabolic networks :
  - *Reddy, V. N., Mavrovouniotis, M. L. and Liebman, M. N. (1993). Petri Net Representation in Metabolic Pathways. In Proc. First Intern. Conf. on Intelligent Systems for Molecular Biology, AAAI Press, Menlo Park, pp. 328-336*
  - *Schuster S, Hilgetag C (1994) On elementary flux modes in biochemical reaction systems at steady state. J Biol Syst 2:165–182*
  - ***Heiner M, Koch I**, Schuster S (2000) Using time-dependent Petri nets for the analysis of metabolic networks. In: Hofestadt R, Lautenbach K, Lange,M (eds) Workshop Modellierung und Simulation Metabolisher Netzwerke*
  - *Heiner M, Koch I, Voss K (2001) Analysis and simulation of steady states in metabolic pathways with Petri nets. In: Workshop and tutorial on practical use of coloured Petri nets and the CPN tools (CPN'01)*
    - *Colored Petri nets based*

Petri net variants in systems biology

- *Many* extensions of Petri nets have been used to model and analyze biopathways.
- Stochastic Petri nets
  - ***Goss, P. J. E. and Peccoud, J. (1998). Quantitative modeling of stochastic systems in molecular biology by using stochastic Petri nets. Proc. Natl. Acad. Sci. USA 95, 6750-6755***
- Continuous Petri nets
- Hybrid Petri nets

Tools based on Petri nets

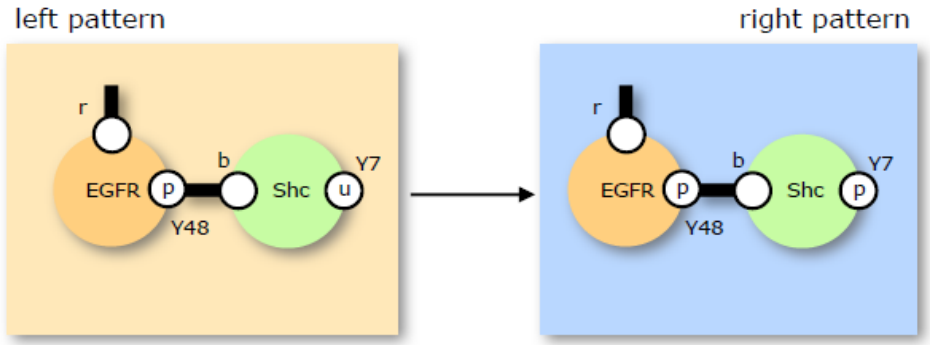
- MonaLisa
  - *Jens Einloft Jörg Ackermann Joachim Nöthen Ina Koch: MonaLisa—visualization and analysis of functional modules in biochemical networks. Bioinformatics, Volume 29, Issue 11, 1 June 2013, Pages 1469–1470*
- Snoopy
  - *M Heiner, M Herajy, F Liu, C Rohr and M Schwarick:p*
    Snoopy – a unifying Petri net tool;
    In Proc. PETRI NETS 2012, Hamburg, Springer, LNCS, volume 7347, pp. 398–407
- ***Cell Illustrator (based on hybrid functional Petri nets)***
  - *Matsuno H, Tanaka Y, Aoshima H, Doi A, Matsui M,* ***Miyano S.***
    Biopathways Representation and Simulation on Hybrid Functional Petri Net.
    In Silico Biology. 2003; 3(3): 389-404

(~~Carl Adam Petri~~, ~~Petri nets~~, Concurrency) and systems biology

- Dynamics of biochemical networks:
  - great deal of concurrency
  - studied/exploited ***seldom***
- Difficult to obtain a fine grained description that exposes the concurrency present.
- ODEs:
  - must know in advance all the molecular species that can arise
    - can give rise to ***huge*** blow up in size
    - when the formation and interactions of complex molecules play a role; often the case!

Rule based modelling: kappa, bngl, ..

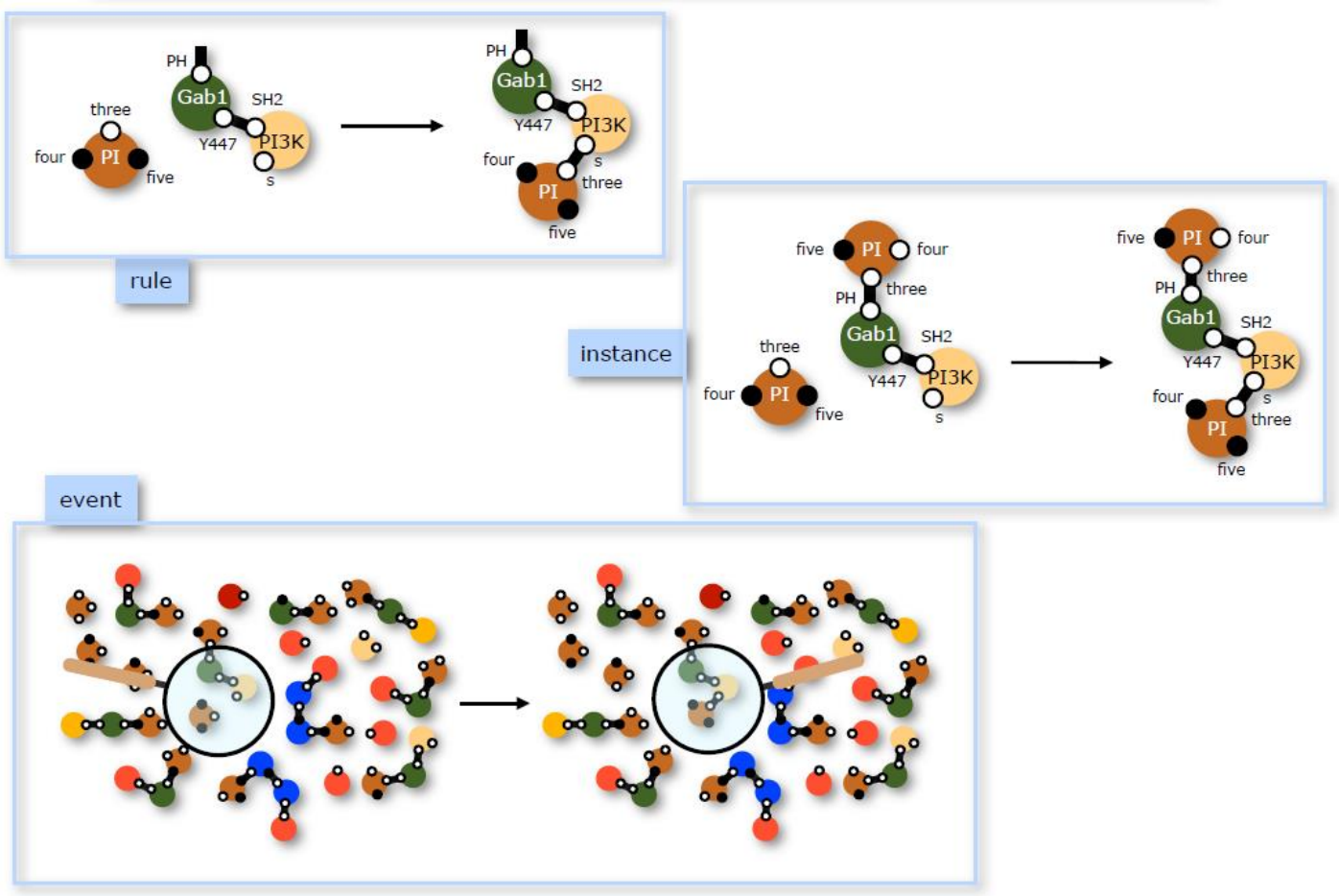
a rule rewrites a pattern:



$$EGFR(r!\_, Y48 \sim p!1), Shc(b!1, Y7 \sim u) \longrightarrow EGFR(r!\_, Y48 \sim p!1), Shc(b!1, Y7 \sim p)$$

https://www.irif.fr/~jkrivine//homepage/Teaching_files/Partie%201%20-%20Introduction.pdf

Rules, Instances, events



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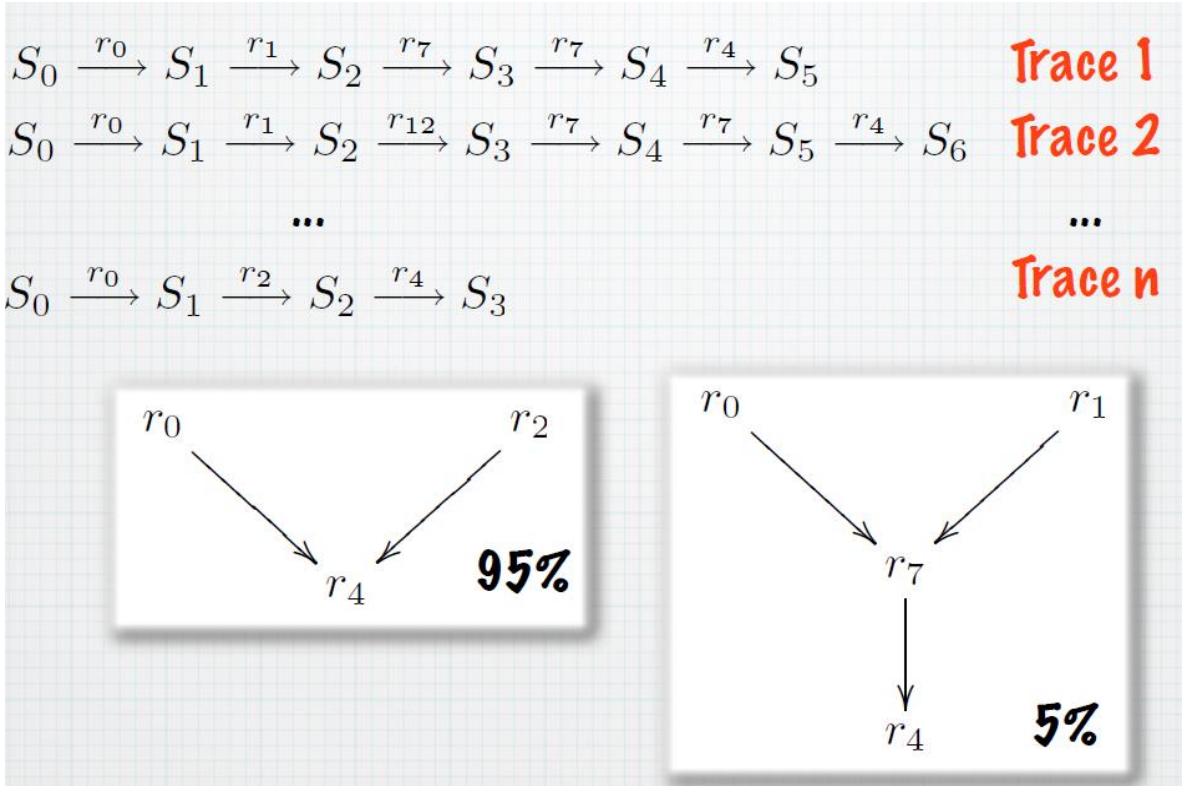
Concurrency



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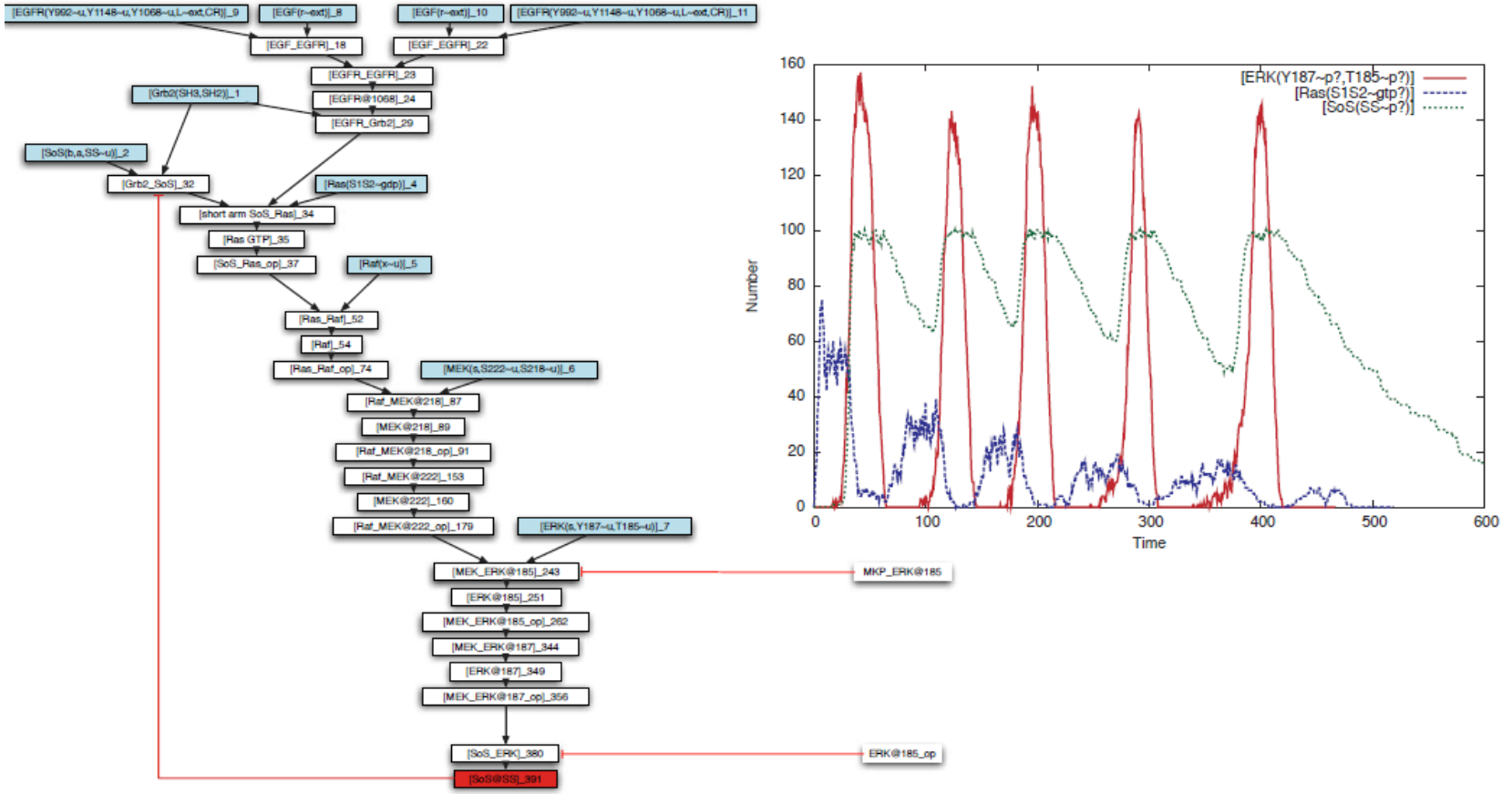
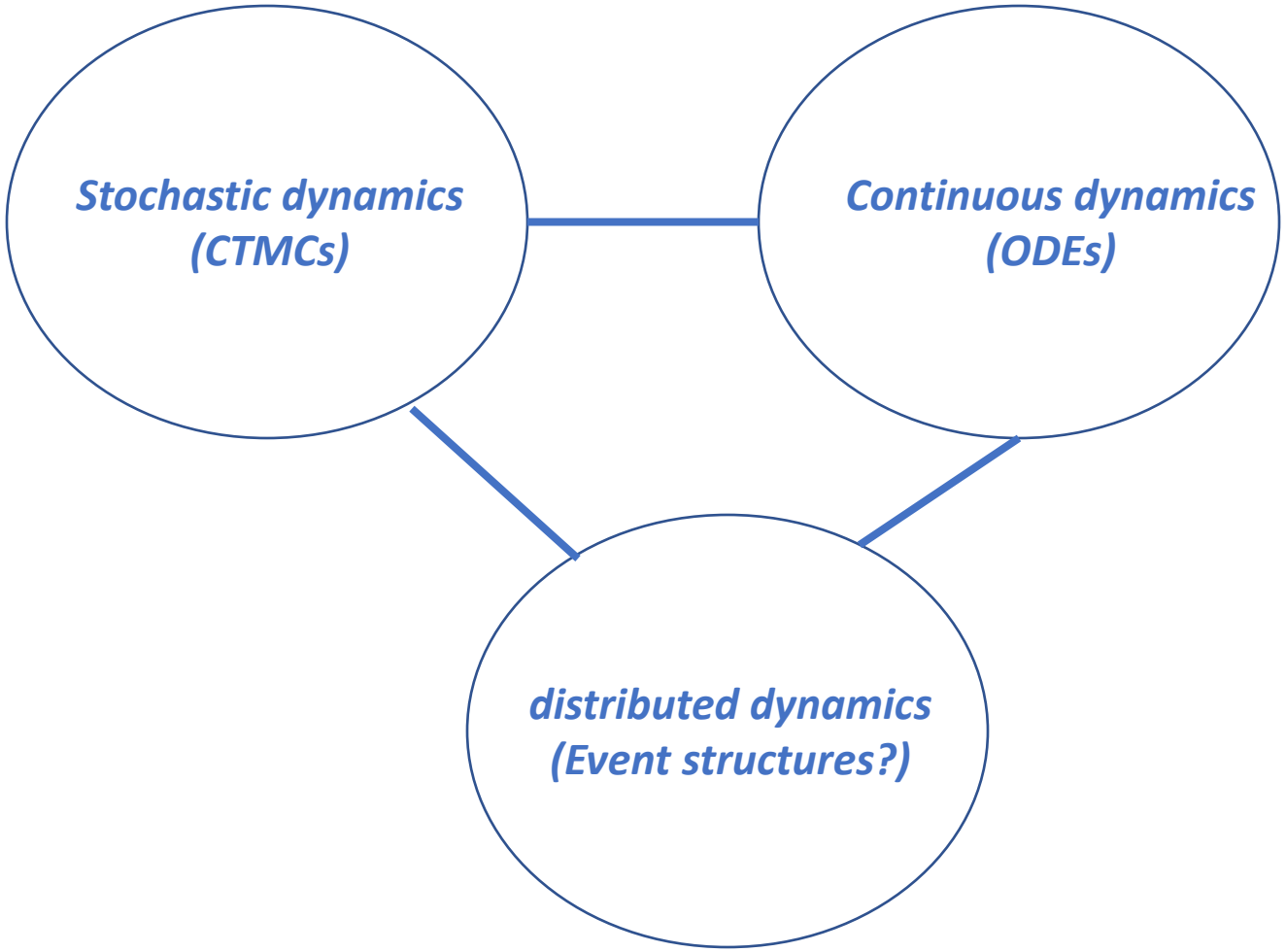
Stories ----------> Event structures



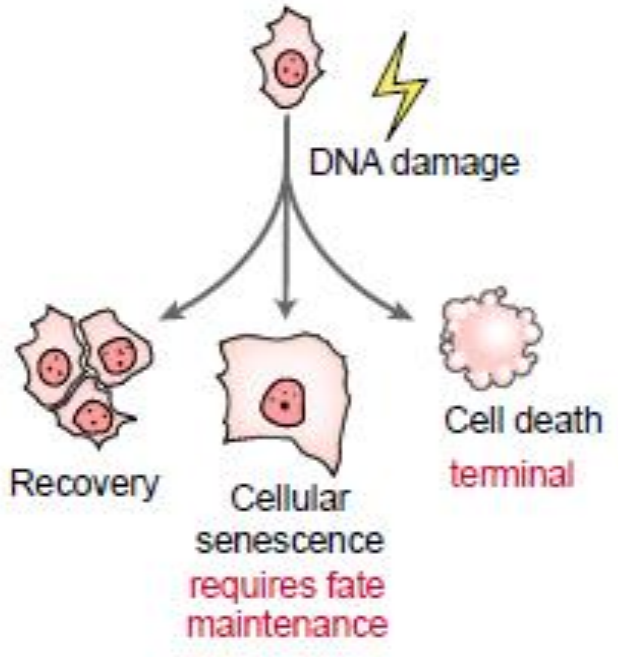
A perspective



- **Not merely descriptive**
- **Must yield a succinct partial order based representation of the state space**
- **Lead to efficient sampling based statistical analysis**

Motivation

- Signaling must be:
  - *robust*: filter out small fluctuations
  - *Sensitive:* respond according to signal strengths/shapes
- Tumor cells rewire their signaling pathways in order to adapt to and resist drug treatments.
  - response to vemurafenib in melanoma patients
- Cell differentiation/proliferation choices in developmental biology



Jose´ Reyes, Jia-Yun Chen,Jacob Stewart-Ornstein, Kyle W. Karhohs, Caroline S. Mock and Galit Lahav. Fluctuations in p53 Signaling Allow Escape from Cell-Cycle Arrest. Molecular Cell 71, 581–591

Marie Csete, John Doyle. Bow ties, metabolism and disease. TRENDS in Biotechnology Vol.22 No.9

Returning to Carl Adam Petri ……

- His research:
  - Uncompromising
  - Commitment to fundamental issues
  - Fit-for-purpose

Returning to Carl Adam Petri ……

- His research:
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  - Fit-for-purpose
- *Health warning:*
  - *Don’t try this at home!*