

# Boolean vs. ODE models of gene regulatory and other systems

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# Biological systems with switch-like behavior

Many biological systems exhibit switch-like behavior. Examples include gene-regulatory networks where at a given time a gene may be either **expressed** or **not expressed**, neuronal networks, where a neuron may either be **firing** or **resting**, in *SI* or *SIS* disease dynamics, an individual can be either **infectious** or **susceptible**.

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Such systems often can be modeled either by ODE systems or by Boolean networks that distinguish only **on** and **off** states.

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Boolean models are much easier to study, but they are further removed from biological reality.

**When can we be assured that a Boolean model  $\mathbb{B}$  and an ODE model  $\mathbb{D}$  of the same biological system make qualitatively equivalent predictions?**

# What do you mean by *the same*?

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The first step is to discretize relevant variables.

# Examples of discretization

- In gene regulation, one may distinguish mRNA concentrations below a threshold  $\Theta$  from mRNA concentrations above a threshold  $\Theta$ .
- In modeling neuronal networks, one may distinguish cross-membrane voltages below a threshold  $\Theta$  from cross-membrane voltages above a threshold  $\Theta$ .

Note that in both of these examples only some variables of the system are being assigned Boolean values **0** or **1**. Other variables of the ODE system (gene product concentrations, gating variables) are being ignored in these examples.

# Another example of discretization

In modeling infectious diseases, an individual is classified as **infectious** if the viral load is **above** a threshold  $\Theta_v$ .

This discretization now can be used to build either agent-based **stochastic** Boolean models  $\mathbb{B}_{agent}$  or **deterministic ODE** *SI* or *SIS* models  $\mathbb{D}$ . The latter are based on the **proportion** of individuals in the *I*-class.

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Now one could study a **second** discretization based on whether this proportion is **below** or **above** a threshold  $\Theta_c$  and compare the predictions of the resulting Boolean model  $\mathbb{B}_{system}$  with those of  $\mathbb{D}$ .

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First we need to choose partitions of the state space  $S_{\mathbb{D}}$  of the ODE system  $\mathbb{D}$  into disjoint regions  $(R_0^i, R_1^i)$ . Then we can assign to every state  $\vec{x}$  of the ODE system  $\mathbb{D}$  a corresponding Boolean state  $\vec{s} = \Phi(\vec{x}) \in S_{\mathbb{B}}$  such that

$$s_i = 0 \Leftrightarrow \vec{x} \in R_0^i,$$

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Note also that an analogous procedure also works for discretizing the ODE states into more than two regions and discrete models with more than two states per variable.



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The map  $\Phi : S_{\mathbb{D}} \rightarrow S_{\mathbb{B}}$  gives us, for every initial state  $\vec{x}(0) \in S_{\mathbb{D}}$ , a function  $\Psi_{\vec{s}(0)} : [0, \infty) \rightarrow S_{\mathbb{B}}$  such that  $\Psi_{\vec{s}(0)}(t) = \Phi(\vec{s}(t))$  for all  $t \in [0, \infty)$ . Let us call this the **continuous-time Boolean trajectory**  $\Delta(\vec{x}(0))$ .

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Now we need to turn this into an actual **discrete-time Boolean trajectory**. The most natural idea would be define

$$\Delta(\vec{x}(0)) = (\vec{s}(0), \vec{s}(1), \vec{s}(2), \dots)$$

as the sequence of **successive** Boolean states that we observe in  $\Psi_{\vec{s}(0)}$ .

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Given  $\mathbb{D}, \mathbb{B}$ , an open region  $U$  of  $S_{\mathbb{D}}$ , and the updating function  $f$  of  $B$ , we say that  $\mathbb{B}$  is **strongly consistent with  $\mathbb{D}$  on  $U$**  if for all  $\vec{x}(0) \in U$  and all  $\tau \in \mathbb{N}$ :

$$\vec{s}(\tau + 1) = f(\vec{s}(\tau)), \quad (1)$$

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If (1) holds for some  $U$  as above such that  $\Phi$  maps  $U$  onto the state space of  $\mathbb{B}$ , then we say that  $\mathbb{D}$  **realizes**  $\mathbb{B}$ .

# Strong consistency may be too much to hope for

Think about a two-dimensional Boolean system  $\mathbb{B}$  where  $f(s_1, s_2) = 11$  iff  $s_1 = s_2 = 0$  and  $f(s_1, s_2) = 00$  otherwise. Consider a discretization of  $(x_1 x_2) \in S_{\mathbb{D}}$  based on thresholds  $\Theta_1, \Theta_2$ .

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But we need (2) only for all  $\vec{x}(0) \in U$ ; so  $\mathbb{B}$  may still be **realized** by some ODE systems  $\mathbb{D}$ .

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- Focus on some interesting  $U$ .
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- Study these problems for some toy models first.

In the remainder of this talk I will briefly review some research that has been done along these lines.

# An interesting class of Boolean systems

Let us call a Boolean system **one-stepping** if

$$H(\vec{s}(\tau), \vec{s}(\tau + 1)) \leq 1$$

for all  $\tau$  along each trajectory where  $H$  denotes Hamming distance. For one-stepping Boolean systems simultaneous crossing of thresholds in the ODE system is not an issue. These Boolean systems can be realized in the sense of strong consistency by many classes of ODE systems.

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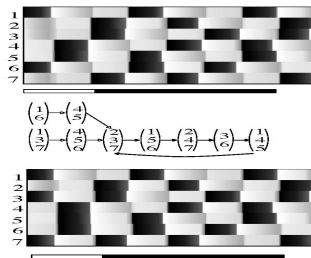
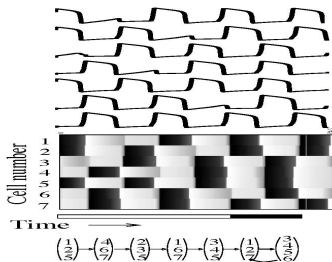
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- Gehrman and Drossel for gene regulatory networks.
- Just *et al.* for a class of toy models.
- Later talks in this session.

# Dynamic clustering in neuronal networks

In several neuronal networks, it has been observed that time appears to progress in distinct episodes in which some subpopulation of cells fire synchronously; however, membership within this subpopulation may change over time. That is, two neurons may fire together during one episode but not during a subsequent episode. This phenomenon is called **dynamic clustering**.



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**Problem:** Are there classes of ODE models, based on Hodgkin-Huxley equations for individual neurons that exhibit dynamic clustering? If so, can the firing patterns be predicted by Boolean approximations?

# A theorem

Terman D, Ahn S, Wang X, Just W, Physica D, 2008

## Theorem

*There exists a broad class of ODE models  $\mathbb{D}$  for neuronal networks such that every model in this class exhibits dynamic clustering.*



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*There exists a broad class of ODE models  $\mathbb{D}$  for neuronal networks such that every model in this class exhibits dynamic clustering. Moreover, for every such  $\mathbb{D}$  there exists a Boolean model  $\mathbb{B}$  that is strongly consistent with  $\mathbb{D}$  on a set  $U$*

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In this theorem we use a version of strong consistency that is based on a slightly altered definition of  $\Delta(\vec{s}(0))$ ; essentially the episodes give us a neat way to discretize time and “next Boolean state” is determined by which neurons fire during the episode; we ignore the slight fuzziness at the boundaries of the episodes.

# Weak consistency

Instead of demanding

$$\vec{s}(\tau + 1) = f(\vec{s}(\tau)), \quad (3)$$

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The classical work of Leon Glass and his collaborators shows that this form of consistency holds for Boolean approximations of a large class of piecewise linear ODE systems.

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- One can get strong consistency under sufficient separation of time scales for all one-stepping Boolean systems.
- For some one-stepping Boolean systems this works only if each agent has at least two variables.
- Every Boolean system can be embedded in a one-stepping Boolean system. Thus with some coding and larger agents, one can get strong consistency for all Boolean systems.

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**How generic is this phenomenon?**

- Investigate **weak consistency for our toy models.**
- Investigate notions of  $\varepsilon$ -**consistency** where switches of the Boolean state that occur within  $\varepsilon$  real time units are treated as simultaneous.



# Collaborators and support

The research group that worked on the toy models included Todd R. Young (Ohio University) and our students Ben Elbert, Mason Korb, Bismark Oduro, and Hanyuan Zhu.

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