Maintenance of Chronobiological Information by P System Mediated Assembly of Control Units for Oscillatory Waveforms and Frequency

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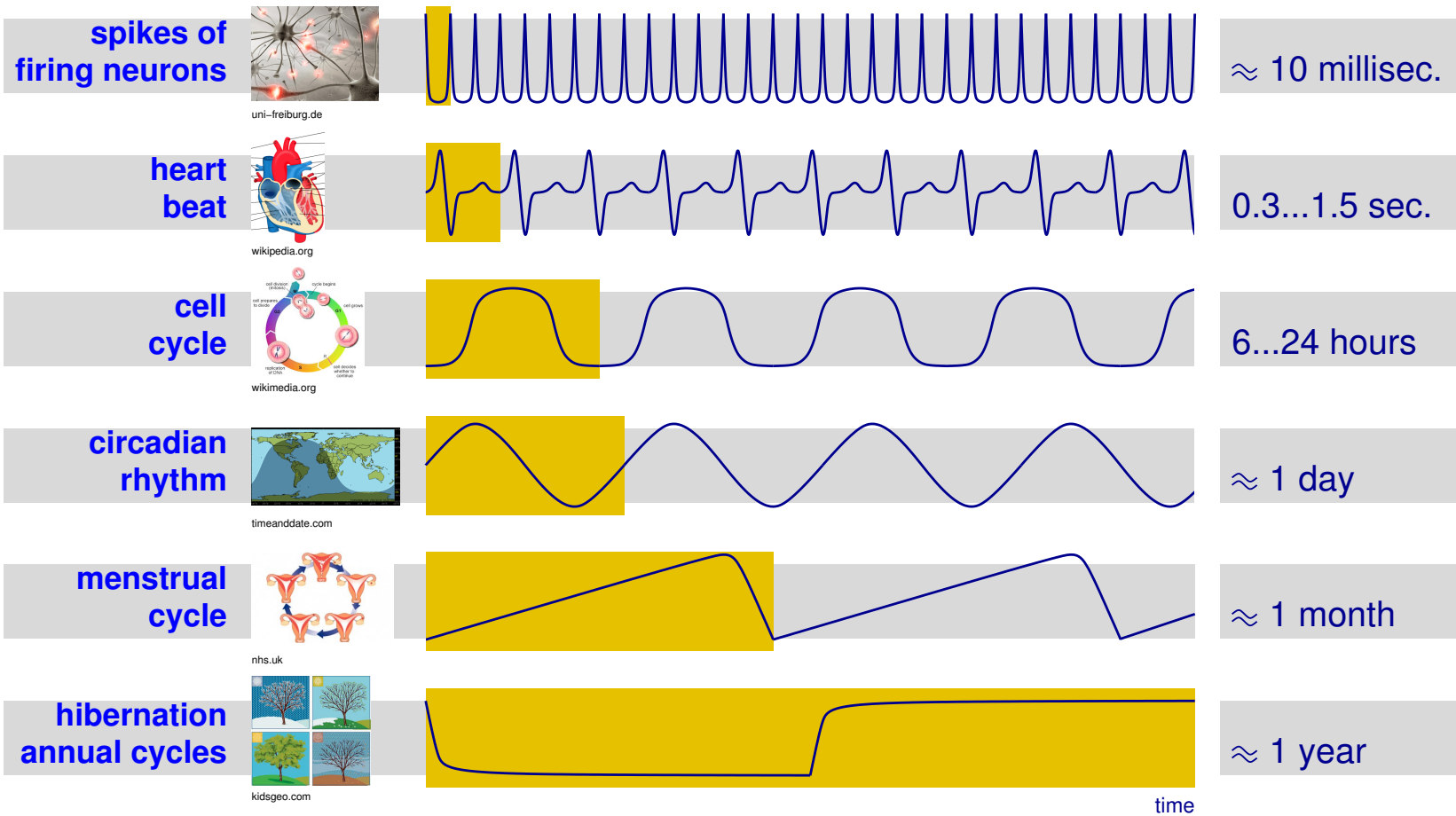
Oscillatory Signals in Biology: Range of Periodicities

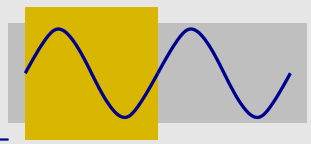


An individual organism comprises a variety of regulated oscillations.

Waveforms of Oscillatory Signals in Biology

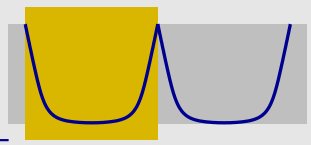
Waveform as additional information carrier beyond frequency

sinusoidal or almost sinusoidal



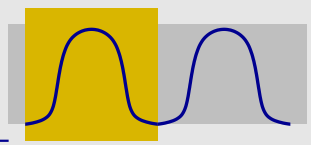
- gradual and smooth alteration
- commonly stable limit cycle
- quite robust against perturbations

spiking



- signal peak for short moment
- fast raise or fall of signal value easy to detect
- average signal level can be kept low

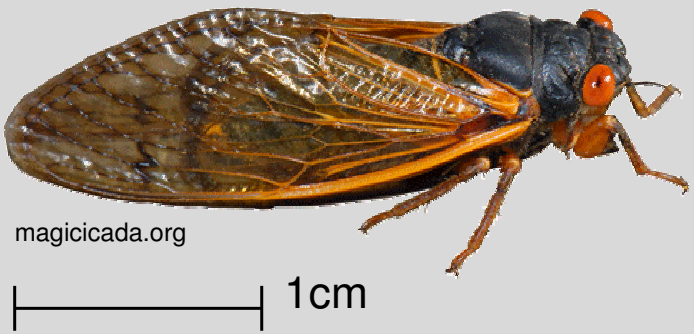
plated

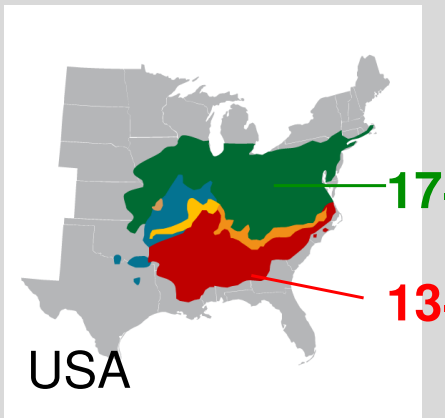


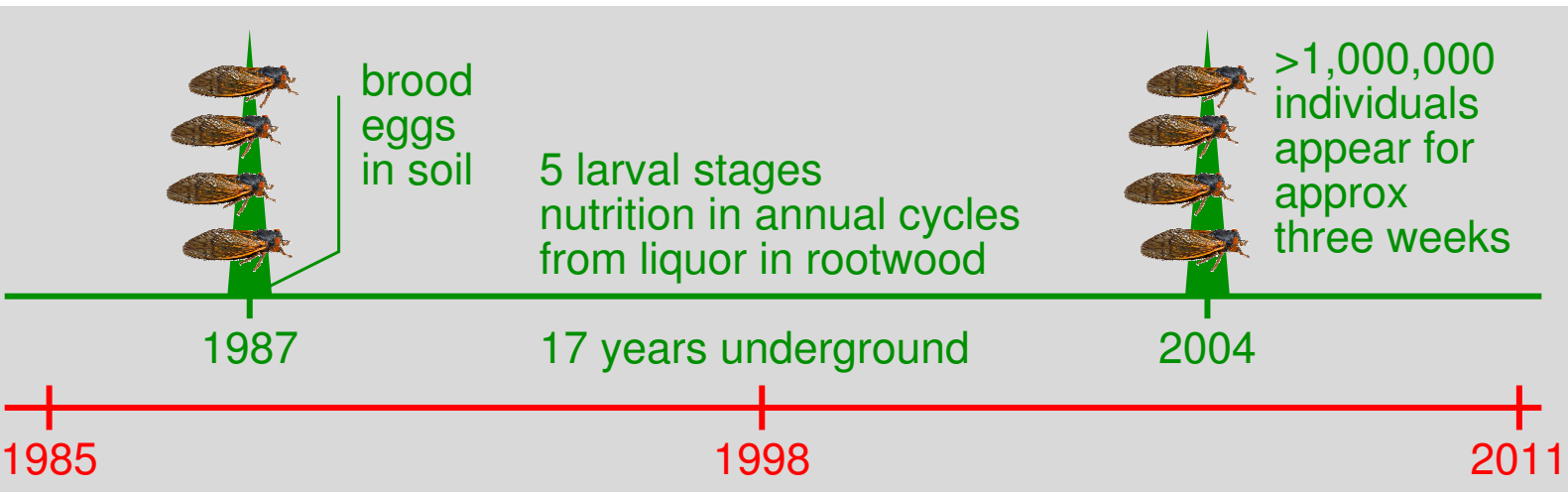
- more or less bistable oscillatory behaviour
- almost rectangular shape towards binarisation
- toggling with weightable balance btw. high/low

Corresponding oscillators for each waveform by small or medium-sized reaction networks

17-years and 13-years Periodical Cicadas with Synchronous Life Cycle







Inspiration and Motivating Questions

- No external stimulus with natural period of 17 or 13 years known up to now
- Molecular mechanism to precisely measure the passage of 17 (or 13) years?
- Need of a chemical frequency divider model, ideally configurable for distinct division ratios
- Low number of slight evolutionary changes sufficient to toggle the life cycle between a variety of years?

$\Longrightarrow$ Assembly of pre-defined chemical modules towards new or extended functionality

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$\Longrightarrow$ Assembly of pre-defined chemical modules towards new or extended functionality

1. Biological Rhythms
2. **P Meta Framework**
   - Non-probabilistic P modules
   - Connectivity of P modules
   - Instructions for composition of P modules
3. Assembly of Frequency Dividers
4. Suprachiasmatic Nucleus

Non-probabilistic P Module

- is able to fulfill an elementary computational task on the fly
- building block of an analog computer or in a control loop
- represents a container encapsulating a formal description of its dynamical behaviour
- specifies the interface of a general real-valued system or its approximation
- aims to bridge building blocks in systems theory and membrane systems

More formally, a P module is a triple $(\downarrow, \uparrow, \square)$ where

$\downarrow = (I_1, \ldots, I_i)$ ..... indicates a list of input signal identifiers
$\uparrow = (O_1, \ldots, O_o)$ ..... indicates a list of output signal identifiers
$\square$ ..... underlying system specification with or without inherent auxiliary signals

Each signal is a real-valued function over time.

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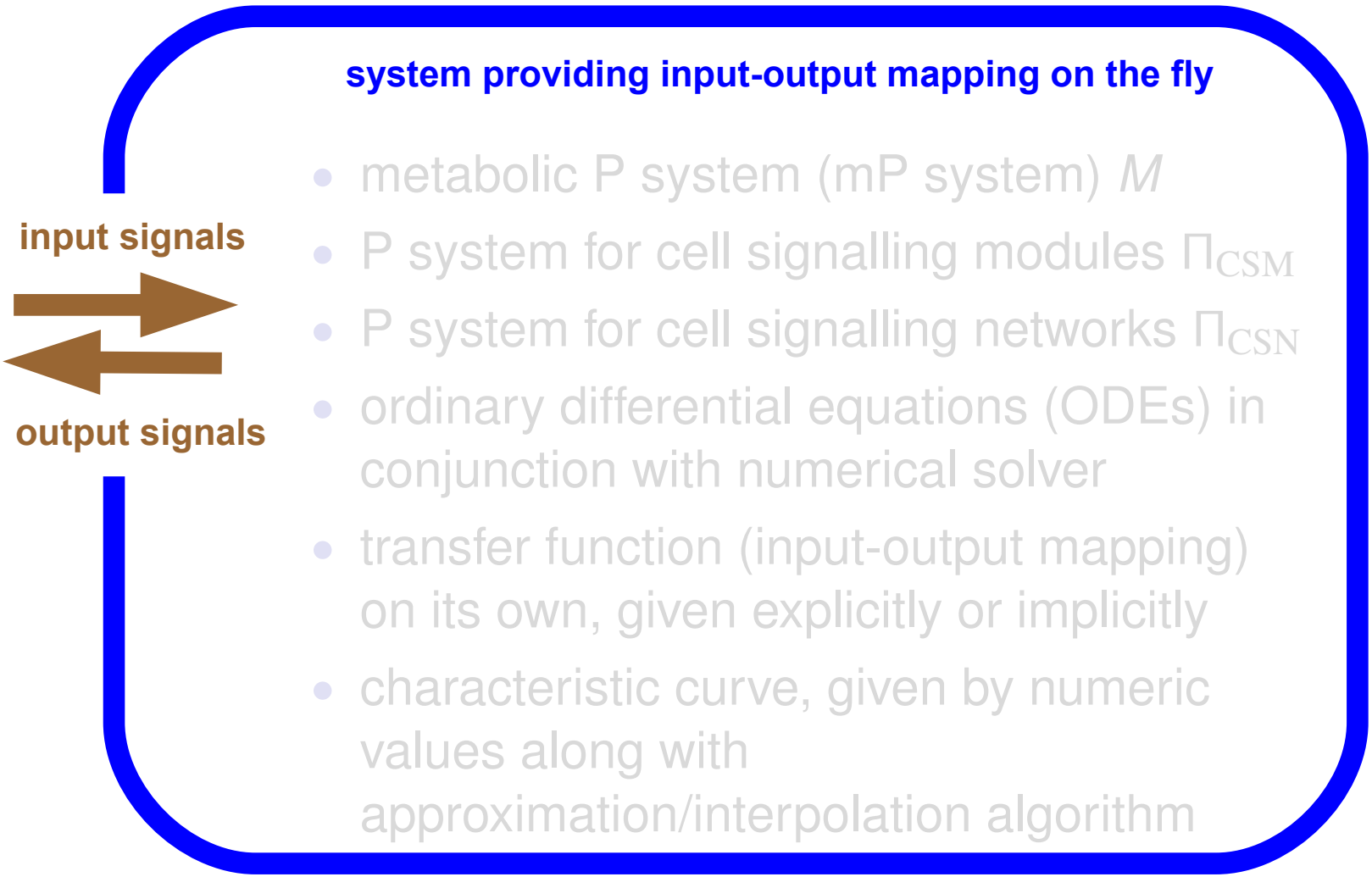
Non-probabilistic P Module as a Processing Unit



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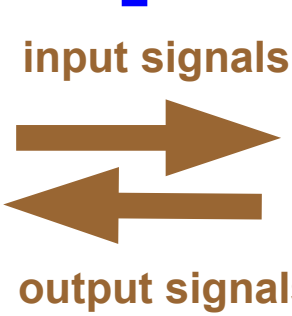

system providing input-output mapping on the fly

- metabolic P system (mP system) *M*
- P system for cell signalling modules Π_{CSM}
- P system for cell signalling networks Π_{CSN}
- ordinary differential equations (ODEs) in conjunction with numerical solver
- transfer function (input-output mapping) on its own, given explicitly or implicitly
- characteristic curve, given by numeric values along with approximation/interpolation algorithm

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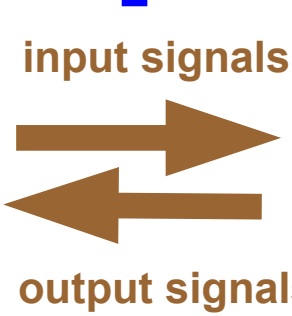

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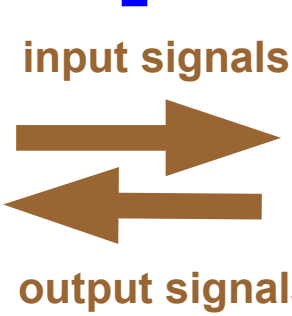

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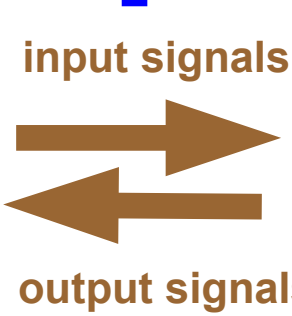

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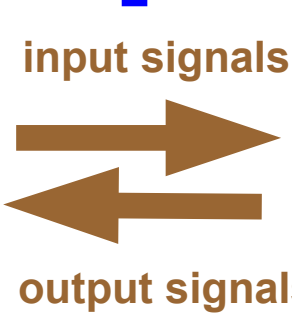

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Non-probabilistic P Module as a Processing Unit

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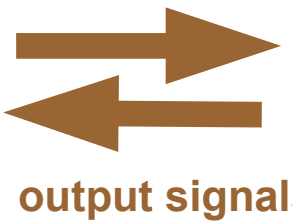

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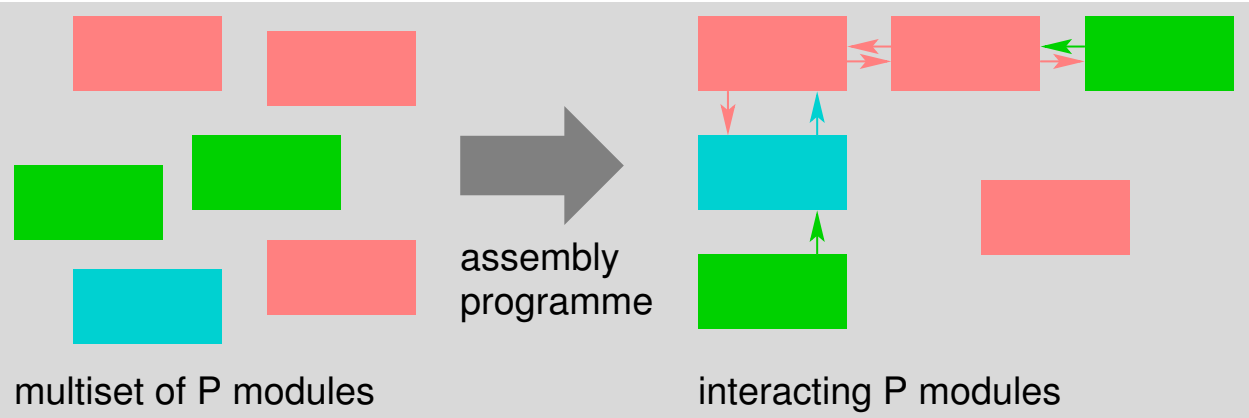
P Meta Framework: Connecting P Modules

Our P meta framework is a construct $\Pi_{\pi\uparrow\downarrow} = (M, P)$ where

M ..... denotes a finite multiset of non-probabilistic P modules

P ..... assembly programme by its connectivity instructions



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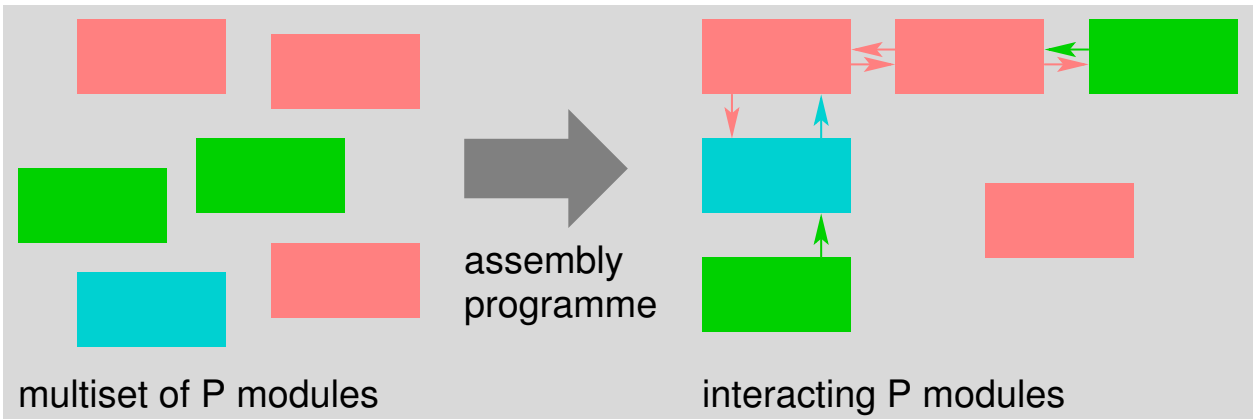

- $\mathrm{supp}(M)$ can be interpreted as the genetic potential of highly conserved reaction units
- Multiplicity of modules $\longrightarrow$ limitation of resources available for module composition

Connectivity Graph of a P Meta Framework

Each P Meta Framework $\Pi_{\pi\uparrow\downarrow} = (M, P)$ comes with a corresponding directed graph $G = (V, E)$, initially

$$\begin{aligned} V &:= \{m[i] \mid m \in \mathrm{supp}(M) \ \wedge \ i \in \{1, \ldots, M(m)\}\} \\ E &:= \emptyset \end{aligned}$$

- Indexing of all instances (copies) $m[i]$ from a P module m allows unique identification
- Let $a = (a_\downarrow, a_\uparrow, a_\square) \in \mathrm{supp}(M)$ and $b = (b_\downarrow, b_\uparrow, b_\square) \in \mathrm{supp}(M)$ be two module instances derived from M.
- An edge $(a, b, R_{a\to b}) \in E$ denotes a connection from a to b where dedicated output species of a act as input species of b.
- Each edge comes with a binary relation $R_{a\to b} \subseteq a_\uparrow \times b_\downarrow$ in which the mapping of a's output species onto b's input species is given.
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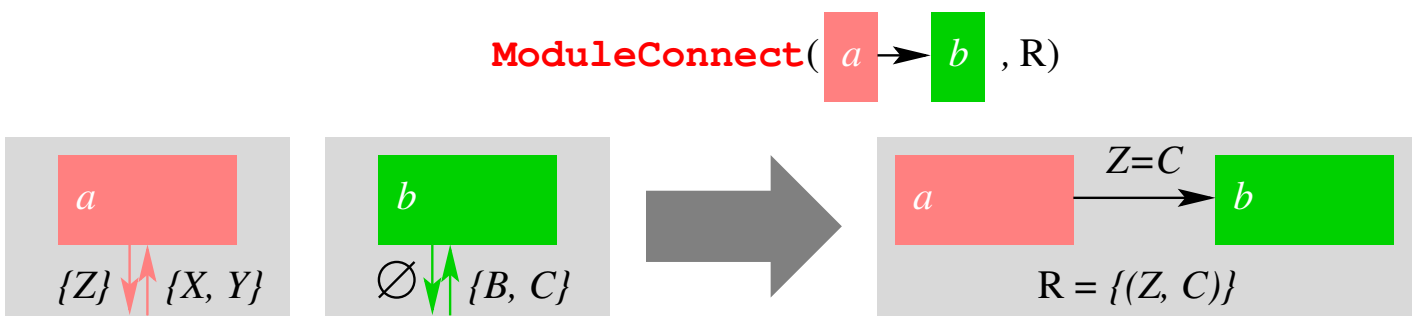
Assembly Programme Instructions (Selection)

- Time-dependent changes of module connectivity
- Time stamp t opens each instruction
- Instruction updates graph $G(V, E)$

t : `ModuleConnect`$(a \to b, R_{a\to b})$

connects some or all of module a's output species to represent b's input species by sharing species identifiers according to the injective binary relation $R_{a\to b} \subseteq a_{\uparrow} \times b_{\downarrow}$.

Edge update scheme: $E := E \cup \{(a, b, R_{a\to b})\}$



Assembly Programme Instructions (Selection)

- Time-dependent changes of module connectivity
- Time stamp t opens each instruction
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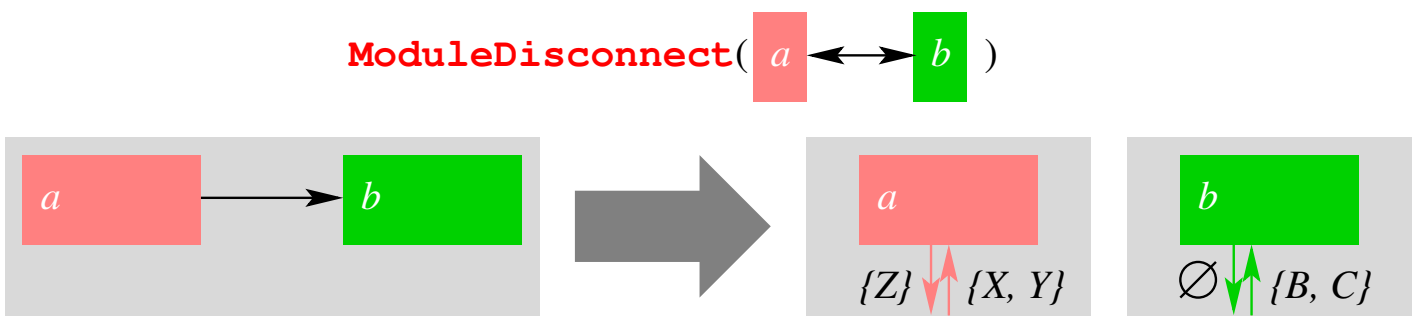
t : `ModuleDisconnect`$(a \leftrightarrow b)$

completely disconnects modules a and b by annihilating all cross-modular species sharings. This comes along with removing $R_{a\to b}$ as well as $R_{b\to a}$, respectively.

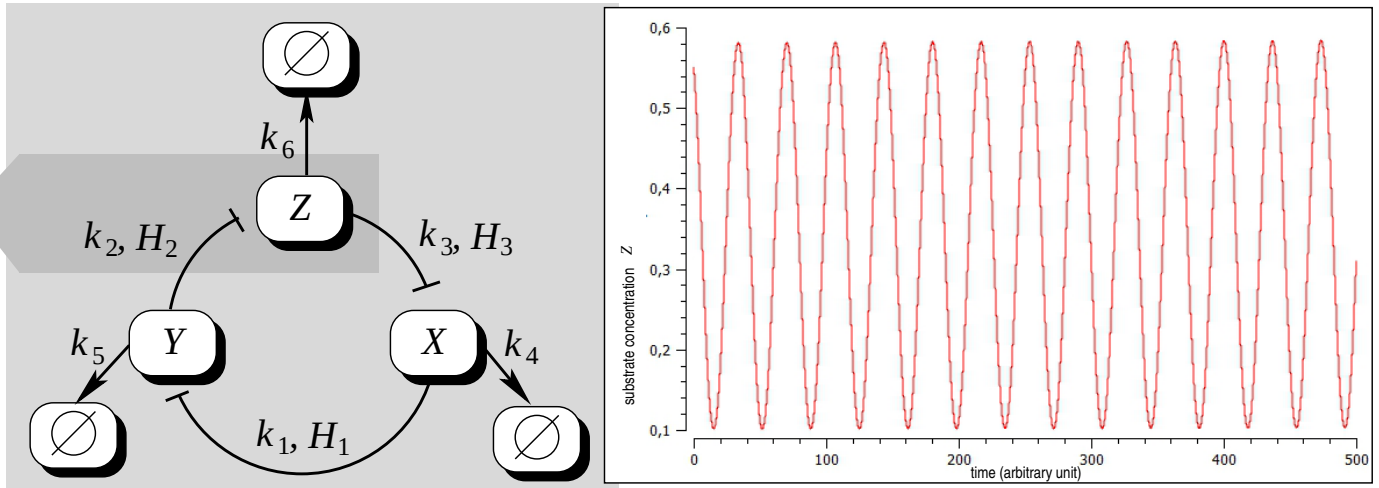
Edge update scheme: $E := E \setminus \{(a, b, R_{a\to b})\} \setminus \{(b, a, R_{b\to a})\}$



1. Biological Rhythms
2. P Meta Framework
3. **Assembly of Frequency Dividers**
   - Chemical frequency divider model 1:17
   - Frequency divider 1:5 by separator removal
   - Frequency divider 1:6 by Repressilator
   - Frequency divider 1:3 by Goodwin module
4. Suprachiasmatic Nucleus

The Repressilator Module

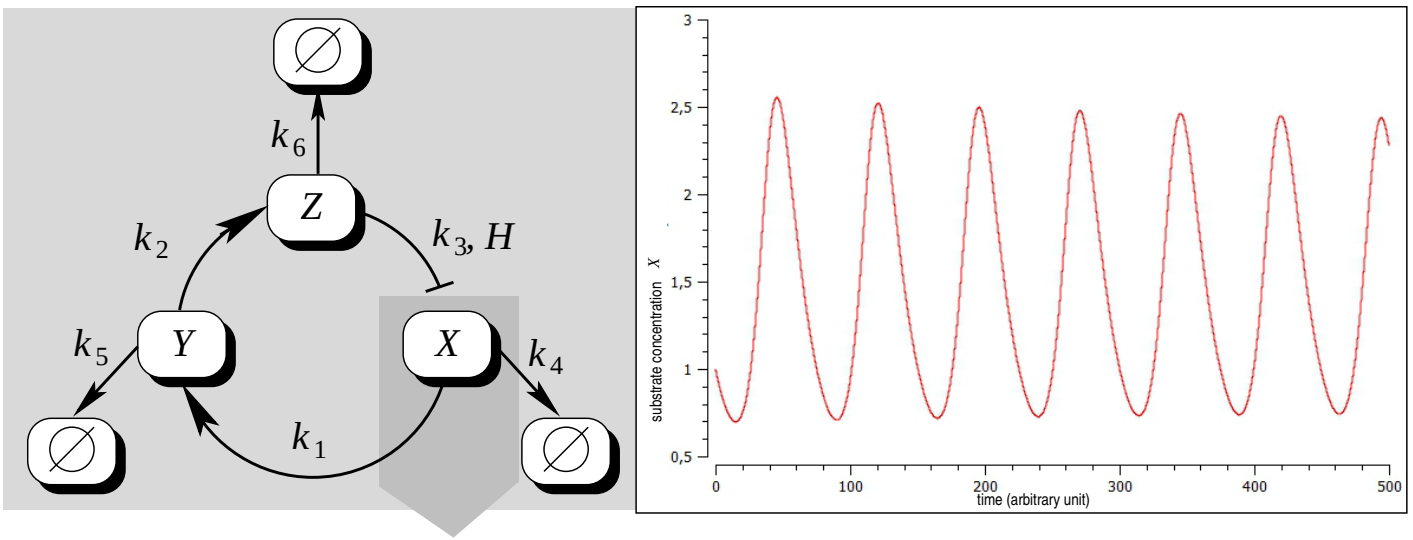
$$\text{repressilator} = (\emptyset, \{Z\}, F)$$



- Oscillation by progressional inhibition in gene regulatory network
- Involves higher-order Hill kinetics
- Velocity of decay reactions mainly determines frequency
- Inherently almost sinusoidal waveform

The Goodwin Module

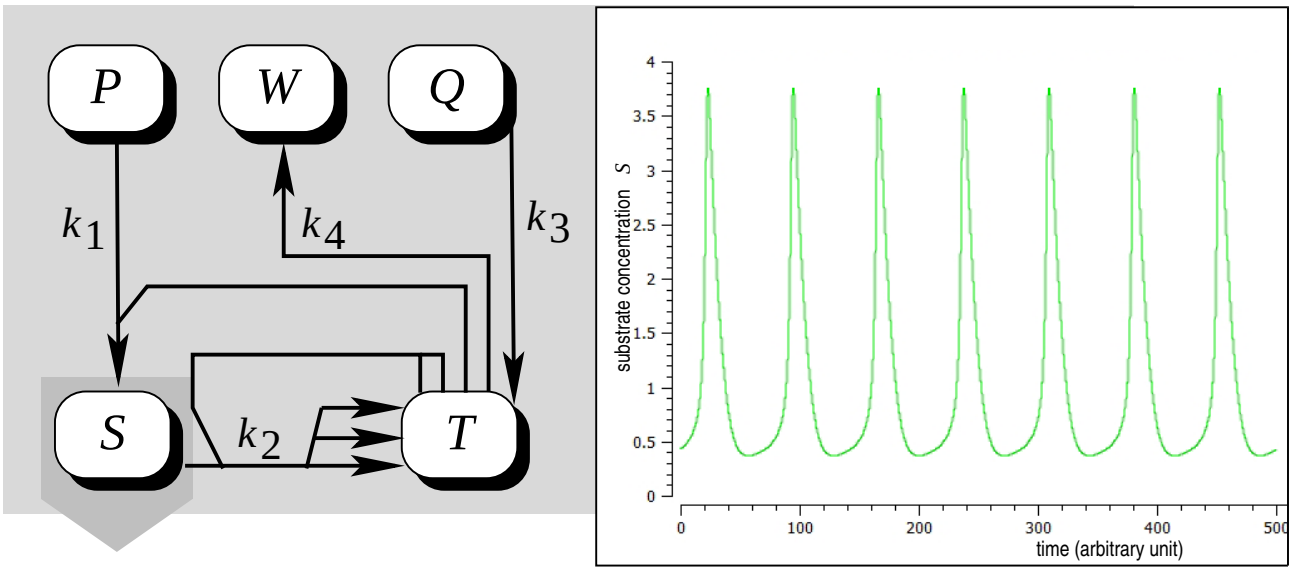
$$\text{goodwin} = (\emptyset, \{X\}, F)$$



- Oscillation by mutual activation and inhibition in gene regulatory network
- Involves higher-order Hill kinetics
- Velocity of decay reactions mainly determines frequency
- Configurable to exhibit almost sinusoidal or plated waveforms

The Brusselator Module

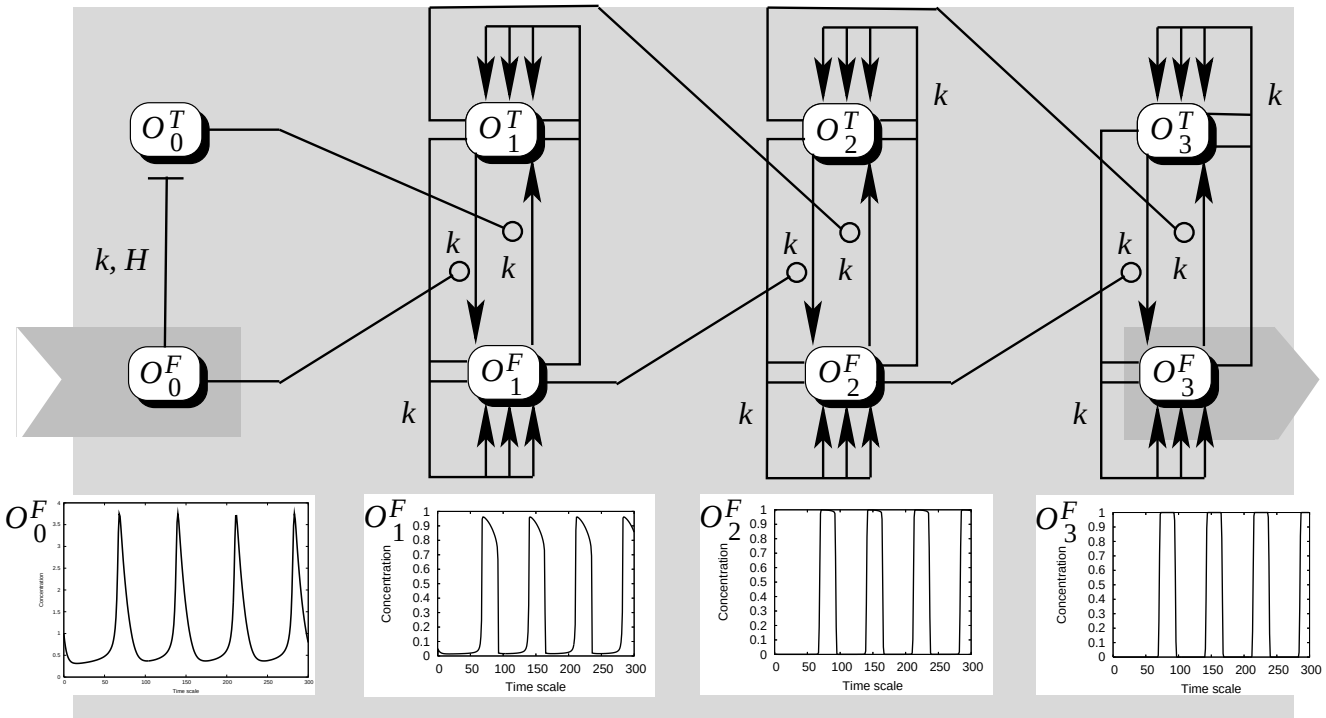
$$\text{brusselator} = (\emptyset, \{S\}, F)$$



- Oscillation by autocatalytic feedback loops
- Exclusively mass-action kinetics
- Velocity of decay in concert with autocatalytic loop determines frequency
- Inherently spiking waveform

The Binary Signal Separator Module

$$\text{separator} = (\{O_0^F\}, \{O_3^F\}, F)$$



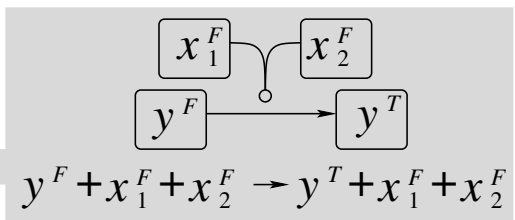
- Converts spiking or sinusoidal oscillations into plated waveform
- Successive binarisation by enzymatically controlled cascade
- Exclusively mass-action kinetics

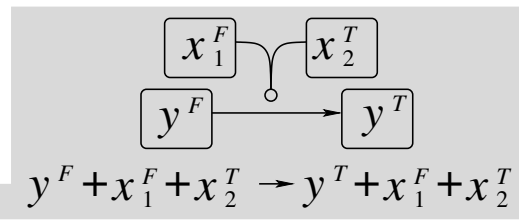
Binary Counter Modulo 17 – Chemical Logic gate

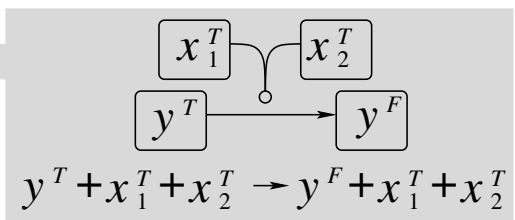
Boolean variable z represented by two correlated species Z^T and Z^F

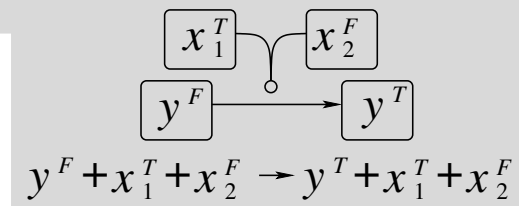
Chemical reaction network for NAND

x_1	x_2	y
0	0	1
0	1	1
1	0	1
1	1	0





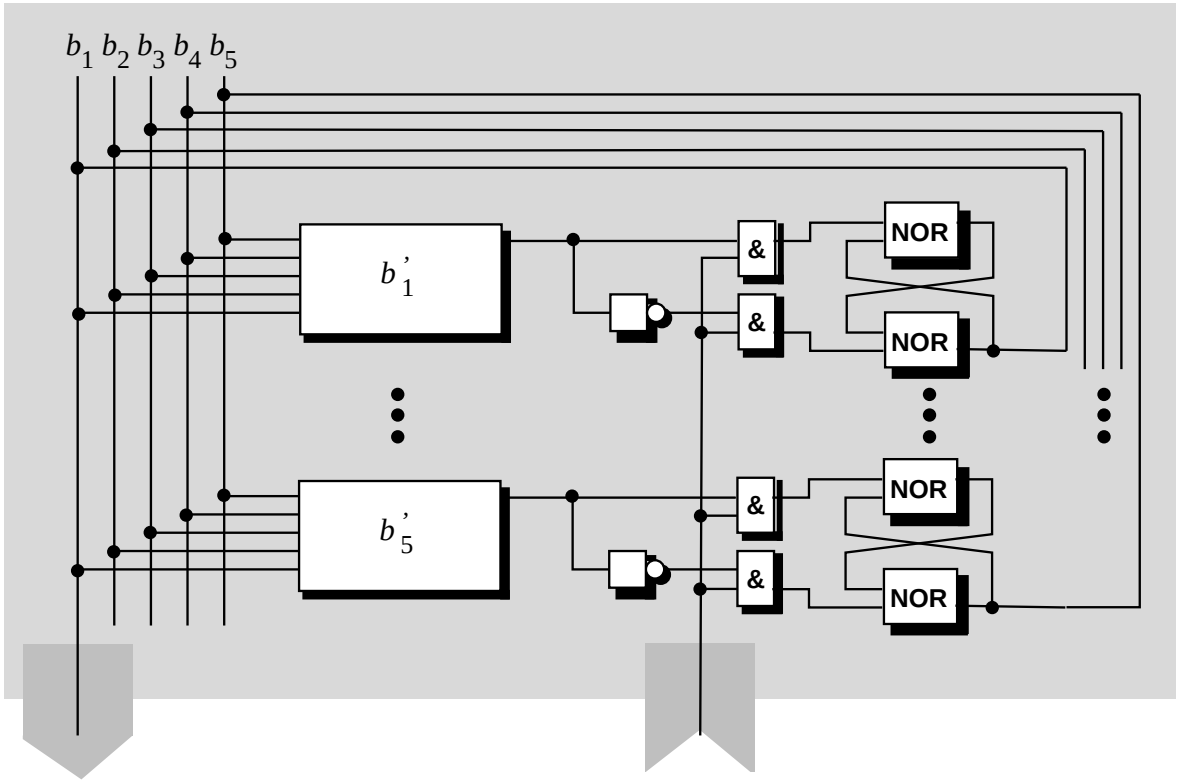




Analogously implementation of other boolean functions

The Binary Counter Modulo 17

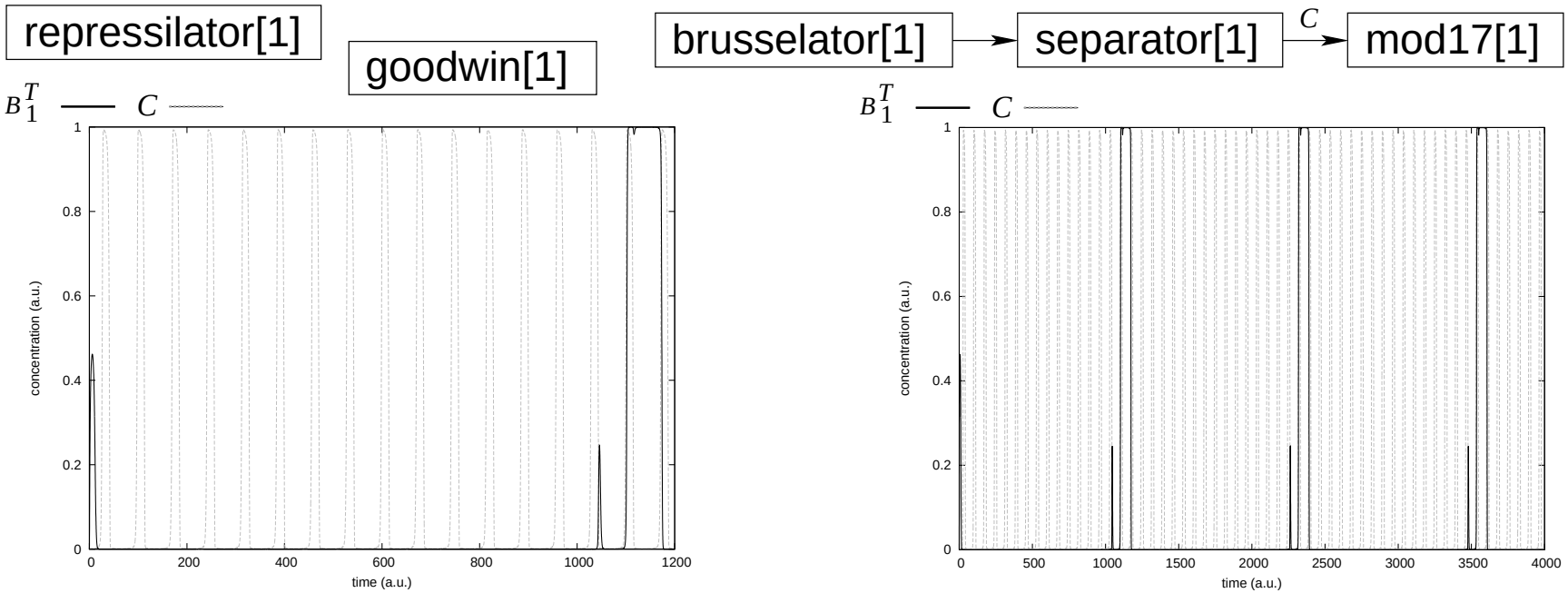
$$\mathrm{mod}17 = (\{C\}, \{B_1^T\}, F)$$



$$
\begin{aligned}
b'_1 &= \bar{b}_1 b_2 \bar{b}_3 \bar{b}_4 \bar{b}_5 \\
b'_2 &= \bar{b}_1 b_2 \vee \bar{b}_1 b_2 \bar{b}_3 \bar{b}_4 \bar{b}_5 \\
b'_3 &= \bar{b}_1 \bar{b}_2 b_3 \vee \bar{b}_1 b_3 \bar{b}_4 \vee \\
&\quad \bar{b}_1 b_2 b_3 b_5 \vee \bar{b}_1 \bar{b}_2 b_4 \bar{b}_5 \\
b'_4 &= \bar{b}_1 b_4 \bar{b}_5 \vee \bar{b}_1 b_2 b_3 b_5 \vee \\
&\quad \bar{b}_1 \bar{b}_2 \bar{b}_3 b_5 \vee \bar{b}_1 \bar{b}_2 \bar{b}_3 b_4 \vee \\
&\quad \bar{b}_1 b_2 b_3 b_4 \\
b'_5 &= \bar{b}_1 \bar{b}_2 \bar{b}_3 \bar{b}_4 \vee \bar{b}_1 \bar{b}_2 b_3 b_4 \vee \\
&\quad \bar{b}_1 b_2 b_3 \bar{b}_4 \vee \bar{b}_1 b_2 \bar{b}_3 b_4
\end{aligned}
$$

- Based on 5-bit Gray code
- Clock signal C increments counter
- Exclusively mass-action kinetics

Composing the Original Frequency Divider 1:17

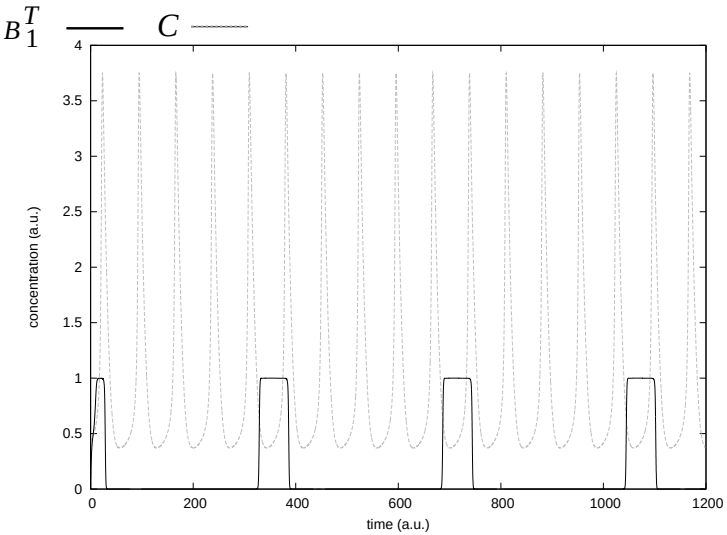


$$
\begin{aligned}
\Pi_{\mathrm{FD17}} &= (M, P) \quad \text{with} \\
M &= \{(\text{brusselator}, 1), (\text{repressilator}, 1), (\text{goodwin}, 1), (\text{separator}, 1), (\text{mod17}, 1)\} \\
P &= \{0 : \texttt{ModuleConnect}(\text{brusselator}[1] \rightarrow \text{separator}[1], \{(S, O_0^F)\}), \\
&\quad\ 0 : \texttt{ModuleConnect}(\text{separator}[1] \rightarrow \text{mod17}[1], \{(O_3^F, C)\})\}
\end{aligned}
$$

Frequency Divider 1:5 by Removal of Signal Separator

repressilator[1] goodwin[1] separator[1] brusselator[1] $\xrightarrow{C}$ mod17[1]

B_1^T	B_2^T	B_3^T	B_4^T	B_5^T
0	0	0	1	1
0	0	1	1	1
0	1	1	1	1
0	1	0	1	1
1	1	0	0	0



$$\Pi_{FD5} = (M, P) \quad \text{with}$$

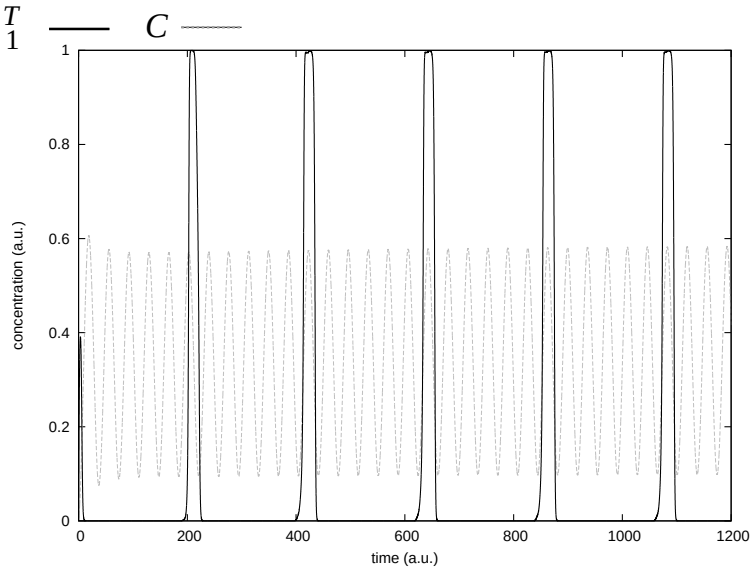
$$M = \{(\text{brusselator}, 1), (\text{repressilator}, 1), (\text{goodwin}, 1), (\text{separator}, 1), (\text{mod17}, 1)\}$$

$$\begin{aligned} P = \{ & 0 : \texttt{ModuleConnect}(\text{brusselator}[1] \rightarrow \text{separator}[1], \{(S, O_0^F)\}), \\ & 0 : \texttt{ModuleConnect}(\text{separator}[1] \rightarrow \text{mod17}[1], \{(O_3^F, C)\}), \\ & 200 : \texttt{ModuleDisconnect}(\text{brusselator}[1] \leftrightarrow \text{separator}[1]), \\ & 200 : \texttt{ModuleConnect}(\text{brusselator}[1] \rightarrow \text{mod17}[1], \{(S, C)\})\} \end{aligned}$$

Frequency Divider 1:6 by Repressilator

goodwin[1] brusselator[1] separator[1] repressilator[1] $\xrightarrow{C}$ mod17[1]

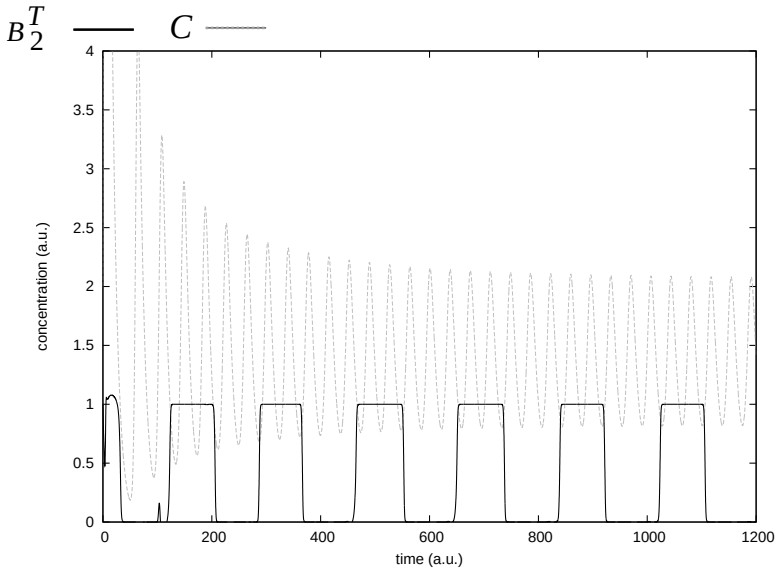
B_1^T	B_2^T	B_3^T	B_4^T	B_5^T
0	0	0	1	1
0	0	1	1	1
0	1	1	0	0
0	1	1	1	0
0	1	0	0	1
1	0	0	0	0



$$\Pi_{\mathrm{FD6}} = (M, P) \quad \text{with}$$
$$M = \{(\text{brusselator}, 1), (\text{repressilator}, 1), (\text{goodwin}, 1), (\text{separator}, 1), (\text{mod17}, 1)\}$$
$$P = \{0 : \texttt{ModuleConnect}(\text{repressilator}[1] \rightarrow \text{mod17}[1], \{(Z, C)\})\}$$

Frequency Divider 1:3 by Goodwin Module

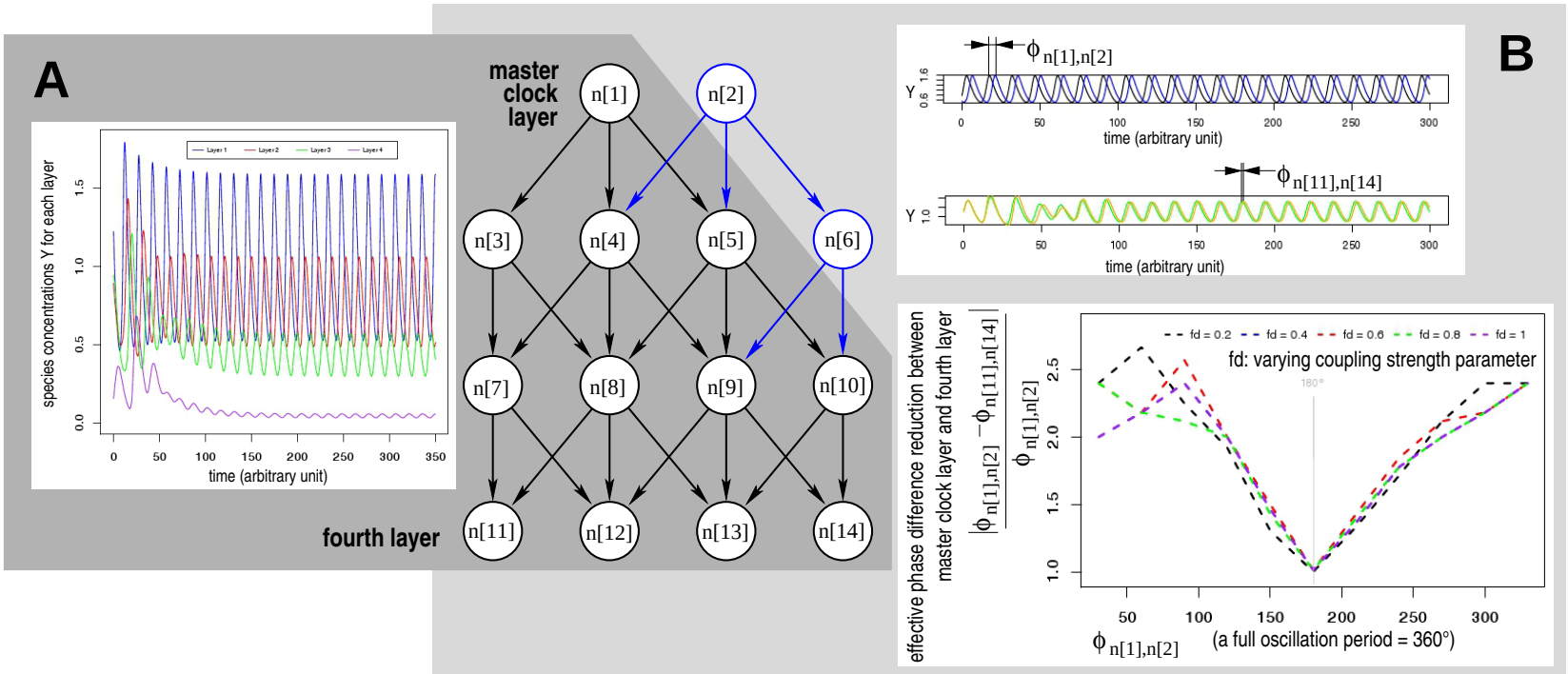
B_1^T	B_2^T	B_3^T	B_4^T	B_5^T
0	0	1	1	0
0	1	1	1	1
1	1	0	0	0



$$\Pi_{FD3} = (M, P) \quad \text{with}$$
$$M = \{(\text{brusselator}, 1), (\text{repressilator}, 1), (\text{goodwin}, 1), (\text{separator}, 1), (\text{mod17}, 1)\}$$
$$P = \{0 : \texttt{ModuleConnect}(\text{goodwin}[1] \rightarrow \text{mod17}[1], \{(X, C)\})\}$$

1. Biological Rhythms
2. P Meta Framework
3. Assembly of Frequency Dividers
4. **Suprachiasmatic Nucleus**
   - Core Oscillator's Interplay in Suprachiasmatic Nucleus
   - Prospectives
   - Acknowledgement

Core Oscillator's Interplay in Suprachiasmatic Nucleus



$$
\begin{aligned}
\Pi_{\mathrm{SCN}} &= (M, P) \quad \text{with} \\
M &= \{(\mathrm{n}, 14)\} \\
P &= \{0 : \texttt{ModuleConnect}(\mathrm{n}[1] \to \mathrm{n}[3], \{(Y, X)\}), \\
&\quad\ 0 : \texttt{ModuleConnect}(\mathrm{n}[1] \to \mathrm{n}[4], \{(Y, X)\}), \ldots, \\
&\quad\ 0 : \texttt{ModuleConnect}(\mathrm{n}[10] \to \mathrm{n}[14], \{(Y, X)\}) \\
&\quad\ 300 : \texttt{ModuleConnect}(\mathrm{n}[2] \to \mathrm{n}[4], \{(Y, X)\}), \ldots, \\
&\quad\ 300 : \texttt{ModuleConnect}(\mathrm{n}[6] \to \mathrm{n}[10], \{(Y, X)\})\}
\end{aligned}
$$

Prospectives

Conclusions

- Assembly and reassembly as well as composition and decomposition of pre-defined reaction network modules on the fly $\longrightarrow$ promising strategy in order to achieve complex systems capable of new, extended, or unexpected functionality
- Framework for an artificial evolution at a granularity of highly conserved genetic ensembles
- P system-based approach features by coping with dynamical structures at a modular level rather than a molecular level
- Simulation studies carried out using CoPaSi along with Gepasi Model Extractor

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- Incorporation of Infobiotics workbench
- Extension of P module library
- Combining advantages of P system-based approaches with analytical examination tools using ODEs

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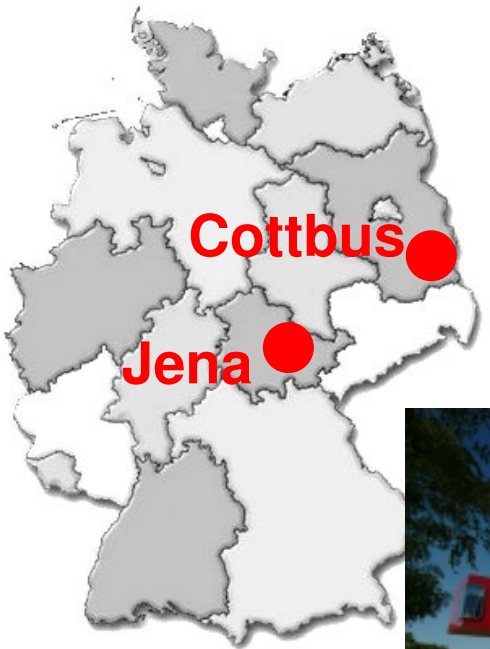

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