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POLITÉCNICA

NETWORKS OF EVOLUTIONARY PROCESSORS (NEP)

NEW VARIANTS TO INVESTIGATE THE FUNCTIONING OF LIVING CELL

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Outline

- New variants of NEP
  - NPEP: Networks of Polarized Evolutionary Processors
  - NEPT: Transducer based on Networks of Evoltuionary Processors
- Bio-inspired architecture based on NEPs
- NEPT and cellular signaling
- NEP and metabolic processes

Networks of Polarized Evolutionary Processors NPEP

- It is the first model involving a **quantitative** evaluation over words.
- **Key feature:** **valuation mapping** which assigns to each string an integer value, depending on the values assigned to its symbols.
- **Quantitative interest:** The important is the sign of the string, not the exact value (*strings are electrically polarized*).
- Nodes without filters but polarized.
- Strings migration simulate the channel between the two cells. *It seems to be more natural*

NPEP Definitions

Definition 1. A *polarized evolutionary processor* over V is a pair (M, α), where:

- M is a set of substitution, deletion or insertion rules over the alphabet V . Formally: $(M \subseteq SubV)$ or $(M \subseteq DelV)$ or $(M \subseteq InsV)$.
- $\alpha \in \{-,0,+\}$ is the polarization of the node.

NPEP Definitions

Definition 2. A *network of polarized evolutionary processors* (NPEP for short) is a 7-tuple

$$\Gamma = (V, U, G, R, \varphi, In, Out),$$

where:

- V and U are the input and network alphabet, respectively, $V \subseteq U$.
- $G = (X_G, E_G)$ is an undirected graph without loops with the set of vertices (*network underlying graph*).
- R: $X_G \rightarrow EP_U$ is a mapping which associates with each node $x \in X_G$ the polarized evolutionary processor $R(x) = (M_x, \alpha_x)$.
- φ is the valuation maping of U^* in **Z**.
- $In, Out, \in X_G$ are the *input* and the *output* node of Γ, respectively.

NPEP definitions

Definition 3: *Configuration* of a NPEP Γ is a mapping $C : X_G \rightarrow 2^{V^*}$ which associates a set of strings with every node of the graph.

Given a string $w \in V^*$, the initial configuration of Γ on w is defined by $C_0(w)(x_I) = \{w\}$ and $C_0(w)(x) = \varnothing$ $\forall\, x \in X_G \setminus \{x_I\}$.

- A configuration can change either by an *evolutionary step* or by a *communication step*.

NPEP definitions

Definition 4: Let Γ be a NPEP, the computation of Γ on the input string $w \in V^*$ is a sequence of configurations $C_0(w)$, $C_1(w)$, $C_2(w)$, . . . , where $C_0(w)$ is the initial configuration of Γ on w, $C_{2i}(w) \Rightarrow C_{2i+1}(w)$ and $C_{2i+1}(w) \vdash C_{2i+2}(w)$, $\forall\, i \geq 0$.

- Note that the configurations are changed by alternative steps.
- By the previous definitions, each configuration $C_i(w)$ is uniquely determined by the configuration $C_{i-1}(w)$.

NPEP definitions

Definition 5: A computation *halts*, if one of the following two conditions is satisfied:

- There exists a configuration in which the set of strings existing in the output node "*Out*" is non-empty.
- No further step is possible.

Transducers based on Networks of Evolutionary Processors - NEPT

- First NEP model being a translator
- **Key feature:** To generate a language able to be processed by others NEPs.
- **Why?:** To encode and decode instances/solutions of a problem when we use NEP as universal problem solvers.
  - It seems to be natural to use NEPs as well.

NEPT characteristics

- Formed by a directed graph whose nodes are evolutionary processors without filters.
- The translation of the input word is the set of words existing in the output node when the computation halts.
- NEPT can simulate the work of generalized sequential machines (*gsm*).
- NEPT are able to compute the set of all words obtained by a given *gsm* by the shortest computations.
- **Pure NEPT:** NEPT with the same input and output alphabet.

NEPT Definitions

Definition 1. *NEPT* is a 7-tuple $\gamma = (V,U,W,D,R, x_I, x_O)$, where:

- V is the input alphabet.
- U is the output alphabet.
- W is the network alphabet, $(V \cup U) \subseteq W$.
- $D = (X_D, E_D)$ is a directed graph with the set of vertices X_D and the set of edges E_D.
- $R : (X_D \setminus \{x_0\}) \rightarrow 2^{Subw} \cup 2^{Delw} \cup 2^{Insw}$ is a mapping which associates with each node different than x_0 *the set of evolutionary rules* that can be applied in that node.
- α: $X_D \rightarrow \{*; l; r\}$; $\alpha(x)$ gives the action mode of the rules of node x on the words existing in that node.
- $x_I , x_O \in X_D$ are the *input* and the *output* node of γ respectively.

NEPT definitions

Definition 2. A *configuration* of a NEPT is a mapping $C: X_D \rightarrow 2^{W^*}$ which associates a set of words with every node of the graph.

A configuration may be understood as the sets of words which are present in any node at a given moment.

Given a word $w \in V^*$, the initial configuration of on w is defined by $C_0^{(w)}(x_I) = \{w\}$ and $C_0^{(w)}(x) = \varnothing$ for all $x \in X_D - \{x_I\}$.

NEPT definitions

Definition 3. Let be a NEPT, the computation of γ on the input word $w \in V^*$ is a sequence of configurations $C_0^{(w)}, C_1^{(w)}, C_2^{(w)}$, where $C_0^{(w)}$ is the initial configuration of defined by $C_0^{(w)}(x_1) = w$ and $C_0^{(w)} = \varnothing$ for all $x \in X_D$, $x \neq x_1$, $C_{2i}^{(w)} \Rightarrow C_{2i+1}^{(w)}$ and $C_{2i+1}^{(w)} \vdash C_{2i+2}^{(w)}$, for all $i \geq 0$.

A computation as above halts if there exists a configuration in which the output node x_0 contains at least one word over W

NEPT definitions

Definition 4. Given a NEPT and an input word $w \in V^*$, we say that translate w into $z \in U^*$ if the computation of on w halts with z in the output node. Formally, we define the transduction function of denoted by as follows:

$$\theta_\gamma(w) = C^k(x_0) \cap U^*$$

provided that the computation of on w halts after $k \geq 1$ steps.

In other words, $\theta_\gamma(w)$ collects all possible words $z \in U^*$ such that w is translated into z.

Furthermore, if L is a language over V, we set

$$\theta_\gamma(L) = \bigcup_{w \in L} \theta_\gamma(w)$$

NEPs Simulating Processes in Living Cell

- The complexity of this cellular process requires models and tools massively parallel able to solve hard problems.
- NEP are simple, efficient and flexible
- Initially we aren't interesting in a quantitative approach

NEPs Simulating Processes in Living Cell

Our starting points:

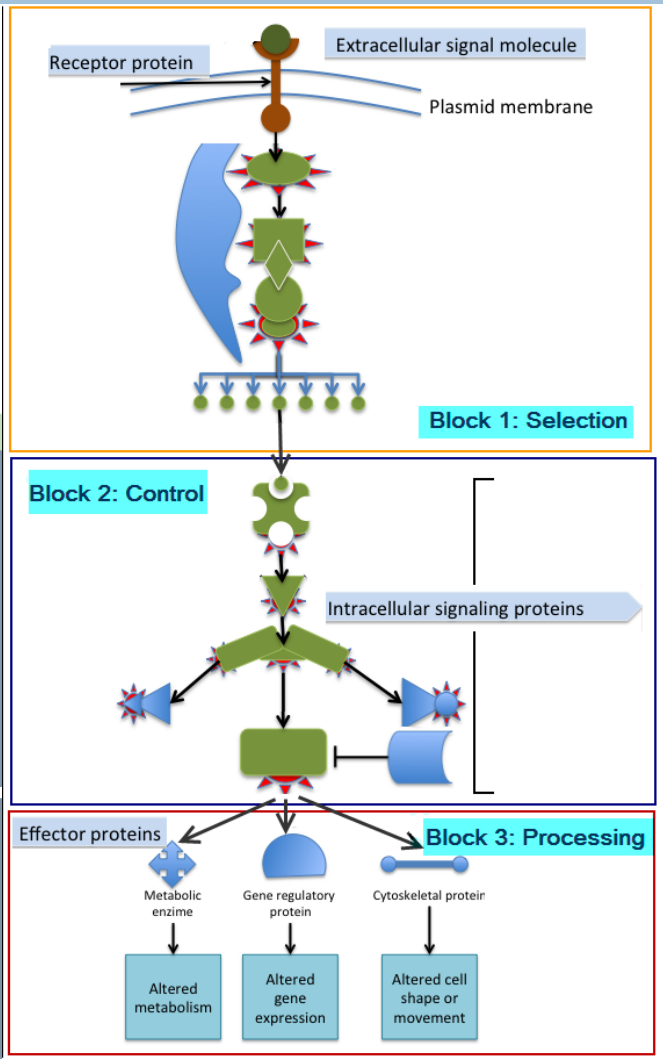
- Cellular dynamic consist in a **set of several processes** working together.
- The main activity in cellular processes is matter transformation by chemical reactions.
- Cellular processes **share and compete** for substances involved in their activities.
- Matter to be transformed by cellular processes, **come from** extra or intra cellular environment.
- Matter transformed by cellular processes **can remains** or **can be sent out of** the cell.
- Chemical **reactions occur in chain/waterfall** and they can be part of different processes.
- Cellular processes **can't be** analyzed in an **isolated way**.

Proposed Bio-inspired Architecture

Selection: involves the reception of a extracellular signal molecule arriving at the cellular membrane and the alteration (**transduction**), amplification and distribution through of the adequate signaling pathway selected. **This layer is implemented by NEPT.**

Control: realizes the control functionality of signaling pathway: either **activate or inhibit** the target proteins (effectors) in order to unleash the respective cellular processes. **This layer is implemented by NPEP.**

Processing: realizes the target process which alters the cellular behavior: shape, movement, metabolism and gene expression. **This layer is implemented by one or several NBP.**



Cellular signaling

- Multicellular organisms are exposed to hundreds of different signal molecules coming from the environment.
- Signal molecules act in many different ways and they influence almost at any aspect of cell behavior.
- Complexity lies in the way in which cells respond to the combinations of signals that they receive.

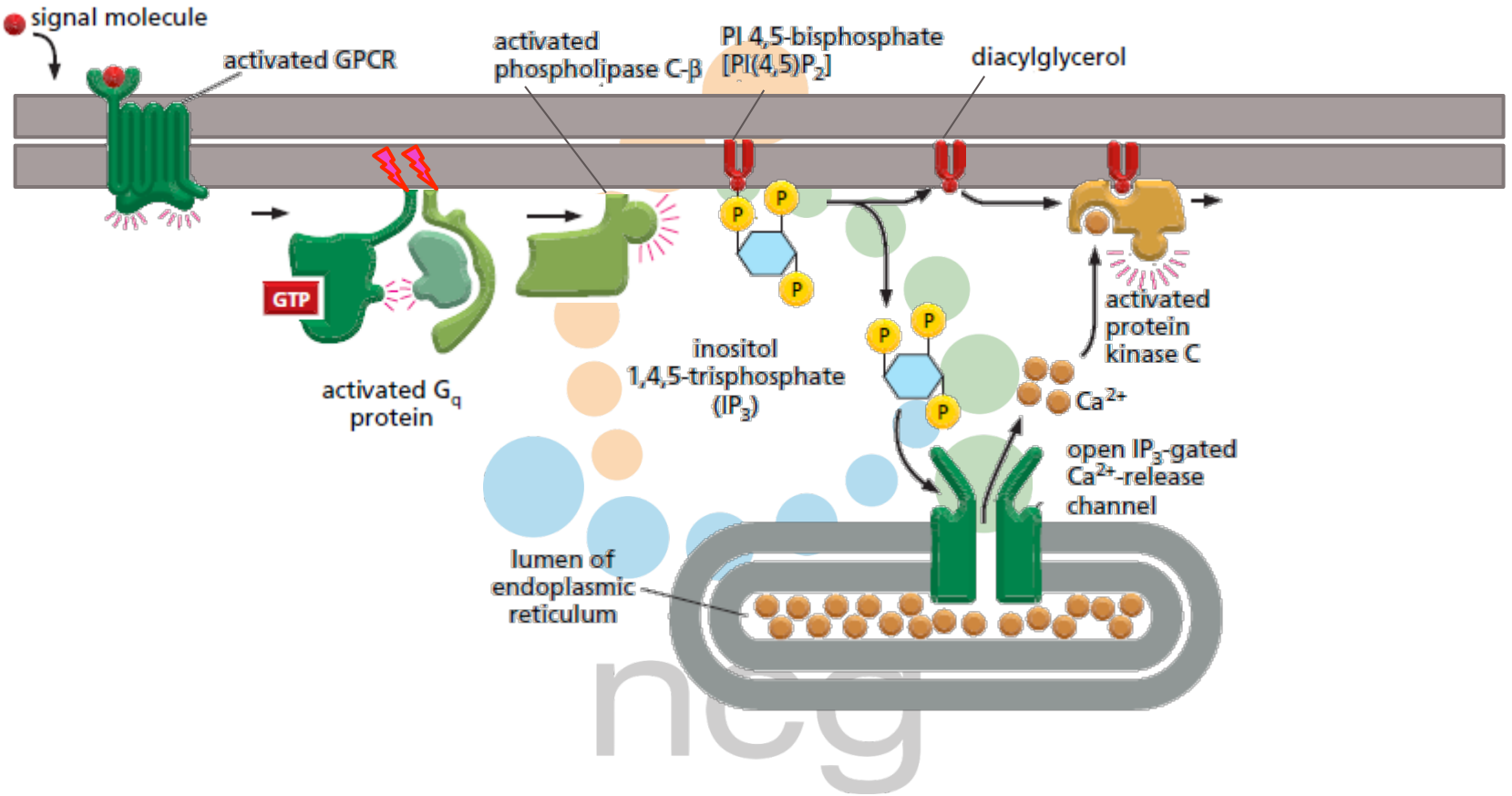
Understand how a cell integrates all of this signaling information in order to make its crucial decisions (division, movement, differentiation, etc.), is one of the biggest challenges in cell biology

Cellular signaling

Cellular signaling involves:

- **Ligands:** extracellular signal molecules.
- **Receptors**: usually proteins that binds the ligands and then produce a response in the target cell.
- **Helpers of receptors:** can be enzymes, proteins bound at the receptors.
- **Intracellular signaling molecules**
  - Small and large: which relay signals received at the cell surface by receptors into the cell.
  - Small intracellular molecules - second messengers

Cellular Signaling



Inositol phospholipid signaling pathway

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NEPT Modeling Inositol Phospholipid Signaling Pathway.

- Pure NEPT Υ_I models the inositol phospholipid signaling pathway by activating phospholipase C-β through the acetylcholine ligand.
- $V = \{A,C,D,G,G_q,I,K,P,R,S\}$
- $U = W = \{ a, c, c', d, F, g, g', i, i', k, M, p, r, s, X, Y, Z\}$

Symbol	Chemical Compound	Symbol	Chemical Compound	Symbol	Chemical Compound
A, a	acetylcholine	C, c, c'	Ca^{2+}	D,d	dyacyglycerol
G,g	GPRC activated	G_q, g'	G_q protein	I, i, i'	inositol 1,4,5-trisphosphate (IP3)
K, k	Protein kinase C (PKC)	P, p	phosholipase Cβ enzyme	R, r	ryanodine
S, s	Ca^{2+} sensor protein				

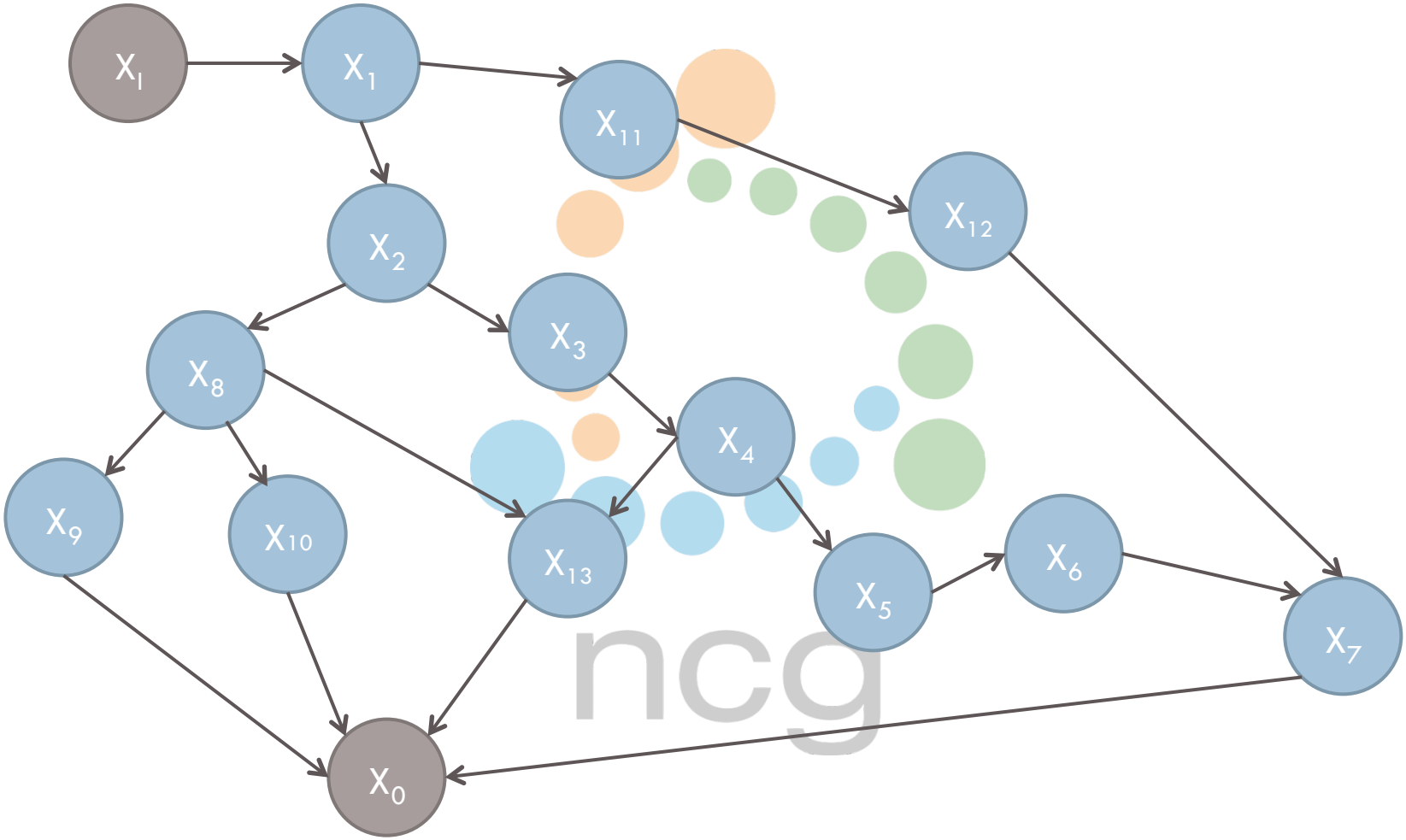
NEPT Modeling Inositol Phospholipid Signaling Pathway.

- Symbols X,Y,F,M,Z are control symbols meaning:
  - **Y**: Propagation of Ca^{2+} by activity of Ca^{2+} sensitive intracellular proteins (dephosphorylation of IP_3 forming IP_2).
  - **X**: Propagation of Ca^{2+} by activity of Ca^{2+} sensitive intracellular proteins (dephosphorylation of IP_3 forming IP_4).
  - **F**: Diacylglycerol activating PKC translocating Ca_{2+} from the cytosol to the cytoplasmic face.
  - **M**: Ca^{2+} from cytosol to the mitochondria.
  - **Z**: Amplification of Ca^{2+} signal in the cytosol through ryanodine receptors.

NEPT Modeling Inositol Phosph.

Node	R	α	Successors
x_I			x_1
x_1	A→ a, G→g, G_q → g'	*	X_2, x_{11}
x_2	P →p, I → i	*	x_3, x_8
x_3	R → r	*	x_4
x_4	C →c	*	X_5, x_{13}
x_5	I → i', S → s	*	x_6
x_6	ε → C' , ε → Z	I	x_7
x_7	K → k	*	x_O
x_8	C → c	*	x_9, x_{10}, x_{13}
x_9	ε→ X	I	x_O
x_{10}	ε → Y	I	x_O
x_{11}	P →p, D→d	*	x_{12}
x_{12}	ε→ F	I	x_7
x_{13}	ε→ M	I	x_O

NEPT Modeling Inositol Phospholipid Signaling Pathway.



NEPT Modeling Inositol Phospholipid Signaling Pathway.

- If w in V* , we claim that

$$\Theta_{\gamma}(w) = \left\{ \Theta^1_{\gamma_2}(w) \cup \Theta^2_{\gamma_2}(w) \cup \Theta^3_{\gamma_2}(w) \cup \Theta^4_{\gamma_2}(w) \right\}$$

where

$$\Theta^1_{\gamma}(w) = (X \mid Y)w' \mid w' \in \{a, c, g, g', i, p\}^* \cup \{D, K, R, S\}^*$$

$$\Theta^2_{\gamma}(w) = Mw' \mid w' \in \{a, c, g, g', i, p, r\}^* \cup \{D, K, S\}^*$$

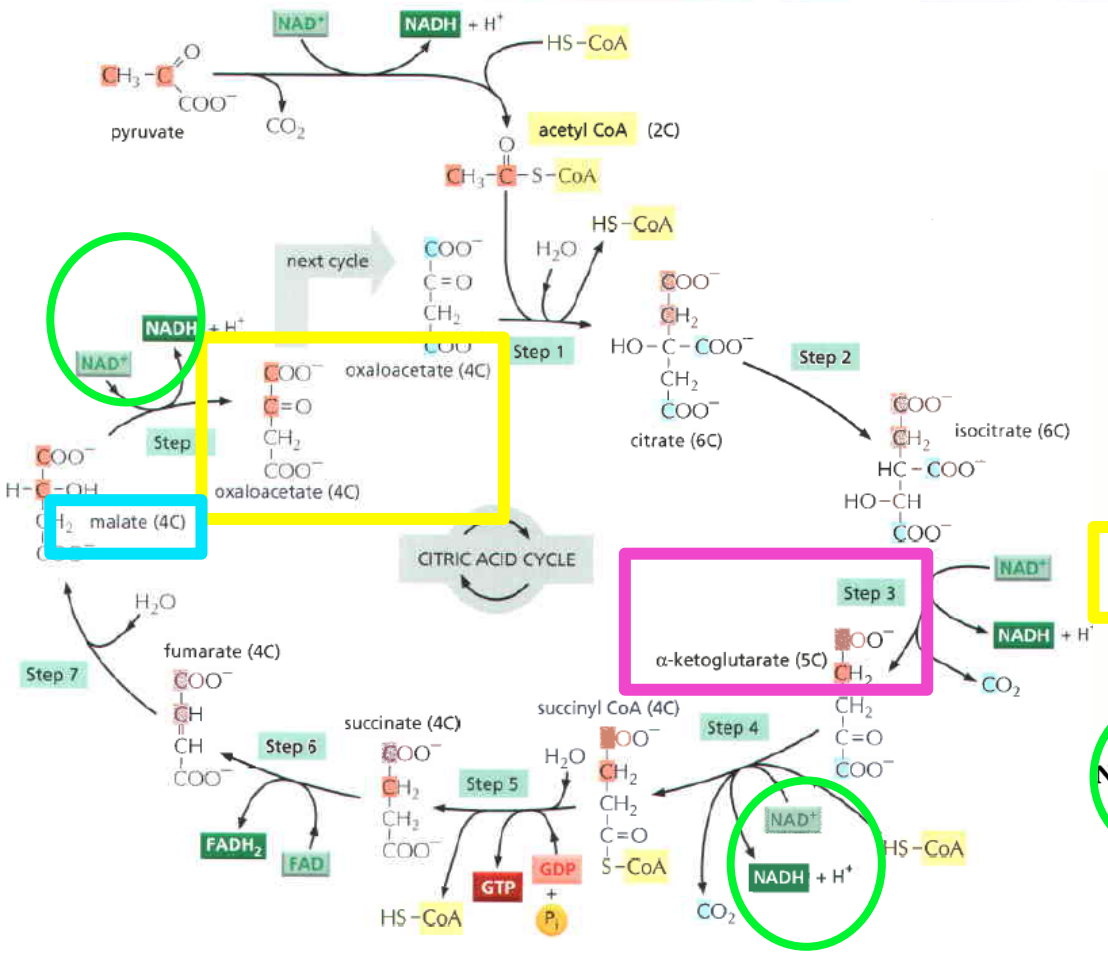
$$\Theta^3_{\gamma}(w) = Fw' \mid w' \in \{a, d, g, g', k\}^* \cup \{I, P, R, S\}^*$$

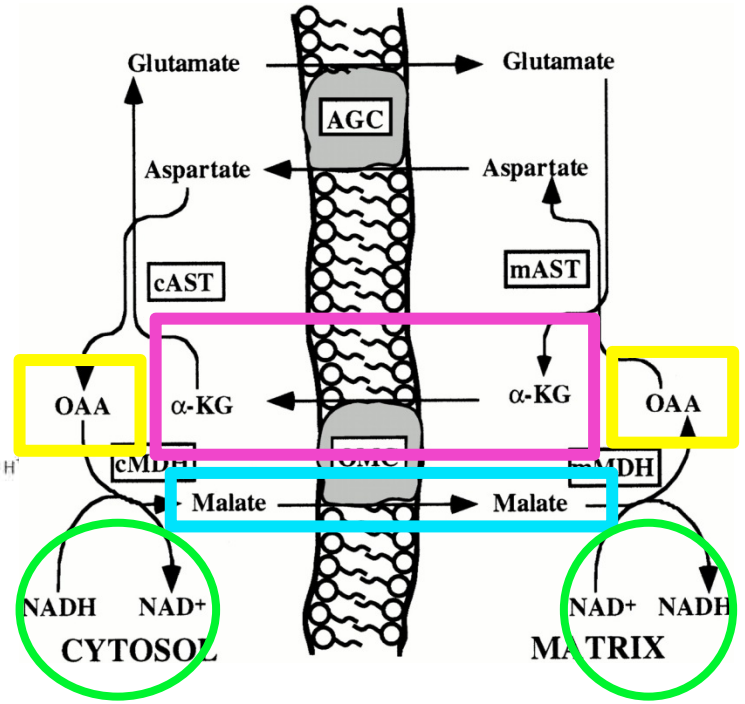
$$\Theta^4_{\gamma}(w) = ZC'w' \mid w' \in \{a, c, g, g', i, i', k, p, r, s\}^* \cup \{D, S\}^*$$

NEP and Metabolic Processes

- Our Goal:
  - To simulate several interconnected metabolic processes by using a multilayer architecture based on NEP.
  - Several NEPs working together can represent the interplay between metabolic processes and the signaling processes can be activate them.
  - For example, Krebs cycle and MAS shuttle pathway, share common enzymes and compete for some substrates such as αKG. Moreover, MAS is altered by signaling by calcium producing either activation or inhibition.

NEP and Metabolic Processes





NEP and Metabolic Processes

- Krebs cycle (acid cycle) is a metabolic process critical in cellular respiration. Some of the target activities of this cycle are controlled by calcium.
- **Calcium** helps to activate others metabolic pathways related, such as the malate-aspartate shuttle pathway (MAS for short) and intramitochondrial αKGDH.
- The interplay between these processes, sharing and competing for calcium, is important for study brain stimulation in vivo.

NEP – Krebs Cycle

- NEP Krebs definition

Let $\gamma_{Ek} = (V, U, G, N, \alpha, \beta, X_I, X_O)$ be the NEP representing the Krebs cycle. The components of this NEP are defined as follows:

- $V = \{PIR, H_2O, NAD^+, HS{-}CoA, GDP{+}P_i, FAD, acetyl\,CoA, NADH{+}H^+, \alpha kG, CIT, ISO, SUL, SUA, FUM, MAL, FADH_2, FAD, ATP, ADP, GTP, GDP + P_i, MDH, OOA, AST, ASP, AGC\}$
- $U = V \cup \{\alpha kGDH\}$
- $N = \{X_I, X_1, X_2, \ldots, X_{11}, X_O\}$ are the evolutionary processors in the network; X_I and X_O are, as usual, the input and output nodes respectively.
- $\beta(x) = s$ (strong) $\forall x \in X_G$. PI, FI are the permitting/forbidden input contexts and PO, FO are the permitting/forbidden output contexts of the filters.

NEP Example – Krebs cycle

Node	M	α	PI	FI	PO	FO
X_I	$PIR \rightarrow acetylCoA$, $H_2O \rightarrow HS-CoA$	*	PIR, H_2O	Ca, Ca'	$HS-CoA$	$acetylCoA$
X_1	$OOA \rightarrow CIT$	*	OOA H_2O	HS-CoA acetylCoA	CIT	$HS-CoA$
X_2	$CIT \rightarrow ISO$	*	CIT H_2O	$HS-CoA$	ISO	$HS-CoA$
X_3	$ISO \rightarrow \alpha kG$ $NAD^+ \rightarrow NADH + H^+$	l	ISO, NAD^+	$HS-CoA$	$\alpha kG, NAD^+$, $NADH + H^+$ $\alpha kgDH$, MAL	$\emptyset$
X_4	$\alpha kG \rightarrow SUL$ $HS-CoA \rightarrow CO_2$ $NAD^+ \rightarrow NADH + H^+$	*	C, O	$\alpha kgDH$ $NADH + H^+$ NAD^+, MAL	CO_2	$\emptyset$
X_5	$SUL \rightarrow SUA$, $H_2O \rightarrow HS-CoA$ $GDP + P_i \rightarrow GTP$	r	$HS-CoA$, $\alpha kG, NAD^+$	CO_2	SUL $NADH + H^+$	CO_2
X_6	$SUL \rightarrow SUA$, $H_2O \rightarrow HS-CoA$, $GDP + P_i \rightarrow GTP$	r	SUL, H_2O, $GDP + P_i$	$NADH + H^+$ CO_2	SUA	$HS-CoA$, GTP
X_7	$SUA \rightarrow FUM$ $FAD \rightarrow FADH_2$	l	SUA, FAD	$HS-CoA$ GTP	FUM	$FADH_2$
X_8	$FUM \rightarrow MAL$	l	FUM	$FADH_2$	MAL	$\emptyset$
X_9	$H_2O \rightarrow \varepsilon$	*	H, O	MAL	$\emptyset$	$\emptyset$
X_{10}	$MAL \rightarrow OOA$ $NAD^+ \rightarrow NADH + H^+$	l	MAL NAD^+	$\emptyset$	OOA	$NADH + H^+$
X_{11}	$OOA \rightarrow OOA$	*	OOA	$NADH + H^+$	PIR	$\emptyset$

NEP – MAS Shuttle

- NEP MAS Shuttle Definition

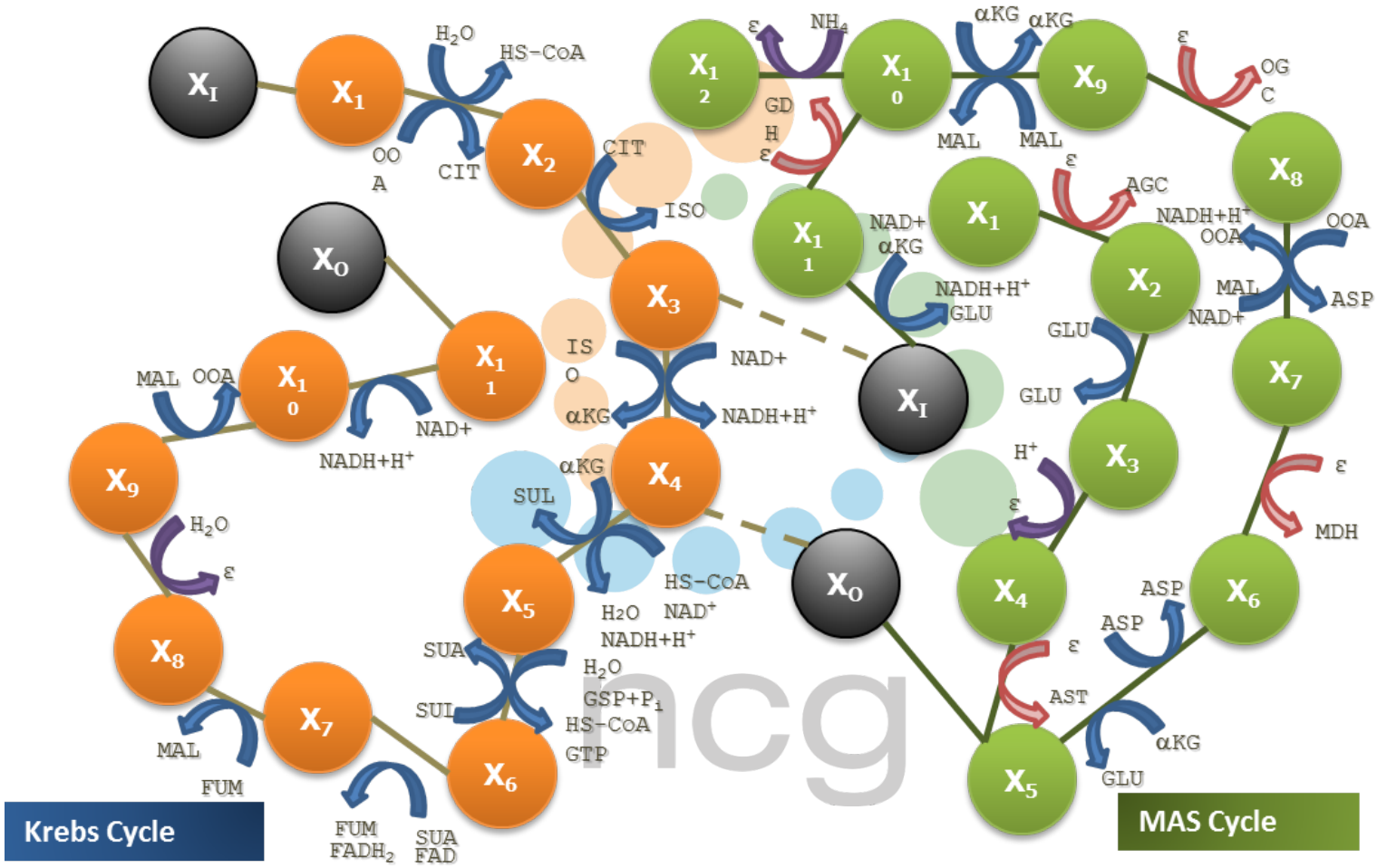
For MAS shuttle we use the NEP $\gamma_{Em} = (V, U, G, N, \alpha, \beta, X_I, X_O)$, with

- $V = U = \{NAD^+, GLU, H^+, ASP, \alpha kG, \alpha kG\, \alpha kGDH, MAL, NADH+ H^+, NH_4, ATP, ADP, GTP, MDH, OOA, AST, ASP, AGC, GDH, Ca, Ca'\}$
- $N = \{X_I, X_1, X_2, \ldots, X_6, \ldots X_{12}, X_O\}$ are the evolutionary processors in the network, where X_I, X_O are the input/output nodes.
- $\beta(x)$ is defined as in γ_{Ek}.

NEP Example – MAS shuttle

Node	M	α	PI	FI	PO	FO
X_I	$\alpha\ kG \rightarrow \varepsilon$	r	αkG	Ca,Ca'	GLU, H^+	AGC
X_1	$\varepsilon \rightarrow AGC$	*	GLU, H^+, AST	αkG	AGC	
X_2	$GLU \rightarrow GLU$	*	GLU,ASP,H^+	αkG	GLU, ASP	AGC
X_3	$H^+ \rightarrow \varepsilon$	*	GLU,ASP	αkG	GLU, ASP	AGC
X_4	$\varepsilon \rightarrow AST$	r	GLU,OOA	$NADH + H^+$	AST, ASP	αkG
X_5	$GLU \rightarrow \alpha\ kG$ $ASP \rightarrow\ ASP$	*	GLU, ASP OOA	$NADH + H^+$	αkG, ASP	AST
X_6	$\varepsilon \rightarrow MDH$	r	NAD^+, MAL	αkG	MDH,$NADH + H^+$	OOA
X_7	$OOA \rightarrow ASP$ $NAD^+ \rightarrow NADH + H^+$ $MAL \rightarrow OOA$	*	OOA NAD^+ MAL	αkG	$NADH + H^+$ OOA	MDH
X_8	$\varepsilon \rightarrow OGC$	r	MAL, αkG	NAD^+	OGC, αkG, MAL	$NADH + H^+$
X_9	$MAL \rightarrow MAL$ $\alpha\ kG \rightarrow \alpha\ kG$	*	MAL, αkG $NADH + H^+, NH_4$	OGC	MAL, αkG, NAD^+, GLU	GDH
X_{10}	$\varepsilon \rightarrow GDH$	r	GLU, $NADH + H^+$ αkG	MAL	GDH	αkG
X_{11}	$\alpha\ kG \rightarrow GLU$ $NAD^+ \rightarrow NADH + H^+$	*	$\alpha kG, NAD^+$	MAL	GLU $NADH + H^+$	GDH
X_{12}	$NH_4 \rightarrow \varepsilon$	*	$NH_4, \alpha kG$ $NADH + H^+$	ASP	H^+, GLU	GDH

Krebs NEP and MAS NEP



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Using NPEP to Activate or to Inhibit Signaling

- The amount of some chemical compound can produce the inhibition or activation of cellular pathways.
- We use NPEP to evaluate words produced by a NEPT in order to drive them to a specific NEP.
  - Polarization indicates if a determined string is neutral (0), activates (+) or inhibits (-) the process represented by a NEP.
  - Polarization in strings that reach the output node are useful in order to activate/inhibit different networks.

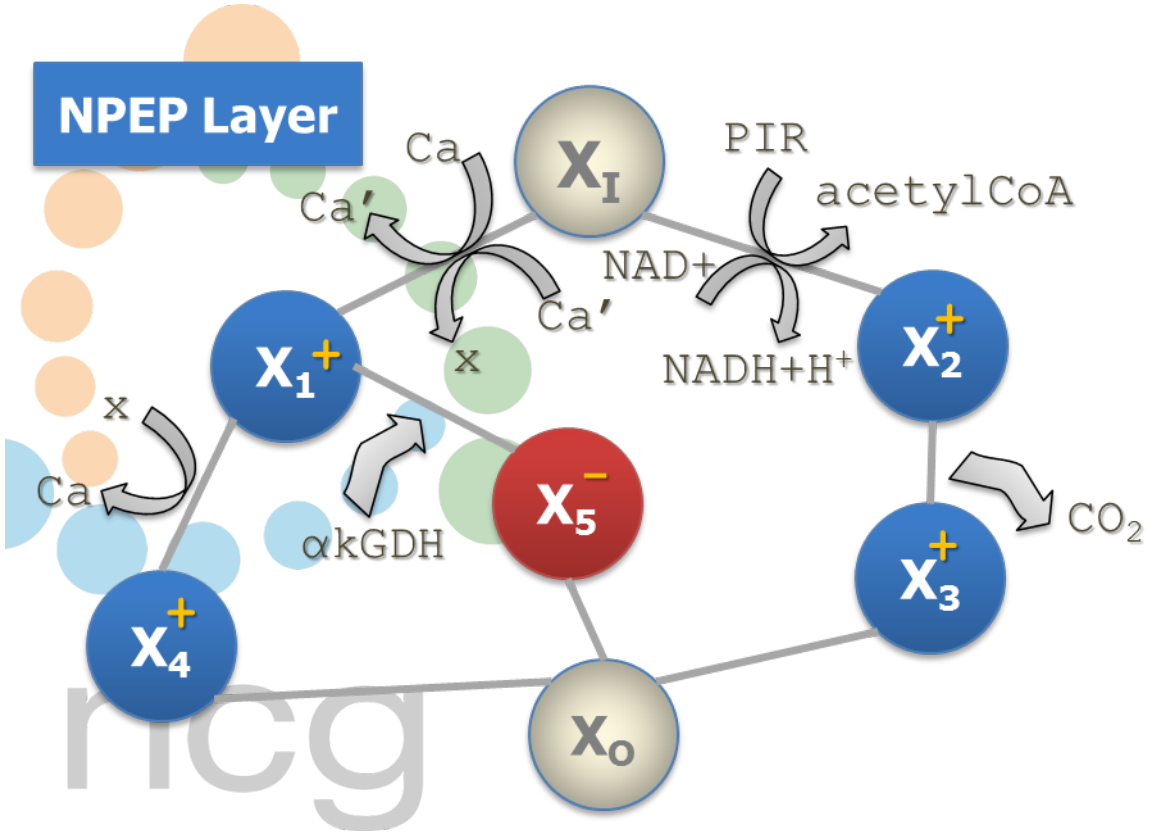
Using NPEP to Control others NEP's

- It can be defined a NPEP γ_P, to control the corresponding NEP γ_{EK} Krebs/γ_{Em} MAS cycles.

- $V = \{Ca, Ca', H_2O, CO_2, NAD^+, NADH + H^+, S - CoA, HS - CoA, GLU, \alpha kG, CIT, ISO, SUC, SUA, FUM, MAL, FADH_2, FAD, ATP, ADP, GTP, GDP + P_i, MDH, OOA, AST, ASP, AGC, PIR, acetylCoA\}$
- $U = V \cup \{\alpha KGDH, x\}$
- The valuation mapping $\varphi : U^* \longrightarrow \mathbb{Z}$ is given by
  $\varphi(PIR) = \varphi(NAD^+) = \varphi(CO_2) = 1$
  $\varphi(Ca) = \varphi(x) = 0$
  $\varphi(Ca') = -1$
  $\varphi(z) = 0$ otherwise.
- $N = \{X_I, X_1, X_2, \ldots, X_5, X_O\}$ are the evolutionary processors of the NPEP (X_I, X_O are the input/output nodes respectively).

Using NPEP to Control others NEP's

Node	R	δ
X_1	$Ca \rightarrow Ca', Ca' \rightarrow x$	+
X_2	$PIR \rightarrow acetylCoA$, $NAD^+ \rightarrow NADH + H^+$	+
X_3	$CO_2 \rightarrow \varepsilon$	+
X_4	$x \rightarrow Ca$	+
X_5	$\varepsilon \rightarrow \alpha kGDH$	-
X_O	$\emptyset$	+



Finally… the "proposed" system!