Application of Membrane Systems to Biological Processes

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Aims and Motivations

- Use the framework of P systems for defining models of specific cellular phenomena or cellular structures
  - flexibility
  - extensibility
- Design appropriate software simulators to return meaningful information to biologists
- Motivate further cooperations between the fields of P systems and Molecular Biology

Aims and Motivations

- Systems biology:
  - known biological data $\rightarrow$ define a possible model
  - check correctness and effectiveness of the model via software simulations
  - use the model/software to predict unknown behaviours of the system
  - use the model/software to analyse dynamic properties of the system:
    - robustness
    - feedback/feedforward loops
    - periodic behaviours
    - chaotic behaviours
    - …

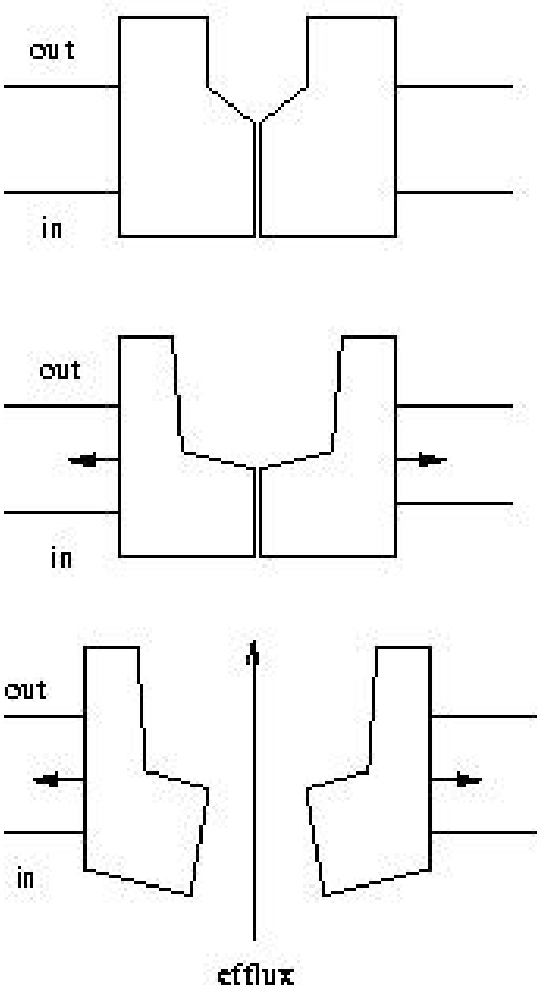
Membrane systems and biology

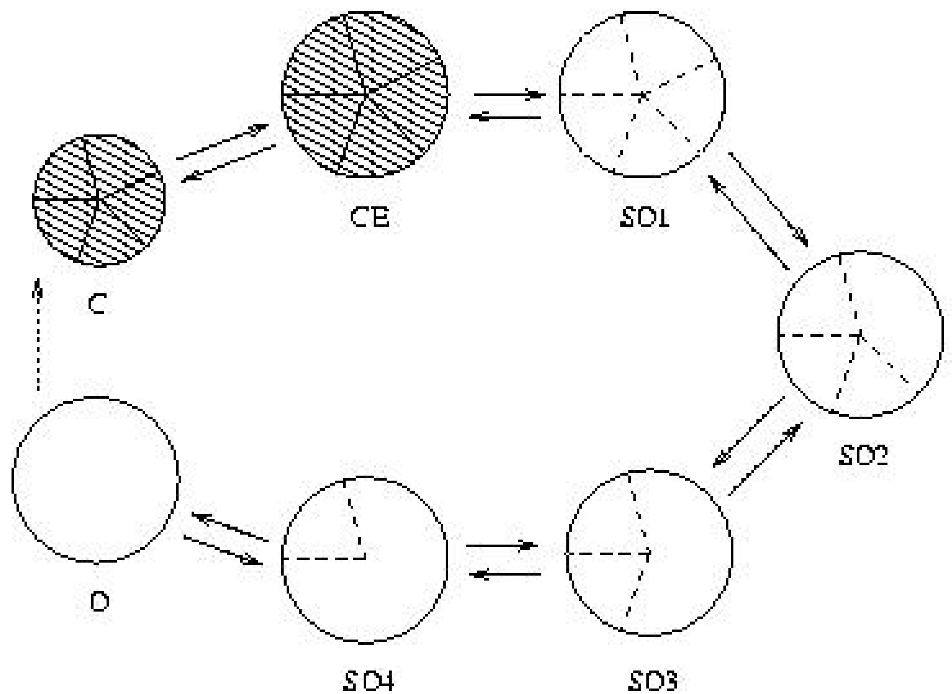
- Simulation of various cell processes
  - Mechanosensitive channels
  - Sodium-Potassium pump
  - Gemmation of mobile membranes

P models for mechanosensitive channels

- Mechanosensitive channels (MscL)
  - Homopentameric protein channels which open in response to membrane stretch and deformation, due to mechanical forces:
    - they are directly gated by the membrane *tension*
    - no extra-membrane component is required for the gating
    - they allow the rapid exit of different chemicals and the sudden decrease of the osmotic pressure

P models for mechanosensitive channels





Mechanosensitive channels

- Patch clamping:
  - a negative pressure is applied to a portion of the cellular membrane
  - description with P systems: *in vitro* model
  - software simulations

- Hypotonic shocks:
  - an addition of water to the external medium causes an increase in the osmotic pressure (due to different internal/external concentrations)
  - description with P systems: *in vivo* model

In vitro model

In vitro P model

- Data from experiments on bacteria E. Coli
- Environment and bacterial region
- Variable parameter for membrane tension:

$$Env\ [_t\ Reg$$

t in the set *Tension* = $\{t_C, t_{CE}, t_{SO1}, t_{SO2}, t_{SO3}, t_{SO4}, t_O, t_L\}$

(t denotes any status of the channel)

- Evolution rules with associated probabilities, depending on applied pressure:

$$\langle p, apply \rangle\ [_t\ \rightarrow_{prob}\ [_{t'}$$

In vitro model

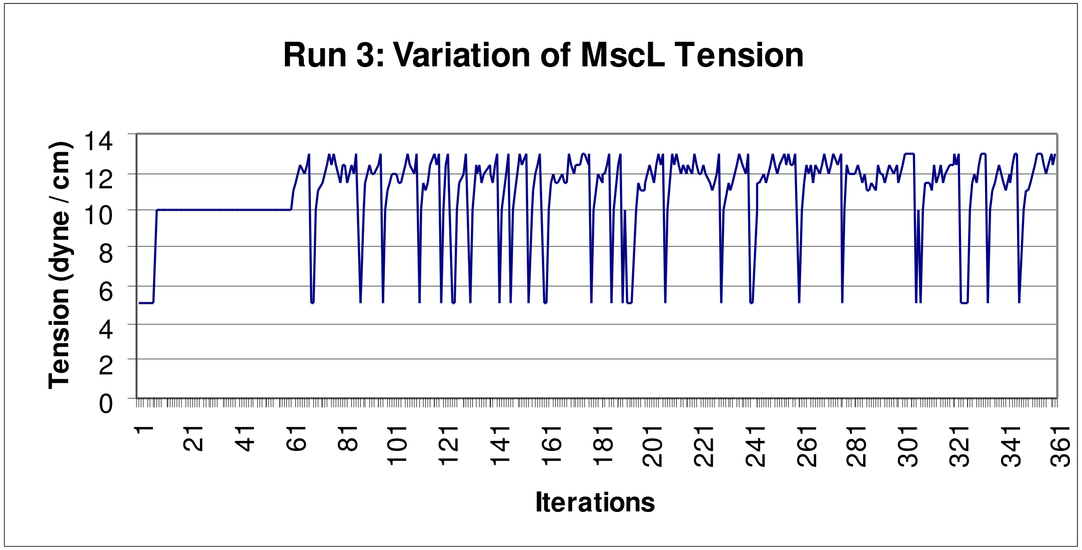
- Components:
  - evolution rules with associated probabilities
  - evolution rules depending on artificially applied pressure

$$<p, apply> [_t \rightarrow_{prob} [_{t'}$$

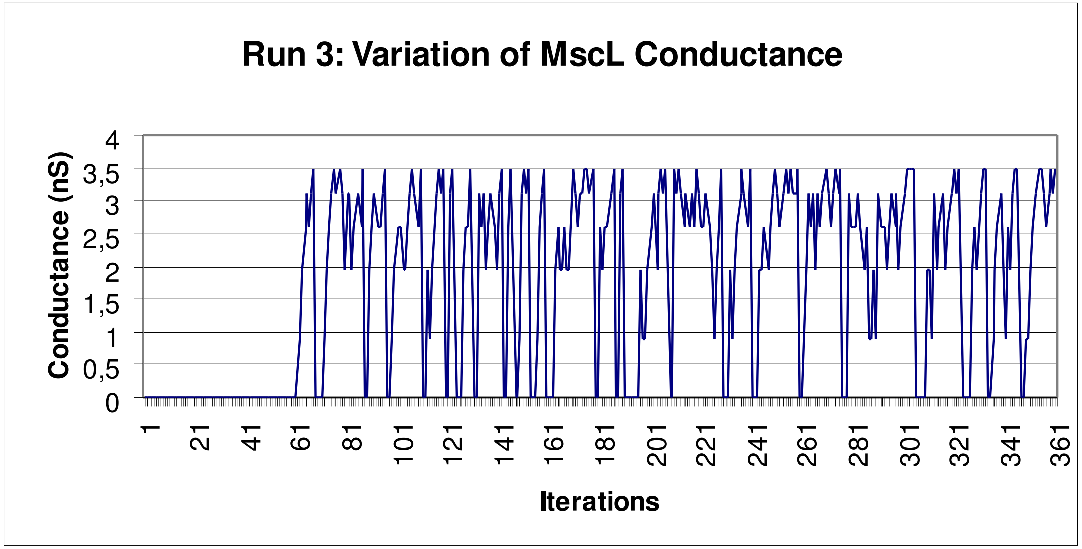
- Applicability of the model (defined for a single channel) to a population of channels

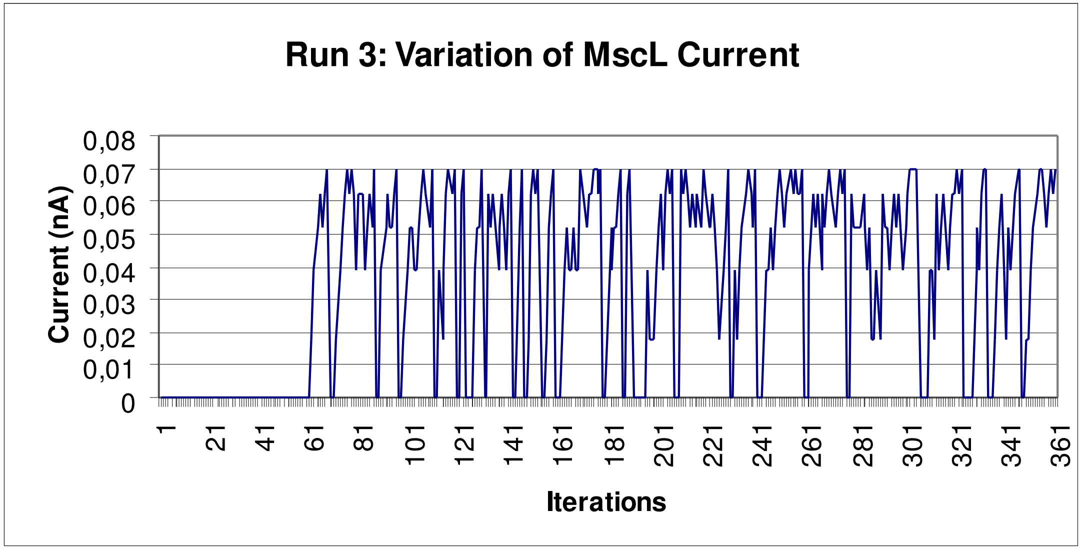
In vitro model - simulations

- Simulation results for emergent quantities (tension, current, conductance):
  - *EdnaCo*, a complex system simulator (by Max Garzon, University of Memphis)
  - cluster of 24 Pcs



In vitro model - simulations





In vivo model

- Description of channel activity during hypotonic shocks in natural or laboratory environments
- Components:
  - environment
  - bacterial region
  - variable parameter for membrane tension

$$M_{Env} [_t M_{Reg}$$

with M_{Env}, M_{Reg} multisets over $V_{chem} \cup \{w\}$, *t* in the set
Tension = $\{t_{close0}, t_{close1}, t_{substate}, t_{open}, t_{lysis}\}$

In vivo model

- Components:
  - definition of concentration of objects
  - evolution rules depending on addition of water and concentration of objects

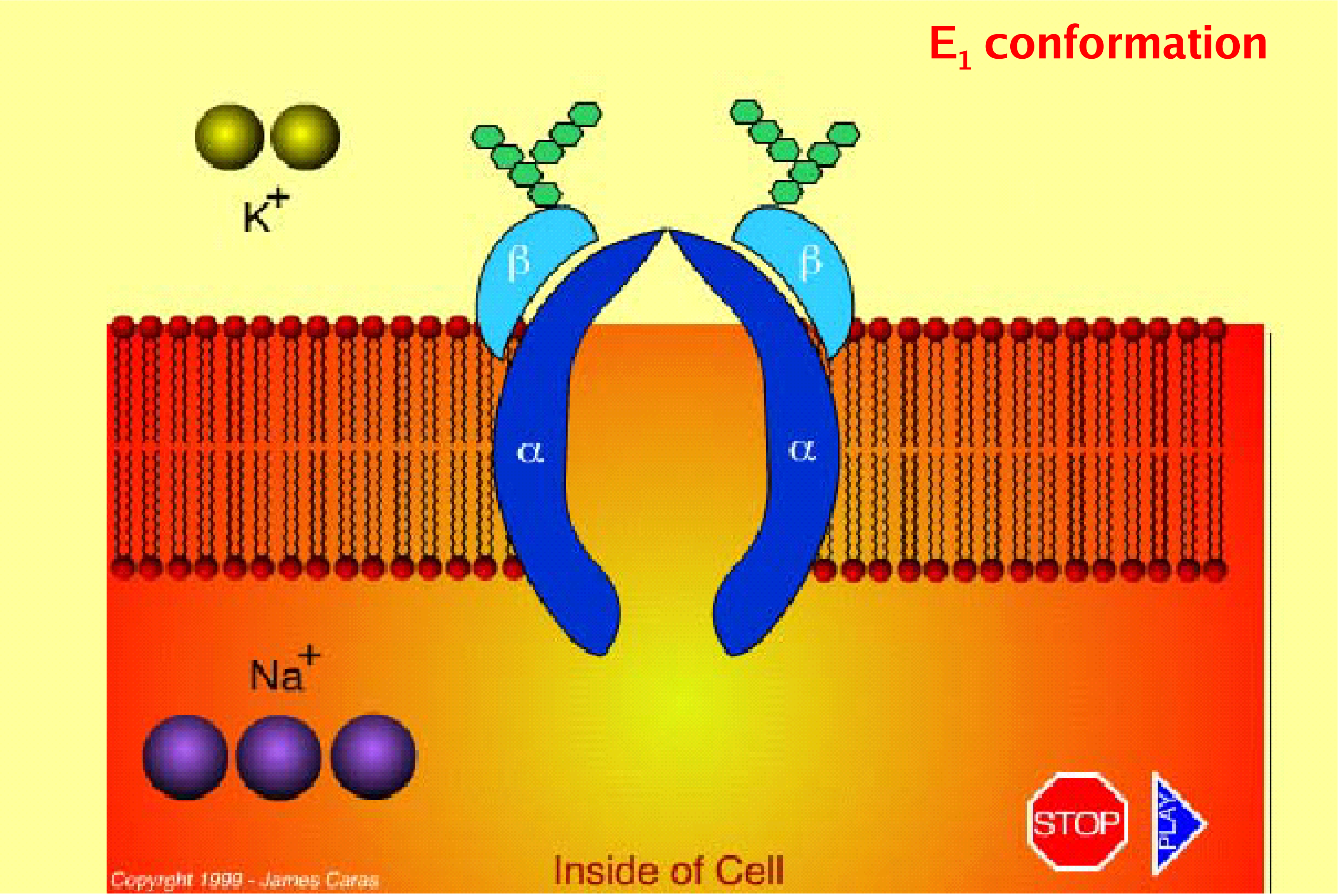
$$\langle w^{k}, add \rangle \, [_{t} \;\rightarrow^{C(x,y)} [_{t'}$$

- Analysis of subsequent activation cycles
- Soundness with different living conditions of other prokaryotes

Sodium-potassium pump

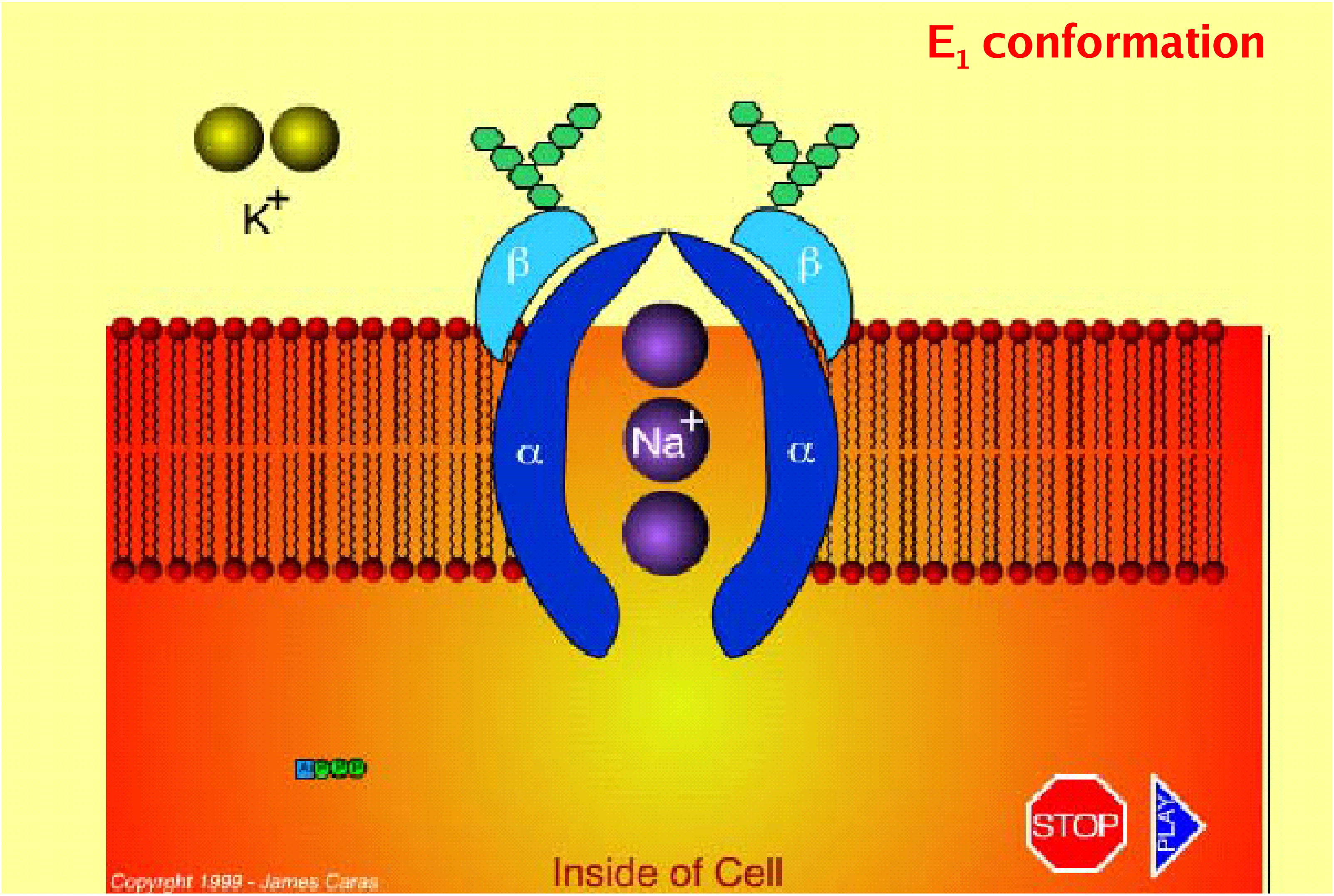
- Establishment of the appropriate cellular concentrations of sodium and potassium ions
- Transport of 3 sodium ions outwards and 2 potassium ions inwards
- Consumption of 1 molecule of ATP :
  ATP= ADP+P
- Different conformations of the pump:
  - open inside or open outside (high/low affinity)
  - phosphorylated or not phosphorylated
  - occluded states

The sodium-potassium pump



http://www.brookscole.com/chemistry_d/templates/student_resources/shared_resources/animations/ion_pump/ionpump.html

The sodium-potassium pump



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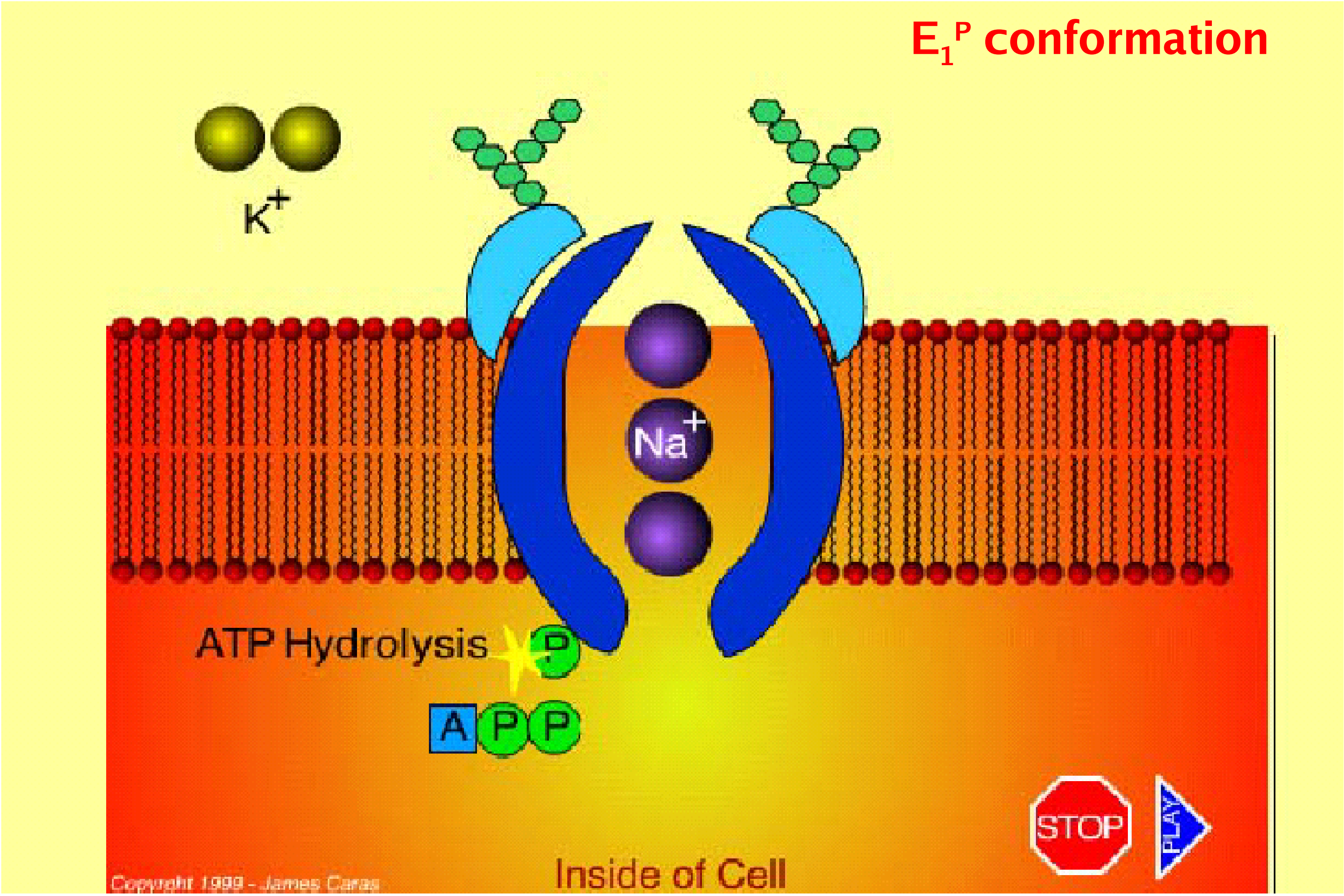

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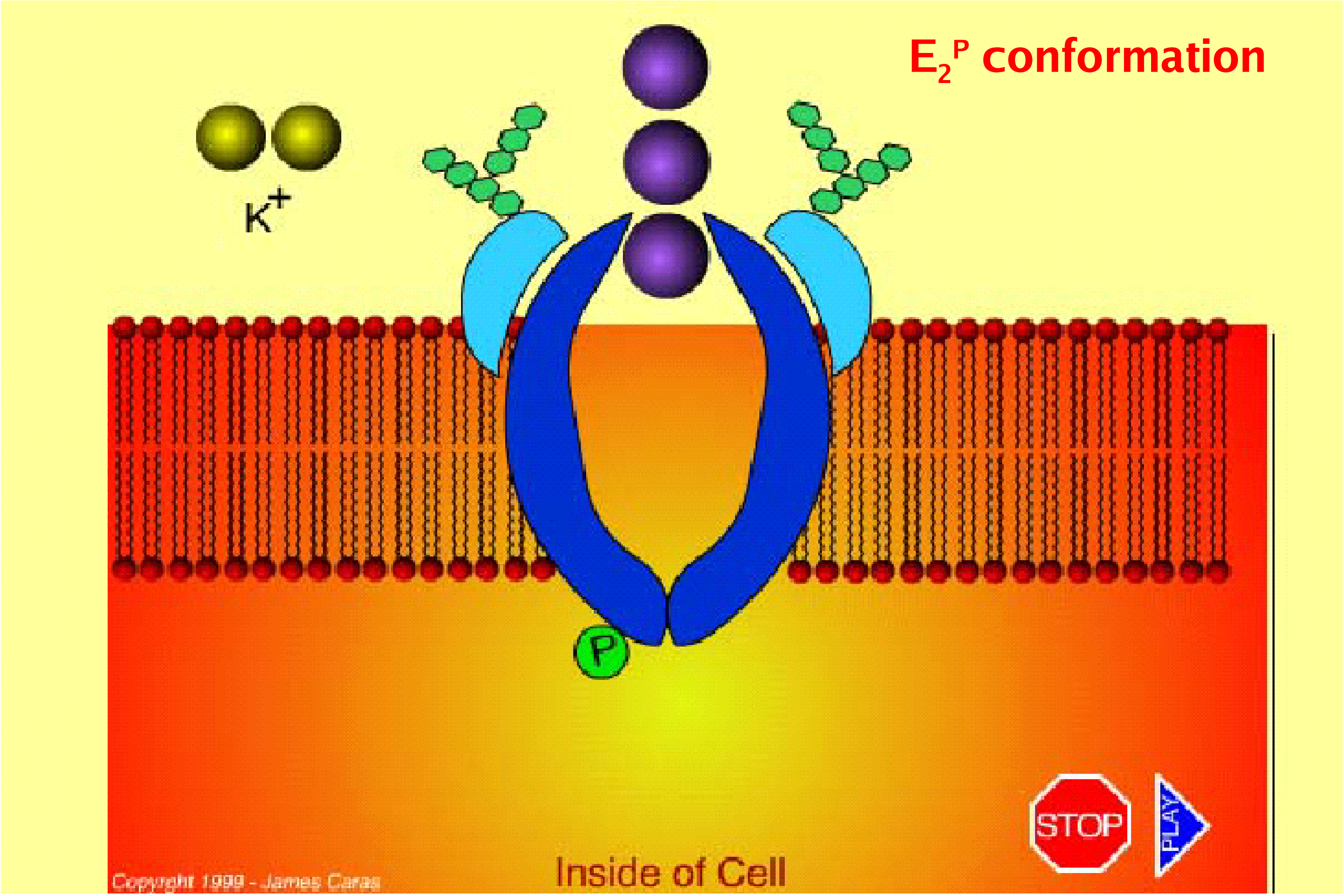

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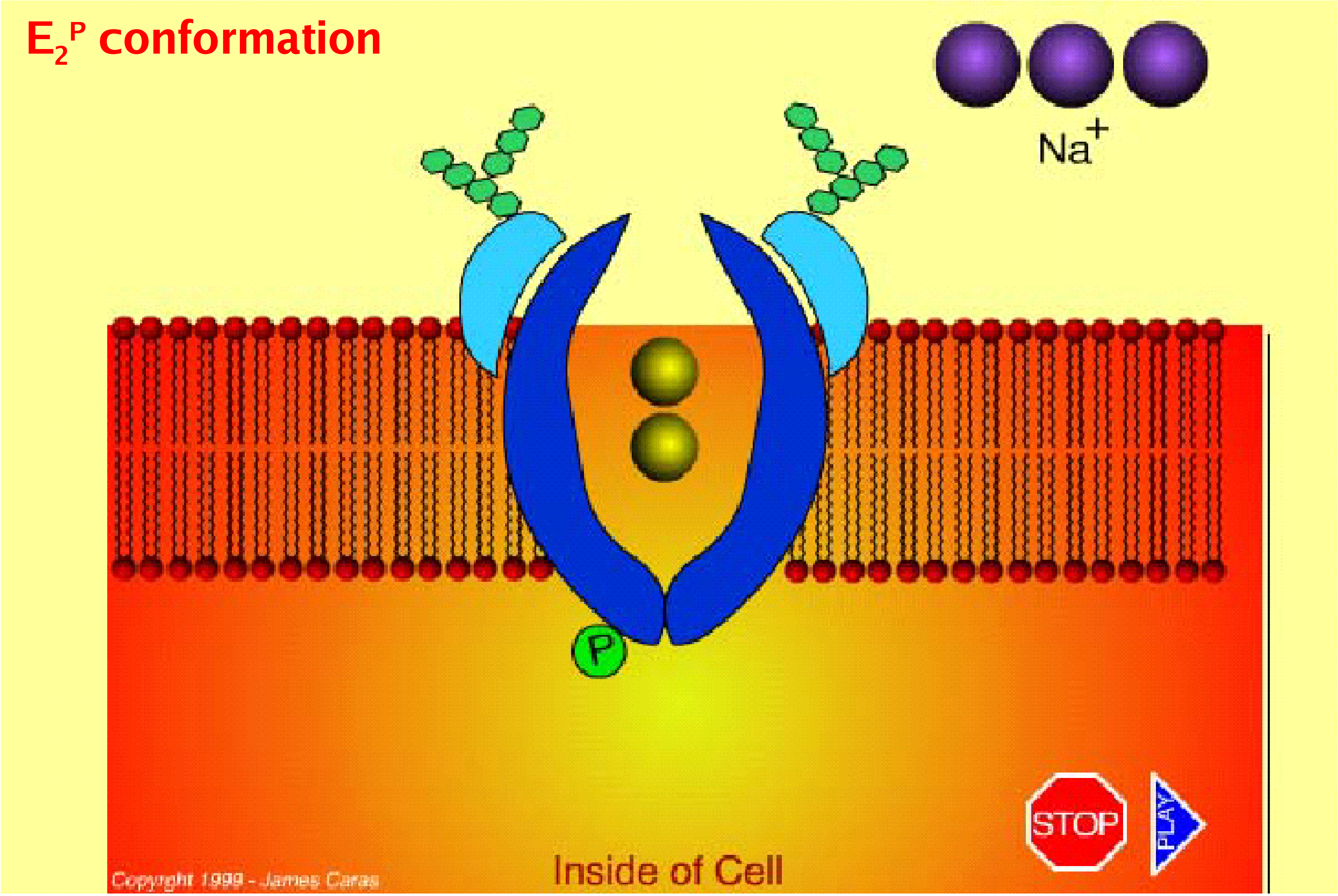

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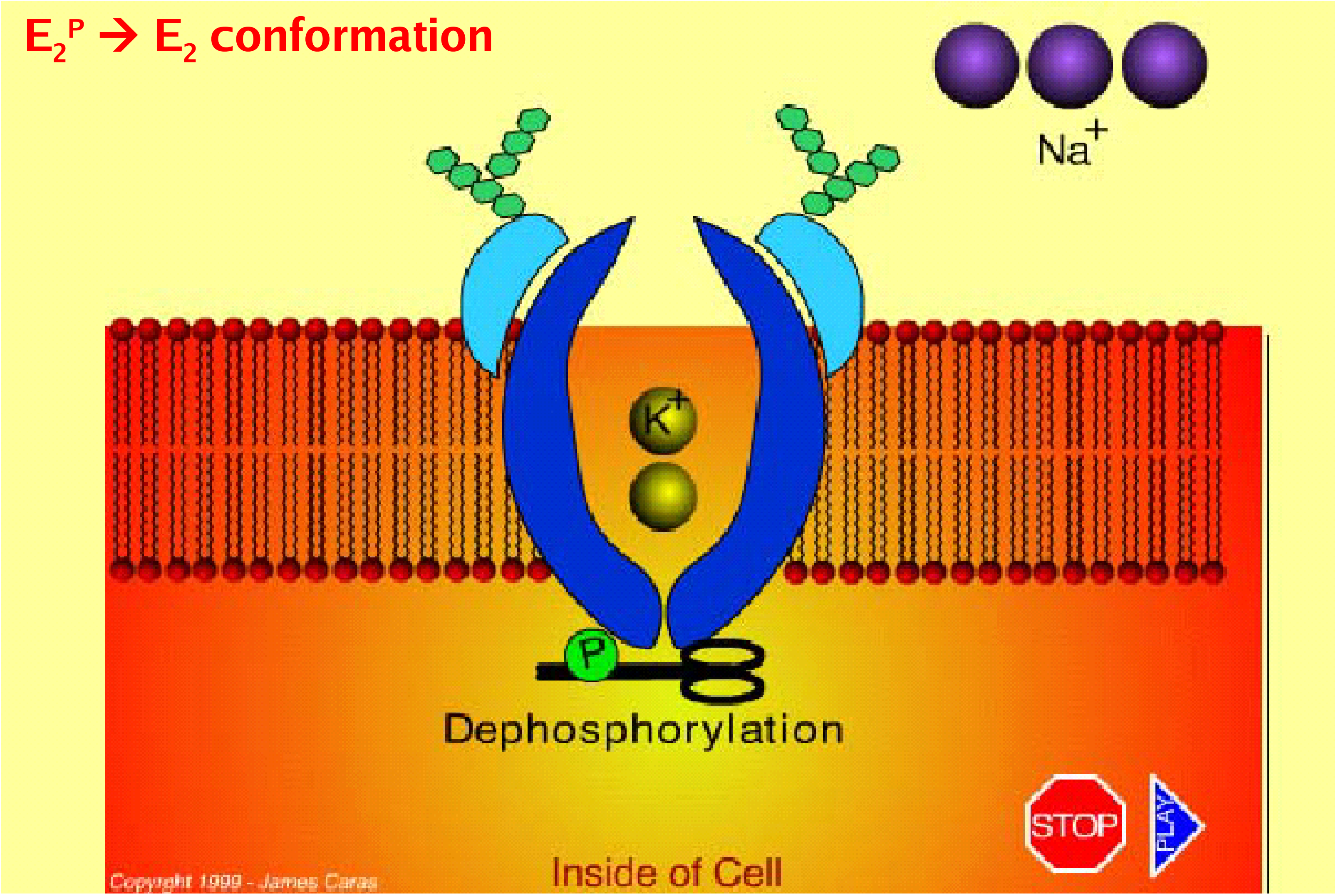

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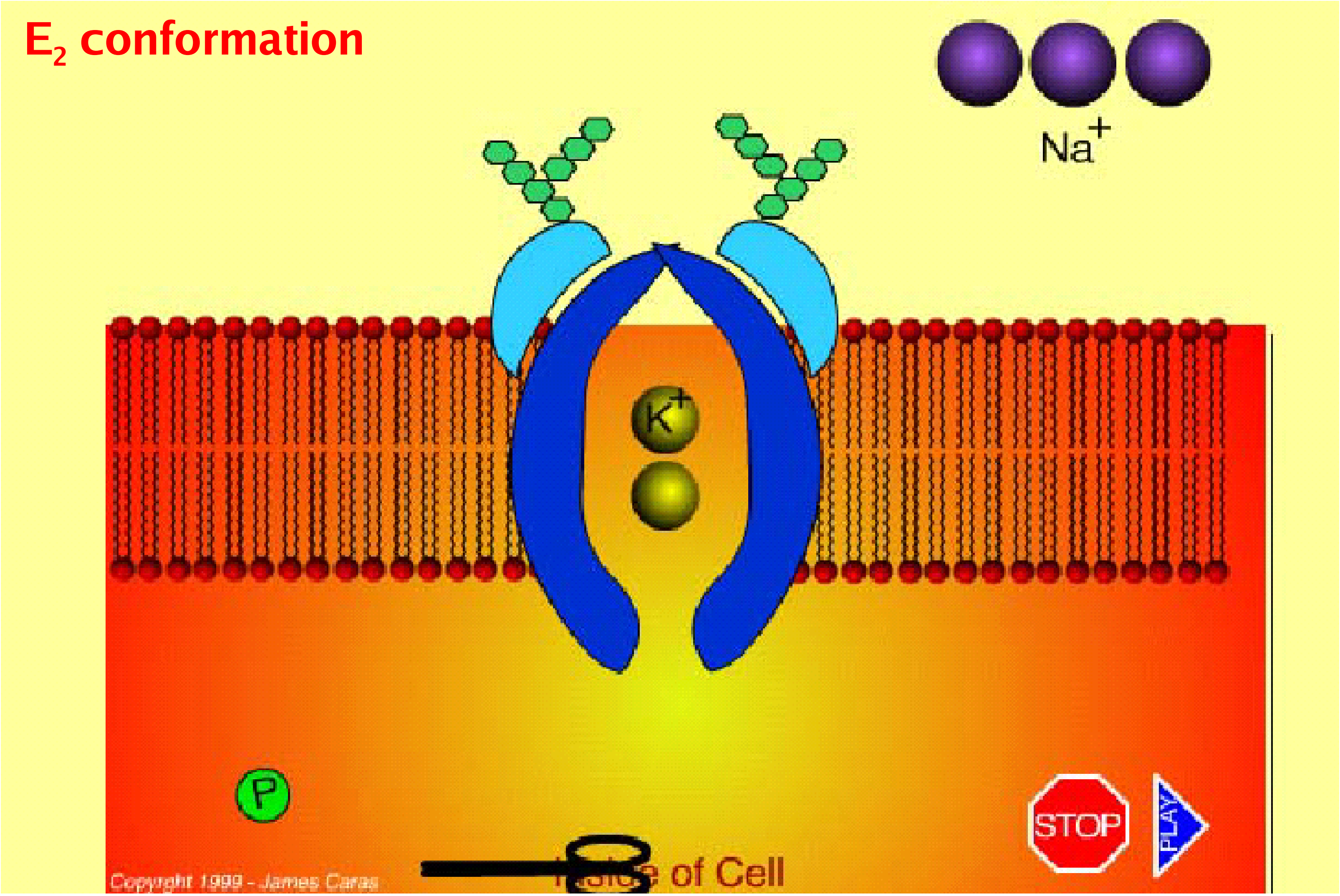

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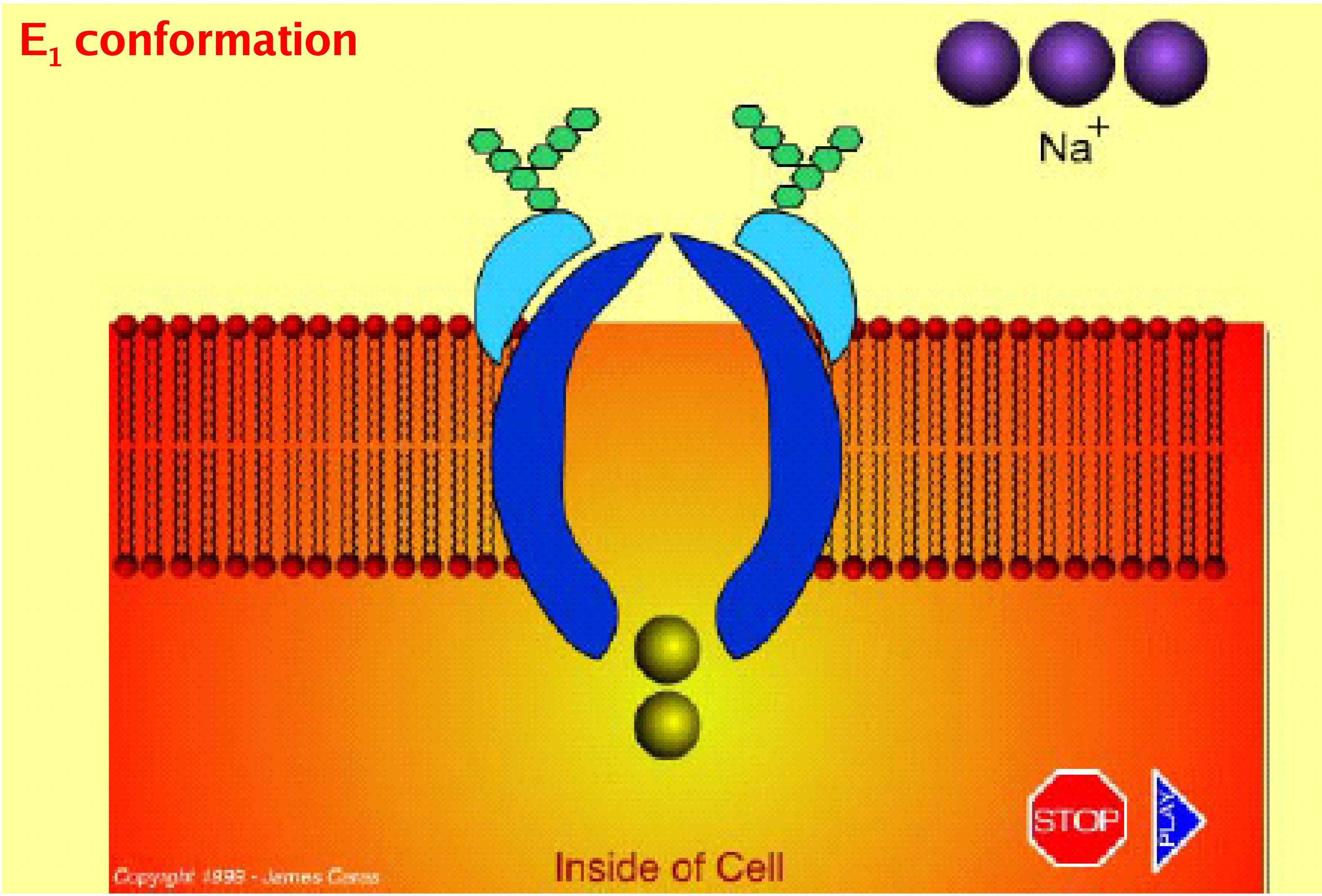
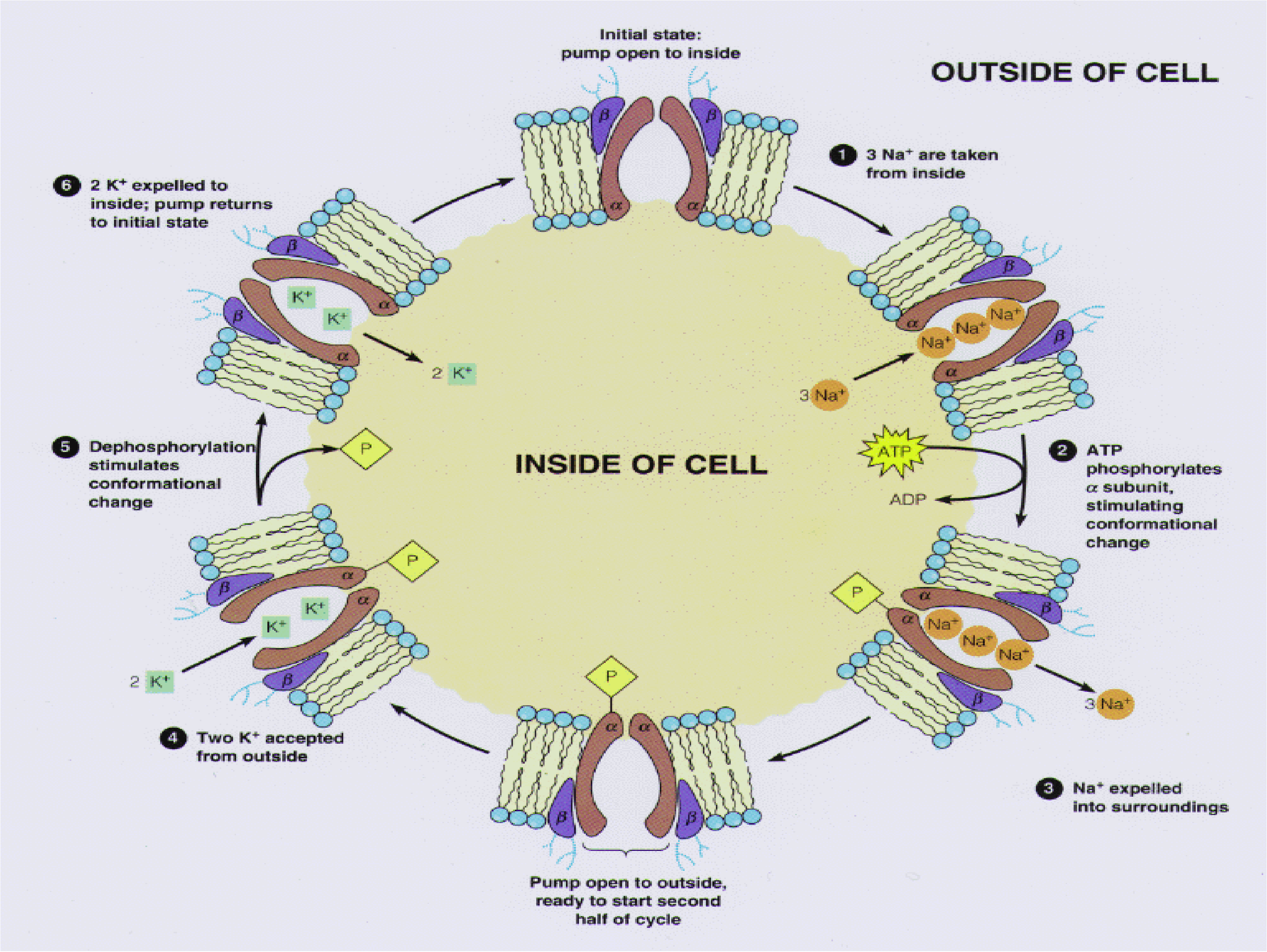
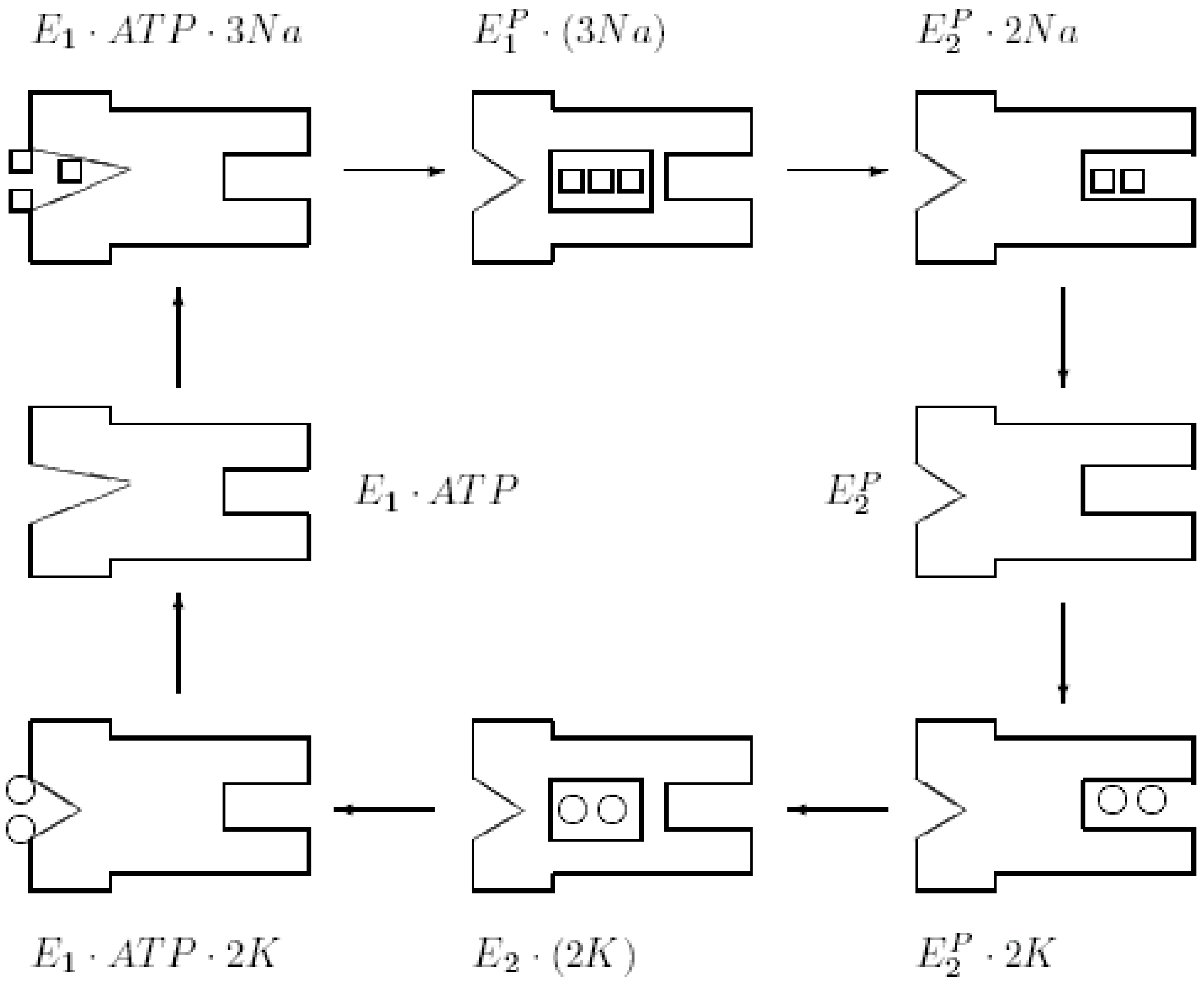


Sodium-potassium pump



Sodium-potassium pump

Post-Albers cycle with occluded states



Sodium-potassium pump

- P model → 8 rules
- Environment, cytoplasmic region, bilayer:

Env [Bilayer | Region

- Alphabet V = {Na, K, ATP, ADP, Ᵽ}
  - alphabet for occluded states V_{occ} = {Na, K}
- Variable membrane label L ∈ {$E_1 \cdot$ATP, E_1^P, E_2, E_2^P}
  - denotes different conformations of the pump
  - labels for occluded states L ∈ {E_1^P, E_2}
- Evolution rules modify (also) the label of the membrane
- Threshold conditions for pump activation

P model for Na-K pump

- Alphabet: {Na, K, ATP, ADP, P}

- Membrane structure with bilayer:

  out [| in |] out

- Initial multisets:
  - inside: Na^n, K^m, ATP^s
  - outside: Na^p, K^q
  - bilayer: empty

P model for Na-K pump

- Multiple membrane-labelling:

$$L \in \{E_1, E_2, E_1^P, E_2^P\}$$

- Evolution rules modify (also) the label of the membrane
  - Na and K are never modified but only communicated
  - P is both an object and (part of) a membrane label

P model for Na-K pump

- Binding rules:

$$b_{out,\ within}:\ x[\ |_L \rightarrow [x|_L,$$

$$b_{in,\ within}:\ [\ |_L\ x \rightarrow [x|_L,$$

- Unbinding rules:

$$u_{within,\ in}:\ [x|_L \rightarrow [\ |_L,\ x$$

$$u_{within,\ out}:\ [x|_L \rightarrow x\ [\ |_L,$$

- Threshold condition for pump activation

P model for Na-K pump

Env [Bilayer | Reg

activation condition

$$r_1 : [\ |_{E1}\ Na^3 \rightarrow [Na^3|_{E1}$$

$$r_2 : [Na^3|_{E1}\ ATP \rightarrow [Na^3|_{E1P}\ ADP \quad (ATP \rightarrow ADP + P)$$

$$r_3 : [Na^3|_{E1P} \rightarrow Na^3\ [\ |_{E2P}$$

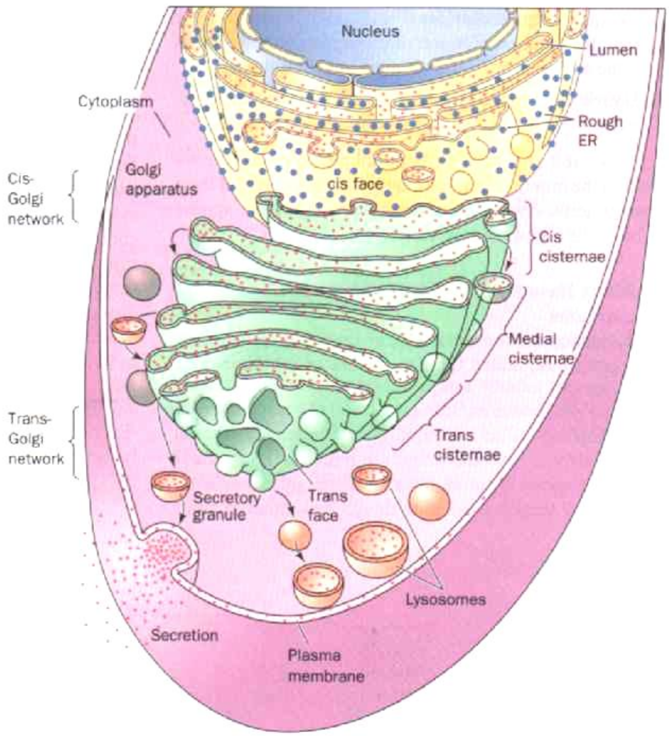
$$r_4 : K^2\ [\ |_{E2P} \rightarrow [K^2|_{E2P}$$

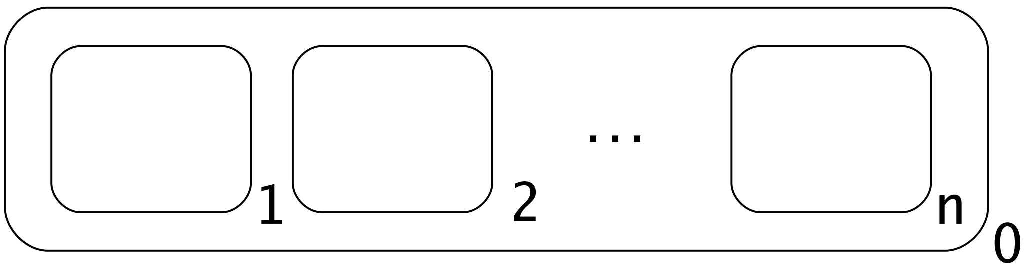
$$r_5 : [K^2|_{E2P} \rightarrow [K^2|_{E2}\ P$$

$$r_6 : [K^2|_{E2} \rightarrow [\ |_{E1}\ K^2$$

Gemmation of mobile membranes

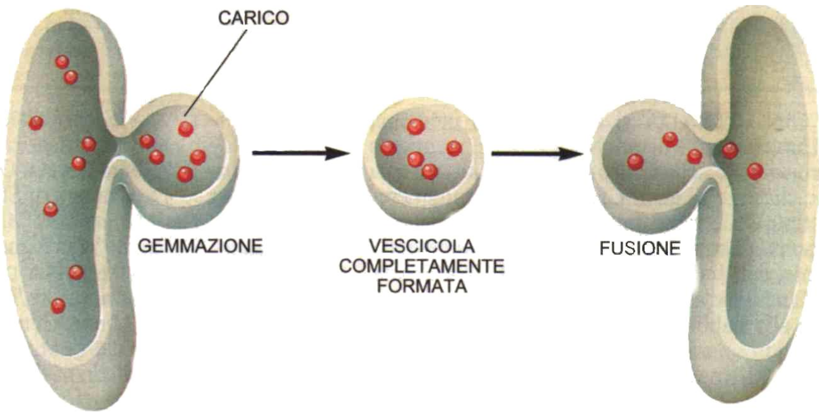
- Inspired by the structure and the functioning of Golgi apparatus in eukaryotic cells





P systems with mobile membranes

- Use of evolution rules of biochemical inspiration:
  - mutation, replication, splitting rules
- Predynamical rules $\rightarrow$ use of mobile membranes for the communication of strings



P systems with mobile membranes

- Gemmation and fusion of mobile membranes