Nov 8: **Eric Deeds**, University of California at Los Angeles
"The evolution of cellular individuality"

Nov 15: **Daniel Merkle**, University of Southern Denmark
"Graph rewriting and chemistry"

Nov 22: **Jean Krivine**, IRIF, Université de Paris
"From molecules to systems: the problem of knowledge representation in molecular biology"

Nov 29: **Eric Smith**, Earth Life Sciences Institute, Tokyo
"Easy and Hard in the Origin of Life"

Dec 13: **Yarden Katz**, Harvard Medical School, Boston
"Cells as cognitive creatures"

Jan 10: **Massimiliano Esposito**, University of Luxembourg
"Thermodynamics of Open Chemical Reaction Networks: Theory and Applications"

Jan 17: **Aleksandra Walczak**, ENS Paris
"Prediction in immune repertoires"

Jan 24: **Tommy Kirchhausen**, Harvard Medical School
"Imaging sub-cellular dynamics from molecules to multicellular organisms"
1. The Topology of the Possible
   (La représentation de l’information biologique)

2. Propagation of Genetic, Phenotypic, and Molecular information
   (Limites de la transmission de l’information biologique)

3. Modeling cellular information processing the classical way
   (Modélisation ‘classique’ du traitement de l’information cellulaire)

4. Modeling cellular information processing the rule-based way
   (Modélisation basé sur les règles; introduction)

5. Examples of rule-based models
   (Modélisation basé sur les règles; examples)

6. Causality in rule-based dynamics
   (Causalité)

7. Combinatorial scaffolding
   (Echafaudage combinatoire)

8. Cellular learning?
   (Apprentissage cellulaire?)
Copying a Polymer (Single-Step)
Copying a Polymer (Single-Step)
Copying a Polymer (Contact Map)
Copying a Polymer (Multi-Step)

intermediate state
The purpose of Multi-Step is to allow for proofreading.
Free Energy Landscape of Proofreading

\[ k_{i\rightarrow j}^R = \omega \exp \left( \frac{(E_i^R + \mu_{i\rightarrow j} + \delta_{i\rightarrow j})}{RT} \right) \]

\[ k_{i\rightarrow j}^W = \omega \exp \left( \frac{(E_i^W + \mu_{i\rightarrow j})}{RT} \right) \]

\[ k_{j\rightarrow i}^R = \omega \exp \left( \frac{(E_j^R + \delta_{i\rightarrow j})}{RT} \right) \]

\[ k_{j\rightarrow i}^W = \omega \exp \left( \frac{E_j^W}{RT} \right) \]
The Purpose of Multi-Step is to Allow for Proofreading
Copying a Polymer (Multi-Step)

intermediate state
Copying a Polymer: End Cases

intermediate state

a problem…
Copying a Polymer: End Cases

“test” unbinding
6. Causality
'EGFR.EGFR'  \( \rightarrow \) EGFR(L\[,\]CR\[,\]N\[,\]C\[,\] \rightarrow \) EGFR(L\[,\]CR\[,\]N\[,\]C\[,\], \EGFR(L\[,\]CR\[,\]N\[,\]C\[,\])  \( @ 'k_{on}'/2 \)

'EGFR/EGFR'  \( \rightarrow \) EGFR(L\[,\]CR\[,\]N\[,\]C\[,\], \EGFR(L\[,\]CR\[,\]N\[,\]C\[,\])  \( @ 'k_{off}'/2 \)

'EGF.EGFR'  \( \rightarrow \) EGFR(r\[,\], \EGFR(L\[,\]CR\[,\]))  \( @ 'k_{on}' \)

'EGFR/EGFR'  \( \rightarrow \) EGFR(r\[,\], \EGFR(L\[,\]CR\[,\]))  \( @ 'k_{off}' \)

'Shc.Grb2'  \( \rightarrow \) Shc(Y\{p\}[\], Grb2(SH2[\], \rightarrow \) Shc(Y\{p\}[\], Grb2(SH2[\]))  \( @ 5 'k_{on}' \)

'Shc/Grb2'  \( \rightarrow \) Shc(Y\{p\}[\], Grb2(SH2[\], \rightarrow \) Shc(Y\{p\}[\], Grb2(SH2[\]))  \( @ 'k_{off}' \)

'EGFR.Grb2'  \( \rightarrow \) EGFR(Y1092(p)[\], Grb2(SH2[\], \rightarrow \) EGFR(Y1092(p)[\], Grb2(SH2[\]))  \( @ 'k_{on}' \)

'EGFR/Grb2'  \( \rightarrow \) EGFR(Y1092(p)[\], Grb2(SH2[\], \rightarrow \) EGFR(Y1092(p)[\], Grb2(SH2[\]))  \( @ 'k_{off}' \)

'EGFR.Shc'  \( \rightarrow \) EGFR(Y1172(p)[\], Shc(PTB[\], \rightarrow \) EGFR(Y1172(p)[\], Shc(PTB[\]))  \( @ 'k_{on}' \)

'EGFR/Grb2'  \( \rightarrow \) EGFR(Y1172(p)[\], Shc(PTB[\], \rightarrow \) EGFR(Y1172(p)[\], Shc(PTB[\]))  \( @ 'k_{off}' \)

'Grb2.SoS'  \( \rightarrow \) Grb2(SH3n[\], SoS(PR[\], S\{u\})  \( @ 'k_{on}' \)

'Grb2/SoS'  \( \rightarrow \) Grb2(SH3n[\], SoS(PR[\], S\{u\})  \( @ 'k_{off}' \)

'EGFR.int'  \( \rightarrow \) EGFR(CR\[,\]N\[,\]C\[,\], \EGFR(CR\[,\]N\[,\]C\[,\])  \( @ 'k_{on}' \)

'EGFR/int'  \( \rightarrow \) EGFR(CR\[,\]N\[,\]C\[,\], \EGFR(CR\[,\]N\[,\]C\[,\])  \( @ 'k_{cat}' \)

'pY1092@EGFR'  \( \rightarrow \) EGFR(N\[,\], EGFR(C[\], Y1092(u)[\], \rightarrow \) EGFR(N\[,\], EGFR(C[\], Y1092(u)[\])  \( @ 'k_{cat}' \)

'pY1172@EGFR'  \( \rightarrow \) EGFR(N\[,\], EGFR(C[\], Y1172(u)[\], \rightarrow \) EGFR(N\[,\], EGFR(C[\], Y1172(u)[\])  \( @ 'k_{cat}' \)

'uY1092@EGFR'  \( \rightarrow \) EGFR(Y1092(p)[\], \rightarrow \) EGFR(Y1092(p)[\])  \( @ 'k_{cat}' \)

'uY1172@EGFR'  \( \rightarrow \) EGFR(Y1172(p)[\], \rightarrow \) EGFR(Y1172(p)[\])  \( @ 'k_{cat}' \)

'pY@Shc'  \( \rightarrow \) Shc(PTB[\], Y(u)[\], \rightarrow \) Shc(PTB[\], Y(u)[\])  \( @ 'k_{cat}' \)

'uY@Shc'  \( \rightarrow \) Shc(Y(u)[\], \rightarrow \) Shc(Y(u)[\])  \( @ 'k_{cat}' \)

'EOI'  \( \rightarrow \) Grb2(S\[,\], SH3n[\], SoS(PR[\])  \( @ 100 \)
our (fictional) guinea pig: Sos recruitment
Dynamics of Occurrences of an Event of Interest

EGF, EGFR, Grb2 = 5,000
Sos = 10,000
Shc = 8,000
volume = \(2 \times 10^{-14} \text{ l}\)
total agents = 33,000
Kd = 10 nM (= 2,400 molecules)
Seeking Explanations

- Static influence
- Dynamic influence
- Causality as “non-independence”
- Causality via counterfactuals
A direct positive influence exists if the pattern that constitutes the gluing instruction between $\mathcal{R}_r$ and $\mathcal{L}_s$ is modified by rule $r$. 
A direct negative influence exists if the pattern that constitutes the gluing instruction between $\mathcal{L}_r$ and $\mathcal{L}_s$ is modified by rule $r$. 

A gluing instruction
An indirect positive influence of rule $r$ satisfies only part of the $\mathcal{L}_s$ condition of rule $s$.

An indirect positive influence exists if the pattern that constitutes the gluing instruction between $\mathcal{R}_r$ and $\mathcal{L}_s$ is modified by rule $r$ and the gluing is not a site graph.
Influence is Not Transitive
The Static Influence Map
Seeking Explanations

- Static influence
- Dynamic influence
- Causality as “non-independence”
- Causality via counterfactuals
\( \Delta_t(r \leadsto s) = \begin{cases} \frac{\alpha_s(i + 1) - \alpha_s(i)}{\alpha_s(i)} & \text{if event } i \text{ is due to rule } r \\ 0 & \text{otherwise} \end{cases} \)

change of \( s \)-activity due to \( r \) in \([t, t + \tau]\)
KaiABC Oscillator (Simplified)
KaiABC Synchronisation (Simplified)

system behavior

\( t = 58 \)
Dynamic Influence Networks in a Molecular Clock (Kai-ABC)

with Angus Forbes, University of California at Santa Cruz
The dynamic influence network

with Angus Forbes Lab @ UCSC
Seeking Explanations

- Static influence
- Dynamic influence
- Causality as “non-independence”
- Causality via counterfactuals
Type causality

- general statements
- predictions
- forward-looking

Actual causality

- focus on particular events
- less useful for prediction, but still useful for intervention
- backward-looking
Events and Traces

- **Trace:** $e_1 e_2 e_3 e_4 \ldots \ldots e_n$
- **An Event:** $e$, $\text{pre}(e) \subseteq Q$, $\text{eff}(e) : \text{pre}(e) \rightarrow Q$

- **Label:**
- **Context (before):**
- **Context (after):**

- **Rule $r$ + Embedding:**

- **States of the World:**

- **Time:**

- **EOI:**
$e_1 \diamond e_2$ iff for every context $c$ it is the case that

c $\vdash e_1$
c $\vdash e_2$

implies

c $\vdash e_1 e_2$
c $\vdash e_2 e_1$

$\text{eff}(e_1 e_2) = \text{eff}(e_2 e_1)$

whether these events are independent, depends on context:
trace equivalence

\[ e_1 \diamond e_2 \Rightarrow t.e_1e_2.t' \sim t.e_2e_1.t' \]

precedence

\[ (\neg (e_i \diamond e_j) \land i < j) \Rightarrow e_i < e_j \]

precedence-preserving permutations

\[ \{123, 213\} \]

\[ \{312546, 231546, \ldots\} \]
With regard to causality, precedence

\[ e_i < e_j \]

comes in two flavors:

“immediate causality”

\[ e_1 \rightarrow e_2 \quad \text{if} \quad \exists c \quad c \vdash e_1 e_2 \land c \nvdash e_2 \]

“non-causal precedence”

\[ e_1 \nvdash e_2 \quad \text{if} \quad \exists c \quad c \vdash e_2 \land c \nvdash e_1 e_2 \]
Causal and Non-Causal Precedence

(1 has to occur before 2, but does not cause 2; yet contributes causally to 3)

non-causal precedence

causal precedence
negative influence (indicates logical precedence)

causality
(1 is needed for 3, but must happen before 2)

no influence relation!
A Simple Example

b

u

p

EOI
From Trace to Causal Past

1. **(I)**
   - Swap order
   - 
     - e
     - e'
   - e
   - e'

2. **(II)**
   - 
     - e
     - e'
   - e
   - e'

3. **(III)**
   - 
     - e
     - e'
   - e
   - e'

4. **(IV)**
   - 
     - e
     - e'
   - e
   - e'
From Trace to Causal Past
From Trace to Causal Past

Graphical representation of the process from trace to causal past.
From Trace to Causal Past
From Trace to Causal Past
From Trace to Causal Past
From Trace to Causal Past
From Trace to Causal Past
From Trace to Causal Past
The Causal Past Does not Capture Necessity

γ could have occurred before α
α then voided the conditions for γ
β reintroduced them

causal past
Minimality and the Concept of "Story"

causal past

"story"
The Causal Past of Sos Recruitment
“keep event $E_i$ in the causal past”  \hspace{1cm} e_i \in \{T, F\}

value of quark $x$ in the precondition of $E_i$  \hspace{1cm} (x, v) \in \text{pre}(E_i)

$e_i \Rightarrow$
Compressing The Causal Past

“keep event $E_i$ in the causal past” \quad $e_i \in \{T, F\}$

value of quark $x$ in the precondition of $E_i$ \quad $(x, v) \in \text{pre}(E_i)$

sets

$(x, v) \in \text{pre}(e_i)$

\[ e_i \Rightarrow e_j \]
Compressing The Causal Past

“keep event $E_i$ in the causal past”  
value of quark $x$ in the precondition of $E_i$  

$e_i \in \{T, F\}$  
$(x, v) \in \text{pre}(E_i)$

$E_j$  
$E_l$  
$E_i$  
EOI

sets  
destroys

$(x, v) \in \text{pre}(e_i)$  
$(x, v) \in \text{pre}(e_i)$

$e_i \Rightarrow e_j \land \neg e_l$
“keep event $E_i$ in the causal past” \quad $e_i \in \{T, F\}$

value of quark $x$ in the precondition of $E_i$ \quad $(x, v) \in \text{pre}(E_i)$

Compressing The Causal Past

\begin{align*}
E_j & \quad \text{sets} \quad (x, v) \in \text{pre}(e_i) \\
E_l & \quad \text{destroys} \quad (x, v) \in \text{pre}(e_i) \\
E_i & \\
\text{EOI} & 
\end{align*}

\[ e_i \Rightarrow e_j \land \bigwedge_{l \in B_{ji}} \neg e_l \]

with \quad $B_{ji} = \{l \mid j < l < i \land (x, v') \in \text{eff}(E_l) \land v' \neq v\}$
Compressing The Causal Past

“keep event $E_i$ in the causal past”  $e_i \in \{T, F\}$

value of quark $x$ in the precondition of $E_i$  $(x, v) \in \text{pre}(E_i)$

Compressing The Causal Past

$C_{i,x,v} \equiv e_i \Rightarrow \forall j \in A_{ji} \left( e_j \land \left[ \land l \in B_{ji} \neg e_l \right] \right)$

with  $A_{ji} = \{ j \mid j < i \land (x, v) \in \text{eff}(E_j) \}$

with  $B_{ji} = \{ l \mid j < l < i \land (x, v') \in \text{eff}(E_l) \land v' \neq v \}$
Compressing The Causal Past

“keep event $E_i$ in the causal past” $e_i \in \{T, F\}$

value of quark $x$ in the precondition of $E_i$ $(x, v) \in \text{pre}(E_i)$

sets destroys

$(x, v) \in \text{pre}(e_i)$ $(x, v) \in \text{pre}(e_i)$

$\left(\land_{i, x, v} C_{i, x, v}\right) \land e_{\text{EOI}}$

find the minimum number of truth-value assignments such that this is satisfied!

with $C_{i, x, v} \equiv e_i \Rightarrow \forall j \in A_{ji} \left( e_j \land \left[ \land_{l \in B_{ji}} \neg e_l \right] \right)$

with $A_{ji} = \{ j \mid j < i \land (x, v) \in \text{eff}(E_j) \}$

with $B_{ji} = \{ l \mid j < l < i \land (x, v') \in \text{eff}(E_l) \land v' \neq v \}$
compression with SAT solver
A formal pathway is a **compressed** precedence relation among events that were **necessary** to obtain an instance of the EOI.
story 2
"INUS Causality" (Mackie)

**Story 1**
- Intro EGF
- Intro EGFR
- Intro EGF
- Intro EGFR
- EGF.EGFR
- EGF.EGFR
- EGFR.EGFR
- EGFR.int
- pY1092@EGFR
- Intro Grb2
- Intro SoS
- EGFR. Grb2
- Grb2. SoS
- EOI
- EGF. Shc
- pY@Shc
- Intro Grb2
- Intro SoS
- Shc. Grb2
- Grb2. SoS
- EOI

**Rules necessary for the EOI**

**Rules necessary for this pathway to the EOI**

**Story 2**
- Intro EGF
- Intro EGFR
- Intro EGF
- Intro EGFR
- EGF.EGFR
- EGF.EGFR
- EGFR.EGFR
- EGFR.int
- pY1172@EGFR
- Intro Shc
- EGF. Shc
- pY@Shc
- Intro Grb2
- Intro SoS
- Shc. Grb2
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EGF, EGFR, Grb2 = 5,000
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Kd = 10 \text{ nM} \equiv 2,400 \text{ molecules}